Acetaldehyde

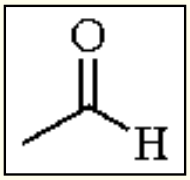

[75-07-0] · C_2H_4O · Acetaldehyde · (MW 44.05)

(reagent used as two-carbon electrophilic component in a wide array of reactions)

Physical Data: mp -123.5 °C; bp 21 °C; *d* 0.788 g cm^{-3}.

Solubility: sol H_2O, alcohol, ether, and most organic solvents.

Form Supplied in: colorless liquid; widely available.

Purification: shaken with powdered $NaHCO_3$ for 30 min; dried over $CaSO_4$, and fractionally distilled at 760 mmHg through a 70 mm Vigreux column.

Handling, Storage, and Precautions: bottles may develop pressure and should be cooled before opening. To help prevent polymerization and autoxidation, store under nitrogen atmosphere and refrigerate. Acetaldehyde is a cancer suspect agent and should be used only in a well-ventilated fume hood. Toxicity (oral) rat LD_{50}: 661 mg kg^{-1}. Incompatible with strong acids, strong bases, oxidizing and reducing agents. Decomposes on prolonged exposure to air.

1,2-Additions.

Acetaldehyde reacts with a myriad of nucleophilic reagents, generally providing excellent yields of the two-carbon extended secondary alcohols. Aryl-,[1] alkynyl-,[2] and alkyllithiums[3] react rapidly with acetaldehyde even at low temperature. A chiral vinyllithium reagent at low temperature reacts stereoselectively to afford a 10:1 mixture of diastereomeric alcohols (eq 1).[4] Aryl[5] or alkyl[6] Grignard reagents behave in an analogous manner with acetaldehyde to give the secondary alcohols or the methyl ketones[7] upon subsequent oxidation. Allyl organometallics react with varying degrees of stereocontrol depending on the metal and conditions to give the corresponding homoallylic alcohols.[8] Chiral allylboronates also react with acetaldehyde at -78 °C to afford the homoallylic alcohols with high enantioselectivity.[9] *trans*-Epoxides are produced selectively through the Darzens reaction of acetaldehyde with halomethyl sulfones under basic phase transfer conditions.[10] Classical Wittig reagents[11] and Horner-Emmons phosphonate[12] ylides react with acetaldehyde to give the alkene.

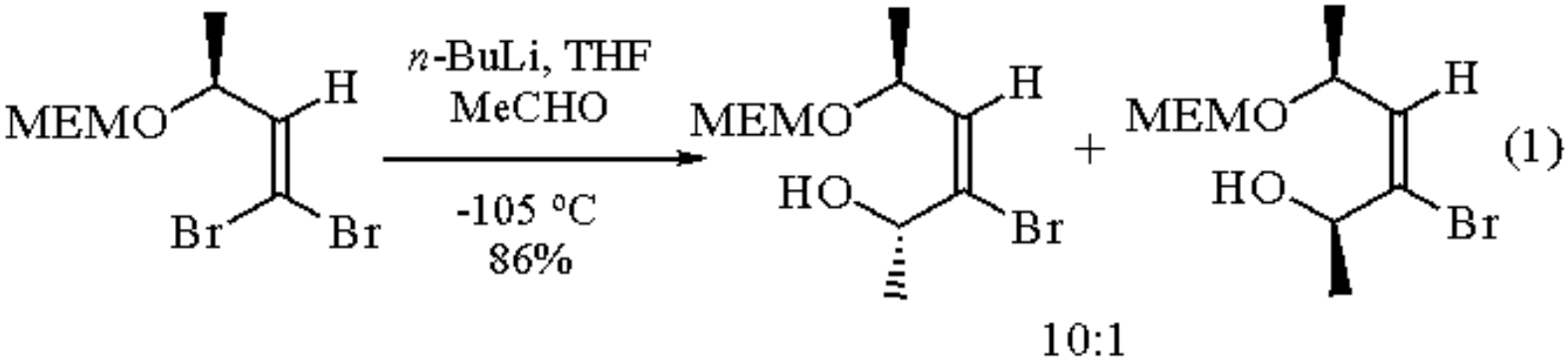

Aldol Additions.

Acetaldehyde serves as an electrophilic partner in the aldol condensation with a wide array of enolates.[13] Knoevenagel condensation of acetaldehyde with active methylene compounds in the presence of base provides good yields of the ethylidene substituted compounds.[14] Addition of two equivalents of an active methylene compound to acetaldehyde results in a Michael addition of the second equivalent to the initially formed ethylidene.[15] Tollens reaction of acetaldehyde with formaldehyde gives pentaerythritol.[16] The addition of acetaldehyde in a Baylis-Hillman condensation with ***Ethyl Acrylate*** using ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO) as catalyst gives a 90% yield of the allylic alcohol.[17] The stereoselective aldol reaction of acetaldehyde with achiral[18] and chiral[19] imide enolates has received much attention and is a proven method for controlling acyclic relative and absolute stereochemistry.[13] For example, the boron enolate of a norephedrine-derived propionyloxazolidine reacts with acetaldehyde to afford in 90% yield and >98% de the *syn* aldol product (eq 2).[19a] Acetaldehyde also smoothly undergoes nitro-aldol condensation to the corresponding nitro alcohols.[20] The lithium enolates of a variety of heterocycles react with acetaldehyde to give good yields of product alcohols.[21] In addition, the zinc,[22] copper,[23] and boron[24] enolates of esters and ketones provide aldol products with acetaldehyde.

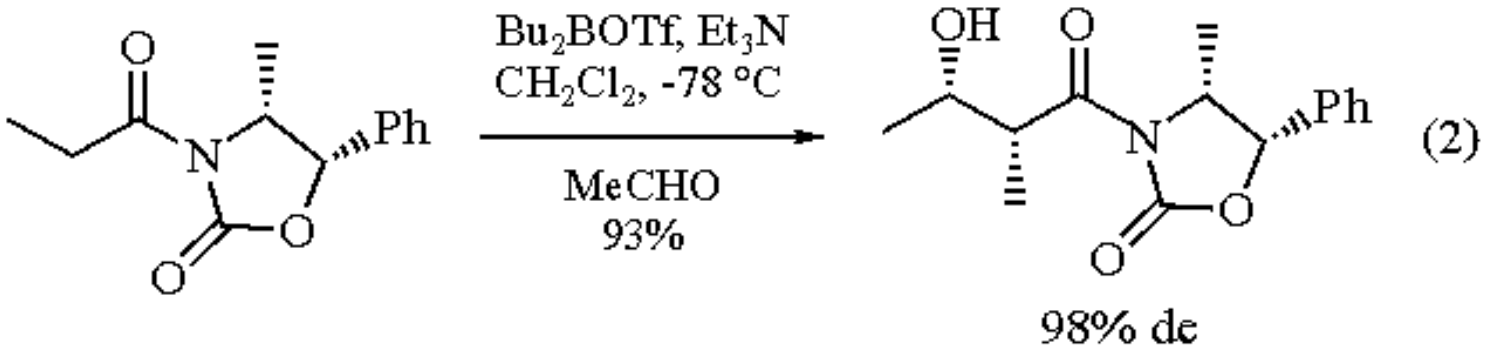

Mannich and Mannich-Type Reactions.

Although not as commonly used as ***Formaldehyde***, acetaldehyde undergoes many synthetically useful Mannich reactions. Intramolecular Mannich reaction of acetaldehyde has been utilized to produce the natural product myrtine (eq 3).[25] The intramolecular Mannich reaction has also been used in the synthesis of proline derivatives.[26] Nucleophiles as diverse as dialkyl phosphites[27] and amines[28] or aryl radicals[29] may also add to the intermediate imine of acetaldehyde in Mannich-type reactions. A historically significant reaction of acetaldehyde in this mode is the Strecker synthesis of alanine, whereby cyanide is added to the adduct of ammonia and acetaldehyde followed by hydrolysis of the intermediate α-aminonitrile.[30] The Pictet-Spengler reaction utilizing acetaldehyde is an important ring-forming reaction.

Acetaldehyde has been extensively used in the synthesis of the biologically active β-carbolines from tryptophan derivatives through this cyclization.[31] Other ring systems such as tetrahydroisoquinolines[32] and dihydrooxazines[33] have also been formed employing Pictet-Spengler cyclization with acetaldehyde.

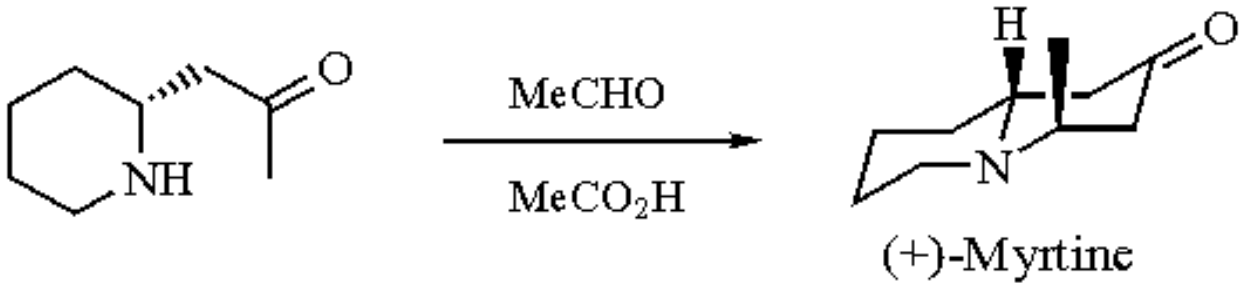

(3)

Metal and Other Promoted Condensations.

In the mixed Tishchenko reaction using ***Aluminum Isopropoxide*** as promoter, acetaldehyde is predominately the oxidized partner. Thus when condensed with benzaldehyde, benzyl acetate is the major product.[34] Recently an interesting and synthetically useful stereoselective intramolecular Tishchenko reduction of β-hydroxy ketones using acetaldehyde and promoted by ***Samarium(II) Iodide***, affording *anti*-1,3-diol monoacetates, has been reported (eq 4).[35] The stereoselective pinacol cross-coupling of acetaldehyde with other higher-order aldehydes that contain chelating functionalities has been achieved using a vanadium(II) reagent.[36] The photochemical addition of acetaldehyde in the presence of molecular oxygen to α,β-unsaturated esters and ketones provides excellent yields of the 1,4-dicarbonyl compounds (eq 5).[37]

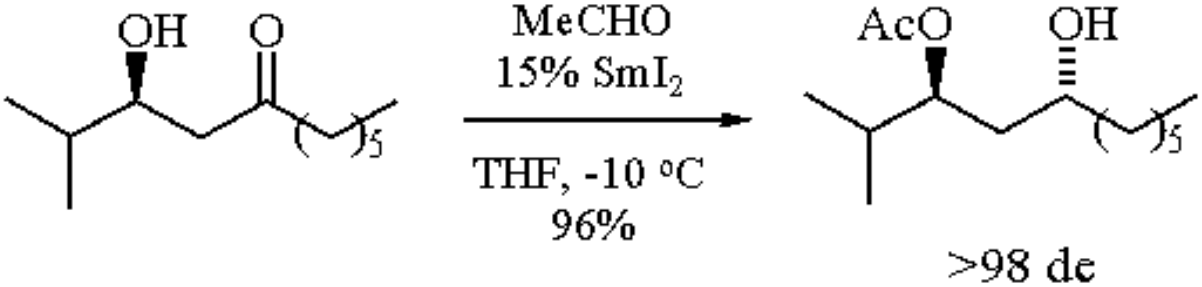

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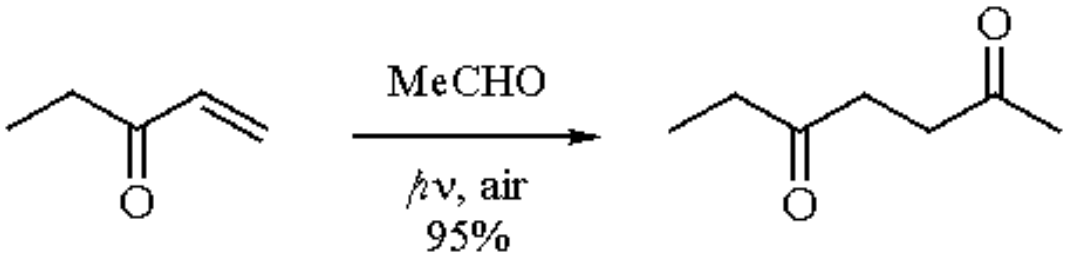

(5)

Pericyclic Reactions.

The thermal ene reactions of acetaldehyde and other aliphatic aldehydes with alkenes are generally not very productive.[38] However, acetaldehyde can be induced to undergo ene reactions with a variety of alkenes under Lewis acid activation. ***Dimethylaluminum Chloride*** has been used to promote the ene reaction between the relatively reactive 1,1-di-, tri-, and tetrasubstituted alkenes (eq 6).[39] With the more unreactive monosubstituted terminal alkenes, the more

Lewis acidic ***Ethylaluminum Dichloride*** must be employed to obtain reasonable yields of ene products with acetaldehyde.[40] Acetaldehyde is a relatively unreactive dieneophile towards dienes. The hetero-Diels-Alder reaction of acetaldehyde has been reported under high pressure acceleration with 1-alkoxydienes to afford good yields of dihydropyrans with modest *endo* selectivity.[41]

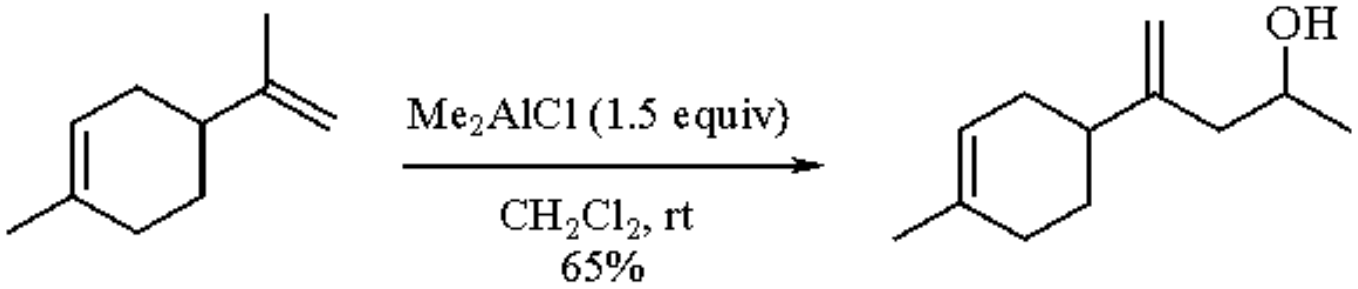

(6)

Paraldehyde and Other Acetaldehyde Derivatives.

Paraldehyde has historically been used as a stabile and less volatile form of acetaldehyde in a wide array of chemical reactions.[42] However, since its classification as a controlled substance, its restricted availability has led to its limited use in modern synthetic organic chemistry. Acetaldehyde can be generated from paraldehyde through acid catalyzed degradation of the trimer and isolated by distillation.[43] The diethyl acetal of acetaldehyde, commonly known as acetal, may be generated from acetaldehyde or paraldehyde, ethanol, and calcium chloride.[44] Acetaldehyde and paraldehyde have also been used for the protection of diols as their ethylidene acetals.[45]

Related Reagents.

Acetaldehyde N-t-Butylimine; ***Acetaldoxime***; ***Crotonaldehyde***; ***Dimethylaluminum Chloride***; ***Ethyl Vinyl Ether***; ***Formaldehyde***; ***Formaldehyde-Dimethylamine***; ***Vinyl Acetate***.

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Thomas J. Sowin & Laura M. Melcher

Acetaldehyde 3-Bromopropyl Ethyl Acetal

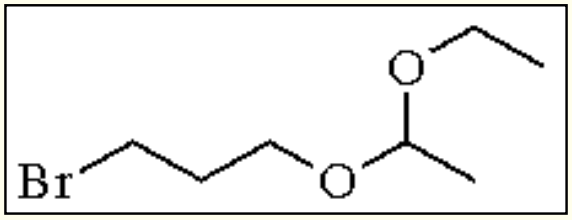

[34399-67-2] · $C_7H_{15}BrO_2$ · Acetaldehyde 3-Bromopropyl Ethyl Acetal · (MW 211.1)

(electrophilic or nucleophilic hydroxypropylation reagent[1])

Alternate Name: 1-bromo-3-(1-ethoxyethoxy)propane.

Physical Data: colorless liquid, bp 49-51 °C/1 mmHg.[1]

Solubility: sol common organic solvents (i.e. diethyl ether, THF, 1,3-propanediol).

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Method: the reagent has been prepared from 3-bromo-1-propanol and ***Ethyl Vinyl Ether*** using dichloroacetic acid as the catalyst.[1] The choice of the catalyst was reported to be crucial to the success of the procedure. This preparation provided the product in 92% yield.

Purification: purification was performed by vacuum distillation, bp 49-51 °C/1 mmHg.[1]

Handling, Storage, and Precautions: the reagent is acid sensitive and is stored at -30 °C over powdered sodium carbonate.[1] This is an alkylation reagent; proper protective equipment should be worn and use restricted to a fume hood.

Introduction.

Acetaldehyde 3-bromopropyl ethyl acetal (**1**) has been utilized as an electrophilic 3-bromo-1-propanol equivalent and as a source of a nucleophilic three-carbon hydroxypropyl synthon.

Nucleophilic Addition.

1-Lithio-3-(1-ethoxyethoxy)propane, prepared from (**1**) and ***Lithium*** in diethyl ether, has been added to aldehydes,[2] ketones (eq 1),[1,3] lactones (eq 2),[4] lactams,[5] and chlorosilanes.[6] Although the THP ether has also been utilized, the ethoxyethyl ether is hydrolyzed under milder conditions.[7] The corresponding organocopper reagent has been added to α,β-unsaturated ketones and alkyl halides.[8,9]

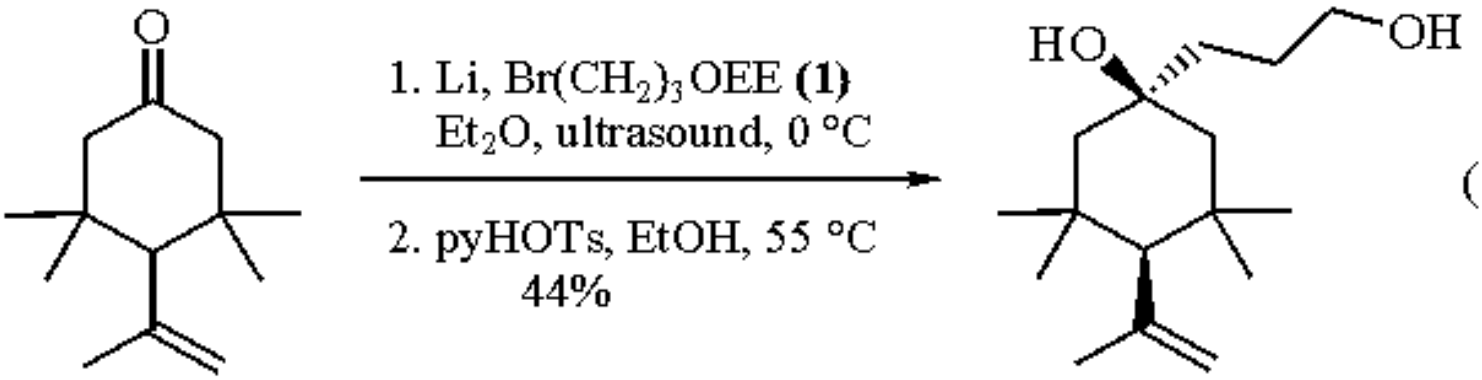

(1)

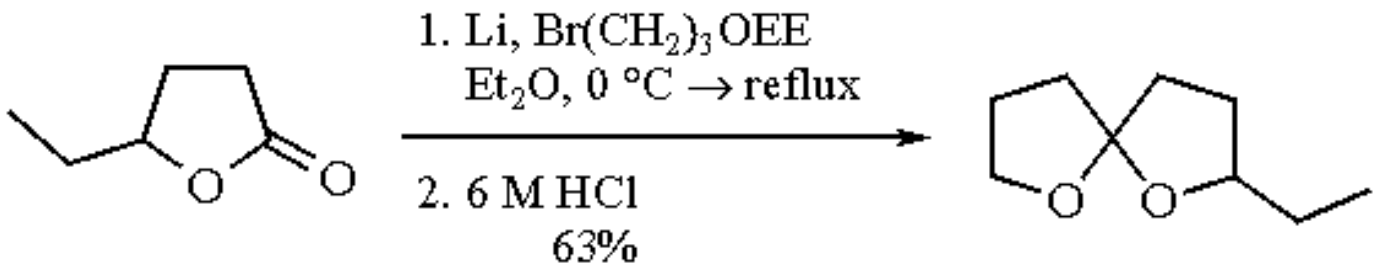

(2)

The Grignard reagent prepared from (**1**) has been added to β-alkoxy enones (eq 3) and coupled with allylic bromides.[10-12]

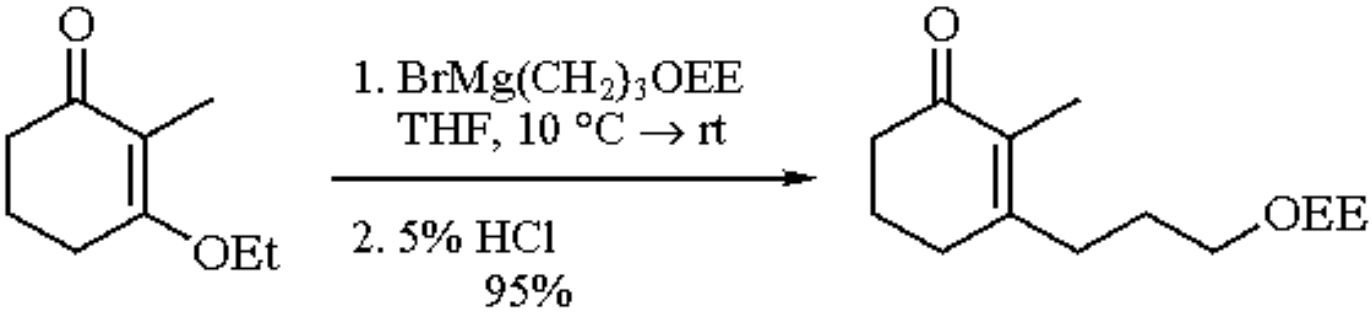

(3)

Alkylation.

Carbanions derived from *N*,*N*-dimethylhydrazones have been alkylated with (**1**) (eq 4).[13,14] The hydrolysis conditions utilized to regenerate the ketone do not allow for the isolation of the protected alcohol product. This can be overcome with the THP ether.[14] Multifunctionalized ethers have also been synthesized using (**1**).[15]

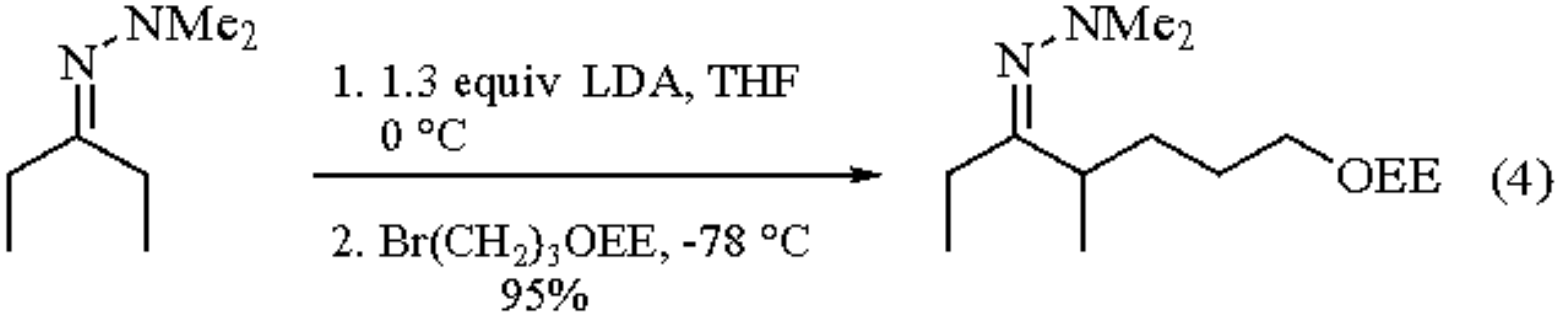

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Acetaldehyde *N*-*t*-Butylimine

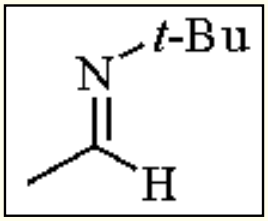

[7020-80-6] · $C_6H_{13}N$ · Acetaldehyde *N*-*t*-Butylimine · (MW 99.17) (*E*)

[62058-77-9]

(acetaldehyde equivalent; synthesis of α,β-unsaturated aldehydes)

Alternate Names: *N*-ethylidene-1,1-dimethylethylamine; *N*-(ethylidene)-*t*-butylamine; *N*-ethylidene-2-methyl-2-propaneamine.

Physical Data: bp 25-28 °C/95 mmHg; *n*19.2D 1.4005.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: ^{1}H NMR; GC.

Preparative Methods: condensation of freshly distilled ***Acetaldehyde*** with ***t-Butylamine*** without solvent.[1-4] The way the reactants are mixed is crucial. *t*-Butylamine is added dropwise to 1 equiv of the aldehyde at -10 to 0 °C (eq 1). The reaction mixture is further stirred at rt for 10 min after which solid KOH is added (about 10 g per mol). After separation of the water layer, the imine is distilled over KOH using a Vigreux column. It was reported that azeotropic removal of the water, formed during the reaction, with an organic solvent, nonmixable with water, gave good results.[5] However, it was found that this procedure with dichloromethane as solvent gave an end product which was always contaminated with the solvent.[4]

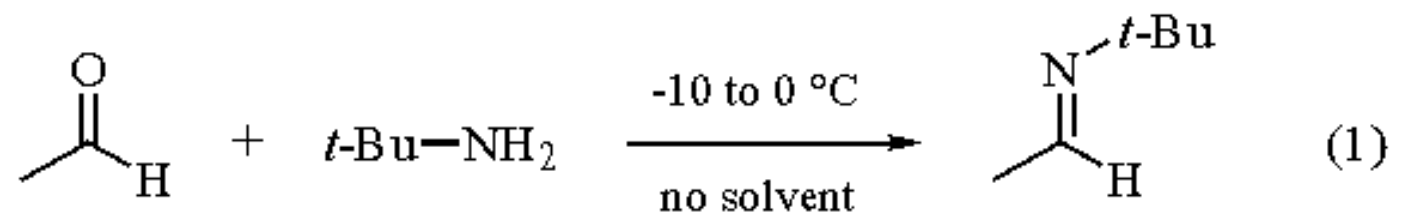

Handling, Storage, and Precautions: very sensitive to hydrolysis; store in closed vessels under an inert atmosphere in the refrigerator. Use of the freshly distilled reagent is recommended. Use in a fume hood.

Introduction.

Imines derived from acetaldehyde and lower alkylamines, e.g. ethylamine, are extremely difficult to handle under basic reaction conditions.[6] More bulky derivatives such as acetaldimines derived from cyclohexylamine and preferably *t*-butylamine are much more stable and can be used as a ready acetaldehyde equivalent.

Reactions of Metalated Acetaldehyde *N*-*t*-Butylimine.

Lithiation of aldimines results in a change from (*E*) to (*Z*) configuration.[7] A facile carbon-carbon bond rotation in 1-azaallyllithium reagents is readily observed by variable temperature ^{1}H NMR spectroscopy.[8] Lithiation is most frequently performed by ***Lithium Diisopropylamide*** or ***Lithium Diethylamide*** in THF or diethyl ether. Lithiated acetaldehyde *t*-butylimine is readily α-monoalkylated by alkyl bromides, but α,α-dialkylation is difficult to avoid.[4] This acetaldimine has been used to prepare the alkaloid stenusine, the spreading agent of the beetle *Stenus comma* (eq 2).[4,9] Attempts to perform the synthesis starting from acetaldehyde *N*-ethylimine failed.[4]

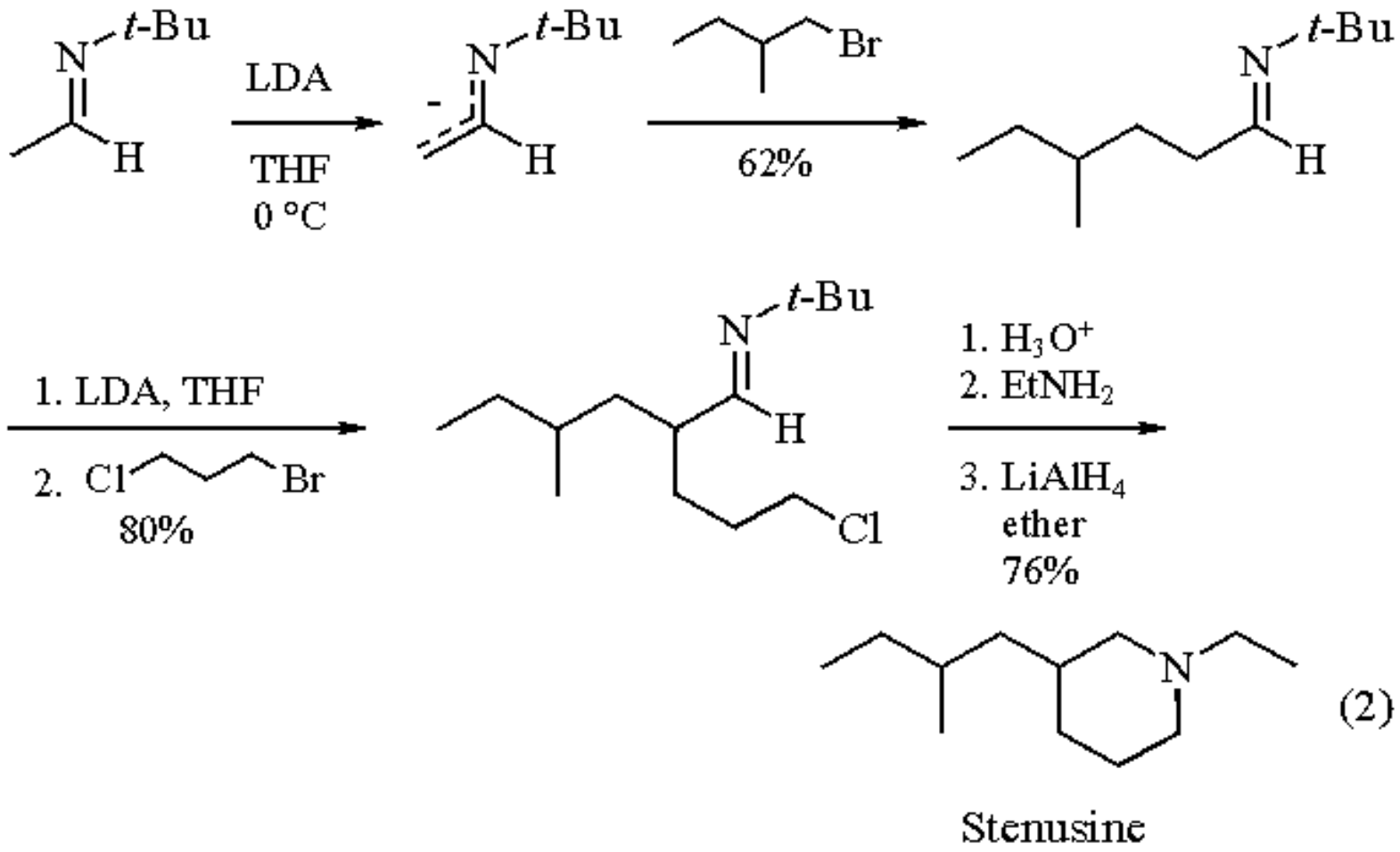

(2)

Similar α-deprotonations and α-alkylations of acetaldehyde cyclohexylimine have been performed with ***Potassium-Graphite*** and alkyl bromides, respectively.[10] o-Halo aldehydes (eq 3),[11] 4-bromo-4-pentenal,[12] and 5-chloro-4-alkenals[12] are accessible from the same aldimine after deprotonation and reaction with α,o-dihaloalkanes, ***2,3-Dibromopropene***, and 3-chloroallyl chloride, respectively.

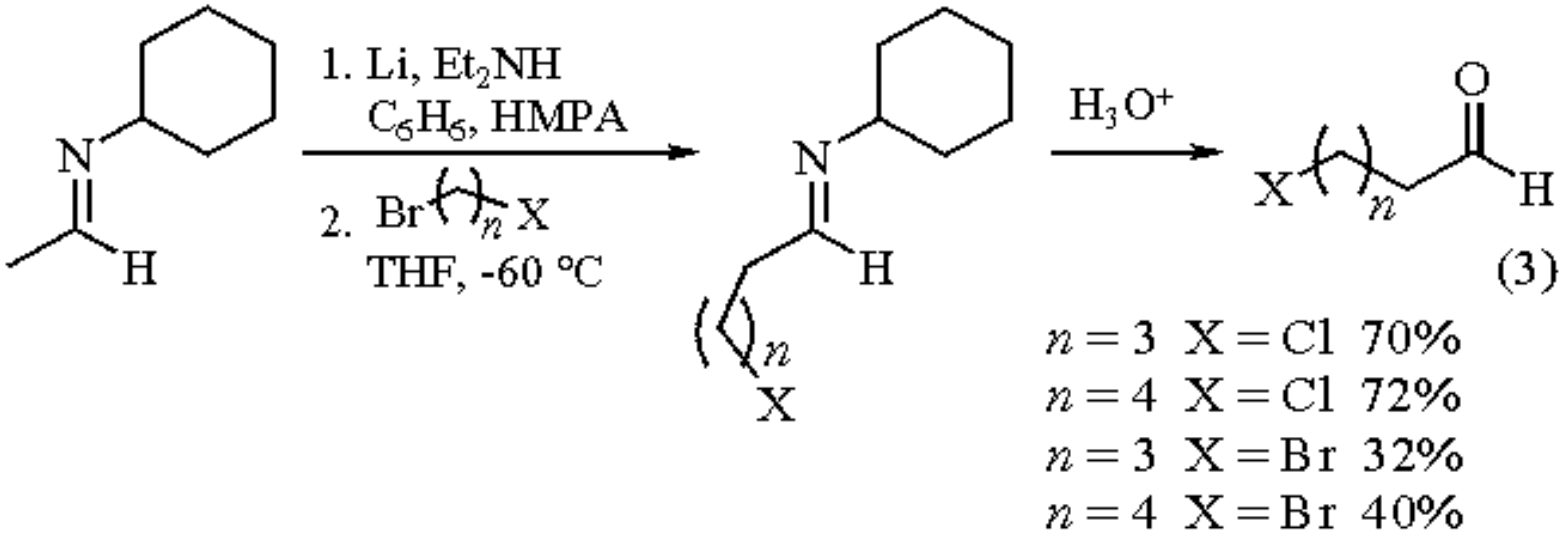

(3)

Acetaldehyde *t*-butylimine is an extremely versatile building block for the synthesis of α,β-unsaturated aldehydes by lithiation, subsequent reaction with diethyl chlorophosphate, further reaction with aldehydes or ketones, and final hydrolysis (eq 4).[13] Examples include 3-cyclohexylpropenal (**1**),[13] (*E*,*E*)-4-(phenylthiomethyl)-2,4-hexadienal (**2**),[14] polyoxygenated cyclohexanes (**3**)[15] and others.[16,17] An alternative method consists of α-trimethylsilylation of acetaldehyde *t*-butylimine followed by deprotonation and reaction with a carbonyl compound (eq 5).[17,18] α,α-Disilylation is accomplished similarly and leads also via condensation with aldehydes to a wide range of (*E*)-α,β-unsaturated aldehydes (eq 6).[19,20] It should be pointed out also that directed aldol condensations between lithiated acetaldehyde imines and aldehydes or ketones have been frequently reported (eq 7).[6,21] Other electrophiles, e.g. nitriles,[22,23] carboxylic esters,[6] and enones,[6,24] lead to the expected reaction products.

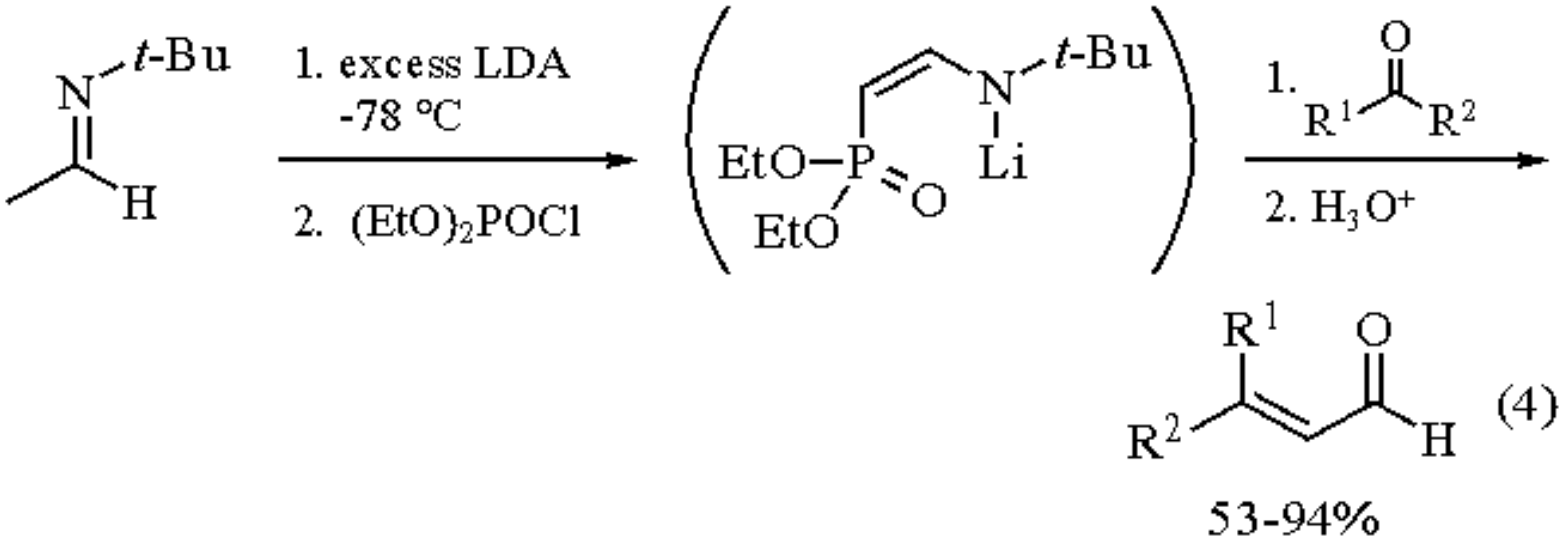

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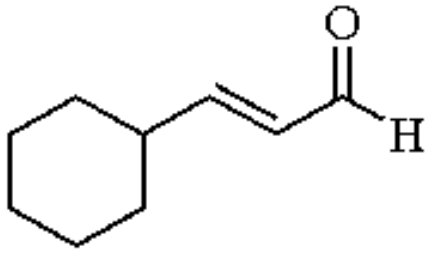

(1) 76%

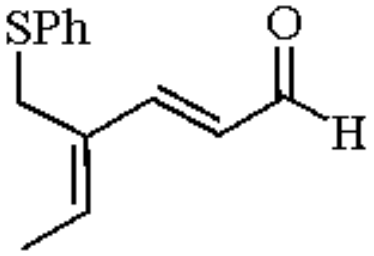

(2) 72%

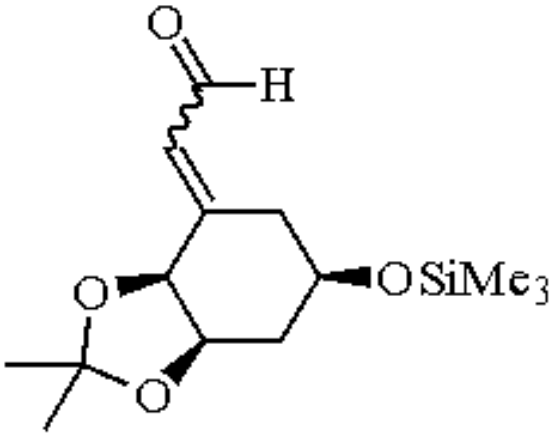

(3) 63% (E:Z = 3:2)

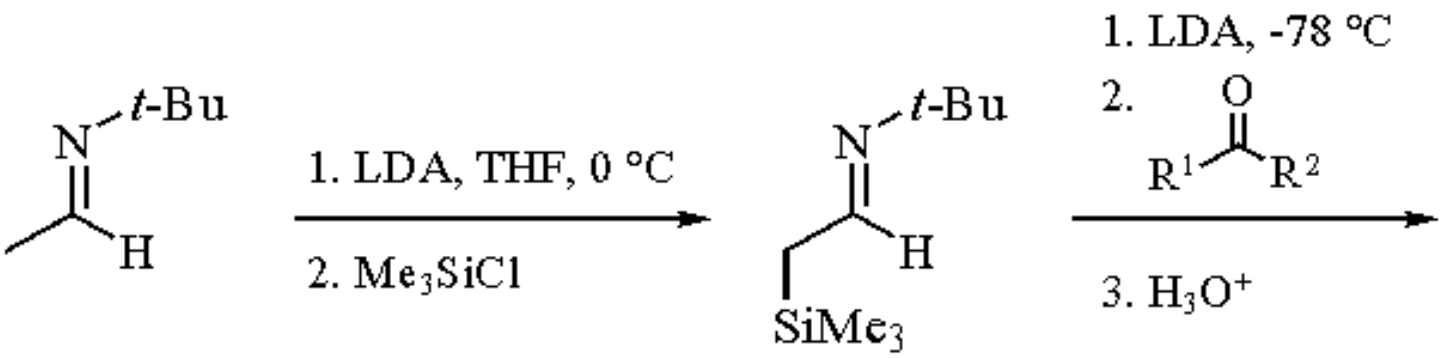

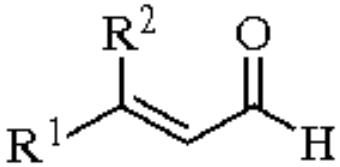

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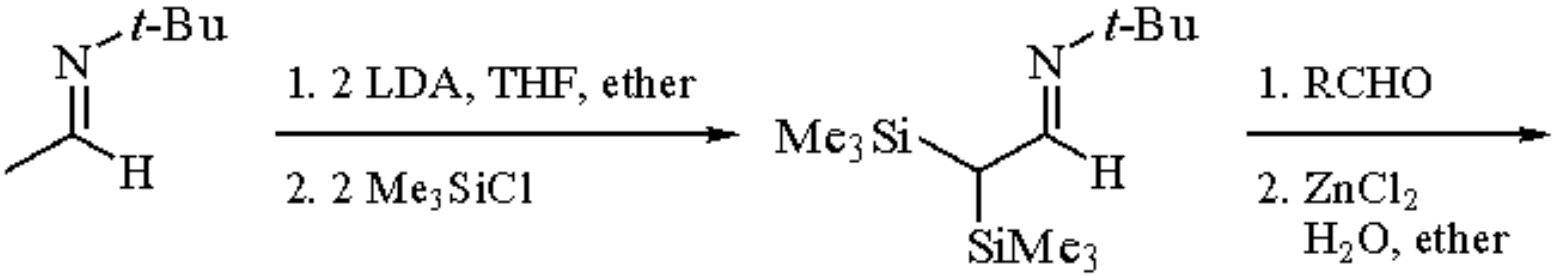

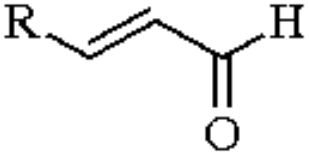

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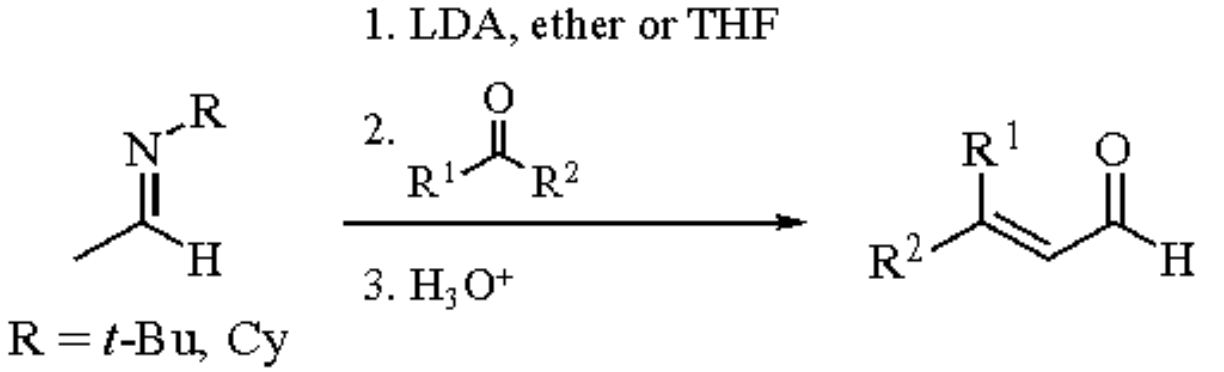

Nitration can be accomplished after deprotonation and reaction with ethyl nitrate, but the reaction takes a partially different course with propyl nitrate (eq 8).[25] In a similar way, β-enamino and β-iminosulfoxides are obtained by using menthyl *p*-toluenesulfinate.[26] Lithiated acetaldehyde *t*-butylimine reacts with chlorophosphites to give α-phosphorylated imines, which are in equilibrium with their enamino form.[27,28] Without the initial deprotonation step, *N*-phosphorylation takes place.[29]

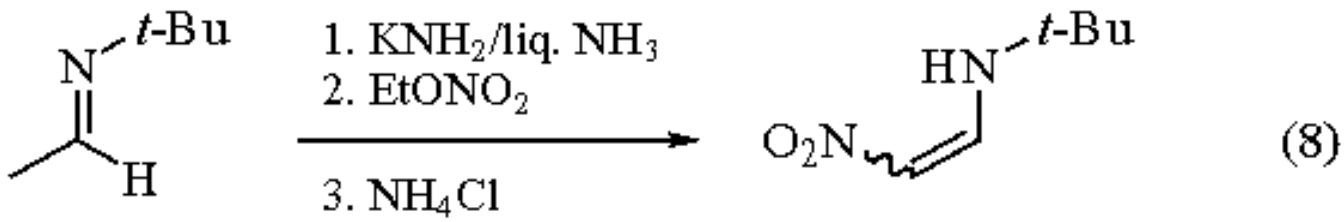

α-Functionalization.

Acetaldehyde *t*-butylimine is α,α,α-trichlorinated with ***N-Chlorosuccinimide*** at room temperature (eq 9).[30] The resulting chloral imine is a suitable substrate for conversion into α,α-dichloroacetimidates, α-cyano-β,β-dichloroenamines, α,β,β-trisulfenylated enamines, and β,β,β-trichloroamines.[30] The reaction of acetaldehyde *t*-butylimine with aromatic nitroso compounds affords α-(*N*-hydroxy-*N*-aryl)aminoaldimines or α-diimines.[31,32]

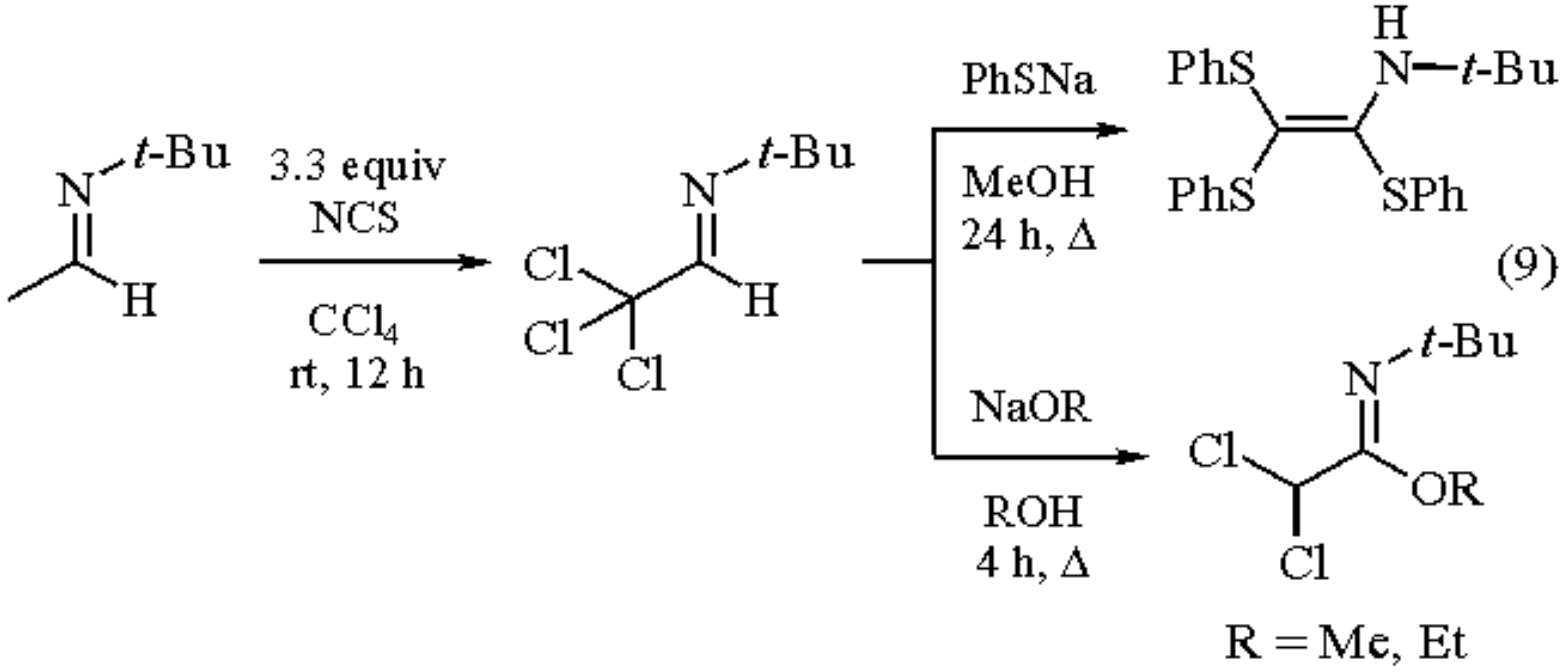

Synthesis of Heterocycles.

Condensation of acetaldehyde *t*-butylimine with enamines at 150-220 °C affords rearranged 1-azabutadienes via cycloreversion of an azacyclobutene intermediate, formed by [2 + 2] cycloaddition of the reactants (eq 10).[33] Further reaction of the 1-azabutadienes with enamines in the presence of *p*-toluenesulfonic acid produces pyridines (eq 10).[33]

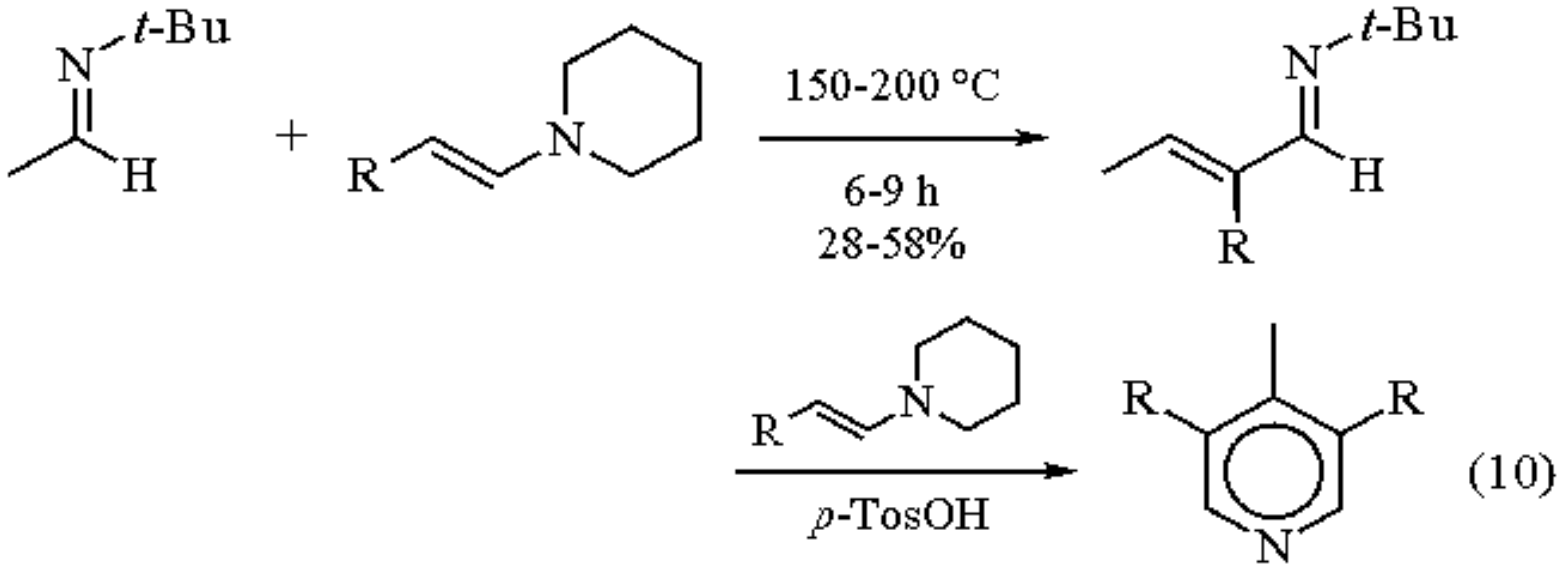

A very convenient synthesis of the imidazole nucleus consists of the reaction of acetaldehyde *t*-butylimine with ***p-Tolylsulfonylmethyl Isocyanide*** (TosMIC) in the presence of *t*-butylamine (eq 11).[34] The same aldimine is readily oxygenated by peroxy acids to the corresponding oxaziridine.[35-37] Asymmetric oxidations have been performed with monoperoxycamphoric acid.[35,36]

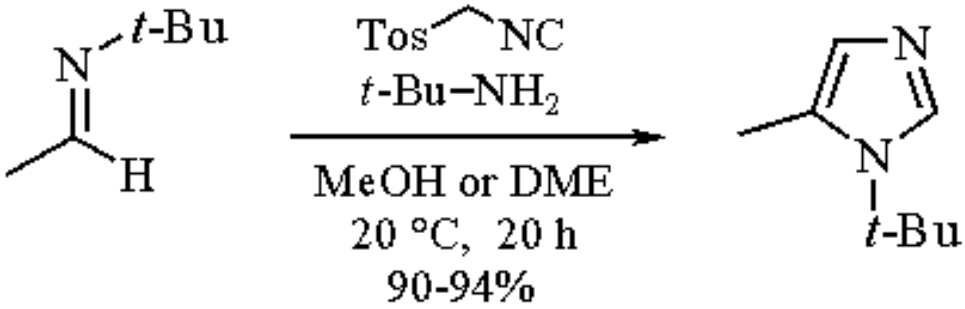

(11)

Reactions at the Imino Bond.

Nucleophilic addition of dimethyl phosphite across the imino bond of acetaldehyde *t*-butylimine without any solvent delivers the addition product (eq 12).[38] Functionalization at the nitrogen atom is accomplished with ***Phosgene***, which gives the *N*-vinylcarbamoyl chloride (eq 13).[39,40] Upon thermolysis, α,β-unsaturated isocyanates and *t*-butyl chloride are produced (eq 13).[40] Functionalized *N*-nitrosodialkylamines are accessible from acetaldehyde *t*-butylimine via reaction with ***Nitrosyl Chloride*** and, for example, ***Ethanethiol*** (eq 14).[41]

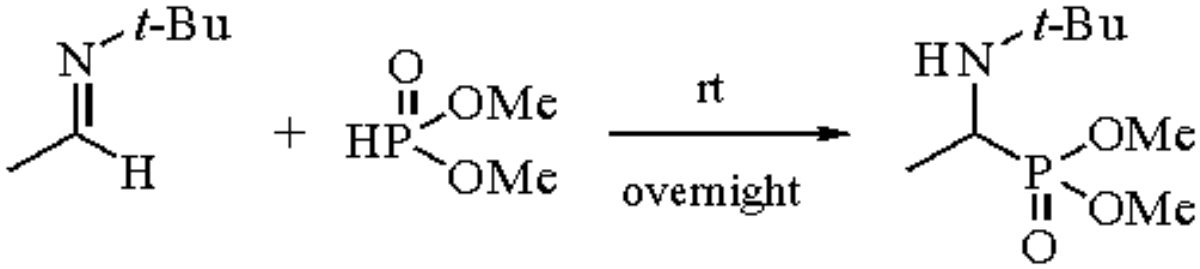

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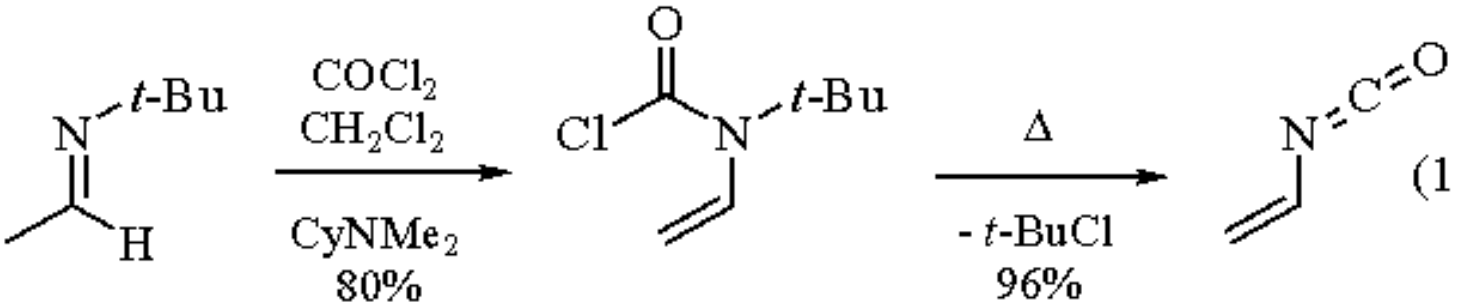

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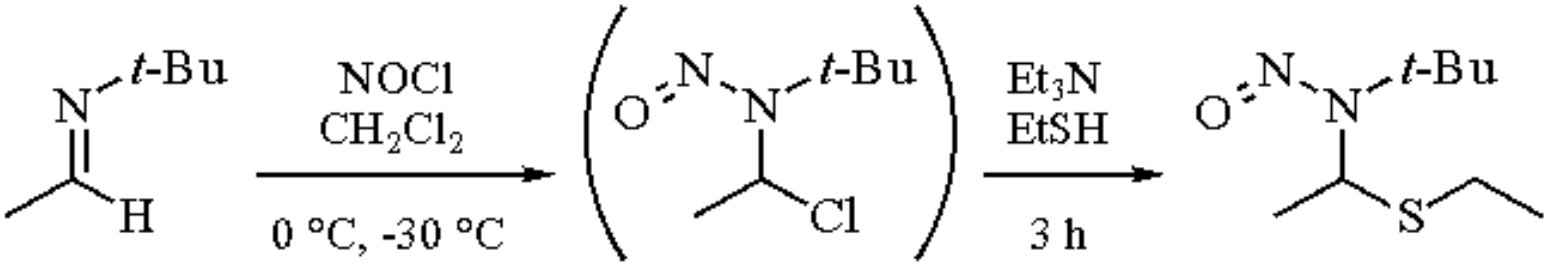

(14)

Related Reagents.

Acetaldoxime; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***2-Chloro-2-methylpropanal N-Isopropylimine***; ***1-***

(N,N-Dimethylamino)-2-methyl-1-propene; ***Propionaldehyde t-Butylimine***.

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Acetaldoxime

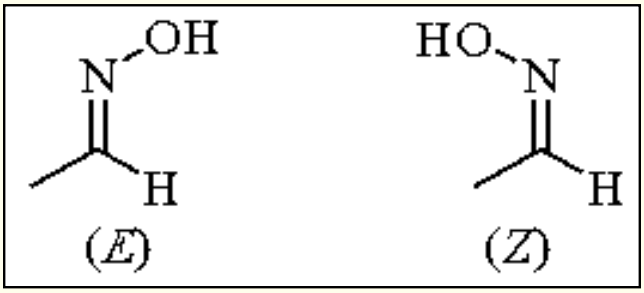

[107-29-9] · C_2H_5NO · Acetaldoxime · (MW 59.07) (*E*)

[5780-37-0] (*Z*)

[5775-72-4]

(acetaldehyde equivalent; acetylation of arenes via diazonium salts;[1] synthesis of aldoximes;[2] rearrangement into acetamide;[3,4] synthesis of heterocycles, e.g. 2-isoxazolines,[5] imidazoles;[6] thiazolidines;[7] precursor for acetonitrile oxide, a useful 1,3-dipole for cycloadditions;[8] 1,3-dipolar cycloaddition[5,9,10])

Alternate Name: acetaldehyde oxime.

Physical Data: (*E*) and (*Z*) mixture bp 114-115 °C; mp 47 °C.

Solubility: sol most organic solvents, e.g. THF, $CHCl_3$, benzene, xylene, diethyl ether, 1,2-dichloroethane.

Form Supplied in: widely available commercially. Commercial samples, which had been refrigerated for several months, showed (*Z*):(*E*) ratios of 10-20:1.[2]

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Method: reaction of freshly distilled ***Acetaldehyde*** with ***Hydroxylamine*** hydrochloride in the presence of a base (eq 1).[3,11]

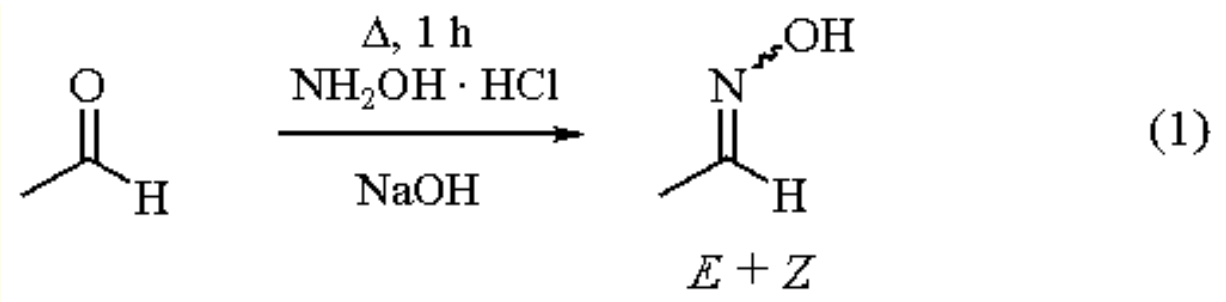

Handling, Storage, and Precautions: the oxime is preferably freshly prepared. The freshly prepared solid compound decomposes slowly on standing. Use in a fume hood.

Introduction.

Unsymmetrical oximes, like acetaldoxime, occur as a mixture of (*E*) and (*Z*) isomers across the carbon-nitrogen double bond (often referred to as *syn* and *anti* isomers, respectively). The position of the equilibrium changes with the conditions. A frequently reported equilibrium is situated around 40% (*E*) in the pure state and 46% (*E*) in aqueous acid,[12] but the position of the equilibrium is independent of the temperature and the concentration of the acid.[13] (*Z*)-Acetaldoxime can be prepared by slow crystallization of a freshly distilled mixture of (*E*)/(*Z*) isomers.[13] ^{1}H NMR[11,14] and ^{13}C NMR[15] have been used to establish the (*E*)/(*Z*) configurations of oximes.

Acetylation of Arenes via Diazonium Salts.

The reaction of acetaldoxime with aromatic diazonium salts affords oximes of acetophenones, which are hydrolyzed in acid medium to give aryl methyl ketones (eq 2).[1]

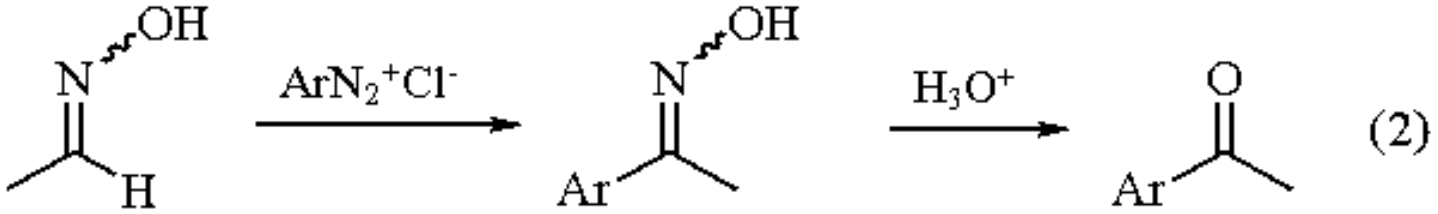

α-Alkylation of Acetaldoxime.

Deprotonation of acetaldoxime with 2 equiv of ***n-Butyllithium*** at -78 °C generates the dianion which reacts with ***Benzyl Bromide*** or 1-iodopropane to give excellent yields of α-alkylated (*Z*)-oximes (eqs 3 and 4).[2] α,α-Dialkylation by further alkylation in similar way has been achieved (eq 4).[2] It is generally known that ketone oximes can be deprotonated and alkylated regiospecifically *syn* to the oxime hydroxy group.[16,17] It is essential to perform the deprotonation and alkylation at -78 °C as otherwise no α-alkylated oximes are isolated, the major byproducts being nitriles.[16]

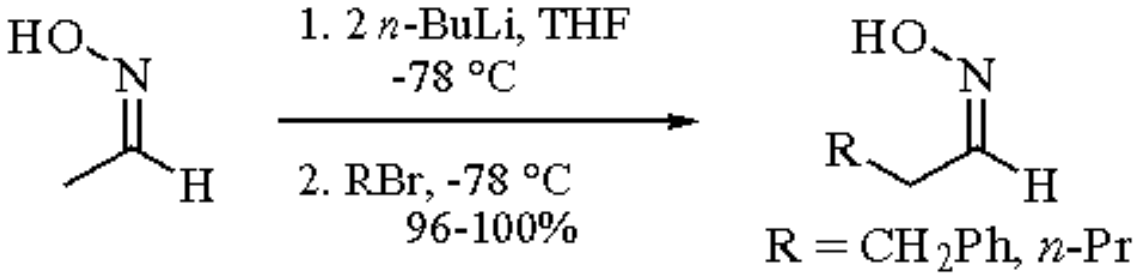

(3)

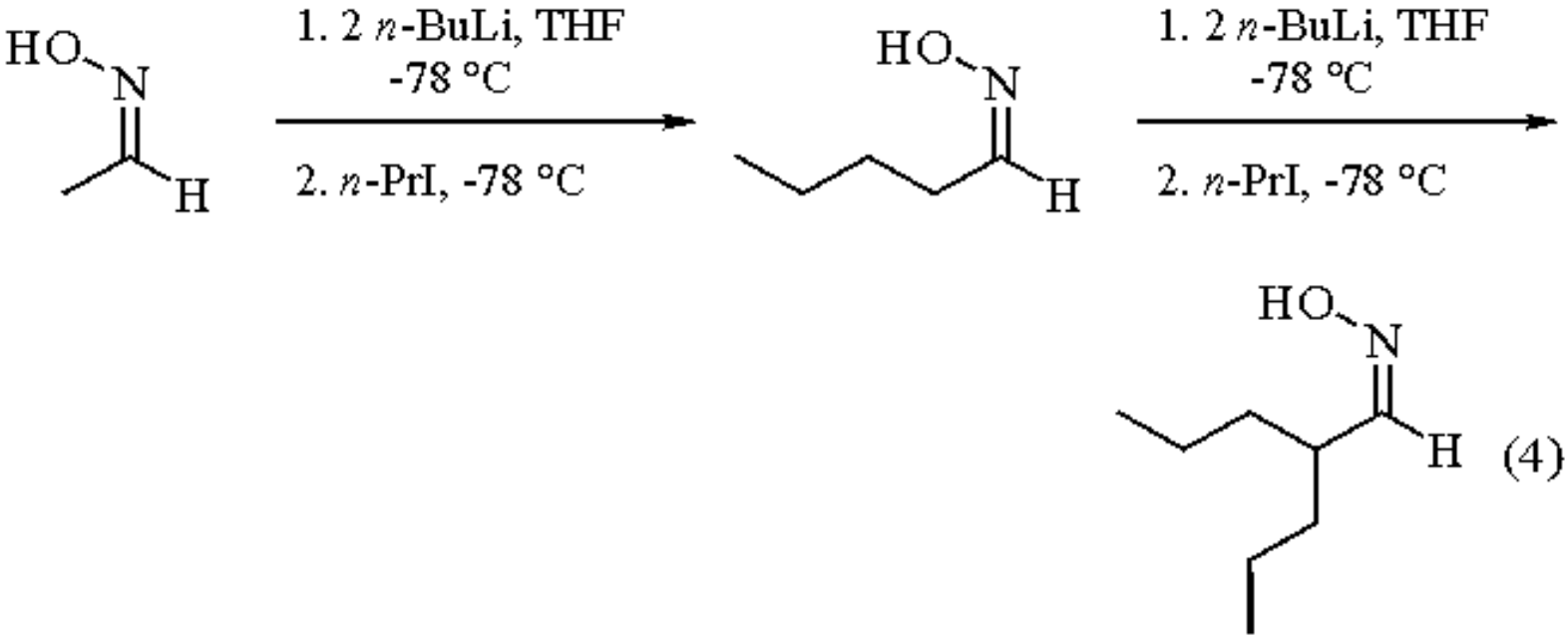

(4)

Rearrangement into Acetamide.

Heating of acetaldoxime in xylene in the presence of 0.2 mol % ***Nickel(II) Acetate***[3] or silica gel[4] as catalyst caused isomerization into acetamide (eq 5).

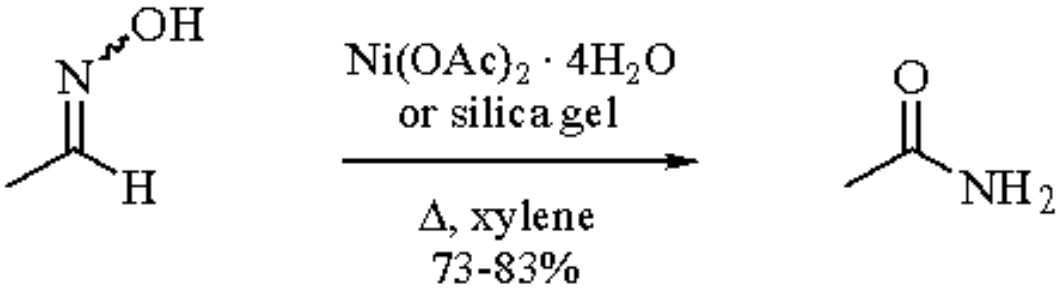

(5)

Synthesis of Heterocycles.

Chlorination of acetaldoxime with ***N-Chlorosuccinimide***[5] or ***Chlorine*** gas[8,18] in chloroform affords acetohydroxamic acid chloride, which suffers dehydrochlorination with ***Triethylamine*** to give ***Acetonitrile N-Oxide***. The latter 1,3-dipole undergoes 1,3-dipolar cycloaddition to alkenes giving 2-isoxazolines in a one-pot procedure (eq 6).[5] This reaction is also suitable for the construction of more complex molecules such as the conversion of a 6-ethylideneolivanic acid derivative into the corresponding spiroisoxazoline (eq 7).[8]

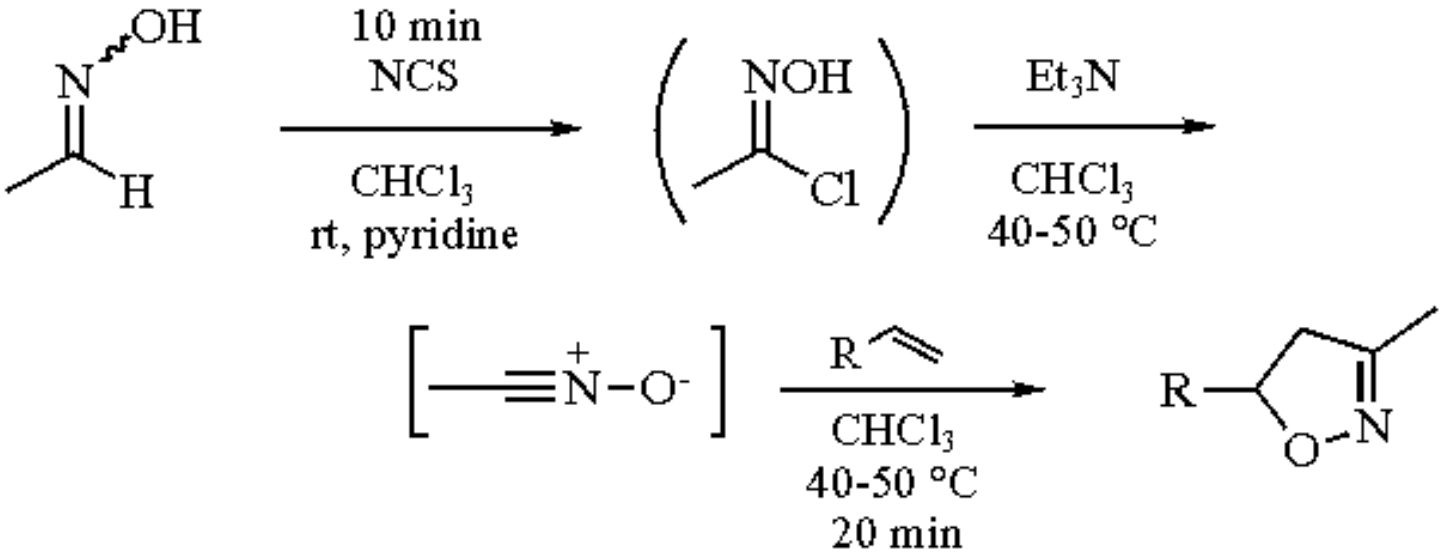

(6)

R = *n*-Bu	61%
R = CH=CHMe	72%
R = C≡CH	14%
R = Ph	84%

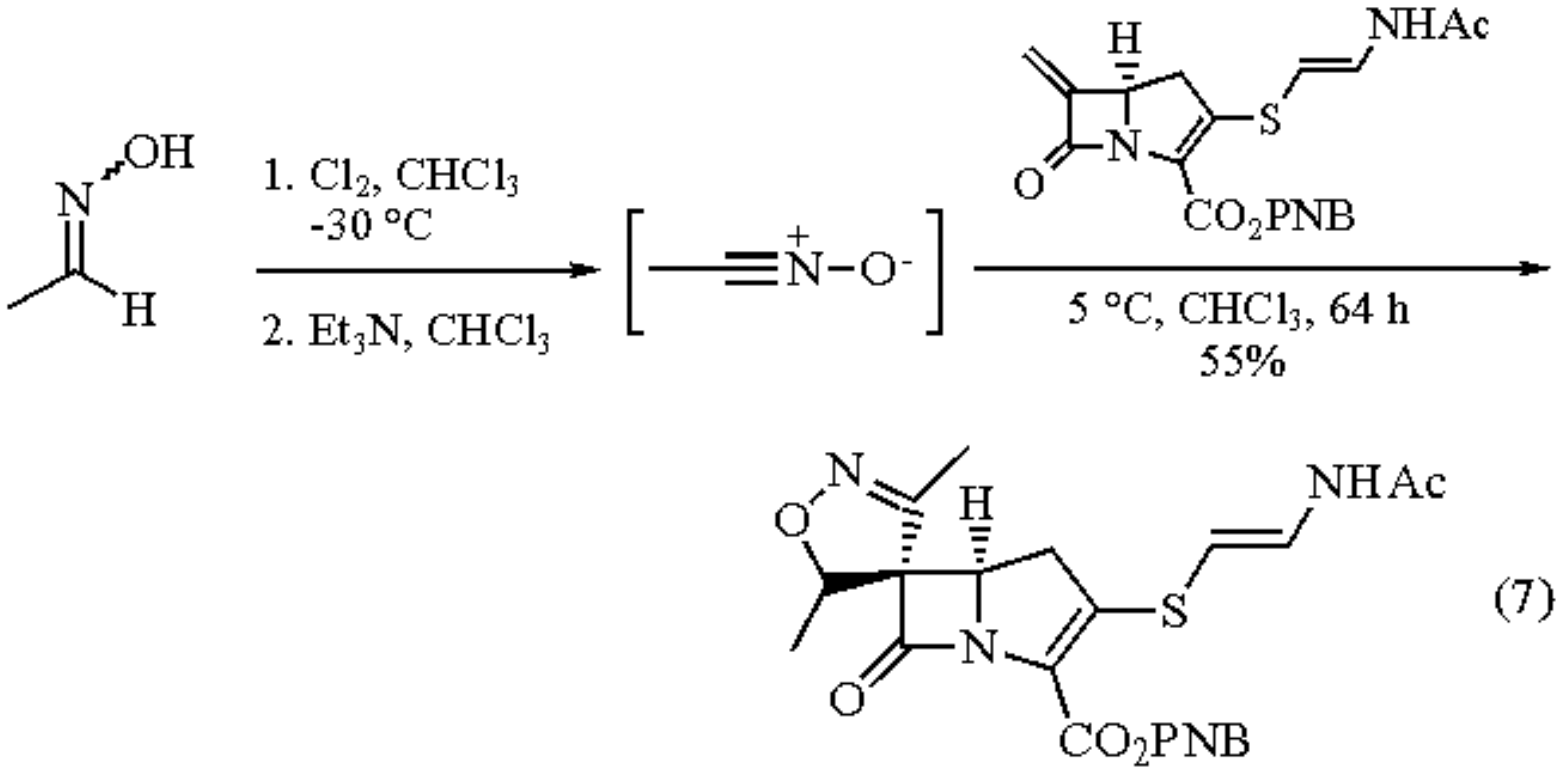

(7)

The cyclocondensation of acetaldoxime with biacetyl monooxime yields 1-hydroxy-2,4,5-trimethylimidazole 3-oxide,[19] originally believed to be 4-hydroxy-3,4,6-trimethyl-1,2,5-oxadiazine.[20] The reaction is preferably performed in liquid sulfur dioxide in the presence of catalytic amounts of hydrogen chloride (eq 8),[6] and works as well with other α-oximino ketones (eq 9).[21]

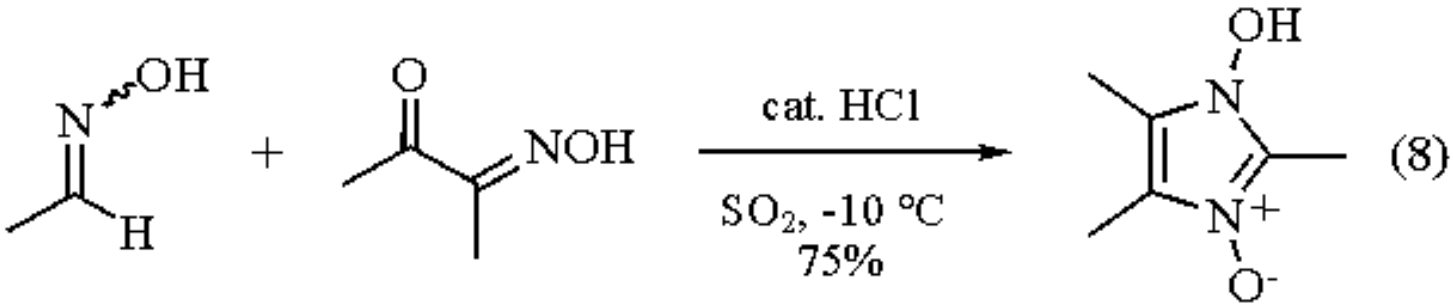

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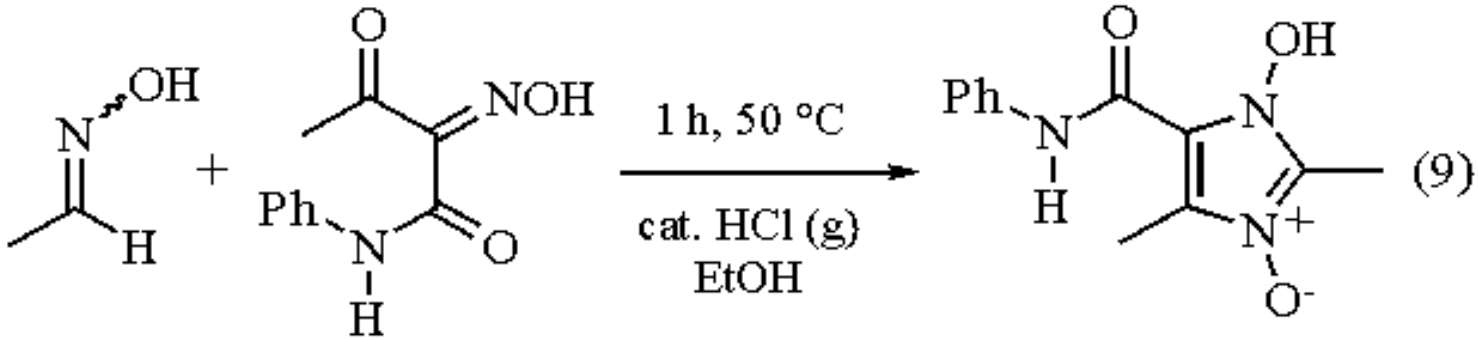

(9)

Upon reaction of acetaldehyde oxime with 2,2-dimethylthiirane, ring expansion to 3-hydroxy-2,5,5-trimethylthiazolidine occurs (eq 10).[7]

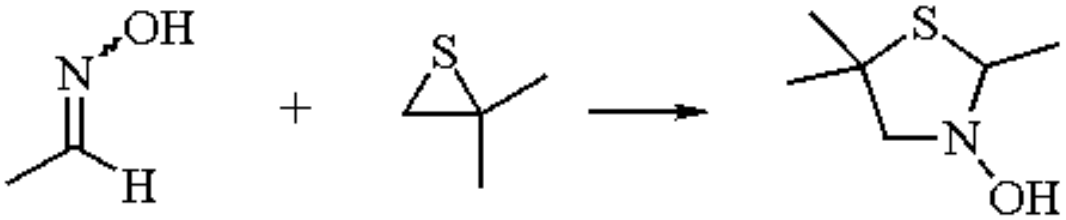

(10)

1,3-Dipolar Cycloaddition.

Acetaldoxime cycloadds very slowly to ***Methyl Acrylate*** and ***Acrylonitrile***, giving 2:1 adducts as mixtures of regioisomers and stereoisomers (eq 11).[10] The palladium-catalyzed cycloaddition of the reagent to 1,3-butadiene yields an isoxazolidine via the intermediacy of a nitrone which undergoes 1,3-dipolar cycloaddition (eq 12).[9]

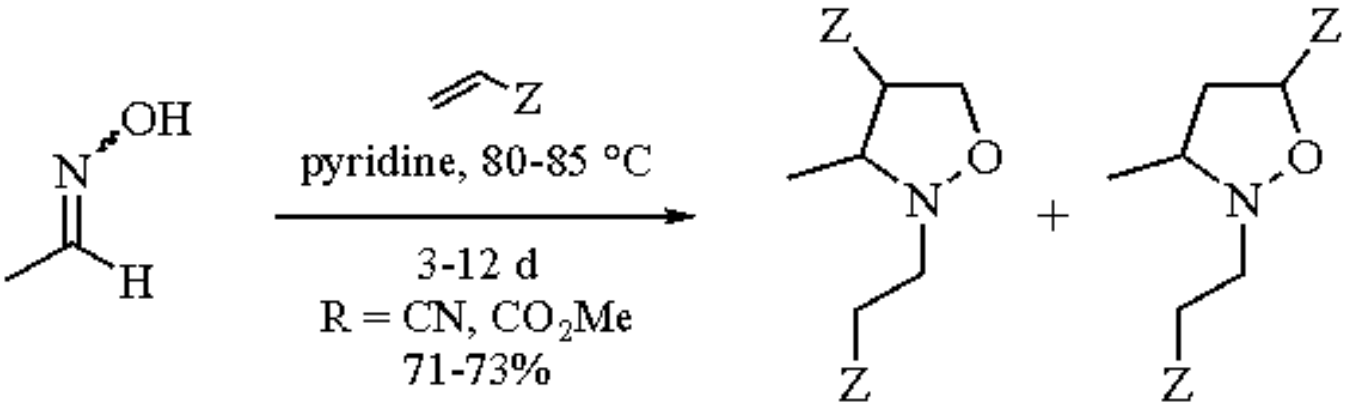

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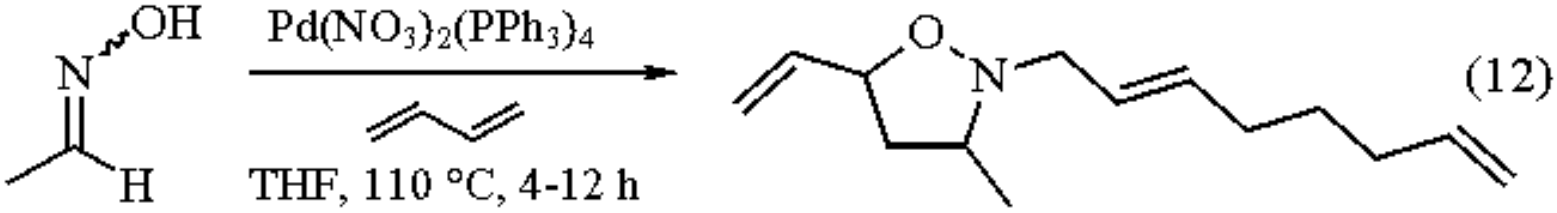

Addition Reactions Across the Carbon-Nitrogen Double Bond.

Cyanotrimethylsilane adds to acetaldoxime to give the cyanated adduct (eq 13),[22] while allylboronates behave similarly to afford the adduct, which disproportionates and can subsequently be cleaved to the alkenic hydroxylamine (eq 14).[23]

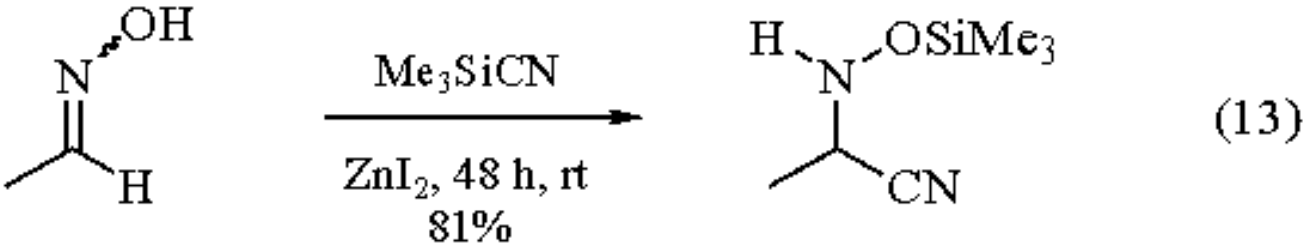

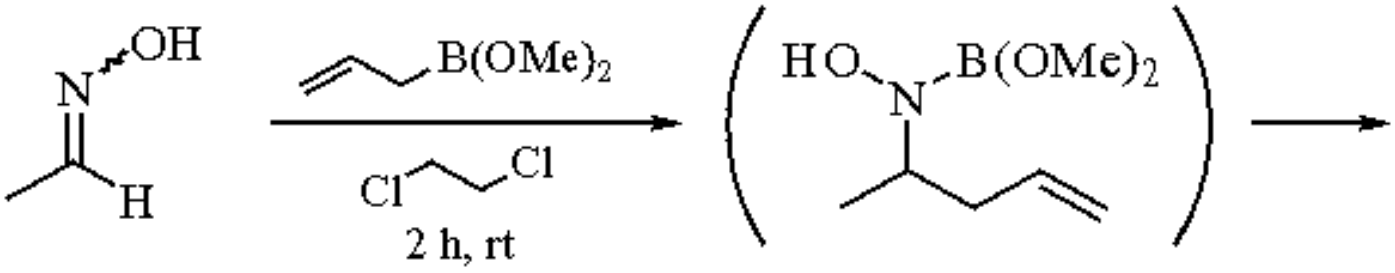

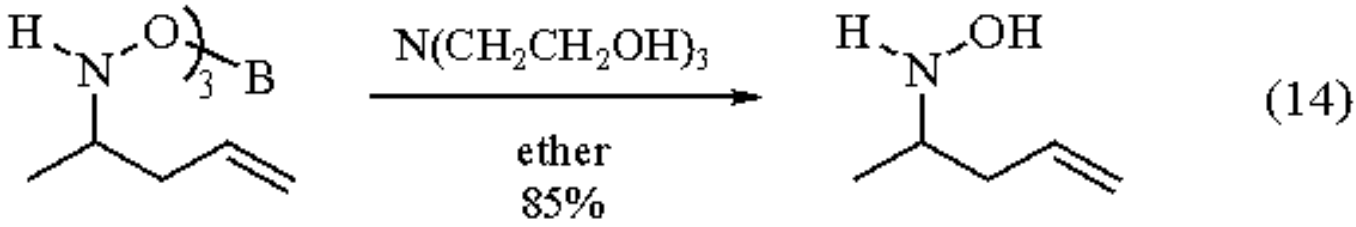

O-Functionalization.

α-Bromo aldoximes are difficult to obtain. Direct α-bromination of aldoximes with a variety of brominating agents was not successful, but smooth bromination of the *O*-silylated derivative was accomplished (eq 15).[24] Functionalization at the oxygen atom has been accomplished with organogermanium[25] and organoarsenium[26] reagents (eq 16), while *O*-alkylation has been performed with the sodium salt of acetaldoxime and an α-bromo ketone.[27] ***Lithium Aluminum Hydride*** readily effected hydrogenolysis of the N-O bond to afford the corresponding 1,2-diol (eq 17).[27]

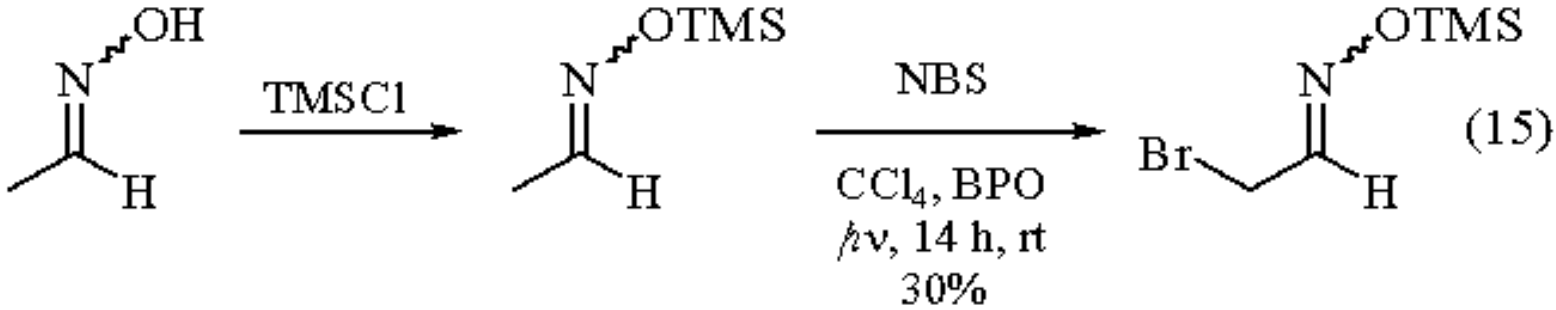

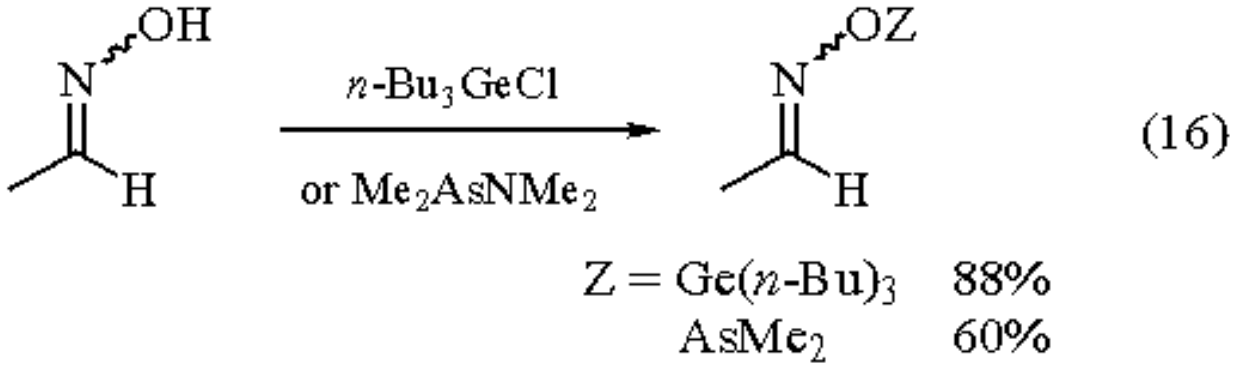

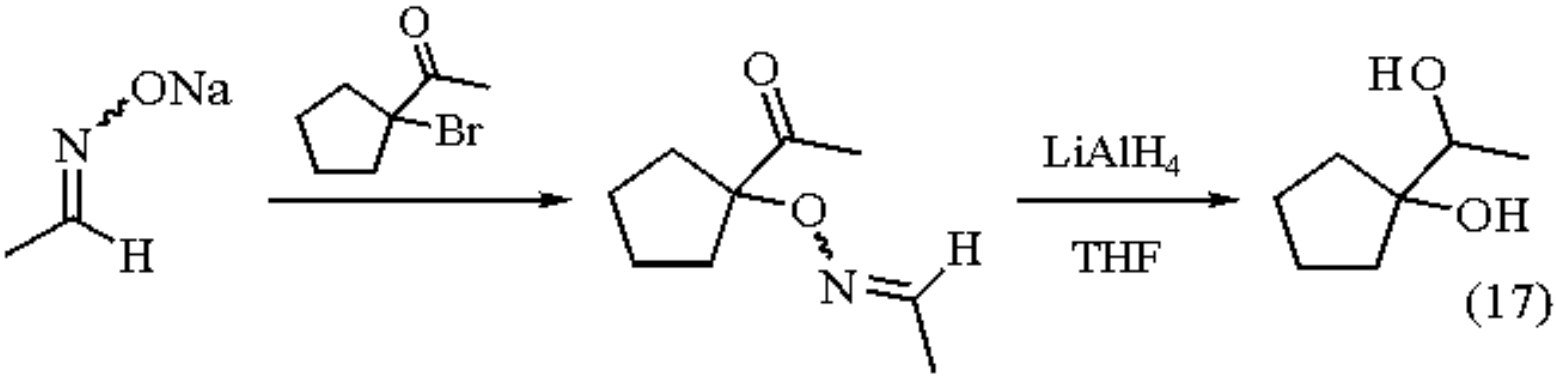

Miscellaneous.

Thermal decomposition of alkyl peresters or peroxides in H-donor solvents, e.g. cycloalkanes or ethers, in the presence of acetaldoxime afforded C-1 alkylated products.[28] The reaction involves carbon radical addition to the carbon-nitrogen double bond.

Related Reagents.

Acetaldehyde; ***Acetaldehyde N-t-Butylimine***; ***Acetonitrile N-Oxide***; ***Formaldoxime***; ***Hydroxylamine***.

---

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p-Acetamidobenzenesulfonyl Azide

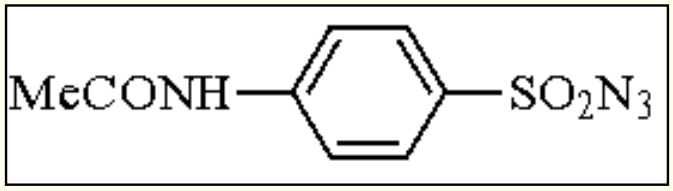

[2158-14-7] · $C_8H_8N_4O_3S$ · *p*-Acetamidobenzenesulfonyl Azide · (MW 240.24)

(reagent for diazo function transfer to activated methylene groups;[1] can functionalize double bonds by cycloaddition reactions[9,10])

Alternate Name: *p*-ABSA.

Physical Data: mp 106-108 °C;[1] 112-114 °C.[2] Decomposition begins at about 120 °C in an open cup system.

Solubility: sol CH_2Cl_2; sparingly sol toluene; insol petroleum ether.

Form Supplied in: colorless or slightly brown crystals.

Analysis of Reagent Purity: ^{1}H NMR, IR, elemental analysis.

Preparative Methods: the title reagent can be prepared by nitrosation of *p*-acetamidobenzenesulfonyl hydrazide,[2,3] by reaction of *p*-acetamidobenzenesulfonyl chloride with ***Sodium Azide*** in acetone solution,[1] or more conveniently under phase transfer conditions with CH_2Cl_2/water in the presence of tetraethylammonium chloride[1] or with benzene/water in the presence of Aliquat 336 (99% yield at rt in 0.5 h).[4]

Purification: recrystallization from toluene.

Handling, Storage, and Precautions: relatively safe reagent and no special instructions for its storage and handling are mentioned in the literature. Proper caution should be used as with all azide reagents. Use in a fume hood.

Diazo Transfer Reagent.

p-Acetamidobenzenesulfonyl azide offers some advantages in safety and ease of product separation and was recommended[1,5] as an alternative and substitute for the standard reagent, ***p-Toluenesulfonyl Azide***,[6] in diazo transfer

chemistry. The reaction times with *p*-ABSA are longer than with other azides.[1a]

Thus far, the reagent has only been employed in the direct transfer of a diazo function to methylene groups flanked by one or two carbonyls.

Well-known diazodicarbonyl compounds, including diazodimedone, diazoisopropylidenemalonic acid, diazomalonic, and diazoacetoacetic acid esters[1] as well as optically active esters of diazoacetoacetic acid (eq 1)[5] are readily available from *p*-ABSA and Et_3N in good yields (72-95%).

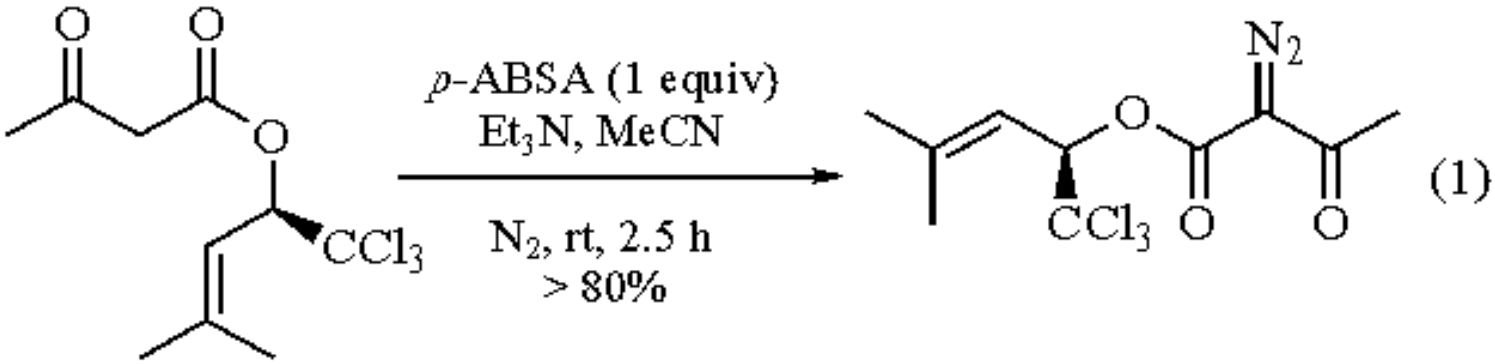

In the presence of a stronger base (***Sodium Ethoxide*** in ethanol) the *p*-acetamidobenzenesulfonyl amide of diazomalonic acid ethyl ester was obtained as the major product from diethyl malonate.[3]

p-ABSA also proves to be a versatile and effective reagent for the synthesis of various vinyldiazomethanes with one or two electron withdrawing groups (EWG) (eq 2).[1,7,8] When two EWG are in a parent substrate, ***Triethylamine*** is usually an effective base,[1,7] but with less acidic systems, ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** is required for good yields of vinyldiazomethanes.[8] The presence of a vinyl group apparently enhances the transformation.[1]

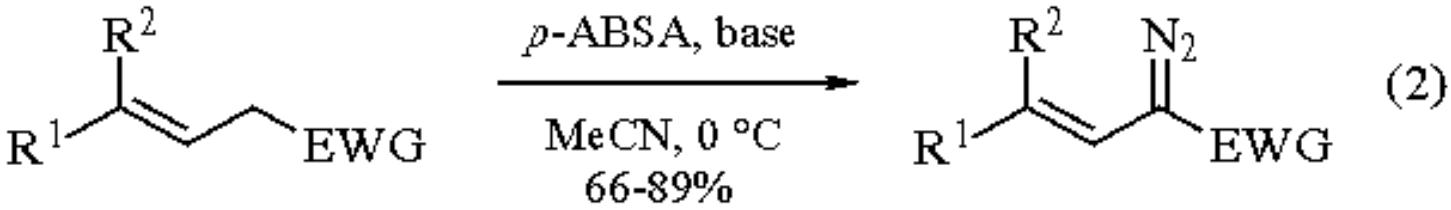

$$EWG = CO_2R,\ COR,\ SO_2$$

$$R^1 = CO_2R,\ SO_2R,\ Ph,\ SPh;\ R^2 = H,\ Alk,\ OAlk$$

Activation of a methylene by one carbonyl group as in dihydro-2-indolone, affords a relatively low yield of diazoindolone (39%) with *p*-ABSA and Et_3N as the base.[1a]

Functionalization of Double Bonds.

Nucleophilic double bonds of indole, *N*-methylindole, and tetrahydropyridine readily add to the 1,3-dipole moiety of *p*-ABSA to give, as the final products, indolidylidene-[9] and piperidylidene-2-arylsulfonamides (eq 3)[10] in good

yields.

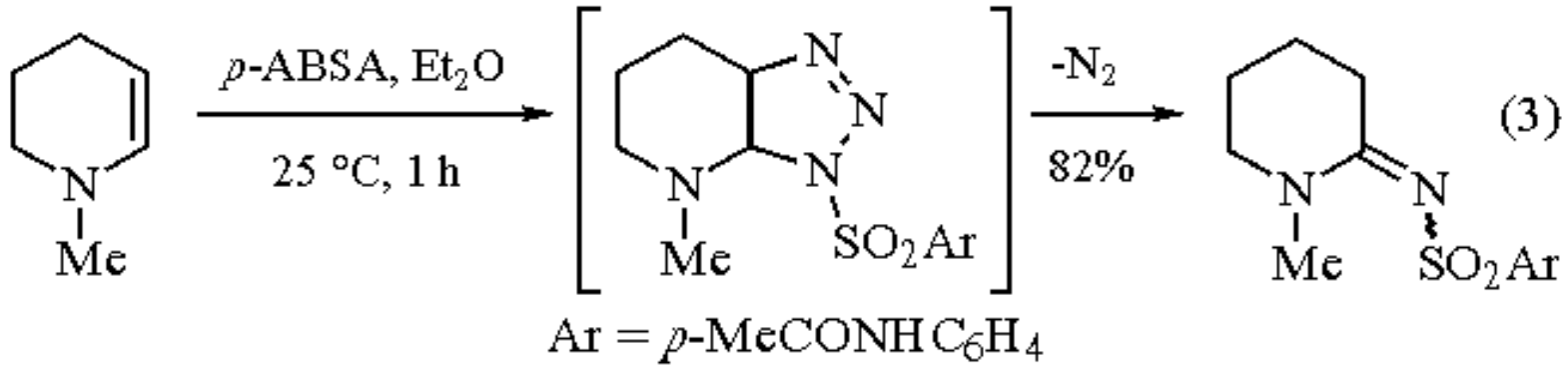

Nitrenogenic Source.

Catalytic decomposition of *p*-ABSA by platinum(II) complexes,[11] thermolysis at fairly high temperatures (above 130-150 °C) in *o*- and *p*-xylenes, *N*,*N*-dimethylaniline,[2] or pyridine,[2,12] and reaction with triphenylstibine[13] gives rise to the formal insertion or addition products of *p*-acetamidobenzenesulfonylnitrene into the corresponding substrates in good to moderate yields.

Related Reagents.

p-Dodecylbenzenesulfonyl Azide; ***Methanesulfonyl Azide***; ***p-Toluenesulfonyl Azide***.

---

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Valerij A. Nikolaev

4-Acetamido-2,2,6,6-tetramethyl-1-piperidinyloxyl[1]

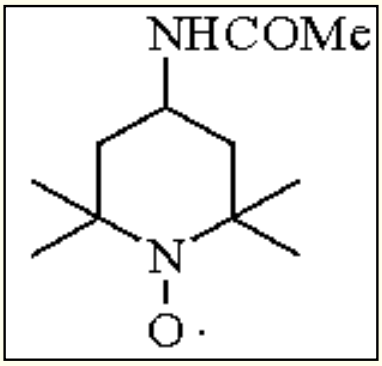

[14691-89-5] · $C_{11}H_{21}N_2O_2$ · 4-Acetamido-2,2,6,6-tetramethyl-1-piperidinyloxyl · (MW 213.30)

(reagent and catalyst for selective oxidation of alcohols[2])

Alternate Names: 4-acetamido-TEMPO; 4-acetylamino-TEMPO.

Physical Data: mp 146-147 °C,[2] 147.5 °C.[3]

Solubility: nearly insol hexane, ether; sol ethanol, acetone, acetonitrile, methylene chloride; slightly sol water, from which it can be recrystallized.

Form Supplied in: red or pink solid, commercially available.

Preparative Method: can be easily prepared in high yield from 4-amino-2,2,6,6-tetramethylpiperidine.[2]

Handling, Storage, and Precautions: completely stable and nonhygroscopic.

Oxidation of Alcohols.

4-Acetamido-TEMPO is a representative of the nitroxide radicals (**1**) which have been used as reagents or catalysts for the oxidation of organic compounds.[1] Several nitroxide radicals have been converted to the corresponding oxoammonium salts (**2**) and used as stoichiometric oxidizing reagents.[1] Nitroxide radicals have also been used as catalysts in the the presence of a secondary, stoichiometric oxidant (see ***2,2,6,6-Tetramethylpiperidin-1-oxyl***).[1]

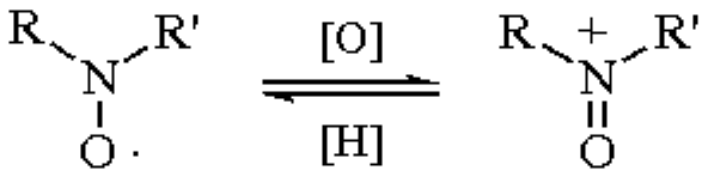

(1) **(2)**

4-Acetamido-TEMPO (**3**) is not, itself, a reagent for the oxidation of alcohols. Rather, it serves as a convenient precursor for the in situ preparation of an oxoammonium salt (**4**), which is the true oxidant. The oxoammonium salt (**4**) is the product of the acid-catalyzed disproportionation of (**3**) to (**4**) and (**5**) in the presence of ***p-Toluenesulfonic Acid*** (eq 1) and is a highly selective reagent for alcohol oxidation (eq 2).[1] The reactions are carried out in methylene chloride in which TsOH.H_2O is essentially insoluble. The only products of the reaction are the desired carbonyl compound product (**7**) and the hydroxylamine salt (**5**), which is completely insoluble in methylene chloride. Product isolation simply involves the filtration of (**5**) and the evaporation of methylene chloride. Compound (**5**) can be converted back to the nitroxide radical (**3**) in quantitative yield.[2]

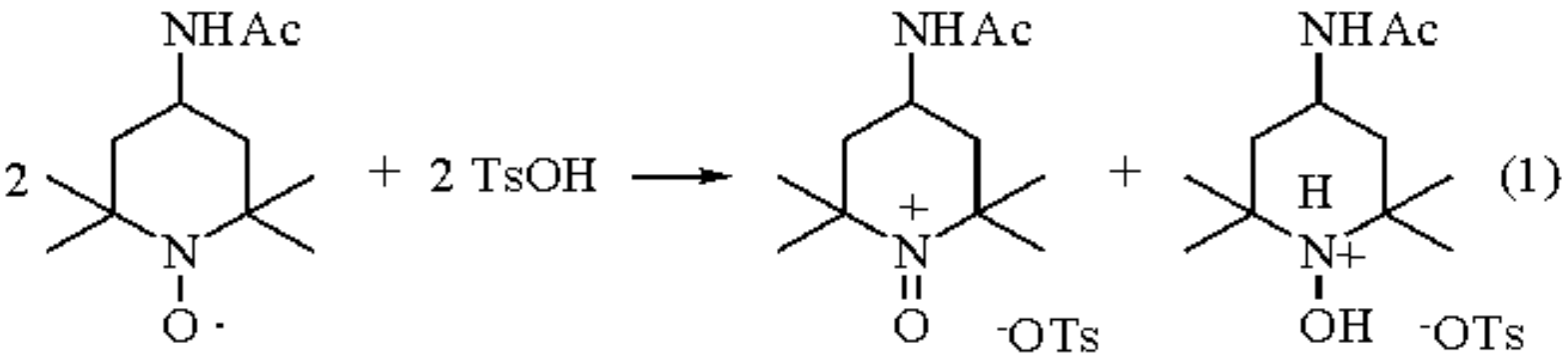

(3) **(4)** **(5)**

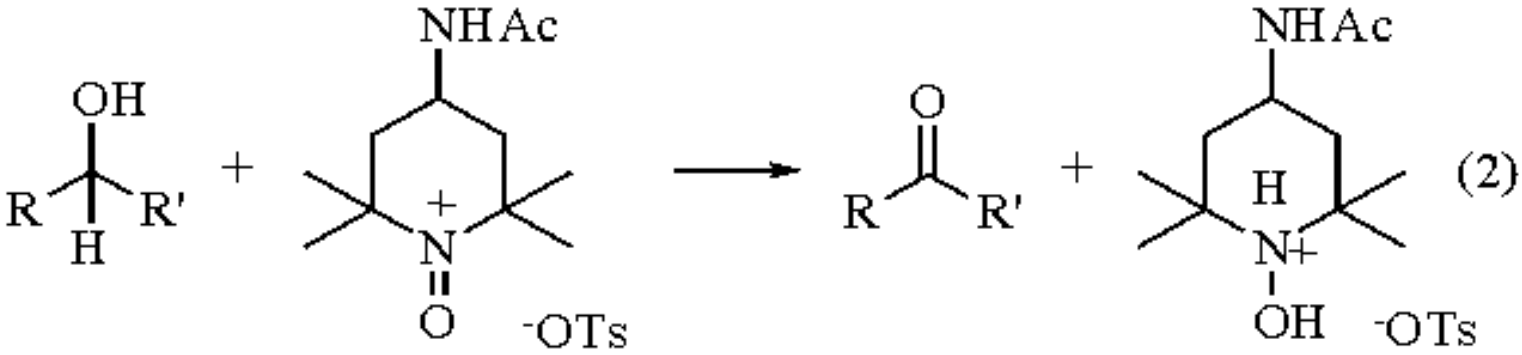

(6) **(4)** **(7)** **(5)**

The reaction has been used for the oxidation of a variety of alcohols with excellent yields of isolated products.[2] Primary alcohols are converted to the corresponding aldehydes, and no over-oxidation is observed. Secondary alcohols react as well as primary alcohols and provide the corresponding ketones. The mildness of this reaction has been demonstrated by the oxidations of nerol (**8**) and geraniol (**9**) to the corresponding *cis*-citral (**10**) and *trans*-citral (**11**).

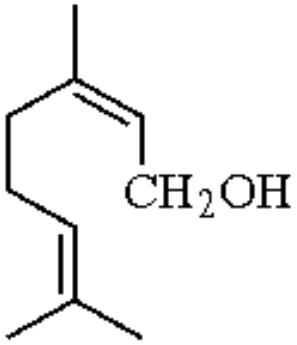

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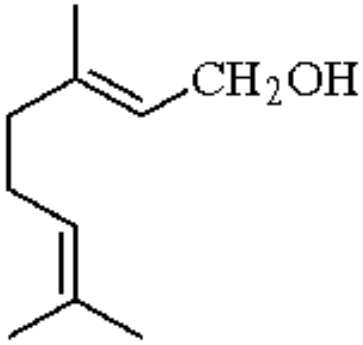

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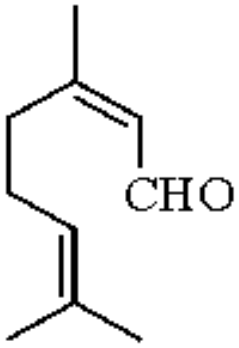

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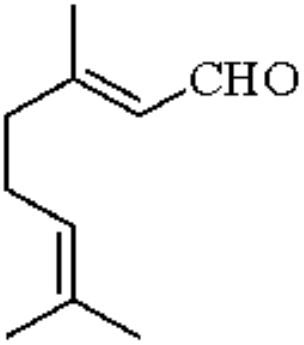

(11)

Oxidation with this reagent does not take place when there is an oxygen or nitrogen in the β-position to the alcohol being oxidized and does not take place with 1,2-diols or sugars. Amines,[1,4] thiols,[5] phenols,[6] indoles,[7] benzyl ethers,[1] and ketones (very slow)[1] react with oxoammonium salts and may interfere with alcohol oxidation. However, sulfides, most ethers, amides, esters, and double bonds do not react with oxoammonium salts and should not interfere.[1]

A number of other oxoammonium salts have been described in the literature.[1] In addition, TEMPO-type nitroxide radicals have been used as specific catalysts for the oxidation of alcohols using one or several secondary, stoichiometric oxidants.[1,8] Neither 4-acetamido-TEMPO nor any of its derivatives have been used in this manner, but they should function satisfactorily.

---

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Acetic Acid[1]

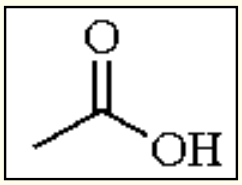

[64-19-7] · $C_2H_4O_2$ · Acetic Acid · (MW 60.05)

(common organic reaction solvent; reagent for protonolysis of organometallic compounds,[5,6] synthesis of aromatic methyl ketones,[10] lactones,[15] heterocycles[13])

Alternate Name: ethanoic acid.

Physical Data: weak organic acid, pK_a 4.77; *d*204 1.049 g cm^{-3}; mp 14.7 °C; bp 118 °C (30 °C/31 mmHg). Forms azeotropes with many common solvents, such as benzene, pyridine, DMF, and dioxane.

Solubility: miscible with water, ethanol, acetone, benzene, ether, and carbon tetrachloride; insol CS_2.

Form Supplied in: widely available as glacial acetic acid, >98% purity.

Analysis of Reagent Purity: analyzed by titration with base.[2,18] High purity grades of acetic acid (>99%) are determined by the freeze-point method. Formic acid content can be determined by a redox titration based on oxidation with lead tetraacetate. Methods for analysis of trace impurities such as water, iron, or chlorine are known.

Purification: among many methods, distillation over traces of oxidants in the presence of Ac_2O is effective.[19]

Handling, Storage, and Precautions: acetic acid is flammable with a flash point of 40 °C.[3] This hazard is often overlooked by the practicing chemist and has been the source of laboratory accidents. Acetic acid is a corrosive material. Basic safety equipment including eye protection, gloves, and a chemical apron should be worn during all operations with acetic acid. Vapors will cause intense irritation to mouth, nose, eyes, skin, and upper respiratory tract. Use of an appropriate NIOSH/MSHA respirator is recommended. Use in a fume hood.

Acetic Acid as Reaction Solvent.

The most common use of acetic acid in organic synthesis is as a reaction solvent. Many types of organic compounds

are highly soluble in this reagent, and the stability of acetic acid towards many reagents is good. Examples of reactions often performed in acetic acid include bromination, hydrolysis, solvolysis, reductions, and hydrogenations. A discussion of acetic acid as a reaction solvent with a given reagent will be found in the detailed treatments of individual reagents.

Protonolysis of Organometallic Compounds.

Alkylboranes are readily cleaved by protonolysis with acetic acid.[4] In contrast, organoboranes are stable to water, mineral acids, and aqueous base. This reaction provides a convenient alternative to catalytic hydrogenation in cases where catalyst poisoning or selectivity would be problematic (eq 1).[4] The hydroboration of alkynes followed by protonolysis with acetic acid is a selective sequence producing *cis*-alkenes (eq 2).[5]

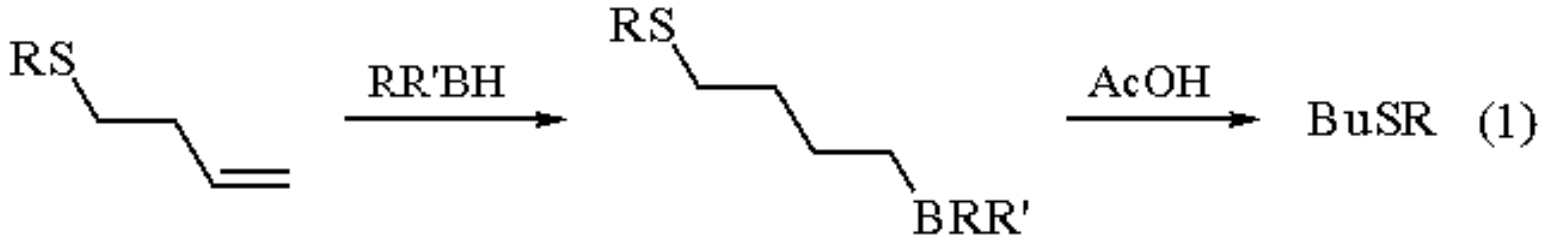

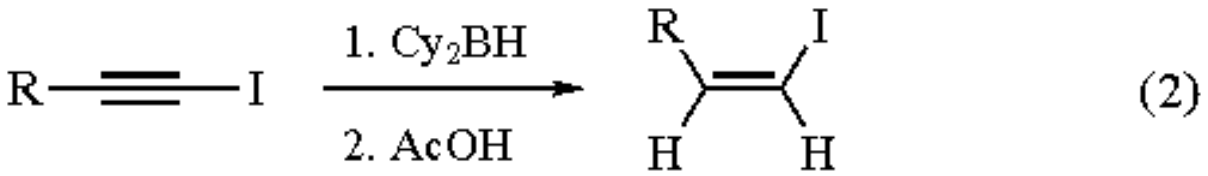

Tetraorganoborates containing alkenyl or alkynyl groups react with acetic acid in a completely different manner, leading to the formation of new carbon-carbon bonds. The reader is referred to relevant articles dealing with organoborates for discussions of this reaction.

Acetic acid has been used to cleave organosilicon intermediates produced during the Peterson reaction (eq 3).[6] The acid-catalyzed elimination is *anti*; this complements the base-catalyzed elimination, which is *syn* (eq 4).

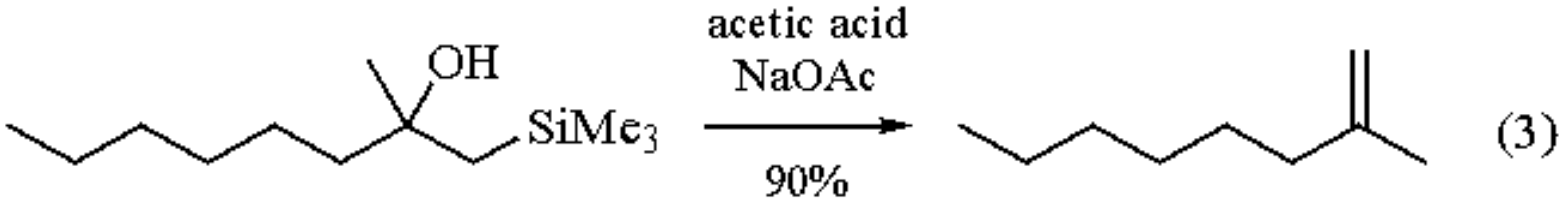

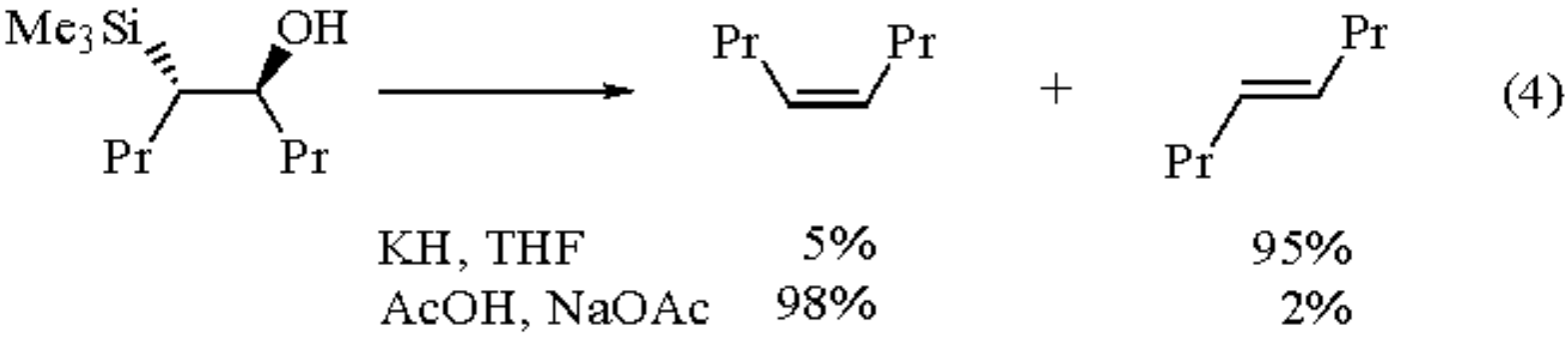

Acetic acid promotes the stereospecific conversion of trimethylsilyl epoxides to enol acetates (eq 5).[7] In all cases studied, addition of the acetate nucleophile is α to the silyl group. The stereochemistry of the overall reaction is consistent with nucleophilic addition and inversion, followed by *anti* β-elimination.

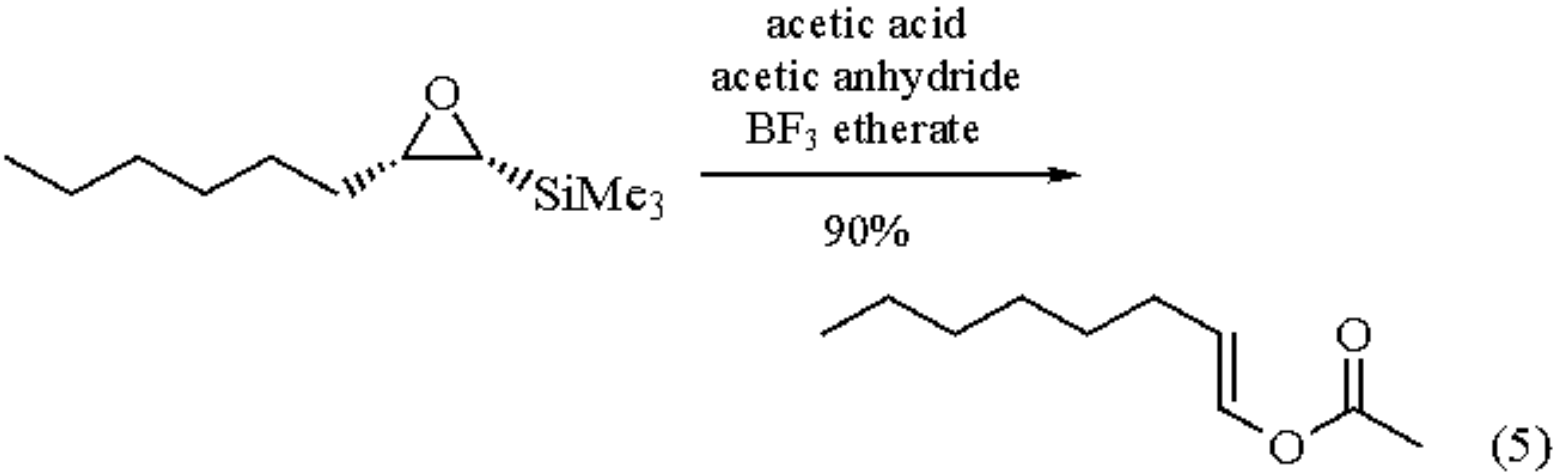

Cleavage of a trimethylsilylmethylcyclopropane by an acetic acid-***Boron Trifluoride*** trifluoride complex results in formation of a terminal alkene (eq 6).[8]

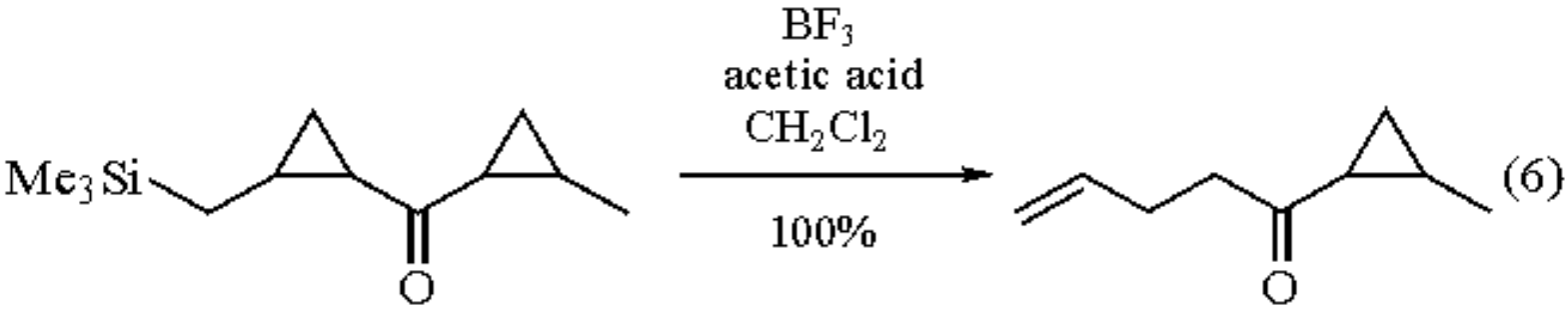

Selective cleavage of a 1,2-disilylalkene allows synthesis of the 2-trimethylsilyl-1-alkene, which is not accessible through direct hydrosilation (eq 7).[9]

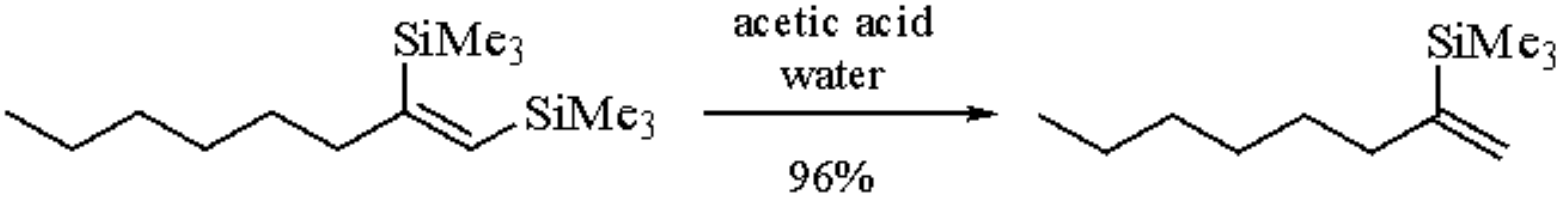

(7)

Acetylation of Aromatic Compounds.

Acetic acid will acetylate electron-rich aromatic compounds such as phenols or anisoles. Best results are achieved with ***Boron Trifluoride***[10] (eq 8) or ***Trifluoroacetic Anhydride***[11] (eq 9) as an acid catalyst, although other acids such as ***Zinc Chloride***[12] have been used.

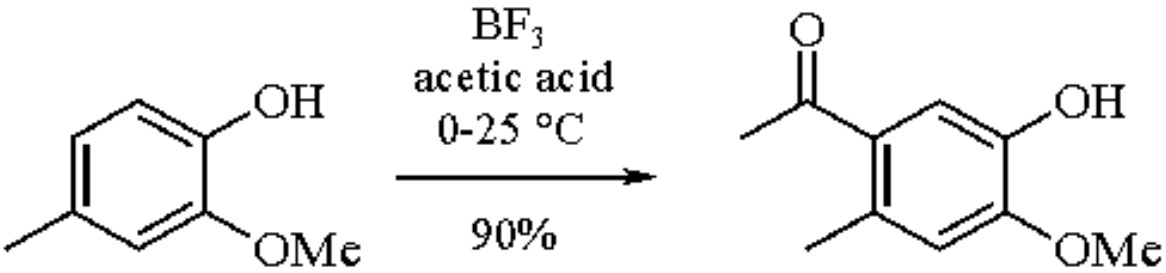

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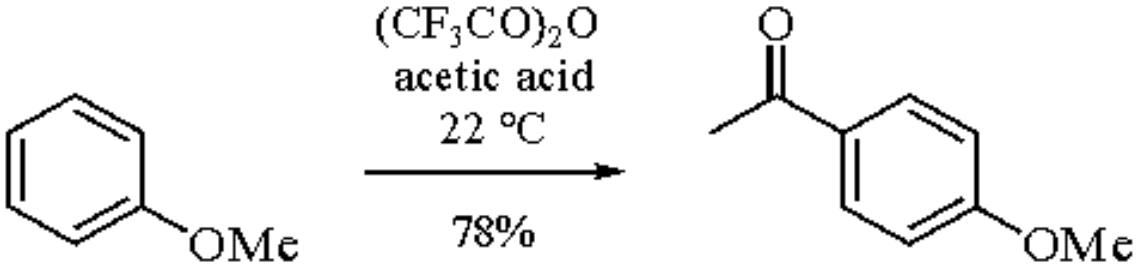

(9)

Synthesis of Heterocycles.

Amino alcohols are cyclized to methyloxazolines by condensation with acetic acid (eq 10).[13]

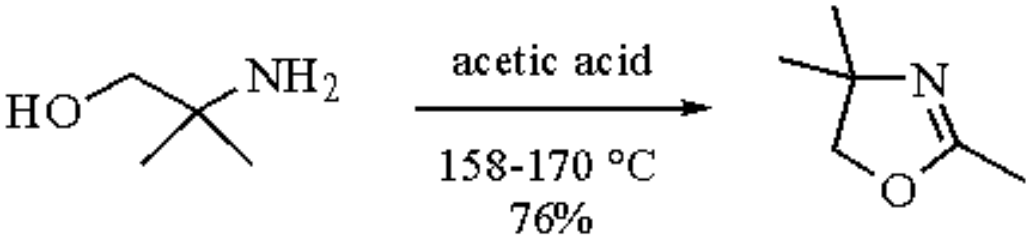

(10)

A variety of other heterocyclic systems have been formed by dehydration or rearrangement in acetic acid (eqs 11 and 12).[14]

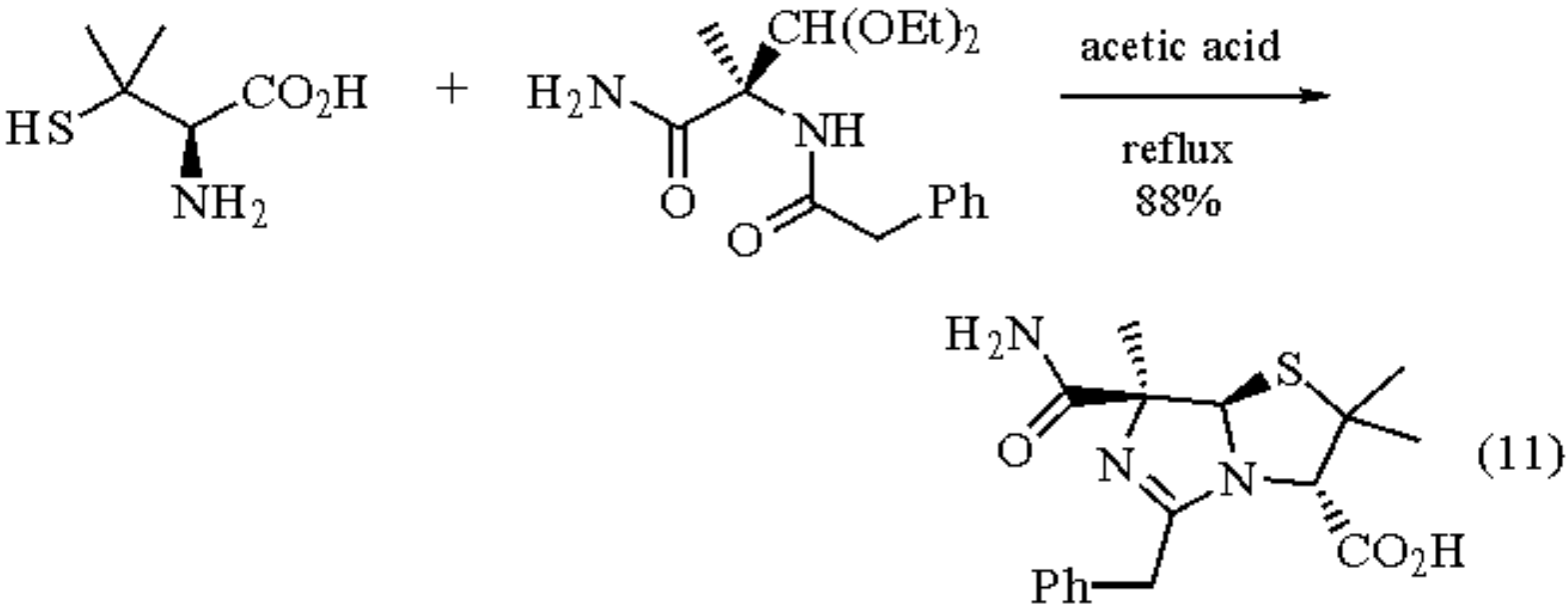

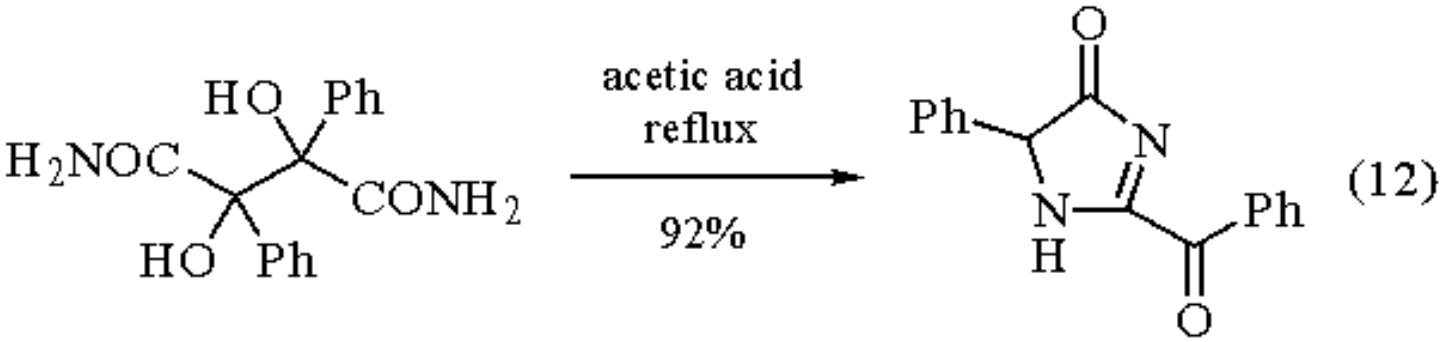

Formation of Lactones.

Treatment of alkenes with ***Manganese(III) Acetate*** in acetic acid leads to formation of lactones.[15] The reaction is general for all alkenes and carboxylic acids, but best yields are obtained with terminal alkenes and acetic acid. Only the lactone of the γ-hydroxy acid is produced. The most convenient laboratory procedure[15a] uses manganese(II) acetate and ***Potassium Permanganate*** to form manganese(III) acetate in situ (eq 13). The mechanism of the reaction involves addition of a carboxymethyl radical to the alkene; the carboxymethyl radicals are generated by thermolysis of the manganese(III) acetate.

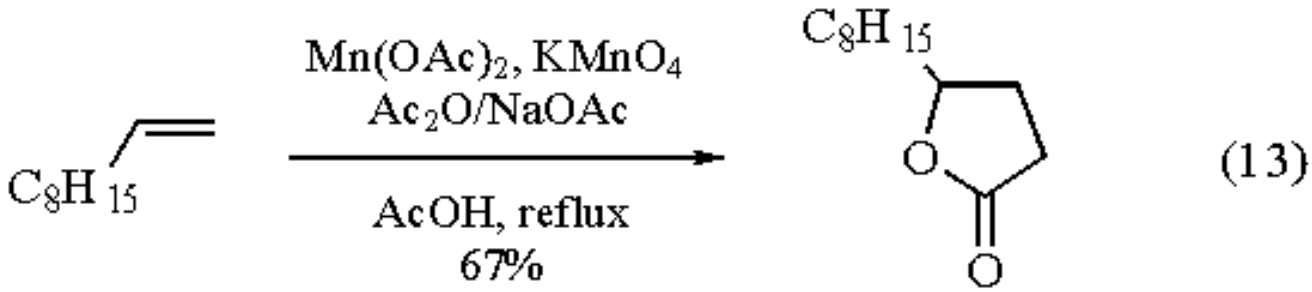

Other carboxylic acids can be used in place of acetic acid. Of these, ***Cyanoacetic Acid*** is particularly reactive due to the high stability of the α-cyano radical intermediate (eq 14).[15a,16] Lactones are efficiently formed by the intramolecular reaction of unsaturated acids (eq 15).[17]

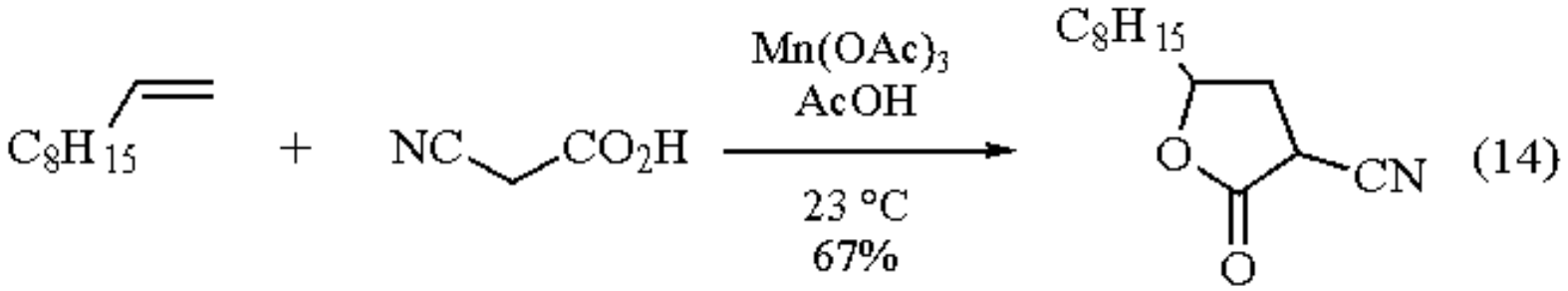

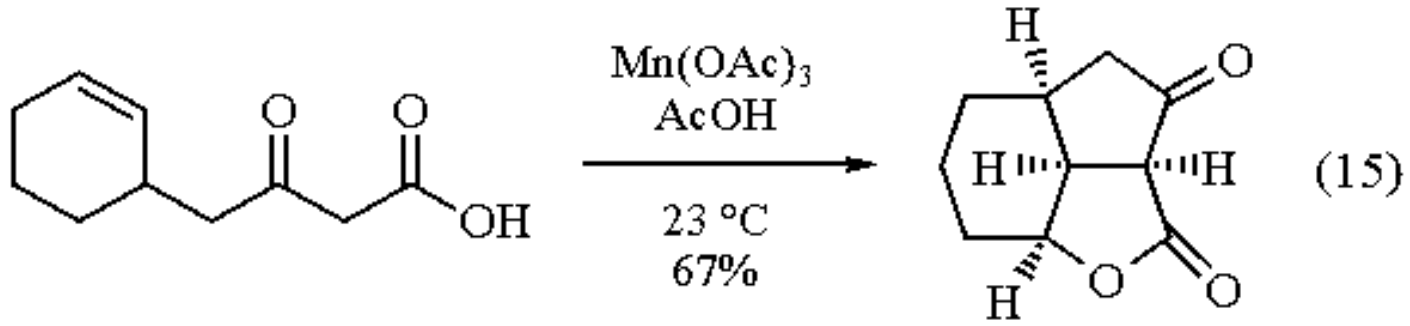

Related Reagents.

Acetic Anhydride; ***Formic Acid***; ***Glyoxylic Acid***; ***Oxalic Acid***; ***Propionic Acid***; ***Trifluoroacetic Acid***.

---

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Kirk F. Eidman

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Acetic Anhydride[1]

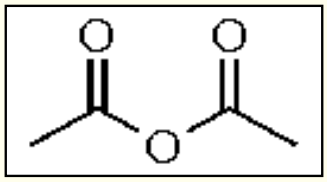

[108-24-7] · $C_4H_6O_3$ · Acetic Anhydride · (MW 102.09)

(useful for the acetylation of alcohols,[2] amines,[3] and thiols,[4] oxidation of alcohols,[5] dehydration,[6] Pummerer[7] reaction, Perkin[8] reaction, Polonovski[9] reaction, *N*-oxide reaction,[10] Thiele[11] reaction, ether cleavage,[12] enol acetate formation,[13] *gem*-diacetate formation[14])

Physical Data: bp 138-140 °C; mp -73 °C; *d* 1.082 g cm^{-3}.

Solubility: sol most organic solvents. Reacts with water rapidly and alcohol solvents slowly.

Form Supplied in: commercially available in 98% and 99+% purities. Acetic anhydride-d_6 is also commercially available.

Analysis of Reagent Purity: IR, NMR.[15]

Preparative Methods: acetic anhydride is prepared industrially by the acylation of ***Acetic Acid*** with ***Ketene***.[1b] A laboratory preparation of acetic anhydride involves the reaction of sodium acetate and ***Acetyl Chloride*** followed by fractional distillation.[16]

Purification: adequate purification is readily achieved by fractional distillation. Acetic acid, if present, can be removed by refluxing with CaC_2 or with coarse magnesium filings at 80-90 °C for 5 days. Drying and acid removal can be achieved by azeotropic distillation with toluene.[17]

Handling, Storage, and Precautions: acetic anhydride is corrosive and a lachrymator and should be handled in a fume hood.

Acetylation.

The most notable use of acetic anhydride is for the acetylation reaction of alcohols,[2] amines,[3] and thiols.[4] Acids, Lewis acids, and bases have been reported to catalyze the reactions.

Alcohols.

The most common method for acetate introduction is the reaction of an alcohol with acetic anhydride in the presence of pyridine.[2] Often, ***Pyridine*** is used as the solvent and reactions proceed nearly quantitatively (eq 1).

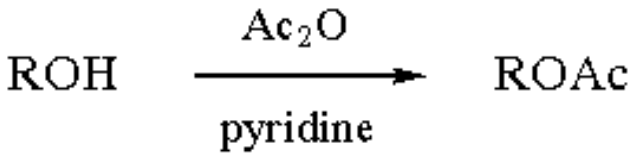

(1)

If the reaction is run at temperatures lower than 20 °C, primary alcohols can be acetylated over secondary alcohols selectively.[18] Under these conditions, tertiary alcohols are not acylated. Most alcohols, including tertiary alcohols, can be acylated by the addition of DMAP (***4-Dimethylaminopyridine***) and ***Acetyl Chloride*** to the reaction containing acetic anhydride and pyridine. In general, the addition of DMAP increases the rate of acylation by 10^4 (eq 2).[19]

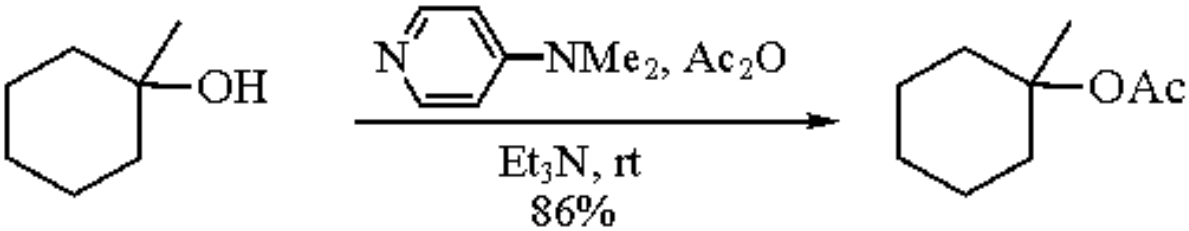

(2)

Recently, Vedejs found that a mixture of ***Tri-n-butylphosphine*** and acetic anhydride acylates alcohols faster than acetic anhydride with DMAP.[20] However, the combination of acetic anhydride with DMAP and ***Triethylamine*** proved superior. It is believed that the Et_3N prevents HOAc from destroying the DMAP catalyst.

Tertiary alcohols have been esterified in good yield using acetic anhydride with calcium hydride or calcium carbide.[21] *t*-Butanol can be esterified to *t*-butyl acetate in 80% yield under these conditions. High pressure (15 kbar) has been used to introduce the acetate group using acetic anhydride in methylene chloride.[22] Yields range from 79-98%. Chemoselectivity is achieved using acetic anhydride and ***Boron Trifluoride Etherate*** in THF at 0 °C. Under these conditions, primary or secondary alcohols are acetylated in the presence of phenols.[23]

α-D-Glucose is peracetylated readily using acetic anhydride in the presence of ***Zinc Chloride*** to give α-D-glucopyranose pentaacetate in 63-72% yield (eq 3).[24]

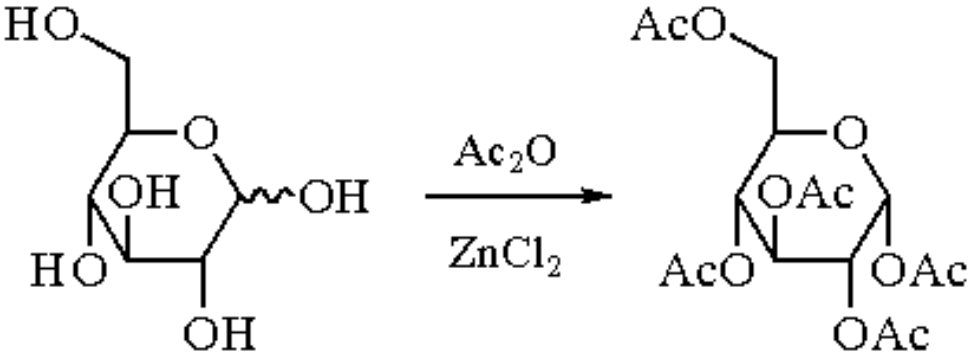

(3)

Under basic conditions, α-D-glucose can be converted into β-D-glucopyranose pentaacetate in 56% yield (eq 4).

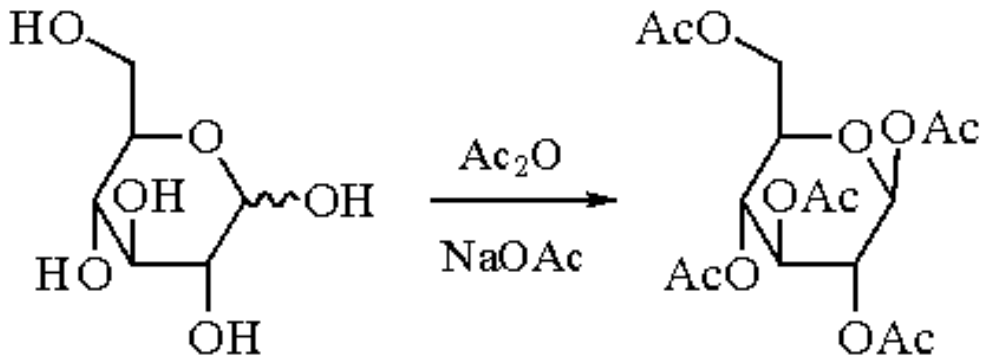

(4)

In the food and drug industry, high-purity acetic anhydride is used in the manufacture of aspirin by the acetylation of salicylic acid (eq 5).[25]

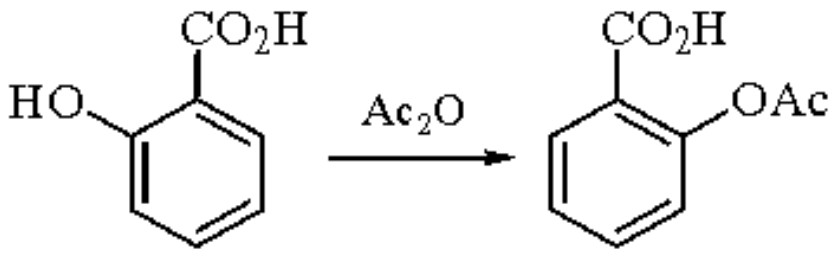

(5)

Amines.

The acetylation of amines has been known since 1853 when Gerhardt reported the acetylation of aniline.[3] Acetamides are typically prepared by the reaction of the amine with acetic anhydride (eq 6).

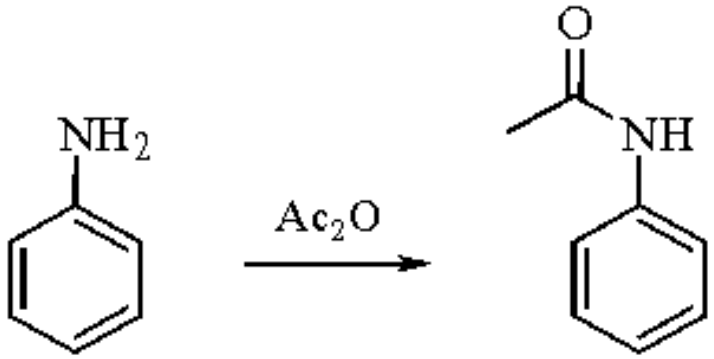

(6)

A unique method for selective acylation of secondary amines in the presence of primary amines involves the use of ***18-Crown-6*** with acetic anhydride and triethylamine.[26] It is believed that the 18-crown-6 complexes primary alkylammonium salts more tightly than the secondary salts, allowing selective acetylation.

In some cases, tertiary amines undergo a displacement reaction with acetic anhydride. A simple example involves the reaction of benzyldimethylamine with acetic anhydride to give dimethylacetamide and benzylacetate (eq 7).[27]

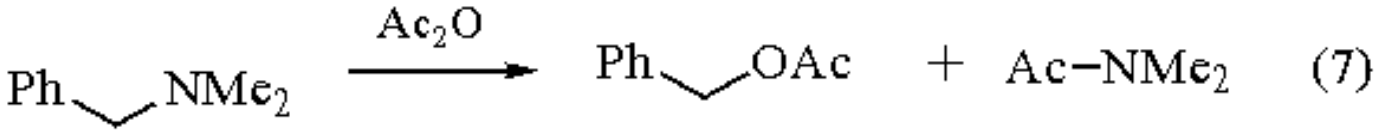

Allylic tertiary amines can be displaced by the reaction of acetic anhydride and sodium acetate.[28] The allylic acetate is the major product, as shown in eq 8.

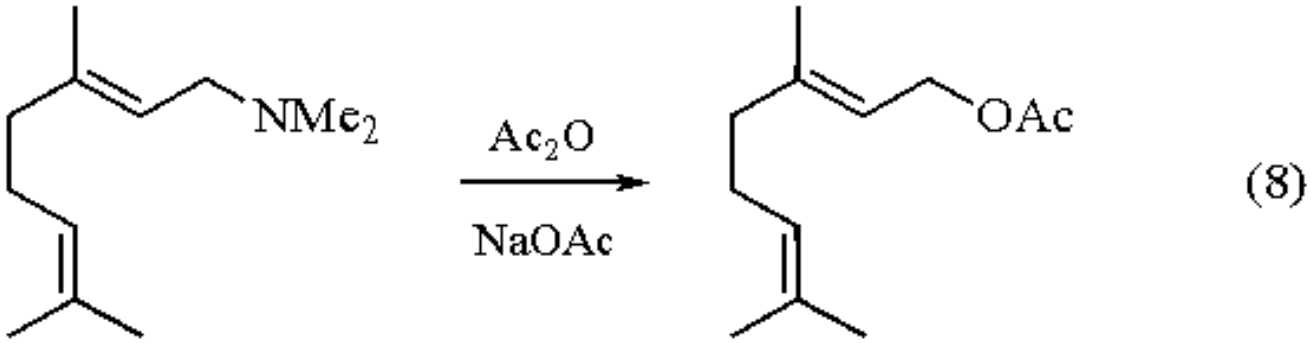

Cyclic benzylic amines may undergo ring opening upon heating with acetic anhydride (eq 9).[29]

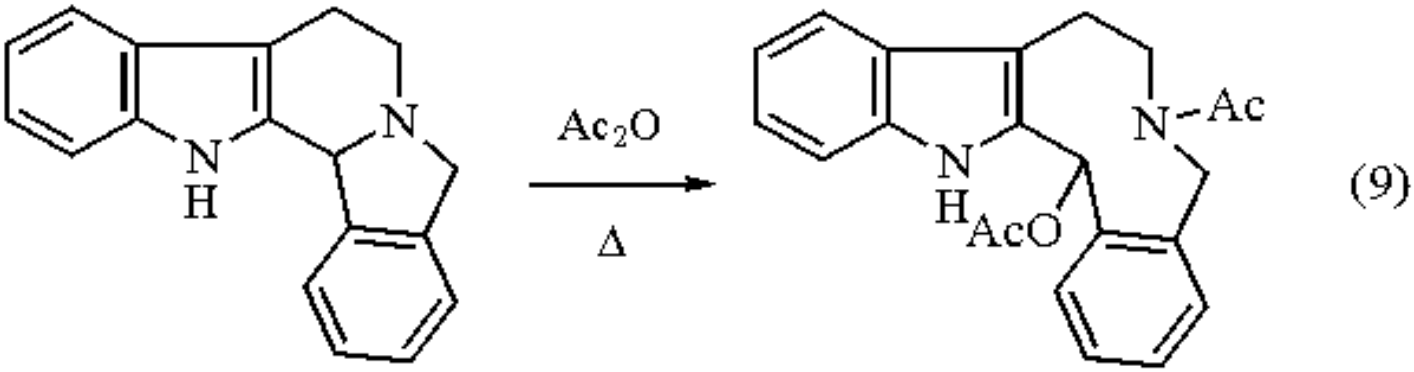

α-Amino acids react with acetic anhydride in the presence of a base to give 2-acetamido ketones.[30] This reaction is known as the Dakin-West reaction (eq 10) and is believed to go through a oxazolone mechanism. The amine base of choice is 4-dimethylaminopyridine. Under these conditions, the reaction can be carried out at room temperature in 30 min.

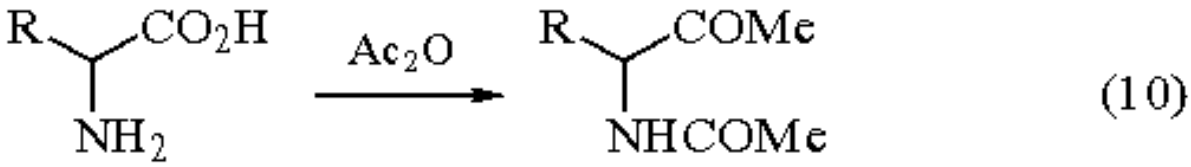

Cyclic β-amino acids rearrange to α-methylene lactams upon treatment with acetic anhydride, as shown in eq 11.[31]

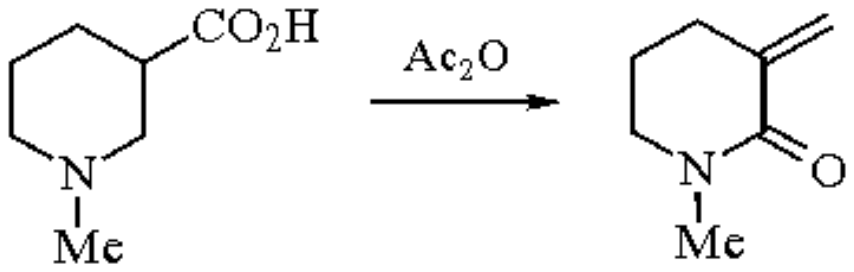

(11)

Thiols.

S-Acetyl derivatives can be prepared by the reaction of acetic anhydride and a thiol in the presence of potassium bicarbonate.[4] Several disadvantages to the *S*-acetyl group in peptide synthesis include β-elimination upon base-catalyzed hydrolysis. Also, sulfur to nitrogen acyl migration may be problematic.

Oxidation.

The oxidation of primary and secondary alcohols to the corresponding carbonyl compounds can be achieved using ***Dimethyl Sulfoxide-Acetic Anhydride***.[5] The reaction proceeds through an acyloxysulfonium salt as the oxidizing agent (eq 12).

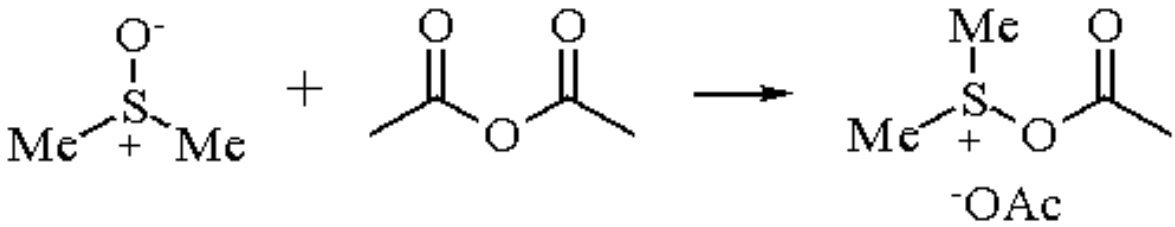

(12)

The oxidations often proceed at room temperature, although long reaction times (18-24 h) are sometimes required. A side product is formation of the thiomethyl ethers obtained from the Pummerer rearrangement.

If the alcohol is unhindered, a mixture of enol acetate (from ketone) and acetate results (eq 13).[32]

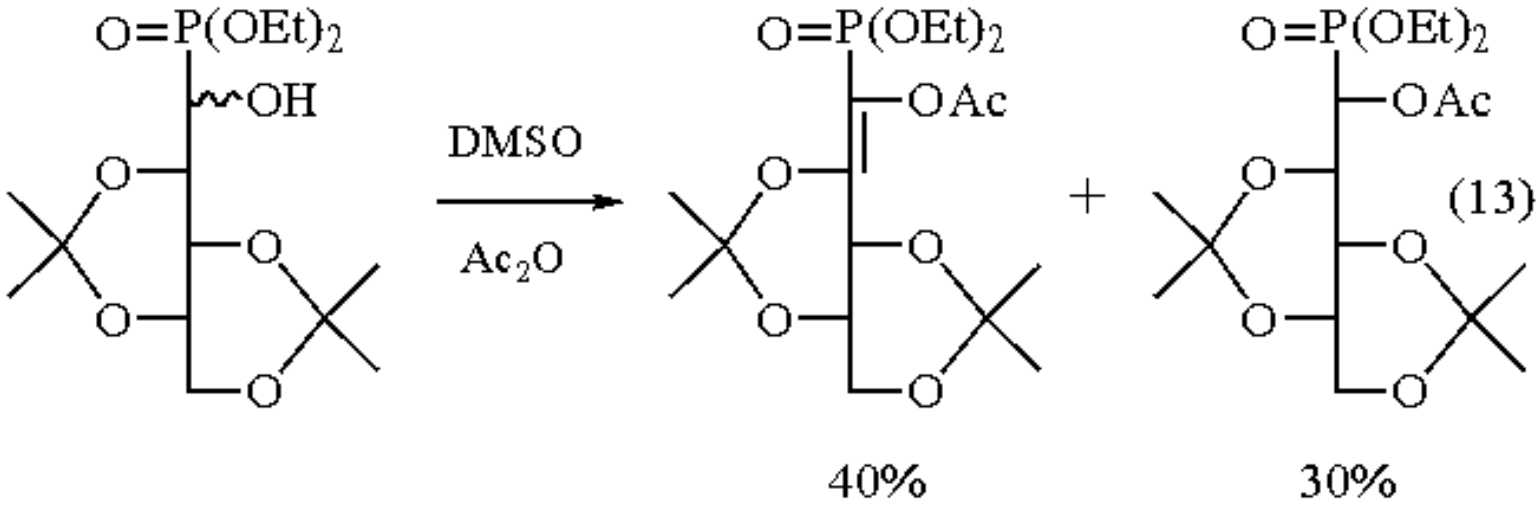

(13)

The oxidation of carbohydrates can be achieved by this method, as Hanessian showed (eq 14).[33]

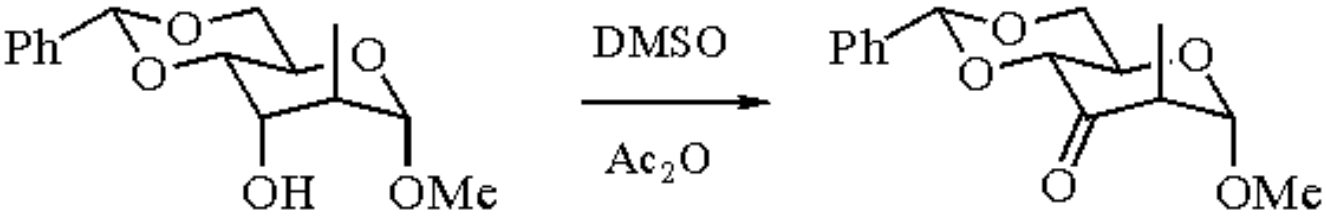

(14)

Aromatic α-diketones can be prepared from the acyloin compounds; however, aliphatic diketones cannot be prepared by this method.[34] The reaction proceeds well in complex systems without epimerization of adjacent stereocenters, as in the yohimbine example (eq 15).[35] This method compares favorably with that of ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***.

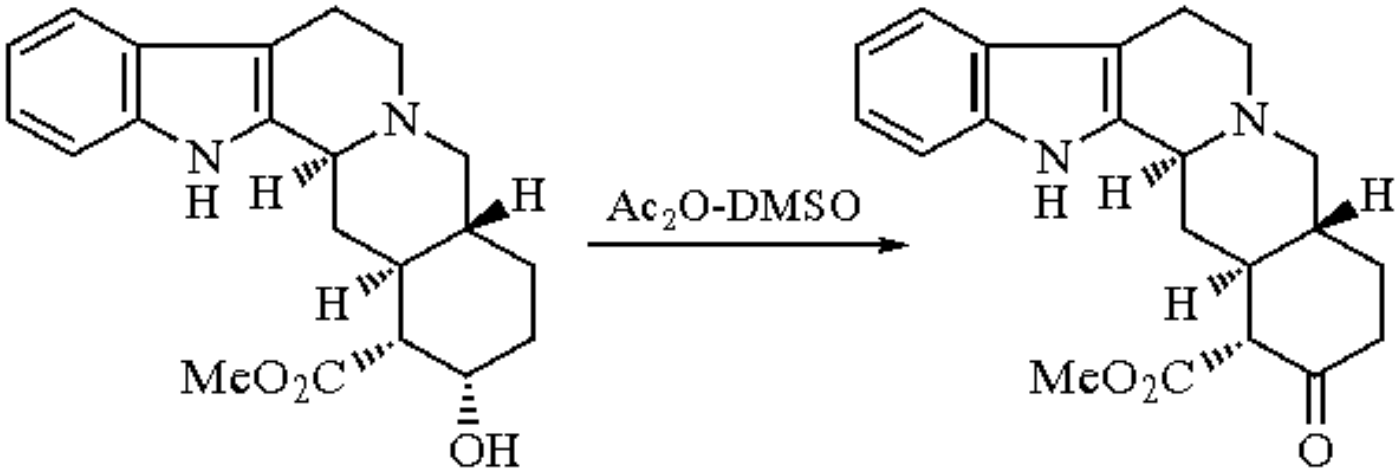

(15)

Dehydration.

Many functionalities are readily dehydrated upon reaction with acetic anhydride, the most notable of which is the oxime.[6] Also, dibasic acids give cyclic anhydrides or ketones, depending on ring size.[36]

An aldoxime is readily converted to the nitrile as shown in eq 16.[37]

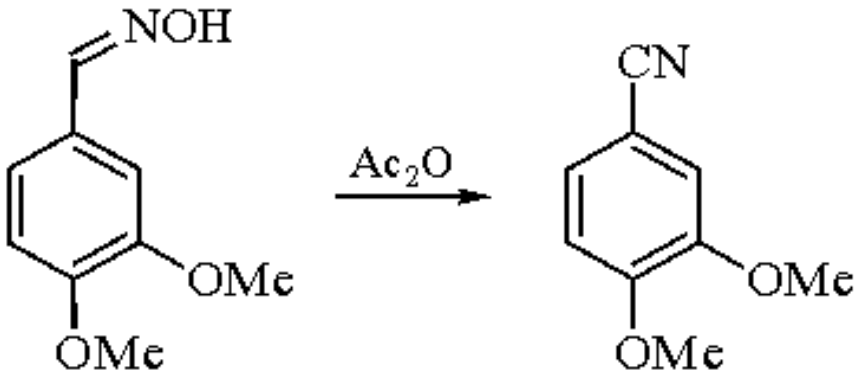

(16)

When oximes of α-tetralones are heated in acetic anhydride in the presence of anhydrous ***Phosphoric Acid***,

aromatization occurs as shown in eq 17.[38]

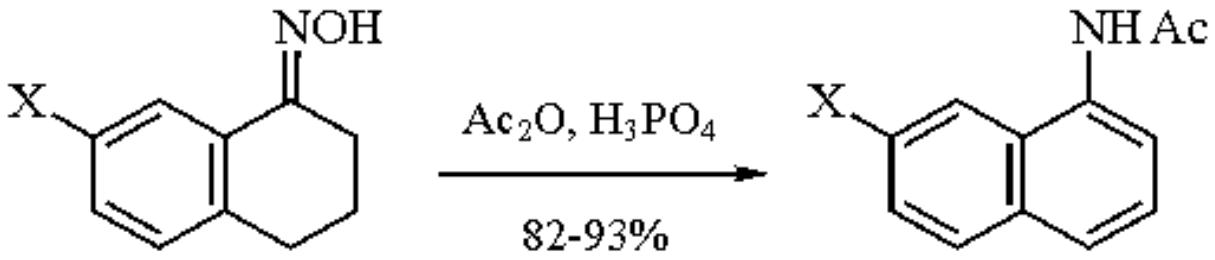

(17)

Oximes of aliphatic ketones lead to enamides upon treatment with acetic anhydride-pyridine, as shown in the steroid example in eq 18.[39]

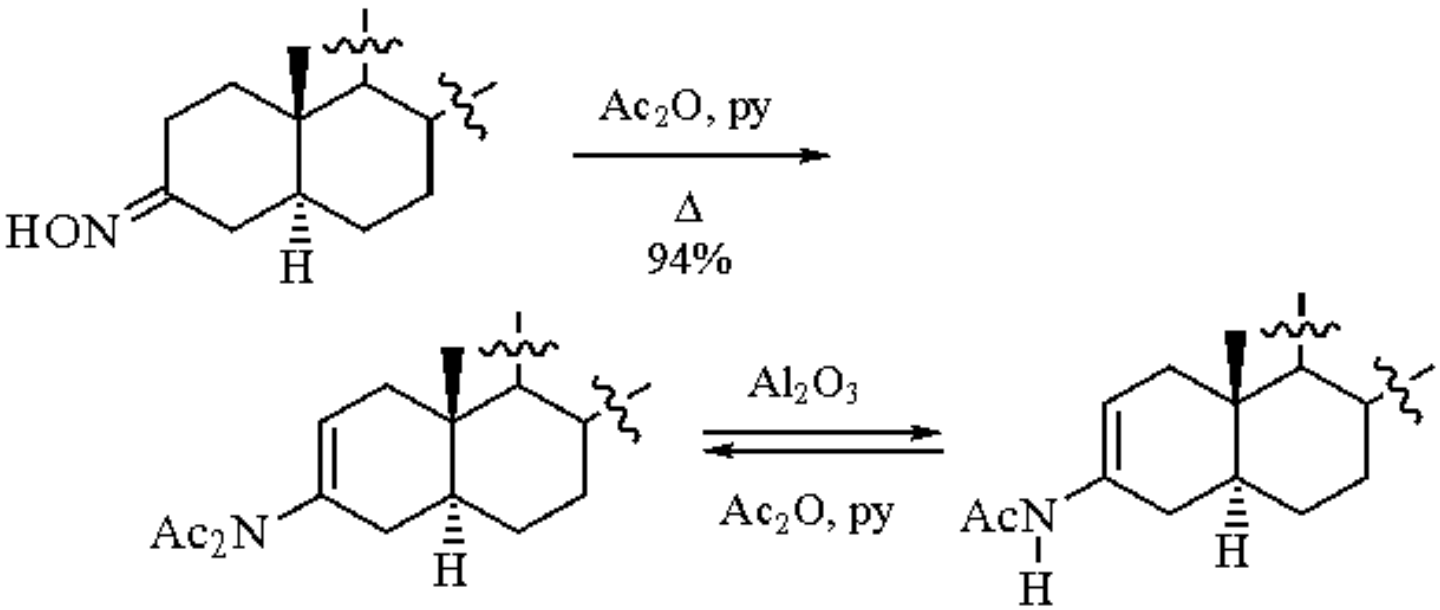

(18)

Upon heating with acetic anhydride, dibasic carboxylic acids lead to cyclic anhydrides of ring size 6 or smaller. Diacids longer than glutaric acid lead to cyclic ketones (eq 19).[36]

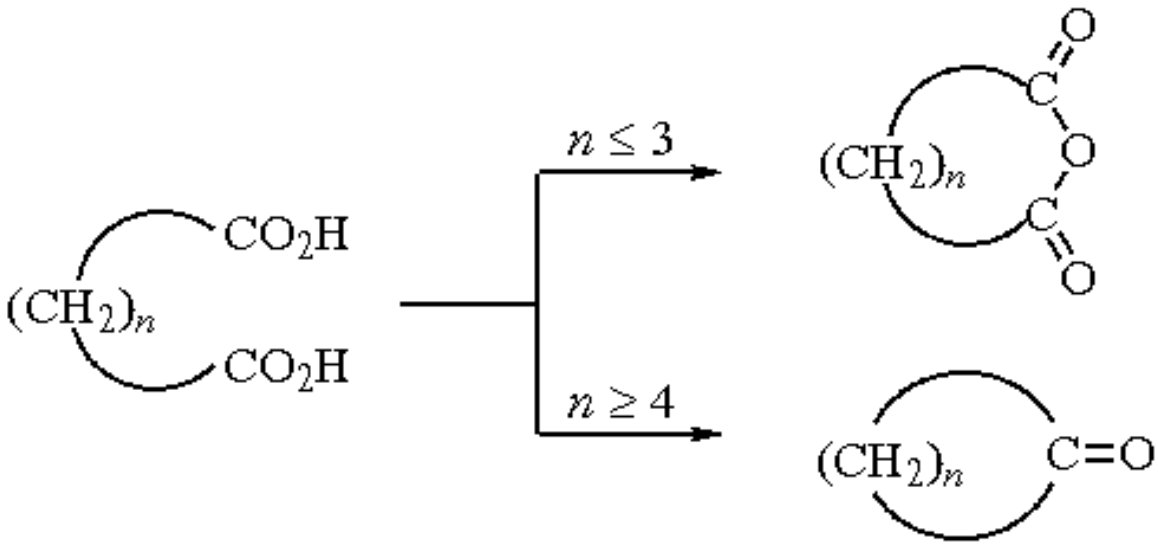

(19)

N-Acylanthranilic acids also cyclize when heated with acetic anhydride (eq 20). The reaction proceeds in 81% yield with slow distillation of the acetic acid formed.[40]

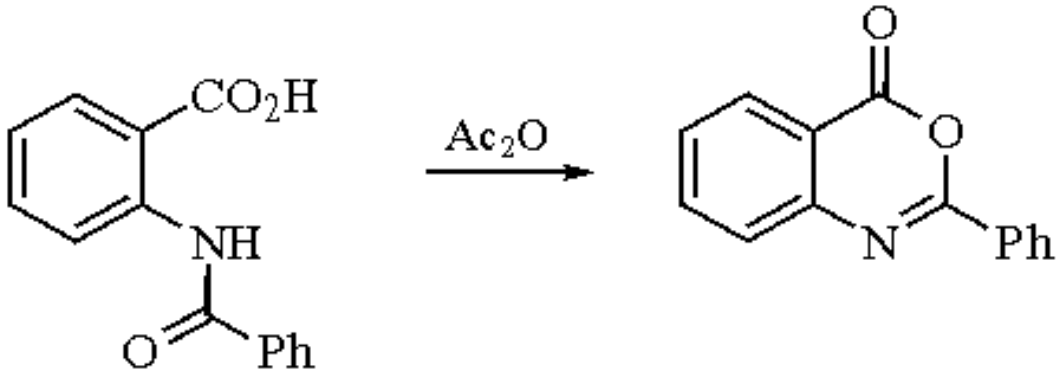

(20)

Pummerer Reaction.

In 1910, Pummerer[7] reported that sulfoxides react with acetic anhydride to give 2-acetoxy sulfides (eq 21). The sulfoxide must have one α-hydrogen. Alternative reaction conditions include using ***Trifluoroacetic Anhydride*** and acetic anhydride.

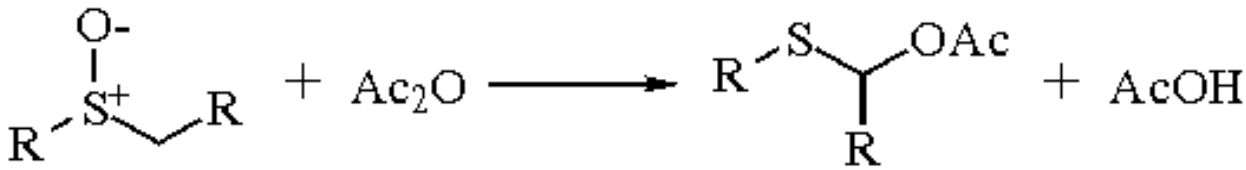

(21)

β-Hydroxy sulfoxides undergo the Pummerer reaction upon addition of sodium acetate and acetic anhydride to give α,β-diacetoxy sulfides. These compounds are easily converted to α-hydroxy aldehydes (eq 22).[41]

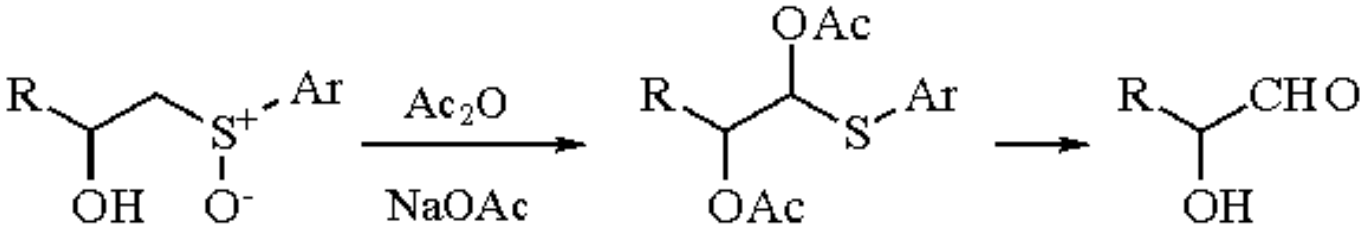

(22)

2-Phenylsulfonyl ketones rearrange in the presence of acetic anhydride-sodium acetate in toluene at reflux to give *S*-aryl thioesters (eq 23).[42] Upon hydrolysis, an α-hydroxy acid is obtained.

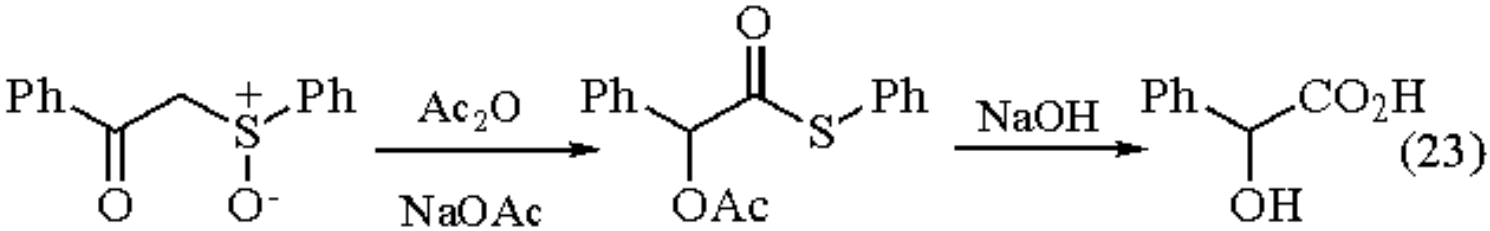

(23)

In the absence of sodium acetate, 2-phenylsulfonyl ketones give the typical Pummerer product. Since β-keto sulfoxides

are available by the reaction of esters with the dimsyl anion, this overall process leads to one-carbon homologated α-hydroxy acids from esters (eq 24).[42]

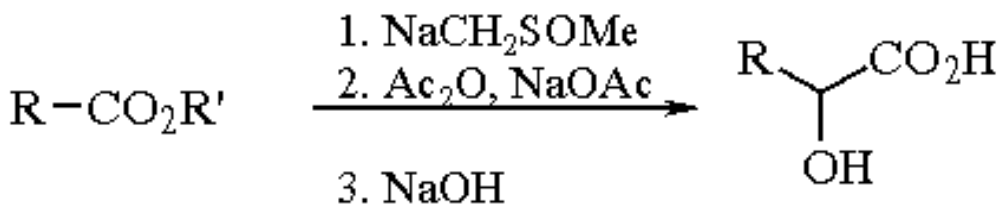

(24)

Also, 2-phenylsulfonyl ketones can be converted to α-phenylthio-α,β-unsaturated ketones via the Pummerer reaction using acetic anhydride and a catalytic amount of ***Methanesulfonic Acid*** (eq 25).[43]

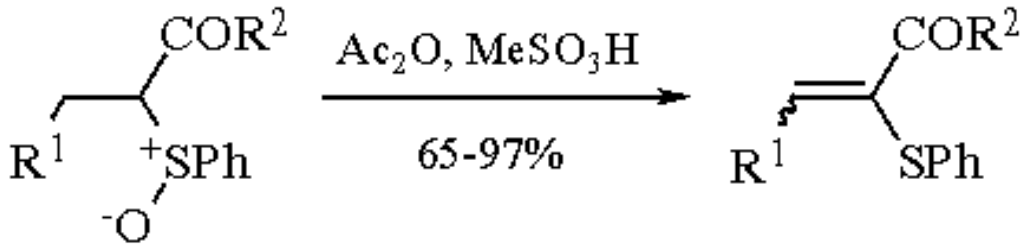

(25)

The Pummerer reaction has been used many times in heterocyclic synthesis as shown in eq 26.

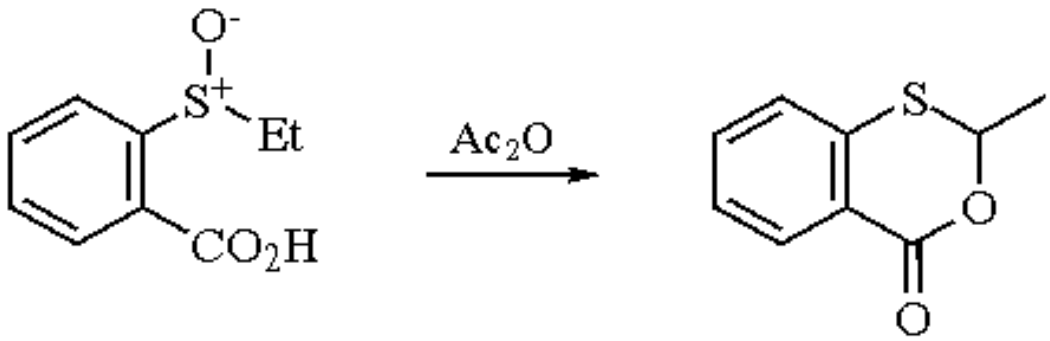

(26)

The Pummerer rearrangement of 4-phenylsulfinylbutyric acid with acetic anhydride in the presence of ***p-Toluenesulfonic Acid*** leads to butanolide formation (eq 27).[44] Oxidation with ***m-Chloroperbenzoic Acid*** followed by thermolysis then leads to an unsaturated compound.

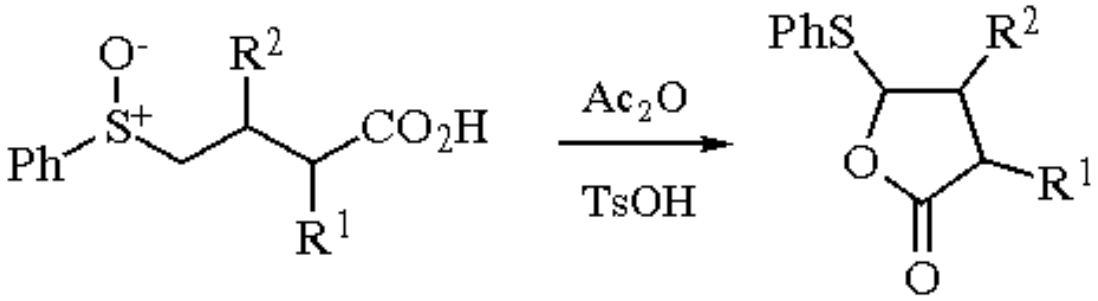

(27)

An unusual Pummerer reaction takes place with penicillin sulfoxide, leading to a ring expansion product as shown in eq 28.[45]

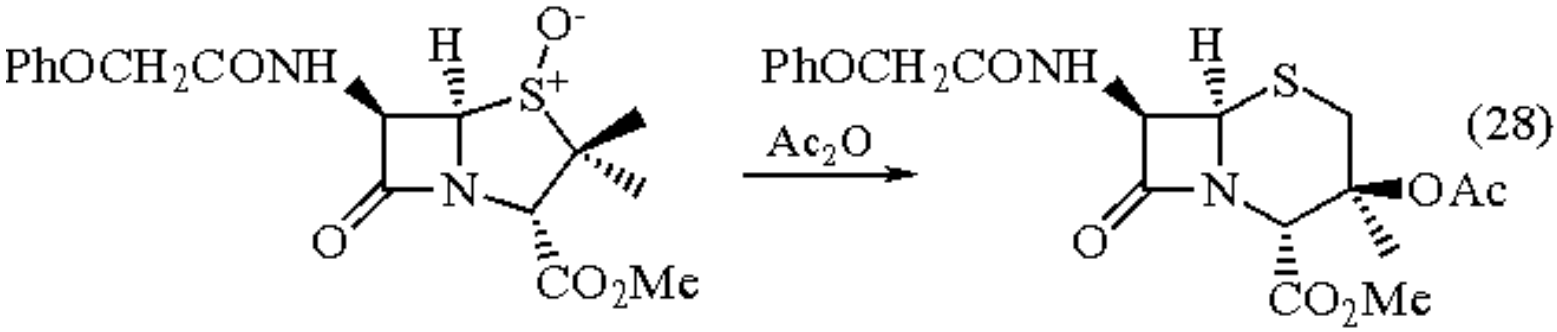

(28)

This led to discovery of the conversion of penicillin V and G to cephalexin,[46] a broad spectrum orally active antibiotic (eq 29).

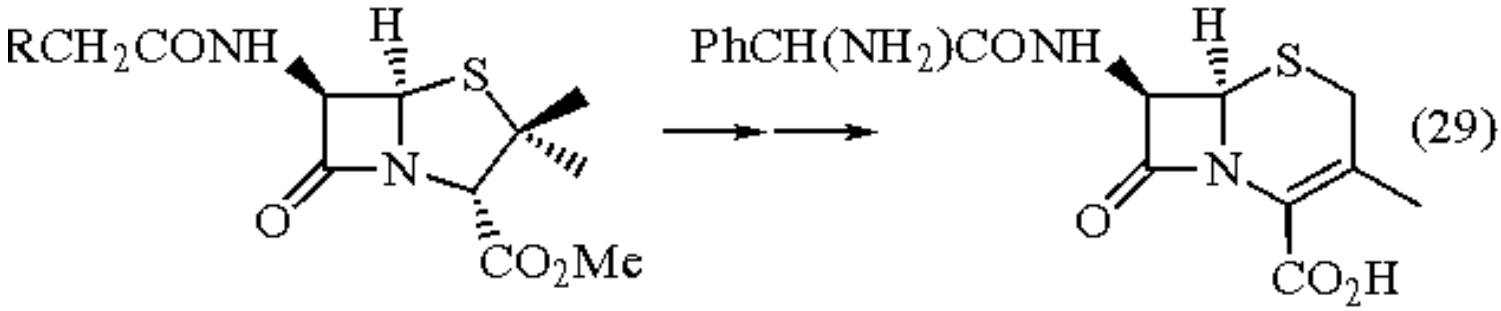

(29)

A Pummerer-type reaction was carried out on a dithiane protecting group to liberate the corresponding ketone (eq 30).[47] These were the only reaction conditions which provided any of the desired ketone.

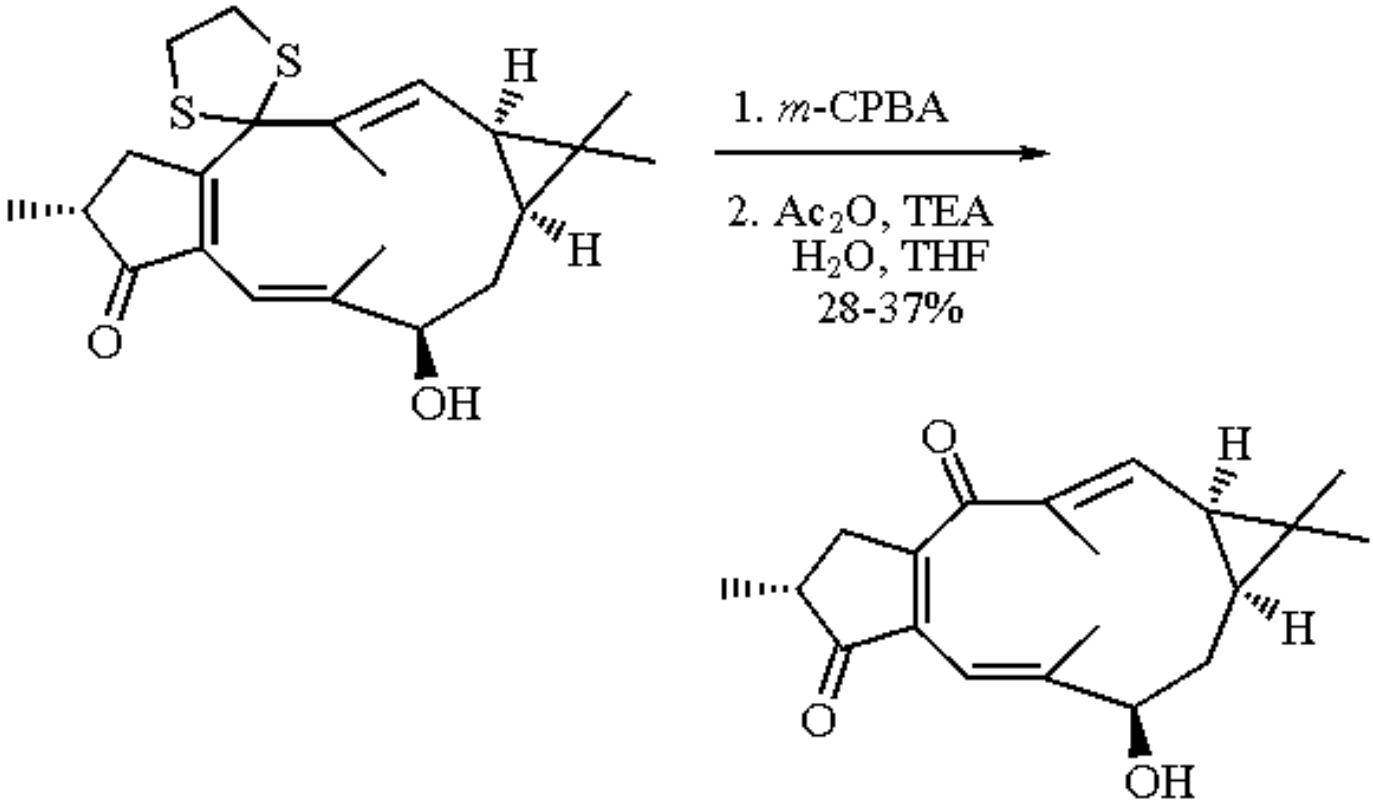

(30)

Perkin Reaction.

The Perkin reaction,[8] developed by Perkin in 1868, involves the condensation of an anhydride and an aldehyde in the presence of a weak base to give an unsaturated acid (eq 31).

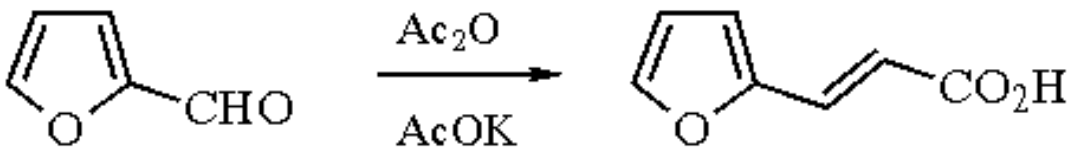

(31)

The reaction is often used for the preparation of cinnamic acids in 74-77% yield (eq 32).

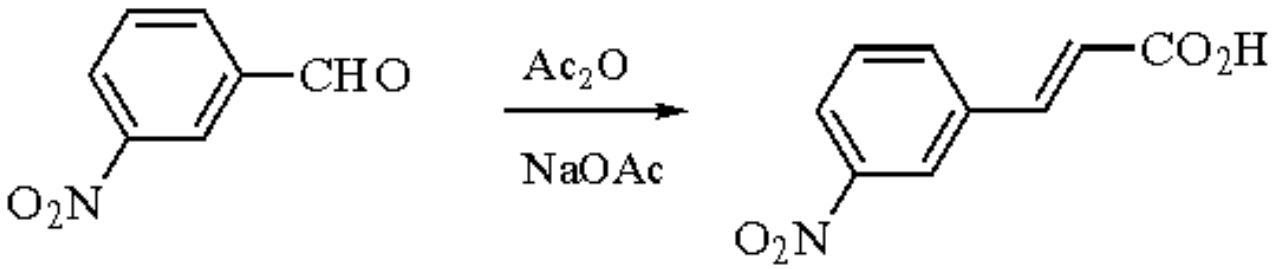

(32)

Aliphatic aldehydes give low or no yields of acid. Coumarin can be prepared by a Perkin reaction of salicylaldehyde and acetic anhydride in the presence of triethylamine (eq 33).

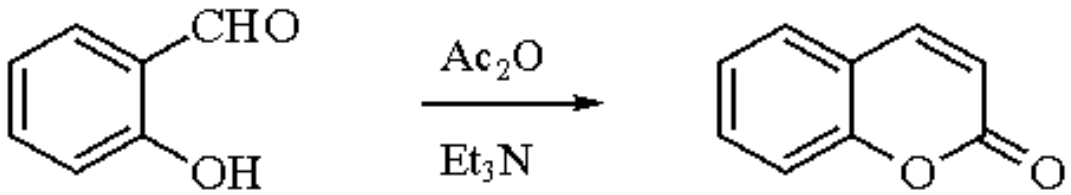

(33)

Polonovski Reaction.

In the Polonovski reaction,[9] tertiary amine oxides react with acetic anhydride to give the acetamide of the corresponding secondary amine (eq 34).

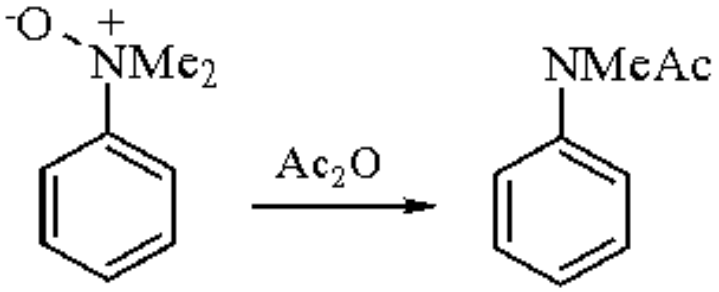

(34)

In nonaromatic cases, the Polonovski reaction gives the *N*-acylated secondary amine as the major product and the deaminated ketone as a minor product (eq 35).[48]

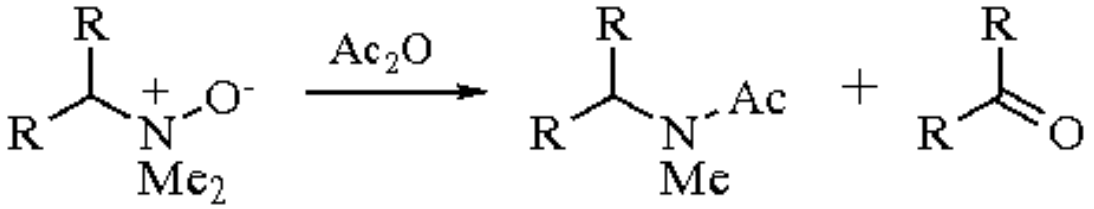

(35)

This reaction has been extended to a synthesis of 2-acetoxybenzodiazepine via an *N*-oxide rearrangement (eq 36).

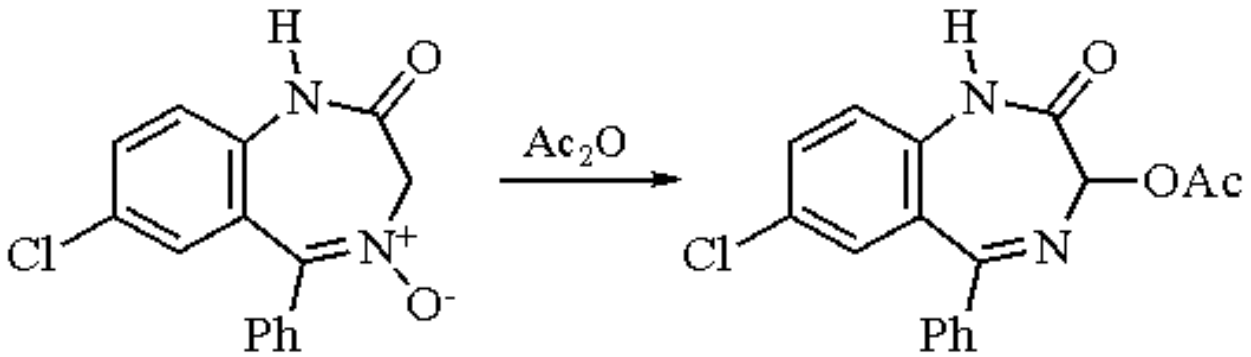

(36)

An application of the Polonovski reaction forms β-carbonylenamines. *N*-Methylpiperidone is reacted with *m*-CPBA followed by acetic anhydride and triethylamine to give the β-carbonyl enamine (eq 37).[49]

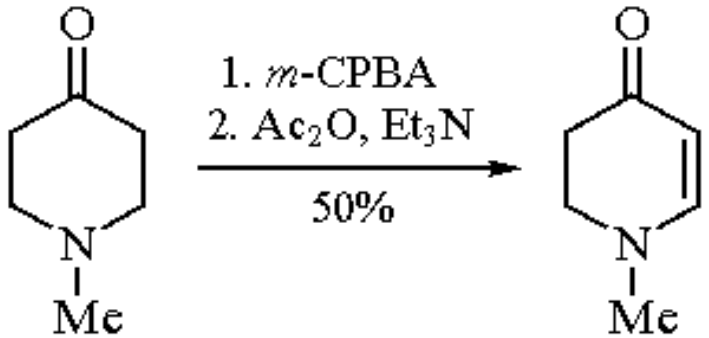

(37)

Reaction with *N*-Oxides.

Pyridine 1-oxide reacts with acetic anhydride to produce 2-acetoxypyridine, which can be hydrolyzed to 2-pyridone (eq 38).[10]

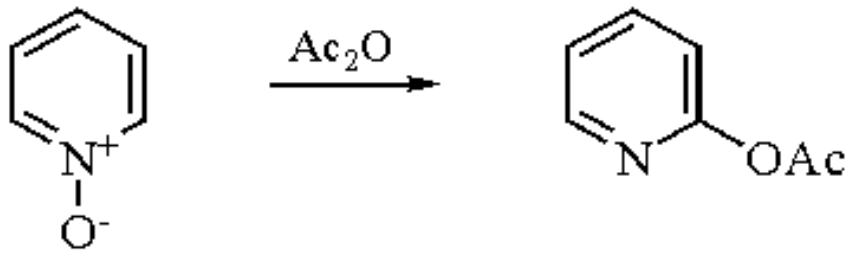

(38)

Open chain *N*-oxides, in particular nitrones, rearrange to amides (almost quantitatively) under acetic anhydride conditions (eq 39).[50]

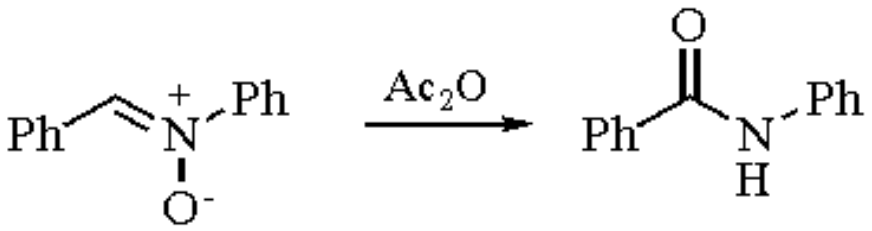

(39)

Heteroaromatic *N*-oxides with a side chain react with acetic anhydride to give side-chain acyloxylation (eq 40).[51]

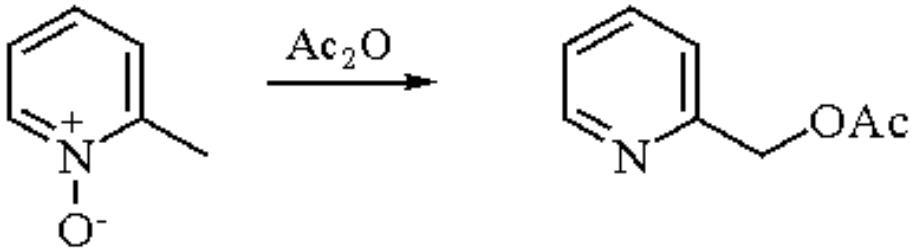

(40)

This reaction has been used in synthetic chemistry as the method of choice to form heterocyclic carbinols or aldehydes.

Thiele Reaction.

The Thiele reaction converts 1,4-benzoquinone to 1,2,4-triacetoxybenzene using acetic anhydride and a catalytic amount of ***Sulfuric Acid***.[11] Zinc chloride has been used without advantage. In this reaction, 1,4-addition to the quinone is followed by enolization and acetylation to give the substituted benzene (eq 41).

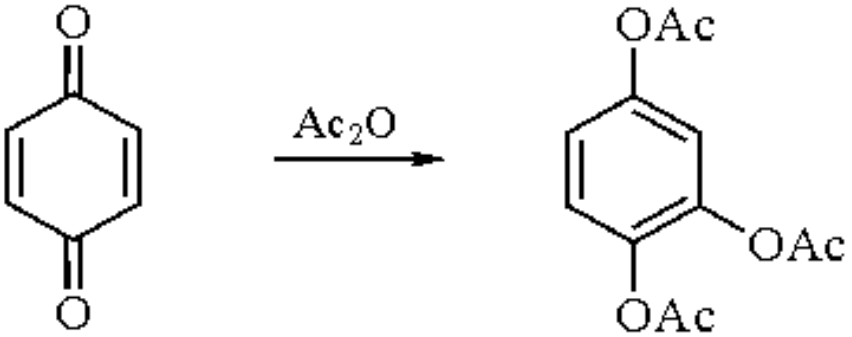

(41)

With unhindered quinones, BF_3 etherate is a more satisfactory catalyst but hindered quinones require the more active sulfuric acid catalyst. 1,2-Naphthoquinones undergo the Thiele reaction with acetic anhydride and sulfuric acid or boron trifluoride etherate (eq 42).

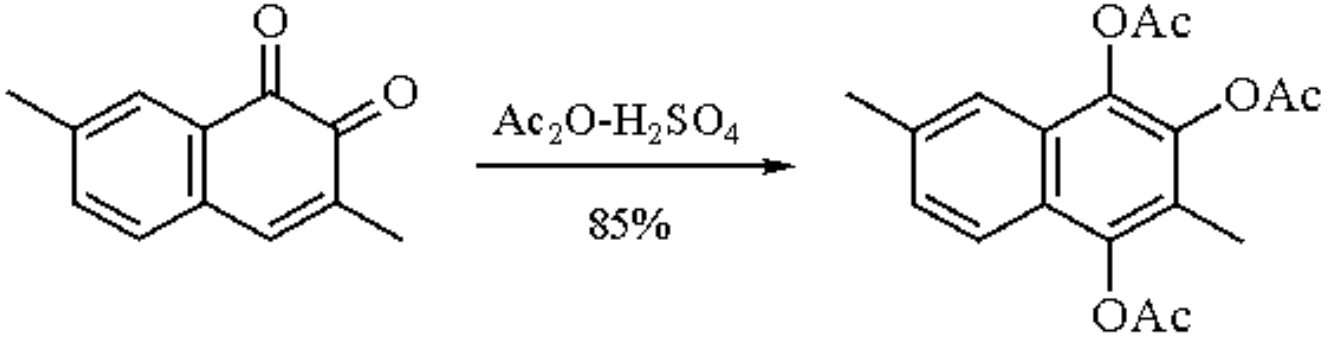

(42)

Ether Cleavage.

Dialkyl ethers can be cleaved with acetic anhydride in the presence of pyridine hydrochloride or anhydrous ***Iron(III) Chloride***. In both cases, acetate products are produced. As shown in eq 43, the tricyclic ether is cleaved by acetic anhydride and pyridine hydrochloride to give the diacetate in 93% yield.[12]

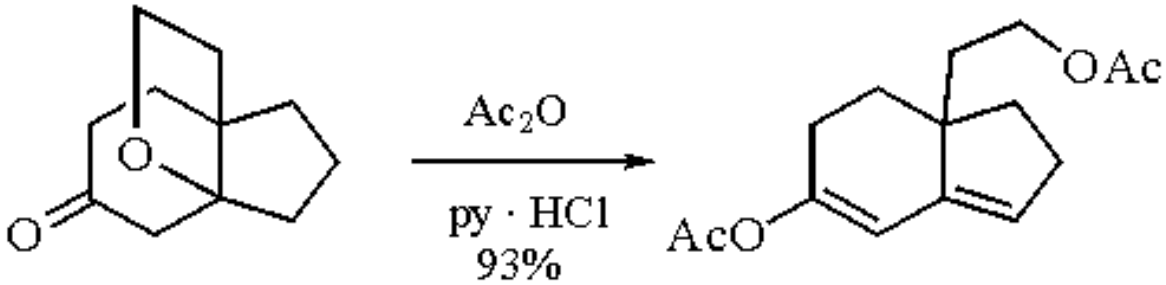

(43)

Simple dialkyl ethers react with iron(III) chloride and acetic anhydride to produce compounds where both R groups are converted to acetates (eq 44).[52]

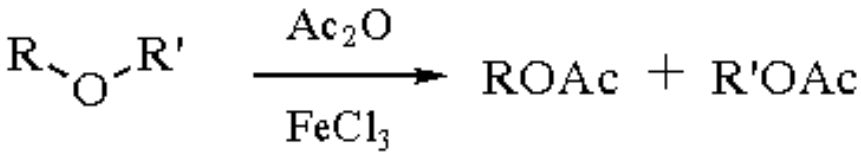

(44)

Cleavage of allylic ethers can occur using acetic anhydride in the presence of iron(III) chloride (eq 45). The reaction takes place without isomerization of a double bond, but optically active ethers are cleaved with substantial racemization.[53]

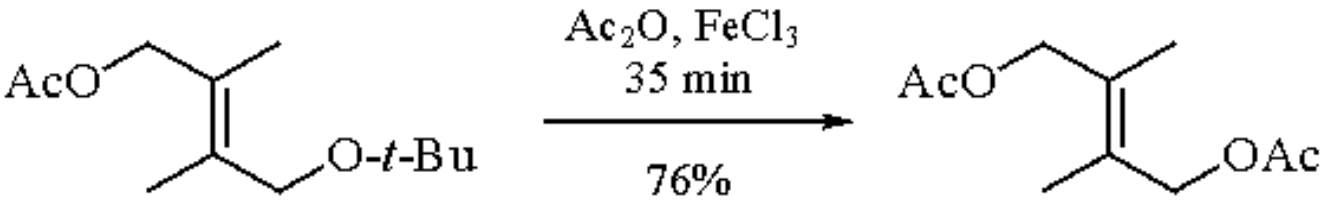

(45)

Cleavage of aliphatic ethers occurs with the reaction of acetic anhydride, boron trifluoride etherate, and ***Lithium Bromide*** (eq 46). The ethers are cleaved to the corresponding acetoxy compounds contaminated with a small amount of unsaturated product.[54] In some cases, the lithium halide may not be necessary.

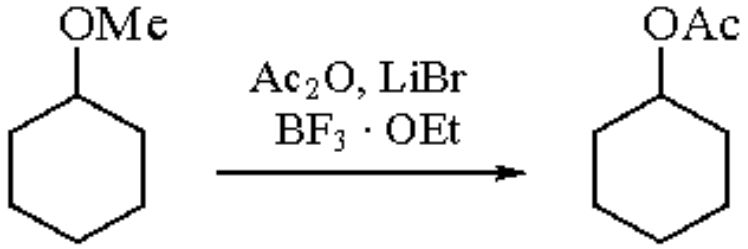

(46)

Cyclic ethers are cleaved to o-bromoacetates using ***Magnesium Bromide*** and acetic anhydride in acetonitrile (eq 47).[55]

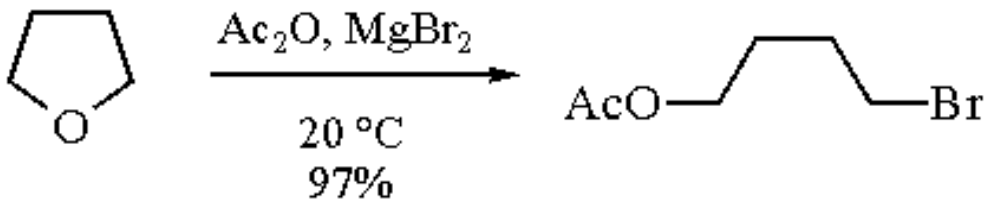

(47)

The reaction occurs with inversion of configuration, as shown in eq 48.

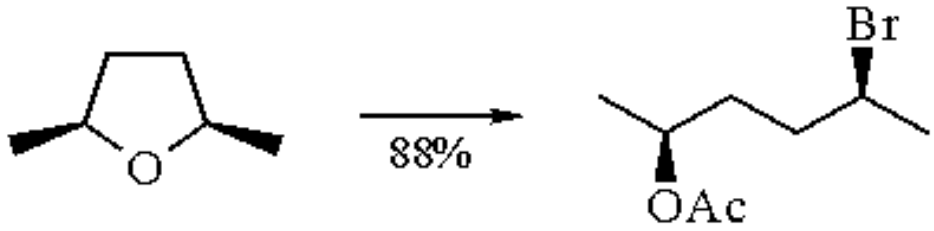

(48)

Trimethylsilyl ethers are converted to acetates directly by the action of acetic anhydride-pyridine in the presence of 48% HF or boron trifluoride etherate (eq 49).[56]

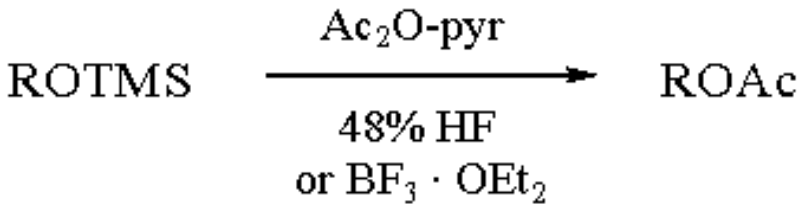

(49)

Miscellaneous Reactions.

Primary allylic alcohols can be prepared readily by the action of *p*-toluenesulfonic acid in acetic anhydride-acetic acid on the corresponding tertiary vinyl carbinol, followed by hydrolysis of the resulting acetate.[57] The vinyl carbinol is readily available from the reaction of a ketone with a vinyl Grignard reagent. Overall yields of allylic alcohols are very good (eq 50).

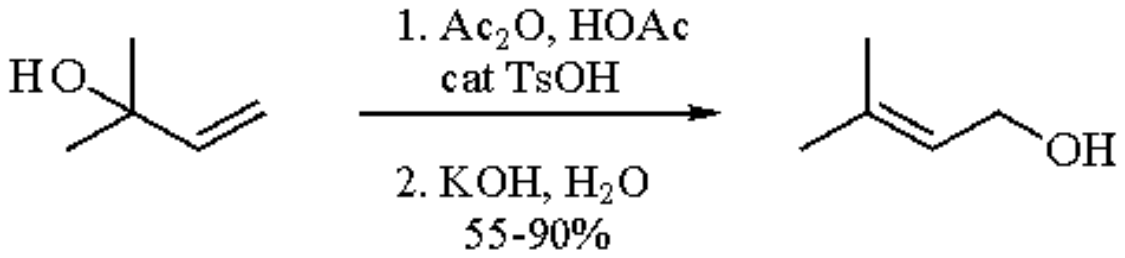

(50)

Enol lactonization occurs readily on an α-keto acid using acetic anhydride at elevated temperatures.[58] The reaction shown in eq 51 proceeds in 89% yield. In general, acetic anhydride is superior to acetyl chloride in this reaction.[59]

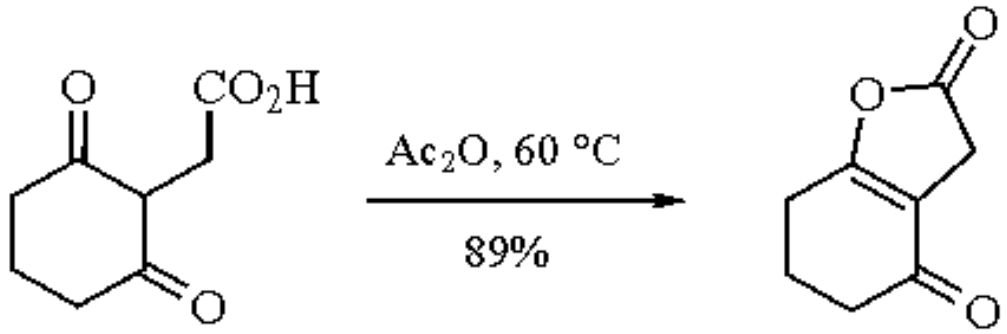

(51)

Aliphatic aldehydes are easily converted to the enol acetate using acetic anhydride and potassium acetate (eq 52).[13] This reaction only works for aldehydes and is the principal reason for the failure of aldehydes to succeed in the Perkin reaction. Triethylamine and DMAP may also catalyze the reaction.

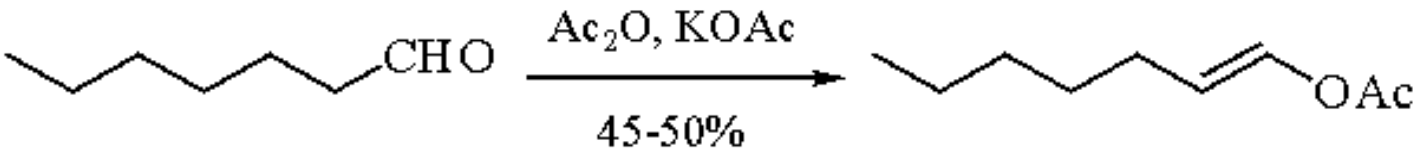

(52)

A cyclopropyl ketone is subject to homoconjugate addition using acetic anhydride/boron trifluoride etherate. Upon acetate addition, the enol is trapped as its enol acetate (eq 53).[60]

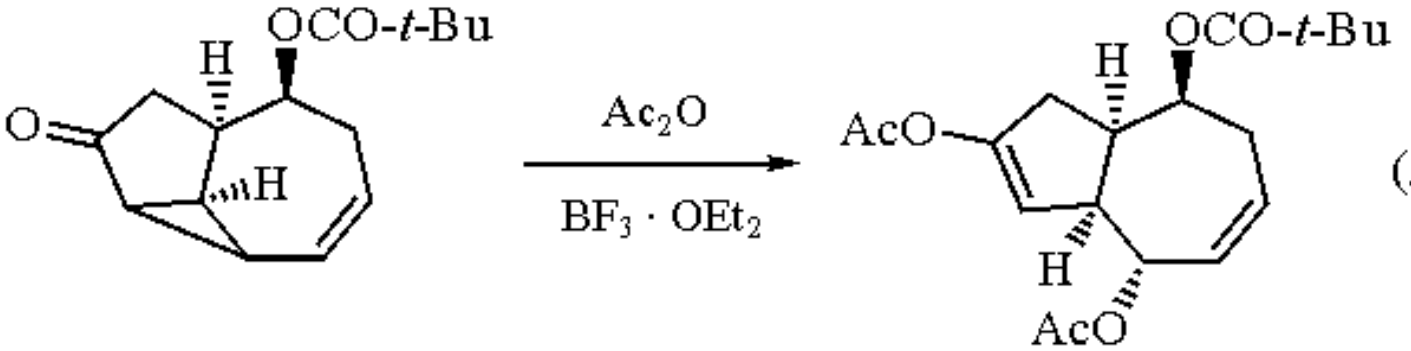

(53)

When an aldehyde is treated with acetic anhydride/anhydrous iron(III) chloride, geminal diacetates are formed in good to excellent yields.[14] Aliphatic and unsaturated aldehydes can be used in this reaction as shown in eqs 54-56. Interestingly, if an α-hydrogen is present in an unsaturated aldehyde, elimination of the geminal diacetate product gives a 1-acetoxybutadiene.

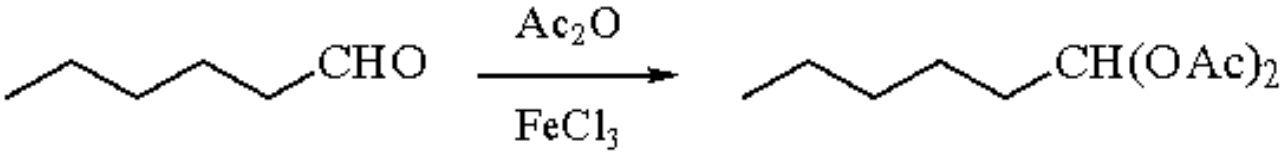

(54)

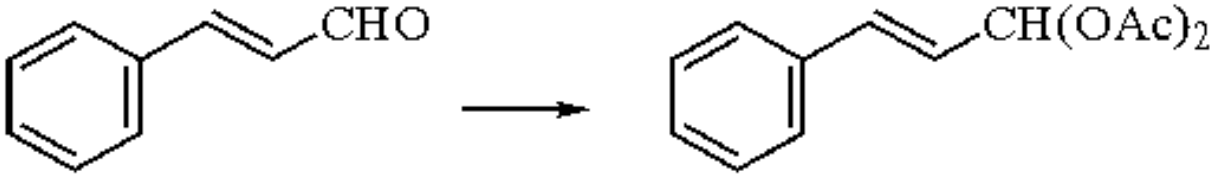

(55)

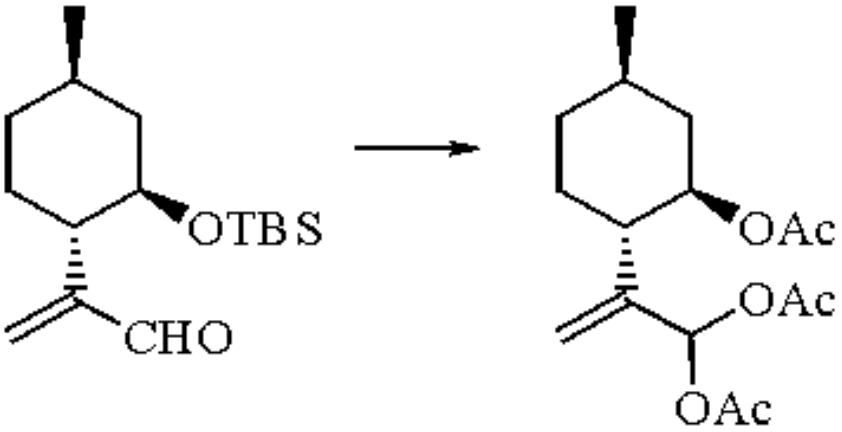

(56)

If an aldehyde is treated with acetic anhydride in the presence of a catalytic amount of ***Cobalt(II) Chloride***, a diketone is formed (eq 57).[61]

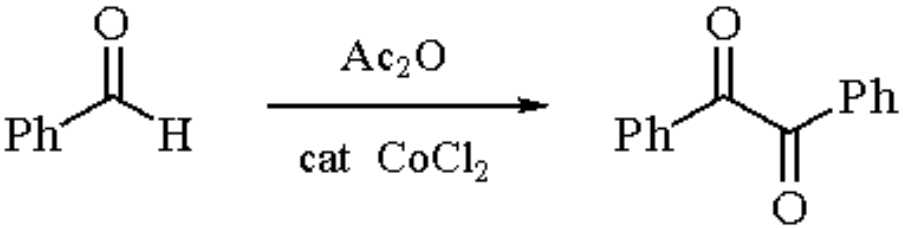

(57)

However, if 1.5 equiv of cobalt(II) chloride is added, the geminal diacetate is formed (eq 58).[62]

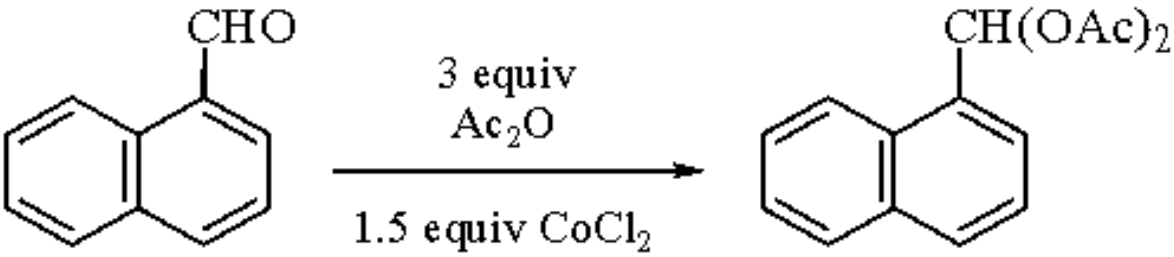

(58)

Apparently, the reaction in eq 58 occurs only when the starting material is polyaromatic or with compounds whose carbonyl IR frequency is less than 1685 cm^{-1}.

Acetic anhydride participates in several cyclization reactions. For example, enamines undergo a ring closure when

treated with acetic anhydride (eq 59).[63]

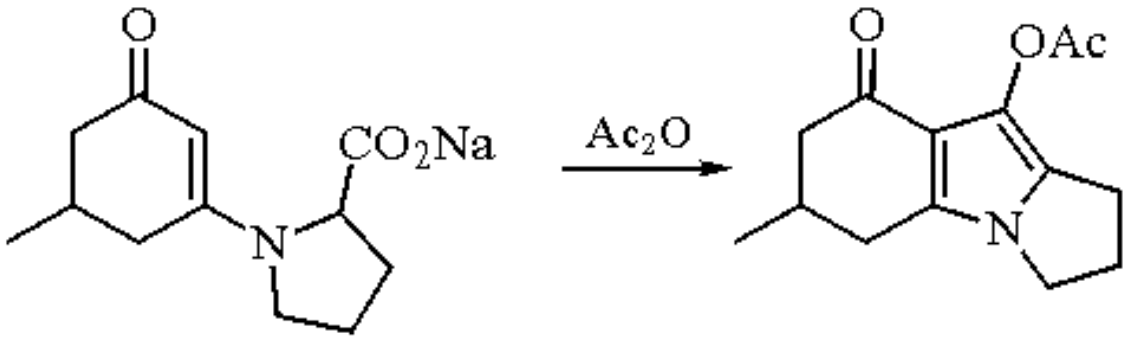

(59)

o-Diamine compounds also cyclize when treated with acetic anhydride (eq 60).[64]

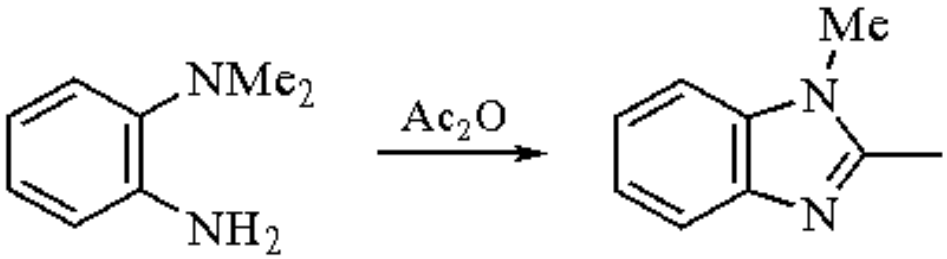

(60)

Twistane derivatives were obtained by the reaction of a decalindione with acetic anhydride, acetic acid, and boron trifluoride etherate (eq 61).[65]

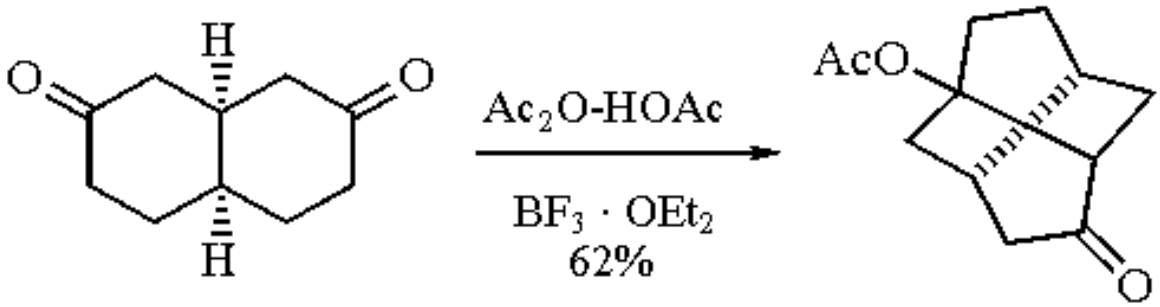

(61)

A condensation/cyclization reaction between an alkynyl ketone and a carboxylic acid in the presence of acetic anhydride/triethylamine gives a butenolide (eq 62).[66]

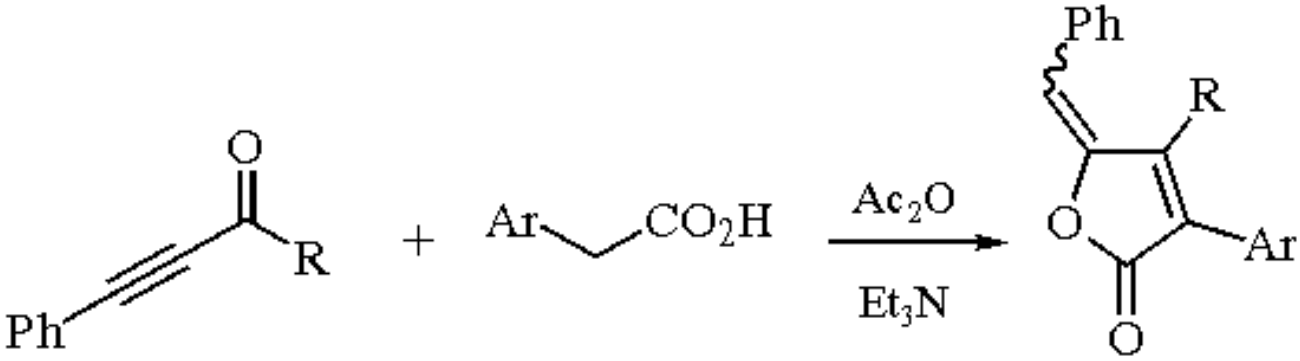

(62)

A few rearrangement reactions take place with acetic anhydride. A Claisen rearrangement is involved in the formation of the aromatic acetate in eq 63.[67] The reaction proceeds in 44% yield even after 21 h at 200 °C.

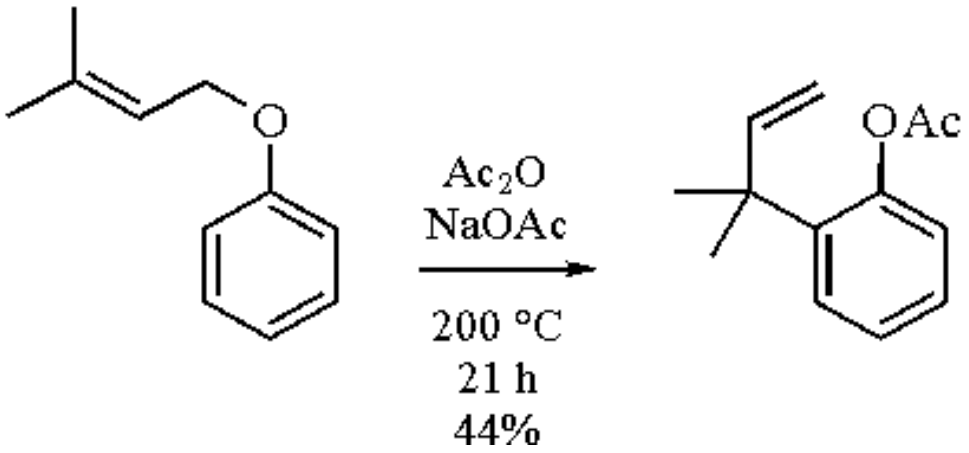

(63)

Complex rearrangements have occured using acetic anhydride under basic conditions, as shown in eq 64.[68]

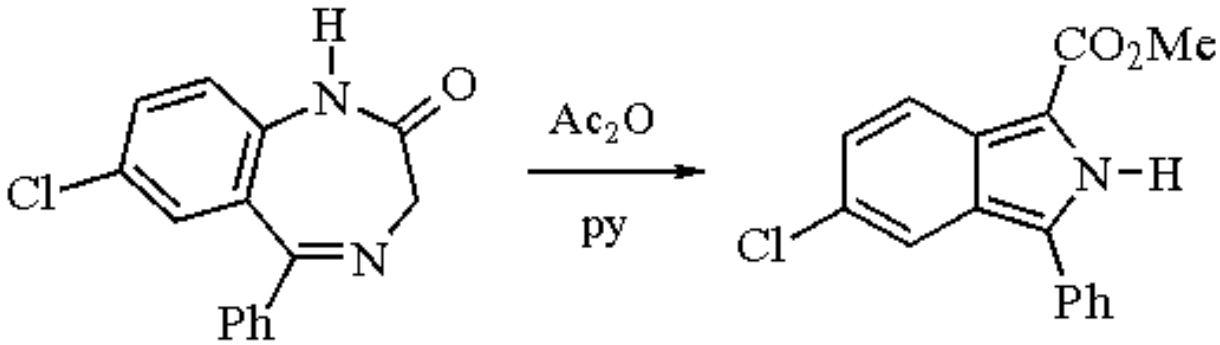

(64)

Aromatization occurs readily using acetic anhydride. Aromatization of α-cyclohexanones occurs under acidic conditions to lead to good yields of phenols (eq 65).[69] However, in totally unsubstituted ketones, aldol products are formed.

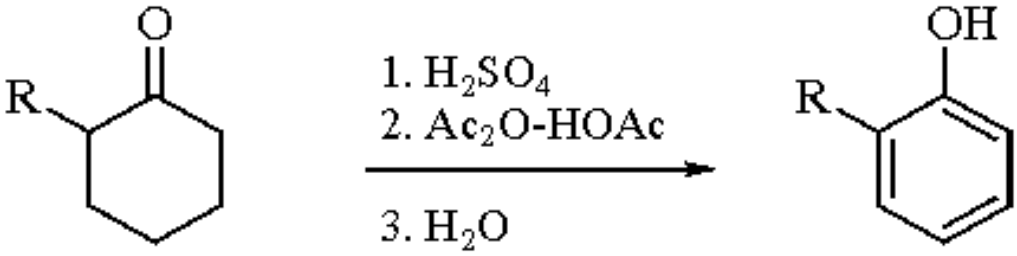

(65)

Aromatization of 1,4- and 1,2-cyclohexanediones leads to cresol products (eq 66) in over 90% yield.[70]

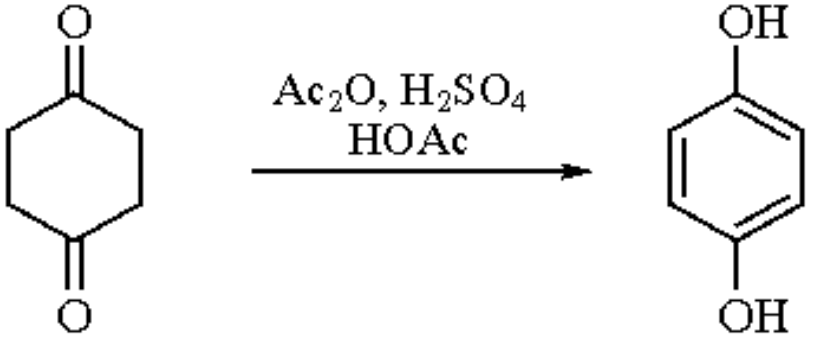

(66)

Alkynes and allenes are formed by the acylation of nitrimines using acetic anhydride/pyridine with DMAP as catalyst (eqs 67 and 68).[71] Nitrimines are prepared by nitration of ketoximes with nitrous acid.

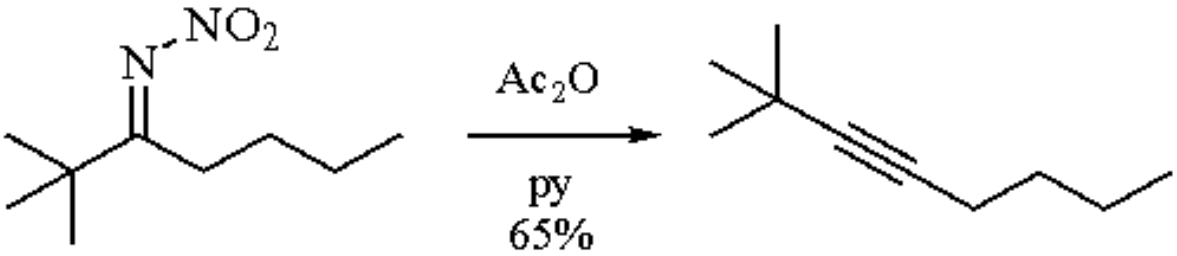

(67)

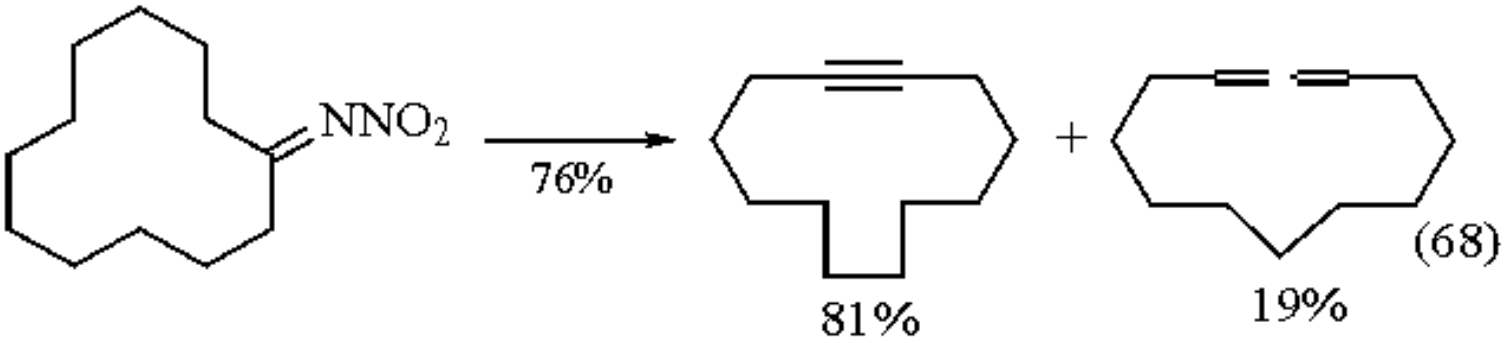

(68)

Lastly, acetic anhydride participates in the Friedel-Crafts reaction.[72] ***Polyphosphoric Acid*** is both reagent and solvent in these reactions (eq 69).

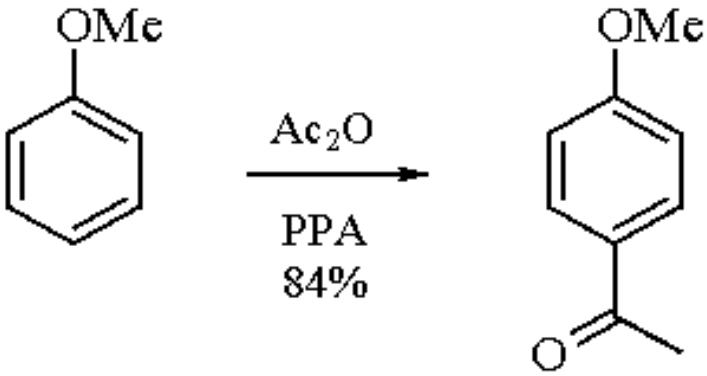

(69)

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Acetic Formic Anhydride[1]

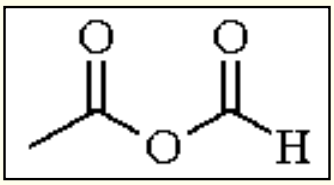

[2258-42-6] · $C_3H_4O_3$ · Acetic Formic Anhydride · (MW 88.06)

(useful formylating agent for the hydroxyl,[2] phenol,[3] and amine groups[4] as well as other heteroatoms;[5] useful for the synthesis of aldehydes from aromatic Grignard reagents,[6] for the preparation of formyl fluoride,[7] and for the preparation of diazoacetaldehyde[8])

Alternate Name: AFA.

Physical Data: bp 27-28 °C/10 mmHg.

Analysis of Reagent Purity: IR, NMR, MS.[1]

Preparative Methods: acetic formic anhydride is not comercially available. The easiest method of preparation is by the reaction of sodium formate and ***Acetyl Chloride*** in dry ether as reported by Krimen.[9] Alternatively, ***Ketene*** and ***Formic Acid*** form the title compound at room temperature or below.[10] Acetic formic anhydride can be prepared rapidly in situ by stirring formic acid, acetyl chloride, and ***Triethylamine*** in THF at -70 °C for 10 min.[11] AFA is found in a mixture of formic acid (excess) with ***Acetic Anhydride***.[1] The mixture is more accurately described as formic acid-acetic anhydride mixture (FAM) and is also used as a formylating agent.

Purification: by fractional distillation at low pressure.

Handling, Storage, and Precautions: acetic formic anhydride decomposes slowly at room temperature and faster at elevated temperatures, giving acetic acid and carbon monoxide. Due to gas evolution, AFA is best stored at 4 °C in a flask fitted with a polyethylene stopper since sealed samples can explode. The compound is an eye and skin irritant and should be handled in a fume hood.

O-Formylations.

Acetic formic anhydride (AFA) as well as formic acid-acetic anhydride mixture (FAM) can be used to formylate alcohols and phenols.[2,3] While the yields of formates are high, the reaction takes from 50 to 80 days (eq 1).

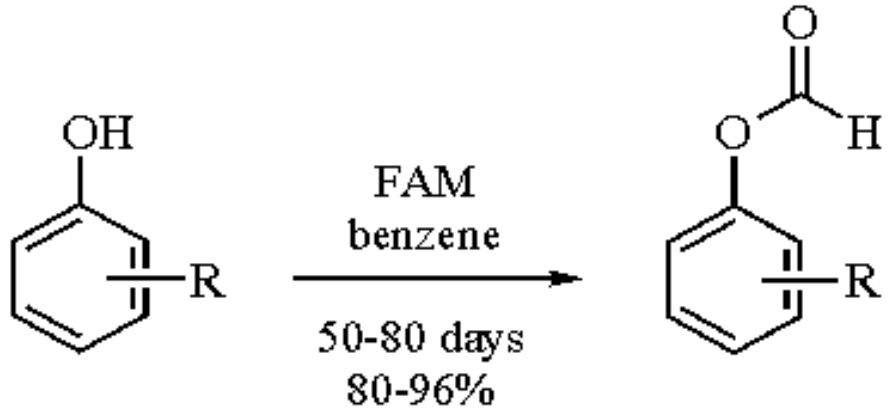

(1)

An improved method for formation of aryl formates uses pure AFA with the addition of tertiary amine bases or sodium formate.[12] The reaction takes place at 20 °C, is complete in 24-48 h, and gives excellent yields of formate. The procedure is general and is an easy method of preparation of pure aryl formates in high yield with no acetate byproducts. The reaction can be applied to aryl groups with electron donating or electron withdrawing substituents.

Phenolic ketones cyclize to isoflavones with AFA catalyzed by sodium formate or ***Triethylamine*** (eq 2).[13]

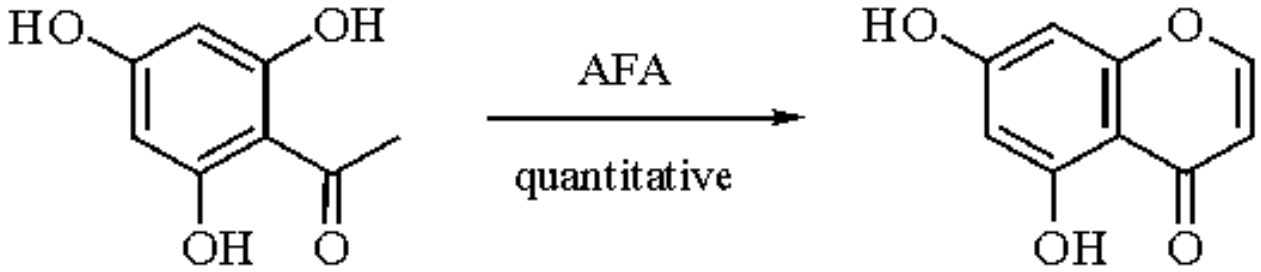

(2)

Salicylamide is formylated in 53% yield using AFA with ***Pyridine*** at 0 °C (eq 3).[14] Interestingly, no rearrangement to *N*-formylsalicylamide occurs under these reaction conditions. This protocol is superior to formic acid or ethyl formate which give the *N*-formyl compound exclusively.

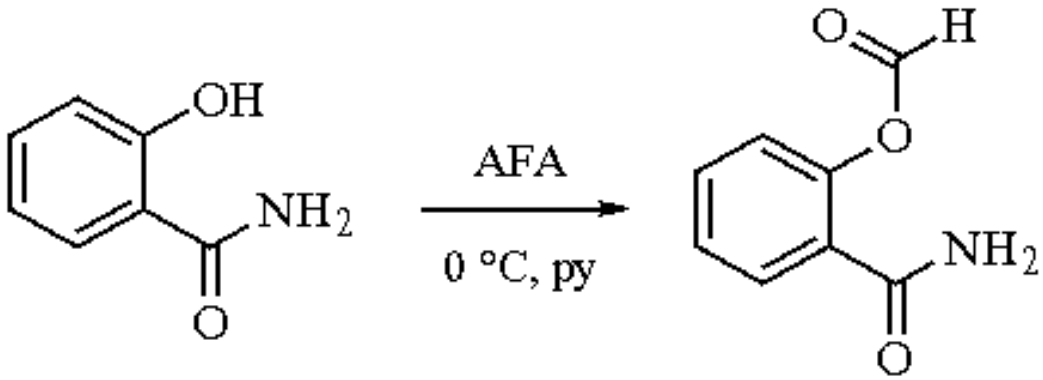

(3)

Aliphatic alcohols can be converted to their formates using FAM.[2] Tertiary alcohols yield formate esters exclusively, while secondary and primary alcohols yield mixtures of formate and acetate. Formylation of primary and secondary alcohols can be enhanced by the addition of tertiary nitrogen bases or sodium formate.

Tertiary alcohols that are typically dehydrated upon acetylation yield formates under these reaction conditions. *O*[12a]-

Formyltetracycline (**1**) can be prepared in high yield using AFA.[15]

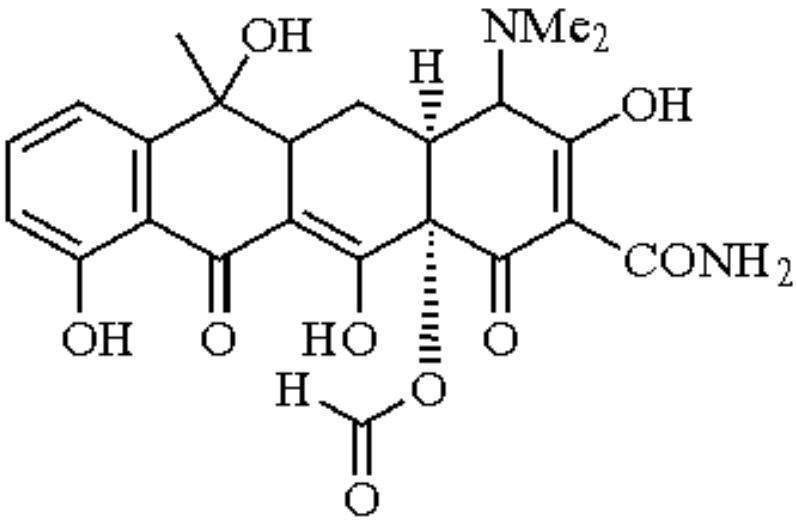

(1) O^{12a}-Formyltetracycline

Complex hydroxy acids such as gibberellin A3 react with acetic formic anhydride in pyridine to give the 3-*O*-monoformyl derivative (**2**) and the *O*-diformyl derivative in 85% and 13% yields, respectively.[16]

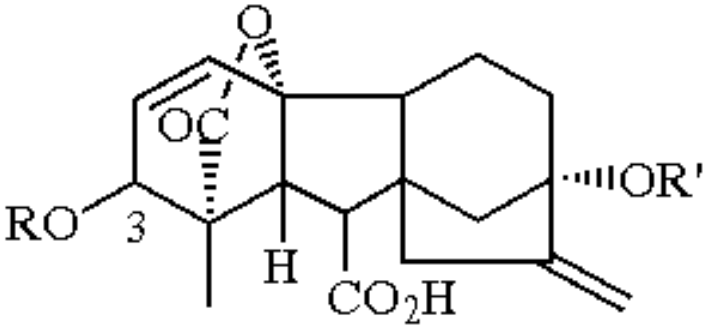

(2) O^{3}-Formylgibberellin A3; R = CHO, R' = H

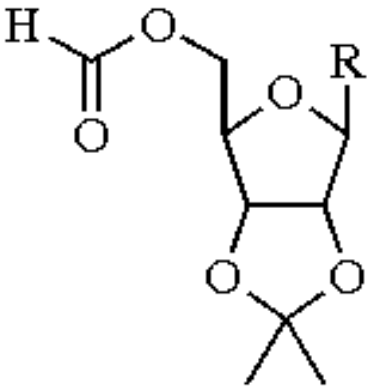

(3)

Acetic formic anhydride formylates the sugar moiety of some nucleosides such as uridine and others.[17] Polyformylation occurs on all free hydroxyl groups. The 5´-hydroxyl of nucleosides can be formylated efficiently to give a 5´-*O*-formyl derivative (**3**).[18] The selective hydrolysis of formate esters in hot methanol compared with acetates makes formylation an attractive protecting group for some nucleosides.

N-Oxides of tertiary amines are deoxygenated in nearly quantitative yield using AFA (eq 4).[19] The reaction is general for trialkylamine *N*-oxides and *N*,*N*-dialkylarylamine *N*-oxides. Heteroaromatic *N*-oxides and sulfoxides are unchanged under these reaction conditions.[20]

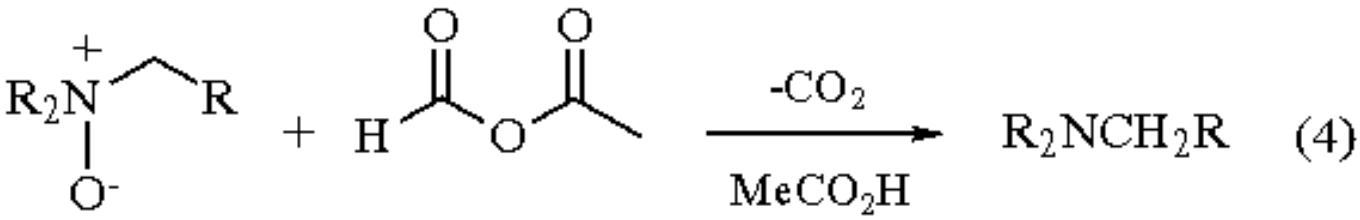

N-Formylations.

Ammonia can be monoformylated using AFA at 0 °C in dry ether as shown in eq 5.[21] No polyformylated products were detected in the reaction.

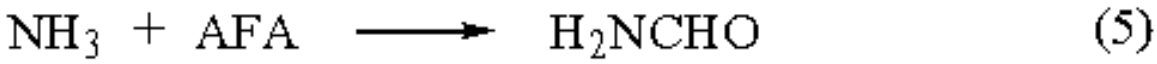

Many aliphatic and aromatic amines (primary and secondary) have been formylated successfully using AFA or FAM.[4] Primary amines can be monomethylated in a one-pot procedure using excess FAM which gives a monoformylated intermediate (eq 6).[22] Weakly basic and sterically hindered amines are also reactive.

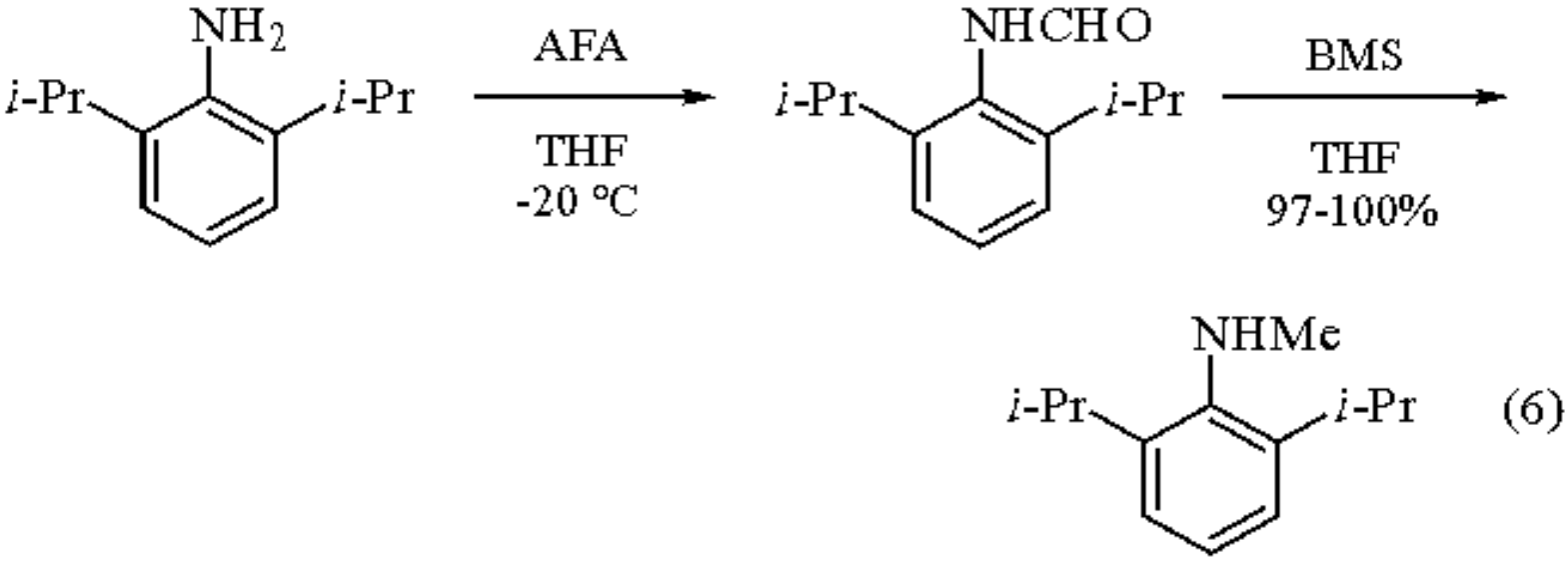

Heterocyclic compounds have been *N*-formylated at the side chain or ring nitrogen using AFA or FAM. Some examples, (**4**),[23] (**5**),[24] (**6**),[25] and (**7**),[26] are shown.

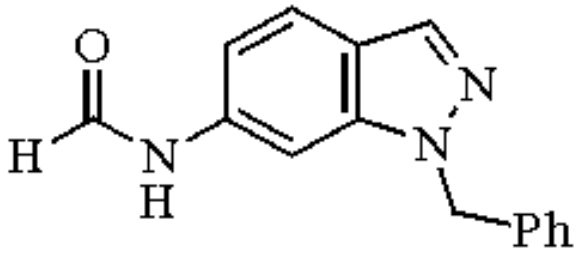

(4)

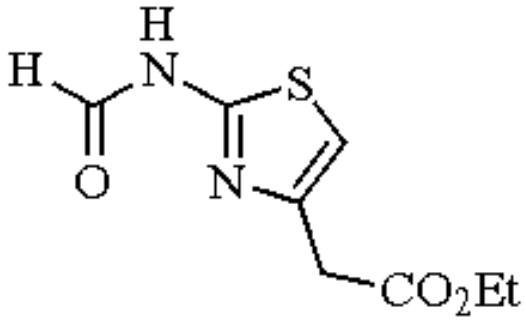

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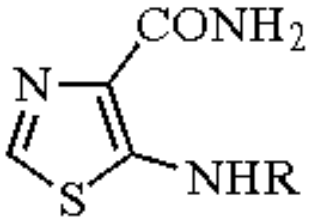

(6)

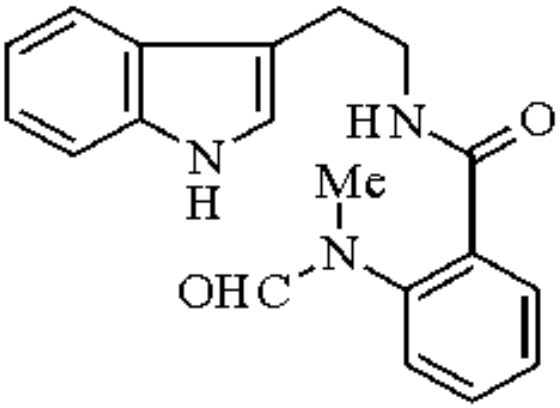

(7)

N-Formylation of amino acids has been achieved using FAM without racemization. An excess of FAM is required; however, AFA can be used in a 2-3 molar excess. Most amino acids have been formylated in 70-94% yields without formation of the acetate.[27]

The formyl group is very useful as a blocking group in peptide synthesis. The formyl group can be introduced without racemization and is selectively removed by mild acid hydrolysis without affecting the peptide linkage. Since the *N*-formyl group is stable toward basic hydrolysis, saponification of esters in amino acids can be achieved. Thus the peptide chain can be extended at the amino or carboxyl ends.

C-Formylations.

A few examples of *C*-formylation reactions have been reported in the literature. The first involves formylation of indole derivatives in the 3-position when this position is free.[28]

Aromatic Grignard reagents react with AFA to give good yields of aldehydes as the only carbonyl product formed without formation of alcohol.[6] However, aliphatic Grignard reagents and AFA lead to substantial amounts of methyl ketone and alcohol formation.

C-Formylation of diazomethane with AFA leads to ***Diazoacetaldehyde*** (eq 7).[8] Diazoacetaldehyde is a precursor of formylcarbene. It has also been used for ethanalation of alkenes.

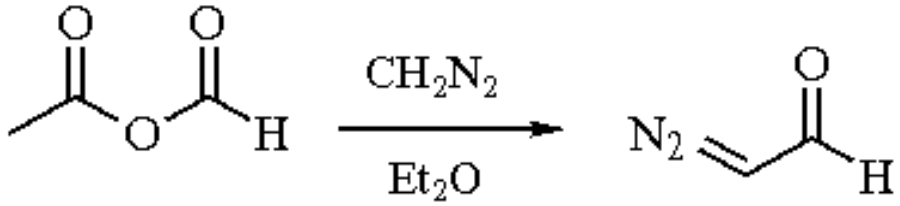

(7)

Formyl Fluoride.

Anhydrous HF reacts with AFA to yield ***Formyl Fluoride*** in 68% yield. A small amount of acetyl fluoride was also formed.[7] Formyl fluoride is the only known stable halide of formic acid. It has been used in a Friedel-Crafts type reaction to produce aromatic aldehydes (eq 8).

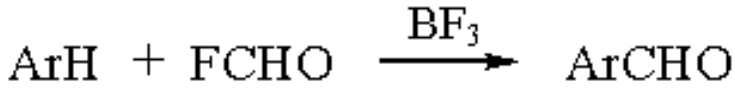

(8)

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Acetoacetic Acid[1]

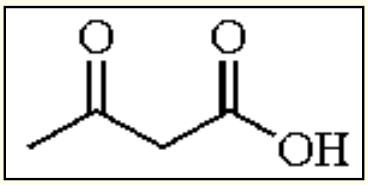

[541-50-4] · $C_4H_6O_3$ · Acetoacetic Acid · (MW 102.09)

(acetone enolate equivalent in alkylations,[2] carbonyl additions,[3] conjugate additions,[4] and diazonium ion coupling reactions[5])

Alternate Name: 3-oxobutanoic acid.

Physical Data: mp 36-37 °C; pK_a 3.58; enol content: carbon tetrachloride (35 °C), 49%; DMSO-d_6 (35 °C), 10.8%; D_2O (0 °C), <2%.[6]

Solubility: sol H_2O, alcohol.

Preparative Methods: traditionally prepared by base hydrolysis of ***Ethyl Acetoacetate***.[3,7] A high yield synthesis by acid hydrolysis of ***Diketene*** is also reported.[6]

Handling, Storage, and Precautions: acetoacetic acid is extremely hygroscopic but can be stored under vacuum in a freezer for several weeks with little change. It decomposes rapidly to acetone and carbon dioxide when heated above the melting point. Use in a fume hood.

Functionalization of the active methylene group in acetoacetic acid by reaction with electrophiles and subsequent in situ decarboxylation provides a convenient one-step synthesis of α-substituted acetone derivatives.

Alkylations.

Dilithio acetoacetate can be generated from acetoacetic acid and ***n-Butyllithium*** at 0 °C and then alkylated to give an adduct which decarboxylates at room temperature to give α-alkylated acetone (eq 1).[2]

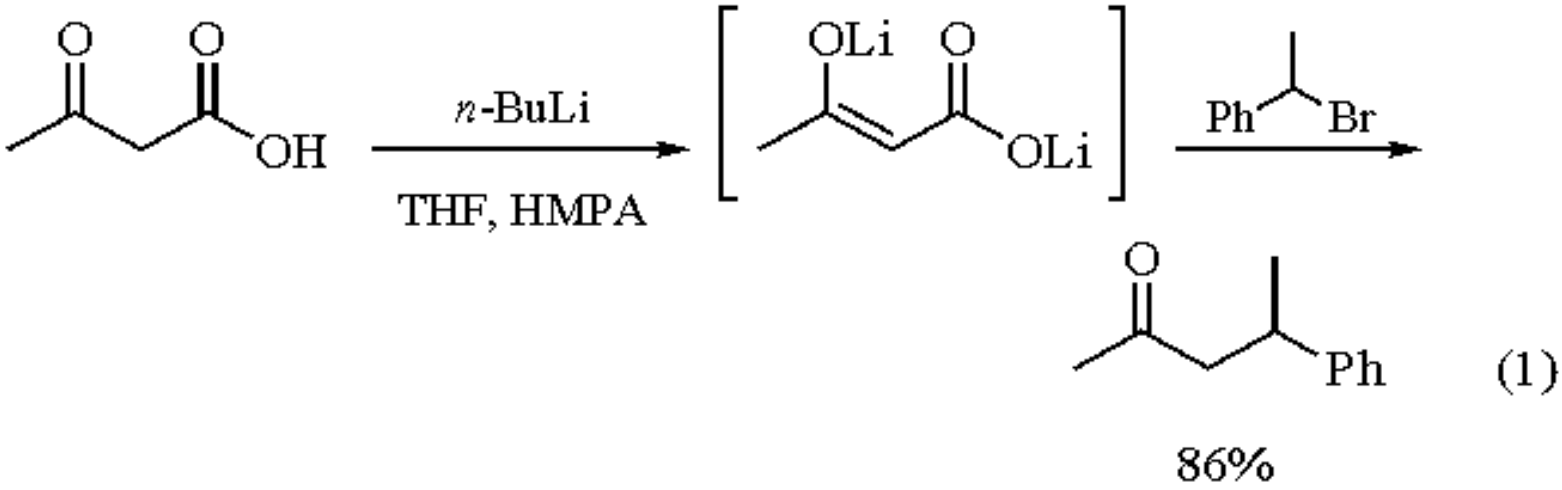

Addition and Condensation Reactions.

Acetoacetic acid reacts with aliphatic aldehydes in the presence of ***Pyridine*** to give α,β-unsaturated methyl ketones in good yields (eq 2).[3,8] Aromatic aldehydes are generally less reactive under these conditions and give mixtures of β-ketols and enones. Exclusive formation of β-ketol is observed when the phenyl ring bears a strong electron withdrawing substituent (eq 2).[3,8] Although ketones generally do not condense with acetoacetic acid, the corresponding enamine derivatives can be used as ketone equivalents and, in this case, the condensation proceeds without an added base.[9]

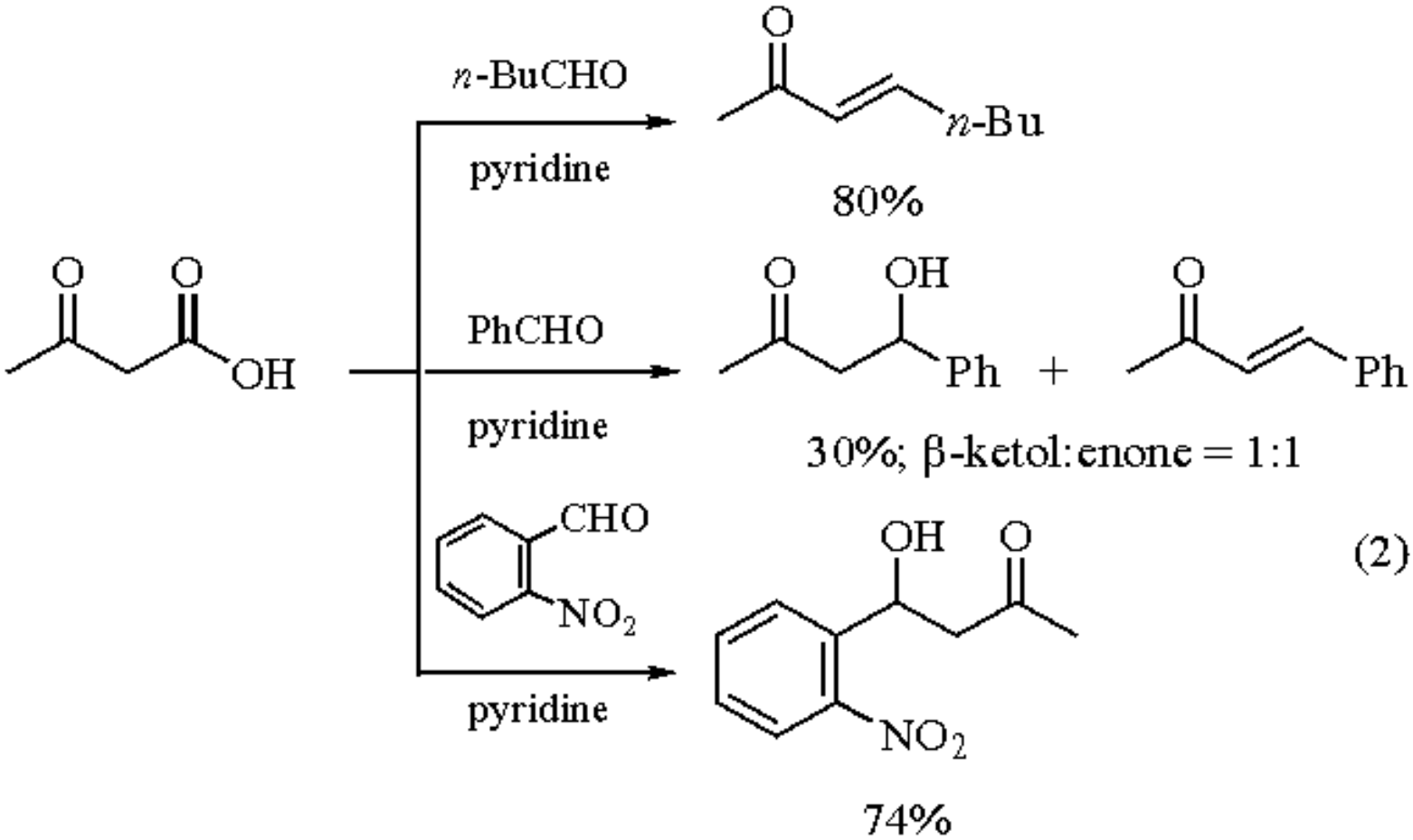

The addition of acetoacetic acid to an imine double bond and subsequent decarboxylation can be used in the preparation of α-acetonylated piperidine[10-12] and pyrrolidine derivatives (eq 3).[13] Base catalyzed 1,4-addition of acetoacetic acid to α,β-unsaturated ketones provides β-acetonyl ketones in good yield (eq 4).[14,15]

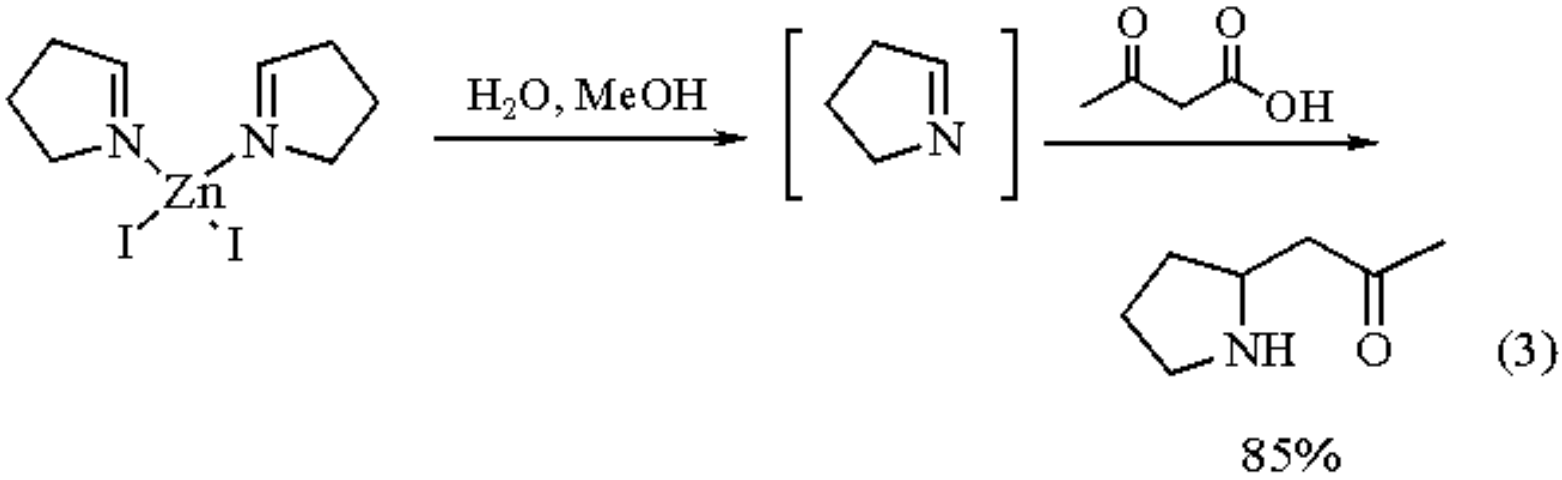

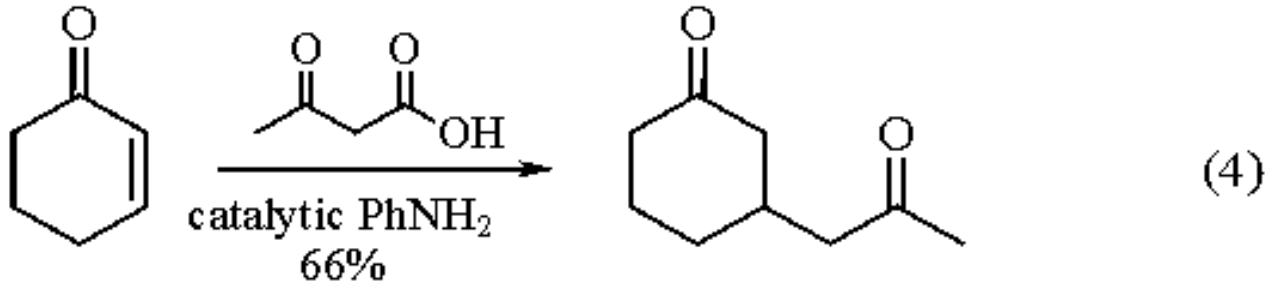

Diazonium Coupling Reactions.

Coupling of arenediazonium salts with acetoacetic acid provides a useful preparation of pyruvaldehyde monohydrazones (eq 5).[16-18] Symmetrical acetylformazan derivatives are produced via the coupling of two equivalents of diazonium salts.[19] Sequential treatment of acetoacetic acid with two different arenediazonium salts results in unsymmetrical acetylformazan derivatives.[20]

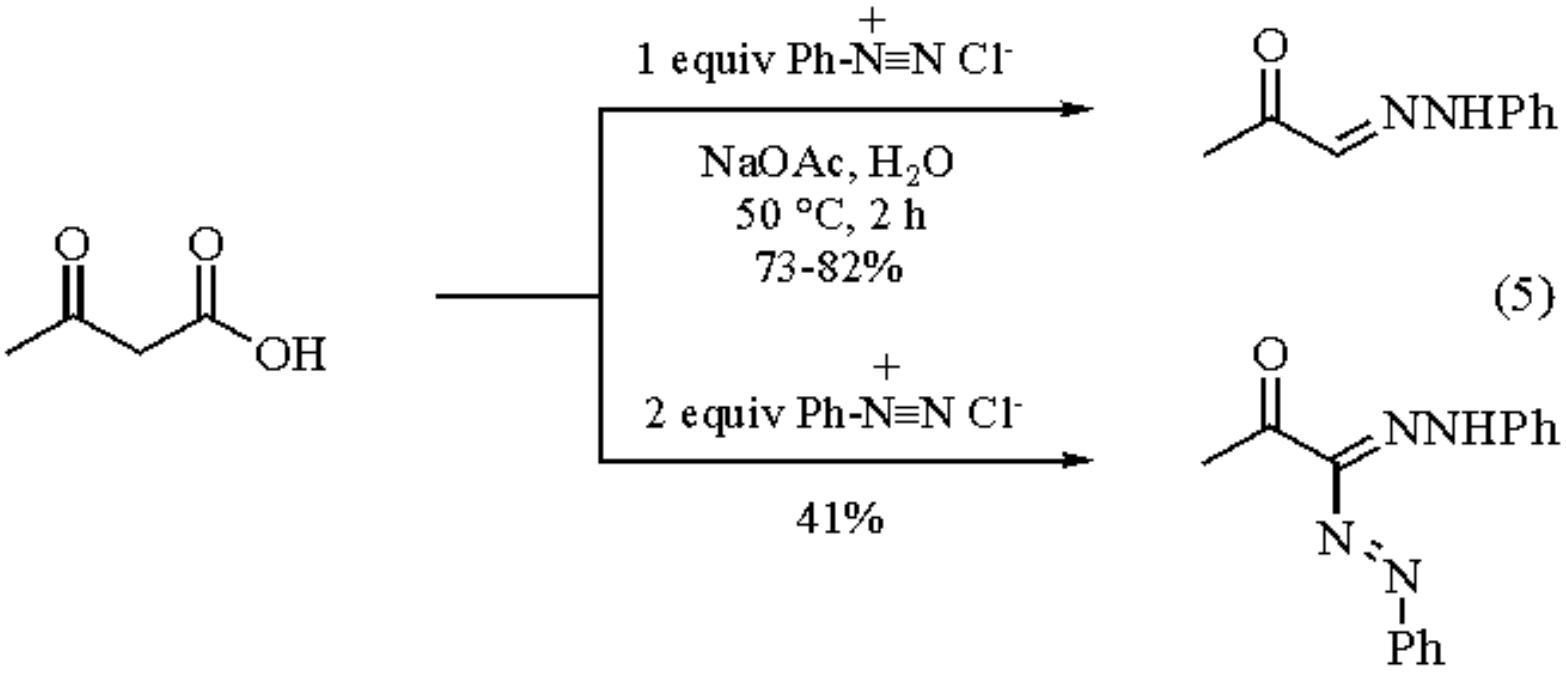

(5)

Related Reagents.

Acetone; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***Ethyl Acetoacetate***; ***Ethyl 4-Chloroacetoacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***Methyl Dilithioacetoacetate***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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(*S*)-Aceto(carbonyl)(cyclopentadienyl)-(triphenylphosphine)iron

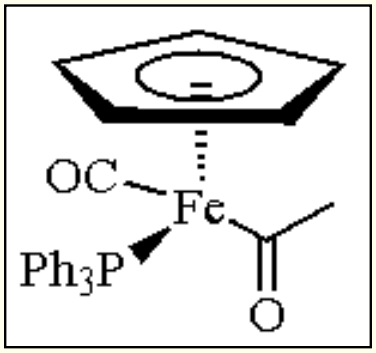

[36548-60-4] · $C_{26}H_{23}FeO_2P$ · (*S*)-Aceto(carbonyl)(cyclopentadienyl)-(triphenylphosphine)iron · (MW 454.29)

(chiral acetate enolate equivalent which can be deprotonated with BuLi or LDA in THF at -78 °C; the enolate reacts stereoselectively with a variety of achiral, prochiral, and chiral electrophiles to generate functionalized organoiron compounds from which the iron can subsequently be removed[1])

Physical Data: mp 142 °C; $[\alpha]^{22}$ +288° (*c* 0.004, C_6H_6), $[\alpha]^{20}$ +160° (*c* 0.04, C_6H_6).

Solubility: insol H_2O; sol THF, $CHCl_3$, CH_2Cl_2, acetone.

Form Supplied in: orange solid.

Handling, Storage, and Precautions: can be stored in air for days with little decomposition. The solid is best stored under nitrogen for long periods of time. More air sensitive when in solution, especially chlorinated hydrocarbons. Like all metal carbonyls, it is best handled in a fume hood.

Preparation and Determination of Absolute Stereochemistry.

The preparation of racemic aceto(carbonyl)(cyclopentadienyl)(triphenylphosphine)iron (**2**) was first reported in 1966.[2] Brunner subsequently recognized that the iron atom in the complex was a chiral center and first reported the preparation of the (+)- and (-)-enantiomers in 1972.[3] Two groups[4,5] recognized in the early 1980s that the enolate of this compound might serve as a chiral acetate enolate equivalent. The absolute configuration of the (+)-enantiomer was reported in 1986[6a] and confirmed in 1988.[7] Alternative preparations of (*S*)-(+)-(**2**) involving kinetic reductions

were published in late 1993.[6b,c] The first reported preparation[3a] of (*S*)-(+)-(**2**) begins with treatment of $[CpFe(CO)_2(PPh_3)]^+PF_6^-$ with sodium mentholate to produce the menthol ester diastereomers which were separated by fractional crystalliza tion.[3b] The (-)-menthol ester (**1**) was then treated with MeLi (1.5 M in Et_2O) (slow addition of the MeLi produces acetyl (**2**) of the highest optical purity)[3c] in THF at -30 °C (eq 1). Aqueous workup and alumina chromatography produced the (*S*)-(+)-acetyl (**2**). A resolution procedure for the separation of the related trimethyl- and triethylphosphine substituted acetyls has also been reported.[8]

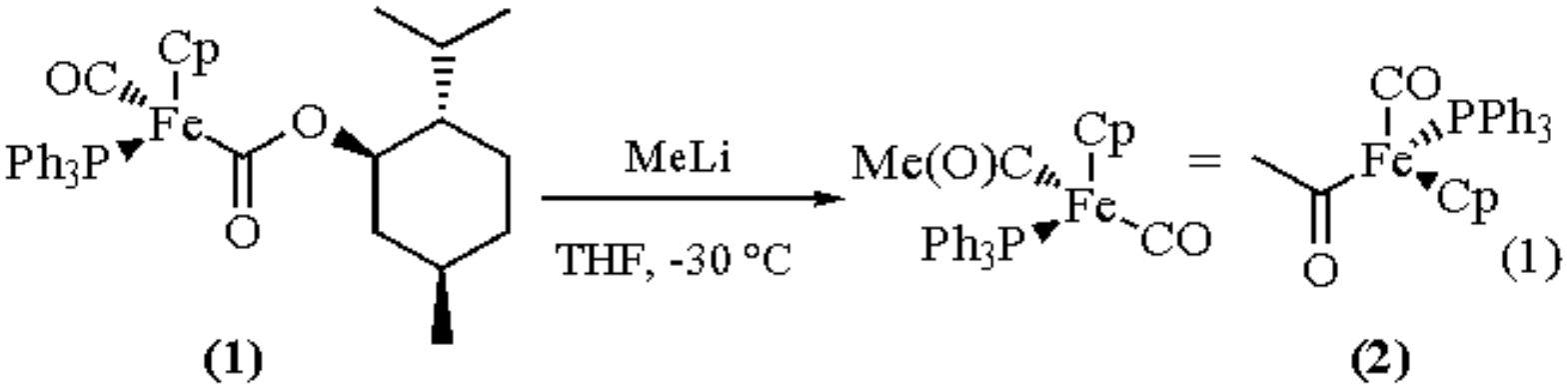

Enolate Generation and Subsequent Alkylation or Oxidation.

The (*S*)-(+)-acetyl complex (**2**) is cleanly deprotonated to the configurationally stable enolate anion (**3**) upon treatment with ***n-Butyllithium*** or ***Lithium Diisopropylamide*** in THF at -78 °C.[1] The enolate (**3**) is alkylated in an almost quantitative yield when treated with a variety of alkyl iodides (eq 2). Alkylation of (**3**) with (*R*)-chloromenthyl ether produced (**5**) which was used to establish the absolute stereochemistry of (**2**) (eq 3).[6,1f] Subsequent deprotonation of these alkylated products (**4**) is believed to produce (*E*)-enolates (**6**) which can be alkylated cleanly from the enolate face away from the triphenylphosphine ligand (eq 4).[1]

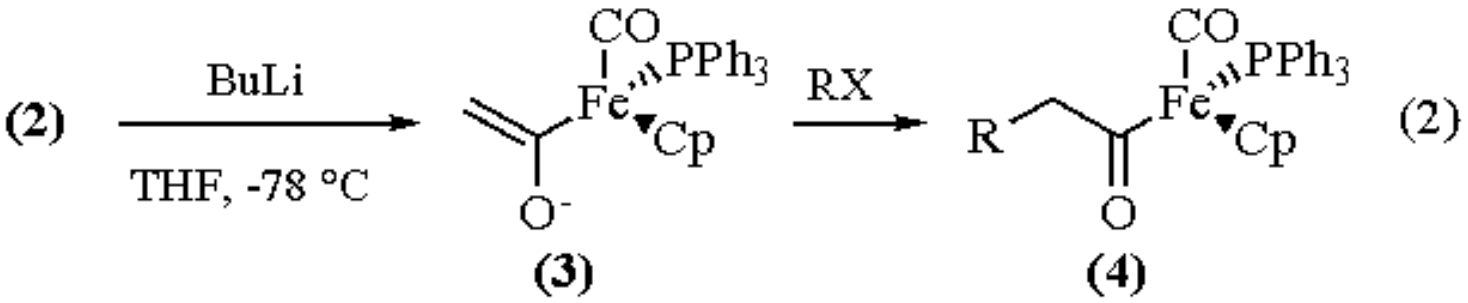

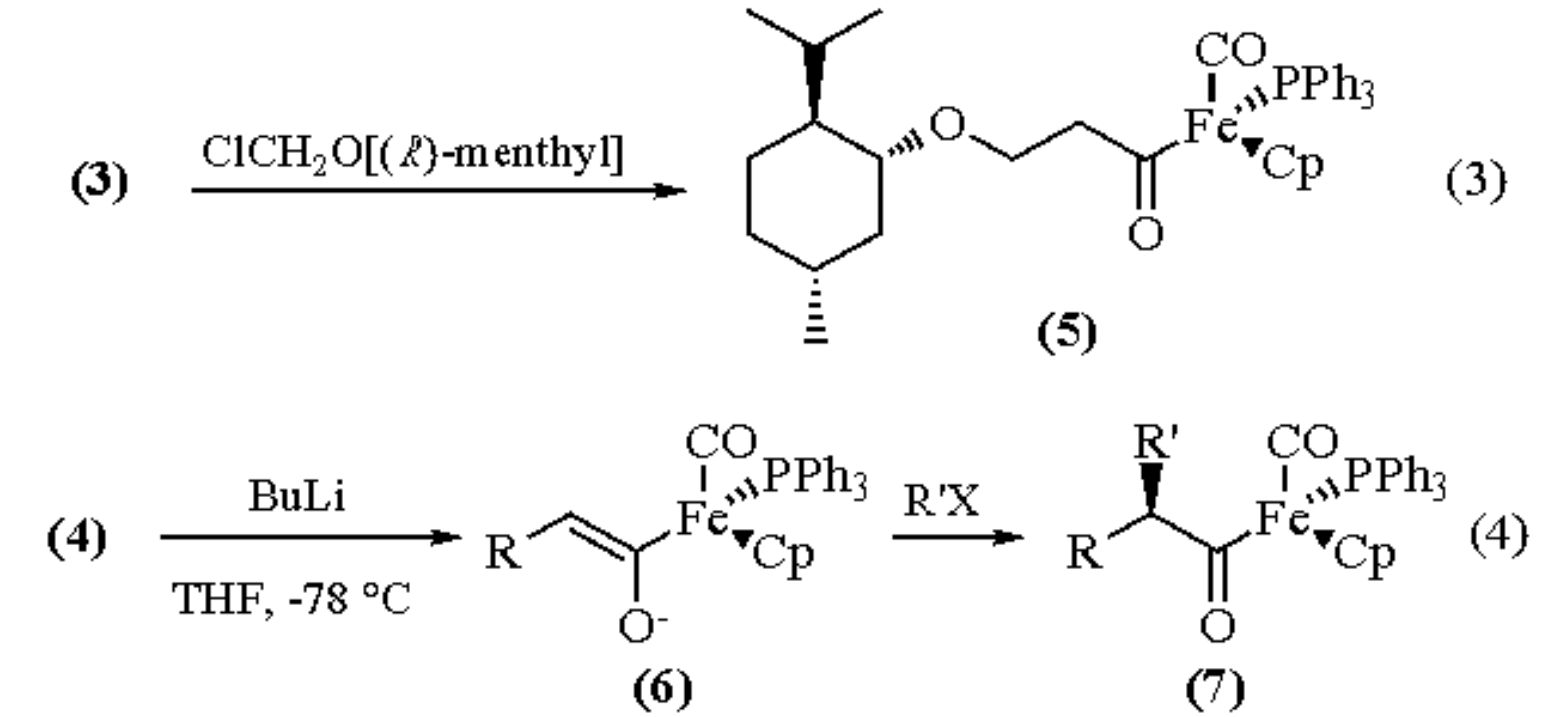

This sequential alkylation chemistry has been used to synthesize (-)-epicaptopril (**9**) (eq 5)[1b,9] as well as (*S*)-(+)-2-methylhept-4-ynoate (**10**), a key intermediate for the side chain of prostacyclin ZK96480 (eq 6).[10]

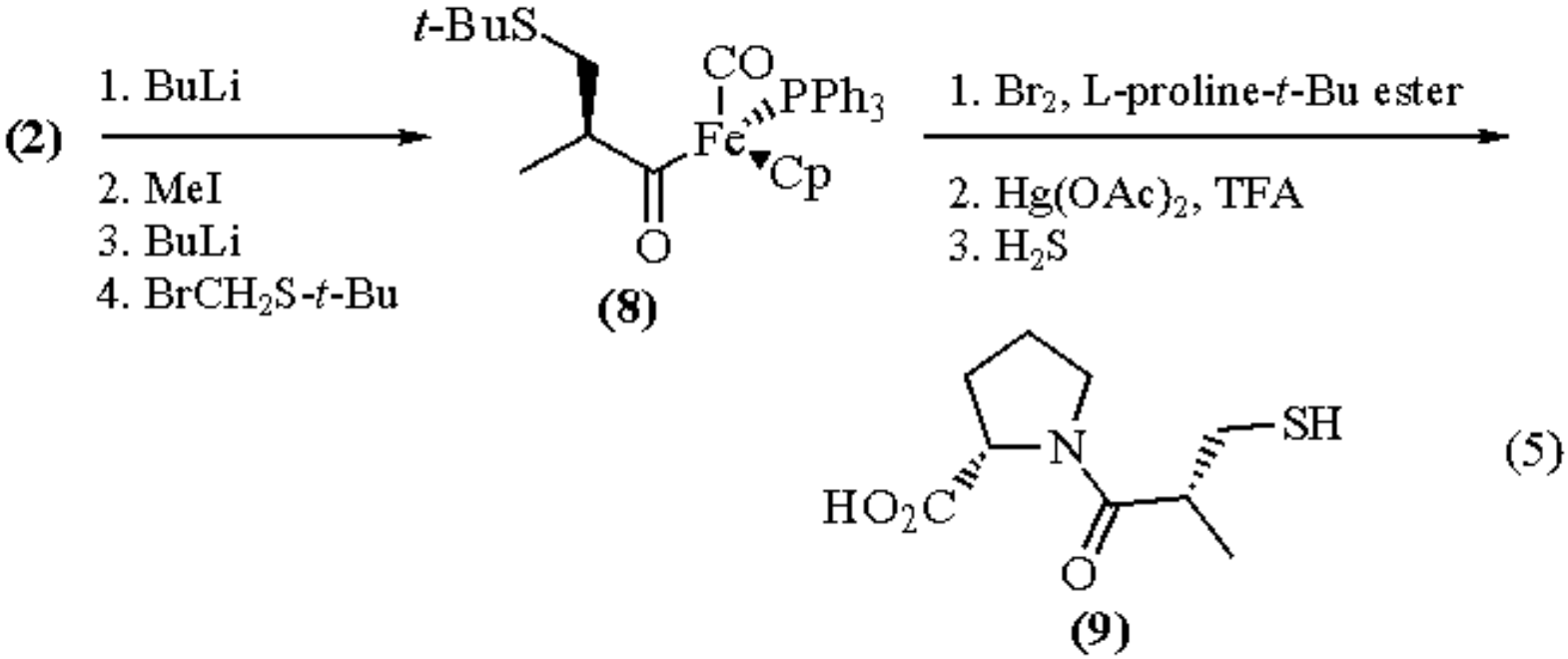

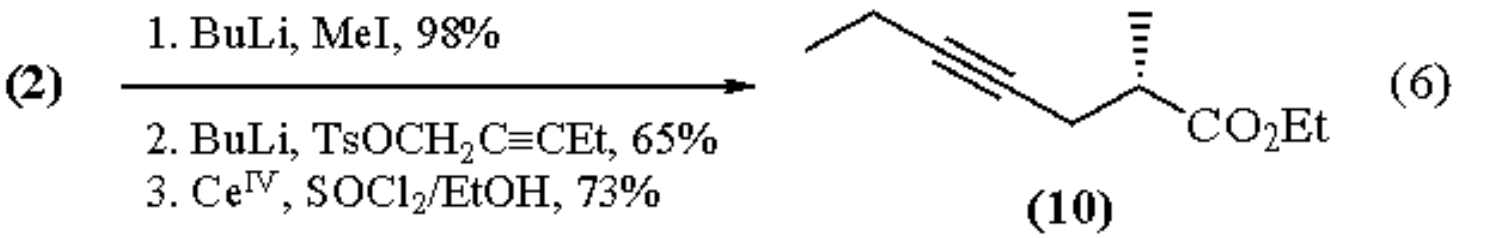

Related alkylation chemistry of (**2**) has provided a route to chiral succinic acid derivatives (**11**) (eq 7).[11] In this chemistry, acetyl complex (**2**) was used to produce a succinoyl complex which was subsequently deprotonated α to the ester and alkylated with primary and secondary alkyl halides. This sequence of reactions has been used to produce the succinate fragment of actinonin,[11a] as well as a variety of other succinic acid and amide derivatives.[11b,c]

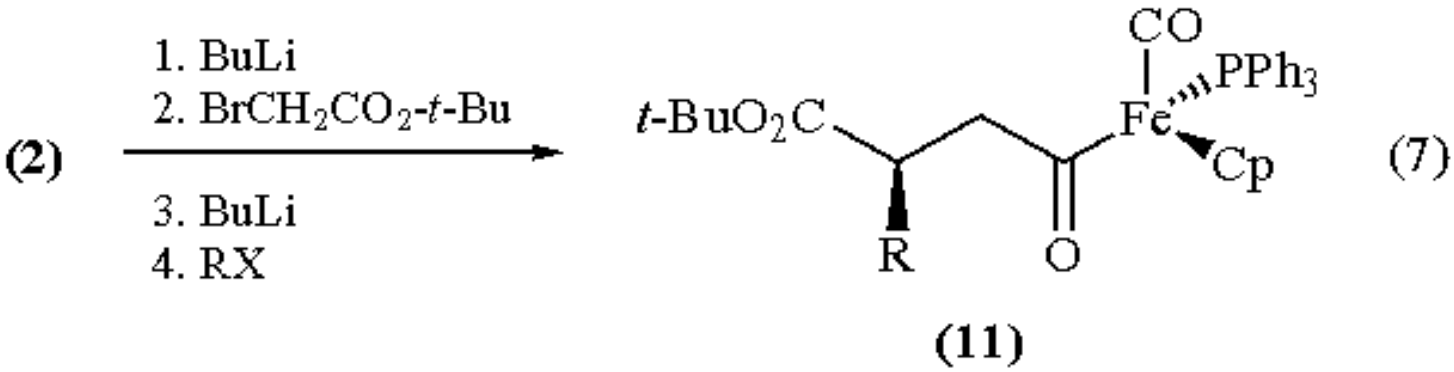

α-Oxidation of the enolate (**3**) has also been reported. Deprotonation of (**4**) (R = Me) followed by treatment with ***Diphenyl Disulfide*** generated a thioether complex which was oxidized to the sulfoxide and used in an asymmetric synthesis of sulfoxides.[12] Enolate (**3**) has also been trapped with MoOPH (***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)***) and benzylated to produce the α-benzyloxyacetyl complex.[13] Enolate generation from the α-benzyloxyacetyl followed by alkylation with two equivalents of racemic 1-phenylethyl bromide provided almost exclusively the alkylation product derived from reaction with (*S*)-1-phenylethyl bromide. This sequence demonstrated the power of the $CpFe(CO)(PPh_3)R$ fragment as a chiral recognition element. Recently, treatment of (**3**) with ***Chlorodiphenylphosphine*** has been shown to produce chiral phosphine (**12**) which was subsequently used as a ligand in the preparation of several palladium complexes (eq 8).[14]

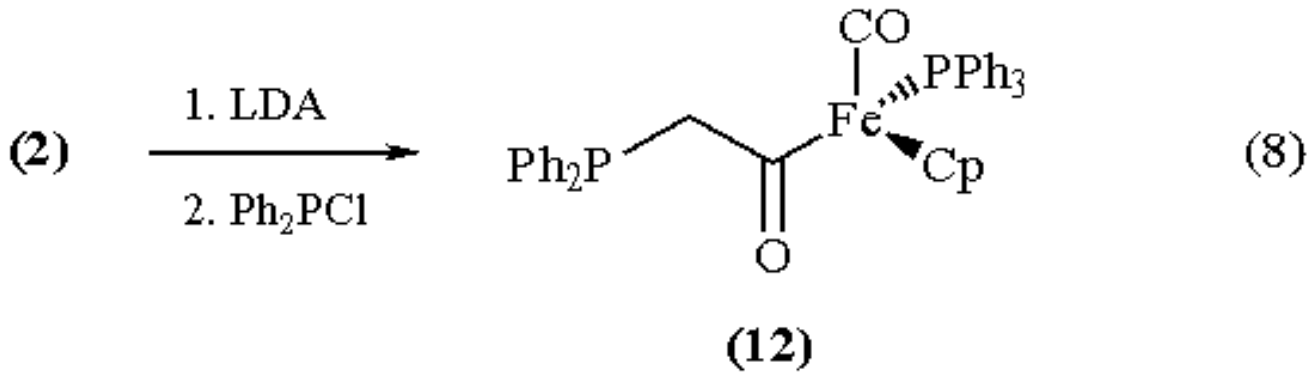

Aldol and Related Condensations.

The fact that the enolate of the racemic iron acetyl will participate in diastereoselective aldol condensations and that enolate counterions have a large effect on the diastereoselectivity of those reactions has been known for some time.[1] More recently, an alkylation/aldol sequence involving (**2**) was used to prepare complex (**13**) of known absolute configuration. Complex (**13**) was used to assign, by chemical correlation, the absolute configuration to a series of marine cyclic epoxides (eq 9).[15] Similar aldol chemistry followed by iron-carbon bond cleavage using ***Bromine*** has been used to prepare a series of optically active β-lactones (**15**)[16] including tetrahydrolipstatin (eq 10).[17]

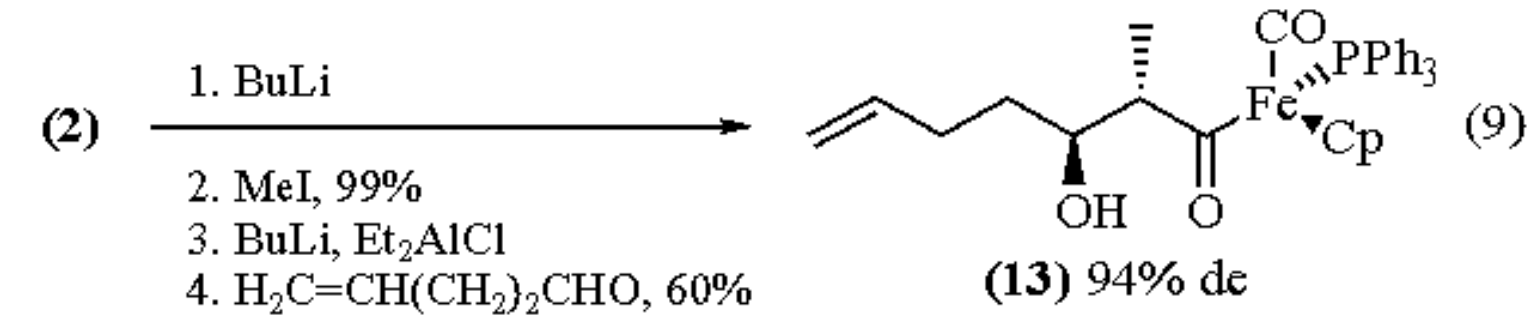

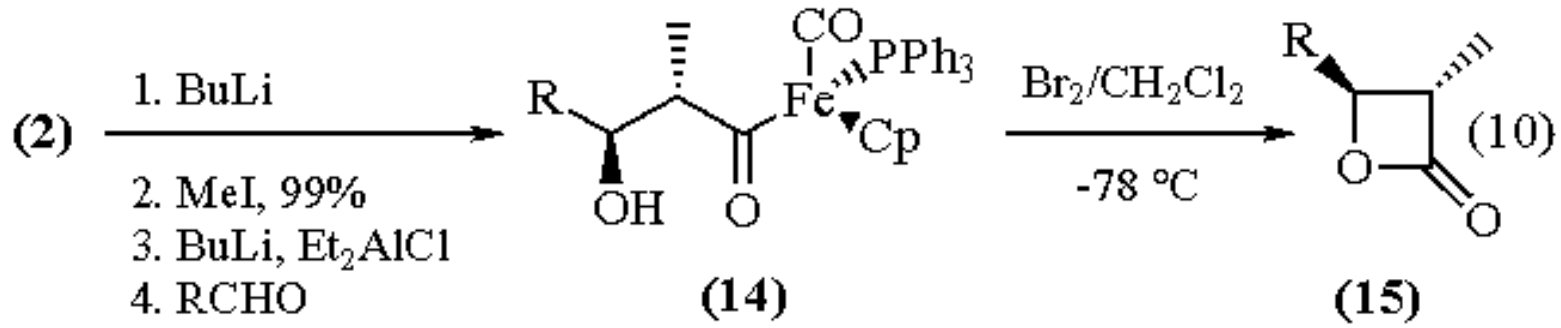

Examples of aldol condensations involving chiral aldehydes have also been reported. Condensation of the aluminum enolate derived from (**2**) with Boc-L-prolinal has been shown to proceed in a highly stereoselective manner and the iron chirality overpowered the latent stereoselectivity inherent in Boc-L-prolinal.[18] Subsequent deprotection and demetalation of (**16**) produced (-)-(1*R*,8*S*)-1-hydroxypyrrolizidin-3-one (**17**) (eq 11). Aldol condensation between the tin(II) and aluminum enolates derived from (**2**) and 2,3-isopropylidene-D-glyceraldehyde also proceeded with high stereoselectivity and the iron once again had the overwhelming directing effect on the stereochemical outcome of these condensations (eq 12).[19]

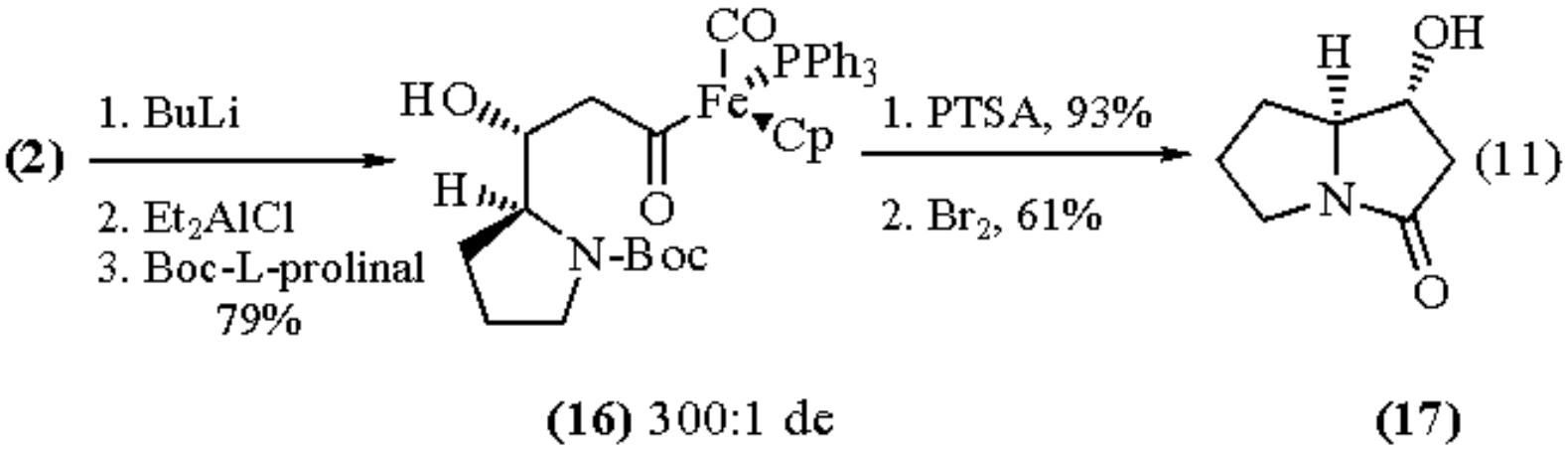

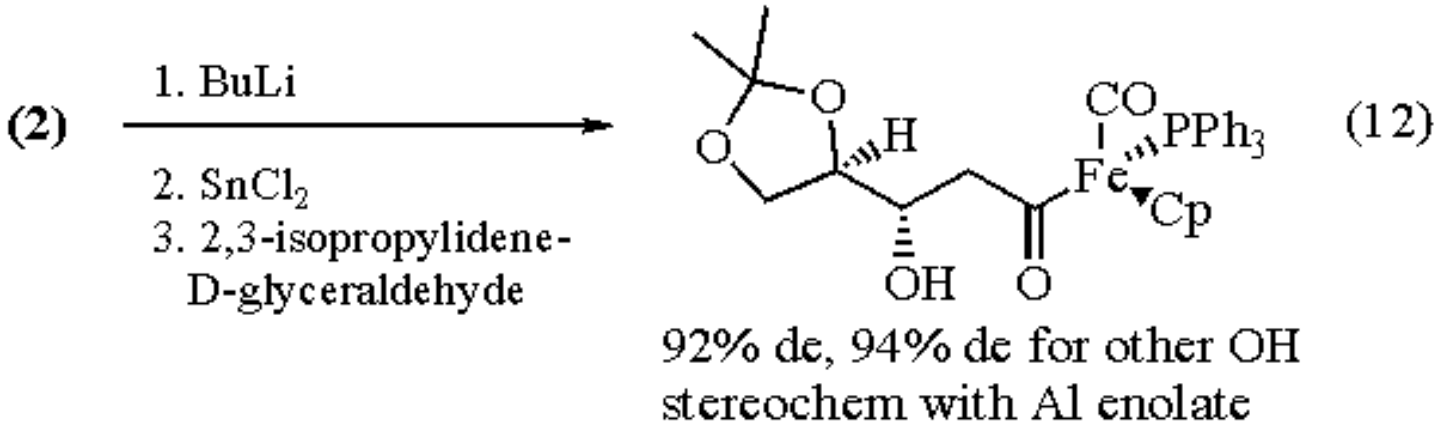

(12)

Synthesis and Reaction Chemistry of α,β-Unsaturated Acyl Complexes Derived from (2).

Two methods for the preparation of optically active (*E*)- and (*Z*)-α,β-unsaturated iron acyls from (**2**) have been reported.[1f] One method involves aldol condensation of (**2**) with aldehydes followed by *O*-methylation to produce diastereomeric acyls (**18**). This mixture (**18**) is then treated with ***Sodium Hydride*** to produce predominantly (*E*)-α,β-unsaturated acyl complexes (**19**) (eq 13).[20] Alternatively, (**2**) can be deprotonated and treated with ***Chlorotrimethylsilane*** to produce the *C*-silylated complex which is subsequently deprotonated and treated with an aldehyde.[1f,21] This Peterson alkenation produced mixtures of the isomers (*E*)-(**19**) and (*Z*)-(**20**) which could be separated via chromatography (eq 14). The (*Z*) isomers (**20**) with γ-protons are deprotonated when treated with strong bases and selectively alkylated α to the carbonyl.[1f] The (*E*) isomers and (*Z*) isomers without γ protons participate in stereoselective Michael additions and Michael addition/alkylation sequences.[1f,20-22] Most often this chemistry has been used to prepare optically active β-lactams and amides (**21**) and (**22**) (eqs 15 and 16).

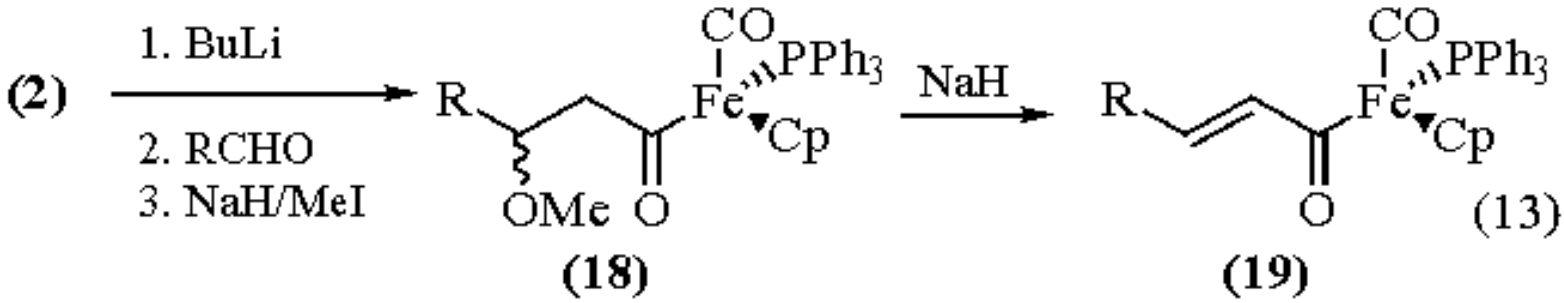

(13)

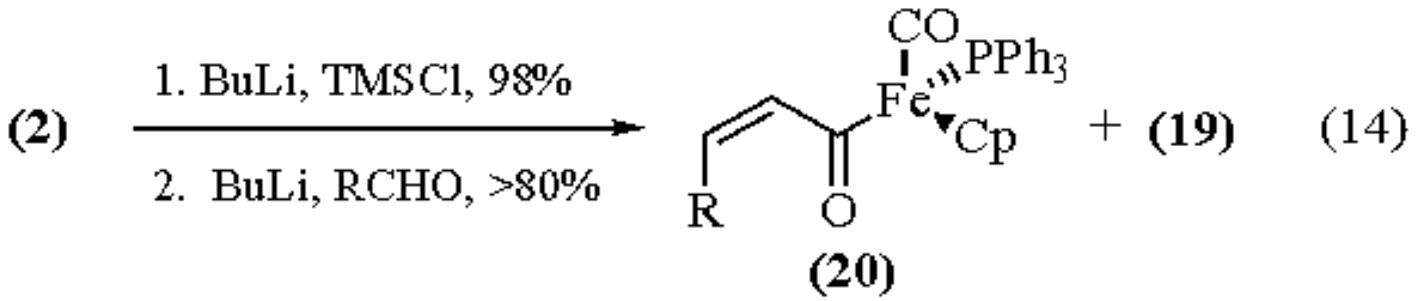

(14)

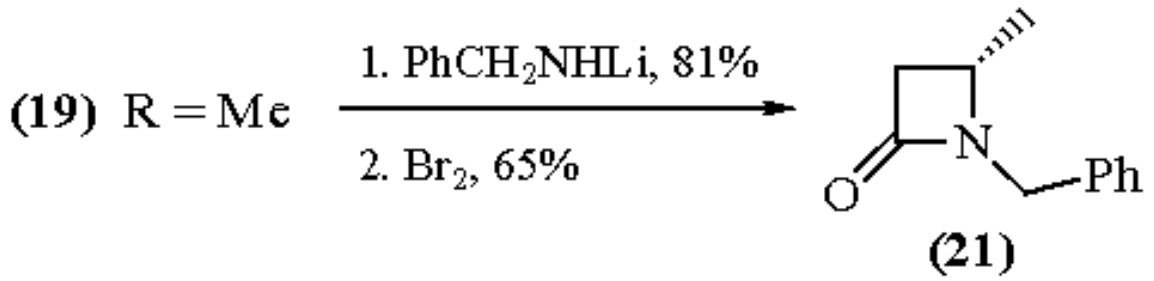

(15)

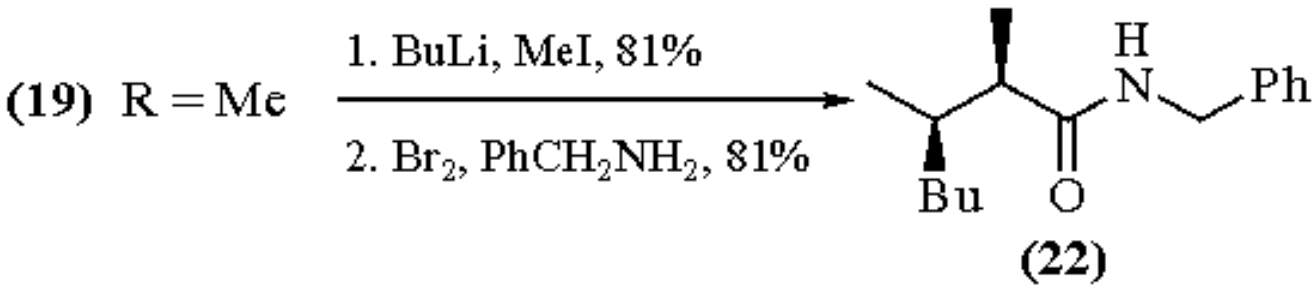

(16)

The (*E*)- and (*Z*)-α,β-unsaturated acyls (**19**) and (**20**) have also been methylenated as part of an asymmetric route to cyclopropanecarboxylic acid derivatives.[23] The acryloyl complex, which has been used in asymmetric Diels-Alder reactions[24] as well as a verapamil precursor synthesis,[25] has not been prepared in optically active form from (**2**), but can be prepared via an elimination reaction from (**5**).[24,25]

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Acetone

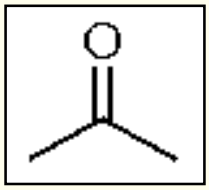

[67-64-1] · C_3H_6O · Acetone · (MW 58.08)

(widely used solvent; versatile synthetic reagent)

Alternate Name: 2-propanone.

Physical Data: mp -94 °C; bp 56.5 °C; *d* 0.788 g cm^{-3}; fp -18 °C.

Solubility: sol water, alcohol; miscible with most organic solvents.

Form Supplied in: colorless liquid, widely available.

Handling, Storage, and Precautions: slightly toxic; central nervous system depressant; highly flammable liquid; vapors may form explosive mixtures with air; reacts vigorously with strong oxidizing and reducing agents.

Protection of Diols.

Both 1,2- and 1,3-diols can be protected as acetonides by reaction with acetone (eq 1).[1] Acetonides are resistant to basic and nucleophilic reagents, and can be readily cleaved by aqueous acid.

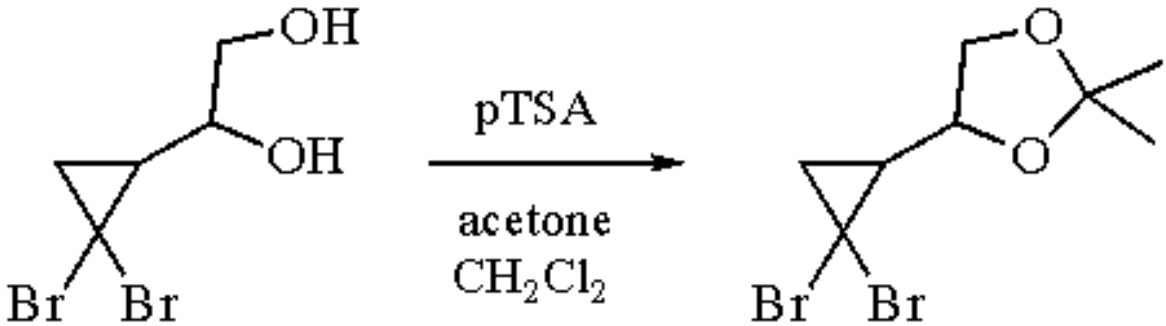

(1)

Ketene Formation.

Ketene can be prepared by distillation of acetone through a combustion tube packed with pieces of heated porcelain.[2] An improved method of ketene formation from acetone utilized a ketene lamp, which afforded an 80-90% yield of ketene from acetone.[3] Another method, which utilized a pyrolyzing coil, has been reported.[4]

Photochemical Alkylation.

Cyclic ethers undergo an acetone-initiated photochemical addition to terminal alkenes (eq 2).[5] The reaction can be photochemically induced without ketone initiation; however, the ketone-initiated reactions are faster and higher yields are obtained. The photosensitized amidation of aromatic substrates in acetone has been reported.[6]

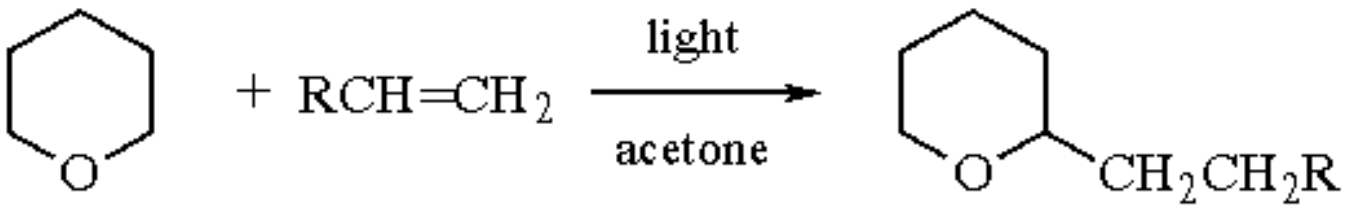

(2)

Oxidations.

Acetone is widely utilized as a solvent for the oxidation of trimethylsilyl ethers to ketones,[7] alcohols to ketones,[8] alcohols to acids,[9] alkynes to diones,[10] aldehydes to acids,[11] and alkynic carbinols to alkynic ketones.[8]

Solvent for the Formation of Alkyl Iodides.

Alkyl iodides can be prepared from chlorides and bromides by utilizing ***Sodium Iodide*** in acetone. The reaction (sometimes called the Finkelstein reaction) is an equilibrium which is driven by the precipitation of sodium chloride or sodium bromide.[12] This methodology has also been utilized to synthesize alkyl halides from sulfonates,[13] phosphinates,[14] and selenonates.[15]

Regeneration of Ketones.

Acetone undergoes an exchange reaction with tosylhydrazones to regenerate ketones in high yields (eq 3).[16] This mild method has been applied to the regeneration of ketones from oximes,[17] arylhydrazones,[17] and thiazolidines.[18]

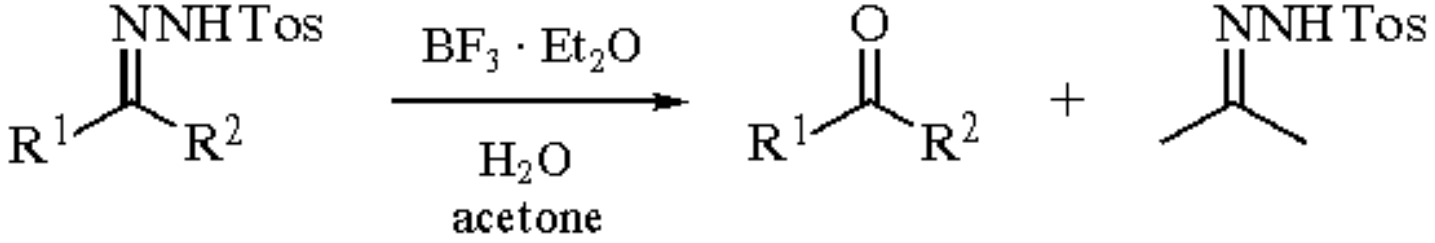

(3)

Related Reagents.

2,2-Dimethoxypropane; ***2-Methoxypropene***.

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Acetone Cyanohydrin

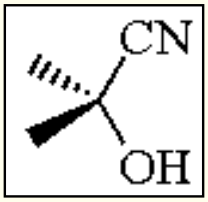

[75-86-5] · C_4H_7NO · Acetone Cyanohydrin · (MW 85.11)

(hydrogen cyanide source easier to handle and less toxic than HCN; transhydrocyanation; epoxide cleavage; formylation of arenes)

Physical Data: mp -19 °C; bp 82 °C/23 mmHg; bp 95 °C/760 mmHg; *d* 0.932 g cm^{-3}; *n*20D = 1.3992; fp 63 °C.

Solubility: freely sol water, usual organic solvents; insol petroleum ether, carbon disulfide.

Form Supplied in: light yellow liquid; widely available.

Analysis of Reagent Purity: IR: 3480 (s, OH); 2420 (w, CN); ^{1}H NMR: 1.65 (s, 6*H*); 3.68 (br, 1*H*).

Handling, Storage, and Precautions: use in a fume hood. Highly toxic and harmful liquid. May be fatal if inhaled, swallowed, or absorbed through skin (toxicity data: oral (rat) LD_{50} 0.17 g kg^{-1}; skin (rabbit) LD_{50} 17 mg kg^{-1}). Causes severe irritation, while high concentrations are extremely destructive to tissues of mucous membranes and upper respiratory tract, eyes, and skin. Symptoms of exposure may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, or even cyanosis. Keep tightly closed and away from heat and open flame. Store in cool and dry place; combustible. Incompatible with strong acids, strong bases, strong oxidizing agents, and strong reducing agents. Thermal decomposition may produce hydrogen cyanide, carbon monoxide, and carbon dioxide.

Transhydrocyanation (Cyanohydrin Formation).

Acetone cyanohydrin has long been known to interchange HCN with aldehydes or ketones to form their corresponding cyanohydrins.[1] The reaction is catalyzed by bases and the cyanohydrin product is subject to rapid racemization due to the reversible nature of the reaction.[2] However, subsequent acetylation of the cyanohydrin product with ***Isopropenyl Acetate*** acetate using a lipase from *Pseudomonas cepacia* (Amano) as catalyst furnishes preferentially the (*S*)-isomer (eq 1),[3] while the unreacted (*R*)-isomer is continuously racemized through reversible transhydrocyanation.

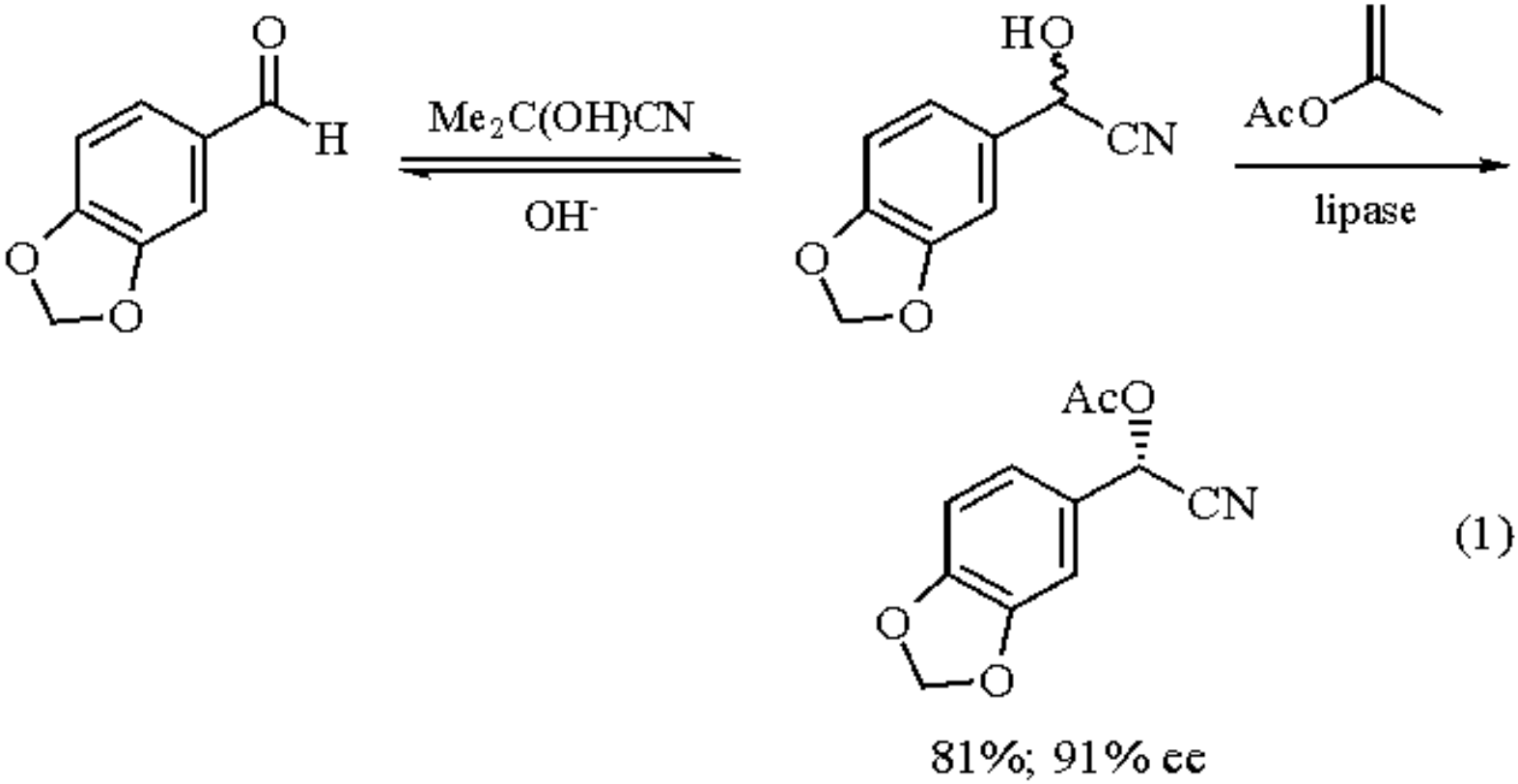

(1)

(*R*)-Cyanohydrins are obtained in high enantiomeric purity by a one-step biocatalyzed reaction of aromatic or aliphatic aldehydes with acetone cyanohydrin. In this case the use of powered almond meal provides an inexpensive catalyst which eliminates the need to purify and immobilize the enzyme, leading to products with high enantiomeric purity (eq 2).[4] Similar products are obtained using the flavoprotein D-oxynitrilase (EC 4.1.2.10) as catalyst.[5]

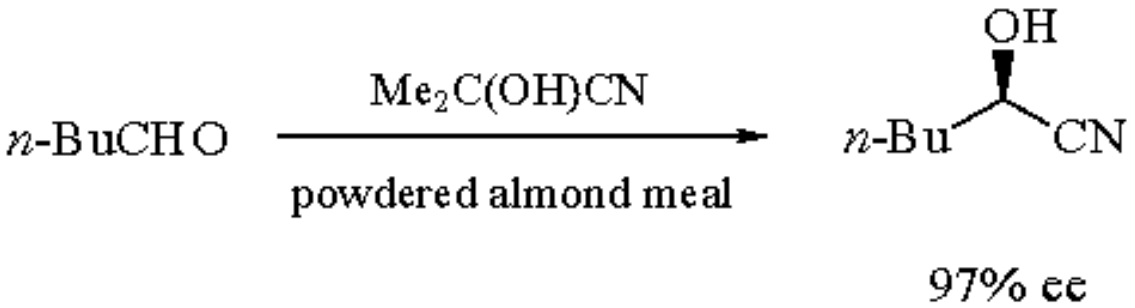

(2)

Cyanohydrins of steroid ketones are prepared by HCN exchange with acetone cyanohydrin without the presence of a catalyst, since the product precipitates from solution. Thus the 17-monocyanohydrins of steroidal 3,17-diones are prepared in practically quantitative yield (eq 3).[6] Similarly, α-silyloxynitriles are prepared from *O*-trimethylsilylated acetone cyanohydrin by transcyanosilylation[7] in the presence of ***Potassium Cyanide*** and ***18-Crown-6***.

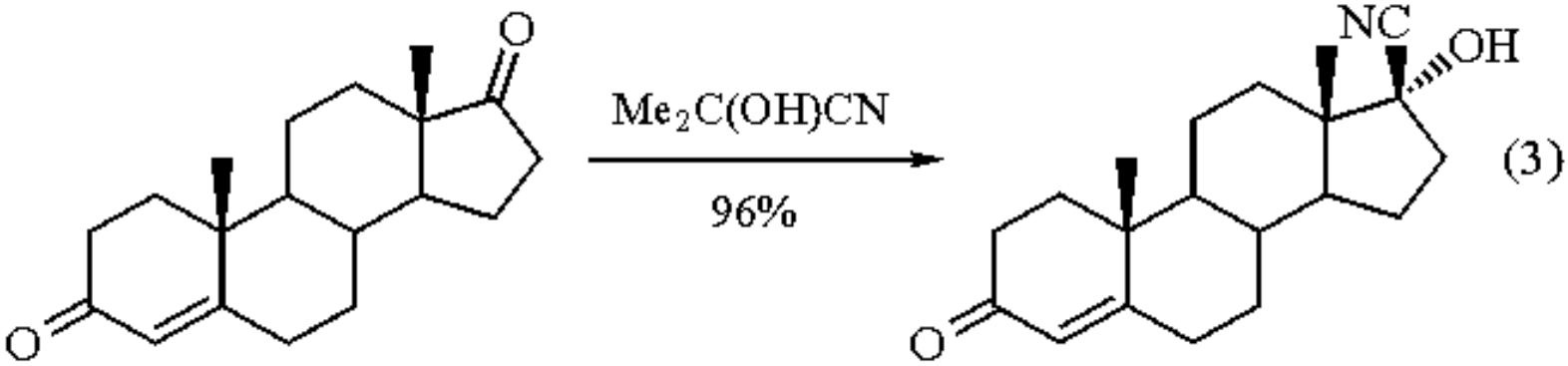

Hydrogen Cyanide Addition.

Acetone cyanohydrin is used as a ***Hydrogen Cyanide*** source which is easier to handle and less toxic than HCN.[1,8] Thus the Michael addition of HCN to α,β-unsaturated ketones is achieved by an exchange with acetone cyanohydrin in 10% aq Na_2CO_3. This reaction is found to proceed in excellent yield with chalcones[9] or steroid ketones.[10] Similar addition with high stereoselectivity using acetone cyanohydrin in conjunction with naked cyanide ions (KCN in nonpolar aprotic solvent containing 18-crown-6) has also been reported (eq 4).[11] On the other hand, addition of HCN to aldimines using acetone cyanohydrin furnishes α-aminonitriles (eq 5).[12]

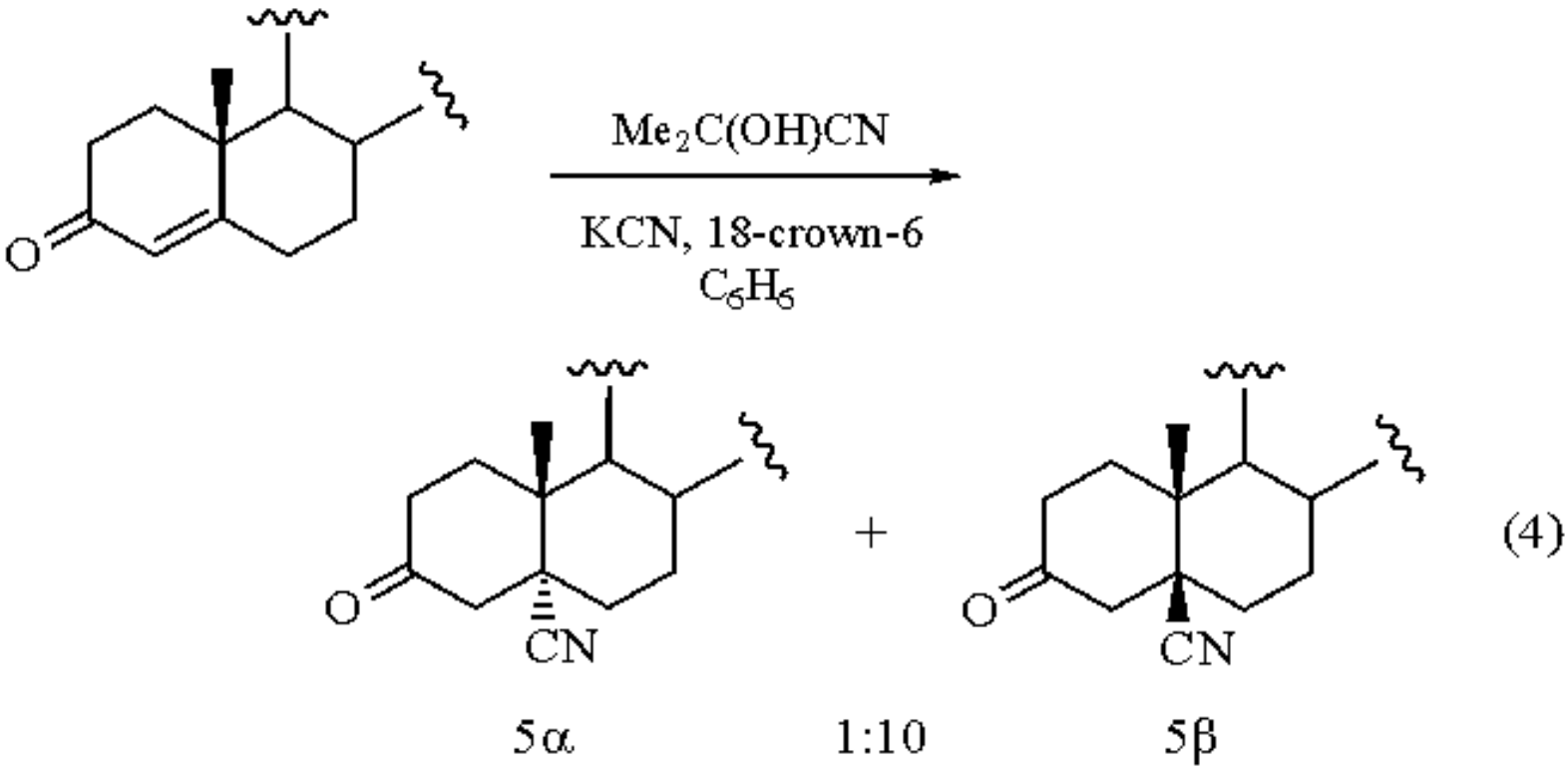

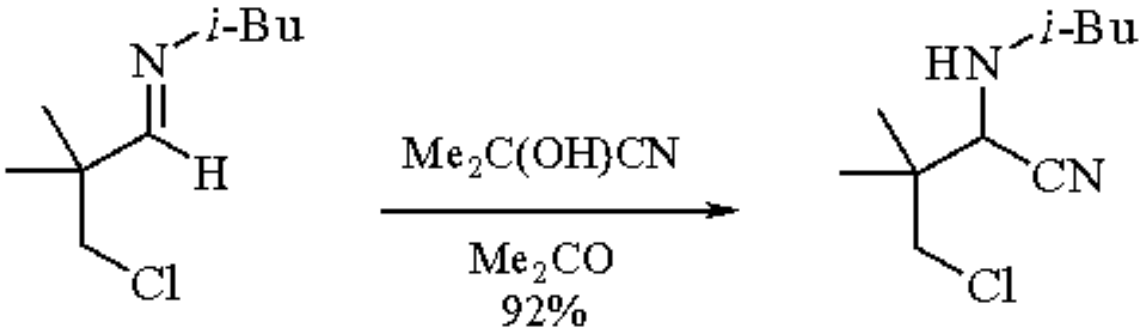

(5)

Ring Opening.

Acetone cyanohydrin with stoichiometric ***Triethylamine*** opens 1,2-epoxides regiospecifically to give β-hydroxynitriles. The addition of cyanide occurs at the least substituted carbon (eq 6).[13] The same conditions are applied for the cyclopropane ring opening of methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate in almost quantitative yields.[14]

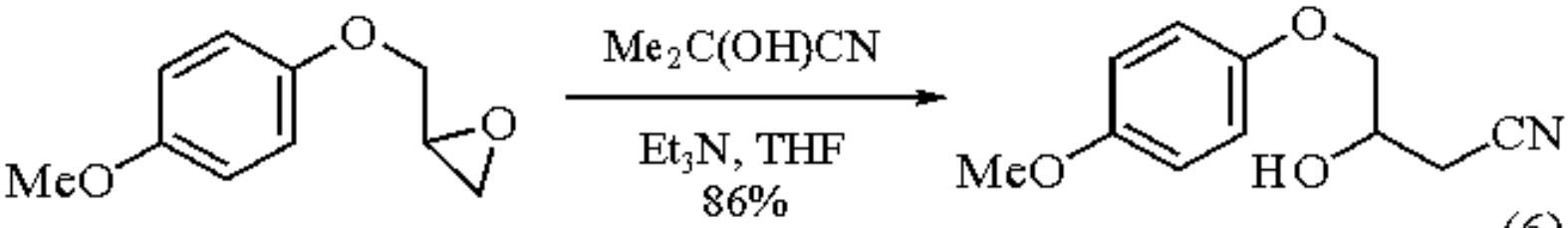

(6)

Aromatic Formylation.

Acetone cyanohydrin has been proposed as an easy-to-handle formylation reagent for arenes, thus replacing the hazardous hydrogen cyanide in the Gatterman reaction (eq 7).[15]

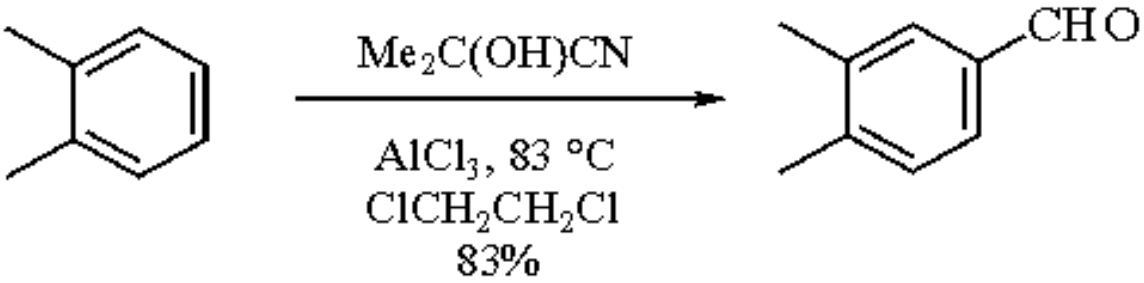

(7)

Acetone Cyanohydrin Nitrate.

Caution: moderately explosive, bp 65-66 °C/10 mmHg. Prepared by nitration of acetone cyanohydrin with fuming ***Nitric Acid*** and ***Acetic Anhydride*** (eq 8),[16] this reagent is unique for the conversion of amines to nitramines under alkaline conditions. Thus primary nitramines are obtained in 50-60% yield, while aliphatic and alicyclic secondary nitramines are produced in yields varying from 55-80% (eq 8).[17] The reagent is also useful for the nitration of a variety of active methylene compounds (in the form of their sodio derivatives), providing a general route for the

synthesis of α-nitro esters (eq 9).[18]

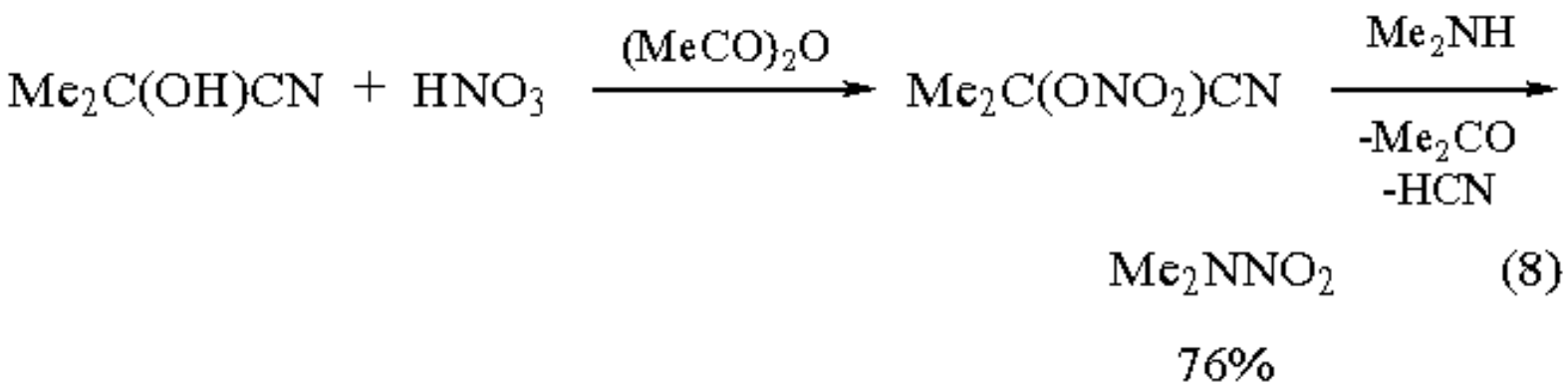

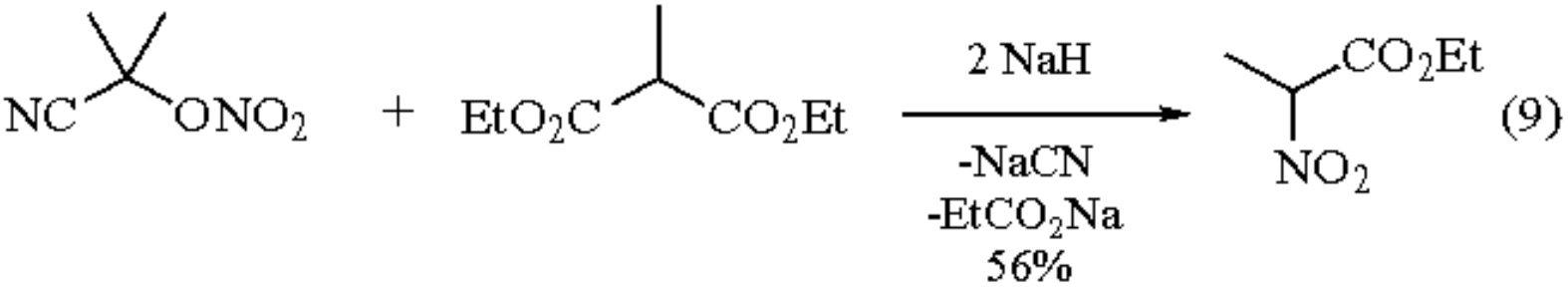

Related Reagents.

t-Butyldimethylsilyl Cyanide; ***Cyanotrimethylsilane***; ***Diethylaluminum Cyanide***; ***Hydrogen Cyanide***; ***Potassium Cyanide***; ***Sodium Cyanide***; ***Tetraethylammonium Cyanide***; ***Zinc Cyanide***.

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18. Emmons, W. D.; Freeman, J. P. *JACS* **1955**, *77*, 4391.

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Acetone Cyclohexylimine

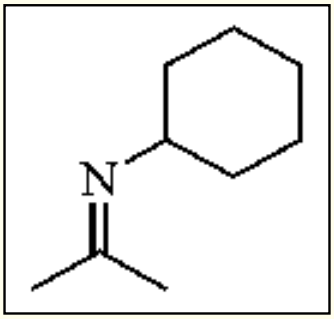

[6407-36-9] · $C_9H_{17}N$ · Acetone Cyclohexylimine · (MW 139.24)

(acetonyl equivalent via lithiation and reaction with electrophiles;[1] mild directed aldol condensation;[2] Pd-catalyzed α-arylation of ketones[3])

Alternate Name: N-(2-propylidene)cyclohexylamine.

Physical Data: bp 180.6 °C,[4] 70-72 °C/16 mmHg,[5] 30 °C/1.8 mmHg;[6] *n*20D 1.4671.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: GC; ^{1}H NMR; IR (presence of ketone by hydrolysis).

Preparative Methods: condensation of ***Acetone*** with cyclohexylamine with or without various solvents (eq 1).[4-7] The removal of water is performed afterwards with solid ***Sodium Hydroxide***.[4]

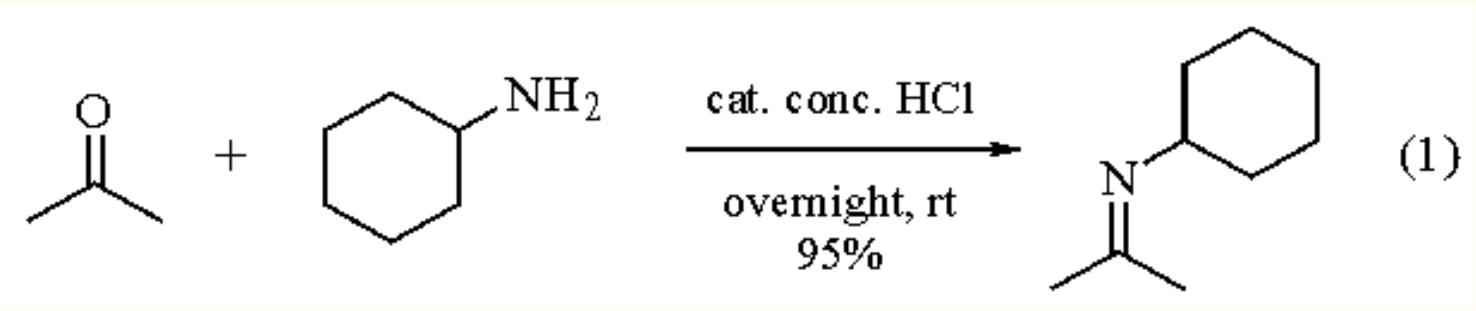

Handling, Storage, and Precautions: very sensitive to hydrolysis; storage in closed vessels under inert atmosphere in the refrigerator. It is recommended to prepare the reagent freshly before each preparation. After some weeks of storage, purification by distillation is recommended. Use in a fume hood.

Introduction.

Acetone cyclohexylimine is the most frequently used acetone imine. Some attention will be given to the *N*-isopropyl analog, while lower alkyl derivatives, e.g. acetone methylimine, are too labile for general use.

Introduction of Acetonyl Group.

In general, most enolates have to be kept and reacted at -78 °C or lower in order to obtain useful results, as otherwise self-condensation reactions and nonselective reactions take place. This disadvantage can be circumvented by working with imines instead of ketones.[2,8] Imines derived from acetone and methylamine or ethylamine are difficult to handle, while the relatively stable *N*-cyclohexylimine derived from acetone offers no problems in handling.[2] One inconvenience is certainly the more complex NMR spectra of the reaction products. Since the desired end-products are usually carbonyl compounds, formed by acidic hydrolysis of these imines, the *N*-cyclohexyl group is only a temporary disadvantage. The most common use of acetone cyclohexylimine is their conversion into their nucleophilic lithiated salts, i.e. 1-azaallylic anions (metalloenamines), which are much more stable than enolates and which do not suffer from proton transfer during further reactions with electrophiles. Acetone cyclohexylimine is readily deprotonated by ***Lithium Diethylamide*** (mostly in benzene-HMPA),[1] ***Lithium Diisopropylamide*** (in ether or THF),[2] or ***n-Butyllithium*** (in THF) (eq 2).[9] Less frequently used deprotonating agents are ***Potassium-Graphite***[10] or ***Potassium on Alumina***.[11]

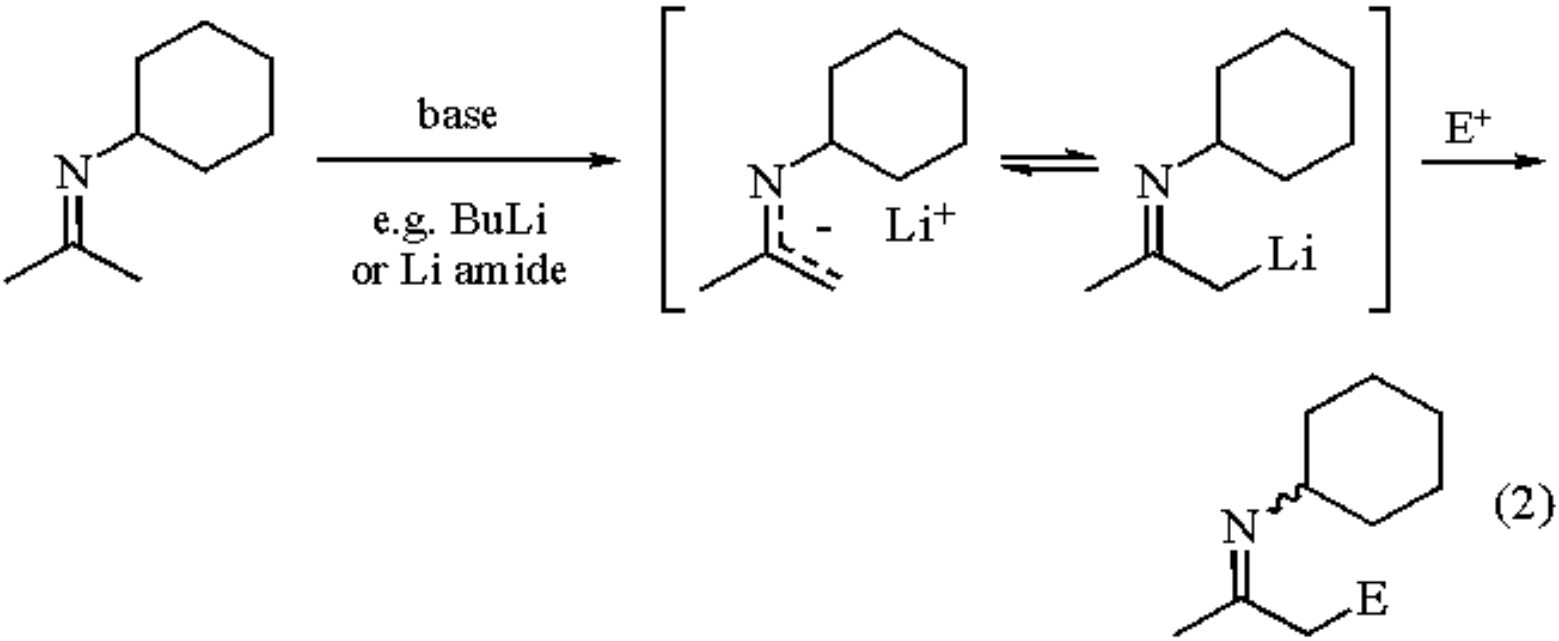

(2)

The deprotonation is usually followed by the reaction with an electrophile (E^+), affording the α-substituted ketimine (eq 2). Lithiation of imines has *syn* selectivity (eq 3; the formula represents a gross structure, not indicating the definitive position of the Li counterion).[12,13]

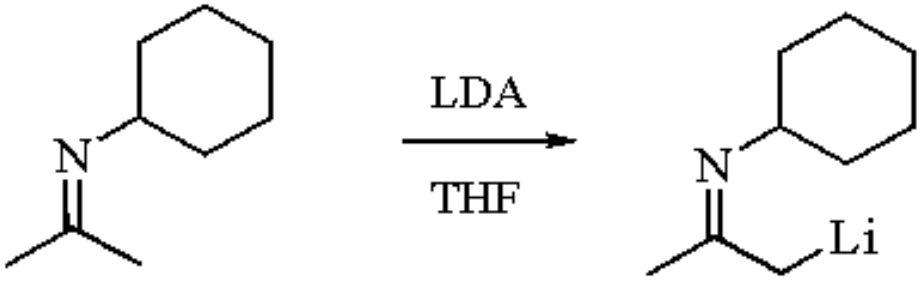

(3)

Lithiated acetone cyclohexylimine reacts smoothly with alkyl and allyl halides to form the α-alkylated or α-allylated imines, which are readily hydrolyzed by aqueous acid to afford the corresponding acetonylated compounds (eq 4).[1] Higher analogs, e.g. 2-butanone *N*-cyclohexylimine, after deprotonation, react regiospecifically with electrophiles at the methyl group.[1] Double alkylations of acetone cyclohexylimine at the α- and α´-position and subsequent hydrolysis into α,α´-dialkylated acetones have been reported (eq 5).[1] In a similar way, o-halo ketones (eq 6),[1,14] γ,δ-unsaturated-γ-halo ketones (eq 7),[1a] 1,4-diones (eq 7),[1a] γ,δ-unsaturated-δ-halo ketones,[1b] and 1,5-diones[1b] are accessible.

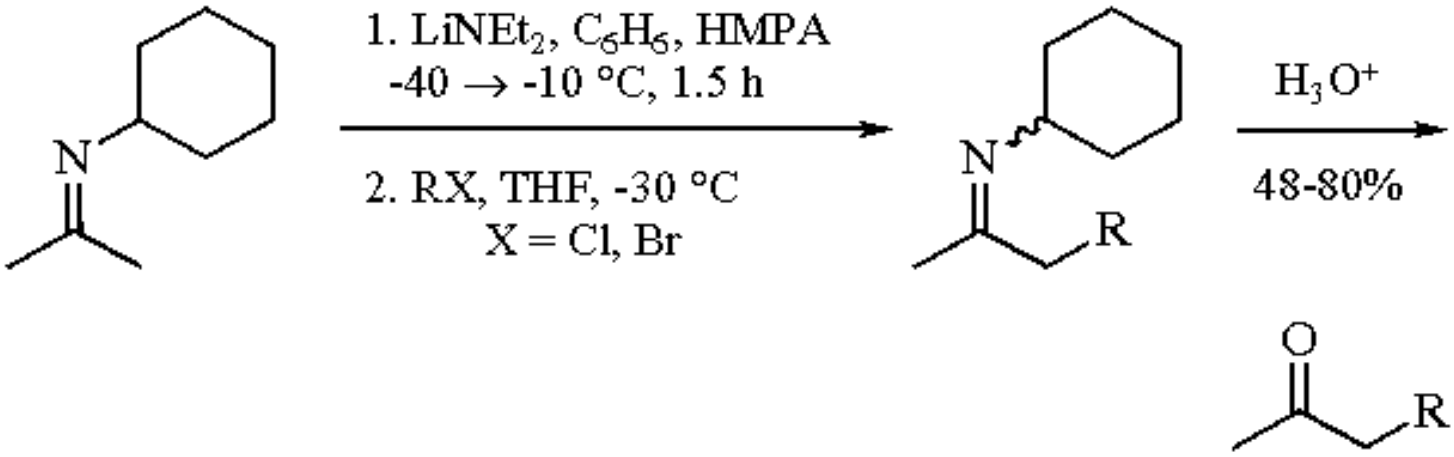

(4)

R = *n*-C_8H_{17} (X = Cl); R = *n*-C_7H_{15} (X = Br)
R = $Me_2CHCH_2CH_2$ (X = Br); R = CH_2CH_2Ph (X = Br)
R = $CH_2{=}C(Me)CH_2$ (X = Cl); R = $CH_2{=}CHCH_2$ (X = Br)
R = $MeCH{=}CHCH_2$ (X = Br)

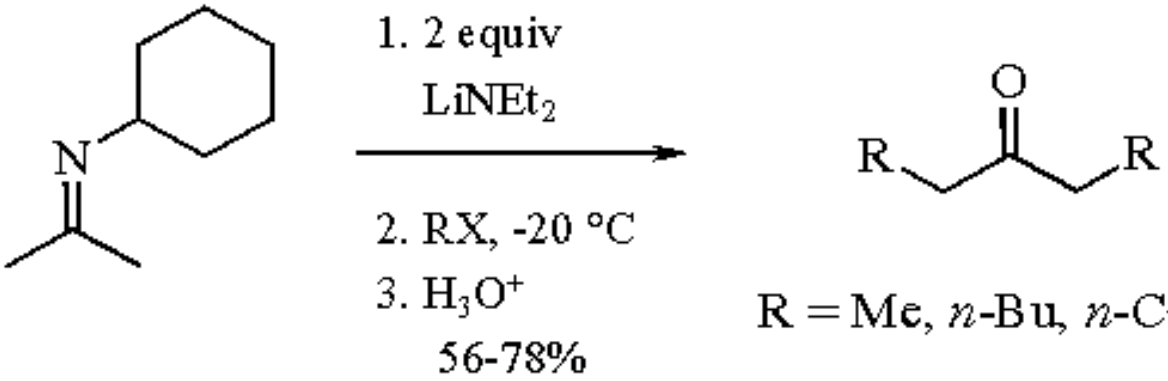

(5)

R = Me, *n*-Bu, *n*-C_7H_{15}

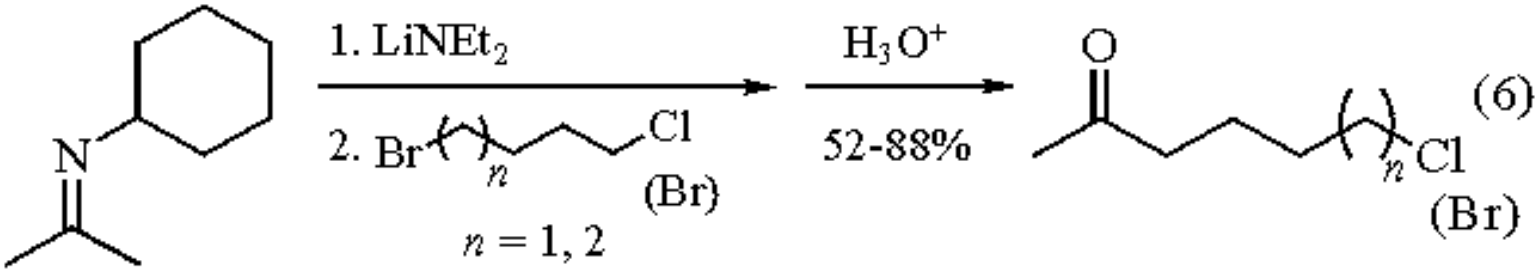

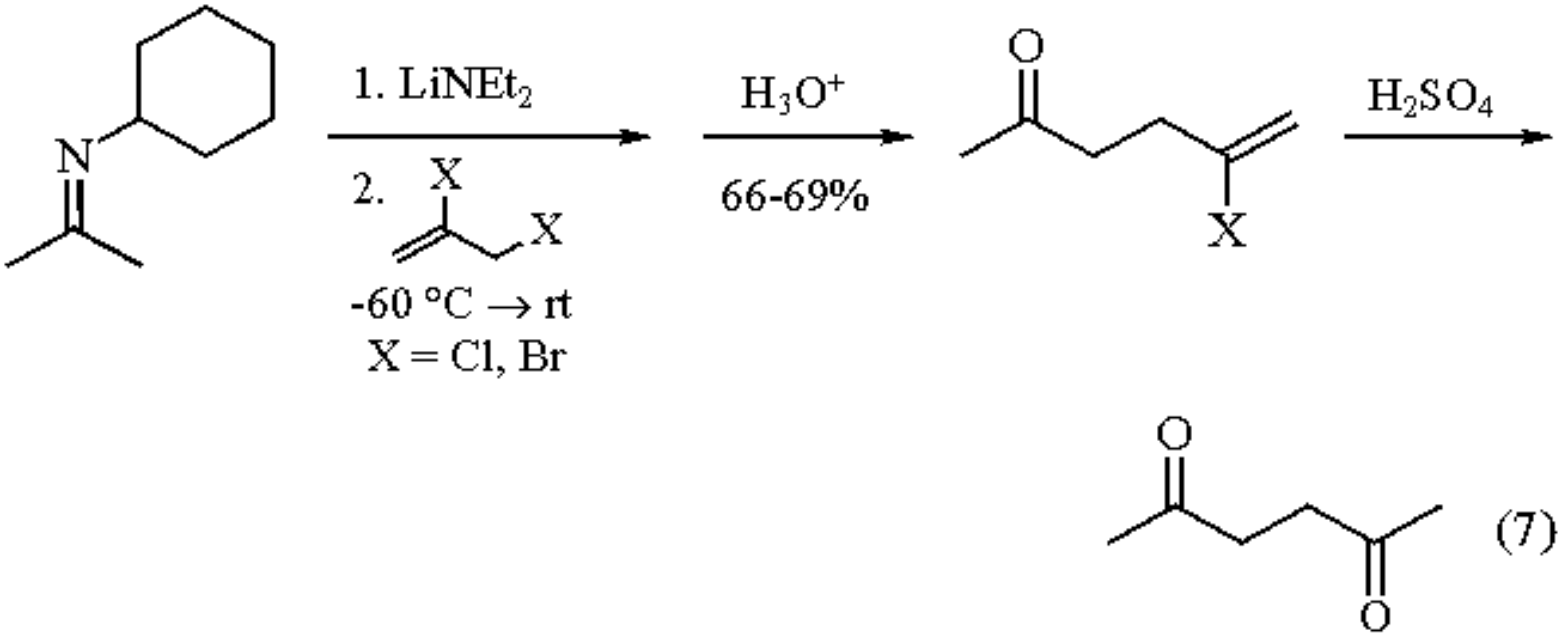

1-Azaallylic anions have been utilized for the synthesis of dihydrojasmone (eq 8),[1a,29] geranylacetone,[15] *cis*-jasmone,[29] and other functionalized 2-alkanones.[16] Similar α-alkylations have been performed with aldimines.[17-19]

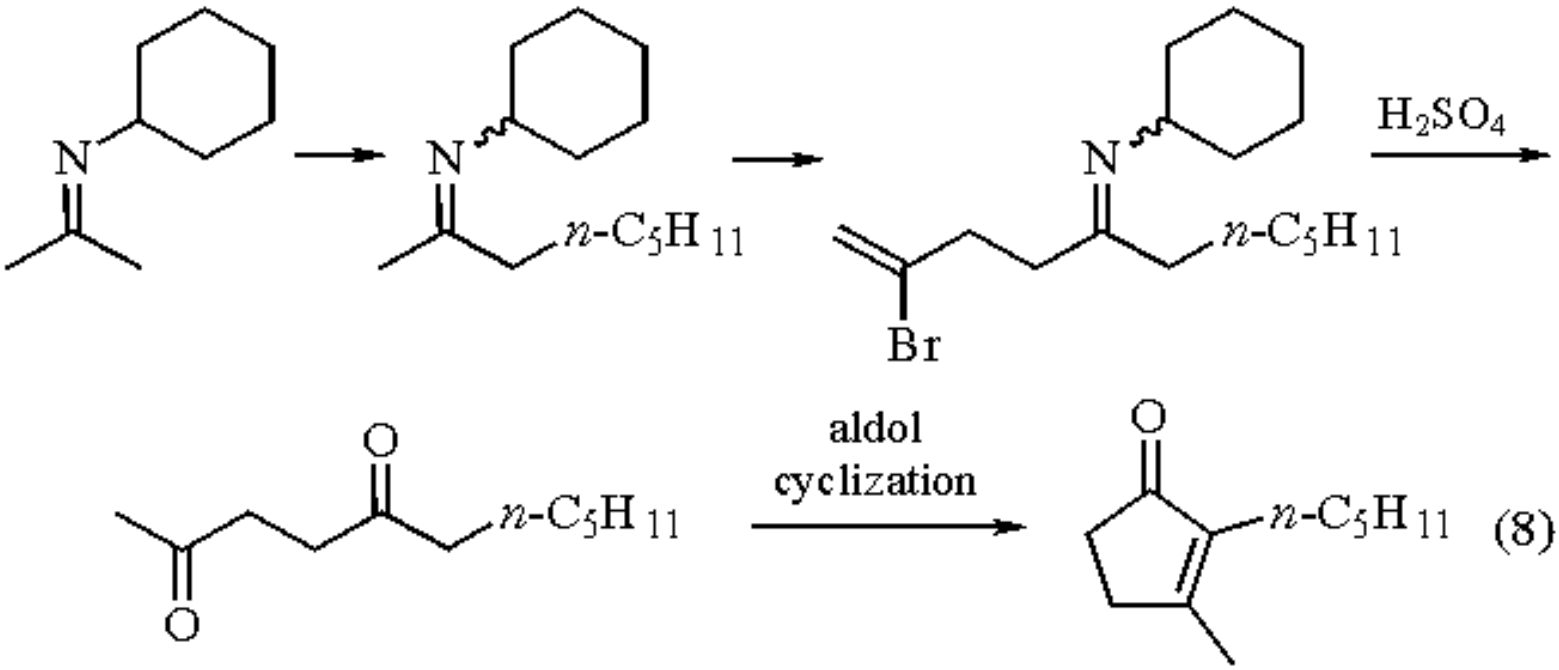

The use of potassium-graphite (C_8K) in THF[10] or highly dispersed potassium on alumina in THF[11] at room temperature is an alternative method for the lithiation of acetone cyclohexylimine, but the alkylated acetones are obtained in moderate to low yields (eqs 9 and 10). Better yields of acetonylation products are obtained by lithiation of acetone *N*-isopropylamine with ***Lithium*** in THF in the presence of graphite[30] or phenanthrene[31] as hydrogen acceptor, followed by reaction of the lithio salt with electrophiles, e.g. iodobutane, to afford α-monoalkylated acetones after acidic hydrolysis.

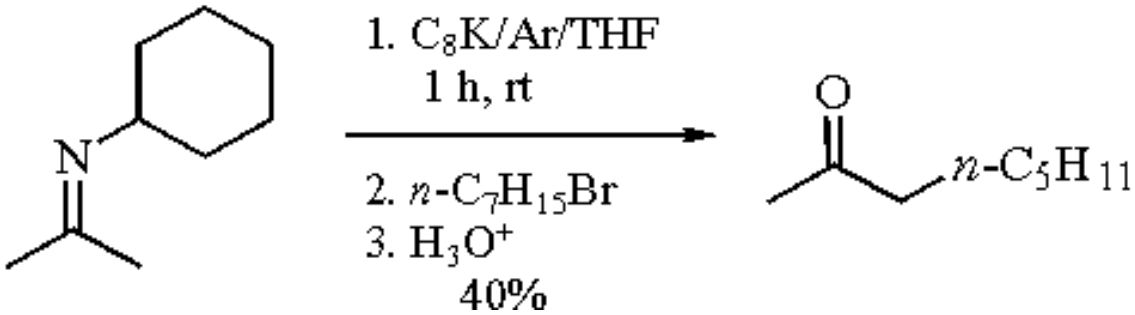

(9)

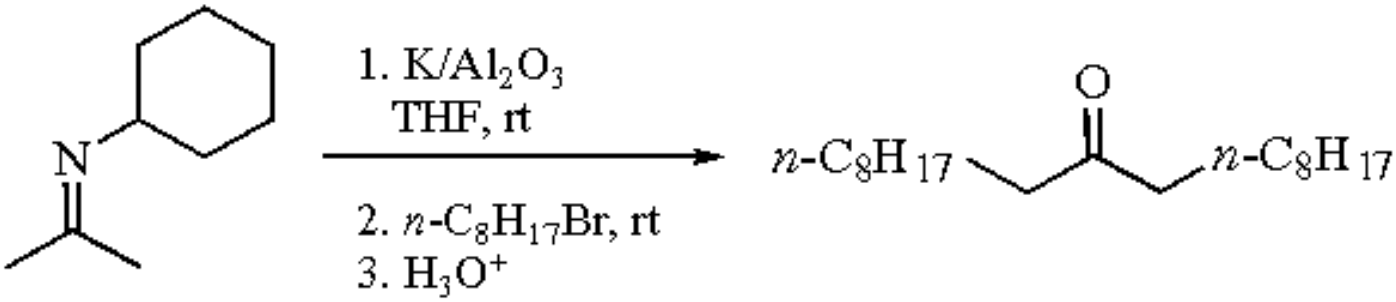

(10)

Directed Aldol Condensation.

Lithiated acetone cyclohexylimine reacts with benzophenone to afford the corresponding isolable β-hydroxy ketimine, which undergoes hydrolysis and dehydration on treatment with aqueous sulfuric acid, while the ketol is obtained under milder hydrolytic conditions using silica gel and water (eq 11).[20] Similar condensations of lithiated acetone cyclohexylimine with benzonitrile or ethyl chloroformate afforded a β-amino-α,β-unsaturated imine[21] or an enamino ester,[2] respectively (eqs 12 and 13).

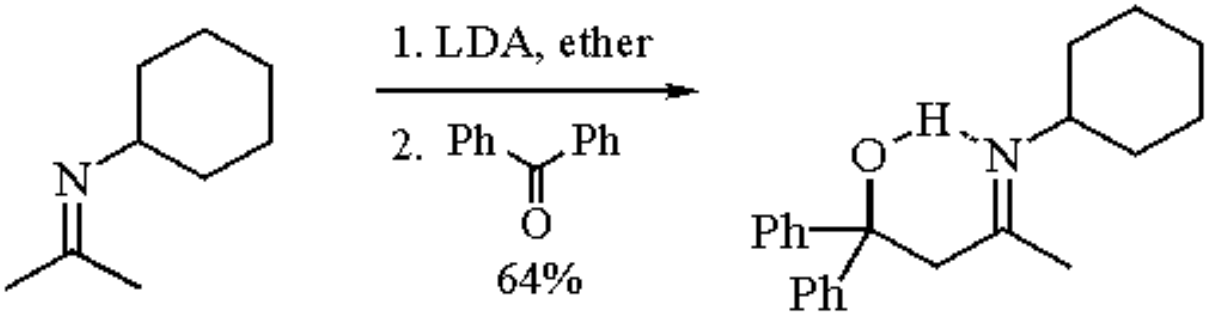

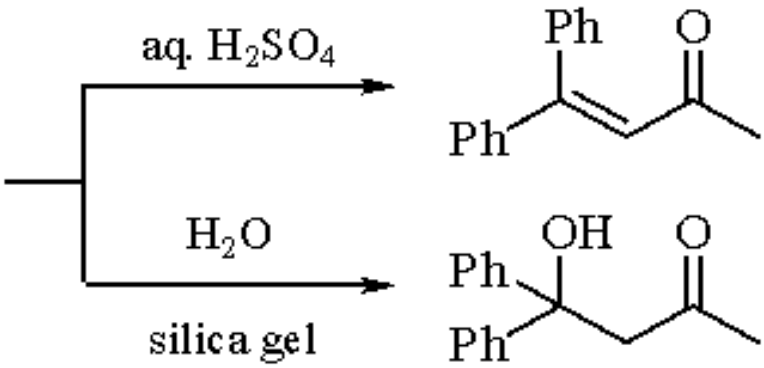

(11)

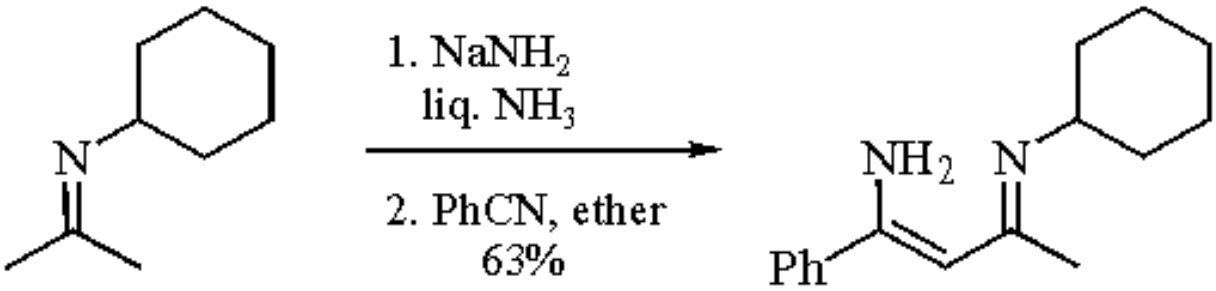

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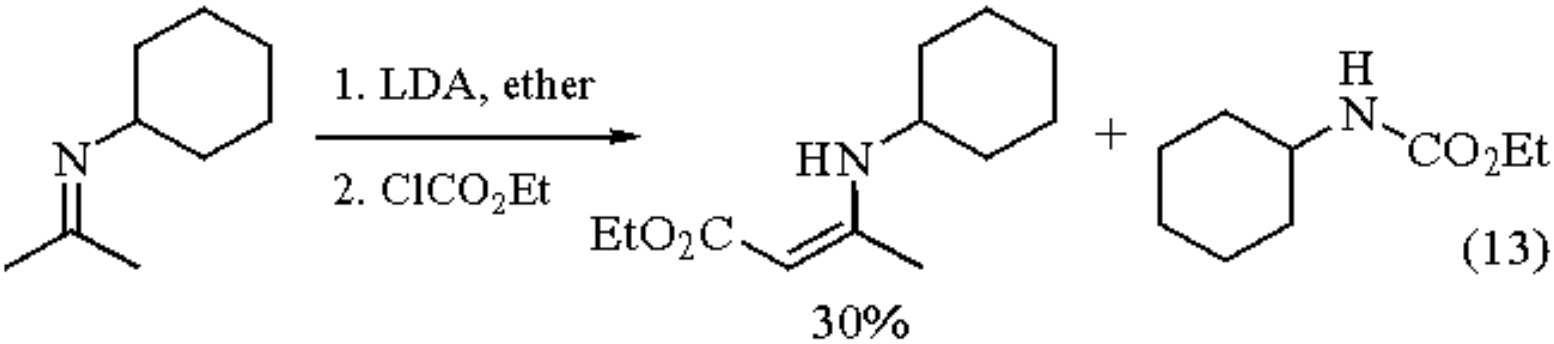

(13)

Palladium-Catalyzed Arylation.

Condensation of acetone cyclohexylimine with bromobenzene in the presence of sodium *t*-butoxide, ***Palladium(II) Acetylacetonate***, and tris(*N*-cyclohexyl-*N*-methylamino)phosphine in THF is reported to afford phenylacetone after hydrolysis (eq 14).[3]

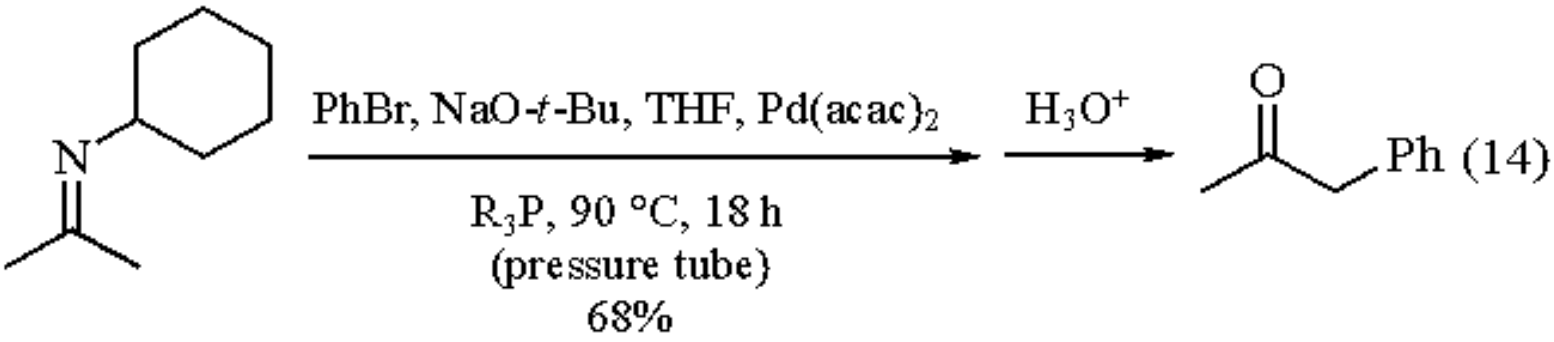

Reactions of 1-Azaallyl Anions with Michael Acceptors.

Lithiated acetone cyclohexylimine reacts with α-methylthiovinyl sulfoxides to give the Michael adducts, which are suitable precursors for γ-keto aldehydes (eq 15).[22]

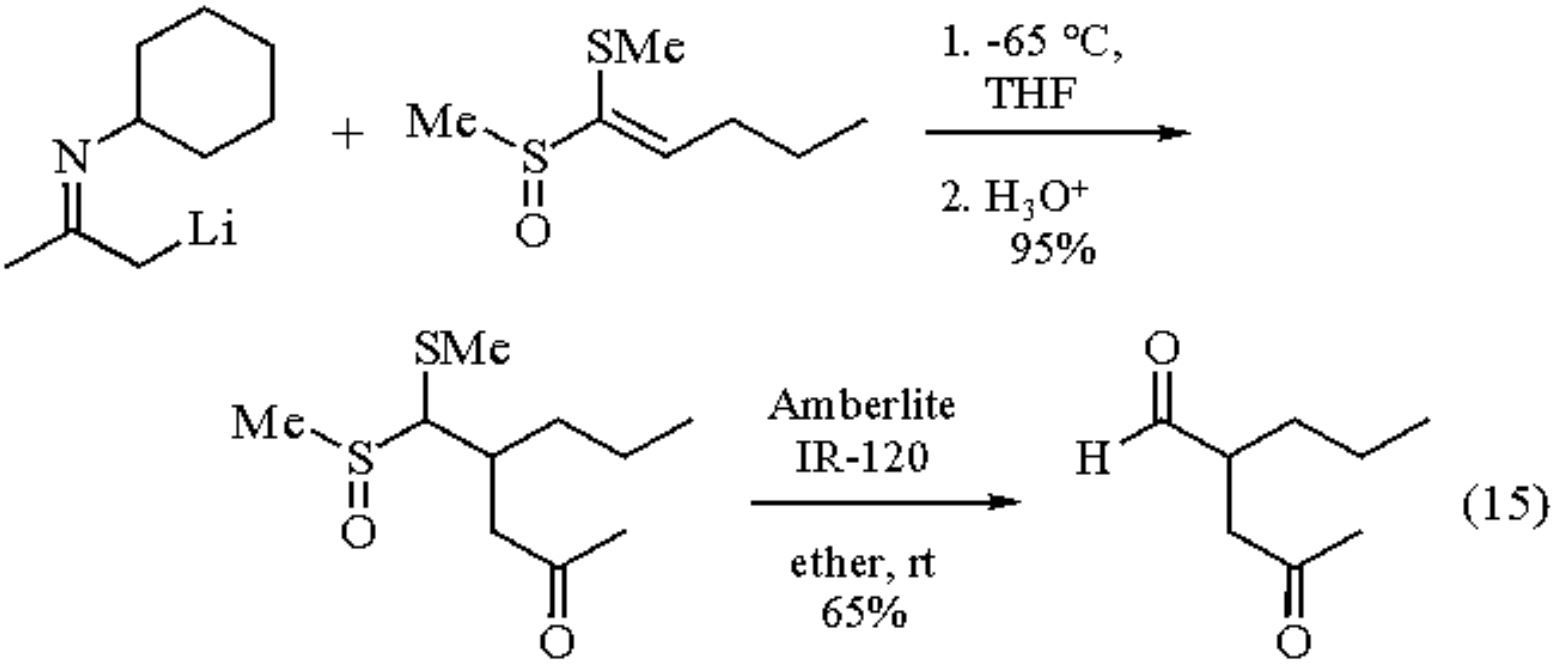

Lithiation of acetone cyclohexylimine and further treatment with ***Copper(I) Iodide*** produces a copper azaallyl species which undergoes Michael addition to 2-methyl-2-cyclopentenone, the resulting adduct being trapped by ***Chlorotrimethylsilane*** (eq 16).[9] However, it has been reported that lithiated acetone cyclohexylimine condensed with 2,6,6-trimethyl-2-cyclohexenone to give the 1,2-adduct (eq 17).[23] Lithiated acetone cyclohexylamine gives a 9,10-adduct with acridine (eq 18).[21]

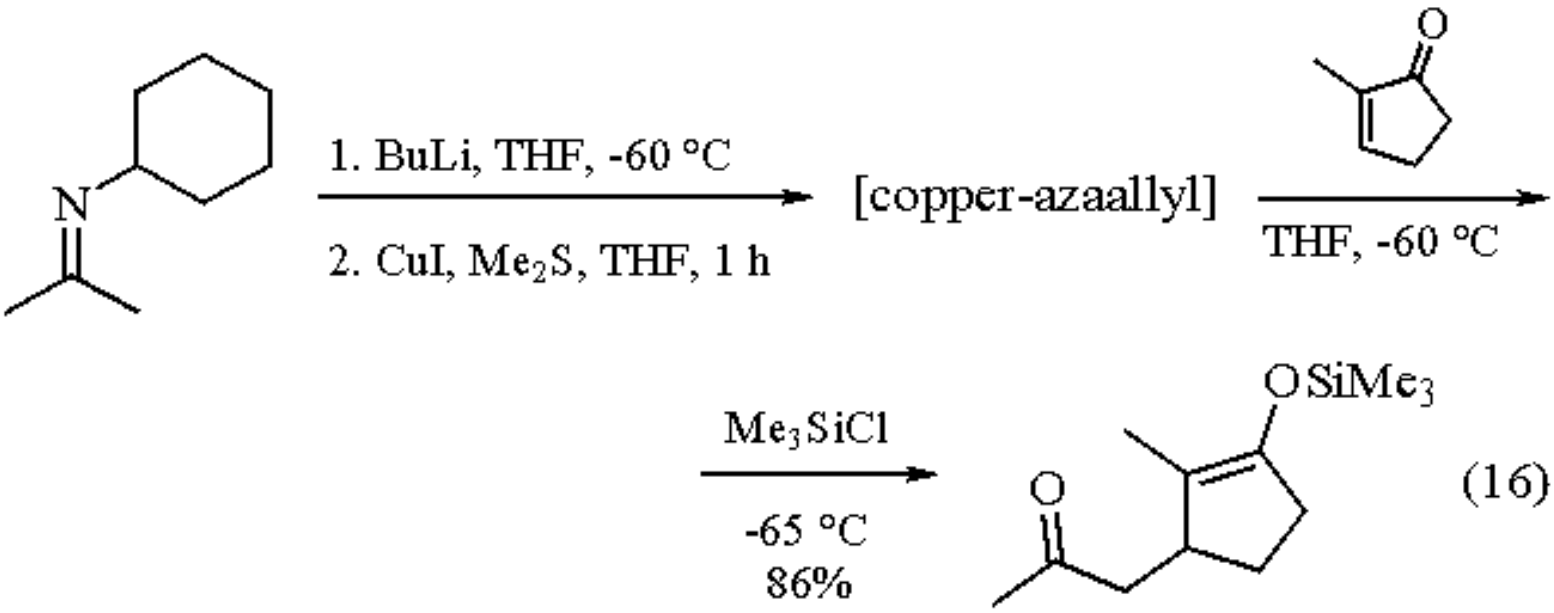

(16)

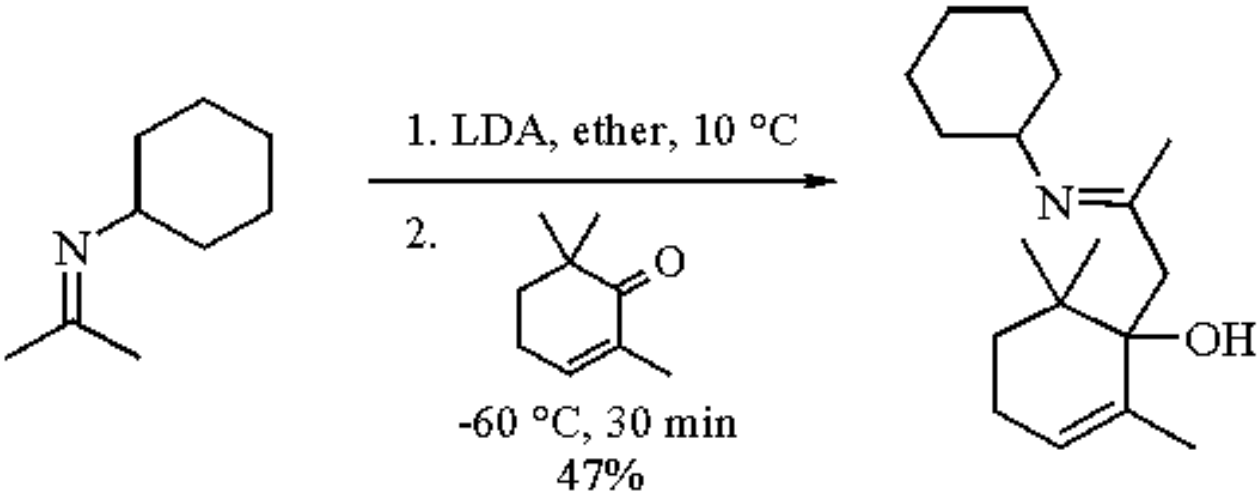

(17)

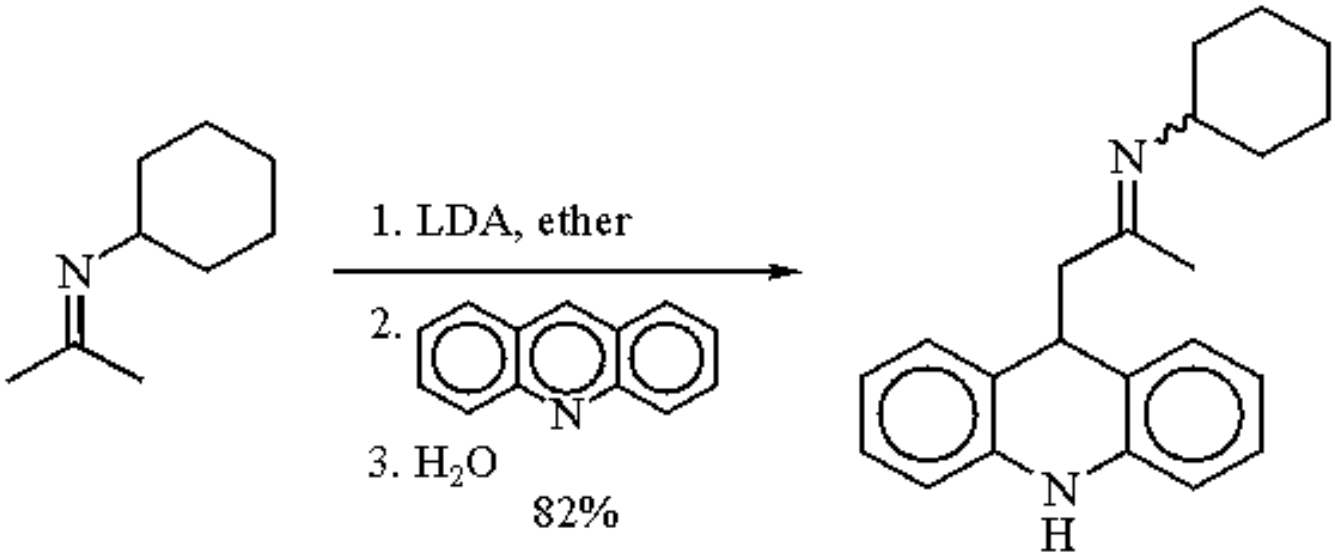

(18)

Lithiated acetone isopropylimine adds to the double bond of α-(*N*-methyl-*N*-phenylamino)acrylonitrile to give the Michael adduct, which is alkylated and ring closed to afford 2,5-dimethyl-1-isopropylpyrrole (eq 19).[38]

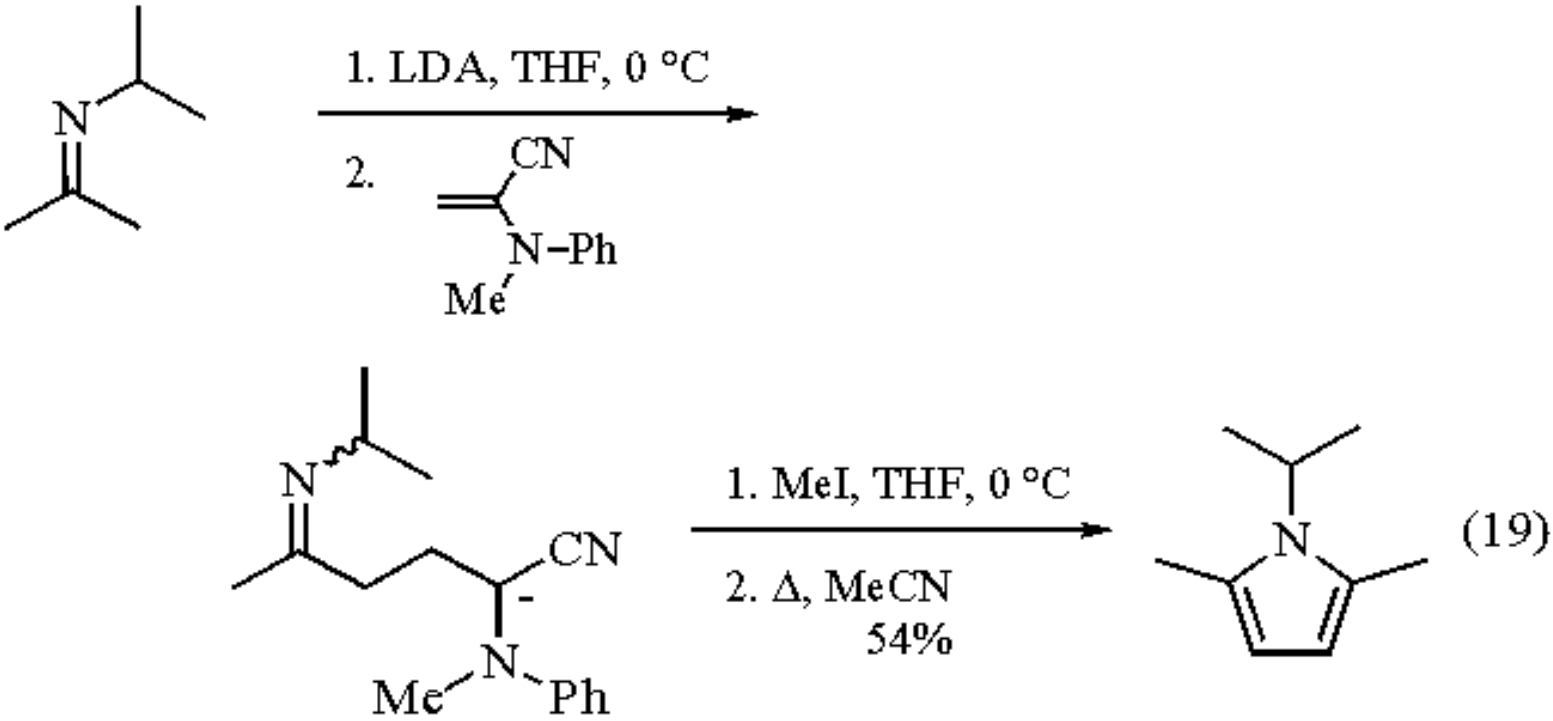

The reaction of acetone cyclohexylamine with ***Methyl Acrylate*** without added base has been investigated in detail. Several reactions take place depending on the concentrations; in particular, *C*-alkylation but no *N*-alkylation products are observed (eq 20).[24] The lack of *N*-alkylation contradicts a previous report which stated that only *N*-alkylation took place.[25,26]

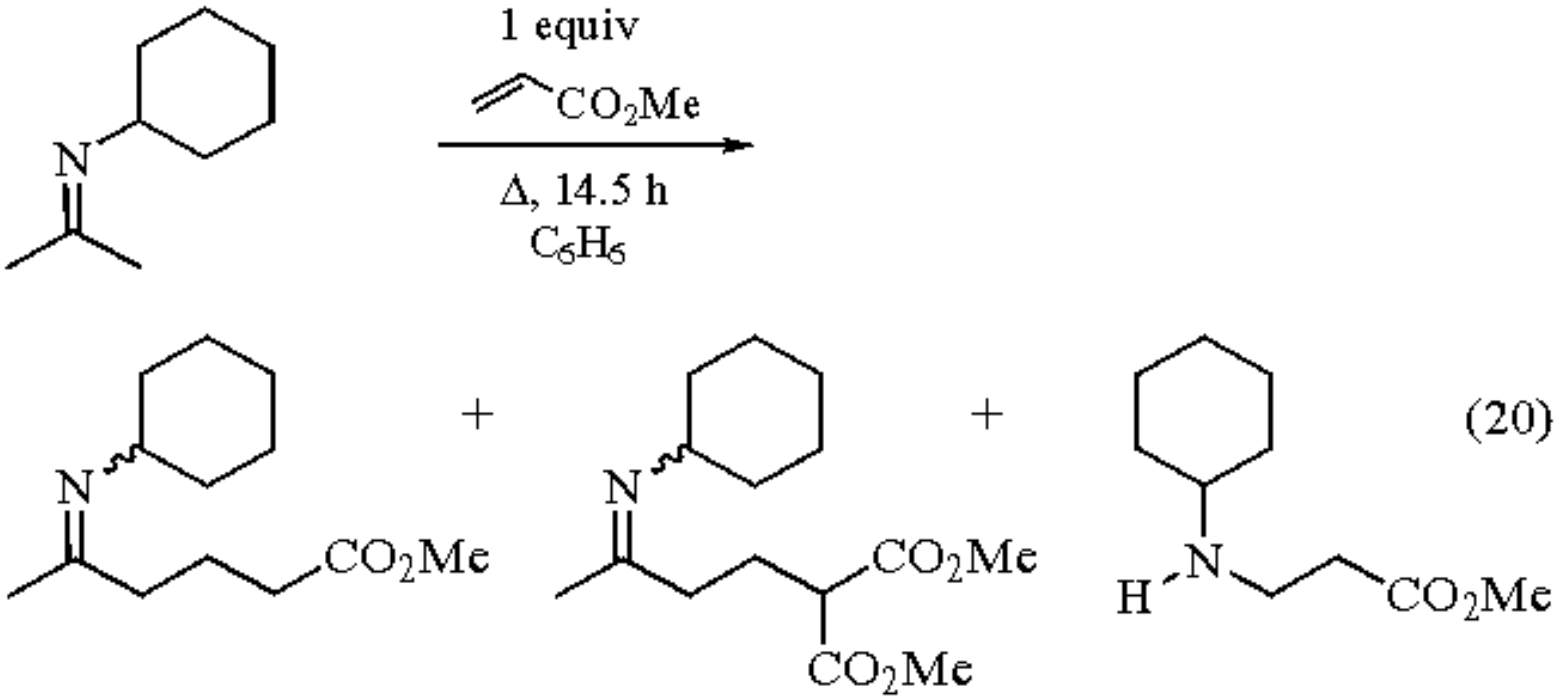

Δ, 14.5 h, conc. 0.8M	49%	14%	20%
neat, rt, 13 d	40%	52%	68%
neat, rt, 2 months (2 equiv acrylate)	4%	86%	8%

Direct condensation of excess acetone *N*-isopropylimine with ***Methyl Vinyl Ketone*** is a suitable method for the synthesis of 3-methyl-2-cyclohexenone via subsequent Michael addition, intramolecular aldol condensation, and hydrolysis (eq 21).[32]

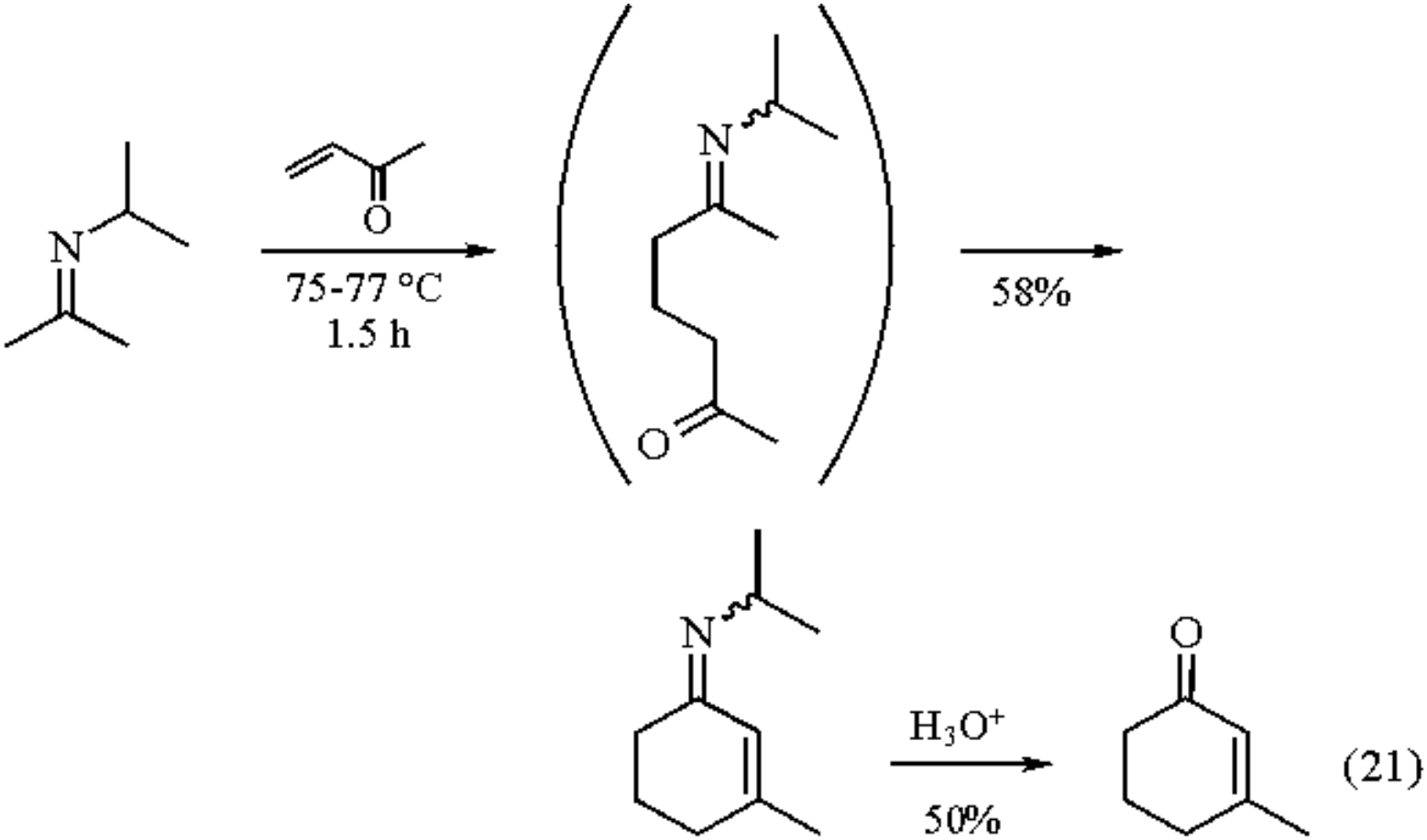

(21)

Miscellaneous.

Oxidation of acetone cyclohexylimine with ***m-Chloroperbenzoic Acid*** gives 2-cyclohexyl-3,3-dimethyloxaziridine (eq 22),[6] while the condensation with pyridinium iodides in DMSO affords indoles.[27] Complete exchange of all six α-hydrogens of acetone cyclohexylimine has been accomplished through photolysis (125 W mercury lamp) in acetone-d_6.[28] Acetone *N*-isopropylimine reacts with nitroso-arenes through an ene reaction to form nitrones via intermediate hydroxylamines and aminyl oxides.[33] Carbonyl diisocyanate condenses with acetone *N*-isopropylimine in ether to give the labile [1,3,5]triazino[2,1-*b*]-1,3,5-oxadiazine-4,8-dione, which is hydrolyzed into hexahydro-*N*,3-diisopropyl-2,2-dimethyl-4,6-dioxo-1,3,5-triazine-1-carboxamide (eq 23).[34]

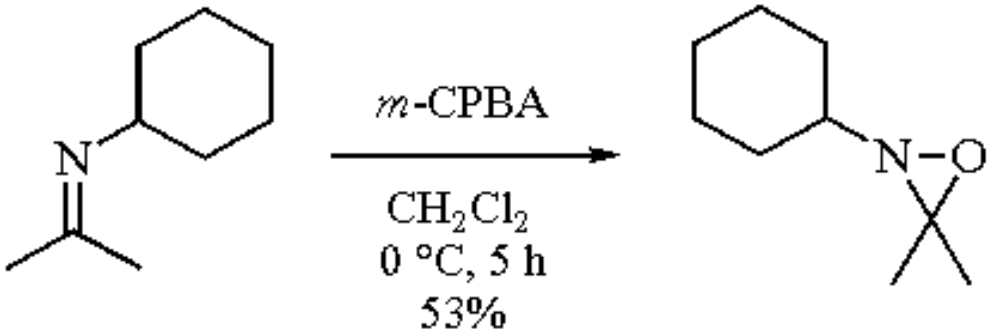

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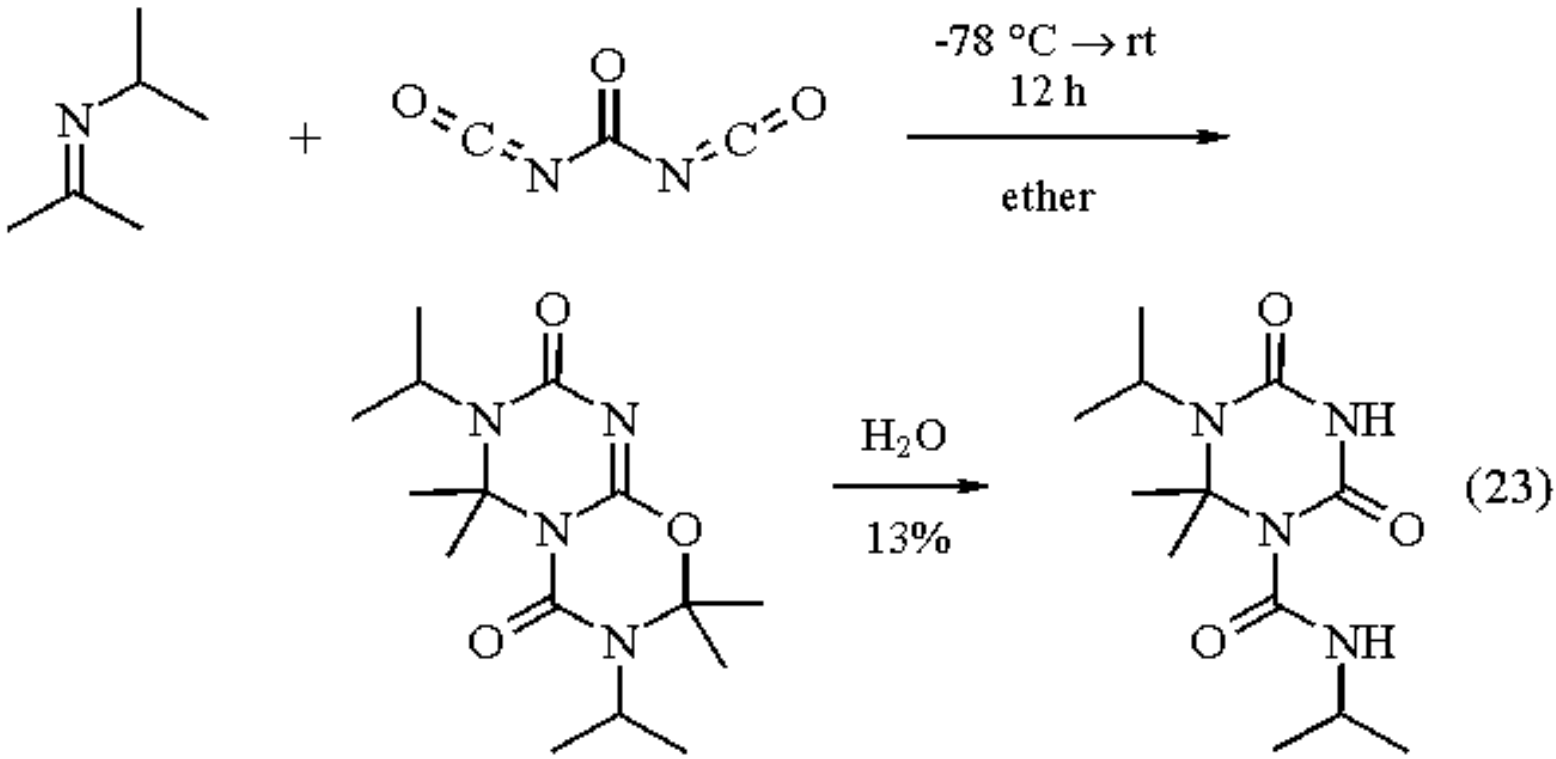

Heating acetone *N*-isopropylimine with ***Triethylborane*** at 100 °C for 7 days produced diethyl-substituted vinylaminoboranes (eq 24).[35]

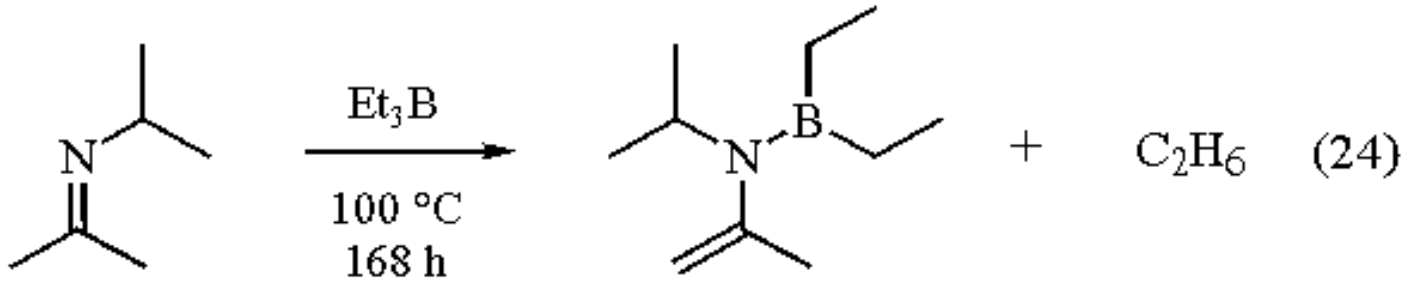

The Ni-ligand catalyzed reaction of acetone *N*-isopropylimine with 1,3-butadiene generated unsaturated amines (eq 25).[36,37]

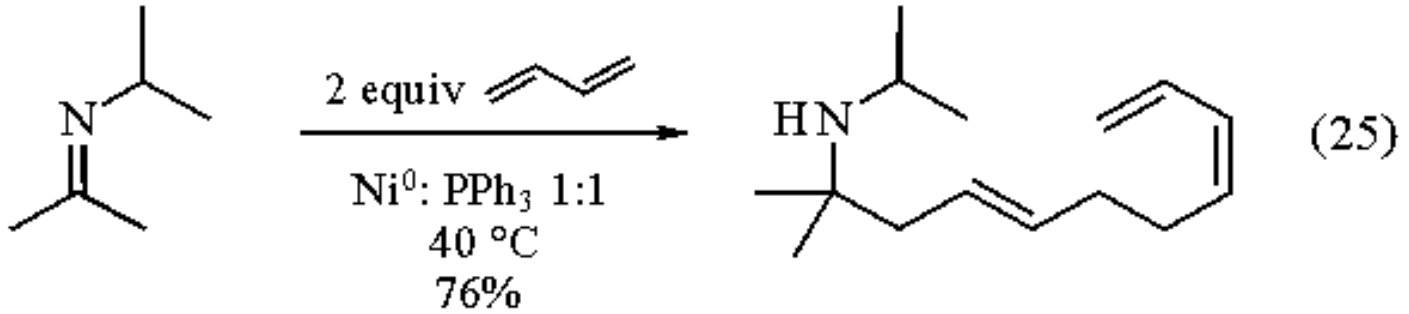

Lithiated acetone cyclohexylamine condenses with chloro- or ***Bromoacetone*** to afford 1-cyclohexyl-2,4-dimethylpyrrole (eq 26).[39] The same imine is converted into 1-cyclohexyl-3,3-dimethyldiaziridine by reaction with ***Chloramine*** (eq 27).[5]

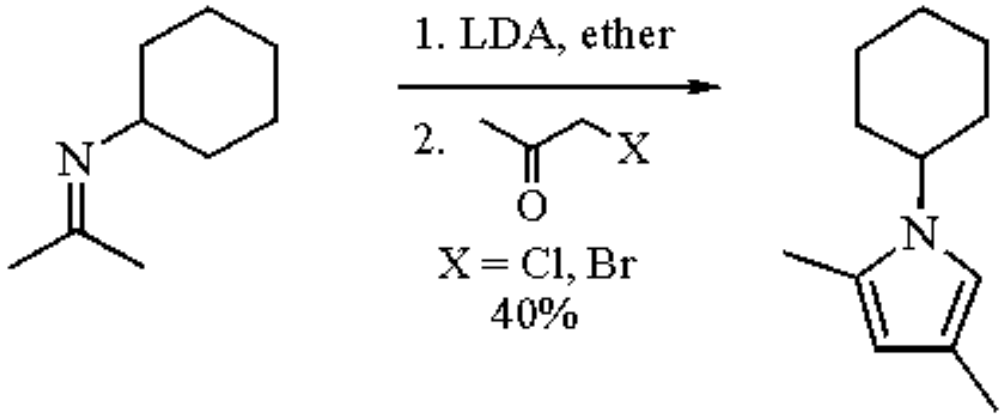

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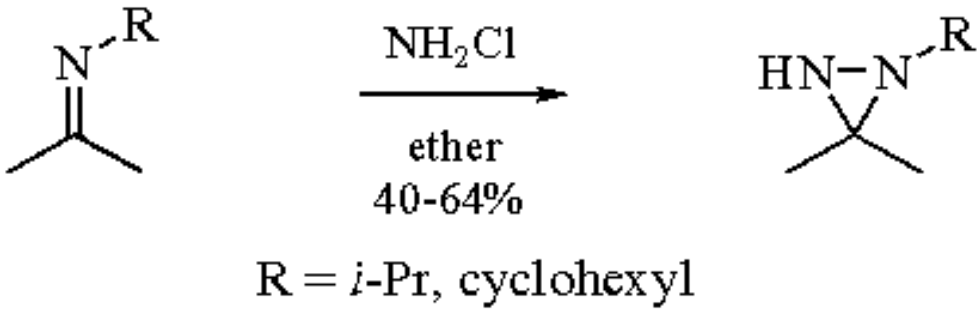

(27)

Related Reagents.

Acetaldehyde N-t-Butylimine; ***Acetone Hydrazone***; ***Diketene***; ***N,N-Dimethylhydrazine***; ***Ethyl Acetoacetate***; ***2-Methoxypropene***; ***Methyl Dilithioacetoacetate***; ***Propionaldehyde t-Butylimine***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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Acetone Hydrazone[1]

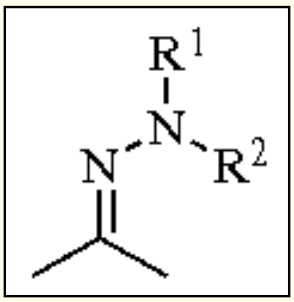

(**1**; $R^1 = R^2 = H$)

[5281-20-9] · $C_3H_8N_2$ · Acetone Hydrazone · (MW 72.11) (**2**; $R^1 = H$, $R^2 = Ph$)

[103-02-6] · $C_9H_{12}N_2$ · Acetone Phenylhydrazone · (MW 148.21) (**3**; $R^1 = R^2 = Me$)

[13483-31-3] · $C_5H_{12}N_2$ · Acetone Dimethylhydrazone · (MW 100.17)

(metalated dimethylhydrazones as anion equivalents are especially useful for regioselective alkylations[1,2] and as precursors of unsymmetrical ketone hydrazones;[1,3] *gem*-dimethyl synthons in cycloaddition reactions[4])

Physical Data: (**1**) *n*22D 1.4607, colorless liquid, bp 124-125 °C; (**2**) mp 42 °C, rhombic crystals, bp 163 °C/50 mm Hg; (**3**) light yellow liquid, bp 94-95.5 °C (92-94 °C[5]).

Solubility: sol alcohol, ether, THF, CH_2Cl_2.

Analysis of Reagent Purity: (**1**) nitrogen evolution upon treatment with glacial acetic acid; acetone azine is a common impurity; (**2, 3**) IR or NMR spectroscopy.

Preparative Methods: (**1**) is best prepared by either of two methods: from the acetone azine[7] or by an exchange reaction between ***Hydrazine*** and (**3**) in the presence of glacial acetic acid.[6,8] Both methods give nearly quantitative yields of (**1**), but the latter method produces hydrazone without azine contamination. The general method for the preparation of phenylhydrazones can be applied to the synthesis of (**2**).[1a,9] Equimolar amounts of ***Acetone*** and ***Phenylhydrazine*** are refluxed gently in aqueous ethanol with catalytic amounts of glacial acetic acid. The phenylhydrazone separates out upon cooling and can be recrystallized from aqueous ethanol. The synthesis of (**2**) by reaction of acetone, ammonia, and aniline in the presence of water has also been reported.[9b] The dimethylhydrazone can be prepared in very high yield by a general procedure for ketones using anhydrous ***N,N-Dimethylhydrazine***.[6,8] Hydrazines should be handled with care because of their toxicity. *Caution*! Anhydrous hydrazine is also highly reactive with oxidizing agents; the syntheses should be carried out behind a protective screen, in a fume hood.

Handling, Storage, and Precautions: (**1**) usually prepared just before use; unstable in the pure liquid state; disproportionates slowly to hydrazine and acetone azine at rt. Use in a fume hood. It is claimed that simple hydrazones can be stored indefinitely with minimal deterioration in the absence of moisture in the solid state at low temperature.[6] Azine formation is rapid in the presence of moisture. Regeneration of old samples is accomplished by heating the hydrazone at 100 °C for 12-16 h before distillation.[7] Hydrazones (**2**) and (**3**) are relatively stable and can be stored for long periods of time without deterioration.

Hydrazone Oxidations.

The reactions of ketone hydrazones depend largely on the degree and kind of substitution on the *N*-amino group. Hydrazone (**1**) ($R^1 = R^2 = H$) is most prone to oxidation. Oxidation of (**1**) in the presence of ***Mercury(II) Oxide*** or ***Silver(I) Oxide*** and KOH serves as the easiest route to ***2-Diazopropane***.[10] The latter undergoes 1,3-cycloaddition reactions with electrophilic C=C bonds to form substituted pyrazoles,[11] vinylic and epoxy quinones,[12] and pyrazolines.[13] With ***Diphenylacetylene*** a pyrazole is formed that can be subsequently photolyzed to a conjugated alkynylcyclopropane.[14] Thus (**1**), being a precursor of 2-diazopropane, serves as a potential source of *gem*-dimethyl groups in cycloaddition reactions.

Oxidative denitrogenation has also been accomplished by a variety of electrophilic reagents. With HgO/***Mercury(II) Acetate***, (**1**) forms an acetoxy adduct that yields 4-acetoxy-4-methylvaleronitrile upon reaction with ***Acrylonitrile***.[15] In general, simple ketone hydrazones react with excess ***Benzeneselenenyl Bromide*** in the presence of a hindered guanidine base to afford phenyl vinyl selenide[16] or with excess ***Iodine*** in triethylamine-THF to afford vinyl iodides.[17] 1-Alkenyl cobalt complexes are formed in the presence of a Co-dioxygen complex. Subsequent reduction by ***Sodium Borohydride*** produces propene from (**1**) and *cis* alkenes from higher aliphatic ketone hydrazones.[18]

Phenylhydrazone (**2**) couples to form a C-N dimer as the oxidation product when treated with ***Potassium Permanganate*** in acetone. Upon heating, the dimer gives a vicinal bis(azo)alkane (eq 1).[19]

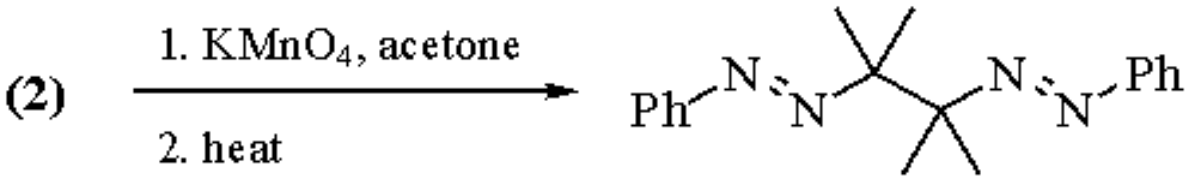

(1)

Oxidation of (**3**) generally leads to C=N bond cleavage and has been utilized most successfully to regenerate acetone and other ketones from their dialkylhydrazones. Oxidizing agents that are commonly used for this purpose include ***Ozone*** at low temperature,[20a] ***Sodium Perborate***, ***Sodium Periodate***, and H_5IO_6.[20] With ***Selenium(IV) Oxide***, however, oxidation leads to α-carbonylation in high yield.[21]

Heterocycles.

1,3-Dipolar cycloaddition reactions involving hydrazones offer a very versatile means of synthesizing five-membered heterocyclic rings. Cycloadditions between (**1**) and nitrile oxides form oxadiazolines in modest yields.[22]

Cyclocondensation of benzoylhydrazinoacrylate from (**1**) affords aminoquinolonecarboxylates.[23] An alternative to the Piloty-Robinson pyrrole synthesis has been used by Baldwin[24] to prepare pyrroles from any enolizable aldehyde or ketone via azines synthesized from the corresponding hydrazones. The reaction is shown for (**1**) (eq 2).

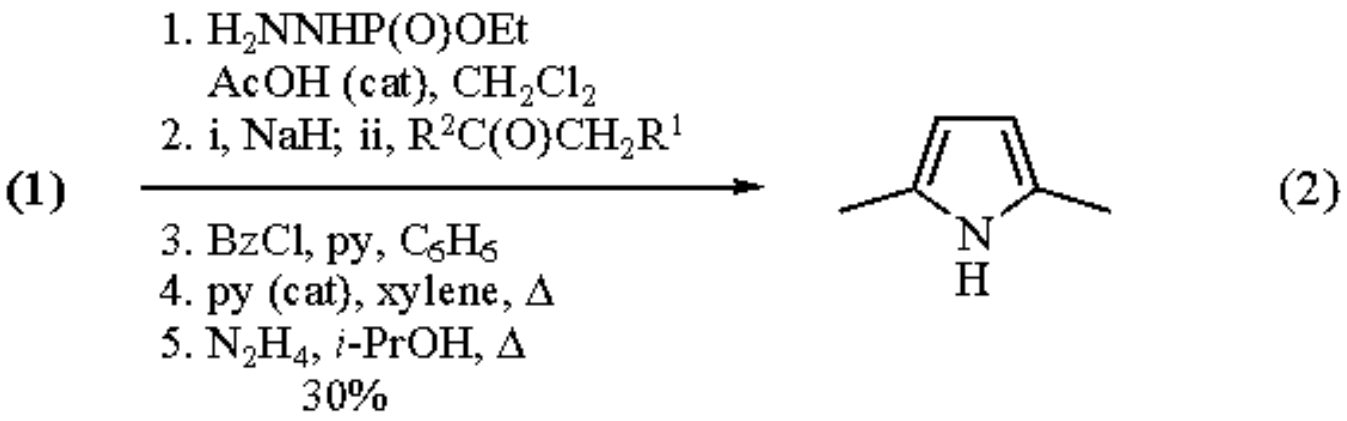

The Fischer indole synthesis provides an efficient route for the synthesis of indoles and related compounds from phenylhydrazones. Heating (**2**) in the presence of ***Zinc Chloride***, ***Formic Acid***/H_2SO_4, formic acid/HCl, or modified alumina catalysts provides 2-methylindole in modest to high yields. Indole formation is favored when anhydrous acid catalysts are used at high temperature to promote formation of the ene-hydrazine intermediate (eq 3).[25,26] In addition, β-lactams[27] and triazolinones[28] have also been synthesized from (**2**). Some cyclic diaza compounds containing other heteroatoms have been prepared from phenylhydrazones. Cycloaddition with thiocyanates or ***Carbon Disulfide*** leads to the formation of substituted thiadiazolidines (eq 4).[29] Treating (**2**) with ***Phosphorus(III) Chloride*** or $AsCl_3$ results in the formation of diazaphosphole and diazaarsole in modest yields (eq 5).[30]

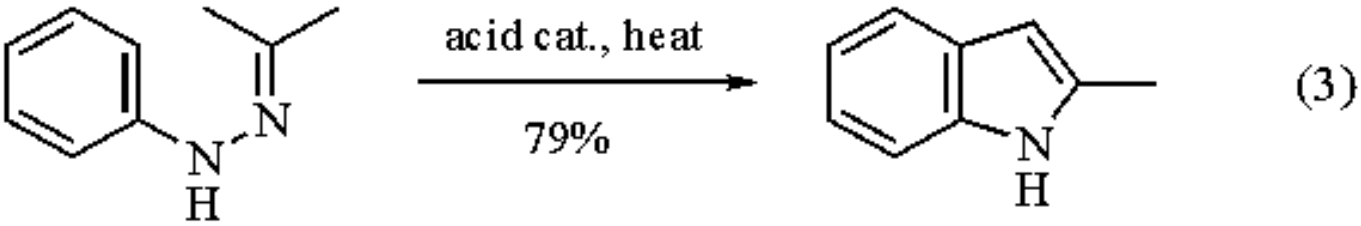

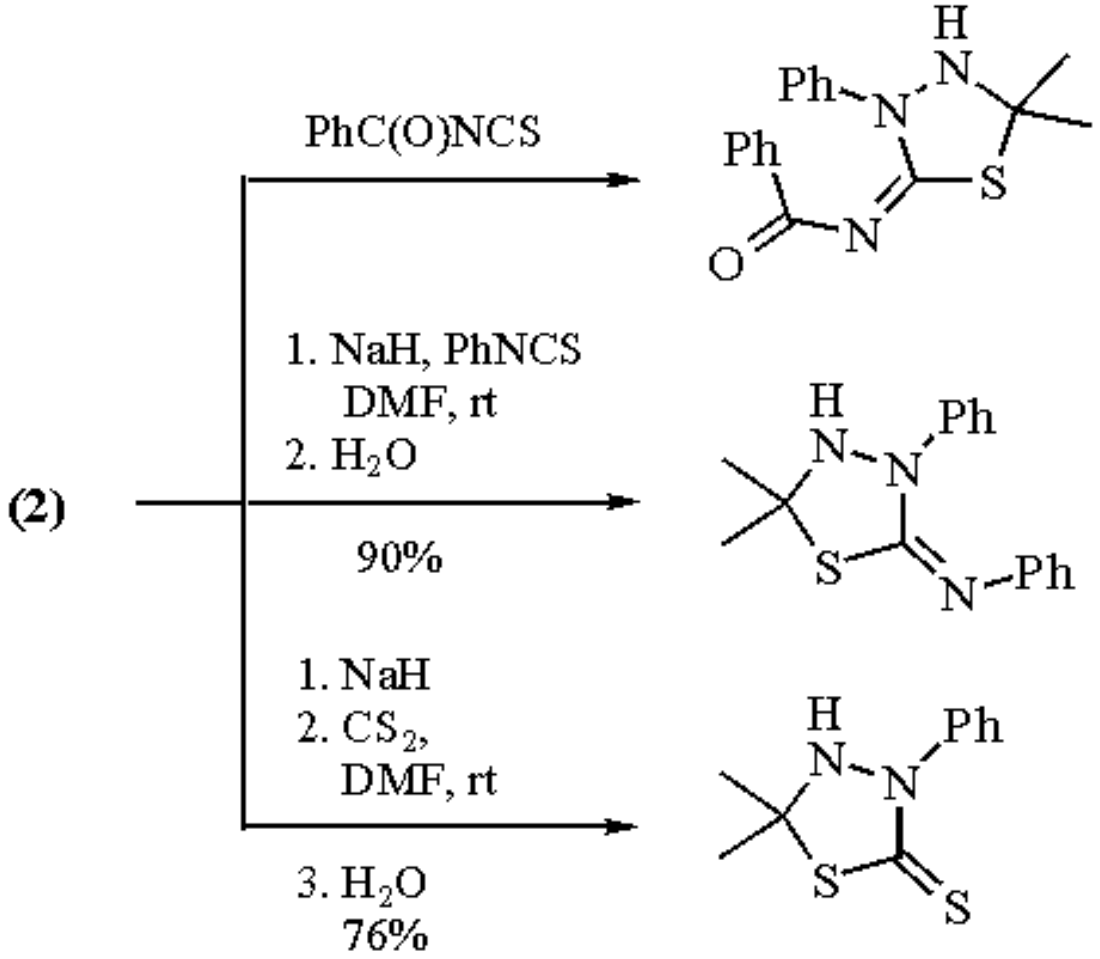

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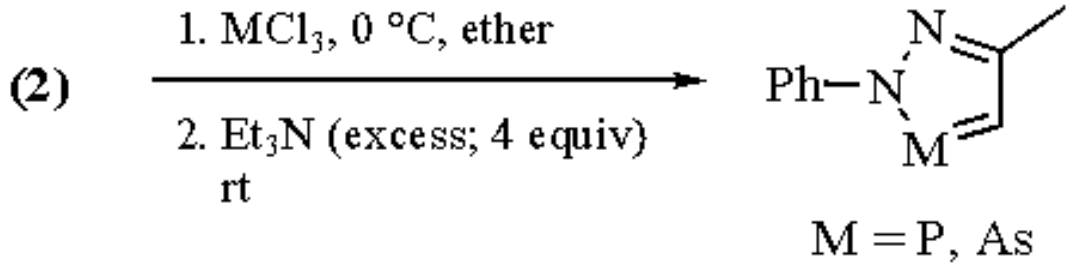

(5)

With (**3**) and other ketone dimethylhydrazones, formation of heterocycles occurs via annulation reactions of their condensation or alkylation products. The strategy involves either a Michael-type addition or 1,2-addition of the azaallyl anion of (**3**) to carbonyl compounds or esters followed by a ring closure step to afford dihydropyridines[31] and substituted pyridines.[32] 1-Pyrrolines have also been prepared in good yield by alkylation of the anion of (**3**) with o-iodo azide followed by treatment with ***Triphenylphosphine*** (eq 6).[33]

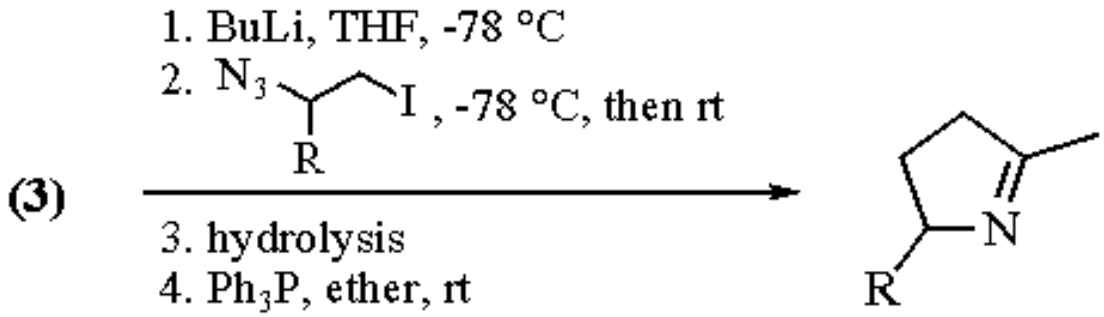

(6)

Metalation and Anion Formation.

Hydrazones react with strong bases to deprotonate the amide NH as well as the α-carbon. Deprotonation usually occurs on the less substituted α-position. The anions thus formed are not isolated, but are used immediately in synthesis. *N*-Deprotonation proceeds smoothly and almost exclusively with equimolar amounts of NaH,[29,34,35] $NaNH_2$ or KNH_2 in liquid ammonia,[36] LDA at 0 °C, KDA, *n*-BuLi, or *t*-BuLi at -78 °C.[37-39] Anions generated by hydride deprotonations of (**2**) have been used in *N*-alkylation reactions with alkyl halides[34] and in a cycloaddition reaction with phenyl isothiocyanate (eq 4).[29] Alternatively, equilibrium deprotonations using 50% aqueous NaOH with a phase-transfer catalyst or NaOH in DMF may be used to generate the azaanion in the presence of alkyl halides.[34,40] The lithium anion of (**2**) can undergo *N*-sulfonation and is also used in the synthesis of siladiazacyclopentenes (eq 7).[41,42]

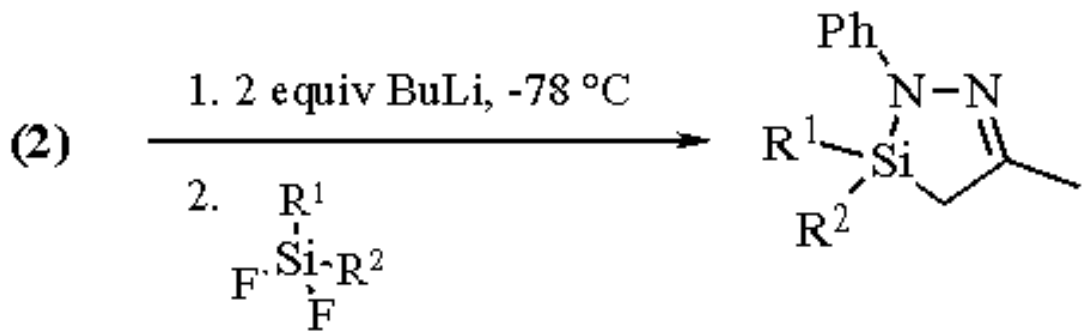

Carbanions from (**3**) and *N*-deprotonated (**1**) and (**2**) are most commonly generated by reaction with an alkyllithium reagent at -78 °C or LDA at 0 °C using THF or THF/HMPA as solvents. KDA can also be used and has been preferred by some workers due to a more rapid reaction rate and a wider range of hydrazone substrates.[39] The azaallyl lithium and potassium reagents thus generated have limited thermal stability due to side reactions arising from addition to the sp^2 carbon.[43] Transmetalation of the azaallyl lithium anion of (**3**) with either CuI-Me_2S[39,44] or CuI-*i*-Pr_2S[38] provides a route to the formation of the corresponding homocuprate derivative. The mixed cuprate is obtained if Cu^I thiophenoxide is used.[38b]

Alkylations.

Dimethylhydrazone (**3**) serves as a presursor of unsymmetrical ketone hydrazones via α-alkylation reactions involving allyl and alkyl halides, dihalides, tosylates, and epoxides. Compounds (**4**)-(**10**) are examples of compounds prepared from (**3**) and the appropriate alkylating agent. Most of the alkylation products serve as intermediates in the asymmetric synthesis of a wide variety of natural products, e.g. exogonol,[45] rutamycin antibiotics,[46] insect pheromones,[5a,47] lycopodium alkaloids,[48] homotropanes,[49] pyrenophorin,[50] zingeron,[51] and the jasmonoids.[52] The use of (**3**) is preferred over acetone in these reactions because the latter tends to undergo self-aldol condensation in the presence of base rather than *C*-alkylation. Alkylation occurs at the less substituted carbon of unsymmetrical derivatives of (**3**)[36] unless there is an anion stabilizing group present. A study by Rapoport showed a 50:1 preference for the monoalkylation product.[49a] Other functional groups are not usually affected during alkylation or carbonyl regeneration. However, partial debenzylation or hydrolysis of the THP ether upon prolonged heating has been observed in Cu-catalyzed hydrolysis.[49]

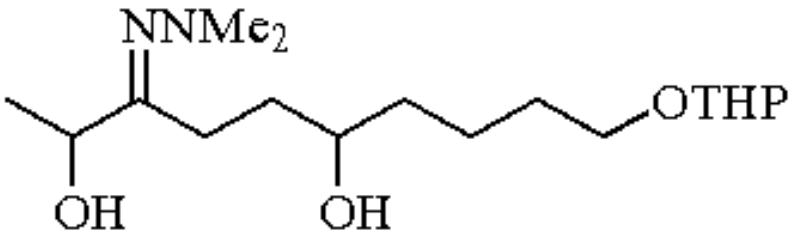

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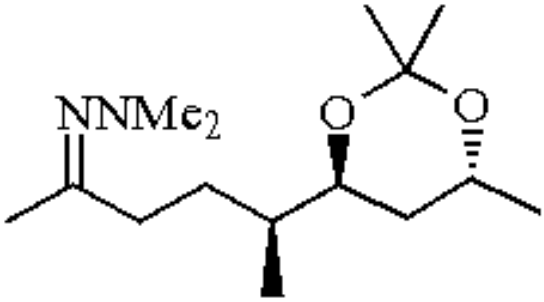

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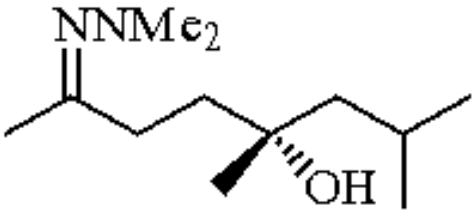

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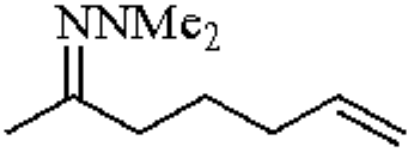

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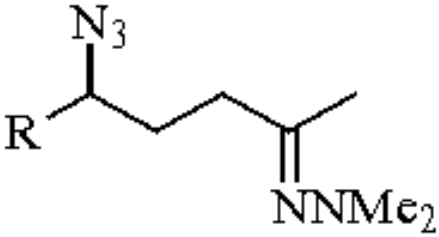

(8) 56%

(9) 93%

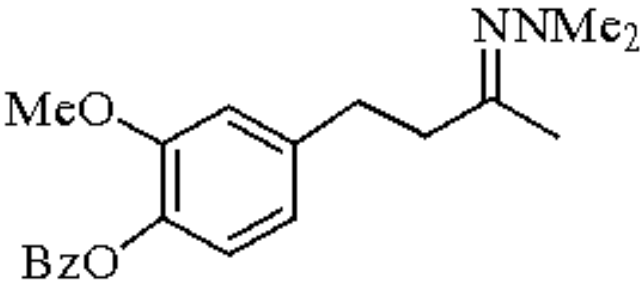

(10)

Alkylation also provides a method for synthesis of isotopically labeled hydrazones.[53] Use of allyl bromide and 4-bromo-1-butene furnishes unsaturated dimethylhydrazones that can be cleaved by ozonolysis to produce 1,4- and 1,5-keto aldehydes in good yields. These compounds are used in annulation reactions to produce medium-sized rings.[54]

Condensation Reactions.

Anions of (**1**) may undergo condensation reactions with carbonyl compounds and nitriles. Aldol-type condensations using trianions of simple hydrazones have been reported.[19] The monolithium salt of (**1**) adds to acetonitrile and *t*-butyl chloride to yield an amidrazone which can then be cyclized to a triazoline (eq 8).[55]

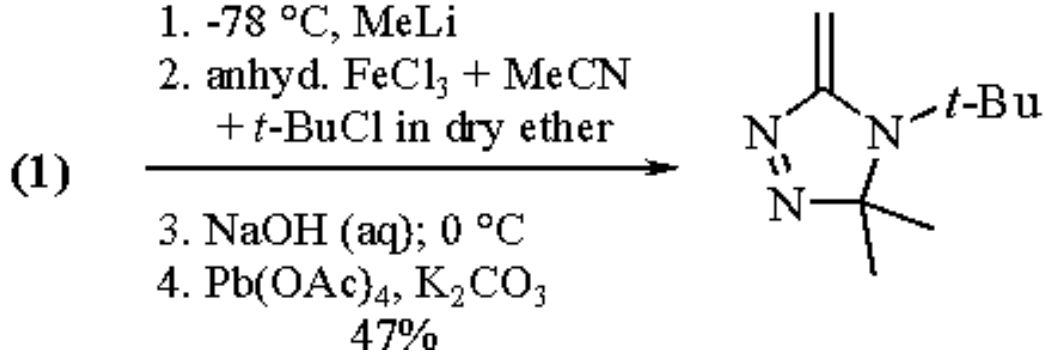

(8)

Phenylhydrazone (**2**) adds to acetyl isocyanate to give aryl-substituted triazolinones upon elimination of acetone (eq 9).[54] The azaallyl lithium reagent from (**3**) undergoes aldol-like reactions with carbonyl compounds to give high yields of β-hydroxyhydrazones. The strategy described by Corey and Enders[37] entails generation of the anion by BuLi, addition of the aldehyde or ketone to yield the β-hydroxy hydrazone, and oxidative cleavage using $NaIO_4$ in methanol at pH 7 to regenerate the carbonyl compound. This approach has been applied to the synthesis of compounds (**11**)-(**15**) (yields are shown). Periodate does not affect the β-hydroxy groups in these compounds. Ester hydrazone (**18**) was used as an intermediate in the synthesis of α-pyrones (2*H*-pyran-2-ones).[56]

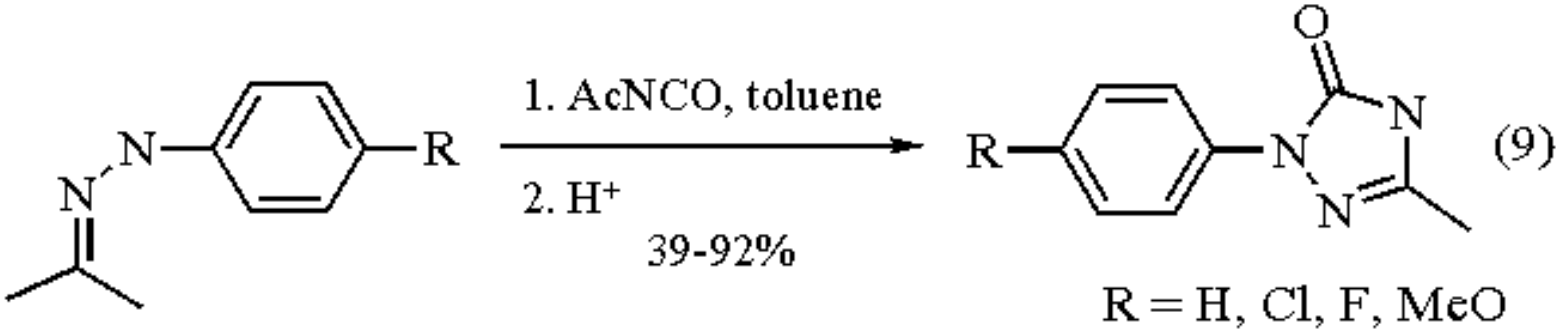

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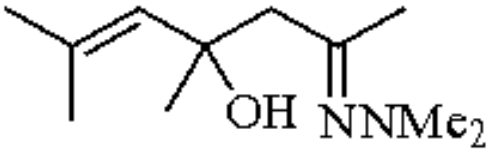

(11) 95%

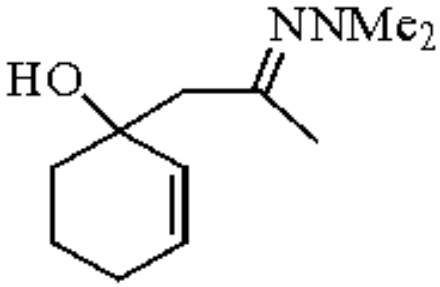

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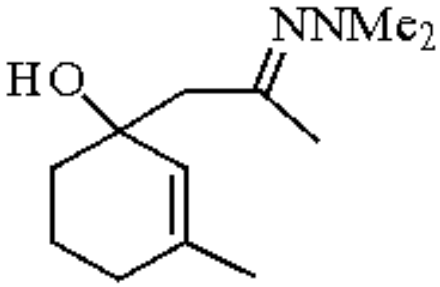

(13) 99%

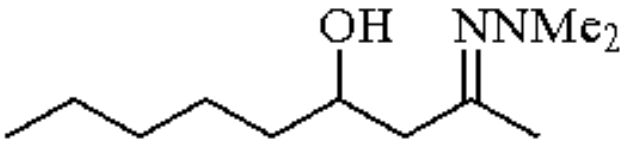

(14) 90%

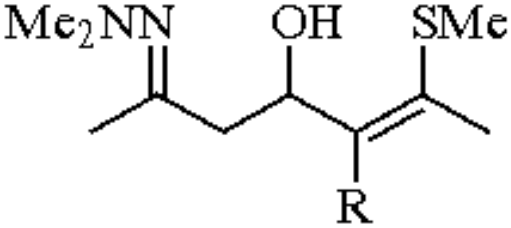

(15) 80%

A stereoselective aldol-type synthesis of (+)-*S*-[6]-gingerol (60% ee) was achieved via a chiral α-sulfinylhydrazone from an unsymmetrical ketone hydrazone derived from (**3**) (eq 10).[57,58] This synthesis complements Ender's synthesis of (-)-*R*-[6]-gingerol (36% ee) via SAMP-hydrazone.[51]

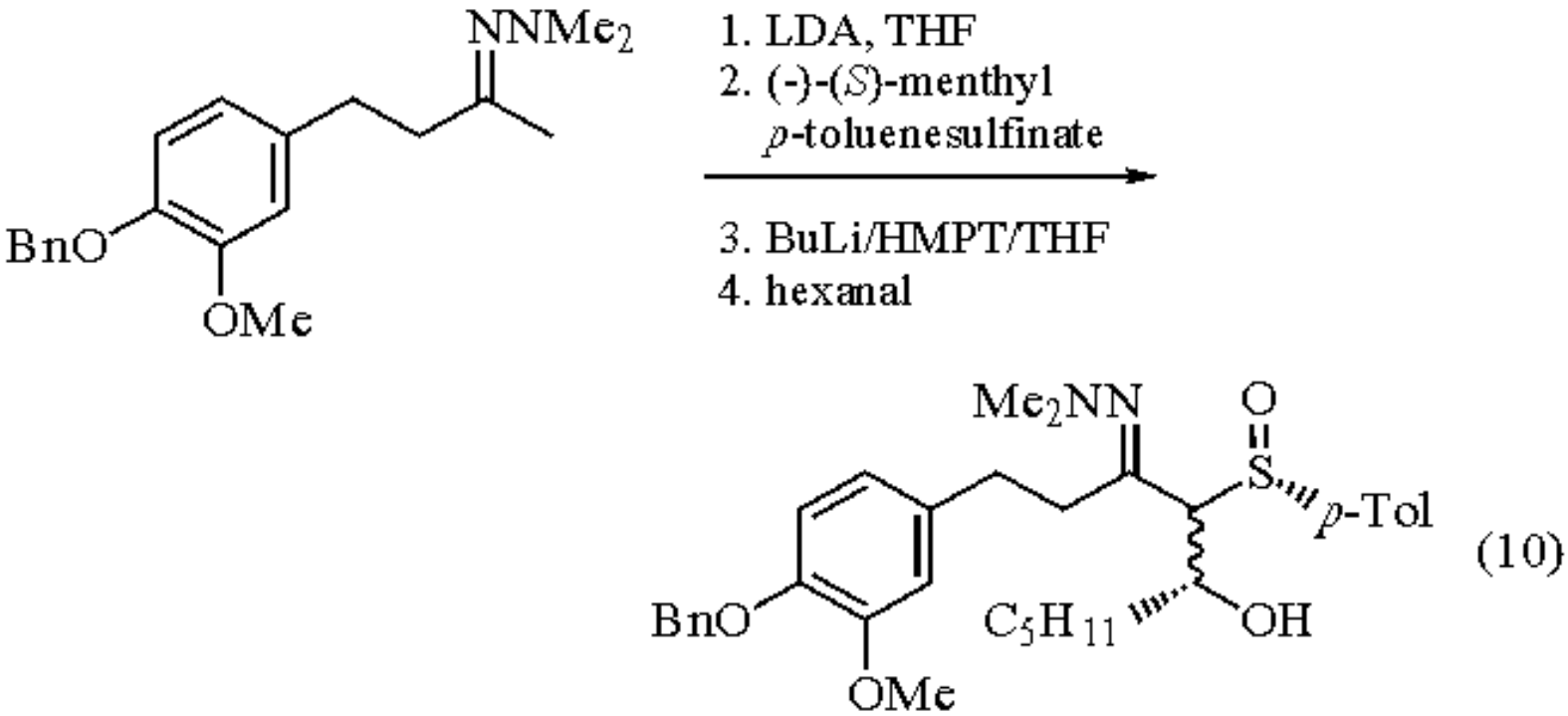

(10)

In the presence of α,β-unsaturated ketones, mixed and homocuprates of (**3**) undergo conjugate addition to form 1,5-ketohydrazones (**16**)-(**18**).[37,38] Heathcock used the homocuprate to prepare a synthesis intermediate of lycopodine. However, Sakurai's method using methallyltrimethylsilane provided higher yields (90%) of the same compound.[47]

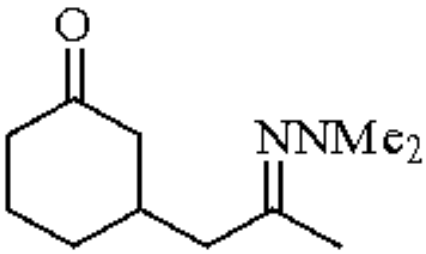

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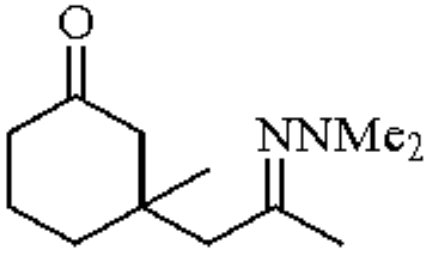

(17)

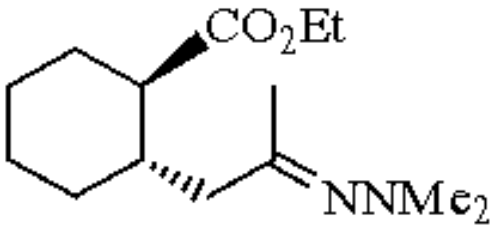

(18)

An alternative route to β-keto hydrazones involves a Claisen-type condensation of (**3**) with *N*-methoxy-*N*-methylbenzamide (eq 11)[59a] and a variety of acylating agents.[59b] With carbon disulfide, lithium dimethylhydrazonoalkanedithioate is the initial product from which alkyl dithiolates can be prepared in good yields by reaction with various alkyl iodides.[60] The azaallyl potassium from (**3**) undergoes conjugate addition to vinyl sulfones. The adduct serves as an intermediate in annulation reactions for seven-membered rings.[61]

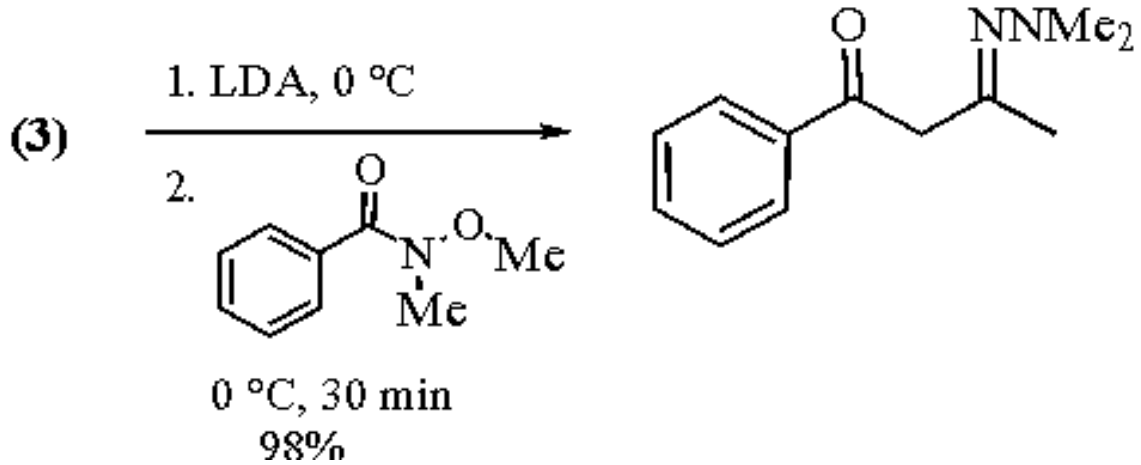

(11)

Removal of the hydrazone group is often one of the steps in these reactions. Bergbreiter[1c] gives a comprehensive list of oxidative and hydrolytic regeneration schemes for ketone and aldehyde hydrazones.

Other Reactions.

Wolf-Kishner reduction of (**1**) to propane occurs in the presence of strong alkali at high temperature. Hydrogenation of (**2**) using Pd/C catalyst affords isopropylamine.[62] Heating (**2**) in base results in its isomerization to methylphenyldiimide.[63] With difluoramine, *N*-fluoroketimine is produced in a vigorous reaction.[64] *N*-Acylation of (**3**) in the presence of various acid chlorides produces ene-hydrazides in high yields.[65]

Related Reagents.

Acetoacetic Acid; ***Acetone***; ***Acetone Cyclohexylimine***; ***2-Diazopropane***; ***N,N-Dimethylhydrazine***; ***Ethyl Acetoacetate***; ***Hydrazine***; ***Phenylhydrazine***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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Acetonitrile[1]

MeCN

[75-05-8] · C_2H_3N · Acetonitrile · (MW 41.05)

(solvent for inorganic and organometallic reagents; undergoes addition reactions to nitrile group; anion is nucleophilic reagent; Ritter reaction reagent; oxidizing agent in combination with H_2O_2)

Alternate Names: methyl cyanide; ethanenitrile; cyanomethane.

Physical Data: mp -45 °C; bp 81.6 °C; *d* 0.787 g cm^{-3} (20 °C).

Solubility: miscible with water and most organic solvents (but not petroleum); forms constant boiling mixture containing 16% water, bp 76 °C.

Form Supplied in: colorless liquid; widely available. *Drying:* fractional distillation from CaH_2 or P_2O_5.

Analysis of Reagent Purity: GLC; HPLC grade (99.9+% purity) commercially available.

Handling, Storage, and Precautions: flammable volatile liquid; keep dry; toxic vapor; mild lachrymator; possible skin irritant; evolves toxic fumes if heated to decomposition; incompatible with fuming HNO_3, N_2O_4/In, 2-cyano-2-propylnitrate, ClF/F_2, Cl_3HSi/diphenyl sulfoxide, metal perchlorates, $HClO_4$, fuming H_2SO_4, heat/conc. H_2SO_4, and *N*-fluoro compounds.[2]

Solvent Properties.

Acetonitrile is neutral, aprotic, polar (3.9 D) with a dielectric constant of 38 at 20 °C; it promotes ionic processes in solution. It is suitable for a wide range of physical organic techniques including HPLC, UV (λ > 190 nm), and electrochemistry.[3] However, its outstanding ability is to facilitate reaction between organic substrates and inorganic materials (eq 1).[4] These reagents include: Group 1 and 2 salts; Ag^{I}, Ce^{IV}, Cu^{I}, Cu^{II}, Fe^{III}, Hg^{II}, Mn^{IV}, Mn^{VII}, Pd^{II}, Rh^{III}, Ru^{IV}, Sn^{II}, Te^{IV}, and Tl^{III} salts; R_4N^+, ArN_2^+, $MeCO^+$, NO_2^+, and Ph_3RP^+ salts. In some cases, such as $CuCl_2.(MeCN)_2$ and $PdCl_2.(MeCN)_2$, the complexes involved are isolable.[5]

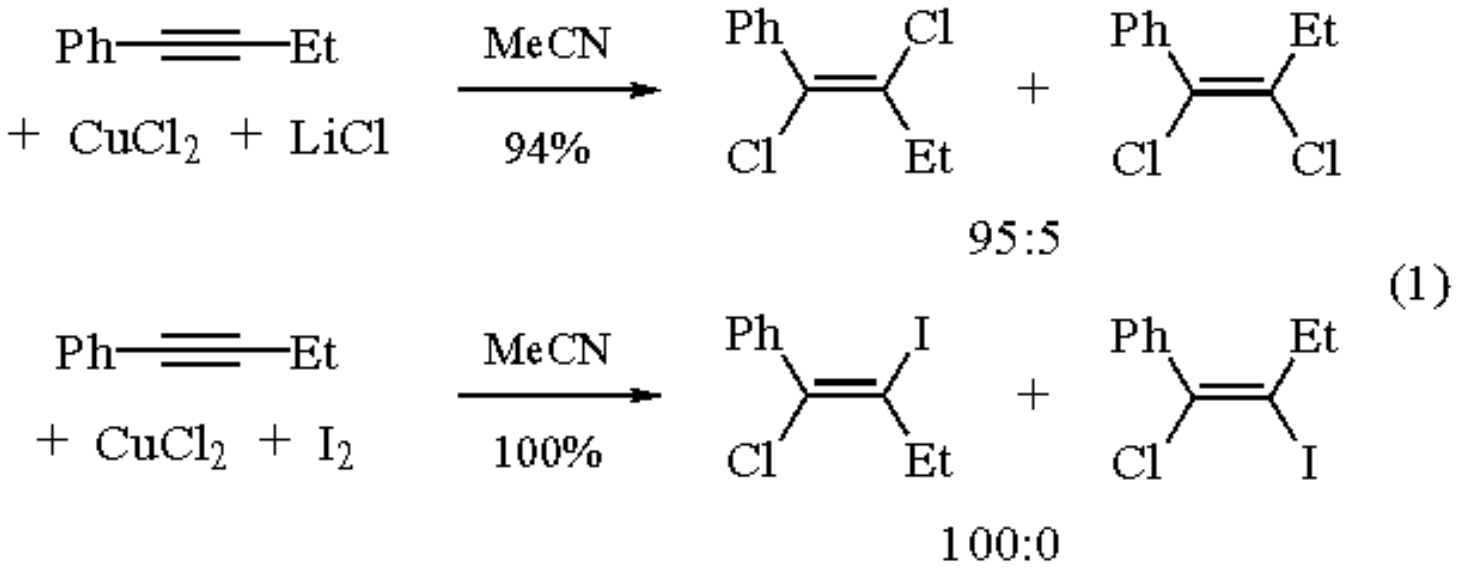

Reactions at Methyl.[6]

Deprotonation of acetonitrile using strong base affords the nitrile-stabilized anion,[7a] which can add to other nitrile molecules producing diacetonitrile[7b] or the trimer 4-amino-2,6-dimethylpyrimidine (eq 2).[7c] The dimerization process is the forerunner of the Thorpe-Ziegler synthesis of large ring systems.[8] Mixed β-enaminonitriles[9a] or diacetonitrile itself[9b] undergo condensation with carbonyl compounds, producing pyridine derivatives.

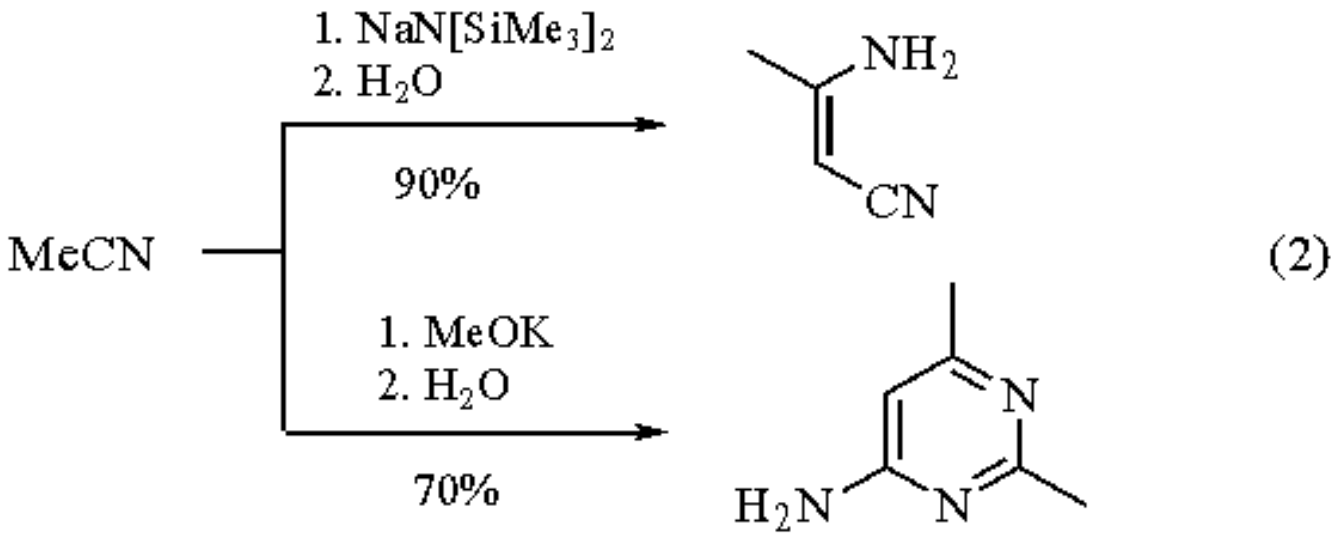

The anion performs conventional substitution reactions with alkyl halides and epoxides,[6] but ***Cyanomethylcopper*** is especially effective for cyanoalkylation of allylic halide reagents (eq 3).[10] Esters react with the monoanion yielding β-ketonitriles, which are readily converted by ***Boron Trifluoride*** or ***Polyphosphoric Acid*** into the corresponding β-ketoamides (eq 4).[11]

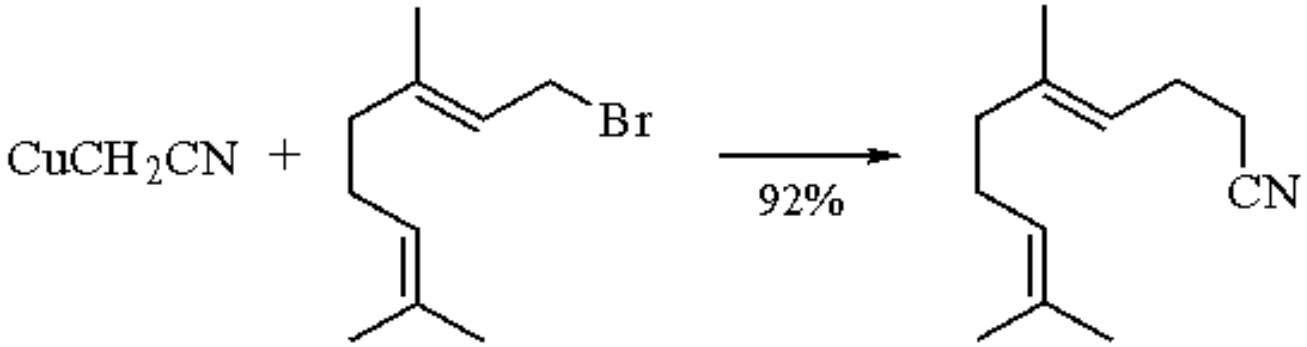

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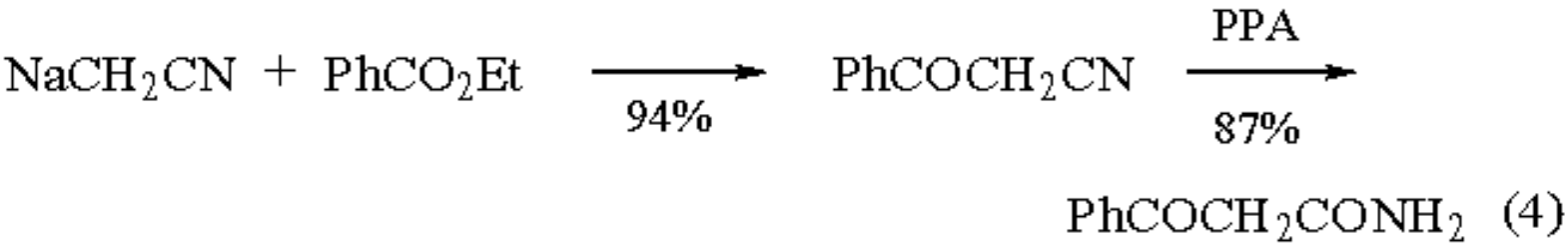

(4)

Aldol-type condensations with aldehydes and ketones produce the cyanomethyl alcohols[12a] or unsaturated nitriles (eq 5),[12b] depending on the chosen conditions. Acetonitrile anion results in exclusively 1,2-addition to conjugated enones in THF at -78 °C, in contrast to the behavior of other nitriles.[12c]

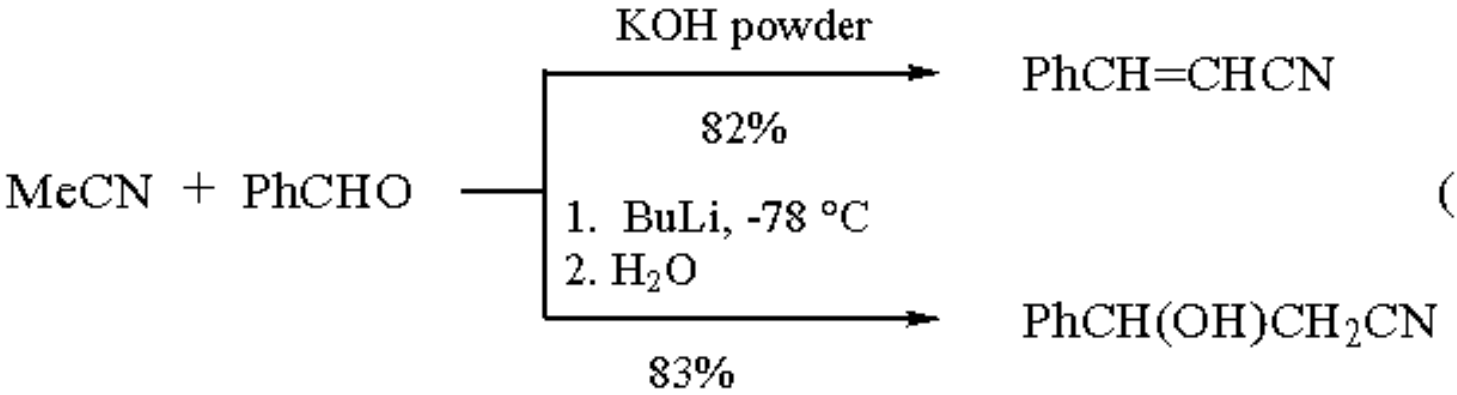

(5)

Addition Reactions.[13]

Acetonitrile yields acetophenone derivatives (eq 6) when reacted with phenols (or phenolic ethers) and Lewis acids (Hoesch reaction).[14] It reacts with alcohols in the presence of dry HCl to yield imidates (Pinner reaction)[15a] which can react with further alcohol to produce orthoacetate esters,[15b] or with amines to yield acetamidines (eq 7).[15c,d]

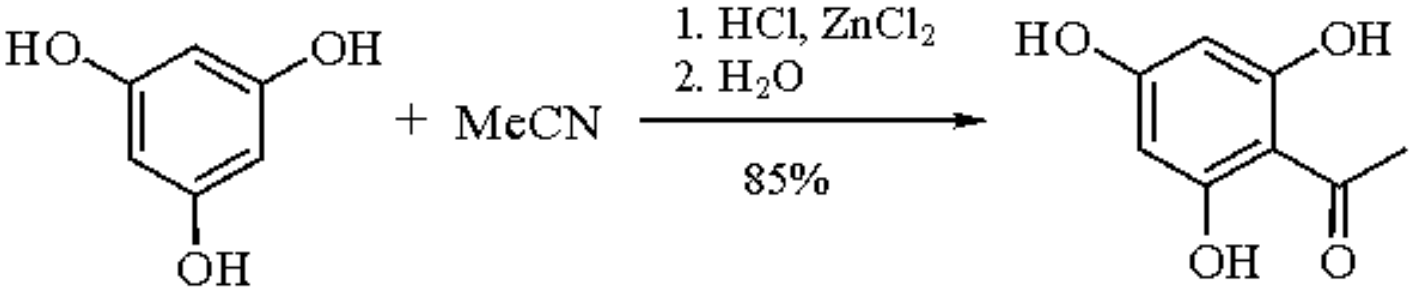

(6)

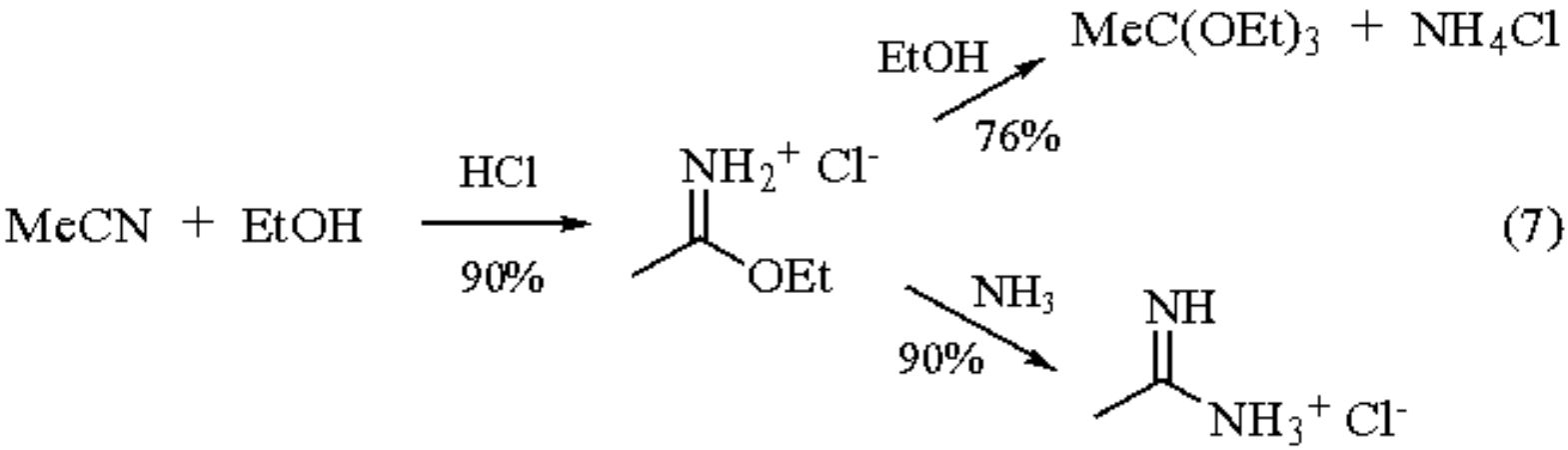

(7)

The Blaise reaction[16] of bromo esters with acetonitrile produces β-keto esters (eq 8) in a process analogous to the Reformatsky reaction. Acetonitrile reacts with ammonia and hydrogen sulfide to yield thioacetamide. Higher thioamides can be produced by reacting this with nitriles and distilling the lower boiling MeCN from the resulting equilibrium mixture.[17]

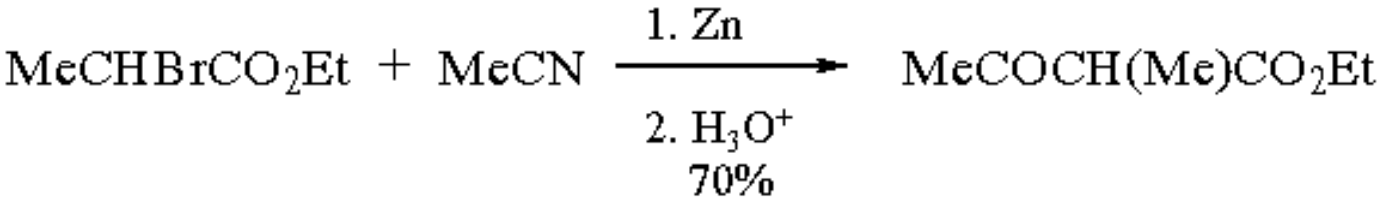

(8)

Acetonitrile also reacts with thiols to yield thioimidates,[15a] with amines to give acetamidines,[18] and with 1,2-amino alcohols to produce 2-oxazolines (eq 9).[19]

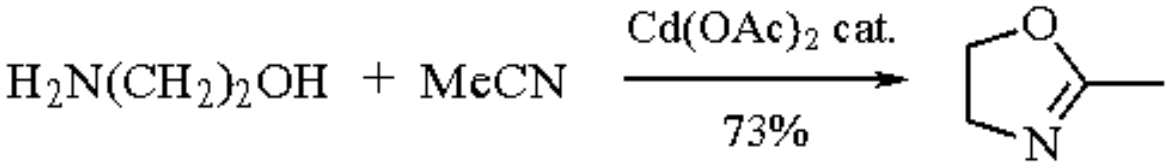

(9)

Ritter-Type Reactions.[20]

The acetonitrile nitrogen atom is an extremely weak nucleophile, but attacks carbenium ions to yield a nitrilium ion, which proceeds to an imidate and then undergoes hydrolysis to the amide (eq 10).[21] Since carbenium ions may be generated from a very wide range of functional groups under strongly acidic conditions, the Ritter reaction provides a facile one-flask route to *N*-alkylacetamides. As expected, the carbenium ions may participate in rearrangement or transannular reactions before undergoing substitution (eq 11).[22] Alternatively, the nitrilium ion may be generated via other electrophilic reagents[23] (eq 12),[24] and it can also undergo intramolecular closure to yield heterocyclic products (eq 13).[25]

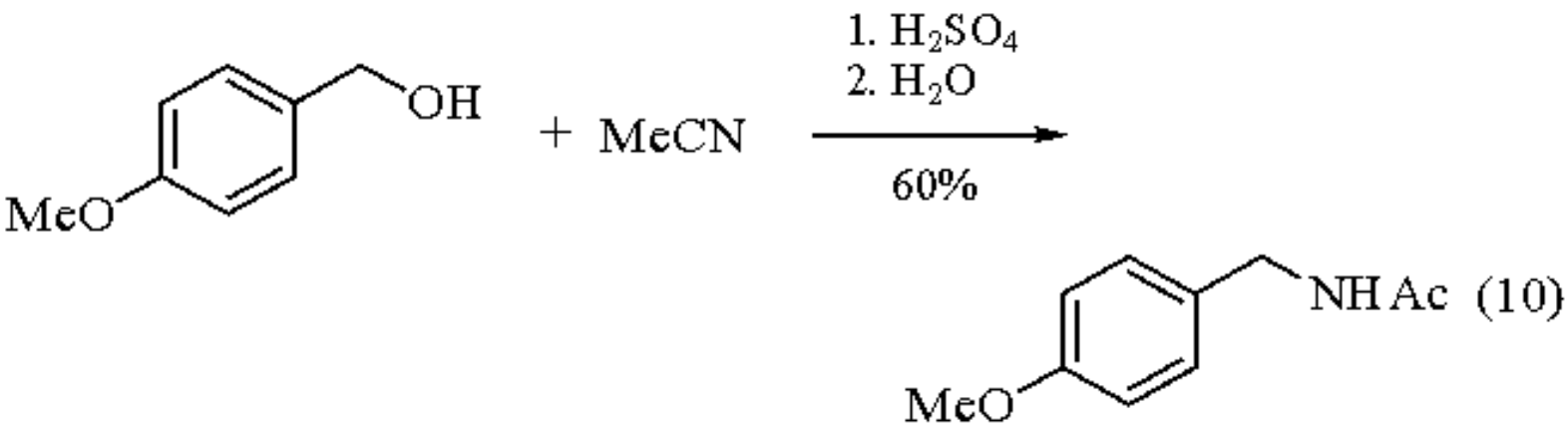

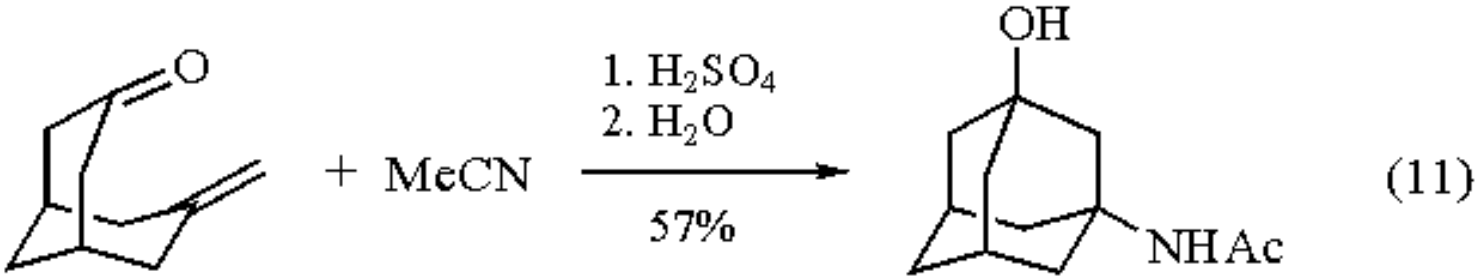

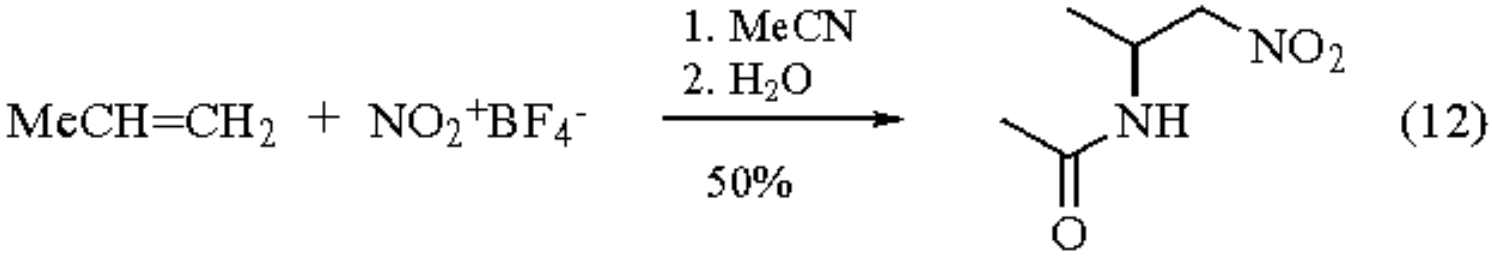

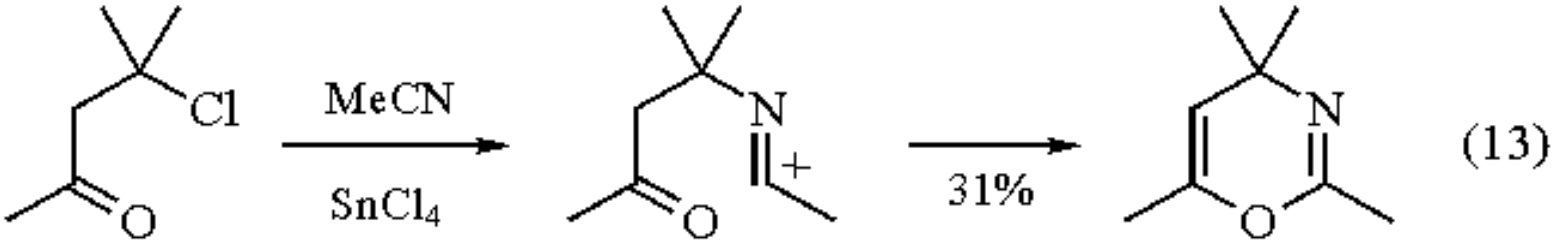

Reactions with Hydrogen Peroxide and Base.

The Radziszewski reaction[26] describes the formation of amide products and dioxygen when nitriles are treated with ***Hydrogen Peroxide*** solution under basic conditions. Yields of aliphatic amides[27a] are 50-70%, while those of aromatic amides[27b] are typically 80-95%. This reaction proceeds via the intermediacy of the peroxyimidic acid (eq 14).[28] If an alkene functionality is present, then it is epoxidized with concomitant reduction of the peroxyimidic acid to the amide (the Payne oxidation)[29] in a simple one-flask process. A convenient procedure is to react the alkene and nitrile with H_2O_2 in methanol using potassium hydrogen carbonate as the base (pH ca. 8).[30a]

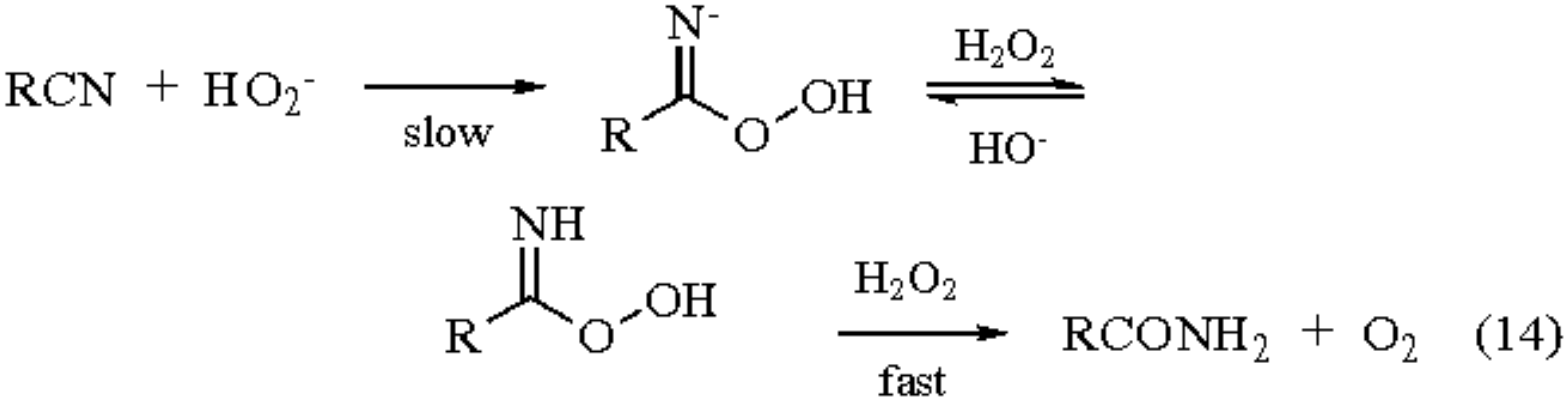

The Payne oxidation has the advantage that the oxidant is generated in situ, while the mildly basic conditions ensure that labile epoxides do not undergo acid-catalyzed degradation (eq 15)[30b] and competing Baeyer-Villiger oxidations may be suppressed (eq 16).[29c] In some cases the peroxycarboxylic acid and Payne processes may give differing outcomes,[31a] stereochemistry,[31b] or regioselectivity.[31c] While both benzonitrile and acetonitrile are commonly employed, the latter reagent has operational advantages. Its oxidation products are water soluble and easily removed during reaction workup, whereas the benzamide coproduct requires a more complex separation.

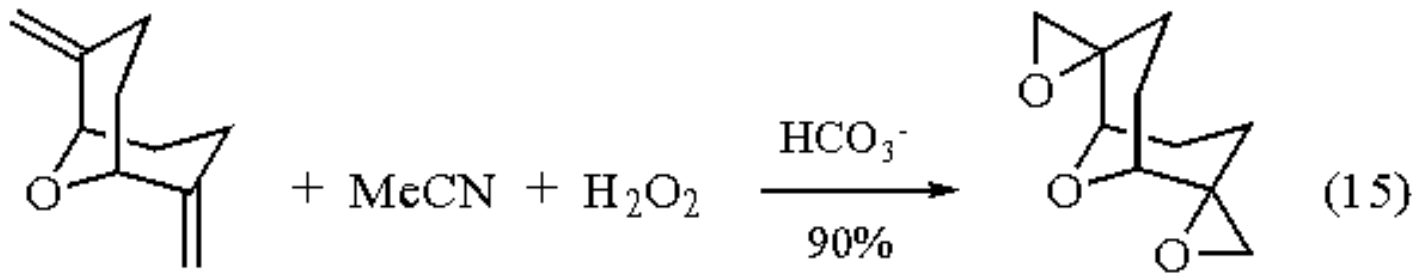

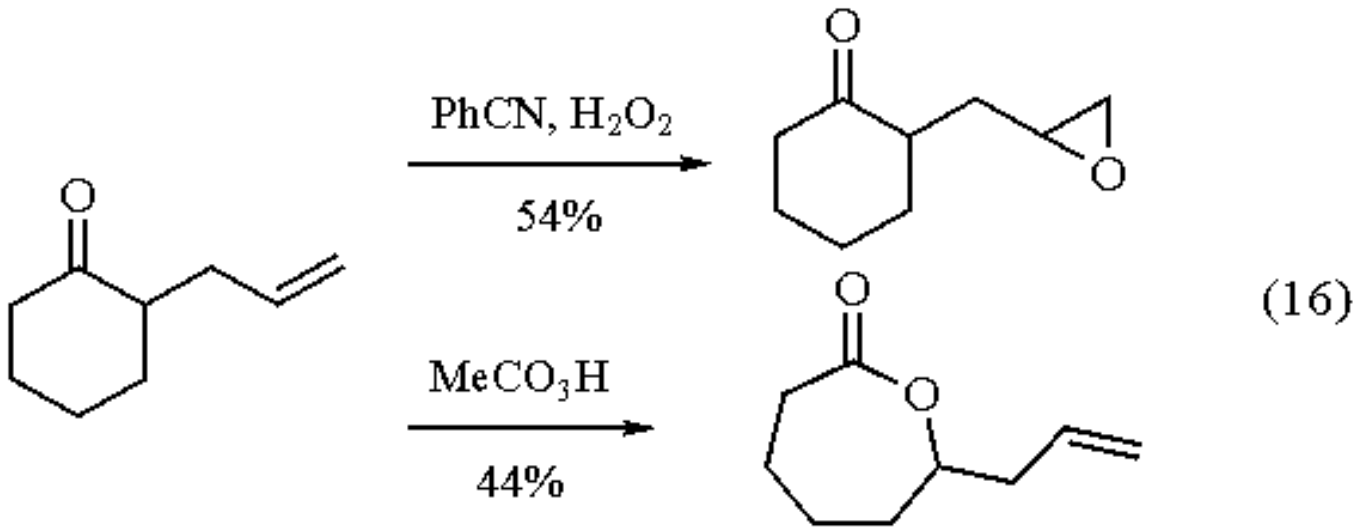

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Acetonitrile *N*-Oxide[1]

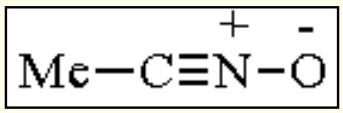

[7063-95-8] · C_2H_3NO · Acetonitrile *N*-Oxide · (MW 57.05)

(reactive 1,3-dipolar reagent useful for [3 + 2] cycloadditions,[2] isoxazolines (intermediates useful for natural product synthesis),[3] isoxazoles,[4] heterocycle synthesis[5])

Physical Data: reactive intermediate generated in situ.

Solubility: sol petroleum ether, ether, benzene, dichloromethane, ethanol, chloroform; insol cold (-60 °C) petroleum ether.

Analysis of Reagent Purity: spectroscopic data have been recorded at low temperature:[6,7] NMR (-40 °C) ^1H: CH_3 (δ 2.26); ^{13}C: CH_3 (δ 0.8), CN (δ 35.6); IR (EtOH), 2315 cm^{-1}.

Preparative Methods: the reagent is most commonly generated in situ from ***Nitroethane*** by treatment with ***Phenyl Isocyanate***/***Triethylamine*** at rt (the Mukiayama method).[8] Other reagents (AcCl, Ac_2O, or $POCl_3$[9]) may be used in place of PhNCO. Acetonitrile oxide may be generated by flash vacuum pyrolysis (FVP) of 3,4-dimethylfuroxan,[6,10] by hypochlorite oxidation of acetaldehyde oxime,[4b] or from acetohydroxamoyl chloride.[7] Decomposition (mainly dimerization to 3,4-dimethylfuroxan) is reported[1b] to take place within minutes of generation at 18 °C (however, see Brandi[7]).

1,3-Dipolar Cycloaddition.

Isoxazolines from cycloaddition of acetonitrile oxide to alkenes (eqs 1 and 2)[11,12] are often used intermediates for synthesis of natural products.[3,13] For example, isoxazolines may be elaborated into α,β-unsaturated carbonyl compounds,[14] 1,3-amino alcohols,[15] 3-hydroxycarbonyl compounds[16] (and 2-alkylated or 2-hydroxylated derivatives),[17] and pyrroles.[18]

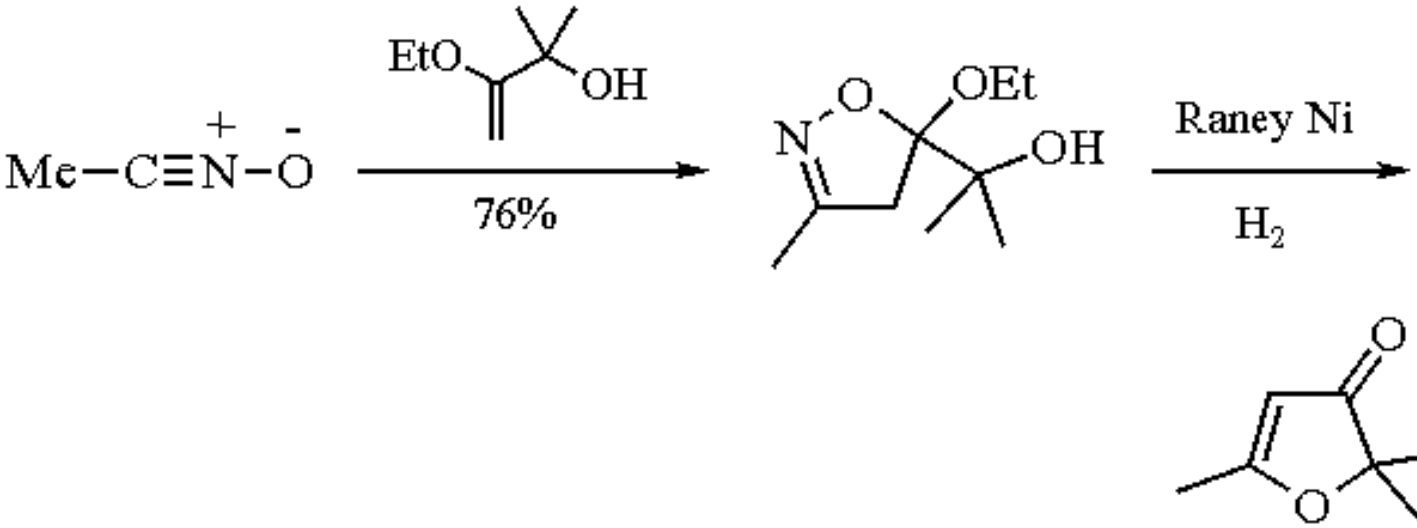

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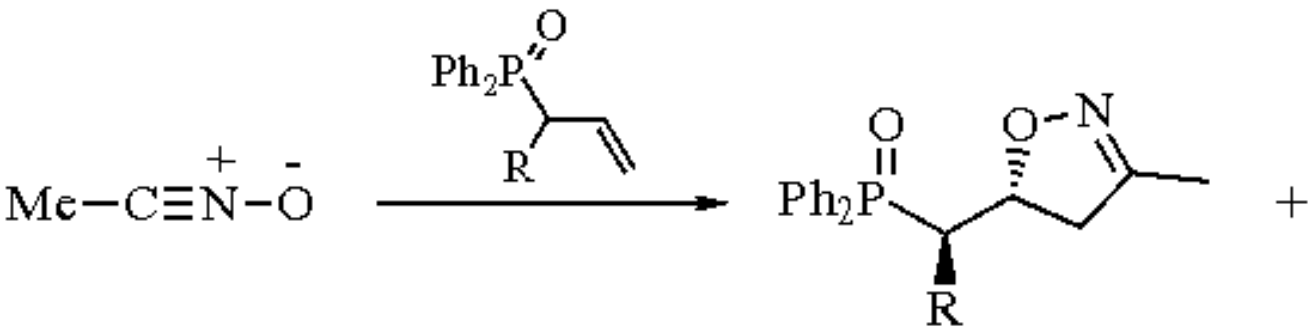

major

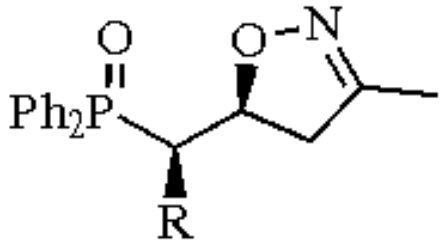

(2)

minor

The regioselectivity[2] and diastereoselectivity[12,19] of the cycloaddition of nitrile oxides to alkenes has been reviewed. Optically active isoxazolines are formed from acryloyl derivatives bearing bornyl,[8b] cyclitols,[20] or sultams[21] as chiral auxiliaries.

Alkynes produce isoxazoles (eqs 3 and 4),[4] whereas other unsaturated substrates yield a variety of heterocycles (e.g. thioesters -> 1,4,2-oxathiazolines,[5] imines -> 1,2,4-oxadiazolines,[22] and isothiocyanates -> imino-1,4,2-oxathiazoles[23]).

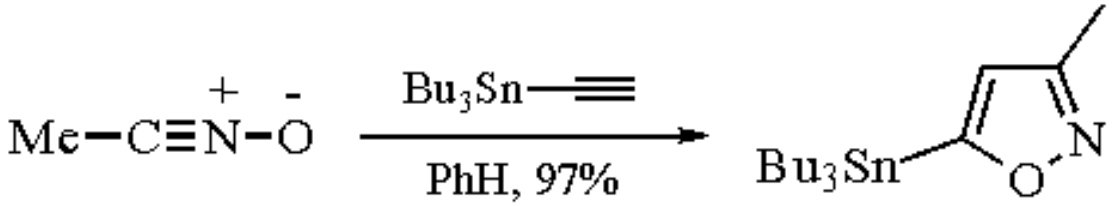

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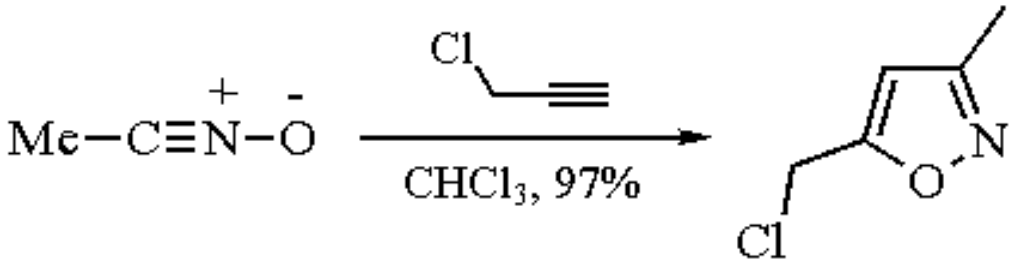

(4)

Related Reagents.

Triphenylacetonitrile N-Oxide.

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Acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate

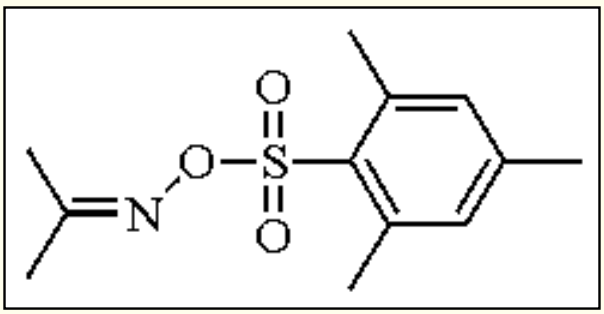

[81549-07-7] · $C_{12}H_{17}NO_3S$ · Acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate · (MW 255.20)

(electrophilic aminating reagent for Grignard reagents[1])

Physical Data: mp 95-96.5 °C; *d* 1.12 g cm^{-3}.

Solubility: sol ether, THF; slightly sol benzene; insol hexane.

Preparative Method: ***Acetone*** reacts with ***Hydroxylamine*** hydrochloride in methanol-aq. NaOH solution to yield acetoxime,[2] which is also commercially available. Acetoxime reacts with 2,4,6-trimethylbenzenesulfonyl chloride in triethylamine-DMF to yield acetoxime *O*-(2,4,6-trimethylphenylsulfonyl)sulfonate.[3]

Electrophilic Amination.

The addition of organometallic reagents to oximes[4] has found limited applicability due to the low electrophilicity of oximes and the α-deprotonation requiring the use of a considerable excess of organometallic reagent (eq 1). There are various scattered reports of reactions of Grignard reagents and organolithiums with oximes that furnish amines, amino acids, aziridines, β-amino alcohols, and other products.[5] Ketoximes and their *O*-substituted derivatives can also serve as electrophilic aminating reagents for Grignard reagents and organolithiums (eq 2).[5] So far, acetoxime,[6,7] butanone oxime,[6] cyclohexanone oxime,[8] benzaldoxime,[9] isobutyrophenone oxime,[10] tetraphenylcyclopentadienone oxime *O*-tosylate,[11] and acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate[1] have been used for amination of Grignard reagents and organolithiums.

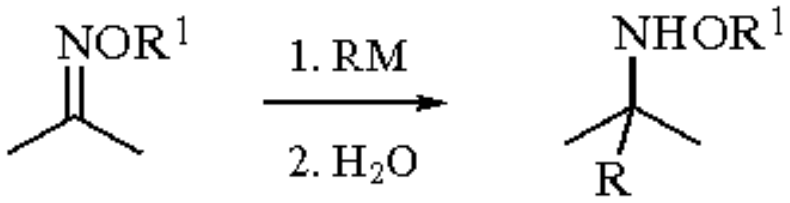

(1)

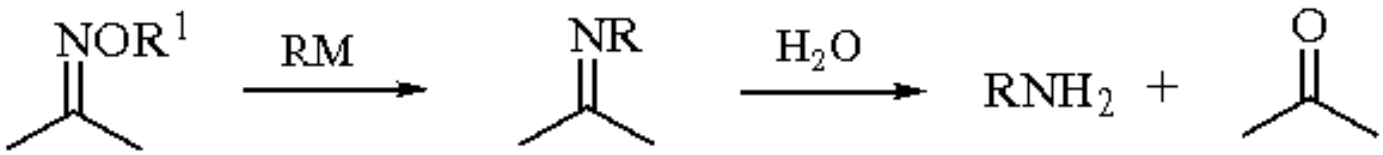

(2)

M = Li, MgBr

Acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate aminates aryl and cyclohexyl Grignard reagents in moderate to good yields (eq 3).[1] The use of ***Copper(I) Iodide*** or $MgCl_2$ as a catalyst in the amination of aryl Grignard reagents decreases the reaction time remarkably and/or increases the yield. On addition of 10 mol % of CuI or 20 mol % of $MgCl_2$ in the amination of phenylmagnesium bromide, the yield of aniline is 59% after heating at 75 °C for 22 h compared to 58% in an uncatalyzed reaction of 40 h at the same temperature. On the addition of 7 mol % of $MgCl_2$ in the amination of *p*-tolylmagnesium bromide, the yield of *p*-toluidine is 56% after heating at 75 °C for 23 h compared to 36% in an uncatalyzed reaction of 43 h at the same temperature. The use of phenyllithium, phenylzinc chloride, and bromomagnesium diphenylcuprate results in 6%, 0%, and 22% yields respectively.

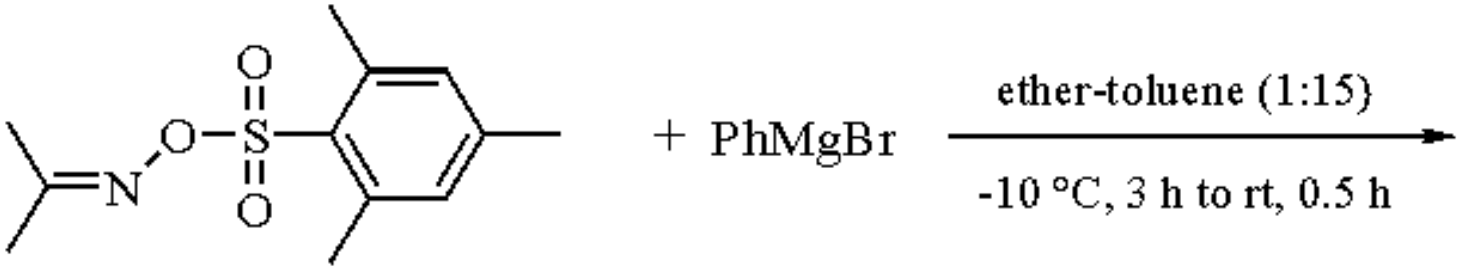

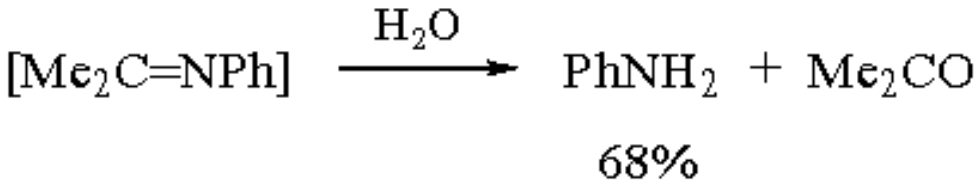

(3)

When comparisons are made between the electrophilic aminating abilities of oximes reported so far, acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate is seen to be more effective than acetoxime, but less effective than ***Tetraphenylcyclopentadienone Oxime O-Tosylate***. However, the molar ratio of Grignard reagent to oxime that is needed has been reported to be 7:1 in in the amination with tetraphenylcyclopentadienone oxime *O*-tosylate compared to 1.5:1 in the amination with acetoxime *O*-(2,4,6-trimethylphenyl)sulfonate. The yield of aniline obtained by aminating phenylmagnesium bromide with acetoxime,[6,7] butanone oxime,[6] cyclohexanone oxime,[8] isobutyrophenone oxime,[10] and tetramethylphenylcyclopentadienone oxime *O*-tosylate[11] is 62%, 12%, 25%, 17%, and 95%, respectively.

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2-Acetoxyacrylonitrile

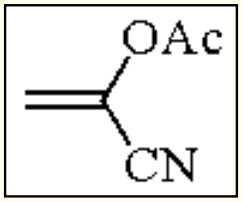

[3061-65-2] · $C_5H_5NO_2$ · 2-Acetoxyacrylonitrile · (MW 111.10)

(ketene equivalent for use in the Diels-Alder reaction;[1] undergoes other cycloaddition reactions; reacts with nucleophiles and radicals)

Physical Data: bp 80-82 °C/30 mmHg; *d* 1.040 g cm^{-3}.

Solubility: sol most organic solvents other than pure hydrocarbons.

Form Supplied in: neat light-yellow liquid.

Analysis of Reagent Purity: ^{1}H NMR, ^{13}C NMR.

Preparative Methods: due to the expense of the commercial material it has been suggested[2] that for large scale use, preparation[3] is more reasonable.

Handling, Storage, and Precautions: highly toxic; use only in a fume hood. Reagent can be absorbed through the skin. Always wear gloves when handling this reagent.

[4 + 2] Cycloaddition Reactions.

Historically, 2-acetoxyacrylonitrile was the first ketene equivalent developed for the Diels-Alder reaction.[1] Thus the title compound reacts thermally with cyclopentadiene to yield the cycloadduct (**1**) which upon treatment with base produces norbornenone (**2**) (eq 1).[4] Since this first report, 2-acetoxyacrylonitrile and ***2-Chloroacrylonitrile*** have been the two most popular ketene equivalents used in the Diels-Alder reaction. Dienes which have been shown to react with 2-acetoxyacrylonitrile include substituted cyclopentadienes[5] and cyclohexadienes,[6] fulvenes,[7] cycloalkadienones,[8] polycyclic aromatics,[9] furans,[2,10b] isobenzofurans,[11] dihydropyridines,[12] vinylcycloalkenes,[13] and acyclic dienes.[14] In the case of furans the reaction is usually catalyzed by high pressure[2,10a,c] or Lewis acids.[10b] The reaction shown in eq 1 has been catalyzed with ***Lithium Perchlorate***.[15]

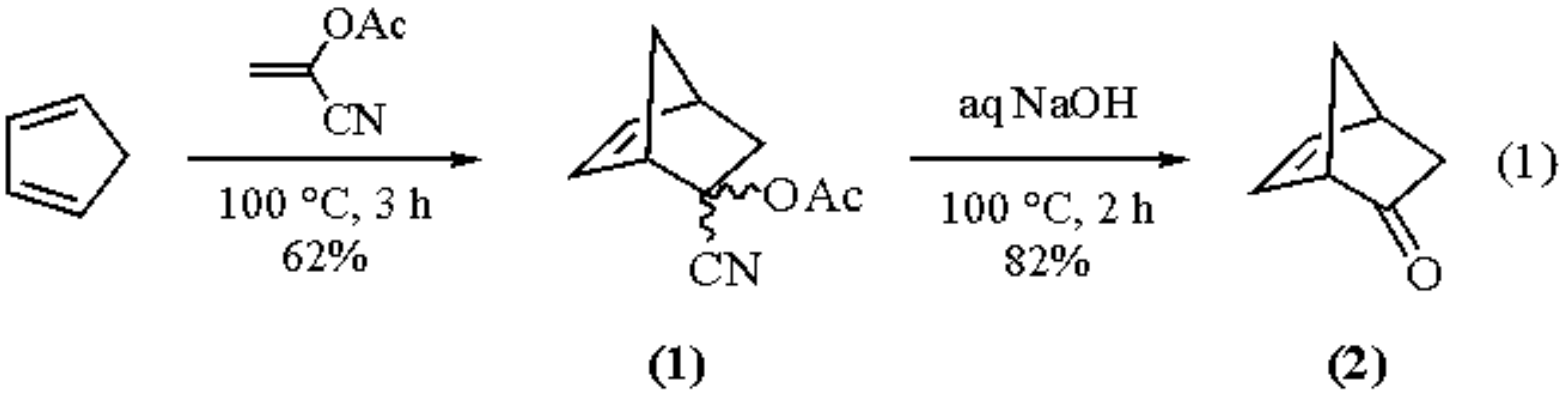

An early comparison between 2-chloro- and 2-acetoxyacrylonitrile indicated that the chloro derivative was slightly more reactive and more regioselective in its reaction with cyclohexadienes.[6a] However, 2-acetoxyacrylonitrile does offer some advantage in that the resulting cycloadduct can, at times, be more easily manipulated. For example, the furan adduct (**3**) was converted to the desired ketone (**5**) by treatment with base followed by exposure to formalin (eq 2).[2,10] The formalin is used to convert residual cyanohydrin (**4**) to the ketone.[10b] The corresponding adduct from 2-chloroacrylonitrile did not yield ketone (**5**) when treated with base. In an another example, adduct (**6**) was converted to ketone (**7**) as shown (eq 3).[13a] This two-step procedure[14b] diminished an unwanted isomerization of the double bond to the more stable α,β-unsaturated enone.[13b,c] Finally, in at least one instance the intermediate α-acetoxynitrile was reduced to a vicinal amino alcohol with ***Lithium Aluminum Hydride***.[6b]

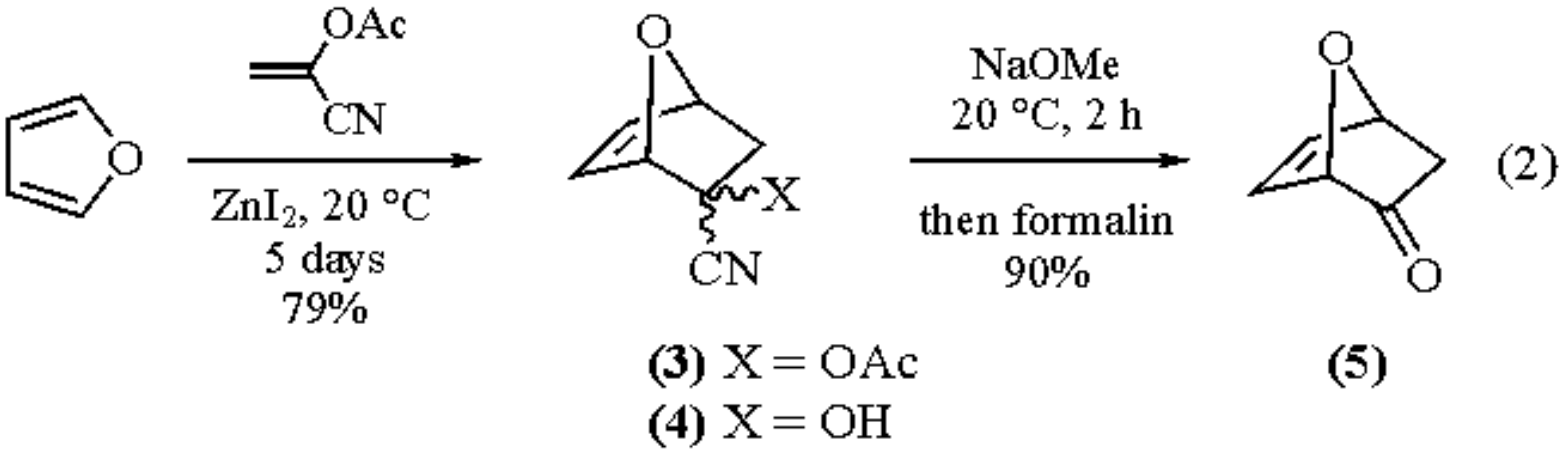

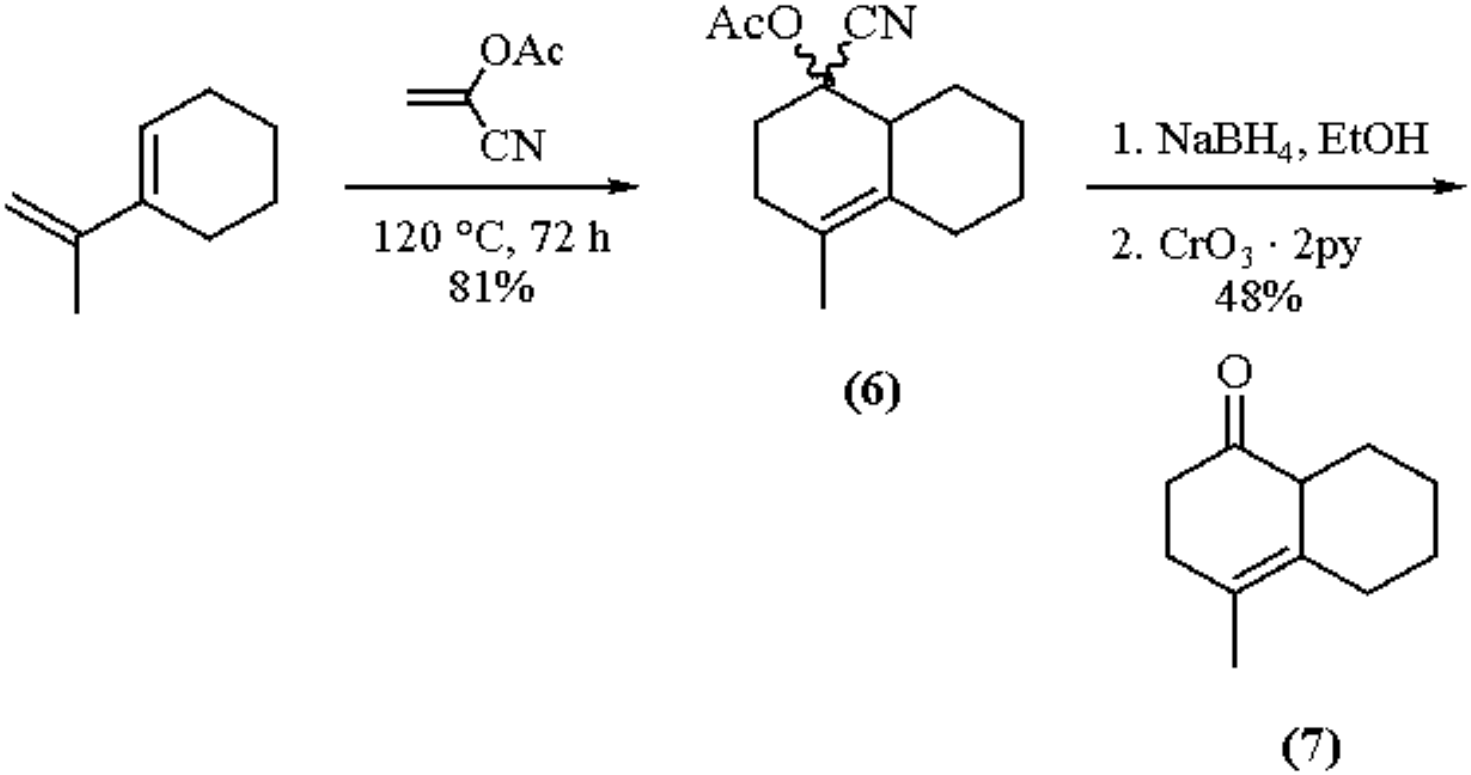

(3)

The preparation of ketone (**5**) in optically pure form[10b,16] has been achieved by use of chiral α-carboxyacrylonitriles derived from camphanic acid[16a] as well as from tartaric acid.[16c] In general the facial selectivity exhibited in the cycloaddition is moderate and the obtention of one stereoisomer is dependent on selective recrystallization. Ketone (**5**) has been used extensively in chiral synthesis.[16c]

Other Reactions.

2-Acetoxyacrylonitrile undergoes both [2 + 3][17] and [2 + 2][18] cycloaddition reactions. Cyclopropanation of 2-acetoxyacrylonitrile with a variety of diazoalkanes represents a facile route to cyclopropanone cyanohydrins (eq 4).[17b] As is expected for an electron deficient alkene, 2-acetoxyacrylonitrile reacts with both nucleophiles[19] and radicals[20] in a conjugate-type addition.

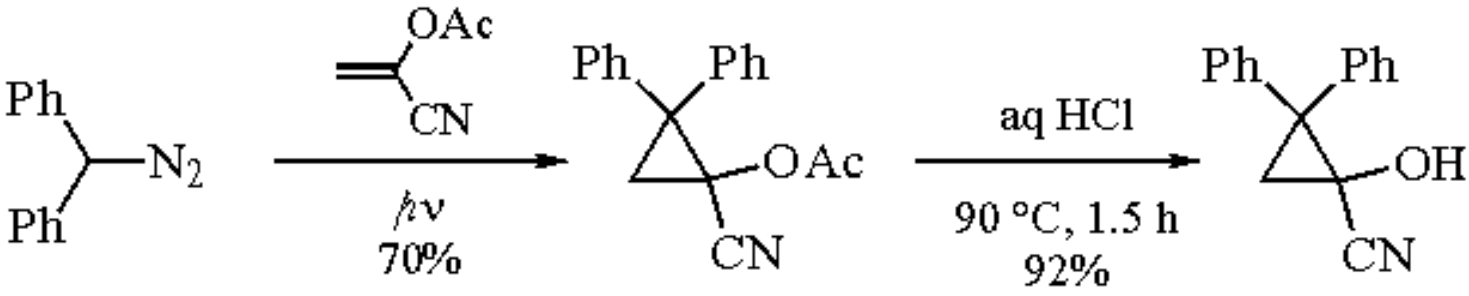

(4)

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1-Acetoxy-1,3-butadiene

[1515-76-0] · $C_6H_8O_2$ · 1-Acetoxy-1,3-butadiene · (MW 112.13)

(2π or 4π partner in cycloaddition reactions;[1] mono-oxygenation allows high levels of regiocontrol[2])

Alternate Name: 1,3-butadienyl acetate.

Physical Data: bp 60-61 °C/40 mmHg; *d* 0.945 g cm^{-3}.

Form Supplied in: colorless liquid, available as an unspecified mixture of (*E*) and (*Z*) isomers.[3]

Handling, Storage, and Precautions: classified as a flammable liquid and is reputed to be toxic. Compound polymerizes upon extended storage and can be regenerated by distillation. Avoid polymerization initiators. Diene performs best when stored in the cold.

Preparation.

1-Acetoxy-1,3-butadiene (**1**)[4] is commercially available as a mixture of (*E*) and (*Z*) isomers, and can be prepared by reaction of ***Crotonaldehyde*** with acetic anhydride-sodium acetate to provide the diene as an isomeric mixture in ~60% yield.[5a] Pure (*E*)-1-acetoxy-1,3-butadiene can be prepared in high yield by the slow addition of crotonaldehyde to refluxing ***Isopropenyl Acetate*** containing catalytic amounts of *p*-toluenesulfonic acid and copper acetate. After distillation to remove acetone and excess isopropenyl acetate, (*E*)-1-acetoxy-1,3-butadiene can be isolated by vacuum distillation in >80% yield.[5]

Reactivity.

1-Acetoxy-1,3-butadiene (**1**) is primarily used as a 4π partner in $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition reactions of the normal electron demand type, and reacts well with electron-deficient dienophiles.[1] The presence of the weakly electron-donating 1-acetoxy substituent on this open-chain diene imparts a useful degree of regio- and stereoselectivity in cycloaddition reactions;[2] *ortho-endo* adducts predominate and often single isomers are obtained exclusively (eq 1).[6] This high *ortho* selectivity can be rationalized using frontier molecular orbital (FMO) theory.[7] Ab initio STO-3G calculations of energies and coefficients of the frontier molecular orbitals for the *s-cis* conformation of diene (**1**) have been reported.[8] The moderately electron-rich diene (**1**) has been found to be slightly more reactive toward polarized

dienophiles than simple dienes;[5a,9] however, the reported incompatibility of the diene with Lewis acids precludes most low-temperature Lewis acid-catalyzed reaction conditions and limits the general utility of diene (**1**).[8] Reactions employing an excess of a mixture of (*E*,*Z*)-1-acetoxy-1,3-butadiene can potentially yield single cycloadducts due to the increased reactivity of the (*E*) isomer compared to the (*Z*) isomer, thereby obviating the need for purification of individual diastereomers of (**1**).

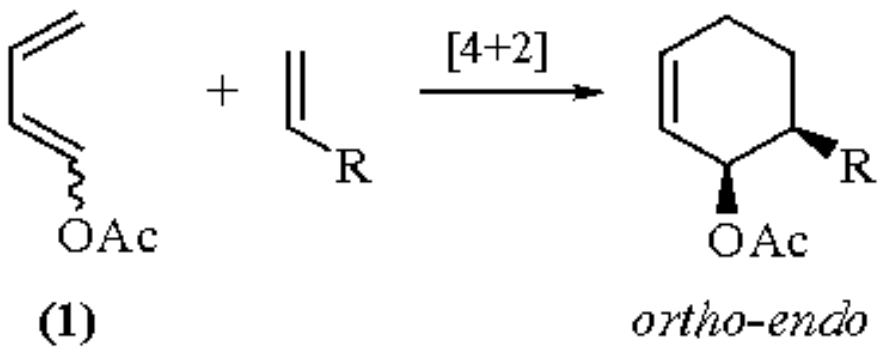

(1)

Cycloaddition Reactions.

Reactions utilizing diene (**1**) and ***Acrolein*** or crotonaldehyde were reported to afford single cycloadducts in moderate to fair yield with good regioselectivity.[10] However, since that early report, the most frequent use of 1-acetoxy-1,3-butadiene in cycloaddition reactions involves coupling with naphthoquinone derivatives (eq 2). The importance of this reaction is twofold: (1) the cyclohexenyl acetate cycloadduct provides a useful framework upon which further modifications can be made; and (2) either regioisomeric cycloadduct can lead to aromatic products (either spontaneously or promoted) via 1,4-elimination of acetic acid followed by tautomerization to a dihydroquinone system. Employing these tactics, many naphthoquinone,[11] anthracycline,[6e,12] azaanthraquinone,[13] and tetracycline[14] derivatives have been efficiently constructed, and this general use as a butadienyl synthon constitutes a significant portion of the literature on diene (**1**).[6a,e,14,15]

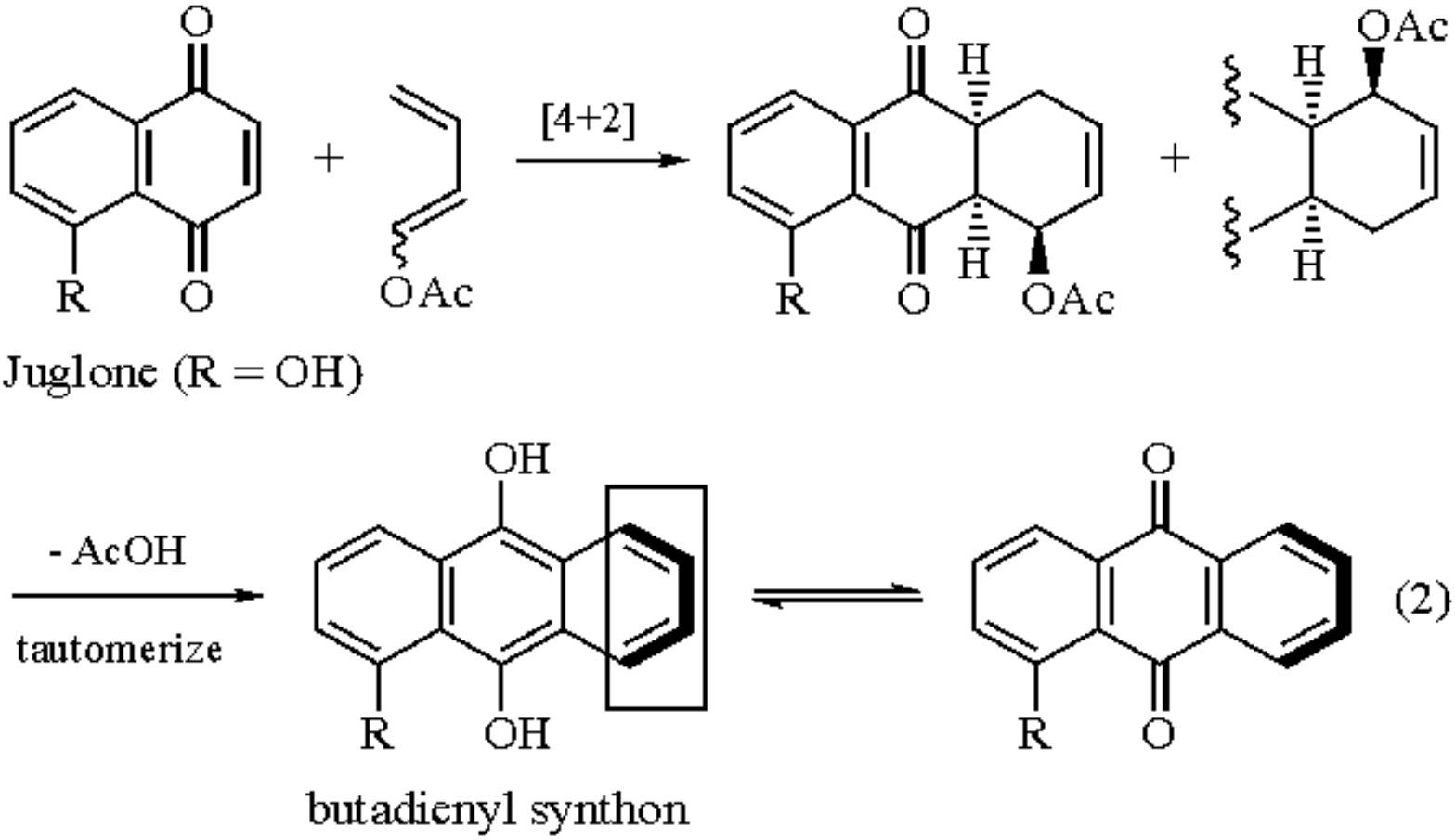

4-Demethoxydaunomycinone (**2**)[12c] and (±)-terramycin (**3**)[14] are representative examples of natural products constructed employing a Diels-Alder strategy with diene (**1**).

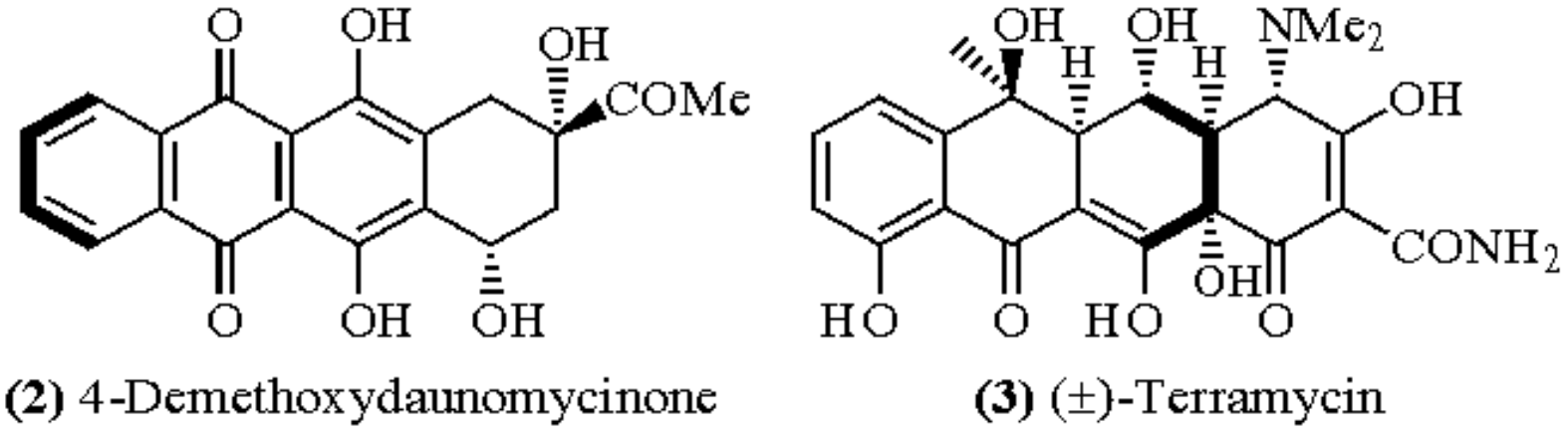

Highly regioselective cycloaddition reactions have been realized between diene (**1**) and a wide variety of dienophiles, including substituted acrylonitrile derivatives,[16] haloquinones (eq 3),[17] substituted enones (eq 4),[8,18] naphthoquinone derivatives,[6e,14,19] nitroalkenes,[9] alkenyl sulfones,[19,20] alkenyl metal carbene complexes (eq 5),[21] substituted maleimides,[22] and several others.[23] Useful levels of diastereoselection have been achieved in several of these systems.[6c,18a,21,22,23c]

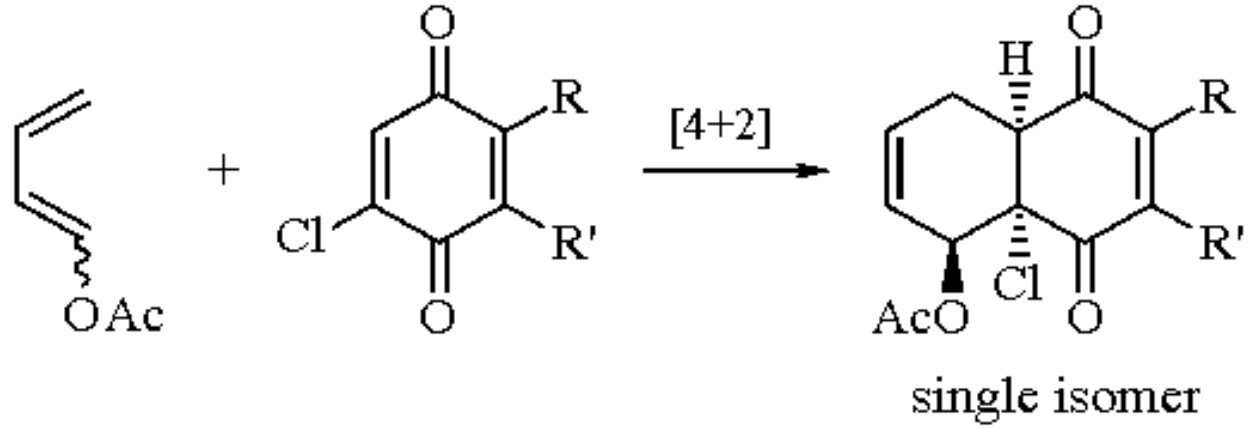

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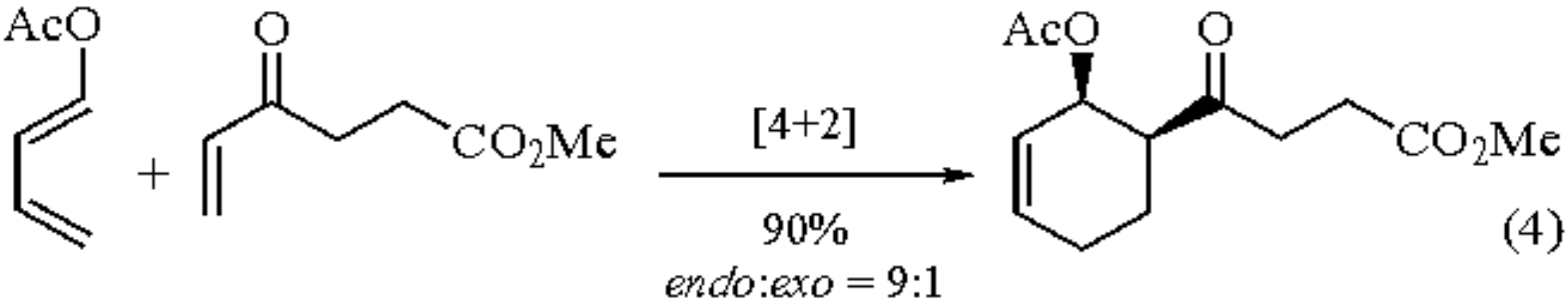

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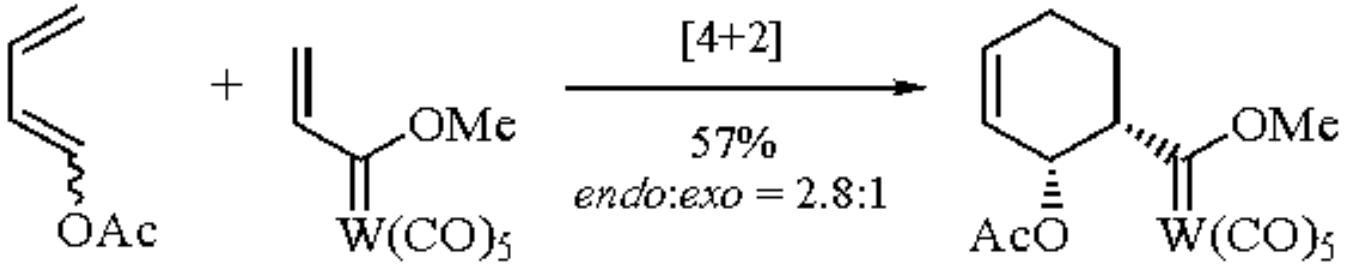

(5)

While these Diels-Alder reactions afford predominately the *ortho-endo* adducts, *ortho-exo* product formation predominates in cycloaddition reactions between diene (**1**) and bridgehead enones (eq 6)[24] or unsymmetrical tropones,[25] presumably due to repulsive secondary FMO interactions.[26]

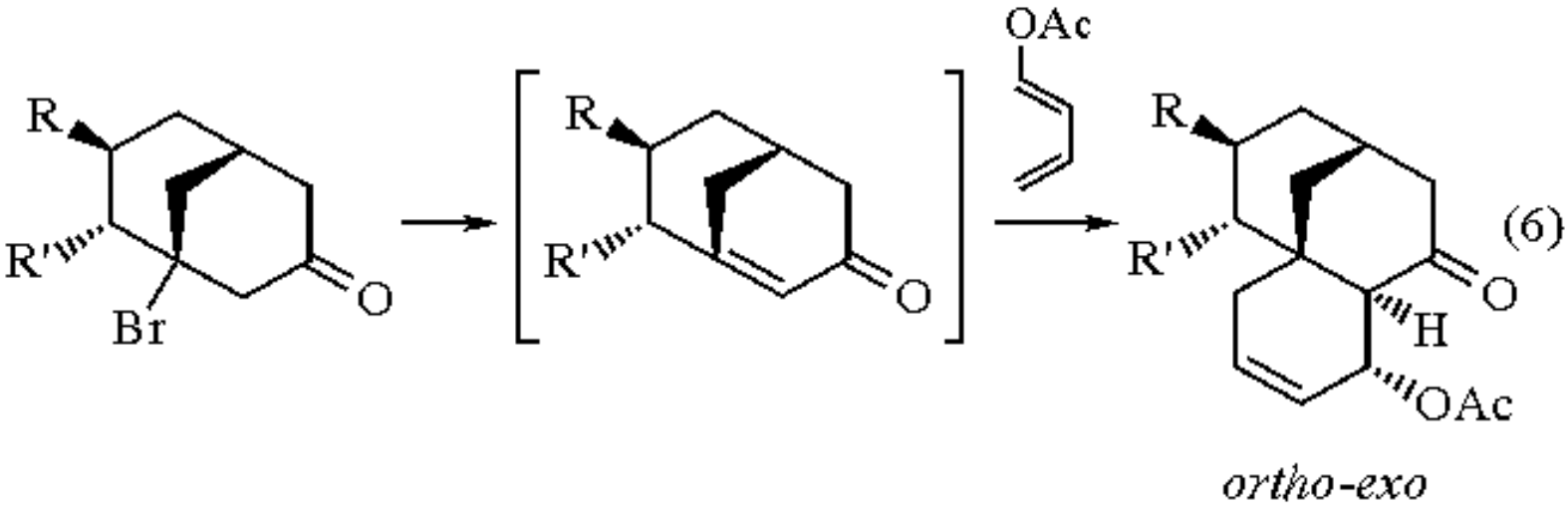

(6)

Examples of successful Lewis acid-catalyzed cycloaddition reactions of diene (**1**) are limited. ***Boron Trifluoride***

Etherate-mediated cycloaddition between juglone and diene (**1**) afforded a single cycloadduct in 97% isolated yield,[11] whereas uncatalyzed versions of the same reaction afford <50% of the same adduct.[17a] Boron trifluoride etherate[27a] and ***Tin(IV) Chloride***[28] have also been used to enhance[27] or reverse[29] regioselectivity in cycloaddition reactions employing diene (**1**).

An example of an asymmetric Diels-Alder reaction involving diene (**1**) has been reported.[30] Use of a binaphthol-based borane catalyst in the reaction of juglone with diene (**1**) afforded a single adduct in good yield with >98% enantiomeric excess (eq 7).

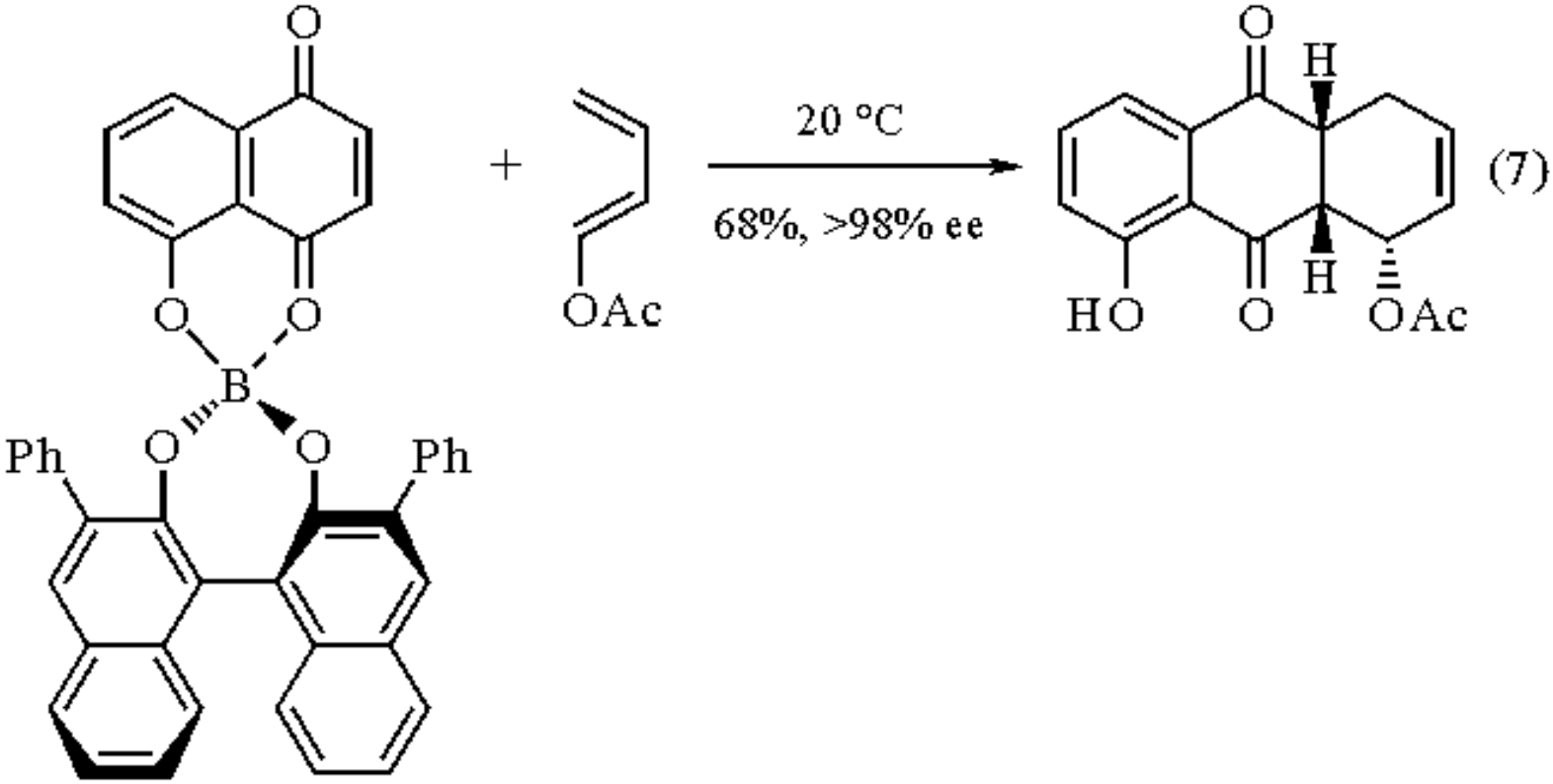

1-Acetoxy-1,3-butadiene participates in other cycloaddition reactions as well. Assembly of an azetidinone system, a key substructure in the total synthesis of (±)-thienamycin, was accomplished by [2 + 2] cycloaddition of diene (**1**) and ***Chlorosulfonyl Isocyanate*** (eq 8).[31] Diene (**1**) has also been employed as the 2π partner in a 1,3-dipolar cycloaddition reaction.[32]

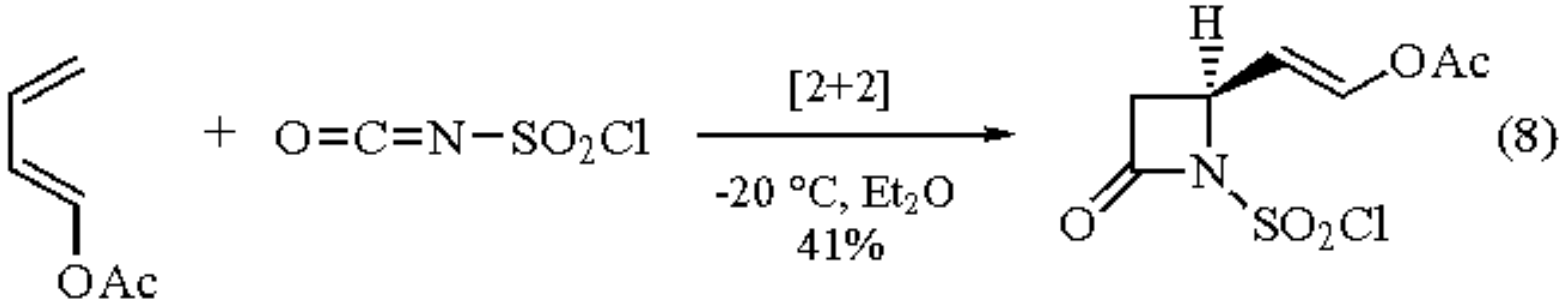

A highly *endo*-selective cycloaddition for the construction of bicyclo[4.4.1]undecane systems using a photochemical metal-mediated cycloaddition reaction between (η^6-cycloheptatriene)chromium tricarbonyl and diene (**1**) (eq 9) has been reported.[33] In an example of a thermal [6 + 4] cycloaddition reaction, diene (**1**) and unsymmetrical tropone

derivatives afforded predominately *exo* adducts in modest yields.[25b] This type of Diels-Alder strategy was utilized in the synthesis of [4](2,7)troponophane.[25c]

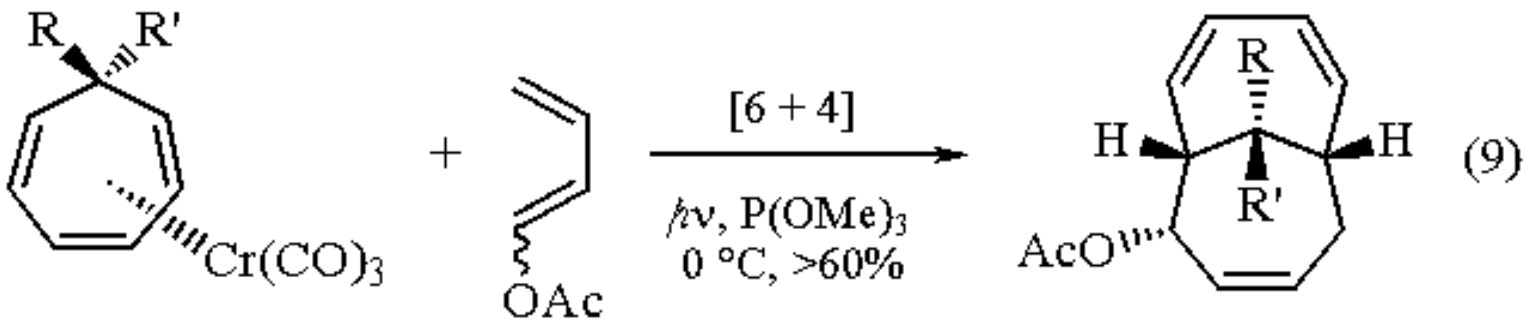

Miscellaneous Reactions.

Diene (**1**), formally a dienol acetate, undergoes anodic oxidation and regioselective γ-methoxylation, which provides a key intermediate in a method for 1,4-carbonyl transposition.[34] A palladium-assisted heteroannulation of diene (**1**) with organomercurials also has been reported (eq 10).[35]

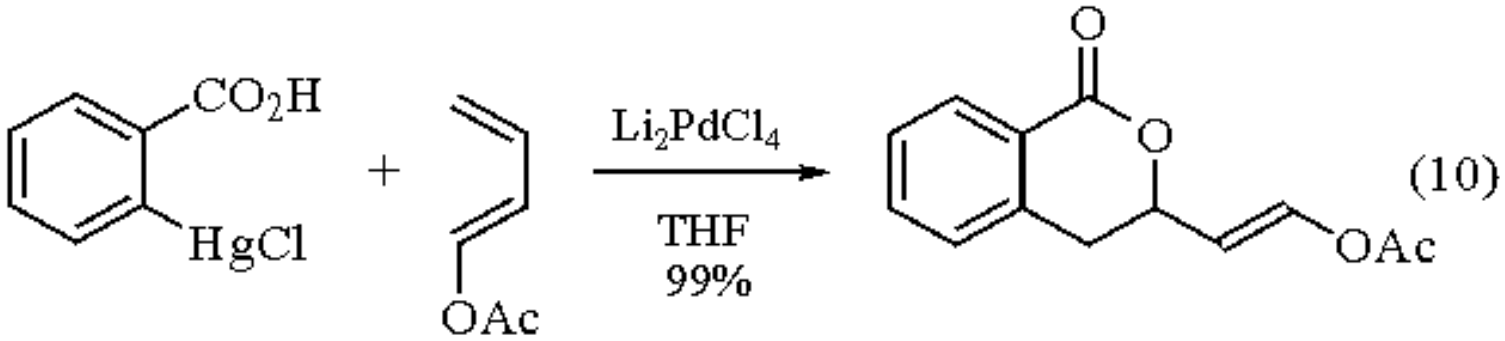

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2-Acetoxyisobutyryl Chloride

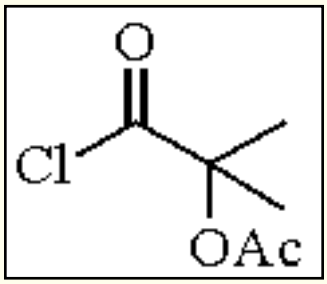

[40635-66-3] · $C_6H_9ClO_3$ · 2-Acetoxyisobutyryl Chloride · (MW 164.592)

(useful for converting *cis*-diols to *trans*-chloroacetates[1] followed by epoxide formation[2])

Alternate Name: Moffatt reagent.

Physical Data: bp 55-56 °C/6 mmHg; *d* 2.236 g cm^{-3}.

Form Supplied in: liquid of 95% purity commercially available.

Preparative Methods: can be prepared by the acylation of 2-hydroxyisobutyric acid (***Acetyl Chloride***, ***Acetic Acid***) followed by reaction with ***Thionyl Chloride***.[1,3]

Handling, Storage, and Precautions: corrosive and a lachrymator and should be handled accordingly.

2-Acetoxyisobutyryl chloride has been used to convert *cis*-diols to *trans*-chloroacetates (eq 1).[1] *trans*-Diols give many products due to their inability to form the cyclic acetoxonium ion intermediate. Nucleophilic attack occurs primarily at the acetoxy carbonyl group due to the bulky substituents α to the acid chloride carbonyl.

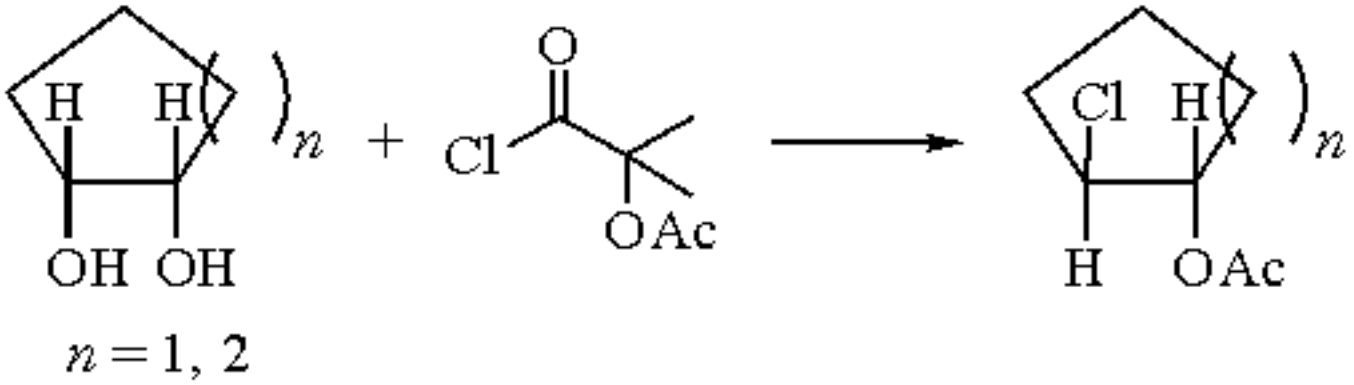

(1)

Ribonucleosides also react smoothly with 2-acetoxyisobutyryl chloride. In this case, a chloroacetate compound was obtained but with retention of configuration due to participation of the C-2 carbonyl group of the uracil ring (eq 2).[1,4]

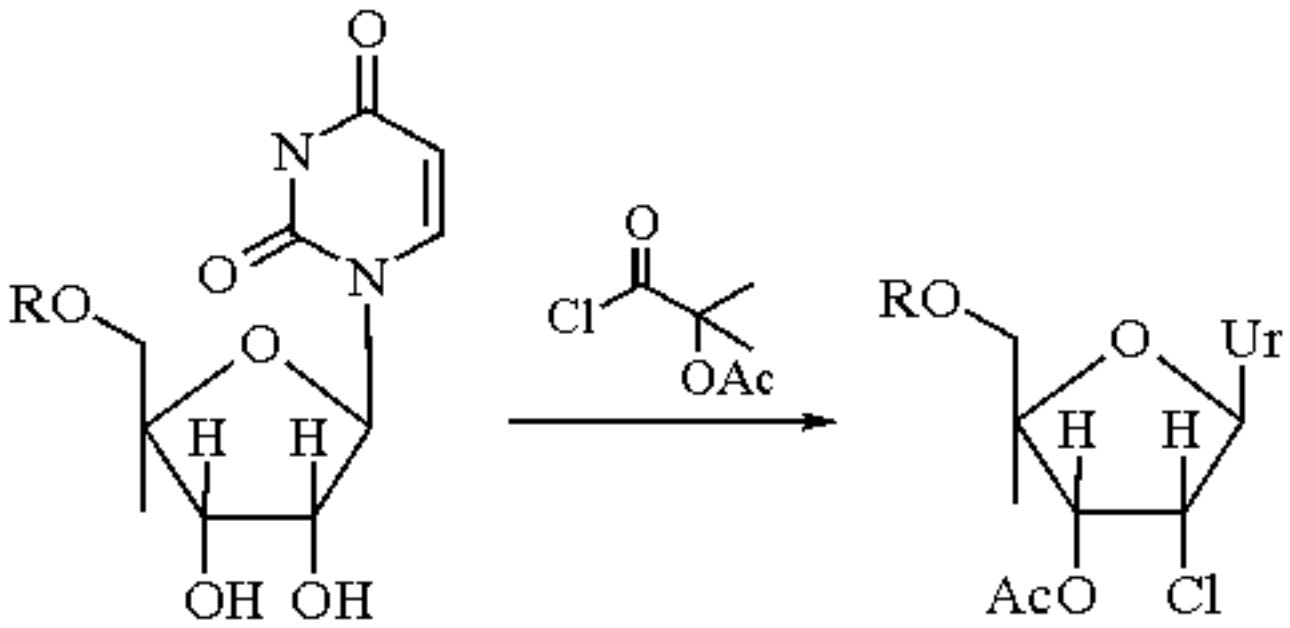

(2)

Recently, the Moffatt reagent has been used in the total synthesis of complex natural products.[5] The chloroacetate compound is easily converted into an epoxide in excellent yield and on a large scale (eq 3).[2] 2-Acetoxyisobutyryl bromide has been employed similarly in natural product synthesis.[6]

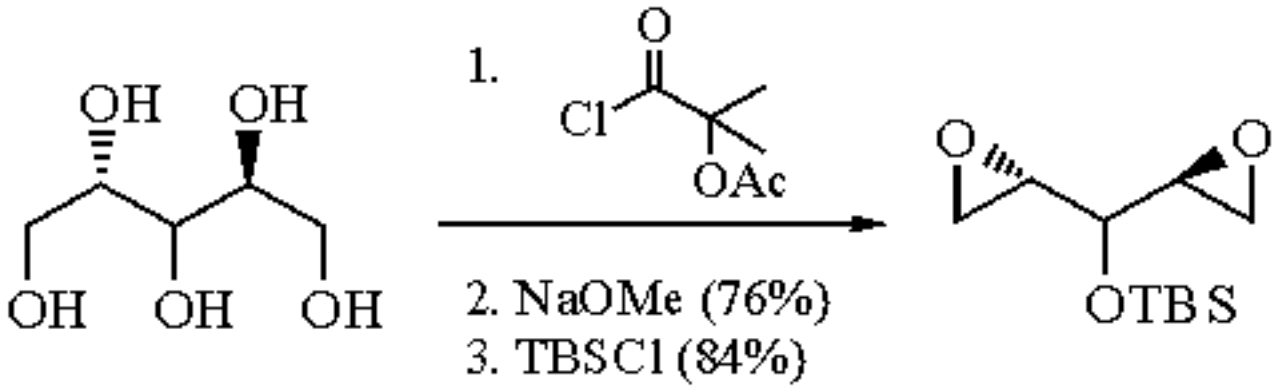

(3)

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3-Acetoxy-2-trimethylsilylmethyl-1-propene[1]

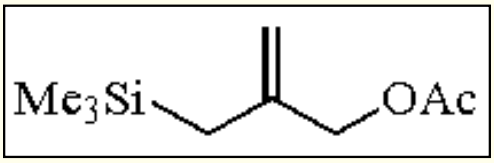

[72047-94-0] · $C_9H_{18}O_2Si$ · 3-Acetoxy-2-trimethylsilylmethyl-1-propene · (MW 186.33)

(precursor for palladium trimethylenemethane cycloaddition reactions)

Physical Data: bp 68-70 °C/6.5 mmHg;[2] 60-61 °C/2.5 mmHg.[3]

Solubility: sol most organic solvents.

Preparative Methods: commercially available but expensive. Several preparations of (**1**)[2-4] or the precursor alcohol (**2**)[5,6] have been reported. The simplest involves the direct silylation of methallyl alcohol (eq 1).[4,5]

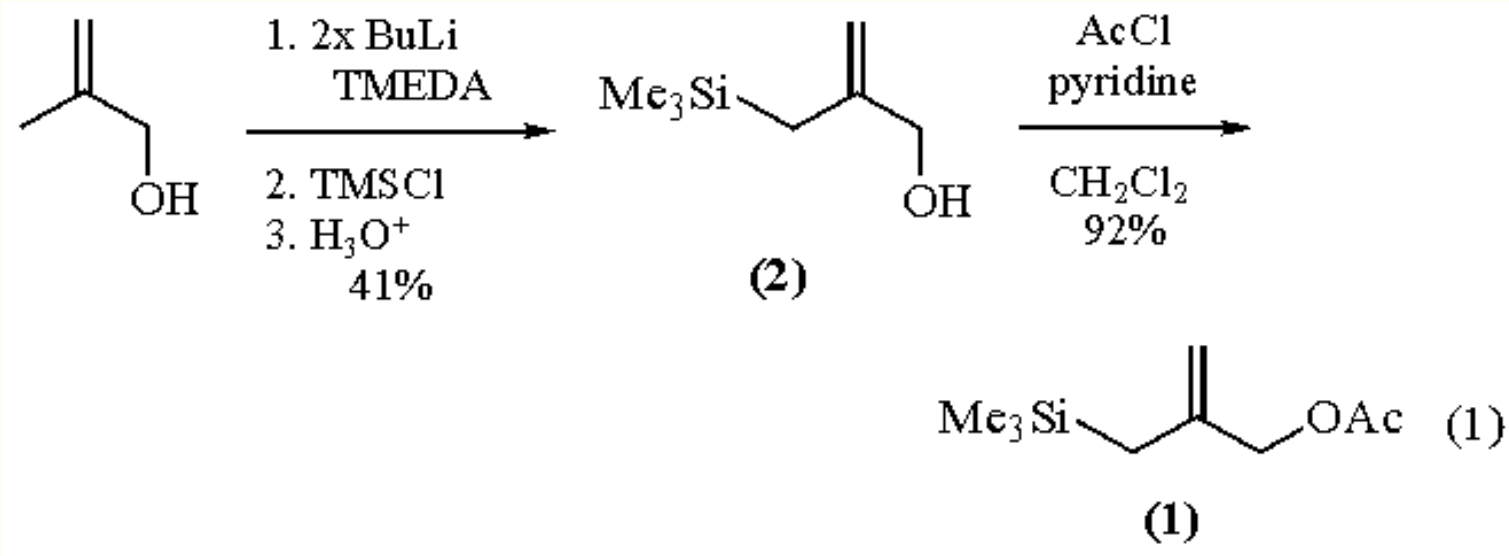

Handling, Storage, and Precautions: volatile, irritant, flammable.

Introduction.

The development by Trost and co-workers of palladium-trimethylenemethane (TMM) cycloadditions employing the title reagent (**1**) and related reagents was a seminal advance in ring-construction methodology. The generality and versatility of these reactions is illustrated below by their use in [3 + 2] cycloadditions to form both cyclopentanes and heterocycles, [3 + 4] and [3 + 6] cycloadditions, and applications in total synthesis.

Methylenecyclopentanes.

Many lines of evidence indicate that in the presence of catalytic Pd^0, (**1**) forms the reactive intermediate palladium-TMM complex (**3**).[7-9] This complex appears to be zwitterionic in character, but its reactivity is governed mainly by its nucleophilicity/basicity. Thus the TMM reactions work best and almost exclusively with electron-deficient alkenes. It appears that in most cases the cycloaddition is stepwise, with the initial Michael-like reaction followed by nucleophilic attack on a cationic π-allylpalladium complex (eq 2). The ion-pair nature of the intermediate (**4**) is thought to be the source of some unusual stereochemical effects which give the reactions some of the characteristics of concerted cycloadditions.[10,11]

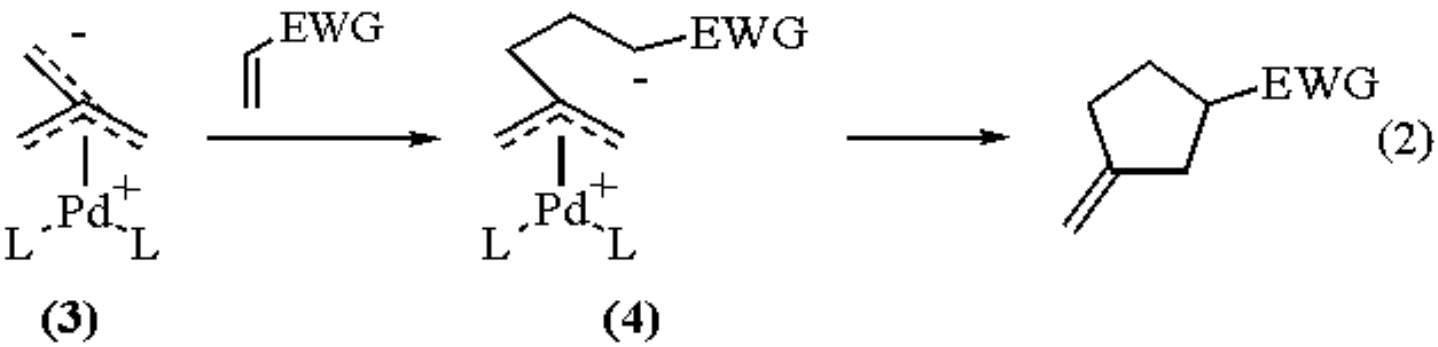

The corresponding methylenecyclopentanes are readily formed from a wide variety of activated alkenes, such as unsaturated esters, lactones, and nitriles, enones, vinyl sulfones, and nitroalkenes.[4] The breadth of utility of this reaction is exemplified below by its use as key steps in syntheses of albene (eq 3),[12] brefeldin A (eq 4),[13] hirsutene (eq 5),[14] the core spirocarbocyclic rings of the ginkgolides (eq 6),[15] cephalotaxine (eq 7),[16] and kempanes (eq 8).[17] The use of doubly activated alkenes, as in eq 8, is of particular advantage in the annulation of 2-cycloalkenones.[17b]

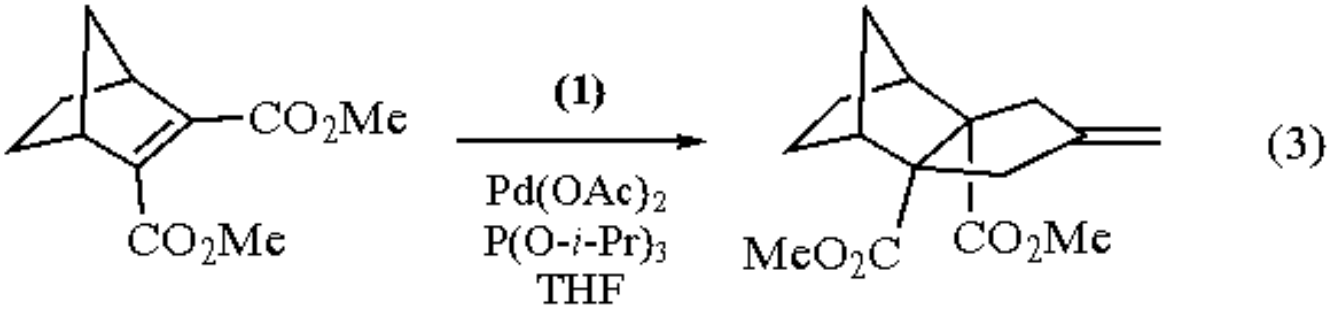

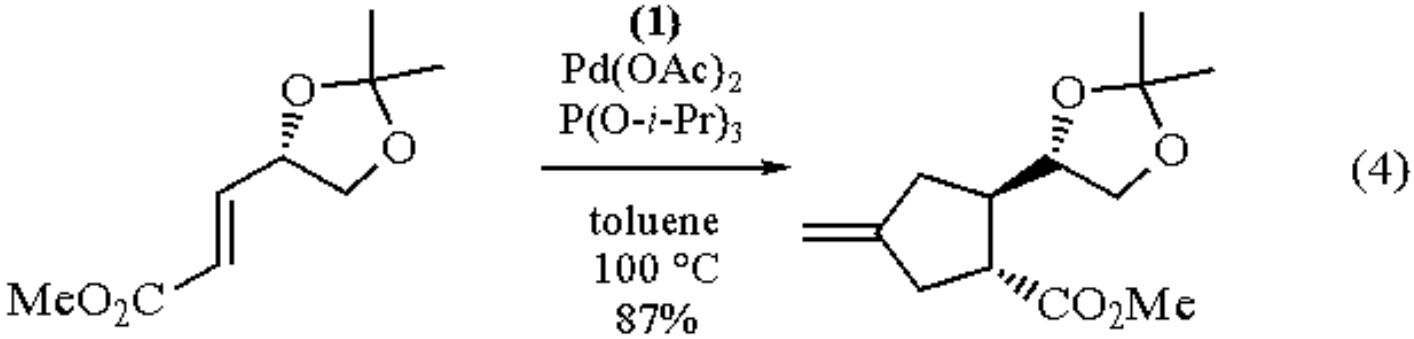

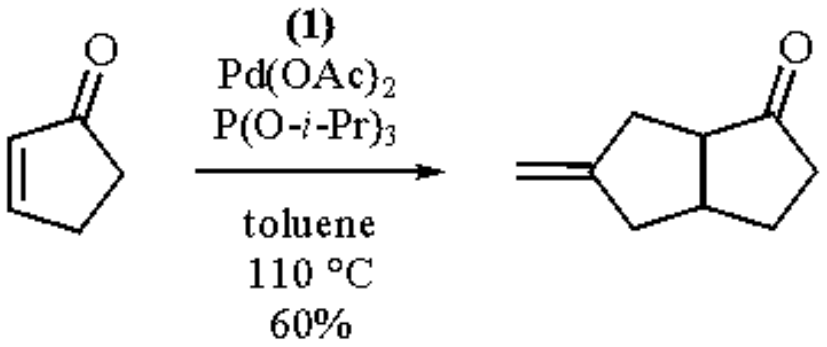

(5)

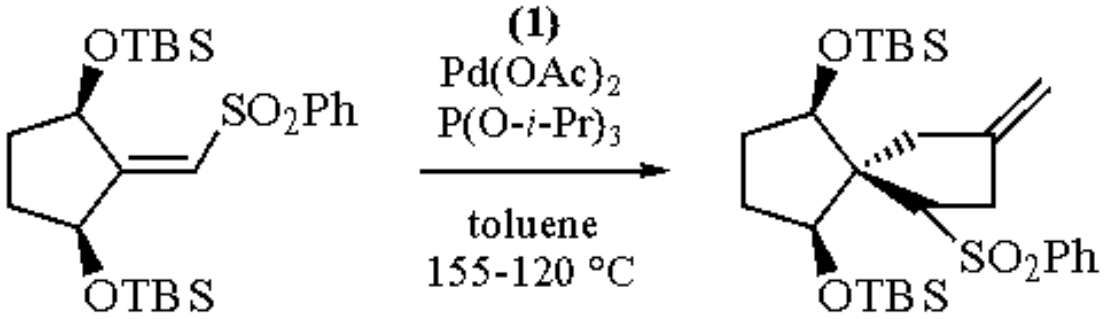

(6)

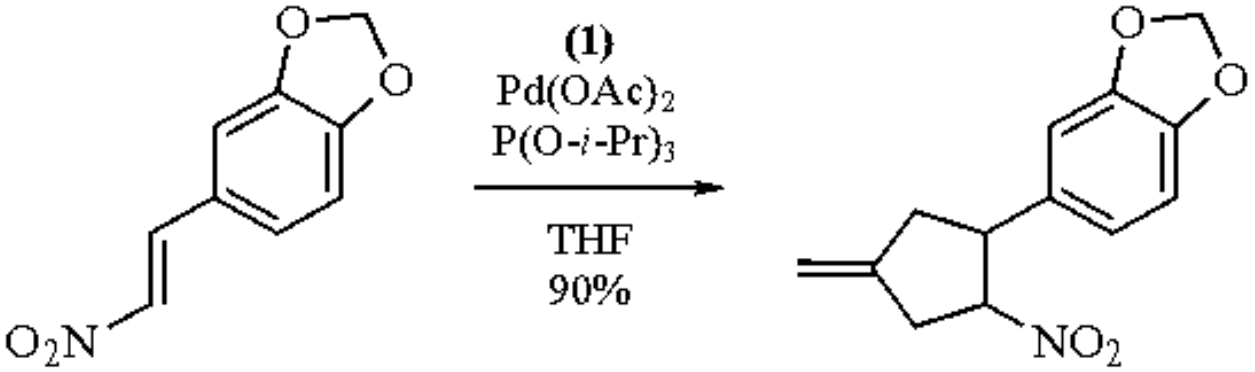

(7)

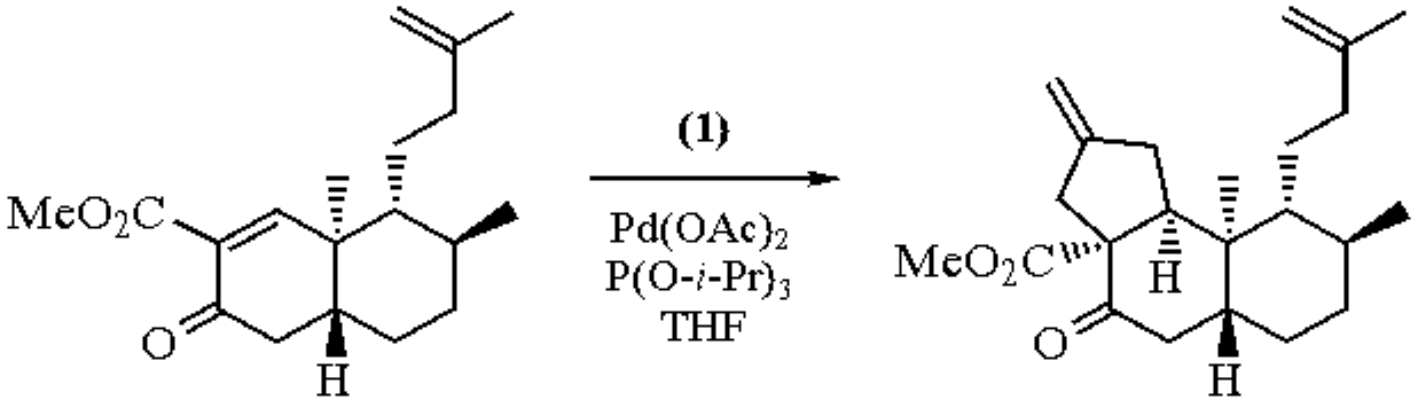

(8)

The adducts from vinyl sulfones are readily converted to cyclopentenones.[18] Vinyl sulfoxides are also acceptors for Pd-TMM cycloadditions. The use of optically pure vinyl sulfoxides allows for reasonable asymmetric induction (eq 9).[19] Outstanding asymmetric induction has been observed using chiral alkylideneoxazepadiones (eq 10).[20]

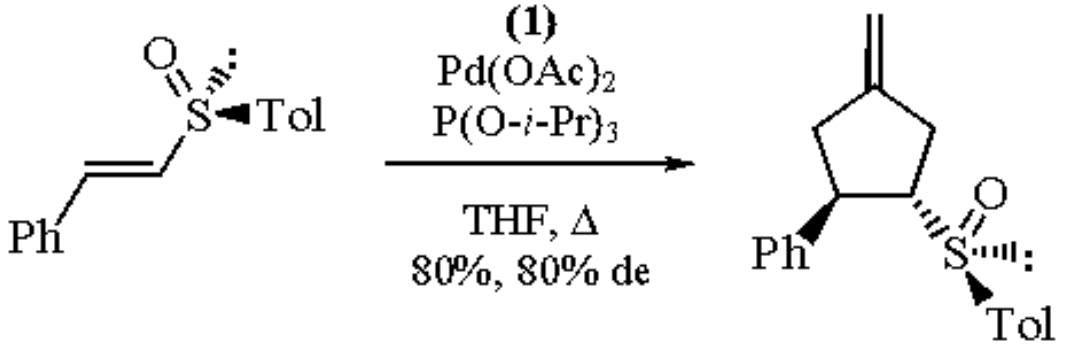

(9)

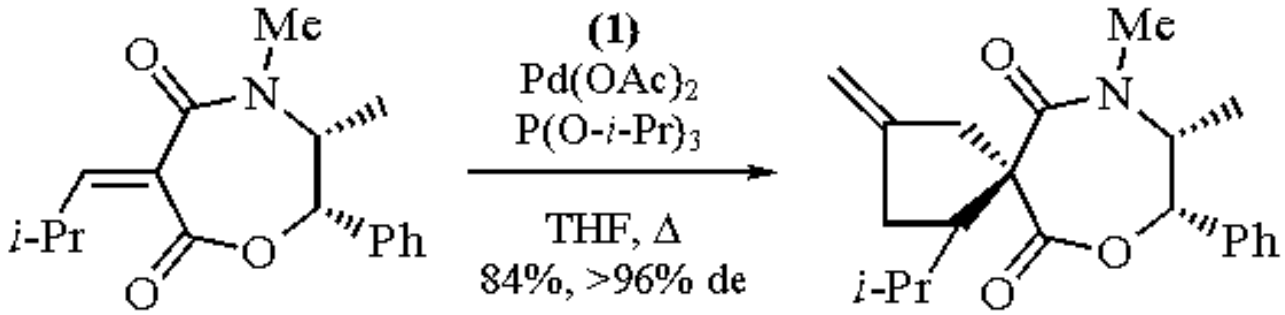

(10)

Methylenecyclopentenes.

Although Pd-TMM cycloadditions with alkynes are unsuccessful, the formation of methylenecyclopentenes from alkynes can be accomplished via the cyclopentadiene adduct (eq 11).[21]

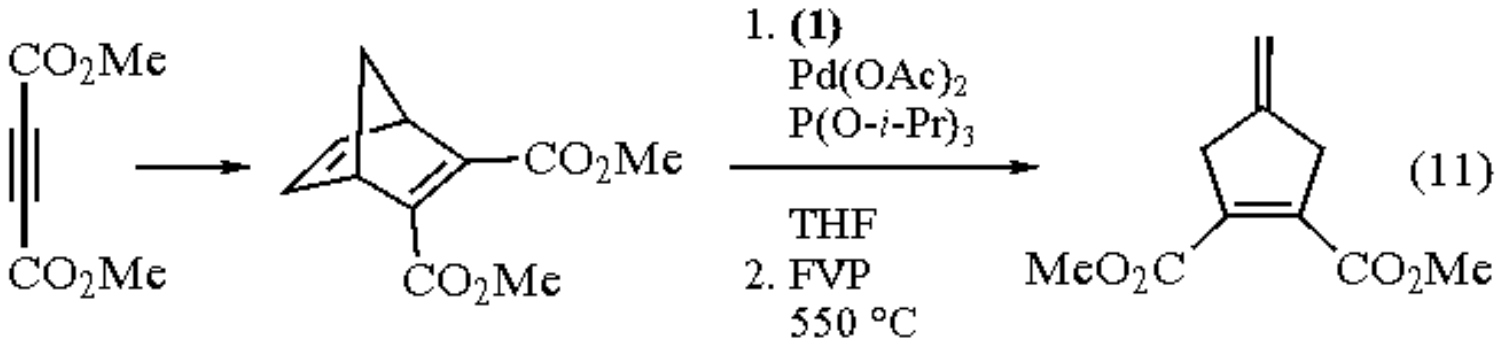

(11)

Heterocycles.

Aldehydes can be converted to methylenetetrahydrofurans using tributyltin acetate or trimethyltin acetate as a cocatalyst (eq 12).[22] Most ketones are completely unreactive to Pd-TMM chemistry, but some oxacyclohexanones are readily annulated (eq 13), apparently due to activation of the carbonyl by the ring oxygen(s).[23] In reactions of α,β-unsaturated aldehydes and ketones, the competition between conjugate (alkene) and 1,2 (carbonyl) cycloadditions often favors reaction of the alkene. The cocatalyst ***Tris(acetylacetonato)indium*** can be used to favor the 1,2-cycloaddition.[24]

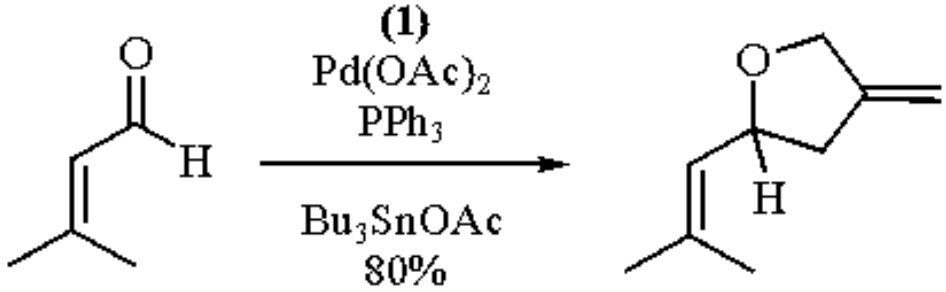

(12)

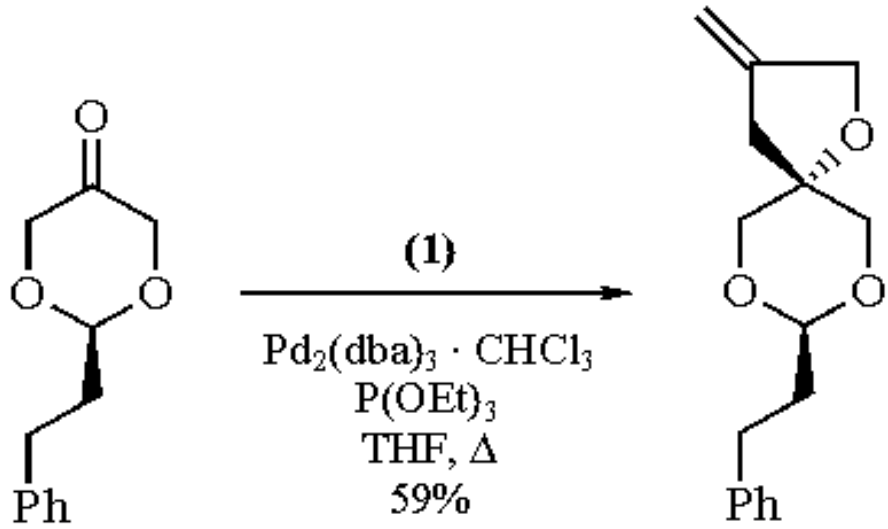

(13)

Methylenepyrrolidines can be formed in Pd-TMM reactions with imines (eq 14). These reactions have also been accomplished using nickel catalysts.[25]

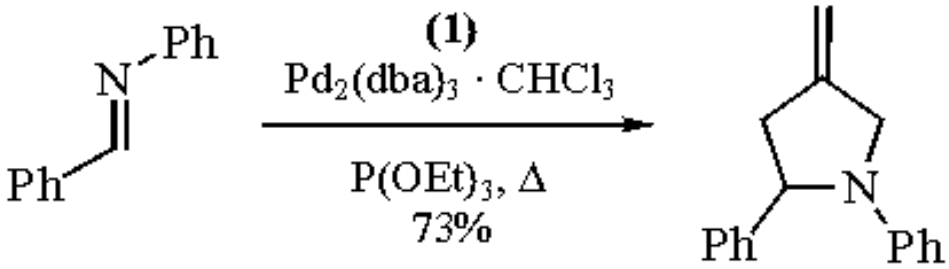

(14)

[4 + 3], [6 + 3], and [3 + 3] Cycloadditions.

As suggested by the stepwise mechanism of eq 2, appropriately chosen dienes and trienes should undergo [4 + 3] and [6 + 3] cycloadditions in Pd-TMM reactions. Thus pyrones readily undergo [4 + 3] cycloadditions (eq 15),[26] and tropones undergo [6 + 3] cycloadditions (eq 16).[27] The main key to obtaining the higher order cycloadditions appears to be the use of all *s-cis* dienes and trienes.[28]

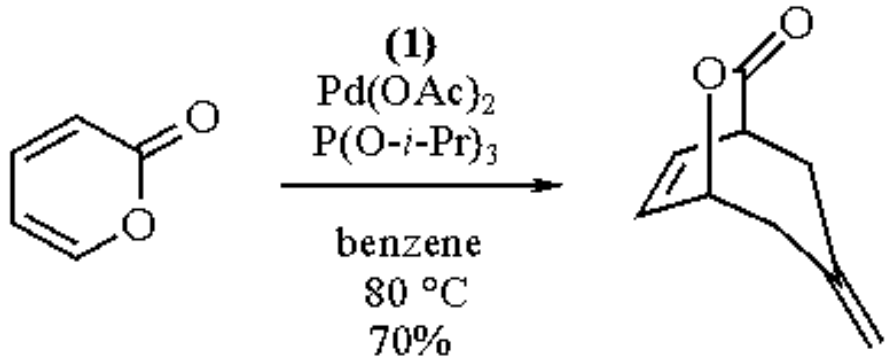

(15)

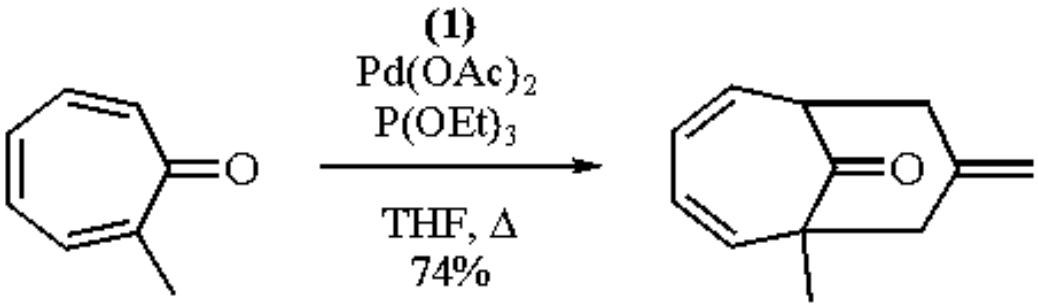

(16)

In a reaction that illustrates the nucleophilic character of the Pd-TMM intermediate (**3**), activated aziridines can undergo a [3 + 3] cycloaddition (eq 17),[29] presumably via initial nucleophilic ring opening of the aziridine by the Pd-TMM.

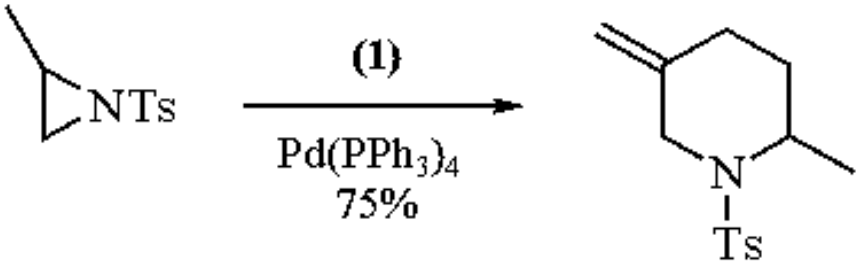

(17)

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Acetyl Bromide

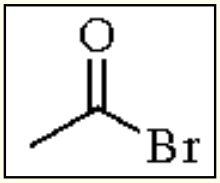

[506-96-7] · C_2H_3BrO · Acetyl Bromide · (MW 122.95)

(bromoacylation of carbonyl compounds;[1] selective *O*-acetylation;[3,4] addition to carbon-nitrogen double bond of unsubstituted cyclic imidates;[6] coupling with vinylcopper reagents;[7] hydrohalogenation of alkynes[8])

Physical Data: mp -96 °C; bp 75-77 °C; colorless liquid; *d* 1.663 g cm^{-3}.

Solubility: sol organic solvents; reacts violently with water, alcohols, and oxidizing agents.

Handling, Storage, and Precautions: corrosive and lachrymator; keep bottle tightly closed. Reacts violently with water. Store under nitrogen. Store in a cool dry place.

Bromoacylation.

The reaction of aldehydes and ketones with acetyl bromide to prepare α-bromoalkyl esters has been known in the literature since the early 1900s.[2] The low yields are a consequence of the fact that the reaction is an equilibrium and that the reactants can revert to starting materials if heated in the presence of the Lewis acid catalyst.[1] Yields are favorable in the case of aliphatic, α,β-unsaturated, and aromatic aldehydes and aliphatic ketones (eq 1). Highest yields are obtained at low temperatures (-10 °C).[1]

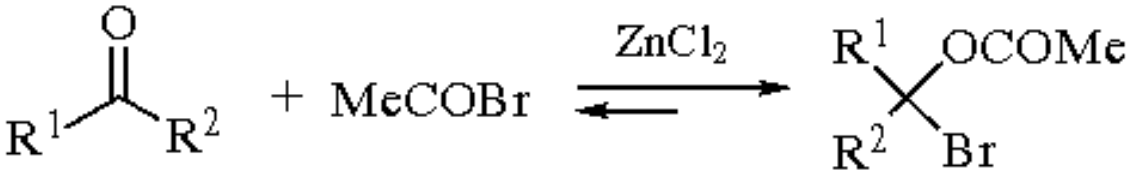

(1)

Addition of acetyl bromide to a solution of 5-methyluridine in acetonitrile heated at reflux gave the bromo ester in 97% yield (eq 2).[3]

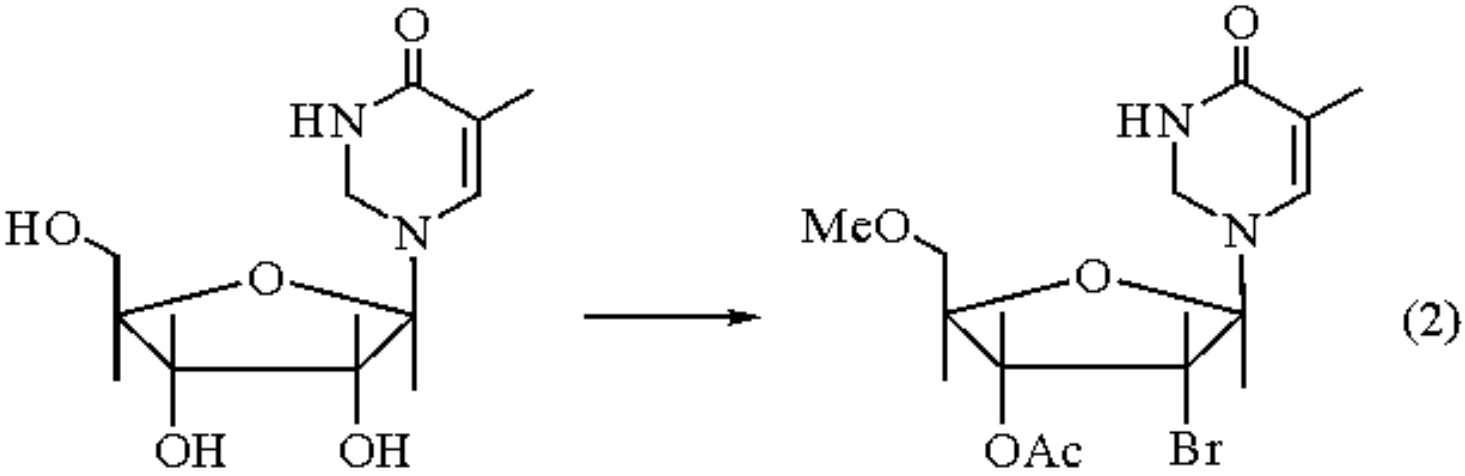

Acetylation.

Hydroxy groups can be selectively acetylated in the presence of primary and secondary amino groups with acetyl bromide and ***Trifluoroacetic Acid***. Diacetylapomorphine (**1**) was obtained in 70% yield using this system.[4] Acetylation of apomorphine with ***Acetic Anhydride*** and base or acid afforded the ring-opened product (**2**).[5]

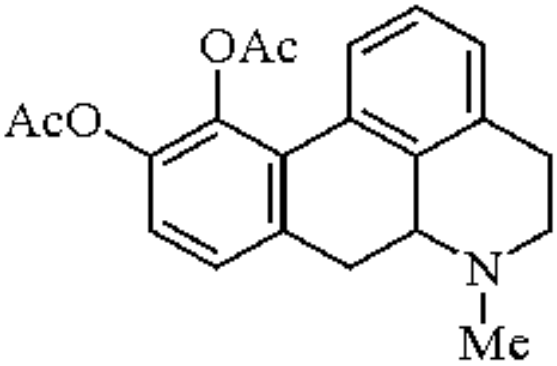

(1)

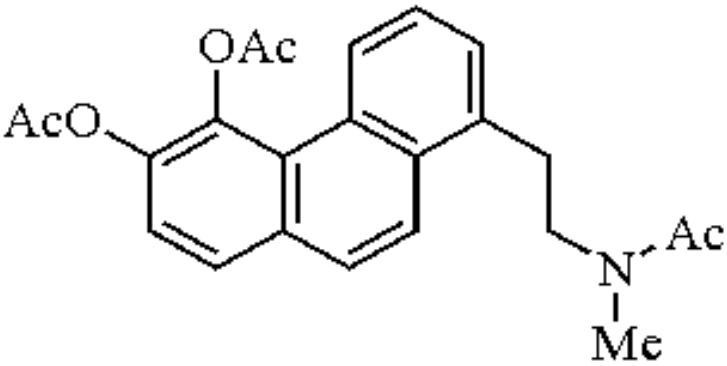

(2)

Miscellaneous Reactions.

Acetyl bromide reacts with unsubstituted cyclic imidates to yield ring-opened products (eq 3).[6] (*Z*)-Alkenyllithium cuprate reagents are very reactive towards acetyl bromide and give (*Z*)-α,β-enones in moderate yield (eq 4).[7] Terminal alkynes which usually undergo slow addition of HBr in solution afford bromides in good yield on treatment with acetyl bromide over alumina (eq 5).[8]

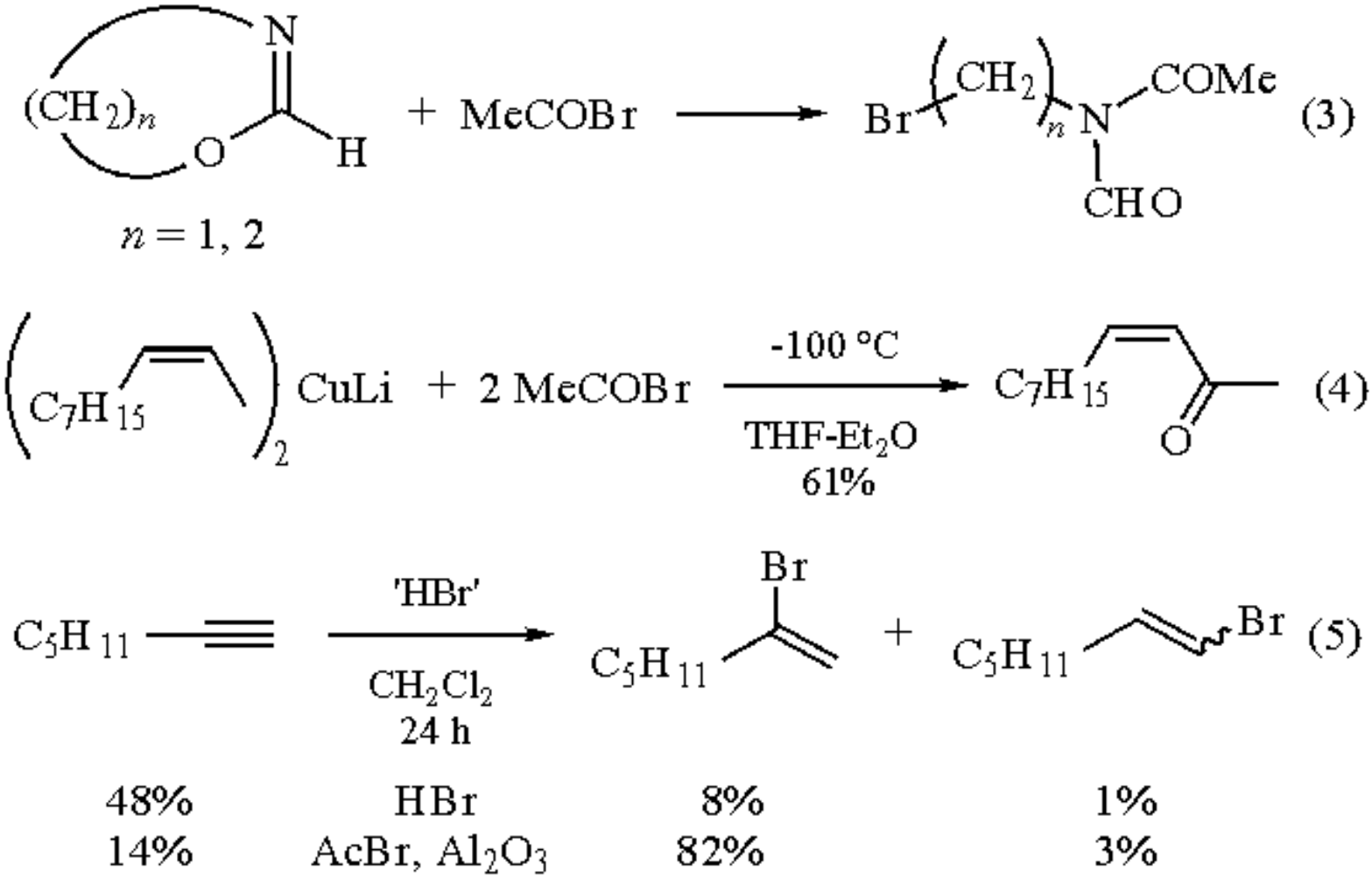

Related Reagents.

Acetyl Chloride; ***Acetic Anhydride***.

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1. (a) Neuenschwander, M.; Bilger, P.; Christen, K.; Iseli, R.; Kyburz, R.; Muhle, H. *HCA* **1978**, *61*, 2047. (b) *ibid.*, **1978**, *61*, 2059. (c) *ibid.*, **1978**, *61*, 2165. (d) Bigler, P.; Muhle, H.; Neuenschwander, M. *S* **1978**, 593.
2. (a) Descude, M. *BSF* **1902**, 867. (b) Ulich, L. H.; Adams, R. *JACS* **1921**, *43*, 660. (c) French, H. E.; Adams, R. *JACS* **1921**, *43*, 651.
3. Mansuri, M. M.; Starrett, J. E.; Wos, J. A.; Tortolani, D. R.; Brodfuehrer, P. R.; Howell, H. G.; Martin, J. C. *JOC* **1989**, *54*, 4780.
4. Borgman, R. J.; McPhillips, J. J.; Stitzel, R. E.; Goodman, I. J. *JMC* **1973**, *16*, 630.
5. Borgman, R. J.; Smith, R. V.; Keiser, J. E. *S* **1975**, 249.
6. Kobayashi, S., Isobe, M., Saegusa, T. *BCJ* **1982**, *55*, 1921.

7. Jabri, N., Alexakis, A., Normant, J. F. *T* **1986**, *42*, 1369.
8. Kropp, P. J.; Daus, K. A.; Crawford, S. D.; Tubergen, M. W.; Kepler, K. D.; Craig S. L.; Wilson, V. P. *JACS* **1990**, *112*, 7433.

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Acetyl Chloride[1]

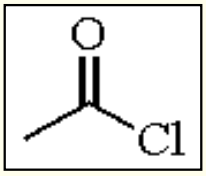

[75-36-5] · C_2H_3ClO · Acetyl Chloride · (MW 78.50)

(useful for electrophilic acetylation of arenes,[2] alkenes,[2a,3] alkynes,[4] saturated alkanes,[3a,5] organometallics, and enolates (on C or O);[6] for cleavage of ethers;[7] for esterification of sterically unhindered[8] or acid-sensitive[9] alcohols; for generation of solutions of anhydrous hydrogen chloride in methanol;[10] as a dehydrating agent; as a solvent for organometallic reactions;[11] for deoxygenation of sulfoxides;[12] as a scavenger for chlorine[13] and bromine;[14] as a source of ketene; and for nucleophilic acetylation[15])

Physical Data: bp 51.8 °C;[1a] mp -112.9 °C;[1a] *d* 1.1051 g cm^{-3};[1a] refractive index 1.38976.[1b] IR (neat) ν 1806.7 cm^{-1};[16] ^1H NMR ($CDCl_3$) δ 2.66 ppm; ^{13}C NMR ($CDCl_3$) δ 33.69 ppm (q) and 170.26 ppm (s); the bond angles (determined by electron diffraction[17]) are 127.5° (O-C-C), 120.3° (O-C-Cl), and 112.2° (Cl-C-C).

Analysis of Reagent Purity: a GC assay for potency has been described;[18] to check qualitatively for the presence of HCl, a common impurity, add a few drops of a solution of crystal violet in chloroform;[19] a green or yellow color indicates that HCl is present, while a purple color that persists for at least 10 min indicates that HCl is absent.[1b]

Preparative Methods: treatment of ***Acetic Acid*** or sodium acetate with the standard inorganic chlorodehydrating agents (PCl_3,[1b,23] SO_2Cl_2,[1a,24] or $SOCl_2$[1b,25]) generates material that may contain phosphorus- or sulfur-containing impurities.[1b,23a,26] Inorganic-free material can be prepared by treatment of HOAc with $Cl_2CHCOCl$ (Δ; 70%),[27] PhCOCl (Δ; 88%),[28] $PhCCl_3$ (cat. H_2SO_4, 90 °C; 92.5%),[29] or phosgene[30] (optionally catalyzed by DMF,[30e] magnesium or other metal salts,[30a,b,d] or activated carbon[30b,c]), or by addition of hydrogen chloride to acetic anhydride (85-90 °C; practically quantitative).[1a,31]

Purification: HCl-free material can be prepared either by distillation from dimethylaniline[11c,20] or by standard degassing procedures.[20c,21]

Handling, Storage, and Precautions: acetyl chloride should be handled only in a well-ventilated fume hood since it is volatile and toxic via inhalation.[22] It should be stored in a sealed container under an inert atmosphere. Spills should be cleaned up by covering with aq sodium bicarbonate.[1a]

Friedel-Crafts Acetylation.

Arenes undergo acetylation to afford aryl methyl ketones on treatment with acetyl chloride (AcCl) together with a Lewis acid, usually ***Aluminum Chloride***$_3$. This reaction, known as the Friedel-Crafts acetylation, is valuable as a preparative method because a single positional isomer is produced from arenes that possess multiple unsubstituted electron-rich positions in many instances.

For example, Friedel-Crafts acetylation of toluene (AcCl/$AlCl_3$, ethylene dichloride, rt) affords *p*-methylacetophenone predominantly (*p*:*m*:*o* = 97.6:1.3:1.2; eq 1).[32]

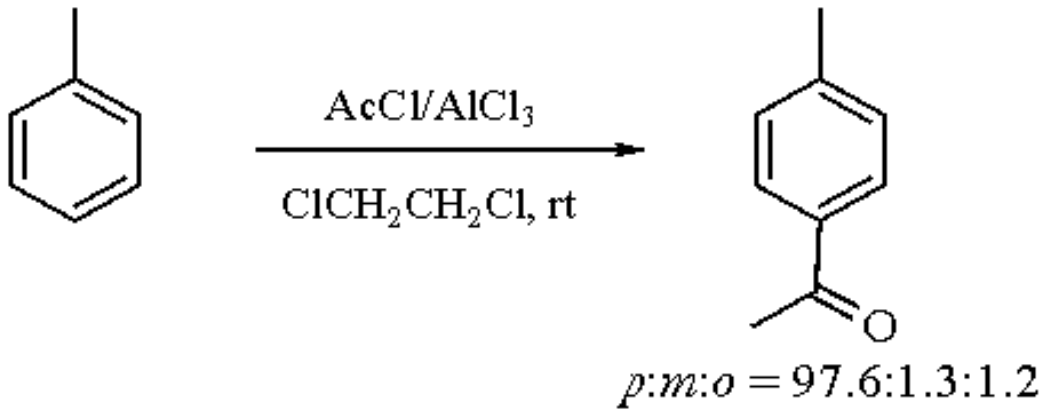

(1)

Acetylation of chlorobenzene under the same conditions affords *p*-chloroacetophenone with even higher selectivity (*p*:*m* = 99.5:0.5).[33] Acetylation of bromobenzene[33] and fluorobenzene[33] afford the *para* isomers exclusively. The *para*:*meta*[34] and *para*:*ortho*[32,34] selectivities exhibited by AcCl/$AlCl_3$ are greater than those exhibited by most other Friedel-Crafts electrophiles.

Halogen substituents can be used to control regioselectivity. For example, by introduction of bromine *ortho* to methyl, it is possible to realize *meta* acetylation of toluene (eq 2).[35]

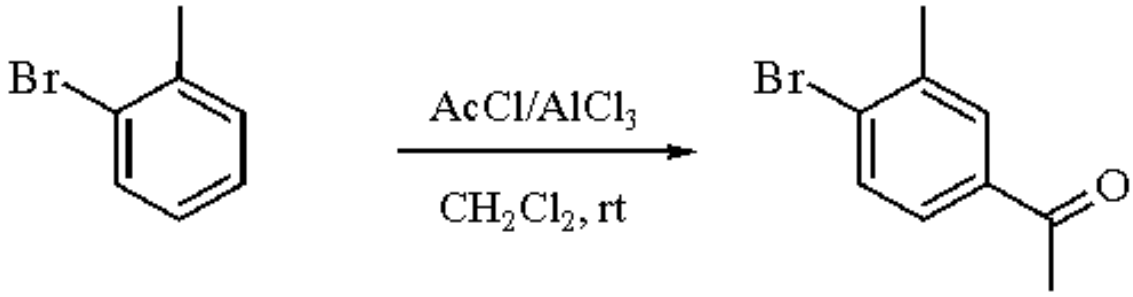

(2)

Regioselectivity is quite sensitive to reaction conditions (e.g. solvent, order of addition of the reactants, concentration, and temperature). For example, acetylation of naphthalene can be directed to produce either a 99:1 mixture of C-1:C-2 acetyl derivatives (by addition of a solution of arene and AcCl in CS_2 to a slurry of $AlCl_3$ in CS_2 at 0 °C) or a 7:93 mixture (by addition of the preformed AcCl/$AlCl_3$ complex in dichloroethane to a dilute solution of the arene in dichloroethane at rt).[36] Similarly, acetylation of 2-methoxynaphthalene can be directed to produce either a 98:2 mixture of C-1:C-6 acetyl derivatives (using the former conditions) or a 4:96 mixture (by addition of the arene to a solution of the preformed AcCl/$AlCl_3$ complex in nitrobenzene).[37] Also, acetylation of 1,2,3-mesitylene can be directed to produce either a 100:0 mixture of C-4:C-5 isomers or a 3:97 mixture.[36c]

Frequently, regioselectivity is compromised by side reactions catalyzed by the HCl byproduct. For example, acetylation of

p-xylene by treatment with $AlCl_3$ followed by Ac_2O (CS_2, Δ, 1 h) produces a 69:31 mixture of 2,5-dimethylacetophenone and 2,4-dimethylacetophenone, formation of the latter being indicative of competitive acid-catalyzed isomerization of *p*-xylene to *m*-xylene.[38] Also, although acetylation of anthracene affords 9-acetylanthracene regioselectively, if the reaction mixture is allowed to stand for a prolonged time prior to work-up (rt, 20 h) isomerization to a mixture of C-1, C-2, and C-9 acetyl derivatives occurs.[39]

These side reactions can be minimized by proper choice of reaction conditions. Isomerization of the arene can be suppressed by adding the arene to the preformed $AcCl/AlCl_3$ complex. This order of mixing is known as the Perrier modification of the Friedel-Crafts reaction.[40] Acetylation of *p*-xylene using this order of mixing affords 2,5-dimethylacetophenone exclusively.[38] Isomerization of the product aryl methyl ketone can be suppressed by crystallizing the product out of the reaction mixture as it is formed. For example, on acetylation of anthracene in benzene at 5-10 °C, 9-acetylanthracene crystallizes out of the reaction mixture (as its 1/1 $AlCl_3$ complex) in pure form.[39] Higher yields of purer products can also be obtained by substituting ***Zirconium(IV) Chloride***[41] or ***Tin(IV) Chloride***[42] for $AlCl_3$.

AcCl is not well suited for industrial scale Friedel-Crafts acetylations because it is not commercially available in bulk (only by the drum) and therefore must be prepared on site.[1] The combination of ***Acetic Anhydride*** and anhydrous ***Hydrogen Fluoride***, both of which are available by the tank car, is claimed to be more practical.[43] On laboratory scale, $AcCl/AlCl_3$ is more attractive than Ac_2O/HF or $Ac_2O/AlCl_3$. Whereas one equivalent of $AlCl_3$ is sufficient to activate AcCl, 1.5-2 equiv $AlCl_3$ (relative to arene) are required to activate Ac_2O.[36a,37b,38,44] Thus, with Ac_2O, greater amounts of solvent are required and temperature control during the quench is more difficult. Also, slightly lower isolated yields have been reported with Ac_2O than with AcCl in two cases.[36a,45] However, it should be noted that the two reagents generally afford similar ratios of regioisomers.[36a,38,46]

Acetylation of Alkenes.

Alkenes, on treatment with $AcCl/AlCl_3$ under standard Friedel-Crafts conditions, are transformed into mixtures of β-chloroalkyl methyl ketones, allyl methyl ketones, and vinyl methyl ketones, but the reaction is not generally preparatively useful because both the products and the starting alkenes are unstable under the hyperacidic reaction conditions. Preparatively useful yields have been reported only with electron poor alkenes such as ethylene (dichloroethane, 5-10 °C; >80% yield of 4-chloro-2-butanone)[47] and ***Allyl Chloride*** (CCl_4, rt; 78% yield of 5-chloro-4-methoxy-2-pentanone after methanolysis),[48] which are relatively immune to the effects of acid.

The acetylated products derived from higher alkenes are susceptible to protonation or solvolysis which produces carbenium ions that undergo Wagner-Meerwein hydride migrations.[49] For example, on subjection of cyclohexene to standard Friedel-Crafts acetylation conditions ($AcCl/AlCl_3$, CS_2 -18 °C), products formed include not only 2-chlorocyclohexyl methyl ketone (in 40% yield)[50] but also 4-chlorocyclohexyl methyl ketone.[2a,51] If benzene is added to the crude acetylation mixture and the temperature is then increased to 40-45 °C for 3 h, 4-phenylcyclohexyl methyl ketone is formed in 45% yield (eq 3).[49a,b]

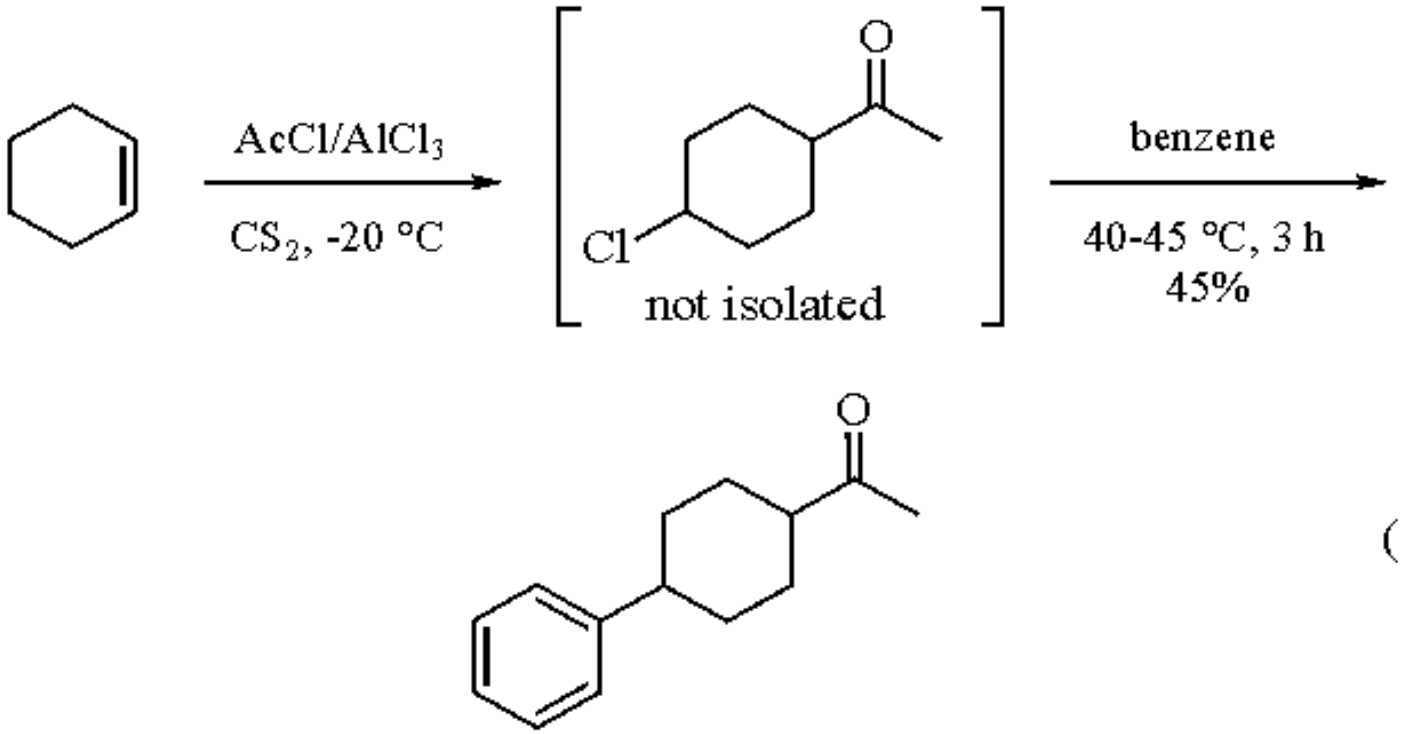

(3)

Wagner-Meerwein rearrangement also occurs during acetylation of methylcyclohexene, even though the rearrangement is anti-Markovnikov (β-tertiary -> γ-secondary; eq 4).[52] Acetylation of *cis*-decalin[53] (see Acetylation of Saturated Alkanes section below) also produces a β-tertiary carbenium ion that undergoes anti-Markovnikov rearrangement. The rearrangement is terminated by intramolecular *O*-alkylation of the acetyl group by the γ-carbenium ion to form a cyclic enol ether in two cases.[49c,53]

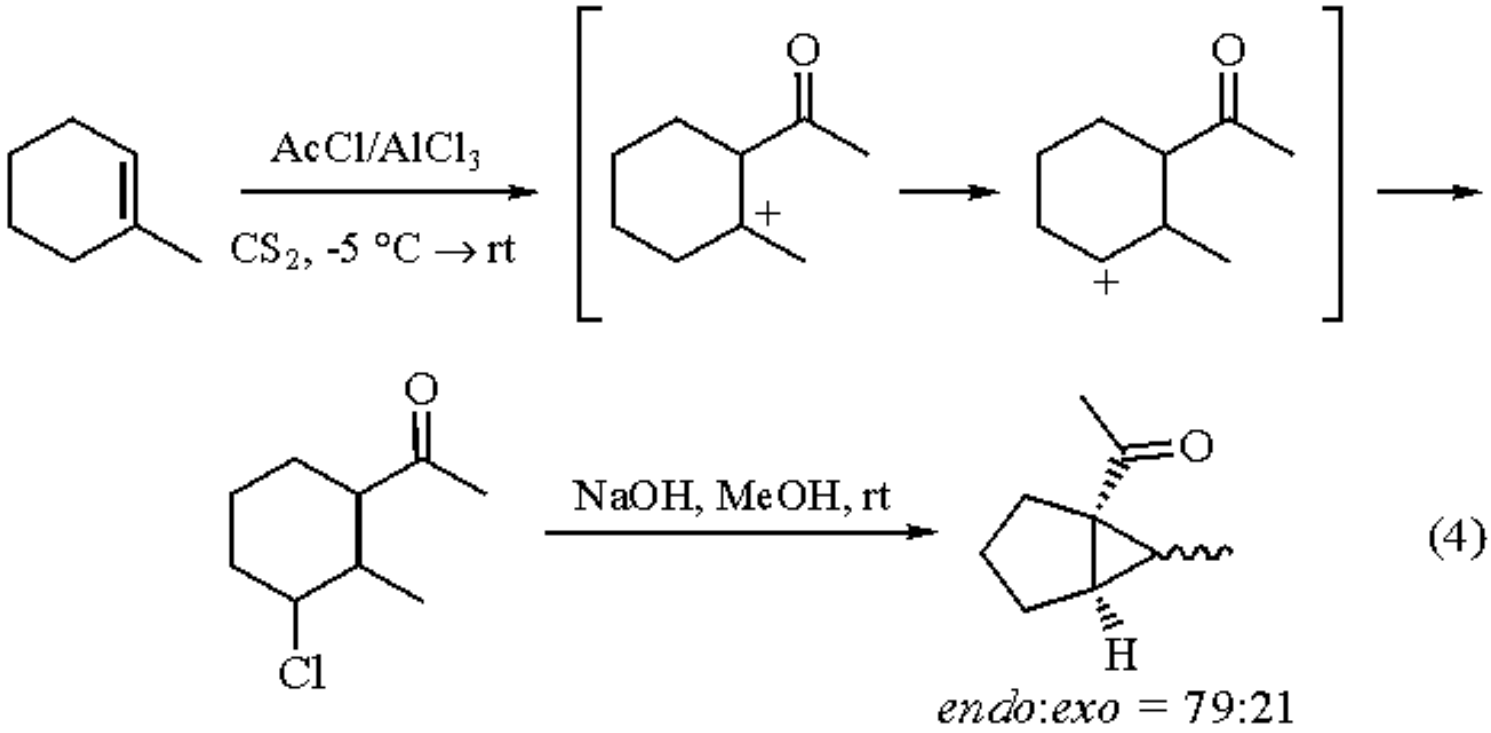

(4)

Higher alkenes themselves are also susceptible to protonation. The resulting carbenium ions decompose by assorted pathways including capture of chloride (with $SnCl_4$ as the catalyst),[51,54] addition to another alkene to form dimer or polymer,[5b,55] proton loss (resulting in *exo/endo* isomerization), or skeletal rearrangement.[56]

Higher alkenes can be acetylated in synthetically useful yield by treatment with AcCl together with various mild Lewis acids. One that deserves prominent mention is ***Ethylaluminum Dichloride*** (CH_2Cl_2, rt), which is useful for acetylation of all classes of alkenes (monosubstituted, 1,2-disubstituted, and trisubstituted).[57] For example, cyclohexene is converted into an 82/18 mixture of 3-acetylcyclohexene and 2-chlorocyclohexyl methyl ketone in 89% combined yield.

The following Lewis acids are also claimed to be superior to $AlCl_3$: Zn(Cu)/CH_2I_2 (AcCl, CH_2Cl_2, Δ), by which cyclohexene is converted into acetylcyclohexene in 68% yield (after treatment with KOH/MeOH);[58] $ZnCl_2$ (AcCl, Et_2O/CH_2Cl_2, -75 °C -> -20 °C), by which 2-methyl-2-butene is converted into a 15:85 mixture of 3,4-dimethyl-4-penten-2-one and 4-chloro-3,4-dimethyl-2-pentanone in quantitative combined yield;[59] and $SnCl_4$, by which cyclohexene (AcCl, CS_2, -5 °C -> rt) is converted into acetylcyclohexene in 50% yield (after dehydrochlorination with $PhNEt_2$ at 180 °C),[60] methylcyclohexene (CS_2, rt) is converted into 1-acetyl-2-methylcyclohexene in 48% yield (after dehydrochlorination),[52] and camphene is converted into an acetylated derivative in ~65% yield.[49c]

Conducting the acetylation in the presence of a nonnucleophilic base or polar solvent is reported to be advantageous. For example, methylenecyclohexane can be converted into 1-cyclohexenylacetone in 73% yield by treatment with $AcSbCl_6$ in the presence of Cy_2NEt (CH_2Cl_2, -50 °C -> -25 °C, 1 h)[61] and cyclohexene can be converted into 3-acetylcyclohexene in 80% yield by treatment with $AcBF_4$ in $MeNO_2$ at -25 °C.[62]

Employment of Ac_2O instead of AcCl is also advantageous in some cases. For example, methylcyclohexene can be converted into 3-acetyl-2-methylcyclohexene in 90% yield by treatment with $ZnCl_2$ (neat Ac_2O, rt, 12 h).[63]

Finally, alkenes can be diacetylated to afford pyrylium salts by treatment with excess AcCl/$AlCl_3$,[55b,56,64] albeit in low yield (eq 5).[64a]

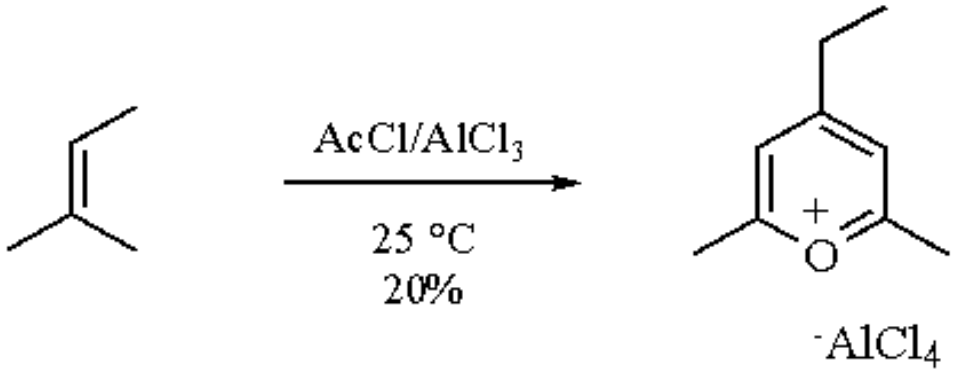

(5)

Acetylation of Alkynes.

Under Friedel-Crafts conditions (AcCl/$AlCl_3$, CCl_4, 0-5 °C), acetylene undergoes acetylation to afford β-chlorovinyl methyl ketone in 62% yield[4] and under similar conditions ($AcSbF_6$, $MeNO_2$, -25 °C) 5-decyne undergoes acetylation to afford 6-acetyl-5-decanone in 73% yield.[65]

Acetylation of Saturated Alkanes.

Saturated alkanes, on treatment with a slight excess of AcCl/$AlCl_3$ at elevated temperature, undergo dehydrogenation (by hydride abstraction followed by deprotonation) to alkenes, which undergo acetylation to afford vinyl methyl ketones. The hydride-abstracting species is believed to be either the acetyl cation[66] or $HAlCl_4$,[67] with most evidence favoring the former. Perhaps because the alkenes are generated slowly and consumed rapidly, and therefore are never present in high enough concentration to dimerize, yields are typically higher than those of acetylation of the corresponding alkenes.[53b,68] A similar hypothesis has been offered to explain the phenomenon that the yield from acetylation of tertiary alkyl chlorides is typically higher than the yield from acetylation of the corresponding alkenes.[55b,64a] For example, methylcyclopentane on treatment with AcCl/$AlCl_3$ (CH_2Cl_2, Δ) undergoes acetylation to afford 1-acetyl-2-methylcyclopentene in an impressive 60% yield (eq 6).[53b,66a]

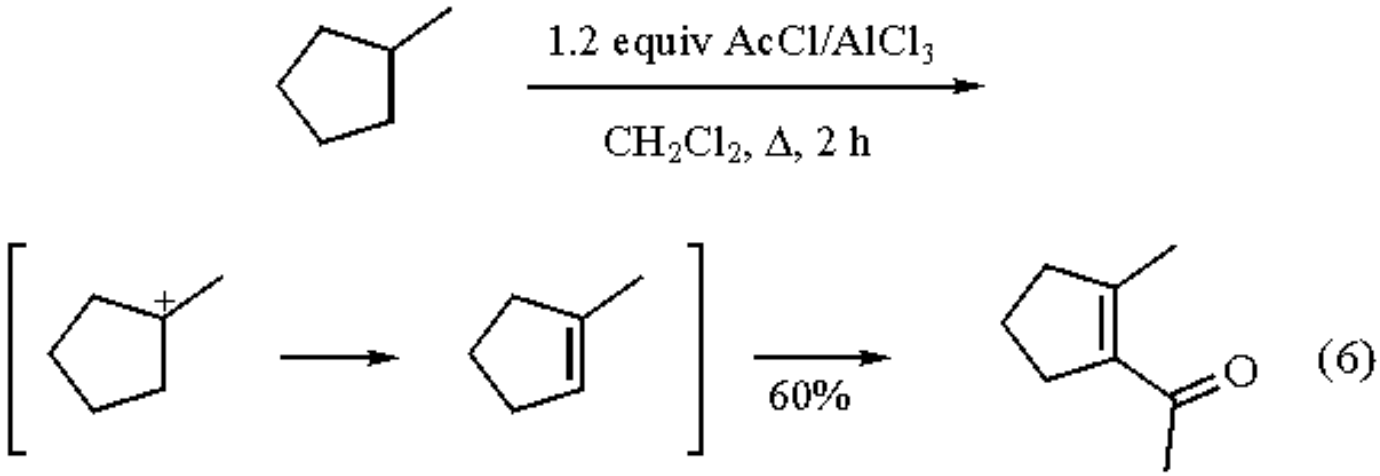

If the reaction is carried out with excess alkane, a second hydride transfer occurs, resulting in reduction of the enone to the corresponding saturated alkyl methyl ketone.[69,70] For example, stirring AcCl/$AlCl_3$ in excess cyclohexane (30-35 °C, 2.5 h) affords 2-methyl-1-acetylcyclopentane in 50% yield (unpurified; based on AcCl)[55a,69,71] and stirring AcCl/$AlBr_3$ in excess cyclopentane (20 °C, 1 h) affords cyclopentyl methyl ketone in 60% yield (based on AcCl; eq 7).[55c]

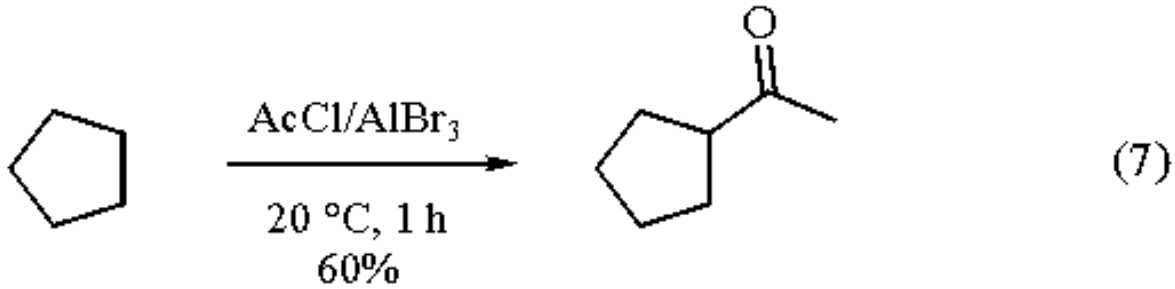

If the reaction is carried out with a substoichiometric amount of alkane, the product is either a 2:1 adduct (if cyclic)[53b,66a] or pyrylium salt (if acyclic).[66b,68b]

Unbranched alkanes also undergo acetylation, but at higher temperature, so yields are generally lower. For example, acetylation of cyclohexane by AcCl/$AlCl_3$ requires refluxing in $CHCl_3$ and affords 1-acetyl-2-methylcyclopentene in only 36% yield.[55c,72]

Despite the modest to low yields, acetylation of alkanes provides a practical method for accessing simple methyl ketones because all the input raw materials are cheap.

Coupling with Organometallic Reagents.

Coupling of organometallic reagents with AcCl is a valuable method for preparation of methyl ketones. Generally a catalyst (either a Lewis acid or transition metal salt) is required.

Due to the large number and varied characteristics of the organometallics, comprehensive coverage of the subject would require discussion of each organometallic reagent individually, which is far beyond the scope of this article. Information pertaining to catalyst and condition selection should therefore be accessed from the original literature; some seminal references are given in Table 1.

Table 1 Catalyst Selection Chart[i,ii]

Organo-metallic	R = Alkyl	Vinyl	Aryl	Alkynyl	Allyl[iii]
RLi	N[73 iv]				
R_2Mg	N[74 iv]				
RMgX	Fe[75]				
	Cu[76]				
	Mn[76b,77]				
	D[78]				
	N[79]				
$RCuL^-$	N[80]	N[81]	N[80,82]	N[80,83]	N[84]
				I[83a]	
RZnL	Pd[85,86]	Pd[85]	Pd[87]	Pd[85]	N[88 iv]
	D[89]		D[89]	N[90]	
	N[91]				
RCdL	N[91c,92]		N[91c,92b,d,e]		
RHgL	Al[93]	Al[94]	Al[93]		Al[95]
	Pd[96]	Ti[94 v]	Pd[96,97]		
RBL_3^-	N[98]		N[99,100 vi]	N[101 vi]	
$RAlL_2$	N[102]	N[85,102b]			
	Cu[103]	Pd[85]			
R_4Al^-	Fe[104]	Pd[85]			
	Cu[104]				

	Cu[104]				
$RTlL_2$	N[105]		N[105]		
$RSiL_3$	Al[106,107]	Al[107,108,109 vii]		Al[107,110]	[107,111,112 viii] Al[113 ix]
					Ti[114 x]
$RGeL_3$	Al[106b]				
$RSnL_3$	Pd[115]	Pd[115,116]	Pd[117]	Pd[118]	Rh[119 x]
	Al[106b]	Ti[120 iv]	N[117c]		N[121,122 iv]
$RBiL_2$			Pd[123]		
$RTiL_2$					N[124 iv]
$RZrL_3$	N[125]				
RVL_2			N[126]		
RMnL	Cu[127]	Cu[127]	Cu[127]	Cu[127]	Cu[127]
	N[128]	N[128]	N[128]	N[128]	
RRh			N[129]		
RNiL		N[130]			N[130,131]

[i] Codes (in headings): L = unspecified ligand and X = halogen; codes (in entries): N = no catalyst required, Fe = Fe^{III} salt, Cu = Cu^{I} salt, Mn = Mn^{I} salt, D = dipolar aprotic additive, I = LiI, Pd = Pd^{0} or Pd^{II} salt, Al = $AlCl_3$, Ti = $TiCl_4$, and Rh = $ClRh(PPh_3)_3$. [ii] Coupling occurs at metal-bearing carbon with retention of configuration to afford RCOMe unless otherwise indicated. [iii] Coupling occurs at g-carbon unless otherwise indicated. [iv] Product is tertiary alcohol. [v] Coupling occurs with inversion of configuration. [vi] Coupling occurs at b-carbon. [vii] Coupling occurs at d-carbon. [viii] Substrate is allenic silane and product is furan. [ix] Substrate is propargylsilane. [x] Coupling occurs at a-carbon.

C-Acetylation of Enolates and Enolate Equivalents.

β-Diketones can be synthesized by treatment of metal enolates with AcCl. *O*-Acetylation is often a significant side

reaction, but the amount can be minimized by choosing a counterion that is bonded covalently to the enolate[6] such as copper[132] or zinc,[133] and by using AcCl rather than Ac_2O.[6a] Proton transfer from the product β-diketone to the starting enolate is another common side reaction.[134] Alternative procedures for effecting *C*-acetylation that avoid or minimize these side reactions include Lewis acid-catalyzed acetylation of the trimethylsilyl enol ether derivative (AcCl/cat. $ZnCl_2$, CH_2Cl_2 or CH_2Cl_2/Et_2O, rt)[135] and addition of ketene to the morpholine enamine (AcCl/Et_3N, $CHCl_3$, rt).[136]

Analogously, esters can be *C*-acetylated by conversion into the corresponding silyl ketene acetal followed by treatment with AcCl. Depending on the coupling conditions (neat AcCl[137] or AcCl/Et_3N[138]), either the *cis*-β-siloxycrotonate ester or the corresponding β,γ-isomer is produced (eqs 8 and 9). The third possible isomer (*trans*-β-siloxycrotonate) is accessible either by silylation of the acetoacetic ester (TMSCl, Et_3N, THF, Δ)[139] or by $HgBr_2/Et_3SiBr$-catalyzed equilibration of the *cis* isomer.[137]

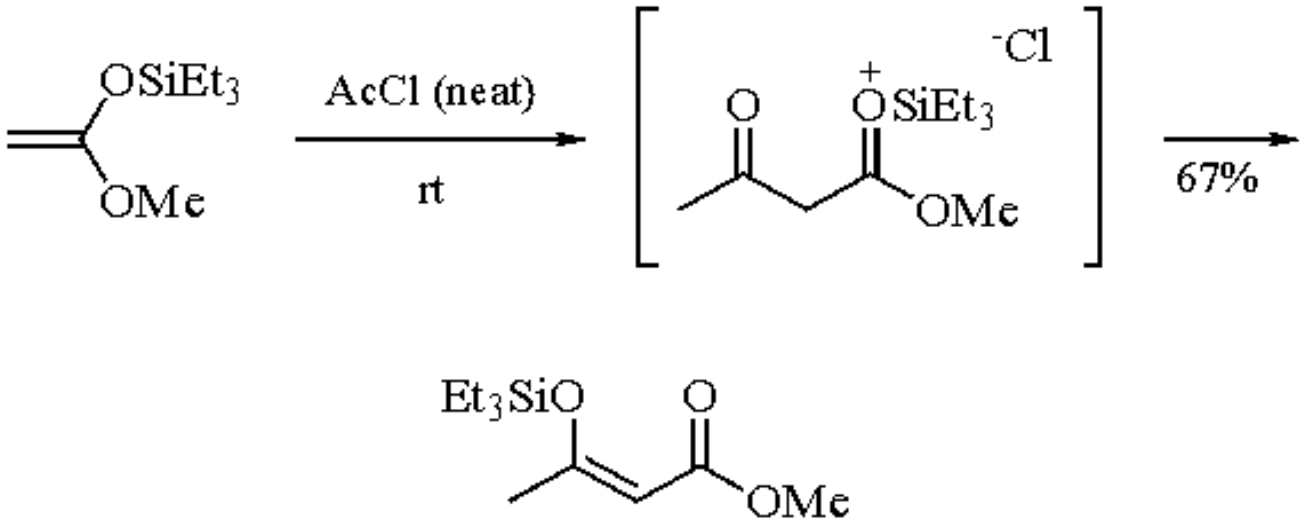

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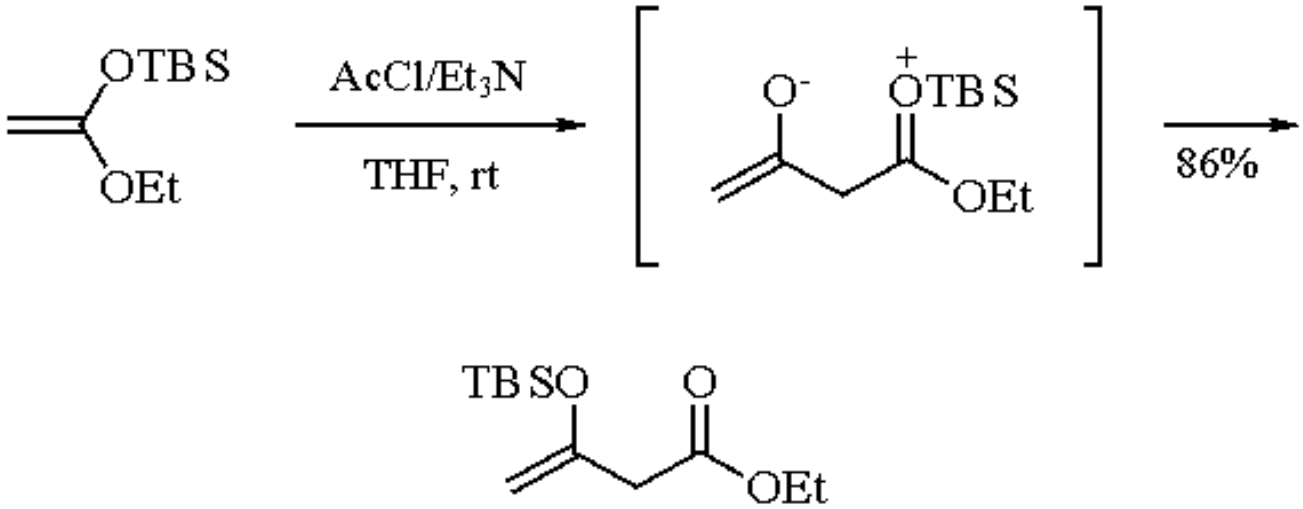

(9)

The silyl ketene acetal strategy can also be used to effect γ-acetylation of α,β-unsaturated esters (AcCl/cat. $ZnBr_2$, CH_2Cl_2, rt)[140] and β-ketoesters (AcCl, Et_2O, -78 °C).[141]

Enol Acetylation.

Enol acetylation of ketones can be effected by formation of a metal enolate in which the metal is relatively dissociated[6]

(such as potassium[142] or magnesium[143]) followed by quenching with AcCl. Alternatively, enol acetates can be synthesized directly from the ketones. For example, 3-keto-$\Delta^{4,6}$-steroids can be converted into $\Delta^{2,4,6}$-trienol acetates by treatment with AcCl/$PhNMe_2$ or into $\Delta^{3,5,7}$-trienol acetates by treatment with AcCl/Ac_2O.[144]

Acetyl Bromide (AcBr) is apparently superior to AcCl as a catalyst for enol acetylation, based on a report that 17β-benzoyloxyestra-4,9(10)-dien-3-one is converted into estradiol 3-acetate-17-benzoate in higher yield at much lower temperature using AcBr rather than AcCl (87.5% yield with 1:2 AcBr:Ac_2O, CH_2Cl_2, rt, 1 h (eq 10) vs. 81.0% yield with 1:2 AcCl:Ac_2O, Δ, 4.5 h).[145]

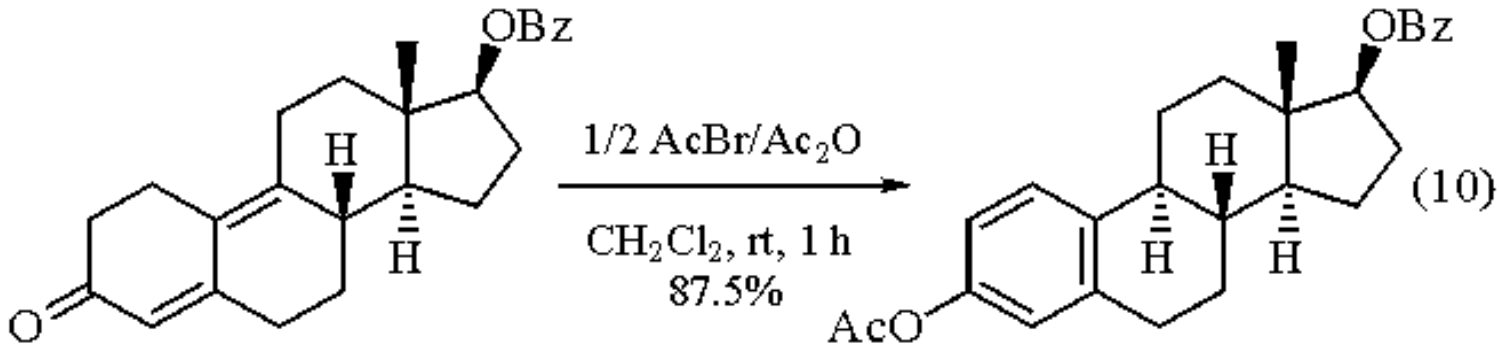

β-Keto esters can be converted into either *trans* or *cis* enol acetates. The *trans* isomer is accessible by treatment with AcCl/Et_3N (HMPA, rt)[146] or AcCl/DBU (MeCN, 5 °C -> rt; eq 11),[147] while the *cis* isomer is accessible by treatment with isopropenyl acetate/HOTs.[146] Each isomer couples with dialkylcuprates with retention of configuration to afford stereoisomerically enriched α,β-unsaturated esters.[146,148]

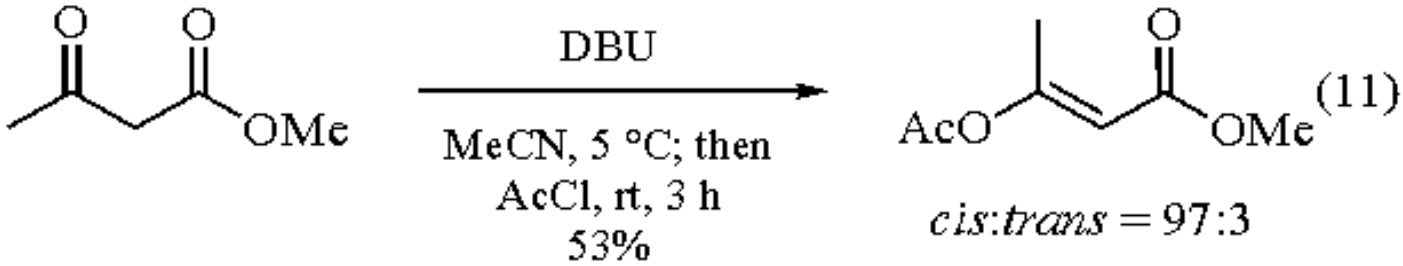

Attempted enol acetylation of β-keto esters by quenching the sodium enolate[146,147] or magnesium chelate[149] with AcCl afforded *C*-acetylated products.

Adducts with Aldehydes and Ketones.

AcCl combines with aldehydes[150] (cat. $ZnCl_2$ or $AlCl_3$[150f]) to afford α-chloroalkyl acetates. The reaction is reversible,[151] but at equilibrium the ratio of adduct to aldehyde is usually quite high, and the reaction is otherwise clean (92% yield for acetaldehyde,[150e] 97% yield for benzaldehyde; eq 12[150f]).

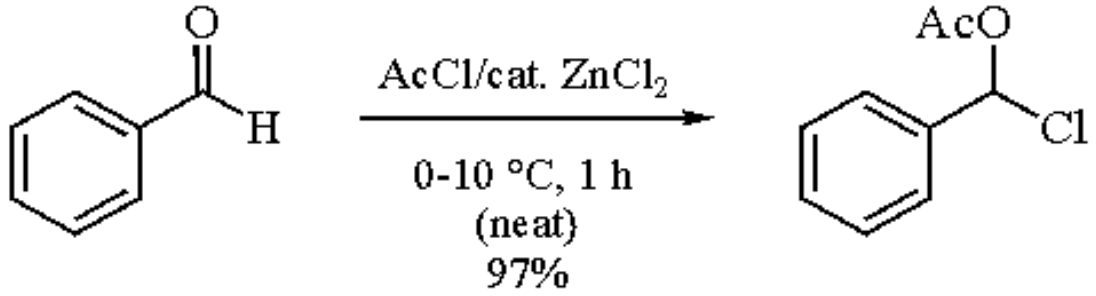

(12)

AcCl also adds to ketones,[150e,151,152] but the adducts are much less thermodynamically stable, so significant amounts of the starting materials are present at equilibrium.[151,152a,b] The equilibrium can be biased in favor of the adduct by employing high concentration, low temperature, a nonpolar solvent, excess AcCl, or AcBr or AcI instead of AcCl.[151,153] For example, the acetone/AcCl adduct can be obtained in good yield (85%) by treatment of acetone with excess (2 equiv) AcCl (cat. $ZnCl_2$, CCl_4, -15 °C).[152c]

Reduction of the aldehyde/AcBr adducts[151,154] with ***Zinc*** or ***Samarium(II) Iodide*** to α-acetoxyalkylzinc[154,155] and -samarium[156] compounds, respectively, completes an umpolung of the reactivity of the aldehyde.

Cleavage of Ethers.

THF can be opened by treatment with AcCl in combination with either ***Sodium Iodide*** (MeCN, rt, 21 h; 91% yield of 4-iodobutyl acetate)[157] or a Lewis acid such as $ZnCl_2$ (Δ, 1.5 h; 76% yield of 4-chlorobutyl acetate),[158] $SnCl_4$,[159] $CoCl_2$ (rt, MeCN; 90%),[160] $ClPdCH_2Ph(PPh_3)_2/Bu_3SnCl$ (63 °C, 48 h; 95%),[161] $Mo(CO)_6$ (hexane, Δ; 78%),[162] $KPtCl_3(H_2CCH_2)$, and $[ClRh(H_2CCH_2)_2]_2$ (rt; 75% and 83%, respectively).[163] Acyclic dialkyl ethers can also be cleaved efficiently and in many cases regioselectively.[159]

Many of these methods are applicable to deprotection of ether-type protecting groups. For example, benzyl and allyl ethers can be deprotected by treatment with AcCl/cat. $CoCl_2$[160] or AcCl/cat. $ClPdCH_2Ph(PPh_3)_2$/cat. Bu_3SnCl.[161] Dimethyl acetals can be cleaved selectively to aldehydes in the presence of ethylene acetals (AcCl/cat. $ZnCl_2$, Me_2S/THF, 0 °C),[164] or to α-chloro ethers (AcCl/cat. $SOCl_2$, 55 °C).[165] Tetrahydropyranyl (THP) ethers[166] and *t*-butyl ethers[167] can be deprotected by stirring in 1:10 AcCl:HOAc (40-50 °C).

Finally, *t*-alkyl esters can be cleaved to anhydrides and *t*-alkyl chlorides by treatment with AcCl ($MeNO_2$, 70 °C).[168]

Esterification.

Although AcCl is intrinsically more reactive than Ac_2O, in combination with various acylation catalysts the reverse reactivity order is exhibited. For example, Ac_2O ***4-Dimethylaminopyridine*** (DMAP) acetylates ethynylcyclohexanol three times faster than AcCl/DMAP ($CDCl_3$, 27 °C).[169] Also, isopropanol does not react with AcCl/Bu_3P (CD_3CN, -8 °C; <5% conversion after 30 min), but after addition of sodium acetate reacts rapidly to form isopropyl acetate (complete in <10 min).[170] As a general rule, therefore, Ac_2O is preferable for acetylation of hindered alcohols while AcCl is preferable for selective monoacetylation of polyols.[171]

Examples of selective acetylations involving AcCl include: acetylation of primary alcohols in the presence of secondary alcohols by AcCl/2,4,6-collidine or *i*-$PrNEt_2$ (CH_2Cl_2, -78 °C);[8,172] acetylation of primary alcohols in the presence of

secondary alcohols,[173] and secondary alcohols in the presence of tertiary alcohols,[174] by AcCl/pyridine (CH_2Cl_2, -78 °C); monoacetylation of a 2,4-dihydroxyglucopyranose by AcCl/pyridine/-15 °C (Ac_2O/pyridine/0 °C is less selective);[175] and acetylation of steroidal 5α-hydroxyls (not 5β) by AcCl/$PhNMe_2$ ($CHCl_3$, Δ).[176]

Although Ac_2O/DMAP[177] and Ac_2O/Bu_3P[170] are the preferred reagents for acetylation of most hindered alcohols, satisfactory results can be obtained with AcCl in combination with $PhNMe_2$ ($CHCl_3$, Δ),[178] $PhNEt_2$ ($CHCl_3$, Δ),[179] AgCN (benzene or HMPA, 80 °C),[180] magnesium powder (Et_2O, Δ; 45-55% yield of *t*-BuOAc),[181] and Na_2CO_3 (cat. $PhCH_2NEt_3Cl$, CH_2Cl_2, Δ; 79% yield of *t*-BuOAc).[182] Use of the combination of AcCl/DMAP is not recommended since unidentified byproducts may be generated.[169]

Although acetylations with AcCl/pyridine produce an acidic byproduct (pyridine hydrochloride), it is possible to acetylate highly acid-sensitive alcohols such as 2-(tributylstannylmethyl)allyl alcohol (eq 13)[9b] and 2-(trimethylsilylmethyl)allyl alcohol[9a] with AcCl/pyridine in >90% yield without competing protiodestannylation or protiodesilylation by selecting a solvent (CH_2Cl_2, 0 °C) in which the pyridine hydrochloride is insoluble.

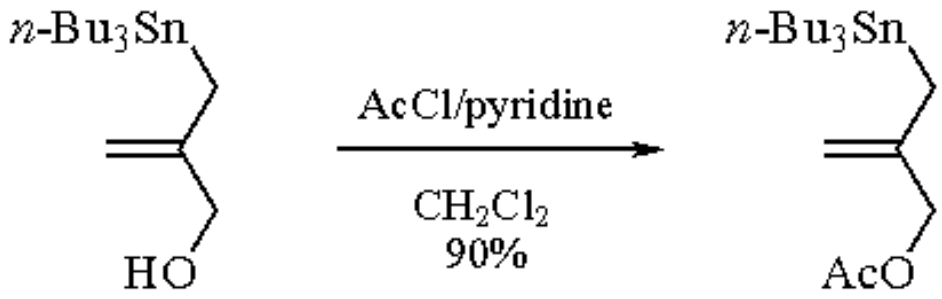

(13)

Alternatively, acid-sensitive alcohols may be acetylated by deprotonation with ***n-Butyllithium*** (THF, -78 °C)[183] or ***Ethylmagnesium Bromide*** (Et_2O, rt)[184] followed by quenching with AcCl.

Finally, by using a chiral tertiary amine as the base, it is possible to effect enantioselective acetylations. For example, racemic 1-phenethyl alcohol has been partially resolved by treatment with AcCl in combination with (*S*)-(-)-*N*,*N*-dimethyl-1-phenethylamine (CH_2Cl_2, -78 °C -> rt; ee of acetate 52%, ee of alcohol 59.5%).[185]

Generation of Solutions of Anhydrous Hydrogen Chloride in Methanol.

Esterification of alcohols by AcCl proceeds in the absence of HCl scavengers. For example, on addition of AcCl to methanol at rt, a solution of hydrogen chloride and methyl acetate in methanol forms rapidly.[10] This reaction provides a more practical method for access to solutions of HCl in methanol than the apparently simpler method of bubbling anhydrous HCl into methanol because of the difficulty of controlling the amount of anhydrous HCl delivered. Solutions of anhydrous HCl in acetic acid can presumably be prepared analogously by addition of AcCl and an equimolar amount of H_2O to HOAc.

Primary,[186] secondary,[187] and tertiary alcohols[178a,188] also react with AcCl, but the product is the alkyl chloride rather than the ester in most cases. Thus as a preparative esterification method this reaction has limited generality.

AcCl also reacts with anhydrous *p*-toluenesulfonic acid (3-4 equiv AcCl, Δ) to afford acetyl *p*-toluenesulfonate in 97.5%

yield along with anhydrous HCl.[189] AcCl does not react with HOAc to generate HCl and Ac_2O, at least in appreciable amounts.[31]

Dehydrating Agent.

AcCl reacts with H_2O to afford HCl and HOAc rapidly and quantitatively[31b] and thereby qualifies as a strong dehydrating agent. Examples of reactions in which AcCl functions as a dehydrating agent include: cyclization of dicarboxylic acids to cyclic anhydrides (neat AcCl, Δ);[190] cyclization of keto acids to enol lactones (neat AcCl, Δ);[191] dehydration of nitro compounds into nitrile oxides (by treatment with NaOMe followed by AcCl);[192] and conversion of allylic hydroperoxides into unsaturated ketones (AcCl/pyridine, $CHCl_3$, rt).[193] The dehydrating power of AcCl has been invoked as a possible explanation for its effectiveness for activation of zinc dust.[194]

In Situ Generation of High-Valent Metal Chlorides.

Many high-valent metal chlorides are useful as reagents in organic synthesis but are difficult to handle due to their moisture sensitivity. AcCl can be used to generate such reagents in situ from the corresponding metal oxides[11] or acetates.[195] Examples include: α-chlorination of ketones by treatment with AcCl/***Manganese Dioxide*** (HOAc, rt);[196] *cis*-1,2-dichlorination of alkenes by treatment with AcCl/$(Bu_4N)_4Mo_8O_{26}$ (CH_2Cl_2, rt);[197] and dichlorination of alkenes by treatment with AcCl/MnO_2/$MnCl_2$ (DMF, rt).[198] Attempts to dichlorinate alkenes by treatment with AcCl/MnO_2 in THF, however, failed due to cleavage of THF to 4-chlorobutyl acetate.[196,199] A milder reagent that can be used to activate MnO_2 for dichlorination of alkenes in THF is ***Chlorotrimethylsilane***.[199]

Solvent for Organometallic Reactions.

Because of its cheapness, volatility, and ability to form moisture-stable solutions of metal chlorides, AcCl is useful as a solvent for reactions involving hygroscopic metal salts.[11] For example, AcCl has been used as a co-solvent for 1,2-chloroacetoxylation of alkenes by ***Chromyl Chloride*** (1:2 AcCl:CH_2Cl_2, -78 °C -> rt).[200]

Reaction with Heteroatom Oxides.

The key step in a method for α-acetoxylation of aldehydes involves rearrangement of an AcCl-nitrone adduct (eq 14).[201] Analogous methods for α-benzoylation and α-pivaloylation are higher yielding.

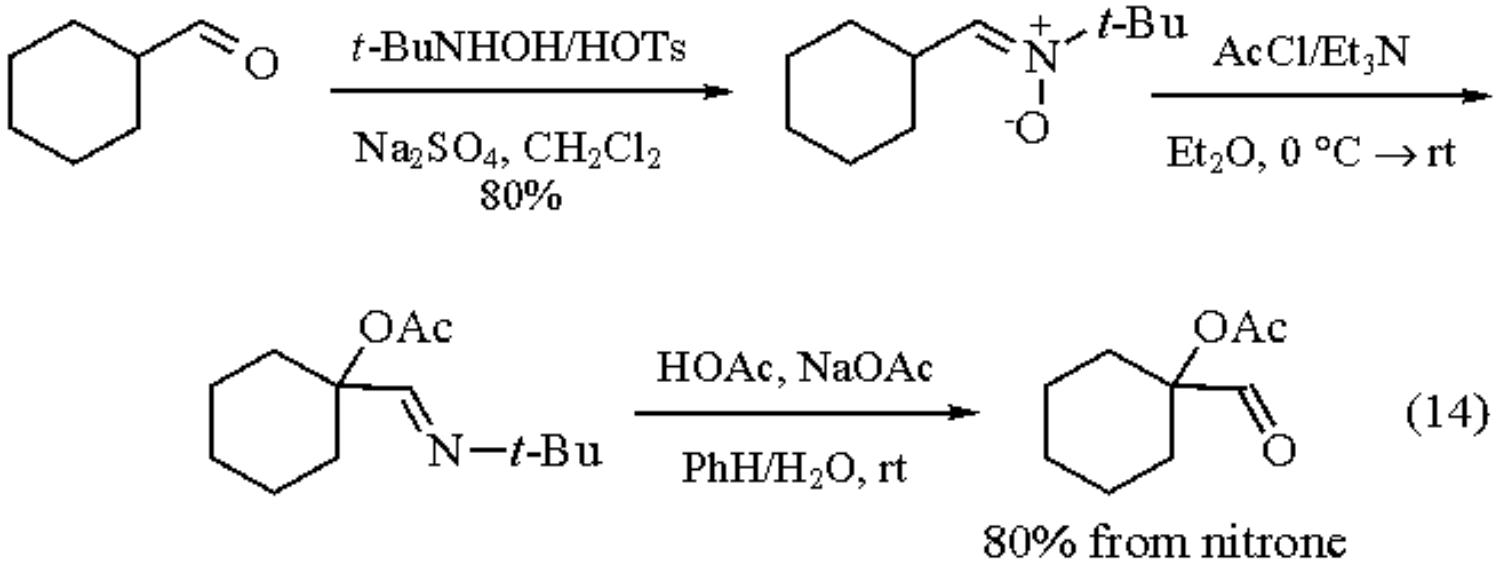

(14)

β-Nitrostyrenes cyclize to indolinones on treatment with AcCl ($FeCl_3$, CH_2Cl_2, 0 °C; eq 15).[202]

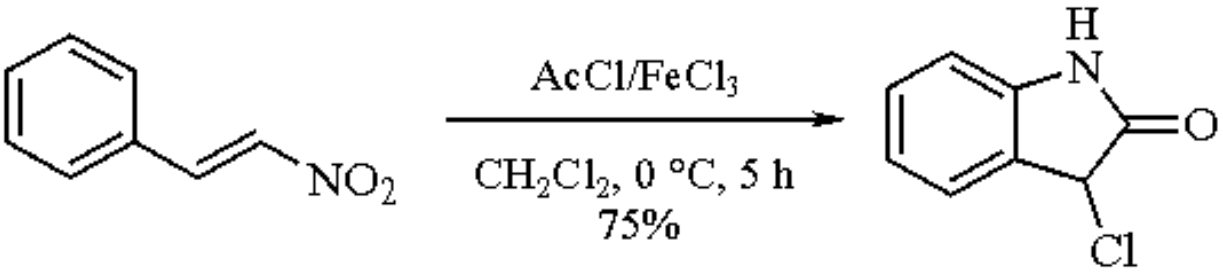

(15)

A high-yielding method for deoxygenation of sulfoxides to sulfides involves treatment with 1.1 equiv ***Tin(II) Chloride*** in the presence of a catalytic amount (0.4 equiv) of AcCl (MeCN/DMF, 0 °C -> rt).[12] The mildness of this method is demonstrated by its usability for deoxygenation of a cephalosporin sulfoxide (eq 16).

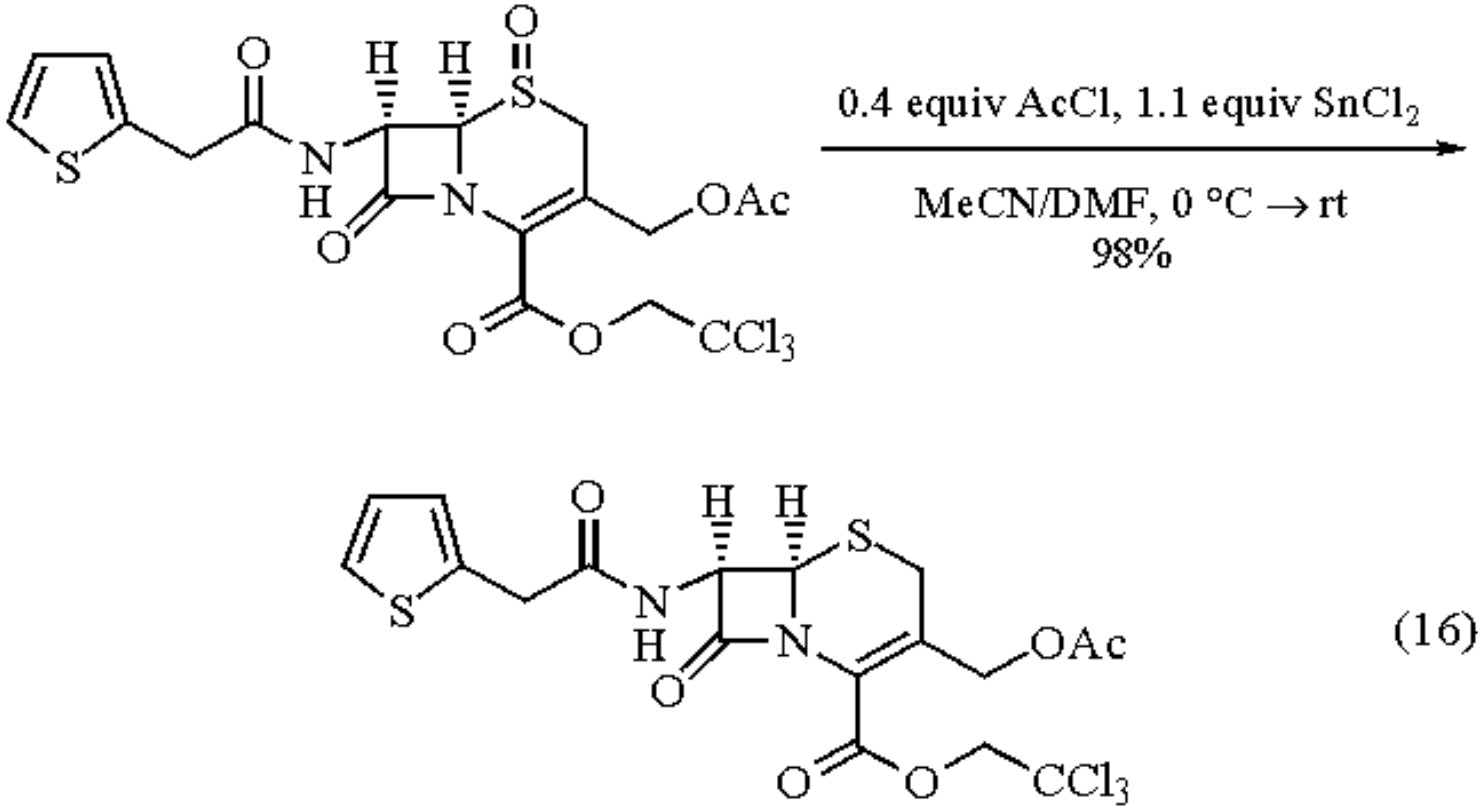

Another method for deoxygenation of sulfoxides involves treatment with two equiv AcCl (CH_2Cl_2, rt);[203] the oxidized byproduct is claimed to be gaseous chlorine.[203]

Chlorine and Bromine Scavenger.

AcCl (cat. H_2SO_4, 40-70 °C) scavenges Cl_2 efficiently (to afford chloroacetyl chloride in 87.1% yield).[13] AcCl also scavenges Br_2 efficiently at 35 °C.[14]

Source of Ketene.

AcCl reacts with ***Triethylamine*** at low temperature (-20 °C) to afford acetyltriethylammonium chloride.[204] This salt functions as a source of ketene (or the functional equivalent). For example, it reacts with silyl ketene acetals (THF, rt) to afford silyl enol ethers of acetoacetic esters (eq 9),[138] with α-alkoxycarbonylalkylidenetriphenylphosphoranes (CH_2Cl_2, rt) to afford allenic esters,[205] with enamines (Et_2O, 0 °C) to afford cyclobutanones,[136a] with certain acyl imines (Et_2O, 0 °C) to form formal [4 + 2] ketene cycloadducts,[206] and with certain nonenolizable imines (Et_2O, rt) to afford formal [4 + 2] diketene cycloadducts in up to 55% yield.[207] Also, on refluxing in Et_2O in the absence of a trapping agent, diketene is formed in 50% yield.[208]

AcCl/$AlCl_3$ decomposes to acetylacetone on heating ($CHCl_3$, 54-61 °C, 6 h; 82.5% yield after aqueous work-up).[209] The mechanism presumably involves ketene as an intermediate. However, an attempt to trap the ketene was unsuccessful.[210]

N-Acetylation.

Primary and secondary amines can be *N*-acetylated to form acetamides by treatment with AcCl under Schotten-Baumann conditions (aq NaOH),[211] but hydrolysis of AcCl is a significant competing side reaction.[212] Use of Ac_2O (2.5 equiv; Δ, 10-15 min) is therefore recommended.[211]

Tertiary amines react with AcCl to afford acetylammonium salts. Ordinarily, these salts fragment to ketene on warming (see above). However, those that possess a labile alkyl group fragment by loss of the alkyl group (von Braun cleavage). For example, bis(dimethylamino)methane reacts with AcCl (Et_2O, rt) to afford chloromethyldimethylamine,[213] a useful Mannich reagent, and 1,3,5-trimethylhexahydro-*s*-triazine reacts with AcCl ($CHCl_3$, Δ, 1 h) to afford chloromethylmethyl acetamide,[214] a useful amidomethylation reagent.[215] Also, aziridines react with AcCl (PhH, 0 °C) to afford chloroethylacetamides.[216] Allylic amines react with in situ-generated AcI (AcCl/CuI, THF, rt) to afford acetamides.[217]

AcCl also activates pyridines toward nucleophilic addition. For example, phenylmagnesium chloride adds to pyridine in the presence of AcCl (cat. CuI, THF, -20 °C -> rt) to afford, after catalytic hydrogenation, *N*-acetyl-4-phenylpiperidine in 65% yield.[218] Also, AcCl catalyzes the reaction between sodium iodide and 2-chloropyridine to afford 2-iodopyridine (MeCN, Δ, 24 h; 55%).[219]

N-Acetylation of enolizable imines to afford enamides can be accomplished by treatment with AcCl/$PhNEt_2$. For example, treatment of crotonaldehyde cyclohexylimine with AcCl followed by $PhNEt_2$ (toluene, rt) affords the enamide in 88% yield.[220]

Primary urethanes can be *N*-acetylated to afford imides by treatment with AcCl (100 °C, 1 h).[221] Alternatively, urethanes can be converted into acetamides by treatment with AcBr (120-130 °C)[221] or in situ-generated AcI[222] (MeCN, 60 °C).[223]

Finally, a convenient method for preparation of ***N-Trimethylsilylacetamide*** (MSA), a useful trimethylsilyl transfer reagent, involves treatment of ***Hexamethyldisilazane*** with AcCl (hexane, Δ; 88%).[224]

S-Acetylation.

Both aliphatic and aromatic thiols can be *S*-acetylated by treatment with AcCl (cat. $CoCl_2$, MeCN, rt).[225]

Nucleophilic Acetylation.

AcCl together with SmI_2 (MeCN, rt) or $SmCp_2$ delivers the acetyl anion synthon to ketones to afford the corresponding acyloins (eq 17).[15]

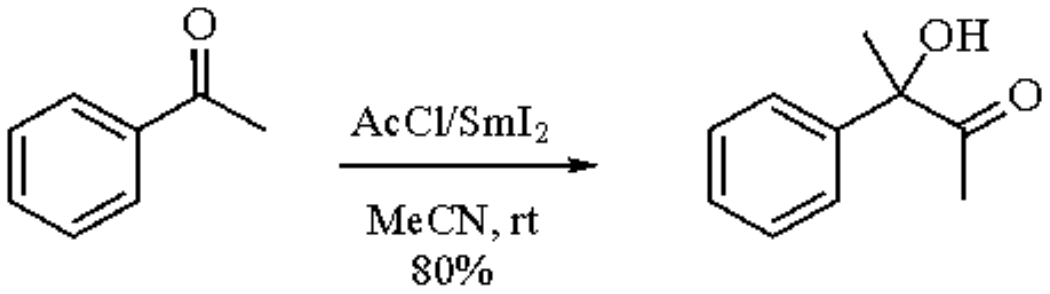

(17)

Related Reagents.

Acetic Anhydride; ***Acetyl Bromide***; ***Acetyl Fluoride***.

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Acetyl Cyanide[1]

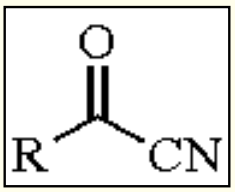

(R = Me)

[631-57-2] · C_3H_3NO · Acetyl Cyanide · (MW 69.06) (R = Ph)

[613-90-1] · C_8H_5NO · Benzoyl Cyanide · (MW 131.13)

(versatile electrophile useful for selective acylation, cyanohydrin synthesis, and cycloaddition reactions)

Alternate Names: 2-oxopropanenitrile; pyruvonitrile.

Physical Data: AcCN: bp 92.3 °C; *d* 0.9745 g cm^{-3}; BzCN: mp 30-32 °C; bp 206 °C; *d* 1.106 g cm^{-3}.

Preparative Methods: acyl cyanides are readily prepared from the reaction of acyl halides with ***Copper(I) Cyanide***,[2a] ***Sodium Cyanide***,[2b] or ***Cyanotrimethylsilane***[2c] and via the oxidation of cyanohydrins.[2d]

Handling, Storage, and Precautions: AcCN and its analogs are highly toxic; use in a fume hood.

Acylation.

Acyl cyanides are useful for the selective acylation of alcohols[3] and amines[4] (eq 1). This process is utilized in the reaction of AcCN with orthoesters[5a,b] and amido acetals,[5c] resulting in the substitution of an alkoxy group with a cyano group (eq 2). In addition, aldehydes are cyanoacylated with benzoyl cyanide (BzCN).[1a] Lithium ketone enolates react cleanly with acyl cyanides, producing 1,3-diketones uncontaminated by *O*-acylated or diacylated products (eq 3).[6] Other efficiently acylated carbon nucleophiles include Grignard reagents,[7] primary nitroalkanes,[8] dithianes,[9] nitrosoamines,[10] and active methylene compounds.[11] A one-pot synthesis of pyridines utilizes AcCN as the trapping agent with an intermediate ketone enolate (eq 4).[12]

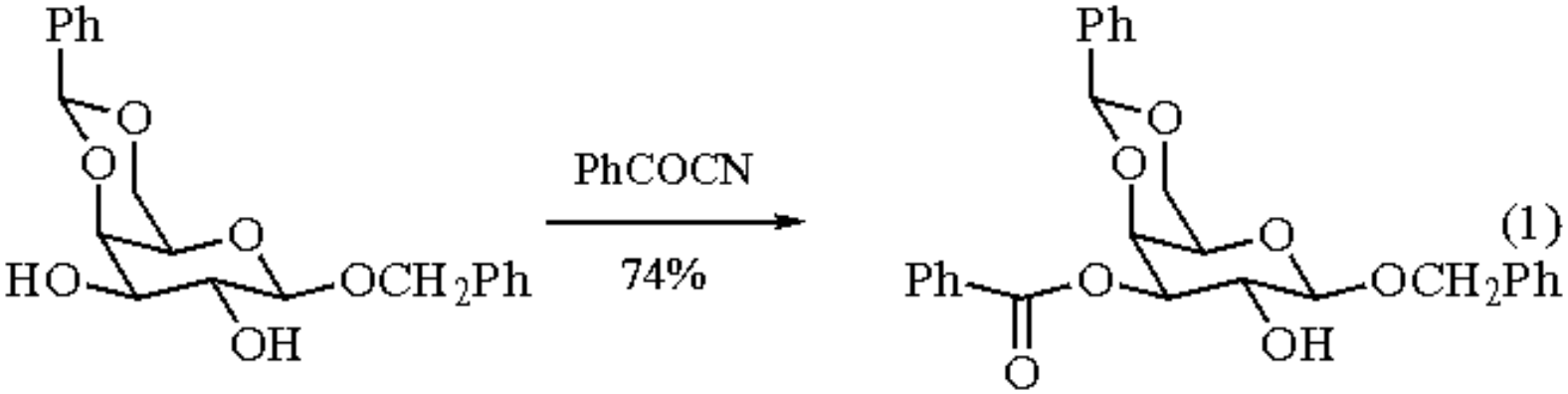

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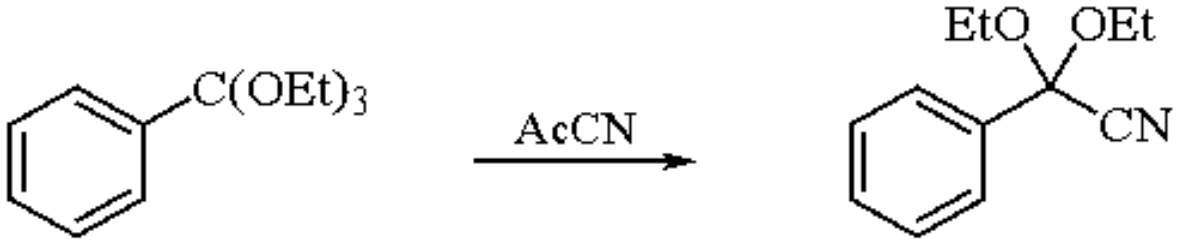

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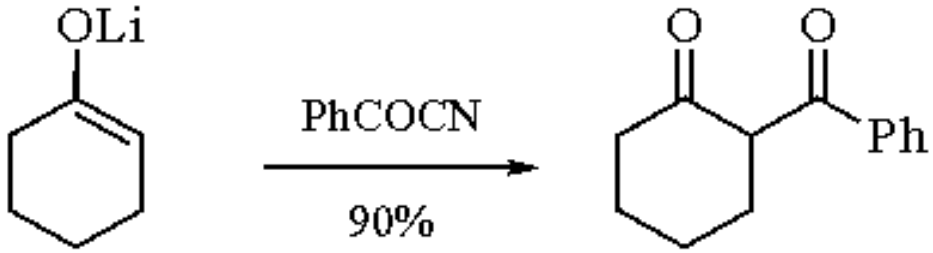

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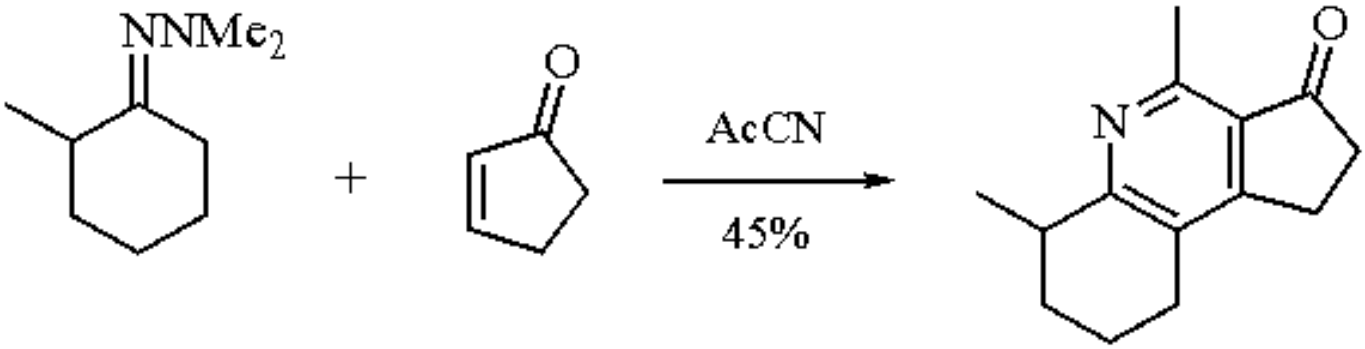

(4)

Treatment of trimethylsilyl ketene acetals with BzCN in the presence of ***Titanium(IV) Chloride*** affords α-benzoylcarboxylates.[13] In contrast, attack of the nucleophile at the nitrile carbon of BzCN is observed when the same reaction is performed in the absence of catalyst. Nitrile attack is also the preferred mode in the ***Nickel(II) Acetylacetonate*** catalyzed reaction of 1,3-dicarbonyls with BzCN.[14]

A synthesis of 4-chlorooxazoles from aromatic aldehydes and BzCN formally involves the addition of HCl across the nitrile bond (eq 5).[15]

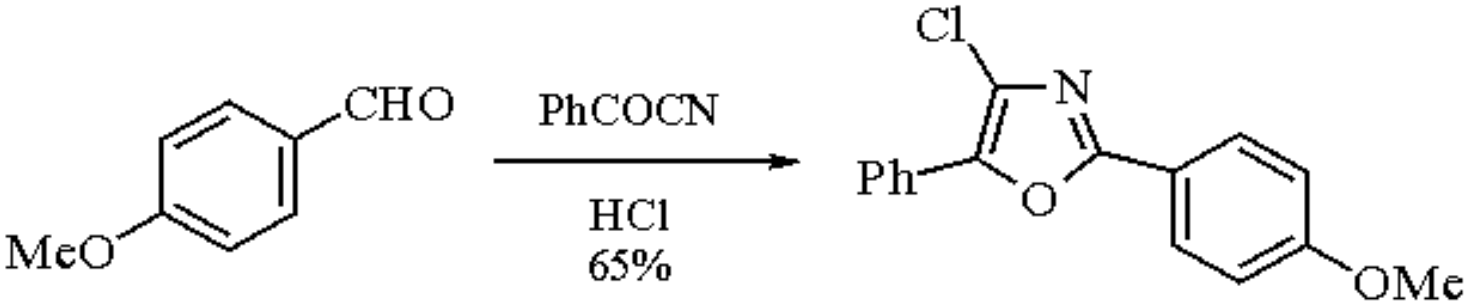

(5)

Cyanohydrin Synthesis.

The addition of silyl enol ethers to AcCN in the presence of $TiCl_4$ affords the corresponding β-hydroxy ketone which retains the cyano functionality (eq 6).[16] Similar results are found with allylsilanes.[16] Retention of the cyano group is also accomplished in the Wittig reaction of dihalomethylenephosphorus ylides with BzCN.[17] Acidic treatment of phenol and AcCN provides a cyano containing bis-adduct (eq 7).[18] Reductive coupling of aldehydes and ketones with BzCN by ***Titanium(III) Chloride*** affords an intermediate cyanohydrin diol, which upon base treatment produces the mixed benzoin.[19]

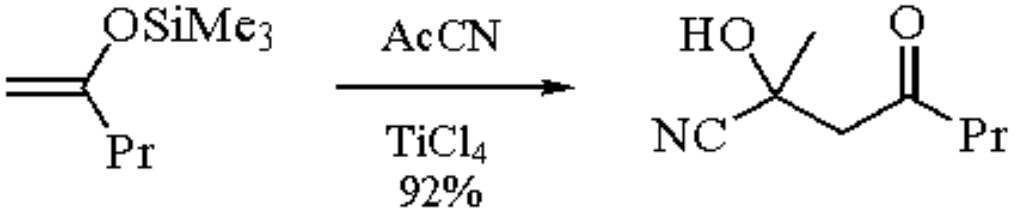

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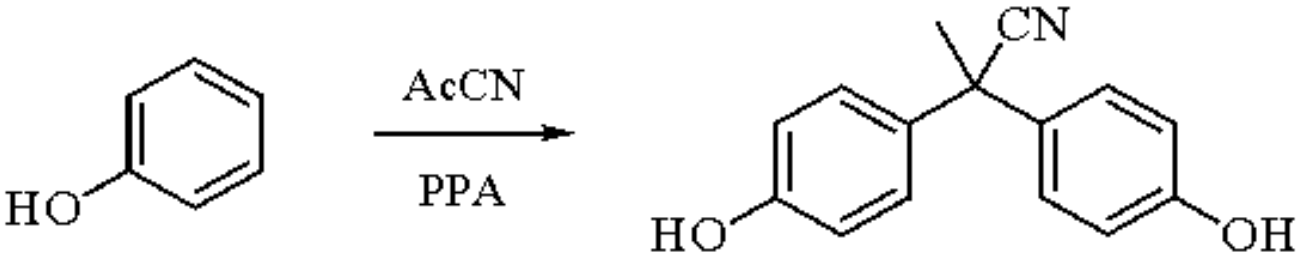

(7)

Cycloadditions.

In the presence of ***Zinc Chloride***, AcCN serves as a dienophile in hetero-Diels-Alder reactions (eq 8).[20] Acyl cyanides are also reactive toward photochemically generated *o*-quinodimethanes[21] and act as substrates in the Paterno-Büchi reaction with furan.[22] In addition, AcCN is useful for the preparation of optically pure 1-cyanovinyl esters which serve as dienophilic equivalents of ***Ketene*** in [4 + 2] cycloadditions.[23]

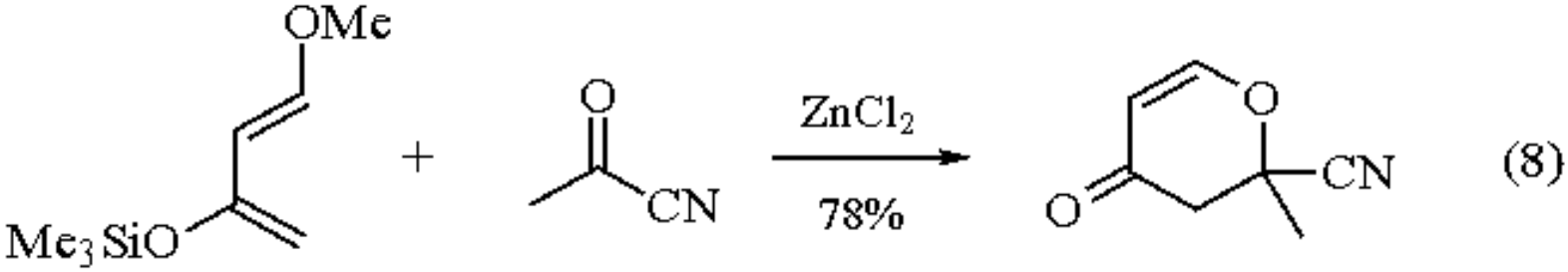

Related Reagents.

Acetic Anhydride; ***Acetyl Bromide***; ***Acetyl Chloride***.

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Acetylene

HC≡CH

[74-86-2] · C_2H_2 · Acetylene · (MW 26.04)

(ethynylation reagent,[1] hydrosilylation,[23] carbonylation,[24-26] cycloadditions,[31-33] cyclotrimerization[34])

Alternate Name: ethyne.

Physical Data: bp -83 °C.

Form Supplied in: widely available as compressed gas. *Drying:* can be purified by passing through a trap at -80 °C followed by a column of sulfuric acid and then through a column of sodium hydroxide.[2]

Handling, Storage, and Precautions: flammable, colorless gas which possesses a garlic odor; use only with adequate ventilation; skin irritant. The low electrical conductivity of acetylene requires that care must be taken to eliminate any static charge buildup. Use in a fume hood.

Ethynylation.

Due to the sp hybridization of acetylene's σ-bonds the methine proton has a pK_a of about 25 and can be removed with strong bases to form the acetylide anion.[3] Sodium acetylide is commonly prepared by deprotonation with sodium amide. ***Lithium Acetylide*** can be conveniently prepared using ***n-Butyllithium***, while the corresponding Grignard reagent is commonly generated by treatment with ***Ethylmagnesium Bromide***.[4] Alkyl cuprates undergo nucleophilic addition to acetylene.[5] The dianion of acetylene is available by using higher temperatures during deprotonation.[6] A variety of other counter cations of the acetylide ion have also been formulated, usually starting from the acetylides previously mentioned.[1a] The acetylide anion undergoes nucleophilic addition to a wide range of electrophiles such as halides,[7] alkyl halides,[8] alkyl sulfonates,[9] epoxides,[10] aldehydes,[11] ketones,[12] esters,[13] and imides.[14] In certain cases the yields of addition may be improved by additives such as ethylenediamine[15] or ***Copper(I) Iodide***.[16] When the electrophile is hindered, elimination may become the predominant pathway. This problem may be avoided with trialkylborane electrophiles (eq 1).[17] After treatment with iodine, the intermediate borate yields the substituted alkyne via migration of one of the alkyl groups. This sequence is not as sensitive to steric effects as simple substitutions with halides. Higher yields can be obtained if ***Lithium (Trimethylsilyl)acetylide*** is used instead (see also ***Trimethylsilylacetylene***).

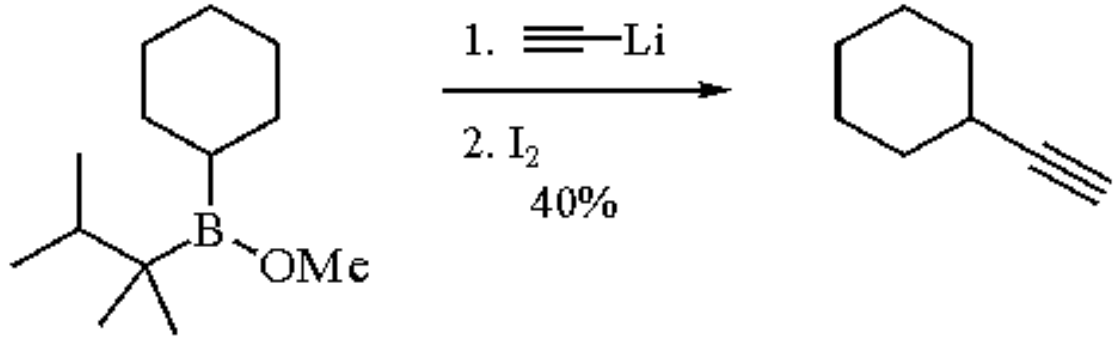

(1)

The nucleophilicity of the acetylide anion is such that discrimination between several electrophilic centers within a substrate is possible (eq 2).[18]

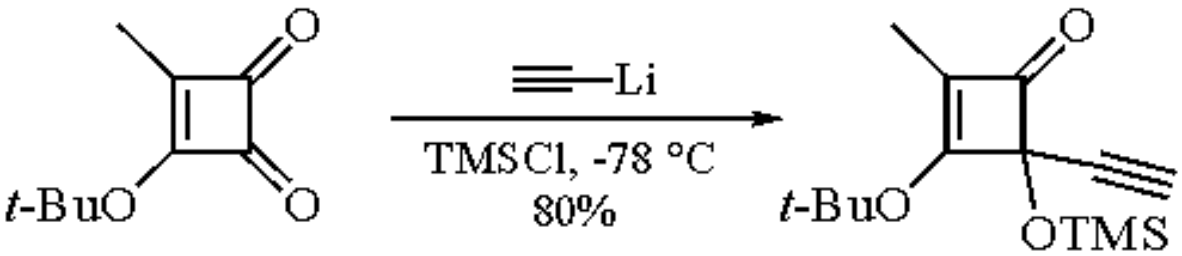

(2)

The regioselectivity of acetylide additions are sensitive to the counter cation. For example, ethynyltriisopropoxytitanium acetylide, prepared from ethynyllithium and ***Chlorotitanium Triisopropoxide***, gives a single addition product with pyrimidin-2(1*H*)-ones while the Grignard and lithium acetylides give mixtures of regioisomers (eq 3).[19] There are also examples of diastereoselective additions of acetylide anions to ketones (eq 4).[20]

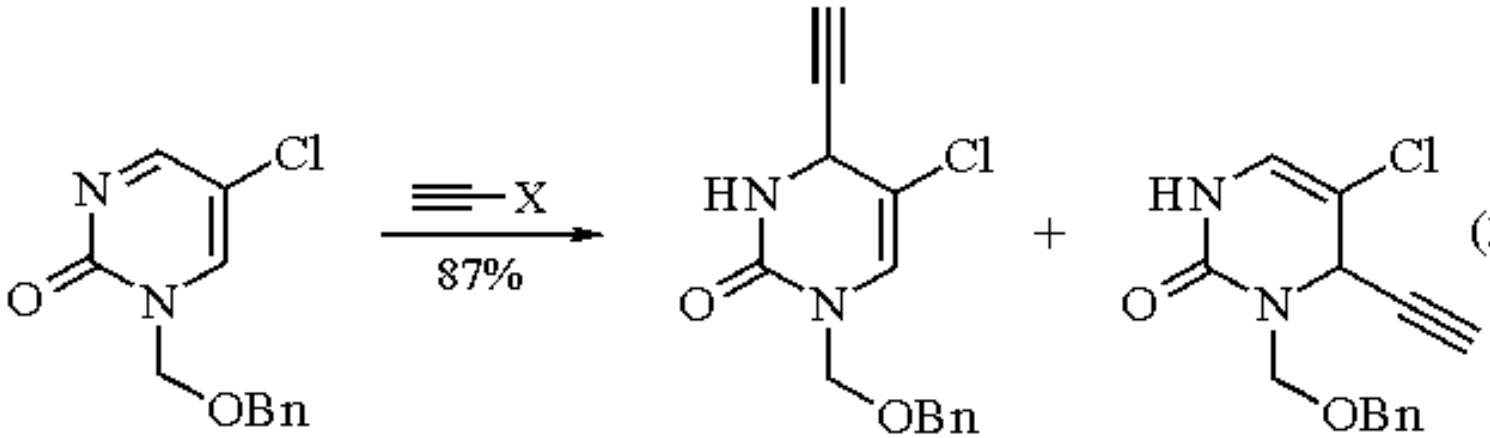

(3)

X = Li	20	80
MgBr	50	50
$Ti(O\text{-}i\text{-}Pr)_3$	0	100

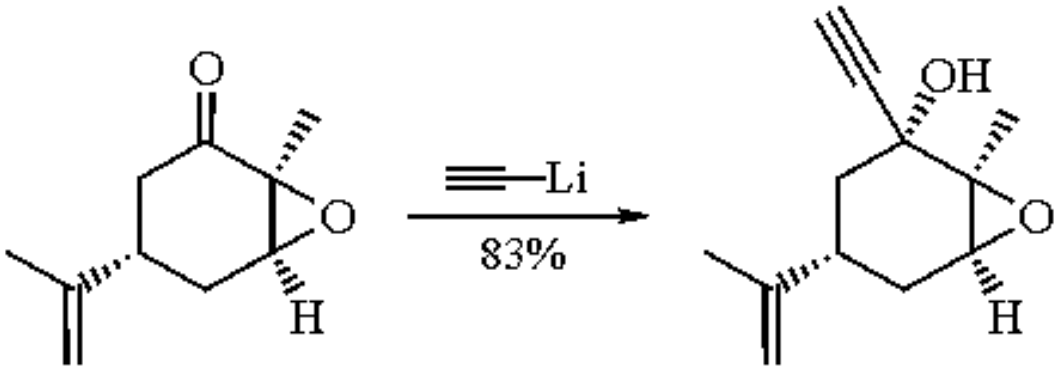

(4)

The acetylide anion is useful for the synthesis of enynes which have been used in palladium catalyzed cyclizations (eq 5).[21]

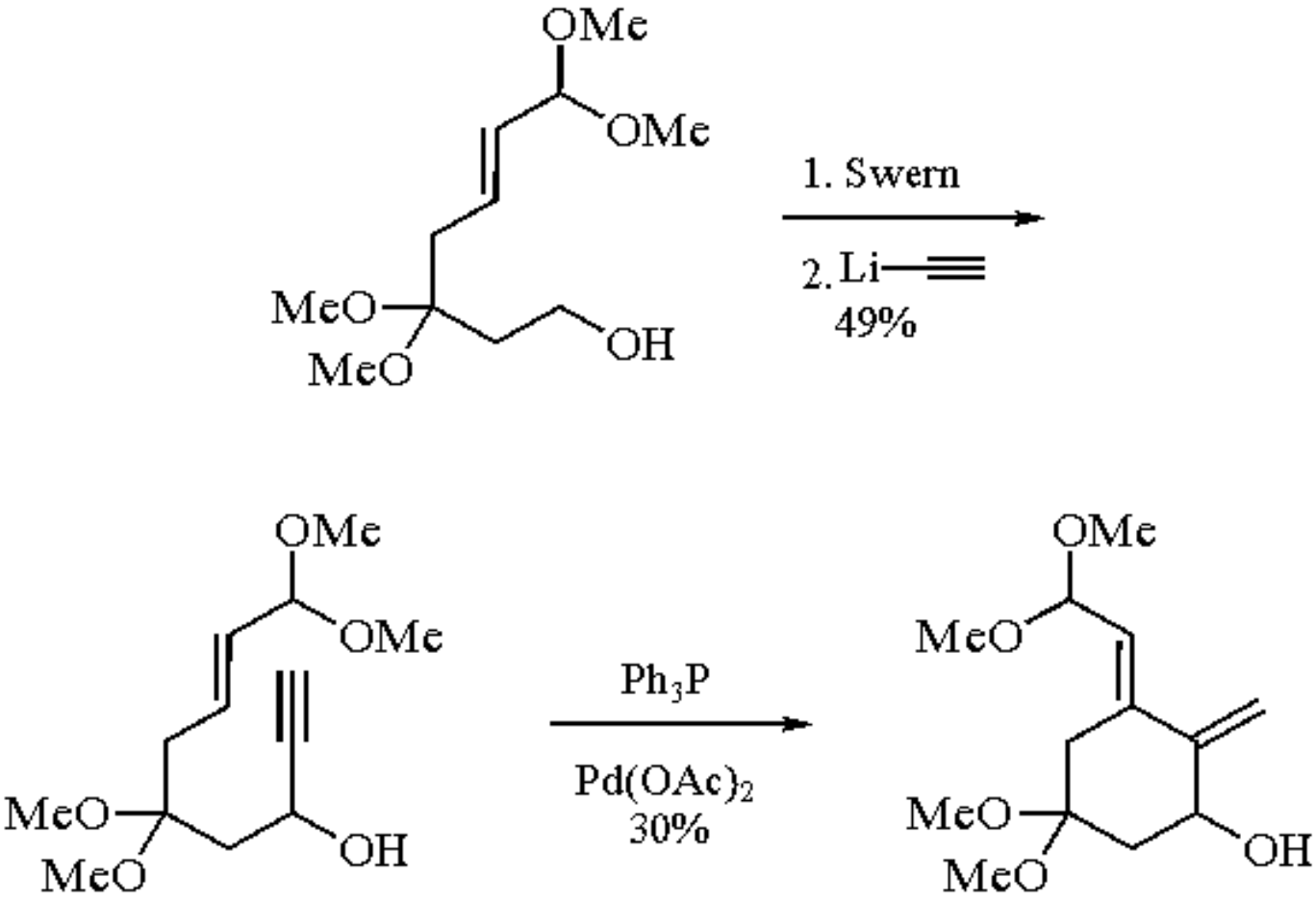

(5)

Ethynylation of aryl halides (Stephens-Castro coupling) with the copper acetylide is synthetically effective when one of the acetylenic methine protons is protected.[22]

Hydrosilylation.

Acetylene can be converted[23] into a vinylsilane under appropriate hydrosilylation conditions using Pt, Rh, Ru, or Al catalysts, but the initial 1:1 product can react further to give a 1,2-disilylethane. Examples of these processes are shown in eq 6.

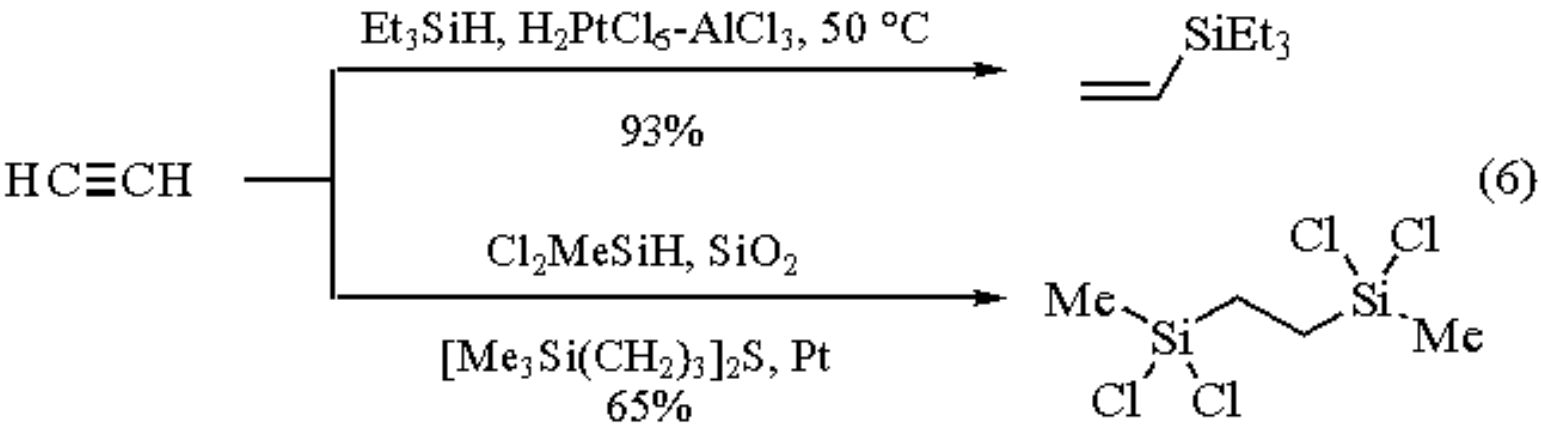

Reactions with CO and CO_2.

Alkynes react with CO_2 and secondary amines in the presence of ruthenium complexes to afford vinyl carbamates (eq 7).[24] Mononuclear ruthenium complexes and $[RuCl_2(norbornadiene)]_n$ or ***Ruthenium(III) Chloride*** have been shown to be the best catalysts for monosubstituted alkynes and acetylene, respectively.

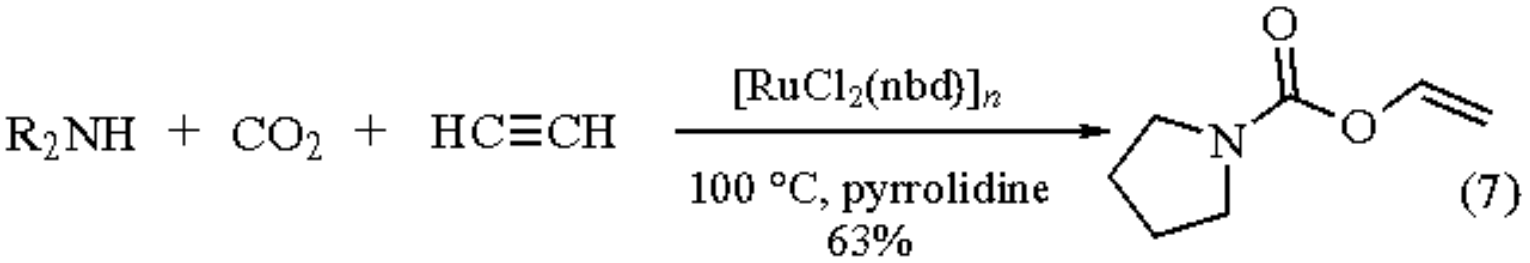

Acetylene reacts[25] with CO and O_2 in presence of ***Palladium(II) Chloride*** to give dimethyl maleate in 90% yield. Organic acids have been formed by treating acetylene with CO and Ni or Pd catalysts.[25a] Acetylene reacts with CO in presence of $Co_2(CO)_8$ to give an (*E*)-bisbutenolide in aprotic solvents (eq 8), while the (*Z*)-isomer is obtained in the presence of tetramethylurea.[26]

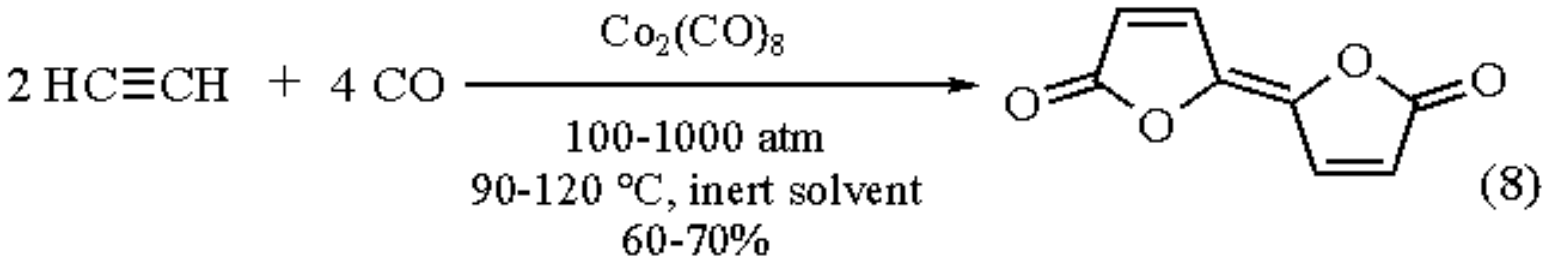

Addition.

Acyl chlorides add across acetylene to give β-chloroenones in CCl_4 in the presence of ***Aluminum Chloride*** (eq 9).[27]

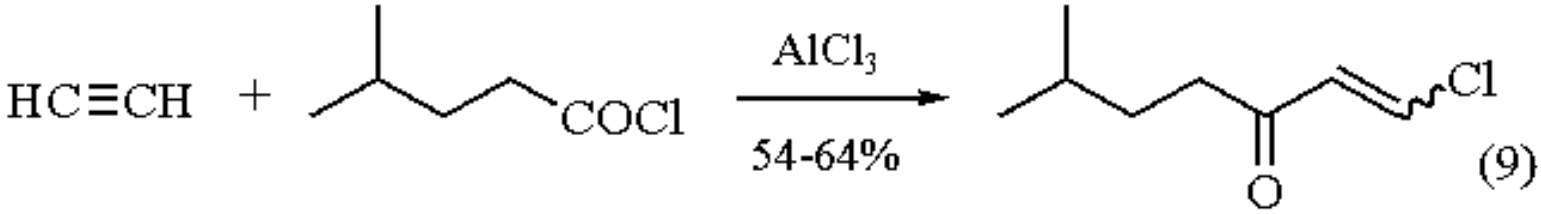

The acid catalyzed hydration of acetylene to acetaldehyde followed by condensation to give crotonaldehyde is a well known reaction first studied by Berthelot in 1862.[28] Although more efficient procedures have been developed since then, the mechanism of hydration of acetylene has not yet been unambiguously resolved.[29] Kinetic data based on NMR experiments suggest that a vinyl cation is probably an intermediate.[30]

Cycloadditions.

Acetylene has low reactivity in Diels-Alder reactions and reacts with electron rich dienes only under severe conditions.[31] The reaction of dienes with vinyl bromide and subsequent elimination of HBr from the adduct leads to the same product as direct addition of acetylene. In addition a number of compounds have been suggested as acetylene surrogates, such as 2-phenyl- and ***2-Thiono-1,3-dioxol-4-ene***,[32] and phenyl vinyl sulfoxide.[33] Vinylene thioxocarbonate and 2-phenyl-1,3-dioxol-4-ene, on reaction[9] with anthracene in benzene at 170 °C for 16 h, gave the corresponding adducts in 60 and 65% yield, respectively. The [4 + 2] adducts yield the corresponding alkene upon treatment with trivalent phosphorus or *n*-butyllithium respectively. Similarly, heating anthracene and phenyl vinyl sulfoxide in chlorobenzene for 120 h afforded dibenzobarrelene in 83% isolated yield (eq 10).[9]

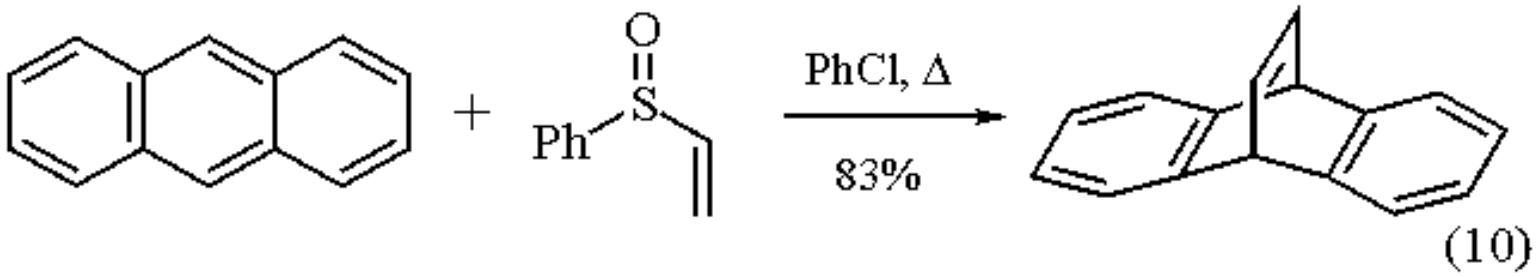

The following example (eq 11) involves in situ reductive extrusion of an oxygen atom. It has been suggested that the liberated PhSOH appears capable of deoxygenating isobenzofurans and related molecules.

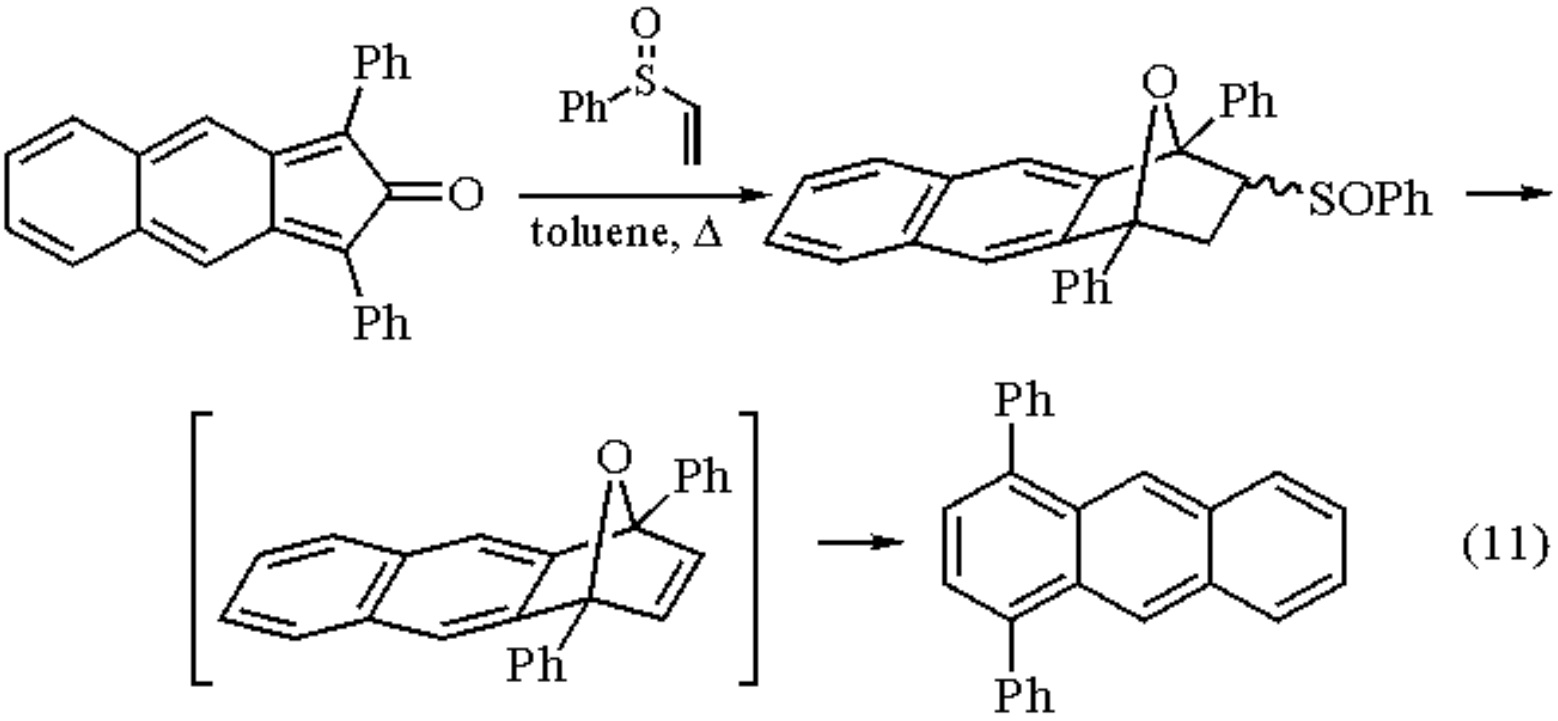

(11)

Cyclotrimerization.

In addition to acetylene, many mono- or disubstituted alkynes undergo cyclotrimerization in the presence of transition metal complexes. Acetylene itself trimerizes to give benzene. Trimerization of unsymmetrically substituted alkynes gives rise mostly to benzenes in which the most sterically demanding substituents occupy positions 1, 2, and 4 around the ring and to a lesser extent a 1,3,5-substitution pattern is also obtained.[34] Although numerous mechanistic pathways have been postulated, depending on the metal involved, a common feature involves intermediacy of metallocyclopentadienes and complexation with a third alkyne which inserts to give a transient metallocycloheptatriene, leading finally to reductive elimination of the metal and the benzene product.

Selective intermolecular co-cycloaddition has been achieved, exploiting the relative unreactivity of phosphine nickel carbonyls towards trimerization of internal alkynes.[35,36] Thus two molecules of acetylene and one molecule of an internal alkyne give a mixture of the unsubstituted and substituted benzenes (eq 12).

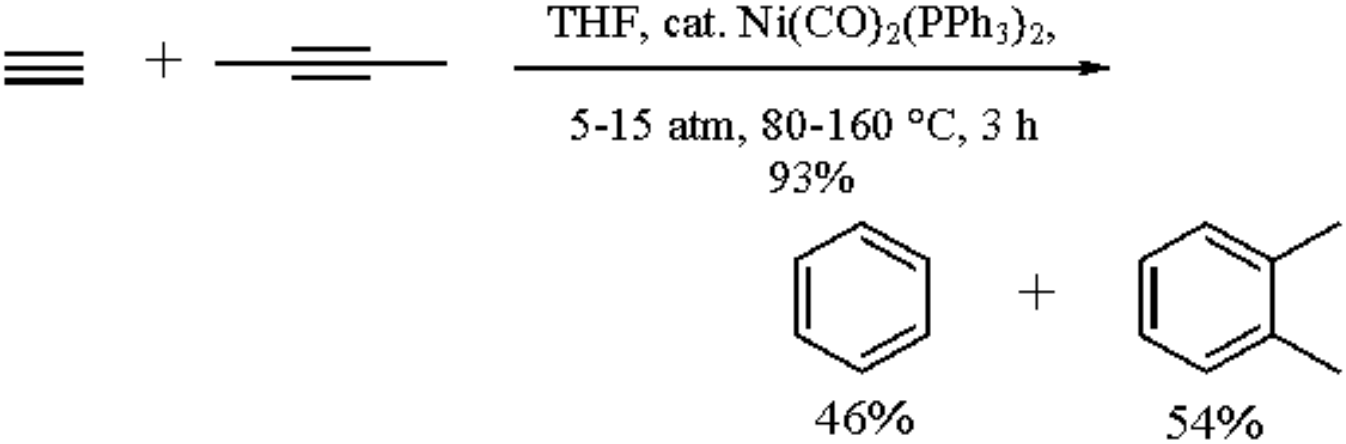

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Acetyl Fluoride

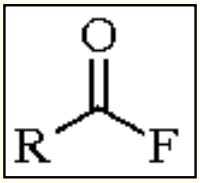

(MeCOF)

[557-99-3] · C_2H_3FO · Acetyl Fluoride · (MW 62.04) (EtCOF)

[430-71-7] · C_3H_5FO · Propionyl Fluoride · (MW 76.07) (PhCOF)

[455-32-3] · C_7H_5FO · Benzoyl Fluoride · (MW 124.11)

(precursors to acylium salts; acylating agents)

Physical Data: MeCOF: bp 20-21 °C; *d* 1.0024 g cm^{-3}; EtCOF: bp 42-44 °C; *d* 0.972 g cm^{-3}; PhCOF: bp 159-161 °C; *d* 1.140 g cm^{-3}.

Preparative Methods: acetyl fluoride (but not other acyl fluorides) is most conveniently prepared by addition of ***Acetyl Chloride*** to a solution of ***Potassium Fluoride*** in AcOH; reaction is immediate. Warming the solution and condensing the gas gives nearly quantitiative yields.[1] Procedures applicable to the preparation of a variety of acyl fluorides include reaction of the acid chloride or anhydride with nucleophilic fluorides[2] and fluorination of the carboxylic acid.[3]

Handling, Storage, and Precautions: samples of acetyl fluoride sealed in glass ampoules slowly form a pyrylium salt.[4] Acetyl fluoride is a corrosive lachrymator. Use in a fume hood.

Preparation of Acylium Salts.

Addition of Lewis acidic metal fluorides to a variety of acyl fluorides produces acylium salts (**1**), isolable as stable white solids (eq 1).[5] Reaction of acyl fluorides with SO_3 produces acyl fluorosulfates (**2**) (eq 2).[6] Both (**1**) and (**2**) are powerful acylating agents.[5,6]

$$RCOF + MF_x \xrightarrow[-78 \rightarrow 0\ ^\circ C]{F_2CCl_2} RCO^+ MF_{x+1}^- \quad (1)$$

(1)

$$MF_x = BF_3, PF_5, SbF_5, AsF_5$$

$$RCOF + SO_3 \longrightarrow RCO_2SO_2F \quad (2)$$

(2)

Acylation at Carbon.

Acyl fluorides usually have no advantages over acid chlorides for Friedel-Crafts reactions;[7] however, with some poylcyclic aromatic substrates the acyl fluoride-BF_3 system exhibits exceptional regioselectivity (eq 3).[8] Silyl enol ethers are *C*-acetylated by reaction with acetyl fluoride and BF_3 (eq 4).[9] Lower yields are obtained with preformed acetyl tetrafluoroborate. Reaction of Tl^I enolates of β-dicarbonyl compounds with acetyl fluoride in ether gives *C*-acylated products in high yield.[10]

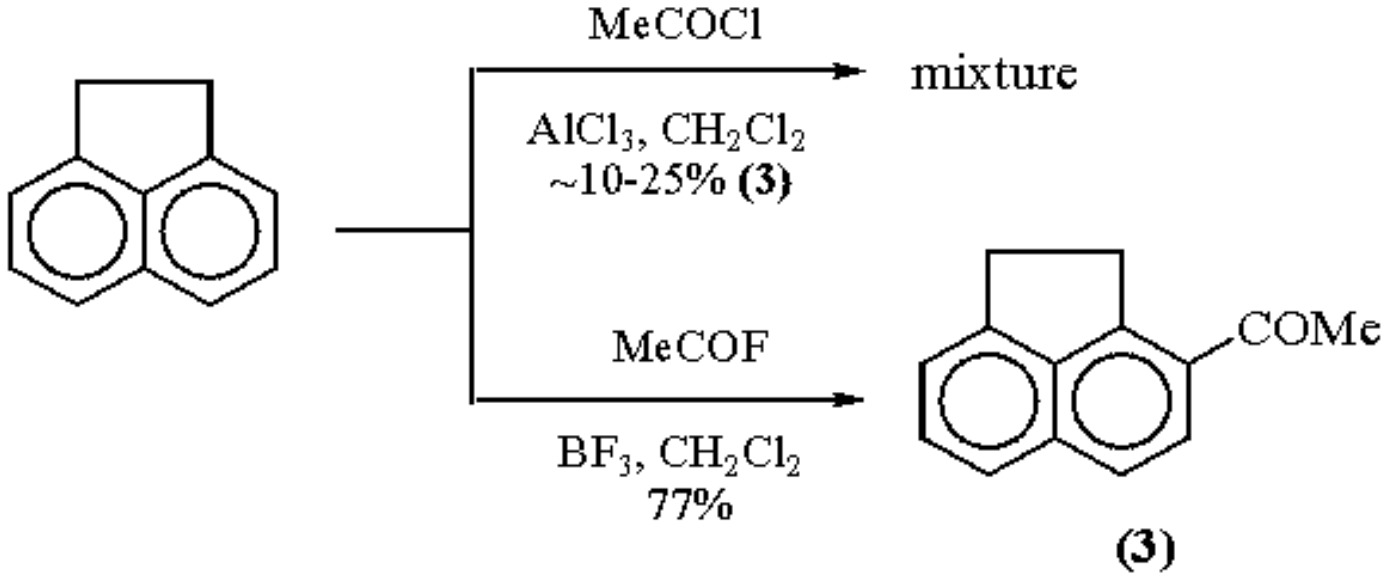

(3)

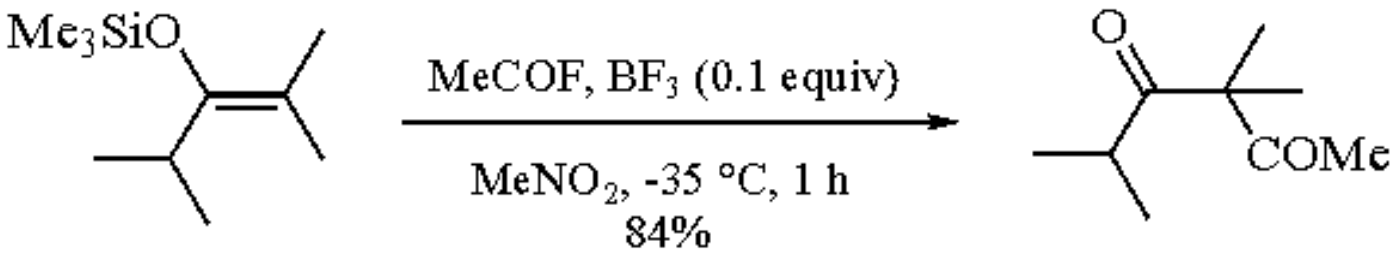

(4)

Acylation at Oxygen.

Esters of a variety of perfluoro alcohols are obtained by acylation of the metal alkoxides with acyl fluorides.[11] Acetyl fluoride, in the presence of acid catalysts, cleaves certain methyl ethers via an acyl oxonium ion intermediate (eq 5).[12]

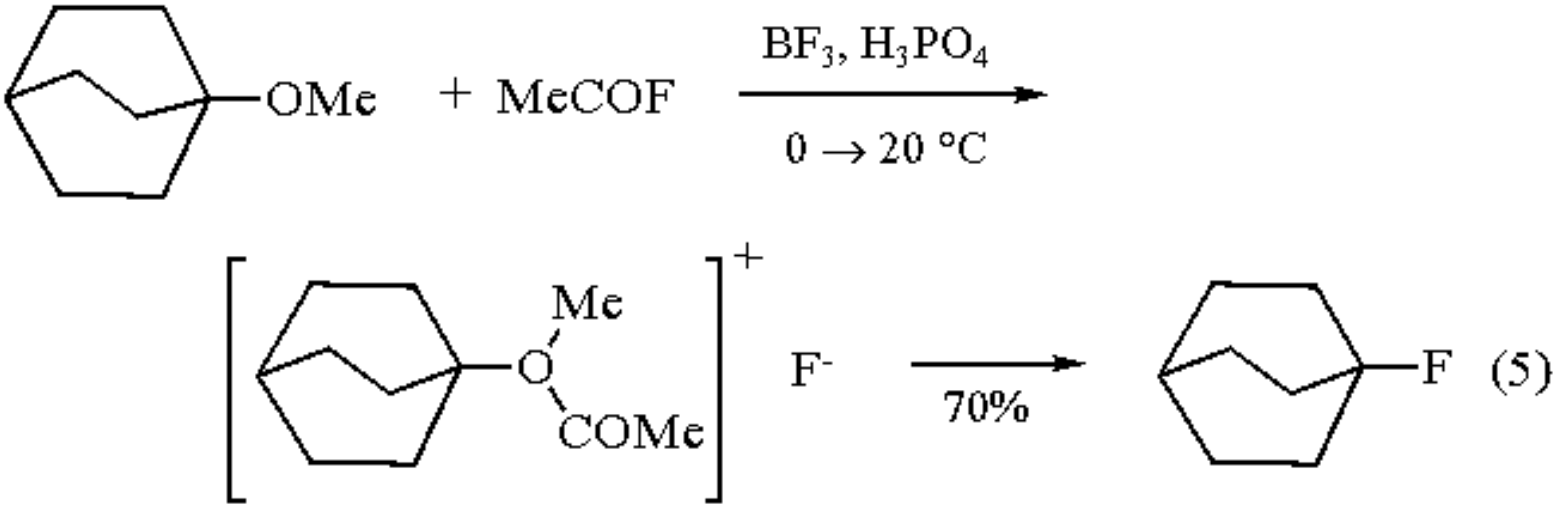

Related Reagents.

Acetyl Bromide; ***Acetyl Chloride***; ***Acetyl Methanesulfonate***; ***Chloroacetyl Fluoride***.

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Acetyl Hypofluorite[1]

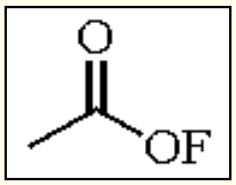

[78948-09-1] · $C_2H_3FO_2$ · Acetyl Hypofluorite · (MW 78.04)

(convertion of alkenes into fluorohydrin derivatives;[2] aromatic fluorination;[3] instrumental in introducing the ^{18}F isotope in sugars and other biologically important compounds for positron emitting tomography studies;[4] fluorination on a carbon α to carbonyl;[5] activation of pyridine derivatives[6])

Physical Data: mp -96 °C; bp approx +53 °C; ^{19}F NMR +168.5 ppm; thermal decomposition to MeF and CO_2.[7]

Analysis of Reagent Purity: AcOF oxidizes iodides to iodine which is then titrated ($AcOF + 2KI + H^+ \rightarrow KF + AcOH + K^+ + I_2$).

Handling, Storage, and Precautions: as with all hypofluorites this reagent should be treated with care. When not in solution, or when very concentrated, it may explode.[8] Solutions of up to 0.3 M in $CFCl_3$ at -78 °C or in MeCN at -45 °C are stable for days, but at rt the half-life is around 2-4 h. No data about the toxicity are available, but some hypofluorite derivatives such as CF_3OF and F_2O are known to be toxic. Use in a fume hood.

Acetyl hypofluorite, prepared in 1981 by reacting F_2 with AcONa,[9] was the first hypofluorite to possess a hydrogen-containing alkyl group in the vicinity of the O-F bond. The fluorine in this reagent is of electrophilic nature, as can be judged from reactions with enol acetates[10] or enolates[5b] when α-fluoro carbonyl derivatives are produced (eqs 1 and 2). Similar conclusions can be drawn from its reactions with unsymmetrical alkenes. Apart from regioselectivity, the addition of AcOF across double bonds is also stereospecific, resulting from a preferential *syn* addition[10,11] (eq 3), a mode characteristic of all reagents with electrophilic fluorine.

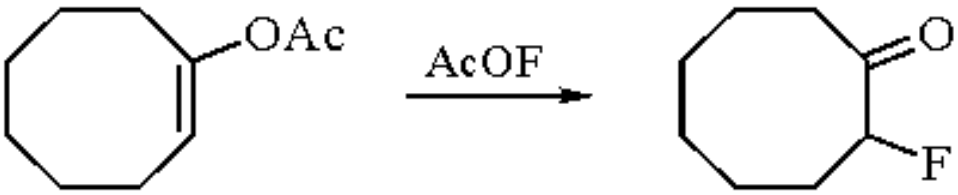

(1)

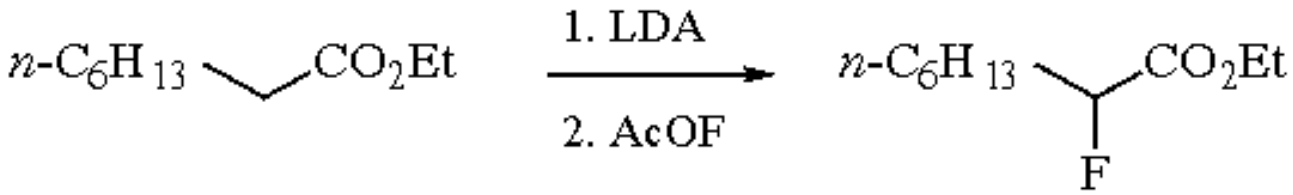

(2)

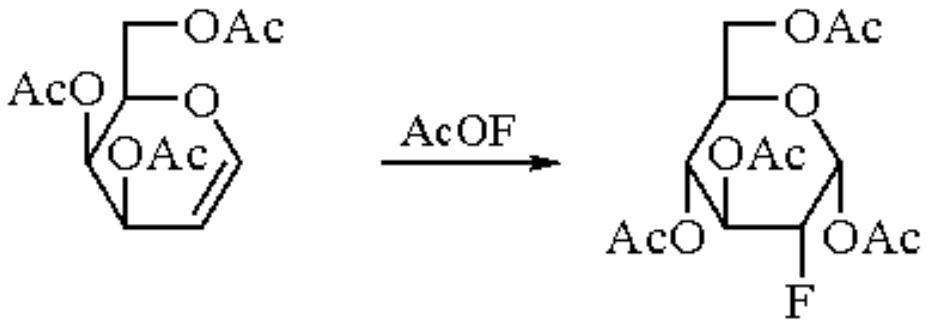

(3)

The electrophilic nature of the fluorine was also used for aromatic substitution of activated aromatic rings with predominant *ortho* fluorination (eq 4).[3,12] This procedure was used for direct fluorination of the opiatic peptide dermorphine (eq 5).[13]

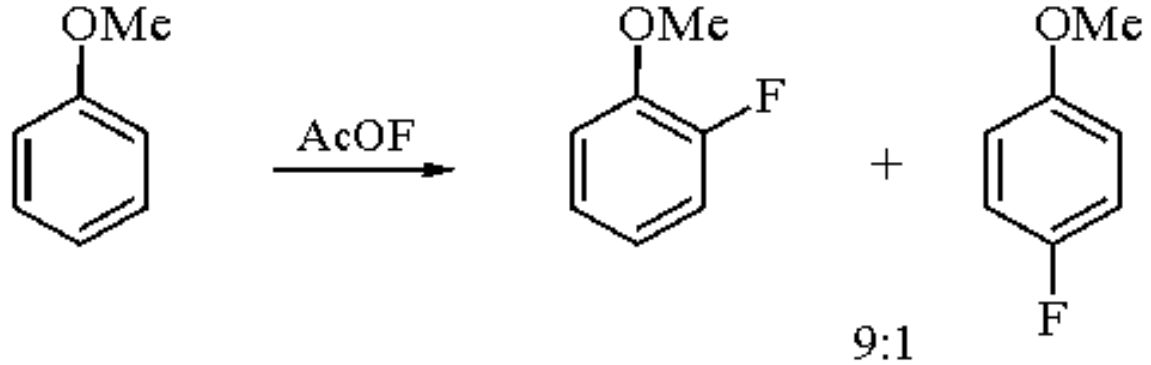

(4)

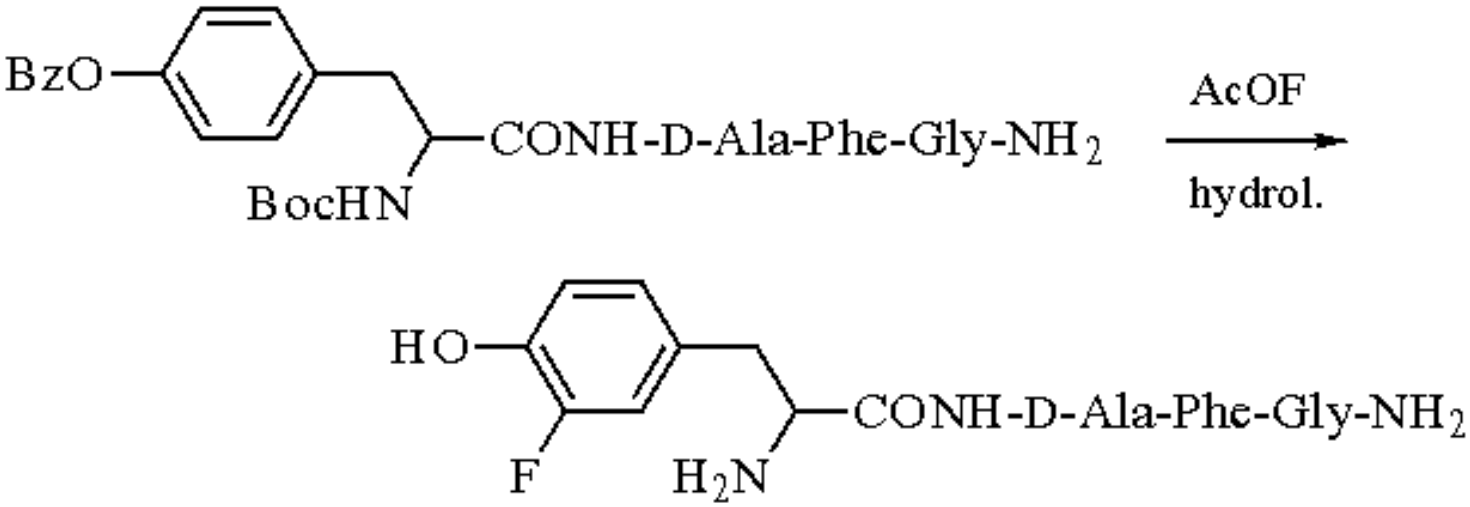

(5)

Aromatic fluorination was also achieved via substitution of an Ar-M bond. It seems that the best metals are tin[14] and mercury. The latter was used for synthesis of fluorodopa derivatives (eq 6).[15]

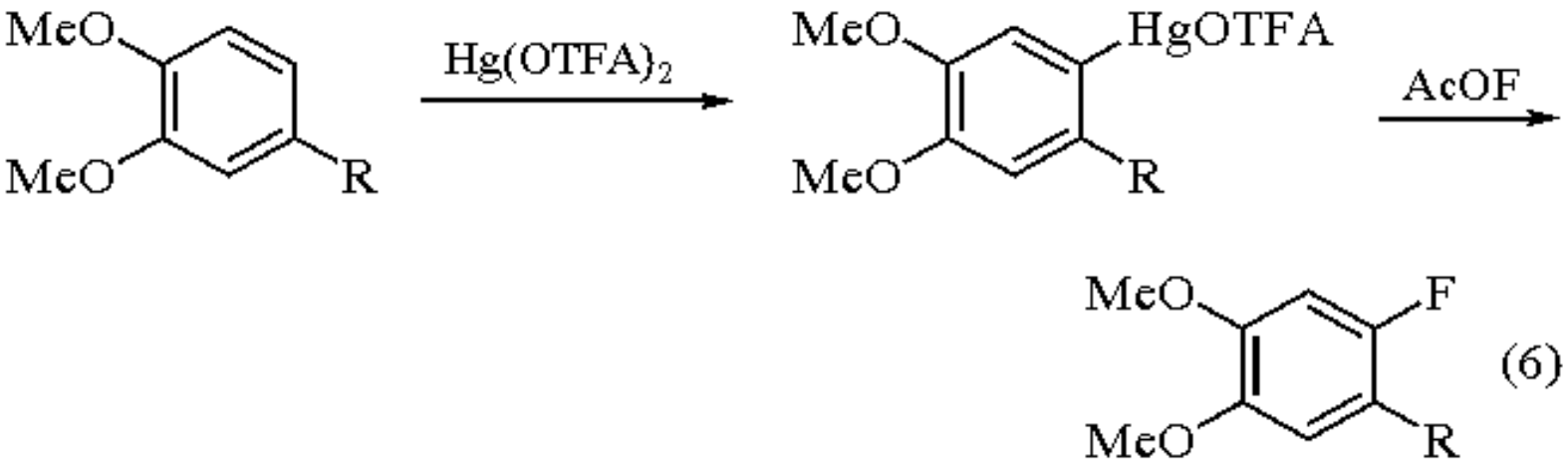

(6)

AcOF was used exclusively for introducing the ^{18}F isotope in order to construct compounds suitable for positron emitting tomography (PET). Among numerous examples, we will mention here the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose[16] and [^{18}F]fluorodopa,[4,17] both used for brain studies, 6-[^{18}F]fluorometaraminol (eq 7) as a heart imaging agent,[18] and [^{18}F]fluoro-2-oxoquasepam (eq 8) with a strong affinity to benzodiazepine receptors.[19]

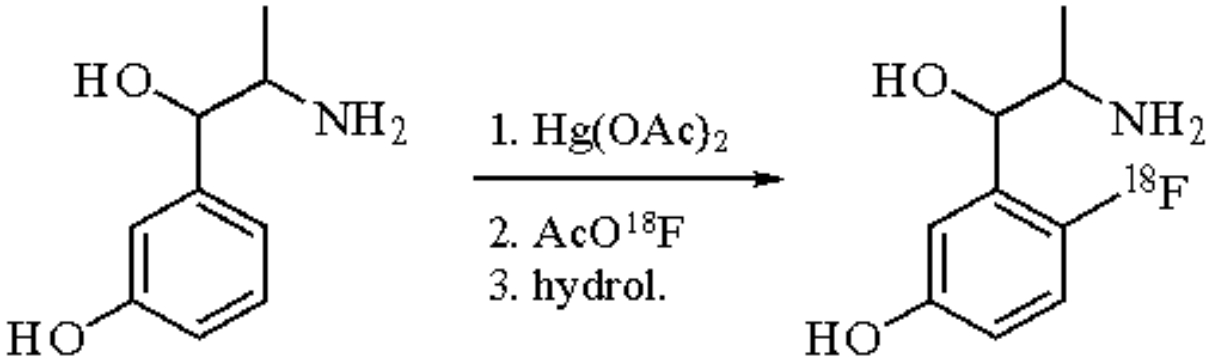

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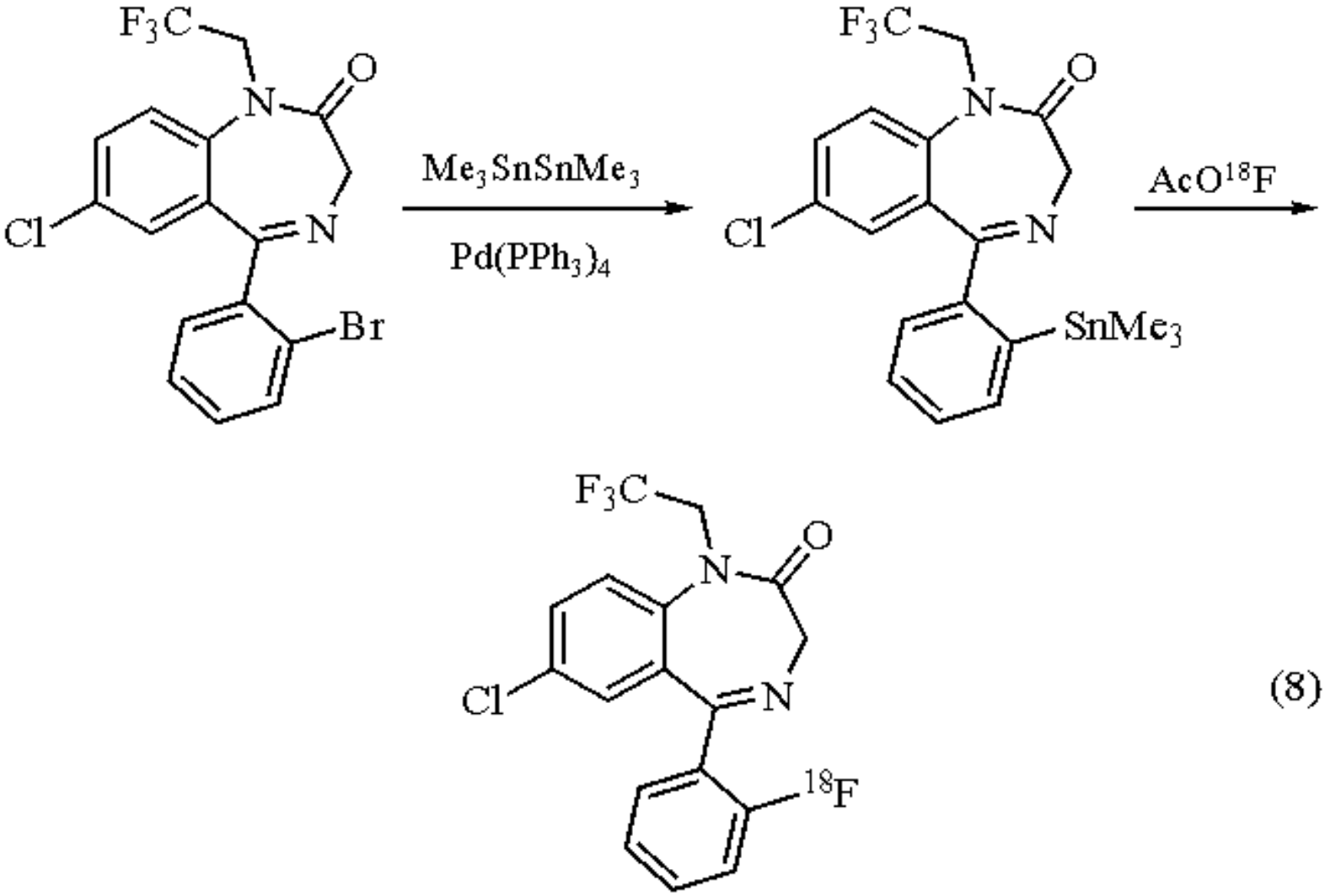

(8)

AcOF was also used for activating the inert pyridine ring. The reaction takes advantage of the electrophilic power of the fluorine which is able to attack the nitrogen atom. As a result, the 2-position becomes very susceptible to nucleophilic attacks by either the remaining acetate or nucleophilic solvents, if present (eq 9). The elimination of HF is a strong driving force for the reaction, explaining the speed at low temperatures.[6]

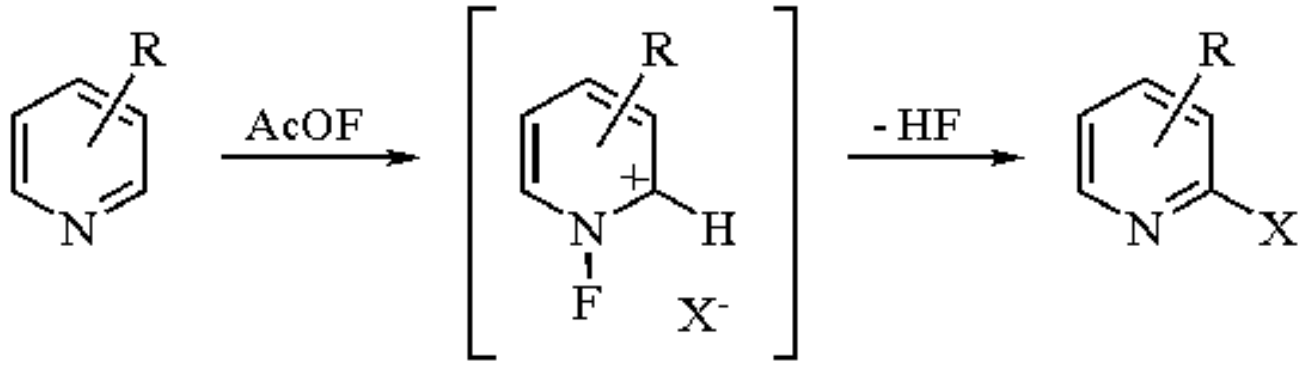

(9)

X	Solvent
OAc	$CFCl_3$
Cl	CH_2Cl_2
Br	MeBr
OR	ROH

---

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Acetyl Methanesulfonate[1]

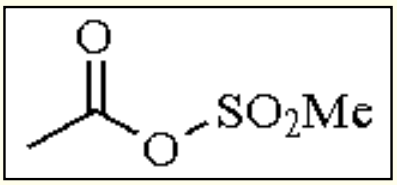

[5539-53-7] · $C_3H_6O_4S$ · Acetyl Methanesulfonate · (MW 138.14)

(reagent for ether cleavage,[2] for the cleavage of activated cyclopropanes as partial structures of cyclopropyl ketones,[3-6] and for acetylation of aromatic rings[7])

Physical Data: bp 50 °C/10^{-2} mmHg; mp 33-36 °C.

Solubility: sol MeCN, CH_2Cl_2.

Form Supplied in: not available commercially.

Preparative Methods: can be prepared on a large scale (1 mol) from ***Acetyl Chloride*** and ***Methanesulfonic Acid*** by heating at reflux followed by fractional distillation (85% yield).[1]

Purification: white/colorless solid upon distillation.

Handling, Storage, and Precautions: slightly hygroscopic. However, no particular precautions are required upon exposure to air for a short period of time. Stable if stored at 4 °C for several months. Use in a fume hood.

Ether Cleavage.

Acetyl methanesulfonate (AcOMs) can be used to cleave both acyclic and cyclic ethers.[2] The reaction parallels the Lewis acid promoted cleavage (i.e. S_N1-type process). The reactivity order is tertiary >> secondary > primary ethers. Cyclic ethers can also be cleaved with the expected rate trends. Unsymmetrical ethers give mixtures.

Cyclopropane Cleavage.

Acetyl methanesulfonate is a very efficient reagent for selective opening of the ring in cyclopropyl ketones. In the latter context, AcOMs is the trigger for the cleavage of a cyclopropane followed by spiroannulation yielding a tricyclic intermediate en route to (epi-)cedrone (eq 1).[3]

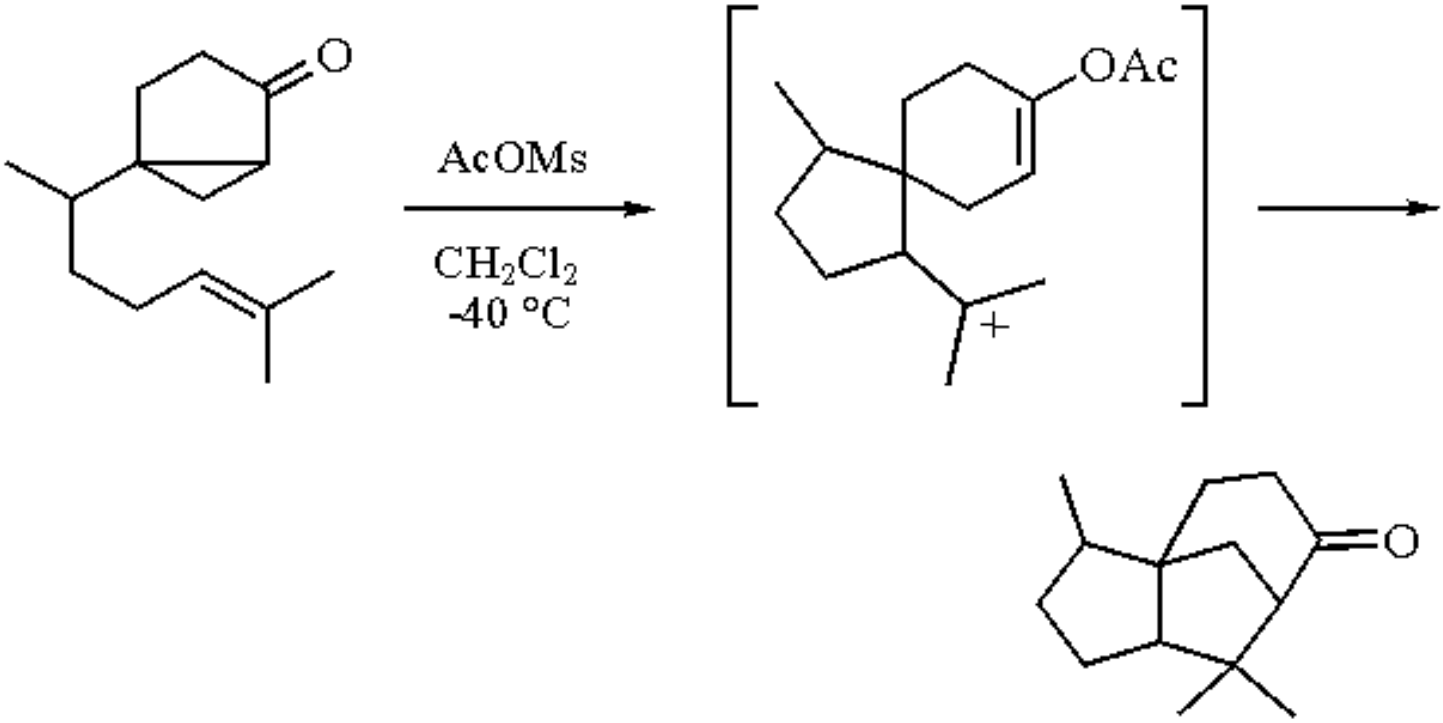

(1)

If no intramolecular trapping of cationic-type intermediates is possible, AcOMs adds to cyclopropyl ketones regiospecifically, affording enol acetates (eqs 2-5, X = OMs) with good (eq 2) to excellent (eq 3) regio- and stereocontrol of the cyclopropane cleavage.[4] Subtle steric factors seemingly dominate such addition processes as they are consistent with an overall S_N2-type mechanism.[4] Furthermore, if these substrates are combined with AcOMs in the presence of ***Tetramethylammonium Bromide*** or iodide, the parent bromo or iodo enol acetates are the products (eqs 2-5, X = Br or I).[4,5] Activation of the ketone moiety of these substrates by AcOMs is likely to increase the electrophilicity of the cyclopropane, allowing introduction of nucleophiles (Br^- or I^-) which are insufficiently reactive alone. Tetramethylammonium salts are used for these transformations because of their solubility and their potential to effect configurational equilibration in organic solvents.

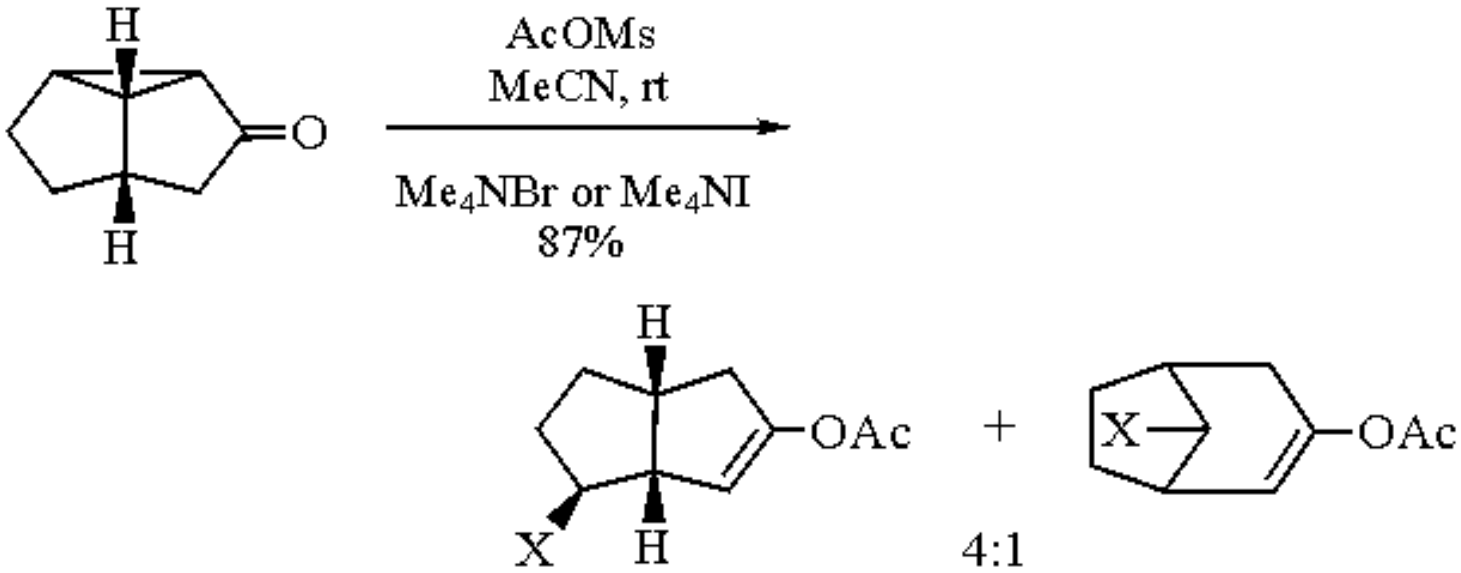

(2)

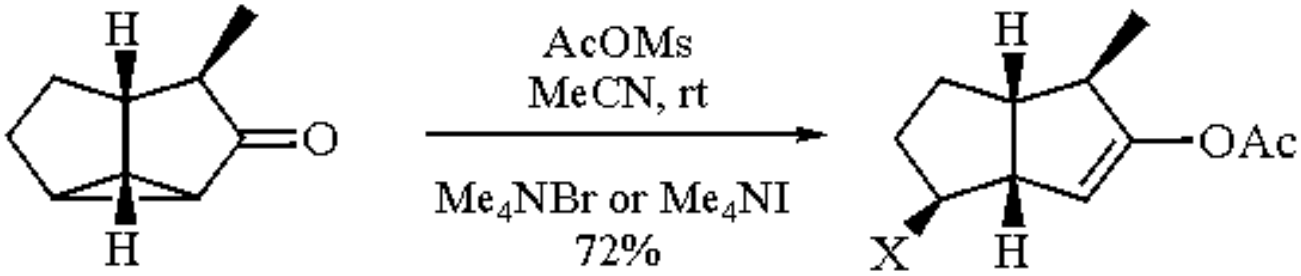

(3)

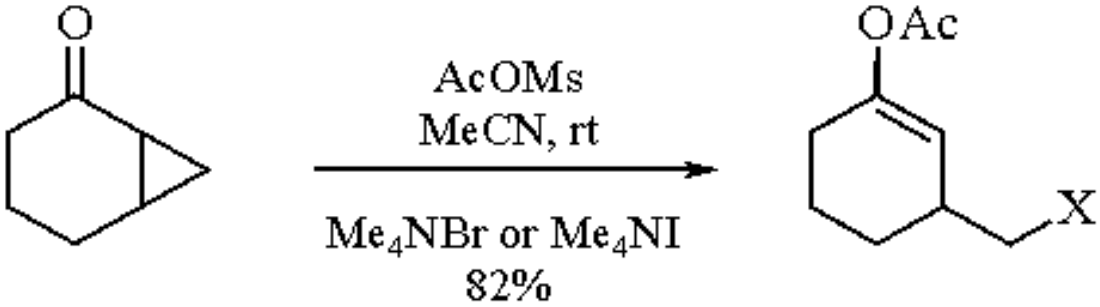

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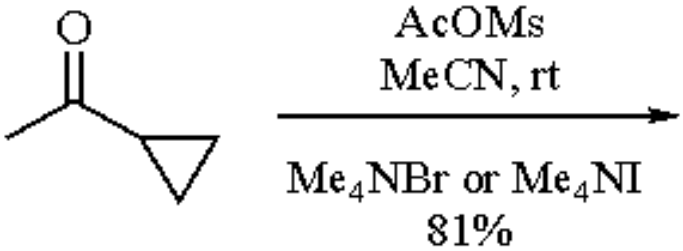

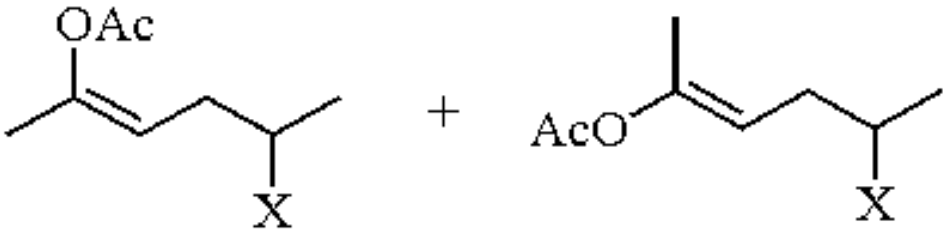

(5)

3:1

A reaction cascade of three high-yield consecutive steps is triggered by AcOMs in the case of a tricyclooctanone derivative (eq 6).[6,7] If this reaction, which proceeds at room temperature, is run with one equiv of AcOMs (1 h), an enol acetate (eq 6) is obtained with complete stereochemical control. Prolonged reaction time (10 h) and the use of 2.2 equiv of AcOMs leads to cyclization of ring B (eq 7, R = H; after work-up with water). Beneficially, smooth and exclusive C-2 acetylation of the aromatic ring is found to be completed within 24 h when an excess (4-6 equiv) of the reagent is employed (eq 7, R = Ac). As a result, a 2-acetyl-C,18-bisnor-13α,17α-estradiol derivative is assembled. Analogously, ring A acetylation allows a short and clean access to 2-hydroxyestrone 3-methyl ether.[7] The same reference also cites successful acetylations of anisole to *p*-methoxyacetophenone as well as of cyclopentene and cyclohexene to the respective 1-acetylcycloalkenes.

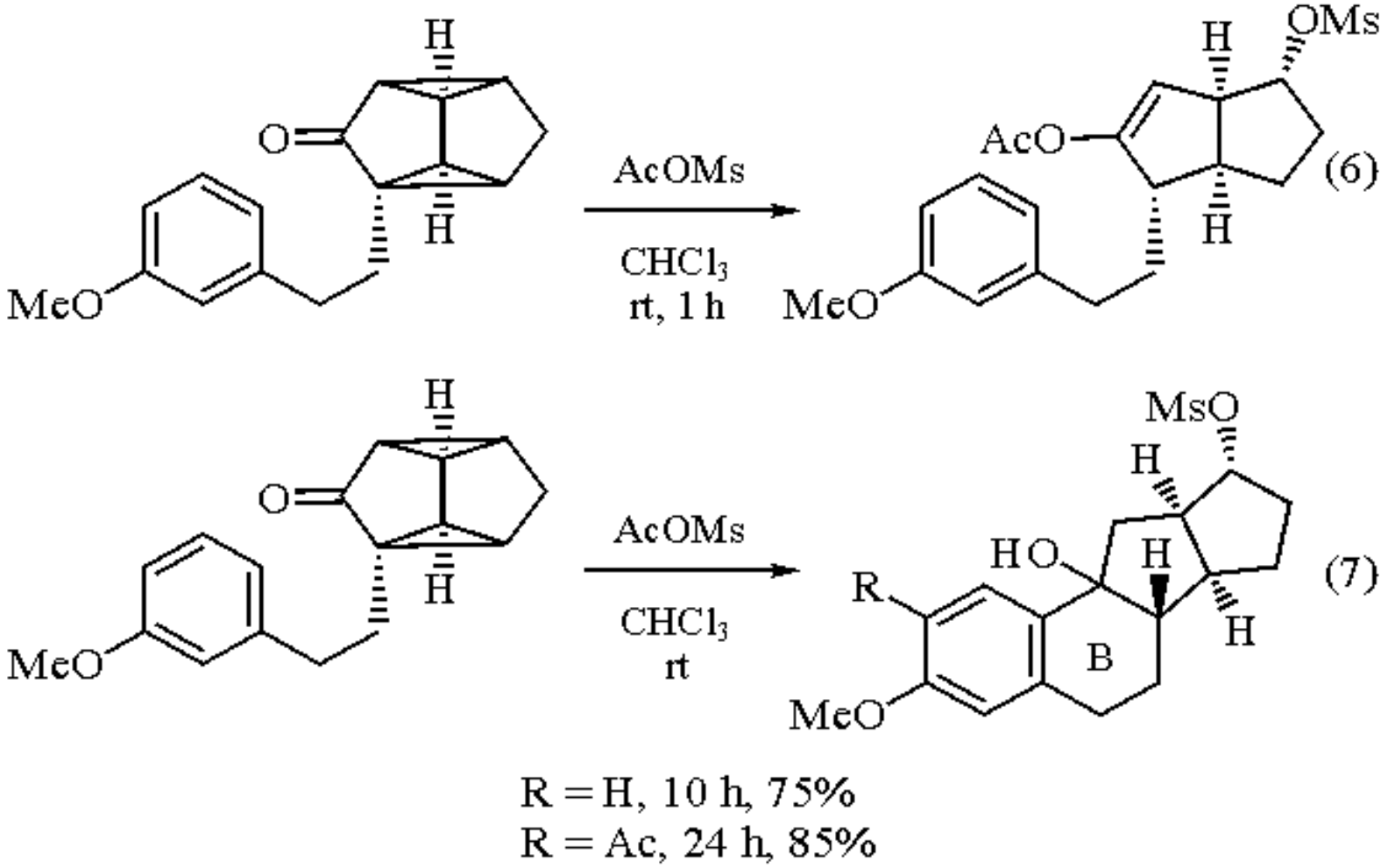

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Gamal Mikhail

Bayer, Leverkusen, Germany

Acetylmethylenetriphenylphosphorane

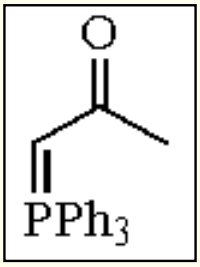

[1439-36-7] · $C_{21}H_{19}OP$ · Acetylmethylenetriphenylphosphorane · (MW 318.36)

(stabilized ylide for Wittig alkenation of aldehydes; precursor to vinylphosphonium salts; synthesis of 1,2,3-triazoles and pyrazoles; cyclocondensation on α,β,γ,δ-unsaturated carbonyls)

Physical Data: mp 203-205 °C.

Solubility: sol methanol, chlorinated solvents, low pH water.

Form Supplied in: fine white powder.

Preparative Methods: treatment of ***Triphenylphosphine*** with chloro- or ***Bromoacetone*** provides the phosphonium salt (eq 1). Deprotonation with a weak base such as bicarbonate in cold water provides the crude ylide which may by isolated by filtration.

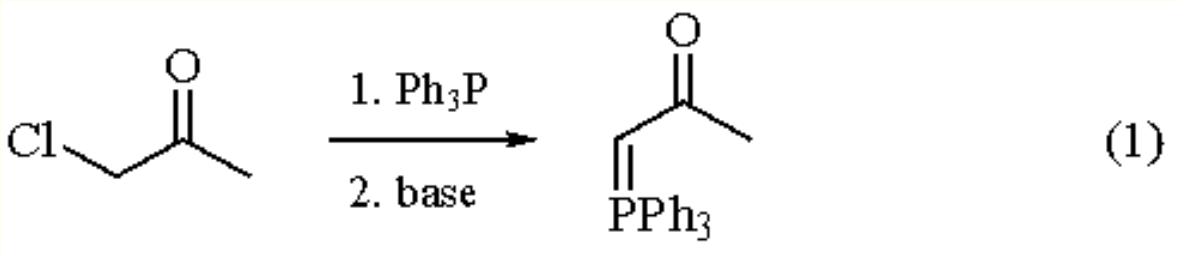

Handling, Storage, and Precautions: may be handled in atmosphere for short periods; will decompose in water at pH > 9.

Wittig Alkenations.

The title ylide is primarily used in the literature to synthesize α,β-unsaturated methyl ketones in a Wittig reaction (eq 2).

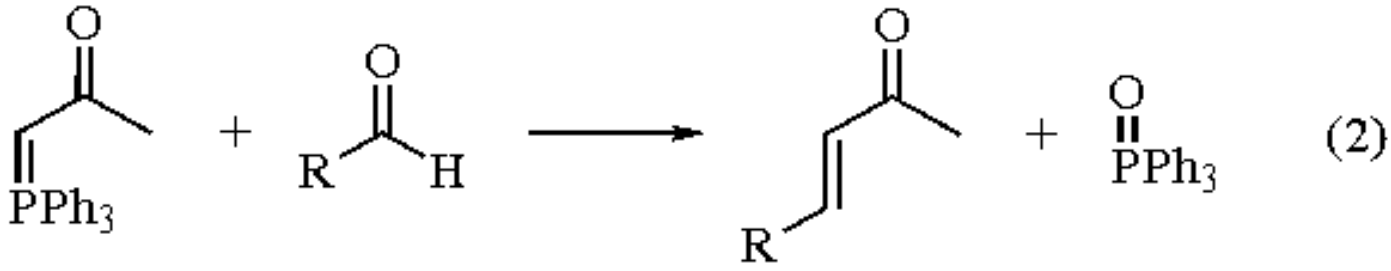

This reagent is a close relative to the related stabilized ylide ***(Methoxycarbonylmethylene)triphenylphosphorane*** which will provide an α,β-enoate, while the title reagent provides the corresponding enone from the same aldehyde.[1] The reaction is generally *trans* selective in nonpolar solvents like methylene chloride, chloroform, and aromatics. It is rather quick but not as selective in alcoholic solvents. The stabilized ylides are also rather unreactive to most ketones. The Horner-Emmons-Wadsworth alkenation utilizing a phosphonate ester is used for the same purpose and will react with ketones to provide the trisubstituted alkenes in high yield.

The title reagent is also a critical substrate in the synthesis of a variety of substituted phosphorus compounds. Cooke[2] has carried out metalations at the methyl group with ***n-Butyllithium*** followed by treatment with an alkyl halide to provide the substituted ylide (eq 3). He follows with a hydrolysis of the phosphonium portion to provide a good yield of the saturated ketone. Other workers[3] have also used this synthesis as a route to substituted enones.

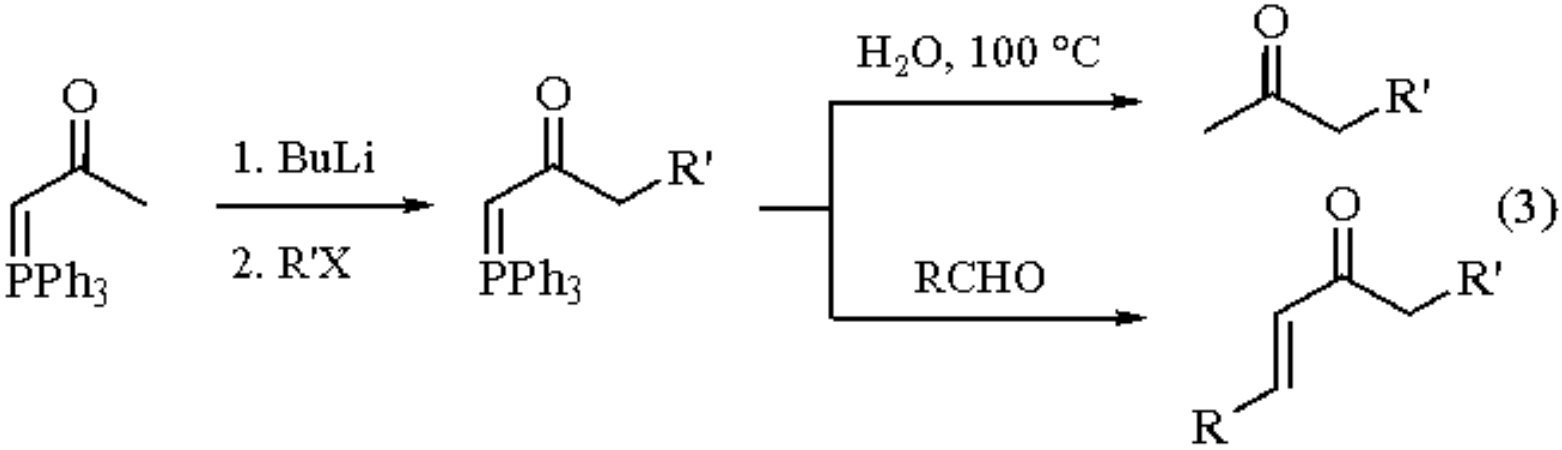

Vinylphosphonium Salts.

The neutral form of the ylide is also mildly nucleophilic. It is, however, an ambident nucleophile. It will react with alkyl halides although only methyl or ethyl iodide or benzyl bromide provide synthetically useful yields (eq 4).[4] The primary product is that of *O*-alkylation but this product rearranges on heating to the *C*-alkyl product.[5] It has also been shown that the *O*-alkyl products, which are vinylphosphonium salts, will also react with sodium alkoxide to form alkoxyvinyldiphenylphosphine oxides.[6]

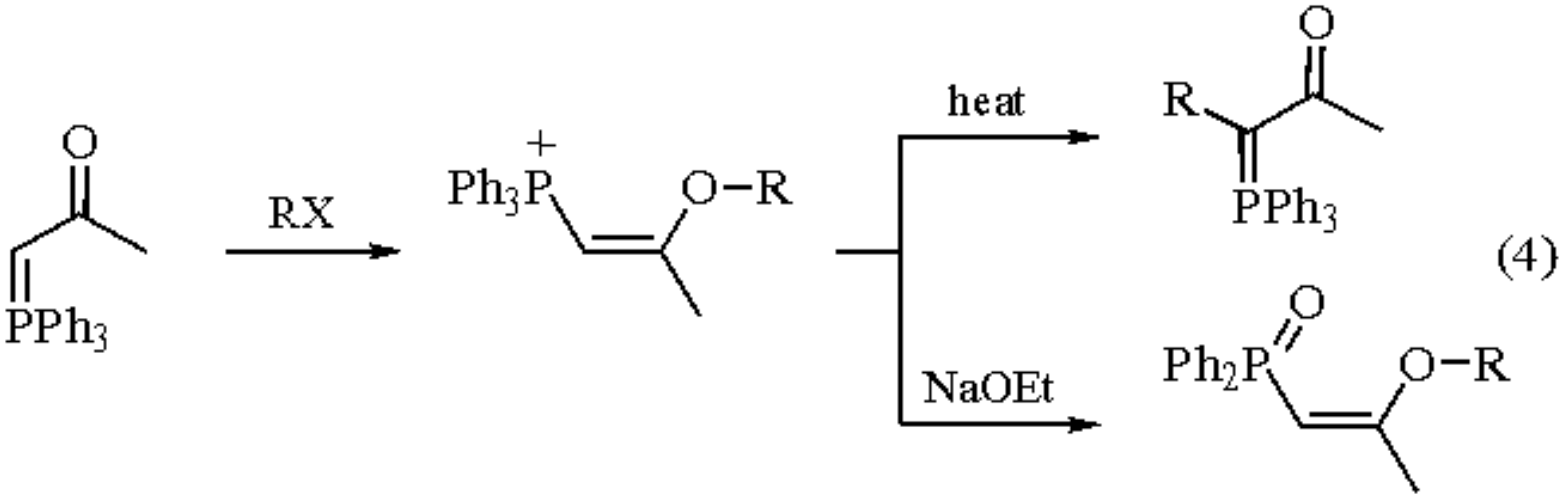

(4)

Heterocycle Synthesis.

The nucleophilicity of phosphorus ylides is also apparent in their reactions with 1,3-dipoles or their equivalents to generate heterocycles. Reaction with alkyl or aryl azides provides a high yield route to 1,2,3-triazoles (eq 5).[7] The initial step of the postulated mechanism is similar to the first step of the Wittig reaction, namely attack of the nucleophilic carbon of the ylide onto the electrophilic end nitrogen of the azide to form a betaine intermediate. Attack of the internal nitrogen onto the carbonyl to form a five-membered ring, followed by elimination of triphenylphosphine oxide, provides the triazole. In similar fashion, treatment of the ylide with hydrazonyl halides provides a useful route to a variety of substituted pyrazoles (eq 6).[8] This mechanism is similar to the triazole formation in that the nucleophilic ylide attacks the electrophilic carbon of the hydrazonyl halide, displacing chlorine. Proton abstraction by added ***Triethylamine*** from the hydrazone, followed by cyclization and elimination of triphenylphosphine oxide, provide the pyrazole.

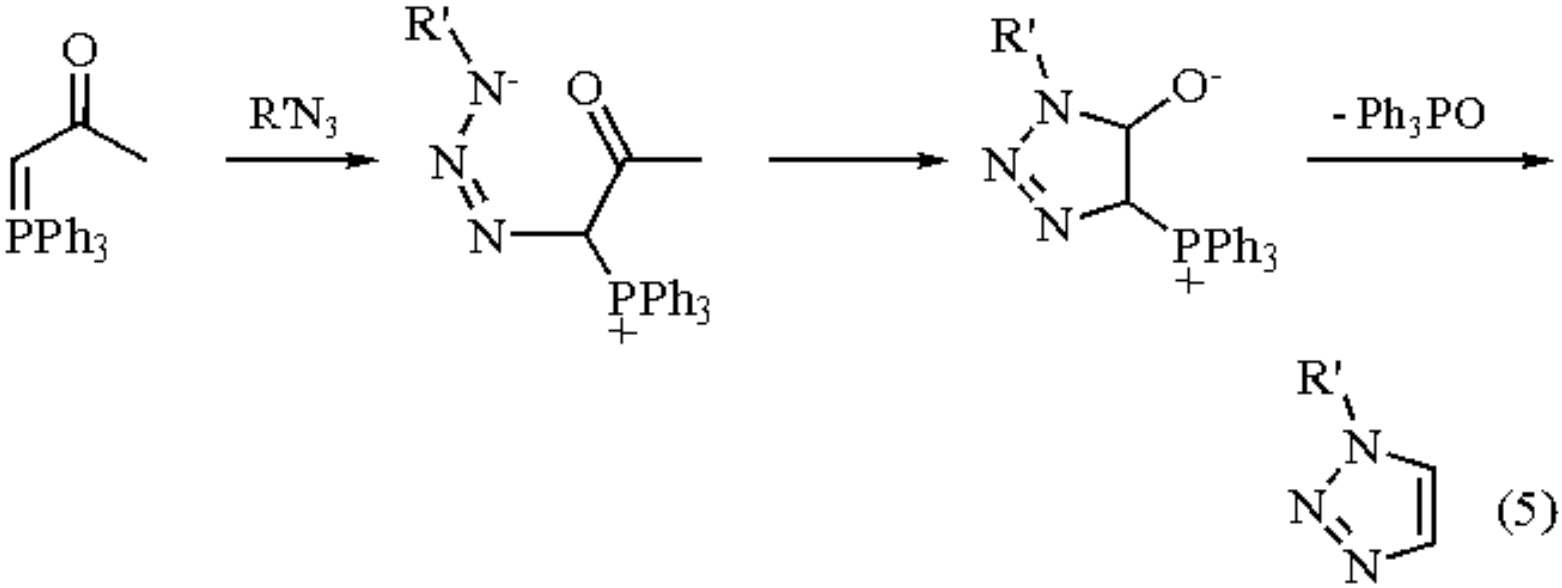

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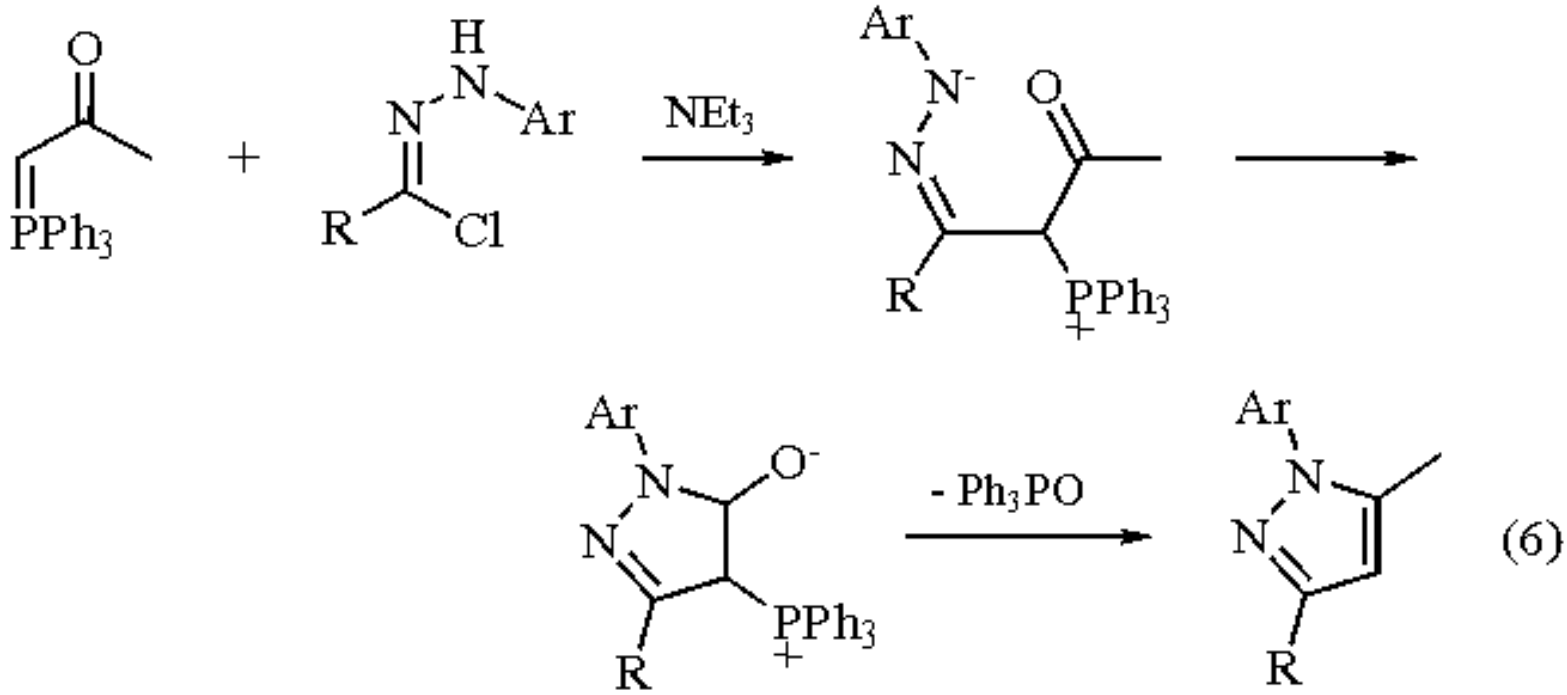

One last application is in the reaction of the ylide at the δ-position of an α,β,γ,δ-unsaturated carbonyl system (eq 7). This reaction begins with addition of the ylide to form an enolate/betaine which then attacks the carbonyl of the ylide to form a six-membered ring followed by elimination of triphenylphosphine oxide.[9] Although the reaction goes in low yield it provides an interesting synthesis of some bicyclic systems.

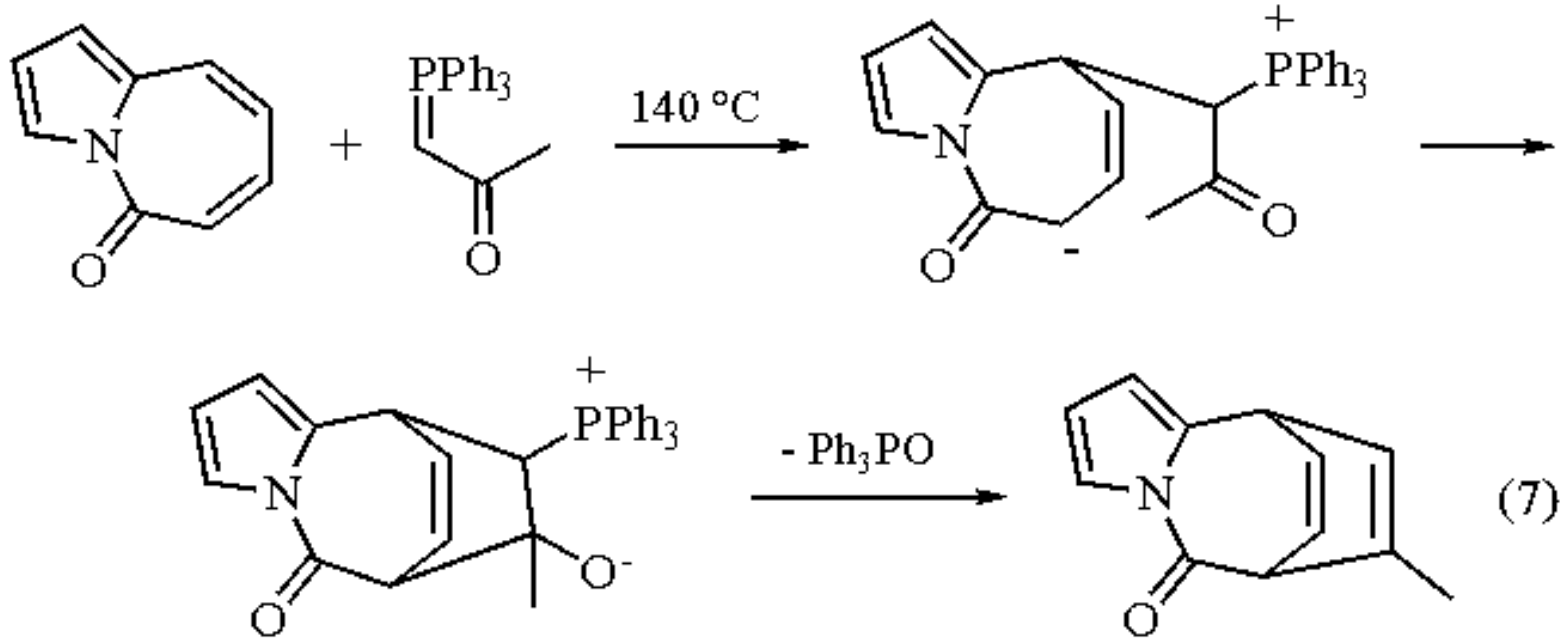

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Acetyl Nitrate[1]

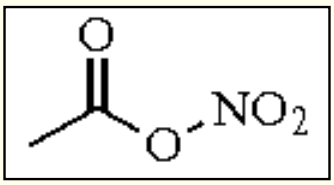

[591-09-3] · $C_2H_3NO_4$ · Acetyl Nitrate · (MW 105.05)

(nitrating agent for arenes and selected nonaromatics;[9-13] can functionalize alkenes to β-nitroacetates;[14-17] oxidizes thioethers and disulfides to sulfoxides[22])

Physical Data: colorless, mobile liquid; bp 22 °C/70 mmHg,[2] 2-3 °C/14 mmHg;[3] *d* 1.24 g cm^{-3}.

Solubility: miscible with common organic solvents.

Analysis of Reagent Purity: physicochemical studies indicate a dependence on preparatory method and starting material ratios, as well as age. In commonly used Ac_2O/HNO_3 mixtures, acetyl nitrate, HOAc, and excess Ac_2O are present if the Ac_2O/HNO_3 ratio is >1; if <1, H_2O and even N_2O_5 can be present.[6]

Preparative Methods: a typical approach is to add conc ***Nitric Acid*** (38 mL) slowly to stirred, cooled ***Acetic Anhydride*** (150 mL).[7] In the earliest report,[2] N_2O_5 was dissolved in Ac_2O; though less practical, this is recommended for preparing anhydrous inorganic nitrates.[5] Other methods involve reaction of HNO_3 and ketene,[3] or AcCl and $AgNO_3$ in MeCN in the presence of the substrate to be nitrated.[8]

Handling, Storage, and Precautions: unstable and explosive upon heating.[2,4] Isolation or distillation is not recommended unless extreme care is taken; freshly prepared solutions should be employed. Controlled thermolysis at ~60 °C leads to *N*-oxides, tetranitromethane,[2] and a yellow oil.[5] Highly acidic; avoid skin contact. Reactions should be conducted in a well-ventilated fume hood.

Electrophilic Nitrations.

Solutions of acetyl nitrate behave as NO_2^+ AcO^-, with no sign of acetylation.[9] Its synthetic utility is often quite comparable with that of other nitronium reagents, e.g. reaction with toluene gives a mixture of *o*-, *m*-, and *p*-nitrotoluenes in a 60:3:37 ratio at rt,[9] and biphenyl yields *o*- and *p*-nitro derivatives in a 58:42 ratio (87% yield).[10] Naphthalene and pyrene give the corresponding 1-nitro derivatives, while 3-fluoroanthracene and phenanthrene result in nitration at the 9-position.[11] Regioselectivity of the nitration reaction can be solvent dependent; in most solvents, reaction with phenanthrene leads to 9-nitrophenanthrene, but in CH_2Cl_2 or nitrobenzene the 1-nitro isomer

dominates.[12] Enols can react analogously, as demonstrated with acetoacetate esters (eq 1).[13]

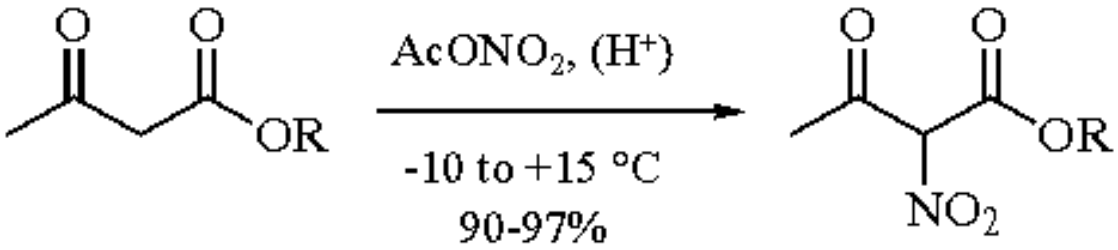

(1)

Addition to Alkenes.

Simple alkenes react with acetyl nitrate to give β-nitroacetates, although nitroalkenes and nitronitrates are often also formed (eq 2).[14]

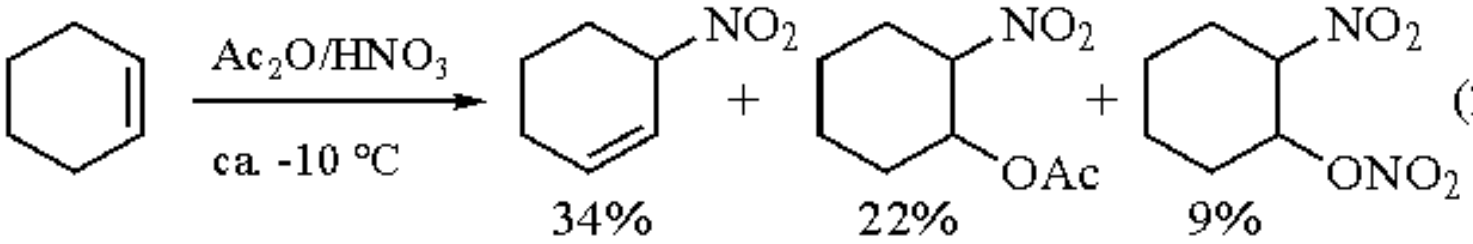

(2)

Others have found more complex reaction mixtures in this case, and with other cycloalkenes,[15] making the synthetic usefulness doubtful; another example concerns methyl-2-furoate.[16] Reaction of $AcONO_2$ with 4-methylstilbene yielded the DL-*threo* derivative (eq 3),[17] in line with the nitronium acetate character of the reagent. Cyclic dienes[18] also mostly give product mixtures (eq 4).[19]

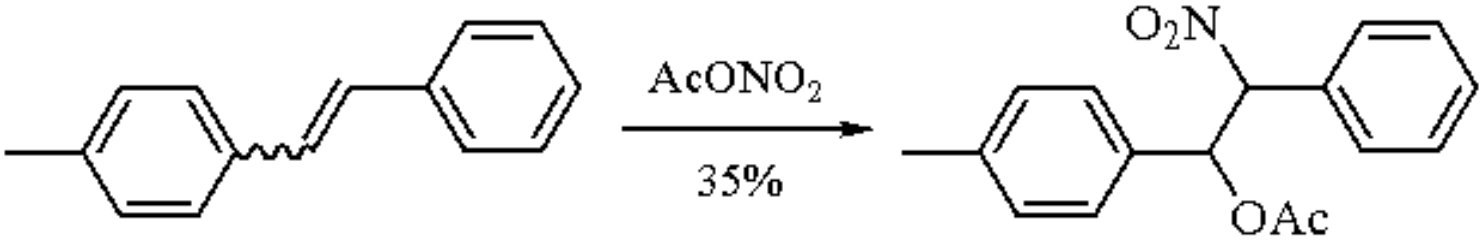

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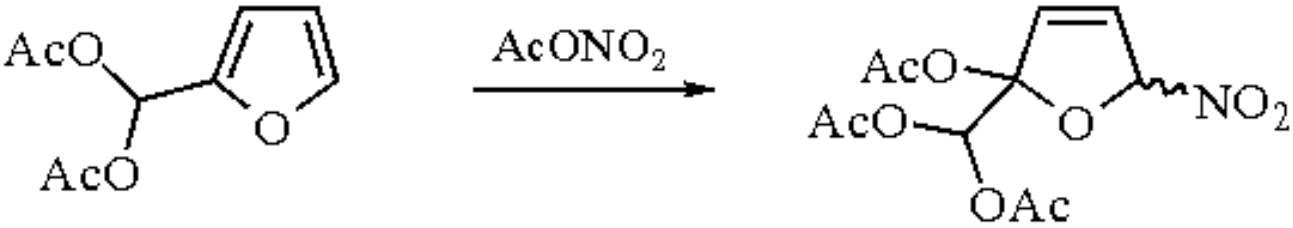

(4)

cis:*trans* = 1:7

Other Applications.

Alcohols can be converted to their nitrates (eq 5),[20] and tertiary amines give nitrosamines in fair yields (eq 6).[21]

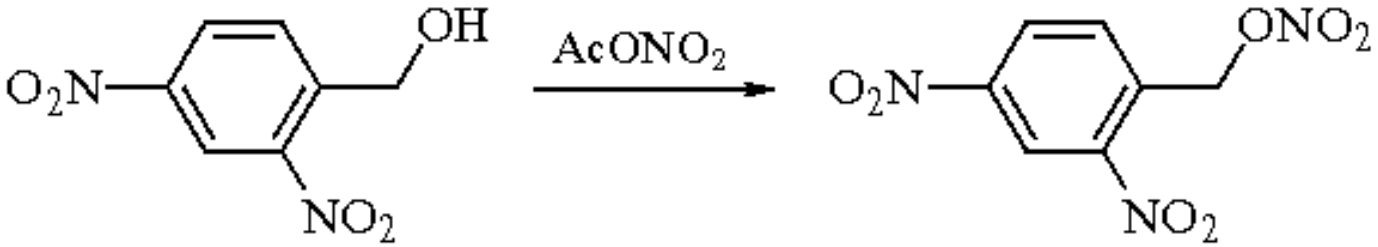

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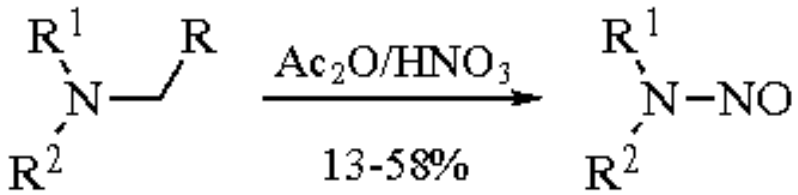

(6)

Acetyl nitrate reacts rapidly with thioethers and disulfides to give sulfoxides, even at temperatures far below 0 °C; no further oxidation to sulfones occurs, even with an excess of reagent, and yields are near quantitative (eqs 7 and 8).[22] With sulfides that are susceptible to Pummerer-type reactions with Ac_2O, the use of ***Benzoyl Nitrate*** is preferred.

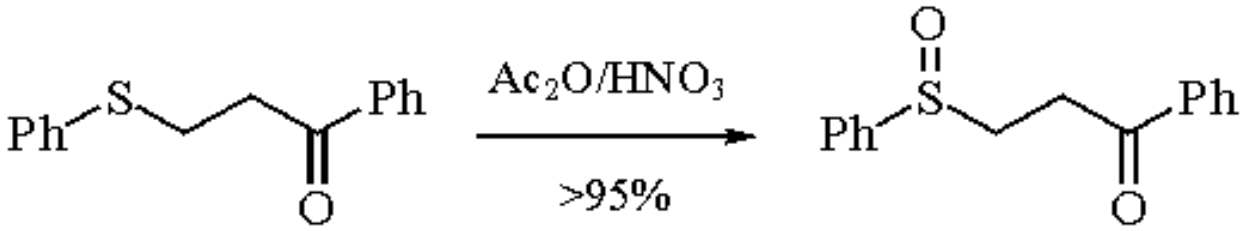

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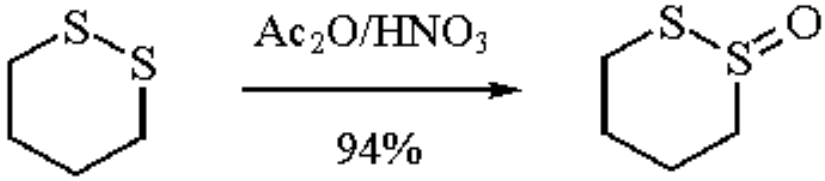

(8)

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Acetyl *p*-Toluenesulfonate

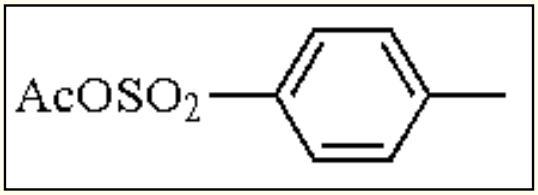

[26908-82-7] · $C_9H_{10}O_4S$ · Acetyl *p*-Toluenesulfonate · (MW 214.24)

(selective ether cleavage agent;[1] acylating agent[2])

Physical Data: mp 54-56 °C; *d* 1.092 g cm^{-3}.

Solubility: sol acetonitrile, dichloromethane, toluene.

Form Supplied in: colorless crystals; commercially available, or readily prepared from ***Acetyl Chloride*** and ***p-Toluenesulfonic Acid***.[3]

Analysis of Reagent Purity: NMR spectroscopy; traces of free acid and sulfonic anhydride may be present.

Handling, Storage, and Precautions: the solid is readily hydrolyzed, so it must be protected from contact with moisture; thermal decomposition is also possible.

Ether Cleavage.

Reaction conditions are relatively mild (25-130 °C, 2-48 h, usually in acetonitrile) and added Lewis acid catalysts are not necessary for effective reaction. Higher yields are more often obtained than with other reagents, and cleavage of unsymmetrical ethers occurs with high regioselectivity (eqs 1-4).[1,4,5]

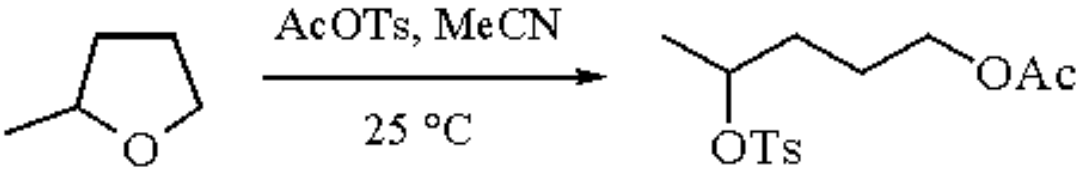

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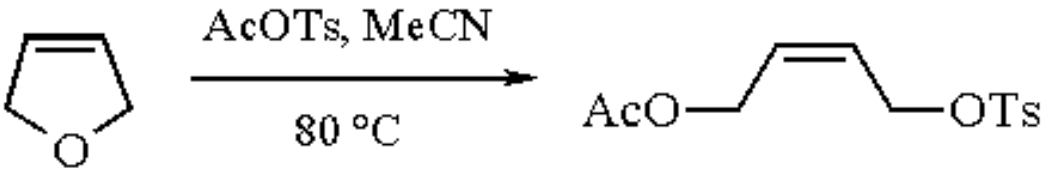

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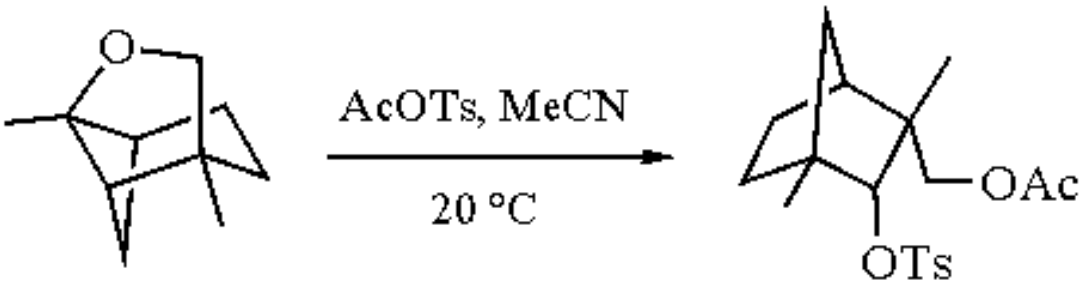

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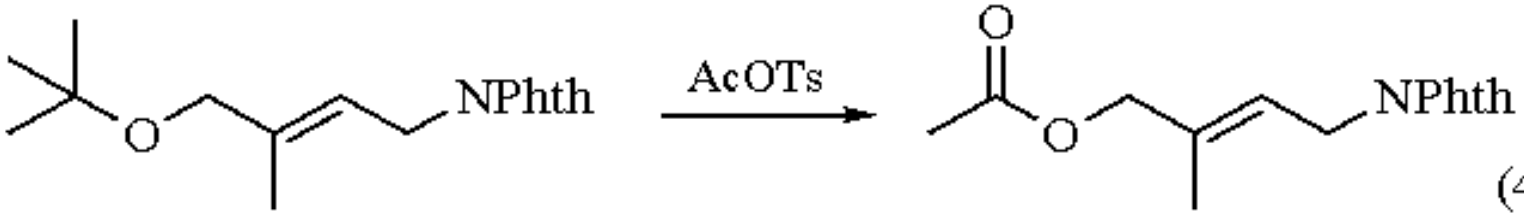

(4)

The mechanism of cleavage of ethers is thought to proceed by initial acylation of the ether oxygen, followed by S_N1-like cleavage to an acetate and an ion pair, which can collapse to give the tosylate. Thus cleavage of mixed ethers should favor cleavage of the bond to the more substituted carbon. In addition, the longer lifetime of a carbocation thus generated allows alternative pathways to compete with immediate ion pair collapse.

Mixed acetate sulfonate diesters are obtained from cyclic ethers. These have useful synthetic applications since the tosylate group is readily displaced by nucleophiles.

Acetylation Agent.

Acetyl *p*-toluenesulfonate is also used as a mild acetylation agent[2] for furans (eq 5), thiophenes (eq 6), and anisoles (eq 7). High yields (75-96%) are readily attained using a 10-50% excess of reagent under mild reaction conditions (25 °C to reflux, 2-24 h, in acetonitrile or benzene). Once again, no Lewis acids are necessary. Acetyl *p*-toluenesulfonate is also a highly reactive acetylation agent for anilines, alcohols, and phenols.

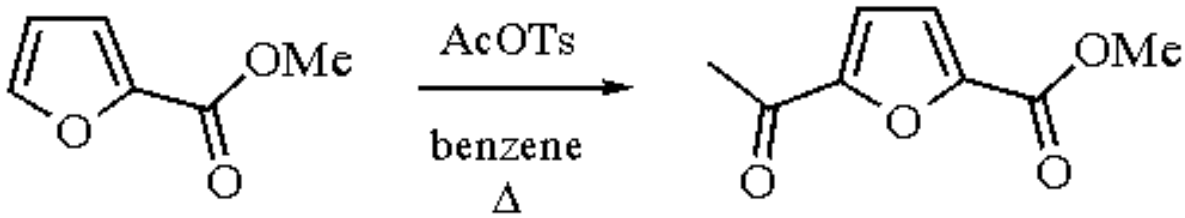

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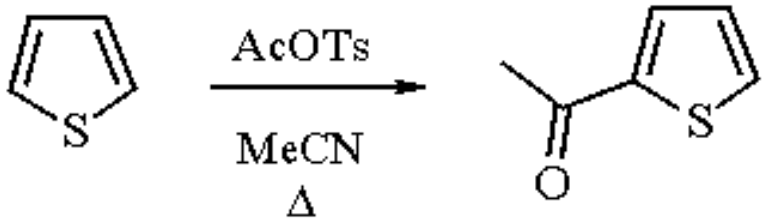

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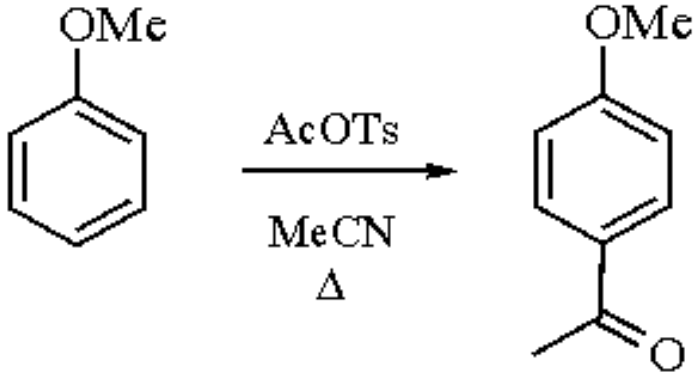

(7)

Related Reagents.

Acetyl Methanesulfonate; ***Boron Tribromide***; ***Iodotrimethylsilane***.

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1. (a) Karger, M. H.; Mazur, Y. *JACS* **1968**, *90*, 3878. (b) Karger, M. H.; Mazur, Y. *JOC* **1971**, *36*, 532.
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Peter P. Giannousis

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Acrolein

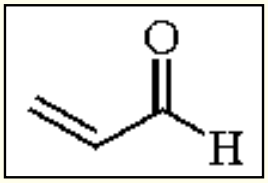

[107-02-8] · C_3H_4O · Acrolein · (MW 56.06)

(electrophile in 1,2- and 1,4-addition reactions; diene; dienophile)

Alternate Name: propenal.

Physical Data: mp -87 °C; bp 53 °C; *d* 0.839 g cm^{-3}; n_D 1.4017.

Solubility: sol water, alcohols, most organic solvents.

Form Supplied in: colorless liquid (stabilized with 0.1 wt % hydroquinone); widely available.

Purification: purified by fractional distillation under nitrogen, drying with anhydrous $CaSO_4$, and then distilling under vacuum, preferably in the dark. To avoid formation of diacryl, a small amount of catechol or hydroquinone should be placed in the receiver flask.

Handling, Storage, and Precautions: the liquid is flammable. Polymerization occurs in the presence of base or strong acids or upon exposure to light. Therefore it must be stored in the dark in the presence of 0.1 wt % catechol or hydroquinone. The liquid has a pungent odor and is highly toxic. Skin and mucous membranes become irritated upon exposure, while inhalation may cause lachrymation and an asthmatic reaction. Use in a fume hood.

Oxidations and Reductions.

Each functional group in acrolein can react selectively and in some cases both react. Acetal formation has been achieved using transacetalization conditions.[1] Oxidation with ***Hydrogen Peroxide*** in the presence of a catalytic amount of SeO_2 leads to acrylic acid.[2] while oxidation under controlled pH conditions gives glycidaldehyde in excellent yield.[3] Selective reduction of the alkene can be achieved with ***Octacarbonyldicobalt***/H_2[4] or via treatment with ***Triethylsilane*** in the presence of Wilkinson's catalyst (***Chlorotris(triphenylphosphine)rhodium(I)***) followed by hydrolysis of the silyl enol ether.[5a] Selective reduction using hydrogen and a Pd^{II}/ferrocenylamine sulfide catalyst has been described.[5b]

Addition Reactions.

Acrolein undergoes addition reactions at the carbonyl group (1,2-addition) and/or the electron deficient alkene (1,4-addition). The site of attack depends on the nucleophile and the reaction conditions. Under equilibrating conditions the 1,4-addition product is preferred.

The ratio of 1,2- to 1,4-addition of carbon nucleophiles to acrolein is strongly dependent on the nature of the organometallic species, especially on the polarity of the carbon-metal bond (eq 1). In general, the proportion of 1,2-addition product increases with more electropositive metal counterions. Moreover, due to the high reactivity of aldehydes, 1,2-addition often competes in processes where 1,4-addition is usually the favored pathway.

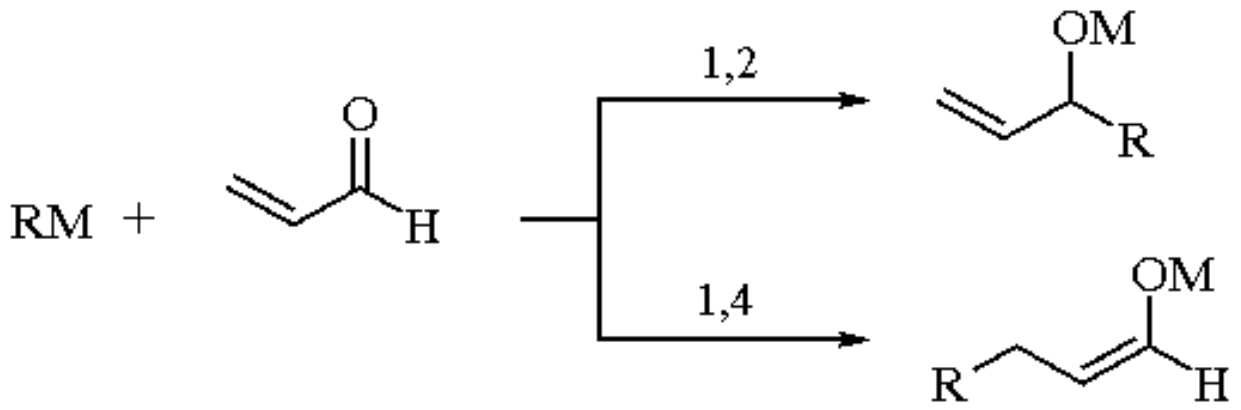

(1)

Organolithium reagents react with acrolein exclusively via 1,2-addition when the reaction is performed in THF at -78 °C.[6] Grignard reagents give mainly carbonyl addition products.[7] Organoberyllium, -zinc, and -cadmium also add exclusively to the carbonyl group,[8] as do organocerium and -titanium reagents.[9] Low enantioselectivity (24%) was observed in the addition of ***n-Butyllithium*** to acrolein in the presence of a chiral tetraamine ligand (DEB).[10]

Phosphonate anions react at the carbonyl group to yield substituted butadienes ultimately.[11]

Thiols undergo selective 1,4-addition to acrolein, whereas ***Triphenylphosphine*** induces polymerization.[12] Cyanide ion adds to acrolein but it is more efficient to react the α,β-unsaturated imine followed by hydrolysis.[13]

Stabilized carbanions, such as malonate and other active methylene compounds, undergo 1,4-addition (Michael reaction) to give 1,5-dicarbonyl compounds under mild conditions.[14] Phase transfer catalysts have been used to promote the reaction.[14c] When the reaction is carried out between unsaturated aldehydes and (3-ethoxycarbonyl-2-oxopropylidene)triphenylphosphorane, a 3 + 3 cyclohexenone annulation occurs to give cyclohexenones (eq 2).[15] The yield is modest for acrolein, but improves upon substitution at the α- or β-positions.

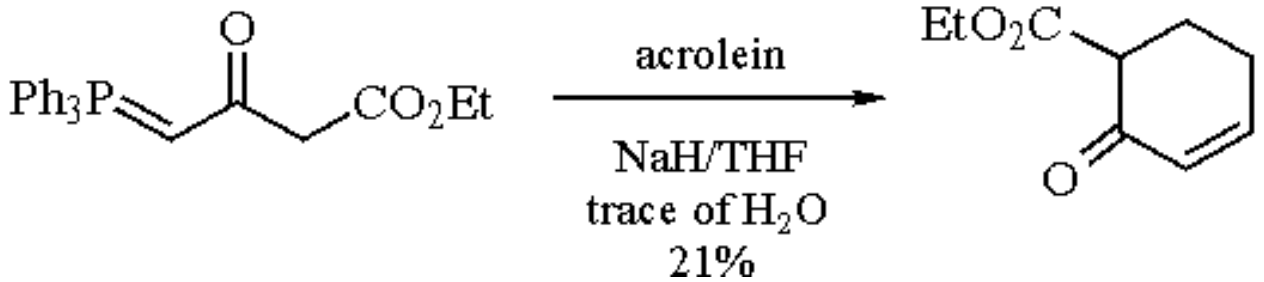

(2)

Substituents on the malonate can result in additional transformations of the Michael adducts. For example, if the nucleophile has a 2-substituent bearing a ketone, the intermediate aldehyde enolate closes onto the ketone providing a formylcyclopentene in 50% yield.[16] Reaction of bromomalonates with acrolein in the presence of NaOEt results in an efficient route to formylcyclopropanes. Similar products are formed in the reaction of a stabilized *S*-ylide with acrolein (eq 3).[17] Carbene addition to acrolein has also been achieved using nickel catalysts.[18]

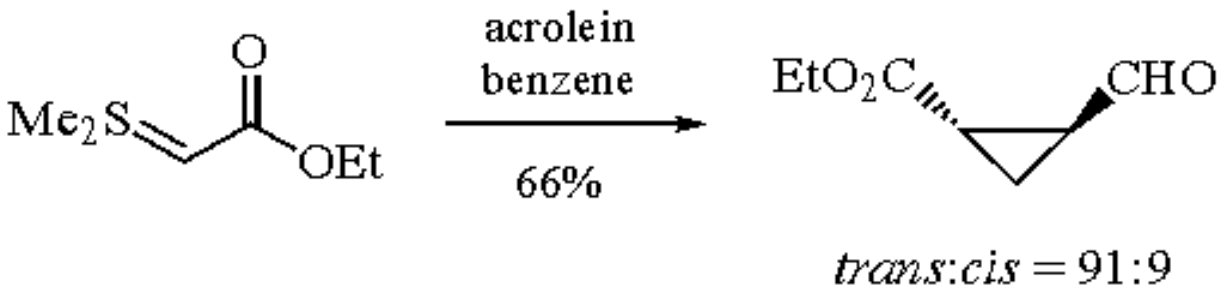

(3)

A highly enantioselective rhodium catalyzed version of the Michael addition to acrolein has been recently developed.[19] The catalyst, prepared in situ from $RhH(CO)(PPh_3)_3$ and the chelating chiral diphosphine ligand TRAP (TRAP = 2,2´´-bis[1-(diphenylphosphino)ethyl]-1,1´´-biferrocene), provides high yields and good ee's using 1 mol % of rhodium (eq 4).

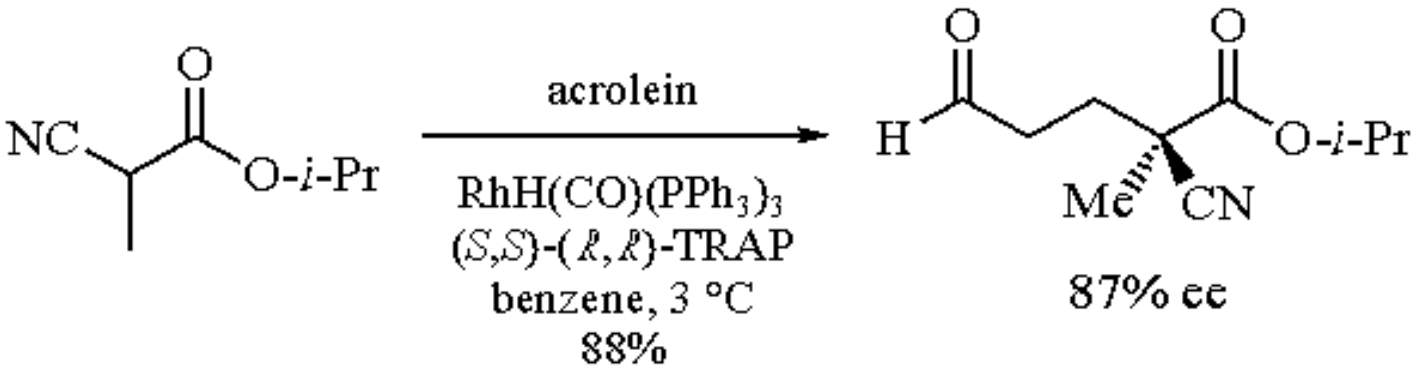

(4)

While scattered examples of 1,4-additions of nonstabilized carbanions have been described, the first systematic study of cuprate addition to enals was carried out by Normant.[20] Cuprates derived from organolithium reagents gave low yields,[21] whereas the best results were obtained using cuprates prepared from Grignard reagents. ***Chlorotrimethylsilane*** improved the 1,4-addition process (eq 5).[20]

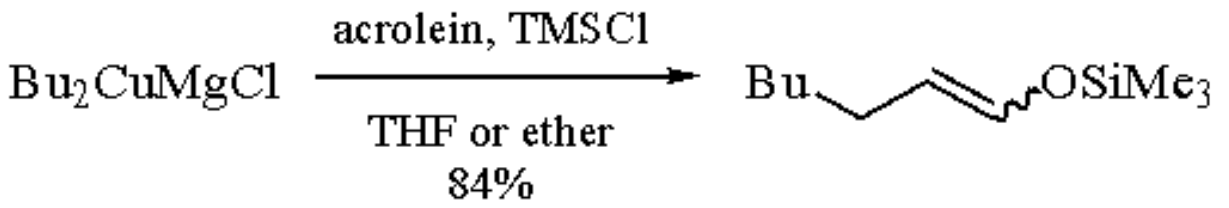

(5)

Aryl halides react with acrolein in the presence of palladium catalysts to give aryl and diaryl derivatives via a mono or double Heck process respectively.[22]

Organoboranes undergo 1,2- or 1,4-addition to acrolein depending on the R group. Alkylboranes undergo 1,4-addition in a reaction which is catalyzed by the presence of water. There is considerable evidence for a radical chain

mechanism.[23] Allylboranes undergo selective 1,2-addition with a variety of aldehydes including acrolein. Chiral boranes (R^2 = Me, OMe, R^1 = H, Me) derived from α-pinene react to give the alcohols in up to 90% ee (eq 6).[24]

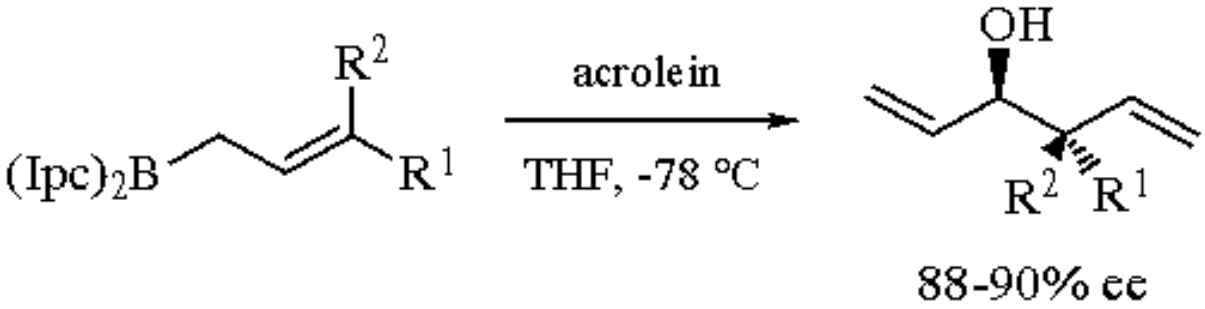

(6)

In contrast, allylic silanes undergo stereoselective 1,4-addition (Sakurai reaction), silyl migration, and ring closure in a novel cyclopentane annulation reaction (eq 7).[25]

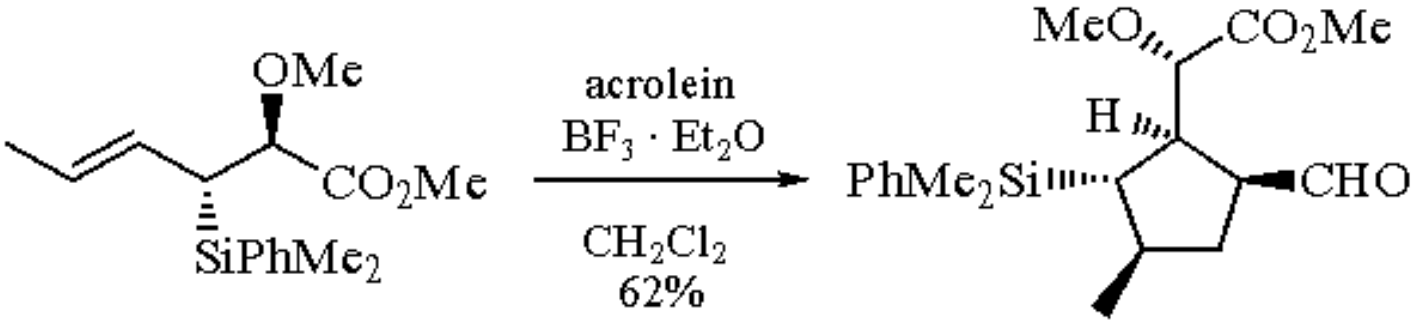

(7)

Carbon radicals also add to electron deficient alkenes including acrolein.[26] A key feature of this reaction is the compatibility of several functional groups which would not be tolerated using carbanion chemistry. Furthermore, the reaction can be carried out in organic as well as aqueous media, depending on the mode of radical preparation. With 2-iodoethanol, a conjugate addition-cyclization sequence occurs providing six-membered lactols in good yield (eq 8).[27] It is noteworthy that no elimination of the β-oxygen occurs under these conditions.

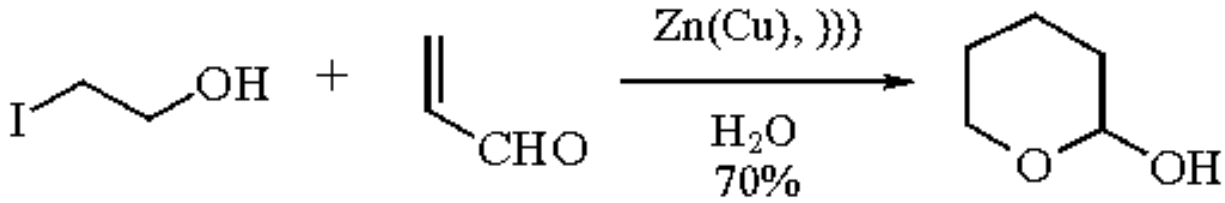

(8)

Hydrogen Bromide adds efficiently to the alkene in acrolein.[28] Treatment of acrolein with HBr and ***1,3-Propanediol*** provides a route to γ-bromoacetals,[29a] which have been widely used as β-homoenolate equivalents. Thus γ-ketoaldehydes are prepared by a three-step procedure involving conversion of the bromide to the Grignard reagent, addition of an acid chloride, and hydrolysis of the acetal.[29b]

Aldol Condensation Reactions.

Reaction of the magnesium enolate of a thioamide with acrolein gives predominantly (73-89%) the *syn* aldol adduct.[30] Similar results were obtained with a ketone enolate, though little selectivity was noted for an enolate

derived from an α-alkoxypropionate.[31,32] Selectivities exceeding 50:1 were noted in the reaction of a lithium enolate of a chiral thioester.[33] Asymmetric aldol condensation using an enolate bearing the Evans chiral auxiliary has also been reported with acrolein to give a single diastereomer in high yield (eq 9).[30]

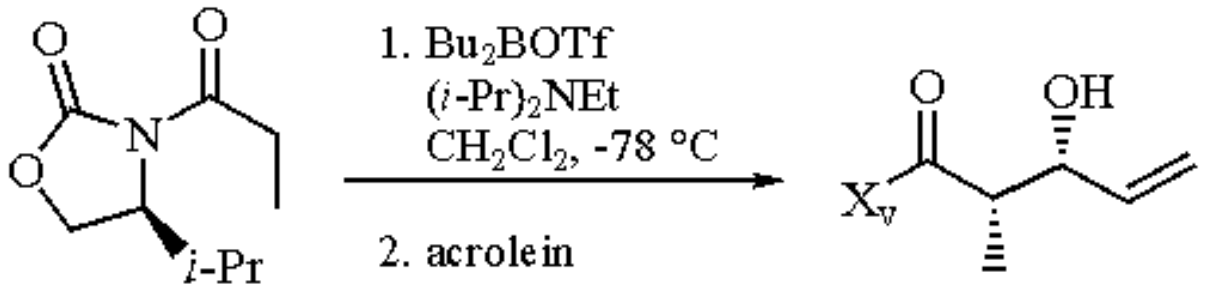

(9)

Pericyclic Reactions.

The ene reaction of (-)-β-pinene with acrolein was shown to proceed at 135 °C in 17 h to give 30% of the ene adduct (a formal conjugate addition).[34] However, Lewis acid catalysis allowed the reaction to be run at a much lower temperature.[35] Thus an alkylidenecycloalkane such as 1-methylene-2,6-dimethylcyclohexane reacts with acrolein in the presence of ***Dimethylaluminum Chloride*** at 0 °C, to provide a decalin system in 57% yield (eq 10). This annulation procedure is based on two sequential ene reactions in which acrolein serves as the double enophile partner.[36]

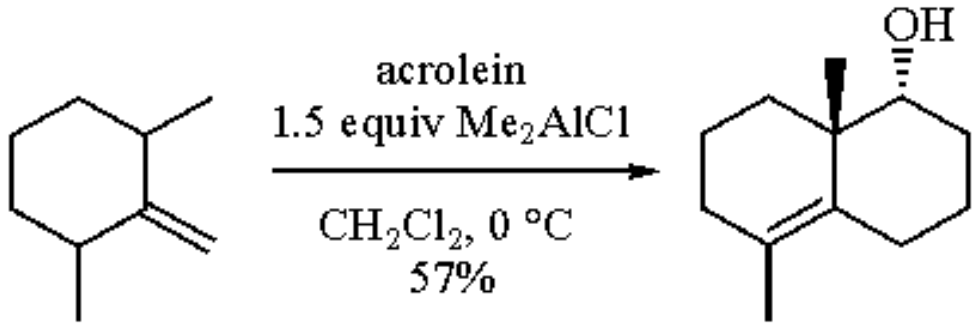

(10)

β-Alkylation of acrolein has been achieved by indirect multi-step methods. One approach uses a [3,3]-sigmatropic rearrangement of an allylic thionocarbamate as the key step.[37] For example, addition of *n*-BuLi to acrolein, followed by treatment with thiocarbamoyl chloride, provides 2-heptenal after sulfenylation and hydrolysis.

A second method is based on the umpolung strategy. An acetal of 3-phenylsulfonylpropanal, which can be prepared in three steps from acrolein and ***Thiophenol***, can be deprotonated, alkylated, and the acetal hydrolyzed to provide a β-sulfonylated aldehyde, which undergoes a retro-Michael addition to give the (*E*)-β-substituted acrolein.[12]

Cycloadditions.

Acrolein has been used as both a dienophile and a diene in Diels-Alder reactions as illustrated below. The dimer of acrolein is formed under thermal conditions providing a single regioisomer.[38] The dimer is a useful building block in organic synthesis.[38] Cycloaddition between acrolein and vinyl ethers typically requires heating in an autoclave at 160-

200 °C.[39] The reaction temperature can be reduced to 50 °C when mild Lewis acid catalysts such as $Yb(fod)_3$[40] are used, providing a powerful synthetic route to dihydropyrans.[41] The hetero Diels-Alder reaction very efficiently leads to spiroacetal compounds when the appropriate vinyl ether is used (eq 11).[42] Enamines[43] and ynamines[44] also react to yield amino-dihydropyrans and aminopyrans respectively. Both 5,6- and 5,5-spiroacetals can be obtained using acrolein as the diene component.

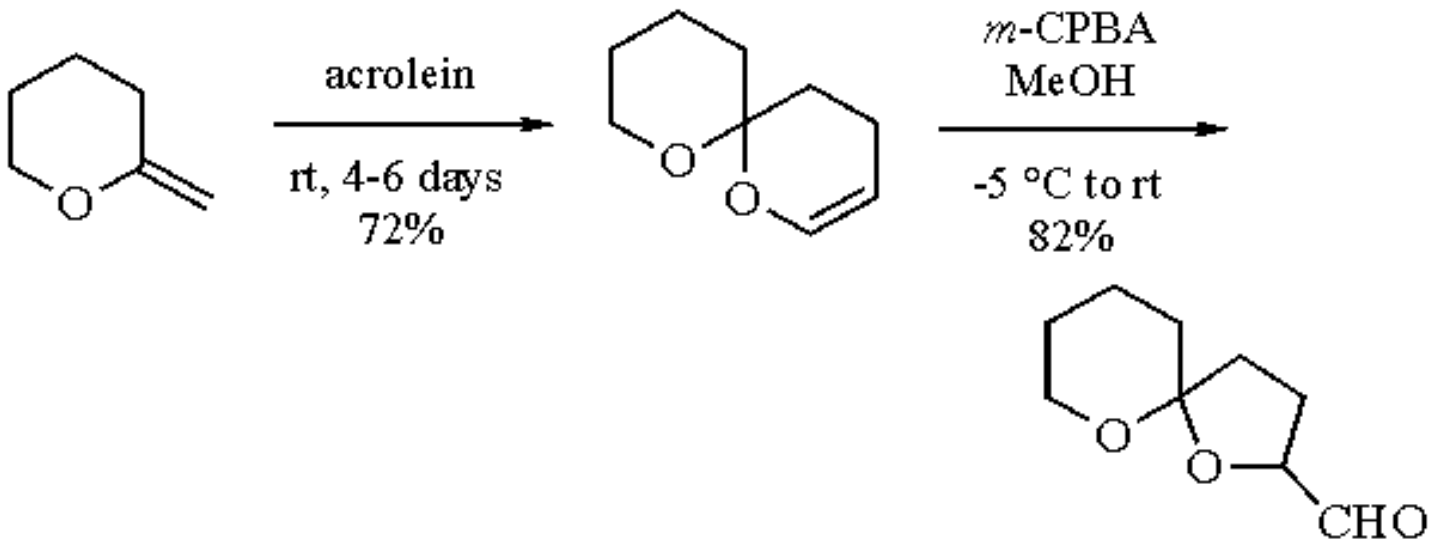

(11)

There are many examples in which acrolein is used as a dienophile.[45] Electron rich,[46] electron poor,[47] as well as a variety of substituted dienes react smoothly with acrolein at temperatures ranging from rt to 120 °C to yield substituted cyclohexene derivatives, often with complete regiocontrol.[48] Cyclohexadienes,[49] dimethylenehexahydropyrazines,[50] and various furans[51] provide rapid entry into bicyclo[2.2.2]octanes, octahydroquinoxalines, and oxabicyclo[2.2.1] compounds, respectively. While Diels-Alder cycloadditions of dienes with acrolein can be slow at elevated temperatures and atmospheric pressure, rates can be increased by factors of 10-1000 by application of higher pressures[52] or using a Lewis acid catalyst.[53] However, very mild Lewis acids are required since polymerization occurs readily with stronger Lewis acids.[54] The increase in reaction rates is accompanied by improved regioselection. Yb,[40] Fe,[54] W,[55] and Ru[56] based complexes are among the mildest catalysts reported to date (eq 12).

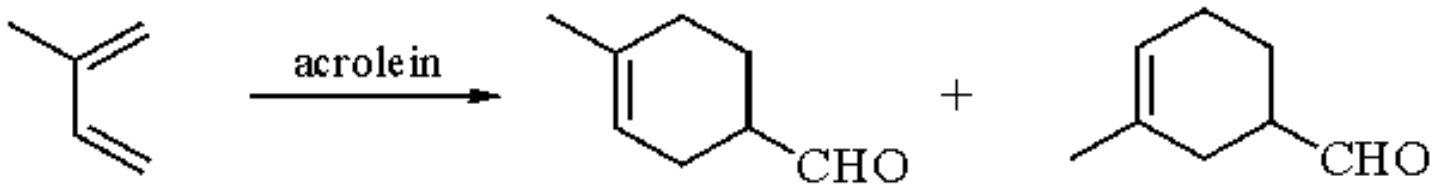

(12)

25 °C, no catalyst, 2700 h	70:30
25 °C, 2 mol% Ru catalyst, 5 h	99:1

There are a few reports of asymmetric cycloadditions with acrolein. A diastereomeric excess of 64% was obtained using an (*S*)-*O*-methylmandeloxy substituted diene.[57] Cycloadditions mediated by a chiral Lewis acid have also been described.[58] An 80% enantiomeric excess was observed in the cycloaddition between cyclohexadiene and acrolein catalyzed by a chiral (acyloxy)borane.

A cycloaddition between acrolein and a pyrilium ion was reported to be highly regioselective and moderately stereoselective, yielding an oxabicyclo[3.2.1]octene.[59]

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Acrylic Acid

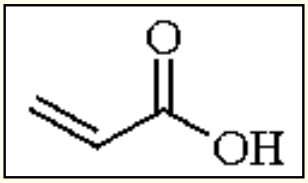

[79-10-7] · $C_3H_4O_2$ · Acrylic Acid · (MW 72.06)

(acylating agent, electrophile in 1,4-addition reactions, dienophile in Diels-Alder reactions)

Alternate Name: propenoic Acid.

Physical Data: mp -13 °C; bp 139 °C; *d* 1.051 g cm^{-3}; n_D 1.4224.

Solubility: miscible with water, alcohol, ether, acetone, and benzene.

Form Supplied in: colorless liquid (stabilized with 200 ppm hydroquinone monomethyl ether); widely available.

Purification: can be purified by steam distillation, or vacuum distillation through a column packed with copper gauze to inhibit polymerization (this treatment also removes inhibitors such as methylene blue that may be present). Azeotropic removal of the water with benzene converts wet acrylic acid into the anhydrous material.

Handling, Storage, and Precautions: polymerization occurs readily in the presence of oxygen. The liquid is toxic, corrosive, has an acrid odor, and fumes. Use in a fume hood.

Deuterated Acrylic Acid.

(*Z*)- and (*E*)-3-deuterioacrylic acids can be obtained from a stereospecific sodium amalgam reduction of the corresponding (*Z*)- and (*E*)-3-bromoacrylic acids in the presence of D_2O.[1]

Reactions of the Carboxylic Acid Group.

Conversion of acrylic acid to acryloyl chloride[2] and to the mixed anhydride using ***Acetic Anhydride*** have been achieved. Subsequent reaction with alcohols and amines gives esters and amides. Other mild reaction conditions to activate the carboxyl group are known.[4] For example, DCC/DMAP(cat)/alcohol[5] and DEAD/Ph_3P/alcohol systems[6]

have been used successfully. Using ***1,3-Dicyclohexylcarbodiimide***, the reactive intermediate rearranges to an amide in the absence of an external nucleophile.[7] Preparation of the amide by treatment with an in situ prepared phosphazo compound,[8] and amidation catalyzed by Ph_3SbO-P_4S_{10} in the presence of an amine,[9] are among the mildest methods available. The amide and ester adducts have frequently been used as dienophiles (achiral and chiral) in Diels-Alder reactions.[5-7] Synthesis of the analogous thiocarboxylic *S*-acid under mild conditions is best achieved using the Ph_3SbO-P_4S_{10} sulfuration system (eq 1).[10]

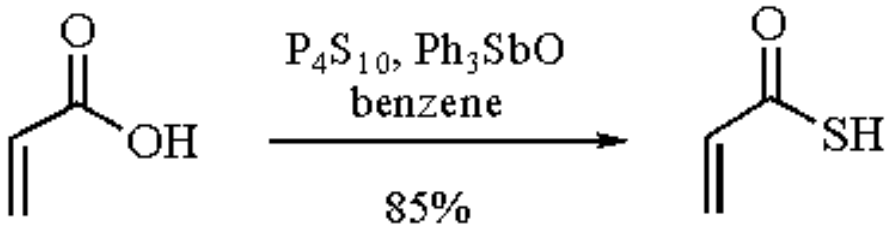

(1)

Reactions with the Double Bond.

Functional group transformations of the double bond have also been explored. Selective reduction of the double bond has been achieved in the presence of a variety of catalytic systems. Rh^{II}/H_2,[11] $Mo^0/PhSiH_3$,[12] and Pd^{II}/H_2[13] based systems give high yields and are extremely selective. Treatment of acrylic acid with hydrochloric acid gives 3-chloropropanoic acid,[14] while the Meerwein arylation with an arenediazonium ion yields the corresponding α-bromohydrocinnamic acid derivative.[15] Cyclopropanation using MeLi/LiBr and CH_2Cl_2 yields mixtures of halocyclopropyl ketones and alcohols in very good yield.[16] Regioselective hydrogermylation with trichlorogermane in concentrated hydrochloric acid provides exclusively 3-trichlorogermylpropanoic acid (eq 2).[17]

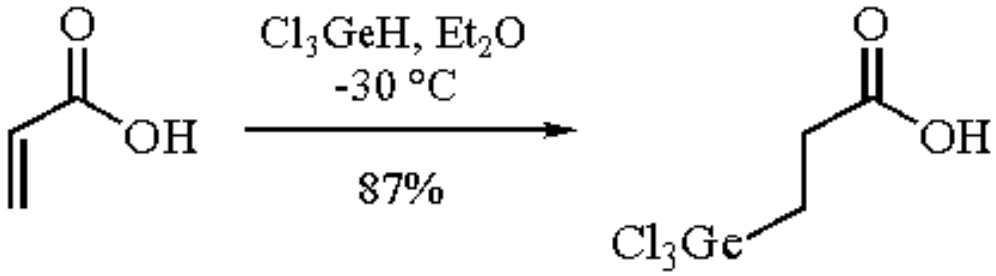

(2)

The preparation of succinic acid has been achieved from acrylic acid via a regioselective nickel catalyzed β-hydrocarboxylation.[18] Recently, methylmalonic acid was prepared via an α-hydrocarboxylation. Using a catalytic amount of ***Pentacarbonyliron*** in the presence of $Ca(OH)_2$/*i*-PrOH/H_2O, under a CO atmosphere, the diacid was obtained in good yield (eq 3).[19] Oxidation of the double bond to give glyceric acid has been achieved using permanganate oxidation.[20]

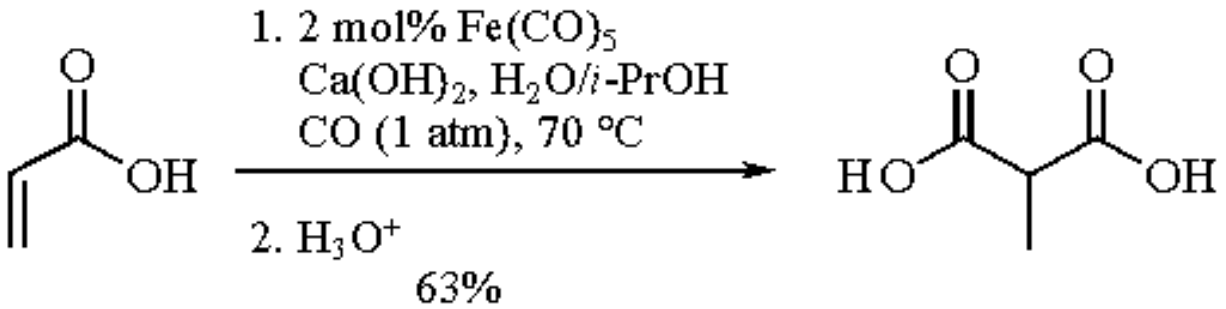

Cross Coupling Reactions.

Substituted acrylic acids are obtained via a palladium-catalyzed coupling of aryl or vinyl halides with acrylic acid (Heck reaction).[21] The reaction proceeds in organic[22] as well as aqueous[23] media (eq 4). Similar products are obtained when vinylmercury(II) chlorides are treated with acrylic acid in the presence of a stoichiometric amount of palladium (eq 5).[24]

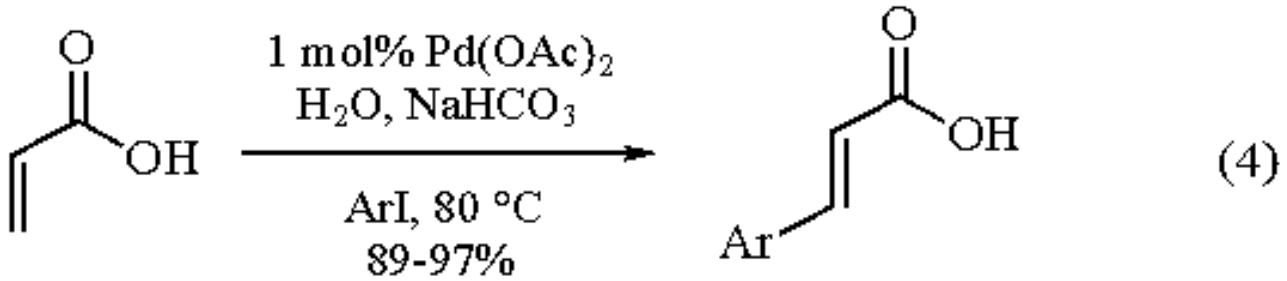

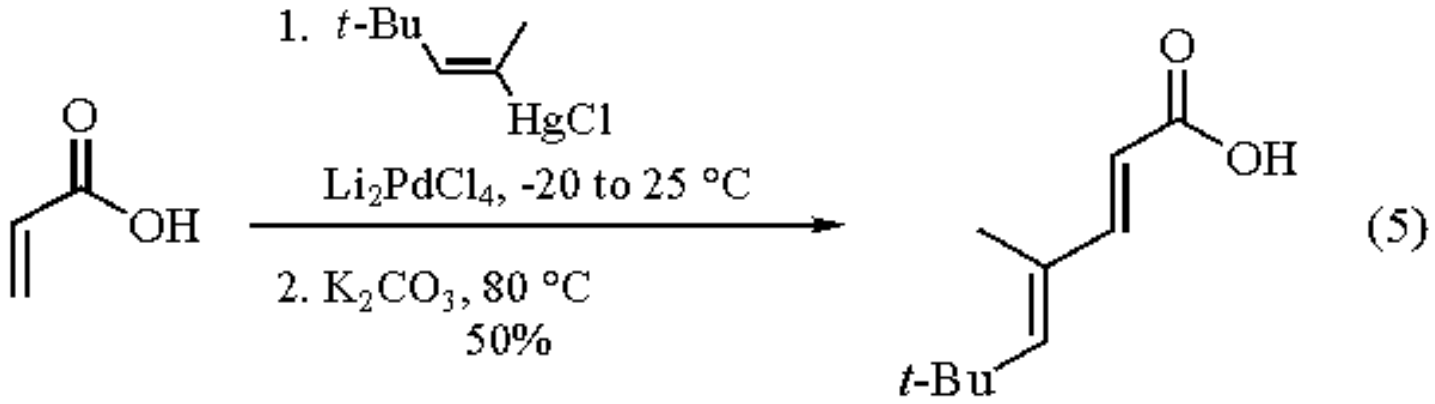

Addition Reactions to the Double Bond.

Acrylic acid can serve as a Michael acceptor in its reactions with alcohols,[25] thiols,[26] sulfinates,[27] and phospines.[28] Addition of *p*-toluenesulfinate provides 3-(*p*-toluenesulfonyl)propanoic acid, which has been used as a β-acyl anion equivalent upon double deprotonation with ***n-Butyllithium*** at -78 °C.[27b]

The acidity of acrylic acid precludes various nucleophilic addition strategies due to protonation of the nucleophile. While dialkylcopper reagents (R_2CuLi) do not react with acrylic acids, $RCu.BF_3$ are known to add to substituted acid derivatives.[29] Acrylic acid also undergoes an ene reaction with ***Isobutene*** to yield the corresponding adduct in 51% yield.[30] The double bond in acrylic acid can also serve as a radical acceptor. Optically active alanyl radical reacts

with acrylic acid to yield aminoadipic acid with no racemization observed (eq 6).[31]

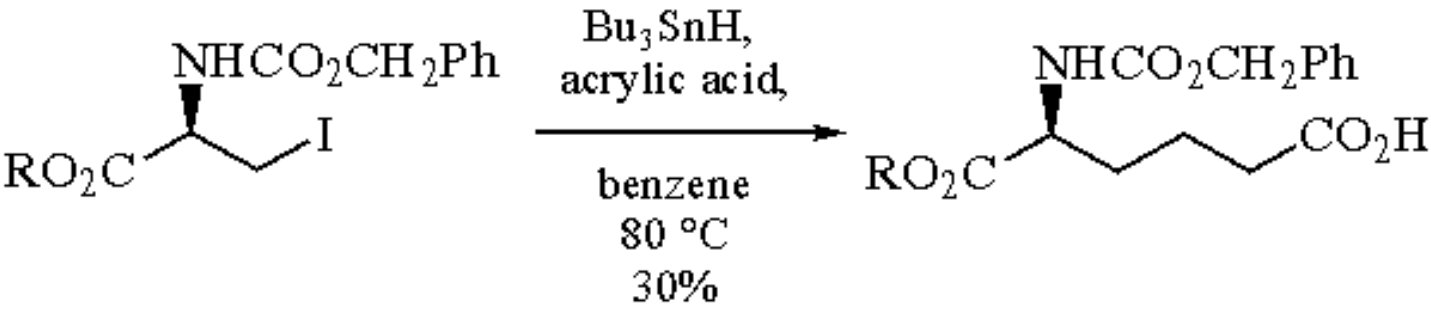

(6)

Diels-Alder Reaction.

Although acrylic acid has not been as widely used in Diels-Alder reactions as other simple dienophiles, a variety of dienes undergo cycloaddition with acrylic acid. Alkyl-,[32] silyl-,[33] and acetoxy-substituted[34] butadienes, various substituted furans,[35] cyclopentadienes,[36] cyclohexadienes,[37] anthracenes,[38] and pyridones[39] are among the dienes shown to react successfully with acrylic acid.[40] Cyclohexenes, (oxa) bicyclic compounds, and heterocyclic adducts are obtained. The *ortho* and *para* regioisomers usually predominate in reactions of acrylic acid with 1- and 2-substituted butadienes, respectively.[32,41] While the *endo* to *exo* selectivity may vary from poor to good (depending on the diene), repeated fractional recrystallizations of the carboxylic acid adducts often lead to pure products.[34a,35b] Generally, the reactions require stirring for several days at room temperature[35] or, when the product is thermally stable, heating at 100-160 °C for several hours in the presence of hydroquinone (a polymerization inhibitor). Catalysis using Cu^{I} has been reported, while attempted catalysis using Lewis acids such as iron(III) chloride, tin(IV) chloride, and zinc chloride resulted in polymerization.[35a] Recently, ***Diborane*** has been shown to catalyze cycloadditions of acrylic acid via acyloxyboranes.[34b,42] For example, addition of 10 mol% of the ***Borane-Tetrahydrofuran*** complex to the acrylic acid at 0 °C, followed by the diene at -78 °C, resulted in the fast formation of the Diels-Alder adduct. Precomplexation of the borane-THF complex with a monoacylated tartaric acid at 0 °C resulted in the formation of a chiral acyloxyborane, which mediated the reaction between acrylic acid and cyclopentadiene, to give the adduct with 78% enantiomeric excess (eq 7).

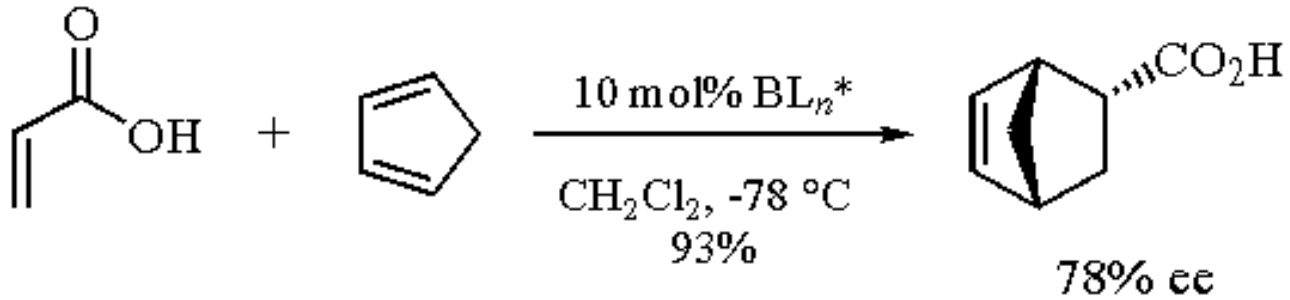

(7)

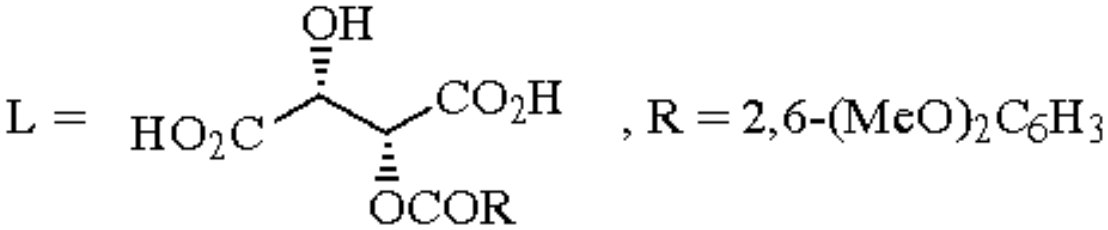

Dipolar cycloadditions with acrylic acid are known but not widely used in synthesis.[43]

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Acrylonitrile

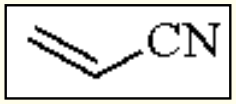

[107-13-1] · C_3H_3N · Acrylonitrile · (MW 53.06)

(electrophile in 1,4-addition reactions; radical acceptor; dienophile; acceptor in cycloaddition reactions)

Physical Data: mp -83 °C; bp 77 °C; *d* 0.806 g cm^{-3}; n_D 1.3911.

Solubility: miscible with most organic solvents; 7.3 g of acrylonitrile dissolves in 100 g of water at 20 °C.

Form Supplied in: colorless liquid (inhibited with 35-45 ppm hydroquinone monomethyl ether); widely available.

Purification: the stabilizer can be removed prior to use by passing the liquid through a column of activated alumina or by washing with a 1% aqueous solution of NaOH (if traces of water are allowed in the final product) followed by distillation. For dry acrylonitrile, the following procedure is recommended. Wash with dilute H_2SO_4 or H_3PO_4, then with dilute aqueous Na_2CO_3 and water. Dry over Na_2SO_4, $CaCl_2$, or by shaking with molecular sieves. Finally, fractional distillation under nitrogen (boiling fraction of 75-75.5 °C) provides acrylonitrile which can be stabilized by adding 10 ppm *t*-butyl catechol or hydroquinone monomethyl ether. Pure acrylonitrile is distilled as required.[1a]

Handling, Storage, and Precautions: explosive, flammable, and toxic liquid. May polymerize spontaneously, particularly in the absence of oxygen or on exposure to visible light, if no inhibitor is present. Polymerizes violently in the presence of concentrated alkali. Highly toxic through cyanide effect. Use in a fume hood.

Deuterioacrylonitrile.

Deuterium-labeled acrylonitrile can be obtained by reduction of propiolamide-d_3 with ***Lithium Aluminum Hydride***, followed by D_2O workup. The resulting acrylamide can then be dehydrated with P_2O_5.[1b]

Reactions of the Nitrile Group.

Various functional group transformations have been carried out on the nitrile group in acrylonitrile. Hydration with concentrated ***Sulfuric Acid*** at 100 °C yields acrylamide after neutralization.[2] Secondary and tertiary alcohols produce

N-substituted acrylamides under these conditions in excellent yield (Ritter reaction).[3] Heating in the presence of dilute sulfuric acid or with an aqueous basic solution yields acrylic acid.[4] Imido ethers have been prepared by reacting acrylonitrile with alcohols in the presence of anhydrous hydrogen halides.[5] Anhydrous ***Formaldehyde*** reacts with acrylonitrile in the presence of concentrated sulfuric acid to produce 1,3,5-triacrylylhexahydrotriazine.[6]

Reactions of the Alkene.

Reduction with hydrogen in the presence of Cu,[7] Rh,[8] Ni,[9] or Pd[10] yields propionitrile. Acrylonitrile can be halogenated at low temperature to produce 2,3-dihalopropionitriles. For example, reaction with ***Bromine*** leads to dibromopropionitrile in 65% yield.[11] Also, treatment of acrylonitrile with an aqueous solution of ***Hypochlorous Acid***, gives 2-chloro-3-hydroxypropionitrile in 60% yield.[12] α-Oximation of acrylonitrile has been achieved using Co^{II} catalysts, ***n-Butyl Nitrite*** and phenylsilane.[13]

Nucleophilic Additions.

A wide variety of nucleophiles react with acrylonitrile in 1,4-addition reactions. These Michael-type additions are often referred to as cyanoethylation reactions.[14] The following list illustrates the variety of substrates which will undergo cyanoethylation: ammonia, primary and secondary amines, hydroxylamine, enamines, amides, lactams, imides, hydrazine, water, various alcohols, phenols, oximes, sulfides, inorganic acids like HCN, HCl, HBr, chloroform, bromoform, aldehydes, and ketones bearing an α-hydrogen, malonic ester derivatives, and other diactivated methylene compounds.[15] Stabilized carbanions derived from ***Cyclopentadiene*** and fluorene and 1-5% of an alkaline catalyst also undergo cyanoethylation. The strongly basic quaternary ammonium hydroxides, such as ***Benzyltrimethylammonium Hydroxide*** (Triton B), are particularly effective at promoting cyanoethylation because of their solubility in organic media. Reaction temperatures vary from -20 °C for reactive substrates, to heating at 100 °C for more sluggish nucleophiles. The 1,4-addition of amines has recently been used in the synthesis of poly(propyleneimine) dendrimers.[16]

Phosphine nucleophiles have been reported to promote nucleophilic polymerization of acrylonitrile.[17]

Addition of organometallic reagents to acrylonitrile is less efficient than to conjugated enones. Grignard reagents react with acrylonitrile by 1,2-addition and, after hydrolysis, give α,β-unsaturated ketones.[18] Lithium dialkylcuprate (R_2CuLi) addition in the presence of ***Chlorotrimethylsilane*** leads to double addition at the alkene and nitrile, giving a dialkyl ketone.[19] Yields of only 23-46% are obtained in the conjugate addition of *n*-$BuCu.BF_3$ to acrylonitrile.[20] An enantioselective Michael reaction has been achieved with titanium enolates derived from *N*-propionyloxazolidone (eq 1).[21]

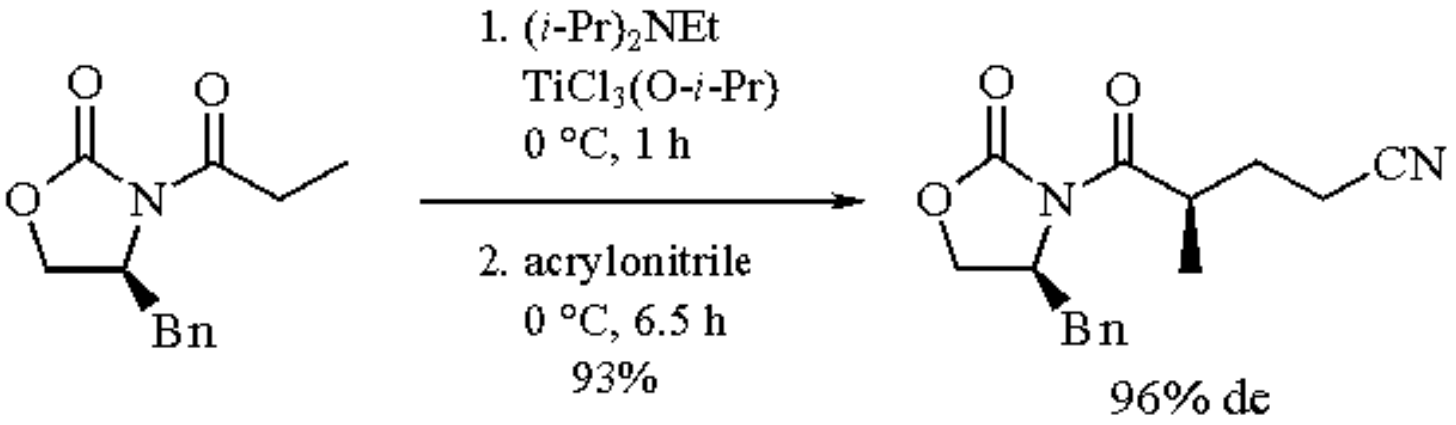

(1)

Acrylonitrile fails to react with trialkylboranes in the absence of oxygen or other radical initiators. However, secondary trialkylboranes transfer alkyl groups in good yield when oxygen is slowly bubbled through the reaction mixture.[22] Primary and secondary alkyl groups can be added in excellent yields using copper(I) methyltrialkylborates.[23] Reaction of acrylonitrile with an organotetracarbonylferrate in a conjugate fashion provides 4-oxonitriles in moderate (25%) yields.[24]

Transition Metal-Catalyzed Additions.

Palladium-catalyzed Heck arylation and alkenylation occurs readily with acrylonitrile (eq 2).[25] Double Heck arylation is observed in the Pd^{II}/montmorillonite-catalyzed reaction of aryl iodides with acrylonitrile.[26]

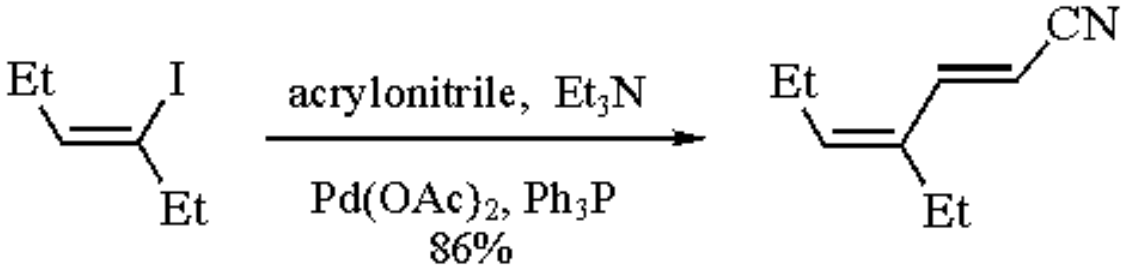

(2)

Pd^{II} catalyzed oxidation of the double bond in acrylonitrile in the presence of an alcohol (Wacker-type reaction) produces an acetal in high yield.[27] When an enantiomerically pure diol such as ***(2R,4R)-2,4-Pentanediol*** is used, the corresponding chiral cyclic acetal is produced (eq 3).[28]

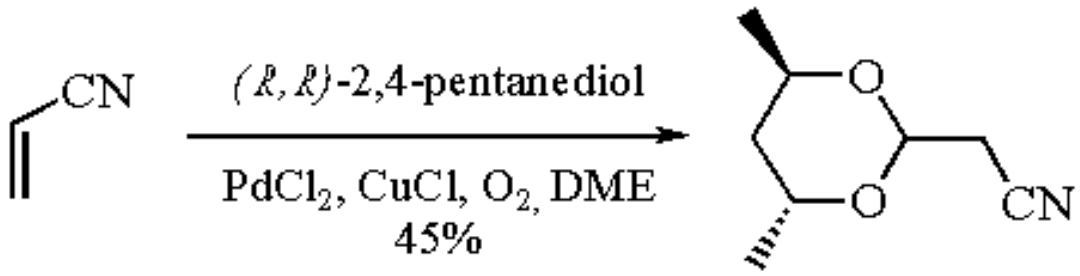

(3)

Hydrosilation[29a] of acrylonitrile with $MeCl_2SiH$ catalyzed by nickel gives the α-silyl adduct. The β-silyl adduct is obtained when copper(I) oxide is used.[29b] The regioselectivity of the cobalt catalyzed hydrocarboxylation to give

either the 2- or 3-cyanopropionates can also be controlled by the choice of reaction conditions.[30] Hydroformylation of acrylonitrile has also been described.[31]

Cyclopropanation of the double bond has been achieved upon treatment with a Cu^{I} oxide/isocyanide or Cu^{0}/isocyanide complex. Although yields are low to moderate, functionalized cyclopropanes are obtained.[32,33] Photolysis of hydrazone derivatives of glucose in the presence of acrylonitrile provides the cyclopropanes in good yield, but with little stereoselectivity.[34] Chromium-based Fischer carbenes also react with electron deficient alkenes including acrylonitrile to give functionalized cyclopropanes (eq 4).[35]

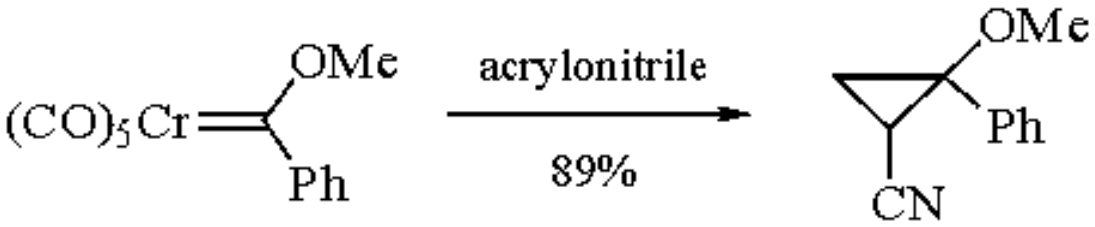

(4)

Radical Additions.

Carbon-centered radicals add efficiently and regioselectively to the β-position of acrylonitrile, forming a new carbon-carbon bond.[36,37] Such radicals can be generated from an alkyl halide (using a catalytic amount of ***Tri-n-butylstannane***, alcohol (via the thiocarbonyl/Bu_3SnH), tertiary nitro compound (using Bu_3SnH), or an organomercurial (using $NaBH_4$). The stereochemistry of the reaction has been examined in cyclohexanes and cyclopentanes bearing an α-stereocenter.[36] Cr^{II} complexes, vitamin B_{12}, and a Zn/Cu couple have been shown to mediate the intermolecular addition of primary, secondary, and tertiary alkyl halides to acrylonitrile.[38] Acyl radicals derived from phenyl selenoesters and Bu_3SnH also give addition products with acrylonitrile (eq 5).[39]

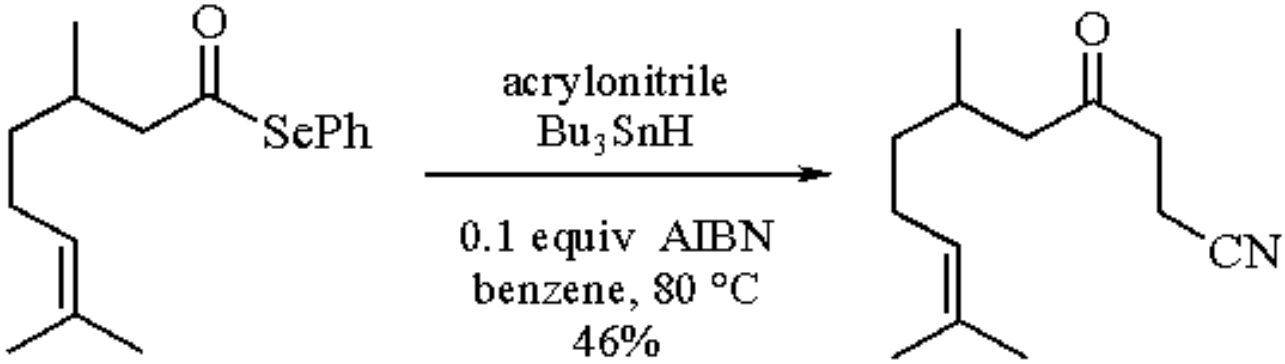

(5)

Radical additions with acrylonitrile have been used to prepare *C*-glycosides[36,37b] and in annulation procedures.[37c] Acrylonitrile has also been used in a [3 + 2] annulation based on sequential radical additions (eq 6).[40]

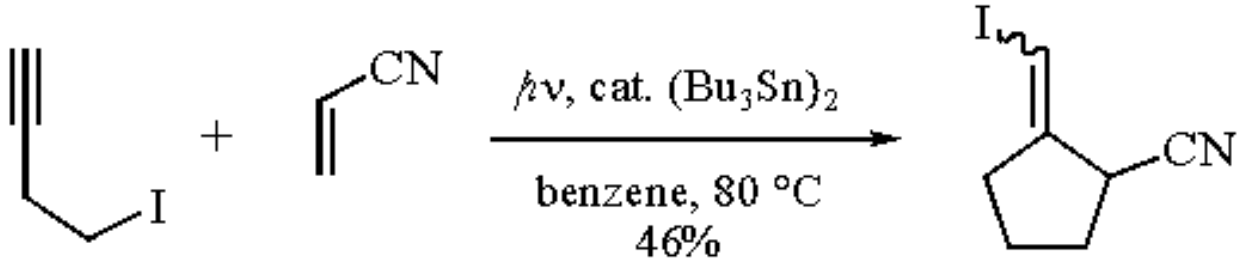

(6)

Alkyl and acyl Co^{III} complexes add to acrylonitrile and then undergo β-elimination to give a product corresponding to vinylic C-H substitution.[41] This methodology is complementary to the Heck reaction of aryl and vinyl halides, which fails for alkyl and acyl compounds.[25]

Radicals other than those based on carbon also add to acrylonitrile. Heating acrylonitrile and tributyltin hydride in a 2:3 molar ratio in the presence of a catalytic amount of ***Azobisisobutyronitrile*** yields exclusively the β-stannylated adduct in excellent yield.[42] Hydrostannylation in the presence of a Pd^0 catalyst gives only the α-adduct (eq 7).[42c]

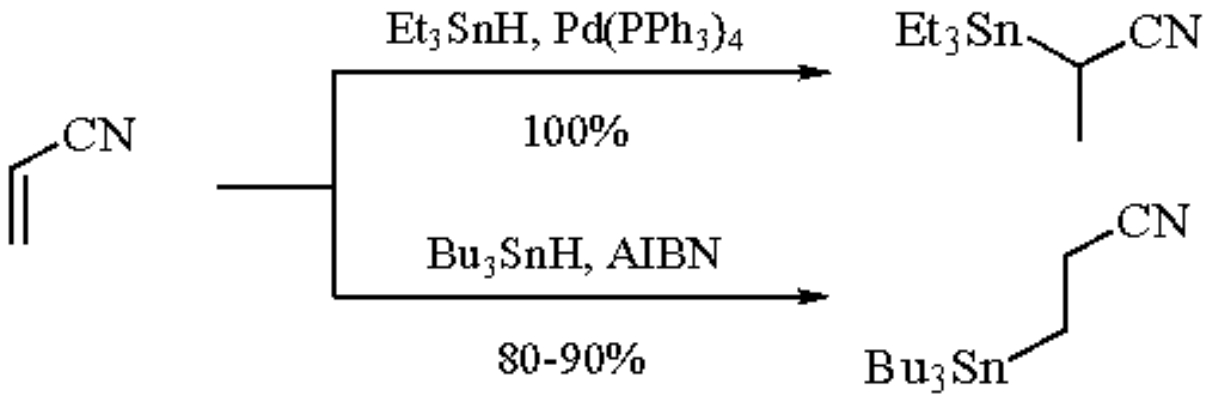

(7)

Treatment of ethyl propiolate with Bu_3SnH in the presence of acrylonitrile results in addition of a tin radical to the β-site of the alkyne followed by addition to acrylonitrile. Use of excess acrylonitrile results in trapping of the radical followed by an annulation reaction, providing trisubstituted cyclohexenes.[43]

Thioselenation of the alkene using ***Diphenyl Disulfide***, ***Diphenyl Diselenide***, and photolysis gives the α-seleno-β-sulfide in 75% yield by a radical addition mechanism.[44] Similarly, ***Tris(trimethylsilyl)silane*** adds to acrylonitrile at 80-90 °C using AIBN to give the β-silyl adduct in 85% yield.[45]

Pericyclic Reactions.

In the presence of a suitable alkene, the double bond in acrylonitrile undergoes a thermally induced ene reaction in low to moderate yield. For example, when (+)-limonene and acrylonitrile are heated in a sealed tube, the corresponding ene adduct is produced in 25% yield.[46]

The thermal [2 + 2] dimerization of acrylonitrile has been known for many years. Good regioselectivity is observed but the yield is low and a mixture of stereoisomers is produced.[47] *Cis*-1,2-dideuterioacrylonitrile was used in this reaction to study the stereochemical outcome of the cycloaddition. It was concluded that a diradical intermediate was involved.[1b]

Other [2 + 2] reactions have been reported. Regioselective cycloaddition between a silyl enol ether and acrylonitrile yields a cyclobutane in the presence of light and a triplet sensitizer.[48a] Reaction between acrylonitrile and a ketene silyl acetal in the presence of a Lewis acid gives either substituted cyclobutanes or γ-cyanoesters depending on the Lewis acid and solvent (eq 8).[48c]

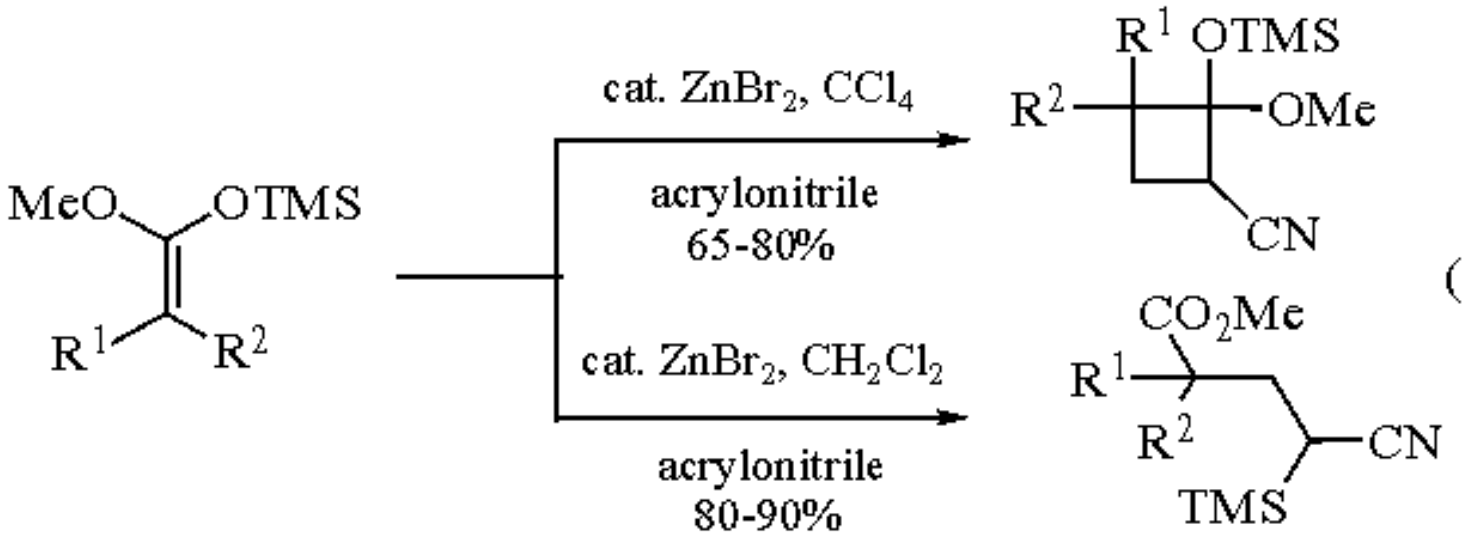

(8)

Dihydropyridines undergo stereoselective cycloaddition with acrylonitrile under photolytic conditions.[48c] The combination of a Lewis acid (***Zinc Chloride***) and photolysis promotes cycloaddition between benzene and acrylonitrile.[48d] Allenyl sulfides undergo Lewis acid catalyzed [2 + 2] cycloaddition with electron deficient alkenes including acrylonitrile with good regioselectivity but little stereoselectivity (eq 9).[49]

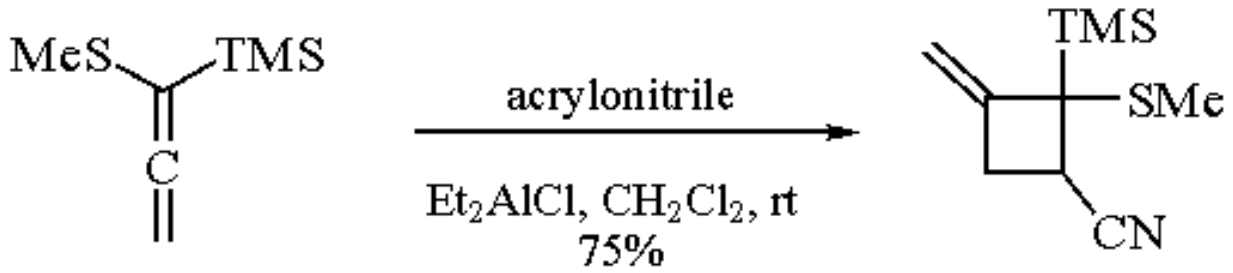

(9)

Metal catalysts promote [3 + 2] cycloaddition reactions with acrylonitrile, leading to carbocyclic compounds. Reaction of acrylonitrile with a trimethylenemethane (TMM) precursor in the presence of Pd^0 provides an efficient route to methylenecyclopentanes in moderate yield (40%).[50] A similar yield is obtained when a Ni^0 or Pd^0 catalyzed cycloaddition is employed starting from methylenecyclopropane.[51] Moreover, a variety of substituted methylenecyclopropanes have also been used to furnish substituted methylenecyclopentanes (eq 10).[51b]

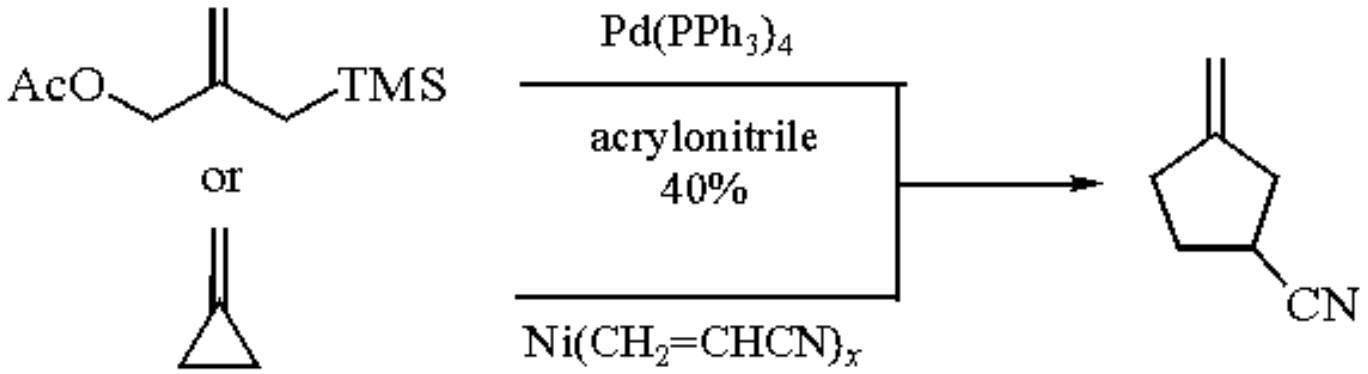

(10)

Five-membered heterocycles can be prepared from acrylonitrile by dipolar cycloadditions. Acrylonitrile undergoes efficient cycloaddition with 1,3-dipolar species[52] including nitrile oxides, nitrones, azomethine ylides, azides, and diazo compounds.[53] Cycloaddition of acrylonitrile with an oxopyrilium ylide generates stereoisomeric oxabicyclic compounds with excellent regioselectivity (eq 11).[54]

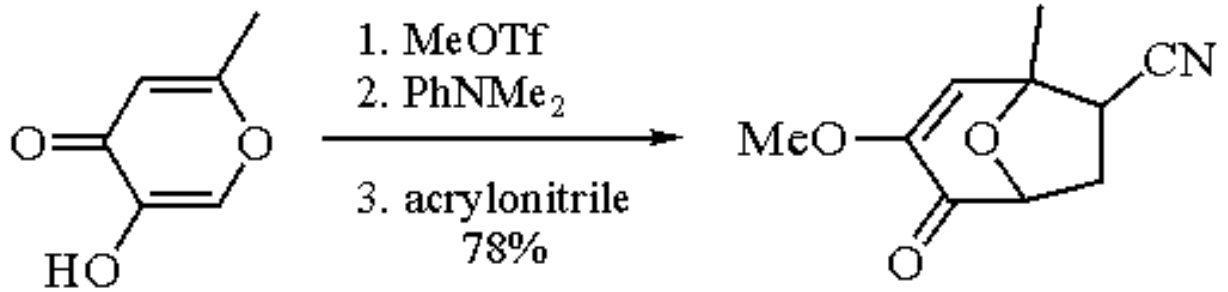

(11)

The dipolar cycloaddition of acrylonitrile with a hydroxypyridinium bromide is also highly regioselective.[55]

The [2 + 2 + 2] homo Diels-Alder cycloaddition between acrylonitrile and norbornadiene, substituted norbornadienes, or quadricyclane, has also been described under thermal and metal catalyzed conditions.[56] The effect of ligands and substituents on the stereo- and regioselectivity of the nickel catalyzed process has been investigated (eq 12).[56c,d]

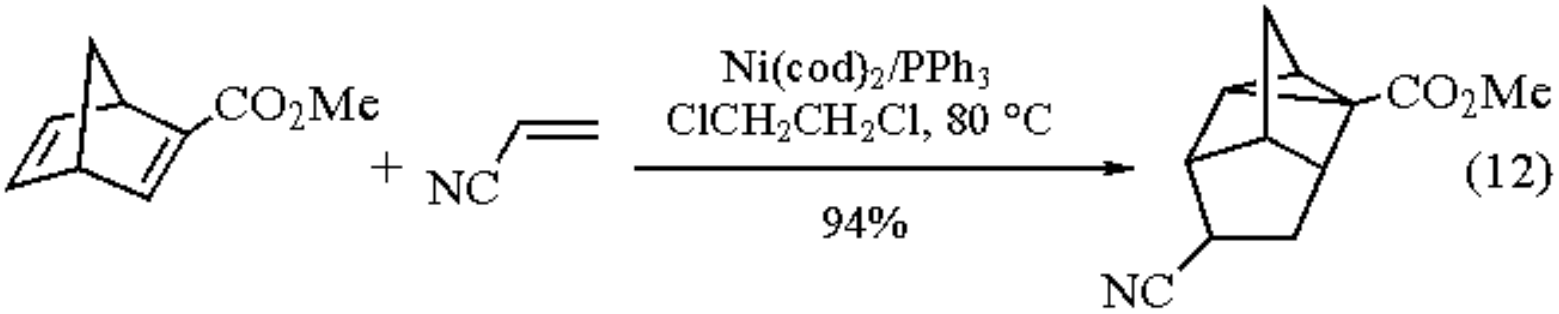

(12)

Cobalt catalysts (***Octacarbonyldicobalt***) also promote the cycloaddition of 1,6-diynes with acrylonitrile, yielding cyclohexadienes which are readily aromatized.[57]

Diels-Alder reactions using acrylonitrile have been widely reported with many different dienes. These include alkyl, aryl, alkoxy, alkoxycarbonyl, amido, phenylseleno, phenylthio, and alkoxyboranato substituted butadienes.[58] Reactions between acrylonitrile and furans, thiophenes, and thiopyrans have been reported. In some instances, Lewis

acids accelerate the reaction.[59] Heterodienes including 2-azabutadienes and the 4-(oxa, aza, and thio) derivatives also undergo cycloaddition. Reactive dienes such as *o*-quinodimethanes,[60] benzofurans,[61] and dimethylbenzodioxanes react efficiently with acrylonitrile (eq 13).[62]

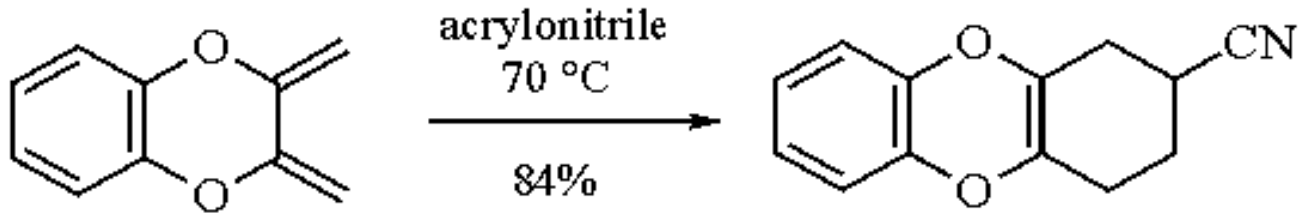

(13)

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Allene

$CH_2=C=CH_2$

[463-49-0] · C_3H_4 · Allene · (MW 40.07)

(used in photochemical, thermal, and transition metal mediated cycloadditions; precursor of allenyl- and propargyllithium; electrophile with cuprates)

Alternate Name: 1,2-propadiene.

Physical Data: mp -136 °C; bp -34 °C; flammable gas.

Solubility: insol H_2O; sol THF, pet ether, benzene.

Form Supplied in: gas (lecture bottle); widely available.

Preparative Method: reaction of ***2,3-Dichloropropene*** with ***Zinc*** in ethanol.[1]

Handling, Storage, and Precautions: flammable gas; handle in a fume hood.

Metalated Allenes.

Allene can be metalated at -70 °C to produce allenyllithium which reacts with alkyl halides to give high yields of terminal allenes (eq 1).[2,3] Generally less than 5% of the alkyne is obtained. The dianion of allene can also be prepared and treated with electrophiles such as alkyl halides and carbonyl compounds (eqs 2 and 3).[4-7] The regiochemistry of the alkylation is dependent on the choice of solvent: more coordinating solvents and solvent combinations typically provide the allene products[6] while less polar solvents produce the substituted alkynes.[4] The intermediate acetylides can be exposed to an additional electrophile to allow the formation of two new carbon-carbon bonds.[3,7]

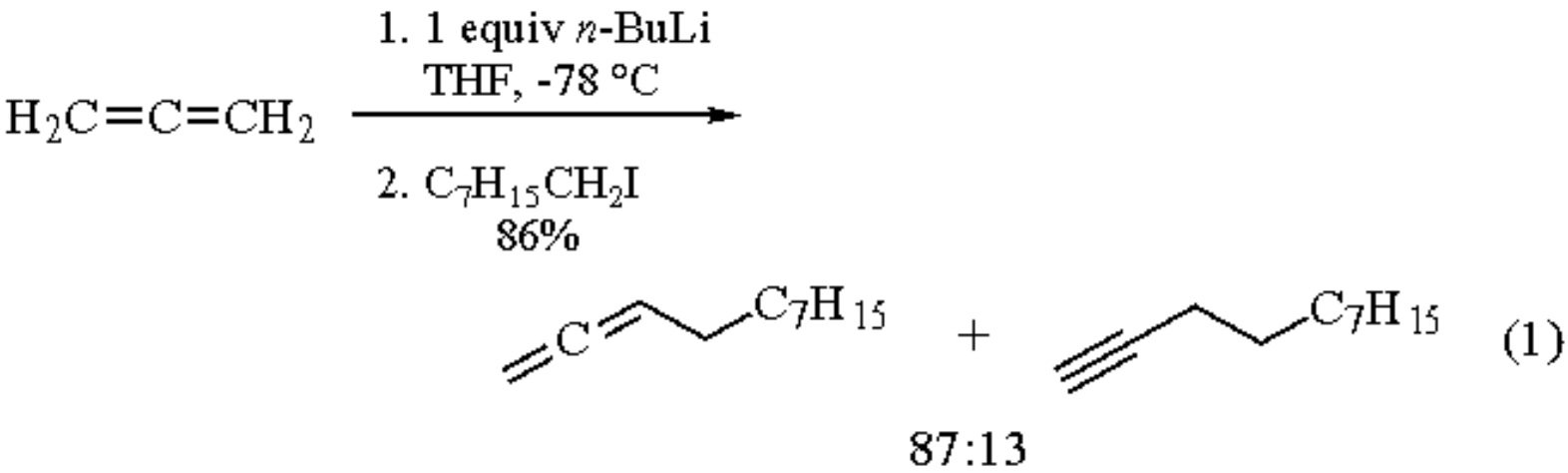

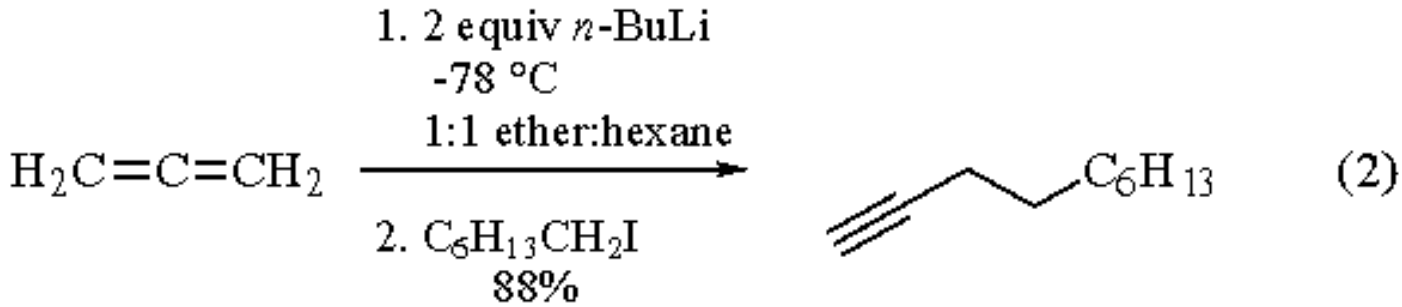

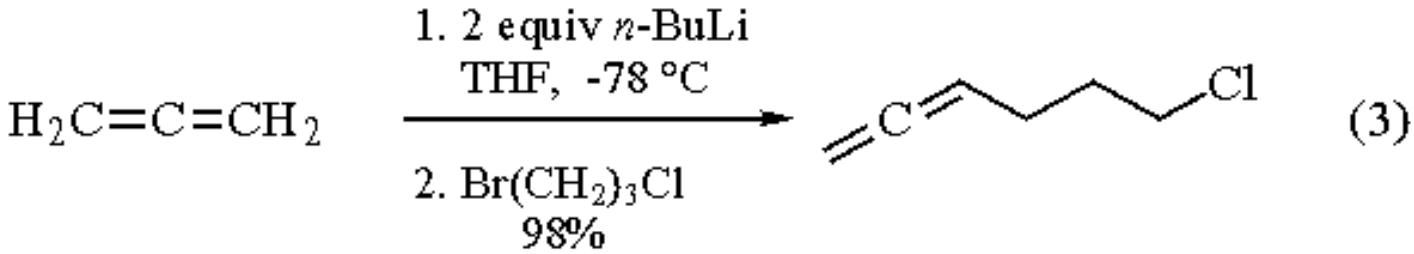

Photochemical Cycloadditions.

Allene has been used extensively in intermolecular [2 + 2] photocycloaddition reactions.[8] Cyclohexenones (eq 4),[9] cyclopentenones (eq 5),[10] and functionalized enones (eq 6)[11] undergo cycloaddition with allene with excellent and predictable regioselectivity and in uniformly high yields. The stereochemistry of cycloaddition of allene to 4-substituted cyclohexenones has been interpreted by attack of allene on the enone excited state which is substantially pyramidalized at the β-carbon (eq 7).[12,13]

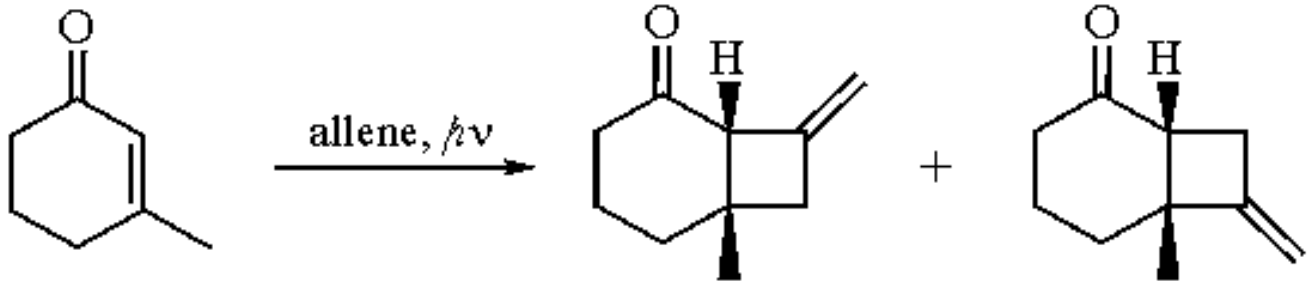

(4)

-78 °C 100% 100:0
25 °C 4:1

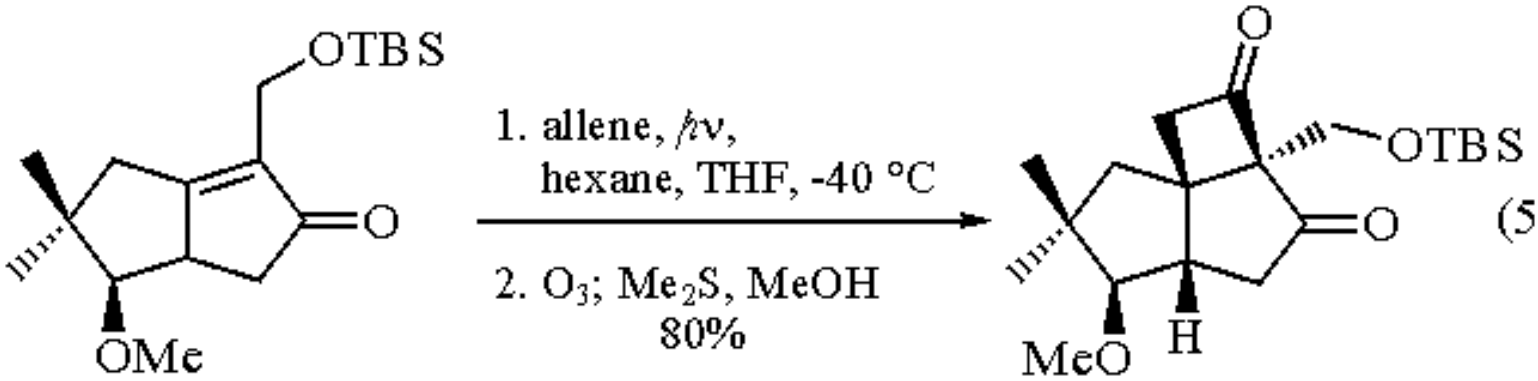

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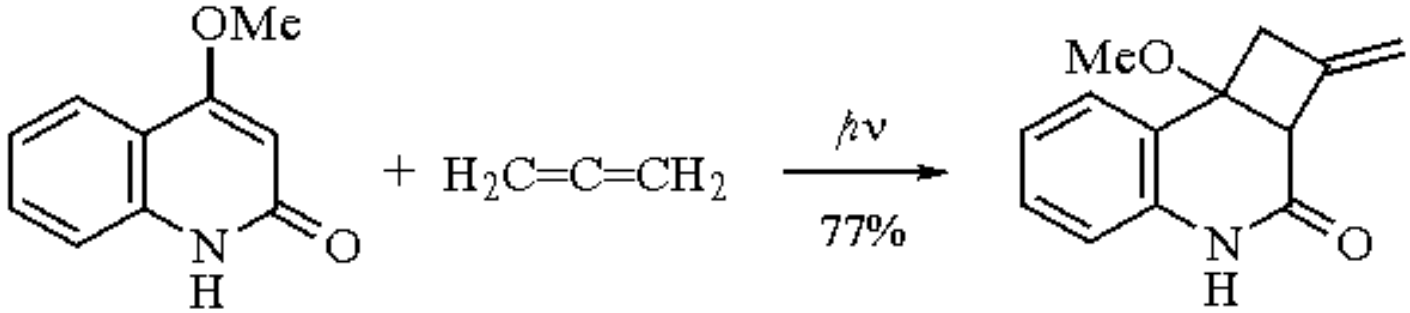

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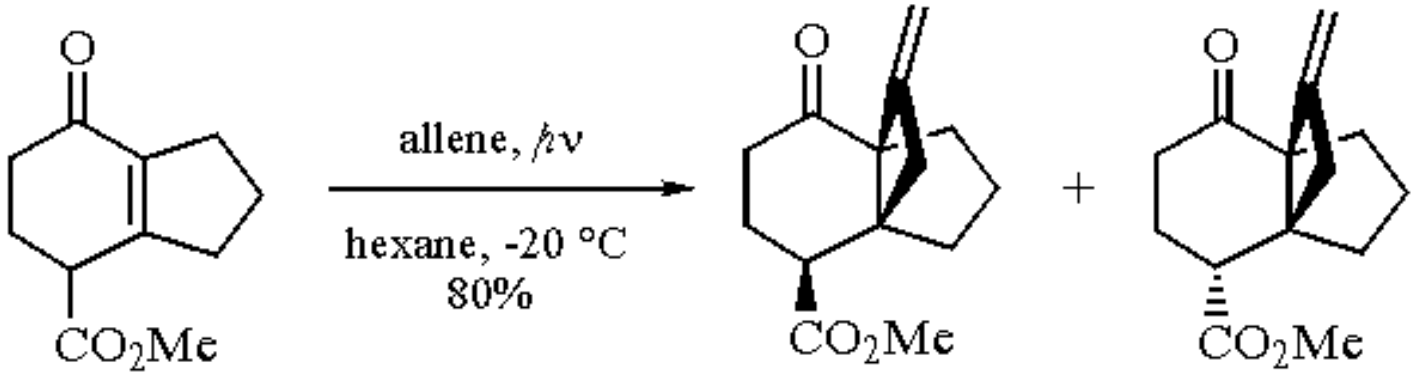

(7)

13:1

Thermal Cycloadditions.

Allene undergoes various thermal cycloadditions including thermal [2 + 2] cycloadditions (eq 8),[14] Diels-Alder reactions (eq 9),[15,16] and nitrone cycloadditions.[17]

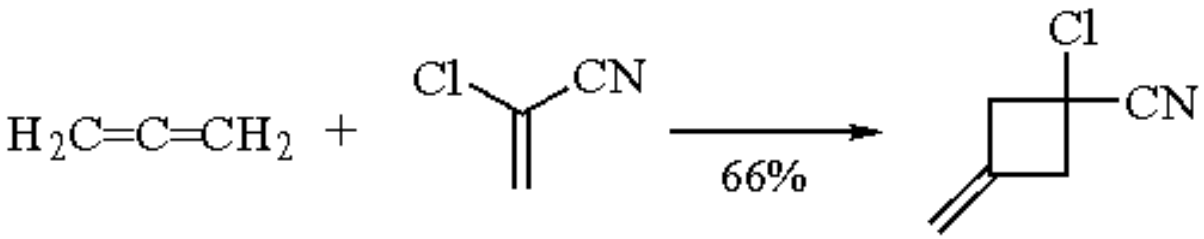

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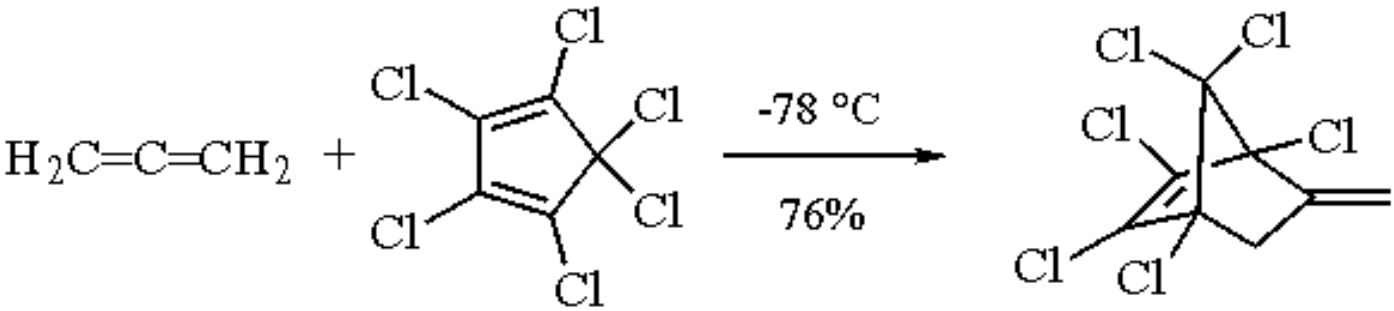

(9)

Organometallic Catalyzed Reactions.

Allene reacts readily with ***Palladium(II) Chloride*** to form a π-allyl complex[18] and many palladium catalyzed transformations of allene have been reported. Carbopalladation reactions provide ready access to 2-substituted 1,3-dienes (eq 10),[19] bis-stannylation (eq 11) produces high yields of the vinylallylstannanes,[20] and the analogous reaction with bis-silanes has been reported.[21] Substituted acrylates and butenoates are available from the palladium catalyzed carbonylation of allene (eq 12).[22]

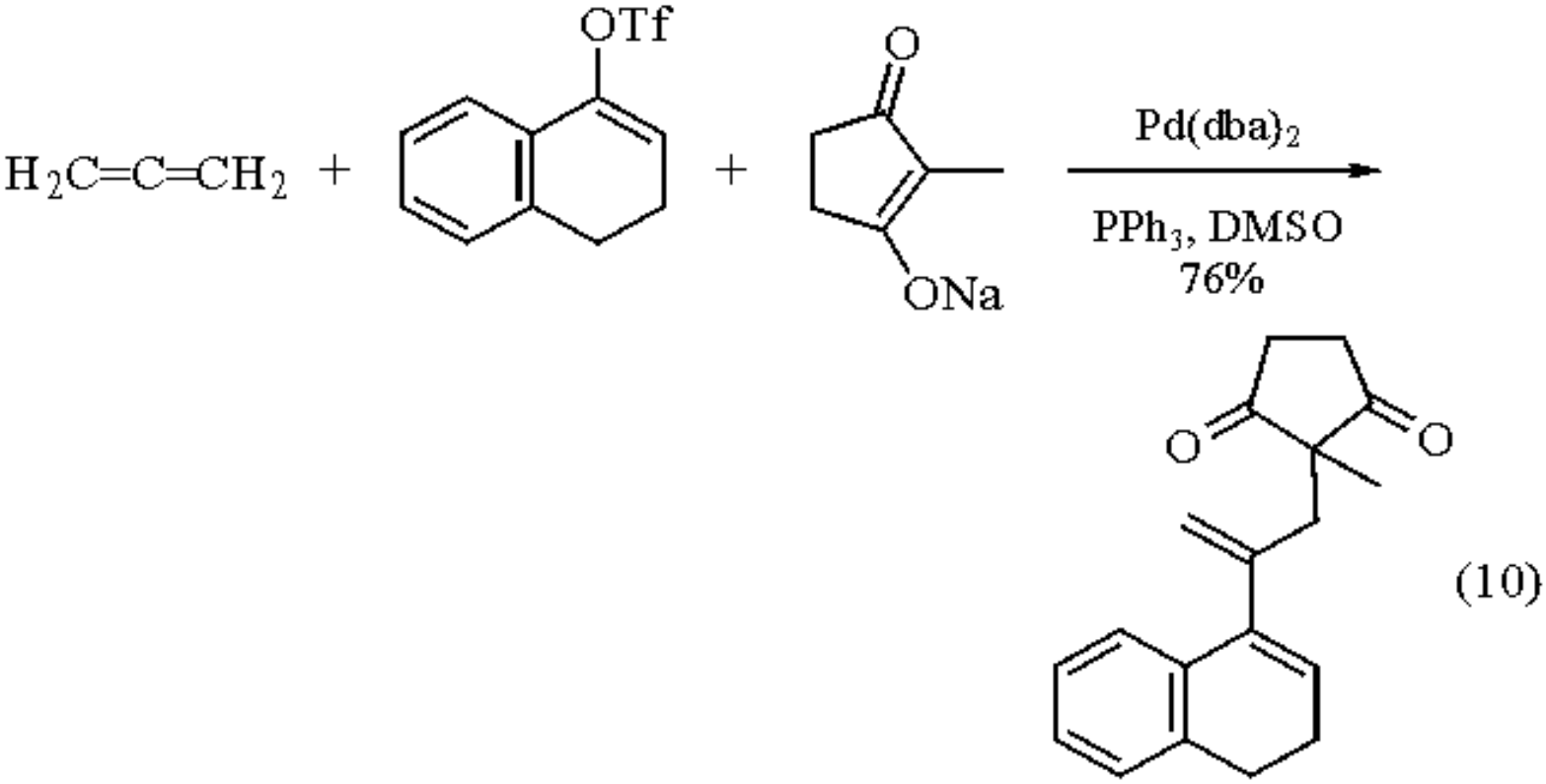

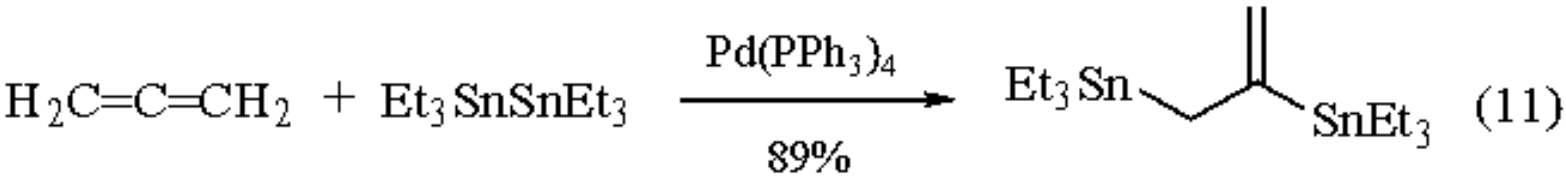

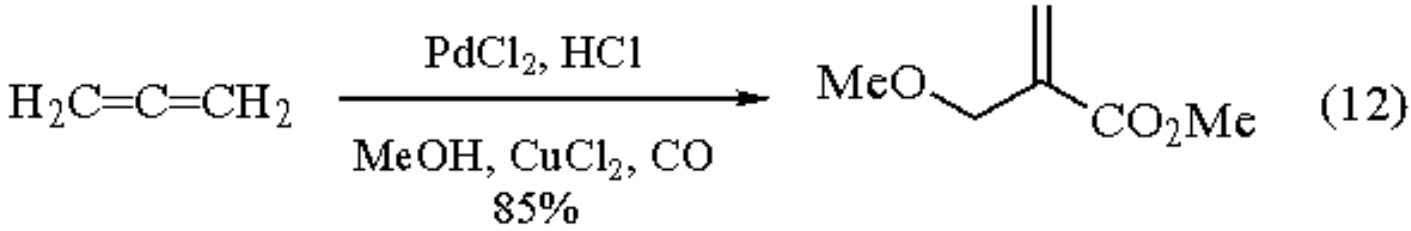

Nickel(II) catalysis has been utilized to prepare 4-methyl-4-pentenoic acid from allene[23] and substituted allenes have been prepared from ketones by treatment with a titanacyclobutane (eq 13).[24]

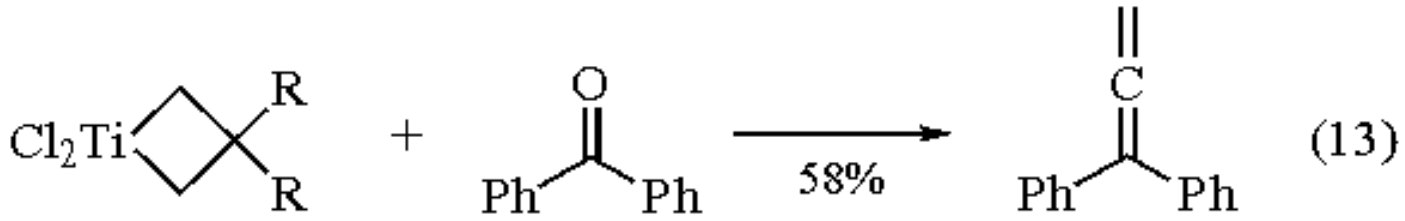

Isopropenyl Stannanes, Silanes, and Germanes.

The reaction of allene with stannyl and silyl cuprates gives isopropenylsilanes[25] and -stannanes[26] (eqs 14 and 15) in excellent yield. Triphenylisopropenylgermane can be prepared from allene and triphenylgermane in the presence of ***Triethylborane***.[27] In addition, haloboration of allene with boron tribromide and anisole produces a 2-bromoallylboronate (eq 16),[28] and electrophilic addition of phenylselenium bromide to allene provides 2-phenylselenoallyl bromide (eq 17).[29]

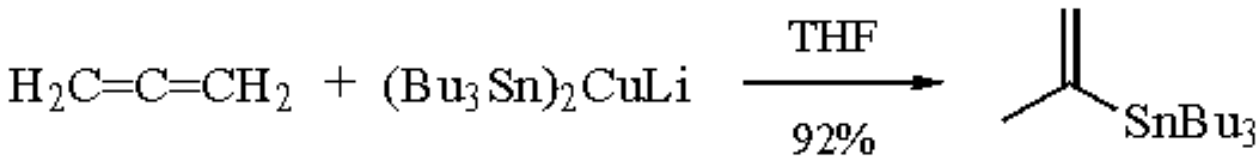

(14)

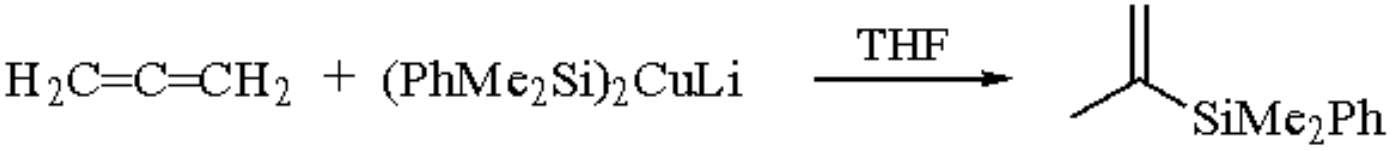

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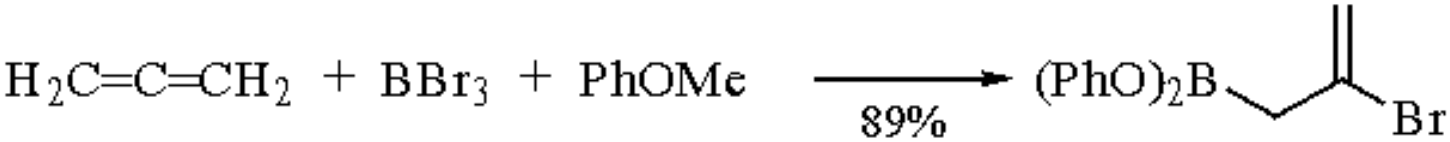

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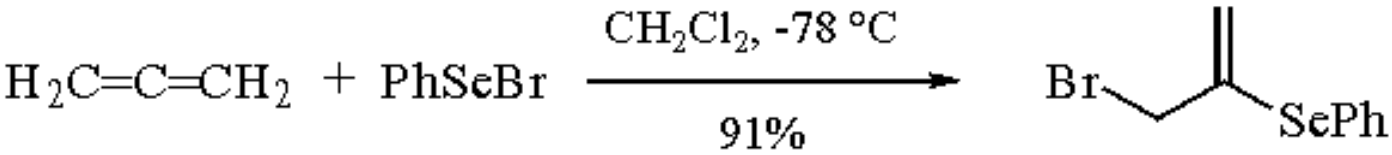

(17)

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Allenylboronic Acid

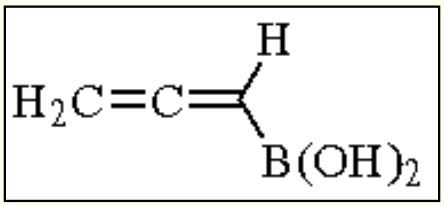

[83816-41-5] · $C_3H_5BO_2$ · Allenylboronic Acid · (MW 83.88)

(propargylating reagent for carbonyl groups; chiral allenylboronic ester as a reagent for enantioselective alkylation;[1] 1,3-asymmetric induction in propargylation of β-hydroxy ketones[2])

Physical Data: mp 150 °C (dec).

Solubility: sol ether, alcohol.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$-Me_2SO-d_6) δ 4.48 (d, *J* = 5.8 Hz, 1H), 4.51 (d, *J* = 7.2 Hz, 1H), 4.83 (dd, *J* = 5.8 and 7.2 Hz, 1H), 6.52 (br s, 2H).

Preparative Method: from ***Propargylmagnesium Bromide*** and ***Trimethyl Borate***.[1]

Handling, Storage, and Precautions: allenylboronic acid can be stored at -20 °C under argon. In air, it catches fire within several minutes. It should only be used in a fume hood.

Allenylboronic Acid.[1]

Treatment of propargylmagnesium bromide with trimethyl borate followed by acidic workup gives, after recrystallization from hexane-ether, a single crystalline boronic acid in 40-60% yield (eq 1).[3] As far as can be described, a single compound results from this preparation.

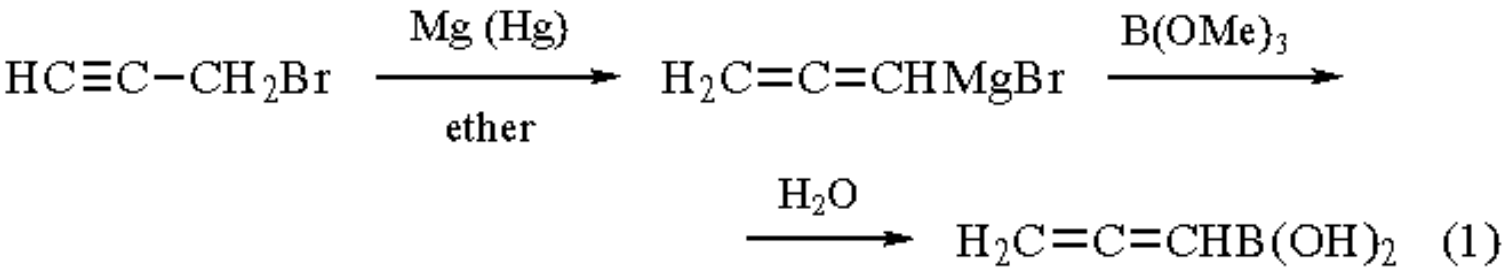

Allenylboronic acid is an ambident nucleophile and its reactions with carbonyl compounds can be envisioned to occur either at the α or γ position. Treatment of cyclohexanecarbaldehyde with allenylboronic acid in toluene containing 4 equiv. of pentanol and molecular sieves produces exclusively the homopropargylic alcohol (**1**) in 40% yield. This result suggests that the reaction proceeds through the cyclic transition state (**2**).

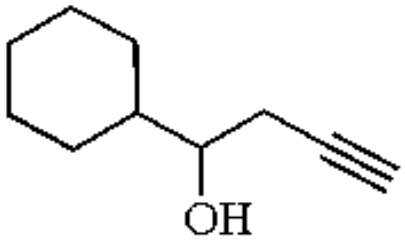

(1)

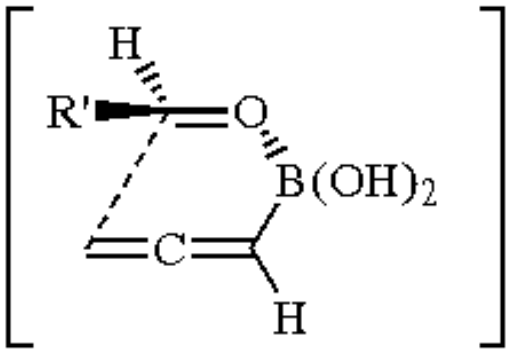

(2)

Chiral Allenylboronic Esters.[1]

Condensations of aldehydes with chiral allenylboronic esters provide β-alkynic alcohols with an exceptionally high degree of enantioselectivity (eq 2). The reagents prepared using bulky tartrate esters like 2,4-dimethyl-3-pentyl as the chiral auxiliary are more enantioselective than reagents prepared from ethyl or isopropyl esters of tartaric acid. These results have been rationalized by the transition state shown in structure (**4**), in which the ester alkoxy group exerts a screening influence on the prochiral carbonyl compound such that R´ is positioned as far away from CO_2R as possible.

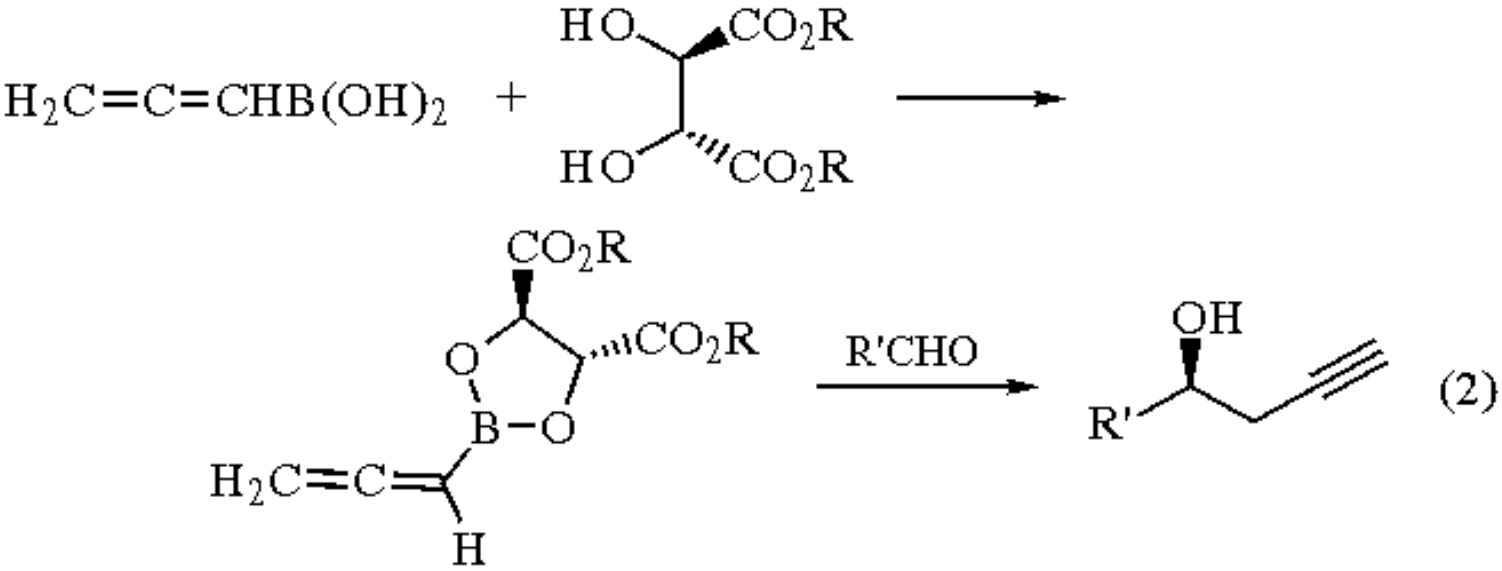

(3)

R′ = cyclohexyl	R = Et	91% ee
	i-Pr	92% ee
	2,4-dimethyl-3-pentyl	98% ee

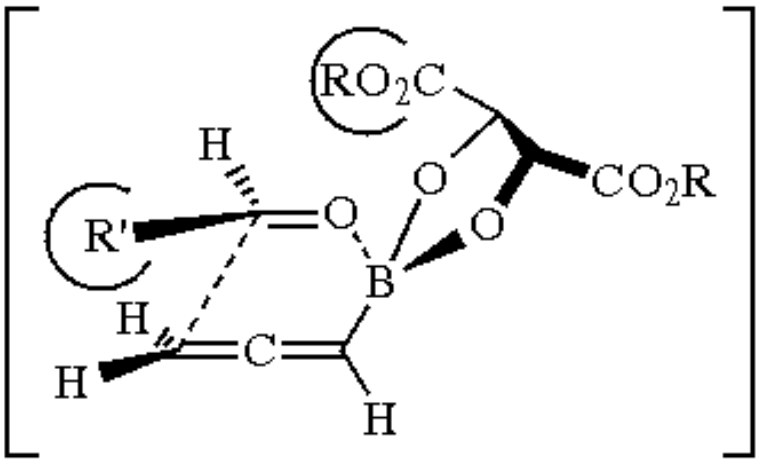

(4)

Condensation with aromatic aldehydes appears to be considerably less efficient than the reaction with saturated aldehydes. In addition, only low yields (<50%) of the homopropargylic alcohol are obtained by the reaction with a variety of unsaturated aldehydes with this reagent, indicating that the use of saturated aldehyde is crucial to the success of the asymmetric propargylation reaction. Additional results are summarized in Table 1. This method has been applied to the synthesis of (-)-ipsenol, as summarized in eq 3.[1b,4]

Table 1 Asymmetric Condensation of Allenyl Reagents (**3**) (R = 2,4-dimethyl-3-pentyl)

Aldehyde (equiv.)	Yield (%)	% ee
Hexanal (1.5)	81	94
Hexanal (5.0)	72	97
Cyclohexanecarbaldehyde (1.5)	88	98
Cyclohexanecarbaldehyde (3.0)	89	>99
Isovaleraldehyde (1.5)	78	99
Isovaleraldehyde (3.0)	74	>99
(*S*)-Citronellal (1.5)	74	92
(*S*)-Citronellal (5.0)	90	99
(*R*)-Citronellal (1.5)	67	98

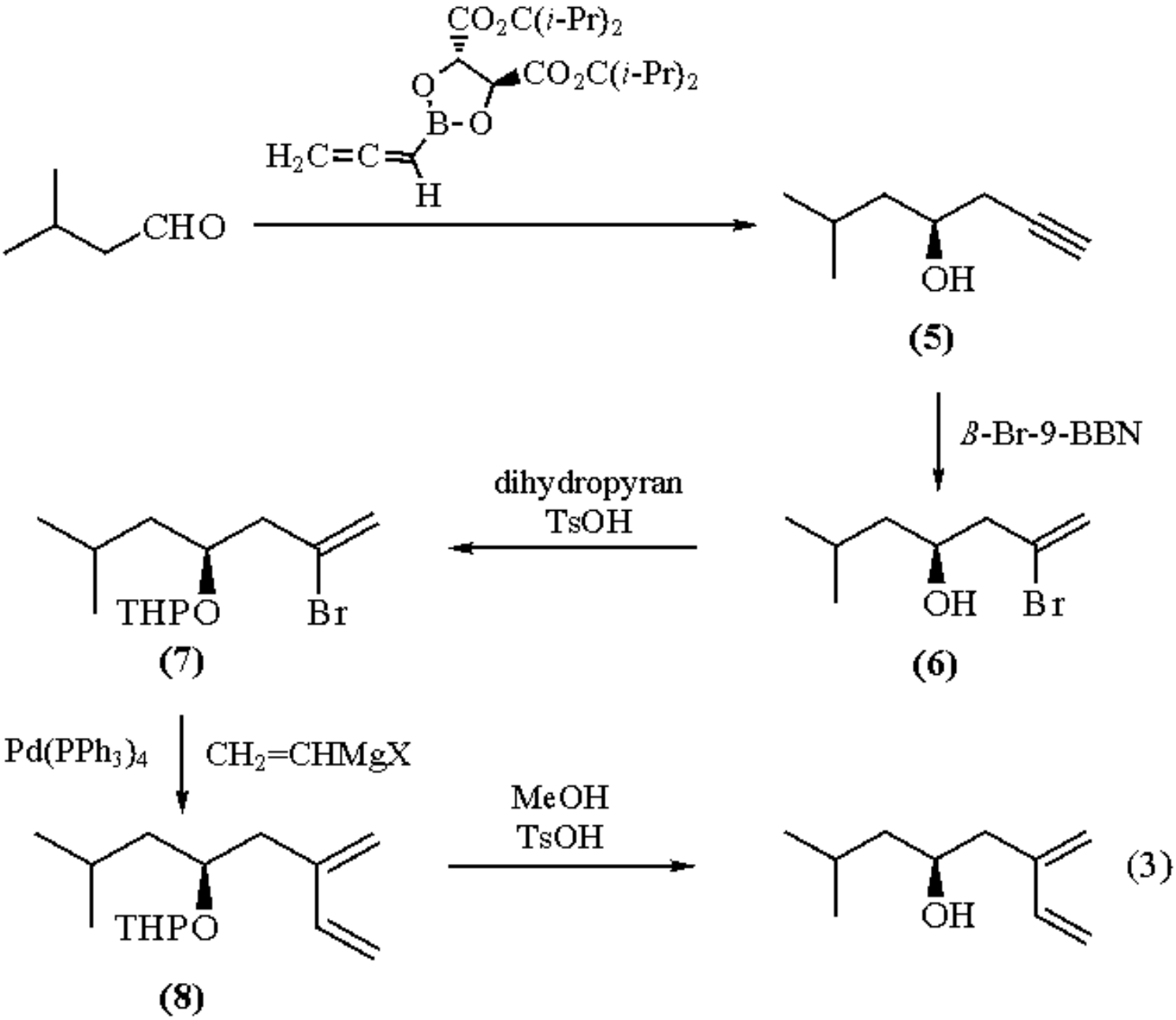

1,3-Asymmetric Induction.[2]

The reaction of allenylboronic acid with carbonyl compounds is slow relative to the reaction of allenylboronic esters.[1] However, the reaction of allenylboronic acid (1.2 equiv.) with β-hydroxy ketones in anhydrous ether at rt in the presence of molecular sieves (5Å for 20 h), followed by treatment with basic ***Hydrogen Peroxide***, yields the *threo* diol (**10**) with excellent levels of 1,3-asymmetric induction (>99%, eq 4). Additional results are summarized in eqs 5-7. The yields in all cases are >90%. The reaction of propargylmagnesium bromide with (**9**) in ether affords a mixture of the *threo* and *erythro* diols, in agreement with related nonselective processes.[5]

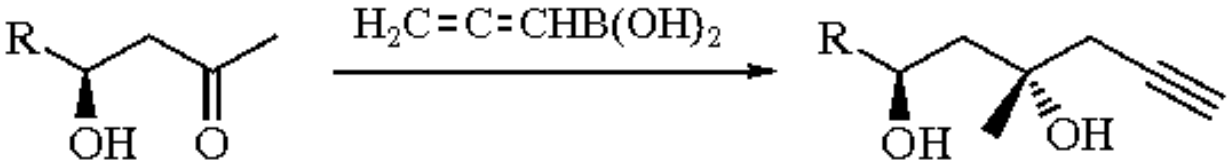

(4)

(9) **(10)**

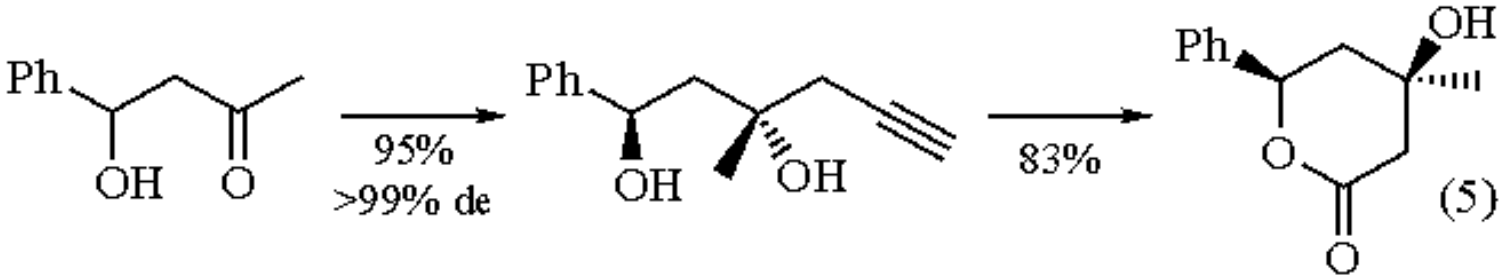

(5)

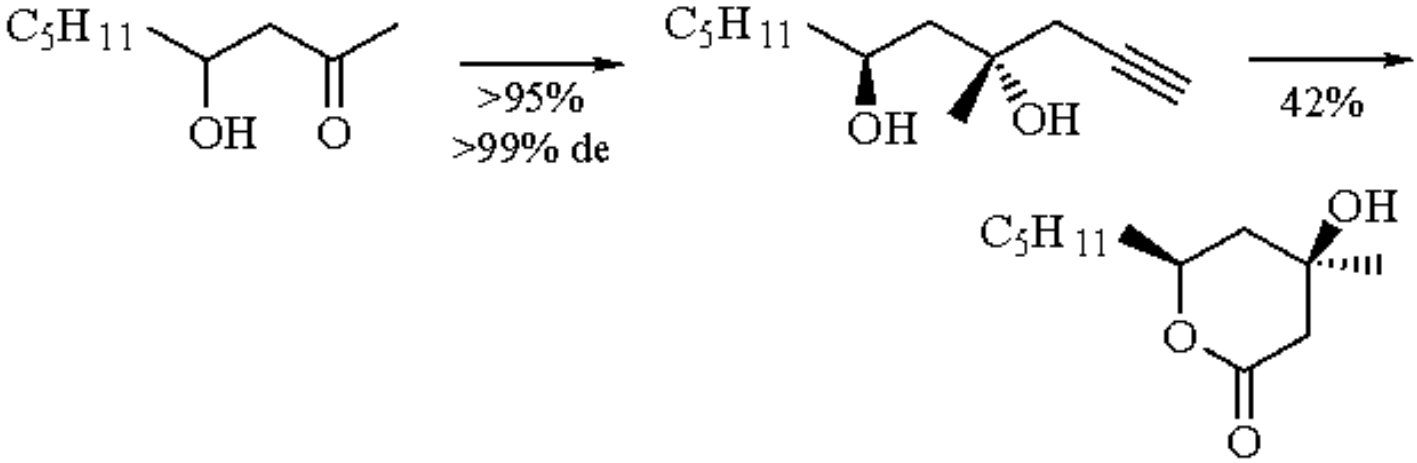

(6)

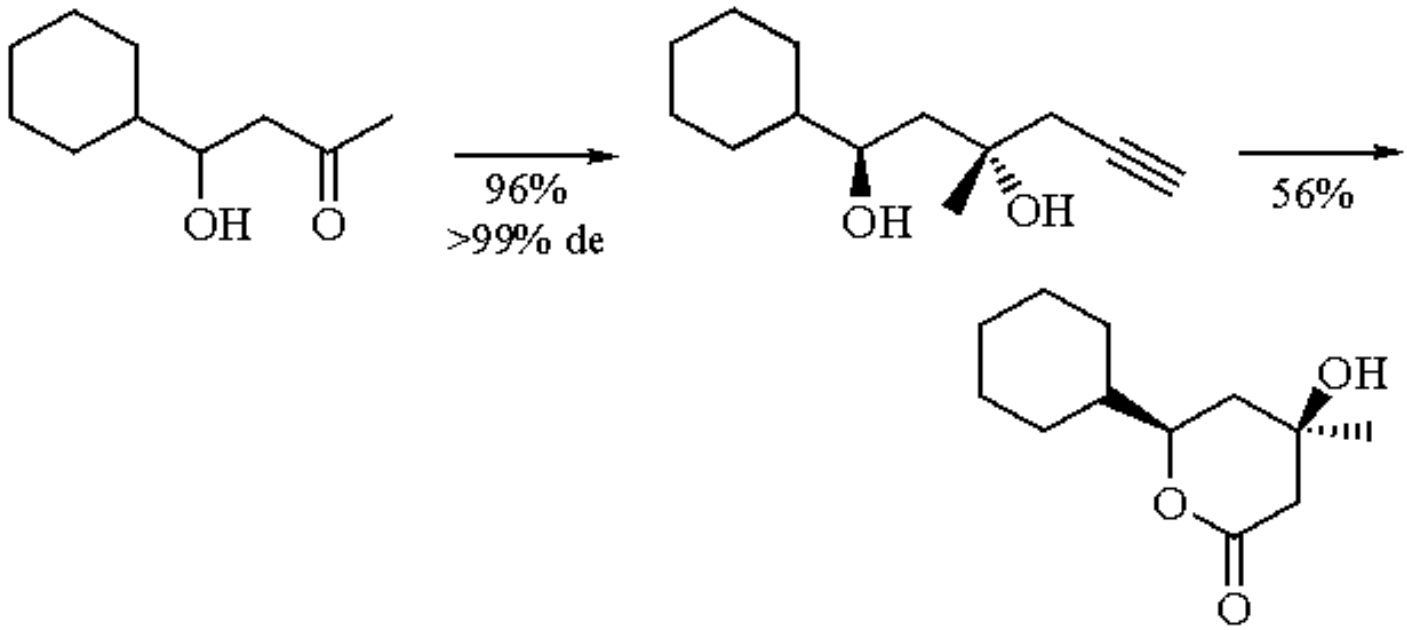

(7)

The very high levels of stereoselectivity observed in these reactions strongly suggest the existence of the covalently bonded organometallic (**11**) as a reactive intermediate (eq 8). Indeed, treatment of a mixture of cyclohexanone and *s*-phenethyl

alcohol with allenylboronic acid gave none of the expected homopropargylic alcohol under the above reaction conditions. Furthermore, treatment of a mixture of the ketone (**9**; R = cyclohexyl) and 2-hexanone with allenylboronic acid produced the diol (**10**) as a sole product.

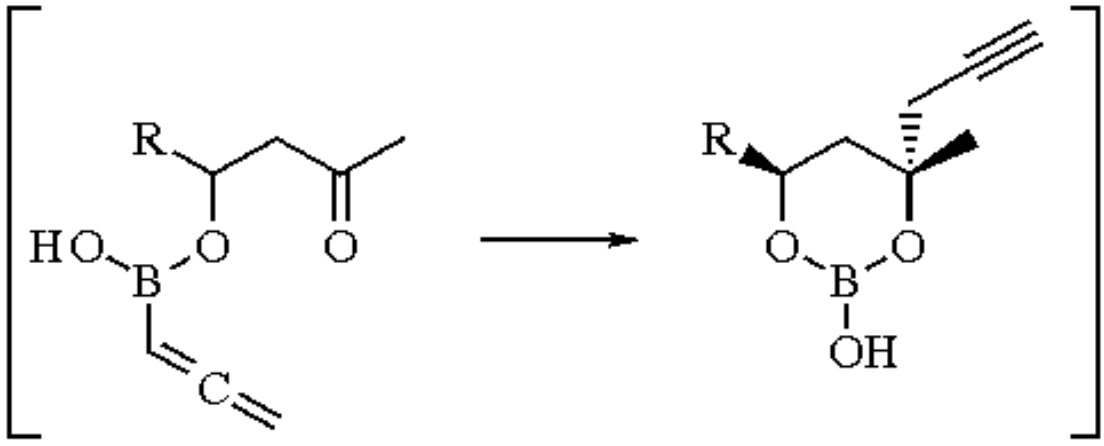

(8)

(11)

Treatment of *threo* diols (**10**) with ***Ruthenium(III) Chloride-Sodium Periodate***[6] gave the corresponding lactones in excellent yield (eqs 5-7).

The use of this method for the preparation of a diastereomer of the β-hydroxy-δ-lactone substituent of the HMG CoA reductase inhibitor mevinolin[7,8] is summarized in eq 9. Unfortunately, however, the product has the (4*S*,6*R*) configuration rather than the most active (4*R*,6*R*) configuration.[7]

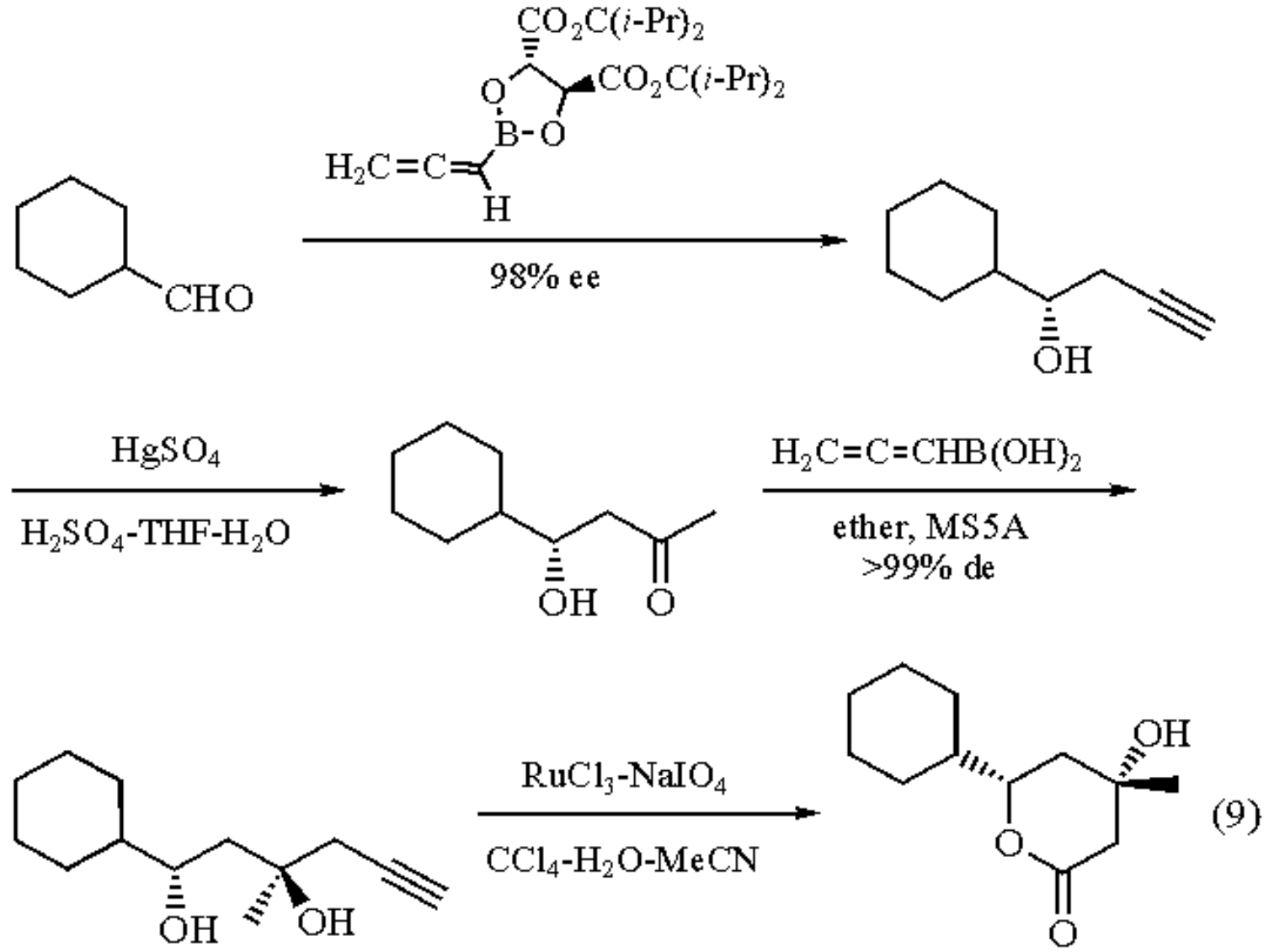

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Allenyl Chloromethyl Sulfone

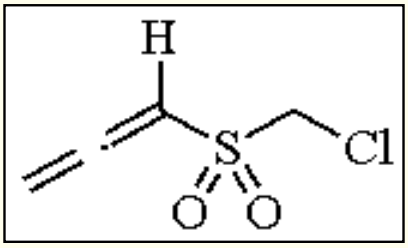

[126696-78-4] · $C_4H_5ClO_2S$ · Allenyl Chloromethyl Sulfone · (MW 152.60)

(dienophile whose Diels-Alder adducts give 1,3-dienes with base, thus allowing two-step cyclohomologation of dienes[1])

Physical Data: mp 39-39.5 °C.

Solubility: sol common organic solvents.

Form Supplied in: colorless solid; not commercially available.

Preparative Methods: the reagent is prepared by addition of chloromethylsulfenyl chloride, $ClCH_2SCl$, to ***Propargyl Alcohol*** to give *S*-chloromethylpropargyl sulfenate, $ClCH_2SOCH_2C$&tbond;CH, which via 2,3-sigmatropic rearrangement gives allenyl chloromethyl sulfoxide, $ClCH_2SOCH{=}C{=}CH_2$, which eventually, on oxidation, gives the title reagent (47%).[1]

Handling, Storage, and Precautions: potential alkylating agent; use in fume hood.

Cycloadditions.

Allenyl chloromethyl sulfone is a potent dienophile whose Diels-Alder adducts give 1,3-dienes with bases via the Ramberg-Bäcklund rearrangement, thus allowing two-step cyclohomologation of dienes. Other examples of this class of reagents include chloromethyl tetradeca-1,2-dienyl sulfone [$Me(CH_2)_{10}CH{=}C{=}CHSO_2CH_2Cl$] and chloromethyl 3-methylbuta-1,2-dienyl sulfone [$Me_2C{=}C{=}CHSO_2CH_2Cl$]. As shown in eq 1, allenyl chloromethyl sulfone functions as a synthetic equivalent of 1,2,3-butatriene in Diels-Alder reactions. The synthetic sequence can be used iteratively as shown in eq 2.

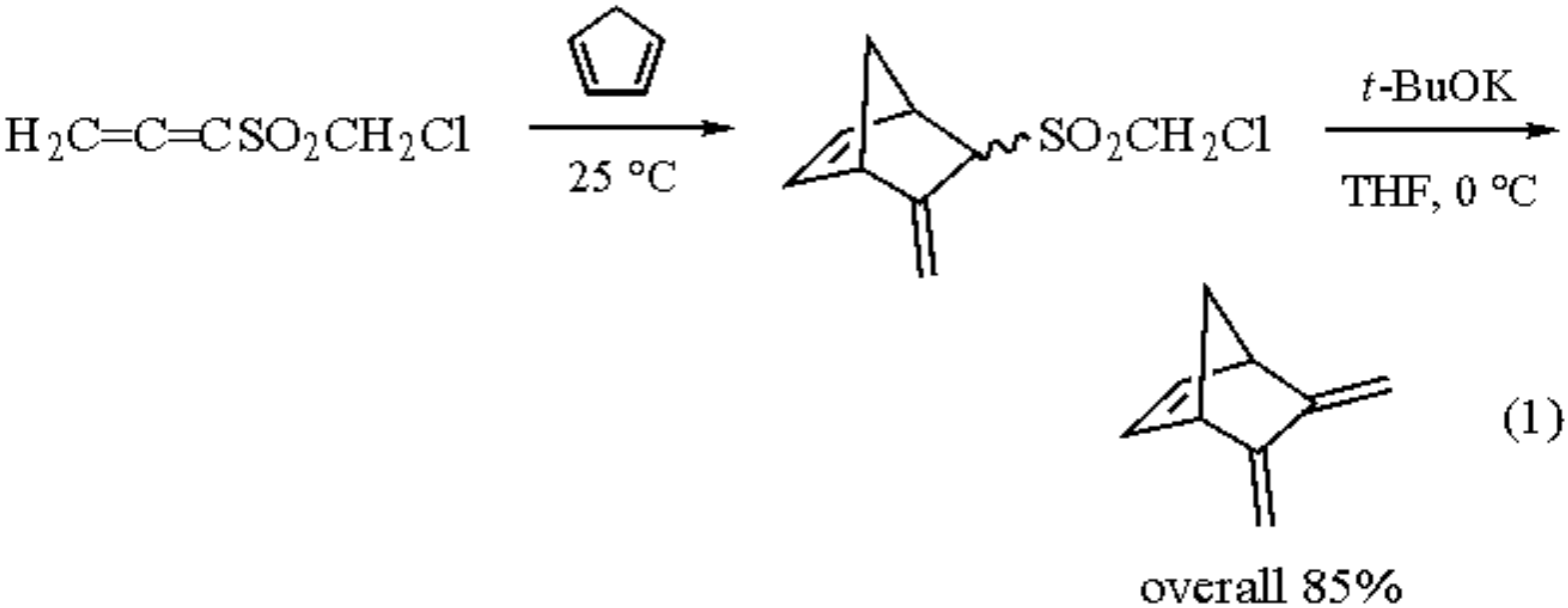

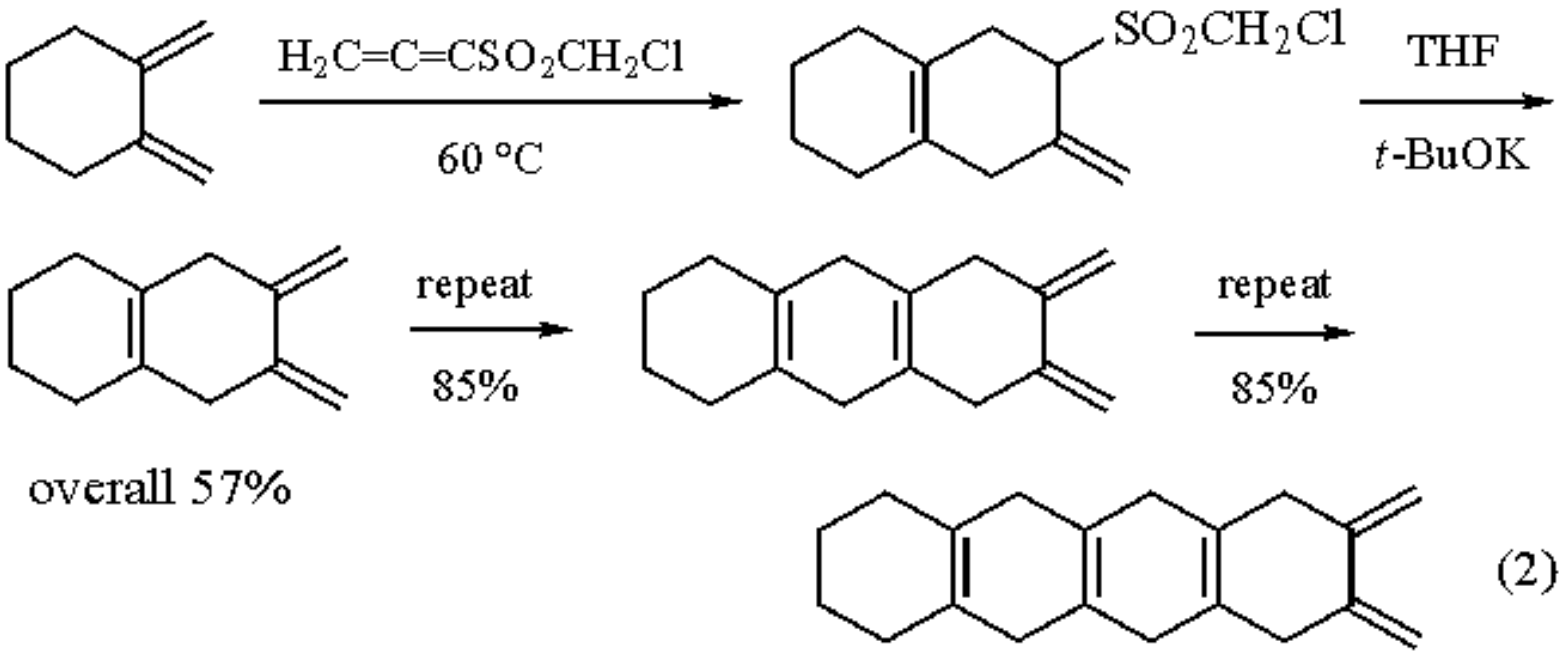

It is notable that chloromethylsulfenyl chloride, used in the synthesis of the title reagent (as well as other halomethylsulfenyl bromides), is a versatile reagent for the synthesis of conjugated polyenes, enones, and 1,3-oxathiole 1,1-dioxides.[2]

---

1. Block, E.; Putman, D. *JACS* **1990**, *112*, 4072.
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Allenyllithium

$CH_2=C=CHLi$

[51760-92-0] · C_3H_3Li · Allenyllithium · (MW 45.99)

(allows the preparation of functionalized monosubstituted allenes[1-3] and conjugated allenic ketones;[4] adds regioselectively to vinyl epoxides[5,6])

Physical Data: ^{13}C NMR solution data in THF[7] have been reported. Allenyllithium solutions show a strong IR absorption[8] at 1885 cm^{-1}.

Solubility: at -60 °C, allenyllithium is slightly sol THF-hexane (1:1) but sol ether-THF.[9]

Form Supplied in: prepared in situ and used directly.

Preparative Methods: in situ under nitrogen by reaction of ***n-Butyllithium*** in hexane with ***Allene*** in THF at -65 °C for 10 min,[8-10] or from ***Bromoallene*** by metal-halogen exchange.[10]

Handling, Storage, and Precautions: solutions are unstable and should be kept below -60 °C.[3b]

This reagent adds to a variety of electrophiles to give allenic and/or alkynic compounds depending on both the substrate and the solvent used.

Addition to Halides.

In THF solution, allenyllithium reacts readily with alkyl halides[10] at low temperature to afford mainly monosubstituted allenes along with some alkynic compounds (easily removed by $AgNO_3$ treatment). Addition of 1 equiv. of ***Hexamethylphosphoric Triamide*** suppresses the formation of alkynes.[1,11] Alkylation with functionalized halides has been studied.[2,3] Addition to 1-iodo-2-trimethylsilylethane leads to β-allenylsilane in good yield (eq 1).[2] γ-Chloroallene is easily accessible by alkylation with 1-bromo-3-chloropropane (eq 2).[3]

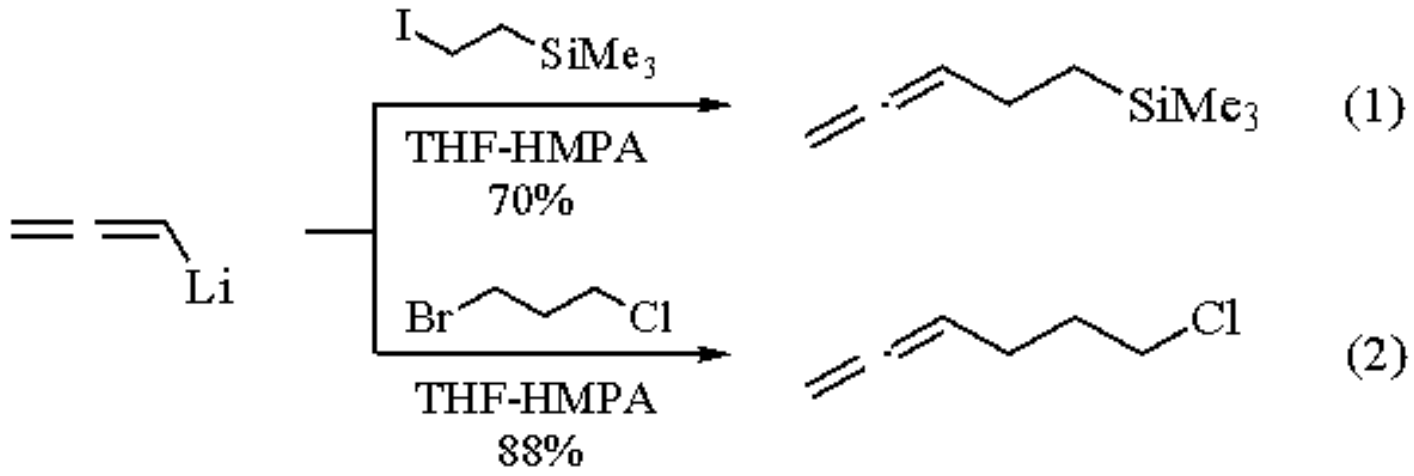

Condensation of the reagent with ***Chlorotrimethylsilane*** leads to a mixture of silylated allene and alkyne (eq 3).[8,12]

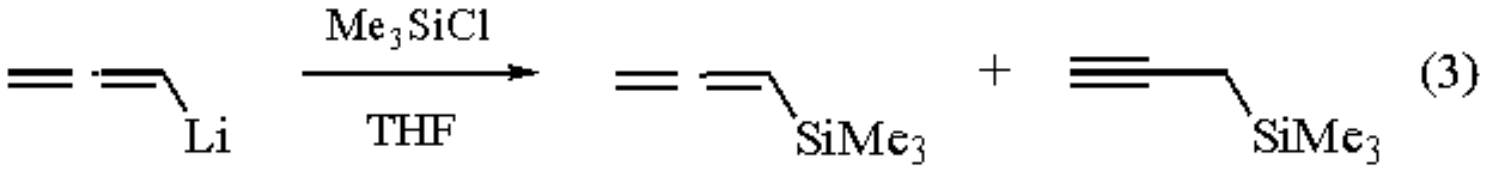

Addition to Carbonyl Compounds.

Cyclopentanone reacts with allenyllithium to afford a 1:1 mixture of α-allenic and β-alkynic alcohols (eq 4).[13] On the other hand, benzophenone gives exclusively homopropargyl alcohol (eq 5).[8] Pure allenic acid is obtained by addition to carbon dioxide (eq 6).[14]

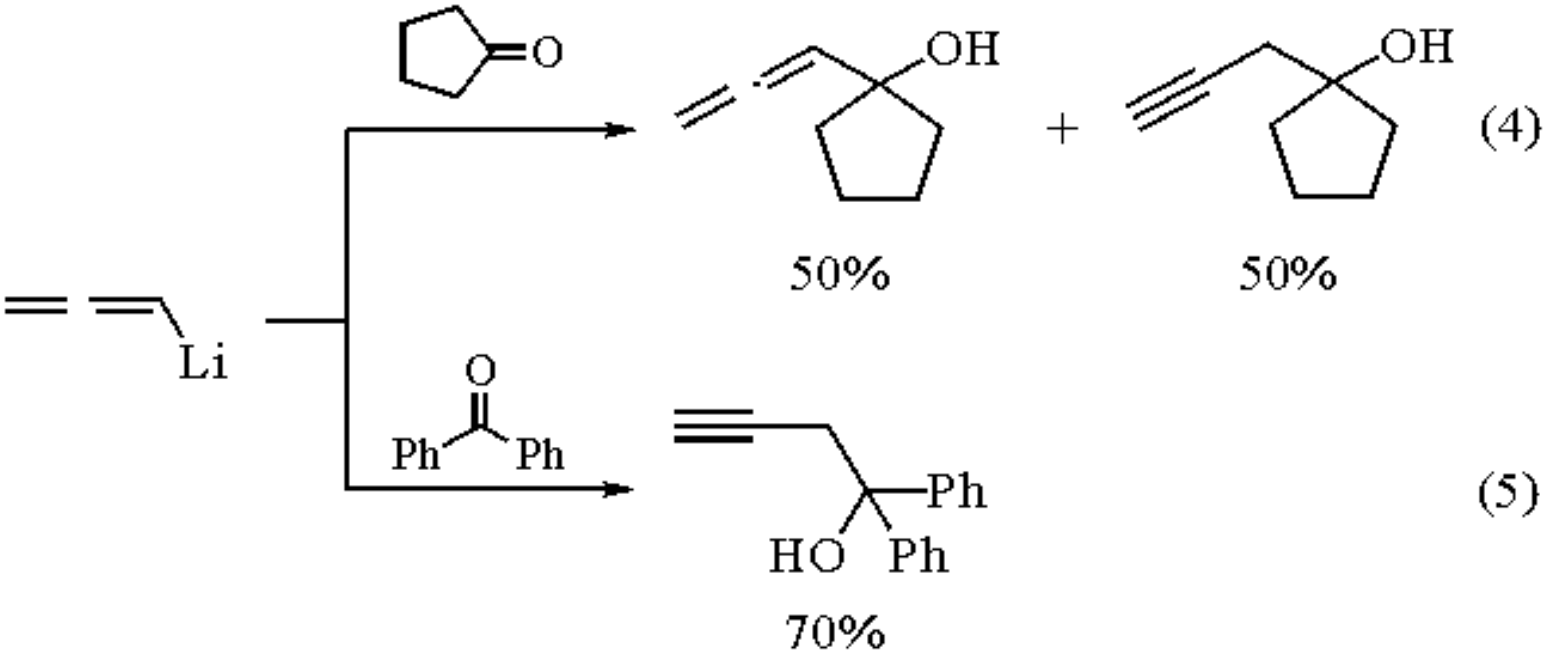

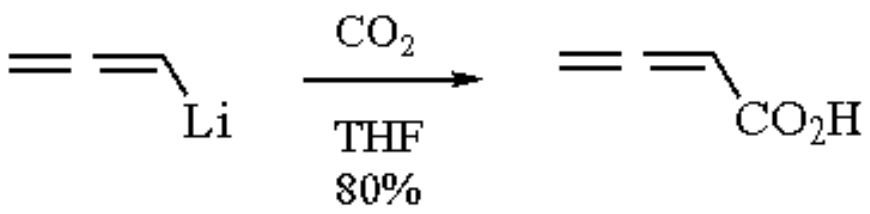

(6)

Addition to Epoxides.

Ethylene Oxide reacts with allenyllithium to afford an equal mixture of β-allenic and γ-alkynic alcohols (eq 7).[15] In the presence of HMPA, ***1,3-Butadiene Monoxide*** reacts with allenyllithium to give β-allenic α´-alkenic alcohols (eq 8).[5] On the other hand, cyclic vinyl epoxides suffer ring opening by means of the S_N2' mechanism in the presence of CuBr.Me_2S (see ***Copper(I) Bromide***) (eq 9).

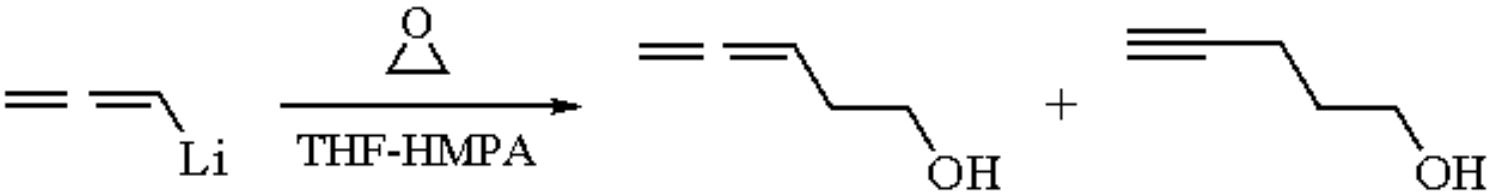

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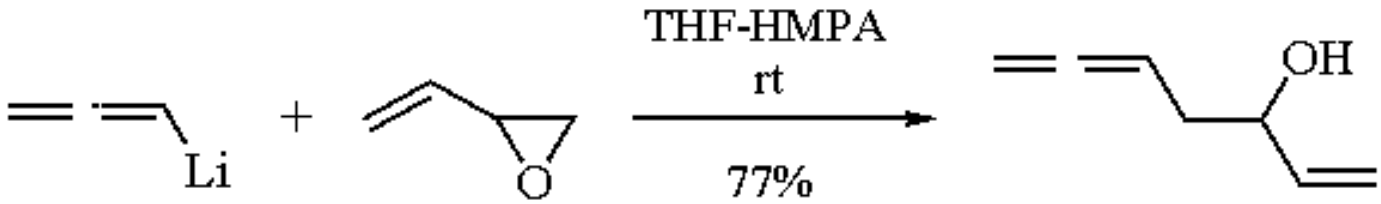

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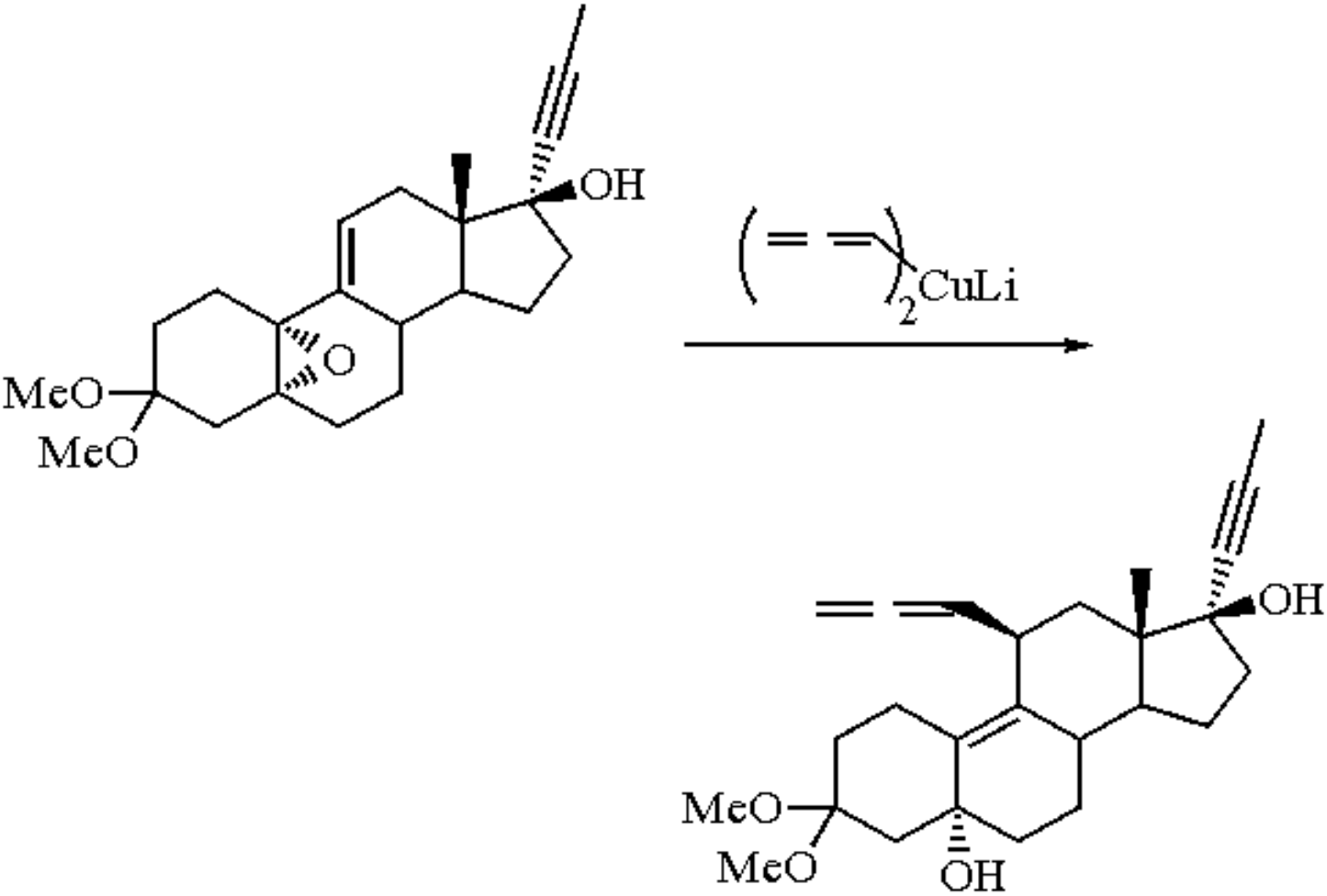

(9)

Addition to Amides.

Reaction with *N*,*N*-dimethylamides at -78 °C affords pure conjugated allenic ketones (eq 10).[4]

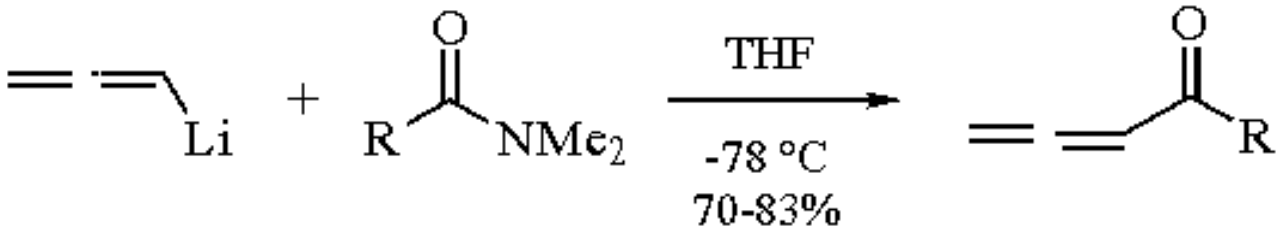

(10)

Substituted Allenyllithiums.

Numerous substituted allenyllithium reagents have been prepared.[3b,12] Methylacetylenes with diverse substituents can be metalated at the methyl group to produce 1-substituted allenyllithiums (**1**) (eq 11), e.g. R = Me,[16] *n*-Pr,[17] *i*-Pr,[18] *n*-Bu,[18] *t*-Bu,[18] Et_2N,[19] PhS,[20] R_3Si.[21] Metalation also works well on propargyl ethers,[22] sulfides,[22] selenides,[23] and amines[22] of the type R-C&tbond;C-CH_2X. In addition, most mono-, di-, and trisubstituted allenes can be metalated.[13] An informative study of regiochemistry in allenyllithium reactions has been carried out using 3,3-dimethylallenyllithium.[24]

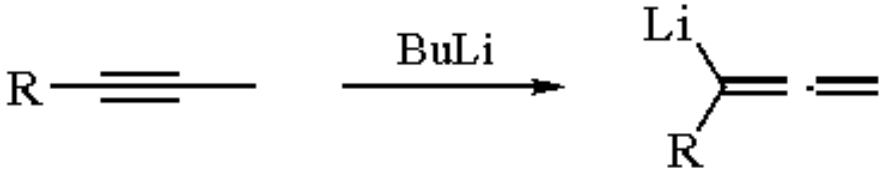

(11)

(1)

Related Reagents.

Allenylboronic Acid; ***1,3-Dilithiopropyne***; ***3-Lithio-1-triisopropylsilyl-1-propyne***; ***1-Methoxyallenyllithium***; ***Propargylmagnesium Bromide***.

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Allylamine

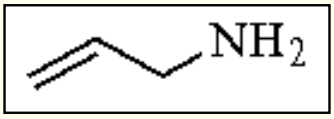

[107-11-9] · C_3H_7N · Allylamine · (MW 57.11)

(used in synthesis of secondary or tertiary allylamines and -amides and heterocyclic compounds[1])

Alternate Name: 2-propen-1-amine.

Physical Data: bp 56.6 °C/756 mmHg; *d* 0.762 g cm^{-3}; mp -88 °C; fp -28 °C;*n* 20D 1.4205; dipole moment 1.31 D (benzene; 25 °C); pK_a 9.49 (H_2O; 25 °C).

Solubility: miscible with water, alcohol, ether, chloroform.

Form Supplied in: colorless liquid, commercially available.

Handling, Storage, and Precautions: corrosive. Highly toxic. Lachrymator. Use only in a chemical fume hood. Use chemical resistant gloves, safety goggles. Do not breathe vapor. Avoid contact with eyes, skin, and clothing. Wash thoroughly after handling. Keep tightly closed. Store in a cool dry place. Extremely flammable.

Allylamine acts as a typical amine towards acylating and alkylating agents and in the formation of imines with aldehydes and ketones. The double bond is also unremarkable in its chemical behavior.

N-Acylation.

Acylations of the amino function can be performed with the usual reagents, such as acid anhydrides,[2] acid chlorides,[3] enol esters,[4] lactones,[5] and carboxylic acids in the presence of molecular sieves[6] or other activating agents (e.g. eq 1).[7] *N*-Allylcarbamates are obtained upon acylation of allylamine with reagents like ***Benzyl Chloroformate*** or ***Di-t-butyl Dicarbonate*** in the presence of base.[8] Another route to carbamates consists of saturation of an allylamine solution with carbon dioxide and reaction of the ionic carbamate thus obtained with ***Benzyl Chloride*** or dimethyl carbonate (eq 2).[9] Iodolactonization of the ionic carbamates leads to oxazolidinones (eq 3).[10] Diacylations of allylamine to *N*-allylimides are known;[2a] an interesting application is the facile preparation of 1,4-disubstituted piperazine-2,4-diones with iminodiacetic acid derivatives (eq 4).[11]

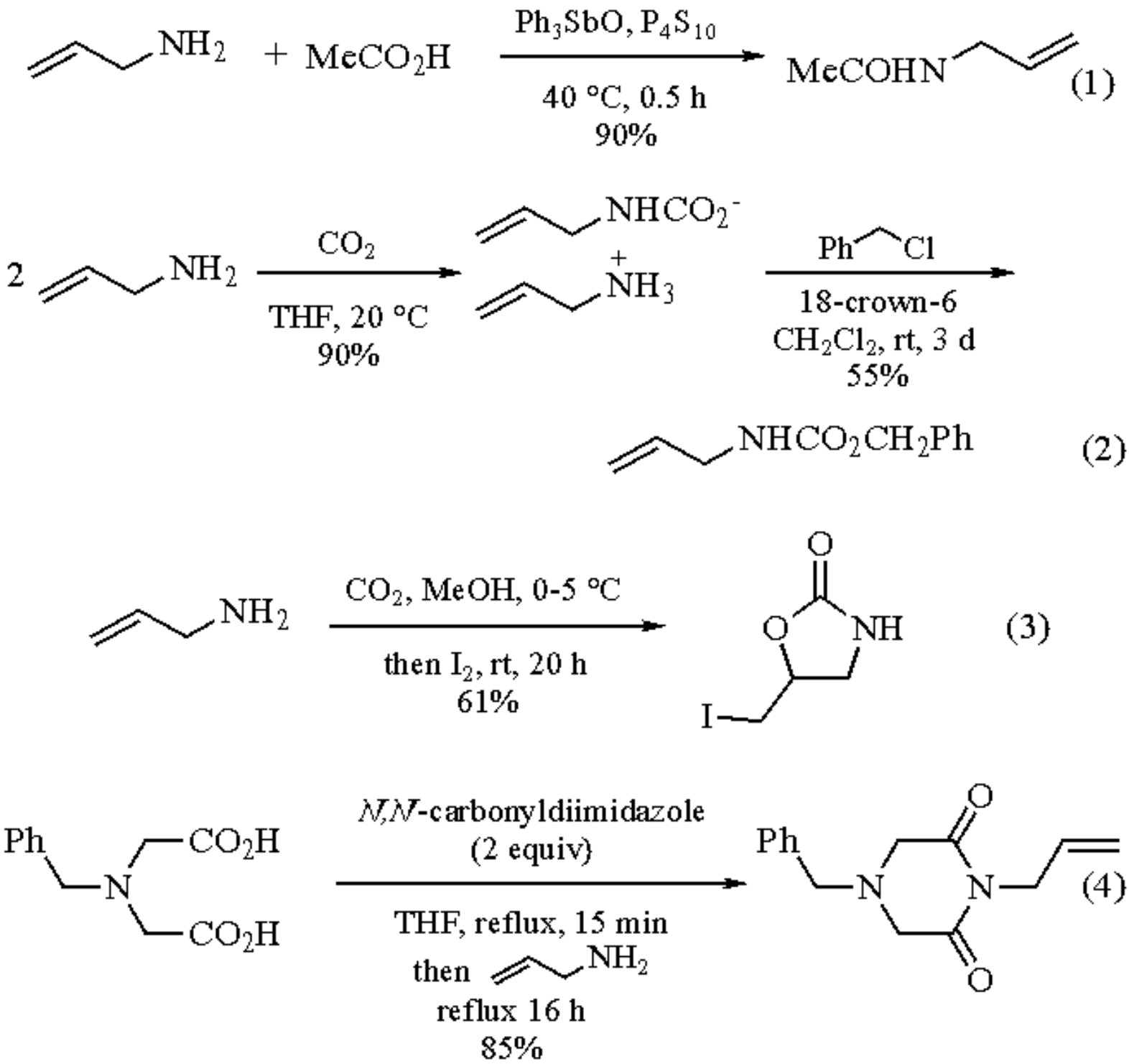

N-Alkylation.

Allylamine can be converted under mild conditions into secondary amines with functionalized alkyl chlorides, bromides, and tosylates.[12] Alkylations through conjugate addition to α,β-unsaturated nitriles[13] and α,β-unsaturated ketones are known (eq 5).[14]

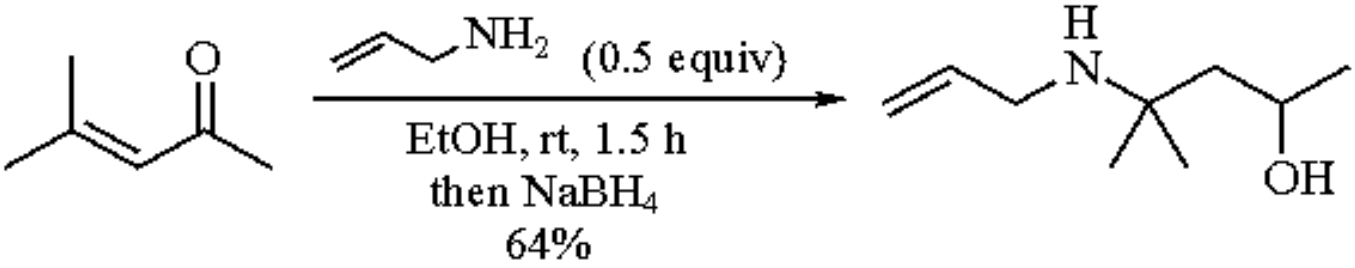

In connection with the search for efficient routes to β-lactam antibiotics, *N*-allylazetidines have been prepared by dialkylation of allylamine. Thus *t*-butyl 2,4-dibromobutyrate led to the azetidine derivative in moderate yield (eq 6).[15] Allylamine attacks the readily available (*R**,*R**)-bromobenzyloxirane (**1**) at the less substituted oxirane carbon and then at the benzylic bromide to give the *trans*-azetidine derivative in reasonable yield (eq 7).[16]

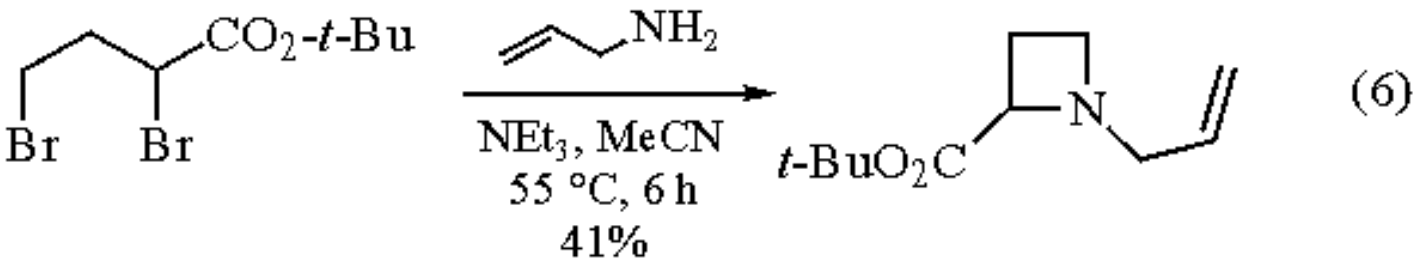

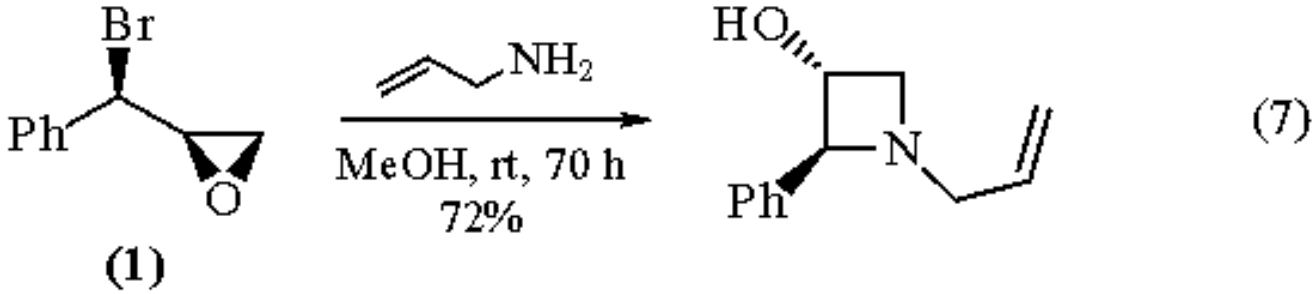

Imine Formation.

Reaction of allylamine with aldehydes[17] (eq 8)[17a] and ketones[18] gives rise to imines. Addition of Lewis acids or molecular sieves may be necessary (eq 9).[18b] Reductive aminations of ketones with allylamine can be performed in the presence of reducing agents like zinc-modified cyanoborohydride (eq 10).[19]

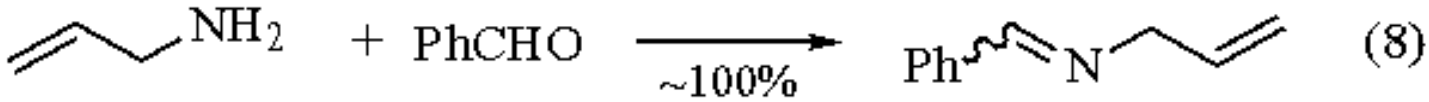

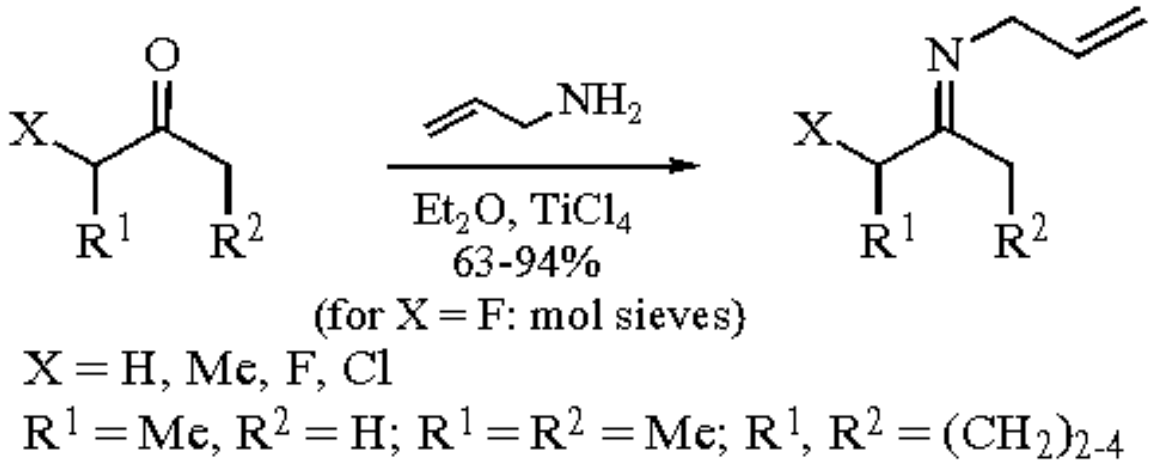

(9)

X = H, Me, F, Cl

R^1 = Me, R^2 = H; R^1 = R^2 = Me; R^1, R^2 = $(CH_2)_{2-4}$

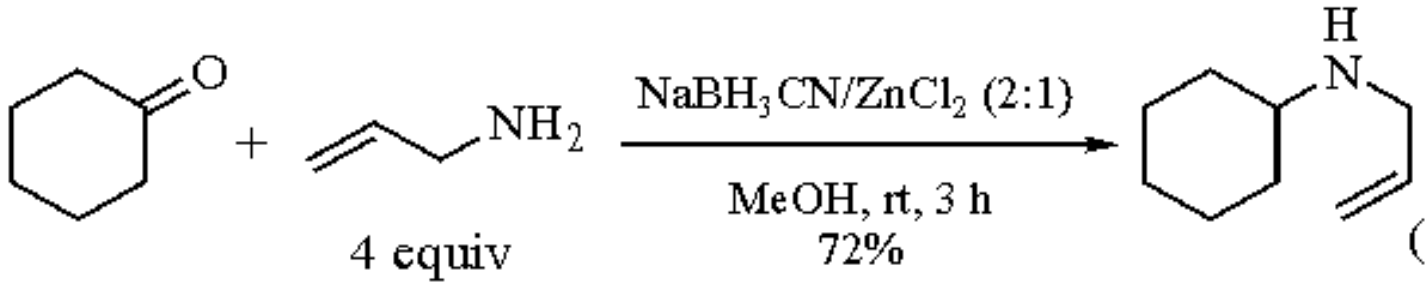

(10)

An important route to β-lactam antibiotics proceeds via condensation of imines with ester enolates to form the β-lactam ring. Allylimines are used in this condensation because the *N*-allyl protecting group from β-lactams can be easily removed by standard methods, thus providing access to β-lactams with a variety of other *N*-substituents. In a highly interesting example of this condensation, the chiral (*S*,*S*)-diazaborolidine (**2**) is used in the asymmetric synthesis of β-lactams from achiral esters and allylimines. Reaction of the (*Z*)-boron enolate, prepared from *S*-*t*-butyl thiopropionate with triethylamine, with *N*-allylimines derived from various aldehydes at -78 °C proceeds with high diastereoselectivity and high enantioselectivity to afford the β-amino acid esters. Treatment of these esters with ***t*-Butylmagnesium Chloride** results in ring closure to the *trans*-substituted β-lactam derivatives (eq 11).[20] In another approach to β-lactams, the allylimines are treated with DBU to afford 2-aza-1,3-dienes which react with acid chlorides to provide the *cis*-substituted β-lactams (eq 12).[21]

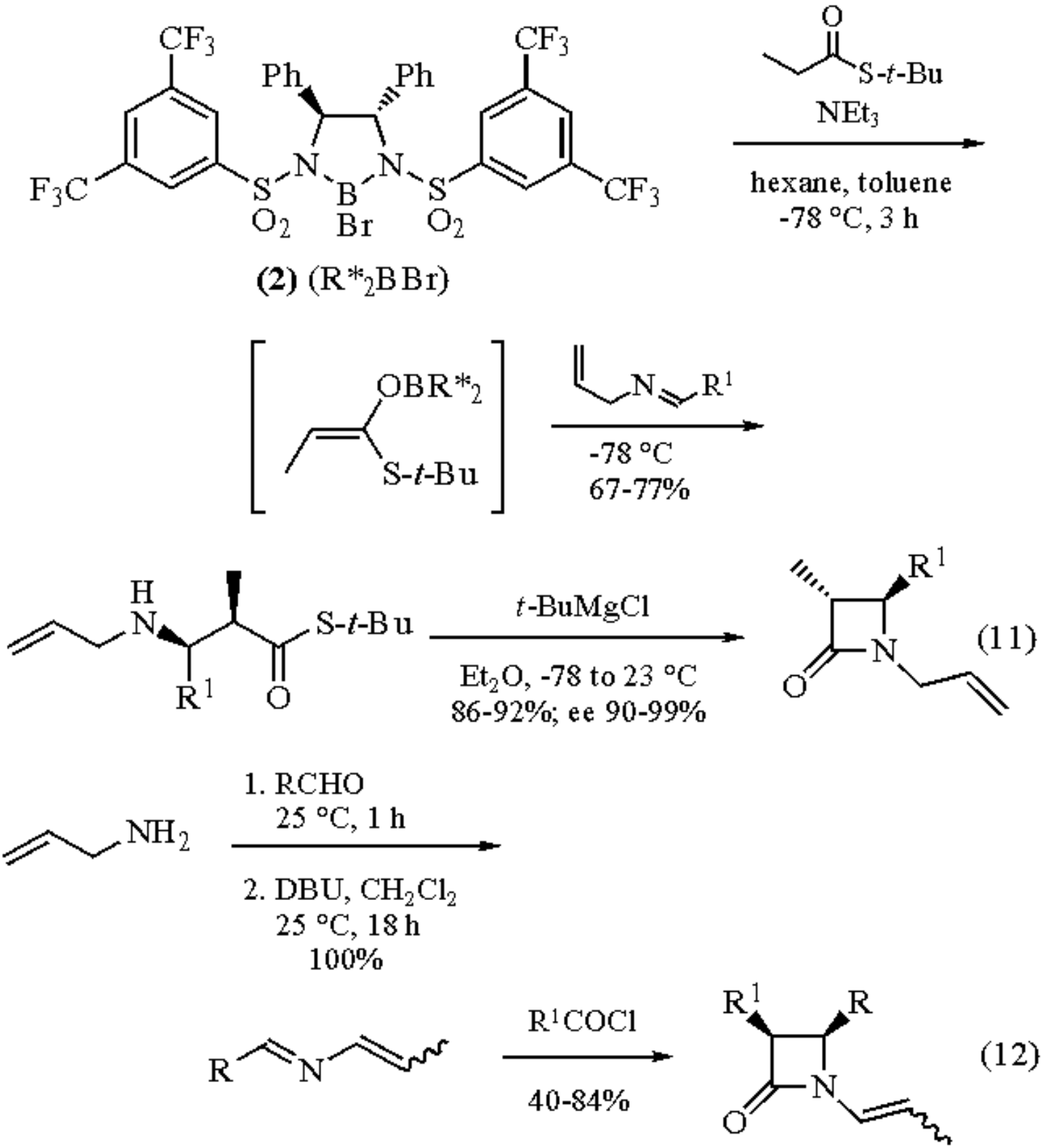

Reactions at the C=C-Bond.

The double bond shows the usual reactions, such as addition of bromine[22] or hydrogen halides,[23] Friedel-Crafts reaction (eq 13),[24] Diels-Alder reaction (eq 14),[25] or Pd-catalyzed cyclopropanation with ***Diazomethane*** (eq 15).[26]

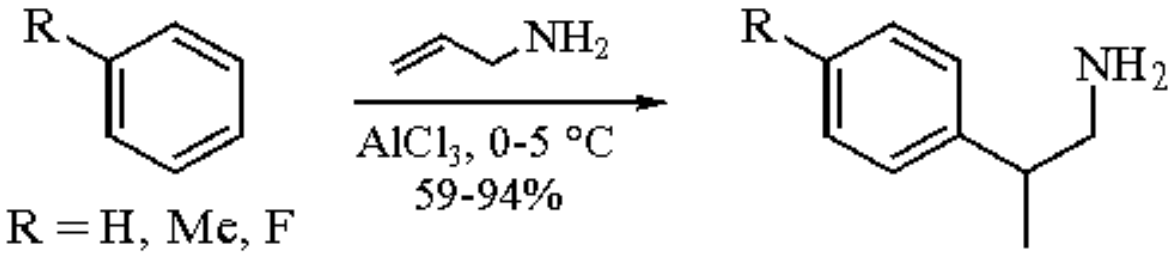

(13)

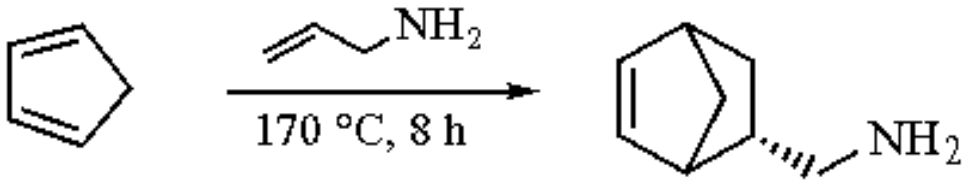

(14)

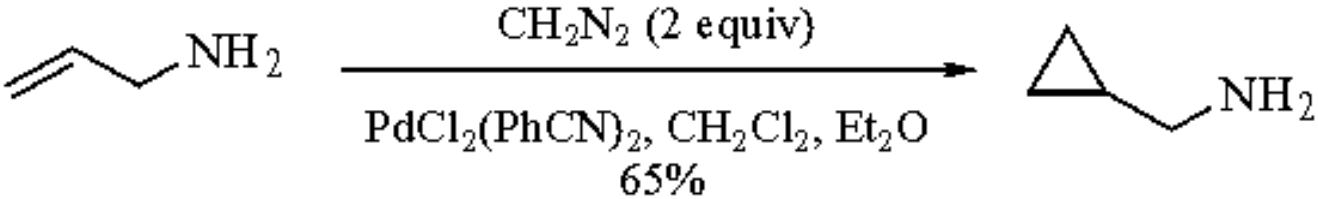

(15)

Related Reagents.

O-Allylhydroxylamine; ***O-Benzylhydroxylamine Hydrochloride***; ***t-Butylamine***.

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University of Amsterdam, The Netherlands

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B-Allyl-9-borabicyclo[3.3.1]nonane

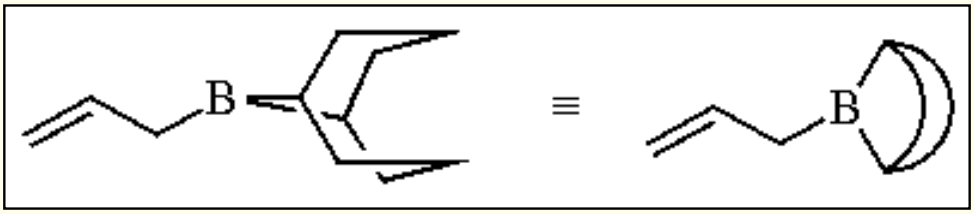

[53317-08-1] · $C_{11}H_{19}B$ · *B*-Allyl-9-borabicyclo[3.3.1]nonane · (MW 162.07)

(allylating reagent for aldehydes, ketones, acid chlorides, amides, and acid anhydrides;[2] reagent for diastereo- and enantioselective allylation of aldimines;[6,8] diastereoselective allylation of acetals[9])

Alternate Name: allyl-9-BBN.

Physical Data: bp 41.5-42 °C/0.05 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: prepared from ***Allyl Bromide*** and *B*-methoxy-9-BBN according to a literature procedure.[1] Crotyl-9-BBN and 2-methallyl-9-BBN are similarly prepared from the corresponding allylic bromides.

Handling, Storage, and Precautions: the neat liquid is highly flammable and must be stored in the absence of air and moisture. Allyl-9-BBN may be kept as a CH_2Cl_2 or THF solution under N_2 atmosphere.[2] Use in a fume hood.

Allylation of Carbonyl Compounds.[2]

The reaction of allyl-9-BBN with carbonyl compounds occurs cleanly with the allyl group undergoing transfer to the carbonyl carbon and the boron group to the carbonyl oxygen. Aldehydes and ketones react in a 1:1 stoichiometry, while acid chlorides, esters, and *N*,*N*-dimethylamides react with 2 equiv of the allylborane, and acid anhydrides utilize 4 equiv. Simple protonolysis of the boronic esters thus formed, either with water or ***Ethanolamine***, affords excellent yields of the corresponding homoallylic alcohols.[2] The allylation of chiral aldehydes with allyl-9-BBN normally produces low diastereoselectivity via nonchelated Cram transition states.[3] The Cram/anti-Cram stereoselectivity in the allylation of (**1**)-(**3**)[3] and (**4**)[4] is 1:1-1.3:1, with only a slight preference for the *syn* diastereomers.

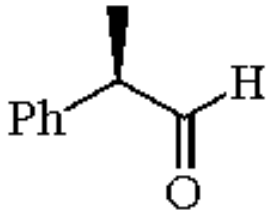

(1)

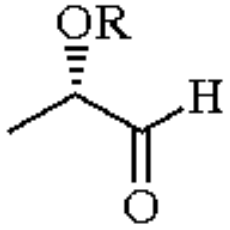

(2)

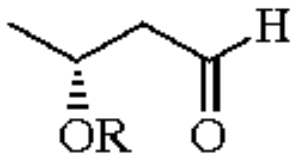

(3)

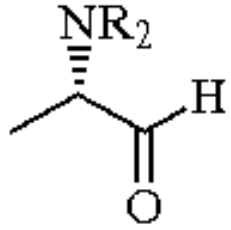

(4)

Allylation of Imines.

In contrast to the reactions with chiral aldehydes, the reactions with certain aldimines are highly or completely *syn* selective (eq 1).[5,6] The aldimine having a chiral center at the α-position of the nitrogen substituent affords the Cram product (*syn* isomer) with high diastereoselectivity upon treatment with allyl-9-BBN (eq 2).[5,6] The chiral α-imino ester, prepared from *n*-butyl glyoxylate and (*S*)-phenethylamine, reacts with allyl-9-BBN to give the allylation product with 92% de in 92% yield, which is hydrogenated to the butyl ester of L-norvaline.[6,7]

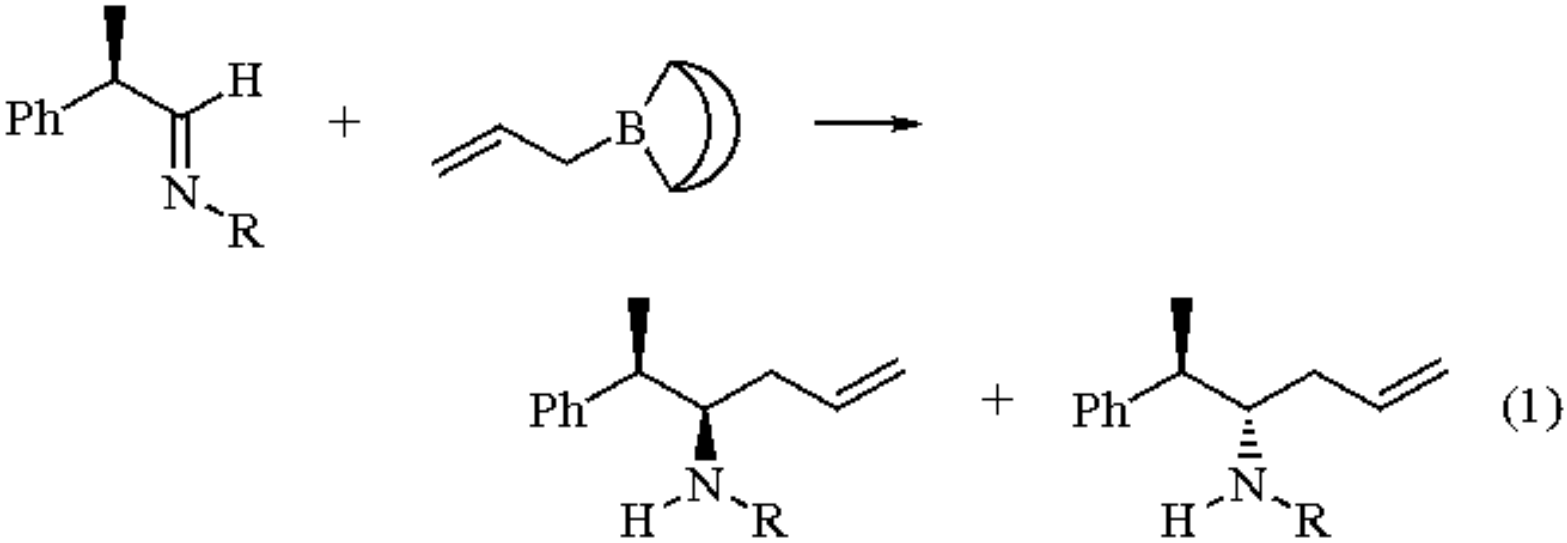

(1)

R = *n*-Pr	96:4
i-Pr	100:0

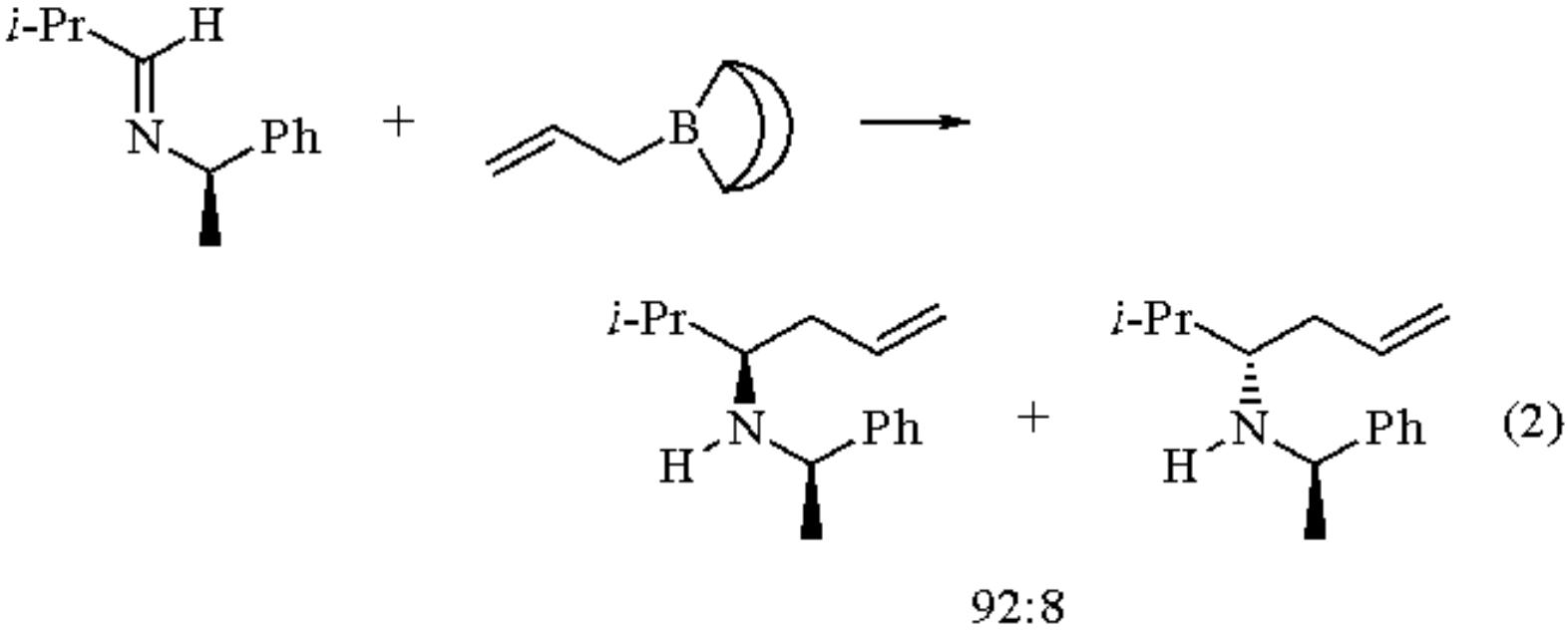

Aldimines derived from (**2**) gave the nonchelation product either exclusively or predominantly, regardless of the substituents at nitrogen (eq 3).[8] On the other hand, the aldimine derived from (**3**) afforded the nonchelation adduct with good diastereoselectivity only when the (*R*)-phenethylamine group was used as an amine (eq 4).[8]

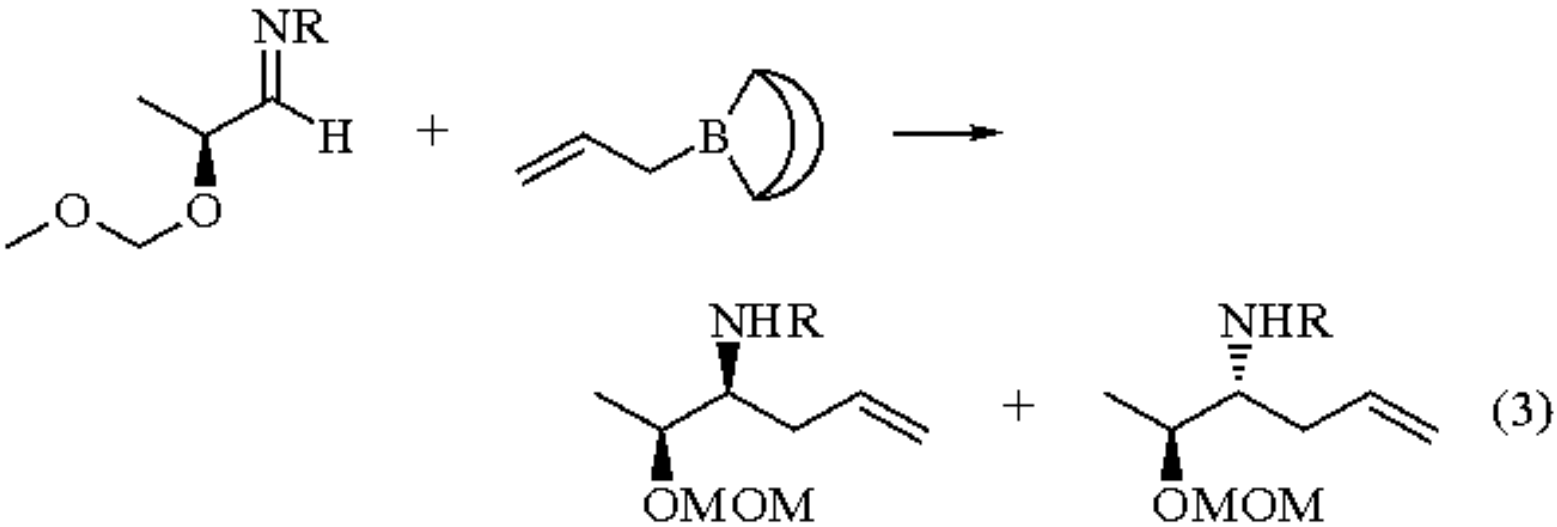

R = (*S*)-CH(Me)Ph	3 : 97
i-Pr	0 : >99
(*R*)-CH(Me)Ph	0 : >99

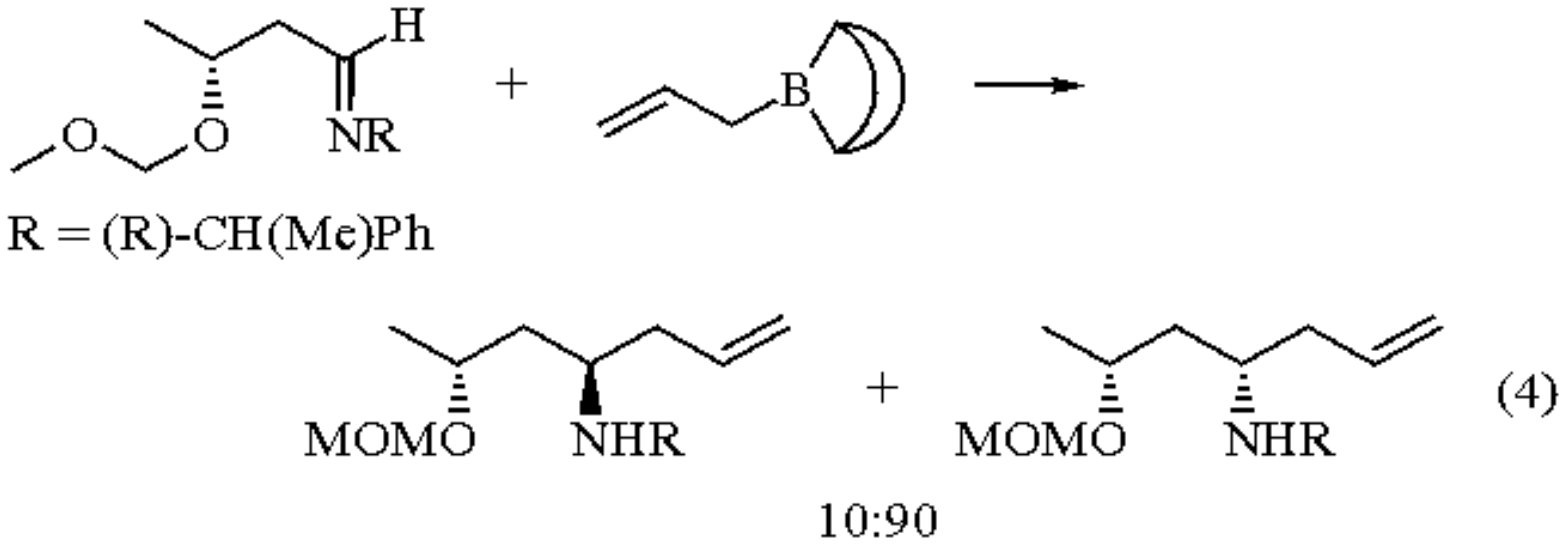

Allylation of Acetals.

Treatment of the chiral steroidal acetal (*S*,*R*,*R*) isomer, prepared from the steroidal aldehyde and (2*R*,4*R*)-(-)-pentanediol, with allyl-9-BBN in the presence of ***Titanium(IV) Chloride*** followed by the usual workup gave the (*S*,*S*) isomer exclusively (eq 5).[9] On the other hand, the reaction of the (*S*,*S*,*S*) acetal isomer, prepared from the steroid aldehyde and (2*S*,4*S*)-(+)-pentanediol, with allyl-9-BBN produced an 88:12 mixture of the (*S*,*S*) and (*S*,*R*) isomers, suggesting that the 1,2-asymmetric induction is primarily controlled by the Cram rule rather than the chiral acetal template.

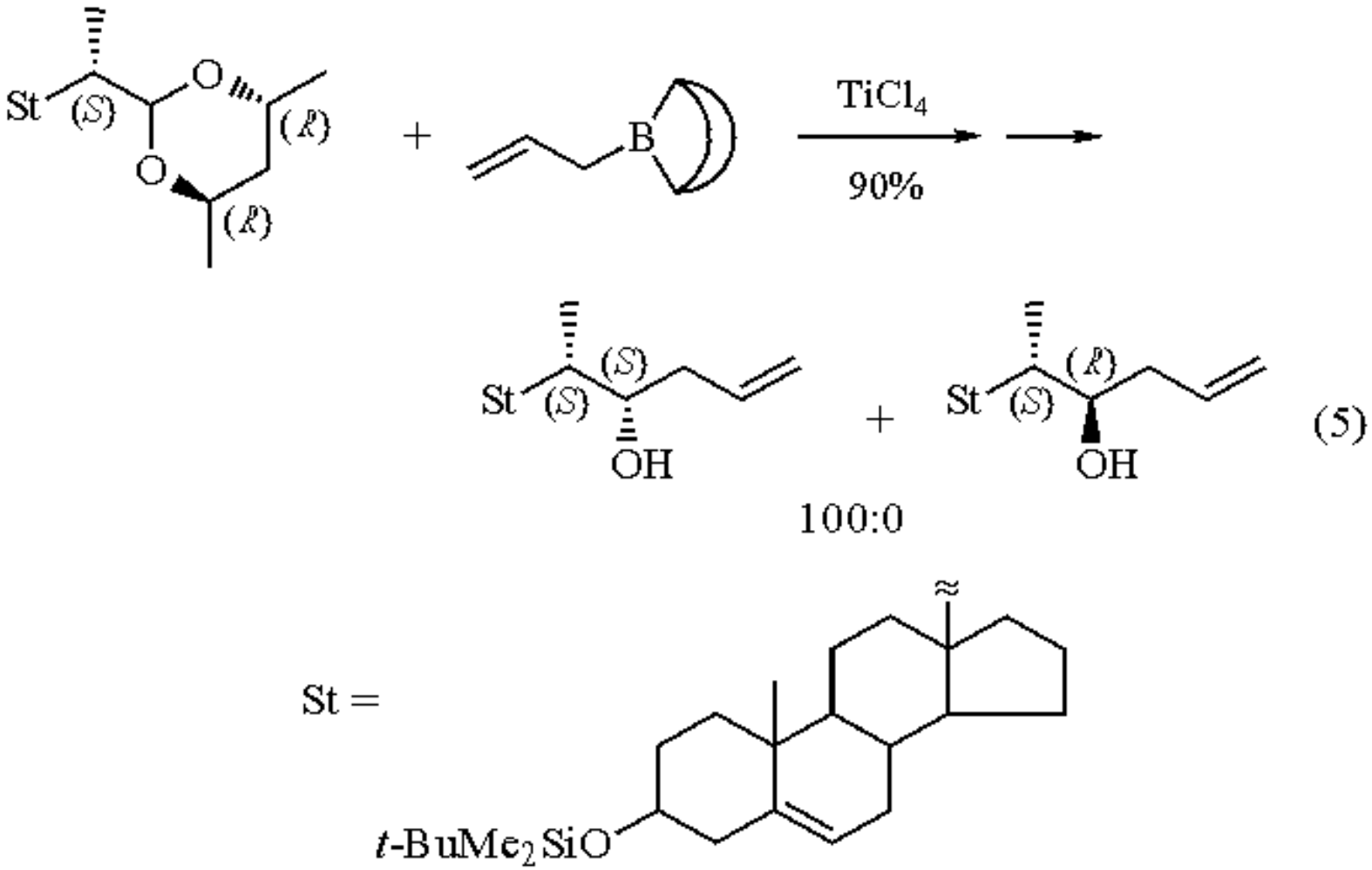

The $TiCl_4$-mediated reaction of the chiral acetal (*S*,*R*,*R*) isomer, prepared from (3*S*)-3-*t*-butyldimethylsiloxybutanol and (2*R*,4*R*)-(-)-pentanediol, with allyl-9-BBN gave the corresponding homoallyl alcohol in 90% yield with predominant formation (90:10) of the chelation product,[10] indicating that the 1,3-asymmetric induction is dictated by chelation rather than the acetal template.

---

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Allyl Bromide

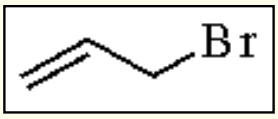

[106-95-6] · C_3H_5Br · Allyl Bromide · (MW 120.99)

(electrophilic allylating agent attacking C, N, O, S, Se, and Te nucleophiles; homoallylic alcohols obtained selectively from aldehydes by various organometallic intermediates; addition reactions provide further reagents of wide applicability)

Physical Data: mp -119.4 °C; bp 71.3 °C; *d* 1.398 g cm^{-3}.

Solubility: miscible with organic solvents; sparingly sol H_2O.

Form Supplied in: yellow to brown liquid.

Purification: wash with water and with aqueous $NaHCO_3$. Dry ($MgSO_4$ or Na_2SO_4) and fractionally distill.

Handling, Storage, and Precautions: highly toxic; cancer suspect agent. Protect from light in brown glass.

Allylating Agent.

Carbon alkylation generally requires nucleophilic carbanions; thus the allylation of PhC&tbond;CH is promoted with powdered ***Potassium Hydroxide*** alone or with ***Tetra-n-butylammonium Bromide*** in dioxane.[1] Dimeric side products (allyl ether, Ph_2C_4) and rearrangement enynes (PhC&tbond;CCH=CHMe; *E/Z*, 3:1) accompany PhC&tbond;$CCH_2CH=CH_2$. Carbanions from acetoacetic esters,[2a,2b] ketones,[2c] malonates (K_2CO_3-Me_2CO or PhH),[3] acetonitrile,[4a] and cyanoacetates[4b] readily undergo allylation (eq 1); the necessary base may be generated electrochemically, as in the use of pyrrolidone anion to bring about allylation of dimethyl 2-(trifluoromethyl)malonate.[5] Perfluoro-2-methyl-2-pentyl carbanion is generated by the addition of F^- (KF or CsF) to $(CF_3)_2CFCF=CFCF_3$; upon allylation (RX; X = Cl, Br, I) the rearranged product $(CF_3)_2C(R)CF_2CF_2CF_3$ results.[6] Mn enolates of dialkyl ketones may be allylated (RBr; THF-sulfolane); thus Pr_2CO gives PrCOCH(R)Et in 98% yield.[7]

$$\text{X-CH}_2\text{-Y} + [\text{X-CH-Y}]^- \xrightarrow{\text{RBr}} \text{X-CHR-Y} \qquad (1)$$

$$\text{X, Y} = \text{R'CO, CO}_2\text{R', CN, H}$$

The homoallylic alcohols $RCH(OH)CH_2CH{=}CH_2$ are formed from the reaction of RCHO and allyl bromide through organometallic intermediates, especially those involving allyl magnesium bromide. Ketones react similarly, but more slowly. The conventional Barbier-Grignard processes have been replaced by a reductive allylation. Thus Al brings about the reaction (i) in the presence of catalytic amounts of $PbBr_2$ in DMF, aq THF, and/or aq MeOH[8a] or (ii) in the presence of $BiCl_3$ in aq THF.[8b] The process may be specific to aldehydes; Pb-Me_3SiCl-Bu_4NBr in DMF promotes allylation of aldehydes without significantly attacking ketones or α-hydroxycarboxylic esters, while esters, lactones, acid anhydrides, and acid chlorides are effectively inert.[9] Correspondingly, homoallylic alcohols are formed from aldehydes and allyl chloride, bromide, or iodide using Zn-$BiCl_3$ or Fe-$BiCl_3$, but ketones, esters, and benzoic acid are unaffected and do not interfere.[10] Fe or Al with $SbCl_3$ in aq DMF behaves similarly.[11] Electrochemical variants are reported in which Bi acts as the reductant towards the aldehyde.[12] Aldehydes and ketones react in the presence of Ph_3Bi to give homoallylic alcohols or their allylic ethers.[13] Zn alone in DMF gives 86% yields with allyl bromide and MeCH=CHCHO;[14a] Cd in DMF similarly shows only 1,2-addition with RCHO or RCOR´ (eq 2).[14b] A complex involving Ph_2CO and Yb provides Ph_2RCOH (R = allyl) with allyl bromide.[15]

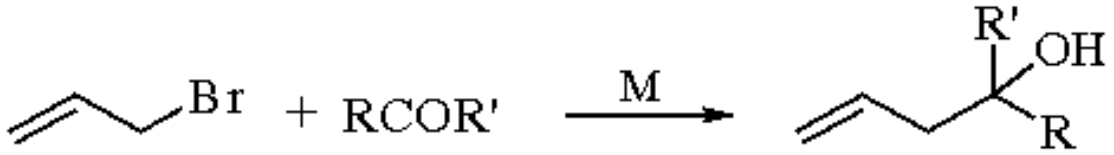

(2)

R = H, alkyl; M = Zn, Cd, Al etc.

Asymmetric allylation occurs in a number of appropriately substituted systems. The Schiff base between (+)-camphor and $H_2NCHR´P(O)(OEt)_2$ is metalated (***n-Butyllithium***) and then reacts with allyl bromide to give the (1*S*,4*S*) analog (R = allyl) with >95% diastereomeric excess (eq 3). Sequential hydrolysis provides the (*S*)-ester and the (*S*)-phosphonic acid without appreciable racemization;[16a] (1*R*,2*R*,5*R*)-(+)- and (1*S*,2*S*,5*S*)-(-)-2-hydroxy-3-pinanone behave analogously.[16b] The bis(cyclohexylidene) acetal of D-galactodialdehyde similarly gives Schiff bases with α-alkylated glycine esters; these may be metalated (BuLi) and the anion quenched with allyl bromide with 76% diastereomeric excess.[17] ***Lithium Diisopropylamide*** metalation of a chiral lactam enolate and allylation s imilarly provides a considerable diastereomeric enhancement.[18] Formation of the enol from tetralone with (*R*)-$RCH_2CHPhN(CH_2CH_2OCH_2$-$CH_2OMe)Li$ (R = piperidino) and allylation provides (*R*)-2-allyl-1-tetralone in 92% enantiomeric excess and 89% overall yield; ***Lithium Bromide*** is a necessary co-reagent (eq 4).[19]

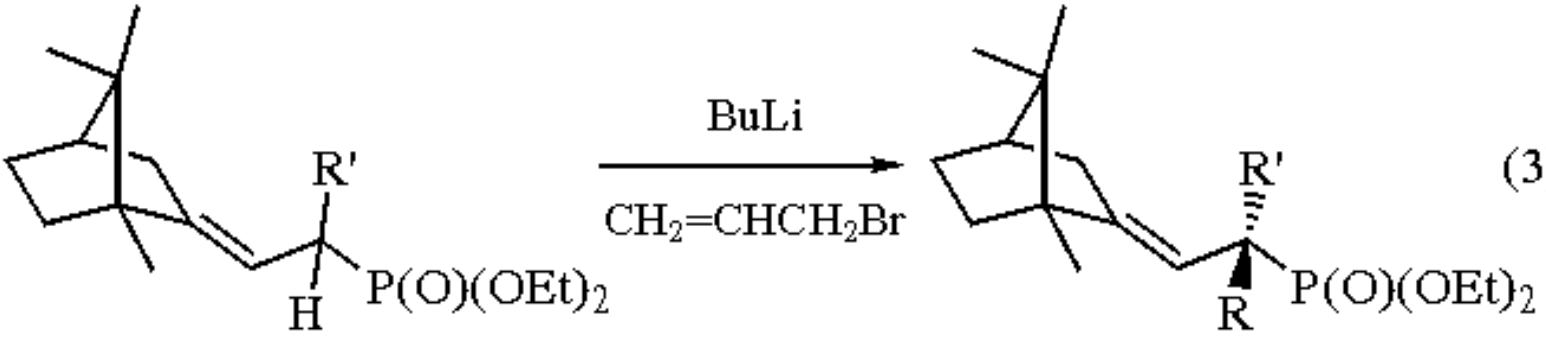

(3)

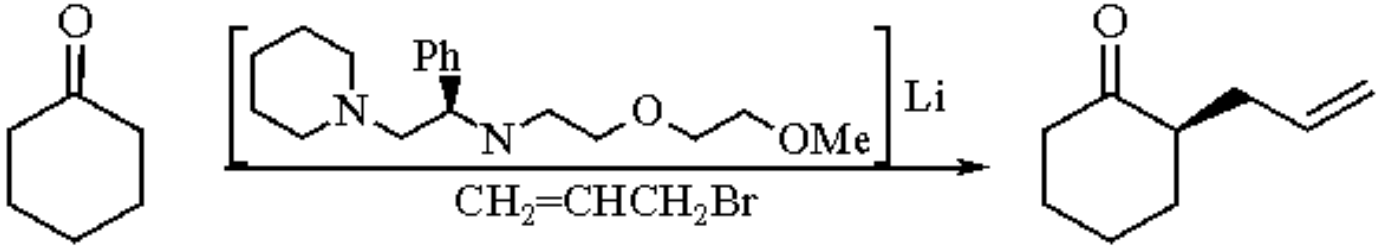

(4)

Similarly, allylation of the lactam by allyl bromide-LDA[20] proceeds stereospecifically to give (**1**).

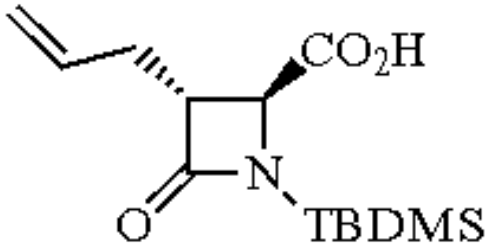

(1)

Allylation of Ni complexes of some Schiff bases with glycine are reported[21] to yield *S*-α-allylglycine. A three-step synthesis of α-amino acid HCl salts relies upon diastereoselective allylation of a glycine enolate synthon with >97.6% de and in 73-90% yield.[22] *N*,*N*-Dimethylhydrazones of α,β-unsaturated aldehydes[23a] and $RCH_2CH{=}CHCH{=}CHCHO$[23b] metalate (BuLi) and allylate with rearrangement, giving $RCH(R')(CH{=}CH)_nCHO$ analogs (R´ = allyl; *n* = 1 or 2). $Ph_2C{=}NCH_2CO_2$-*t*-Bu undergoes allylation (RBr, 50% aq NaOH, CH_2Cl_2, rt) in the presence of chiral PTC based upon cinchonine; the products show considerable ee (50-60%).[24]

Carbonyl insertion occurs when Me_3P-coordinated π-allyl Pd complexes are treated with CO in CH_2Cl_2 at rt, giving 3-butenoyl derivatives,[25] and allylation of a vinyl rhenium CO complex provides an allyl vinyl ketone complex.[26] Organotin species couple with allyl bromide (catalyzed by Pd complexes); while β-elimination may supervene, CHO, CO_2H, and OH groups do not interfere.[27a] Similar coupling occurs with $RSiMe_3$ or $RSiMe_2F$ and allyl bromide,[27b] but alkenylboranes in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** give alkenes by allyldeboronation.[27c] ***Tetracarbonylnickel*** with allyl bromide (RBr) gives π-allyl nickel bromide complexes. These can act as intermediates in the coupling of allylic systems either symmetrically[28a] or to give substituted alkenes by unsymmetrical coupling (eq 5).[28b]

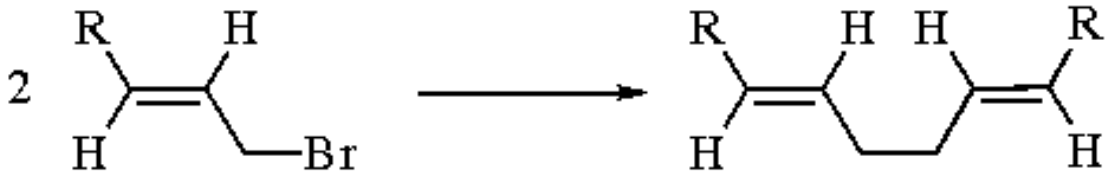

(5)

π-Allyl nickel bromide complexes allylate C-2 of benzoquinones.[28c] Oxygen-centered attack occurs readily; the K salt of L-ascorbic acid (**2**) gives (allyl bromide-Me_2CO) a lactone (**3**) which with ***Palladium(II) Chloride*** in aq DMF provides (40%) a bicyclic ketone in which the allylic side chain has become the acetonyl ($MeCOCH_2$) residue (eq 6).[29]

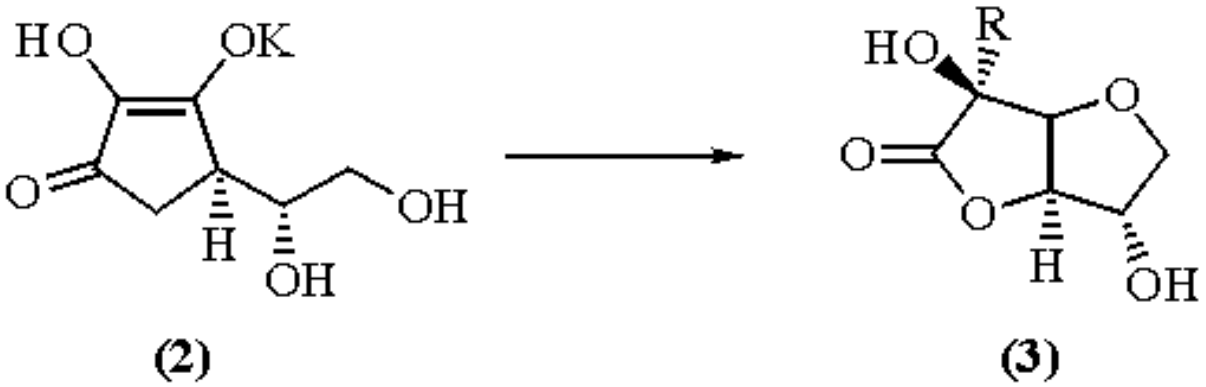

(6)

Stannylation of monoalkylated oxiranes by ***Trimethylstannyllithium*** gives lithium alkoxides $XOCH(R)CH_2SnMe_3$ (X = Li) which react conventionally with allyl bromide to give the corresponding allyl ether (X = allyl).[30] Attack at oxygen may also be achieved using other displaced groups. Stannylene acetals of acyclic diols are monoallylated using F^- in a mild, selective, and high yield process.[31]

N-Allylation takes place easily; phthalimide reacts readily with allyl bromide (K_2CO_3-PEG 400; 90 °C).[32] Indoles[33a] and pyrazoles[33b] may be allylated on nitrogen using PTC such as Bu_4NBr (eq 7).

(X = N, CH) (7)

Salts such as Na phenylsulfinate form allyl esters; Al_2O_3, ultrasound, and microwaves all influence the yield.[34] Correspondingly, sulfur,[35,36] selenium,[36] or tellurium[37] attack is preparatively useful (eq 8).

$$RBr + R'X^- \longrightarrow R'XR + Br^- \quad (X = O, S, Se, Te) \quad (8)$$

Alkyl coupling reactions, mediated by Cu, are exemplified by the synthesis of $CF_3CH_2CH{=}CH_2$ using $(CF_3)_2Cu^{III}$(*N*,*N*-diethyldithiocarbamato),[38a] or using FO_2SCF_2I in DMF.[38b]

The allyl system is susceptible to further chemistry, notably epoxidation and other addition processes; the intermediates in such processes may show their own idiosyncratic chemistry[39] as in the cyclization of the thioallyl substituent (**4**) (eq 9), itself obtained by allylation of the thiophenoxide.

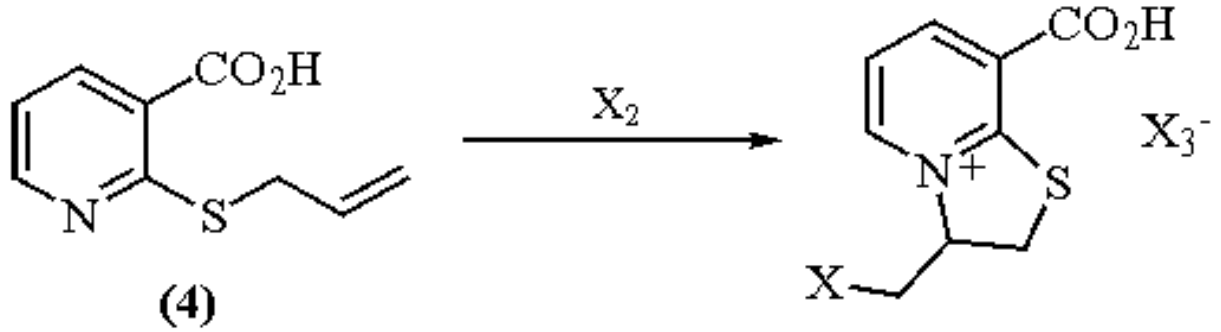

Related Reagents.

Allyl Chloride; ***Allyl Iodide***.

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Allyl Chloride[1]

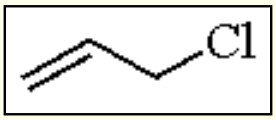

[107-05-1] · C_3H_5Cl · Allyl Chloride · (MW 76.53)

(allylating agent which attacks C, O, N, S, Se, Te nucleophiles; organometallic derivatives provide homoallyl alcohols; expected electrophilic addition reactions)

Physical Data: mp -136.4 °C; bp 44.6 °C; *d* 0.938 g mL^{-1}.

Solubility: miscible with organic liquids.

Form Supplied in: colorless liquid, discoloring on standing and exposure to air.

Purification: wash with concd HCl, then with aq Na_2CO_3 and dry ($CaCl_2$). Impurities include isomers and chloropropanes; efficient fractional distillation is essential.[2a]

Handling, Storage, and Precautions: volatile, flammable, toxic, irritant, alkylating agent.

Usually manufactured by high temperature chlorination of propene;[2b] hence the incidence of isomeric and polychlorinated impurities. Allyl chloride allylates ethyl acetoacetate derivatives (40% aq KOH, Bu_4NBr, rt, 3 h) to give 2,2-diallyl analogs (92% yield, 97% pure).[3] Malonic esters are similarly alkylated under dehydrating conditions (RCl, Bu_4NBr, NaOH in PhMe).[4] Alkyl carboxylic acids may be allylated at the α-position when the Na salt (NaH-xylene, 135 °C, 2 h) is treated with ***Lithium Diethylamide*** at 125-135 °C until loss of Et_2NH is complete, followed by treatment with RCl at ~85 °C over some hours.[5] Ruthenium or osmium σ-acetylide complexes (e.g. **1**)[6] undergo allylation (at the alkyne system). Some such substitutions (e.g. methanolysis) are apparently Cu catalyzed;[7,8] an example is the formation of 3-allylpentane-2,4-dione (72%), when Cu + $Cu(ClO_4)_2$ is added to the reagents in Et_2O (eq 1).[8]

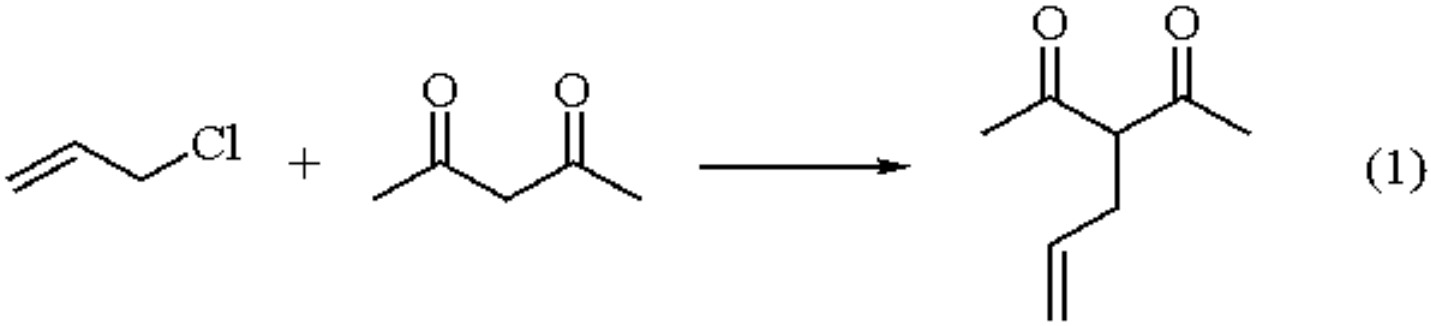

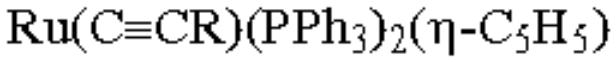

(1)

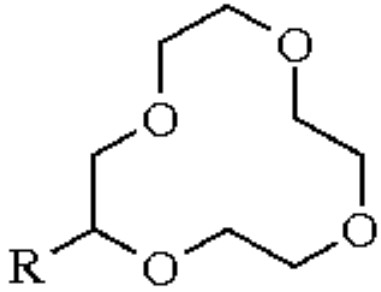

(2)

In the presence of peroxides (e.g. ***1,1-Di-t-butyl Peroxide***) crown ethers add to allyl chloride via the α-hydrogen abstracted radical to form, for example, 2-(3´-chloropropyl)-1,4,7,10-tetraoxacyclododecane (**2**; R = $Cl(CH_2)_3$). While the yields are poor (8-10%) the product is apparently isolable,[9] and affords a route to functionalized crown ethers.

The reductive allylation process (eq 2) occurs with aldehydes in the presence of Bi,[10a,10b] $Al/BiCl_3$,[10b,10c] $Al/PbBr_2$,[11] Zn,[12] and $Fe/BiCl_3$.[10b] Acid chlorides in the presence of Cp_2Sm afford allyl ketones.[13] Dry stirring ***Magnesium*** turnings in an inert atmosphere greatly promotes the formation of allylmagnesium chloride without the formation of biallyl and similar products.[14] In addition to the expected range of Grignard reactions based upon allylmagnesium chloride, allyl chloride reacts with ***Lithium Diisopropylamide*** to form α-chloroallyllithium, which undergoes the expected reactions with RCl, RCHO, R_3SiCl, and R_3SnCl (eq 3).[15]

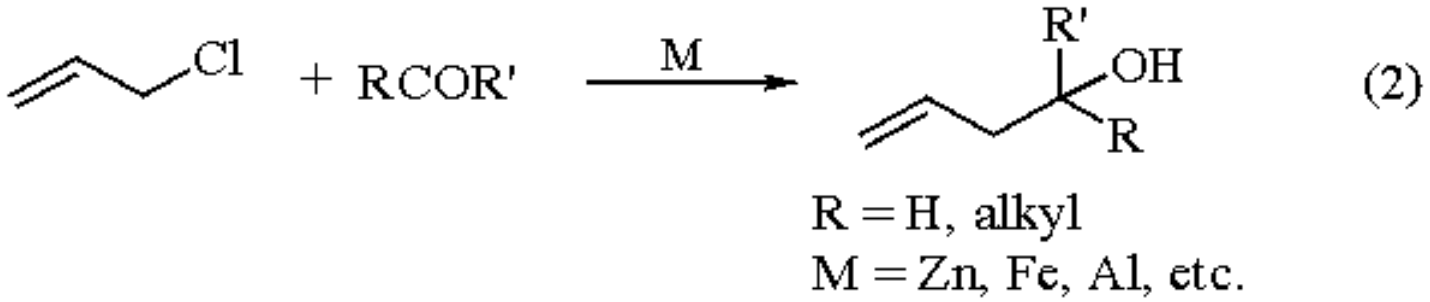

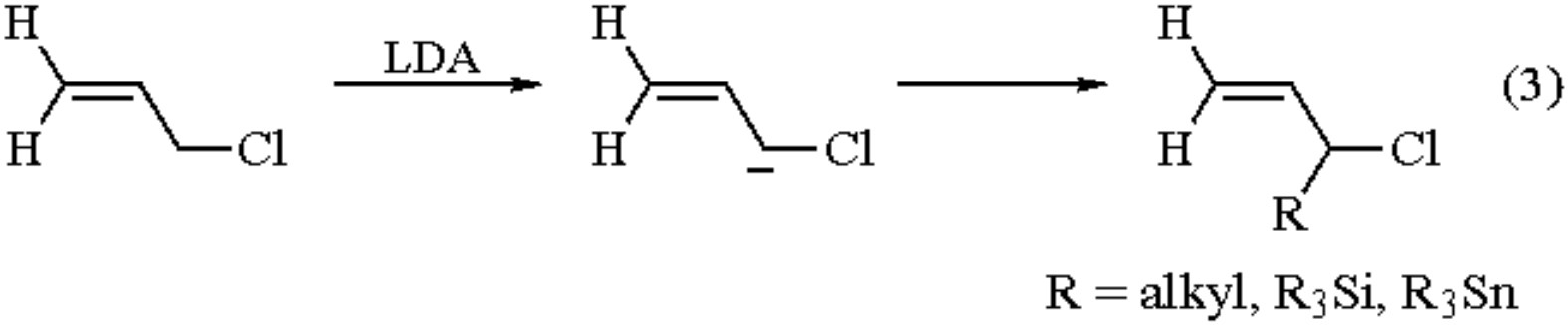

Allyllithium (RLi) itself is made by cleavage of $RSnPh_3$ (from RBr, Mg, and Ph_3SnCl)[16a,16b] or of allyl aryl ethers (Li, THF, -15 °C) (eq 4).[16c]

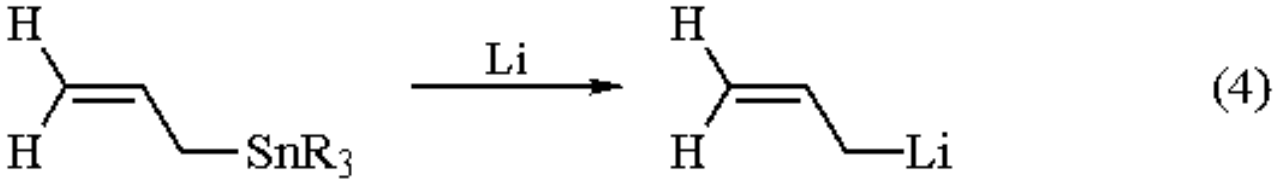

The protected glycine ester derivative (**3a**) affords a reagent with 2LiCl.CuCN which allylates with allyl chloride to give the product (**3b**) without loss of the stereochemical identity at the carbon atom α to the protected amino group (eq 5).[17] Allyl chloride also alkylates glycine chiral ester Schiff bases in the presence of chiral Pd complexes.[18] The allylation of the monomenthyl ester of cyclopentane-1,2-dicarboxylic acid by RCl (R = allyl) gives the compound (**4**) in which the allyl halide has approached from the more hindered side of the molecule. Allyl tosylate gives the sterically preferred orientation; the differences in behavior are rationalized in terms of interaction between the Li of the enolate reagent and the Cl of RCl.[19]

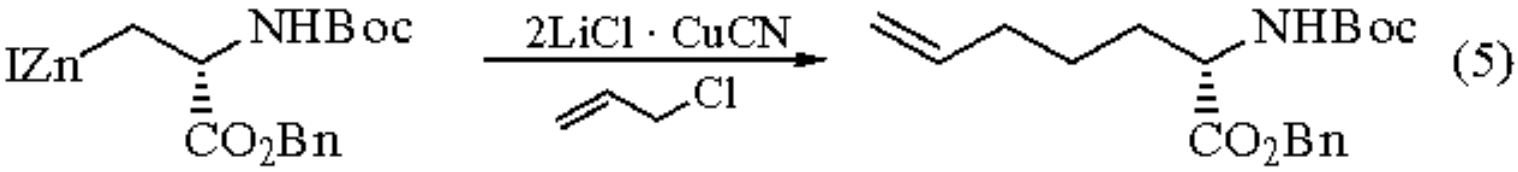

(3a) **(3b)**

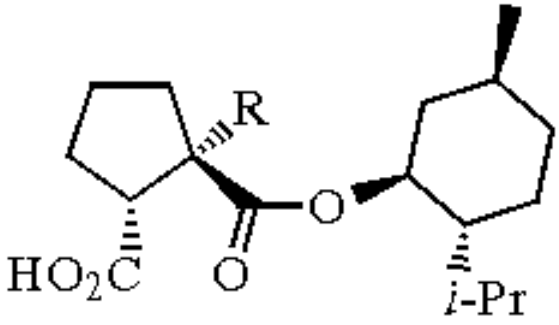

(4)

Traditional nucleophilic attack is represented by reaction with ArO^- in the synthesis of allyl aryl ethers in a study of

the Claisen reaction,[20] and with ***Sodium Sulfide*** to give R_2S,[21] and in the analogous preparation of R_2Te.[22] Friedel-Crafts allylation of benzene represents an alternative route to the synthesis of propylbenzene after hydrogenation, since rearrangement occurs when propyl halides are subject to this reaction; hydrated ***Iron(III) Chloride*** proved to be a gentle, if inefficient, catalyst for such allylations.[23]

The use of Ru or Rh chlorides on polyethylenimine to promote the addition of $CXCl_3$ to unsaturated systems such as allyl chloride (eq 6) extends the older application of Lewis acids such as ***Aluminum Chloride***.[24] The addition of ***Diborane*** to allyl chloride provides (γ-chloropropyl)boranes which then provide cyclopropane;[25a] with ***Sodium Amide***, allyl chloride gives cyclopropene (low yield).[25b]

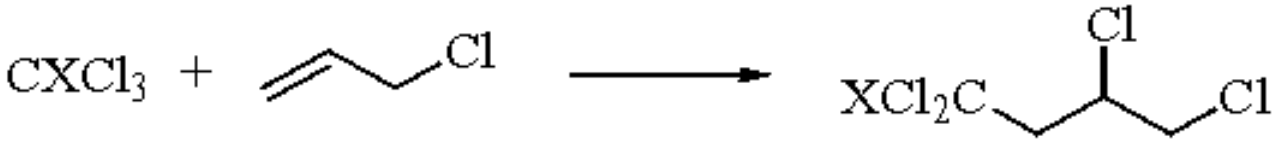

(6)

Related Reagents.

Allyl Bromide; ***Allyl Iodide***.

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Allyl Chloroformate

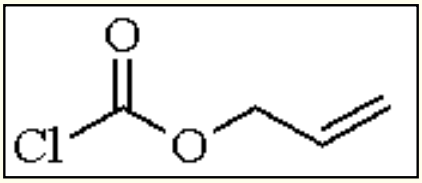

[2937-50-0] · $C_4H_5ClO_2$ · Allyl Chloroformate · (MW 120.54)

(preparation of allyl carbamates and allyl carbonates;[1a] may be used for preparation of α-allyl carbonyls and α,β-unsaturated carbonyls[4])

Physical Data: bp 109-110 °C; *d* 1.136 g cm^{-3}; fp 31 °C.

Solubility: sol most organic solvents.

Form Supplied in: clear, colorless liquid.

Handling, Storage, and Precautions: keep cold. Reacts with moist air. May contain small amounts of phosgene.

Protecting Group.

Allyl chloroformate has been used to prepare the allyl carbamate protecting groups for amines (eq 1)[1] and the alkyl allyl carbonate group for protecting alcohols (eq 2).[1a] These blocking groups are useful because they are stable to acidic and some basic conditions but are easily removed under aprotic conditions with palladium or nickel catalysis in the presence of nucleophiles (eqs 3 and 4).[1a,2]

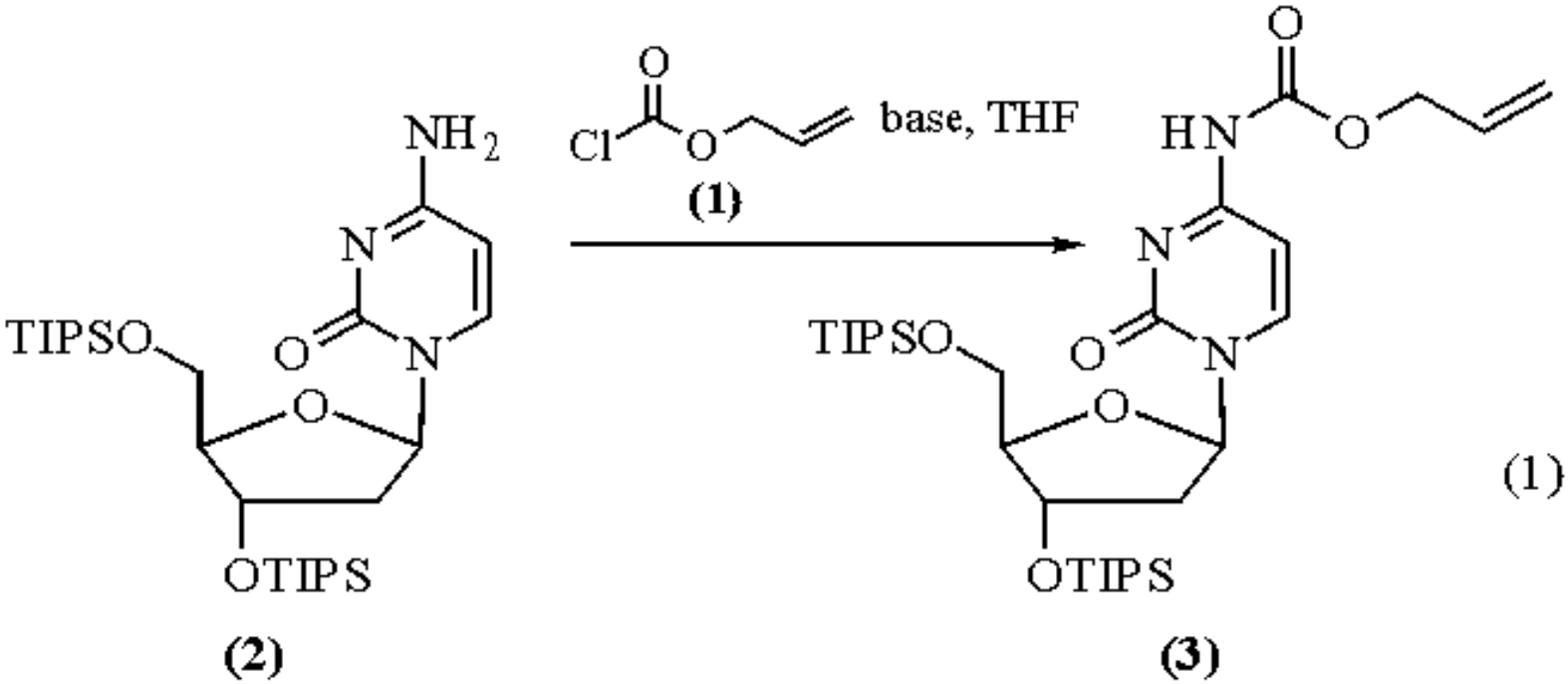

(1)

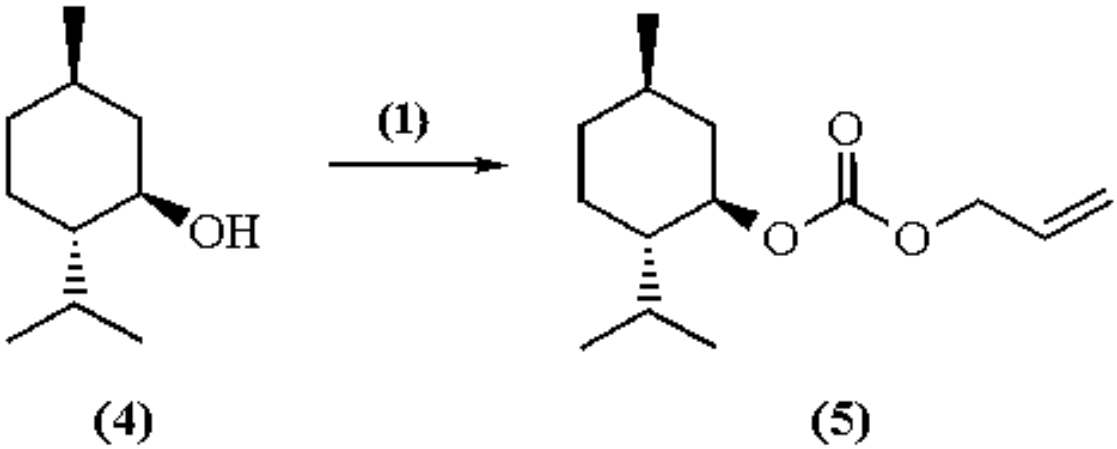

(2)

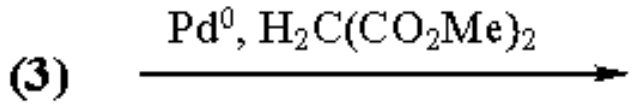

(3)

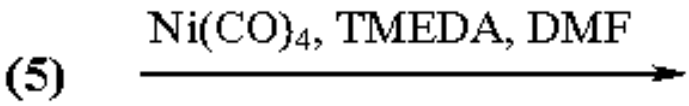

(4)

Preparation of α-Allyl and α,α-Diallyl Ketones.

Allyl enol carbonates formed from the reaction of enolates with allyl chloroformate rearrange in the presence of palladium(0) catalysts to provide α-allyl and α,α-diallyl ketones (eq 5).[3]

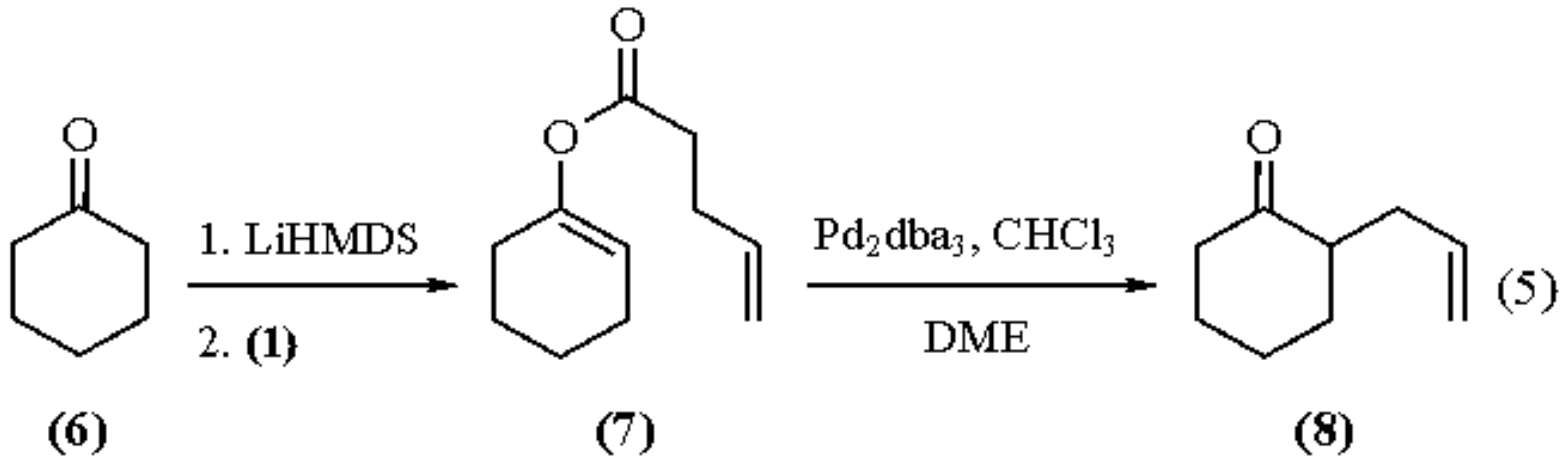

Preparation of Unsaturated Ketones, Aldehydes, and Nitriles.

Allyl enol carbonates and allyl esters provide good yields of α,β-unsaturated products when treated with palladium(II) and the appropriate ligand. The choice of ligand is critical to the optimal yield of either α-allylated product or unsaturated product (eq 6).[4]

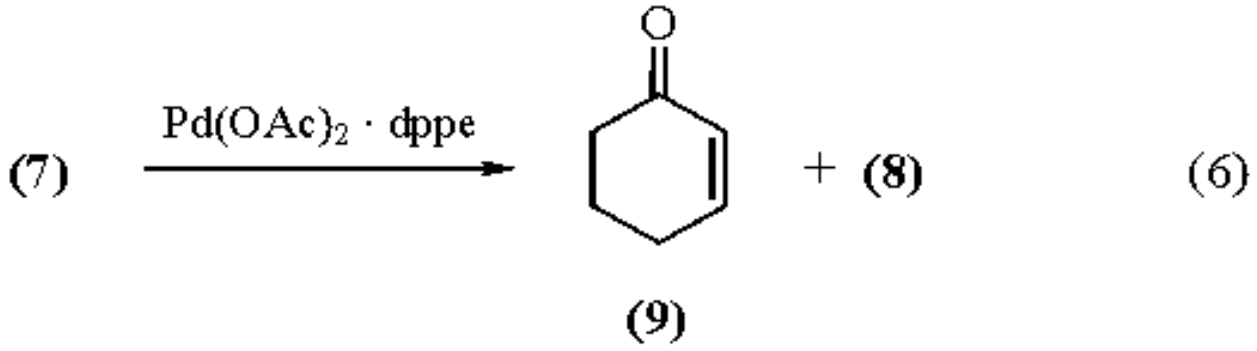

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Paul M. Herrinton

Allylcopper[1]

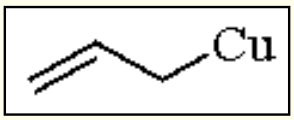

[37974-18-8] · C_3H_5Cu · Allylcopper · (MW 104.62)

(reagent for allyl transfer to enones,[2] acid chlorides,[3] aldehydes,[3] and imines[4])

Alternate Name: 2-propenylcopper.

Preparative Methods: prepared by reaction of ***Allyllithium*** or allylmagnesium halides and ***Copper(I) Iodide***, or by reaction of allyl halides and activated copper metal.

Handling, Storage, and Precautions: sensitive to air and moisture. Use in a fume hood.

Allylcopper and ***Lithium Diallylcuprate*** were initially prepared by House and Fischer in 1969.[5] Addition of allylcopper to cyclohexenone occurred in excellent yield, but β-substituted enones resulted only in 1,2-addition products (eq 1).

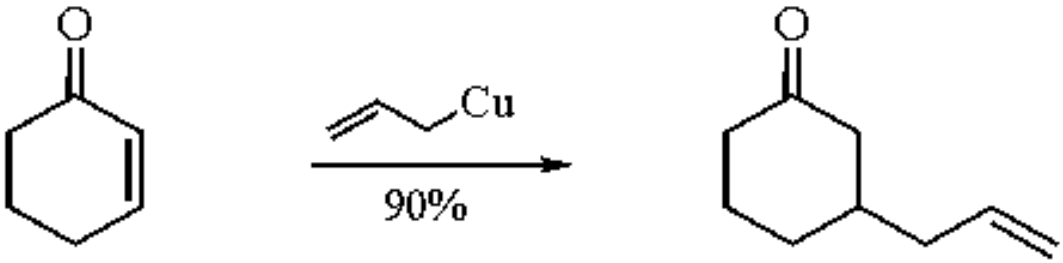

(1)

In a more recent study, Bertz and Dabbagh disclosed that the extent of 1,2-addition in the reaction of allylcopper with cyclohexenone was dependent on the reaction solvent.[6] There have been reports on the difficulties associated with regiocontrol in the reactions of allylcopper and lithium diallylcuprate.[2,3] Hutchinson and Fuchs speculated that lithium diallylcuprate existed as an equilibrium mixture of bis-η^3-allyl and η^1-allyl-η^3-allyl species.[7] Only the η^1-allyl species was able to undergo conjugate addition due to the fact that this complex was formally a 16-electron complex, whereas the 18-electron bis-η^3-allyl complex could not undergo conjugate addition. Lipshutz and co-workers[2] developed a method for the preparation of allylcopper which provided an apparent solution to the problems associated with the reagent generated under the conditions reported by House.[5] Preparation of the neutral allylcopper reagent from ***Allyllithium*** (obtained from transmetalation of allyltributyltin with butyllithium) and ***Copper(I) Iodide*** solubilized by ***Lithium Chloride*** resulted in a reagent that undergoes 1,4-addition with sterically hindered enones (eq 2). The conjugate addition reaction required the presence of ***Chlorotrimethylsilane*** for reproducible results. The

allylcopper reagent could also be obtained from ***Allylmagnesium Bromide*** and soluble copper iodide-***Lithium Bromide*** in THF. The Grignard-derived allylcopper reacted with a hindered cyclopentenone to give the 1,4-adduct in very good yield (eq 3).

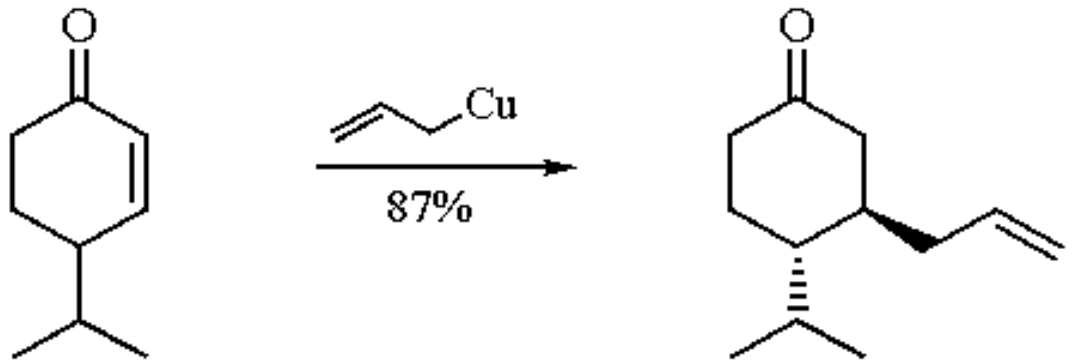

(2)

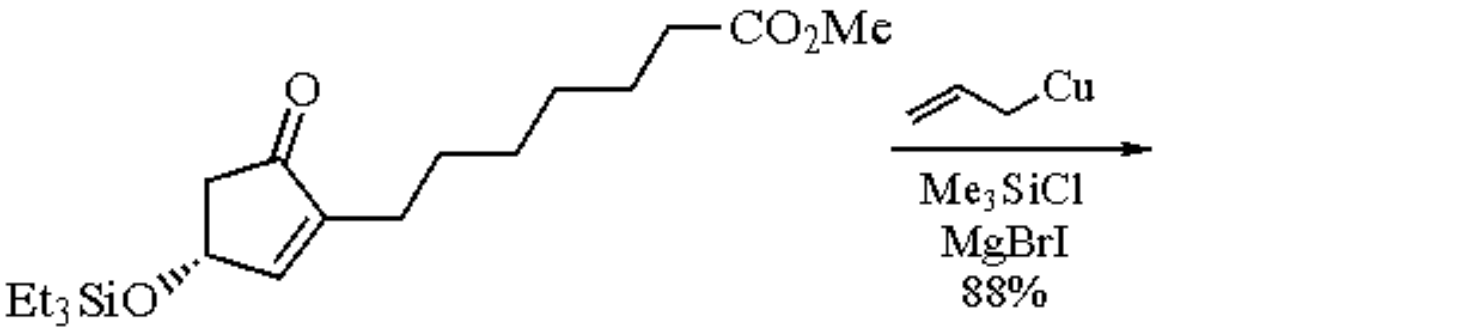

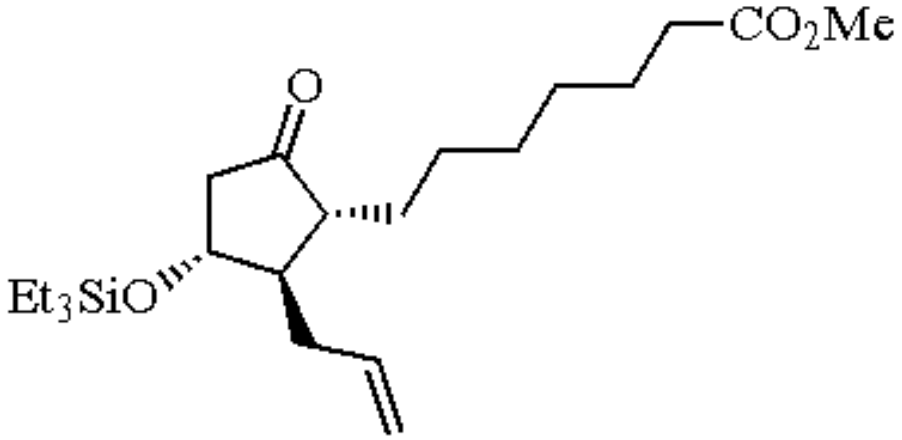

(3)

Lipshutz noted that the allylcopper reagent prepared from soluble copper(I) complexes exhibited atypical reactivity when compared to other less reactive neutral organocopper reagents. 1,2-Addition becomes competitive with 1,4-addition reactions of allylcopper in cases where dialkylcuprate reagents predominately give the 1,4-addition product. Yamamoto and co-workers reported that allylcopper prepared by the method of Lipshutz undergoes conjugate addition to ethyl 4-benzyloxypent-2-enoate, while the same reagent prepared by the method of House did not react (eq 4).[8]

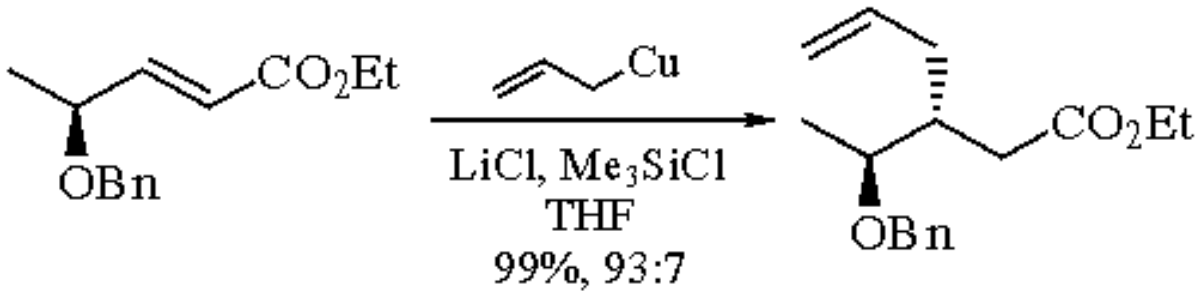

(4)

However, Shultz and Harrington noted that allylcopper prepared by the Lipshutz method did not provide a conjugate addition product in reaction with a 2-amido substituted cyclohexenone.[9] Only copper bromide-catalyzed addition of allylmagnesium bromide provided the 1,4-addition product in modest yield. More recently, Rieke and co-workers have reported the direct preparation of allylcopper from ***Allyl Chloride*** or allyl acetate using activated copper metal generated from the reaction of ***Lithium Naphthalenide*** with soluble ***Copper(I) Cyanide***-lithium bromide.[3] Allylcopper formed in this fashion reacted cleanly with acid chlorides to provide ketones in good yields (eq 5).

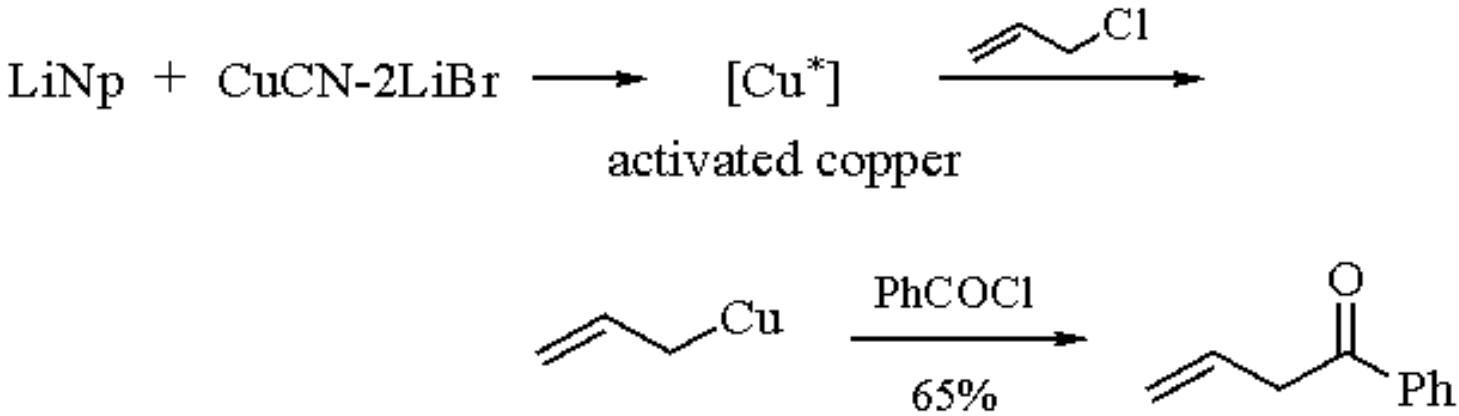

(5)

1,2-Addition products could be obtained with aldehydes and ketones, and 1,4-addition reactions with enones were also realized in the presence of trimethylsilyl chloride. Substituted allyl halides readily produce the corresponding allylcopper derivative. Conjugate addition of the substituted allylcopper reagents occurs exclusively by α-attack of the allyl group (eq 6). The activated copper metal method also allows for the generation of substituted allylcopper reagents bearing remote functional groups such as enones, ketones, esters, nitriles, alkyl chlorides, or carbamates.

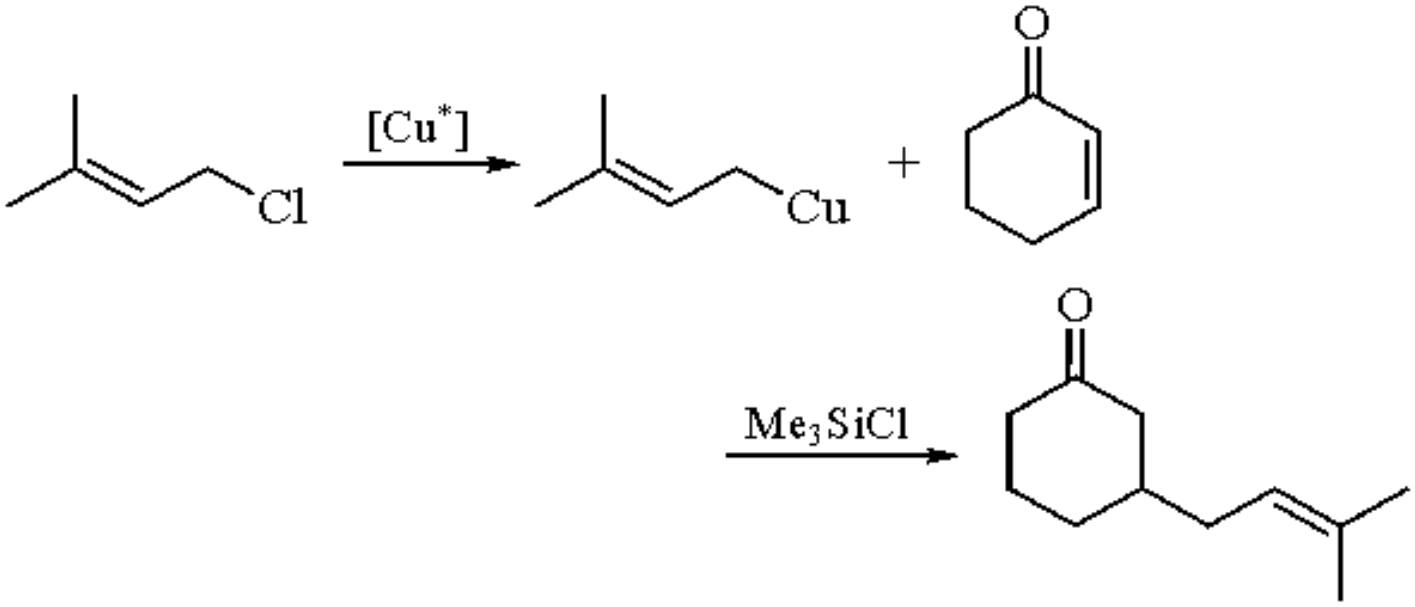

(6)

Conjugate addition reactions of allylcopper obtained by reaction of allylmagnesium halides with copper(I) salts is also common. Corey and co-workers reported that allylcopper prepared from allylmagnesium chloride and copper iodide added to alkynic esters in a 1,4-fashion to provide the dienyl ester products in good yield.[10] Paquette and co-workers demonstrated that the enolate generated by allylcopper addition to an enone could be trapped by addition of trimethysilyl chloride to the reaction (eq 7).[11] Crimmins and co-workers have been able to trap the intermediate formed by allylcopper addition to an alkynic ester by an intramolecular acylation reaction (eq 8).[12] In this example, the initial allyl addition product isomerizes to the *trans*-propenyl substituent upon work-up. Displacement reactions of allylcopper obtained from allylmagnesium halides have also been used in an improved synthesis of allyl sulfones.[13] Allylcopper has also undergone 1,2-addition to imines to provide homoallylic amines with excellent enantioselectivity (eq 9).[4] The high enantioselectivity of the reaction was attributed to the formation of a rigid chelated complex.

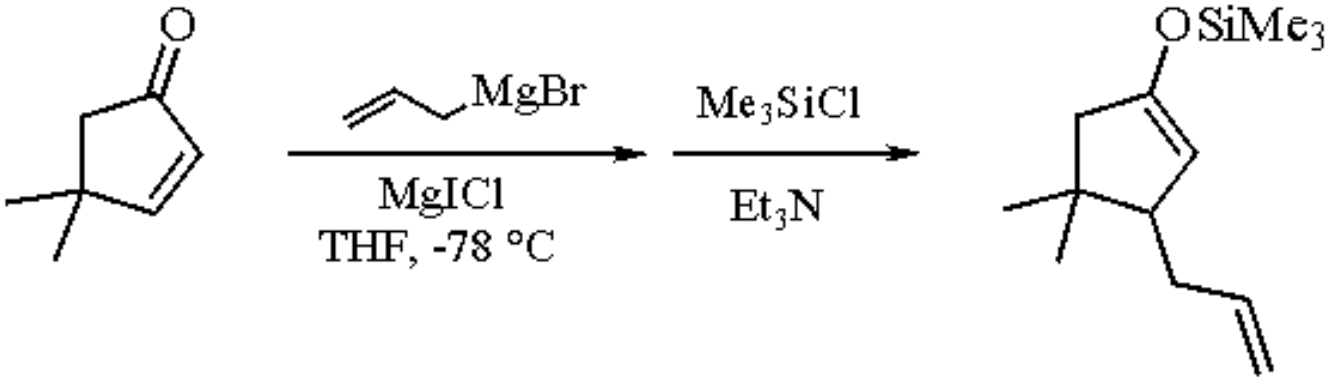

(7)

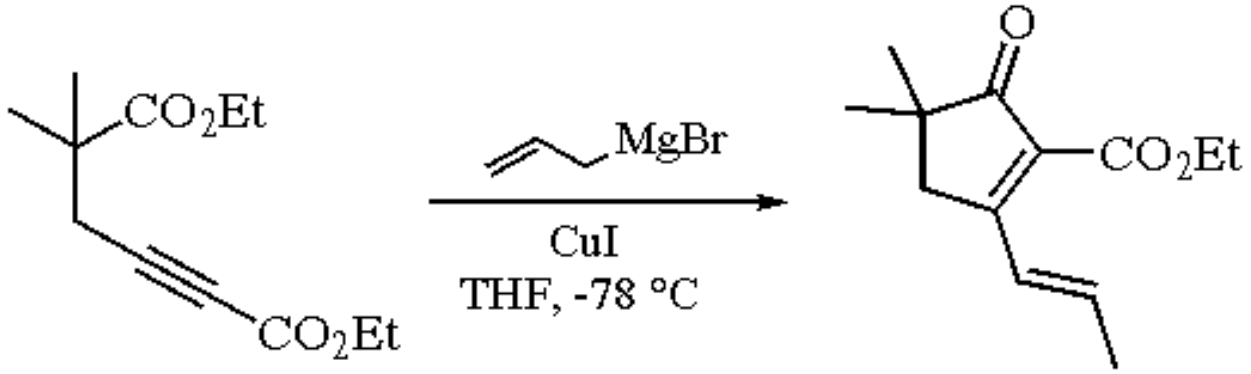

(8)

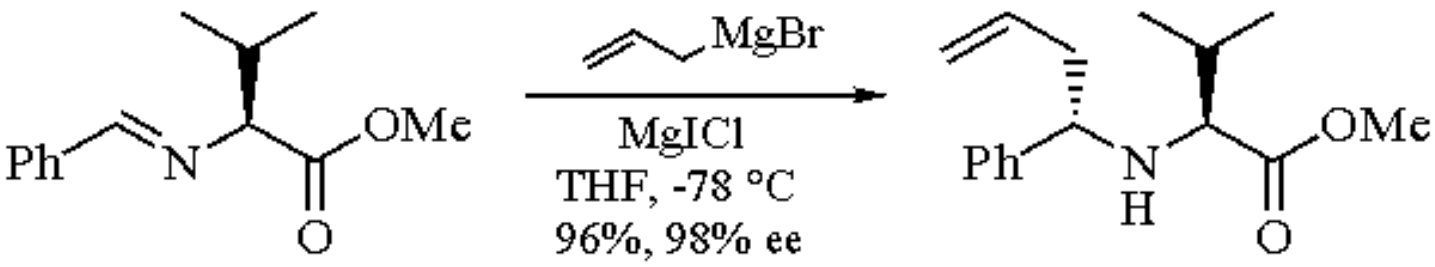

(9)

Related Reagents.

Lithium Diallylcuprate; ***Allylmagnesium Bromide-Copper(I) Iodide***.

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Allyldibutyltin Chloride[1]

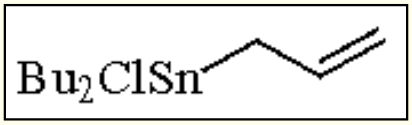

[64549-05-9] · $C_{11}H_{23}ClSn$ · Allyldibutyltin Chloride · (MW 309.46)

(versatile reagent, together with other related halides, for the allylation of carbonyl compounds to form homoallylic alcohols,[2] halotetrahydropyrans,[3] allyl ethers,[4] alkenyl-*N*-alkyl carbamates,[5] and esters[6])

Alternate Names: allyldibutylchlorotin; dibutylchloro-2-propenylstannane.

Physical Data: bp 103 °C/15 mmHg; *d* 1.2 g cm^{-3}.

Solubility: insol cold water, sol alcohols and common organic solvents.

Form Supplied in: colorless liquid; commerically unavailable. *Drying:* the usual procedure is vacuum distillation. A saturated aqueous solution of allyldibutyl tin chloride disproportionates to diallyldibutyltin and dibutyltin dichloride; protonolysis of the allyl-tin bond is very slow.

Handling, Storage, and Precautions: very easy to handle without special precautions. Nevertheless, storage in the refrigerator and in dark bottles is recommended. Its toxicity has been determined to be comparable to that of ***Tri-n-butylchlorostannane***. Use in a fume hood.

Preparation of Allyltin Halides.

A list of isolated and well-established allyltin halides is provided in Table 1, together with procedures for their preparation.

Table 1 Preparative Procedure for Allyltin Halides

Compound	bp (°C/mmHg)	Preparative procedure[a]
$Me_2(CH_2{=}CHCH_2)SnCl$	84 85/21	R[8]
$Pr_2(CH_2{=}CHCH_2)SnCl$	81 81.5/0.1	RA[2c]
$Bu_2(CH_2{=}CHCH_2)SnCl$	103/0.3	R, RA[2a c]
$Bu_2(CH_2{=}CHCH_2)SnBr$	85 89/0.03	C[9]
$Ph_2(CH_2{=}CHCH_2)SnBr$		C[9]
$(CH_2{=}CHCH_2)_3SnCl$	100/0.5	R[2a]
(*E*/*Z*)-$Bu_2(CH_3CH{=}CHCH_2)SnCl$	102/0.2	R, RA[2d,7,11,12]
$Me(CH_2{=}CHCH_2)SnCl_2$		R[8]
$Bu(CH_2{=}CHCH_2)SnCl_2$	91/0.25	R, RA[2c]
(*E*/*Z*)-$Bu(CH_3CH{=}CHCH_2)SnCl_2$	92/0.06	R, RA[3a,10]
$(CH_2{=}CHCH_2)_2SnBr_2$	77 79/2	DS[12]
$(CH_3CH{=}CHCH_2)_2SnBr_2$	104 106/0.2	DS[12]
$(CH_2{=}CHCH_2)SnCl_2Br$	75 78/0.1	DS[2c]

[a] R = redistribution, DS = direct synthesis, RA = reversible allylstannation, C = Sn C bond cleavage.

The general procedures for preparing allyltin halides listed in Table 1 are as follows.

Redistribution (R) reactions of allyl- and mixed allylorgano-tins with organotin or tin(IV) halides (eqs 1 and 2).[1c,2a-d,3a,8]

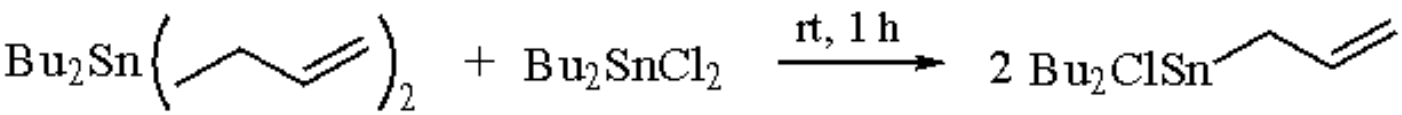

(1)

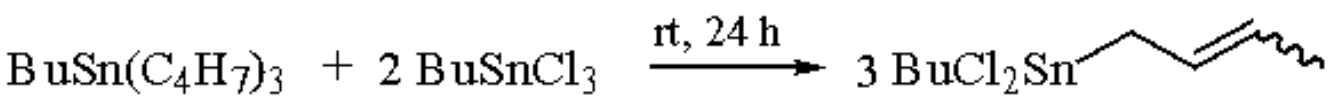

(2)

C_4H_7 = *E*-crotyl, *Z*-crotyl, or 1-methylallyl *E*:*Z*, various ratios

Reversible allylstannation (RA), i.e. thermal decomposition of β-organostannoxyalkenes of the type $Bu_{3-n}Cl_nSn$--O--CRR´-CHR´´-CH=CH_2 where n = 1 and 2, R, R´ are alkyl groups, and R´´ is H or Me (eq 3).[2c,7,10-12]

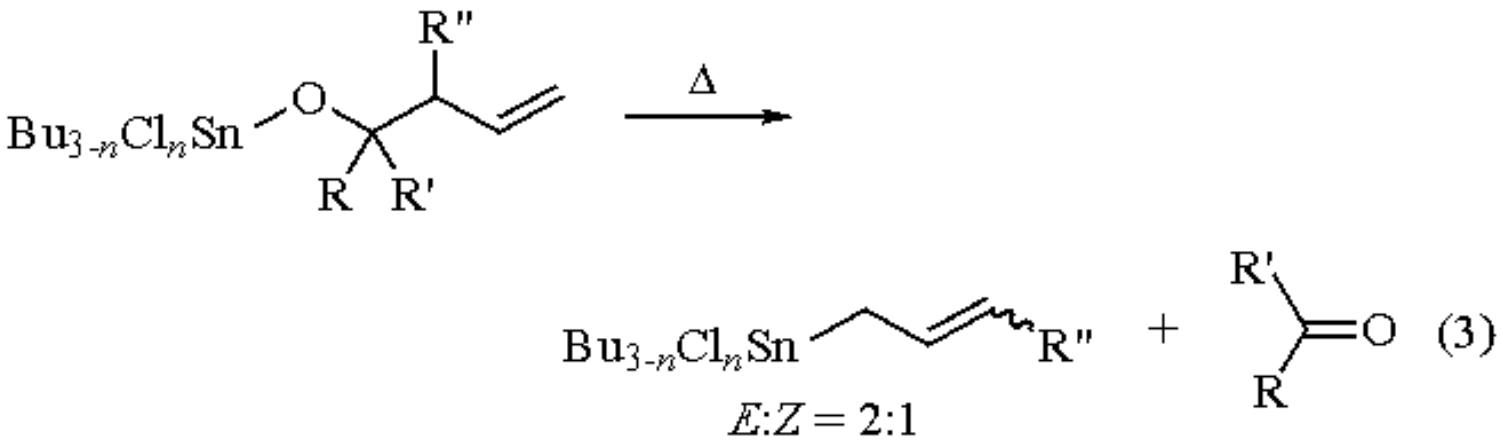

Direct synthesis (DS), i.e. oxidative additions of tin(II) halides to allyl halides (eq 4).[1c,2c,12]

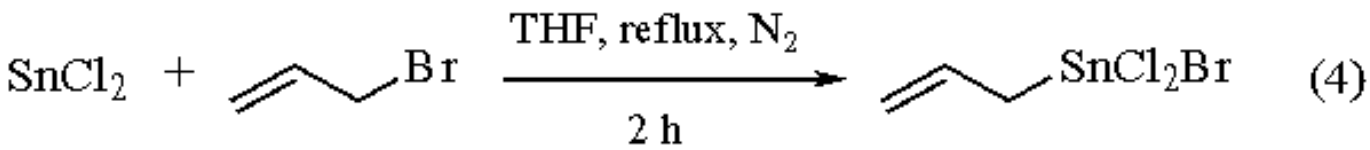

Cleavage (C) of appropriate unsymmetrical organotins (eq 5).[9]

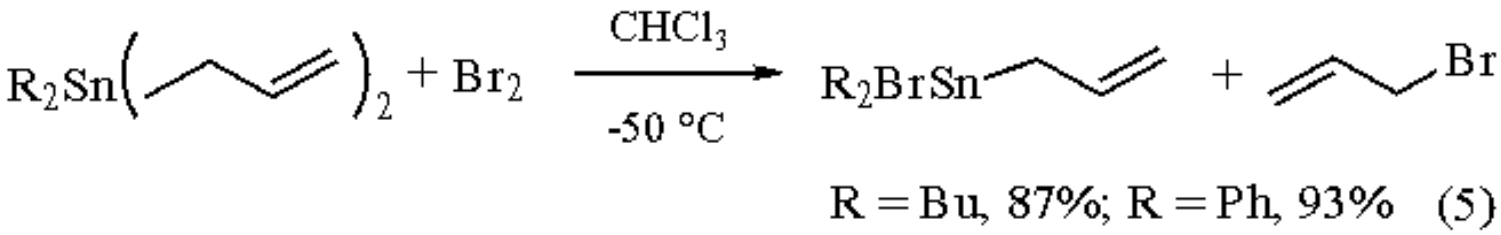

The redistribution reaction is one of the most efficient preparation methods because many allyltin halides can be generated and used in situ,[1c] e.g. the system $Bu_3SnCH_2CH{=}CH_2/SnCl_4$ gives rise to $CH_2{=}CH{-}CH_2SnCl_3$. In the same way, the unstable isomers $R_{3-n}X_nSnCH(CH_3)CH{=}CH_2$ (n = 1-3) can be prepared in situ and then allowed to react with selected substrates.[13]

Allylstannation of Carbonyl Compounds with Allyltin Halides.

When allyldibutyltin chloride is allowed to react with aldehydes and ketones, exothermic additions take place, affording homoallylic alcohols in good yields (eq 6).[2a,c] The reactions occur under mild conditions. They can be carried out neat, in solution, or in the presence of air or water.[14]

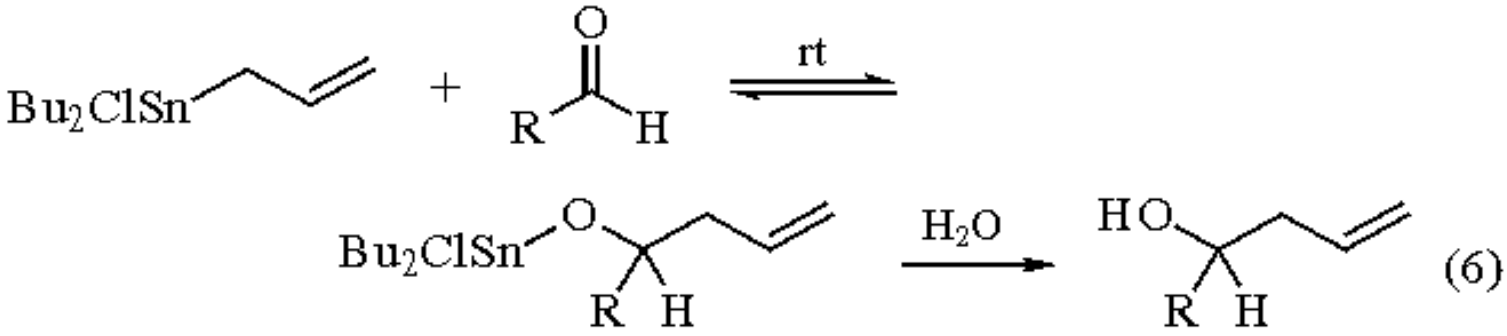

The tin atom in allyltin halides possesses enhanced electrophilic character compared to the parent compounds R_3SnAll (All = allyl or allylic group), which are chemically inert towards carbonyl compounds under the same conditions. The Lewis acidity of tin seems to be the driving force for the high reactivity since allylation can be efficiently achieved at -78 °C (eq 7).[15]

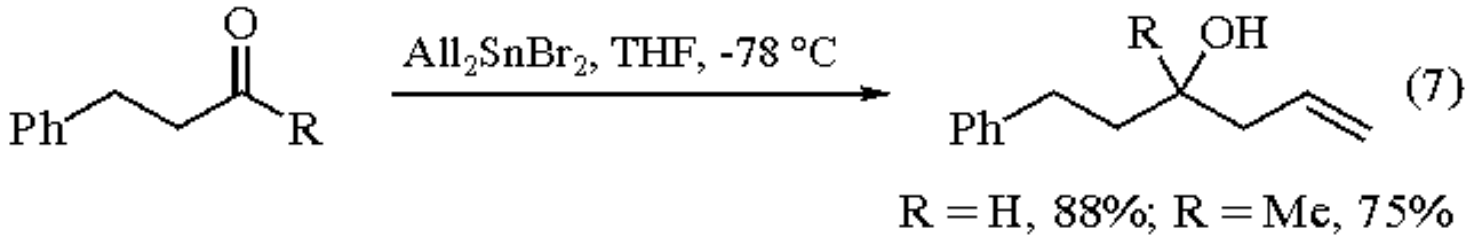

The following order of reactivity has been found: $BrCl_2SnAll$ > $BuCl_2SnAll$ > $Bu_2ClSnAll$ >> Bu_3SnAll. Allylstannation of carbonyl compounds by these reagents can be performed in the presence of water to afford homoallylic alcohols directly. It can be carried out even in the presence of an acidic aqueous solution of $HClO_4$ (0.1-4 M).[14d] When crotyltins are used, the stereochemical outcome depends on the acid concentration. As a matter of fact, the stereochemical course of crotylstannation reactions, that is the recovery of *anti* and/or *syn* as well as (*E*) and/or (*Z*) homoallylic alcohols, starting from isomeric mixtures of (*E*/*Z*)-crotyltin derivatives, depends on the experimental conditions. Poor *anti* selectivity (<=66%) results from reactions of some aldehydes with isomeric mixtures of isolated crotyltins,[2d] while *syn* selectivity (72-77%) is encountered when equilibrated mixtures of the system (*E*/*Z*)-$Bu_3SnCrot/Bu_2SnCl_2$ are employed.[2f] (*Z*) Selectivity (89-100%) occurs when the unstable isomer $Bu_2ClSnCH(Me)CH{=}CH_2$ is generated in situ in the presence of the aldehydes (eq 8).[13a,b]

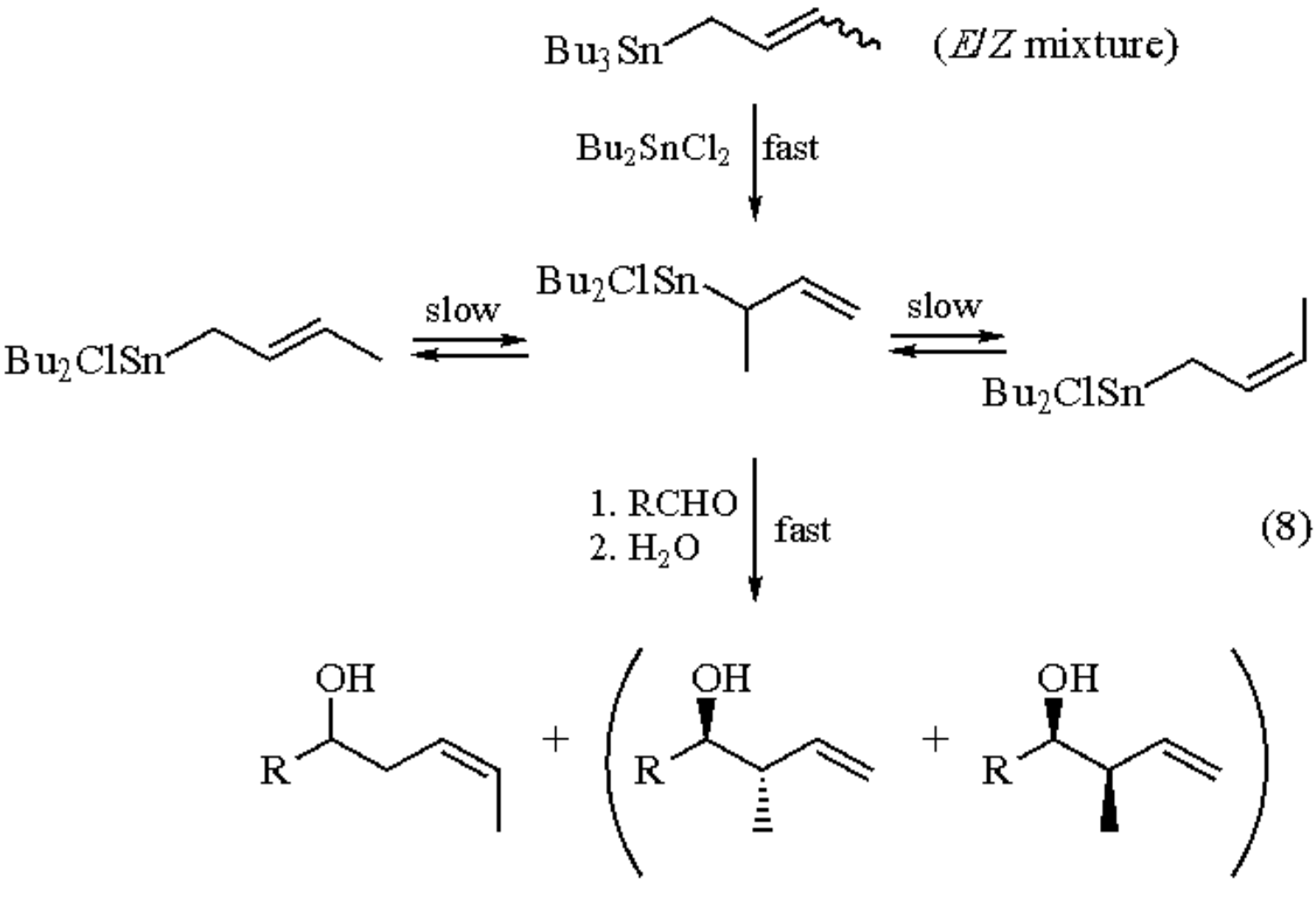

R	*Z*	(*anti* + *syn*)
Et	89	11
i-Pr	93	7
t-Bu	~100	traces
Ph	~100	traces

4-Halo-2,6-dialkyltetrahydropyrans are easily synthesized using allyltin di- and trihalide derivatives (eq 9).[3a-e]

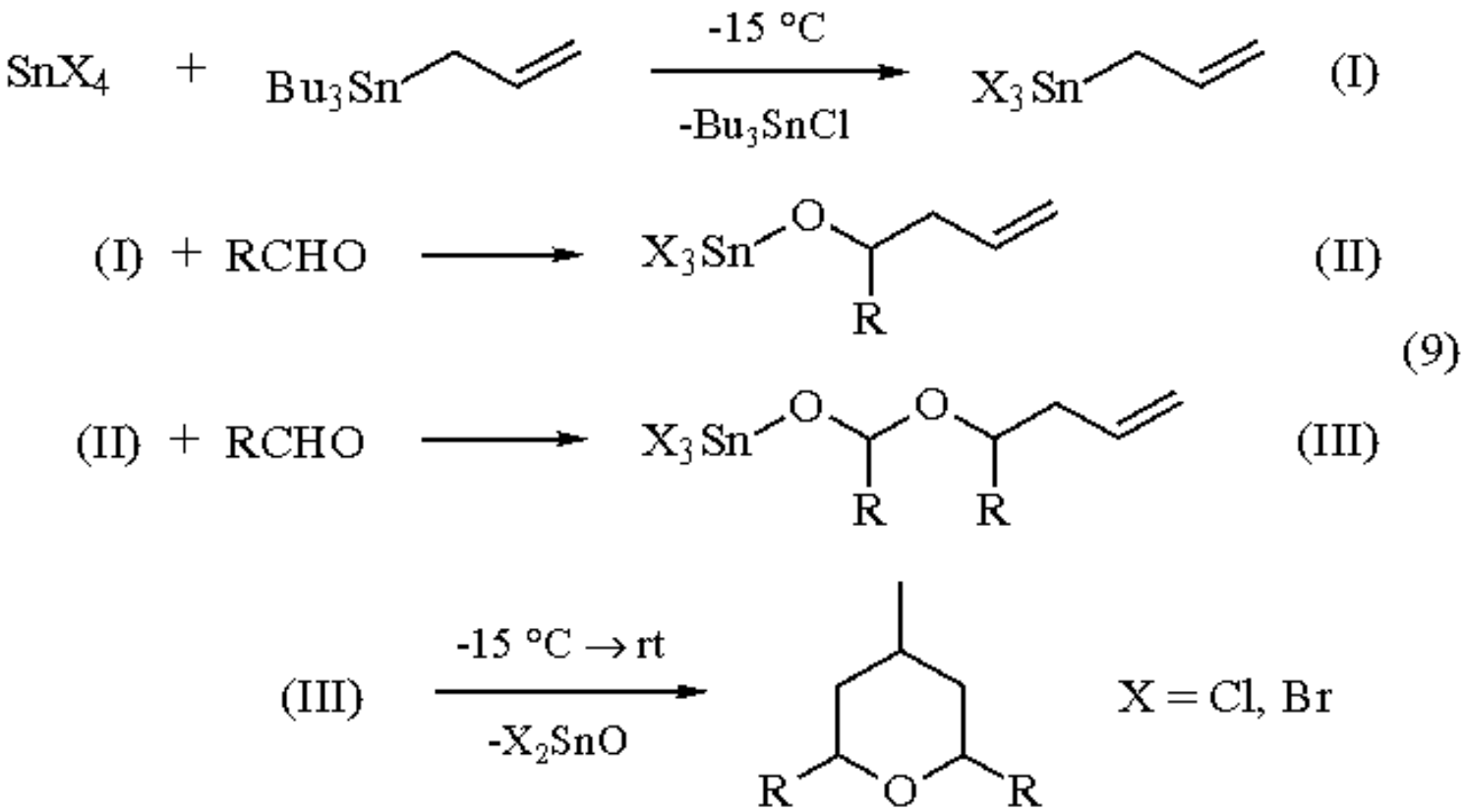

(*E*/*Z*)-4-Halo-2,6-dialkyl-3-methyltetrahydropyrans are produced from the corresponding crotyl halides.[3d] Alkoxides of the type $BuCl_2Sn$-O-CH(CH=CHR)CH_2CH=CH_2 and $BuCl_2$-Sn--O--CH(CH=CHR)CH(R´)CH=CH_2 (R = Me or Pr, and R´ = Me), prepared via allylstannation of α,β-unsaturated aldehydes, give rise to isomeric mixtures of allyl ethers through an intermolecular reaction (eq 10).[4]

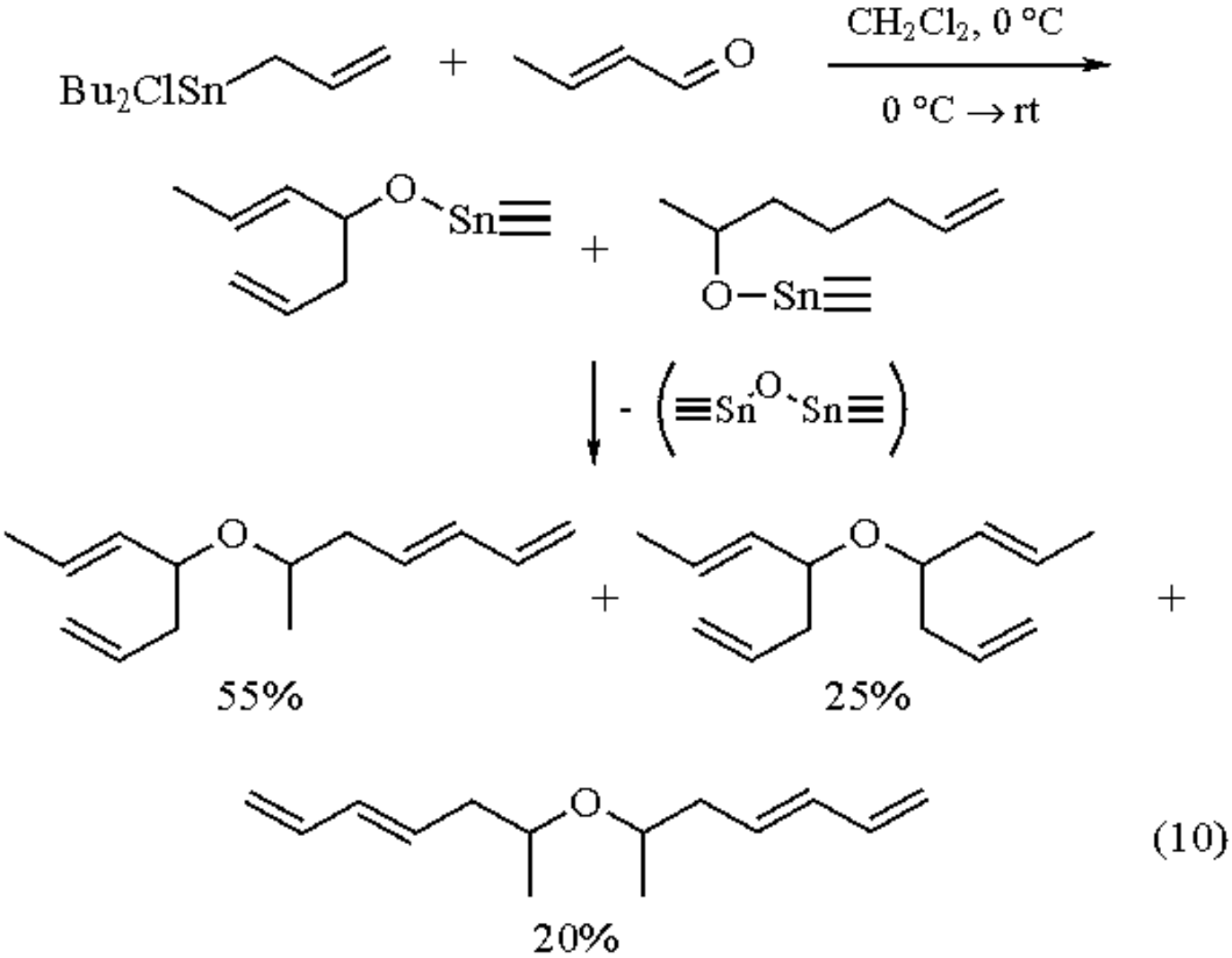

(10)

Alkenyl-*N*-alkyl carbamates can be produced in an one-pot synthesis by combining $Bu_2ClSnCH_2CH{=}CH_2$, RCHO, and EtNCO (eq 11).[5]

Adduct A´ is formed through two distinct steps: step (a) deals with the selective allylstannation of the aldehyde to form adduct A (the insertion of EtNCO into the Sn-allyl bond does not occur), while the subsequent step (b) arises due to the ability of tin alkoxides to react with isocyanates.[16]

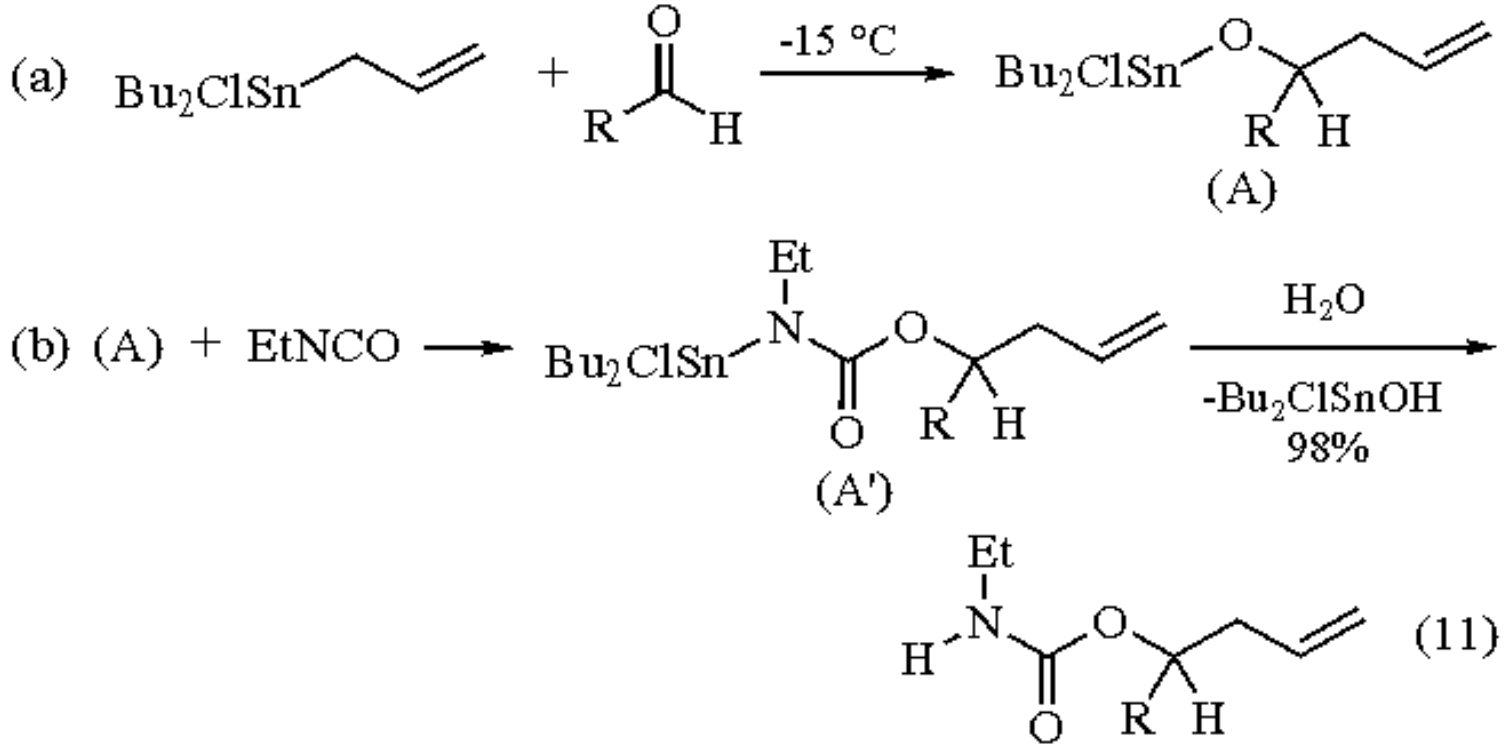

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Allyldicarbonylcyclopentadienyliron[1]

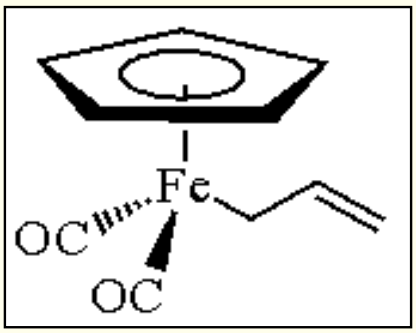

[38960-10-0] · $C_{10}H_{10}FeO_2$ · Allyldicarbonylcyclopentadienyliron · (MW 218.04)

(allyl 1,3-dipole equivalent which undergoes [3 + 2] cycloaddition with electrophilic carbon[2] and heteroatom[3] dipolarophiles; reagent for the Lewis acid-promoted allylation of aldehydes and unactivated ketones;[4] reacts with cationic oxyallyl iron complexes to give [3 + 3] cycloadducts[5])

Physical Data: amber oil which decomposes at ~65 °C.

Solubility: sol all common organic solvents.

Preparative Methods: prepared under an inert atmosphere by the addition of excess ***Allyl Chloride*** to a degassed THF solution of ***Sodium Dicarbonylcyclopentadienylferrate*** at 0 °C.[6] The mixture is stirred for 15 min, warmed to room temperature over 1 h, and concentrated in vacuo. The residue is extracted with pentane, filtered, then concentrated in vacuo to give $Cp(CO)_2Fe(CH_2HC{=}CH_2)$ in 96% crude yield.[7]

Purification: may be protonated with HBF_4 to give the cationic propene complex, $Cp(CO)_2Fe(\eta^2\text{-}H_2C{=}CHMe)^+BF_4^-$, which is precipitated with Et_2O and washed with a large volume of Et_2O. $Cp(CO)_2Fe(CH_2HC{=}CH_2)$ is then regenerated with Et_3N prior to use.[7,8]

Handling, Storage, and Precautions: all manipulations involving $Cp(CO)_2Fe(CH_2HC{=}CH_2)$ should be carried out under an inert atmosphere. Solvents should be thoroughly dried and degassed. The toxicity of allyldicarbonylcyclopentadienyliron has not been fully investigated. For comparative data, see $Cp(CO)_2FeI$ or ***Bis(dicarbonylcyclopentadienyliron)*** (Sigma-Aldrich Material Safety Data Sheets available).

Cycloaddition Reactions.

Allyldicarbonylcyclopentadienyliron (hereafter referred to as allyl-Fp) is a 1,3-dipole equivalent which undergoes [3 + 2] cycloaddition reactions with electron deficient alkenes (eq 1) to give high yields of the corresponding

cyclopentannulation products.[7] The reaction occurs in two steps. Initial attack of the γ-carbon of $Cp(CO)_2Fe(CH_2HC{=}CH_2)$ on the electron-deficient carbon atom generates a zwitterionic iron alkene complex (**1**), which collapses to form the metalated cyclopentane product (see eq 2). Allyl-Fp also reacts with electrophilic heteroatom dipolarophiles such as *N*-tosyl isocyanates and *N*-sulfonylurethanes to give γ-lactams and -sultams, respectively.[3]

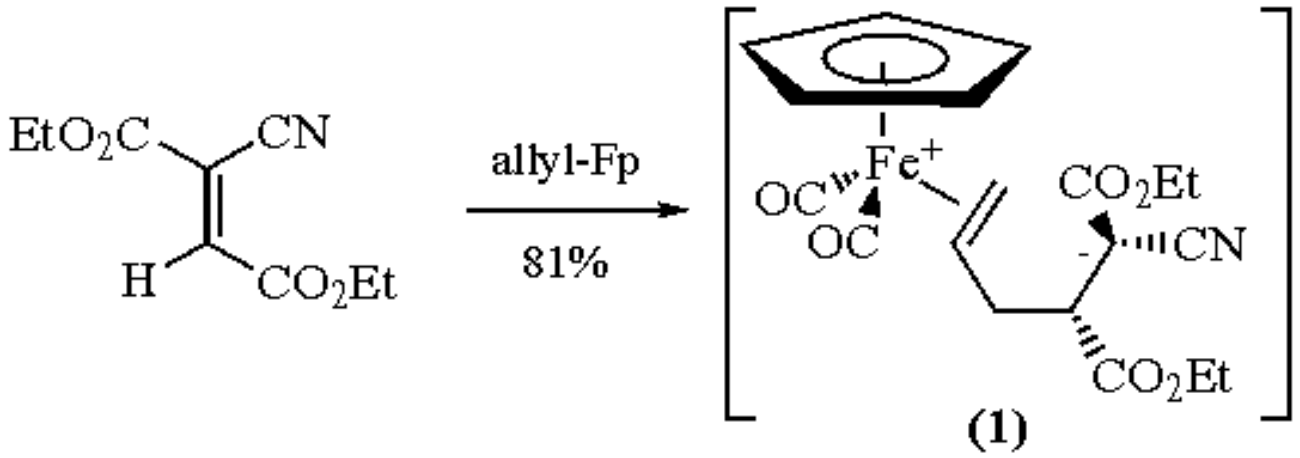

(1)

Cyclohexenones react with allyl-Fp to give *cis*-fused hydrindane products.[9] The reaction is promoted by the addition of Lewis acids such as ***Aluminum Bromide***; electron-deficient cycloalkenones such as 1-ethoxycarbonylcyclohexenone undergo cyclopentannulation in the absence of added Lewis acid. These reactions are sensitive to steric effects at the 3-position of the cycloalkenone.

A variety of methods have been developed for demetalation of the cyclopentyl iron complexes.[7] Esters are obtained by oxidation with ***Cerium(IV) Ammonium Nitrate*** (CAN) in ethanol under a carbon monoxide atmosphere (eq 2). Proteolytic demetalation with HCl has been employed to generate cyclopentanes; however, reversal of the cycloaddition is sometimes observed, and is a major drawback of this method.[7,10]

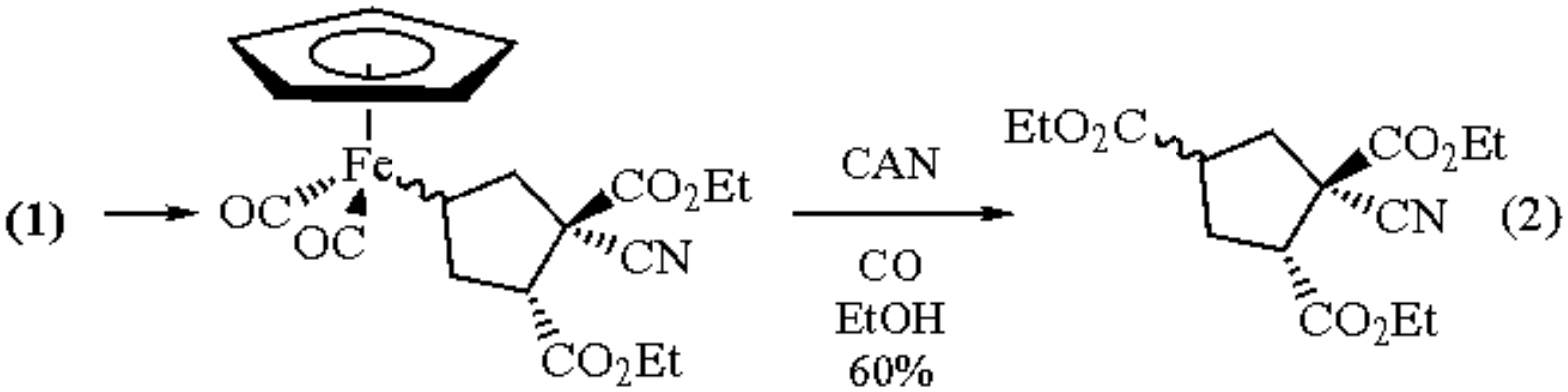

Metal-complexed alkenes have been shown to react with allyl-Fp to give bimetallic condensation products in moderate yields. For simple alkene complexes such as $Cp(CO)_2Fe(\eta^2\text{-}H_2C{=}CHR)^+BF_4^-$ (R = H, Me, Ph), the reaction proceeds readily with little regiospecificity.[10] Acrolein complexes (eq 3) react regiospecifically to give the product of Michael-type addition to the complexed enal.[10] ***Sodium Iodide*** in acetone selectively removes the cationic iron group from the alkene.[10] The alkyl-iron bond is selectively cleaved by treatment with HCl.[10]

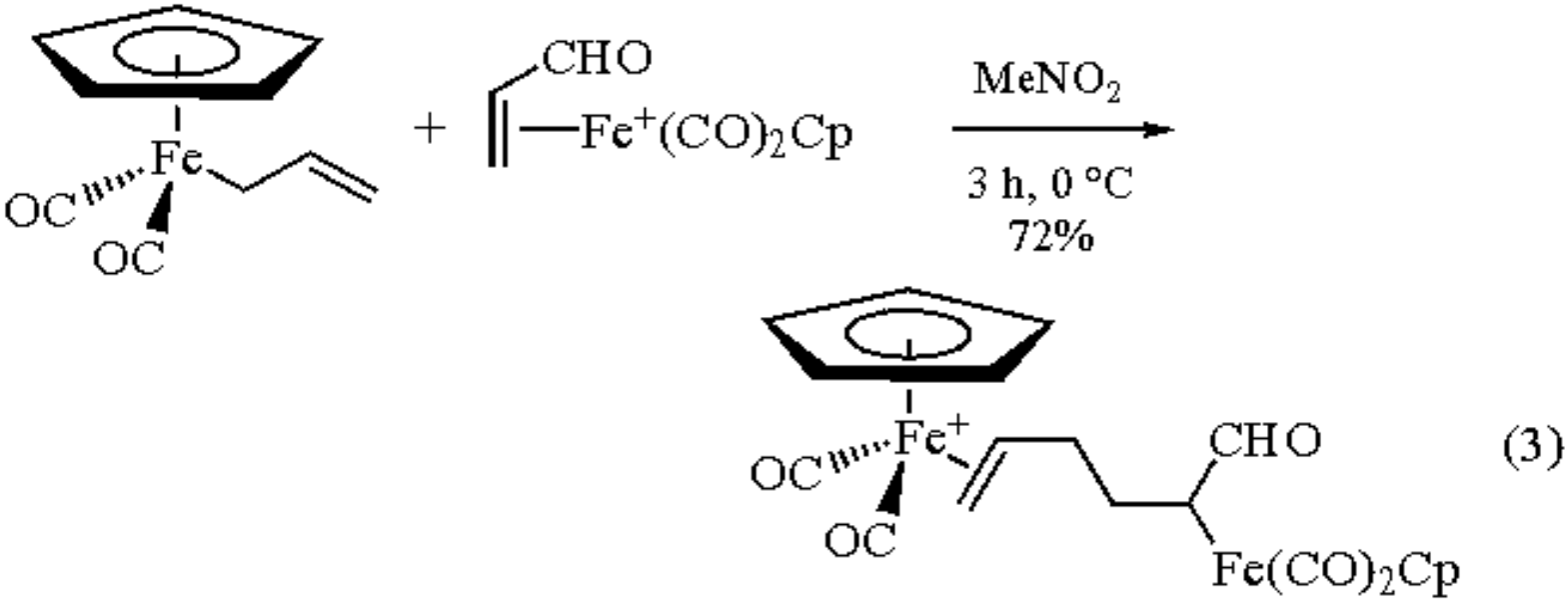

A variety of cationic tricarbonyl tropyliumiron complexes add allyl-Fp to give bimetallic hydroazulene complexes via [3 + 2] cycloaddition in moderate to good yields.[11] The cyclopentane ring in the product is *cis*-fused to the seven-membered ring, *trans* to the iron tricarbonyl unit. The product may be further functionalized by addition of electrophiles or nucleophiles.[11c]

In addition to [3 + 2] cycloadditions with two-carbon dipolarophiles, allyl-Fp undergoes a [3 + 3] cycloaddition reaction with cationic oxyallyl iron complexes.[5] The oxyallyl complex is generated in situ by refluxing a CH_2Cl_2 solution of ***Nonacarbonyldiiron*** and an α,α´-dibromo ketone. The yields for the reaction are moderate for tetrasubstituted, trisubstituted, or α,α´-disubstituted ketones; monosubstituted dibromo ketones fail to give cyclic products.

Allylation of Aldehydes and Ketones.

Allyl-Fp also reacts with aldehydes and ketones in the presence of Lewis acids such as ***Boron Trifluoride Etherate***.[4] Under these conditions the cationic iron alkene complex does not undergo internal trapping to give a substituted tetrahydrofuran. Instead, the iron alkene complex is isolated, which may be demetalated with sodium iodide in wet acetone to give the homoallyl alcohol (overall isolated yields range from 50-98%). In this respect the reagent is reminiscent of allylsilane or -stannane reagents. However, the ability to isolate a homoallyl alcohol with iron coordinated to the alkene gives the potential for further elaboration which is not available with silanes and stannanes.

Finally, it must be mentioned that homologs of allyl-Fp, such as methallyl-,[1] 2-[12] or 3-methoxyallyl-,[13] and propargyldicarbonylcyclopentadienyliron,[14] undergo many similar transformations. These related reagents allow for further versatility and unique reactivity.

Related Reagents.

Dicarbonyl(cyclopentadienyl)(isobutene)iron Tetrafluoroborate.

---

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14. See, for example, Ref. 11(a) and references therein.

Todd L. Underiner

The Procter & Gamble Co., Cincinnati, OH, USA

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B-Allyldiisocaranylborane[1]

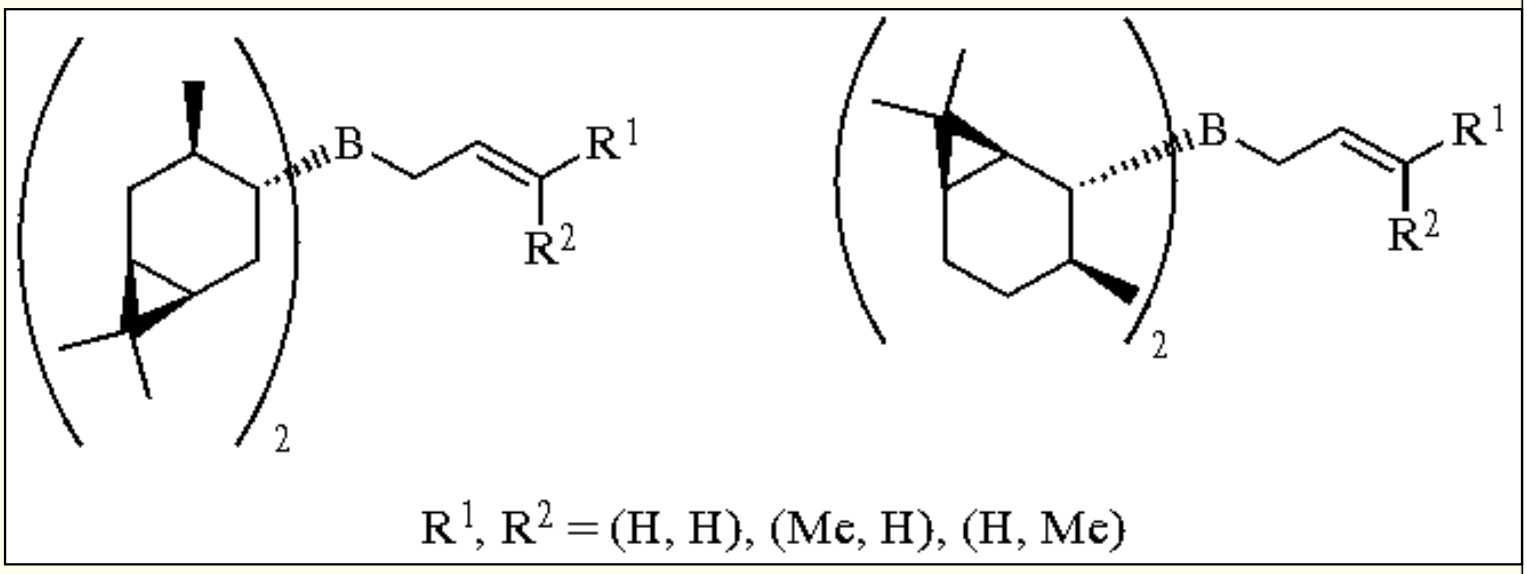

(4-^{d}Icr$_2$BAll)

[92055-65-7] · $C_{23}H_{39}B$ · *B*-Allyldiisocaranylborane · (MW 326.38) (2-^{d}Icr$_2$BAll)

[124821-92-7] · $C_{23}H_{39}B$ · *B*-Allyldiisocaranylborane · (MW 326.38) (4-^{d}Icr$_2$BCrt^{Z})

[103818-03-7] · $C_{24}H_{41}B$ · *B*-Crotyldiisocaranylborane · (MW 340.41) (4-^{d}Icr$_2$BCrt^{E})

[103882-37-7] · $C_{24}H_{41}B$ · *B*-Allyldiisocaranylborane · (MW 340.41) (2-^{d}Icr$_2$BCrt^{Z})

[130540-34-0] · $C_{24}H_{41}B$ · *B*-Allyldiisocaranylborane · (MW 340.41) (2-^{d}Icr$_2$BCrt^{E})

[130609-25-5] · $C_{24}H_{41}B$ · *B*-Allyldiisocaranylborane · (MW 340.41)

(reagents for the asymmetric allyl- and crotylboration of aldehydes to produce secondary homoallylic alcohols[2] and β-methylhomoallylic alcohols[3])

Solubility: these reagents are prepared and used in situ at -78 °C in Et_2O (Icr$_2$BAll) or THF (Icr$_2$BCrt).

Preparative Methods: both reagents are derived from the corresponding *B*-methoxydiisocaranylborane which is prepared in two steps from (+)-3- or (+)-2-carene (eqs 1 and 2). Note: only the (+) isomer of 3-carene occurs naturally; (+)-2-carene is obtained by base-catalyzed isomerization, and both are commercially available.

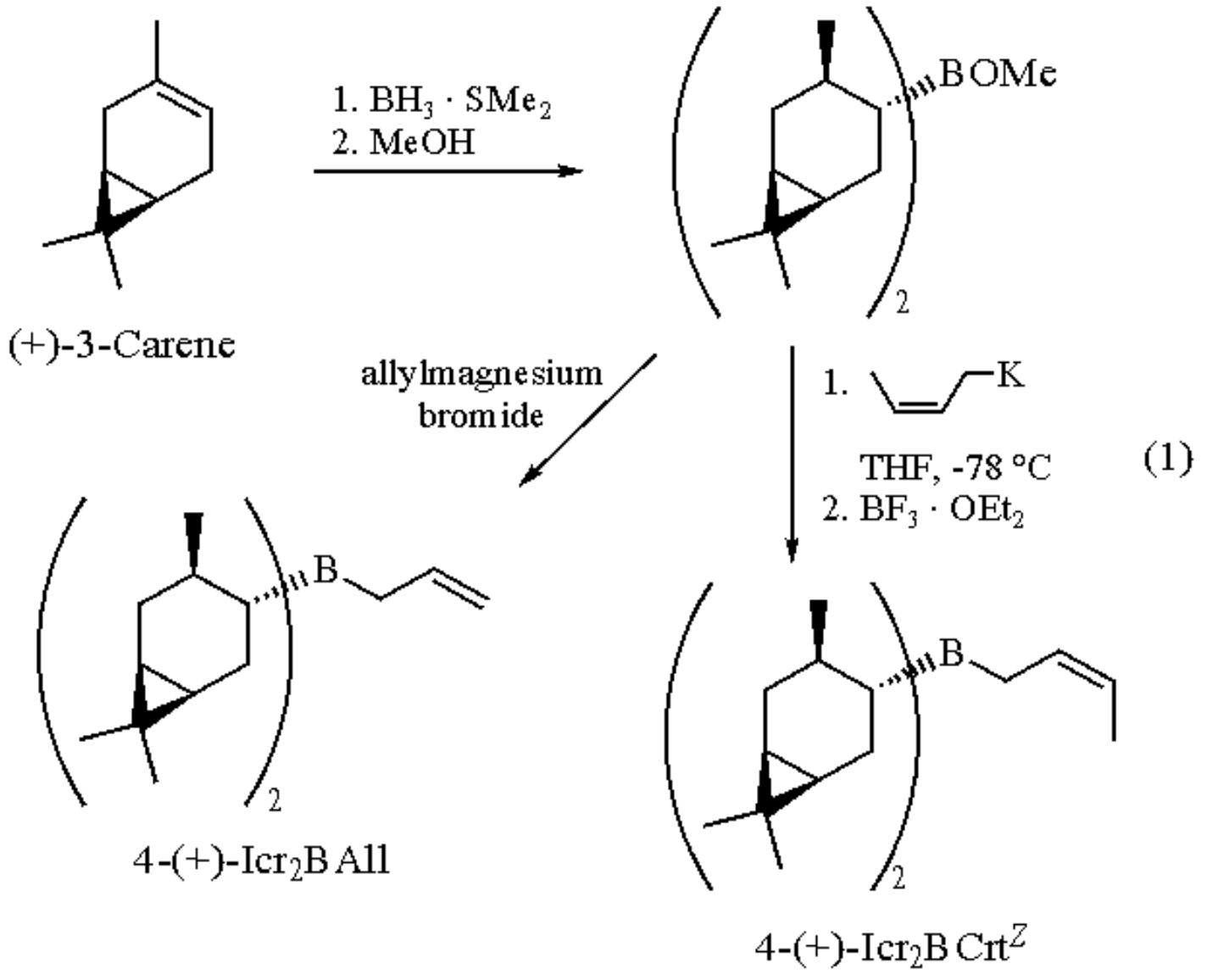
1. BH3 · SMe2
2. MeOH
BOMe
2
(+)-3-Carene
allylmagnesium bromide
1. K
THF, -78 °C
2. BF3 · OEt2
(1)
B
2
4-(+)-Icr2B All
B
2
4-(+)-Icr2B Crt^Z

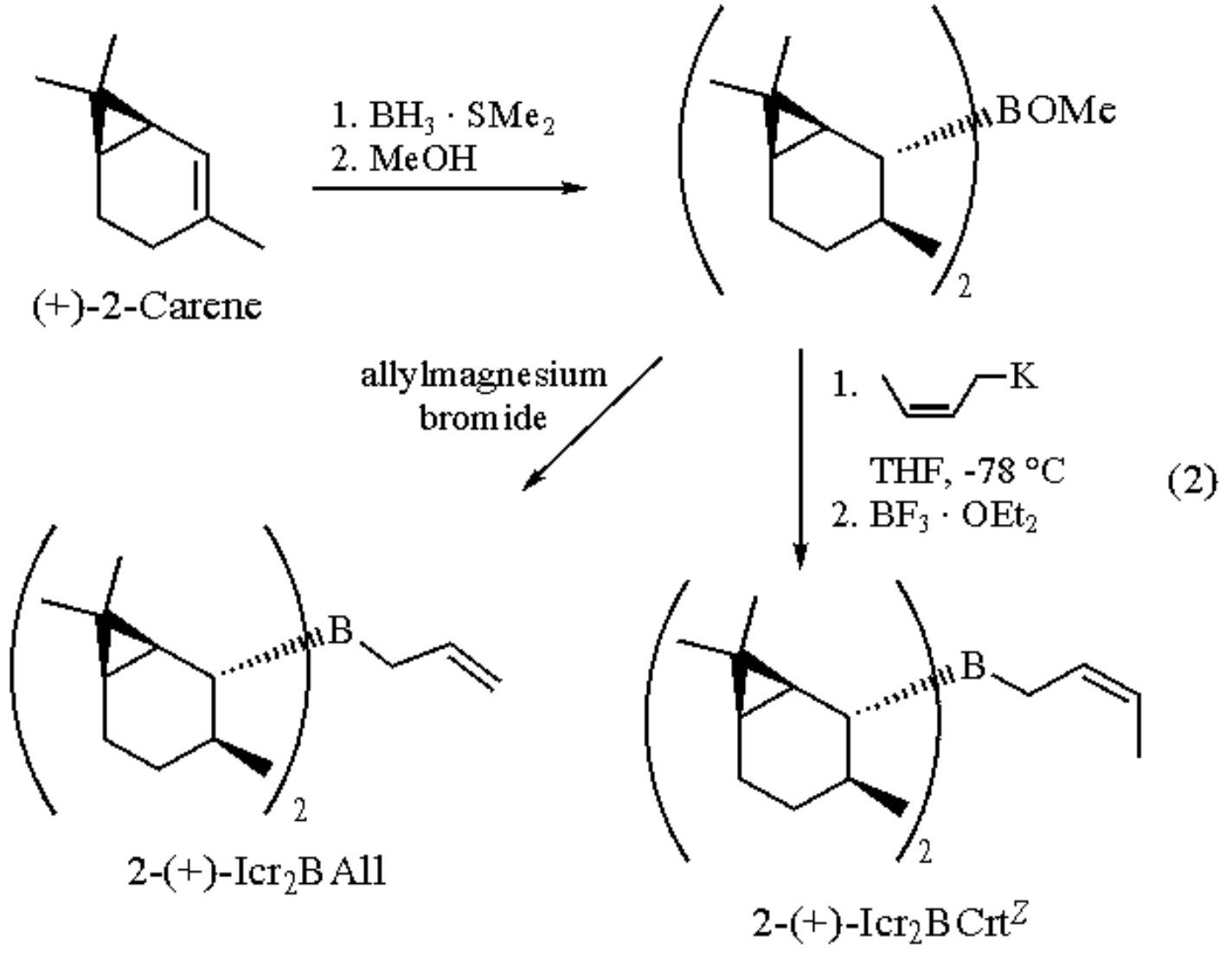

Allylboration of Aldehydes.

The *B*-allyldiisocaranylboranes (Icr_2BAll) condense with aldehydes with exceptional levels of enantioselectivity (98- &egt; 99% ee) to form, upon workup, secondary homoallylic alcohols.[2] While both regioisomers of this reagent (2-$^{d}Icr_2BAll$ and 4-$^{d}Ipc_2BAll$) are derived from the (+)-terpene, they exhibit complementary reactivity to form enantiomeric products (eqs 3 and 4). The degree of enantioselection achieved in the condensation of Icr_2BAll with aldehydes is superior to other means of allylboration[1] (see also ***B-Allyldiisopinocampheylborane***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***(R,R)-2,5-Dimethylborolane***).

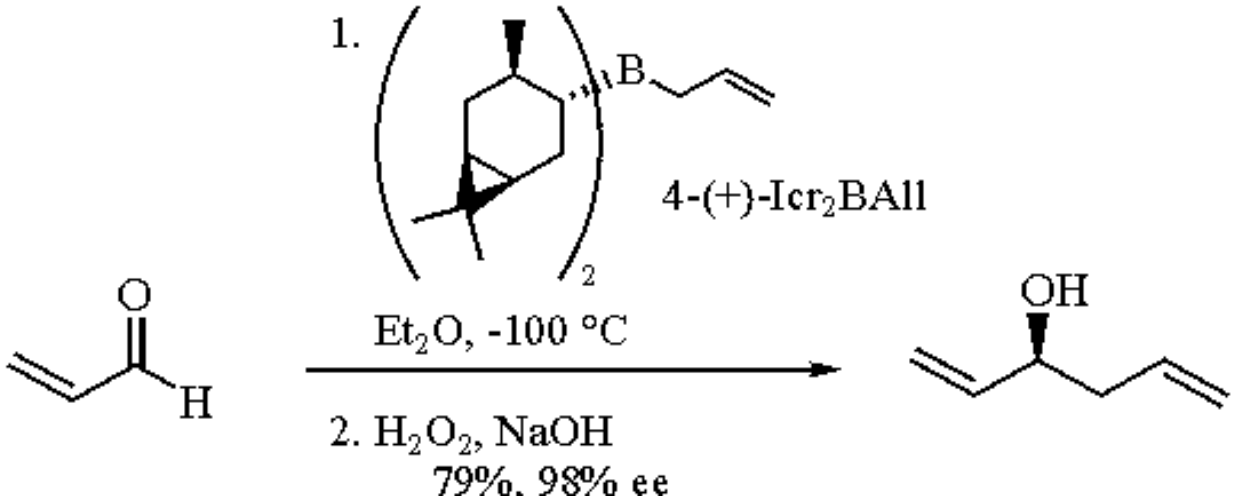

(3)

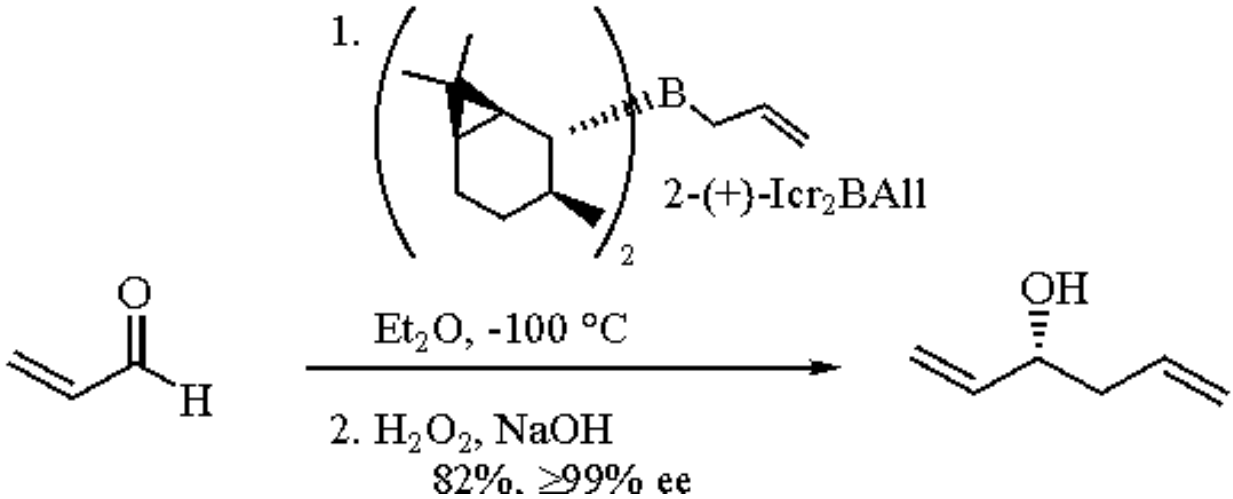

(4)

Crotylboration of Aldehydes.

The crotyl analogs of this reagent (Icr_2BCrt) likewise provide very high levels of enantio- and diastereoselectivity (&egt;99% de) when condensed with aldehydes.[3] By varying the geometry of the crotyl group (*Z* or *E*) and the (+)-carene isomer used in the reagent preparation (2- or 3-carene), all four of the possible β-methyl homoallylic alcohol products can be obtained (eqs 5 and 6). As with allylborations, the condensation of *B*-crotyldiisocaranylboranes with aldehydes provide higher levels of enantioselection than the other crotylboration reagents[3] (see also ***B-Crotyldiisopinocampheylborane***; (*Z*) and (*E*)-***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***(R,R)-2,5-Dimethylborolane***).

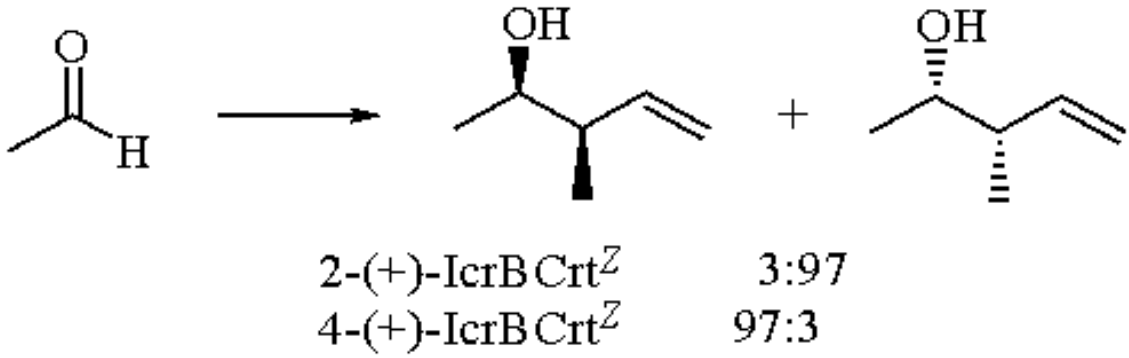

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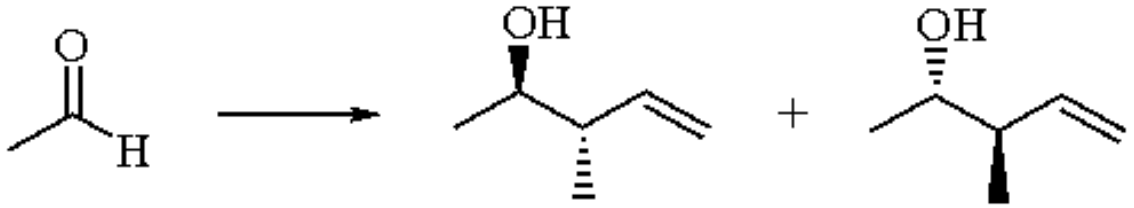

(6)

2-(+)-IcrB Crt^{E}	2:98
4-(+)-IcrB Crt^{E}	97:3

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1. Brown, H. C.; Ramachandran, P. V. *PAC* **1991**, *63*, 307.
2. (a) Brown, H. C.; Jadhav, P. K. *JOC* **1984**, *49*, 4089. (b) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *JACS* **1990**, *112*, 2389. (c) Racherla, U. S.; Brown, H. C. *JOC* **1991**, *56*, 401.
3. (a) Brown, H. C.; Bhat, K. S. *JACS* **1986**, *108*, 5919. (b) Brown, H. C.; Randad, R. S. *T* **1990**, *46*, 4457.

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B-Allyldiisopinocampheylborane[1]

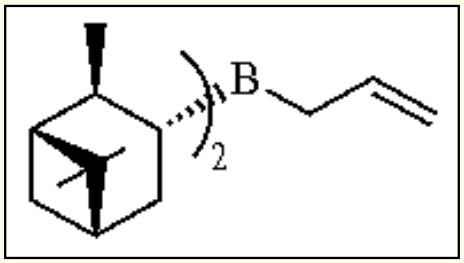

(+)-(Ipc_2BAll)

[85116-38-7] · $C_{23}H_{39}B$ · *B*-Allyldiisopinocampheylborane · (MW 324.36) (-)-(Ipc_2BAll)

[106356-53-0]

(reagent for the asymmetric allylboration of aldehydes to produce homoallylic alcohols[2,3])

Solubility: most often used as the crude preparation in Et_2O; however, reactions have also been conducted in CS_2, $CHCl_3$, CH_2Cl_2, toluene, and THF.

Analysis of Reagent Purity: ^{11}B NMR (δ +78, diethyl ether).

Preparative Methods: prepared in three steps from either (+)- or (-)-α-pinene (eq 1) (see also ***B*-Methoxydiisopinocampheylborane**).

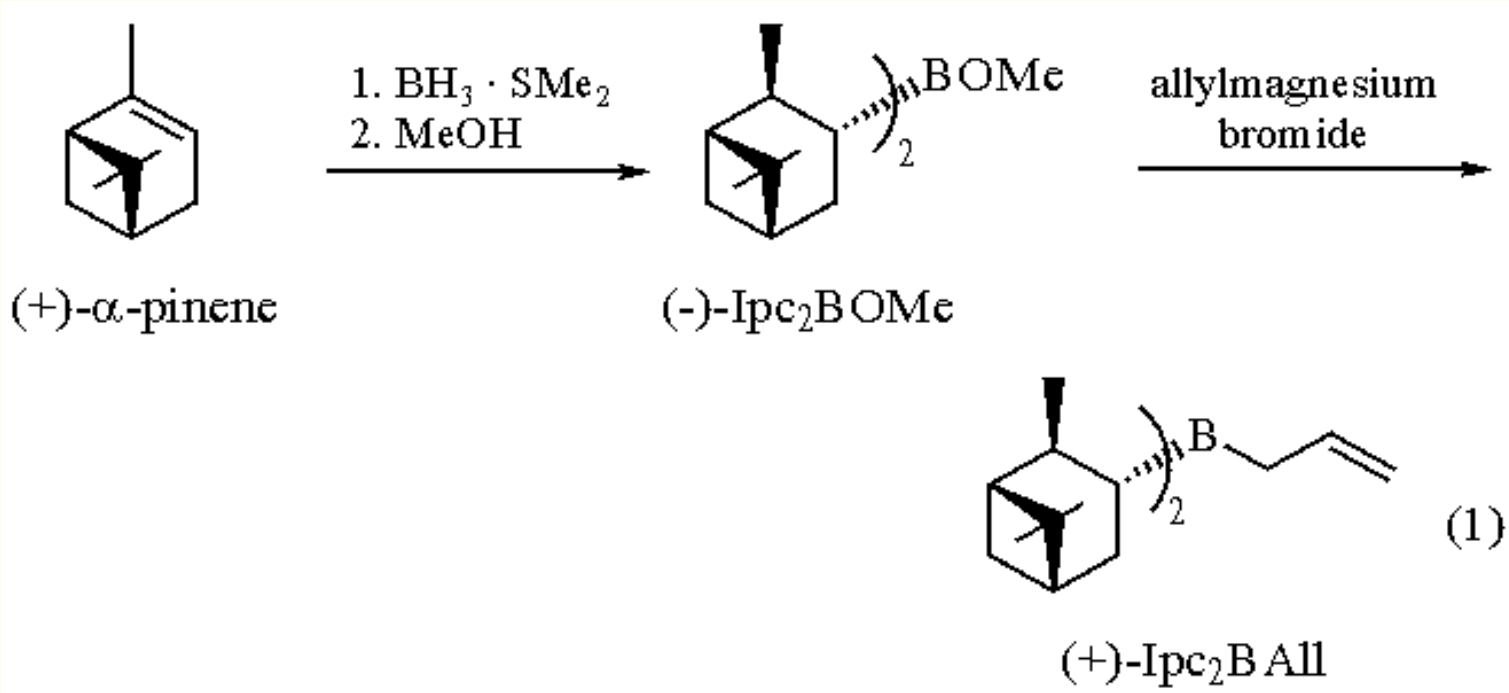

Handling, Storage, and Precautions: removal of magnesium salts from the crude reagent preparation is accomplished by solvent exchange into pentane and filtration. Concentration in vacuo provides the neat allylborane as a colorless liquid that can be stored under argon atmosphere for an extended period of time.

Addition to Aldehydes.

Condensation of *B*-allyldiisopinocampheylborane (Ipc_2BAll) with aldehydes occurs in good yield (50-90%) and with excellent enantioselection (83-96% ee) to provide secondary, homoallylic alcohols.[2] Improvements in the original procedure have produced a salt-free reagent preparation that can increase the enantioselectivity of many additions to &egt;99% ee (eqs 2 and 3).[3]

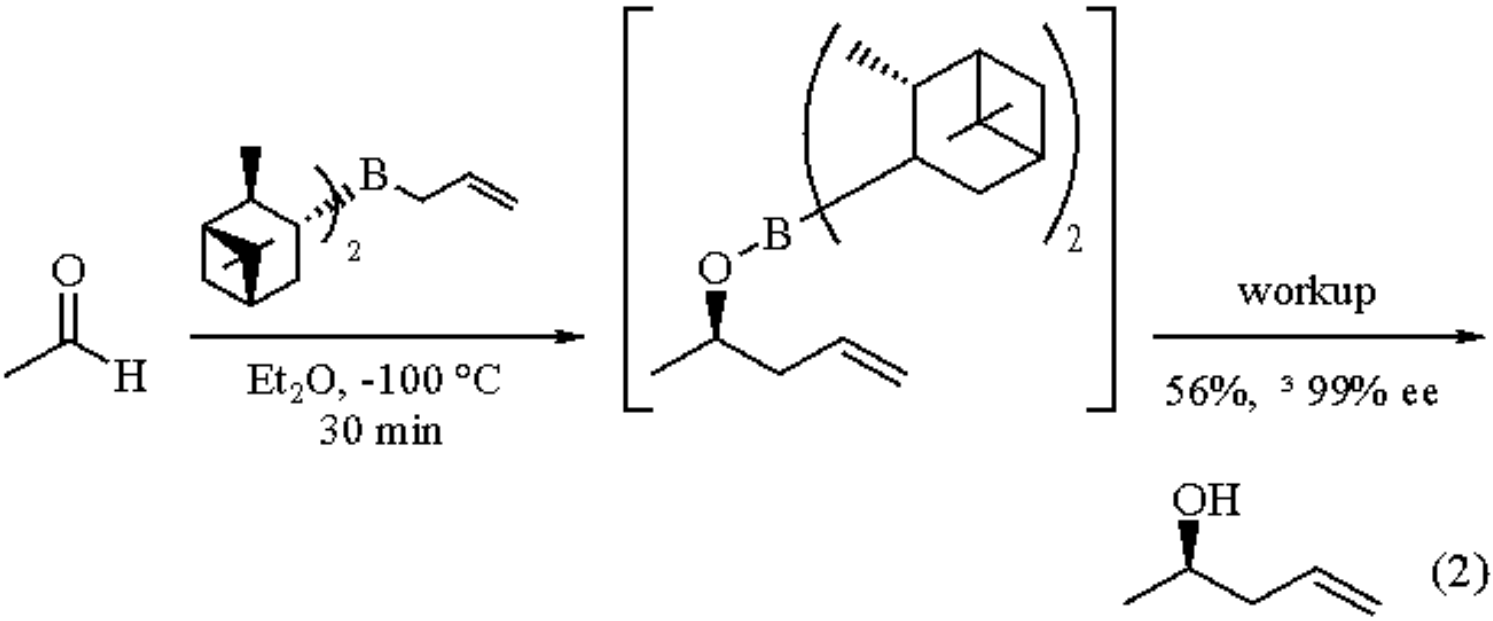

(2)

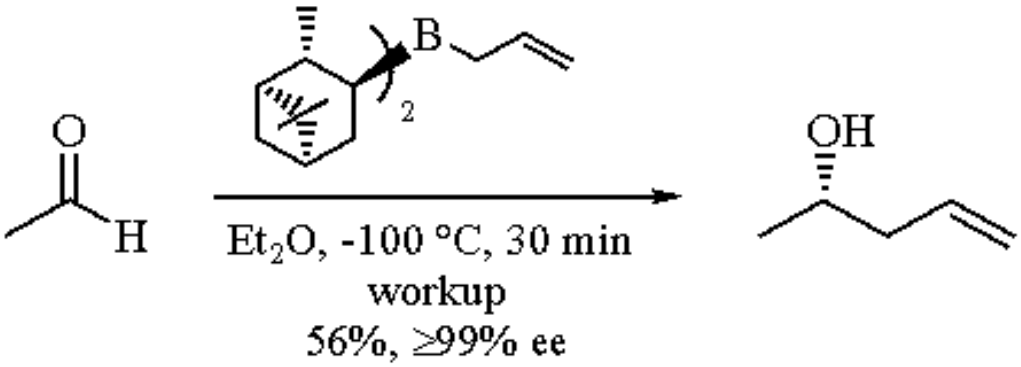

(3)

Several methods have been employed in the reaction workup to decompose the initial borinic ester adduct (eq 4).[2,4] An oxidative workup procedure (H_2O_2, NaOH) delivers the desired alcohol product along with 2 equiv of isopinocampheol. The elimination workup (*i*-PrCHO, $BF_3.OEt_2$) allows for recovery of the starting α-pinene, whereas the amino alcohol workup (ethanolamine or 8-hydroxyquinoline) precipitates the diisopinocampheylborinate-amino alcohol adducts which are removed by filtration, and which can also be recycled.

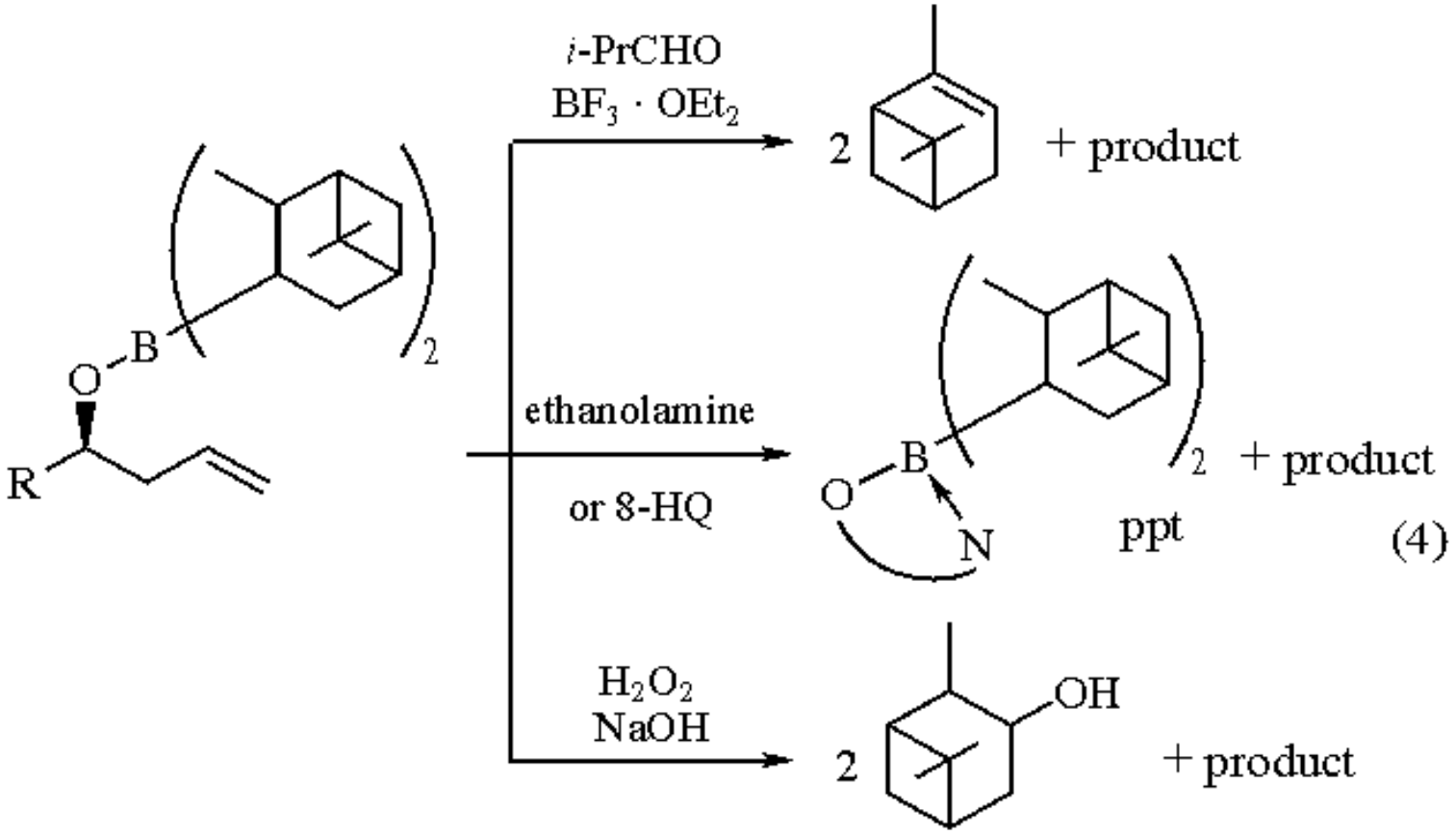

The (+)- and (-)-Ipc_2BAll reagents have been condensed with a variety of aldehyde structures[2,5] with no reported reversal of enantiospecificity. Because of this strict fidelity of addition, these reagents have been used in the structure determination of several natural products.[6] In the case of α-substituted aldehydes, however, an erosion of diastereofacial selectivity is sometimes observed for mismatched reactant pairs (eqs 5-7).[7]

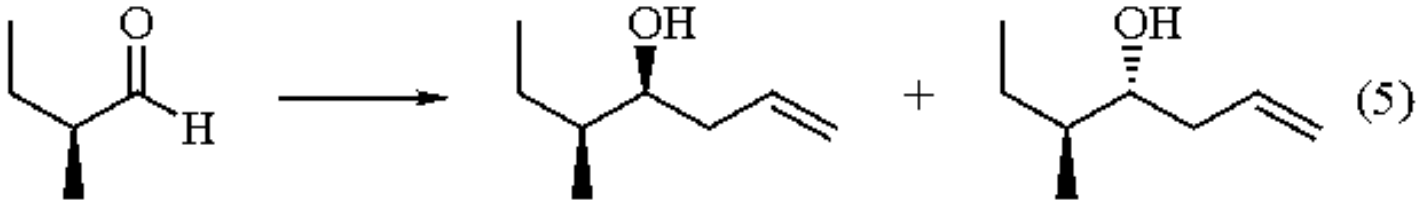

(+)-Ipc_2B All 96:4
(-)-Ipc_2B All 5:95

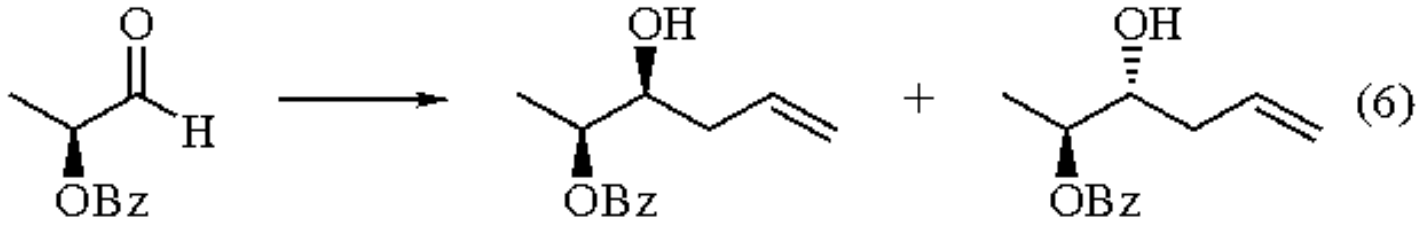

(+)-Ipc_2B All 96:4
(-)-Ipc_2B All 6:94

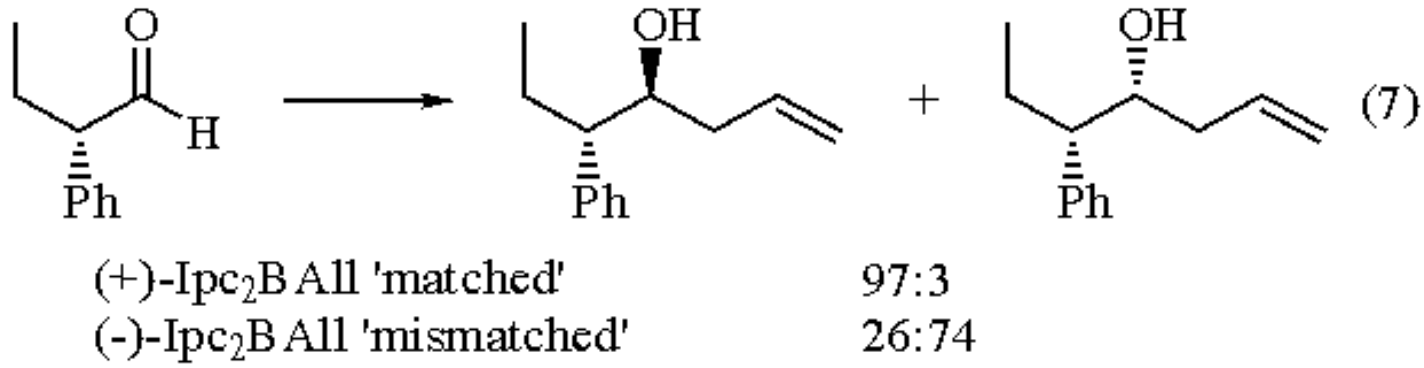

These reagents have been used for the conversion of C_s symmetrical chains into chiral, nonracemic products. A double condensation with *meso* dialdehydes can produce either optically active diol product (eq 8).[8]

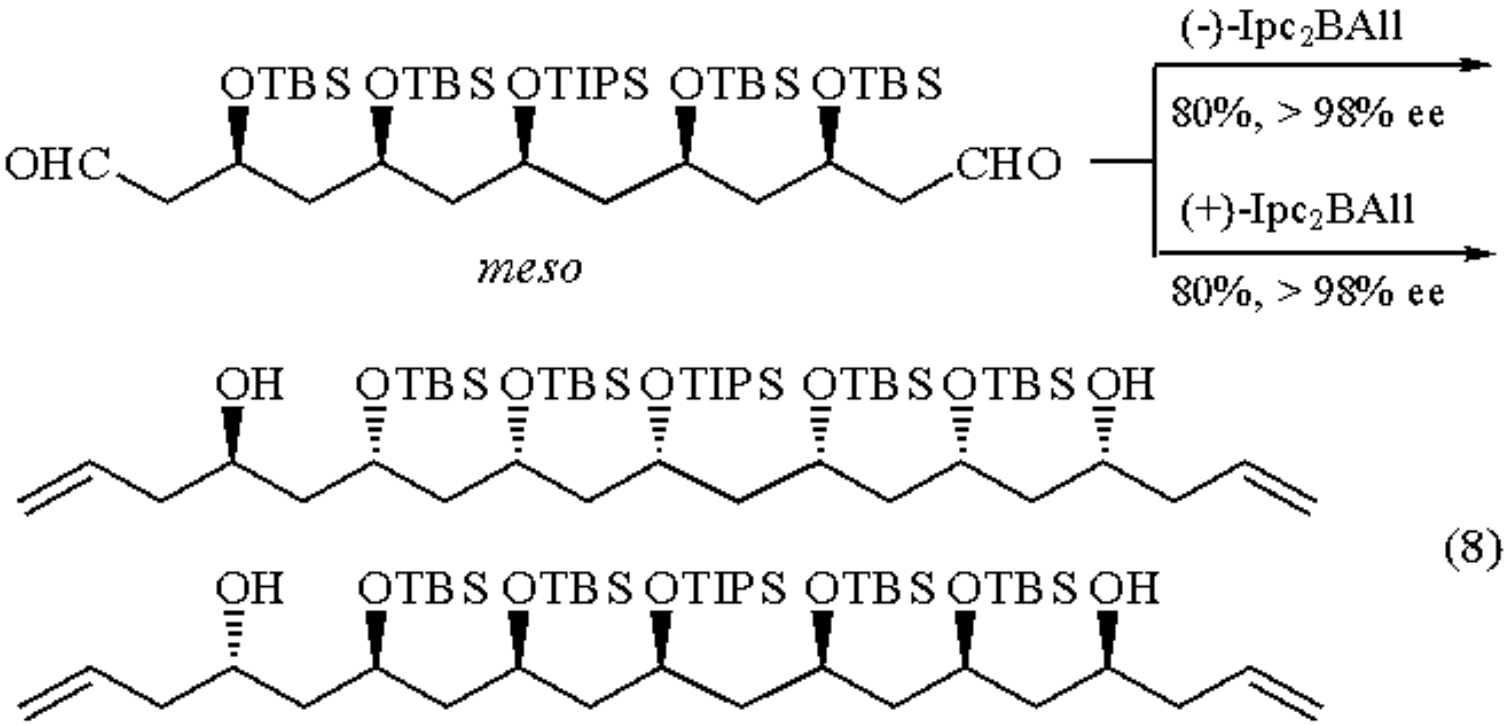

B-Allyldiisopinocampheylborane compares favorably in both yield and enantioselectivity to alternate methods of asymmetric allylboration[1] (see also ***B-Allyldiisocaranylborane***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***(R,R)-2,5-Dimethylborolane***).

Addition to Ketones.

Condensation of Ipc_2BAll with methyl ketones proceeds with modest to good enantioselectivity. Unlike with aldehydes, the degree of enantioselection is highly dependent upon ketone structure (eq 9).[2]

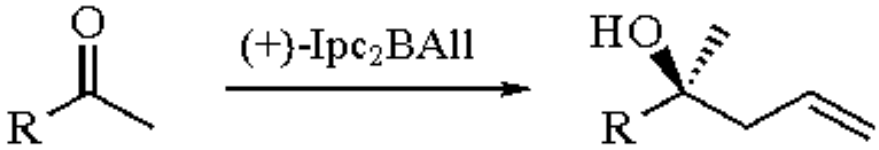

(9)

R = ethyl	yield (%) = 68	ee (%) = 50
vinyl	79	35
phenyl	63	5
ethynyl	76	75

B-Methallyldiisopinocampheylborane and Related Reagents.

Derivatives of the reagent containing substituted allyl groups have been used for the synthesis of more highly functionalized homoallylic alcohols (see also ***B-Crotyldiisopinocampheylborane*** and ***B-Allyldiisocaranylborane***). In general, these reagents are prepared in a manner analogous to Ipc_2BAll or by hydroboration of the corresponding diene with diisopinocampheylborane. For example, reagents containing alkyl substituents, such as *B*-methallyldiisopinocampheylborane and *B*-(3,3-dimethylallyl)diisopinocampheylborane, condense with aldehydes to give the corresponding substituted homoallylic alcohols (eqs 10 and 11).[9] An alkenyl-substituted derivative, *B*-2´-isoprenyldiisopinocampheylborane, has been used for the asymmetric isoprenylation of aldehydes (eq 12).[10]

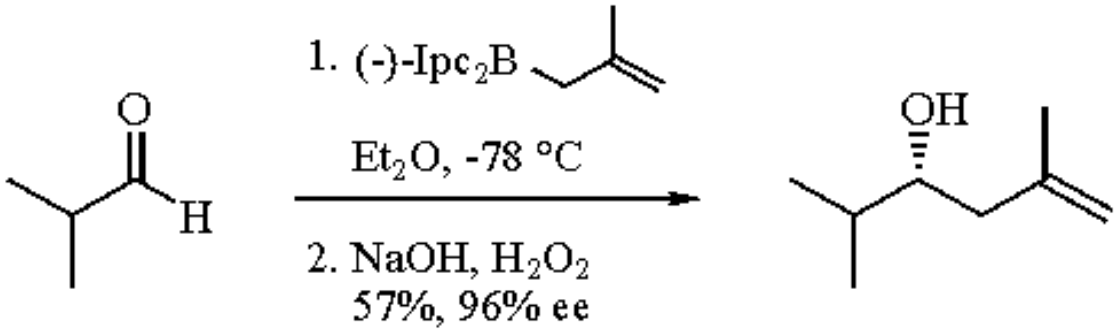

(10)

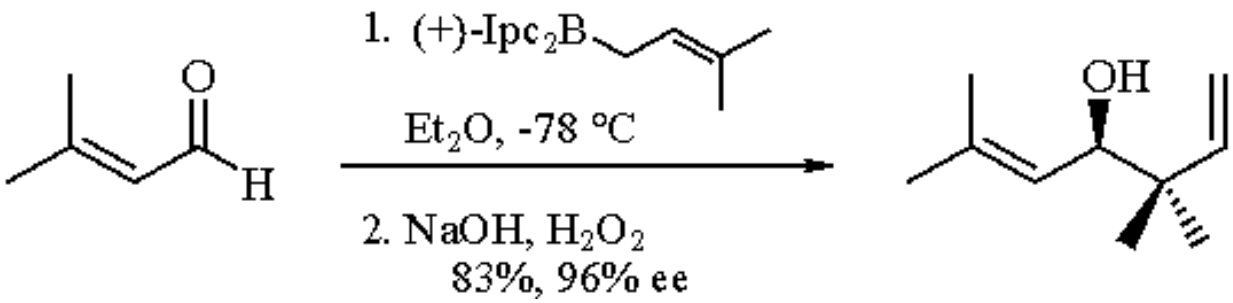

(11)

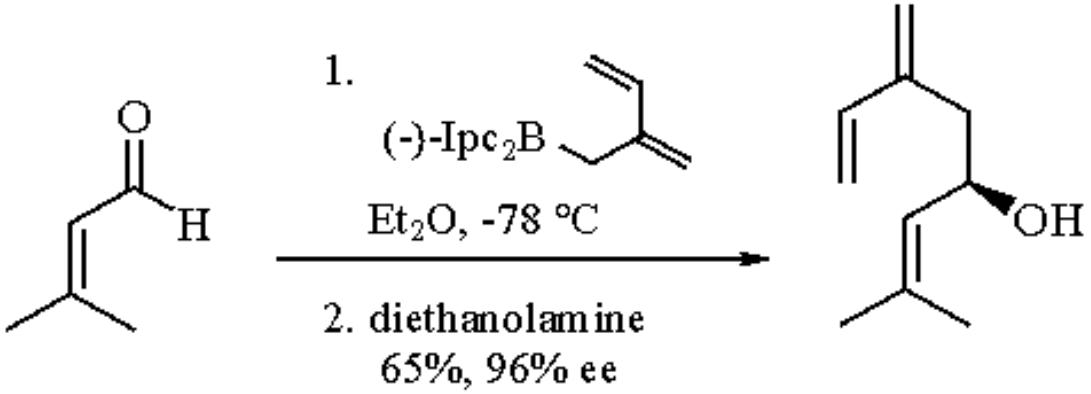

(12)

Derivatives containing heteroatoms have allowed for the preparation of allylic 1,2-diols and amino alcohols by this method. Aldehydes react with *B*-[(*Z*)-3-(methoxymethyloxy)allyl]diisopinocampheylborane to give monoprotected diol adducts.[11] 1,2-Diols can be obtained directly by condensation with *B*-[(*E*)-3-((diisopropylamino)dimethylsilyl)allyl]diisopinocampheylborane followed by an oxidative reaction workup (eqs 13 and 14).[12]

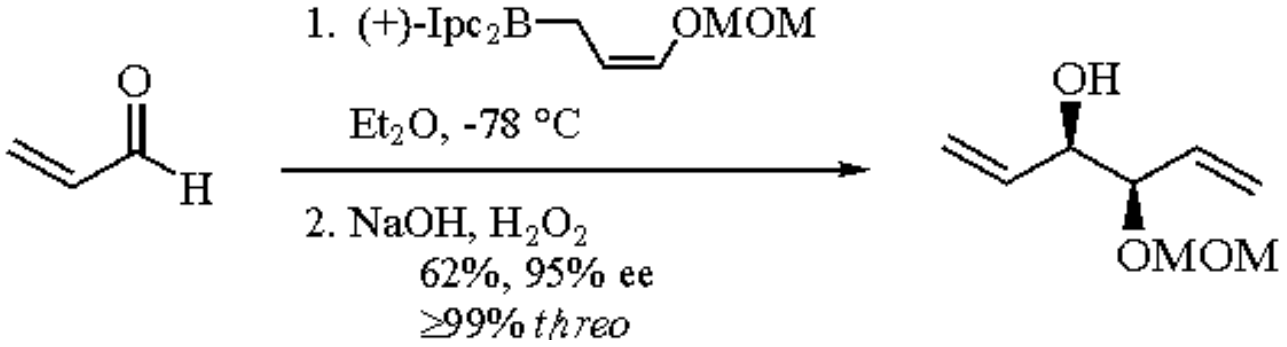

(13)

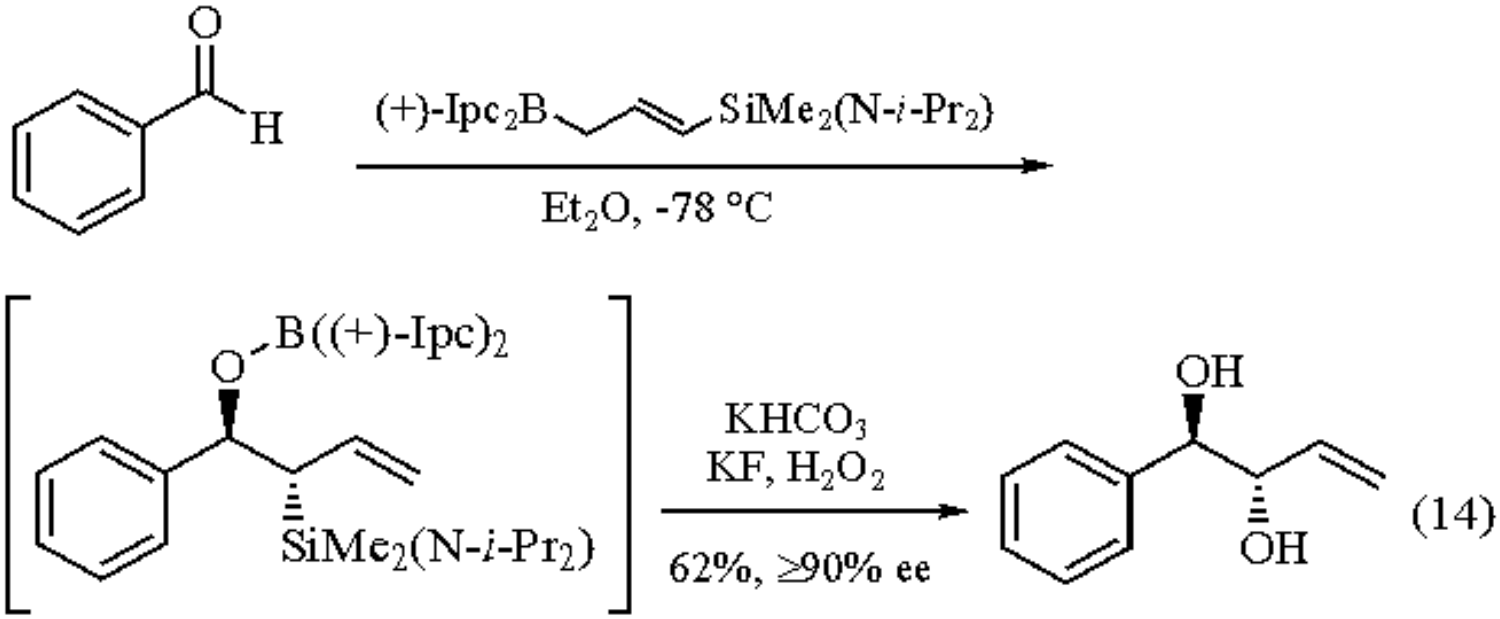

(14)

Amine-containing reagents, such as *B*-[(*E*)-3-(diphenylamino)allyl]diisopinocampheylborane, react in a similar manner to provide 1,2-amino alcohols (eq 15).[13] A further variation on this reagent is where the allylic group is contained in a ring. The cyclohexenyl reagent *B*-(cyclohex-2-enyl)diisopropylcampheylborane and the related cycloheptenyl and cyclooctenyl versions have been described.[14] At low temperatures (< -25 °C), these boranes are stable toward allylic isomerization and transfer with complete diastereoselectivity to provide *erythro* products (eq 16).

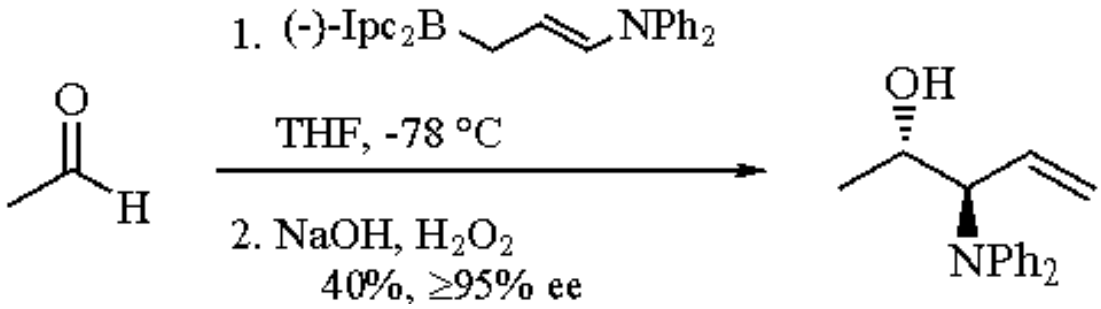

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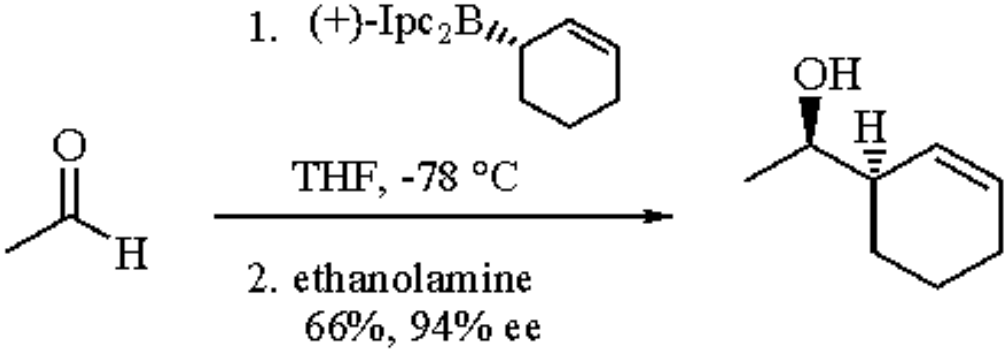

(16)

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1. Brown, H. C.; Ramachandran, P. V. *PAC* **1991**, *63*, 307.
2. (a) Brown, H. C.; Jadhav, P. K. *JACS* **1983**, *105*, 2092. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *JOC* **1986**, *51*, 432.
3. Racherla, U. S.; Brown, H. C. *JOC* **1991**, *56*, 401.
4. Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. *JOC* **1992**, *57*, 6608.
5. For a representation of functionality that is tolerated in this reaction see: (a) Stork, G.; Zhao, K. *JACS* **1990**, *112*, 5875. (b) Nicolaou, K. C.; Groneberg, R. D.; Stylianides, N. A.; Miyazaki, T. *CC* **1990**, 1275. (c) Rychnovsky, S. D.; Rodriguez, C. *JOC* **1992**, *57*, 4793. (d) Racherla, U. S.; Liao, Y.; Brown, H. C. *JOC* **1992**, *57*, 6614.
6. (a) Schreiber, S. L.; Goulet, M. T. *JACS* **1987**, *109*, 8120. (b) Nicolaou, K. C.; Ahn, K. H. *TL* **1989**, *30*, 1217. (c) Mori, Y.; Kohchi, Y.; Noguchi, H.; Suzuki, M.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *T* **1991**, *47*, 4889.
7. (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *JOC* **1987**, *52*, 319. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *JOC* **1989**, *54*, 1570.
8. Wang, Z.; Deschênes, D. *JACS* **1992**, *114*, 1090.
9. (a) Brown, H. C.; Jadhav, P. K. *TL* **1984**, *25*, 1215. (b) Brown, H. C.; Jadhav, P. K.; Perumal, P. T. *TL* **1984**, *25*, 5111. (c) Truesdale, L. K.; Swanson, D.; Sun, R. C. *TL* **1985**, *26*, 5009.
10. (a) Brown, H. C.; Randad, R. S. *TL* **1990**, *31*, 455. (b) Brown, H. C.; Randad, R. S. *T* **1990**, *46*, 4463.
11. (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *JACS* **1988**, *110*, 1535. (b) Burgess, K.; Chaplin, D. A.; Henderson, I.; Pan, Y. T.; Elbein, A. D. *JOC* **1992**, *57*, 1103. (c) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *CC* **1992**, 1236.
12. (a) Barrett, A. G. M.; Malecha, J. W. *JOC* **1991**, *56*, 5243. (b) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Malecha, J. W.; Parkinson, C. J. *CC* **1992**, 1240.
13. Barrett, A. G. M.; Seefeld, M. A. *CC* **1993**, 339.
14. (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *JACS* **1985**, *107*, 2564. (b) Brown, H. C.; Bhat, K. S.; Jadhav, P. K. *JCS(P1)* **1991**, 2633.

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Allyldiphenylphosphine Oxide[1]

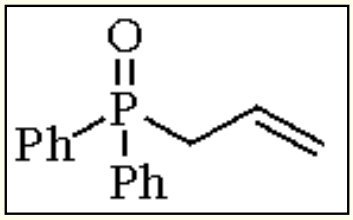

[4141-48-4] · $C_{15}H_{15}OP$ · Allyldiphenylphosphine Oxide · (MW 242.26)

(reagent for Wittig-Horner reaction;[2] substrate for carbon-phosphorus heterocycle[3] and 1,3-dipolar cycloaddition[4])

Physical Data: mp 108-109 °C;[5] ^{1}H and ^{31}P NMR studies have been reported.[6]

Solubility: sol THF; slightly sol ether; insol hexane.

Form Supplied in: white solid; commercially available.[7]

Preparative Methods: two processes have most commonly been used: (1) rearrangement of allyl diphenylphosphinite[2,8,12] and (2) Arbuzov reaction of alkyl diphenylphosphinite with ***Allyl Bromide***.[9,13] Other new methods have been also developed.[10,14] Structurally related analogs prepared include: 2-methylallyldiphenylphosphine oxide,[15] 2-phenylallyldiphenylphosphine oxide,[15] 1-methoxyallyldiphenylphosphine oxide,[16] crotyldiphenylphosphine oxide,[17] and 1-substituted allylic diphenylphosphine oxide.[18]

Purification: recrystallization from ether/hexane,[2] benzene/petroleum ether,[8] cyclohexane,[9] or benzene.[10]

Handling, Storage, and Precautions: thermally stable up to 150 °C.[11]

Wittig-Horner Reaction.

Lithiated allyldiphenylphosphine oxide condenses with aldehydes in THF-HMPA solution to give (*E*)-1,3-dienes directly and stereoselectively in good yield[2] (for synthesis of 1,3-dienes, see also ***Allylidenetriphenylphosphorane***). This process has been utilized for the synthesis of (*E*)-trienes (eq 1).[19] Condensation with ketones also affords 1,3-dienes (eq 2).[2,20]

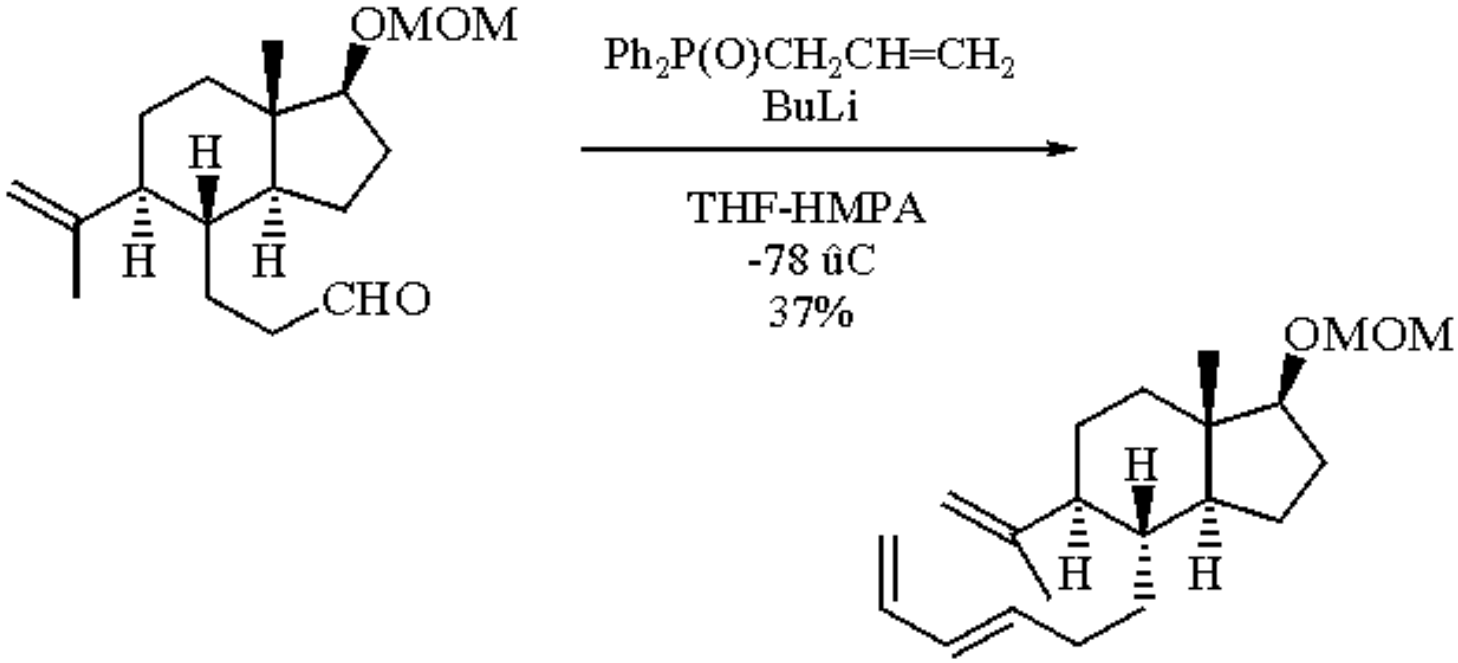

(1)

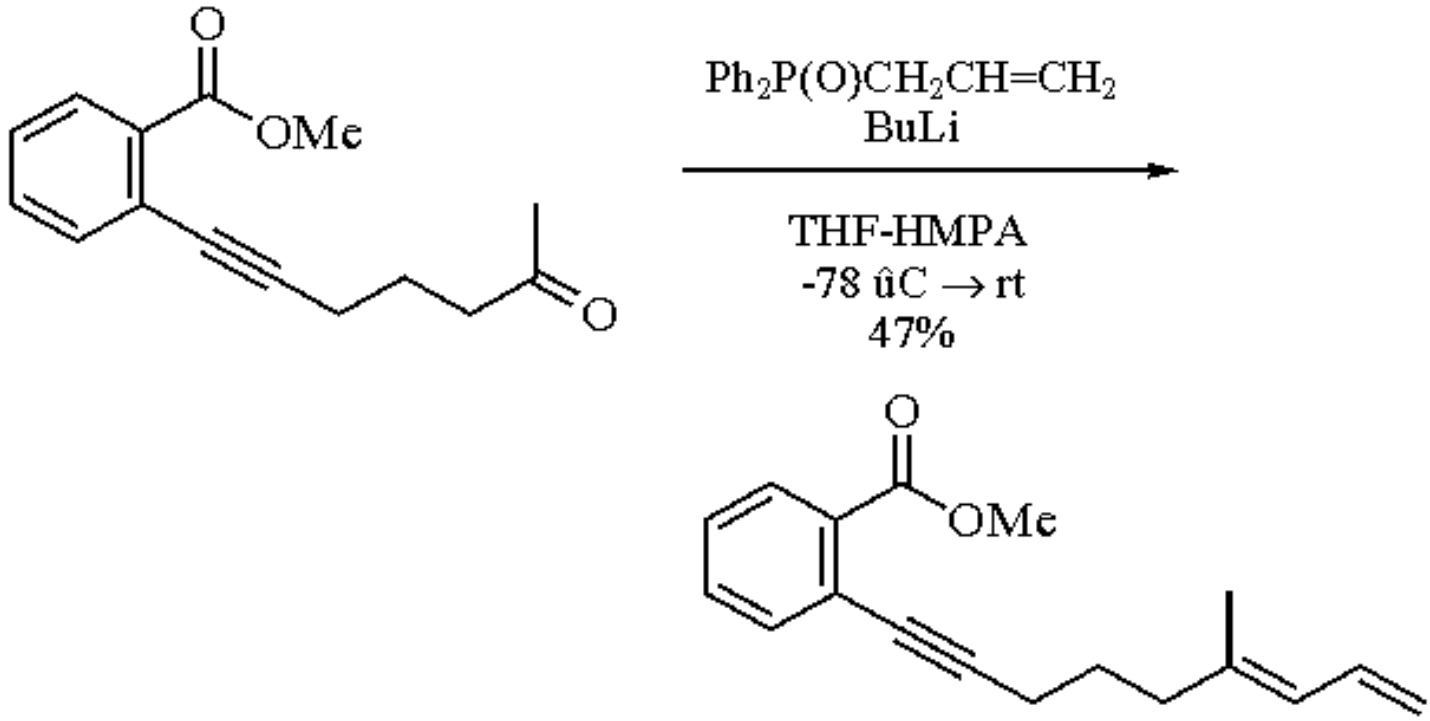

(2)

(*Z*)-Dienes can be prepared with high selectivity by use of a titanium reagent prepared from diphenylphosphinoallyllithium, the metalation product of allyldiphenylphosphine (eqs 3 and 4).[2a,2c]

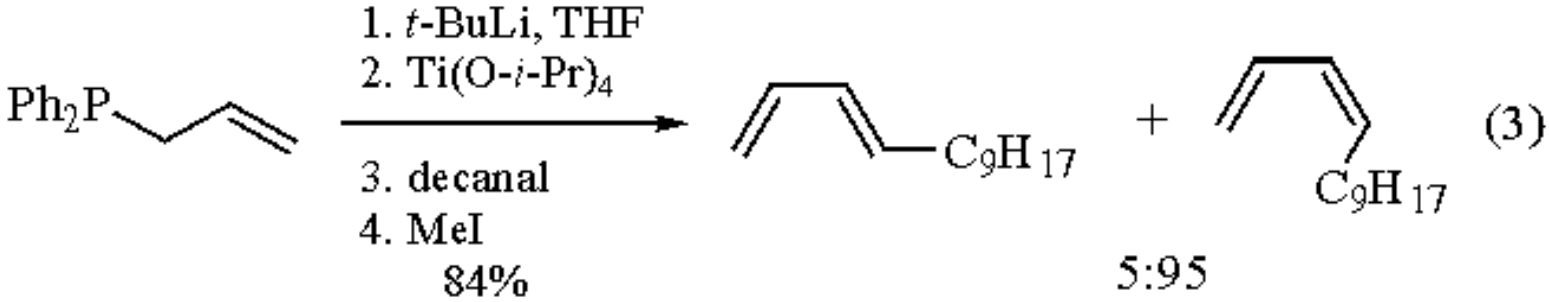

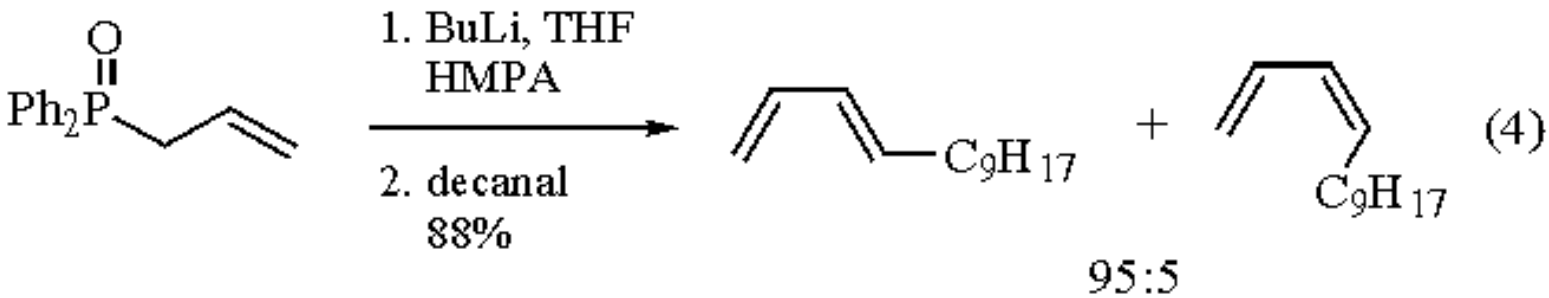

The Wittig-Horner reaction of structurally related allylic diphenylphosphine oxides has been widely studied by Warren.[18,21] In the absence of HMPA, reaction of lithiated allylic diphenylphosphine oxide with aldehyde affords the Wittig-Horner intermediate alcohol which can be transformed into the 1,3-diene by ***Sodium Hydride*** in DMF (eq 5).[18a,21a,21b]

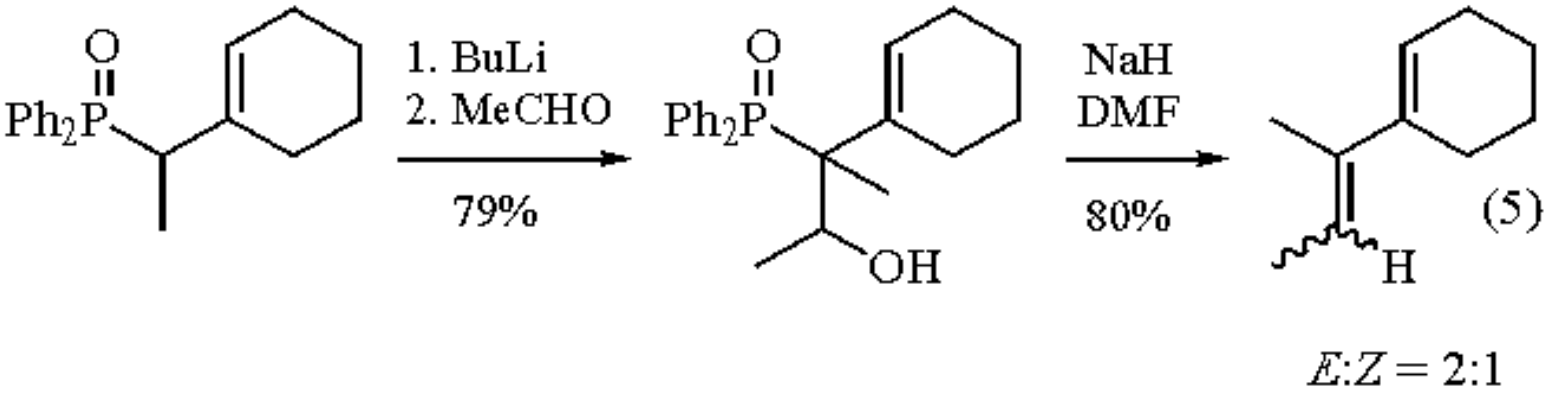

Geometrically homogeneous crotyldiphenylphosphine oxide can be used to give conjugated diene in which the original (*Z*) or (*E*) geometry is retained.[17] 1-Methoxyallyldiphenylphosphine oxide ylides react at the γ-allylic terminus with aldehydes.[22]

Other Reactions.

Cyclization of allyldiphenylphosphine oxide occurs in the presence of 115% ***Polyphosphoric Acid*** (PPA) at 180-200 °C to give carbon-phosphorus heterocycles in modest yield (eq 6).[3] Allyldiphenylphosphine oxide undergoes 1,3-dipolar cycloaddition with nitrile oxide to give 3,5-disubstituted Δ^2-isoxazolines (eq 7).[4]

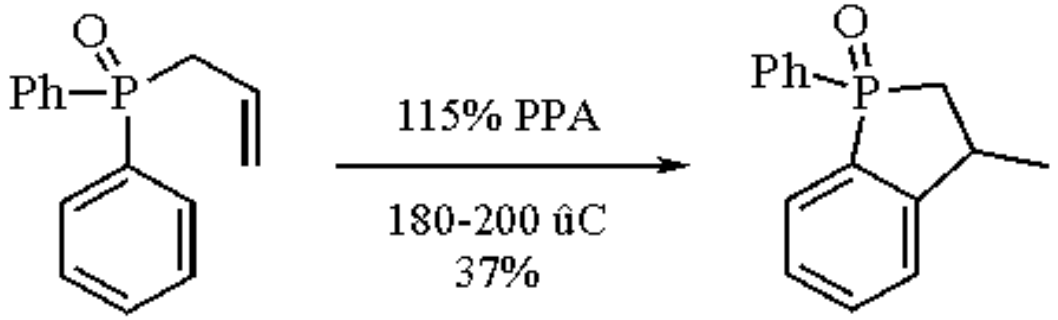

(6)

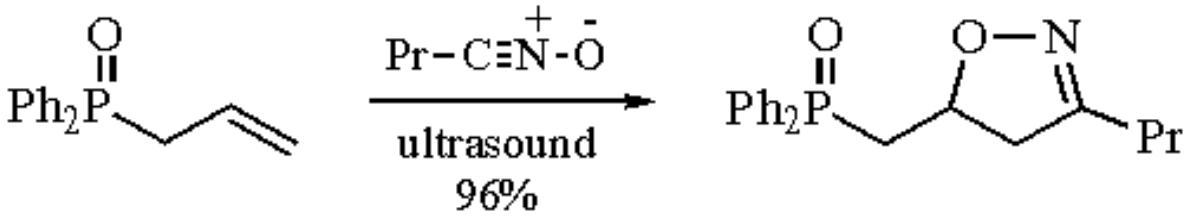

(7)

Related Reagents.

Allylidenetriphenylphosphorane; ***Allyltributylstannane***; ***Allyltriphenylphosphonium Bromide***; ***Trimethylsilylallyllithium***.

---

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O-Allylhydroxylamine

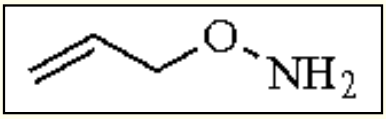

[6542-54-7] · C_3H_7NO · *O*-Allylhydroxylamine · (MW 73.11)

(*O*-allyloximes, pyridine synthesis)

Alternate Name: O-2-propenylhydroxylamine.

Physical Data: bp 80 °C, IR 3350 cm^{-1}. The reagent is typically prepared as the hydrochloride salt which is a white solid that may be recrystallized from EtOH and ether.

Preparative Methods: ***Allyl Bromide*** (39 mL, 0.46 mol) is added dropwise with stirring to a suspension of anhydrous K_2CO_3 (43 g) and commercially available *N*-hydroxyphthalimide (50 g, 0.31 mol) in DMSO (500 mL) at 25 °C. After addition, the mixture is stirred at room temp for 24 h and then poured into cold water (3 L). The precipitate is collected, washed with water, and dried. Recrystallization from EtOH gives *N*-allyloxyphthalimide (87%), mp 56-57 °C. A mixture of *N*-allyloxyphthalimide (10 g, 0.05 mol), hydrazine hydrate (5 mL, 0.1 mol), and EtOH (100 mL) is refluxed for 2 h and then cooled and poured into 3% aqueous Na_2CO_3 (500 mL). The solution is extracted with ether. The ether extract is washed with water and then 5 mL of conc HCl are added. Evaporation gives a solid which is recrystallized from EtOH and ether to afford *O*-allylhydroxylamine hydrochloride as a white solid (eq 1). The free amine can be liberated by distillation from KOH (bp 80 °C)[1] or by treatment with ammonia in situ.[2] It may be conveniently stored as the *N*-allyloxphthalimide intermediate which is converted to *O*-allylhydroxylamine hydrochloride as needed.

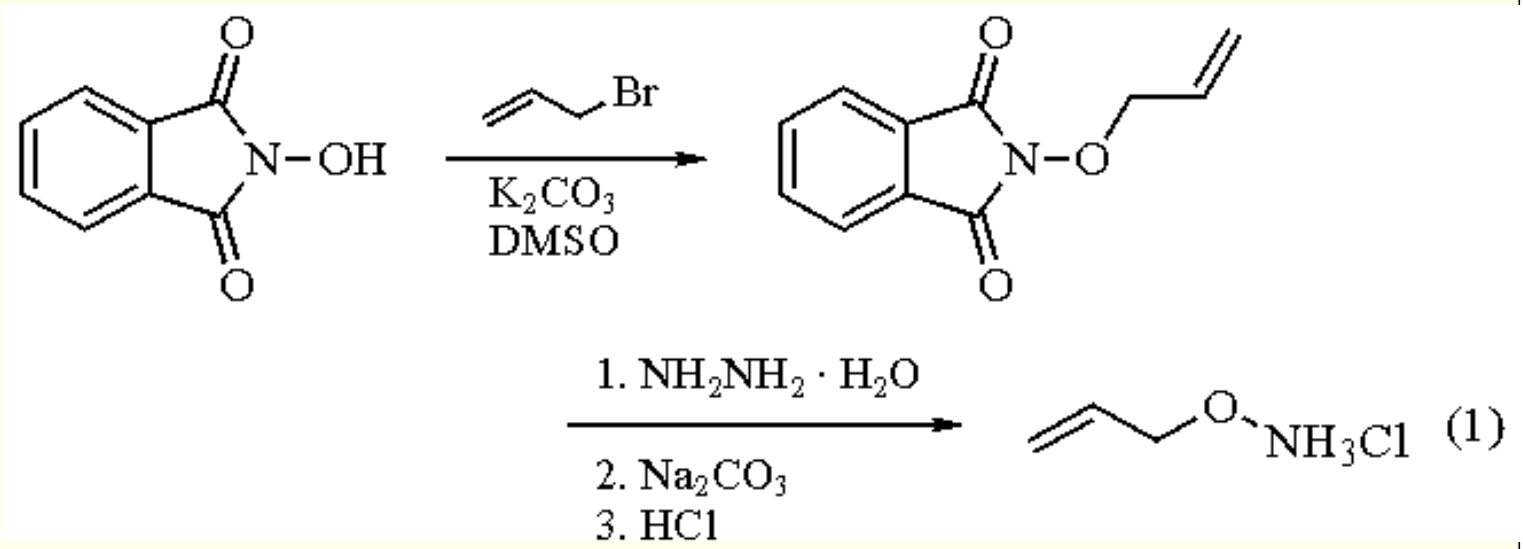

Handling, Storage, and Precautions: use in a fume hood.

Synthesis of Pyridines.

The reagent reacts with ketones to provide *O*-allyloximes in generally good yields. These materials may, in turn, be pyrolyzed by heating in a sealed tube at about 180 °C to undergo an electrocyclization which has been proposed to proceed through a nitrile oxide intermediate.[1,2] The final step involves oxidation of a dihydropyridine and therefore it is important *not* to exclude air from the pyrolysis. The intermediate in eq 2 can be derived by allylation of the corresponding oxime; however, this process is generally inferior to the *O*-allylhydroxylamine approach.

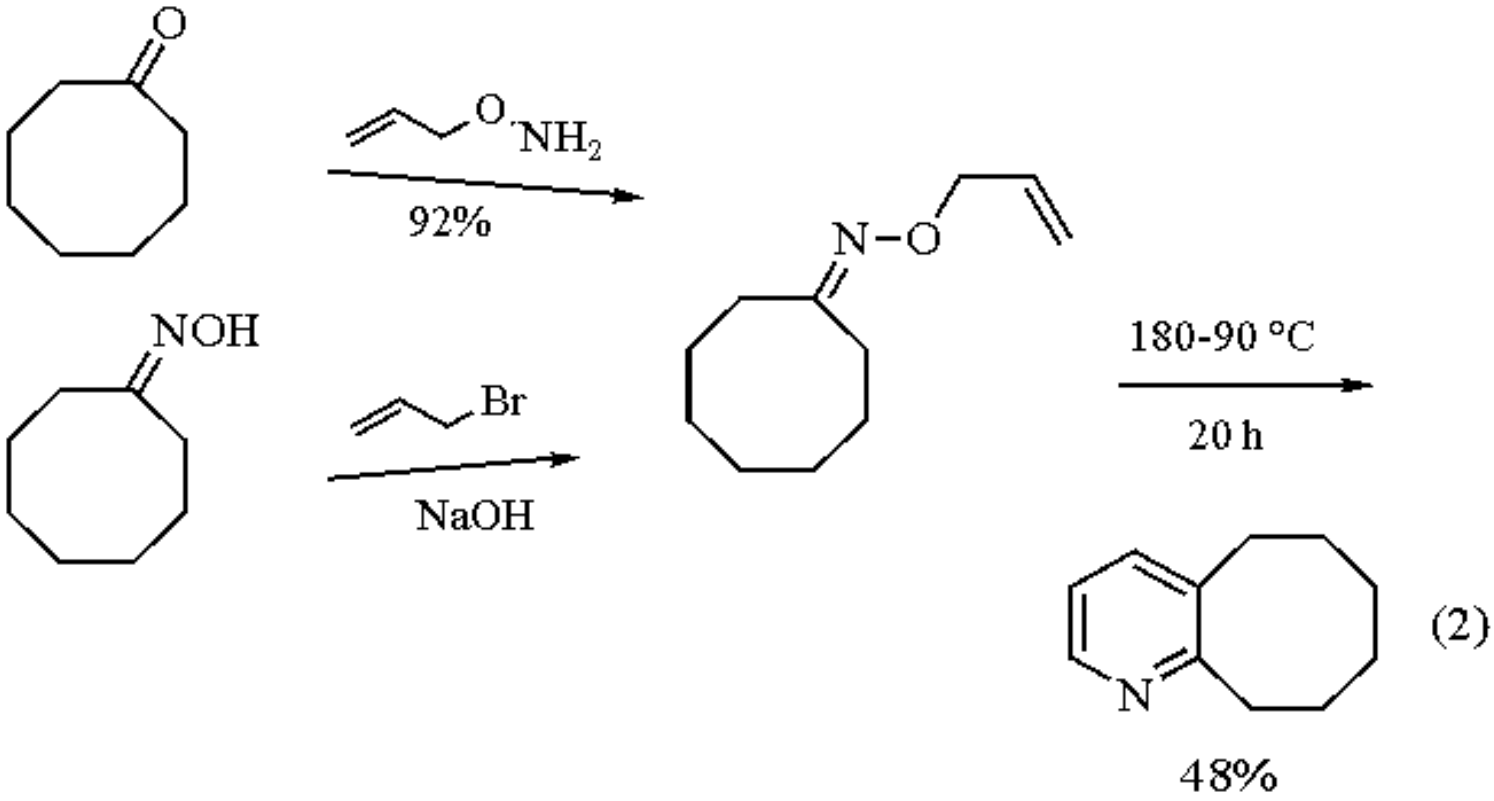

(2)

Twofold application of this method to provide bipyridines is unsuccessful. The bridged bipyridine which would be derived from 1,2-cyclooctanedione is better prepared by a stepwise approach wherein the product of eq 2 can be converted to its α-keto derivative and then the second pyridine ring incorporated as before (eq 3).[3,4]

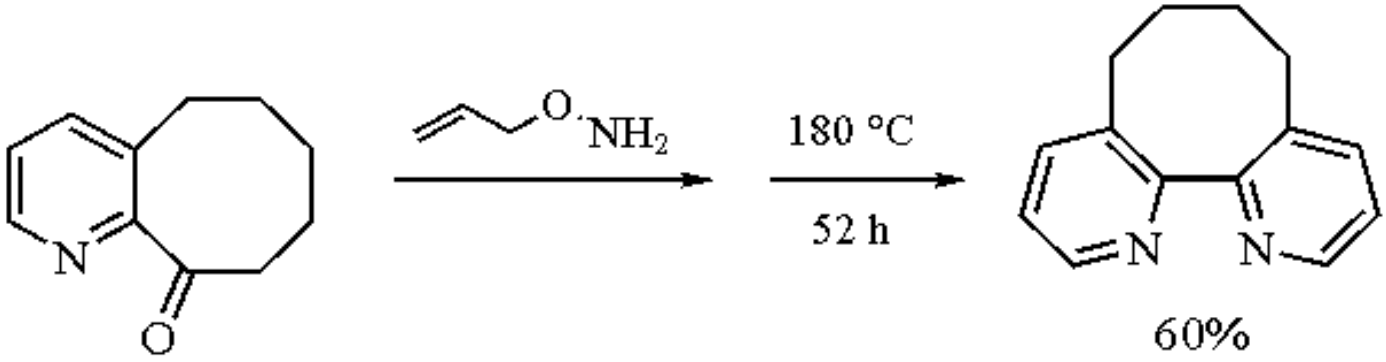

(3)

Related Reagents.

Allyl Bromide; ***(Z)-β-Aminoacrolein***; ***N-Cyclohexylhydroxylamine***; ***Hydroxylamine***; ***Propargyl Aldehyde***.

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Allylidenetriphenylphosphorane[1]

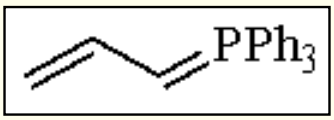

[15935-94-1] · $C_{21}H_{19}P$ · Allylidenetriphenylphosphorane · (MW 302.36)

(Wittig reagent for 1,3-diene synthesis[2] and Michael addition reaction[3])

Physical Data: ^{13}C and ^{31}P NMR solution studies,[4] X-ray structures of the molybdenum and tungsten complexes,[5] and the heat of formation (ΔH) have been reported.[6]

Solubility: sol THF,[7] toluene.[8]

Form Supplied in: prepared in situ and used directly.

Preparative Methods: this Wittig reagent is generally prepared from ***Allyltriphenylphosphonium Bromide*** or chloride by treatment with ***n-Butyllithium*** or ***Phenyllithium***.[2,3,9] Structurally related analogs have been prepared by the similar methods: 2-butenylidenetriphenylphosphorane;[10] 3-methyl-2-butenylidenetriphenylphosphorane;[10] (*E*)-2-octenylidenetriphenylphosphorane;[11] (*E*)-pentadienylidenetriphenylphosphorane;[11] (*E*)-2,4-hexadienylidenetriphenylphosphorane;[12] 2-alkynylidenetriphenylphosphorane;[12] allylidenetributylphosphorane.[13] γ-Alkyl-substituted allylidenetriphenylphosphorane can be also obtained by the reaction of diisobutylaluminum alkylideneamide with methylidenetriphenylphosphorane.[14]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture.

Wittig Reaction.

Allylidenetriphenylphosphorane usually reacts at the α-carbon with aldehydes to give a mixture of (*E*)- and (*Z*)-1,3-dienes directly in good yield (eq 1).[2] This process has been utilized for synthesis of an intermediate of leukotriene B_4 (eq 2).[15] The Wittig reaction with ketones occurs at higher temperature (eq 3).[16] In contrast, the γ-substitution product is preferentially formed in the condensation with aldehydes, when allylidenetriphenylphosphorane is generated with DBU in refluxing methanol.[17]

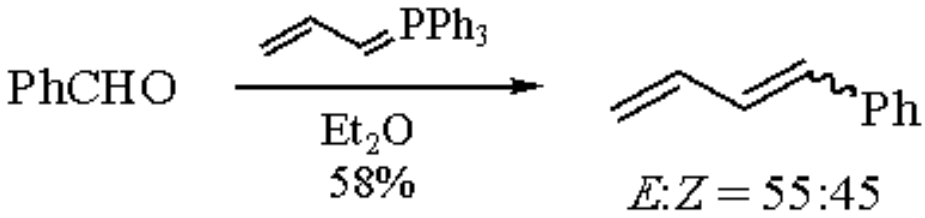

(1)

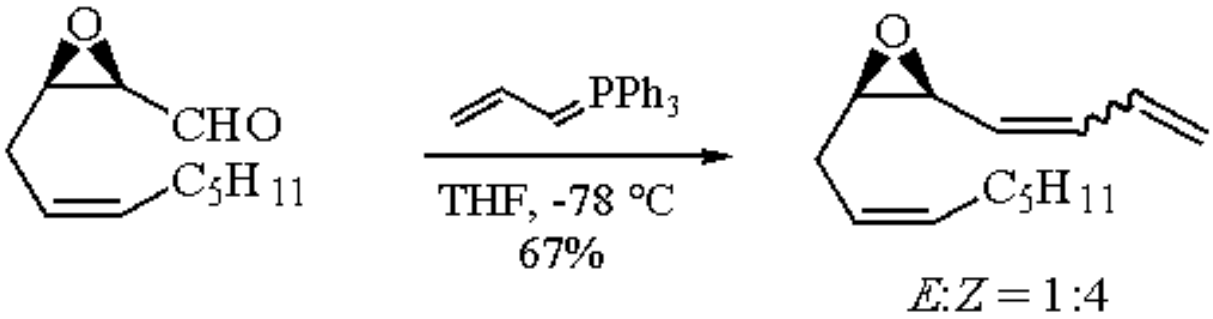

(2)

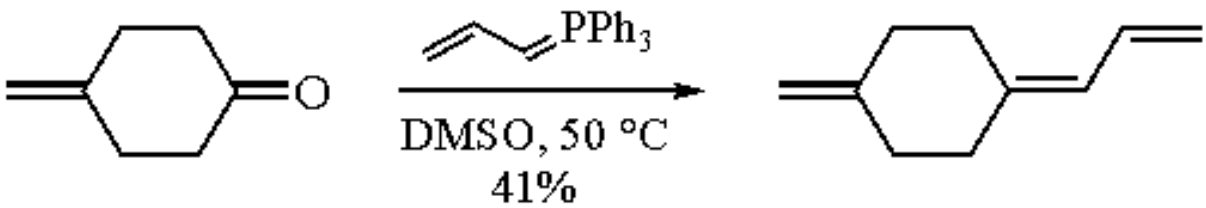

(3)

Structurally related allylidenetriphenylphosphoranes have been widely employed for the Wittig alkenation reaction.[11-13] Reaction of (*E*)-2-octenylidenetriphenylphosphorane with acrolein gives a 3:2 mixture of (*E*)- and (*Z*)-trienes (eq 4).[11] In this reaction the geometry of the starting (*E*)-2-octenylphosphonium bromide is preserved during both ylide formation and subsequent reaction with aldehyde.

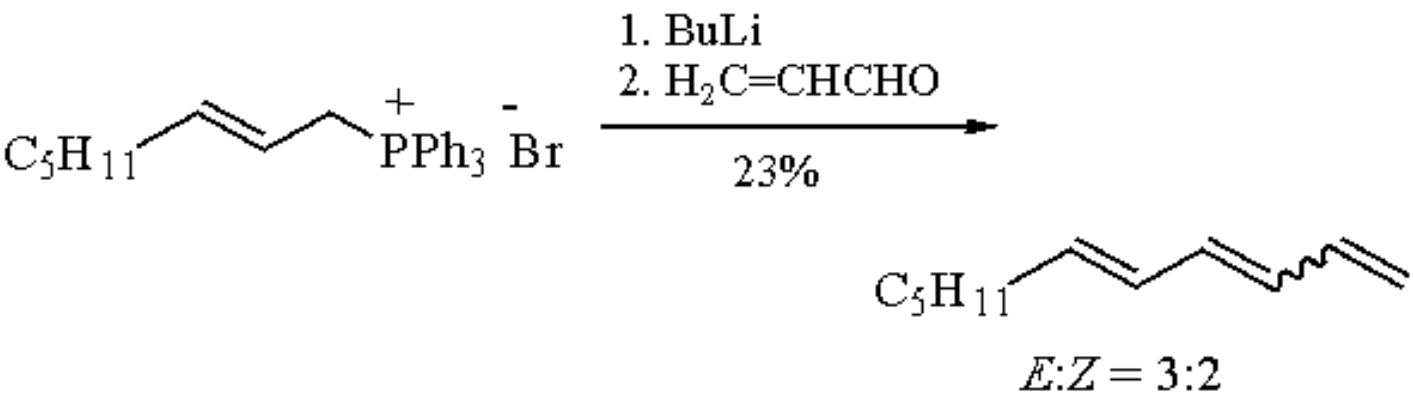

(4)

The stereochemistry of the Wittig alkenation of aldehydes with allylic phosphorus ylides has been extensively studied by Tamura et al.[18] Selective synthesis of (*Z*)-1,3-dienes has been achieved by the condensation of an allyltitanium reagent, generated from allyldiphenylphosphine, with aldehydes[19] (for synthesis of (*E*)-1,3-dienes, see also ***Allyldiphenylphosphine Oxide***).

Conjugate Addition.

Allylidenetriphenylphosphorane reacts with an enone to give a cyclic 1,3-diene (eq 5).[3,20] In this reaction the addition

of the γ-position of the ylide to the β-carbon of the enone occurs first, and then the generated ylide (**1**) undergoes an intramolecular Wittig condensation to produce the 1,3-diene. Strained bridgehead alkene (**2**) has been also successfully synthesized by this method.[20b] In contrast, reaction with a β-chloro-α,β-unsaturated ketone followed by treatment with benzaldehyde yielded triene (**3**).[21]

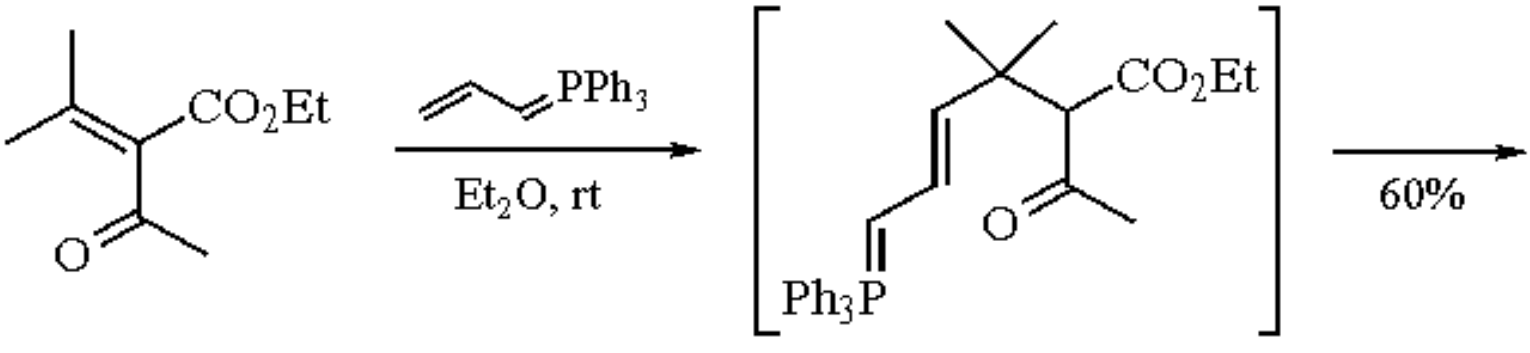

(1)

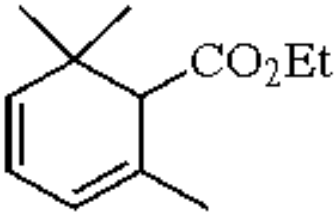

(5)

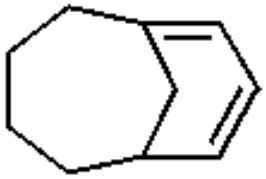

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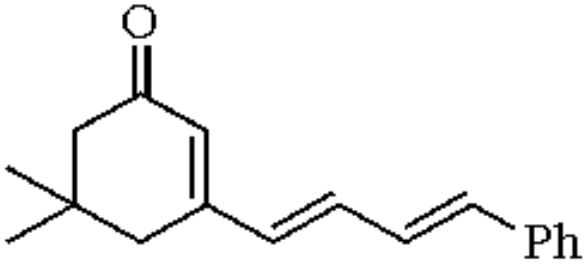

(3)

Other Reactions.

Addition of allylidenetriphenylphosphorane to benzyne and subsequent treatment with HBr affords cinnamylphosphonium bromide.[22] Silylation with ***Chlorotrimethylsilane*** occurs regiospecifically at the γ-position.[23] Reaction with isocyanate gives 3-pyridylidenephosphorane.[24]

---

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15. (a) Mills, L. S.; North, P. C. *TL* **1983**, *24*, 409. (b) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *JACS* **1980**, *102*, 7984.
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22. Zbiral, E. *M* **1967**, *98*, 916.
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Allyl Iodide

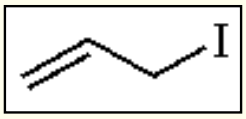

[556-56-9] · C_3H_5I · Allyl Iodide · (MW 167.99)

(allylating agent which attacks C, O, N, S, Se, Te nucleophiles; organometallic derivatives provide homoallyl alcohols; expected electrophilic addition reactions)

Physical Data: mp -99.3 °C; bp 103.1 °C; *d* 1.848 g cm^{-3}.

Solubility: miscible with organic liquids.

Form Supplied in: yellow liquid, discoloring on heating, standing, and exposure to air.

Purification: wash with aq Na_2SO_3 to remove iodine, dry ($MgSO_4$), and distil under reduced pressure (~20 mmHg).[1] Protect from light.

Handling, Storage, and Precautions: store in a light-tight vessel at 0 °C. Volatile, flammable, toxic, irritant alkylating agent. Light sensitive.

Allyl iodide (RI) is usually prepared by ion exchange (NaI-Me_2CO) of allyl chloride or from allyl alcohol using reagents such as ***Diphosphorus Tetraiodide***.[2] The weak C-I bond facilitates both heterolytic and homolytic displacement reactions (eq 1). Thus Barbier-Grignard type processes may also be achieved using Sb,[3] Ga,[4] In,[5] Bi,[6,7] or $BiCl_3$-metal combinations.[7] Cerium powder with allyl iodide provides organocerium species which with ketones give a mixture of secondary alcohol, pinacol dimerization product, and Barbier-Grignard product. With aldehydes the major product is the pinacol product.[8] In contrast, allyl iodide with Al and Ce/Hg in THF at 0 °C under N_2 for 5 h gives excellent yields of the tertiary alcohol with a range of ketones.[9] Other such reductive allylation methods use $CrCl_3$ + 0.5 mol $LiAlH_4$, which seems to provide Cr^{II} which with RI or RBr in THF gives allyl Cr^{II} species. These may lead to biallyl formation or to the Barbier-Grignard reaction with ketones and aldehydes, but not with nitriles or carboxylates (eq 2).

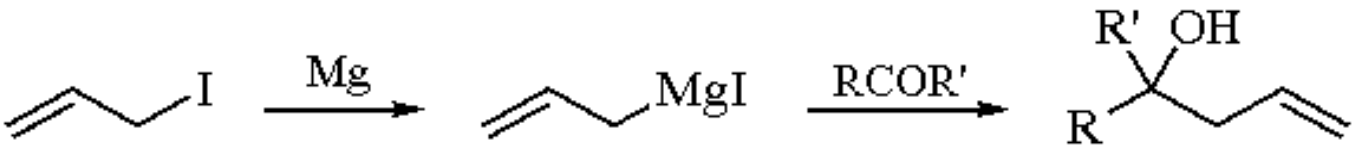

(1)

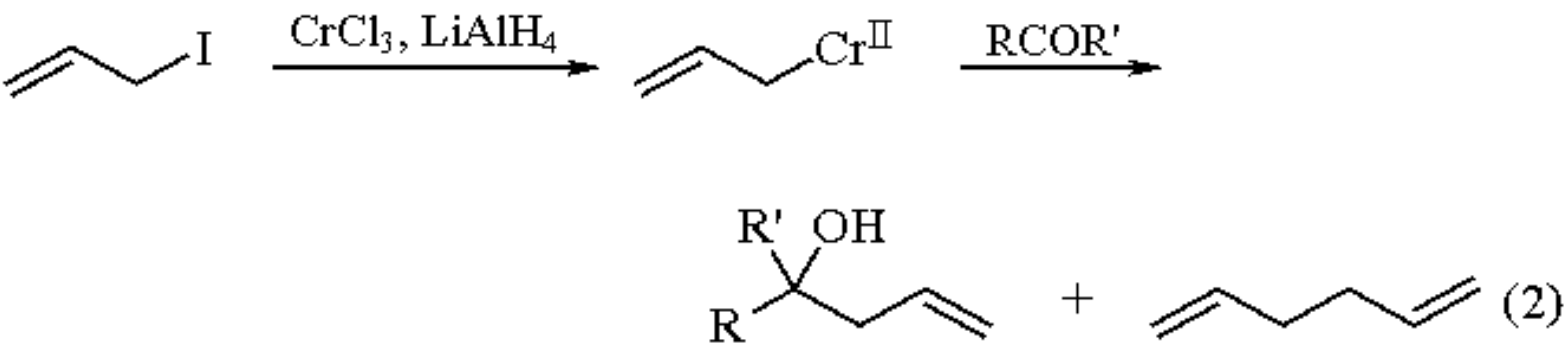

Allyl chloride behaves similarly, but in DMF and not THF.[10] ***Samarium(II) Iodide*** (THF, N_2, rt) encourages the reaction of aldehydes with RI to give secondary alcohols (eq 3);[11] so also does Sn^{II}, both as the carboxylate[12] and as the halide,[12,13] especially the fluoride.[13] Acyl chlorides similarly react with RI in the presence of SmI_2.[14] The reduction may also be brought about electrochemically; RI (and other allyl halides) provides $Me_2C(R)OH$ with Me_2CO (0.5 M Bu_4NClO_4 in HMPA)[15a] and adds across &cvbond;C=C&dvbond; in diethyl fumarate ($Et_4N^+C_7H_7SO_3^-$ in DMF) to give the 2-allylsuccinate system (eq 4).[15b]

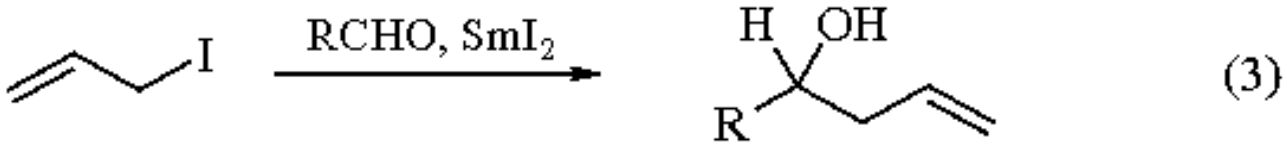

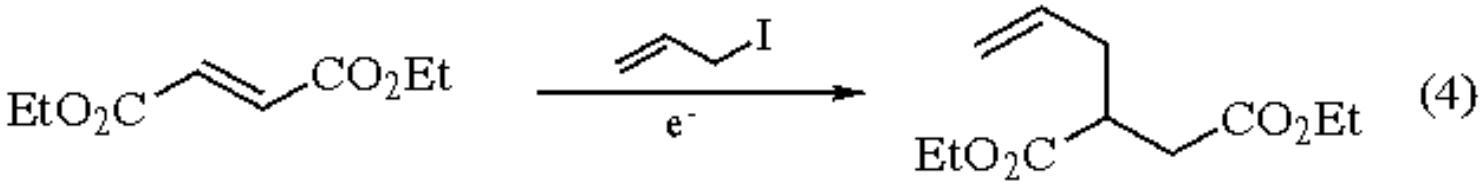

The analogous photochemical addition of RI to benzaldehydes is promoted by lanthanum iodides.[16]

Carbanions (e.g. (**1**), generated from NaH in DMF) allylate without rearrangement (eq 5),[17] while Na salts of penta-2,4-dione enolates allylate exclusively at C-3 (DMSO, RI)[18] and lithio derivatives of silylated acrylate esters (MeLi) show similar specificity of allylation.[19] The stereoselective attack of chiral malonic half-esters,[20] dimethyl tartrate stannylene acetal,[21] chiral imide enolates,[22] and chiral nitro keto imines[23] proceeds well and with high diastereoselectivity. Simple exchange reactions provide radiolabeled products; $Ag^{18}F$ and $Ag^{83}Br$ react with RI in the gas phase to provide high-level $R^{18}F$ and $R^{83}Br$.[24] Iodolactams also undergo stereospecific *N*-allylation.[25] ***Diphenyl Diselenide*** provides PhSeR in the presence of SmI_2.[26]

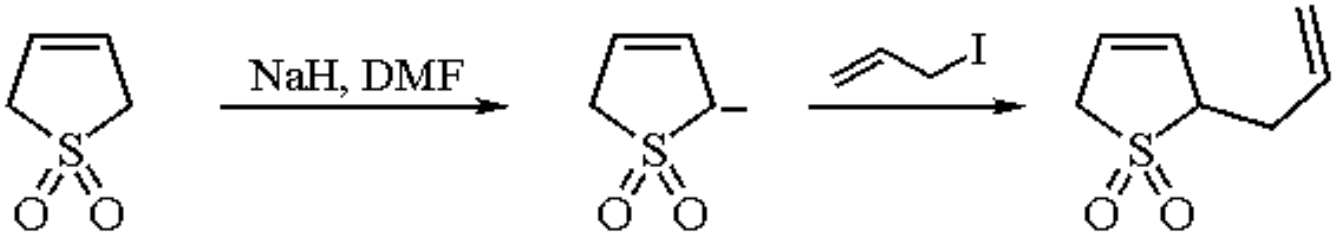

(5)

(1)

Related Reagents.

Allyl Bromide; ***Allyl Chloride***.

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Roger Bolton

Allyllithium[1]

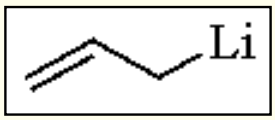

[3052-45-7] · C_3H_5Li · Allyllithium · (MW 48.01)

(allylating agent in substitutions and additions; used to attach allyl groups to other metals and nonmetals)

Physical Data: colorless solid, pyrophoric in air.[2] Crystals of complex with ***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine*** showed monomeric ion pairs by X-ray.[3] IR,[4] Raman,[4b] UV,[5] and ^1H,[3,6] ^{13}C,[7] and ^7Li[8] NMR spectra have been reported on solutions.

Solubility: sol in ethers with degrees of association 1.4-10; sparingly sol in alkanes.[2]

Form Supplied in: prepared in situ and used directly.

Preparative Methods: from allyl phenyl ether and Li in THF/ether is recommended for large scale, tin-lithium exchange between allyltins and phenyllithium for pure samples.[9] Halogen-metal exchange is impractical due to fast Wurtz coupling. Allyllithium can also be made at -78 °C by the reaction of ***n-Butyllithium*** with allyl methyl (or phenyl) selenide,[10] and by metallating propene with butyllithium.[11]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas to exclude oxygen and moisture.

Nucleophilic Substitutions at Carbon.

Resonance-stabilized Li reagents such as allyllithium are stronger nucleophiles but weaker bases than alkyllithium reagents, permitting displacement of Br^- and I^- from cyclohexyl and cyclopentyl systems in Wurtz-type couplings (eq 1).[12] The allyl group extends chains by three carbon atoms and can be readily converted into many other groupings. Optically active secondary halides and tosylates react with inversion.[13]

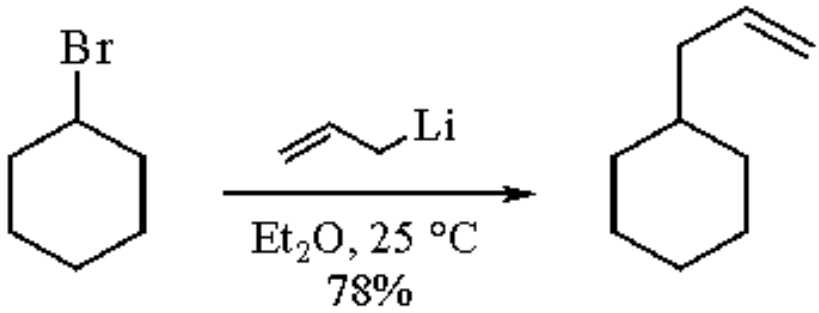

(1)

High-yield displacements also occur at the less-hindered carbons of epoxides (eq 2).[14]

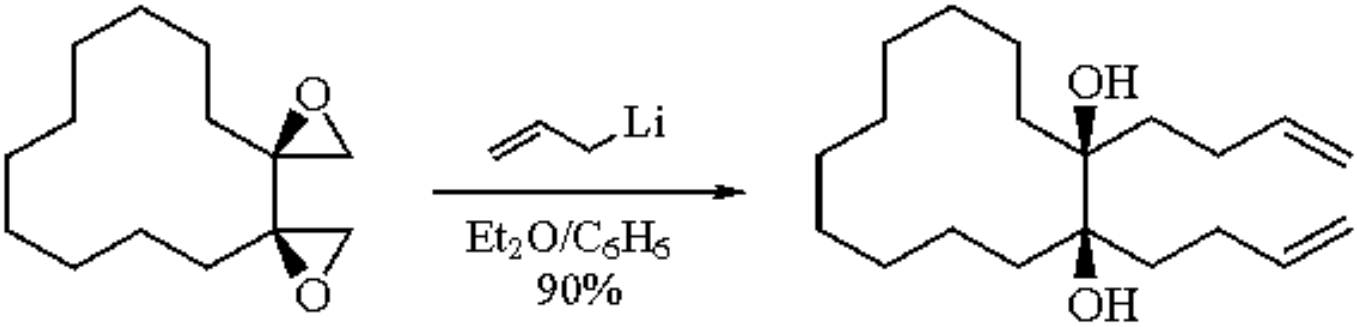

(2)

Nucleophilic Substitutions at Other Nonmetals.

Allyllithium reacts with aryl arylsulfonates at sulfur to give allyl aryl sulfones (eq 3).[15] Similar reactions occur to produce aryl allyl sulfoximines.[16]

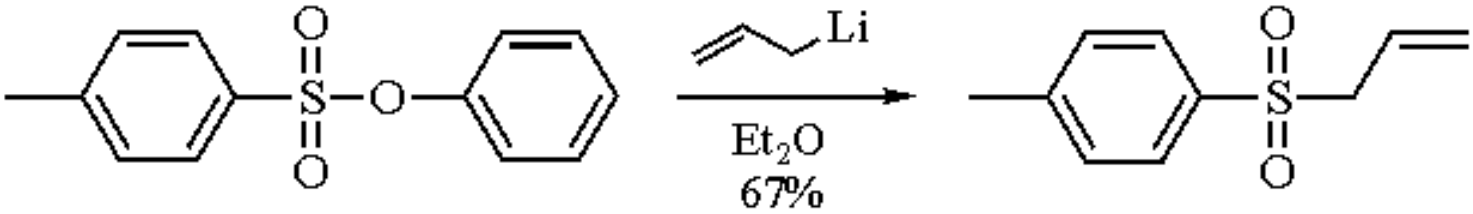

(3)

Additions to Double Bonds.

Allyllithium adds to aldehydes[17] and ketones (if aromatic, by electron transfer),[18] allylic alcohols (eq 4),[19] imines,[20] ketenimines,[21] thionolactones,[22] α,β-unsaturated thioamides (by 1,4-addition),[23] and lithium carboxylates.[24]

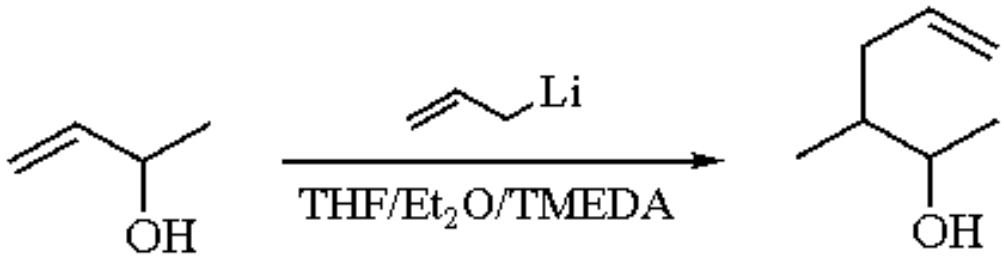

(4)

Metal Exchange.

Allyllithium is reacted with copper salts to make lithium diallylcuprate, often used for conjugate addition of allyl groups to α,β-unsaturated carbonyl compounds.[25]

Related Reagents.

Allylcopper; ***Allylmagnesium Bromide***; ***Crotyllithium***; ***Lithium Diallylcuprate***; ***Methallyllithium***.

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Allylmagnesium Bromide[1]

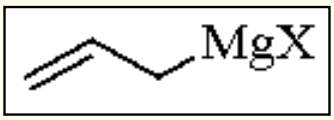

(X = Br)

[1730-25-2] · C_3H_5BrMg · Allylmagnesium Bromide · (MW 145.29) (X = Cl)

[2622-05-1] · C_3H_5ClMg · Allylmagnesium Chloride · (MW 100.84)

(allylating agents capable of easy addition to carbonyl compounds,[15-23] nitro compounds[57] and nitriles,[58-61] imines[43-50] and aza aromatics,[51-56] unactivated alkenes,[30-42] and of displacement reactions on halo compounds[6,24-28,53,54])

Physical Data: Br: fp -40 °C; *d* 0.851 g cm^{-3} (commercial reagent). Cl: fp -17 °C; *d* 0.995 g cm^{-3} (commercial reagent).

Solubility: Br: very sol ether. Cl: slightly sol ether; sol THF.

Form Supplied in: Br: 1.0 M solution in Et_2O packaged under N_2. Cl: 2.0 M solution in THF packaged under N_2.

Preparative Methods: allylmagnesium bromide and chloride can be easily prepared by direct reaction of ***Magnesium*** with ***Allyl Bromide*** and ***Allyl Chloride***, respectively[2-5] in diethyl ether and/or tetrahydrofuran. An excess of Mg (preferably 10%) is recommended.[6,7] Prior amalgamation of *very pure* Mg[3,4] suppresses the formation of 1,5-hexadiene. An improved preparation[8] uses a THF slurry of Mg, obtained by co-condensation in a rotating solution reactor.[9] Preactivation of Mg by dry stirring in an inert atmosphere is also highly beneficial.[10] Allylpotassium can be readily converted into the magnesium analogs by simply adding a solution of ***Magnesium Bromide*** in THF.[11,12] Most of the work on allylic Grignards has been carried out with the bromide. Indeed, the bromide can be prepared in slightly higher yield than the chloride and shows a greater solubility in ether.[1]

Handling, Storage, and Precautions: both moisture-sensitive; highly inflammable; react violently with water; induce burns. Bottles of these reagents should be flushed with N_2, kept tightly sealed to preclude contact with oxygen, and stored far from sparks. In case of contact with eyes and skin, wash immediately with abundant water.

Structure of Allylmagnesium Halides.

NMR data[3a] of several allylic Grignard reagents support the view that allylMgBr exists as a rapidly equilibrating mixture of the two classical structures (**1**) and (**2**) ($t_{1/2}$ <0.001 s) or as the bridged structure (**3**) (eq 1). This is supported by application of the Saunders isotopic perturbation technique[13] as well as by ^{25}Mg NMR studies.[14]

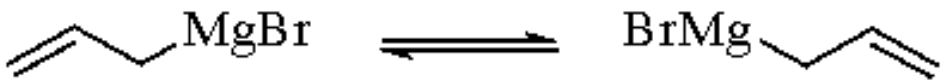

(1)

(1) **(2)**

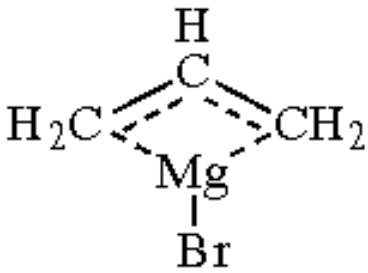

(3)

Reactions with Carbonyls.

Allylmagnesium halides react with carbonyl compounds to produce carbinols; 1,2-addition occurs with α,β-unsaturated carbonyls.[1,15d,16-18] Addition takes place also with severely hindered ketones, which with most other Grignards undergo either reduction or enolization. Allylmetallation of carbonyls offers a complementary approach to the aldol reaction for acyclic stereocontrol.[15]

Complex (**4**), prepared by reacting the crystalline chiral complex $Cp(OR^*)_2TiCl$ with allylMgBr, adds to aldehydes to give homoallylic alcohols[19] with 85-94% ee (eq 2).

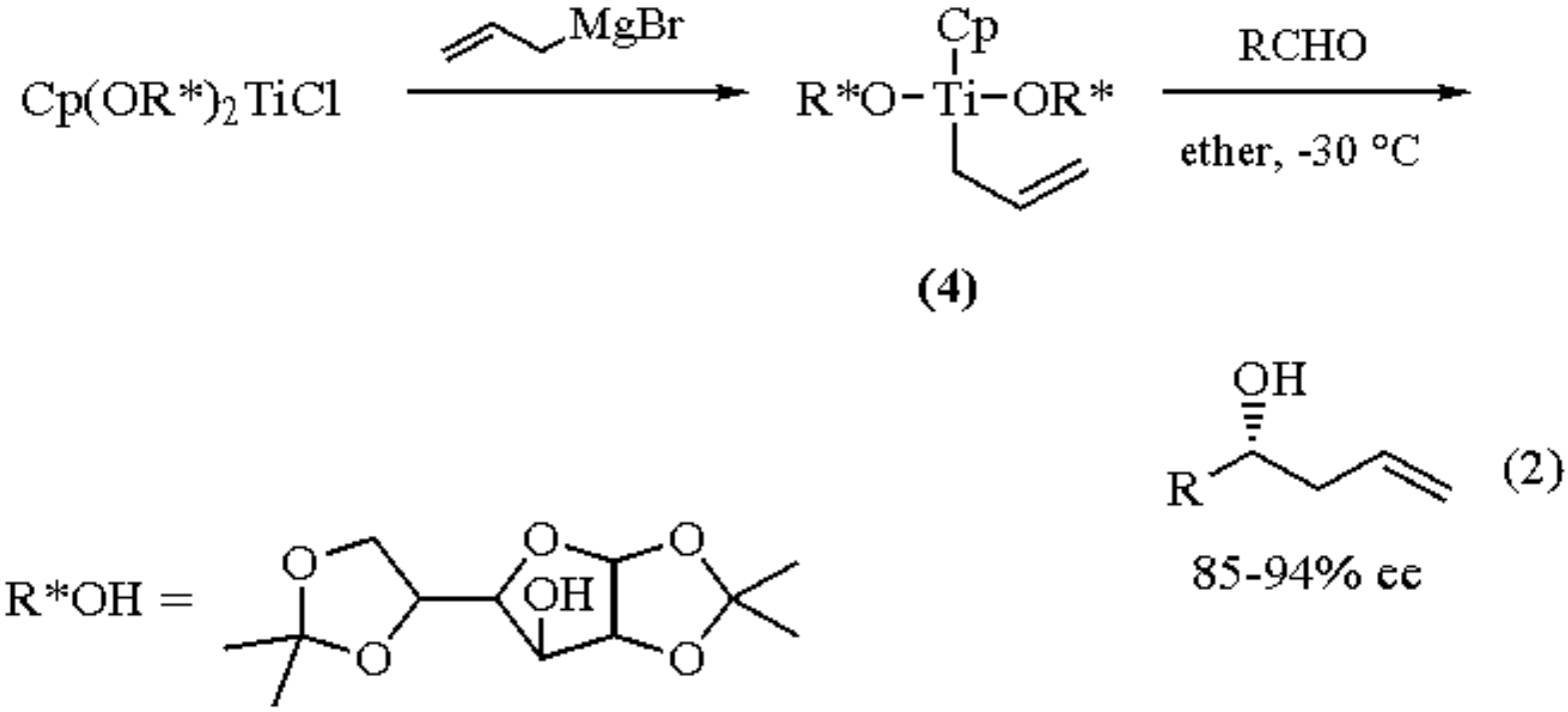

Homoallylic alcohols have also been synthesized by ring opening of vinylic oxetanes[20] with copper-catalyzed allylmagnesium halides. C_2 homologation of aldehydes and ketones to 2-alkenals uses allylMgBr.[21]

AllylMgBr adds to the C=O of imides to give different products depending upon the imide.[22]

A new synthesis of propenyl ketones involves reaction of an ester with 2 equiv of allylMgCl, furnishing a tertiary bis-homoallylic alcohol that fragments at 80 °C to a mixture of β,γ- and α,β-unsaturated ketones.[23]

Displacement Reactions.

The coupling of allylmagnesium halides with halogenated compounds provides a useful one-step method for introducing an alkenic bond directly into a molecule.[1,15d] Allylic Grignard halides couple with alkyl, allylic, and benzylic halides.[6,24] Sometimes, allylMgCl gives higher yields than the more commonly used allylMgBr.[24a] Alkylation in the presence of ***Copper(I) Iodide*** is much faster.[25]

AllylMgBr couples with fluoroalkenes in a rather unexpected manner.[26] Allylmagnesium halides can be hydroxymethylated in a two-step one-pot procedure by 1-chloro-2-(chloromethoxy)ethane.[27] A new synthesis of dienes, with the double bonds in predetermined positions, involves reaction of an α-chloro ketone with an allyl Grignard in ether at -60 °C followed by treatment with ***Lithium*** powder (eq 3).[29]

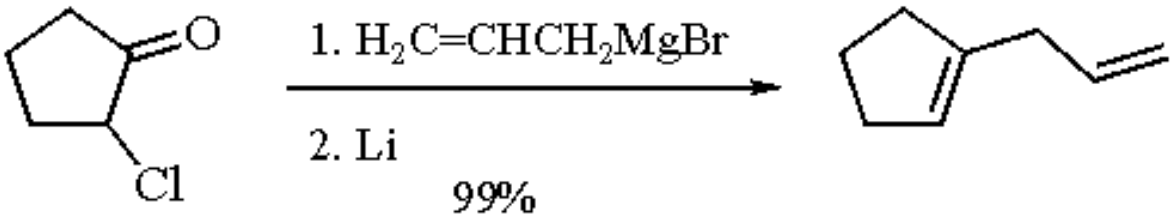

(3)

An efficient synthesis of 3-*t*-aminopropanols is based on the regioselective ring opening of tetrahydro-1,3-oxazines with allylMgCl.[28]

Allylmagnesium halides have been used to prepare different organometallics.[1,15d]

Addition to Alkenic Bonds.

Allylmagnesium halides add smoothly to activated and some unactivated double bonds. Intermolecular and uncatalyzed carbomagnesiation of unfunctionalized alkenes, such as ***Ethylene*** and 1-octene, has been reported.[31-33] AllylMgCl[30] reacts with more than 90% regioselectivity with ***1,3-Butadiene*** (Mg at C-2) to afford 2,6-heptadienylmagnesium chloride (**5**) that, with a second carbomagnesiation, leads to 1:2 adduct (**6**), which undergoes a fast ring closure to (**7**) (eq 4).

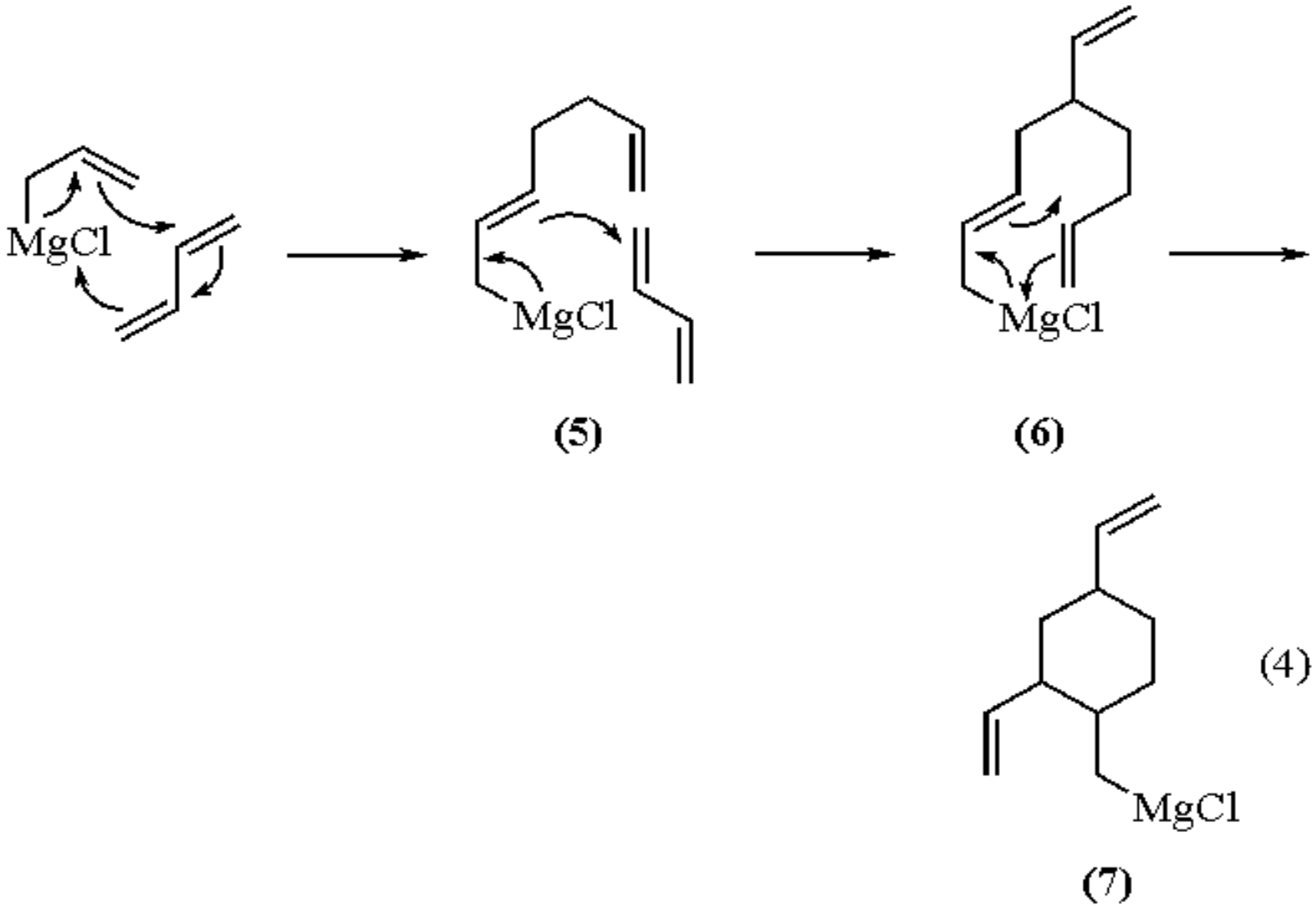

(4)

The intramolecular carbomagnesiation involving reactive allylic Grignard reagents has been extensively studied.[34-38] The presence of a neighboring hydroxy, alkoxy, or amino group facilitates the addition of allylmagnesium halides.[39-42]

Addition to Azomethine Linkages.

Allylmagnesium halides add to the azomethine linkage easier than the alkyl counterparts. Highly asymmetric syntheses of β- and γ-amino acids with good stereocontrol have been described;[43] the crucial step is the addition reaction of allylMgBr to chiral *N*-benzylidene-*p*-toluenesulfinamides followed by the elaboration of the allylic group (eq 5).

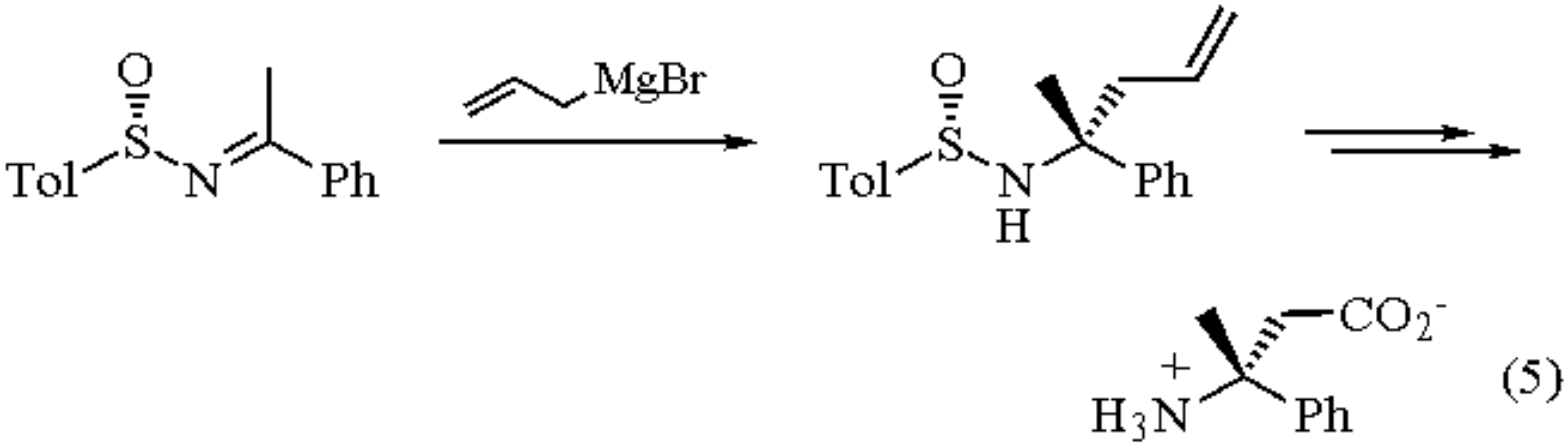

(5)

Resonance stabilization of the allyl anion results in a greater ionization of the carbon-metal bond and hence greater reactivity. This promotes addition to C=N linkages usually unaffected by nonresonance-stabilized organometallic reagents.[44] Thus the reaction of allylmagnesium halides with achiral aldimines affords homoallylamines.[45] The stereochemistry of the addition has been studied.[46]

The addition of allylmagnesium halides to the *O*-protected α-hydroxy-*N*-trimethylsilylimines (**8**), generated in situ, proceeds in a highly *anti* stereocontrolled manner to produce α-amino alcohols[47] that can be oxidized to α-amino acids (eq 6).[48]

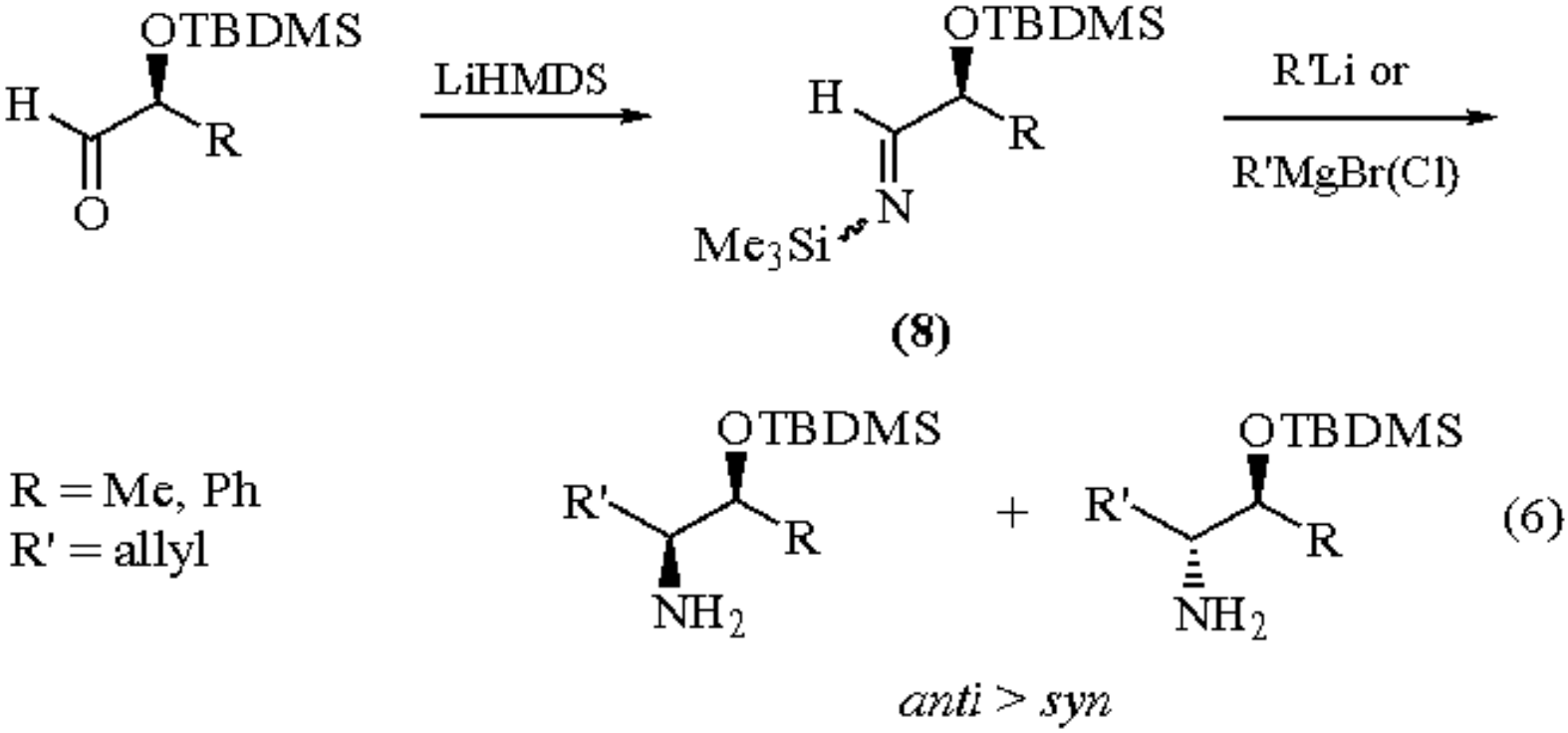

AllylMgBr, complexed with ***Cerium(III) Chloride***, adds to chiral (*E*)-alkoxymethyl oxime ether (**9**) to give the corresponding (*S*)-amine derivative stereoselectively, while allyllithium gives mainly the opposite (*R*)-isomer (eq 7).[49]

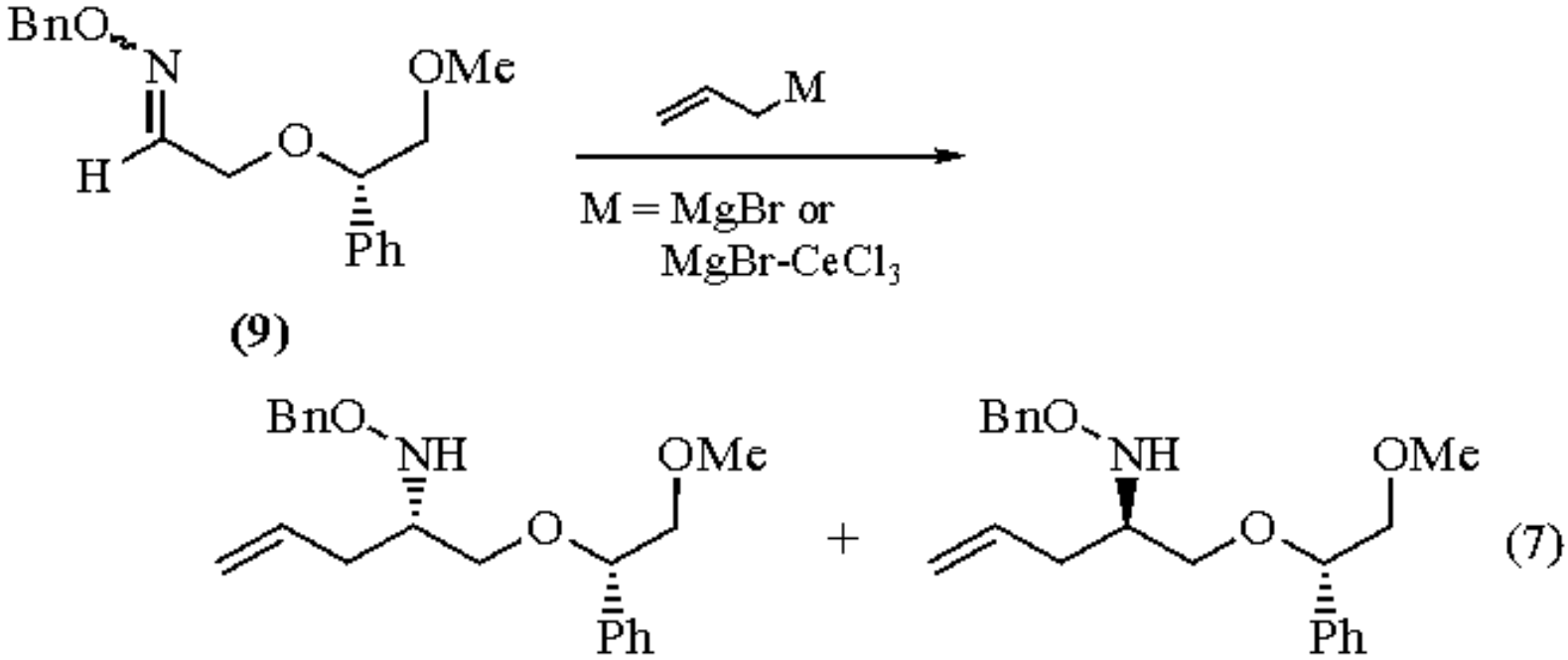

Allylmagnesium halides also add to imines, iminium salts, *N*-hetero substituted imines (oximes, sulfenimines, etc.), *gem*-amino ethers, *gem*-amino nitriles, ethers, peroxides, disulfides, epoxides, acids and their derivatives, amides, orthoformates, *O*-alkylated oximes.[15d,50]

AllylMgBr adds to the C=N double bond of several aza aromatics to form allylated aza aromatics.[51]

The reaction of 2-hetero substituted benzothiazoles with allylMgBr affords 2-allylbenzothiazole or 2,2-diallylbenzothiazoline or *N*-triallylmethyl-*o*-aminobenzenethiol depending upon the experimental conditions;[52] a novel ring-opening reaction of the benzothiazole system with allylic Grignards has been reported.[53] 2-Alkylbenzoxazoles also react with allylic Grignards, undergoing ring opening to *N*-diallylalkyl-*o*-aminophenols, while 2-chlorobenzoxazole affords the cross-coupling product.[54] Mono and bis addition reactions of the allylic Grignard reagents to the C=N bond of quinoxalines afford high yields of allyldihydroquinoxalines and diallyltetrahydroquinoxalines; dehydrogenation with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** leads to monoallyl- and diallylquinoxalines.[55] Similarly, reaction with pyrimidines furnishes excellent yields of allylpyrimidines.[56]

Reactions with Nitro Compounds and Nitriles.

Allylmagnesium halides react with both aromatic and aliphatic nitro compounds via addition to the nitro group, leading to allylamines or to *N*-hydroxyallylamines (eq 8).[57]

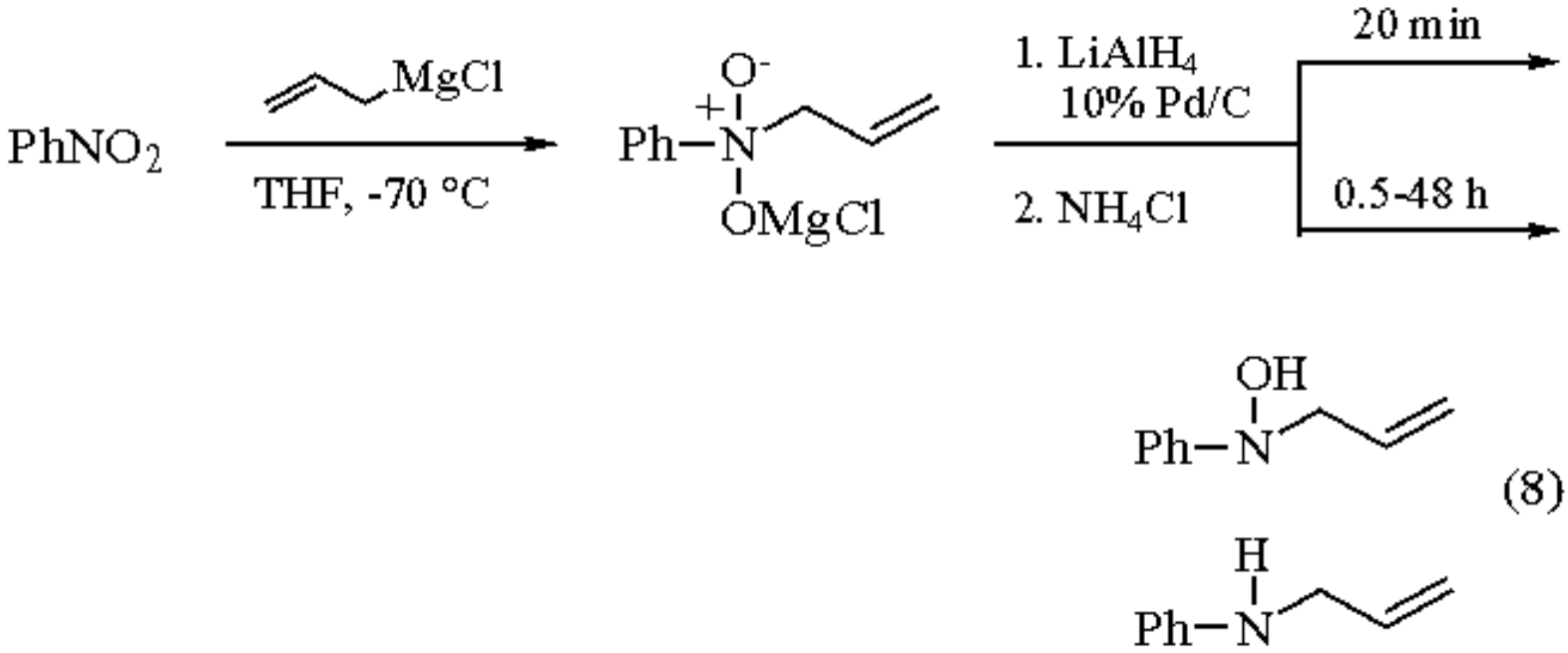

(8)

Allylmagnesium halides add to alkyl, aralkyl, and alkenyl cyanides in a preferred 2:1 ratio to yield trisubstituted primary amines.[58-60] The allyl groups on the carbinamine products are susceptible to catalytic hydrogenation to give *t*-alkyl primary amines, most of which are otherwise difficult to synthesize. Aryl nitriles react with allylmagnesium halides, leading to tetrahydropyridines.[61]

Related Reagents.

Allyllithium; ***Crotylmagnesium Bromide***; ***Methallylmagnesium Chloride***; ***3-Methyl-3-buten-1-ynylcopper(I)***.

---

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Allylmagnesium Bromide-Copper(I) Iodide

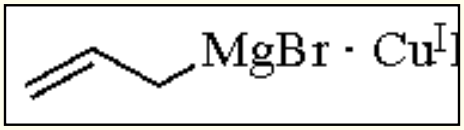

[1730-25-2] · C_3H_5BrMg · Allylmagnesium Bromide-Copper(I) Iodide · (MW 145.29)

[7681-65-4] · CuI · Allylmagnesium Bromide-Copper(I) Iodide · (MW 190.44)

(regioselective alkylation;[2] stereo- and regioselective addition to propargylic alcohols;[3] can add to vinylic oxetanes to give homoallylic alcohols[5])

Preparative Methods: allylmagnesium bromide-copper(I) iodide complexes are prepared in situ under anhydrous conditions by reacting ***Allylmagnesium Bromide*** (**1**) with ***Copper(I) Iodide*** (**2**) in varying molar ratios.[1]

Handling, Storage, and Precautions: use in a fume hood.

Regioselective Alkylation.

Treatment of (**1**) (1.3 equiv) with octyl iodide in the presence of (**2**) (10 mol %) gave 1-undecene (eq 1). In the absence of (**2**) the reaction was slow (22% product after 28 h at 0 °C).[2]

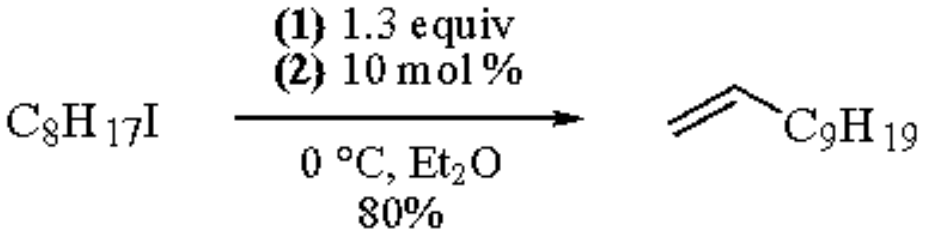

(1)

Stereo- and Regioselective Addition to Propargylic Alcohols.

Primary propargylic alcohols undergo regio- and stereoselective additions of (**1**) in the presence of 10 mol % of (**2**) to give allylic alcohols (**3**) (eq 2).[3]

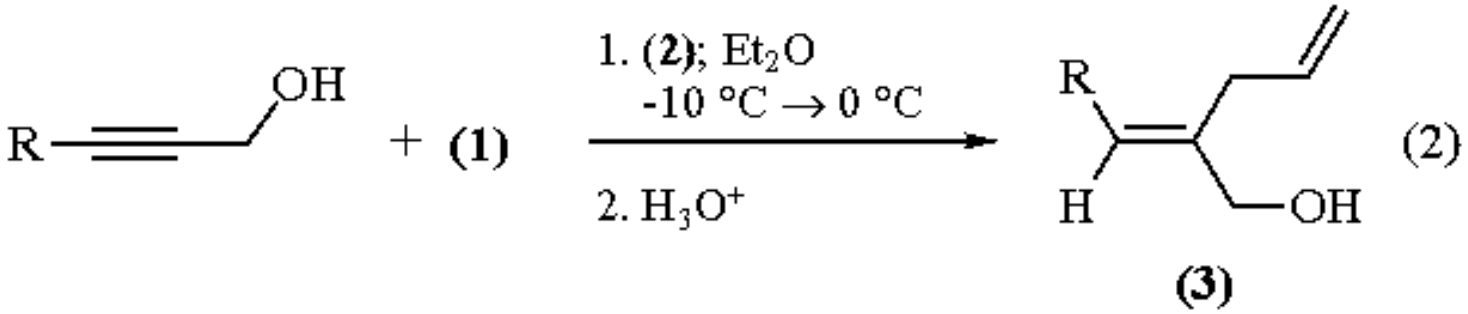

R = H, 60%; R = Me, 79%; R = Ph, 77%; R = Bu, 73%

Negishi et al. used this methodology in a synthesis of stereodefined exocyclic alkenes (**4**) (eq 3).[4]

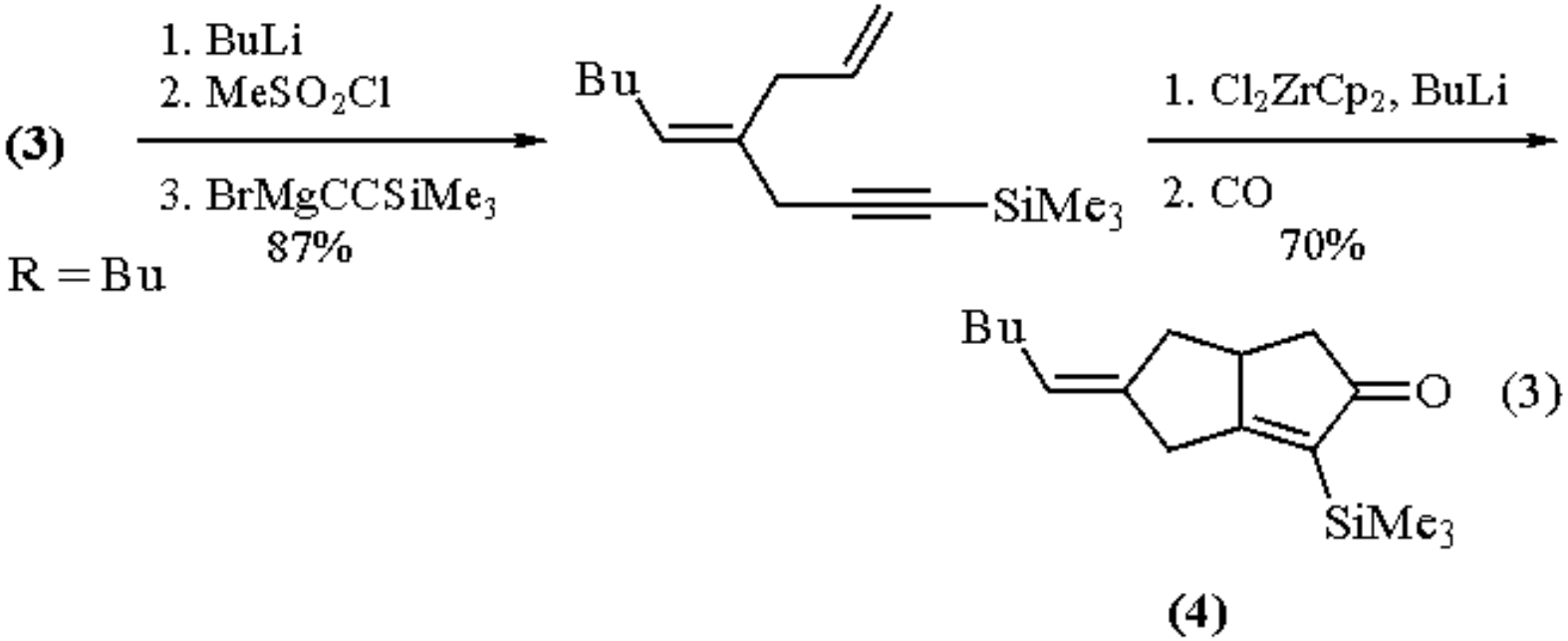

Synthesis of Homoallylic Alcohols.

Vinylic oxetanes undergo regioselective ring opening to afford homoallylic alcohols (eq 4); preference for the (*E*) isomer was observed.[5]

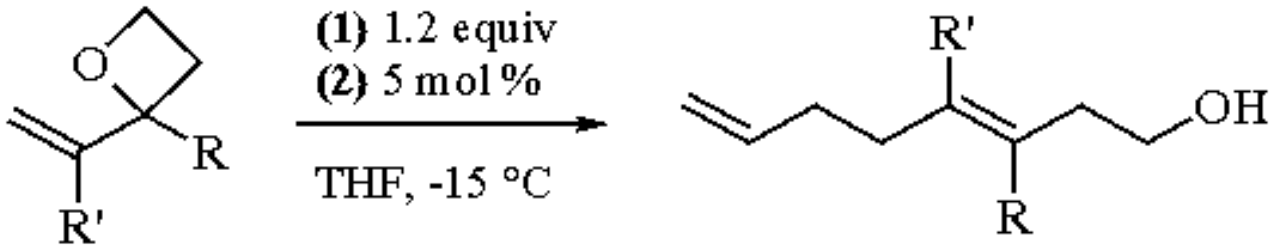

(4)

R	R'	% yield	*E*:*Z* ratio
H	H	56	66:34
H	Me	55	58:42
Me	H	54	70:30

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1. For a recent review of organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135.
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Allyl Phenyl Selenide[1]

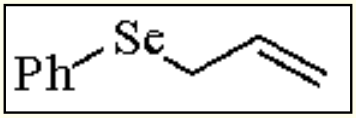

[14370-82-2] · $C_9H_{10}Se$ · Allyl Phenyl Selenide · (MW 197.14)

(metalated derivatives are ambident nucleophiles;[2,4,6-9,11,15] sigmatropic rearrangements produce allyl alcohols and amines;[9-12] cleavage of Se-C bond provides a source of allyl anions,[13] cations,[6,14,15] and radicals[16,17])

Alternate Name: (2-propenylseleno)benzene.

Physical Data: bp 65-68 °C/1 mmHg;[2] 82-83 °C/3 mmHg.[3]

Solubility: insol water; sol most organic solvents.

Preparative Methods: from ***Allyl Bromide***,[2,4] chloride, or mesylate[4] and sodium benzeneselenolate (prepared by reduction of ***Diphenyl Diselenide***,[2,4] or deprotonation of ***Benzeneselenol***).[3] Numerous other procedures have been used, including the reaction of allylsilanes with ***Benzeneselenenyl Chloride***,[5a] allyl acetates with ***Phenyl Trimethylsilyl Selenide***,[5b] allyl halides with PhSeTl,[5c] and allylamines with PhSeLi (Ru catalyzed).[5d]

Purification: distillation in vacuo[2,3] or chromatography on silica gel[4] before use.

Handling, Storage, and Precautions: the compound is stable indefinitely in the freezer, but will slowly turn yellow at room temperature and in ambient light due to the formation of diphenyl diselenide. The compound is not excessively malodorous when pure, but should be prepared and handled in a fume hood due to the toxic nature of many organoselenium compounds.

Metalation.

Allyl phenyl selenide (**1**) is metalated with ***Lithium Diisopropylamide*** in THF at -78 °C (eq 1).[6,7] The 1-phenyselenoallyllithium (**2**) formed reacts principally at the α-position with alkyl halides and epoxides,[6] and at the γ-position with aldehydes and ketones.[6,8] If (**2**) is treated with ***Triethylaluminum*** prior to reaction with carbonyl compounds, mainly α-hydroxyalkylation is observed.[8] Representative regioselectivities are shown in eq 2.

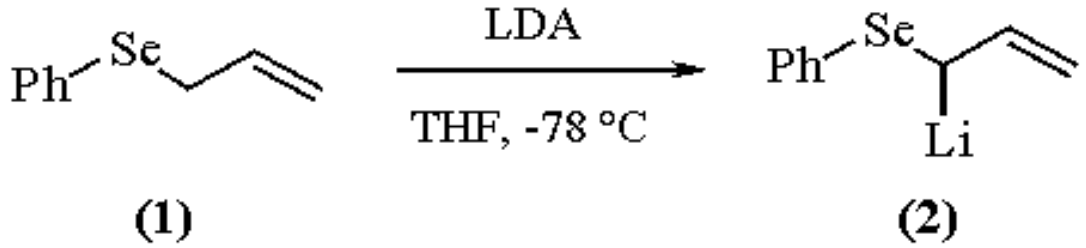

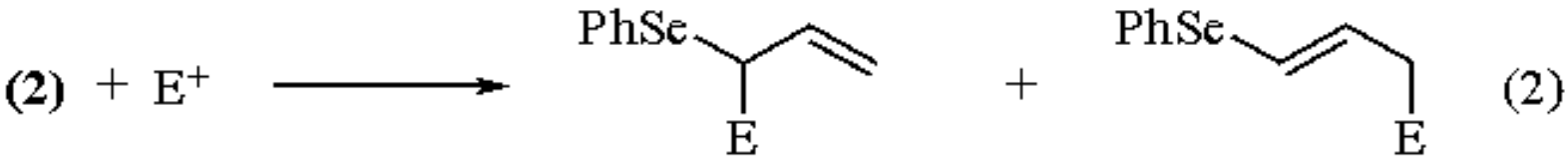

MeI	18:22
s-BuBr	76:24
Me_3SiCl	82:18
PhCOMe	15:85
PhCOMe, Et_3Al	78:22
EtCHO	12:88
EtCHO, Et_3Al	100:0

Altered reactivity and well-defined regioselectivity can also be achieved by prior conversion to phenylselenoallylstannanes (**3**), which react at the α-position with cationic electrophiles such as iminium salts (eq 3).[9]

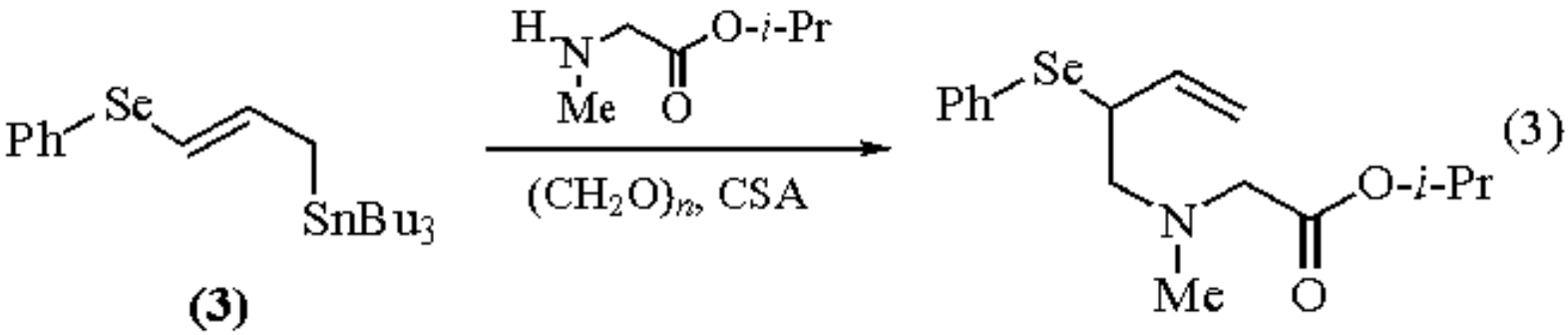

Like other stabilized organolithium reagents, (**2**) adds predominantly 1,2 to enones such as cyclopentenone in THF (1,2-adduct, α:γ = 62:18; 1,4-adduct, α:γ = 10:8) but gives exclusively 1,4-addition (α:γ = 81:5) when 1 equiv of ***Hexamethylphosphoric Triamide*** is added.[2]

[2,3] Sigmatropic Rearrangements.

A common application of allylic selenides is oxidation to form transient selenoxides, which undergo facile [2,3] sigmatropic rearrangement at low temperatures. In contrast to sulfur analogs, where the sulfoxide is usually favored, the equilibrium strongly favors the selenenate esters over the selenoxide,[10] so the rearrangement is very clean, requires no trapping reagents, and can typically be performed at 0 °C or lower.

An interesting extension is amination, in which allyl selenides are treated with an *N*-chloroamine (such as anhydrous ***Chloramine-T***) or primary amide or carbamate in the presence of ***N-Chlorosuccinimide***. This forms the selenimide in situ, which rearranges to an *N*-allylsulfonamide, -amide, or -carbamate (eq 4).[11]

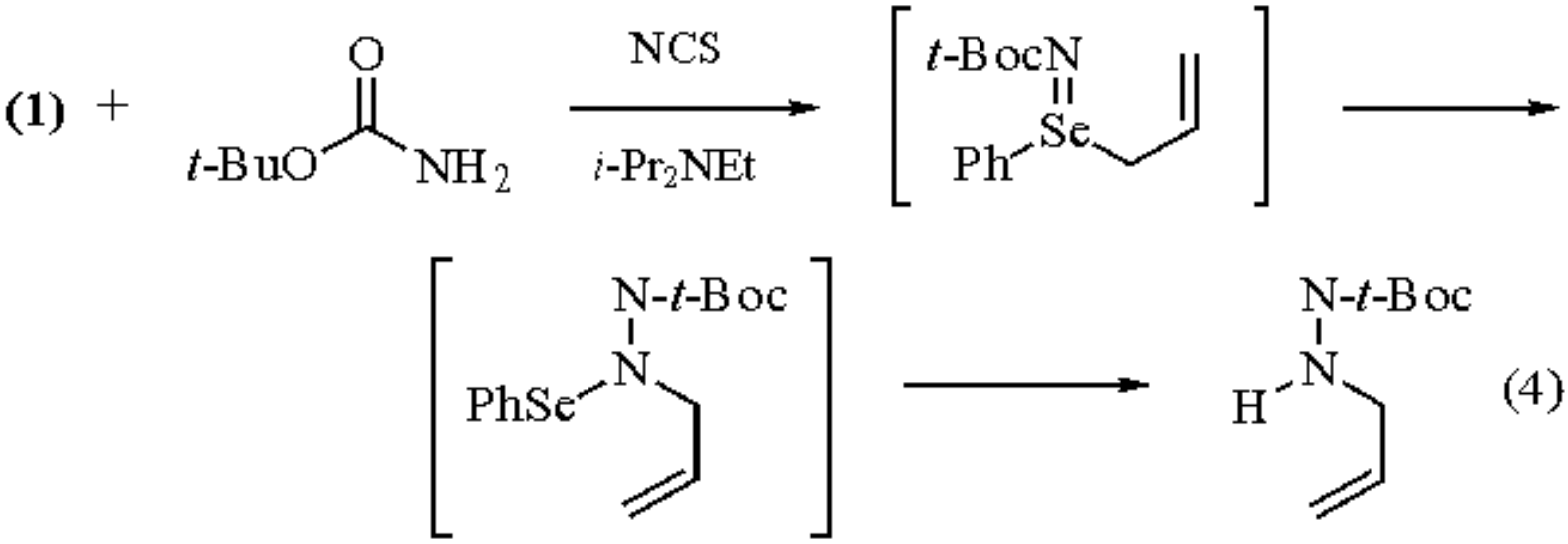

Allylselenonium ylides also undergo sigmatropic rearrangements. The diazo-β-lactam (**4**) reacts with (**1**) with copper catalysis to form the allylated selenide (**5**) (eq 5).[12]

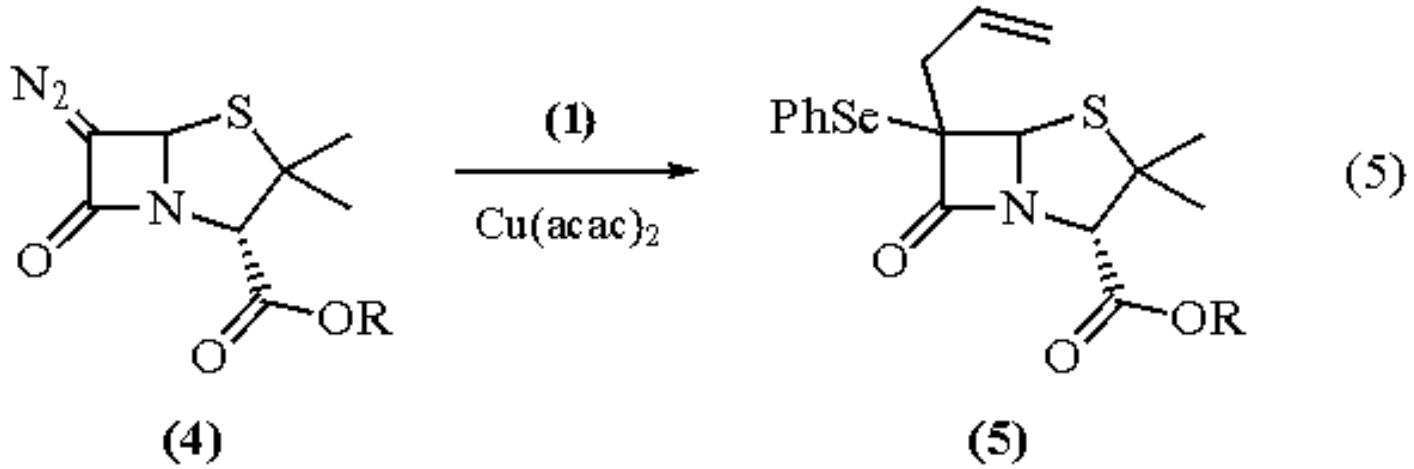

Allylic Rearrangement of Allyl Selenides.

Unsymmetrically substituted allyl selenides undergo easy allylic isomerization on irradiation or with acid catalysis, usually to favor primary over secondary selenides.[9,11] Such processes can be applied to the alkylation products of (**2**) to effect regiocontrolled further transformations, such as a second metalation and alkylation,[11] or oxidative,[9] or aminative [2,3] sigmatropic rearrangements.[11] Eq 6 presents an example involving an aminomethylated methallyl selenide.[9]

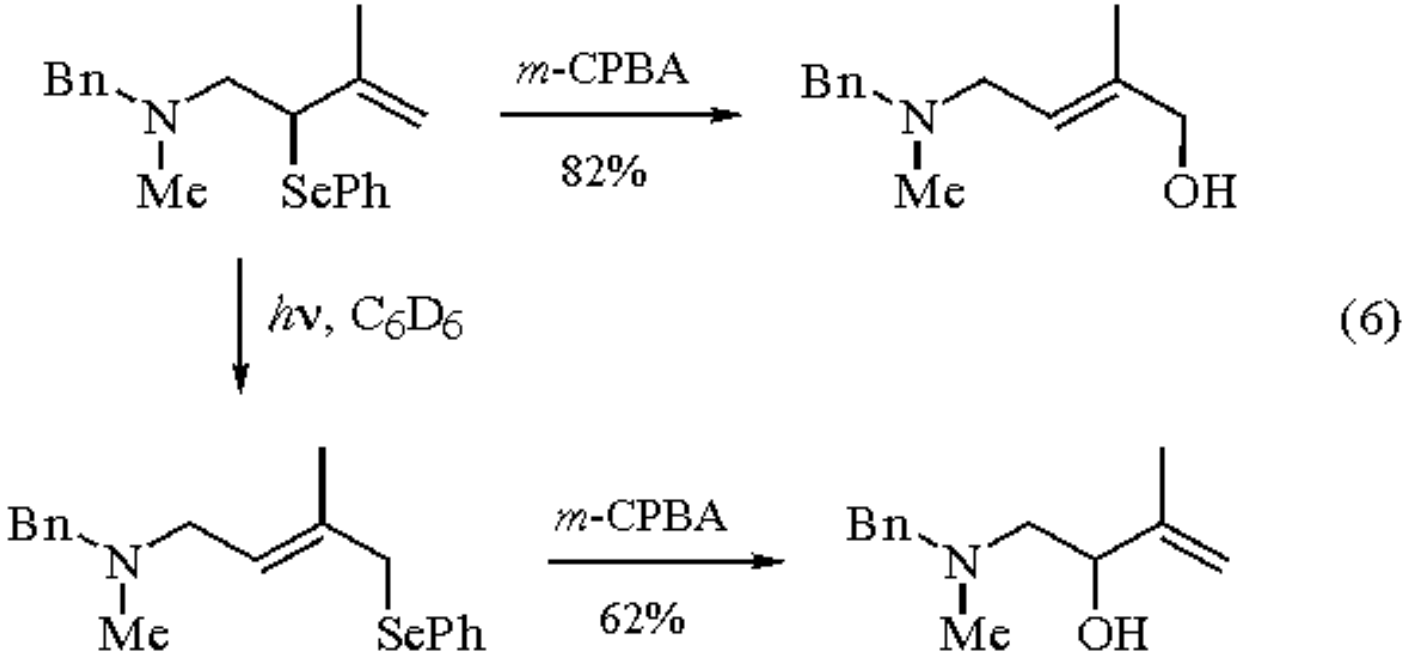

Allyl Phenyl Selenide as an Allylation Reagent.

The relatively weak C-Se bond in (**1**) and its alkylation products can be exploited to produce anionic and cationic allyl synthons. Treatment of (**1**) with ***n-Butyllithium*** results in Li/Se exchange to form ***Allyllithium***. Other allyl selenides also work.[13]

Allyl selenides (**3**) undergo coupling with organocuprates[6] and Grignard reagents in the presence of nickel catalyst.[14] The reaction of (**1**) with ***Triethylborane*** forms the alkylated allylboronate (**6**) by B to C alkyl transfer with displacement of the PhSe group. This boronate complex can be trapped with aldehydes, or allowed to rearrange to (**7**) before trapping, to give regioisomeric homoallyl alcohols (**8**) and (**9**), in ratios of 94:6, and 9:91, respectively (eq 7).[15]

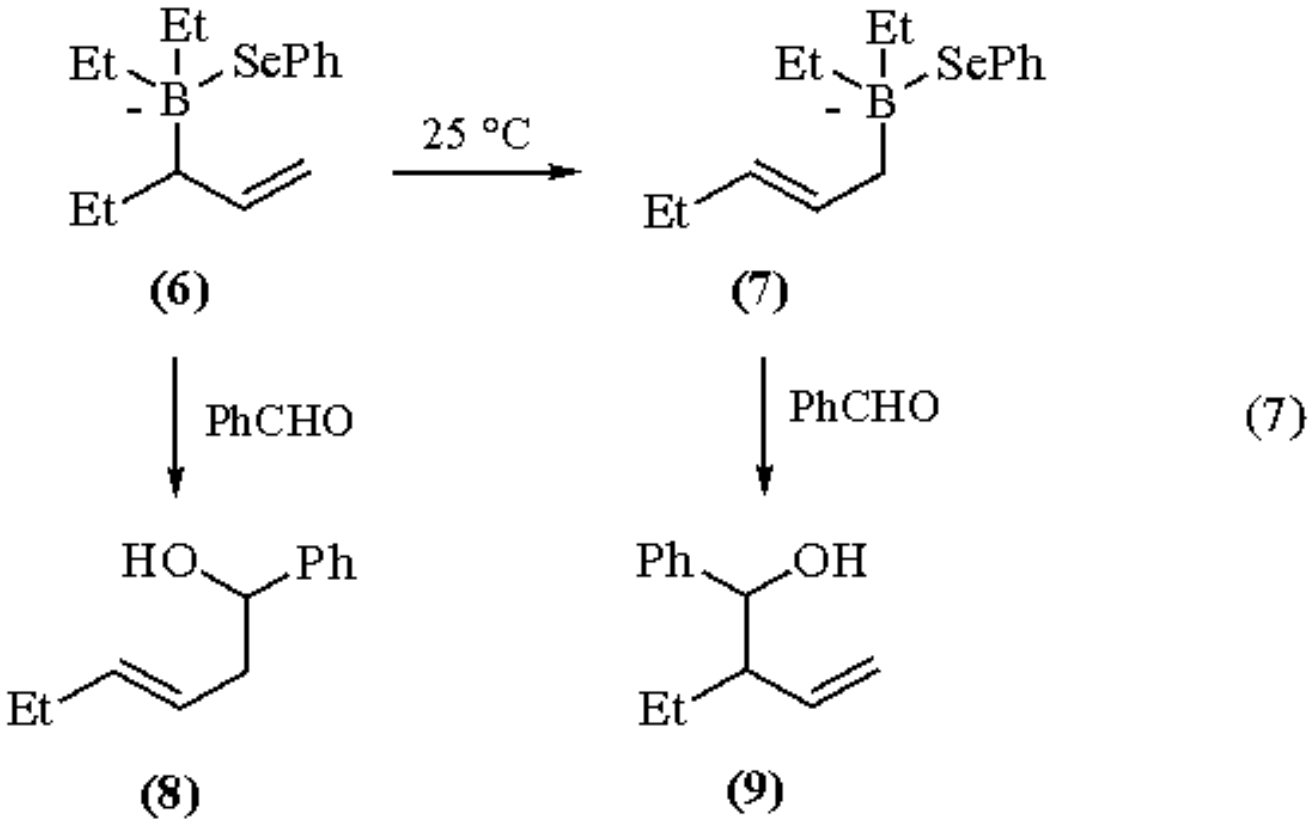

(7)

There are also reports of allyl radical transfer from (**1**) to carbon[16] and sulfur (sulfonyl) centered radicals.[17]

Related Reagents.

Allyl Phenyl Sulfide.

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Allyl Phenyl Sulfide[1]

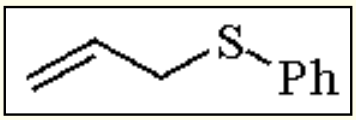

[5296-64-0] · $C_9H_{10}S$ · Allyl Phenyl Sulfide · (MW 150.24)

(metalated derivatives are ambident nucleophiles; undergo reductive lithiation; precursors to sulfonium salts and sulfur ylides which undergo rearrangement)

Physical Data: bp 48-49 °C/0.43 mmHg; *d* 1.0220 g cm^{-3}.

Solubility: insol water; sol most organic solvents.

Form Supplied in: colorless liquid of 98% purity as obtained commercially.

Preparative Method: from ***Allyl Bromide*** and sodium thiophenolate in ethanol.[2]

Purification: distillation in vacuo prior to use.

Handling, Storage, and Precautions: must be handled in a fume hood due to stench caused by contamination with ***Thiophenol***. The pure sulfide has a more agreeable odor with a sweet overtone. No special precautions are necessary when handling in the atmosphere for weighing and transferring. In order to avoid autoxidation the sulfide should be stored in a well sealed vessel with exclusion of oxygen and moisture at 4 °C.

Metalation.

Treatment of allyl and alkylallyl phenyl sulfides with ***n-Butyllithium*** in THF gives lithiated reagents which predominantly react with alkyl halides in THF at C-α although substantial γ-alkylation takes place in certain cases.[1] α-Regioselectivity is enhanced by replacing phenyl with 2-pyridyl, thiazolyl, *N*-methylimidazolyl and others.[1a,1d] ***Hexamethylphosphoric Triamide*** decreases regioselectivity of alkylation.[1a] Lithiated prenyl phenyl sulfide adds to acetone primarily through C-α in the presence of [2.2.2]cryptate, whereas predominant addition through C-γ takes place in the absence of additives; ***1,4-Diazabicyclo[2.2.2]octane*** and ***N,N,N´,N´-Tetramethylethylenediamine*** have no effect on this regiochemistry.[3] Transmetalation may also be used to enhance regioselectivity in carbonyl addition.[1d] Lithiated allyl phenyl sulfide upon transmetalation with ***Titanium Tetraisopropoxide*** adds through C-α with carbonyl compounds,[4] and to a proline derivative (eq 1),[5] although the lithiated reagent alone reacts in the same way with indene oxide.[6] While the lithiated sulfide reacts with enones in THF at -78 °C to give mixtures of α- and γ-

carbonyl (or 1,2) adducts, HMPA (1.5 equiv.) induces kinetically controlled conjugate (or 1,4) addition through C-α.[7] This observation has been exploited in syntheses of prostaglandins,[8] and estra-1,3,5(10)-triene-6,11,17-trione.[9] The conjugate addition of the lithiated sulfide to 3-methylbutenenitrile in the presence of HMPA proceeds through C-α.[10] Stereoselectivity is rarely observed in addition reactions involving lithiated allyl phenyl sulfide, with exceptions being provided by the reactions involving 3-methylbutenenitrile[10] and the transmetalated sulfide with carbonyl compounds[4] and proline.[5]

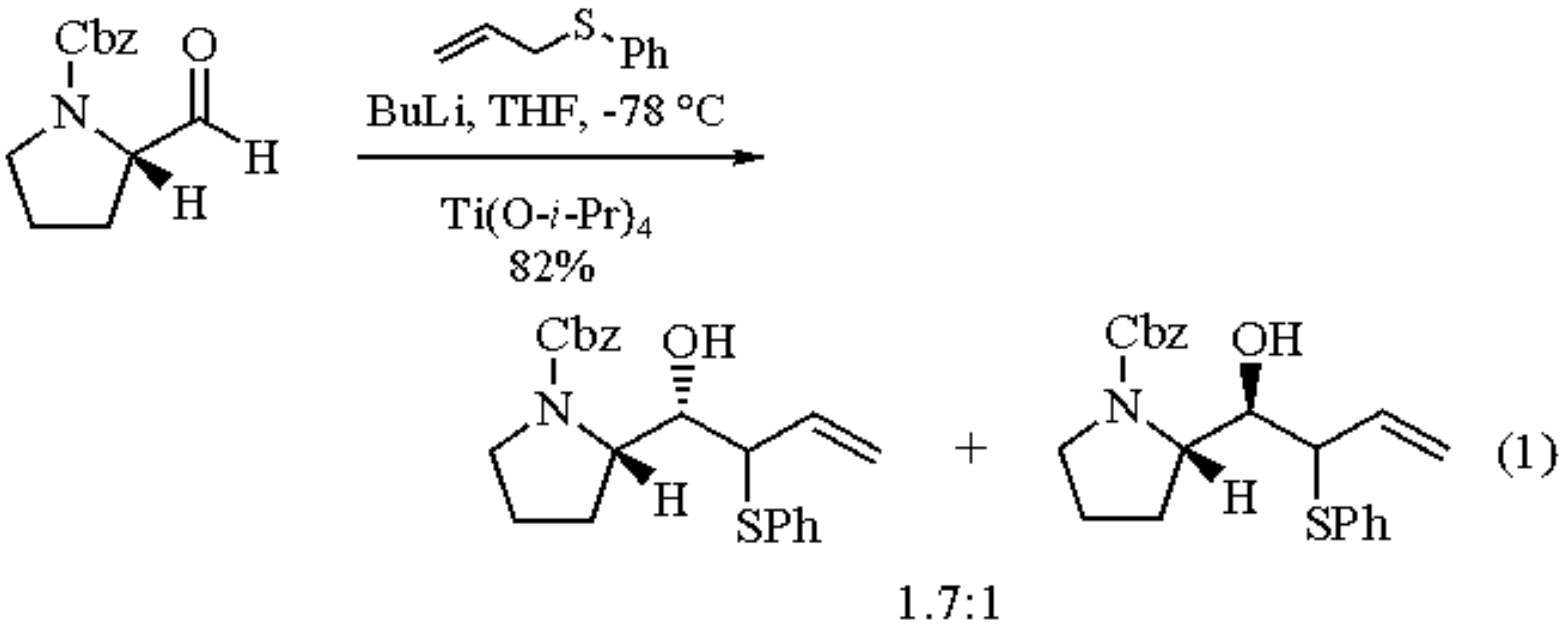

Reductive Metalation.

Reductive lithiation with ***Lithium Naphthalenide*** or ***Lithium 1-(Dimethylamino)naphthalenide*** provides an efficient means of replacing the phenylthio group in a wide variety of substituted allyl phenyl sulfides with lithium to give allyllithium reagents not readily obtainable by other methods.[11]

Allylic Displacement.

Allyl phenyl sulfide undergoes displacement by Grignard reagents catalyzed by nickel phosphine complexes.[12] However, regioselectivity in alkylallyl cases is poor. Treatment of allylic sulfides bearing a thiazoline substituent with ***Iodomethane*** generates allylic iodides, a reaction driven by formation of methyliminium intermediates (eq 2).[13] Addition of alkyl radicals, generated from alkyl halides by a mixture of a cobalt(III) complex and zinc, to C-γ of allyl phenyl sulfide (and sulfone, see ***Allyl Phenyl Sulfone***) followed by loss of a phenylthio radical produces the alkylated product in high yield.[14]

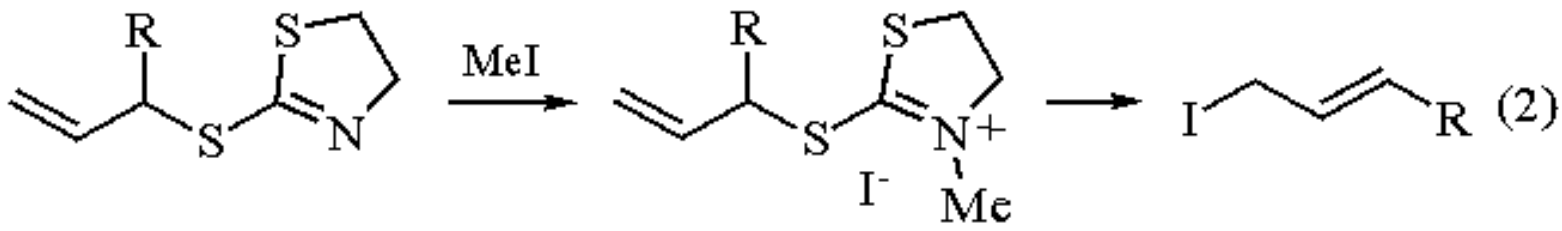

Sigmatropic Rearrangements.

When the phenyl group is replaced by methylene attached to a charge-stabilizing group[15] or a group capable of undergoing transmetalation with lithium,[16] lithiation generates an α´-lithiated species which undergoes [2,3]-thia-Wittig rearrangement to homoallylic thiols (eq 3). The use of sulfur cation radicals in organic synthesis is rare. However, the cation radical derived from allyl phenyl sulfide and ***Cerium(IV) Ammonium Nitrate*** couples with silyl enol ethers to give a sulfonium adduct which rearranges to γ,δ-alkenyl-α-phenylthio ketones in high yields (eq 4).[17] Rearrangement of sulfonium ylides generated by the addition of carbenes to allyl sulfides proceeds to give (*E*)-homoallylic sulfides;[1b,1c,18] chirality in relevant cases is thereby transferred from C-1 to C-3 (eq 5).[19] Allyl phenyl sulfide undergoes Lewis acid-catalyzed conjugate addition to propiolic esters to give sulfonium allenes which rearrange to α-allyl-β-phenylthiovinyl esters.[20] The sulfide and related compounds also undergo a catalyzed [3,3]-thio-Claisen rearrangement to give *o*-allylbenzenethiols.[1b,21]

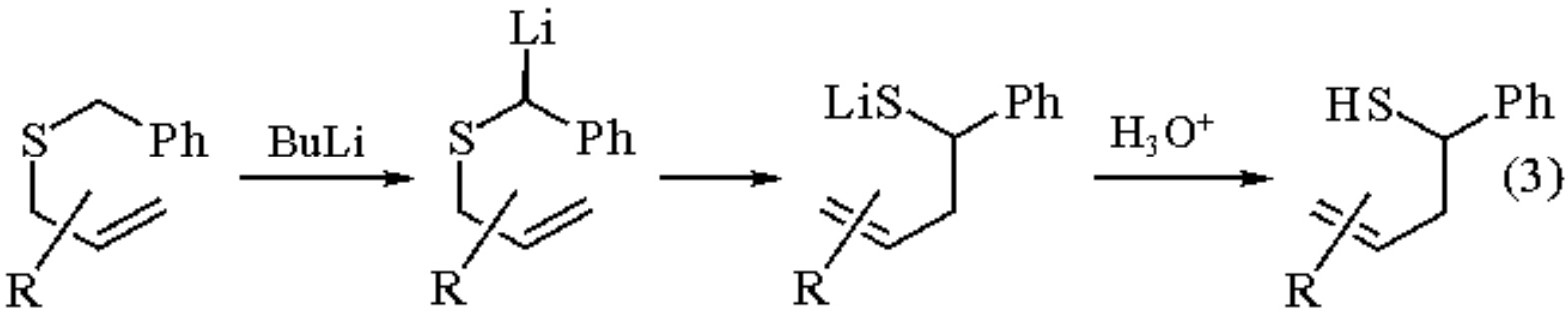

(3)

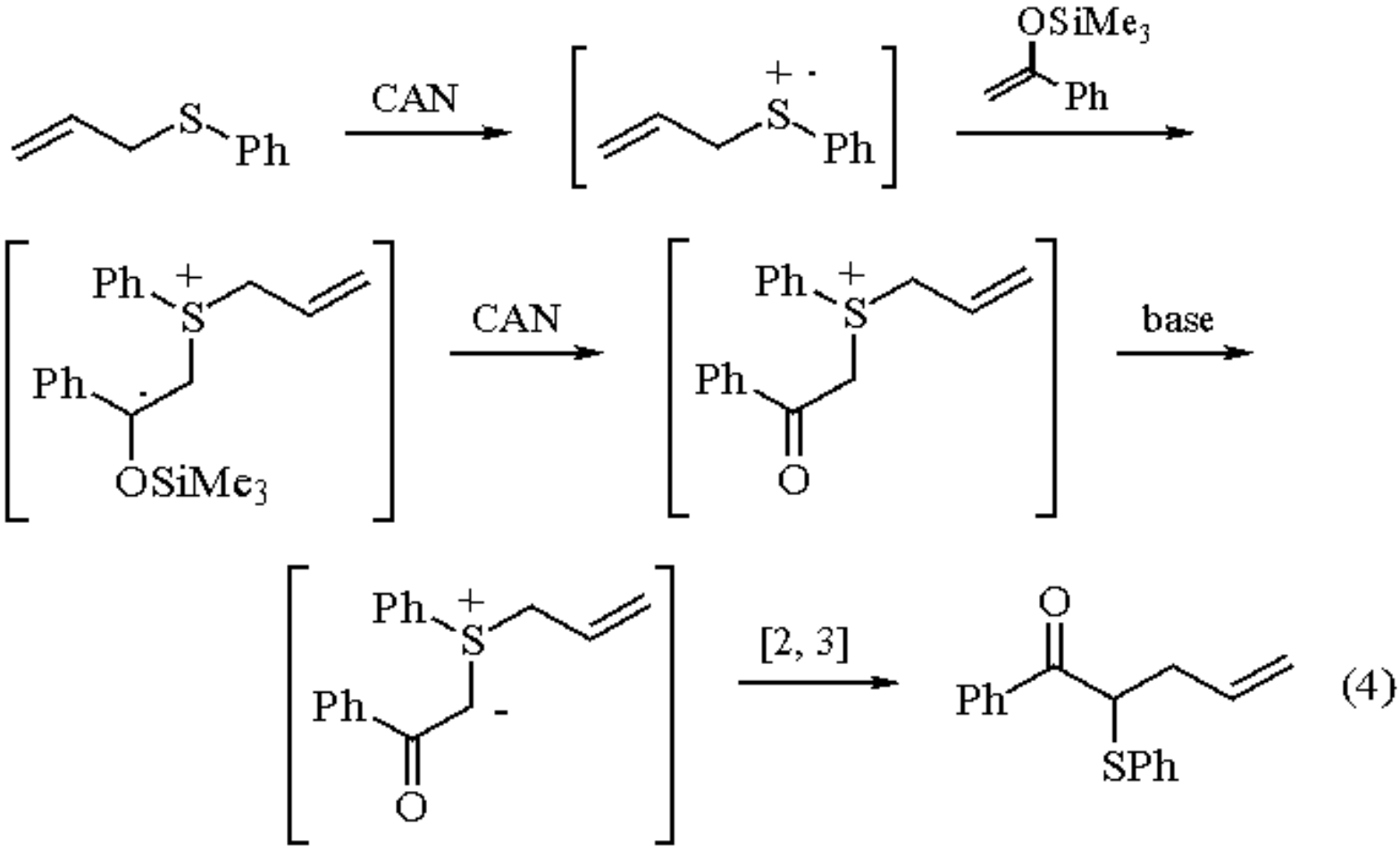

(4)

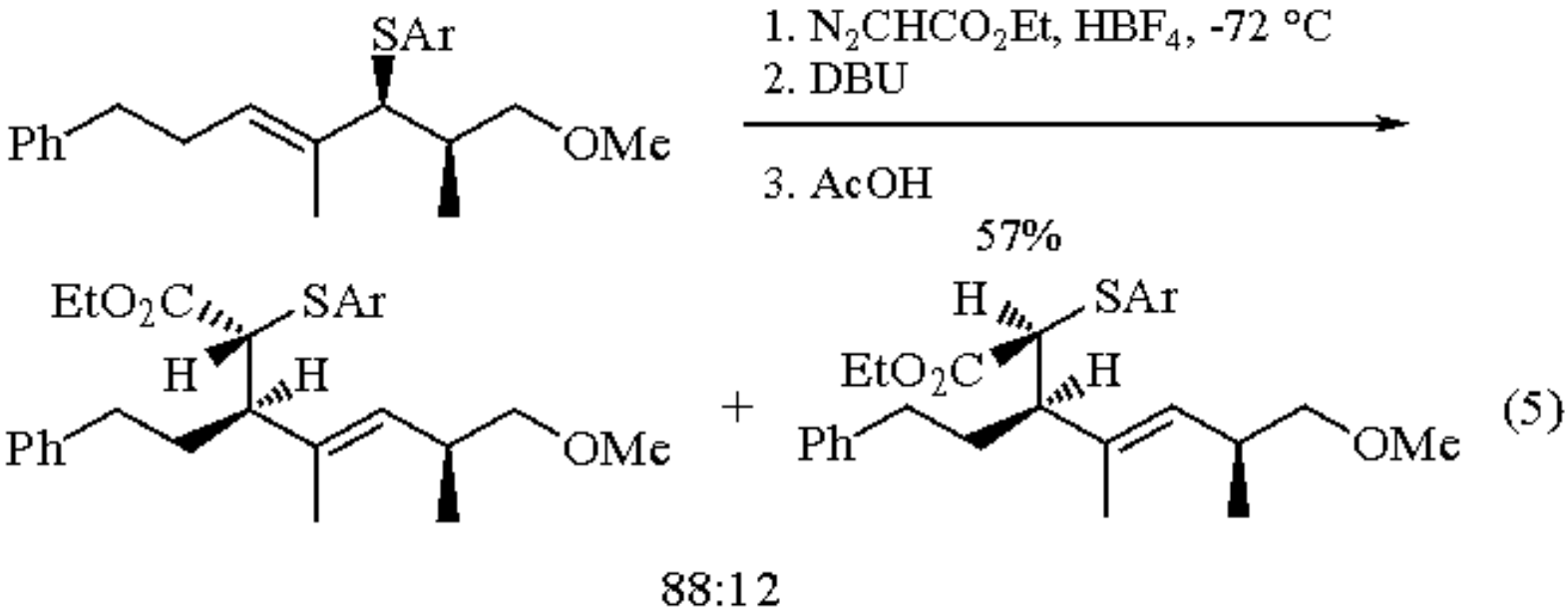

Related Reagents.

Allyl Phenyl Selenide; ***Allyl Phenyl Sulfone***; ***Allyl Phenyl Sulfoxide***.

---

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Allyl Phenyl Sulfone

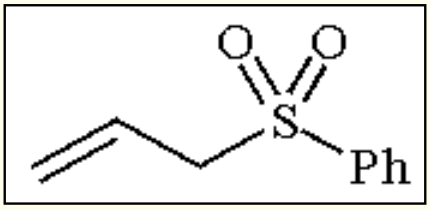

[16212-05-8] · $C_9H_{10}O_2S$ · Allyl Phenyl Sulfone · (MW 182.24)

(metalated derivatives serve as ambident nucleophiles; reacts as a 1,1-allylic dianion or 1,1-allylic dipole equivalent[1])

Alternate Name: 1-phenylsulfonyl-2-propene.

Physical Data: bp 111-113 °C/0.5 mmHg; *d* 1.189 g cm^{-3}.

Solubility: insol water; sol most organic solvents.

Form Supplied in: colorless liquid with purity >98% as obtained commercially.

Preparative Method: from ***Allyl Bromide*** and benzenesulfinate in ethanol according to the original procedure[2] is most straightforward and avoids the use of strong-smelling thiols.

Purification: distillation in vacuo prior to use.

Handling, Storage, and Precautions: the sulfone is a stable compound and is handled without special precaution.

Metalation.

Treatment with ***n-Butyllithium*** in THF produces lithiated allyl phenyl sulfone. Structurally, the lithiated reagent is akin to a lithium dienolate in that it possesses an O-Li contact, and a C-1-S bond which has double bond character, although the X-ray structure of the diglyme solvate indicates that C-1 does not possess full sp^2 character.[3] In THF, the reagent alkylates through C-α in a manner similar to the sulfide and sulfoxide.[1] Carbonyl addition also proceeds in this mode.[4] However, with Michael acceptors, the behavior is intermediate between that of the sulfide and sulfoxide: acyclic unsaturated ketones and unsaturated esters undergo predominantly conjugate (or 1,4-) addition through C-α while cyclic enones preferentially undergo conjugate addition through C-γ.[5,6] The addition proceeds under kinetic control with high diastereoselectivity and is analogous to the sulfoxide reaction (see ***Allyl Phenyl Sulfoxide***).[6c]

However, ***Hexamethylphosphoric Triamide*** causes conjugate addition to both acyclic and cyclic enones through C-α to occur, the latter reaction paralleling that of the lithiated sulfide (see ***Allyl Phenyl Sulfide***).[6] Lithiated allyl phenyl sulfone adds through C-α to a bisepoxide to give a single adduct which, after internal proton transfer, undergoes cyclization to a precursor of brefeldin A (eq 1).[7]

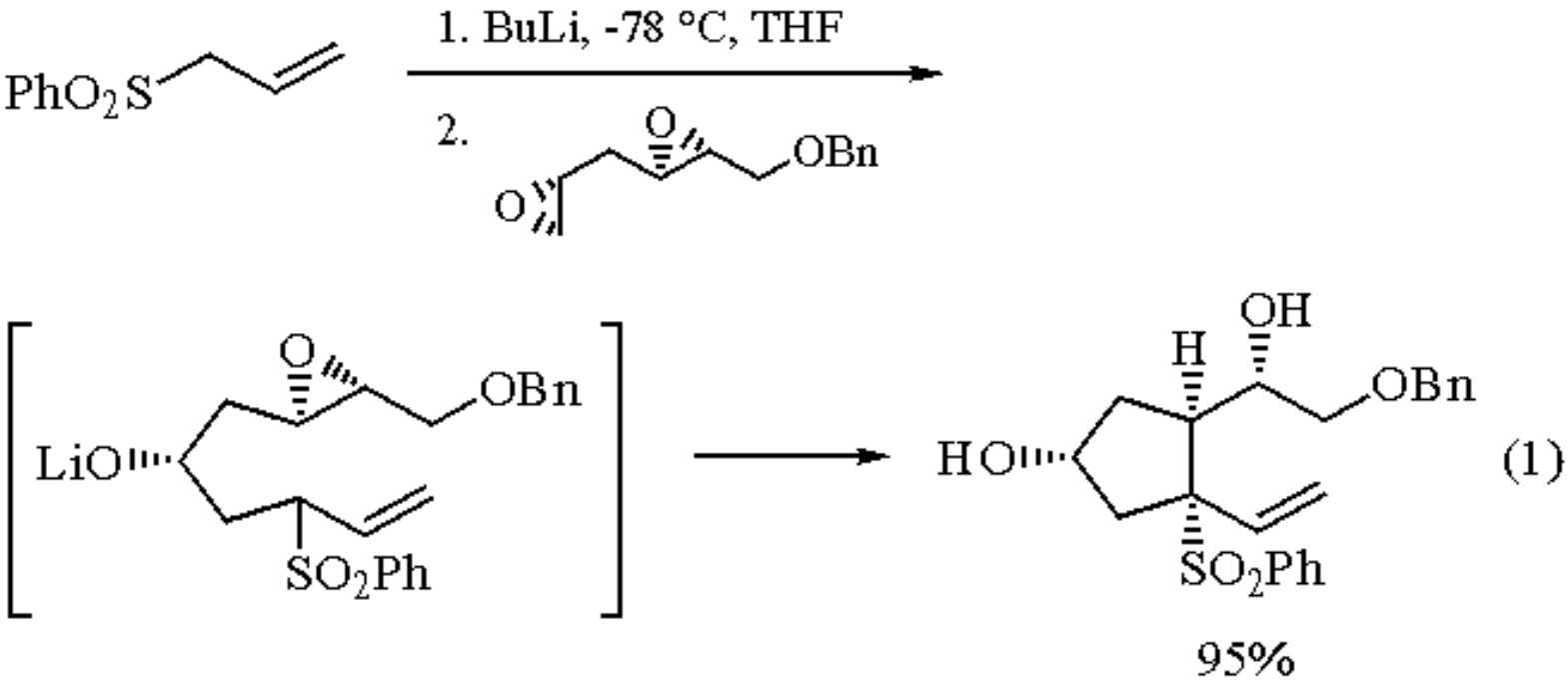

Sulfonyl Leaving Group.

Allylic phenyl sulfones undergo regio- and stereoselective allylic displacement by lithium dialkylcuprates[8] and sodium diethyl malonate in the presence of Pd^0 catalysts[9] in good yields. Like the sulfides, the sulfones undergo radical fragmentation.[10] Addition of tributyltin radical followed by loss of the arylsulfonyl radical affords the allylically transposed stannane. Acid hydrolysis then gives the terminal alkene without contamination with the other regioisomer.[10a,10b] The reaction is not applicable to γ-alkylallylic sulfones. The stannane reacts with *sym*-trioxane in the presence of a Lewis acid catalyst with concomitant destannylation, thereby rendering the allylic sulfone functionally equivalent to a 1,1-dianion (eq 2).[10b] Alkenes are prepared by α-alkylation of lithiated allyl phenyl sulfone followed by conversion into the vinyl sulfone with ***Potassium t-Butoxide*** in THF,[11,12] and then reductive cleavage of the phenylsulfonyl group with lithium in ethylamine.[11] α-Alkylation of lithiated allylic phenyl sulfones bearing other alkyl or functional groups followed by base-induced elimination[13] or reductive cleavage[14] is used in the synthesis of polyenes such as vitamin A and squalene. The weak Lewis basicity of the sulfonyl group enables allylic phenyl sulfones to be activated by Lewis acids in Friedel-Crafts alkylation of aromatic rings with displacement of the phenylsulfonyl group.[15] Thus alkylation of lithiated allyl phenyl sulfone followed by the Friedel-Crafts reaction renders the sulfone functionally equivalent to a 1,1-dipole. A conjugate addition-enolate trapping sequence commencing with DMPU-induced conjugate addition of lithiated prenyl tolyl sulfoxide to 2-methylcyclopentenone provides an adduct which undergoes Lewis acid-catalyzed intramolecular cyclization to a 1,11-epithio steroid (eq 3).[15b] The dipolar characteristic of allylic sulfones is also illustrated in the synthesis of chrysanthemic acid from lithiated prenyl phenyl sulfone.[16] The conjugate adduct with dimethylacrylate undergoes an internal nucleophilic displacement of the phenylsulfonyl group to form the cyclopropane (eq 4). A preparation of prephytoene is carried out in similar fashion.[17] Lithiated allyl phenyl sulfone couples with iodocarbenoids to form 1-iodo-1,3-dienes in high yields and with high stereoselectivity for the *E*-isomer.[18]

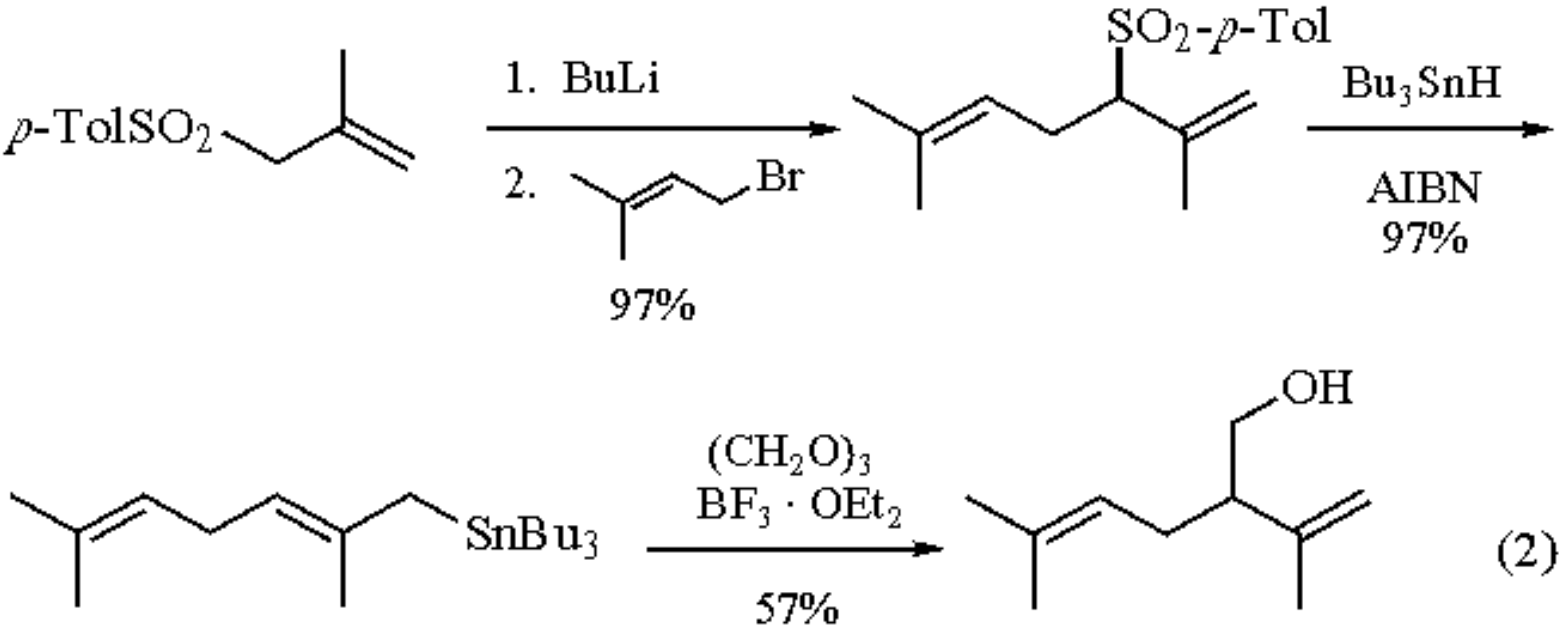
p-TolSO2
1. BuLi
2.
Br
97%
SO2-p-Tol
Bu3SnH
AIBN
97%
SnBu3
(CH2O)3
BF3 · OEt2
57%
OH

(2)

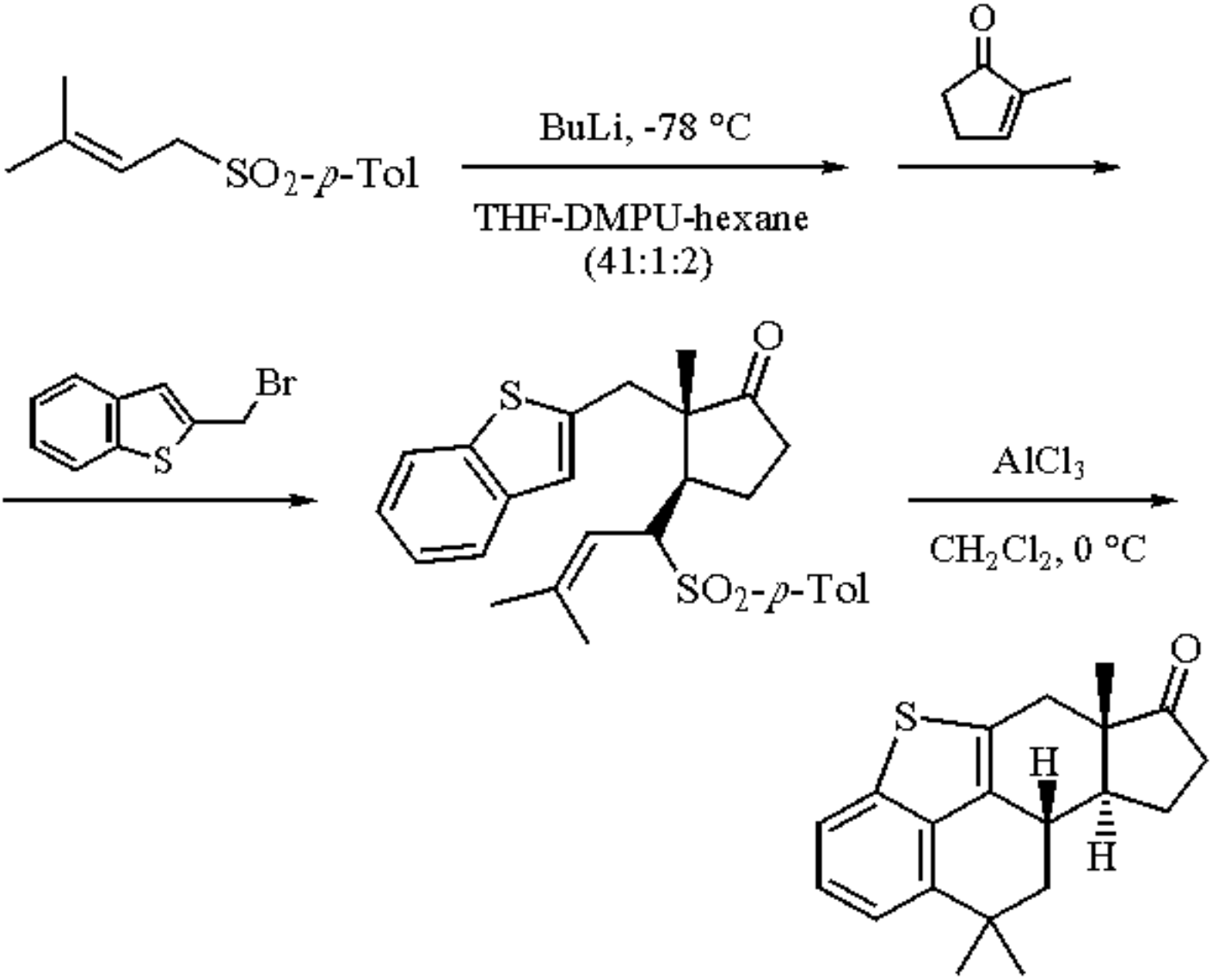
SO2-p-Tol
BuLi, -78 °C
THF-DMPU-hexane
(41:1:2)
O
Br
S
S
O
SO2-p-Tol
AlCl3
CH2Cl2, 0 °C
S
O
H
H

(3)

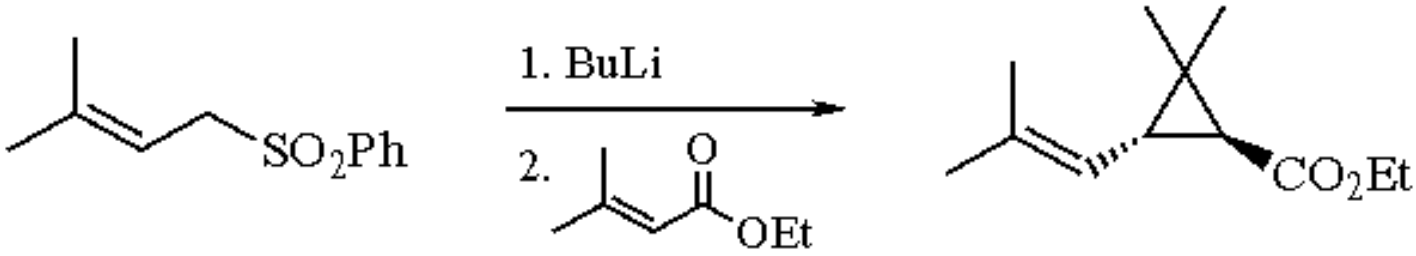

(4)

Related Reagents.

Allyl Phenyl Sulfide; ***Allyl Phenyl Sulfoxide***; α-***Phenylsulfonylethyllithium***.

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Allyl Phenyl Sulfoxide[1]

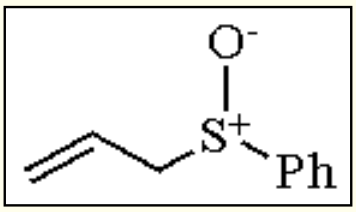

[19093-37-9] · $C_9H_{10}OS$ · Allyl Phenyl Sulfoxide · (MW 166.23)

(allylic sulfoxides undergo allylic rearrangement to form sulfenate esters, allowing the generation of allylic alcohols; metalated derivatives serve as ambident nucleophiles; precursors to Pummerer intermediates)

Physical Data: bp 103-104 °C/0.36 mmHg; *d* 1.1205 g cm^{-3}.[2]

Solubility: insol water; sparingly sol hexane; sol most other organic solvents.

Preparative Methods: oxidation of ***Allyl Phenyl Sulfide*** in dichloromethane with ***m-Chloroperbenzoic Acid*** acid (1.2 equiv) added slowly as a solution in dichloromethane at -70 °C affords the sulfoxide in high yields with minimal over-oxidation to the sulfone. The *m*-chlorobenzoic acid formed may be removed simply by filtration. Other oxidizing agents such as ***Sodium Bromite***[3] and ***Trifluoroperacetic Acid***[4] afford the sulfoxide in yields greater than 80% and are also highly selective.

Purification: distillation in vacuo prior to use.

Handling, Storage, and Precautions: no special precautions are required. The sulfoxide may be handled normally at the bench for general weighing and transferring. However, for maximum shelf-life it is recommended that it be stored at 4 °C in a sealed vessel with exclusion of oxygen and moisture.

Sulfoxide-Sulfenate Rearrangement.

The important observation by Mislow and co-workers that allyl phenyl sulfoxide and other allylic sulfoxides may be prepared from allylic sulfenate esters, obtained from the corresponding allylic alcohol and an electrophilic sulfenylating agent,[5] in an equilibrating [2,3]-sigmatropic rearrangement was the key to establishing the synthetic utility of these compounds. Conversely, the sulfoxide may be converted into the allylic alcohol by intercepting the intermediate sulfenate ester formed in the equilibrium with the sulfoxide by treatment with a thiophilic reagent typically ***Trimethyl Phosphite***, tertiary phosphine, or secondary amine in methanol, which cleaves the sulfenate ester. Stereocontrol of the rearrangement is dependent on the types of groups attached to the allylic substituent. Selectivity for the (*E*) isomer occurs when R^1 is larger than R^2 (eq 1)[1a,1c] or when both R^1 and R^3 are alkyl groups and R^2 is a proton.[1c,6] In order to achieve (*E*) selectivity for 2,3,3-trisubstituted systems, a substituent at C-1 of the allylic

sulfoxide must have β-branching (eq 2).[7]

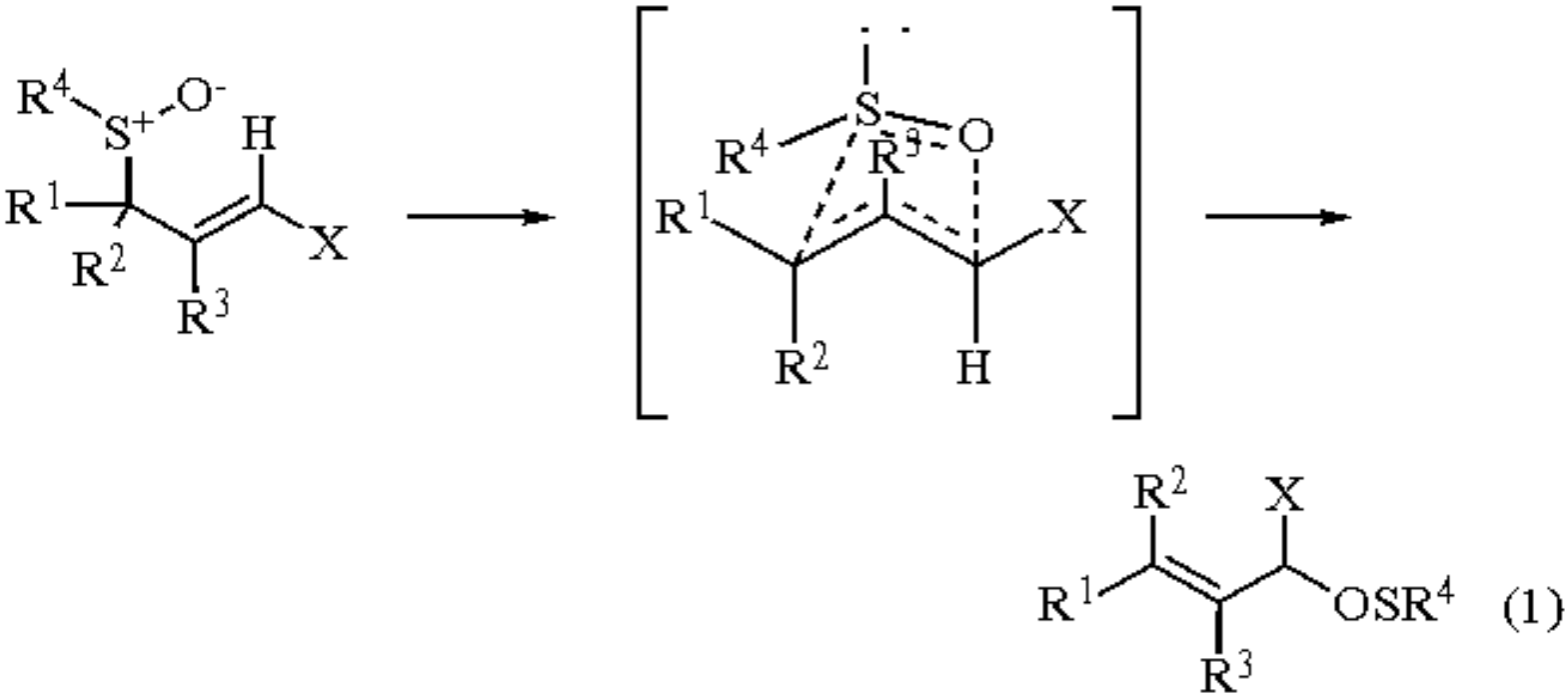

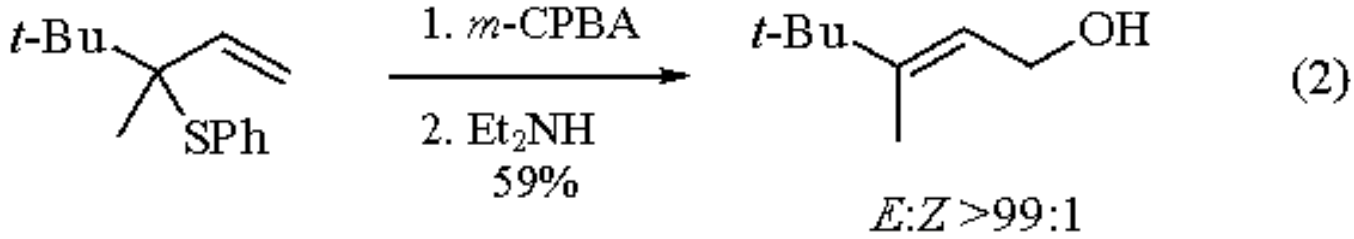

(2)

Whilst optically active allyl tolyl sulfoxides may be prepared from allyl Grignard reagents and ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***,[5a,8] the sulfoxide-sulfenate rearrangement causes facile epimerization at the sulfur atom. Racemization is generally less facile when the nonallylic substituent is alkyl rather than aryl.[5a] Thus, approaches to allylic sulfoxides derived from camphor[9] and 10-mercaptoisoborneol[10] have been developed wherein the configurational stability is promoted by a neighboring hydroxyl group. In another approach the rearrangement is not suppressed but rather is rendered highly stereoselective by the use of a bulky arylbiphenyl chiral auxiliary so that the other diastereomer is disfavored on thermodynamic grounds (eq 3).[11]

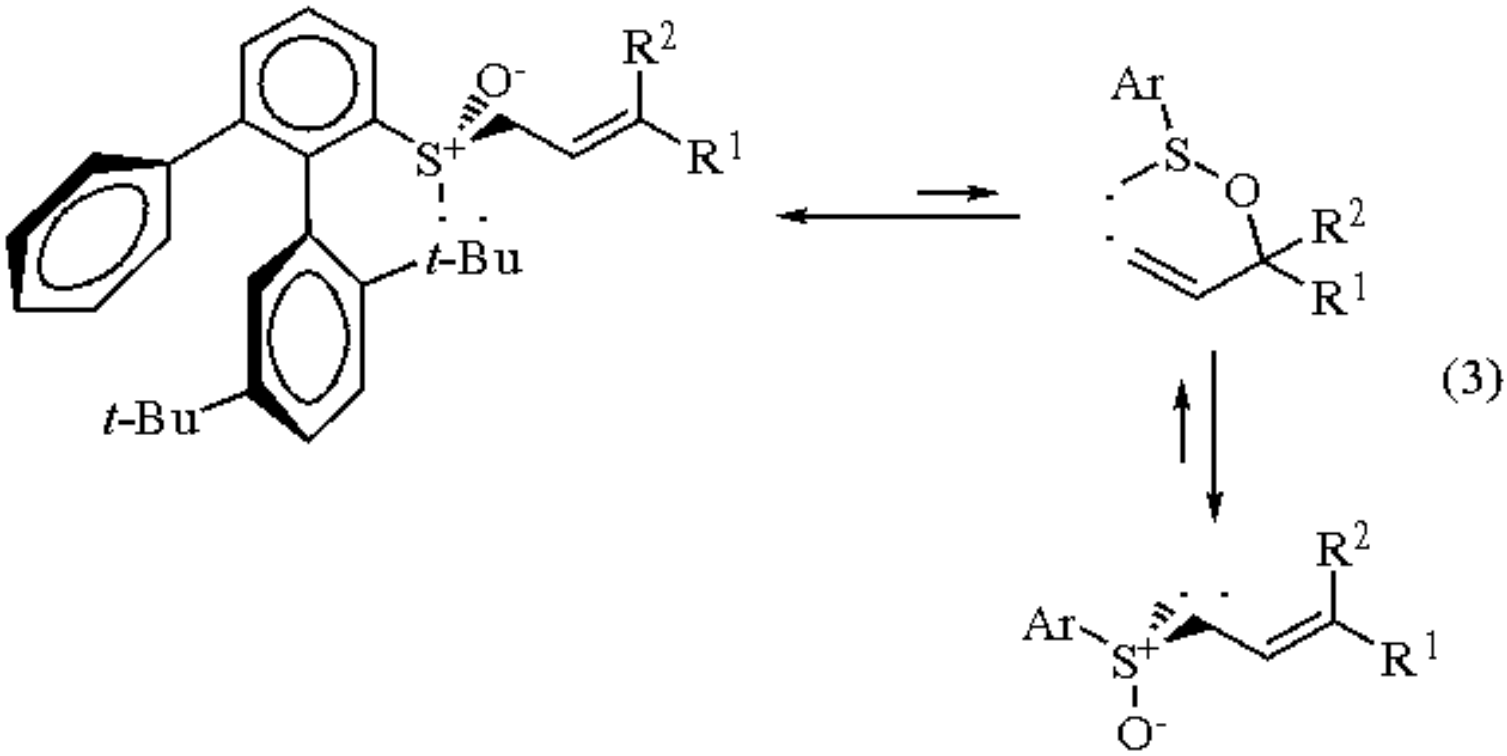

Metalation.

Treatment of allyl phenyl sulfoxide[12] with ***Lithium Diisopropylamide*** in THF produces the lithiated sulfoxide. Alkyllithium reagents are not generally successful because of competing displacement at sulfur. The lithiated reagent is likely to be structurally akin to a lithium dienolate in that it possesses an O-Li contact, and a C-1-S bond which has double bond character.[12] Reaction with alkyl halides proceeds preferentially at the α-carbon;[1,13] however, regioselectivity is somewhat better than for allyl phenyl sulfide. Subsequent conversion of the α-substituted sulfoxide into the allylically transposed alcohol renders the starting sulfoxide operationally equivalent to a 3-hydroxyvinyl anion.[1c,13] Reaction with cyclic enones is predominant conjugate (or 1,4) addition through the γ-carbon, a regiochemical outcome which is not disrupted by external chelating agents.[14,15] This regioselectivity has been exploited for lithiated allyl *p*-tolyl sulfoxide in a synthesis of pentalenolactone (*E*)-methyl ester[16] and for lithiated 1-pentylallyl phenyl sulfoxide in syntheses of racemic prostaglandin I_2 analogs[14a] and racemic 11-deoxyprostaglandin E_1 (eq 4).[14b] Both the pronounced tendency of the lithiated reagent to undergo conjugate addition and the sigmatropic rearrangement of the neutral reagent to provide the allylic alcohol are well illustrated in the latter synthesis. The vinyl sulfoxide product (**1**) is converted via the intermediate allylic sulfoxide into the allylic alcohol (**2**) by means of ***Potassium t-Butoxide*** in *t*-butanol to give the 13*SR* isomer. The acetate is then converted into the allylically transposed allylic acetate (**3**) by means of $PdCl_2$.2MeCN (see ***Palladium(II) Chloride***) to form the 15*SR* diastereomer. For lithiated (*E*)- and (*Z*)-allylic sulfoxides bearing an alkyl group at C-3, highly stereoselective conjugate additions to cyclopentenone take place to give *syn* and *anti* vinylic sulfoxides such that the configuration at the two new stereogenic centers and at sulfur is rigidly defined by the double bond geometry of the allylic sulfoxide (eq 5).[15b,15d]

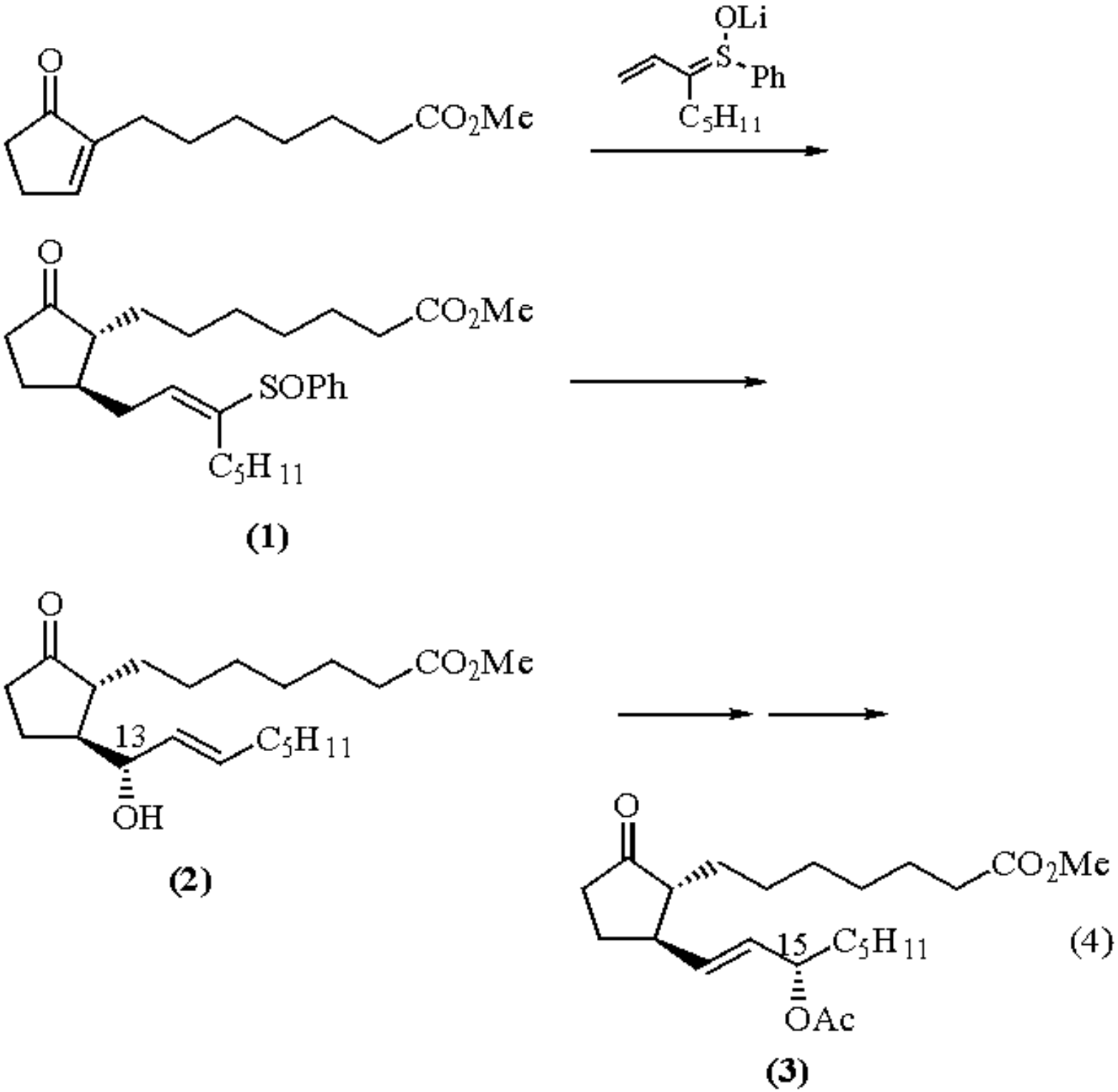
OLi
S
Ph
C_5H_{11}
O
CO_2Me
SOPh
C_5H_{11}
(1)
13
C_5H_{11}
OH
(2)
15
C_5H_{11}
OAc
(3)
(4)

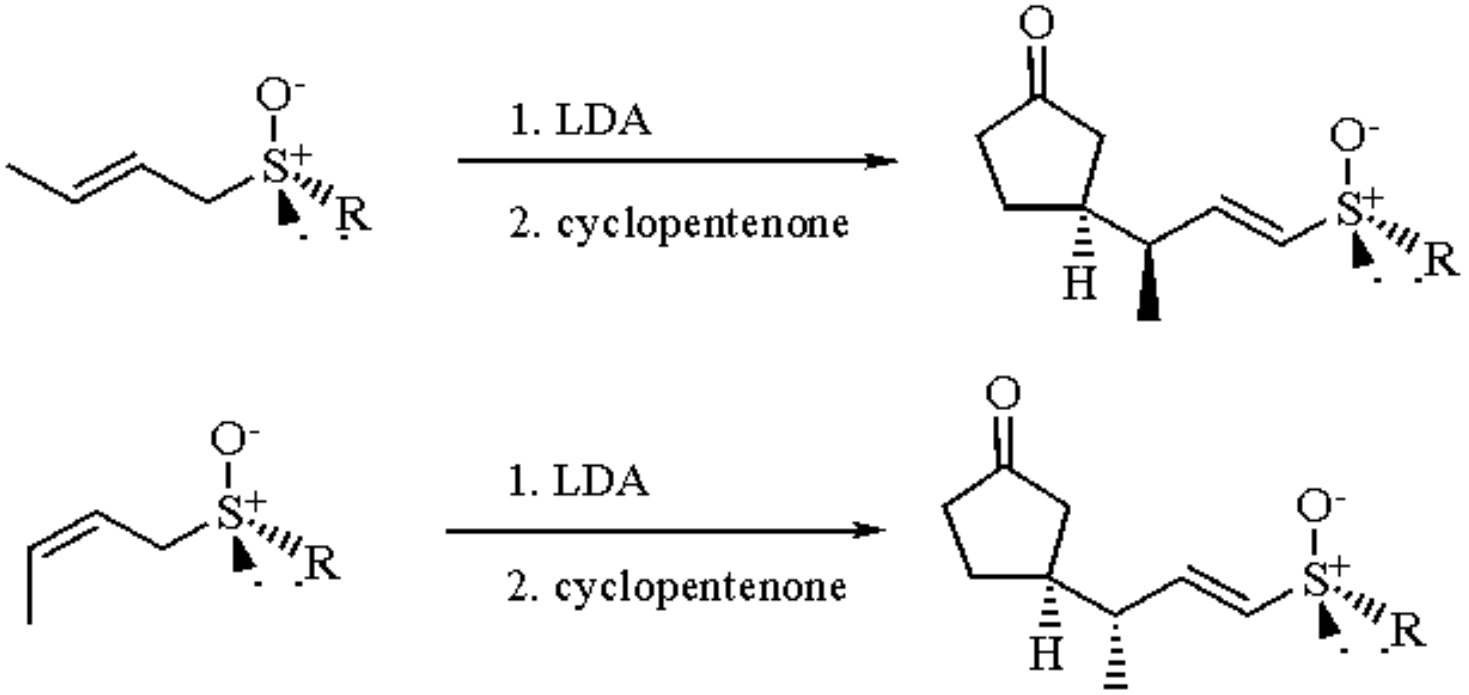

(5)

The conjugate addition proceeds under kinetic control[15a] and is explained by invoking a *trans*-decalyl-like transition state model.[15b,15d] By using optically pure allylic sulfoxides, single enantiomeric products are obtained. The use of camphor as the nonallylic substituent enables single enantiomeric allyl sulfoxides to be prepared[9] and these undergo conjugate addition to cyclopentenones with complete face selectivity (eq 6),[9b] albeit in moderate yields (50-60%). The use of an arylbiphenyl chiral auxiliary attached to sulfur affords in some cases higher yields of the adducts with good to excellent diastereoselectivity.[11b]

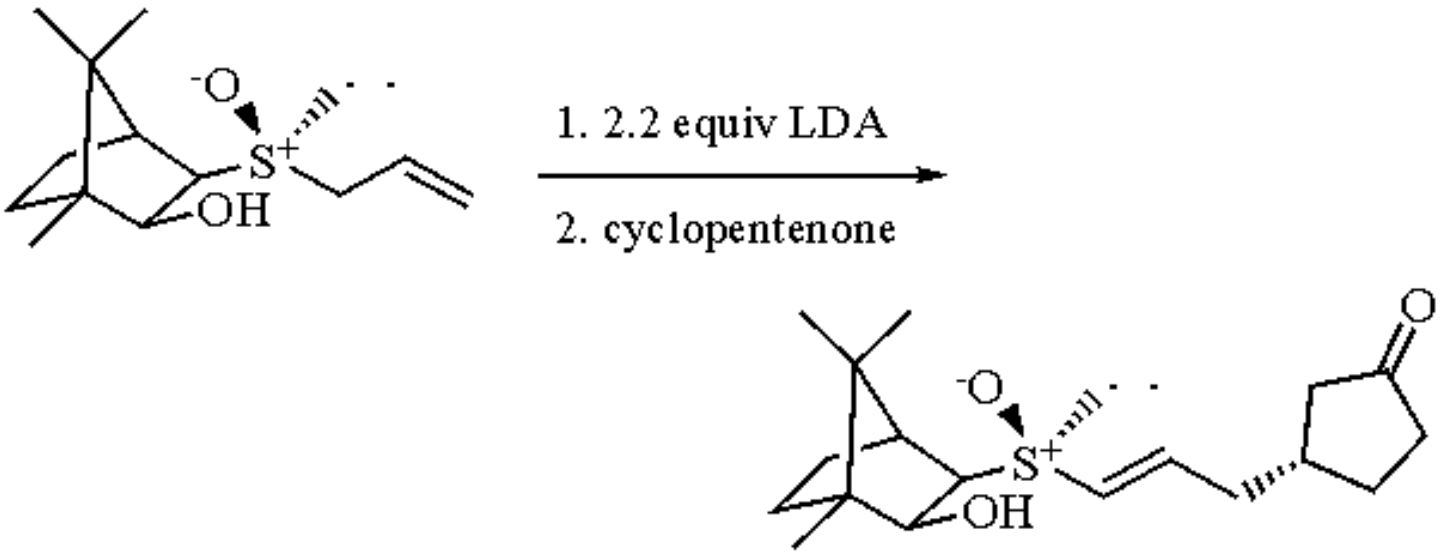

(6)

Similarly, lithiated reagents from optically pure *p*-tolyl allylic sulfoxides[5a] undergo conjugate addition to a variety of cyclic enones, and the adducts have been converted into (+)-pentalenene,[17] (+)-hirsutene,[18] and (+)- and (-)-13-epoxytrichothec-9-ene.[19] In other cases, configurational integrity of the products is maintained during conversion into bicyclo[2.2.1]heptanones[14d,20,21] and bicyclo[3.3.0.]octanones.[21,22] The regio- and stereoselectivity of reactions of lithiated allyl phenyl sulfoxide with carbonyl compounds is not as pronounced as that with cyclopentenones.[23] Nevertheless, the introduction of additives to modify the reactivity of the reagent has made carbonyl addition a

synthetically useful transformation.[24] Whereas reaction with α-methyl aldehydes gives a mixture of α- and γ-adducts, addition of ***Hexamethylphosphoric Triamide*** enhances α-addition while transmetalation with cadmium(II) encourages γ-addition (eq 7).[24a] This outcome is contrary to that observed with the carbonyl addition of metalated allyl sulfides (see ***Allyl Phenyl Sulfide***). For alkoxyaldehydes, use of lithiated 2-pyridyl allyl sulfoxide gives higher α-selectivity and superior yields,[24b] a reactivity paralleling that of the corresponding sulfide.

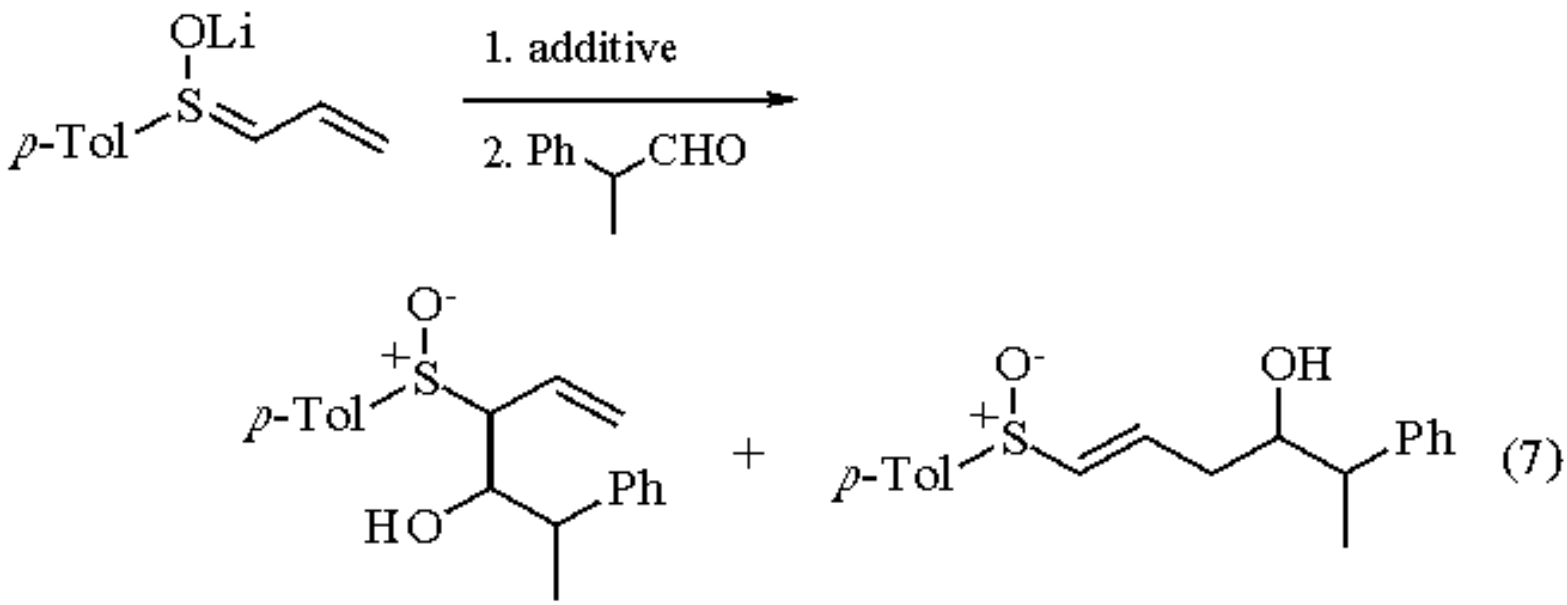

HMPA	9:1	75%
$CdCl_2$	1:14	68%

The α-adducts obtained from the reaction of lithiated allyl *p*-tolyl sulfoxide with aldehydes in the presence of HMPA,[24] and of lithiated prenyl phenyl sulfoxide with 1,2-epoxy-2-methyl-3-butene,[25] are converted via the sulfoxide-sulfenate rearrangement into functionalized diols (eq 8).

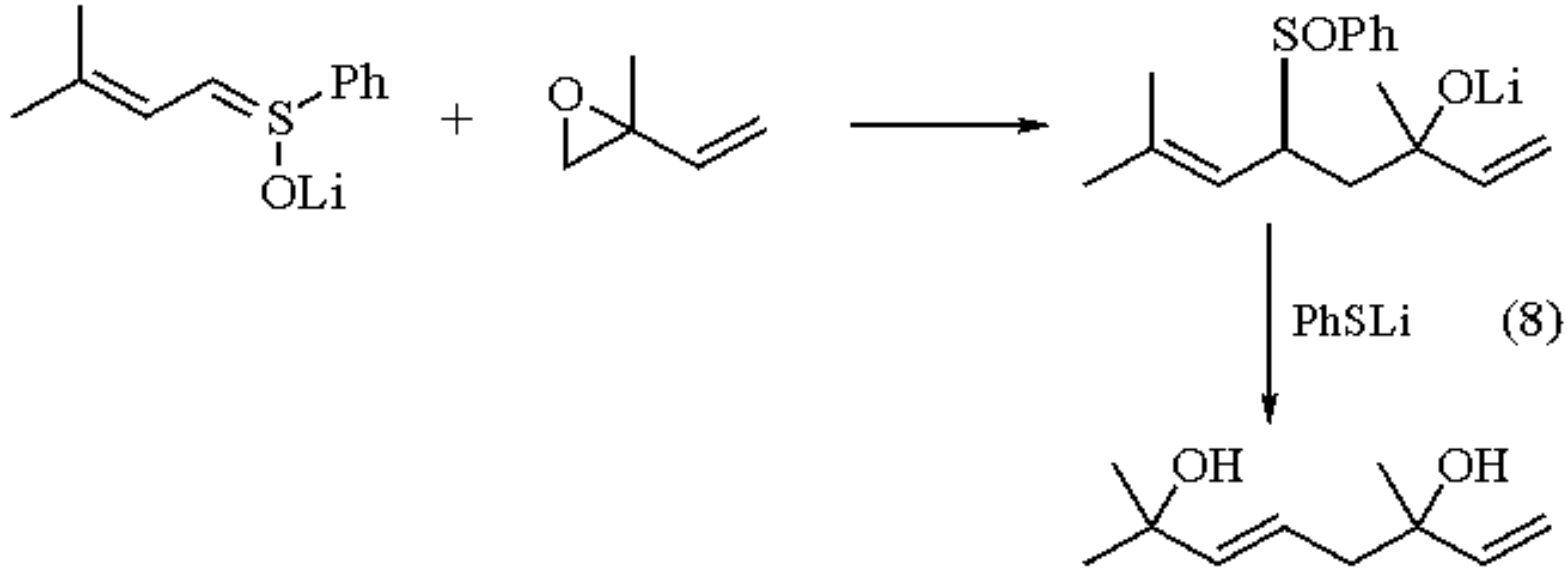

Vinylthionium Ions.

Polarity reversal may be achieved by converting allyl phenyl sulfoxide into the corresponding vinylthionium ion or equivalent via a Pummerer reaction. Such an electrophilic species also has ambident reactivity and may react with nucleophiles through the α- or the γ-carbon (eq 9).[26]

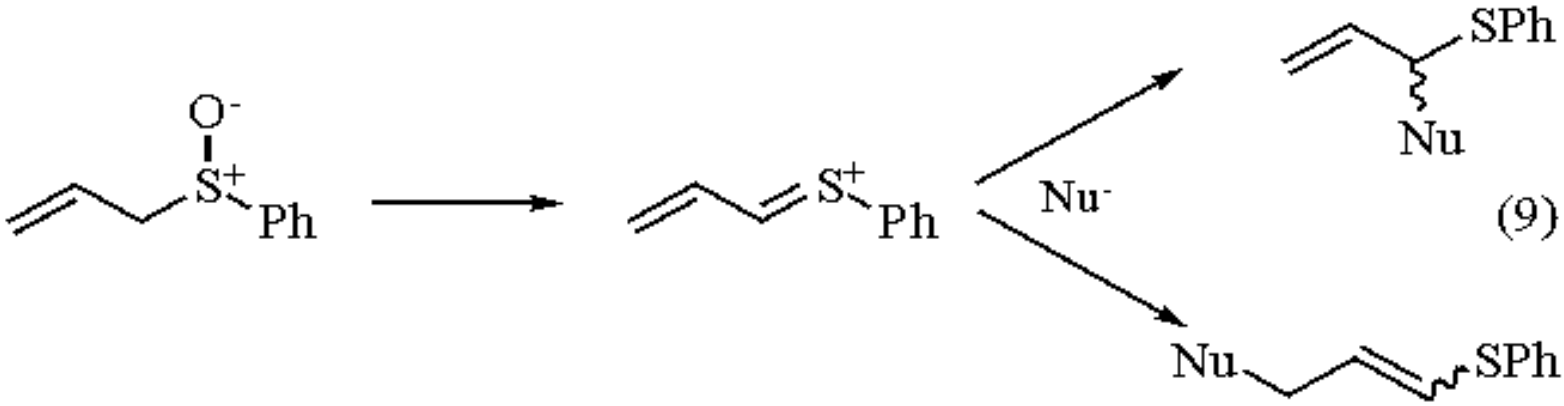

(9)

Thus allyl phenyl sulfoxide reacts with silyl enol ethers in the presence of ***Trimethylsilyl Trifluoromethanesulfonate*** and ***Diisopropylethylamine*** with high γ-selectivity. The reaction proceeds in good yields, although the scope is limited to the parent allyl system and to 2-alkylallyl aryl sulfoxides (eq 10).[26a]

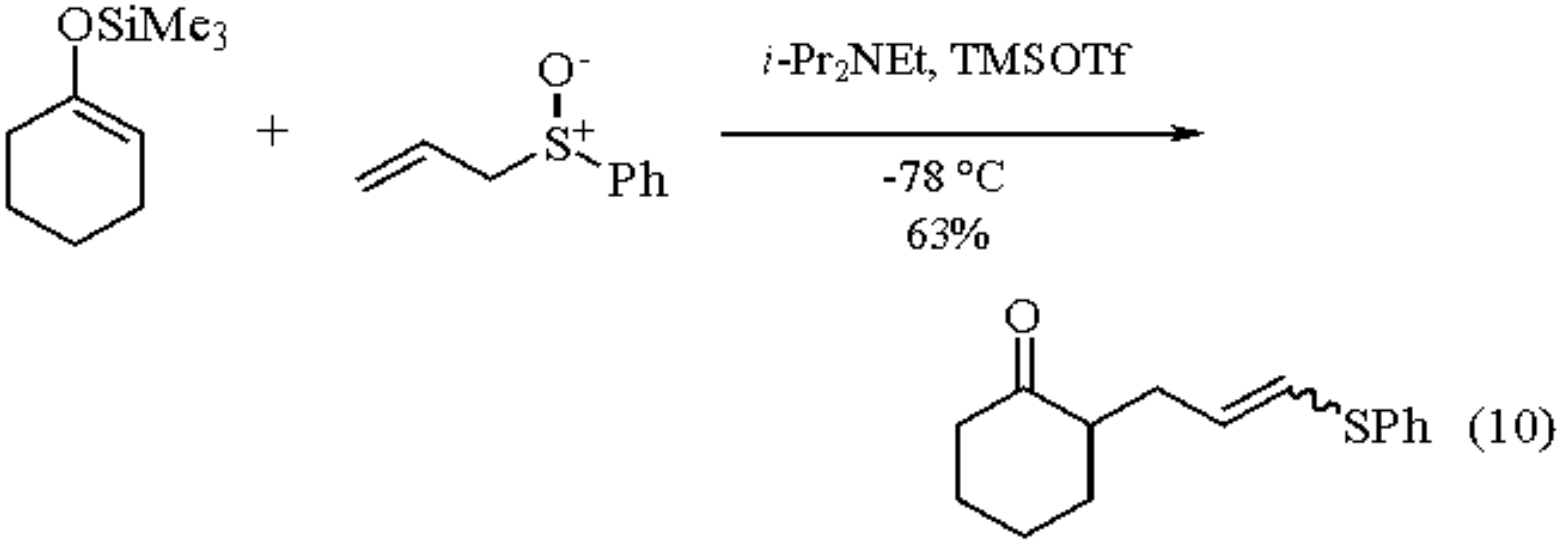

(10)

In the absence of the silyl enol ether the vinylthionium ion is converted by the tertiary amine in high yield into a quaternary ammonium salt which can be alkylated with dimethyl sodiomalonate in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** in 60% yield.[26b] The use of *N*,*N*-diethyl(trimethylsilyl)amine as the tertiary amine to generate the quaternary salt followed by silyl group removal with ***Trimethylsilyl Trifluoromethanesulfonate*** affords the neutral amine adduct, a masked Mannich derivative, in 90% yield (eq 11).[26b] (α-Trimethylsilyloxy)allyl phenyl sulfide is generated in 53% yield from allyl phenyl sulfoxide and trimethylsilyl ketene acetals in the presence of ***Zinc Iodide*** in acetonitrile via the silyl-Pummerer reaction.[27] Transfer of the silyl group from the ketene acetal to the sulfoxide oxygen leads to a sulfonium intermediate which then traps the liberated silyloxide (eq 12).

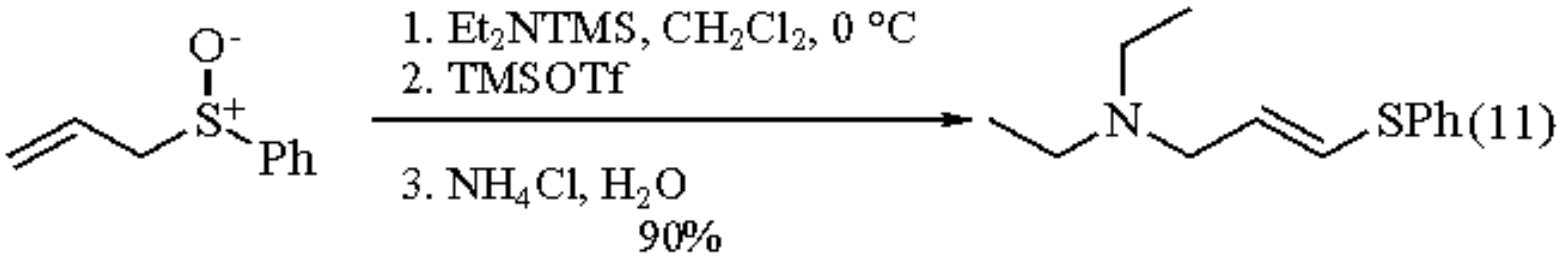

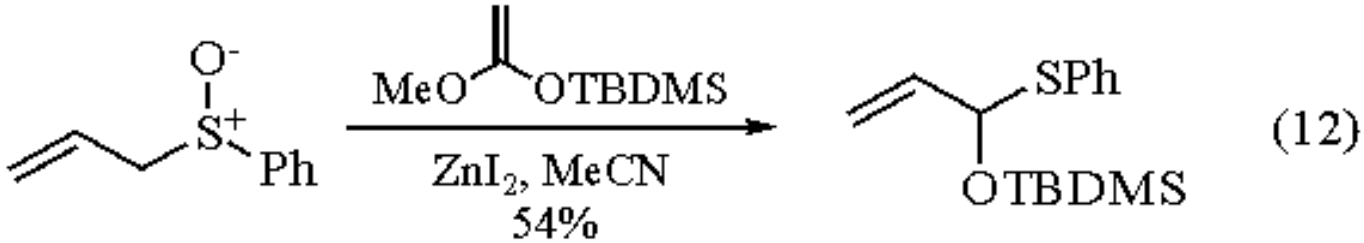

Nucleophilic Substitution of the Sulfinyl Group.

Allylic substitution of the sulfinyl and the sulfonyl (see ***Allyl Phenyl Sulfone***) group in 1-alkyl-2-methylallylic sulfoxides and sulfones by lithium dialkylcuprates proceeds with high regio- and stereoselectivity to give trisubstituted alkenes.[28]

Related Reagents.

Allyldiphenylphosphine Oxide; ***Allyl Phenyl Selenide***; ***Allyl Phenyl Sulfide***.

---

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Allyltitanium Triphenoxide[1]

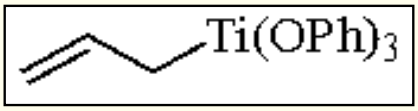

[130004-39-6] · $C_{21}H_{20}O_3Ti$ · Allyltitanium Triphenoxide · (MW 368.27)

(reagent for the regioselective allylation of epoxides at the most substituted carbon;[2] the crotyl homolog reacts stereoselectively with aldehydes[3] and ketones[4])

Solubility: reactions are normally performed in THF.

Form Supplied in: not available commercially.

Preparative Methods: the reagent is prepared in situ by reacting the corresponding Grignard derivative in THF at -78 °C -> -30 °C with $ClTi(OPh)_3$.[3] The latter is prepared by refluxing ***Chlorotitanium Triisopropoxide*** and phenol in toluene, with the azeotropic removal of isopropanol. Reactions of the reagent with epoxides are normally performed at -78 °C, while reactions with aldehydes and ketones are started at -100 °C.

Organotitanium Reagents.

The conversion of allyl or crotyl organometallics to derivatives of the general type $RCH{=}CHCH_2TiX_3$ (X = OR´ or NR''_2) or the corresponding titanates $RCH{=}CHCH_2TiX_4MgCl$ (X = OR´ or NR''_2) often results in significant improvements in the chemo-, regio-, diastereo-, and enantioselectivity of these reagents.[1] The increased steric and electronic requirements of the titanated species lead to a synthetically useful modulation of the nucleophilicity, Lewis basicity, and Lewis acidity of these reagents. Also, in the case of crotylmetals, titanation often produces configurationally homogeneous systems, resulting in an enhanced diastereoselectivity during carbonyl additions.

Regioselective Allylation of Epoxides.

The reaction of unsymmetrical epoxides with carbon nucleophiles at their most substituted position is generally a difficult transformation. Normally these epoxides react with organocopper reagents and other similar nucleophiles in an S_N2 manner at their least substituted carbon. In the case of styrene oxides (eq 1), a variety of allyltitanium derivatives,[1d] including $CH_2{=}CHCH_2Ti(OPh)_3$,[2] favor allylation at the most substituted epoxide carbon, presumably via an S_N1-like pathway.

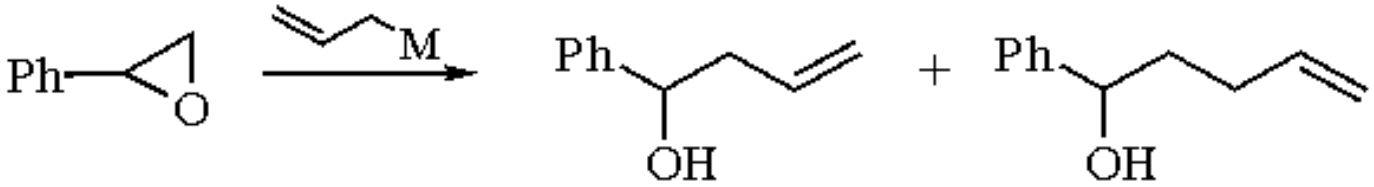

(1)

M =	MgCl	70:30
	$Ti(O\text{-}i\text{-}Pr)_4MgCl$	>99:<1
	$Ti(O\text{-}i\text{-}Pr)_3$	>99:<1
	$Ti(OPh)_3$	>99:<1

Similar reactivity and selectivity is usually not observed with alkyl-substituted epoxides. The use of $CH_2{=}CHCH_2Ti(O\text{-}i\text{-}Pr)_3$ in these cases gives substantial amounts of a hydride reduction product Meerwein-Ponndorf-Verley reduction. A good reagent for this purpose, however, is $CH_2{=}CHCH_2Ti(OPh)_3$, which gives, in high yields, almost exclusively the products of allylation at the most substituted epoxide carbon (eq 2).[2]

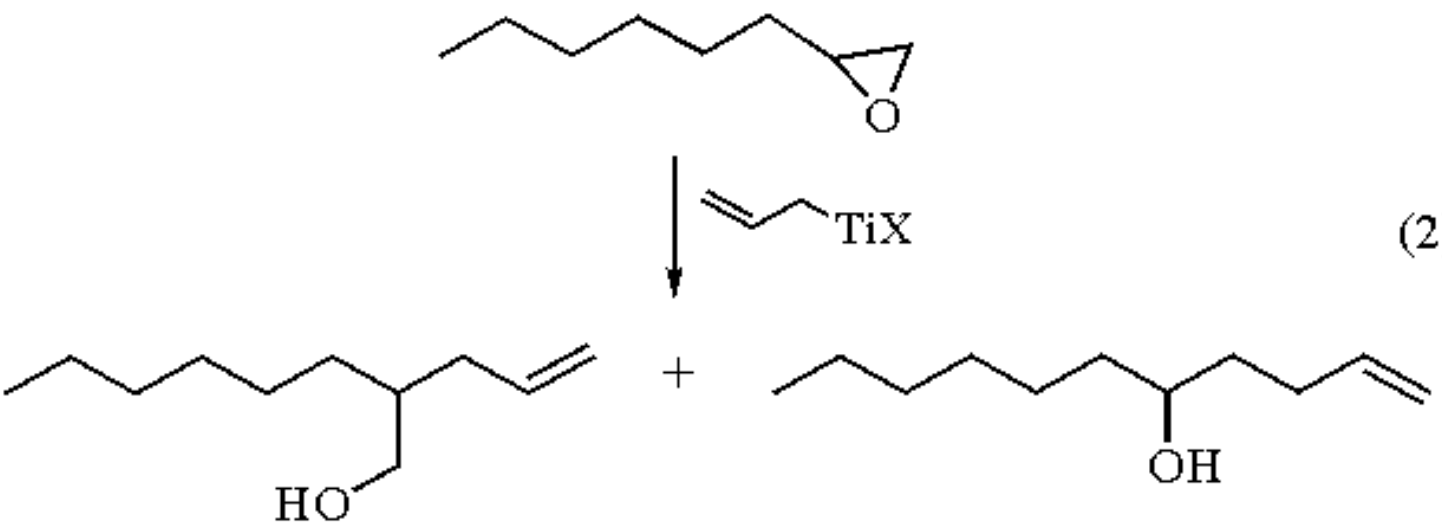

(2)

X = O-*i*-Pr, 1:1
X = OPh, 22:1

When the most substituted carbon is chiral, the reaction proceeds with a high degree of inversion of configuration (eq 3).[2]

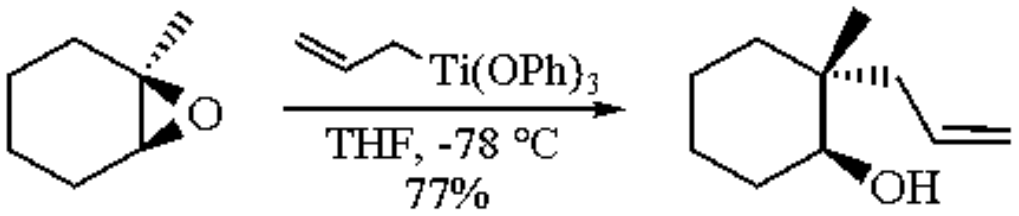

(3)

trans:*cis* = 10:1

Stereoselective Addition to Aldehydes and Ketones.

Although allyltitanium reagents of the general type $CH_2{=}CHCH_2TiX_3$ (X = OR´ or NR´´$_2$) add to carbonyl compounds in a highly chemoselective manner,[1] the use of the triphenoxy derivative (X = OPh) does not offer any significant advantages over other more readily available variants (e.g. X = O-*i*-Pr). In the case of crotyltitanium species, however, the triphenoxytitanium derivative is one of the most diastereoselective (eq 4).[3]

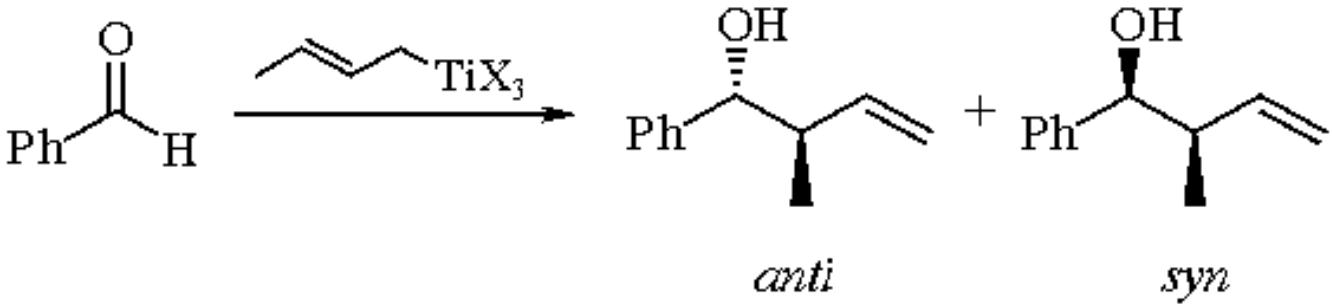

(4)

X =		
	OPh	85:15
	O-*i*-Pr	80:20
	NEt_2	70:30
	NMe_2	52:48

More bulky phenolic substituents do not result in improved diastereoselectivity (eq 5).[3]

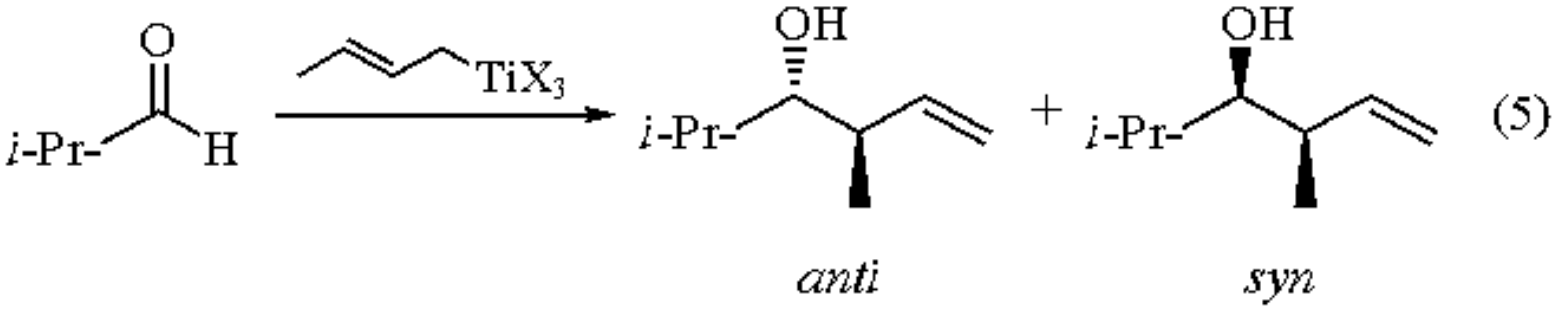

X =	OBu	78:22
	O-*i*-Pr	84:16
	NEt	85:15

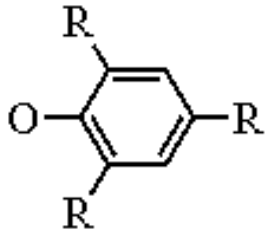

R = *t*-Bu	90:10
R = Me	92: 8
R = H	96: 4

A similar reaction takes place with ketones, although the diastereoselectivity depends on the relative size of the large (R_L) and small (R_S) substituents (eq 6).[4]

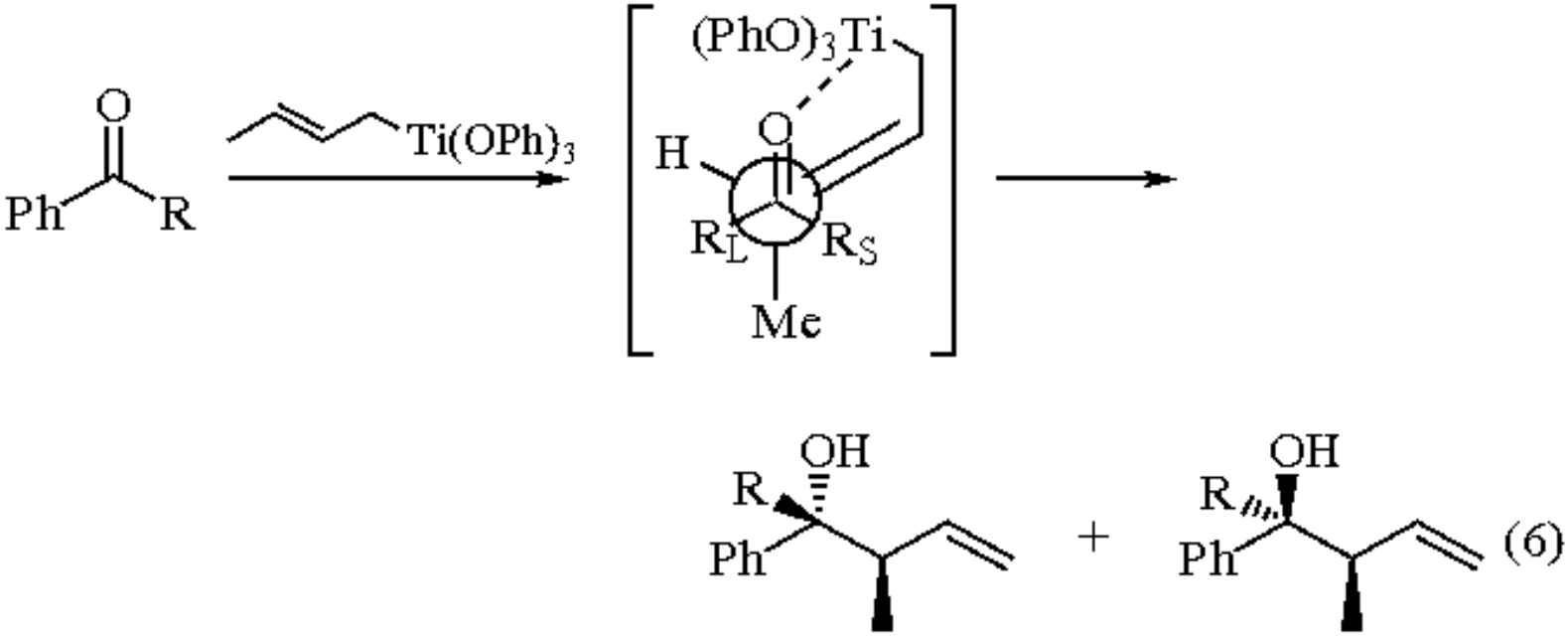

R =		
	Me	90:10
	Et	74:26
	i-Pr	55:45
	t-Bu	3:97

---

1. (a) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Hoffmann, R. W. *AG(E)* **1982**, *21*, 555. (c) Weidmann, B.; Seebach, D. *AG(E)* **1983**, *22*, 31. (d) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986. (e) Roush, W. R. *COS* **1991**, *2*, 1. (f) Ferreri, C.; Palumbo, G.; Caputo, R. *COS* **1991**, *1*, 139. (g) Yamamoto, Y.; Asao, N. *CRV* **1993**, *93*, 2207.
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Nicos A. Petasis

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Allyltributylstannane[1]

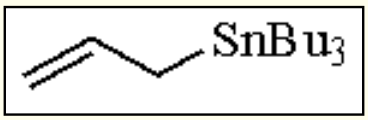

[24850-33-7] · $C_{15}H_{32}Sn$ · Allyltributylstannane · (MW 331.11)

(allylating reagent for many compounds, including alkyl halides, carbonyl compounds, imines, acetals, thioacetals, and sulfoximides)

Alternate Name: allyltributyltin.

Physical Data: bp 88-92 °C/0.2 mmHg; fp > 110 °C; *d* 1.068 g cm^{-3}.

Solubility: sol dichloromethane, diethyl ether, THF, toluene, benzene.

Form Supplied in: colorless liquid; widely available.

Purification: distillation.

Handling, Storage, and Precautions: all organotin compounds are highly toxic.

Allylstannanes are widely used as allyl anion equivalents.[1] They are less reactive than the corresponding magnesium or lithium reagents and, hence, can be classified as storable organometallic reagents.[13b] This reduced activity increases the ease of handling in the laboratory; however, higher reaction temperatures or activation with Lewis acids are necessary. The relative reactivities of allyltriphenylsilane, -germane, and -stannane with diaryl carbenium ions are 1, 5.6, and 1600, respectively.[2] Allyltributylstannane is more reactive than ***Allyltriphenylstannane*** by three orders of magnitude. Allyl- and crotyltrialkyltin reagents undergo transmetalation reactions with strong Lewis acids through an S_E2' pathway.[3] Competing transmetalation processes can affect the mechanistic pathway and product distribution.[4] Radical processes can also be exploited in allylation reactions employing stannanes.[5] Because of the high toxicity of organotin reagents, allyltributyltin is more widely used than the more volatile allyltrimethyltin.

Additions to Aldehydes.

Allyltrialkyltin reagents, such as allyltributyltin (**1**), react with carbonyl compounds[1] to form homoallylic alcohols under photolytic,[6] thermal,[7] high pressure,[8] or, more commonly, Lewis acidic conditions.[9] The order of reactivity is aldehydes > methyl ketones > internal ketones. A number of stereochemical issues are important when substituted allylic stannanes are utilized (see ***Crotyltributylstannane*** for details).

Selective conversion of protected α-hydroxy aldehydes (**2**) to monoprotected derivatives of *syn*- or *anti*-1,2-diols by reaction with allyltrialkylstannanes is realized with judicious choice of Lewis acid and protecting group.[10] ***Magnesium Bromide***, ***Titanium(IV) Chloride***, and ***Zinc Iodide*** favor *syn* products (**3**), especially with the benzyloxy derivative (**2a**), while use of ***Boron Trifluoride Etherate*** favors the *anti* products (**4**), particularly with the *t*-butyldimethylsilyl ether (**2b**) (eq 1).

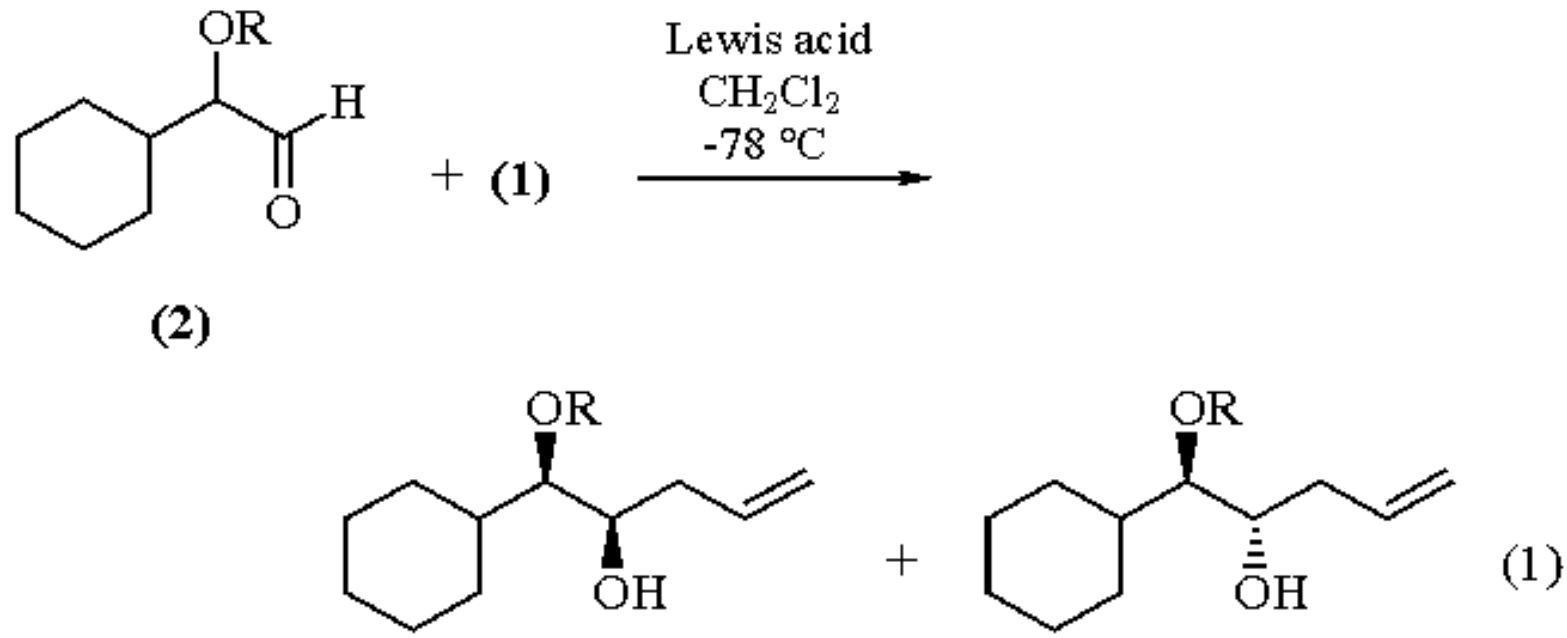

(2a) R = CH_2Ph	**(3a)**	$MgBr_2$	250 : 1	**(4a)**
		BF_3-OEt_2	39 : 61	
(2b) R = $SiMe_2$-*t*-Bu	**(3b)**	$MgBr_2$	21 : 79	**(4b)**
		BF_3-OEt_2	9 : 91	

The ***Tin(IV) Chloride*** promoted allylation of α-methylthio aldehydes with allyltriphenyltin is highly selective for *anti* products, while the selectivity from $BF_3.OEt_2$ mediation is variable.[11] A very mild promoter system, 5 M ***Lithium Perchlorate*** in diethyl ether, was used to allylate dialdose derivatives with high selectivity.[12] Acetals, ethers, and silyl ethers survive the allylation of aldehydes with this promoter.

β-Alkoxy aldehydes, with alkyl groups at C-2, readily form stable chelates with $TiCl_4$, $SnCl_4$, and $MgBr_2$ and consquently show high levels of *anti* selectivity in allylations with allyltributyltin.[13] High levels of diastereofacial selectivity in the Lewis acid mediated additions of allylstannanes to β-alkoxy aldehydes with substituents at C-3 are achieved when (a) the protecting group permits effective bidentate chelation between the aldehyde carbonyl and the ether oxygen and (b) the protecting group provides enough steric bulk to force C-3 substituents into an axial position in the six-membered chelate formed with the Lewis acid. $TiCl_4$ shows the highest *anti* selectivity when the protecting group is benzyl (R = *n*-hexyl; 96:1) and poor selectivity for methyl protection (R = *n*-hexyl; 3.8:1) (eq 2). $SnCl_4$ provides poor selectivities for all C-3 alkyl substituted β-alkoxy aldehydes. These results are consistent with predictions based upon ground state solution structures which show that the preferred conformation for $TiCl_4$ and

$MgBr_2$ chelates has the alkyl group in a pseudoaxial position when the protecting group is ethyl or benzyl. Chelation is not involved in the reactions of α-or β-siloxy aldehydes.[14] In $TiCl_4$ promoted allyltriphenylstannane additions to β-alkoxyaldehydes with a methyl group at C-3, benzyl protection provides superior *anti* selectivity (29:1) to (methylthio)methyl (2:1) and (benzyloxy)methyl (9:1) groups.[15]

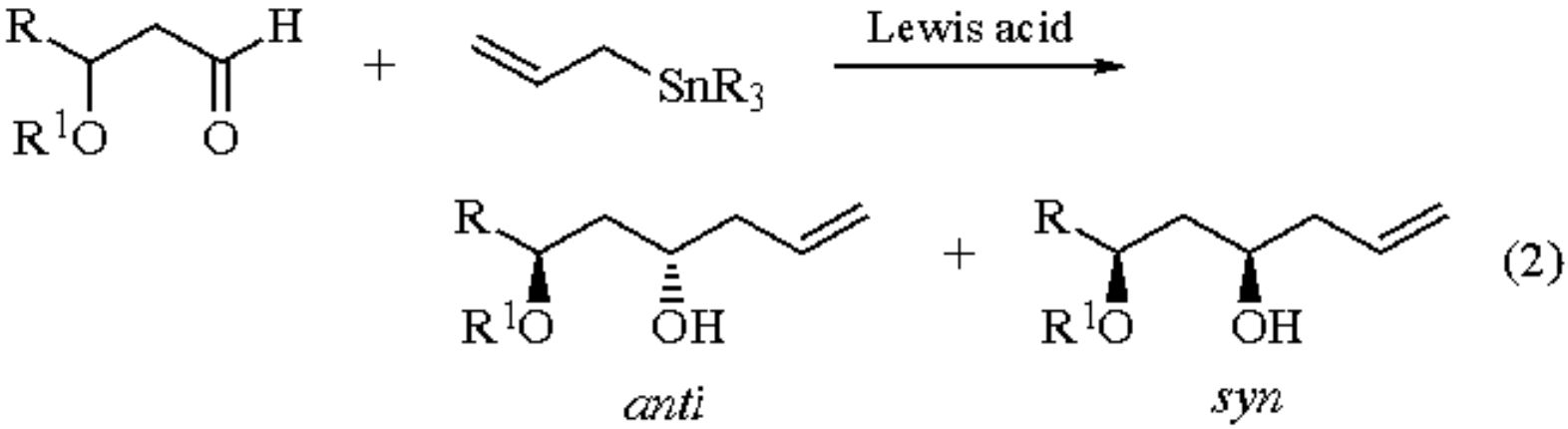

Allylation of Ketones.

While irradiation of mixtures of aromatic ketones and allyltrialkylstannanes usually affords coupling products which are allylated at the carbonyl carbon,[6a,b] selective allylation at the α-carbon of aromatic α,β-epoxy ketones is observed (eq 3).[16] Yields of the α-allyl-β-hydroxy aryl ketones are highest when the *para* substituent is an electron-withdrawing group (CN) and lowest when it is an electron donor (MeO). Quinones undergo 1,4-monoallylation with allyltributyltin in the presence of BF_3 etherate (eq 4). However, 4-substituted 1,2-naphthoquinones and sterically hindered 3,5-di-*t*-butyl-*o*-quinones undergo 1,2-addition (eq 5).[17]

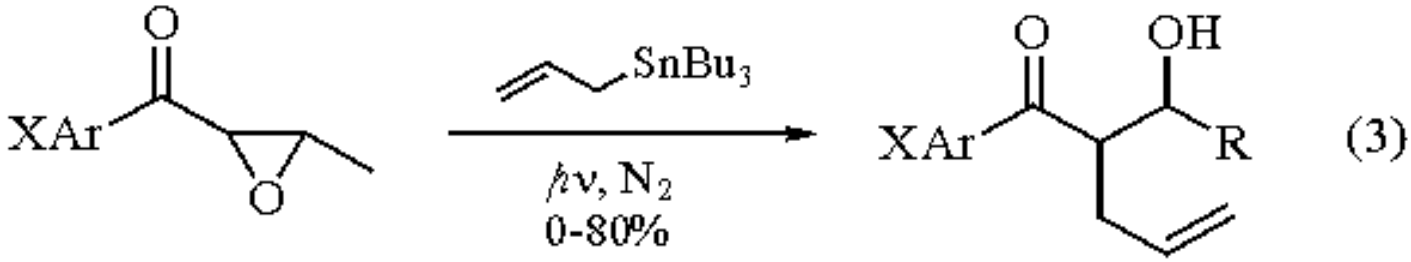

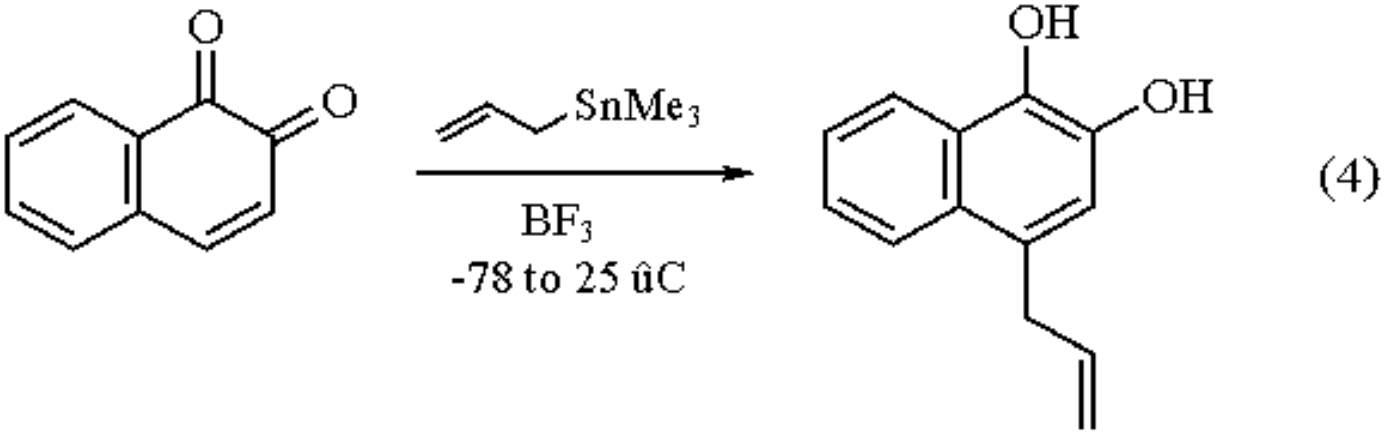

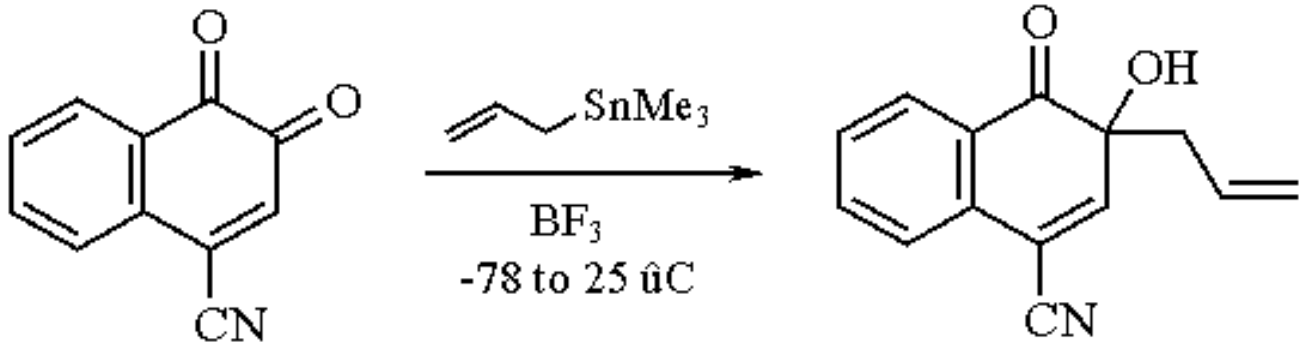

(5)

Allyltributylstannane in the presence of BF_3 etherate is a more efficient α-allylating reagent for quinones than the allylsilane-$TiCl_4$ reagent system. Eleutherin and isoleutherin were synthesized, in part, by this method.[18]

Unsymmetrical aryl alkyl α-diketones are regioselectively allylated by allylstannanes at the benzylic carbon under photolytic conditions and allylated at the acyl carbon in the presence of BF_3 etherate (eq 6).[19] Stannylated cyclopentanes are formed from the reaction of allyltributylstannane with aluminum trichloride-activated α,-β-unsatured acyliron complexes.[20] Stereochemistry about the alkene is preserved in this reaction.

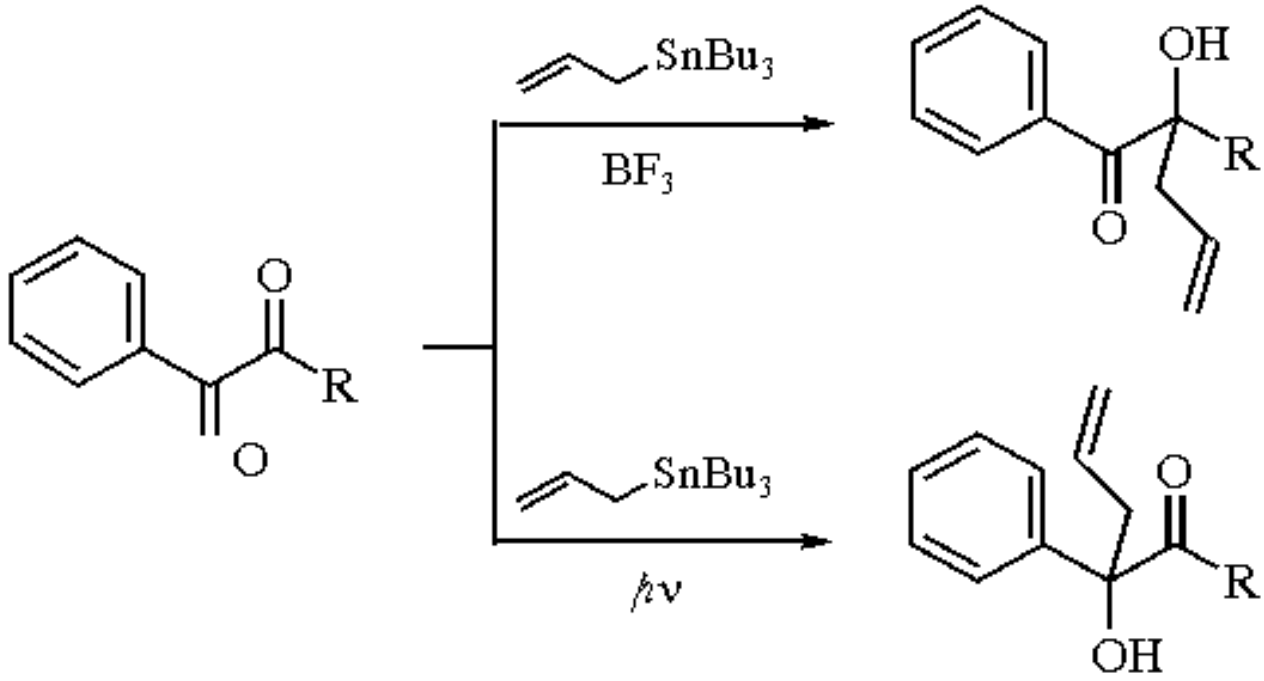

(6)

Allylation of Organohalides.

Alkyl halides[21] and selenides[22] are allylated by allylstannes under thermal (with ***Azobisisobutyronitrile***), photochemical (with a tungsten lamp), or palladium-catalyzed conditions in high yield (eqs 7 and 8). Palladium catalyzes many reactions of allyltin reagents with various electrophiles, including allyl halides, aryl iodides and bromides, activated aryl chlorides, acid chlorides, vinyl halides, vinyl triflates, α-halo ketones and esters, and α-halo lactones.[23]

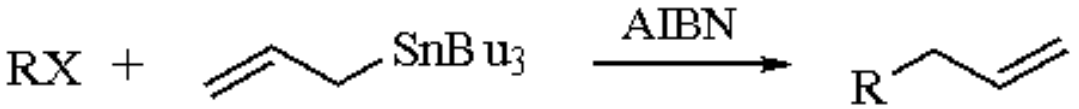

(7)

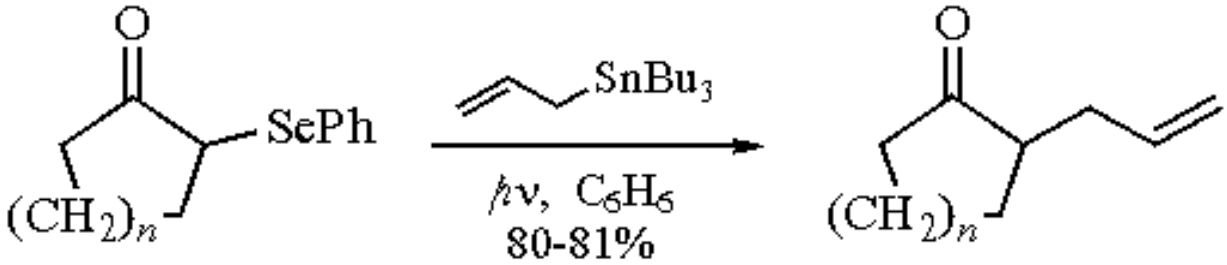

(8)

Aliphatic, aromatic, and heterocyclic acid chlorides react with allyltrialkylstannanes to give ketones in high yield (eq 9). Functional groups such as nitro, nitrile, haloaryl, methoxy, ester, and aldehyde are tolerated. An alternative palladium-catalyzed ketone synthesis involves the coupling of primary, secondary, or tertiary halides with carbon monoxide and allyltin (eq 10). Allyltributyltin adds to α-alkoxy-β-siloxy acylsilanes, with high *syn* selectivity (*syn*:*anti* = 91:9) in the presence of ***Zinc Chloride***.[24] A monoprotected *syn*-1,2,3 triol results from protiodesilylation. The palladium-catalyzed reaction of α-halo ketones with acetonyl- and allylstannanes produces oxiranes, oxetanes, and tetrahydrofurans in good yield.[25] Most allylic acetates do not react, although cinnamyl acetate and allyl acetate are exceptions.

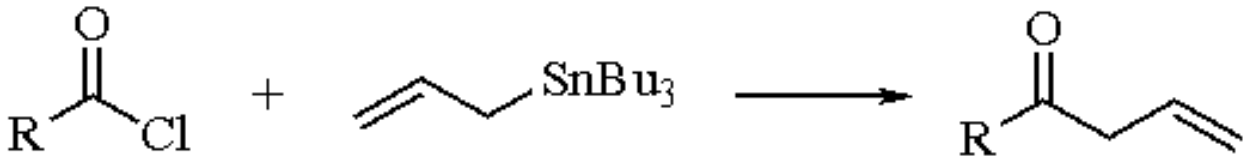

(9)

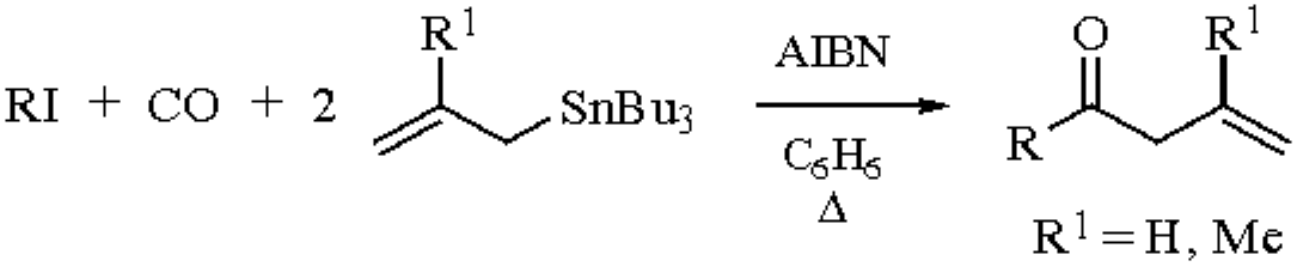

(10)

Stille Reaction.

The reaction between phenyl triflates (a vinyl triflate) and allylic stannanes is useful for the synthesis of substituted aromatic compounds (eq 11).[26] The reaction works well with most highly substituted phenols except for hexasubstituted ones.[27] The reaction has been extended to the less expensive aryl fluorosulfonates[28] and aryl arenesulfonates.[29] These reactions proceed in good yield unless the aryl ring contains electron-donating substituents.

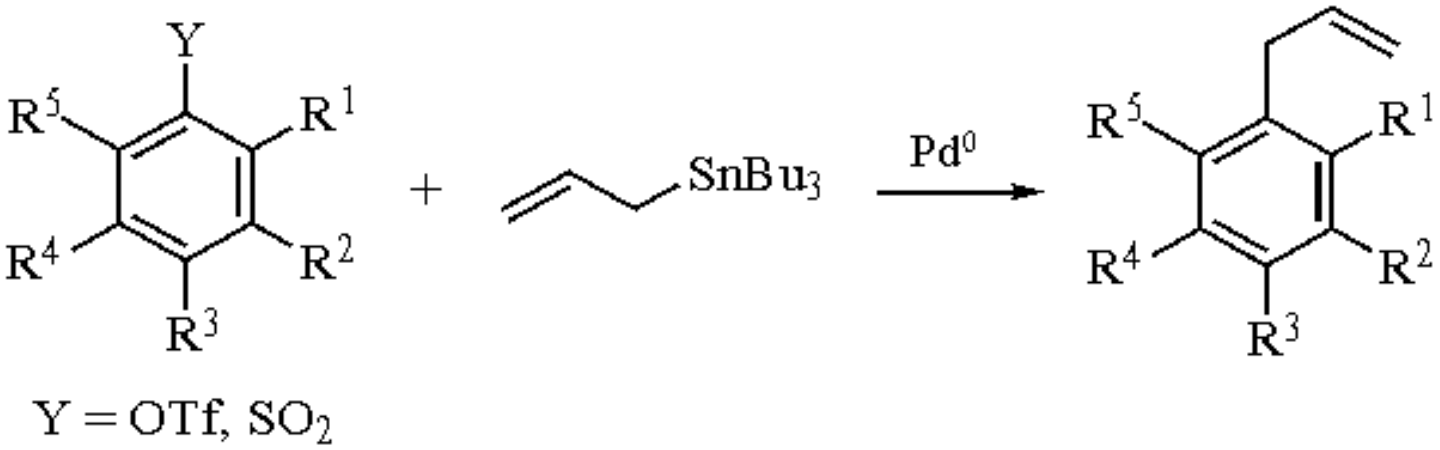

(11)

Allylation of Acetals.

In the presence of a Lewis acid, 1,3-dioxolanes can be allylated with allyltributylstannanes or allylsilanes.[30] The Lewis acid promoted cleavage of chiral acetals with allylstannes affords chiral ethers with reported diastereoselectivites of > 500:1 (eq 12).[31] Allylation of monothioacetals and dithioacetals occurs in a highly *syn* selective fashion to form homoallyl sulfides in good yield, particularly with $GaCl_3$ as the Lewis acid promoter.[32]

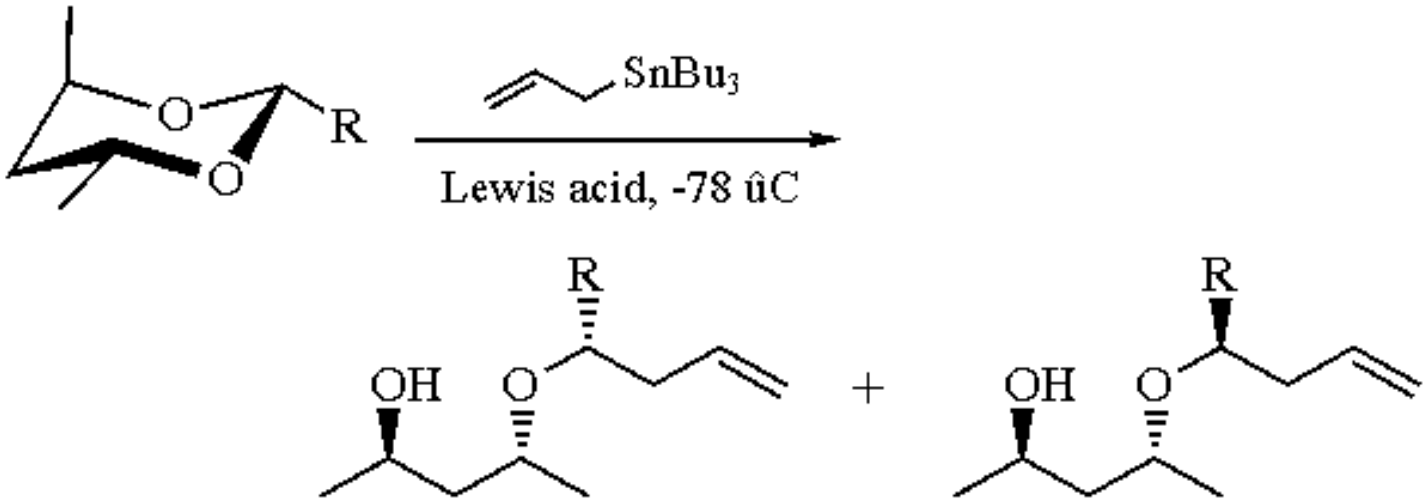

(12)

Allylation of Imines.

Aldimines are converted to homoallylamines by allyltributyltin with Lewis acid promotion in moderate to high yield.[33] Likewise, β-methyl homoallylamines (predominantly *syn*) result from the reaction of ***Crotyltributylstannane*** with the $TiCl_4$ chelate of aldimines. In the $TiCl_4$-mediated allylstanne addition to (**5**), the Cram product is favored (92:8) (eq 13).[34]

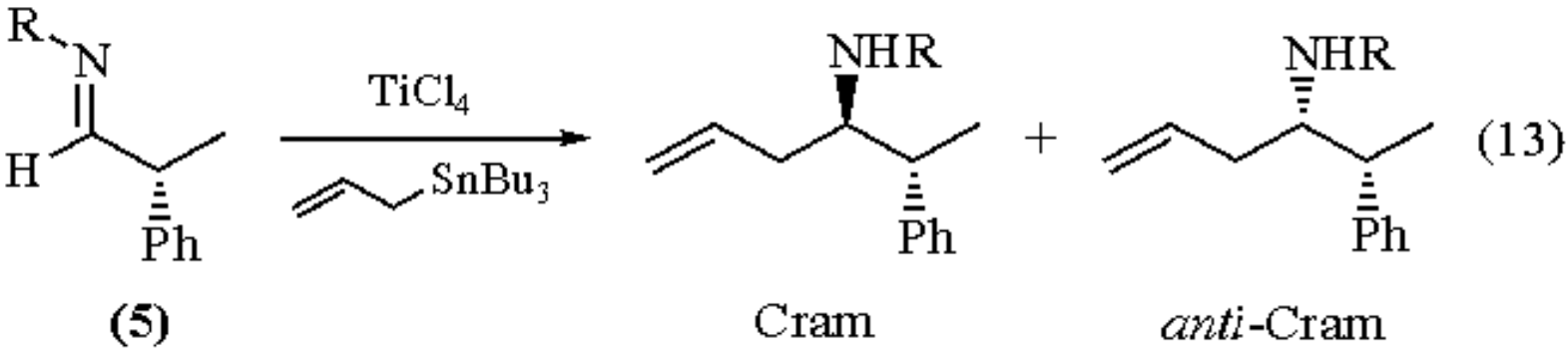

Allyltributyltin is also useful for α-allylations of *N*-acyl heterocycles, including pyridinium salts.[35] Isoquinolines (or dihydroisoquinolines) can be simultaneously acylated and allylated by the addition of α,β,γ,δ-unsaturated acyl chloride and allyltributyltin. The resulting adduct undergoes a Diels-Alder cyclization yielding an isoquinoline alkaloid precursor (eq 14).[36] Acylation and allylation of imidazoles is a particularly useful route to highly substituted 2-allylimidazolines (eq 15).[37]

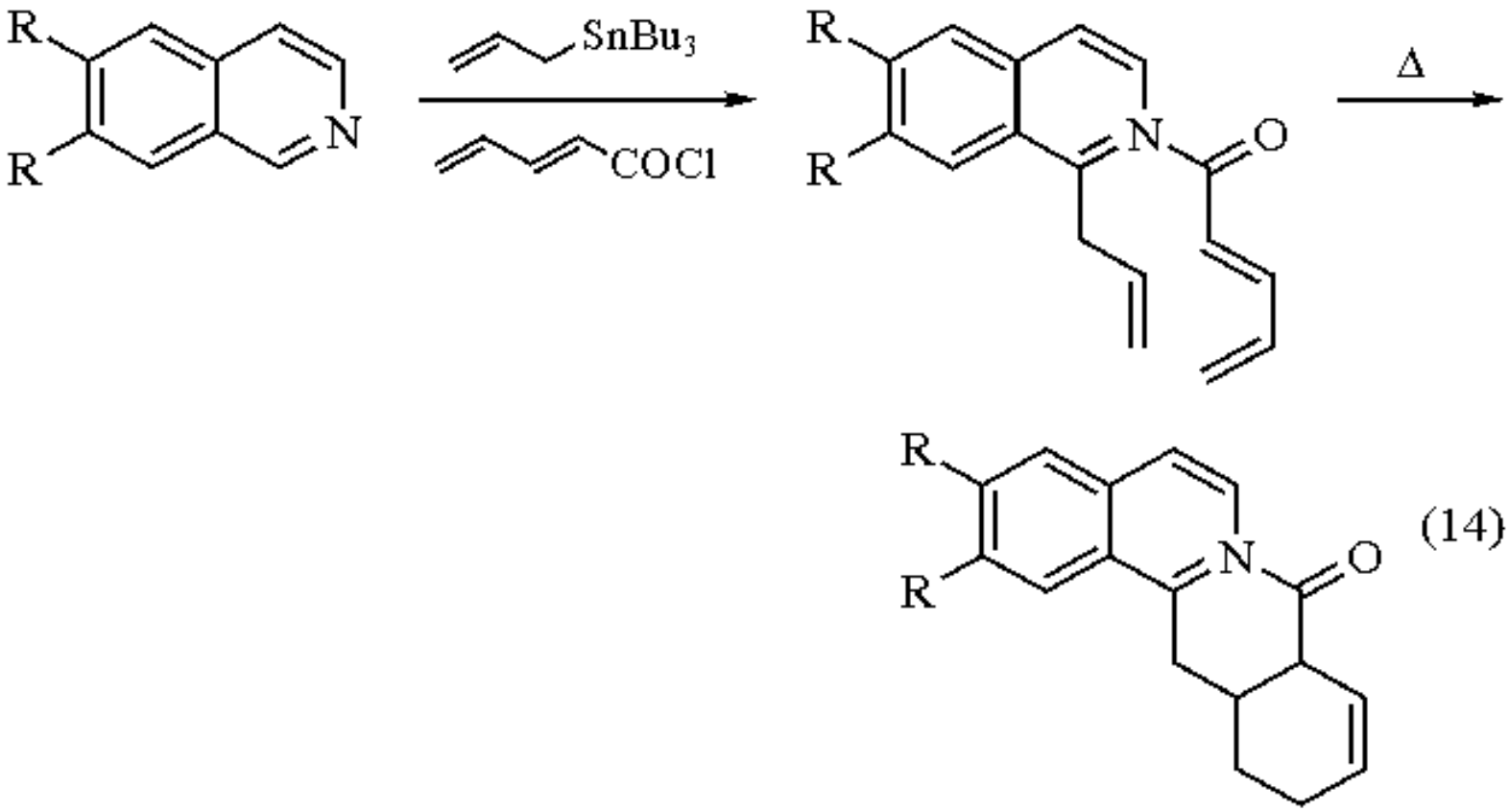

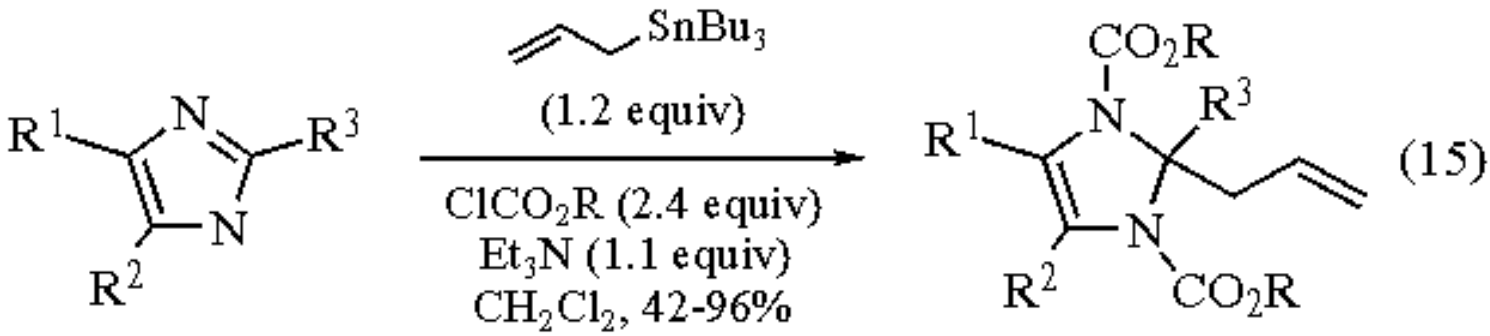

Acylimininium ions, formed by the reaction of α-alkoxy carbamates with Lewis acids, undergo allyl transfer from allylstannanes or silanes (eq 16).[38]

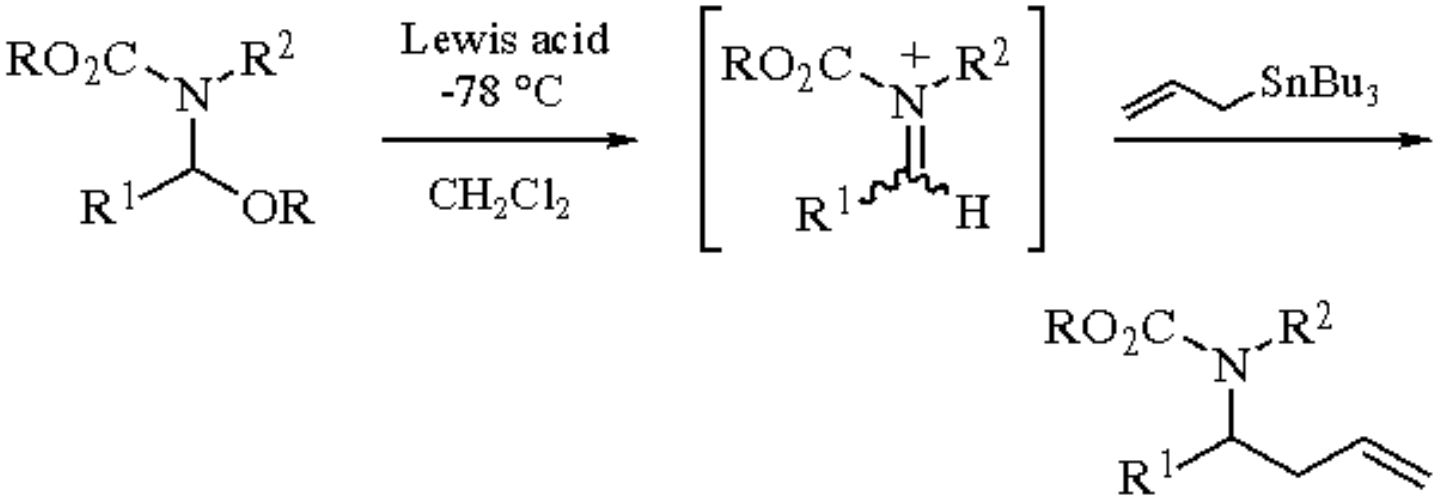

(16)

Allylation of Sulfoximidoyl Chlorides.

A variety of *S*-allylsulfoximines can be synthesized in high yield by the allylation of sulfoximidoyl chlorides (eq 17).[39] Thiocarbonates are also allylated under photolytic conditions.[40]

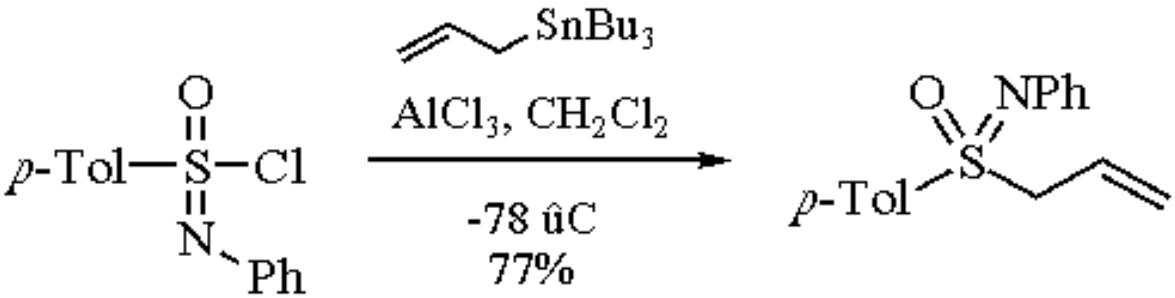

(17)

Radical Allylations.

In addition to ionic pathways, radical processes can also be employed in allylations using stannanes.[5,21] The 1,2-asymmetric induction in radical allylations of α-alkoxycarbonyl radicals has been investigated. The observed selectivities, ranging from 1:1 to 99:1, are consistent with transition-state models which incorporate favorable stereoelectronic effects and the minimization of $A^{1,2}$, $A^{1,3}$, and torsional strain.[41] The camphorsultam derivative (**6**) undergoes thermal allylation (10% AIBN, 80 °C, benzene) with stannanes to give the allylated products in excellent yield with diastereoselectivities of 12:1 (eq 18).[42] Allyl transfer to quinones and α,β-epoxy ketones by single electron transfer pathways has also been investigated.[43]

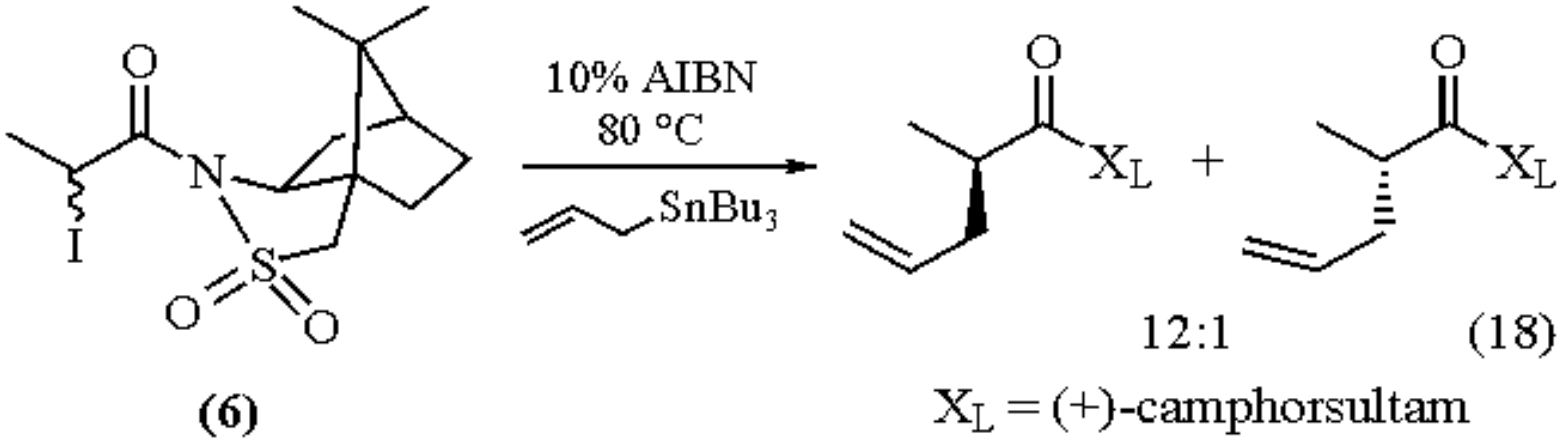

Related Reagents.

Allyltriphenylstannane; ***Crotyltributylstannane***.

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Allyl Trichloroacetimidate[1]

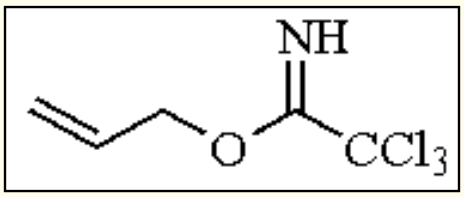

[51479-73-3] · $C_5H_6Cl_3NO$ · Allyl Trichloroacetimidate · (MW 202.47)

(delivers allyl group under mild conditions;[2] used in the preparation of N-containing intermediates[1])

Physical Data: bp 74 °C/11 mmHg.

Solubility: sol hexane, ether, dichloromethane.

Preparative Methods: typical procedure:[2] ***Sodium Hydride*** (0.5 g, 21 mmol) is slurried in anhydrous ether (20 mL) under a nitrogen blanket. Allyl alcohol (210 mmol) is introduced in ether (30 mL) dropwise with stirring to the slurry. After 20 min, the homogeneous solution is cooled to 0 °C and ***Trichloroacetonitrile*** (20 mL, 200 mmol) is added over 15 min. The mixture is allowed to warm to 20 °C over 60 min and then concentrated to a syrup. Pentane (20 mL) containing methanol (0.8 mL, 21 mmol) is added followed by vigorous shaking, filtration, and concentration of the filtrate and pentane washings (2 × 20 mL). The product imidate is obtained as a clear liquid (90-97%). No further purification is required. Alternatively, the imidate can be prepared by using sodium methoxide as a catalyst instead of sodium hydride. Other procedures for the preparation of allyl trichloroacetimidate have been reported.[3,4]

Handling, Storage, and Precautions: allyl trichloroacetimidate can be stored in solutions of hexane for up to 2 months at 0 °C. Preparation of allyl trichloroacetimidate should be performed in a well ventilated hood to avoid exposure to trichloroacetonitrile vapors.

O-Allylation and Protecting Group Delivery.

Protecting groups have become an important part of natural and unnatural product chemistry. In oligosaccharide synthesis, they are vital in obtaining the desired compounds because of the various sites at which reaction can occur if hydroxyl groups, for example, are left unprotected. Allyl groups are one of the many substituents used as a protecting group. This group can be delivered to a free hydroxyl group via a trichloroacetimidate derivative. More importantly, the use of allyl trichloroacetimidate allows the protection of an alcohol to take place in the presence of an ester. This is due, in part, to the fact that this reagent is applied under mildly acidic conditions. For example, a rhamnoside is dissolved in dichloromethane and to it is added allyl trichloroacetimidate in cyclohexane followed by a catalytic amount of triflic acid. After 18 h at 20 °C the allylated product is isolated after neutralization with $NaHCO_3$ and

chromatography (eq 1).[2,5]

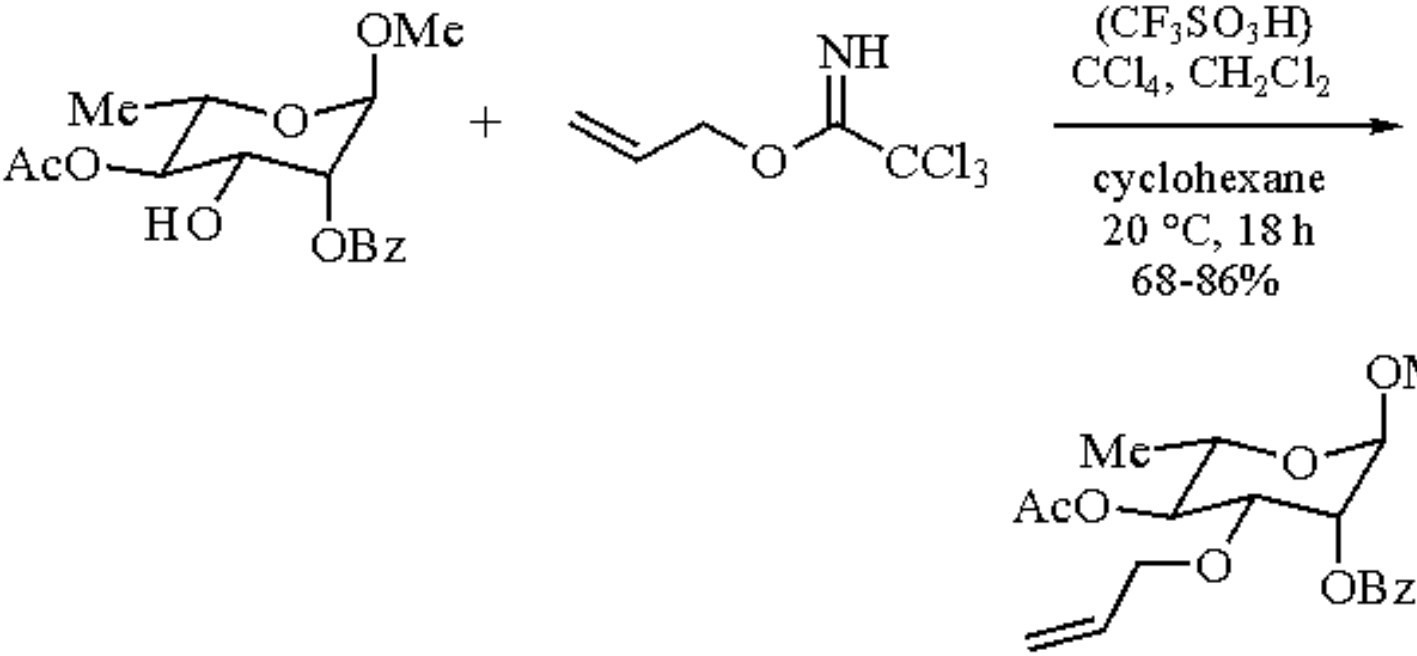

(1)

Substituted tetrahydrofurans have been prepared by using allyl trichloroacetimidate to generate allyl ether intermediates. For example, the hydroxy ester prepared from ***Methyl Bromoacetate*** and isobutyraldehyde reacts with allyl trichloroacetimidate and a catalytic amount of ***Trifluoromethanesulfonic Acid*** to give the allylic ether ester in 80% yield (eq 2).[6] The resulting tetrahydrofuran-3-one is prepared in four steps with high stereoselection, which is attributed to the use of ***Copper(II) Acetylacetonate*** as the cyclization catalyst.

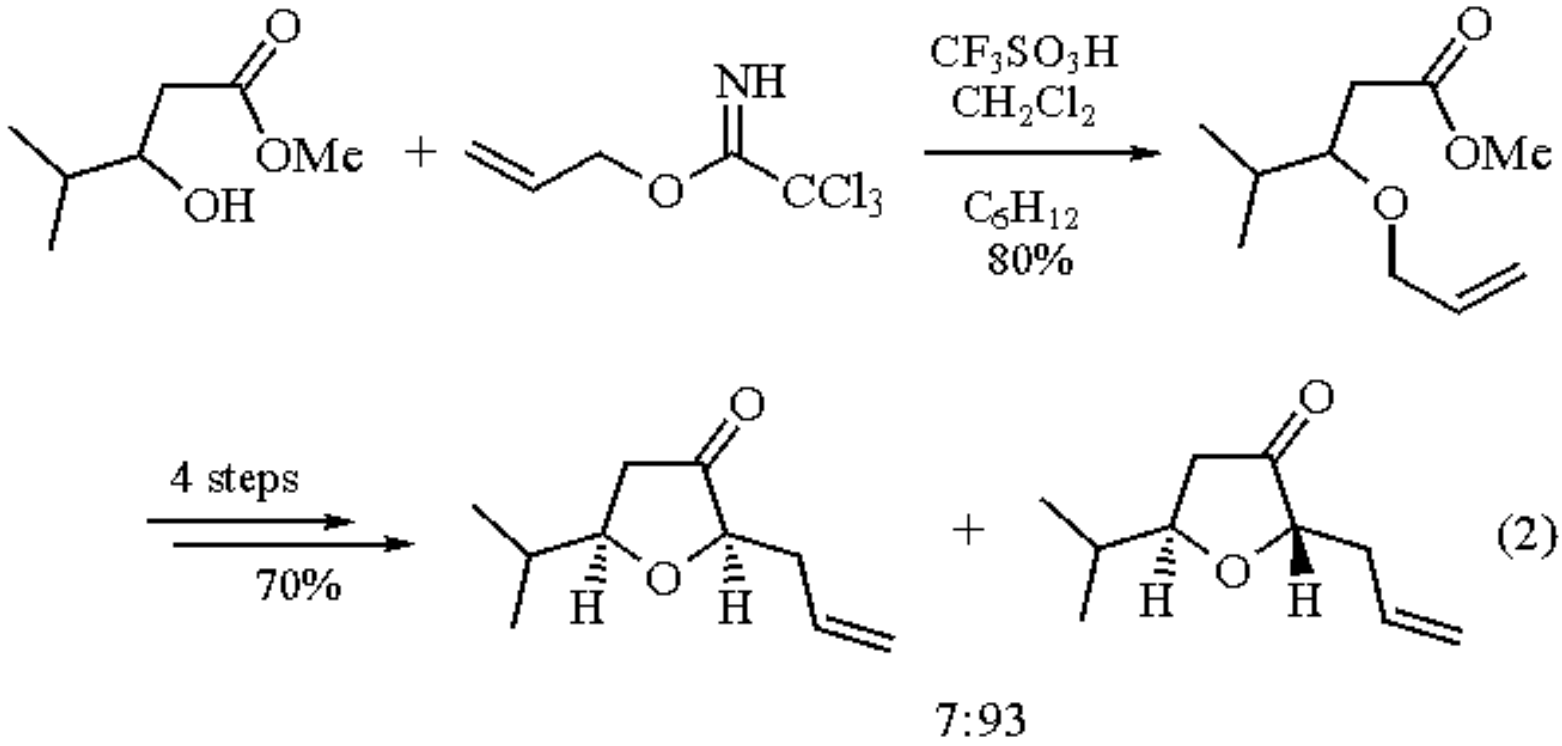

(2)

7:93

α-Amino acids can be prepared from allylic alcohols using allylic trichloroacetimidates. Thermal 1,3-transposition of the imidate group of allyl trichloroacetimidate is accomplished in refluxing xylene. Oxidation and acidic hydrolysis

afford the corresponding α-amino acid (eq 3).[7] Other acids prepared by this methodology include imidates derived from benzyl alcohol, 4,4-dimethyl-2-pentenol, and 2-butenol.

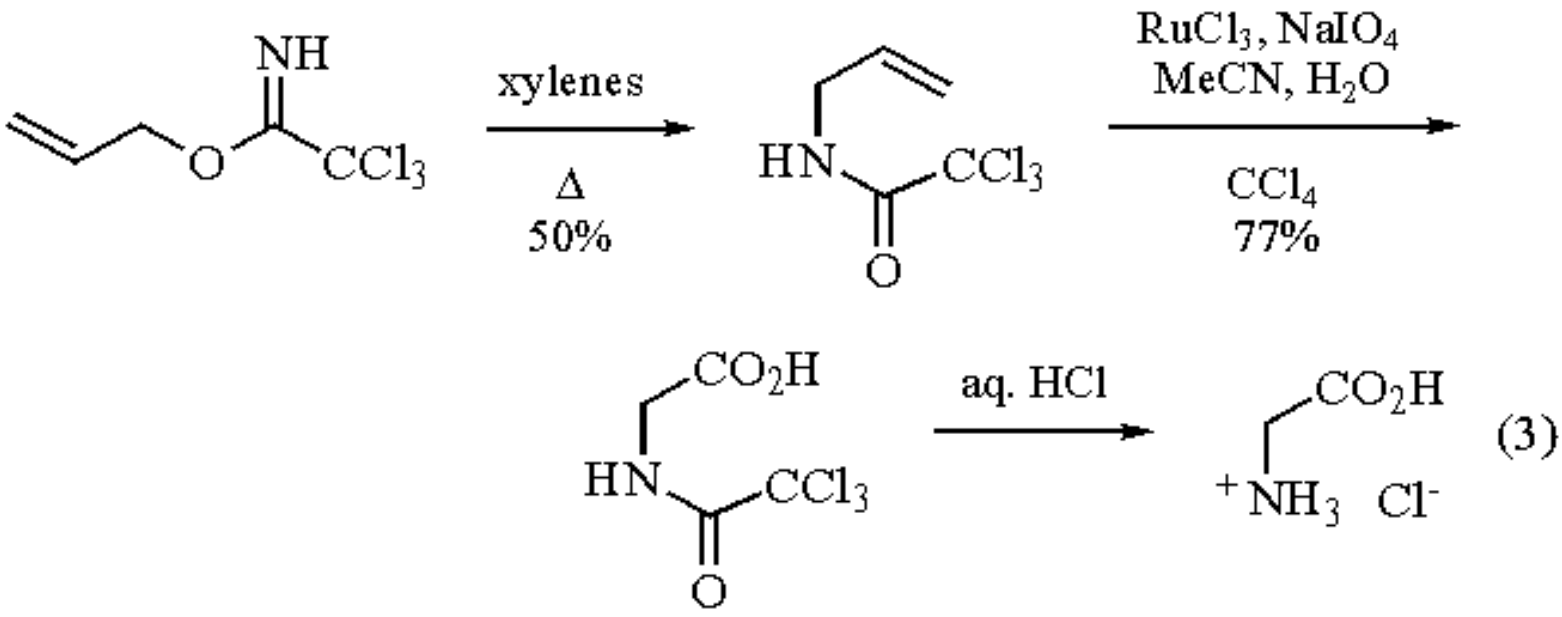

(3)

Allyl trichloroacetimidate has also been used to deliver an acetaldehyde equivalent in the preparation of β-hydroxy-α-amino acid derivatives. An *anti*-Phe-Leu mimetic was prepared in four steps from the *O*-allyl ether of *N*-phthaloyl-L-phenylalanyl-L-serine. This allyl ether was prepared from allyl trichloroacetimidate and the β-hydroxy-α-amino acid in 60-74% yield (eq 4).[8]

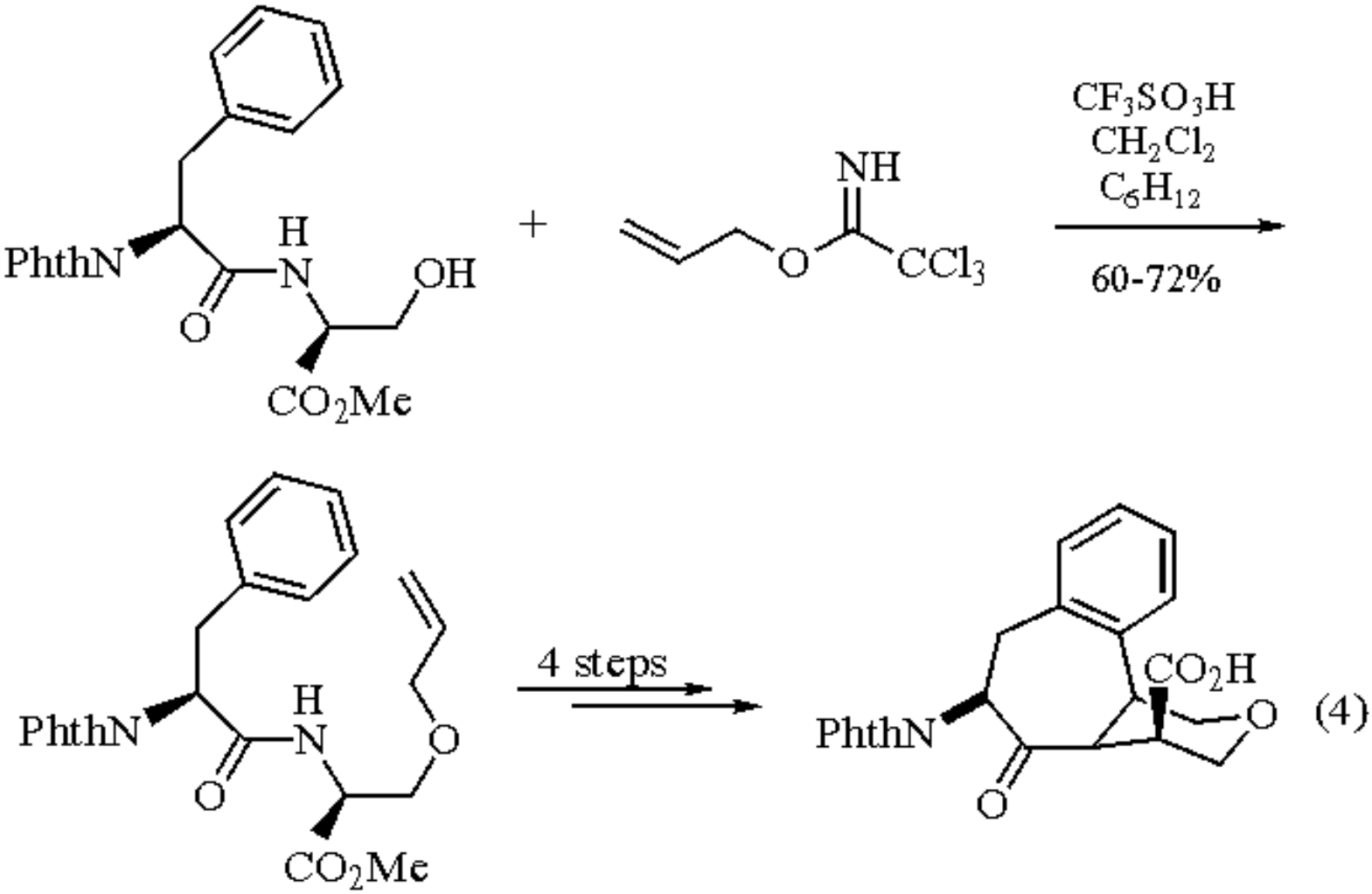

Benzyl groups can be used to protect alcohols in place of the allyl group with comparable yields. For example, under similar reaction conditions, an isopropylidene protected pyranoside was treated with benzyl trichloroacetimidate at room temperature to give a benzyl ether in 82% yield (eq 5).[1,9]

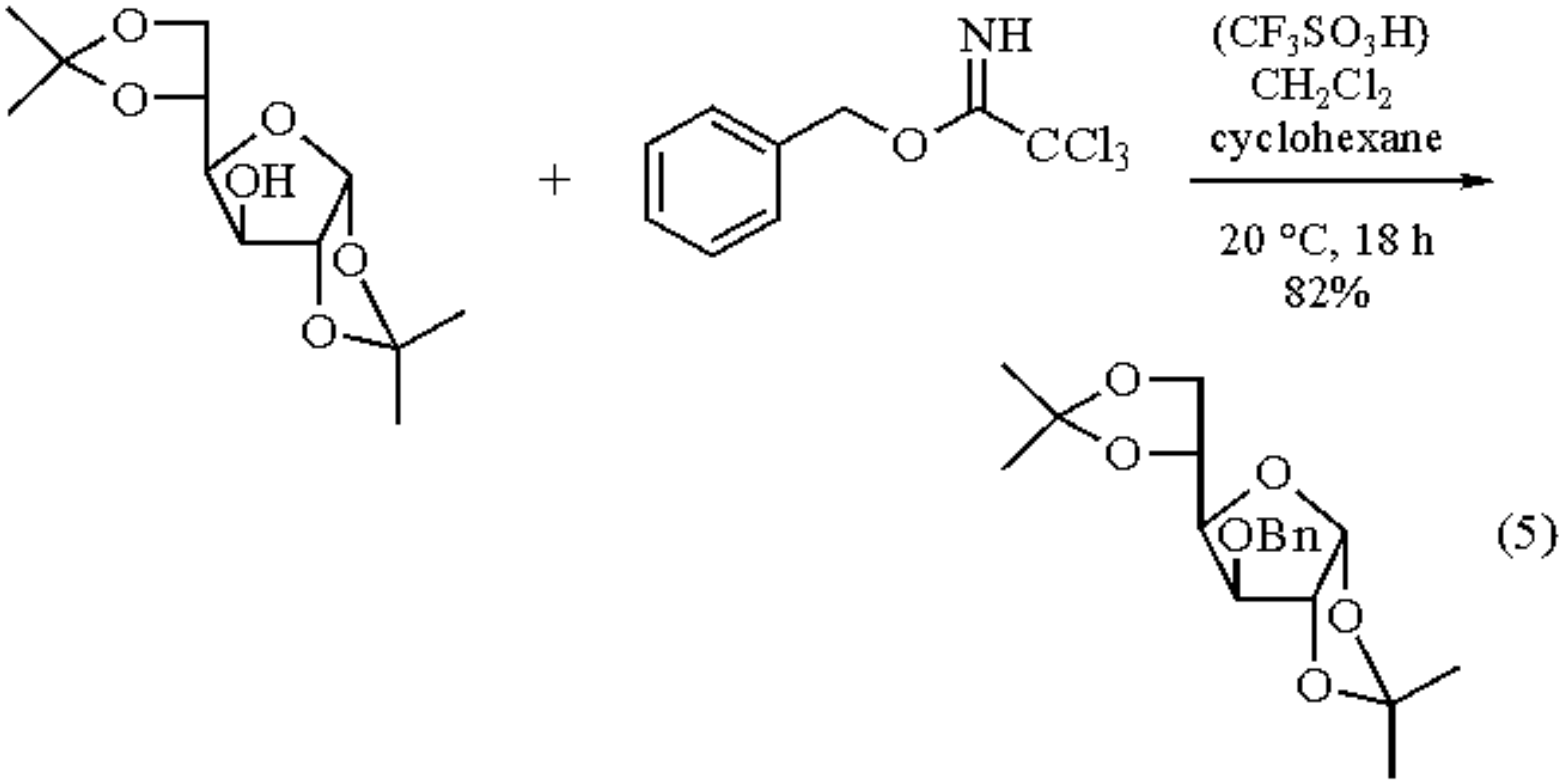

N-Containing Compounds from Imidates.

The synthetic procedure to make allyl trichloroacetimidate has been useful for other allylic imidate systems.[1] For example, geraniol trichloroimidate is prepared by reacting geraniol with sodium hydride in ether. The cooled (-10 °C) solution is treated with ***Trichloroacetonitrile*** followed by work-up with a methanolic-pentane solution to give the corresponding imidate. Amines and amides are prepared from these intermediates. Thermal rearrangement of the imidate, followed by hydrolysis, gives rise to 1,3-transposition of hydroxyl and amino groups. The amine is produced in 61% yield (eq 6).[4,10]

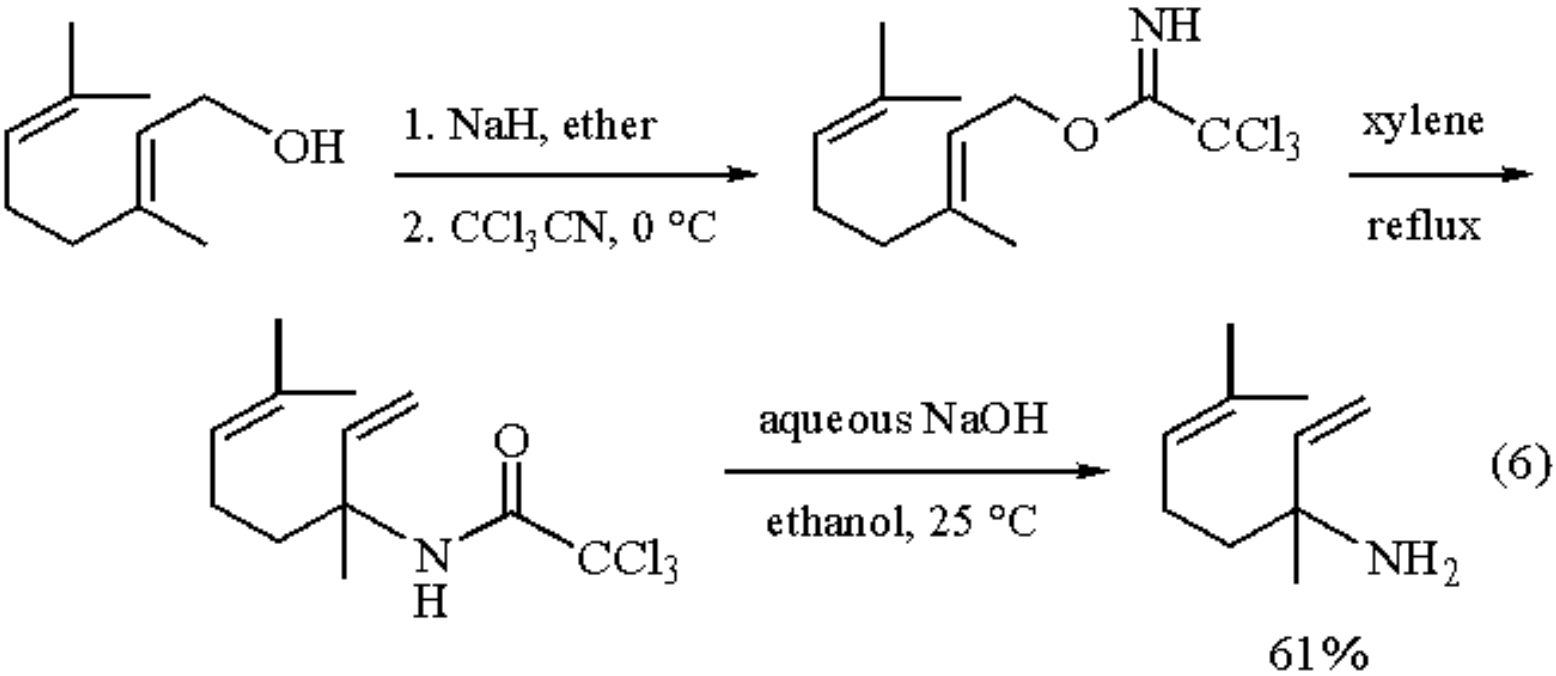

Related imidates can undergo [3,3]-sigmatropic rearrangements by using a palladium(II) catalyst instead of heat. For example, an allyl trichloroacetimidate rearranges to the corresponding amide when catalyzed by ***Bis(benzonitrile)dichloropalladium(II)*** in THF (eq 7).[11] The reaction goes in 8% yield with complete chirality transfer.

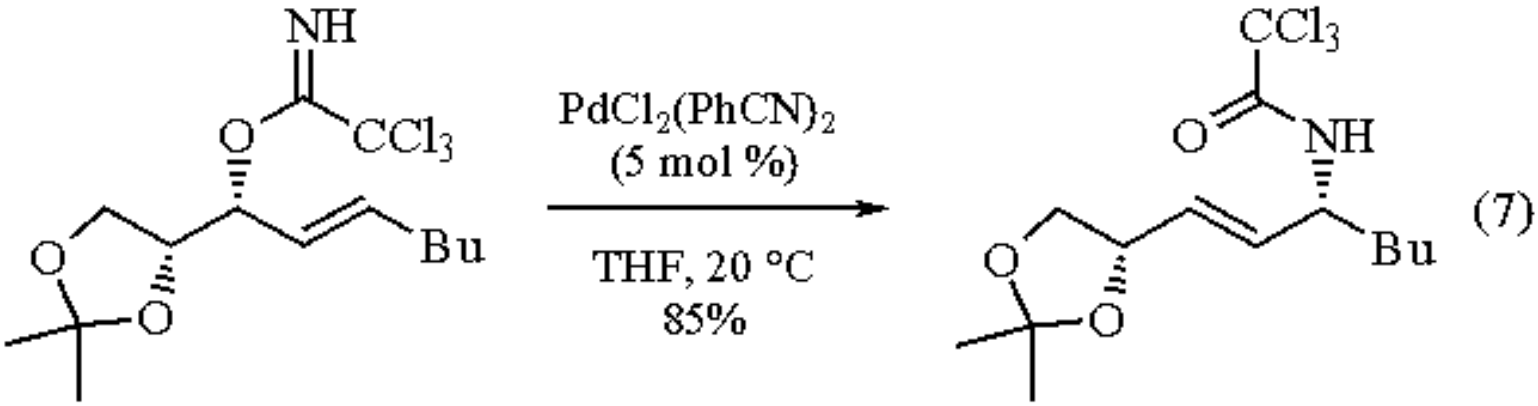

Allylic trichloroacetimidates undergo iodocyclization to give the corresponding 4,5-dihydro-1,3-oxazines. The regioselection of the reaction depends on the alkene geometry of the starting allyl imidate (eq 8).[12]

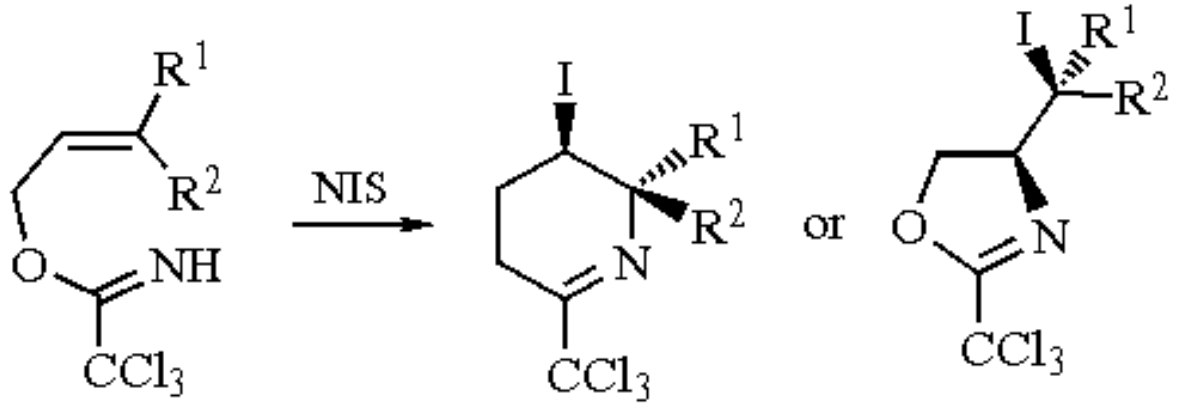

(8)

$R^1 = Et, R^2 = H$	90%	-
$R^1 = H, R^2 = Et$	-	88%
$R^1 = Pr, R^2 = H$	87%	-
$R^1 = H, R^2 = C_{15}H_{31}$	-	90%
$R^1 = H, R^2 = Ph$	-	92%

Imidates have been used in the synthesis of other organic systems, such as coupling reactions in carbohydrate synthesis[13] and Claisen-type rearrangements (see also ***Trichloroacetonitrile***).[14]

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Allyl Trifluoromethanesulfonate

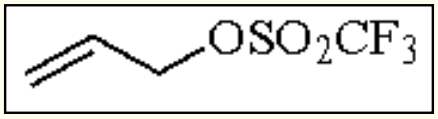

[41029-45-2] · $C_4H_5F_3O_3S$ · Allyl Trifluoromethanesulfonate · (MW 191.16)

(extremely reactive allylating agent;[1,2] attacks a variety of S-, P-, N-, or O-containing molecules;[2] ring expansion reaction[3])

Alternate Name: allyl triflate.

Physical Data: d 1.47 g cm^{-3}.

Solubility: sol chlorinated hydrocarbons.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: IR (neat, cm^{-1}) 2970 (w), 1413 (m), 1281 (s), 1248 (s), 1194 (s), 1149 (m), 913 (m); ^1H NMR (CCl_4, ppm) δ 6.03 (m, 1H), 5.43 (m, 2H), 4.92 (m, 2H); ^{19}F NMR (ppm) φ 74.5 (s).

Preparative Methods: allyl triflate is prepared by the reaction of ***Trifluoromethanesulfonic Anhydride*** (1 equiv) and allyl alcohol (1 equiv) in the presence of pyridine (1 equiv) in carbon tetrachloride at 0 °C.[1] The insoluble pyridine salt is removed by filtration through sodium sulfate, and the resulting solution is used directly for allylation reactions. The yield of the reaction is reported to be 75 ± 5% based on quantitative NMR analysis of aliquots.

Purification: a pure sample may be obtained by distillation (safety shield).[2] The product must be trapped in a cold receiver (-78 °C).

Handling, Storage, and Precautions: allyl triflate must be stored at -78 °C in a vented flask. The half-life of the neat reagent is ~10 min at room temperature, and the reagent in carbon tetrachloride solution completely decomposed in 3 days at room temperature. Allyl triflate reacts violently with nitrogen, or oxygen-containing solvents such as DMSO, DMF, or acetonitrile. The reagent is an extremely reactive allylating agent, and contact or inhalation should be avoided. Use in a fume hood.

S-Allylation-Ring Expansion.[3]

Allyl triflate is an extremely reactive allylating agent and reacts readily with 2-vinylthiapentane (**1**). α-Vinyl-*S*-allylsulfonium salt (**2**) thus obtained undergoes a 2,3-sigmatropic rearrangement upon treatment with a base (***1,8-Diazabicyclo[5.4.0]undec-7-ene***) (eq 1). Two rearrangement products (**3**) and (**4**) were obtained in the ratio of 1:1 that were derived from endocyclic and exocyclic ylides, respectively. Repeated application of this sequence to the eight-membered ring sulfide (**4**) produced medium- and large-sized ring sulfides. No products derived from the endocyclic ylides were observed in the ring expansion sequence from cyclic sulfide (**4**). 2-Vinylthiane also undergoes allylation and a 2,3-sigmatropic rearrangement sequence to produce a 1:2 mixture of cyclic sulfides (**7**) and (**8**) (eq 2). An improved ratio of products (**7**:**8** = 1:24) was obtained by using ***Lithium Diisopropylamide*** at -70 °C for ylide generation, and forcing the rearrangement to occur rapidly under dilute conditions (eq 3). The 2,3-sigmatropic rearrangement of six-membered rings takes place with remarkable stereospecificity,[4] and only the *trans* isomer of nine-membered ring sulfide (**8**) was observed.

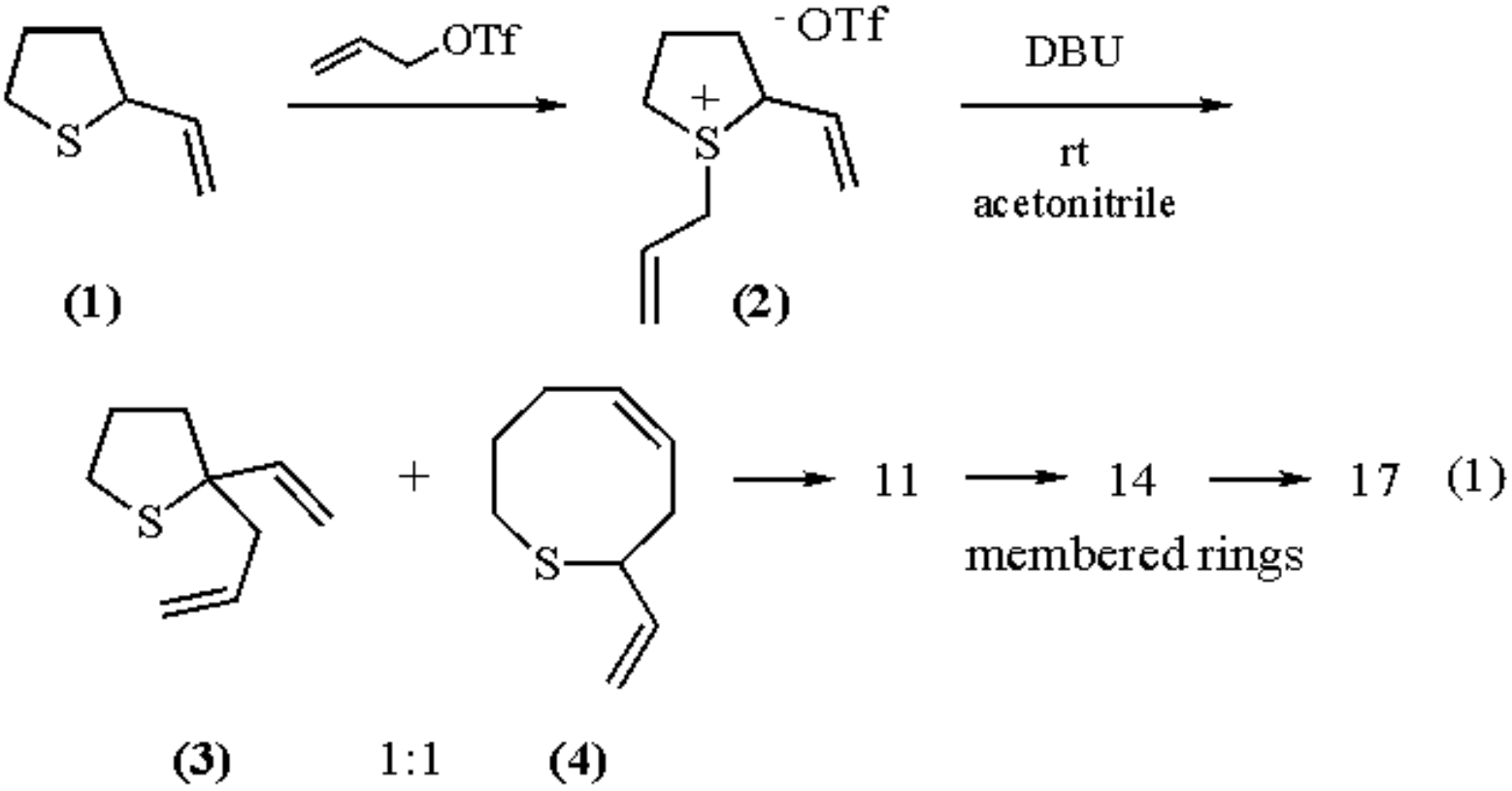

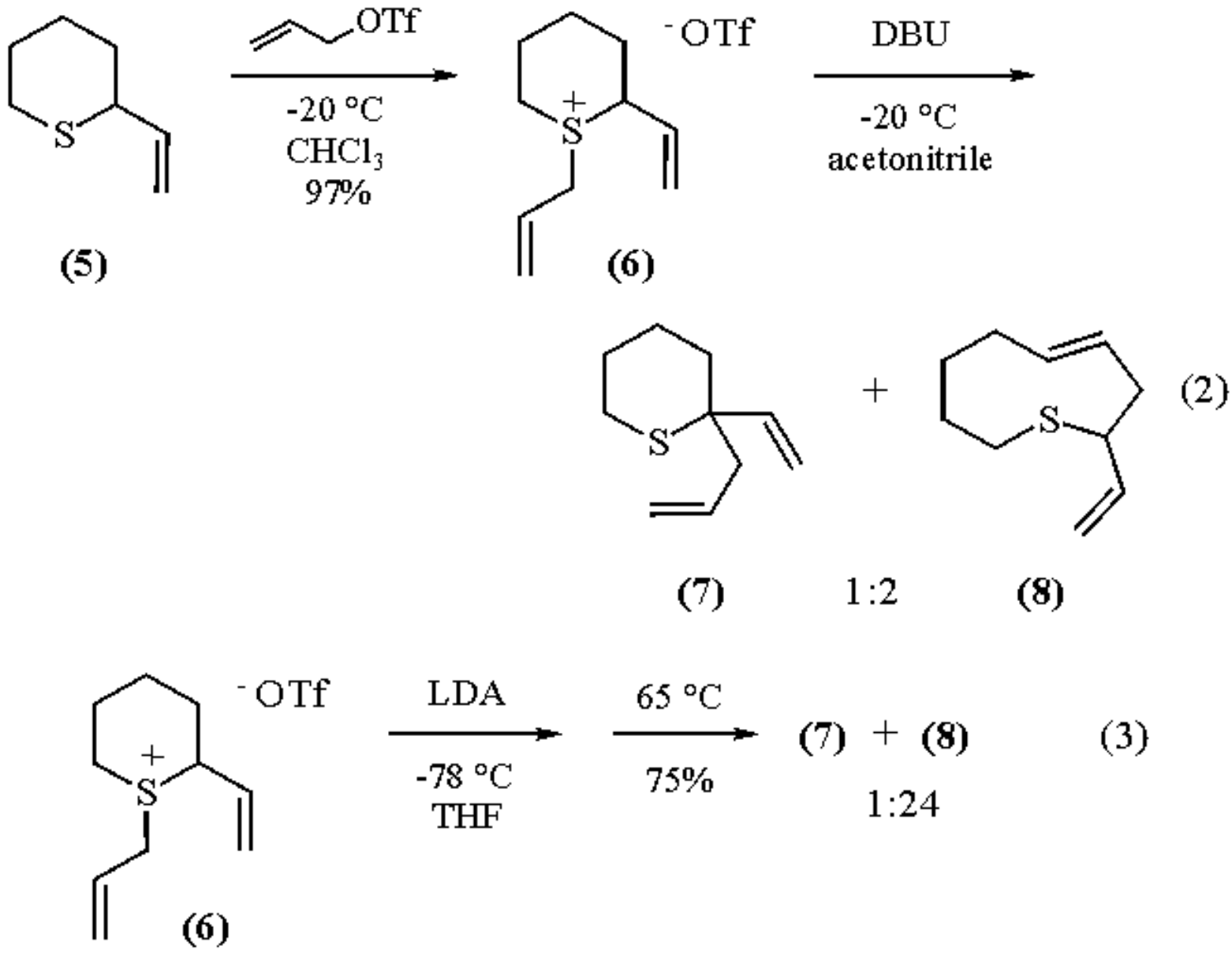

C-, *N*-, *O*-Allylation.

5-Chloromercuriuridine (**9**) undergoes a palladium-catalyzed *C*-allylation reaction with allyl triflate (eq 4).[5] Transmetalation of 5-chloromercuriuridine (**9**) and ***Palladium(II) Chloride*** generates the organopalladium(II) complex (**10**), which then reacts with allyl triflate to produce C-5 allyl-substituted uridine (**11**) in 52% yield. *N*-Allylation of *O*-trimethylsilyloxime (**12**) with allyl triflate is a convenient method for nitrone synthesis (eq 5).[6] The initial allylation produces the (*E*)-nitrone, which then isomerizes to the more stable (*Z*)-isomer. Allyl triflate reacts with alcohols to give *O*-allylation products. Alcohols of low nucleophilicity which contain electron-withdrawing substituents such as 2,2-dinitropropanol, 2,2,2-trinitroethanol, and 2,2-dinitro-1,3-propanediol even react with allyl triflate to produce the corresponding allyl ethers in 53%, 33%, and 28% yield, respectively.[1] These etherification reactions were carried out at room temperature in the presence of Na_2SO_4 as a heterogeneous acid scavenger.

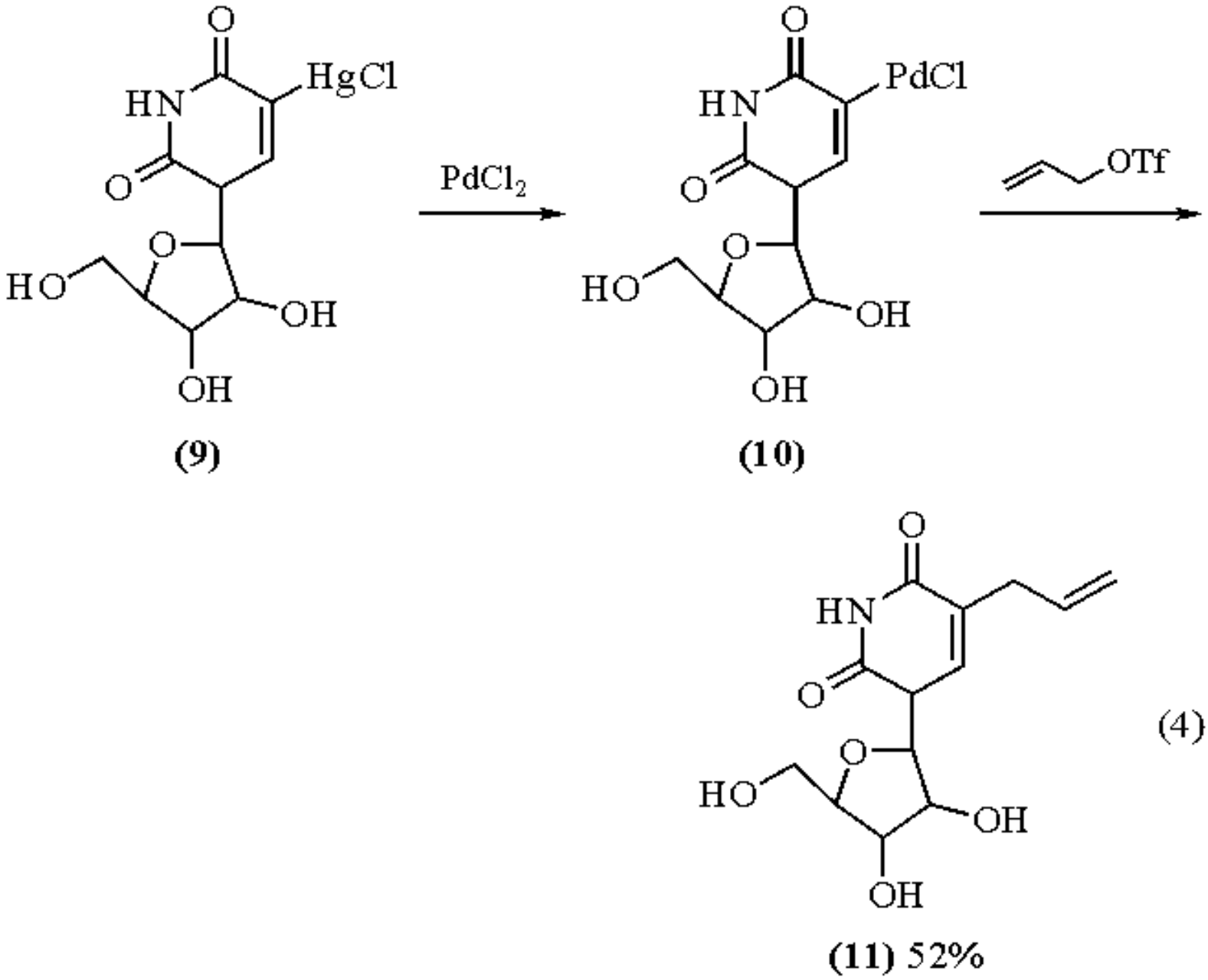

(4)

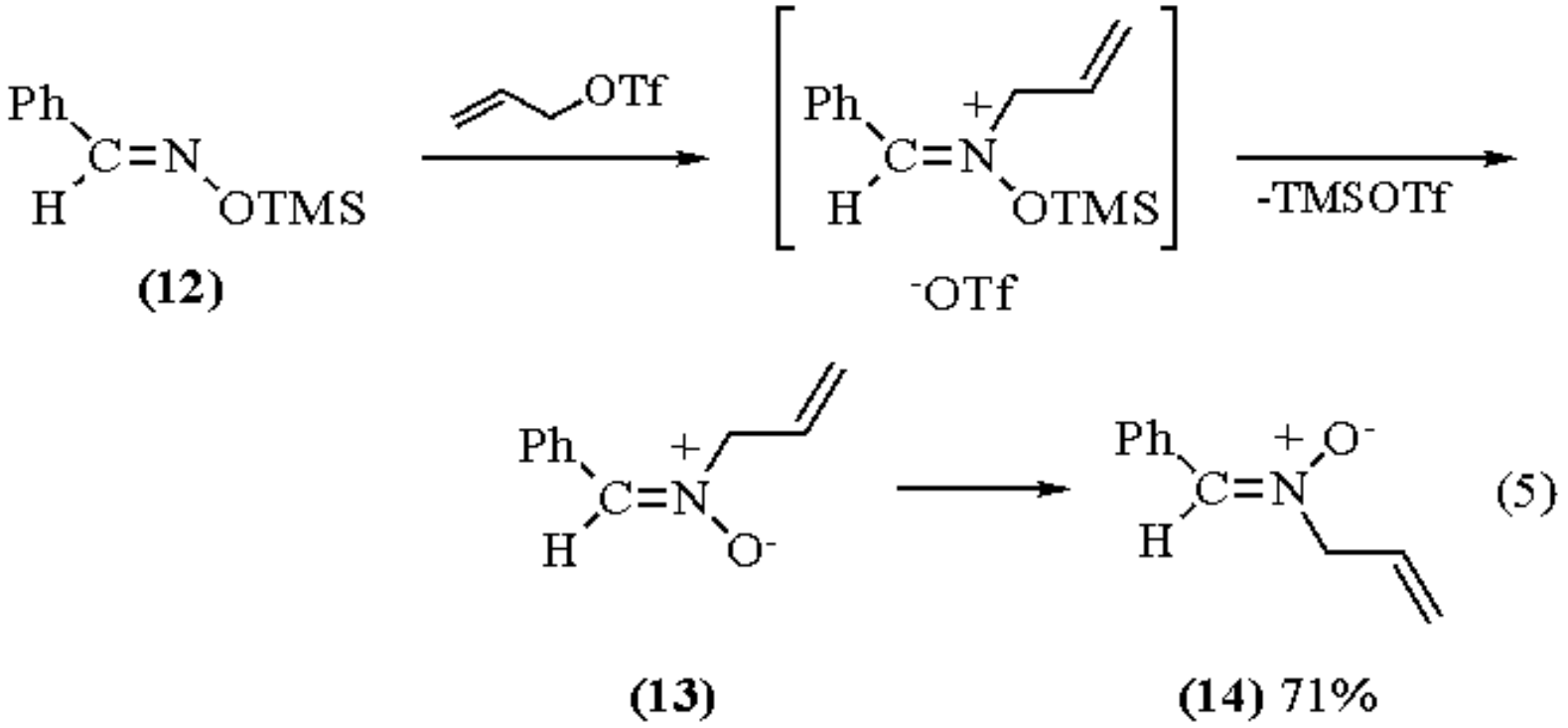

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Allyltrimethylgermane[1]

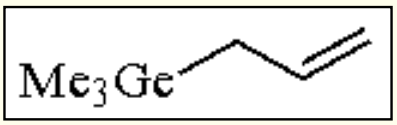

[762-66-3] · $C_6H_{14}Ge$ · Allyltrimethylgermane · (MW 158.78)

(allylation reagent for electrophilic[2,3] and nucleophilic reactions[4,5])

Physical Data: bp 101 °C.

Solubility: sol ether, hexane, and dichloromethane; insol H_2O.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: ^{1}NMR or GC.

Preparative Methods: to a solution of MeMgCl (2.3 M, 395 mL) in diethyl ether was added dropwise allyltrichlorogermane (61 g, 0.277 mol) in nitrogen. The mixture was refluxed for 10 h. After quenching with water, the mixture was extracted with diethyl ether. Careful distillation afforded allyltrimethylgermane (68%).[9]

Allylgermanes are nucleophilic species which react with electrophiles with allylic inversion.[1] Lewis acid-catalyzed Michael addition of the substituted allylgermane (**1**) to the unsaturated ester (**2**) takes place at the γ-position of (**1**) with migration of the double bond (eq 1).[2] The stereoselectivity of Lewis acid-promoted allylation of chiral dioxane acetals (**3**) depends on the allylmetal reagent and increases in the order allylsilanes < allylgermanes < allylstannanes, which parallels increased nucleophilicity (eq 2).[3] Similar results were obtained by the reaction of the monothioacetal (**6**) with allylmetal reagents in the presence of ***Trimethylsilyl Trifluoromethanesulfonate*** (eq 3). Allylgermane showed ca. 80% *syn* selectivity irrespective of the stereochemistry of (**6**), while the reaction of allylstannane was highly dependent on the stereochemistry of the reagent. The reaction of less nucleophilic allylgermane proceeds through an S_N1 mechanism involving an oxonium ion, while allylstannane reacts through an S_N2-type mechanism.[6]

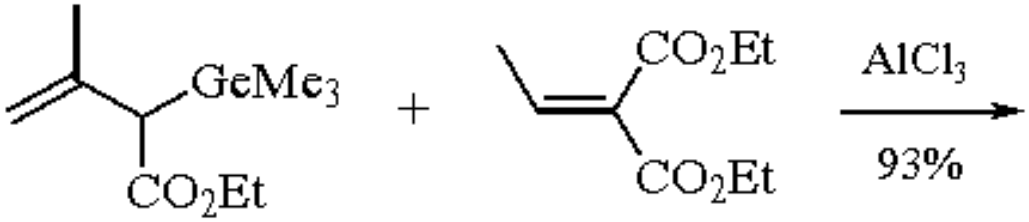

(1) **(2)**

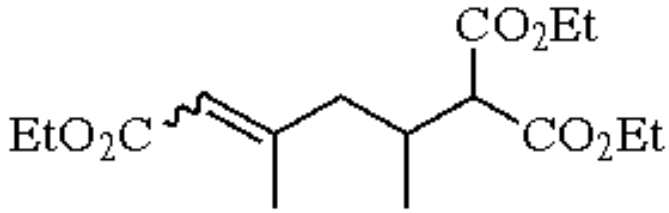

(1)

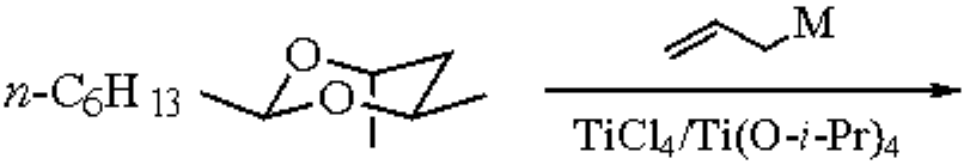

(3)

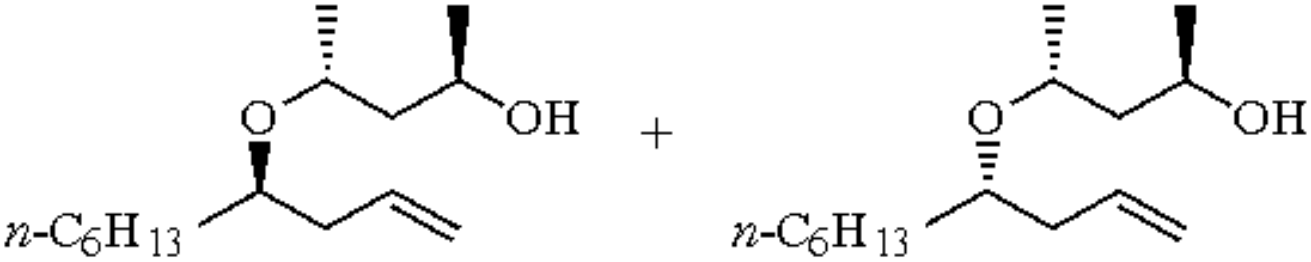

(2)

(4) **(5)**

M :	Me_3Si	**(4)/(5)** :	58/1
	Me_3Ge		100/1
	n-Bu_3Sn		270/1

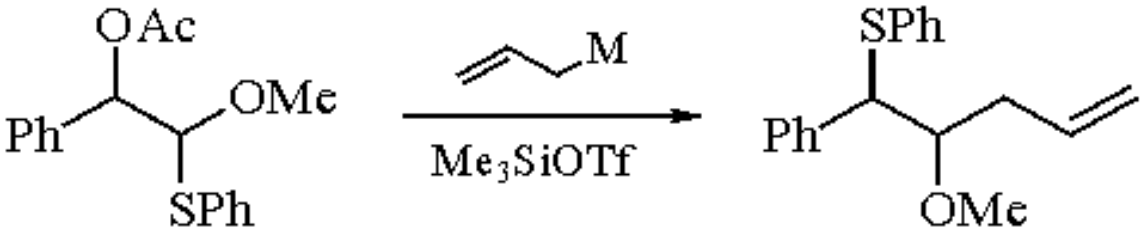

(3)

(6) **(7)**

anti-**(6)**	M : Me_3Ge	*syn*-/*anti*-**(7)** :	84/16
syn-**(6)**	Me_3Ge		73/27
anti-**(6)**	Me_3Sn		96/4
syn-**(6)**	Me_3Sn		14/86

Aromatic compounds undergo allylation with allylgermanes by reaction with ***Iodosylbenzene*** in the presence of ***Boron Trifluoride Etherate*** (eq 4).[4] The reaction involves generation of allyliodine(III) species, which can act as an allyl cation equivalent. Allylthallium(III) species, generated from the reaction of allylgermanes with thallium(III) salts, allylate aromatic compounds, alcohols, carboxylic acids, and nitriles.[5]

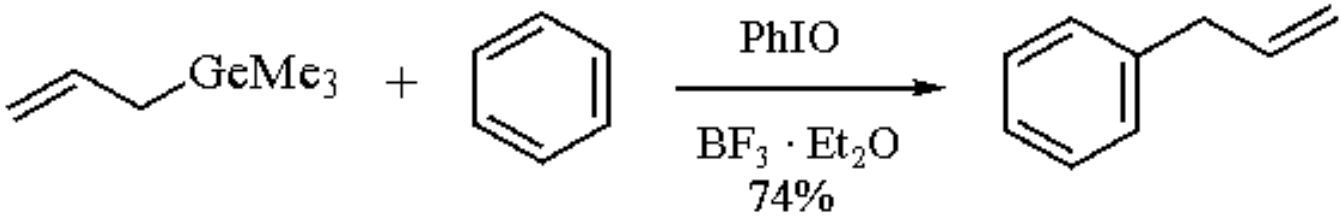

(4)

The photochemical reaction of allylgermane with 1,4-dicyanonaphthalene gives 1-allyl-4-cyanonaphthalene, which probably involves electron transfer from allylgermane to the electron-deficient 1,4-dicyanonaphthalene (eq 5).[7] Thermal ene reaction of allylgermane with ***Diethyl Azodicarboxylate*** gives a mixture of stereoisomers of vinylgermanes (eq 6).[8]

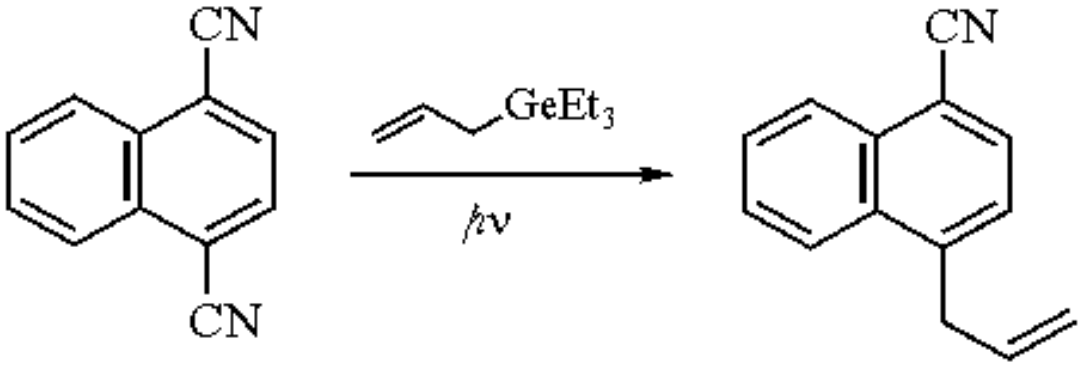

(5)

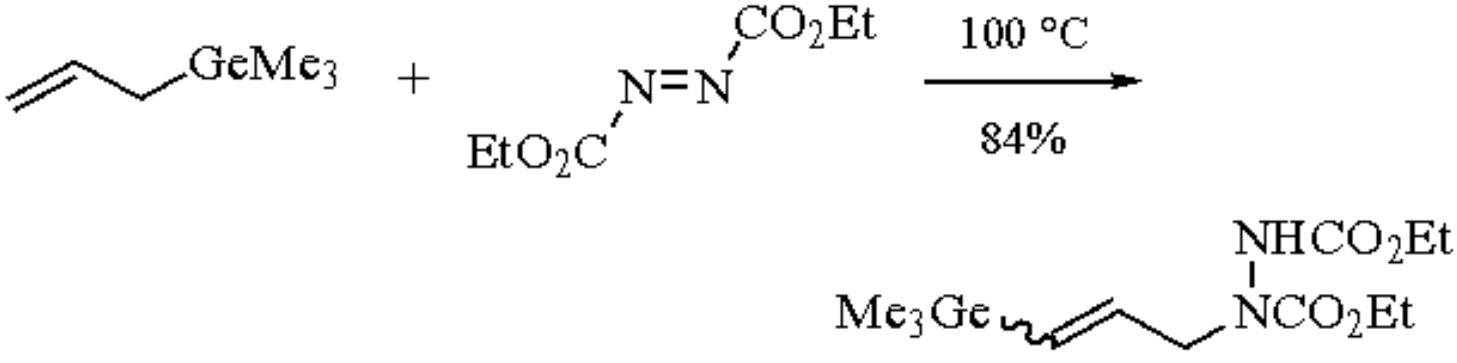

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2. Yamamoto, Y.; Okano, H.; Yamada, J. *TL* **1991**, *32*, 4749.
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Allyltrimethylsilane[1]

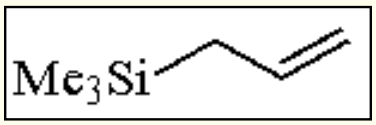

[762-72-1] · $C_6H_{14}Si$ · Allyltrimethylsilane · (MW 114.26)

(carbon nucleophile for the introduction of allyl groups by Lewis acid-catalyzed or fluoride ion-catalyzed reaction with acid chlorides, aldehydes, ketones, iminium ions, enones, and similar carbon electrophiles)

Physical Data: bp 85-86 °C, *d* 0.717 g cm^{-3}.

Solubility: freely sol all organic solvents.

Form Supplied in: colorless liquid. Methods for the synthesis of allylsilanes in general have been reviewed.[3]

Analysis of Reagent Purity: δ 5.74 (1H, ddt, *J* 16.9, 10.2 and 8), 4.81 (1H, dd, *J* 16.9 and 2), 4.79 (1H, dd, *J* 10.2 and 2), 1.49 (2H, d, *J* 8) and -0.003 (9H, s).[2]

Handling, Storage, and Precautions: inflammable; the vapor is irritating to the skin, eyes, and mucous membranes.

As a Carbon Nucleophile in Lewis Acid-Catalyzed Reactions.

Allyltrimethylsilane is an alkene some 10^5 times more nucleophilic than propene, as judged by its reactions with diarylmethyl cations.[4] It reacts with a variety of cationic carbon electrophiles, usually prepared by coordination of a Lewis acid to a functional group, but also by chemical or electrochemical oxidation,[5] or by irradiation in the presence of 9,10-dicyanoanthracene.[6] The electrophile attacks the terminal alkenic carbon to give an intermediate cation, and the silyl group is lost to create a double bond at the other terminus. Among the more straightforward electrophiles are acid chlorides (eq 1),[7] aldehydes and ketones (eq 2),[8] their acetals (eq 3),[9] and the related alkoxyalkyl halides (eq 4),[10] iminium ions, and acyliminium ions (eqs 5 and 6),[11,12] and tertiary and allylic or benzylic alkyl halides (eqs 7 and 8).[13,14]

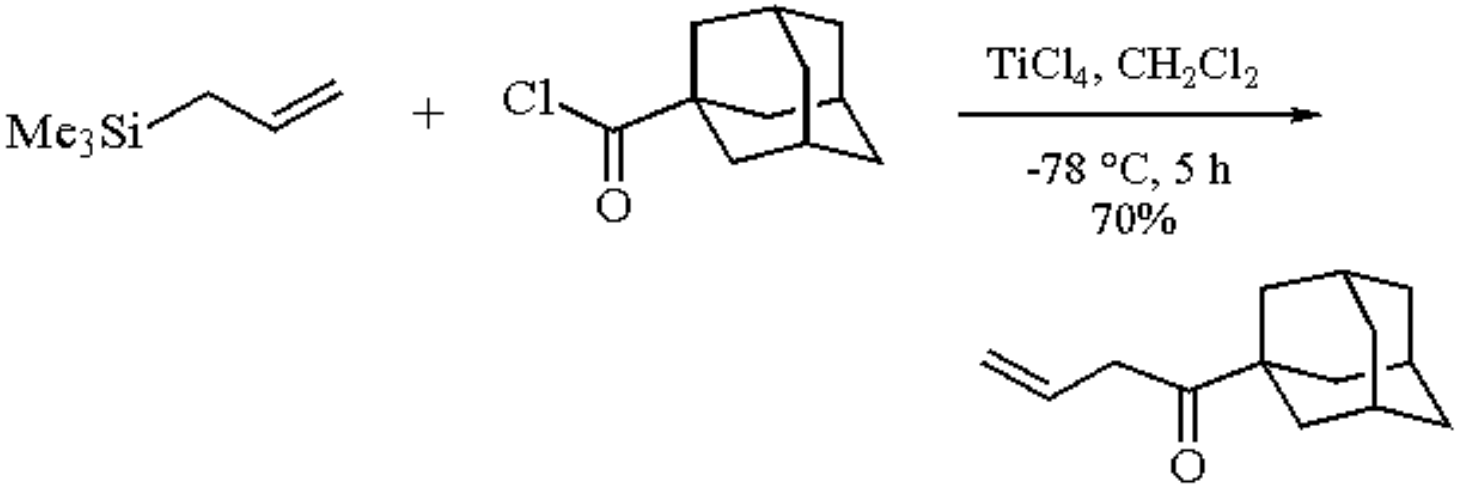
Me3Si
Cl
O
TiCl4, CH2Cl2
-78 °C, 5 h
70%
O

(1)

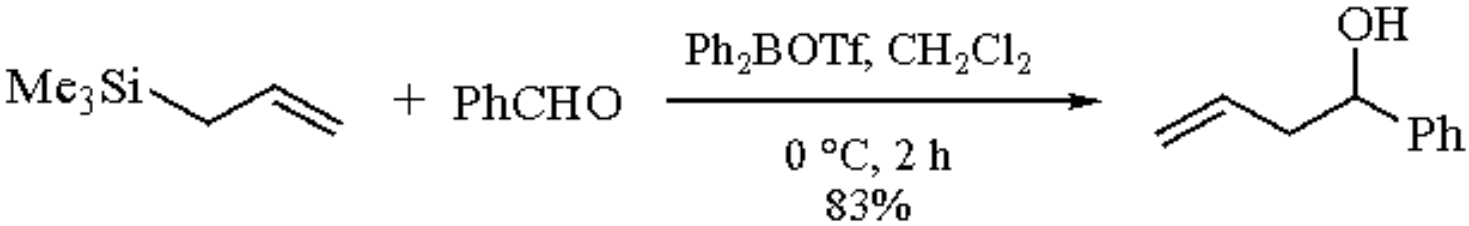
Me3Si
PhCHO
Ph2BOTf, CH2Cl2
0 °C, 2 h
83%
OH
Ph

(2)

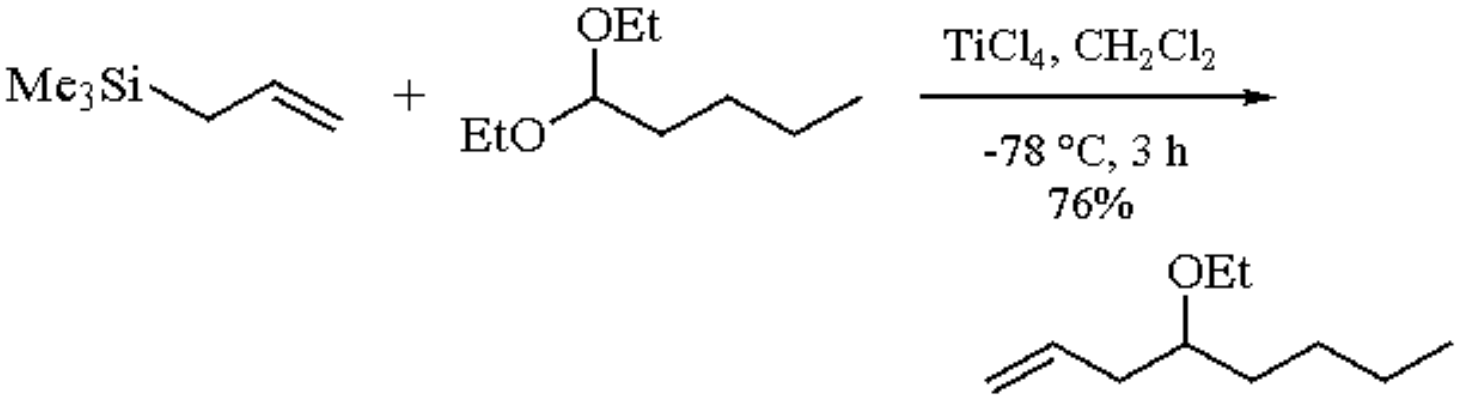
Me3Si
OEt
EtO
TiCl4, CH2Cl2
-78 °C, 3 h
76%
OEt

(3)

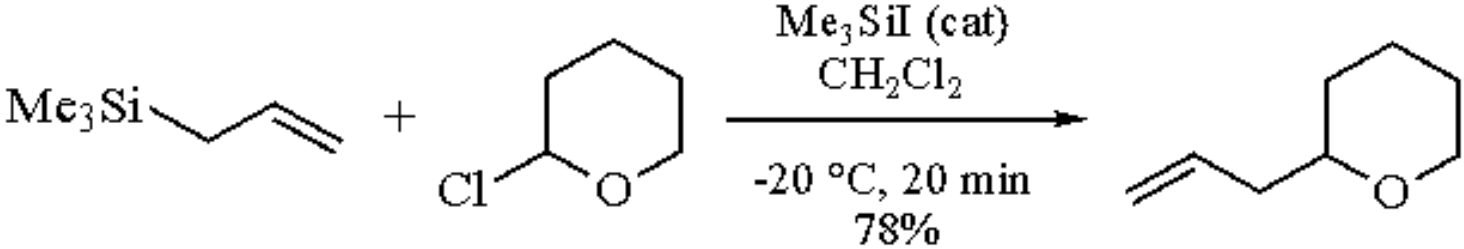
Me3Si
Cl
O
Me3SiI (cat)
CH2Cl2
-20 °C, 20 min
78%
O

(4)

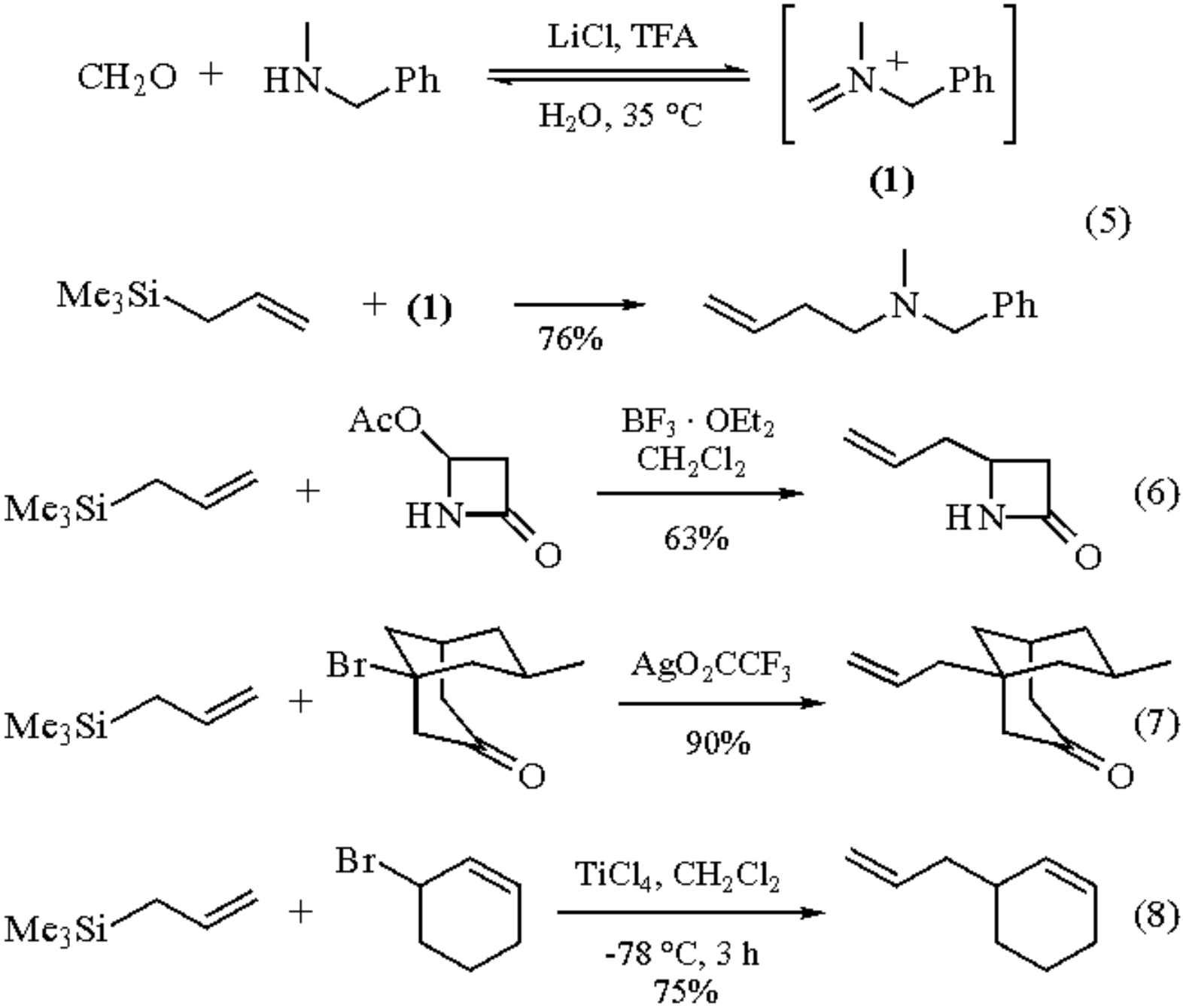

The reaction with acetals does not always need the acetal itself to be synthesized: it can be made in the same flask by mixing the allylsilane, the aldehyde, the silyl ether of the alcohol, and a catalytic amount of an acid such as ***Diphenylboryl Trifluoromethanesulfonate***,[15] ***Trimethylsilyl Trifluoromethanesulfonate***,[16] or ***Fluorosulfuric Acid***.[17]

The further reaction of the double bond in the first-formed product is an occasional complication, as in the formation of tetrahydropyrans from aldehydes when ***Aluminum Chloride*** is the Lewis acid (eq 9),[18] and of piperidines from primary amines and formaldehyde (eq 10).[11]

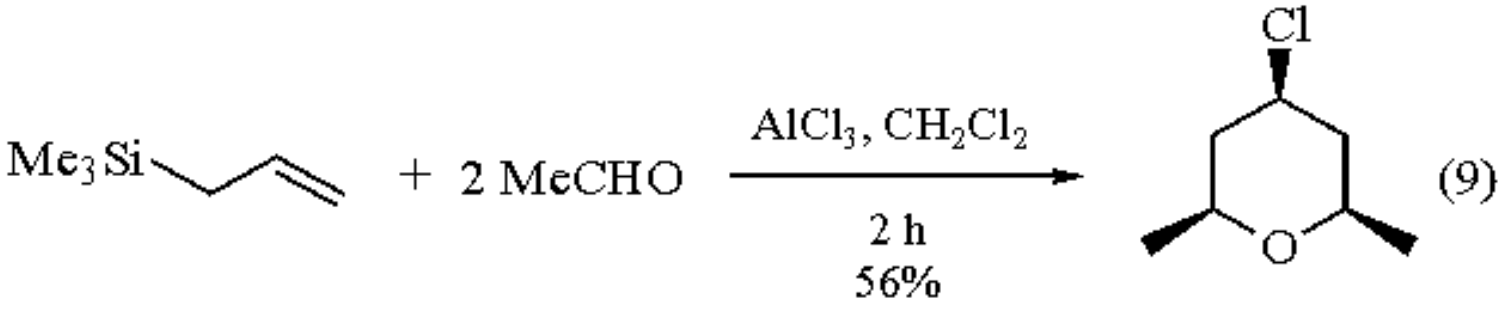

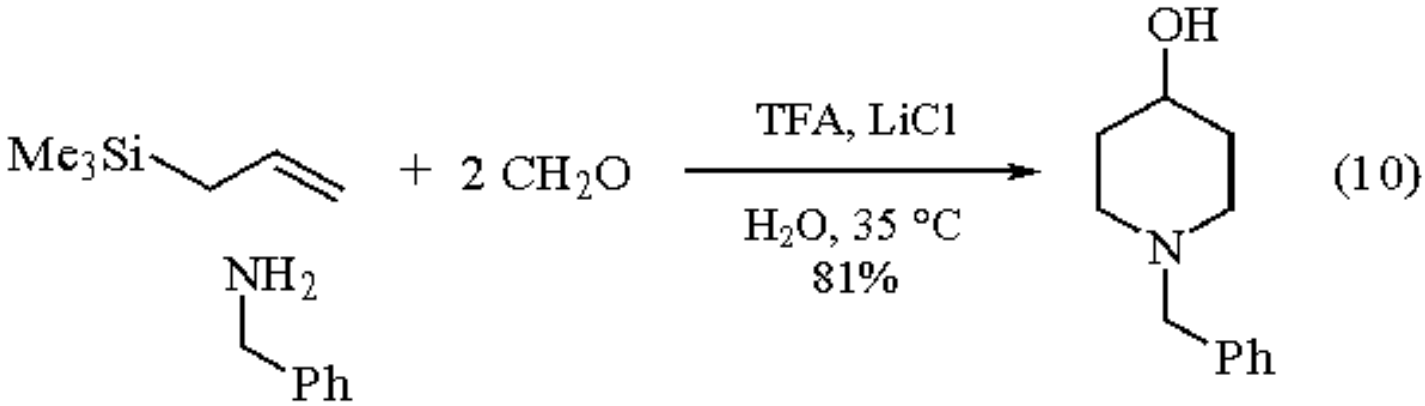

α,β-Unsaturated esters, aldehydes, ketones, and nitriles generally react in Michael fashion in what is called a Sakurai reaction (eq 11).[19] The intermediate silyl enol ether may be treated with a second electrophile to set up two C-C bonds in one operation (eq 12).[20] Occasionally the silyl group is not lost from the intermediate cation but migrates instead to give a cyclopentannulation byproduct (eq 13).[21]

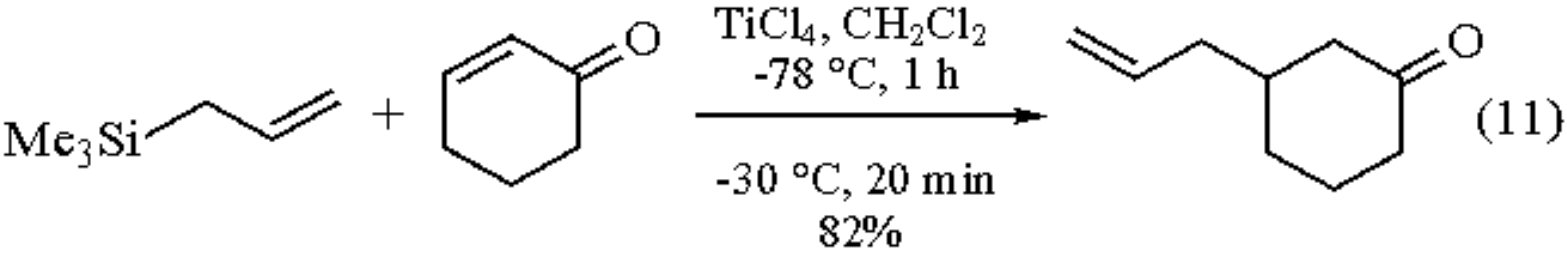

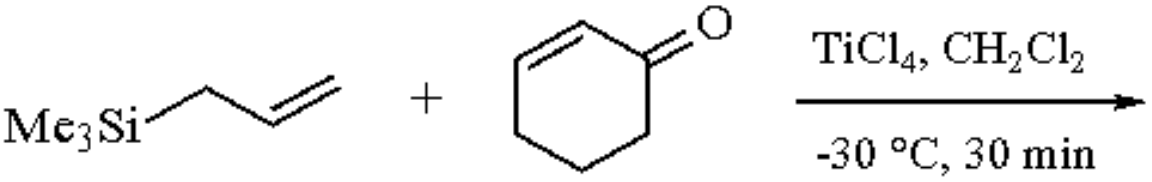

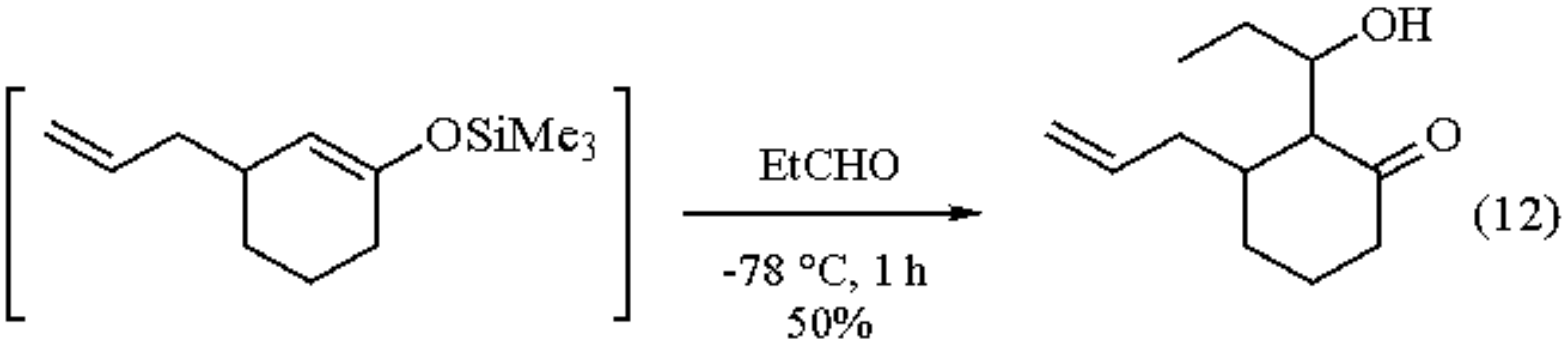

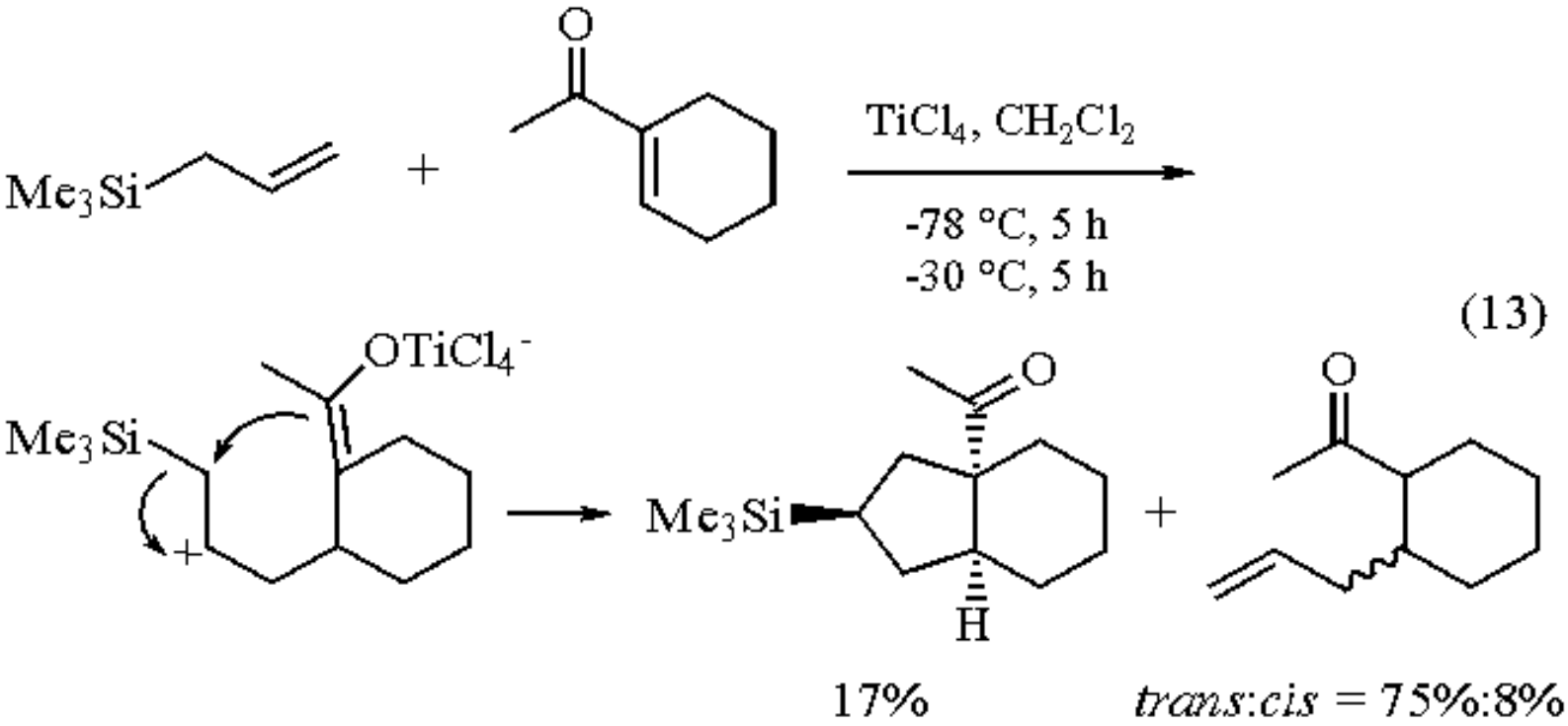

α,β-Unsaturated nitro compounds initially give nitronic acid derivatives, which can be reduced directly with ***Titanium(III) Chloride*** to give the corresponding ketone (eq 14).[22]

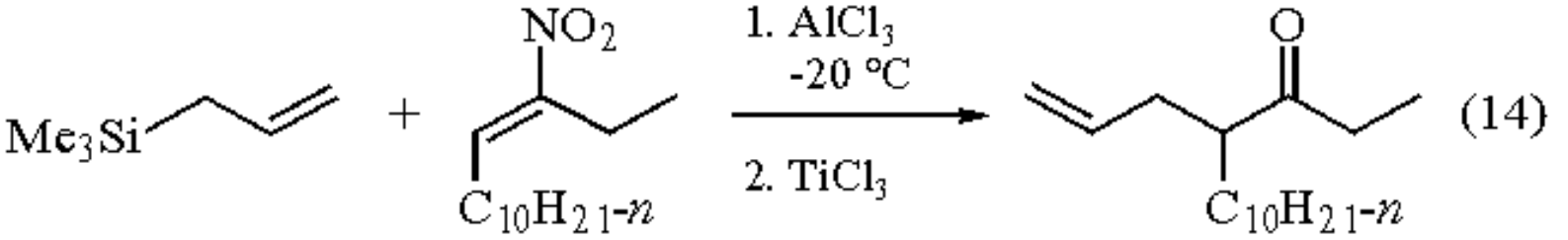

Some electrophiles require a separate activation step, as in the stereospecific reaction of alkenes with benzenesulfenyl chloride (eq 15).[23] The intermediate that actually reacts with the allylsilane is presumably the episulfonium ion. There is a corresponding reaction of epioxonium ions derived from 2-bromoethyl ethers.[24] Intramolecular hydrosilylation of an ester generates an acetal, which reacts with allyltrimethylsilane in the usual way and with high stereocontrol to make an *anti* 1,3-diol derivative (eq 16).[25]

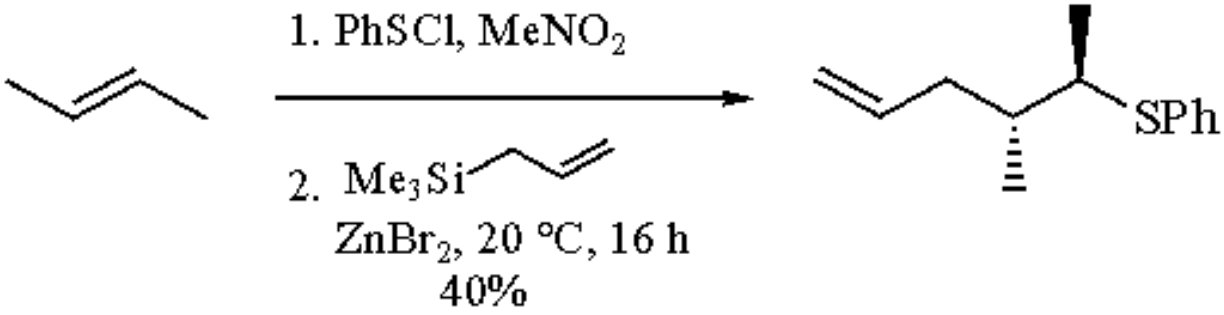

(15)

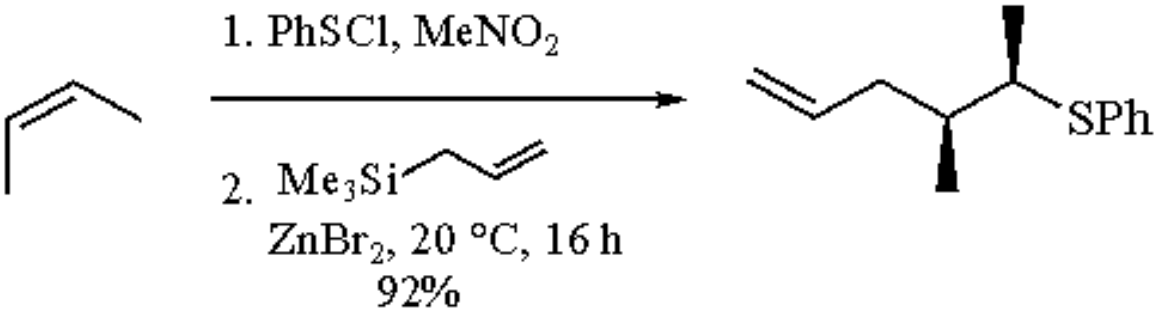

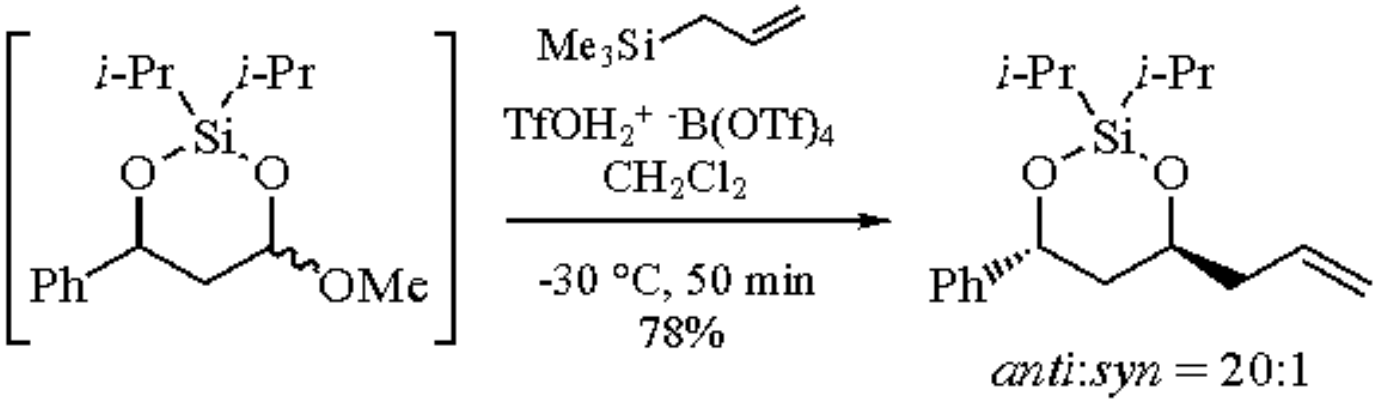

(16)

The reactions with α- or β-oxygenated aldehydes can be made to give high levels of stereocontrol in either sense by choosing a chelating or nonchelating Lewis acid (eq 17).[26]

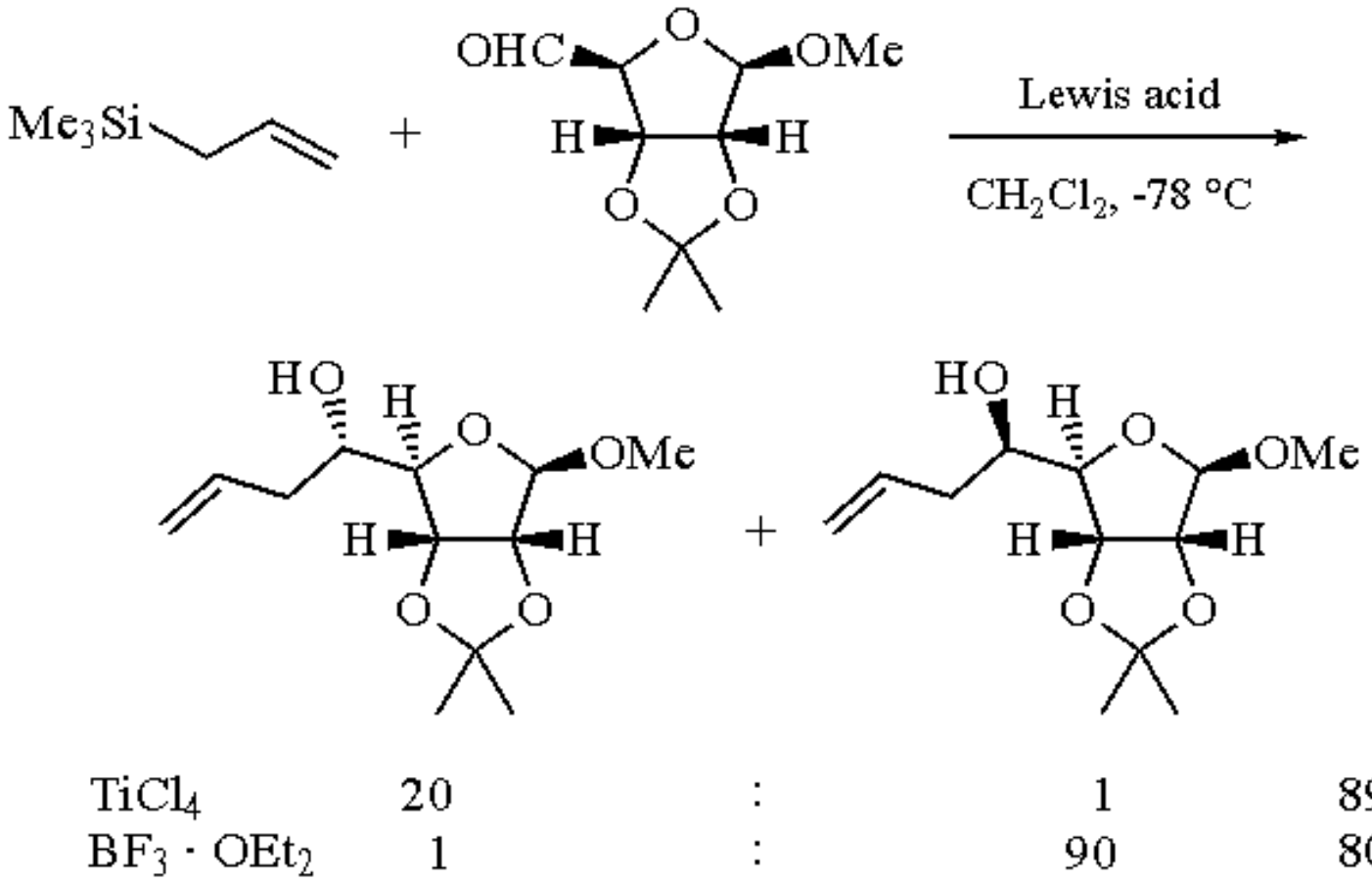

Sugar acetals (eq 18)[27] and glycal 3-acetates (eq 19)[28] and related compounds react stereoselectively in favor of axial attack at the anomeric carbon.

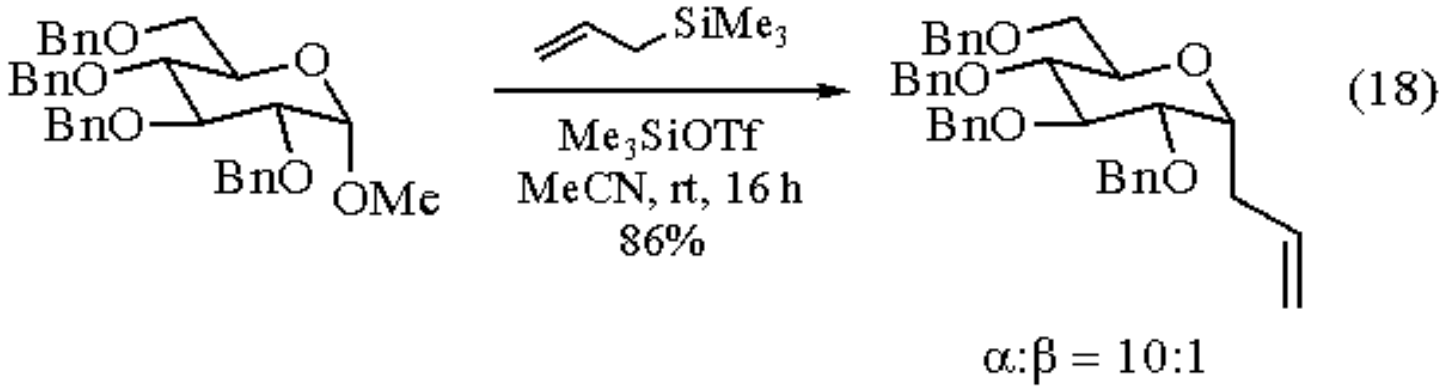

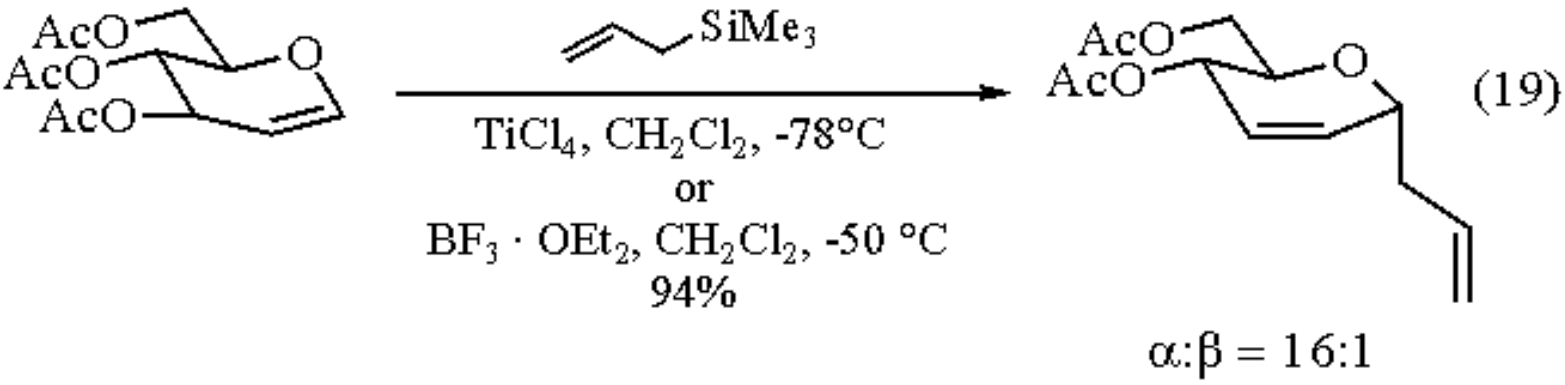

The choice of Lewis acid in all these reactions is often important in getting the best results, one Lewis acid being much the best in several cases. Most are used in molar amounts, but some, especially ***Iodotrimethylsilane***, ***Trimethylsilyl Trifluoromethanesulfonate***, and the more powerful trifluoromethanesulfoxonium tetrakis(trifluoromethanesulfonyl)boronate[29] [$TfOH_2^+B(OTf)_4^-$], have the advantage that they can be used in catalytic quantities. In addition to the Lewis acids illustrated, the following less obvious Lewis acids have also been used with one or more of the electrophiles: ***Triphenylmethyl Perchlorate***,[30] titanocene ditriflate,[31] ***Lithium Perchlorate***,[32] ***Tin(IV) Chloride*** in the presence of either ***Tin(II) Trifluoromethanesulfonate***[33] or ***Zinc Chloride***,[34] ***Antimony(V) Chloride***,[35] ***Chlorotrimethylsilane*** combined with indium chloride,[36] ***Ethylaluminum Dichloride***,[37] and ***Diphenylboryl Trifluoromethanesulfonate***.[38] Among carbon electrophiles not illustrated are quinones,[39] cyclopropanedicarboxylic esters,[40] oxetanes,[41] nitriles,[42] dithioacetals,[43] diselenoacetals,[44] the intermediate sulfur-stabilized cation from a Pummerer rearrangement,[45] and propargyl ethers with[46] or without[47] octacarbonyldicobalt complexation.

As a Carbon Nucleophile in Uncatalyzed Reactions.

Some electrophiles do not need Lewis acids, being already cationic and electrophilic enough to react with allyltrimethylsilane. Examples are the dithianyl cation (eq 20),[48] the tricarbonyl(cyclohexadienyl)iron cation (eq 21),[49] (π-allyl) tetracarbonyliron cations,[50] and ***Chlorosulfonyl Isocyanate*** (CSI).[51] Other reagents react directly by cycloaddition, but need further steps to achieve an overall electrophilic substitution, as in the reactions with nitrones (eq 22).[52]

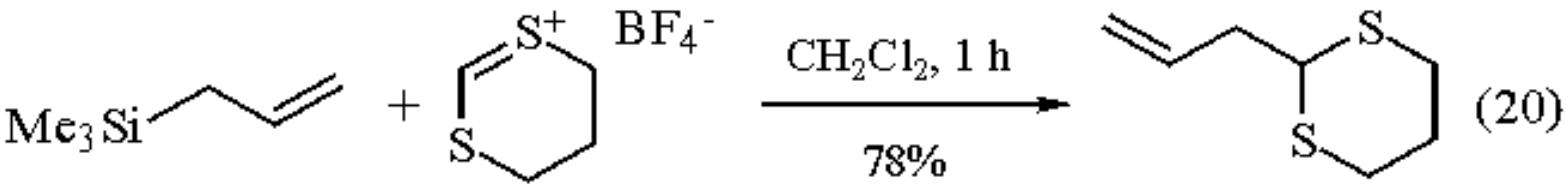

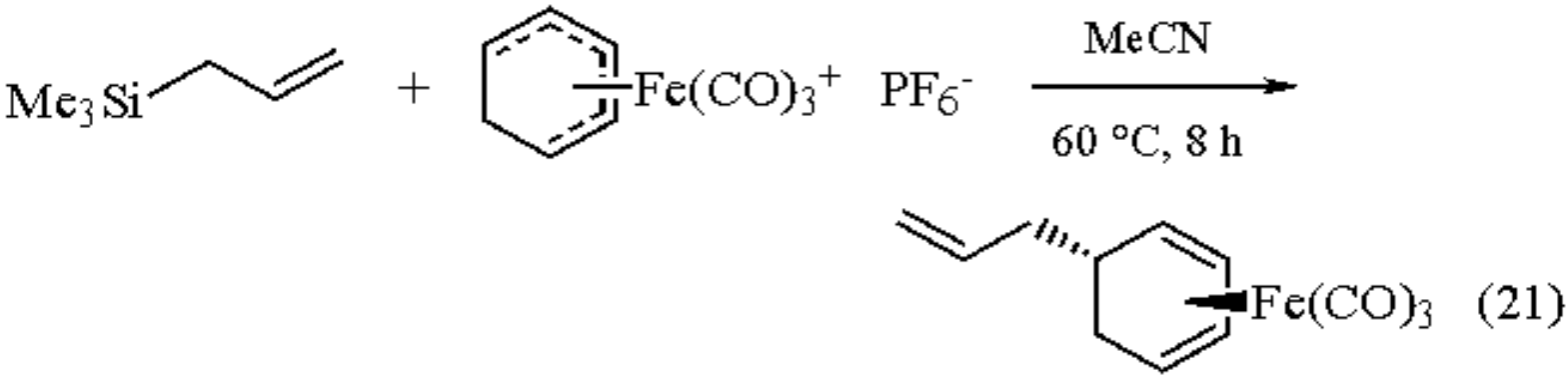

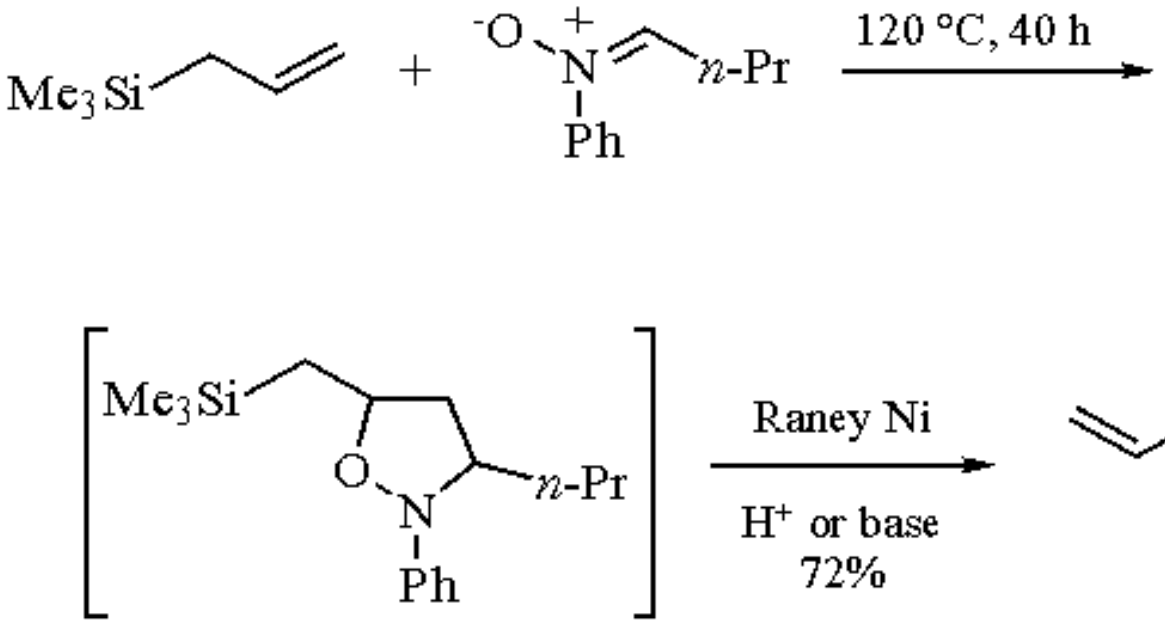

(22)

Although heteroatom (N-, P-, O-, S-, Se-, and halogen-based) electrophiles react with allylsilanes, the products with allyltrimethylsilane itself are usually too simple for this to be an important synthetic method. An exception perhaps is the reaction with ***Palladium(II) Chloride***, which gives the π-allylpalladium chloride cation.[53]

As a Carbon Nucleophile in Fluoride Ion-Catalyzed Reactions.

The reactions with aldehydes, ketones (eq 23),[54] and α,β-unsaturated esters (eq 24)[55] can also be catalyzed by fluoride ion, usually introduced as ***Tetra-n-butylammonium Fluoride*** (TBAF), or other silicophilic ions such as alkoxide. These reactions produce silyl ether intermediates, which are usually hydrolyzed before workup. The stereochemistry of attack on chiral ketones can sometimes be different for the Lewis acid- and fluoride ion-catalyzed reactions.[56] In addition some electrophiles only react in the fluoride-catalyzed reactions, as with the addition to trinitrobenzene giving an allyl Meisenheimer complex.[57]

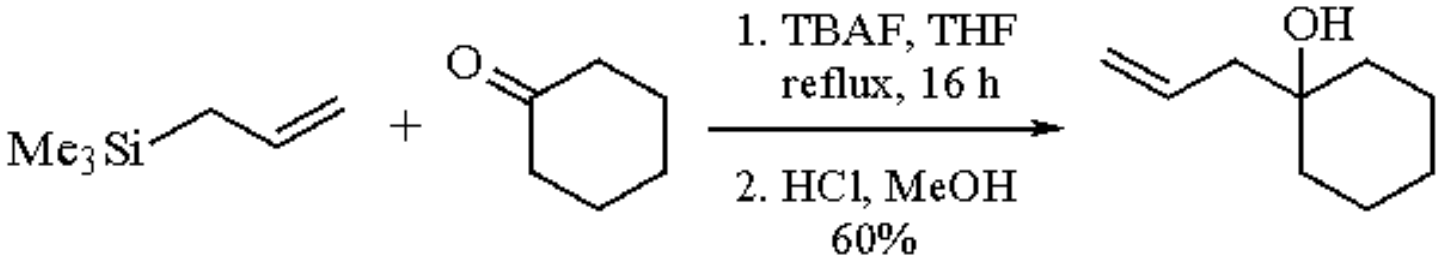

(23)

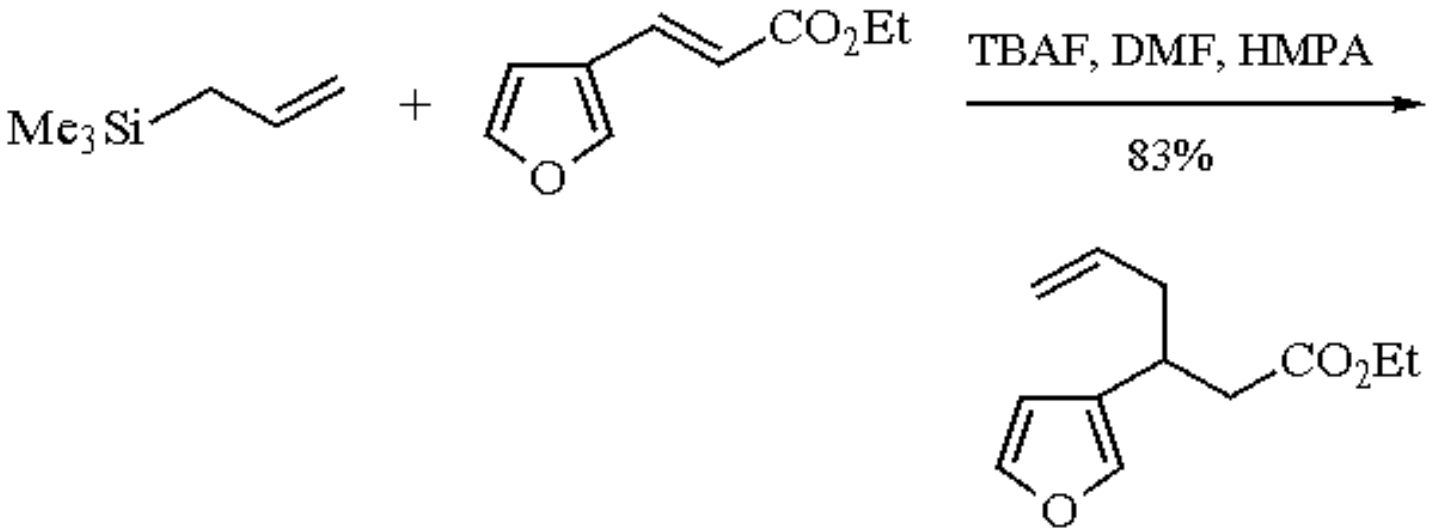

(24)

Other Reactions.

Allyltrimethylsilane reacts with some highly electrophilic alkenes, carbonyl compounds, azo compounds, and singlet oxygen to a greater or lesser extent in ene reactions that do not involve the loss of the silyl group, and hence give vinylsilanes in a solvent-dependent reaction (eq 25).[58]

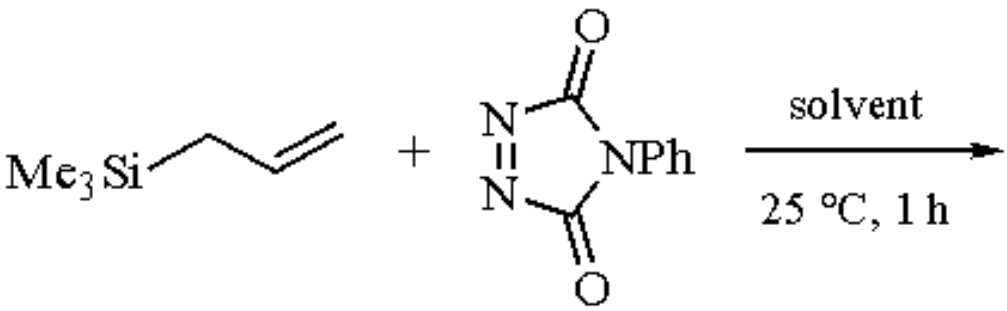

(25)

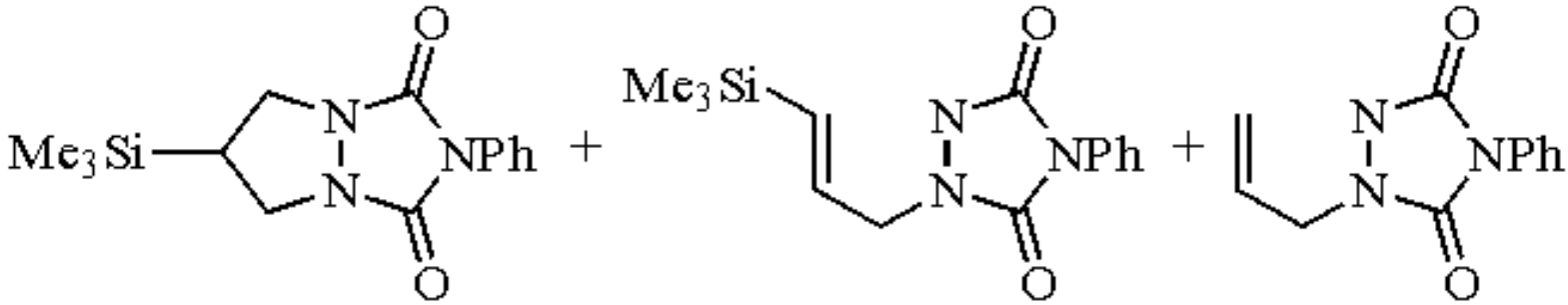

benzene	18	:	73	:	9
MeCN	6	:	28	:	67

Hydroalumination (and hydroboration) take place regioselectively to place the aluminum (or boron) atom at the terminus, creating a 3-trimethylsilylpropyl nucleophile.[59] Radicals attack allyltrimethylsilane at the terminus, and the intermediate radical reacts further without the trimethylsilyl group being expelled, as the corresponding germanium, tin, and lead groups are.[60] Treatment with strong bases gives trimethylsilylallyl-metal compounds (see

Trimethylsilylallyllithium and ***Allyltrimethylsilylzinc Chloride***).

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Allyltrimethylsilylzinc Chloride

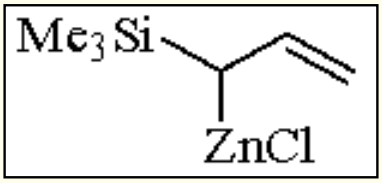

[89822-47-9] · $C_6H_{13}ClSiZn$ · Allyltrimethylsilylzinc Chloride · (MW 214.09)

(allylmetal reagent; useful for synthesis of spiro-γ-lactones[1])

Preparative Methods: deprotonation of ***Allyltrimethylsilane*** with ***n-Butyllithium*** in THF at -78 °C or ***s-Butyllithium*** in THF/TMEDA, followed by the addition of ***Zinc Chloride***.[1,2] The reagent is prepared in situ and used directly.

Spiro-γ-lactone Synthesis via Reactions with Carbonyl Compounds.

Although lithiated allyltrimethylsilane adds to simple ketones with good regioselectivity (eq 1),[2] its addition to 17-ketosteroids produces a mixture of α and γ adducts. Transmetalation of allyltrimethylsilyllithium with $ZnCl_2$ leads to a reagent (allyltrimethylsilylzinc chloride) which adds with complete regioselectivity to this type of hindered ketone (eq 2).[1] The resulting silylated homoallylic alcohols can be converted by a simple succession of steps to valuable steroidal γ-lactones. It is interesting to note that the 4-hydroxybutenylsilane obtained by the addition of the allyltrimethylsilyl anion to adamantan-2-one undergoes some unusual transformations[3] in the presence of ***N-Bromosuccinimide***, leading to the oxetane (**1**) via a 4-*exo*-tet ring opening[4] of the intermediate bromonium ion (eq 3). The extent of α and γ selectivity can be fine-tuned by changing the metal, and very high α-regioselectivity is observed using magnesium as the counterion.[5] Similarly, the addition of ***Triethylaluminum*** to the lithium reagent leads to a high α-regioselectivity (eq 4).[6] A stereocontrolled synthesis of *anti*-homoallylic alcohols is possible by preparing the corresponding allylic boronic ester and subsequent reaction with an aldehyde. A stereoselective elimination allows the preparation of either (*E*)- or (*Z*)-dienes (eq 5).[7] The isomeric reagent (**1**) is a useful reagent for the preparation of 2-substituted polyfunctional allylic silanes (eq 6).[8]

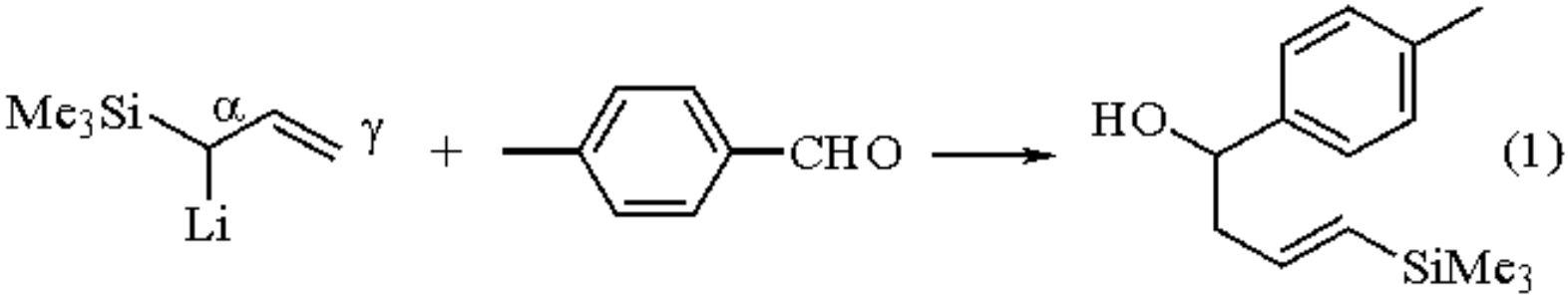
Me3Si
α
γ
Li
+
CHO
HO
SiMe3
(1)

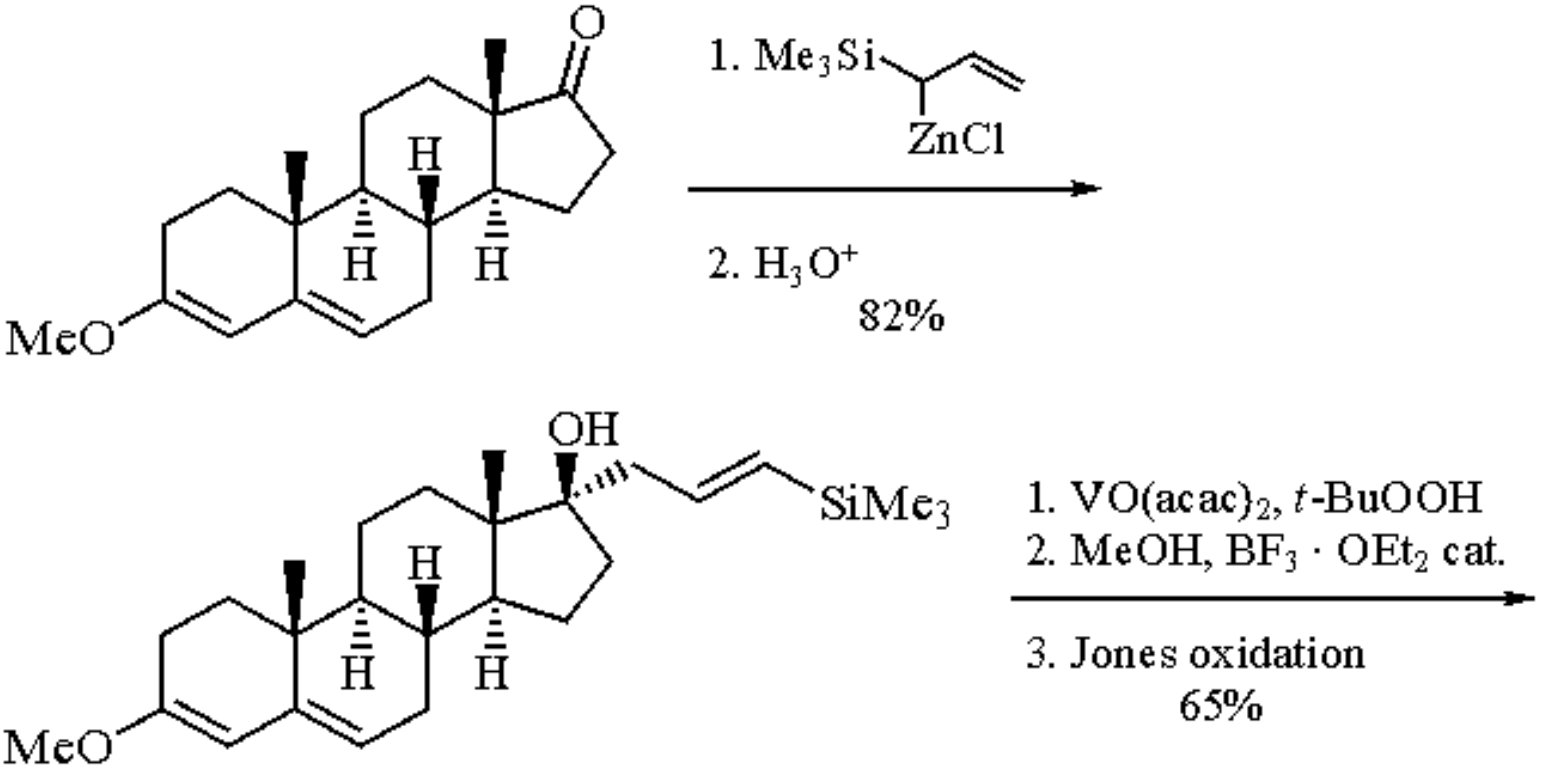
O
H
H
H
MeO
1. Me3Si
ZnCl
2. H3O+
82%
OH
SiMe3
H
H
H
MeO
1. VO(acac)2, t-BuOOH
2. MeOH, BF3 · OEt2 cat.
3. Jones oxidation
65%

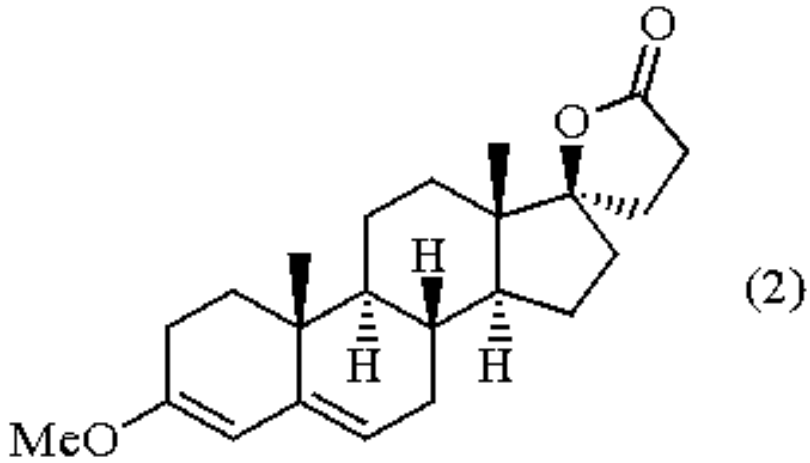
O
O
H
H
H
MeO
(2)

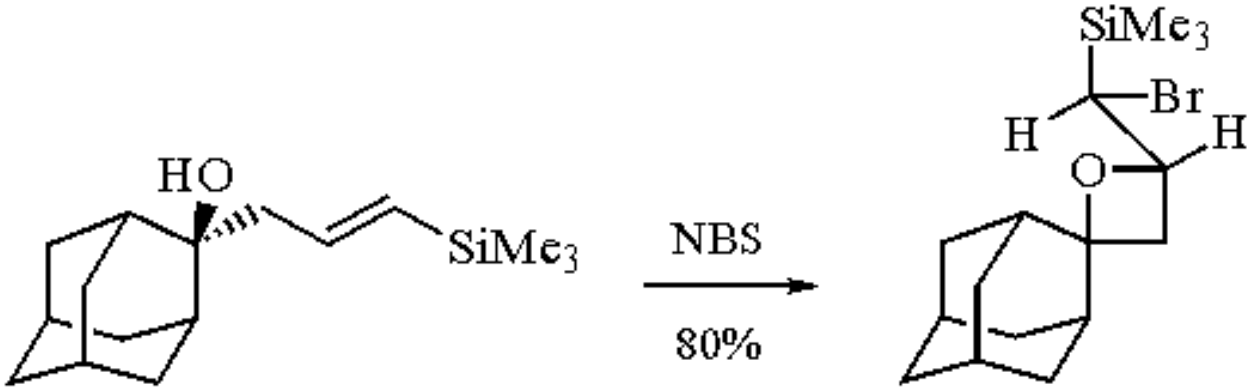

(3)

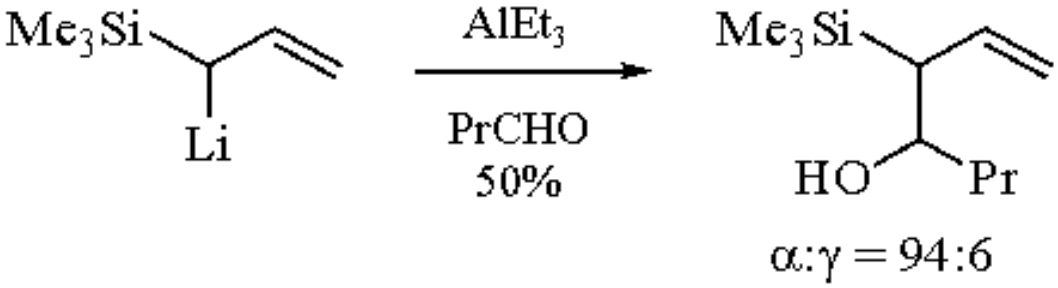

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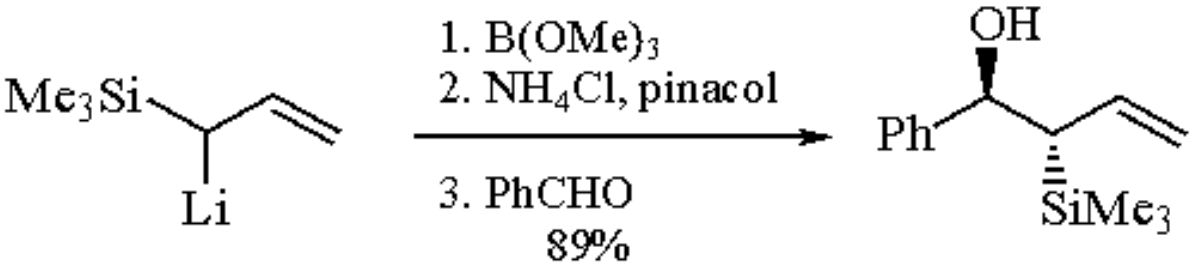

(5)

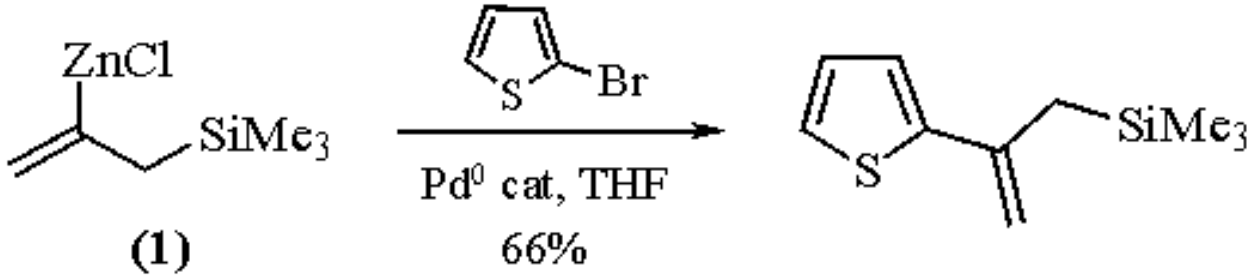

(6)

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Allyltriphenylphosphonium Bromide[1]

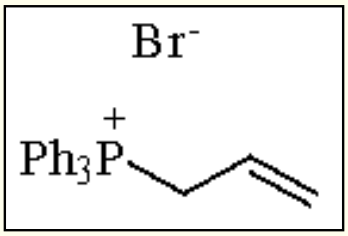

[1560-54-9] · $C_{21}H_{20}BrP$ · Allyltriphenylphosphonium Bromide · (MW 383.27)

(conjugate diene-forming reagent, ring-forming reagent[1])

Alternate Name: 2-propenyltriphenylphosphonium bromide.

Physical Data: mp 225-227 °C; pK_a;[3a] ^{1}H,[4a] ^{13}C,[4b] ^{31}P NMR spectra;[4b] MS;[5] X-ray PES spectra.[6]

Solubility: sol acetonitrile; distribution of (**1**) between water and organic solvents.[3b]

Form Supplied in: white powder, mp 222-225 °C.

Handling, Storage, and Precautions: hygroscopic, irritant. Use in a fume hood.

Preparation of allyltriphenylphosphonium bromide (**1**)[1] was accomplished by allowing ***Allyl Bromide*** to react with ***Triphenylphosphine*** in benzene.[2] A couple of drops of methanolic ***Benzyltrimethylammonium Hydroxide***[2c] or ***Triethylamine***[2d] in refluxing acetonitrile converts (**1**) into 1-propenyltriphenylphosphonium bromide (**2**) (eq 1).[2c,d]

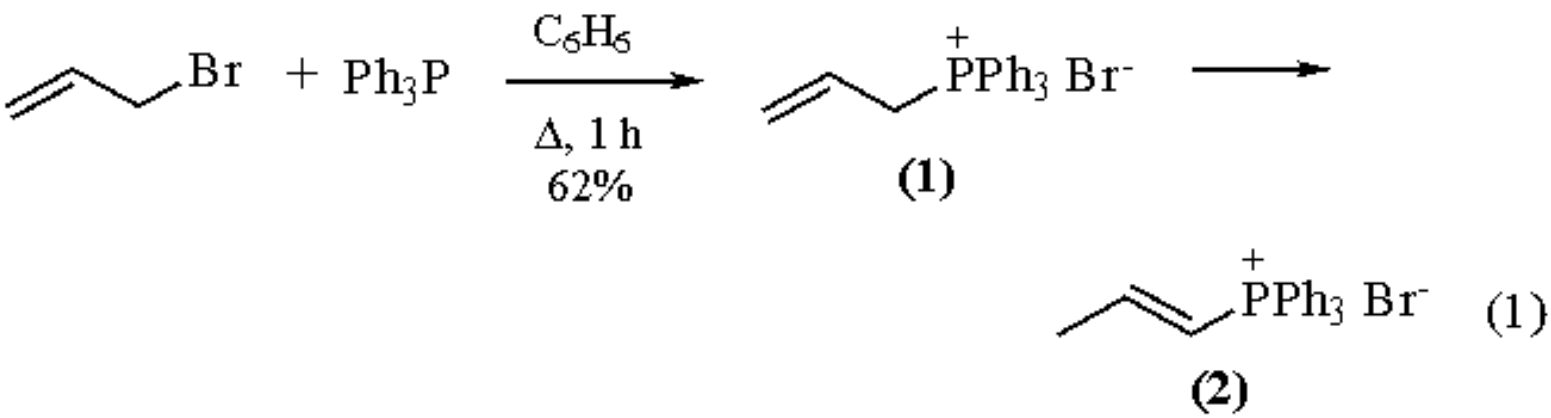

The first alkenation reaction was accomplished using ***Phenyllithium*** as the base to convert (**1**) into the phosphorane (**3**)[2a] followed by benzaldehyde to give a 50:50 (*E*):(*Z*) ratio of (**4**) (eq 2).[2a]

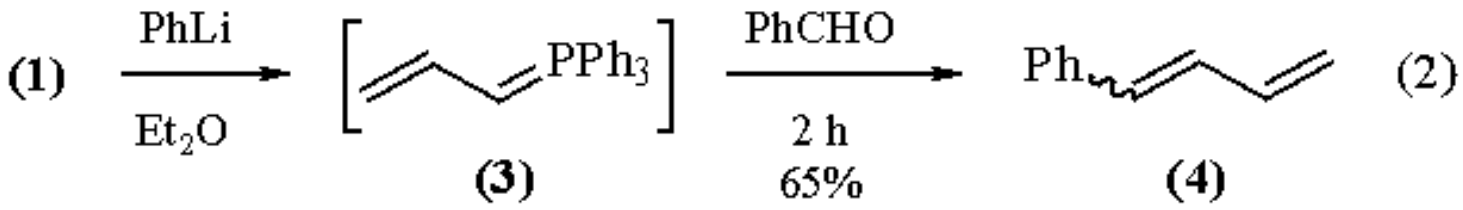

The preparation of phosphorane (**3**) for use in alkenation reactions has been accomplished using a large number of base/solvent pairs, such as PhLi/Et_2O,[2] ***n-Butyllithium***/hexane,[7] *n*-BuLi/Et_2O,[8a,b] *n*-BuLi/THF,[8c] ***Methyllithium***/Et_2O,[8d] LiOEt/EtOH,[9] ***Potassium Carbonate***/toluene,[10] and ***1,8-Diazabicyclo[5.4.0]undec-7-ene***/THF[11] (the latter has been used on the fluoroborate, instead of the bromide salt). The aldehyde, in a gaseous state, has also been passed over a solid bed of K_2CO_3 mixed with the phosphonium salt (**1**) suspended in Carbowax 6000 at 150 °C.[12] In a few cases the species used as the base has also contained an aldehydic function, which undergoes the Wittig alkenation reaction and then cyclizes,[13] such as the reaction of (**1**) with sodiopyrrolaldehyde (eq 3).[13a]

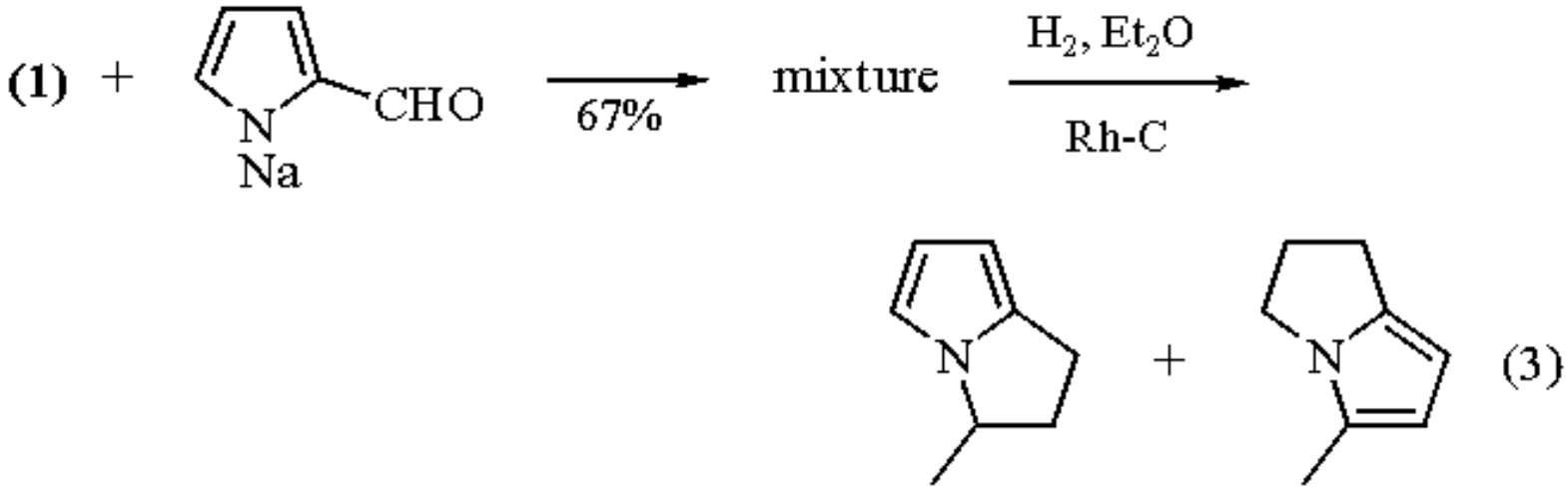

Addition-elimination followed by the alkenation reaction has been accomplished with the nucleophilic site on (**3**) being the γ-position (eq 4).[14]

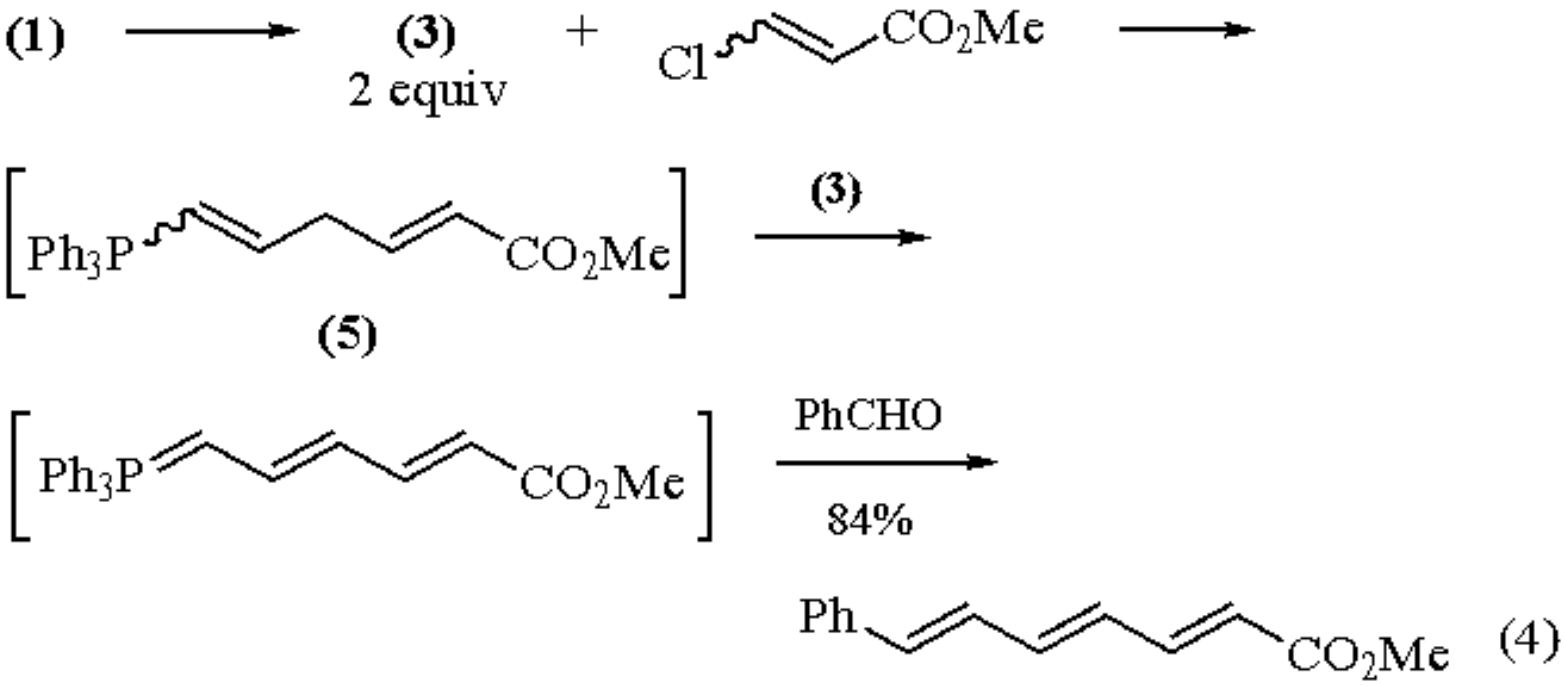

Rings have been formed in reasonable yields via a variety of sequences, such as γ-addition of (**3**) followed by reylidation and the Wittig reaction (eq 5),[15] γ-addition followed by cyclization and proton transfer (eq 6),[16] and alkenation followed by electrocylization (eq 7).[17]

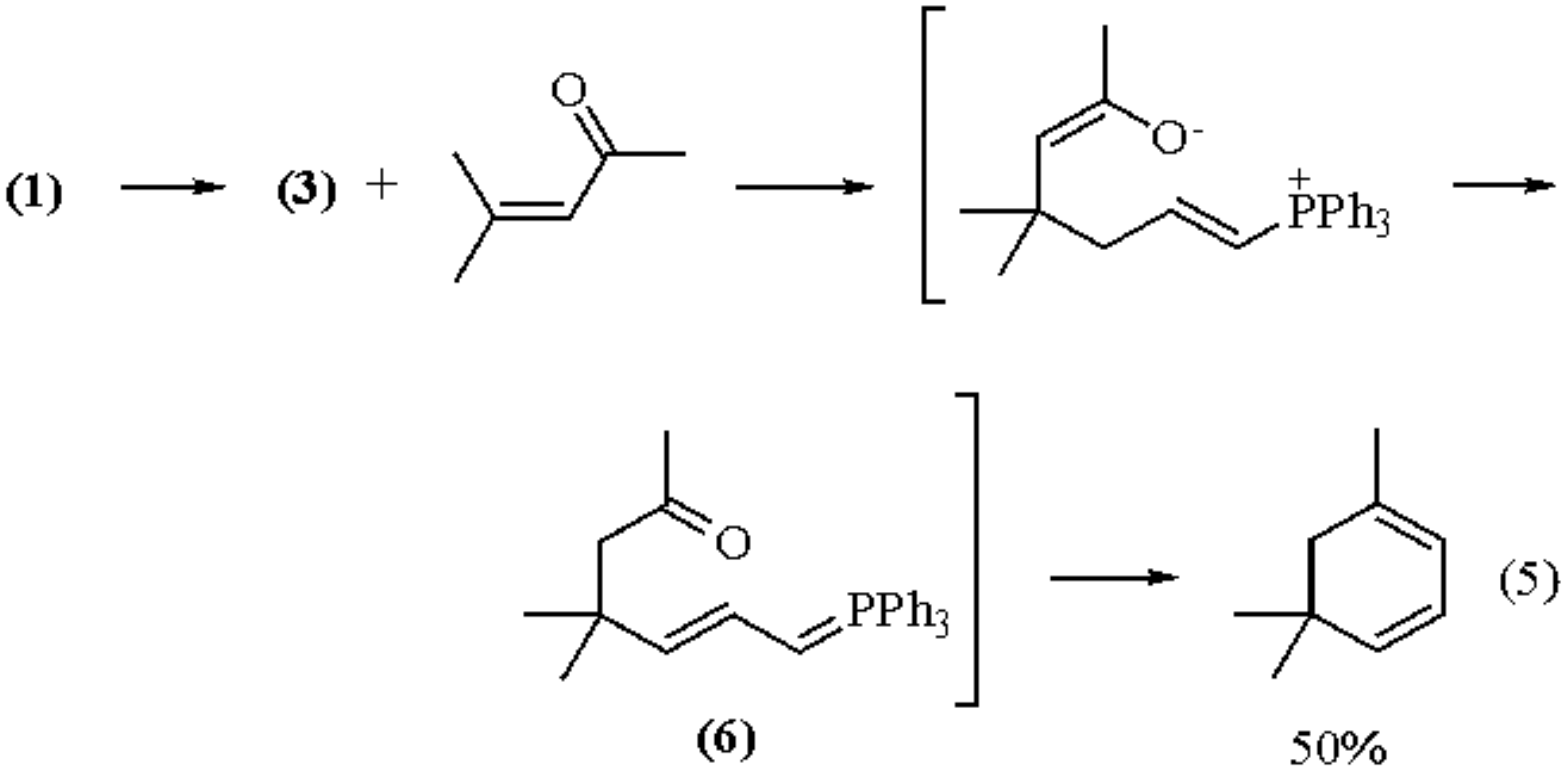

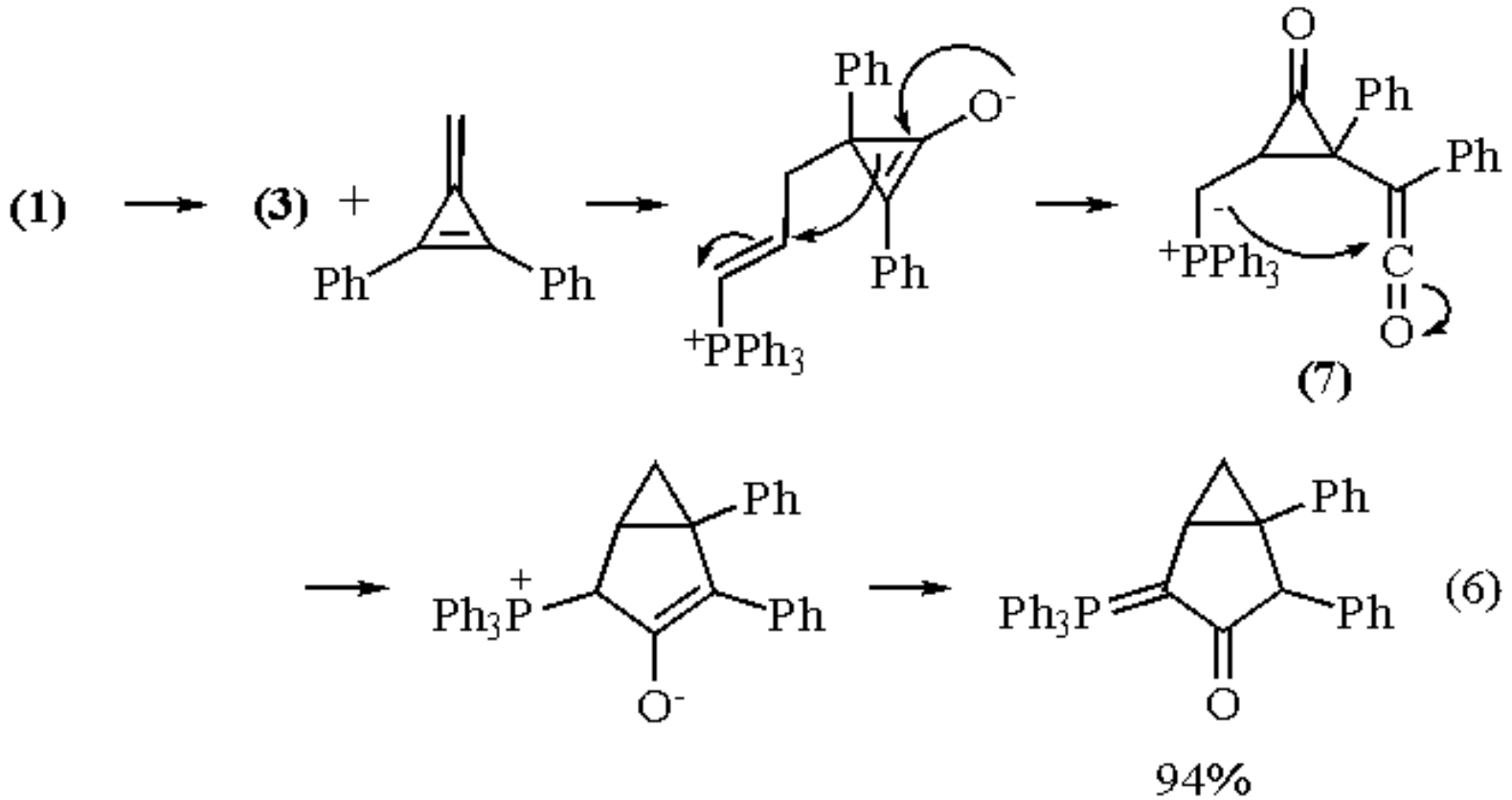

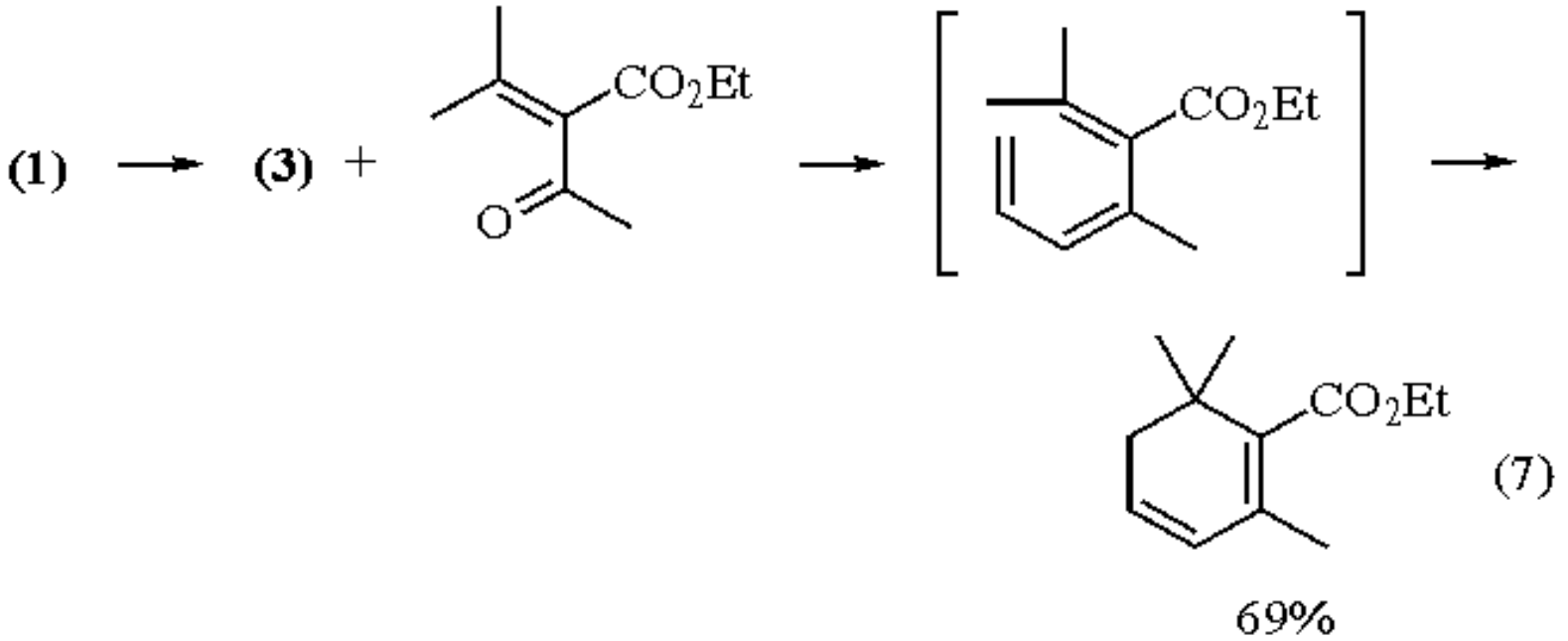

Although this last example is depicted as a Wittig alkenation reaction followed by electrocyclization, it is possible that, as with the example illustrated by eq 5,[15] the reaction involves a γ-addition followed by reylidation and then Wittig alkenation. There is an example of a Wittig alkenation of a ketonic function (a cyclohexanone moiety) by (**3**);[8b] however, there are numerous cases where a compound containing both aldehydic and ketonic functional groups only yields a product from the reaction of the former group.[7c,8d,8e] The ylide (**3**) is generally too stable to react with ketones.

The dianionic phosphonium species (or ylidic anion) (**8**) has been formed by treating (**1**) with 2 equiv of *n*-BuLi.

Reaction with a carbonyl followed by aqueous acid quenching gives a product which arises from γ-addition and alkenation (eq 8).[7n]

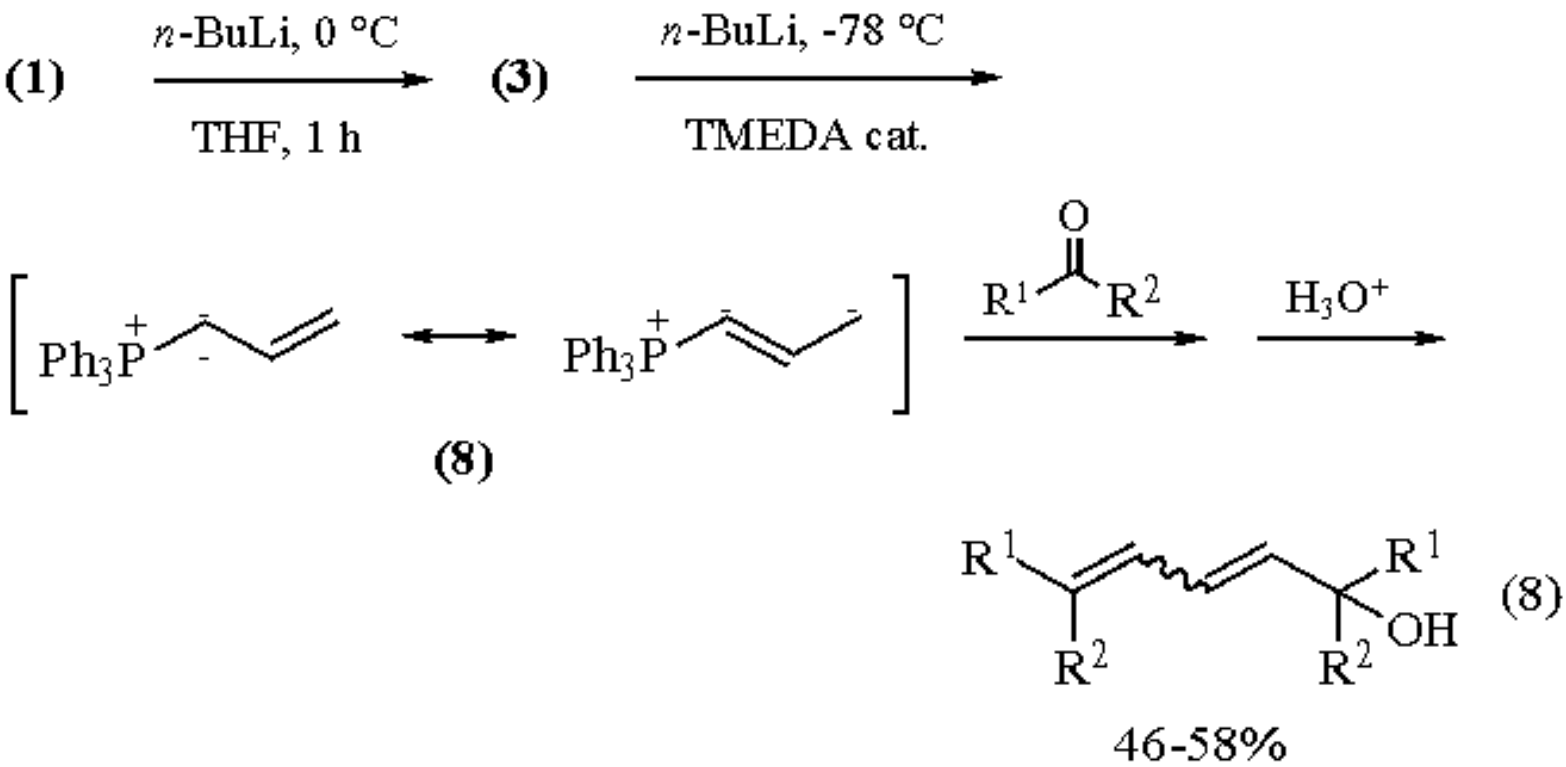

Addition of methyldichlorosilane to the double bond of (**1**) has been observed (eq 9).[18] Some high-yield syntheses of π-allylphosphonium ylide complexes have been reported.[19]

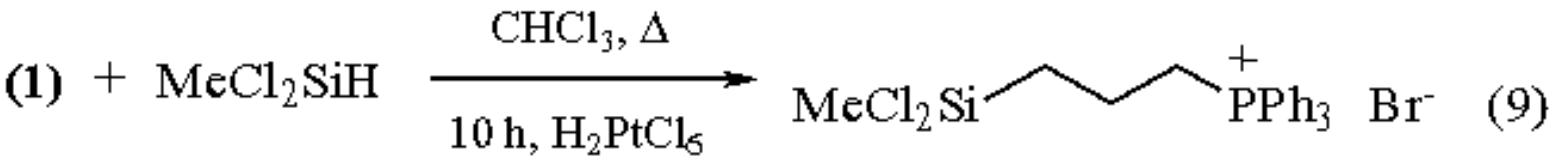

With respect to the geometric isomerism of alkenes formed from (**3**), no definitive studies have been undertaken. However, the majority of the products reported gave (*Z*):(*E*) ratios ranging from 60:40 to 100% (*Z*).[7a,7d,7e,7h,7i,7l,8e,13b,13d,20] Three papers reported (*Z*):(*E*) ratios near[10] or at 1.[2a,21] A few papers reported (*Z*):(*E*) ratios around 40:60[7f,8a,12,22,23] or smaller.[11] Altering the solvent polarity was said to change the (*Z*):(*E*) ratio from 20:80 to 70:30; however, no details were reported.[8a]

Related Reagents.

Allyldiphenylphosphine Oxide.

---

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Allyltriphenylstannane[1]

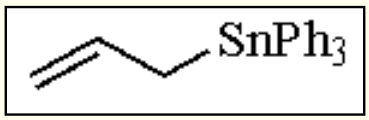

[76-63-1] · $C_{21}H_{20}Sn$ · Allyltriphenylstannane · (MW 391.08)

(widely used allylating agent as an allyl anion equivalent directly or by transmetalating to other allylmetals,[2,3] radical chain transfer reagent, and source of allyl radical[4])

Alternate Names: allyltriphenyltin; (2-propenyl)triphenylstan-nane.

Physical Data: mp 73-74 °C (recryst. from ligroin).[5]

Solubility: sol THF, methylene chloride, chloroform, and benzene.

Form Supplied in: white solid in over 97% purity (microanalysis).

Analysis of Reagent Purity: CH microanalysis, IR,[6] ^{1}H,[7] or ^{13}C NMR spectroscopy.

Handling, Storage, and Precautions: poison by intravenous route; ivn-mus LD_{50}: 100 mg kg^{-1};[8] no significant reactivity with aqueous systems. Use in a fume hood.

Generation of Allyllithium.

Allyllithium may be generated effectively upon treatment of allyltriphenyltin with ***Phenyllithium*** in ether.[2,3] The resulting allyllithium may be further converted into allylboronate complexes upon treatment with trialkylboranes.[3]

Lewis Acid-Mediated Allylation Reactions.

Although allyltriphenyltin has been extensively used as a reagent for nucleophilic allylation under Lewis acid catalysis,[1] it does not appear to offer a particular advantage in terms of yield and reactivity when compared with the same reaction with ***Allyltributylstannane*** (e.g. eq 1).[9]

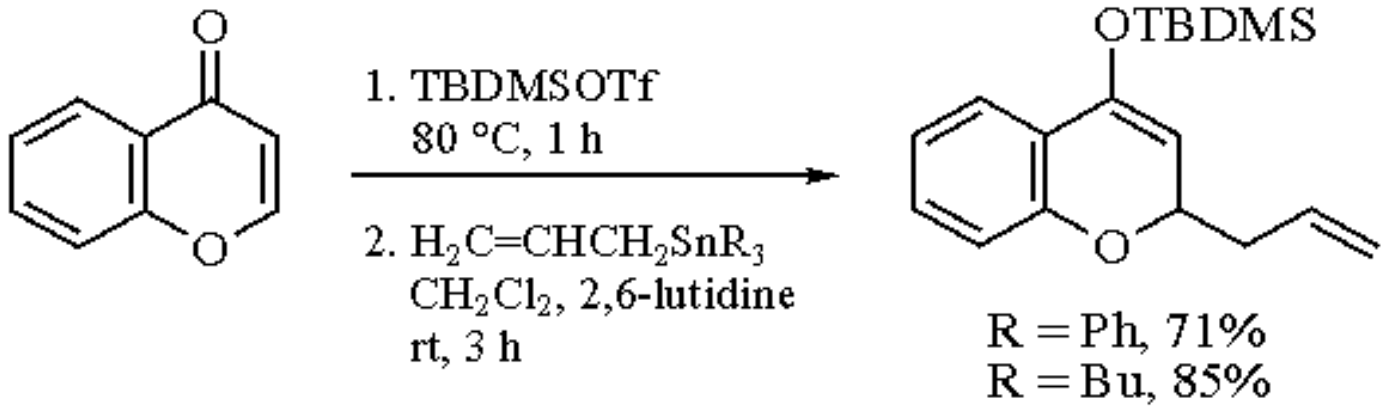

(1)

A number of highly stereoselective allylation reactions have been developed which involve treatment of Lewis acid-chelated α- or β-heteroatom substituted aldehydes with allytriphenyltin. While α-benzyloxy aldehydes undergo allylation favoring *anti* adducts in the presence of ***Tin(IV) Chloride*** (eq 2), α-thiomethyl aldehydes produce allylated products with high *syn*/*anti* ratios (typically, 94-97:6-3) in excellent yield.[10] β-Alkoxy aldehydes give rise to allyl adducts generally with high *anti* selectivity (e.g. eq 3).[10] Variations in *anti/syn* ratio caused by the different protecting groups as well as Lewis acids have been rationalized on the basis of the conformational preferences of the chelated α-alkoxy aldehydes.[11a] The highly 1,3-diastereoselective allylation reaction has been applied to the total synthesis of (-)-colletol.[11b]

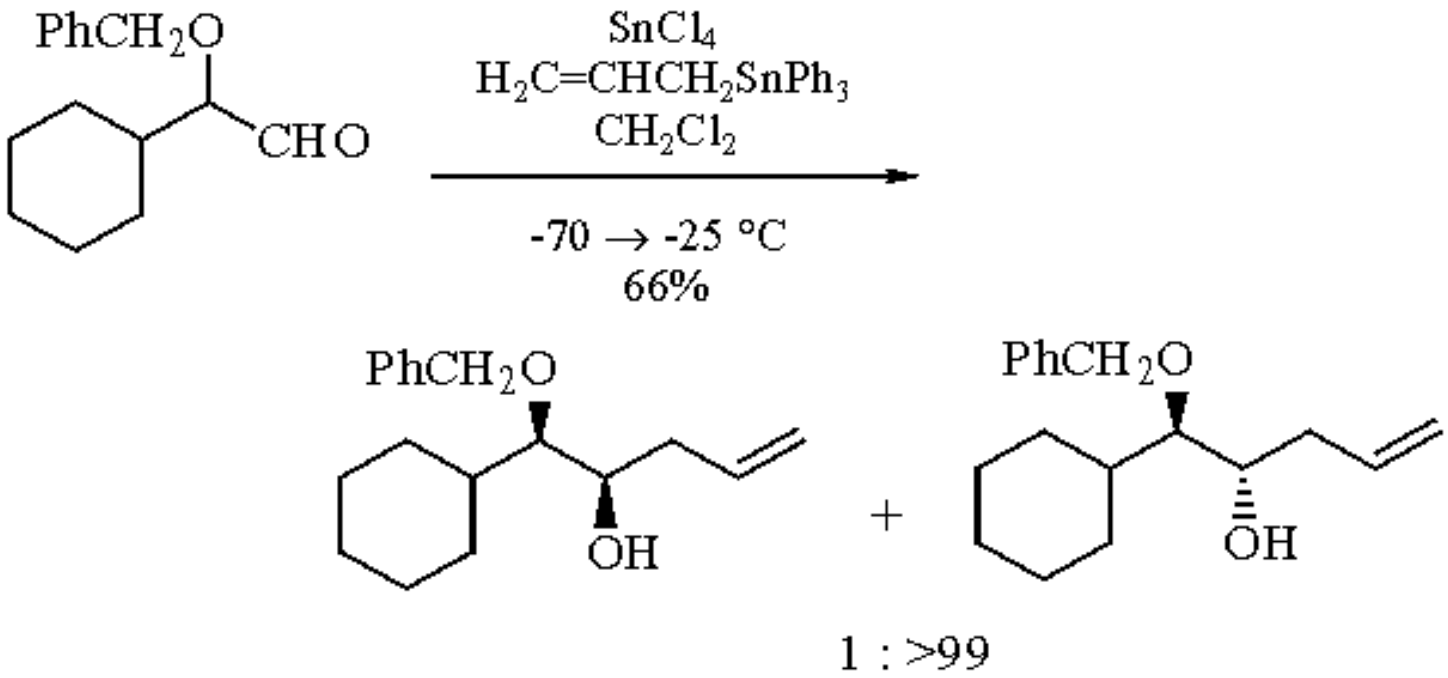

(2)

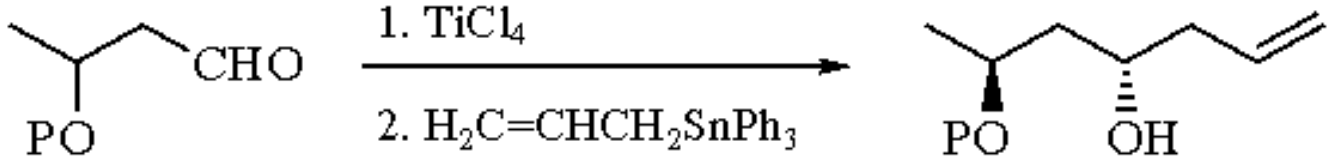

(3)

P	*anti*/*syn*
MTM	2:1
BOM	9:1
$PhCH_2$	29:1

An allyl group is added stereoselectively to chiral dioxane acetals upon reaction with allyltriphenyltin in the presence of ***Titanium(IV) Chloride***/***Titanium Tetraisopropoxide***, although the use of allyltributyltin in place of allyltriphenyltin gives better diastereoselectivity (eq 4).[12] A $TiCl_4$ catalyzed Michael-type addition of an allyl group onto 1-nitroalkadienes followed by addition of ***Triethylamine*** provides a nitrile oxide equivalent which undergoes intramolecular 1,3-dipolar cycloadditions to give isoxazolines (eq 5).[13] A novel [3 + 2] cycloaddition involving allylstannanes and α,β-unsaturated acyliron complexes has also been reported[14] (see ***trans-Cinnamyltributylstannane***).

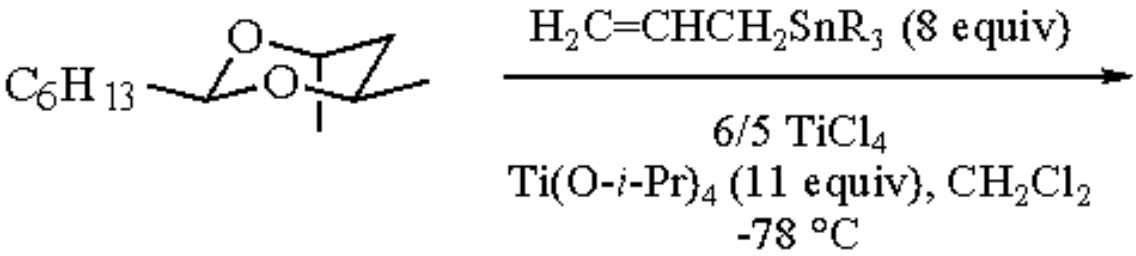

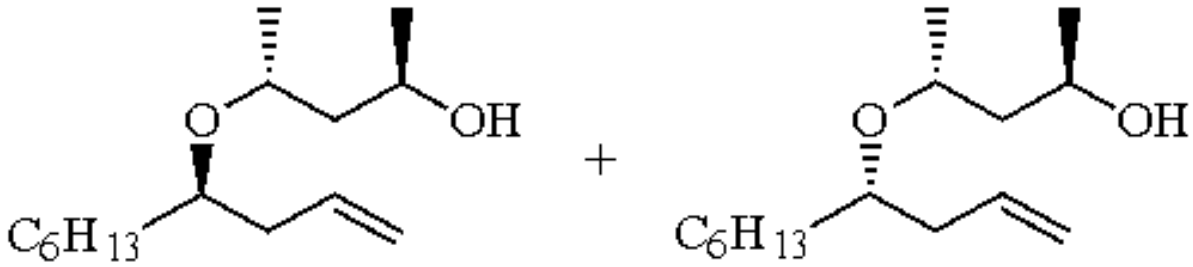

(4)

R = Ph, 100%	90:1
R = Bu, 100%	270:1

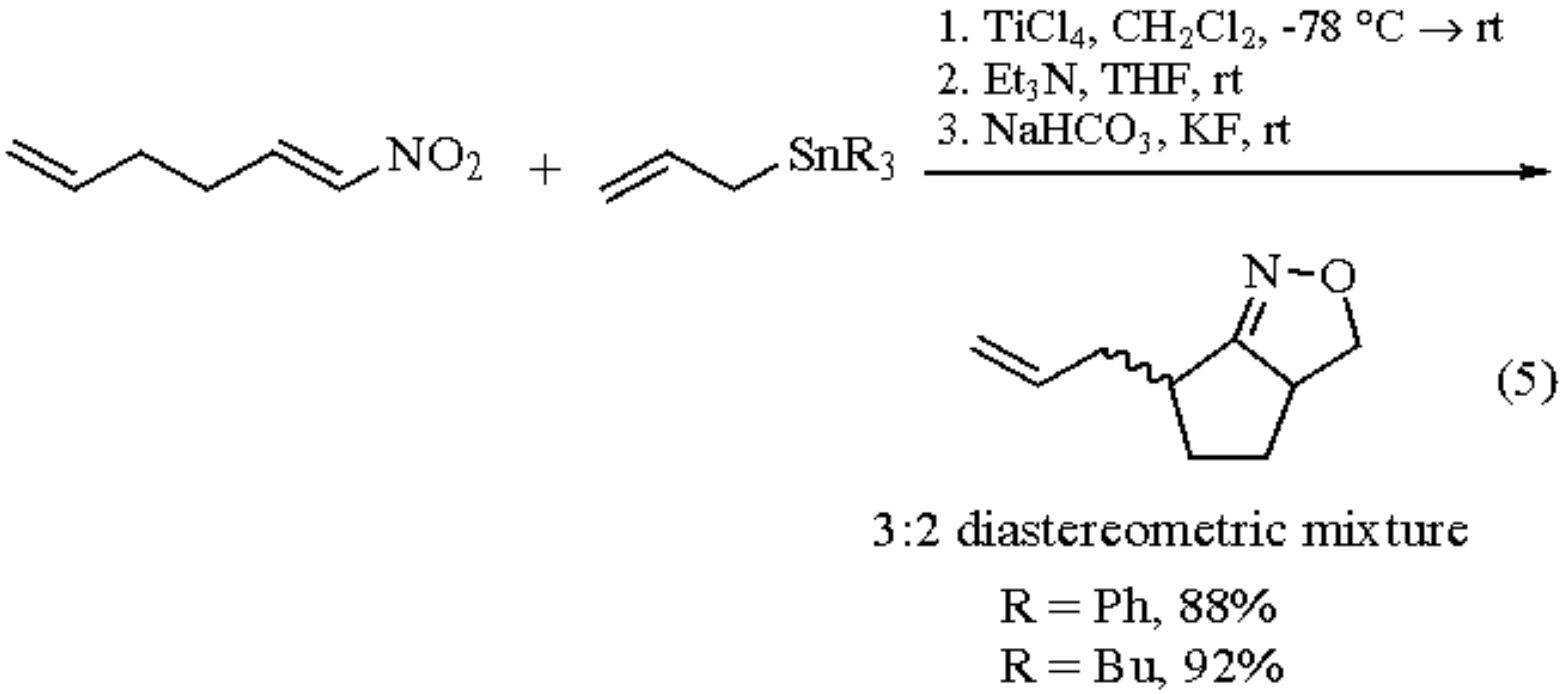

Allyltriphenyltin can serve as an excellent radical chain transfer agent as well as a source of an allylic radical, as shown in eq 6.[4] Interestingly, when ***Triphenylstannane*** is used instead of allyltriphenyltin, a mixture of α- and β-methylcepham is obtained (eq 7).[4]

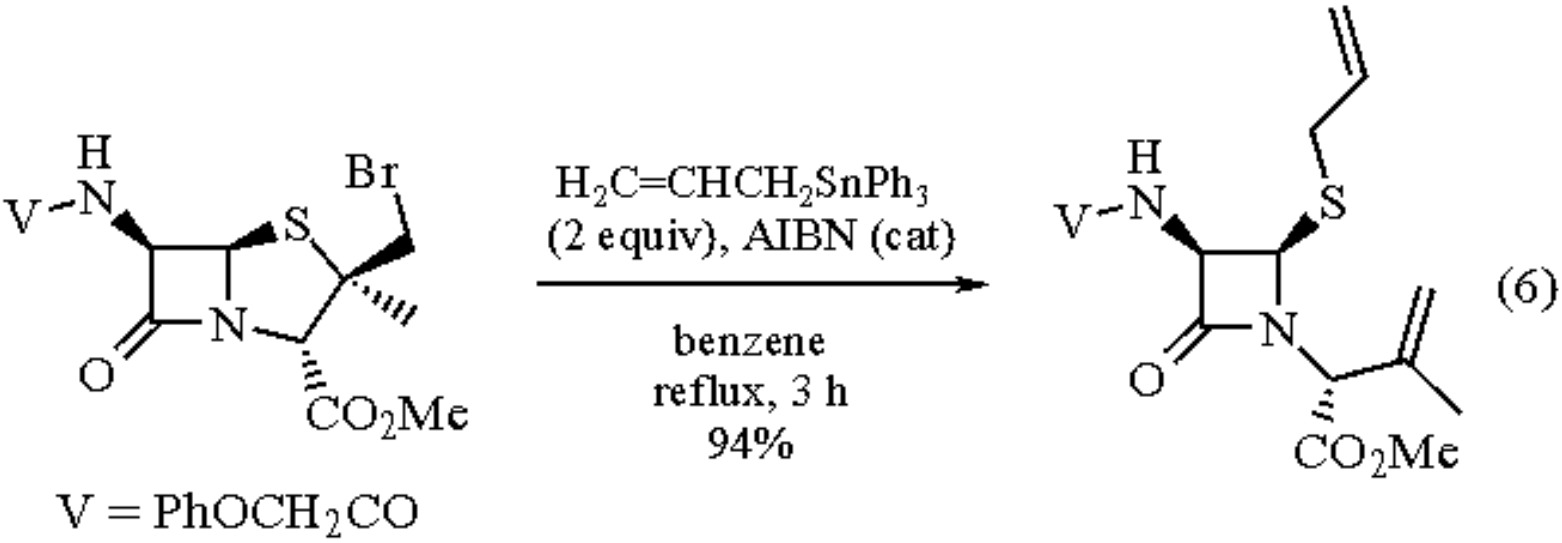

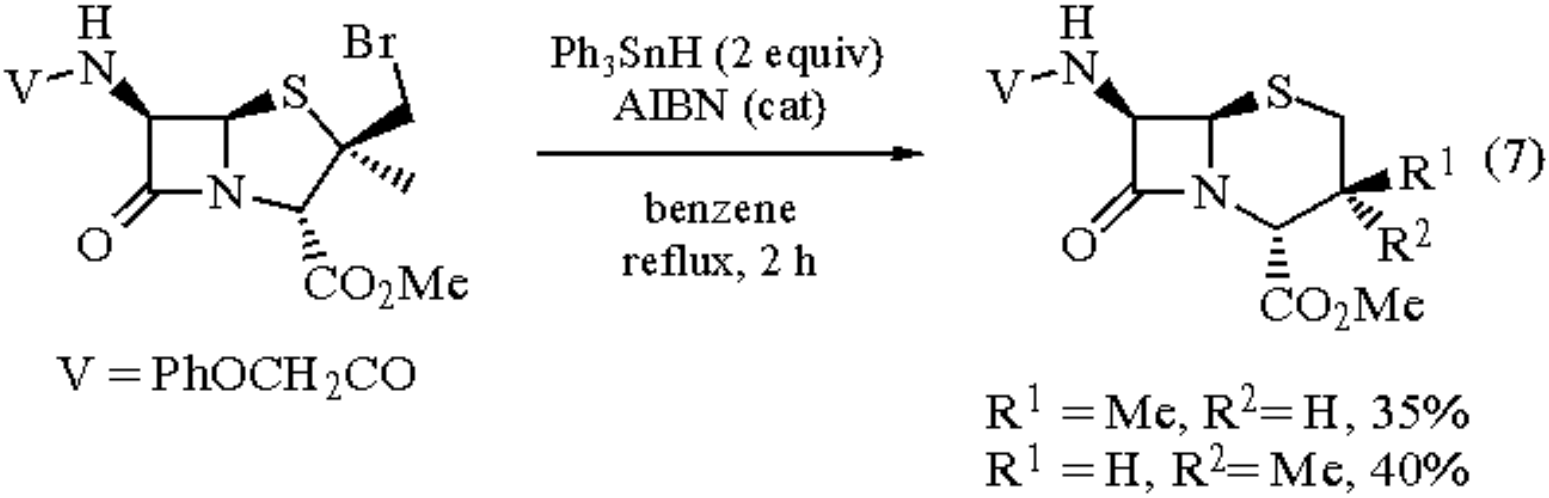

Related Reagents.

B-Allyl-9-borabicyclo[3.3.1]nonane; ***Allyltributylstannane***.

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Alumina[1]

Al_2O_3

[1344-28-1] · Al_2O_3 · Alumina · (MW 101.96)

(a mildly acidic, basic, or neutral support for chromatographic separations; a reagent for catalyzing dehydration, elimination, addition, condensation, epoxide opening, oxidation, and reduction reactions)

Alternate Name: γ-alumina.

Physical Data: mp 2015 °C; bp 2980 °C; *d* 3.97 g cm^{-3}.

Solubility: slightly sol acid and alkaline solution.

Form Supplied in: fine white powder, widely available in varying particle size (50-200 µm; 70-290 mesh), in acidic (pH 4), basic (pH 10), and neutral (pH 7) forms. *Drying:* the activity of alumina has been classified by the Brockmann scale into five grades. The most active form, grade I, is obtained by heating alumina to 200 °C while passing an inert gas through the system, or heating to ~400 °C in an open vessel, followed by cooling in a dessicator. Addition of 3-4% (w/w) water and mixing for several hours converts grade I alumina to grade II. Other grades are similarly obtained (grade III, 5-7%; grade IV, 9-11%; grade V, 15-19% water).[2,3]

Handling, Storage, and Precautions: inhalation of fine mesh alumina can cause respiratory difficulties. Alumina is best handled under a fume hood and stored under dry, inert conditions.

Introduction.

Alumina is one of the most widely used packing materials for adsorption chromatography and is available in acidic, basic, and neutral forms. Use of the correct type is important to avoid unwanted reactions of the substrate being purified.[1,3] Possessing both Lewis acidic and basic sites, alumina has been found to catalyze a wide range of reactions, generally under conditions that are milder and more selective than comparable homogeneous reactions.[1]

Dehydration and Eliminations.

One of the earliest uses of alumina as a catalyst was for the dehydration of alcohols.[4,5] These reactions generally require high temperature and yield primarily non-Saytzeff products. Complex terpenes have been dehydrated with

Pyridine or ***Quinoline*** doped alumina (eq 1).[6b] Numerous other groups can be eliminated in the presence of alumina, including OR, OAc, O_3SR, O_2SR, and halides.[1,7] Some of these eliminations proceed under mild conditions,[1] often during chromatographic purification (eq 2).[7d] Sulfonates can be eliminated in the presence of acid and base sensitive groups, without skeletal rearrangements. However, a large excess of properly activated alumina is required, and poor stereo- and regiocontrol are observed.[7e] Dehydrohalogenations, particularly dehydrofluorinations, occur readily over alumina (eq 3).[8] Stereoselective syntheses of vinyl halides have been developed that take advantage of desilicohalogenation[9] or deborohalogenation[10] of vinylsilane or vinylboronic acid derived dihalides. Benzol[*c*]thiophene has been synthesized by dehydration of a sulfoxide precursor.[11] The oxidation of selenides to selenoxides and their elimination to alkenes can be accomplished in one step using basic alumina and ***t-Butyl Hydroperoxide*** in THF.[12]

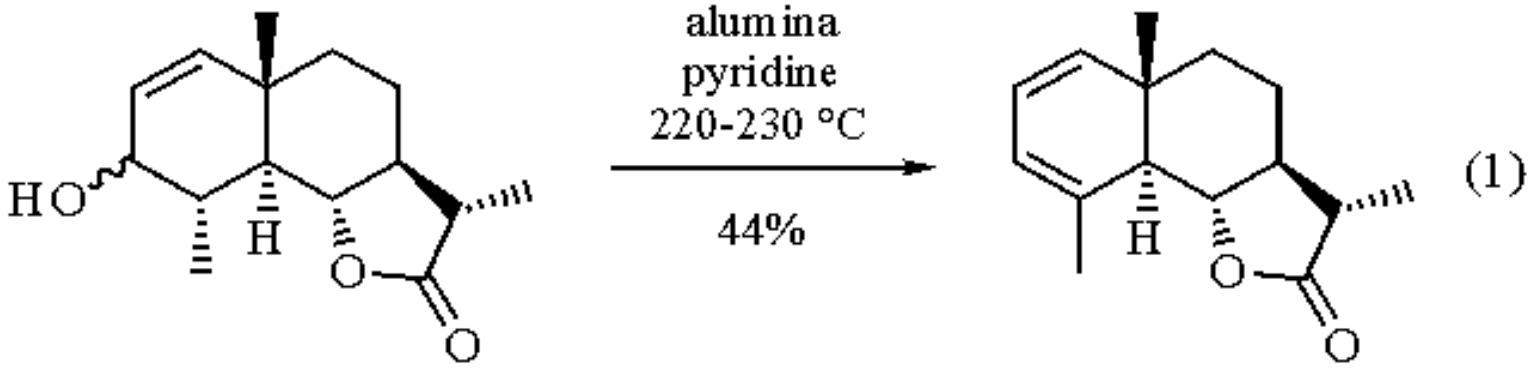

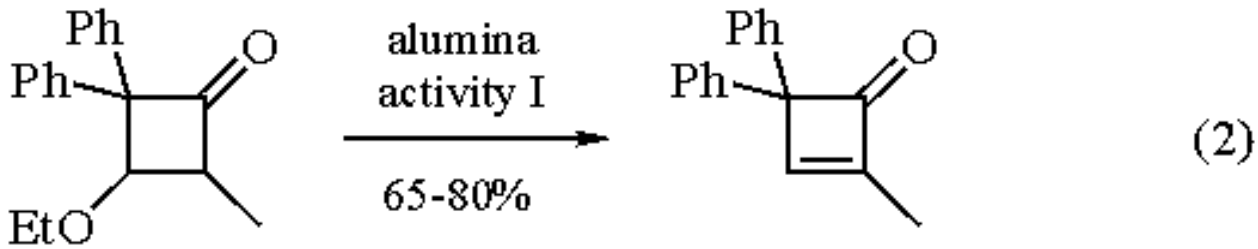

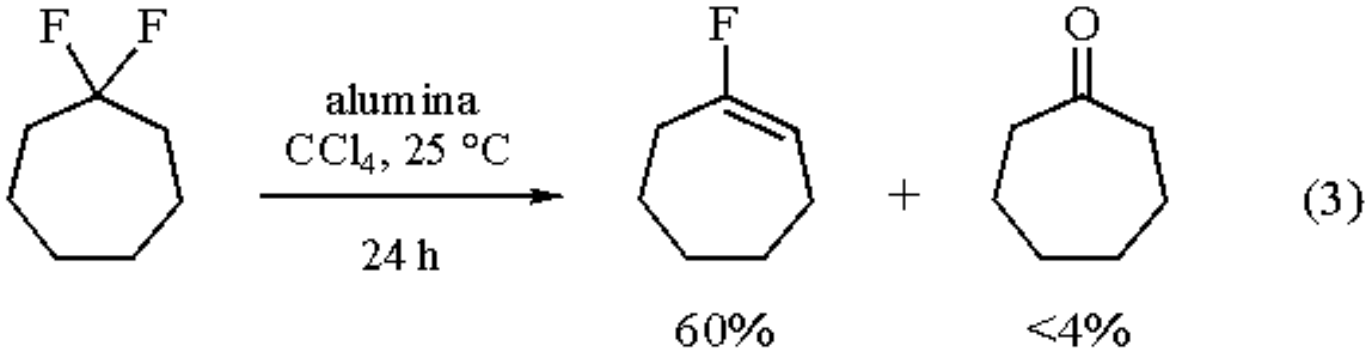

Alumina has been used for various dehydration reactions, including those leading to piperidines,[13] pyrroles (eq 4) and pyrazoles,[14] and other heterocycles.[15] It is also an effective catalyst for the selective protection of aldehydes in the presence of ketones.[16]

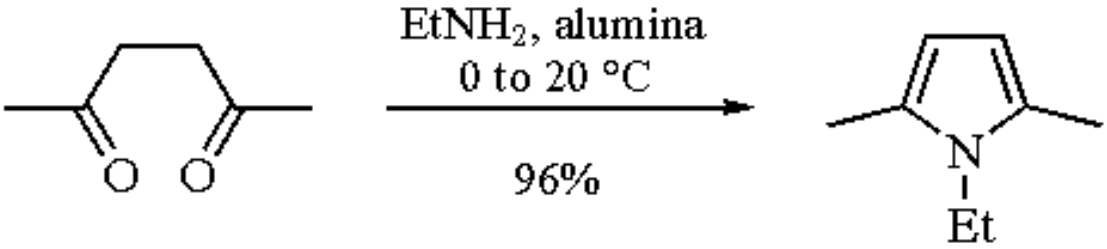

(4)

Addition and Condensation Reactions.

Alumina promotes the addition of various heteroatom species, whether by electrophilic or nucleophilic processes. In contrast to the elimination reactions described earlier, alumina also promotes the intramolecular addition of OH and OR groups to isolated (eq 5)[6c] and carbonyl-activated alkenes.[17] It is also reported to catalyze the conjugate addition of other nucleophiles, such as amines.[18] In the presence of alumina, ***Iodine*** can be used to iodinate aromatics, hydroiodinate alkenes, and diiodinate alkynes (eq 6).[19] Hydrochlorinations and hydrobrominations of alkenes and alkynes give the Markovnikov products, with good stereoselectivity.[20]

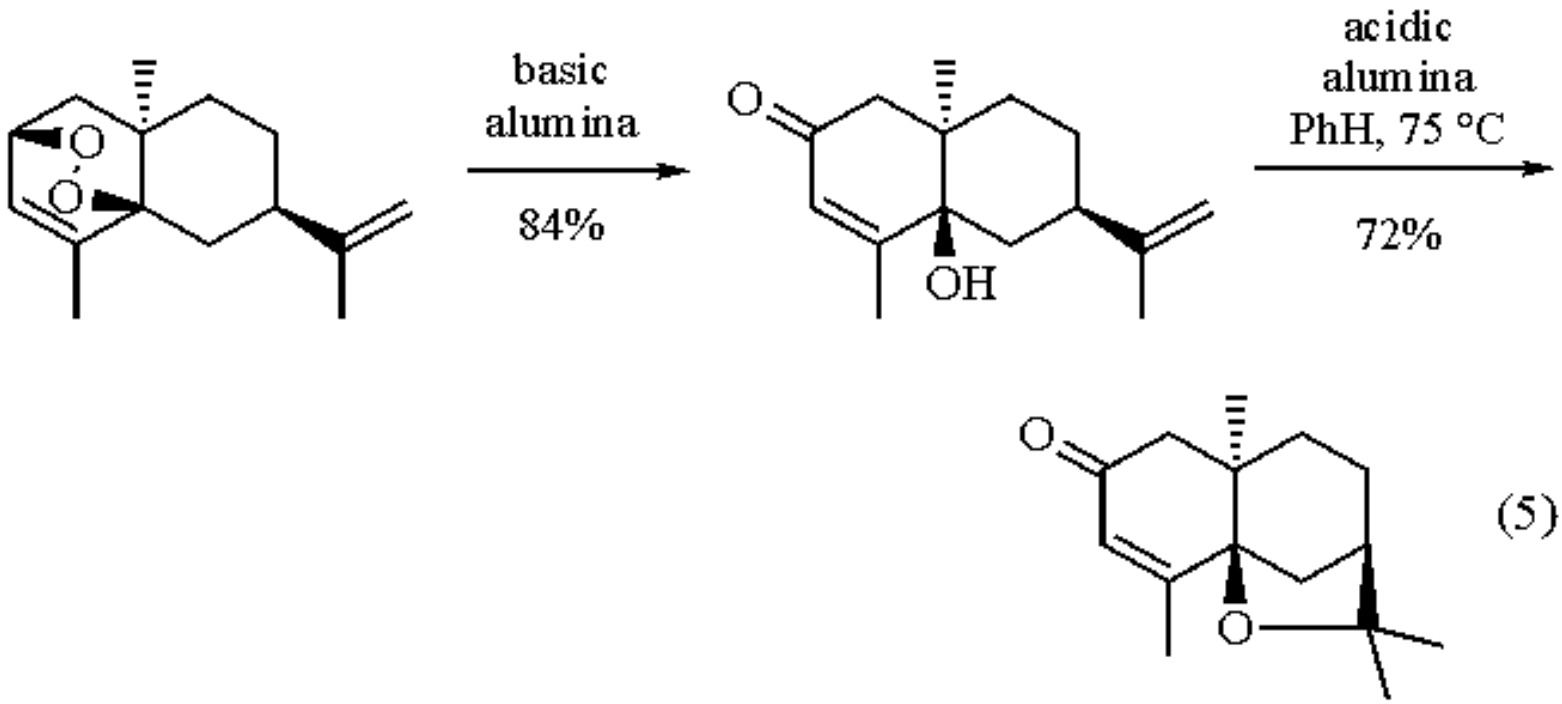

(5)

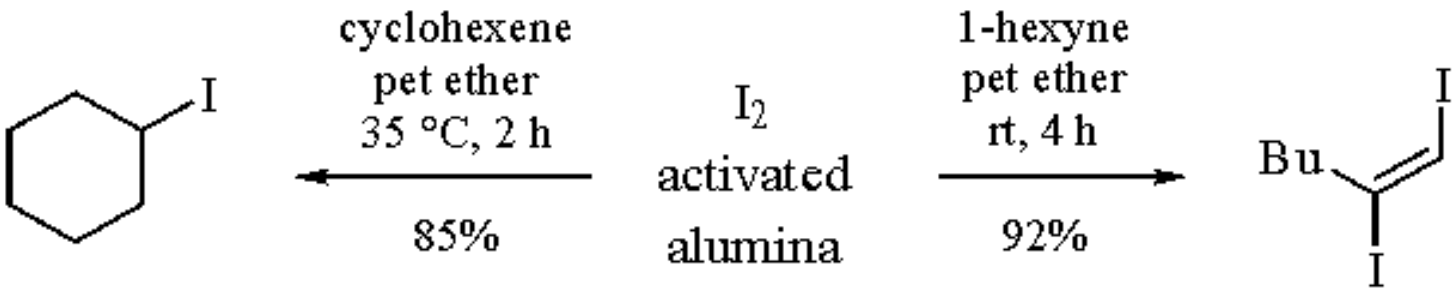

(6)

Aldol-type condensations between aldehydes and various active methylene compounds,[21] Michael reactions (eq 7),[22] as well as Wittig-type reactions[23] can be carried out on alumina under mild conditions, often without a solvent. An

interesting nitroaldol reaction-cyclization sequence gives 2-isoxazoline 2-oxides with good diastereoselectivity (eq 8).[24]

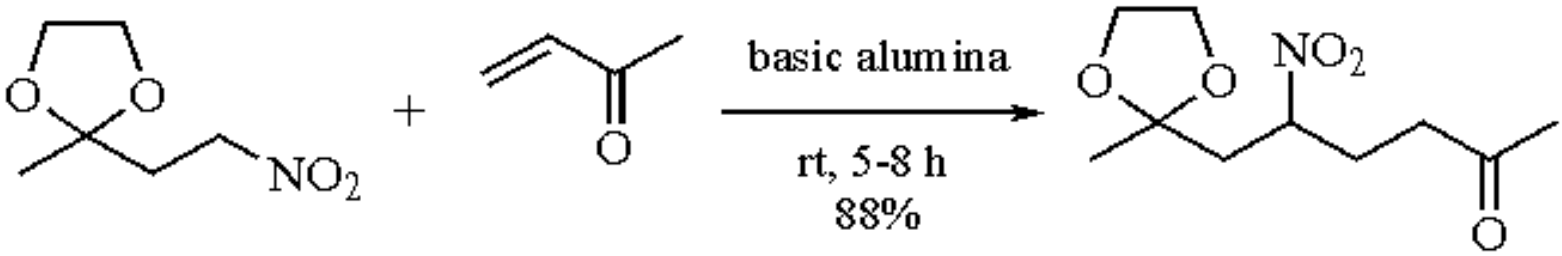

(7)

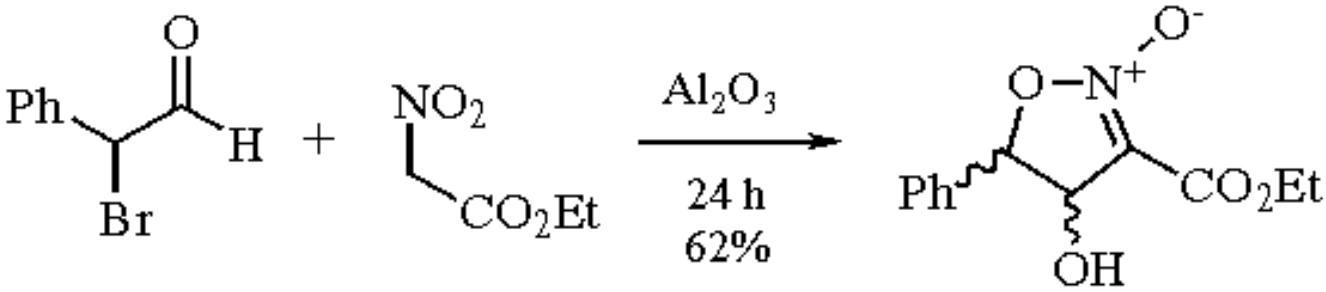

(8)

trans:*cis* = 9:1

Orbital symmetry controlled reactions that have been promoted by alumina include the Diels-Alder,[25] the ene,[26] and the Carroll rearrangement.[27] These reactions proceeded under milder conditions and with greater stereoselectivity. In a spectacular example, chromatographic purification promoted a diastereoselective intramolecular Diels-Alder that produced the verrucarol skeleton (eq 9).[25b]

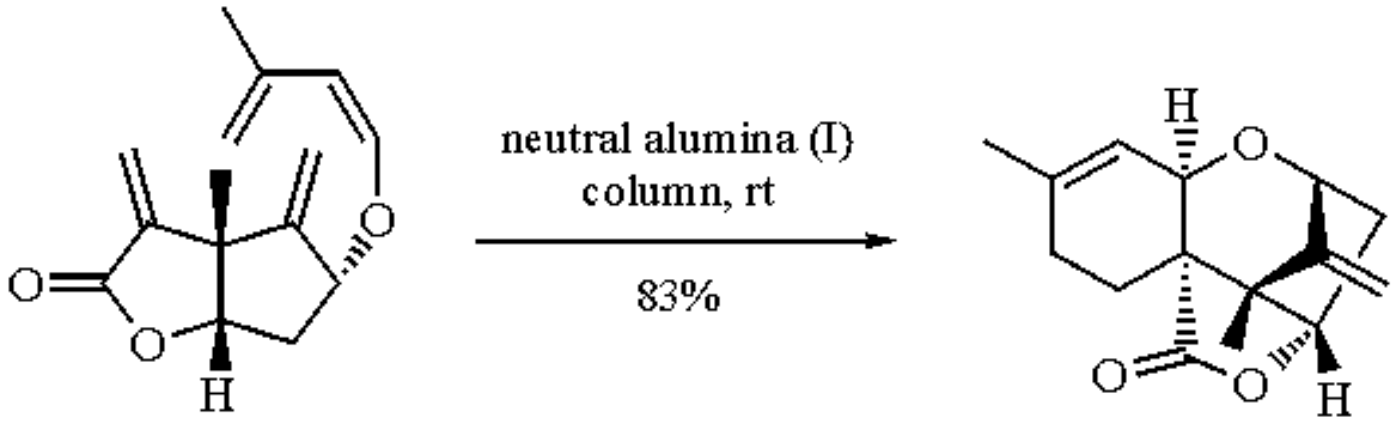

(9)

Alkylation reactions that have been induced by alumina include per-*C*-methylation of phenol,[28] intramolecular alkylation to yield a spiro-fused cyclopropane,[29] and *S*-[30] and *O*-alkylations (eq 10).[31] The activation of ***Diazomethane*** by alumina has provided methods for the conversion of ketones to epoxides[32] and for the selective monomethylation of dicarboxylic acids.[33] Basic alumina has been used for the generation and trapping of dichlorocarbene.[34]

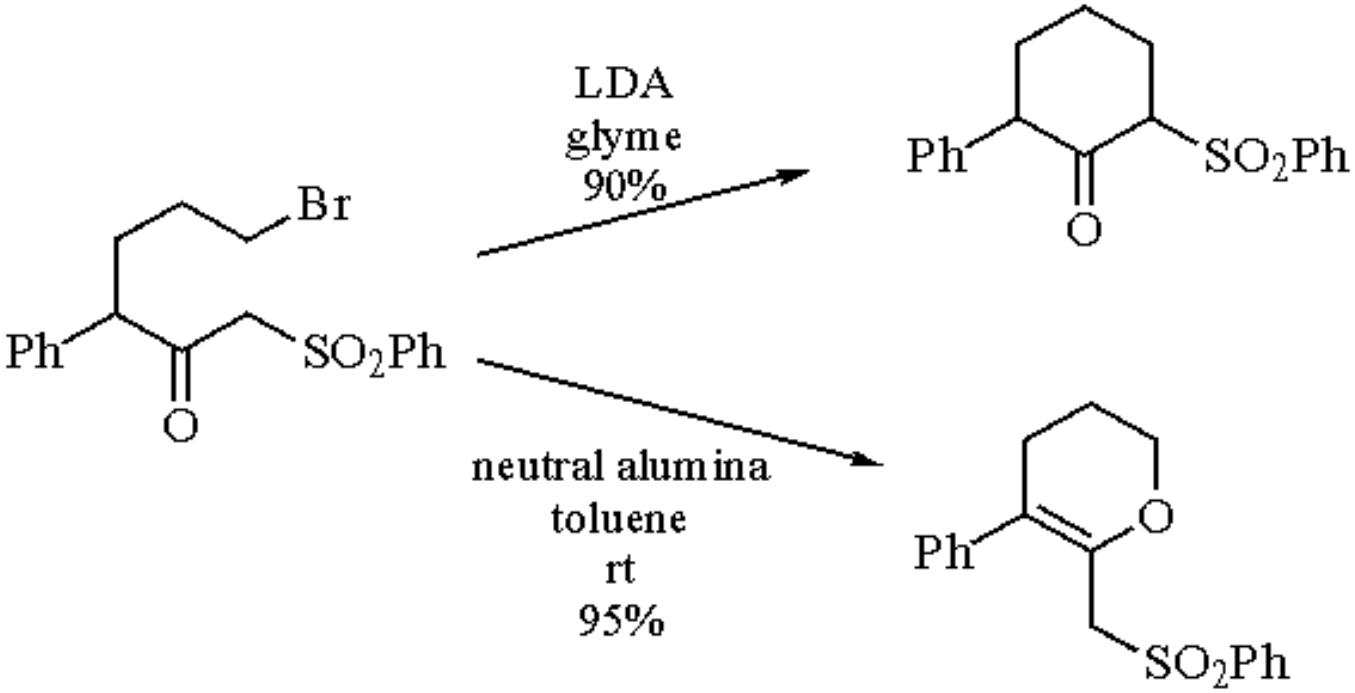

(10)

Epoxides.

Epoxides can be opened under mild, selective conditions using alumina impregnated with a variety of nucleophiles, such as alcohols, thiols, selenols, amines, carboxylic acids (eq 11),[35] and peroxides.[36] Use is made of this process in a route to (*Z*)-enamines (eq 12).[37] Formation of C-C bonds by intramolecular opening of epoxides has been reported (eq 13),[38] as have alumina catalyzed epoxide formations[23,39] and rearrangements.[40]

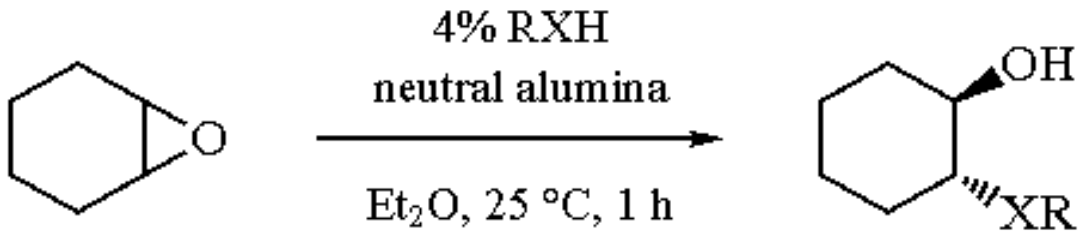

(11)

RX = MeO, 66%; PhS, 70%, PhSe, 95%; *n*-BuNH, 73%

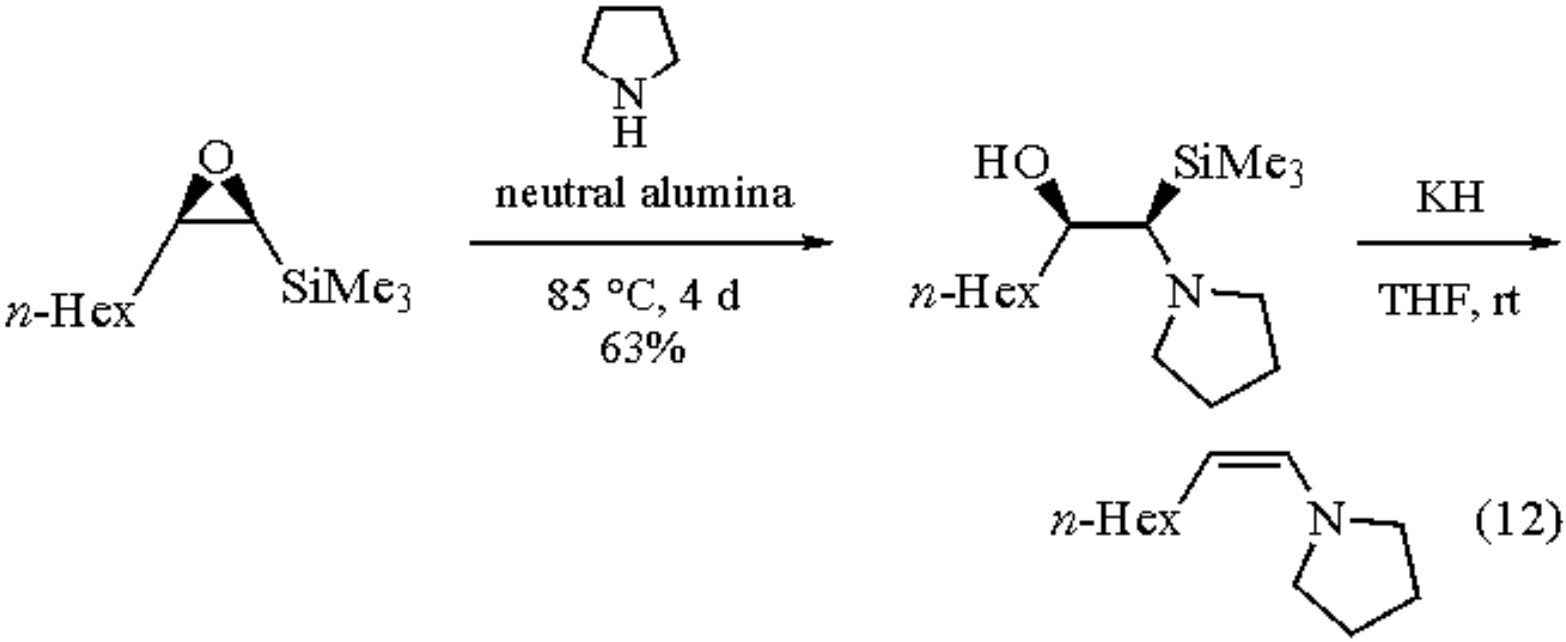

(12)

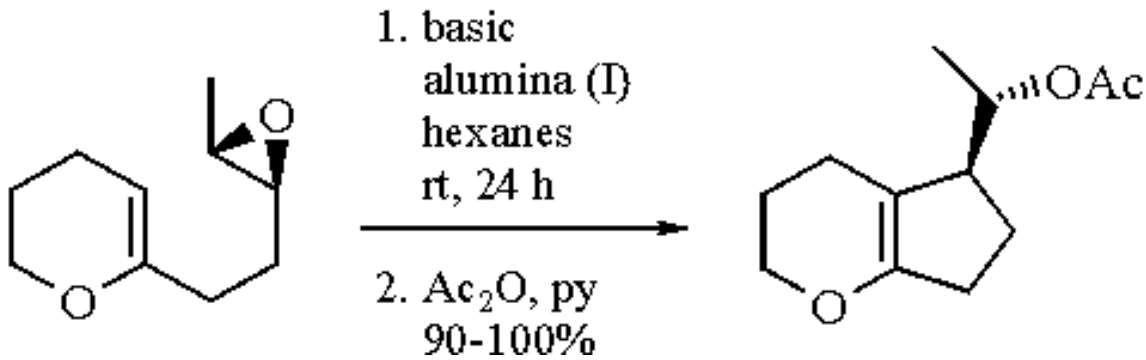

(13)

Oxidations and Reductions.

Posner has shown that Oppenauer oxidations, with Cl_3CCHO or PhCHO as the hydrogen acceptors, are greatly accelerated in the presence of activated alumina.[41] Secondary alcohols are oxidized selectively over primary alcohols (eq 14) and groups susceptible to other oxidants (sulfides, selenides, and alkenes) are unaffected. Even cyclobutanol, which is prone to fragmentation with one-electron oxidants, can be oxidized to cyclobutanone in 92% yield.

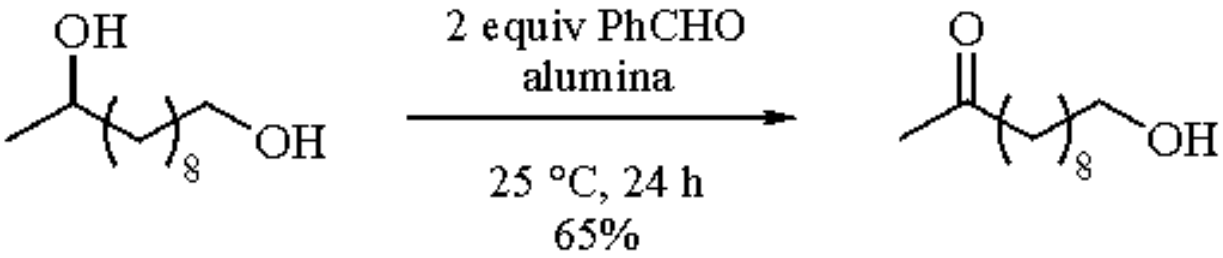

(14)

The complementary reduction reaction (Meerwein-Ponndorf-Verley), using isopropanol as the hydride donor, is also facilitated by alumina and allows the selective reduction of aldehydes over ketones.[42] Functional groups that survive these conditions include alkene, nitro, ester, amide, nitrile, primary and secondary iodides, and benzylic bromide.

Air oxidation of a fluoren-9-ol to the fluoren-9-one and thiols to disulfides are accelerated on the alumina surface.[43] Alumina has also been used as a solid support for a variety of inorganic reagents,[44] and for immobilizing chiral catalysts.[45]

Miscellaneous Reactions.

Many rearrangements are catalyzed by alumina.[1] The Beckmann rearrangement[46] of the *O*-sulfonyloxime shown gives the expected amide with activated alumina, and the corresponding oxazoline with basic alumina (eq 15).[46d] Alumina has long been used for isomerization of β,γ-unsaturated ketones to the conjugated ketones.[47] Isomerizations of alkynes to allenes,[48] and allenes to conjugated dienoates[49] have also been reported (eq 16).

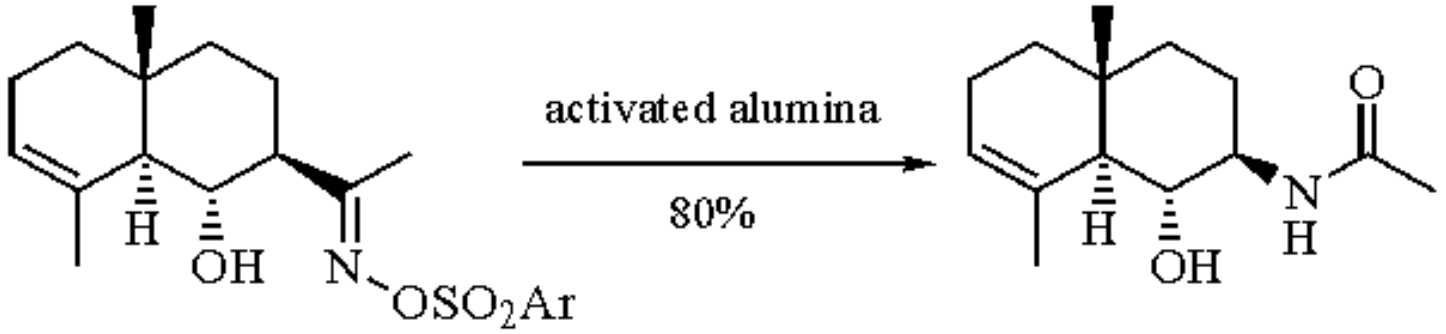

(15)

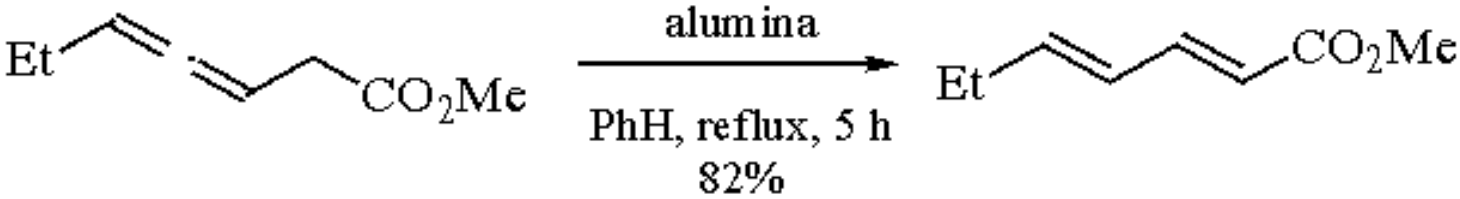

(16)

Alumina promotes the hydrolysis of acetates of primary alcohols,[50] the deacylation of imides,[51] the hydrolysis of sulfonylimines,[52] and the decarbalkoxylation of β-keto esters and carbamates.[53] It can also be used for acylations and esterifications, with high selectivity for primary alcohols over secondary alcohols.[54]

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Aluminum[1]

Al

[7429-90-5] · Al · Aluminum · (MW 26.98)

(reducing agent for many functional groups;[1] can aluminate double bonds[2] or insert into carbon-halogen bonds; promotes propargylation of carbonyl compounds; in combination with metallic Sn or $PbBr_2$ mediates Barbier-type allylation of carbonyl compounds or imines)

Physical Data: mp 660.37 °C; bp 2467 °C; *d* 2.702 g cm^{-3}; *E*°(aq) Al^{3+}/Al^0 = -1.66 V.

Solubility: reacts with dil HCl, H_2SO_4, KOH, and NaOH, hot AcOH; insol conc HNO_3.

Form Supplied in: silver-white, malleable, ductile metal; widely available in foil, granules, ingot, pellets, powder, rod, shot, wire.

Handling, Storage, and Precautions: Al foil is moisture sensitive, powder is moisture sensitive and flammable. Aluminum is reputed to be practically nontoxic.

Functional Group Reductions.

Aluminum will reduce ketones or aldehydes to alcohols or saturated hydrocarbons, nitro compounds and Shiff bases to amines, and alkyl halides to alkanes. Aluminum also effects reductive dimerization of ketones and dehalogenation of polyhalogenated compounds. In combination with ***Nickel(II) Chloride*** hexahydrate in THF, metallic Al will reduce acyl chlorides, anhydrides and nitriles, epoxides, and disulfides. Moreover, aluminum exhibits pronounced chemoselectivity in reduction of polyfunctionalized compounds.[3]

Aromatic ketones are especially readily reduced by aluminum. Reduction of 2-methyl-2-phenyl-1-indanone with Al in *i*-PrOH proceeds with diastereoselectivity (*trans*/*cis* ratio in alcohol formed is 90:10) better than that observed with Li, Na, or K.[4] Quinone (**1**) is reduced with Al in 85% H_2SO_4 to the 6,13-dihydro product (**2**) (eq 1) while the 6-hydroxy derivative is formed in reaction of (**1**) with Cu in 96% H_2SO_4.[5]

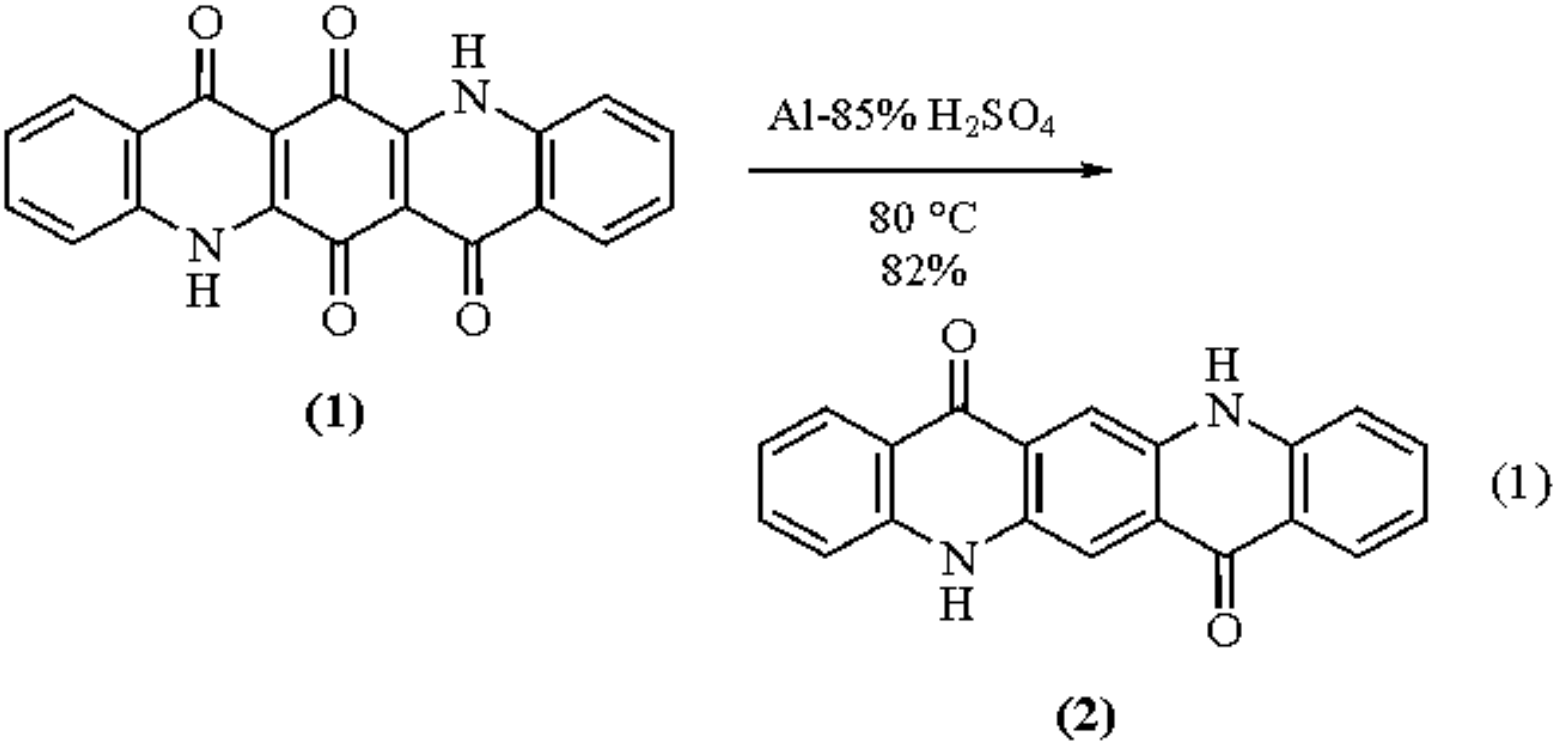

Reductive dimerization of tetralone to 3,3´,4,4´-tetrahydro-1,1´-binaphthyl is mediated by Al foil activated with ***Mercury(II) Chloride***.[6] A facile reduction of aromatic ketones and aldehydes into corresponding alcohols is readily achieved employing Al powder in combination with $NiCl_2.6H_2O$ in THF.[3]

Reduction of (thiazolyl)(acylaminomethyl)ketones with the reagent prepared from Al dissolved in *i*-PrOH in the presence of ***Aluminum Chloride***,[7a] and oxidation of aluminum tris(3-pentanoxide-1,2-d_5) (from the alcohol, Al shot, and a trace of $HgCl_2$) with benzophenone,[7b] can be considered special cases of modified Meerwein-Ponndorf-Verley and Oppenauer reactions.

Aromatic nitro compounds are reduced to anilines with Al powder in AcOH-HCl[8] or with Al-$NiCl_2.6H_2O$.[3] Reactions of nitrobenzene with Al turnings (heating in aq H_2SO_4)[9a] or Al-Fe alloy (in 50% NaOH)[9b] afford *p*-aminophenol and *N*,*N*´-diphenylhydrazine, respectively.

Al foil activated with $HgCl_2$ and Hg is capable of reducing both aliphatic[10a] and aromatic Shiff bases[10b] to secondary amines. For aromatic substrates, the process is substantially complicated by reductive dimerization of the azomethines. It is this particular reagent (not other metals such as Na, Mg, or Zn) that causes unusual ring contractions of lumazines[11a] and pterines[11b] to theophyllines (eq 2) and guanines respectively, via a radical anion formed upon C=N double bond reduction.

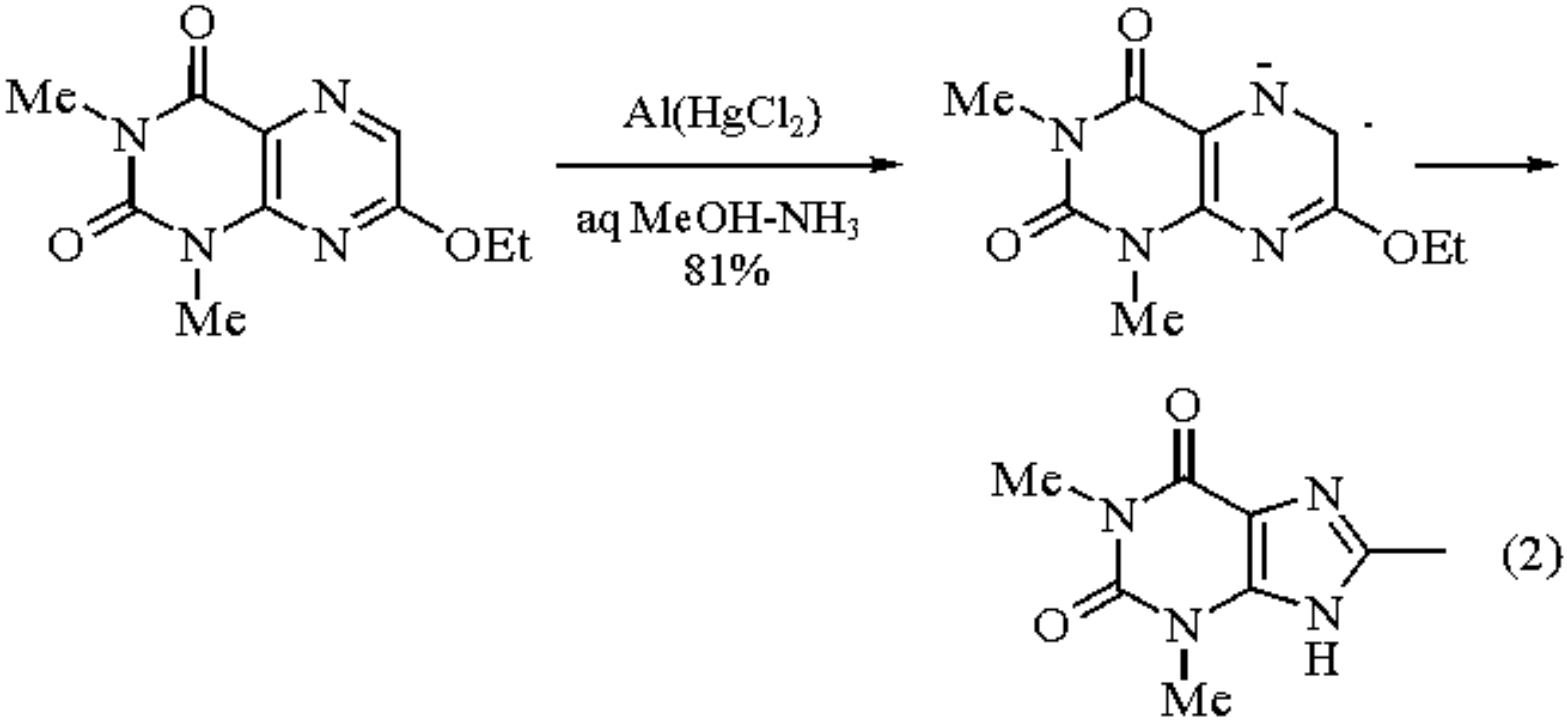

1,2-Dehalogenation occurs when polyhalogenated substrates react with Al turnings in the presence of $AlCl_3$.[12] For alicyclic compounds it is a stereospecific process (eq 3).[12b]

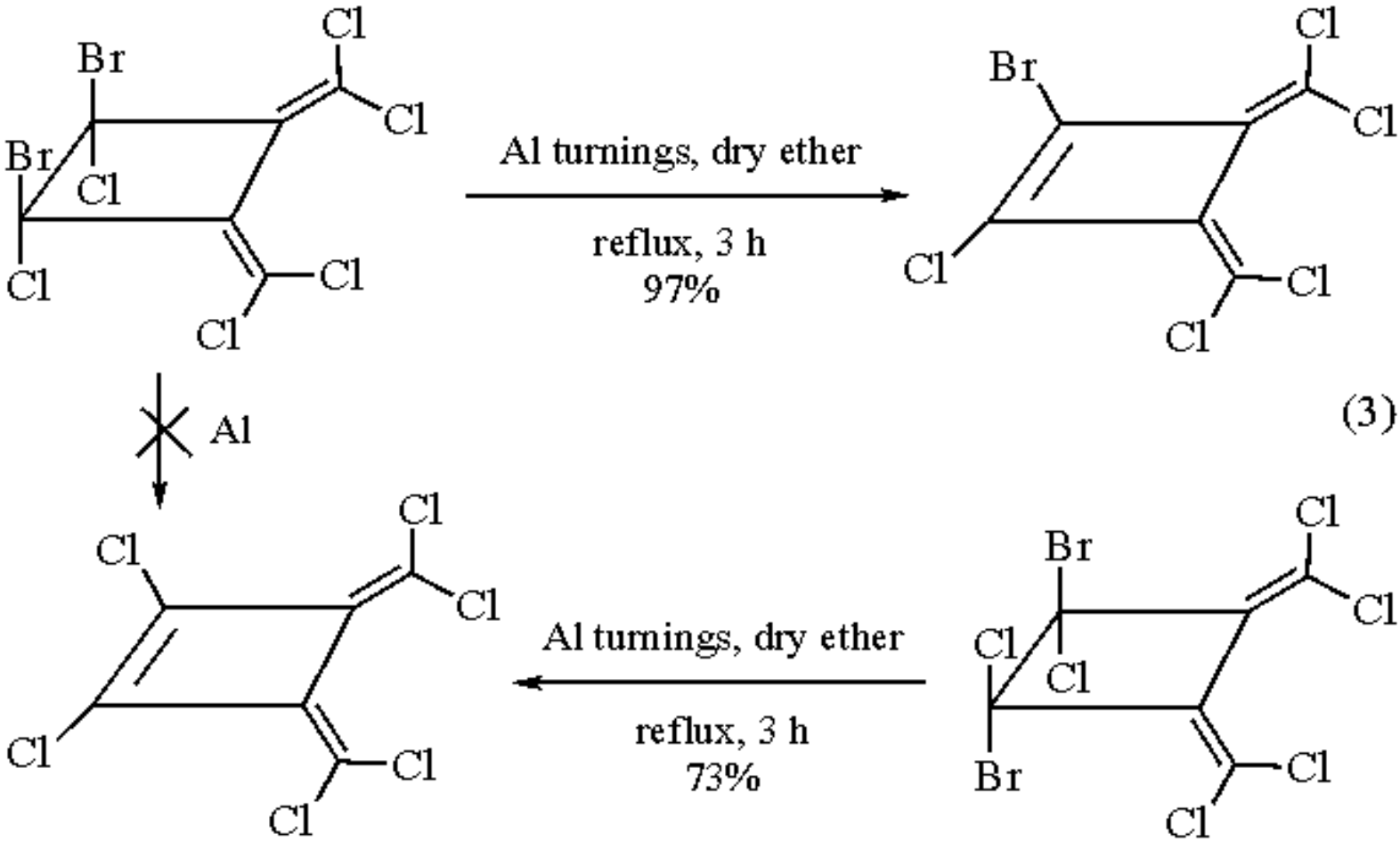

When 2-5% NaOH is added, Al (powder or turnings) reduces 1,1-dibromocyclopropanes or 7,7-dibromonorcaranes

into monobromides with modest *cis* or *exo* stereoselectivity.[13] A small amount of Al powder promotes halide exchange and 3-chlorophthalide is converted almost quantitatively into 3-bromophthalide in a reaction with dry HBr.[14]

On refluxing with an excess of an alkyl or aryl halide, Al inserts into the carbon-halogen bond.[15] Primarily a mixture of sesquihalides (**3**) is formed (eq 4).[15] With alkyl halides,[16] the sesquihalide mixture formed in situ can be easily reduced to produce trialkylaluminum compounds (eq 5).[16c] In case of aryl halides, (**3**) is an excellent reagent for transfer of an aryl moiety from Al to other elements (P, Sn) (eq 6).[17] Mixture (**3**) also reacts with organic halides to form organoaluminum compounds. However, a more versatile method of synthesis involves the reductive replacement of Hg from organomercury compounds with Al (eq 7).[18]

$$\underset{X = Cl,\ Br,\ I}{RX} + Al \longrightarrow \underset{\textbf{(3)}}{R_2AlX} + RAlX_2 \qquad (4)$$

$$2\ Al + 3\ Mg + 6\ BuI + 2\ PhOEt \xrightarrow[\substack{90\text{-}105\ ^\circ C \\ 80\%}]{octane} 2\ AlBu_3 \cdot PhOEt + 3\ MgI_2 \qquad (5)$$

$$Ph_3Al_2Cl_3 + PCl_3 \xrightarrow[91\%]{PhCl,\ rt \rightarrow 180\text{-}200\ ^\circ C,\ 2\ h} Ph_3P + 2\ AlCl_3 \qquad (6)$$

$$3\ [H_2C{=}CH(CH_2)_2]Hg + 2\ Al \xrightarrow[\substack{rt,\ 2\ weeks \\ 100\%}]{sealed\ tube} 2\ [H_2C{=}CH(CH_2)_2CH_2]_3Al + 3\ Hg \qquad (7)$$

Reduction of element-halogen bonds by Al or Al-promoted cleavage of other bonds is widely used in synthesis of organoboron,[19] organosilicon,[20] organogermanium,[21] and organophosphorus compounds,[22] as well as π-complexes of titanium,[23] vanadium,[23b] and zirconium.[24] Al powder in combination with $AlCl_3$ and ***Iodine*** (or ***Iodomethane***) induces borylation of C_6H_6 with ***Boron Trichloride*** to form $PhBCl_2$.[19a] Mixtures of amines and triarylborates are reduced to borazanes by aluminum-iodine.[19b] On electrochemical reduction with a sacrificial Al anode, chlorosilanes undergo dimerization[20a] or cross-coupling if two different chlorosilanes react.[20b] Tetraalkylgermanes are cleaved by the system Al-I_2 to yield iodogermanes.[21]

A mild and neutral reducing system of Al-$NiCl_2$.6H_2O-THF reduces enones to saturated aldehydes (eq 8),[3] nitriles to amines, acid chlorides and anhydrides to aldehydes, disulfides to thiols, and epoxides to the alcohols. Isolated double bonds, carboxylic acids, esters, lactones, primary, benzyl and allyl halides, aliphatic aldehydes and ketones as well as aliphatic nitro compounds are inert to this agent.[3]

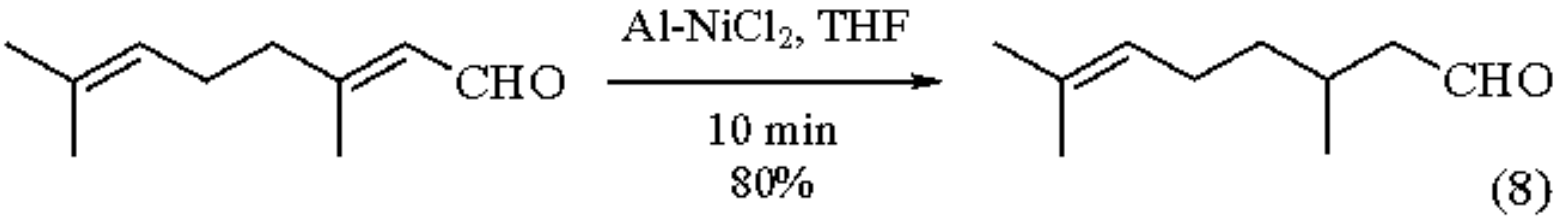

In combination with ***Antimony(III) Chloride***, metallic Al smoothly reduces both aliphatic and aromatic aldehydes to alcohols (yield 50-98%). Reduction proceeds chemoselectively and PhCHO is preferably reduced in competition with PhCOMe. Unlike Al-$NiCl_2$, reduction of α,β-unsaturated aldehydes with this system occurs only at the C=O group, leaving C=C double bonds intact.[25]

Reactions of Aluminum Alkoxides and Phenoxides.

A facile method of alcohol dehydration is based on thermal decomposition of the derived Al alkoxide which, depending on the alcohol structure, commences in the range of 200-270 °C.[26] Al foil ($HgCl_2$-activated) in *i*-PrOH promotes deoxygenation of epoxides, giving the corresponding alkenes.[27]

Friedel-Crafts Alkylation Catalyst.

Aluminum catalyzes *ortho*-alkylation of anilines and phenols with alkenes.[28,29] Preformed aluminum anilides or phenoxides exhibit high susceptibility toward alkene attack and usually *o,o´*-dialkylated products predominate.[29a,b] Selective *ortho*-alkylation of phenol can be accomplished using aluminum soft drink cans as the reagent (eq 9).[28]

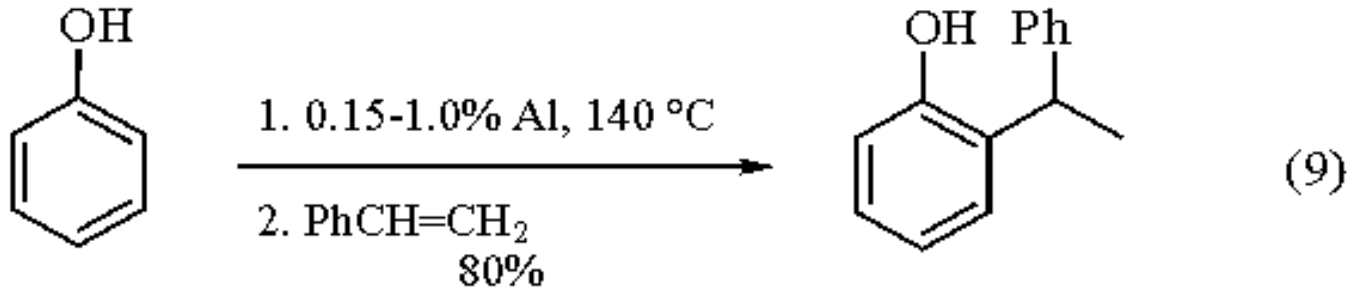

Alumination Agent.

A facile hydroalumination of carbon-carbon double bonds yielding trialkylaluminum compounds takes place in a three-component mixture consisting of an alkene, hydrogen, and Al (eq 10).[2] The process involves intermediate formation of a dialkylaluminum hydride which adds to the third alkene molecule, affording the trialkylaluminum. To elucidate the mechanism of the reaction, direct synthesis of organoaluminum compounds in the condensed phase from

Al vapor and alkene is of noticeable importance.[30]

$$2\,Al + 3\,H_2 + 3\,H_2C{=}CMe_2 \longrightarrow 2\,(Me_2CHCH_2)_3Al \quad (10)$$

Selective Propargylation.

The problem of propargyl group introduction in various substrates without propargyl-allenyl rearrangement has been addressed using alumination (Al in the presence of $HgCl_2$) of propargylic bromides followed by addition of a carbonyl substrate to the organoaluminum reagent formed in situ.[31] This approach has been used to prepare propargylic alcohols from ketones[32a] and aldehydes,[32b] propargylic ethers from α-chloro ethers[33a] and acetals,[33b] acetals of propargylic carbaldehydes from orthoformates (eq 11),[34] homopropargylic ethers and sulfides from chloromethyl ethers and sulfides.[35] Propargylic compounds prepared in this manner have been used in the synthesis of spirilloxanthin, 3,4-dehydro-rhodopin,[32a] ecdysteroid analogs,[35] and lycorine precursors.[36]

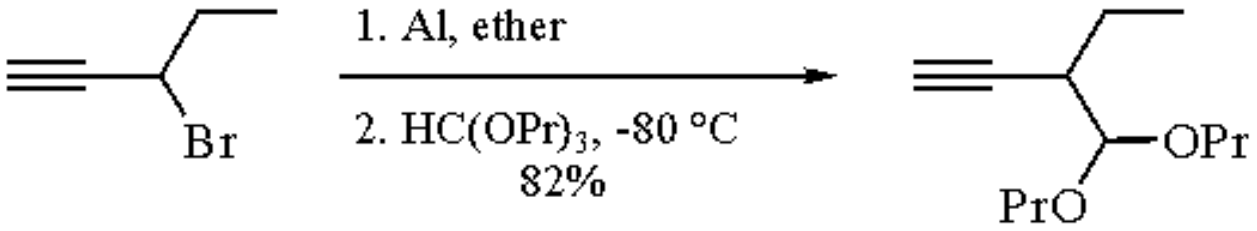

(11)

Aluminum is presumably a unique partner for condensations of this type because, for example, Zn always gives a mixture of alkynic and allenic alcohols.[31,32a]

Aluminum-Tin(0) and Aluminum-Tin(II) Systems.

A strong impetus for current applications of Al in organic synthesis has resulted from a study on allylation of carbonyl compounds mediated by the combination of stoichiometric amounts of metallic Al and ***Tin***, and the observation of extensive acceleration in the presence of water.[37] Typical procedures suggest that a carbonyl compound, allylic bromide, Al, and Sn should be used in a ratio 1:1.2-2:1:1. Allylation with unsymmetrically substituted allylic halides proceeds with complete rearrangement in the allylic unit and shows considerable diastereoselectivity (eq 12).[37a] Intramolecular versions of the reaction have been used in syntheses of five- and six-membered cyclic alcohols.[37c]

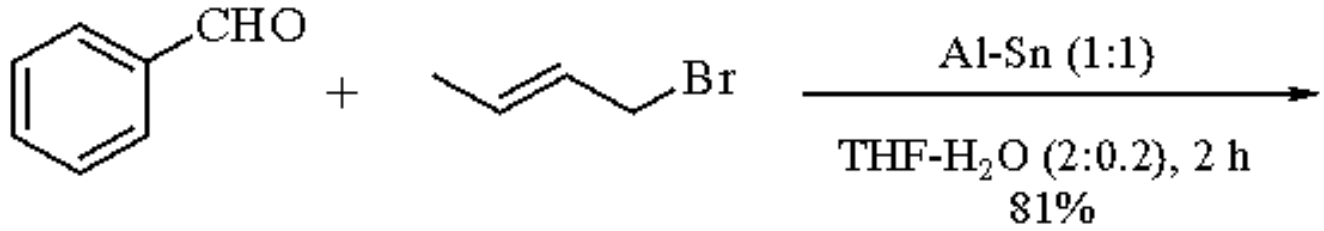

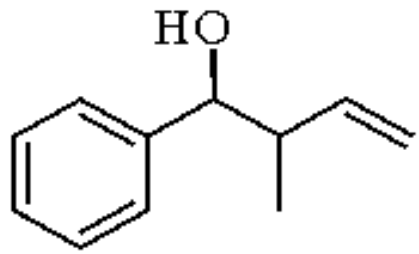

(12)

erythro:*threo* = 78:22

A combination of Al powder (2 equiv) and ***Tin(II) Chloride*** (0.1 equiv) in an organic solvent is even more active than the Al-Sn couple and addition of water to the solvent enhances the allylation rate remarkably.[38] Carbonyl compounds are almost inert to allylation if 1 equiv of Al and only 0.1 equiv of Sn is used,[38] whereas metallic Sn or $SnCl_2$ in aprotic solvents convert allylic halides to allylstannanes in situ, which readily allylate carbonyl substrates[39] with complete rearrangement in the entering allylic unit.[39a] It has been established that Al effects both oxidative addition of metallic Sn to allyl halide and reductive regeneration of Sn^0 from Sn^{II} and Sn^{IV} for a recycle use.[38] Thus all allylation reactions in Al-Sn or Al-Sn^{II} systems can be considered as aluminum-promoted and tin-recycled processes.

Al-Sn mediated condensation of aldehydes with α-(bromomethyl)acrylates[40] represents a facile synthesis of α-methylene-γ-butyrolactones (eq 13).[40a] This procedure is more efficient than allylations promoted by Cr^{II} (see ***Chromium(II) Chloride*** and ***Lithium Aluminum Hydride***).[40b]

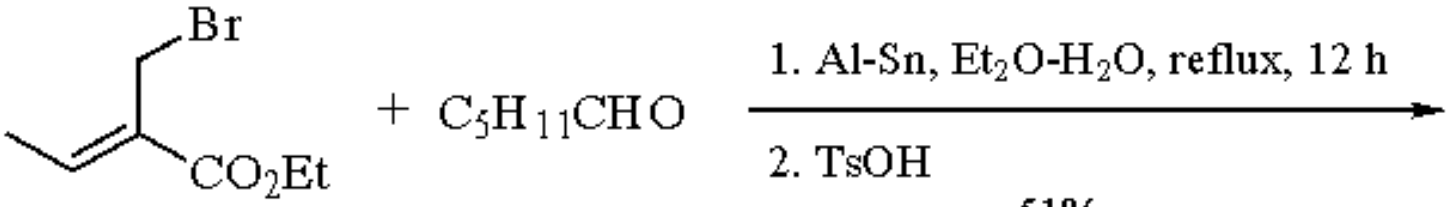

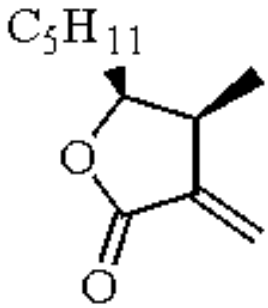

(13)

Almost exclusive *threo* diastereoselectivity is characteristic of the reactions of cinnamyl chloride with aldehydes promoted by Al-Sn[41a] or Al-$SnCl_2$.[41b] Aldehydes containing a chiral center adjacent to the C=O group afford *threo*

Cram and *threo* anti-Cram products with the former predominating (eq 14) in contrast to magnesium-mediated reactions of the same partners, which give all four possible diastereomers.[41a]

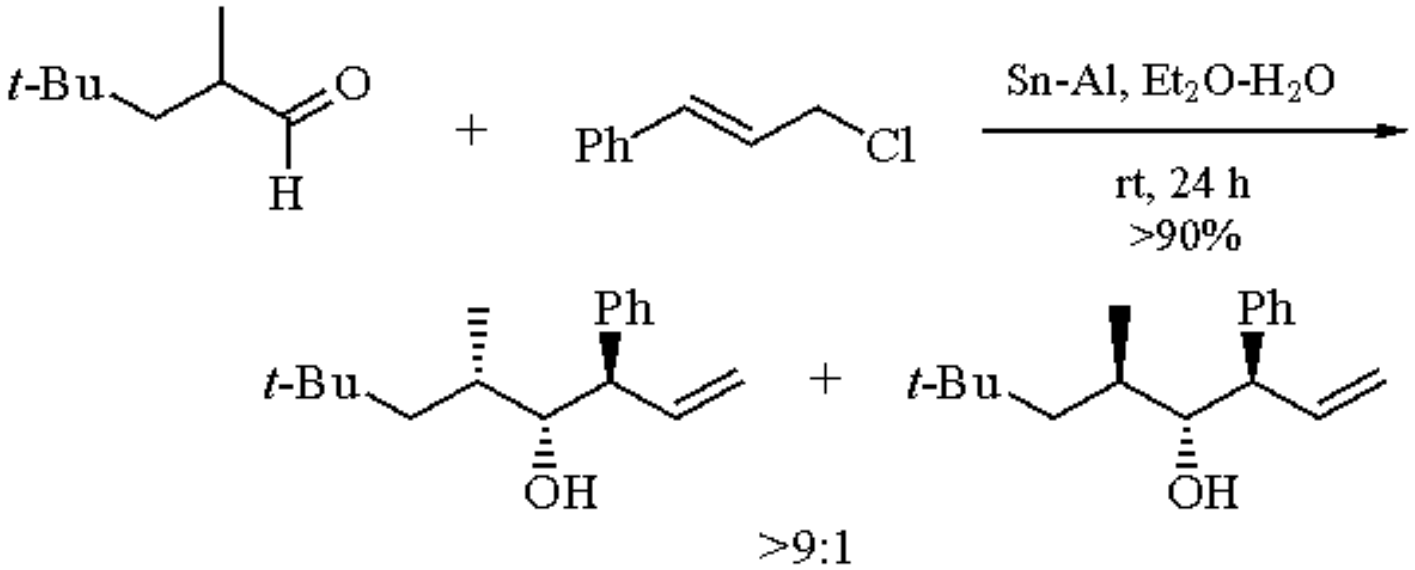

(14)

Unlike other allylation processes mediated by Al-Sn, no isomerization of the allylic unit is observed in the reaction of aromatic aldehydes with CH_2=$CHCF_2Cl$ in the presence of Al-10% $SnCl_2$ in EtOH-AcOH-H_2O. This reaction regiospecifically leads to 1-aryl-2,2-difluoro-3-buten-1-ols.[42]

Aluminum-Lead Bromide.

Three main processes, Barbier-type allylations, reductive coupling of carbonyls, and addition of polyhaloalkanes to carbonyls are mediated by this system which has been extensively studied in the past decade. $PbBr_2$ is used in a catalytic amount (molar ratio Al foil:$PbBr_2$ = 100:1-5), of great importance because of the hazardous properties of lead.

Al-$PbBr_2$ promoted allylation of various carbonyl compounds can be performed at ambient temperature in DMF, aqueous THF, or aqueous MeOH while nonaqueous THF, MeOH, and MeCN are not suitable. A moderate excess of allylic bromide (10-100% relative to carbonyl substrate) is recommended. Under these conditions the addition to α,β-enones proceeds regiospecifically in a 1,2-fashion (eq 15).[43]

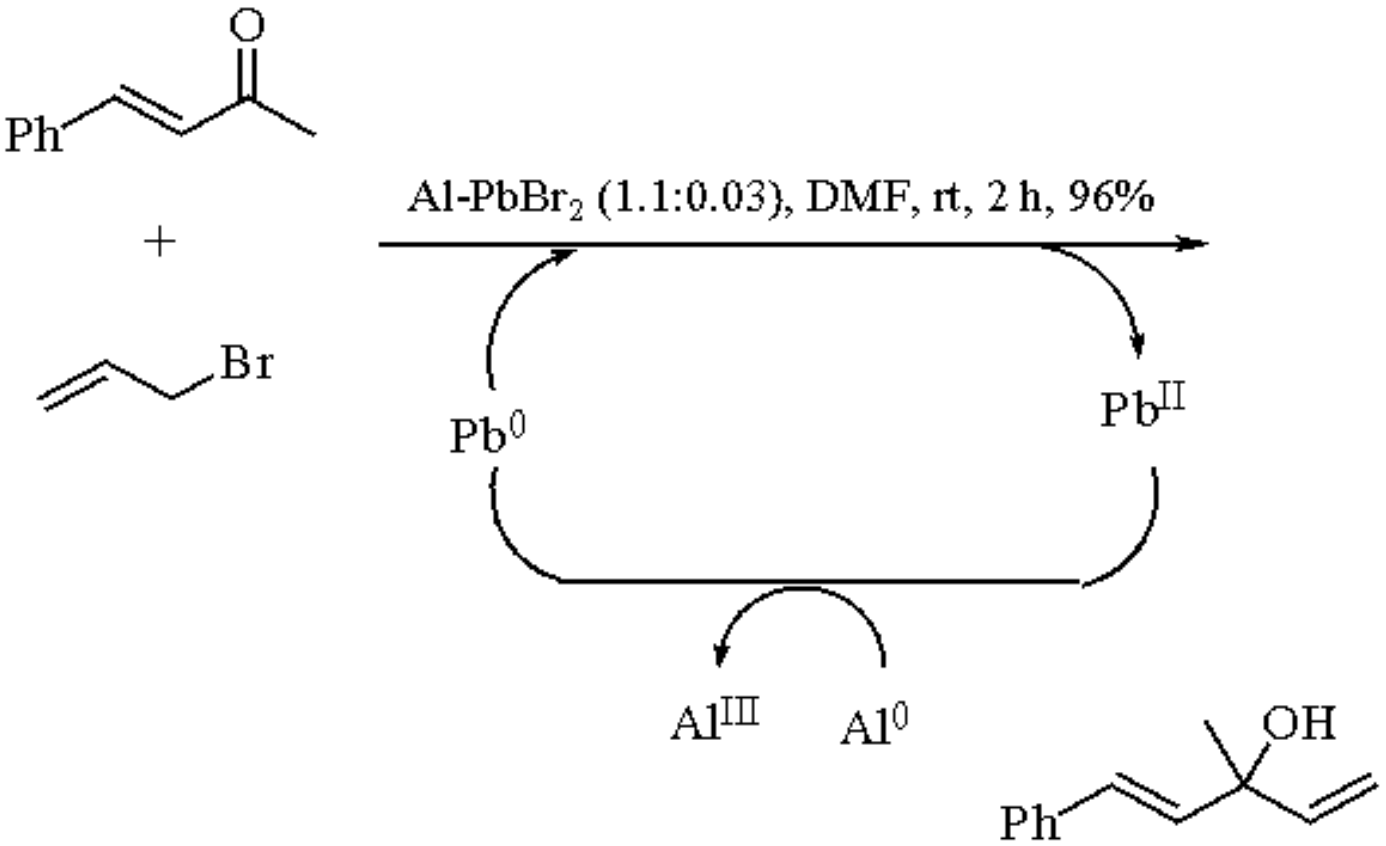

(15)

Metallic Al itself does not promote allylation which is, however, mediated by Pb-Bu_4NBr.[44] The observed stoichiometry (carbonyl substrate:CH_2=$CHCH_2Br$:Pb = 1:1:1) suggests that the reaction involves an active organolead(II) rather than organolead(IV) reagent, in contrast to the tin promoted reactions.[38,39] The in situ generated Pb^0 is much more effective than commercially available Pb and turnover of the Pb^0 catalyst in the range 14-77 is attained.[43]

This type of Barbier-type allylation has been applied to C-3 chain elongation of cephalosporins.[45]

Acetals $RCH(OMe)_2$ (**4**) as masked carbonyl compounds also undergo Barbier-type allylation mediated by Al-$PbBr_2$-$AlBr_3$ (molar ratio 1:0.03:0.1) to form homoallylic ethers (**5**).[46] The presence of ***Aluminum Bromide*** is critical because no allylation product is formed in the absence of this co-catalyst. Reaction pathways depend strongly on quantities of reactants and reagents, especially in the case of acetals of aromatic aldehydes. An increase of $AlBr_3$ from 0.1 to 0.5 equiv is accompanied by reductive homocoupling to 1,2-diaryl-1,2-dimethoxyethanes (**6**). If the ratio CH_2=$CHCH_2Br$ to (**4**) is higher than 2:1, commonly used in such processes, diallylation and reductive homocoupling of monoallylated products effectively compete with monoallylation. The results reveal formation of cations (**7**) in the presence of $AlBr_3$ as an acid catalyst. The cations are either further allylated or reduced by Pb^0 to furnish dimers (**6**) (eq 16).[46] Replacement of $AlBr_3$ with ***Trifluoroacetic Acid*** (TFA) (1 equiv) causes a complete shift of the reaction toward formation of homocoupling products (**6**) from arene and heteroaromatic carbaldehyde acetals.[47] To promote homocoupling, although less efficiently, VCl_3 or ***Cobalt(II) Chloride*** or ***Tin(II) Bromide*** can be also employed instead of $PbBr_2$ in the Al-$PbBr_2$-TFA redox system.

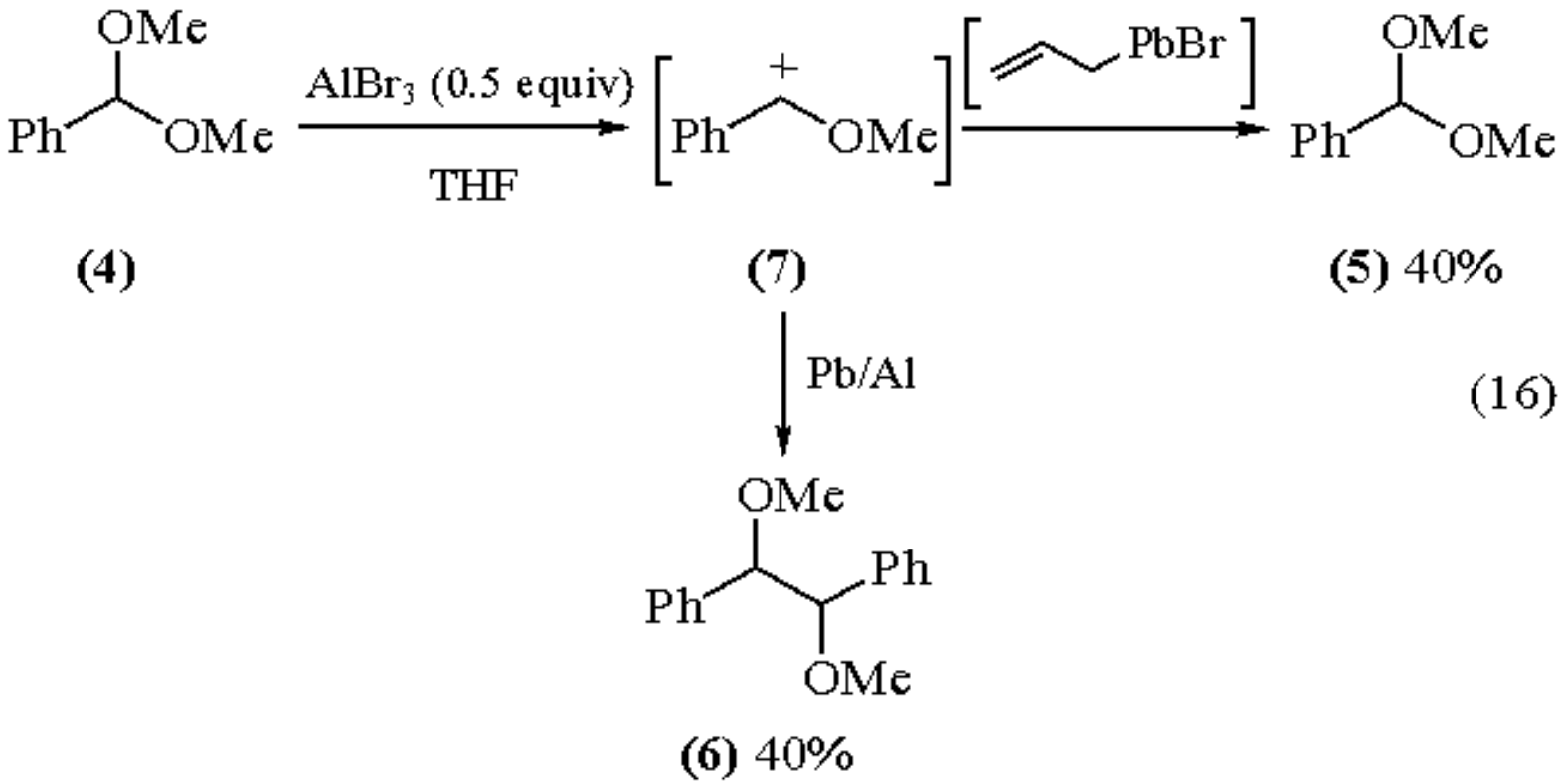

An extremely facile procedure for *C*-allylation of imines involves direct mixing of imines and $CH_2{=}CHCH_2Br$ with a catalytic amount of $PbBr_2$ (0.03 equiv) and Al foil (1 equiv) in ether containing ***Boron Trifluoride Etherate*** (1.1 equiv) (eq 17).[48] With almost the same efficiency, aromatic and aliphatic aldimines undergo electroreductive Barbier-type allylation using an Al anode/$PbBr_2$/Bu_4NBr/THF/Pt cathode system where a combination of sacrificial Al anode and Pb^0/Pb^{II} operates as a mediator for anodic and cathodic electron transfer processes, respectively.[49]

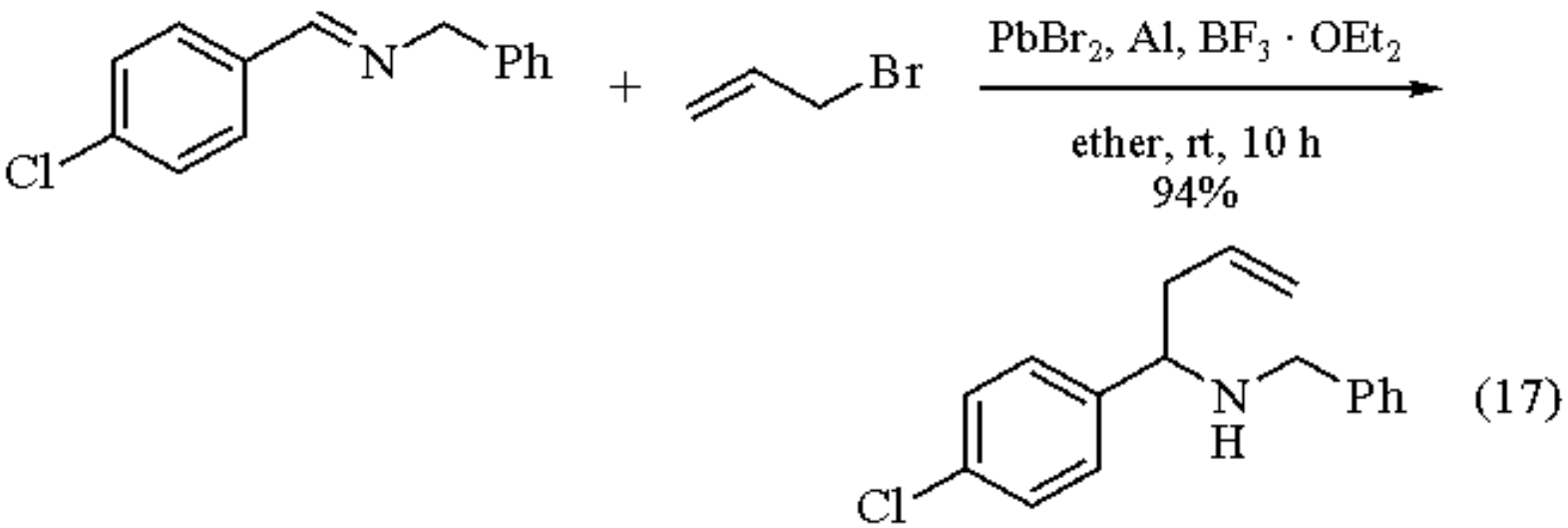

Regarding the chemical allylation of imines, $PbBr_2$ and the $BF_3.OEt_2$ couple can be replaced with a catalytic amount (0.05 equiv) of ***Titanium(IV) Chloride***. This system is highly advantageous in chirality transfer from L-valine into a homoallylic amine (diastereomeric ratio greater than 20:1) (eq 18).[50]

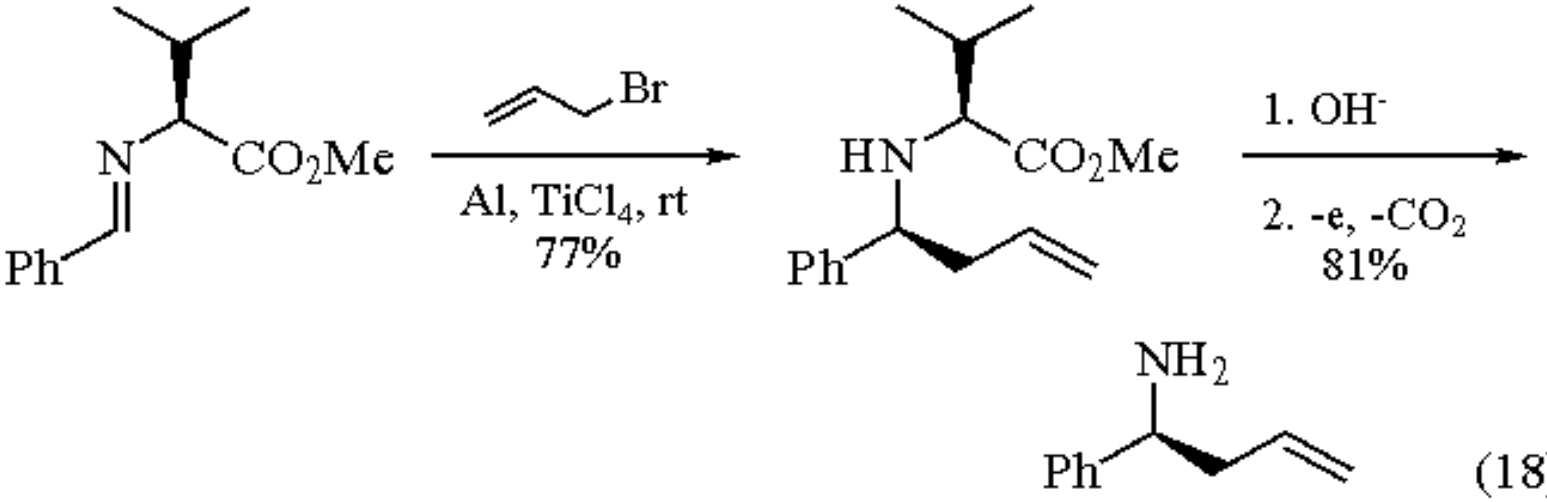

(18)

Similar to the transformations observed for acetals,[46,47] introduction of TFA in the Al-$PbBr_2$ system allows reductive dimerization of *N*-alkylimines to vicinal diamines.[51]

Reductive dimerization of allylic as well as benzylic bromides is mediated by the Al-$PbBr_2$ system in DMF. In the case of allylic bromides dimerization is complicated by allylic rearrangement and gives a mixture of isomeric 1,5-hexadienes. Benzylic bromides only give 1,2-diarylethanes.[52] The same reactions are also induced by metallic Pb-Bu_4NBr in DMF.[52]

An Al/$PbBr_2$/$NiCl_2$(bipy) (molar ratio 0.7:0.1:0.1) system promotes reductive dimerization of 2-arylvinyl halides to form 1,4-diaryl-1,3-butadienes, precursors of terphenyl derivatives (eq 19). The process is almost stereospecific and both double bonds in the dimer retain the C=C bond configuration of the starting vinyl halide. The reaction is carried out in DMF or MeOH at ambient temperature with KI (1.5 equiv) added. No dimerization is observed if THF, MeCN, CH_2Cl_2, or C_6H_6 are used as solvent or in the absence of either $NiCl_2$ or $PbBr_2$. The latter can be replaced by $BiCl_3$, $SnBr_2$, or $GeCl_4$, but dimer yields are remarkably decreased.[53]

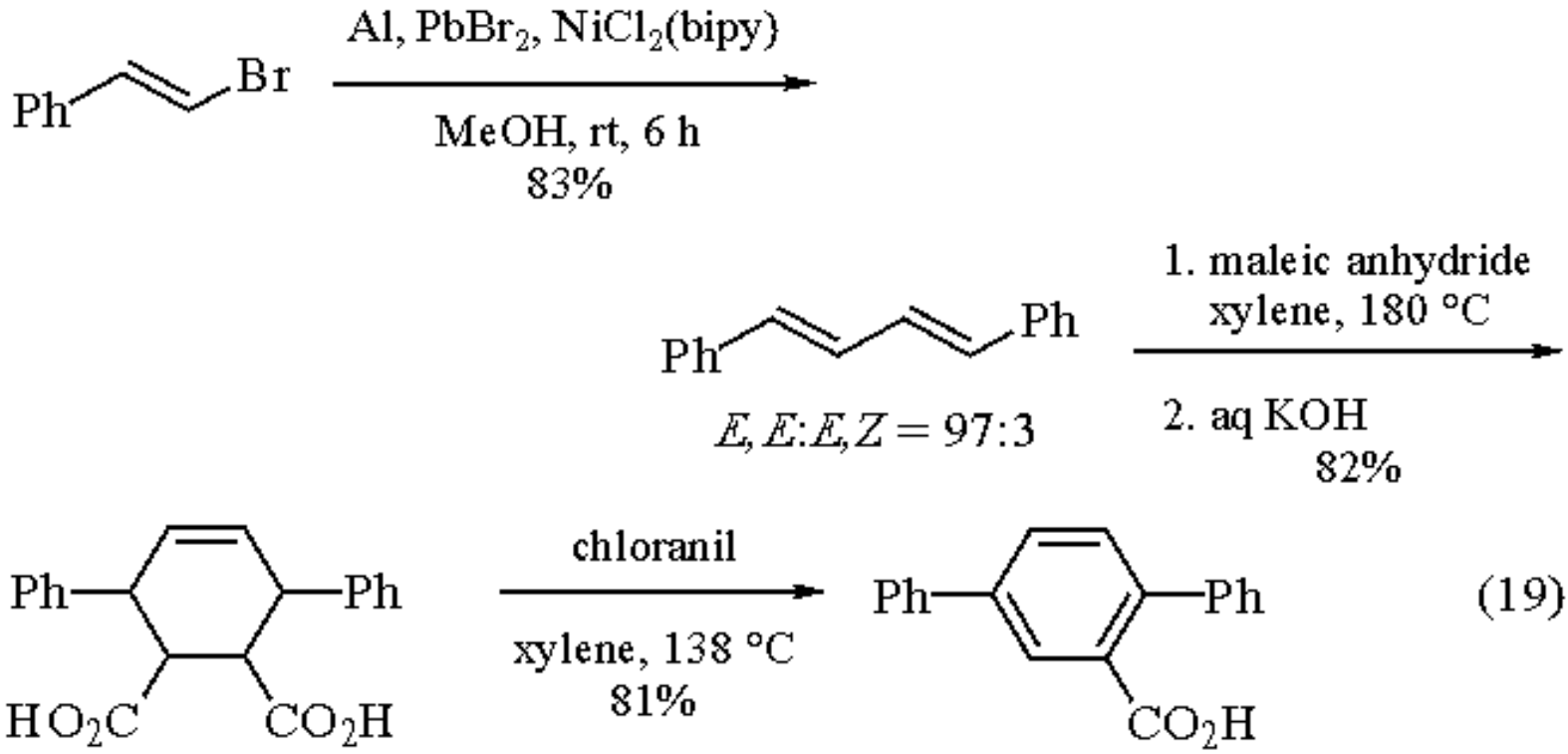

(19)

Both aromatic and aliphatic aldehydes undergo Al-$PbBr_2$ mediated reductive addition of polyhalomethanes CX_3Y (X = Cl, Br; Y = Cl, Br, CN, $CONH_2$). The reaction (aldehyde:CX_3Y:Al:$PbBr_2$ = 1:2-4:1.2:0.1) is performed in DMF, yielding α-(trihalomethyl)carbinols (**8**) in almost quantitative yield. These can be subjected to further reductive elimination with Al-$PbBr_2$ in MeOH containing aq HCl to produce 1,1-dihaloalkenes (**9**). When carbinols (**8**) react in DMF, reduction of the trihalomethyl group to a dihalomethyl occurs instead of elimination (eq 20).[54] This approach has been used in the stereospecific synthesis of pyrethroid insecticide precursors[54] and arylacetic acids.[55]

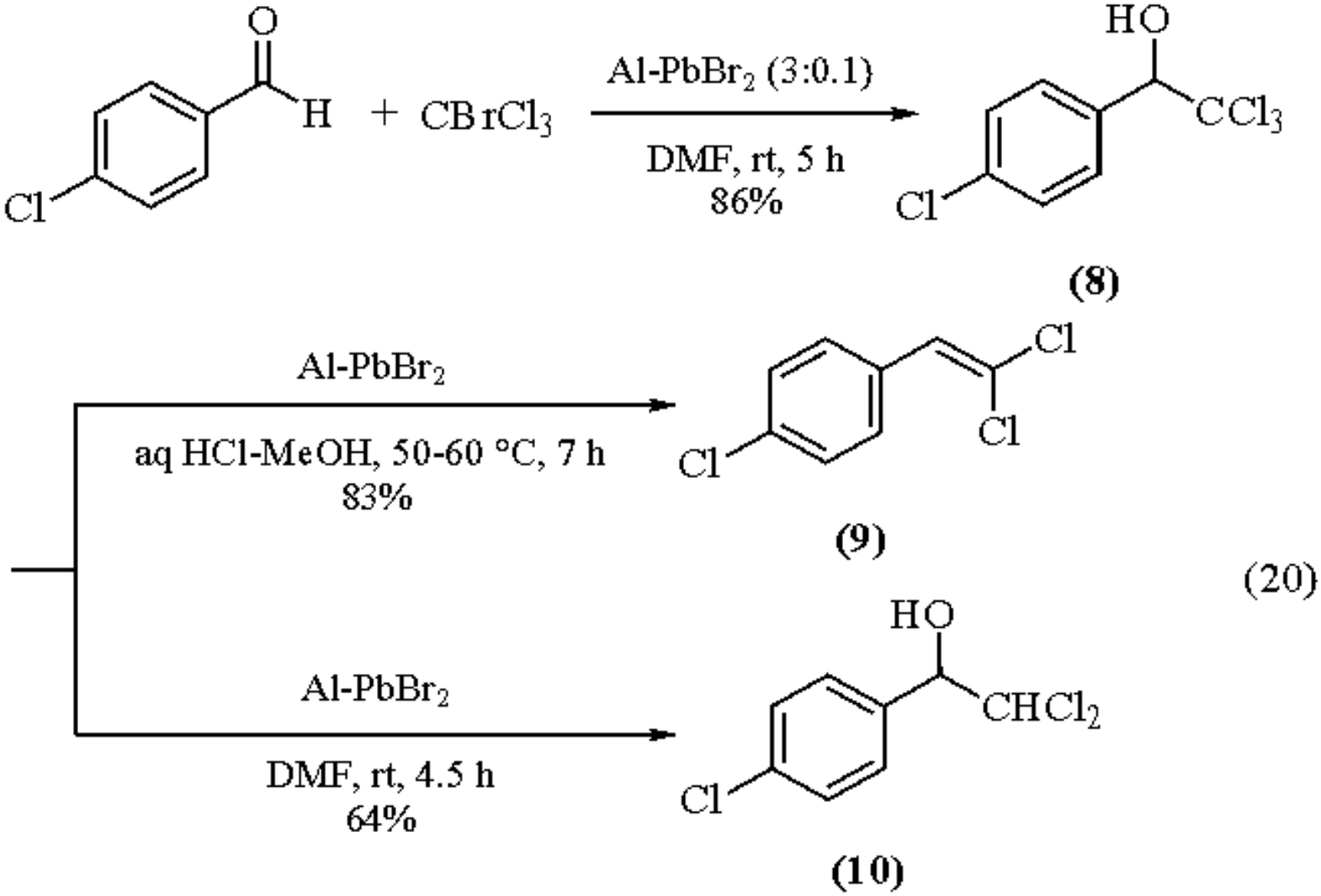

In the same way, a CF_3CCl_2 unit can be introduced into aldehydes via a reaction with CF_3CCl_3. This process is chemospecific and no adducts resulting from C-F bond cleavage are formed.[56]

The Al-$PbBr_2$ system is also capable of mediating a facile reductive removal of bromine atoms from 6-bromo- and 6,6-dibromopenicillanate derivatives (in MeOH/aq 1% HBr (9/1)),[57] and has been used in prenylation reactions of *p*-benzoquinones and naphthoquinones.[58]

Aluminum-Bismuth(III) Chloride.

Al powder in combination with catalytic amounts of $BiCl_3$ in aqueous THF at ambient temperature promotes efficient Barbier-type allylation of aldehydes.[59] The reaction occurs with allylic rearrangement in the entering unit and stereoselectively gives the *erythro* product. The reaction involves allylbismuth reagent formation through the oxidative addition of an allylic halide to Bi^0 generated by the reduction of $BiCl_3$ with Al. Metallic Bi is also capable of allylating aldehydes to homoallylic alcohols in aprotic DMF, but not in an aqueous solvent.[60a] Metallic Zn or Fe also can be used with $BiCl_3$ instead of Al.[60b]

The system also induces alkylation of immonium cations. The procedure is experimentally simple due to its being performed in aqueous media.[61] Among other alkylation agents, methyl and benzyl halides have been used for the first

time in this Barbier reaction system (eq 21).[61b]

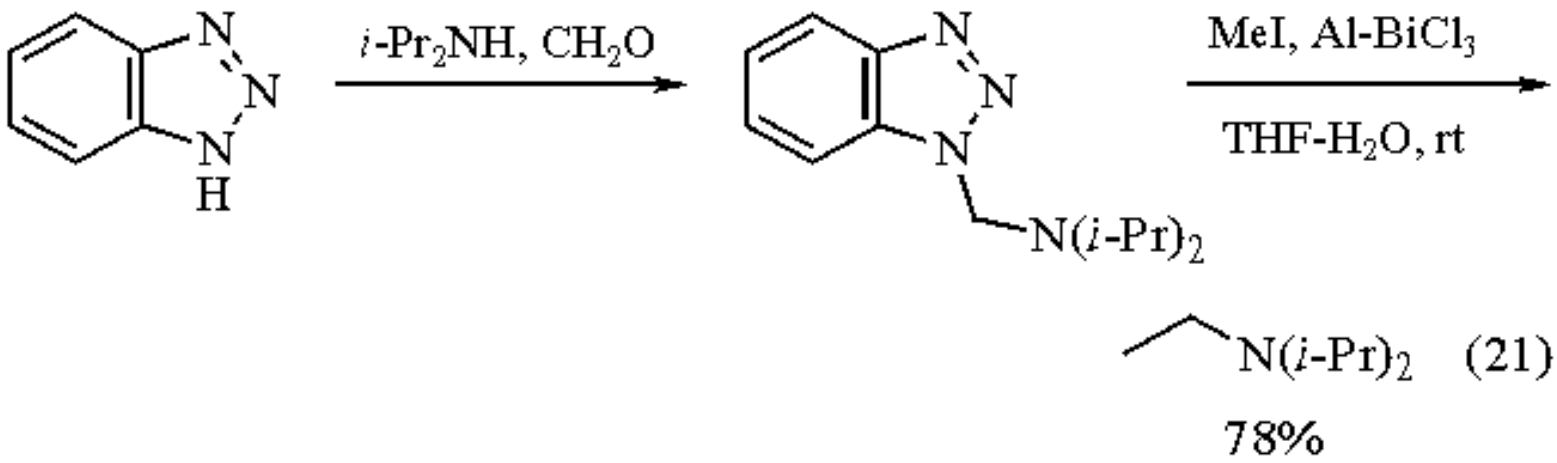

(21)

Aluminum-Antimony(III) Chloride and Aluminum-Indium(III) Chloride.

Both systems promote Barbier-type allylation of aldehydes. However, in contrast to $InCl_3$, which is required only in a catalytic amount for a reaction in aqueous THF,[62] more than stoichiometric amounts of $SbCl_3$ are used in DMF-H_2O (3:1) and NaI is added to activate allylic bromides (aldehyde:allylic halide:Al:$SbCl_3$:NaI = 1:1.2:2:1.5:1.2).[63] Similar to the Al-$PbBr_2$ system,[58] Al-$InCl_3$ also mediates prenylation of naphthoquinones.[62] Al in combination with a catalytic amount of $SbCl_3$ induces acetalization of carbonyl compounds.[63]

Aluminum-Nickel Alloy.

In alkali medium this reagent is employed for chemical reductions.[64] Al affects liberation of hydrogen which actually plays the role of reducing agent (eq 22).

$$NiAl + 3NaOH \longrightarrow Ni + Na_3AlO_3 + 1.5\ H_2 \qquad (22)$$

Besides reduction of carbonyl compounds, organic halides, and nitriles,[64b] in recent years numerous compounds containing N-N and N-O bonds (hydroxylamines, hydrazines, *N*-nitrosoamines, *N*-oxides) have been reduced to amines.[65] A few heterocycles are also reduced by this reagent, and high temperatures, high pressures, or a hydrogen atmosphere are not required. Corresponding tetrahydro derivatives are produced from pyridines, quinolines, and pyrazines, whereas pyrimidines, pyridazines, oxazoles, and isoxazoles undergo reductive cleavage of C-N, N-N, or N-O bonds to yield saturated diamines or diamino alcohols (see ***Raney Nickel***).[66]

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Aluminum Amalgam[1]

Al-Hg

[11146-30-8] · Al · Aluminum Amalgam · (MW 26.98)

(reducing agent for many functional groups,[1] effects reductive dimerization of unsaturated compounds, can cleave carbon-element and element-element bonds.)

Physical Data: shiny solid.

Preparative Methods: ***Aluminum*** turnings (oil-free) are etched with dilute ***Sodium Hydroxide*** to a point of strong hydrogen evolution and the solution is decanted. The metal is washed once with water so that it retains some alkali, then treated with 0.5% ***Mercury(II) Chloride*** solution for 1-2 min, and the entire procedure is repeated. The shiny amalgamated metal is washed rapidly in sequence with water, ethanol, and ether and used at once.[2] Aluminum amalgam (**1**) reacts vigorously with water with liberation of hydrogen in the amount equivalent to the amount of aluminum present and can be used to dry organic solvents (ether, ethanol).[2a] Aluminum amalgam can be also prepared from aluminum foil, which is cut into strips ~10 cm × 1 cm and immersed, all at once, into a 2% aqueous solution of $HgCl_2$ for 15 s. The strips are rinsed with absolute alcohol and then with ether and cut immediately with scissors into pieces ~1 cm square, directly into the reaction vessel.[2b] Before immersion, each strip may be rolled into a cylinder ~1 cm in diameter. Each cylinder is amalgamated, rinsed successively with ethanol and ether and then placed in the reaction vessel.[2c]

Handling, Storage, and Precautions: moisture-sensitive. Precautions should be taken as it readily reacts with water with hydrogen evolution. Can be stored under dry ether. Toxic.

C=C Bond Reduction.

Alkenic substrates are transformed into saturated compounds upon reaction with Al-Hg. Substrates with carbon-carbon double bonds activated by electron-withdrawing substituents are most easily reduced.[3] The reaction may proceed with asymmetric induction and high chemoselectivity, leaving other functionalities unchanged (eq 1).[4] Reduction of 1,3-dienes[5a] and α-nitroalkenes[5b] results in 1,4-addition of hydrogen to the π-system. Aluminum amalgam can also promote reductive dimerization of α,β-unsaturated acid esters.[6a,b]

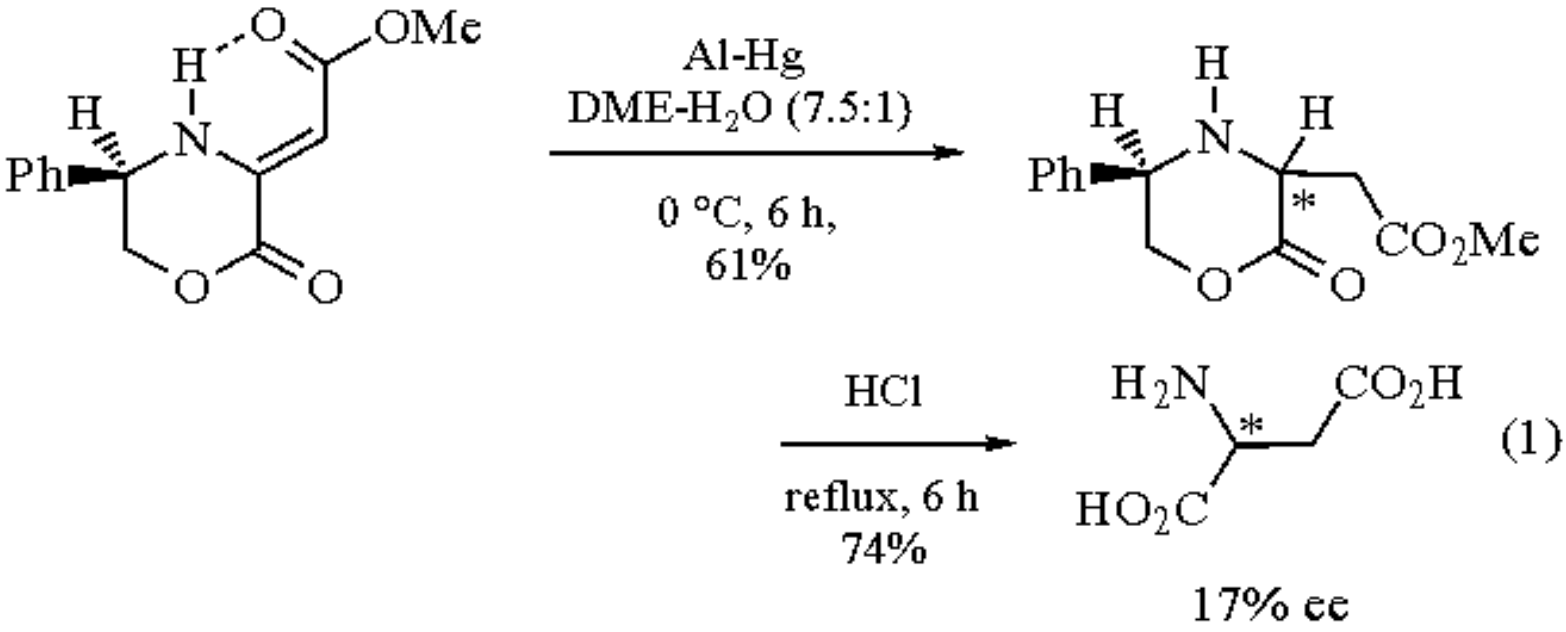

C=O Bond Reduction.

Cycloalkanones and aldehydes are reduced to the corresponding alcohols (eq 2). Acyclic ketones remain almost inert.[7]

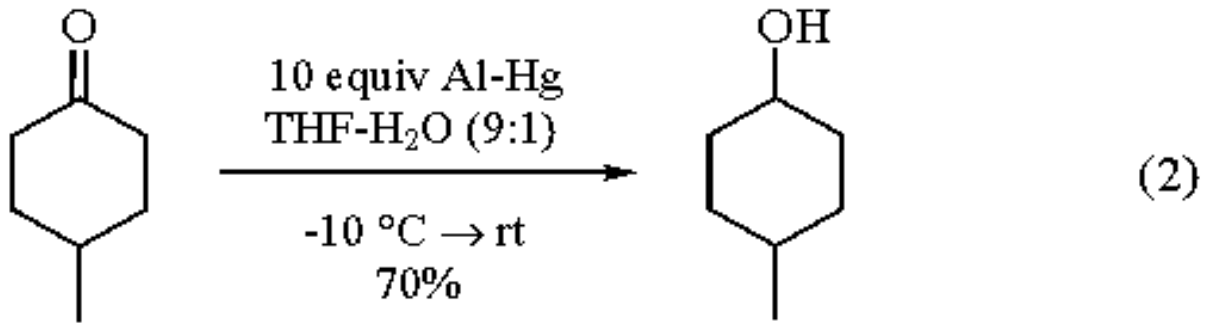

In spite of the ability of carboxylic acid esters to be reduced to alcohols,[8] in oxosuccinic acid esters only the ketone carbonyl group is reduced.[9]

Ultrasound-promoted reduction of the C=O group of *N*-substituted phthalimides leads to hydroxylactams. The ultrasonic irradiation provides rapid fragmentation of the amalgam, giving a reactive dispersion and accelerates the reaction owing to the increase of mass transport between the solution and the Al/Hg surface where reduction occurs. The reaction is highly sensitive to substrate structure and *N*-benzylglutarimide and *N*-benzylsuccinimide are not reduced.[10]

Reductive dimerization of carbonyl compounds to pinacols does not always effectively compete with reduction to alcohols, but in certain cases it becomes the main process (eq 3).[7,11] Factors which determine reduction-dimerization ratios include steric inhibition, torsion strain, and angle strain.[7]

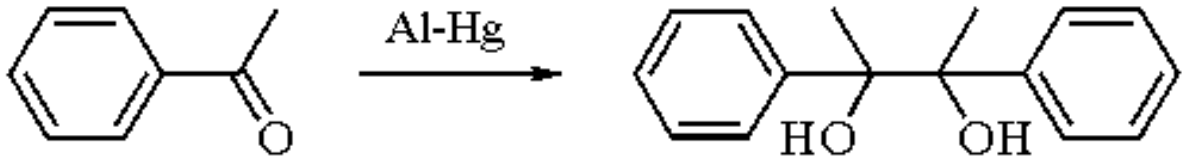

(3)

CH_2Cl_2, reflux, 1-4 h, 21-38%
C_6H_6-EtOH (1:1), reflux, 4 h, 95%
THF-H_2O (9:1), -10 °C → rt, 94%

A special case of reduction involves removal of the carbonyl oxygens from anthraquinones[12a,b] and related compounds[13] with rearomatization (eq 4).[12b]

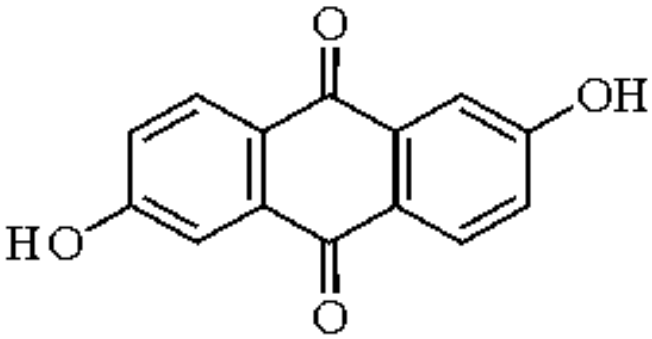

Al-Hg, EtOH-H_2O (4:9)
sat aq NH_4OH

60-65 °C, 2 h
78%

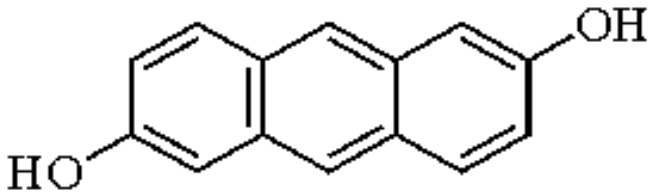

(4)

C=N Bond Reduction.

Aluminum amalgam reduces Schiff bases to the corresponding amines.[14] Among these reactions of great importance is the reduction of Δ^2-thiazolines to thiazolidines, [15-17] widely used in the synthesis of aldehydes (eq 5),[15] β-hydroxy aldehydes, and homoallylic alcohols.[16]

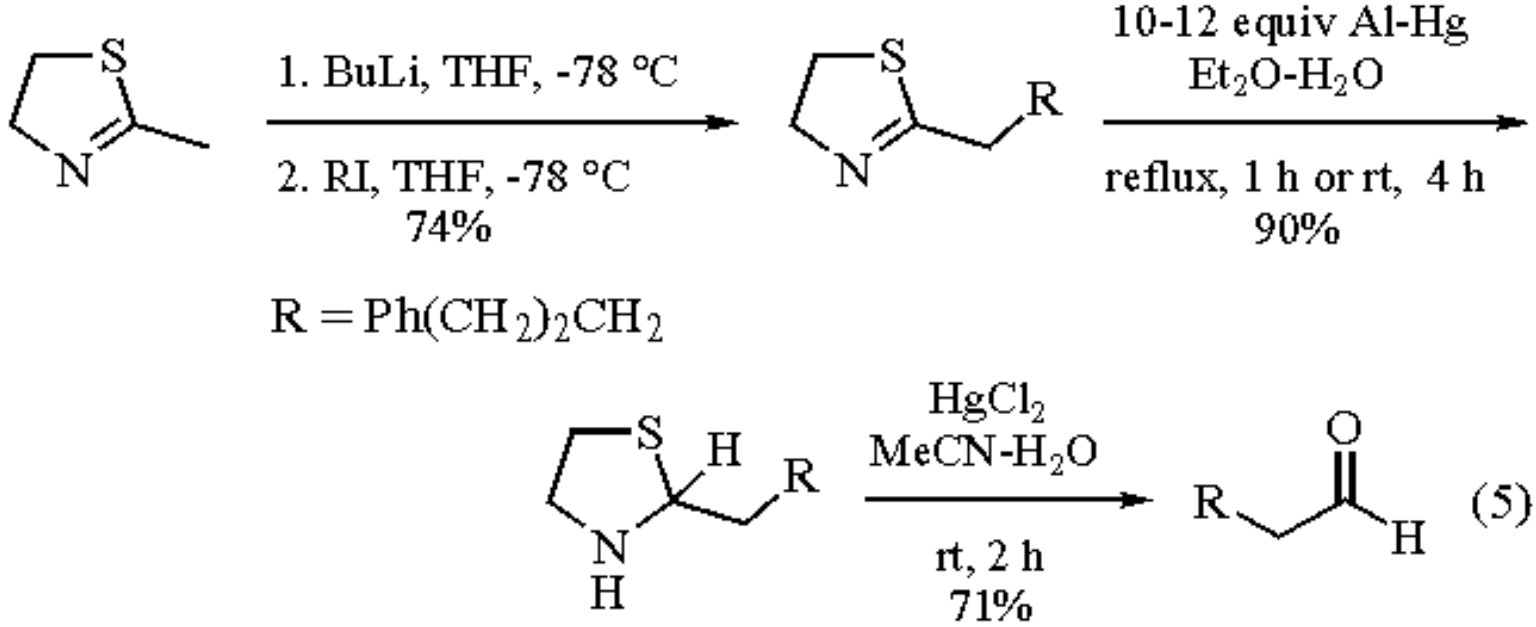

(5)

Aluminum amalgam also induces reductive dimerization of Schiff bases[14a,18] to produce 1,2-diamines. This process has been used in macrocyclic ring closure.[18a] In respect to reductive dimerization of Δ^1-pyrrolines, aluminum amalgam is much more effective than ***Zinc*** in aqueous NH_4Cl.[18b] Similar to Schiff bases, oximes are also readily reduced to corresponding amines,[19] while reduction of hydrazides provides hydrazines.[20]

NO_2 and N_3 Group Reduction.

Aluminum amalgam reduction is an excellent method for deoxygenation of aliphatic and aromatic nitro groups to produce amines[21] (eq 6).[21d] Nitro alkenes can be chemoselectively reduced, retaining the C=C bond.[21a] In moist ether the reduction can be stopped at the stage of hydroxylamine formation.[22]

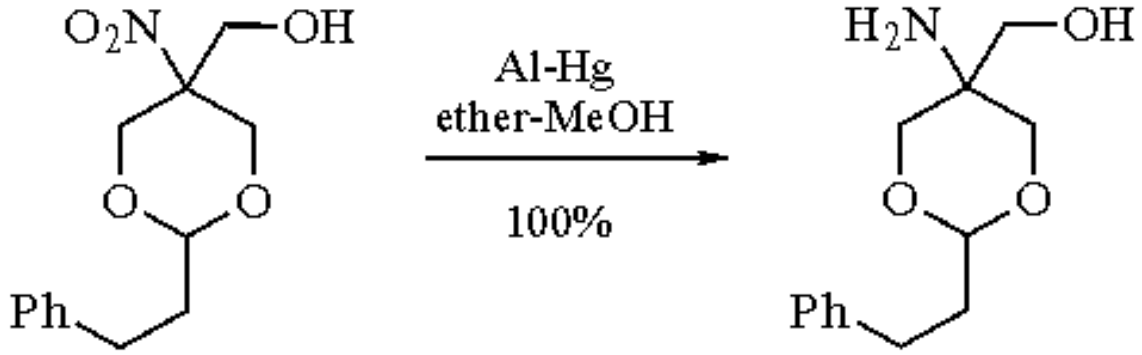

(6)

Organic azides are also readily reduced to the corresponding amines. The procedure has been used in a general synthesis of α,β-unsaturated α-amino acids.[23]

Reactions of Carbon-Halogen Bonds.

Organic halides exhibit diverse behavior in reactions with Al-Hg. Thus a trichloromethyl group has been reduced to a dichloromethyl group.[24] At the same time, Al inserts into the C-Br bond of silylated propargyl bromide affording the

allenylaluminum reagent, whereas only direct metalation without rearrangement has been observed in metalation with ***Zinc Amalgam*** (eq 7).[25]

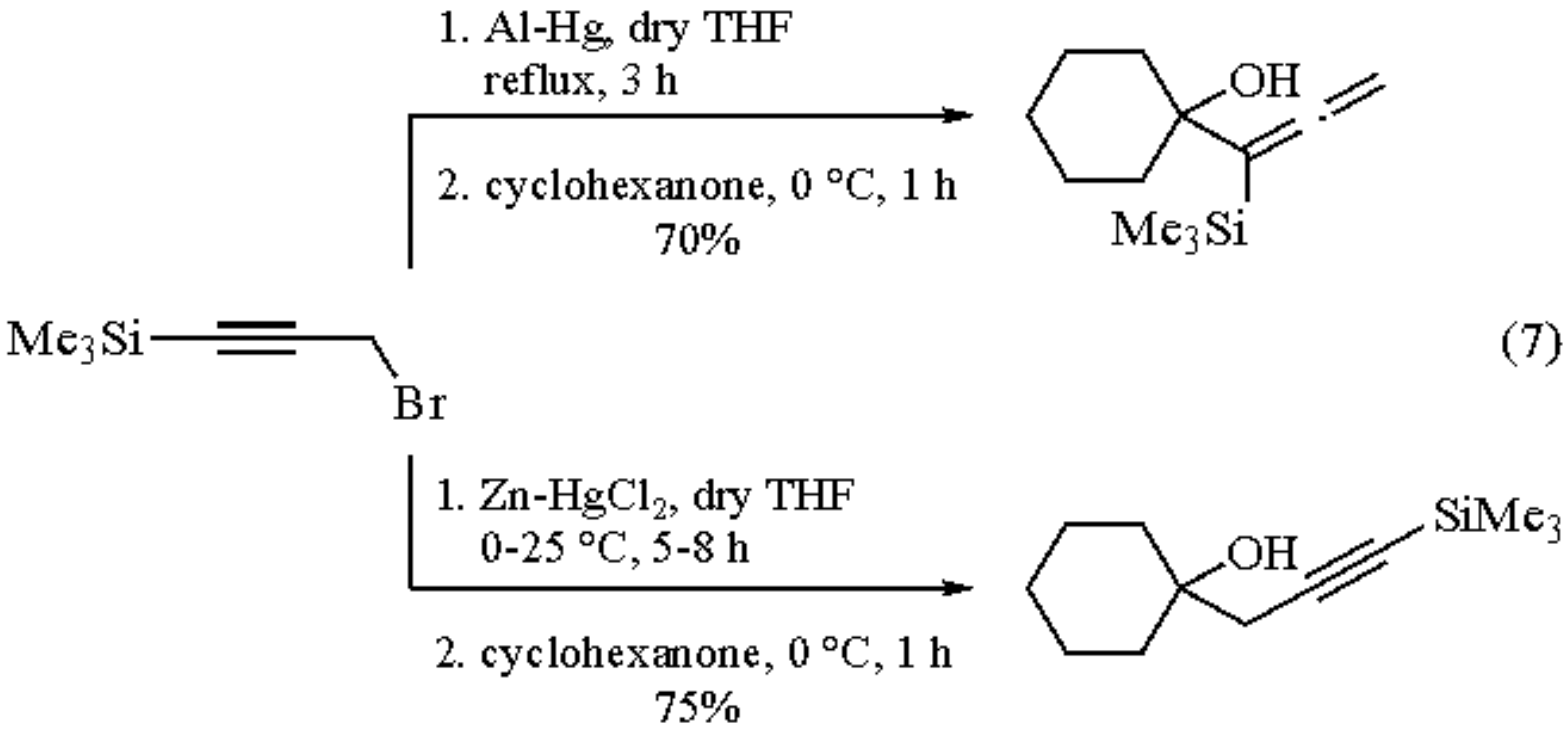

(7)

Mild reductive deacetoxybromination of glycosyl bromides offers an approach to glucals bearing acid-sensitive substituents (eq 8).[26]

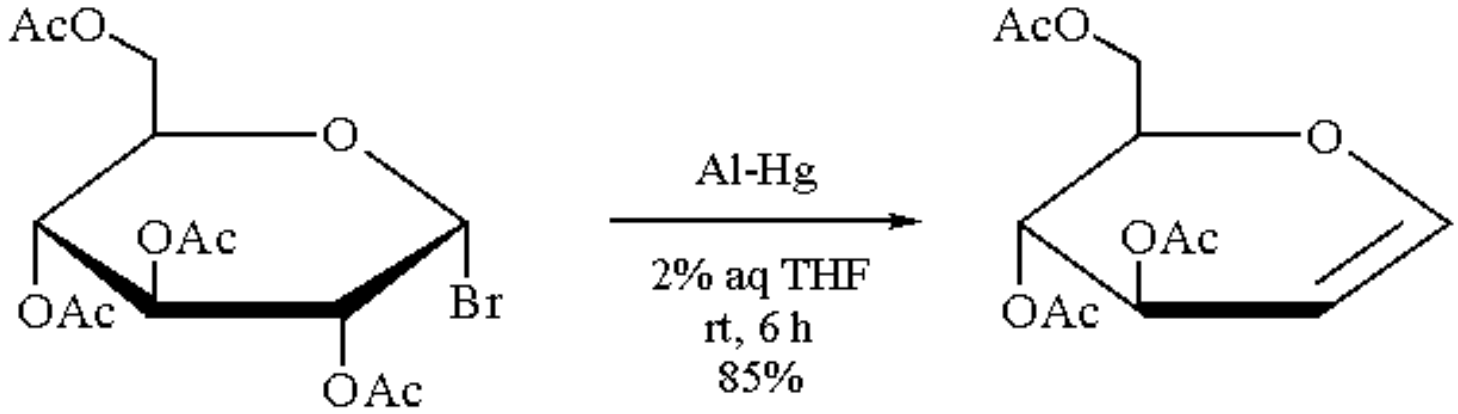

(8)

C-O Bond Cleavage.

Ether linkages of various substrates, for example glycosides,[27] 1,3-dioxolanes,[28] tetrahydrofurans,[29,30] and oxiranes,[31] undergo reductive cleavage with formation of alcohols. Among the reactions listed, the reductive cleavage of epoxides (eq 9)[32a] is presumably of the most importance. It has been widely used in the synthesis of prostaglandins,[31a,b,32] steroids,[31c,d] erythronolide B,[33] and vitamin precursors.[34]

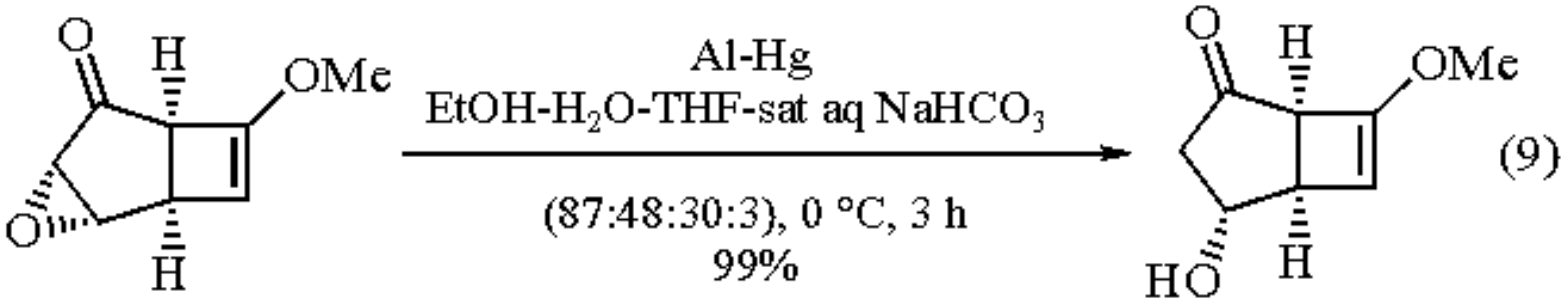

Deoxygenation of certain terpene oxides with Al foil activated by $HgCl_2$ has been reported instead of reduction to the desired alcohols.[35]

N-O and N-N Bond Cleavage.

On exposure to excess Al-Hg in aqueous THF at 0 °C for several hours, N-O bonds in bicyclic Diels-Alder adducts are readily cleaved.[36] Mild conditions provide a highly chemoselective process and carbon-carbon double bonds and acid labile functional groups survive, in contrast to the alternative methods employed such as catalytic hydrogenolysis or reduction with ***Zinc-Acetic Acid***.[36a] The reaction occurs with high stereoselectivity and the product is formed with a *cis* disposition of N- and O-containing substituents (eq 10).[36]

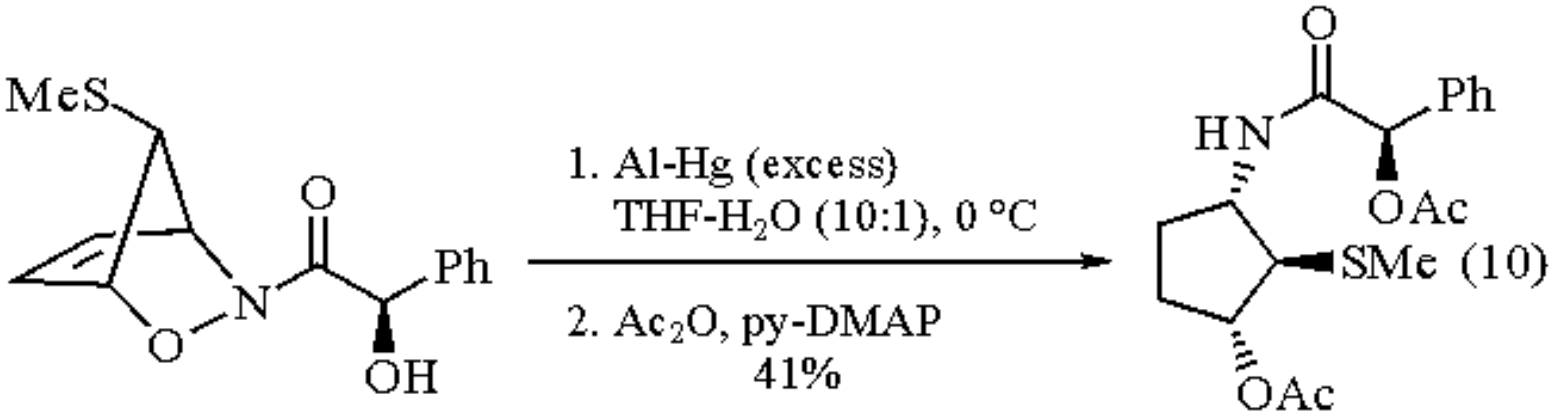

Aluminum analgam is also highly effective in reductive cleavage of N-N bonds to produce amines.[37]

Reductive Desulfurization.

The ability of Al-Hg to reduce C-S bonds is widely used in organic synthesis in conjunction with methodology involving reactions of highly reactive α-sulfinyl- and α-sulfonylalkyl carbanions[2b,38] as well as (α-sulfoximidoyl)alkyl carbanions.[39] Removal of the activating sulfur substituent is frequently accomplished using Al-Hg. The methodology offers facile synthetic approaches to ketones,[2b,38,40] enones,[41] di- and triketones,[40,42] hydroxy ketones (eq 11),[43] unsaturated acids,[44] and γ-oxo-α-amino acids.[45]

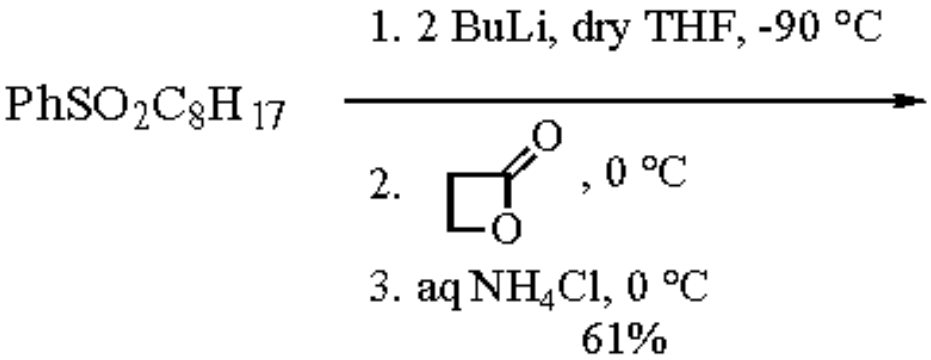

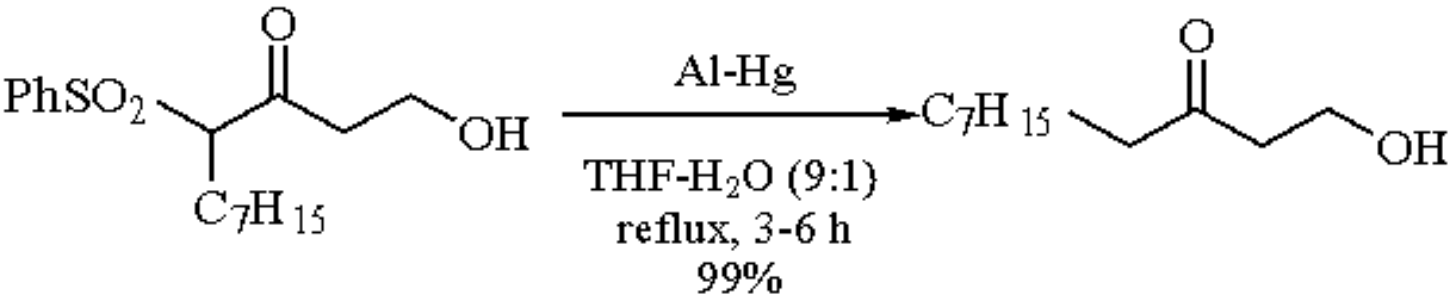

(11)

Readily removed on treatment with Al-Hg asymmetric sulfinyl and sulfonimidoyl groups may serve as chiral auxiliaries in enantiocontrolled synthesis of 3-substituted cycloalkanones[46] and 3-hydroxy[47] and 3-arylcarboxylic acid esters.[48]

Aluminum amalgam mediated cleavage of C-S bonds plays an important role in sulfoximine-based alkenation of carbonyl compounds via β-hydroxysulfoximines[49] (eq 12).[49b]

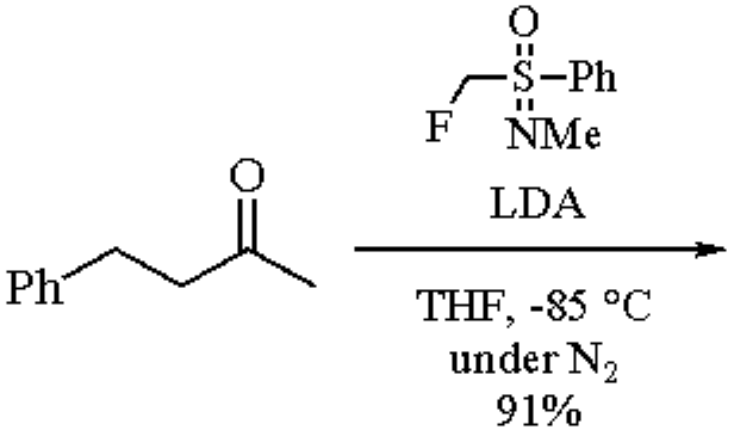

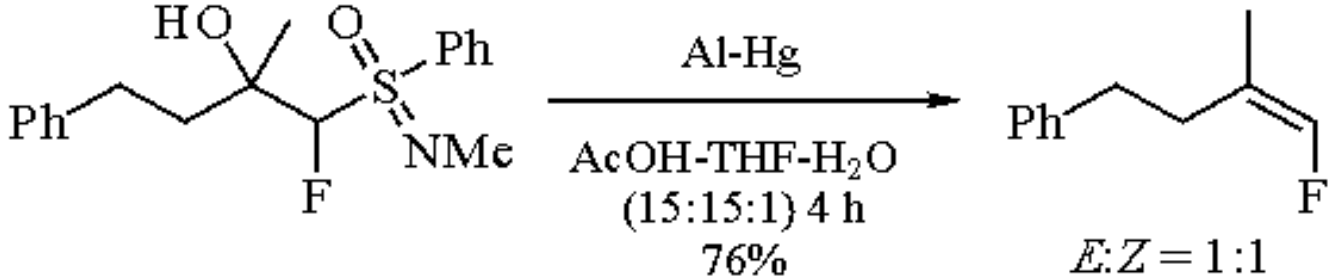

(12)

Aluminum amalgam can also be employed in reductive elimination of phenylthio groups from 2-phenylthioalkanones,[50] stereospecific reduction of sulfoximines,[51] selective cleavage of the sulfinyl sulfur-methylene carbon bond in the presence of a disulfide moiety,[52] and reductive scission of S-S and S-N bonds.[53,54]

For some reactions mediated by aluminum activated with mercury(II) chloride, also see ***Aluminum***.

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Aluminum Bromide

$AlBr_3$

[7727-15-3] · $AlBr_3$ · Aluminum Bromide · (MW 266.72)

(Lewis acid catalyst similar to $AlCl_3$; useful in oxacycle,[1] cyclopentanone,[3] and conjugated cyclopentenone[4] synthesis; halogenations;[6] reductive deoxygenation of ketones and secondary alcohols;[7] selective ether cleaving reagent;[8] isomerization catalyst;[12] Friedel-Crafts catalyst[16])

Physical Data: mp 97 °C; bp 268 °C; *d* 3.01 g cm^{-3}.

Solubility: sol CS_2, alcohols, ether, acetone, hydrocarbons, nitrobenzene, $Br(CH_2)_2Br$.

Form Supplied in: commercial grade white to yellowish-brown deliquescent solid; colorless is pure. Also available as a 1.0 M solution in CH_2Br_2. Exists as a dimer (Al_2Br_6) in solid and liquid phases.

Handling, Storage, and Precautions: use in a fume hood; fumes strongly in air; violent reaction with H_2O; corrosive to skin. Keep tightly closed and protected from moisture. Decomposes upon heating in air to Br_2 and alumina.

Oxacycle Synthesis.

Unsaturated alcohols react with aldehydes in the presence of $AlBr_3$ to give 4-bromooxacycles in a stereoselective manner (eq 1).[1] Tetrahydropyrans are formed in the all-*cis* configuration. Seven-membered rings are produced as a mixture of isomers at the bromide position. This method has a synthetic advantage over similar allylsilane procedures[2] in that larger rings can be prepared.

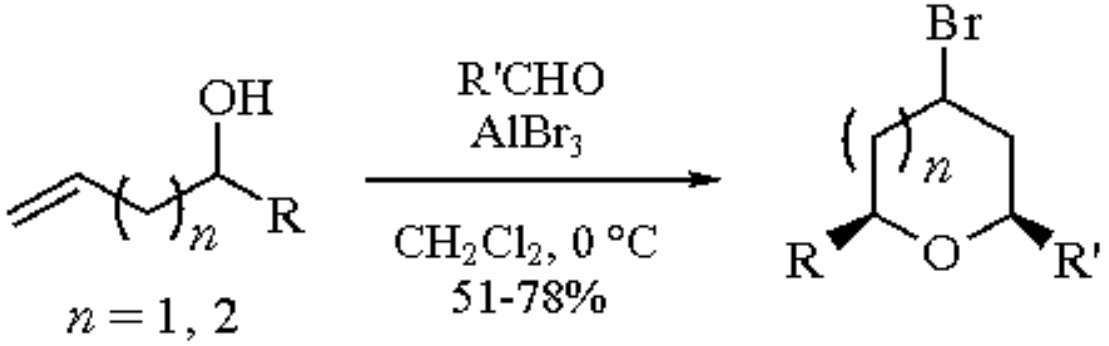

(1)

Cyclopentanone Synthesis.

Ring expansion of 1-acyl-1-(alkyl or arylthio)cyclobutanes to cyclopentantones occurs readily in the presence of 1 equiv $AlBr_3$ (eq 2).[3] This method has been used to provide good yields (68-86%) of 2-, 2,4-, and 2,5-substituted cyclopentanones. ***Aluminum Chloride*** and ***Iron(III) Chloride*** were also effective in this conversion; however, $BF_3.Et_2O$ and protic acids do not work.

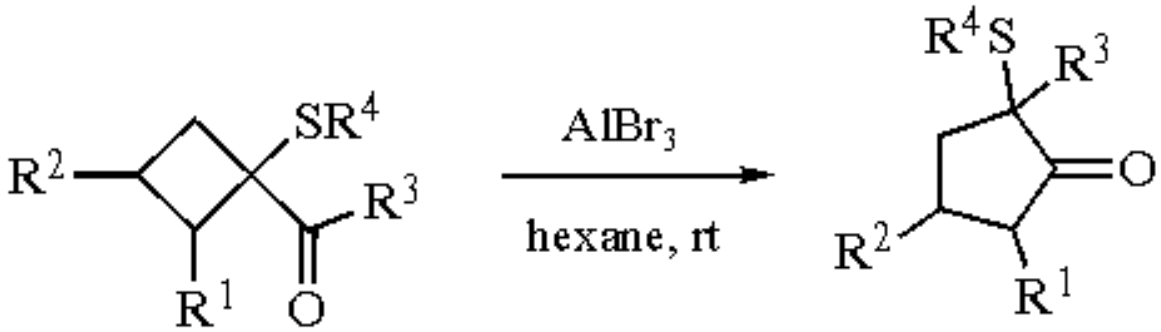

(2)

Conjugated Cyclopentenone Synthesis.

Decomplexation of 1,3-butadieneiron tricarbonyl complexes by $AlBr_3$ leads to conjugated cyclopentenones under mild conditions.[4] The diene must be unsubstituted at the 4-position but substitution at all other positions is tolerated. This cyclocarbonylation is stereospecific, depending only on the configuration of the diene complex (eq 3). Spirocyclic compounds can be formed using an appropriate precursor (eq 4). The method serves as a valuable alternative to the intramolecular Pauson-Khand reaction. One apparent limitation is that bicyclic cyclopentenones with an angular alkyl group cannot be prepared.

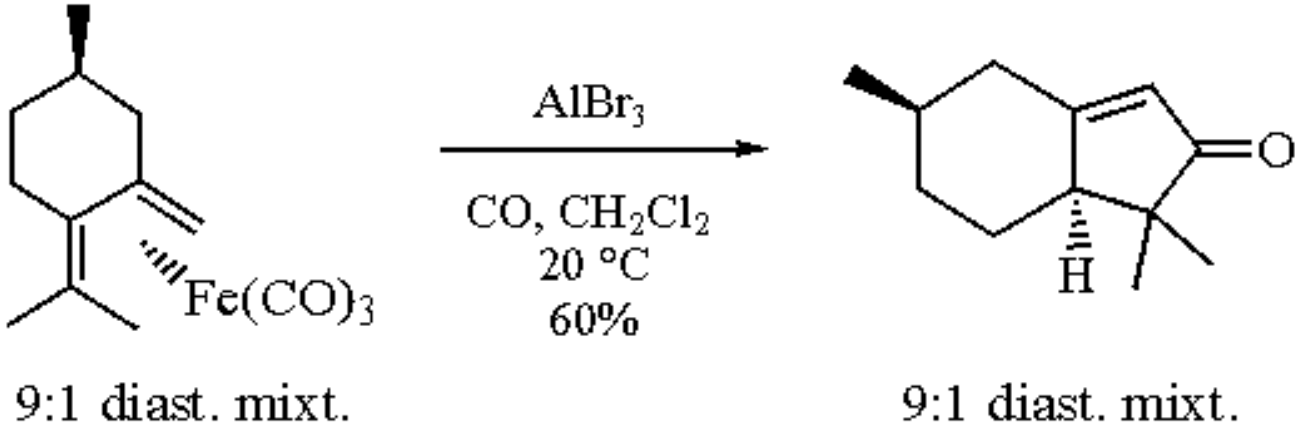

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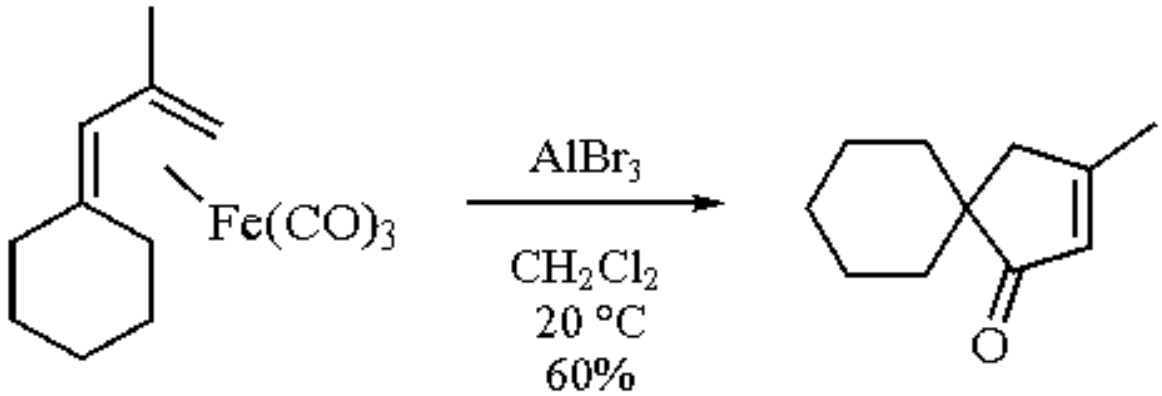

(4)

Halogenations.

A novel photochemical ring contraction of 1-naphthols to 3-halomethylindanones is promoted by $AlBr_3$ or $AlCl_3$ (eq 5).[5] The halogen substituent is derived from the halogenated solvent. In CH_2Cl_2, chlorides are the major product; in CH_2Br_2, bromides are produced regardless of whether $AlBr_3$ or $AlCl_3$ is used.

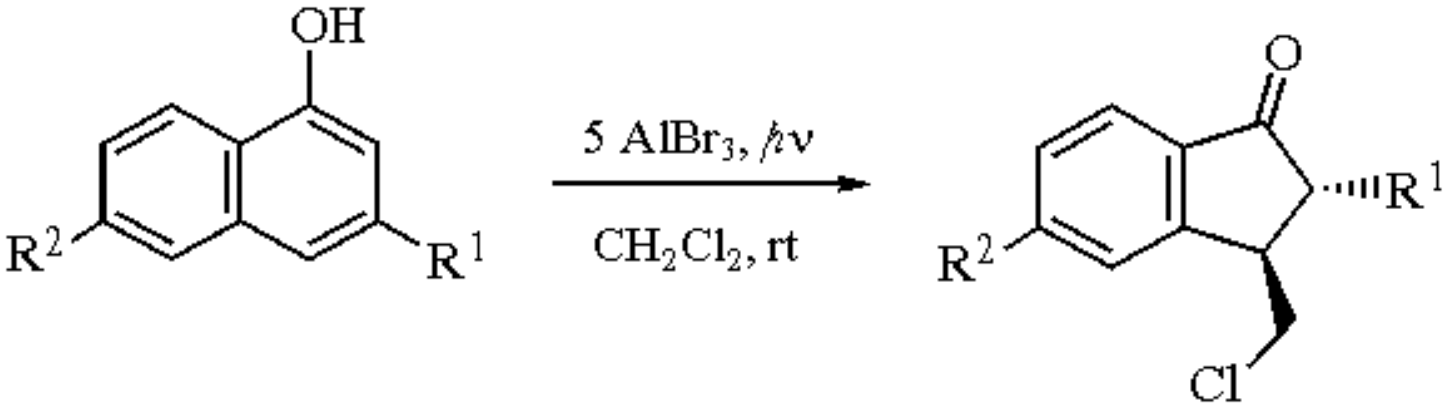

(5)

Thiophenes can be regioselectively brominated by $AlBr_3$ in the presence of ***Benzeneseleninyl Chloride*** (eq 6).[6a] Furans are halogenated in low yield and pyrroles are unreactive.

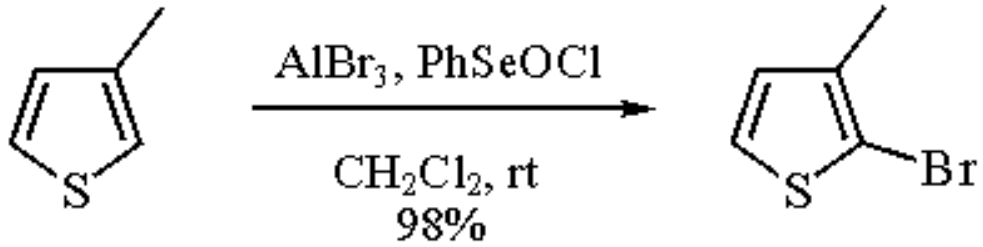

(6)

Bridgehead halogen exchange in polycyclic substrates is catalyzed by $AlBr_3$ in halogenated solvents and proceeds readily in fair to good yield (50-90%).[6b] For bromination, CH_2Br_2 or $CHBr_3$ solvent is used. Iodinations are carried out in MeI or CH_2I_2 and chlorinations in $CHCl_3$ or CCl_4. Bromoalkylation of 1-bromoadamantane occurs when subjected to ethylene or vinyl bromide in the presence of $AlBr_3$ to give 1-bromo- or 1,1-dibromo-2-(1-adamantyl)ethane, respectively.[6c] Yields are dependent on the quality of the $AlBr_3$. Bromination of the bridgehead position of adamantanone by $AlBr_3$/*t*-BuBr (so-called sludge catalyst) provides an improved, high yielding synthesis of 1-bromo-4-adamantanone.[6d]

C-O Bond Cleavages.

Reductive deoxygenation of ketones and secondary alcohols to the corresponding methylene hydrocarbons in excellent yield can be accomplished by the ***Diisobutylaluminum Hydride***/$AlBr_3$ reagent system.[7] In some cases, the addition of a catalytic amount of Cp_2MCl_2 (M = Ti, Zr) or ***Nickel(II) Acetylacetonate*** is required. Diaryl, alkyl aryl, or dialkyl ketones and secondary alkyl or benzylic alcohols undergo this reaction but primary alcohols or phenols do not.

Anhydrous $AlBr_3$ in MeCN or CS_2 is useful for the removal of methyl ethers and in some instances selective cleavage is possible.[8] The 5-MeO group in 3,5,6,7-tetramethoxyflavones and the 3-MeO group in 3,6,7-trimethoxy-5-tosyloxyflavones are selectively cleaved in nearly quantitative yield without debenzylation (eq 7).[8a] It is superior to $AlCl_3$ in some ether cleavages[8b] since it is a stronger Lewis acid and more soluble in organic solvents. An excellent reagent for phenol ether cleavage (except diphenyl ether) is the pyridinium salt of $AlBr_3$.[8c]

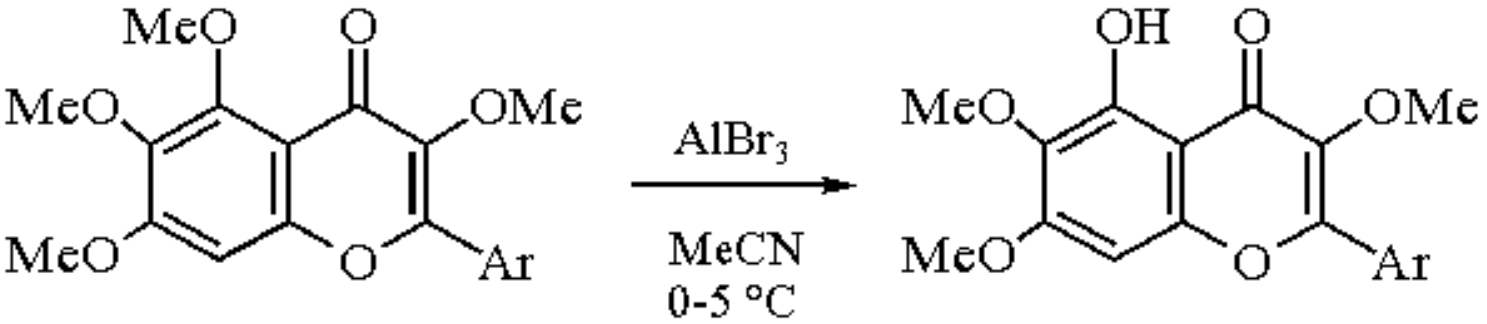

(7)

$AlBr_3$ is an efficient reagent for epoxide cleavage giving high yields of the bromohydrin. It does not show much regioselectivity in the case of substituted substrates.[9] The hydroxylation of cyclic acetals with ***Hydrogen Peroxide*** can be catalyzed by $AlBr_3$ as well as with other reagents (especially $SeBr_4$) to give esters of the type

$RCO_2(CH_2)_nOH$ (R = H, aryl, alkyl; *n* = 2-3).[10] Disulfide cleavage with $AlBr_3$ has been reported to give cyclized products in certain systems (eq 8).[11]

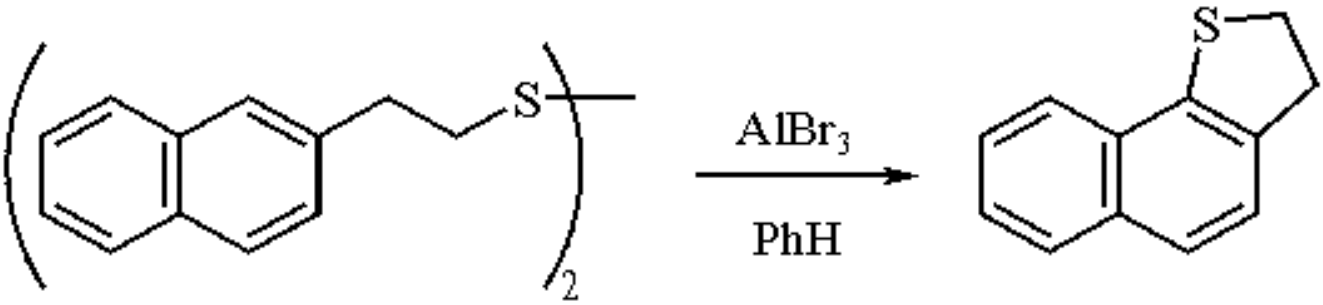

(8)

Rearrangements.

The $AlBr_3$ sludge catalyst has been extensively used as an effective isomerization reagent in numerous adamantane, diamantane, and triamantane syntheses (eq 9).[12] A wide variety of polycyclic hydrocarbons can be rearranged to these ring systems. Perhydrogenated phenanthrene rearranges to give mainly *trans*,*syn*,*trans*-perhydroanthracene by the action of $AlBr_3$/HBr in dimethylcyclohexane.[13]

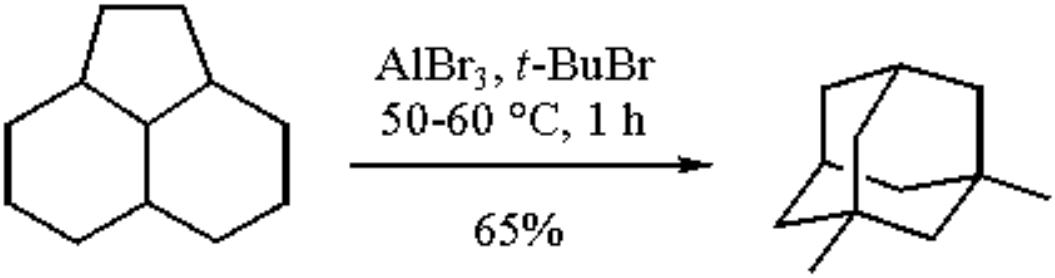

(9)

A facile rearrangement of α-bromoethyldiethylborane (eq 10) occurs when treated with Lewis acids.[14] $AlBr_3$ is very effective for this conversion. $AlCl_3$ or ***Silver(I) Tetrafluoroborate*** also give high yields. The half-life for rearrangement is 0-5 min with these catalysts.

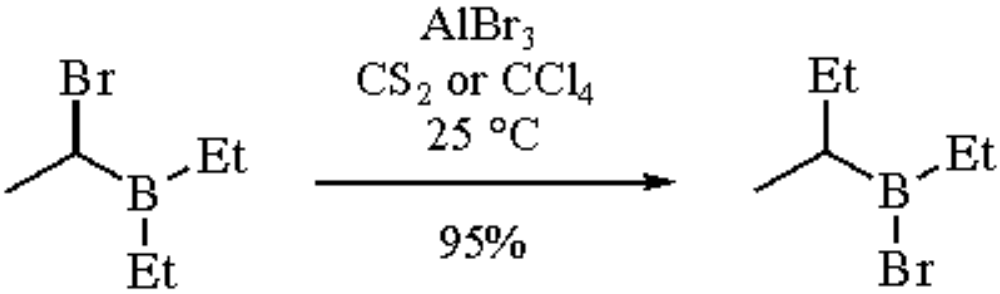

(10)

Diphenylacetylene undergoes dimerization with $AlBr_3$ to give 1,2,3-triphenylazulene.[15] The yield is very dependent on the purity of $AlBr_3$ used. Yields are enhanced by the addition of a small amount of V^{2+} or Ni^{2+}, whereas Ti^{3+}, V^{4+}, Cr^{2+}, Cr^{3+}, Fe^{3+}, or Zn^{2+} almost completely suppress azulene formation.

Friedel-Crafts Reactions.

$AlBr_3$ is a superior reagent for intramolecular Friedel-Crafts cyclization of o-phenylalkanoic acid chlorides ($Ph(CH_2)_nCOCl$; n = 8-15) to the paracyclophanes (eq 11).[16a] Under high dilution conditions, the yields are generally twice as high as that with $AlCl_3$. Negligible yields of medium-sized cyclophanes (n = 8, 5.3%) are obtained. Yields tend to increase with increasing ring size (n = 15, 70%). Other examples of its use as a Friedel-Crafts catalyst and in the Fries rearrangment of phenol esters appear in the literature.[16b-f]

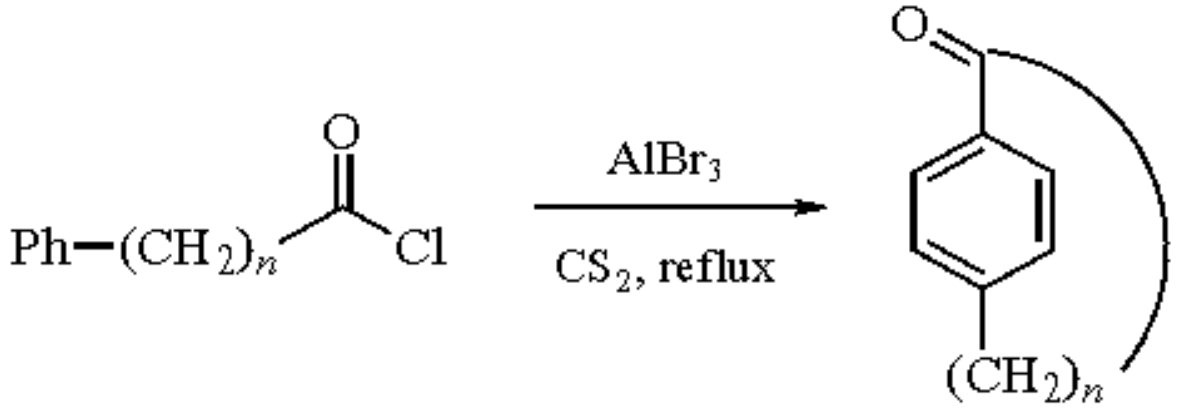

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Aluminum *t*-Butoxide[1]

$Al(O\text{-}t\text{-}Bu)_3$

[556-91-2] · $C_9H_{27}AlO_3$ · Aluminum *t*-Butoxide · (MW 246.32)

(metal alkoxide used in Meerwein-Ponndorf-Verley reduction of ketones[2] and Oppenauer oxidation of alcohols[3])

Physical Data: white powder; mp >300 °C (sealed tube); dimeric structure in benzene; can be recryst from benzene; sublimes at 180 °C.

Solubility: v sol organic solvents, especially alcohols, benzene, toluene, and xylene.

Preparative Method: prepared by reacting ***Aluminum*** shavings with dry *t*-butyl alcohol using a catalytic amount of ***Mercury(II) Chloride***.[1c,1e]

Handling, Storage, and Precautions: use in fume hood. Air and moisture sensitive; extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin and should be handled with appropriate caution. Contact via inhalation route is particularly hazardous.

Meerwein-Ponndorf-Verley Reduction.

The reagent has been used for the reduction of 3-keto steroids, affording predominantly the axial alcohol. Thus reduction of the monoethylene ketal of 3,20-pregnanedione with the reagent in *s*-butyl alcohol, followed by transketalization, gave 3β-hydroxy-5β-pregnan-20-one in modest excess over the 3α-epimer.[2] Separation and oxidation of the undesired epimer followed by reduction as above gave, after several cycles, high conversion of the dione to the desired 3β-alcohol (eq 1)

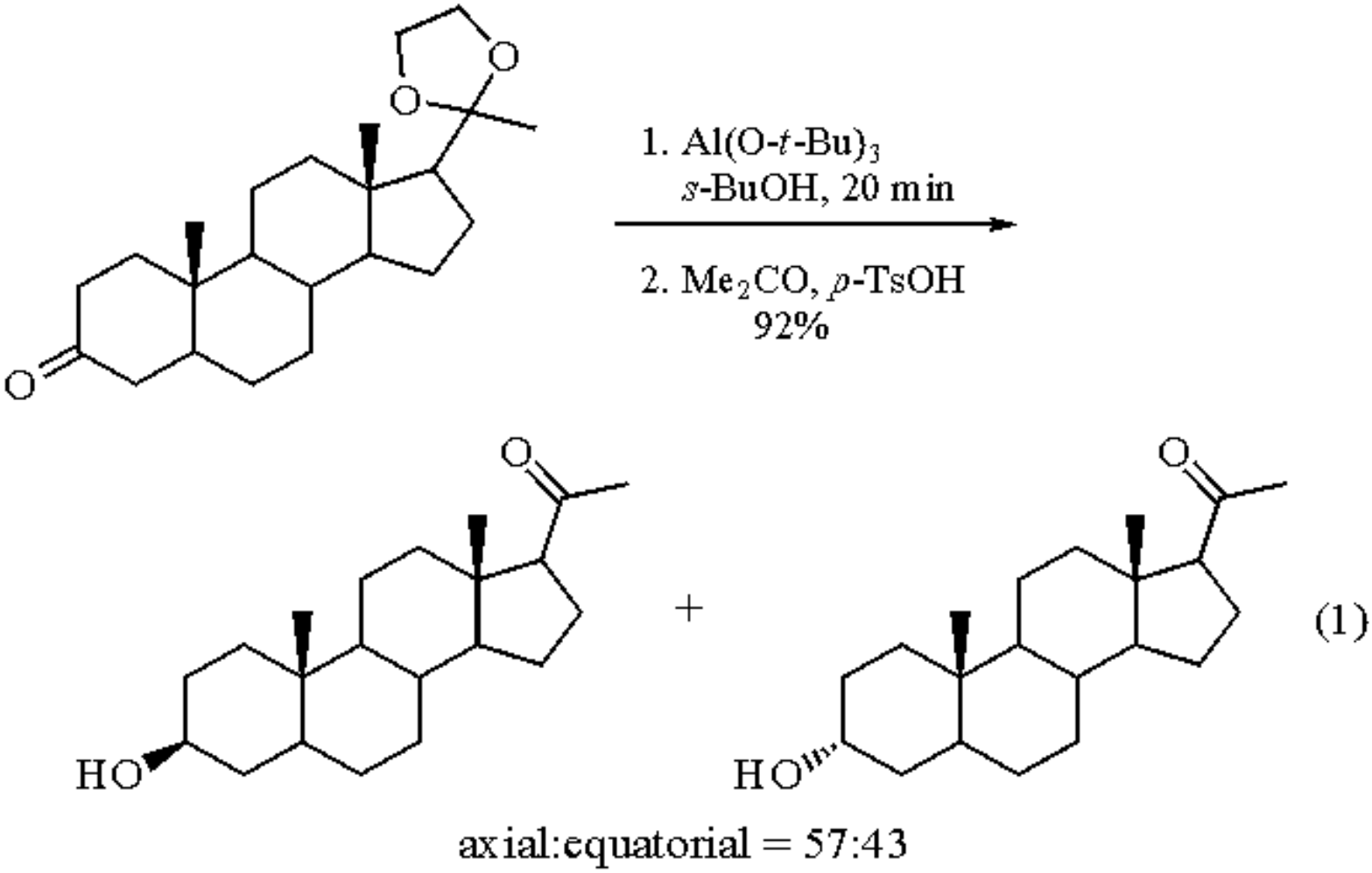

Oppenauer Oxidation.

Aluminum *t*-butoxide is frequently the reagent of choice for this mild oxidation of secondary alcohols to ketones. Since most other oxidizable groups remain unaffected, the method has found wide use in the steroid field, as illustrated by the oxidation of cholesterol to cholest-4-en-3-one (eq 2).[3] The accompanying double bond migration commonly occurs during reactions of steroids of this type.

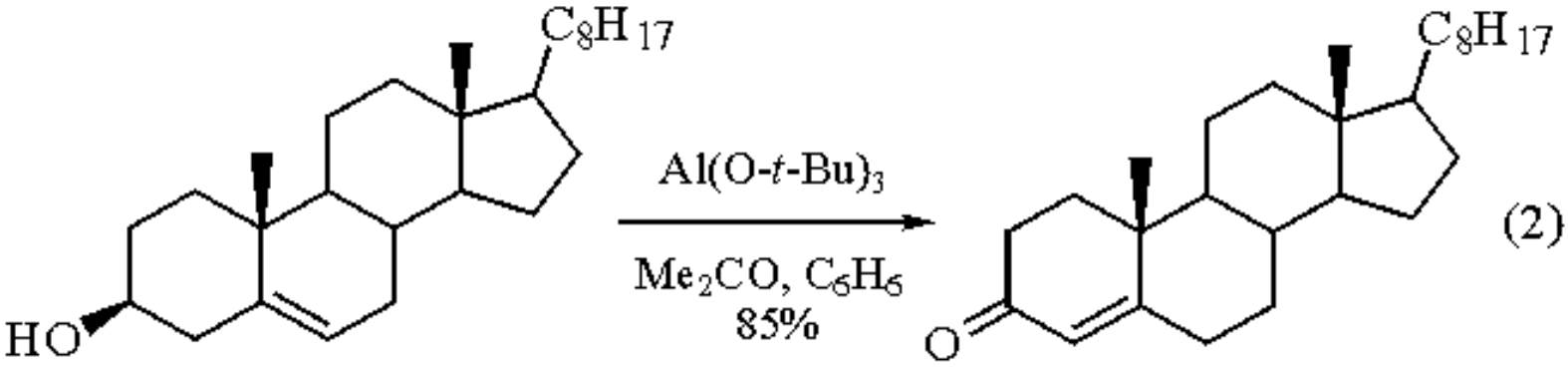

Aldol Condensation.

The reagent has also found limited use as a base for the aldol condensation of methyl ketones, as illustrated by the preparation of dypnone from acetophenone (eq 3).[4]

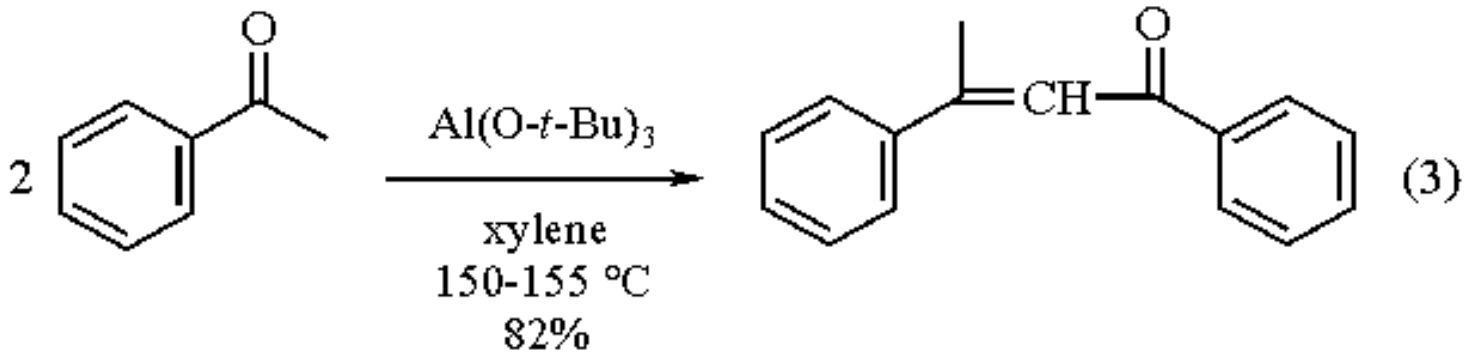

Amine Alkylation.

In the presence of catalytic amounts of ***Raney Nickel*** W-2 and aluminum *t*-butoxide, primary and secondary amines are alkylated by alcohols (eqs 4 and 5).[5]

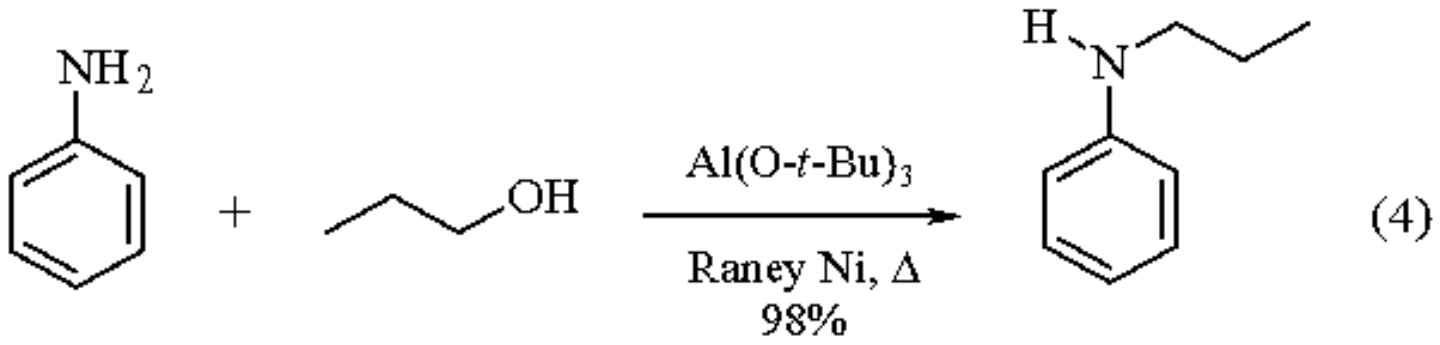

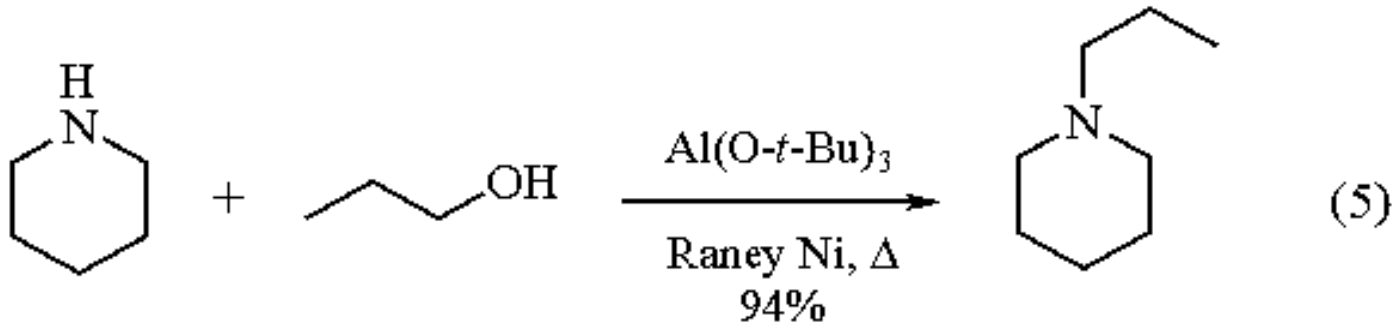

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Aluminum Chloride[1]

$AlCl_3$

[7446-70-0] · $AlCl_3$ · Aluminum Chloride · (MW 133.34)

(Lewis acid catalyst for Friedel-Crafts, Diels-Alder, [2 + 2] cycloadditions, ene reactions, rearrangements, and other reactions)

Physical Data: mp 190 °C (193-194 °C sealed tube); sublimes at 180 °C; *d* 2.44 g cm^{-3}.

Solubility: sol many organic solvents, e.g. benzene, nitrobenzene, carbon tetrachloride, chloroform, methylene chloride, nitromethane, and 1,2-dichloroethane; insol carbon disulfide.

Form Supplied in: colorless solid when pure, typically a gray or yellow-green solid; also available as a 1.0 M nitrobenzene solution.

Handling, Storage, and Precautions: fumes in air with a strong odor of HCl. $AlCl_3$ reacts violently with H_2O. All containers should be kept tightly closed and protected from moisture.[1c] Use in a fume hood.

Friedel-Crafts Chemistry.[1,2]

$AlCl_3$ has traditionally been used in stoichiometric or catalytic[3] amounts to mediate Friedel-Crafts alkylations and acylations of aromatic systems (eq 1).

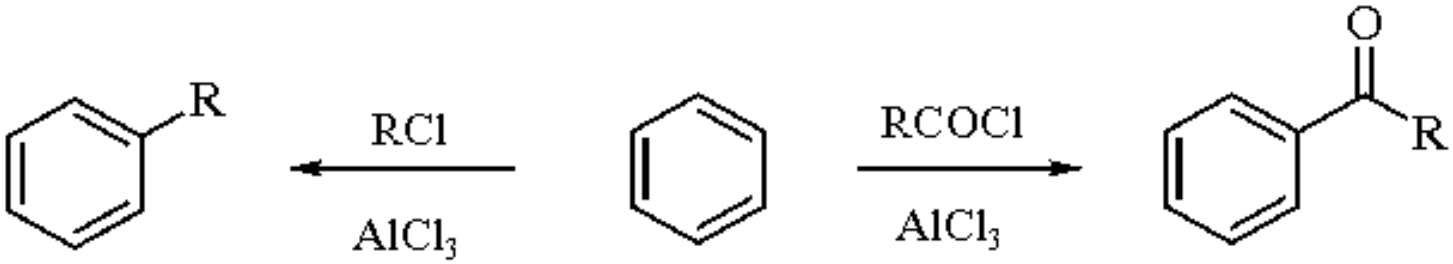

(1)

This is a result of the Lewis acidity of $AlCl_3$ which complexes strongly with carbonyl groups.[4] Adaptations of these basic reactions have been reported.[5] In chiral systems, inter- and intramolecular acylations have been achieved without the loss of optical activity (eq 2).[6]

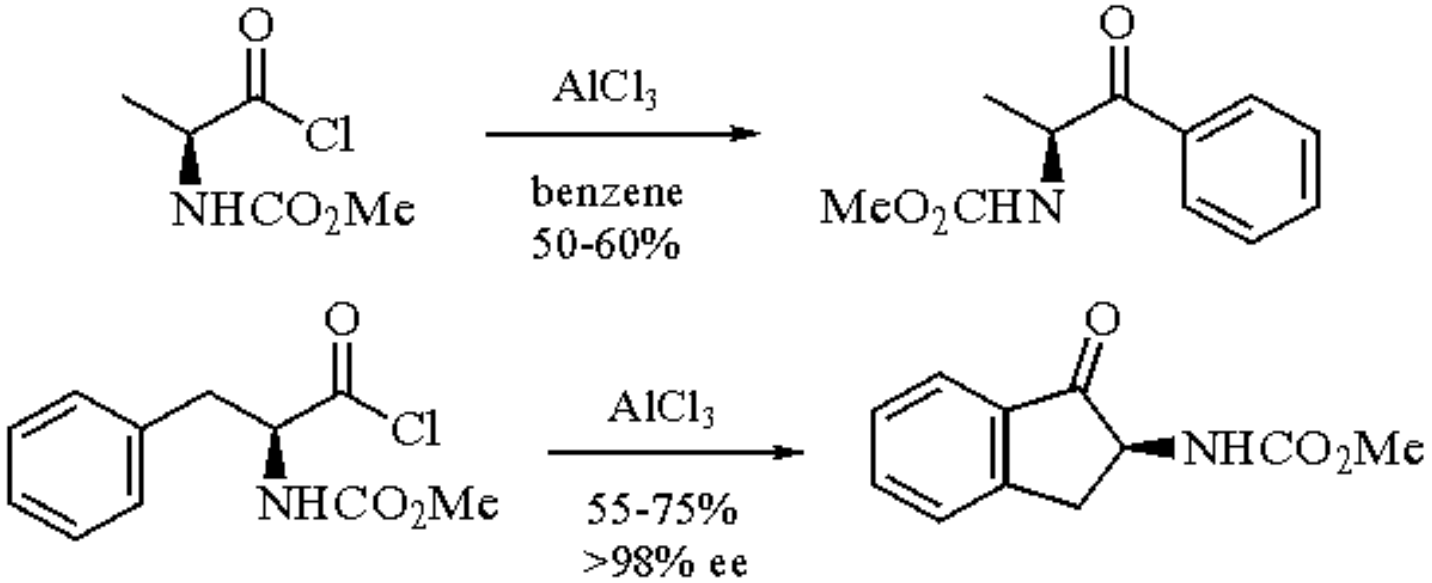

(2)

Friedel-Crafts chemistry at an asymmetric center generally proceeds with racemization, but the use of mesylates or chlorosulfonates as leaving groups has resulted in alkylations with excellent control of stereochemistry.[7] The reactions proceed with inversion of configuration (eq 3). Cyclopropane derivatives have been used as three-carbon units in acylation reactions (eq 4).[8] In conjunction with triethylsilane, a net alkylation is possible under acylation conditions (eq 5).[9] These conditions are compatible with halogen atoms present elsewhere in the molecule. Acylation reactions of phenolic compounds with heteroaromatic systems have also been accomplished (eq 6).[10]

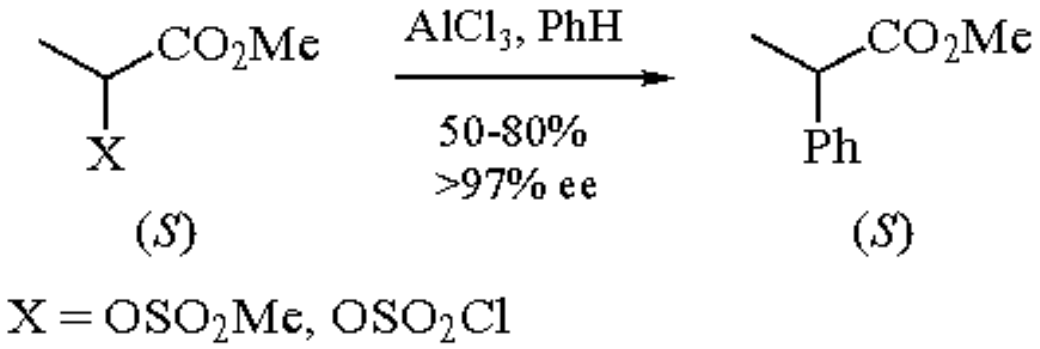

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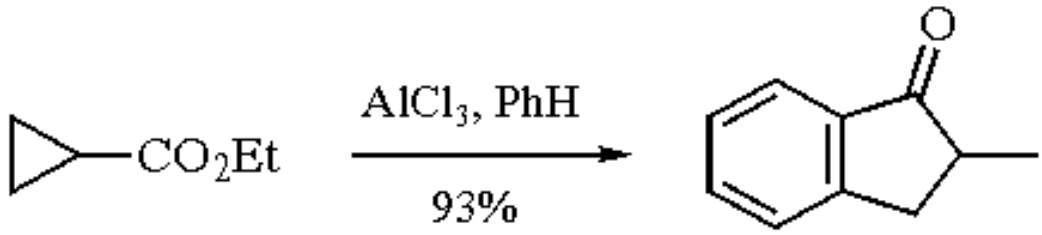

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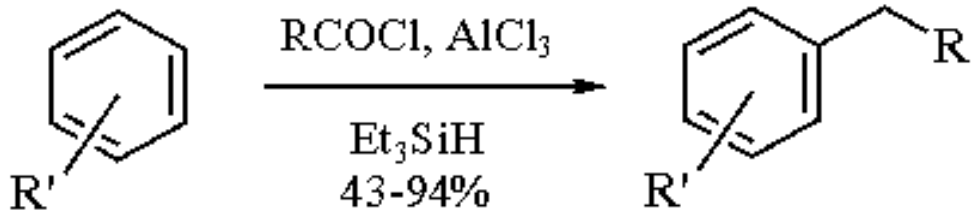

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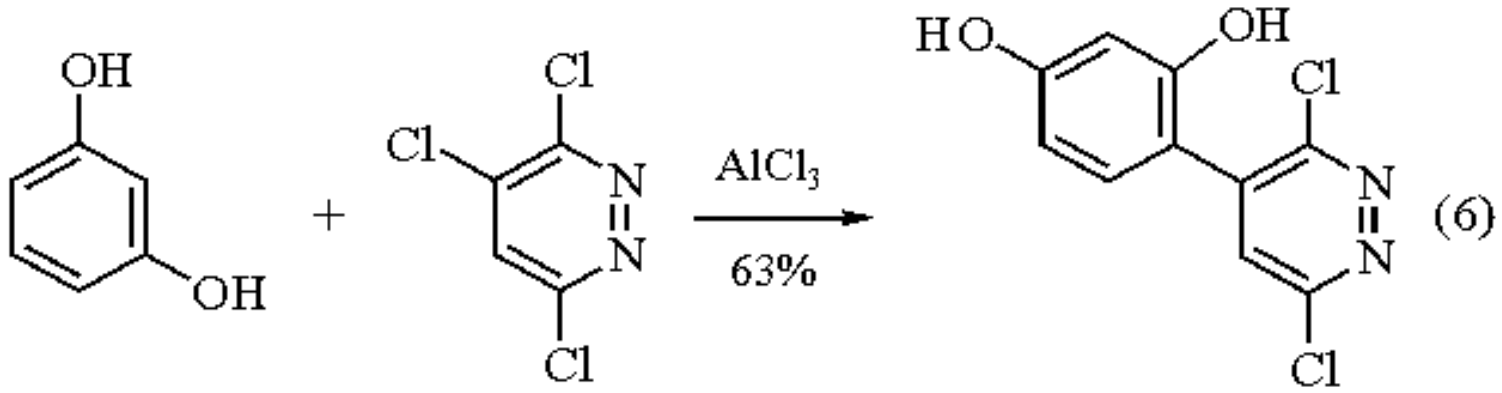

Treatment of aryl azides with $AlCl_3$ has been reported to give polycyclic aromatic compounds (eq 7),[11] or aziridines when the reactions are run in the presence of alkenes (eq 8).[12]

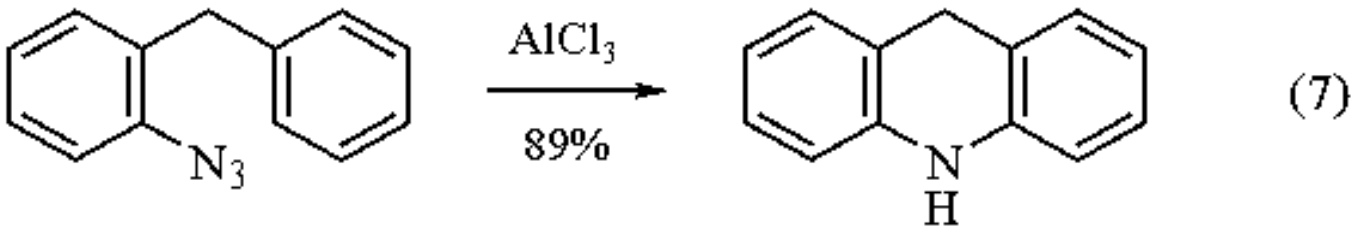

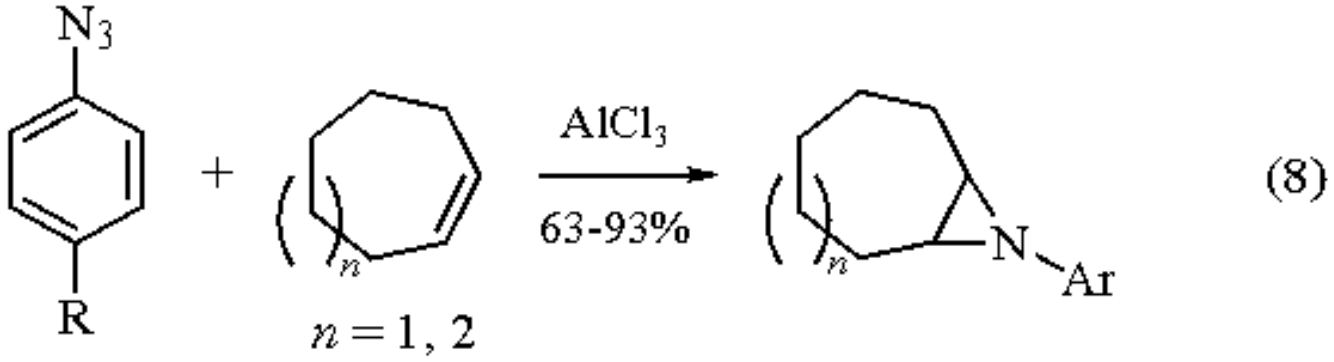

The scope of Friedel-Crafts chemistry has been expanded beyond aromatic systems to nonaromatic systems, such as alkenes and alkynes and the mechanistic details have been investigated.[13] The Friedel-Crafts alkylation[14] and acylation[15] of alkenes provide access to a variety of organic systems (eq 9). The acylation of alkynes provides access to cyclopentenone derivatives (eq 10).[16] In addition, one can use this chemistry to access indenyl systems[17] and vinyl chlorides.[18] Allylic sulfones can undergo allylation chemistry (eq 11).[19]

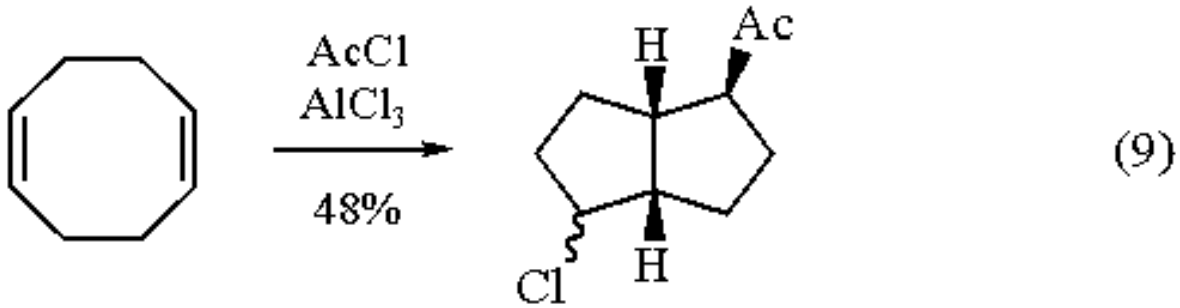

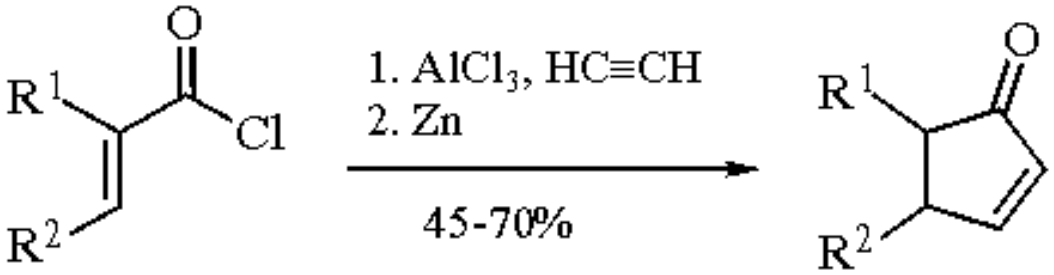

(10)

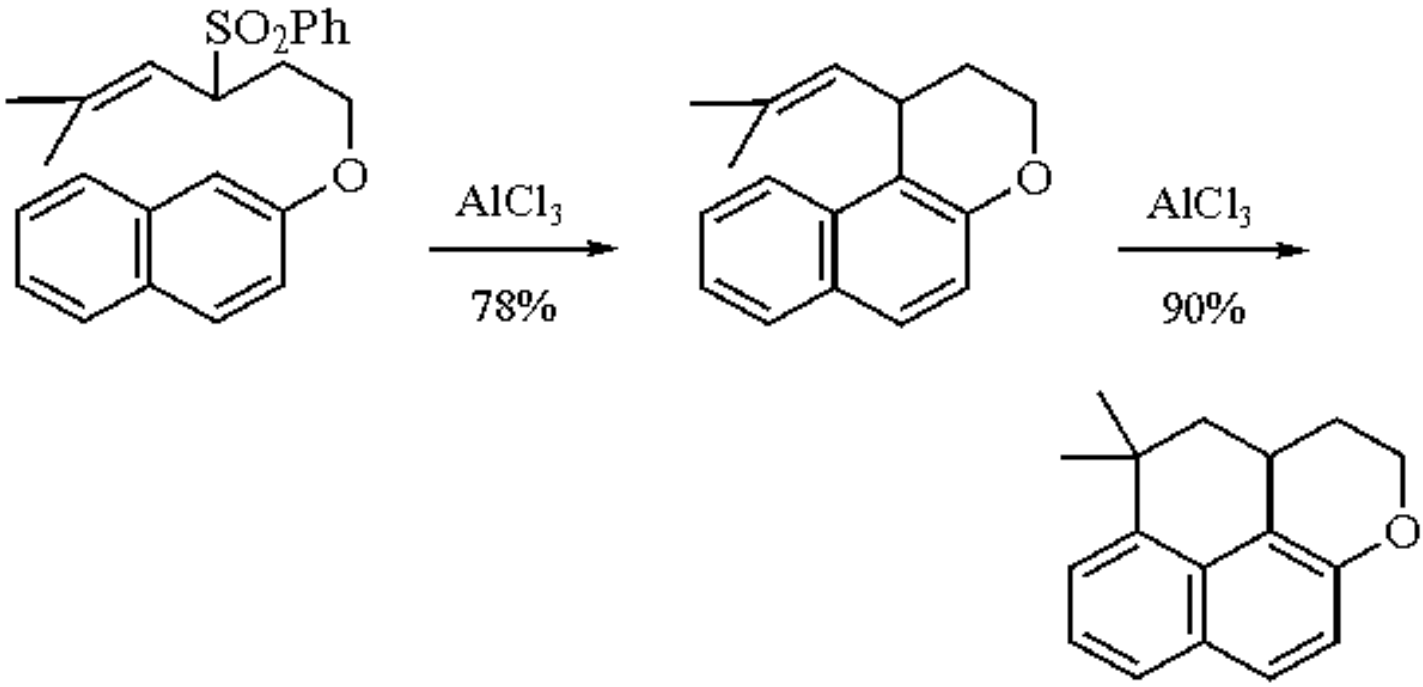

(11)

The use of silyl derivatives in Friedel-Crafts chemistry has not only improved the regioselectivity but extended the scope of these reactions. Substitution at the *ipso* position occurs with aryl silanes (eq 12).[20] The ability of silyl groups to stablize β-carbenium ions (β-effect) affords acylated products with complete control of regiochemistry (eq 13).[21]

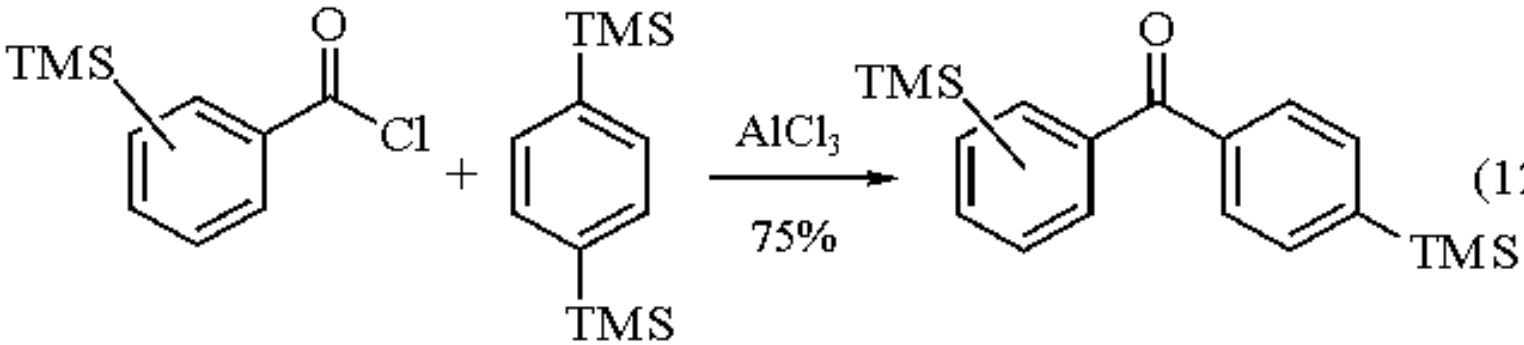

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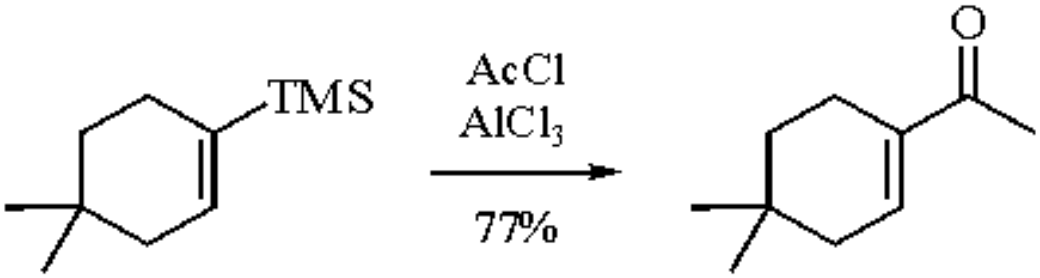

(13)

The use of silylacetylenes gives ynones (eq 14),[22] cyclopentenone derivatives (eq 15),[23] and α-amino acid derivatives (eq 16).[24]

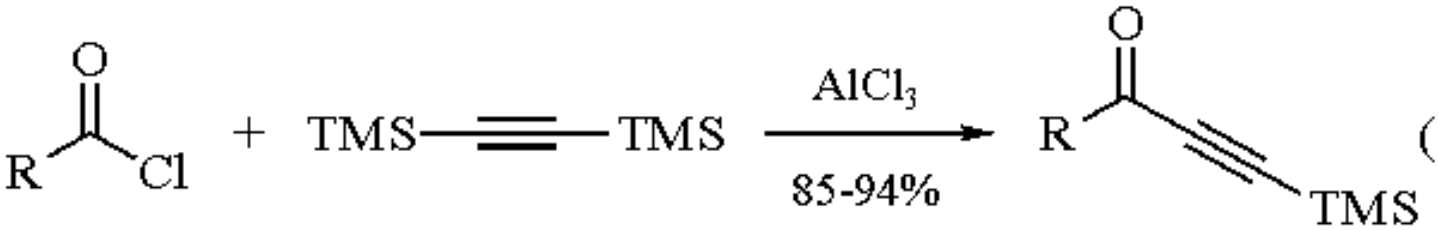

(14)

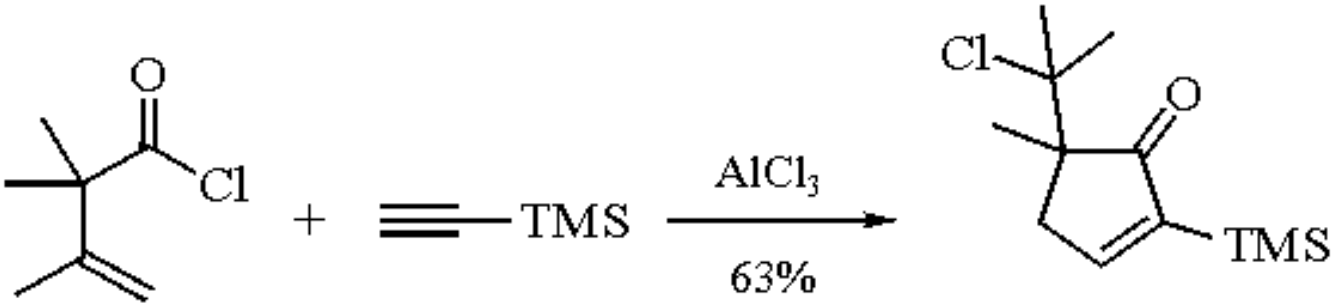

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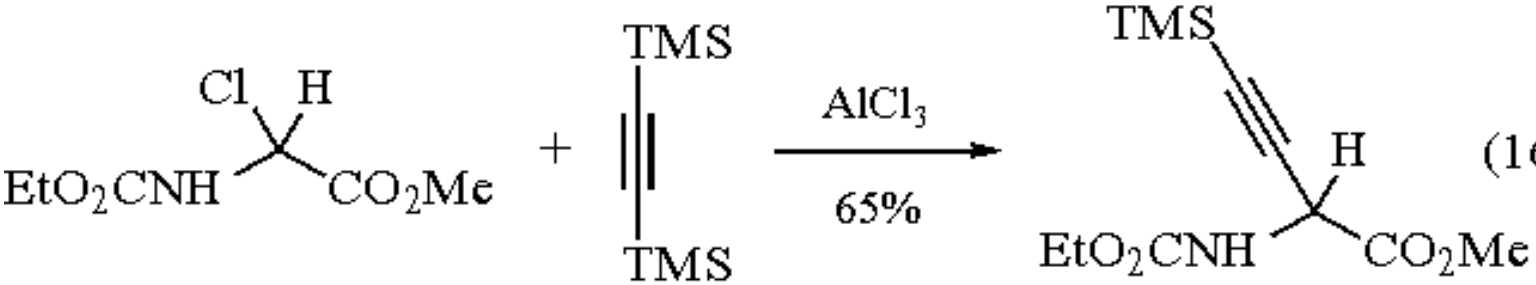

(16)

Propargylic silanes undergo acylation to generate allenyl ketones (eq 17),[25] while alkylsilanes afford cycloalkanones (eq 18).[26]

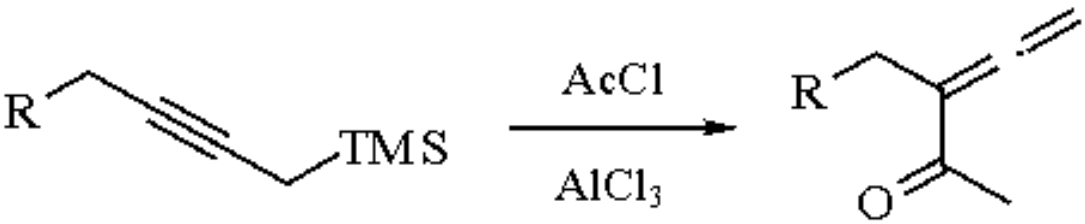

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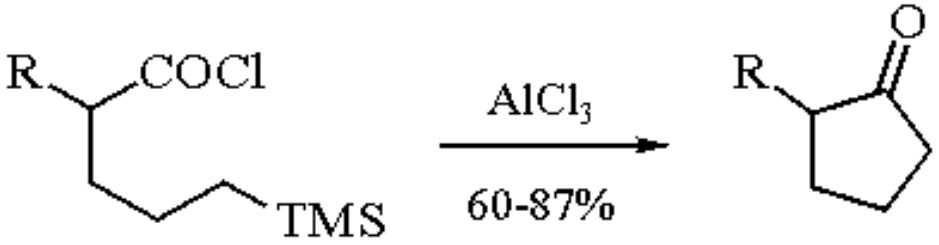

(18)

Several name reactions are promoted by $AlCl_3$. For example, the Darzens-Nenitzescu reaction is simply the acylation of alkenes. The Ferrario reaction generates phenoxathiins from diphenyl ethers (eq 19).[27] The rearrangement of acyloxy aromatic systems is known as the Fries rearrangement (eq 20).[28] Aryl aldehydes are produced by the Gatterman aldehyde synthesis (eq 21).[29] The initial step of the Haworth phenanthrene synthesis makes use of a Friedel-Crafts acylation.[30] The acylation of phenolic compounds is called the Houben-Hoesch reaction (eq 22).[31] The Leuckart amide synthesis generates aryl amides from isocyanates (eq 23).[32]

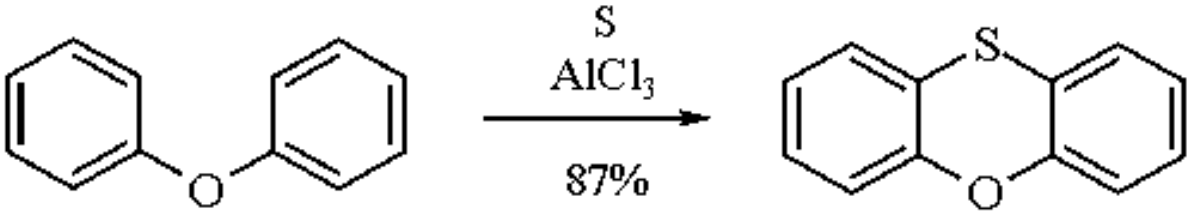

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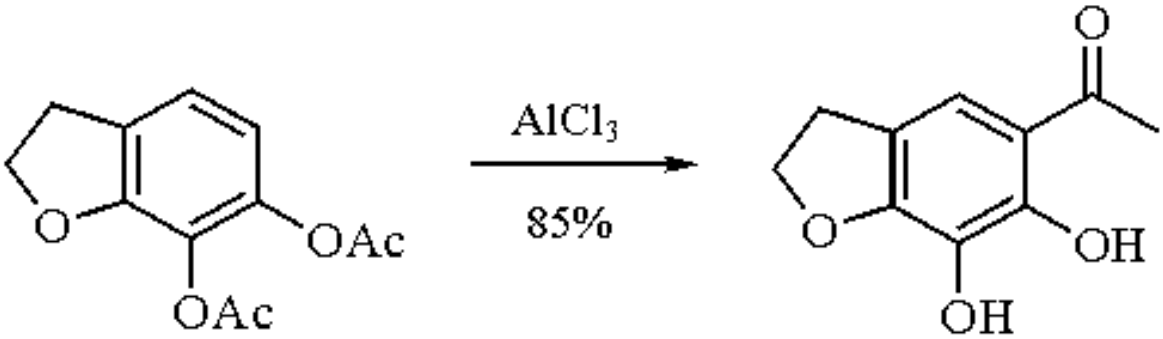

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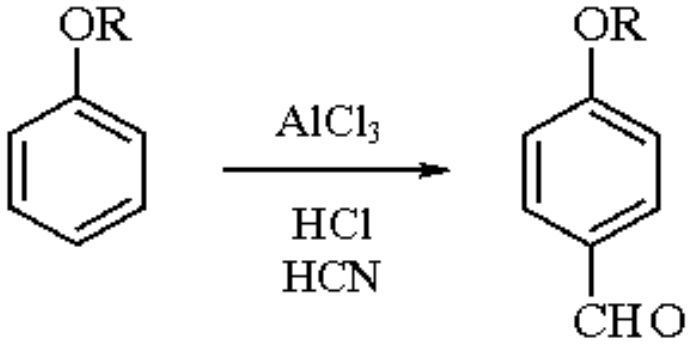

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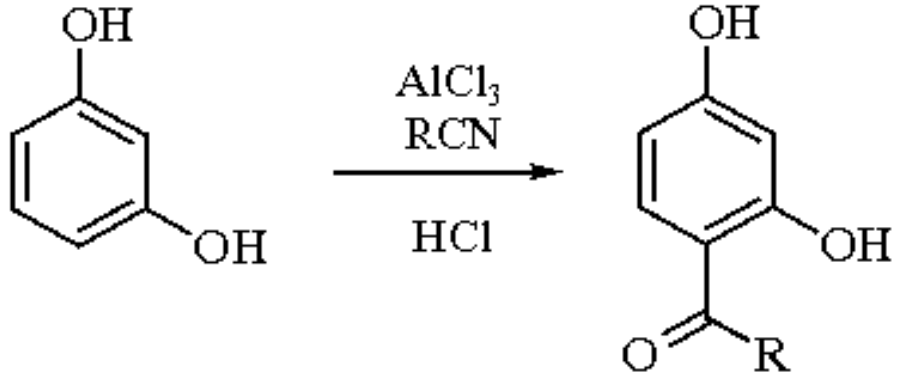

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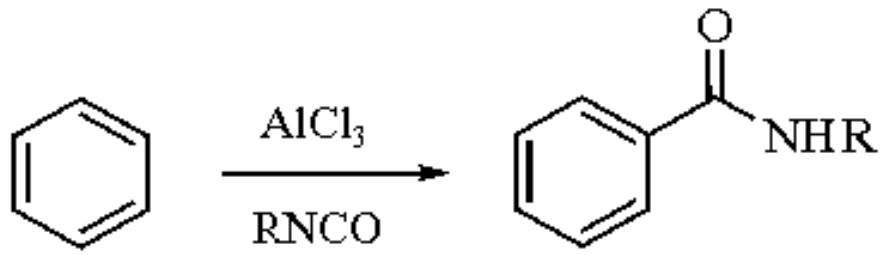

(23)

Amides can also be obtained by $AlCl_3$ catalyzed ester amine exchange which proceeds primarily without racemization of chiral centers (eq 24).[33] The reaction of phenols with β-keto esters is known as the Pechmann condensation (eq 25).[34] Aryl amines are used in the Riehm quinoline synthesis (eq 26).[35] Aromatic systems may be coupled via the Scholl reaction (eq 27)[36] and indole derivatives are prepared in the Stolle synthesis (eq 28).[37] In the Zincke-Suhl reaction, phenols are converted to dienones (eq 29).[38]

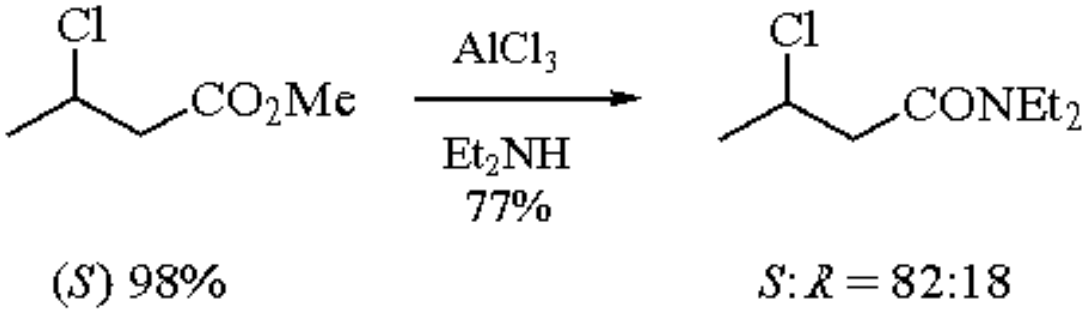

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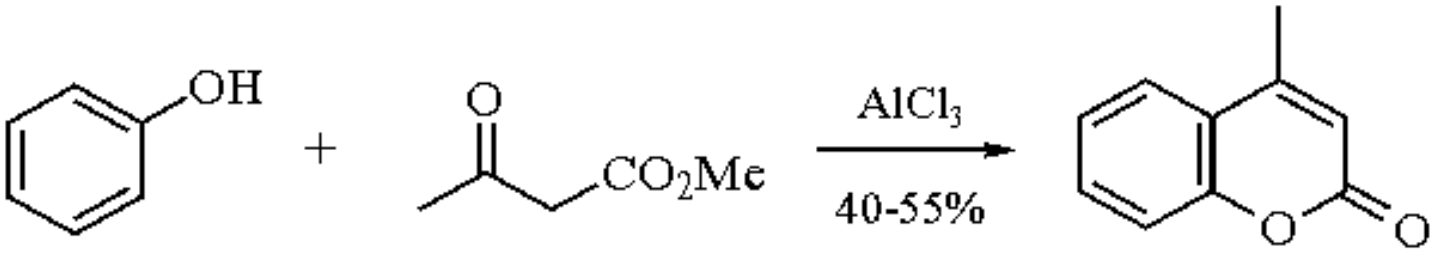

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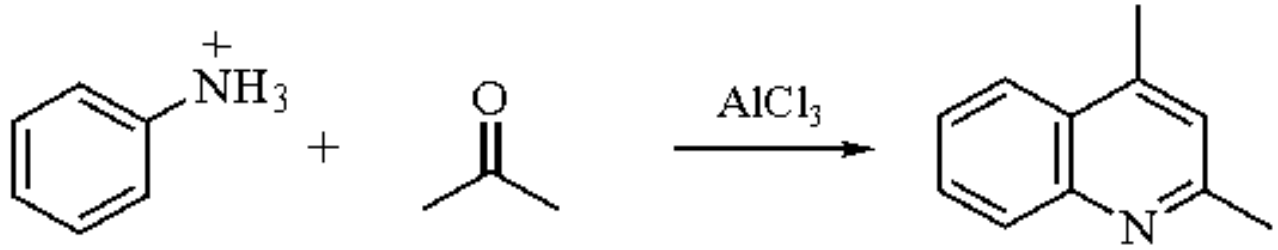

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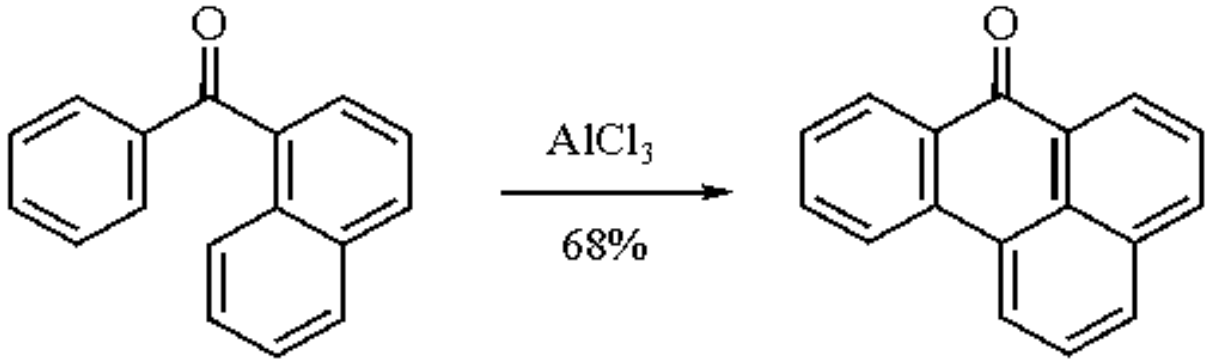

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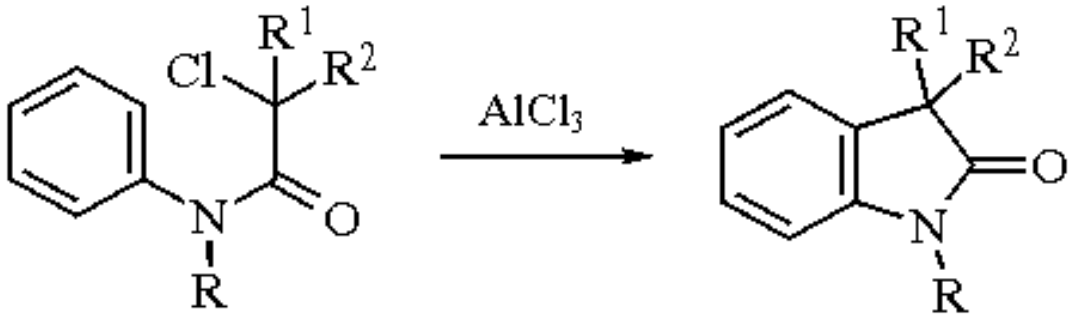

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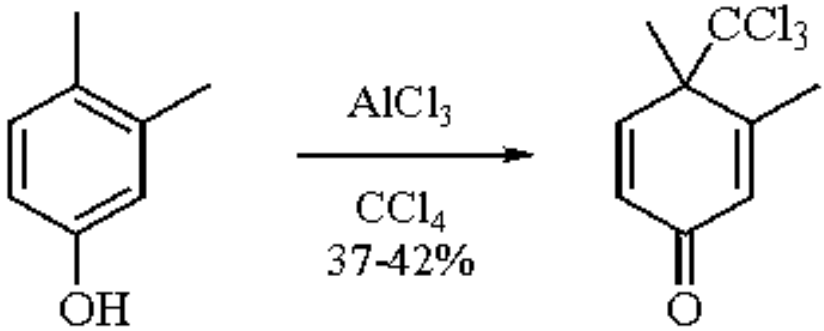

(29)

Diels-Alder Reactions.

There is some evidence that $AlCl_3$ catalysis of Diels-Alder reactions changes the transition state from a synchronous to an asynchronous one.[39] This also enhances asymmetric induction by increasing steric interactions at one end of the dieneophile. There are many examples of $AlCl_3$ promoted Diels-Alder reactions (eq 30).[40] Hetero-Diels-Alder reactions can be used to generate oxygen (eq 31)[41] and nitrogen (eq 32)[42] containing heterocycles.

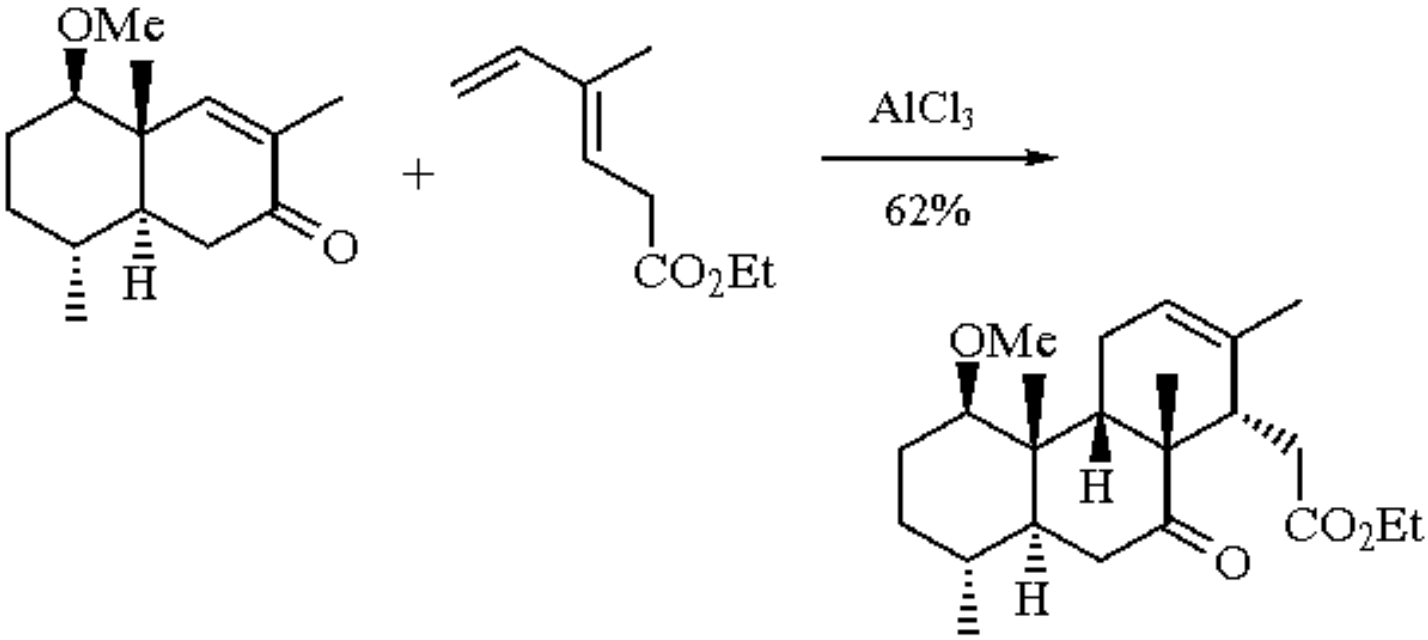

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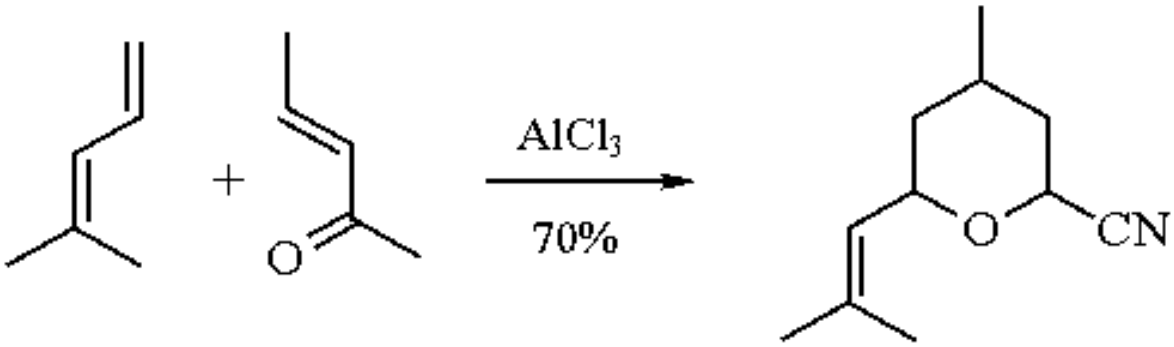

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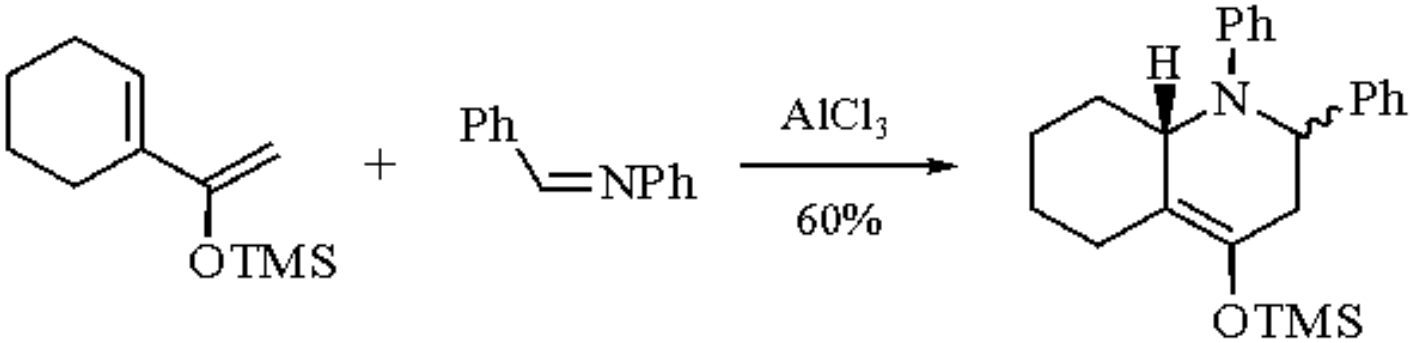

(32)

$AlCl_3$ can also be used to catalyze [2 + 2] cycloaddition reactions (eq 33)[43] and ene reactions (eq 34).[44]

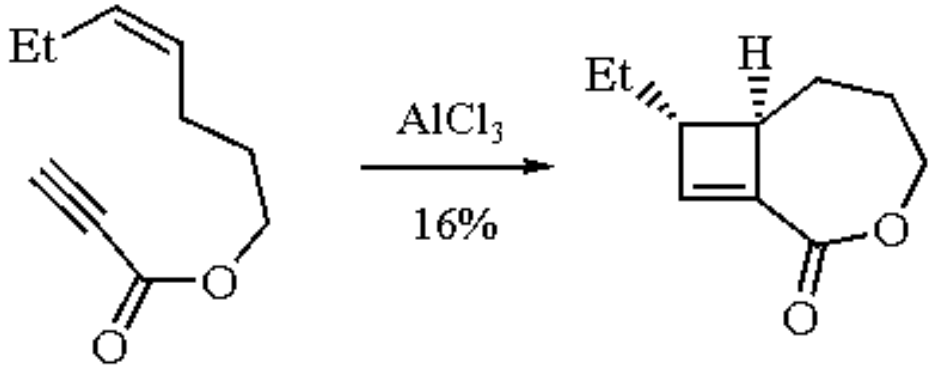

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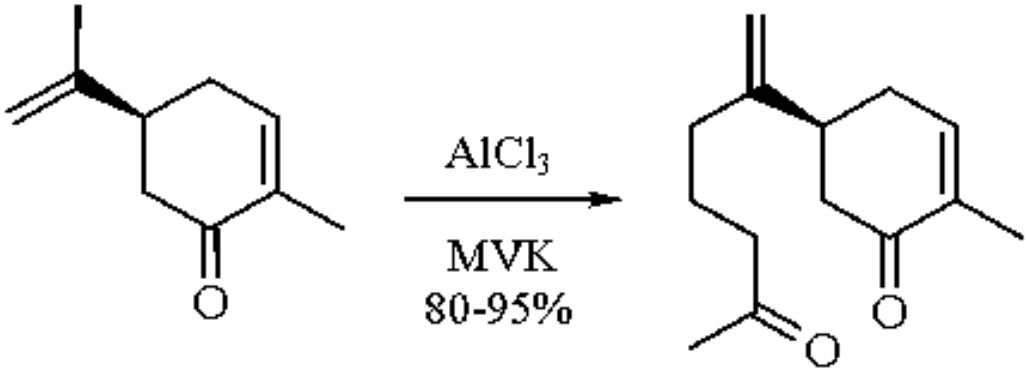

(34)

Rearrangements.

$AlCl_3$ catalyzed rearrangement of hydrocarbon derivatives to adamantanes has been well documented (eq 35).[45] Other rearrangements have been used in triquinane synthesis (eq 36).[46]

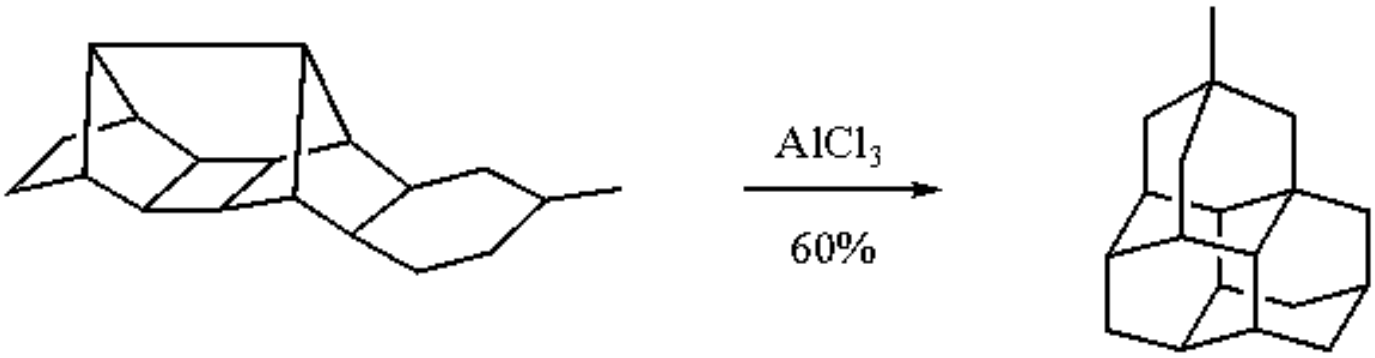

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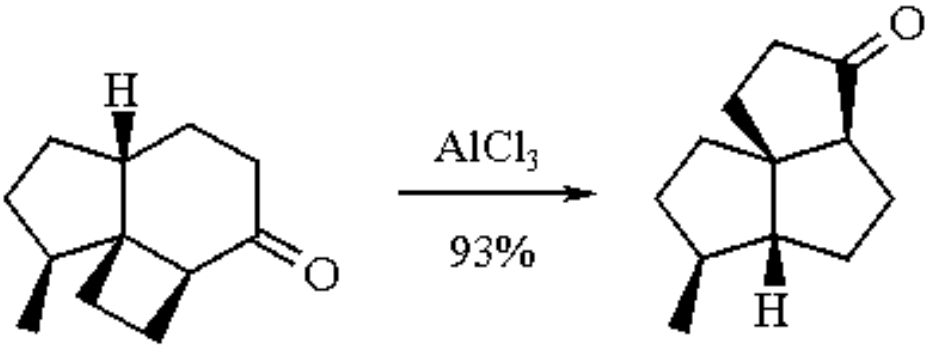

(36)

Miscellaneous Reactions.

$AlCl_3$ has been used to catalyze the addition of allylsilanes to aldehydes and acid chlorides (eq 37).[47] Cyclic ethers (pyrans and oxepins) have been prepared with hydroxyalkenes (eq 38).[48] The course of reactions between aldehydes and allylic Grignard reagents can be completely diverted to α-allylation by $AlCl_3$ (eq 39).[49] The normal course of the reaction gives γ-allylation products.

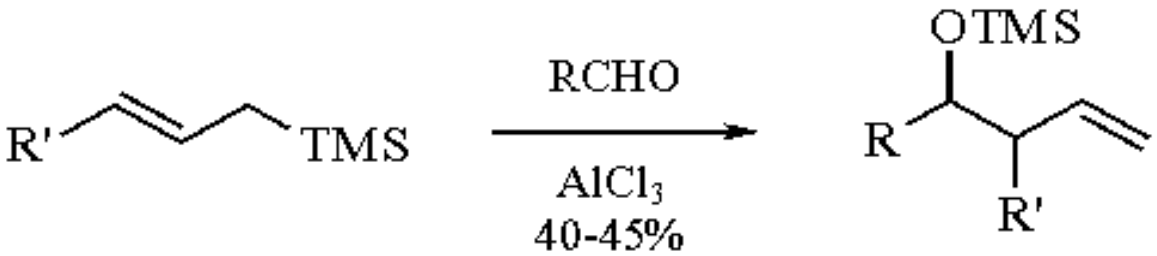

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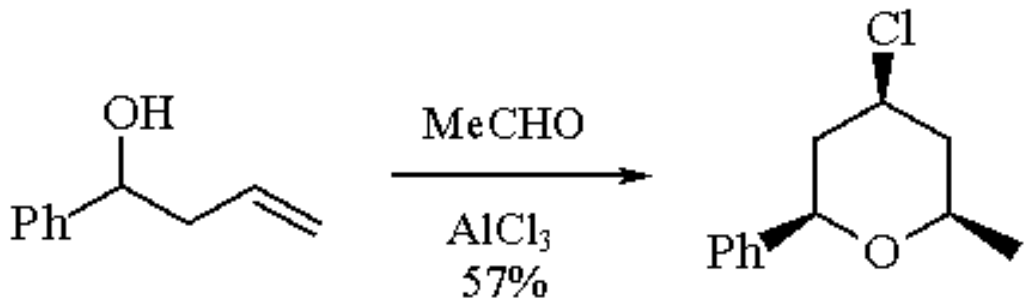

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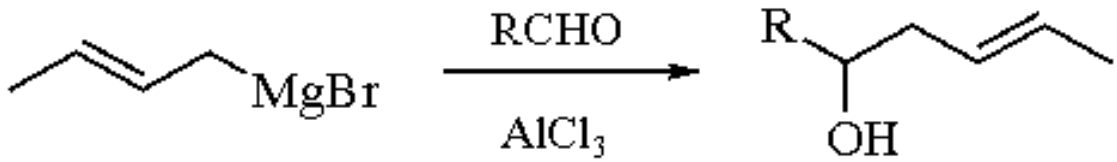

(39)

$AlCl_3$ can be used to remove *t*-butyl groups from aromatic rings (eq 40),[50] thereby using this group as a protecting element for a ring position. $AlCl_3$ has also been used to remove *p*-nitrobenzyl (PNB) and benzhydryl protecting groups (eq 41).[51] The combination of $AlCl_3$ and ***Ethanethiol*** has formed the basis of a push-pull mechanism for the cleavage of many types of bonds including C-X,[52] C-NO_2,[53] C=C,[54] and C-O.[55] Furthermore, $AlCl_3$ has been used to catalyze chlorination of aromatic rings,[56] open epoxides,[57] and mediate addition of dichlorophosphoryl groups to alkanes.[58]

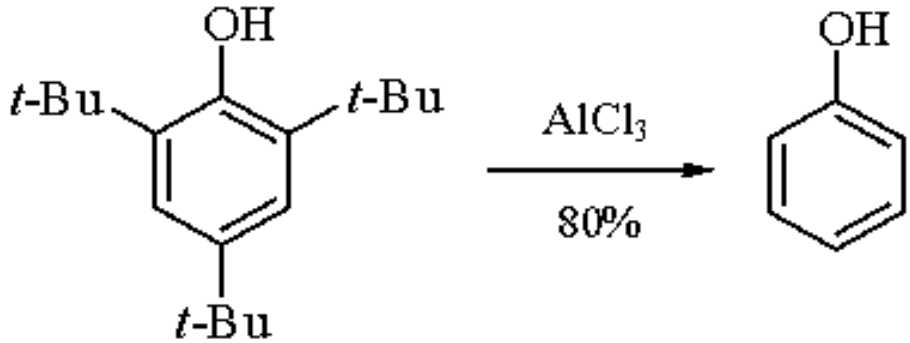

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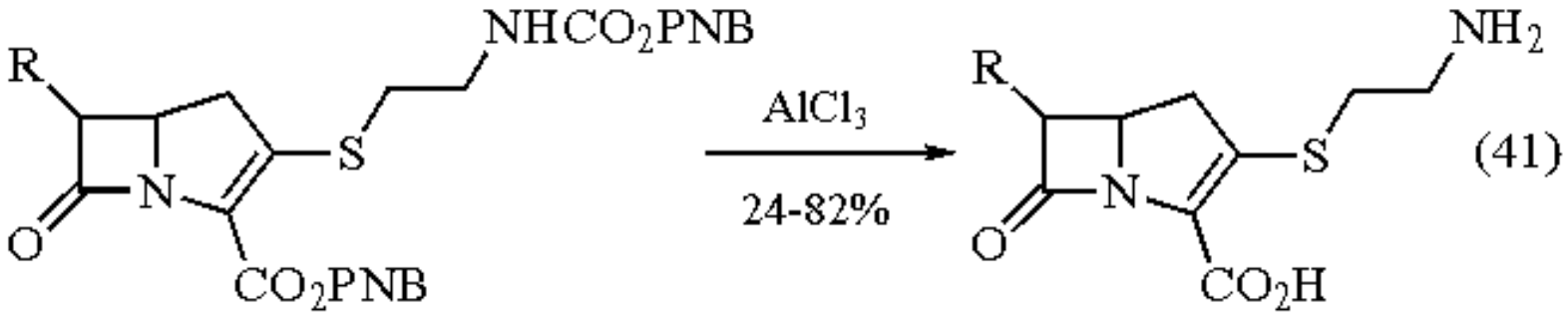

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Aluminum Cyclohexoxide[1]

$Al(OCy)_3$

[-] · $C_{18}H_{33}AlO_3$ · Aluminum Cyclohexoxide · (MW 324.42) (Al)

[7429-90-5] · Al · Aluminum Cyclohexoxide · (MW 26.98) (CyOH)

[108-93-0] · $C_6H_{12}O$ · Aluminum Cyclohexoxide · (MW 100.18)

(reducing agent for anthraquinone-related ring systems)

Preparative Method: prepared in situ from ***Aluminum*** in refluxing cyclohexanol.[2]

Handling, Storage, and Precautions: use in a fume hood. The reagent should be freshly prepared just prior to use. Many aluminum alkoxides are extremely irritating to skin, eyes, and mucous membranes and should be handled with appropriate caution. Contact via inhalation route is particularly hazardous.

Reduction.

The reagent has been used by several groups for the reduction of anthraquinone and related derivatives to the corresponding anthracene ring systems under what are essentially Meerwein-Ponndorf-Verley reduction conditions.[1] Thus treatment of anthraquinone[2] or tetramethylanthraquinone[3] with the reagent in boiling cyclohexanol afforded anthracene and 2,3,6,7-tetramethylanthracene, respectively, in good yield (eq 1).

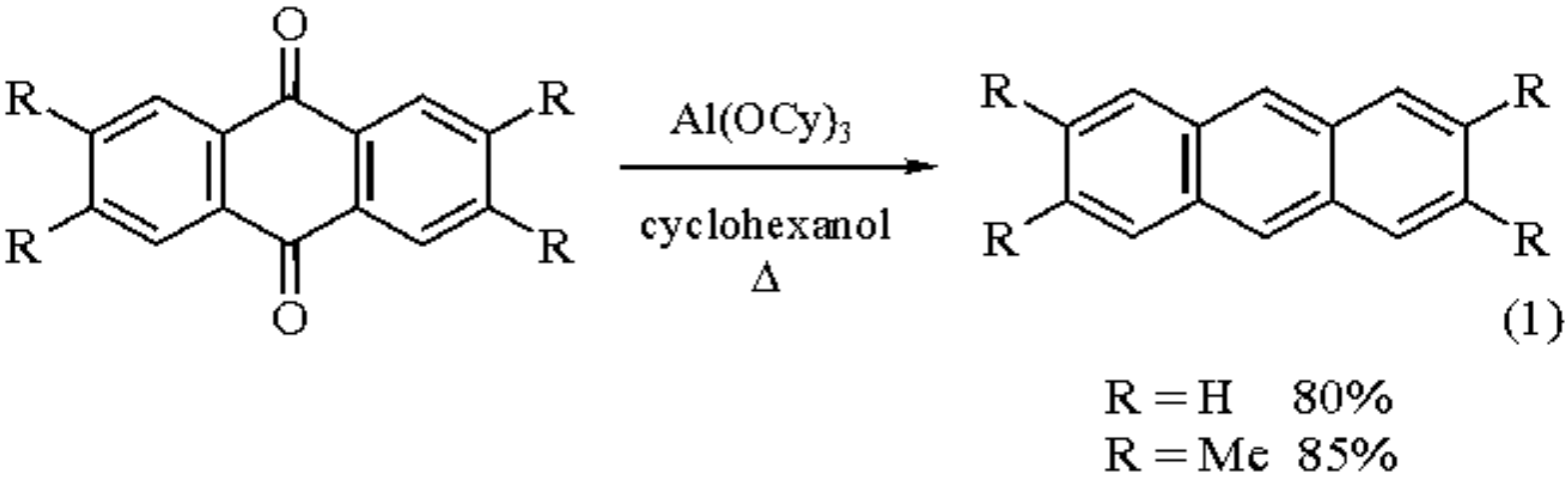

The polycyclic aromatic hydrocarbons benz[*a*]anthracene[4] and 2,3,6,7-dibenzanthracene (pentacene)[5] have been prepared in a similar fashion (eqs 2 and 3).

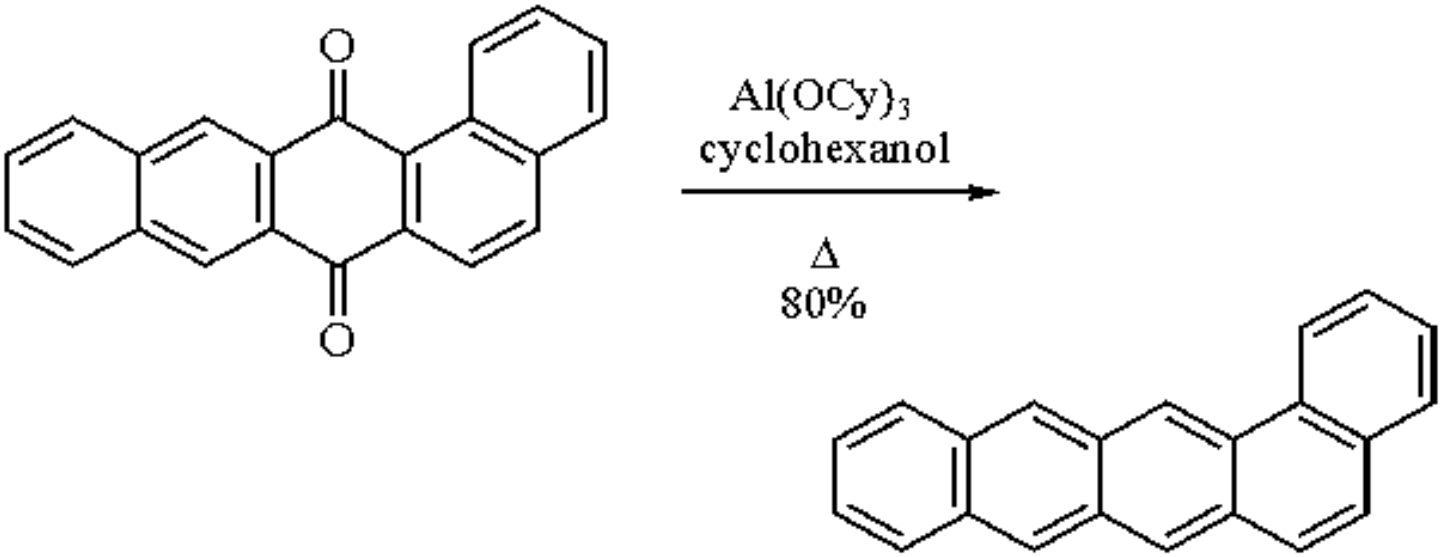

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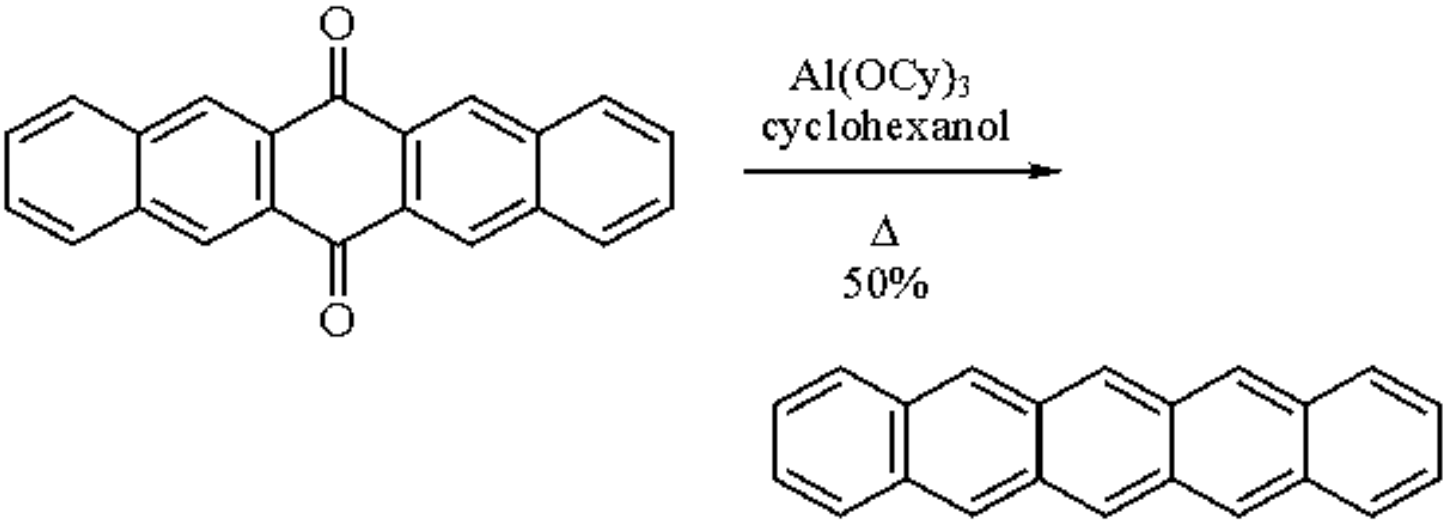

(3)

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Aluminum Ethoxide[1]

$Al(OEt)_3$

[555-75-9] · $C_6H_{15}AlO_3$ · Aluminum Ethoxide · (MW 162.16)

(reagent for reduction of aldehydes to alcohols;[2] catalyst for conversion of aldehydes to esters[3])

Physical Data: mp 157-160 °C; liq bp 200 °C/6-8 mmHg; mixture of oligomers in solution; physical properties drastically affected by traces of moisture.

Solubility: sol hot xylene, cholorobenzene, other high boiling solvents.

Form Supplied in: available as white powder.

Preparative Method: react ***Aluminum*** filings with absolute ethanol using small amounts of ***Mercury(II) Chloride*** or ***Iodine*** as catalysts.[4]

Handling, Storage, and Precautions: use in a fume hood; air and moisture sensitive; extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes and skin, and should be handled with appropriate caution. Contact via inhalation route is particularly hazardous.

Reductions.

The reagent, while commercially available, may be conveniently prepared prior to use.[4] It has been used in Meerwein-Ponndorf-Verley reductions for the selective conversion of α-halo aldehydes and α,β-unsaturated aldehydes to the corresponding alcohols. For example, reaction of chloral with aluminum ethoxide in ethanol as solvent gives acetaldehyde and the aluminum salt of trichloroethanol. Subsequent treatment of the salt with sulfuric acid liberates trichloroethanol in excellent yield (eq 1).[4] Similar high-yield reductions have been carried out on bromal, cinnamaldehyde, and various halogenated cinnamyl and crotyl aldehydes.[2,5]

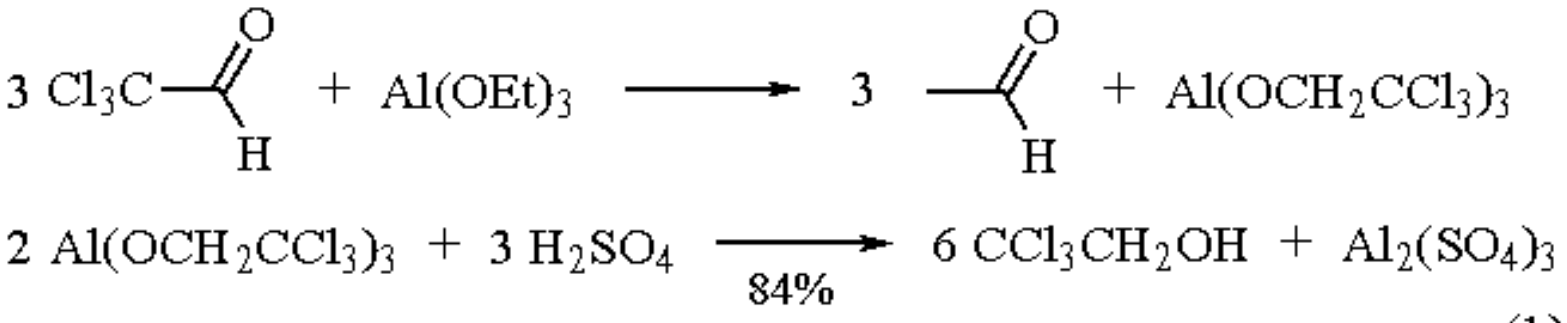

(1)

Esters from Aldehydes.

When Tishchenko treated a variety of aldehydes with a catalytic amount of aluminum ethoxide in the absence of solvents, he obtained primarily esters derived from oxidation of one half of the aldehyde and reduction of the other half. Extensive studies later verified this early work.[6] Although alkali metal alkoxides have been used successfully in the Tishchenko reaction for aldehydes lacking α-hydrogens,[3b] aluminum ethoxide is almost invariably the catalyst of choice in those cases where aldol condensations would otherwise predominate. For example, treatment of butanal, 2-ethylbutanal, or octanal with aluminum ethoxide (5% by weight relative to the aldehyde) gave the corresponding esters in good yield (eq 2).[6b] Crossed Tishchenko reactions generally give mixtures of products.

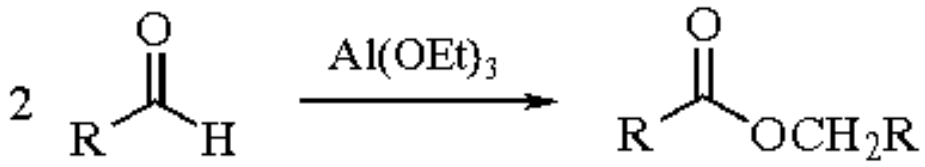

(2)

R = *n*-Pr	81%
R = Et_2CH	70%
R = $Me(CH_2)_6$	69%

Aluminum ethoxide in xylene has also been used to polymerize terephthalaldehyde into high molecular weight chains in a Tishchenko-like process.[7]

---

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Aluminum Hydride[1]

AlH_3

[7784-21-6] · AlH_3 · Aluminum Hydride · (MW 29.99)

(reducing agent for many functional groups; used in hydroalumination of alkynes; allylic rearrangements)

Alternate Name: alane.

Physical Data: colorless, nonvolatile solid in a highly polymerized state; mp 110 °C (dec). X-ray data have also been obtained.[2]

Solubility: sol THF and ether; precipitates from ether after standing for approximately 30 min depending upon method of preparation.

Analysis of Reagent Purity: hydride concentration can be determined by hydrolyzing aliquots and measuring the hydrogen evolved.[3]

Preparative Methods: can be prepared by treating an ether solution of ***Lithium Aluminum Hydride*** with ***Aluminum Chloride*** (eq 1).[4] This affords an ether solution of AlH_3 after precipitation of LiCl. Solutions have to be used immediately otherwise AlH_3 precipitates as a white solid which consists of a polymeric material with ether. The solvent can be removed and the solid redissolved in THF.[5] Alternatively, THF solutions can be prepared directly according to one of the reactions shown in eqs 2-4.[5,6]

$$3\ LiAlH_4 + AlCl_3 \longrightarrow 4\ AlH_3 + 3\ LiCl \qquad (1)$$

$$2\ LiAlH_4 + BeCl_2 \longrightarrow 2\ AlH_3 + LiBeH_2Cl_2 \qquad (2)$$

$$2\ LiAlH_4 + H_2SO_4 \longrightarrow 2\ AlH_3 + Li_2SO_4 + 2\ H_2 \qquad (3)$$

$$2\ LiAlH_4 + ZnCl_2 \longrightarrow 2\ AlH_3 + 2\ LiCl + ZnH_2 \qquad (4)$$

Handling, Storage, and Precautions: solutions of AlH_3 are not spontaneously inflammable.[3] However, since AlH_3 has reactivity comparable to $LiAlH_4$, one should follow similar handling and precautions as those exercised for $LiAlH_4$. Solutions of AlH_3 are prepared in situ but are known to degrade after 3 days, and long term storage of solutions is not possible. Use in a fume hood.

Functional Group Reductions.

Reductions by alane take place primarily by a two-electron mechanism.[7,8] However, evidence for a SET pathway exists.[9] AlH_3 will reduce a wide variety of functional groups.[4] These include aldehydes, ketones, quinones, carboxylic acids, anhydrides, acid chlorides, esters, and lactones, from which the corresponding alcohol is the isolated product. Amides, nitriles, oximes, and isocyanates are reduced to amines. Nitro compounds are inert to AlH_3. Sulfides and sulfones are unreactive, but disulfides and sulfoxides can be reduced. Tosylates are also not reduced by AlH_3.

The reduction of ketones with AlH_3 has selectivity different from other hydride reagents (eqs 5 and 6).[10] The hydroxymethylation of ketones via a two-step procedure has also been accomplished (eq 7).[11] The conversion of α,β-unsaturated ketones to allylic alcohols can be carried out with very good selectivity using AlH_3 (eq 8);[12] however, DIBAL is the reagent of choice for this transformation (see ***Diisobutylaluminum Hydride***).[12c]

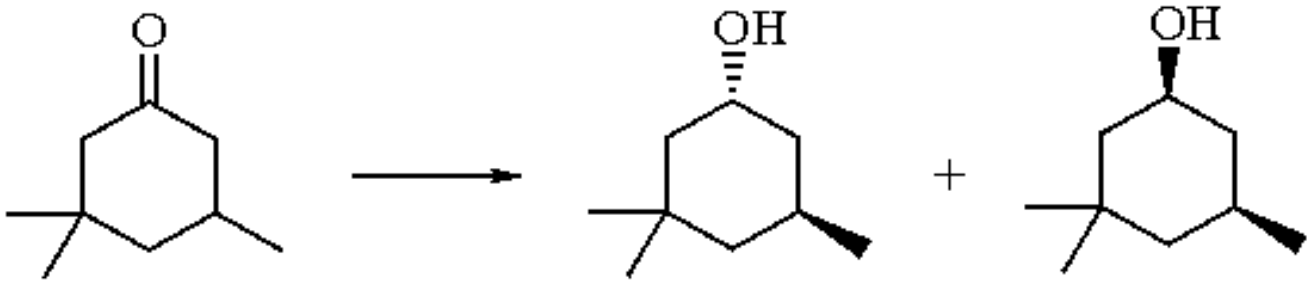

(5)

$LiAlH_4$	*trans*:*cis* = 1.9:1
AlH_3	7.3:1

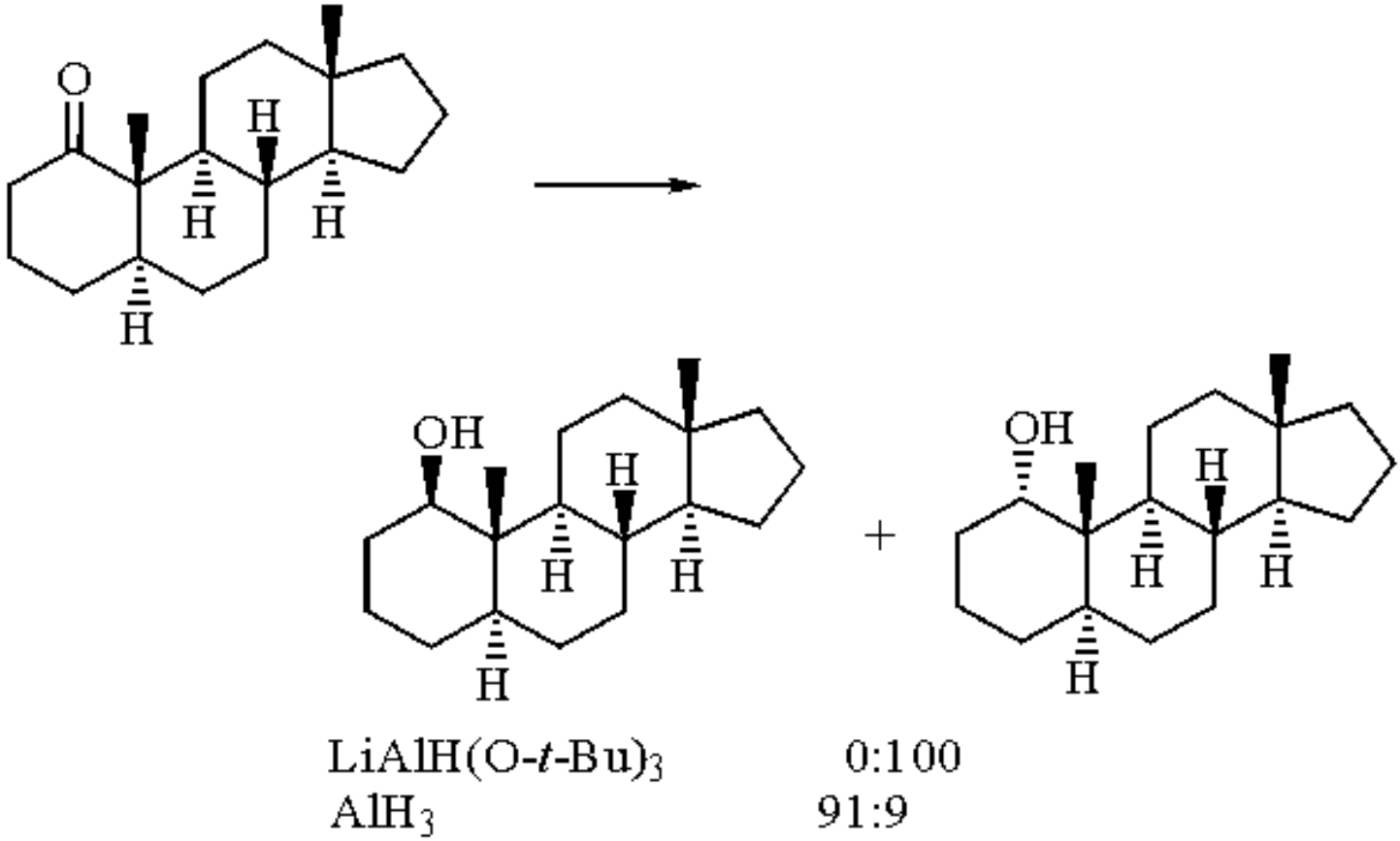

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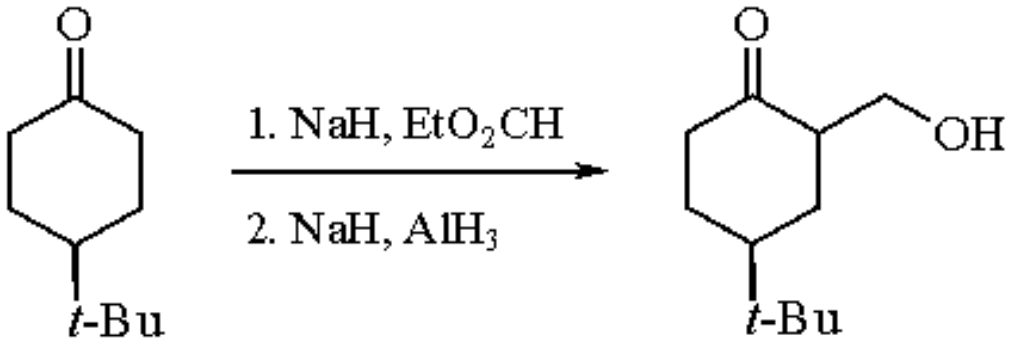

(7)

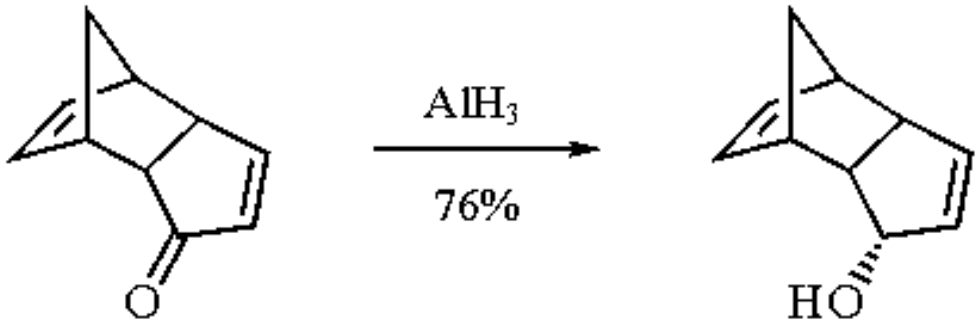

(8)

Carboxylic acids and esters are reduced more rapidly by AlH_3 than by $LiAlH_4$, whereas the converse is true for alkyl halides. As a result, acids and esters can be reduced in the presence of halides (eq 9). In addition, esters can be reduced in the presence of nitro groups (eq 10). This stands in contrast to $LiAlH_4$ in which nitro groups are reduced. Acetals can also be reduced to the half protected diol as illustrated in eq 11.[13]

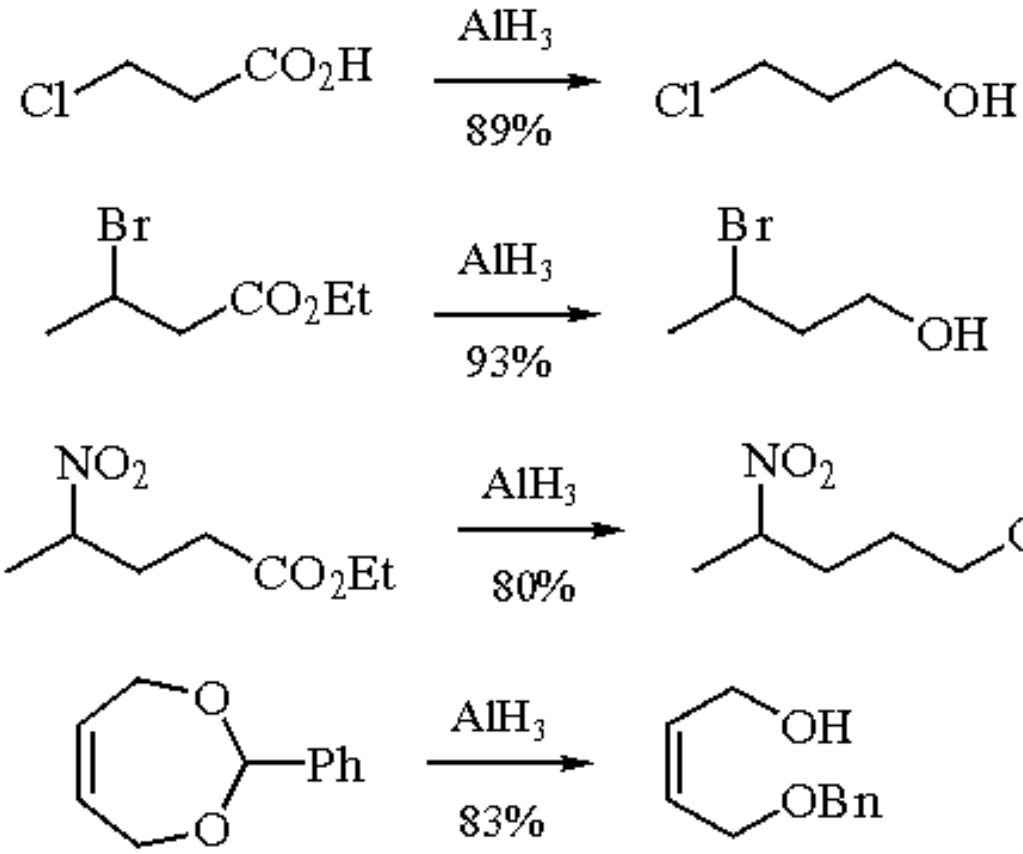

(9)

(10)

(11)

In reductions of amides to amines there is a competition between C-O and C-N bond cleavage which depends upon the reaction conditions. This complication does not occur with AlH_3. A quantitative yield of amine is obtained with short reaction times. Conjugated amides can be cleanly reduced to the allylic amine (eq 12).[6]

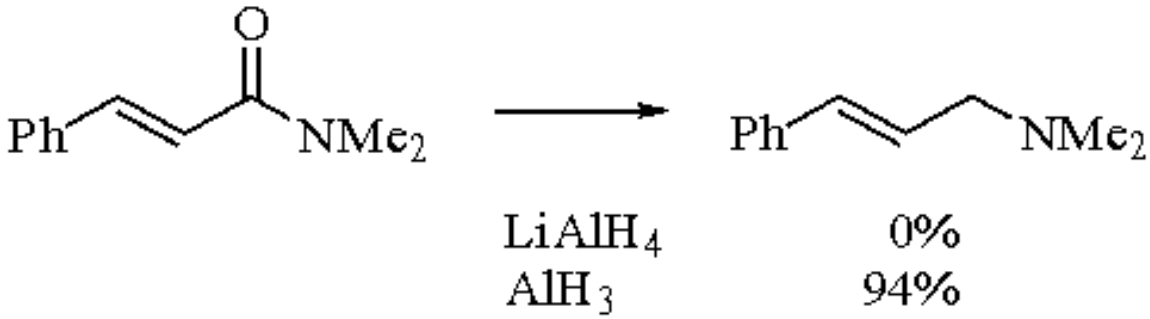

(12)

The less basic AlH_3 appears to be better than $LiAlH_4$ for reducing nitriles with relatively acidic α-hydrogens to amines, and enolizable keto esters to diols (eq 13).[6]

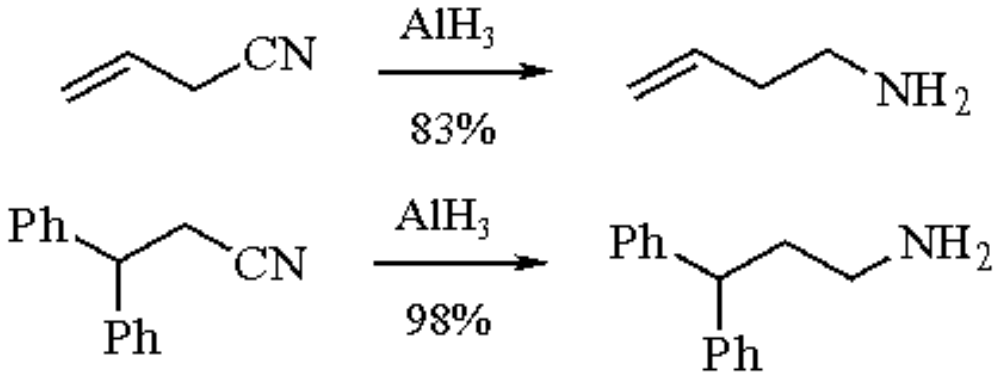

(13)

The reduction of β-lactams to azetidines can be accomplished with AlH_3 (eq 14),[14] while ring opening was observed with $LiAlH_4$. AlH_3 can also convert enamines to the corresponding alkenes (eq 15).[15]

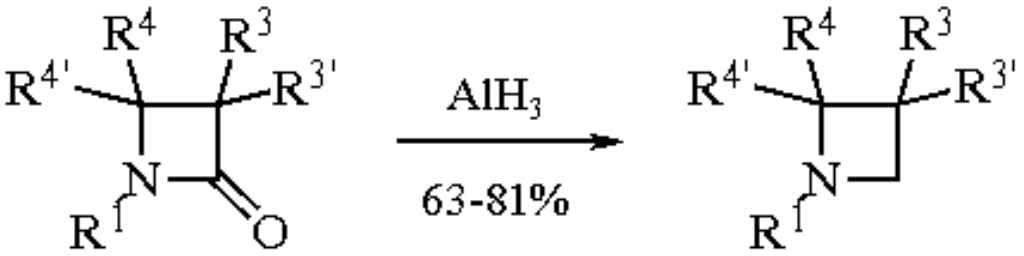

(14)

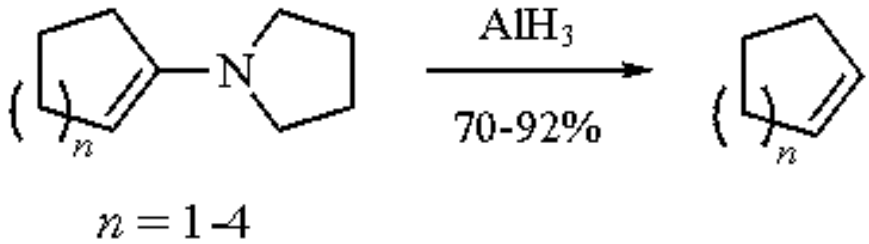

(15)

While alkyl halides are usually inert to AlH_3, the reduction of cyclopropyl halides to cyclopropanes (eq 16)[16] and glycosyl fluorides to tetrahydropyrans (eq 17)[17] are known.

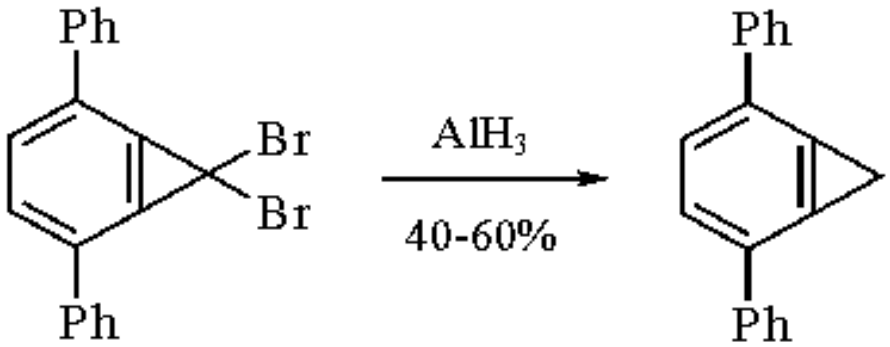

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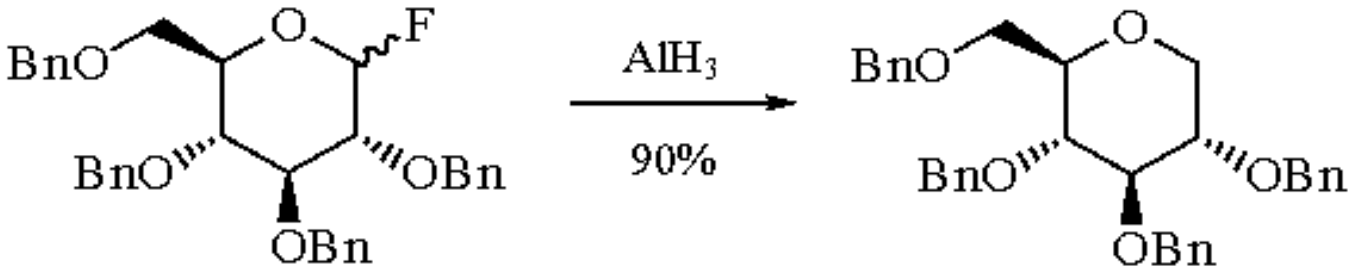

(17)

Desulfurization of sultones is rapid and proceeds in good yield with AlH_3 while $LiAlH_4$ affords poor yields with long reaction times (eq 18).[18]

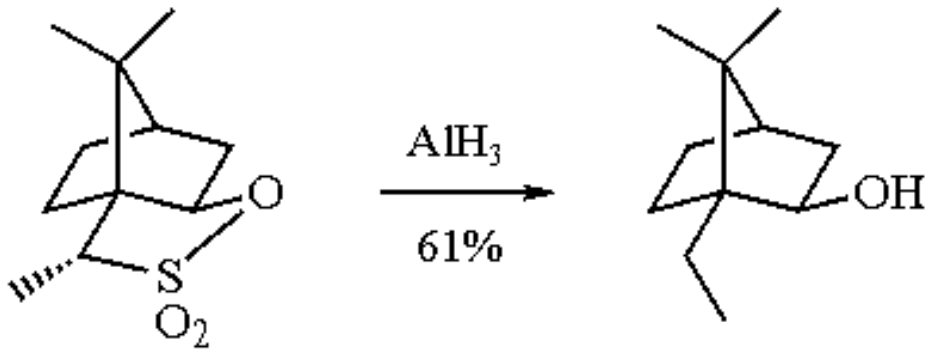

(18)

Epoxide Ring Opening.

With most epoxides, hydride attack occurs at the least sterically hindered site to give the corresponding alcohol (eq 19).[19] However, due to the electrophilic nature of AlH_3 compared to $LiAlH_4$, it is possible for ring opening to occur at the more hindered site. With phenyl substituted epoxides, mechanistic studies have shown that attack at a benzylic carbenium ion or a 1,2-hydride shift followed by hydride attack gives products with the same regiochemistry but with different stereochemistry (eq 20).[6,20] The stereoselectivity of AlH_3 mediated epoxide openings has been studied in depth.[21]

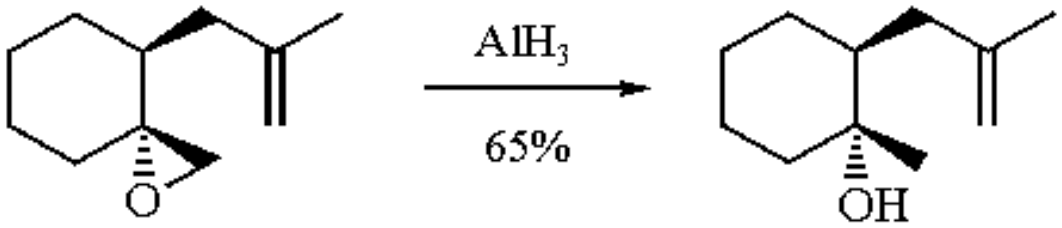

(19)

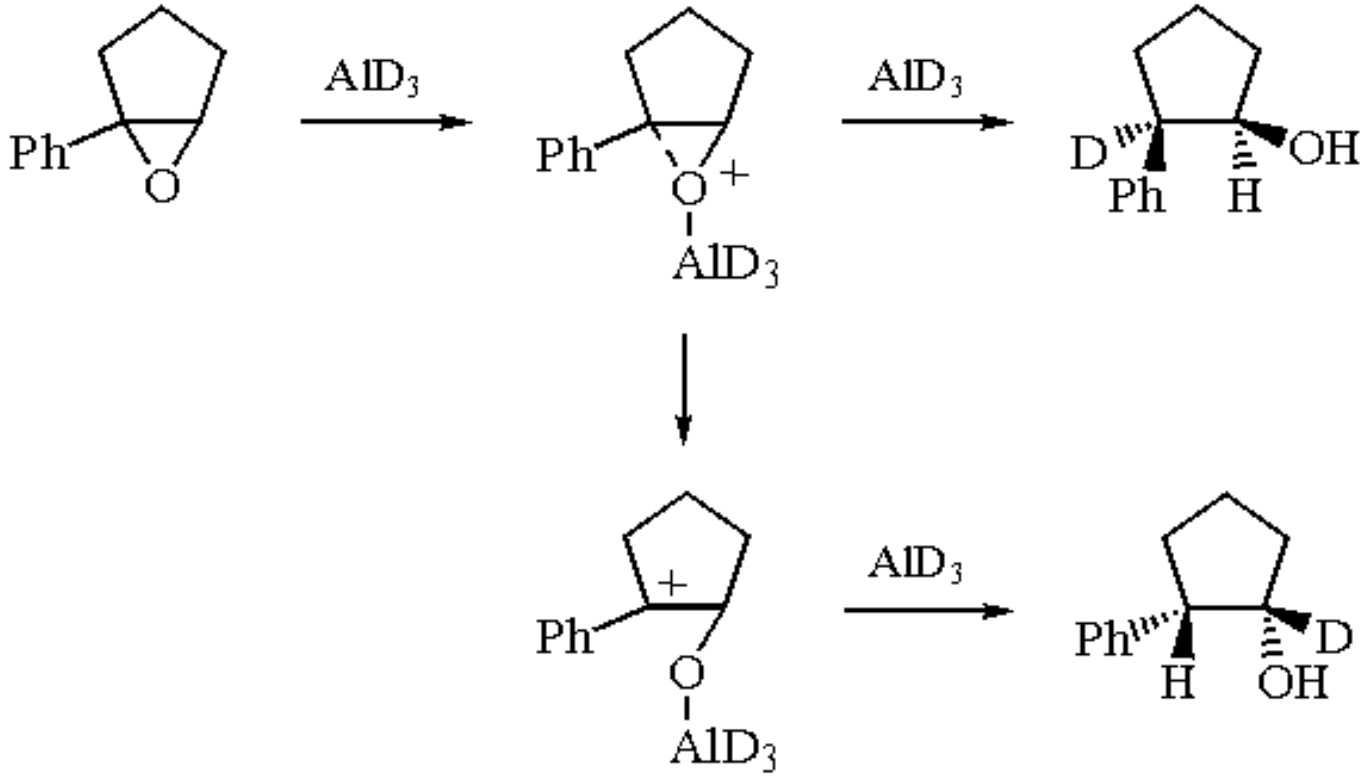

(20)

Hydroalumination.

The addition of AlH_3 across a triple bond has been shown to occur in propargylic systems.[22] When the reactions are quenched with ***Iodine***, AlH_3 gives the 2-iodo-(*E*)-alkene while $LiAlH_4$ gives the 3-iodo-(*E*)-alkene (eq 21). AlH_3 can also be used in conjunction with ***Titanium(IV) Chloride*** to carry out a reaction similar to a hydroboration.[23] Thus 1-hexene is converted to hexane upon aqueous work-up or to the corresponding alcohol upon exposure of the reaction intermediate to oxygen (eq 22). Similar results were obtained with nonconjugated dienes.

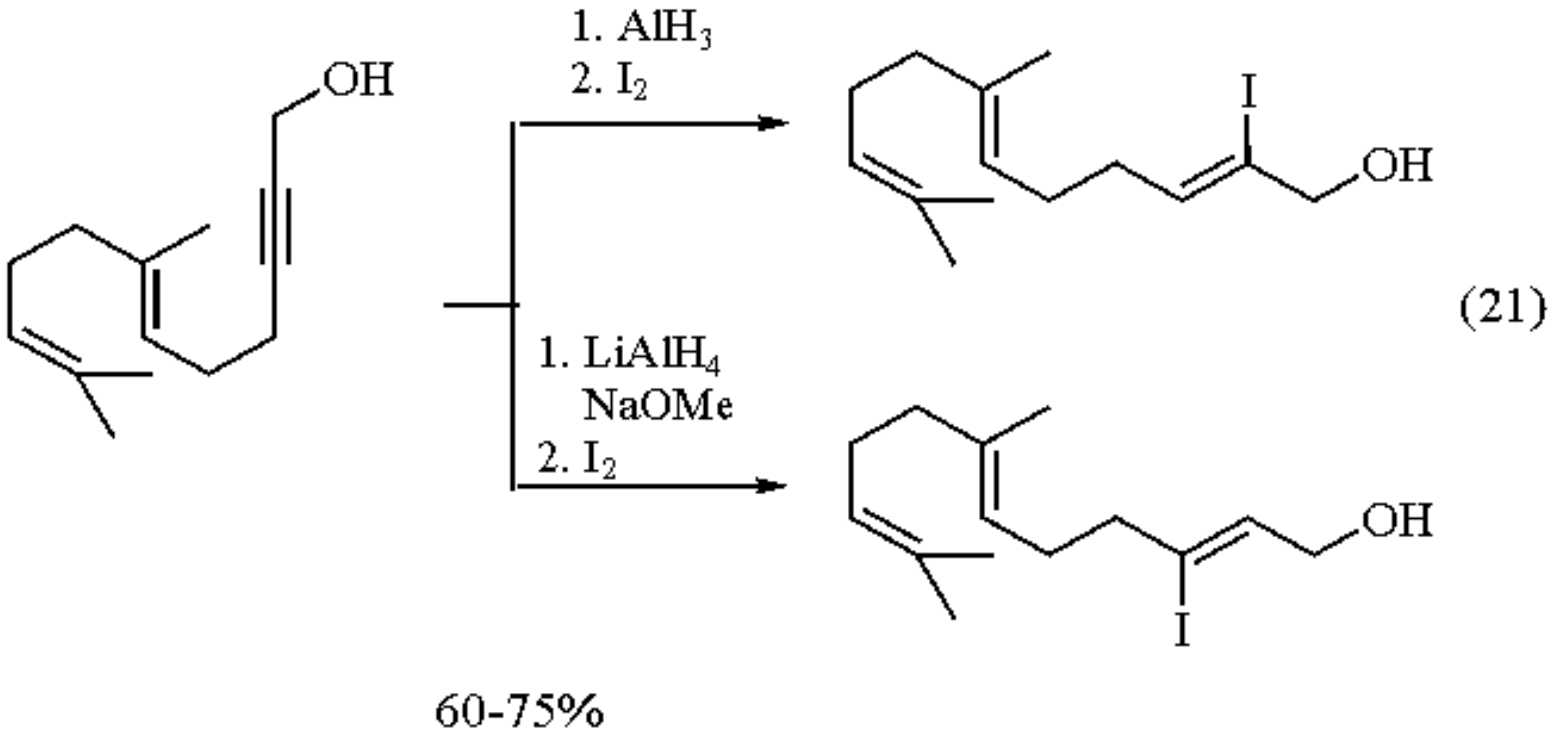

Allylic Rearrangements (S_N2').

The S_N2' displacement of a good leaving group to give the rearranged allylic system can be carried out with AlH_3.[24] This reaction appears not to be sterically demanding as a variety of displacements are possible (eq 23).

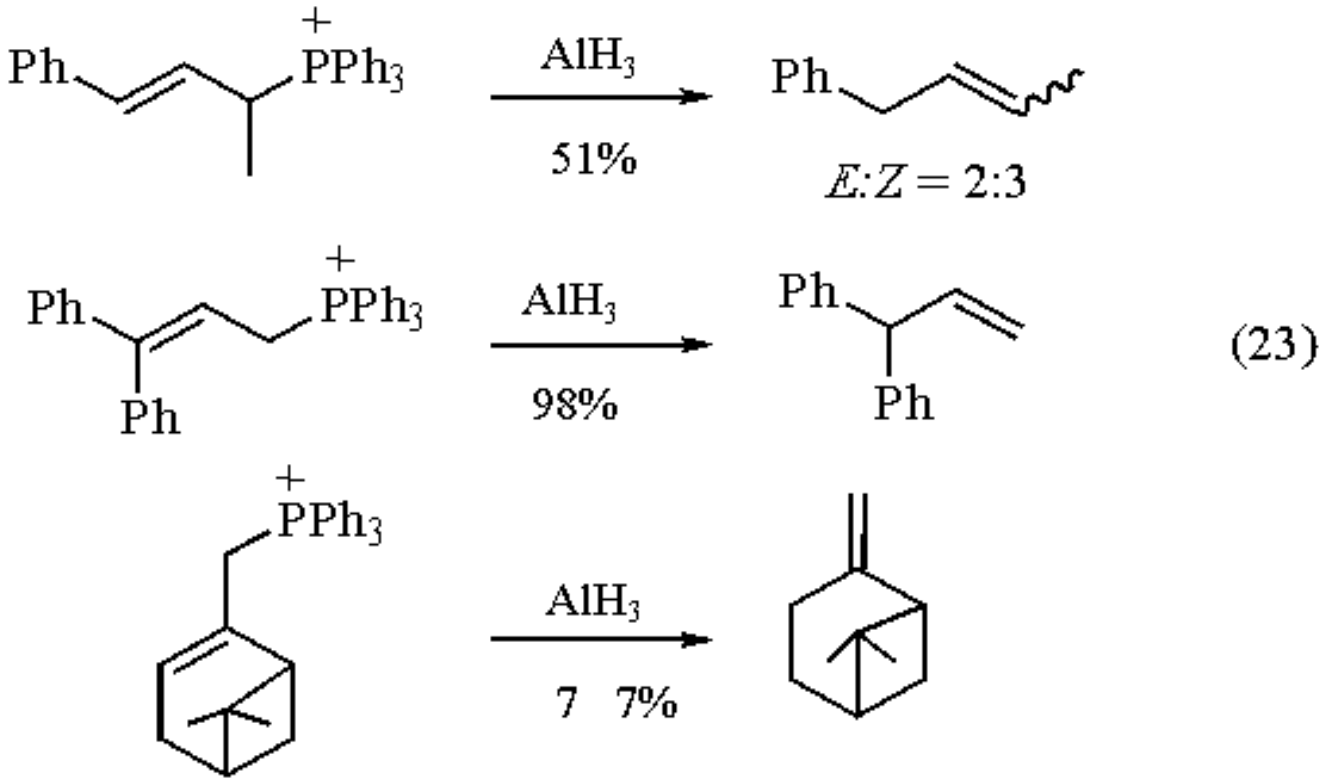

Preparation of allenes from propargylic systems can also be accomplished.[24] Most systems show a preference for *syn* elimination; however, mesylates prefer an *anti* mode of elimination (eq 24). This same procedure has been used to prepare fluoroallenes (eq 25).[25]

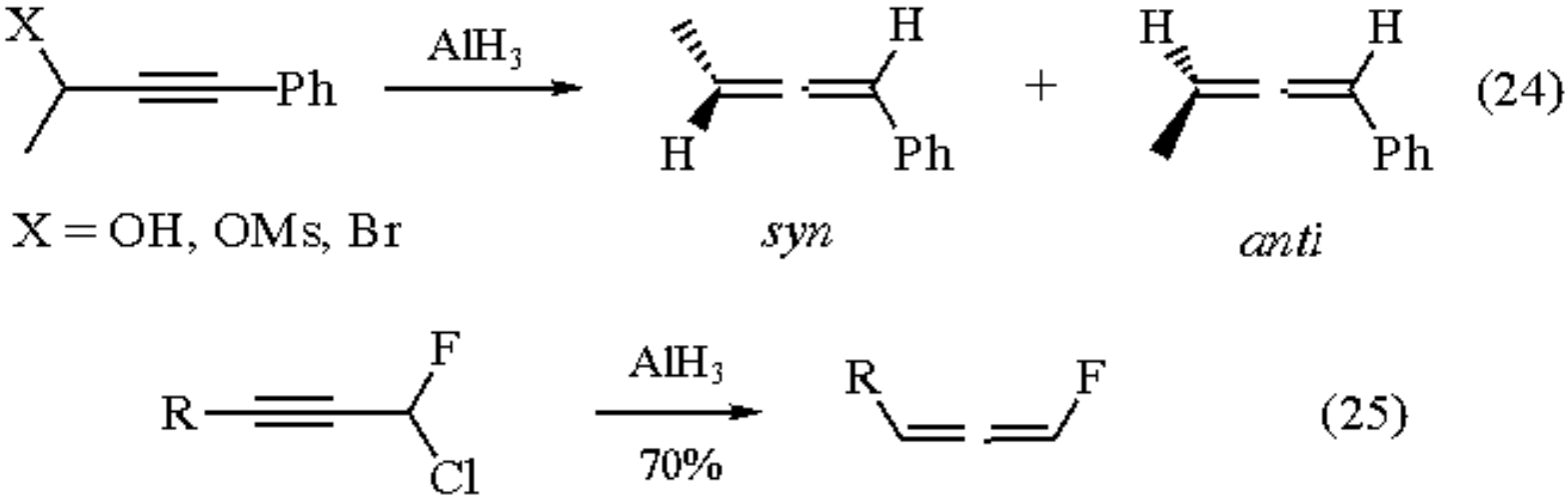

Dialkylaluminum hydrides also behave as hydroalumination reagents (see ***Diisobutylaluminum Hydride***) and are more commonly used than AlH_3.

---

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Aluminum Iodide

AlI_3

[7784-23-8] · AlI_3 · Aluminum Iodide · (MW 407.72)

(cleavage of O-N and S-O bonds;[1] reductive dehalogenation of α-halocarbonyls;[2] deoxygenation of epoxides and vicinal diols;[3,4] ether, acetal, and ester cleaving reagent;[5] iodination of allylic, benzylic, and tertiary alcohols;[4a] hydroiodination of alkenes and alkynes;[6] Friedel-Crafts catalyst[7])

Physical Data: mp 191 °C; bp 382 °C; *d* 3.98 g cm^{-3}.

Solubility: sol CS_2, alcohols, ether, liq. NH_3.

Form Supplied in: white leaflets if pure; commercial grade yellowish to blackish-brown lumps. Exists as the dimer (Al_2I_6) in solid and gas phases.

Preparative Method: some applications require freshly prepared AlI_3. This is conveniently done by heating clean ***Aluminum*** foil with ***Iodine*** in dry MeCN or CS_2 under nitrogen with refluxing for 3 h or until the iodine color disappears. The solution obtained can be directly used for the reaction.

Handling, Storage, and Precautions: use in a fume hood; fumes in moist air; strong exothermic reaction with H_2O; corrosive; moderately toxic. Keep tightly closed and protected from light.

Cleavage of N-O and S-O Bonds.

AlI_3 in MeCN is a general reagent for deoxygenation of *N*-arylnitrones, azoxybenzenes, and *N*-arene *N*-oxides in high yield.[1a] It provides an efficient and facile preparation of *o*-aminobenzophenones by a highly selective reductive cleavage of O-N bonds in 2,1-benzoisoxazoles (eq 1).[1b] Chromone 3-aldonitrones are converted by a facile AlI_3-catalyzed rearrangement to the 3-carboxamides.[1c] Ketoximes undergo Beckmann rearrangement to the carboxamide while aldoximes are readily dehydrated to the nitrile in the presence of AlI_3.[1d] Aryl or alkyl sulfonyl chlorides and sulfoxides are reduced to the disulfide and sulfide, respectively.[1e]

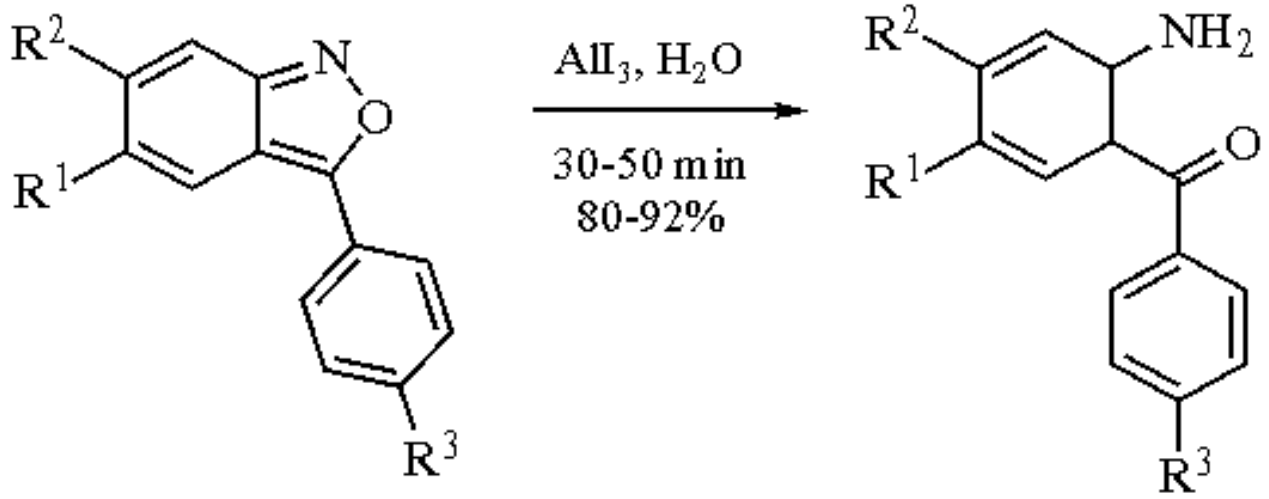

(1)

R^1 = Cl, Br, NO_2, Ac
R^2 = H, Me
R^3 = H, OH

Cleavage of C-X and C-O Bonds.

In the AlI_3-mediated reductive dehalogenation of α-halocarbonyl compounds, aluminum enolates are readily generated and can be trapped via aldol reactions (eq 2).[2] The deoxygenation of oxiranes with AlI_3 proceeds at room temperature in MeCN or benzene to give high yields (typically >90%) of alkenes.[3] With less reactive epoxides the iodohydrin can be isolated. Certain vicinal diols (*cis* and *trans* secondary-tertiary and allylic bis-secondary) are converted to the alkene by this reagent (eq 3).[4a] Bis-secondary *vic*-diols remain unchanged.

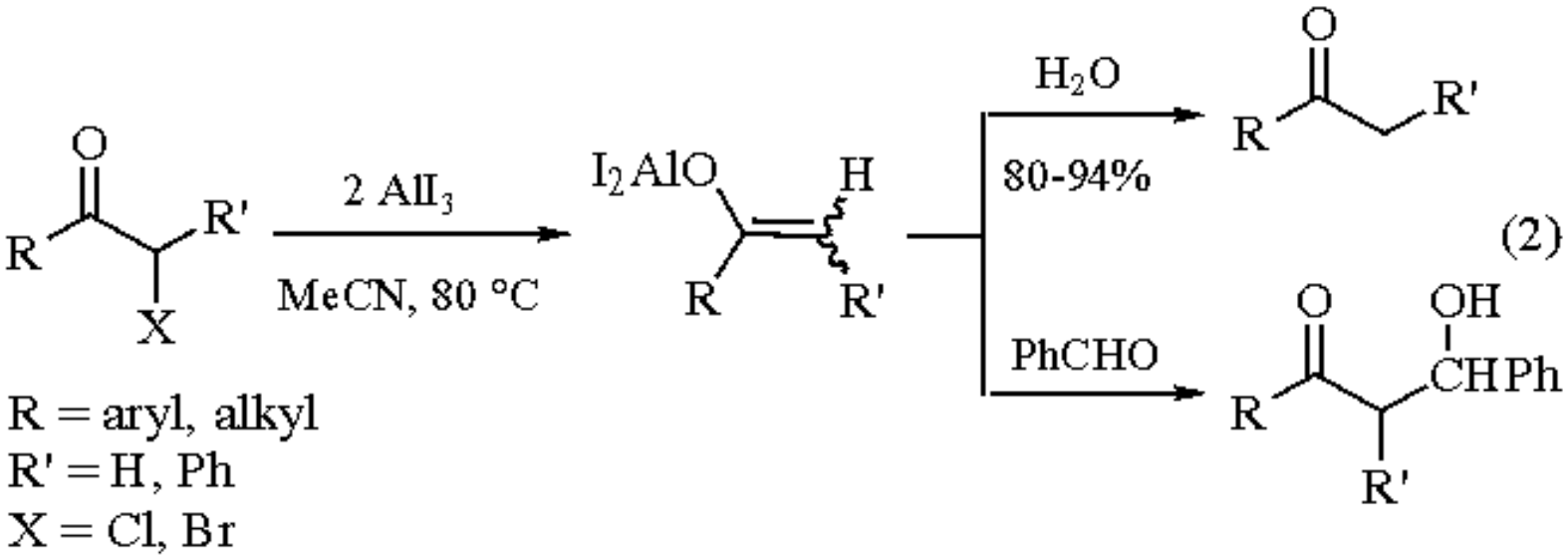

(2)

R = aryl, alkyl
R' = H, Ph
X = Cl, Br

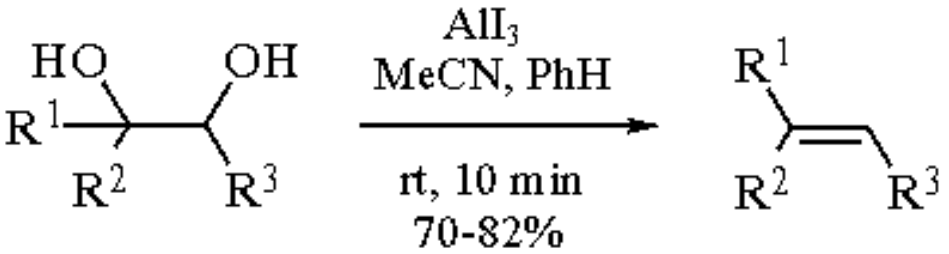

(3)

R^1-R^3 = alkyl, allyl

AlI_3 is a highly regioselective ether cleaving reagent, in some cases having a novel cleavage pattern.[5a] Aryl alkyl ethers are cleaved with 1 equiv AlI_3 to give the phenol and alkyl iodide. Selective ether cleavage is possible in the presence of benzoate esters. This method can be improved by the addition of quaternary ammonium iodide salts which give higher yields in shorter reaction times.[5b] AlI_3 exhibits superior regioselectivity over ***Aluminum Chloride*** or ***Aluminum Bromide*** in the cleavage of epoxides to the halohydrin.[5c] It is also an efficient reagent for deprotection of a wide variety of carboxylic esters (2 equiv AlI_3).[5d] Phenol esters, however, undergo Fries rearrangement. A nonaqueous procedure for conversion of acetals to the carbonyl compound is provided using this reagent.[5e] Thioacetals are unreactive under these conditions. Allylic, benzylic, and tertiary alcohols are regioselectively converted to the corresponding iodide by AlI_3. Saturated primary and secondary alcohols are unaffected. Aryl methyl ethers were shown to survive at short reaction times.[4a]

Miscellaneous Reactions.

Good yields of hydroiodinated product are formed by treatment of alkenes and alkynes with AlI_3 and H_2O via in situ generation of ***Hydrogen Iodide***.[6] The use of AlI_3 as a Friedel-Crafts catalyst is limited since it frequently gives lower yields than either $AlCl_3$ or $AlBr_3$. One exception occurs in the isopropylation of benzene.[7] An interesting AlI_3-catalyzed addition of MeCN has been reported (eq 4) but this does not appear to be a general reaction.[8]

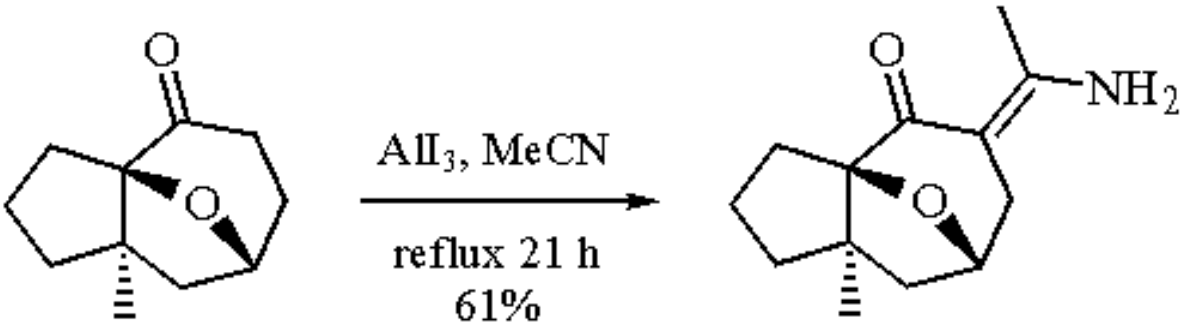

(4)

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Aluminum Isopropoxide[1]

$Al(O\text{-}i\text{-}Pr)_3$

[555-31-7] · $C_9H_{21}AlO_3$ · Aluminum Isopropoxide · (MW 204.25)

(mild reagent for Meerwein-Ponndorf-Verley reduction;[1] Oppenauer oxidation;[13] hydrolysis of oximes;[16] rearrangement of epoxides to allylic alcohols;[17] regio- and chemoselective ring opening of epoxides;[20] preparation of ethers[21])

Alternate Name: triisopropoxyaluminum.

Physical Data: mp 138-142 °C (99.99+%), 118 °C (98+%); bp 140.5 °C; *d* 1.035 g cm^{-3}.

Solubility: sol benzene; less sol alcohols.

Form Supplied in: white solid (99.99+% or 98+% purity based on metals analysis).

Preparative Methods: see example below.

Handling, Storage, and Precautions: the dry solid is corrosive, moisture sensitive, flammable, and an irritant. Use in a fume hood.

NMR Analysis of Aluminum Isopropoxide.

Evidence from molecular weight determinations indicating that aluminum isopropoxide aged in benzene solution consists largely of the tetramer (**1**), whereas freshly distilled molten material is trimeric (**2**),[2] is fully confirmed by NMR spectroscopy.[3]

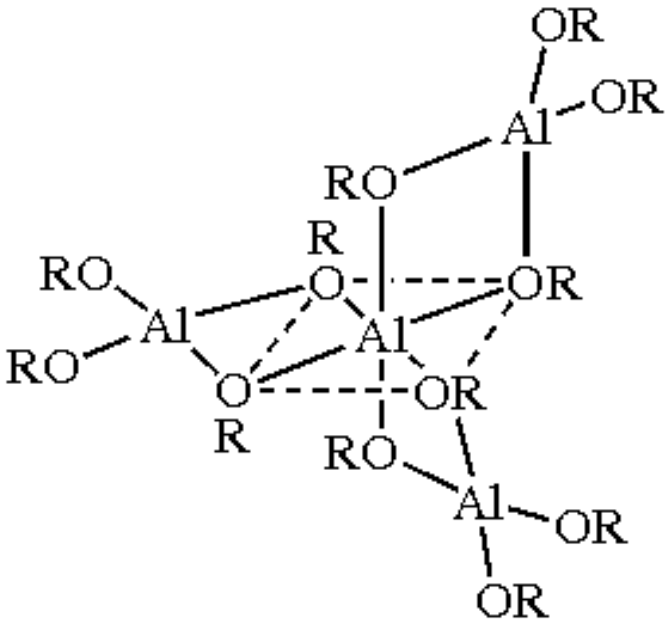

(1)

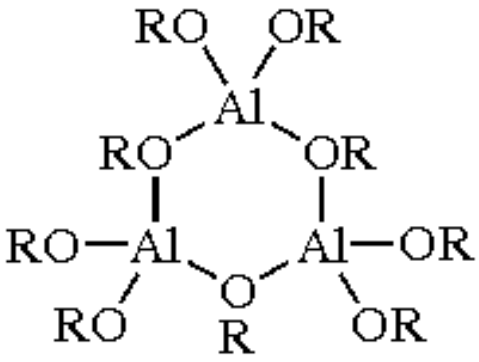

(2)

Meerwein-Ponndorf-Verley Reduction.

One use of the reagent is for the reduction of carbonyl compounds, particularly of unsaturated aldehydes and ketones, for the reagent attacks only carbonyl compounds. An example is the reduction of crotonaldehyde to crotyl alcohol (eq 1).[1] A mixture of 27 g of cleaned ***Aluminum*** foil, 300 mL of isopropanol, and 0.5 g of ***Mercury(II) Chloride*** is heated to boiling, 2 mL of carbon tetrachloride is added as catalyst, and heating is continued. The mixture turns gray, and vigorous evolution of hydrogen begins. Refluxing is continued until gas evolution has largely subsided (6-12 h). The solution, which is black from the presence of suspended solid, can be concentrated and the aluminum isopropoxide distilled in vacuum (colorless liquid) or used as such. Thus the undistilled solution prepared as described from 1.74 mol of aluminum and 500 mL of isopropanol is treated with 3 mol of crotonaldehyde and 1 L of isopropanol. On reflux at a bath temperature of 110 °C, acetone slowly distills at 60-70 °C. After 8-9 h, when the distillate no longer gives a test for acetone, most of the remaining isopropanol is distilled at reduced pressure and the residue is cooled and hydrolyzed with 6 N sulfuric acid to liberate crotyl alcohol from its aluminum derivative.

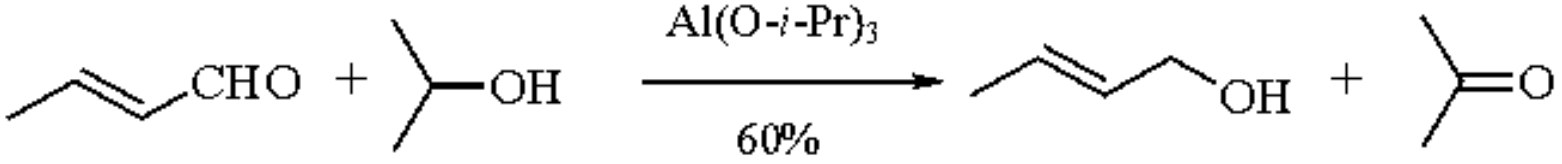

(1)

The Meerwein-Ponndorf-Verley reduction of the ketone (**3**) involves formation of a cyclic coordination complex (**4**) which, by hydrogen transfer, affords the mixed alkoxide (**5**), hydrolyzed to the alcohol (**6**) (eq 2).[4] Further reflection suggests that under forcing conditions it might be possible to effect repetition of the hydrogen transfer and produce the hydrocarbon (**7**). Trial indeed shows that reduction of diaryl ketones can be effected efficiently by heating with excess reagent at 250 °C (eq 3).[5]

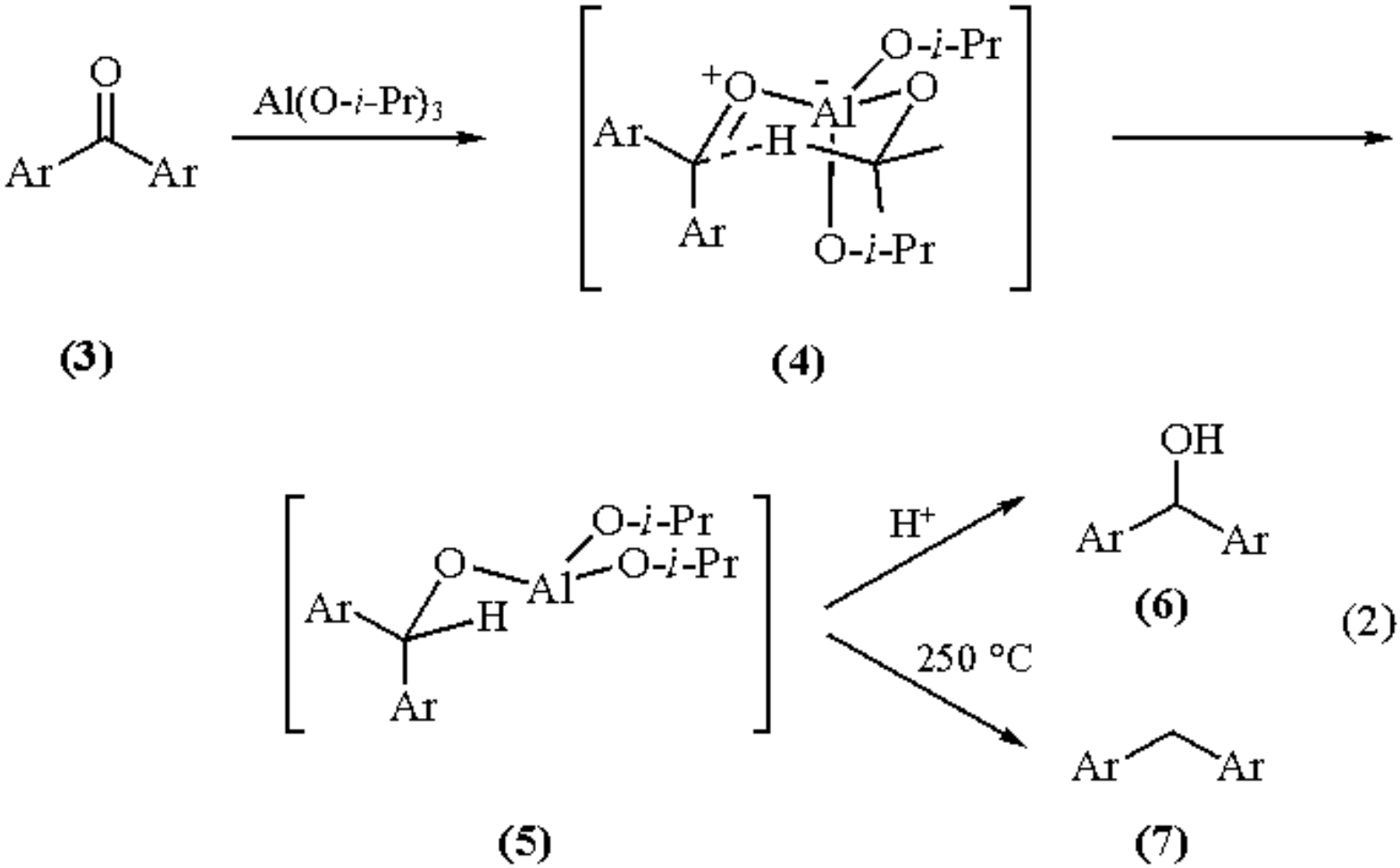

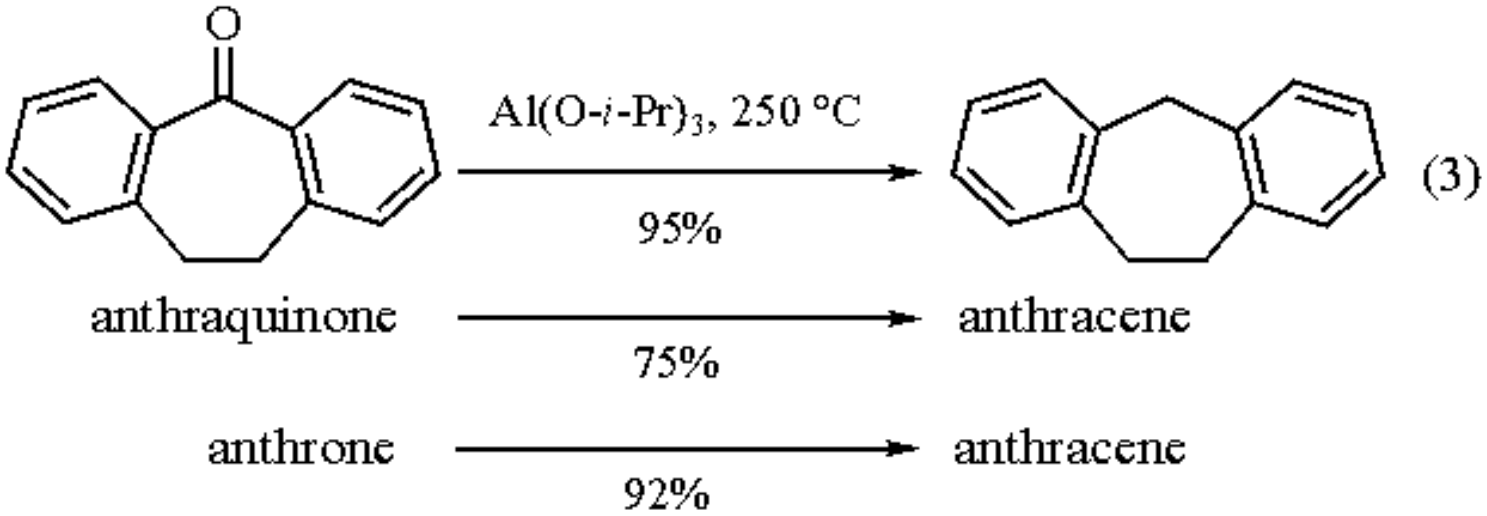

A study[6] of this reduction of mono- and bicyclic ketones shows that, contrary to commonly held views, the reduction proceeds at a relatively high rate. The reduction of cyclohexanone and of 2-methylcyclohexanone is immeasurably rapid. Even menthone is reduced almost completely in 2 h. The stereochemistry of the reduction of 3-isothujone (**8**) and of 3-thujone (**11**) has been examined (eqs 4 and 5). The ketone (**8**) produces a preponderance of the *cis*-alcohol (**9**). The stereoselectivity is less pronounced in the case of 3-thujone (**11**), although again the *cis*-alcohol (**12**) predominates. The preponderance of the *cis*-alcohols can be increased by decreasing the concentration of ketone and alkoxide.

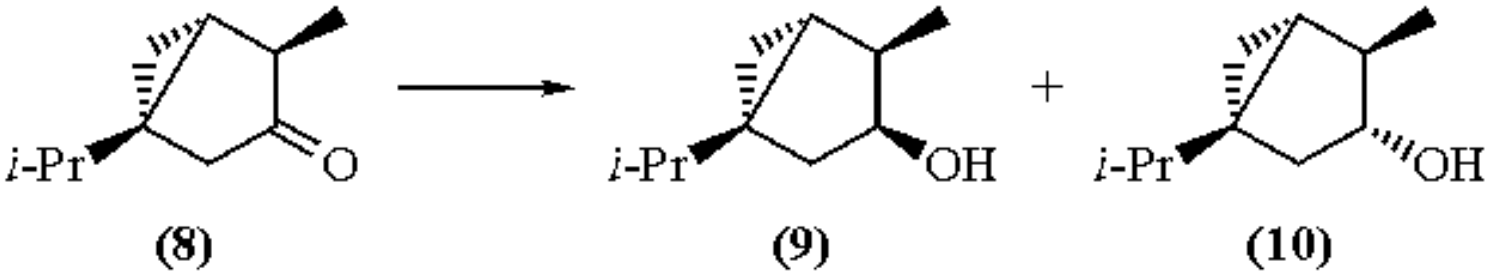

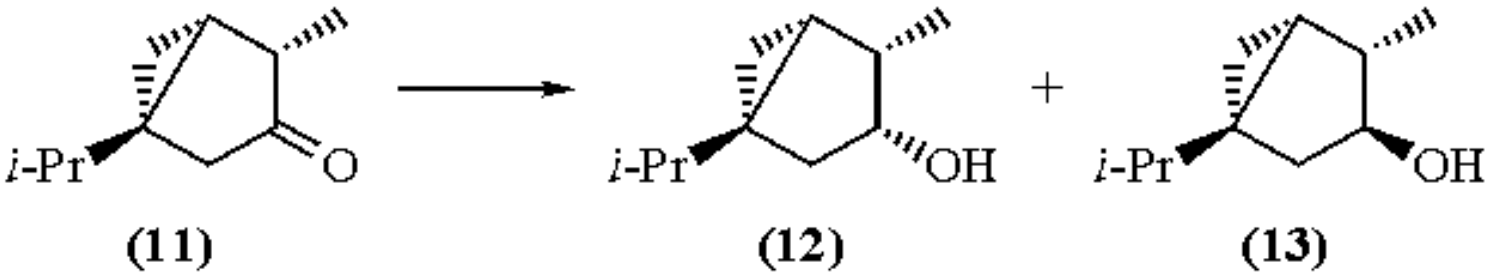

This reducing agent is the reagent of choice for reduction of enones of type (**14**) to the α,β-unsaturated alcohols (**15**) (eq 6). Usual reducing agents favor 1,4-reduction to the saturated alcohol.[7]

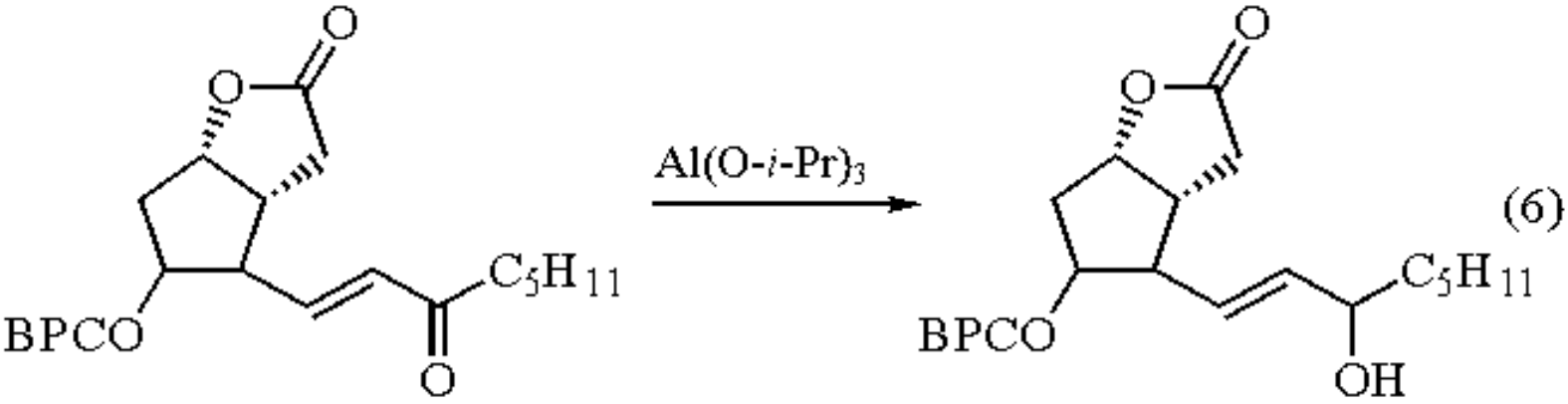

(14)
BPC = biphenylcarbonyl

(15)
20%, each isomer

The Meerwein-Ponndorf-Verley reduction of pyrimidin-2(1*H*)-ones using ***Zirconium Tetraisopropoxide*** or aluminum isopropoxide leads to exclusive formation of the 3,4-dihydro isomer (eq 7).[8] The former reducing agent is found to be more effective.

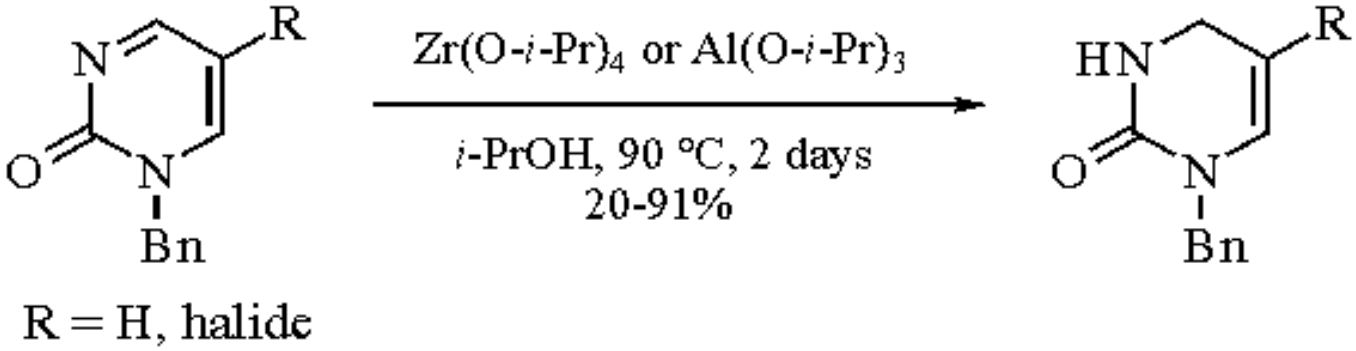

Reductions with Chiral Aluminum Alkoxides.

The reduction of cyclohexyl methyl ketone with catalytic amounts of aluminum alkoxide and excess chiral alcohol gives (*S*)-1-cyclohexylethanol in 22% ee (eq 8).[9]

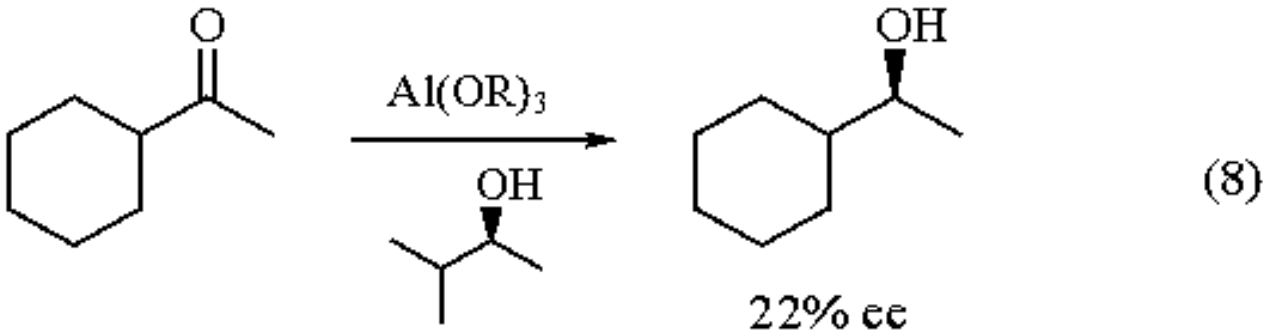

Isobornyloxyaluminum dichloride is a good reagent for reducing ketones to alcohols. The reduction is irreversible and subject to marked steric approach control (eq 9).[10]

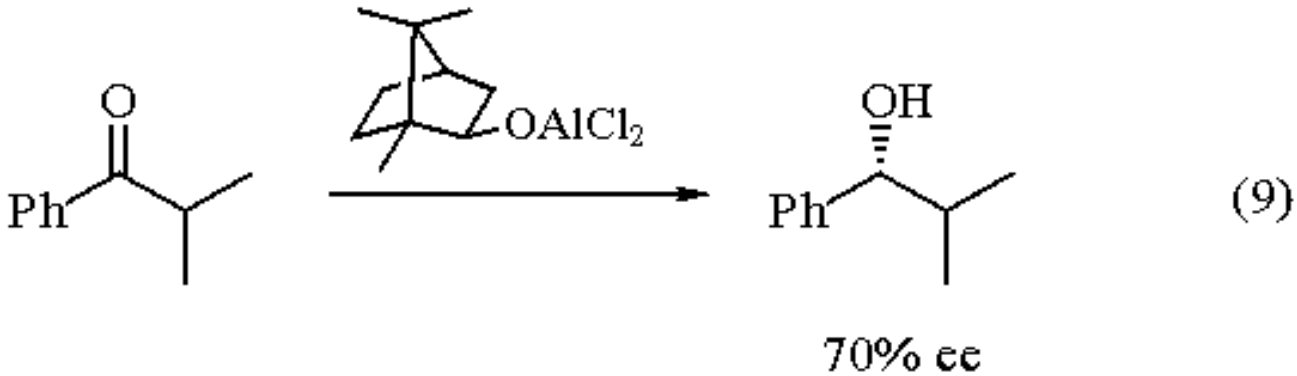

Diastereoselective Reductions of Chiral Acetals.

Recently, it has been reported that ***Pentafluorophenol*** is an effective accelerator for Meerwein-Ponndorf-Verley reduction.[11] Reduction of 4-*t*-butylcyclohexanone with aluminum isopropoxide (3 equiv) in dichloromethane, for example, is very slow at 0 °C (<5% yield for 5 h), but in the presence of pentafluorophenol (1 equiv), the reduction is cleanly completed within 4 h at 0 °C (eq 10). The question of why this reagent retains sufficient nucleophilicity is still open. It is possible that the *o*-halo substituents of the phenoxide ligand may coordinate with the aluminum atom, thus

increasing the nucleophilicity of the reagent.

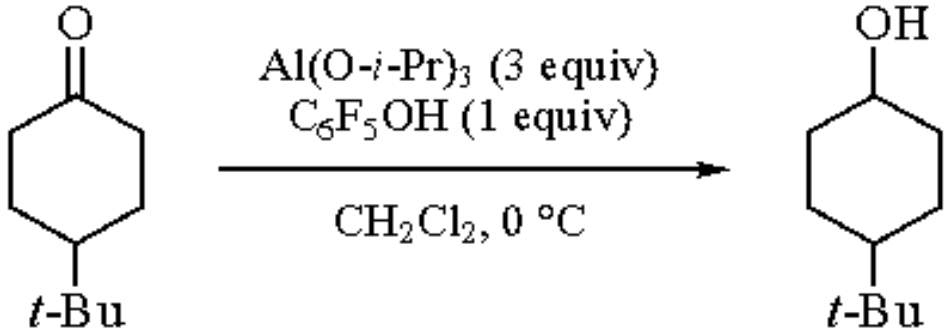

(10)

Chiral acetals derived from (-)-***(2R,4R)-2,4-Pentanediol*** and ketone are reductively cleaved with high diastereoselectivity by a 1:2 mixture of diethylaluminum fluoride and pentafluorophenol.[11] Furthermore, aluminum pentafluorophenoxide is a very powerful Lewis acid catalyst for the present reaction.[12] The reductive cleavage in the presence of 5 mol % of $Al(OC_6F_5)_3$ affords stereoselectively retentive reduced β-alkoxy ketones. The reaction is an intramolecular Meerwein-Ponndorf-Verley reductive and Oppenauer oxidative reaction on an acetal template (eq 11).

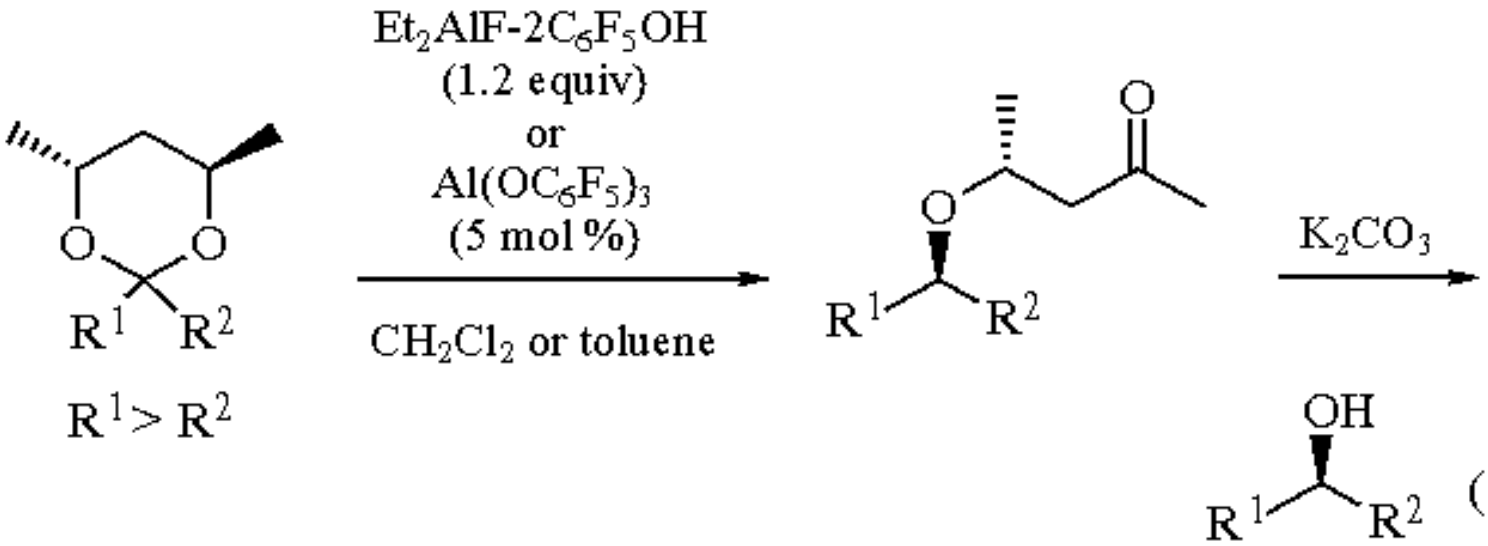

(11)

The direct formation of α,β-alkoxy ketones is quite useful. Removal of the chiral auxiliary, followed by base-catalyzed β-elimination of the resulting β-alkoxy ketone, easily gives an optically pure alcohol in good yield. Several examples of the reaction are summarized in Table 1.

Table 1 Reductive Cleavages of Acetals Using $Al(OC_6F_5)_3$ Catalyst

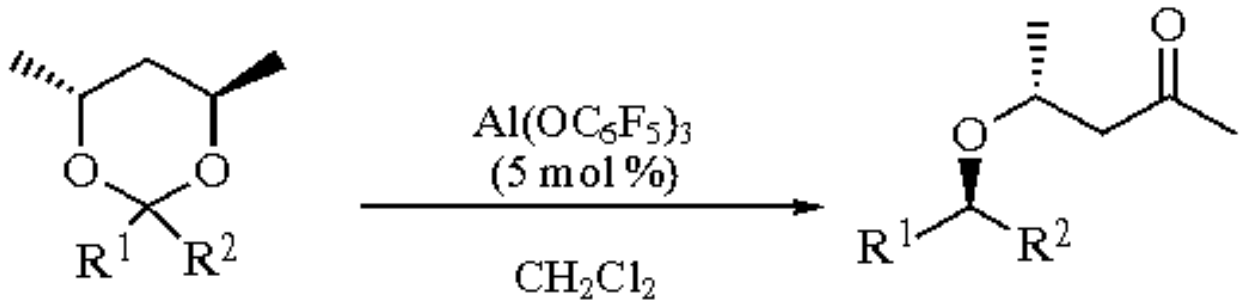

R^1	R^2	Yield (%)	Ratio (*S*:*R*)
C_5H_{11}	Me	83	82:18
i-Bu	Me	61	73:27
i-Pr	Me	90	94:6
Ph	Me	71	>99:1
Ph	Et	78	92:8
c-Hex	Me	89	95:5
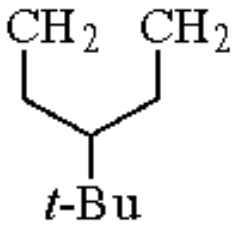		67	81:19 (*trans*:*cis*)

Although the detailed mechanism is not yet clear, it is assumed that an energetically stable tight ion-paired intermediate is generated by stereoselective coordination of $Al(OC_6F_5)_3$ to one of the oxygens of the acetal; the hydrogen atom of the alkoxide is then transferred as a hydride from the retentive direction to this departing oxygen, which leads to the (*S*) configuration at the resulting ether carbon, as described (eq 12).

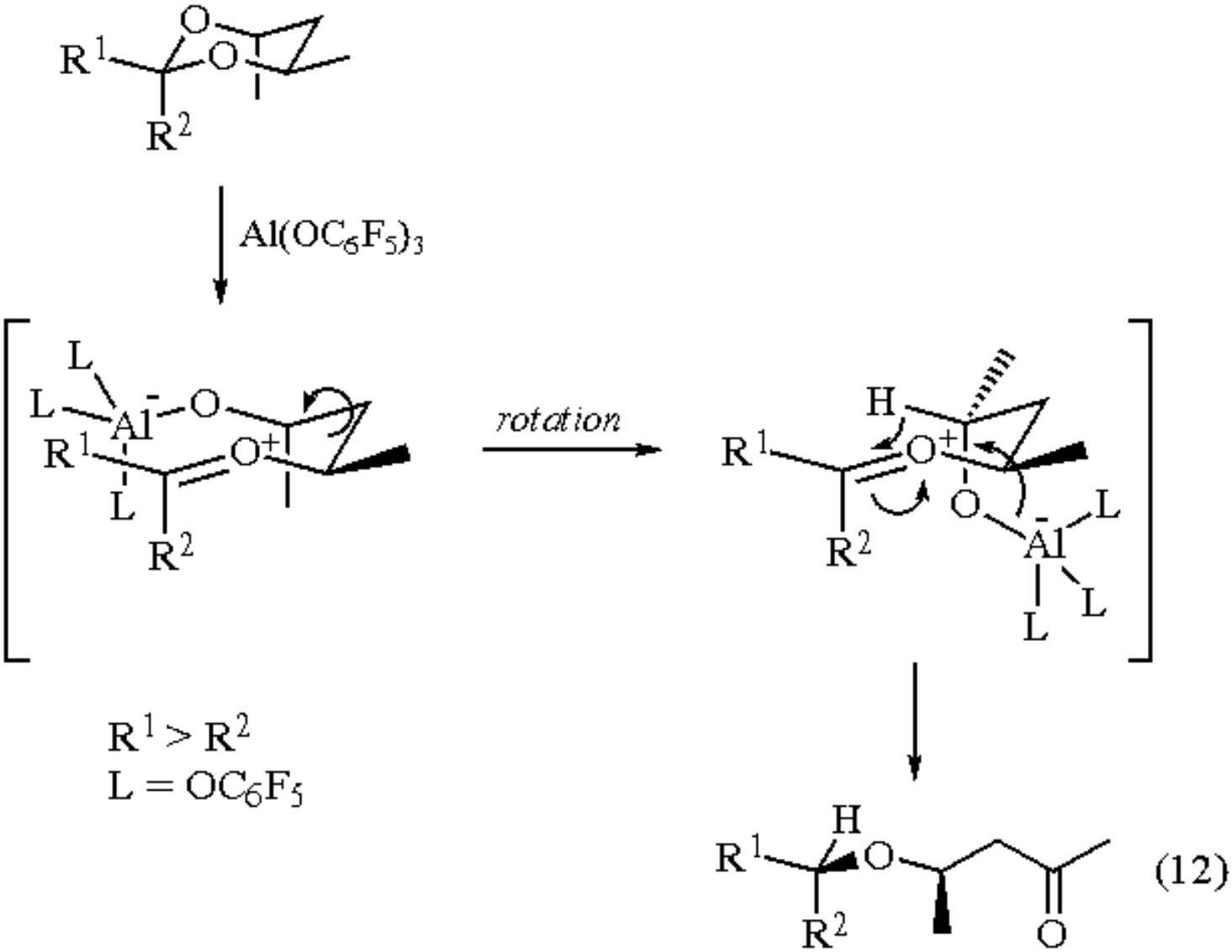

Oppenauer Oxidation.[13]

Cholestenone is prepared by oxidation of cholesterol in toluene solution with aluminum isopropoxide as catalyst and cyclohexanone as hydrogen acceptor (eq 13).[14]

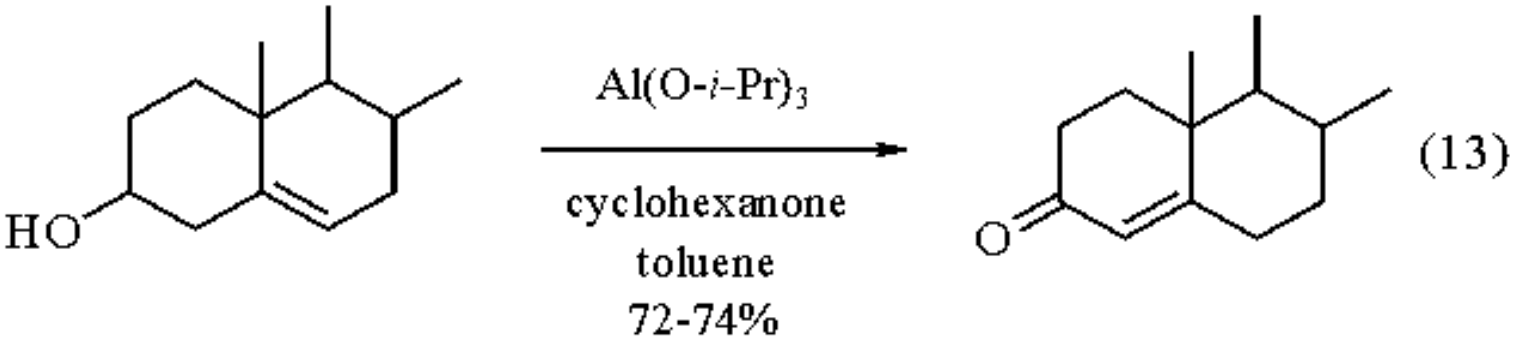

A formate, unlike an acetate, is easily oxidized and gives the same product as the free alcohol.[15] For oxidation of (**16**) to (**17**) the combination of cyclohexanone and aluminum isopropoxide and a hydrocarbon solvent is used: xylene (bp

140 °C at 760 mmHg) or toluene (bp 111 °C at 760 mmHg) (eq 14).

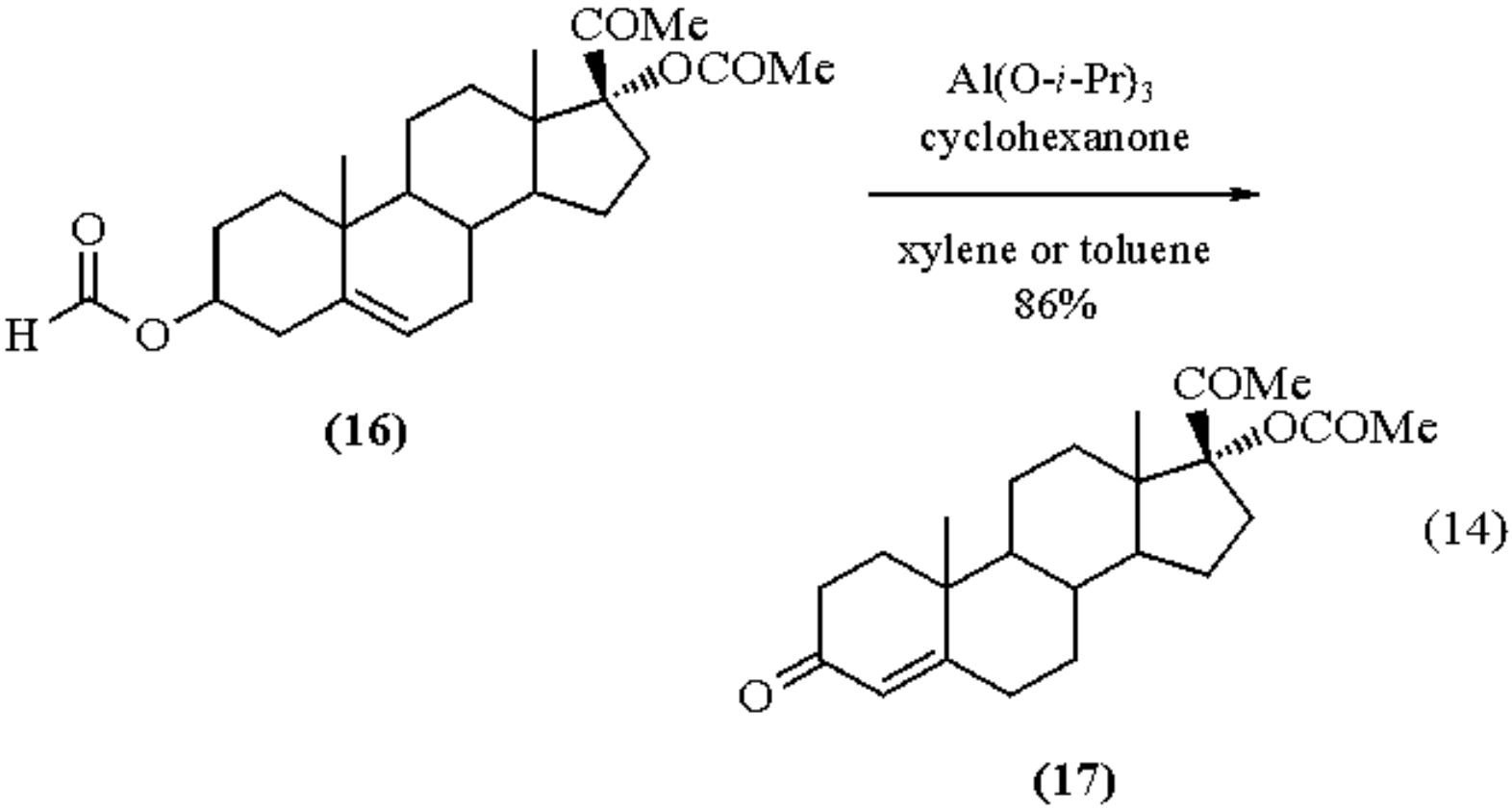

(14)

Hydrolysis of Oximes.[16]

Oximes can be converted into parent carbonyl compounds by aluminum isopropoxide followed by acid hydrolysis (2N HCl) (eq 15). Yields are generally high in the case of ketones, but are lower for regeneration of aldehydes.

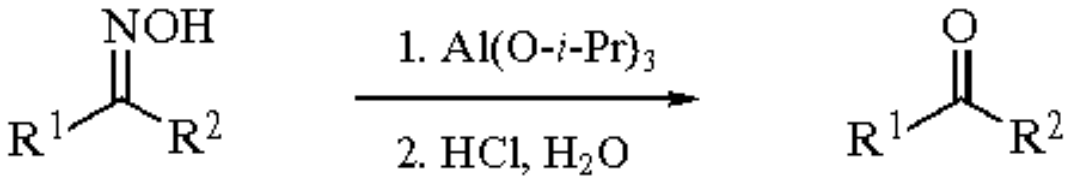

(15)

Rearrangement of Epoxides to Allylic Alcohols.

The key step in the synthesis of the sesquiterpene lactone saussurea lactone (**21**) involved fragmentation of the epoxymesylate (**18**), obtained from α-santonin by several steps (eq 16).[17] When treated with aluminum isopropoxide in boiling toluene (N_2, 72 h), (**18**) is converted mainly into (**20**). The minor product (**19**) is the only product when the fragmentation is quenched after 12 h. Other bases such as potassium *t*-butoxide, LDA, and lithium diethylamide cannot be used. Aluminum isopropoxide is effective probably because aluminum has a marked affinity for oxygen and effects cleavage of the epoxide ring. Meerwein-Ponndorf-Verley reduction is probably involved in one step.

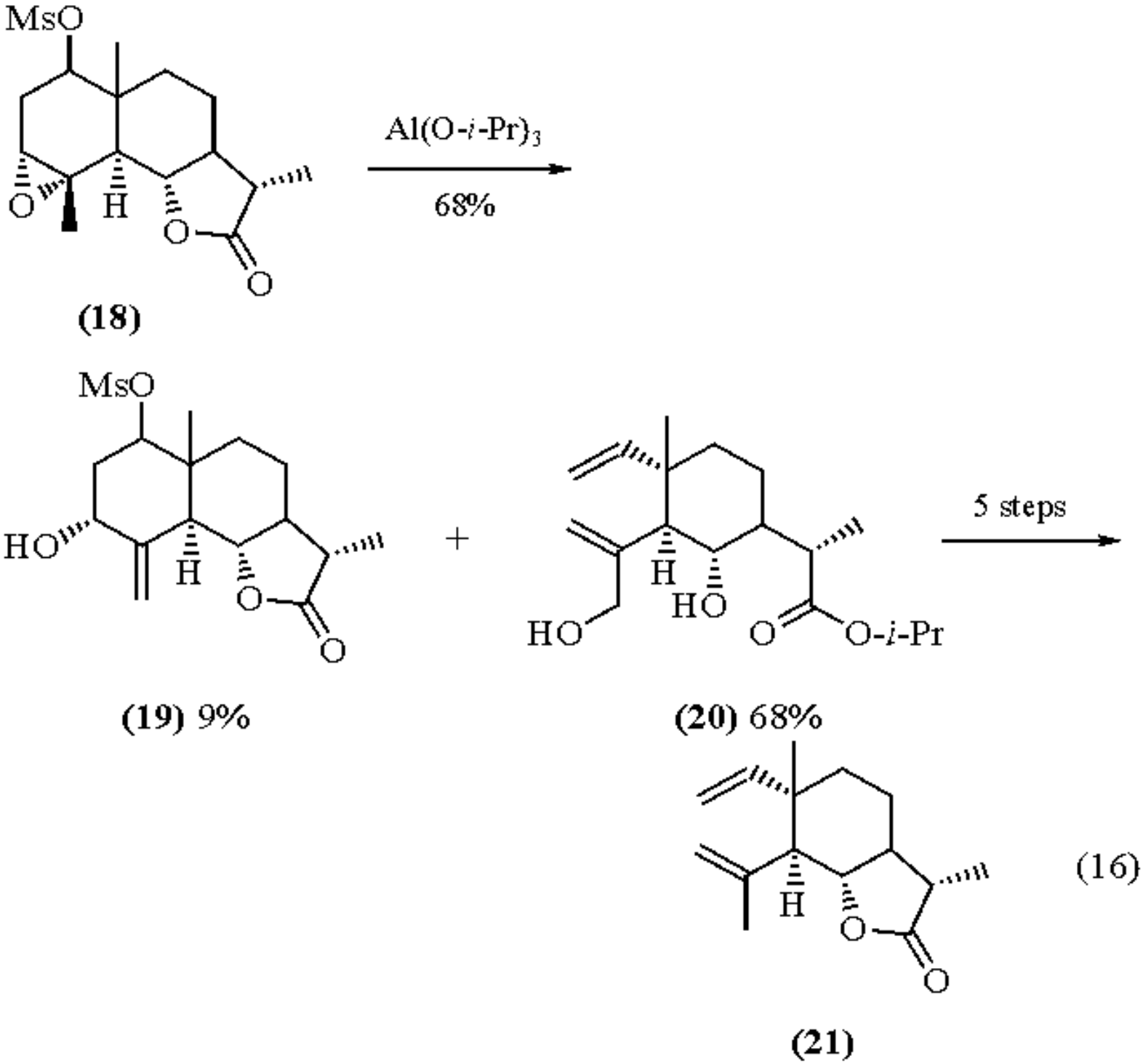

(16)

α-Pinene oxide (**22**) rearranges to pinocarvenol (**23**) in the presence of 1 mol % of aluminum isopropoxide at 100-120 °C for 1 h.[18] The oxide (**22**) rearranges to pinanone (**24**) in the presence of 5 mol % of the alkoxide at 140-170 °C for 2 h. Aluminum isopropoxide has been used to rearrange (**23**) to (**24**) (200 °C, 3 h, 80% yield) (eq 17).[19]

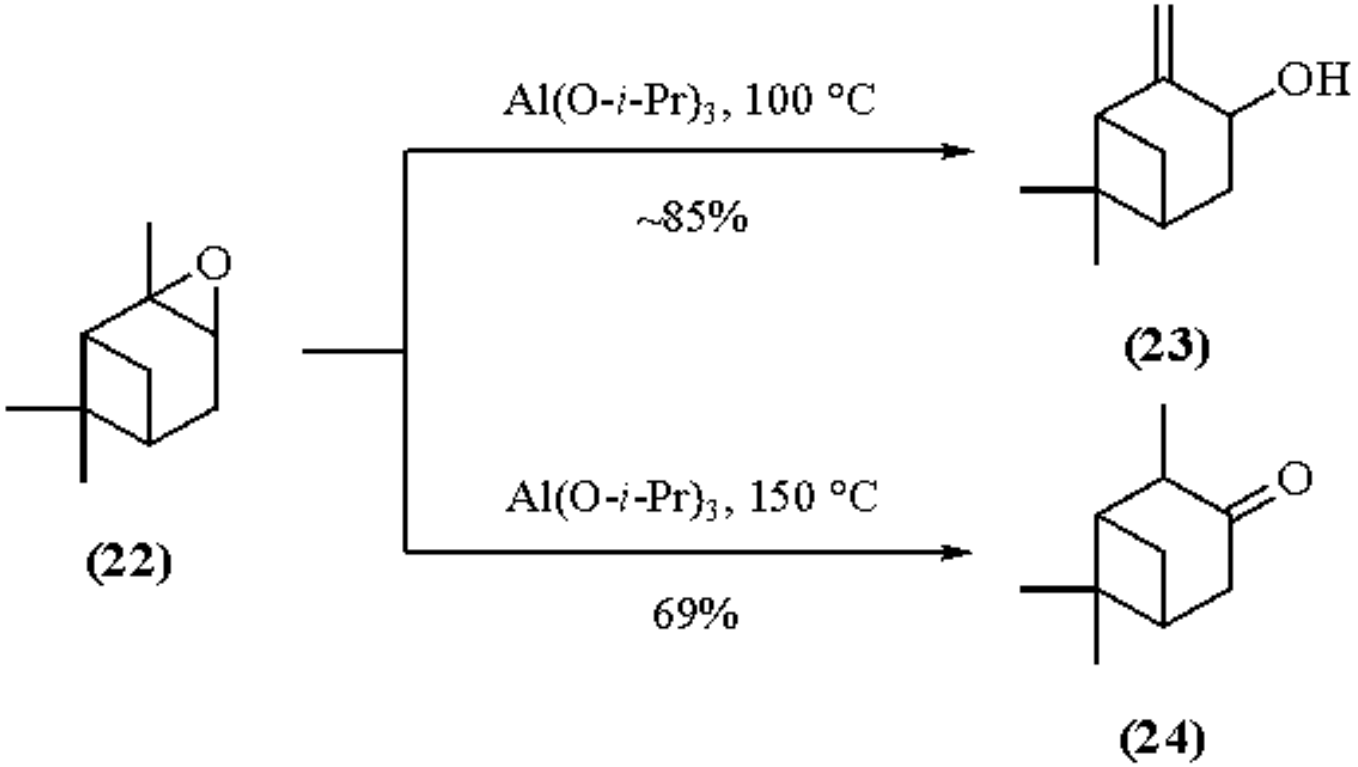

Regio- and Chemoselective Ring Opening of Epoxides.

Functionalized epoxides are regioselectively opened using trimethylsilyl azide/aluminum isopropoxide, giving 2-trimethylsiloxy azides by attack on the less substituted carbon (eq 18).[20]

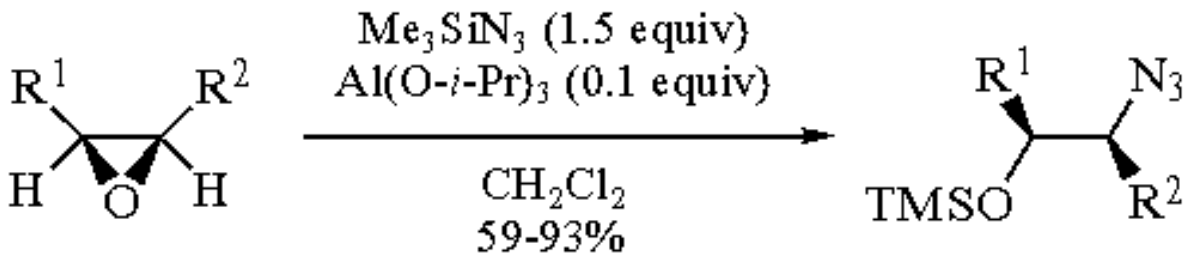

(18)

Preparation of Ethers.

Ethers ROR´ are prepared from aluminum alkoxides, $Al(OR)_3$, and alkyl halides, R´X. Thus EtCHMeOH is treated with Al, $HgBr_2$, and MeI in DMF to give EtCHMeOMe (eq 19).[21]

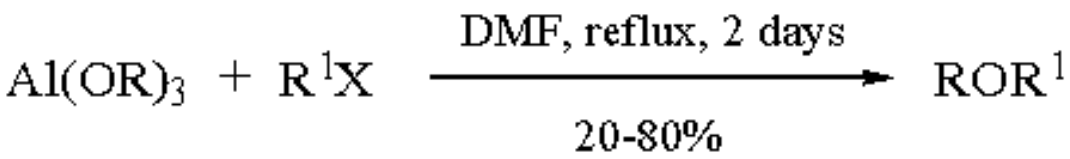

(19)

$R, R^1 = \text{alkyl}; X = \text{halide}$

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Aluminum Thiophenoxide[1]

$Al(SPh)_3$

[15821-77-9] · $C_{18}H_{15}AlS_3$ · Aluminum Thiophenoxide · (MW 354.49)

(used in preparation of phenylthioesters[2] and ketene bis(phenylthio) acetals[3])

Preparative Method: to a solution of 29 mL of 2.35 M ***Trimethylaluminum*** in hexane in 250 mL of deoxygenated xylene is added dropwise 20 mL of ***Thiophenol*** over a 5 min period. The solution is stirred at 25 °C for 10 min and heated at reflux for 48 h. The flask is transferred to a glove bag and the white solid is removed by filtration, washed with benzene, transferred to vials, and dried overnight in a vacuum desiccator.[2]

Handling, Storage, and Precautions: the reagent can be prepared as above and used directly as a suspension in xylene. Use in a fume hood.

Phenylthioesters.[2]

This reagent converts simple esters into phenylthioesters at 5 °C (4 h) or at 25 °C (1 h) in quantitative yields (eq 1).

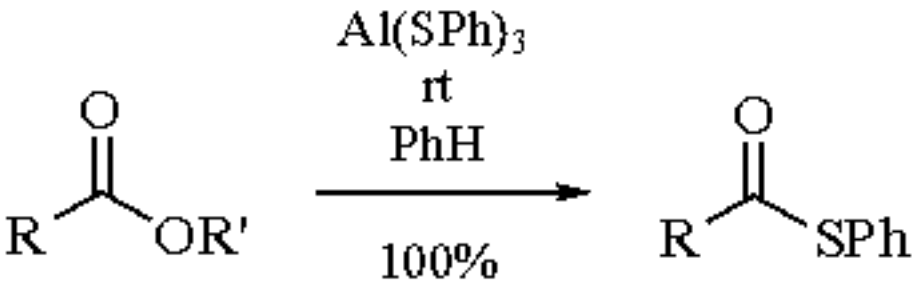

(1)

$R = Me_2CH$, $R' = Me$; $R = Ph$, $R' = Et$;
$R = cyclohexyl$, $R' = Me$; $R = 3\text{-cyclohexenyl}$, $R' = Me$

The products from α,β-unsaturated esters are contaminated with 3-(phenylthio)thioesters, while using $B(SPh)_3$ in refluxing xylene gave complementary results. A keto group at the 3-position inhibits the reaction while such a group at the 4-position leads to production of the thioacetal of the thioester when 2.5 equiv of the reagent are used.

For preparation of other thioesters, see also dialkylaluminum thiolates such as ***Diethylaluminum Thiophenoxide***.

Ketene Bis(phenylthio) Acetals.[3]

Reaction of the title reagent with carboxylic acids or esters in refluxing benzene or xylene results in simple ketene bis(phenylthio) acetals. Yields are almost quantitative if the acid or ester is branched at the α- or β-position. When there is no branching at the α- or β-positions, an important byproduct is a tris(phenylthio) orthoacetate, a useful precursor of the ketene bis(phenylthio) acetal (eq 2).

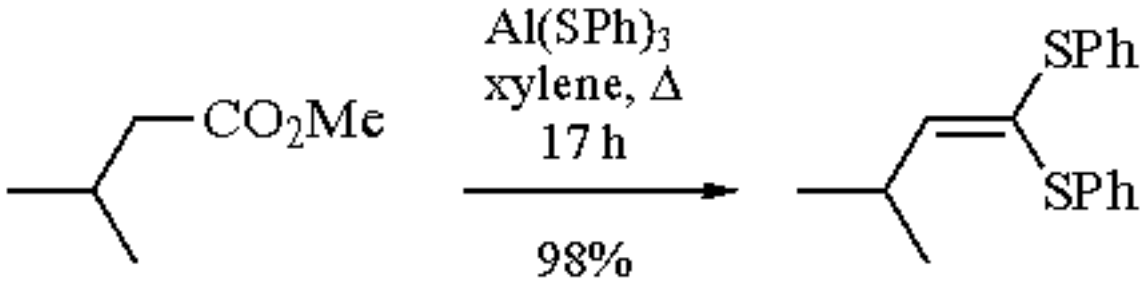

(2)

Reaction of the reagent with α,β-unsaturated esters results in a 1,1,3-tris(phenylthio)-1-alkene in 70-85% yield (eq 3).

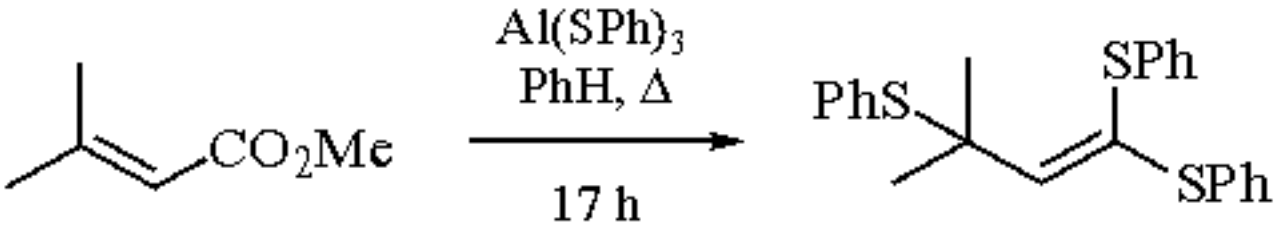

(3)

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(*Z*)-β-Aminoacrolein

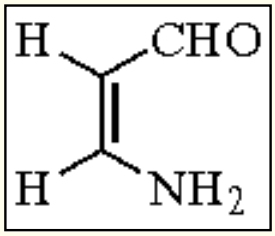

[25186-34-9] · C_3H_5NO · (*Z*)-β-Aminoacrolein · (MW 71.08)

(pyridine synthesis, Friedländer synthon, β-amino aldehyde)

Alternate Name: 3-amino-2-propenal.

Physical Data: yellow solid, mp 105-106 °C.

Solubility: sol alcohol and water.

Preparative Methods: the reagent is highly reactive towards self-condensation and is best when freshly prepared. One method of preparation involves the reaction of ***Ammonia*** with ***Propargyl Aldehyde*** (propynal) in the presence of ethanol in a sealed tube.[1] This method is somewhat erratic, propargaldehyde is not commercially available, and the stereochemistry of the resulting double bond is most likely *trans*. A modified route, proceeding through 1,1,3,3-tetraethoxypropane, has also been reported.[2] The most satisfactory preparation of β-aminoacrolein involves the partial hydrogenation of isoxazole.[3,4] A solution of commercially available isoxazole (5 g, 0.073 mol) in anhyd MeOH (100 mL) containing 1.0 g of ***Raney Nickel*** was hydrogenated at 40 psi until one equivalent of hydrogen had been absorbed and hydrogen uptake had ceased (eq 1). The mixture was filtered to remove the catalyst and the solvent was evaporated to give 4.2 g (82%) of a yellow solid, mp 96-97 °C. Recrystallization from chloroform-petroleum ether (1:1) gave crystals, mp 104-105 °C.

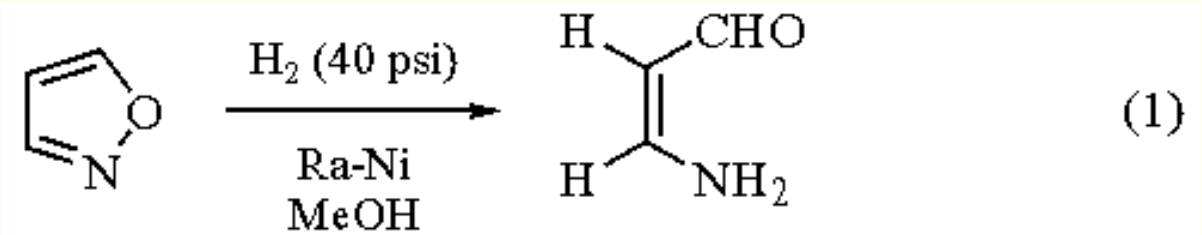

Handling, Storage, and Precautions: the reagent should be used immediately although it can be stored under inert atmosphere at 0 °C in the dark for several days. Analysis by NMR (D_2O) shows three equal area peaks at δ 5.41 (dd), 7.50 (d), and 8.70 (d). Repurification can be effected by sublimination if necessary. Use in a fume hood.

Pyridine Synthesis.

In a series of three papers, Breitmaier and Bayer demonstrated that the reagent was effective in the preparation of 2,3-substituted pyridines.[5] For example, the Friedländer condensation of β-aminoacrolein with cyclohexanone leads to 5,6,7,8-tetrahydroquinoline in moderate yield (eq 2). The reaction works well for other cyclic ketones but unfortunately fails with cyclobutanone.

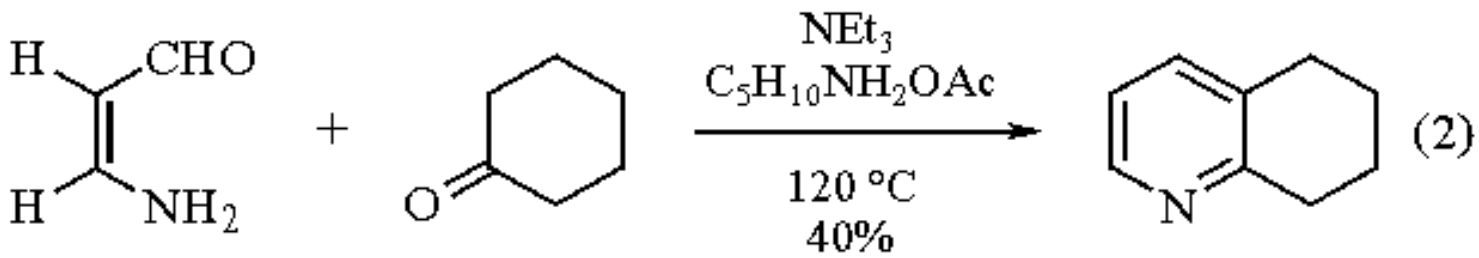

This same approach has been extrapolated to the preparation of 3,3´-polymethylene bridged derivatives of 2,2´-bipyridine, albeit in relatively low yields (eq 3).[6]

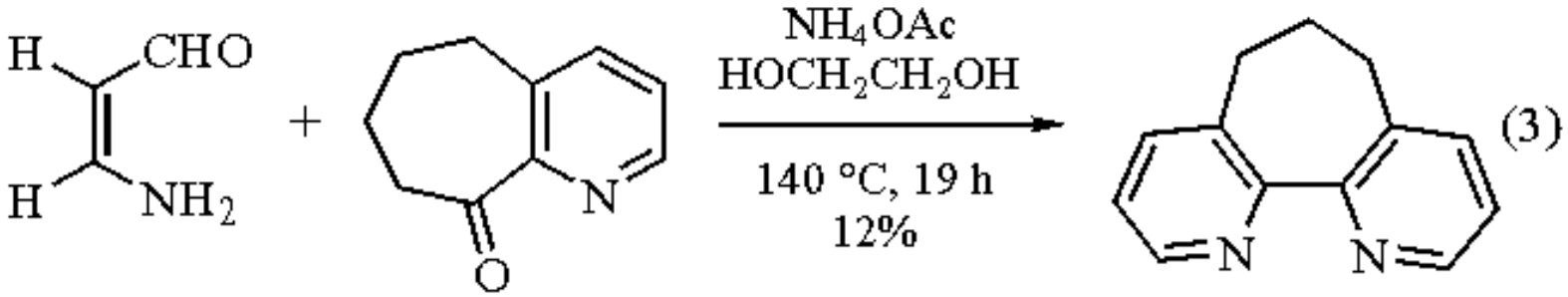

The reaction may be employed with appropriate diketones to create two pyridine rings simultaneously and represents a direct route to doubly bridged derivatives of 2,2´;6,2´´-terpyridine (eq 4). As expected, the yields are even lower and other routes to these same compounds have been developed.[7]

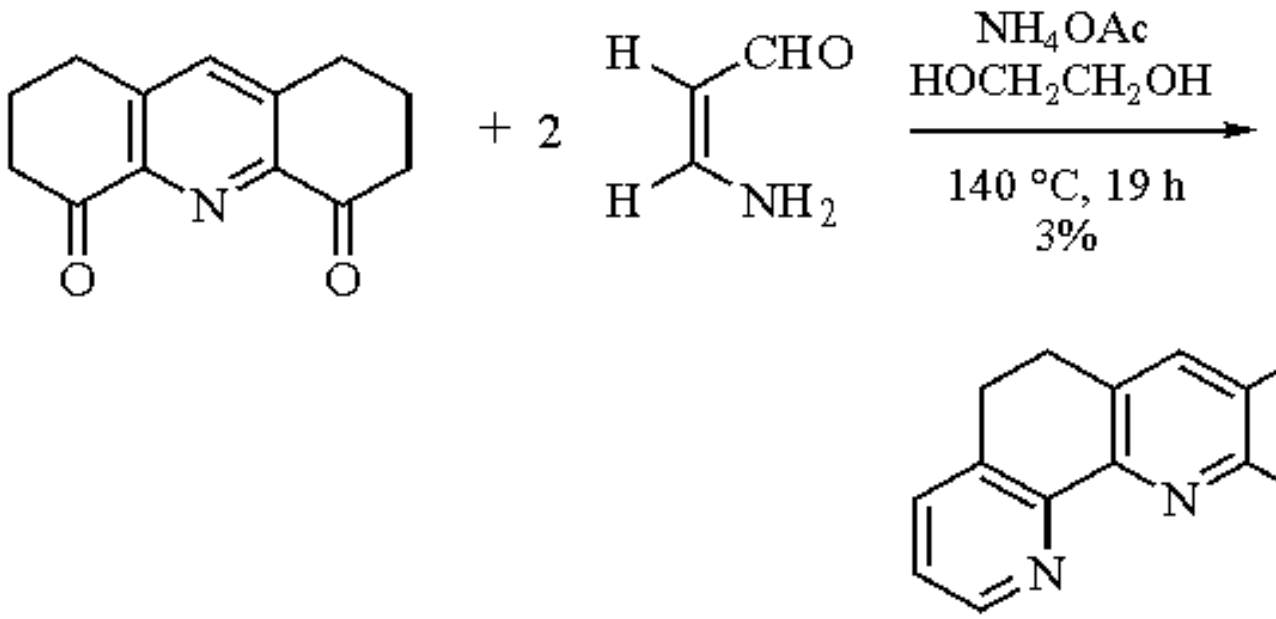

(4)

Related Reagents.

Acrolein; ***2-Aminobenzaldehyde***; ***O-Allylhydroxylamine***; ***3-Ethoxyacrolein***.

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2-Aminobenzaldehyde[1]

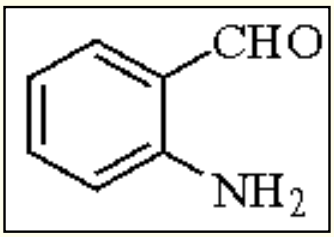

[529-23-7] · C_7H_7NO · 2-Aminobenzaldehyde · (MW 121)

(Friedländer synthon; quinoline synthesis; *o*-amino aldehyde)

Alternate Names: 2-formylaniline; 1-amino-2-formylbenzene.

Physical Data: mp 38-39 °C.

Solubility: sol ether, alcohol.

Preparative Methods: the reagent is best when freshly prepared. At one time it was commercially available but samples more than a few months old were found to be essentially useless due to oligomerization. The propensity of the reagent to self-react and the resulting oligomer structures have been extensively discussed.[1a] A useful preparative method involves ***Iron(II) Sulfate*** reduction of 2-nitrobenzaldehyde.[2] The key to success is limiting the reaction time to 8-10 min and immediate, rapid steam distillation of the reaction product. The precursor is commercially available from a variety of sources and its preparation has also been reported.[3] A supposedly simplified procedure has been suggested but it does not differ significantly from the earlier method.[4]

Purification: can be effected by steam distillation from saturated NaCl solution.

Handling, Storage, and Precautions: the reagent can be stored for periods of up to several months under an inert atmosphere at 0 °C in the dark. The mp is a good general indicator of purity and the NMR spectrum should show an aldehyde proton integrating 1:4 against the aromatic protons. Use in a fume hood.

Quinoline Synthesis.

The reagent is most useful for the preparation of quinolines via the Friedländer condensation where 2-aminobenzaldehyde (2-AB) is the prototype *o*-amino aldehyde reaction partner. The reaction with acetaldehyde to form quinoline was first reported in 1882[5] and involves two dehydration steps, the sequence of which is not well established although initial formation of an imine intermediate appears more likely (eq 1).

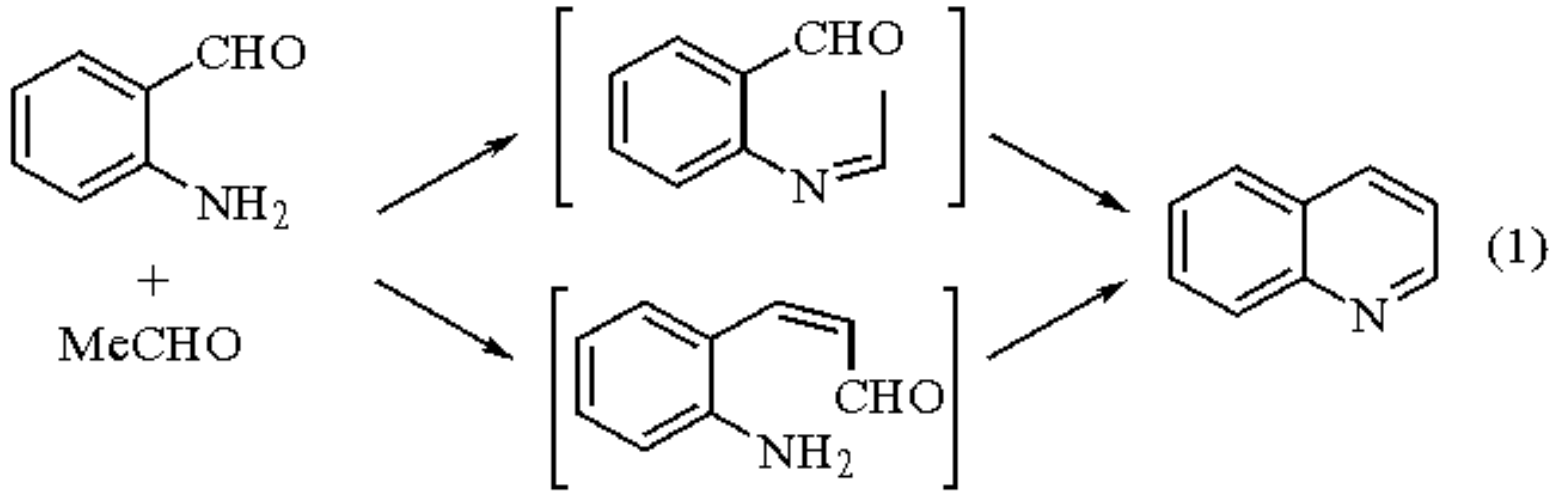

The reaction is normally not suitable for the formation of quinolines unsubstituted on the pyridine ring and aldehyde partners are generally unsatisfactory under base-catalyzed conditions. Ketones react more smoothly and even cyclobutanone gives an acceptable yield 2,3-cyclobutaquinoline (eq 2).[6] A review on the Friedländer synthesis which appeared in 1982 gives an extensive compilation of this reaction involving 2-AB as well as other *o*-amino aldehydes.[1b]

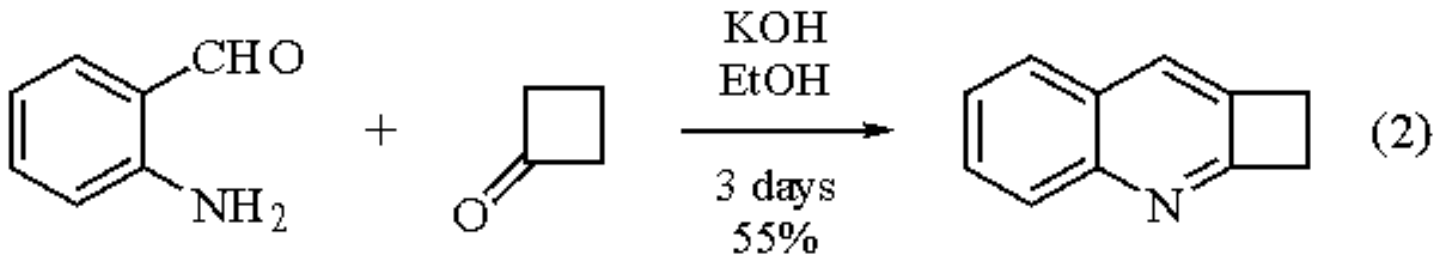

The regiochemistry of condensations with unsymmetrical ketones is often pH dependent. In the base-catalyzed reaction of 2-AB with ethyl 3-oxopyrrolidine-1-carboxylate, two products were formed with the dominant one resulting from the more stable enolate or iminate intermediate (eq 3).[7] The same reaction carried out in acetic acid containing sulfuric acid gives a nearly equal mixture of the two regiochemistries.

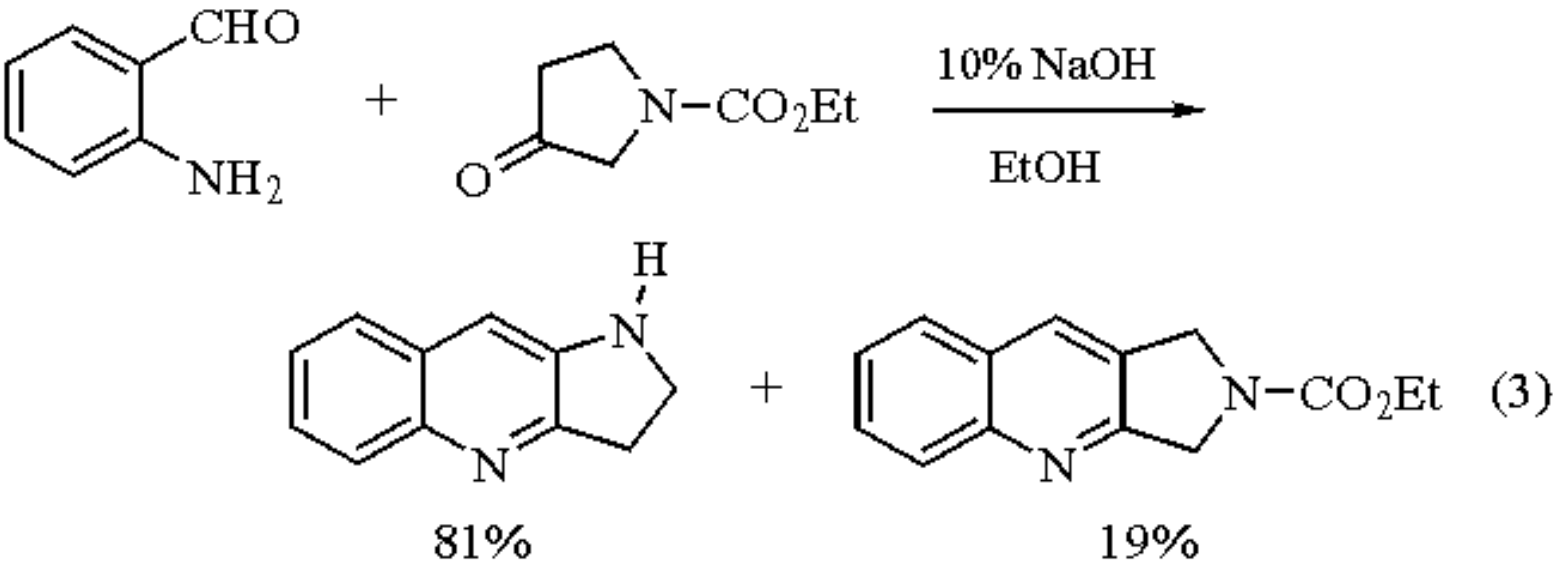

Activation of the carbonyl component considerably facilitates the reaction and only one regioisomer is observed when 2-AB condenses with acetylacetone (eq 4).[8]

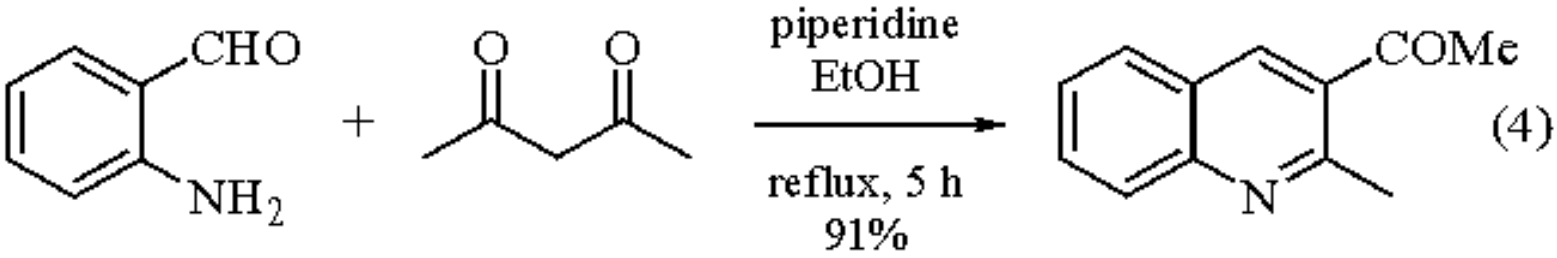

Appropriate β-diketones will condense in a 2:1 fashion to create two quinolines in a single step. Thus 1,2-cyclohexanedione gives a bridged 2,2´-biquinoline (eq 5).[9] In a similar fashion, 1,1´-diacetylferrocene provides a ferrocene substituted with quinoline on each Cp ring.[10]

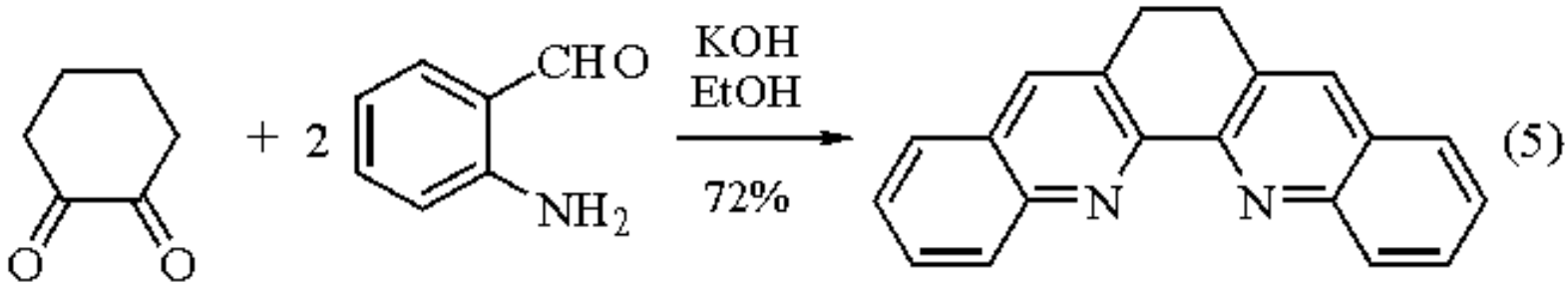

Friedländer condensations are not limited to simple keto groups. In the reaction of 2-AB with naphthalene-1,3-diol the latter may be considered as a bis-enol (eq 6). Under basic conditions the first step involves condensation between the aldehyde group and the enolate at C-4.[11]

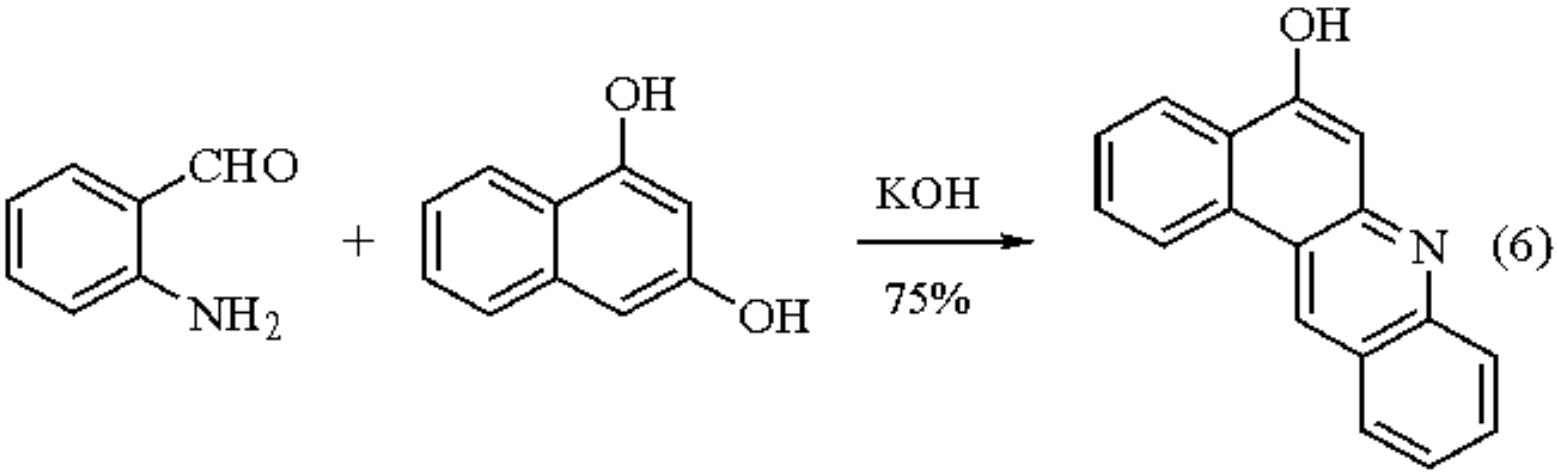

A modification developed by Borsche overcomes some of the difficulties associated with the instability of 2-AB. By employing an arylimine derivative of 2-AB in its place, smooth condensations occur in alkaline ethanolic solution or in the presence of ***Piperidine*** to provide quinolines in yields of 60-90% (eq 7).[12]

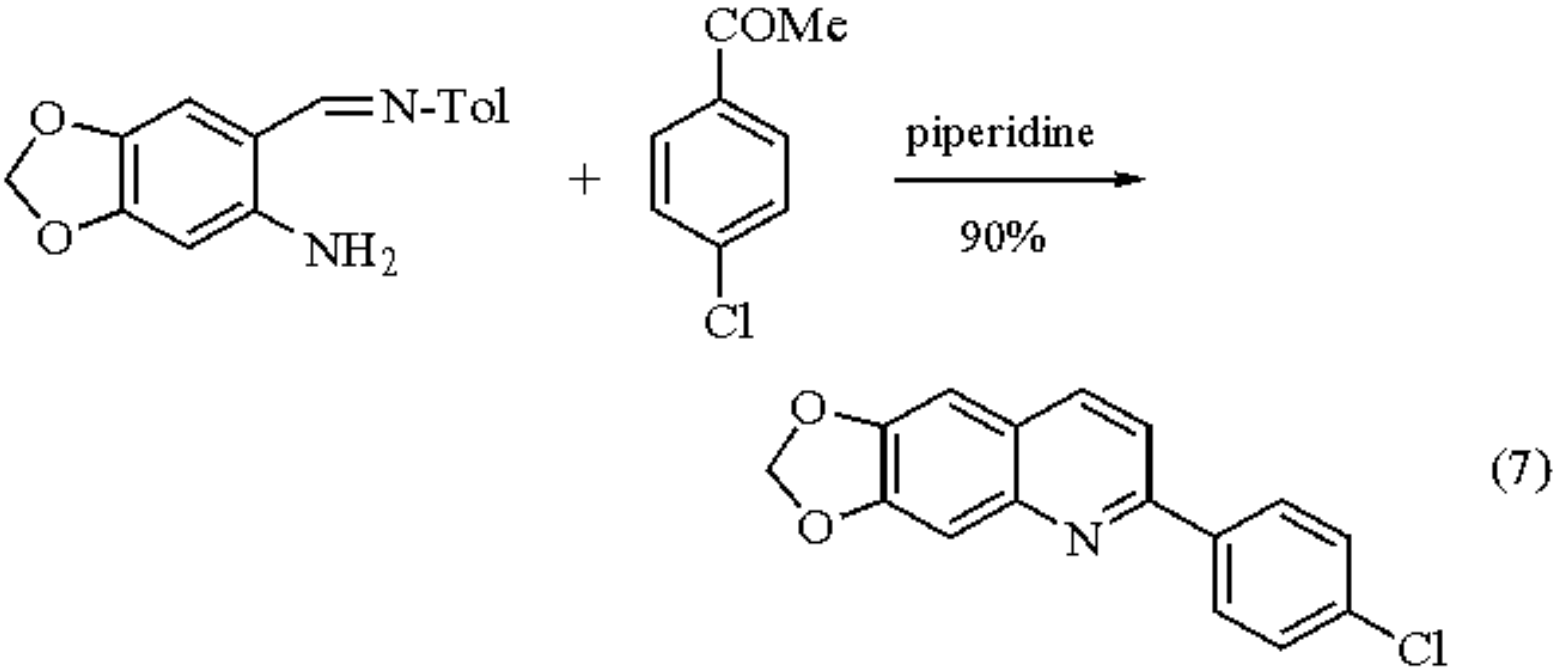

Related Reagents.

(Z)*-β-*Aminoacrolein; ***2-Aminonicotinaldehyde***; ***Cyclobutanone***; ***2,4-Pentanedione***; ***Piperidine***; ***Quinoline***.

---

1. (a) Caluwe, P. *T* **1980**, **36**, 2359. (b) Cheng, C.-C.; Yan, S.-J. *OR* **1982**, **28**, 37. (c) Thummel, R. P. *SL* **1992**, 1.
2. Smith, L. I.; Opie, J. W. *OSC* **1955**, *3*, 56.
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1-Aminobenzotriazole

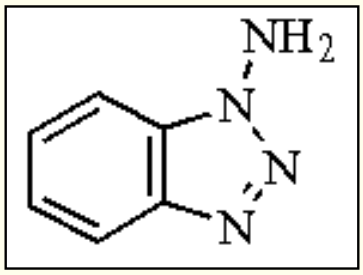

[1614-12-6] · $C_6H_6N_4$ · 1-Aminobenzotriazole · (MW 134.06)

(an important precursor of benzyne, by oxidation with lead tetraacetate;[1] this method of benzyne generation is especially useful for biphenylene formation and other [2 + 2],[1c] [3 + 2],[19] and [4 + 2][22] cycloadditions)

Alternate Name: 1*H*-benzotriazol-1-amine.

Physical Data: colorless to tan solid, mp 83-84 °C;[1c] ^{1}H NMR;[1c] ^{15}N NMR.[2]

Solubility: sol benzene, CH_2Cl_2, $CHCl_3$.

Form Supplied in: commercially available.

Preparative Methods: by amination of benzotriazole with ***Hydroxylamine-O-sulfonic Acid***, or from *o*-nitroaniline by a multistep route.[1c]

Handling, Storage, and Precautions: toxicity and carcinogenicity not known; reacts rapidly with various oxidizing agents to generate benzyne.

Formation of Benzyne.

Campbell and Rees discovered that benzyne is efficiently generated by the ***Lead(IV) Acetate*** (LTA) oxidation of the title compound (**1**), as shown by high yield [4 + 2] trapping with ***Tetraphenylcyclopentadienone*** (**2**) (eq 1).[1] Benzyne is not only formed and trapped efficiently when (**1**) is added to LTA, but also when the order of addition is reversed; the latter is somewhat surprising, since excess (**1**) can function as a nucleophile to destroy benzyne, as observed when oxidation of (**1**) is effected with ***(Diacetoxyiodo)benzene***.[3] A recent modification[4] of the Campbell-Rees method, simultaneous addition of LTA and (**1**) to opposite ports of a stirred flask, has led to improvement in some applications, e.g. [4 + 2] reactions with oxazoles,[4] vinyl isocyanates,[5] and 1,2,4-triazines.[6]

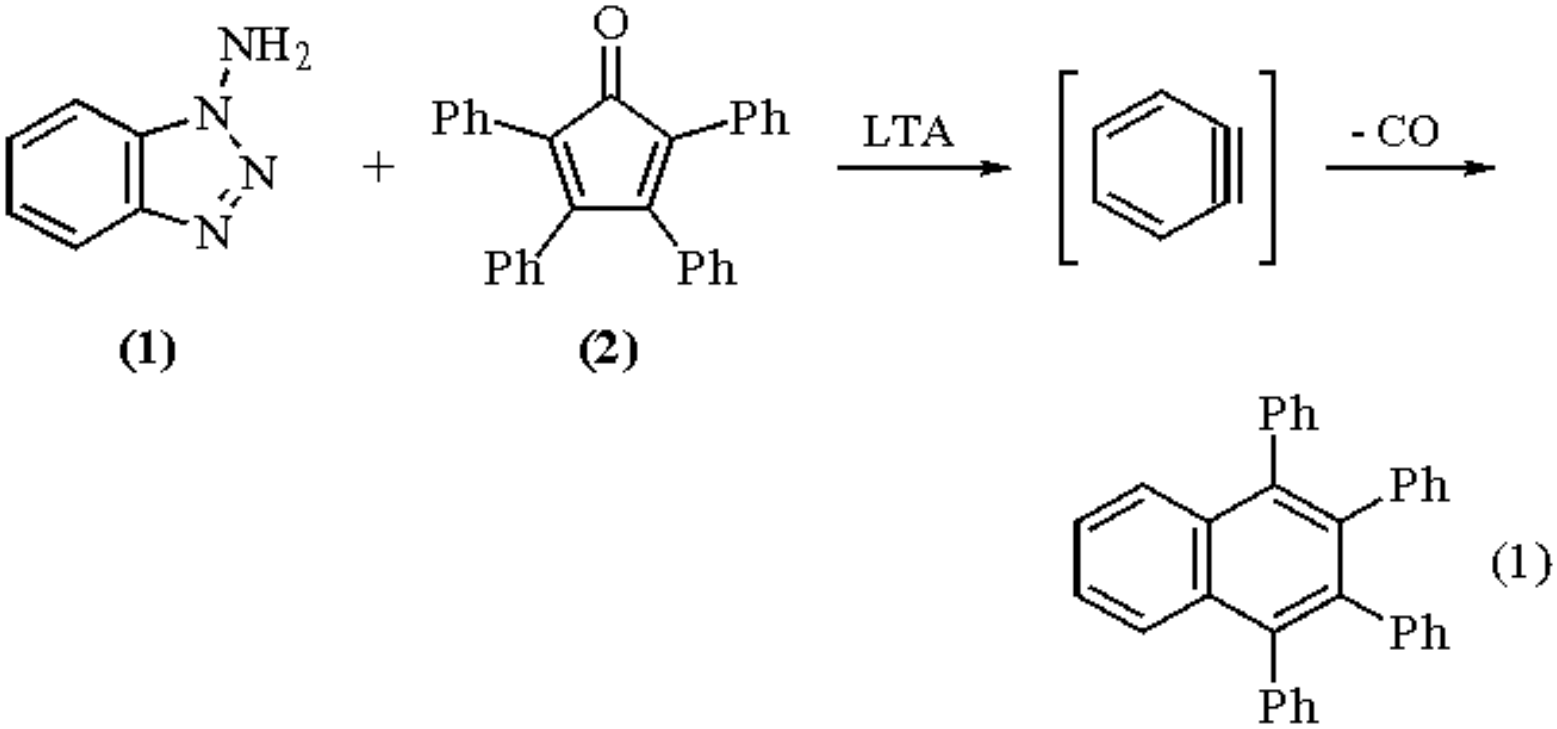

The major advantages of the (**1**) + LTA method, compared with other procedures for generating benzyne, are: (a) the reaction is rapid over a wide temperature range, from at least -70 to +55 °C;[1c] (b) the reagents are compatible with base-sensitive materials and most functional groups; and (c) although all of the aminobenzotriazole substrates must be prepared, the method has considerable demonstrated generality (see below). Disadvantages (side reactions) stem from the powerful oxidizing ability of LTA, and the formation of HOAc in the reaction.

Preparative Methods.

Campbell and Rees also developed two preparative routes to (**1**).[1c] These remain the methods of choice for (**1**), as well as for analogs. The simpler procedure involves amination of benzotriazole with NH_2OSO_3H, which gives a mixture of (**1**) and 2-aminobenzotriazole (**3**) (eq 2).[1c] Compounds (**1**) and (**3**) can be separated by chromatography, although this may not be important in many applications. The reaction of (**3**) with LTA affords *cis,cis*-muconodinitrile, which reportedly does not interfere with the benzyne formed from (**1**).[1c]

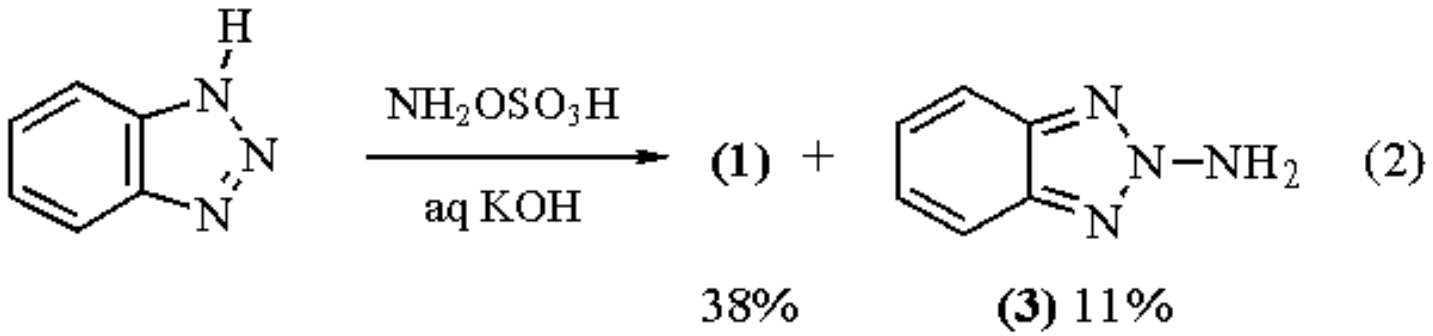

The second preparative method for (**1**) is based on an earlier literature report, improved by Campbell and Rees.[1] Diazotization of *o*-nitroaniline followed by treatment with diethyl malonate gives the derivative (**4**); reduction of the nitro group and cyclization via diazotization affords (**5**), which is then hydrolyzed to (**1**) (eq 3).

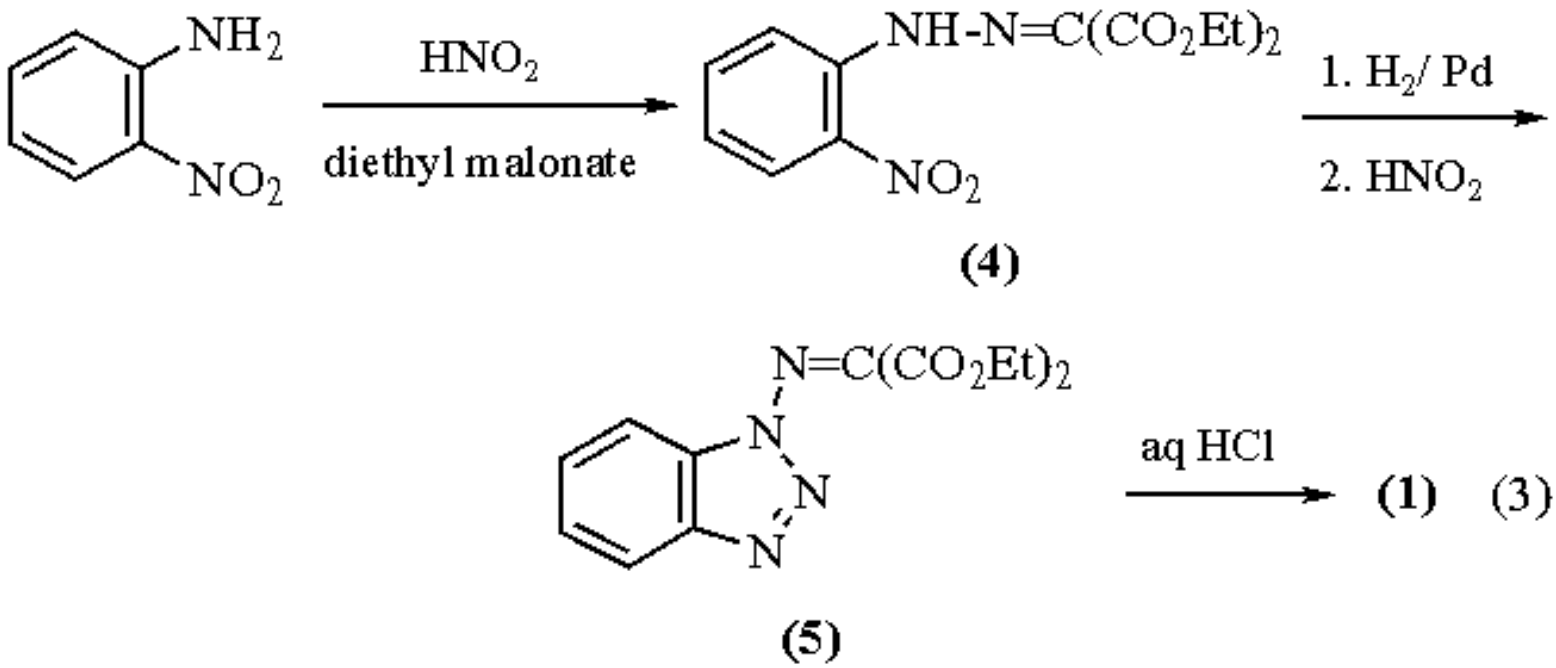

Analogs of (1).

The known substituted derivatives, benzologs, and heteroaromatic analogs of (**1**) that have been used to generate arynes are displayed as structures (**6**)-(**22**),[1c,5,7-14] along with the related nonoxidative precursor of benzyne (**23**),[15] and the aminotriazene precursor of cycloheptyne (**24**).[16]

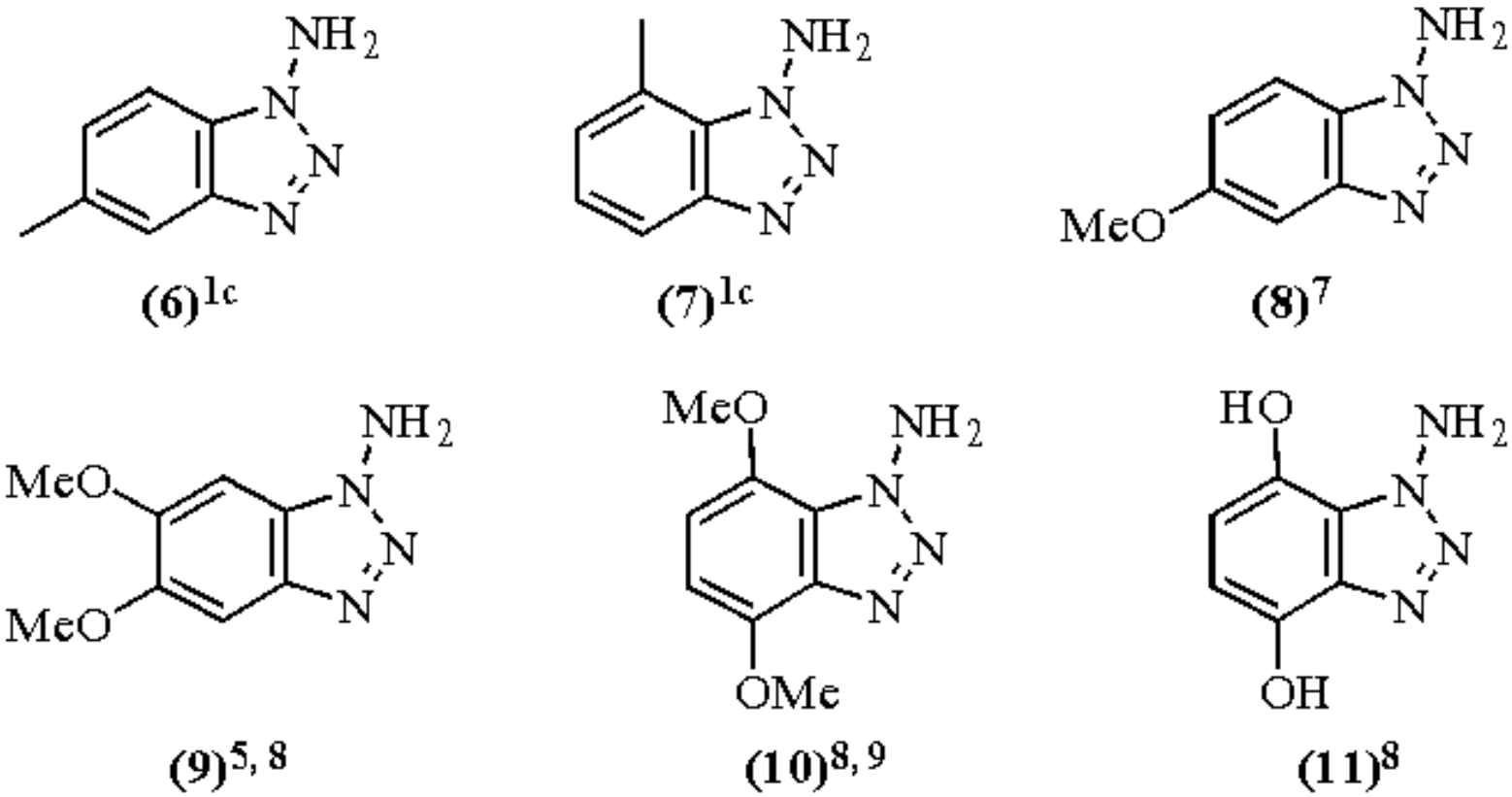

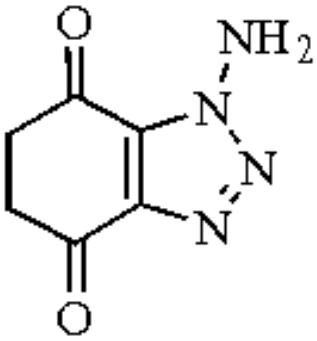

(12)[10]

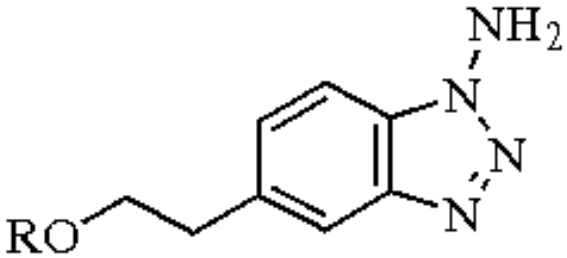

(13a) R = H[10]

(13b) R = polym-CO-

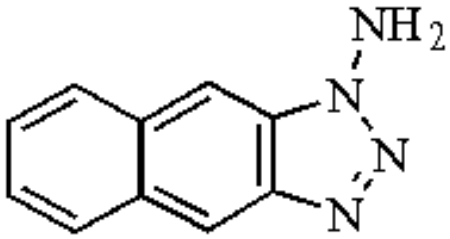

(14)[11a]

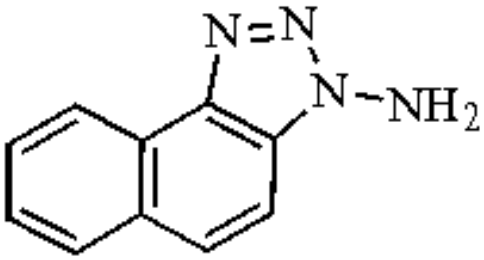

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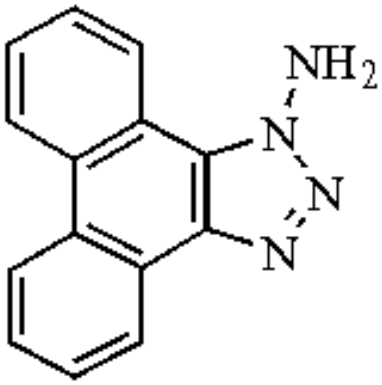

(16)[11b]

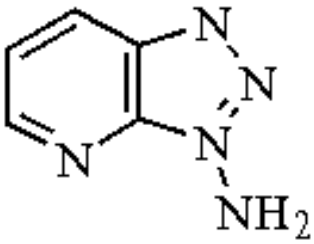

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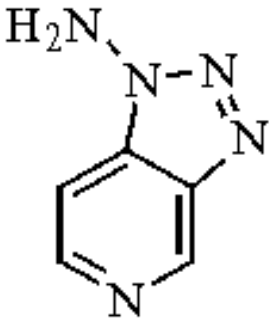

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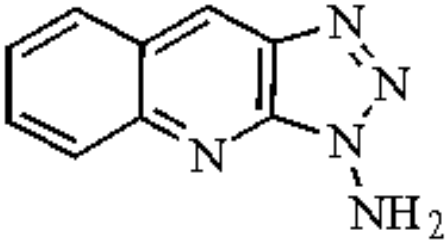

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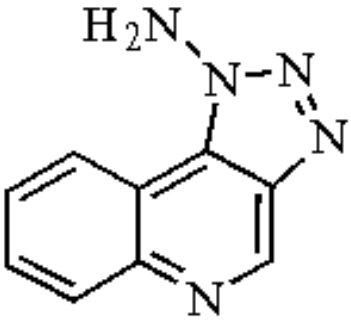

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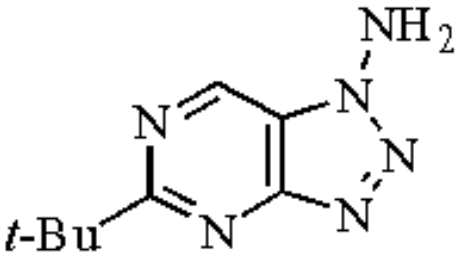

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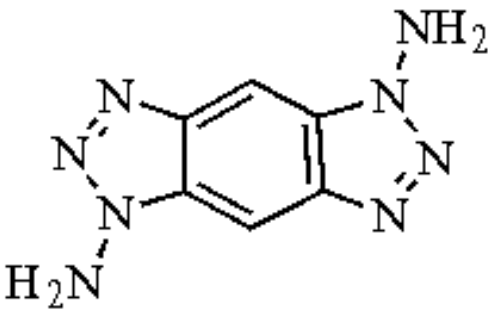

(22)[14]

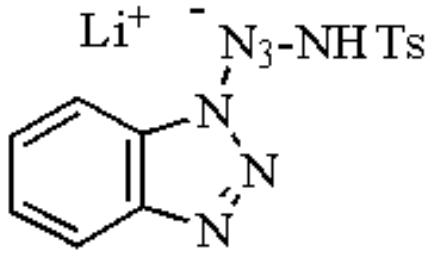

(23)[15]

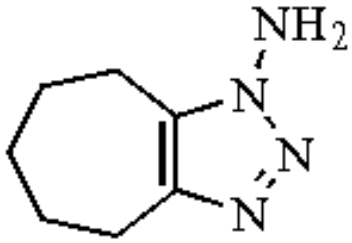

(24)[16]

[2 + 2] Reactions.

One of the most striking and unusual features of the LTA oxidation of (**1**) is the high yield of *o*-biphenylene (**25**) that is formed when the reaction is carried out in the absence of an efficient aryne-trapping agent (eq 4).[1c] The high yield of (**25**) requires that the benzyne concentration exceed [10^{-7}], even if the [2 + 2] reaction occurs at the diffusion-controlled limit. In order to attain such concentrations, a combination of rapid formation and relatively slow side-reaction loss of the aryne is needed.

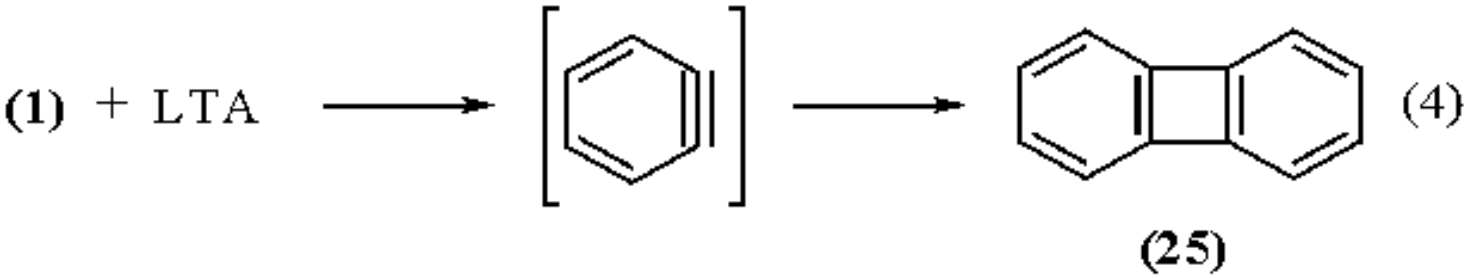

(4)

(25)

Analogous [2 + 2] homodimerizations have been observed for the arynes generated from (**6**),[1c] (**7**),[1c] (**8**),[7] (**10**),[8] (**13a**) (but not polymer-bound **13b**),[10] (**14**),[11a] (**15**),[11a] and (**23**)[15] (which decomposes thermally to form benzyne). Specific attempts to form [2 + 2] homodimers of arynes derived from (**9**),[8] (**16**),[11b] (**17**)-(**20**),[12b] and (**22**)[14] all failed; cycloheptyne does not react rapidly with itself, and no [2 + 2] homodimer is seen in reactions of (**24**) with LTA.[16]

Crossed aryne [2 + 2] reactions have been observed in LTA oxidations of mixtures of (**1**) + (**8**),[7] (**1**) + (**10**),[8] (**1**) + (**14**),[11a] (**1**) + (**15**),[11a] and, interestingly since no homodimer is formed from (**16**), (**1**) + (**16**)[11b] and (**14**) + (**16**)[11b] (shown in eq 5), but not (**15**) + (**16**).[11b] Angular benzannulation is thought to diminish the lifetime of arynes, making the last reaction especially unfavorable.[11b]

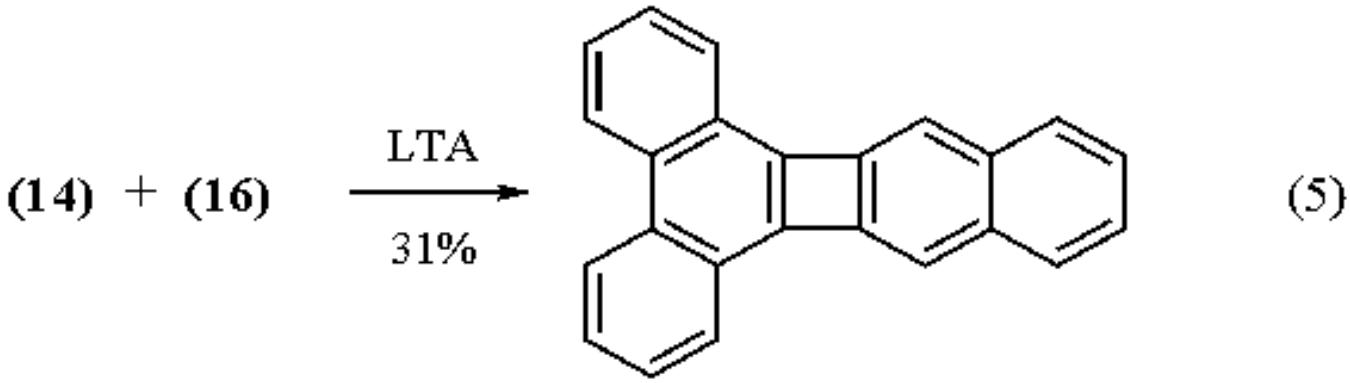

The Campbell-Rees procedure, as well as the anthranilic acid/alkyl nitrite method for generating benzyne, failed to give [2 + 2] product with 1,1-dichloro-2-methylpropene.[17] The bis-aryne precursor (**22**) also failed to give [2 + 2] products with vinyl acetate, or 1,1-dimethoxyethylene.[14] The latter alkene may be too rapidly oxidized by LTA. The homodimerization of benzyne is more rapid than [2 + 2] reactions of (*E*)- and (*Z*)-dichloroethene and vinyl acetate, under the original Campbell-Rees procedure.[18] The modified procedure[4] may lead to improvement.

[3 + 2] Cycloadditions.

The (**1**) + LTA method for generating benzyne is suitable for cycloadditions with mesionic compounds such as 3-phenylsydnone (**26**), which forms indazole (**27**) by extrusion of CO_2 from the initially formed adduct (eq 6).[19] Some related sulfur-containing mesionic species afford isolable adducts that undergo quite different extrusion processes under thermal or photochemical conditions.

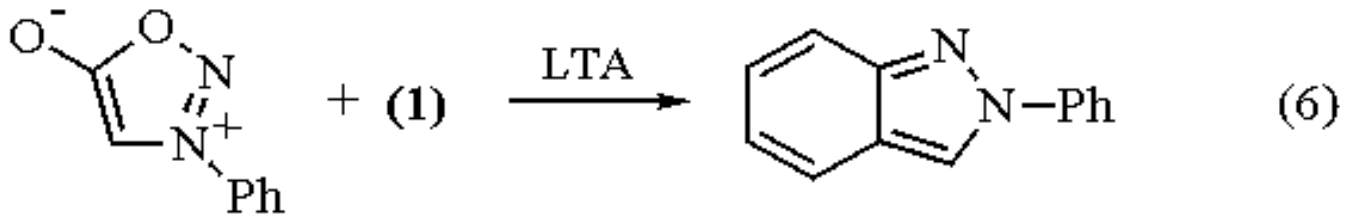

(26) (27)

Benzyne from (**1**) + LTA also reacts with CS_2 to give the dithiacarbene intermediate (**28**) (eq 7).[20] The further reactions of (**28**) depend on the reaction conditions.

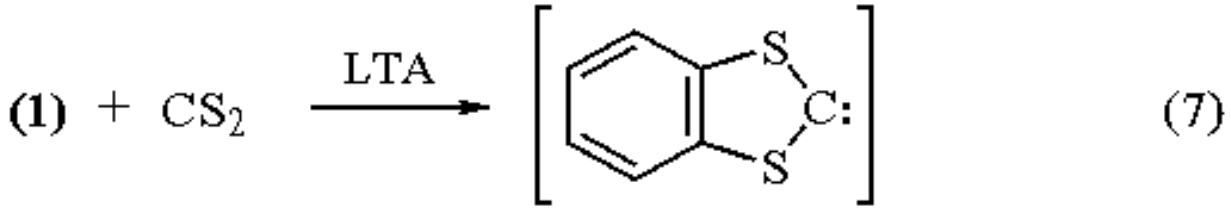

(28)

[4 + 2] Cycloadditions.

Diels-Alder reactions are often (but not always, cf. thiophene[21]) more successful with the Campbell-Rees than with other benzyne-forming approaches. Further improvements are possible for many [4 + 2] reactions by use of the modified method mentioned earlier,[4] and by carrying out the reactions at lower temperatures.[4b] The inverse temperature/yield relationship of Diels-Alder reactions of cycloheptyne nicely illustrates this point.[16]

A wide range of diene partners has been used for cycloaddition with benzyne derived from (**1**). Oxazoles, depending upon substituents and temperature, can give isolable cycloadducts (e.g. **29**), which can in turn be converted to the analogous isobenzofuran (eq 8).[4] Vinyl isocyanates afford lactams (eq 9).[5,22] Isoquinolines are formed in the reaction with 1,2,4-triazines (eq 10).[6] Compound (**1**) has also been used with metallocyclodienes such as substituted sila-[23] and germacyclopentadienes,[24] and digermacyclohexadienes.[25] The adducts have been used to generate reactive intermediates such as dimethylsilylene (eq 11).[23] Another notable example is the Diels-Alder reaction of azulene; interestingly, simultaneous addition of (**1**) and LTA was used in this study, but no comparison with the original Campbell-Rees conditions was noted. The cycloaddition takes place at the cyclopentadiene site as shown (eq 12).[26]

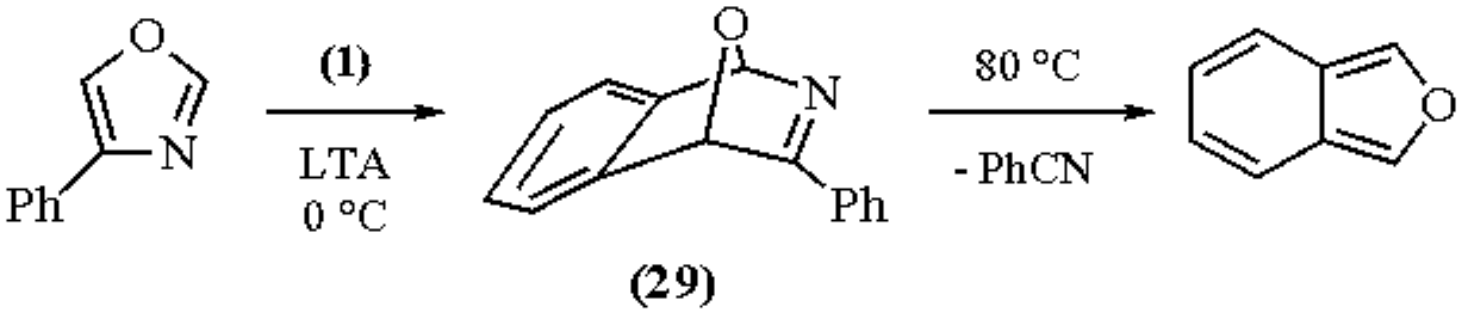

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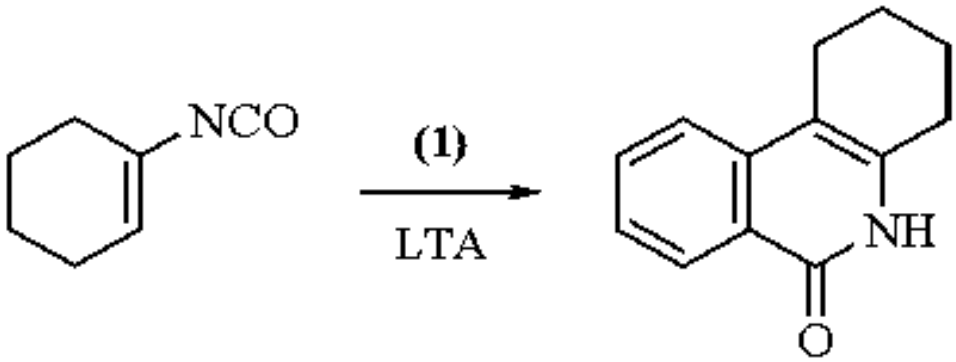

(9)

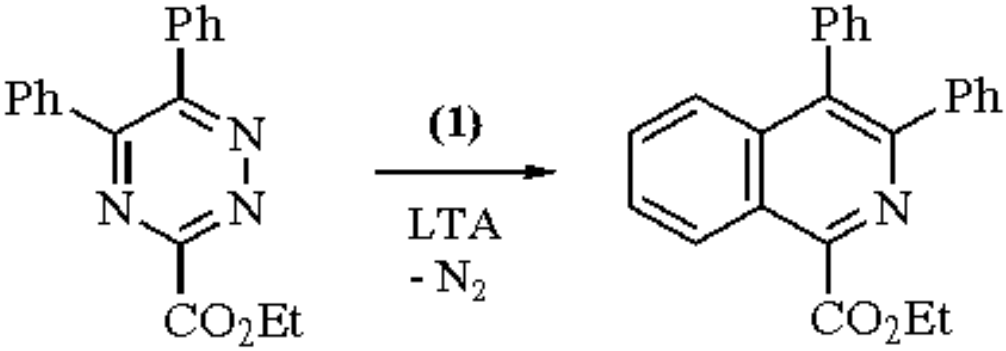

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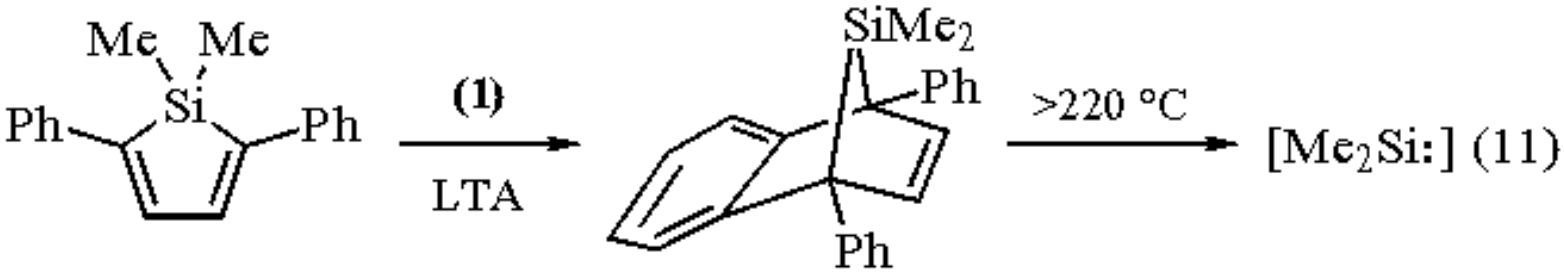

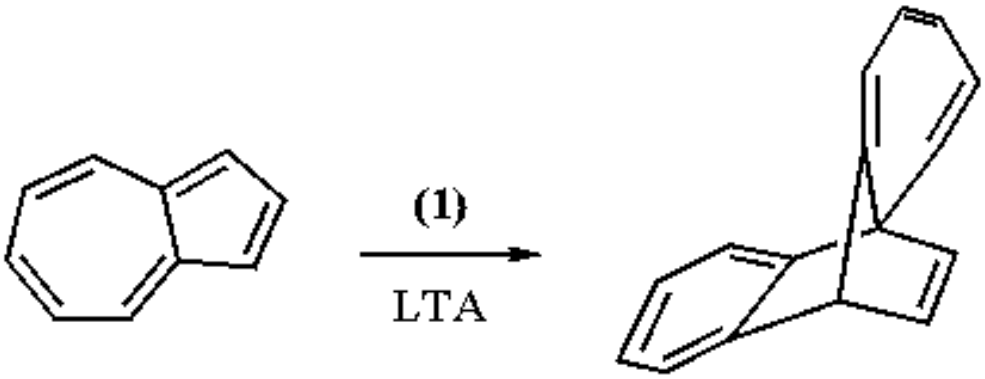

(12)

The very efficient reaction of benzyne with tetracyclone (**2**; see eq 1) has made it the diene of choice for demonstrating the formation of an aryne, and in some instances this reaction may be the *only* evidence for aryne formation; for example, 2,3-pyridyne from (**17**) was trapped by (**2**) in only 4% yield.[12] Less efficient dienes include furan and anthracene; triptycene was isolated in only 12% yield by Campbell and Rees,[18] but this reaction may have been partly limited by the solubility of anthracene. Limited solubility of the interesting bis-aryne precursor (**22**) also caused difficulties in some of its reactions.[14]

Other oxidizing agents were examined by Campbell and Rees, but none were found to be as good as $Pb(OAc)_4$ for useful aryne applications.[27] ***N-Bromosuccinimide*** apparently generates benzyne efficiently, but the reactive intermediate is largely trapped by rapid reaction with bromine. If a particular application requires the absence of acid, the (hazardous) benzyne precursor (**23**) can be used.

A possible alternative and related benzyne precursor, demonstrated only by reaction with (**2**), in 25% yield, is the nitrosobenzotriazole (**30**) (eq 13).[28]

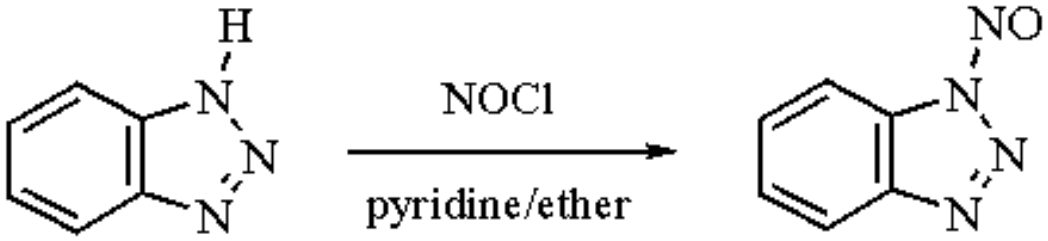

(13)

(30)

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(*S*)-1-Amino-2-hydroxymethylindoline

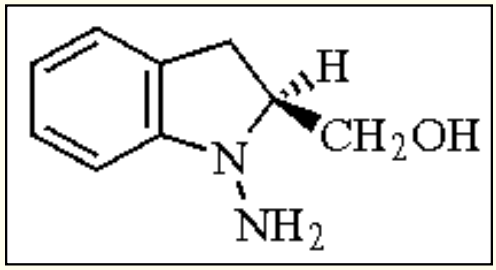

[27719-98-8] · $C_9H_{12}N_2O$ · (*S*)-1-Amino-2-hydroxymethylindoline · (MW 164.208)

(stereospecific synthesis of α-substituted α-amino acids from α-keto acids[1])

Physical Data: mp 81.5-82.7 °C (racemate).

Solubility: readily sol methanol, ethanol; insol hexane, ether.

Preparative Methods: 2-hydroxymethylindoline is resolved with (*S*)-(+)-***Mandelic Acid*** to give (*S*)-(+)-2-hydroxymethylindoline, which is then nitrosated and reduced to produce (*S*)-(**1**) (eq 1).[1] (*R*)-(**1**) is also available by a similar procedure.

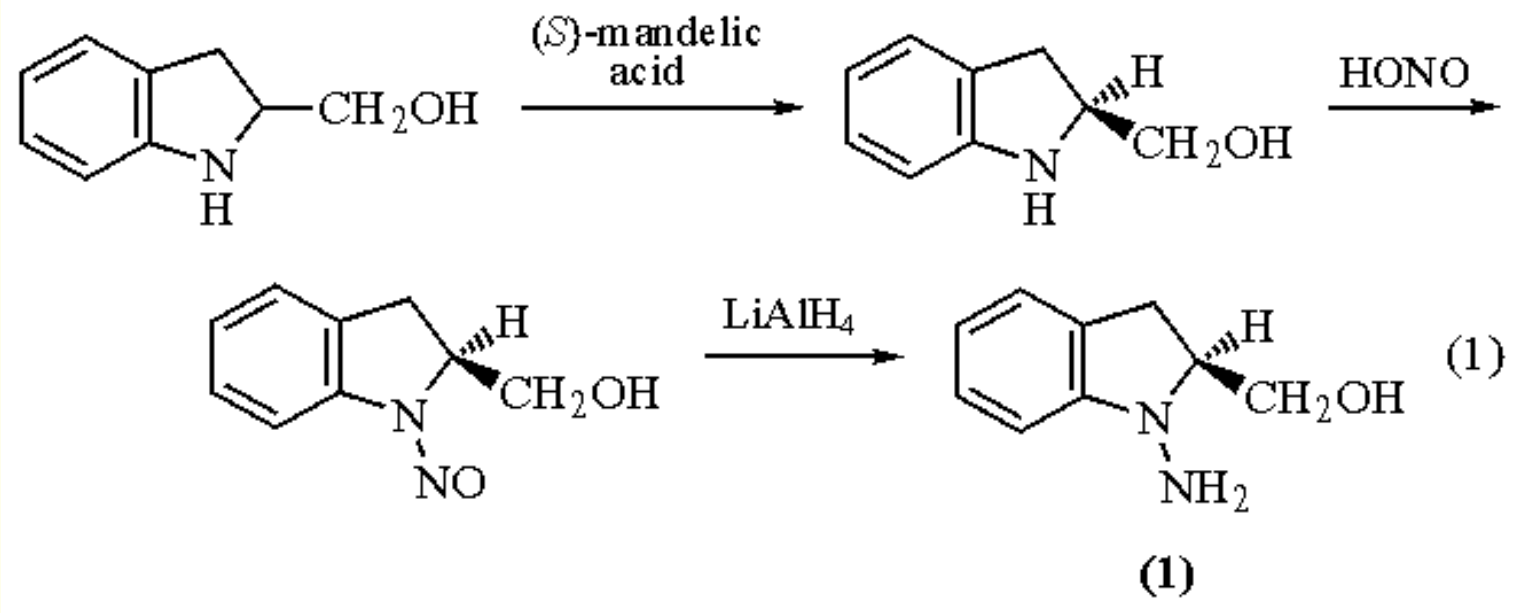

Purification: recrystallization from methanol/ether.

Handling, Storage, and Precautions: the reagent is very air sensitive. Store under nitrogen or argon at -20 °C. Use in a fume hood.

The enantiospecific synthesis of natural and unnatural α-amino acids has been reviewed.[2] Some of the most successful approaches involve the stereoselective hydrogenation of chiral dehydroamino acid derivatives. Many of these transformations are equivalent to the stereoselective reductive amination of α-keto acids (eq 2).[3] For example, catalytic reduction of the imines of α-keto acids with chiral α-methylbenzylamine gives α-substituted α-amino acids with 12-80% ee (eq 3).[4]

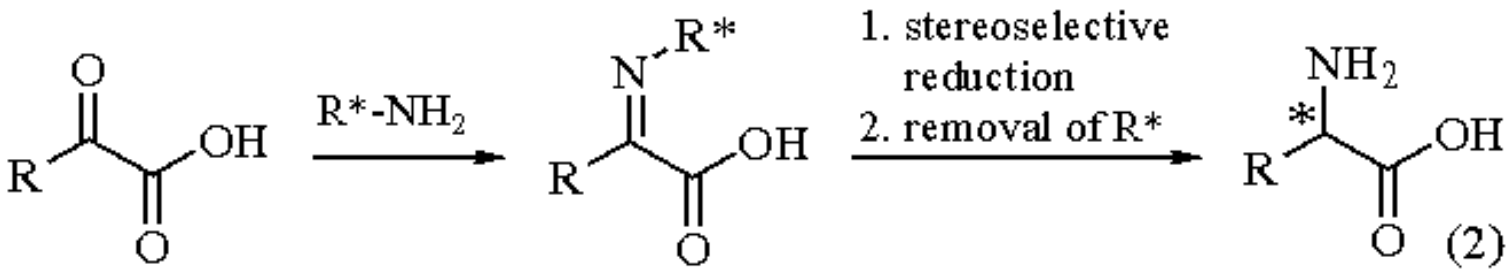

(2)

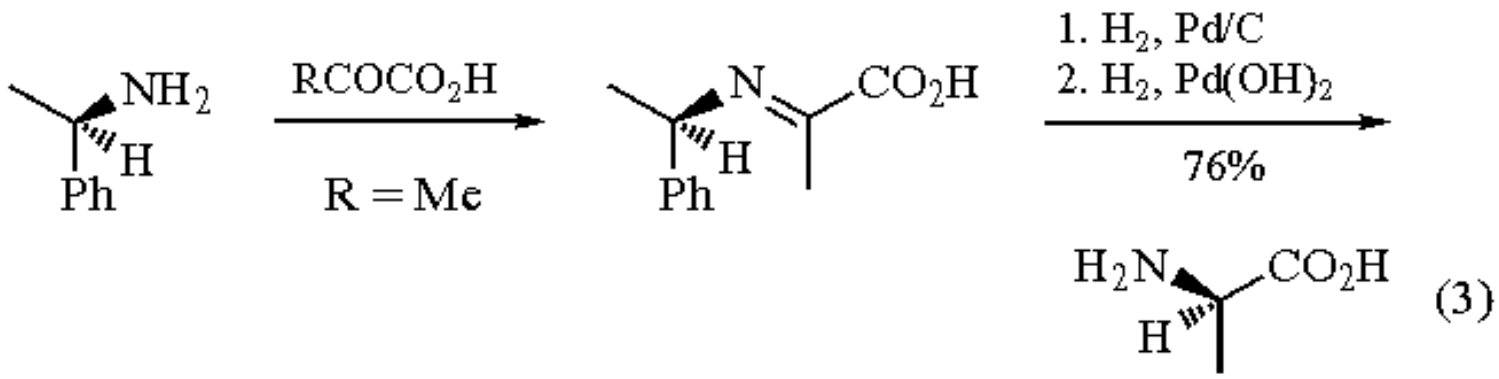

(3)

Compound (**1**) and its enantiomer provide a variation on the same theme of stereospecific reductive amination. In this case, reduction of a chiral cyclic hydrazone (derived from an α-keto acid and (**1**)) with ***Aluminum Amalgam*** in wet DME proceeds with high stereoselectivity. Reductive cleavage of the N-N bond and ester hydrolysis complete the procedure, which produces α-amino acids with high optical purity (eq 4).[1] The source of chirality is recovered by conversion of the resulting indoline-2-methanol back into (**1**).[1]

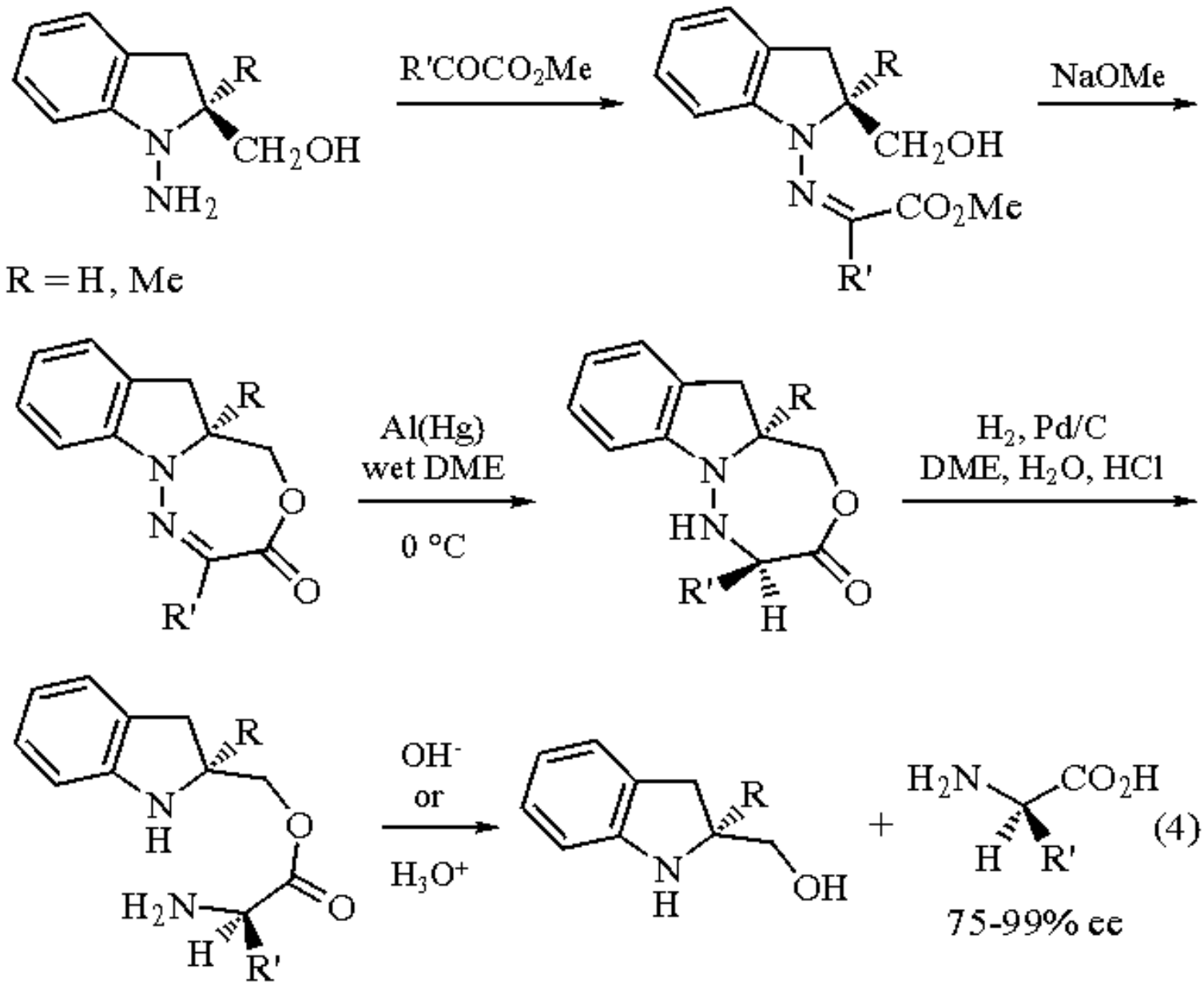

Related reagents that have been used successfully for these purposes include (**2**) and (**3**).[1,5] In general, (**3**) appears to generate product with higher enantiomeric purity than either (**1**) or (**2**).

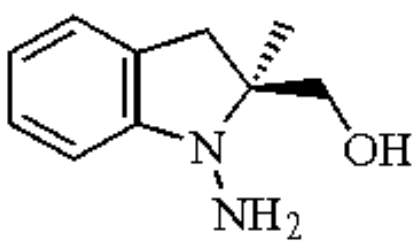

(2)

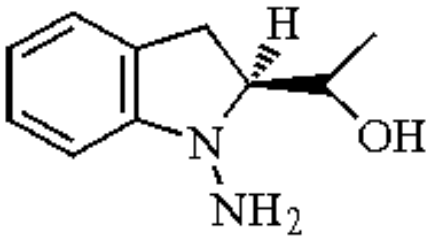

(3)

Other chiral amine reagents that have been used to effect similar stereospecific reductive aminations include 1,2-diamines[6] and 1,2-amino alcohols (eq 5).[7,8]

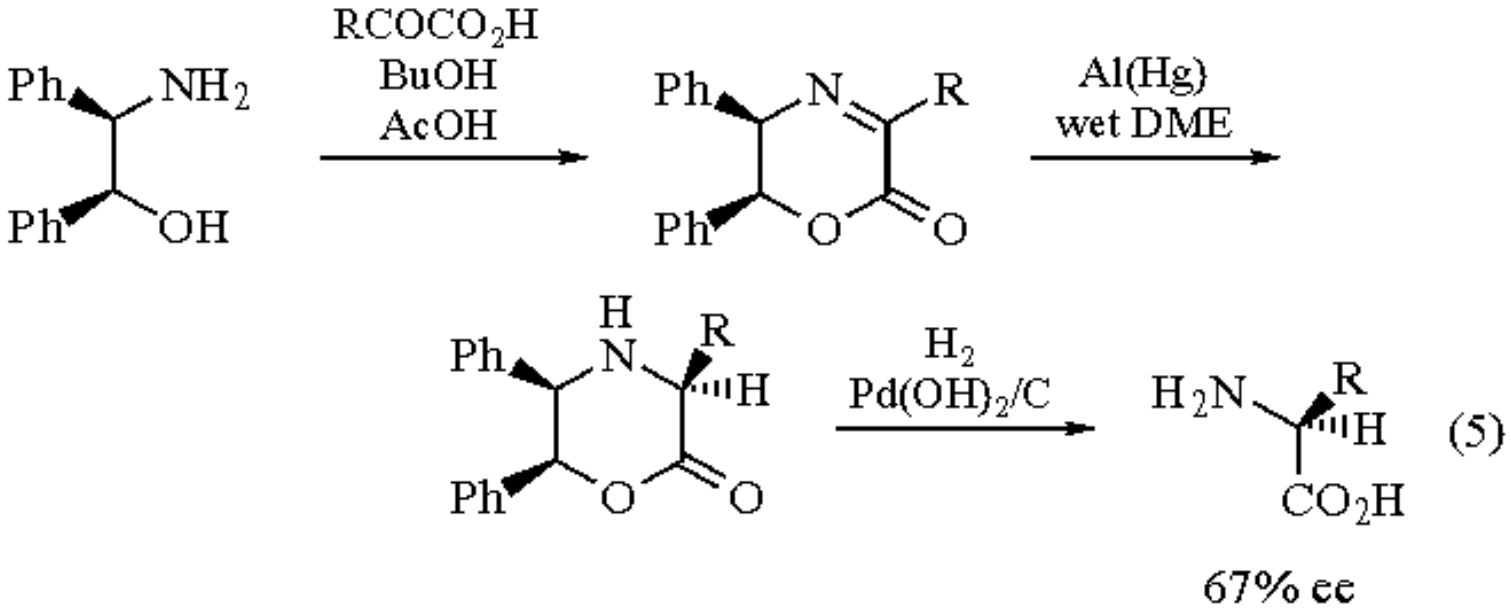

Stereospecific reduction of chiral diketopiperazine derivatives from proline and α-keto acids also provide a versatile route to α-amino acids (eq 6).[9,10] The selectivity of the reduction is highly dependent on the nature of the R´ group on the nitrogen atom.

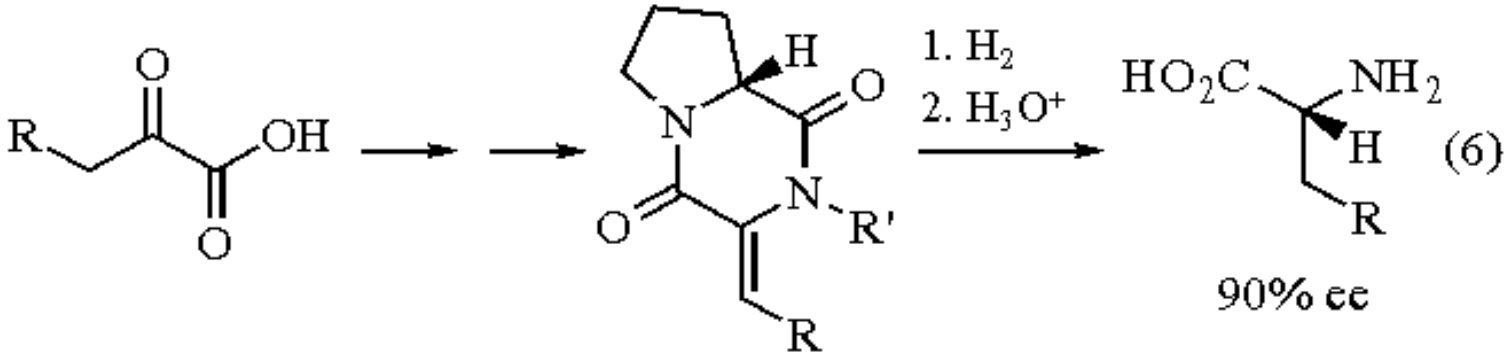

A related synthetic approach involves the biomimetic transamination of α-keto acids with chiral pyridoxamine analogs (eq 7)[11] or achiral pyridoxamine analogs in the presence of a chiral ligand.[12,13]

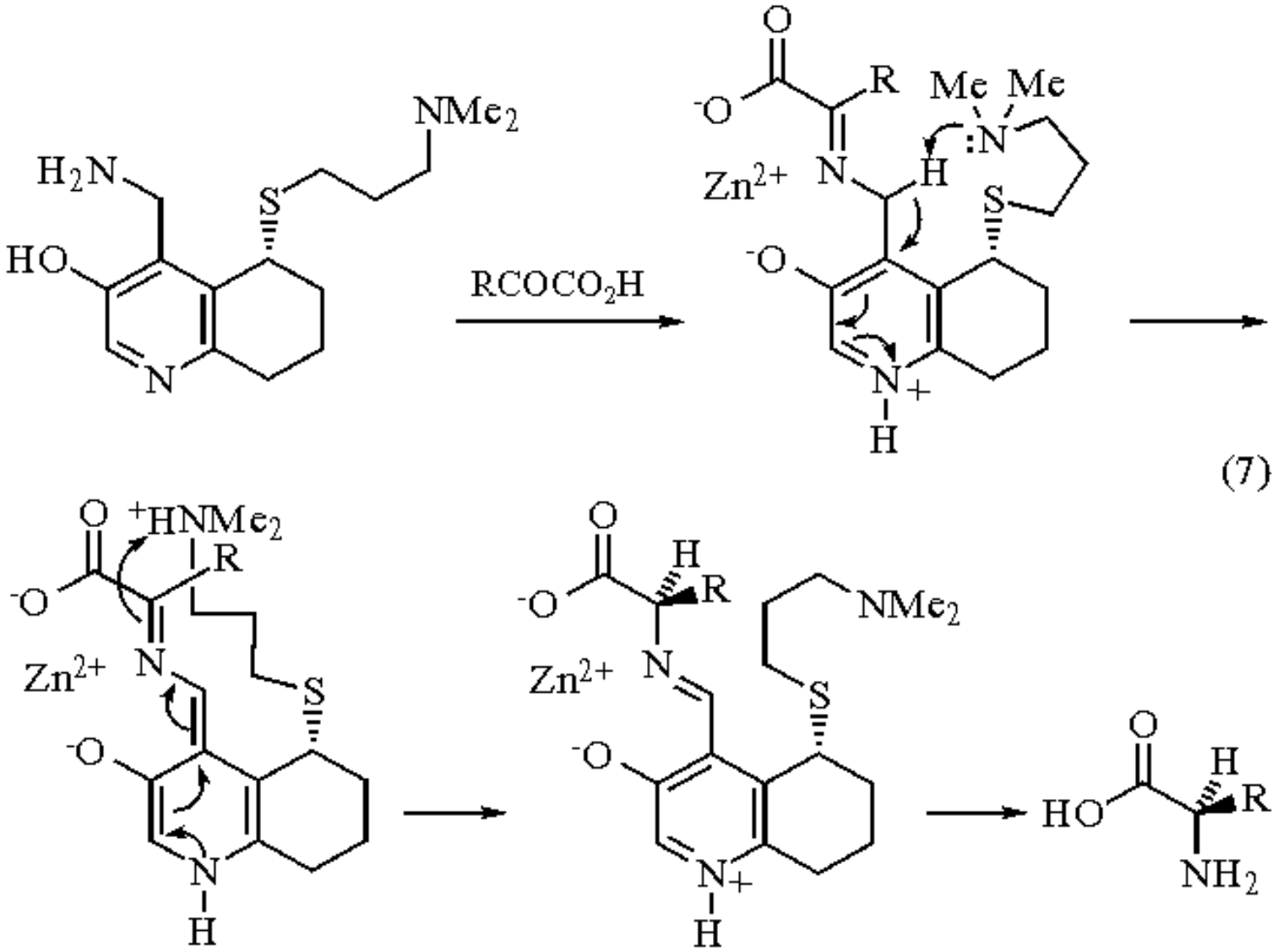

Related Reagents.

(S)-1-Amino-2-methoxymethylpyrrolidine.

---

1. Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *JACS* **1970**, *92*, 2476.
2. (a) Haemers, A.; Mishra, L.; Van Assche, I.; Bollaert, W. *Pharmazie* **1989**, *44*, 97. (b) *Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D. Ed.; Academic: Orlando, 1985; Vol. 5.
3. Babievskii, K. K.; Latov, V. K. *RCR* **1969**, *38*, 456.
4. (a) Harada, K.; Matsumoto, K. *JOC* **1967**, *32*, 1794. (b) Hiskey, R. G.; Northrop, R. C. *JACS* **1961**, *83*, 4798.
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7. Jiao, X. Y.; Chen, W. Y.; Hu, B. F. *SC* **1992**, *22*, 1179.
8. Vigneron, J. P.; Kagan, H.; Horeau, A. *TL* **1986**, *9*, 5681.
9. Bycroft, B. W.; Lee, G. R. *CC* **1975**, 988.
10. Poisel, H.; Schmidt, U. *CB* **1973**, *106*, 3408.
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12. Deschenaux, R.; Bernauer, K. *HCA* **1984**, *67*, 373.

Aminoiminomethanesulfonic Acid

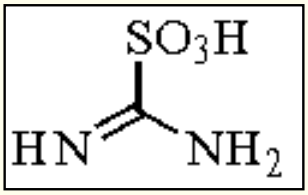

[1184-90-3] · $CH_4N_2O_3S$ · Aminoiminomethanesulfonic Acid · (MW 124.13)

(parent compound and its derivatives guanylate amines; some derivatives give triazoles with azide and aminoiminoethanenitriles with cyanide as nucleophile)

Alternate Name: formamidinesulfonic acid.

Physical Data: mp 131-131.5 °C when highly pure; around 125 °C with dec before purification.

Solubility: sol water; slightly sol methanol, ethanol; insol ether.

Preparative Methods: by the oxidation of thiourea or aminoiminomethanesulfinic acid (formamidinesulfinic acid) with ***Peracetic Acid***. Many substituted aminoiminomethanesulfonic acids can be prepared in the same way.[1,2] Others have utilized ***Hydrogen Peroxide*** with sodium molybdate as a catalyst to oxidize the corresponding thioureas to a variety of monosubstituted aminoiminomethanesulfonic acids; the substituents include phenyl, 2-methylphenyl, 4-fluorophenyl, *n*-propyl,[3] cyclohexylmethyl, *S*-α-methylbenzyl, cyclooctyl, and benzhydryl.[4]

Purification: recrystallize from glacial acetic acid.

Handling, Storage, and Precautions: stable for at least a few weeks at room temperature. After drying, it remains stable for at least 5 months if kept in a freezer. Thiourea and its metabolites (probably oxidized thiourea) are tumorigenic and cause lung edema. All direct contact with the compound should be avoided; for example, a dust mask should be worn. All residues should be destroyed with strong bleach solution. Many substituted thioureas and their metabolites are also biologically active. Use in a fume hood.

Synthesis of Guanidines from Amines.

Aminoiminomethanesulfonic acid (**1**) reacts with a variety of primary amines, including ***t-Butylamine***, to give 50 - 80% yields of the corresponding guanidines (eq 1). This reaction is more facile than guanidine syntheses starting with *S*-alkylisothioureas.[2] Reactions of primary and secondary amines with monosubstituted (phenylamino)- and (*n*-propylamino)iminomethanesulfonic acids also give good to excellent yields of the corresponding guanidines.

Treatment of (*n*-propylamino)iminomethanesulfonic acid with a hindered amine, *t*-butylamine, leads to a good yield of the corresponding triazine instead of the guanidine.[3]

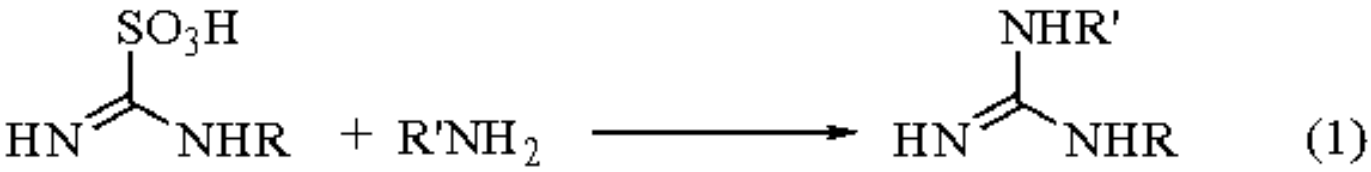

Reaction of aminoiminomethanesulfonic acid with a variety of amino acids gives yields of guanidino acids ranging from 5 -80%. Reactions of some amino acids do not lead to an isolable product. Similar results are obtained with (phenylamino)iminomethanesulfonic acid and (phenylamino)(phenylimino)methanesulfonic acid.[1]

Other Nucleophilic Substitution Reactions.

Nucleophilic substitution of a variety of substituted aminoiminomethanesulfonic acids with cyanide leads to the corresponding aminoiminoethanenitriles in 30-87% yield. A number of substituted aminoiminomethanesulfonic acids react with ***Sodium Azide*** in acetic acid to give the corresponding 5-aminotetrazole. This reaction is subject to pronounced steric hindrance. ***Hydroxylamine*** and ***Cyanamide*** also give nucleophilic substitution of the sulfonic acid group.[5]

Agelasidine-A analogs were prepared in two steps by treatment of a chloroethyl sulfone with ***Ammonia*** followed by aminoiminomethanesulfonic acid (eq 2). Direct displacement of chloride using guanidine furnished the dienyl analog in comparable yield.[6]

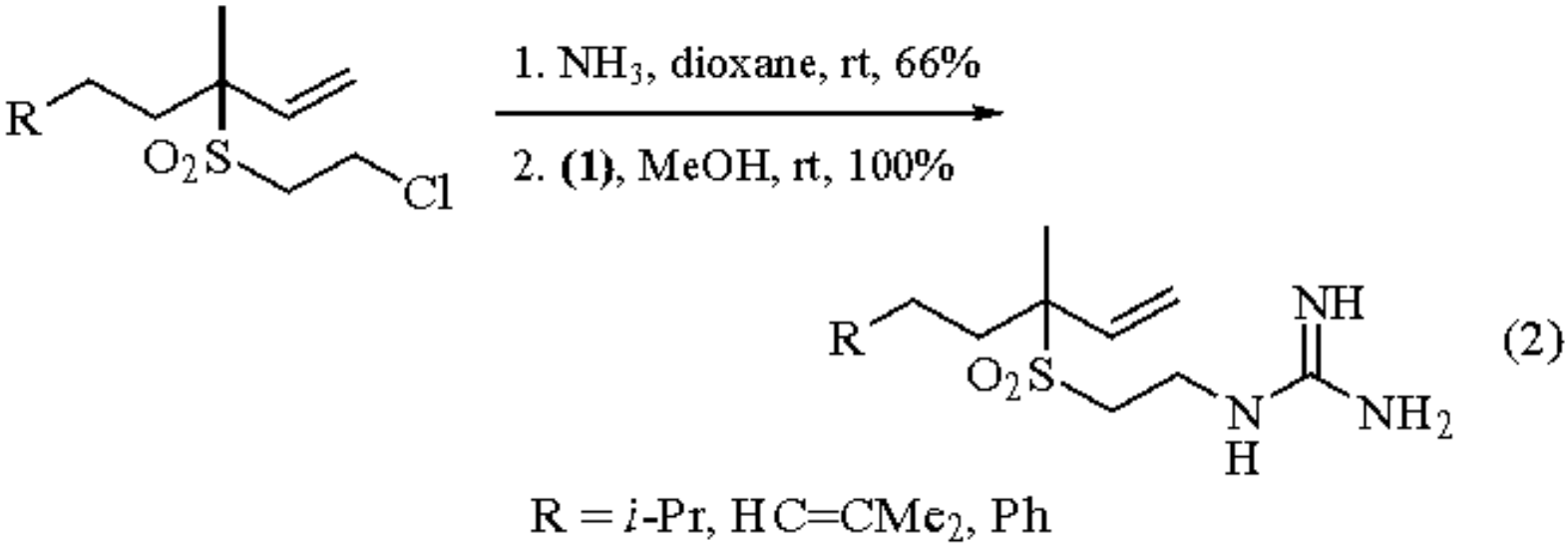

Guanylation of 3*R*-methyl-L-arginine with aminoiminomethanesulfonic acid followed by protection with adamantyloxycarbonyl chloride produced the bis-Adoc protected arginine derivative, a key intermediate in the total synthesis of lavendomycin.[7] In contrast, both (3*R*)- and (3*S*)-hydroxy-L-arginine have been prepared by guanylation of the tridentate copper complexes of *threo*- and *erythro*-2-hydroxy-L-ornithine using *S*-methylisothiourea.[8] Aminoiminomethanesulfonic acid has been used in the synthesis of an α-hydroxy ester *C*-terminal homo-L-arginine tripeptide for evaluation as a thrombin inhibitor.[9] The synthesis of a partially modified retro-inverso T-cell epitope

analog required preparation of the malonylarginine intermediate (**2**) using aminoiminomethanesulfonic acid as the guanylating agent (eq 3).[10]

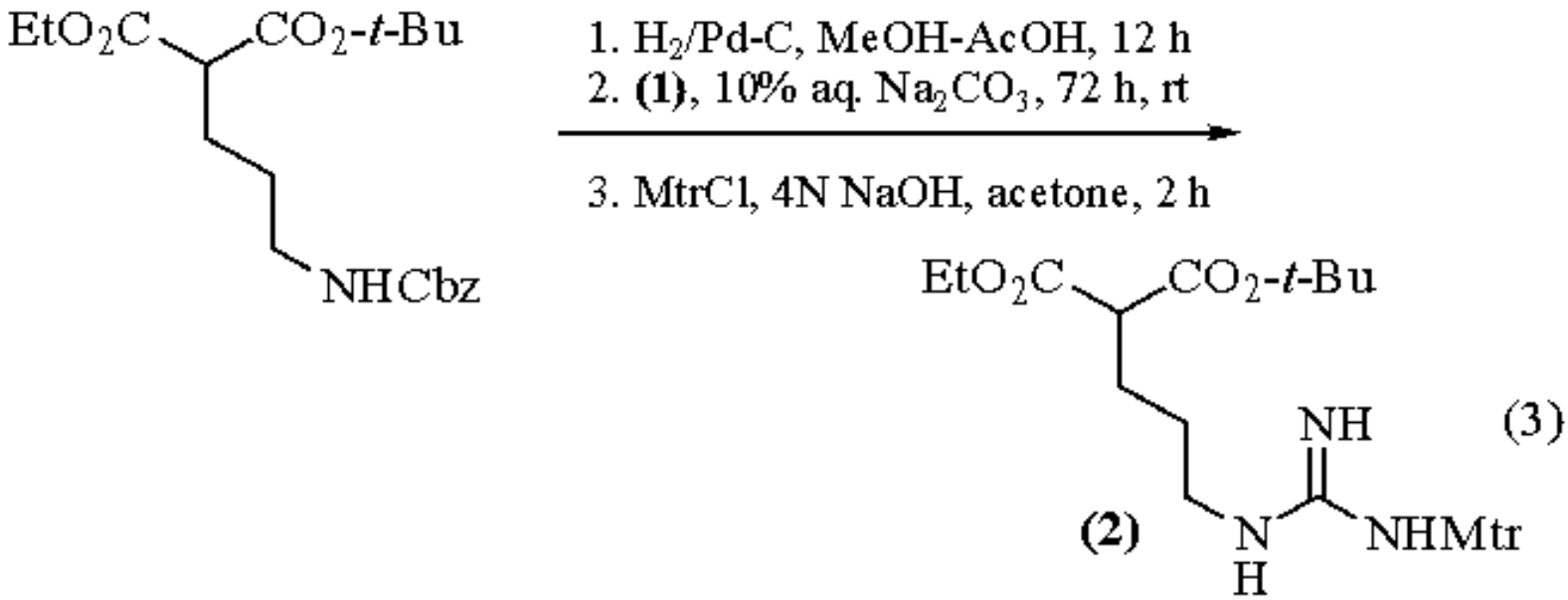

Mtr = 2,3,6-trimethyl-4-methoxybenzenesulfonyl

Conversion of 3,6-bis(*t*-butyldimethylsilyl)-*N*-(3-aminopropyl)normorphine to the corresponding guanidine analog has been accomplished in high yield using aminoiminomethanesulfonic acid. Interestingly, all attempts to convert the N atom of morphine directly to the analogous guanidine were unsuccessful.[11] Guanylation of the *N*-(4´-aminobutyl)cinnamanilide (**3**) with aminoiminomethanesulfonic acid followed by alkylation with prenyl bromide furnished caracasanamide (**4**) in high yield (eq 4).[12] Alternatively, (**4**) could be prepared by reaction of (**3**) with cyanamide (**5**)[12] or from guanylation using the bis-Boc *S*-methylisothiourea (**6**) followed by cleavage with TFA.[13]

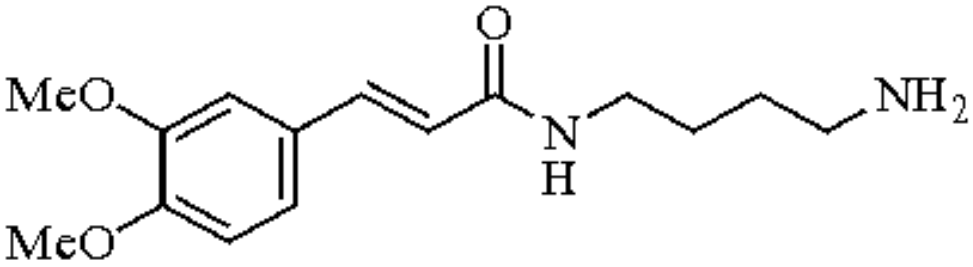
MeO
MeO
O
N
H
NH2

(3)

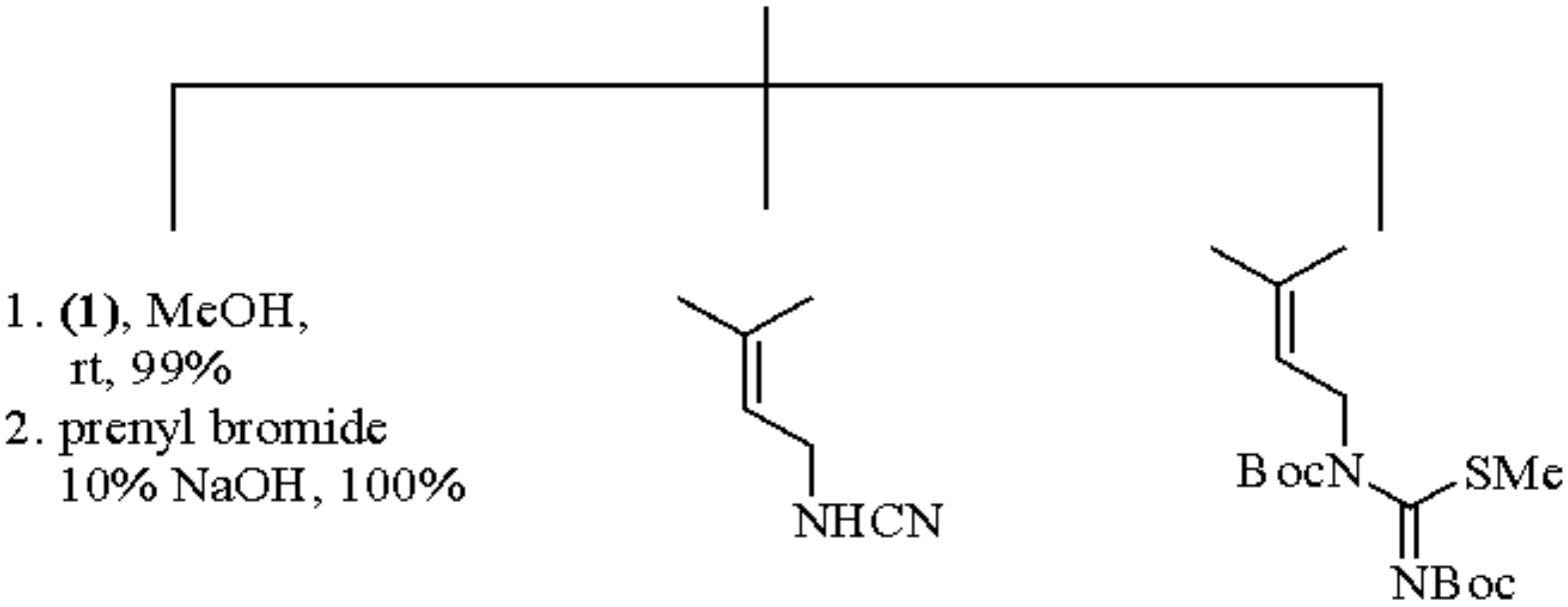
1. (1), MeOH,
rt, 99%
2. prenyl bromide
10% NaOH, 100%
NHCN
BocN
SMe
NBoc

(5) **(6)**

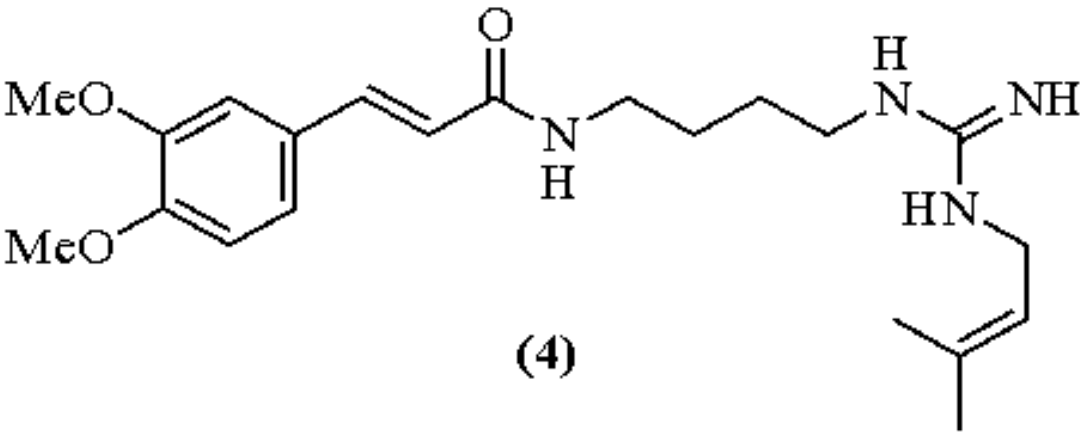
MeO
MeO
O
N
H
H
N
NH
HN

(4)

Related Reagents.

Cyanamide; ***Guanidine***; ***S-Methylisothiourea***; ***O-Methylisourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

---

1. Miller, A. E.; Bischoff, J. J. *S* **1986**, 777.
2. Kim, K.; Lin, Y.-T.; Mosher, H. S. *TL* **1988**, *29*, 3183.
3. Maryanoff, C. A.; Stanzione, R. C.; Plampin, J. N.; Mills, J. E. *JOC* **1986**, *51*, 1882.
4. Muller, G. W.; Walters, D. E.; DuBois, G. E. *JMC* **1992**, *35*, 740.
5. Miller, A. E.; Feeney, D. J.; Ma, Y.; Zarcone, L.; Aziz, M. A.; Magnuson, E. *SC* **1990**, *20*, 217.
6. Suryawanshi, S. N.; Rani, A.; Bhakuni, D. S. *IJC(B)* **1991**, *30B*, 1089.
7. Schmidt, U.; Mundinger, K.; Mangold, R.; Lieberknecht, A. *CC* 1990, 1216.
8. Wityak, J.; Gould, S. J.; Hein, S. J.; Keszler, D. A. *JOC* **1987**, *52*, 2179.
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10. Dürr, H.; Goodman, M.; Jung, G. *AG(E)* **1992**, *31*, 785.
11. Jackson, W. R.; Copp, F. C.; Cullen, J. D.; Guyett, F. J.; Rae, I. D.; Robinson, A. J.; Pothoulackis, H.; Serelis, A. K.; Wong, M. *Clin. Exp. Pharmacol. Physiol.* **1992**, *19*, 17 (*CA* **1992**, *117*, 82 892p).
12. Crombie, L.; Jarrett, S. R. M. *JCS(P1)* **1992**, 3179.
13. Delle Monache, G.; Botta, B.; Delle Monache, F.; Espinal, R.; De Bonnevaux, S. C.; De Luca, C.; Botta, M.; Corelli, F.; Carmignani, M. *JMC* **1993**, *36*, 2956.

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(*S*)-1-Amino-2-methoxymethylpyrrolidine[1]

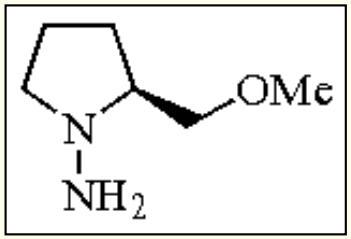

[59983-39-0] · $C_6H_{14}N_2O$ · (*S*)-1-Amino-2-methoxymethylpyrrolidine · (MW 130.19)

(chiral auxiliary; Enders' reagent; diastereo- and/or enantioselective alkylations,[2,3] aldol reactions,[4] Michael additions[5] and reductive or alkylative aminations,[6] resolutions,[7] ee determinations[8])

Alternate Name: SAMP.

Physical Data: bp 186-187 °C; *d* 0.977 g cm^{-3}; *n*20D 1.4650; α20D -80 to -82° (neat).

Solubility: sol H_2O, ether, dichloromethane.

Form Supplied in: colorless liquid or as crystalline colorless oxalate.

Handling, Storage, and Precautions: storage at 0-4 °C under argon atmosphere.

Since the pioneering times of the mid-1970s, (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and its enantiomer RAMP have been among the most powerful chiral auxiliaries in asymmetric synthesis, with a very broad range of applications. As a proline derivative it generally shows high stereoselectivities due to the rigidity of the five-membered ring and the ability to coordinate metal fragments[9] (see also ***(S)-2-Methoxymethylpyrrolidine***, SMP).

The procedure involves the transformation of carbonyl compounds to the corresponding SAMP or RAMP hydrazones, metalation, trapping of the intermediate azaenolates with various electrophiles, and either hydrazone cleavage (carbonyl compounds) or hydrazone reduction/N-N bond cleavage (amines).

The synthetic utility of the SAMP/RAMP hydrazone method is demonstrated in particular in the stereoselective alkylation of aldehyde[2] and ketone[3] SAMP/RAMP hydrazones. A great number of natural products have been synthesized using this method, like the principal alarm pheromone of the leaf cutting ant *Atta texana* (eq 1),[3a] the C(1)-C(15) segment of FK 506 (eq 2),[2b] the amino acid MeBMT (eq 3),[2c] and (-)-methyl kolavenate (eq 4).[3b]

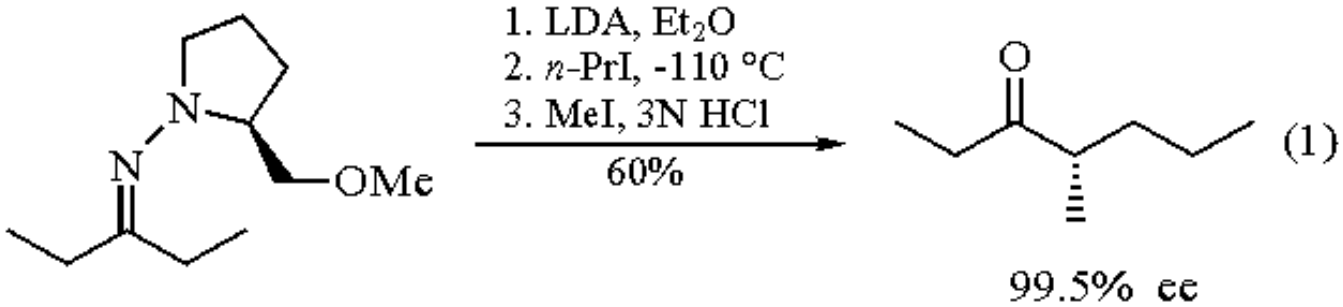
1. LDA, Et2O
2. n-PrI, -110 °C
3. MeI, 3N HCl
60%
N
N
OMe
O
(1)
99.5% ee

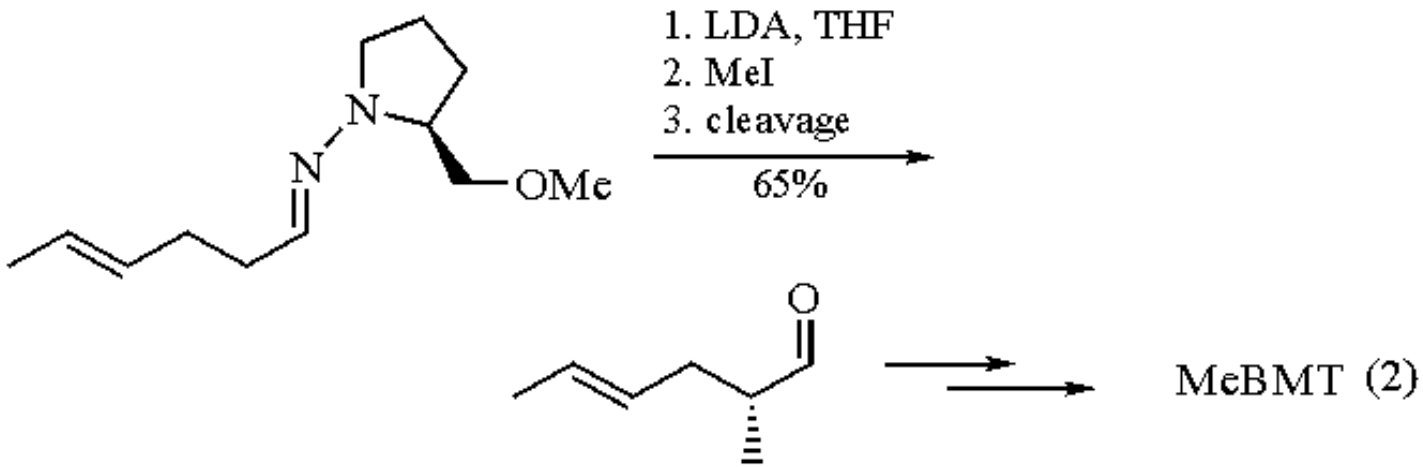
1. LDA, THF
2. MeI
3. cleavage
65%
N
N
OMe
O
MeBMT (2)

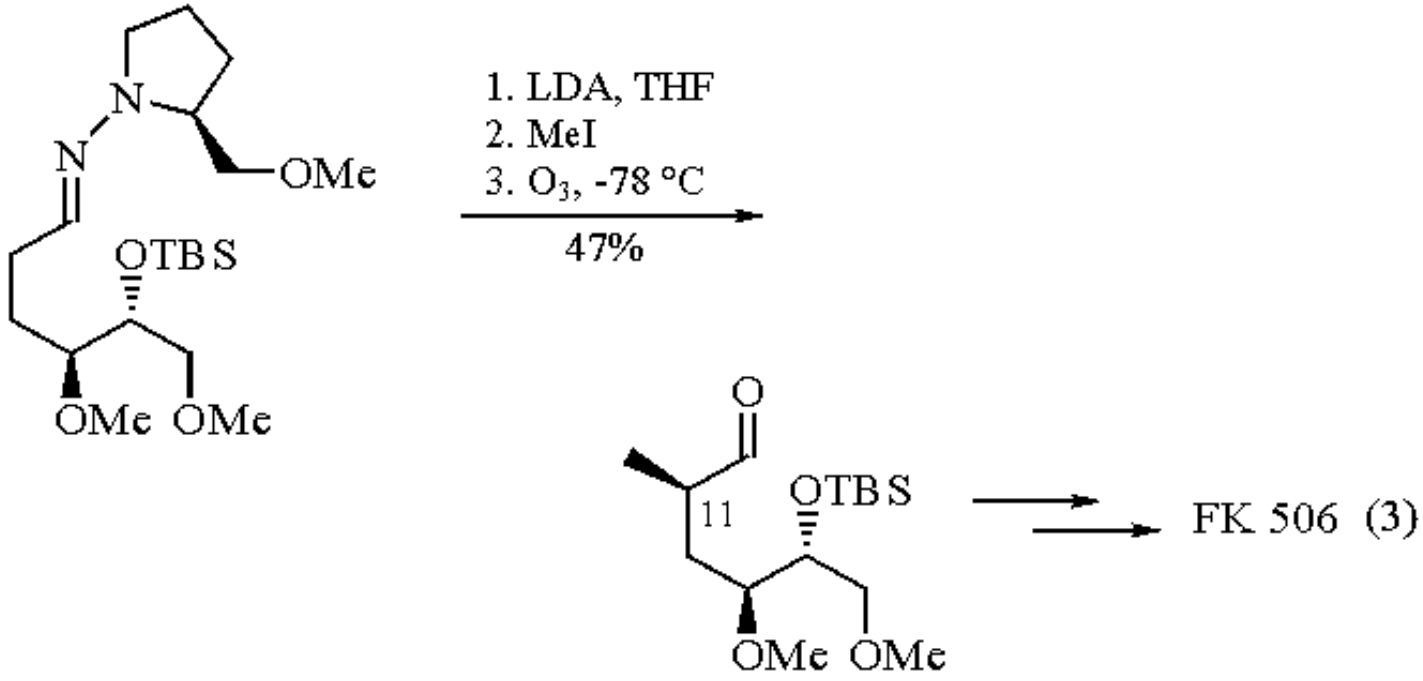
N
N
OMe
OTBS
OMe OMe
1. LDA, THF
2. MeI
3. O3, -78 °C
47%
O
11
OTBS
OMe OMe
FK 506 (3)

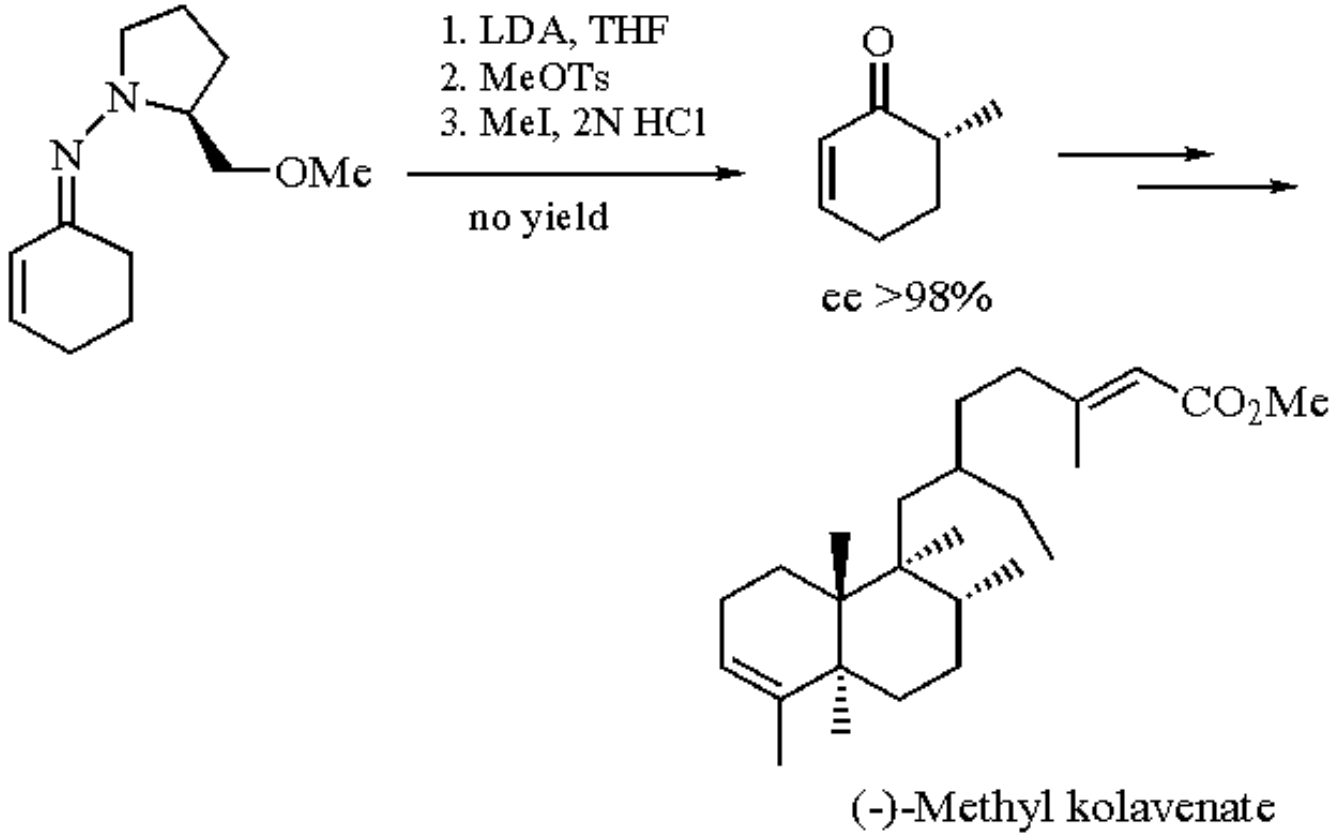

(4)

2,2-Dimethyl-1,3-dioxan-5-one SAMP/RAMP hydrazones[3f-j] were used as dihydroxyacetonephosphate equivalents in the synthesis of C_2 symmetric ketones (eq 5),[3g] aza sugars with novel substitution patterns,[3h] or C_5 to C_9 deoxy sugars.[3i] SAMP hydrazones of 2-oxo esters represent novel phosphoenolpyruvate (PEP) equivalents.[3k,l] α,α-Disubstituted spiroacetals are accessible via the alkylation of ketone SAMP/RAMP hydrazones.[3m]

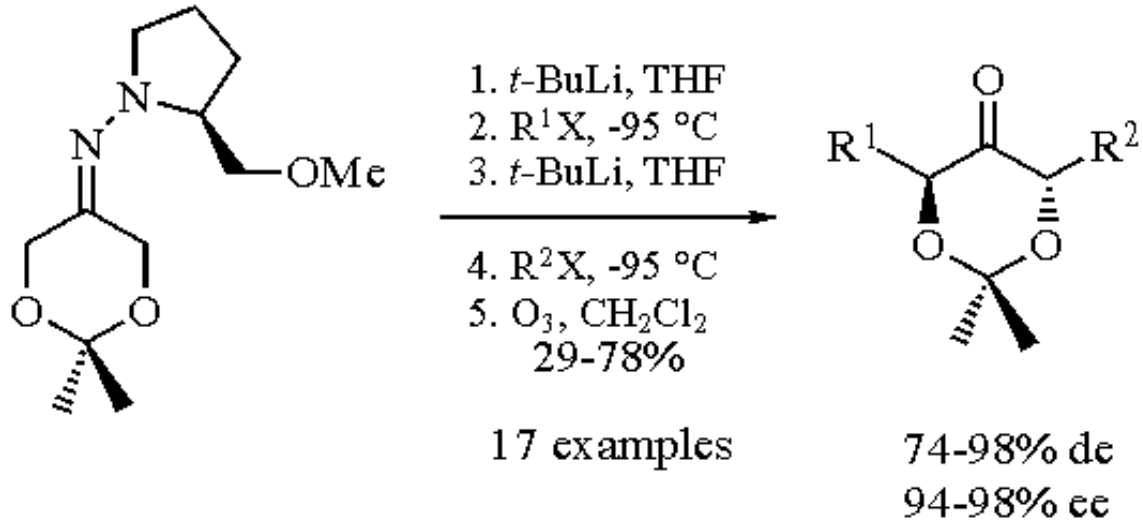

(5)

The aggregation pheromone of *Drosophila mulleri*, (*S*)-2-tridecanol acetate, is obtainable by alkylation of propiophenone SAMP hydrazone followed by a Baeyer-Villiger reaction of the ketone (eq 6).[3n]

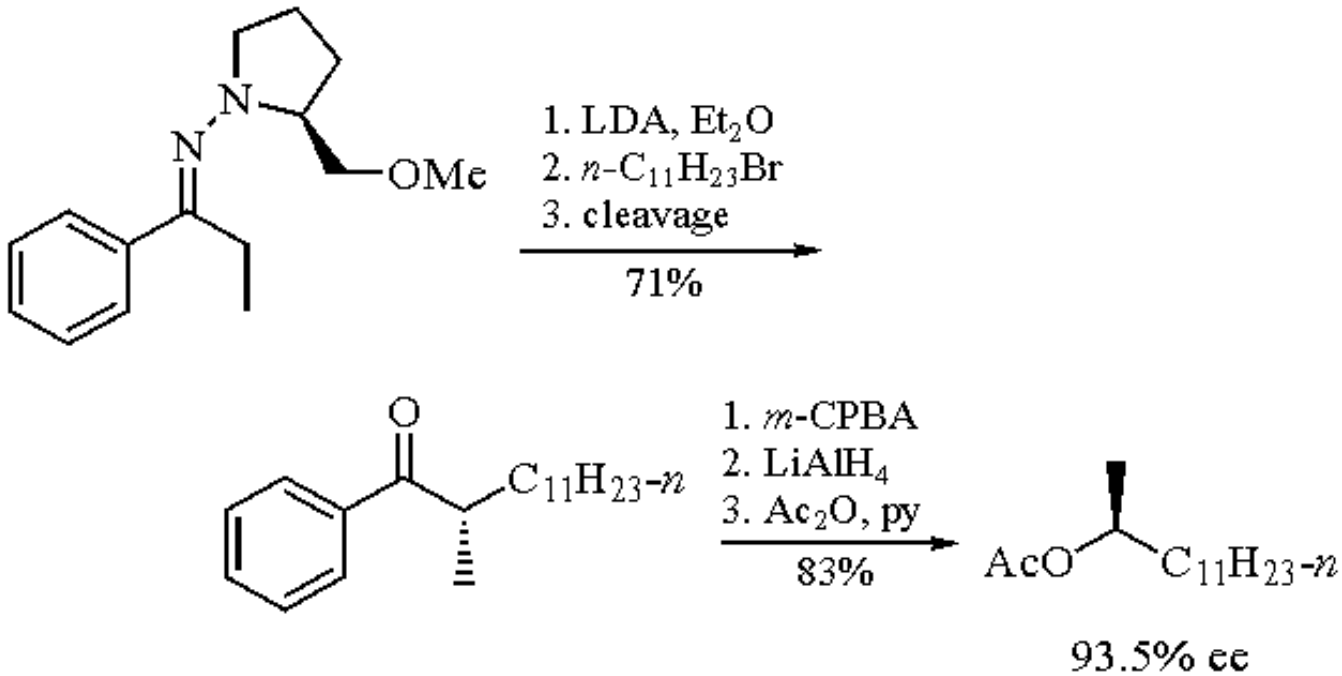

(6)

The relative and absolute configuration of Stigmatellin A, one of the most potent inhibitors of the electron transport chain, was determined via alkylation of diethyl ketone SAMP hydrazone.[3o]

The aldol reaction is the preferred method for the stereoselective synthesis of 1,3-dioxygenated building blocks. In 1978, Enders et al.[4a,b] reported the first enantioselective aldol reaction in the difficult case of α-unsubstituted β-ketols using SAMP and RAMP. Diastereo- and enantiomerically pure *syn*-β-ketols are available by aldol reaction of SAMP/RAMP hydrazones (eq 7).[4c]

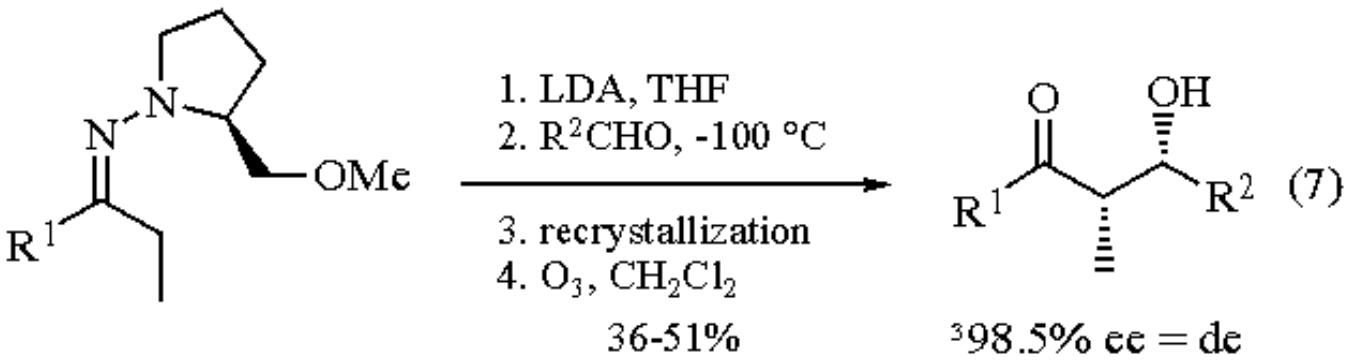

The aggregation pheromone of the rice and maize weevil was synthesized by aldol reaction of an enantiomerically pure α-silyl ketone, obtained by the SAMP/RAMP hydrazone method,[10a-d] with various aldehydes (eq 8).[4d]

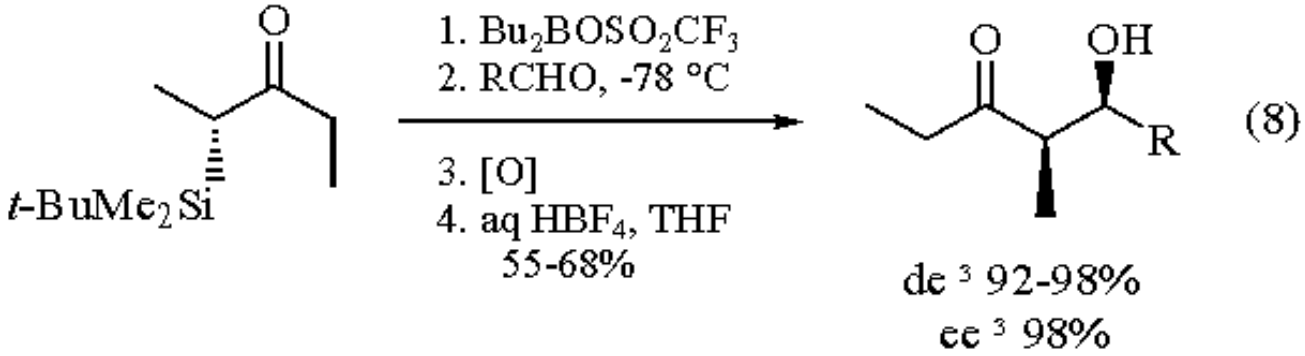

The utility of the SAMP/RAMP hydrazone method in dia-stereo- and enantioselective Michael additions was demonstrated in the synthesis of 5-oxo esters[5a-e] (eq 9),[5b] δ-lactones (eq 10),[5c,e,f] oxo diesters and dinitriles,[5g] heterocyclic compounds (eq 11),[5h] MIRC (Michael initiated ring closure) reactions,[5i] and 2-substituted 4-oxo sulfones.[5i]

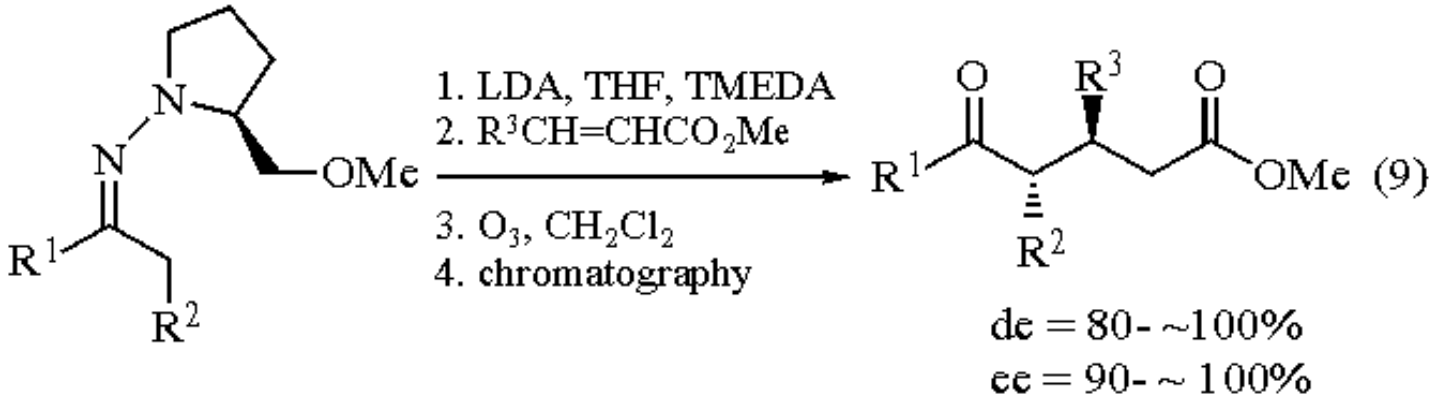

(9)

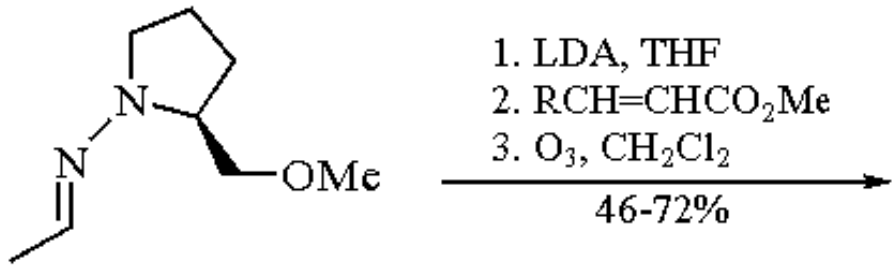

R= alkyl, aryl

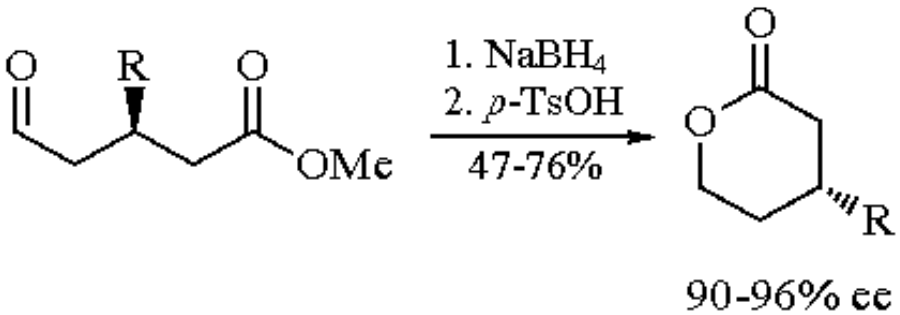

(10)

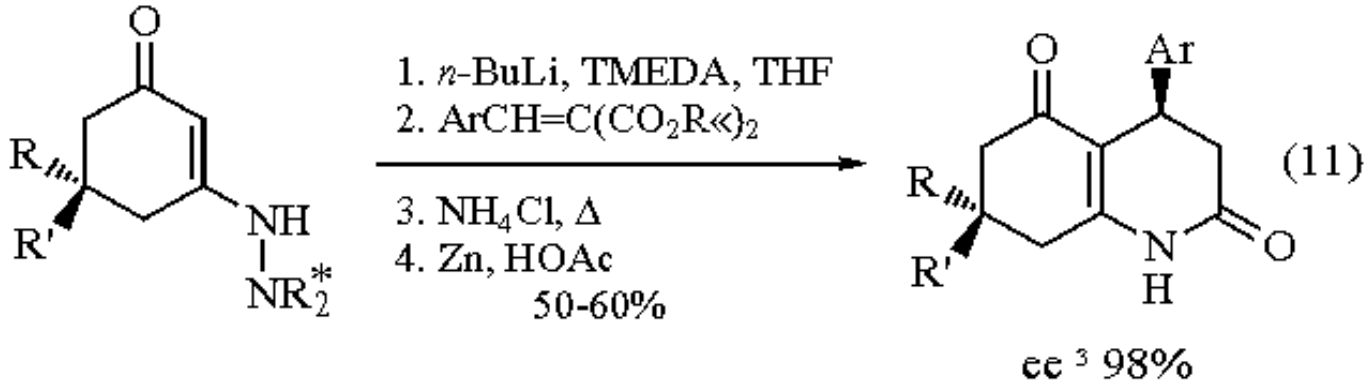

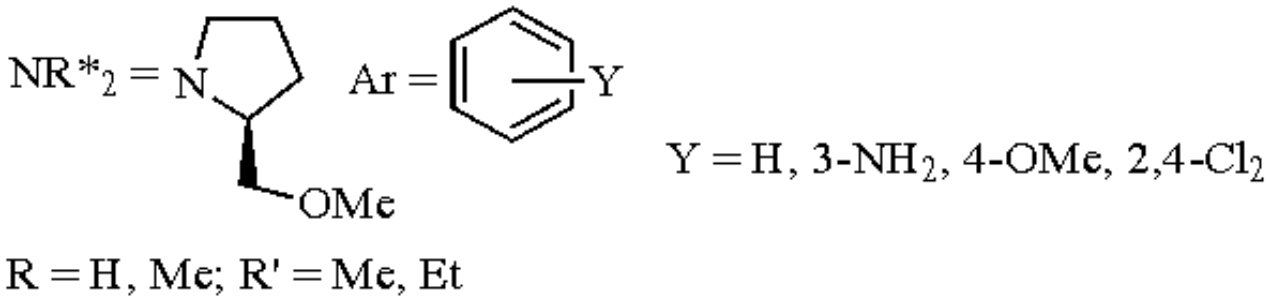

Organotin reagents can be added to cyclic α,β-unsaturated SAMP/RAMP hydrazones (eq 12).[5k]

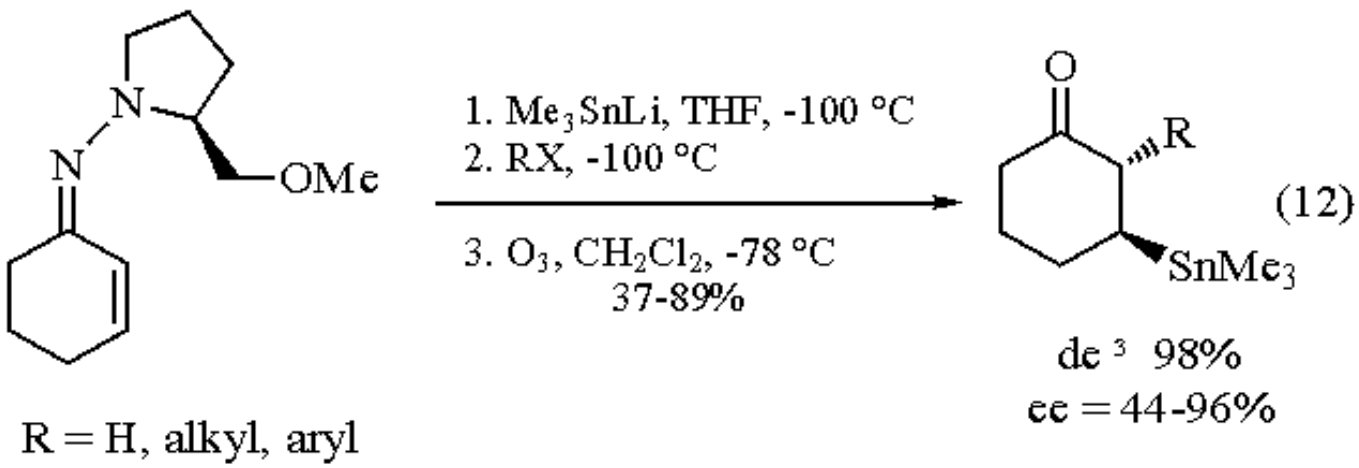

Lithiated N-protected SAMP can be used as an ammonia equivalent in Michael and tandem Michael additions to α,β-unsaturated esters (eq 13).[5l] Furthermore, SAMP and RAMP can be employed for the asymmetric synthesis of α- and/or β-substituted primary amines with high regio-, diastereo-, and enantioselectivities.[6] This variant involves hydrazone reduction with a subsequent N-N bond cleavage and can be combined with a prior α-alkylation, as described above.

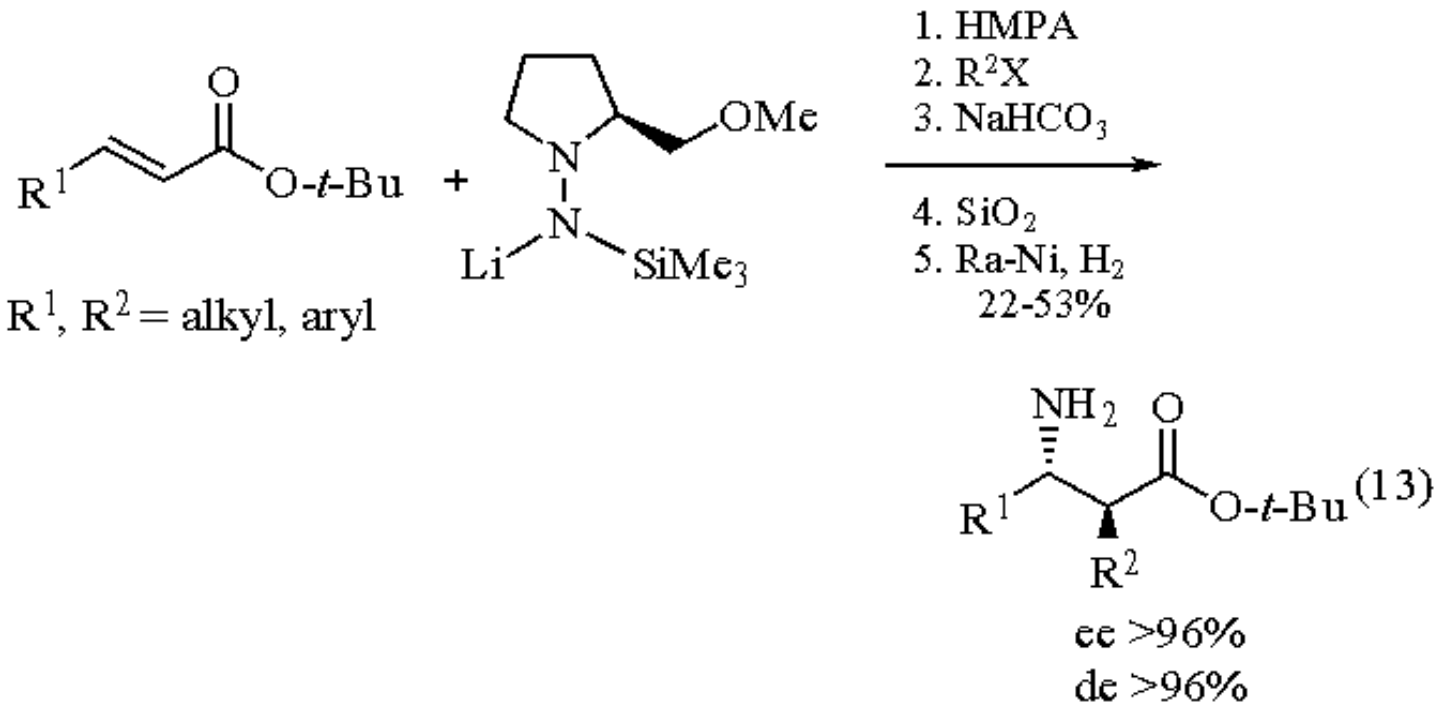

This method was recently used in the synthesis of different natural products, like the ladybug defence alkaloid harmonine,[6d] α- and β-amino acetals and acids (eq 14),[6e,f] and both enantiomers of the hemlock alkaloid coniine,[6g] utilizing the nucleophilic 1,2-addition of organolithium and -lanthanoid reagents to SAMP/RAMP hydrazones.

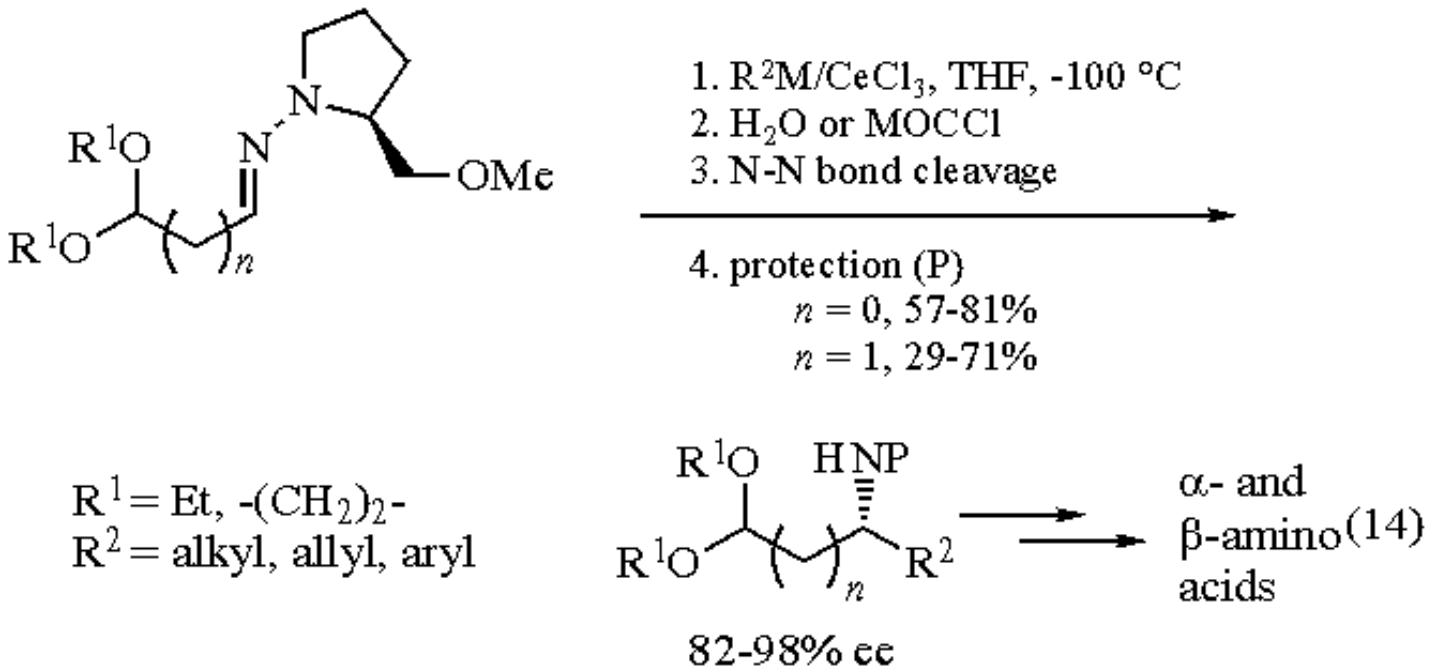

The alkylation of SAMP/RAMP hydrazones with heteroelectrophiles leads to enantiomerically pure α-silyl aldehydes and ketones (eq 15),[10a-d] α-sulfenyl aldehydes and ketones (eq 16),[10e] and α-hydroxy aldehydes and ketones (eq 17).[10f]

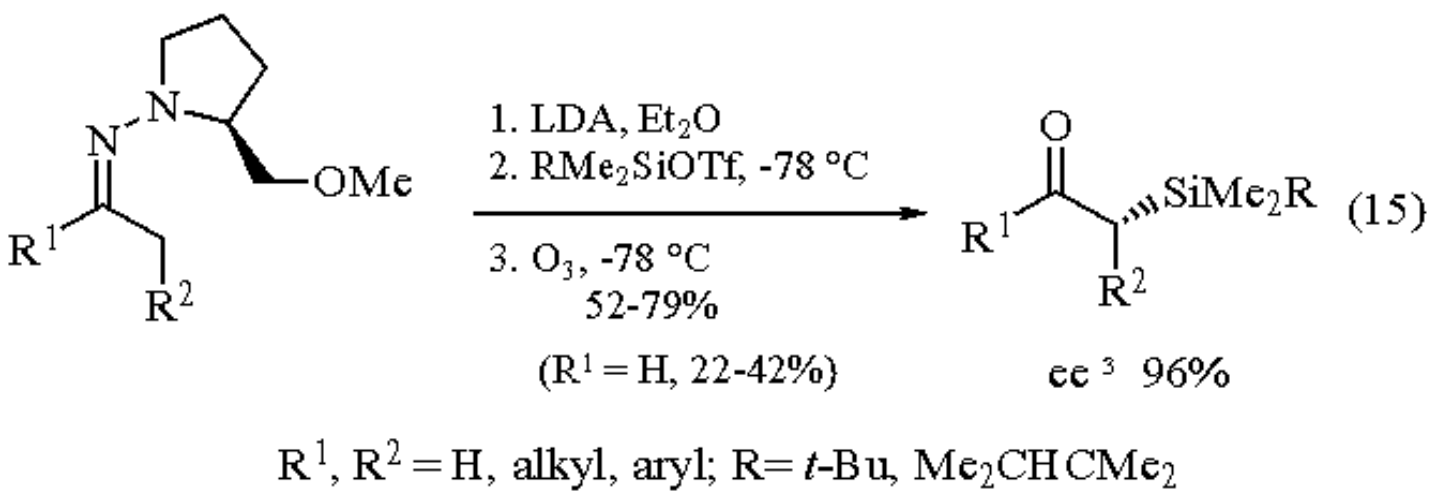

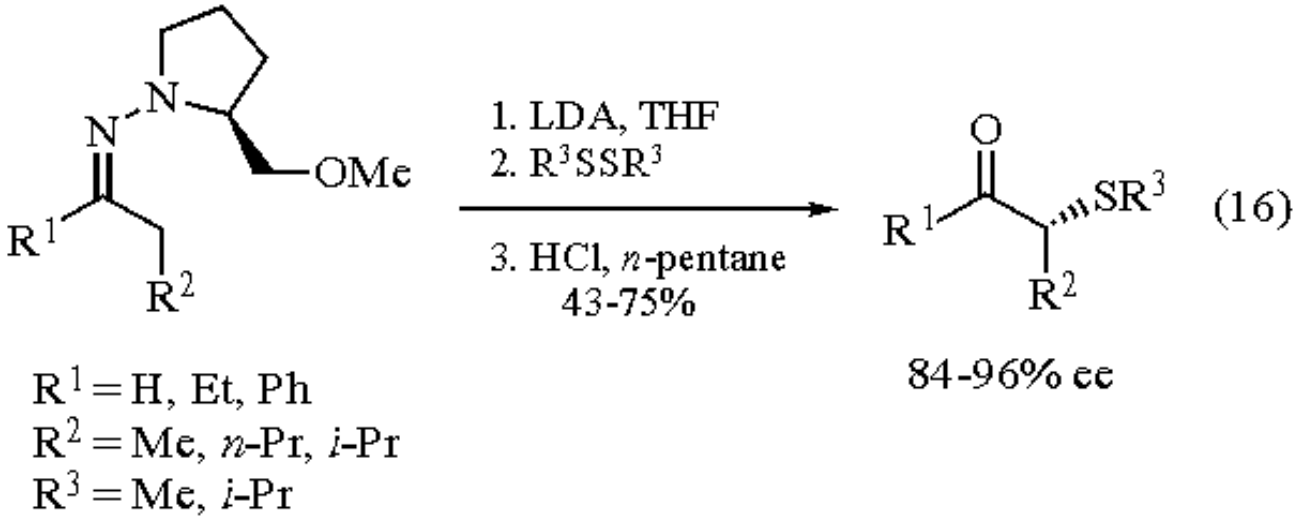

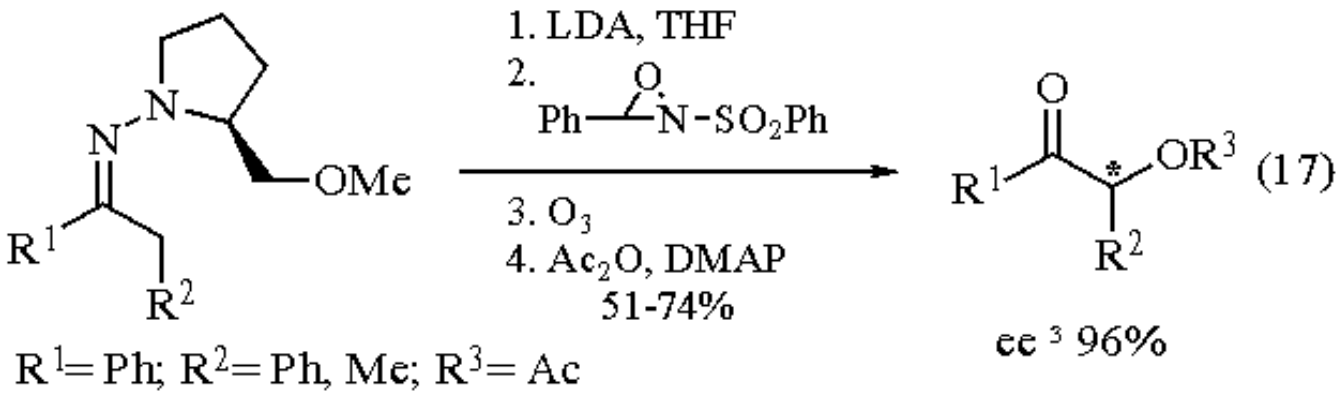

These very interesting chiral building blocks are employed in aldol reactions,[4d] and in the synthesis of enantiomerically pure vicinal diols (eq 18)[10g,h] and 3-oxo esters and acids bearing quarternary stereogenic centers (eq 19).[10i]

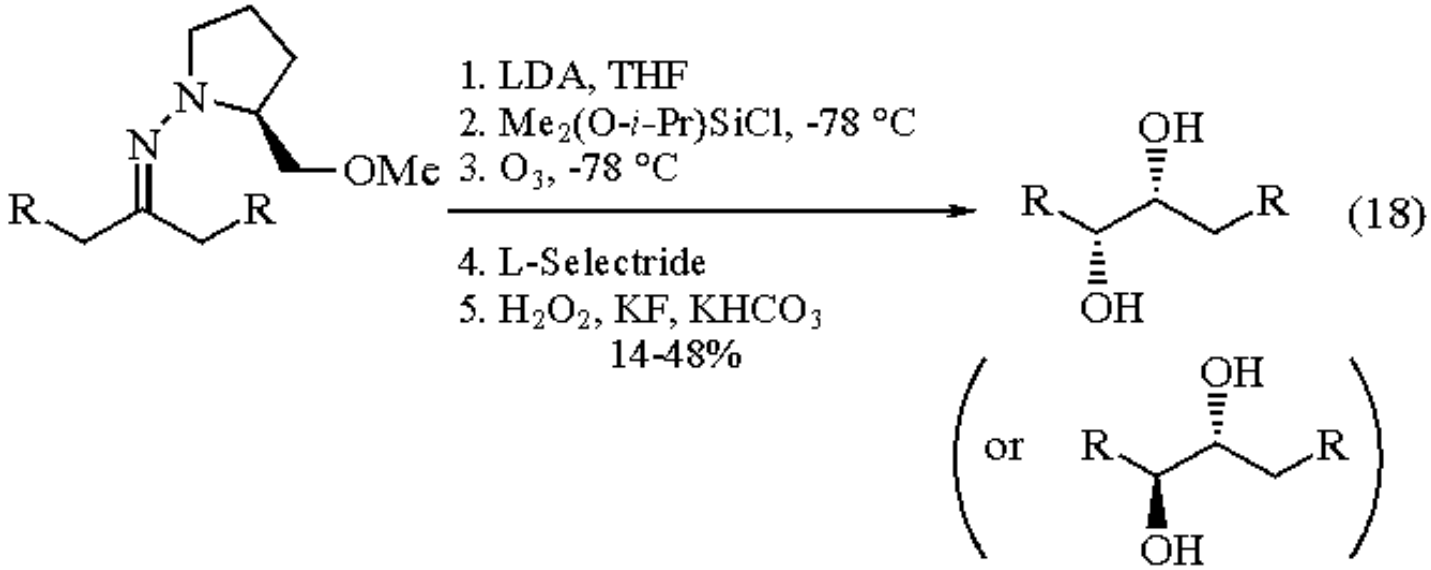
1. LDA, THF
2. Me2(O-i-Pr)SiCl, -78 °C
3. O3, -78 °C
4. L-Selectride
5. H2O2, KF, KHCO3
14-48%
OMe
OH
or

(18)

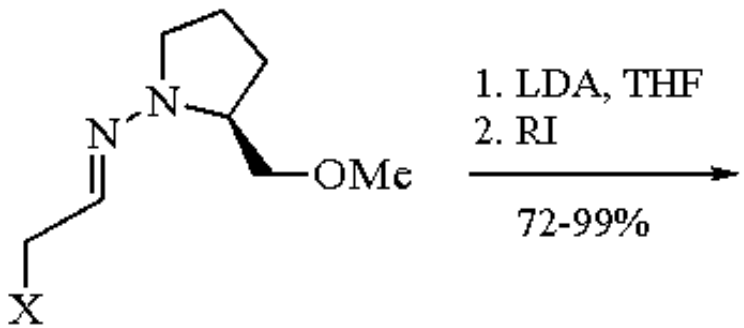
1. LDA, THF
2. RI
72-99%
OMe

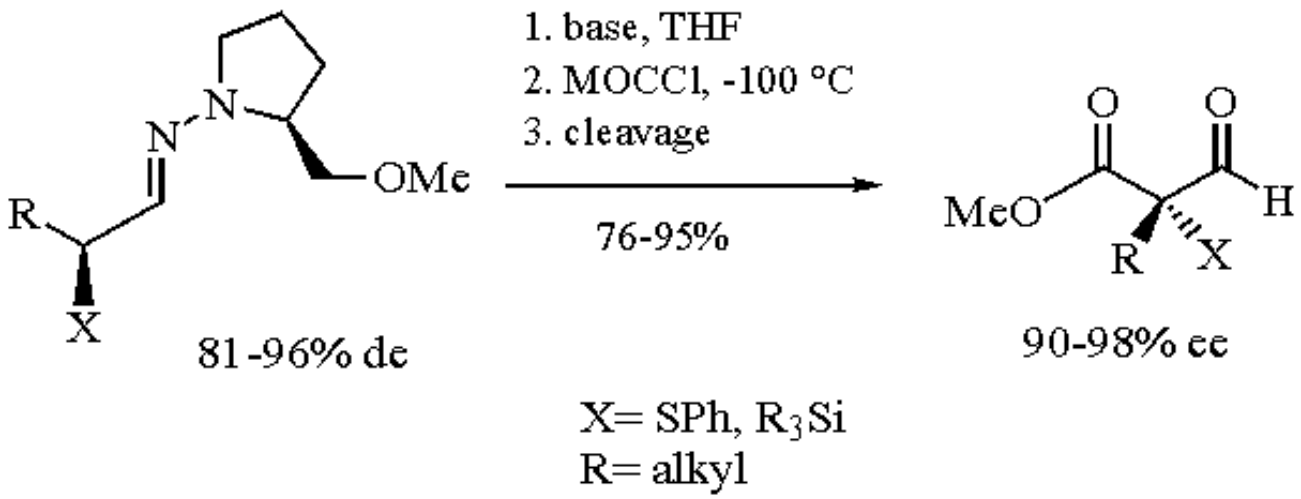
1. base, THF
2. MOCCl, -100 °C
3. cleavage
76-95%
OMe
MeO
81-96% de
90-98% ee
X= SPh, R3Si
R= alkyl

(19)

Further applications can be mentioned briefly. SAMP was used in the resolution of 4-demethoxy-7-deoxydaunomycinone,[7] in ee determinations (Scheme 1),[8] as a chelate for tetracarbonylmolybdenum complexes,[11] in intramolecular Heck reactions,[12] as polysilylated hydrazine,[13] in the enantioselective synthesis of isoquinuclidines,[14] and in the conversion of hydrazones to aldehydes[15] and nitriles.[16] The structure of a chiral lithium SAMP hydrazone azaenolate has been determined.[17] In cases where SAMP did not lead to satisfactory inductions, a modified auxiliary, (*S*)-1-amino-2-dimethylmethoxymethylpyrrolidine (SADP),[18] enhanced the stereochemical control.

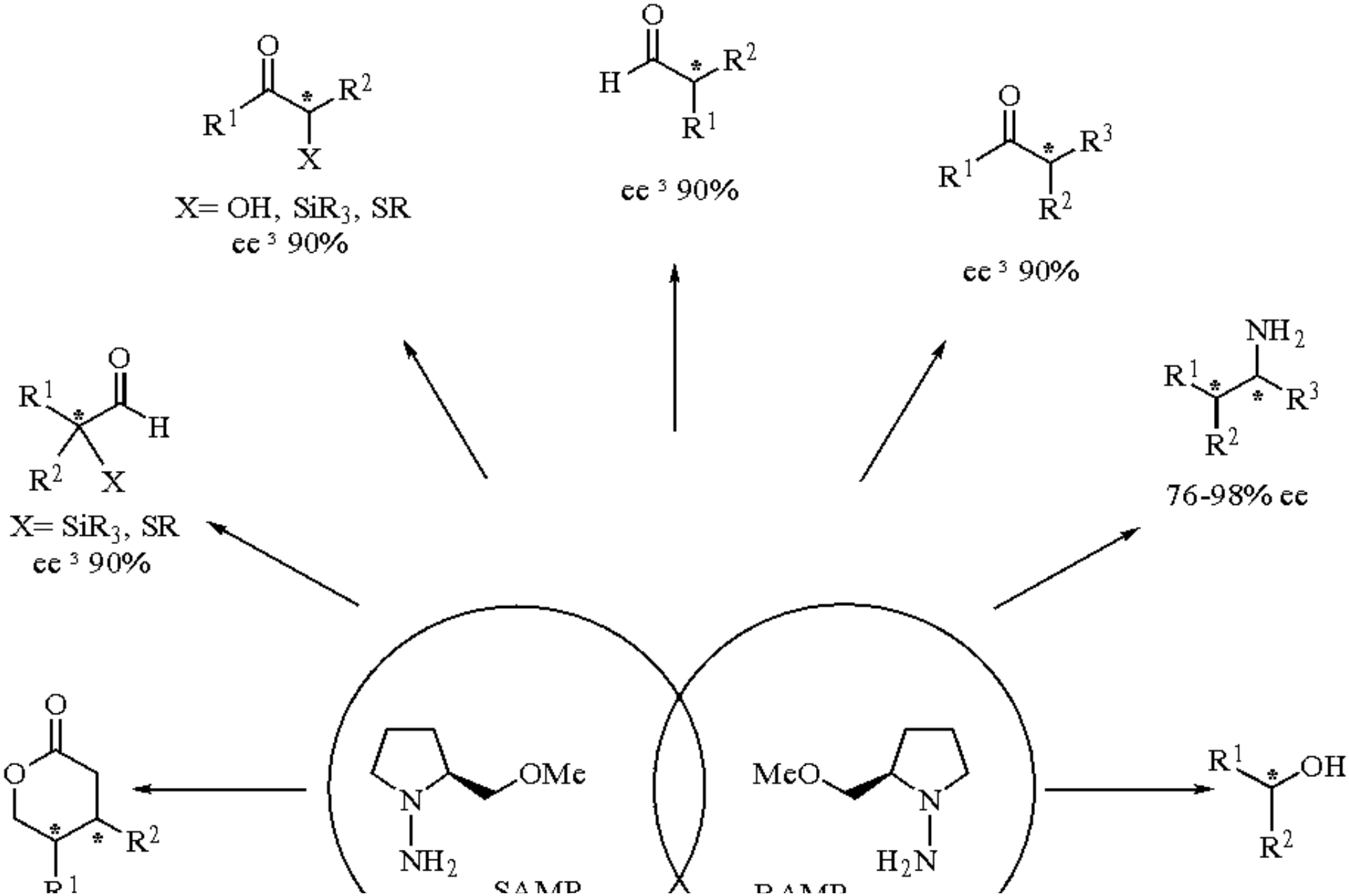

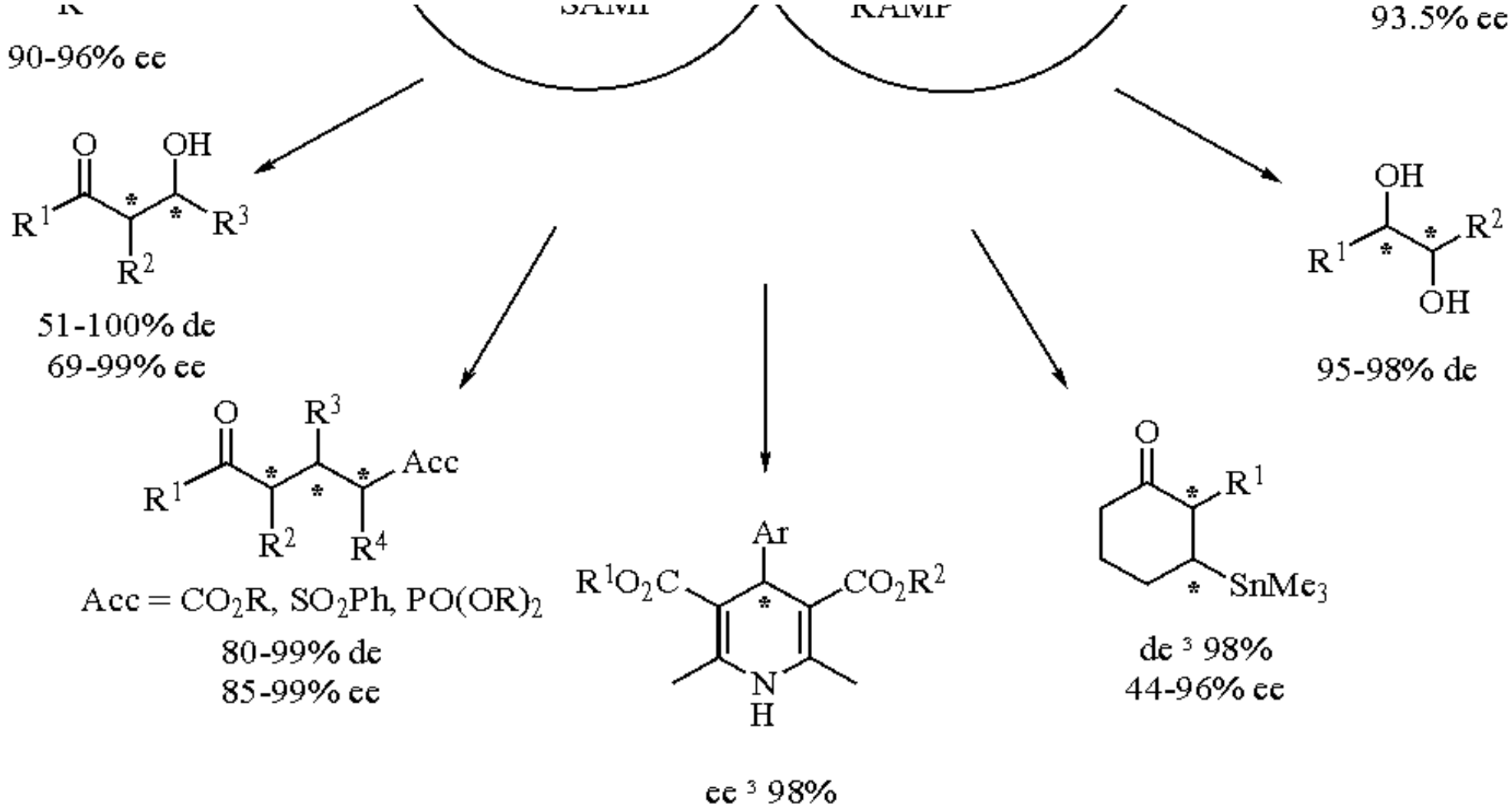

Scheme 1

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S. I. *ACS* **1981**, *B35*, 555. (d) Mori, K.; Nomi, H.; Chuman, T.; Kohno, M.; Kato, K.; Noguchi, M. *T* **1982**, *38*, 3705. (e) Fischer, J.; Kilpert, C.; Klein, U.; Steglich, W. *T* **1986**, *42*, 2063. (f) Enders, D.; Bockstiegel, B. *S* **1989**, 493. (g) Enders, D.; Gatzweiler, W.; Jegelka, U. *S* **1991**, 1137. (h) Enders, D.; Jegelka, U. *SL* **1992**, 999. (i) Enders, D.; Jegelka, U.; Dücker, B. *AG* **1993**, *105*, 423; *AG(E)* **1993**, *32*, 423. (j) Enders, D.; Jegelka, U. *TL* **1993**, *34*, 2453. (k) Enders, D.; Dyker, H.; Raabe, G. *AG* **1992**, *104*, 649; *AG(E)* **1992**, *31*, 618. (l) Enders, D.; Dyker, H.; Raabe, G. *SL* **1992**, 901. (m) Enders, D.; Gatzweiler, W.; Dederichs, E. *T* **1990**, *46*, 4757. (n) Enders, D.; Plant, A. *LA* **1991**, 1241. (o) Enders, D.; Osborne, S. *CC* **1993**, 424. (p) Sainsbury, M.; Williams, C. S.; Naylor, A.; Scopes, D. I. C. *TL* **1990**, *31*, 2763. (q) Sainsbury, M.; Mahon, M. F.; Williams, C. S.; Naylor, A.; Scopes, D. I. C. *T* **1991**, *47*, 4195. (r) Ziegler, F. E.; Becker, M. R. *JOC* **1990**, *55*, 2800. (s) Warshawsky, A. M.; Meyers, A. I. *JACS* **1990**, *112*, 8090. (t) Andersen, M. W.; Hildebrandt, B.; Hoffmann, R. W. *AG* **1991**, *103*, 90; *AG(E)* **1991**, *30*, 90. (u) Clark, J. S.; Holmes, A. B. *TL* **1988**, *29*, 4333. (v) Carling, R. W.; Curtis, N. R.; Holmes, A. B. *TL* **1989**, *30*, 6081. (w) Curtis, N. R.; Holmes, A. B.; Looney, M. G.; Pearson, N. D.; Slim, G. C. *TL* **1991**, *32*, 537. (x) Hart, T. W.; Guillochon, D.; Perrier, G.; Sharp, B. W.; Toft, M. P.; Vacher, B.; Walsh, R. J. A. *TL* **1992**, *33*, 7211.

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2-Amino-3-methyl-1,1-diphenyl-1-butanol[1]

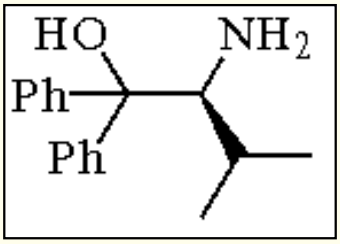

(*S*)

[78603-95-9] · $C_{17}H_{21}NO$ · 2-Amino-3-methyl-1,1-diphenyl-1-butanol · (MW 255.36) (.HCl)

[130432-39-2] (R)

[86695-06-9] (.HCl)

[56755-20-5]

(precursor to Itsuno's reagent, a chiral oxazaborolidine catalyst[1] used for the enantioselective reduction of prochiral ketones,[2] oxime *O*-ethers,[2c,d,3] and imines[4])

Alternate Name: 1,1-diphenylvalinol.

Physical Data: mp 94-95 °C; $[\alpha]_{589}$ -127.7° (*c* 0.693, $CHCl_3$) for the (*S*) enantiomer.

Solubility: very sol THF, CH_2Cl_2, MeOH; not very sol water.

Preparative Method: from valine methyl ester hydrochloride and excess ***Phenylmagnesium Bromide*** in 56% yield.[2]

Purification: recrystallization from ethanol-water (10:1).

Handling, Storage, and Precautions: no special information available. In general, however, it is advisable that all reactions with this reagent be conducted in a well ventilated fume hood. Care should be exercised to avoid contact of this reagent and the derived oxazaborolidine catalyst with the eyes and skin.

Stoichiometric Enantioselective Ketone Reduction.

The oxazaborolidine-borane complex (**3**) prepared in situ from diphenylvalinol (**1**) and ***Borane-Tetrahydrofuran*** (2 mol equiv) (eq 1) will enantioselectively reduce a variety of prochiral ketones (eq 2, Table 1).[2] Free oxazaborolidine (**2**) is

ineffective stoichiometrically as an enantioselective reducing agent. The asymmetric catalyst (**3**) works best for the reduction of aryl alkyl ketones, providing very high levels of enantioselectivity (94-100% ee). In the case of dialkyl ketones, the best enantioselectivity (78% ee) is obtained for the reduction of *t*-butyl methyl ketone. Reduction of acylsilanes affords the corresponding carbinols in moderate to high enantioselectivity (50-94% ee).[5]

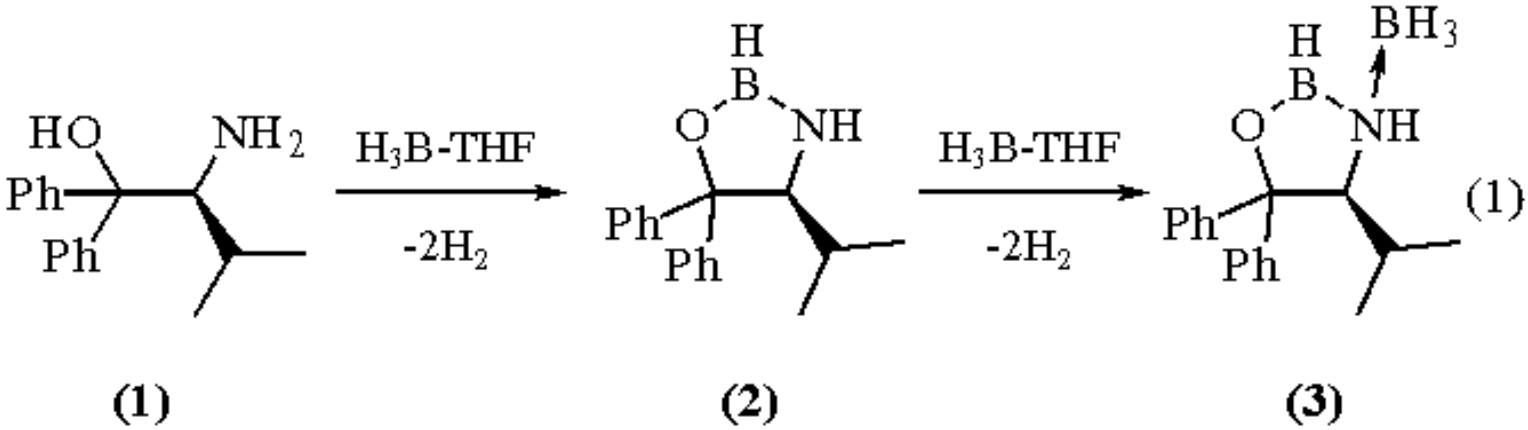

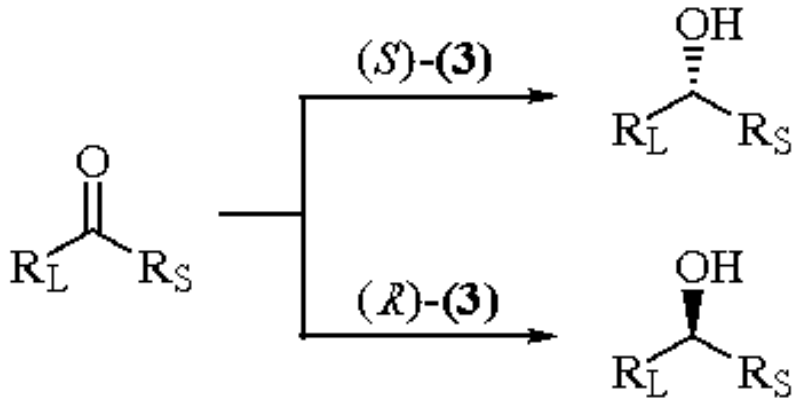

(2)

Table 1 Stoichiometric Enantioselective Reduction of Prochiral Ketones

R_L	R_S	Enantiomeric purity[a] (%)	Absolute configuration[b]
Ph	Me	94	*R*
Ph	Et	94	*R*
Ph	*n*-Pr	96	*R*
Ph	*n*-Pr	6[c]	*R*
Ph	*n*-Bu	100	*R*
n-Pr	Me	55	*R*
i-Pr	Me	60	*R*
t-Bu	Me	78	*R*
Ph	CH_2Cl	96[d]	*S*

[a] Enantiomeric purity based on the optical rotation of the product vs. the maximum value reported. [b] Absolute configuration of the product obtained using the catalyst derived from (*S*)-diphenylvalinol (**1**). [c] Reaction using free oxazaborolidine (**2**). [d] Catalyst derived from (*S*)-diphenylleucinol.

Reduction of α-chloroacetophenone using the catalyst prepared from the related (*S*)-diphenylisoleucinol (**4**) and borane gives (*S*)-chlorohydrin (**5**), which is readily transformed to (*S*)-styrene oxide (eq 3).[3a] The reduction affords the (*S*) enantiomer of (**5**) due to chlorine having a higher priority in nomenclature, not a change in the enantiofacial selectivity of the asymmetric catalyst.

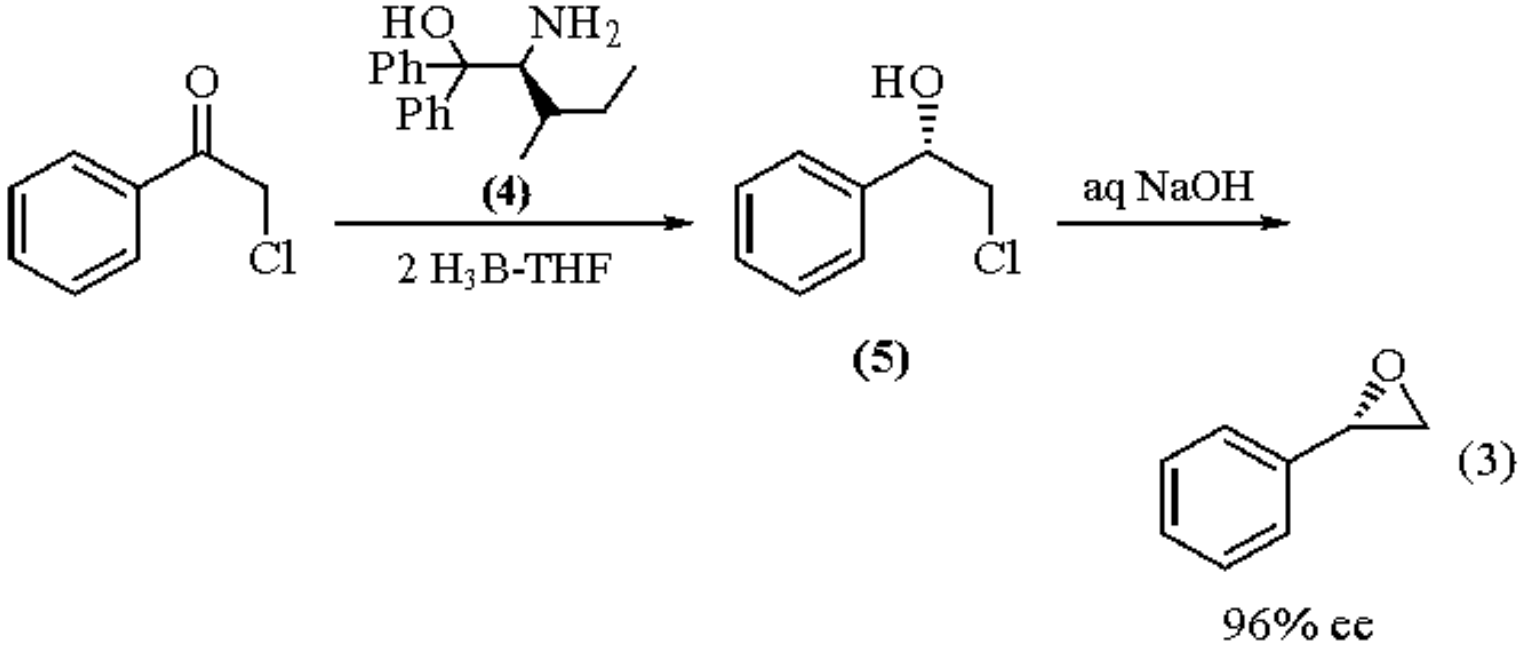

Catalytic Enantioselective Ketone Reduction.

Although free oxazaborolidine (**2**) is ineffective by itself as an enantioselective reducing agent, Corey demonstrated that it can be used catalytically (0.025-0.5 equiv) with excess borane (0.6 mol equiv) for the enantioselective reduction of acetophenone (eq 4).[6] A mechanism was proposed to explain the behavior of the catalyst. Initial coordination between the Lewis acidic ring boron and the ketonic oxygen activates the ketone towards reduction. Intramolecular hydride transfer from the BH_3 coordinated to the ring nitrogen then occurs via a six-membered ring cyclic transition state. In addition, oxazaborolidine (**6**) prepared from α,α-diphenyl-2-pyrrolidinemethanol (eq 5) was reported to be an even better catalyst for the reduction of ketones. For a more detailed discussion, see the entries for α,α-***Diphenyl-2-pyrrolidinemethanol*** and ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***.

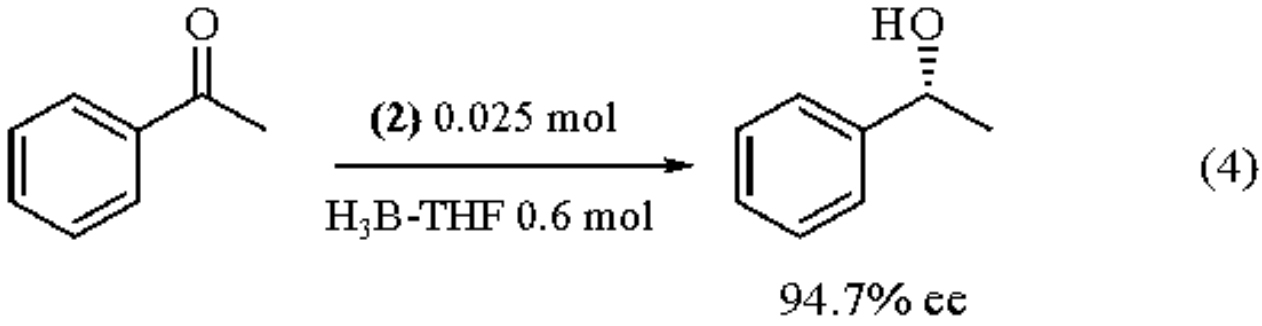

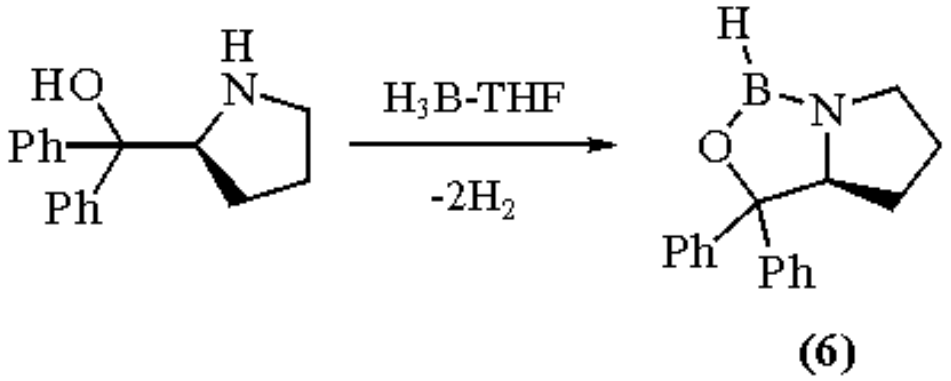

(5)

Recently, Katz employed oxazaborolidine (**2**) to catalyze the enantioselective reduction of ketone (**7**) (eq 6). The resultant carbinol was used for the synthesis of optically active helical metallocene oligimers.[7]

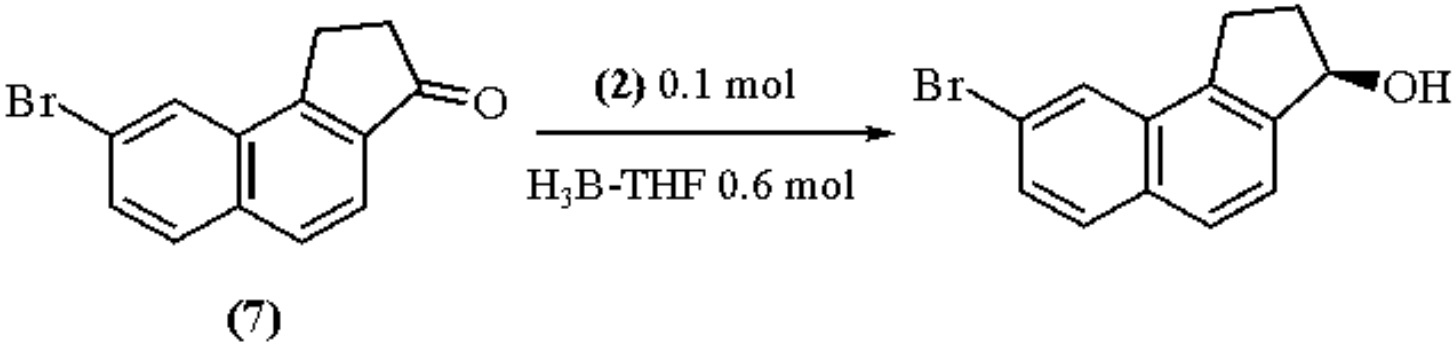

(6)

Enantioselective Reduction of Oxime *O*-Ethers.

In addition to the reduction of prochiral ketones, oxazaborolidine (**3**) has been used (both stoichiometrically and catalytically with borane-THF) to catalyze the enantioselective reduction of prochiral ketoxime *O*-ethers to the corresponding amine (eq 7).[2c-d,3] Unlike the ketone reduction described above, the (*S*)-oxazaborolidine catalyst gives (*S*)-amines. The best enantioselectivity is obtained for the case where R = Me (Table 2). Addition of a Lewis acid, such as ***Aluminum Chloride***, to the oxime increases the rate of reduction (complete reaction in 3 h vs. 24 h).

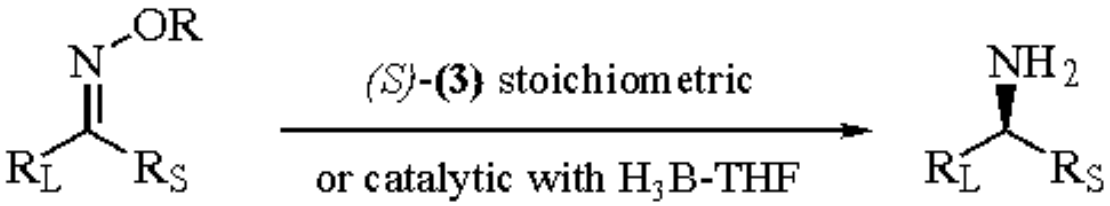

(7)

Table 2 Enantioselective Reduction of Prochiral Ketoxime *O*-Ethers

R_L	R_S	R	Enantiomeric purity[a] (%)	Absolute configuration[b] (%)
Ph	Me	H	0.6	*S*
Ph	Me	Me	99	*S*
Ph	Me	Et	81	*S*
Ph	Me	Bn	95	*S*
Ph	Me	Bn	90[c]	*S*
Ph	Me	Bn	94[d]	*S*
Ph	Me	Bn	89[d,e]	*S*
Ph	Me	TMS	62	*S*
Ph	Me	Ac	8.7	*R*

[a] Enantiomeric purity based on the optical rotation of the product vs. the maximum value reported. [b] Absolute configuration of the product obtained using a stoichiometric amount of the (*S*)-catalyst (**3**). [c] Reduction using 0.25 mol equiv of the catalyst with excess borane THF. [d] Reduction using the catalyst derived from (*S*)-diphenyl-*O*-benzyltyrosenol. [e] $AlCl_3$ added to the ketoxime *O*-ether prior to reduction.

Enantioselective Reduction of Imines.

Oxazaborolidine (**3**) also enantioselectively reduces *N*-substituted ketimines to the corresponding *N*-substituted amine in low to moderate ee (eq 8, Table 3).[4a] In this case the enantioselectivity is the same as the reduction of ketones; thus the (*S*)-oxazaborolidine catalyst gives (*R*)-amines. Oxazaborolidine (**3**) is reported to provide higher enantioselectivity than oxazaborolidine (**6**). An interesting application of this reaction is the preparation of a (a*RS*,*S*) diastereomerically enriched (63% de) sample of the more active atropisomers of the herbicide Metalochlor (eq 9).[4b]

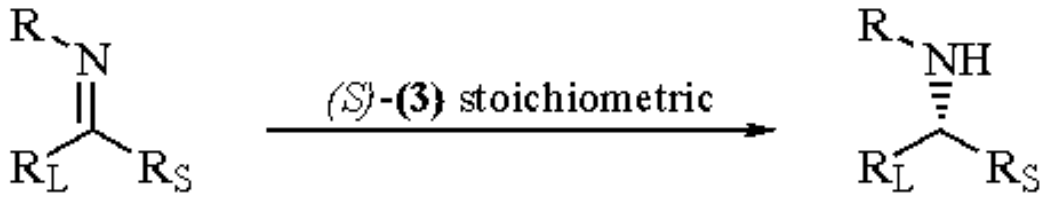
R
N
R_L
R_S
(S)-(3) stoichiometric
R
NH
R_L
R_S

(8)

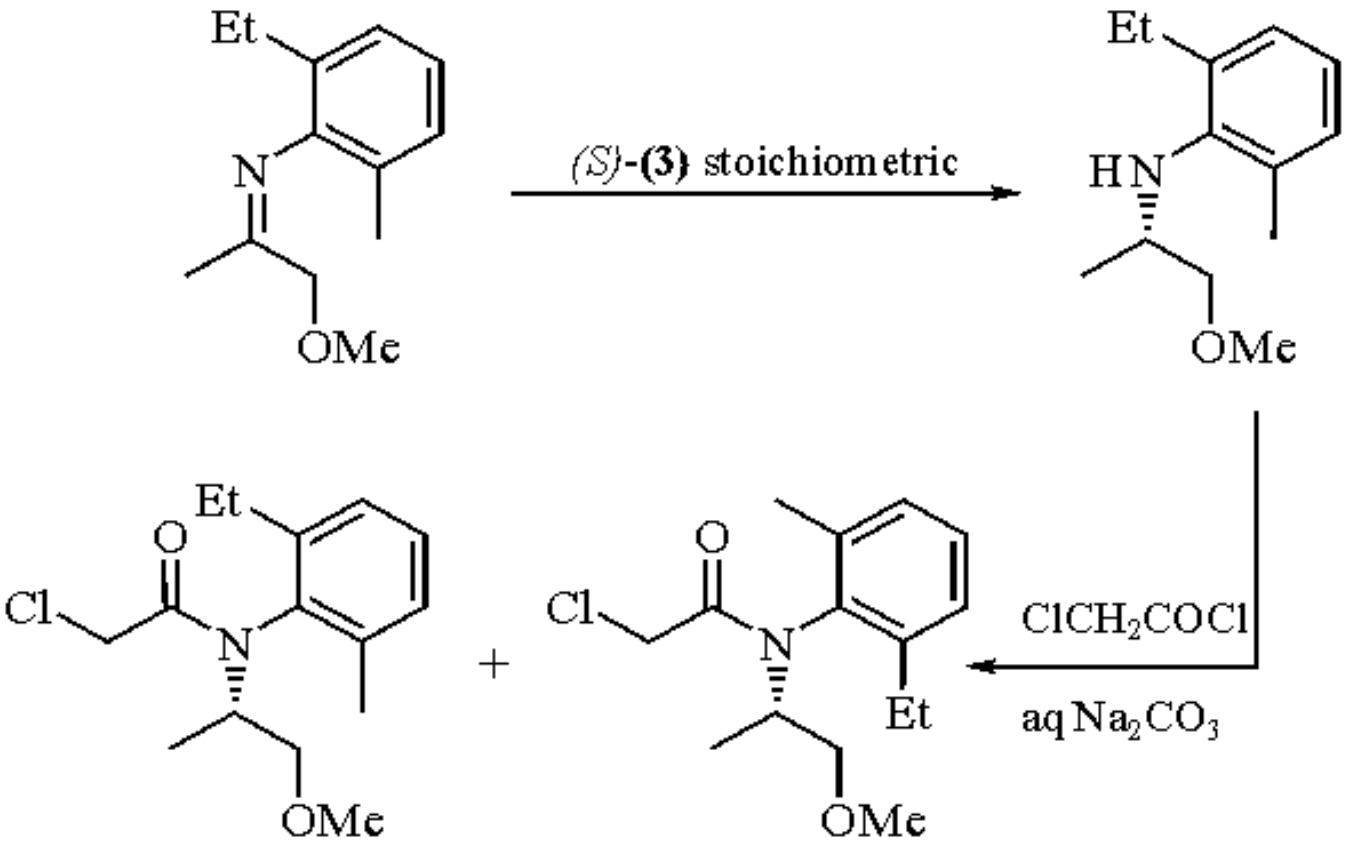
Et
N
OMe
(S)-(3) stoichiometric
Et
HN
OMe
ClCH2COCl
aq Na2CO3
Et
O
Cl
N
OMe
+
O
Cl
N
Et
OMe

(9)

Table 3 Enantioselective Reduction of Prochiral Imines

R_L	R_S	R	Enantiomeric purity[a] (%)	Absolute configuration[b]
Ph	Me	Ph	73	*R*
Ph	Et	Ph	87	*R*
Ph	*n*-Pr	Ph	88	*R*
Ph	Me	Bn	46	*R*
Et	Me	Ph	9[c]	*R*

[a] Enantiomeric purity based on the optical rotation of the product vs. the maximum value reported. [b] Absolute configuration of the product obtained using a stoichiometric amount of the catalyst derived from (*S*)-1,1-diphenylvalinol.

Related Reagents.

α,α-***Diphenyl-2-pyrrolidinemethanol***; ***Ephedrine-borane***; ***Norephedrine-Borane***; ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***.

---

1. (a) Wallbaum S.; Martens, J. *TA* **1992**, *3*, 1475. (b) Singh, V. K. *S* **1992**, 605.
2. (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *CC* **1983**, 469. (b) Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *JCS(P1)* **1983**, 1673. (c) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *JOC* **1984**, *49*, 555. (d) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *JCS(P1)* **1985**, 2039. (e) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *JCS(P1)* **1985**, 2615.
3. (a) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *BCJ* **1987**, *60*, 395. (b) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *JCS(P1)* **1989**, 1548. (c) Itsuno, S.; Sakurai, Y.; Shimizu, K.; Ito, K. *JCS(P1)* **1990**, 1859.
4. (a) Cho, B. T.; Chun, Y. S. *JCS(P1)* **1990**, 3200. (b) Cho, B. T.; Chun, Y. S. *TA* **1992**, *3*, 337.
5. Buynak, J. D.; Strickland, J. B.; Hurd, T.; Phan, A. *CC* **1989**, 89.
6. Corey, E. J.; Bakshi, R. K.; Shibata, S. *JACS* **1987**, *109*, 5551.
7. Katz, T. J.; Sudhakar, A.; Teasley, M. F.; Gilbert, A. M.; Geiger, W. E.; Robben, M. P.; Wuensch, M.; Ward, M. D. *JACS* **1993**, *115*, 3182.

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2-Aminonicotinaldehyde[1]

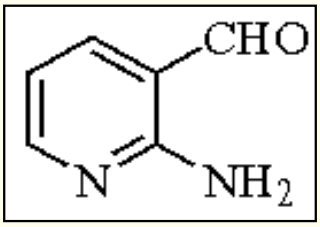

[7521-41-7] · $C_6H_6N_2O$ · 2-Aminonicotinaldehyde · (MW 122)

(1,8-naphthyridine synthesis; Friedländer synthon; β-amino aldehyde)

Alternate Name: 2-amino-3-pyridinecarbaldehyde.

Physical Data: yellow solid, sublimes readily, mp 98-99 °C.

Solubility: ether, ethyl acetate: good; dichloromethane: poor.

Preparative Methods: the reagent is best when freshly prepared. A multistep procedure starting from 2-amino-3-picoline has been improved upon by a simple two-step approach. Sulfamation of nicotinamide with ammonium sulfamate (both commercially available) provides 2-(3´-pyridyl)pyrido[2,3-*d*]pyridimine which may be hydrolyzed in 2 N HCl to provide the reagent (eq 1).[1] Substituted derivatives of the reagent may be prepared via a similar intermediate.[2]

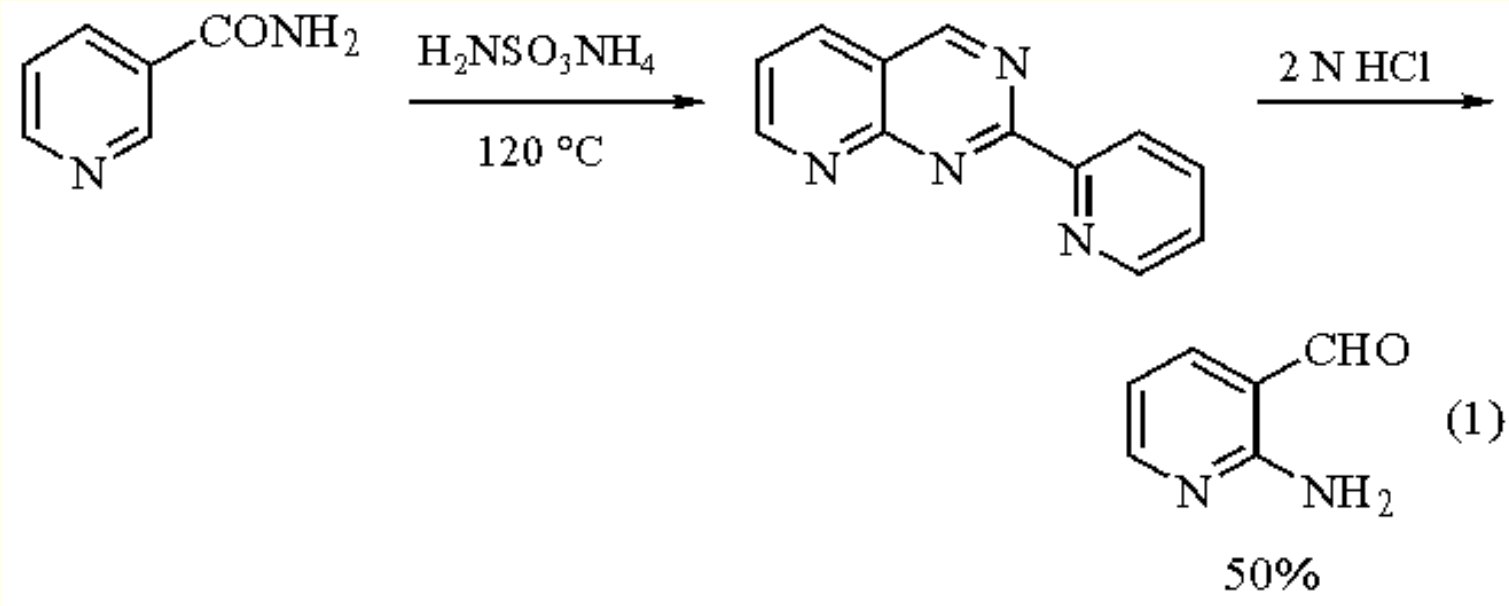

(1)

Handling, Storage, and Precautions: the reagent is somewhat more stable than ***2-Aminobenzaldehyde*** and may be stored for up to several months at 0 °C under an inert atmosphere. Sublimation is a convenient method for the separation of higher oligomers which may accumulate during storage. Use in a fume hood.

1,8-Naphthyridine Synthesis.

The Friedländer condensation of 2-aminonicotinaldehyde with various ketones provides a convenient one-step access to the 1,8-naphthyridine nucleus. Other naphthyridine isomers are available from related pyridine *o*-aminoaldehydes.[1b] The reaction is generally carried out by combining the reactants in ethanol, adding several mL of saturated methanolic KOH and refluxing for 1-4 h. Appropriate diketones will afford two sequential condensations. Reactions with the three isomeric cyclohexanediones are regiospecific and proceed in the direction predicted by the more active methylene position (eq 2).[3-5]

Related Reagents.

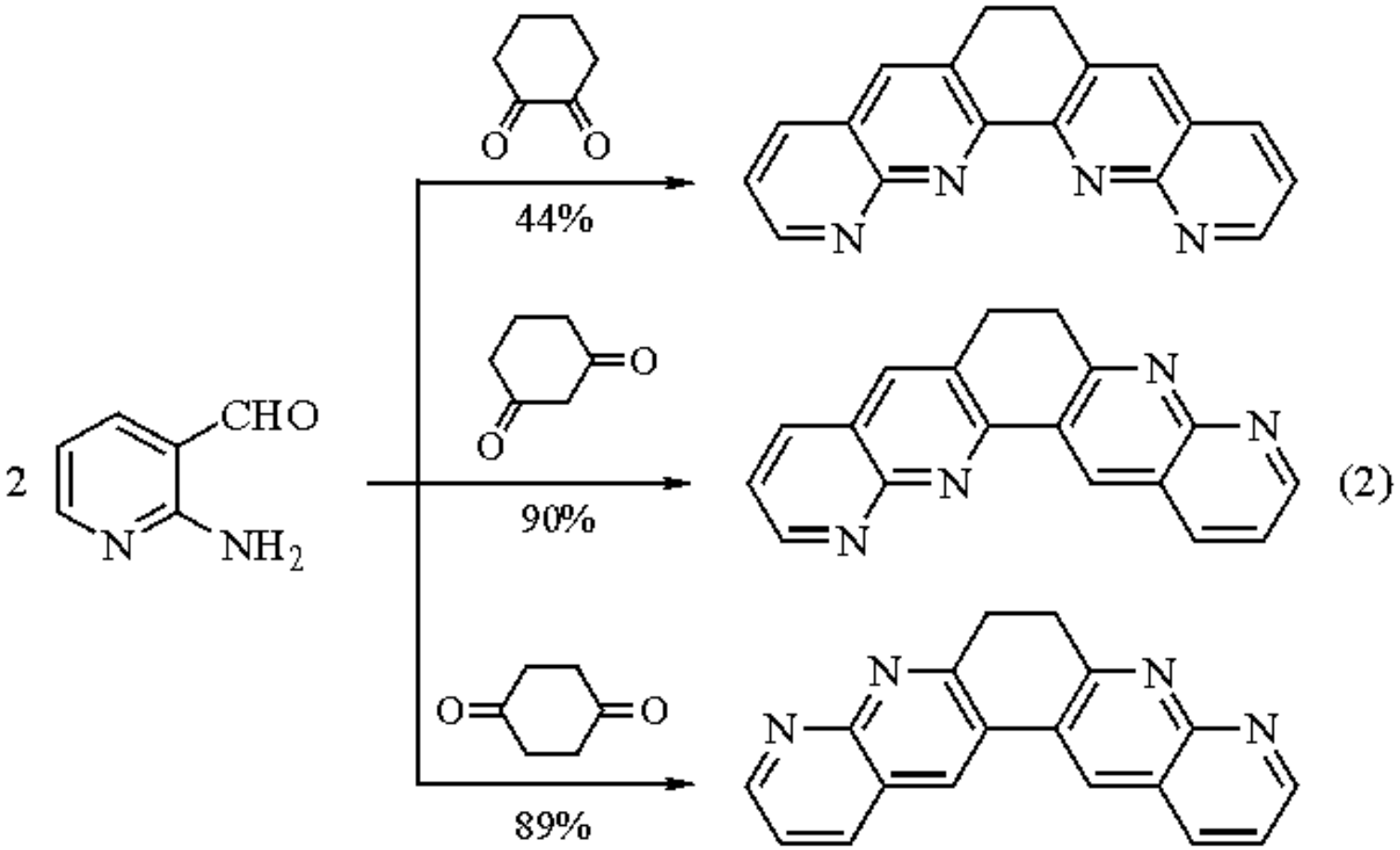

(Z)*-β-*Aminoacrolein; ***2-Aminobenzaldehyde***; ***1,3-Cyclohexanedione***; ***Quinoline***.

---

1. (a) Caluwe, P. *T* **1980**, *36*, 2359. (b) Cheng, C.-C.; Yan, S.-J. *OR* **1982**, *28*, 37. (c) Thummel, R. P. *SL* **1992**, 1.
2. Majewicz, T. G.; Caluwe, P. *JOC* **1974**, *39*, 720.
3. Evens, G.; Caluwe, P. *JOC* **1975**, *40*, 1438.
4. Majewicz, T. G.; Caluwe, P. *JOC* **1975**, *40*, 3407.
5. Thummel, R. P.; Lefoulon, F.; Cantu, D.; Mahadevan, R. *JOC* **1984**, *49*, 2208.

Ammonia[1]

NH_3

[7664-41-7] · H_3N · Ammonia · (MW 17.03)

(weak base;[2] essential nonaqueous solvent medium for dissolving metal reactions;[3] precursor of organic nitrogen compounds including amines,[4] unsubstituted amides,[5] heterocycles[1,6])

Physical Data: mp -78 °C; bp -33.3 °C/760 mmHg; *d* liq. NH_3 0.682 g cm^{-3} (-33.3 °C/760 mmHg).

Solubility: very sol water (47.8% w/w, 0 °C), methanol, ethanol; also sol chloroform, ether.

Form Supplied in: although gaseous at room temperature, anhydrous NH_3 is usually supplied as the liquified form in stainless steel cylinders which are sometimes fitted with an eductor tube to permit convenient and rapid extraction of liquid NH_3 when the cyclinder is inverted or tipped on its side. NH_3 is also readily available as aqueous solutions (ammonium hydroxide) in various concentrations. *Drying:* commercial anhydrous NH_3 can be used as supplied in many applications though in some cases drying is required to ensure optimum yield. Gaseous NH_3 can be dried by passing through a column of NaOH pellets, whereas liquid NH_3 can be dried using sodium metal (sufficient to obtain a persistent deep-blue coloration) or CaH_2 followed by distillation under nitrogen directly into the reaction vessel.

Handling, Storage, and Precautions: since NH_3 is highly corrosive, cylinders must be equipped with the appropriate stainless steel valves and fittings. As a consequence of its comparatively high enthalpy of vaporization (23.5 kJ mol^{-1}), reactions involving liquid ammonia can be carried out on laboratory scale without the need for external cooling since an insulating layer of ice quickly builds up around the outside of the reaction vessel.

NH_3 is highly toxic; inhalation of the vapor can cause edema of the respiratory tract, spasm of the glottis, and asphyxia. All reactions involving anhydrous ammonia must be conducted in a well-ventilated fume hood.

▪

As a consequence of the lone pair of electrons on the nitrogen, ammonia is both a weak base (K_b 1.8×10^{-5}) and a nucleophile, two properties which account for most of its reagent chemistry.[2] Ammonia reacts readily and reversibly with mineral and organic acids to form salts (eq 1) which, being stable solids, are often used as convenient sources of

ammonia. Since ammonia is an extremely weak acid (pK_a estimated to be ~38),[7] the amide anion is a very strong base.

$$:NH_3 + HX \rightleftharpoons NH_4^+X^- \qquad (1)$$

Ammonia in Dissolving Metal Reactions.

In addition to dissolving a wide range of organic compounds and inorganic salts, anhydrous liquid NH_3 can act as a solvent for the Group 1 and 2 metals, producing deep-blue colored solutions which conduct electricity and are strongly reducing. The physical and chemical properties of such solutions are usually attributed to solvated electrons.[3,8] In the presence of a catalyst such as anhydrous $Fe(NO_3)_3$, solutions of sodium and potassium in liquid NH_3 are conveniently converted into the amide salts ($M^+NH_2^-$), which are very strong bases.[9]

Solutions of Li, Na, and K metals in liquid NH_3, usually in the presence of a proton source like ethanol, have been extensively used for the partial reduction of a variety of benzene derivatives and polyfused aromatic compounds (the Birch reduction);[2] typically, benzene gives 1,4-cyclohexadiene (eq 2) whereas naphthalene is reduced to the tetrahydro derivative. *o*-Methoxybenzoic acid (also its salts and esters) can be converted to 2-alkylcyclohexenones (eq 3).[10] Similar reaction conditions have been utilized for the ring opening of cyclopropanes,[11] the transformation of conjugated enones to the saturated carbonyl compounds[12] or their 2-substituted derivatives,[13] the stereospecific reduction of disubstituted alkynes to (*E*)-alkenes,[14] the hydrodehalogenation of *gem*-dihalides,[15] and the reductive cleavage of polysulfides to thiols.[16]

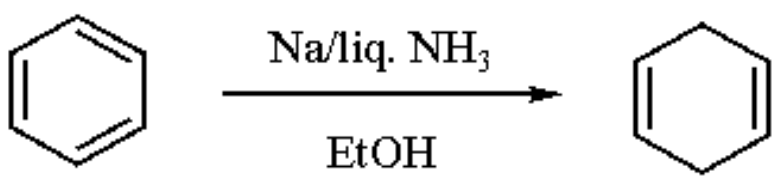

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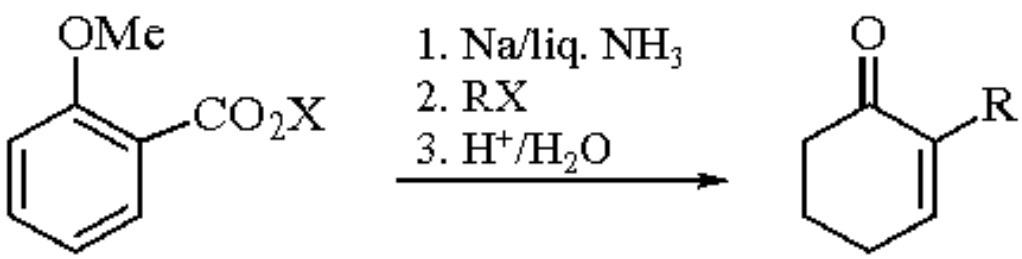

(3)

Alkylation of Ammonia.

Direct reactions between ammonia and alkyl halides are complex and generally produce mixtures of the salts of the primary, secondary, and tertiary amines, and also quarternary salts (eqs 4-7). The final composition of the product mixture depends on the relative initial concentrations of the reactants, the nature of the reaction solvent, and the steric requirements of the alkyl groups. The reactions generally exhibit the characteristics of S_N2 type displacements (reaction rate with respect to the alkyl group: primary > secondary > tertiary) and the ease of halogen displacement follows the expected order I > Br > Cl > F.[4b] Reactions carried out in liquid ammonia tend to give mixtures of primary and secondary amines, whereas in methanolic ammonia more complex mixtures of the primary, secondary, and tertiary

amines are obtained.[17] Separation of the various amine products by distillation is usually easier for higher alkyl substituents, e.g. *n*-octyl.[18]

$$:NH_3 + RX \rightleftharpoons RNH_3^+X^- \quad (4)$$

$$R\ddot{N}H_2 + RX \rightleftharpoons R_2NH_2^+X^- \quad (5)$$

$$R_2\ddot{N}H + RX \rightleftharpoons R_3NH^+X^- \quad (6)$$

$$R_3\ddot{N} + RX \rightleftharpoons R_4N^+X^- \quad (7)$$

With dihaloalkanes, intramolecular cyclization will occur to form five- to seven-membered heterocyclic compounds as appropriate, though even in favorable cases, over reaction can occur (eq 8).[19] Tribromoalkanes have also been used to synthesize novel azabicyclic systems (eq 9),[20] and l-azaadamantane (eq 10).[21]

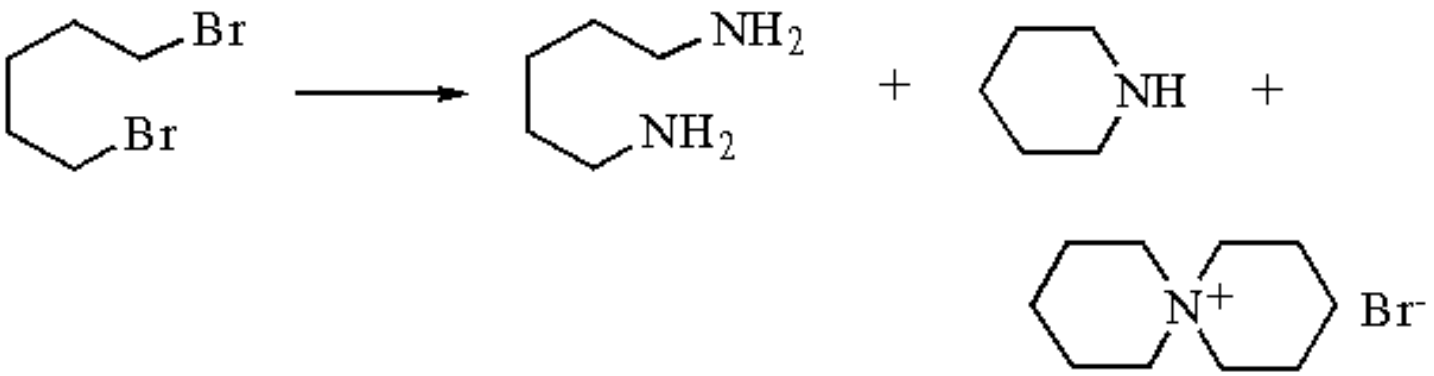

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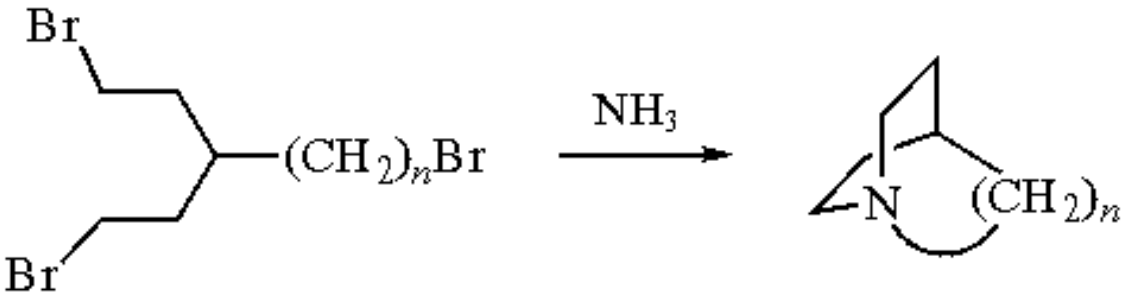

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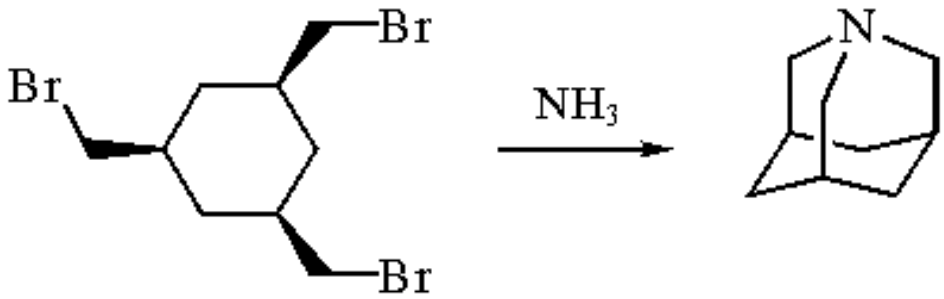

(10)

Amination of Aromatic and Heteroaromatic Compounds.

Although amination of simple aryl halides to yield anilines by *ipso* substitution of the halo group is more usually carried out using ***Potassium Amide*** in liquid NH_3, NH_3 itself can also be used but requires elevated temperatures and pressure, and a copper catalyst.[22] Thus, for example, aniline is obtained from chlorobenzene (200 °C, Cu cat.),[23] 3,4-dimethylaniline from 4-bromo-*o*-xylene (195 °C, Cu/CuCl),[24] and *p*-trifluoromethylaniline from *p*-chlorotrifluoromethylbenzene (200 °C, CuCl/KF).[25]

The amination reaction proceeds more smoothly if the benzene ring is activated by strongly electron-withdrawing groups, particularly NO_2, in the *o*- and *p*-positions. The ease of halide displacement follows the sequence F > Br > Cl > I.[22b] Nitro groups have also been displaced from 2,3-dinitrotoluene.[26]

Naphthol derivatives can be transformed to the corresponding amines by treatment with aqueous ammonia in the presence of sulfite or bisulfite ion at elevated temperatures (the Bucherer reaction) (eq 11);[27] the analogous transformation with phenols is known, but is less common.[28]

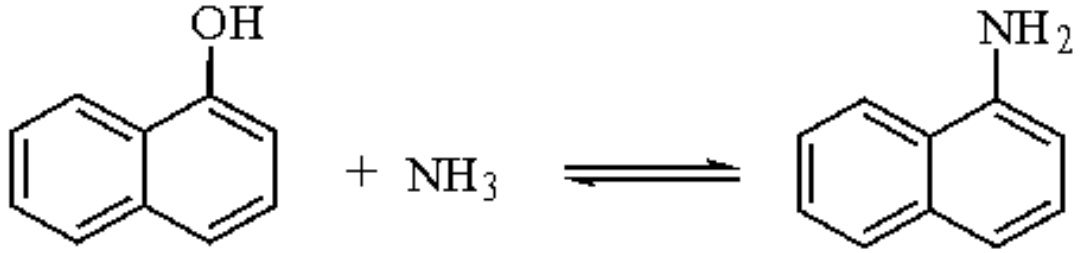

(11)

Heteroaromatic compounds, particularly pyridines and diazines, are more susceptible to amination with NH_3 than arenes. Although the amination reactions generally proceed under milder conditions, they may also be catalyzed by Cu salts. Typical examples include the Cu-catalyzed conversion of 3-bromopyridine to 3-aminopyridine, and 2-chloro-3-aminopyridine to 2,3-diaminopyridine,[29] the aminolysis of fluoro-[30] and chloropyrazines[31] on treatment with aqueous NH_3 at room temperature and 180 °C respectively, the displacement of the methoxy group in 4-methoxypyrimidone to give cytosine on treatment with methanolic ammonia at 100 °C (eq 12),[32] and the selective transformation of 2,6-dichloropurine to the corresponding 6-amino-2-chloro derivative under similar conditions (eq 13).[33] Treatment of solutions of 3-halo-2-alkylisothiazolium salts in acetonitrile with excess ammonia yields exclusively the *N*-monosubstituted 3-isothiazoles via a ring opening/recyclization process (eq 14).[34] Irradiation of solutions of 6-phenyl- and 6-*t*-butyl-4-halopyrimidines in liq NH_3 with UV light affords the corresponding 4-amino derivatives.[35]

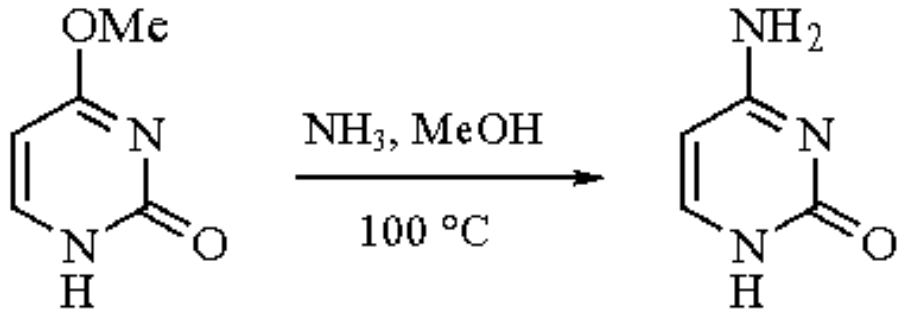

(12)

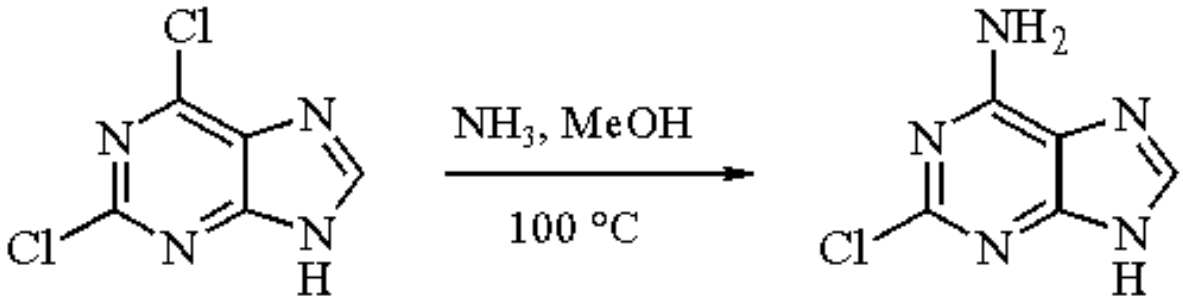

(13)

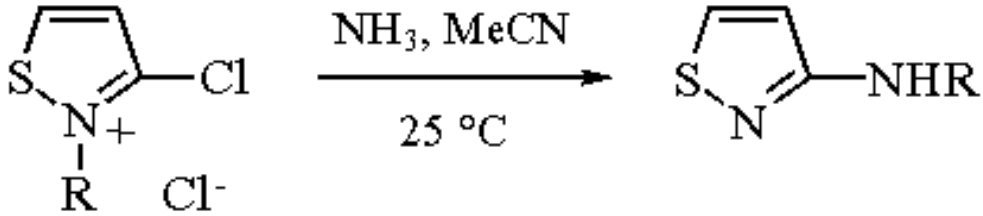

(14)

Highly π-electron deficient nitroaza heterocycles (including pyridines, diazines, and their respective benzo compounds) react with ***Potassium Permanganate*** in liq NH_3 to give amino compounds via an S_NH mechanism involving the initial formation of a σ-adduct with NH_3 which is subsequently oxidized by the permanganate.[36] The reactions can be highly regioselective and give high product yields (>80%) (eq 15).[37] For less π-electron deficient compounds, the combination KNH_2/liq NH_3/$KMnO_4$ has been used.[38]

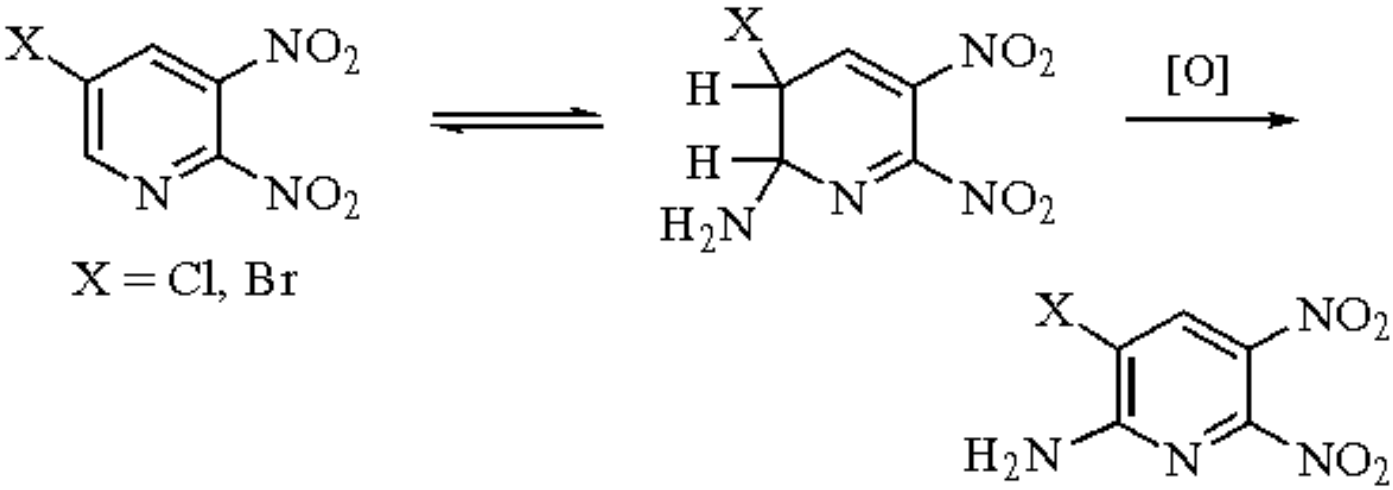

(15)

α-Amino Acids.

Ammonia reacts readily with α-halo carboxylic acids to yield the corresponding α-amino acids (eq 16). The reactions are conveniently carried out using a large excess of ammonia with either ammonium chloride[39] or formaldehyde[40] present to suppress further alkylation. The displacement normally proceeds with inversion of configuration[41] unless the adjacent β-position is substituted.[42]

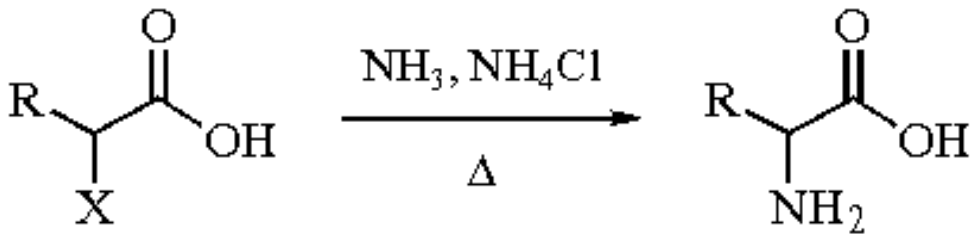

(16)

Ring-Opening of Epoxides and Aziridines.

Epoxides, possessing a relatively high degree of ring strain, readily open on treatment with ammonia to give 1,2-amino alcohols, usually with a high degree of regio- and stereoselectivity.[43] Consistent with an S_N2 mechanism, nucleophilic attack by the ammonia occurs at the sterically least hindered carbon center of the epoxide, e.g. with propene,[44] butene,[45] and styrene[45,46] oxides (eq 17). The ring opening proceeds in a *trans* fashion with concomitant inversion of configuration, e.g. *trans*-2-butene oxides give *erythro*-amino alcohols, whereas the *cis* compounds afford the diastereoisomeric *threo*-amino alcohols (eq 18).[47] Aminolysis of cyclopentene[48] and cyclohexene[49] oxides produces the corresponding *trans*-amino alcohols; the cyclohexane derivative is also obtained from the reaction of *trans*-chlorohydrin with aqueous ammonia at room temperature.[48] Substitution at the 3-position directs the incoming ammonia to the more distal carbon center (eq 19).[50] With epoxides derived from six-membered ring compounds which have rigid geometries, the amino and hydroxy groups in the resulting product are normally *trans* diaxially related, an important consideration in the stereoselective syntheses of amino sugars.[43,51]

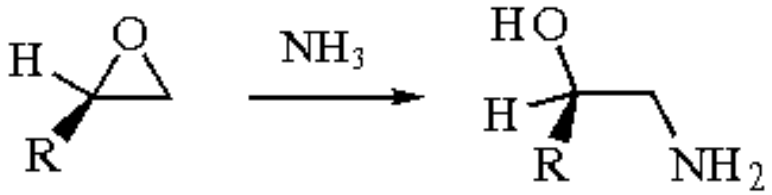

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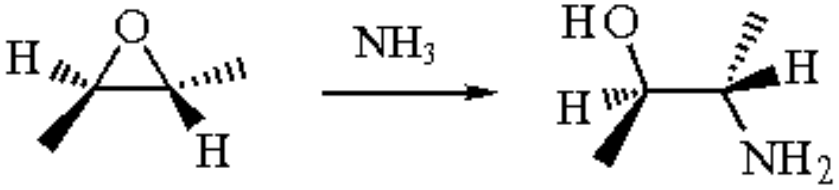

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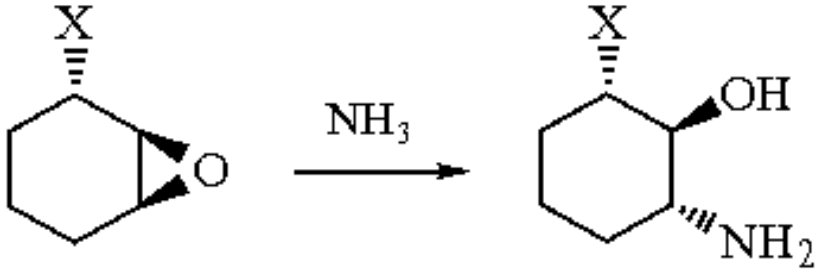

(19)

X = OMe, OPh

Ring opening of aziridines by anhydrous NH_3 in the presence of ammonium chloride proceeds smoothly at 100 °C to give 1,2-diamines.[52] The regio- and stereochemical preferences of this reaction have been shown to be similar to those

observed for epoxides.[47]

α-Amino Nitriles.

These key intermediates in the Strecker synthesis of amino acids (see below) can be prepared from the reaction of cyanohydrins with ammonia.[53] α-Amino nitriles (yields 80-95 %) can be conveniently prepared from α-silyloxy nitriles on treatment with ammonia in methanol (eq 20).[54]

(20)

Amidines.

Formamidine Acetate, a relatively nonhygroscopic salt, is conveniently obtained in high yield from the reaction of ***Triethyl Orthoformate*** with ammonia in acetic acid at 115 °C (eq 21). The corresponding acetamidine salt is prepared in a similar fashion using NH_4Cl in ammonia.[55]

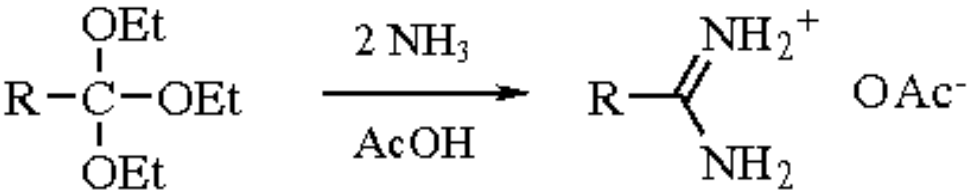

(21)

Primary Amides.

Nucleophilic substitution by ammonia at the carbonyl carbon of a carboxylic acid or a related derivative provides a general synthetic route to unsubstituted or primary amides (eq 22).[5] The order of reactivity is carboxylic acids < esters < anhydrides < acyl chlorides.

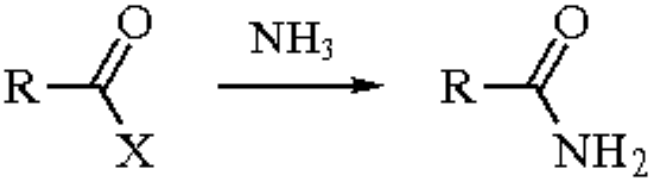

(22)

$X = OH, OR, Cl, OCOR, OCO_2R$

Since direct reaction between a carboxylic acid and NH_3 requires vigorous reaction conditions (reaction temperatures 170-200 °C), excess NH_3, and continuous removal of the water formed, this method is only suitable for amides derived from thermally stable acids; at higher temperatures, nitrile formation competes. Nonetheless, the primary amides from

a series aliphatic carboxylic acids (C_2-C_{18}) have been prepared by this approach.[56,57] Under similar reaction conditions, cyclic imides (favorable for ring sizes 5 and 6) can be obtained from diacids and NH_3.[58]

Although esters react cleanly with ammonia to give the corresponding amides, the reported conditions to effect the transformation are still reasonably vigorous, e.g. excess conc aq NH_3/NH_4Cl at 100 °C,[59] or liq NH_3 at 165-180 °C.[60] Ethyl cyanoacetate affords cyanoacetamide on shaking with aqueous NH_3.[61] As an alternative method, esters are transformed to primary amides under mild conditions ($CH_2Cl_2/T < 40$ °C) using Me_2AlNH_2 (2 equiv), generated in situ from $AlMe_3$ and NH_3.[62]

The ammonolysis of acyl chlorides has been used extensively as a standard laboratory procedure for the preparation of primary amides, the reactions are rapid and exothermic and usually carried out in solvent.[5,60,63] To ensure completion of reaction, a minimum of a twofold excess of ammonia is required since it reacts with the HCl liberated. Instead of ammonia, ammonium acetate in acetone can be used with acyl chlorides.[64]

Carboxylic acid anhydrides readily undergo ammonolysis to give the corresponding primary amide.[5] With cyclic anhydrides, cyclic imides are formed, e.g. phthalic anhydride gives phthalimide.[58]

Treatment of mixed anhydrides, generated in situ from carboxylic acids and ***Ethyl Chloroformate***, with anhydrous ammonia provides primary amides under mild conditions;[5,65] product yields are claimed to be superior to those obtained using acyl chlorides.[66]

Reactions conditions for the ammonolyses of substituted esters and acyl chlorides can usually be adapted to be compatible with a range of functionality including unsaturation,[67] halo,[68,69] hydroxyl,[70] amino,[71] and acetal groups.[72] For example, α-halocarboximides can be obtained from the corresponding acid chlorides[68] or esters[69] with conc aq NH_3 by maintaining the reaction temperature below 0 °C.

Aromatic or allylic aldehydes can be converted into primary amides by reaction with NH_3 using either ***Nickel(II) Peroxide*** in dry Et_2O at -20 °C,[73] or ***Sodium Cyanide*** and ***Manganese Dioxide*** in isopropanol at 0 °C.[74] Amination of aliphatic and aryl aldehydes has also been accomplished using ***N-Bromosuccinimide*** with AIBN as an initiator in the presence of NH_3; radical substitution of the aldehydic hydrogen by Br generates an acyl bromide which reacts rapidly with the NH_3 present.[75]

Primary amides are obtained from the thermal,[76a] photochemical,[76b] or metal ion (e.g. Ag^+) catalyzed[77] rearrangement of α-diazo ketones in the presence of ammonia (Wolff rearrangement). In cases where the required diazo ketone can be generated in situ from an acyl chloride and ***Diazomethane***, the overall transformation is an homologation (the Arndt-Eistert synthesis) (eq 23).[77]

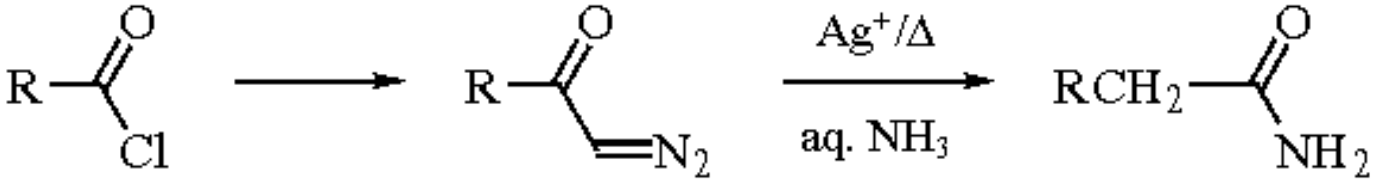

(23)

The Ugi Reaction.

Ammonia, usually in the form of an ammonium salt of a carboxylic acid, reacts with a mixture of isocyanides and aldehydes to give bis-amides in moderate yield (~50%) (the Ugi reaction) (eq 24).[78] The scope of the reaction is considerably more limited with ammonia than with amines.

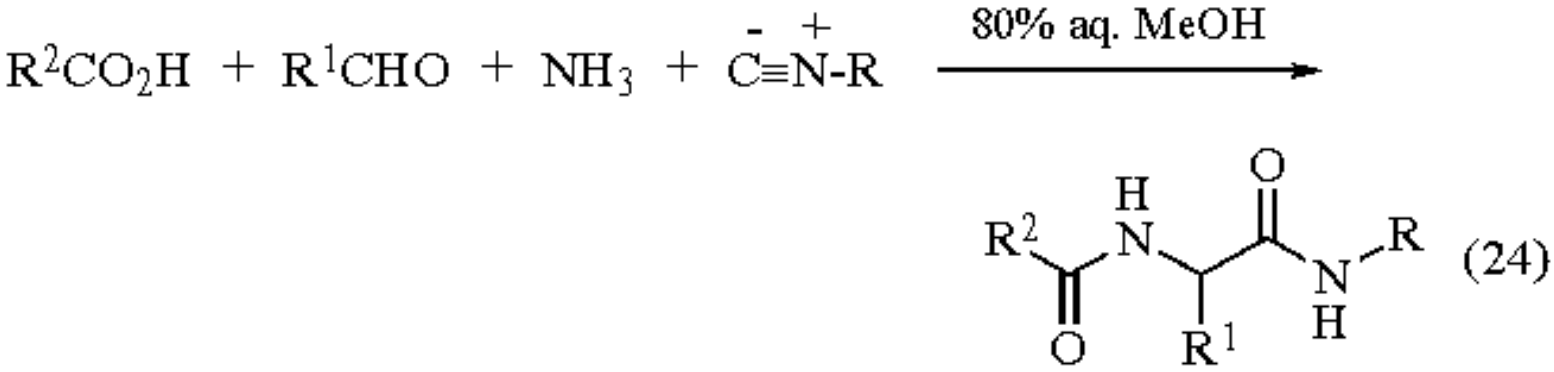

Addition of Ammonia to Alkenes and Alkynes.

Since it is intrinsically nucleophilic, NH_3 does not form adducts readily with simple alkenes. Under high temperature (200 °C) and pressures (800-1000 atm), and in the presence of Na metal, ethylene, propene, isobutene, and cyclohexene react with NH_3 to give the corresponding amines in low yield (15-30%).[79] Similarly, 2-phenylethylamine is obtained from styrene in 8% yield.[80] NH_3 does, however, undergo nucleophilic addition to Pd^{II} and Pt^{II} complexes derived from 1,5-dienes; subsequent reduction of the adducts with ***Sodium Borohydride*** releases the amines, e.g. 2-aminohexane (93%) and cyclooctylamine (57%) are obtained from 1,5-hexadiene and 1,5-cycloocatdiene, respectively.[81]

Simple alkenes undergo aminosulfenylation on treatment in turn with ***Dimethyl(methylthio)sulfonium Tetrafluoroborate*** followed by ammonia (eq 25).[82]

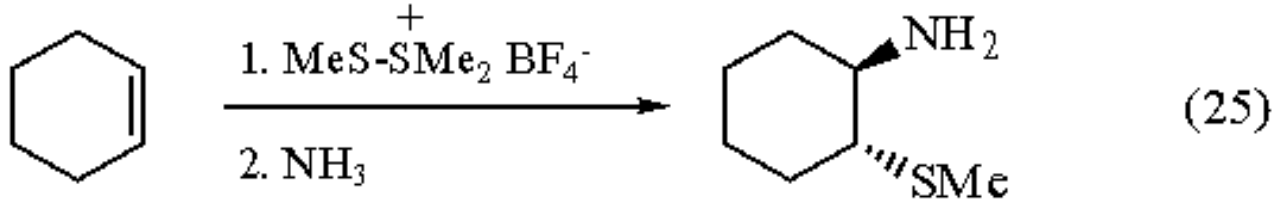

Alkenes with electron withdrawing substituents (carbonyl, nitrile, alkoxycarbonyl) are susceptible to Michael addition to form, at least initially, the β-amino adducts. With systems unsubstituted at the β-position, multiple addition usually occurs affording the di- and triadducts even with a large excess of ammonia (eq 26). Thus, the diadduct is the major product from the addition of NH_3 to acrylonitrile at 30 °C even with a significant excess of NH_3. When the reaction is carried out with a large excess of NH_3 (>threefold) at 110 °C for short reaction times, the monoadduct is the major component of the reaction mixture.[83] Ethyl acrylate reacts readily with NH_3 to give the corresponding di- and triadducts which are separable by distillation.[84]

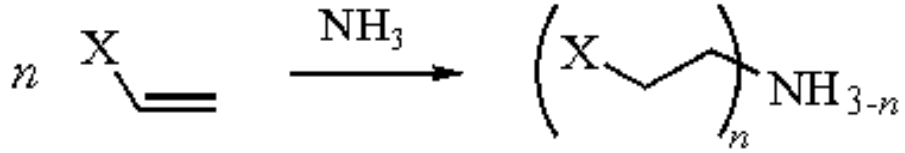

(26)

Substitution at the β-position of α,β-unsaturated systems inhibits multiple addition. Thus crotonic acid,[85] ethyl crotonate,[86] and mesityl oxide[87] all form the corresponding β-amino compounds. 1-Nitropropene and butene also form monoadducts with ammonia which tend to be unstable.[88] Sorbic acid undergoes double addition of NH_3 to give 3,5-diaminohexanoic acid.[89]

As with alkenes, reactions between simple alkynes and NH_3 generally take place under forcing reaction conditions, producing complex product mixtures containing 1,2-diamines, piperidines, etc.[90] Conjugated dialkynes react with NH_3 in the presence of CuCl catalyst to give pyrroles (eq 27).[91]

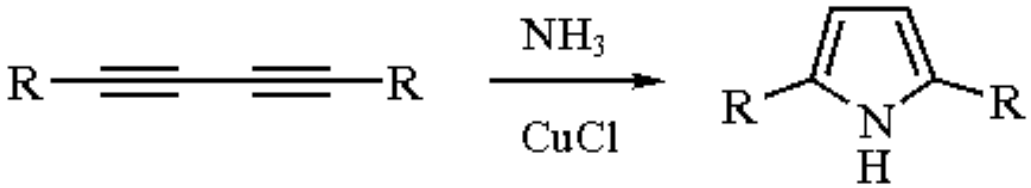

(27)

Addition of Ammonia to Heterocumulenes.

NH_3 adds across the carbon-carbon double bond of ketenes to give primary amides, usually in good yield (cf. the Wolff rearrangement mentioned above) (eq 28).[92]

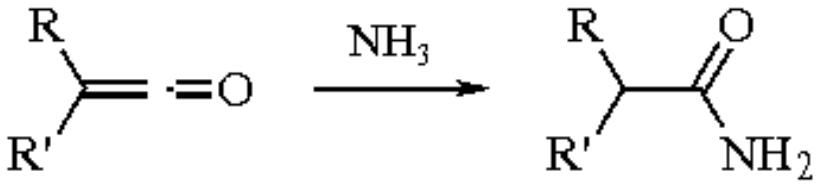

(28)

With isocyanates and isothiocyanates, the addition of NH_3 takes place specifically across the carbon-nitrogen double bond, producing ureas[93] and thioureas, respectively (eq 29).[94]

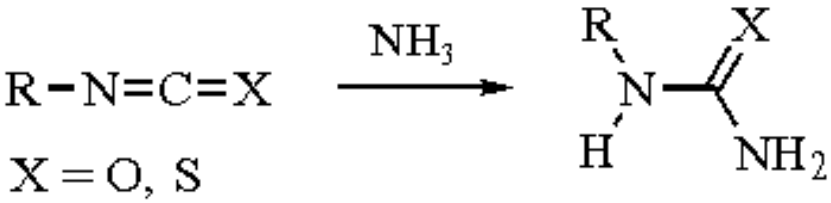

(29)

Amidines.

Alkyl and aryl nitriles react with ammonia in the presence of ammonium salts to give amidine salts, usually in yields

of the order of 80% (eq 30).[95] The reaction between nitriles and $MeAl(Cl)NH_2$, generated in situ from $AlMe_3$ and NH_4Cl, provides an alternative general synthetic route to amidines.[96] Dinitriles of suitable chain length give cyclic imidines on treatment with NH_3 in methanol at 100 °C (eq 31).[97]

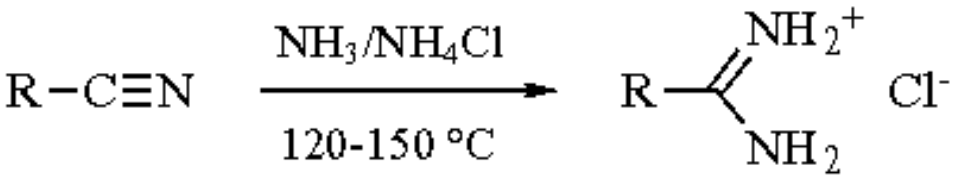

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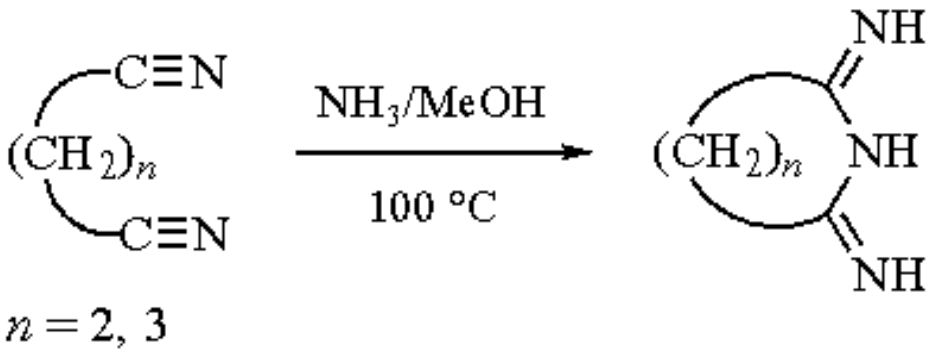

(31)

Addition of Ammonia to Carbonyl Compounds.

Nucleophilic addition of NH_3 to an aldehyde or ketone affords initially a hemiaminal which subsequently dehydrates to an imine (eq 32). Imines which are not readily isolable except those derived from perfluoroalkyl[98] or diaryl ketones[99] usually react further. Condensations of ammonia with (a) formaldehyde yield the polycyclic adduct hexamethylenetetramine (eq 33),[100] (b) *n*-alkanals and arylacetaldehydes form the trimeric hexahydrotriazines (eq 34),[101] and (c) aromatic aldehydes give hydrobenzaminidines (eq 35).[102]

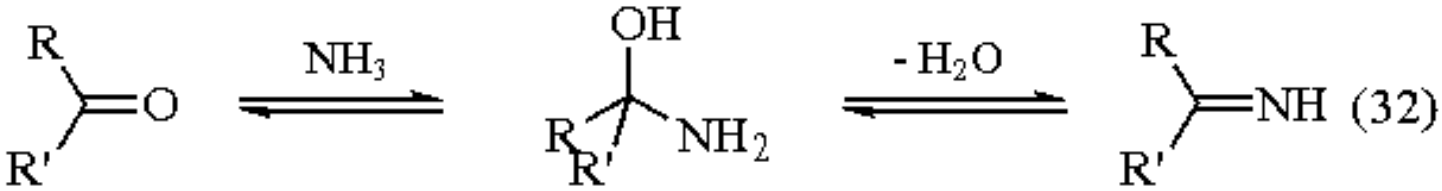

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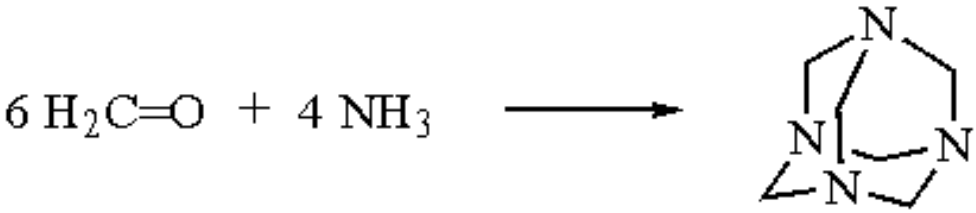

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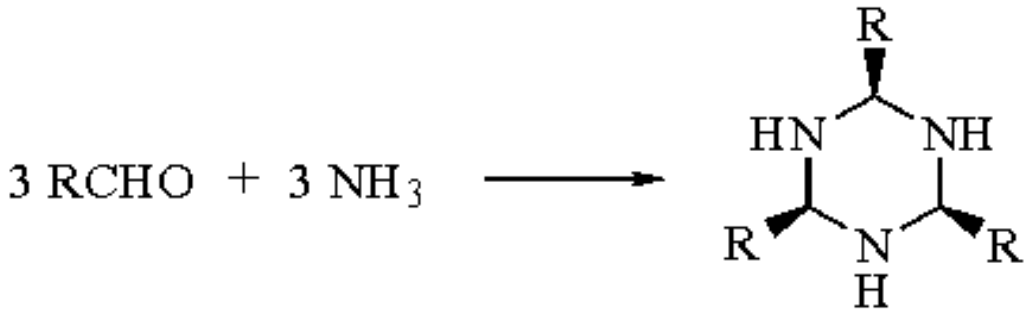

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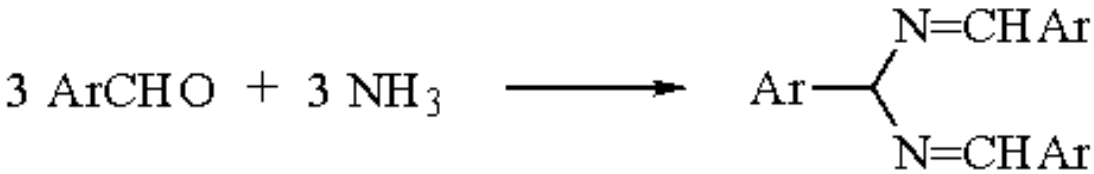

(35)

Reductive Amination.

Catalytic hydrogenation (Ni, Pt, Rh) of mixtures of aldehydes or ketones (usually in ethanol) and NH_3 affords primary amines, presumably by hydrogenation of the intermediate imine (eq 36).[103] Aliphatic carbonyl compounds with at least five carbon atoms (lower molecular weight compounds are too reactive) or aromatic aldehydes are found to be most suitable. Since the primary amines formed initially are potential substrates for reaction, further alkylation may occur giving secondary and tertiary amines.

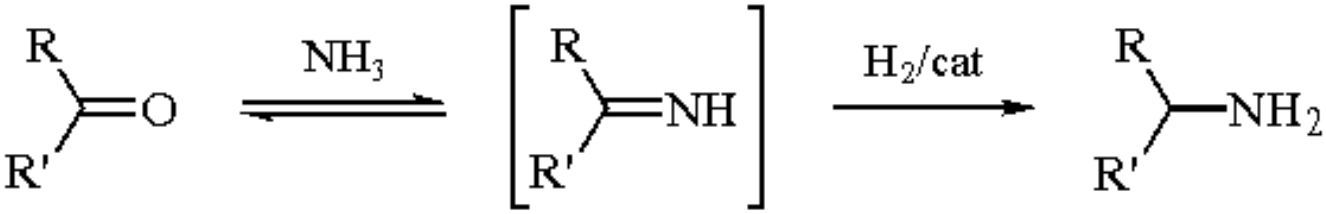

(36)

Treatment of aromatic aldehydes or aliphatic ketones, which are not soluble in water, with either NH_3/***Formic Acid*** or ***Ammonium Formate*** yields the corresponding primary amines (Leuckart reaction).[104]

Mannich Reaction.

The product mixtures from condensation reactions between ketones which possess at least one α-hydrogen atom, ***Formaldehyde***, and NH_3 are generally more complex than those obtained from the corresponding reactions in which the NH_3 is replaced by a secondary amine such as dimethylamine.[105] Thus acetophenone affords a mixture of the di- and triadducts rather than the expected β-amino ketone (Mannich base) (eq 37).[106] Mannich reactions involving dibenzyl ketones with formaldehyde and NH_3 in a relative molar ratio of 1:5:2 respectively give adamantane-like diaza ketones in good yields (eq 38).[107]

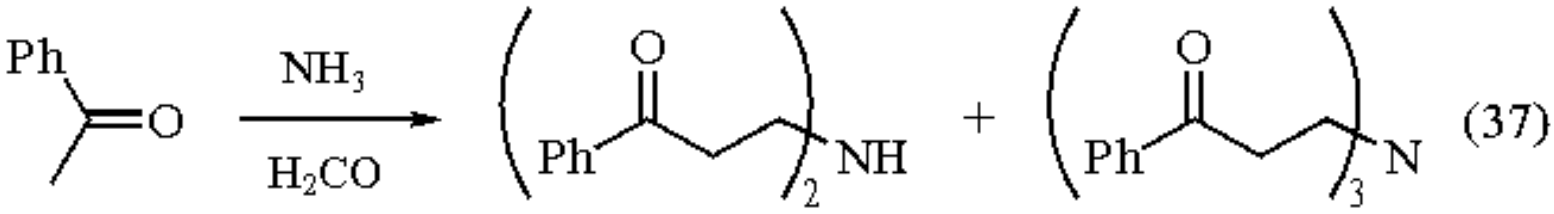

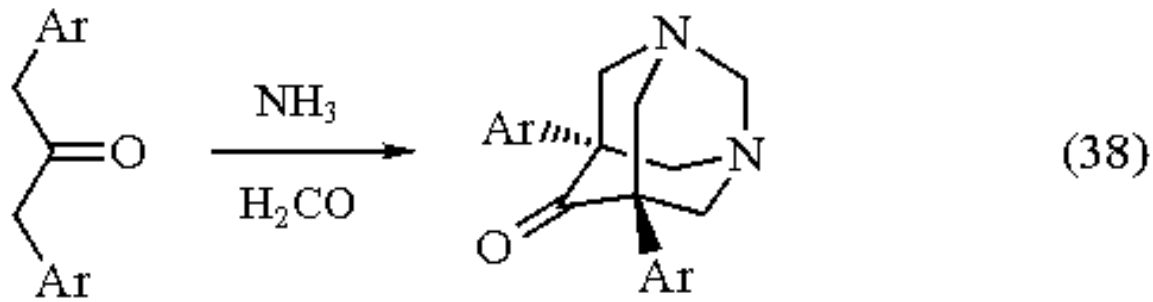

Strecker Synthesis of α-Amino Acids.

Aldehydes react with ***Hydrogen Cyanide*** in the presence of ammonia to yield an α-amino nitrile which on subsequent hydrolysis is converted to an α-amino acid (eq 39).[108] α-Substituted α-amino acids can be prepared from ketones.[109] α-Silyloxy nitriles offer an alternative route to the required intermediate amino nitriles (see eq 20).[54]

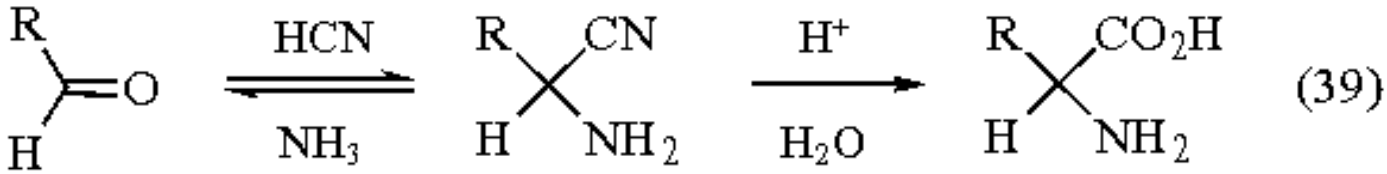

Willgerodt Reaction.

Heating mixtures of alkyl aryl ketones with ammonium polysulfide (or sulfur and dry NH_3) affords primary amides or the ammonium salts of the carboxylic acid (eq 40).[110] Side reactions become more pronounced as the chain length increases.

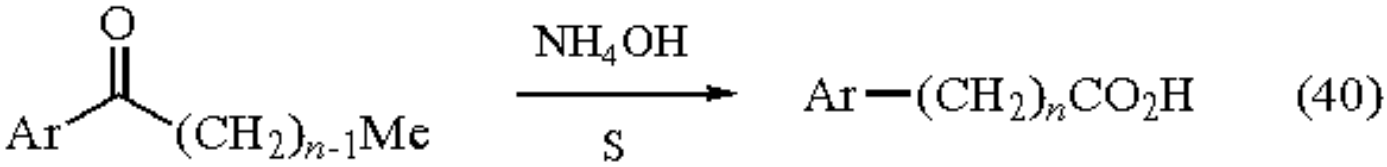

With acyclic and cyclic aliphatic ketones (2 equiv), sulfur, and NH_3, Δ^3-thiazoline derivatives can be obtained. In addition, treatment of methyl ketones, which can only be thiolated on the methyl group (e.g. acetophenone and pinacolone), with a large excess of sulfur (~eightfold) affords Δ^3-imidazoline-5-thiones.[111]

Nitriles.

Gas phase co-pyrolyses of (a) aliphatic mono- or dicarboxylic acids over silica gel at 500 °C[112] or (b) primary alcohols over a 15% Cu/alumina catalyst at 300 °C[113] with NH_3 afford mono- or dinitriles as appropriate in good yield.

Benzaldehydes are converted to the corresponding benzonitriles on treatment with NH_3 in the presence of either ***Iodine***[114] or ***Lead(IV) Acetate***.[115]

Miscellaneous Reactions Involving Ammonia.

Liq NH_3 is found to be a convenient medium and a mild base for the deprotection of FMOC-protected amino acids (eq 41).[116] Removal of N^{α}-benzyloxycarbonyl protecting groups for sulfur-containing peptides by Pd-catalyzed hydrogenolysis proceeds smoothly in liq NH_3 because poisoning of the catalyst is substantially diminished.[117]

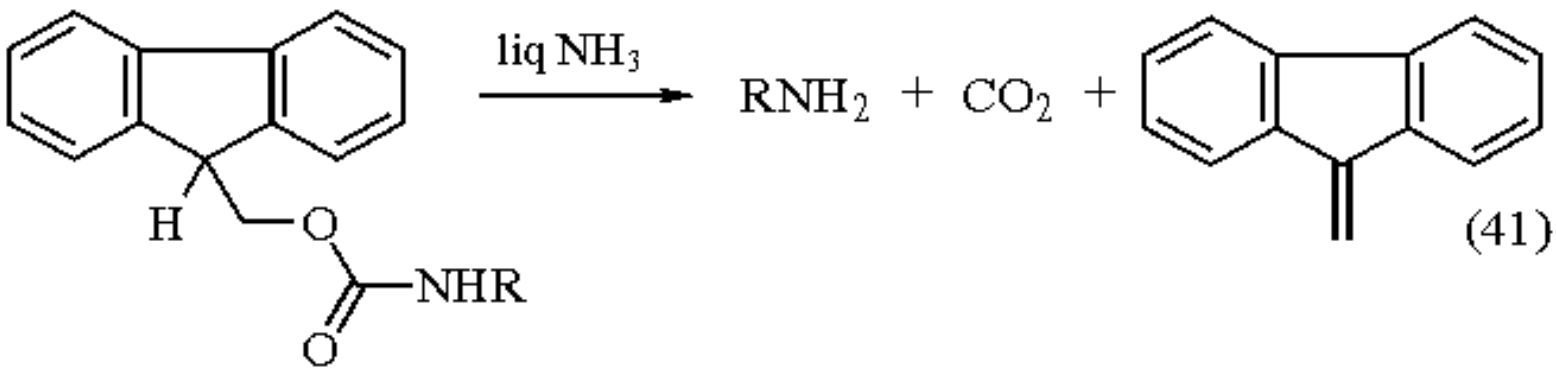

α-Acetyl-β-keto esters are readily deacylated on treatment with gaseous NH_3 in dry Et_2O (eq 42).[118]

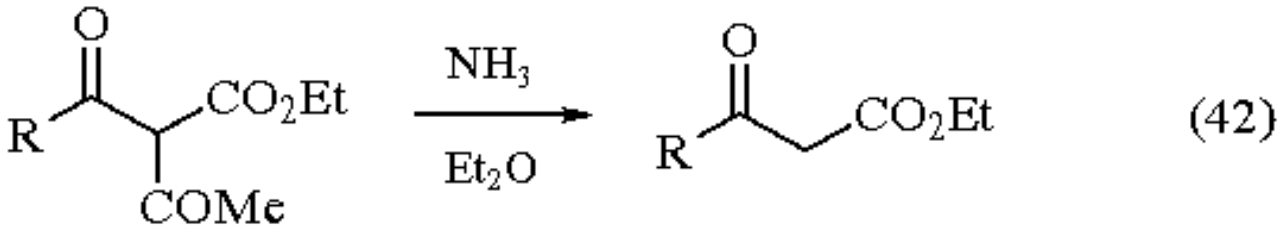

NH_3 is a participating solvent in ozonolysis reactions; ozonolyses of indene and indole in the presence of NH_3 afford isoquinoline and quinazoline, respectively.[119] Diamines are obtained in 50-60% yield from cyclic alkenes by a sequence involving ozonolysis in methanol and partial reduction of the resulting reaction mixture followed by catalytic hydrogenation over Rh or ***Raney Nickel*** at 200-400 psi/50 °C.[120]

The ***Borane-Ammonia*** complex, prepared in situ from NH_3 and diborane or available commercially, reduces carbonyl compounds rapidly; aldehydes are selectively reduced in the presence of aliphatic and aromatic acyclic ketones.[121] Moreover, the NH_3-BH_3 complex reacts faster than $NaBH_4$ with hindered ketones.

Ammonia in the Synthesis of Nitrogen-Containing Heterocycles.

Ammonia has been used extensively for the introduction of nitrogen atoms into heterocyclic ring systems. Space does not permit an adequate discussion of the various methods. For further details, see the general overview by Jeyaraman[1] and specialist monographs and reviews for systems such as pyridines,[6a,b] pyrroles,[6c,d] and diazines.[122]

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Ammonium Formate

HCO_2NH_4

[540-69-2] · CH_5NO_2 · Ammonium Formate · (MW 63.06)

(used as a source of ammonia;[1] a hydrogen source for catalytic transfer hydrogenation reactions;[2,7-9,10-13,17,18] hydrogenolysis of functional groups[3-6,8,14,15,19,20])

Physical Data: mp 119-121 °C; *d* 1.27 g cm^{-3}.

Solubility: sol water, alcohols.

Form Supplied in: crystalline solid.

Analysis of Reagent Purity: base titration.

Handling, Storage, and Precautions: hygroscopic.

Source of Ammonia.

Ammonium formate can be used as a source of nonvolatile ammonia (eq 1),[1] but much of its use is as a hydrogen transfer agent in conjunction with heterogeneous or homogeneous catalysts.[2]

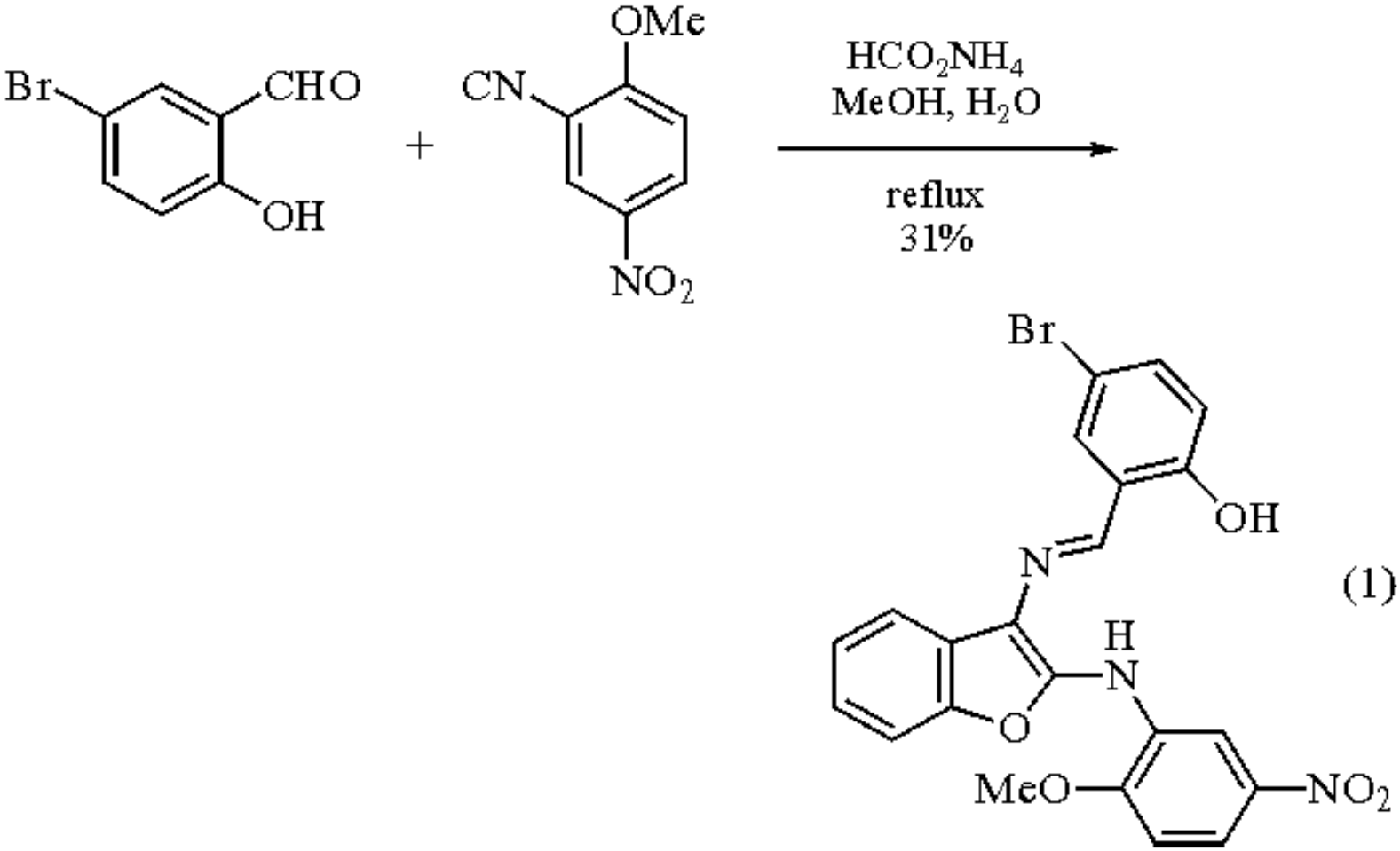

Hydrogenations.

Catalytic transfer hydrogenation of *N*-benzyl protecting groups using 10% ***Palladium on Carbon*** as the catalyst and ammonium formate as the hydrogen source generally gives primary and secondary amines in excellent yields.[3] In the case of 1-benzyl-2,3-dihydroindoles, the one-pot dehydrodebenzylation gave indoles as the major products along with minor amounts of *N*-benzylindoles (eq 2).[4]

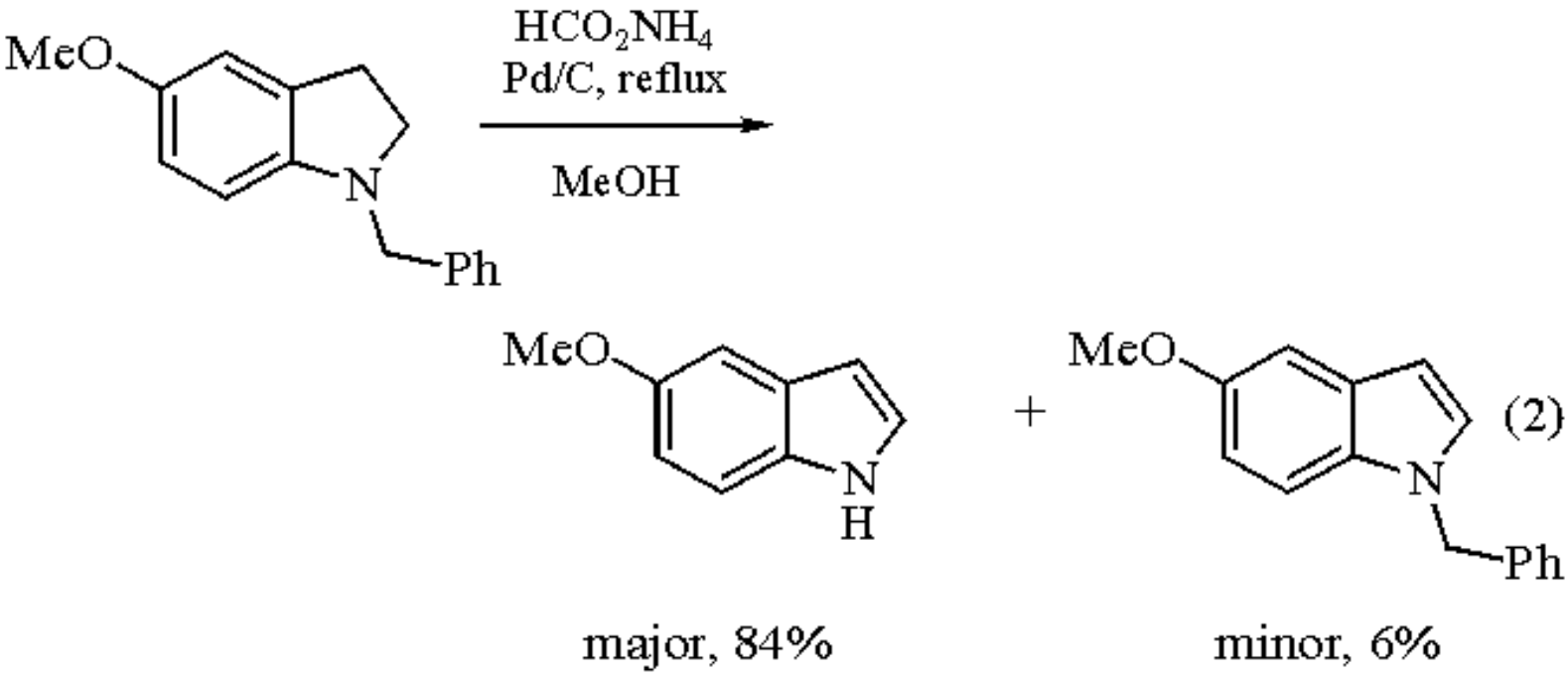

Regioselective stepwise debenzylation of 1,3-dibenzyluracils was observed with this catalytic transfer hydrogenation system (eq 3). Functional groups such as esters, alcohols, nonbenzylic ketones or ethers, carboxylic acids, amides, acetals, and nitriles are stable under the reaction conditions.[5]

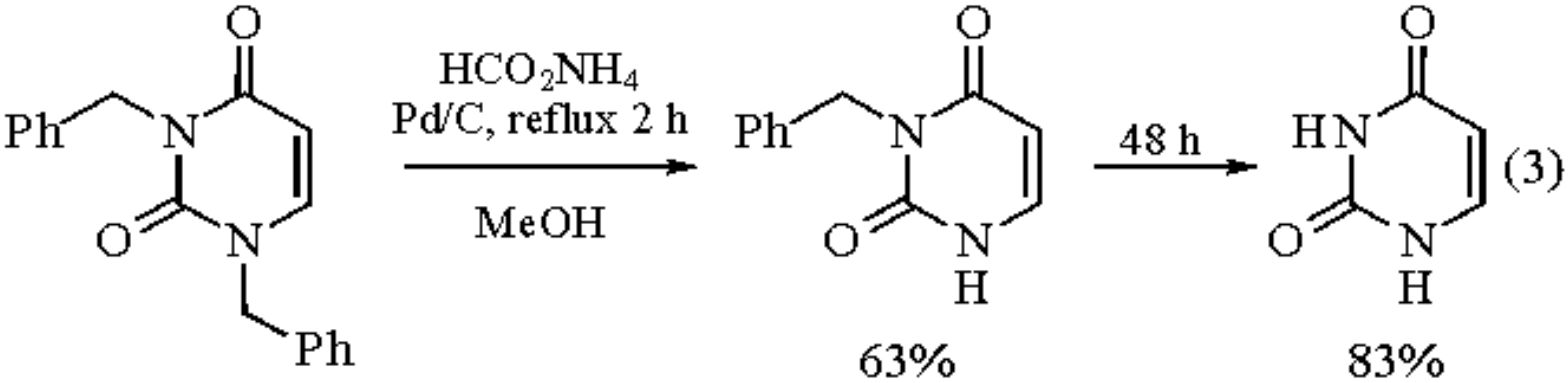

Interestingly, even *N*-((β-phenylethyl)oxy)carbonyl and 2-phenylethyl benzoates can be deblocked with ammonium formate in the presence of 10% Pd/C or ***Palladium(II) Acetate***.[6]

Aryl ketones are selectively reduced to the secondary alcohols or to the hydrocarbons by careful selection of the reaction temperature and solvent. The alcohol is formed in MeOH at rt[7] and the hydrogenolysis product is produced at 110 °C in acetic acid. Diaryl ketones also provided diarylmethanes under the latter reaction conditions.[8] ***Raney Nickel*** can also participate in the catalytic transfer hydrogenation reaction. The combination of Raney nickel and ammonium formate reduces aryl alkyl ketones to alcohols at rt in >90% yield.[9]

Nitro groups are readily reduced to amines. Alkyl nitro compounds are reduced to the amines with retention of configuration.[10] Certain appropriately substituted nitro compounds do not give amines under the reaction conditions. α,β-Unsaturated nitroalkenes gave oximes (eq 4),[11] γ-nitro ketones gave cyclic nitrones (eq 5),[12] and 2-nitro-β-nitrostyrenes gave indoles (eq 6).[13]

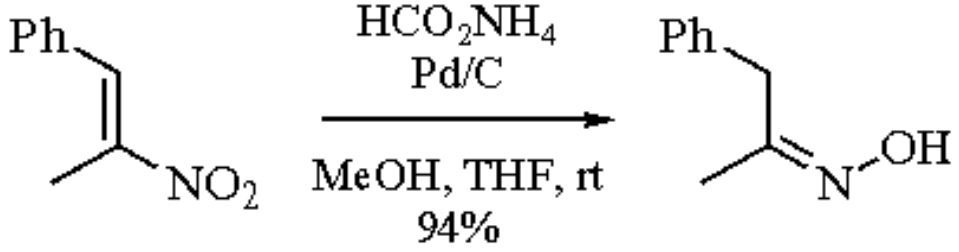

(4)

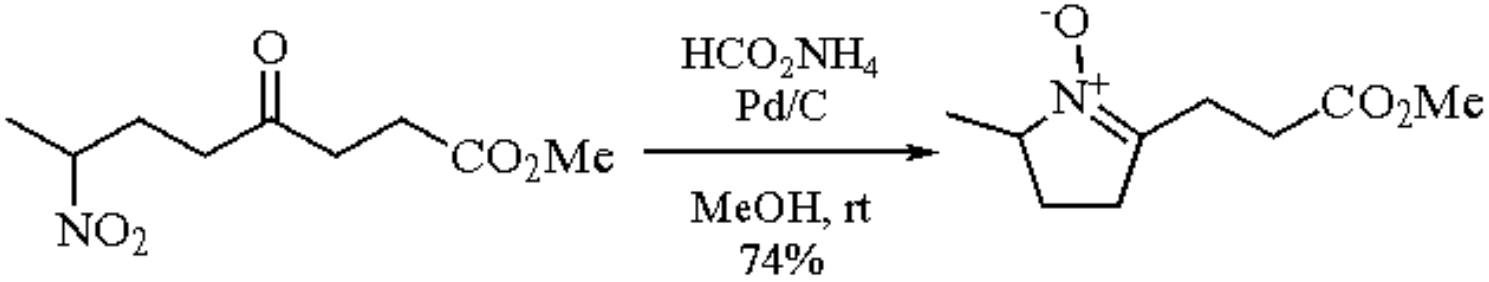

(5)

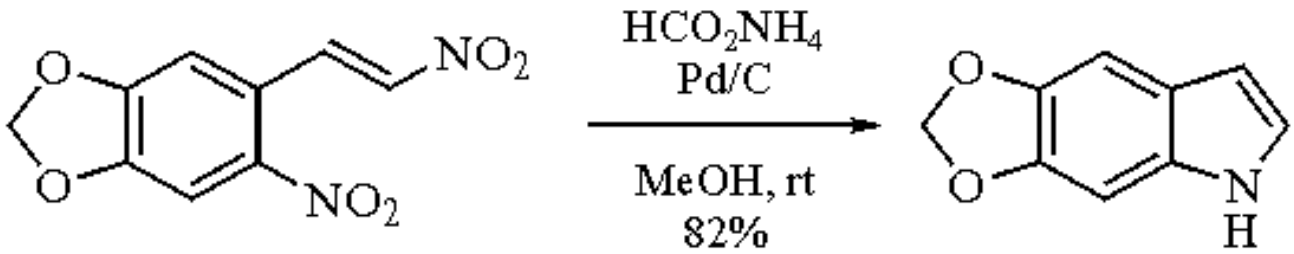

(6)

Azides and pyridine *N*-oxides are reduced to amines[14] and pyridines,[15] respectively, with this reaction system. Allyl β-keto carboxylates are decarboxylated to form ketones and propene.[16] Alk-2-ynyl carbonates are hydrogenolyzed to 1,2-dienes (allenes).[17]

Selective reduction of quinoline, isoquinoline, and acridine at the nitrogen containing ring has been reported.[18] Concomitant dehalogenation was also observed with chlorinated isoquin-olines.

Hydrogenolysis of allylic compounds such as esters, nitro compounds, halides, phenyl ethers, carbonates, and vinyl epoxides has provided alkenic products.[19] The reactions required the use of homogeneous Pd catalysts. Use of ***Tri-n-butylphosphine*** as ligand gave excellent selectivity to 1-alkenes. More 2-alkenes were formed (up to 66% in one case) when triarylphosphines or trialkyl phosphites were used.[20]

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Ammonium Peroxydisulfate

$(NH_4)_2S_2O_8$

$(NH_4)_2S_2O_8$

[7727-54-0] · $H_8N_2O_8S_2$ · Ammonium Peroxydisulfate · (MW 228.20) $K_2S_2O_8$

[7727-21-1] · $K_2O_8S_2$ · Potassium Peroxydisulfate · (MW 270.32) $Na_2S_2O_8$

[7775-27-1] · $Na_2O_8S_2$ · Sodium Peroxydisulfate · (MW 238.11)

(oxidizing agent for many functional groups;[1] phenols form *p*-hydroxysulfate ester salts (Elbs oxidation), while arylamines give the *o*-aminosulfate esters (Boyland-Sims oxidation)[1m])

Physical Data: E° = -1.92, -1.94 V.[2]

Solubility: sol water, 20 °C: ammonium salt, 2.5 M; potassium salt, 0.17 M; sodium salt, 2.3 M; reasonable solubility in aqueous mixtures with acetonitrile, the lower alcohols, and acetone. Quaternary ammonium salts of peroxydisulfate show much greater solubility in organic solvents.[3]

Form Supplied in: the three salts are commercially available as colorless crystalline solids.

Analysis of Reagent Purity: the commercial materials are typically 98-99% pure and may be analyzed by standard iodometric techniques.

Handling, Storage, and Precautions: the sodium and potassium salts are very stable as dry solids, the ammonium salt less so.[4] Aqueous solutions undergo slow decomposition even at rt.[4] Cases of asthma and skin rashes have been reported among constant users such as hairdressers and industrial workers.

Introduction.

Peroxydisulfate ions are capable of oxidizing virtually all functional groups, even hydrocarbons.[5,6] Mechanistic studies have shown that there are two fundamentally different ways in which this species reacts. At low temperatures (25 °C) and in the absence of catalysts, its reactions are fast only with strong nucleophiles (phenolate ions, amines) and these proceed by simple polar mechanisms. Many other functional groups react so slowly under these conditions as to be essentially inert. At higher temperatures and/or in the presence of catalysts, rapid radical reactions ensue involving the species SO_4^-, the sulfate ion radical. Selectivity can usually be achieved even for this powerful oxidant by careful control of conditions. Peroxydisulfate may be used as a convenient source of peroxymonosulfate, via low-

temperature acid-catalyzed hydrolysis, for use in processes such as the Baeyer-Villiger reaction.[7] The use of the term persulfate should be avoided as it may be confused with peroxymonosulfate (Caro's acid; see ***Monoperoxysulfuric Acid***).

Oxidation of Hydrocarbons.

Conditions for the oxidation of toluene and substituted toluenes can be adjusted, principally by variation in the catalyst (Fe^{II}, Ag^{I}, Cu^{II}) to yield benzaldehyde,[8-11] benzyl acetate,[10,12-14] or benzyl bromide.[12] Benzoic acids and bibenzyls are also formed.[8] Regioselectivity in the oxidation of substituted xylenes has been achieved.[15] Hexamethylbenzene and durene, among others, are converted in 70-90% yield to the corresponding benzyl alcohols via the benzyl nitrates.[16] In the presence of acetates, substituted benzenes and naphthalene are acetoxylated,[17,18] and conditions have been found for conversion of naphthalene to either 1-acetoxynaphthalene or α-(hydroxymethyl)naphthalene acetate.[19] Benzene, fluorobenzene, and anisole may be hydroxylated.[20,21] Quinones are formed from anthracenes, naphthalene, and phenanthrene.[22,23] 9-Methylanthracene gives lepidopterene in good yield (eq 1).[24] Isopropylbenzene reacts with acetate in the presence of Fe^{II} (eq 2).[25]

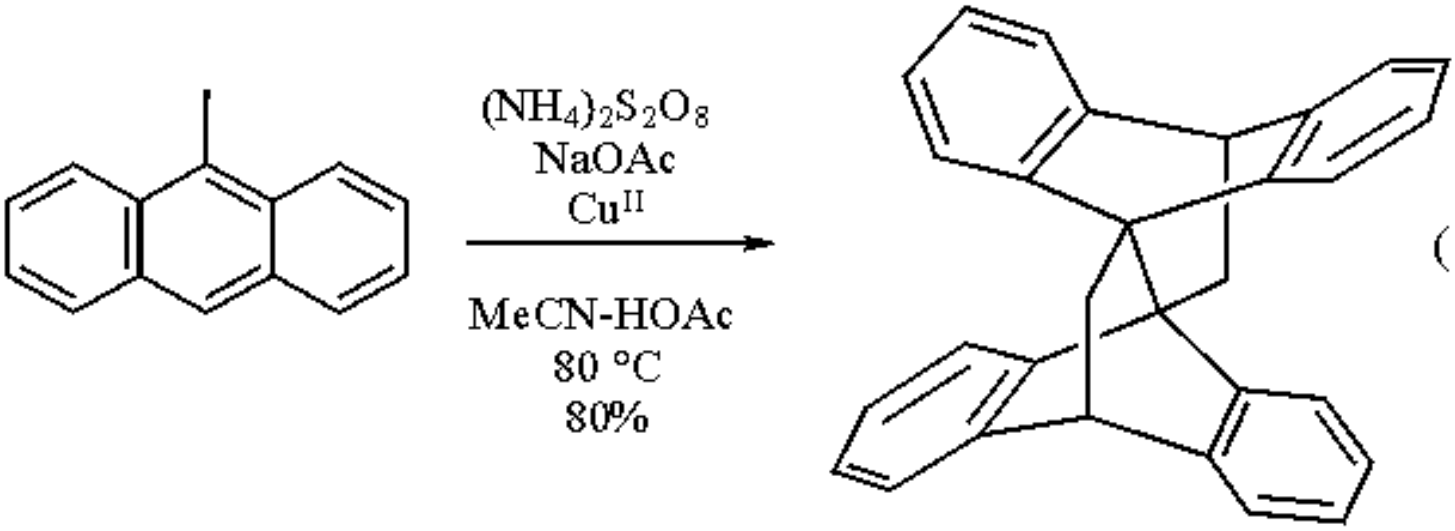

(1)

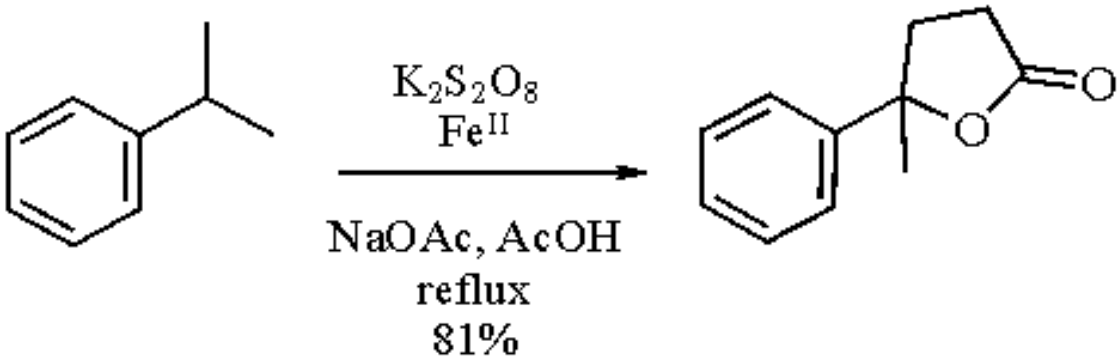

(2)

Oxidation of Alkenes.

Glycol diacetates are produced when alkenes and acetates are treated with peroxydisulfate at 60-80 °C in the presence of Cu^{II} or Fe^{II}, sometimes with good stereocontrol.[26-28] Perfluorochlorocarbons add to alkenes at a lower temperature

in the presence of sodium formate (eq 3).[29] A steroidal alkene is oxidized to a ketone (eq 4).[30] Cyclohexene reacts with peroxydisulfate in acetonitrile-water at 60 °C to yield primarily cyclohexanol with a Ag^{I} or Fe^{II} catalyst, but forms cyclopentanecarbaldehyde or the carboxylic acid in the presence of Cu^{II}.[31,32] Alkenes are methoxyselenated by reaction with ***Diphenyl Diselenide*** and peroxydisulfate in methanol,[33] and certain alkenes undergo ring closure initiated by oxidation of diphenyl diselenide (eq 5), where X is an internal nucleophile.[34] Similar reactions have been observed for one disulfide (bis(4-methoxyphenyl) disulfide).[35] Quinolines, among other electrophiles, trap the radicals produced from alkenes to form adducts at either the 2- or 4-position.[31,36] The etheno bridge of 1,N^6-ethenoadenosine is smoothly removed by treatment with peroxydisulfate at pH 7 and 60 °C (eq 6).[37] In the absence of metal ions, under aqueous acidic conditions, peroxydisulfate is hydrolyzed to Caro's acid,[4] which then reacts with alkenes to yield *trans*-glycols.[38]

$$Cl(CF_2)_{7,8}R' + H_2C{=}CHR \xrightarrow[\text{DMF, 40 °C, 52-87\%}]{(NH_4)_2S_2O_8,\ HCO_2Na} R'(CF_2)_{7,8}CH_2CH_2R \quad (3)$$

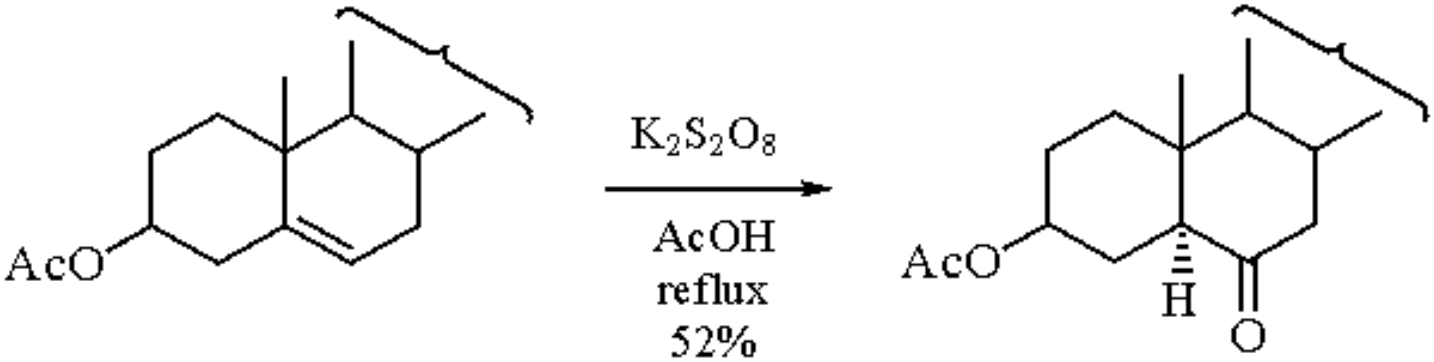

(4)

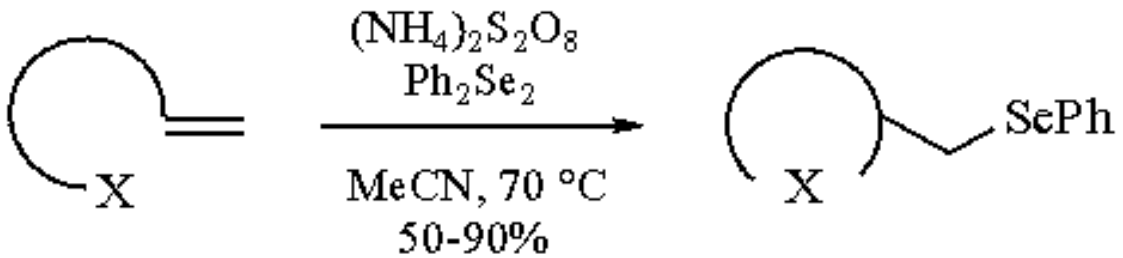

(5)

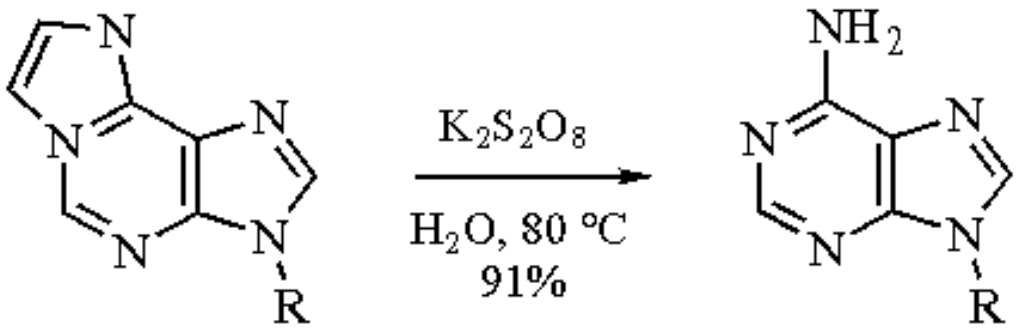

(6)

Oxidation of Alcohols.

Simple primary and secondary alcohols are quantitatively oxidized by peroxydisulfate to the corresponding aldehydes and ketones at 60-80 °C in the absence of catalysts. See also ***Dimethyl Sulfoxide***, ***Dipyridine Chromium(VI) Oxide***, ***Pyridinium Chlorochromate***, ***Pyridinium Dichromate***, ***Tetra-n-propylammonium Perruthenate***, ***Cerium(IV) Ammonium Nitrate***, ***Sodium Dichromate***, ***Silver(I) Carbonate***, ***Nitric Acid***, ***Copper(I) Chloride-Oxygen***, ***Lead(IV) Acetate***, ***Nickel(II) Bromide***, ***Chromium(VI) Oxide***, ***Iodosylbenzene***, and ***Sodium Hypochlorite***. While it is possible to oxidize aldehydes to the corresponding carboxylic acids, this step is relatively slow and, in fact, the aldehyde acts as an inhibitor of further oxidation.[39] Benzyl alcohols (and benzylamines) also give aldehydes under the same conditions,[40] but, in the presence of Ni^{II} and ammonia at room temperature, the benzyl alcohols form the corresponding nitriles in excellent yield.[41] Allylic alcohols can be smoothly converted to the corresponding carbonyl compounds without oxidation of the alkenic bonds by reaction in the presence of a Ni^{II} catalyst, but without ammonia.[42] In the oxidation of a series of substituted 2-phenylethanols, the corresponding bibenzyls were obtained as well as the carbonyl compounds.[43] The intermediate alkoxyl radicals can be trapped by methylquinolines (eq 7),[44] by 4-cyanopyridine,[45] or by *N*-methoxypyridinium fluoroborates.[46] 3-Phenylpropanol cyclizes to a tetrahydrofuran upon reaction with peroxydisulfate in the presence of Cu^{II} (eq 8).[47] Geminal hydroxynitriles undergo rearrangement (eq 9)[48] and a variety of *vic*-glycols are oxidized to the dicarbonyl compounds with Ag^{I} catalysis at moderate temperatures. Both *cis*- and *trans*-glycols react at about the same rate.[49,50]

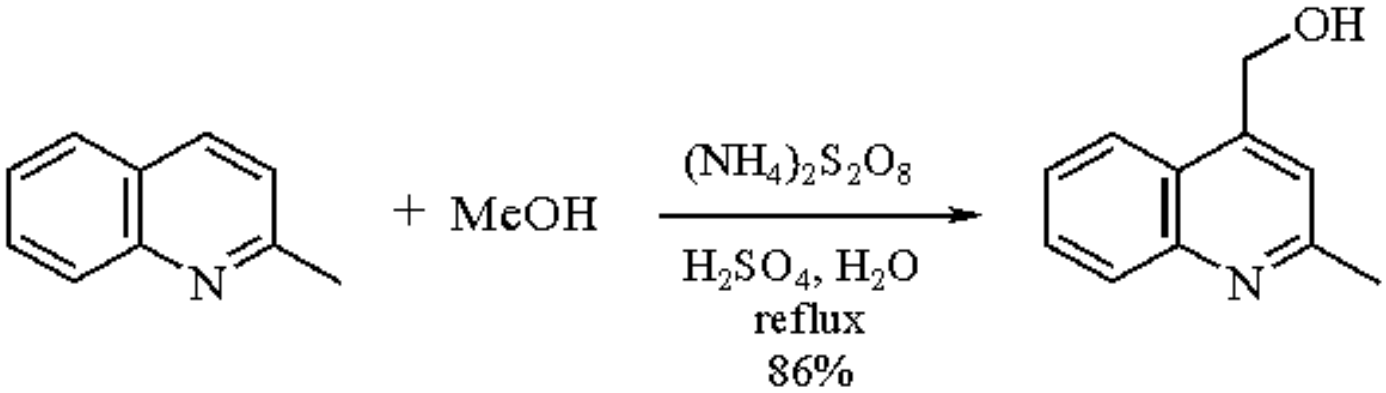

(7)

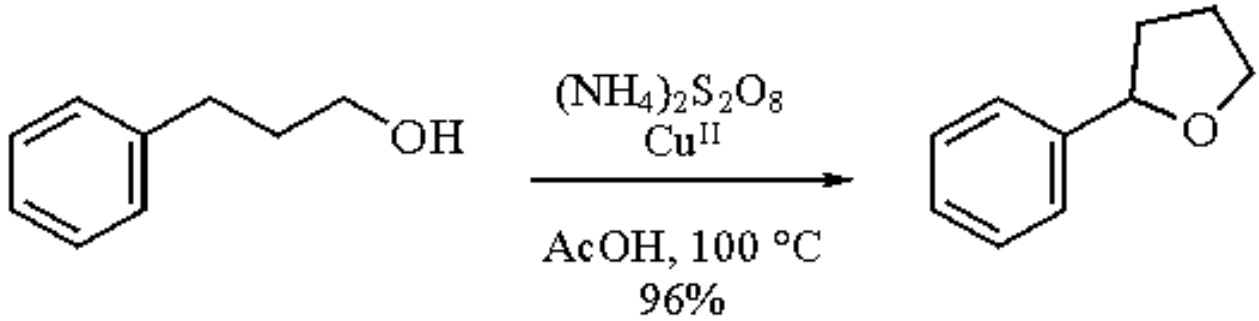

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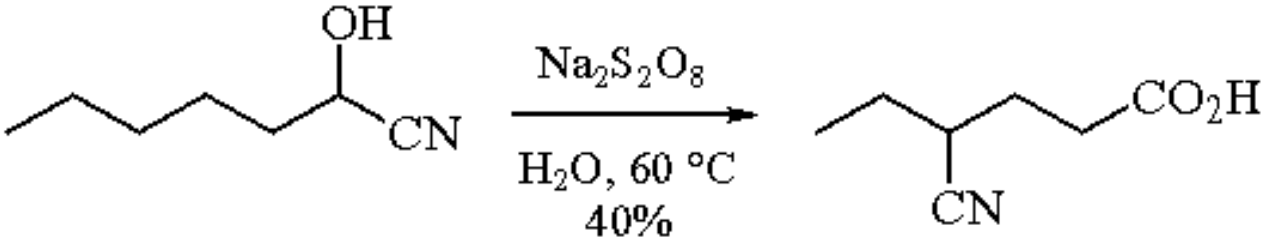

(9)

Oxidation of Ethers.

Ethyl ether undergoes conversion in 60-85% yield to acetaldehyde at 60 °C in water, whereas THF and *p*-dioxane give vinyl ethers.[51] See also ***Ruthenium(VIII) Oxide***. 2,5-Diphenylfuran similarly gives a quantitative yield of *cis*-1,2-dibenzoylethylene (eq 10).[52] The radical from *p*-dioxane, in addition to forming the vinyl ether, may be trapped by 4-methylquinoline.[53]

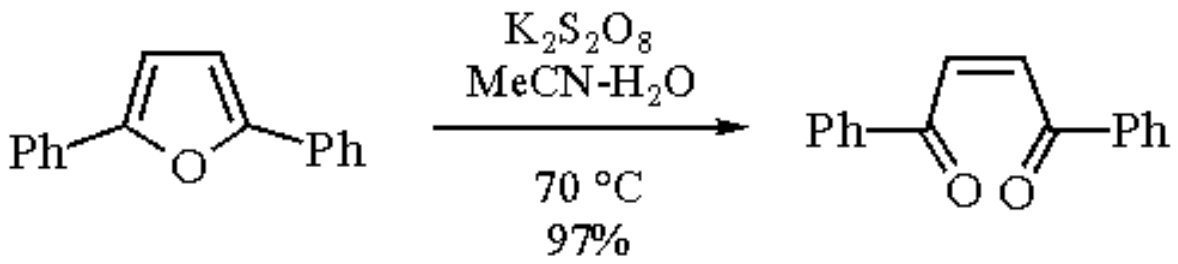

(10)

Oxidation of Aldehydes and Ketones.

Neither aldehydes nor ketones react rapidly with peroxydisulfate, except in the presence of a metal ion catalyst such as Ag^{I}. Aldehydes are oxidized to the corresponding carboxylic acids. Ketones form the carboxylic acids resulting from cleavage on either side of the carbonyl group.[54] Thus benzaldehyde is converted in about 60% yield to benzoic acid using Ag^{I} in water at 45 °C.[55] Other reactions occur with suitable radical traps. The γ-nitriles are formed in good yield in the presence of ***Sodium Cyanide*** (eq 11).[56] Similarly, acyl radicals may be trapped by quinolines[57] or alkenes[58] to form adducts in good yields.

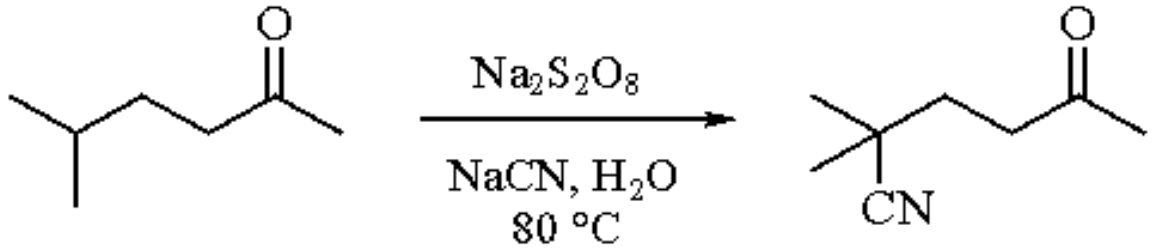

(11)

Oxidation of Aliphatic Amines.

Aliphatic amines are converted in reasonable yield to the corresponding aldimines (eq 12),[59] while the corresponding amino acids form aldehydes (eq 13).[60] Benzylamine forms the aldimine in the absence of catalyst in 67% yield, but in the presence of Ni^{II}, benzonitrile is formed in 84-97% yield.[61,62] This dehydrogenation of primary amines to the nitrile appears to be a general reaction. See also ***Lead(IV) Acetate***, ***Nickel(II) Peroxide***, ***Sodium Hypochlorite Copper(I) Chloride-Oxygen***. Nitriles as well as other products are formed from primary amines using a Cu^{II} catalyst.[63] Secondary amines yield a variety of products, generally in poor yield,[60,64] but piperidines give good yields (40-60%) of 1,1-bipiperidines.[65]

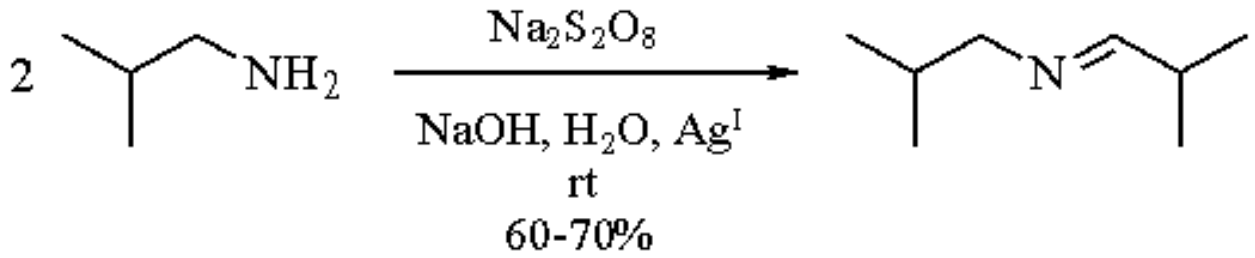

(12)

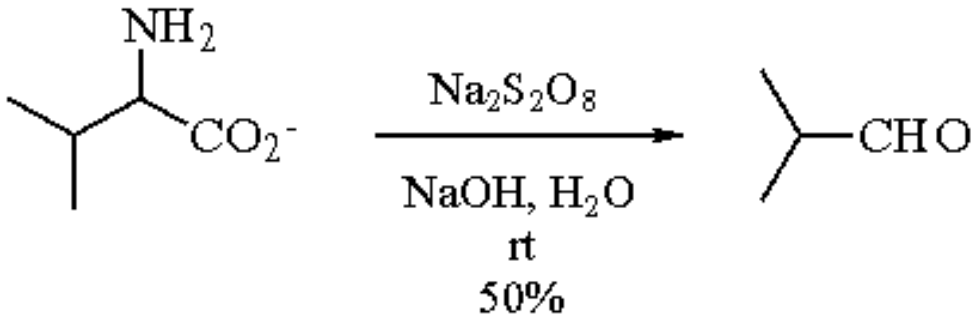

(13)

Transformation of Carboxylic Acids to Peroxy Acids and Decarboxylation.

Carboxylic acids are converted (80-90% yield) to the corresponding peroxy acids at room temperature under phase-transfer conditions.[66] See also ***Hydrogen Peroxide***. With Ag^{I} catalysis at 60 °C the acids are decarboxylated, whereas with both Ag^{I} and Cu^{II} the main products are the alkenes and the alcohols.[67,68] Under other conditions (Ti^{III}), coupling products predominate, as found long ago by Fichter.[69,70] Alkanoic acids with favorable alkyl substituents yield δ- and γ-lactones.[71] Lactones can also be formed from certain aromatic systems (eq 14).[72,73] The radicals formed during decarboxylation can be trapped by quinolines, pyridines, or quinones.[74-77]

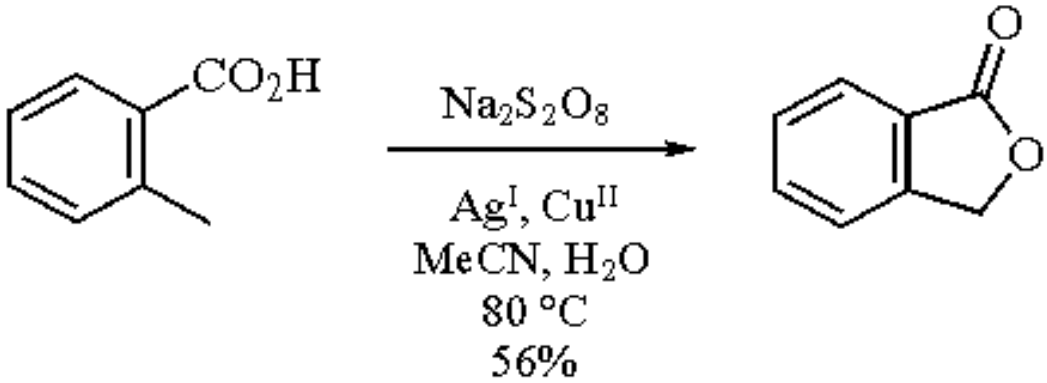

(14)

Transformations of Amides.

Secondary and tertiary amides are dealkylated to the primary amides at 90 °C (eq 15),[78,79] but 2-pyrrolidinone is oxidized under the same conditions to succinimide in 61% yield.[80] Alkanesulfonamides undergo oxidation at the γ-carbon (eq 16).[81] Biphenyls with *ortho*-substituted secondary amide groups can give a variety of cyclization products (eq 17).[82,83] N-Boc L-tyrosine derivatives, when treated with peroxydisulfate and Cu^{II}, yield the *threo*-β-hydroxy derivative via a cyclic carbamate (eq 18).[84] The scope of this synthesis has been extended to related compounds.[85]

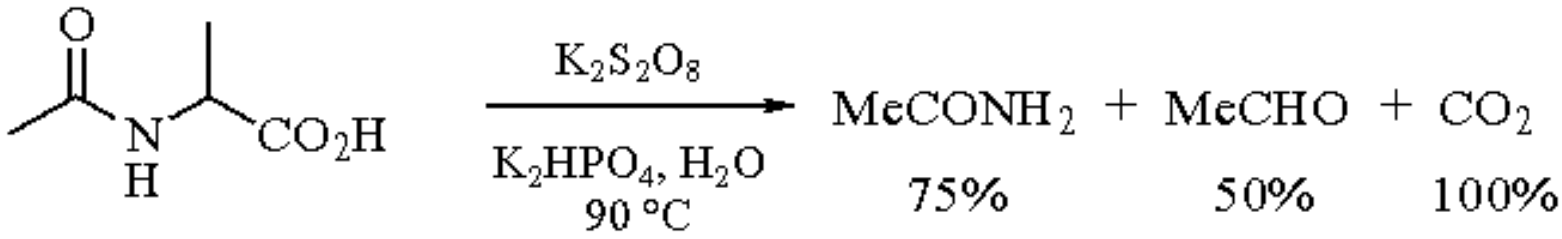
O
N
H
CO2H
K2S2O8
K2HPO4, H2O
90 °C
MeCONH2 + MeCHO + CO2
75%
50%
100%

(15)

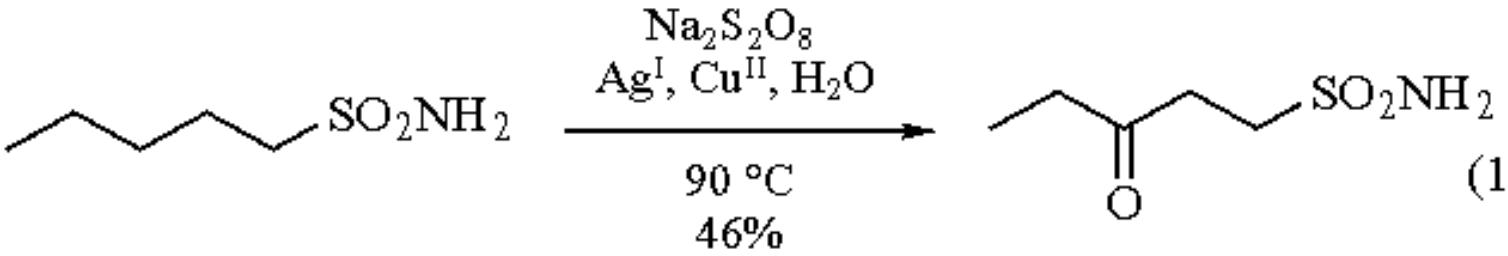
SO2NH2
Na2S2O8
AgI, CuII, H2O
90 °C
46%
SO2NH2
O

(16)

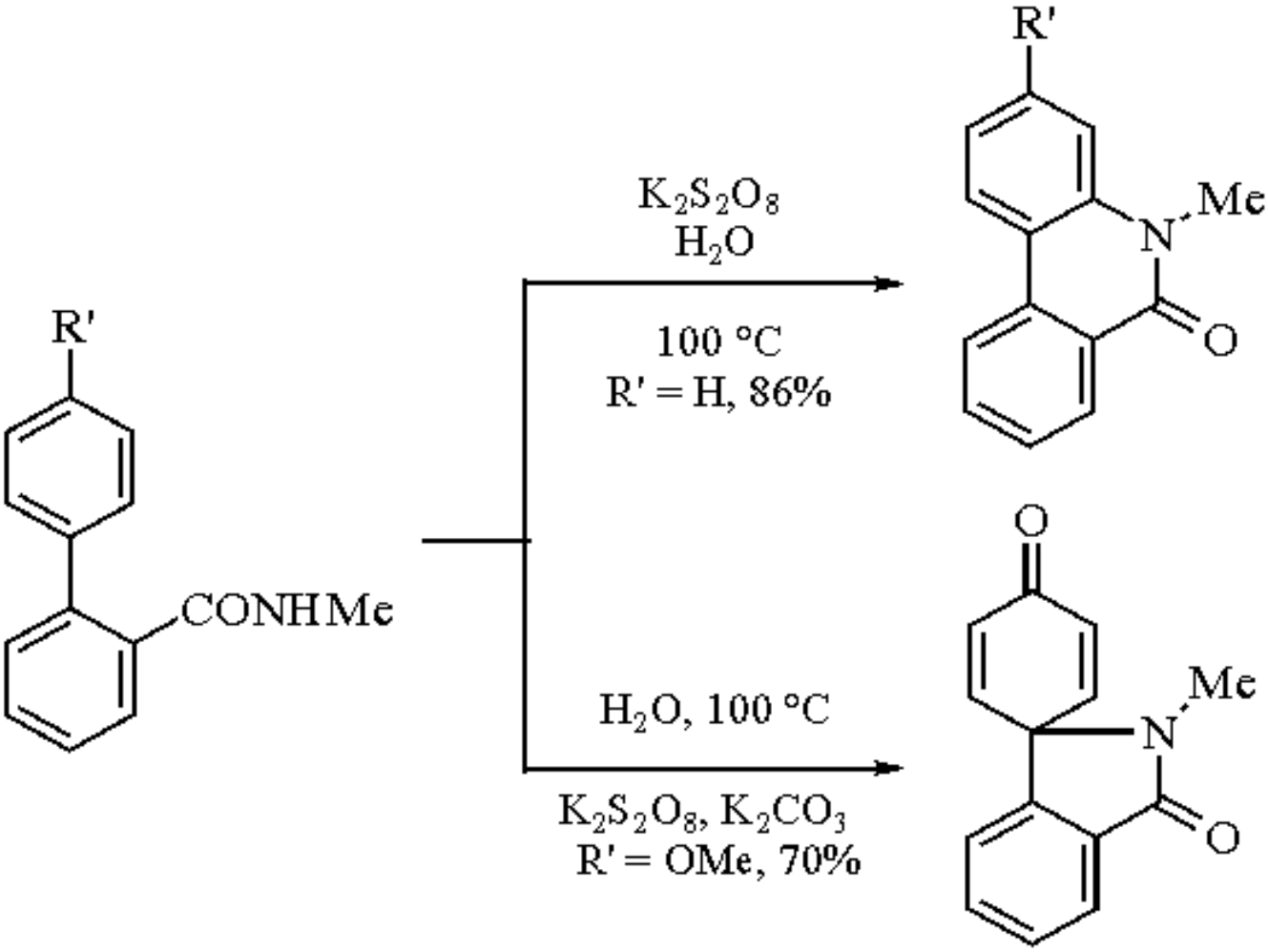
R'
CONHMe
K2S2O8
H2O
100 °C
R' = H, 86%
R'
N
Me
O
H2O, 100 °C
K2S2O8, K2CO3
R' = OMe, 70%
O
N
Me
O

(17)

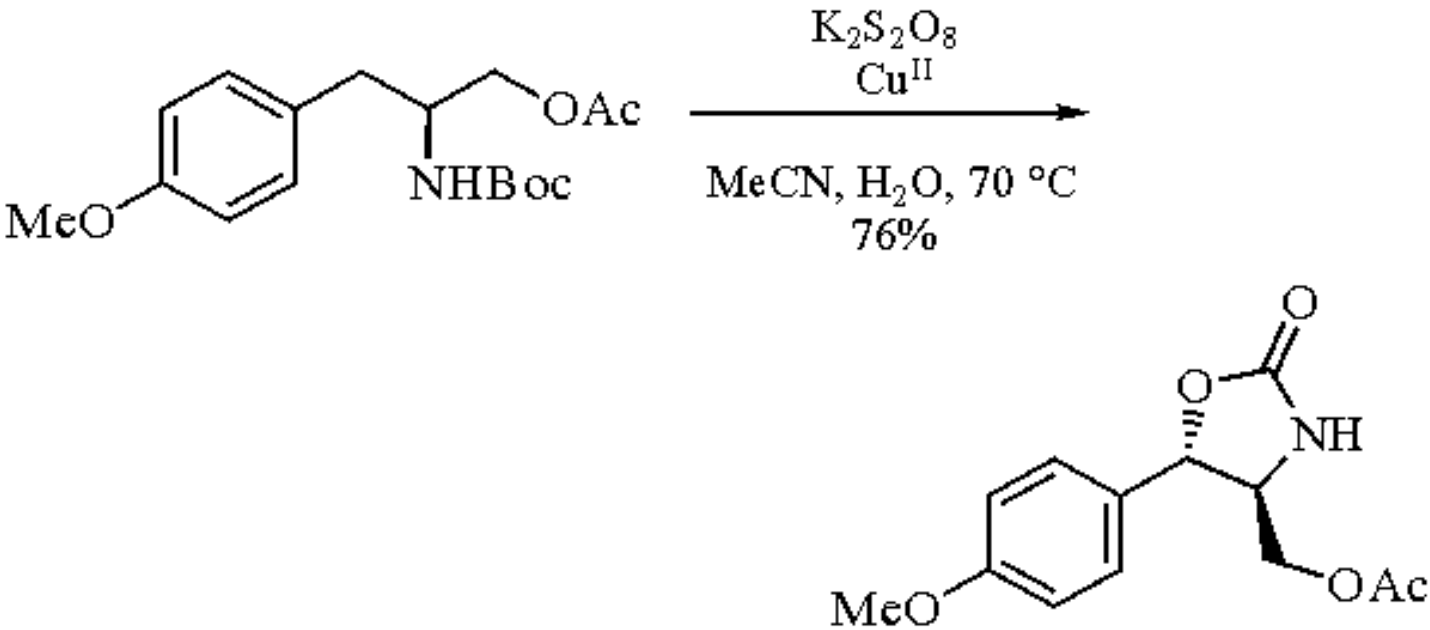

(18)

Oxidation of Phenols to Hydroquinones and of Aryl Amines to Aminophenols.

These phenols and arylamines undergo similar reactions in alkaline aqueous solution at rt in the absence of catalysts (the Elbs and Boyland-Sims oxidations) (eqs 19 and 20). The sulfate esters can be hydrolyzed to the corresponding phenols in acid. These reactions have been reviewed.[1m] The *ortho-para* distribution in the amine oxidation has been examined recently.[86] The sulfate esters from the amine oxidation are accompanied by varying amounts of coupling products, which predominate in acid solution (see Table F in Behrman[1m]).

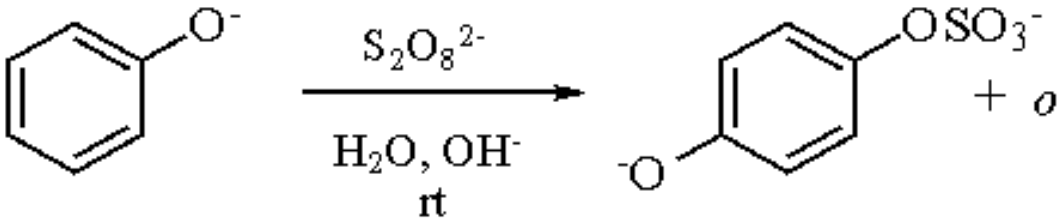

+ *o*-isomer (minor) (19)

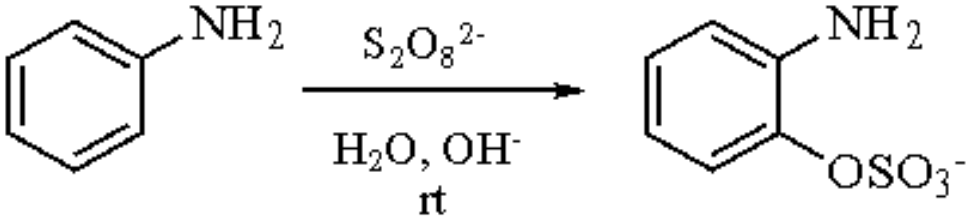

+ *p*-isomer (minor) (20)

Oxidation of Sulfur Compounds.

Peroxydisulfate converts thiols to disulfides,[87] sulfides to sulfoxides,[88] and sulfoxides to sulfones.[89] This last reaction, however, is very slow so that excellent yields of the sulfoxides are available from the sulfides. See also ***Hydrogen Peroxide***, ***Sodium Periodate***, ***t-Butyl Hypochlorite***, ***Calcium Hypochlorite***, ***Sodium Hypochlorite***, ***Sodium Chlorite***, ***Dimethyldioxirane***, ***Nitric Acid***, ***Sodium Perborate***, and peroxy acids.

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Ammonium Sulfide

$(NH_4)_2S$

[12135-76-1] · H_8N_2S · Ammonium Sulfide · (MW 68.14)

(redox agent for alkyl and carbonyl groups in the Willgerodt reaction;[1] reducing agent for nitro functional group;[6] sulfuration agent for many types of functional groups[13])

Physical Data: forms crystals (colorless needles) below -18 °C; decomposes into NH_4SH, NH_3, and ammonium polysulfides at high temperature.

Solubility: sol cold water, ethanol, liquid ammonia; reacts with water to give NH_4SH and NH_4OH.

Form Supplied in: the solution in water (20 wt %) is called ammonium sulfide solution - red and contains about 30% $(NH_4)_2S$, whereas ammonium sulfide - yellow contains 16-20% $(NH_4)_2S$.

Handling, Storage, and Precautions: decomposes into ammonia and ammonium polysulfide in air under light (sunlight); the solution of ammonium sulfide in water is strongly alkaline; keep container tightly closed and in a cool place; odor of NH_3 and H_2S.

Reduction of Carbonyl Functional Groups.

Towards the end of the 19th century, ammonium polysulfide (which usually contains ammonium sulfide) was found to react with aryl alkyl ketones as a redox agent, reducing carbonyls to methylene groups and oxidizing terminal alkyls to carbonyl groups to form the corresponding amides.[1] This reaction is the Willgerodt reaction and has been proposed as a convenient method for the synthesis of amides from ketones, as shown in eq 1.

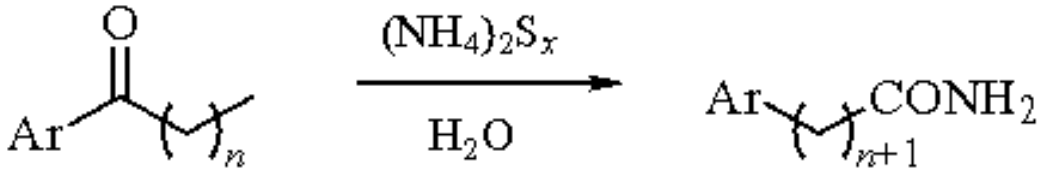

(1)

Similarly, ammonium sulfide has been widely employed to produce various amides and acids, by acting as a redox agent for many types of compounds; for example, aryl alkyl ketones give the corresponding aryl-substituted amides, with yields according to the substituent, as shown in eq 2.[2] Furthermore, unsaturated carboxylic acids (eq 3),[3] aldehydes (eq 4),[4] carbinols,[5] thiols,[9] amines,[6] alkylbenzenes (eq 5),[7] and alkyl halides (eq 6)[7,8] were also found to

react with ammonium sulfide to give the corresponding amides.

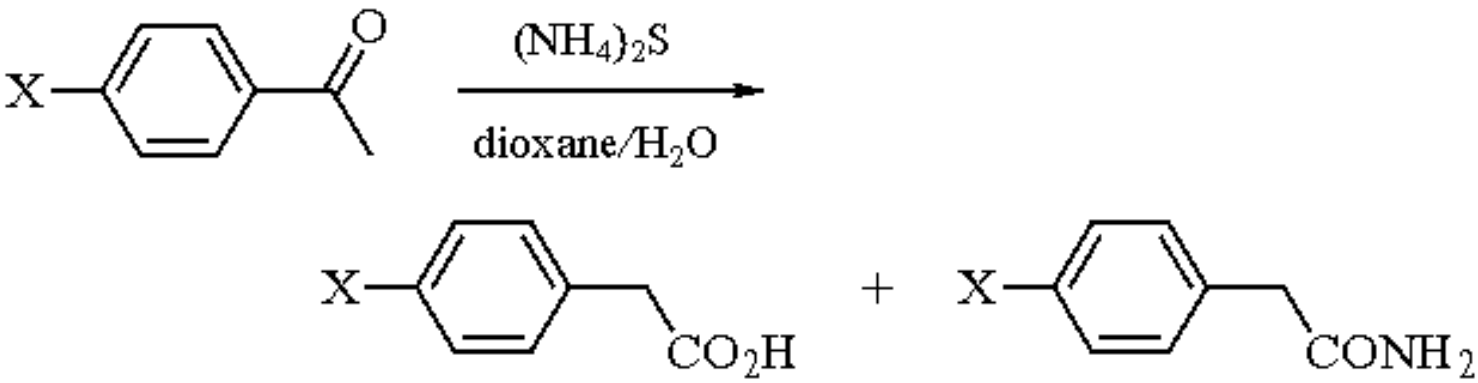

(2)

Yield: X: H > Me > Cl > MeO > I > OH

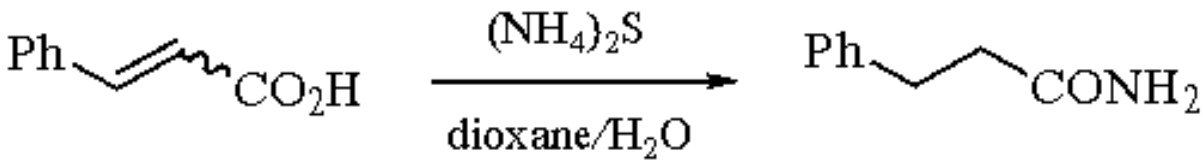

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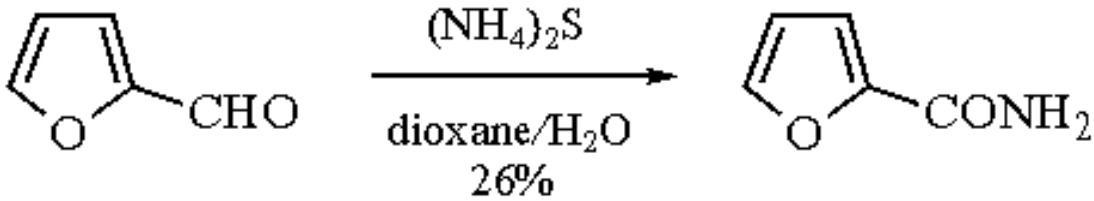

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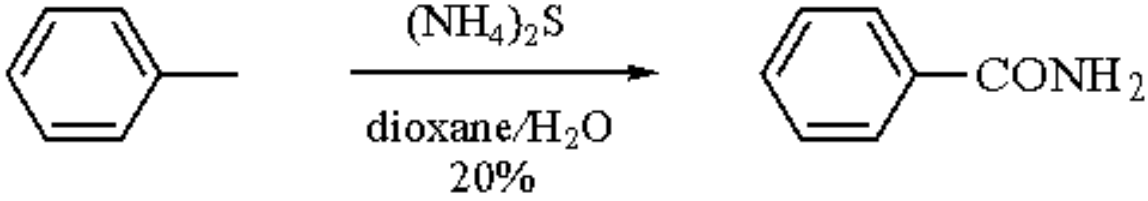

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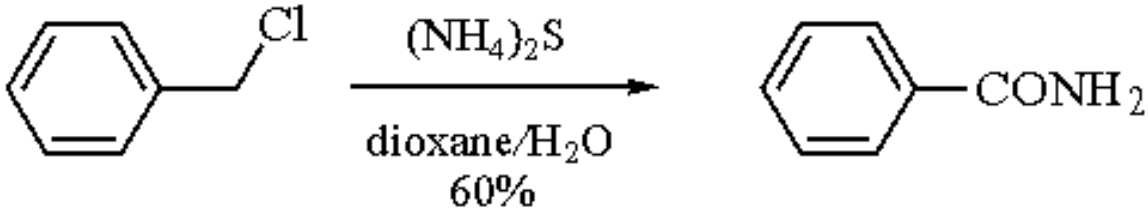

(6)

Interestingly, Cerwonka et al. reported a ^{14}C-tracer (C*) study showing that the two terminal methyl groups are oxidized to carbonyl groups to give two products and that a short carbon chain is more reactive than a long chain in the molecule (eq 7).[9] Although there have been many reports on the Willgerodt reaction and some reaction mechanisms have been proposed, the exact mechanism is not yet clear.

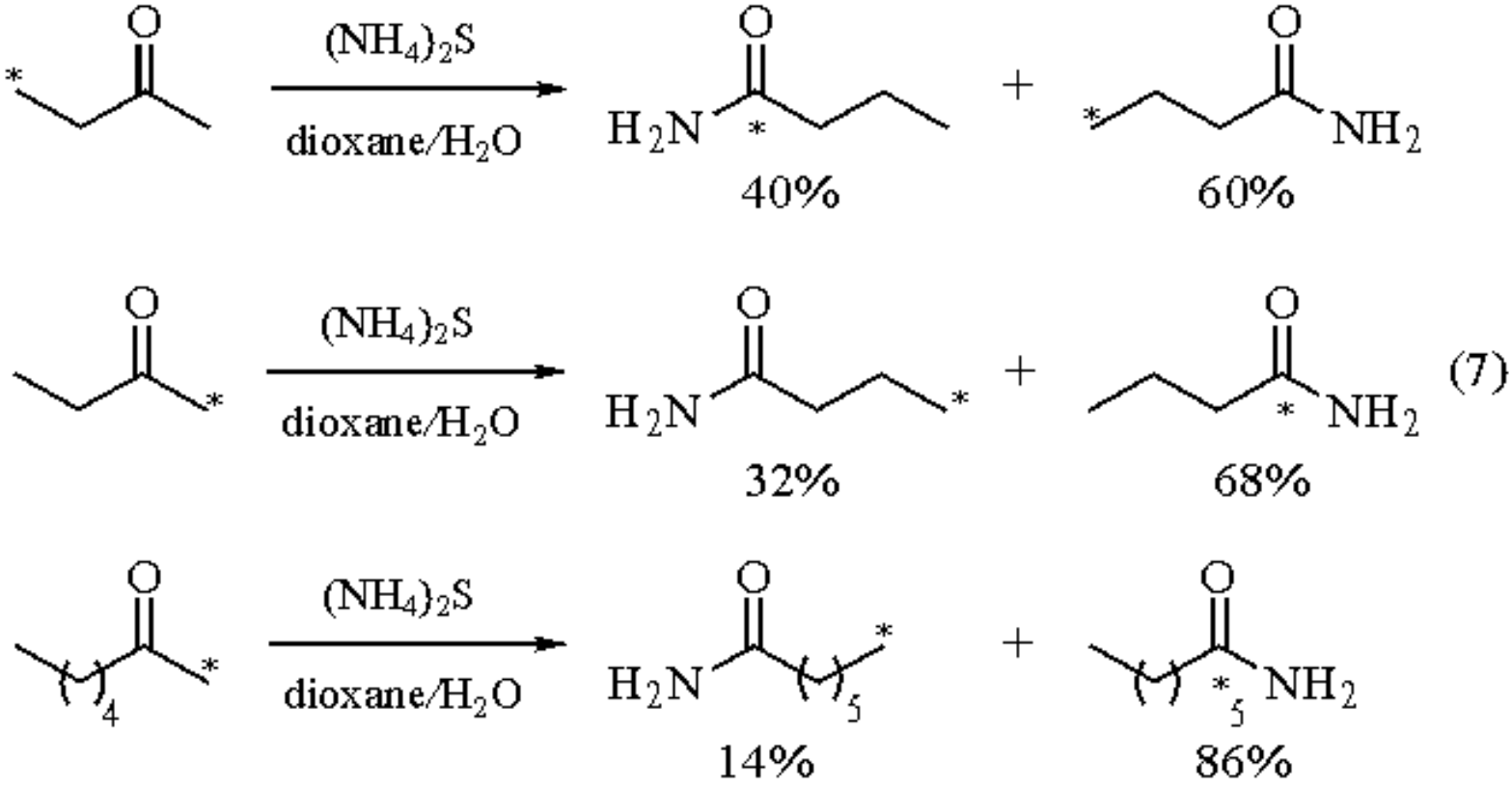

Reduction of Nitro Functional Group.

Ammonium sulfide is used as a good selective reducing agent of a nitro functional group to an amine. For example, 4-nitrophenylacetic acid is reduced selectively with ammonium sulfide to give 4-aminophenylacetic acid in high yield (eq 8).[10]

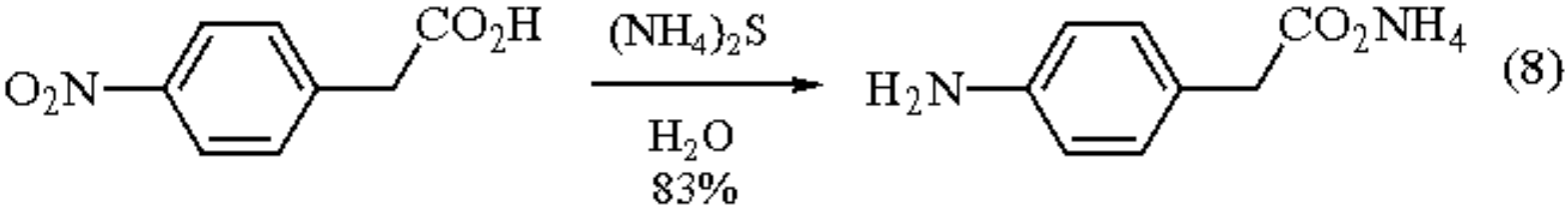

Interestingly, 3-nitrofluorene reacts with ammonium sulfide in DMF to give 3-(*N*-hydroxylamino)fluorene selectively and then can be treated with ^{14}C-labeled MeC*OCl to form 3-(*N*-acetylhydroxylamino)fluorene having a ^{14}C-labeled acetyl group (content 98%) in 58% yield (eq 9).[11] This reaction is important as a convenient method to supply ^{14}C-labeled compounds.

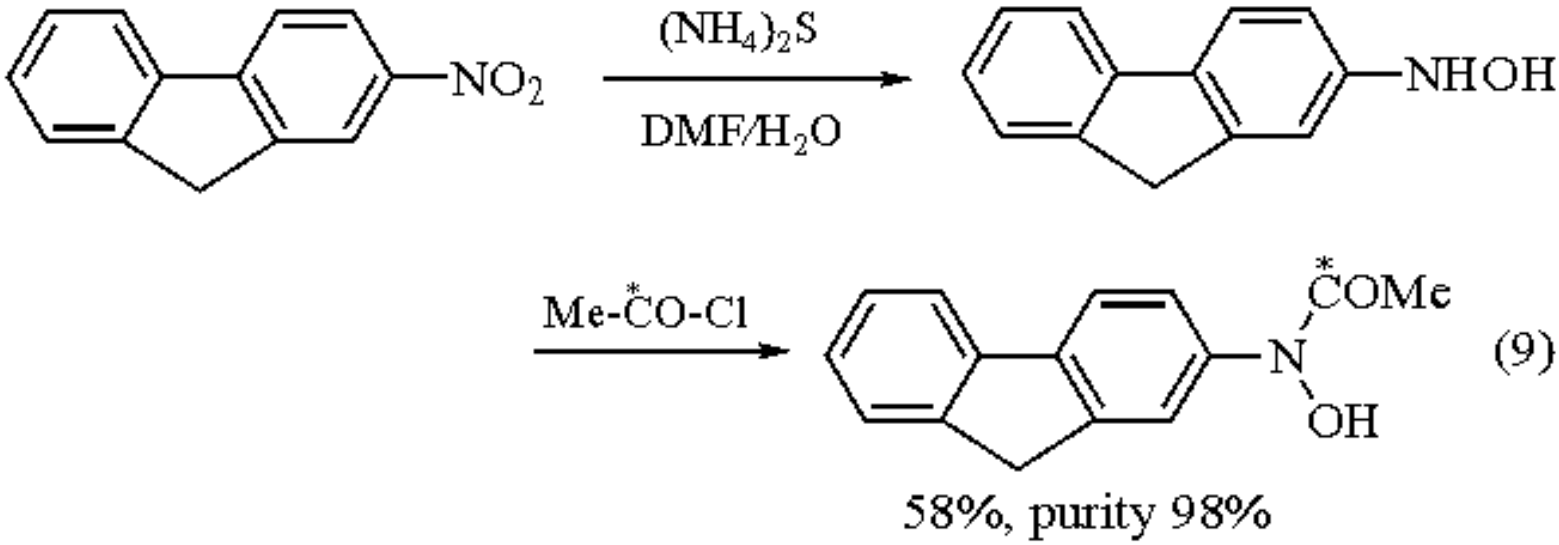

(9)

The treatment of 4-chloro-3,5-dinitrotrifluoromethylbenzene with ammonium sulfide in dioxane-H_2O affords the cyclization-dimerization product 1,6-dinitro-3,8-bis(trifluoromethyl)phenothiazine in 25% yield, while similar treatment in the presence of acetone gives 2,2-dimethyl-7-nitobenzothiazoline in 50% yield (eq 10).[12]

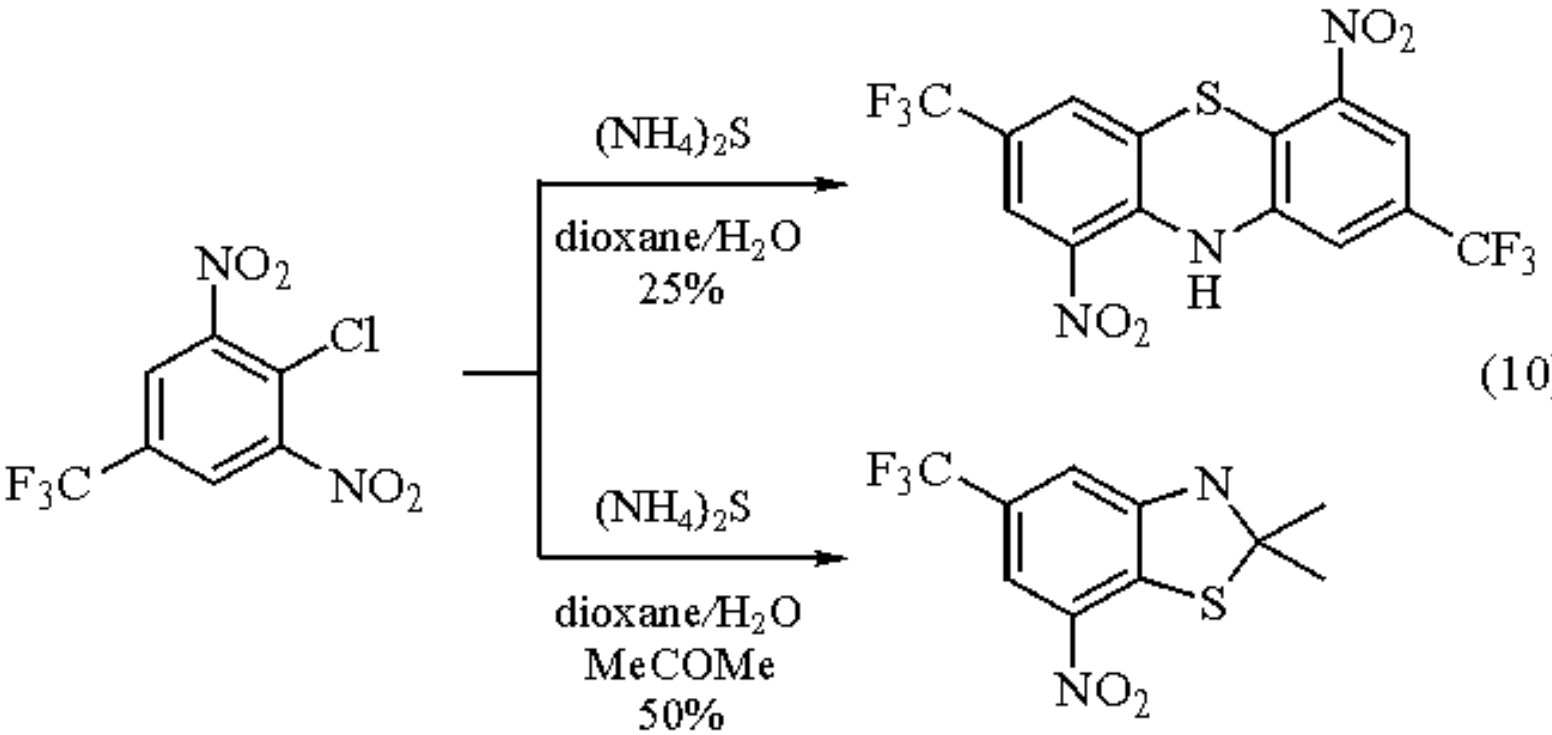

(10)

Sulfuration Agent.

The treatment of a gold(II) phosphorus ylide dimer with ammonium sulfide in THF results in the formation of a symmetrical gold(II) phosphorus ylide (60% yield) containing four- and five-atom polysulfide bridges. The coordination geometry about the gold centers in this structure is best described as square planar. The overall configuration of ylide units is shown to be a twisted boat (eq 11).[13]

$$[Au(CH_2)_2P(Ph)Br]_2 \xrightarrow[\text{THF/H}_2\text{O}\ 60\%]{(NH_4)_2S} [Au(CH_2)_2P(Ph)]_2S_9 \quad (11)$$

In the presence of ammonium sulfide, bis(cyclopentadi-enyl)titanium pentasulfide, which is formed by the reaction of bis(methylcyclopentadienyl)titanium dichloride with ammonium sulfide, reacts with acetone to give $(MeCp)_2TiS_4CMe_2$ in 42% yield (eq 12).[14]

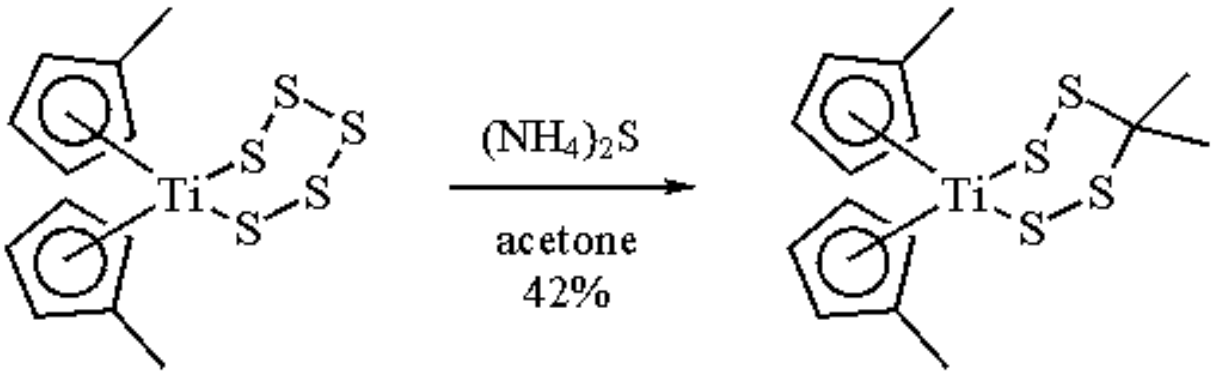

(12)

N-Alkyldithiooxamides are synthesized in good yield by reaction of cyanodithioformates with alkylamine and ammonium sulfide (eq 13).[15] Benzoylphenylalkynes react with ammonium sulfide in 60% dioxane-water at 15 °C to give a mixture of the β-hydroxy-α-thiobenzoylstyrene derivative (30%) and (*E*,*Z*)-β,β´-di(α-benzoylstyryl) sulfide (65%), as shown in eq 14, whereas only the β-hydroxy-α-thiobenzoylstyrene derivative is formed with sodium sulfide.[16]

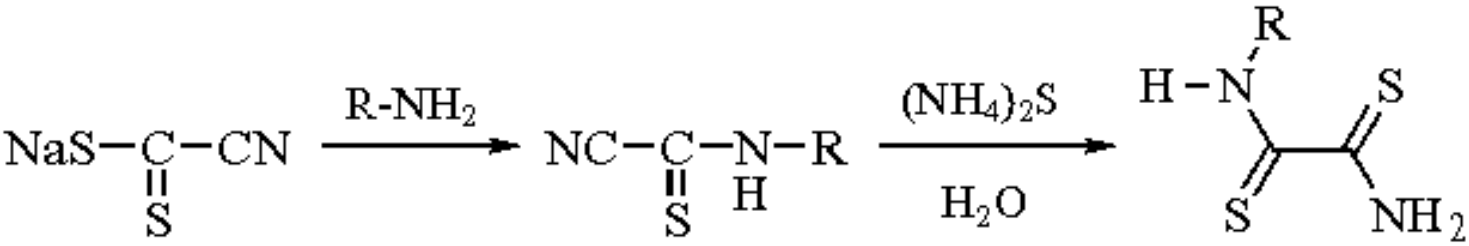

(13)

R = Me 54%
R = Et 41%

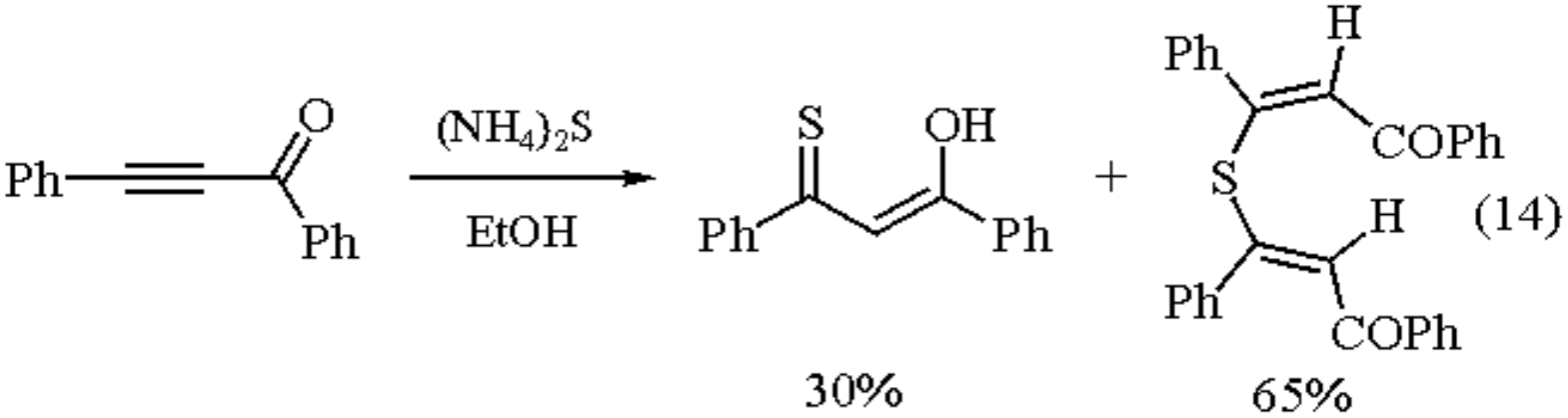

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Ammonium Tetrafluoroborate

NH_4BF_4

[13826-83-0] · BF_4H_4N · Ammonium Tetrafluoroborate · (MW 104.84)

(anion exchange reagent for preparation of isolable diazonium salts;[1] weak acid with nonnucleophilic counterion; electrolyte useful for synthetic electrochemistry[2])

Physical Data: mp 220-230 °C (sublimes); *d* 1.871 g cm^{-3} at 15 °C.

Solubility: sol H_2O.

Form Supplied in: white solid; widely available.

Purification: crystallization from water (1 mL g^{-1}) between 100 °C and 0 °C.

Handling, Storage, and Precautions: toxic by ingestion and inhalation. Irritates and can burn skin, eyes, and mucous membranes. Avoid extreme heat. Ammonium tetrafluoroborate is incompatible with acids, oxidizers, and reducing agents. Decomposition products include fluorides, NOX, and NH_3. Use in a fume hood with safety goggles and chemically resistant gloves and clothing. Use a dust respirator if much dust will be produced during use.

General Comments.

There are hundreds of references for the use of ammonium tetrafluoroborate in the patent literature. Only a few of these references are included here, but the reader should be aware of the wide use of ammonium tetrafluoroborate as a mild acid-base catalyst, proton source, or ammonia source. The lack of nucleophilicity of the fluoroborate spectator counteranion is generally advantageous.

Preparation of Arenediazonium Tetrafluoroborates.

Stable, isolable salts are obtained as filterable precipitates when arenediazonium chloride solutions are treated with NH_4BF_4. This is in contrast to arenediazonium salts with other counterions, which are not generally isolated. Thus *p*-bromobenzenediazonium chloride is converted in high yield to *p*-bromobenzenediazonium

tetrafluoroborate (eq 1). Alternatively, the arenediazonium tetrafluoroborate can be prepared from the arylamine in the presence of NH_4BF_4, whereupon the fluoroborate salt precipitates directly. For example, *p*-anisidine is diazotized to provide *p*-methoxybenzenediazonium tetrafluoroborate in nearly quantitative yield.[1]

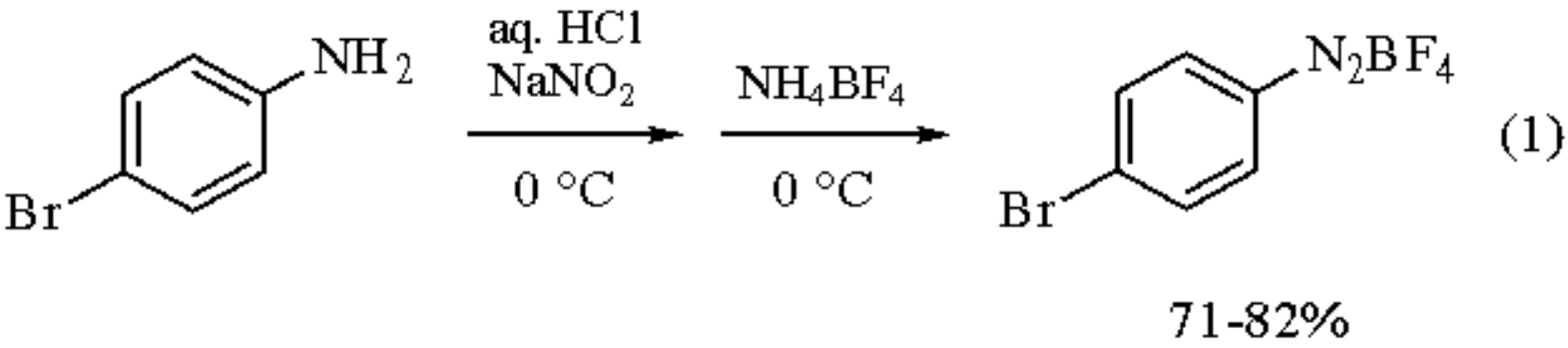

Acid Catalyst.

In a production of a polymethylated tetrahydropyrimidine from acetone and ammonia, NH_4BF_4 serves as a catalyst. The tetrahydropyrimidine is obtained in 82% yield after 5 h at 50 °C.[3] Further reaction of the aforementioned tetrahydropyrimidine with acetone occurs with NH_4BF_4 catalysis at 70 °C, giving the synthetically useful 2,2,6,6-tetramethylpiperidin-4-one.[4]

Elecrochemical Synthesis.

In an electrolytic oxidation of *p*-acetoxybenzaldehyde from *p*-acetoxytoluene, solutions of NH_4BF_4 in low molecular weight alcohol/carboxylic acid mixtures are effective electrolytes.[2] Various metal alkoxides can be prepared by electrochemical oxidation of the metal with R_4NBF_4/alcohol as the supporting electrolyte.[5] Terephthalaldehyde can be produced electrochemically with the use of NH_4BF_4.[6] Polyfluoroalkyl halides can be converted to perfluorocarboxylic acids by electrochemical initiation of ion-radical reaction with oxygen.[7]

Inversion of Chiral Amines.

Conversion of chiral amines to potassium alkanediazotates, followed by treatment with NH_4BF_4 in refluxing NH_3, leads to inverted amines (eq 2). Percentages of inversion range from 50% to 70%, and yields are modest (18-37%) due to formation of significant amounts of alcohols (configuration predominantly retained) and alkenes.[8]

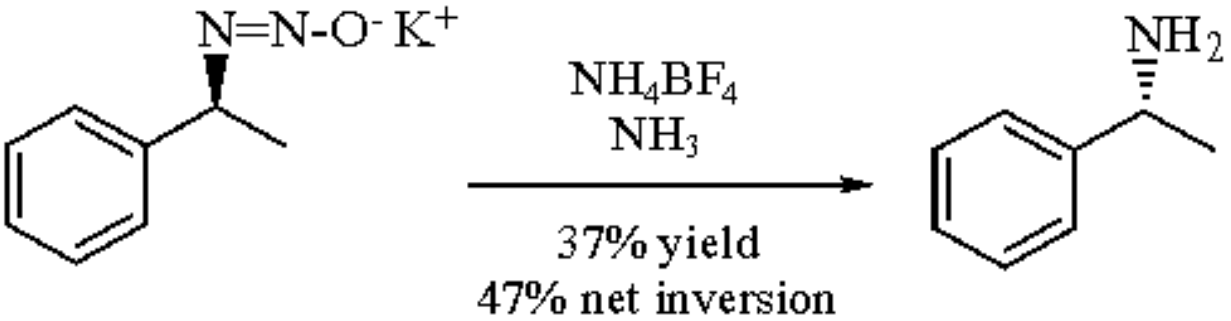

(2)

Reductive Dehalogenation of Aromatic Iodides.

Treatment of methyl 2-iodobenzoate with excess of ***Copper(II) Trifluoromethanesulfonate*** in aq ammonia provides methyl salicylate in 94% yield. The intermediacy of an arylcopper species was demonstrated by isolation of 98% yield of methyl benzoate in the presence of excess NH_4BF_4 (eq 3).[9]

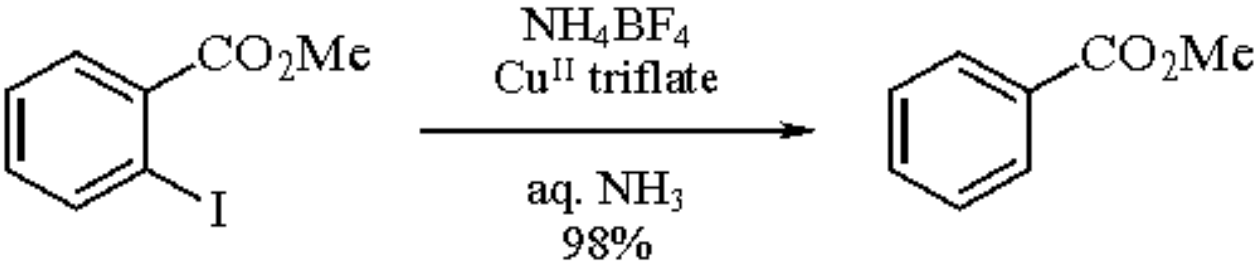

(3)

Additive in Catalytic Systems.

A zeolite impregnated with NH_4BF_4 catalyzed a 99.5% conversion of methanol to mixtures of hydrocarbons (30.4% propene, 19.3% butenes, and 25.6% C_{5+} aliphatics).[10] Catalytic hydrogenation with a $Ru(acac)_3$/tri-octylphosphine catalyst in the presence of NH_4BF_4 results in a selectivity of 100% (79% conversion) for reduction of succinic anhydride to γ-butyrolactone.[11] In catalytic reductive amination of acetone to produce an *N*-isopropyl arylamine, NH_4BF_4 additive imparts very high selectivity (96.8%) to the Fe_2O_3-promoted copper-chromium catalyst system.[12] An $AlCl_3$ catalyst for production of diphenylamine is improved by addition of NH_4BF_4.[13]

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(*S*)-4-Anilino-3-methylamino-1-butanol[1]

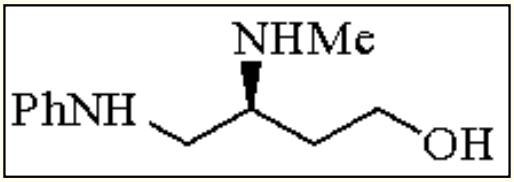

[88733-39-5] · $C_{11}H_{18}N_2O$ · (*S*)-4-Anilino-3-methylamino-1-butanol · (MW 194.27)

(tridentate chiral ligand to modify $LiAlH_4$ for the enantioselective reduction of alkyl phenyl ketones[2] and α,β-unsaturated ketones[3])

Physical Data: bp 139-140 °C; [α]23D -13.7° (*c* 1.0, $CHCl_3$).

Solubility: sol THF.

Preparative Methods: β-benzyl *N*-benzyloxycarbonylaspartate[4] is treated with ethyl chloroformate, *N*-methymorpholine, and aniline. Subsequent reduction of the corresponding anilide with $LiAlH_4$ gives the title reagent in overall 80% yield.[2]

Chiral Ligand of $LiAlH_4$ for the Enantioselective Reduction of Alkyl Phenyl Ketones.

Optically active alcohols are important synthetic intermediates. There are two major chemical methods for synthesizing optically active alcohols from carbonyl compounds. One is asymmetric (enantioselective) reduction of ketones.[1] The other is asymmetric (enantioselective) alkylation of aldehydes.[5] Extensive attempts have been reported to modify ***Lithium Aluminum Hydride*** with chiral ligands in order to achieve enantioselective reduction of ketones.[1] However, most of the chiral ligands used for the modification of $LiAlH_4$ are unidentate or bidentate, such as alcohol, phenol, amino alcohol, or amine derivatives.

Unlike many other chiral ligands, (*S*)-4-amilino-3-methylamino-1-butanol (**1**) is designed as a tridentate chiral ligand anticipating a more rigid complex formation with $LiAlH_4$. The chiral reducing reagent is prepared in situ by mixing $LiAlH_4$ and (**1**) in THF. To this chiral reducing reagent is added alkyl phenyl ketone at -100 °C. Optically active (*S*)-*s*-alcohols with 51-88% ee's are obtained in 84-93% yields (eq 1). The results are summarized in Table 1.

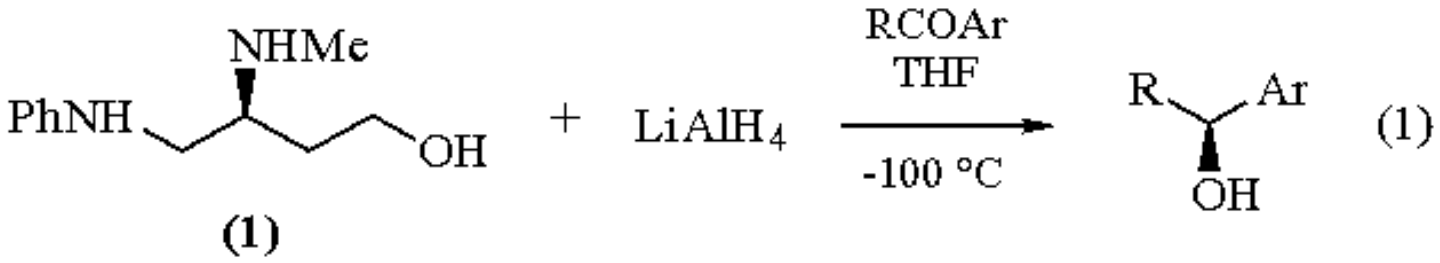

Table 1 Enantioselective Reduction of Alkyl Phenyl Ketones

Ketone	Yield (%)	ee (%)
PhCOMe	87	51
PhCOEt	93	68
PhCOPr-*i*	93	77
PhCOBu-*t*	84	86
a-Tetralone	89	88

The ee's of the obtained alcohols increase according to the increase in steric bulkiness of the alkyl substituents of prochiral ketones. Thus the reduction of *t*-butyl phenyl ketone occurs with 86% ee whereas reduction of acetophenone gives 51% ee. The enantioselective reduction of *t*-butyl phenyl ketone and α-tetralone (86 and 88% ee, respectively) are among the most selective of those reported.[6]

After quenching the reaction, the amino alcohol (**1**) is recovered in a yield of over 85% without any racemization.

Chiral Ligand of $LiAlH_4$ for the Enantioselective Reduction of α,β-Unsaturated Ketones.

Enantioselective reductions of α,β-unsaturated ketones afford optically active allylic alcohols which are useful intermediates in natural product synthesis.[7] Enantioselective reduction of α,β-unsaturated ketones with $LiAlH_4$ modified with chiral amino alcohol (**1**) affords optically active (*S*)-allylic alcohols with high ee's. When 2-cyclohexen-1-one is employed, (*S*)-2-cyclohexen-1-ol with 100% ee is obtained in 95% yield (eq 2). This is comparable with the results obtained using $LiAlH_4$-chiral binaphthol[8] and chiral 1,3,2-oxazaborolidine.[9]

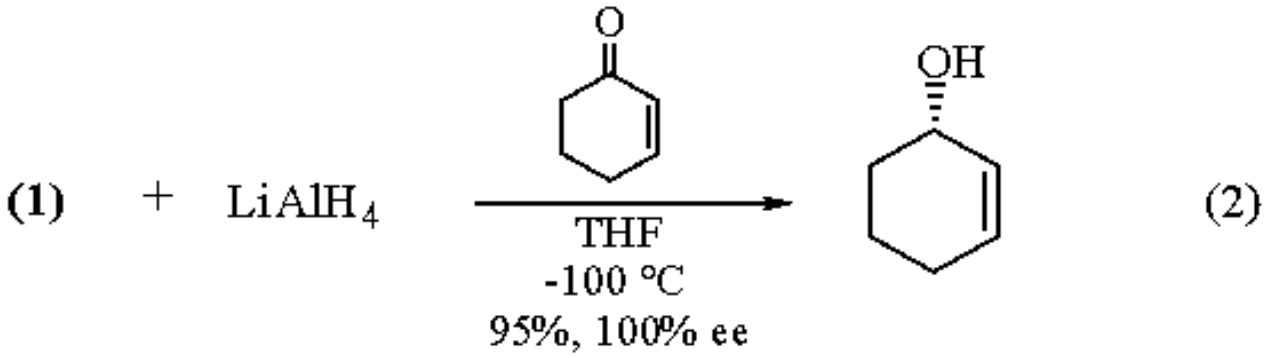

When (*S*)-4-(2,6-xylidino)-3-methylamino-1-butanol (**2**) is used instead of (**1**), (*R*)-2-cyclohexen-1-ol is obtained with less enantioselectivity (13% ee) (eq 3).

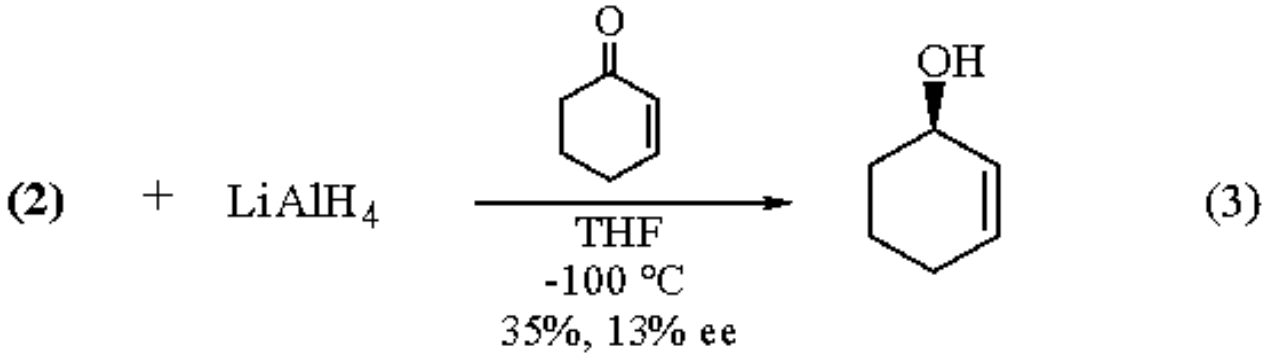

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(2*S*,4*S*)-2-(Anilinomethyl)-1-ethyl-4-hydroxypyrrolidine[1]

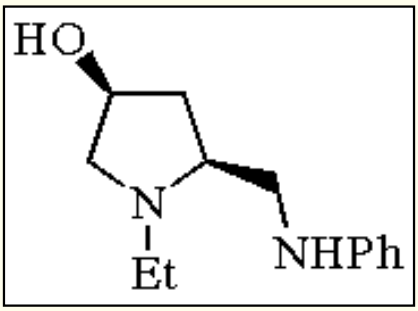

[77973-75-8] · $C_{13}H_{20}N_2O$ · (2*S*,4*S*)-2-(Anilinomethyl)-1-ethyl-4-hydroxypyrrolidine · (MW 220.31)

(chiral catalyst for the enantioselective conjugate addition of thiols to α,β-unsaturated ketones[2] and esters)

Physical Data: bp 150-170 °C/2 mmHg; [α]23D -58.1° (*c* 1.03, EtOH).

Solubility: sol toluene, benzene, CH_2Cl_2, CCl_4, ethanol.

Preparative Methods: (2*S*,4*S*)-1-benzyloxycarbonyl-4-hy-droxyproline (*Z*-allohydroxyproline)[3] is acetylated with ***Acetic Anhydride*** and ***Pyridine*** to give the acetate (**1**). The acetate (**1**) is treated with aniline-***1,3-Dicyclohexylcarbodiimide*** and the subsequent removal of the benzyloxycarbonyl group affords (**2**). Acetylation of (**2**) followed by reduction with ***Lithium Aluminum Hydride*** affords (2*S*,4*S*)-2-(anilinomethyl)-1-ethyl-4-hydroxypyrrolidine (**3**) in 60% overall yield from (**1**) (eq 1).[2]

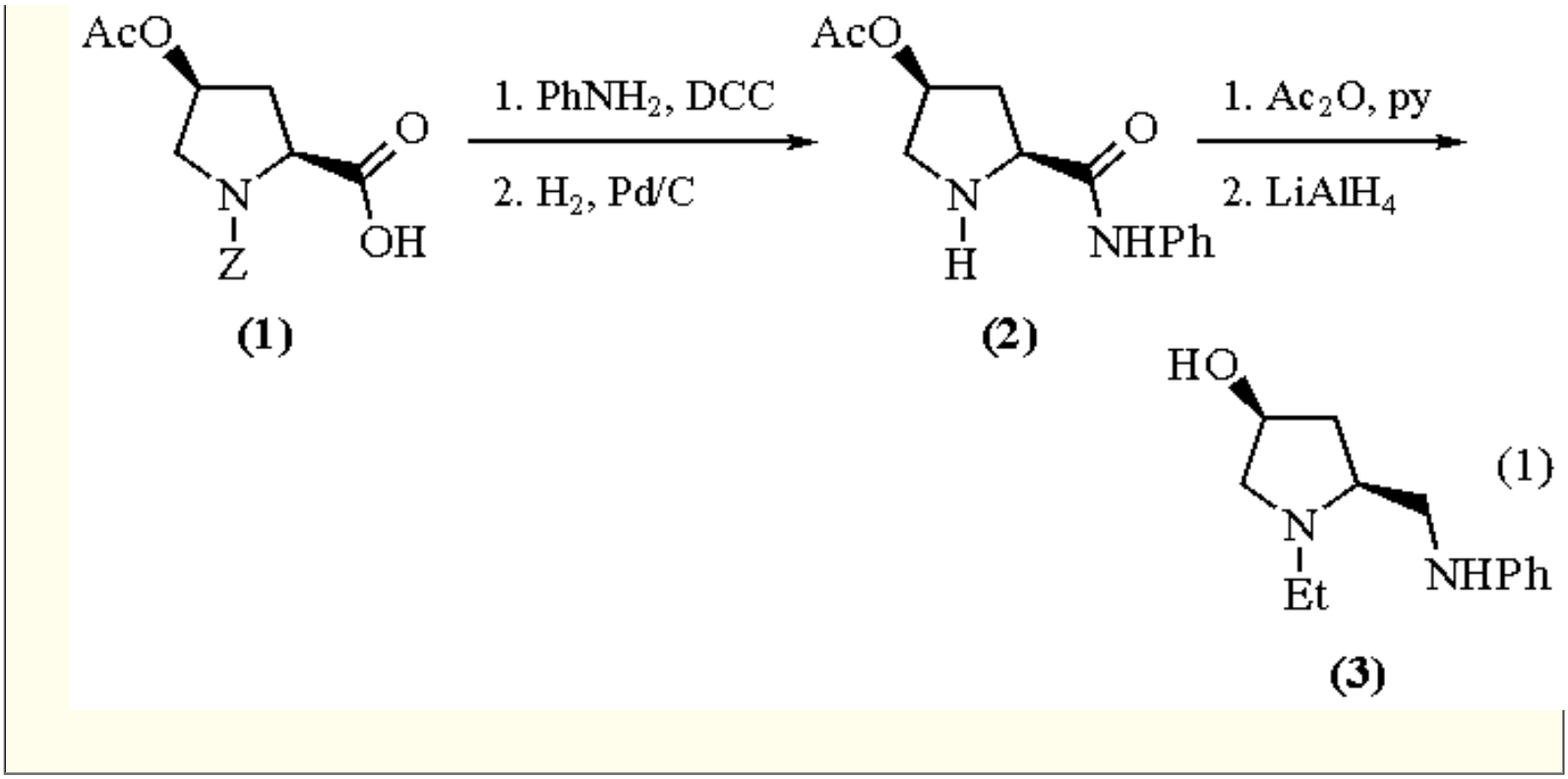

Enantioselective Addition of Thiols to α,β-Unsaturated Ketones and Diisopropyl Maleate.

(2*S*,4*S*)-2-(Anilinomethyl)-1-ethyl-4-hydroxypyrrolidine (**3**) is a chiral amino alcohol which acts as a chiral base catalyst for the enantioselective conjugate addition of aromatic thiols to α,β-unsaturated ketones.[2] When an aromatic thiol is treated with a 2-cycloalkenone in the presence of 1 mol % of amino alcohol (**3**) in toluene at -5 °C, 3-arylthio-1-cycloalkanones with 42-88% ee are obtained in 74-85% yields (eq 2).

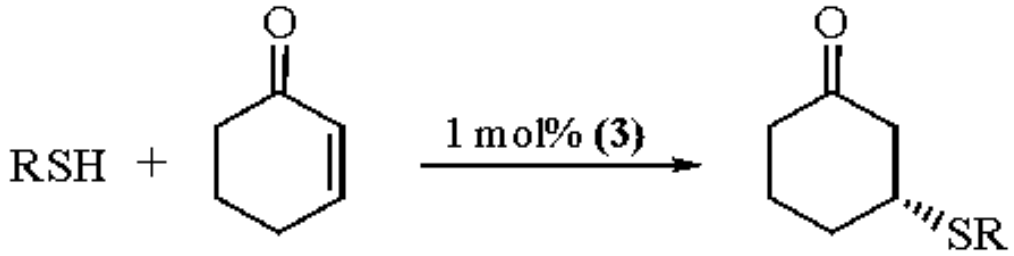

(2)

Table 1 Enantioselective Addition of Thiols to 2-Cyclohexenones Catalyzed by Amino Alcohol **(3)**

R	Enone	Yield (%)	ee (%)
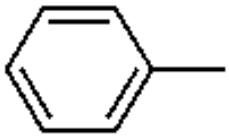	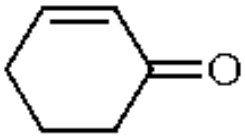	83	77
	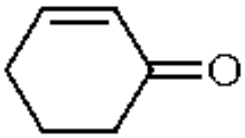	75	73
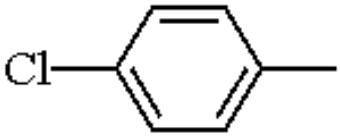	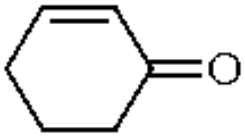	84	47
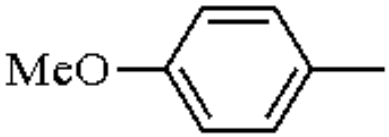	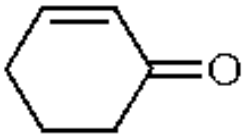	75	83
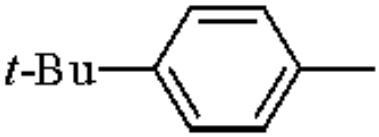	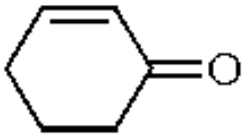	74	88
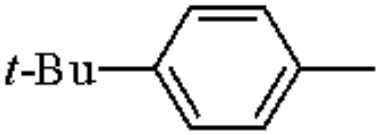	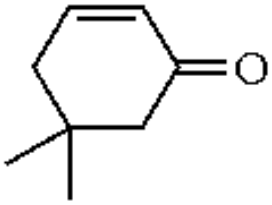	74	42

The results are shown in Table 1. The reaction between various aromatic thiols and 2-cyclohexen-1-one in the presence of (**3**) affords the adduct in good ee. The best selectivity is observed in the addition of 4-*t*-butylbenzenethiol to 2-cyclohexen-1-one using 1 mol % of (**3**). (*R*)-3-(4-*t*-Butylphenylthio)cyclohexan-1-one is obtained in 88% ee. When cinchonine is employed as a chiral catalyst in the same reaction, the corresponding adduct with (*S*) configuration is obtained in 67% ee.[4]

In the addition of benzenethiol to 2-cyclohexen-1-one, the enantioselectivities using (**3**)[2b] and cinchonidine[4b] are 77 and 54% ee, respectively. Thus (**3**) is more enantioselective than cinchonine and cinchonidine in the addition of RSH to 2-cyclohexen-1-one. However, in the addition of 4-*t*-butylbenzenethiol to a substituted enone (5,5-dimethyl-2-cyclohexen-1-one), the cinchonidine catalyst showed higher enantioselectivity (62% ee)[4] than catalyst (**2**) (42% ee).

Cinchonidine is more enantioselective than (**3**) in the addition to acyclic α,β-unsaturated esters. When benzenethiol is allowed to react with diisopropyl maleate using chiral catalyst (**3**), (*R*)-diisopropyl phenylthiosuccinate with 6% ee is obtained. The same reaction employing cinchonine afforded the (*S*) adduct with 81% ee (eq 3).[5]

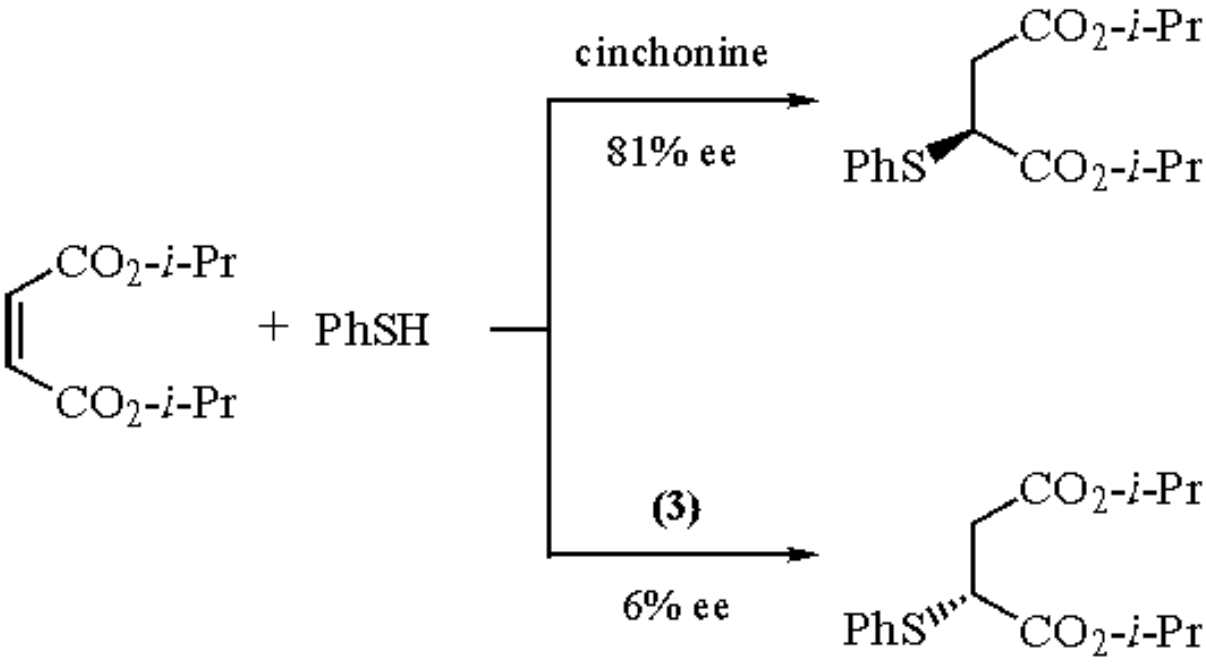

(3)

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(*S*)-2-(Anilinomethyl)pyrrolidine[1]

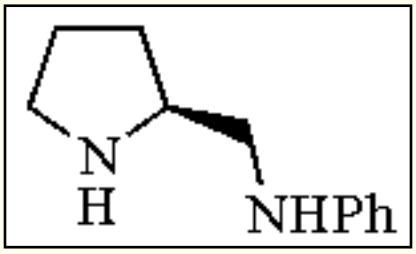

[64030-44-0] · $C_{11}H_{16}N_2$ · (*S*)-2-(Anilinomethyl)pyrrolidine · (MW 176.25)

(chiral ligand of $LiAlH_4$ for enantioselective reduction of ketones;[2] can form chiral aminals for diastereoselective alkylation,[3,4] 1,2-,[5] and 1,4-additions[6])

Physical Data: bp 111-112 °C/0.55 mmHg; [α]24D +19.7° (*c* 1.04, EtOH).

Solubility: sol ether, THF.

Form Supplied in: colorless oil.

Preparative Methods: reaction of (*S*)-*N*-(benzyloxycarbonyl)proline with (1) ethyl chloroformate and *N*-methylmorpholine, (2) aniline, (3) hydrogenolysis with Pd/C, and (4) reduction with $LiAlH_4$ affords the title compound in 59% overall yield.[2b]

Enantioselective Reduction of Ketones.

(*S*)-2-(Anilinomethyl)pyrrolidine (**1**) is a chiral ligand which, in combination with ***Lithium Aluminum Hydride***, generates a chiral reagent for the enantioselective reduction of ketones. (*S*)-1-Phenylethanol with 92% ee is obtained from the enantioselective reduction of acetophenone with $LiAlH_4$-(**1**) (eq 1).[2a,b] When (*S*)-2-(2,6-xylidinomethyl)pyrrolidine is used instead of (**1**), the ee of the alcohol obtained reaches 95%.[2c] The ee's of aromatic alcohols obtained using $LiAlH_4$-(**1**) are comparable with other highly enantioselective reductions[1] and with highly enantioselective alkylation of aldehydes.[7]

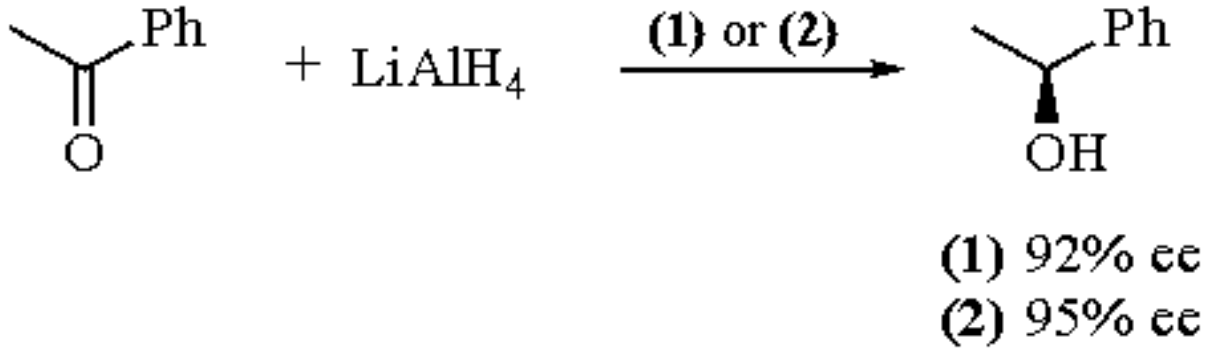

(1)

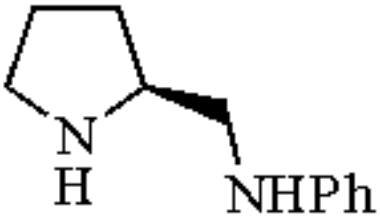

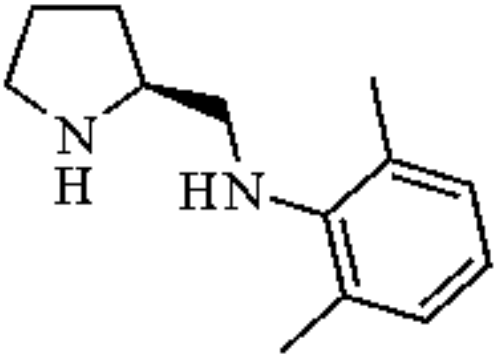

(2)

Diastereoselective Alkylation of Chiral Keto- and Formylaminals.

Diamine (**1**) forms a chiral ketoaminal by condensation with phenylglyoxal monohydrate. Diastereoselective addition of a Grignard reagent to the ketoaminal and subsequent hydrolysis affords optically active *t*-α-hydroxyaldehydes with >94% ee (eq 2).[3a] Various α-hydroxyaldehydes are synthesized by this method.[3b] Diastereoselectivities are comparable with those of the reactions of chiral 1,3-oxathiane.[8]

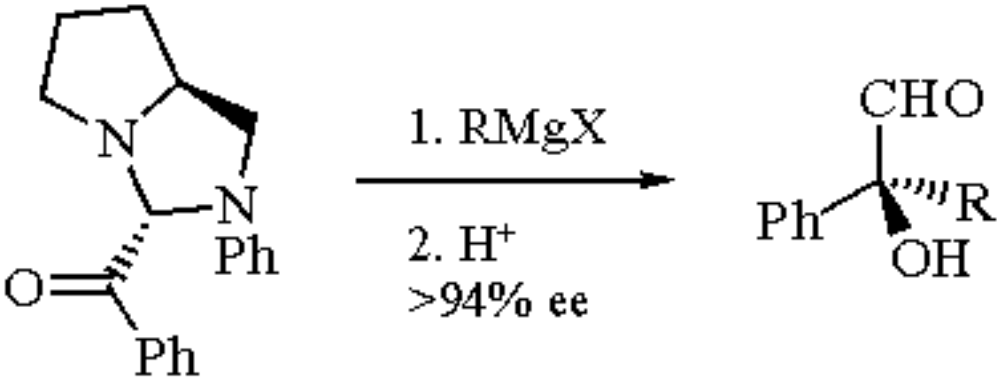

(2)

The method has been applied to the diastereoselective synthesis of naturally occurring compounds such as frontalin (84-100% ee)[3c] and (-)-malyngolide (95% ee).[3d] On the other hand, diastereoselective alkylation

of chiral formylaminal with Grignard reagents and the subsequent hydrolysis afford optically active *S*-α-hydroxyaldehydes with moderate stereoselectivity (60% ee).[4]

Diastereoselective 1,2- and 1,4-Additions of Chiral Aminals.

The organolithium reagent derived from a chiral bromoaminal and BuLi adds to pentanal to afford an optically active lactol. Subsequent oxidation affords the optically active lactone with 88% ee (eq 3).[5]

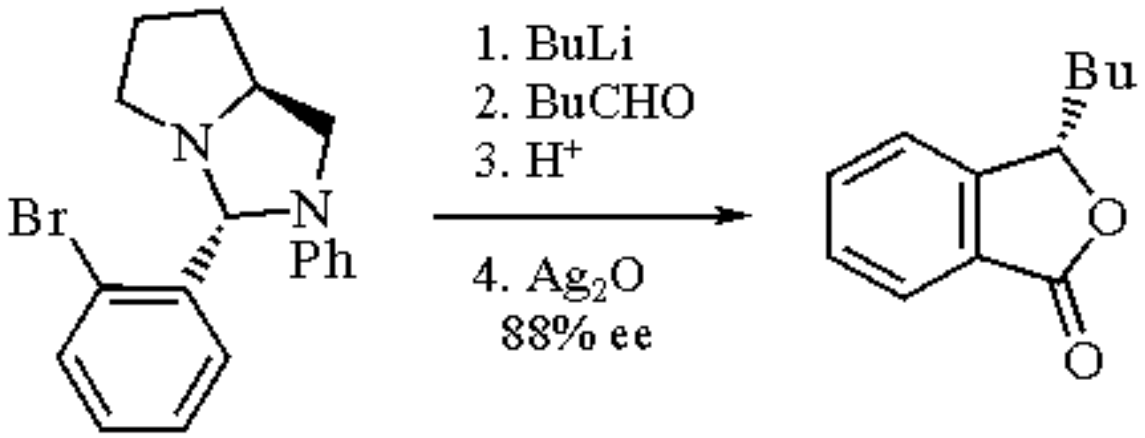

(3)

Diastereoselective 1,4- (conjugate) additions of Grignard reagents to a chiral α,β-unsaturated aminals afford optically active 3-substituted succinaldehydic acid methyl esters with 85-93% ee (eq 4).[6]

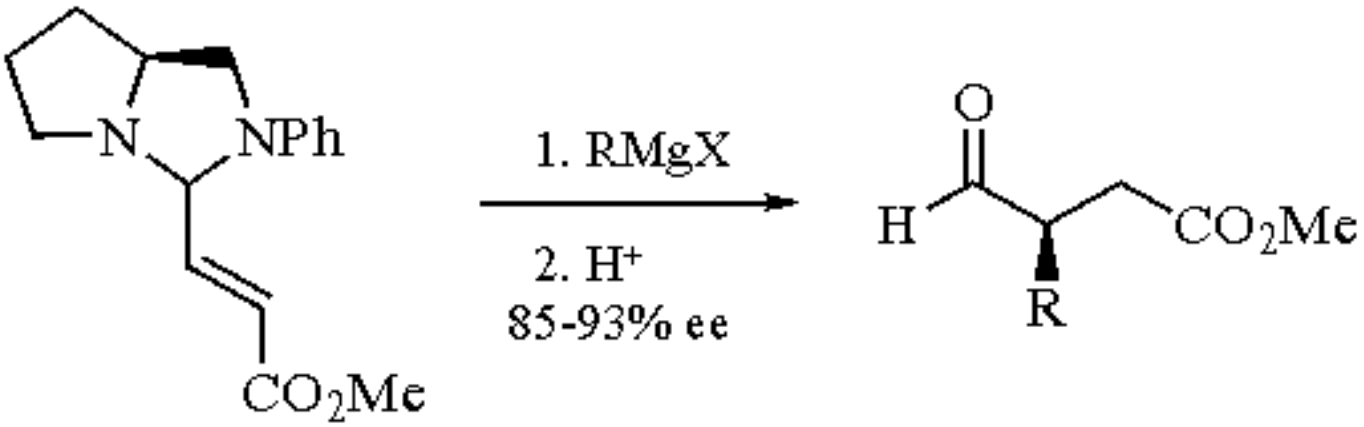

(4)

Related Reagents.

(2S,4S)-2-(Anilinomethyl)-1-ethyl-4-hydroxypyrrolidine; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***; ***(2S,2´S)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine***.

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2. (a) Mukaiyama, T,; Asami, M.; Hanna, J.; Kobayashi, S. *CL* **1977**, 783. (b) Asami, M.; Ohno, H.; Kobayashi, S.; Mukaiyama, T. *BCJ* **1978**, *51*, 1869. (c) Asami, M.; Mukaiyama, T. *H* **1979**, *12*, 499.
3. (a) Mukaiyama, T.; Sakito, Y.; Asami, M. *CL* **1978**, 1253. (b) Mukaiyama, T.; Sakito, Y.; Asami, M. *CL* **1979**, 705. (c) Sakito, Y.; Mukaiyama, T. *CL* **1979**, 1027. (d) Sakito, Y.; Tanaka, S.; Asami, M.; Mukaiyama, T. *CL* **1980**, 1223.
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5. Asami, M.; Mukaiyama, T. *CL* **1980**, 17.
6. Asami, M.; Mukaiyama, T. *CL* **1979**, 569.
7. Soai, K.; Niwa, S. *CRV* **1992**, *92*, 833.
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p-Anisolesulfonyl Chloride[1]

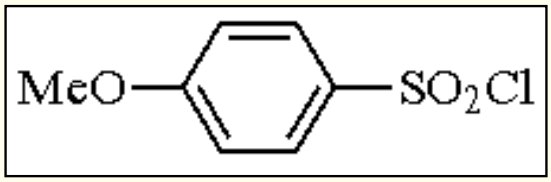

[98-68-0] · $C_7H_7ClO_3S$ · *p*-Anisolesulfonyl Chloride · (MW 206.65)

(versatile sulfonating agent; useful for the preparation of sulfonamides or as an *N*-protecting group[2])

Alternate Name: 4-methoxybenzenesulfonyl chloride.

Physical Data: mp 40-43 °C.

Solubility: sol acetone, acetonitrile, EtOH, MeOH, dioxane, H_2O.

Form Supplied in: solid; widely available 98% pure.

Handling, Storage, and Precautions: corrosive and a lachrymator. Store at room temperature under anhydrous conditions. Use in a fume hood.

Sulfonating Agent.

4-Methoxybenzenesulfonyl chloride has been employed in the preparation of a wide variety of sulfonamides leading to a number of biologically active compounds.[3,4] The nonprostanoid thromboxane (TXA_2) receptor antagonist (**2**) was prepared from the primary amine in the presence of 4-methoxybenzenesulfonyl chloride (**1**) (1.2 equiv) and excess ***Triethylamine*** (eq 1).[3] Arenesulfonyl chlorides have also been used for the synthesis of sulfonyl cyanides[5] and arylthiocyanates.[6]

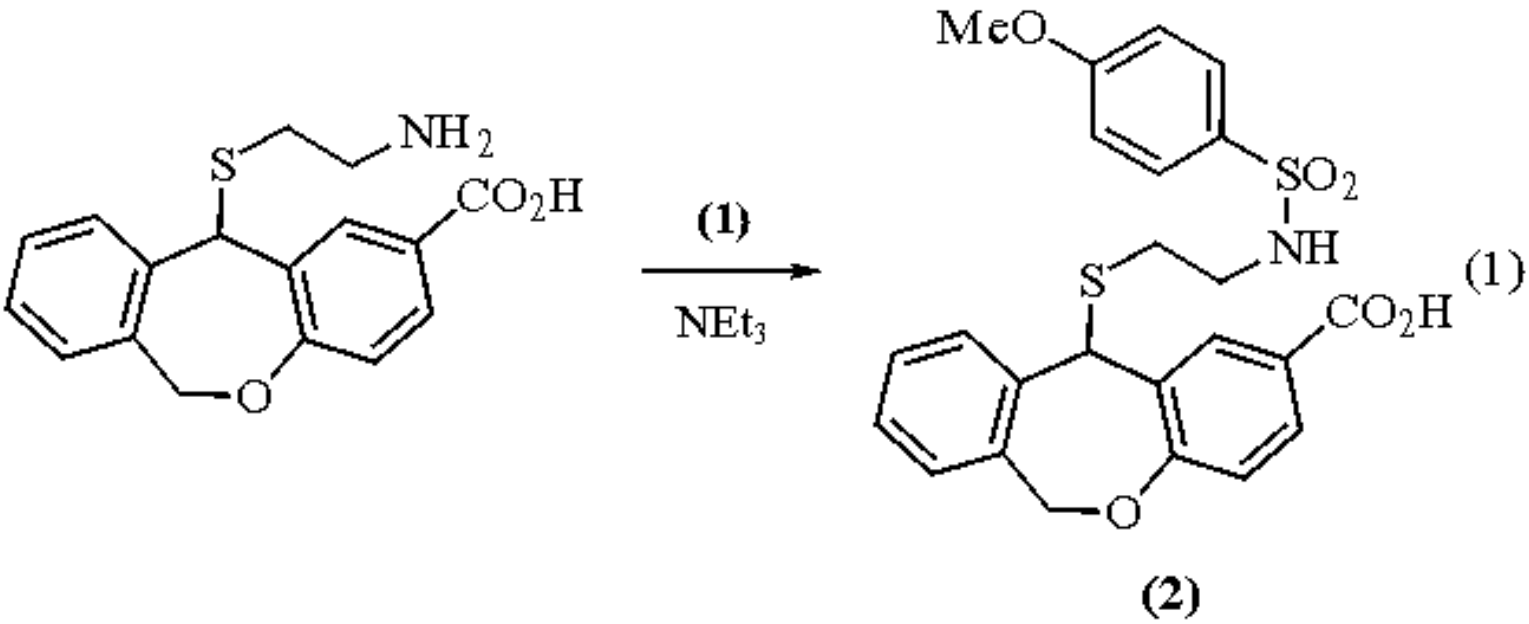

The addition of sulfonyl chlorides to alkenes in the presence of a catalytic amount of ***Dichlorotris(triphenylphosphine)ruthenium(II)*** affords 1:1 adducts.[7] Under these reaction conditions it is believed that sulfonyl radicals, which are confined to the coordination sphere of the metal complex, are involved. When the chiral phosphine (-)-DIOP (***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane***) is used as a ligand, the addition of 4-methoxybenzenesulfonyl chloride to styrene proceeds to provide the (*R*) isomer in 40% ee (eq 2).[8]

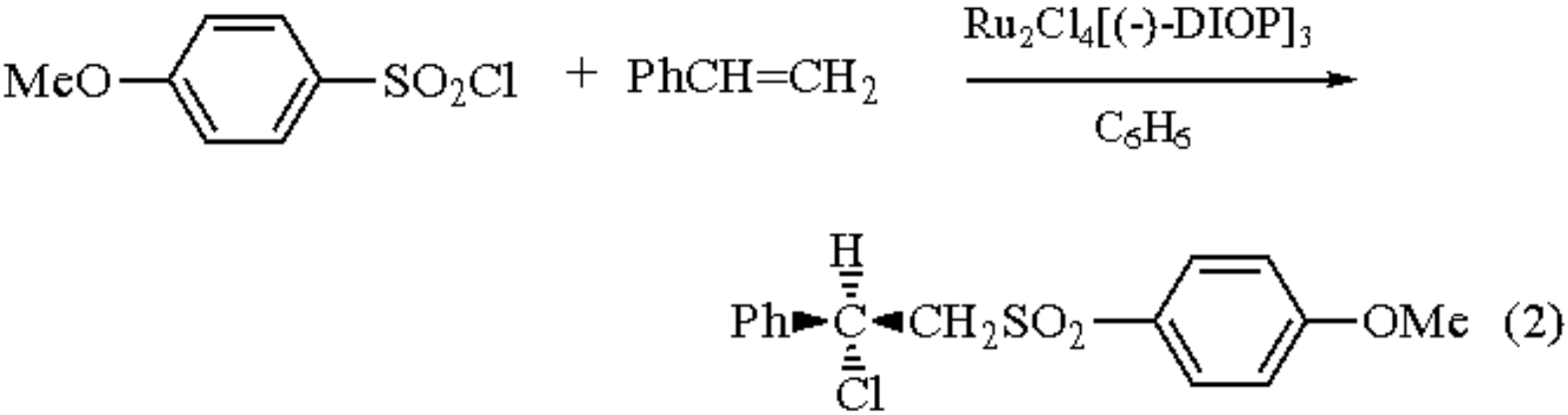

Arenesulfonyl chlorides have also been cross-coupled in the presence of Pd^0 with both vinyl- and allylstannanes to provide the corresponding sulfones.[9]

Solvolysis of Arenesulfonyl Chlorides.

Kinetics on the solvolysis of various arenesulfonyl chlorides indicate an S_N2 mechanism.[10,11]

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Anthranilic Acid

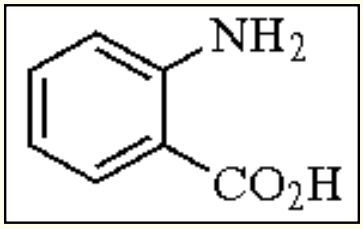

[118-92-3] · $C_7H_7NO_2$ · Anthranilic Acid · (MW 137.14)

(useful benzyne precursor[1]; building block for the synthesis of heterocyclic compounds[2-7])

Physical Data: mp 144-148 °C; *d* 1.412 g cm^{-3}.

Solubility: sol EtOH, AcOEt; partially sol water; insol petroleum ether.

Form Supplied in: yellow powder; widely available.

Benzyne Precursor.

Anthranilic acid can be diazotized to benzenediazonium-2-carboxylate, which is a very useful benzyne precursor. This transformation is usually accomplished under aprotic conditions with ***Isopentyl Nitrite*** (*caution*: isopentyl nitrite is a heart stimulant) (eq 1).[1]

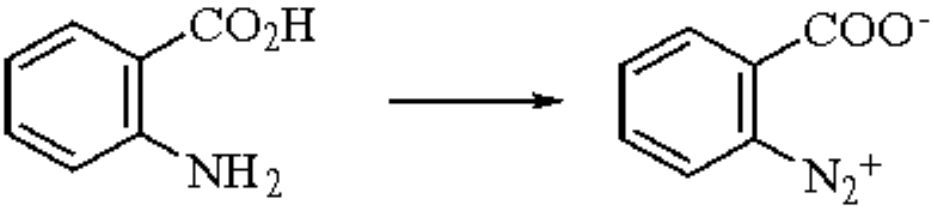

(1)

Synthesis of Heterocycles.

Anthranilic acid reacts with ***Phosgene*** (eq 2)[2] or ***Ethyl 4-Chloroacetoacetate***[3] to afford isatoic anhydride.[2]

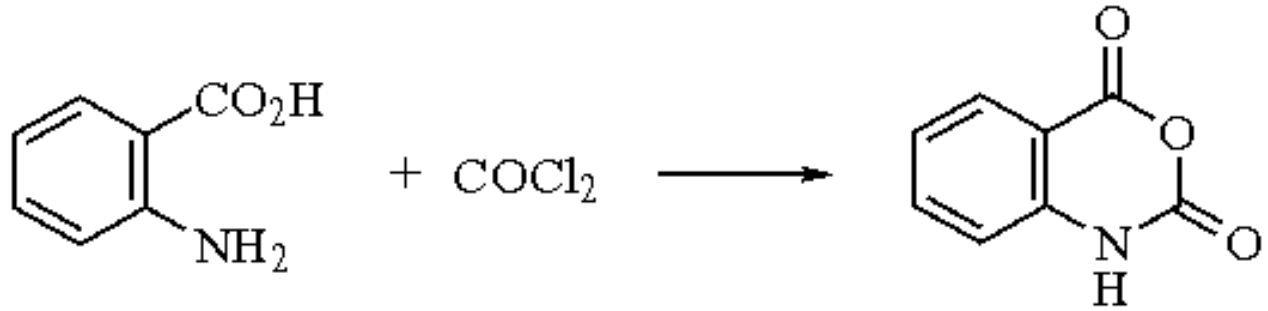

(2)

Benzoxazines have been obtained by treatment of a mixture of anthranilic acid and a substituted benzoic acid with ***Phosphorus Oxychloride*** (eq 3).[4]

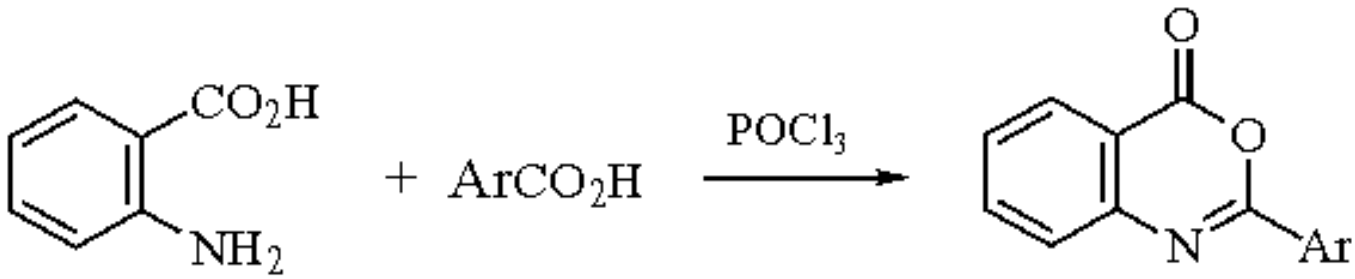

(3)

Reaction of anthranilic acid with methazonic acid under acid conditions, followed by treatment with sodium acetate/acetic anhydride, leads, in moderate yield, to 3-nitroquinol-4-one (eq 4).[5]

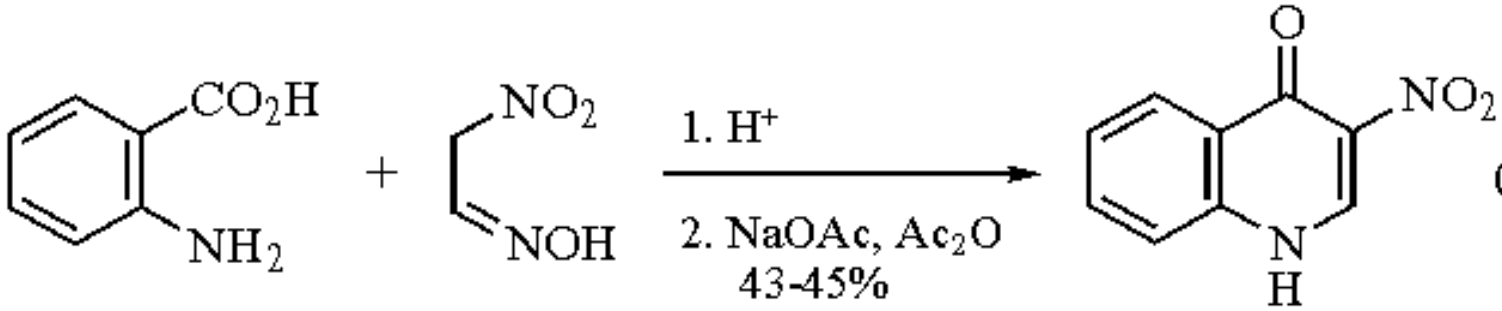

(4)

Acridones can be obtained, by means of the Niementowski modification of the Friedländer synthesis, by heating a mixture of anthranilic acid and a ketone (eq 5).[6]

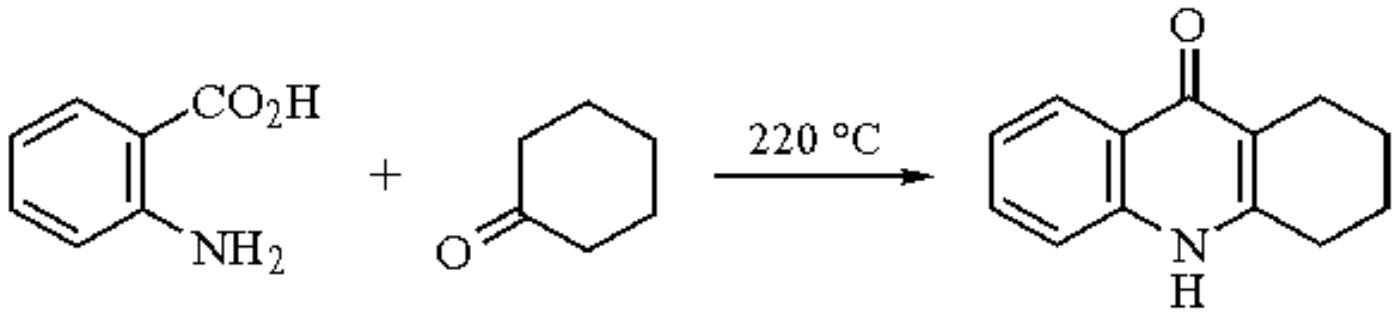

(5)

Condensation with formanilide yields a benzo-1,3-diazine (eq 6).[7]

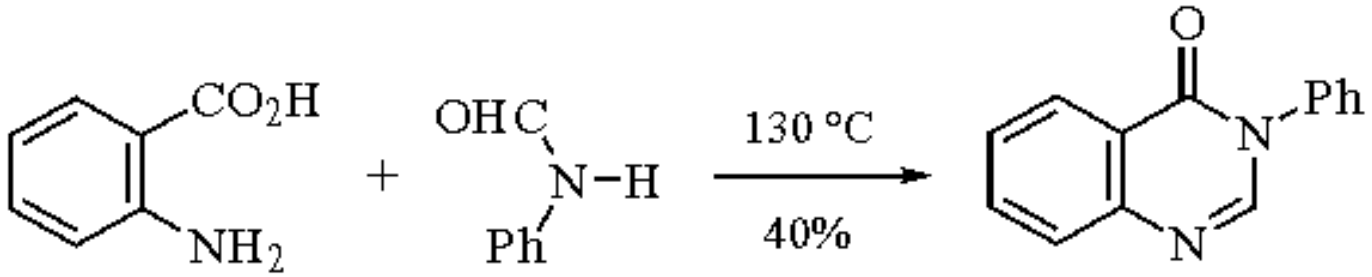

(6)

The following interesting reaction between anthranilic acid and a cyclopropylphosphonium salt has also been reported (eq 7).[8]

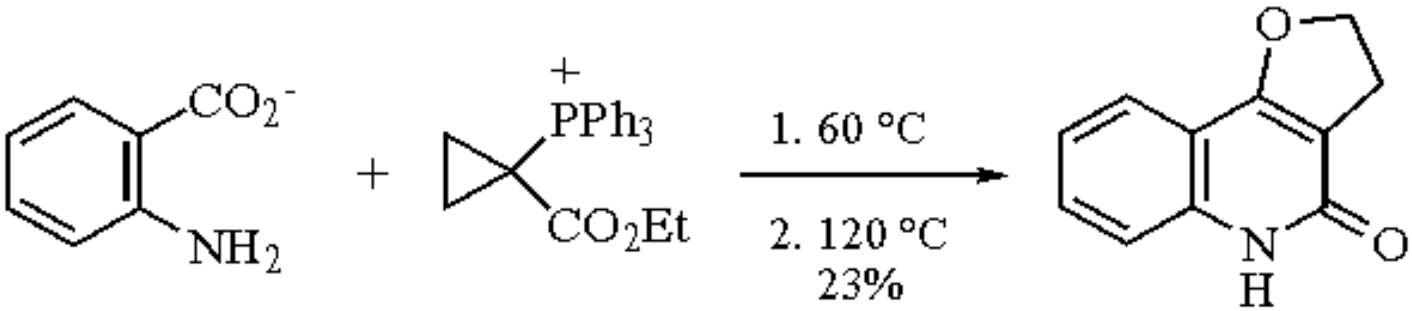

(7)

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Antimony(III) Chloride

$SbCl_3$

[10025-91-9] · Cl_3Sb · Antimony(III) Chloride · (MW 228.11)

(Lewis acid catalyst for electrophilic aromatic substitution;[1,2] halo-[3] and stibinodediazoniation[4] of diazonium salts; fluorination of sulfoxides[5,6] and thioethers[7] with DAST)

Alternate Names: antimony trichloride; trichlorostibine.

Physical Data: mp 73 °C; bp 223 °C, 143 °C/70 mmHg; *d* 3.14 g cm^{-3}.

Solubility: sol H_2O (1 g/10.1 mL, at 25 °C); sol acetone, alcohol, benzene, chloroform, 1,2-dichloroethane, dichloromethane; insol pyridine.

Form Supplied in: colorless, hygroscopic crystals which fume in moist air.

Handling, Storage, and Precautions: poisonous; moisture-sensitive, corrosive, and irritant. For best results, anhydrous $SbCl_3$ should be handled in an anhydrous, inert atmosphere (dry box or glove bag in humid laboratories), or manipulated rapidly to minimize contact with air and moisture. Use in a fume hood.

Electrophilic Aromatic Substitution.

Antimony(III) chloride has been used as a Lewis acid catalyst for Friedel-Crafts reactions. Thus treatment of benzene with benzoyl chloride/$SbCl_3$ at 155 °C gives benzophenone in good yield.[1a] However, this conversion and other Friedel-Crafts reactions catalyzed by $SbCl_3$ are slower, require higher temperatures, and give lower yields than with the more reactive Lewis acids ***Aluminum Chloride***, ***Iron(III) Chloride***, and ***Antimony(V) Chloride***.[1] Treatment of benzene with Cl_2/NOCl and molten $SbCl_3$ (135-145 °C) gives chlorobenzene.[2]

Nonaqueous Diazotization/Halodediazoniation, and Stibinodediazoniation.

Treatment of 2-amino-6-substituted purine nucleosides with *t*-butyl nitrite and catalytic amounts of antimony(III)

chloride in a chlorinated hydrocarbon solvent gave 2-chloro-6-substituted derivatives smoothly (eq 1a). The corresponding 2-bromo analogs were obtained when antimony(III) bromide was used in a brominated hydrocarbon solvent (eq 1b).[3] In contrast, diazotization of aniline with pentyl nitrite followed by addition of $SbCl_3$ gave a stable benzenediazonium/$SbCl_3$ salt.[4a] Such antimony salts can also be prepared by aqueous diazotization,[4b-e] and they have been used for the synthesis of a variety of aryl antimony compounds such as phenylstibonic acids.[4]

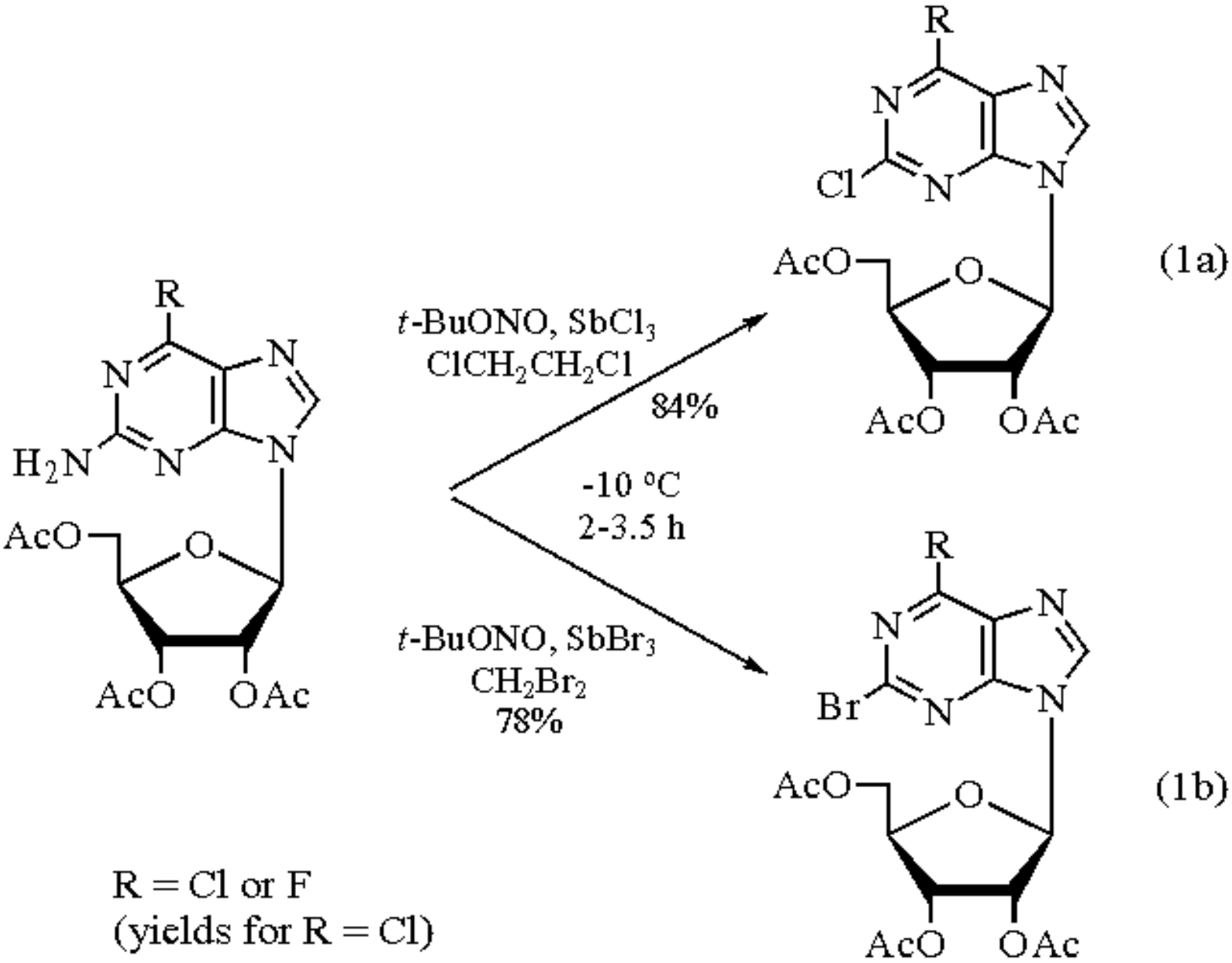

Fluorination of Sulfoxides and Thioethers.

Antimony(III) chloride is a potent catalyst for the conversion of sulfoxides to α-fluoro thioethers with ***N,N-Diethylaminosulfur Trifluoride*** (DAST).[5] Thioanisole sulfoxide gave fluoromethyl phenyl sulfide in 88% yield (eq 2).[5b] ***Zinc Iodide*** was the catalyst originally reported for this fluoro-Pummerer transformation,[6a] but $SbCl_3$ is markedly superior.[5,6b] Since sulfides afford α-fluoro thioethers directly upon treatment with DAST/$SbCl_3$,[7] prior oxidation of sulfides to their sulfoxides is not necessary for this transformation. Thus thioanisole gave fluoromethyl phenyl sulfide in 94% yield (eq 2) and the more complex 2´,3´-di-*O*-acetyl-5´-adenosyl phenyl (and *p*-anisyl)

sulfides gave the 5´-fluoro derivatives in ~60% yields (eq 3).[7] McCarthy has developed access to terminal vinyl fluorides with derived α-fluoro sulfoxides and sulfones.[6]

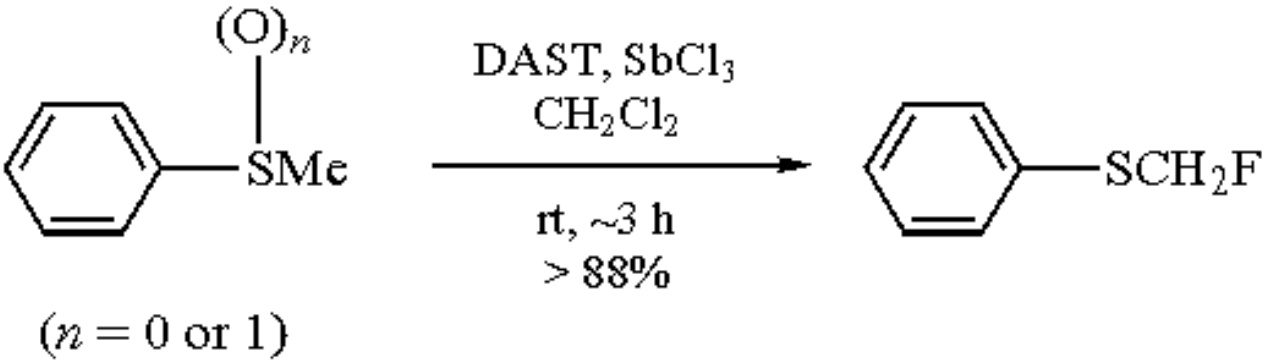

(2)

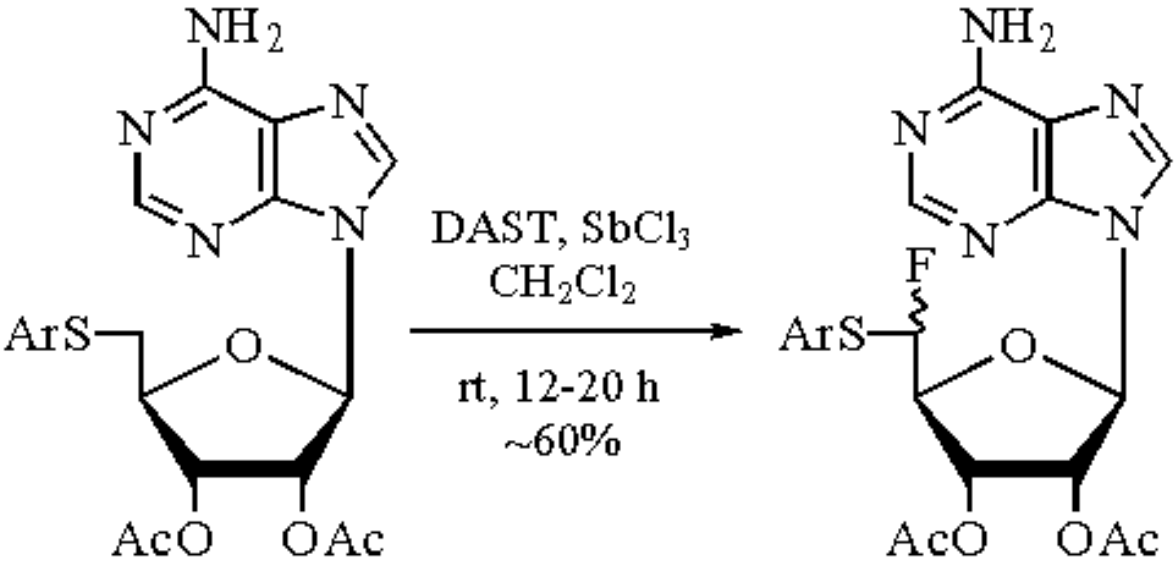

(3)

Antimony(III) Chloride/Reducing Metal Systems.

Zero-valent antimony species prepared by reduction of $SbCl_3$ with aluminum or iron effect allylations of aldehydes with allyl halides at 25 °C to give homoallylic alcohols in high yields.[8a,b] $SbCl_3$/Al or $SbCl_3$/Zn in aqueous DMF (or D_2O/DMF) are efficient systems for the reduction of aldehydes to alcohols.[8b,c] Electroreduction of acetophenone to 1-phenylethanol occurred on a lead cathode in the presence of catalytic $SbCl_3$.[9] Quantitative conversions of aldehydes to their methyl or ethyl acetals have been effected with Al (or Fe)/$SbCl_3$(cat.)/MeOH (or EtOH).[8b]

---

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Antimony(V) Chloride[1]

$SbCl_5$

[7647-18-9] · Cl_5Sb · Antimony(V) Chloride · (MW 299.02)

(Lewis acid,[1] catalyst for Friedel-Crafts reactions, isomerization, and other Lewis acid related chemistry;[1] chlorinating agent; acid system for the preparation of stable carbocation and onium salts[1])

Alternate Name: antimony pentachloride

Physical Data: bp 92 °C/30 mmHg.

Solubility: sol chloroform, carbon tetrachloride.

Form Supplied in: colorless or slightly yellow oily liquid; commercially available.

Handling, Storage, and Precautions: $SbCl_5$ is a corrosive, toxic, and moisture sensitive substance. It can be purified by vacuum distillation. $SbCl_5$ fumes when exposed to atmosphere, and should be stored under anhydrous conditions and handled using proper gloves in a well ventilated hood.

Catalyst in Friedel-Crafts and Related Chemistry.

Aromatic compounds can be readily alkylated under $SbCl_5$ catalysis.[2,3] However, competing chlorination can sometimes complicate the alkylation. The activity of $SbCl_5$ is comparable to that of ***Aluminum Chloride*** and ***Aluminum Bromide*** in the reaction of *s*-butyl chloride with benzene.[2a] It is interesting that dibenzoylchloromethane can be converted to 2-chloro-3-phenylindenone in 80% yield under $SbCl_5$ catalysis (eq 1).[3]

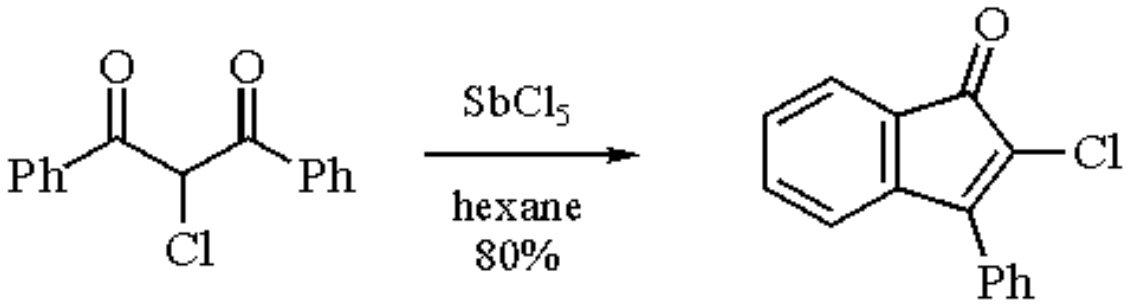

(1)

Both acyl halides and acid anhydrides have been utilized in the acylation of arenes under $SbCl_5$ catalysis.[4,5] Reaction

of 3-acetamidobenzo[*b*]furan with acid chlorides give condensed 1,3-oxazinium salts.[4d] Treatment of the salts with ammonium acetate in acetic acid gives the corresponding benzo[*b*]furano[3,2-*d*]pyrimidines in good yields (eq 2). Similar reactions proceed when 3-acetamidobenzo[*b*]thiophene and indole are used as substrates.[4d] Friedel-Crafts acylation generally requires a stoichiometric amount of Lewis acid. However, catalytic acylation can be achieved with the use of $SbCl_5$ in conjunction with ***Silver(I) Perchlorate***, ***Lithium Perchlorate***, or chlorodiphenylborane.[5] Trichloromethyl phenyl ketones can be readily prepared by reaction of trichlorophosphazoperchloroethane with arenes in the presence of $SbCl_5$ followed by hydrolysis of the reaction mixtures.[6]

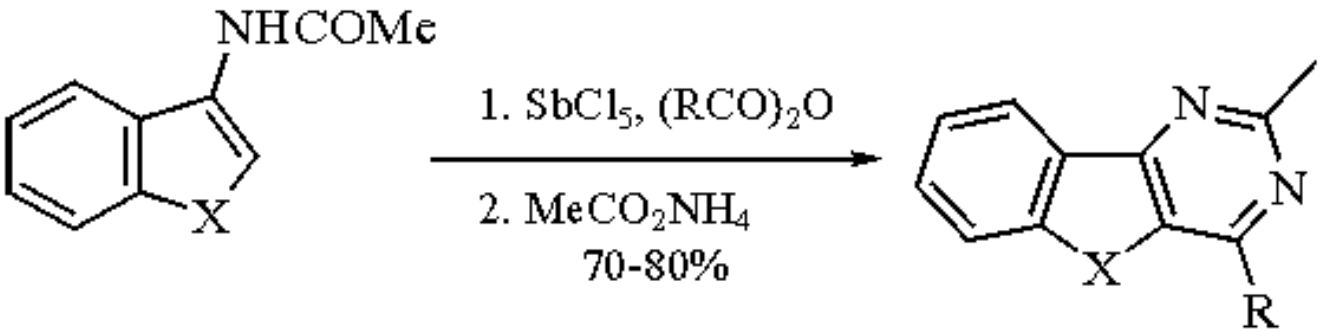

(2)

X = O, S, NH; R = Me Ph

Much of the research work on $SbCl_5$-catalyzed halogenation of arenes has focused on chlorination and bromination of perfluoroalkyl substituted aromatics.[7] Iodination of arenes has also been carried out with ***Iodine*** in the presence of $SbCl_5$.[7c]

Reaction of organic disulfides with electron rich aromatic compounds under $SbCl_5$/***Silver(I) Hexafluoroantimonate*** catalysis affords unsymmetrical aryl sulfides in modest yields.[8a] Electrophilic sulfinylation and sulfonation can be similarly effected by $SbCl_5$.[8b-c] Alkyl- and halobenzenes give thiocyano derivatives when treated with a mixture of $SbCl_5$ and $Pb(SCN)_2$ in CCl_4.[9]

Silyl enolates of α,α-dialkoxy ketones react with furans to form [3 + 2] cycloaddition products in the presence of $SbCl_5$ (eq 3).[10] Cycloaddition also occurs when 2,2-dialkoxycyclopropanecarboxylic esters and carbonyl compounds are treated with $SbCl_5$.[11]

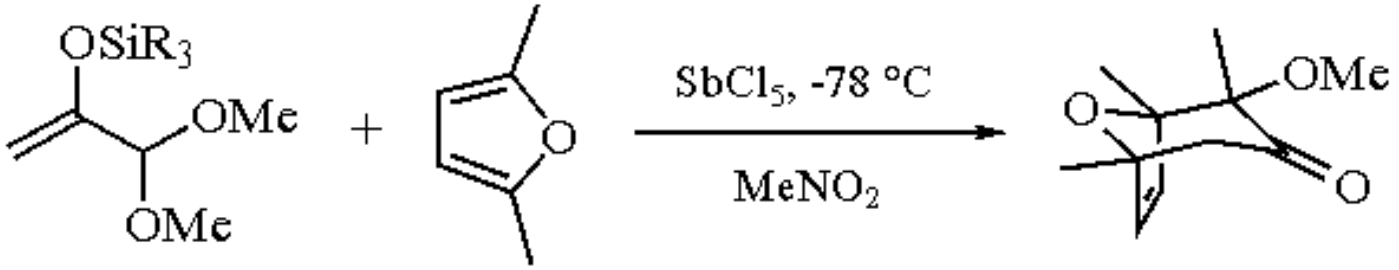

(3)

In the presence of $SbCl_5$ and ***Tin(II) Trifluoromethanesulfonate***, α,β-unsaturated thioesters react with silyl enol ethers to form the corresponding Michael adducts stereoselectively in high yields.[12] Successive treatment of lactones with ketene silyl acetals and certain organosilane-based nucleophiles (triethylsilane, allyltrimethylsilane, trimethylsilyl cyanide, etc.) under $SbCl_5/Me_3SiCl/SnI_2$ catalysis affords α-mono- or α,α-disub-stituted cyclic ethers (e.g. eq 4).[13]

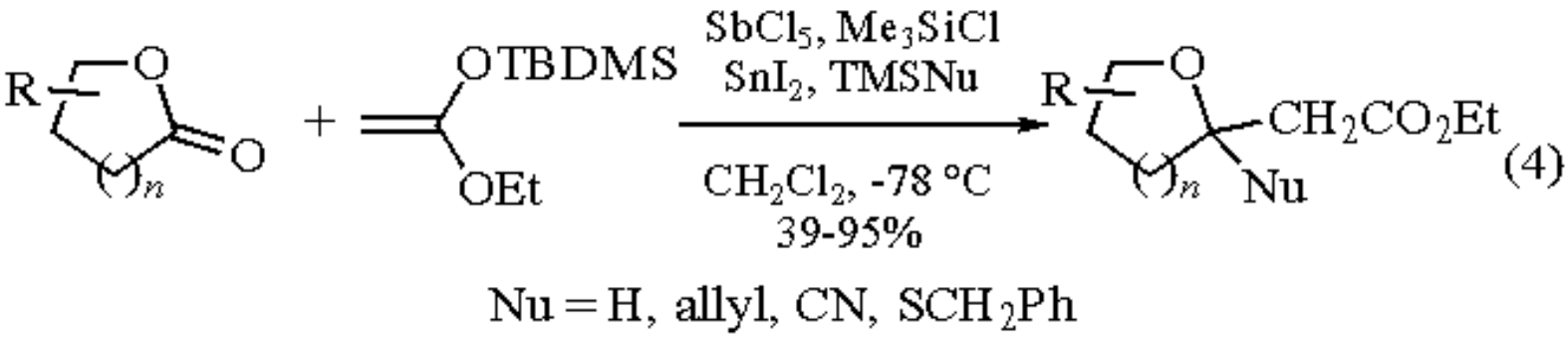

Catalyst in Isomerization and Rearrangements.

Along with many other Lewis acids, $SbCl_5$ has been applied to promote the Fries rearrangement.[14] More recently it has been found that the $SbCl_5/AgSbF_6$ system is an efficient catalyst for Beckmann and pinacol rearrangements.[15] In the presence of $SbCl_5$, (*E*)-2-methoxy-2,4-diphenyl-3-butenenitrile can be isomerized to the corresponding γ-methoxy-α,β-unsaturated carbonitriles in good yield.[16] Methyl 6α-chloropenicillanate rearranges to (3*S*)-6-chloro-2,3,4,7-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylate when treated with $SbCl_5$ in CH_2Cl_2. Under similar conditions, methyl penicillanate and methyl 6β-phthalimidopenicillanate undergo analogous isomerizations (eq 5).[17]

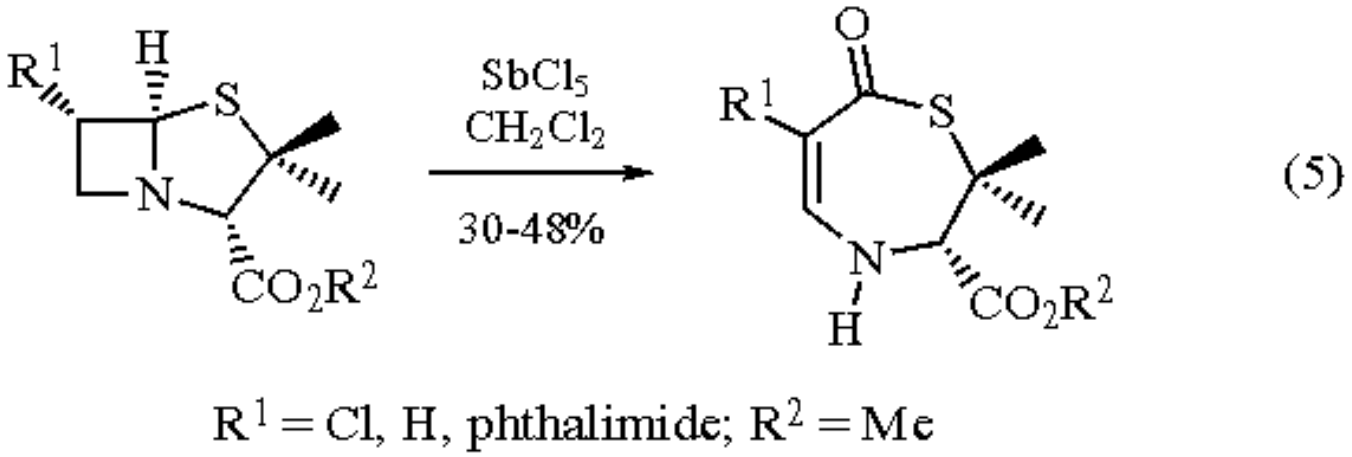

Halogenation.

In addition to its ability as a halogenation catalyst, $SbCl_5$ itself is an excellent chlorinating agent and has been widely applied to chlorination of various organic compounds, including arenes, alkenes, and alkynes.[18-24]

Preparation of Carbocation and Onium Ion Complexes.

$SbCl_5$ has been extensively utilized in the preparation of stable carbocations and onium ions.[25-30] This is facilitated by the ready formation of the stable anion $SbCl_6^-$. The carbocations generated include such stable ions as halophenylcarbenium ions, cyclopropenyl cations, and perchloroallyl cations.[26] Extensive studies have also been carried out on the use of $SbCl_5$ to synthesize onium salts such as alkylidene ammonium salts, 2-azaallenium salts, nitrilium salts,[27] oxonium salts,[28] and sulfonium salts.[29] Reaction of adamantylideneadamantane with $SbCl_5$ gives the

stable chloronium [AdAdCl$^+$][$SbCl_6^-$] salt.[30]

Other Reactions.

1,3-Dithianes can be converted to the corresponding carbonyl compounds in excellent yields in the presence of $SbCl_5$.[31] When epoxides are treated with a catalytic amount of $SbCl_5/AgSbF_6$ in the presence of alkoxytrimethylsilane and triethylsilane, sequential reactions involving rearrangement and reductive condensation give the corresponding ethers in good yields (eq 6).[32] Homologation of ketones with diazoacetic esters can also be catalyzed by $SbCl_5$ (eq 7).[33]

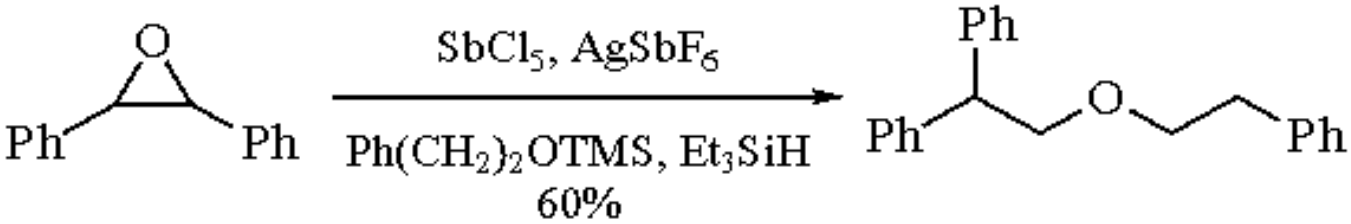

(6)

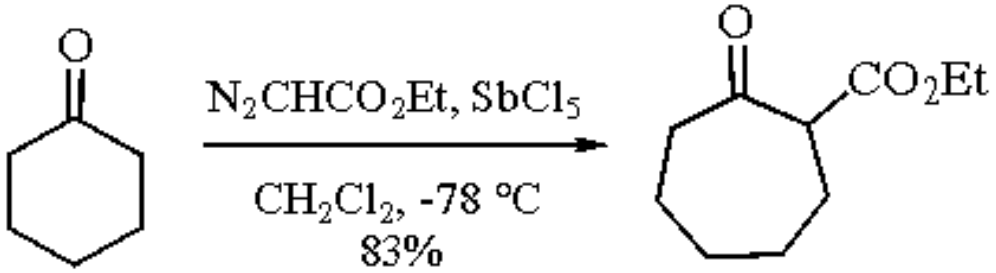

(7)

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Antimony(V) Fluoride[1]

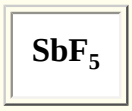

[7783-70-2] · F_5Sb · Antimony(V) Fluoride · (MW 216.74)

(one of the strongest Lewis acids,[1] used as catalyst for Friedel-Crafts reactions, isomerization, and other acid related chemistry;[1] an efficient acid system for preparation of carbocations and onium ions as well as their salts;[1] a fluorinating agent, and a strong oxidant)

Alternate Name: antimony pentafluoride.

Physical Data: bp 149.5 °C.

Solubility: SbF_5 reacts with most organic solvents, forming solids with ether, acetone, carbon disulfide, and petroleum ether. SbF_5 is soluble in SO_2 and SO_2ClF.

Form Supplied in: viscous liquid; commercially available.

Handling, Storage, and Precautions: SbF_5 is extremely corrosive, toxic, and moisture sensitive. It can be purified by distillation. SbF_5 fumes when exposed to atmosphere. It should be stored under anhydrous conditions in a Teflon bottle and handled using proper gloves in a well ventilated hood.

Antimony pentafluoride is one of the strongest Lewis acids reported and is capable of forming stable conjugate superacid systems with HF and FSO_3H (see ***Hydrogen Fluoride-Antimony(V) Fluoride*** and ***Fluorosulfuric Acid-Antimony(V) Fluoride***).[1] Its complex with ***Trifluoromethanesulfonic Acid*** is, however, less stable and cannot be stored for extended periods of time. Nevertheless, CF_3SO_3H/SbF_5 is also a useful acid system when prepared in situ.[2] The most important properties of SbF_5 include its high acidity, strong oxidative ability, and great tendency to form stable anions.[3] The chemistry of SbF_5 is mainly characterized by these properties. The major applications of SbF_5 in organic synthesis include oxidation, fluorination, and as a catalyst for Friedel-Crafts type reactions and other acid related chemistry, and as a medium for preparation of carbocations and onium ions.[1]

Friedel-Crafts and Related Chemistry.

The use of SbF_5 as a Friedel-Crafts catalyst has significantly expanded the scope of these reactions.[3] This is made possible through the strong Lewis acidity and oxidative ability of SbF_5. Influenced by the strong acidity, compounds of otherwise very weak nucleophilicity such as perfluorocarbons can react readily with aromatics. Furthermore, the strong

oxidative ability of SbF_5 enables unconventional substrates such as methane to be oxidized to form positively charged species, which in turn can be applied as electrophilic reagents. On the other hand, these factors also considerably restrict the use of SbF_5 in organic synthesis since the high reactivity makes it a less selective Lewis acid for many reactions.

Alkylation of arenes proceeds readily under SbF_5 catalysis.[3] In addition to alkyl halides, alkyl esters and haloesters have also been applied to alkylate arenes under the reaction conditions.[4] Perfluoro or perchlorofluoro compounds have been similarly used as alkylating agents in the presence of SbF_5.[5] For example, perfluorotoluene reacts with pentafluorobenzene to form perfluorodiphenylmethane in 68% yield after the reaction mixture is quenched with HF. When H_2O is used in the quenching step, perfluorobenzophenone is obtained in 93% yield (eq 1).[5a]

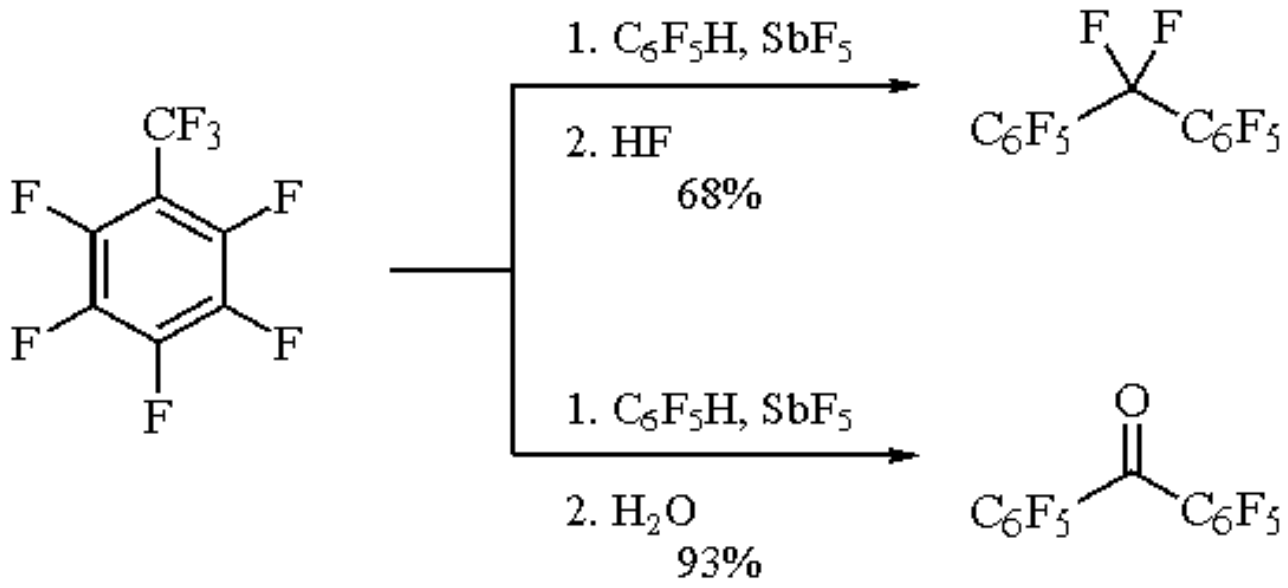

(1)

Acylation of pentafluorobenzene to form ketones either with acid halides or with anhydrides has been achieved with an excess of SbF_5.[6] In the case of dicarboxylic acid dichlorides or anhydrides as acylating agents, diketones are obtained as the reaction products (eq 2). The reaction of the anhydrides of dicarboxylic acids with aromatic compounds does not stop at the keto acid stage, as is the case when other Lewis acids are used. Using phosgene in place of acid chlorides results in the formation of pentafluorobenzoic acid in good yield.[3]

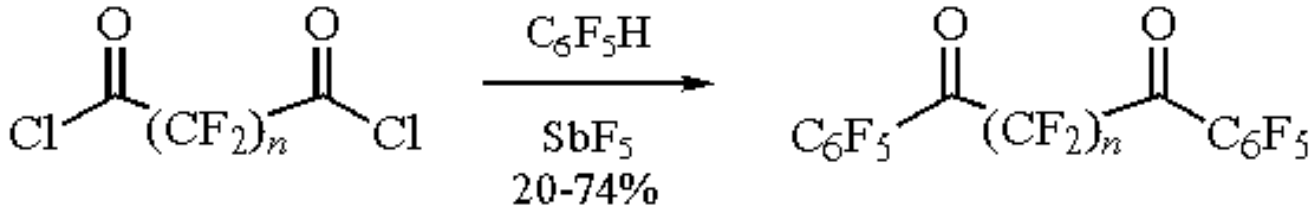

(2)

Perfluorobenzenium salt can be conveniently prepared from the reaction of 1,4-perfluorocyclohexadiene with SbF_5.[7a-c] In the presence of SbF_5, this salt is able to react with three equivalents of pentafluorobenzene to yield perfluoro-1,3,5-triphenylbenzene (eq 3).[7a-c] When 2,2´-di-*H*-octafluorobiphenyl is used as the substrate, perfluorotriphenylene is obtained in 50% yield (eq 4). Perfluoronaphthlenenium ion also reacts with polyfluorinated arenes in a similar fashion.[7a-c] The above reaction offers a facile approach for the preparation of these perfluorinated polynuclear aromatic compounds. Oxidation of perchlorobenzene with SbF_5 in the presence of pentafluorobenzene leads to the formation of coupling products.[7d]

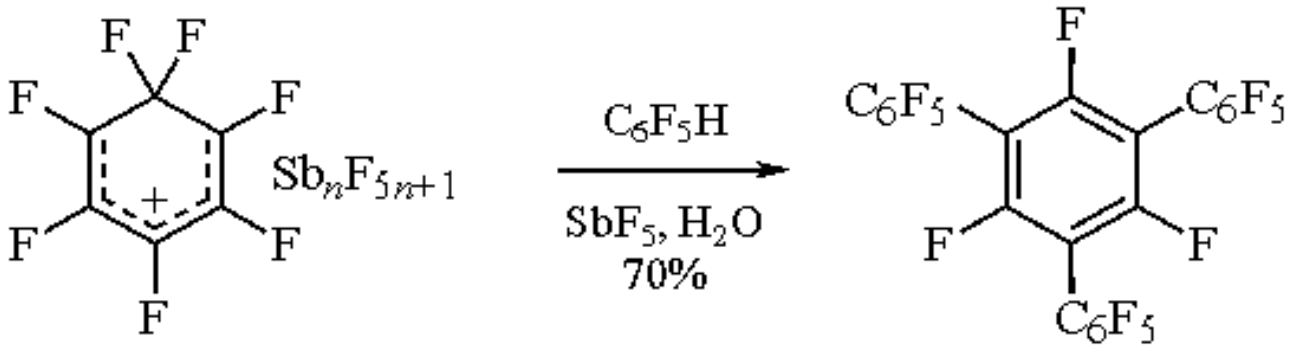

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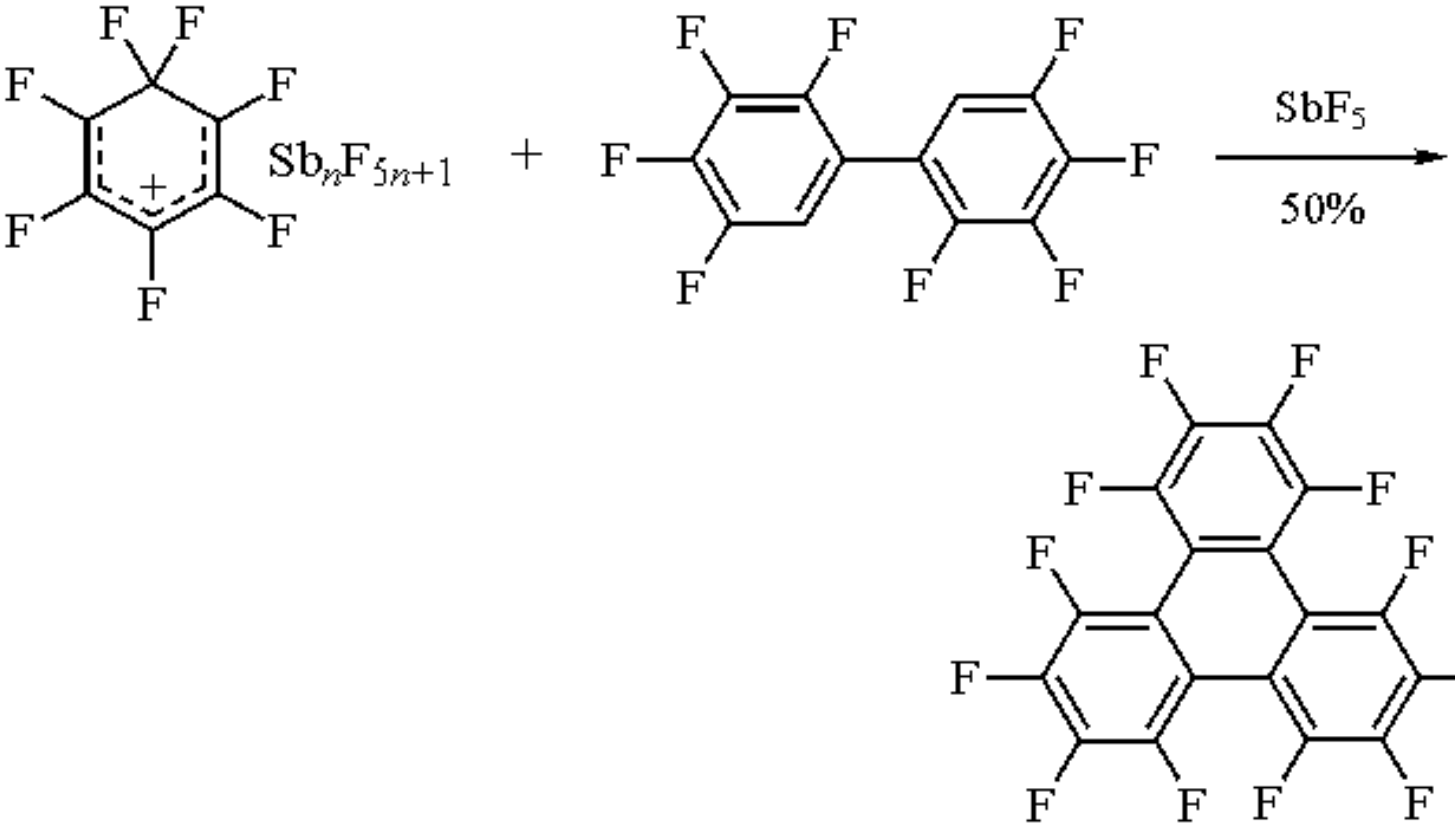

(4)

Friedel-Crafts sulfonylation of aromatics with alkane- and arenesulfonyl halides and anhydrides has been studied.[8] Good yields of sulfones are generally obtained (eq 5). In the case of pentafluorobenzenesulfonyl fluoride with pentafluorobenzene, decafluorodiphenyl sulfone is formed along with decafluorodiphenyl.[8c] A convenient approach for synthesizing symmetrical aryl sulfones is to react aromatics with ***Fluorosulfuric Acid*** in the presence of SbF_5 (eq 6).[9] Certain phenylacetylenes react with SO_2 and benzene in the presence of SbF_5 to form benzothiophene *S*-oxides[10] (eq 7). In some cases, 1,1-diphenylvinylsulfinic acids were also obtained as side products of the reaction. Sulfinyl fluoride reacts with arenes similarly under the catalysis of SbF_5 to give sulfoxides (eq 8).[8c]

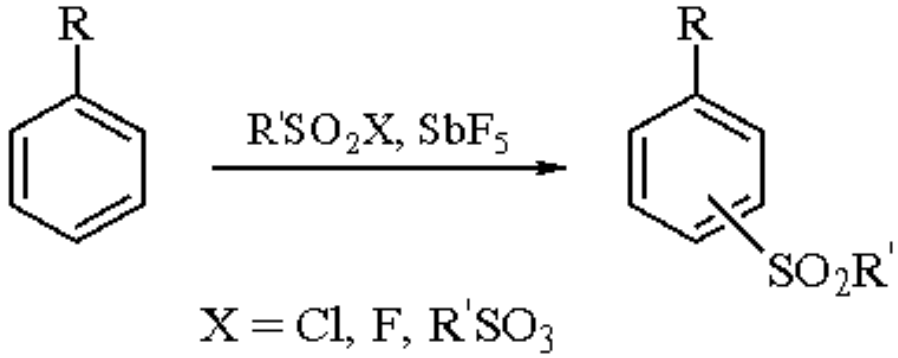

(5)

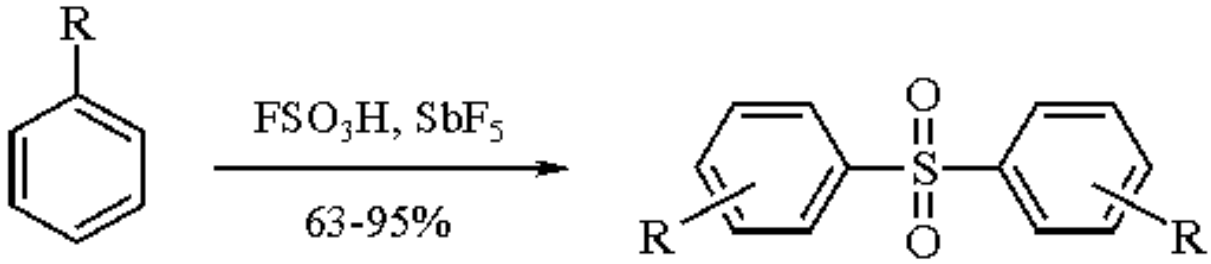

(6)

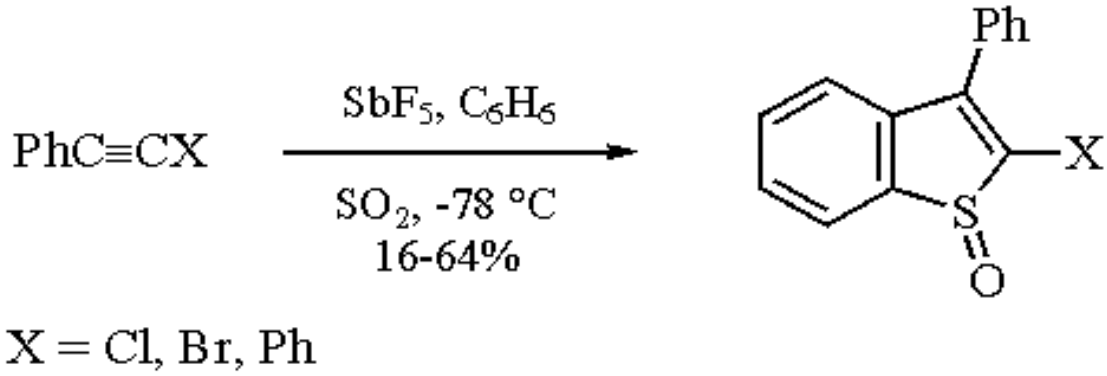

(7)

(8)

Oxidation of elemental sulfur and selenium with SbF_5 leads to the formation of doubly charged polyatomic cations.[11] These cations are able to react with polyfluorinated arenes to form diaryl sulfides or selenides (eq 9).[12a-c] Under similar treatment, polyfluorodiaryl disulfides or diselenides also react with aromatics to form diaryl sulfides and selenides, respectively (eq 10).[12a,12b]

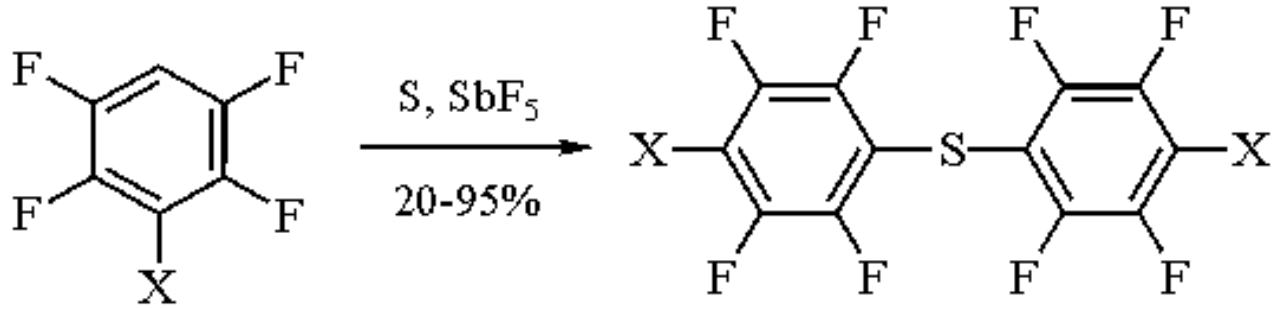

(9)

X = H, F, Br, SMe

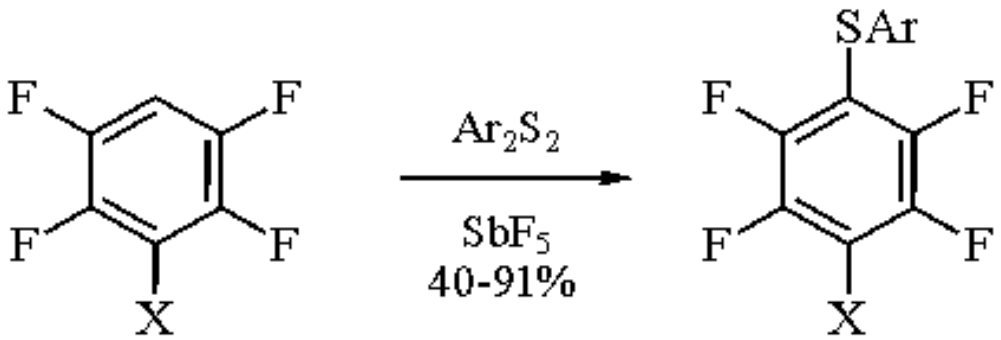

(10)

X = F, Cl; Ar = polyfluoroaryl

In the presence of SbF_5, inorganic halides such as NaCl and NaBr can serve as electrophilic halogenating agents.[5b,13] Even deactivated arenes such as 5*H*-nonafluoroindan can be brominated under the reaction conditions (eq 11).[13b]

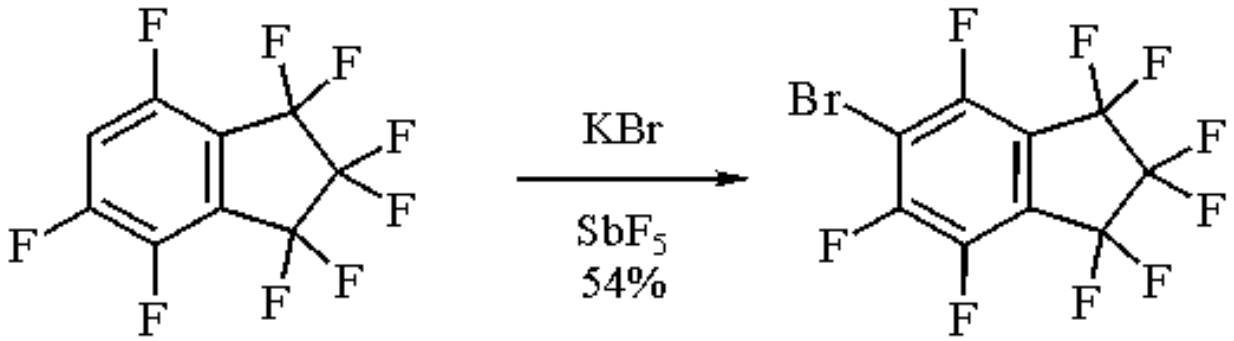

(11)

Functionalization of alkanes has been achieved under SbF_5 catalysis.[3] Halogenation of alkanes is one of the widely studied reactions in this field.[14] A valuable synthetic procedure is the reaction of alkanes with methylene chloride (or bromide) in the presence of SbF_5 (eq 12).[14d] In these reactions, halonium ions are initially formed, which in turn abstract hydride from hydrocarbons. Quenching of the resulting carbocations with halides leads to the desired haloalkanes.

$$RH \xrightarrow[64\text{-}88\%]{CH_2X_2,\ SbF_5} RX \qquad (12)$$

RH = secondary, tertiary alkanes
X = Cl, Br

In the presence of SbF_5, alkyl chlorides are ionized to form carbocations, which can be trapped with CO.[15] Quenching the reaction intermediates with water or alcohols yields the corresponding carboxylic acids or esters. For instance, halogenated trishomobarrelene reacts with CO in SbF_5/SO_2ClF to give, after treatment with alcohol and water, a mixture of acid and ether (eq 13).[15a]

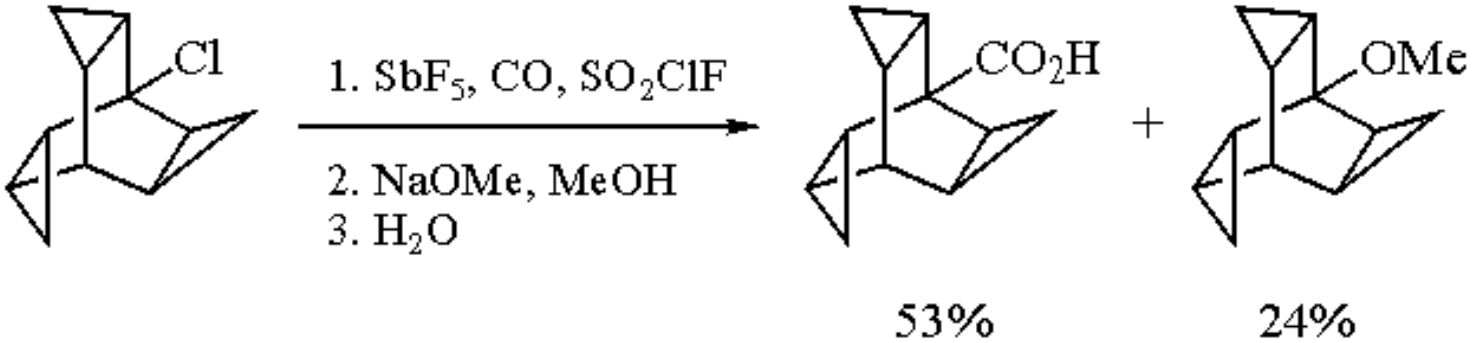

(13)

Studies have been carried out on the alkylation of alkenes in the presence of SbF_5, especially fluoroalkenes.[16] For example, treatment of 1,1,1-trifluoroethane with SbF_5 in the presence of tetrafluoroethylene yields 90% of 1,1,1,2,2,3,3-heptafluorobutane.[16c] Perfluoroallyl or -benzoyl compounds with varying structures have also been utilized as alkyating agents (eqs 14 and 15).[16b,e-h] At elevated temperatures, intramolecular alkylation was observed in certain cases with perfluorodienes, forming perfluorocyclopentenes or perfluorocyclobutenes (eq 16).[17]

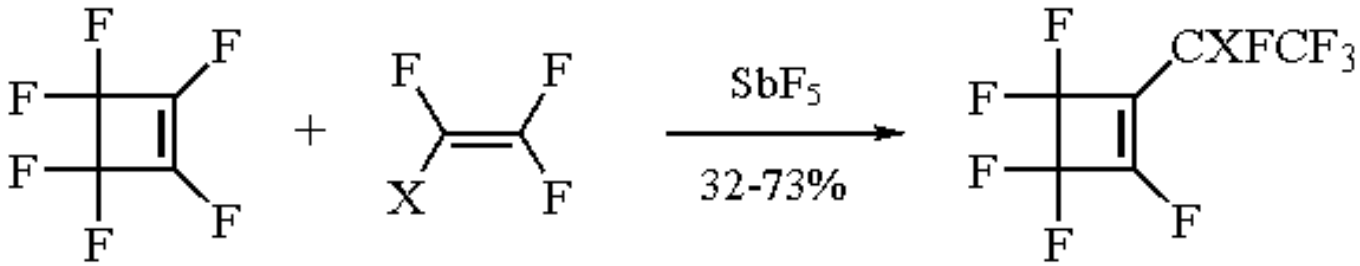

(14)

X = F, CF_3

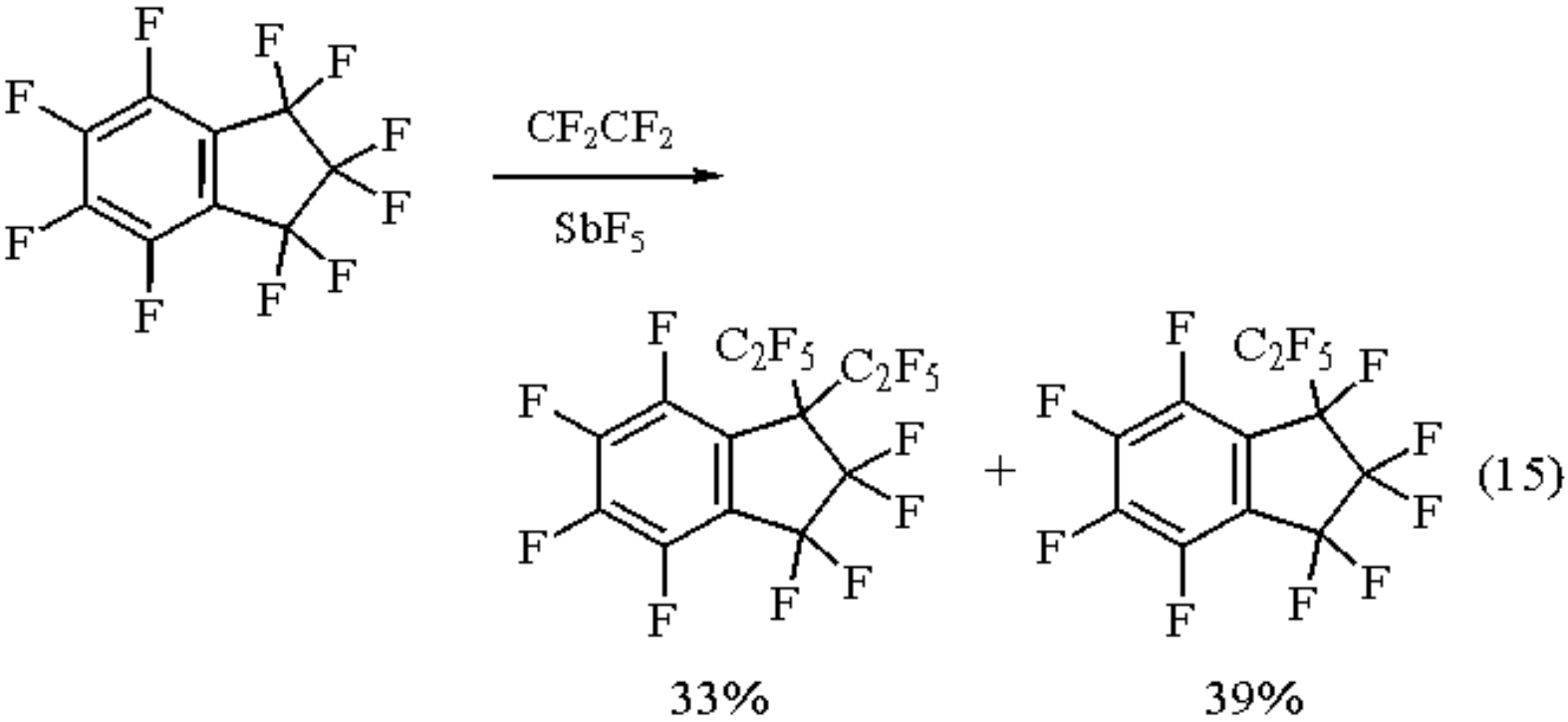

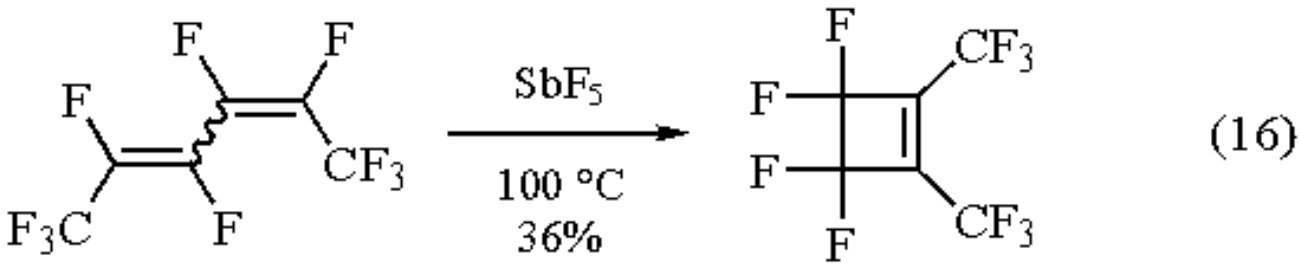

Acylation of alkenes can also be similarly effected with SbF_5.[18] Reaction of acetyl fluoride with trifluoroethylene produces 1,1,1,2-tetrafluorohexane-3,5-dione in 40% yield.[18a] When antimony pentafluoride is used in excess (more than 6 molar equivalents), 1,1,1,2-tetrafluorobutan-3-one is formed as a side product. Benzoyl fluoride reacts with difluoroethylene to form the expected ketone in 39% yield.[18a] α,β-Unsaturated carboxylic acid fluorides have also been used in reactions with perfluoroalkenes.[18b] In these cases, α,β-unsaturated ketones are obtained (eq 17). Enol acetates of perfluoroisopropyl methyl ketone and perfluoro-*t*-butyl methyl ketone react with acetyl fluoride to provide the corresponding β-diketones (eq 18).[18c]

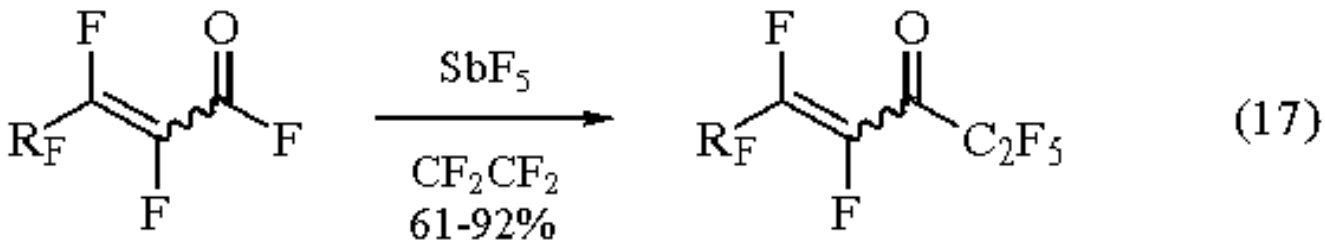

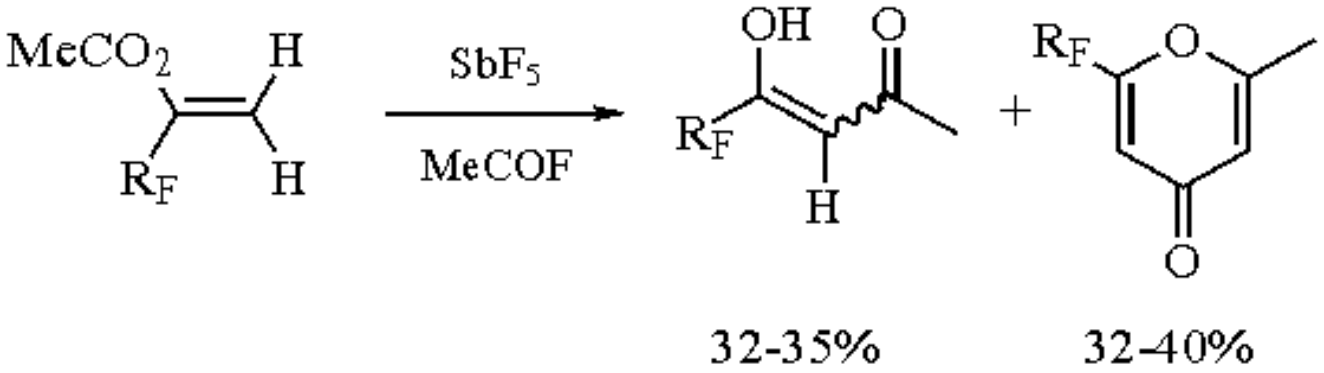

(18)

Oxygenation of dienes with molecular oxygen to form Diels-Alder-type adducts can be effected by Lewis acids and some salts of stable carbenium ions.[19] In the case of ergosteryl acetate, SbF_5 is by far the most active catalyst (eq 19).[19a]

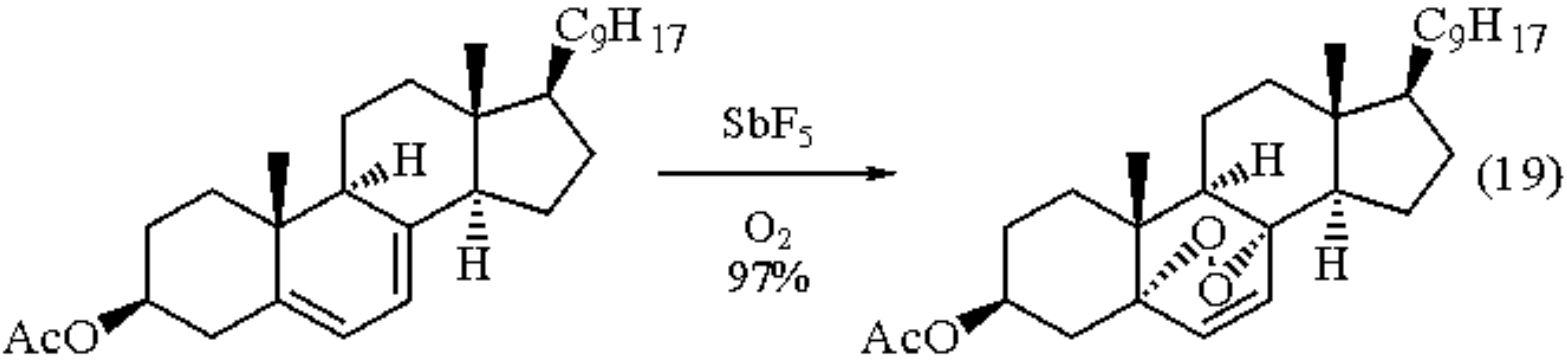

(19)

Isomerization and Rearrangement.

Isomerization of perfluoroalkenes can be realized with SbF_5 catalysis.[20] The terminal carbon-carbon bonds of these alkenes are usually moved to the 2-position under the influence of this catalyst (eq 20). A further inward shift generally occurs only if H or Cl atoms are present in the 4-position of the alkenes. As a rule, the isomerization leads to the predominant formation of the *trans* isomers. Terminal fluorodienes also isomerize exothermally into dienes containing internal double bonds in the presence of SbF_5. With a catalytic amount of SbF_5, perfluoro-1,4-cyclohexadiene disproportionates to hexafluorobenzene and perfluorocyclohexene. The disproportionation proceeds intramolecularly in the case of perfluoro-1,4,5,8-tetrahydronaphthalene. The starting material is completely converted to perfluorotetralin (eq 21).[20f]

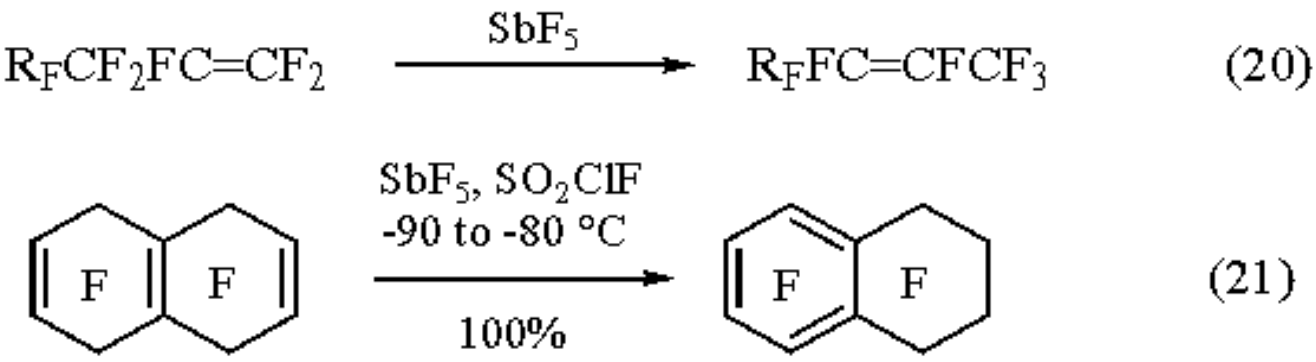

(20)

(21)

Like most Lewis acids, SbF_5 promotes the rearrangement of epoxides to carbonyl compounds,[21] and SbF_5 is an efficient catalyst for this reaction. However, the migratory aptitude of substitutent groups in the reaction under SbF_5 catalysis is much less selective compared to that promoted by weak Lewis acids such as ***Methylaluminum Bis(4-bromo-2,6-di-t-butylphenoxide)***.[21a] Nevertheless, SbF_5 is well suited for the rearrangement of perfluoroepoxides.[21b-e] Excellent yields of ketones are obtained from the reaction. When diepoxides are used, diketones are obtained as the reaction products (eq 22).[21c]

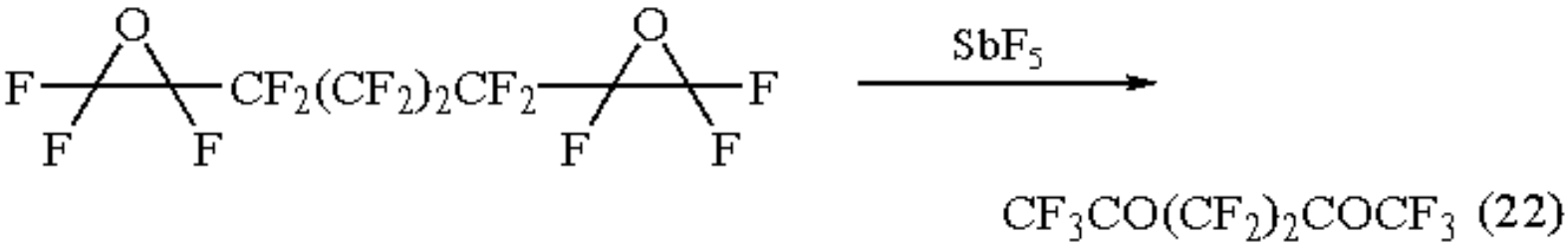

Fluorination and Transformation of Fluorinated Compounds.

SbF_5 is a strong fluorinating agent. However, its use is largely limited to the preparation of perfluoro- or polyfluoroorganic compounds.[22] SbF_5 has also been used for transformation of perfluoro compounds.[22]

When hexachlorobenzene is subjected to SbF_5 treatment, 44% of 1,2-dichloro-3,3,4,4,5,5,6,6-octafluorocyclohex-1-ene is obtained as the major product of the reaction (eq 23).[23] Using $SbCl_5$ as reaction solvent leads to better reaction control, resulting in an increase in the product yield.[23c] In the case of polyfluoronaphthalenes, polyfluorinated tetralins are obtained.[23d] Treatment of hexafluoro-2-trichloromethyl-2-propanol with SbF_5 gives perfluoro-*t*-butyl alcohol in 92% yield (eq 24).[24]

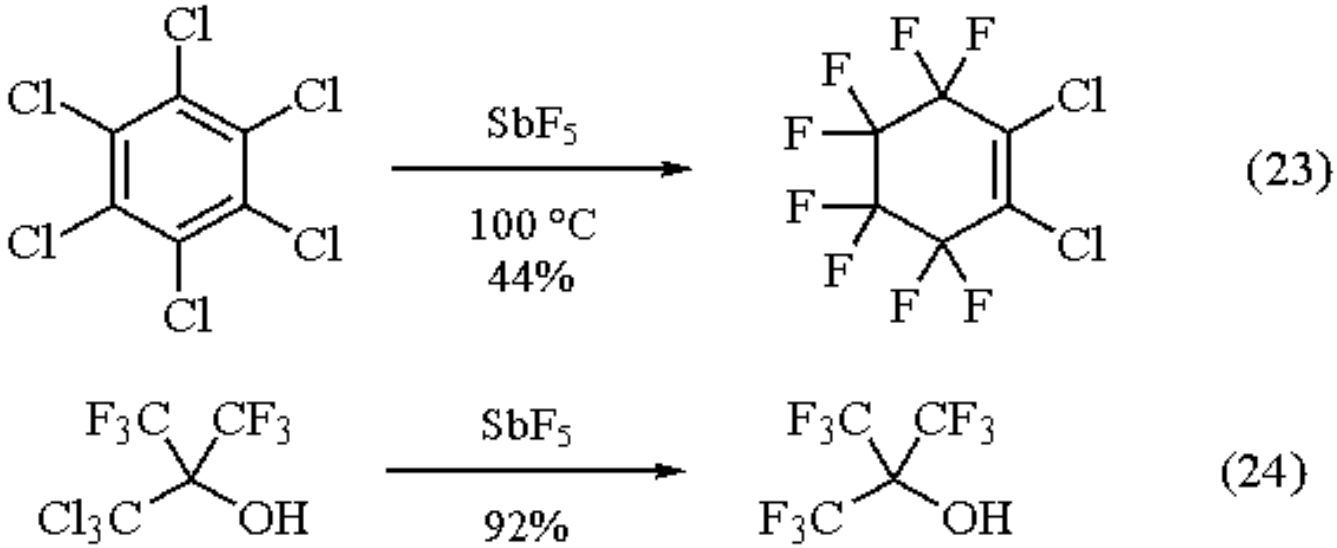

Hydrolysis of CF_3 groups to CO_2H can be induced by SbF_5.[25a] In this reaction, the CF_3-bearing compounds are first treated with SbF_5 and the resulting reaction mixtures are subsequently quenched with water to form the desired products. For example, perfluorotoluene was converted to pentafluorobenzoic acid in 86% yield by this procedure.

When perfluoroxylenes and perfluoromesitylene go through the same treatment, the corresponding di- or triacids are obtained in high yields. It is also possible to partially hydrolyze perfluoroxylenes and perfluoromesitylene through a stepwise procedure and to isolate intermediate products. The hydrolysis procedure is also applicable to other halogen-containing compounds.[25b]

Under SbF_5 catalysis, ***Trifluoromethanesulfonic Anhydride*** is readily decomposed to trifluoromethyl triflate in high yield (eq 25).[26] This method is the most convenient procedure reported for preparation of the triflate.

$$(CF_3SO_2)_2O \xrightarrow[94\%]{SbF_5,\ 25\ ^\circ C} CF_3SO_3CF_3 \qquad (25)$$

Preparation of Carbocations, Onium Ions, and Their Salts.

SbF_5 is a preferred medium for the preparation of carbocations and onium ions.[1] In fact, the first observation of stable carbocations was achieved in this medium.[1,27] By dissolving *t*-butyl fluoride in an excess of SbF_5, the *t*-butyl cation was obtained (eq 26). Subsequently, many alkyl cations have been obtained in SbF_5 (either neat or diluted with SO_2, SO_2ClF, or SO_2F_2). The 2-norbornyl cation, one of the most controversial ions in the history of physical organic chemistry,[28] was prepared from *exo*-2-fluoronorbornane in SbF_5/SO_2 (or SO_2ClF) solution (eq 27).[1] Bridgehead cations such as 1-adamantyl, 1-trishomobarrelyl, and 1-trishomobullvalyl cations have also been similarly prepared with the use of SbF_5.[15a,29]

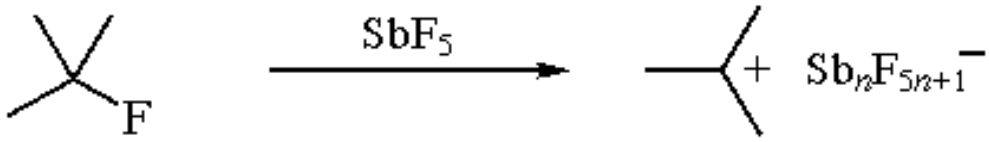

(26)

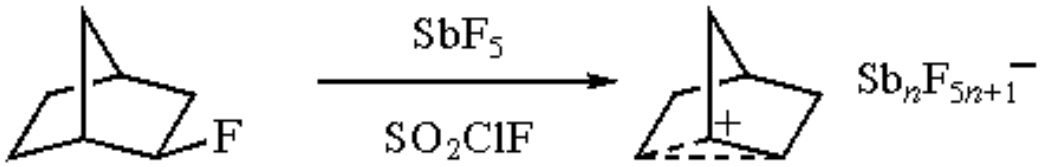

(27)

Carbodications have also been studied.[1] One convenient way of preparing alkyl dications is to ionize dihalides with SbF_5 in SO_2ClF (eq 28). In these systems, separation of the two cation centers by at least two methylene groups is necessary for the ions to be observable.[1] Aromatic dications are usually prepared by oxidizing the corresponding aromatic compounds with SbF_5 (eq 29).[1,30] In the case of pagodane containing a planar cyclobutane ring, oxidation leads to the formation of cyclobutane dication which was characterized as a frozen two-electron Woodward-Hoffmann transition state model (eq 30).[31]

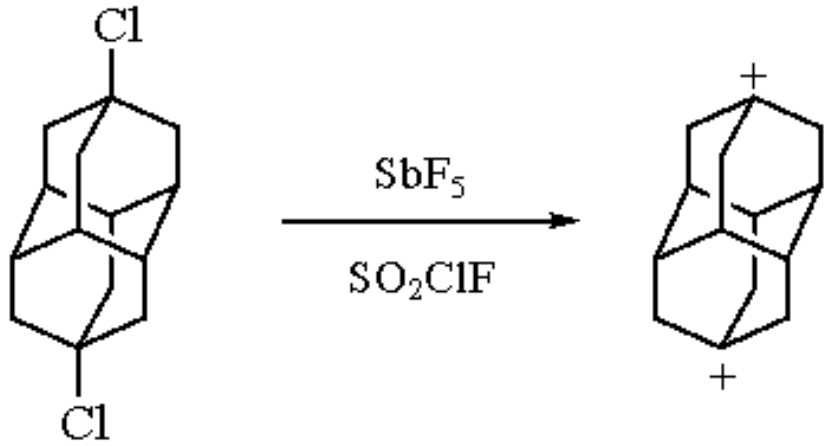

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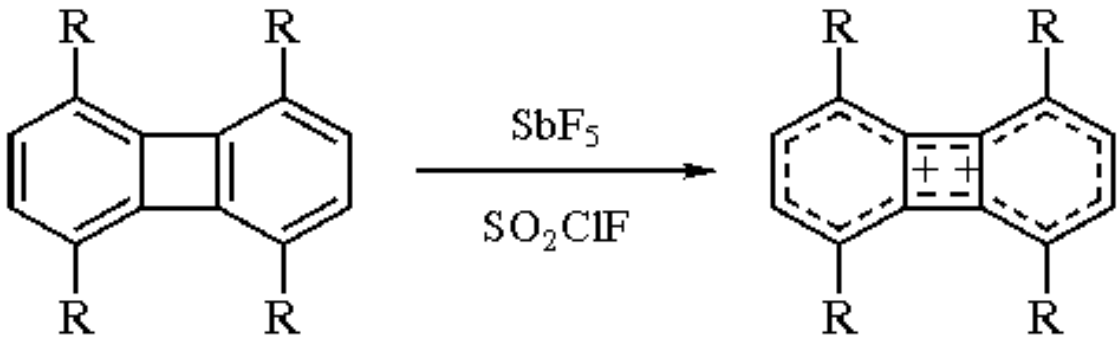

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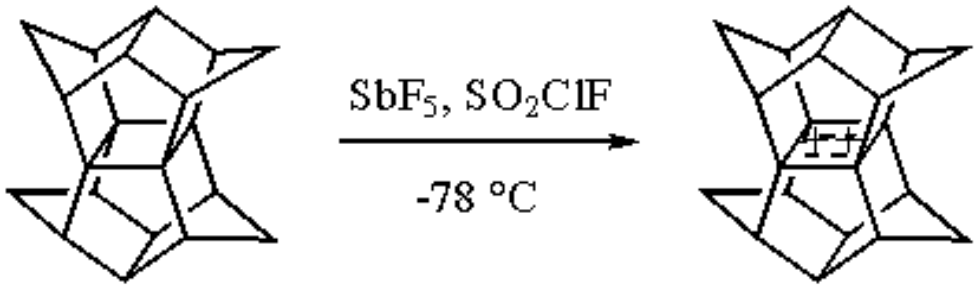

(30)

SbF_5 has also been found useful in the preparation of homoaromatic cations.[1,32] For example, the simplest 2π monohomoaromatic cations, the homocyclopropenyl cations, can be prepared from corresponding 3-halocyclobutenes in SbF_5 (eq 31).[32a]

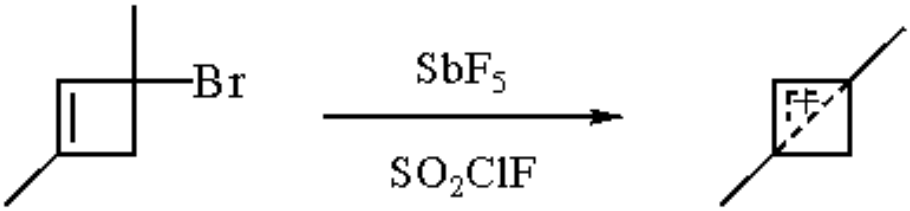

(31)

Perfluorocarbocations are generally prepared with the aid of SbF_5.[33] Perfluorobenzyl cations and perfluorinated allyl cations are among the most well studied perfluorinated carbocations. It was reported that in the perfluoroallyl cations containing a pentafluorophenyl group at the 1- or 2-position, the phenyl groups were partially removed from the plane of the allyl triad (eq 32).[33b]

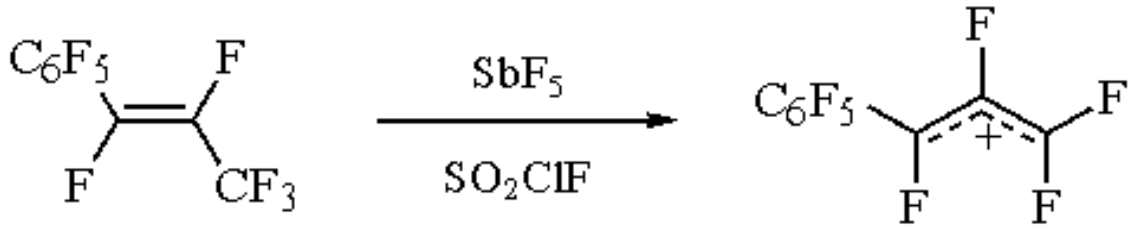

(32)

Use of SbF_5 as ionizing agent offers a convenient route to acyclic and cyclic halonium ions from alkyl halides.[1] Three-membered ring cyclic halonium ions are important intermediates in the electrophilic halogenations of carbon-carbon double bonds.[1] More recently, a stable 1,4-bridged bicyclic bromonium ion, 7-bromoniabicyclo[2.2.1]heptane, has been prepared through the use of SbF_5 involving an unprecedented transannular participation in a six-membered ring (eq 33).[34]

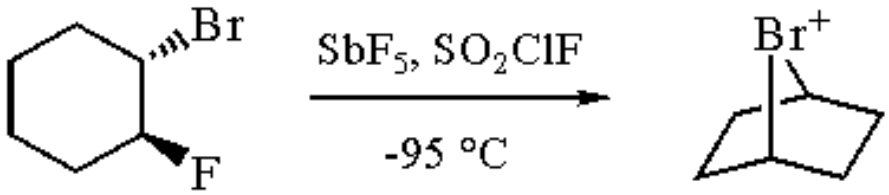

(33)

Other Reactions.

Reaction of α,β-unsaturated carbonyl compounds with diazo compounds generally gives low yields of cyclopropyl compounds. The rapid formation of 1-pyrazolines and their subsequent rearrangement products 2-pyrazolines is the reason for the inefficiency of cyclopropanation of these substrates. However, in the presense of SbF_5, the cyclopropanation of α,β-unsaturated carbonyl compounds with diazocarbonyl compounds proceeds very well to produce the desired products in good yields (eq 34).[35]

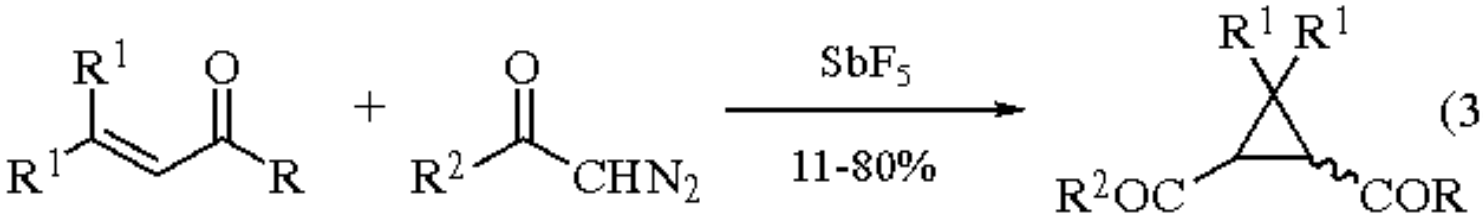

(34)

$R = H, OMe; R^1 = H, Me; R^2 = Ph, OEt$

Related Reagents.

Fluorosulfuric Acid-Antimony(V) Fluoride; ***Hydrogen Fluoride-Antimony(V) Fluoride***; ***Methyl Fluoride-Antimony(V) Fluoride***.

---

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Arsenic(III) Fluoride[1]

AsF_3

[7784-35-2] · AsF_3 · Arsenic(III) Fluoride · (MW 131.92)

(arsenating agent;[2] fluorinating agent[3])

Alternate Name: arsenic trifluoride.

Physical Data: mp -5.95 °C (-8.5 °C); bp 57.8 °C (63 °C); d^{15} 2.73 g cm^{-3}.

Solubility: sol ether, THF, C_6H_6, hydrocarbons, alcohols; hydrolyzes in H_2O.

Form Supplied in: colorless, mobile liquid; commercially available.

Analysis of Reagent Purity: ^{19}F NMR, Raman spectrum.[4]

Preparative Methods: several methods exist for the preparation of arsenic trifluoride.[5]

Purification: the reagent can be purified by distillation at atmospheric pressure in an all-glass or iron system.[5]

Handling, Storage, and Precautions: when heated, AsF_3 decomposes to highly toxic fumes containing As^0.[6] Additionally, it will fume in air and is readily hydrolyzed. Contact with skin results in burns similar to those caused by HF.[5a] Since AsF_3 reacts with glass over time, it should be stored in polyethylene or iron containers.[5] This reagent should be handled in a fume hood.

Use as an Arsenating Agent.

Arsenic trifluoride has seen its most extensive use in organic chemistry as an arsenating agent. Usually, the fluoride ligands are exchanged with another ligand such as an amine (eq 1).[7] Cyclic arsenic compounds can be synthesized in moderate to good yields by using bidentate ligands (eq 2).[2a,8]

$$AsF_3 + 2RNH_2 \xrightarrow[0\ ^{o}C\ to\ rt]{toluene} RNHAsF_4 + RNH_2HF \xrightarrow{-HF} RN{=}AsF \quad (1)$$

R = Et (60%), *i*-Pr (63%), *t*-Bu (67%)

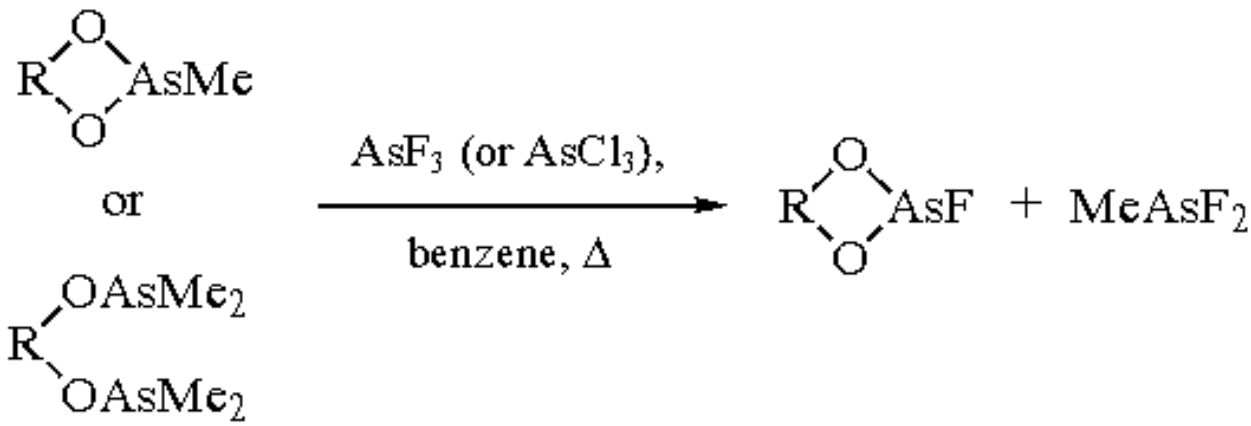

R = -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-,

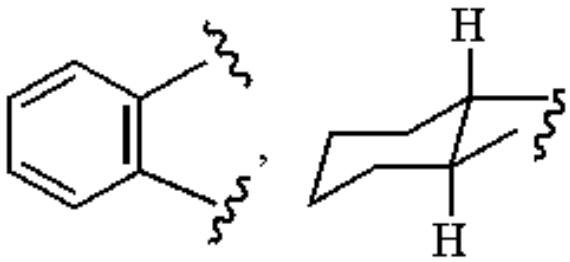

Some advantage has been taken of the strength of the silicon-fluorine bond in these exchange reactions (eqs 3 and 4).[2b,9] Not surprisingly, the product cyclopentadienylarsenic difluoride (eq 4) is unstable and polymerizes upon distillation at 30 °C.[9]

$$3\ t\text{-BuSSiMe}_3 \xrightarrow[-196\ ^{o}C\ to\ rt]{AsF_3,} As(S\text{-}t\text{-Bu})_3 \quad (3)$$

(quantitative)

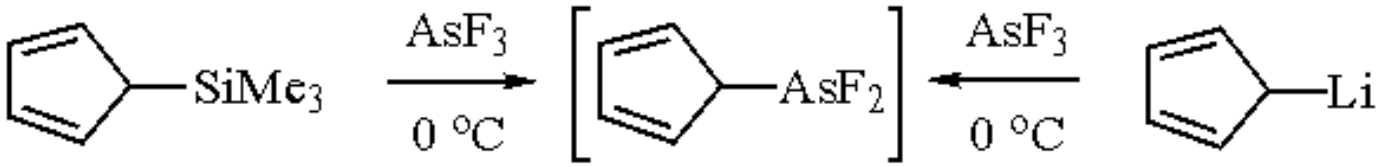

(not isolated)

There is some indication that AsF_3 is less reactive with organic compounds than $AsCl_3$ and the higher homologs (eq 5).[2c,10] Usefully, organoarsenic mono-[11] and difluorides[2c] can be converted to the arsenic hydrides by reaction with

Lithium Aluminum Hydride (eq 6).[11]

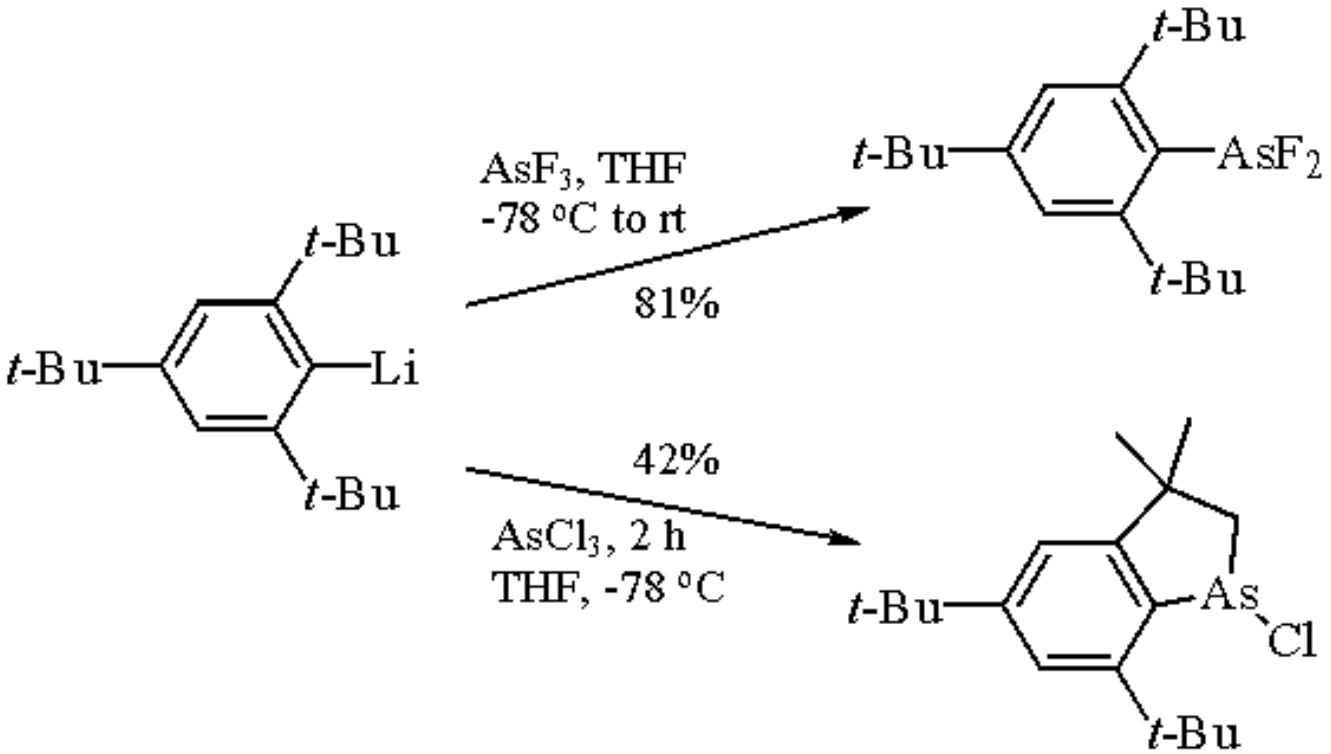

(5)

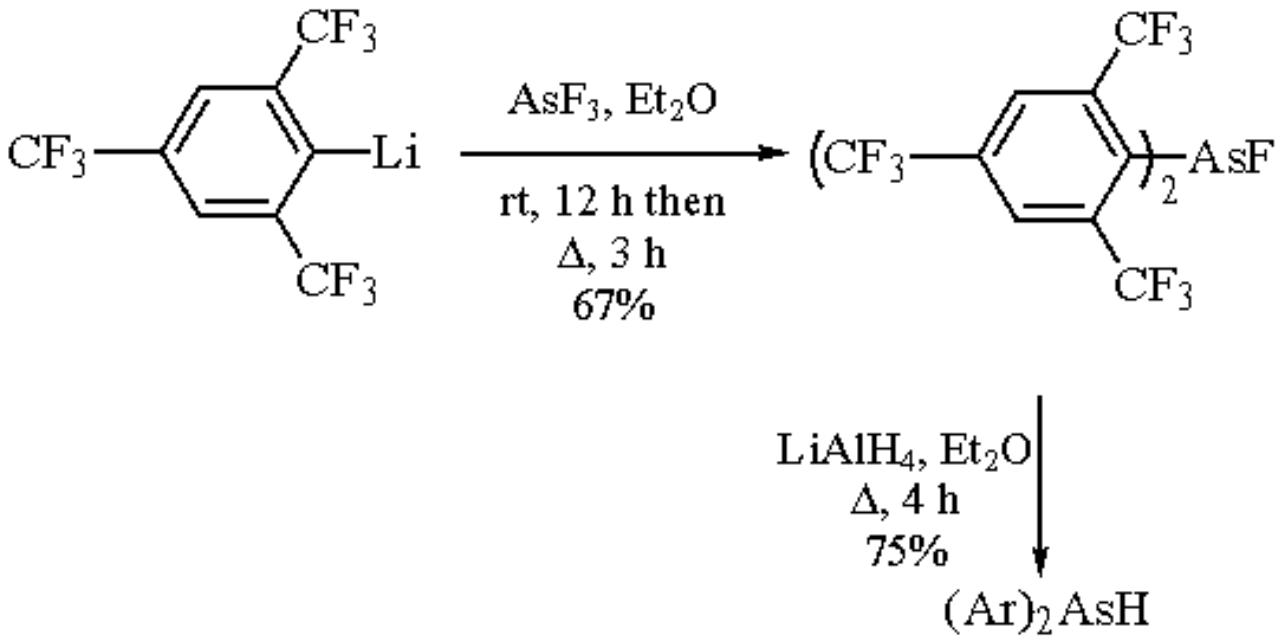

(6)

Importantly, AsF_3 can be added across alkenes in the presence of ***Antimony(V) Fluoride*** (eqs 7 and 8).[12,13] Although stoichiometrically the AsF_3 seems to simply add to the alkene, it is more likely that the reactive species is AsF_2^+SbF-6 in these transformations.[12]

$$AsF_3 + SbF_5 + F_2C{=}CF_2 \xrightarrow[12\ h]{rt} \underset{42\%}{(C_2F_5)_2AsF} + \underset{26\%}{(C_2F_5)_3As} \quad (7)$$

$$AsF_3 + SbF_5 + F_2C{=}CFCl \xrightarrow[6\ h]{rt} \underset{58\%}{(CF_3CFCl)_2AsF} + \underset{14\%}{(CF_3CFCl)_2AsCl} \quad (8)$$

Use as a Fluorinating Agent.

Although milder than SbF_3, AsF_3 can also be used as fluorinating agent. Typically, a ligand exchange reaction occurs in which the fluoride ligands are exchanged for other ligands such as another halide (eq 9).[3,14]

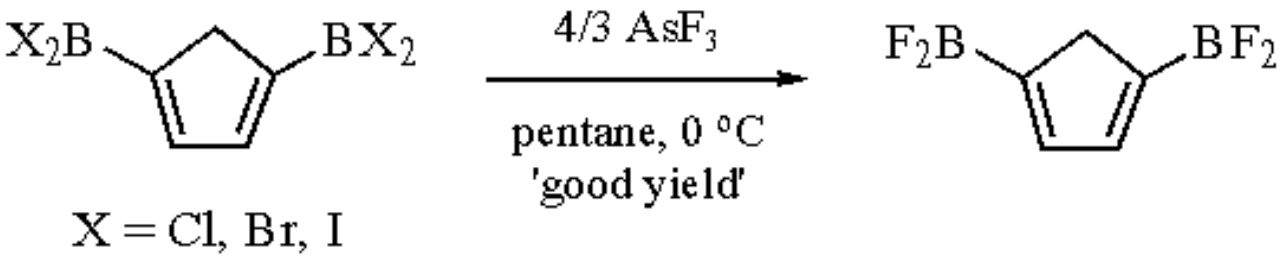

(9)

Fluck et al. have used AsF_3 in several exchange reactions with Et_2N ligands on trivalent phosphorus to generate phosphorus-fluorine bonds (eqs 10 and 11).[15,16]

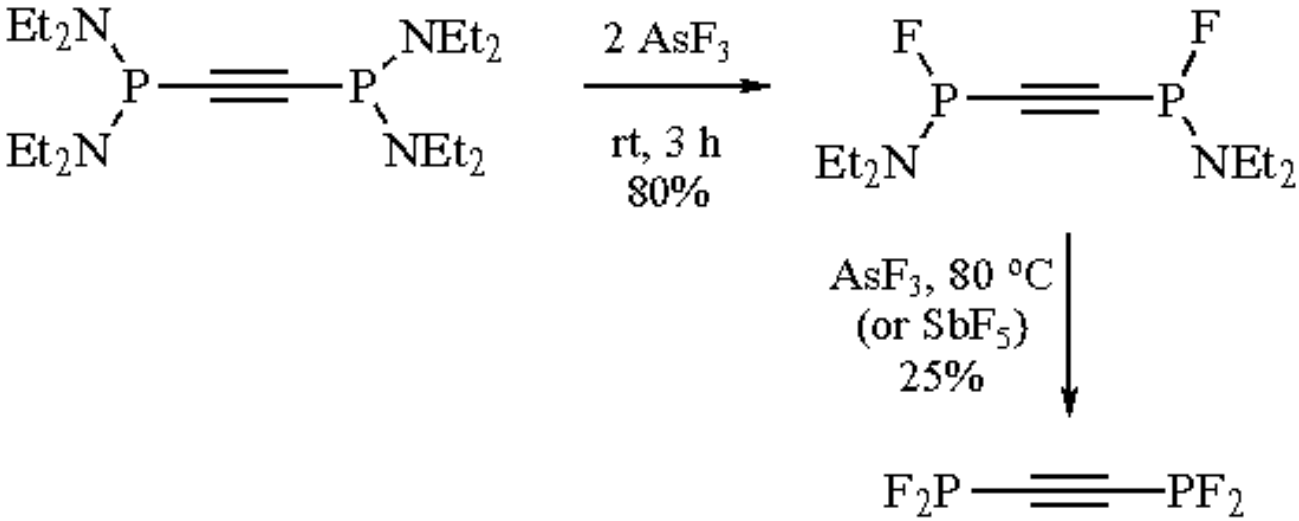

(10)

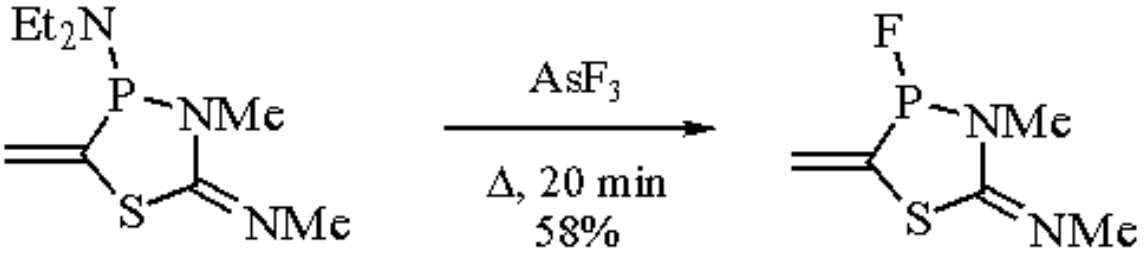

(11)

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L-Aspartic Acid[1]

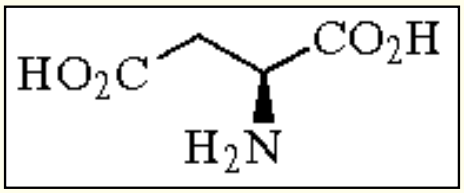

(L)

[56-84-8] · $C_4H_7NO_4$ · L-Aspartic Acid · (MW 133.10) (D)

[1783-96-6] (DL)

[617-45-8]

(chiral reagent used in diastereoselective alkylations[2] and as a ligand for $LiAlH_4$ in asymmetric reductions[3] of enones)

Physical Data: (*S*)-(+),[4a] [α]20D +25°, mp >300 °C (dec.); (*R*)-(-),[4a] [α]20D -24°, mp >300 °C; (±) mp 325-348 °C (dec.).

Solubility: sol in acid and alkali; sol water (1 g/222.2 mL at 20 °C), forming supersaturated solutions easily; insol alcohol.

Form Supplied in: commercially available as a white solid in racemic and optically pure forms.[4]

Diastereoselective Alkylations.

Esters derived from L-aspartic acid have been alkylated at both the α- and β-positions (eq 1).[1,2] β-Alkylations have been more widely used. The amino acid moiety is responsible for the diastereoselection in the β-alkylation process.

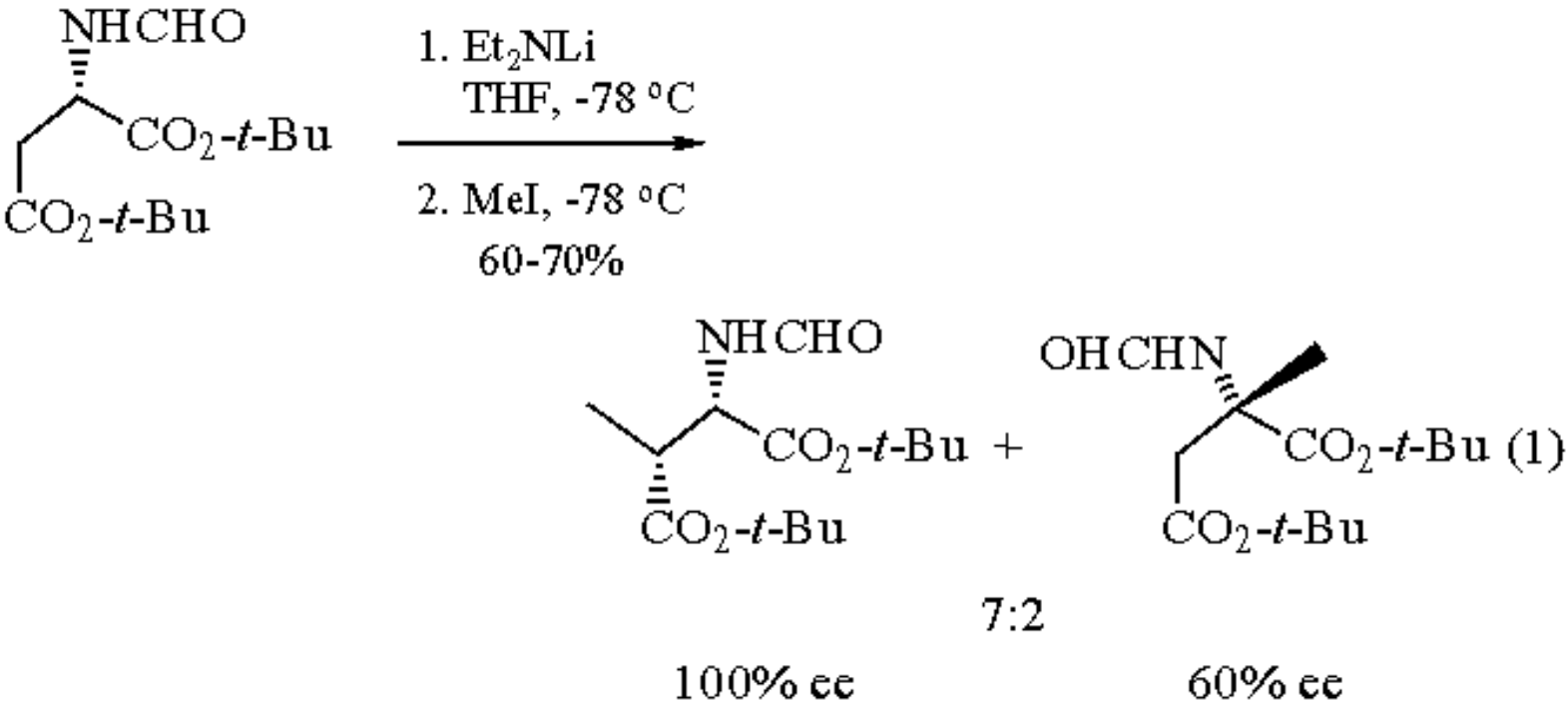

Alkylation of cyclic derivatives of L-aspartic acid (**1**) occurs exclusively at the β-position with good to excellent diastereoselection. One application is the synthesis of chiral β-dicarbonyl equivalents.[5] Equivalents of either enantiomer can be prepared depending on whether the alkylation is performed on a lactone (eq 2) or an oxazoline (eq 3).

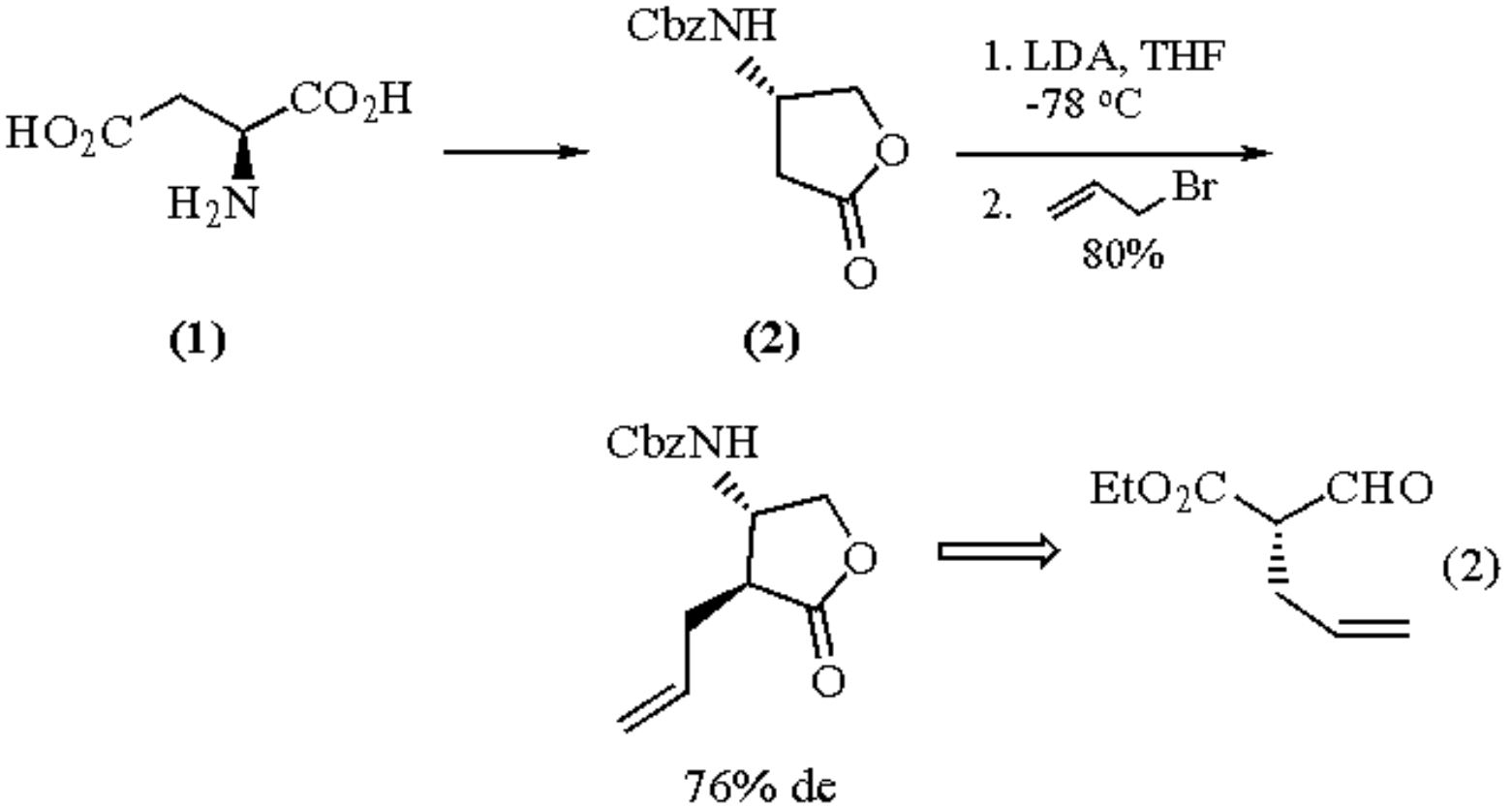

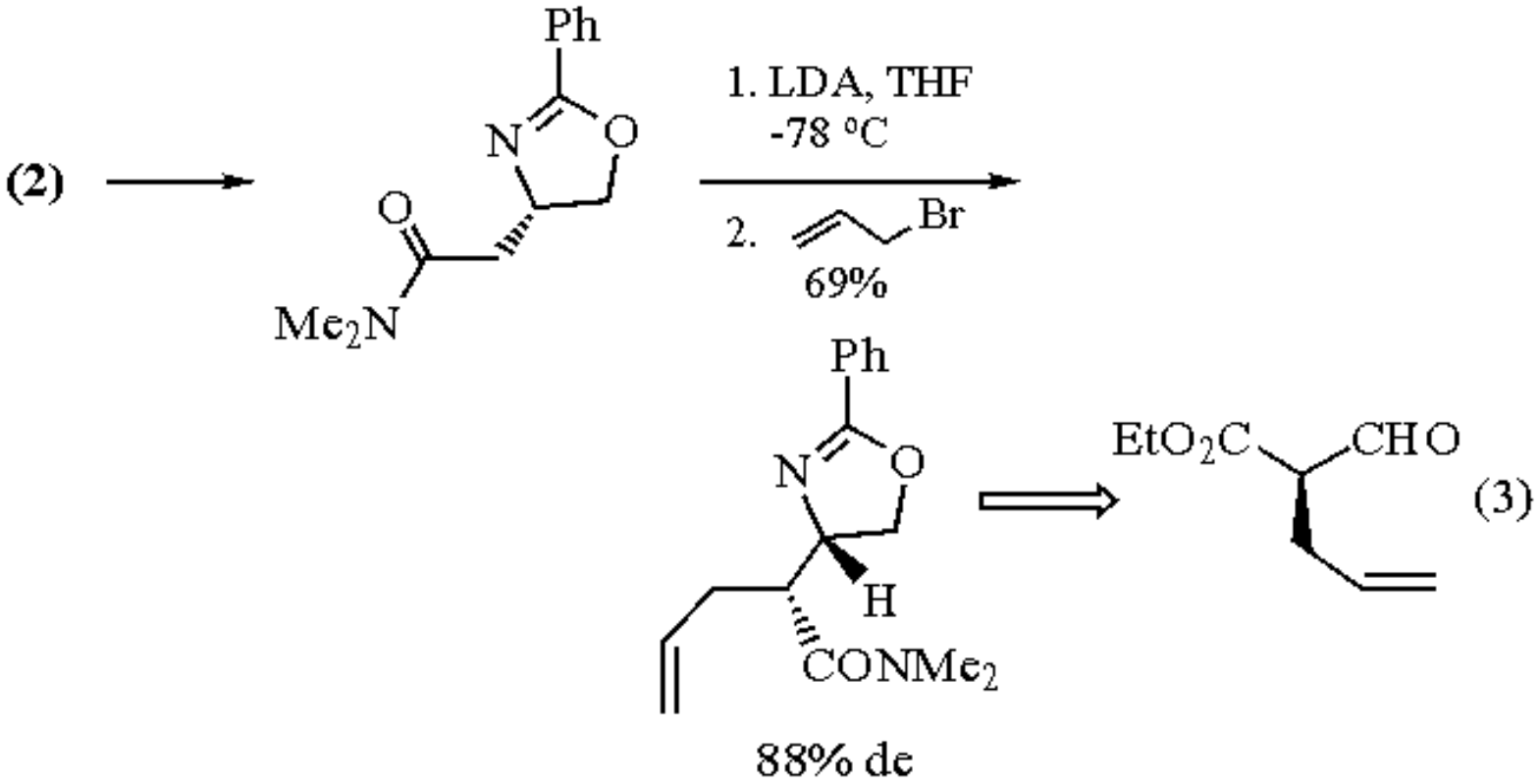

The most commonly used cyclic derivatives of L-aspartic acid are β-lactams (eq 4).[6] For example, excellent regioselectivity and diastereoselectivity are observed in the alkylation of the dianion of (**3**). Other compounds related to (**3**) have been prepared from L-aspartic acid[7] and used in highly diastereoselective alkylations en route to a variety of natural and nonnatural products[8] including β-lactams,[9] γ-lactams,[10] and dihydroisocoumarin derivatives.[11]

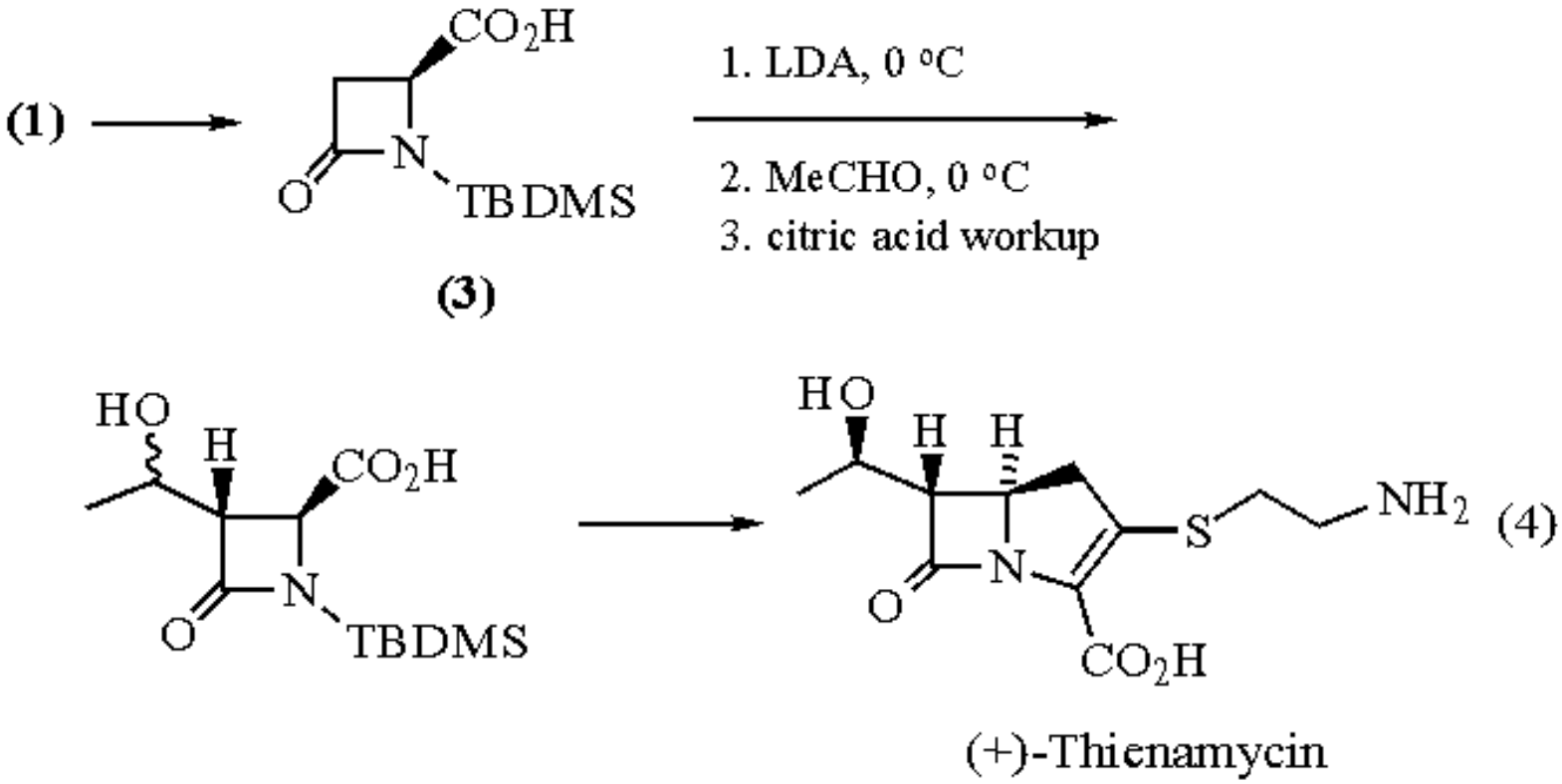

Asymmetric Reductions.

Asymmetric reductions of prochiral ketones to optically active secondary alcohols have been extensively studied.[3] The most common method involves the use of chiral unidentate or bidentate ligands in conjunction with ***Lithium Aluminum Hydride***. However, an (*S*)-aspartic acid derived tridentate ligand has been shown to be very effective in certain cases, presumably due to the rigidity of aluminum complex (**4**) (eqs 5-7).[12]

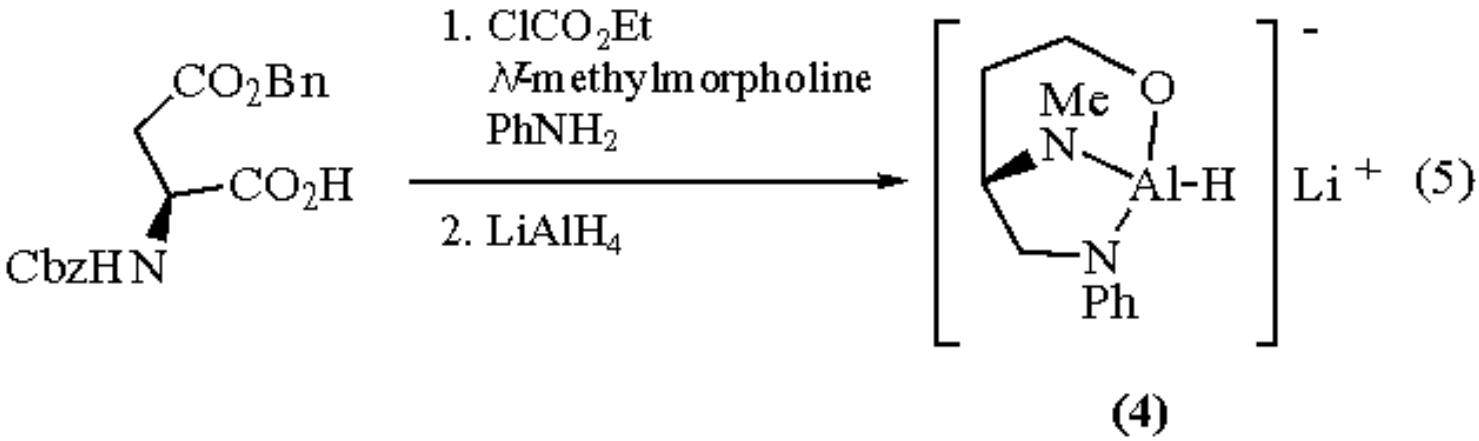

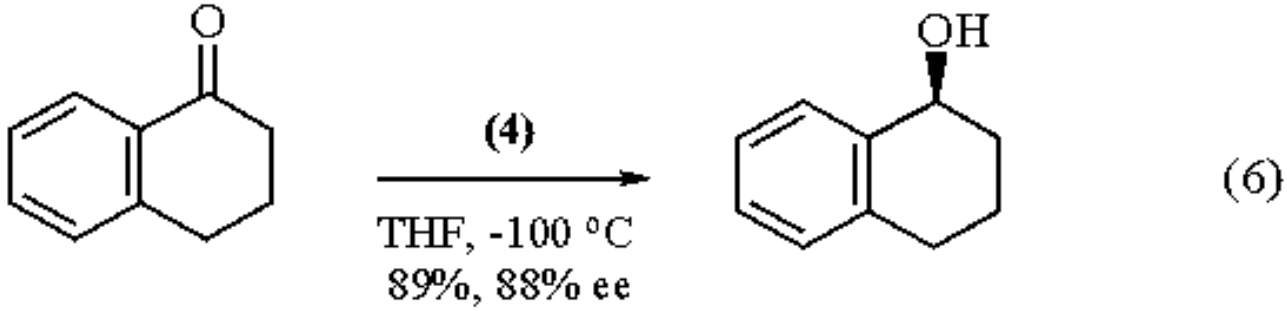

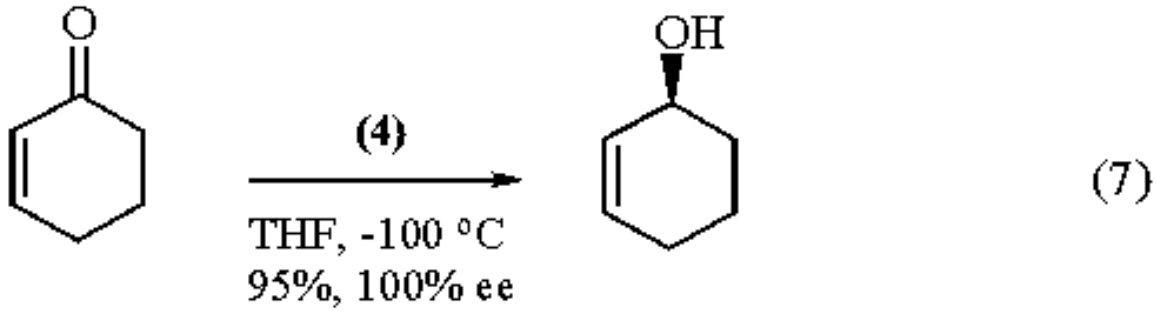

Unfortunately, the complete enantiofacial differentiation of cyclohexenone (eq 7) appears to be an isolated case, as reaction with 3-methylcyclohexenone afforded the corresponding (*S*)-cyclohexanol in only 28% ee. In the absence of a general trend for the outcome of these reductions, the scope of this method seems limited at this point, as opposed to (*S*)-BINAL-H mediated reductions (see ***Lithium Aluminum Hydride*** and subsequent articles).

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2-Azabicyclo[2.2.1]hept-5-en-3-one

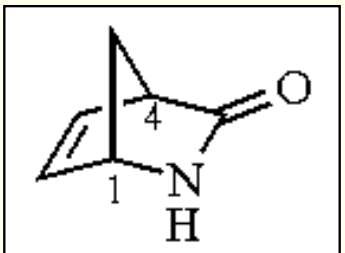

(1*R*,4*S*)-(-)-(**1**)

[49805-30-3] · C_6H_7NO · 2-Azabicyclo[2.2.1]hept-5-en-3-one · (MW 109.13) (±)

[61865-48-3] (1*R*)

[79200-56-9] (1*S*)

[130931-83-8]

(building block for the synthesis of carbocyclic nucleosides, GABA inhibitors, etc.)

Physical Data: mp 55-57 °C; bp 102-106 °C/0.25 mmHg.

Solubility: sol H_2O, MeOH, CH_2Cl_2.

Form Supplied in: off-white solid.

Preparative Methods: from reaction of ***Cyclopentadiene*** with either sulfonyl cyanides[1,2] or ***Chlorosulfonyl Isocyanate***.[3] Both enantiomers can be obtained via enzymic kinetic resolution of the racemate.[4]

2-Azabicyclo[2.2.1]hept-5-en-3-one (**1**) has been used as a building block for the synthesis of an array of compounds with potential pharmacological applications. Either enantiomer of *cis*-3-aminocyclopentanecarboxylic acid (**2**) is accessible from a single enantiomer of (**1**) (eq 1). Compound (**2**) has been shown to act as an agonist at the γ-aminobutyric acid (GABA) receptor.[5]

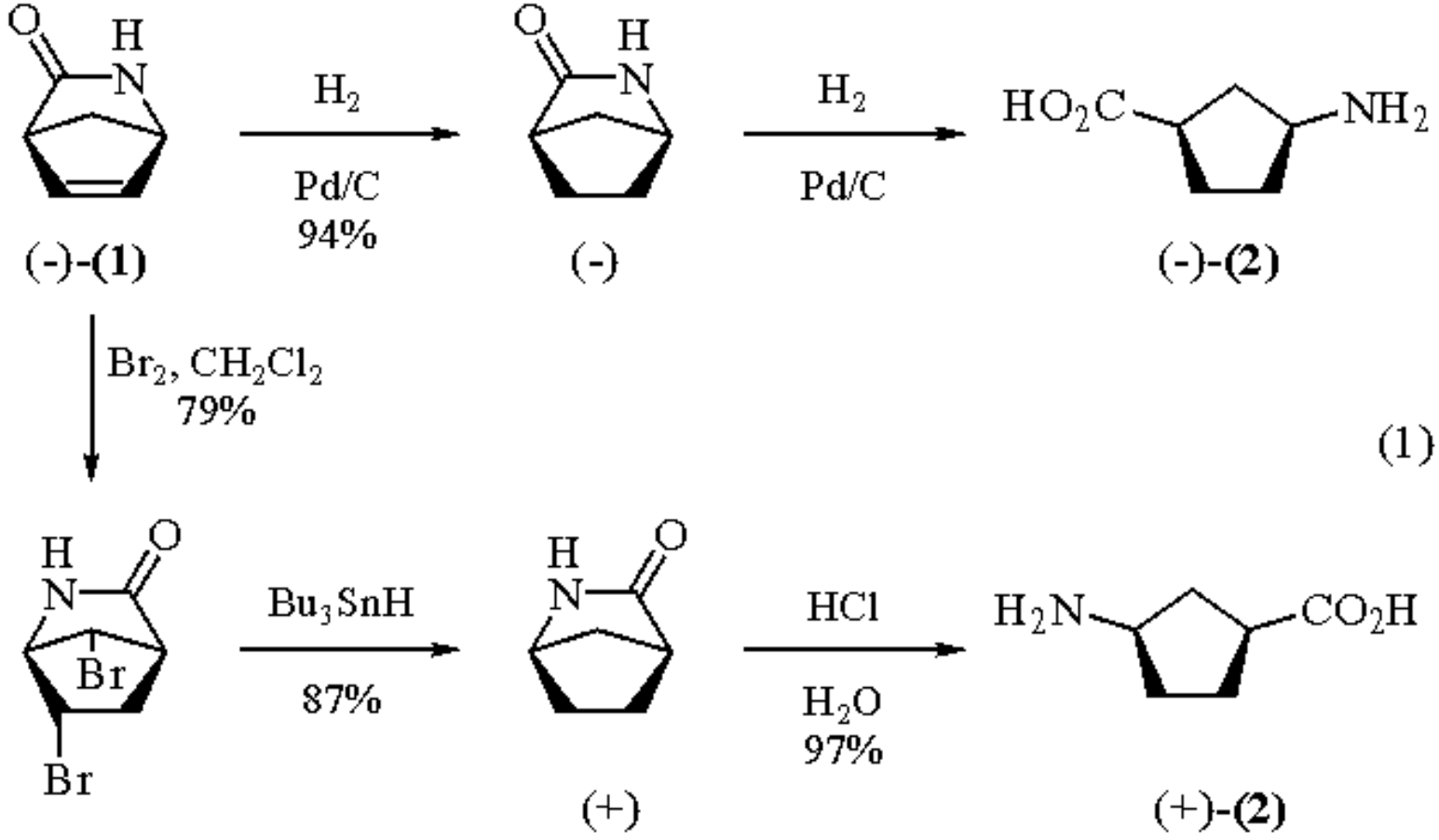

(1)

The (1*R*,4*S*) enantiomer ((-)-**1**) has been used for the preparation of the carbocyclic nucleoside (-)-carbovir (**3**) (eq 2),[6] which has been shown to have similar activity against HIV (RF strain) as AZT (Zidovudine).

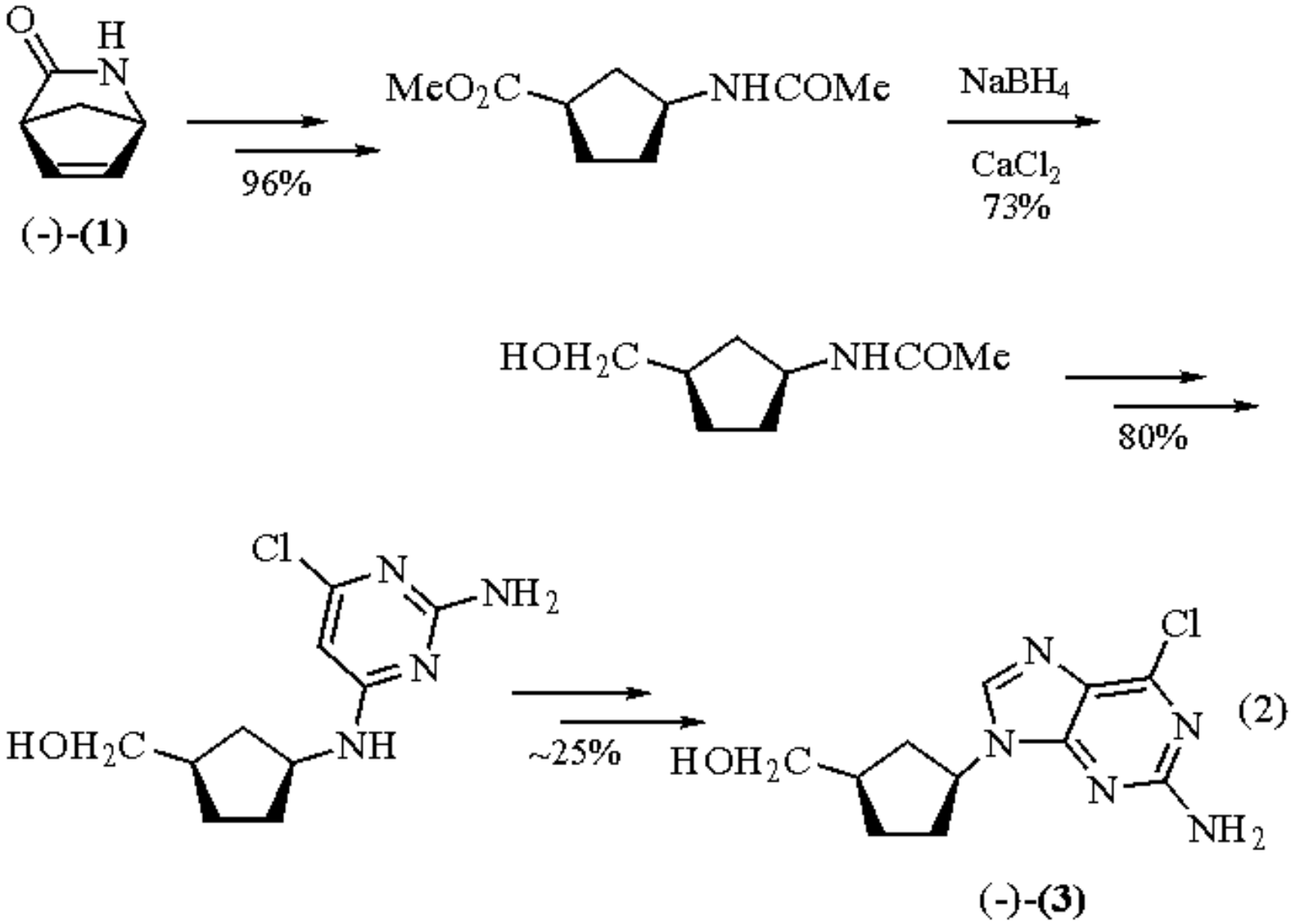

Treatment of (**1**) with ***Potassium Monoperoxysulfate*** (oxone) gave an 80% yield of the *exo*-epoxide (**4**) (eq 3), which is of potential use for the preparation of carbocyclic analogs of 2´-or 3´-deoxyribofuranosylamines.

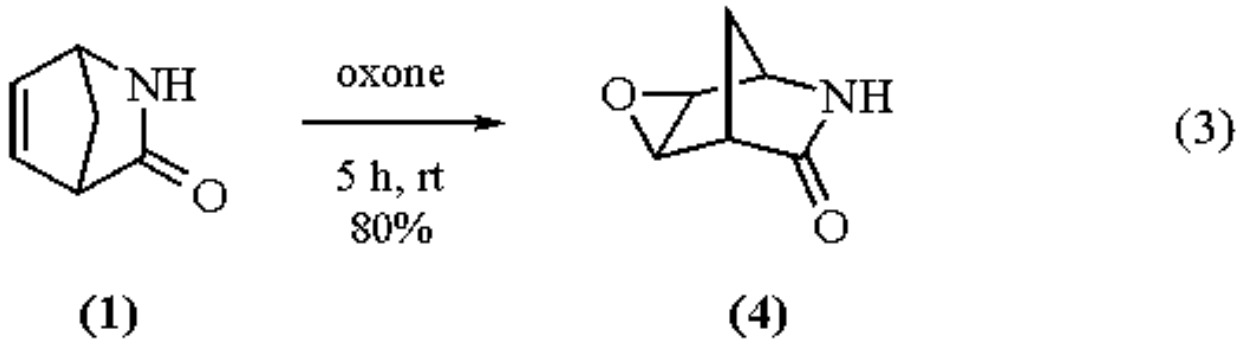

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Azidation Polymer[1]

$$\mathbf{P}\text{-}NR_3^+\ N_3^-$$

(used for nucleophilic substitution of azide for halide or sulfonate;[1-6] for introduction of the azide function[1-6])

Physical Data: polymeric resin in form of beads.[2]

Solubility: insol organic solvents, water.

Form Supplied in: available as azide exchange resin, containing ~3.8 mequiv azide ions per gram of resin.

Preparative Methods: the azidation polymer is prepared[2] from Amberlite IR-400 Cl-ion exchange resin (a quaternary ammonium chloride), which is prewashed first with 1.5 times its volume of warm DMF, twice with MeOH, and finally with water. Then the resin is converted into the azide form by washing with twice its volume of 20% aq sodium azide, followed by three washings with deionized water until the eluents give no precipitate with $AgNO_3$ (eq 1). To remove adhered water (which may lead to alcohol product), the resin is washed three times each with 30% MeOH, 60% MeOH, MeOH, 50% MeOH-ether, and ether (or another organic solvent to be used in the nucleophilic substitution reaction). The resin is dried at rt in vacuum and contains ~2.55 mmol azide ions per gram of polymer.

$$\underset{\text{(Amberlite IR-400)}}{\mathbf{P}\text{-}NR_3^+\ Cl^- + NaN_3} \longrightarrow \underset{\text{Azidation polymer}}{\mathbf{P}\text{-}NR_3^+\ N_3^-} \qquad (1)$$

Handling, Storage, and Precautions: the polymer can be stored for several months, preferably either wet with water or wet with the last washing solvent. It is stable to the hammer test and has a friction parameter of 14.4 kg. It should not be treated with acids because toxic HN_3 is formed. *Caution*: when CH_2Cl_2 is used as a solvent for the displacement reaction and the reaction is allowed to proceed for several days, explosive $CH_2(N_3)_2$ may be formed.[2] Handle reagent in a fume hood.

Synthesis of Alkyl Azides.

A typical procedure for nucleophilic displacement of alkyl halides or tosylates with azide ions:[1] to 4.9 g of azidation polymer (12.5 mmol of azide ions) was added 4 mL of CH_2Cl_2 (see above) or another solvent and 0.265 g (1.06 mmol) of *p*-bromobenzyl bromide. The reaction is followed for disappearance of starting benzyl bromide and after 2 h of mild shaking of the slurry in an horizontal cuvette the polymer is filtered and washed with CH_2Cl_2. Mechanical stirring of the

slurry of azidation polymer and substrate is not recommended because shearing of the polymer beads occurs. Evaporation of the combined solvents gave pure (by ^{1}H NMR) *p*-bromobenzyl azide as an oil in 93% yield.

The use of azidation polymer permits displacement of alkyl halides or tosylates by azide ions at room temperature in any organic solvent, usually within hours, as the reaction is followed to the disappearance of starting alkyl halide.[1] After filtration of the polymeric reagent, a solution of pure alkyl azide is obtained. Further purification is usually not necessary. Iodides are displaced faster than bromides, which react faster than tosylates; alkyl chlorides react slowest.[1] In polar solvents (MeCN, DMF) the displacement is faster than in less polar solvents ($CHCl_3$, ether) and secondary halides react slower than primary ones.[1] The more dilute the slurry, the slower the reaction. Even bromoform is converted at rt slowly (22 days for 50% conversion) to highly explosive triazidomethane.[2]

In MeCN, quantitative conversion of *n*-Bu-X to *n*-Bu-N_3 takes place at rt by means of the azidation polymer in the following approximate times:[1] *n*-Bu-I (1 h), *n*-Bu-Br (3 h), *n*-Bu-OTs (24 h), *n*-Bu-Cl (>7 d), Br-$(CH_2)_4$-Br (24 h).

Benzyl chloroformate is converted to benzyl azidoformate at rt.[1] Allyl azides can be prepared readily from allyl bromides using the reagent. For instance, 5-bromo-1,3-pentadiene is converted in 95% yield to 5-azido-1,3-pentadiene.[3]

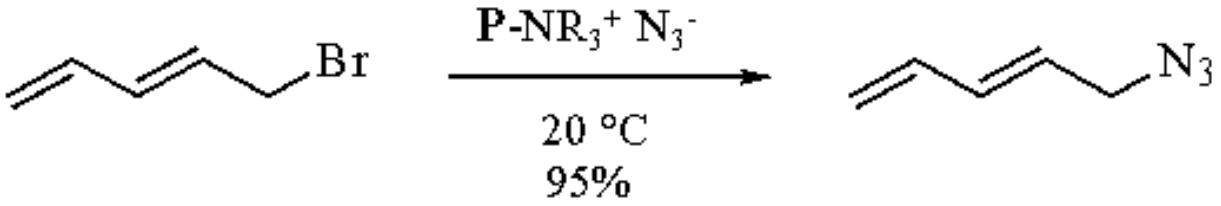

(2)

o-Azido-4-methoxyacetophenone is obtained from the respective phenacyl bromide.[4] Anhydrothymidine after *N*-alkylation with ethyl triflate followed by reaction with the azidation reagent at 0 °C for 16 h gave the 4-azido- and 2-azidothymidine derivatives (eq 3).[5] 1,2-*cis*-Diols have been converted to 1,2-*cis*-azido alcohol benzoates via the *trans*-chlorohydrin benzoate.[6]

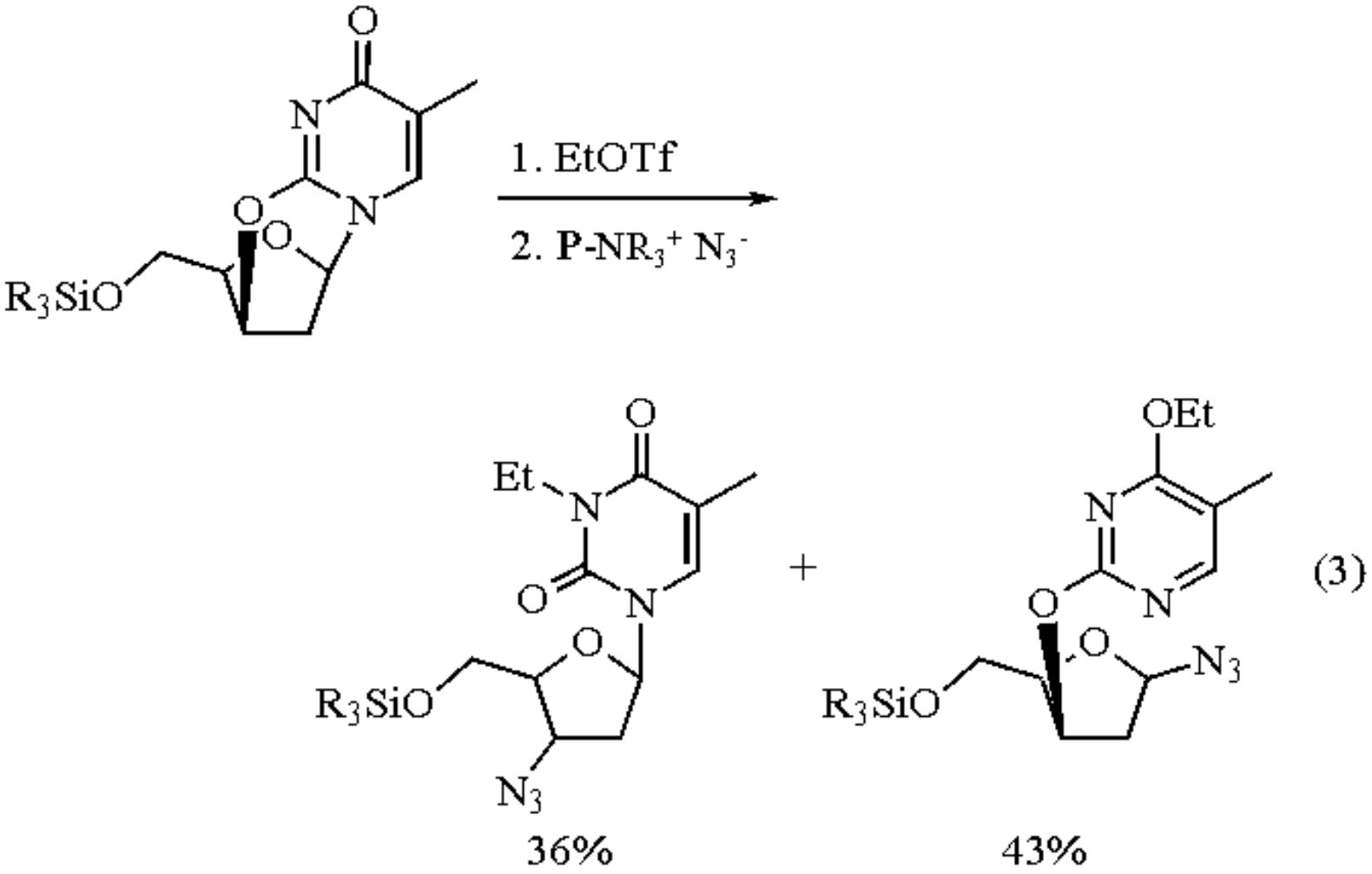

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Alfred Hassner

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Azidoacetyl Chloride[1]

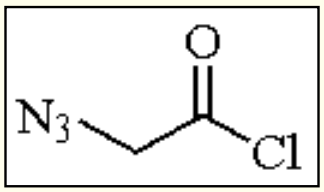

[30426-58-5] · $C_2H_2ClN_3O$ · Azidoacetyl Chloride · (MW 119.52)

(α-amino carbonyl equivalent suitable for the synthesis of amino azetidinones, has been widely used in the synthesis of β-lactam antibiotics;[1-3] can also be used to acylate a variety of nucleophiles to give amino acid derivatives[4,5])

Alternate Name: AAC.

Physical Data: bp 50 °C/20 mmHg.

Solubility: sol most chlorinated and nonchlorinated organic solvents.

Preparative Methods: prepared by azide displacement of halide from the corresponding haloacetic acid, followed by treatment with ***Thionyl Chloride***.[6,7]

Handling, Storage, and Precautions: α-azido carbonyls have been identified as explosives and, as such, should be treated with extreme caution.[7,8] Use in a fume hood.

β-Lactams.

The formation of azetidinones from the addition of acid chlorides or bromides to imines was reported by Staudinger in the early 1900s,[9] but this reaction attracted relatively little attention until it became associated with the synthesis of β-lactam antibiotics. The use of azidoacetyl chloride (AAC) to make amino azetidinones, first demonstrated in 1966 by Bose et al. (eq 1),[10] was rapidly adopted by a number of industrial groups as one step in the synthesis of commercially important β-lactams (eq 2).[11,12] The rapid development of bacterial resistance created a demand for new antibiotics and since these initial reports AAC has been shown to react with imidates,[13] imines,[14,15] acyclic[16,17] and cyclic thioimidates, and related systems to give naturally occurring, synthetic, bicyclic, and monocyclic β-lactams. The experimental procedure is very simple, involving treatment of the acid chloride and imine with ***Triethylamine*** at or below rt, and appears to have changed little from that originally reported.[10] Because of the danger associated with the preparation of AAC, other derivatives of azidoacetic acid suitable for [2 + 2] cycloadditions have also been prepared.[18,19]

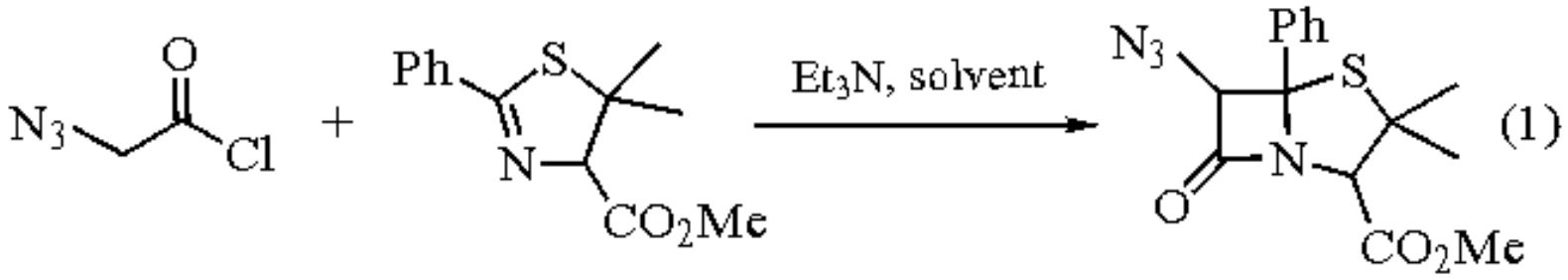

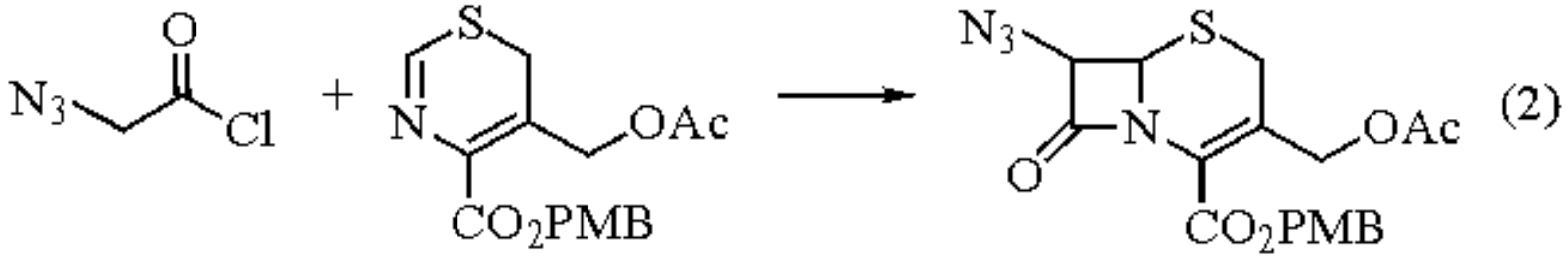

The relative stereochemistry about the C-3-C-4 bond of the azetidinone appears to depend both on the imine and the experimental procedure used. Predominantly or exclusively *trans* adducts are observed from additions to thioformimidates,[20] thiazolines, or thiazines (eq 3),[21,22] and the active configuration of the β-lactam must be obtained via epimerization.[21,22] On the other hand, aldimines give *cis*-azetidinones as the major products.[14,23]

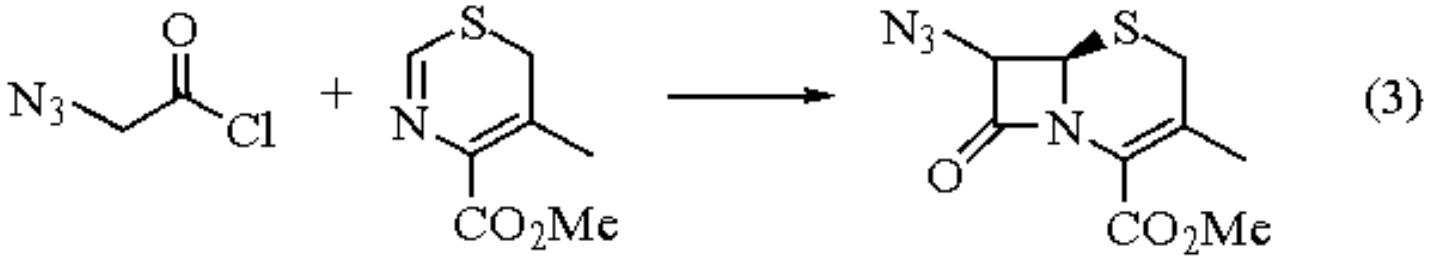

The mechanism of the reaction could involve either a simple [2 + 2] cycloaddition or an imine acylation followed by ring closure.[3,15,24] This is not well understood, and the mechanism may vary with individual examples.

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Arun Ghosh, Marvin J. Miller, Stewart K. Richardson, & Gordon C. Savela

University of Notre Dame, IN, USA

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1-Azido-3,3-dimethyl-1-butene[1]

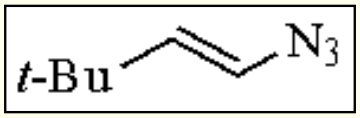

[40168-86-3] · $C_6H_{11}N_3$ · 1-Azido-3,3-dimethyl-1-butene · (MW 125.174)

(used in amination of aromatic and heterocyclic compounds via their lithium derivatives;[2] reaction with alkyllithium compounds leads to alkylated ketones;[3] reaction with sulfoxonium ylides leads to *N*-vinyltriazolines and *N*-vinylaziridines;[4] formation of azirines by thermolysis or photolysis[5])

Solubility: sol most organic solvents.

Form Supplied in: liquid;[6] not available commercially.

Preparative Methods: vinyl azides are prepared in good yield from alkenes by regioselective addition of ***Iodine Azide*** (eq 1) followed by elimination of HI with a base such as ***Potassium t-Butoxide*** or ***1,4-Diazabicyclo[2.2.2]octane***.[6]

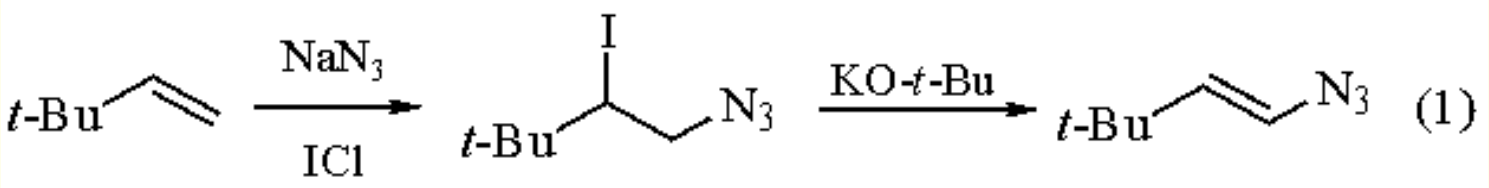

Handling, Storage, and Precautions: decomposes on standing; should be handled with care like other azides because of the possibility of explosion.

Amination of Aromatics (NH_2 Transfer).

The reaction of vinyl azides with organolithium or Grignard reagents (RLi or RMgX) proceeds at the *N*-terminal of the azide function to produce an intermediate vinyltriazene, which is usually not isolated but is transformed on workup with dilute acid to an amine when R is aromatic (eq 2). The yield of aminated product is usually only 50-70%, but is the only acid-extractable product; the vinyldiazonium ion byproduct in this reaction is hydrolyzed to an aldehyde or ketone.

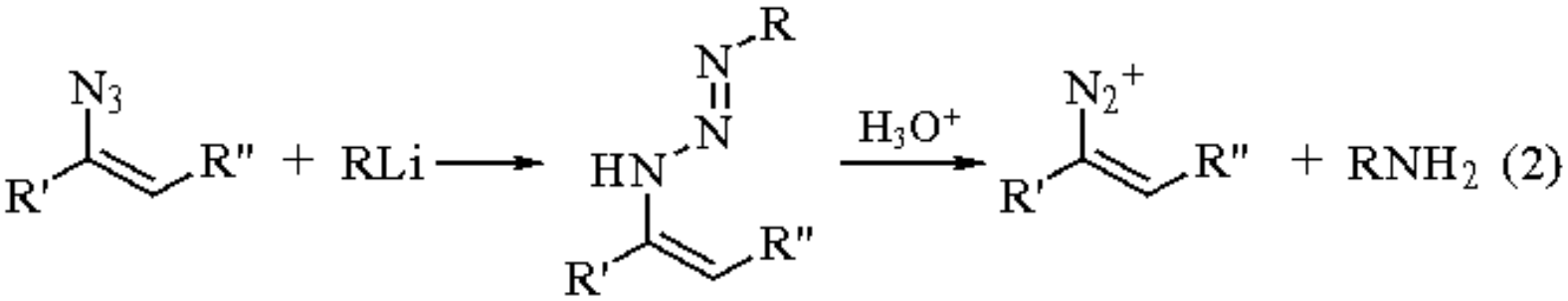

While 1-azido-3,3-dimethyl-1-butene often gives better yields, α-azidostyrene and other vinyl azides may also be used (eqs 3 and 4). Theoretically, the reaction of aromatic lithio or Grignard derivatives with any organic azide could lead to NH_2 transfer, but in practice vinyl azides, in particular 1-azido-3,3-dimethyl-1-butene and phenylthiomethyl azide,[7] are reagents of choice.

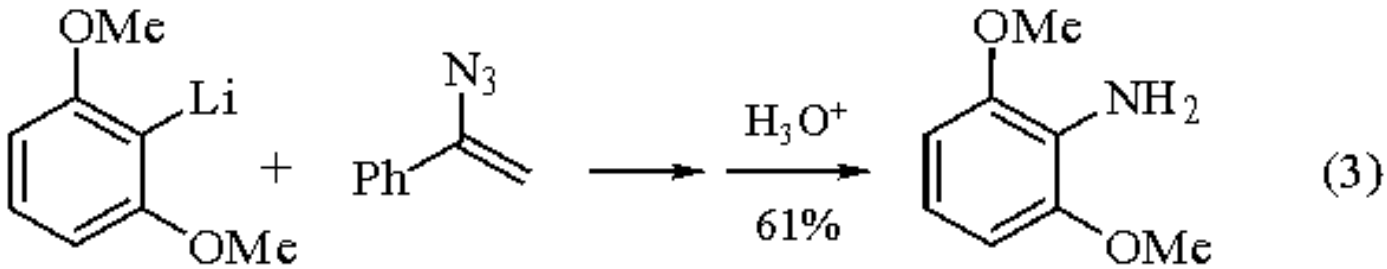

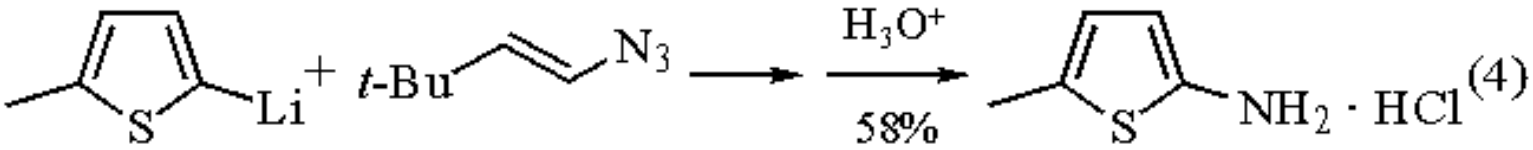

1,3-Dimethoxybenzene (1.5 g, 11 mmol) is transformed into its 2-lithio derivative by treatment with 1 equiv of ***n-Butyllithium*** in THF at 0 °C for 18 h at rt. Azidostyrene is added at -78 °C and after 2 h at rt the mixture is worked up with 10% HCl and then with KOH to obtain the 2,6-dimethoxyaniline.

Formation of Ketones with Alkyl Transfer.

Unlike the amination of ArLi by means of vinyl azides, the reaction of vinyl azides, including 1-azido-3,3-dimethyl-1-butene, with simple aliphatic RLi compounds leads to alkylated ketones (eq 5).[3] In this case, acid-catalyzed decomposition of the vinyltriazene intermediate produces an alkanediazonium ion and an enamine, with subsequent transfer of the alkyl group to the enamine carbon.

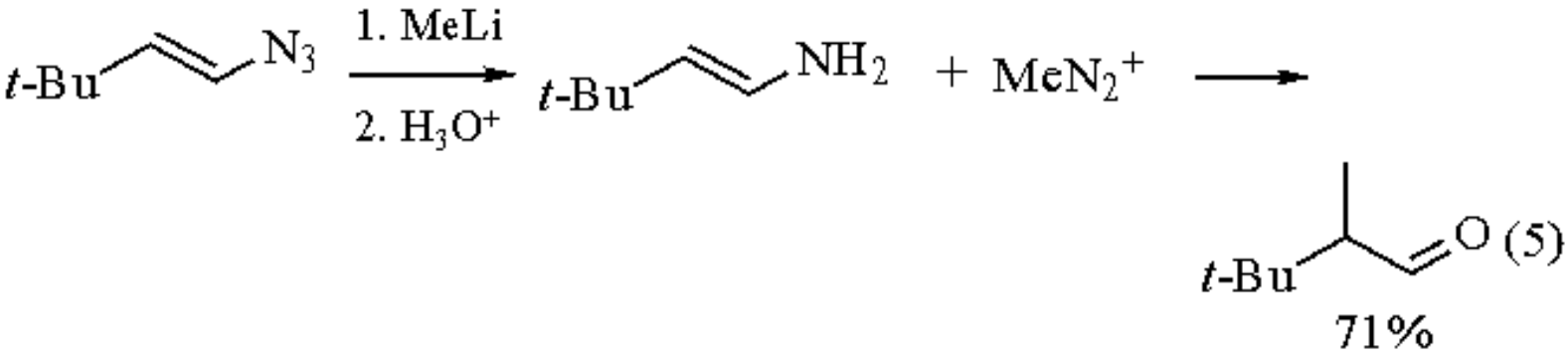

Synthesis of Vinyl Heterocycles.

Reaction of vinyl azides, including 1-azido-3,3-dimethyl-1-butene, with trimethylsulfoxonium ylide leads to *N*-vinyltriazolines. The latter on flash vacuum pyrolysis at ca. 250 °C are transformed into *N*-vinylaziridines in over 90% yield (eq 6).

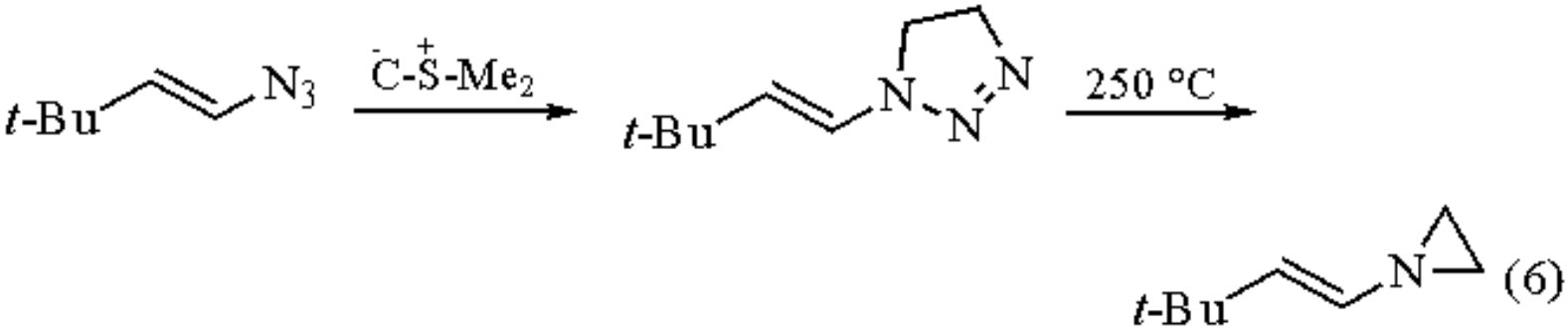

Formation of Azirines.

In general, vinyl azides are excellent starting materials for azirines via thermolysis or photolysis (eq 7). In the case of terminal vinyl azides, such as 1-azido-3,3-dimethyl-1-butene, heating leads to polymers or nitriles.[5]

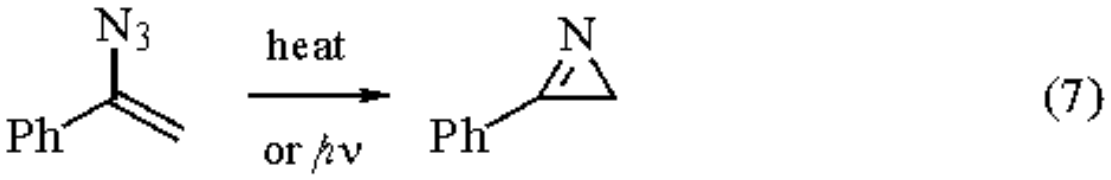

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Azidomethyl Phenyl Sulfide

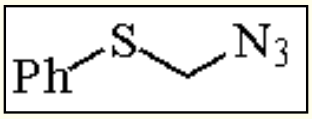

[77422-70-9] · $C_7H_7N_3S$ · Azidomethyl Phenyl Sulfide · (MW 165.22)

(reagent for amination of organomagnesium compounds;[1] allows amination and oxidation of α,α-disubstituted ester enolates via 1,2,3-triazol-5-ones;[1b] a synthetic equivalent of methyl azide for the synthesis of methylaziridines;[2] substituted α-azido sulfides undergo Beckmann-type rearrangements to provide lactams and imino thioethers[3,4])

Physical Data: bp 104-105 °C/5 mmHg; *n*20D 1.5904; *d* 1.168 g cm^{-3}; fp 107 °C.

Solubility: freely sol common organic solvents.

Form Supplied in: colorless to light-gold liquid, ~95% pure.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Method: chlorination of ***Thioanisole*** with ***Sulfuryl Chloride*** followed by treatment of the resultant α-chloro sulfide with ***Sodium Azide*** in acetonitrile.[1a]

Handling, Storage, and Precautions: as with all azides of low or moderate molecular weight, heat or shock can cause vigorous, possibly explosive, nitrogen evolution. Distillation should be performed behind a blast shield at reduced pressure and temperatures less than 110 °C. Similar compounds have been shown to decompose with nitrogen evolution at ~120 °C.[5] Striking neat azidomethyl phenyl sulfide with a hammer fails to cause detonation. Storage under nitrogen in an amber bottle in a refrigerator is recommended. It is incompatible with strong acids, bases, and oxidizing agents. When the reagent is used for the amination of organomagnesium reagents, an intermediate triazene is formed. Certain triazenes are known to be carcinogenic,[6] thus caution in handling these intermediates should be exercised. Rinsing glassware with bleach will dispel the disagreeable odor associated with azidomethyl phenyl sulfide, phenylthiomethyltriazenes, and other sulfur-containing byproducts encountered in the use of this reagent. Handle in a fumehood.

Amination of Organomagnesium Reagents.

Treatment of azidomethyl phenyl sulfide with aryl organomagnesium reagents followed by aqueous workup results in the formation of triazenes. These may be converted to anilines by the action of aqueous ***Potassium Hydroxide*** or

aqueous ***Formic Acid*** (eq 1).[1a,c] Transmetalation of aryllithium compounds to organomagnesium compounds with ***Magnesium Bromide*** etherate is required, since the former are unsuitable for this transformation. The phenylthio group appears to accelerate the reaction with the organomagnesium reagent relative to other substituents.[1b] Aliphatic organomagnesium reagents may also be aminated, but acylation of the intermediate magnesiotriazene at low temperature is required prior to cleavage, resulting in the amidated product (eq 2).[1b] A variety of primary and secondary organomagnesium reagents have been amidated, and several different acylating agents have been used.[1b]

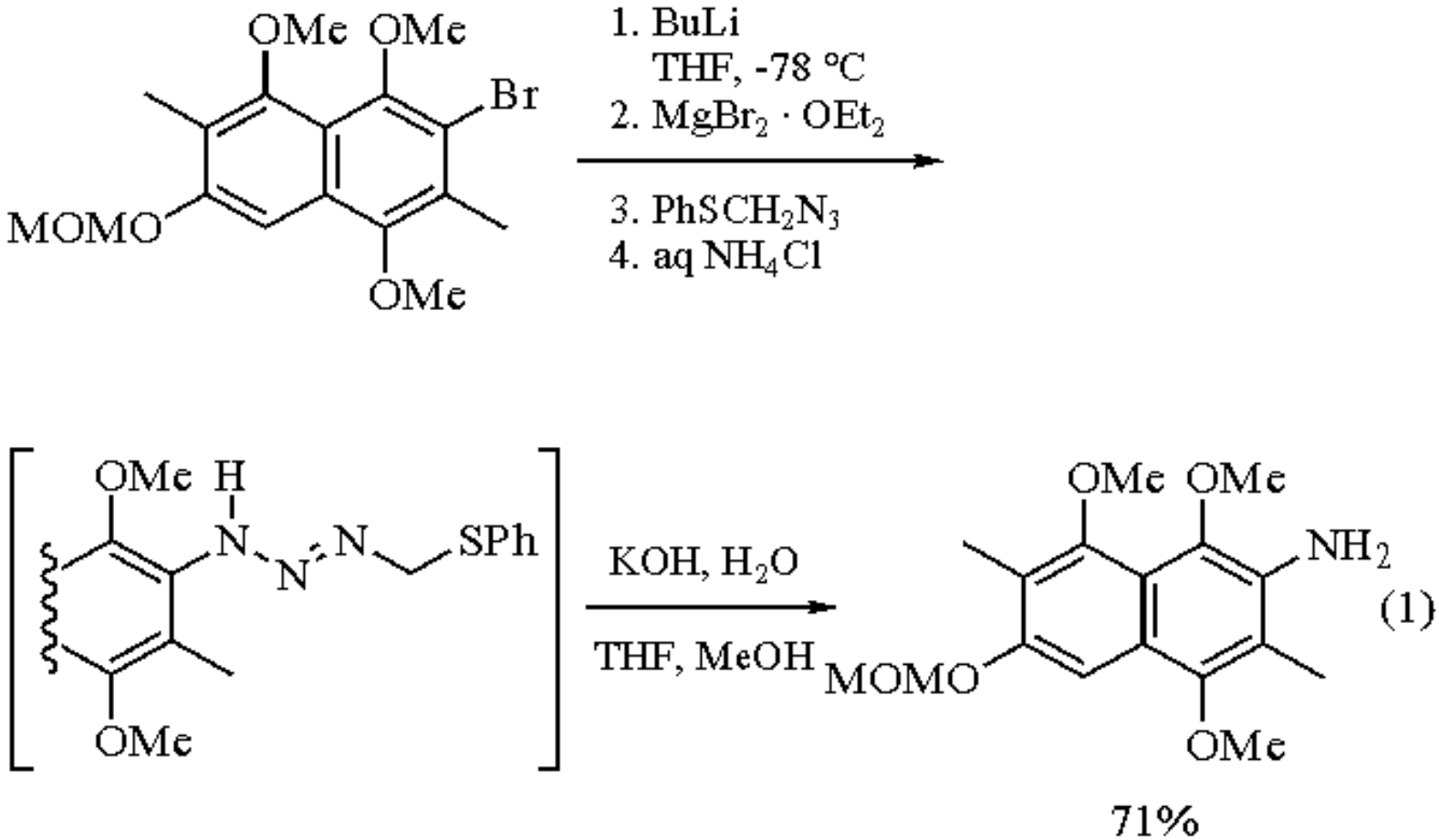

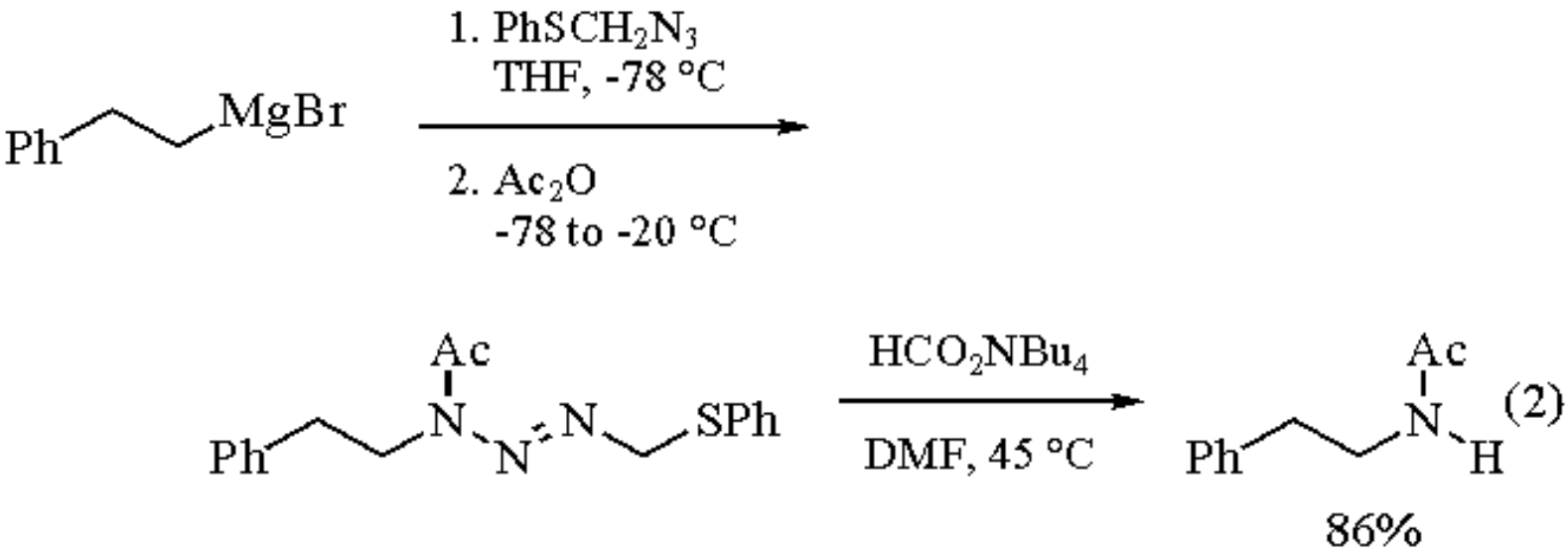

The phenylthio group allows regiocontrol in the acylation and subsequent cleavage reaction. Other reagents for

amination of organomagnesium and organolithium reagents have been published, each with its own advantages and limitations.[7] Some representative reagents are $MeONH_2$/MeLi,[8] $ArONH_2$,[9] $(PhO)_2P(O)ONH_2$,[10] $(PhO)_2P(O)N_3$,[11] $ArSO_2N_3$,[12] $Me_3SiCH_2N_3$,[13] vinyl azides,[14] and oxime derivatives.[15] Amidation with TsON(Li)Boc has been accomplished.[16] Introduction of alkylamino, arylamino, or dialkylamino groups by the amination approach has also been studied.[17]

Amination of Ester Enolates.

Lithium ester enolates react with azidomethyl phenyl sulfide to give 3,5-dihydro-4*H*-1,2,3-triazol-5-ones, which may be converted to α-amino amides with aqueous ***Ammonia*** (eq 3).[1b] The ester enolate must be α,α-disubstituted to avoid aromatization of the triazolone. Treatment of the triazolones with methanolic ***Magnesium Methoxide*** results in the formation of α-methoxy amides.[1b] Other azides have been used to prepare triazolones, which undergo similar solvolysis reactions.[18] Other reagents for the amination of enolates have been examined,[7] including BocN=NBoc[19] and trisyl azide.[20]

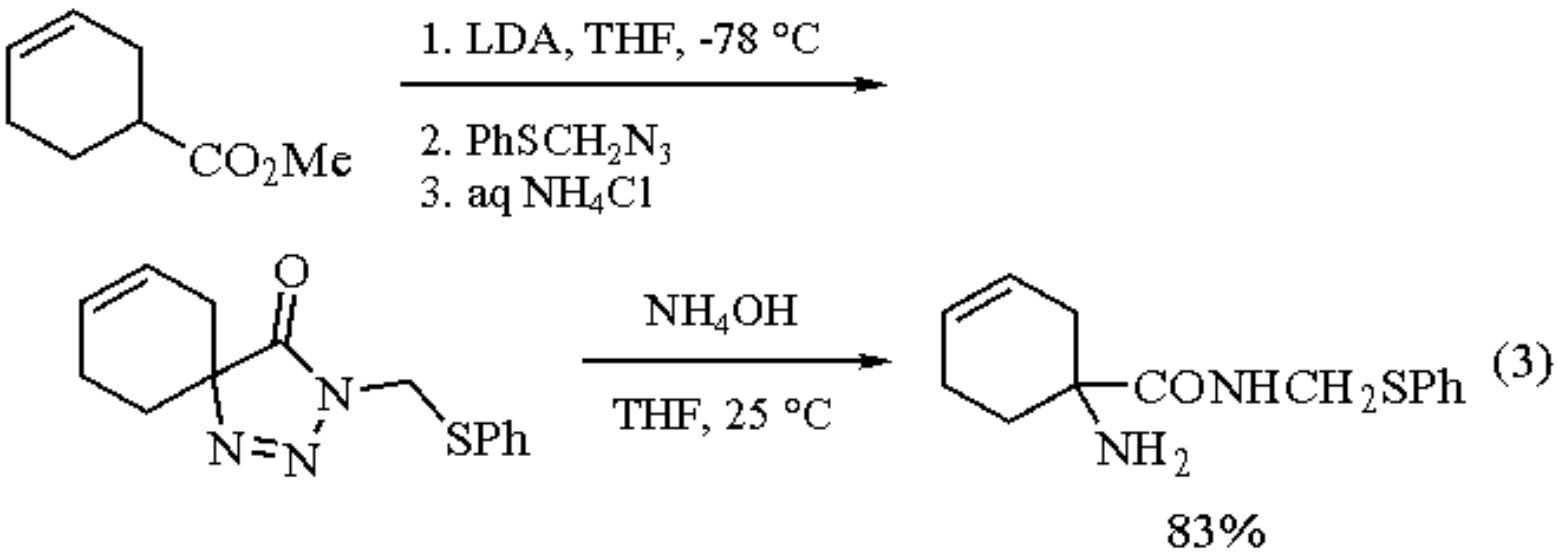

Dipolar Cycloadditions.

A common strategy for the synthesis of aziridines is the dipolar cycloaddition of azides with alkenes followed by thermal or photochemical decomposition of the resultant triazolines. The synthesis of methylaziridines by this approach would require the hazardous compound methyl azide. Azidomethyl phenyl sulfide is a safer synthetic equivalent of methyl azide, since the phenylthio group can be removed by desulfurization (eq 4).[2]

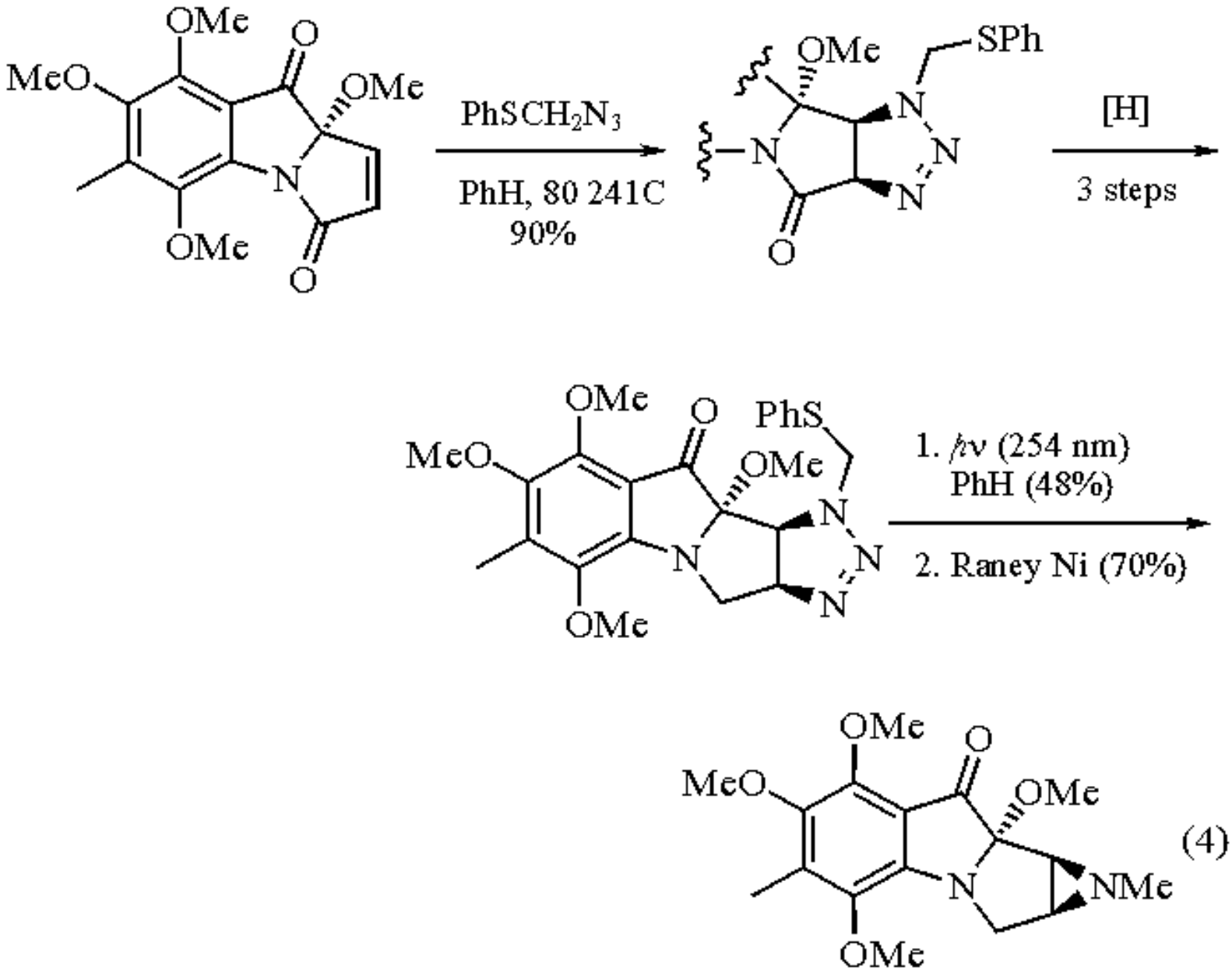

(4)

Rearrangement of α-Azido Sulfides.

An alternative to the Beckmann rearrangement has been developed involving the protic or Lewis acid promoted rearrangement of α-azido sulfides (eq 5).[3,4] Either lactams or imino thioethers may be formed. The thermal-[5] and base-promoted[21] rearrangement of α-azido sulfides has also been studied (eq 6).[5]

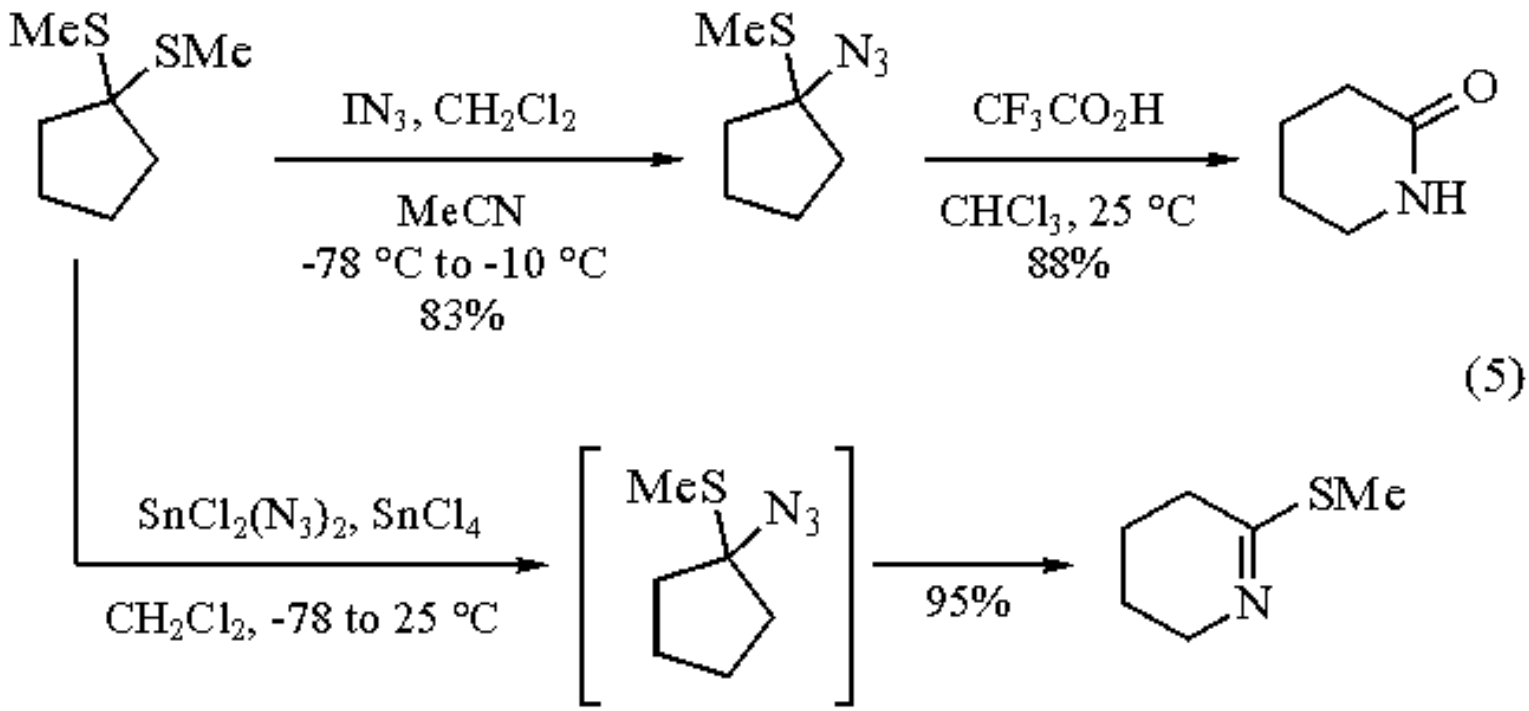

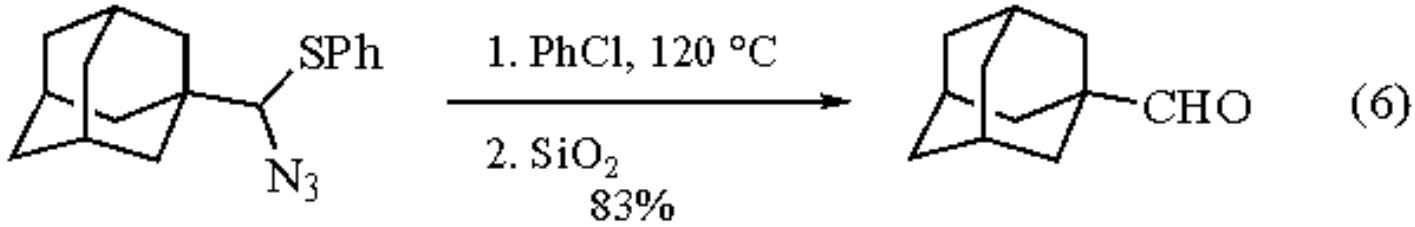

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Azidotrimethylsilane[1]

Me_3SiN_3

[4648-54-8] · $C_3H_9N_3Si$ · Azidotrimethylsilane · (MW 115.21)

(azidation of organic halides, acetals, and esters; α- and β-siloxy azides from carbonyl compounds and epoxides; preparation of heterocyclic compounds; effective substitute for hydrazoic acid)

Alternate Names: trimethylsilyl azide; TMSA.

Physical Data: bp 95-96 °C; *n*20D 1.416; *d* 0.868 g cm^{-3}; fp 23 °C; IR ν_{max} 2100 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.22.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid.

Preparative Methods: several methods for the synthesis of this azide have been reported.[1] The procedure involving aluminum chloride is not recommended, since an explosive product is formed.[2] Azidotrimethylsilane is now commercially available, and a representative synthetic procedure is as follows. A mixture of ***Sodium Azide*** and ***Chlorotrimethylsilane*** is refluxed in di-*n*-butyl ether for 2 days and the azide is safely distilled directly from the reaction vessel. Purer compound (99% content) is obtained by redistillation of the product.

Handling, Storage, and Precautions: the azide, which decomposes at 500 °C,[1b] is more stable thermally than most organic azides and can be stored in a refrigerator for more than one year. It is moisture sensitive, and should be handled with care since it reacts rapidly with water to release toxic hydrazoic acid. Handle in a fume hood.

Many applications of TMSA in organic synthesis have been reported but only representative examples are described herein.

Substitution Reactions.

Benzyl, allyl, and substituted alkyl halides are converted to the corresponding azides in 60-100% yields via reactions with TMSA under neutral conditions in a nonaqueous solvent (eq 1).[3] By using ***Tin(IV) Chloride*** as a catalyst, secondary and tertiary cyclic and polycyclic halides are similarly transformed into the corresponding azides in 50-92%

yields (eq 1).[4]

$$Me_3SiN_3 + RX \longrightarrow RN_3 + Me_3SiX \qquad (1)$$

R = $ArCH_2$, $CH_2CH{=}CH_2$, CH_2CN, CH_2CO_2Et, *c*-C_5H_9, *c*-C_6H_{11}, 1-, 2-, 3-, and 4-adamantyl
X = Cl, Br

Acyl halides react with TMSA to give trimethylsilyl halides and the corresponding isocyanates in a range of 83-98% yields, which are rearranged from the acyl azides via the Curtius degradation (eq 2).[5] However, a reaction of aroyl chlorides with TMSA in the presence of ***Zinc Iodide*** at 0 °C gives the corresponding azides in 85-96% yields (eq 3).[6]

$$Me_3SiN_3 + RCOX \longrightarrow RN{=}C{=}O + Me_3SiX \qquad (2)$$

R = *c*-C_6H_{11}, Ph, *p*-MeC_6H_4, $CH_2{=}CH(CH_2)_8$-, $MeOCOCH_2CH_2$, phthaloyl, etc.

$$Me_3SiN_3 + ArCOX \xrightarrow[0\ °C]{ZnI_2} ArCON_3 + Me_3SiX \qquad (3)$$

The azide reacts with orthoesters at reflux temperature and acetals in the presence of $SnCl_4$ at -78 °C to give the corresponding azides in 40-70% yields (eq 4).[7]

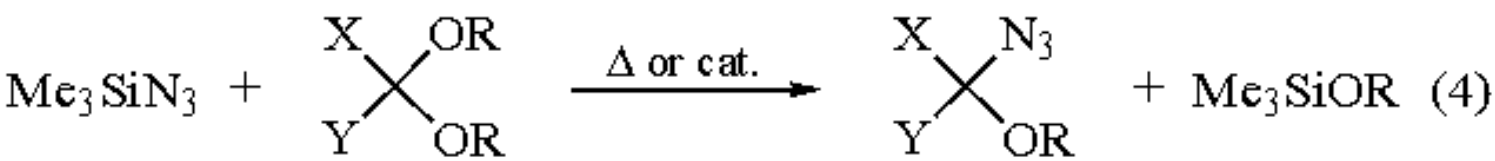

X = alkyl, aryl, alkoxy

α-Siloxy Azides.

TMSA reacts with carbonyl compounds to give α-siloxy azides in the presence of ***Zinc Chloride*** or ***Tin(II) Chloride***. With aldehydes, α-siloxy azides are obtained in 70-80% yields,[8,9] but the yields of these compounds are very low with most ketones.[9] Carbonyl compounds including ketones are stepwisely or directly converted into *gem*-diazides (30-80%), tetrazoles (40-100%), and nitriles (60-100%), depending on the reaction conditions.[9] The reaction sequences are summarized in Scheme 1.

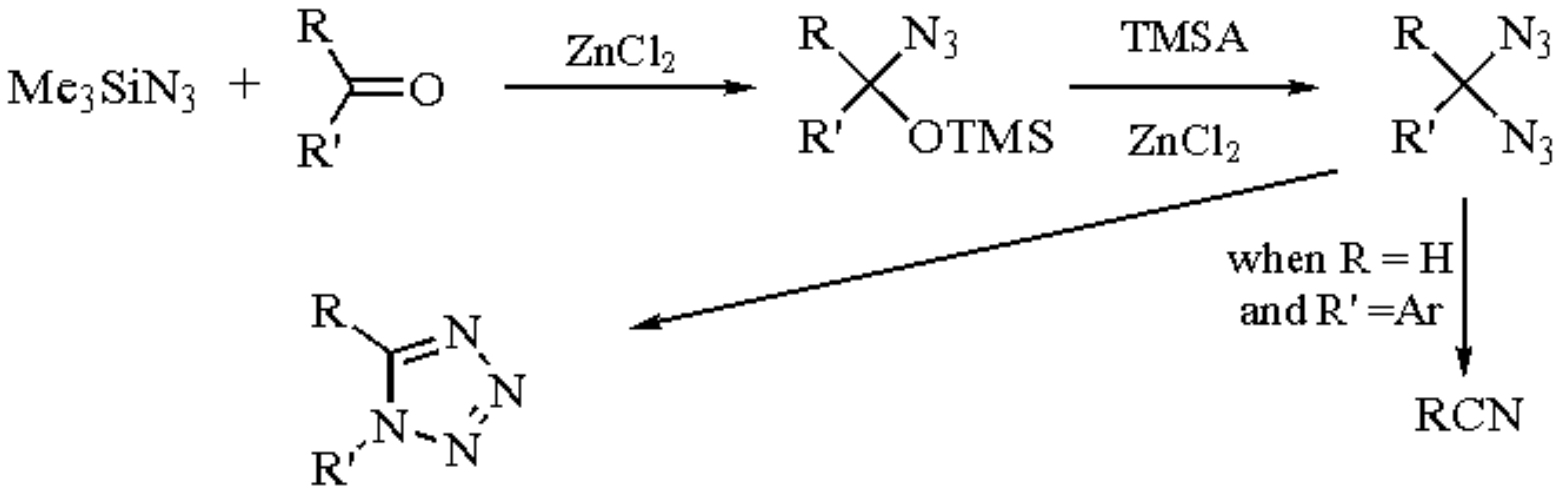

Scheme 1

β-Siloxy Azides.

The azide reacts with epoxides in the presence of zinc chloride,[8b] titanium and vanadium complexes,[10] zinc tartrate,[11] and ***Aluminum Isopropoxide***[12] to give β-siloxy azides in 80-100% yields (eq 5), which are precursors of β-amino alcohols. With cyclohexene oxide, the *trans* isomer is formed exclusively, regardless of the catalyst used.[8b,10] However, the regio- and chemoselectivity of the reactions of other epoxides depend upon the catalyst.[10-12]

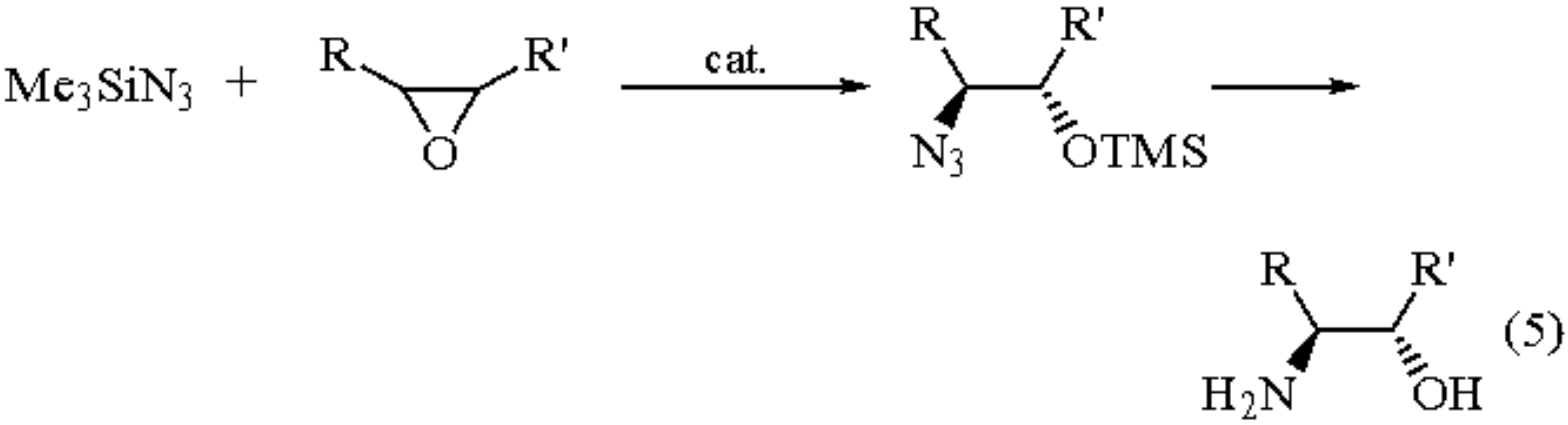

R = Me, R' = H; R = CH_2=CH$(CH_2)_2$, R' = H;
R, R' = -$(CH_2)_n$- (n = 3-5); etc.

Application of this procedure for the regio- and stereoselective synthesis of vinyl azides in the presence of ***Boron Trifluoride Etherate*** complex is summarized in eq 6.[13]

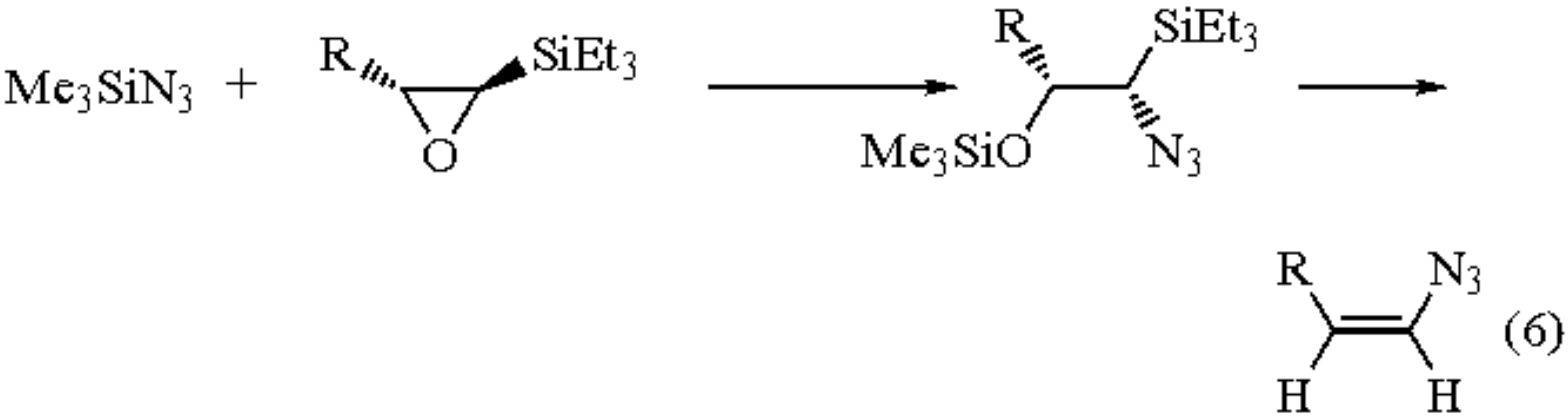

o-Siloxy Isocyanates.

Acyclic anhydrides react with TMSA in a manner similar to acid halides to give equal amounts of trimethylsilyl esters and isocyanates (eq 7).[5b,14] Similarly, cyclic anhydrides react with the azide to give o-trimethylsiloxycarbonyl alk(en)yl isocyanates (eq 8)[14a,15] which are further transformed into 1,3-oxazine-2,6-dione derivatives (70-90%).[14b]

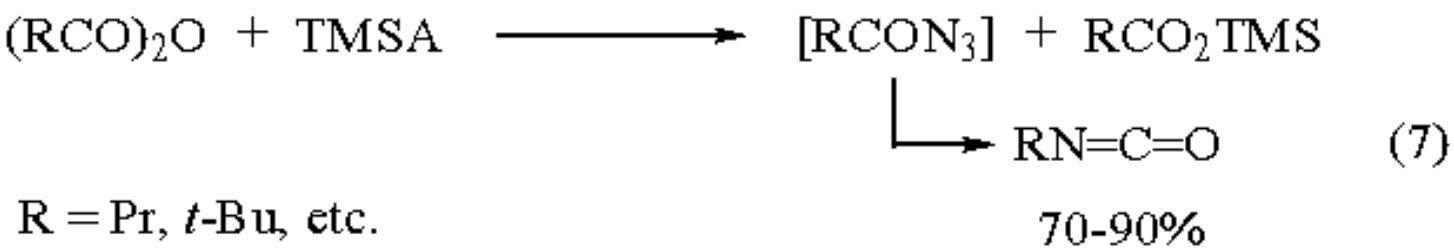

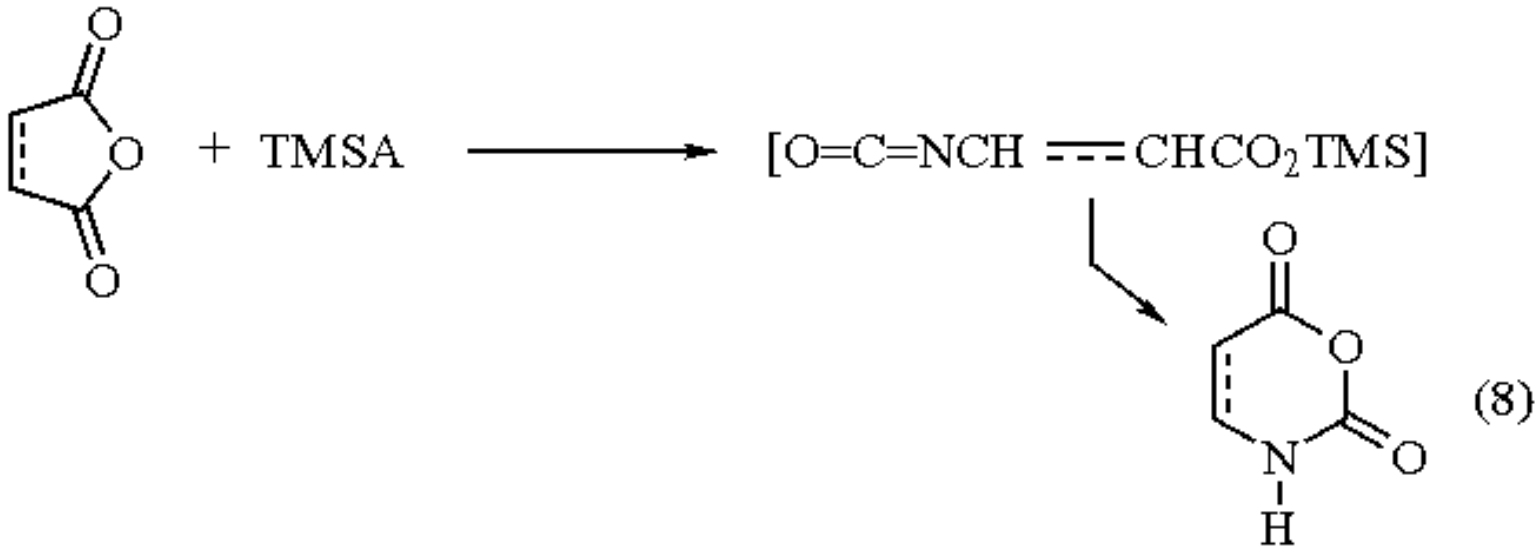

[3 + 2] Cycloaddition.

TMSA, like other alkyl azides, reacts with alkynes and C-hetero multiple bonds to give [3 + 2] cycloaddition products, triazoles and tetrazoles.[1] For example, the reaction of TMSA with 2-butyne gives 4,5-dimethyl-2-trimethylsilyl-1,2,3-triazole in 78-87% yields (eq 9),[16] and TMSA and cyanoferrocene react to give 5-ferrocenyl-2-trimethylsilyltetrazole in 75% yield (eq 10).[17]

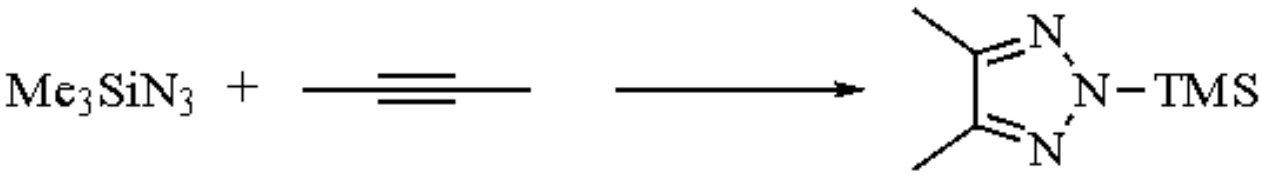

(9)

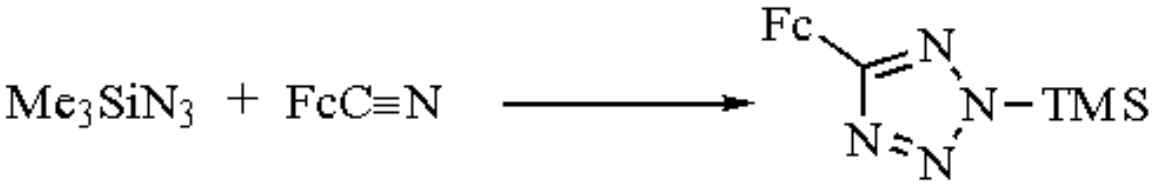

(10)

Fc = ferrocenyl

Lead and Phenyliodoso Azides.

When ***Lead(IV) Acetate*** and phenyliodoso derivatives are used as a catalyst for azidation of alkenic and aromatic compounds (eq 11),[1,18] lead azides and phenyliodoso azides are formed as intermediates.

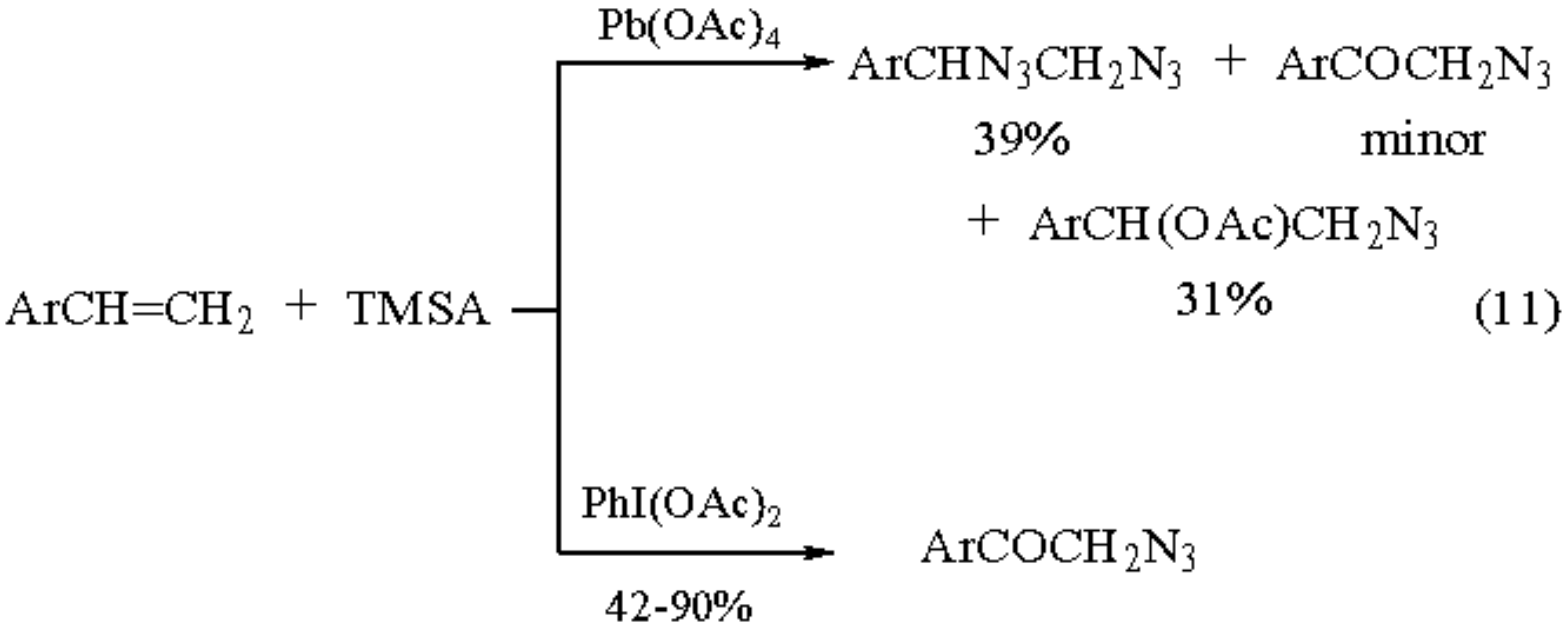

(11)

Miscellaneous.

A combination of the azide and triflic acid is a highly efficient electrophilic aromatic amination reagent system.[19]

Related Reagents.

Hydrazoic Acid; ***Sodium Azide***; ***Tri-n-butyltin Azide***.

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Azidotris(dimethylamino)phosphonium Hexafluorophosphate

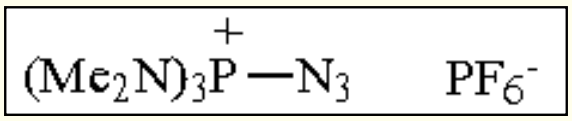

[50281-51-1] · $C_6H_{18}F_6N_6P_2$ · Azidotris(dimethylamino)phosphonium Hexafluorophosphate · (MW 350.19)

(coupling reagent for amides and peptide synthesis via an acyl azide;[1] in the absence of a nucleophile undergoes a Curtius rearrangement to give the corresponding isocyanate;[1,2] by irradiation gives the iminophosphonium salt;[3,4] diazo transfer reagent[5])

Physical Data: mp >250 °C; IR, $\nu(N_3)$ 2176 cm^{-1}.

Solubility: sol acetone, acetonitrile, DMF.

Form Supplied in: crystalline colorless solid; not available from commercial sources.

Preparative Methods: ***Bromine*** (1 equiv) is added dropwise to ***Hexamethylphosphorous Triamide*** (1 equiv) in dry diethyl ether. After the addition is complete, ***Potassium Hexafluorophosphate*** (1 equiv), dissolved in H_2O is added, and the solid formed is filtered and washed with H_2O. After drying under vacuum, the solid is dissolved in acetone and ***Sodium Azide*** (1.5 equiv) is added. The mixture is stirred overnight at 25 °C, then the sodium bromide formed and the excess of sodium azide is filtered off and the solvent is removed under vacuum.

Purification: by crystallization in a mixture of acetone and diethyl ether.

Handling, Storage, and Precautions: is very stable, not hygroscopic, and can be stored indefinitely under vacuum. The related bromine derivative is an exceptionally safe azide, that does not detonate by shock, friction, rapid heating, or even flame.[5] When used in combination with carboxylic acids, the potential carcinogenic ***Hexamethylphosphoric Triamide*** is a side-product and the reagent must be handled with caution.[6]

Coupling Reagent.

Azidotris(dimethylamino)phosphonium hexafluorophosphate has been used as a condensing reagent for the preparation of peptides.[1] Reaction of α-amino protected amino acids or dipeptides with equimolar amounts of α-

carboxyl protected amino acids or dipeptides and ***Triethylamine*** (2 equiv) in DMF proceed cleanly overnight at -10 to 0 °C, giving the corresponding peptides in good yields (81-97%) (eq 1). Neither acylation of the hydroxy group of serine nor dehydration of the side chain of asparagine is reported during the coupling.[1]

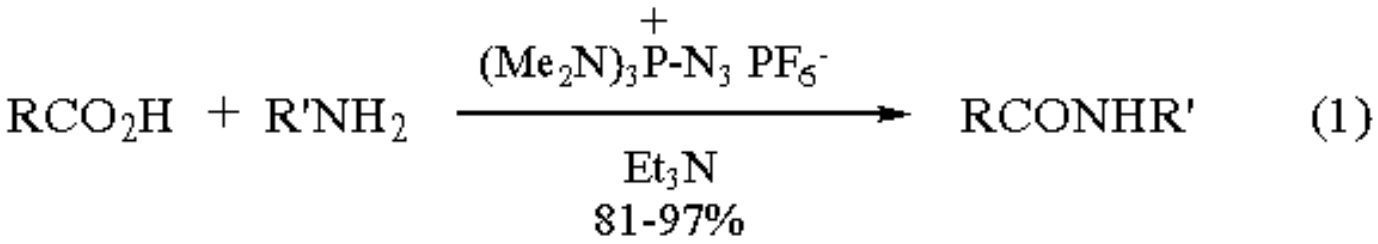

Racemization from azidotris(dimethylamino)phosphonium hexafluorophosphate-mediated couplings is analyzed by different methods. While no racemization is detected by the Anderson[7] and Weinstein[8] methods, the Young[9] method gave some degree (3%) of racemization.

Although azidotris(dimethylamino)phosphonium hexafluorophosphate has not been used in solid-phase peptide synthesis,[10] other commercial phosphonium salt derivatives such as ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (BOP),[11] benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP),[12] or bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP)[13] are commonly used in that strategy.

Isocyanate Formation.

The coupling reaction described above occurs via an acyl azide intermediate, which at 50 °C suffers a Curtius rearrangement to give an isocyanate (eq 2),[1] which can further react with amines to give the corresponding ureas.

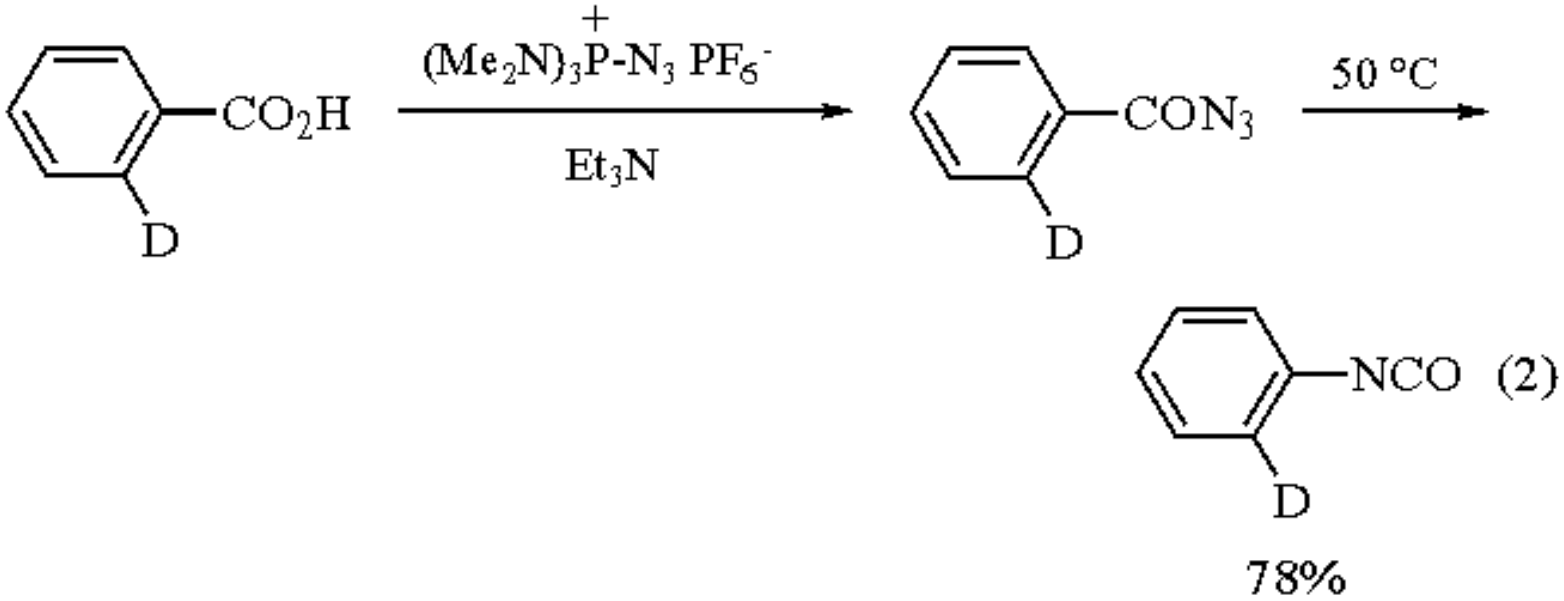

Iminophosphonium Salt Formation.

Irradiation of azidotris(dimethylamino)phosphonium hexafluorophosphate in acetonitrile at 254 nm using a Rayonnet

photochemical reactor for 15 h at 25 °C gives the iminophosphonium salt with release of nitrogen (eq 3). This is the first example reported of a Curtius-type rearrangement involving a charged atom.[3,4]

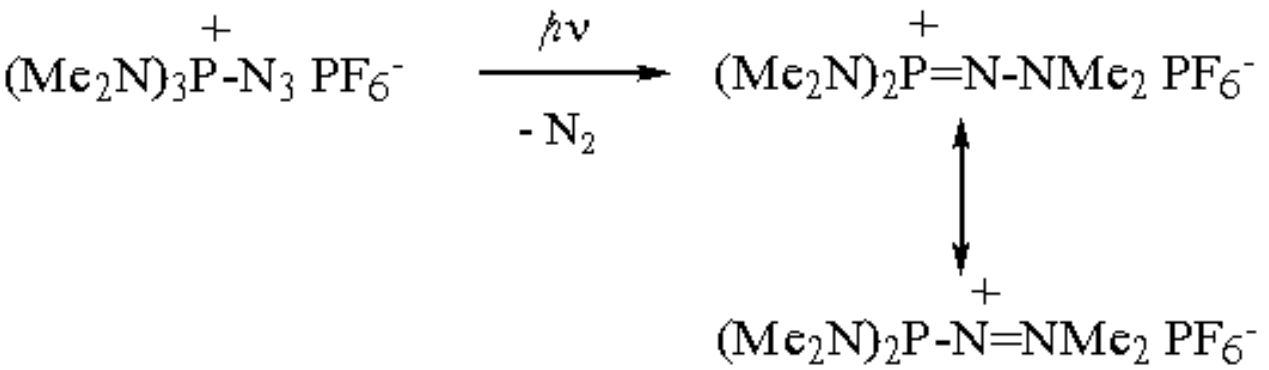

(3)

Diazo Transfer Reagent.

The related compound azidotris(diethylamino)phosphonium bromide has been used for the preparation of diazo products.[5] Active methylene compounds react with azidotris(diethylamino)phosphonium bromide in dry diethyl ether in the presence of only catalytic amounts of base, such as ***Potassium t-Butoxide*** or other alkoxide, yielding the corresponding diazo products in good yields (70-78%) (eq 4).

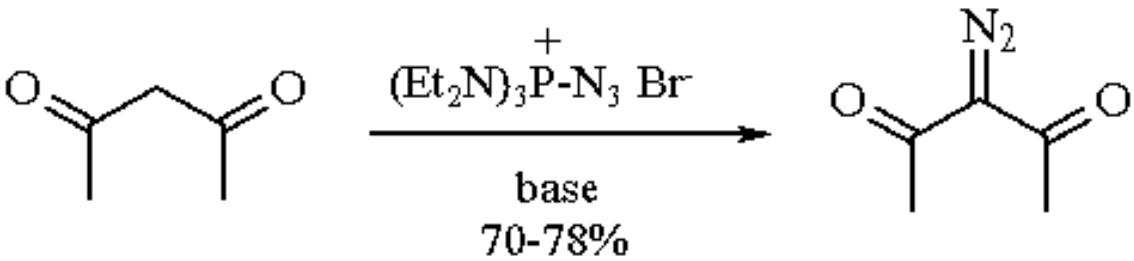

(4)

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2. Masson, M. A.; Dormoy J. R. *J. Labelled Compd. Radiopharm.* **1979**, *16*, 785.
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Aziridine-2-carboxylic Acid[1]

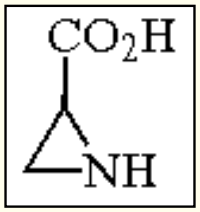

[54080-06-7] · $C_3H_5NO_2$ · Aziridine-2-carboxylic Acid · (MW 87.08)

(building block for chiral amino acids;[2] can be used for synthesis of heterocycles[3])

Physical Data: Li salt: mp 260-268 °C; methyl ester: bp 68 °C/11 mmHg; *n*20D 1.440; nitrile: bp 38 °C/0.1 mmHg; *n*20D 1.475; amide: mp 132-133 °C.

Solubility: esters and nitrile miscible with H_2O, and virtually all organic solvents. Amide and metal salts are soluble in H_2O, lower alcohols, DMF, DMSO.

Form Supplied in: (*S*)-form of Li salt as white solid.

Handling, Storage, and Precautions: free acid is not available, because of its low stability. The only stable aziridinecarboxylic acid is crystalline 3,3-dimethylaziridine-2-carboxylic acid.[4] Salts, esters, and amides are stable.

Synthesis of Derivatives of Aziridine-2-Carboxylic Acids.

Racemic salts, esters, nitriles, and amides are prepared by modified Gabriel synthesis from the reaction of ammonia with vicinal dihalocarboxylic acids.[5] Better yields were obtained by cyclization of β-hydrazinium propionates with base (eq 1).[6]

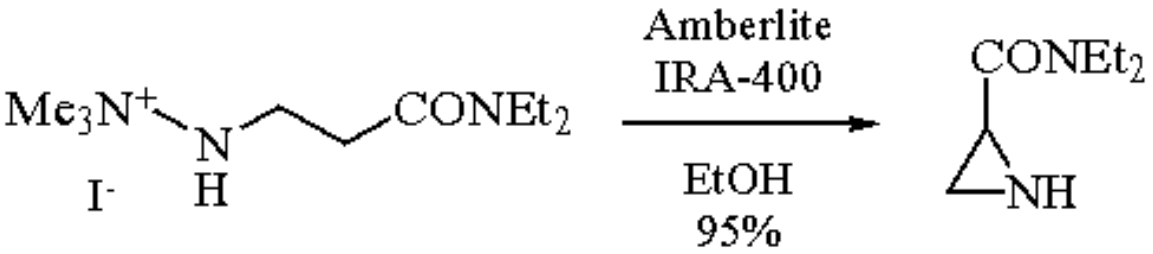

(1)

Various substituted aziridine-2-carboxylic acids have been prepared from the corresponding azirines with nucleophiles.[7] This method is limited because optically pure aziridines and aziridinecarboxylic acids are not easily

obtained. Amination of electron deficient alkenes with 3,3-pentamethyleneoxaziridine,[8] diphenyl sulfimide,[9] and ***O-(Mesitylsulfonyl)hydroxylamine***[10] yields aziridinemono- and dicarboxylic acids. Aziridinecarboxylic acids can be prepared from serine esters,[11a] but not from threonine esters,[11b] using diethoxytriphenylphosphorane. All these methods give racemic aziridines. However, recent investigations have led to chiral aziridines via chiral oxirane-2-carboxylic esters (eq 2),[12a,b] chiral cyclic sulfamidates (eq 3),[11b] D-ribose and D-lyxose,[12c] or functional group transformations of chiral aziridines.[13] High *cis* stereoselectivity is observed when *N*-trimethylsilylimines react with Li enolates of α-halo esters (eq 4).[14a] Complete control of enantioselectivity can be achieved by proper choice of the metal enolate (eq 5).[14b]

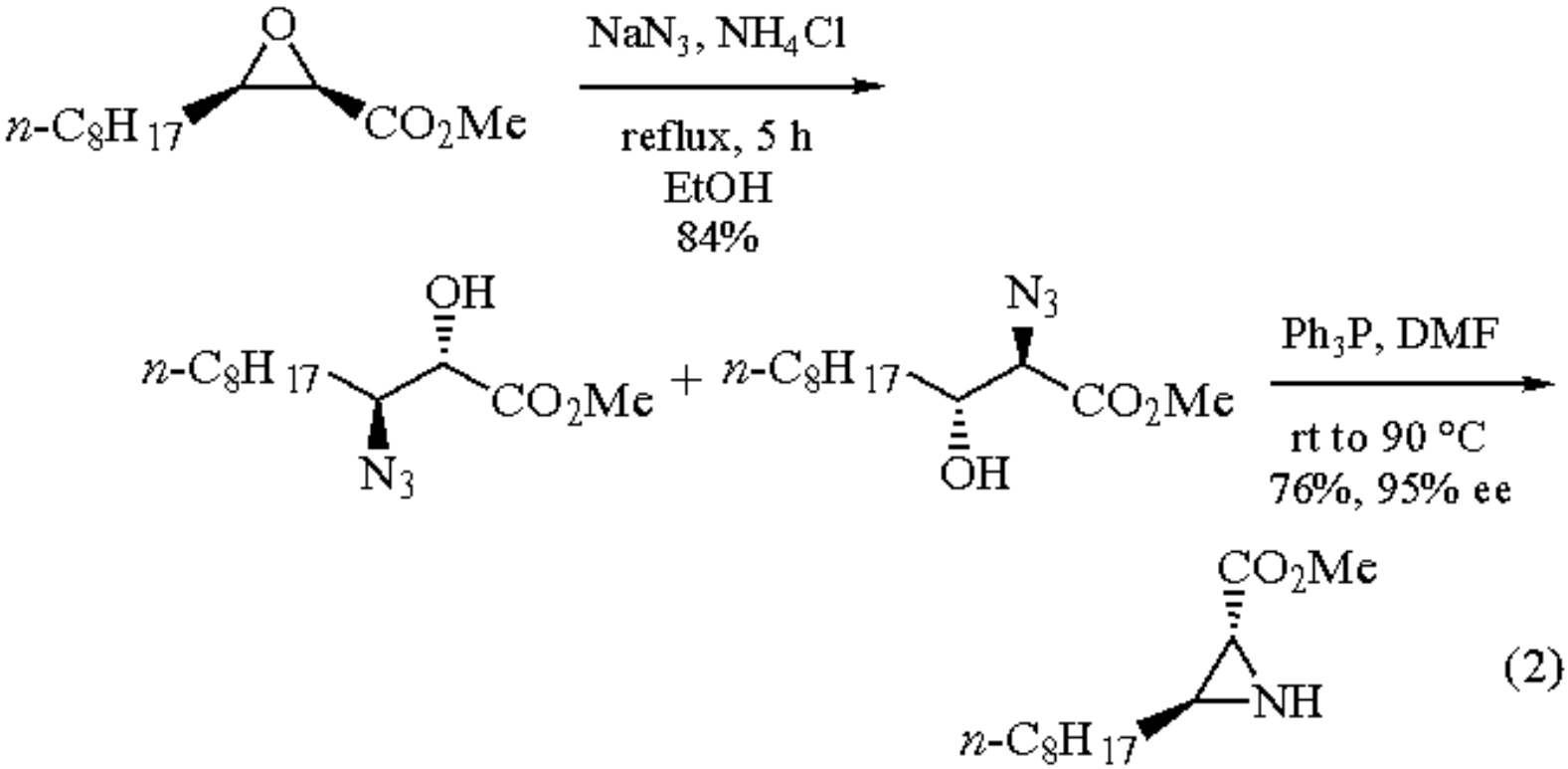

(2)

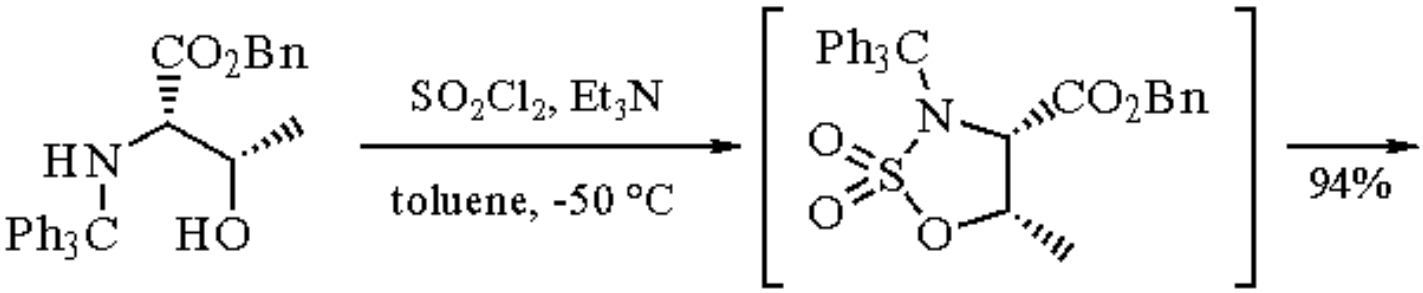

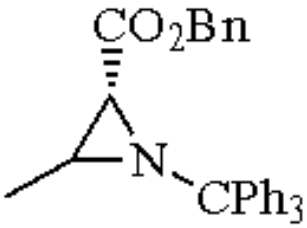

(3)

(2*S*,3*S*)

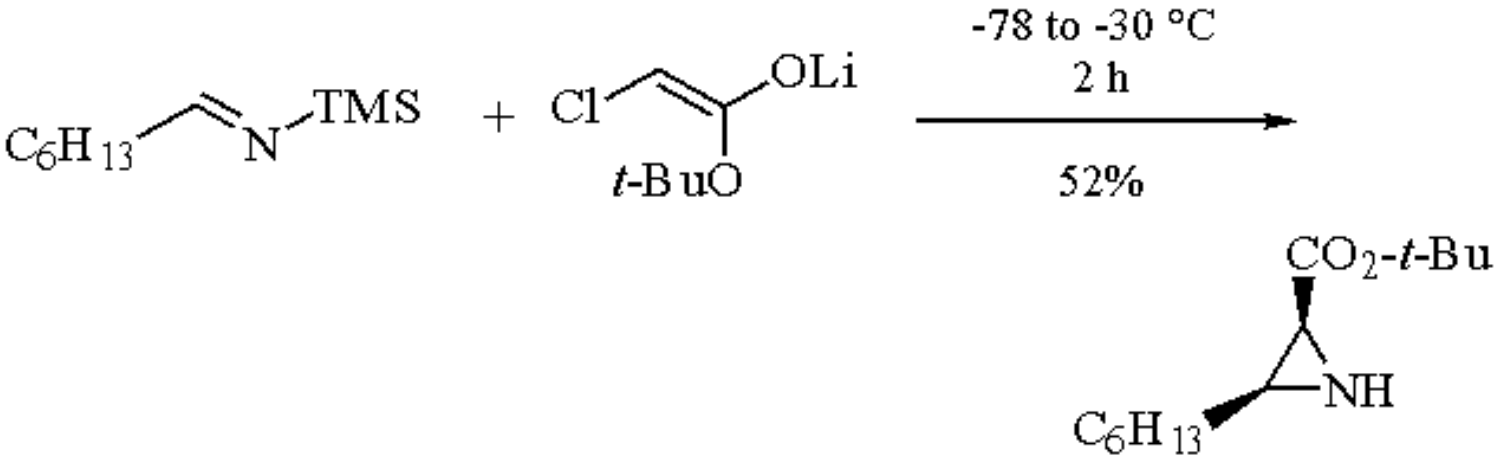

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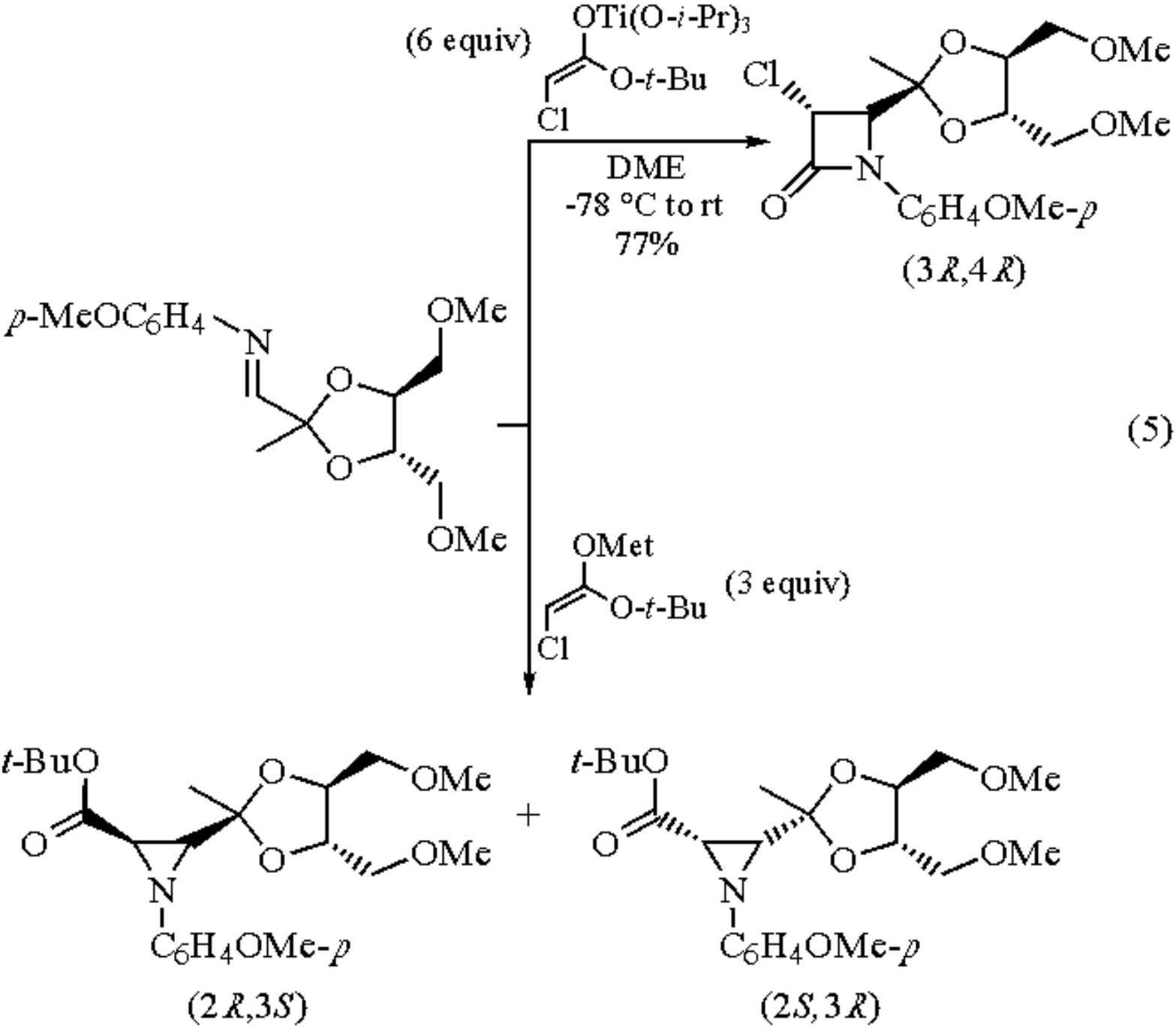

(5)

Met = Li, THF, -78 to -50 °C, 35%, 100:0

Met = Li, THF, -78 to -50 °C, 35%, 100:0
Met = Zn, THF, -78 °C to rt, 59%, 0:100

Ring Cleavage of Aziridines.

Aziridinecarboxylic acids are important building blocks in peptide chemistry.[15] They are easily incorporated using serine or threonine derivatives. Convenient syntheses of actinomycin D,[15b] dehydroamino acid containing peptides,[15c] and phosphopeptides have been achieved.[15d] Thiobenzoic acid has been utilized for the cleavage of the aziridine ring to prepare commercially expensive D-cysteine derivatives (eq 6).[16]

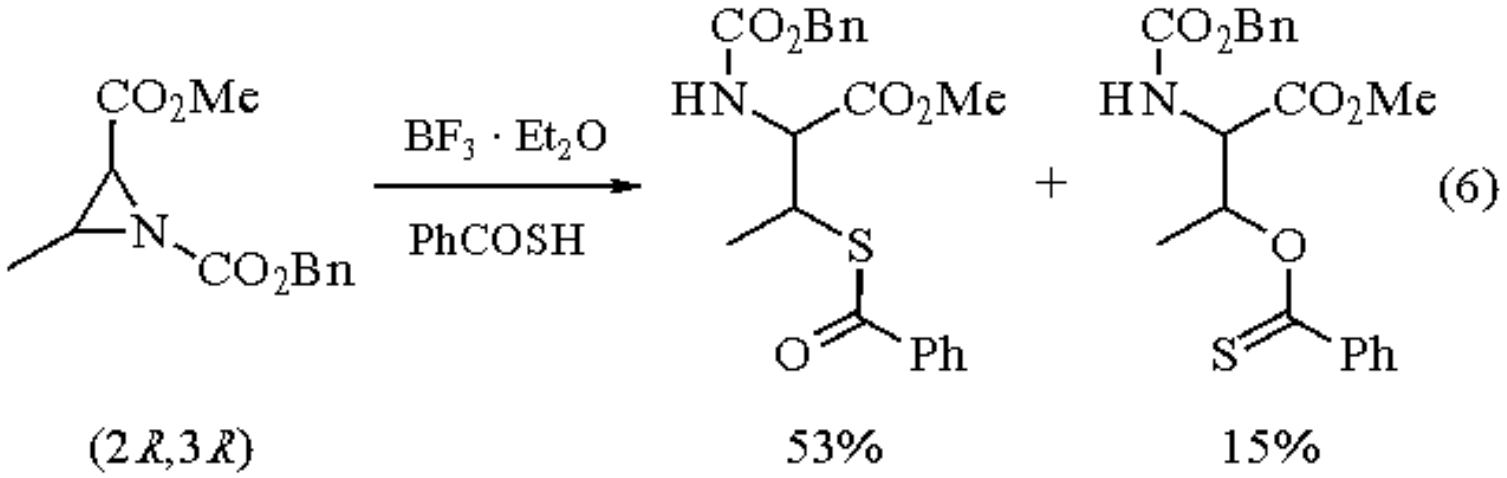

The reaction of aziridinecarboxylic acids with HCl[2,5a,d] or HF[17] usually gives mixtures of isomers, depending on the conditions used. Unsubstituted aziridinecarboxylic acid derivatives form regioisomeric mixtures with indole[18] and thiols,[19] with the predominant product arising from attack at C-2. ***Zinc Trifluoromethanesulfonate*** is the only Lewis acid of a large number examined that promotes the reaction of (2*R*)- or (2*S*)-aziridine-2-carboxylates with indoles to obtain optically pure tryptophans (eq 7),[20] albeit in only moderate yield. Only introduction of N-activating groups (acyl, alkoxycarbonyl, sulfonyl) make possible the S_N2-type ring-opening reactions with various nucleophiles.[2] Indole and ***Thiophenol*** lead to attack at C-3, but ***Azidotrimethylsilane*** leads to attack at C-2.

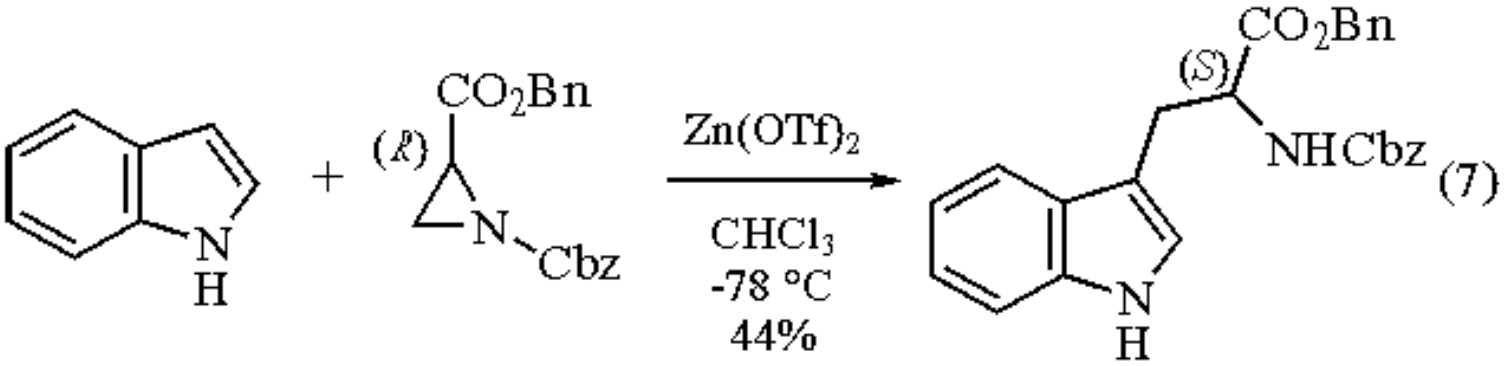

Ring opening of *N*-substituted aziridinecarboxylates with Wittig reagents[2c] (which provide stabilized phosphorus ylides) and organocuprate reagents[2] may be useful for the preparation of amino acids.

Other Reactions.

Activated aziridines react with acetonitrile in the presence of ***Boron Trifluoride Etherate*** leading to imidazolines (eq 8),[2] which yield α,β-diaminocarboxylic acids on standing. Various azabicyclic systems, 1,3-diazabicyclo-[3.1.0]hexan-4-ones, 1,3,4-triazabicyclo[4.1.0]heptan-5-ones (eqs 9 and 10),[3] and 1-azabicyclo[3.3.0]oct-3-enes (eq 11),[21] can be obtained from derivatives of aziridine-2-carboxylic acids.

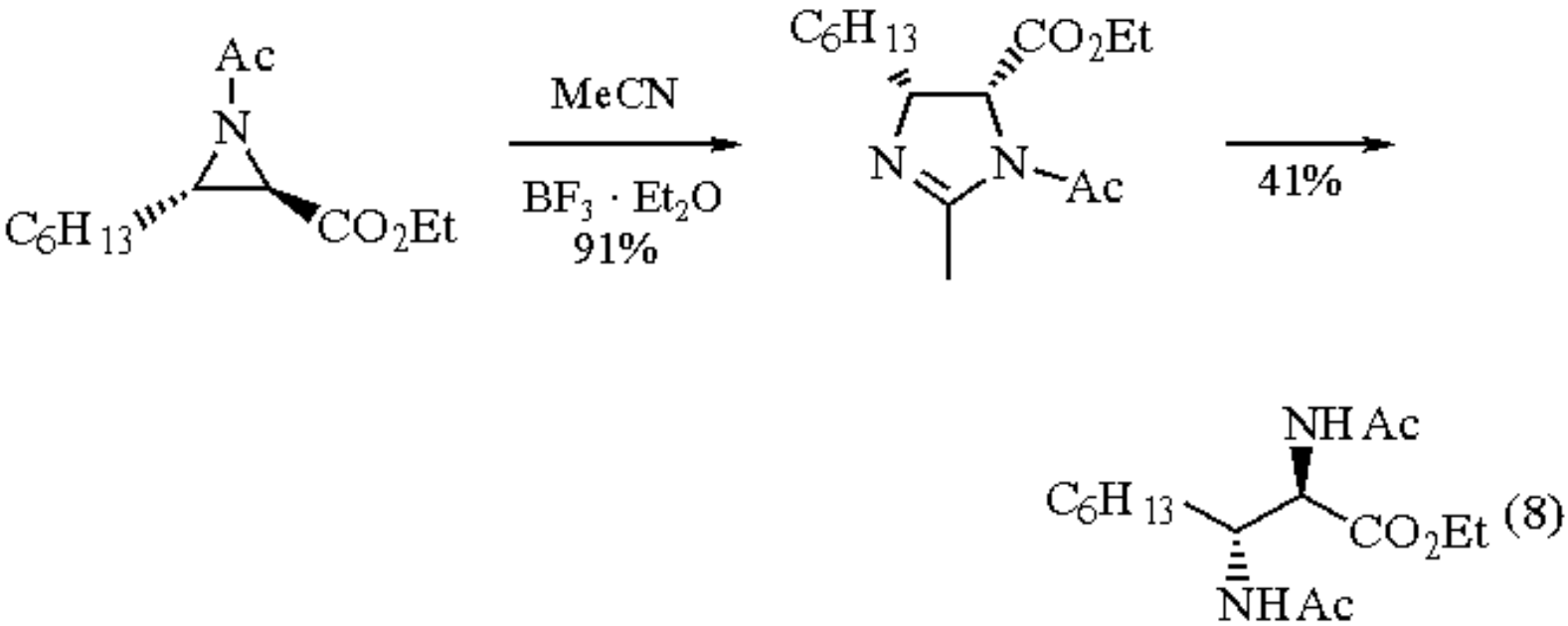

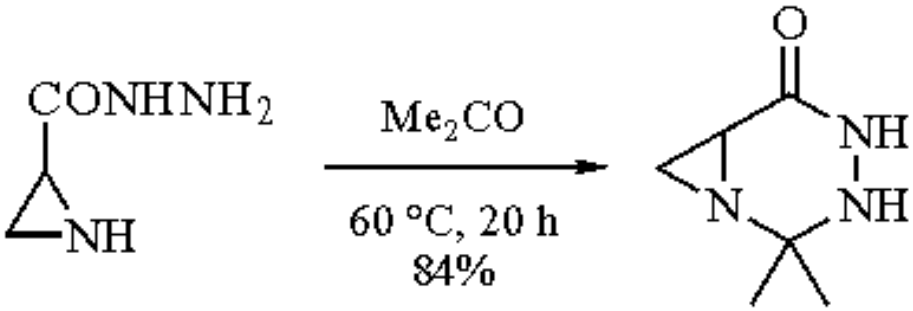

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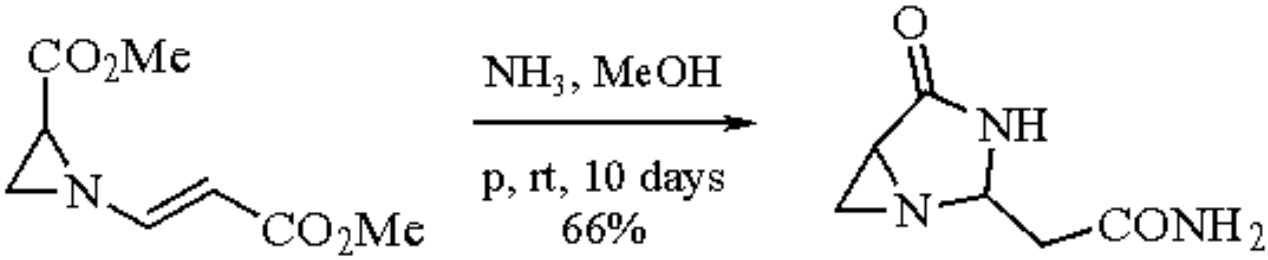

(10)

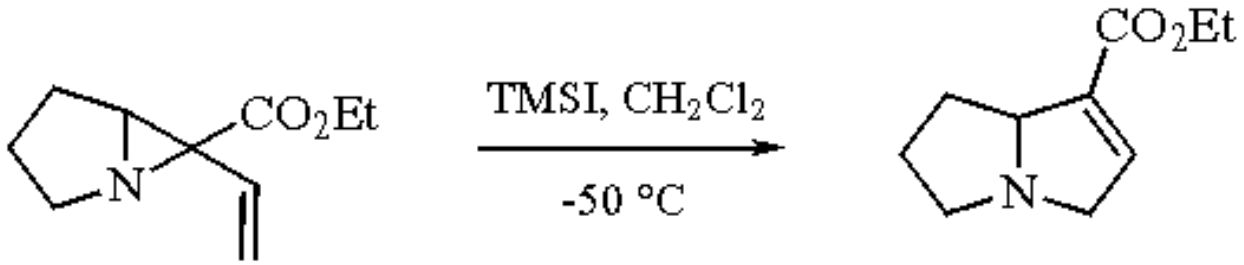

(11)

The Michael addition of acetylenecarboxylates is stereospecific, leading to mostly (*E*) isomers.[22] *C*-Lithioaziridines, accessible by tin-lithium exchange, are converted to aziridinecarboxylic acid derivatives (eq 12).[23]

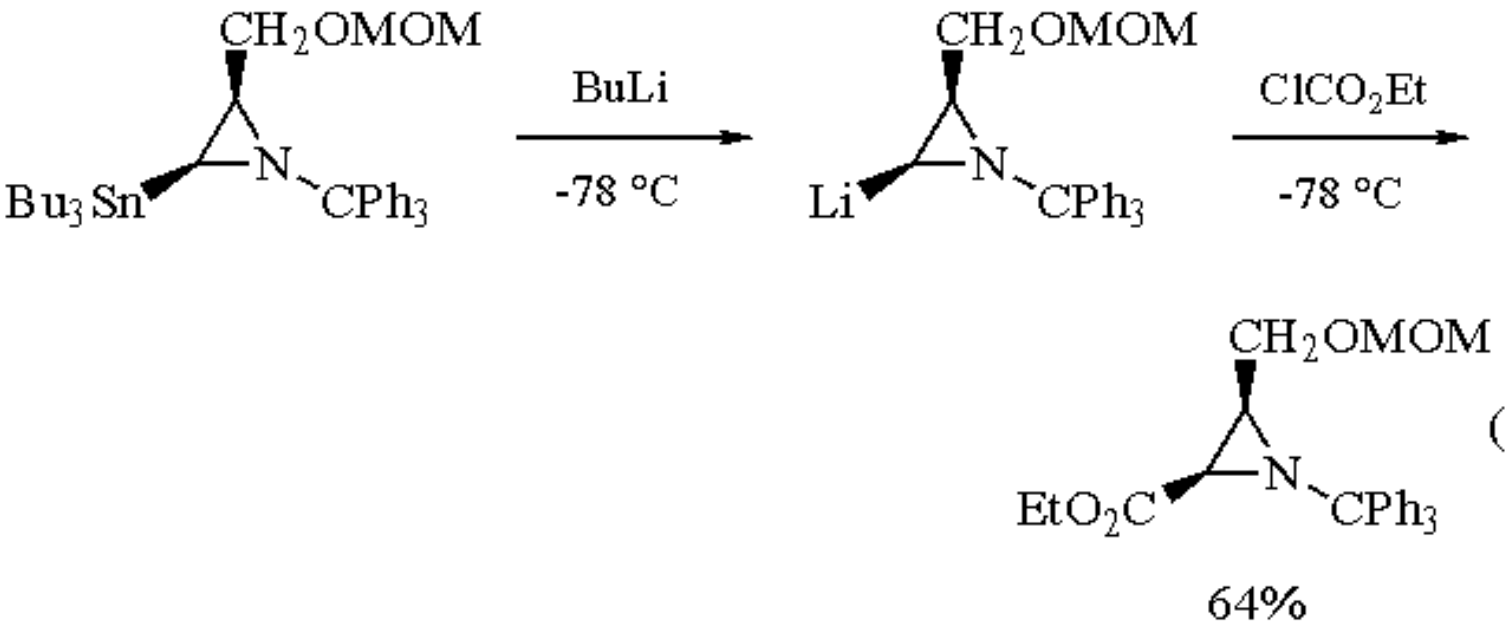

(12)

Derivatives of aziridinemono-[24] and dicarboxylic acids[25] are halogenated with strong Cl^+ donors like ***t-Butyl Hypochlorite***. The latter gives optically active *cis* and *trans* isomers. ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) was used for the dehydrohalogenation step to yield azirine-2-carboxylic acids in low to moderate yields. Other bases (pyridine, triethylamine, KO-*t*-Bu, NaOMe, etc) and halogens (bromo derivatives) did not alter these results.

Related Reagents.

Ethylenimine.

---

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1,1´-Azobis-1-cyclohexanenitrile

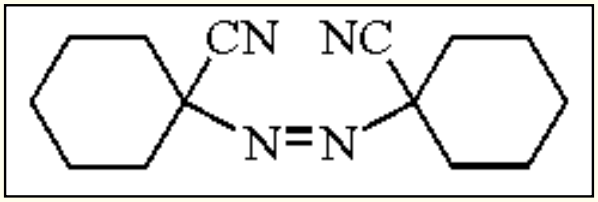

[2094-98-6] · $C_{14}H_{20}N_4$ · 1,1´-Azobis-1-cyclohexanenitrile · (MW 244.34)

(thermally stable radical initiator[1])

Alternate Name: ACN.

Physical Data: mp 114-115 °C.

Solubility: sol benzene, toluene.

Form Supplied in: white solid; widely available commercially.

Purification: recrystallization from methanol.

Handling, Storage, and Precautions: stable indefinitely at rt but prolonged heating at temperatures greater than 80 °C results in rapid decomposition.

ACN has been used as a thermally stable radical initiator. The chair configuration of the cyclohexyl moiety has been given as the reason for its relative thermal stability as compared to other azo-bis(nitrile) derivatives.[1]

Thermal catalysis of ACN-initiated sulfonyl radical-induced addition-cyclization reactions of 1,6 dienes with ***p-Toluenesulfonyl Cyanide*** to give functionalized cyclopentane products as a mixture of stereoisomers in 57-72% yields (eq 1).[2] The *cis* isomer predominated and no cyclohexyl adducts were detected. Photochemically induced cyclization and thermal catalysis with ***Dibenzoyl Peroxide*** gave slightly better yields, with similar stereoselectivity.

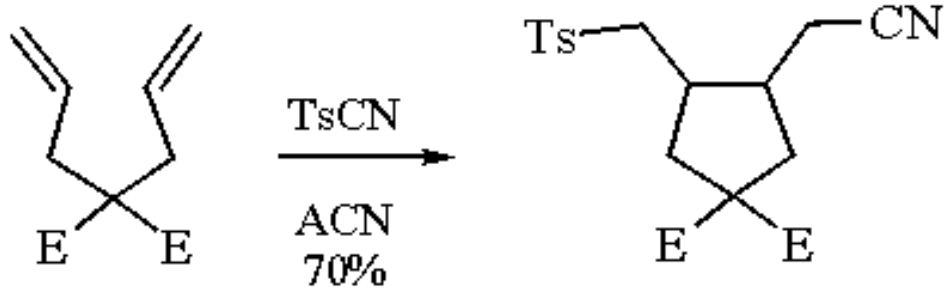

(1)

cis:*trans* = 6.3:1

ACN has been used in the key radical cyclization-trapping step in a prostaglandin synthesis (eq 2).[3] Treatment of the iodoacetal and 4 equiv of the β-stannyl enone with ACN in refluxing toluene gives the bicyclic adduct in 72% purified yield. In contrast, the use of 0.1 equiv of ***Azobisisobutyronitrile*** (AIBN) in benzene at 65 °C as an initiator gives only trace amounts of the desired product. Heating at elevated temperatures with AIBN gives the desired adduct as a mixture of anomers in 43% yield after column chromatography.

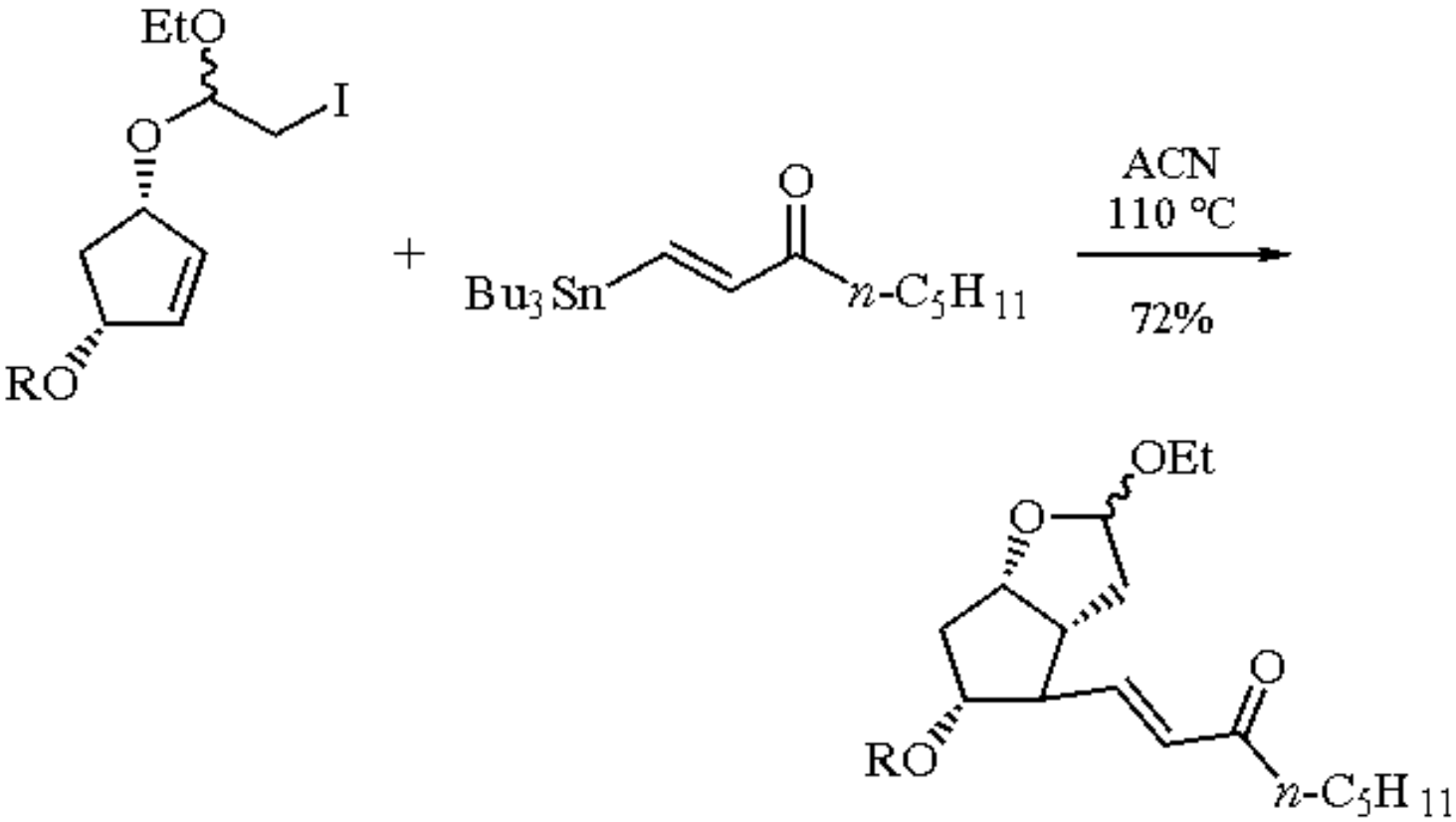

(2)

ACN has been used for the radical addition of alkyl halides to Liebeskind's tri-*n*-butyltin cyclobutenedione reagent to prepare intermediates in the synthesis of the novel NMDA antagonist (eq 3).[4] Typically, 0.1 equiv of ACN is introduced every 12 h to 2 equiv of dione with various alkyl halides to give the addition product in 21-56% yield. Initiation with AIBN requires longer reaction times.

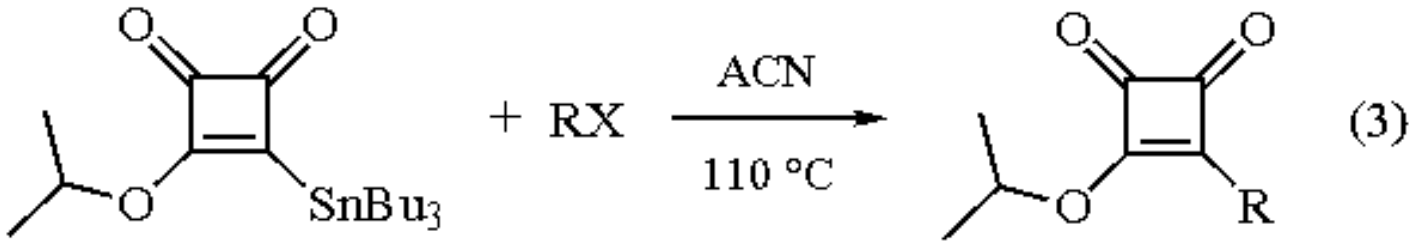

ACN has been used to introduce a tertiary carbon carrying an electronegative group into the 9-position of anthracene, which can lead to triptycene-type compounds in which the stable rotational isomers can be isolated at room temperature.[5]

Due to its high thermal stability, ACN has also been used in physical organic chemistry for kinetic investigations[1,6] and in polymer chemistry.[7]

---

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Azobisisobutyronitrile

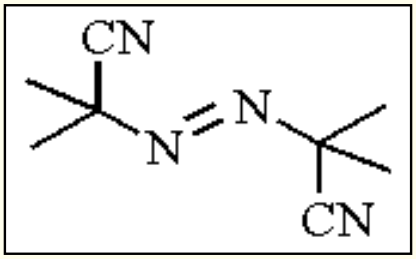

[78-67-1] · $C_8H_{12}N_4$ · Azobisisobutyronitrile · (MW 164.21)

(reagent for initiation of radical reactions)

Alternate Name: AIBN.

Physical Data: mp 103-104 °C.

Solubility: sol benzene, toluene.

Form Supplied in: commercially available as a white powder.

Preparative Method: prepared from the corresponding hydrazine by oxidation with nitrous acid.[1]

Purification: recrystallized from ether.

Handling, Storage, and Precautions: avoid exposure of the reagent to light and heat; store protected from light in a refrigerator or freezer. AIBN is harmful; old or incorrectly stored samples may also present an explosion risk.

Preparation.

Azobisisobutyronitrile (AIBN) and analogs can be prepared by a two-step procedure involving initial treatment of a ketone with ***Hydrazine*** in the presence of ***Sodium Cyanide***, followed by oxidation of the so-formed hydrazine (eq 1).[1,2]

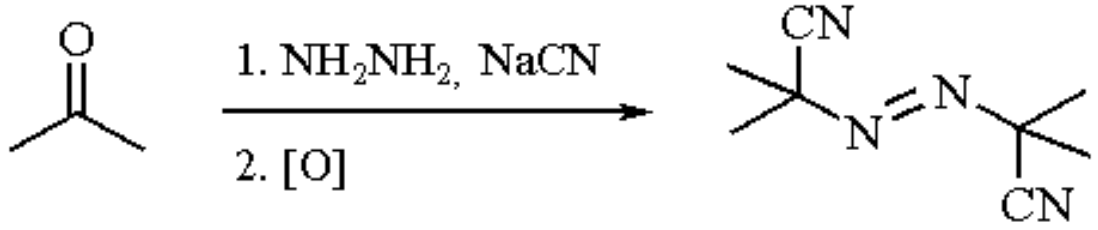

(1)

Use in Radical Chemistry.

AIBN is the initiator most commonly employed in radical reactions, especially those using ***Tri-n-butylstannane***. At temperatures above about 60 °C, AIBN decomposes with evolution of nitrogen to generate isobutyronitrile radicals, which are able to initiate radical chemistry, usually by abstraction of a hydrogen atom from Bu_3SnH or some other donor. The useful working temperature range of AIBN is 60-120 °C, with the half-life at 80 °C being 1 h. In many applications involving C-C bond formation, the radical chemistry is designed to proceed by a chain reaction, and so only small amounts (typically ca. 0.1 equiv) of the initiator is required. For best results, especially at more elevated temperatures, AIBN is best added in portions or as a solution by means of a syringe pump. Typical Bu_3SnH-mediated radical reactions, which involve the use of AIBN as initiator, include cyclizations of alkyl and vinyl radicals (eqs 2 and 3).[3,4]

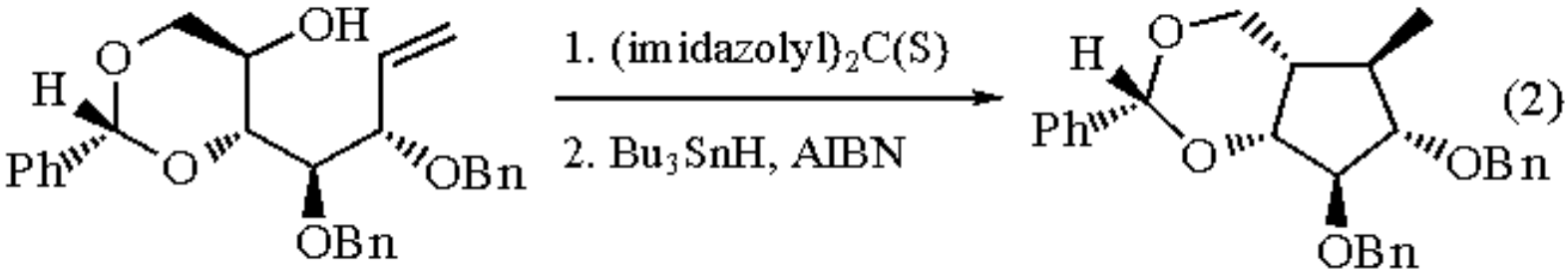

(2)

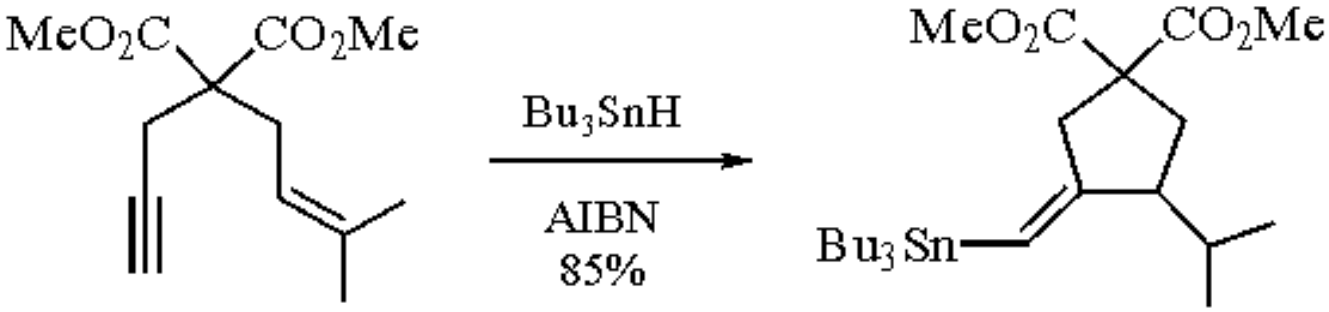

(3)

In eq 2, generation of an alkyl radical is achieved by attack of a tributylstannyl radical on a Barton derivative, whereas in eq 3, the vinyl radical required is generated by addition of the stannyl radical to an alkyne. This type of cyclization has been extended to many types of substrate, including those in which a carbonyl group acts as the acceptor (eq 4),[5] and those in which additional types of radical rearrangement or fragmentation occur (eq 5).[5,6] The latter sequence involves addition of the initially formed radical onto the adjacent carbonyl group, followed by reopening of the so-formed cyclopropanoxy radical in regioselective fashion.[6] The reaction effects a one-carbon ring expansion in good chemical yield.

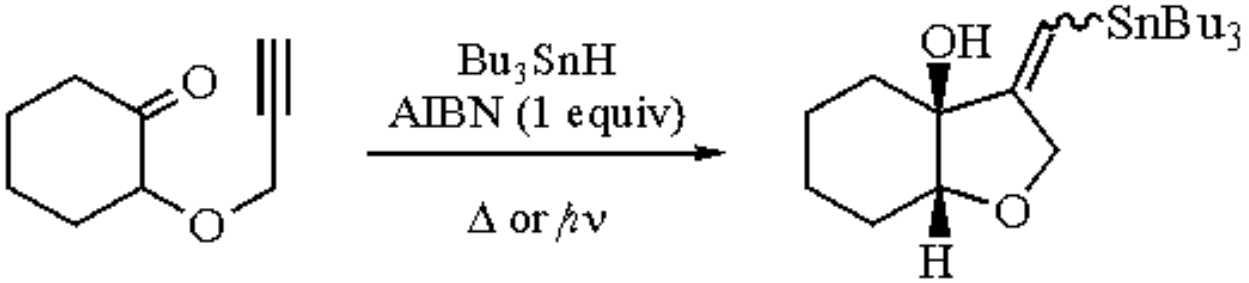

(4)

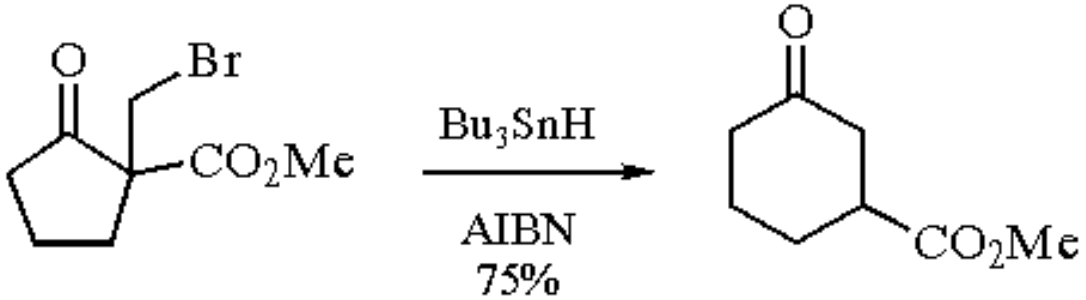

(5)

AIBN can also be used in combination with many other types of radical-generating systems other than those employing Bu_3SnH. Examples include cyclizations using ***Tris(trimethylsilyl)silane***,[7] ***Thiophenol***,[8] ***Diphenylphosphine***,[9] and carbonylation of radicals using Ph_3GeH and CO under pressure[10] (eqs 6-9).

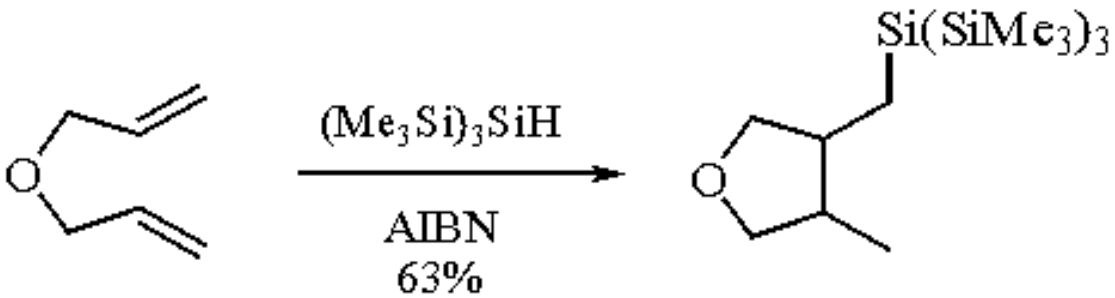

(6)

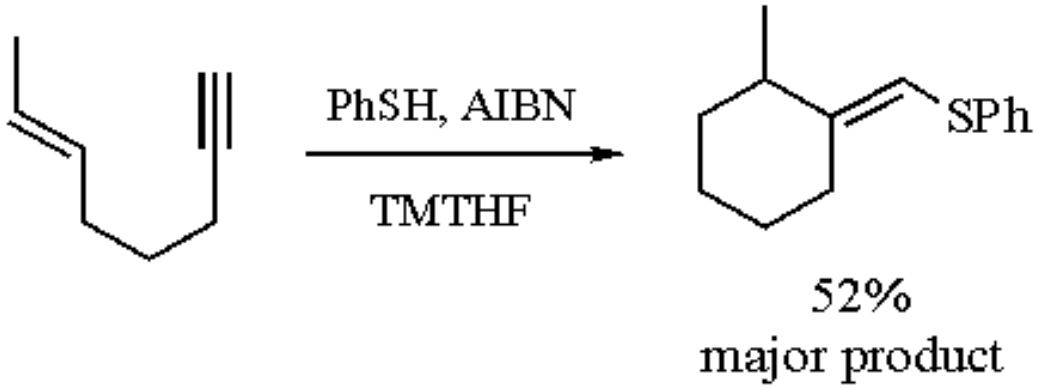

(7)

TMTHF = 2,2,5,5-tetramethyltetrahydrofuran

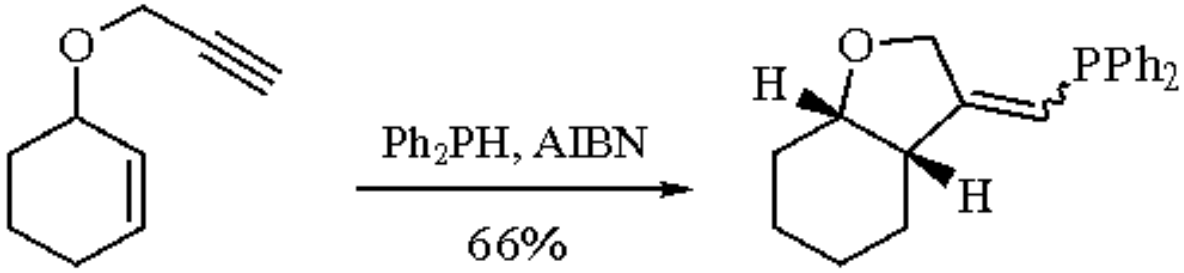

(8)

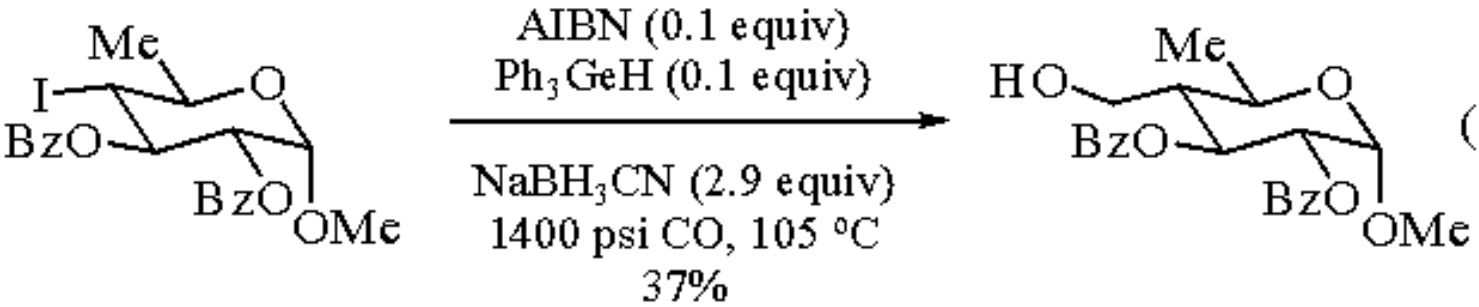

(9)

For certain types of radical reaction, AIBN may not always give optimal results. Keck and Burnett found in their synthesis of $PGF_{2\alpha}$ that the introduction of the lower side chain, involving radical addition onto a β-stannyl enone, was inefficient when AIBN was used as initiator at 65 °C. By conducting the reaction in refluxing toluene (110 °C), and replacing AIBN with the related ***1,1´-Azobis-1-cyclohexanenitrile*** (ACN), a markedly better yield of the desired adduct was obtained (eq 10).[11]

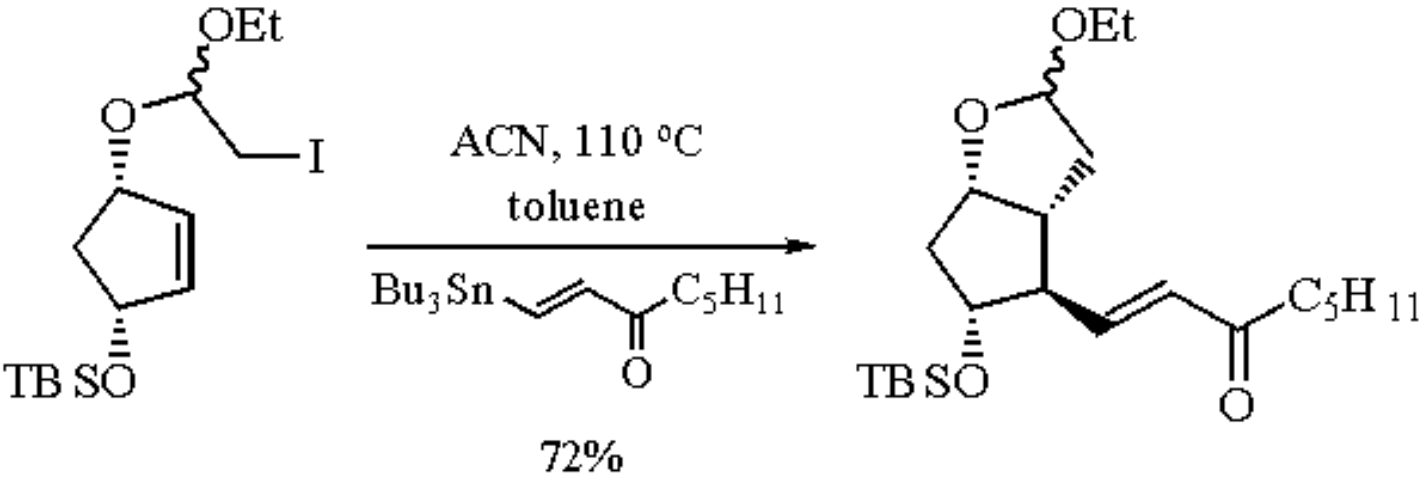

(10)

For reactions which require temperatures above benzene reflux, ACN, which decomposes markedly slower than AIBN, may be a generally useful alternative to AIBN, although this possibility has not been examined in detail. At elevated temperatures, other alternative initiators such as dialkyl peroxides and peresters should also be considered, although the reactivity of the radicals generated from these initiators is quite different to that of the isobutyronitrile radicals generated from AIBN.

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1,1´-(Azodicarbonyl)dipiperidine

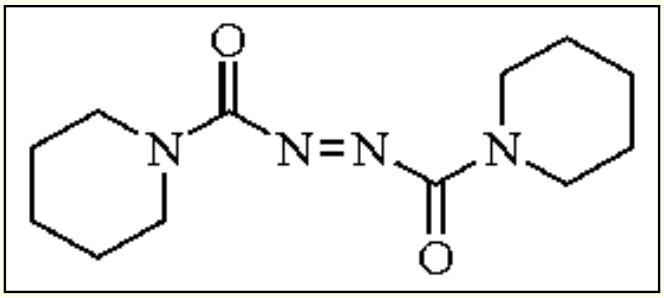

[10465-81-3] · $C_{12}H_{20}N_4O_2$ · 1,1´-(Azodicarbonyl)dipiperidine · (MW 252.32)

(selectively oxidizes a variety of alcohols to the corresponding aldehydes or ketones under basic conditions[1])

Physical Data: mp 134-135 °C.

Solubility: insol petroleum ether; slightly sol methanol; sol ethanol, ether, THF.

Form Supplied in: golden-yellow crystals.

Analysis of Reagent Purity: ^{1}H NMR (CCl_4) δ 1.47-1.88 (12H, br), 3.15-3.77 (8H, br); IR (KBr) 1705 cm^{-1}.

Purification: recrystallized from hexane-benzene (10:1).

Handling, Storage, and Precautions: irritant; stable to storage at room temperature.

Oxidation of Alcohols.

A wide variety of primary and secondary alcohols, after being converted into their bromomagnesium salts by treatment with a slight excess amount (1.2 equiv) of *n*-propylmagnesium bromide or ***t-Butoxymagnesium Bromide***, are oxidized with 1.2 equiv of 1,1´-(azodicarbonyl)-dipiperidine in THF at room temperature to afford the corresponding aldehydes or ketones in high yield (eq 1).[1]

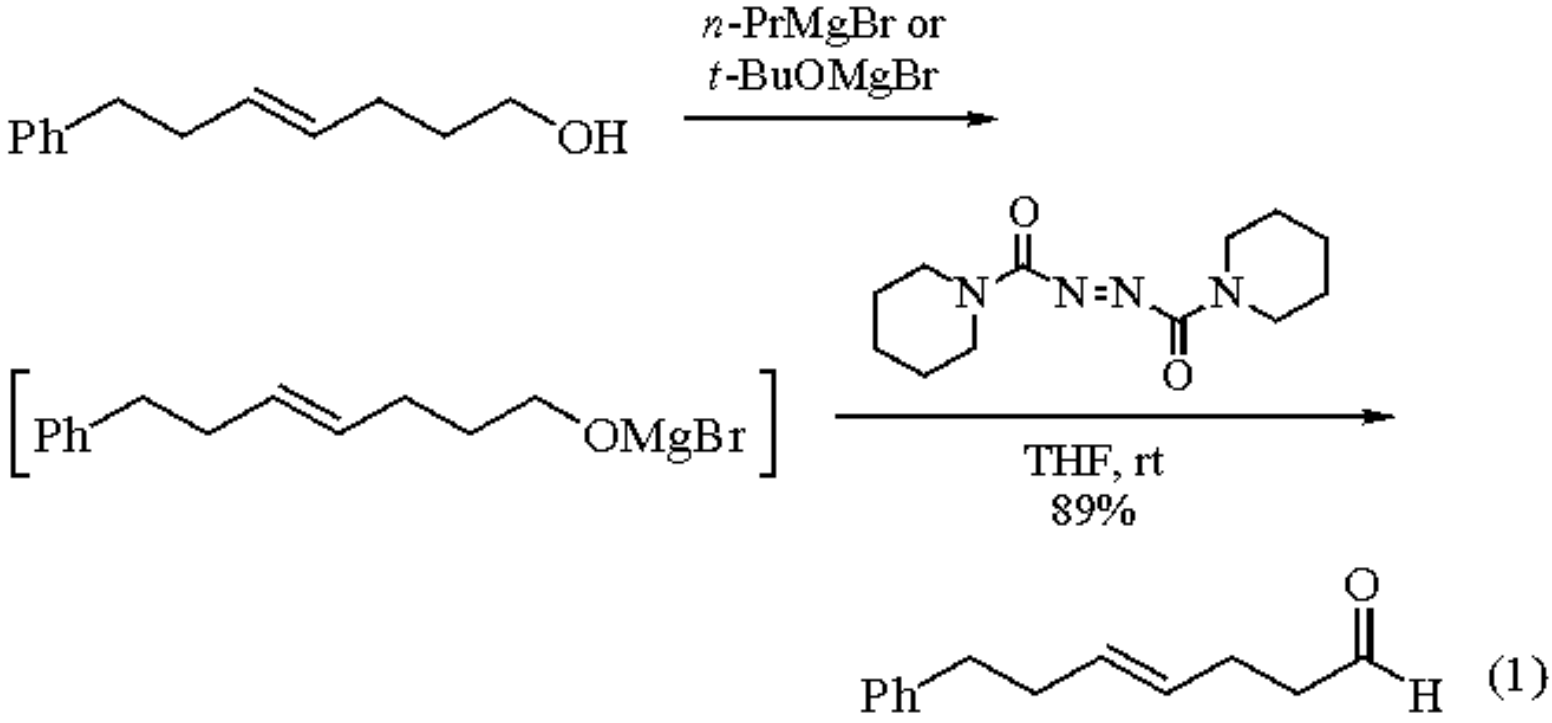

The use of *t*-butoxymagnesium bromide is recommended for the oxidation of the substrates having functional groups which react with Grignard reagents. The oxidation of testosterone proceeds smoothly to give 4-androstene-3,17-dione in high yield by the use of *t*-butoxymagnesium bromide (eq 2).[1]

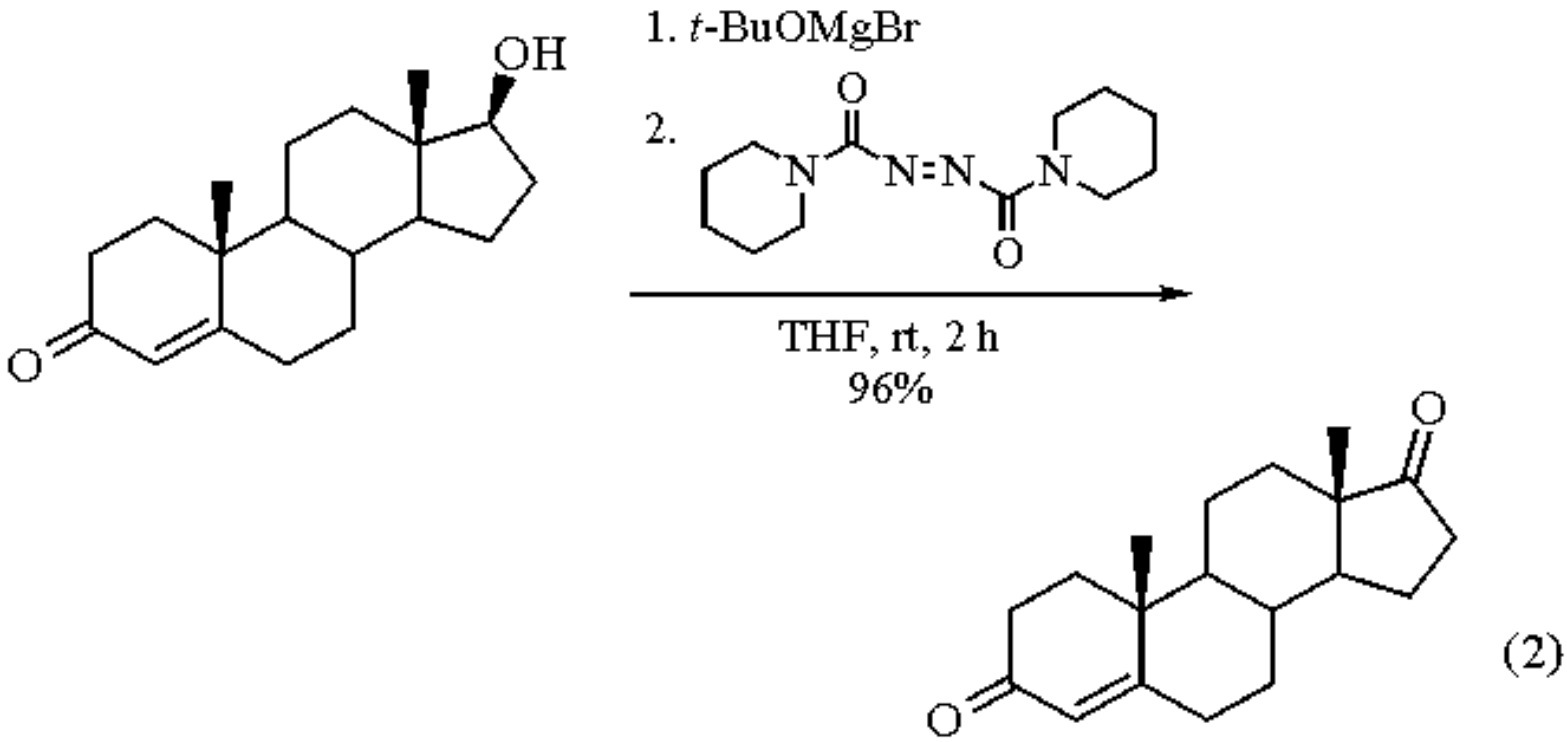

This method has been employed to oxidize a wide range of alcohols incorporating functional groups such as alkenes, epoxides, amines, sulfides (eq 3),[2] allylstannanes (eqs 4 and 5),[3,4] and allenylstannanes (eq 6).[5] Acylstannanes can also be prepared by the oxidation of the lithium salt of 1-stannyl alcohols (eq 7).[6]

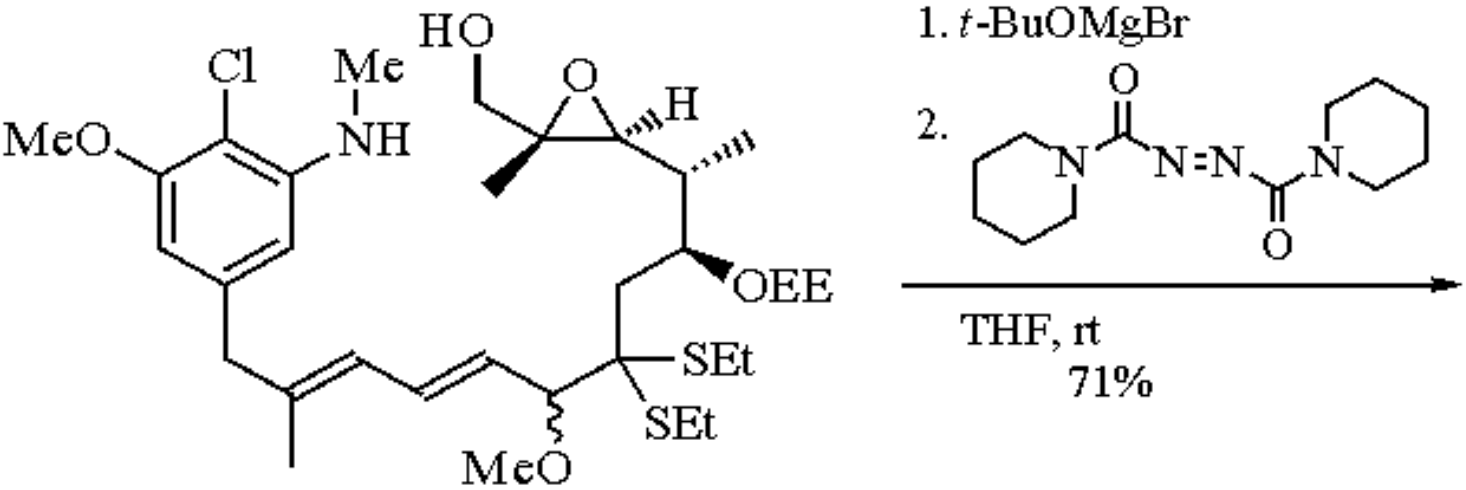

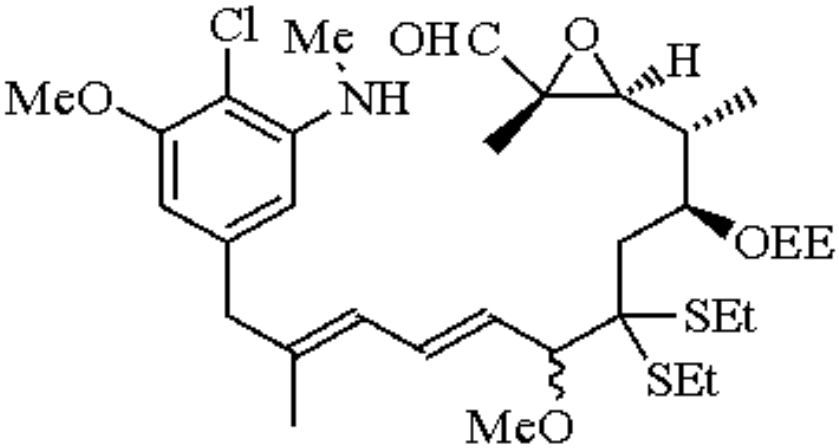

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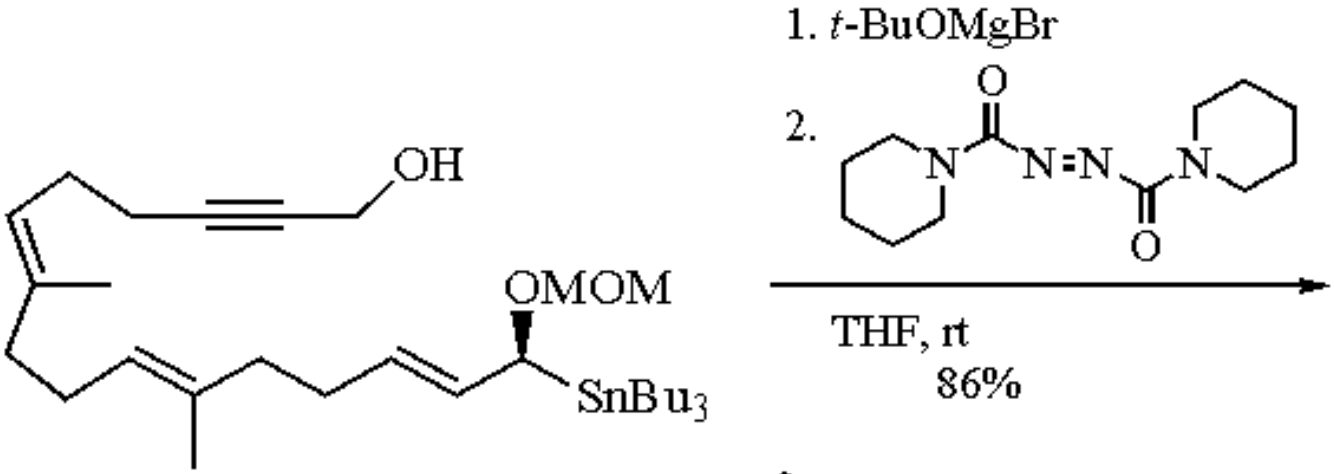

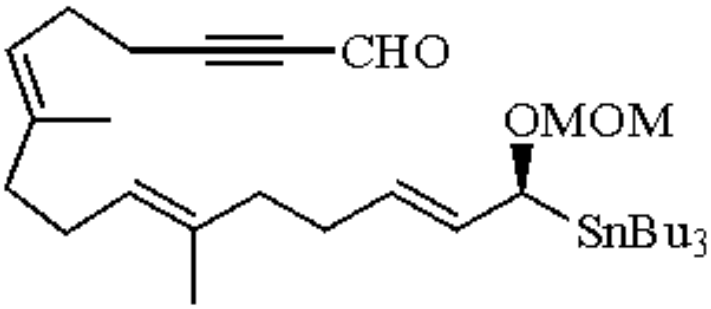

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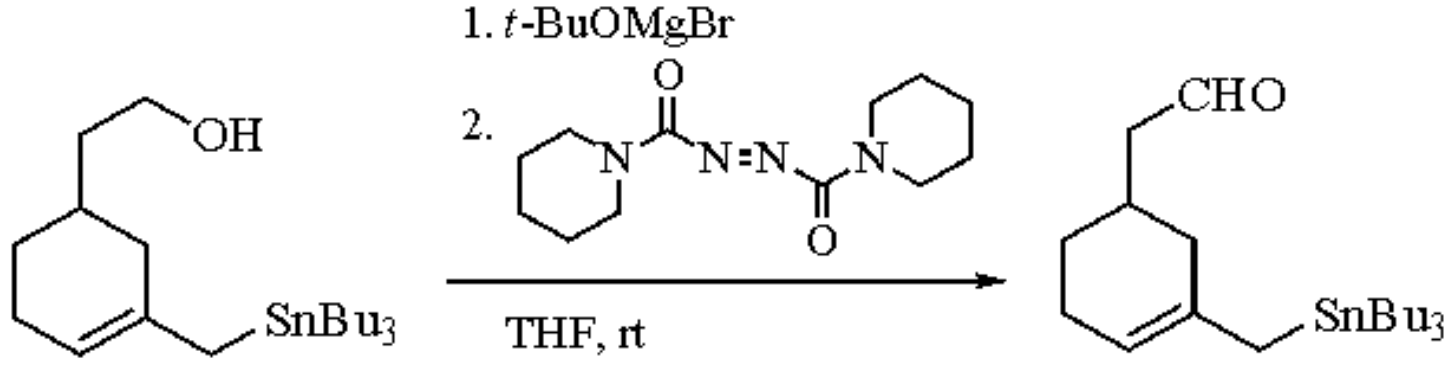

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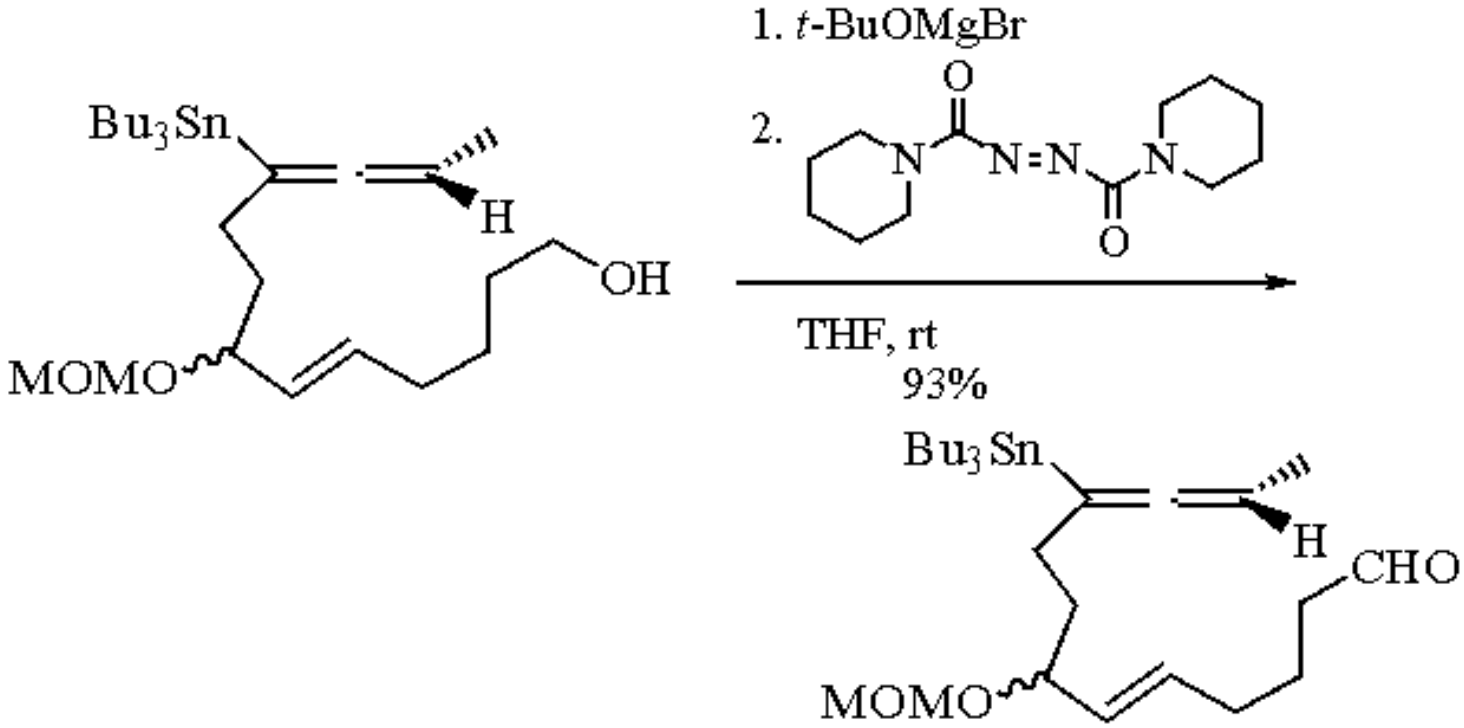

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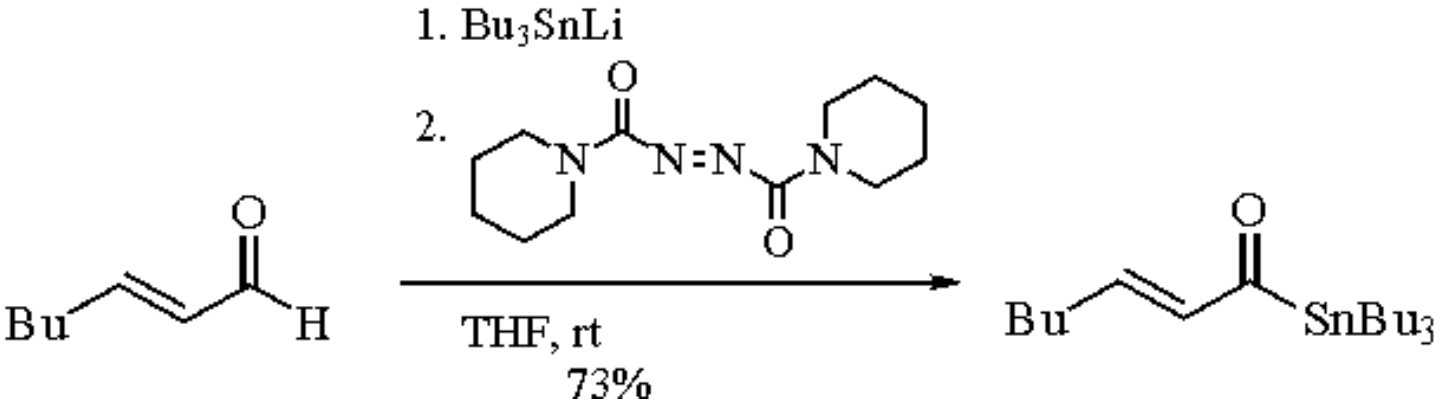

(7)

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Baker's Yeast

(microorganism used as biocatalyst for the reduction of carbonyl groups and double bonds,[1] either under fermenting conditions, immobilized, or ultrasonically stimulated)

Solubility: insol cold and warm H_2O; used as a slurry.

Form Supplied in: yellowish pressed cakes, commercially available as cubes from bakeries or supermarkets, usually produced by brewery companies.

Handling, Storage, and Precautions: the wet cake must be stored in the refrigerator (0-4 °C) and used within the date indicated by the manufacturer.

Baker's Yeast-Mediated Biotransformations.

Baker's yeast (BY, *Saccharomyces cerevisiae*) is readily available and inexpensive, and its use does not require any special training in microbiology. For these reasons, this biocatalyst has enjoyed a wide popularity among organic chemists, so that it can be considered as a microbial reagent for organic synthesis.[2] BY is generally used as whole cells, in spite of the problems connected with rates of penetration and diffusion of the substrates into, and the product from, the cells. However, the crude system is an inexpensive reservoir of cofactor-dependent enzymes such as oxidoreductases.[3] These benefits overcome the complication caused by undesired enzymatic reactions which lead to the formation of byproducts. Well-defined experimental procedures for BY-mediated bioreductions can be found in *Organic Syntheses*.[4] In the usual applications the biotransformations lead to optically active compounds with variable, but generally high, enantioselectivity.[5] The reaction is easily carried out in a heterogeneous medium containing a slurry of the yeast in tap water, in aerobic and fermenting conditions. Typically, the experimental conditions require a variable yeast:substrate ratio (1-40 g $mmol^{-1}$). The yeast is suspended in an aqueous solution of glucose or sucrose (0.1-0.3 M) to start the fermentation and to the fermenting yeast the substrate is added neat or in a suitable solvent, and therefore dispersed into the heterogeneous medium. The reaction is kept at 25-30 °C and, if necessary, additional fermenting BY can be added. At the end, the yeast is filtered off through Celite and the product extracted with organic solvents.

Carbonyl Group Reductions.

Early applications of BY date back to the end of the 19th century and the first examples are reductions of carbonyl compounds.[1c] The widespread applications of this biotransformation are based on some systematic investigations on various ketones[6] and the stereochemical outcome of the reaction is generally described by the so-called Prelog's rule[7] which successfully applies to a great number of structures (eq 1).

The structural variety of carbonyl compounds appears to be almost unlimited since aliphatic, aromatic, and cyclic ketones are good substrates for the bioreduction.[1,5] Also, organometallic carbonyl compounds such as $Cr(CO)_3$-complexed aromatic aldehydes (eq 2)[8] or ketones (eq 3)[9] are enantioselectively reduced by BY.

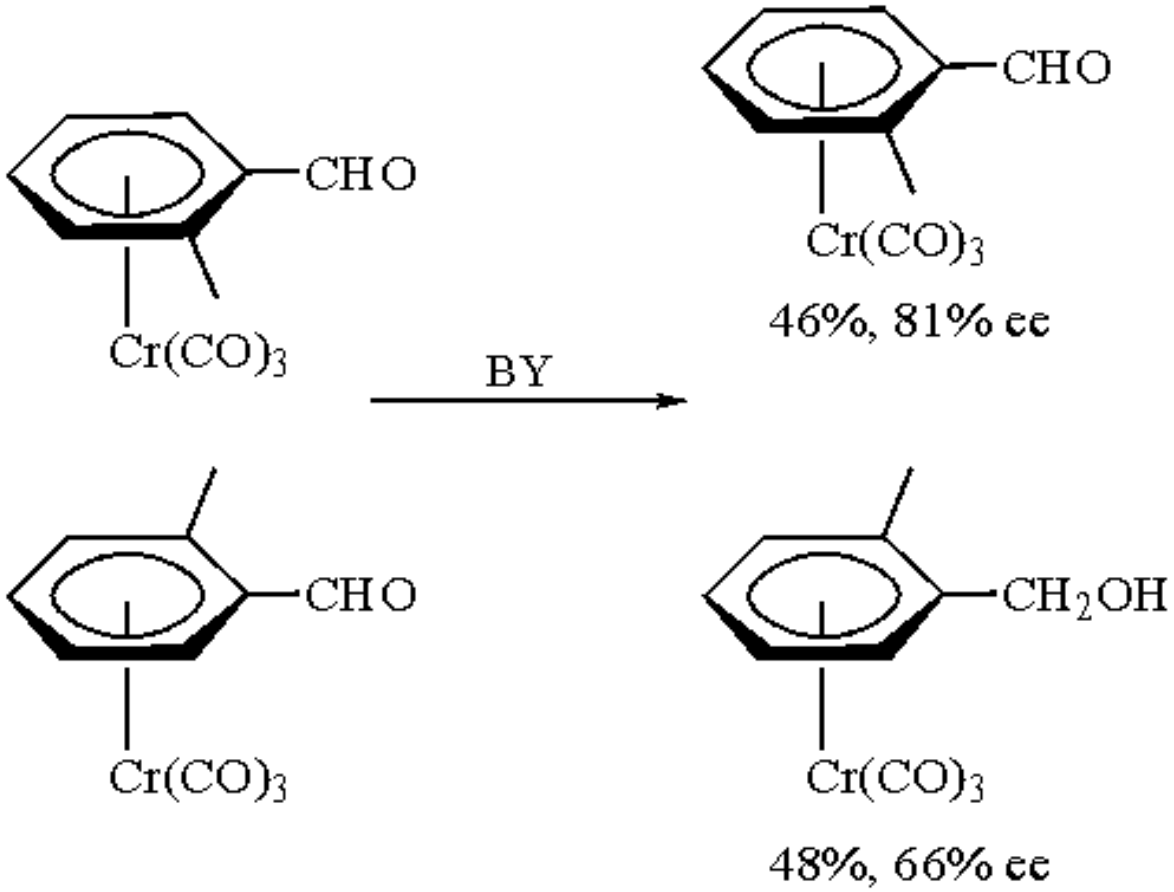

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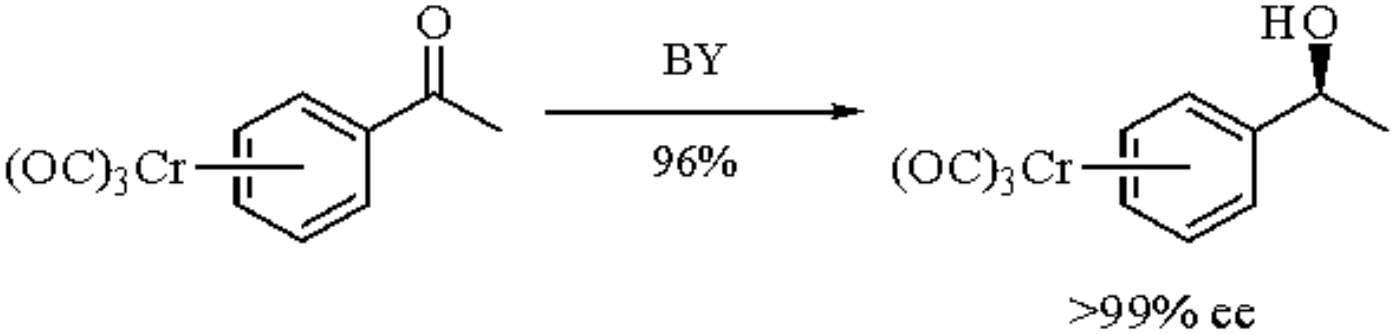

(3)

In general, the enantiomeric excess and the configuration of the optically active alcohols are strongly dependent on the structure of the starting carbonyl compound; many examples of diastereoselective reduction have also been reported.[10] The reduction of an epoxy ketone is accompanied by a stereocontrolled epoxide hydrolytic opening to afford a racemic triol, diastereomerically pure (eq 4).[11]

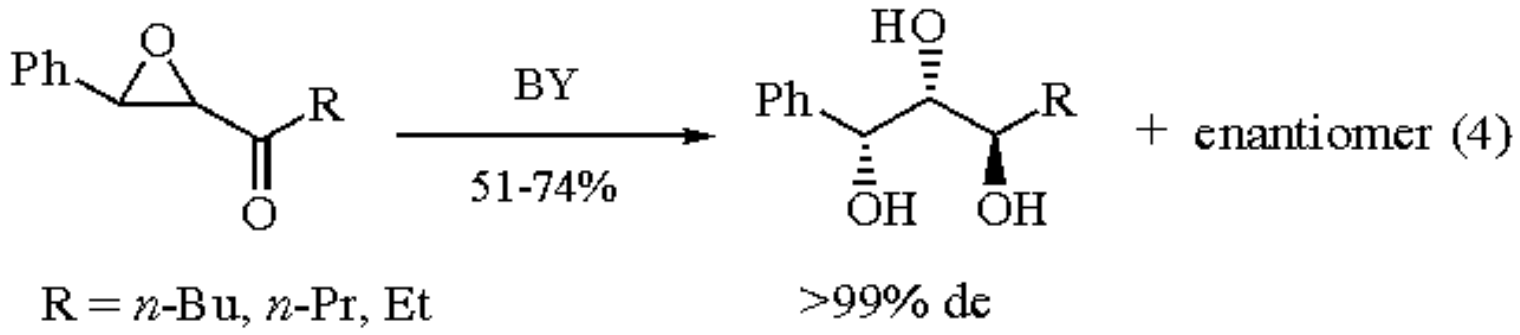

Many experimental procedures have been developed in order to influence the enantioselectivity and the stereochemistry of the products: use of organic media,[12] the addition of various compounds to the incubation mixture,[13] or enclosure in a dialysis tube[14] can be helpful. Immobilized BY can be used in water or in organic solvents for the same purpose.[15] Slight modifications of the substrate can obtain the same result and many examples are available.[16] Several other groups can be present in the carbonyl-containing substrate.[5] For instance, the asymmetric reduction of keto groups in compounds containing a cyclopropyl moiety has been achieved (eq 5).[17]

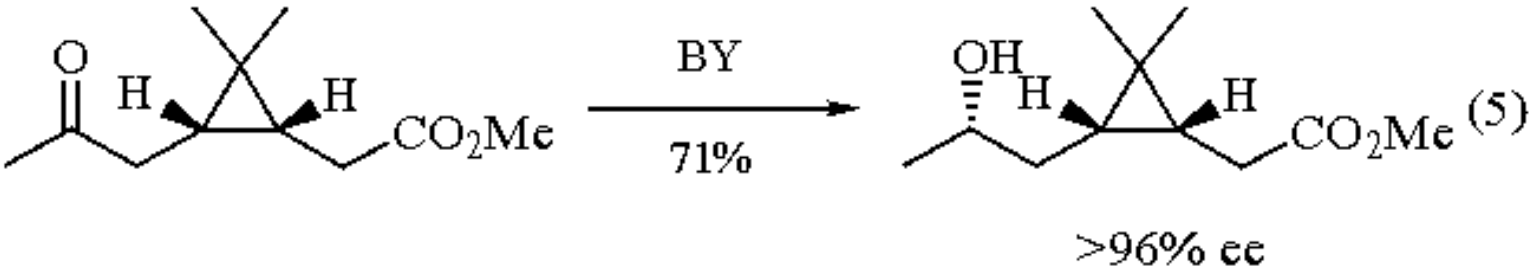

β-Keto esters are reduced to the corresponding hydroxy esters but, since more oxidoreductases are present in the yeast,[18] occasionally different stereochemistry or lowered enantioselectivity are observed. This is well illustrated by the stereochemical outcome of the reduction of a β-keto ester such as ethyl 4-chloroacetoacetate,[16b] when compared to ethyl acetoacetate (eq 6).[4a]

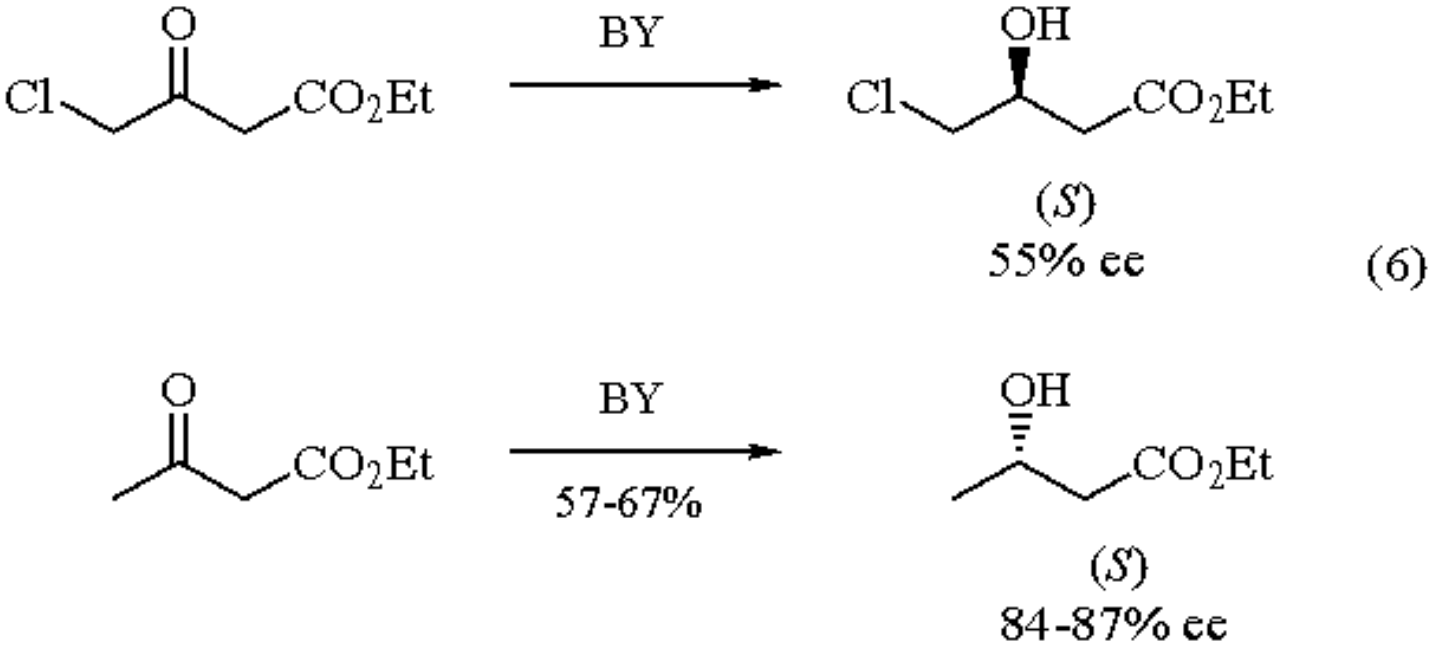

Both γ- and δ-keto acids are reduced to hydroxy acids, which directly cyclize to the corresponding lactones in the incubation media.[19] The pheromone (*R*)-(+)-hexadecanolide has been prepared in this way by reduction of the corresponding δ-keto acid (eq 7).[20]

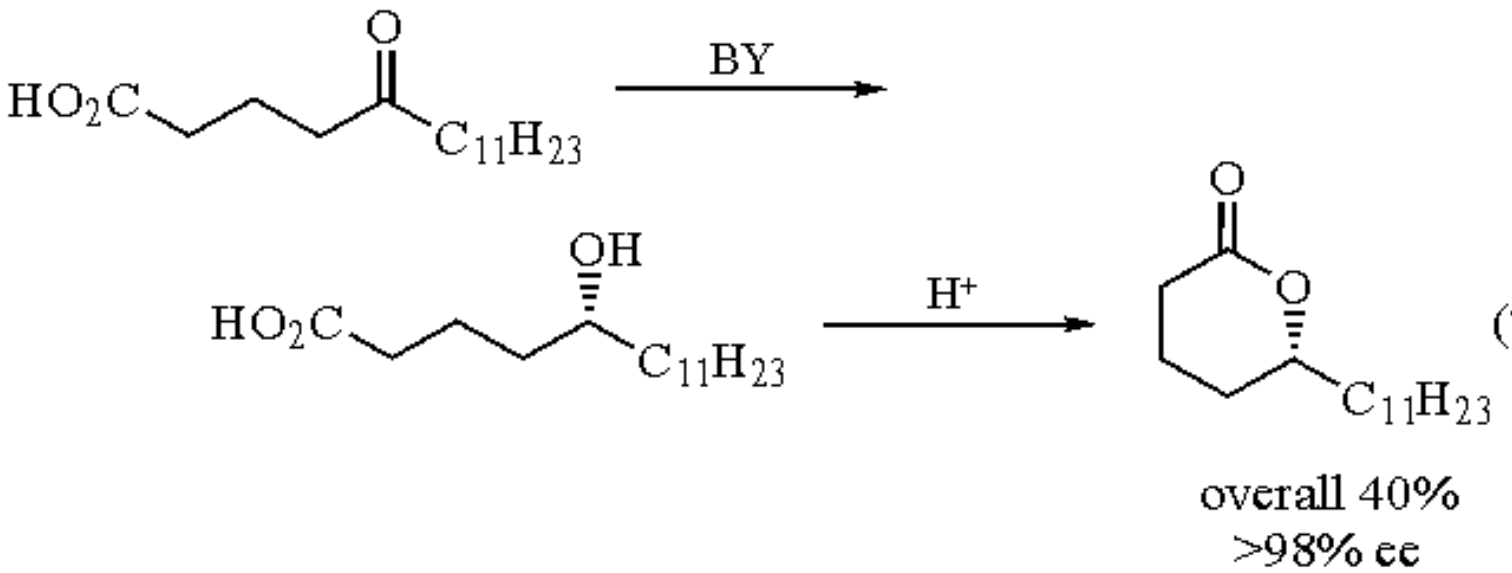

(7)

α-Hydroxy ketones are good substrates for the bioreduction and several optically active 1,2-diols have been prepared.[21] The monobenzoate of dihydroxyacetone is reduced to the corresponding optically pure glycerol derivative (eq 8).[22] In many instances, simple protection of the α-hydroxy group may afford the opposite enantiomer.[23]

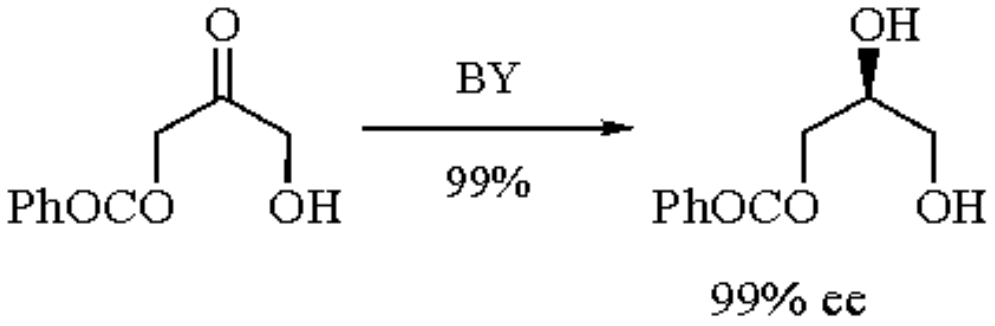

(8)

Activated Double-Bond Hydrogenation.

Fermenting BY is able to carry out the hydrogenation of double bonds which bear certain functional groups. A compound containing an unsaturated acetal and an ester function is directly transformed enantioselectively in a hydroxy acid, later chemically cyclized to the corresponding lactone (eq 9).[24] Other α,β-unsaturated alcohols and aldehydes are efficiently and enantioselectively converted to the corresponding saturated alcohols.[25] 2-Chloro-2-alkenoates (eq 10)[26] or nitroalkenes (eq 11)[27] are enantioselectively hydrogenated, the stereochemistry of the reaction depending on the double bond configuration.

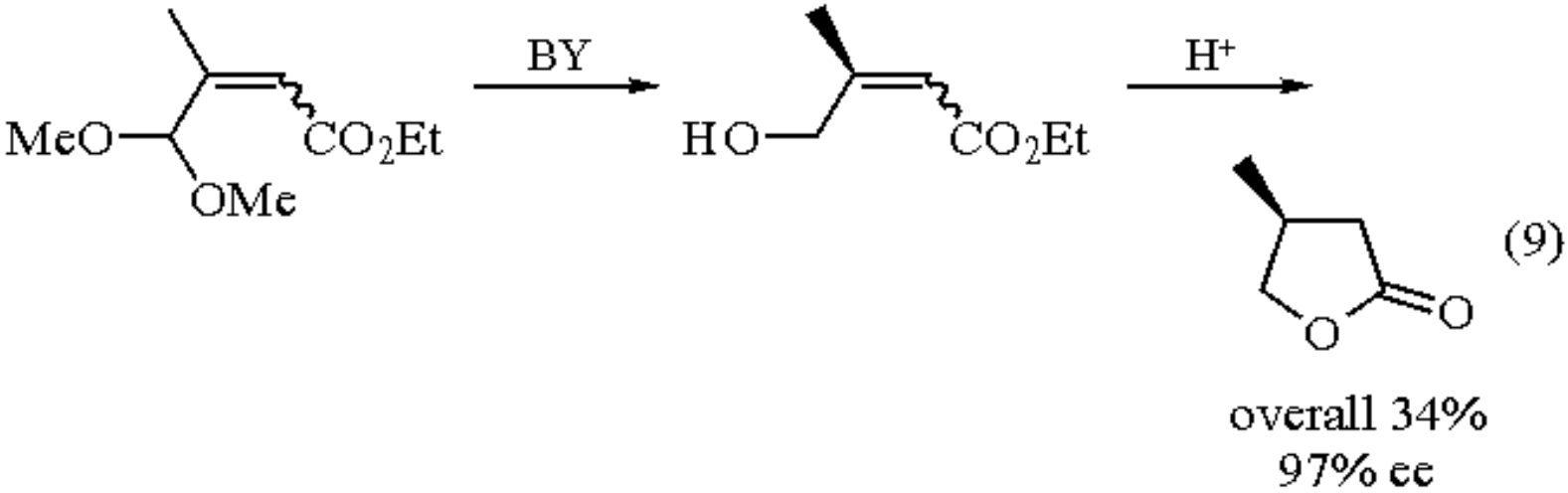

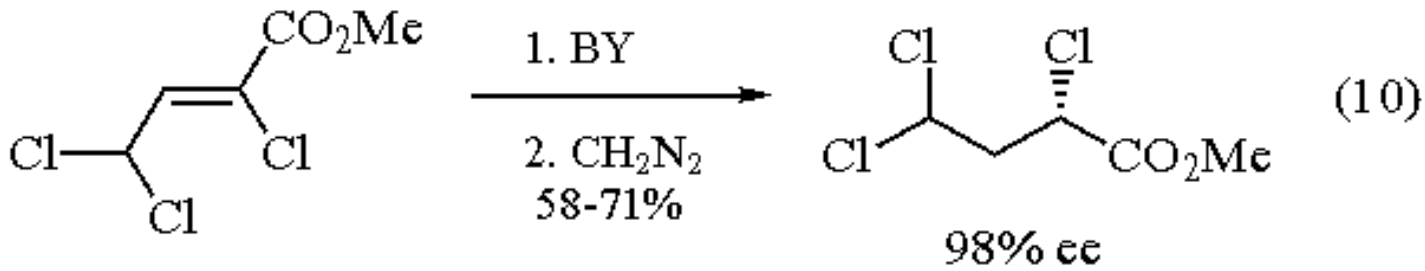

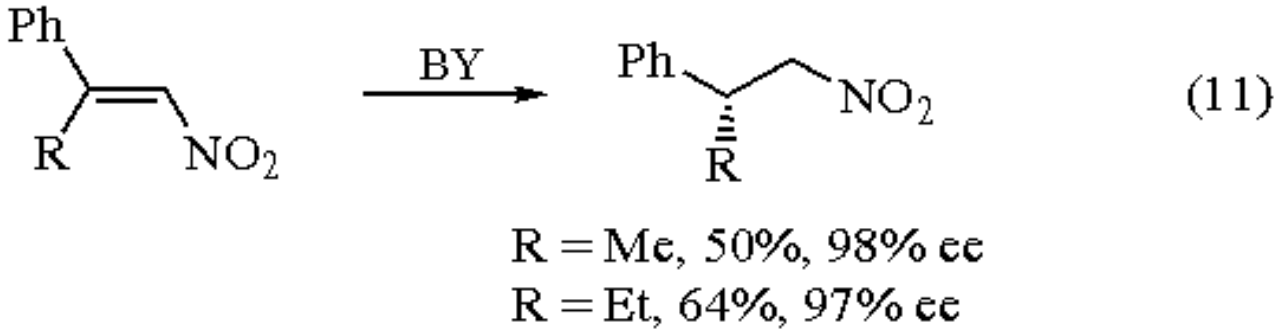

Acyloin Condensations.

The condensation between furfural or benzaldehyde and a two-carbon unit to afford a hydroxy ketone has long been known.[1b] The extension of the reaction to α,β-unsaturated aldehydes has provided access to optically active functionalized diols (eq 12),[28] which are used as chiral intermediates for the synthesis of natural products.[1b]

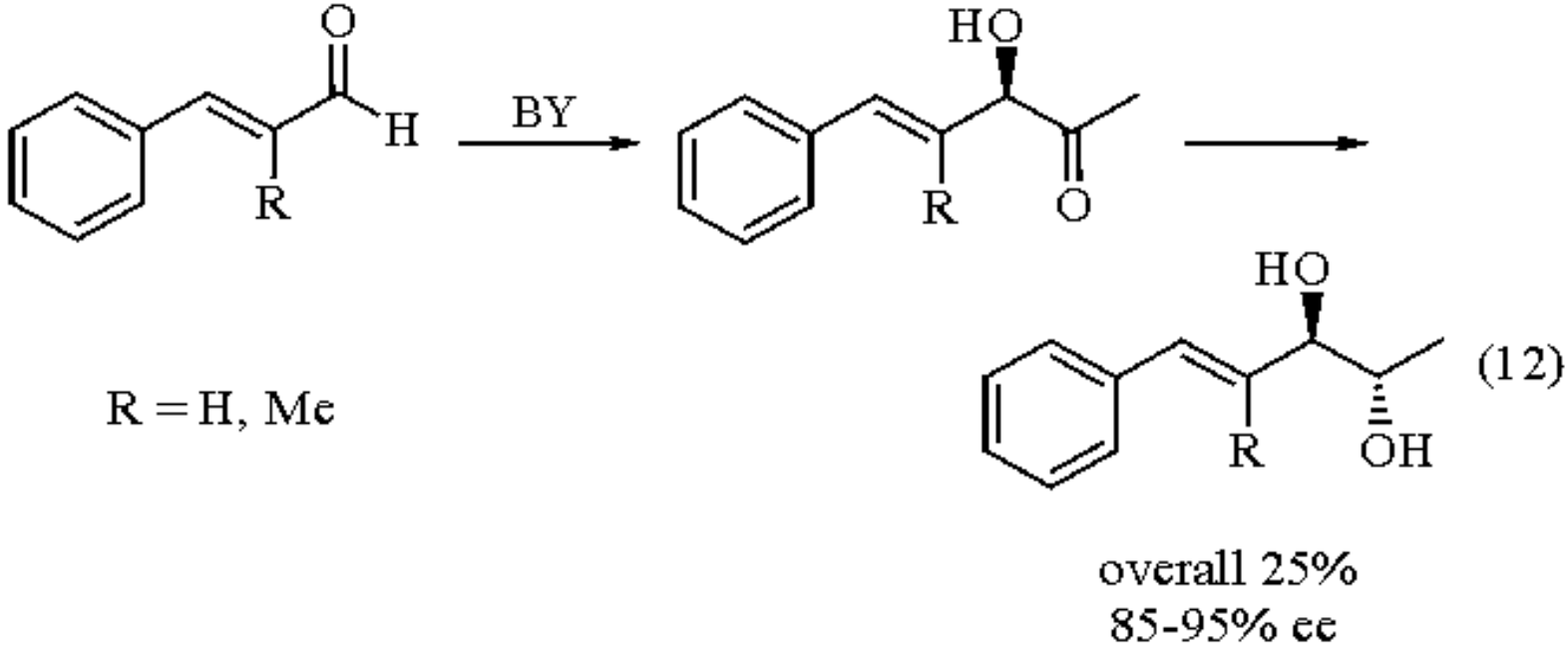

Cyclization of Squalene-like Substrates.

Ultrasonically stimulated BY is a source of sterol cyclase, which catalyzes the cyclization of squalene oxide and squalenoid compounds to lanosterol derivatives (eq 13).[29]

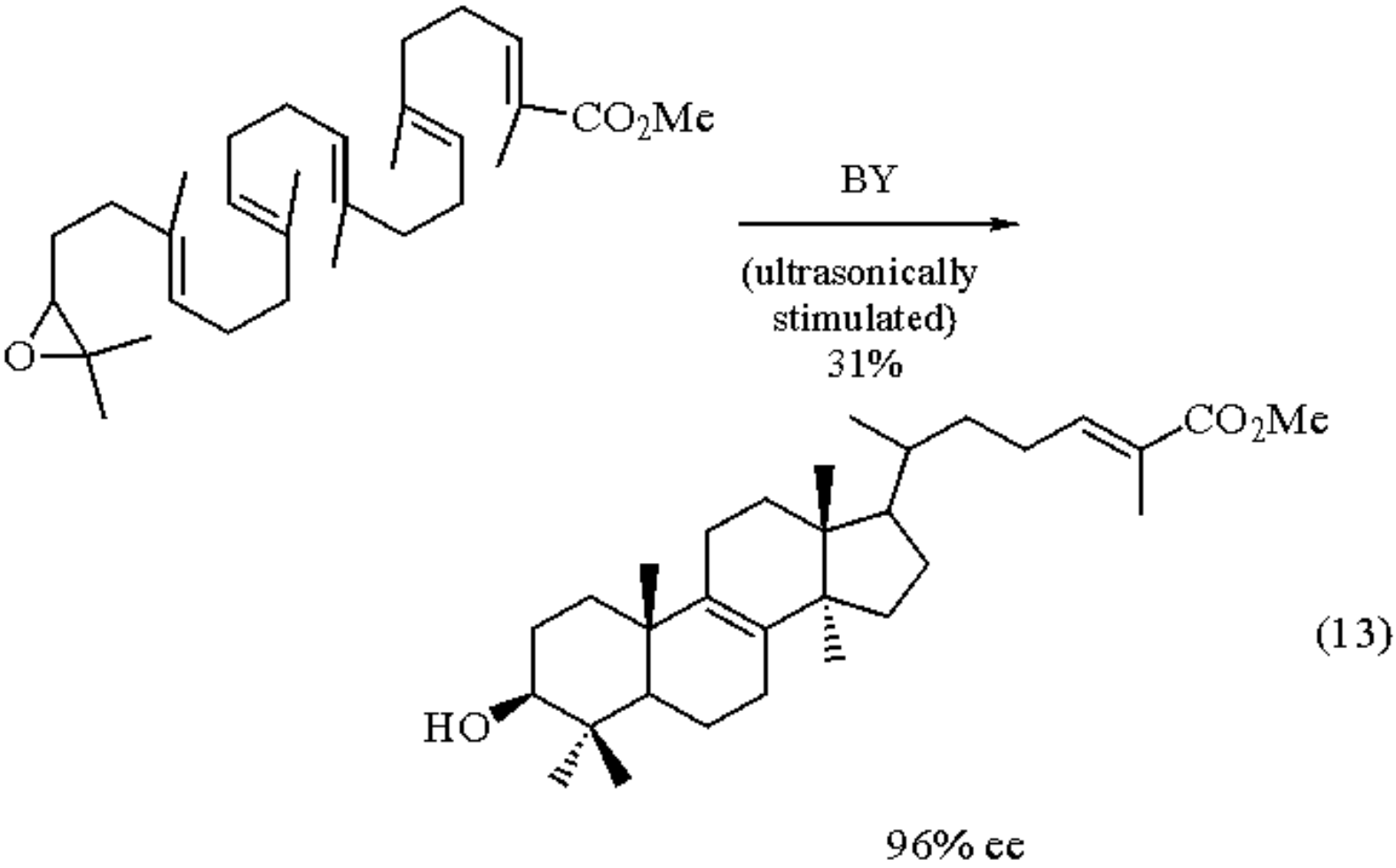

Hydrolyses.

The presence of hydrolytic enzymes in BY is well documented.[30] However, the use of the yeast for biocatalytic ester hydrolysis suffers because of the availability of commercially available purified hydrolases. Nonetheless, the hydrolytic ability of fermenting BY has been proposed for the resolution of various amino acid esters (eq 14).[31] The BY-mediated enantioselective hydrolysis has also been applied to the resolution of acetates of hydroxyalkynes[32] and a hydroxybutanolide.[33]

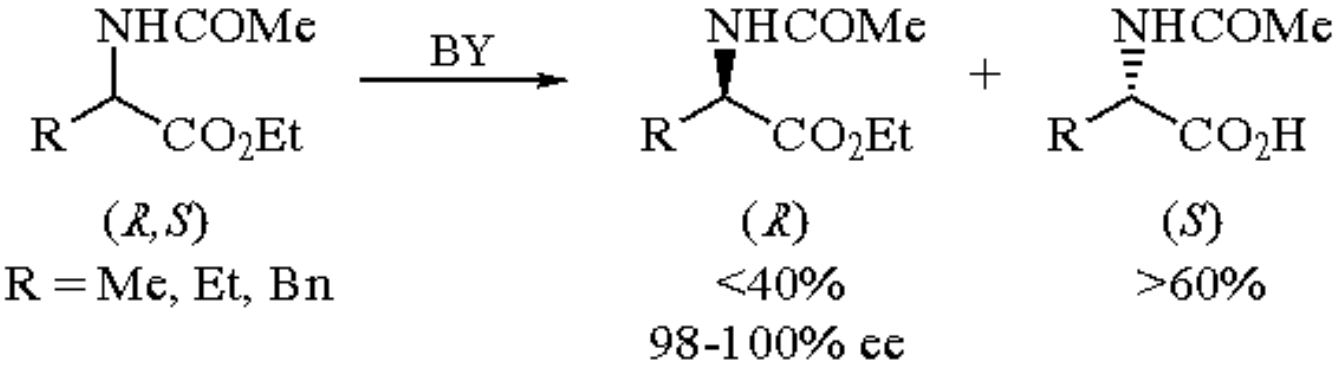

Oxidations.

Reductions are by far the most exploited reactions carried out in the presence of BY. However, a few interesting examples of oxidations are available,[34] such as the dehydrogenation of thiastearates.[35] The regeneration of protected functional groups is possible with BY, which can effect the deprotection of hydrazones[36] and, if ultrasonically stimulated, may release from the oximes the corresponding carbonyl compounds, without further reduction to the alcohols (eq 15).[37]

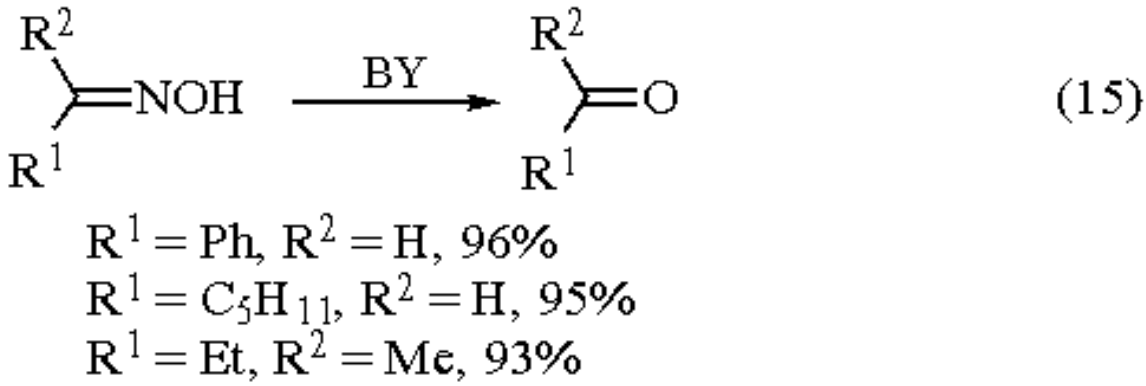

An attractive reaction has been reported for BY, which is able in ethanol to catalyze the oxidative coupling of various thiols to disulfides (eq 16).[38]

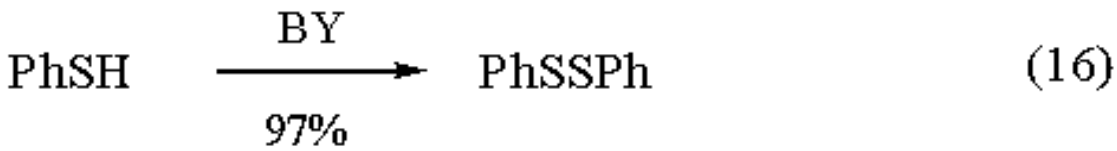

Miscellaneous Reactions.

Many other reactions can be realized in the presence of BY. An interesting hydrolysis-reduction process transformed a derivative of secologanin into two different cyclic compounds, depending on the pH of the incubation.[39] Here, a glucosidase activity afforded the intermediate aldehyde, which could be reduced or rearranged to different products (eq 17).

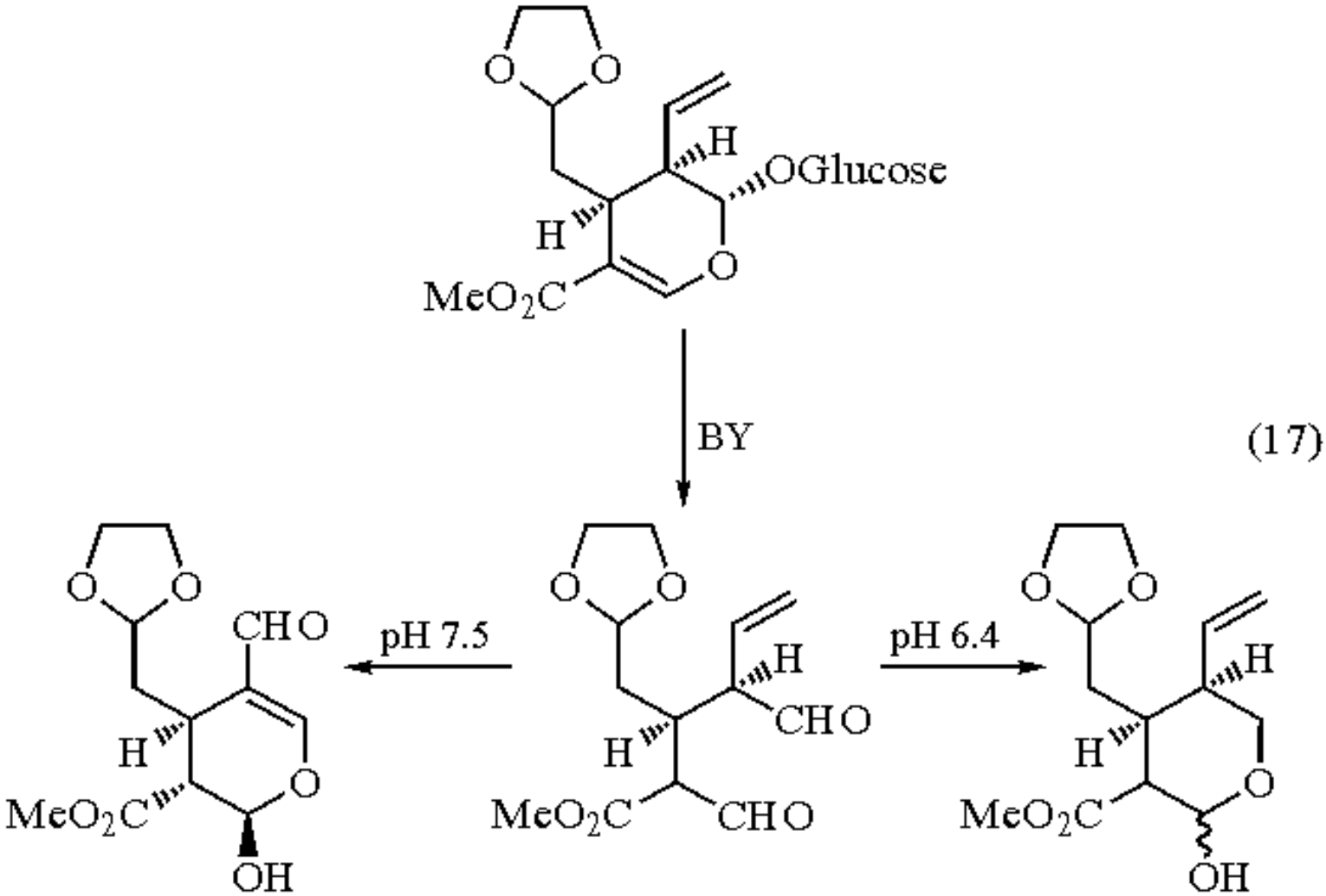

(17)

With BY, the reduction of α,β-unsaturated aldehydes can act together with a hydration process, affording optically active diols in acceptable yields (eq 18).[40]

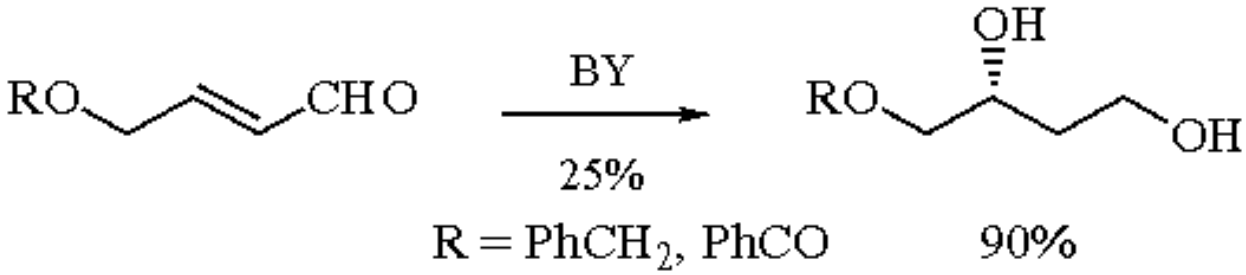

(18)

Some cycloaddition reactions have also been carried out in the presence of BY.[41] The asymmetric 1,3-dipolar

cycloaddition of benzonitrile *N*-oxides to various dipolarophiles led to optically active 2-oxazolines (eq 19).[42]

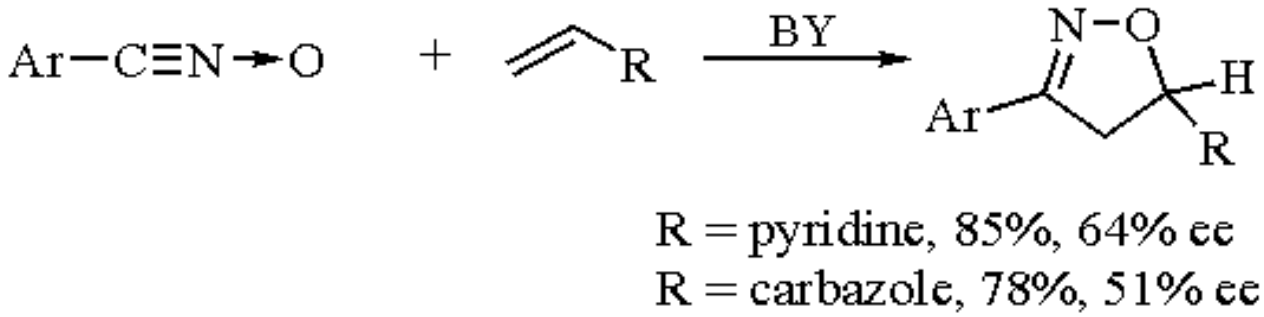

The regio- and enantioselectivity of the reactions depend on the structure of dipolarophiles and the addition of β-cyclodextrin. BY is also able to carry out a Diels-Alder condensation,[41] and a few Michael-type additions are enantioselectively performed in the presence of BY.[43] For example, the addition of amines to α,β-unsaturated esters affords optically active β-amino acid esters (eq 20).[44]

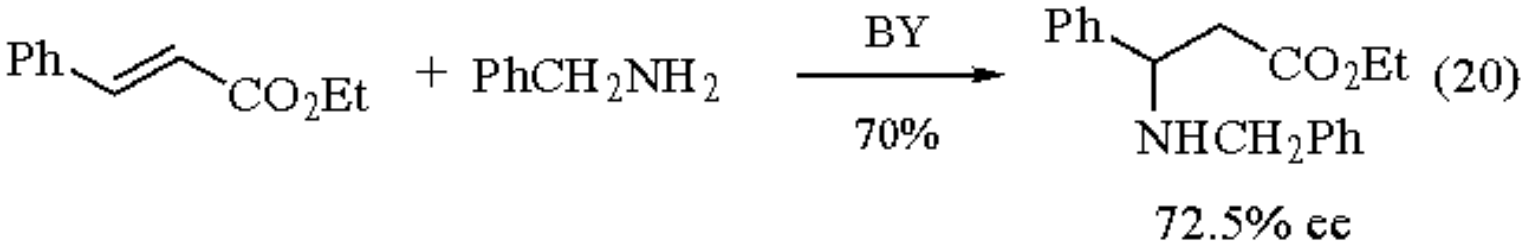

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Enzo Santaniello, Patrizia Ferraboschi, & Paride Grisenti

Barium Hydroxide

$Ba(OH)_2$

[17194-00-2] · BaH_2O_2 · Barium Hydroxide · (MW 171.35) (.H_2O)

[22326-55-2] · BaH_4O_3 · Barium Hydroxide · (MW 189.37) (.8H_2O)

[12230-71-6] · $BaH_{18}O_{10}$ · Barium Hydroxide · (MW 315.48)

(used as a base catalyst in a variety of organic reactions such as decarboxylations, aldol or aldol-type reactions, Claisen-Schmidt reactions, Michael additions, and Wittig-Horner reactions)

Physical Data: $Ba(OH)_2.H_2O$, *d* 3.743 g cm^{-3}. $Ba(OH)_2.8H_2O$, mp 78 °C; *d* 2.180 g cm^{-3}.

Solubility: monohydrate is slightly sol water. Octahydrate is freely sol water and methanol, slightly sol ethanol; practically insol acetone.

Form Supplied in: monohydrate, white solid; octahydrate, transparent crystals or white masses.

Handling, Storage, and Precautions: poison; corrosive. May be fatal if swallowed, inhaled, or absorbed through skin. Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin.[1] Incompatible with acids. Absorbs moisture and CO_2 from air. Use only in a chemical fume hood. Avoid contact with eyes, skin, and clothing. Wash thoroughly after handling. Keep container tightly closed.

Introduction.

The octahydrate, $Ba(OH)_2.8H_2O$, is the most common form. Upon dehydration at elevated temperatures (200-500 °C) it is converted to the anhydrous form. On standing at rt, anhydrous $Ba(OH)_2$ is partially rehydrated and the resulting equilibrium water content is related to the dehydration temperature. The solids resulting from such a treatment are referred to in the literature as activated barium hydroxides. An activated $Ba(OH)_2$ is a mixture of anhydrous $Ba(OH)_2$ and the monohydrate in variable ratios. In the crystal structure, the monohydrate is the main component over the solid surface.[1] The most popular activated $Ba(OH)_2$ is sometimes referred to as C-200 (i.e. dehydrated at 200 °C) and was determined to be $Ba(OH)_2.0.8H_2O$.[2]

Partial Hydrolysis of Dimethyl Dicarboxylates.

The monomethyl ester of undecanedioic acid was prepared by partial hydrolysis of the dimethyl ester with methanolic $Ba(OH)_2$ (eq 1). The precipitation of the barium salt of the monoester prevents further hydrolysis to the diacid. The procedure has an advantage over the fractional distillation of partially esterified diacids, particularly for the high-boiling half esters which may disproportionate at elevated temperatures. This method was not satisfactory for low molecular weight half esters because of the higher solubility of their barium salts in methanol.[3]

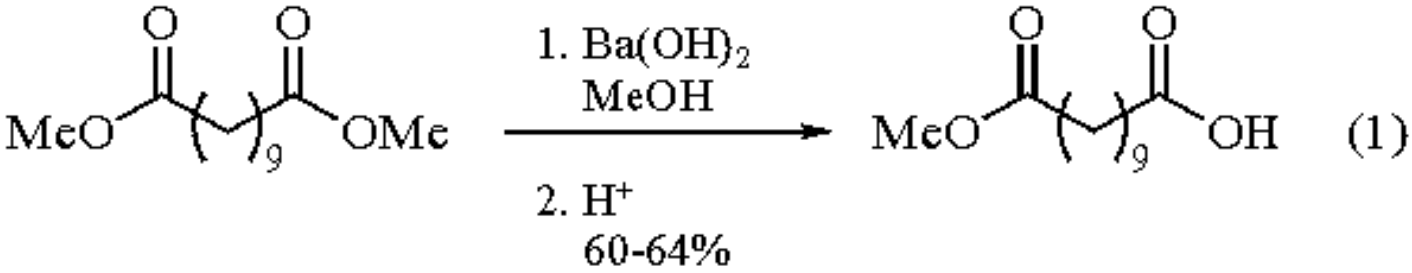

Ketocarboxylic Acids from Ketodicarboxylic Esters.

The ketodicarboxylate derivative (**1**) was hydrolyzed and decarboxylated when treated with $Ba(OH)_2.8H_2O$ in refluxing ethanol for 20 h to give the crystalline γ-keto acid (**2**) in 98% yield (eq 2).[4]

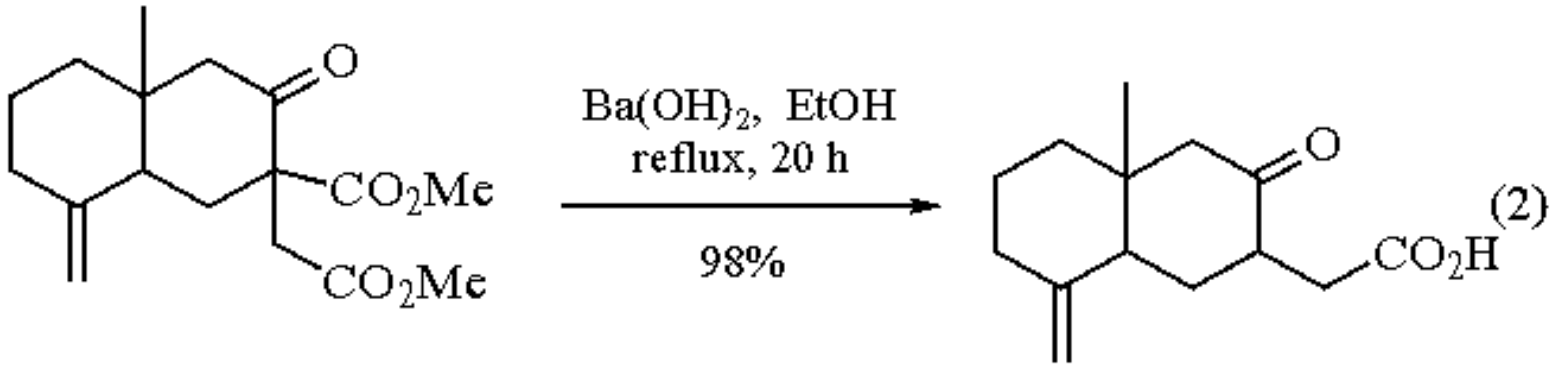

(1) **(2)**

Monocarboxylic Acids from Dicarboxylic Acid Anhydrides.

In the total synthesis of (±)-pentalenolactone, the intermediate dicarboxylic anhydride (**3**) was converted to carboxyenone (**4**) upon treatment with 1.2 equiv of $Ba(OH)_2.8H_2O$ in water and heating at reflux temperature for 5 h (eq 3). The cleavage of the anhydride, the formation of the enone from the β-methoxy silyl enol ether, and the decarboxylation of the vinylogous β-keto barium carboxylate were all achieved in one operation giving the desired product (**4**) in 99% yield.[5]

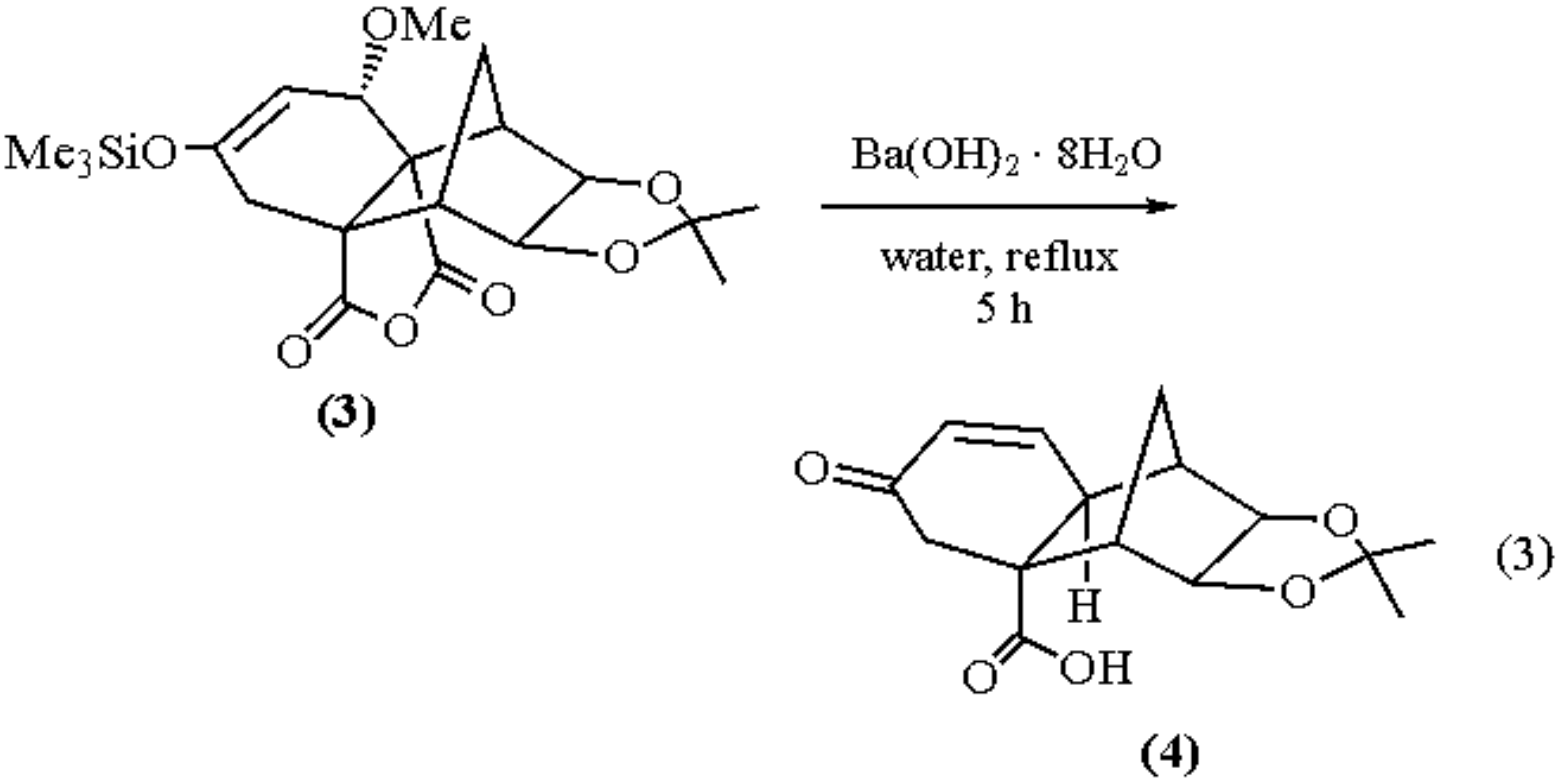

Reaction with α-Chlorolactams: a Stereoselective Favorskii-Type Ring Contraction.

Treatment of the bicyclic α-chlorovalerolactams (**5**), (**6**), and (**7**) with aqueous $Ba(OH)_2$ at reflux temperature promoted a Favorskii-type ring contraction to give the octahydroindoles and octahydroisoindoles (**8**), (**9**), and (**10**) respectively. While chlorolactams (**5**) and (**6**) rearrange in a diastereoselective fashion (eqs 4 and 5), (**7**) gave a 1:1 mixture of (**10a**) and (**10b**) (eq 6). The observed diastereoselectivity was attributed to *cis*-1,3 and *cis*-1,2 steric interactions in (**5**) and (**6**), respectively, and the lack of such interactions in (**7**).[6]

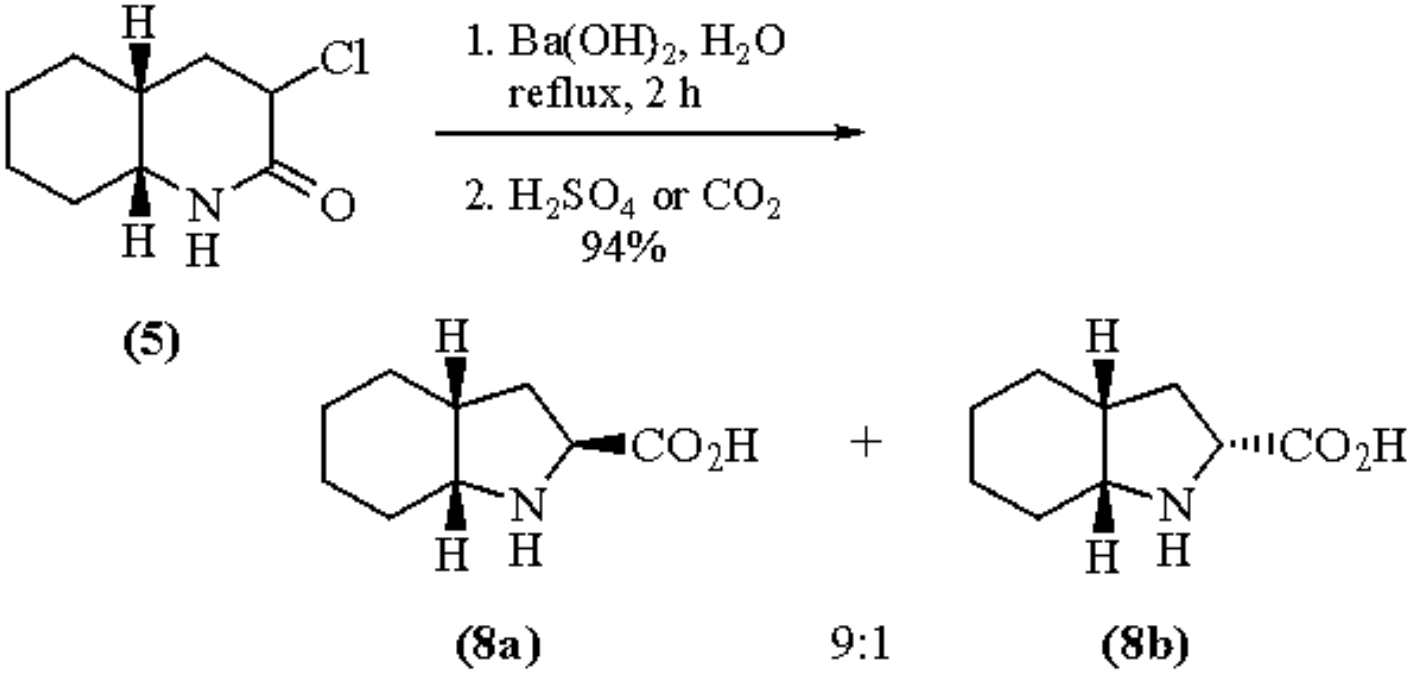
1. Ba(OH)2, H2O
reflux, 2 h
2. H2SO4 or CO2
94%
(5)
(8a)
9:1
(8b)

(4)

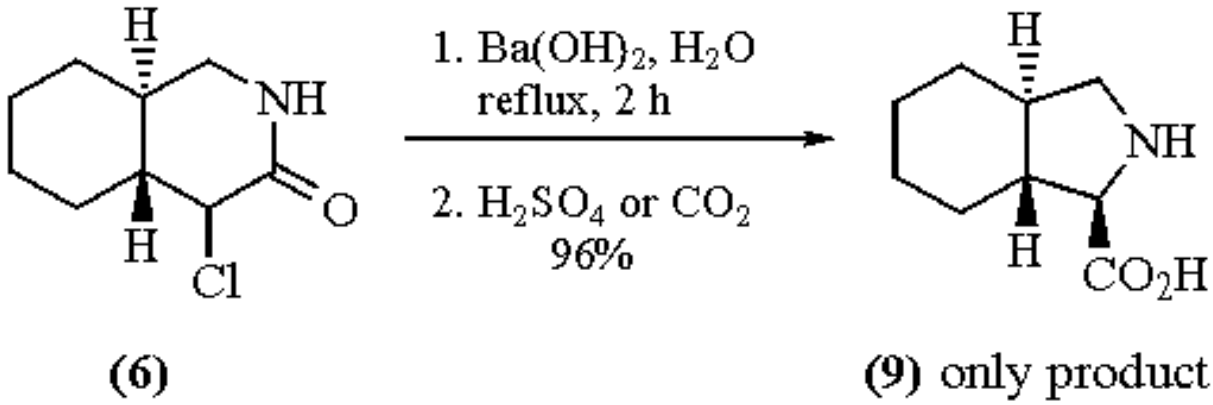
1. Ba(OH)2, H2O
reflux, 2 h
2. H2SO4 or CO2
96%
(6)
(9) only product

(5)

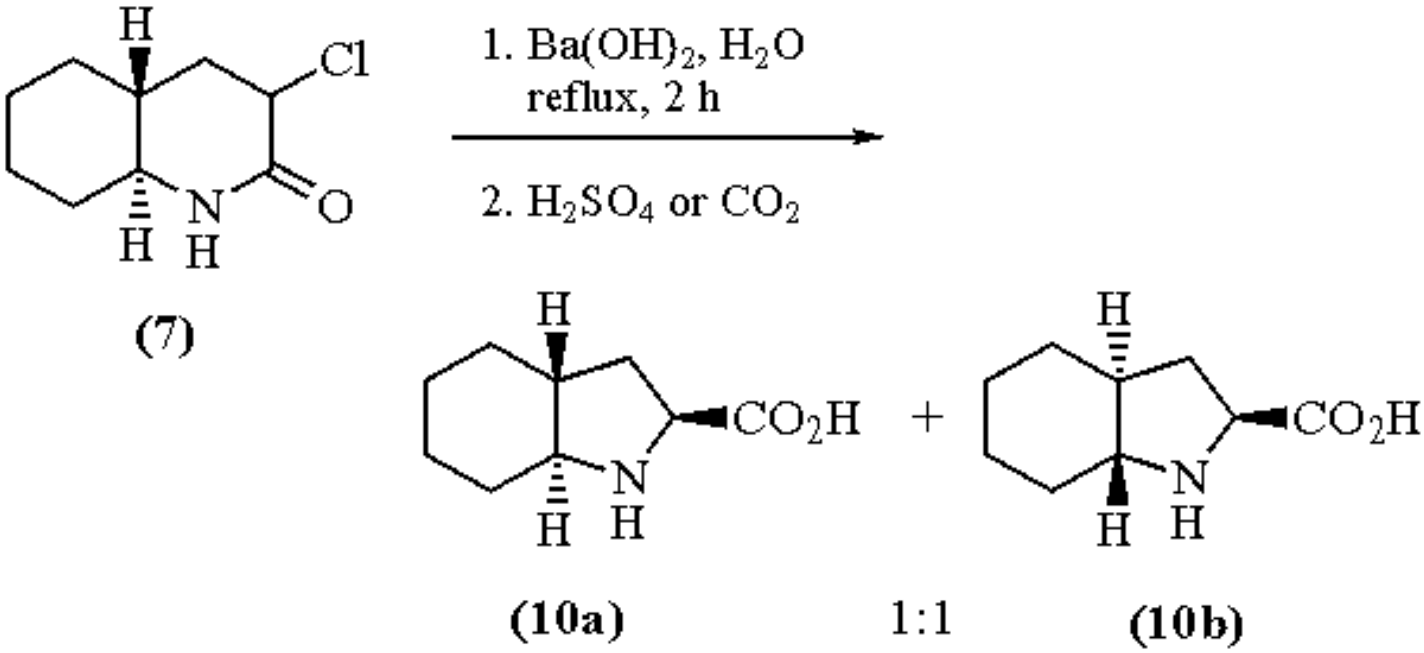
1. Ba(OH)2, H2O
reflux, 2 h
2. H2SO4 or CO2
(7)
(10a)
1:1
(10b)

(6)

Preparation of Diacetone Alcohol.

Heating acetone in a flask fitted with a Soxhlet extractor containing $Ba(OH)_2$ for 95-120 h gave 71% yield of distilled diacetone alcohol (eq 7).[7]

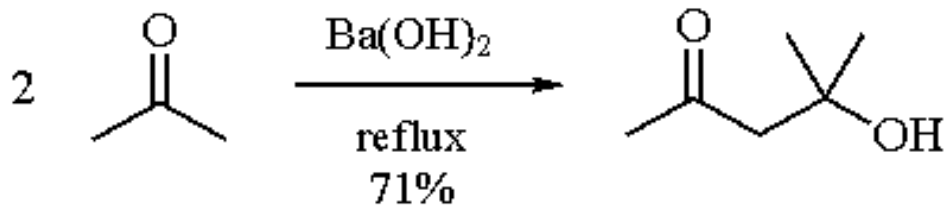

(7)

Heterogeneous Claisen-Schmidt Condensation.

Activated $Ba(OH)_2$ (C-200) was used as a heterogeneous catalyst in Claisen-Schmidt condensations. The method was applied to reactions of various aromatic aldehydes with methyl ketones to give the corresponding styryl ketones. Generally, the aldehyde is mixed with the methyl ketone (2 equiv) and the C-200 catalyst (12%) in ethanol and the mixture is heated at reflux for 1 h. The yields ranged from 25 to 100% (eq 8).[8] The procedure was extended to the synthesis of *o*-hydroxychalcones, e.g. the reaction of *o*-hydroxyacetophenone with benzaldehyde in 96% ethanol and a catalytic amount of C-200 gave *o*-hydroxychalcone in 89% yield (eq 9).[9]

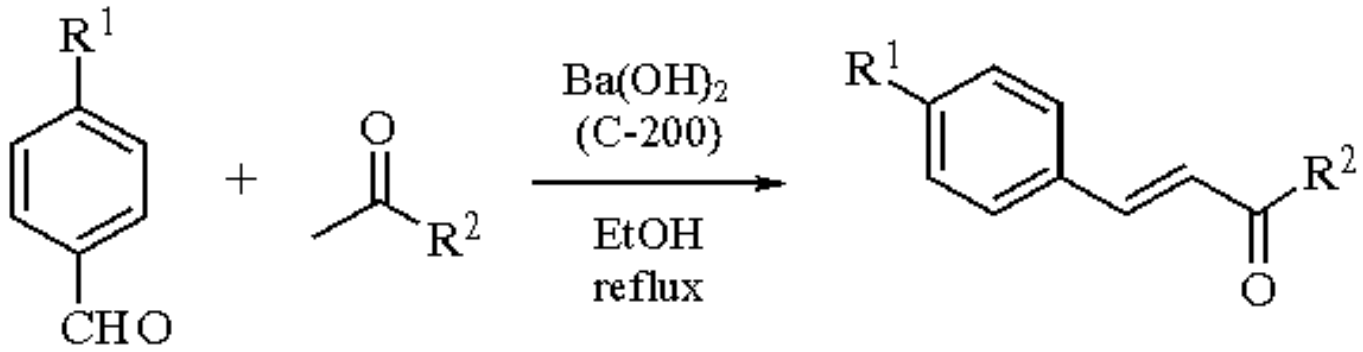

(8)

$R^1 = H$, $R^2 = Ph$, 94-98%; $R^1 = Me$, $R^2 = n\text{-}Pr$, 99-100%; $R^1 = NO_2$, $R^2 = t\text{-}Bu$, 24-25%

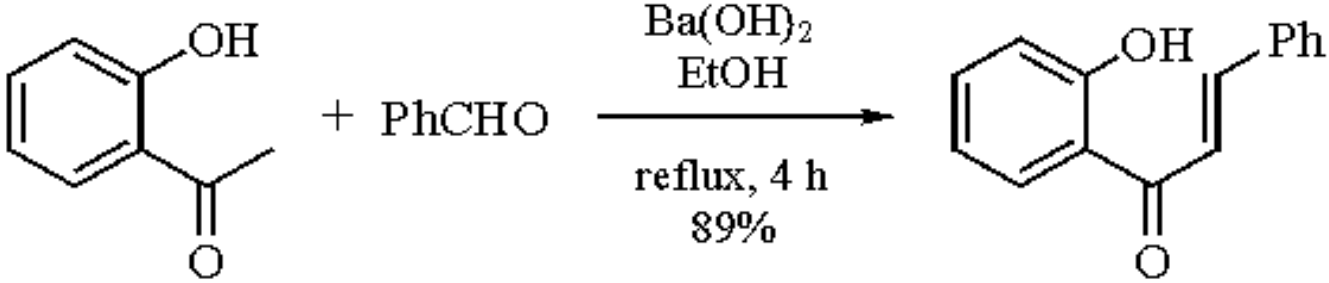

(9)

The yields from these reactions were as good as or better than other methods. Secondary reactions such as the Cannizzaro reaction of aldehydes and aldol additions of ketones were not observed. Unlike other methods, protection of the phenol was not necessary and the product did not cyclize to the flavenone. The absence of cyclized products as

well as the (*E*) configuration of the alkenic bond were explained by a rigid transition state in which the carbanion and aldehyde are adsorbed on the insoluble catalyst surface.[9]

Michael Addition to Chalcones.

Partially dehydrated $Ba(OH)_2$ efficiently catalyzed the Michael additions of active methylene compounds to chalcones. The reaction temperature and amount of catalyst determined the isolated product (eq 10). Thus the reaction of chalcone with ethyl acetoacetate (25 mmol each) at rt in EtOH with 5 mg catalyst gave primarily the Michael addition product (**11**) in 90% yield. By increasing the amount of catalyst to 50 mg at rt, the reaction proceeded further to give the cyclic product (**12**) in 95% yield, resulting from Michael addition followed by intramolecular aldol reaction. The dehydrated cyclic adduct (**13**) was the major product (80%) at reflux temperature.[10]

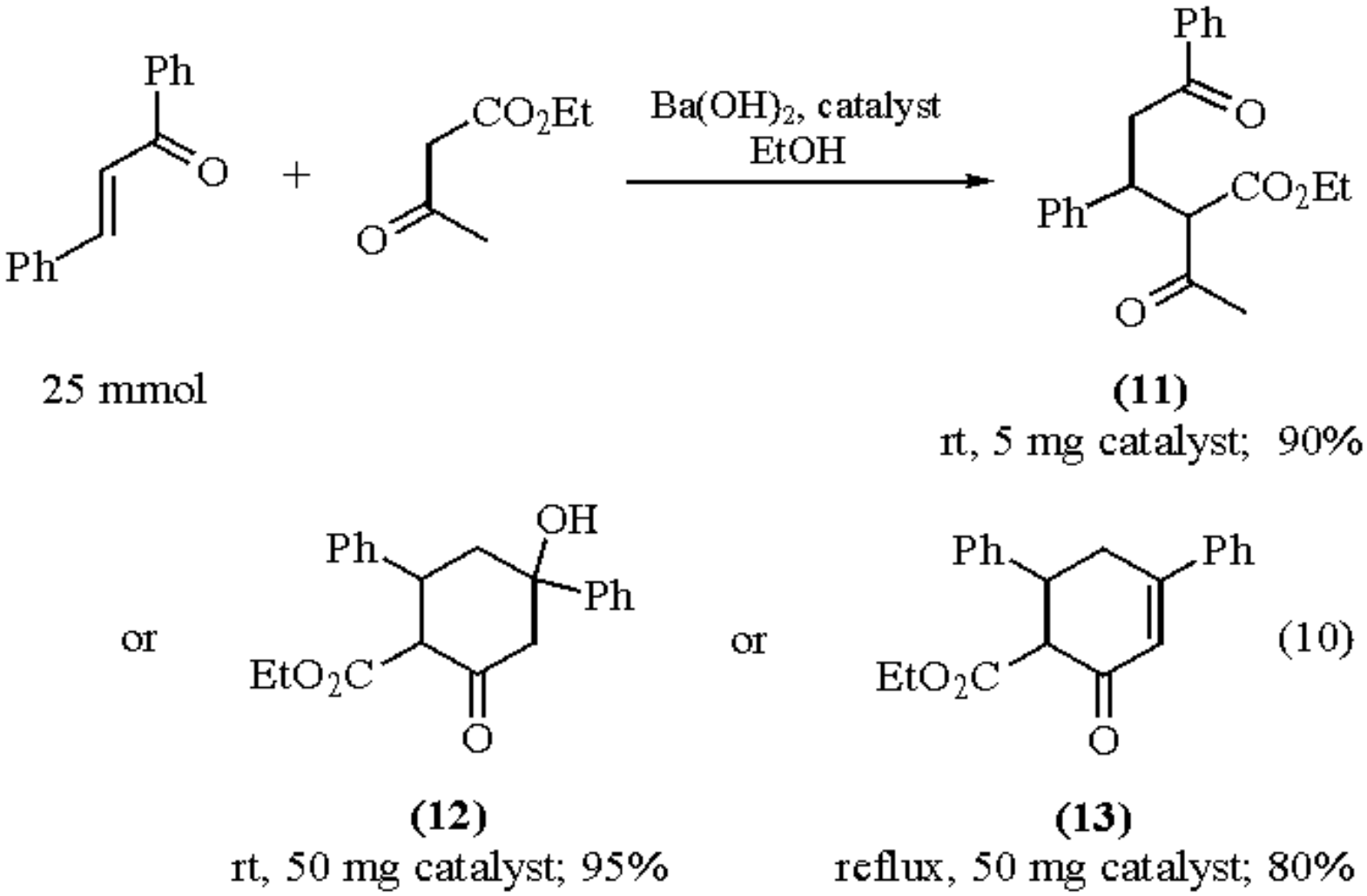

Addition of Diethyl Malonate to Coumarin.

An attempted Michael addition of diethyl malonate to coumarin (**14**) in the presence of solid $Ba(OH)_2$ (C-200) in EtOH gave the unusual 1,2-addition-elimination product (**15**) in 30% yield (eq 11). The result was explained in terms of the structure of the catalyst and the chelation of coumarin to the barium ion of the lattice.[11]

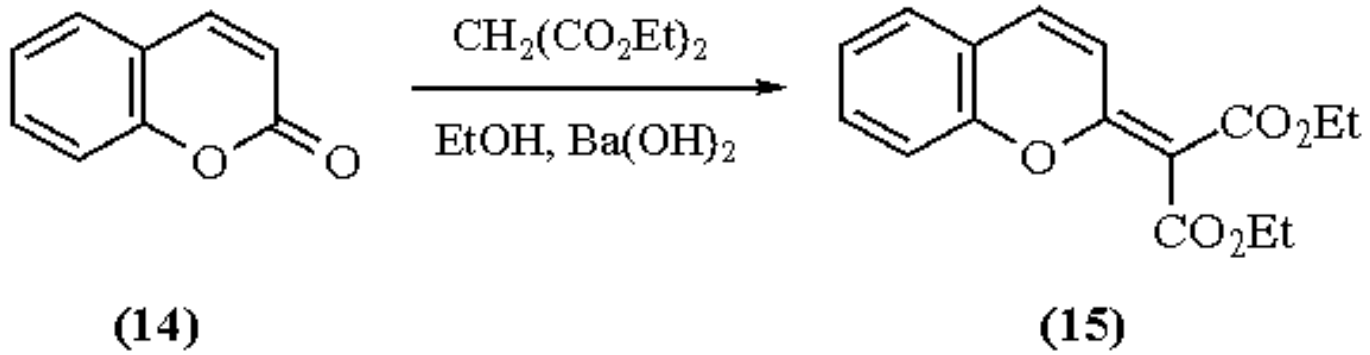

(11)

Synthesis of Δ^2-Isoxazolines and Δ^2-Pyrazolines.

The addition of NH_2OH and $PhNHNH_2$ to chalcone and related enones (**16**) was catalyzed by $Ba(OH)_2$ (C-200) to give good yields of Δ^2-isoxazoline (**17**) and Δ^2-pyrazoline (**18**) derivatives respectively (eq 12). The products were obtained in yields between 65 and 75% and with complete regioselectivity.[12]

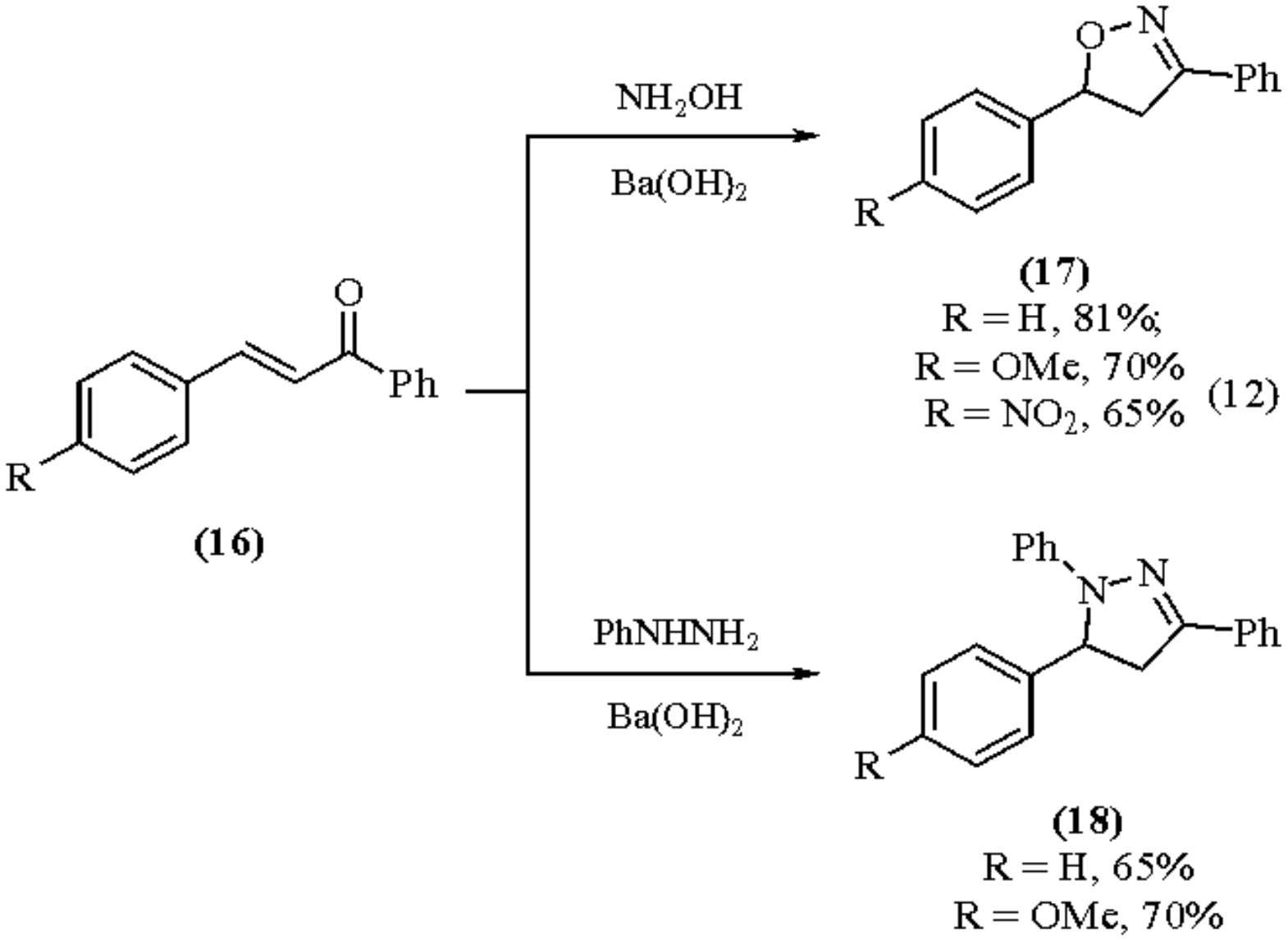

(12)

Oxidation of Benzyl Halides to Benzaldehydes.

Benzyl halides were oxidized to benzaldehydes by ***Dimethyl Sulfoxide*** in the presence of activated $Ba(OH)_2$ (C-200) in 1,4-dioxane. The optimum conditions include the use of a 5 M solution of the aryl halide in 1,4-dioxane with 3 equiv of DMSO and about 0.2 equiv of the $Ba(OH)_2$ catalyst, then heating the mixture at 130 °C for 3 h. The reaction does not take place in the absence of the C-200 catalyst. The effect of each variable in the reaction on the yield was studied, but no specific yields were given for isolated products except for $PhCH_2Cl$, which was reported as 100%. The proposed mechanism of the reaction involves an initial displacement of the halide by DMSO followed by elimination of Me_2S with the aid of the basic OH groups on the catalyst surface (eq 13).[13]

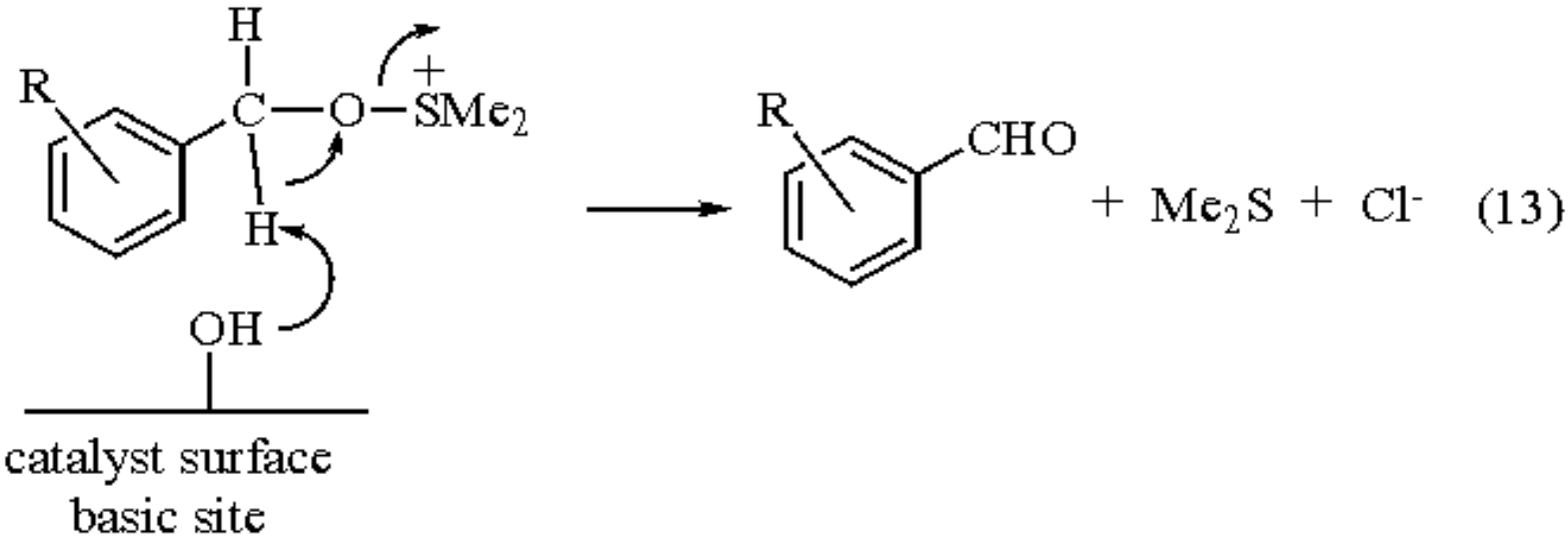

Hydrolysis of 2-Alkoxyimidazolines.

In a procedure for the stereoselective synthesis of vicinal diamines, several alkenes were converted into 2-alkoxyimidazolines (**19**) via consecutive reactions with cyanamide/NBS, HCl/EtOH, and Et_3N/EtOH. The intermediates (**19**) were hydrolyzed with $Ba(OH)_2$ at 120 °C for 18 h (eq 14) to give the diamines (**20**) in 79-99% yields for this step and in 61-71% overall yields.[14]

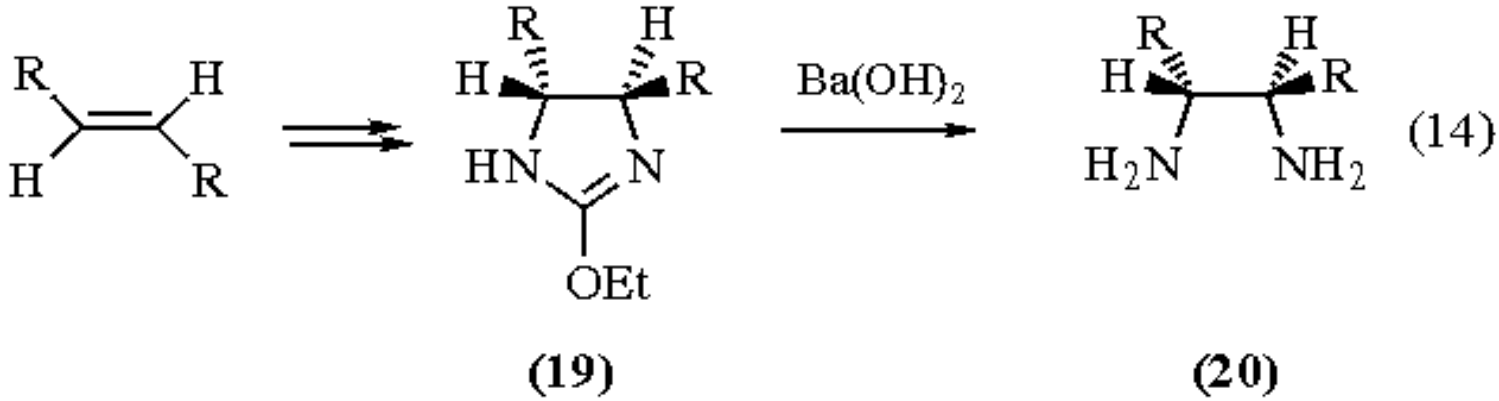

A Skeletal Rearrangement in a 6β,19-Oxido Steroid.

When 6β,19-oxido-2,17-dihydroxyandrosta-1,4-dien-3-one (**21**) was heated at reflux with $Ba(OH)_2.8H_2O$ in pyridine for 22 h, and then worked up under acidic conditions, it rearranged to the furopyranone (**23**) in 80-85% yield (eq 15). The rearrangement included a ring B contraction, a double bond isomerization and a benzylic acid rearrangement. The acidic work-up caused the carboxy intermediate (**22**) to cyclize with the vinyl ether to give (**23**).[15]

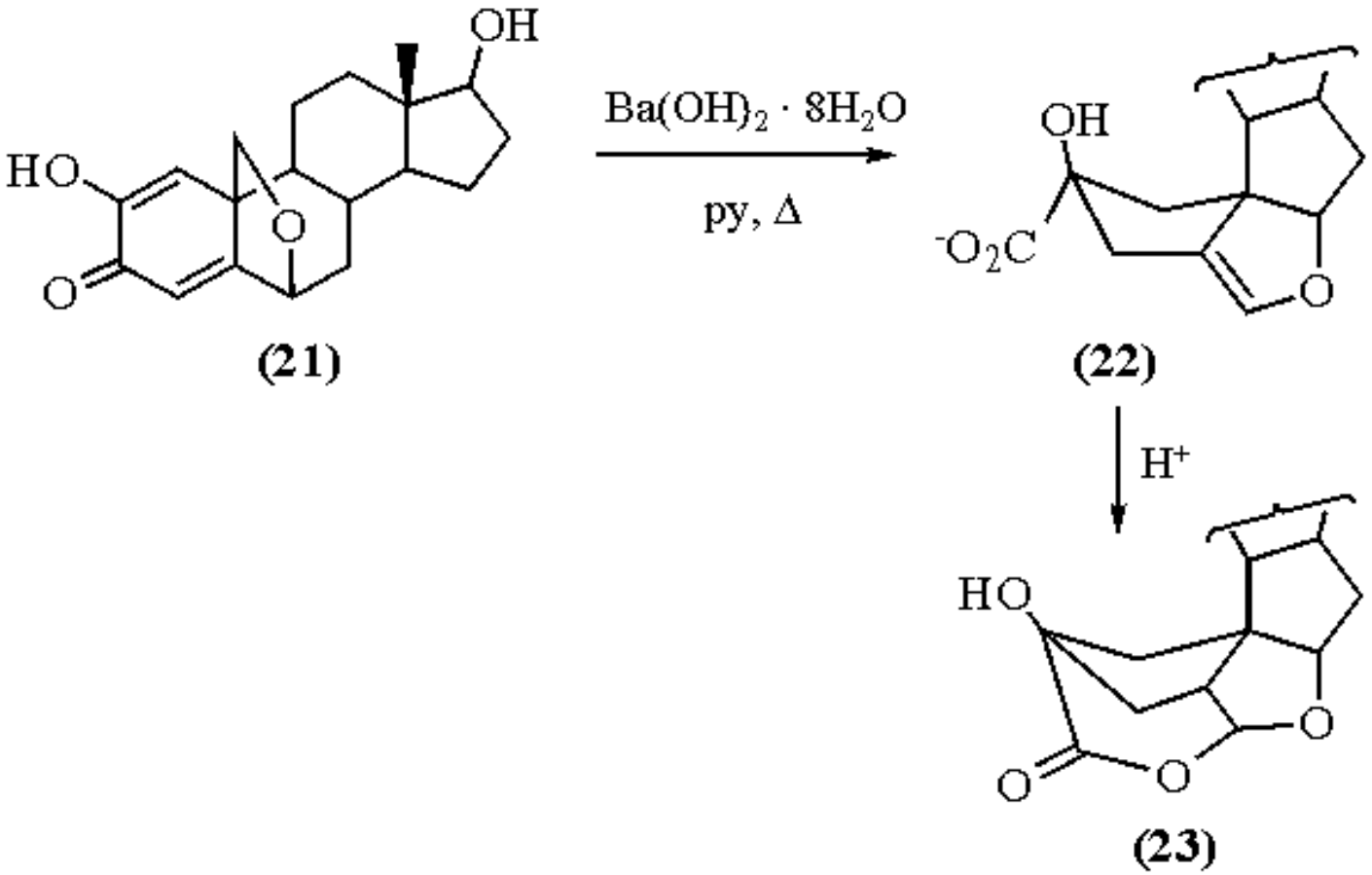

(15)

Wittig-Horner Reaction.

Activated $Ba(OH)_2$ (C-200) catalyzed the reactions of aldehydes with triethylphosphonoacetates (**24**) in 1,4-dioxane in the presence of a small amount of water at 70 °C to give the corresponding 3-substituted ethyl acrylates (**25**) (eq 16). The yields of the products from aromatic aldehydes ranged from 0% for indole-3-carbaldehyde to 100% for furfural and *m*-nitrobenzaldehyde. The method was applied to hindered aldehydes such as pyrene-1-carbaldehyde and to unsaturated aldehydes such as *cis*- or *trans*-citral.[16] The reaction was also applied to various aliphatic aldehydes using 2-oxoalkanephosphonates to give the corresponding (*E*)-α,β-unsaturated ketones in high yields and stereoselectivities.[17]

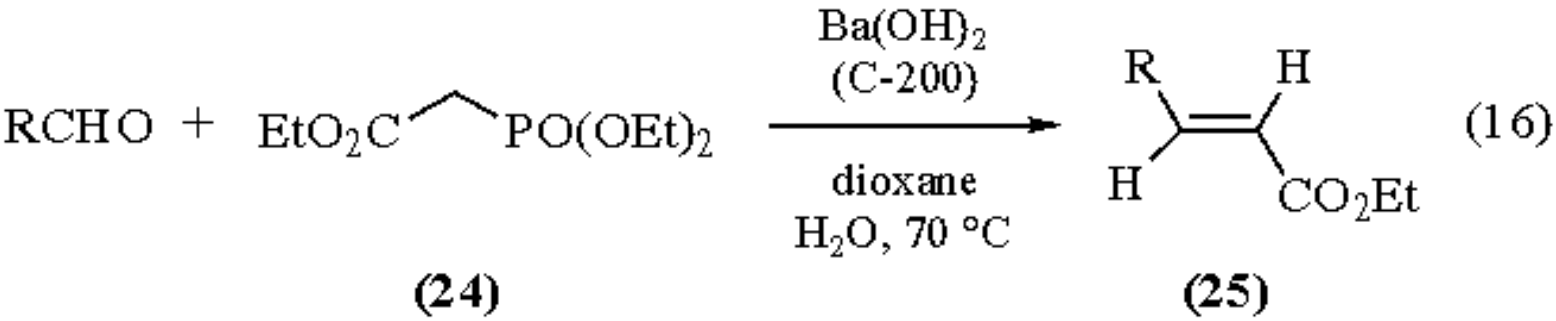

Deacylation of 2-Alkyl-2-halo-1,3-dicarbonyl Compounds.

Treatment of various α-alkyl-α-bromoacetoacetic esters (**26**) with a suspension of anhydrous $Ba(OH)_2$ in absolute ethanol at 0 °C for 30 min effected their deacetylation and gave the corresponding α-bromo esters (**27**) in very good yields without any competing saponification or Favorskii rearrangement (eq 17).[18] The starting α-alkyl-α-bromoacetoacetic esters were prepared from the corresponding acetoacetic esters in two steps (NaH/RX then NaH/Br_2) and used directly in the above reaction. The overall yields for the three-step sequence ranged between 70 and 85%. A similar deacylation of the substituted 4-alkyl-4-chloroheptane-3,5-dione (**28**) was reported in the synthesis of racemic juvenile hormone using $Ba(OH)_2$ in ethanol at 0 °C for 25 min (eq 18) to give the corresponding α-chloro ketone (**29**).[19]

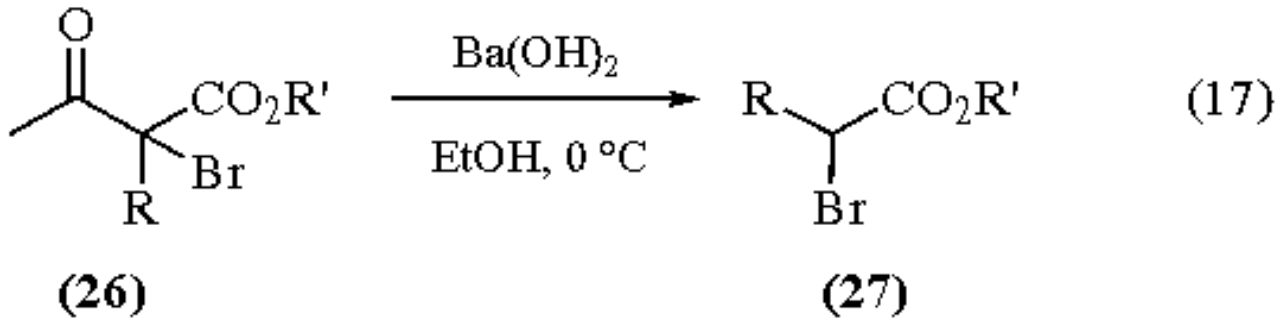

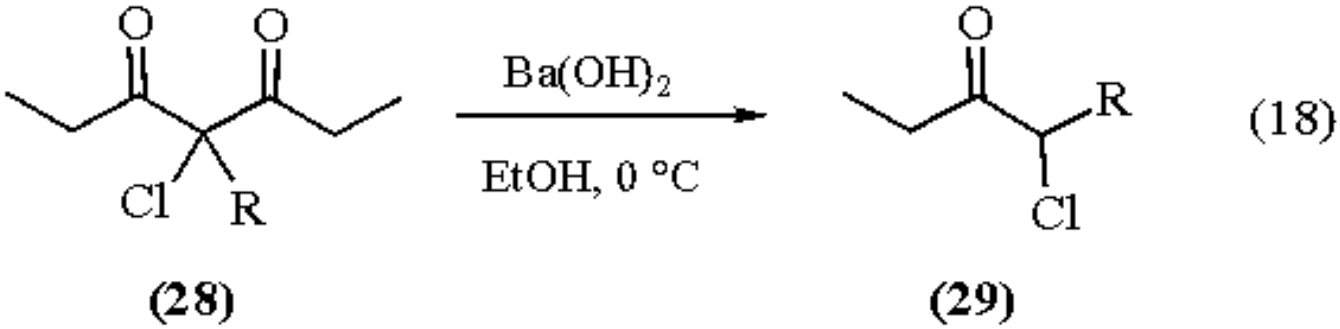

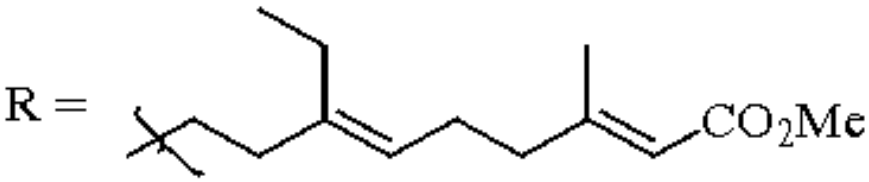

Removal of the *N*-Protecting Benzyloxycarbonyl Group.

The alkynyl amine (**31**) was obtained in 75% yield by removal of the *N*-protecting benzyloxycarbonyl group from the benzyl carbamate (**30**) using 0.15 M $Ba(OH)_2$ in 3:2 glyme-H_2O at reflux temperature for 40 h (eq 19). Other reagents (Me_3SiI, BBr_3, Me_2BBr, BF_3/EtSH, $AlCl_3$/EtSH, MeLi/LiBr, or KOH/EtOH) caused partial destruction of the alkyne.[20]

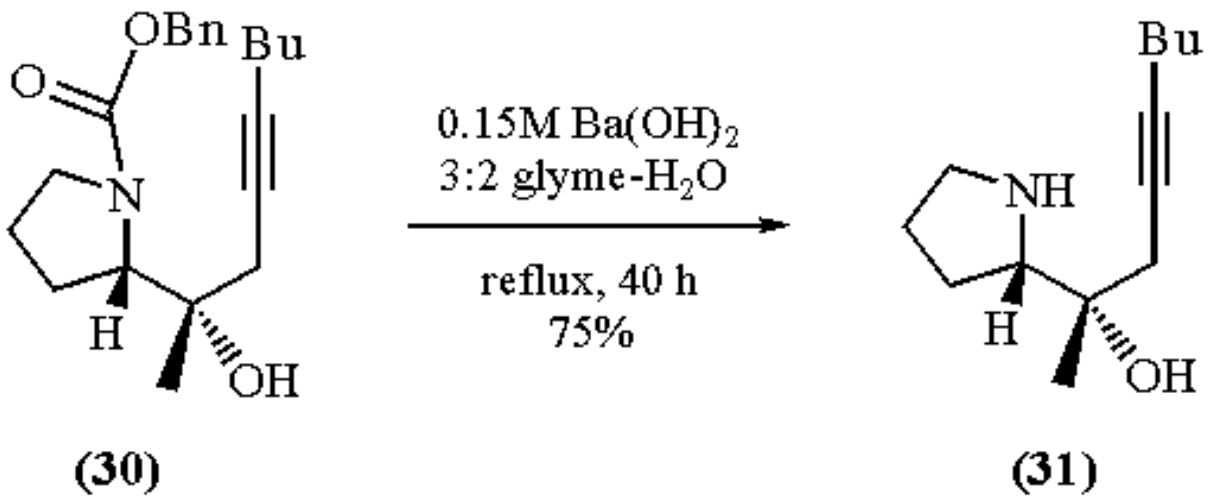

(19)

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Ahmed F. Abdel-Magid

Barium Manganate[1]

$BaMnO_4$

[7787-35-1] · $BaMnO_4$ · Barium Manganate · (MW 256.28)

(selective oxidant; oxidizes allylic and benzylic alcohols to aldehydes; diols give dialdehydes, lactols or lactones)

Solubility: insol most organic solvents.

Form Supplied in: dark green crystals or blue-black powder with chunks; widely available.

Preparative Methods: from aqueous solution of $KMnO_4$, $BaCl_2$, NaOH (1 equiv each), and KI (0.12 equiv); dry crystals by azeotropic removal of H_2O with C_6H_6; yield 60% on a 0.041 mol scale.[2b]

Purification: dry as above or at 100 °C for 24 h, or dry in vacuum oven (120 °C, 20 Torr); store in desiccator, and grind just before use.[3]

Handling, Storage, and Precautions: moisture sensitive; indefinitely stable and active; can be stored for months under dry conditions; use in a fume hood.

Oxidation of Alcohols to Aldehydes.

Barium manganate is a stable Mn^{VI} salt which can be regarded as an alternative to ***Manganese Dioxide***. In general, the yields are equal to or better than those obtained using the latter reagent, and the reaction is more rapid. Barium manganate is claimed to be more attractive on a medium to large scale as its preparation is simple, it is easy to handle, no special activation is required for oxidations, product isolation is facile, and less oxidant is required (1:1 to 1:10 compared to 1:5 to 1:50 for MnO_2).[1,2b] Barium manganate is unreactive towards styrene, toluene, 1-heptylamine, and α,β-unsaturated aldehydes and ketones.[2b] However, some aromatic aldehydes are converted to carboxylic acids and some aliphatic aldehydes polymerize on treatment with barium manganate.[4]

Simple allylic or benzylic alcohols are oxidized rapidly at room temperature (eqs 1 and 2); primary and secondary alcohols are also oxidized,[2,5] but the reaction is much slower (eqs 3 and 4).[2b] The reaction also tolerates sensitive functionality such as C&tbond;C triple bonds (eq 5)[2b] and the furan nucleus (eq 6).[6] For the latter reaction, MnO_2 gives a much reduced yield (38%) and two-phase Jones oxidation results in a complex mixture.

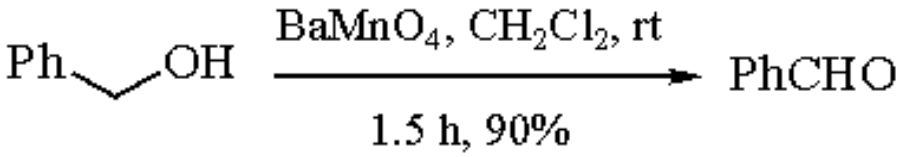

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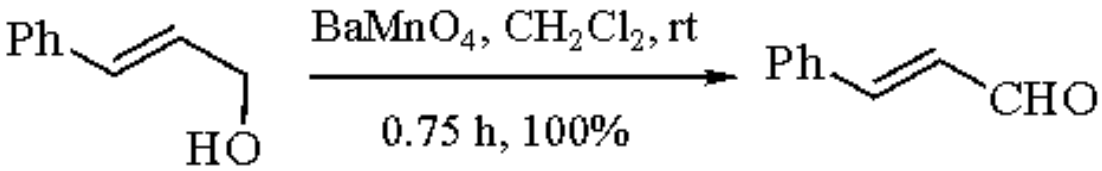

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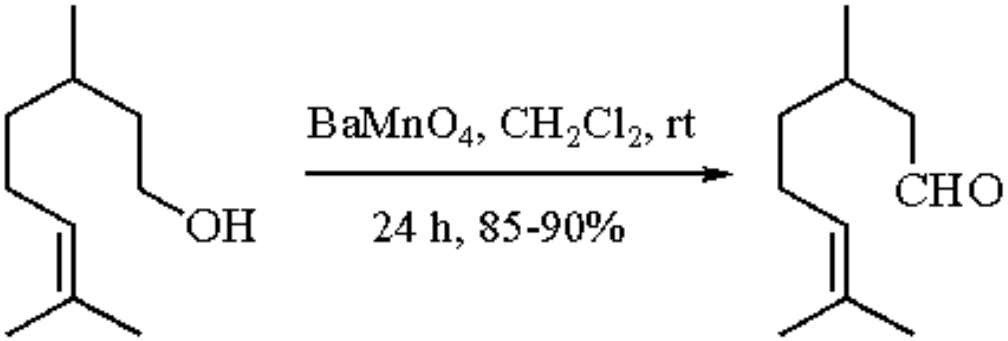

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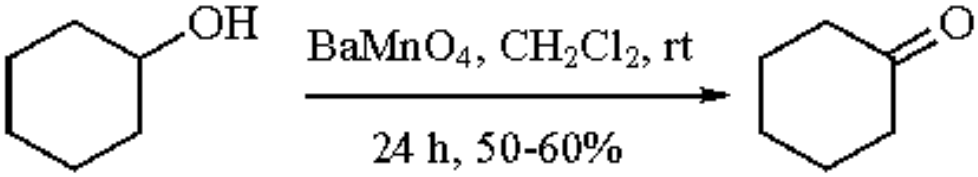

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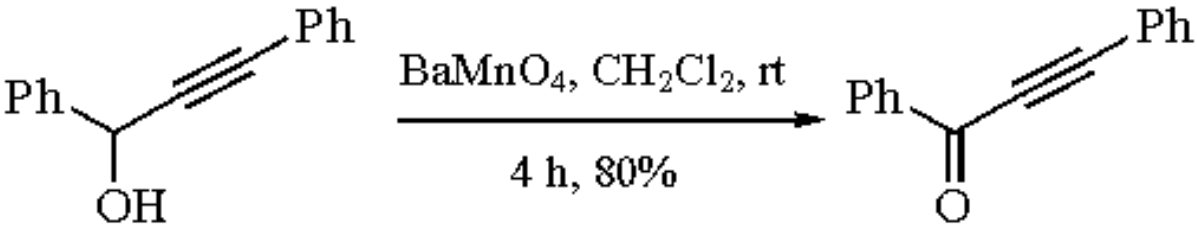

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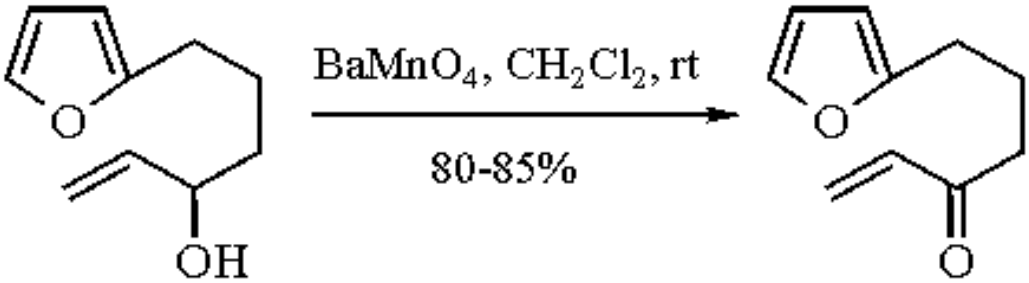

(6)

The oxidation of benzylic and related diols with barium manganate often produces the corresponding dialdehyde (eqs 7-10),[2] but lactones have been produced in some cases (see next section). As with the oxidation of monohydric alcohols, sensitive functionality is usually compatible with the oxidation conditions.

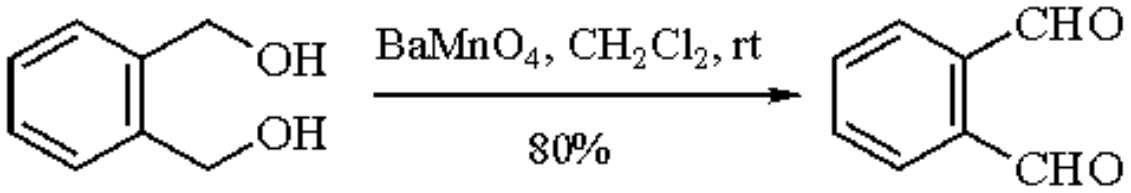

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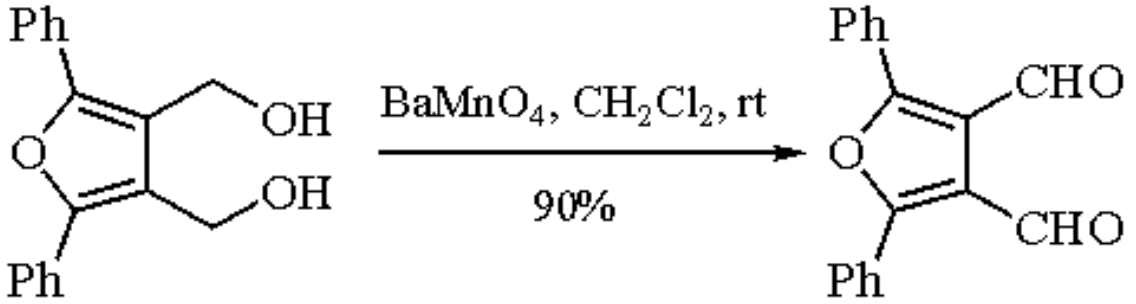

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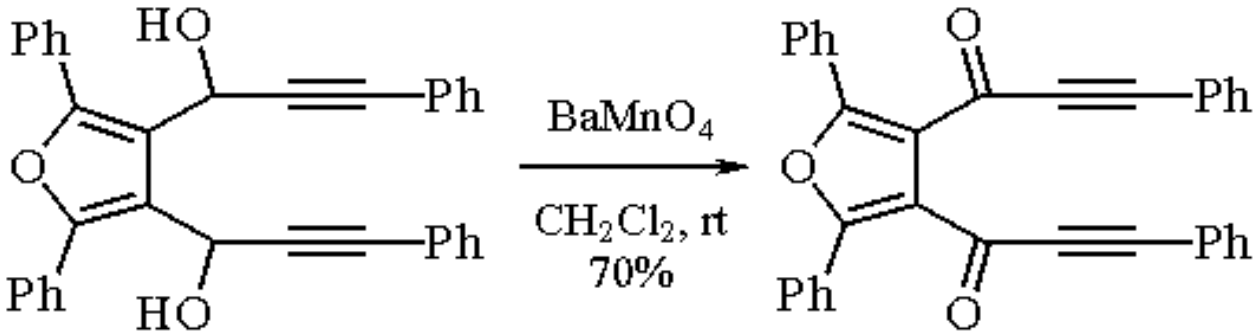

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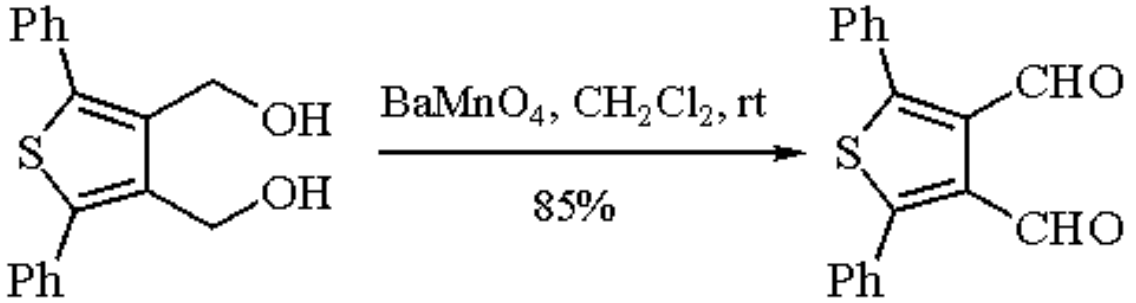

(10)

Barium manganate oxidation of the diol (**1**) produces the dialdehyde (**2**) (eq 11), which was used in a synthesis of the parent [10]annulene derivative.[7]

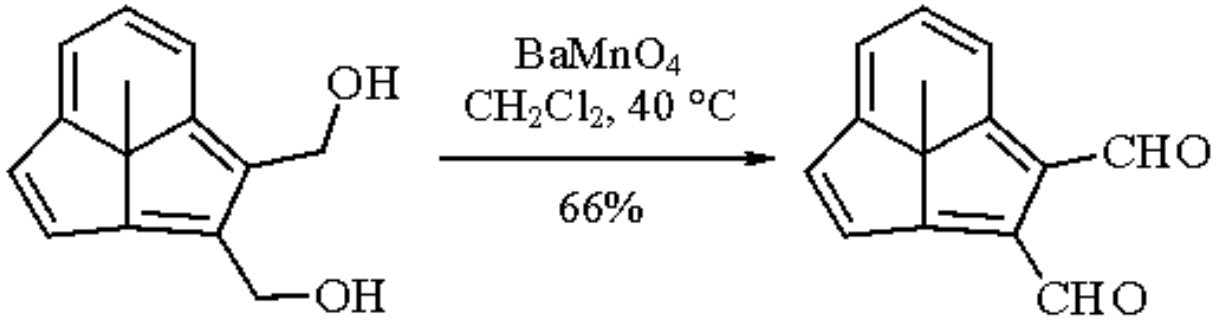

(11)

(1) **(2)**

Oxidation of Diols to Lactones.

In some cases the barium manganate oxidation of benzylic diols has been used to prepare the related lactones (eqs 12-14), although in unsymmetrical substrates the reaction often lacks selectivity.[8] Substitution *ortho* to one of the hydroxymethyl groups appears to be important in determining the success of this reaction, as a related substrate which lacks such substitution gives a high yield of the dialdehyde (eq 15).[7]

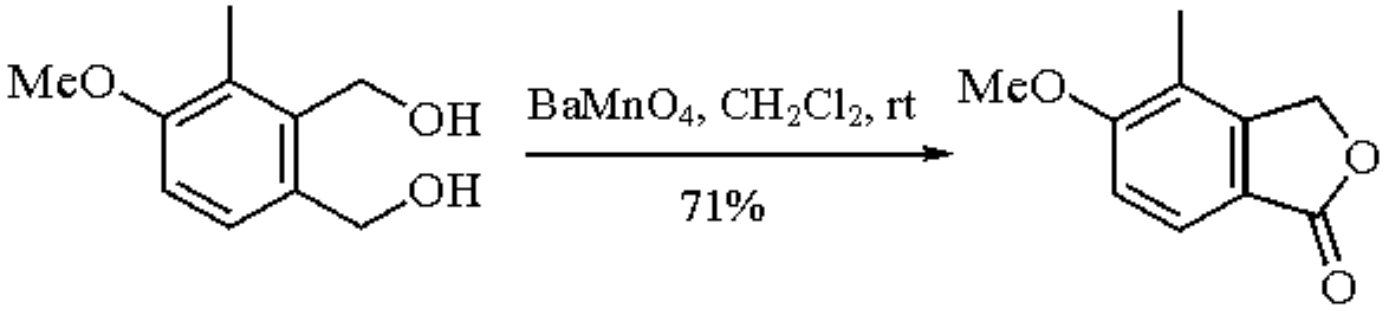

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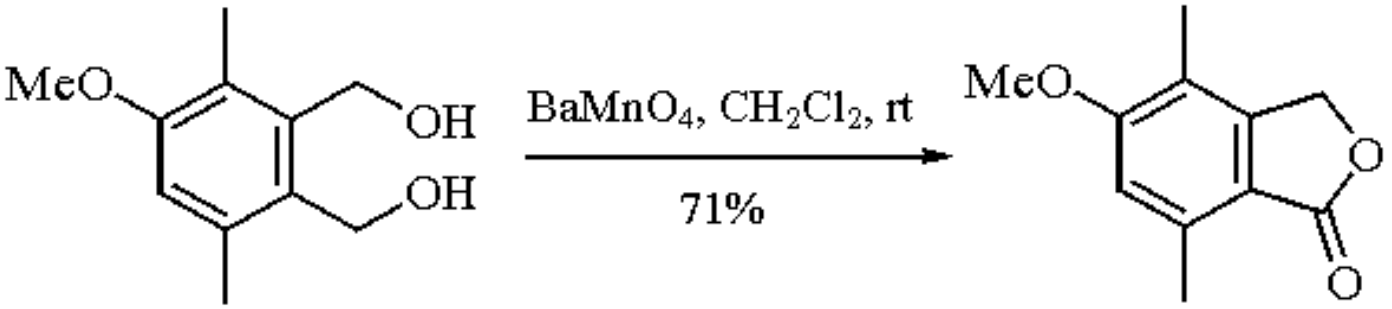

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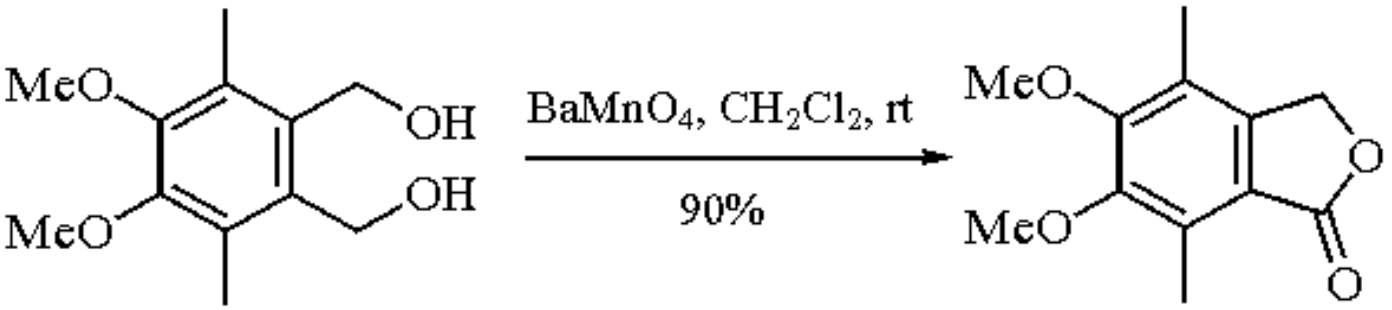

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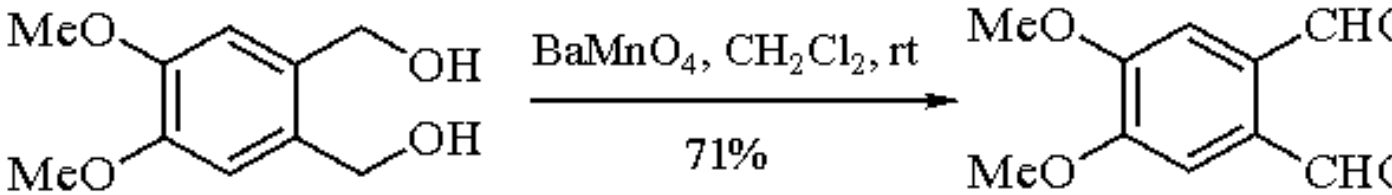

(15)

The barium manganate oxidation of diol (**3**) has been used as a key step in the total synthesis of cinnamolide (**4**). This reaction can be controlled to give the lactol if 1-2 equiv of the oxidant is used, whereas with excess (10-20 equiv) cinnamolide (**4**) is obtained (eq 16).[9]

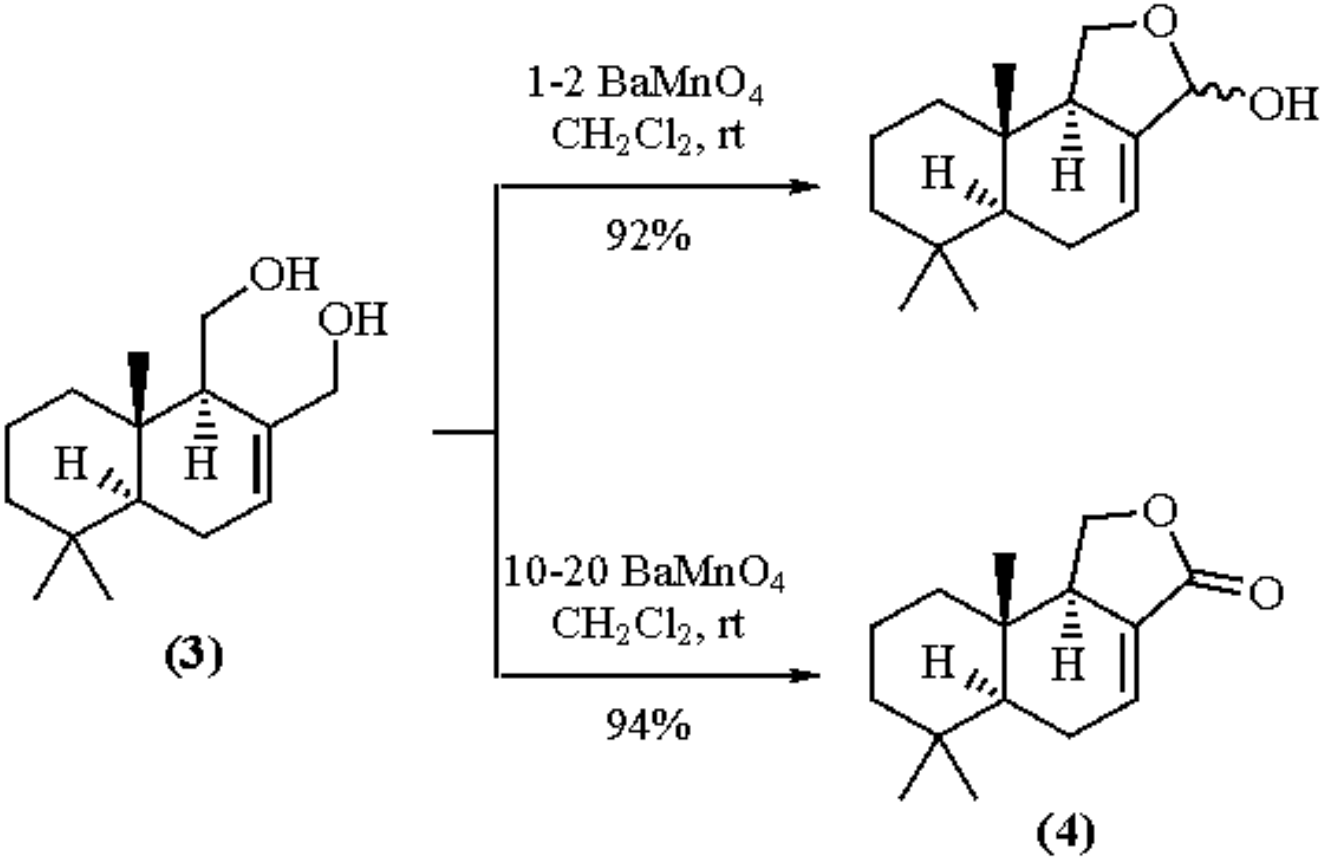

(16)

Other Applications.

Barium manganate has found various other applications in synthesis, including the oxidation of thiols to disulfides (eqs 17 and 18).[10] It is noteworthy that an aromatic amino group is unaffected in this oxidation, as aromatic amines have been reported to yield azo compounds with barium manganate (eq 19).[2b]

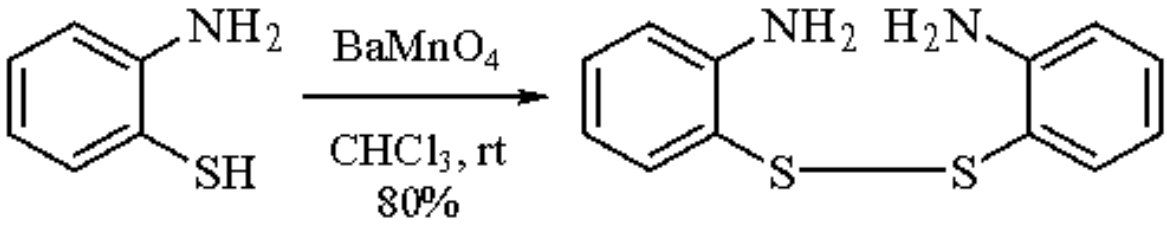

(17)

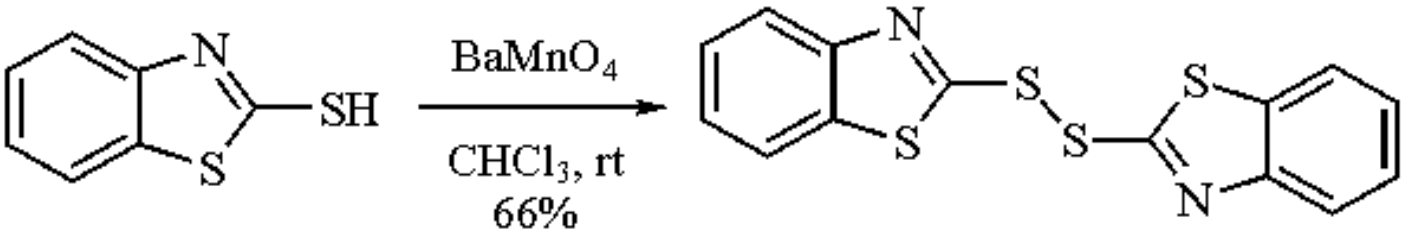

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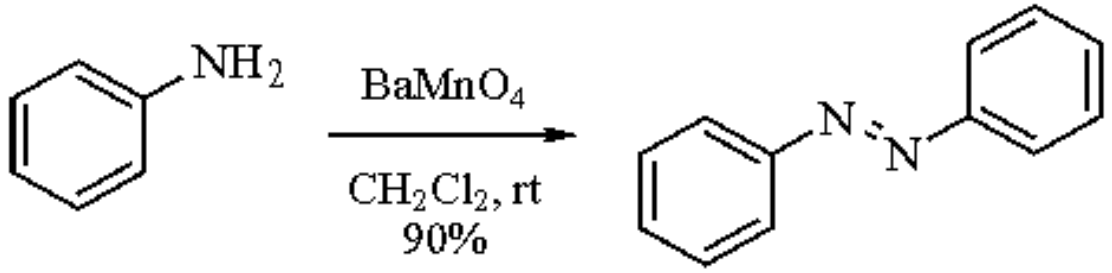

(19)

When hindered phenols are treated with barium manganate, oxidative coupling products are obtained (eq 20).[11]

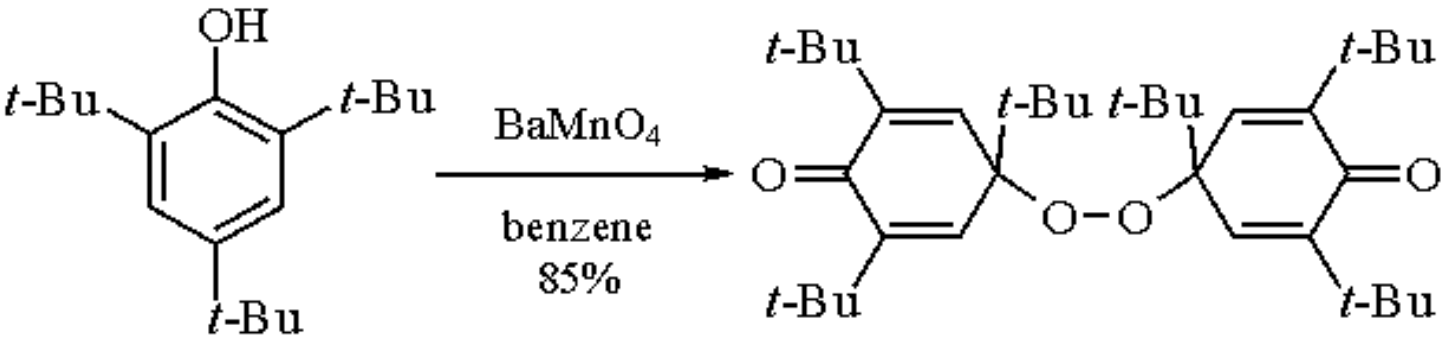

(20)

Barium manganate is reported to be superior to manganese dioxide for the dehydrogenation of 2-imidazolines to imidazoles (eq 21).[3]

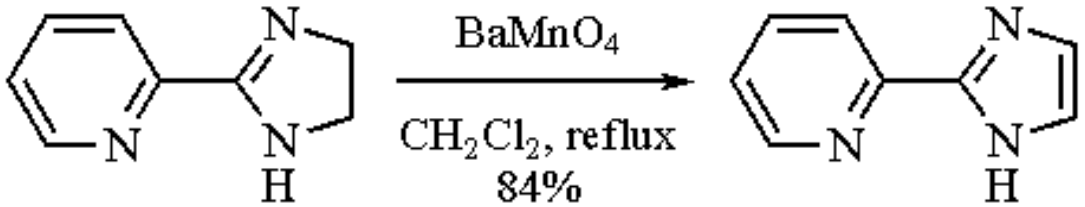

(21)

Longer reaction times also allow some aromatic aldehydes to be oxidized to carboxylic acids (eq 22).[4] Under these conditions, heterocyclic aromatic aldehydes give no oxidation products and aliphatic aldehydes give only polymeric products, which are probably due to aldol reaction pathways.

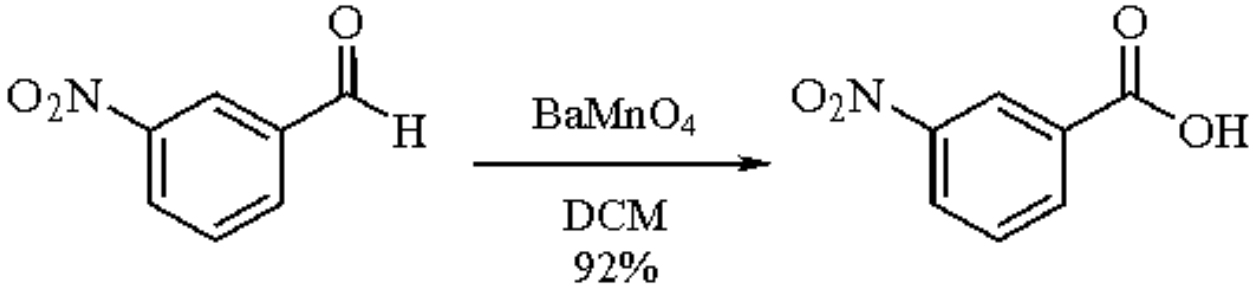

(22)

Barium manganate is able to oxidatively cyclize benzylideneaminoanilines, -phenols, and -thiophenols to benzimidazoles, benzoxazoles, and benzothiazoles, respectively, at ambient temperature (eq 23).[12]

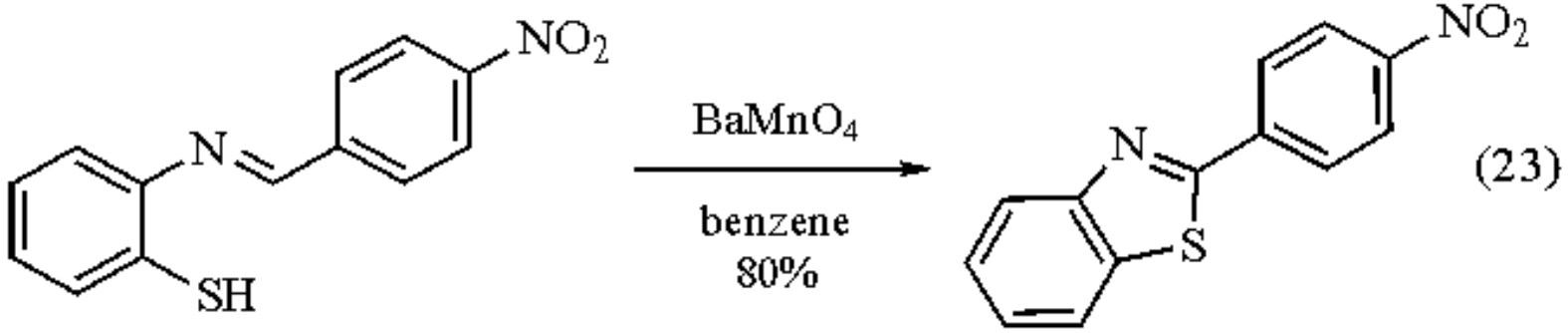

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Benzene(cyclopentadienyl)iron Hexafluorophosphate[1]

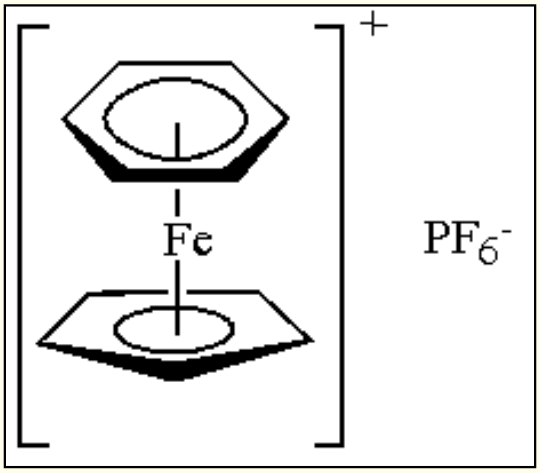

[12176-31-7] · $C_{11}H_{11}F_6FeP$ · Benzene(cyclopentadienyl)iron Hexafluorophosphate · (MW 344.02) (BF_4^- salt)

[1277-51-6] · $C_{11}H_{11}BF_4Fe$ · Benzene(cyclopentadienyl)iron Tetrafluoroborate · (MW 285.86) (free cation)

[51364-24-0] · $C_{11}H_{11}Fe$ · Benzene(cyclopentadienyl)iron Hexafluorophosphate

(electrophilically activated arene complex, undergoes nucleophilic addition,[1,2] nucleophilic substitution of aryl halides,[1,3,4] oxidations and substitutions at benzylic protons,[1,5,6] and photochemical or thermal arene removal[3,7])

Physical Data: mp 200 °C (dec).

Solubility: insol H_2O, Et_2O, THF; sol acetone, MeCN; mod sol CH_2Cl_2.

Form Supplied in: yellow solid; not commercially available. Preparative information is available.[2,8]

Handling, Storage, and Precautions: $[(C_6H_6)FeCp]PF_6$ is air stable. No special storage requirements are indicated. Its toxicity is unreported, but is probably low to moderate.

General Description.

Benzene(cyclopentadienyl)iron hexafluorophosphate is the simplest member of the $[(arene)FeCp]^+$ family, which was first prepared in the late 1950s. Although $[CpFeCl(CO)_2]$ was first used as the synthetic precursor, it was soon recognized that ferrocene itself is a more convenient alternative.[1,2,8] ***Aluminum Chloride*** (or other very strong Lewis acid) is needed to produce the cation. ***Aluminum*** powder is often added also to reduce any ferricinium cation generated during the reaction.

Such preparative conditions must necessarily limit the range of aromatic substrates which can be directly coordinated to the $[CpFe]^+$ fragment. Nevertheless, certain arenes which cannot be added directly can be produced subsequent to coordination via substitution or oxidation reactions. Several review articles on arene-iron complexes feature thorough discussions of preparative considerations and the range of usable a romatics.[1]

Nucleophilic Addition Reactions.

The coordination of a metal fragment to an aromatic molecule causes the arene to take on an electrophilic character.[9] This is especially true when the metal fragment is cationic. Hence $[(C_6H_6)FeCp]^+$ undergoes attack by moderate to strong nucleophiles, such as lithium and Grignard reagents (eq 1).[2] Similarly, hydride may be added using ***Sodium Borohydride*** or ***Lithium Aluminum Hydride***. Some ketones have been shown to react as their enolate anions with $[(arene)FeCp]^+$ in the presence of ***Potassium Hydroxide***.[10] Unless it is quite sterically hindered, the arene is the preferred site of attack on $[(arene)FeCp]^+$; the product therefore contains a cyclohexadienyl ring and is a ferrocene analog. The stereochemistry of attack is invariably *exo* with respect to the metal. Substituent effects are typically rather minor.[2] Exceptions include methoxycarbonyl, cyano, nitro, and tosyl substituted benzenes, which show 10-20:1 preferences for *ortho* attack over *meta* and *para*.[11] Liberation of the ring occurs with rearomatization; thus eq 1 represents an overall nucleophilic aromatic substitution.

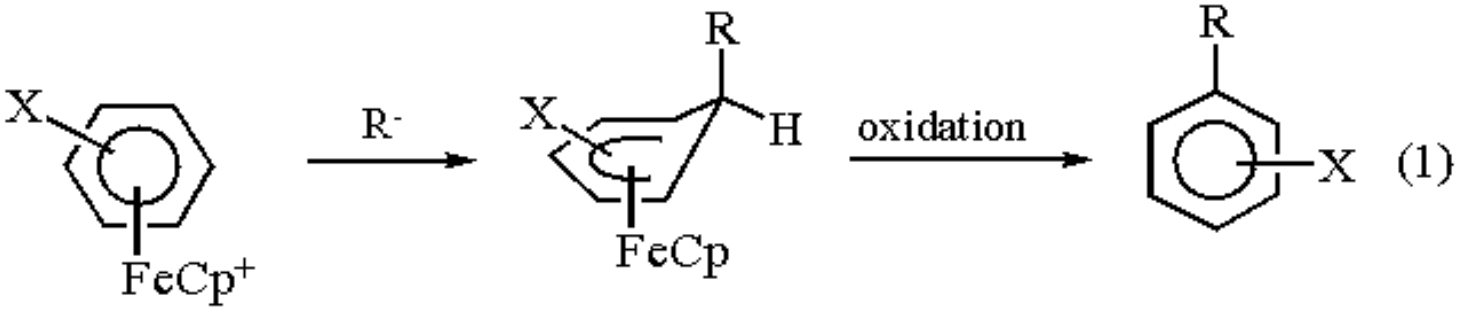

A variety of metal fragments activate trienes (such as arenes) toward electrophilic attack to varying degrees. In Table 1 the relative kinetic activation afforded by various metal fragments (independent of the coordinated triene and the nucleophile) is compared.[9] This parameter is the electrophilic transferability number (T_E). It may be noted that for a given nucleophile, $[(C_6H_6)Mn(CO)_3]^+$ is expected to react at 1.1×10^4 the rate of $[(C_6H_6)FeCp]^+$. The lesser electrophilicity of the iron cation renders it unreactive toward neutral donors, such as phosphines, which add to the manganese complex.

Table 1 Electrophilic Transferability Numbers (T_E) for Organometallic Fragments

Metal fragment	T_E for trienes
$Fe(C_6H_6)^{2+}$	2.0×10^8
$Ru(C_6H_6)^{2+}$	6.0×10^6
$Os(C_6H_6)^{2+}$	1.5×10^6
$Mn(CO)_3^+$	1.1×10^4
$Re(CO)_3^+$	1.0×10^4
$Mn(CO)_2(PPh_3)^+$	1.6×10^2
$FeCp^+$	1.0
$Cr(CO)_3$	very small

Nucleophilic Substitution Reactions.

The halobenzene and nitrobenzene complexes are subject to substitution of X^- or NO_2^- by soft anionic nucleophiles, such as heteroatom donors.[3,4] This reaction is conveniently conducted in the presence of ***Sodium Carbonate*** (eq 2). Stabilized carbanions behave similarly.[12] Hard carbanions, however, usually undergo addition reactions with $[(PhCl)FeCp]^+$. The ease with which substitution reactions occur for $[(PhCl)FeCp]^+$ is similar to that of 2,4-dichloronitrobenzene. Chloride substitution is of course even more facile for $[(PhCl)Mn(CO)_3]^+$.[13]

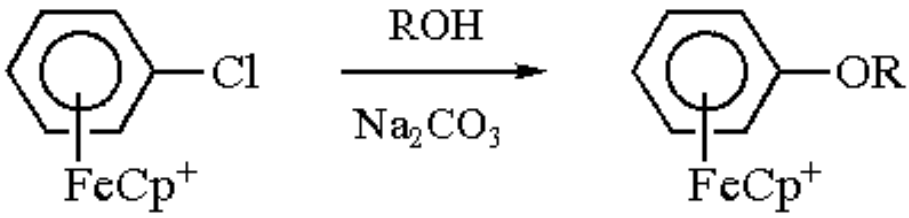

(2)

Reactions at Benzylic Sites.

The $[CpFe]^+$ fragment is stable towards oxidation. This allows the elaboration of coordinated methylbenzenes to benzoic acids (eq 3).[5] Conversion to acid derivatives, i.e. esters, acid chlorides, amides, and nitriles, may subsequently be accomplished. In very specialized instances, benzylic carbons can be oxidized to ketones.[14] Coordinated aniline can be oxidized to coordinated nitrobenzene using hydrogen peroxide and acid. Benzylic protons are rendered especially labile by the electron-withdrawing power of $[CpFe]^+$.[6] Hence ring methyls can be alkylated to produce tentacled benzenes (eq 4).[15]

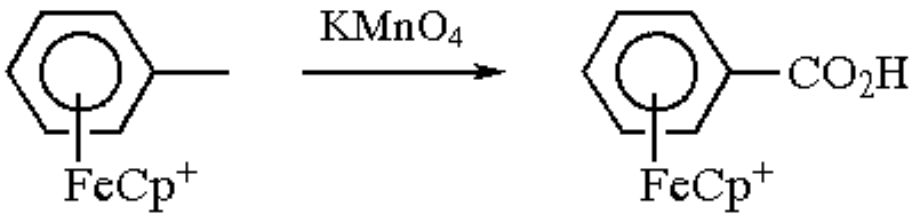

(3)

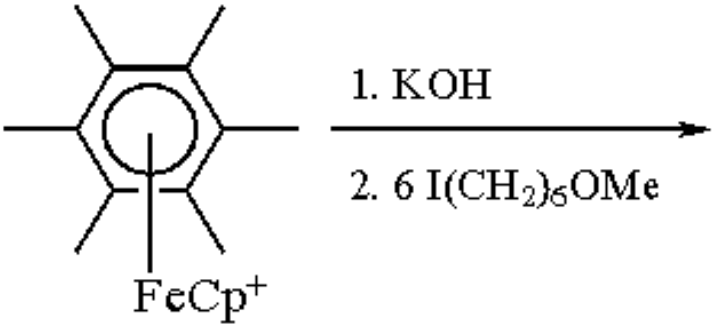

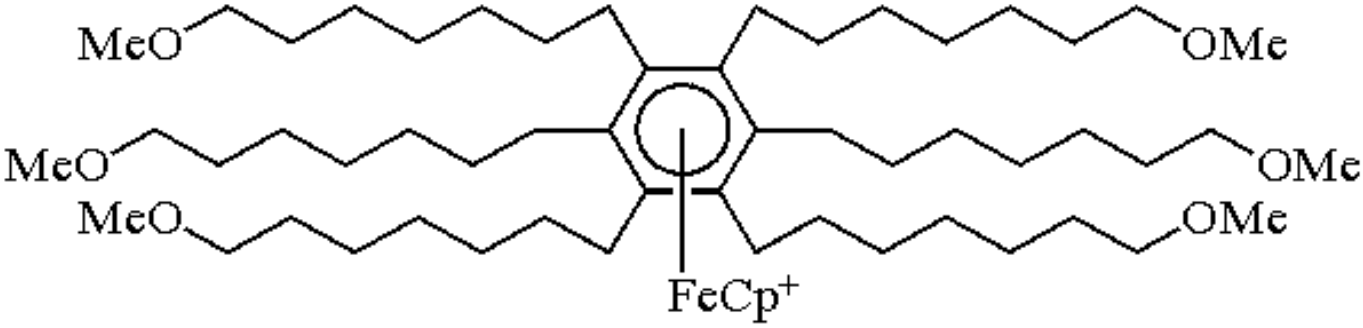

(4)

Arene Removal Reactions.

The aromatic ligand can be photochemically[7] or thermally[3] removed. The liberated $[CpFe]^+$ fragment is then trapped with 3 mol of coordinating solvent or donor ligands. Alternatively, electron-rich aromatics may be used, facilitating arene exchange. However, the scope of the latter chemistry has not been explored in any detail to date.

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Benzenediazonium-2-carboxylate

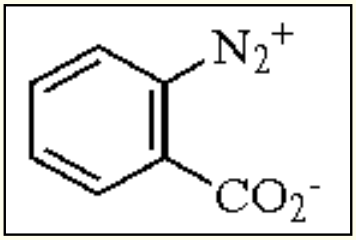

[1608-42-0] · $C_7H_4N_2O_2$ · Benzenediazonium-2-carboxylate · (MW 148.12)

(benzyne precursor[6])

Alternate Name: 2-carboxybenzenediazonium hydroxide inner salt.

Solubility: insol most organic solvents.

Preparative Method: obtained by diazotization of anthranilic acid;[1] the most useful diazotization agent is ***Isopentyl Nitrite*** (caution, heart stimulant!).

Handling, Storage, and Precautions: can be generated in situ,[2] handled as a suspension of the inner salt[1] or the hydrochloride[3] in ethers or halogenated hydrocarbons, or isolated as a dry solid.[1] Solid benzenediazonium 2-carboxylate decomposes explosively on being heated or scraped against a hard surface. The use of the wet compound is safer, but explosions have been reported during experiments using a slurry of the inner salt[4] or the hydrochloride.[5] The safest procedure is generation in situ by aprotic diazotization, but yields are lower. Preparation and handling should be carried out with good shielding.

Generation of Benzyne.[6]

Benzenediazonium-2-carboxylate decomposes on heating to afford benzyne (eq 1). The decomposition temperature depends on the solvent used.[6] This is one of the simplest and most commonly used procedures for the generation of benzyne for synthetic purposes. When diazotization is carried out in situ, secondary products derived from the reaction of benzyne with the starting materials are obtained. Better yields are obtained if the diazonium salt is prepared previously in a separate flask. However, the scale of work is limited to a few grams by safety reasons. Application of this procedure to the generation of substituted benzynes is limited by the availability of starting anthranilic acids. Most of these reactions are carried out in refluxing DME, THF, or 1,2-dichloroethane.

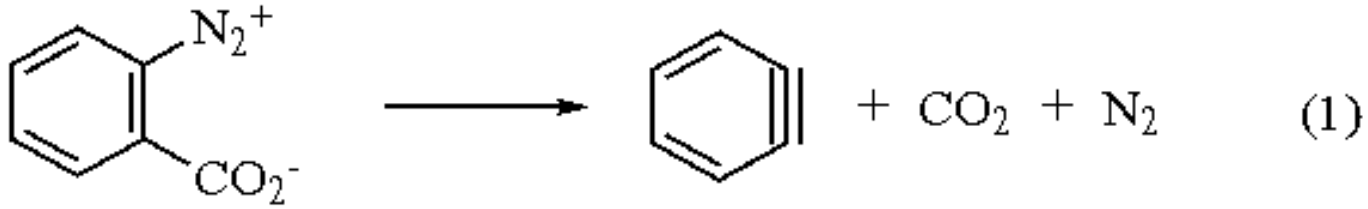

Nucleophilic Additions.[6]

Most nucleophiles react with benzyne to afford an intermediate aryl carbanion, which can be protonated or trapped with another electrophile. Even ethers, which are frequently used as solvents in these reactions, react with benzyne. For example, THF reacts with benzyne to afford an intermediate betaine, which can undergo attack by nucleophiles (eq 2).[7]

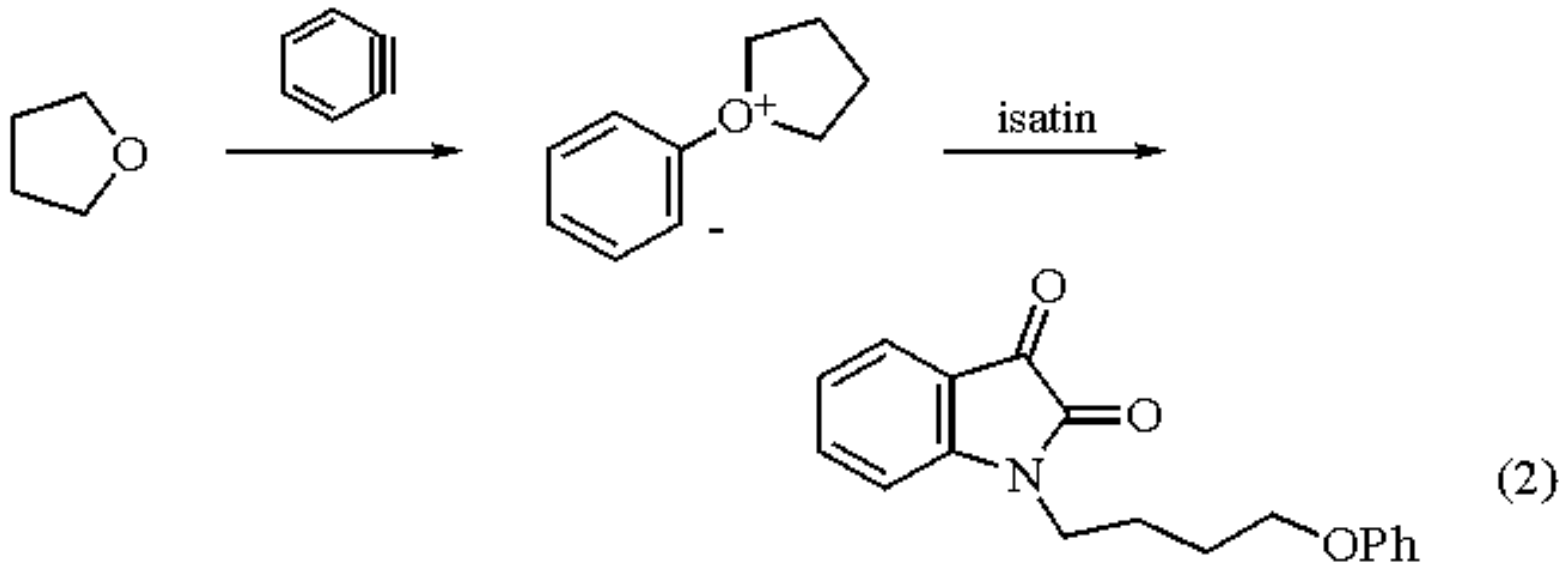

When nucleophile and electrophile belong to the same molecule, annulation takes place. For example, when benzyne is generated from benzenediazonium-2-carboxylate in the presence of enol ethers or enol acetates, benzocyclobutenes are obtained by a formal [2 + 2] cycloaddition (eq 3).[8] These benzocyclobutenes can then be used to generate *o*-quinodimethanes. Halogenated benzocyclobutenes can be obtained in a similar way (eq 4).[9]

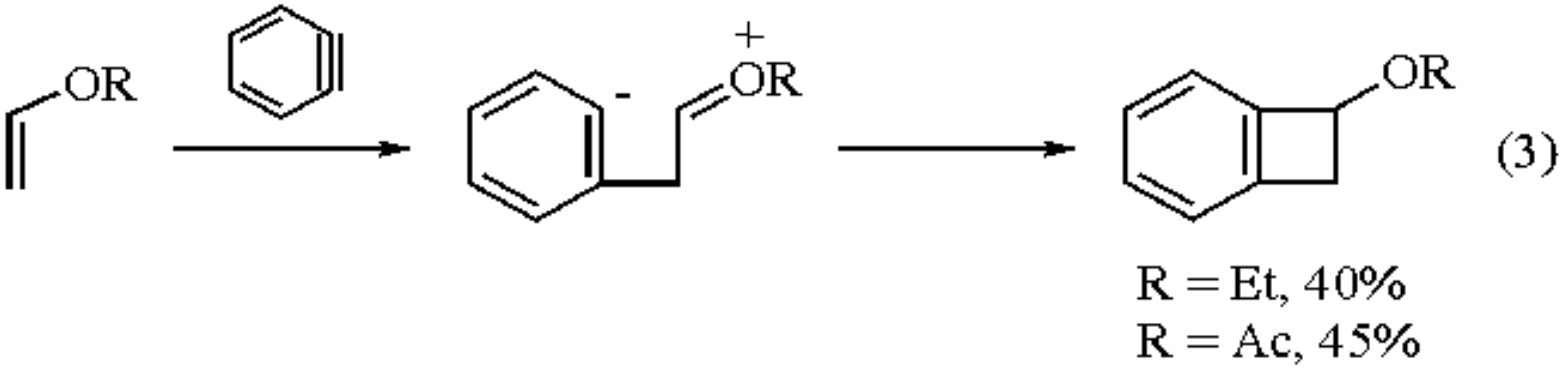

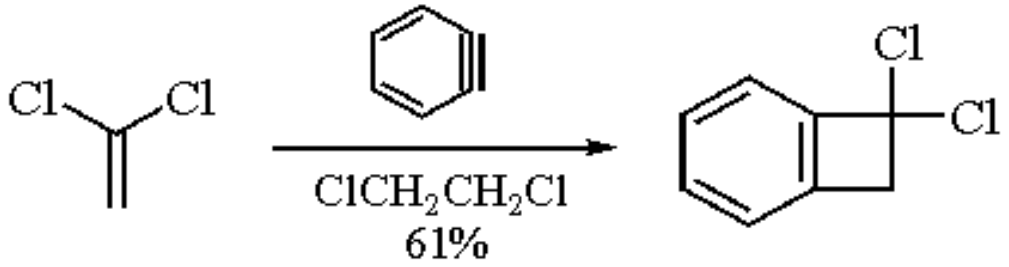

(4)

The benzyne dimer biphenylene is a frequent secondary product in benzyne reactions (eq 5).[6]

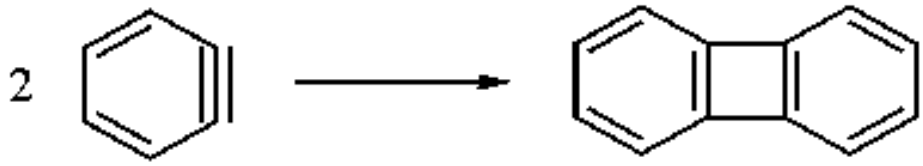

(5)

The high reactivity of benzyne with nucleophiles makes it necessary to protect nucleophilic centers when other types of reaction, such as cycloadditions, are desired. In particular, nucleophilic nitrogens react very fast with benzyne to afford intermediate betaines, which can undergo a variety of transformations. For example, the aporphine alkaloid nuciferine is transformed into a phenanthrene in moderate yield (eq 6).[10]

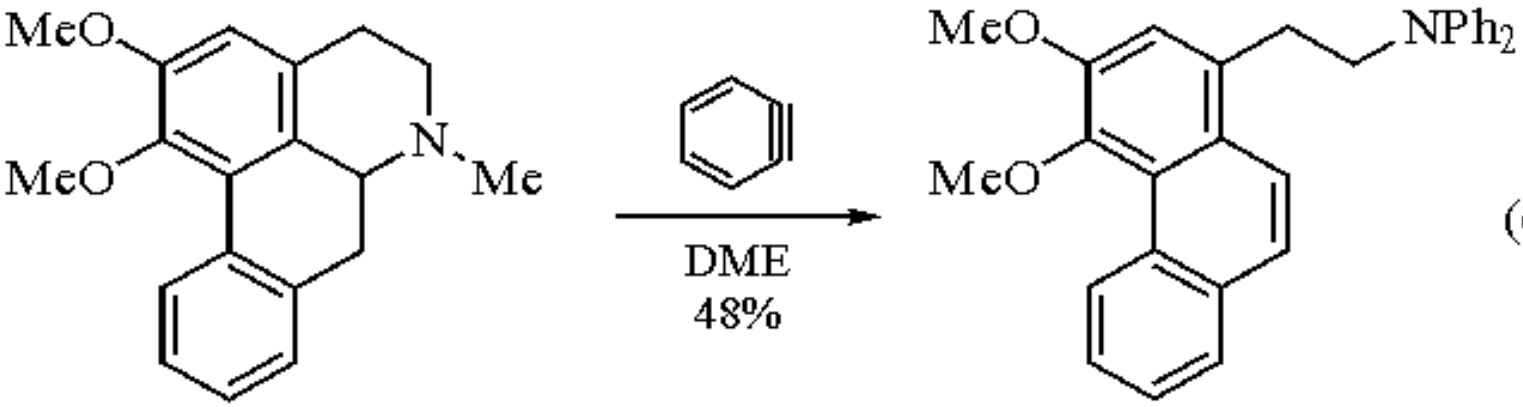

(6)

[4 + 2] Reaction with Acyclic Dienes.[6]

Due to the low yields in the first attempts at cycloadditions between benzyne and acyclic dienes,[7] this reaction was rarely used in synthesis until the 1980s. Its resurrection began with the synthesis of anthracyclinones by reaction of benzyne with an exocyclic diene (eq 7).[11]

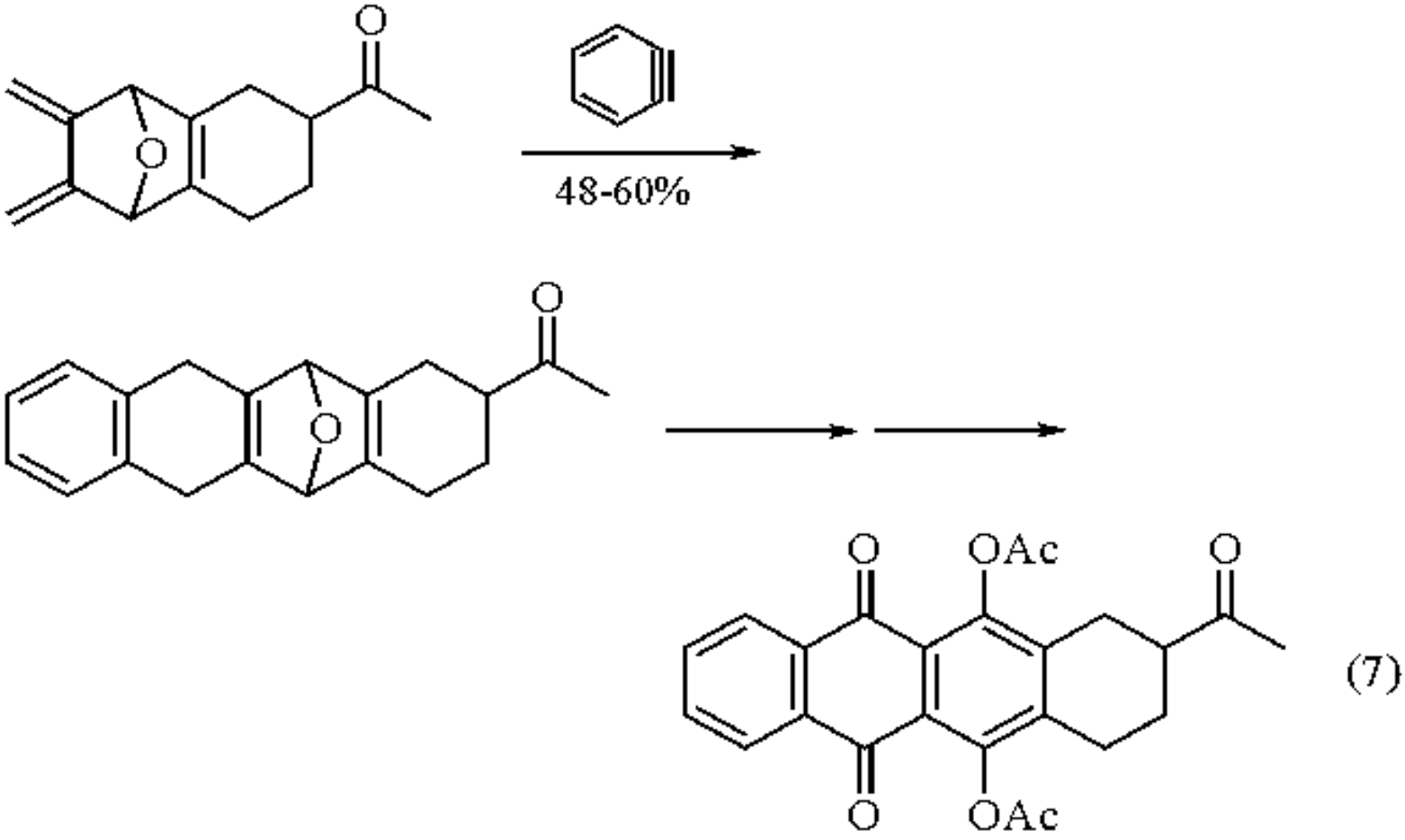

(7)

Benzyne generated from benzenediazonium 2-carboxylate has been reacted with styrenes to afford low yields of phenanthrenes and/or dehydrophenanthrenes.[12] This reaction has been applied in recent years to the synthesis of aporphinoids. When benzyne was generated in a solution of a protected 1-methylene-1,2,3,4-tetrahydroisoquinoline in DME, the corresponding dehydroaporphine was obtained, the initial dehydrophenanthrene cycloadduct having undergone oxidation under the reaction/work-up conditions. Substituted anthranilic acids can be used as precursors of substituted benzynes, but the yield of the cycloaddition is lower. Remarkably, the reaction works regioselectively when *o*-substituted benzynes are used (eq 8).[13]

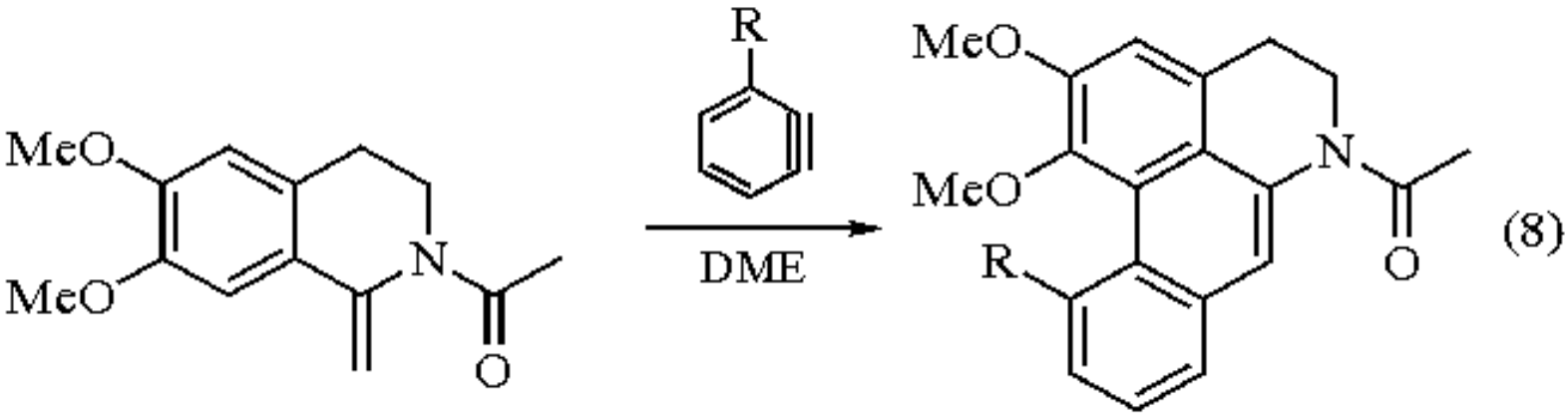

(8)

R = H, 60%; R = OMe, 28%

[4 + 2] Reaction with Cyclic Dienes.[6]

Benzyne generated from benzenediazonium-2-carboxylate reacts with most heterocyclic dienes. A typical example is the reaction with furan, which is frequently used as a trapping agent for benzyne (eq 9).[14] Lower yields of cycloadducts are obtained with the less reactive thiophene (see (2-carboxyphenyl)phenyliodonium hydroxide).[15] Silacyclopentadienes also react with benzyne to afford bicyclic compounds (eq 10).[16]

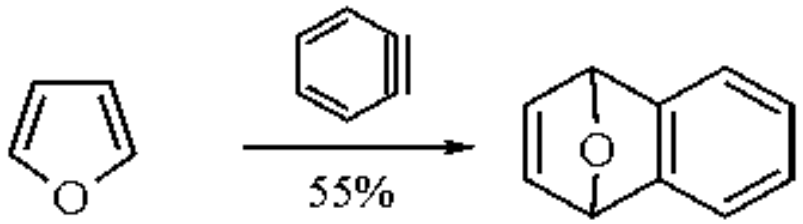

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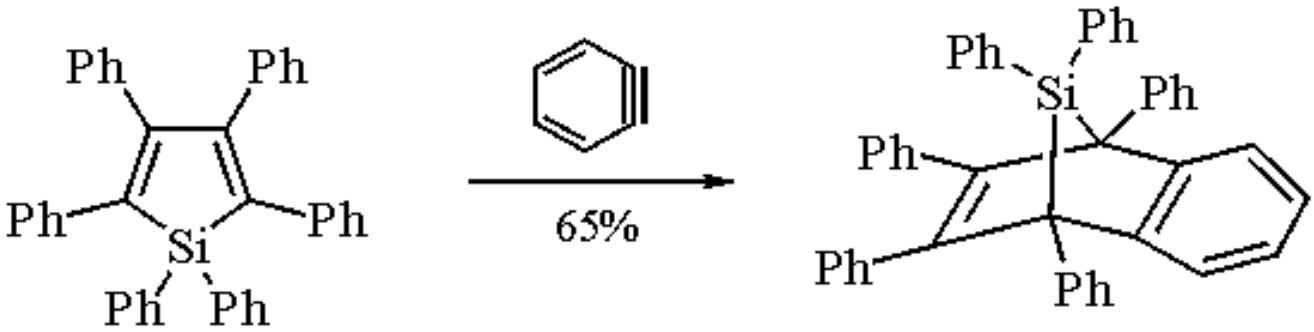

(10)

A sequence of Diels-Alder/retro-Diels-Alder reactions occurs when benzyne is generated in the presence of 1,2-diazines.[6] Eq 11 shows a particular case which includes a Diels-Alder/retro-homo-Diels-Alder sequence.[17]

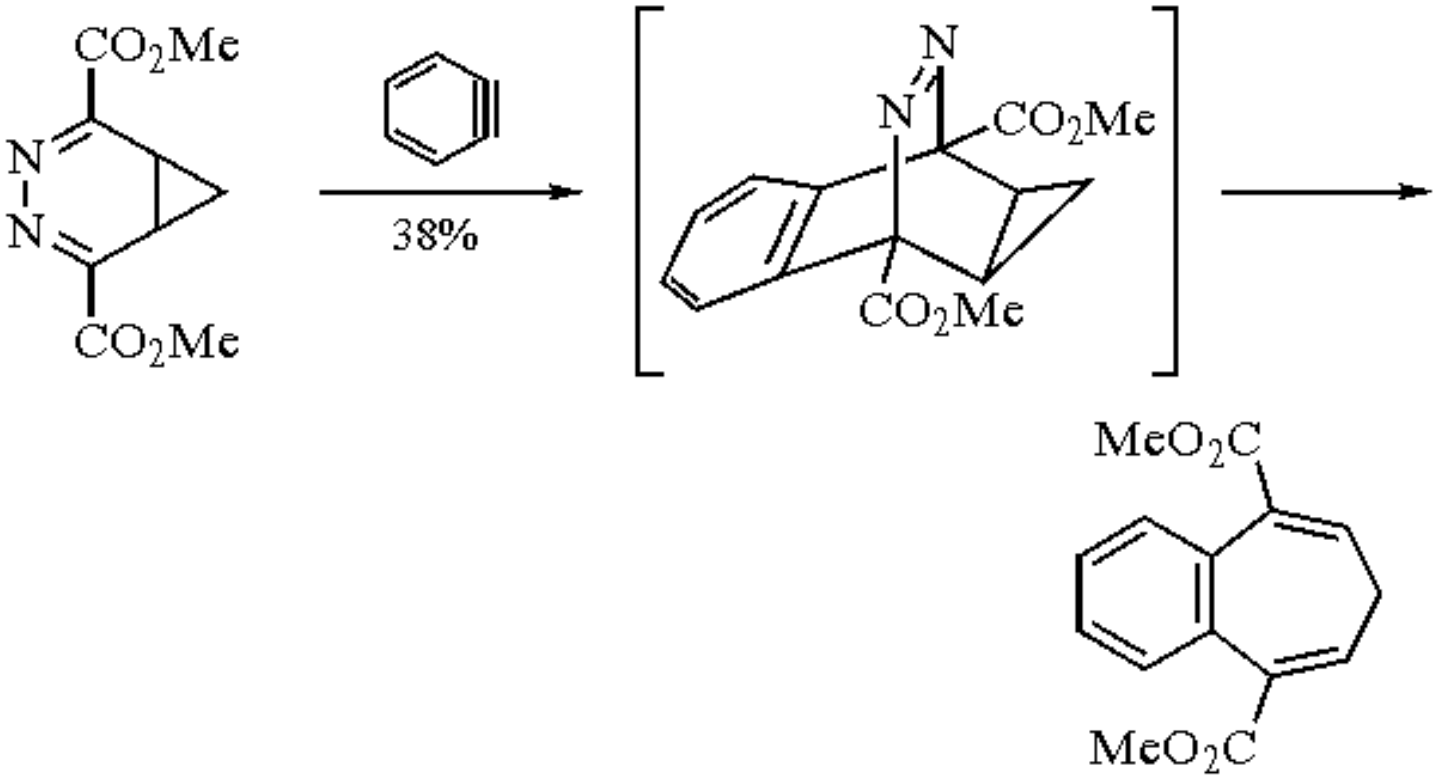

(11)

Bridged hydrocarbons can be easily constructed by cycloaddition of benzyne with cyclic dienes such as dimethylfulvene (eq 12).[18] Even aromatic compounds take part in these reactions. Eq 13 shows the formation of benzobarrelene by cycloaddition of benzyne with an anisole derivative.[19]

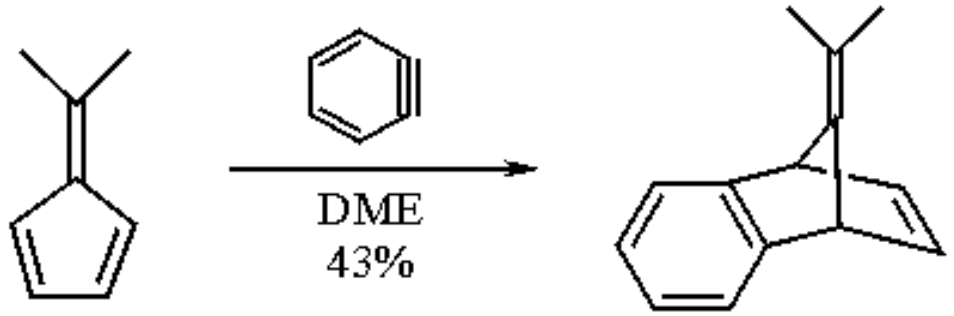

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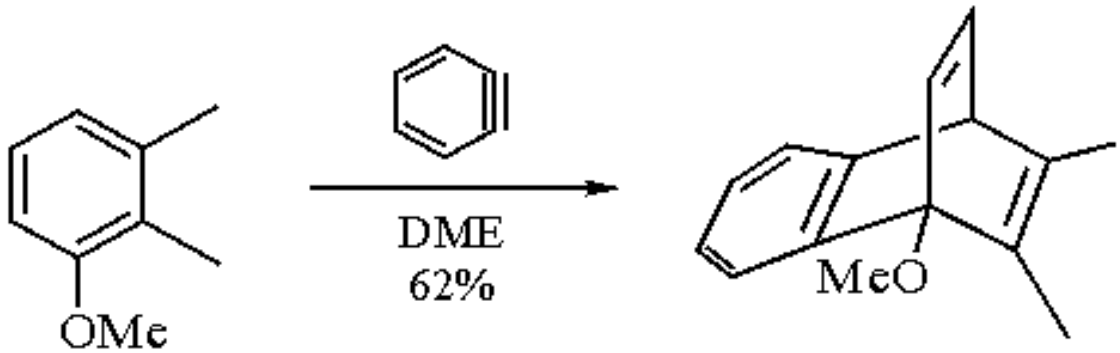

(13)

Benzyne cycloaddition is often the method of choice for the synthesis of triptycenes, azatriptycenes, and related compounds (see ***2-Bromofluorobenzene*** and ***2-Bromoiodobenzene***). In eq 14 an azatriptycene is obtained by the addition of benzenediazonium-2-carboxylate to a refluxing solution of the diene in DME.[20] Benzenediazonium-2-carboxylate hydrochloride has been used to generate benzyne in the key cycloaddition step of the synthesis of complex triptycene derivatives. Propene oxide is added to the reaction mixture to trap the HCl. Remarkably, almost quantitative yields were obtained in this cycloaddition step.[21]

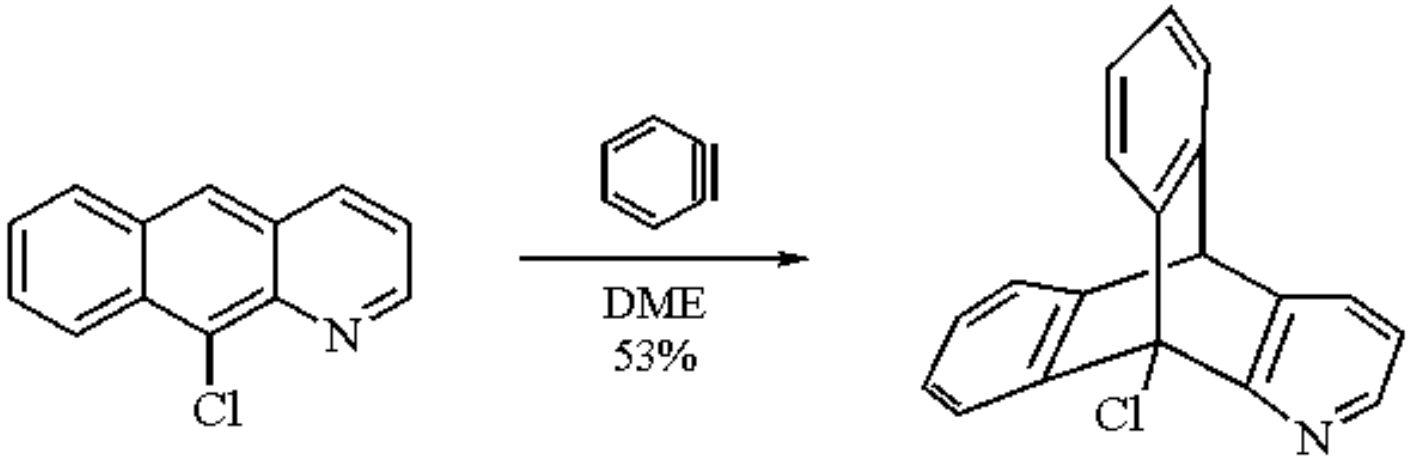

(14)

When benzyne is generated from benzenediazonium-2-carboxylate in the presence of isoquinolopyrroline-2,3-diones, the major products are protoberberines (eq 15).[22] This procedure has also been used for the synthesis of compounds

with a yohimban skeleton. The mechanism of these transformations seems to be rather complex.[7] Naphthopyrroline-2,3-diones react in a similar way with benzyne to afford benzophenanthridines (eq 16). This procedure too can be used with substituted anthranilic acids.[23] A different approach to the same group of isoquinoline alkaloids is based on the cycloaddition of benzyne to a pyrone to form a bicyclic intermediate which loses CO_2 in a retro-Diels-Alder reaction (eq 17).[24] Good yields were also obtained using substituted anthranilic acids.

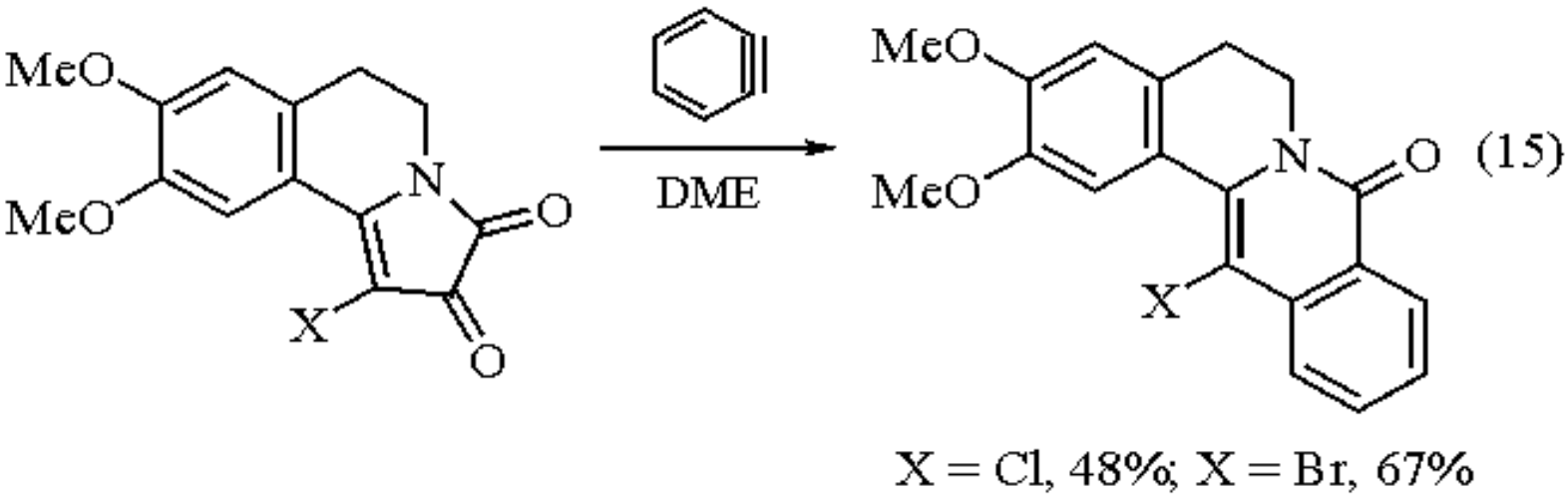

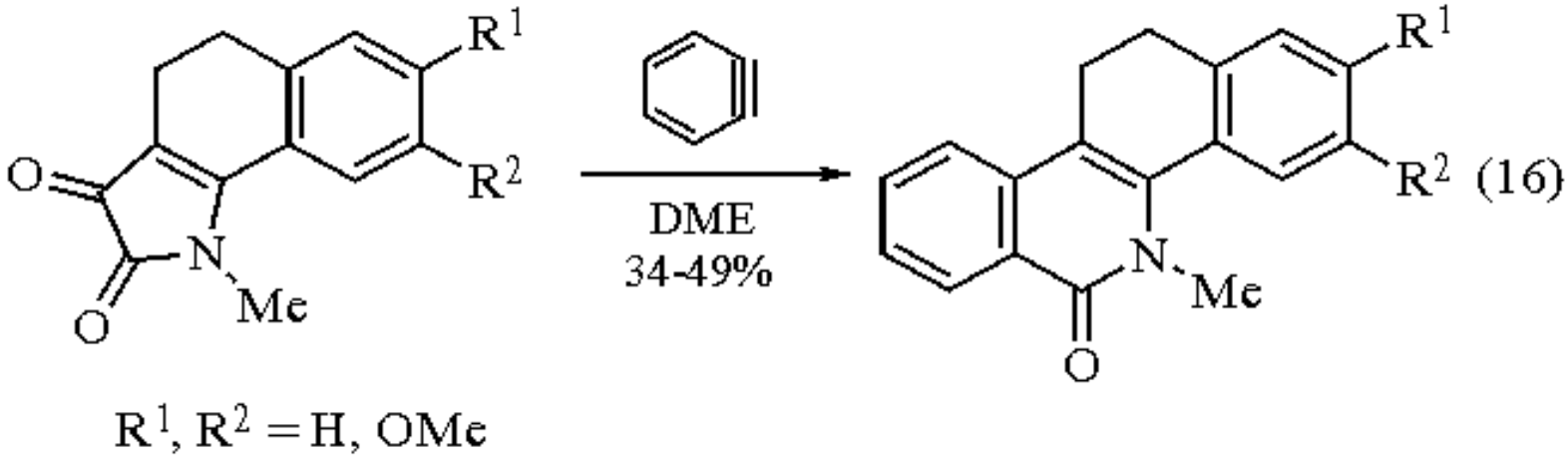

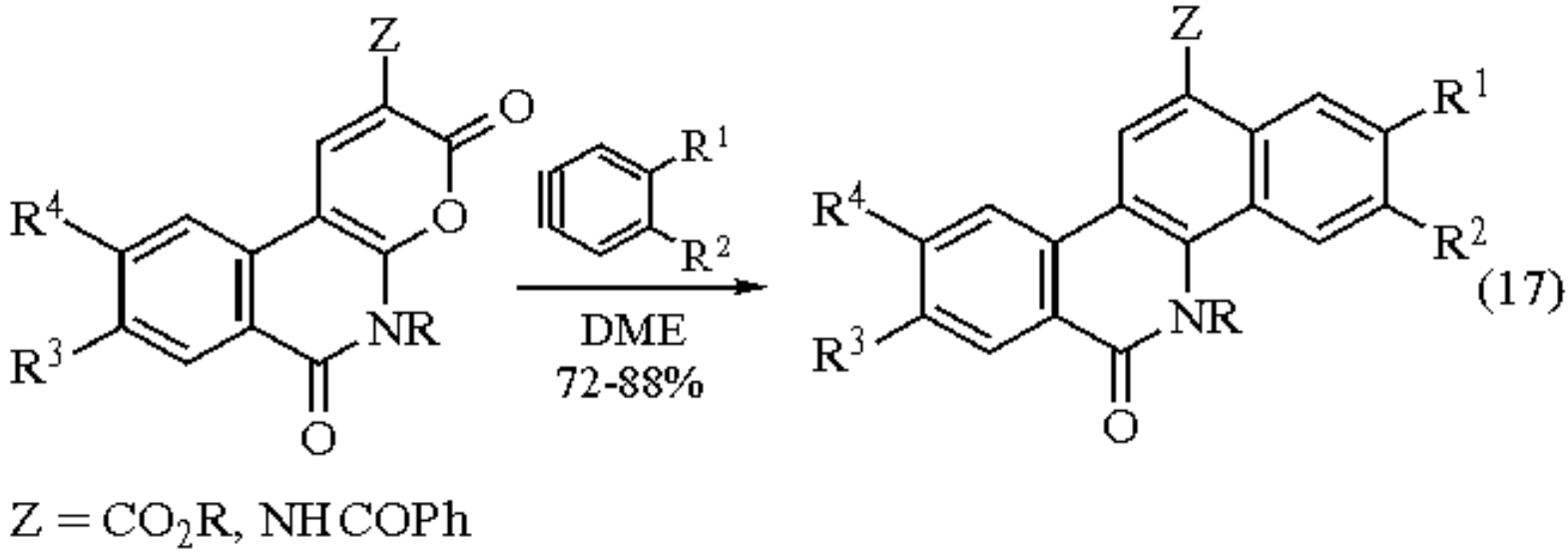

1,3-Dipolar Cycloaddition.

Benzyne generated from benzenediazonium-2-carboxylate also undergoes cycloaddition with 1,3-dipoles such as *N*-oxides (eq 18).[25] 2-Isopentoxy-1,3-benzodithiole is obtained by 1,3-dipolar cycloaddition of carbon disulfide to benzyne, followed by addition of isopentyl alcohol (eq 19).[26]

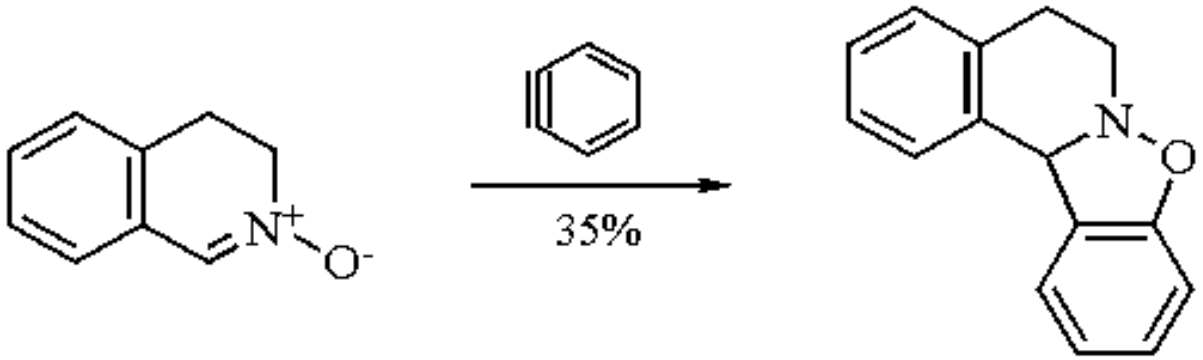

(18)

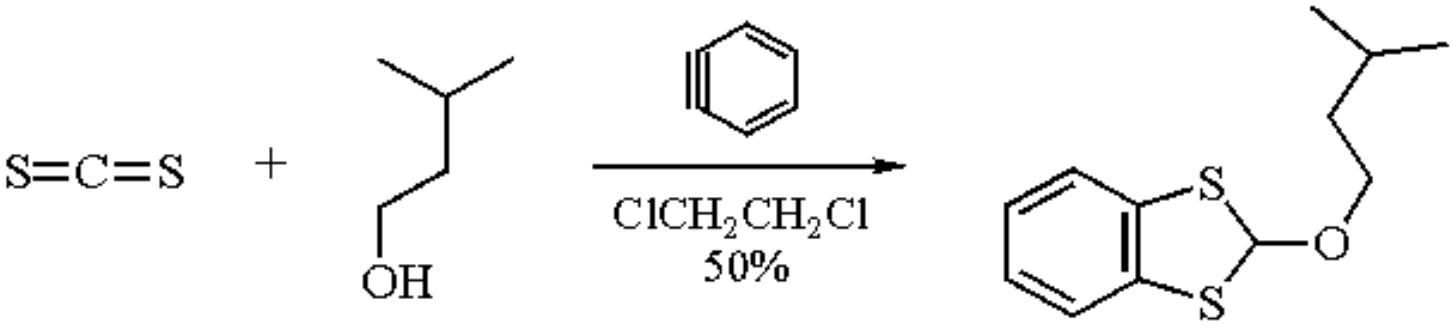

(19)

The reactivity of benzyne generated from benzenediazonium-2-carboxylate with dienes can be modified by the addition of Ag^+. 1,3,5-Cycloheptatriene reacts with benzyne to afford, in 36% yield, a mixture of two products, one resulting from an ene reaction and the second by formal [2 + 2] cycloaddition (eq 20).[27] In the presence of Ag^+ only the [4 + 2] adduct was obtained, although the yield fell to 20% (eq 21).[27]

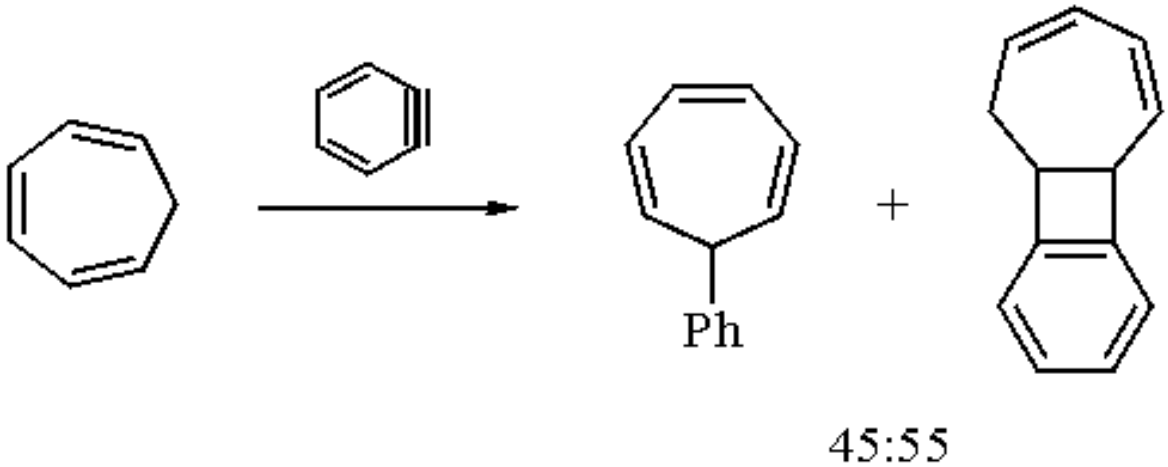

(20)

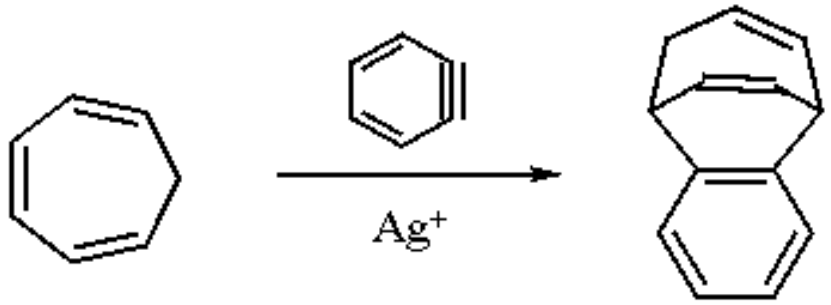

(21)

Related Reagents.

1,2,3-Benzothiadiazole 1,1-Dioxide; ***Diphenyliodonium Carboxylate***.

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Luis Castedo, Concepción González, & Enrique Guitián

Benzenediazonium Chloride[1]

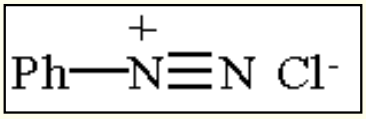

[110-34-5] · $C_6H_5ClN_2$ · Benzenediazonium Chloride · (MW 140.57)

(can form azo compounds by coupling with carbon and hetero nucleophiles,[1a-c,e,f] and a wide variety of benzene derivatives with concomitant dediazoniation;[1] substrate for aromatic substitution)

Alternate Name: phenyldiazonium chloride.

Physical Data: no mp (explodes on heating).

Solubility: very sol H_2O, cold glacial acetic acid; sol abs. ethanol, acetone; insol diethyl ether, $CHCl_3$, benzene.

Form Supplied in: colorless needles, not commercially available. The dry salt can detonate violently and should, therefore, not be isolated as such. Typically, it is prepared by amine diazotization in water or an organic solvent, and the solution or suspension so obtained is used directly.

Analysis of Reagent Purity: usually none (in situ preparation).

Preparative Methods: [1a,b] an aqueous solution of $PhN_2^+Cl^-$ is obtained by adding a stoichiometric amount of $NaNO_2$ at 0-5 °C to the solution obtained from aniline and excess hydrochloric acid in water (eq 1). An excess of nitrite ions at the end of the reaction should be avoided, since they reduce the stability of the diazonium salt solution and can interfere with some further transformations. An excess of HNO_2 is detected with starch-KI paper that turns blue immediately on contact with the reaction solution, and can be destroyed with urea or amidosulfuric acid. A large variety of arenediazonium chlorides and sulfates (using H_2SO_4 instead of HCl) can be prepared by amine diazotization; for less basic and less soluble aromatic amines, the reaction conditions have to be somewhat modified.[2] When the diazotization is carried out with an organic nitrite (typically pentyl nitrite) in an organic solvent such as HOAc, ethanol, or dioxane (eq 1),[3] the solid diazonium salt either separates from the solution or can be precipitated by addition of a nonpolar solvent. The same is true for diazotization of $PhN(SiMe_3)_2$ with NOCl formed in situ from an organic nitrite and Me_3SiCl in dry CH_2Cl_2 (eq 2).[4]

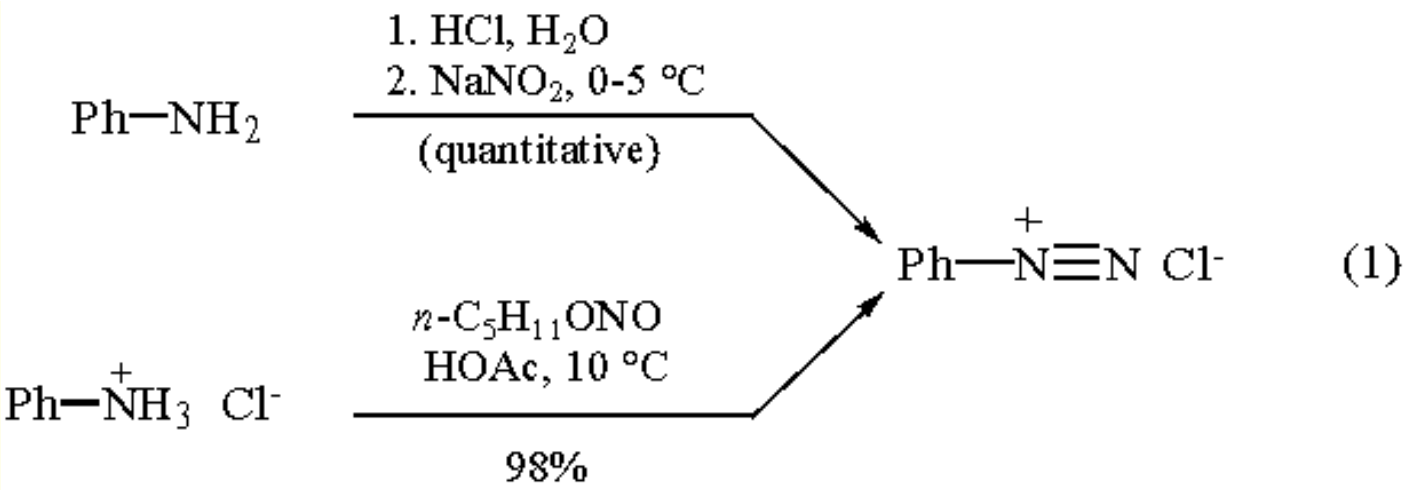

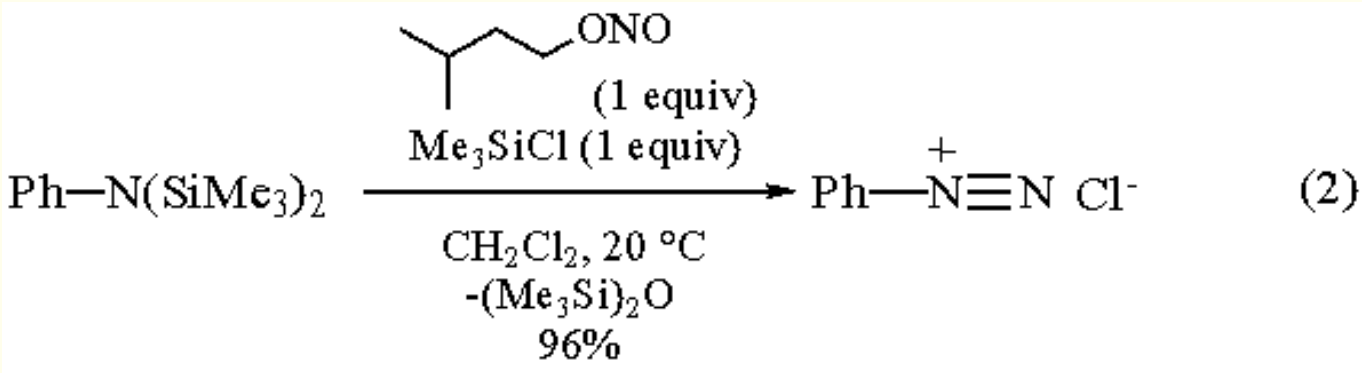

Handling, Storage, and Precautions: dry benzenediazonium chloride explodes on heating, shock, and friction. It deliquesces in moist air with decomposition, but is rather stable in dry air in the dark and in aqueous solution at 0 °C. The decomposition of aqueous solutions of $PhN_2^+Cl^-$ at several temperatures and pH values has been studied by various authors.[5] Less labile than the chloride is the sulfate salt, which does not explode below ca. 100 °C and has a low shock-sensitivity. The salt $(PhN_2^+)_2ZnCl_4^{2-}$, obtained from $PhN_2^+Cl^-$ and $ZnCl_2$, is considered as a stabilized diazonium salt, but an explosion hazard on drying has also been reported.[6] In other arenediazonium salts, both electron-withdrawing and electron-donating *p*-substituents as well as *m*-NO_2, *m*-Br, and *m*-Cl retard the dediazoniation, whereas *m*-MeO and *m*-alkyl groups favor it.[1a,d,7] Arenediazonium salts are stabilized both in the solid state and in solution by complex formation with arenesulfonic acids (especially 1- and 2-naphthalenesulfonic acids),[1a,8] crown ethers, and polyethylene glycols.[1e]

Formation of Covalent Azo Compounds.

The arenediazonium ion reacts at the terminal N atom with a wide range of nucleophiles.[1a,c,7,9] The most important reaction of this type is the synthesis of diarylazo compounds by coupling with phenols, naphthols, aromatic amines, and similar electron-rich aromatic substrates. Electron-rich heteroaromatic and related CH-acidic heterocyclic compounds as well as heteroarenediazonium salts can also participate in this azo coupling reaction which gives access to a great variety of azo dyes and also to azo compounds that are of interest as pharmaceuticals or liquid crystalline materials.[1a,b,f,10,11] In general, the arenediazonium salt is prepared in situ by diazotization of an aromatic amine (see above), and coupled in aqueous solution at pH 3.5-7.0 with another aromatic amine or at pH 5-9 with a phenol derivative. The reaction takes place exclusively at the *p*- and *o*-positions (eqs 3 and 4). The different aspects of this aromatic S_E reaction (mechanism, reactivity, orientation effects) have been studied extensively.[12] In agreement with the electron demand of an aromatic S_E

reaction, the reactivity sequence for substituted phenols and naphthols as coupling components is O^- > NR_2 > NHR > OR &AApprox; OH >> Me.[1a,12] Whereas 1,3,5-trimethoxybenzene couples with PhN_2^+, the more electrophilic 4-nitro- and 2,4-dinitrobenzenediazonium ions are needed for azo coupling with 1,3-dimethoxybenzene and anisole, respectively.[13] With primary or secondary aromatic amines, N-coupling to give triazenes can compete with or dominate over aromatic C-coupling in weakly acidic, neutral or basic solution. The triazenes can undergo an acid-catalyzed intermolecular rearrangement[1a] to the diarylazo compounds. This two-step sequence is sometimes preferred over the direct azo coupling process and has found technical application (eq 5).[14]

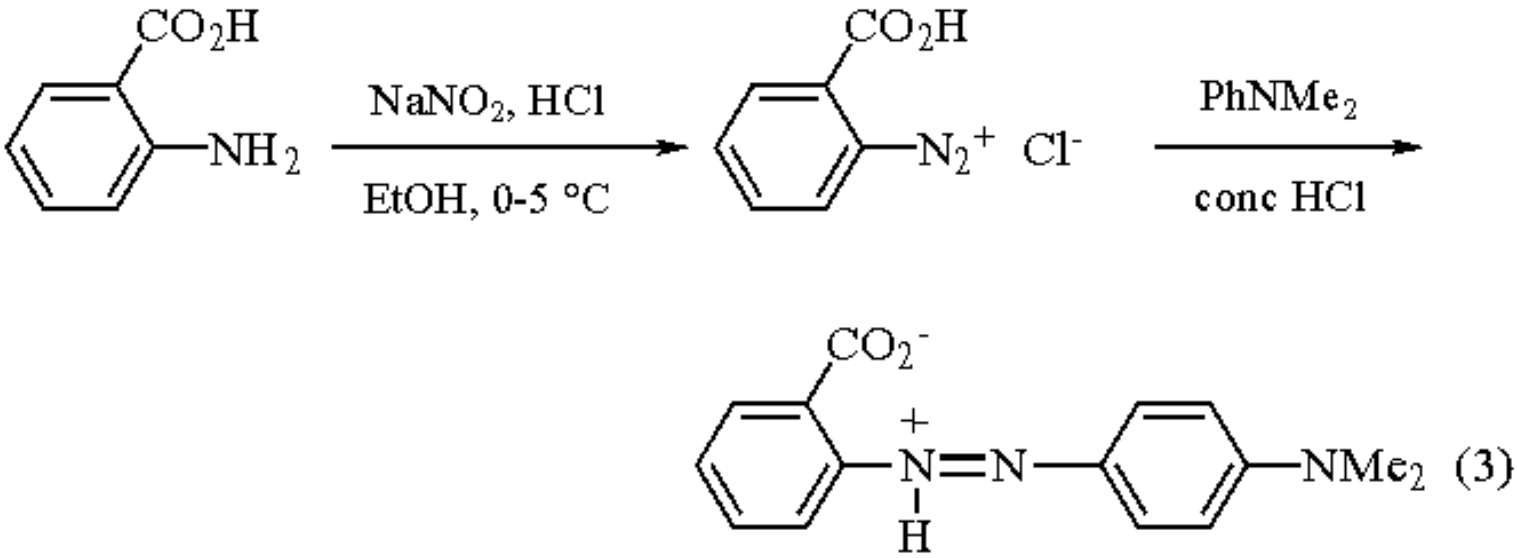

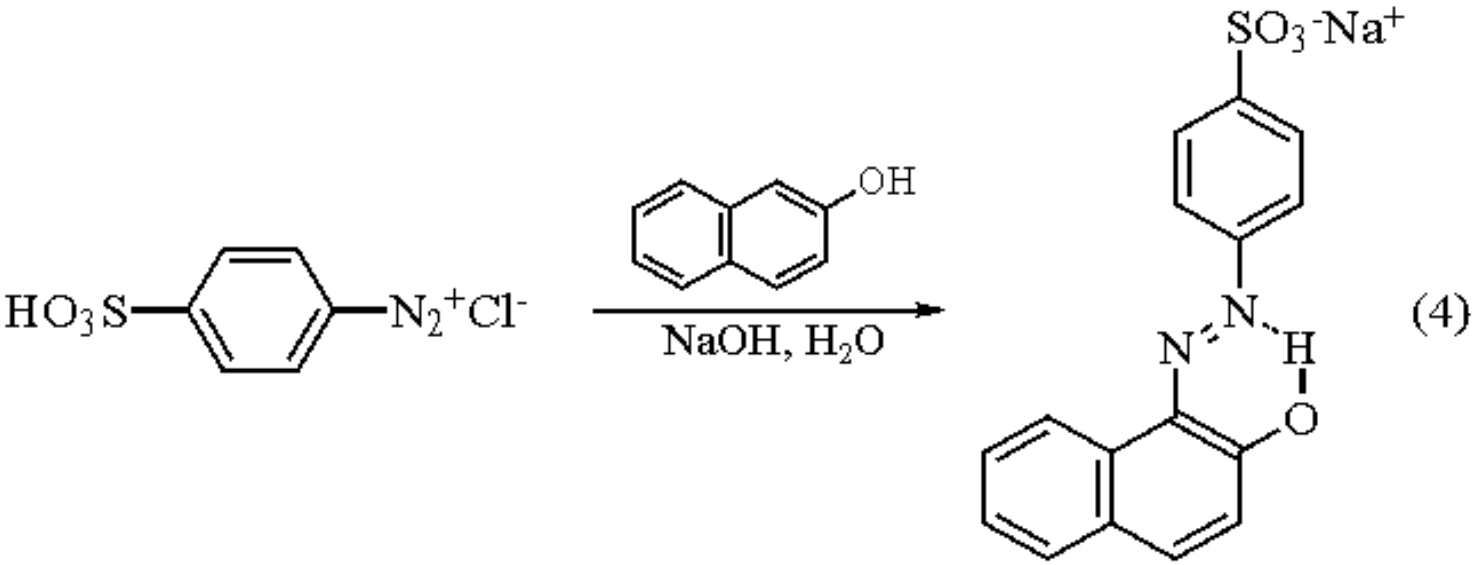

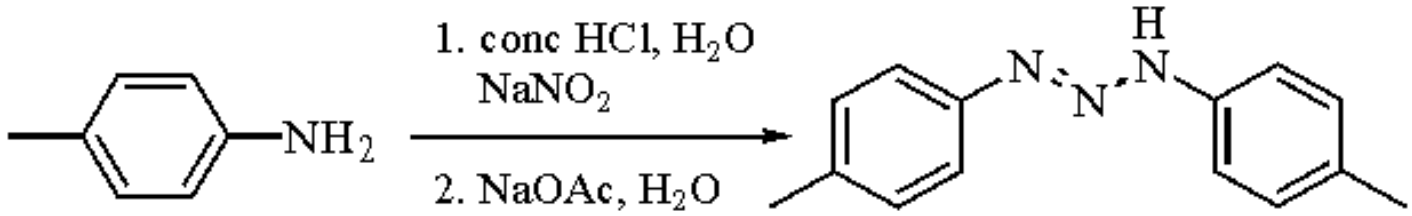

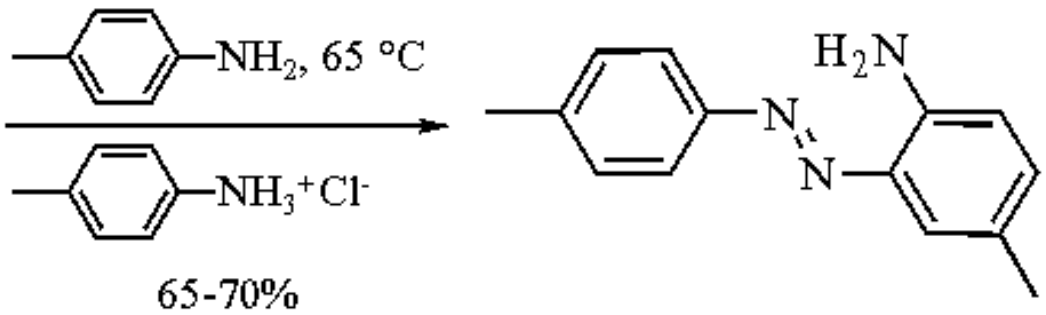

(5)

Azo coupling reactions with in situ generated arenediazonium salts have also been performed on azulenes,[15] 2-alkoxy-1,6-methano[10]annulenes,[16] and tropolones.[1c] Since azo compounds can be reductively cleaved into two amine moieties, the azo coupling route allows the regioselective introduction of NH_2 into an electron-rich aromatic substrate.[17] Furthermore, the chemical stability of the azo group allows modifications on the aromatic nucleus before cleavage (eq 6).[18] The transformations of azulene to 1-aminoazulene[19] and of tropolone to 5-aminotropolone[1c] have been realized similarly.

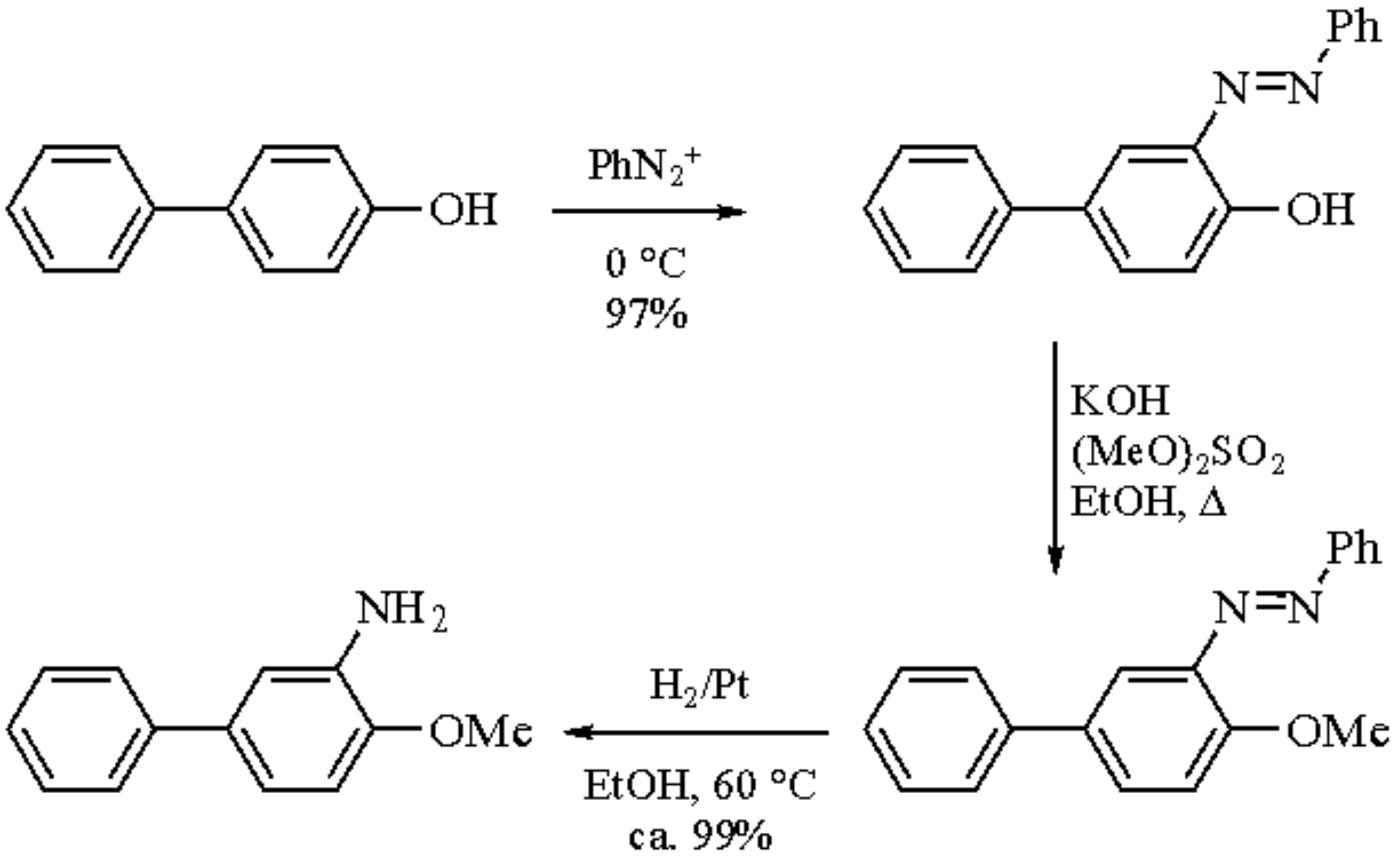

(6)

The covalent azo compounds obtained from ArN_2^+ and CN^- or hetero nucleophiles[1a,c,7,9] are of lesser synthetic importance. Some of them, e.g. *anti*-areneazocyanides (Ar-N=N-CN), *anti*-areneazosulfonates (Ar-N=N-SO_3^-), and

areneazophosphonates ($Ar\text{-}N{=}N\text{-}P(O)(OR)_2$) are thermally stable enough to be useful for further transformations, whereas others split off N_2 more readily to generate aryl radicals by a homolytic pathway. The latter decomposition mode is involved in some synthetically useful transformations of ArN_2^+ salts into functionalized aromatics (see below).

Reduction to Arylhydrazines.

Arenediazonium salts can be converted into arylhydrazines preferably with $SnCl_2$/HCl, Na_2SO_3, or $Na_2S_2O_4$, or by conversion into $Ar\text{-}N{=}N\text{-}SO_3^-$ or $Ar\text{-}N{=}N\text{-}P(O)(OR)_2$ and reduction with Zn/HOAc.[20] While reduction with $SnCl_2$ is most convenient for small-scale preparations, Na_2SO_3 is favored for large batches (eq 7).[21]

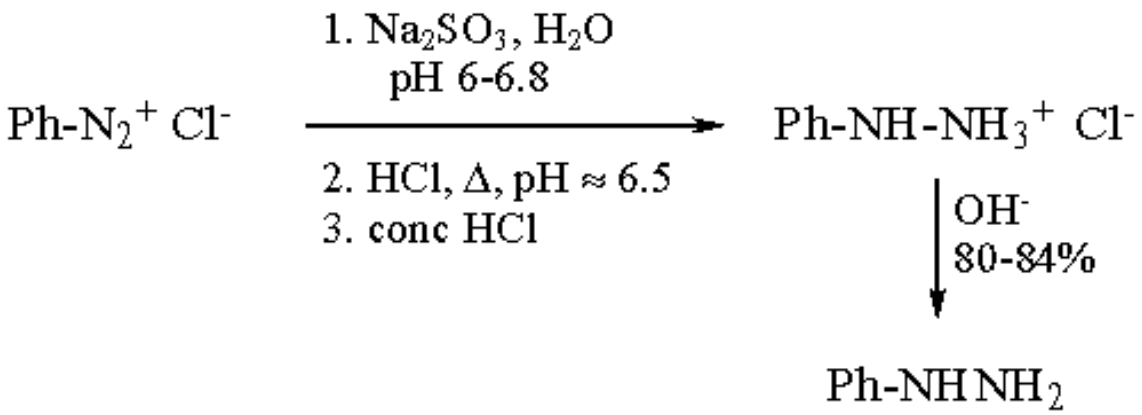

(7)

Formation of Arylhydrazones and Formazans.

Arenediazonium salts can be coupled with many active methylene and methine compounds and also with some CH-acidic methyl groups.[22] The reactions are usually carried out in aqueous solution buffered with NaOAc. Alcohol, pyridine, or HOAc are sometimes added for better solubility of the reactants. 1,3-Diketones, β-keto aldehydes, β-keto esters, malonic esters, β-cyano esters, β-cyano sulfones, and malononitriles all react at the active CH_2 group to give arylhydrazones (eq 8).[23] The reaction of $PhN_2^+Cl^-$ with 2 equiv of ethyl acetoacetate yields 3-ethoxycarbonyl-1,5-diphenylformazan[24] with elimination of the acetyl group. Other β-keto esters, oxaloacetic esters, β-keto acids, and malonic acid monoesters behave analogously, the latter two with elimination of CO_2.[22] Acetone (eq 9) and nitromethane also afford formazans, whereas higher nitroalkanes (RCH_2NO_2) as well as activated methyl compounds such as 2-methylpyridine and 9-methylacridine yield the normal arylhydrazones.[22]

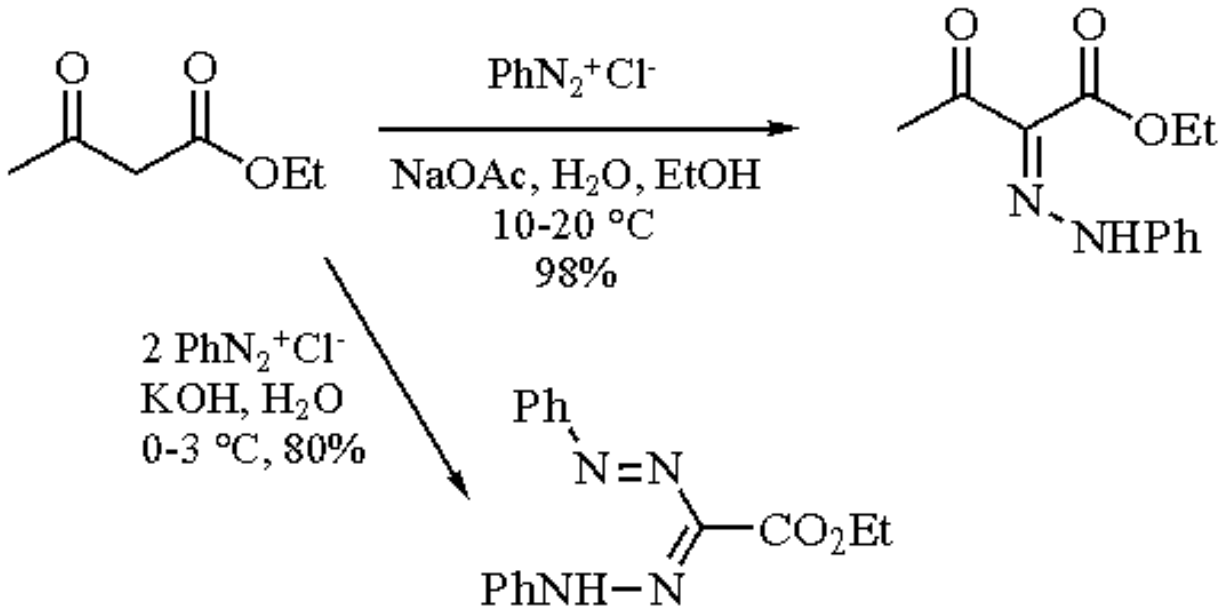

(8)

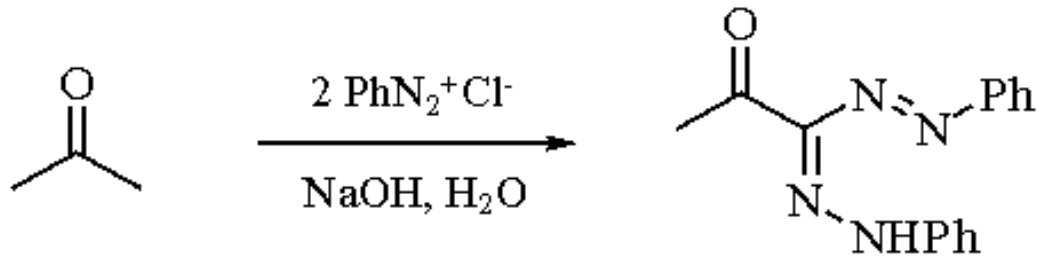

(9)

Methine compounds activated by two electron-withdrawing groups (Z) react with arenediazonium chlorides to give azo compounds that undergo a rapid acid cleavage of the (hetero-)1,3-dicarbonyl system with formation of arylhydrazones (Japp-Klingemann reaction) (eq 10).[25] An aqueous base (NaOH) is sometimes added to facilitate the cleavage reaction. Phenylhydrazones derived from acetoacetic esters can be reduced to amino acid esters und utilized in Fischer-type indole syntheses.[1c,22] By the same sequence, cyclic β-keto esters are cleaved to acyclic o-carboxy-2-arylhydrazono carboxylic esters and can be converted to o-carboxy-α-amino acids or 3-(o-carboxyalkyl)indoles (eq 11).[1c,22,26,27]

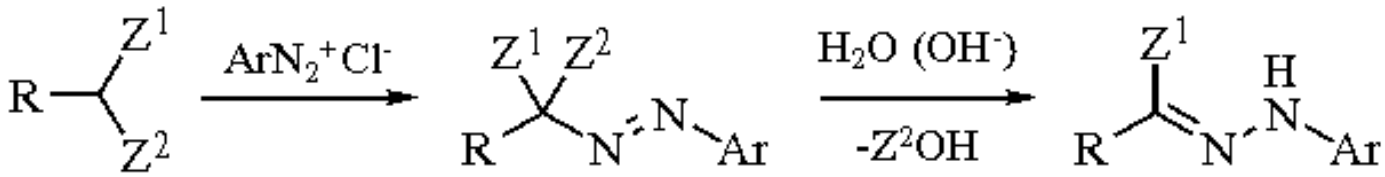

(10)

Z^1	CO_2R	MeCO	MeCO	9-fluorenyl	9-fluorenyl	CN	etc.
Z^2	MeCO	CO_2^-	MeCO	$COCO_2R$	NO_2	CO_2R	

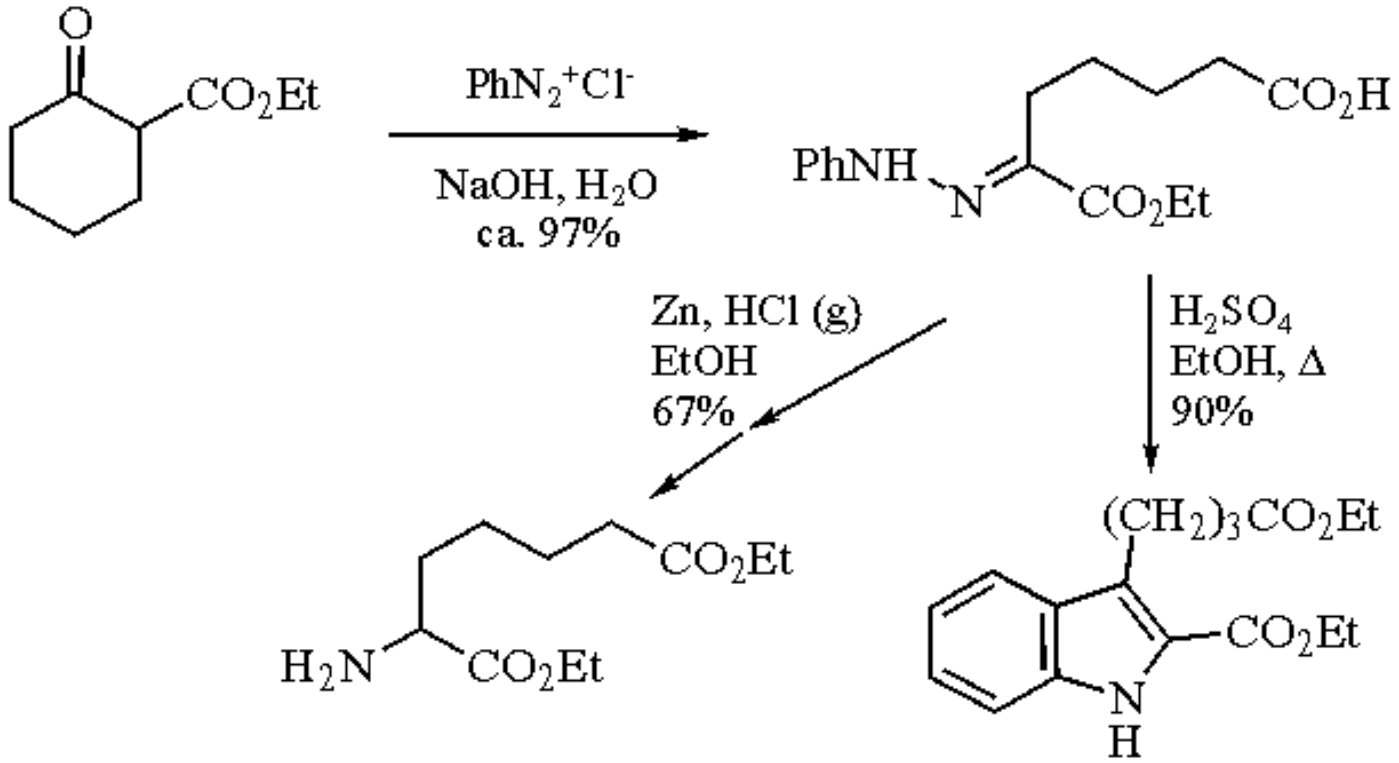

Functionalized Arenes from Aromatic Amines via Arenediazonium Salts.

The N_2^+ group of arenediazonium salts can be replaced by H and a variety of functional groups. These straightforward dediazoniation reactions can occur by heterolytic (S_N1), homolytic, and (for certain *o*-substituted ions) aryne mechanisms.[1d,7,28] Table 1 lists some of the more important transformations; further examples can be found elsewhere.[1c,1f,29] The copper(I)-mediated synthesis of ArCl and ArBr from arenediazonium halides (Sandmeyer reaction) has seen various modifications to improve the yield.[30] A particularly efficient approach is the direct conversion of arylamines into ArCl and ArBr with *t*-butyl nitrite and CuX_2 in anhydrous acetonitrile.[31]

Table 1 Arene Synthesis from ArN_2^+ salts. Replacement of N_2^+ by H and functional groups

Reagent(s)	Product
H_3PO_2; EtOH, D; HCHO, OH^-	ArH[1b,32]
CuX	ArX (X = Cl, Br)[33]
HI (KI, HCl)	ArI[34]
CuCN	ArCN[35]
H_2O, D; conc H_2SO_4, D; Cu_2O, $Cu(NO_3)_2$, H_2O	ArOH[36]
SO_2, $CuCl_2$; SO_2, HCl; SO_2, CuCl, HCl, HOAc	$ArSO_2Cl$[37]
NaN_3	ArN_3[38]

Biaryl Synthesis.

Biaryls can be obtained when a cold aqueous solution of an arenediazonium chloride is added to a mixture of aqueous NaOH (15-40%) or NaOAc and an aromatic solvent (Gomberg-Bachmann reaction[39]). Benzene and many substituted arenes as well as thiophene and pyridine have been used as coupling partners. There is good evidence that the reaction normally proceeds by a free radical chain mechanism, with aryl radicals as reactive species.[7,40] The yields rarely exceed 45%, and positional isomers are sometimes obtained from substituted arenes (eq 12).[41] Higher yields result when isolated arenediazonium salts (see ***Benzenediazonium Tetrafluoroborate***) are employed under PTC conditions. In view of the drawbacks mentioned, the Gomberg-Bachmann reaction must give way to more efficient and selective procedures for the synthesis of more highly substituted and functionalized biaryls.[42] Appropriately substituted arenediazonium salts (chlorides and sulfates) can undergo intramolecular aryl-aryl coupling to give phenanthrene derivatives (Pschorr cyclization[43]), often in acceptable yield. Fluorenes, fluorenones, and phenanthridones can be obtained analogously. The cyclization is most often copper-catalyzed (eq 13), but several other methods also exist.[42a,43] Copper-mediated cyclization of the isolated arenediazonium BF_4 salts in acetone is also in use.[44]

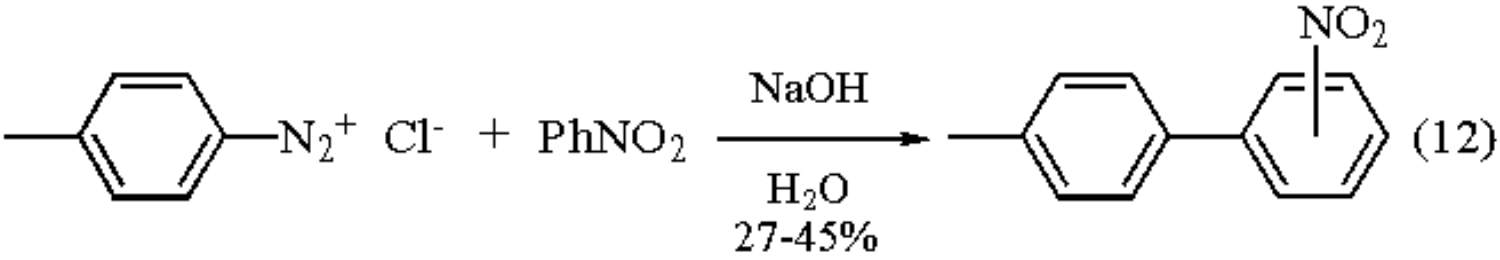

o-:m-:p-NO_2 = 66.0:6.6:27.4

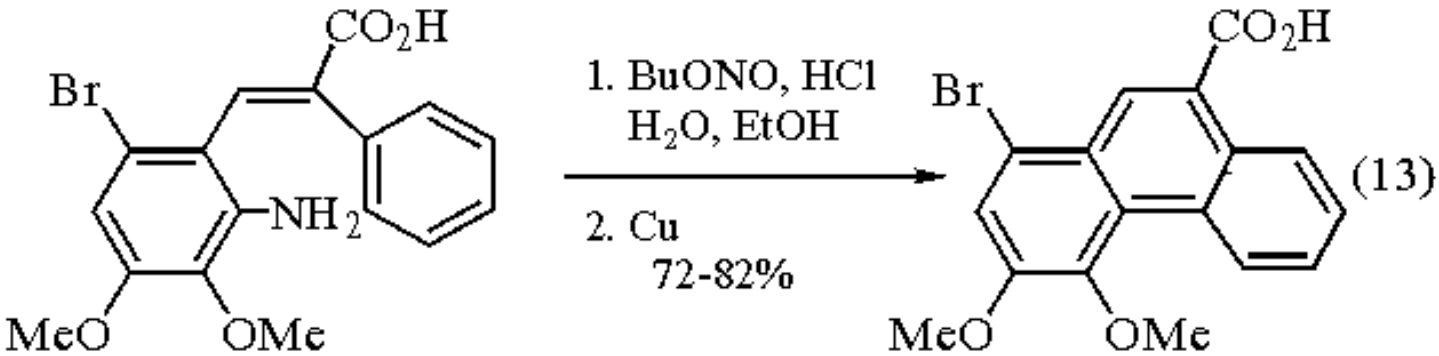

Arylation of Alkenes.

Arenediazonium chlorides react, in aqueous or H_2O-acetone solution and in the presence of Cu^I or Cu^{II} salts, with alkenes by dediazoniation and addition of Ar-Cl across the alkene bond (Meerwein arylation[1b,1f,45]). Alkenes activated by groups such as acyl, cyano, chloro, aryl, vinyl, and ethynyl are best suited for this reaction (eq 14)[45,46] which proceeds via aryl radicals.[45] Elimination of HCl may lead to a formal substitution product under the reaction conditions. Instead of using the preformed arenediazonium chloride, the Meerwein arylation product can be obtained directly and in improved yield from an arylamine by treatment with an alkyl nitrite and $CuCl_2$ in acetonitrile or acetone solutions that contain the alkene (eq 15).[47]

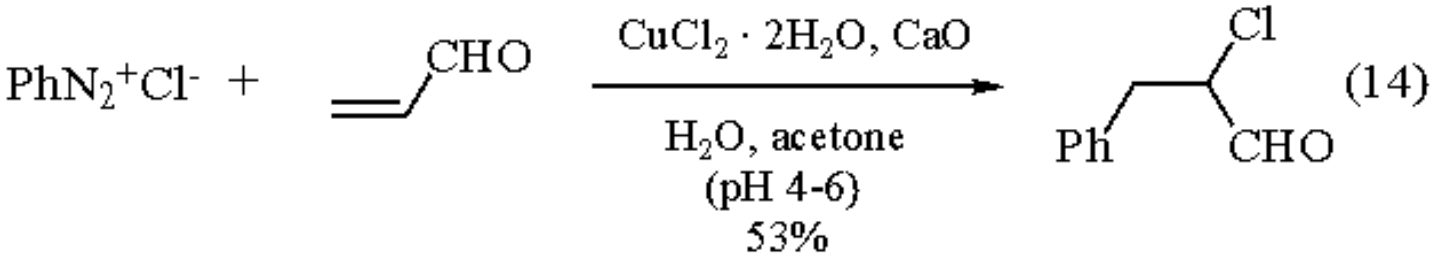

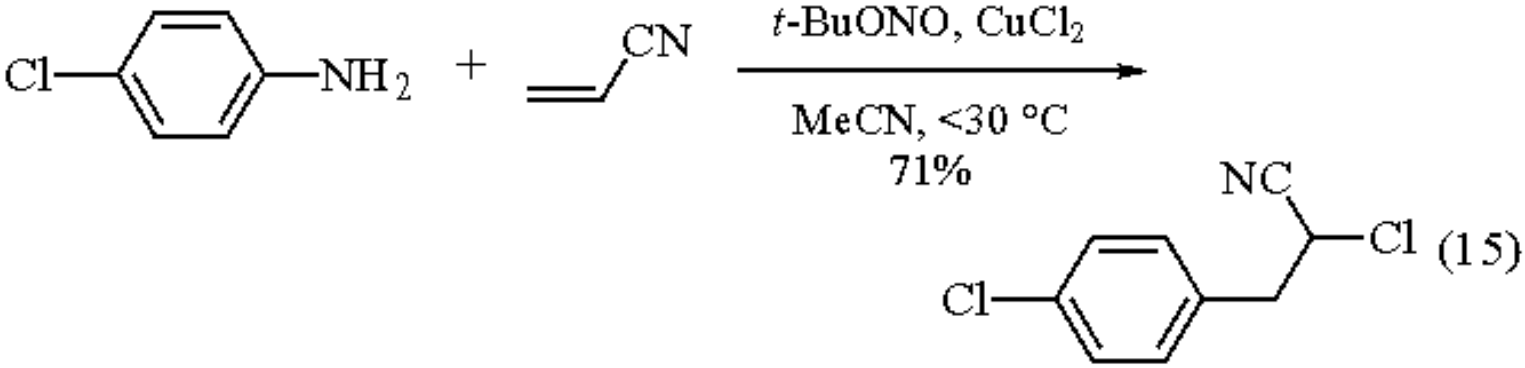

The reductive β-arylation of α,β-unsaturated carbonyl compounds and acrylonitrile can be realized in the presence of an excess of $TiCl_3$ in a solution of water and a water-miscible organic solvent. The best yields have been obtained with methyl vinyl ketone as the substrate (eq 16).[48] When steric and electronic effects divert the attacking aryl radical to the position α to the carbonyl, a different result is obtained.[49] For the Pd-mediated arylation of unactivated alkenes, see ***Benzenediazonium Tetrafluoroborate***. In contrast to the example in eq 16, simple carbonyl compounds do not undergo an analogous arylation reaction. However, *N*-benzylanilines result when an arenediazonium salt is decomposed by $TiCl_3$ in aqueous acid in the presence of an aldehyde and a primary aromatic amine.[50]

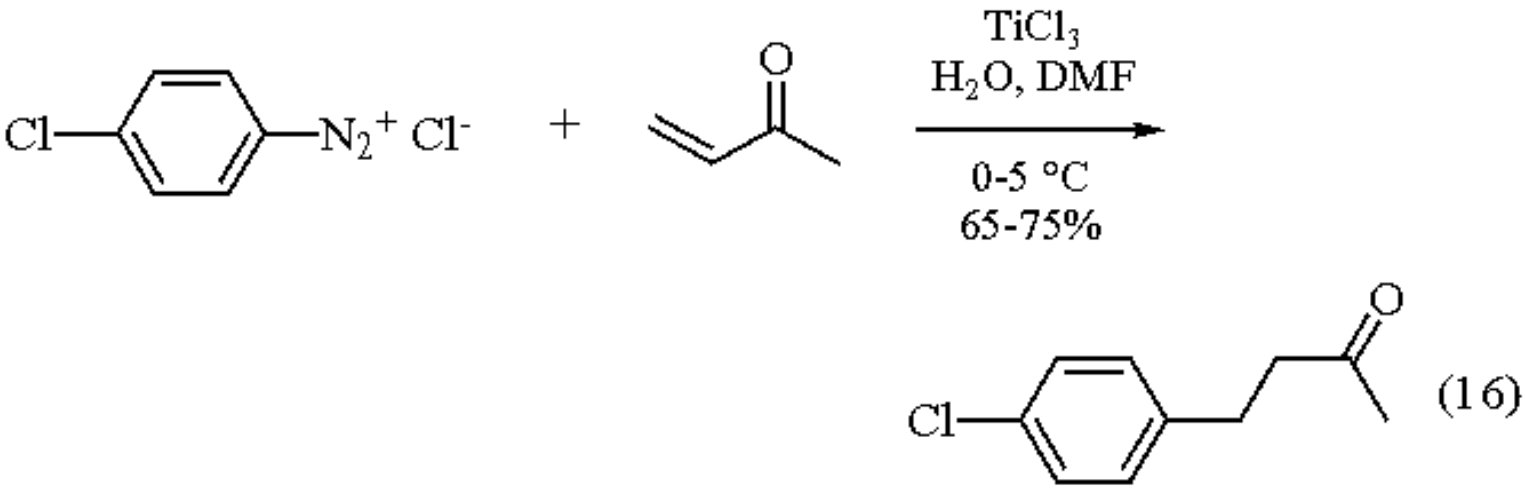

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Benzenediazonium Tetrafluoroborate[1]

[369-57-3] · $C_6H_5BF_4N_2$ · Benzenediazonium Tetrafluoroborate · (MW 191.92)

(much higher stability than the corresponding chlorides;[2] shock-insensitive; often used when pure, isolated arenediazonium salts are needed;[1] reagent for introducing aryl, arylazo, arylhydrazono, or amino groups; forms fluoroarenes upon heating;[3] building block for heterocycles)

Alternate Name: phenyldiazonium tetrafluoroborate.

Physical Data: colorless solid after recrystallization; turns pink at 80 °C; decomposes at 114-116 °C.

Solubility: fairly sol polar solvents such as acetonitrile, acetone, pyridine, DMF, DMSO, and HMPA with decomposition; slightly sol water; insol hydrocarbons and Et_2O; solubilized in nonpolar media by crown ethers.

Form Supplied in: 4-nitrobenzenediazonium tetrafluoroborate is widely available (nearly colorless solid). A large variety of arenediazonium BF_4 salts are readily prepared from aromatic amines (see below).

Preparative Methods: [1a,1d,3,4] The most commonly used procedures consist in diazotization of an aromatic amine ($ArNH_2$) with $NaNO_2$ in aqueous HCl or H_2SO_4 followed by precipitation of the salt with added $NaBF_4$ or fluoroboric acid.[5] Alternatively, the diazotization can be carried out directly in 40-50% aqueous HBF_4.[2c] Aromatic amines that do not dissolve in aqueous mineral acids can be reacted with $NO^+BF_4^-$ in an anhydrous organic solvent or in liquid SO_2.[6] This method can also be applied to *N*-(trimethylsilyl)anilines[7] and for the preparation of those salts that are not easily isolated from water.[8] An improved, high-yielding one-pot procedure[9] employs $ArNH_2$, *t*-BuONO, and $BF_3.Et_2O$ in an anhydrous organic solvent, typically CH_2Cl_2.

Handling, Storage, and Precautions: the dry parent salt can be stored for more than a month at rt or for a few years at -20 °C under N_2 in the dark, but decomposes when exposed to direct sunlight. Rapid recrystallization from warm water[2b] or from acetonitrile-Et_2O is possible without decomposition. Although arenediazonium tetrafluoroborates, in contrast to the chloride salts, are renowned in general for their enhanced thermal stability and shock-insensitivity, some care should nevertheless be taken. Some salts are known to decompose while drying, e.g. 3-methoxybenzenediazonium, 2-methylbenzenediazonium, and certain heteroarenediazonium tetrafluoroborates.[3,10] Avoid contact with metals.

General Reactivity Patterns.

Similar to the chloride salts, arenediazonium tetrafluoroborates can be transformed into covalent azo compounds by addition of a nucleophile and into various functionalized arenes by displacement of the N_2^+ group. While the chloride salts are typically prepared in situ in an acidic aqueous or ethanolic solution, the tetrafluoroborates are usually isolated and can be employed as pure compounds in the solvent of choice or in suspension. Their low solubility in nonpolar organic solvents may be a problem, but it can be overcome by phase-transfer techniques.[1c,11]

Addition to Unsaturated Compounds with Retention of N_2.

Diarylazo compounds (Ar^1-N=N-Ar^2) are obtained by coupling of arenediazonium salts with sufficiently electron-rich (hetero)aromatic substrates. The vast majority of these important azo coupling reactions have been carried out in the reaction media obtained by diazotization of aromatic amines with $NaNO_2$ in aqueous HCl or H_2SO_4 (see ***Benzenediazonium Chloride***). Comparisons of reactivity between in situ generated arenediazonium chlorides and tetrafluoroborates (used as isolated salts) are rare.[12] Thus 4-nitrobenzenediazonium chloride reacts only slowly with indole and its 1-, 2-, and 3-Me derivatives in aqueous neutral solution, whereas the corresponding BF_4 salt in H_2O-ethanol undergoes azo coupling rapidly and almost quantitatively (eq 1).[13a] Similarly, several arenediazonium tetrafluoroborates couple smoothly to 2-amino-4-(alkyl or aryl)-1,3-oxazoles in aqueous $NaHCO_3$ solution, whereas neutral or weakly acidic solutions of salts prepared by in situ diazotization give intractable product mixtures.[13b] In other cases, the use of pure, water-free $ArN_2^+BF_4^-$ salts in an organic solvent may be necessary or may simply give better yields. Examples include azo coupling of $PhN_2^+BF_4^-$ with 2-dimethylaminopyrazoles in MeCN[14] and of λ^5-phosphinines in MeOH-benzene (eq 2).[15] Uncommon substrates such as calixarene,[16] ditellurafulvene,[17] sesquifulvalene,[18] and coordinated cyclooctatetraene[19] are also subject to the reaction.

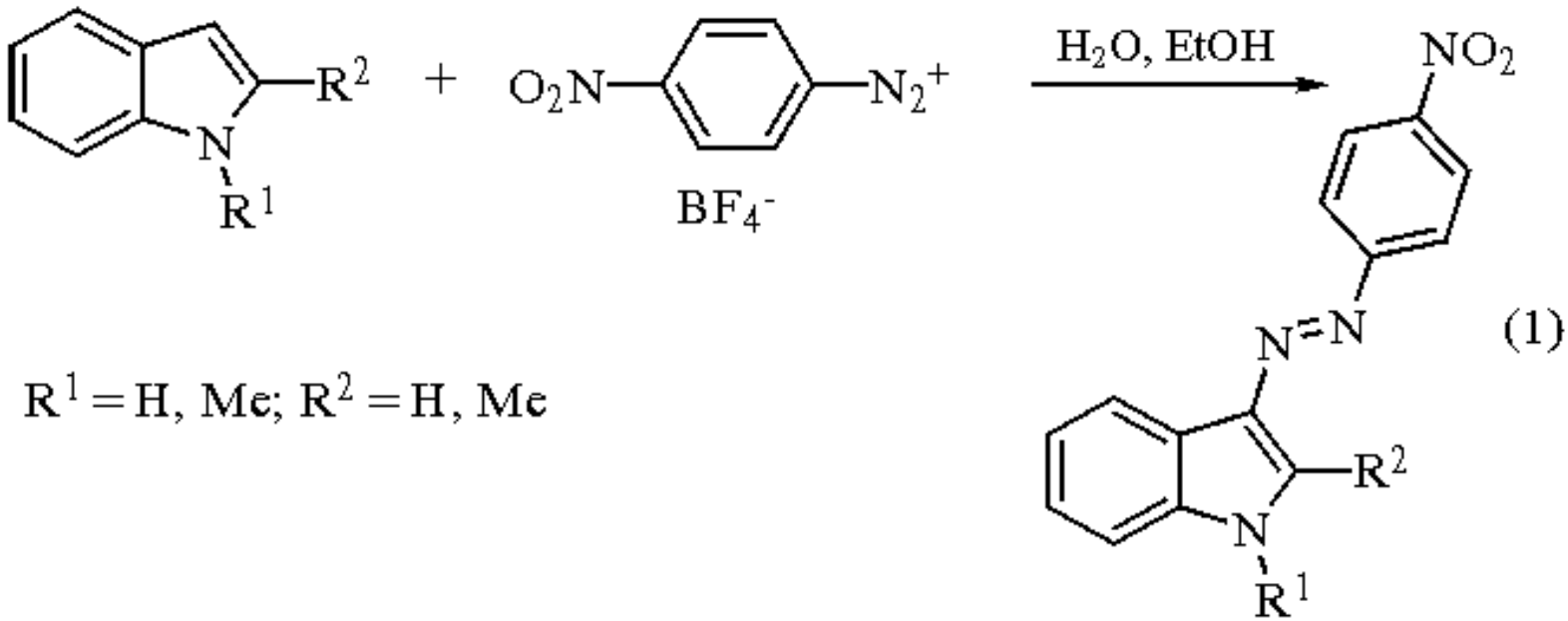

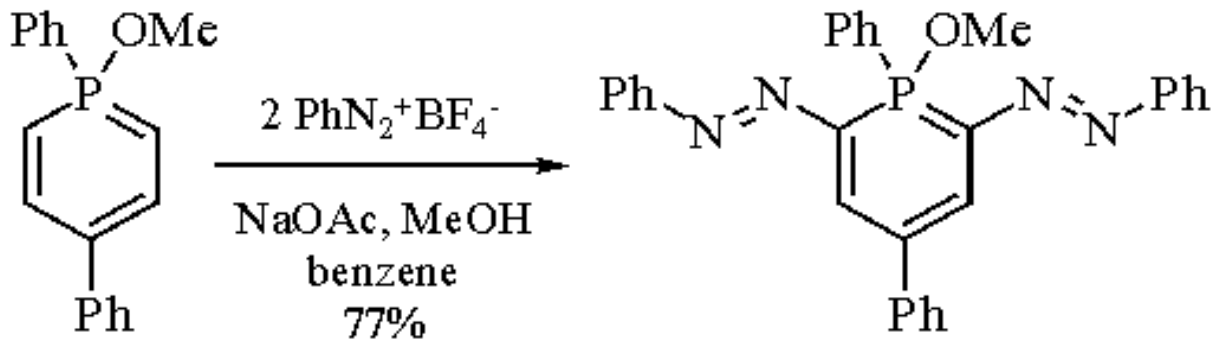

(2)

Azo coupling is promoted by various phase-transfer catalysts such as crown ethers,[20,21] NaOAc,[22] Me_4NCl,[23] and $Na[B(3,5\text{-di-}CF_3\text{-}C_6H_3)_4]$.[24]

Arenediazonium BF_4^- or PF_6^- salts undergo a facile, probably concerted, [2 + 4] cycloaddition to various acyclic methyl- or aryl-substituted 1,3-dienes, and 1,6-dihydropyridazines are isolated (eq 3).[25,26] In contrast, the products isolated with cyclopentadiene result from an initial azo coupling process.[27]

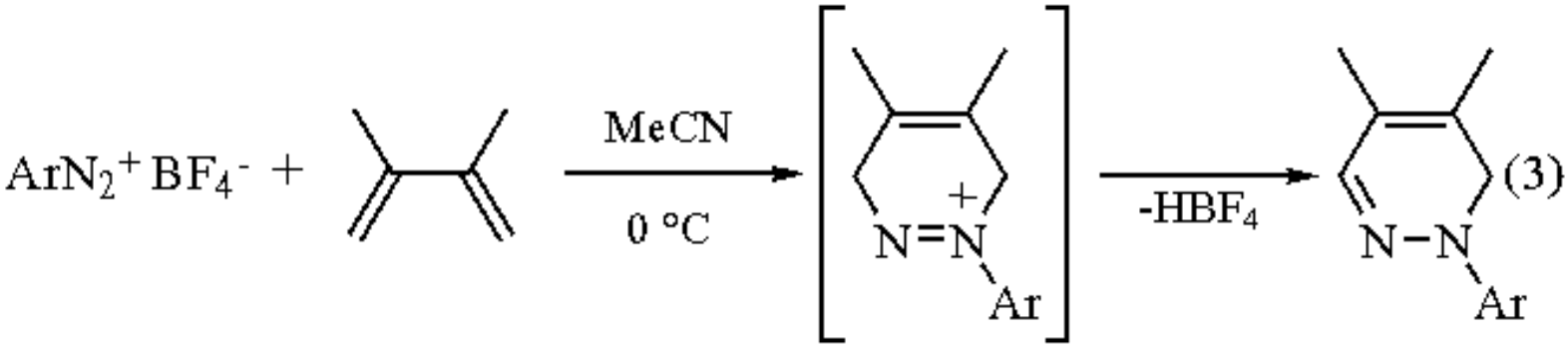

(3)

Azomethine ylides and other 1,3-dipoles also afford cycloadducts with diazonium salts.[28] Ene-type reactions with unsaturated lactones have also been reported.[29]

Addition to Unsaturated Compounds with Loss of N_2 (Introduction of Aryl Groups).

Arylation of alkenic compounds by diazonium salts, yielding saturated or unsaturated products, is known as the Meerwein reaction and is usually catalyzed by copper salts. The procedure can be efficiently applied to intramolecular cyclizations (eq 4).[30] In the presence of iodide ions the reaction takes place without copper salts.[31] Titanium(III) salts also facilitate the addition of alkenic compounds to give reduced products (eq 5).[32] Arylation of ferrocenyl-substituted alkynes and alkenes succeeds without such catalysts.[33]

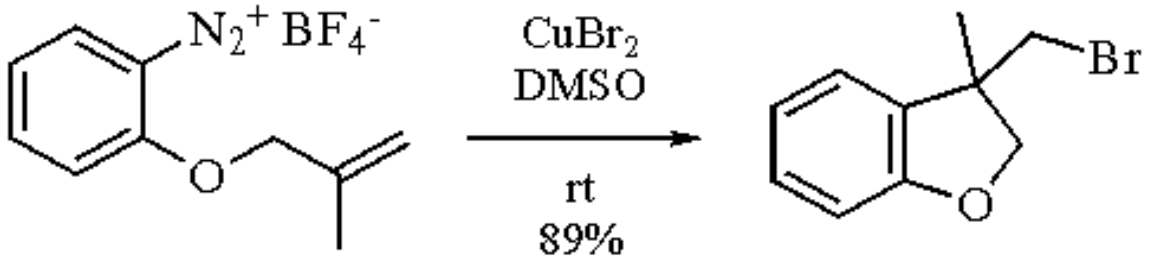

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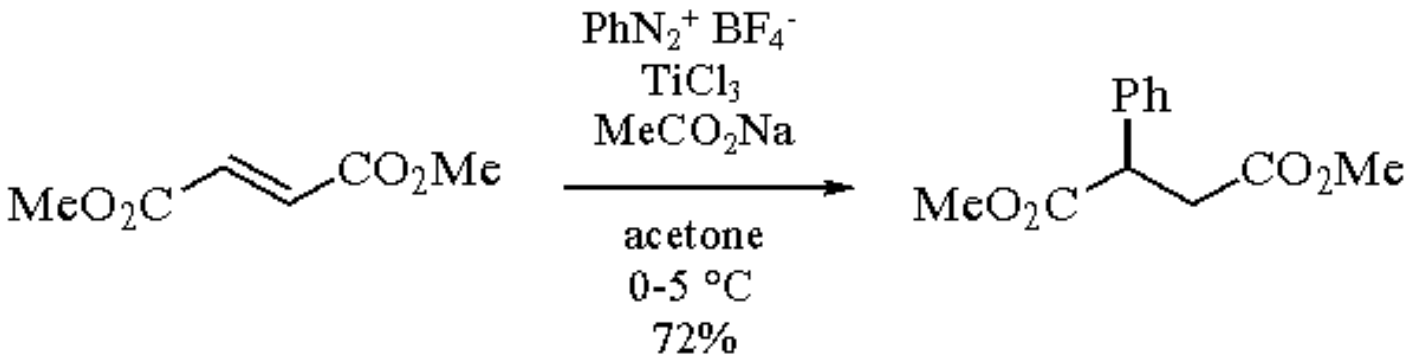

(5)

When the thermal decomposition of $ArN_2^+BF_4^-$ is conducted in the presence of pyridine, biaryls are formed in yields up to 30-40% by a radical mechanism, and no ArF is found.[34] Much higher yields of unsymmetrical biaryls can be obtained when arenediazonium BF_4^- or PF_6^- salts are allowed to react with an aromatic compound in the presence of KOAc and a phase-transfer catalyst[35] (eq 6). This procedure often gives better yields than the classical Gomberg-Bachmann-Hey reaction that employs arenediazonium chlorides in a two-phase system. The method also holds promise for the intramolecular version of aryl-aryl coupling (Pschorr cyclization).[11] Titanium(III) salts enhance *ortho* selectivity in the arylation of phenols.[36]

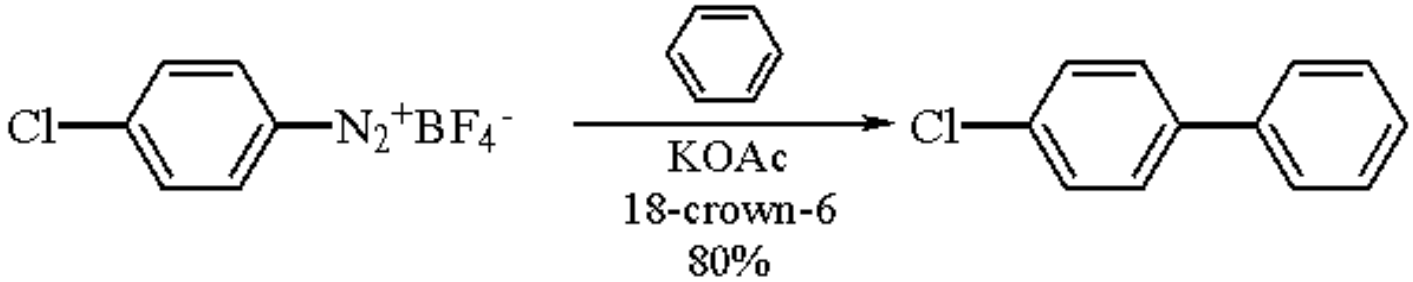

(6)

Diazonium salts add to nitriles with loss of dinitrogen to form *N*-arylnitrilium ions which further react in situ with nucleophiles or aromatics. Hence, intramolecular cyclizations take place starting from *ortho*-substituted diazonium salts (eqs 7 and 8); substituents used are azido,[37] carboxyl,[38] alkylthio,[39] hydroxymethyl,[40] and aryl.[41] In this connection, intermolecular addition of carboxylates to nitrilium ions gives unsymmetrical *N*-arylimides.[42] In place of nitriles, isocyanides also undergo intramolecular cyclizations with *ortho*-substituted diazonium salts.[43] Reactions with carbon monoxide under high pressure[44] or with ***Tetracarbonylnickel***[45] result in the formation of carboxylic acid derivatives.

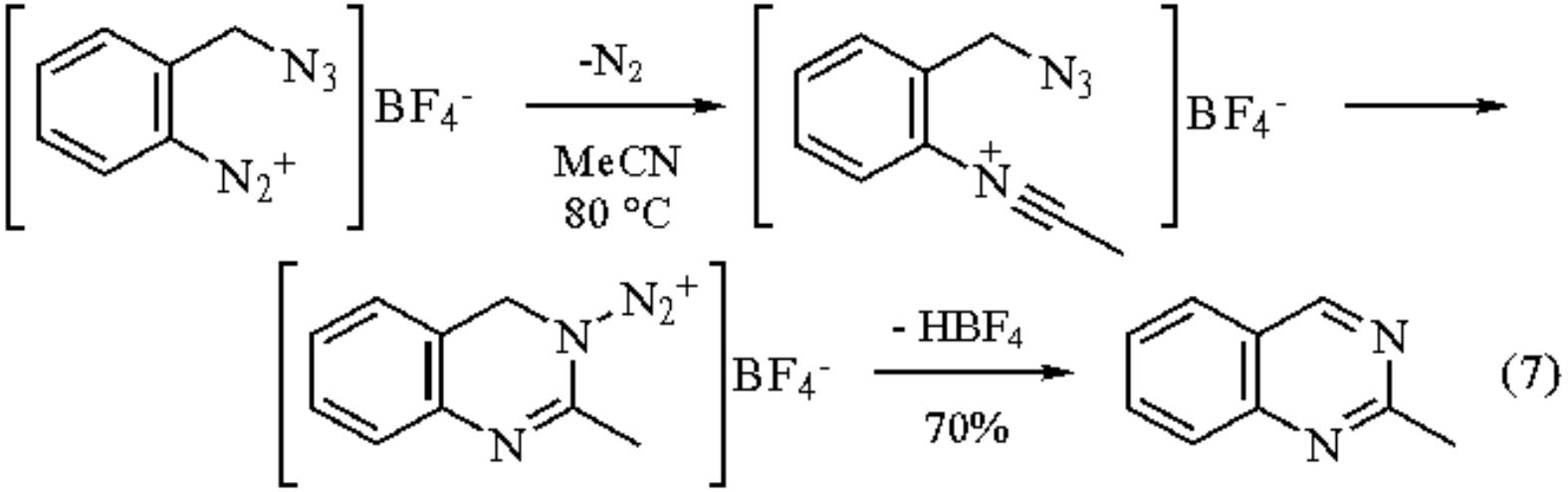

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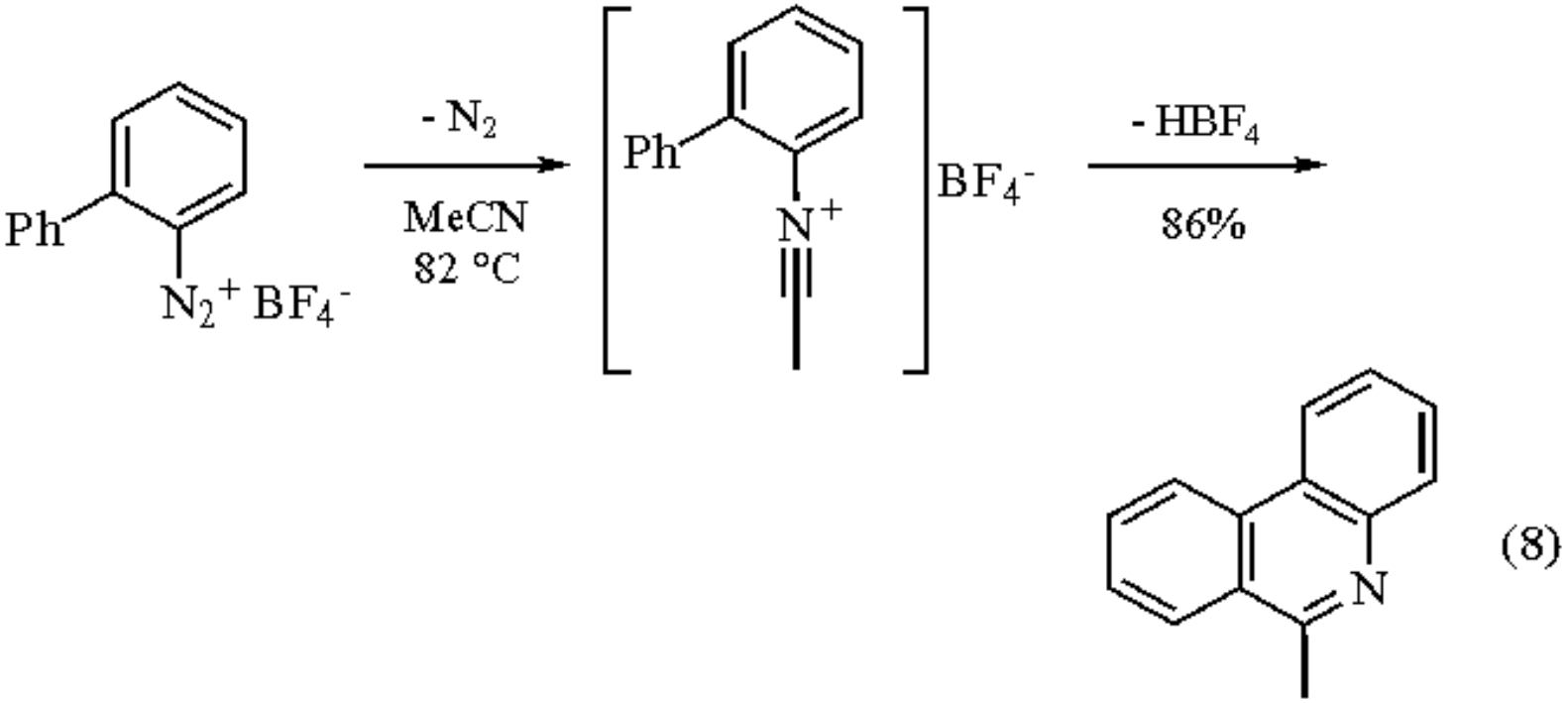

(8)

Coupling with Nucleophiles with Retention of N_2 (Introduction of Azo or Hydrazono Groups).

The coupling of diazonium salts with active methylene compounds is known as the Japp-Klingemann reaction, a process applicable to nucleoside synthesis.[46] On the other hand, α-amination of simple esters is achieved through the hydrogenation of azo or hydrazono esters formed from ketene silyl acetals (eq 9).[47] The reaction with enamines likewise leads to α-iminio hydrazones which readily rearrange to heterocycles (eq 10).[48] The nucleophilic addition of ***p-Tolylsulfonylmethyl Isocyanide*** also results in cyclization, affording triazoles.[49] In addition, lithium enolates of α-substituted ketones,[50] Grignard reagents,[50,51] organozinc reagents,[52,53] and allylsilanes[54] produce corresponding azo or hydrazono compounds. ***Potassium Cyanide*** in the presence of ***18-Crown-6*** yields diazo cyanides that act as efficient dienophiles in the Diels-Alder reaction (eq 11).[55]

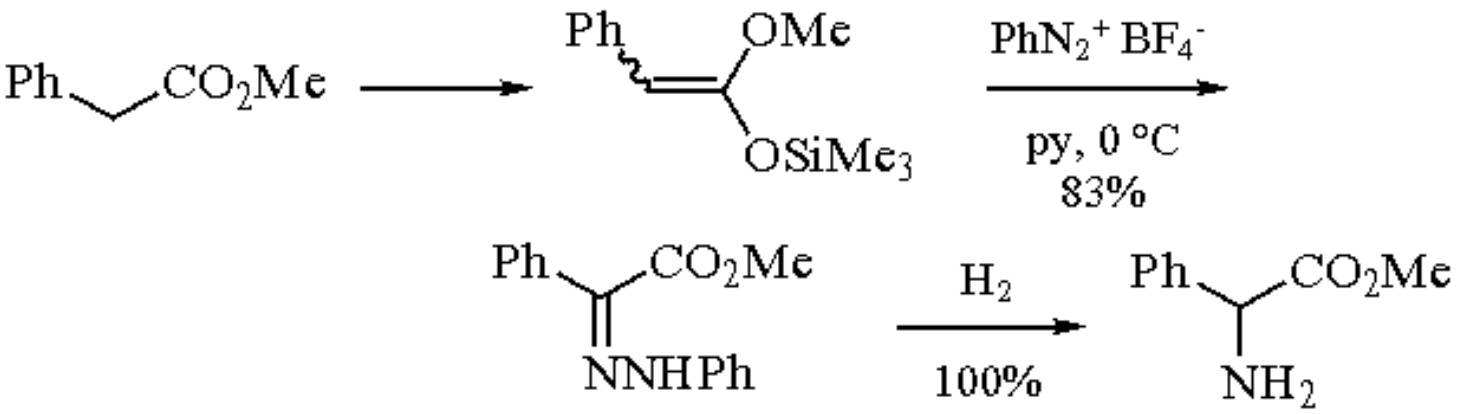
Ph
CO2Me
Ph
OMe
OSiMe3
PhN2+ BF4-
py, 0 °C
83%
Ph
CO2Me
NNHPh
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Ph
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(9)

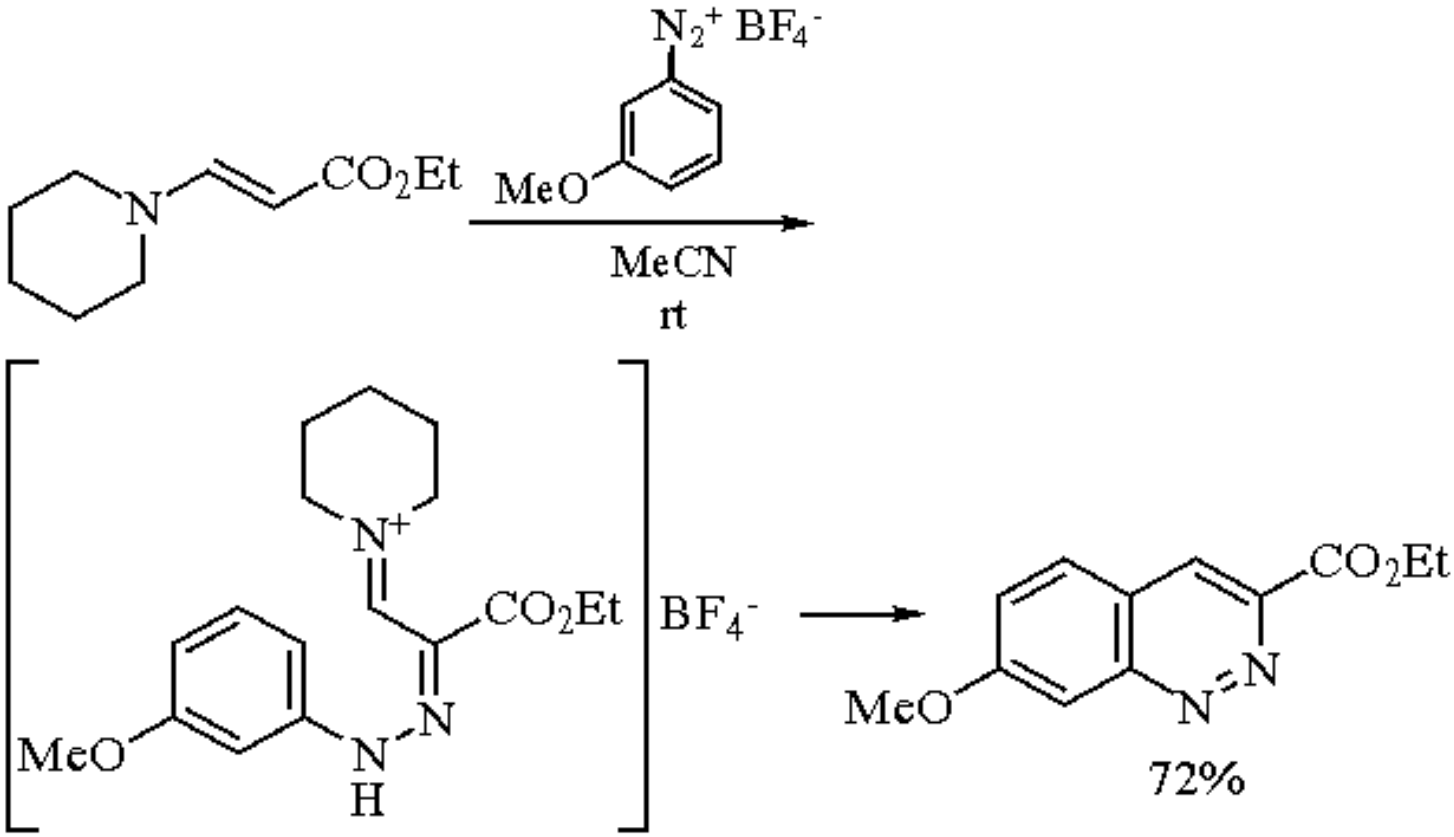
N2+ BF4-
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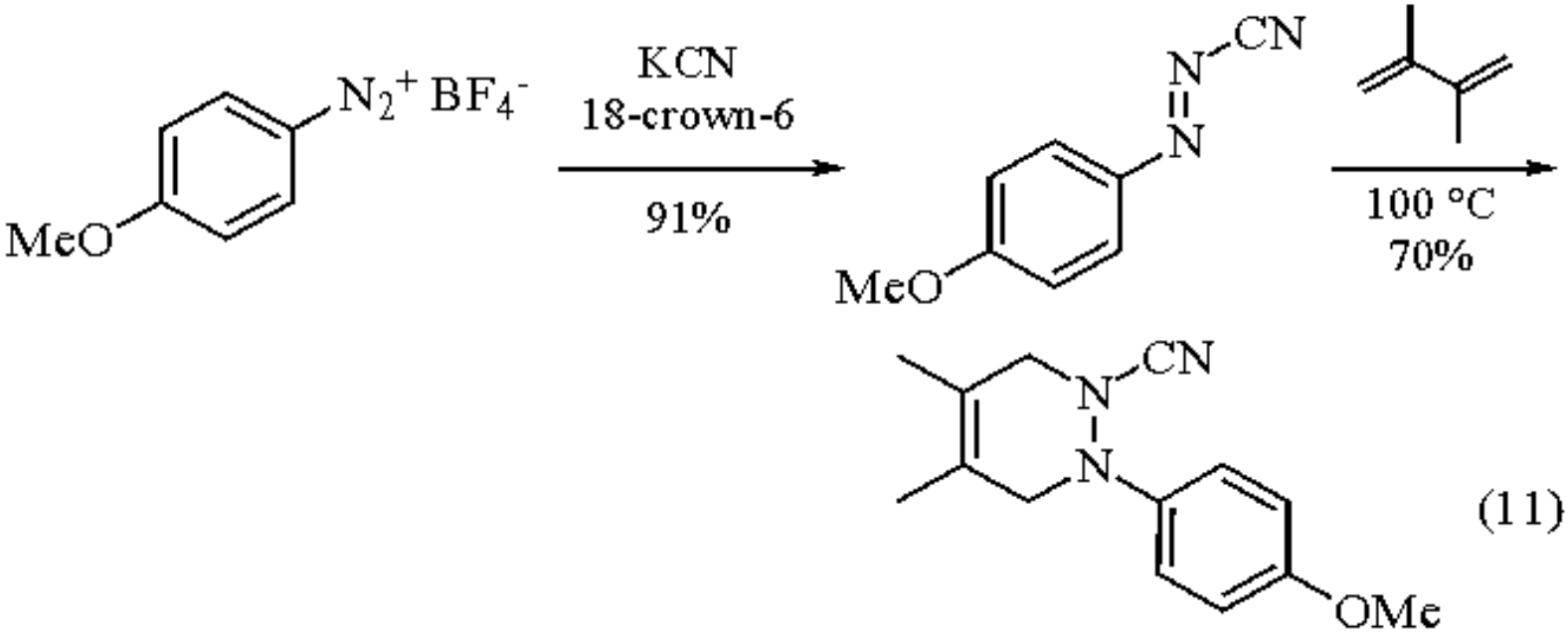

(11)

Amines also combine with the terminal nitrogen of diazonium salts to form triazenes (eq 12),[56] the utility of which is summarized in a review.[57] Couplings with ***Difluoramine*** or isopropyl fluorocarbamate yield azides through triazenes as intermediates.[58] Reaction with hydrazonomethanesulfonates or guanidine derivatives give five-membered azacycles.[59] The addition of sodium sulfinates produces arylazo sulfones.[60]

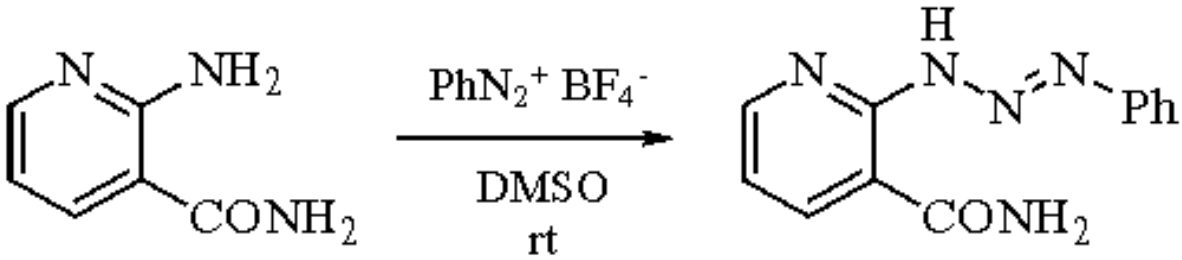

(12)

Coupling with Nucleophiles with Loss of N_2 (Introduction of Aryl Groups).

Arenediazonium salts act as aryl cations toward various nucleophiles. Silyl enol ethers derived from aryl ketones react with diazonium tetrafluoroborates in pyridine to afford α-aryl ketones (eq 13).[61]

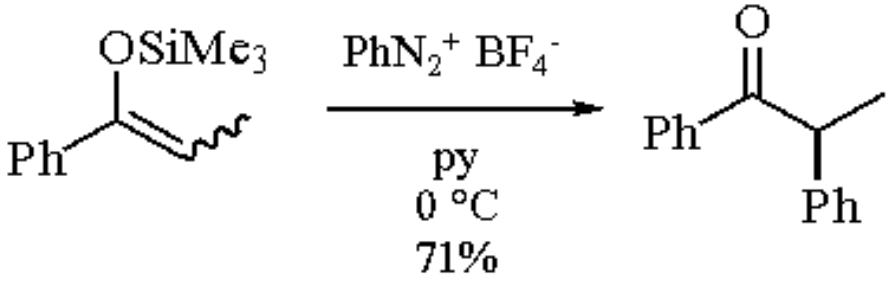

(13)

Solvolysis of diazonium tetrafluoroborates in ***Trifluoromethanesulfonic Acid*** results in the formation of aryl triflates

(eq 14).[62] Similarly, decomposition in methanol[63] or ***Trifluoroacetic Acid***[64] leads to the corresponding ethers or esters; the latter is utilized for phenol synthesis. ***Pyridine N-Oxide*** reacts at the oxygen atom to give *N*-(aryloxy)pyridinium tetrafluoroborates.[65] Phenyl ethers and esters can be prepared via the reaction of trimethylsilyl ethers and esters with PhN_2BF_4.[66]

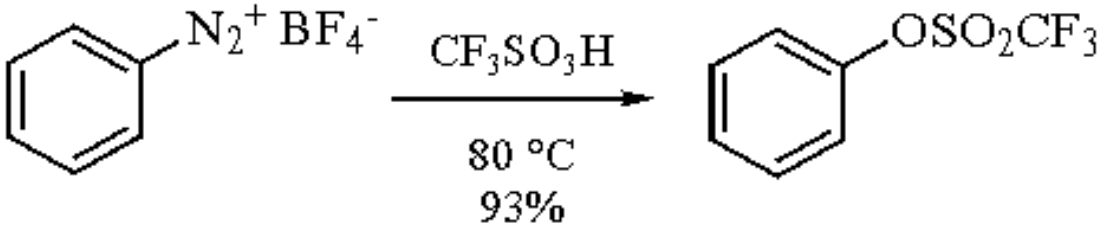

(14)

Unsymmetrical diaryl sulfides are obtained from diazonium fluoroborates and sodium aryl thiolates in DMSO (eq 15).[67] Similarly, aryl thiolesters are formed using thiocarboxylates.[68] Diaryl selenides and diaryl tellurides can be prepared by the reaction of arenediazonium salts with ***Sodium Selenide*** and ***Sodium Telluride*** (eq 16).[69]

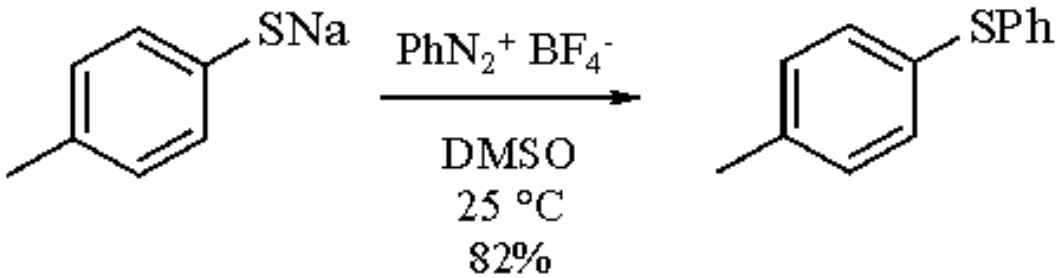

(15)

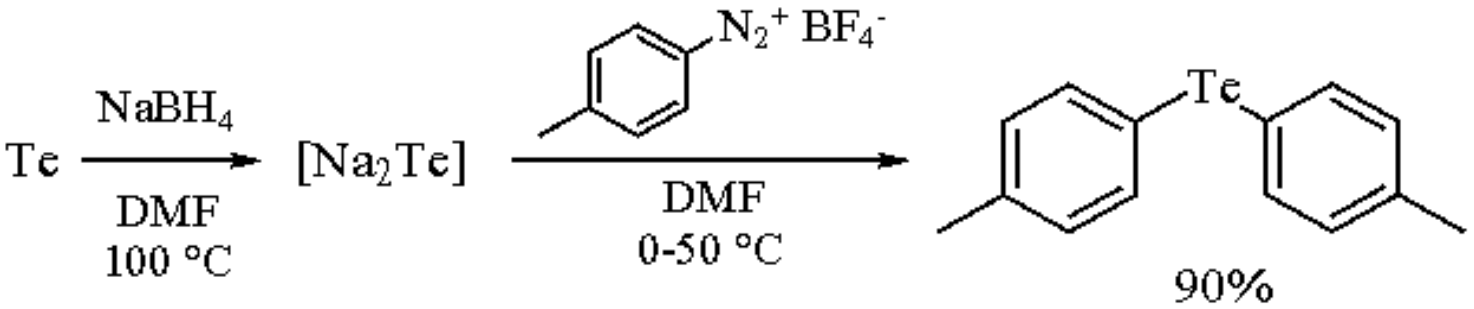

(16)

Controlled thermal decomposition of dry arenediazonium tetrafluoroborates affords fluoroarenes in normally good to high yield (Balz-Schiemann reaction[3]) (eq 17). Typically, the reaction is carried out with the solid salt,[5] but decomposition in suspension or in solution[2b,3,70] has also been reported. Nitroarenediazonium BF_4^- salts are usually mixed with sand, NaF, or $BaSO_4$ to avoid violent decomposition.[3] The BF_3 etherate complex may be useful for an efficient transformation.[71]

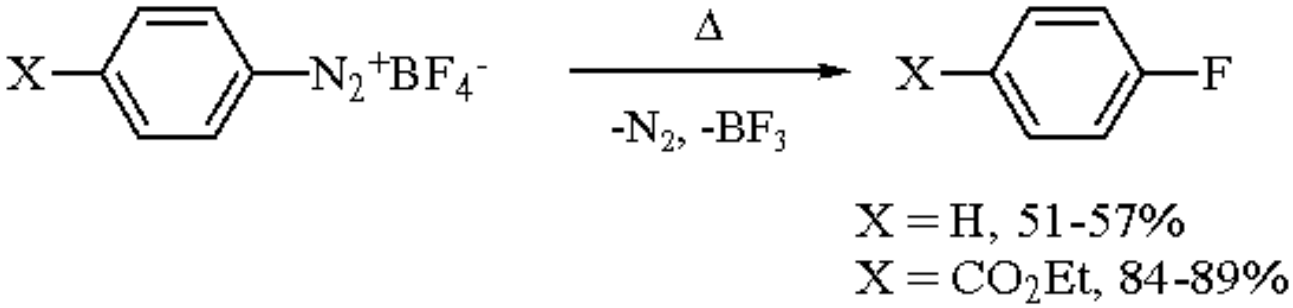

(17)

The formation of fluoroarenes proceeds via an aryl cation intermediate that reacts with the BF_4^- ion in the ion pair,[72] and is accelerated by photolysis.[73] In some cases, the use of hexafluoroantimonates or hexafluorophosphates affords better yields.[74] On the other hand, aryl iodides are obtained via the reaction with ***Potassium Iodide/Iodine*** in DMSO.[75] The reactions with trimethylsilyl halides or ***Azidotrimethylsilane*** yield aryl halides or aryl azides, respectively (eq 18).[76] Organic halides such as $BrCCl_3$ and ***Iodomethane*** also act as halogen sources.[77]

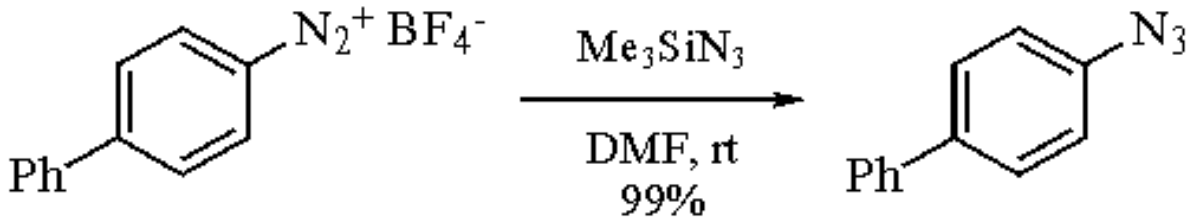

(18)

Diazonium fluoroborates transform iminophosphoranes into phosphonium salts.[78] Similarly, sulfones are converted to sulfoxonium salts which can be reduced in situ to sulfoxides with ***Sodium Borohydride***.[79]

Nucleophilic substitution of diazonium salts in the presence of Cu^I salts is known as the Sandmeyer reaction. Nitro-dediazoniation of diazonium tetrafluoroborate with ***Sodium Nitrite*** in the presence of copper powder occurs smoothly (eq 19).[2c] An important access to arenephosphonic acids is provided by the Cu^I-catalyzed reaction of $ArN_2^+BF_4^-$ salts with ***Phosphorus(III) Chloride*** in an organic solvent, followed by hydrolysis (eq 20).[80] The method tolerates a wide range of substituents.[81] The thermal decomposition of arenediazonium salts in dilute aqueous solution in the presence of Cu_2O and a large excess of $Cu(NO_3)_2$ affords phenols in good yield; notably, this method does not require a strongly acidic medium.[82]

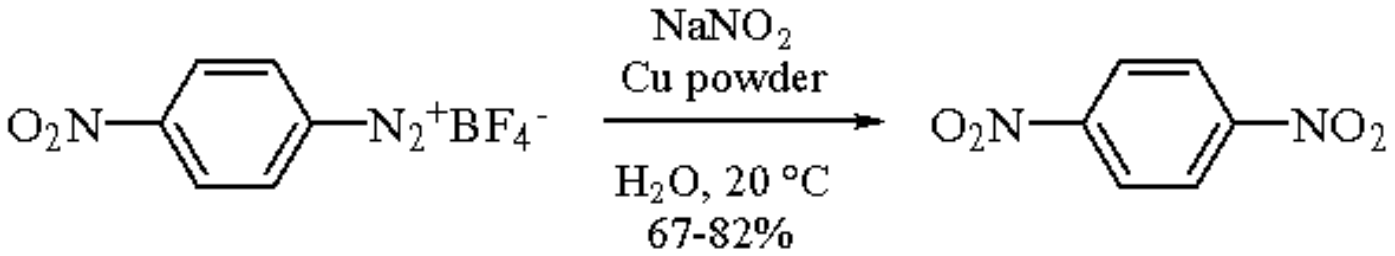

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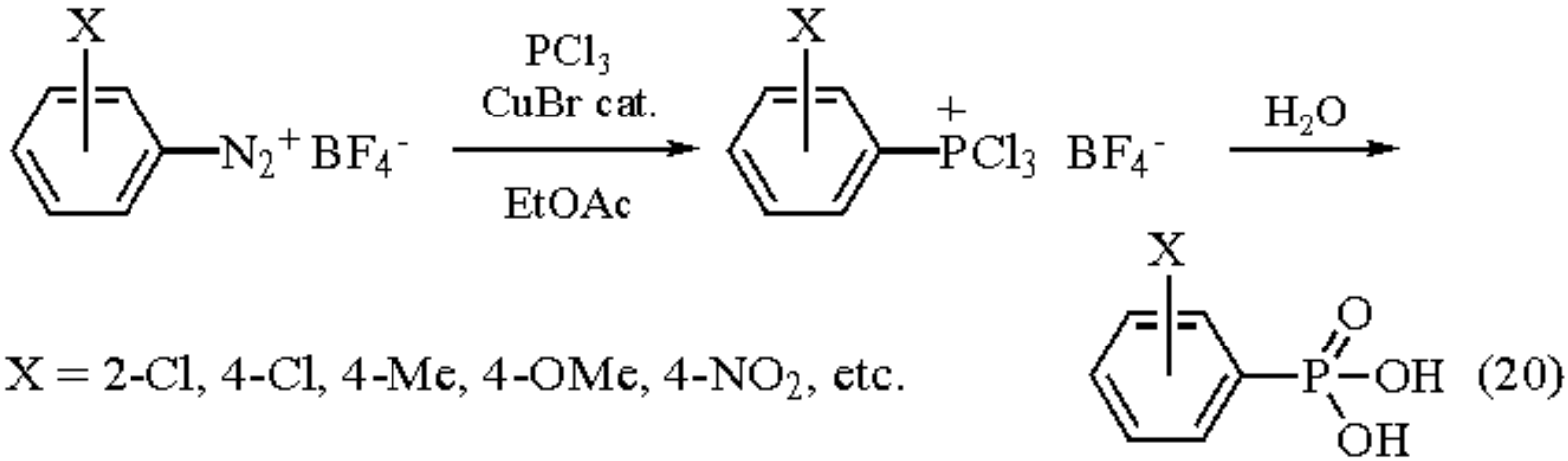

Palladium-Catalyzed Reactions.

Palladium-catalyzed reactions of diazonium salts proceed with nitrogen evolution and provide a mild method to introduce aryl groups.

While the classical, copper salt-catalyzed arylation of alkenes (Meerwein arylation) requires alkene activation by an electron-withdrawing substituent[83] (see ***Benzenediazonium Chloride***), the Pd-catalyzed modification succeeds well not only with acrylic aldehydes and esters, but also with styrene, ethylene, and other non-activated acyclic and cyclic alkenes (eqs 21 and 22).[84] Coupling reactions with isolated $PhN_2^+BF_4^-$ in general give much better yields than with the in situ generated salt $PhN_2^+X^-$ (X = Cl or OAc). In an analogous reaction, silyl-, germyl-, or stannyl-substituted alkenes result in the loss of heteroatom substituents (eq 23).[85-87]

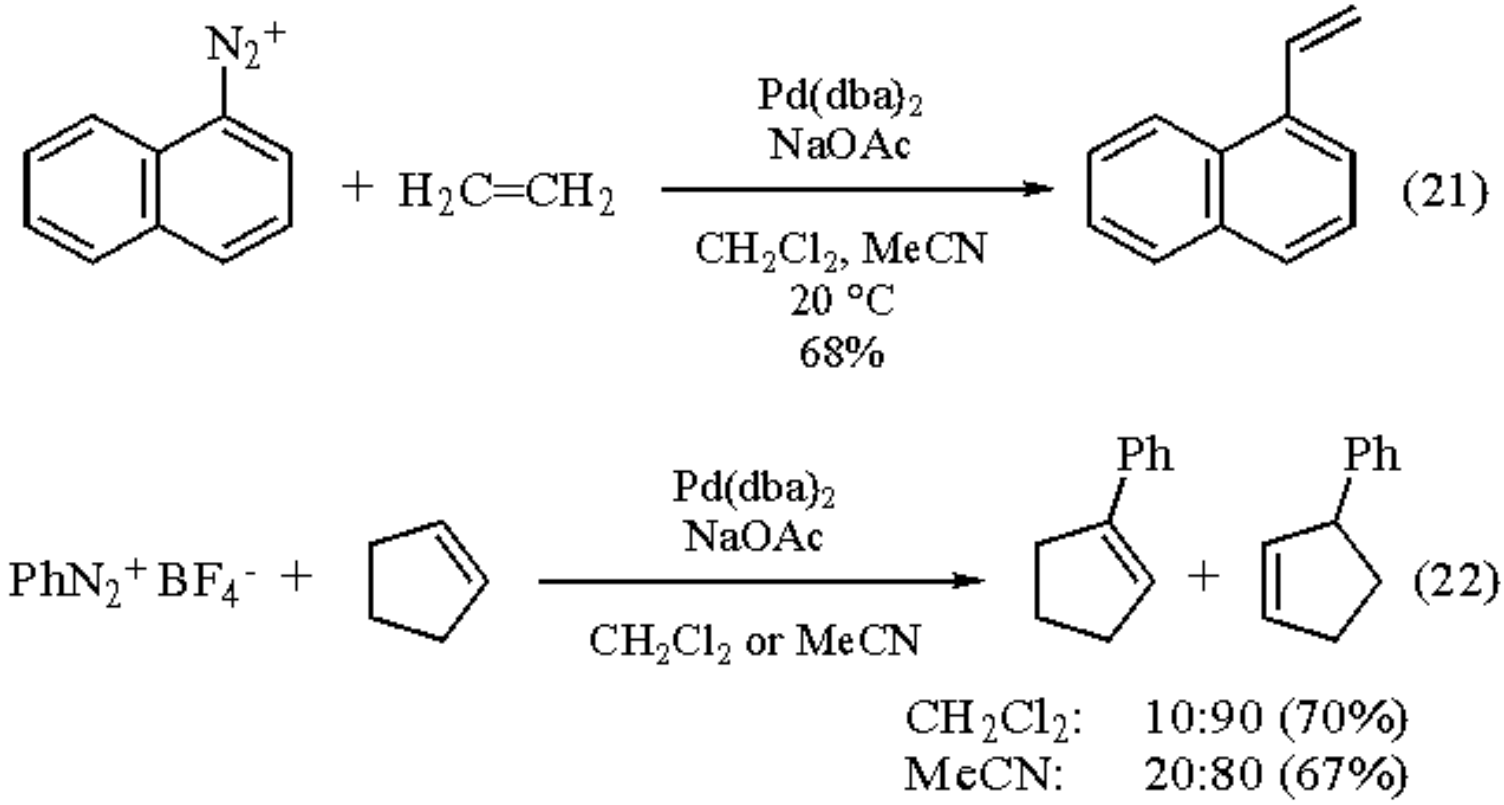

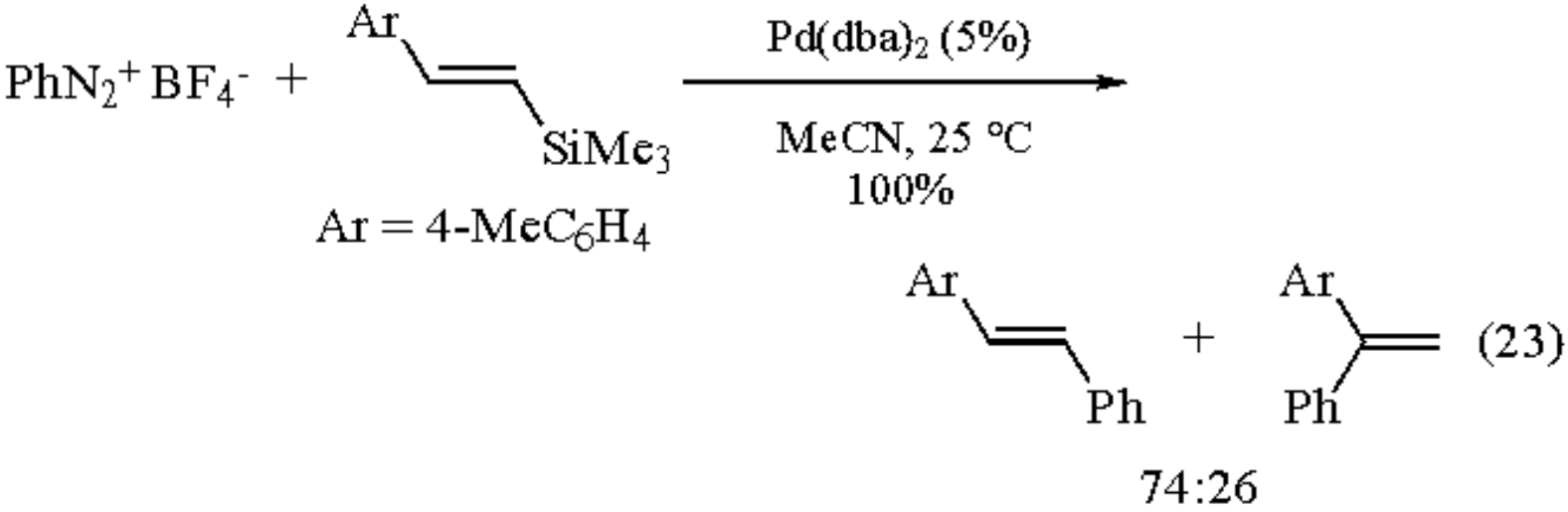

The palladium-catalyzed carbonylation of an arenediazonium tetrafluoroborate with CO in the presence of Et_3SnH or a poly(methylhydrosiloxane) affords substituted benzaldehydes (eq 24).[88] Formation of ArH is sometimes a minor side-reaction, but predominates (81%) in the 2-nitro case. In related Pd-catalyzed reactions, diaryl ketones (eq 25),[89] aryl alkyl ketones,[89] substituted benzoic acids,[90] and mixed arylalkylcarboxylic anhydrides (eq 26)[91] can be obtained. Thermal disproportionation of the latter can be used to prepare homo arenecarboxylic anhydrides.[91]

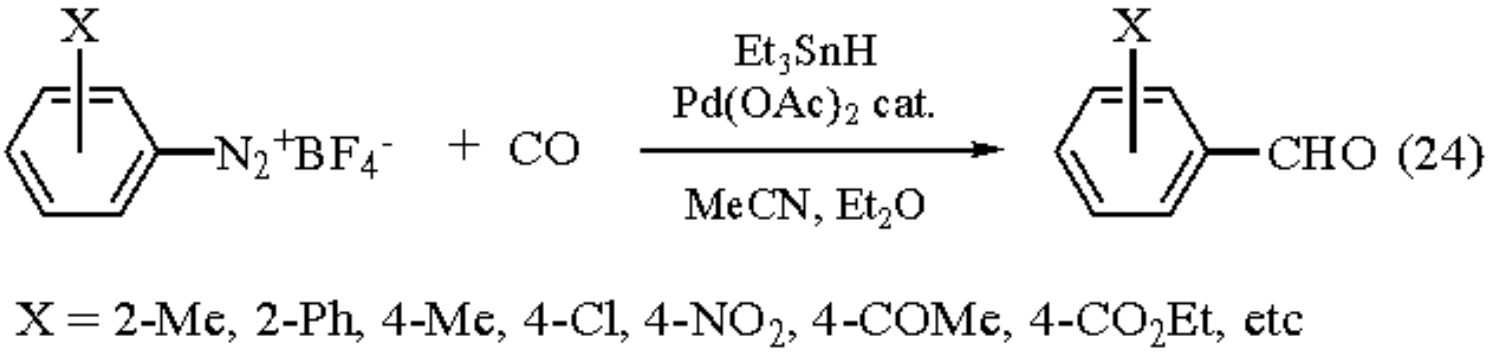

X = 2-Me, 2-Ph, 4-Me, 4-Cl, 4-NO_2, 4-COMe, 4-CO_2Et, etc

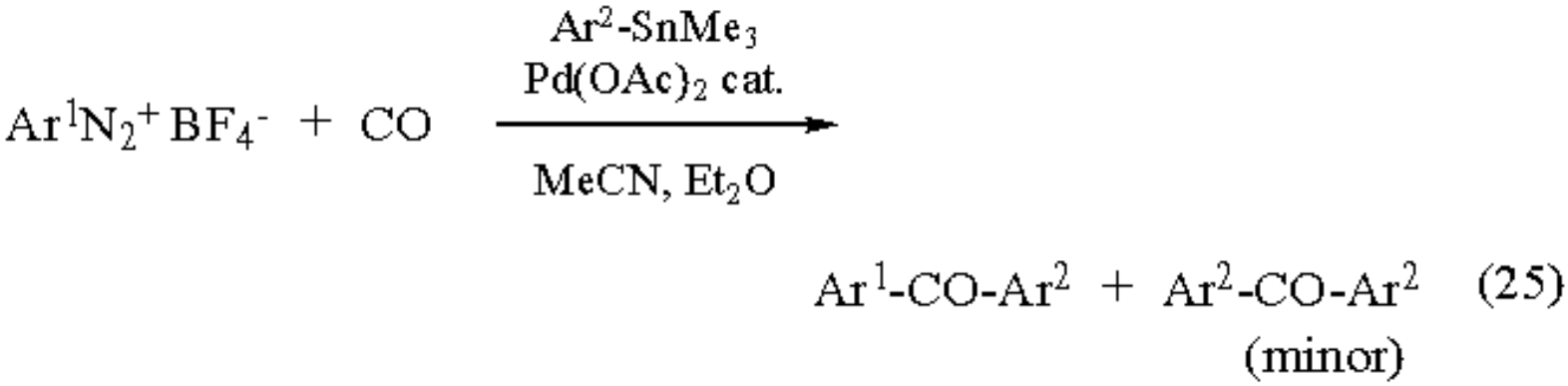

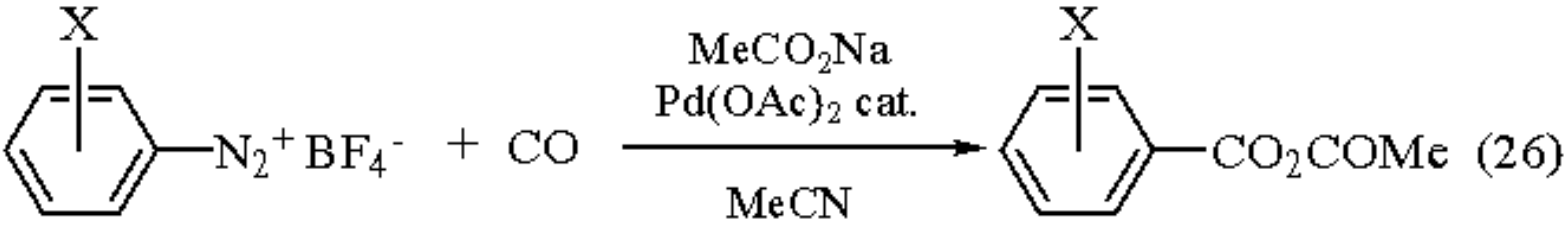

X = 4-I (68%), 3-NO_2 (49%), 4-NO_2 (65%), etc.

Reduction to Arenes.

The removal of an NH_2 function by reductive dediazoniation is an important synthetic operation on the aromatic nucleus. As with other benzenediazonium salts, a number of methods exist for the BF_4^- salts, but the radical-chain reaction with H_3PO_2 is a particularly good method (eq 27).[92] Hydro-dediazoniation with $NaBH_4$ in methanol[93] is also quite convenient, but does not always occur cleanly.[94] Other effective and easily available reducing agents are ***Thiophenol***,[95] hydrosilanes,[96] and hydrostannanes.[96] Decomposition in HMPA[97] or in the presence of crown ethers[98] also gives good results. Catalysis by rhodium phosphine complexes in DMF does not seem very effective.[99]

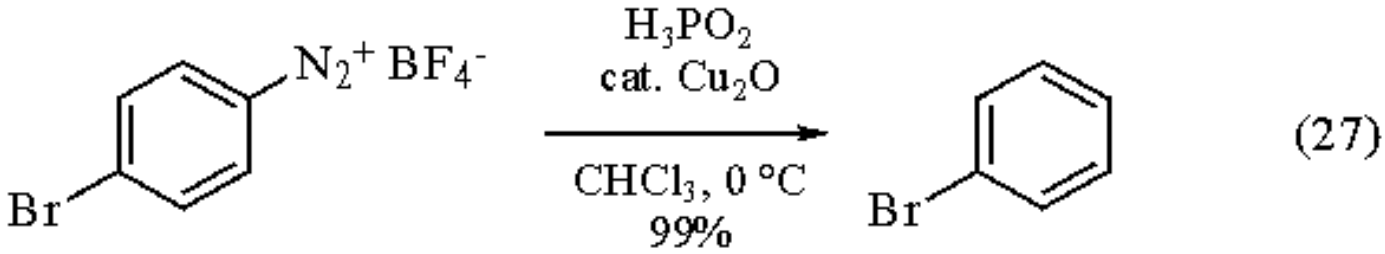

Benzeneselenol is a unique reagent for producing arylhydrazines from diazonium fluoroborates (eq 28); the reaction is applicable to the synthesis of indazolone from *ortho*-carbamoyl diazonium salts.[100]

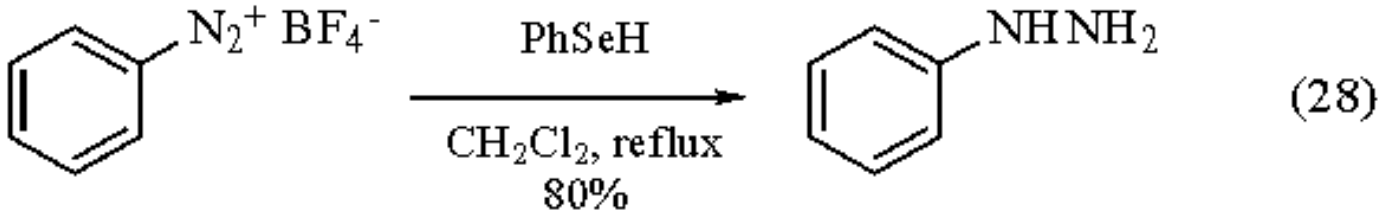

Radical Initiation.

Diazonium fluoroborates can be used as radical initiators. Applied examples are alkylation of heteroaromatics with alkyl iodides[101] and polymerization of vinylic compounds.[102]

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Benzene-1,2-dithiol

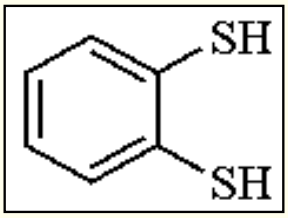

[17534-15-5] · $C_6H_6S_2$ · Benzene-1,2-dithiol · (MW 142.24)

(starting material for the preparation of several organosulfur reagents)

Physical Data: mp 27-28 °C; bp 119-120 °C/17 mmHg; *d* 1.236 g cm^{-3}.

Form Supplied in: deliquescent, bad-smelling solid; commercially available. Aged samples may be contaminated by polymeric disulfides.

Preparative Methods: can be prepared by a number of methods.[1,2]

Handling, Storage, and Precautions: to be kept refrigerated under an inert gas.

The thiol groups of benzene-1,2-dithiol react with a number of reagents to afford compounds of good synthetic potential.

Acyclic Reagents.

The *S*,*S*-dimethyl derivative of the title reagent has been oxidized to the corresponding chiral bis-sulfoxide, which can be viewed as a bifunctional aryl methyl sulfoxide (eq 1).[3]

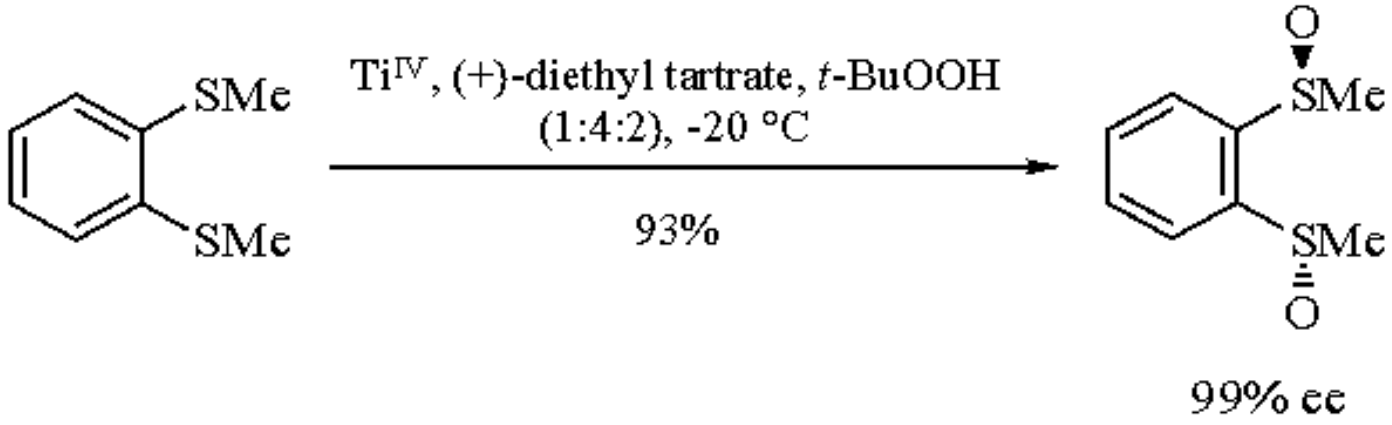

(1)

Five-Membered Rings.

The carbon atom between the two sulfur atoms in benzodithioles can be activated as a carbocation (**1**), carbene (**2**), or carbanion (**3**).

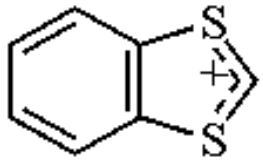

(1)

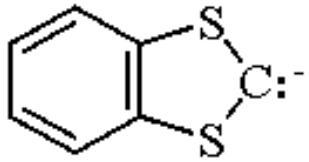

(3)

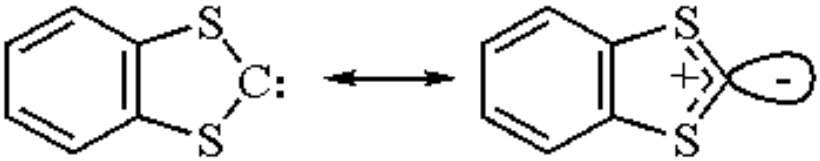

(2)

1,3-Benzodithiolium salts (**1**)[4] are useful for numerous functional group transformations. For example, 1,3-benzodithiolium tetrafluoroborate reacts rapidly with ***Trimethyl Phosphite*** in the presence of ***Sodium Iodide*** to give 2-(*O*,*O*-dimethylphosphonyl)-1,3-benzodithiole. This reagent can be used in Horner-Emmons reactions with various carbonyl compounds for the preparation of benzo-1,4-dithiafulvenes (eq 2).[5a] The double bond of the latter can be hydrogenated under mild conditions and the benzenedithiol eventually removed to generate the aldehyde.[5b] The sequence corresponds to a one-carbon homologation of carbonyl compounds. Other applications include the preparation of 1*D*-aldehydes,[5c] the reduction of sugars,[5d] and the transformation of many carboxylic acid derivatives (eq 3).[5e] 2-Phenyl-1,3-benzodithiolium trifluoromethanesulfonate can be used to convert alcohols into benzyl ethers and benzoates under mild conditions (eq 4).[6]

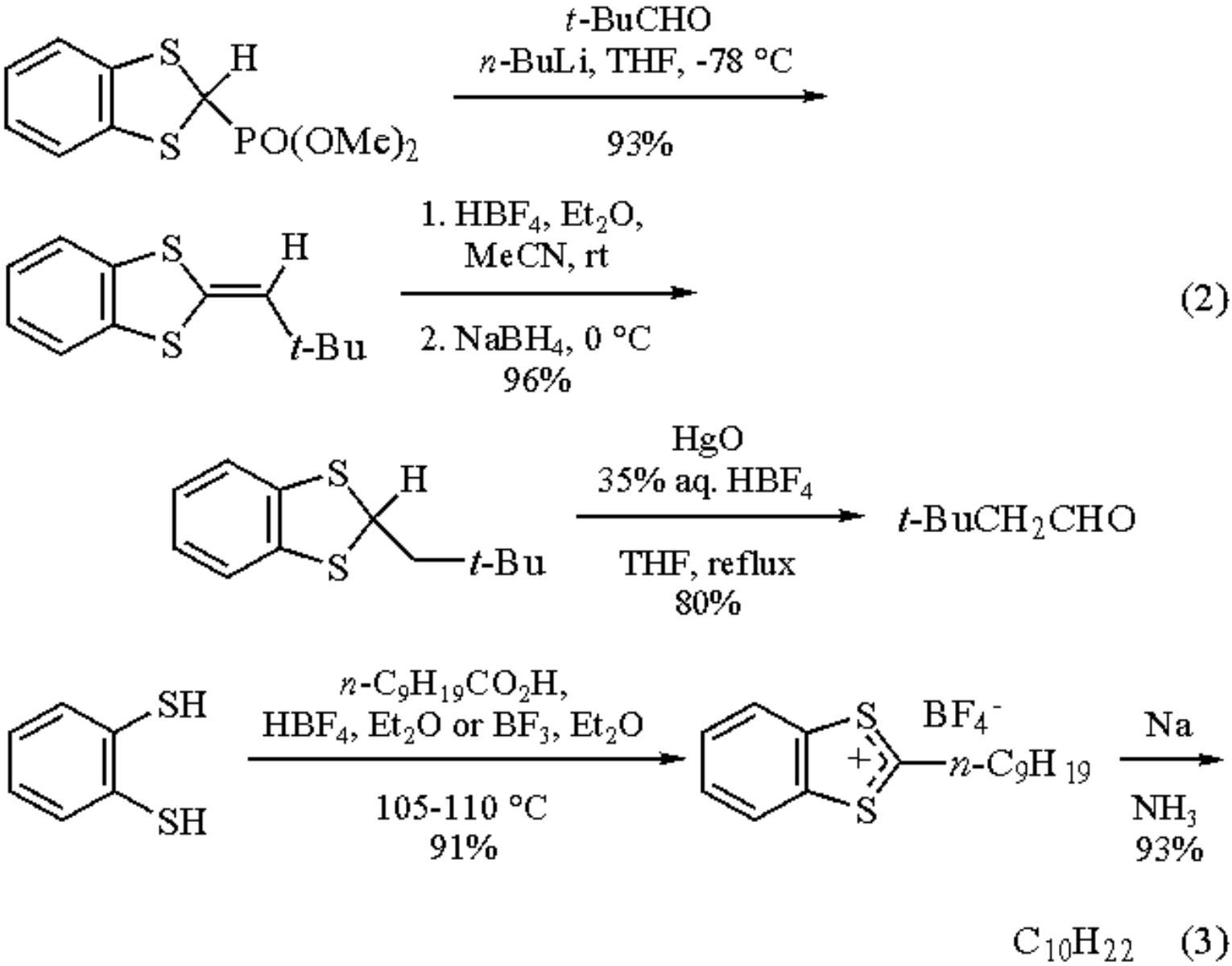
t-BuCHO
n-BuLi, THF, -78 °C
93%
PO(OMe)2
1. HBF4, Et2O,
MeCN, rt
2. NaBH4, 0 °C
96%
t-Bu
HgO
35% aq. HBF4
THF, reflux
80%
t-BuCH2CHO
n-C9H19CO2H,
HBF4, Et2O or BF3, Et2O
105-110 °C
91%
BF4-
n-C9H19
Na
NH3
93%
C10H22

(2)

(3)

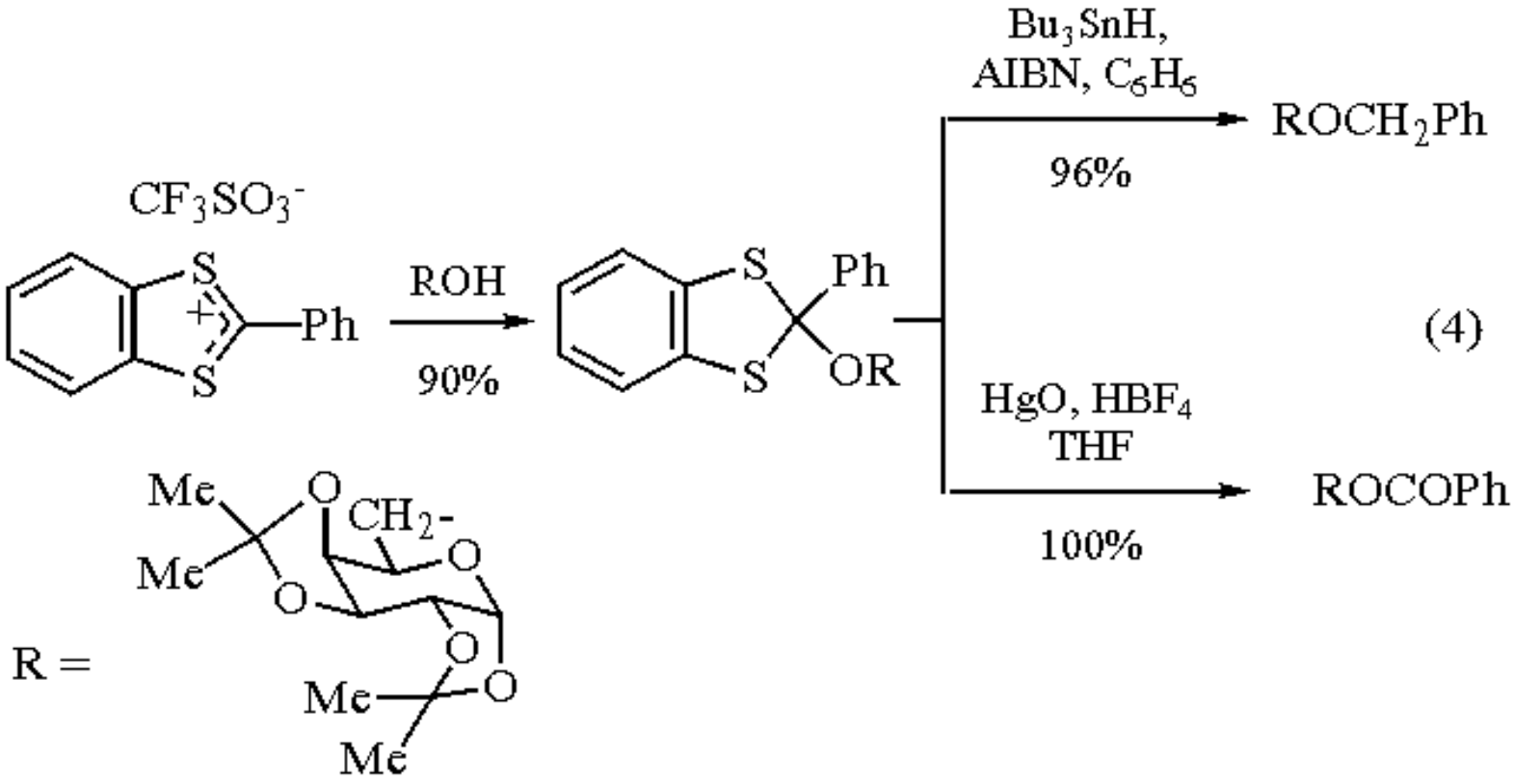

Treatment of the benzenedithiolium tetrafluoroborate with base is one method for generating 1,3-benzodithiole-2-ylidene (**2**).[7] The carbene is also formed as an intermediate in the 1,3-dipolar cycloaddition of carbon disulfide with benzyne.[4] It displays a 6π-electron system and belongs to the class of nucleophilic carbenes capable of reacting with sulfur and selenium metal.[4c]

1,2-Benzenedithiol has found much use in the synthesis of organic metals. A large number of electron-rich compounds have been synthesized with the aim of producing conducting radical cation salts.[8] (**4**), (**5**) and (**6**) are representative compounds derived from the dithiol.

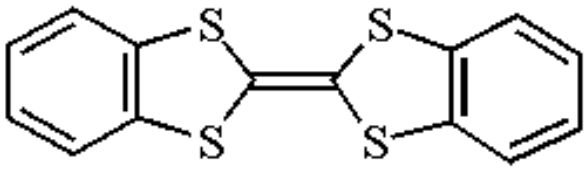

(4)

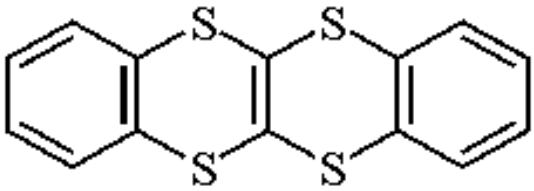

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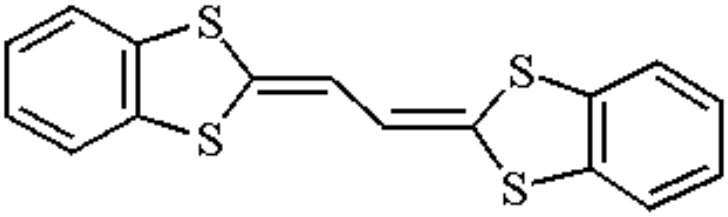

(6)

The ability of the two sulfur atoms in benzodithioles to stabilize a negative charge (unlike the parent 1,3-dithiolane that fragments on treatment with bases) makes these reagents useful as umpoled formyl and acyl anion synthons.[9] As with many other sulfur reagents of this type, the oxides exhibit higher reactivity, but the anion of the tetroxide gives aldol-type products only with difficulty because of its stability. The *trans* dioxide of 1,3-benzodithiole can be transformed via a Mannich reaction into the 2-methylene derivative which exhibits dienophilic properties and high diastereoselection in Diels-Alder cycloadditions (eq 5).[10]

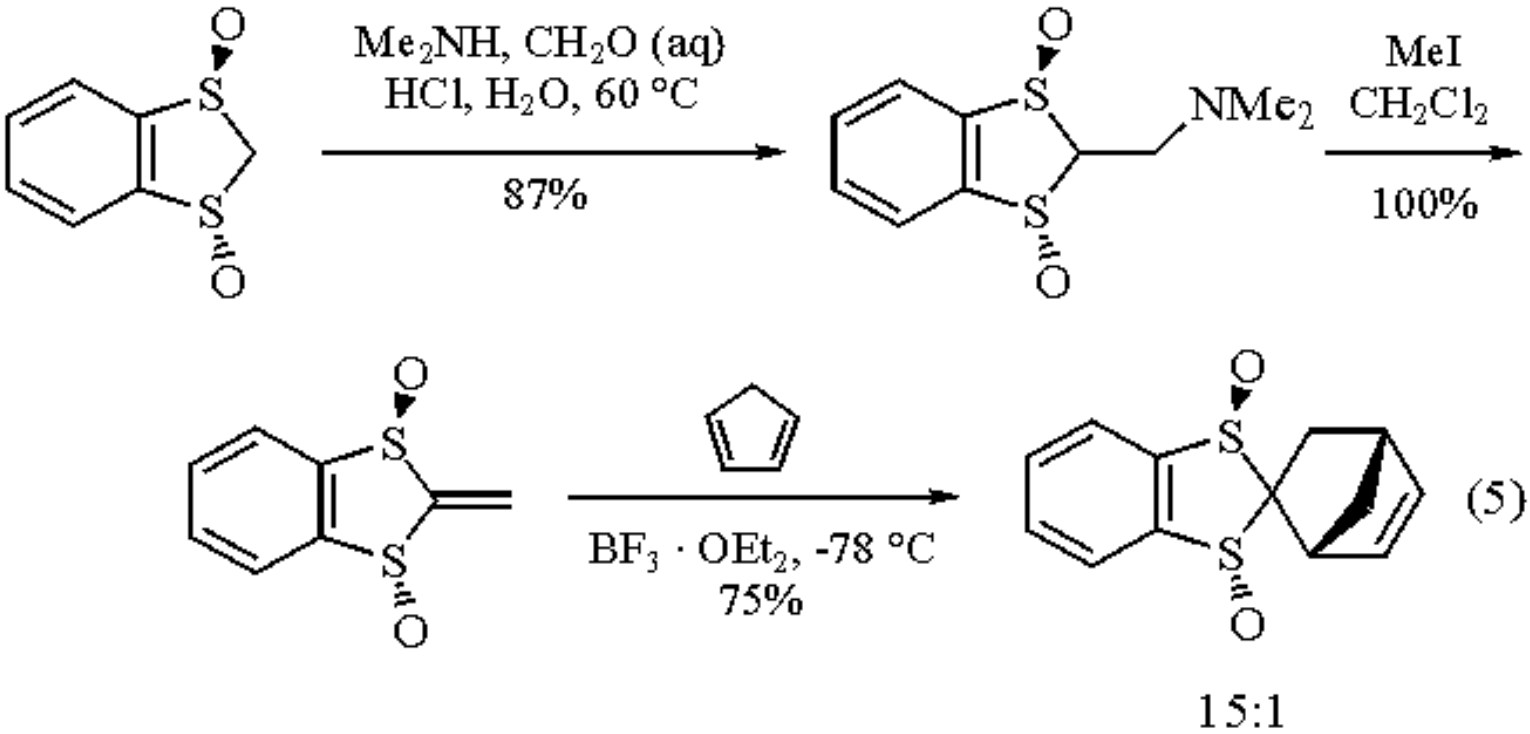

(5)

A number of heteroatoms can be included in the five-membered ring in between the two sulfur atoms. Examples include phosphorus[11] and boron.[12] The latter compound has been shown to catalyze Diels-Alder reactions. A large number of complexes of 1,2-benzenedithiol are also well-known and are currently being investigated.[13]

Six-membered Rings.

1,4-Benzodithiin *S,S,S´,S´*-tetroxide is available from 1,2-benzenedithiol or by other methods.[14] These compounds exhibit exceptional reactivity as dienophiles, higher than the bis(phenylsulfonyl)ethylenes (see ***1,2-Bis(phenylsulfonyl)ethylene***; ***1,1-Bis(phenylsulfonyl)ethylene***). The 2-chloro derivative can be used as C_2 synthon in cycloaddition reactions for the preparation of molecules that are difficult to prepare by other methods (eq 6).[15]

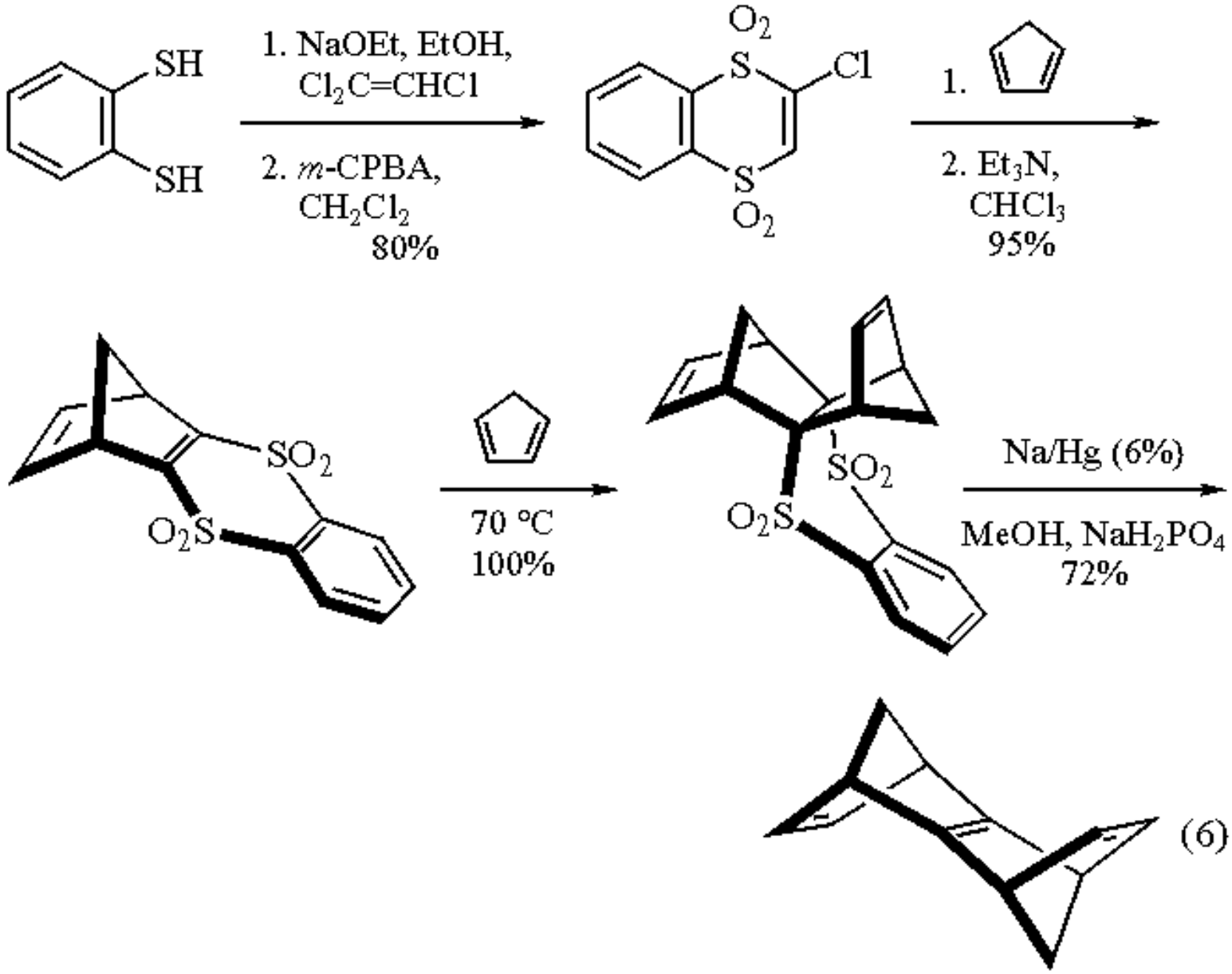

(6)

Seven and Higher-Membered Rings.

Sulfur in liquid ammonia is used in one method of synthesis of benzopentathiepine (eq 7).[16a] This sulfide can be used in the synthesis of heterocycles and as a sulfur transfer reagent.[16b] Benzo-1,3,5,2,4-trithiadiazepine is a 10π aromatic system available from benzene-1,2-dithiol via the bis-sulfenyl chloride shown in eq 8.[17] Higher ring systems (thiocrown heterocycles) can also be prepared.[18]

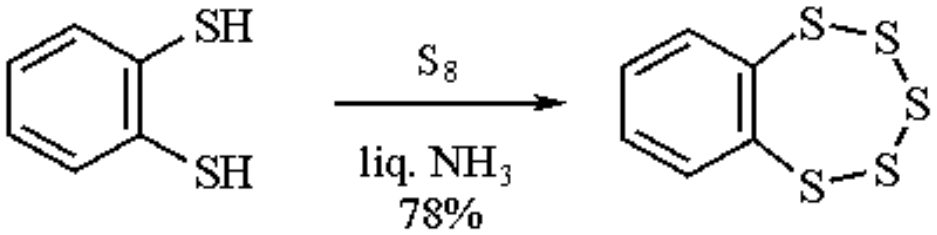

(7)

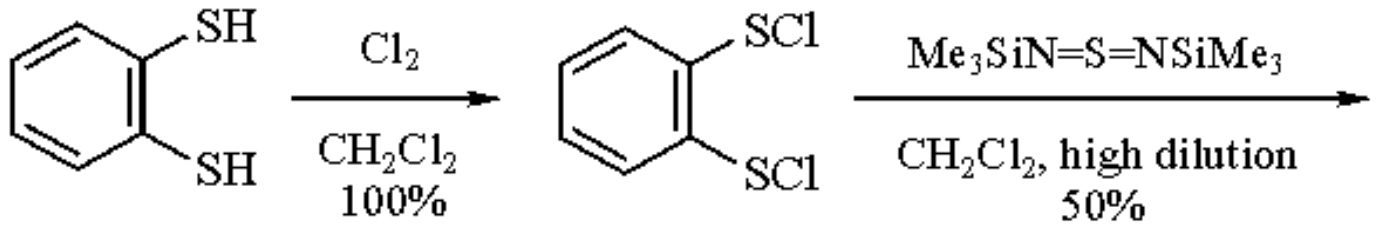

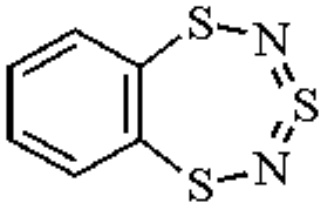

(8)

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Benzeneperoxyseleninic Acid

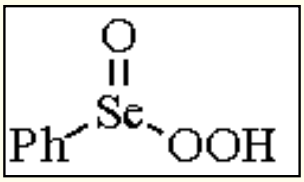

[62885-97-6] · $C_6H_6O_3Se$ · Benzeneperoxyseleninic Acid · (MW 205.07)

(reagent for Baeyer-Villiger reaction and oxidizing agent for many functional groups)

Physical Data: mp 52 °C (with explosion).

Solubility: sparingly sol water, chloroform, and acetonitrile.

Form Supplied in: white powder.

Analysis of Reagent Purity: determination of active oxygen iodometrically (19.5%).[1]

Preparative Methods: the method of preparation involves oxidation of ***Benzeneseleninic Acid*** or ***Diphenyl Diselenide*** with 30% ***Hydrogen Peroxide*** used in excess at -10 °C. In a similar way, 2-nitro- and 2,4-dinitrobenzeneperoxyseleninic acids are obtained with 90% H_2O_2.[1] Peroxyseleninic acids are postulated as active intermediates when organic substrates are treated with H_2O_2 or ***t-Butyl Hydroperoxide*** in the presence of areneseleninic acids or aryl diselenides.[2-8]

Handling, Storage, and Precautions: caution: explosion hazard! Benzeneperoxyseleninic acid decomposes when dried in vacuo. It may be stored in a refrigerator for 1 week. Left to stand in air at rt for 3-4 days, it rearranges to benzeneseleninic acid. In the presence of water, it decomposes to benzeneseleninic acid and H_2O_2. This compound should be handled in a fume hood.

Baeyer-Villiger Oxidation.

The treatment of aromatic aldehydes or aryl methyl ketones with benzeneperoxyseleninic acid gives formates or acetates.[1] Similar results are achieved when H_2O_2 is used as a stoichiometric oxidant in the presence of catalytic amounts of bis(2,4-dinitrophenyl) diselenide (DNPDS), which forms 2,4-dinitrobenzeneperoxyseleninic acid in situ. The crude formate or acetate is hydrolyzed to phenol. This method is suitable for the synthesis of phenols substituted with electron-donating groups (eq 1).[7] In a similar manner, α,β-unsaturated aldehydes are oxidized with H_2O_2 in the presence of 2-nitrophenyl diselenide (NPDS) to a mixture of products containing mainly the vinyl formates; hydrolysis then leads to saturated aldehydes or ketones having the carbon chain shortened by one carbon atom (eq 2).[8]

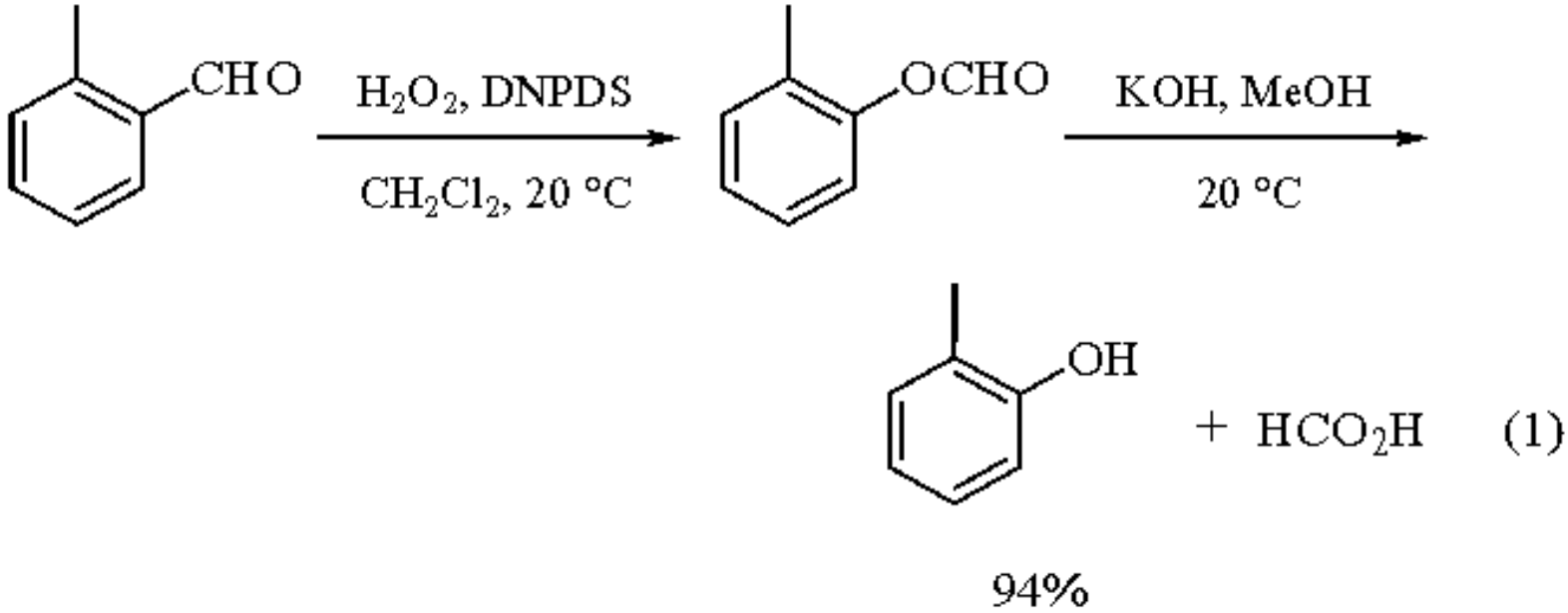

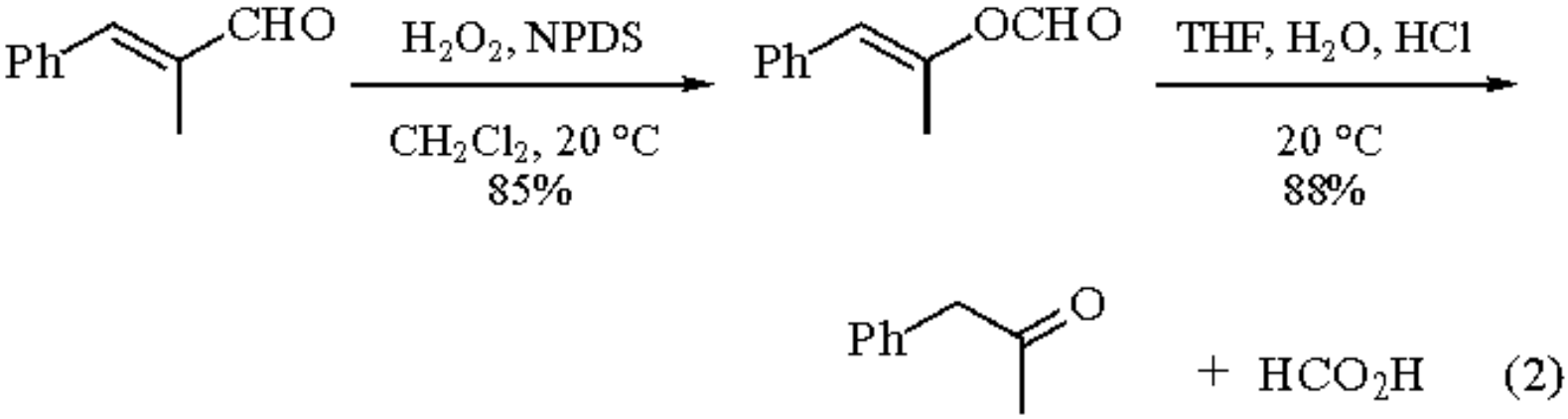

Oxidation of cyclic ketones (eq 3)[5] and epoxidation of alkenes and allylic alcohols is achieved through the intermediate formation of (nonisolated) peroxyseleninic acids.[2-4] Styrene and its analogs are efficiently epoxidized with H_2O_2 in the presence of 2-nitrobenzeneseleninic acid.[6]

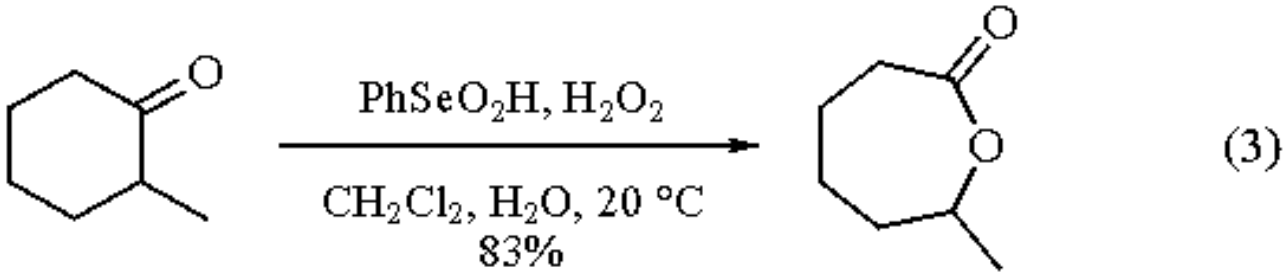

Other Oxidations.

Immobilized benzeneperoxyseleninic acid is a possible intermediate when polymer-bound benzeneseleninic acid (in catalytic amounts) and H_2O_2 or *t*-BuOOH are used for oxidations such as epoxidation, diol synthesis, oxidation of benzylic alcohols to carbonyl species, the Baeyer-Villiger oxidation, and the conversion of phenols into quinones.[9]

Aromatic aldehyde *N*,*N*-dimethylhydrazones are oxidized to nitriles (eq 4)[10] with 2-nitrobenzeneperoxyseleninic acid formed in situ from ***o-Nitrobenzeneseleninic Acid*** (NBSA), while aromatic and aliphatic aldoximes in the presence of primary or secondary alcohols are converted into carboxylic esters (eq 5).[11]

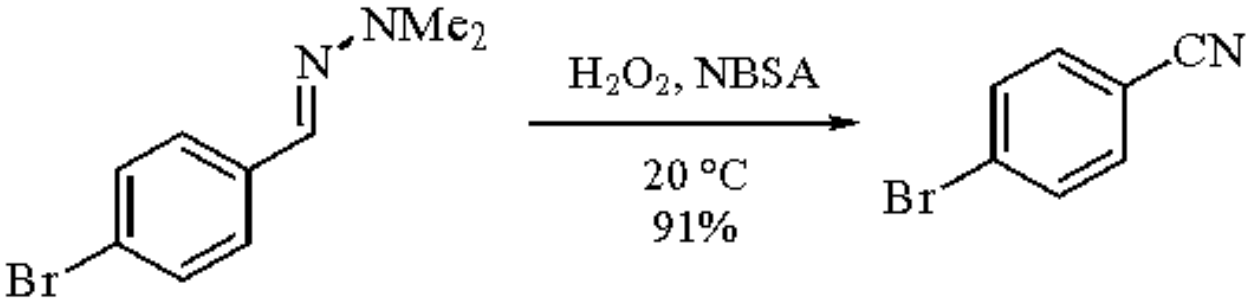

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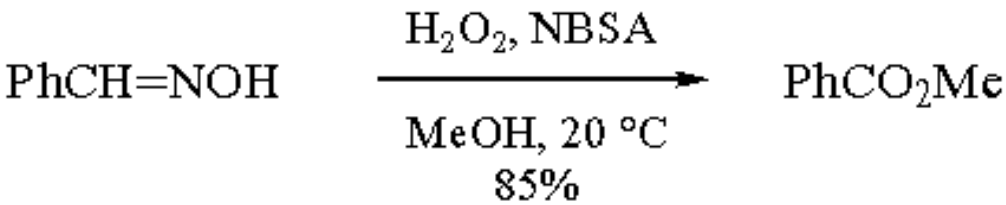

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Technical University of Wroclaw, Poland

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Benzeneselenenyl Bromide[1]

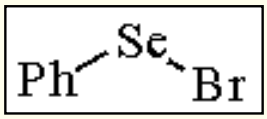

[34837-55-3] · C_6H_5BrSe · Benzeneselenenyl Bromide · (MW 235.97)

(electrophilic selenium reagent for alkene synthesis[2-6])

Physical Data: mp 60-62 °C; bp 134 °C/35 mmHg, 107-108 °C/15 mmHg; sublimes at 25 °C/0.001 mmHg.

Solubility: sol organic solvents such as hexane, CH_2Cl_2, ether, THF.

Form Supplied in: dark-red crystals; commercially available.

Preparative Method: can be quantitatively prepared in situ by treatment of ***Diphenyl Diselenide*** with an equimolar amount of ***Bromine***.[2,3,7]

Purification: recrystallization from petroleum ether or sublimation.

Handling, Storage, and Precautions: highly toxic, unpleasant smell.

Reaction with Ketones and Enols.

Benzeneselenenyl bromide (PhSeBr) is a useful electrophilic organoselenium reagent which exhibits similar reactivity to ***Benzeneselenenyl Chloride*** (PhSeCl). Although the reagent can be substituted by PhSeCl in many reactions, there is a significant difference in reactivity between these reagents.[2] Ketones can be efficiently converted into α-phenylseleno ketones through their lithium or copper enolates.[3,8] This reaction is useful for the transformation of saturated ketones to α,β-unsaturated ketones and the β-alkylation of α,β-unsaturated ketones (eqs 1 and 2). Similarly, enol acetates are converted into α,β-unsaturated ketones by using benzeneselenenyl trifluoroacetate ($PhSeOCOCF_3$),[9] which is prepared in situ by treatment of PhSeCl or PhSeBr with ***Silver(I) Trifluoroacetate*** (eq 3).[3,4] Silyl enol ethers react with PhSeBr to provide α-phenylseleno ketones and aldehydes in good yields (eq 4).[10] On the other hand, PhSeBr adds to enol ethers forming bromoselenenylation adducts regioselectively (eq 5).[11] Unlike PhSeCl, PhSeBr does not usually react well with ketones and aldehydes to form α-phenylseleno carbonyl compounds.[3]

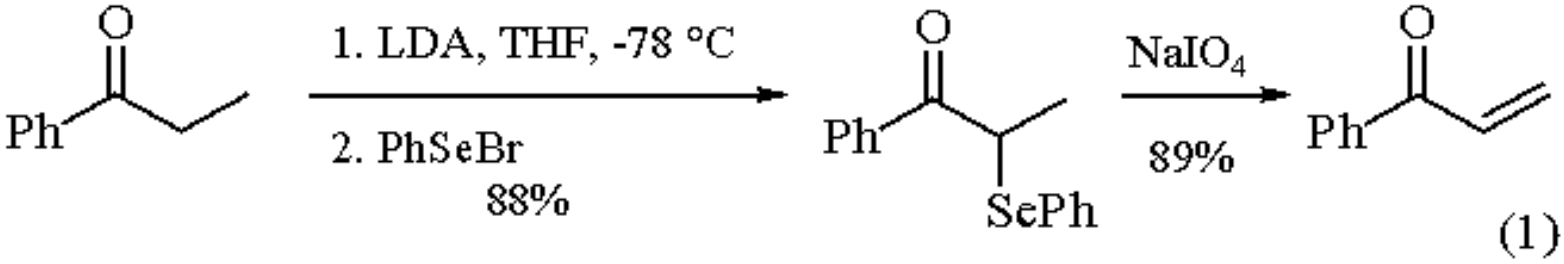

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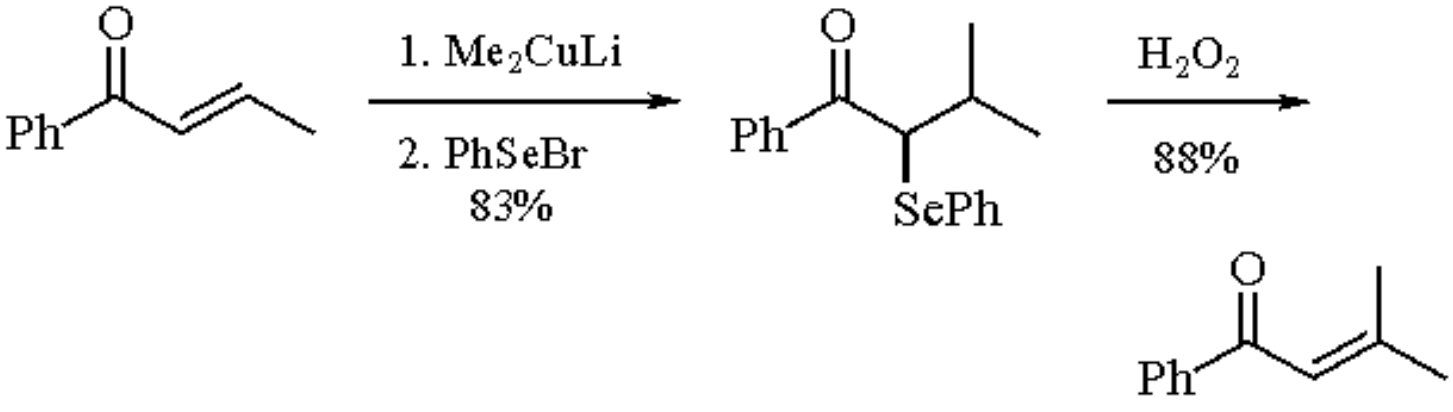

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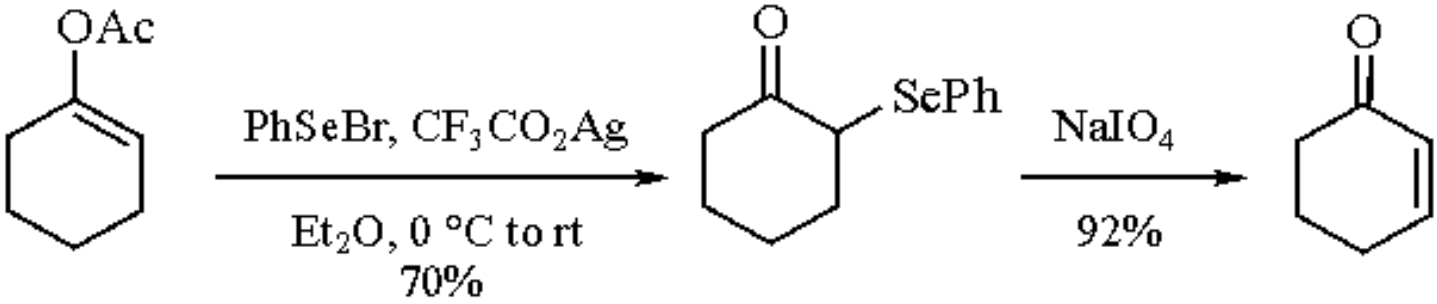

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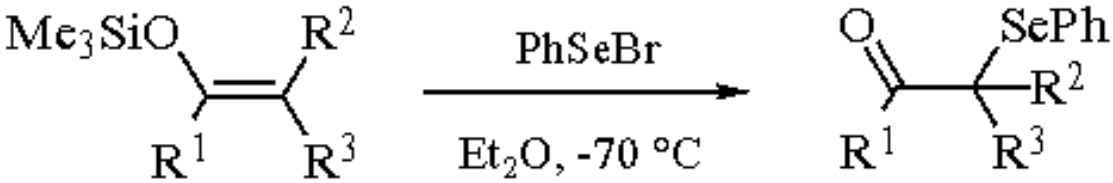

(4)

R^1 = H, alkyl

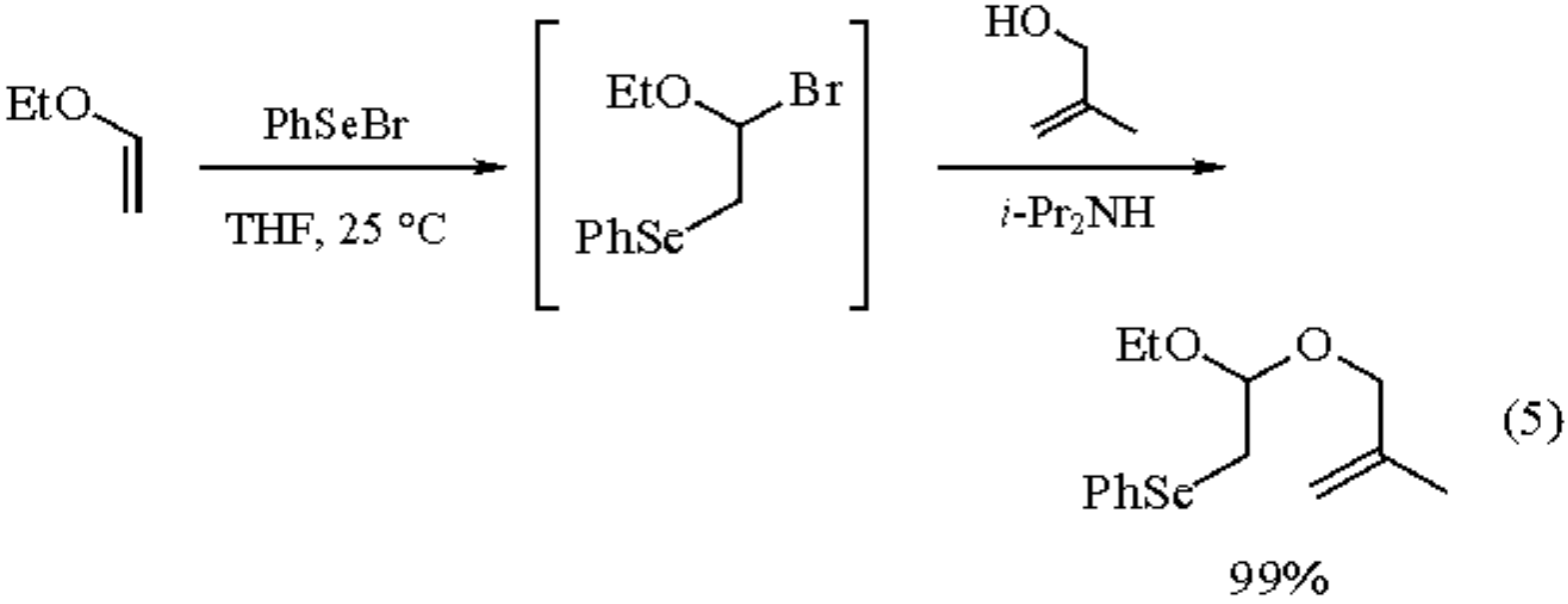

Reaction with Carbanions.

α-Lithiated nitriles[12] and nitroalkanes[13] rapidly react with PhSeBr to afford the corresponding α-phenylseleno compounds, which are oxidized to α,β-unsaturated nitriles and nitroalkanes, respectively (eqs 6 and 7).

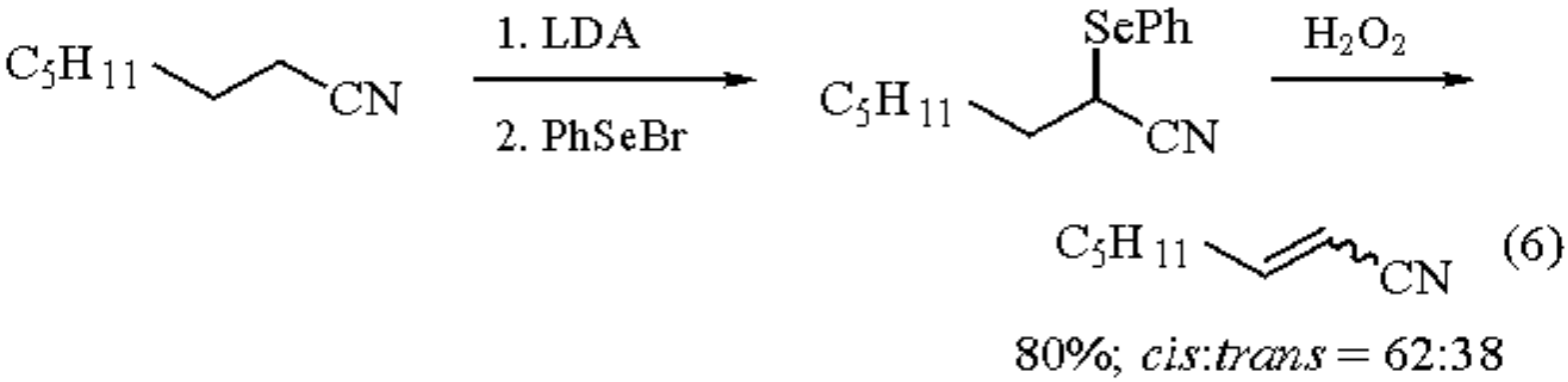

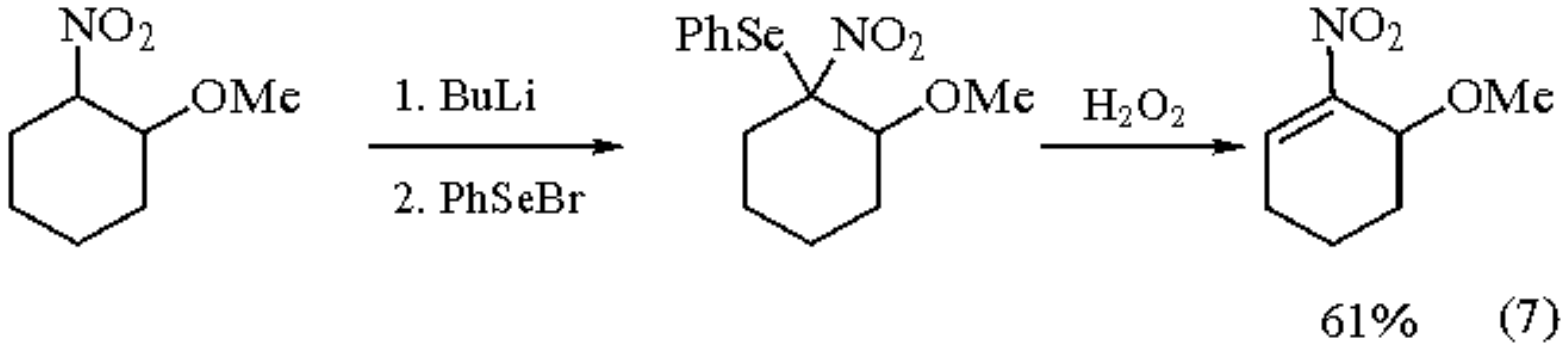

Addition to Alkenes.

PhSeBr reacts with alkenes in aprotic organic solvents to provide bromoselenenylation adducts efficiently.[5] This addition is considered to proceed via a seleniranium ion, a selenium-containing 3-membered cyclic cation, and *trans*

adducts are obtained exclusively. For terminal alkenes the regioselectivity of the addition can be controlled by changing the reaction conditions (eq 8).[6] The products can be easily transformed to vinylic selenides,[6] vinylic and allylic bromides,[14a] or α-phenylseleno ketones.[14b] When the reaction is carried out in alcohol or carboxylic acid, oxyselenenylated products of alkenes are obtained in high yields (eq 9).[5,15]

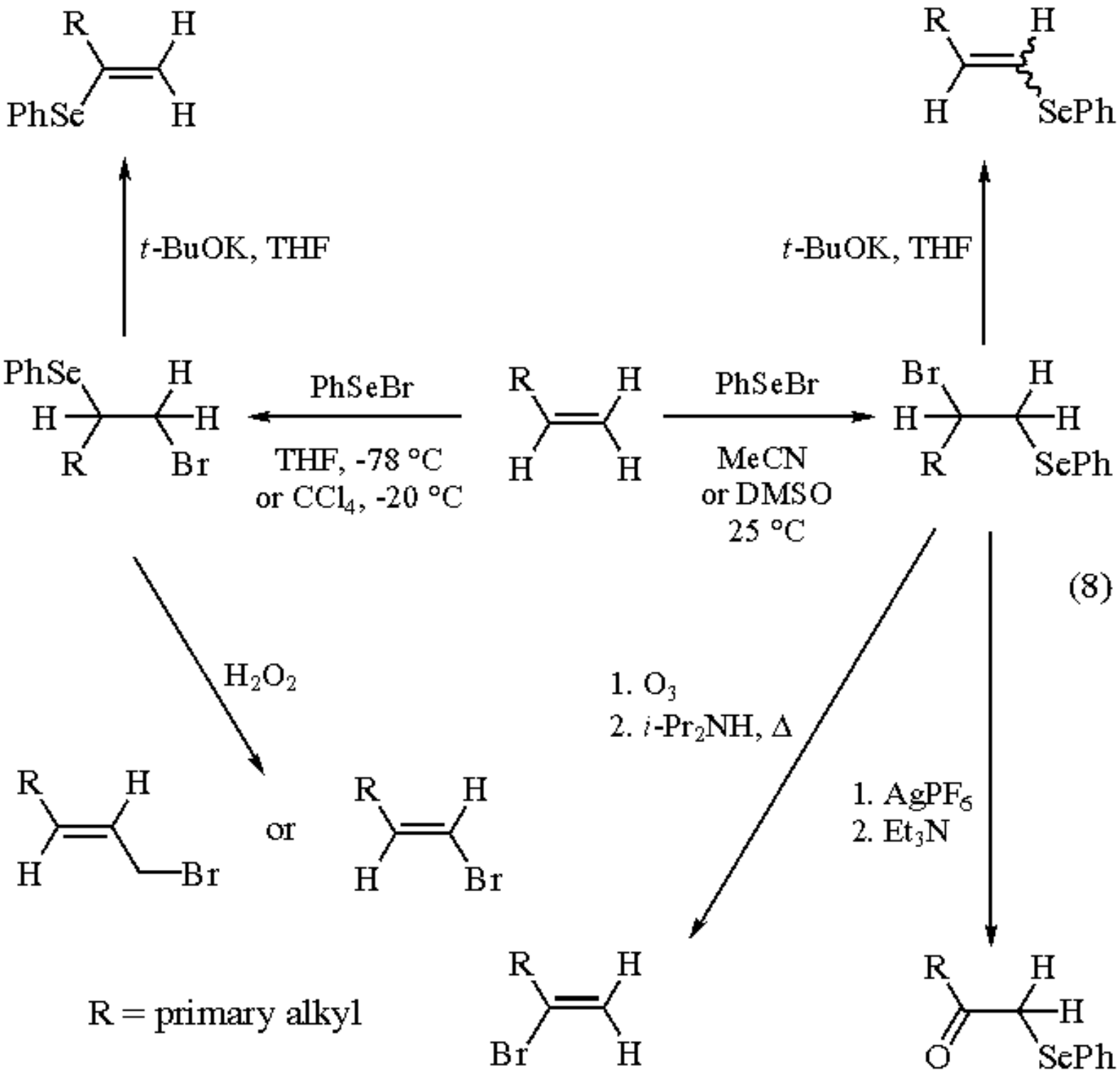

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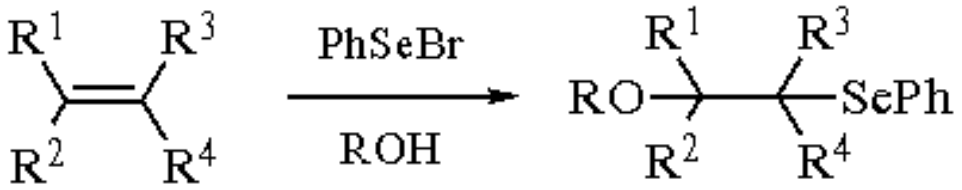

(9)

R = Me, Et, Ac, etc.

Alkynyl Selenide Synthesis.

Terminal alkynes undergo electrophilic substitution by treatment with the reagent prepared from PhSeBr and ***Silver(I) Nitrite***, providing alkynyl selenides in good yields (eq 10).[16]

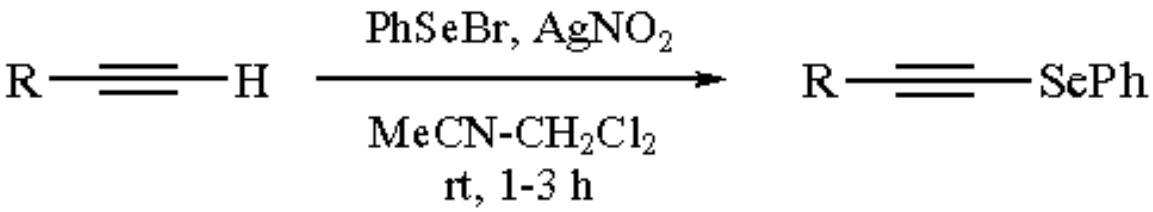

(10)

R = Bu, Ph, OCOEt etc.

Reaction with Ketonic Hydrazones.

In the presence of ***t-Butyltetramethylguanidine***, a strong base, ketonic hydrazones smoothly react with PhSeBr to give phenyl vinyl selenides (eq 11).[17] This reaction requires an excess amount of PhSeBr.

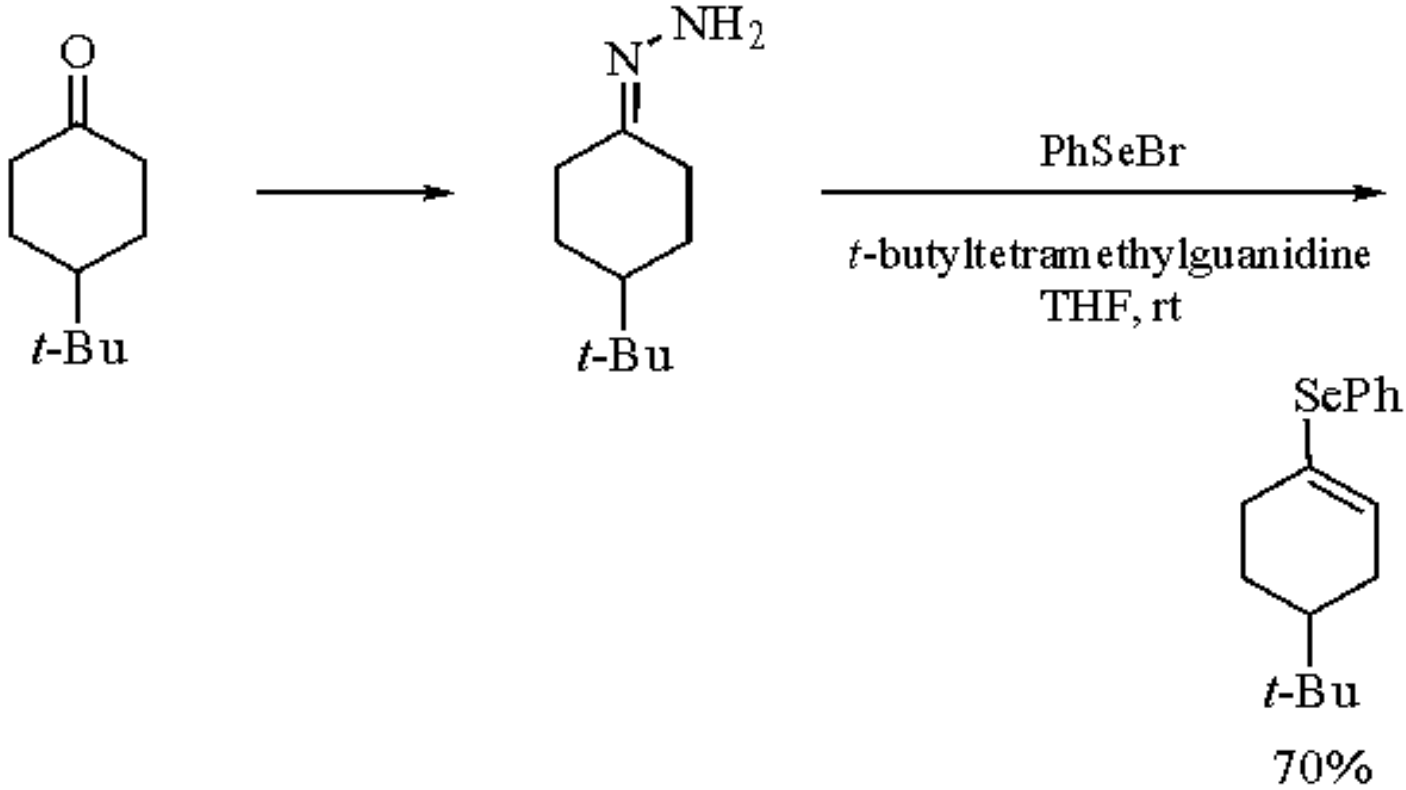

(11)

Related Reagents.

A number of chiral electrophilic selenium reagents have been tested for their possible use in asymmetric synthesis (addition to alkenes, eq 9). Diastereomeric excesses as high as 79% have been achieved for (**1**) (R = *N*-(2,4-dinitrophenyl)prolinoyl),[18] and 93% for the triflate derived from (**2**).[19] Little asymmetric induction was seen in the addition of (**3**) to alkenes.[20] See also ***Benzeneselenenyl Chloride***, ***Benzenesulfenyl Chloride***, ***Phenyl Selenocyanate***, ***2-Pyridineselenenyl Bromide***.

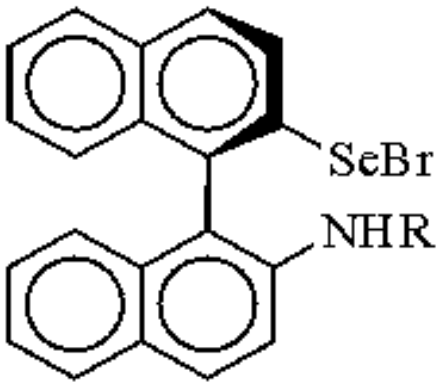

(1)

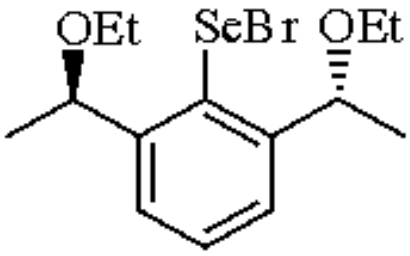

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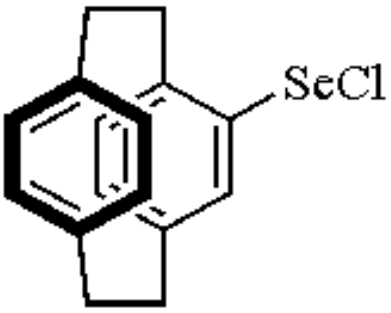

(3)

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Compounds; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1986; Vol. 1. (e) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (f) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987.
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The University of Tokyo, Japan

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Benzeneselenenyl Chloride[1]

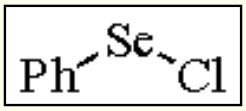

[5707-04-0] · C_6H_5ClSe · Benzeneselenenyl Chloride · (MW 191.52)

(electrophilic selenium reagent for alkene synthesis[2-5])

Physical Data: mp 63-65 °C; bp 95-96 °C/6 mmHg, 120 °C/20 mmHg.

Solubility: sol common organic solvents such as hexane, CH_2Cl_2, and THF.

Form Supplied in: orange crystals; commercially available.

Preparative Methods: synthesized in 84-88% isolated yield by the reaction of ***Diphenyl Diselenide*** with ***Chlorine***.[5,6] Conveniently, benzeneselenenyl chloride can be prepared almost quantitatively in situ by treatment of diphenyl diselenide with an equimolar amount of ***Sulfuryl Chloride*** (SO_2Cl_2).[4,7] Reagent prepared in this way may contain significant amounts of SO_2.

Purification: recrystallized from hexane.

Handling, Storage, and Precautions: highly toxic; unpleasant smell.

Electrophilic Selenium Reagents.

Benzeneselenenyl chloride (PhSeCl) is the most common electrophilic selenium reagent and has been widely employed in the synthesis of a variety of natural and nonnatural products (see also ***Benzeneselenenyl Bromide*** (PhSeBr), ***Phenyl Selenocyanate*** (PhSeCN), ***o-Nitrophenyl Selenocyanate*** (*o*-$NO_2C_6H_4SeCN$), ***Benzeneselenenyl Trifluoromethanesulfonate*** (PhSeOTf), and ***Diphenyl Diselenide*** (PhSeSePh)). Other useful electrophilic selenium reagents ($PhSeOCOCF_3$,[2,8] $PhSeNO_2$,[9,10] PhSeF,[11-13] etc.) are usually prepared in situ from PhSeCl or PhSeBr and the corresponding silver salt.

Addition to Alkenes.

Chloroselenenylation.

PhSeCl adds to alkenes to give chloroselenenylation products in high yields.[2,7,14] The addition proceeds exclusively in the *trans* manner due to intervention of a selenium-bridged cation (a seleniranium ion) as a reaction intermediate (eq 1). Reaction with unsymmetrical alkenes generally provides *trans* adducts with high regioselectivity.[14] As shown in eq 2, terminal alkenes undergo chloroselenenylation to give anti-Markovnikov adducts under kinetic conditions and Markovnikov adducts under thermodynamic conditions.[15] These reaction products are useful intermediates for a variety of organic compounds. For example, upon oxidation with ***Hydrogen Peroxide***,[2] chloroselenenylated alkenes are conveniently transformed to vinylic or allylic chlorides via *syn* elimination of the selenoxides. ***Ozone***,[5] ***Sodium Periodate***,[4] peroxy acids,[4,16] and sulfuryl chloride[15] can also be used as an oxidizing agent. When ***N-Chlorosuccinimide*** is employed as oxidizing agent, PhSeCl catalyzes the conversion of alkenes into vinylic or allylic chlorides.[17] There are many other useful applications of chloroselenenylation, such as the transposition of 1,3-enones (eq 3),[18] transformation of allylsilanes to allyl alcohols,[19] and *cis* chlorination of alkenes.[20]

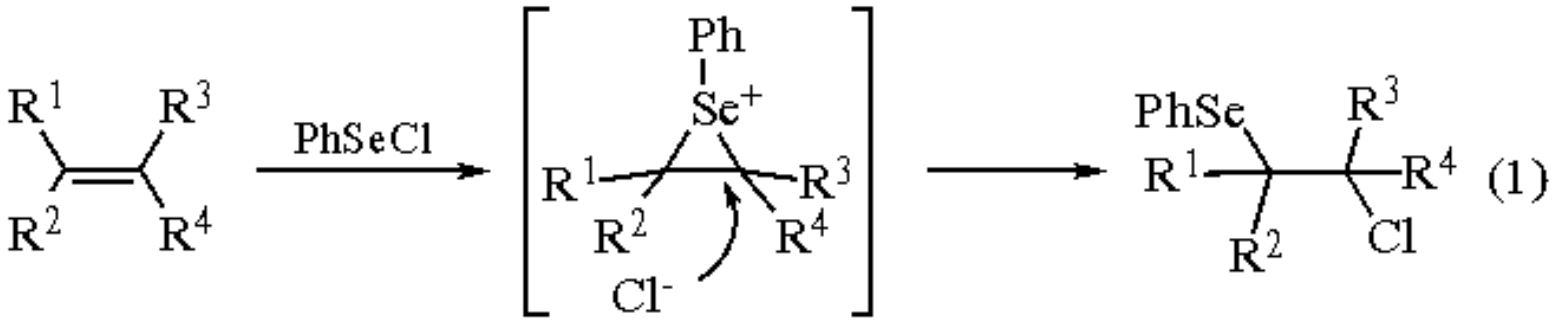

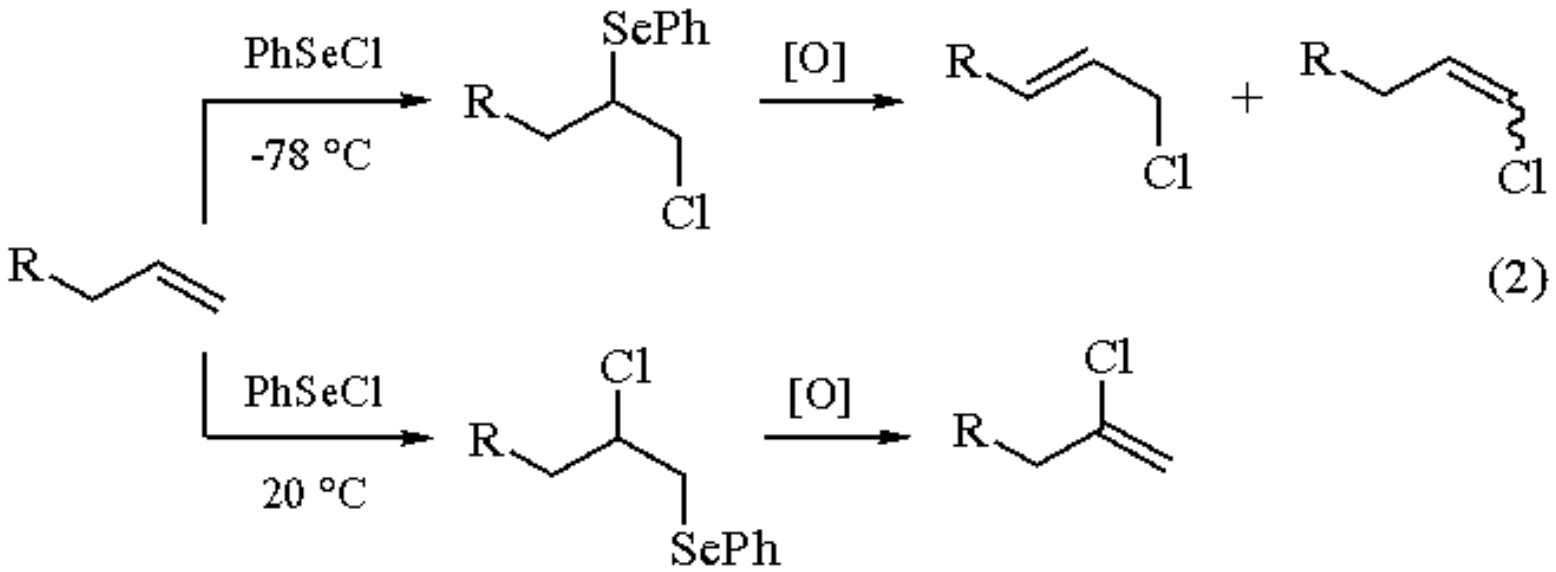

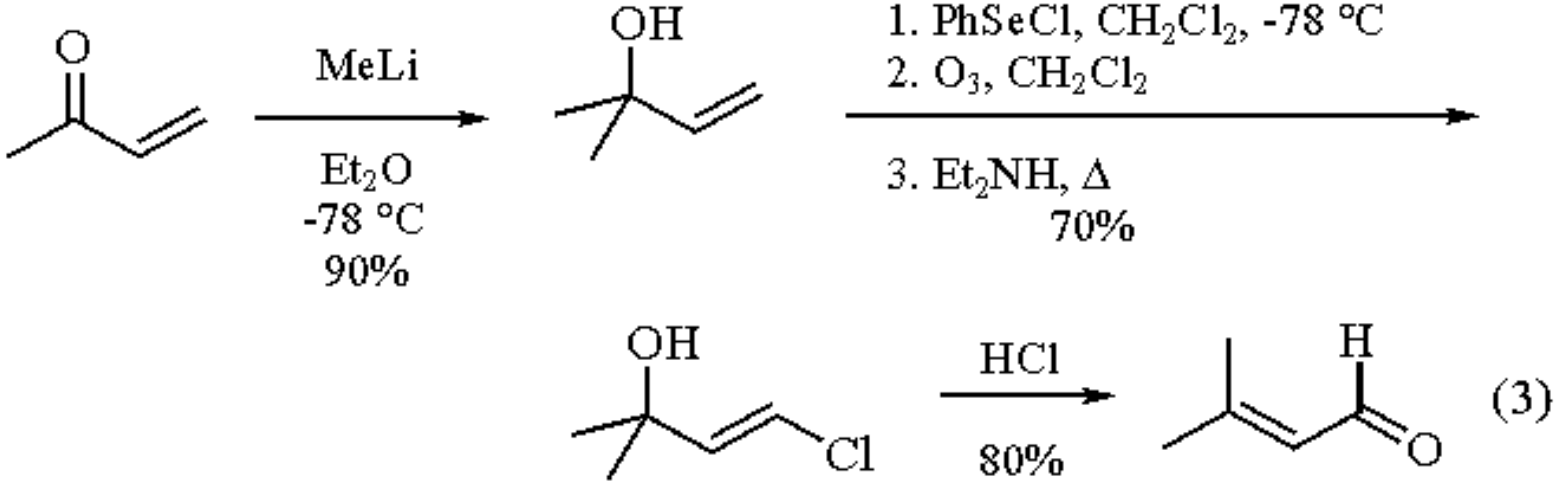

Oxyselenenylation.

Many types of oxyselenenylation reactions of alkenes employing PhSeCl or PhSeBr, such as acetoxy&nbhyph;,[3,21] carboxy-,[22] hydroxy-,[23] alkoxy-,[3,24] and glycosyloxyselenenylation[25] have been reported (eq 4). *Trans* adducts are stereoselectively obtained and are easily transformed to allylic alcohols, ethers, etc., by treatment with hydrogen peroxide. Unsaturated carboxylic acids[26,27] and alcohols[26,28] react with PhSeCl to give lactones and cyclic ethers respectively, in good yields (eqs 5 and 6). The reaction proceeds via intramolecular capture of the seleniranium ion initially formed in the reaction with PhSeCl. The carbonyl[29] and epoxide[30] oxygens as well as the thiol sulfur[31] also react as intramolecular nucleophiles to give 2,6-dideoxyglycosides, cyclic ethers, and cyclic thioethers, respectively. Dienes react with PhSeCl in aqueous acetonitrile to provide cyclic ethers in excellent yields (eq 7).[32]

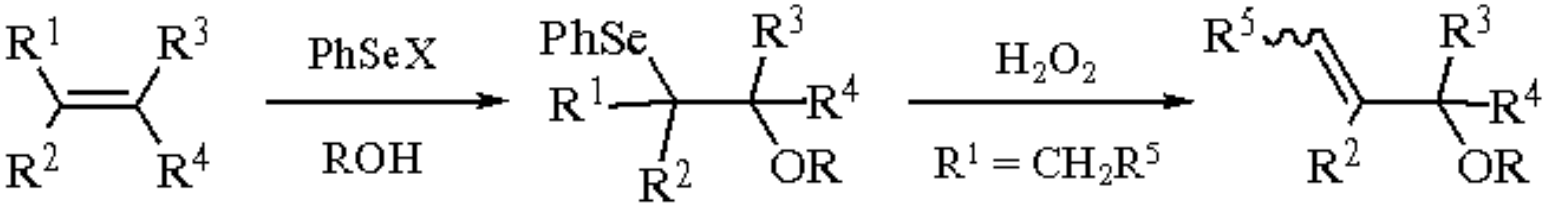

X = Cl or Br; R = Ac, Me, Et, H, etc. (4)

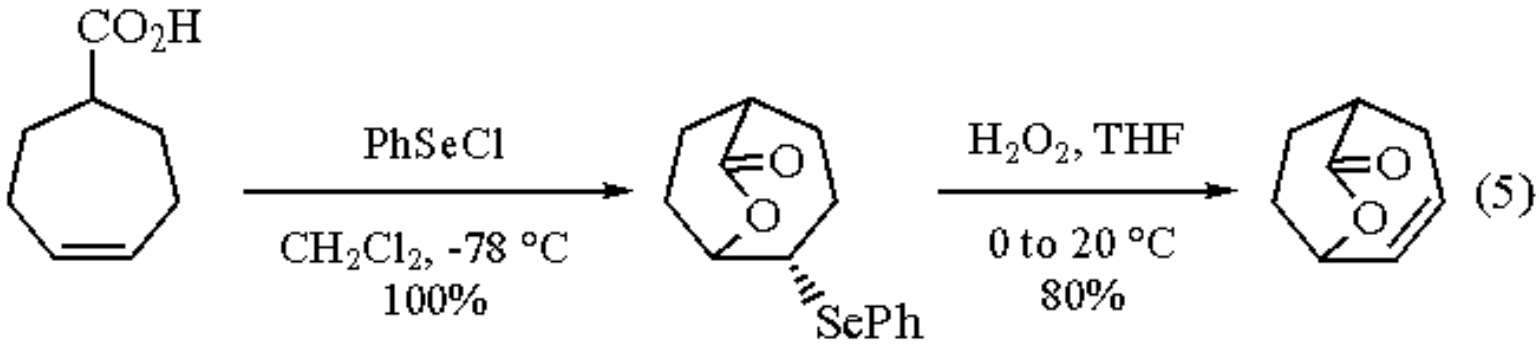

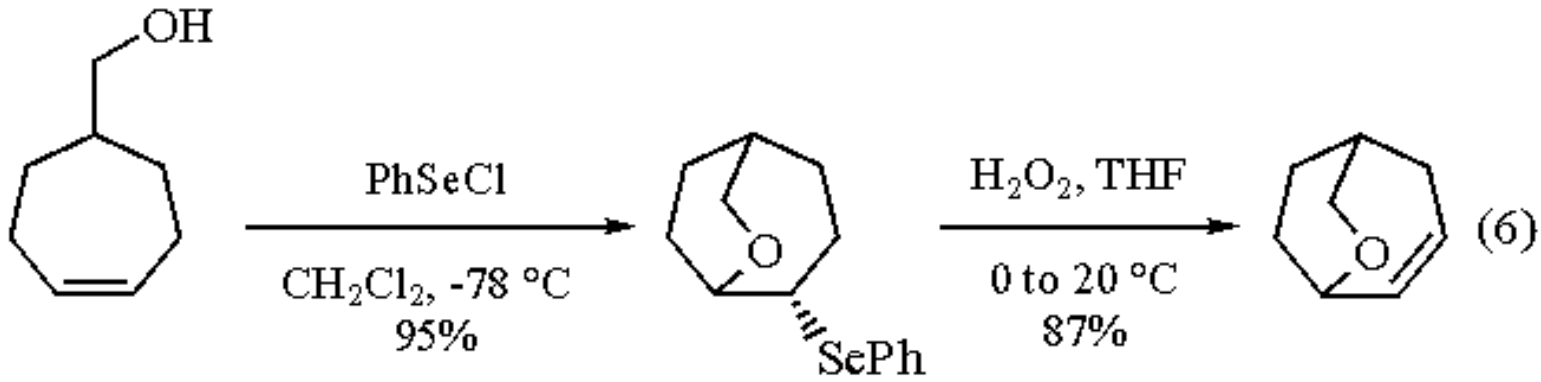

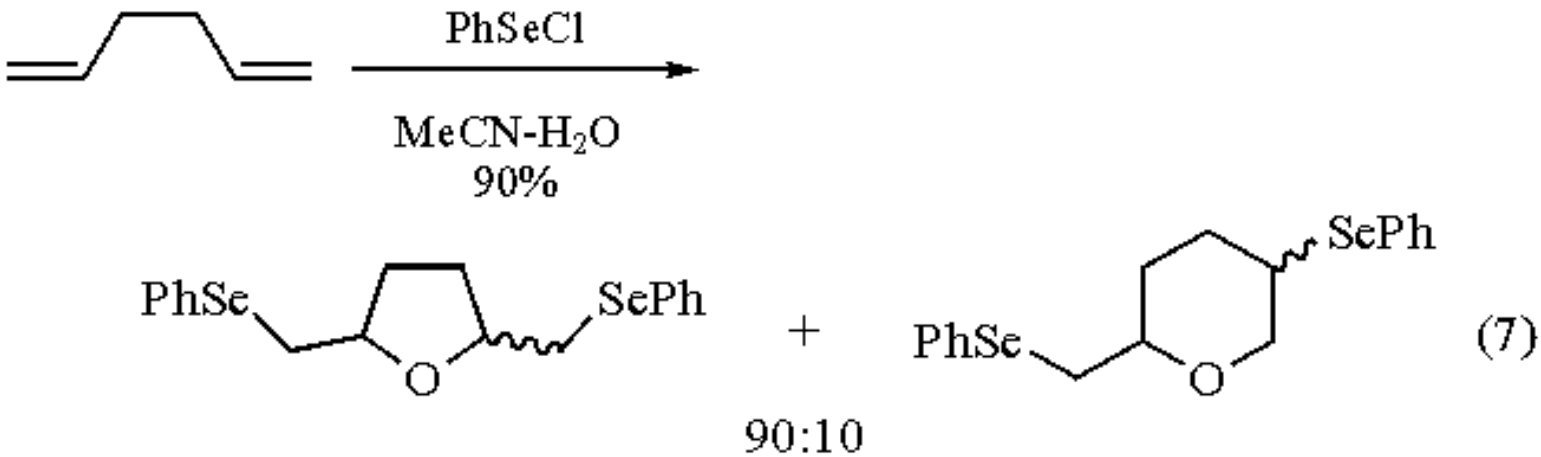

Amidoselenenylation.

Alkenes efficiently undergo amidoselenenylation upon treatment with PhSeCl in aqueous acetonitrile in the presence of ***Trifluoromethanesulfonic Acid*** as an acid catalyst.[33] The produced β-amidoalkyl phenyl selenides can be converted into allylic amides by oxidation with hydrogen peroxide in good yields (eq 8). The reaction of unsaturated urethanes[34] and *N*-alkenylamides[35] with PhSeCl affords pyrrolidine and piperidine derivatives by intramolecular cyclization (eq 9). Similarly, *N*-alkylalkenamides react with PhSeCl to provide lactams.[36]

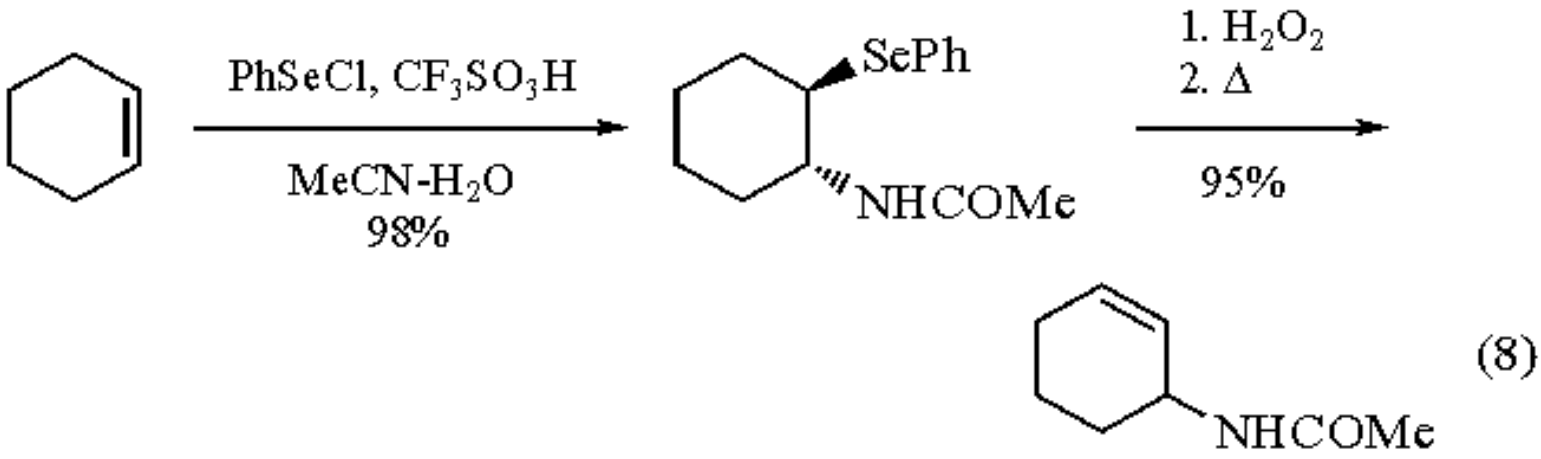

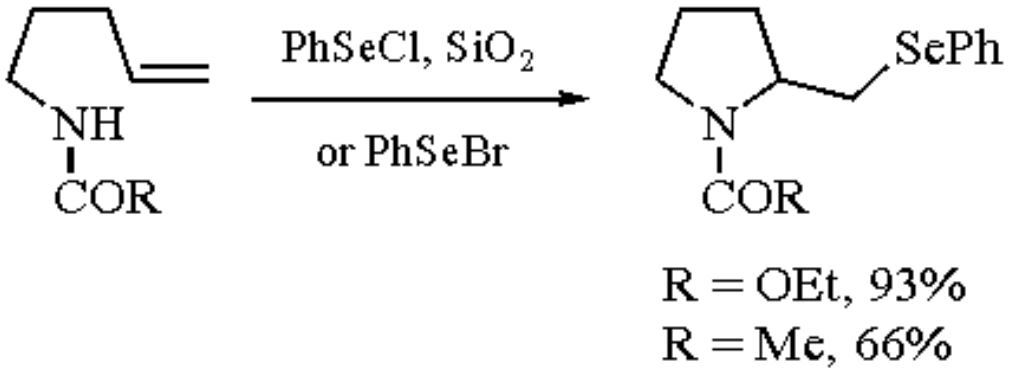

(9)

Nitroselenenylation.

In the presence of ***Mercury(II) Chloride*** the reagent prepared from PhSeCl or PhSeBr and ***Silver(I) Nitrite*** smoothly adds to alkenes giving β-nitroalkyl phenyl selenides (eq 10).[9] This reaction is useful for the preparation of 3,4-epoxy-3-nitro-1-alkenes from dienes[10] and 2-nitro-1-alkenylsilanes from 1-alkenylsilanes.[39]

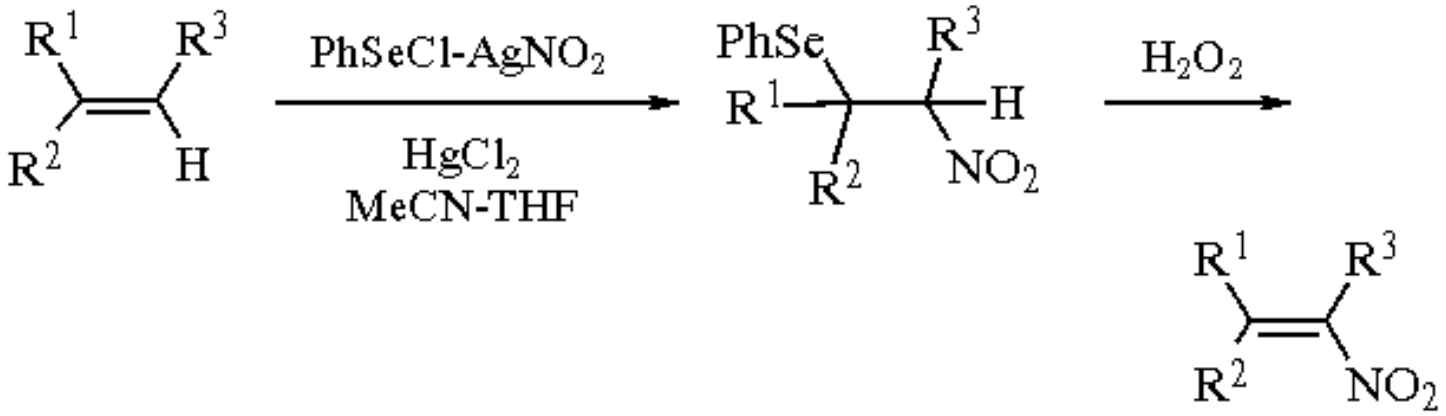

(10)

Cyclization with C-C Bond Formation.

(*Z*,*Z*)-Cyclonona-1,5-diene reacts with PhSeCl in acetic acid to give a bicyclic adduct stereoselectively (eq 11).[40] Similar cyclization of dienes in acetonitrile smoothly proceeds with PhSeI prepared in situ from diphenyl diselenide and ***Iodine***.[37,38] Unsaturated β-keto esters react with PhSeCl to provide cyclohexane derivatives in good yields (eq 12).[41]

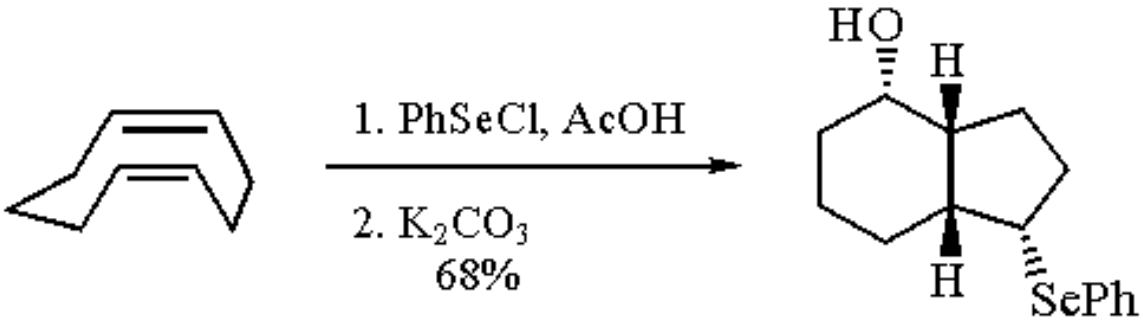

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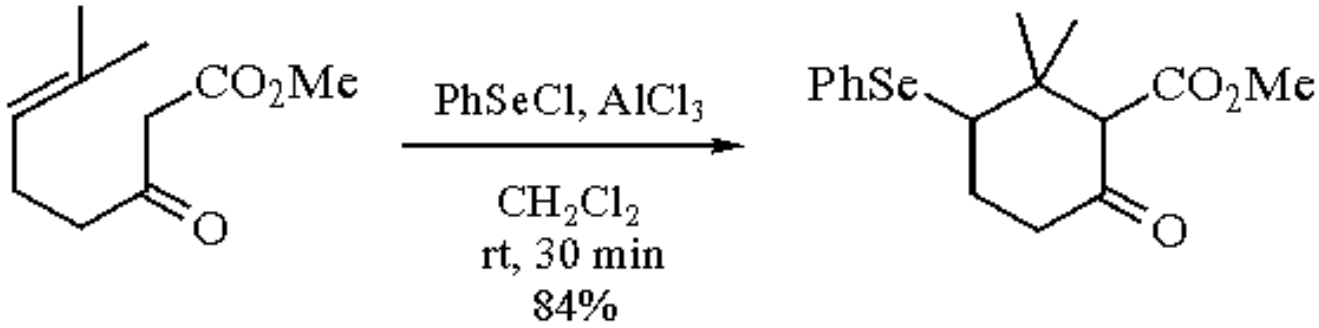

(12)

Fluoroselenenylation.

PhSeF equivalent prepared in situ from PhSeCl or PhSeBr and ***Silver(I) Fluoride*** reacts with alkenes to give β-fluoroalkyl phenyl selenides.[12] The reaction proceeds more smoothly under ultrasound irradiation.[11] The reagent, prepared from diphenyl diselenide and ***Xenon(II) Fluoride***, is also useful for fluoroselenenylation of alkenes.[13] The adducts can be oxidized to allylic fluorides exclusively rather than vinylic fluorides (eq 13).

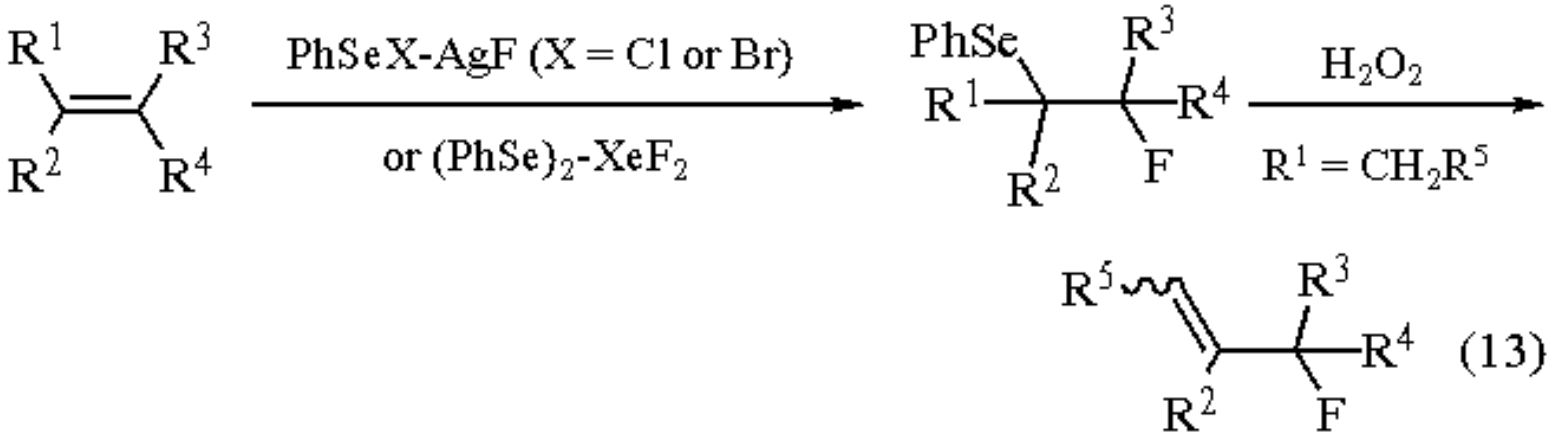

(13)

Selenosulfonation.

Phenyl areneselenosulfonates ($PhSeSO_2Ar$) react with alkenes to give selenosulfonation adducts in the presence of boron trifluoride etherate[42] or under photochemical conditions (eq 14).[43]

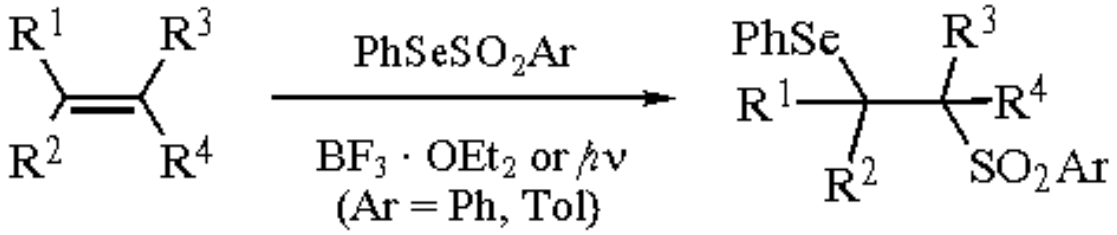

(14)

Addition to Alkynes.

PhSeCl adds to alkynes to form β-chlorovinyl selenides in good yields.[44] The addition proceeds via a selenirenium ion, a selenium-bridged unsaturated cation, and *trans* adducts are exclusively obtained. Similarly, PhSeBr,[45]

$PhSeOCOCF_3$,[2,5] PhSeI,[38b,46] and PhSeF[47] add to alkynes to afford *trans* adducts (eq 15), which can be transformed to many useful synthetic intermediates. For example, 1,4-dichlorobut-2-yne reacts with PhSeCl or PhSeBr, and is converted into dienes, which easily undergo Diels-Alder cycloaddition with methyl vinyl ketone (eq 16).[45b] Areneselenosulfonates ($PhSeSO_2Ar$) also add to alkynes to give similar *trans* adducts.[48] The reaction seems to proceed via a radical intermediate.

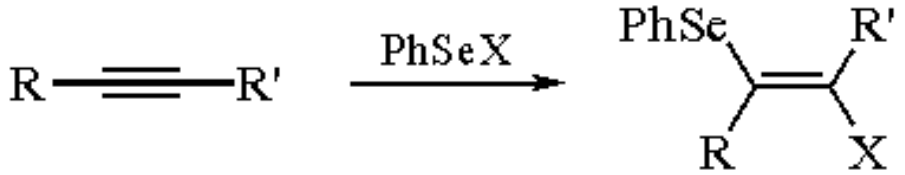

(15)

X = Cl, Br, $OCOCF_3$, I, F

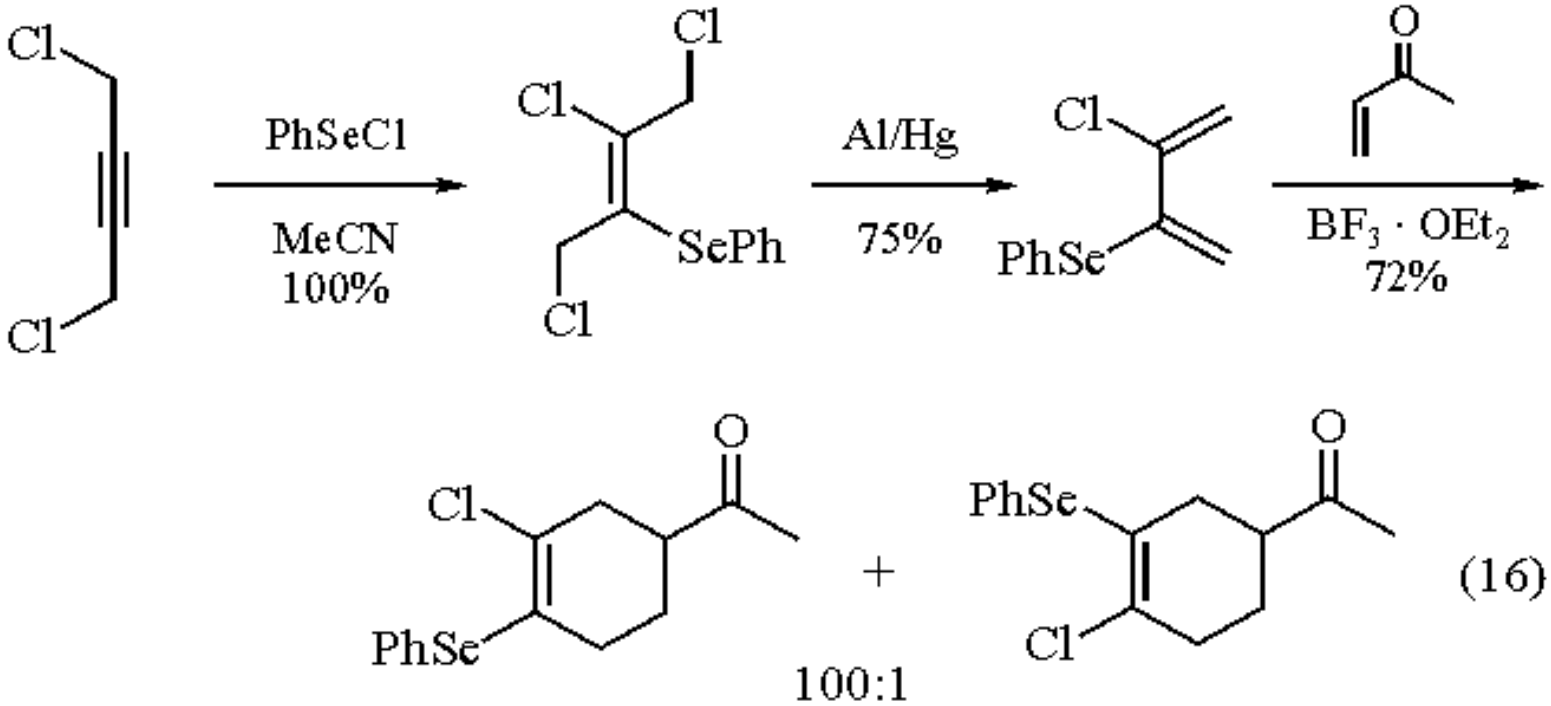

(16)

Reaction with Carbonyl Compounds and Their Derivatives.

Aldehydes and ketones directly react with PhSeCl to provide α-phenylseleno aldehydes and ketones, respectively, in good yields, while esters are converted into α-phenylseleno esters via lithium enolate (eq 17).[4] The reaction of PhSeCl with ketones also efficiently proceeds via lithium enolates.[5] These reaction products smoothly undergo oxidative *syn* elimination of the selenium moiety to give α,β-unsaturated carbonyl compounds in high yields. The reaction can be applied to the conversion of γ-lactones into furans[49] as well as to phenol synthesis from cyclohexene derivatives.[50] Similarly, β-dicarbonyl compounds directly react with PhSeCl in the presence of equimolar ***Pyridine***. The α-phenylselenenylation products are smoothly oxidized to the corresponding unsaturated β-dicarbonyl compounds (eq 18).[51] α,β-Unsaturated ketones also directly react with PhSeCl or PhSeBr in the presence of pyridine to form α-phenylseleneno enones.[52] The products undergo further reaction with PhSeCl to form α-halo enones in good yields (eq 19).

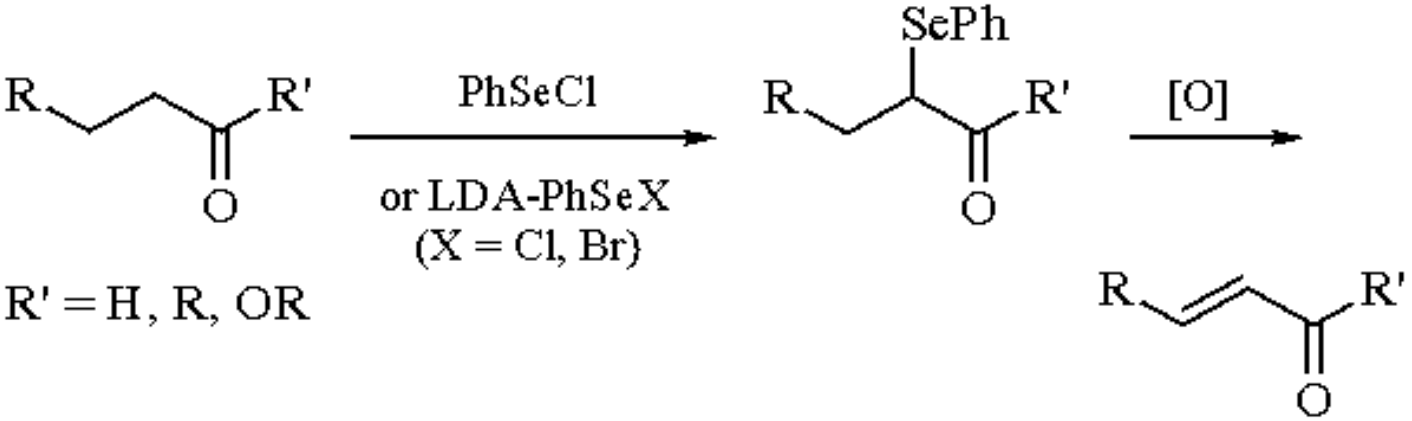

(17)

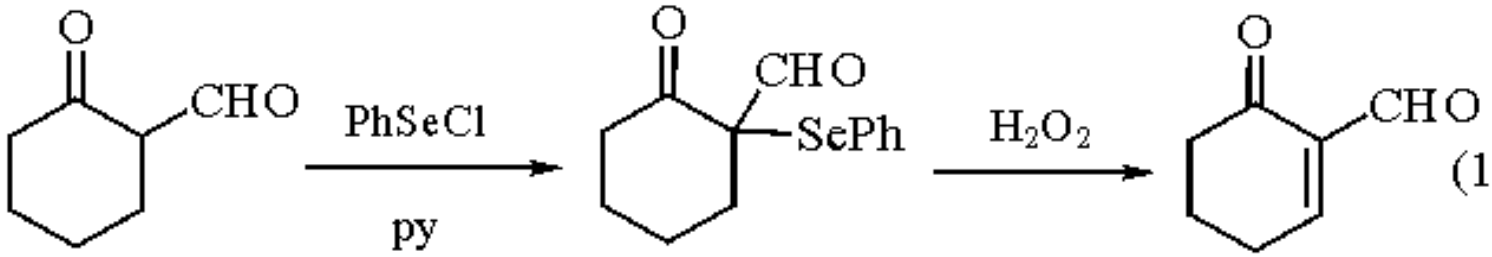

(18)

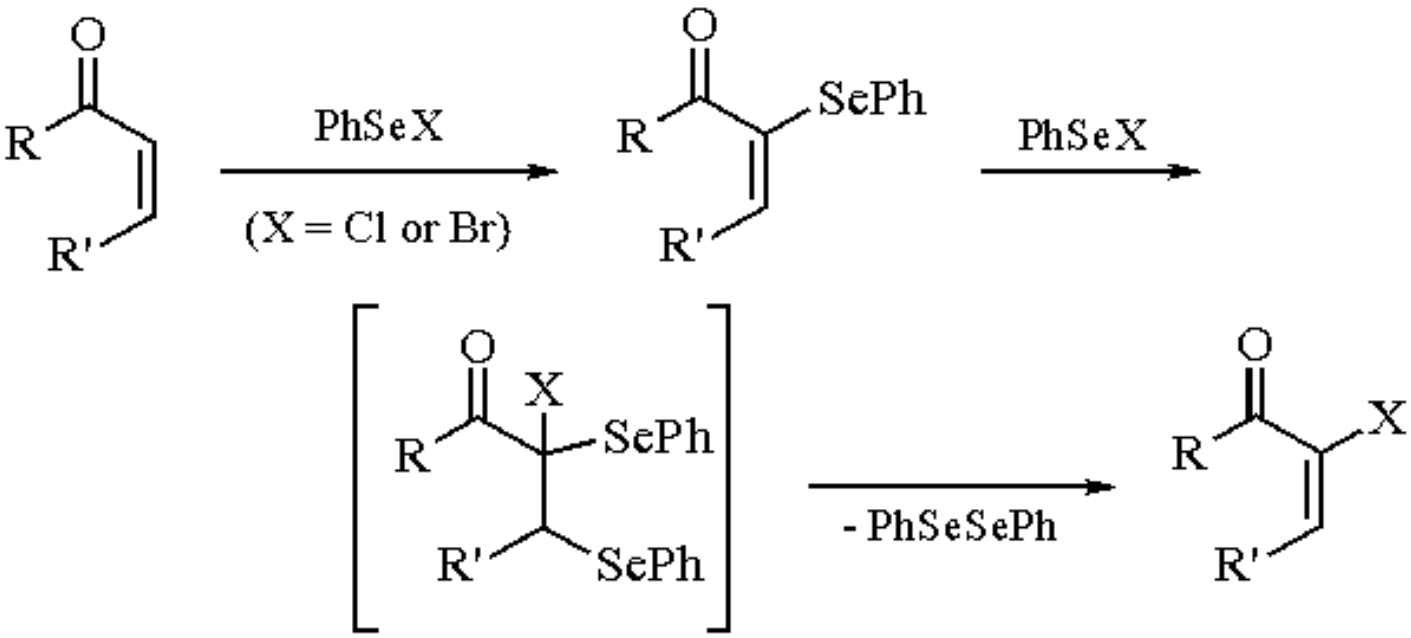

(19)

Enol ethers[53] and enamines[54] react with PhSeCl to give α-phenylseleno aldehydes in good yields (eq 20). On the other hand, cyclic acetals give the corresponding α-phenylseleno acetals by treatment with PhSeCl (eq 21).[53]

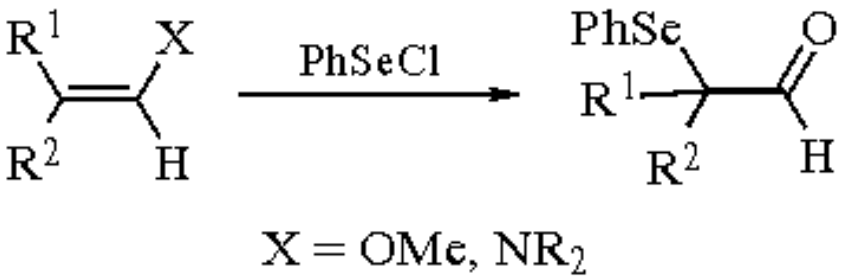

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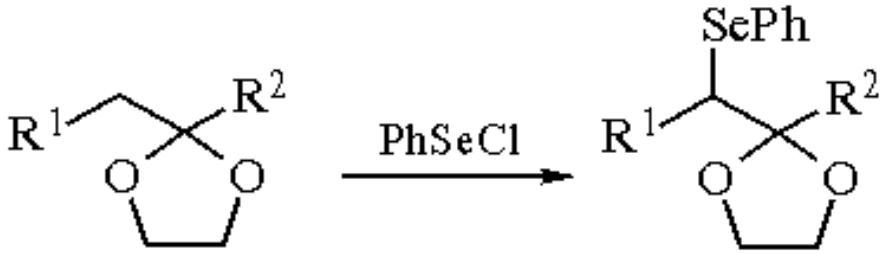

(21)

$R^2 = H$, alkyl

Reaction with α-Diazo Ketones.

PhSeCl rapidly reacts with α-diazo ketones at room temperature to provide α-chloro-α-phenylseleno ketones, which can be converted into α-chloro-α,β-unsaturated ketones by successive oxidation with hydrogen peroxide.[55,56] PhSeBr,[57] PhSeOAc,[57] PhSeSCN,[57] and PhSeF[58] undergo similar reaction with α-diazo ketones to give the corresponding α-substituted-α-phenylseleno ketones in good yields (eq 22).

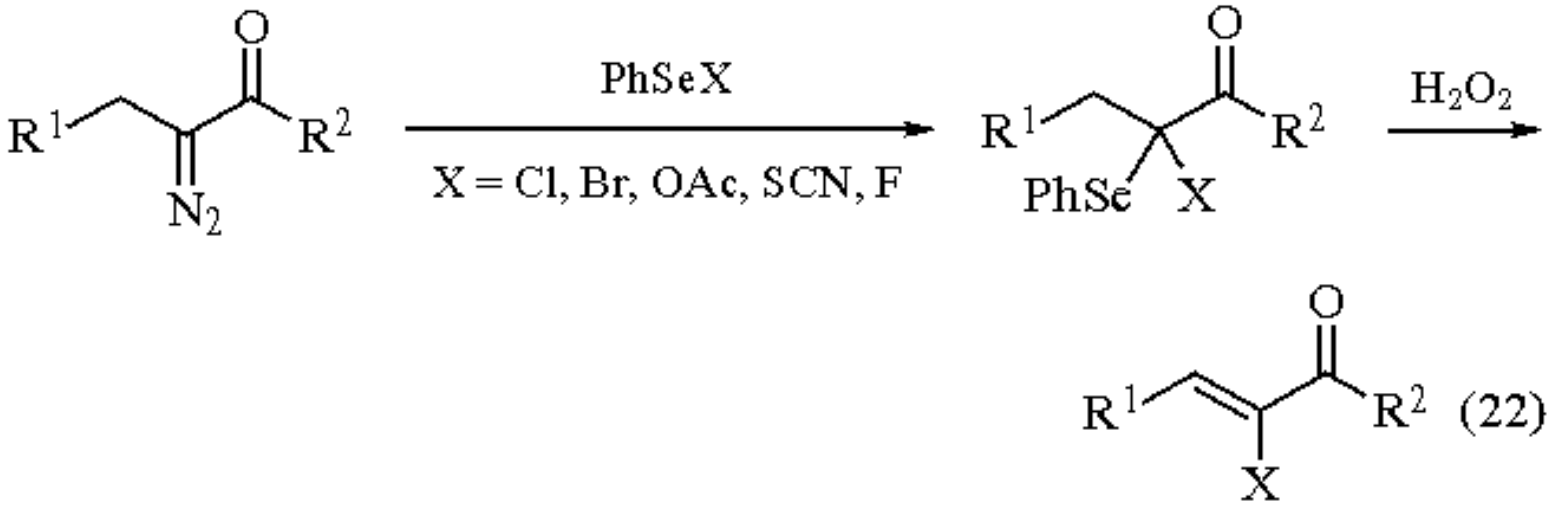

(22)

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Benzeneselenenyl Trifluoromethanesulfonate[1]

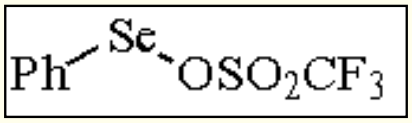

[112238-64-9] · $C_7H_5F_3O_3SSe$ · Benzeneselenenyl Trifluoromethanesulfonate · (MW 305.13)

(a highly electrophilic selenium reagent[2-8])

Alternate Name: benzeneselenenyl triflate.

Preparative Methods: usually prepared in situ by the reaction of ***Benzeneselenenyl Chloride*** with ***Silver(I) Trifluoromethanesulfonate*** in dichloromethane or toluene.[2] Two other economical methods are available. The first is the removal of hydrogen chloride from a mixture of benzeneselenenyl chloride and ***Trifluoromethanesulfonic Acid***.[3] The second is the comproportionation reaction of benzeneseleninic anhydride (see ***Benzeneseleninic Acid***) and ***Diphenyl Diselenide*** in the presence of trifluoromethanesulfonic anhydride.[4]

Handling, Storage, and Precautions: moisture sensitive. The dichloromethane solution free of silver chloride and water can be stored at rt for several weeks in the dark.[3]

Addition Reactions.

Benzeneselenenyl triflate is a highly electrophilic selenium reagent due to the poor nucleophilicity of triflate anion. It adds to alkenes having an intramolecular carboxy or hydroxy group to give cyclic products. For example, γ,δ-unsaturated carboxylic acids react with benzeneselenenyl triflate in dichloromethane to give γ-lactones in high yields (eq 1).[2] Under similar reaction conditions, 5- and 6-hydroxyalkenes are transformed to *exo*-cyclized tetrahydrofuran or -pyran derivatives (eq 2).[5,6] This reaction is useful for one-step conversion of acyclic terpene alcohols and derivatives into mono- or polycyclic compounds.[7] In the reaction with phenylacetylene, benzeneselenenyl triflate gives a *trans* adduct, a vinyl triflate, in high yield, which can be easily hydrolyzed to the ketone (eq 3).[4]

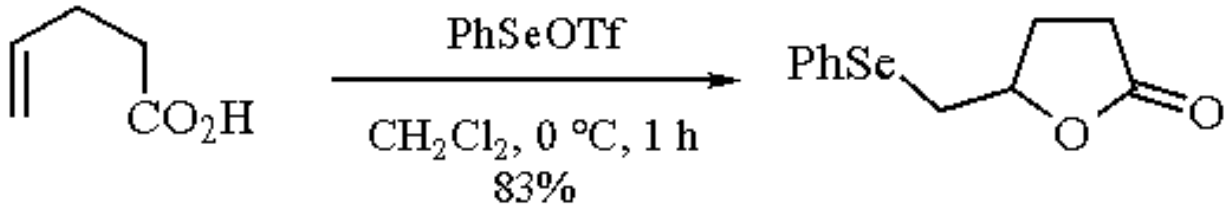

(1)

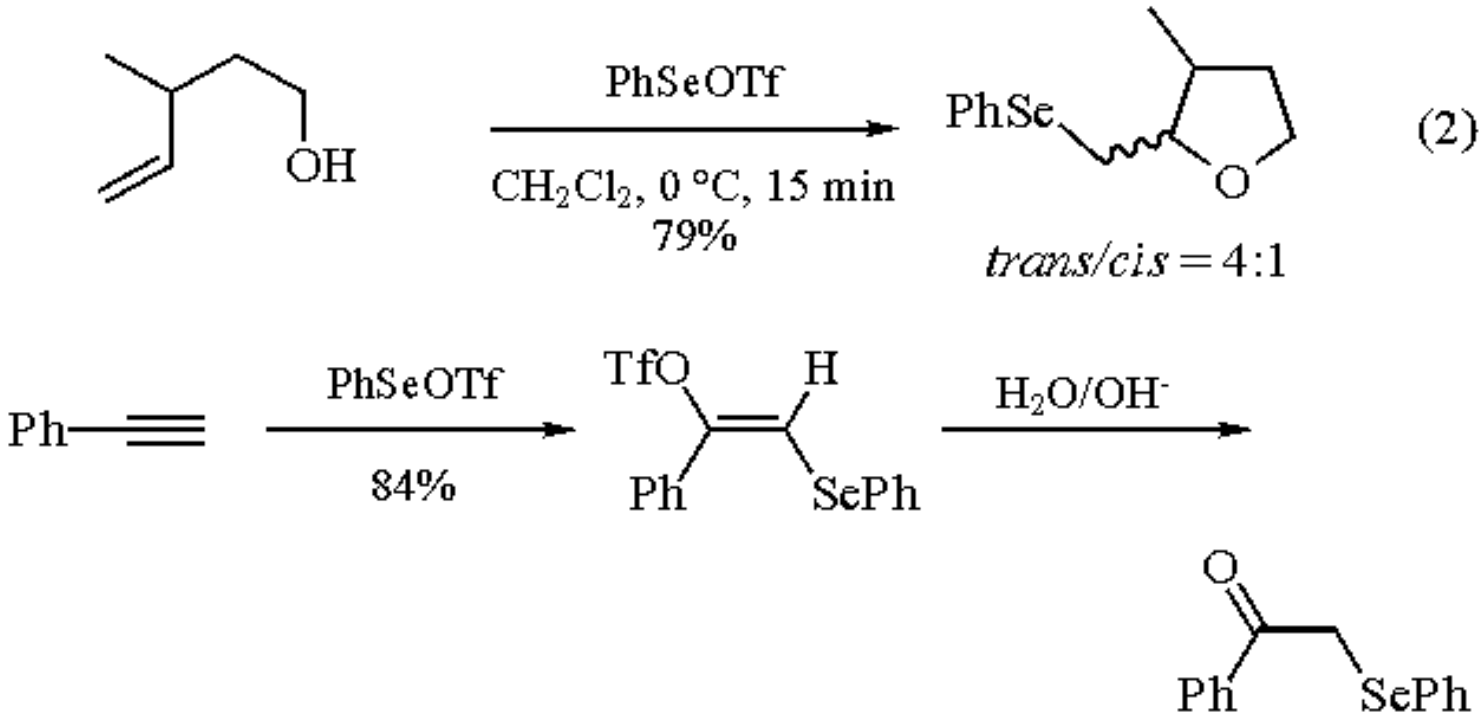

Selenium Polonovski Reaction.

Amine *N*-oxides react with benzeneselenenyl triflate to form selenoxyammonium salts, which rearrange to α-selenoxyamines in the presence of organic bases.[3] The products can be easily converted into secondary or tertiary amine derivatives (eq 4).

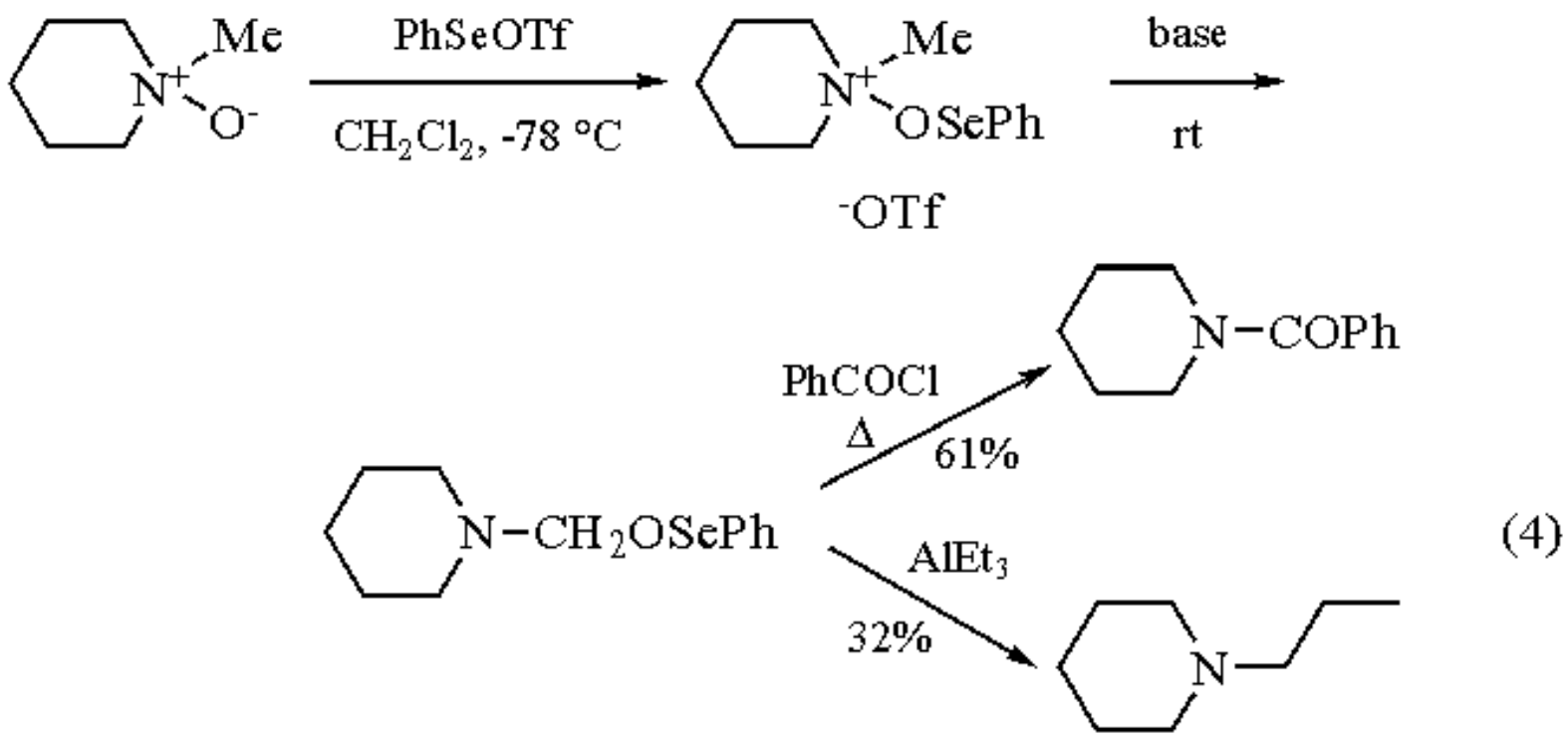

O-Glycosylation.

Alcohols efficiently undergo *O*-glycosylation under mild conditions by treatment with 1-thioglycosides and benzeneselenenyl triflate (eq 5).[8] This reaction can be applied to stereo- and regioselective synthesis of α-cyclodextrin derivatives.[9]

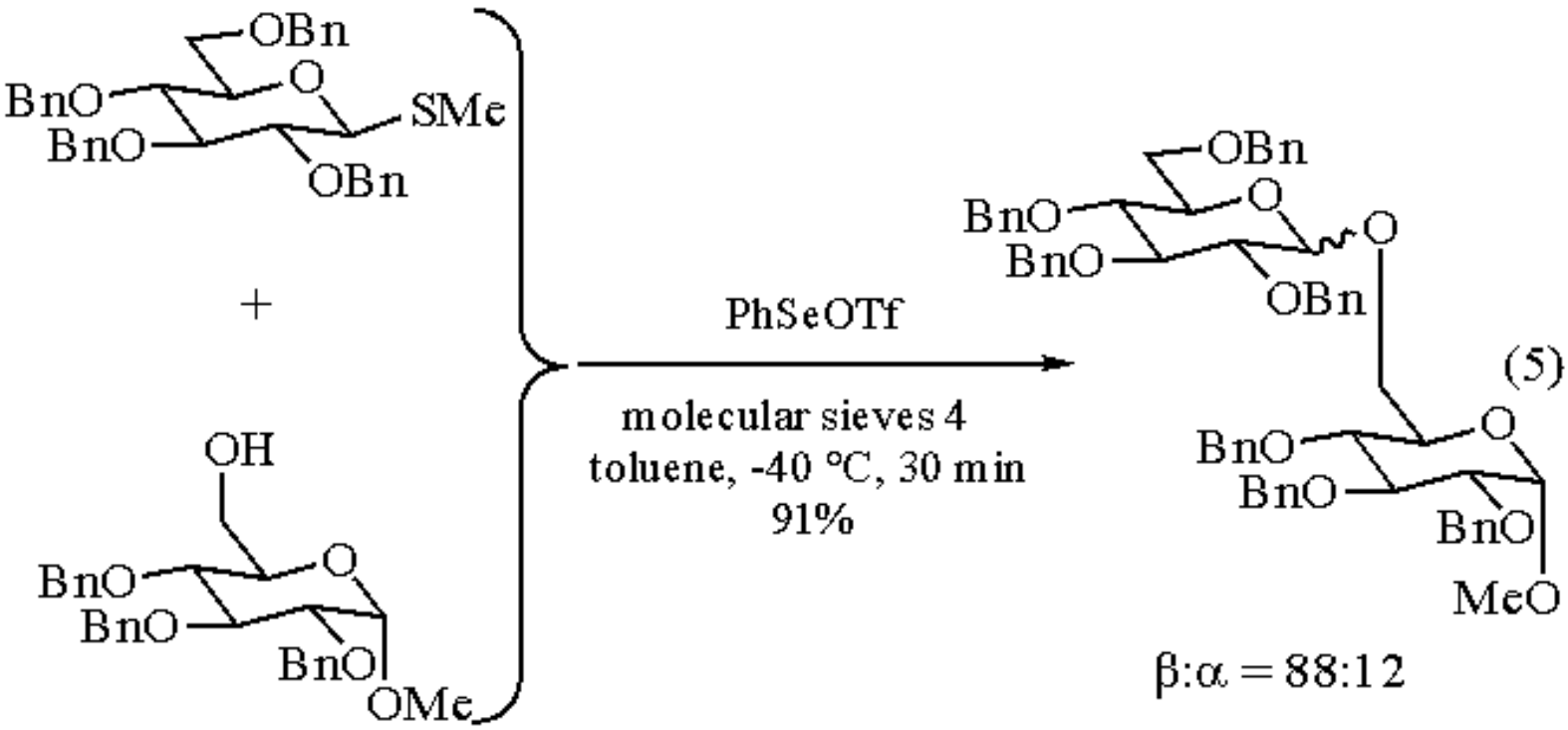

Related Reagents.

Benzeneselenenyl *m*-nitrobenzenesulfonate,[10a] benzeneselenenyl *p*-toluenesulfonate,[10b] (phenylseleno)dimethylsulfonium (PhSe+SMe_2) fluoroborate,[11] and (phenylseleno)methylphenylselenonium (PhSe+SeMePh) fluoroborate[12] can be considered as analogs of benzeneselenenyl triflate. (Phenylseleno)dimethylsulfonium (PhSe+SMe_2) fluoroborate reacts with electron-rich aromatic compounds to give the products of electrophilic substitution (eq 6).[11] On the other hand, (phenylseleno)methylphenylselenonium (PhSe+SeMePh) fluoroborate reacts selectively with allylic silanes to give the corresponding allylic selenides, which easily undergo 2,3-sigmatropic rearrangement to allylic alcohols by oxidation (eq 7).[12]

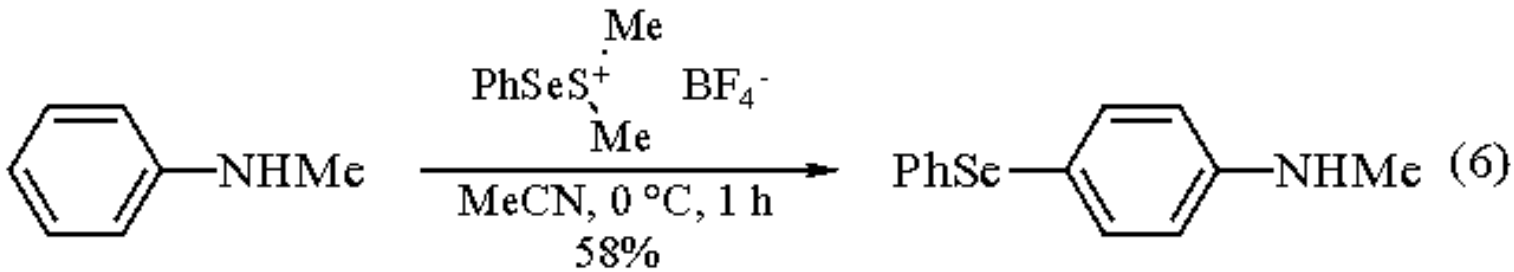

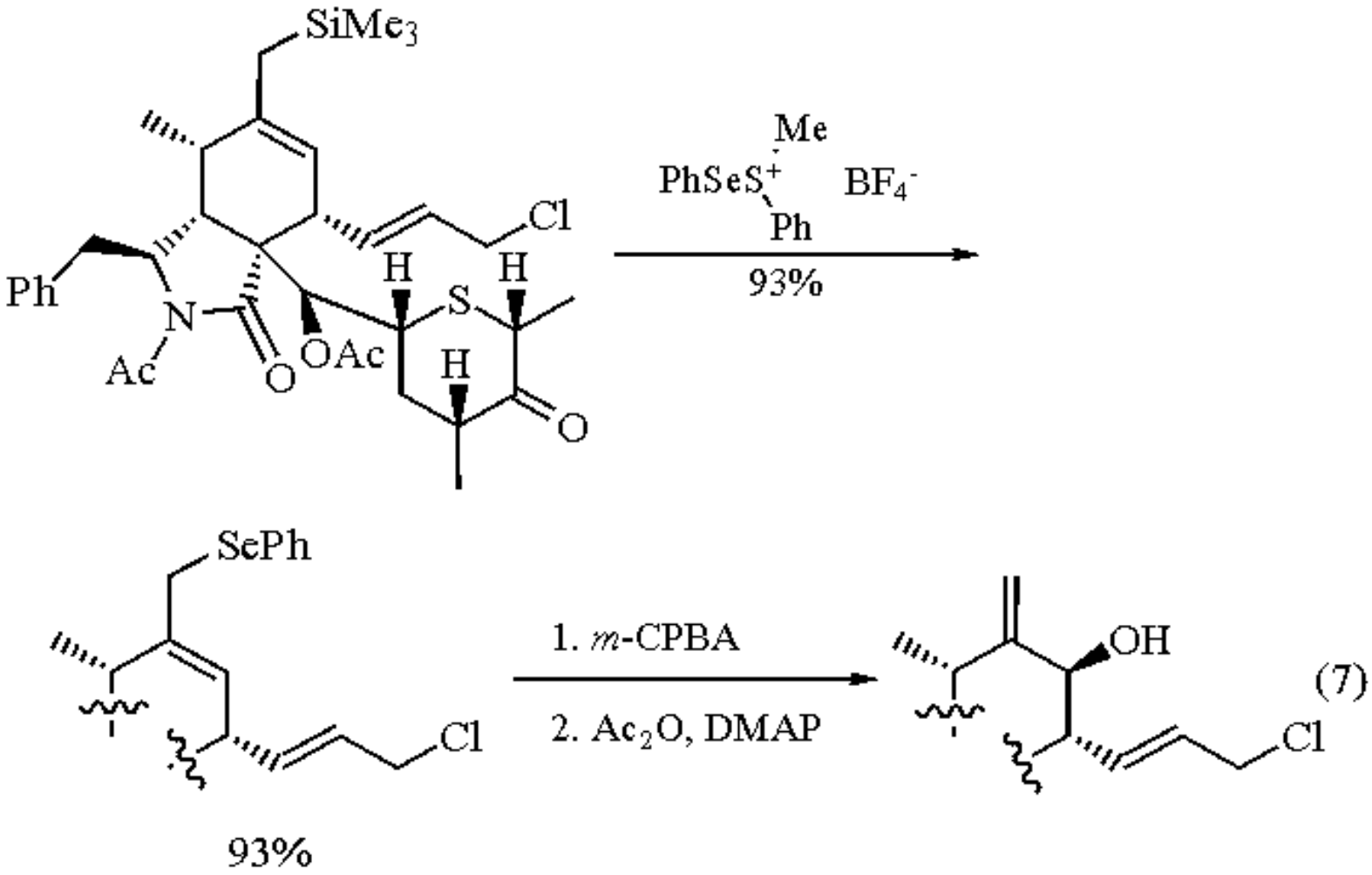

See also ***Benzeneselenenyl Bromide***, ***Benzeneselenenyl Chloride***, ***Benzenesulfenyl Chloride***, and ***2-Pyridinesulfenyl Bromide***.

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Benzeneseleninic Acid

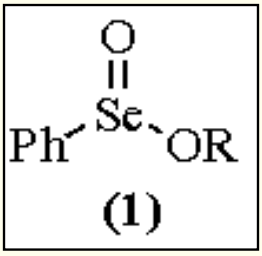

(R = H)

[6996-92-5] · $C_6H_6O_2Se$ · Benzeneseleninic Acid · (MW 189.07) (R = Se(O)Ph) (anhydride)

[17697-12-0] · $C_{12}H_{10}O_3Se_2$ · Benzeneseleninic Anhydride · (MW 360.13)

(oxidizing agents of many functional groups[1])

Physical Data: acid mp 121 °C; anhydride mp 164-165 °C.

Solubility: both compounds sol chloroform, dichloromethane, THF; the acid is amphoteric and sol in water at low and high pH.

Form Supplied in: both compounds are commercially available white solids.

Purification: the anhydride is readily hydrolyzed and may contain substantial amounts of the acid. It can be regenerated from the latter by heating at 120-130 °C under vacuum (ca. 0.1 Torr) for a few hours.

Handling, Storage, and Precautions: the acid is stable to prolonged storage on the shelf; the anhydride should be kept in a desiccator. Both compounds are toxic and can react vigorously with reducing agents; the acid forms an explosive complex with hydrogen peroxide. Use in a fume hood.

Introduction.

Benzeneseleninic anhydride (BSA) is the more commonly used reagent and benzeneseleninic acid probably functions in at least some cases by generating the anhydride in situ. Excess reagent can be removed at the end of a reaction by washing with aqueous K_2CO_3 or KOH. ***Diphenyl Diselenide*** is the usual byproduct and often requires chromatographic separation.

Oxidation of Alcohols and Phenols.

Primary benzylic alcohols are oxidized to the corresponding aldehydes with BSA in refluxing benzene, chlorobenzene, or THF, while various secondary alcohols afford ketones under similar conditions (eq 1).[2] In principle, it is possible to oxidize 3 mol of the alcohol with 1 mol of the anhydride, but in practice an excess of the latter is generally more efficacious. The reagent can also be generated in situ from a catalytic amount of diphenyl diselenide and ***t-Butyl Hydroperoxide***.[2c] The method is relatively mild and tolerates other easily oxidized groups such as selenide and sulfide. Under more forcing conditions, the product sometimes undergoes dehydrogenation (see below).

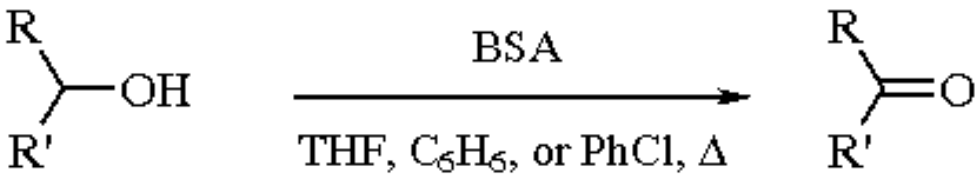

(1)

R,R' = alkyl, aryl, H

Phenols are typically oxidized to *o*-quinones with the anhydride and to *p*-quinones with the acid, often with high regioselectivity and in good yield (eq 2).[3] However, the formation of hydroxydienones, or of coupled products, dominates in some cases (eq 3).[4] When the reaction is performed with BSA in the presence of ***Hexamethyldisilazane***, the corresponding *N*-phenylselenoimine is generally obtained, again with high *ortho* selectivity (eq 4). This provides a means for aromatic amination when used in conjunction with reduction of the imine.[5]

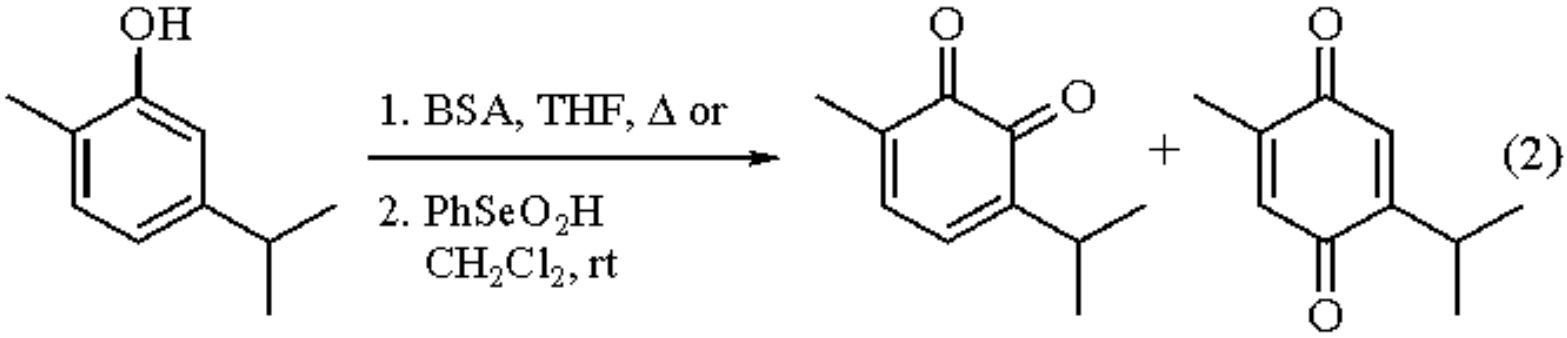

(2)

1.	60%	25%
2.	7%	82%

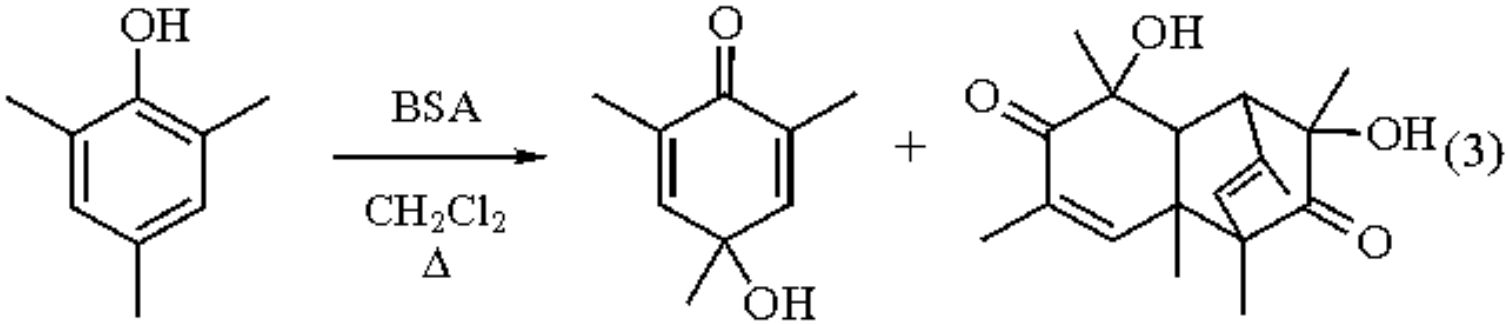

(3)

30% 48%

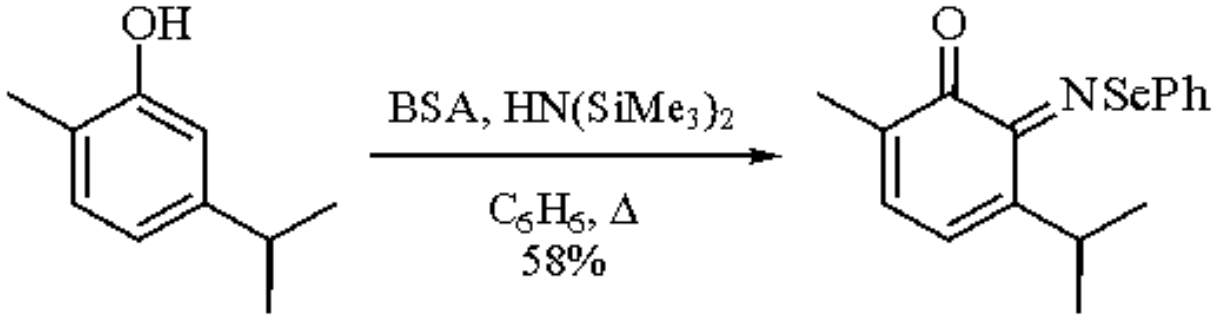

(4)

Dehydrogenation of Carbonyl Compounds.

Ketones, particularly of the steroid or terpenoid variety, produce enones or dienones[6] when heated with the anhydride in chlorobenzene or diglyme at 95-132 °C The method may be used in conjunction with eq 1 to transform alcohols directly to dienones in one step. A further refinement permits the use of catalytic amounts of the anhydride in the presence of a co-oxidant such as iodoxybenzene or *m*-iodoxybenzoic acid (eq 5), which recycles the byproduct diphenyl diselenide.[7] Lactams[2b] and lactones[8] undergo similar dehydrogenations (eq 6), although the former compounds sometimes produce imides[2b] instead.

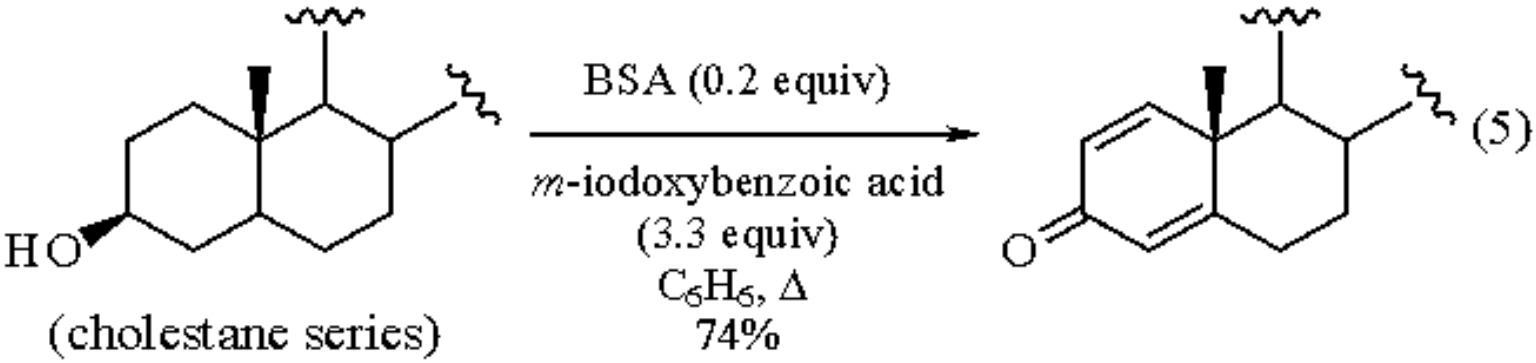

(5)

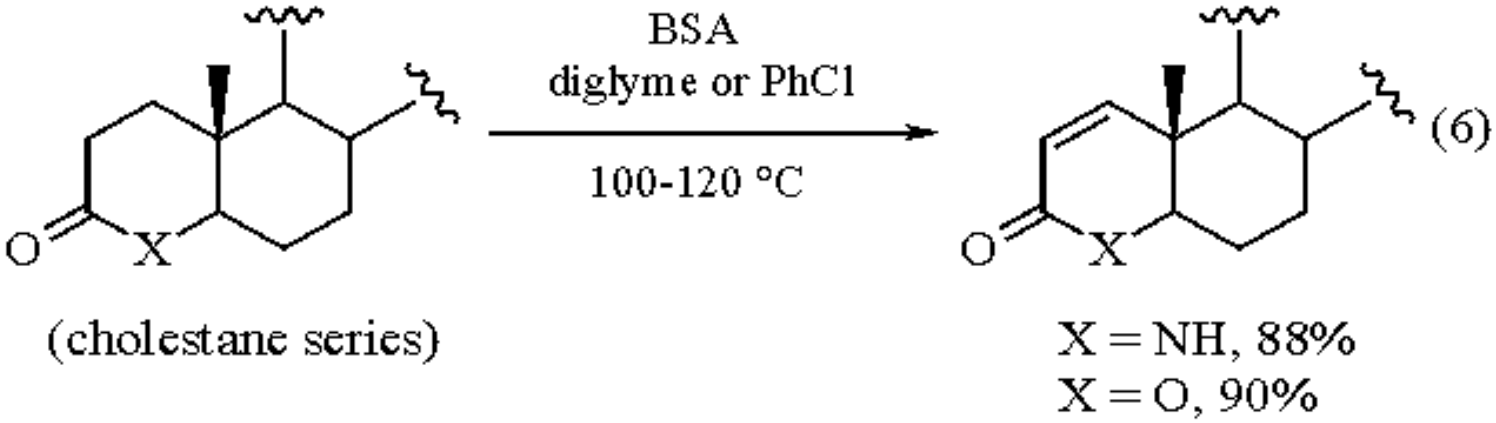

(6)

Oxidation of Amines, Hydrazines, and Hydrazones.

Primary amines afford ketones when oxidized with the anhydride under mild conditions (eq 7).[9] Synthetically useful yields are generally limited to non-enolizable ketones, however. Enamides are oxidized to carbinolamides and other hydroxy or keto derivatives,[10] and indolines produce indoles under similar conditions.[11] Benzeneseleninic acid or

anhydride react with ***Hydrazine*** to generate ***Diimide***,[12] whereas various types of 1,2- and 1,1-disubstituted derivatives produce azo compounds[12,13] and tetrazenes,[14] respectively (eqs 8 and 9), at or below rt. This procedure can also be employed to generate the reactive dienophile *N*-phenyl-1,2,4-triazoline-3,5-dione from *N*-phenylurazole,[15] and to oxidize hydroxylamines to nitroso compounds.[13] *N*-Acylhydrazines (hydrazides) and *N*-alkyl- or *N*-arylsulfonylhydrazines (sulfonhydrazides) are converted into selenoesters[12] and selenosulfonates,[16] respectively, when treated with the seleninic acid under mild conditions (eqs 10 and 11).

$$Ph_2CHNH_2 \xrightarrow[CH_2Cl_2,\ rt]{BSA} [Ph_2C{=}NH] \xrightarrow{H_2O} Ph_2C{=}O \quad (7)$$

97%

$$PhNHNHPh \xrightarrow[CH_2Cl_2,\ rt]{BSA} PhN{=}NPh \quad (8)$$

97%

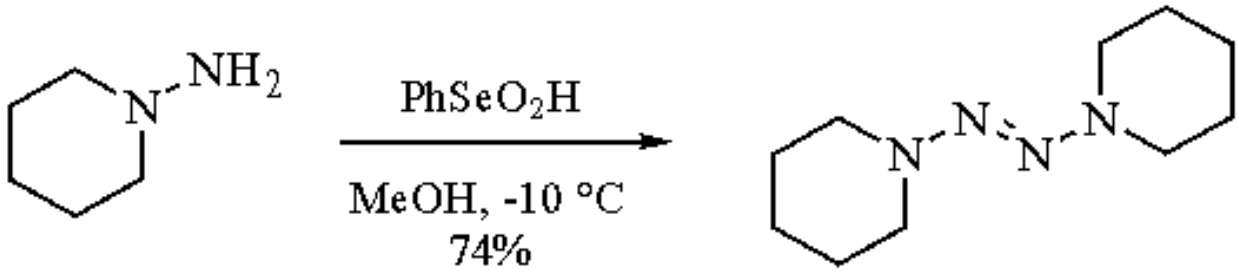

(9)

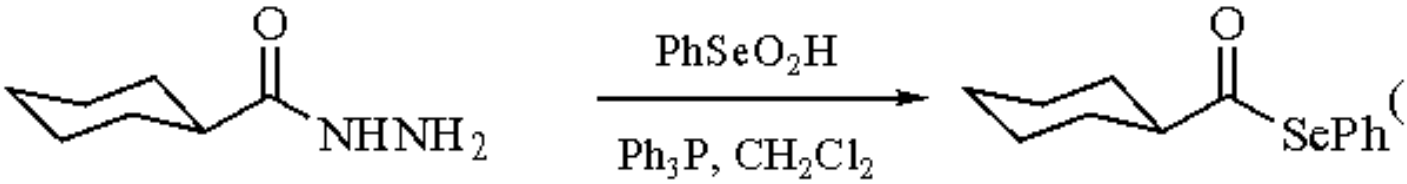

(10)

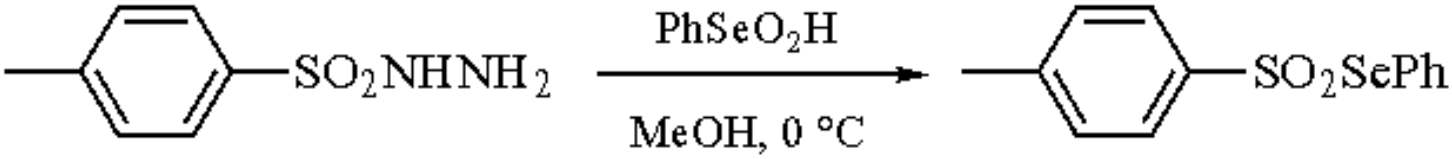

(11)

BSA is a useful reagent for the regeneration of ketones from their hydrazones, oximes, or semicarbazones (eq 12).[13] Phenyl-, *p*-nitrophenyl- and tosylhydrazones react rapidly in warm THF, whereas the 2,4-dinitrophenyl and *N*,*N*-dimethyl derivatives are considerably more resistant. Aldehydes are similarly obtained from their tosylhydrazones or oximes, but not from phenyl- or *p*-nitrophenylhydrazones, which afford *N*-acylazo products instead.

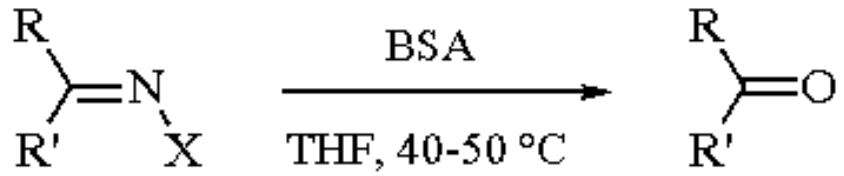

(12)

X = NHAr, NHTs, OH, NHC(O)NH$_2$
R, R' = alkyl, aryl, H

Oxidation of 1,3-Dithiolanes and Thiocarbonyl Compounds.

BSA is also an effective reagent for the deprotection of aldehydes and ketones from their 1,3-dithiolane derivatives (eq 13).[17] The reaction proceeds at or near rt, is applicable to sterically hindered systems, and often gives cleaner results than conventional hydrolytic methods. Moreover, it can be employed under anhydrous conditions, an advantage if other moisture-sensitive groups are present. The similar deprotection of 1,3-dithianes and 1,3-oxathiolanes is, however, generally less efficacious, while selenoacetals afford the parent aldehydes and ketones in typically high yields.[18] The conversion of thiones, xanthates, thionoesters, trithiocarbonates, thioureas, and other thio- and selenocarbonyls into the corresponding carbonyl derivatives can also be accomplished with BSA at rt (eq 14),[19] although enolizable thiones afford more complex products.

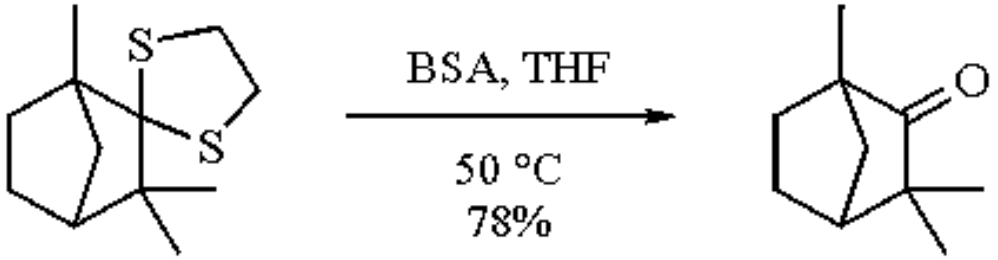

(13)

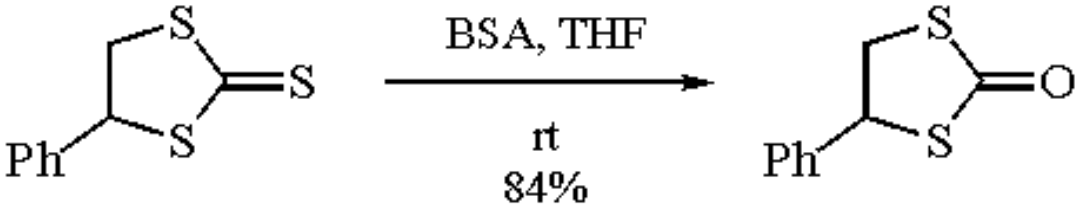

(14)

Miscellaneous Oxidations.

Benzylic hydrocarbons are oxidized to aldehydes in modest to good yields by benzeneseleninic anhydride at elevated temperatures (eq 15).[20] Overoxidation to carboxylic acids and the competing formation of phenylselenenylated derivatives often limits the utility of the method. The comproportionation of benzeneseleninic anhydride with diphenyl diselenide generates electrophilic Se^{II} species in situ. The mixture can thus be employed in the transformation of alkenes to α-phenylseleno ketones or aldehydes.[21] Terminal alkenes afford chiefly the 1-phenylseleno-2-ketone regioisomers (eq 16), whereas the opposite regiochemistry is favored with ethers or esters of allylic alcohols (eq 17). Similarly, the comproportionation of diphenyl diselenide and benzeneseleninic acid,[22] or the reduction of the latter with

Hypophosphorous Acid,[23] in the presence of alkenes results in the addition of PhSeOH to produce β-hydroxy selenides. α-Hydroxylations of polycyclic ketones occur at an adjacent ring junction position when these compounds are heated in refluxing toluene or chlorobenzene with BSA (eq 18).[24] These reactions are, however, sluggish and often produce only modest yields.

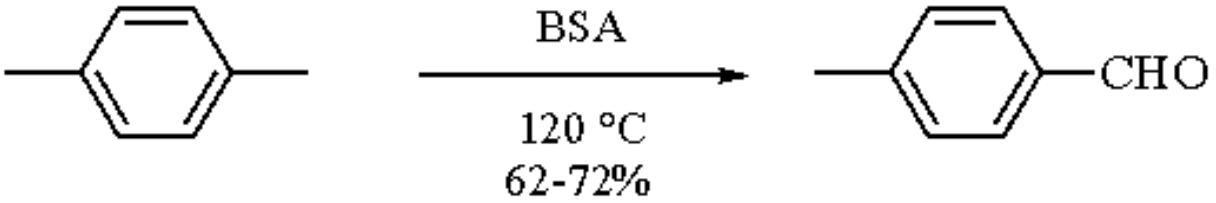

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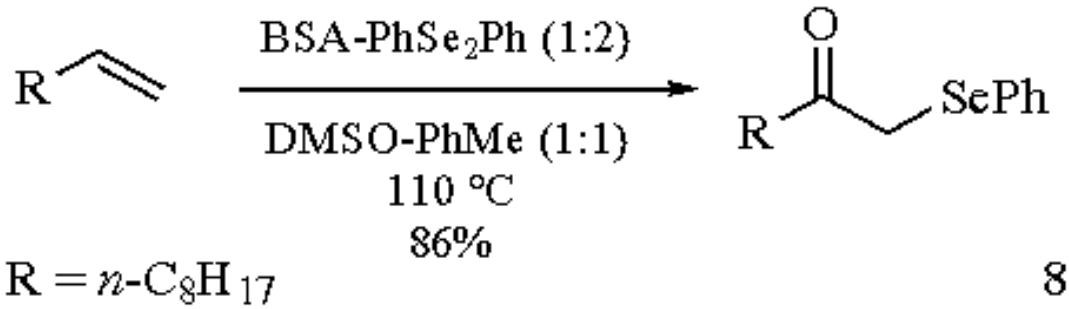

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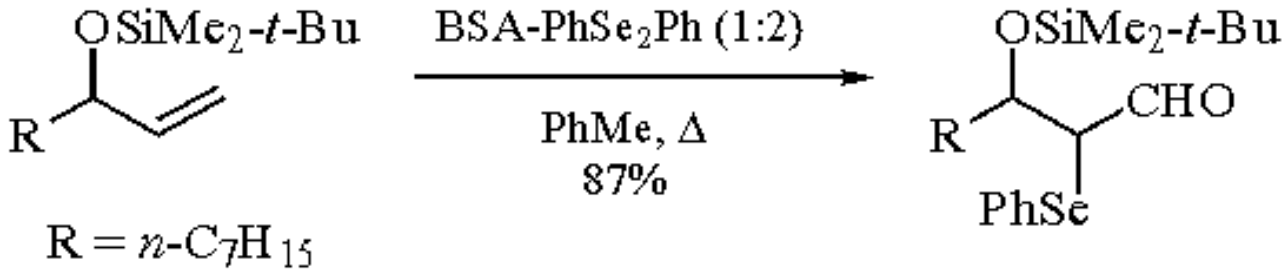

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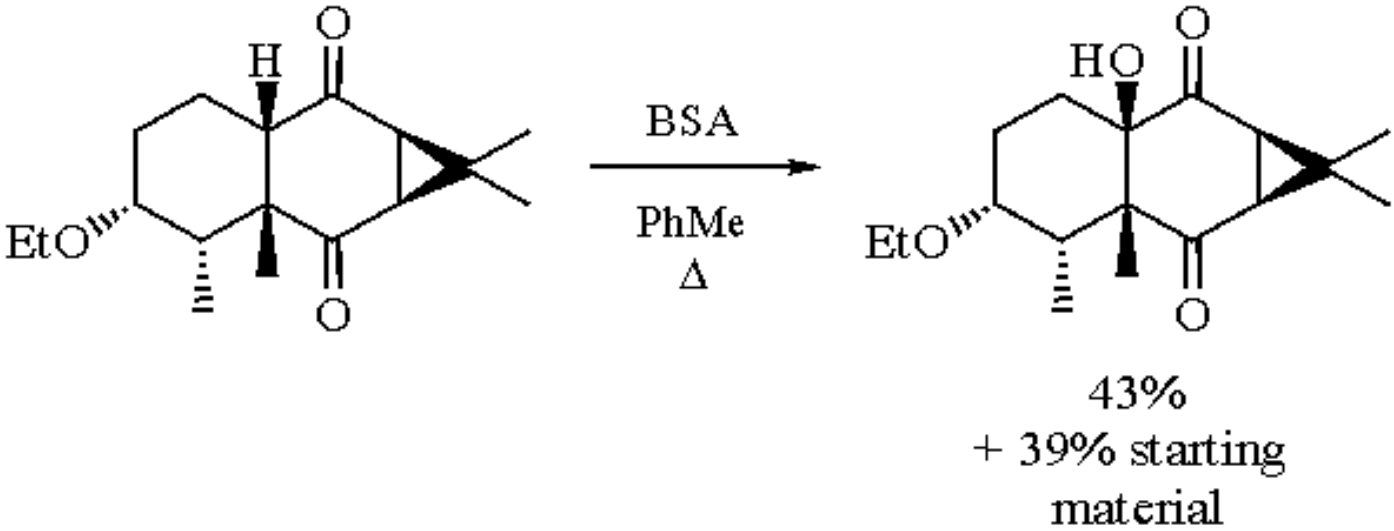

(18)

Benzeneseleninic acid reacts with ***Hydrogen Peroxide*** to produce the corresponding perseleninic acid in situ. The latter is in turn a convenient reagent for the oxidation of sulfides to sulfones, aldehydes to carboxylic acids, alkenes to epoxides, and in Baeyer-Villiger reactions (see ***Benzeneperoxyseleninic Acid***).

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Benzeneseleninyl Chloride

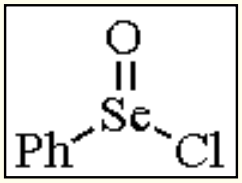

[57204-85-0] · C_6H_5ClOSe · Benzeneseleninyl Chloride · (MW 207.52)

(introduction of α,β-unsaturation in ketones and esters;[1] oxidation of amines[2] and aldoximes;[3] halogenation of alkenes[4] and aromatic compounds[5] with aluminum halides)

Physical Data: mp 75 °C.

Solubility: sol CH_2Cl_2, THF.

Preparative Method: benzeneseleninyl chloride is obtained from the oxidation of ***Benzeneselenenyl Chloride*** in CH_2Cl_2[1] or CCl_4[6] with ***Ozone***.

Handling, Storage, and Precautions: benzeneseleninyl chloride crystals are extremely hygroscopic and care must be taken to avoid moisture. Solutions in CH_2Cl_2 are stable for weeks when stored at -15 °C. Selenium compounds are potentially toxic and should be handled in a fume hood.

Ketone and ester enolates react with benzeneseleninyl chloride to give α-phenylseleninyl intermediates, which undergo selenoxide elimination to form enones upon warming to room temperature.[1,7] Since the conventional two-step selenenylation/oxidation procedure gives higher yields with fewer byproducts (see ***Benzeneselenenyl Bromide***, ***Benzeneselenenyl Chloride***, and ***Diphenyl Diselenide***), the use of benzeneseleninyl chloride is recommended specifically to avoid competing or preferential oxidation (eq 1).[7]

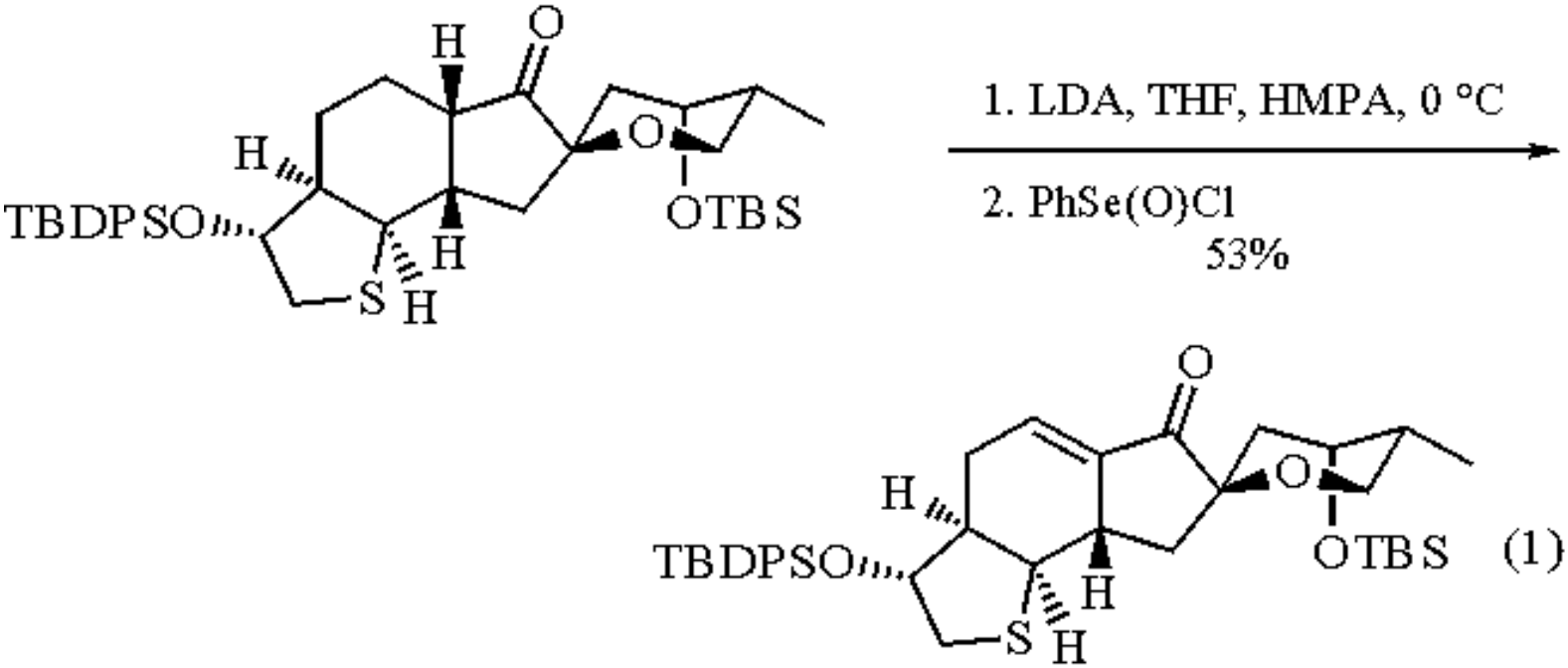

Primary aryl-substituted amines are oxidized cleanly to ketones and nitriles, presumably via an intermediate seleninamide.[2] Although aldoximes are converted to nitriles in 71-96% yields at rt, comparable results are obtained using readily available benzenesulfenyl chloride or benzeneselenenyl chloride.[3]

The addition of an equivalent of ***Aluminum Chloride*** to a solution of benzeneseleninyl chloride in CH_2Cl_2 produces a complex which chlorinates electron-rich aromatic compounds, such as anisole, diphenyl ether, and *N*,*N*-dimethylaniline, exclusively in the *para* position.[5] This complex also regioselectively chlorinates thiophenes[8] and converts alkenes to vinyl chlorides (eq 2).[4,9] Similarly, a highly efficient brominating complex is formed when aluminum bromide is combined with benzeneseleninyl chloride (eq 3).[8]

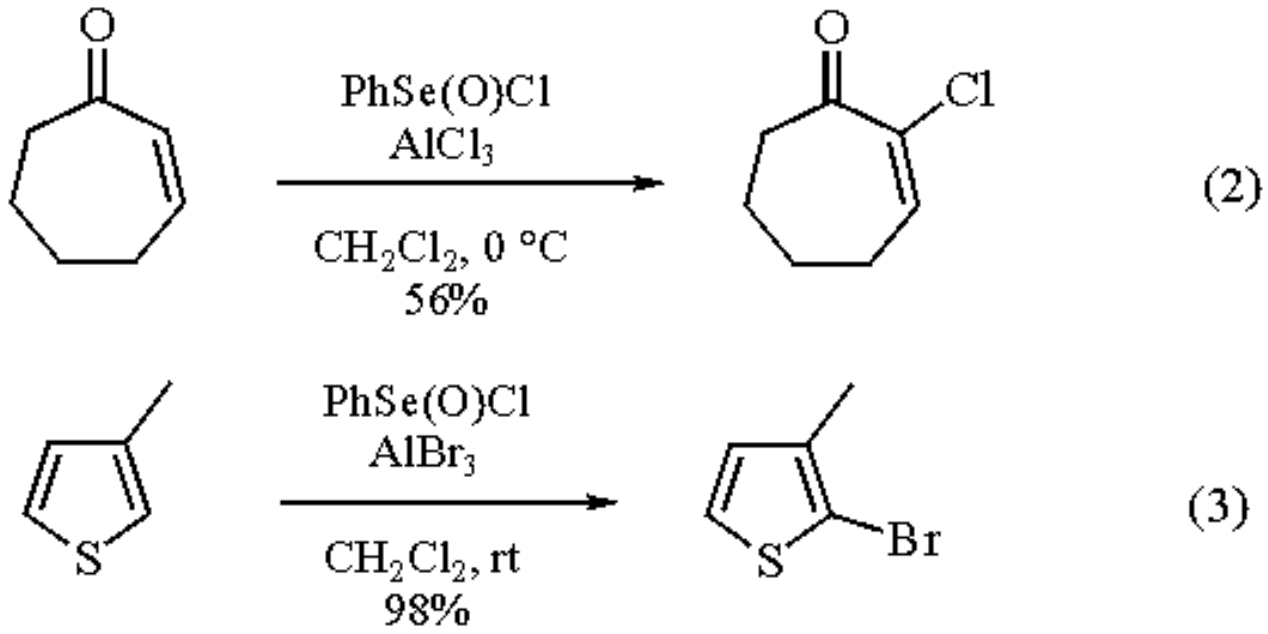

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Benzeneselenol[1]

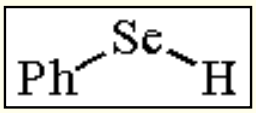

[645-96-5] · C_6H_6Se · Benzeneselenol · (MW 157.07)

(a source of selenolate ions; a selenation reagent for organic halides, alcohols, amines, ethers, alkynes, and carbonyl compounds; a mild reducing agent)

Physical Data: bp 73-74 °C/20 mmHg.

Solubility: sol benzene, Et_2O, THF, acetonitrile; insol H_2O, but sol aq NaOH.

Preparative Methods: benzeneselenol is synthesized by the reaction of ***Phenylmagnesium Bromide*** with metallic ***Selenium***, followed by quenching with aqueous hydrochloric acid.[2a] Similar hydrolysis of sodium selenolate prepared by the reduction of ***Diphenyl Diselenide*** with ***Sodium Borohydride*** is a convenient alternative.[2b] In addition, ***Phenyl Trimethylsilyl Selenide*** can be employed as a useful precursor of benzeneselenol upon treating with methanol.[2c] Purification of benzeneselenol is performed by distillation under reduced pressure. ^{1}H NMR ($CDCl_3$) δ 1.54 (PhSeH); ^{13}C NMR ($CDCl_3$) δ 124.46, 126.45, 129.26, 132.71 (PhSeH).

Handling, Storage, and Precautions: pure benzeneselenol is a colorless liquid, but, on exposure to air, the liquid turns yellow to an extent that depends on the concentration of diphenyl diselenide formed by air-oxidation of PhSeH. Thus, it should be stored under nitrogen in the dark, and is conveniently handled using syringe technique. Use in a fume hood.

Generation of Phenylselenolate Ions.

Benzeneselenol has greater acidity than benzenethiol (pK_a = 5.9 (PhSeH); 6.5 (PhSH)),[2b] and therefore it gives lithium or sodium phenylselenolates in the presence of bases such as MeLi (in Et_2O),[3a] NaH (in THF),[3b,c] and aq NaOH.[3d] Alternatively, phenylselenolate ions are prepared by the reduction of ***Diphenyl Diselenide*** with $NaBH_4$ (in EtOH or DMF),[4] Na (in THF, HMPA, or liq NH_3),[3b,c,5] or NaH (in THF or DMF).[6] Sodium selenolate prepared by the $NaBH_4$ reduction of $(PhSe)_2$ is considered to be a complex with triethyl borate of the form $Na^+[PhSeB(OEt)_3]^-$,[4c] and indeed has lower nucleophilicity in comparison with uncomplexed PhSeNa generated by the reduction of $(PhSe)_2$ with Na (or NaH).[3b,c] The selenolate ions are generally much more sensitive to air (molecular oxygen) compared with PhSeH itself. The oxidation of PhSeH or its anions by air or other oxidizing agents such as H_2O_2 or Br_2 provides a general method for synthesis of diphenyl diselenide,[7] which is a key intermediate compound for preparation of

various organoselenium reagents.

Substitution Reactions.

The selenolate ions generated are widely utilized as reagents for introducing a PhSe group into organic molecules. For example, nucleophilic substitution of organic halides by selenolates leads to the corresponding selenides in good yields (i.e. RX + $PhSe^-$ -> RSePh + X^-).[5a,8] A similar reaction using acid halides affords selenoesters,[9] which are utilized as precursors of acyl radicals (eq 1).[10]

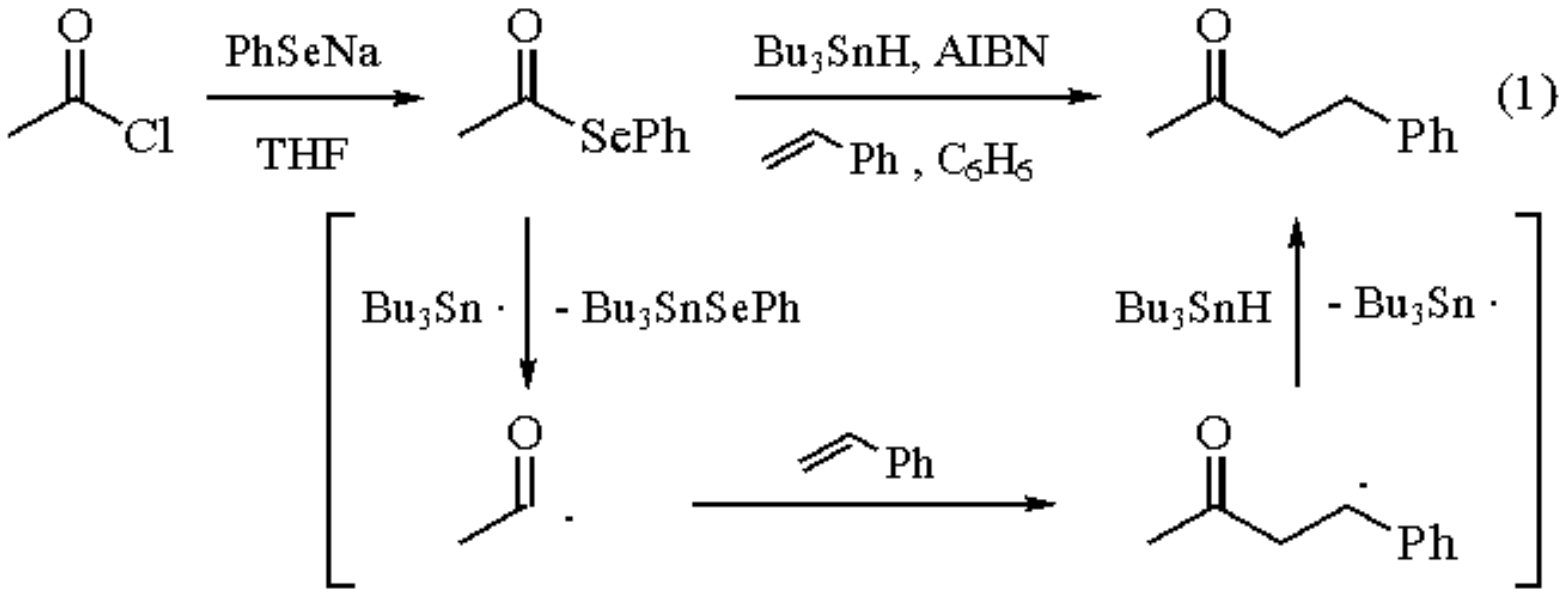

Organic sulfonates also undergo displacement by $PhSe^-$ to give selenides.[5a,11] Amines can be converted into selenides via the nucleophilic displacement of corresponding ditosylamides by selenolate ions (i.e. RNH_2 -> $RNTs_2$ -> RSePh),[12] or by reaction with benzeneselenol at high temperatures.[2b]

Upon treatment of esters with selenolate ions, alkyl-oxygen cleavage reaction occurs to provide carboxylic acids and alkyl selenides (i.e. RCOOR´ + $PhSe^-$ -> RCOOH + PhSeR´).[3b,c] The use of lactones as the substrates leads to the synthesis of o-phenylselenenyl carboxylic acids.[4b,5b,6,13] Ring-opening of epoxides also takes place by $PhSe^-$ to give β-hydroxy selenides,[14a-c] which can be converted into allylic alcohols via oxidative elimination of the phenylseleno group (eq 2).[4a] Acyclic ethers undergo C-O bond cleavage upon a similar treatment.[14d] Furthermore, C-C bond cleavage of activated cyclopropanes by $PhSe^-$ can proceed efficiently.[15]

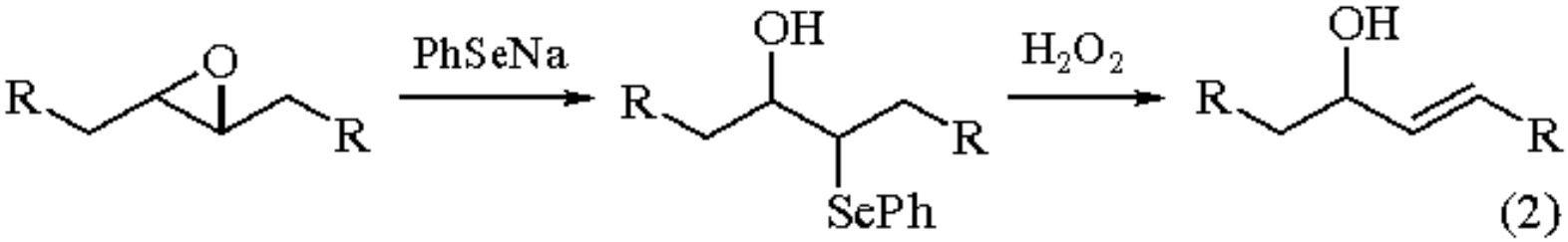

The ring-opening of epoxides[16a] and the alkyl-oxygen cleavage of esters are also attained by the use of benzeneselenol under acidic conditions. For example, alkyl acetates are converted to the corresponding selenides by

the assistance of $BF_3.Et_2O$ (i.e. ROAc + PhSeH -> RSePh).[16b,c] Direct transformation of alcohols to selenides is possible by treatment with PhSeH in the presence of H_2SO_4, HCl, $ZnCl_2$, or $BF_3.Et_2O$ (i.e. ROH + PhSeH -> RSePh).[17]

Other preparative methods of selenides using selenolate ions are the transition metal-catalyzed reactions with organic halides[18a-c] or amines,[18d] and the photostimulated $S_{RN}1$ reactions with aryl or some alkyl halides.[19]

Addition Reactions.

In general, addition of benzeneselenol to unactivated alkenes[20a] hardly proceeds. However, if the alkenes bear a conjugated carbonyl group, such as -CHO, -C(O)R, -COOR, etc., the selenol adds smoothly under acidic,[20b] basic,[20c-f] or neutral[2c] conditions. Similarly, addition to conjugate dienes occurs under neutral conditions to give mainly 1,4-adducts.[21] In the presence of an optically active base such as an alkaloid, the addition of PhSeH to enones proceeds with asymmetric induction (eq 3).[20f]

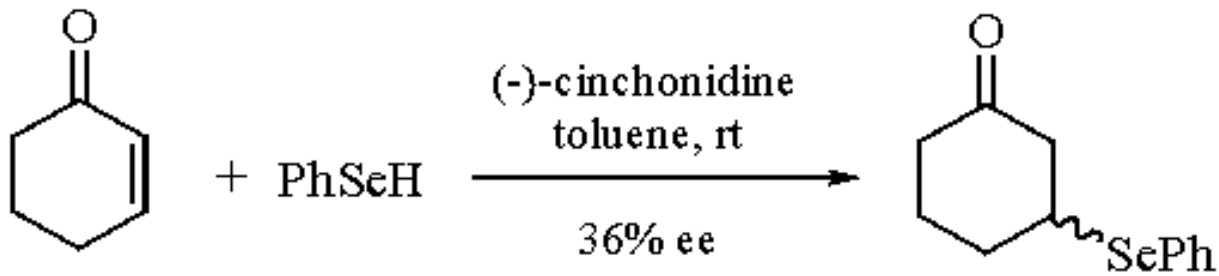

(3)

Addition of benzeneselenol to alkynes is a useful tool for the synthesis of vinylic selenides. Under neutral conditions, the addition is initiated by a trace amount of oxygen contained in the reaction system, and proceeds by a radical chain mechanism. In this case, anti-Markovnikov-type adducts are formed exclusively (eq 4).[22] Contrary to this, when the same reaction is conducted in the presence of a catalytic amount of ***Palladium(II) Acetate***, Markovnikov-type adducts are obtained selectively in place of anti-Markovnikov adducts.[23] When the oxygen-induced radical reaction of allenes with PhSeH is examined, vinylic selenides are formed via the selective attack of PhSe&bdot; at the central carbon atom of allenes.[24]

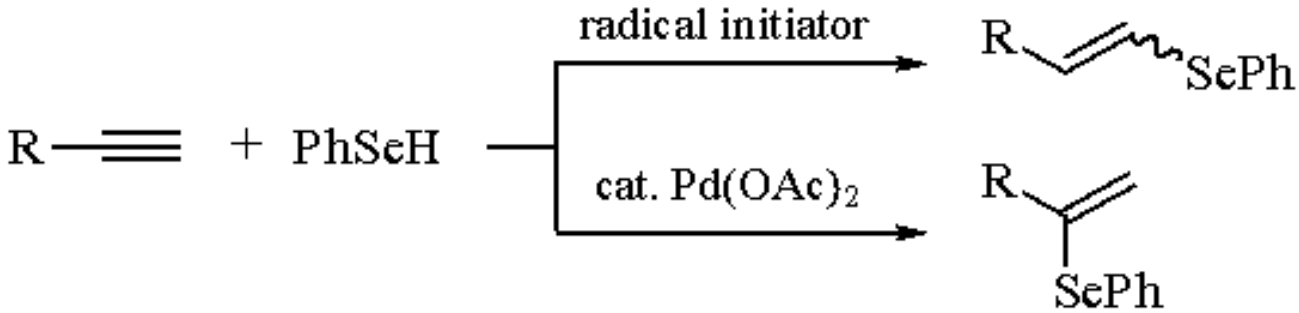

(4)

Lewis acid-assisted addition of benzeneselenol to aldehydes and ketones affords synthetically important selenoacetals, which serve as precursors of α-selenoalkyllithiums (eq 5).[25]

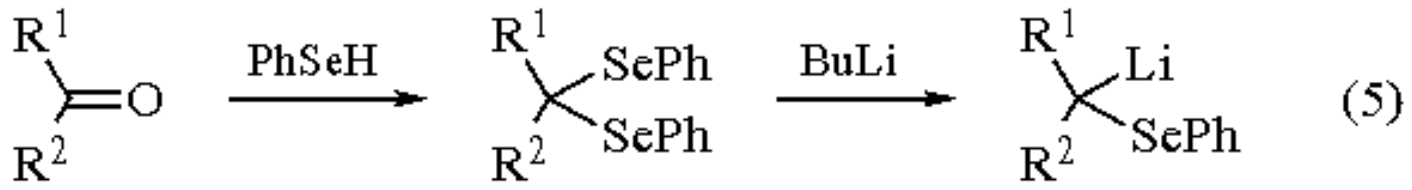

Reduction.

Benzeneselenol is not only a selenation reagent as described above, but is also utilized as a mild reducing agent for various classes of organic compounds. The reduction of the carbon-carbon double bond of α,β-unsaturated carbonyl compounds with PhSeH is caused by an introduction of molecular oxygen into the reaction system[26a] or by irradiation with a sunlamp.[26b] The reduction proceeds by a radical chain mechanism, as illustrated in eq 6.

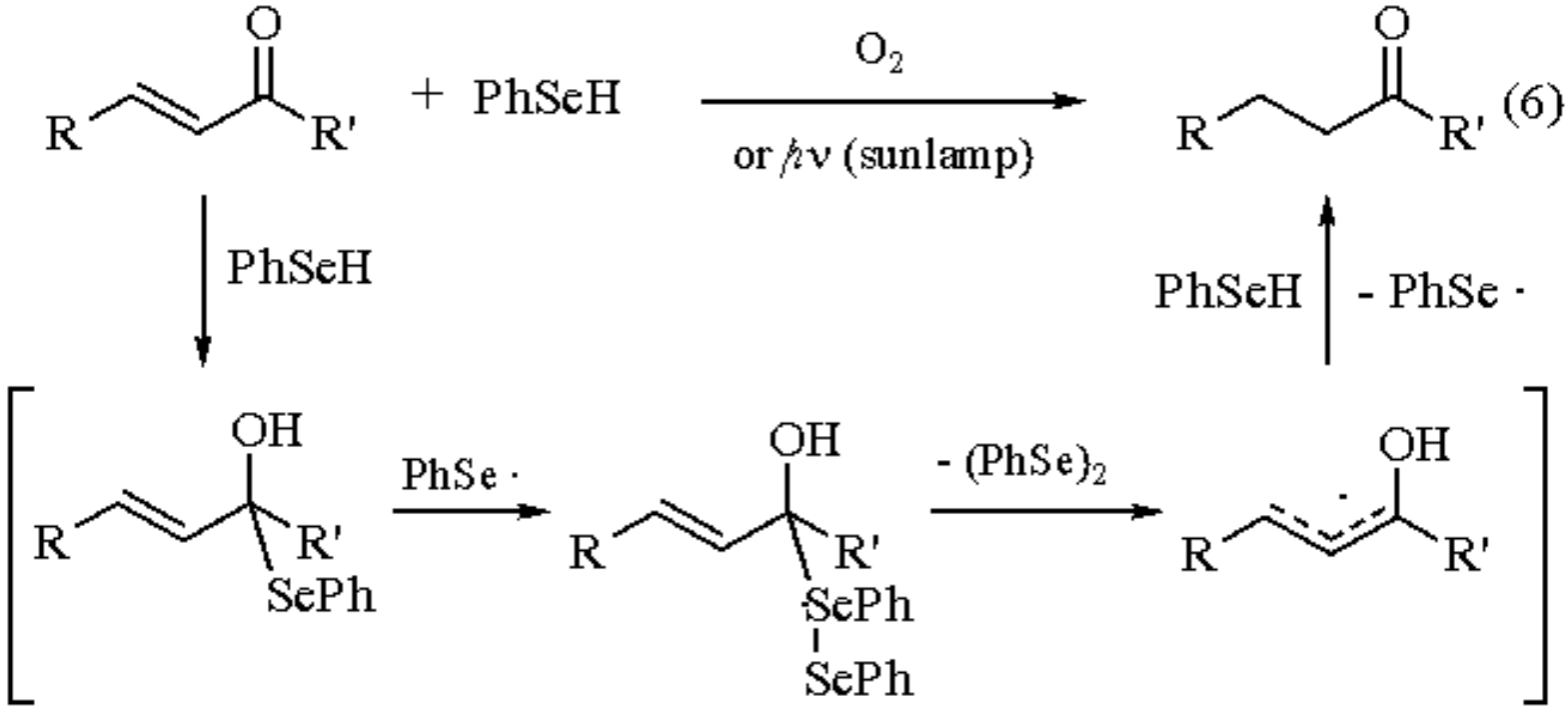

By a similar radical chain mechanism, aromatic aldehydes are reduced to benzylic alcohols at room temperature.[26c] In these reactions, no oxygen incorporation products are formed. This is due to the extremely high hydrogen-donating ability of PhSeH (the rate constant of hydrogen transfer from PhSeH to carbon radicals is estimated as 2.0×10^9 M^{-1} s^{-1} at 20 °C in THF).[27]

In addition, benzeneselenol reduces some nitrogen-containing functional groups such as nitro (NO_2), azo (N=N), and imino groups (C=N) to corresponding amino groups.[28] Organic sulfoxides are reduced to sulfides by treatment with PhSeH as exemplified in eq 7.[29]

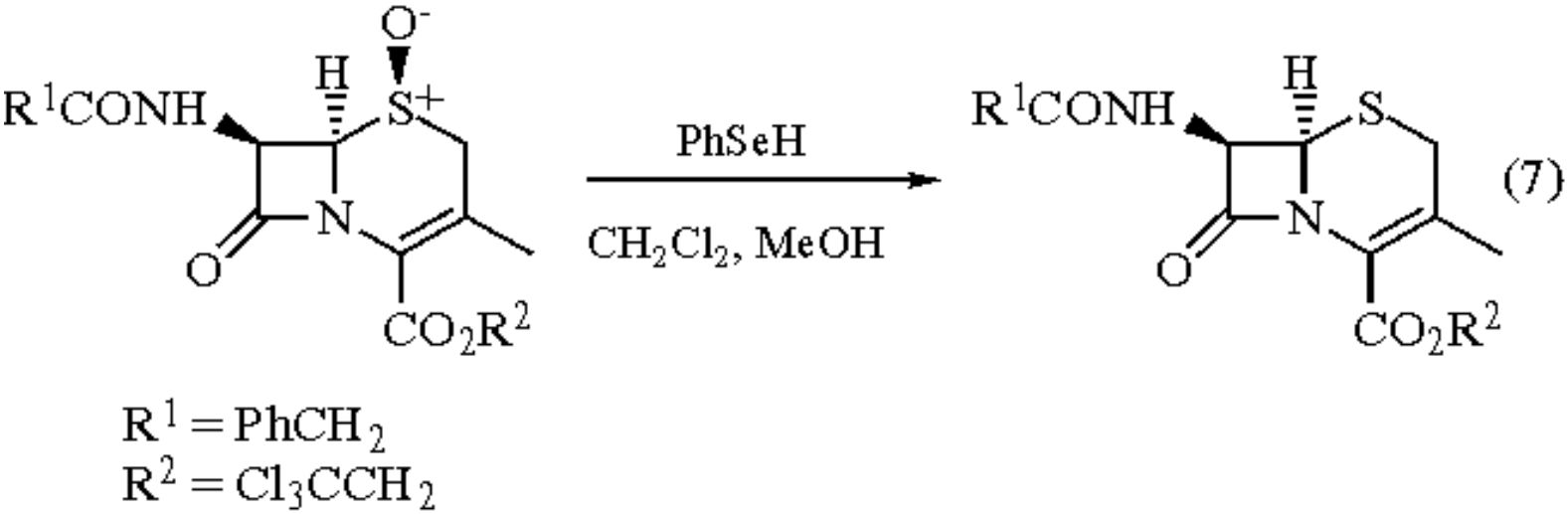

Related Reagents.

Methanethiol; ***Methaneselenol***; ***Thiophenol***.

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Benzenesulfenyl Chloride[1]

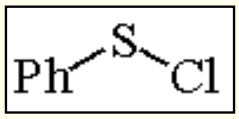

[931-59-9] · C_6H_5ClS · Benzenesulfenyl Chloride · (MW 144.62)

(useful reagent in regio- and stereoselective syntheses,[2] directed alkylation,[3] carbonyl transposition,[4] functionalization of unsaturated groups,[5] sulfenylation of silyl enolates,[6] cycloaddition[7])

Alternate Name: phenylsulfenyl chloride.

Physical Data: bp 88 °C/17 mmHg; 55 °C/3 mmHg; *d* 1.252 g cm^{-3}; n_D^{20} 1.6120.

Solubility: sol pentane, benzene, acetone, $CHCl_3$, CH_2Cl_2, CCl_4.

Form Supplied in: oily, dark red liquid; fumes in air.

Preparative Methods: easily obtained in high yields (90-100%) from ***Thiophenol*** or ***Diphenyl Diselenide*** by chlorination at -5 to 0 °C with chlorine gas[8] or ***Sulfuryl Chloride***.[9] Arenesulfenyl chlorides, including PhSCl, are conveniently prepared from arenethiols and ***N-Chlorosuccinimide*** in dichloromethane solution in quantitative yields and used without isolation in addition reactions to alkenes.[10]

Handling, Storage, and Precautions: extremely hygroscopic and must be carefully protected from moisture. It may be stored for months under dry inert gas in a refrigerator. However, there are two reports on the spontaneous explosion of PhSCl on storage, even in a refrigerator. It is recommended that PhSCl be prepared fresh as needed. Use in a fume hood.

Sulfenylation of Allylic Alcohols.

Sulfenyl (as well as sulfoxide and sulfonyl) groups favor formation of a stabilized carbanion at the neighboring carbon atom by metalation with strong bases, and thus direct sequential alkylation with alkyl halides to the α-position. However, directed γ-alkylation of allylic alcohols can be realized by application of a reversible sulfenate-sulfoxide [2,3]-sigmatropic rearrangement of their benzenesulfenate esters (eq 1).[3,11]

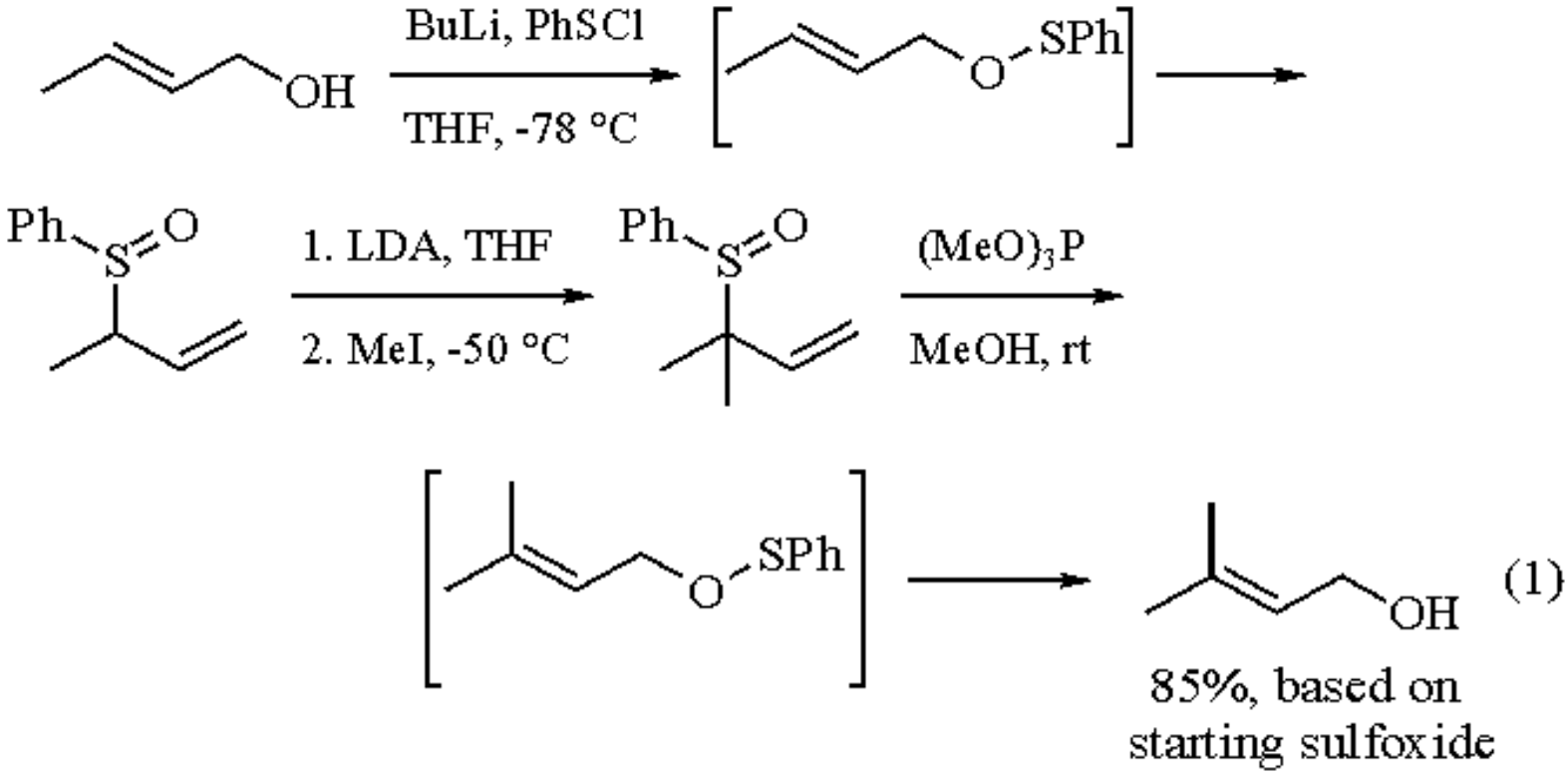

Sequential treatment of an allylic alcohol with ***n-Butyllithium*** and benzenesulfenyl chloride forms the sulfenate ester which spontaneously rearranges to the sulfoxide. The latter is metalated with ***Lithium Diisopropylamide*** (LDA) (*n*-BuLi affords 5-10% of byproducts) and treated with an alkyl iodide to give predominantly an α-alkylated (relative to the sulfoxide group) product. Finally, the alkylated sulfoxide on treatment with ***Trimethyl Phosphite*** and methanol rearranges back to the sulfenate ester and liberates the γ-alkylated allylic alcohol.

Formation of the *trans* isomer is favored, the *trans*:*cis* ratio being 2.7-30.0. Along with the α-alkylation of the sulfoxide, some of the γ-isomer usually forms, the α:γ ratio being 1.1 to >>10 depending on the structure of the sulfoxide. Cyclic allylic alcohols can be alkylated in the same way. The stereochemistry of [2,3]-sigmatropic rearrangements is discussed in Hoffmann's review.[12] The alkylative sulfenate-sulfoxide rearrangement is widely used in stereoselective syntheses of natural products, e.g. to form the side chains of coenzyme ubiquinone-10 and the growth-promoting steroid brassinolide,[13,14] for epimerization of 17-hydroxy-17-vinyl steroids.[15] A transformation of a prostaglandin with 13-*cis*-15β-hydroxy configuration to the inverted natural 13-*trans*-15α-hydroxy configuration (PGE_1) has been achieved employing this rearrangement and *p*-toluenesulfenyl chloride.[16]

The sulfenate-sulfoxide rearrangement can be used for alkylative carbonyl 1,3-transposition in vinyl carbonyl compounds, both acyclic and cyclic. In the case of saturated aldehydes or ketones they are treated at first with ***Vinylmagnesium Bromide*** (or ***Vinyllithium***) to form the allylic alcohol and then sulfenylated as shown in eq 2.[4]

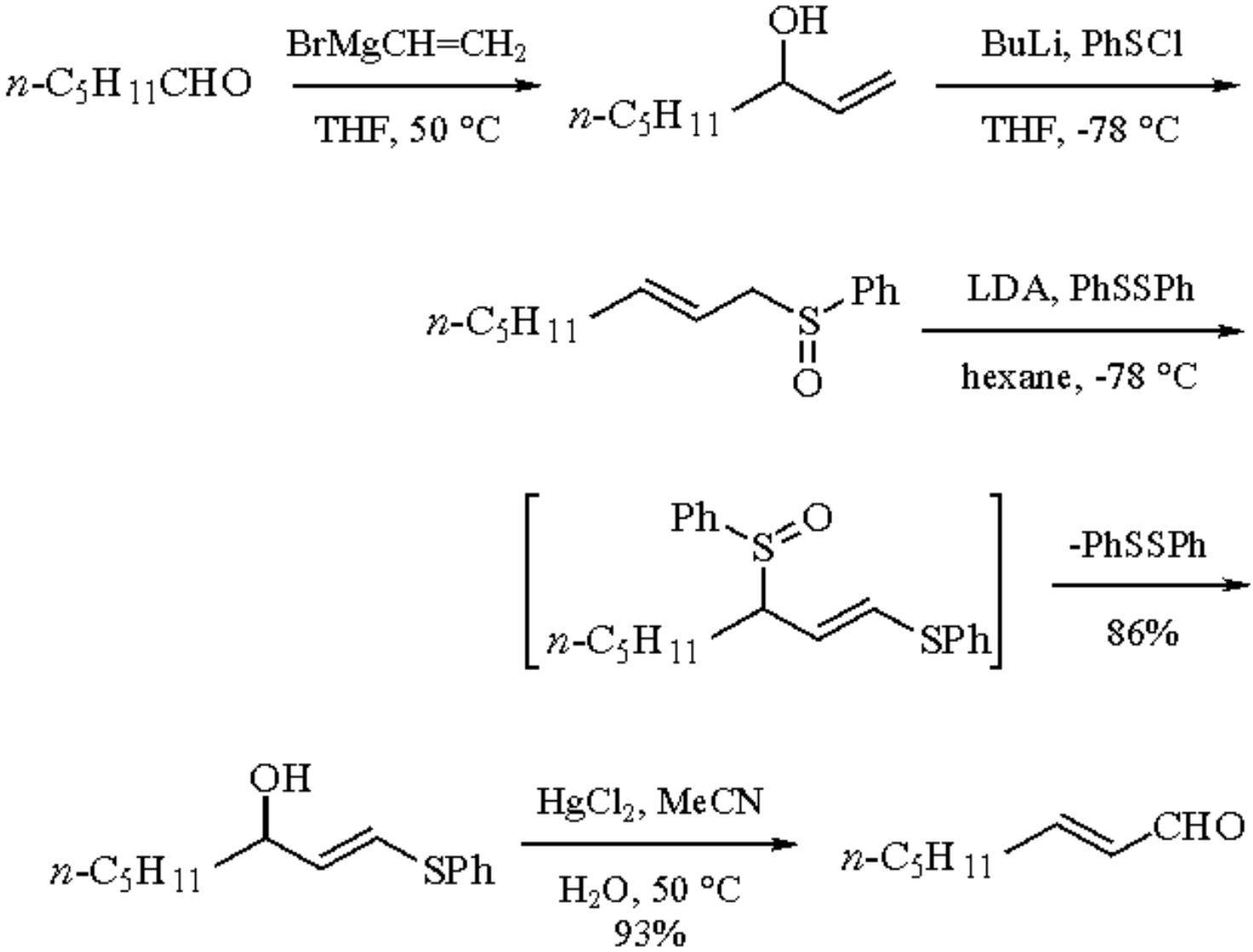

(2)

The sulfoxide formed is lithiated with LDA and sulfenylated with diphenyl disulfide to undergo simultaneous rearrangement and elimination of PhSSPh to yield the enol sulfide. The latter, after hydrolysis with ***Mercury(II) Chloride***, gives the α,β-unsaturated aldehyde. Another example, for a cyclic alkenone, is shown in eq 3.

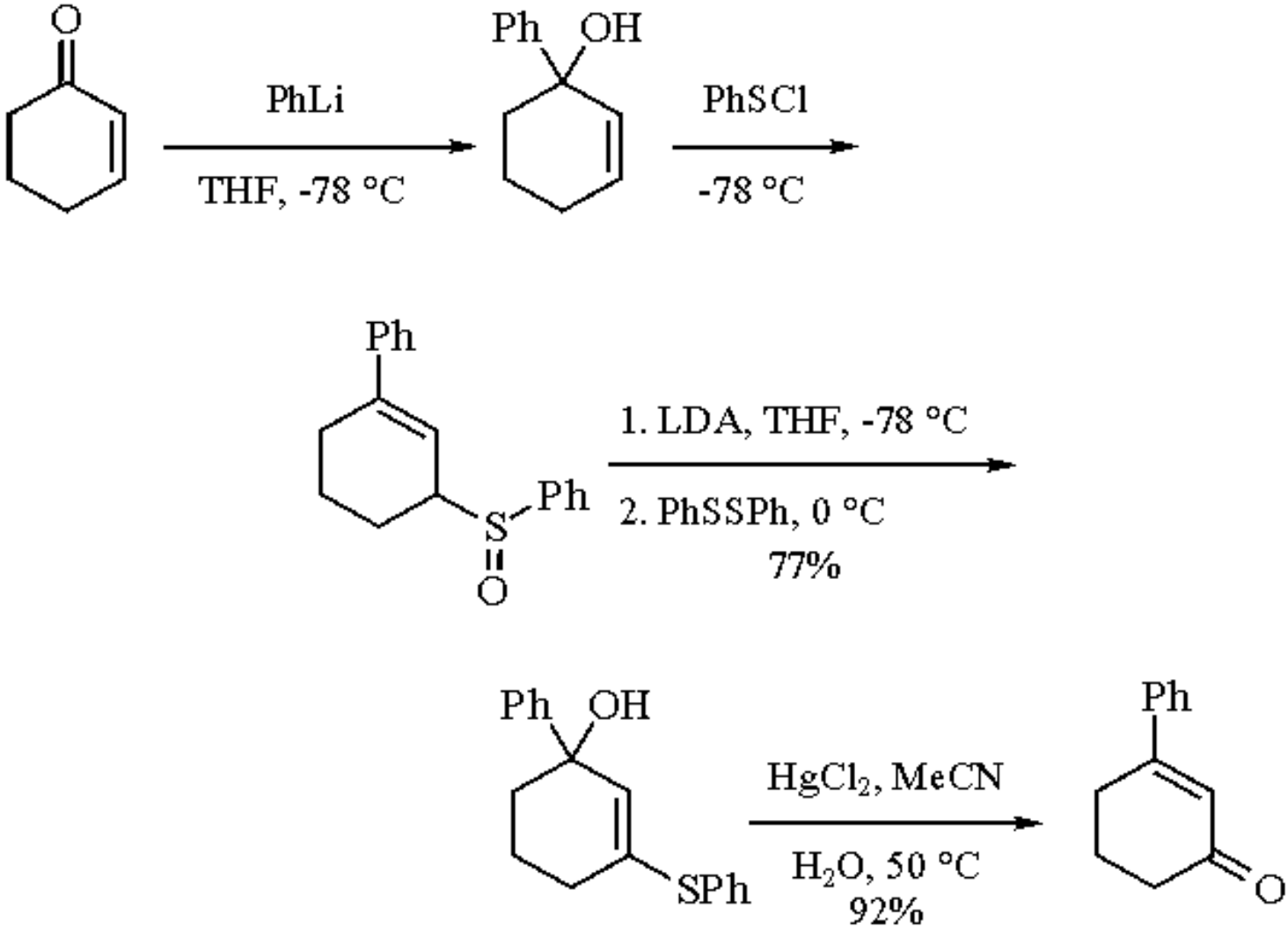

Phenyl sulfoxides, formed by reaction of 3-trimethylsilylallylic alcohols with PhSCl, have been used for the synthesis of unsaturated aldehydes (eq 4).[17] The α-silyl sulfoxide undergoes a sila-Pummerer rearrangement.

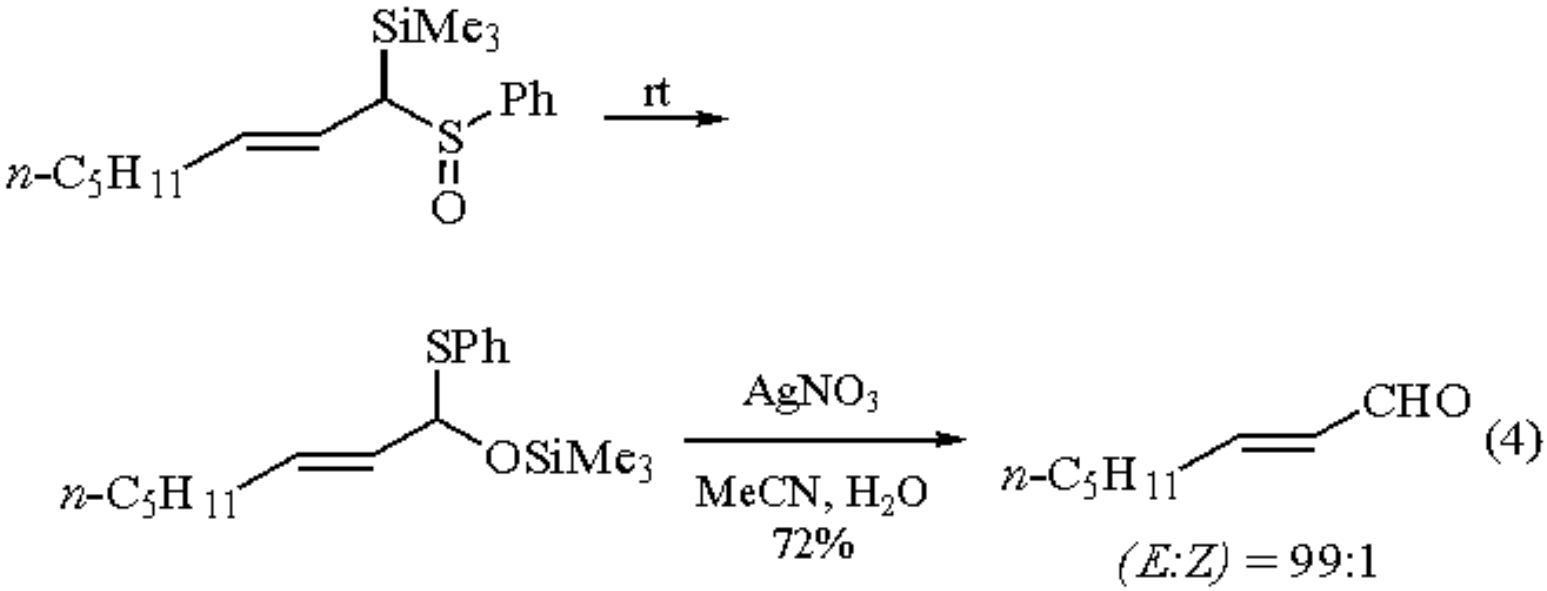

4-Trimethylsilyl-1-buten-3-ol by alkylation of the phenyl sulfoxide produced by reaction with PhSCl, and subsequent

desulfonylation and desilylation by ***Tetra-n-butylammonium Fluoride***, affords (*E*)-1,3-alkadienes in yields >90%.[18]

Sulfenylation of Propargylic Alcohols.

Benzenesulfenates of propargylic alcohols form allene sulfoxides by [2,3]-sigmatropic rearrangement. These can be easily transformed to useful derivatives[2d,e] or cyclized.[2f,h] The starting propargylic alcohols are readily accessible from the reaction of aldehydes or ketones with metal acetylides. Thus β-cyclocitral treated with propynyllithium, followed by PhSCl, after rearrangement affords the triene sulfoxide. Reduction with ***t-Butyllithium*** and methanol (as an internal proton source) yields 72% of the desulfurized hydrocarbon with retention of the double bond configuration (eq 5).[19]

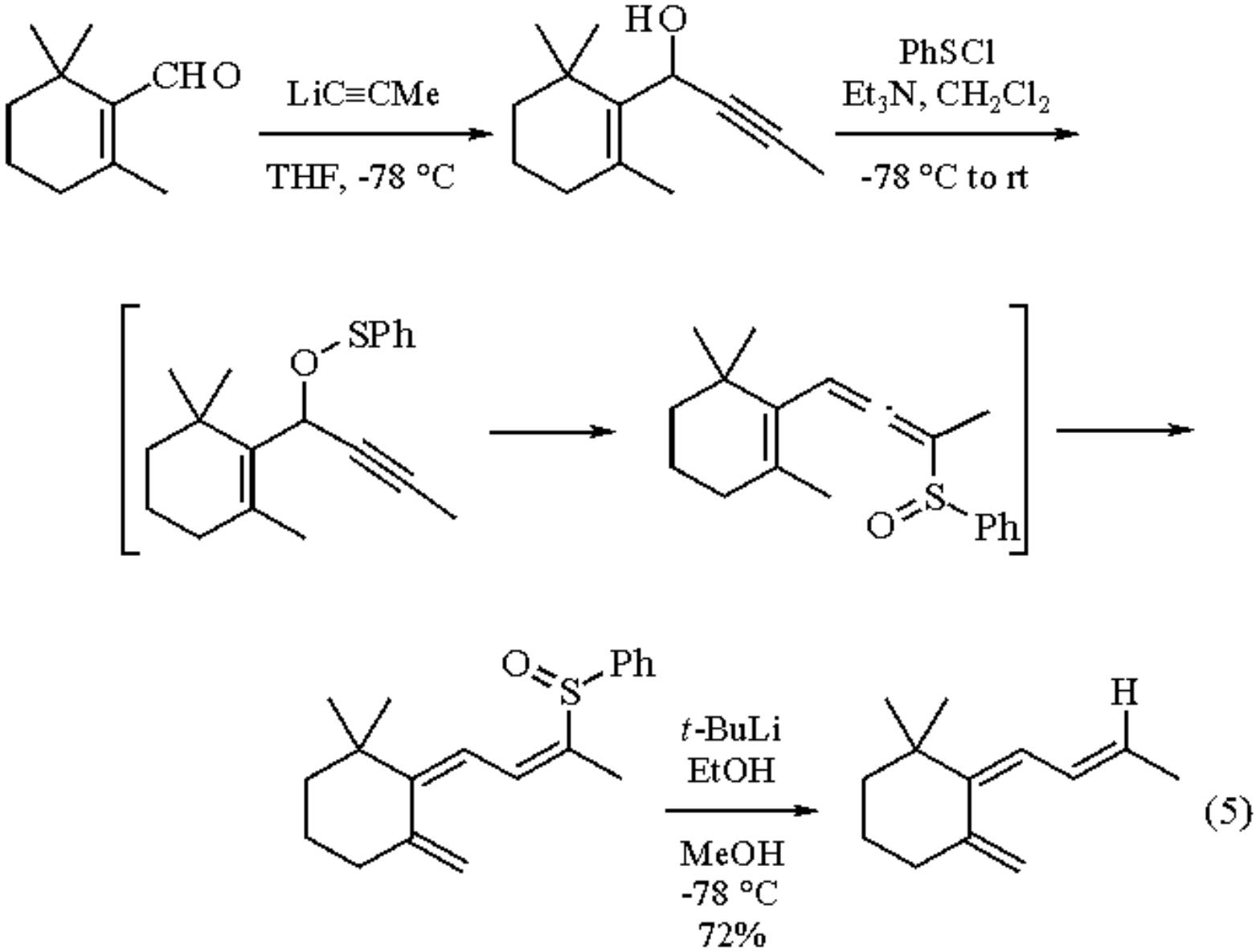

A steroid 17-methylallene sulfoxide has been desulfurized under similar conditions with ***Methyllithium*** to give 72% of the β-methylallene derivative.[20] Trienyl and allenyl phenyl sulfoxides can therefore be desulfurized stereospecifically with retention of configuration using *t*-BuLi or MeLi.

The allene sulfoxide obtained when androst-4-ene-3,17-dione is treated with ***Dipotassium Acetylide*** and PhSCl, is functionalized as shown in eq 6 (only the D-ring of the steroid is shown) to form the corticosteroid structure.[21]

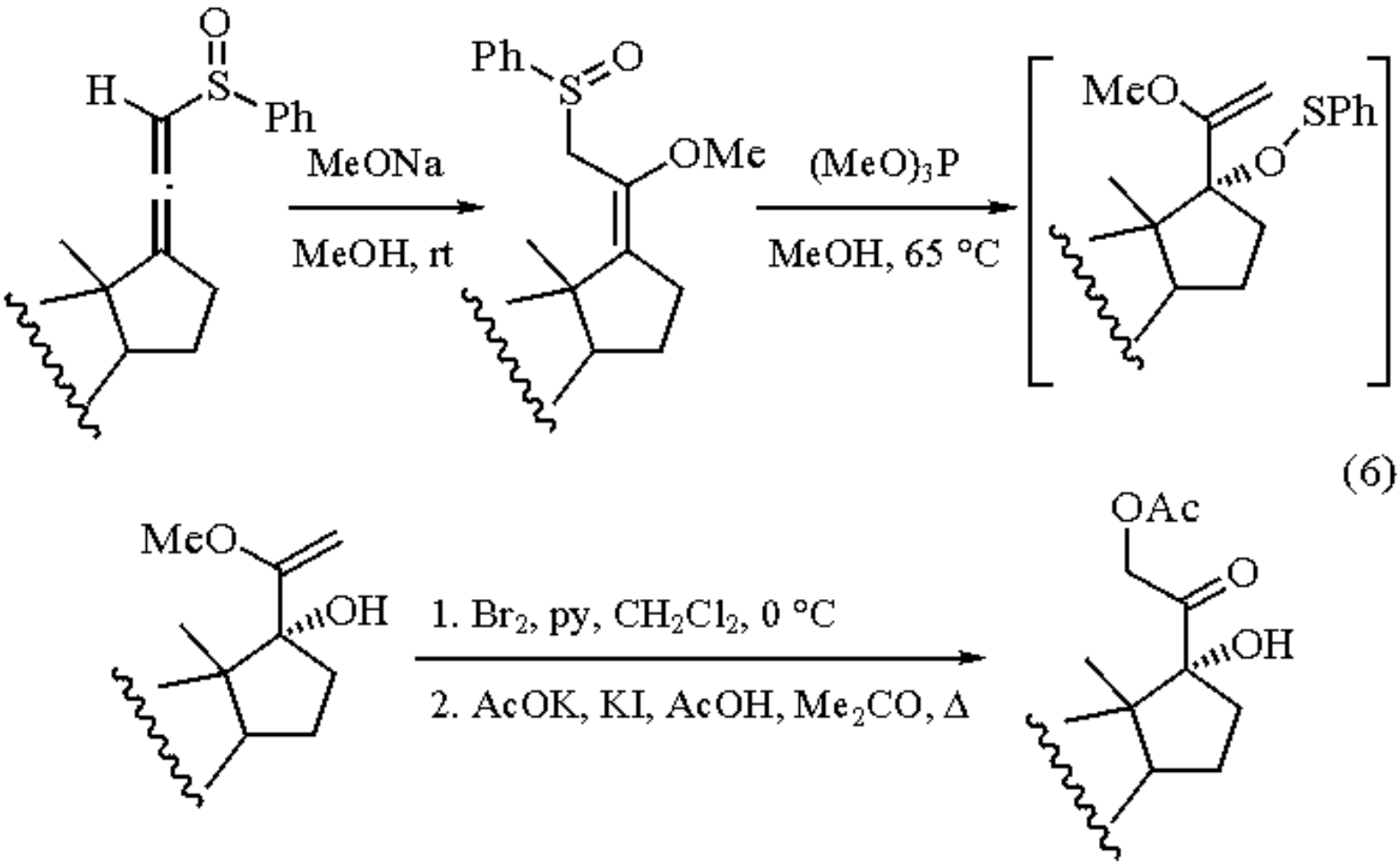

(6)

Phenyl sulfoxides with the *cis*-allenyldiene structure, obtained from corresponding propargylic alcohols, undergo spontaneous electrocyclic ring closure (eq 7).[22] As shown by detailed studies,[22b] the chiral center in the starting propynyl alcohol is stereospecifically transferred to the bridgehead carbon in the cyclized product drimatriene sulfoxide. This type of rearrangement has been used for an enantioselective synthesis of the sesquiterpene (+)-sterpurene.[2h,23]

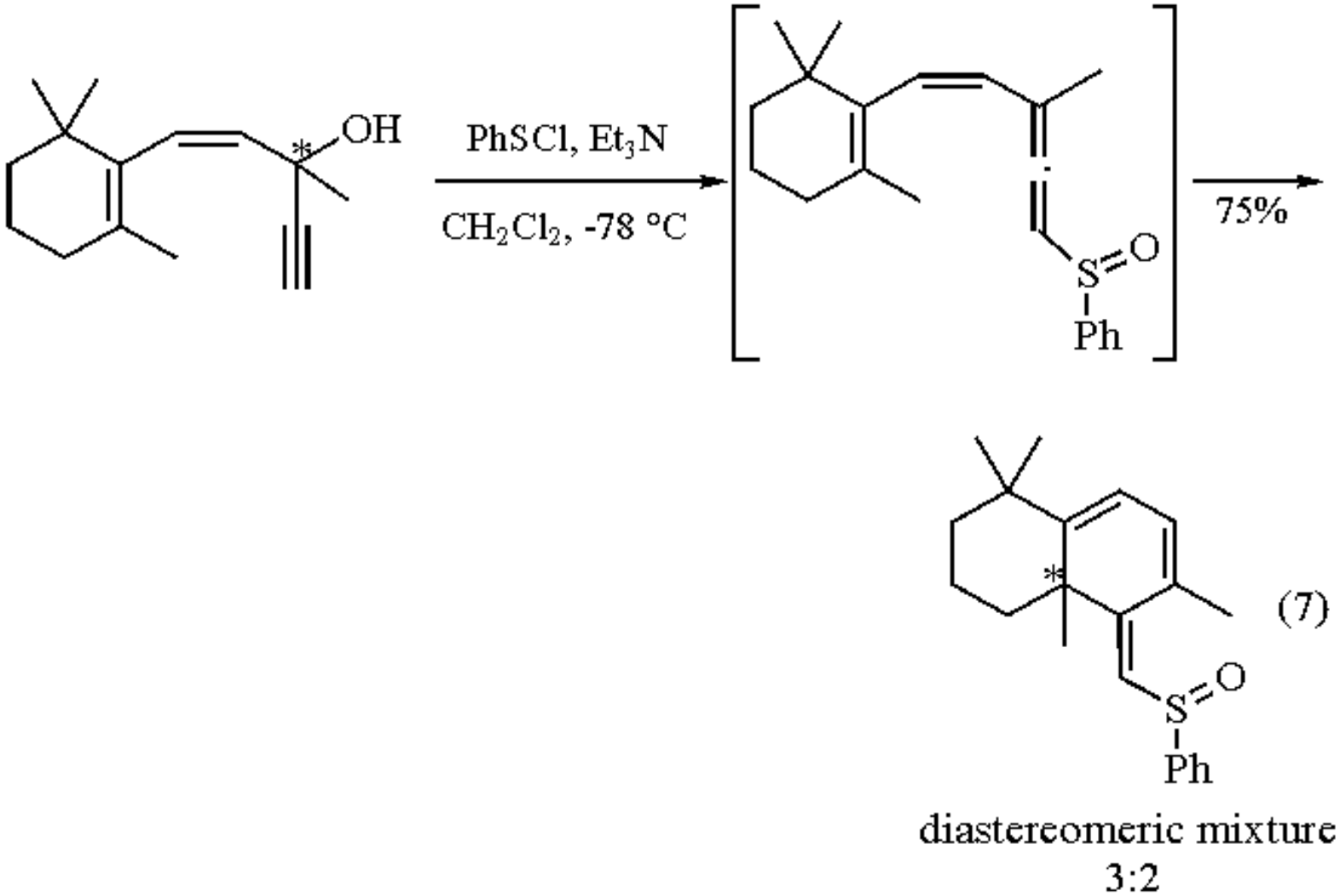

A tandem [2,3]-sigmatropic rearrangement/Michael addition sequence occurs when the hydroxyphenylpropynol is sulfenylated with PhSCl (eq 8).[24] Other substituted benzofurans are obtained in this way.

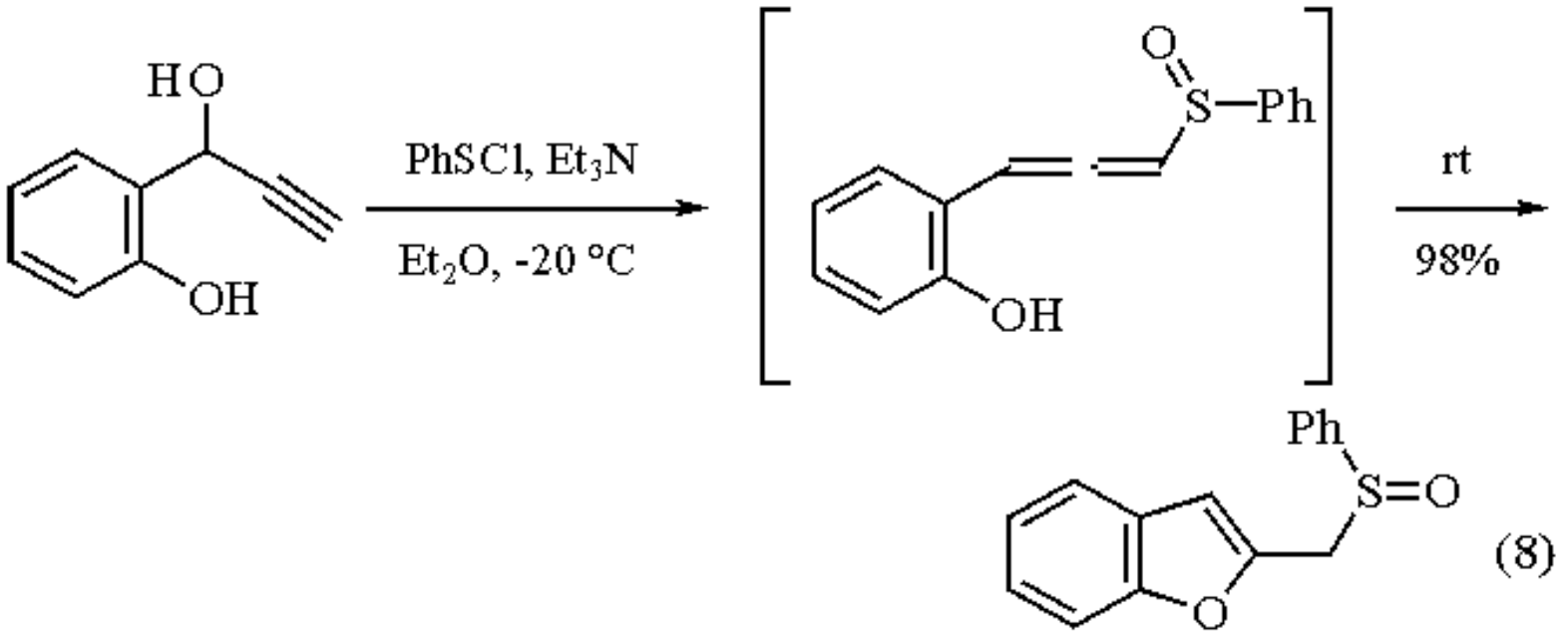

Ketones from Arylacetonitriles.[2a]

Secondary aryl, alkyl, or diaryl acetonitriles, on sulfenylation with PhSCl and subsequent oxidative decyanation by ***N-Bromosuccinimide*** and NaOH, afford aryl, alkyl, or diaryl ketones in good yields (eq 9).[25] Four other oxidative decyanation methods were tested;[25b] the one shown is the best.

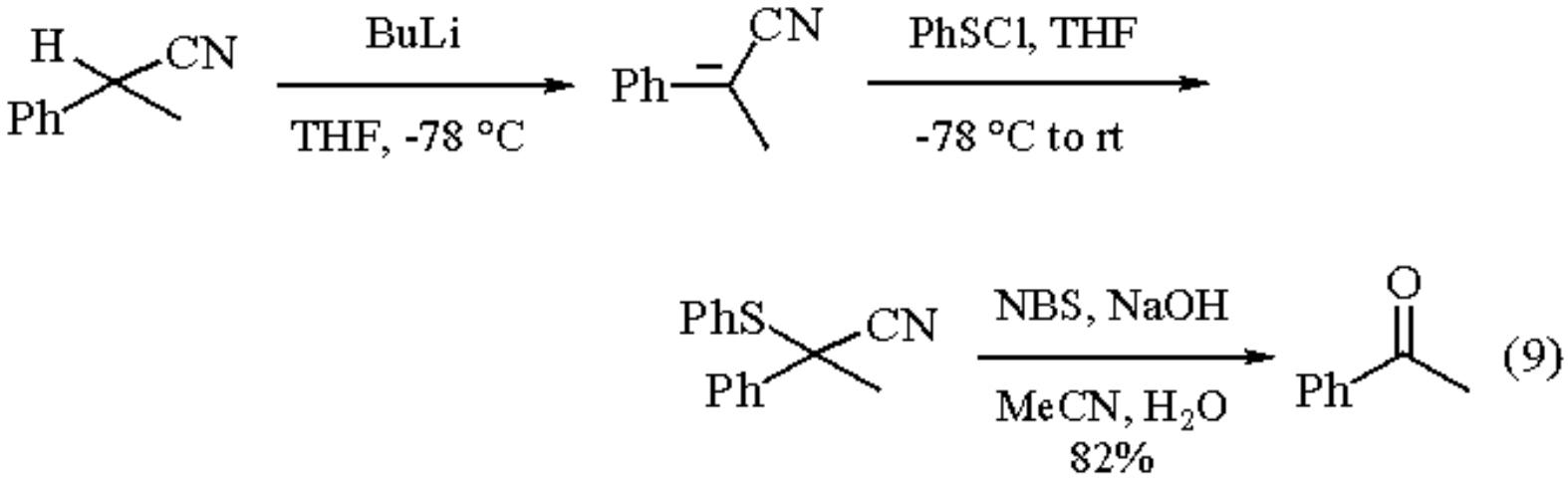

Reaction with α-Diazo Ketones.[2d]

The mild displacement of diazo nitrogen in α-diazo ketones by PhSCl represents a convenient and regiospecific method for functionalization of both cyclic and acyclic ketones at the α-position with halogen and phenylthio substituents (eqs 10-12).[26] These functionalized ketones are useful for a variety of syntheses, particularly phenylthiocyclopentenone for the synthesis of natural products based on 2,3-disubstituted cyclopentanone.[27]

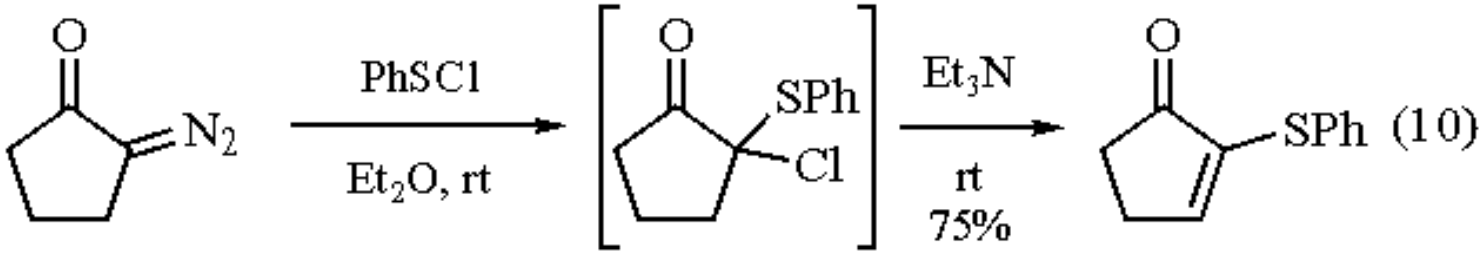

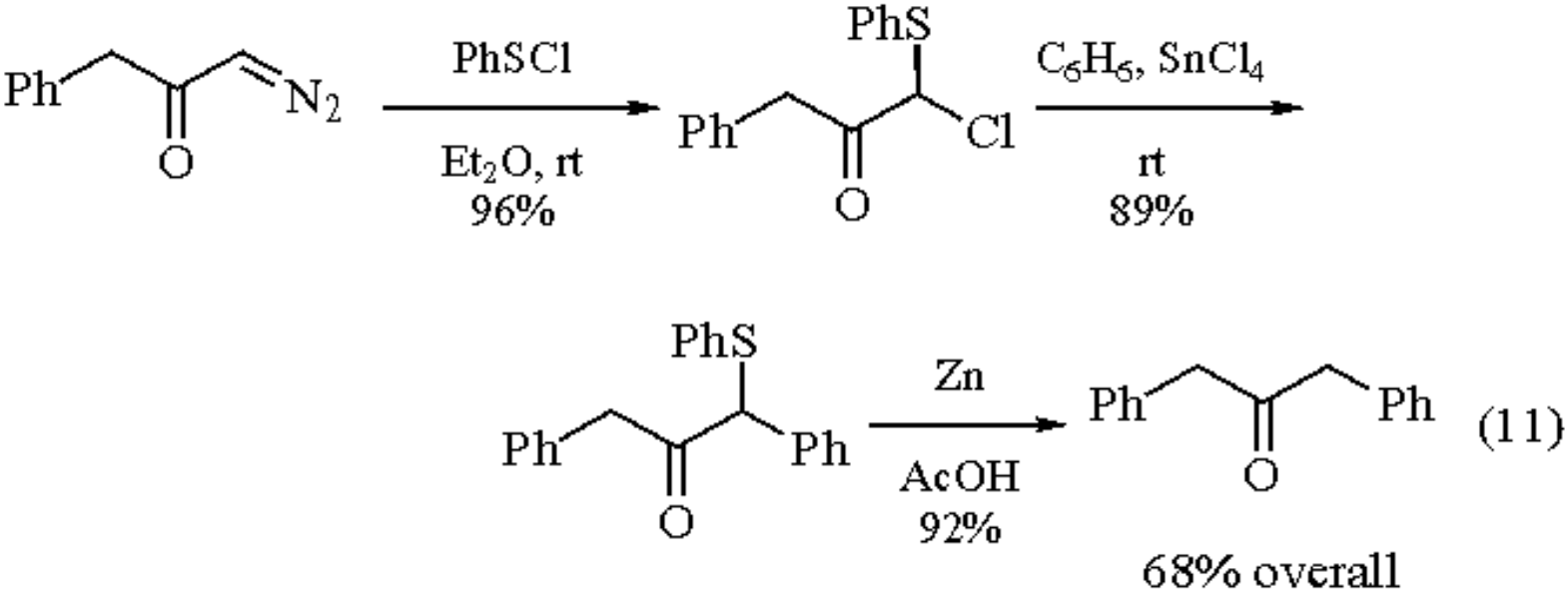

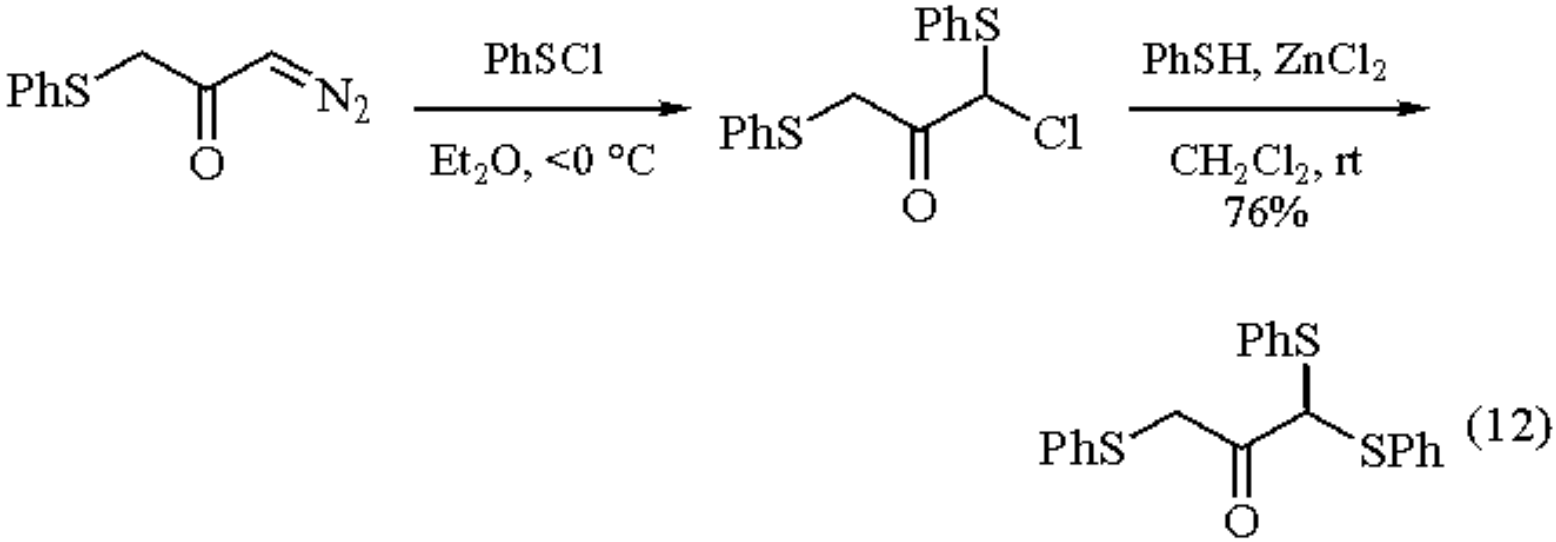

Addition to Alkenic and Alkynic Compounds.

The most commonly used reaction of PhSCl is the addition to double and triple bonds. The regioselectivity of this reaction is not high and is determined mainly by the steric bulk of neighboring groups. Mixtures of regioisomers are usually formed with anti-Markovnikov adducts predominating, which on standing or refluxing in MeCN undergo conversion to Markovnikov products. Addition to cycloalkenes and alkynes is stereoselective and *trans* isomers form almost exclusively. This fact is consistent with an episulfonium ion intermediate.

Combined chlorosulfenylation-dehydrochlorination reactions have great synthetic utility for the conversion of alkenes to cyclic and acyclic vinyl, allyl, or dienyl phenyl sulfides (eqs 13 and 14).[10] The addition reaction is achieved by simply adding the alkene to a cooled (-50 to -78 °C) solution of PhSCl in CH_2Cl_2 and allowing the mixture to warm to rt. The dechlorination is carried out by briefly heating the β-chloroalkyl sulfides with the amidine base ***1,8-Diazabicyclo[5.4.0]undec-7-ene***. Higher yields on dechlorination are achieved with sulfones quantitatively formed by oxidation of the β-chlorosulfides with peroxy acids.

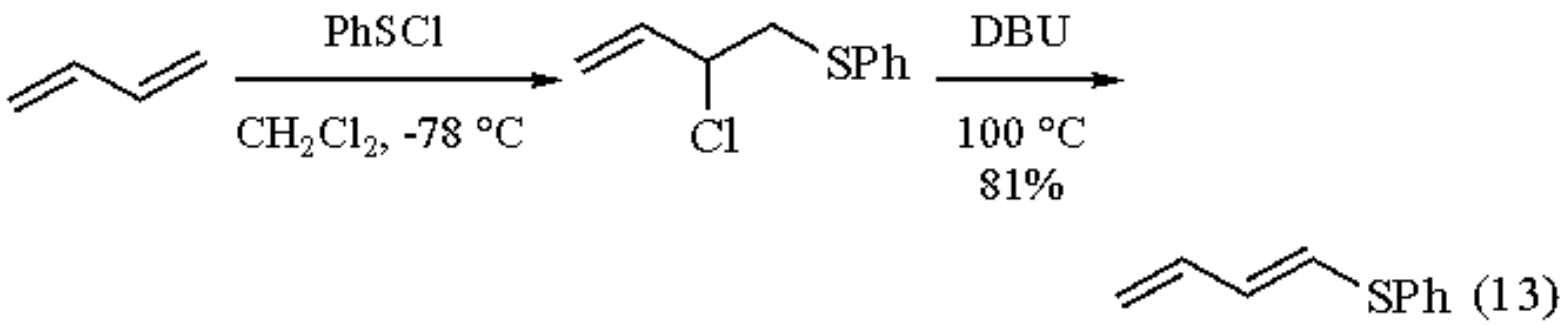

(13)

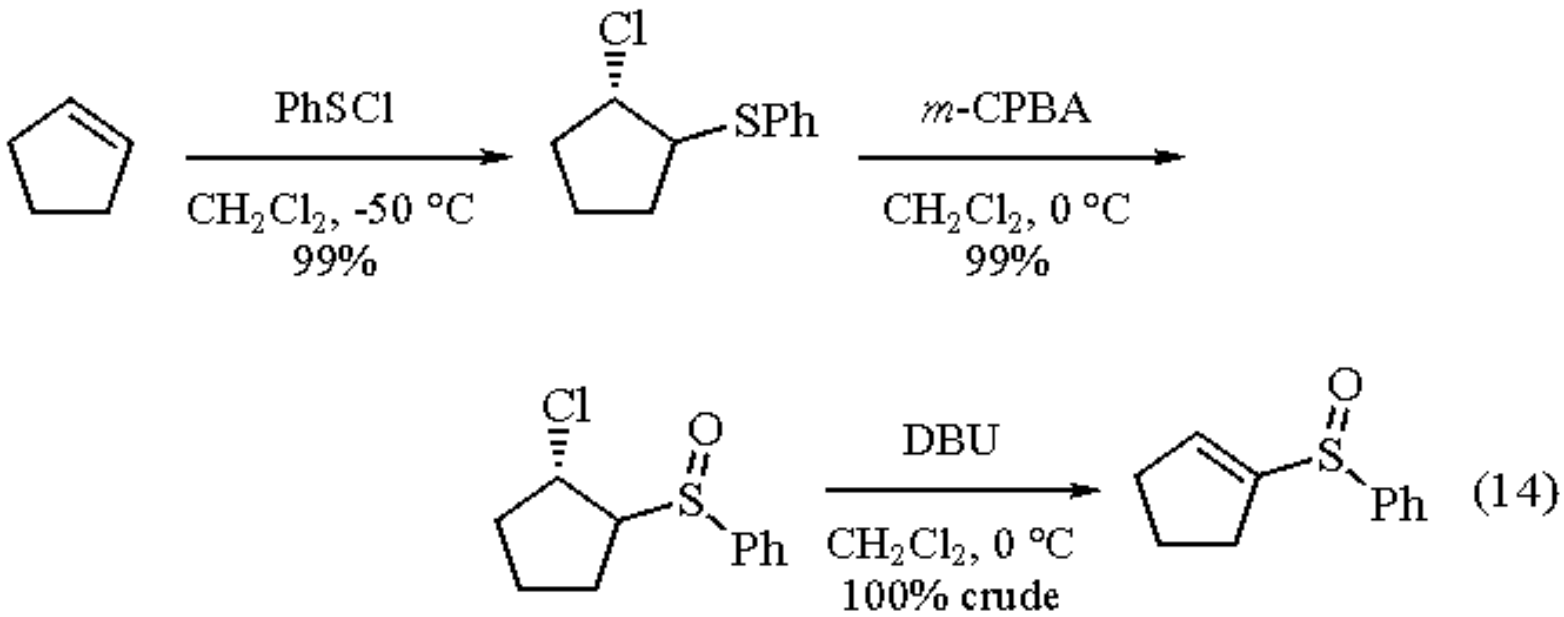

(14)

The addition of PhSCl can be used for functionalization of unsaturated groups,[2d] especially the isopropylidene terminus of natural isoprenoids. The synthetic sequence, as shown for the model compound 2-methylbut-2-ene (eq 15), involves addition of PhSCl, dehydrochlorination of isomeric adducts with Et_3N in DMF to methallyl sulfide, oxidation to the sulfoxide, and its rearrangement to the terminal *trans*-allylic alcohol.[5,28a,c] This procedure is used for the synthesis of the biologically important oxygenated terpenes nuciferal, *ar*-turmerone, ipsdienol, neotorreyol, 6-hydroxydendrolasin, 6-oxodendrolasin, and solanesol.[28a,b]

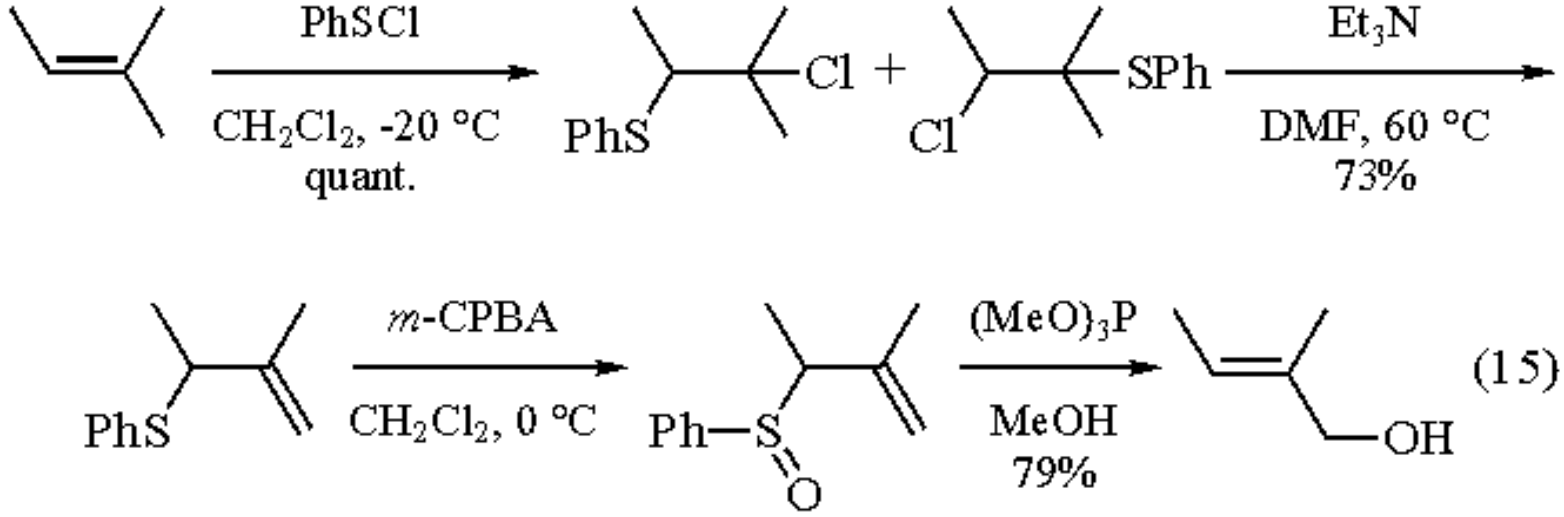

(15)

Complete *cis-trans* alkene isomerization can be achieved by PhSCl addition and dehydrochlorination with *t*-BuOK in

DMSO, which causes *trans* elimination of HCl and formation of vinyl sulfide with inverted configuration.[29]

Selective functionalization of 1,3-dienes by PhSCl involves formation of 1,2-adducts (which convert on heating or storage to 1,4-adducts) and hydrolysis, alcoholysis, or acetolysis of the chlorine in these adducts. The allyl alcohol obtained from the 1,2-adduct may be converted to an epoxide and aldehyde as shown in eq 16.[30]

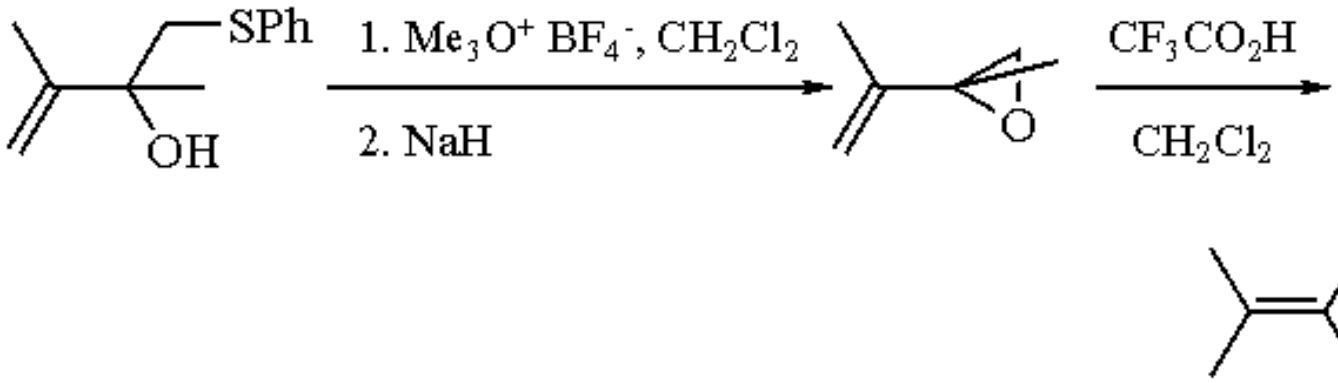

(16)

Adducts of PhSCl to alkenes and cycloalkenes undergo methylation with $Me_2Zn/TiCl_4$ at the chlorine position with complete retention of configuration (controlled by the episulfonium ion intermediate).[2h,31] This one-pot process is termed carbosulfenylation.

Addition to *O*-Silylated Enols and Alkenols.[2d,i]

Silyl enol ethers react smoothly with PhSCl to give α-keto sulfides.[32] The reaction proceeds by addition of PhSCl to the enol double bond and elimination of chlorosilane.[33] *O*-Silylated dienolates (from unsaturated esters, ketones, and aldehydes) undergo γ-sulfenylation with this reagent,[34] with the exception of γ-chloro-substituted dienolates, which give α-products.[35] This type of reaction may be used for stereoselective synthesis of α-sulfenyl-β-hydroxy esters with the *anti* configuration (eq 17).[6] The latter can be converted into either *syn*- or *anti*-epoxides.

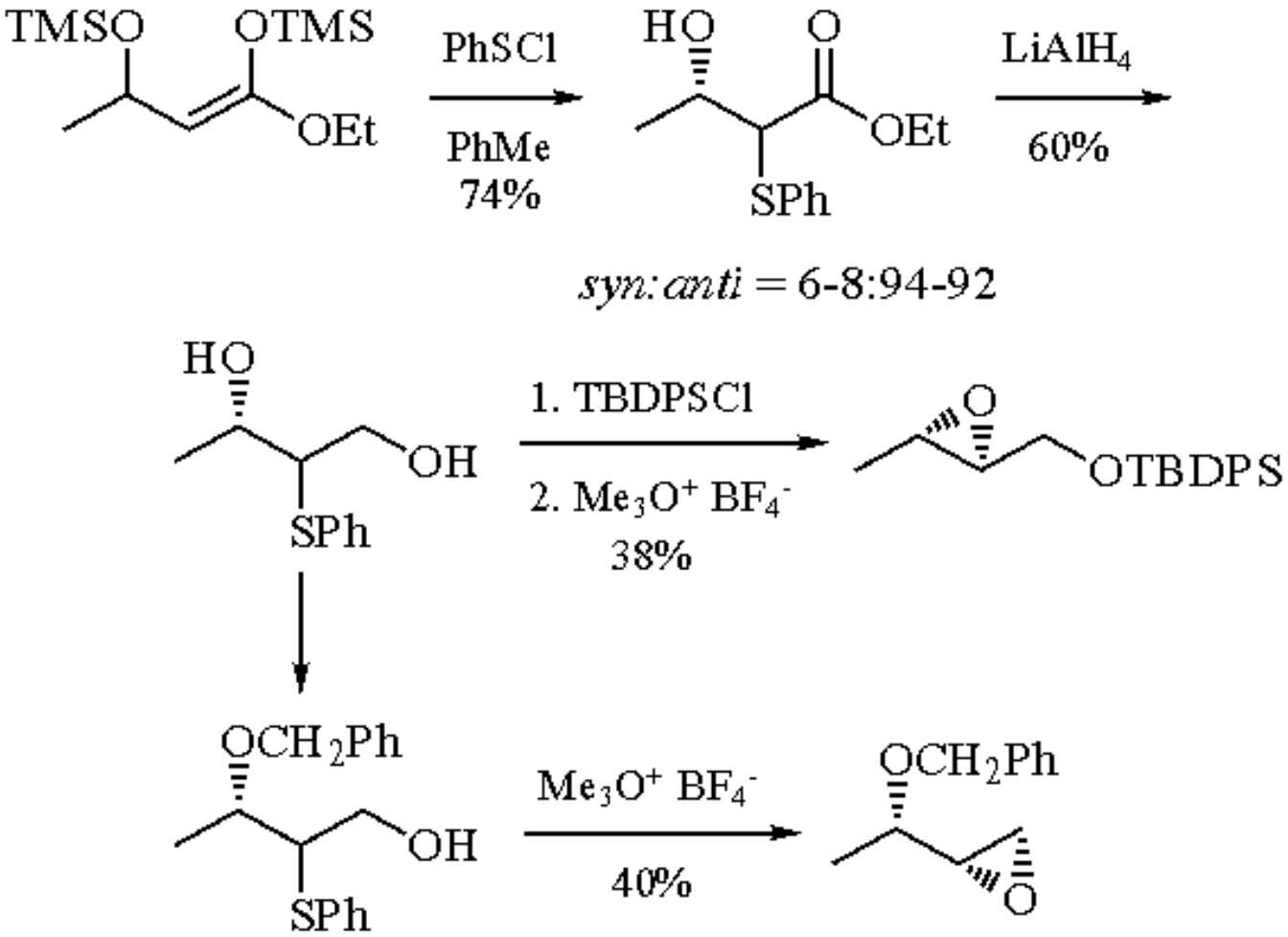

(17)

1-Phenylthiocyclohexanecarbaldehyde, obtained via PhSCl addition to trimethylsiloxymethylenecyclohexane, has been used in stereocontrolled synthesis of allylic alcohols.[36] Benzenesulfenyl chloride adducts of mono- and disubstituted alkenes and cycloalkenes, under ***Zinc Bromide*** catalysis, give stereospecific (*anti*) alkylation of *O*-silylated ester enolates.[37]

t-Butyldimethylsilyl ethers of 1-alkenylcycloalkanols, when treated with PhSCl, readily rearrange to the ring-expanded α-1-phenylthioalkylcycloalkanones via the episulfonium ion (eq 18).[38]

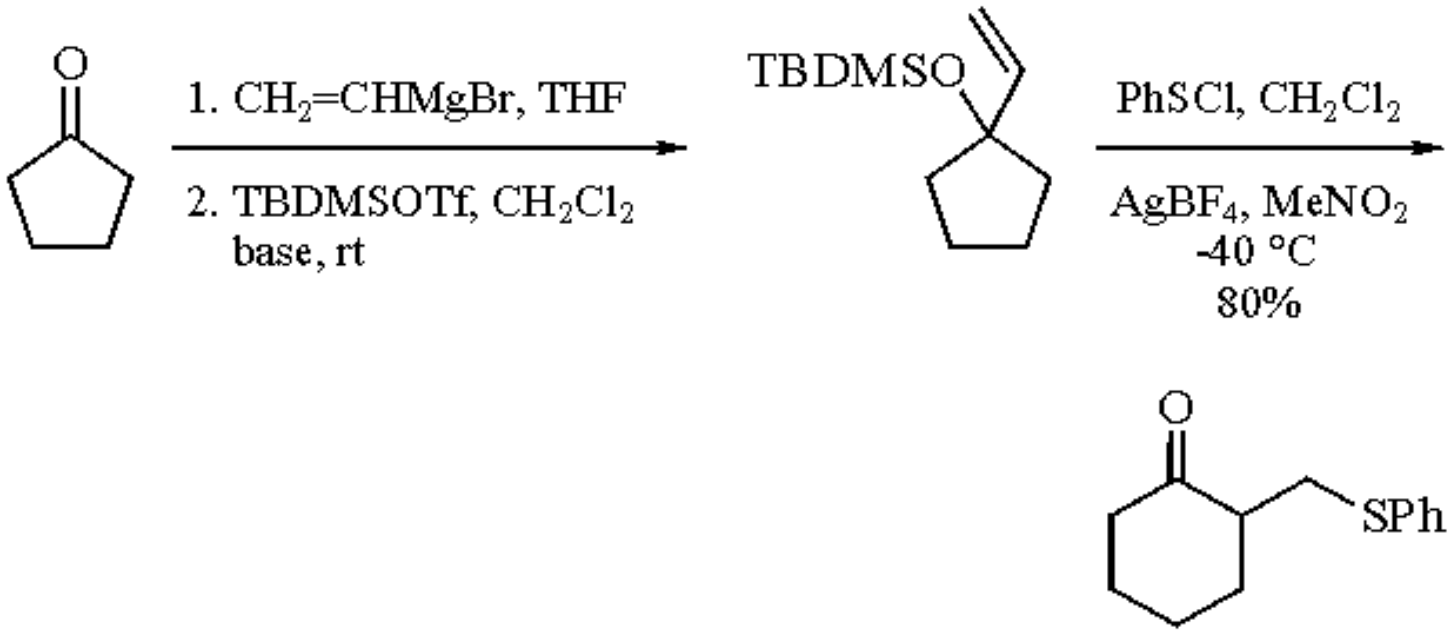

(18)

Cycloaddition.

A range of benzenesulfenyl chloride addition reactions to unsaturated bonds proceeds with simultaneous cyclization to form important compounds, examples of which are depicted below. These reactions include cyclization of isoprenoid β-keto esters (eq 19),[2f,39] homoconjugative cycloaddition to form tricyclenes (precursors of natural sesquiterpenes) (eq 20),[2d,e,7] cyclization of aryloxyphenylalkynes (eq 21),[40] lactonization (eq 22),[2c,41,42] and sulfenocycloamination of unsaturated amides and amines to form lactams, and pyrrolidine and piperidine rings (eqs 23 and 24).[2f,g,43]

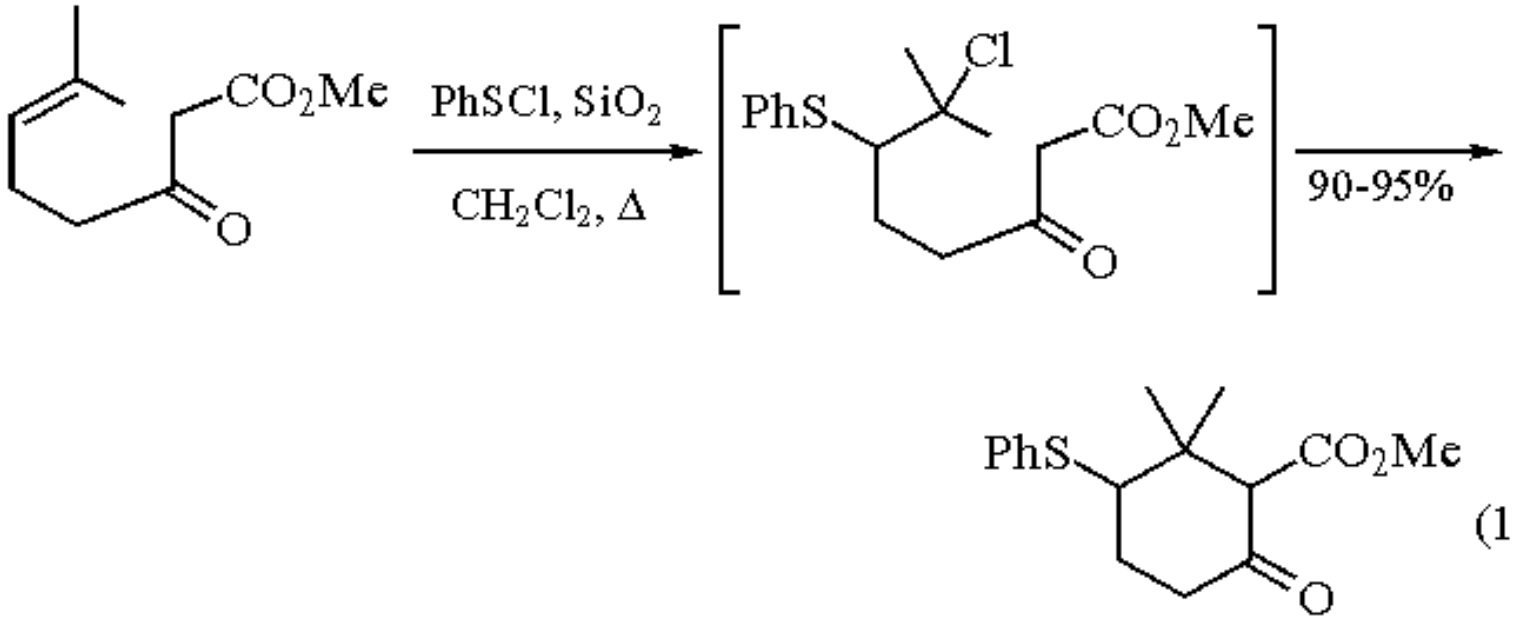

(19)

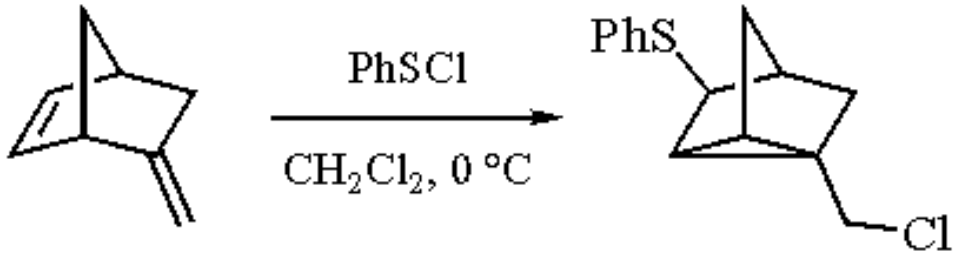
PhSCl
CH_2Cl_2, 0 °C
PhS
Cl

(20)

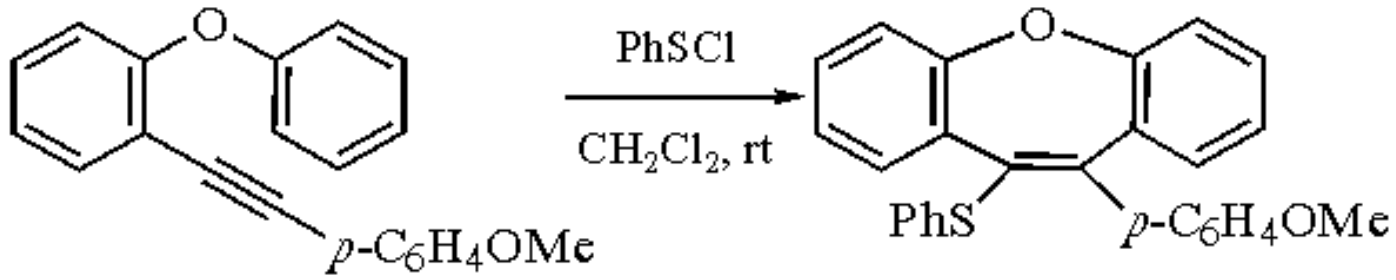
O
PhSCl
CH_2Cl_2, rt
O
PhS
p-C_6H_4OMe
p-C_6H_4OMe

(21)

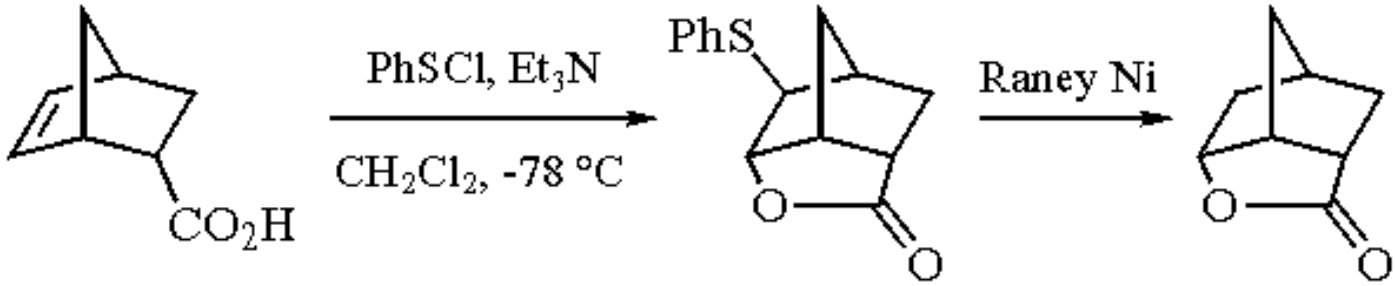
CO_2H
PhSCl, Et_3N
CH_2Cl_2, -78 °C
PhS
O
O
Raney Ni
O
O

(22)

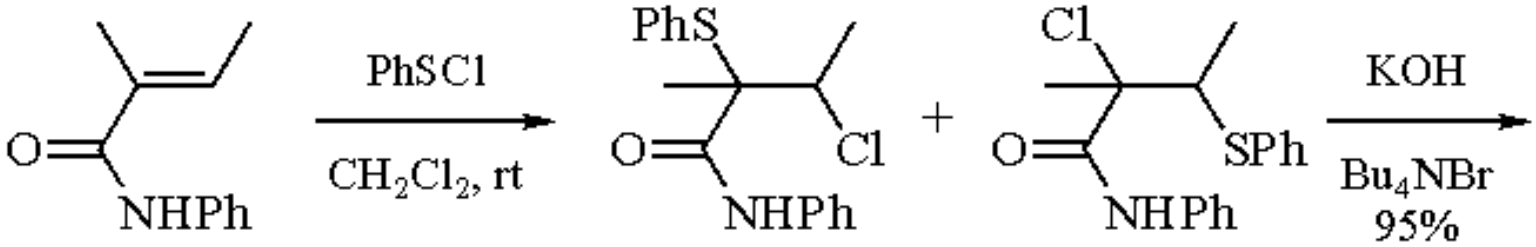
O
NHPh
PhSCl
CH_2Cl_2, rt
PhS
O
Cl
NHPh
+
Cl
O
SPh
NHPh
KOH
Bu_4NBr
95%

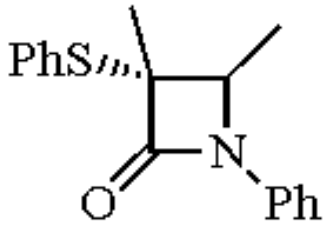
PhS
N
O
Ph

(23)

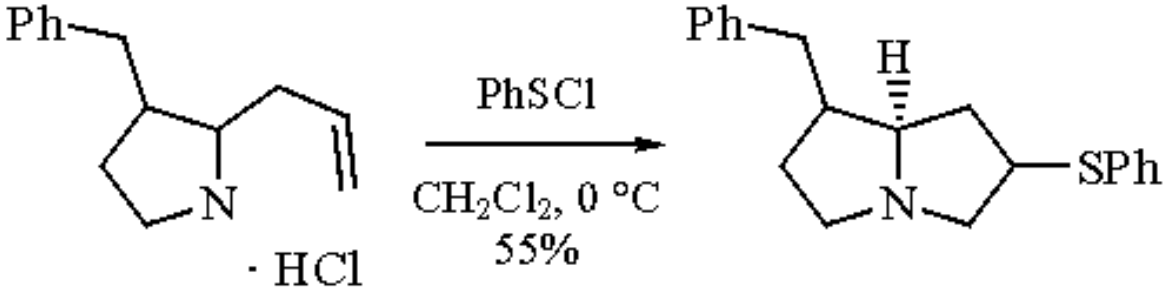
Ph
N
· HCl
PhSCl
CH_2Cl_2, 0 °C
55%
Ph
H
N
SPh

(24)

Related Reagents.

Benzeneselenenyl Bromide; ***Benzeneselenenyl Chloride***; ***2,4-Dinitrobenzenesulfenyl Chloride***; ***Diphenyl Disulfide***; ***o-Nitrobenzenesulfenyl Chloride***; ***N-Phenylthiophthalimide***; ***2-Pyridinesulfenyl Bromide***.

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Benzenesulfinyl Chloride[1]

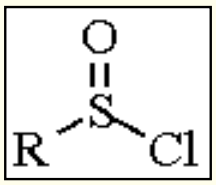

(**1**; R = Ph)

[4972-29-6] · C_6H_5ClOS · Benzenesulfinyl Chloride · (MW 160.62) (**2**; R = *p*-Tol)

[10439-23-3] · C_7H_7ClOS · *p*-Toluenesulfinyl Chloride · (MW 173.64) (±)-(**2**)

[116471-91-1]

(preparation of sulfoxides[2] and sulfones;[3] synthesis of chiral sulfinyl-transfer reagents[4,5])

Physical Data: (**1**) mp 38 °C, bp 71-72 °C/1.5 mmHg; d^{25} 1.3470 g cm^{-3}, *n*25D 1.5770; (**2**) mp 54-58 °C, bp 113-115 °C/3.5 mmHg; *n*23.5D 1.6004.

Solubility: sol Et_2O, $CHCl_3$; decomposes in H_2O and alcohol.

Analysis of Reagent Purity: ^1H NMR,[6b] IR.[6c]

Preparative Methods: reaction of ***Sodium Benzenesulfinate*** or sodium *p*-toluenesulfinate with ***Thionyl Chloride***.[6a]

Handling, Storage, and Precautions: it has been reported that arenesulfinyl chlorides should not be distilled above 2 mmHg pressure because of the danger of explosion.[6d] Care also should be taken to avoid exposure of these sulfinyl chlorides to moisture (i.e. air, skin) owing to decomposition and formation of corrosive HCl.

Preparation of Sulfinyl Compounds.

Arenesulfinyl chlorides react with carbon nucleophiles such as enolates and Grignard reagents to produce sulfinylated compounds capable of undergoing further useful transformations;[2] sulfinyl esters react similarly (see ***Methyl Benzenesulfinate***). Incorporation of the sulfinyl group has been used for the regioselective alkylation of ketones via their dianions;[7] the sulfinyl group can be removed reductively with Al(Hg) (eq 1),[8] or eliminated with concomitant formation of a double bond to form α,β-unsaturated ketones (eq 2).[9] This process is one of the better methods of

introducing a double bond into a molecule; this procedure also has found use as an alternative when the popular phenylselenylation-oxidation method was deemed unsuccessful.[10]

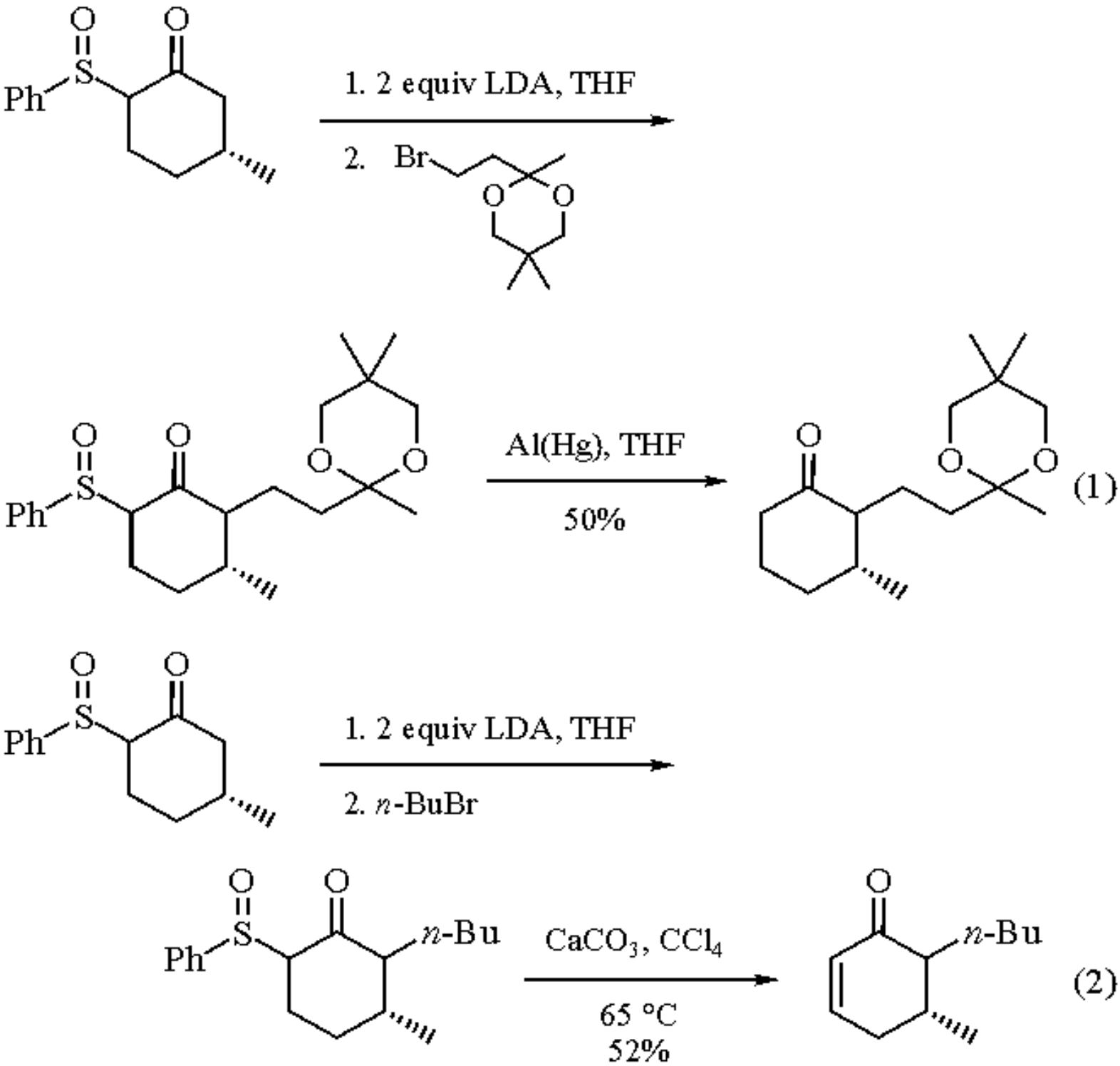

Preparation of Unsaturated Sulfoxides and Sulfones.[2,11,12]

Alkenes can be converted directly to allylic sulfoxides with *p*-toluenesulfinyl chloride in the presence of ***Ethylaluminum Dichloride***[13] or ***Zinc Chloride***[14] via an ene reaction. Treatment of the allylic sulfoxides with

trimethyl phosphite in methanol affords the allylic alcohols via sulfoxide-sulfenate rearrangement in higher yields compared to direct oxidation with ***Selenium(IV) Oxide*** (eq 3).[14] Sulfinylation of higher terpenoids with benzenesulfinyl chloride was found to be more regioselective than the procedure of sulfenylation with benzenesulfenyl chloride followed by oxidation.[14]

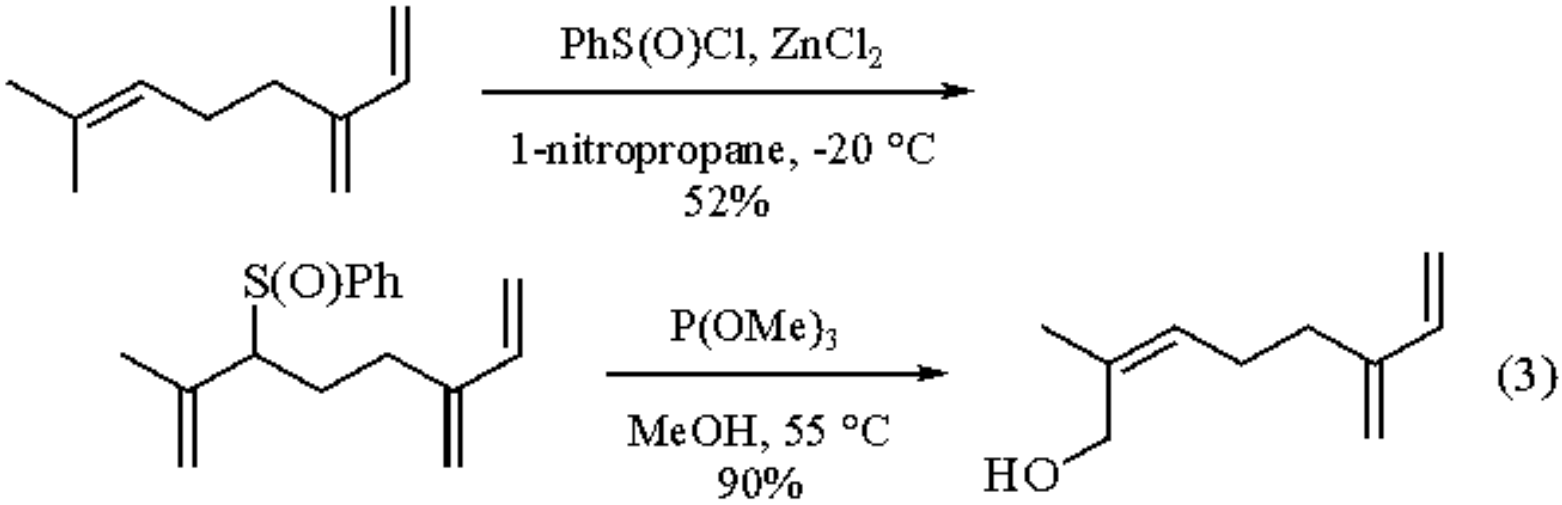

Allylic sulfinic esters, prepared by reaction of *p*-toluenesulfinyl chloride and an allylic alcohol, rearrange on heating to yield allylic sulfones;[15] sulfinic esters of alkynols rearrange to yield sulfonylallenes (eq 4).[16]

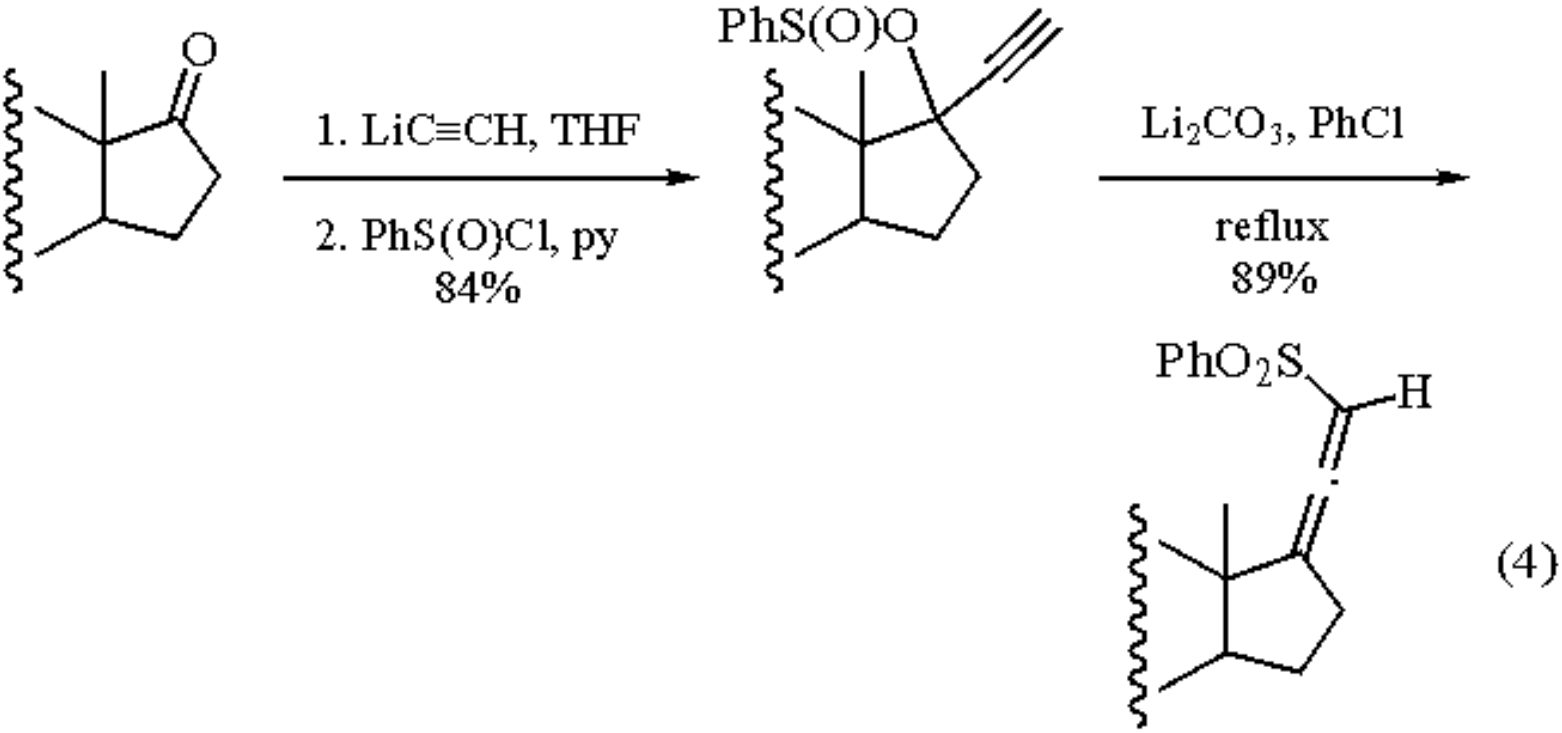

Asymmetric Synthesis.

p-Toluenesulfinyl chloride can be used to prepare menthyl *p*-toluenesulfinates (MenTs) (see ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***), very useful chiral sulfinyl-transfer reagents.[4] Both the (*R*) and the (*S*) isomers can be prepared by reaction of the sulfinyl chloride with either (+)- or (-)-menthol, respectively.[17,18] (See ***Methyl***

Benzenesulfinate for additional discussion on menthyl *p*-toluenesulfinate.) MenTs reacts with a variety of nucleophiles such as metallated esters,[19] dialkylhydrazones,[20] and amides,[21] with inversion of configuration, to form chiral sulfoxides. These substrates are capable of undergoing further enantioselective manipulation to yield optically active compounds in high enantiomeric excess.[22,23]

Chiral vinyl sulfoxides can be prepared from MenTs and metallated vinylic reagents;[24] vinyl sulfoxides are recognized as valuable synthetic intermediates.[11] For example, the conjugate addition of organometallic compounds to enantiomerically pure 2-(*p*-tolylsulfinyl)-2-cyclopentenones occurs with high stereoselectivity; the formation of the desired stereoisomer can be controlled by the presence or absence of a divalent metal complexing agent (eq 5).[24]

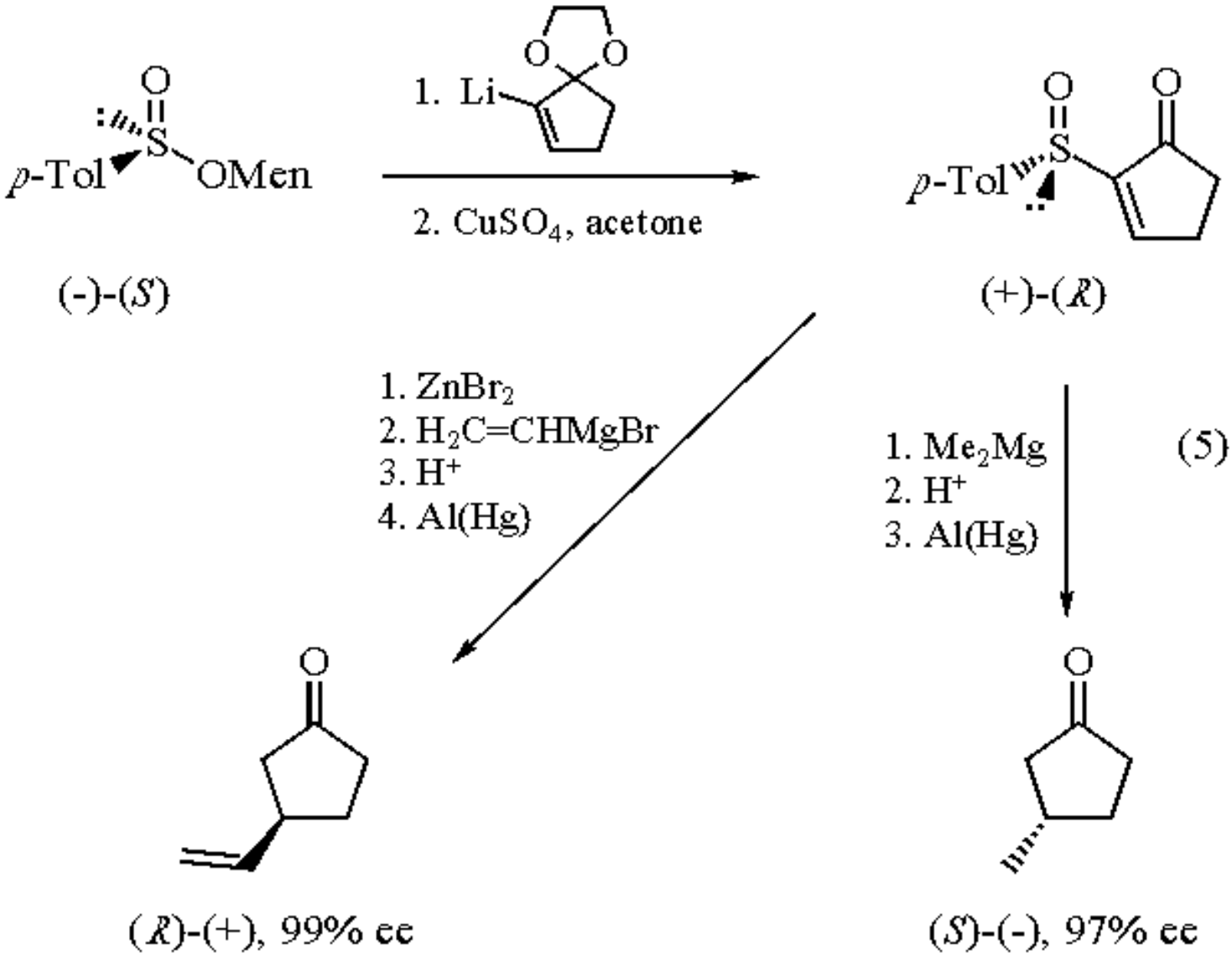

Other routes to chiral vinyl sulfoxides utilizing MenTs include a modified Horner-Emmons procedure that usually results in a mixture of (*E*) and (*Z*) isomers (eq 6),[17] and addition of alkynyl Grignard reagents to MenTs followed by stereospecific reduction to either the (*E*) or (*Z*) isomers (eq 7).[25]

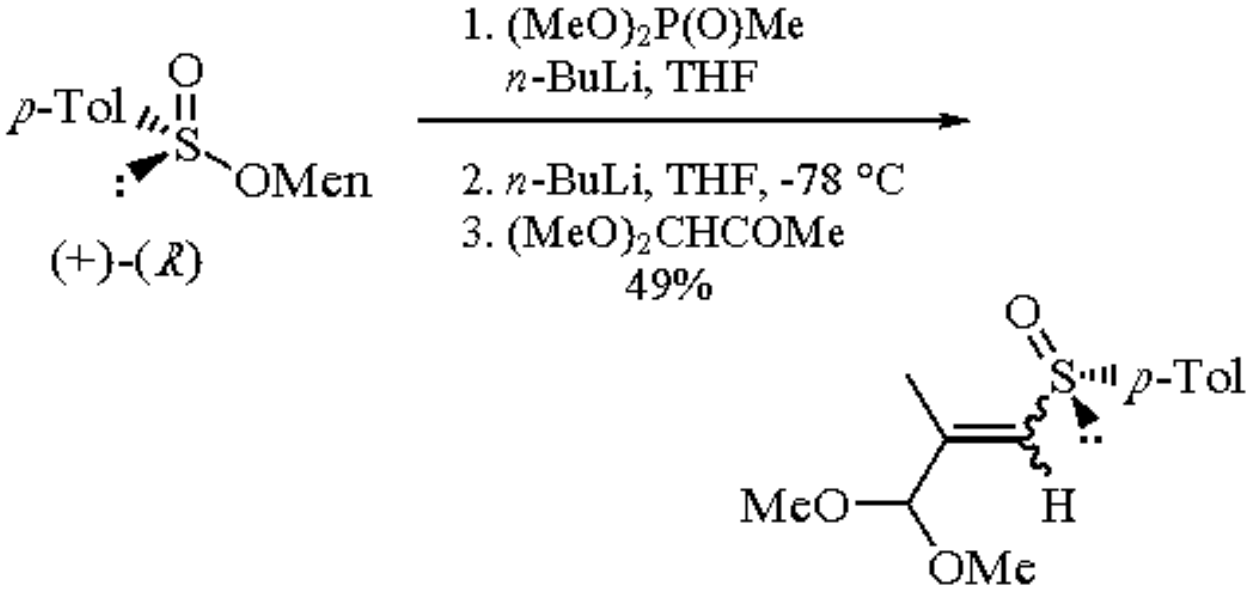

(6)

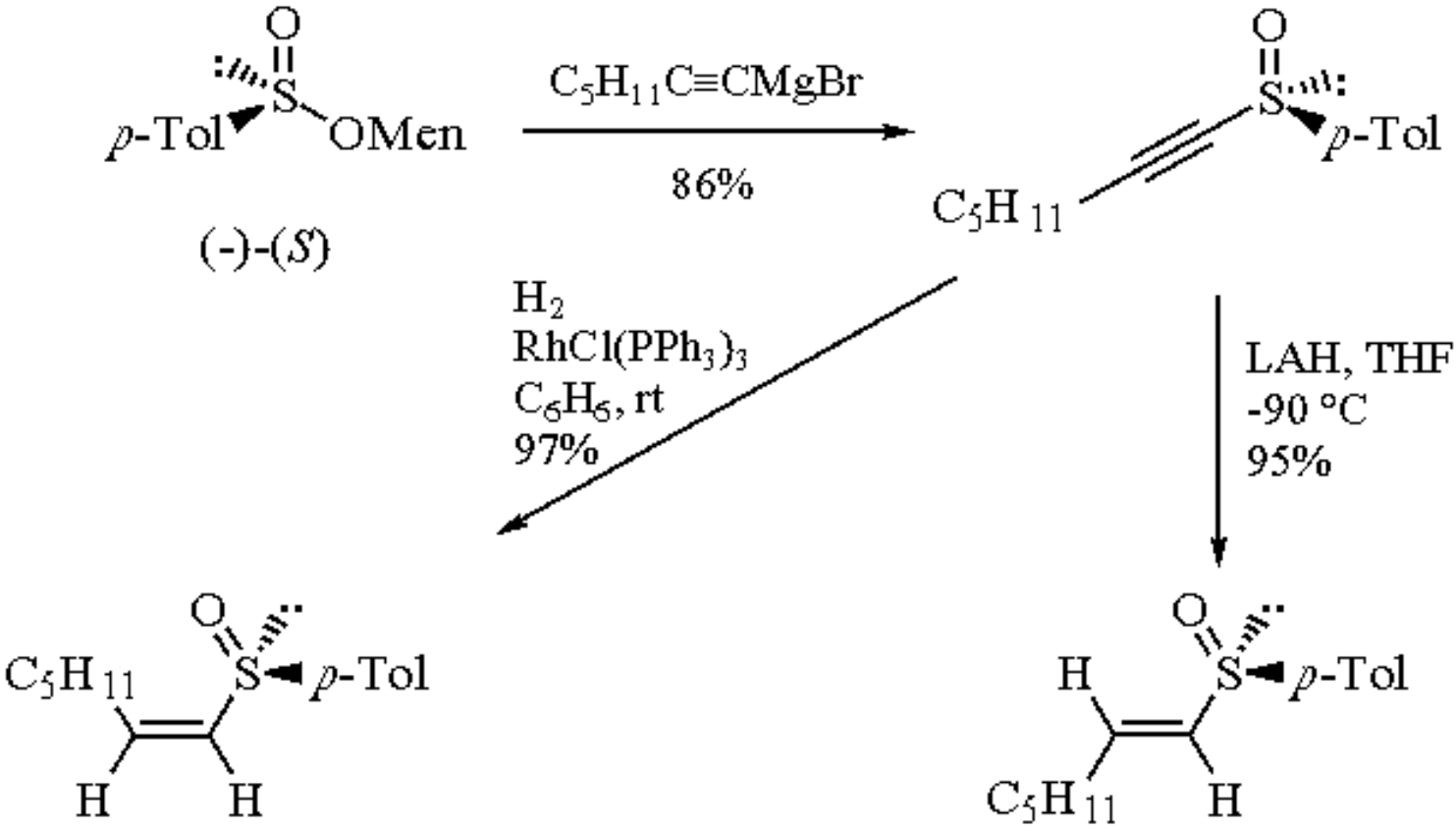

(7)

Recently, a new class of chiral sulfinylating agents have been prepared from oxazolidinones and *p*-toluenesulfinyl chloride (eq 8).[5] These *N*-sulfinyloxazolidinones also react with a wide range of nucleophiles, with inversion of configuration, to form chiral sulfoxides in high yield and enantiomeric excess (ee). These reagents reportedly are purified more easily (crystallization *and* chromatography) than the menthyl esters (crystallization only), and are more reactive than the menthyl *p*-toluenesulfinates.

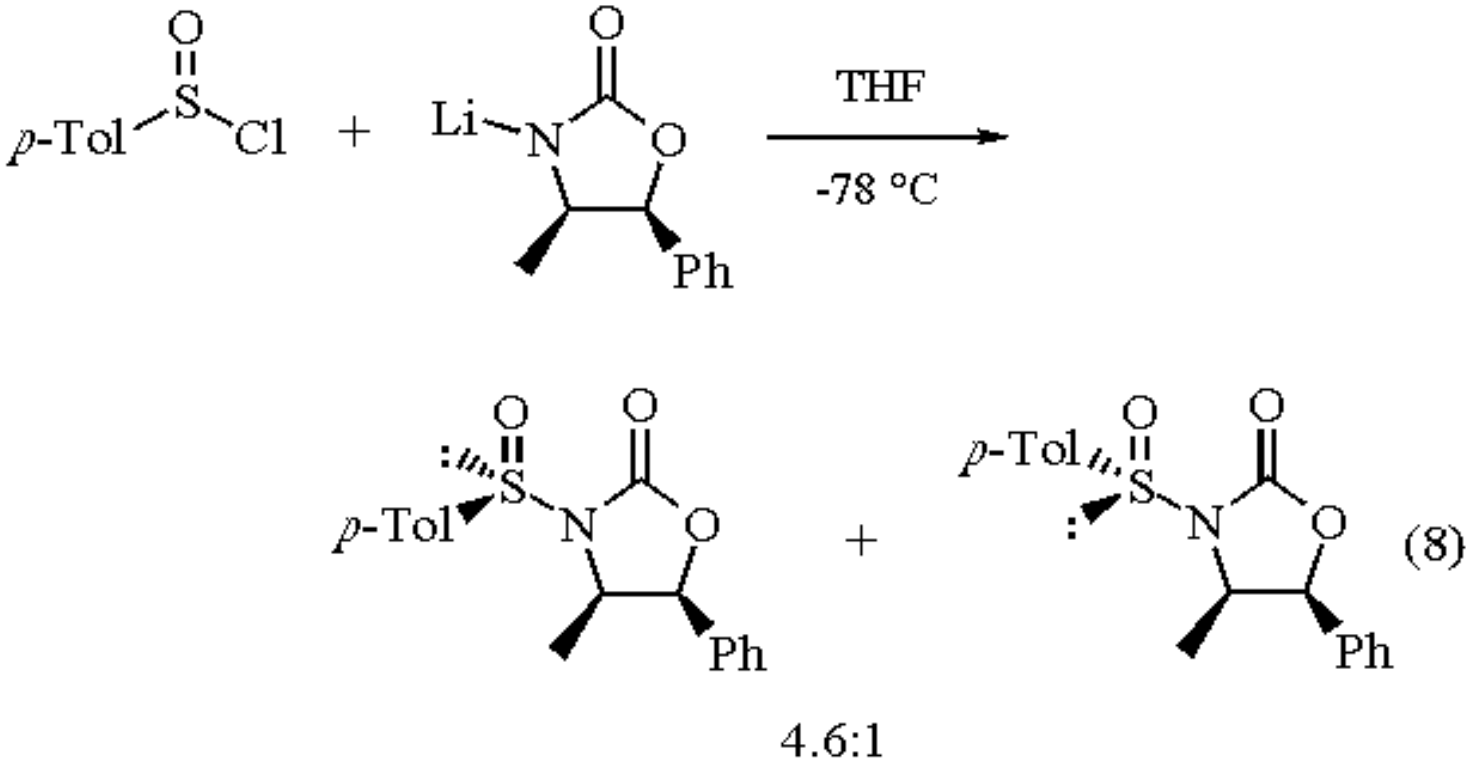

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Benzenesulfonic Anhydride[1]

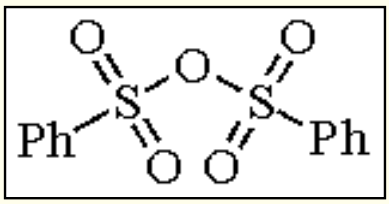

[512-35-6] · $C_{12}H_{10}O_5S_2$ · Benzenesulfonic Anhydride · (MW 298.33)

(mild sulfonating agent; useful for the preparation of sulfonamides, sulfones, and sulfonate esters)

Physical Data: mp 65-80 °C; 88-91 °C after recrystallization from ether.

Solubility: sol diethyl ether, benzene, toluene; insol H_2O.

Preparative Methods: prepared on a large scale by heating benzenesulfonic acid with excess phosphorus pentoxide mixed with an inert support.[1] An inert support of 1:1 Supercel kieselguhr and Gooch asbestos was mixed with phosphorus pentoxide and slowly added to benzenesulfonic acid, first at rt then heating to 100 °C. The resultant mixture was heated at 100 °C for 5 h, 1,2-dichloroethane was added, and the solution was refluxed for 10 min. After cooling and successive filtrations, benzenesulfonic anhydride was recovered in 70% yield.

Handling, Storage, and Precautions: the reagent can be stored at rt for extended periods under anhydrous conditions. Liquefication occurs upon exposure to air for 2.5 h. Explosive when mixed with 90-95% H_2O_2.

General Reactions.

Arenesulfonic anhydrides have been used as precursors for a variety of substituted sulfones, sulfonate esters, and sulfonamides. The Friedel-Crafts reaction of benzenesulfonic anhydride and benzene in the presence of $AlCl_3$ provided diphenyl sulfone in 99% yield (eq 1).[1] This has proved to be milder and more efficient than the similar reaction using ***Benzenesulfonyl Chloride***.[1,2]

$$(PhSO_2)_2O + PhH \xrightarrow{AlCl_3} PhSO_2Ph \qquad (1)$$

Azoxybenzene is known to rearrange in concentrated sulfuric acid to *p*-hydroxyazobenzene.[3] This acid-catalyzed Wallach rearrangement[4] has been extended by using arenesulfonic anhydrides to furnish the corresponding *p*-

arenesulfonyloxyazobenzenes in reasonable yields (eq 2).[5]

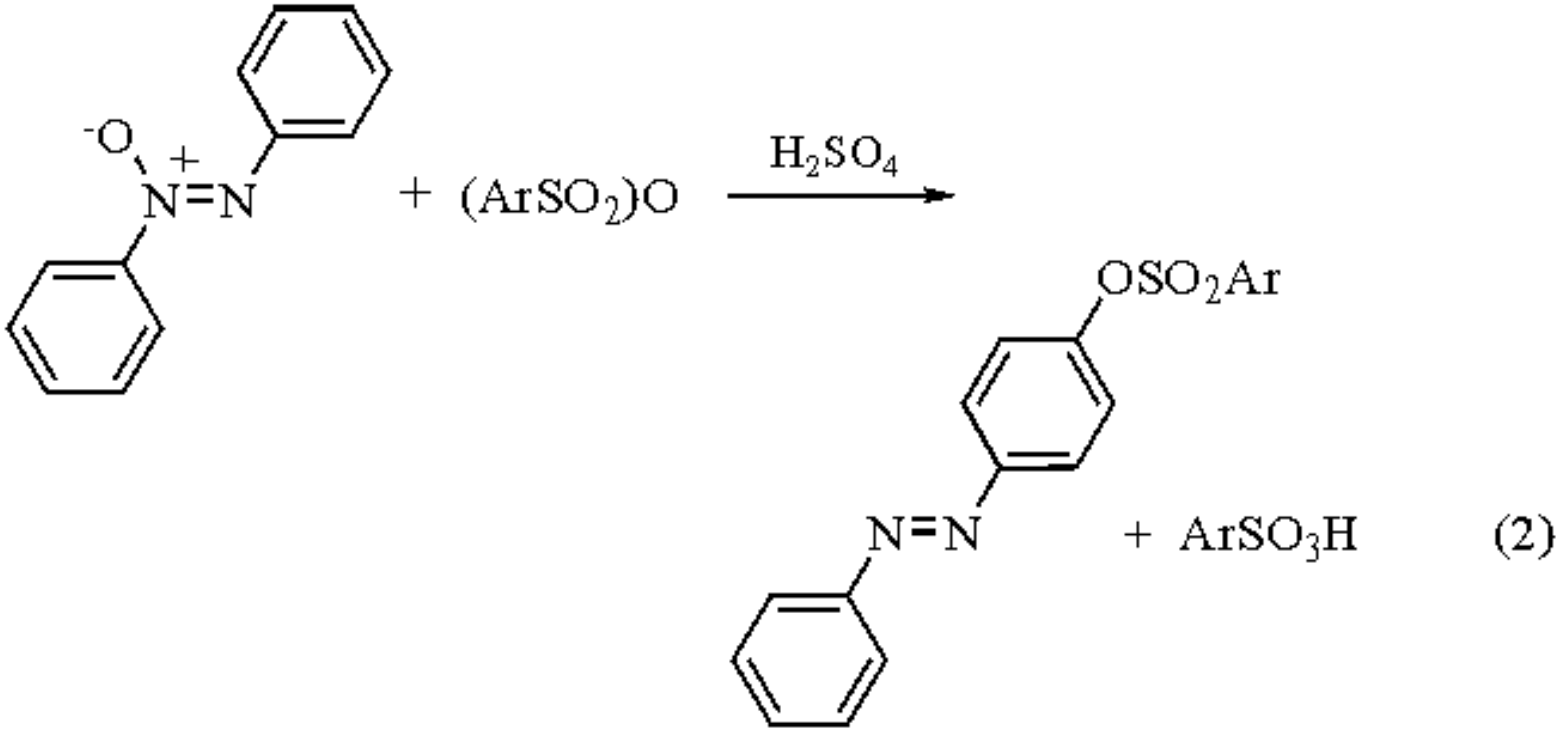

Solvolysis of Benzenesulfonic Anhydride.

Solvolysis of various arenesulfonic anhydrides in aqueous acetone revealed the reaction mechanism to be S_N2 in accord with established results for similar systems.[6]

---

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Benzenesulfonyl Azide

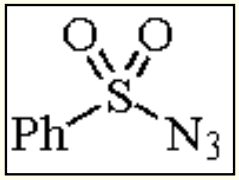

[938-10-3] · $C_6H_5N_3O_2S$ · Benzenesulfonyl Azide · (MW 183.18)

(1,3-dipolar reagent that undergoes cycloaddition to alkenes, enamines and enol ethers;[1] reacts with phosphines and phosphites to form iminophosphoranes[2,3])

Physical Data: mp 105 °C with decomposition.

Solubility: sol most organic solvents.

Preparative Methods: prepared by the reaction of ***Benzenesulfonyl Chloride*** with excess ***Sodium Azide*** in a water-ethanol mixture.[4,5] The formation of ethyl benzenesulfonate as a byproduct may be avoided by addition of neat benzenesulfonyl chloride to an ethanolic solution of sodium azide.[6] A preparation of benzenesulfonyl azide by oxidation of phenylsulfonylhydrazine in the presence of clay-supported iron(III) nitrate (clayfen) has been reported.[7]

Purification: recrystallization from ethanol.

Handling, Storage, and Precautions: crude benzenesulfonyl azide when heated detonates violently.[8] Use in a fume hood.

Dipolar Cycloaddition.

The principal use of benzenesulfonyl azide is in 1,3-dipolar cycloaddition[1] reactions with alkenes and functionally substituted alkenes.[9] The reagent reacts with norbornene to yield an intermediate triazoline which decomposes to an *exo*-aziridine (eq 1).[10,11] In the case of norbornadiene the initially formed aziridine readily rearranges to a ring expanded product (eq 2).[6,12,13]

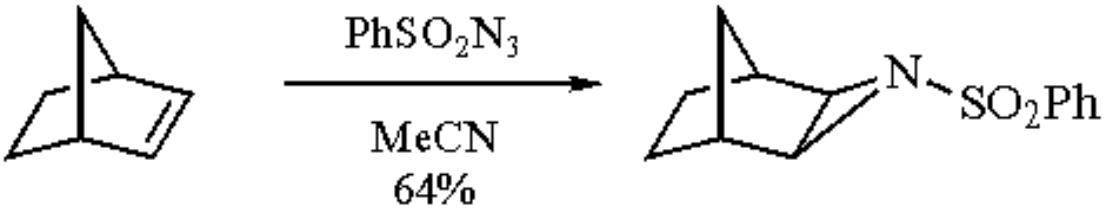

(1)

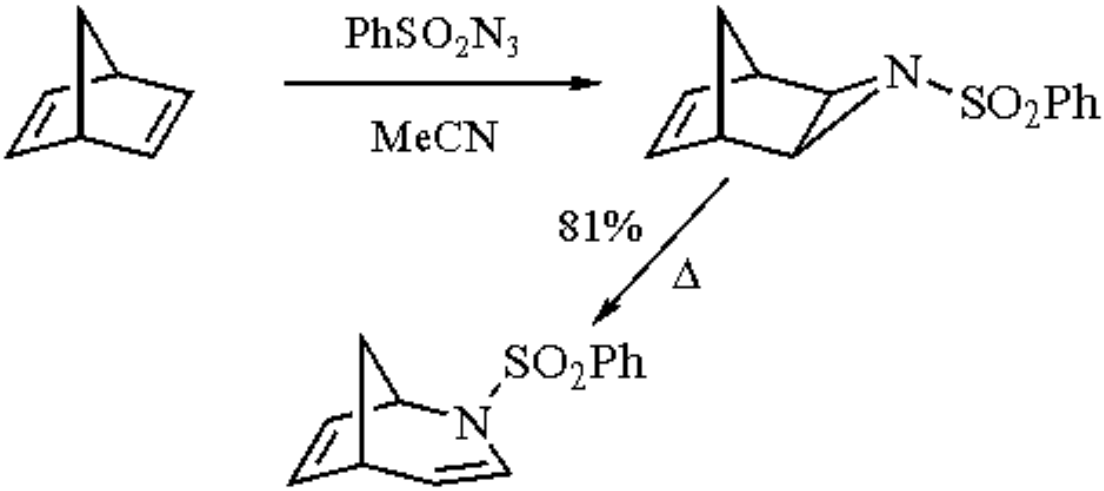

(2)

With *N*-methyl-1,2-dihydropyridine, benzenesulfonyl azide affords an isolable aziridine (eq 3).[14] In contrast, *N*-methyl-1,2,3,4-tetrahydropyridine undergoes cycloaddition, decomposition to the aziridine, and then rearrangement to the corresponding amidine sulfonamide (eq 4).[15]

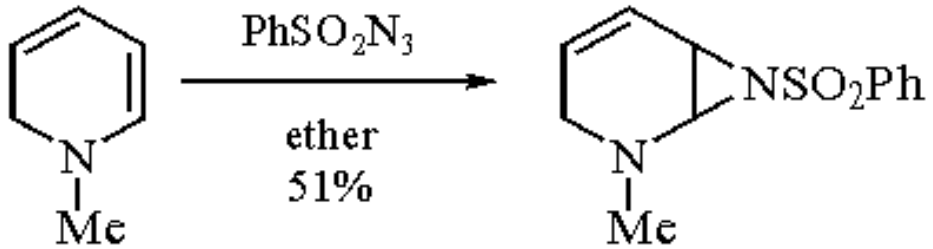

(3)

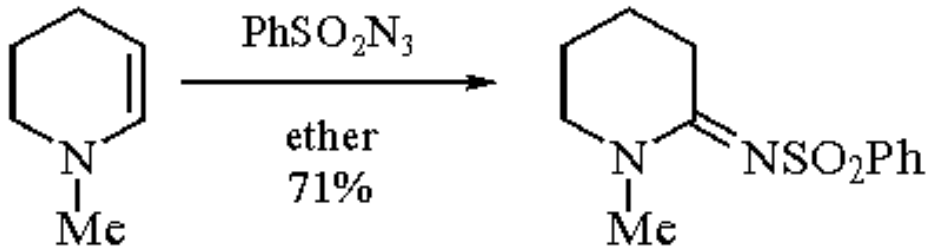

(4)

The reaction of benzenesulfonyl azide with enol ethers follows a different course. Dihydropyran affords imidate (**1**) in crude quantitative yield and when the imidate is heated it rearranges to lactam (**2**) (eq 5).[16] The more sluggish 6-methoxy derivative reacts in refluxing acetonitrile to afford the lactam product directly (eq 6).

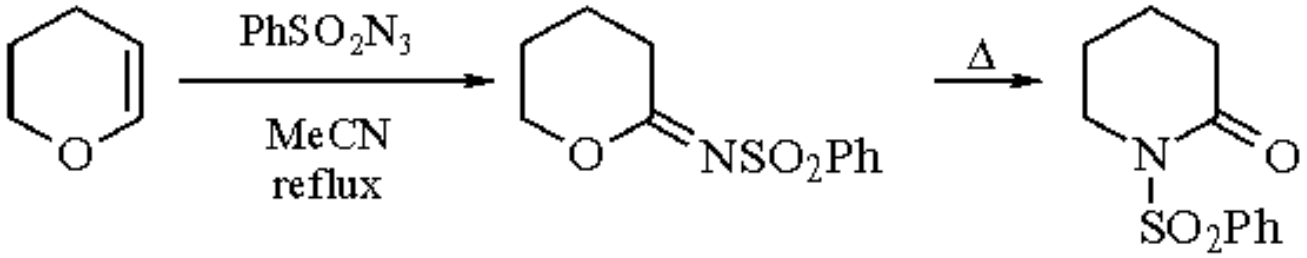

(5)

(1) **(2)**

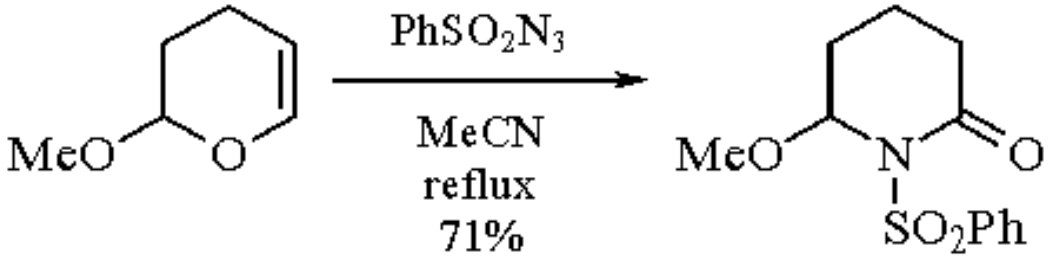

(6)

With enol ethers of cyclic ketones, benzenesulfonyl azide is one of a variety of sulfonyl azides which effect a ring contraction reaction.[17,18] A triazoline is again assumed to be an intermediate in the process (eq 7).

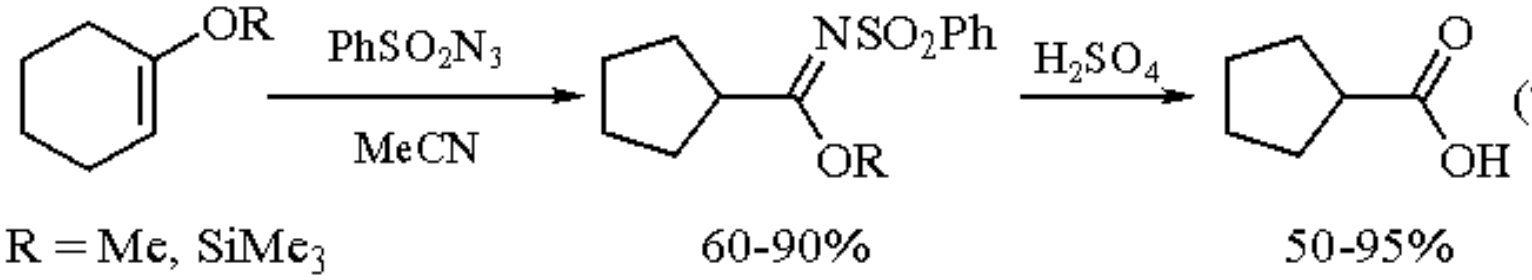

(7)

Cycloaddition of benzenesulfonyl azide to cobaltacycles leads to the production of substituted pyrroles (eq 8).[19]

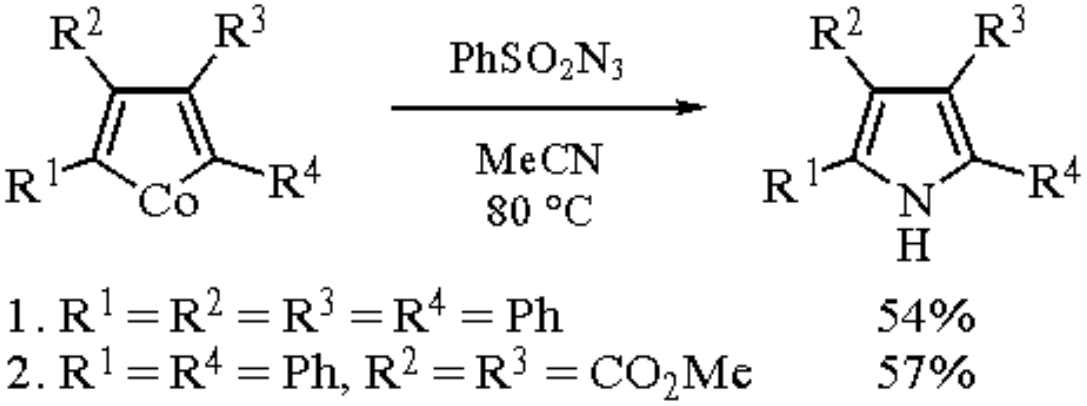

(8)

Formation of Iminophosphoranes.

The reaction of benzenesulfonyl azides with triphenylphosphine (eq 9)[3] or with triphenyl or triethyl phosphite[2] leads to the formation of sulfoniminophosphoranes.

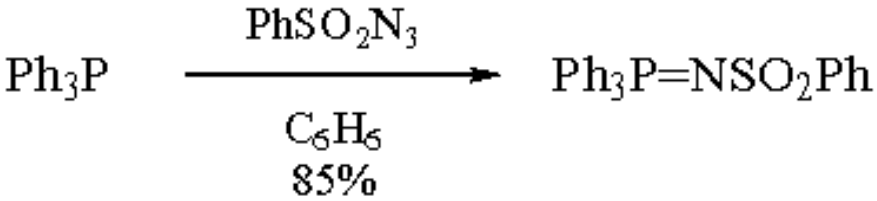

(9)

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Benzenesulfonyl Bromide

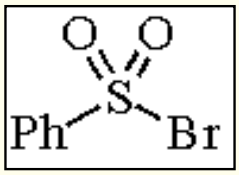

[2297-65-6] · $C_6H_5BrO_2S$ · Benzenesulfonyl Bromide · (MW 221.07)

(used as a sulfonating reagent to produce sulfonamides[2-4] and sulfones[5-8])

Physical Data: mp 19.5 °C; bp 76-78 °C/0.17 mmHg.

Solubility: sol CH_2Cl_2, Et_2O, THF, C_6H_6, MeCN.

Preparative Method: prepared by reaction of sodium benzenesulfonate with bromine in 98% yield.[1]

Handling, Storage, and Precautions: by analogy to ***Benzenesulfonyl Chloride***, benzenesulfonyl bromide should be assumed to be an irritant and harmful by skin absorption and ingestion. Benzenesulfonyl bromide is best used immediately following preparation and may be used in situ. The reagent is moisture sensitive and will react with nucleophilic solvents (e.g. alcohols), liberating HBr and therefore should be stored under an inert atmosphere. Use in a fume hood.

Protection of Nitrogen; Formation of Sulfonamides.

Unlike the corresponding arenesulfonyl chlorides (see ***Benzenesulfonyl Chloride*** and ***p-Toluenesulfonyl Chloride***), benzenesulfonyl bromide has been used much less extensively in organic synthesis. Primary amines[2] and imidazoles (eq 1)[3] have been converted to the corresponding benzenesulfonamides and, with indoles, bromination at C-3 occurs with concomitant sulfonamide formation (eq 2).[4]

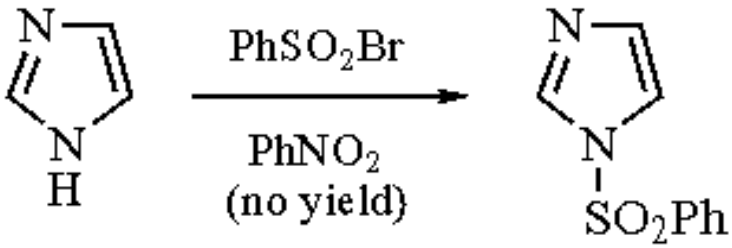

(1)

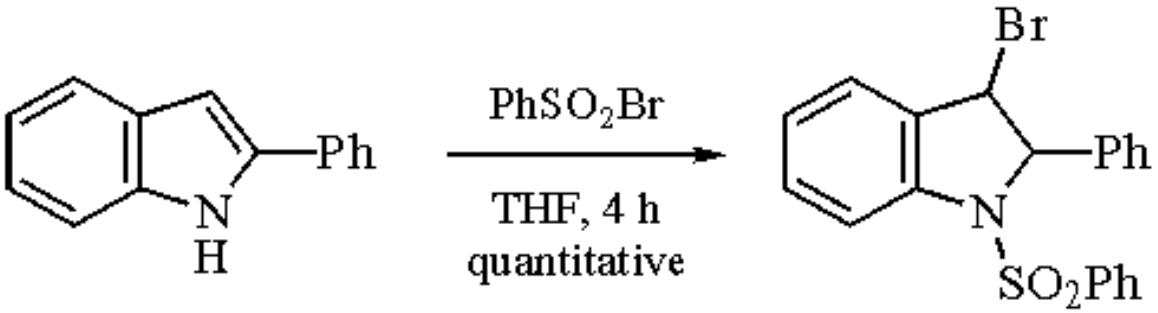

(2)

Addition to Unsaturated Compounds.

Benzenesulfonyl bromide undergoes radical-mediated addition to alkenes and alkynes. Addition to alkenes leads to bromo sulfones, which undergo dehydrobromination to give vinyl sulfones (eq 3).[5]

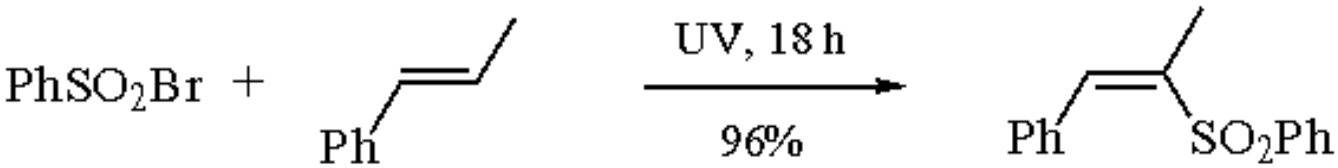

(3)

Addition to vinyl ethers and vinyl esters is regioselective, leading to the corresponding β-alkyloxy/acyloxy sulfone.[6] Addition to alkynes gives vinyl sulfones via a radical pathway. These reactions can be carried out in the presence of peroxide initiators,[7] with Lewis acids such as ***Copper(II) Bromide*** (eq 4),[8] or thermally (eq 5).[8,9]

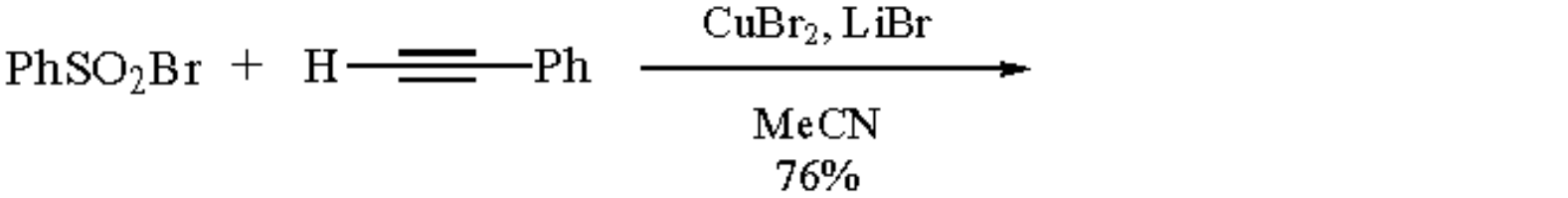

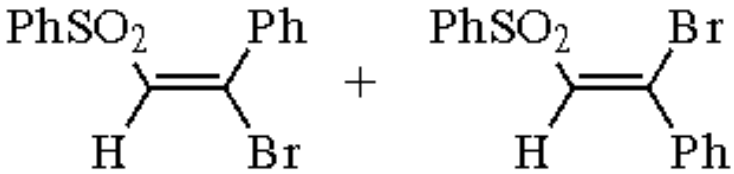

(4)

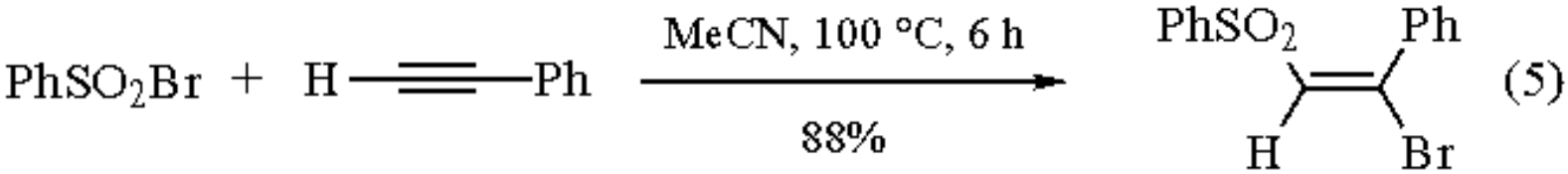

(5)

With enynes, mixtures of addition products resulting from 1,2- and 1,4-addition have been observed.[10,11] Radical addition with tricyclic alkanes has also been observed.[12]

Reaction with Arenes.

Benzenesulfonyl bromide reacts readily with trifluoromethanesulfonyl derivatives, yielding the corresponding mixed anhydrides (eq 6)[13] which have been used to convert arenes to aryl phenyl sulfones under Friedel-Crafts-type conditions.

$$PhSO_2Br + CF_3SO_2Ag \xrightarrow[\text{quantitative}]{MeCN,\ 0°C} PhSO_2OSO_2CF_3 + AgBr \quad (6)$$

---

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Benzenesulfonyl Chloride

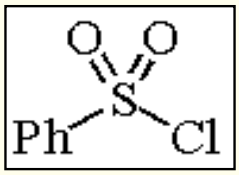

[98-09-9] · $C_6H_5ClO_2S$ · Benzenesulfonyl Chloride · (MW 176.62)

(used in a range of sulfonating reactions to produce sulfonamides,[5-7] sulfonate esters,[8-10] mixed anhydrides,[13] and sulfones [15-17])

Physical Data: mp 13-15 °C, bp 251.5 °C/760 mmHg, 113-115 °C/10 mmHg; *d* 1.384 g cm^{-3}.

Solubility: sol CH_2Cl_2, Et_2O, THF, C_6H_6, MeCN.

Preparative Methods: prepared by reaction of sodium benzenesulfonate with phosphorus pentachloride or phosphorus oxychloride,[1] or by chlorosulfonation of benzene;[2] also commercially available.

Purification: may be purified by distillation at reduced pressure.

Handling, Storage, and Precautions: benzenesulfonyl chloride is an irritant and harmful by skin absorption and ingestion. The reagent is moisture sensitive and will react with nucleophilic solvents (e.g. alcohols), liberating HCl and therefore should be stored under an inert atmosphere. Use in a fume hood.

Identification of Primary Amines; the Hinsberg Test.

Benzenesulfonyl chloride is used to recognize primary amines. A primary amine will react to form an alkali-soluble benzenesulfonamide (containing an acidic NH), whereas secondary amines form sulfonamides which are insoluble in alkali, and tertiary amines do not react.[3] However, the validity of the test is dependent on reaction velocity, concentration, temperature, and solubility[4] and appropriate precautions must be acknowledged.

Protection of Nitrogen; Formation of Sulfonamides.

Benzenesulfonyl chloride is used to protect amines, indoles and other nitrogen based functional groups (eqs 1-3).[5-7] A variety of bases and solvents can be used, depending on the substrate. Other arene- and alkanesulfonyl chlorides can also be used for this purpose (see ***p-Toluenesulfonyl Chloride*** and ***Methanesulfonyl Chloride***). Sulfonamide cleavage may be achieved under either acidic or basic conditions.

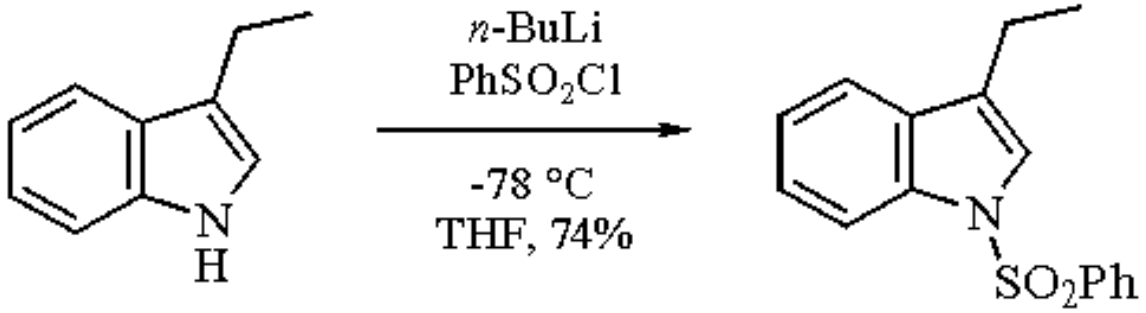

(1)

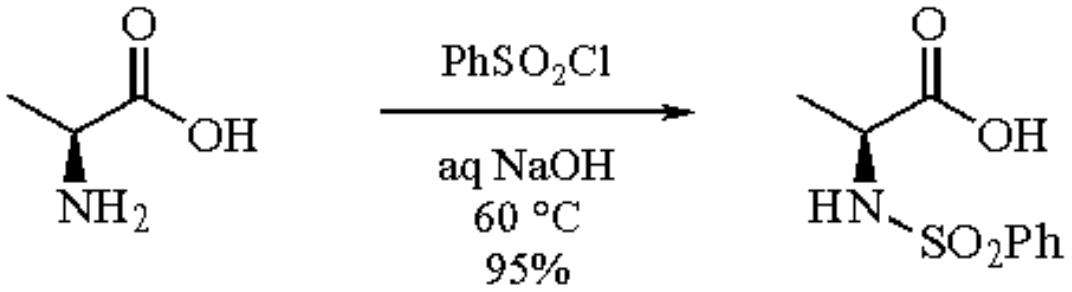

(2)

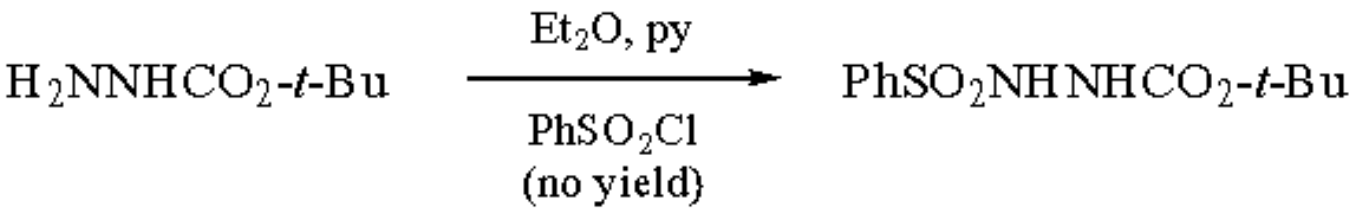

(3)

Formation of Sulfonate Esters.

The reaction of phenols,[8] alcohols,[9] and *N*-hydroxy compounds[10] with benzenesulfonyl chloride produces *O*-sulfonate esters, one application of which is as a good leaving group.

The reaction of 1,4- or 1,5-diols with benzenesulfonyl chloride in the presence of a tertiary amine gives cyclic ethers (eq 4).[11] This procedure can be adapted to give cyclic tertiary amines.[12]

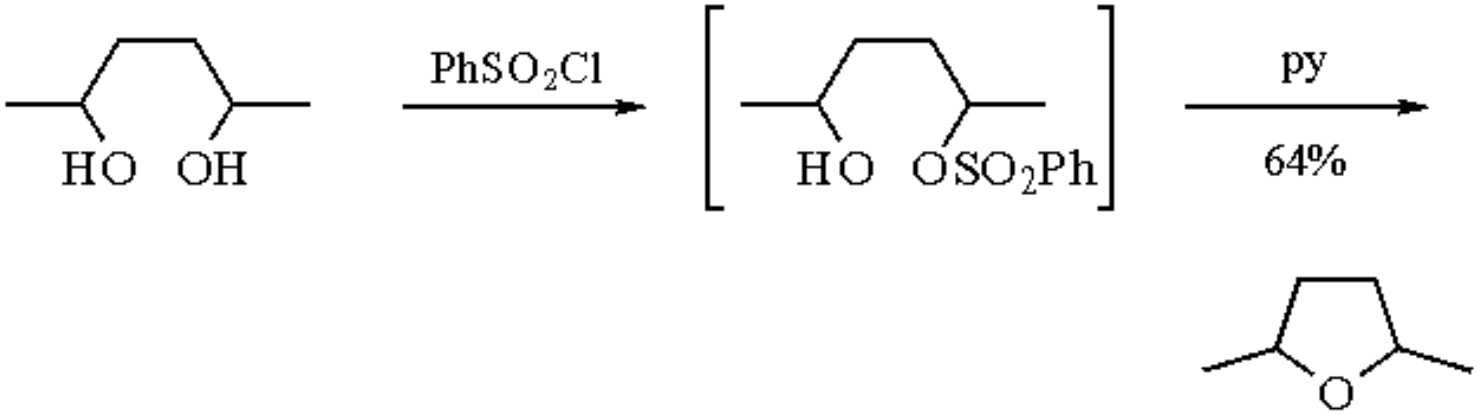

(4)

Formation of Mixed Anhydrides.

Benzenesulfonyl chloride will react with carboxylic acids to give mixed anhydrides,[13] which can be utilized in the formation of alkenes via β-lactone formation followed by fragmentation (eq 5).[14] Direct conversion of the hydroxy acid to the alkene can be achieved by the addition of benzenesulfonyl chloride at 45-50 °C in 55-82% yield.

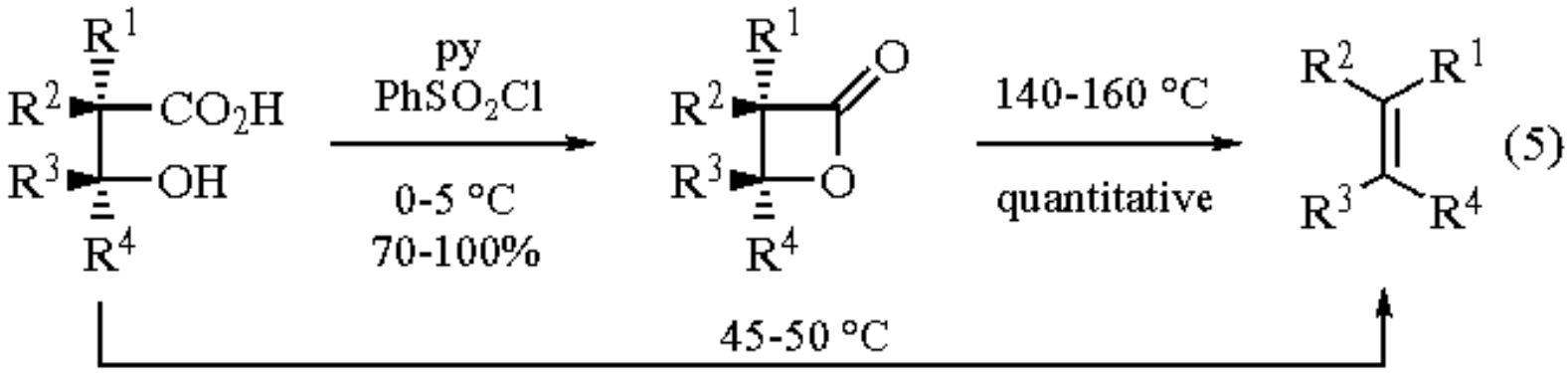

Addition to Unsaturated Compounds.

Benzenesulfonyl chloride will undergo radical addition to alkenes and alkynes under radical conditions (eq 6)[15] or Cu^{II} catalysis (eq 7).[16]

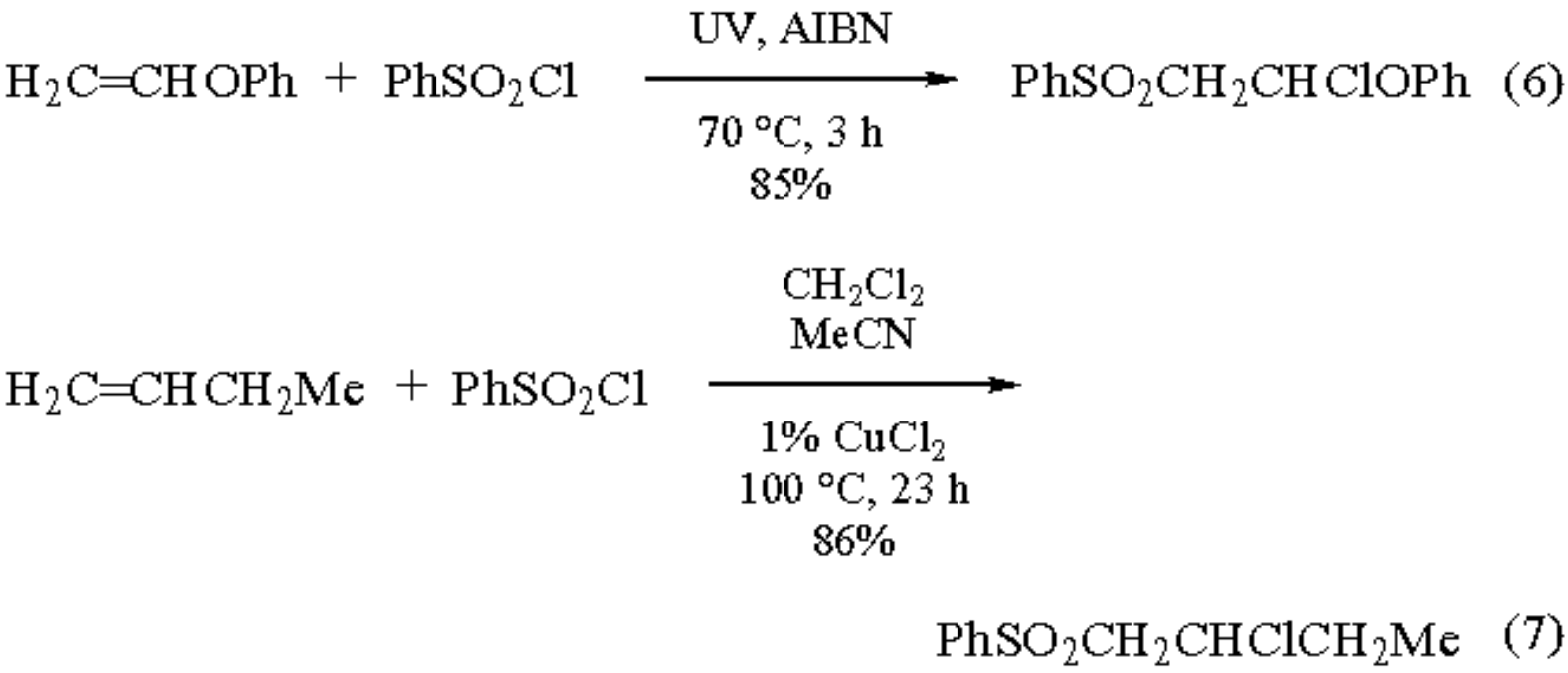

Addition of benzenesulfonyl chloride to trimethylsilyl enol ethers gives β-keto sulfones in good yield (eq 8).[17]

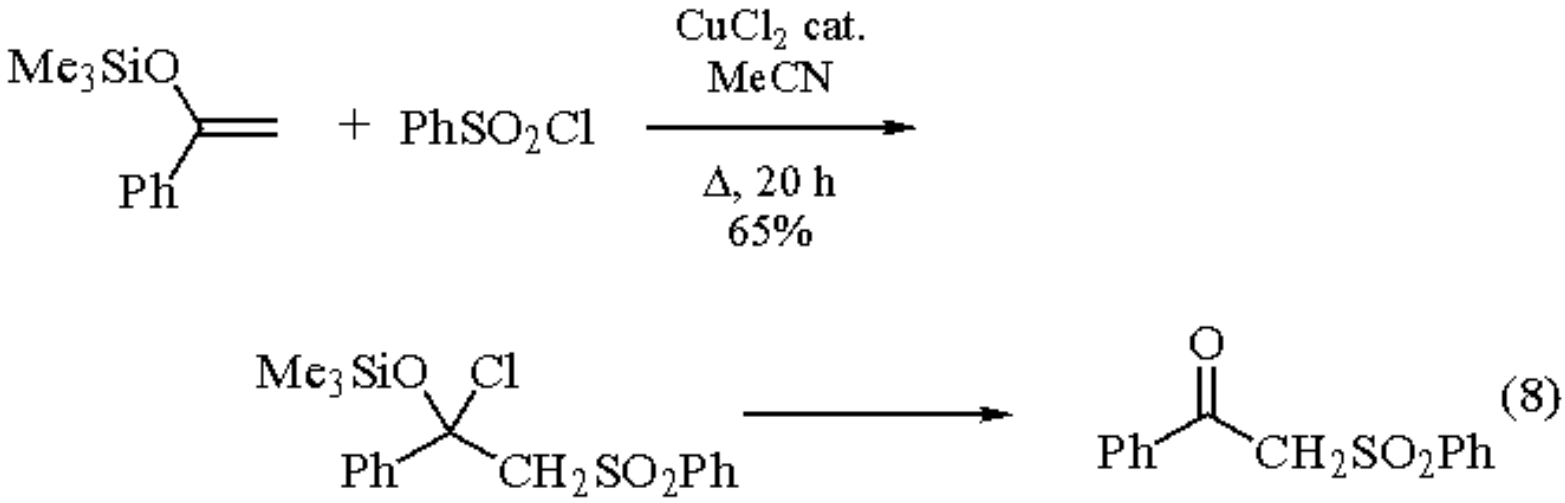

Reaction with Arenes.

Benzenesulfonyl chloride will react with arenes in the presence of ***Aluminum Chloride*** to give biaryl sulfones.[18]

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Hayley Binch

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Benzenesulfonyl Isocyanate

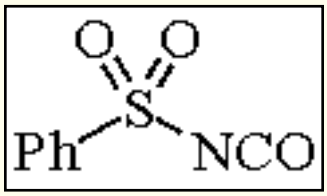

[2845-62-7] · $C_7H_5NO_3S$ · Benzenesulfonyl Isocyanate · (MW 183.18)

(derivatizing agent for alcohols and phenols;[1] used to convert (thio)carbonyl compounds to imino derivatives;[2,3] used in the preparation of β-lactams[4] and a wide variety of heterocycles via cycloaddition reactions)

Physical Data: bp 130 °C/9 mmHg; *d* 1.369 g cm^{-3}.

Solubility: sol chlorinated, aromatic, and ethereal solvents; reacts violently with H_2O, basic and protic solvents.

Form Supplied in: colorless liquid; widely available; more expensive than *p*-toluenesulfonyl isocyanate.

Handling, Storage, and Precautions: lachrymator; corrosive; use only in a fume hood; wear protective gloves and preferably a NIOSH-approved respirator. All transfers and reactions should be carried out under anhydrous conditions. Store in a cool dry place, taking care to avoid contamination with protic, basic, or organometallic materials, as these may induce polymerization. Toxicity data for isocyanates are available.[5]

Hydroxy Derivatization.

First prepared by Billetter in 1904, benzenesulfonyl isocyanate has been found to be an excellent reagent for the preparation of highly crystalline carbamates from hindered primary and secondary alcohols and polynitrophenols in very high yield (eq 1).[1] Indeed, the sulfonyl group not only activates the isocyanate moiety relative to alkyl or aryl substituents,[1,6] but these derivatives are also very easily purified (typically by aqueous extraction). Surprisingly, no reports have been made of amine derivatizations, despite a great potential for this purpose.

$$PhSO_2NCO \xrightarrow[85\text{-}100\%]{ROH} PhSO_2NHCO_2R \qquad (1)$$

R = alkyl, aryl

(Thio)carbonyl to Imide Conversion.

This transformation appears quite general, occurring for ketone, amide, oxamate,[2] and thioamide[3] groups. Heating the (thio)carbonyl derivative with benzenesulfonyl isocyanate leads to a formal [2 + 2] cycloaddition, followed by fragmentation, to give the N-protected imine derivative and CO_2 or COS (eq 2). Although this conversion represents an interesting and general method of preparing imines, (thio)imino esters, amidines, etc., note that removal of the benzenesulfonyl group generally requires vigorous reaction conditions that may, in certain circumstances, destroy the imino derivative.

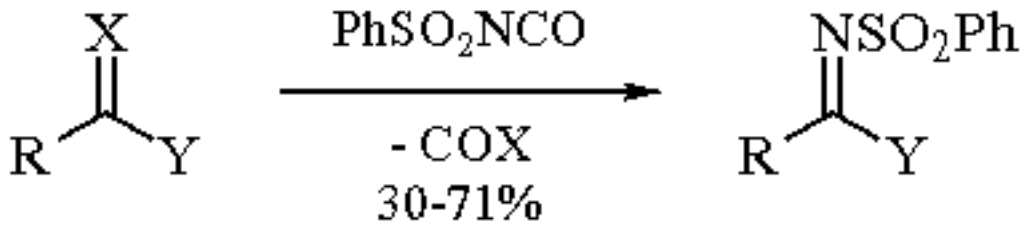

(2)

X = O, S; Y = alkyl, aryl, O, NR^1R^2, S, CO_2R

[2 + 2] and [2 + 3] Cycloadditions.

All isocyanates undergo these reactions to some extent, but benzenesulfonyl isocyanate is several orders of magnitude more reactive for some types of cycloaddition.[6,7] Perhaps the most useful reaction involving this isocyanate is [2 + 2] cycloaddition with enol ethers,[4] ketenes, and thioketenes[8] to afford β-(thio)lactams. This is a very useful entry into N-protected β-lactams, despite the relative difficulty of removing the benzenesulfonyl group without cleaving the β-lactam (eq 3).

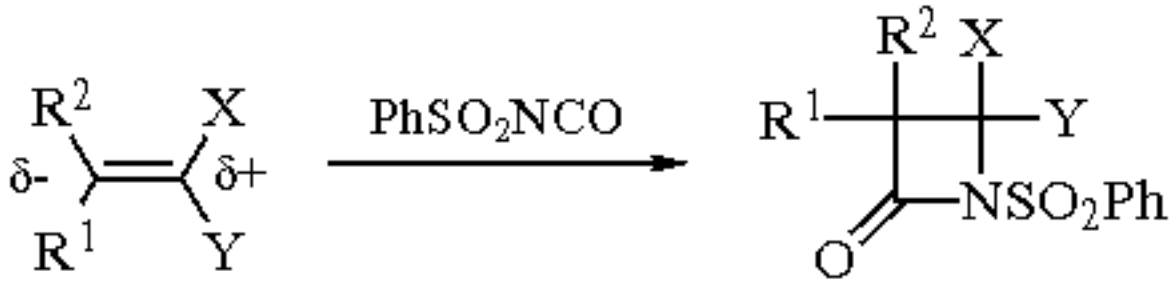

(3)

X, Y = H, OR, =O, =S; R^1, R^2 = H, alkyl, aryl

Interestingly, the analogous N,O-ketene acetals give only acyclic products.[9] A number of [2 + 3] cycloadditions have been reported, including the syntheses of indolin-2-ones,[10] dehydroazepinones,[11] and tetrazolones.[7]

Miscellaneous Uses.

The patent literature contains numerous examples of *N*-benzenesulfonyl carbamate and urea compounds (derived respectively from alcohols and amines) exhibiting pharmaceutically[12] and agriculturally useful properties (e.g. imparting H_2O solubility and functioning as a pharmacophore). Benzenesulfonyl isocyanate itself has also been reported in the patent literature to be of use in polymer chemistry as a dehydrating, stabilizing, and crosslinking agent, and as a catalyst or reagent in the preparation of carbodiimides and other isocyanates. See also ***p-Toluenesulfonyl Isocyanate***.

---

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Benzenetellurinic Anhydride[1]

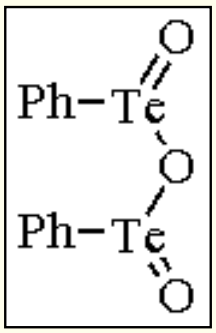

[94971-86-5] · $C_{12}H_{10}O_3Te_2$ · Benzenetellurinic Anhydride · (MW 457.41)

(mild and selective oxidizing agent by itself and as mixed anhydrides;[1-3] catalyst for hydration of ethynyl group;[3] vicinal *syn* diacetoxylating agent of alkenes;[4] electrophiles, as mixed anhydrides, for acetoxytellurinylation of alkenes, cyclofunctionalization of hydroxyalkenes,[5] aminotellurinylation of alkenes, cyclofunctionalization of alkenic carbamates,[6] one-pot synthesis of 2-oxazolidinones from alkenes,[7] amidotellurinylation of alkenes[8] as well as alkynes,[9] one-pot synthesis of 2-oxazolines from alkenes[8] as well as oxazoles from alkynes,[9] and one-pot conversion of allylsilanes to allylamines[10])

Physical Data: mp 220-225 °C.

Solubility: almost insol in common organic solvents except acetic acid. In acetic acid it gradually changes to the mixed anhydride, benzenetellurinyl acetate.

Preparative Methods: benzenetellurinic anhydride is readily obtained as a white solid by alkaline hydrolysis of phenyltellurium trihalides and subsequent acidification with AcOH or by oxidation of ***Diphenyl Ditelluride*** with air or selenous acid.[1] The following arenetellurinic anhydrides are prepared similarly: 4-ethoxybenzene-, mp 234-238 °C (dec); 4-hydroxybenzene-, mp 200 °C (dec); 4-methoxybenzene-, mp 200-205 °C; 4-methylbenzene-, mp 200 °C; 4-phenoxybenzene-, mp 276 °C; 2-naphthalene-, mp 230 °C.[1]

Purification: it was reported that the anhydride could be recrystallized from acetic acid.[11]

Handling, Storage, and Precautions: the anhydride is hygroscopic. It must be dried over P_2O_5 before use and stored as such. Toxicity of this compound is not well-defined. All manipulations are recommended to be done with gloves and in a fume hood.

Oxidation.

Benzenetellurinic anhydride and its congeners[1] readily oxidize thiols to disulfides, phosphines to phosphine oxides, hydroquinones to quinones, thioamides to nitriles, thioesters to esters, xanthates to thioesters, thioureas to carbodiimides, benzyl alcohols to benzaldehydes, and benzoin to benzil, respectively.[2,3] The mixed anhydrides (PhTe(O)OX; X = Ac, $C(O)CF_3$, SO_2CF_3) exhibit similar reactivities as the parent anhydride but also show some different selectivities to thioamides and thioureas to afford thiadiazole and urea derivatives, respectively.[3b]

Catalysis for Ethynyl Hydration.

The *p*-ethoxy congener catalyzes hydration of terminal alkynes in refluxing acetic acid but is inert to internal alkynes (eq 1).[3a]

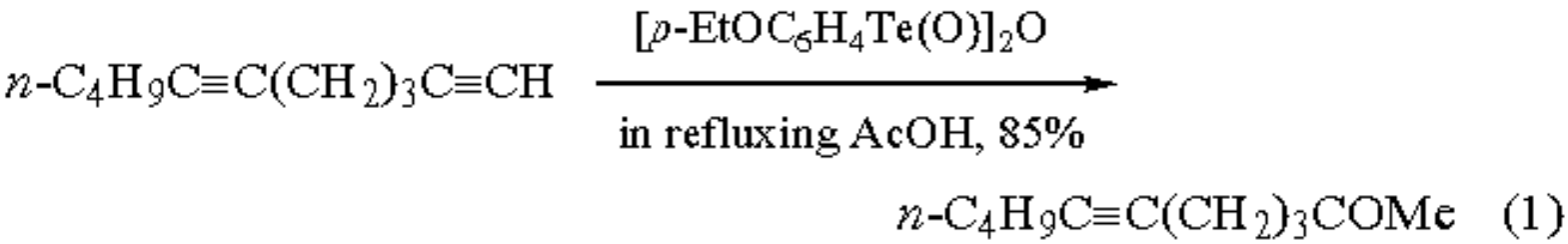

Vicinal *syn* Diacetoxylation.

Under the catalysis of sulfuric acid, the reagent oxidizes alkenes in AcOH to afford vicinal *syn*-diacetates (eq 2).[4] The reaction was assumed to be initiated by benzenetellurenic acid derivatives generated reductively and to proceed via *trans* acetoxytellurenylation followed by S_N2 displacement of the PhTe group by AcOH.

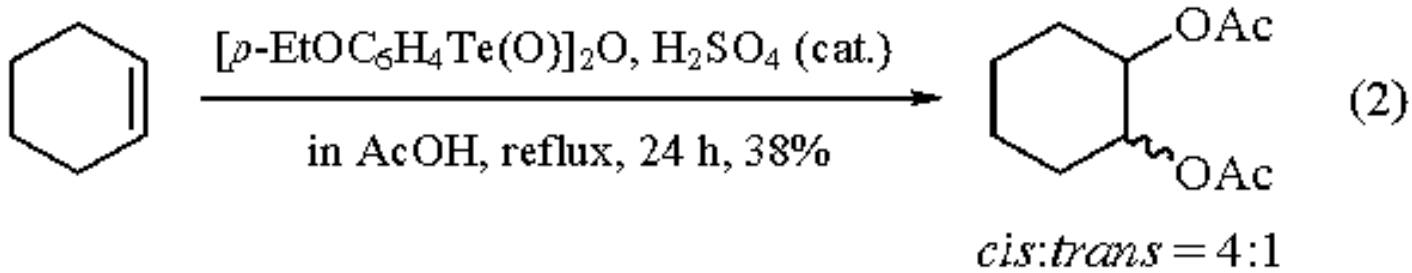

Electrophiles for Acetoxytellurinylation of Alkenes and Cyclofunctionalization of Hydroxyalkenes.

The reagent and its congeners react with alkenes in AcOH to give acetoxytellurinylation products, which are reduced to Markovnikov-type β-acetoxytellurides. They also induce cyclofunctionalization of hydroxyalkenes to 5-, 6-, and 7-membered cyclic ethers. Treatment of the reagents with AcOH or its anhydride readily afford their mixed anhydrides (eq 3; Ar = Ph, *p*-$MeOC_6H_4$-, 2-naphthyl; X = MeCO), which become soluble in common solvents such as CH_2Cl_2 and $CHCl_3$ and perform the same transformation much more rapidly under the catalysis of Lewis acids such as ***Boron Trifluoride Etherate***. These reactions are highly regio- and *trans* stereoselective (eq 4).[5]

$$[ArTe(O)]_2O + 2\,XOH \longrightarrow 2\,ArTe(O)OX + H_2O$$
$$[ArTe(O)]_2O + X_2O \longrightarrow 2\,ArTe(O)OX \qquad (3)$$

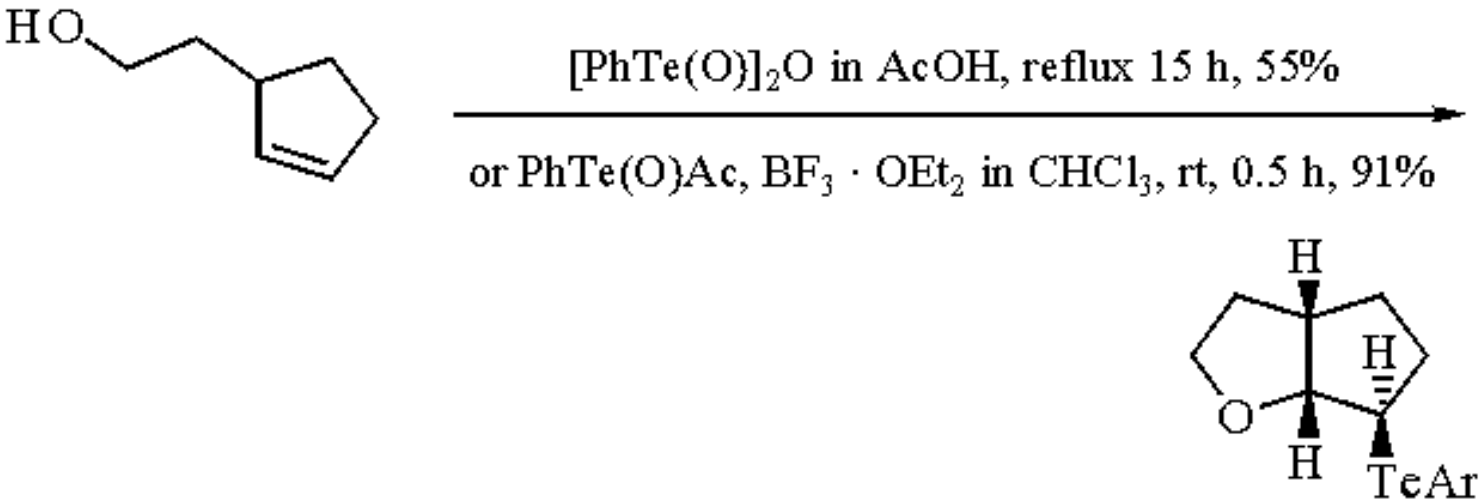

(4)

Electrophiles for Aminotellurinylation, Cyclofunctionalization of Alkenic Carbamates, and One-Pot Synthesis of 2-Oxazolidinones from Alkenes.

The mixed anhydrides of this reagent (eq 3; Ar = Ph, X = MeCO, CF_3CO) with carbamates effect regio- and stereoselective aminotellurinylation of alkenes in the presence of $BF_3.OEt_2$ in $CHCl_3$ to give (2-phenyltellurinyl)alkyl carbamates. The triflate (eq 3; Ar = Ph, X = CF_3SO_2) does it under milder conditions without Lewis acid. This reaction can be extended to cyclofunctionalization of alkenic carbamates into nitrogen heterocycles (eq 5).[6] When the aminotellurinylation is carried out at higher temperature, 2-oxazolidinones are obtained in high yields via a regio- and stereoselective path combined by *trans* addition and intramolecular S_N2 substitution of the PhTe(O) group (eq 6).[7]

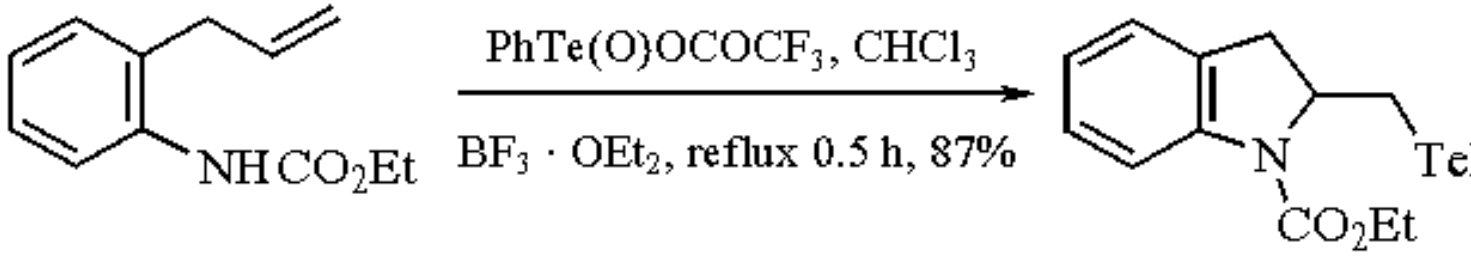

(5)

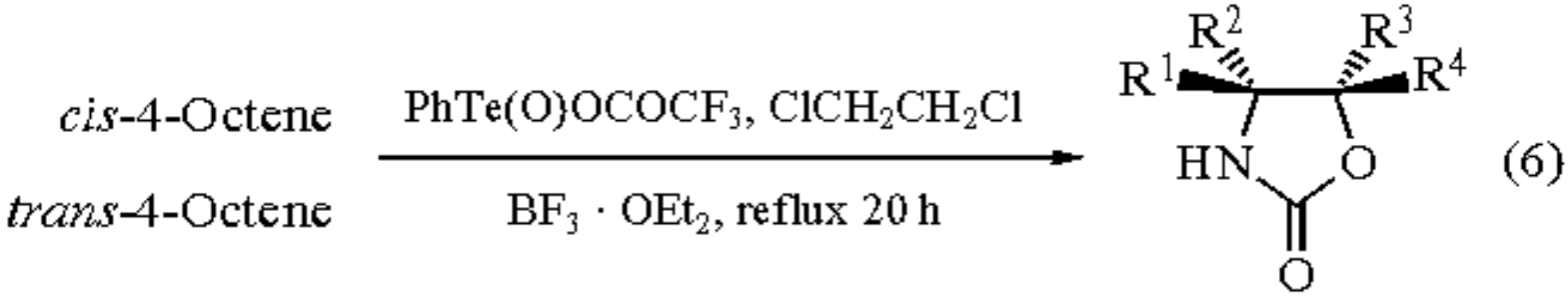

cis: $R^1 = R^4 = n$-Pr, $R^2 = R^3 = H$, 84%
trans: $R^1 = R^3 = n$-Pr, $R^2 = R^4 = H$, 53%

Electrophiles for Amidotellurinylation of Alkenes and Alkynes, and for One-Pot Synthesis of 2-Oxazolines and Oxazoles from Alkenes and Alkynes, respectively.

The mixed anhydride of the reagent (eq 3; Ar = Ph, X = CF_3CO) in the presence of $BF_3.OEt_2$ effects amidotellurinylation of alkenes in MeCN at rt to give 2-acetamidoalkyl phenyl telluroxides, which suffer further intramolecular S_N2 substitution at higher temperature to afford 2-oxazolines in high yields. These reactions are highly regio- and stereoselective (eq 7).[8] The trifluoromethanesulfonic anhydride (eq 3; Ar = Ph, X = CF_3SO_2) combined with MeCN undergoes (*E*) stereoselective amidotellurinylation of alkynes in the presence of a protonic acid. The addition products from terminal alkynes isomerize thermally to (*Z*)-β-acetamidovinyl phenyl telluroxides, whereas those from internal alkynes are transformed into oxazoles via a spontaneous intramolecular cyclization (eq 8).[9]

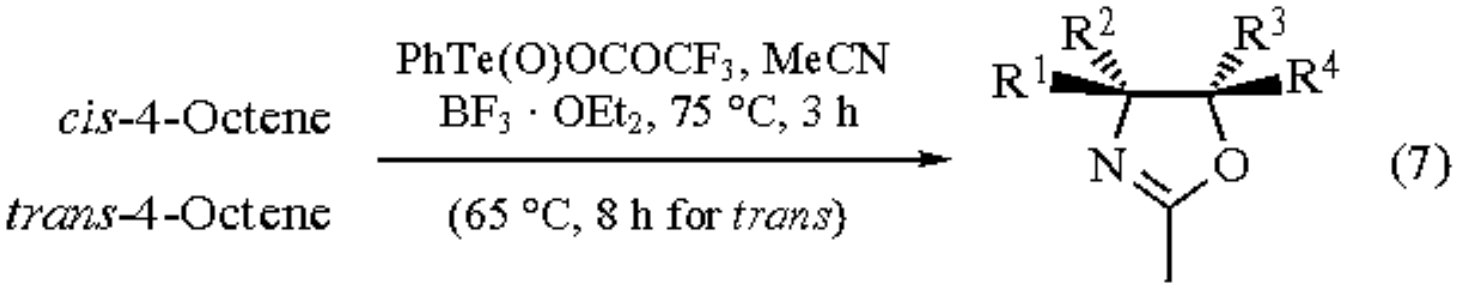

cis: $R^1 = R^4 = n$-Pr, $R^2 = R^3 = H$, 83%
trans: $R^1 = R^3 = n$-Pr, $R^2 = R^4 = H$, 56%

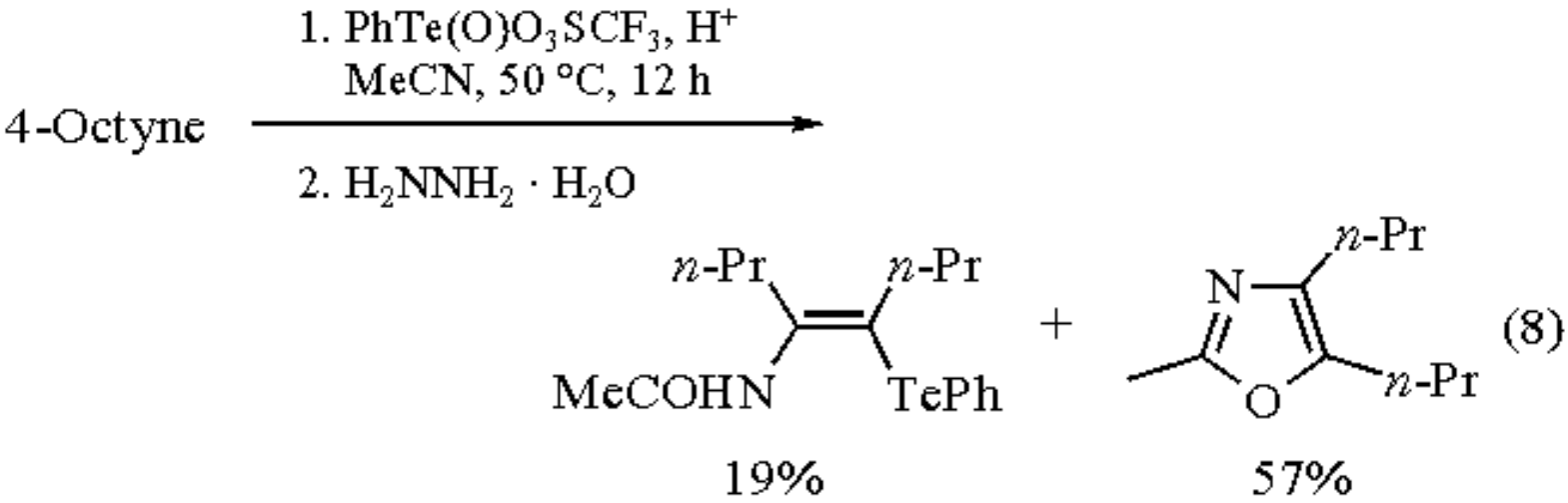

Electrophile for One-Pot Conversion of Allylsilanes to Allylamines.

In the presence of $BF_3.OEt_2$ in $ClCH_2CH_2Cl$, the mixed anhydride of this reagent (eq 3; Ar = Ph, X = CF_3CO) converts at rt allylsilanes to allyl phenyl telluroxides, which are treated in situ with primary or secondary amines at 65 °C to give the corresponding allylamines. The transformation is highly stereoselective. Thus γ-substituted allylsilanes with arylamine give γ-substituted allylamines but with alkylamine give α-substituted allylamines (eq 9).[10]

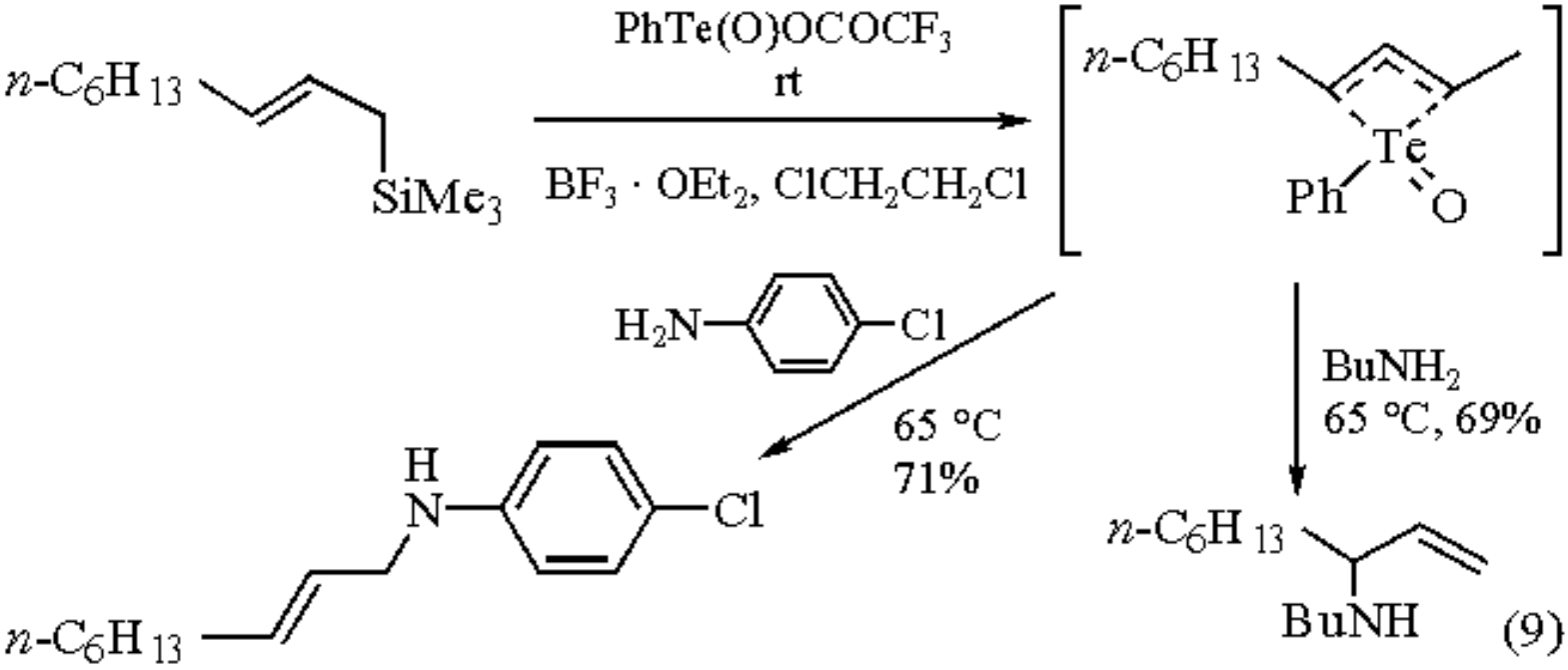

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(η^6-Benzene)tricarbonylchromium

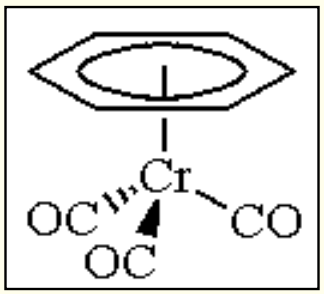

[12082-08-5] · $C_9H_6CrO_3$ · (η^6-Benzene)tricarbonylchromium · (MW 214.14)

(phenyl cation equivalent[1])

Alternate Name: (benzene)chromium tricarbonyl.

Physical Data: mp 161.5-163 °C.

Solubility: sol THF, ether, benzene.

Form Supplied in: yellow crystals.

Preparative Method: for cases where large quantities are needed, it is easily prepared from the reaction of benzene with ***Hexacarbonylchromium***.[2]

Purification: recrystallized from ether/petroleum ether. Can also be purified by column chromatography on silica gel.

Handling, Storage, and Precautions: slightly air sensitive.

Nucleophilic Substitution.

Treatment of (benzene)tricarbonylchromium (**1**) with various nucleophiles at 25 °C, followed by ***Iodine*** oxidation, effects nucleophilic substitution of hydrogen.[1] Nucleophiles derived from carbon acids having a pK_a > ~22 lead to the arylated products (e.g. **3**) in high yield (eq 1). Nucleophilic addition produces the pentadienylchromium complex (**2**) which converts to the substituted arene upon oxidation. Alternatively, treatment of complex (**2**) with ***Trifluoroacetic Acid*** leads to the cyclohexadiene derivatives (**4-6**) (eq 2).[3] Alkyllithium reagents and Grignard reagents are not arylated under these conditions due to competing deprotonation and addition to the carbonyl ligands.

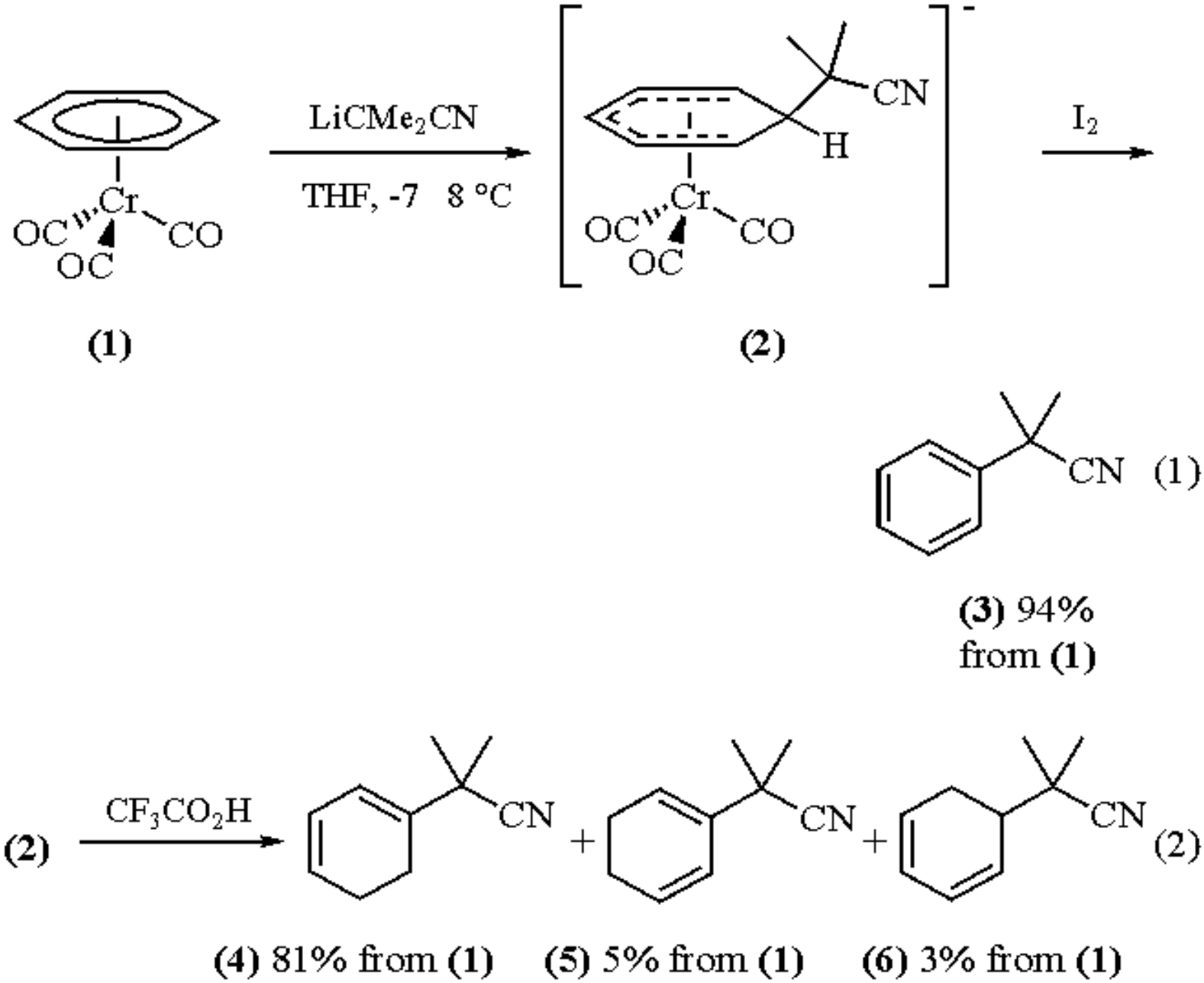

Nucleophilic Addition/Carbonylation.

Nucleophilic addition to (benzene)tricarbonylchromium, followed by treatment with alkyl iodides in the presence of carbon monoxide, leads to *trans*-5-acyl-6-substituted-1,3-cyclohexadiene derivatives (e.g. **7**) (eq 3).[4] Only very reactive carbanions such as 2-lithio-2-alkyl-1,3-dithiane derivatives will undergo this transformation. When less reactive carbanions are employed, the nucleophile undergoes direct alkylation by the alkyl iodide without incorporation of the benzene ring.

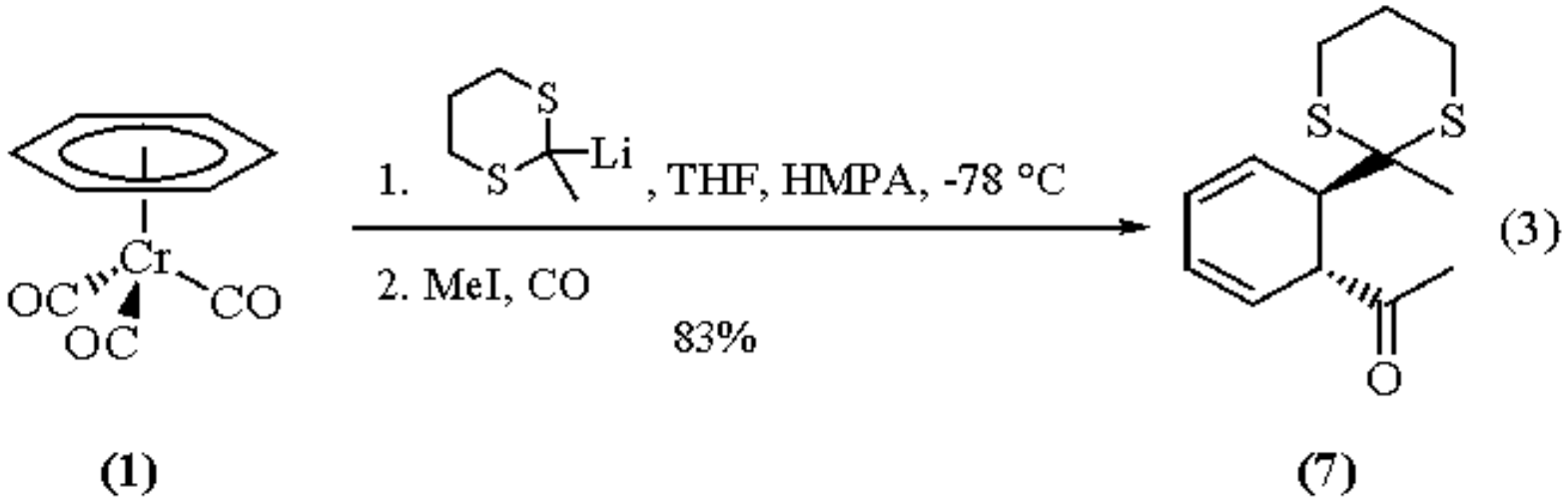

Lithiation.

Treatment of (benzene)tricarbonylchromium with ***n-Butyllithium*** produces the lithiated arene complex (**8**). Treatment of complex (**8**) with electrophiles produces the monosubstituted benzene complexes (e.g. **9**) (eq 4),[5,6] which are converted to the free arenes by treatment with iodine or ***Cerium(IV) Ammonium Nitrate***. (Benzene)tricarbonylchromium thus appears to be substantially more acidic than benzene.

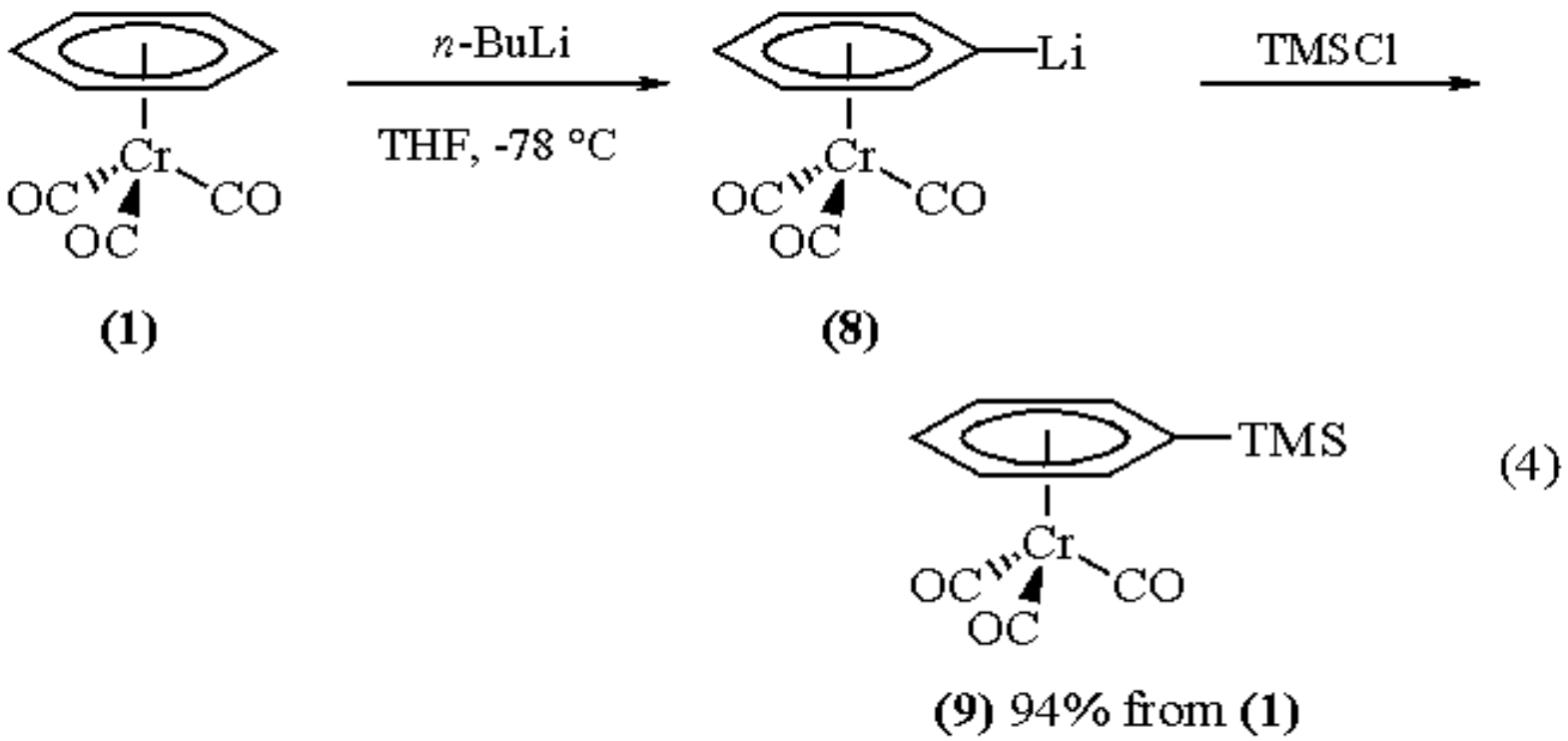

Hydrogenation Catalyst.

(Benzene)tricarbonylchromium catalyzes the hydrogenation of 1,3-dienes (eq 5).[7] The major product is the (*Z*)-alkene resulting from 1,4-addition of hydrogen. Isolated double bonds are not hydrogenated using this catalyst.

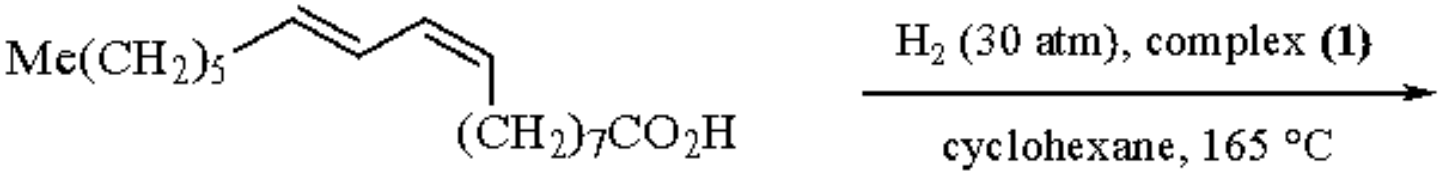

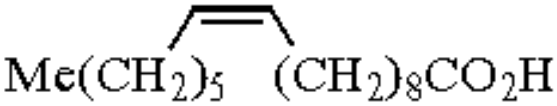

(5)

$Z{:}E = 92{:}8$

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1,3-Benzodithiol-1-ium Tetrafluoroborate[1]

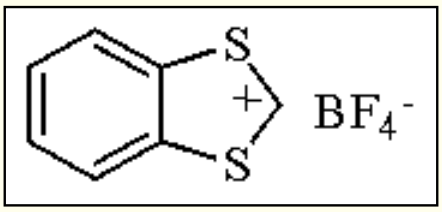

[57842-27-0] · $C_7H_5BF_4S_2$ · 1,3-Benzodithiol-1-ium Tetrafluoroborate · (MW 240.07)

(formyl[2] and methyl cation[3] equivalent; nucleoside hydroxyl protection group;[4] 1,1-dipole equivalent[11])

Physical Data: mp 150-150.5 °C (dec).

Solubility: sol MeCN and DMF (slowly reacts); insol ether.

Form Supplied in: light brown powder.

Preparative Method: treatment of 2-(3-methylbutoxy)-1,3-benzodithiole[2] with ***Tetrafluoroboric Acid*** in ***Acetic Anhydride*** at 0 °C.

Purification: recrystallized from acetic acid or acetonitrile/ether.

Handling, Storage, and Precautions: can be stored in the absence of moisture and light; no toxicity data is currently available; 1,3-benzodithiol-1-ium perchlorate *[32283-21-9]* is also known,[2] but poses a risk of explosion.

Acyl Cation Equivalent.

Benzodithiolium ions react with a wide range of carbon nucleophiles to afford masked aldehyde and ketone products.[2] Electron-rich arenes (eq 1)[5] and active methylene compounds[6] are useful nucleophiles and 2-substituted benzodithiolium ions lead to good yields of 1-deuteroaldehydes upon reaction with $LiAlD_4$ and subsequent hydrolysis.[7]

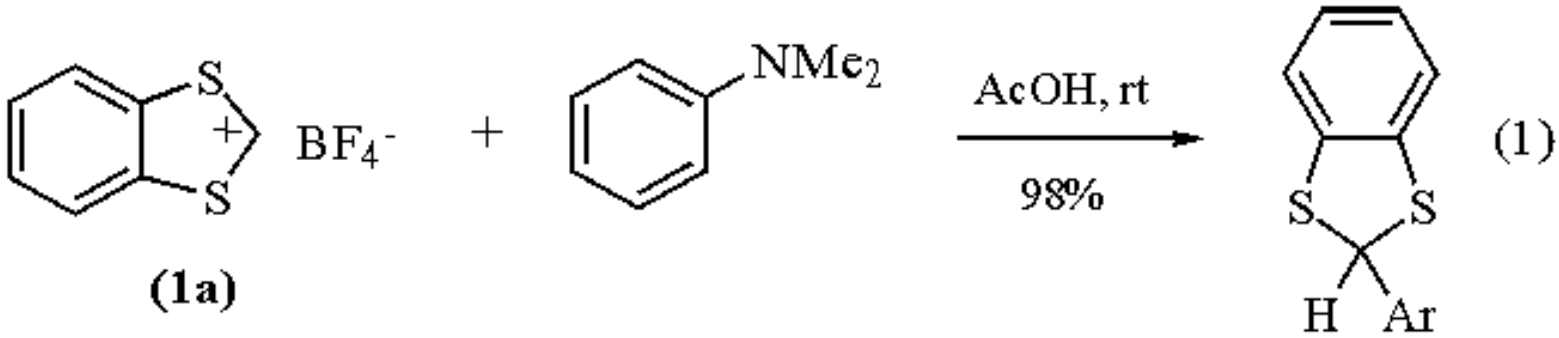

(1a)

Ketone products are available by a reaction sequence involving Grignard reagent addition to the parent cation followed by regeneration of the 2-substituted 1,3-benzodithiolium ion via ***Triphenylmethyl Perchlorate*** mediated hydride abstraction. A second Grignard reagent addition and dithiole hydrolysis completes the sequence (eq 2).[8] ***Chloramine-T*** in conjunction with ***Mercury(II) Chloride*** is a superior method for benzodithiole hydrolysis.[7,8a] Reductive cleavage of the benzodithiole unit can be achieved by treatment with ***Sodium-Ammonia***.[8]

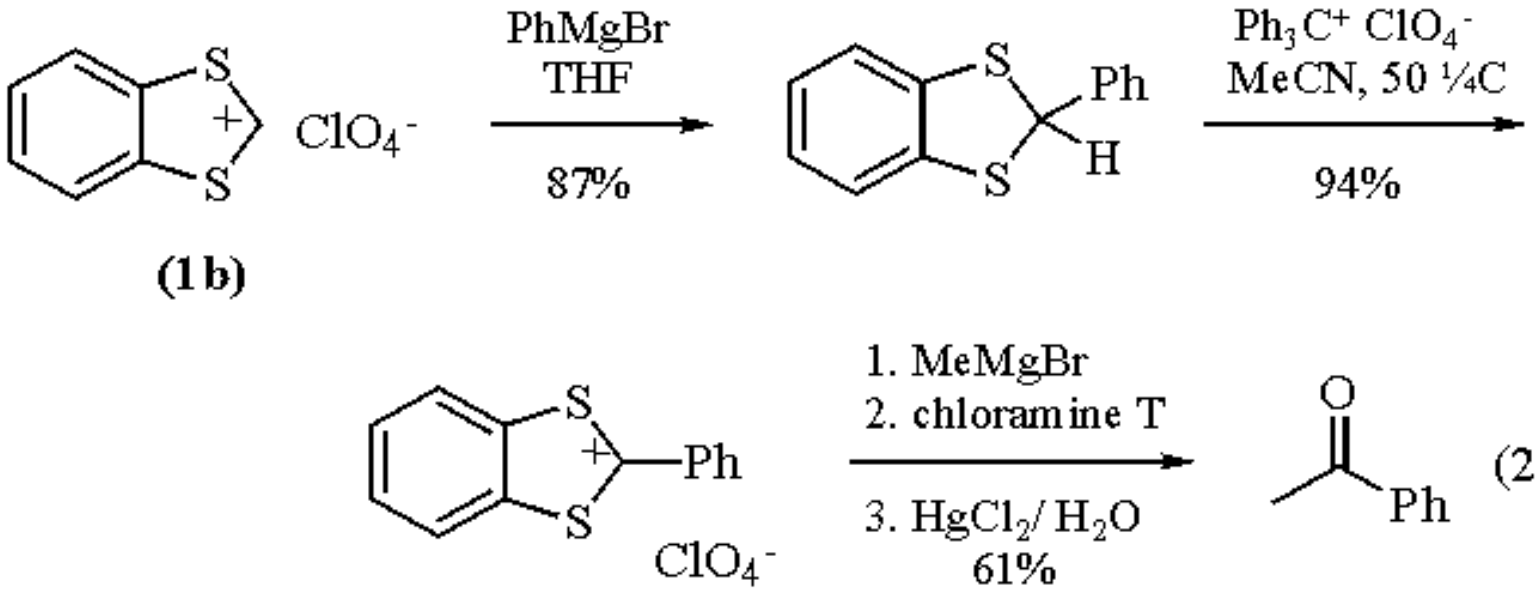

(1b)

Methyl Cation Equivalent.

Mild *N*-methylation of guanosine has been achieved employing 1,3-benzodithiol-1-ium tetrafluoroborate as a masked methyl group. Treatment of the *O*-silylated guanosine derivative (**2**) with (**1a**) provided high yields of (**3**), which on exposure to ***Tri-n-butylstannane*** provided the *N*-methyl compound (**4**) (eq 3).[3] This process can be repeated to afford the corresponding *N*,*N*-dimethyl derivative. A related *O*-methylation sequence is not as effective.[3,9]

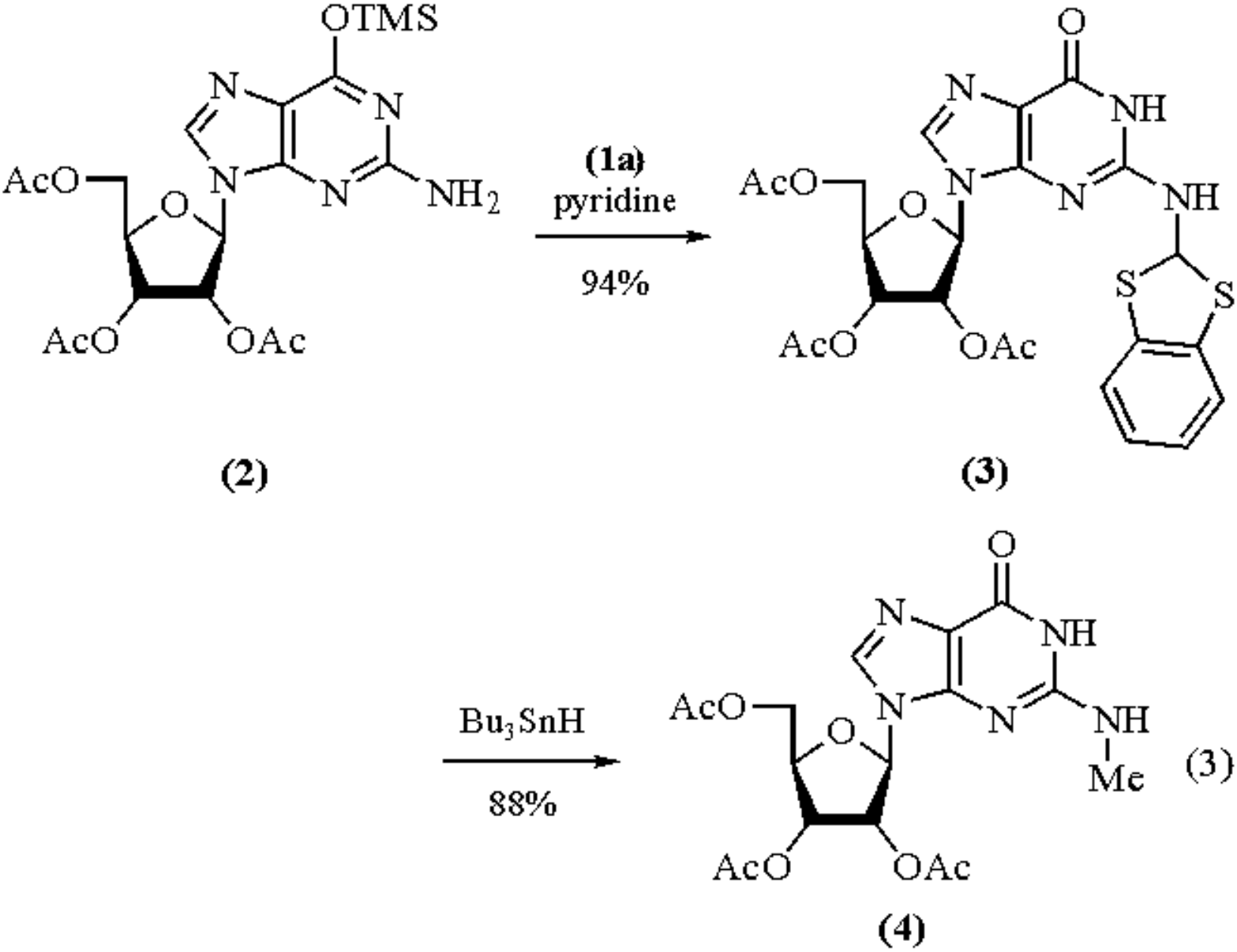

(3)

Nucleoside Hydroxyl Group Protection.

The benzodithiole group has been used as a selective protecting group for the 5´-hydroxyl group of thymidine (eq 4).[4] No competitive reactions with base residues were noted with any of the nucleosides studied. The benzodithiole protection can be cleaved to reveal the free hydroxyl group with 2% aqueous TFA.

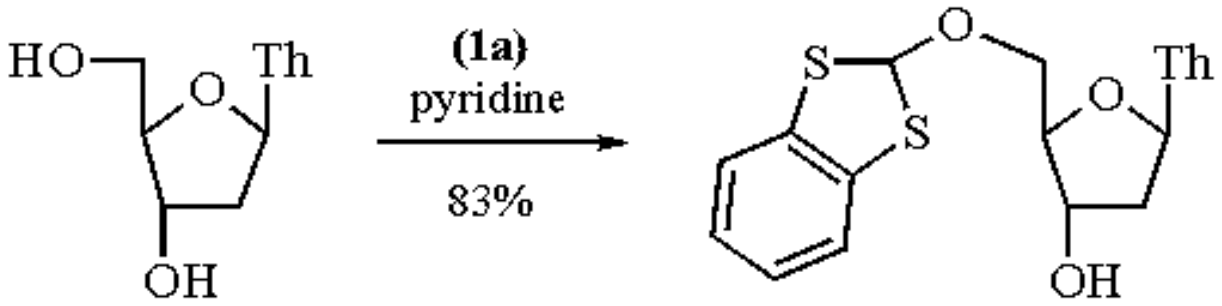

(4)

1,1-Dipole Equivalents.

The parent 1,3-benzodithiole species can be rendered nucleophilic by deprotonation at the 2-position with strong base. A useful reagent for expressing this nucleophilic character is readily available 2-diethoxyphosphinyl-1,3-benzodithiole.[10] Reaction of the 2-lithiated species (**5**) with aldehydes affords excellent yields of ketene dithioacetals suitable for accessing the corresponding substituted benzodithiolium cations for subsequent carbon-carbon bond formation (eq 5).[11]

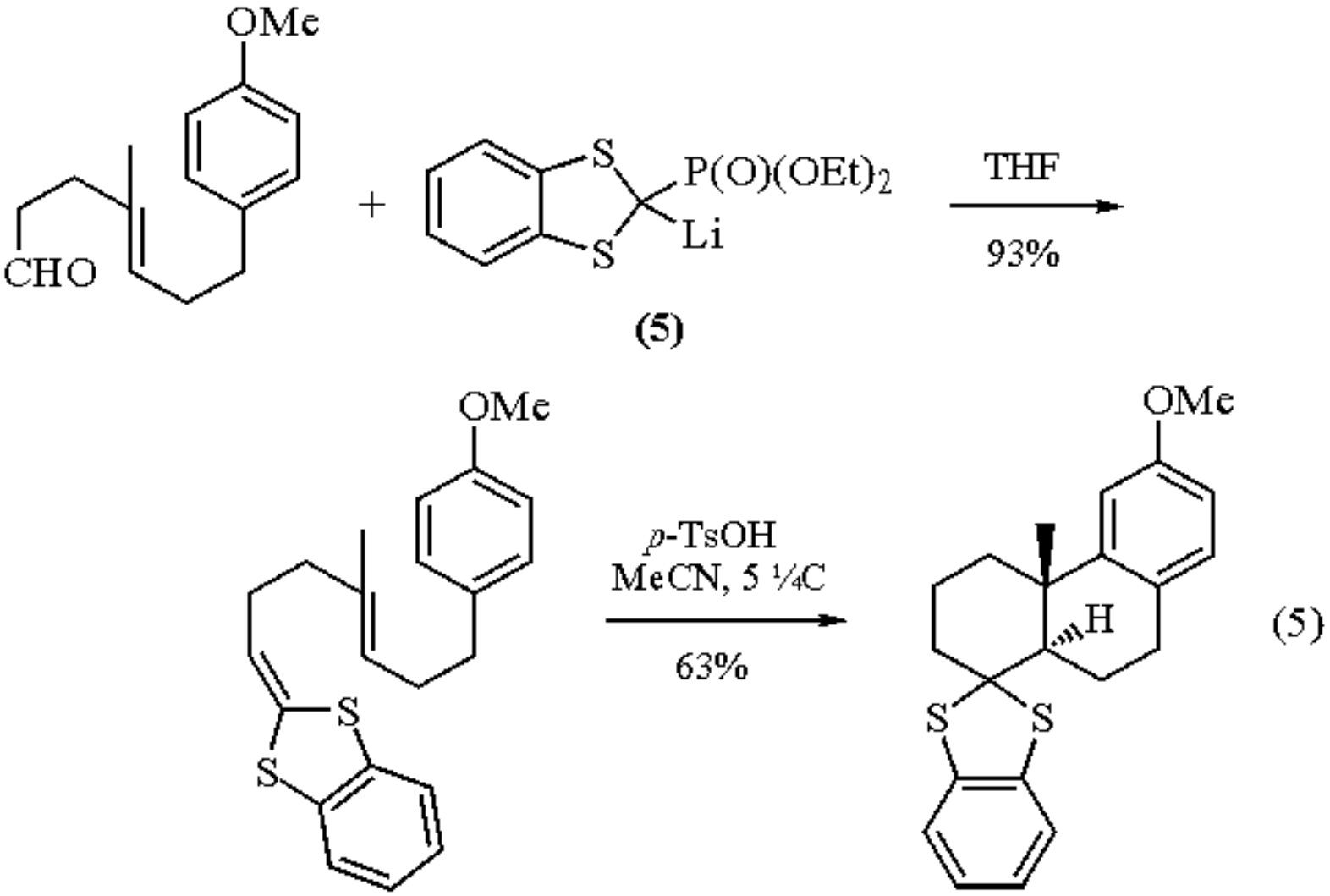

See also ***2-(3-Methylbutoxy)-1,3-benzodithiolane***.

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Benzohydroxamic Acid

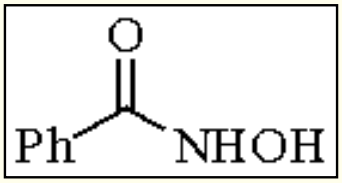

[495-18-1] · $C_7H_7NO_2$ · Benzohydroxamic Acid · (MW 137.14)

(precursor to benzoyl nitroso compounds and used in the synthesis of a wide range of heterocyclic compounds[1])

Physical Data: mp 125 °C.

Solubility: sol water; slightly sol other organic solvents.

Form Supplied in: solid; widely available.

Benzohydroxamic acid shows considerable reactivity towards various functional groups. For example, reaction of this reagent with certain alkynic compounds gives 1,3-oxazoles in good yields (eq 1).[1] Benzohydroxamic acid can also be used as a precursor to the Lossen rearrangement (eq 2).[2]

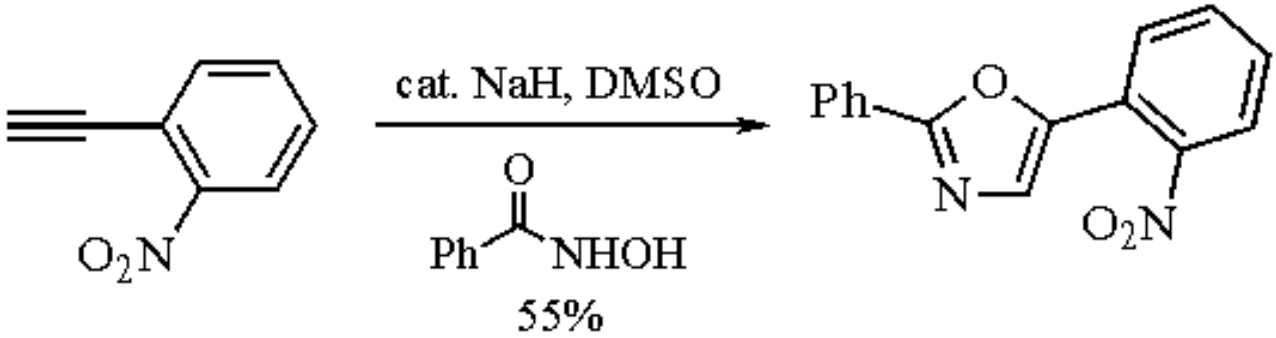

(1)

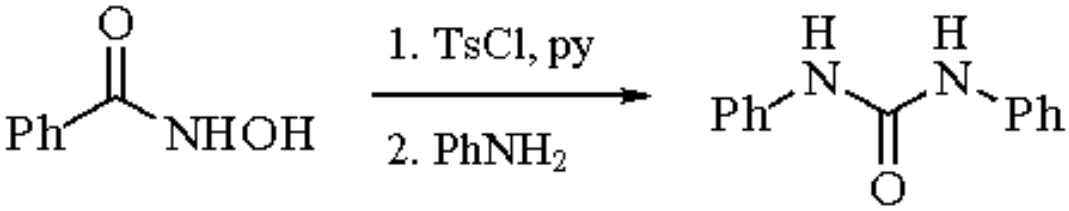

(2)

Oxidation of benzohydroxamic acid with $Pr_4N^+IO_4^-$ in DMF at 23 °C generates a transient benzoylnitroso compound. If the oxidation is carried out in the presence of a diene, cycloaddition products are formed in high yields (eqs 3-5).

For example, oxidation in the presence of cyclohexadiene gives a [2.2.2] bicyclic adduct.[3] Reductive cleavage of the N-O bond of the cycloadduct with the preservation of both the double bond and the amide carbonyl can be readily accomplished in quantitative yield by treating the adduct with an excess of ***Aluminum Amalgam*** in THF-H_2O at 0 °C.

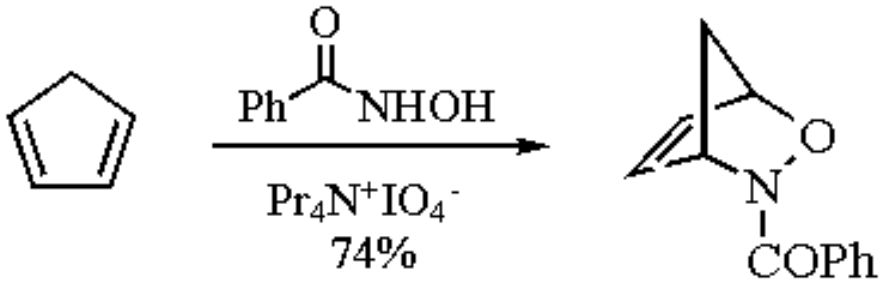

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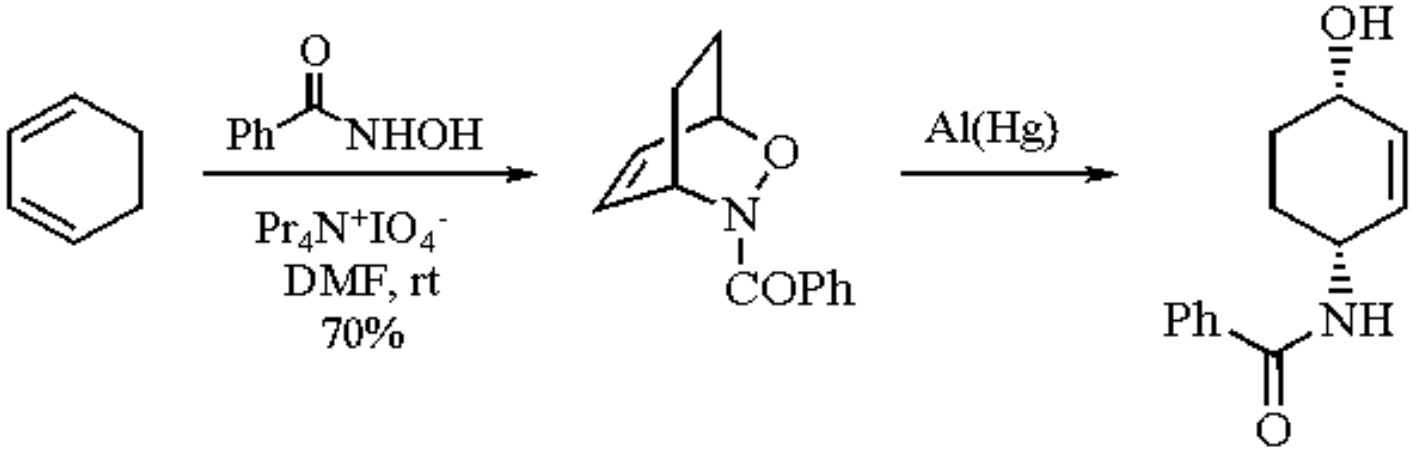

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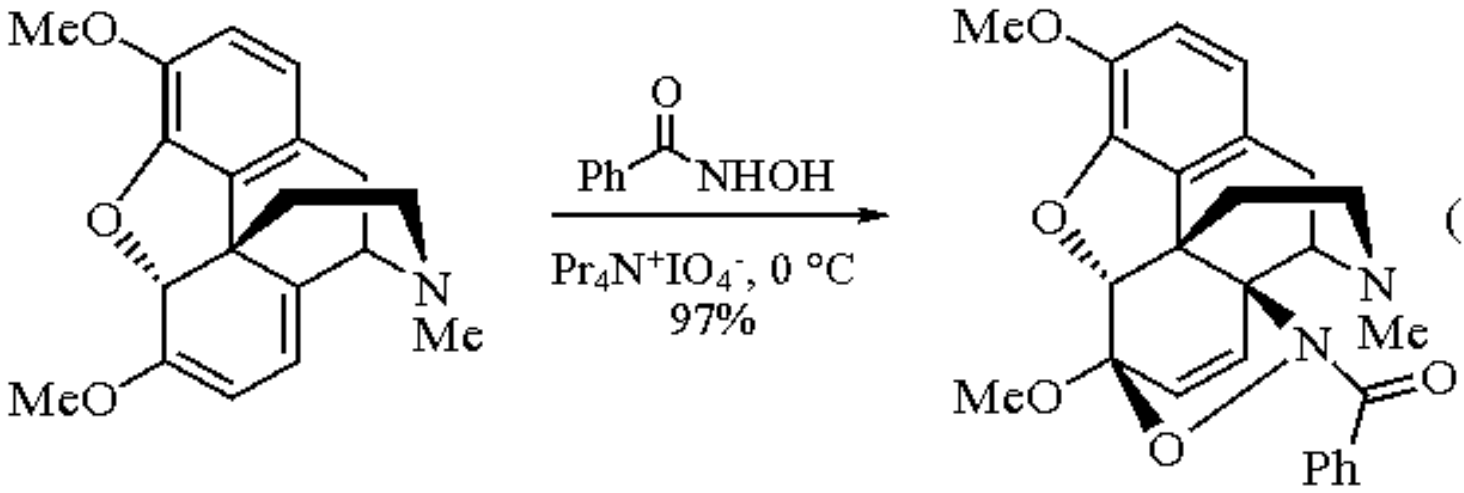

(5)

Eq 6 details the result of a study of the regioselectivity of the [4 + 2] cycloaddition of PhCONO with a 2-substituted 1,3-cyclohexadiene.[4] The ratio of regio adducts is not affected by change in the reaction solvent, temperature, or the source of the nitroso compound.

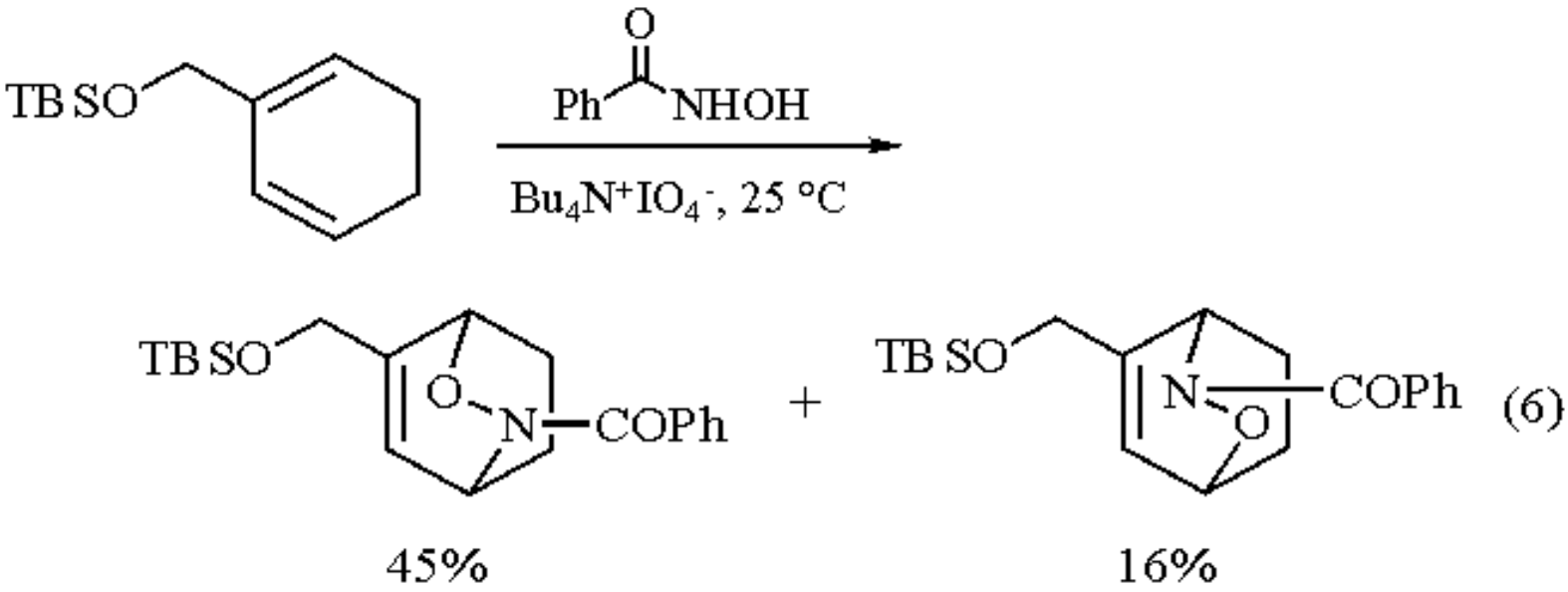

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Benzoic Anhydride

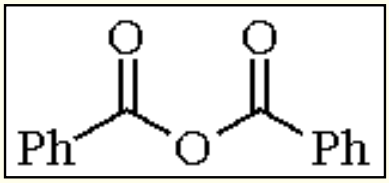

[93-97-0] · $C_{14}H_{10}O_3$ · Benzoic Anhydride · (MW 226.23)

(primarily used as an acylation reagent;[1] can be added to alkynes[2] and carbon-nitrogen double[3] and single bonds[4,5])

Physical Data: mp 42-43 °C; bp 360 °C; *d* 1.199 g cm^{-3}.

Solubility: insol H_2O; sol alcohol, ether, $CHCl_3$, acetone, EtOAc, benzene, toluene, glacial acetic acid, acetic anhydride; slightly sol pet ether.

Form Supplied in: white crystalline solid; widely available.

Purification: benzoic acid is removed by washing with $NaHCO_3$, then water, followed by drying. The reagent can be recrystallized from benzene (0.5 mL g^{-1}) by adding a small amount of pet ether (bp 40-60 °C) and cooling. It can also be distilled at 210-220 °C at 20 mmHg.

Handling, Storage, and Precautions: irritating to eyes, respiratory system, and skin. May decompose on exposure to moist air or water.

Acylation.

The most common use of this reagent is as a protecting group for oxygen[1a,b] and nitrogen[1c] functional groups. The ease of benzoylation and the ready removal of the protecting group under mildly basic conditions render it valuable in organic synthesis.[1a] In addition, this reagent has found many uses as an acylating agent for stabilized carbanions.[1d,e] Its participation in the Friedel-Crafts acylation reaction[1f] is well known and has been extended to processes involving Lewis acid catalysts.[1g] In the presence of ***Titanium(IV) Chloride*** and ***Silver(I) Perchlorate*** as catalysts, this reagent reacts with silyl derivatives of acids and alcohols to give esters via intermediate mixed anhydrides (eq 1).[1h]

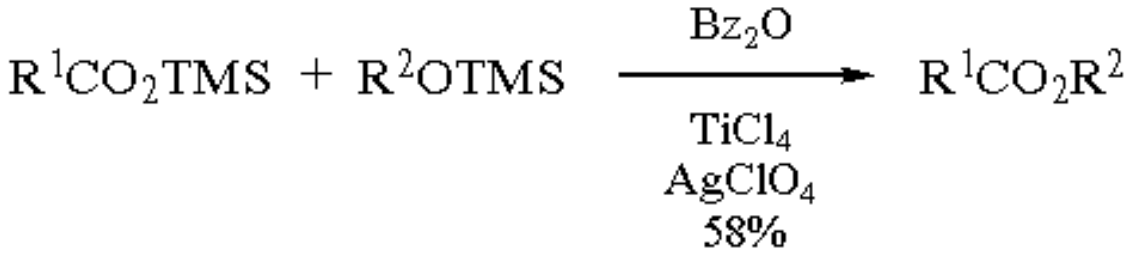

(1)

$R^1 = Ph(CH_2)_2$, $R^2 = Ph(CH_2)_3$

Addition Reactions.

Addition of an excess of this reagent to alkynes, promoted by a Lewis acid, results in formation of 1,3-dicarbonyl compounds (eq 2).[2] This reagent can also add across carbon-nitrogen double[3] and single bonds[4] (eqs 3 and 4). Tertiary amines are dealkylated in the presence of metal salts, resulting in the formation of tertiary amides (eq 5).[5]

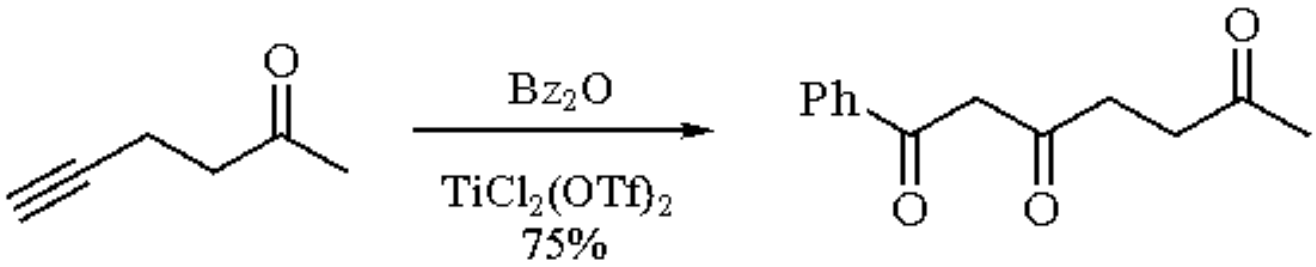

(2)

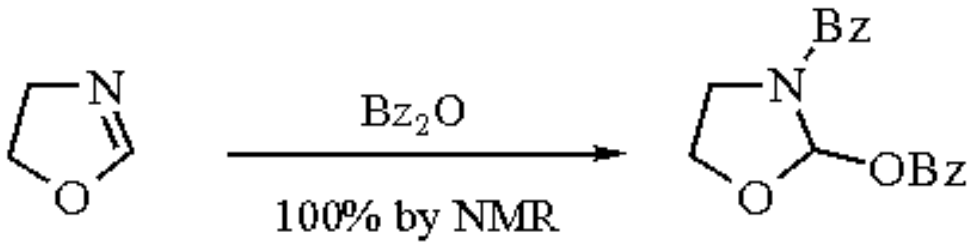

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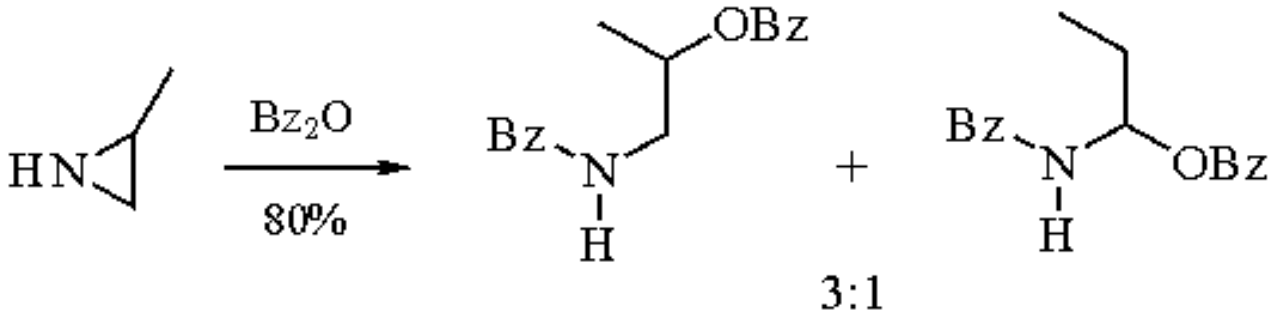

(4)

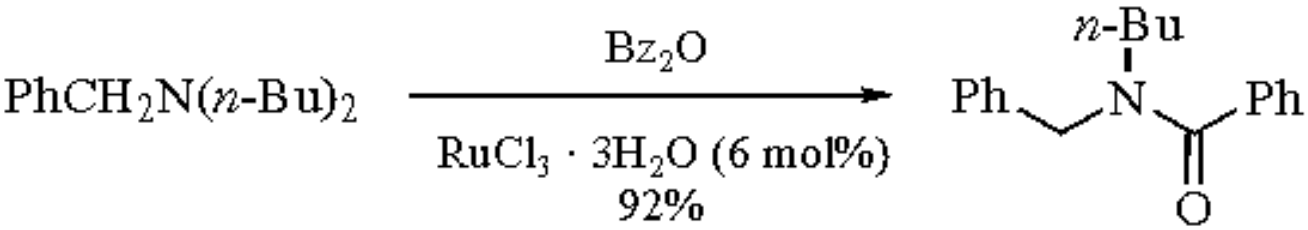

(5)

Miscellaneous Uses.

This reagent has been shown to decarboxylate α-keto acids upon heating with an excess of pyridine, avoiding Perkin-type condensations.[6] Cyclopropenone oximes have been activated by this reagent to study the Beckmann rearrangement of the *O*-benzoylated derivatives.[7] Substitution of an allylic phenyl ether using this reagent, catalytic ***Palladium(II) Acetate***, and ***Triphenylphosphine*** gives mixtures of allylic benzoates (eq 6).[8]

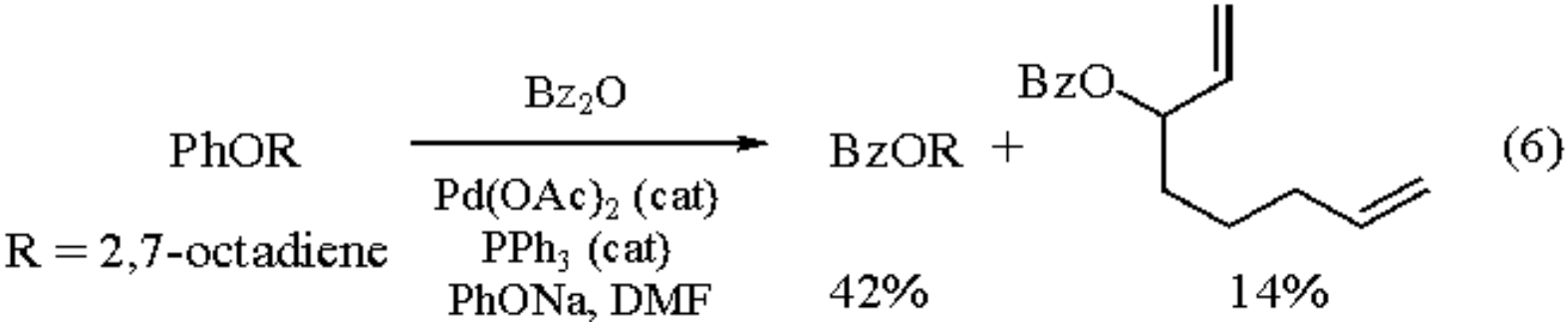

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Benzonitrile Oxide[1]

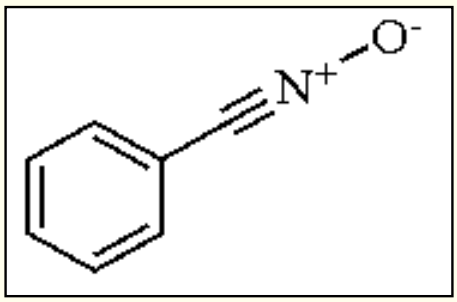

[873-67-6] · C_7H_5NO · Benzonitrile Oxide · (MW 119.12)

(versatile reagent for regio- and stereoselective construction of heterocycles; synthesis of polyfunctionalized acyclic and cyclic compounds[1])

Physical Data: mp 18-19 °C; bp 113 °C/15 mmHg; *d*224 1.10 g cm^{-3}; *n*22D 1.6172.

Solubility: sol ether, benzene, CCl_4.

Form Supplied in: prepared as described below; not commercially available.

Preparative Methods: the most widely employed methods of benzonitrile oxide (**1**) generation involve triethylamine-mediated dehydrohalogenation of benzhydroxamoyl chloride (**2**) (or bromide), readily accessible through chlorination of benzaldoxime,[2a] or dehydration of α-nitrotoluene with PhCNO[2b,c] or $PhSO_2Cl$ or $ClCO_2Et$ and a catalytic amount of Et_3N (Mukaiyama reaction).[2d] A reaction of (**2**) with alkali metal fluorides also provides a facile quantitative generation of (**1**).[2e] Although (**1**) has been obtained as a crystalline solid,[2f] it is commonly generated in situ.[1] Et_3N almost immediately reacts with (**2**),[3] and should be added very slowly to an ice-cooled solution of (**2**) to maintain a low stationary concentration of (**1**) and thereby suppress its dimerization into 3,4-diphenylfuroxan (**3**).[2a] Benzonitrile oxide can also be generated photochemically by irradiation of (**2**) and ***Hexabutyldistannane***,[4a] or via electrochemical oxidation of benzaldoxime.[4b]

Handling, Storage, and Precautions: usually prepared in situ; readily undergoes dimerization on storage; use in a fume hood.

Introduction.

To simplify the representation of (**1**) as an organic dipole (dipole moment 4.00 D at 15 °C),[1a] the nitrilium betaine formula PhC&tbond;+N-O^- is most commonly used. As implied by this structure, reactions with nucleophiles at the

positively charged N atom or with dipolarophiles across the C-N-O system are common with (**1**).

Reactions with Nucleophiles.

Benzonitrile oxide reacts with O-, C-, N-,[5a-c] and S-nucleophiles[5d] to give benzhydroxamic acid derivatives (eq 1).[5d]

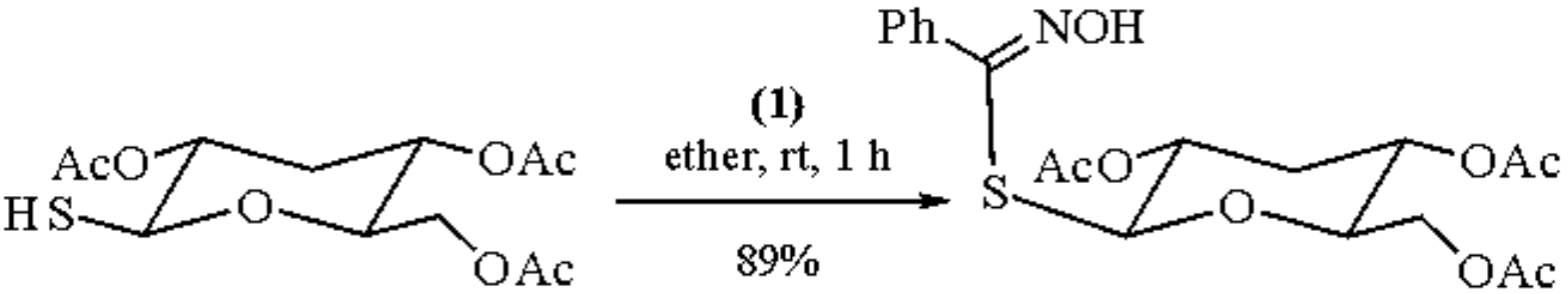

(1)

Nitrogen nucleophiles catalyze dimerization of (**1**),[6a] which may be also promoted under specific acidic conditions (eq 2).[6b] In DMSO, (**1**) undergoes Me_3N-induced polymerization to produce cyclic oligomers.[6c]

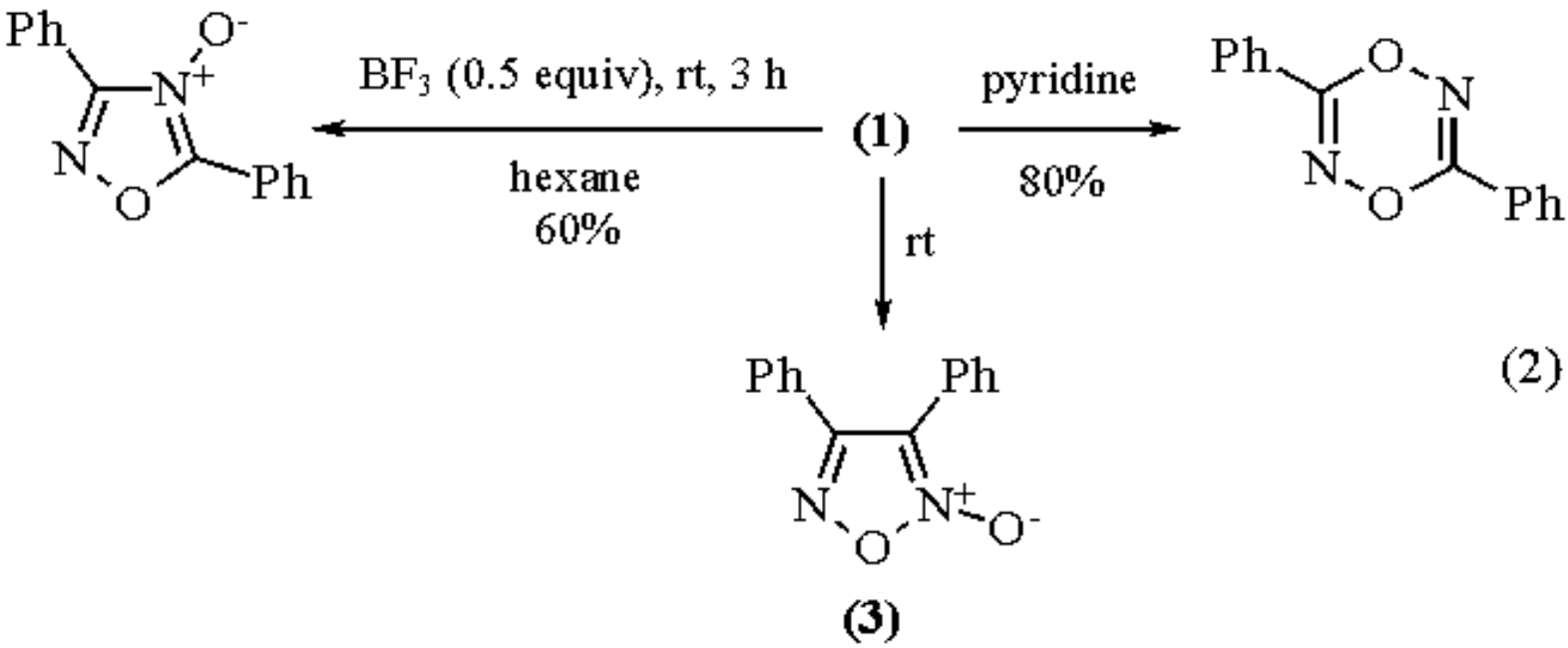

(2)

1,3-Dipolar Cycloaddition.

Benzonitrile oxide demonstrates high reactivity towards numerous dipolarophiles containing multiple carbon-carbon and carbon-heteroatom bonds. It is these [$_{\pi}4_s$ + $_{\pi}2_s$] dipolar cycloadditions (DCA) that are responsible for the considerable synthetic potential of (**1**). DCA of (**1**) with alkenes commonly delivers a mixture of isomeric 5- and 4-substituted 3-phenyl-Δ^2-isoxazolines. Regioselectivity depends on dipolarophile structure. From monosubstituted alkenes, 5-substituted heterocycles are predominantly formed[1a,b,7] and in some cases almost complete regiospecificity is achieved (eq 3).[2e]

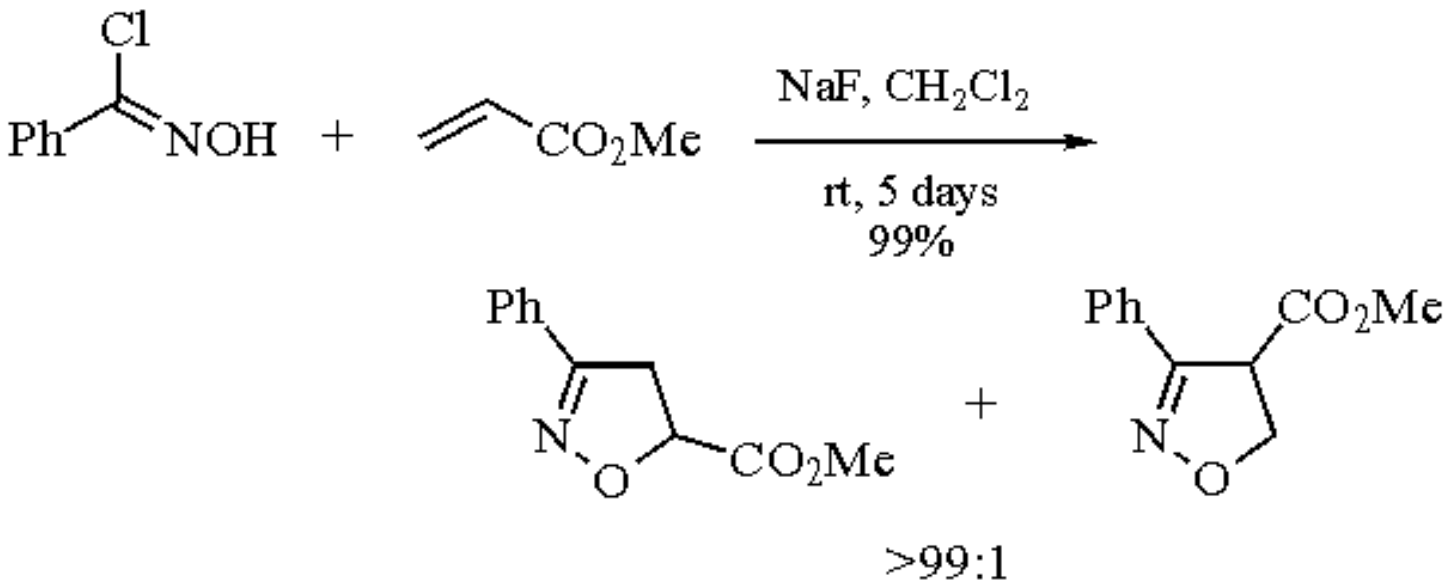

(3)

Ratios of regioisomers produced from disubstituted alkenes are defined by a combination of polar, steric, and hydrogen-bonding factors.[8] Nevertheless, conformational features, substituent effects, and additives can all affect the regiochemistry of 1,3-DCA reactions (eq 4).[9]

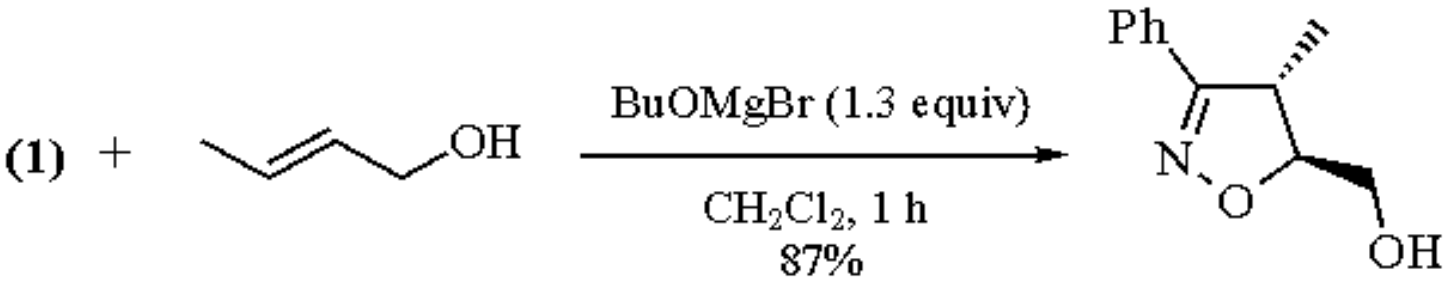

(4)

1,3-DCA of alkenes bearing a chiral residue at the double bond proceed with asymmetric induction.[10] The nature of a substituent in the allylic position of the dipolarophile can affect the ratio of *erythro:threo* products, as shown in eq (5).[10b] The best theoretical model proposed to rationalize such diastereoselectivity assumes conformational control in the transition state of DCA.[10c,e] However, charge transfer and electrostatic effects should not be neglected.[10f]

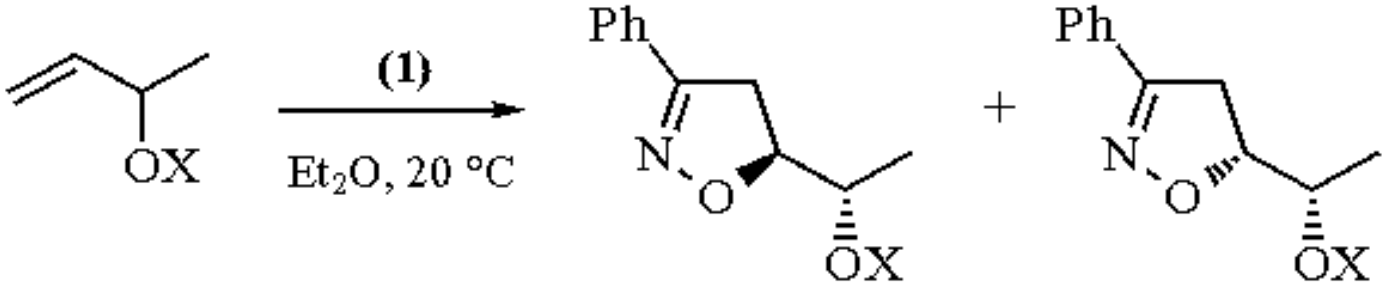

(5)

	erythro:*threo*
X = H	40:60
X = OCH_2Ph	64:36
X = $OSiMe_3$	71:29

Diastereoselective DCA of (**1**) to chiral acrylic dipolarophiles offers an approach to optically active 2-isoxazolines. Initial studies with chiral sulfonamide (**4**) proceed with 56% de and showed attack of (**1**) to occur on the *re* face of (**4**). This suggested that the major diastereomer resulted from the *s-cis* conformer of (**4**) (eq 6).[11] It is worth noting that generally 1,3-DCA of (**1**) with substrates of type (**4**) takes place with lower selectivity than the corresponding Diels-Alder reactions,[11,12] and Lewis acids retard the 1,3-DCA and decrease yields with no improvement in diastereoselectivity. Higher diastereoselectivity (80-90% de) is observed if bornyl crotonates,[13] chiral imides,[14] alkenes containing a chiral imidazolidine controller,[15] or carbohydrates[16] are employed in DCA with (**1**).

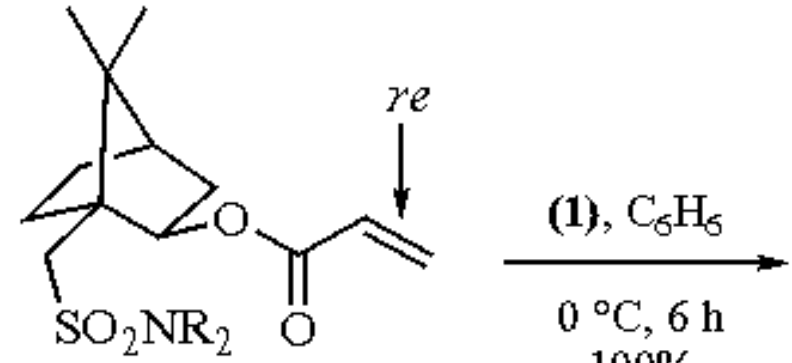

(4) R = cyclohexyl

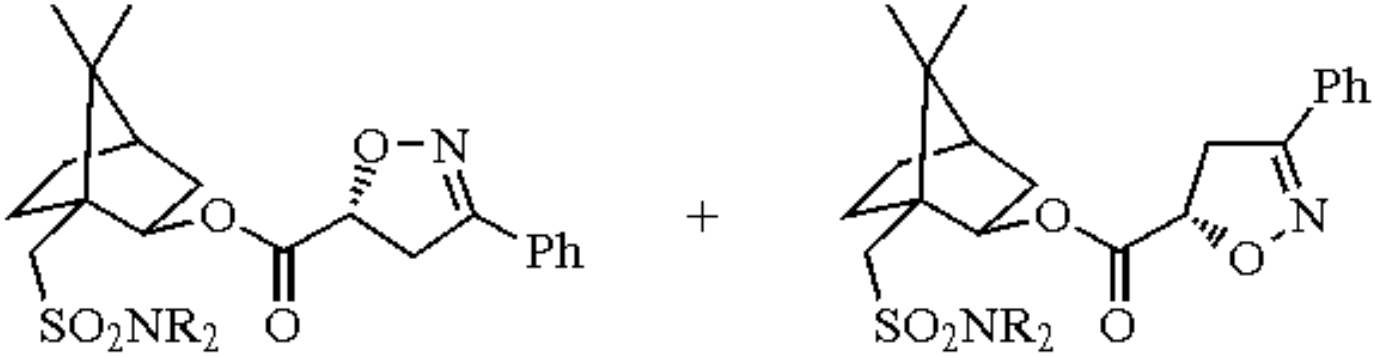

(6)

78:22

Acryloylsultams such as (**5**)[17a] and (*S*)- and (*R*)-(**6**)[17b] are the best auxiliaries for almost complete asymmetric induction yielding, after reduction, enantiomerically pure isoxazolines (eq 7).

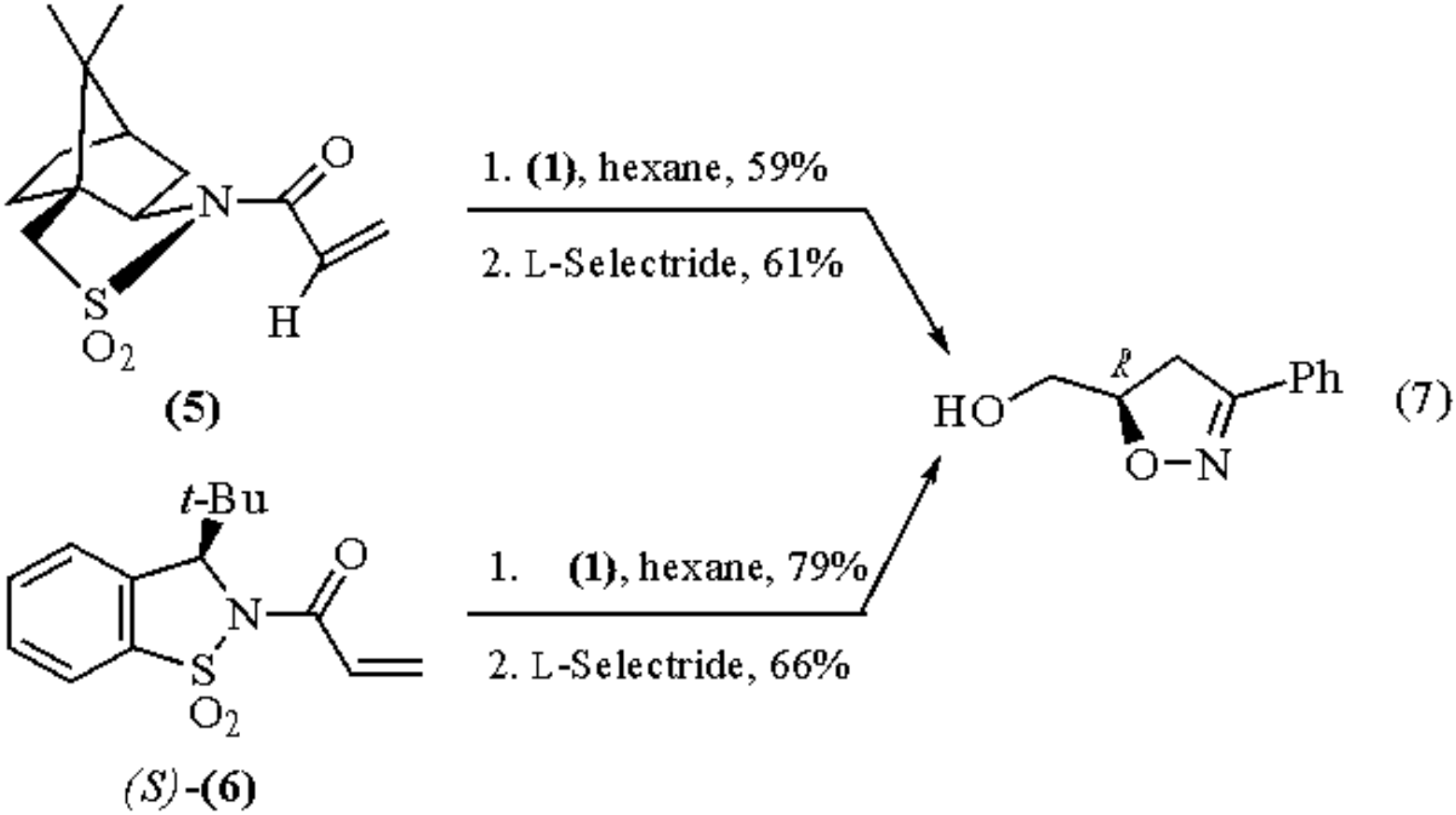

Because the Δ^2-isoxazoline ring can be readily cleaved, this chemistry provides a powerful approach to the synthesis of polyfunctional compounds from alkenes. Upon base-initiated ring-opening, α,β-unsaturated ketones are obtained (eq 8),[18] whereas reductive cleavage offers an approach to β-hydroxy ketones (eq 9),[19] β,γ-enones,[20] β-diketones, and 3(2*H*)-furanones.[21] While the primary products of reduction with ***Raney Nickel***[19,20] are 3-imino alcohols, precursors of β-hydroxy ketones[19] and pyridines,[22] reductive cleavage with ***Lithium Aluminum Hydride*** gives 1,3-amino alcohols.[23] This has been used in the stereoselective synthesis of amino sugars.[23a]

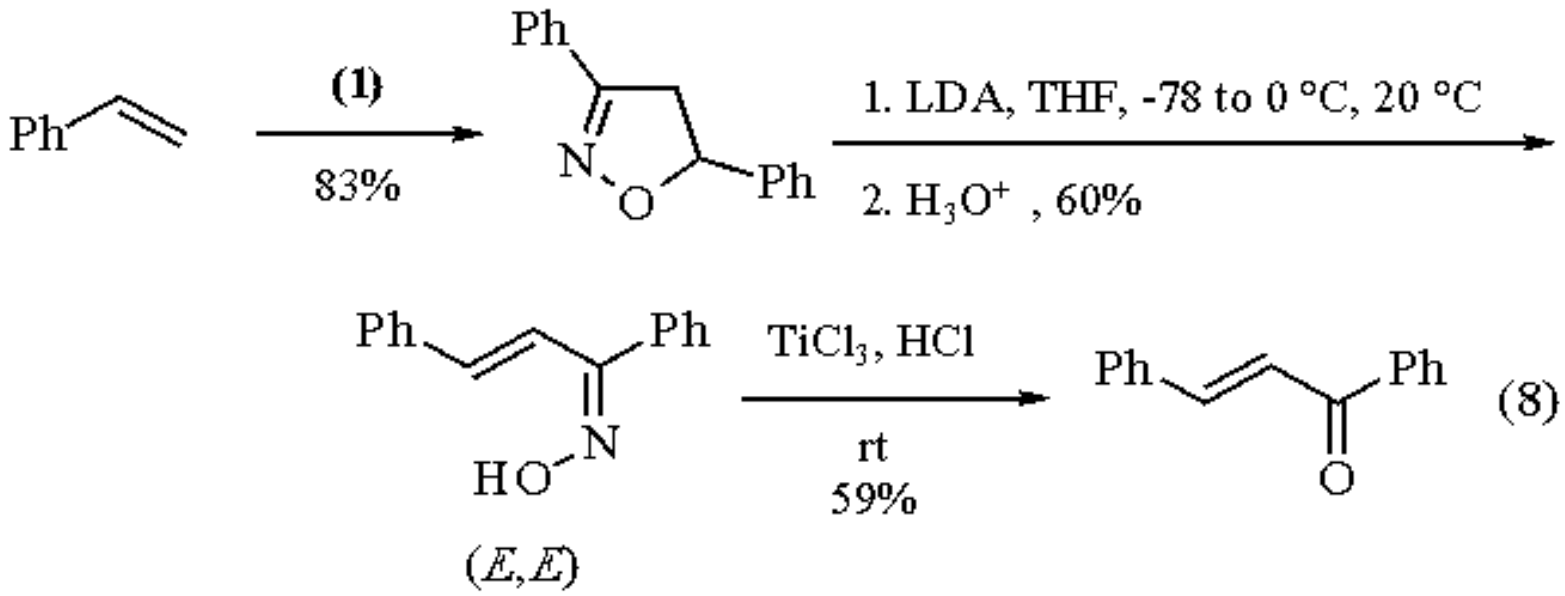

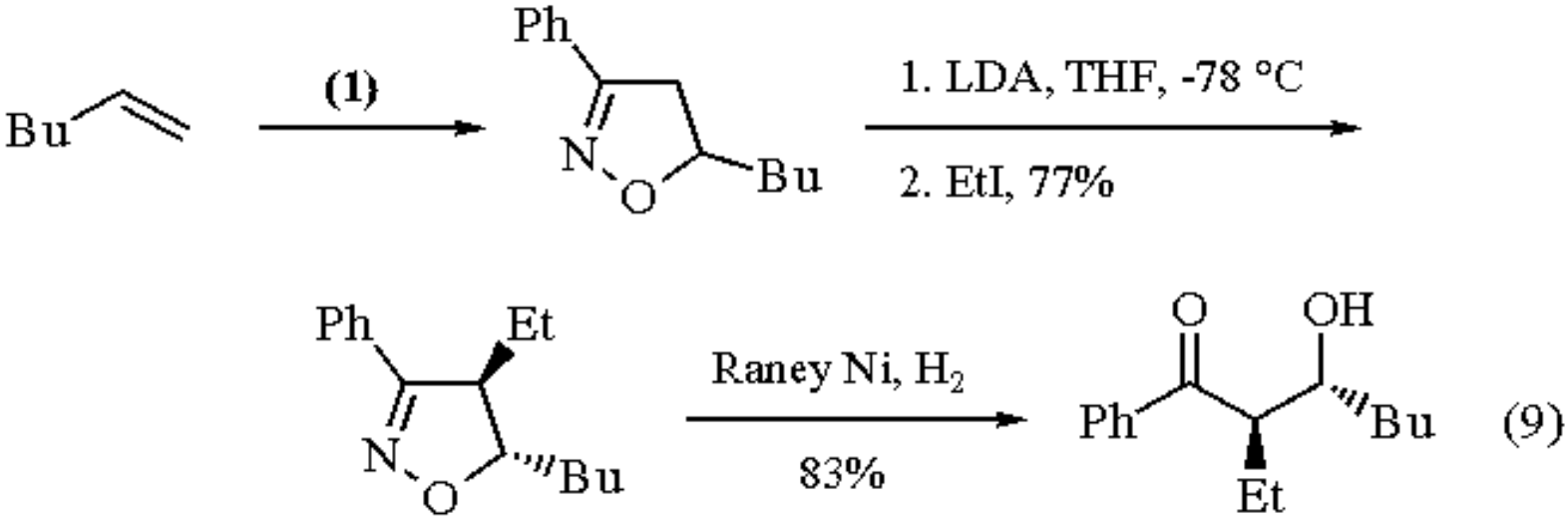

Methodology involving cycloaddition of nitrile oxides to C=C bonds and subsequent cleavage of the resulting Δ^2-isoxazolines has been widely used in natural product synthesis[24] and other synthetic ventures.[25]

1,3-DCA of (**1**) with dipolarophiles containing multiple bonds other than C=C provides a route to various heterocyclic systems.[1a,b,d] Alkynes add (**1**) to produce 3-phenylisoxazoles.[1a,b] Metalated alkynes serve as a handle for introducing a variety of functional groups into the 2-position (eq 10).[26] Alternatively, isoxazoles can be synthesized via DCA of (**1**) with nitroalkenes and subsequent 1,2-elimination of HNO_2.[27]

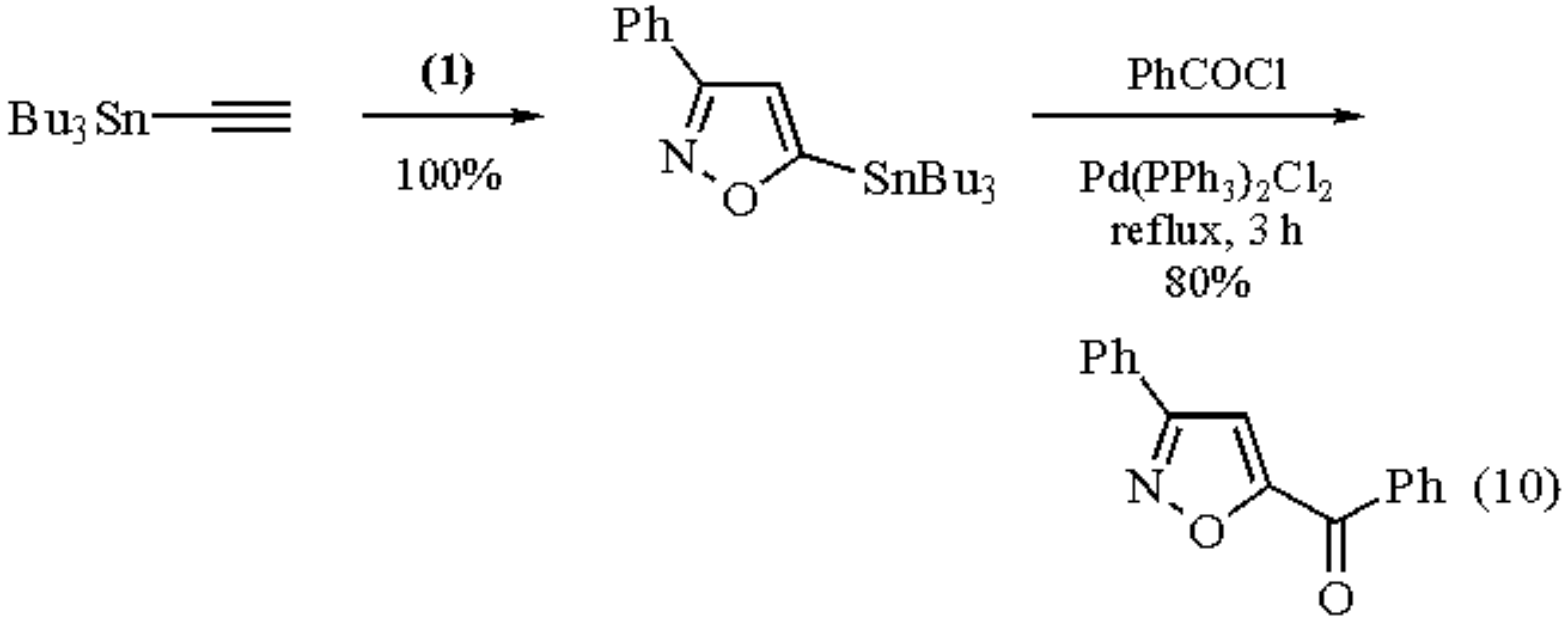

Compounds containing C=N bonds react with (**1**) to produce 1,3,5-oxadiazepines,[28a] Δ^2-1,2,4-oxadiazolines,[28b] and fused 1,2,4-oxadiazolines.[28c-f] In substrates with both C=C and C=N bonds, the 1,3-DCA takes place across the C=N bond.[28b,c] Nitriles react with (**1**) yielding 3-phenyl-1,2,4-oxadiazoles,[29,30] and the C&tbond;N bond successfully competes with C=C in dipolarophile activity.[30b] Dimerization of (**1**) to furoxan (**3**), a common process under 1,3-DCA conditions, can be considered as a particular case of 1,3-DCA of (**1**) to a C&tbond;N bond.[31]

Benzonitrile oxide also reacts with carbonyl groups to produce 1,4,2-dioxazolines. Uncatalyzed DCA is possible with aromatic carbonyl compounds,[2a,32] while aliphatic substrates react only in the presence of ***Boron Trifluoride Etherate***.[33] Upon treatment with ***Potassium t-Butoxide***, 1,4,2-dioxazolines obtained from arenecarbaldehydes lose PhCN to produce the corresponding arenecarboxylic acids (eq 11).[29] Site-specific or site-selective addition to the C=O group is observed in reactions of (**1**) with quinones[34a] or tropone.[34b]

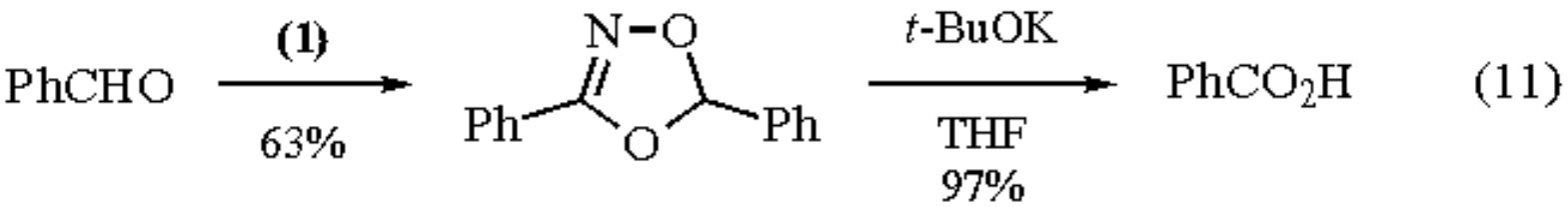

The C=S bond exhibits high dipolarophilic activity in reactions with (**1**) affording 1,4,2-oxathiazolines.[1a,b,35] Although 3,5-diphenyl-λ^3-phosphinin is inert to (**1**), DCA reaction takes place selectively at the P=C bond after complexation with tungsten pentacarbonyl (eq 12).[36]

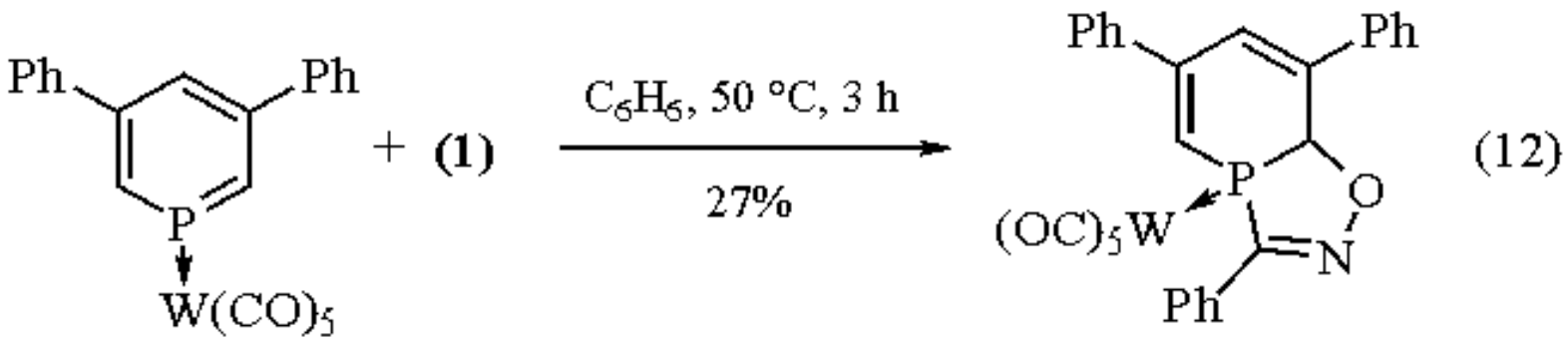

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Benzophenone Imine

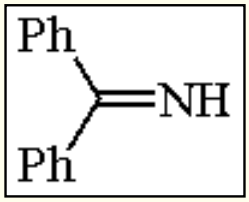

[1013-88-3] · $C_{13}H_{11}N$ · Benzophenone Imine · (MW 181.24)

(reagent for protection of primary amines)

Alternate Name: diphenylketimine.

Physical Data: bp 151-153 °C/10 mmHg.

Form Supplied in: commercially available.

Preparative Methods: prepared by the addition of phenylmagnesium bromide to benzonitrile followed by hydrolysis with MeOH[1] or by reaction of benzophenone with ammonia.[2]

Protected Primary Amines.

Benzophenone imine, a useful protecting group for primary amines (eq 1), is introduced by reaction with the amine salt (CH_2Cl_2, room temperature).[3] The resulting Schiff bases are stable to flash chromatography and have been used in conjunction with other anion-stabilizing groups, especially in the field of amino acid chemistry, to provide activation for proton abstraction.[4] Reaction of protected derivatives with base followed by alkylation with an alkyl halide (cases a (R = H)[5] and d[6,7]), an alkynyl(phenyl)iodonium triflate (case b),[8] or intramolecular alkylation (case c)[9] establish new carbon-carbon bonds at the indicated center.

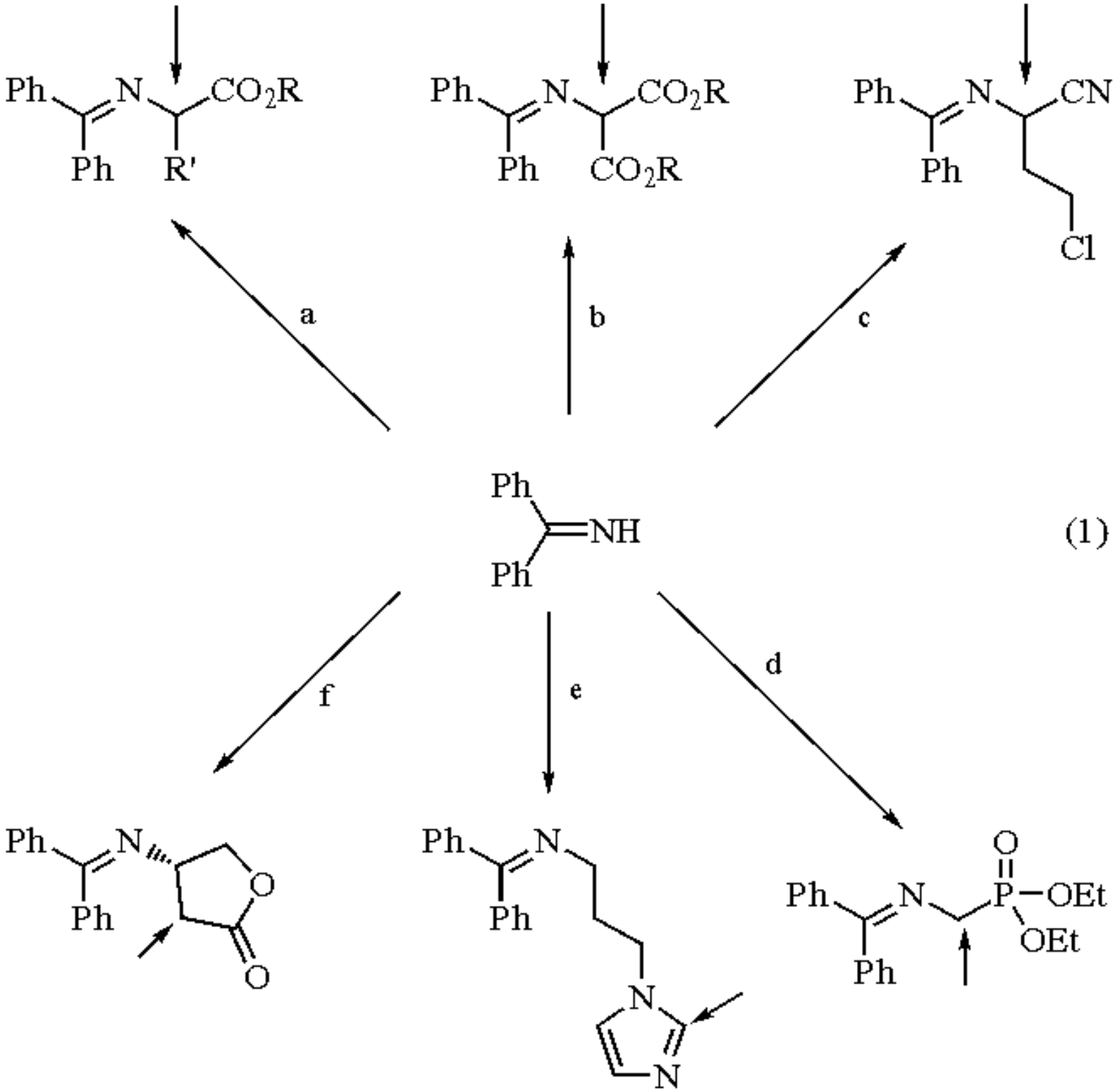

Benzophenone imine can also serve as a simple protecting group to allow acylation (case e)[10] or formylation (case f)[11] at a remote site. Removal is accomplished with either mild acid or catalytic hydrogenolysis.

Other Reactions.

Michael addition to acceptor-substituted alkenes gives protected β-amino acids, nitriles, and ketones (eq 2).[12]

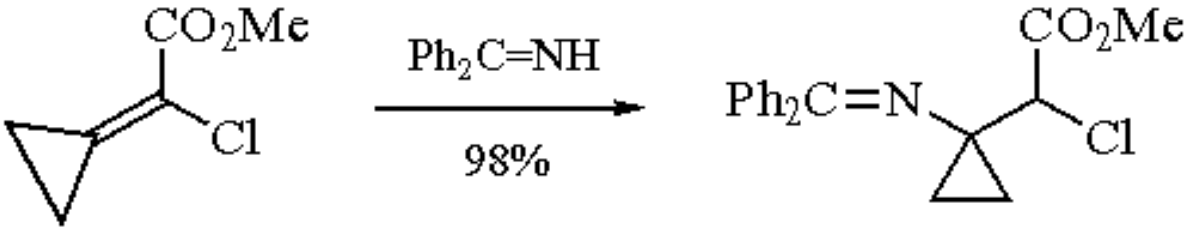

(2)

Reaction of oxalyl chloride with 1 equiv of *t*-BuOH followed by $Ph_2C{=}NH$ results in a protected α-keto amino ester (starting material in eq 3). This compound can be reacted with nonstabilized, semistabilized, stabilized, or heteroatom-substituted phosphonium ylides to give α,β-dehydroamino acid derivatives (eq 3).[13,14] Other reactions of these products have been reported.[15]

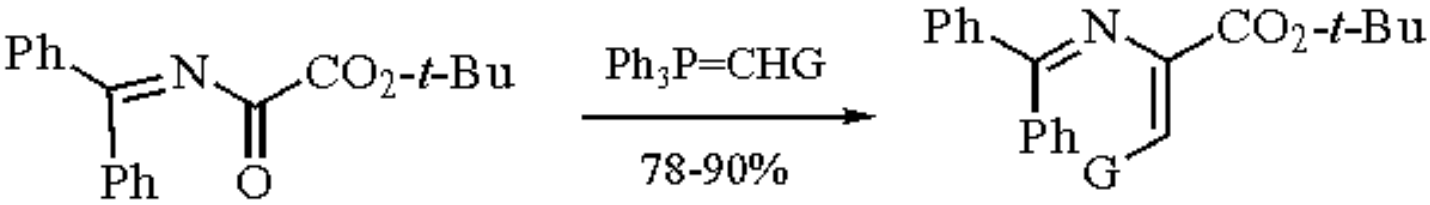

(3)

G = R, Ar, CO_2Et, OMe, Cl, Br

A stereoselective synthesis of β-amino alcohols from the benzophenone Schiff base of α-amino esters has been reported (eq 4).[16] Other reactions from similar protected α-amino acid derivatives include preparations of α- or β-*O*-serine or -threonine glycopeptides,[17] unsymmetrical disulfides of cysteine,[18] and several methods for transesterification[12,19] or related reactions[20] of the benzophenone imines of amino esters.

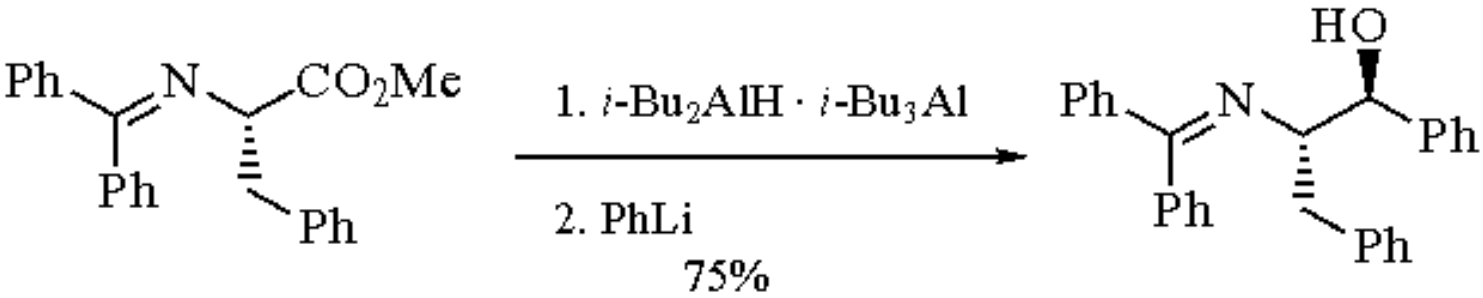

(4)

Related Reagents.

N-(Diphenylmethylene)aminoacetonitrile; ***Ethyl N-(Diphenylmethylene)-2-acetoxyglycinate***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Phthalimide***; ***Sodium Azide***; ***Isocyanic Acid***.

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1,4-Benzoquinone

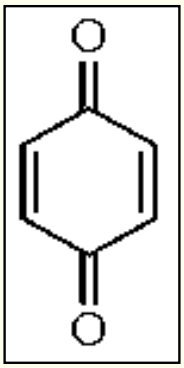

[106-51-4] · $C_6H_4O_2$ · 1,4-Benzoquinone · (MW 108.10)

(useful as an oxidizing[1] or dehydrogenation agent;[2] can function as a dienophile[3] in the Diels-Alder reaction or as a dipolarophile to prepare 5-hydroxyindole derivatives[4])

Alternate Name: p-benzoquinone.

Physical Data: mp 115.7 °C; *d* 1.318 g cm^{-3}.

Solubility: slightly sol water; sol alcohol, ether, hot petroleum ether, and aqueous base.

Form Supplied in: yellowish powder; widely available.

Handling, Storage, and Precautions: the solid has an irritating odor and can cause conjunctivitis, corneal ulceration, and dermatitis. In severe cases, there can be necrotic changes in the skin. Use in a fume hood.

As Oxidizing or Dehydrogenation Agent.

The ease of reduction of 1,4-benzoquinone to hydroquinone by various compounds renders it useful as an oxidizing or dehydrogenation agent.[2,5] The literature shows that 1,4-benzoquinone prefers to oxidize conjugated primary allylic alcohols over other alcohols (eq 1).[6] Kulkarni has demonstrated the selective oxidation of cinnamyl alcohols to cinnamaldehydes in the presence of secondary or benzylic alcohols. Primary alcohols have been oxidized to the corresponding aldehydes by using 1,4-benzoquinone as the hydrogen acceptor and hydrous zirconium(IV) oxide[7] as a catalyst (eqs 2 and 3).[1]

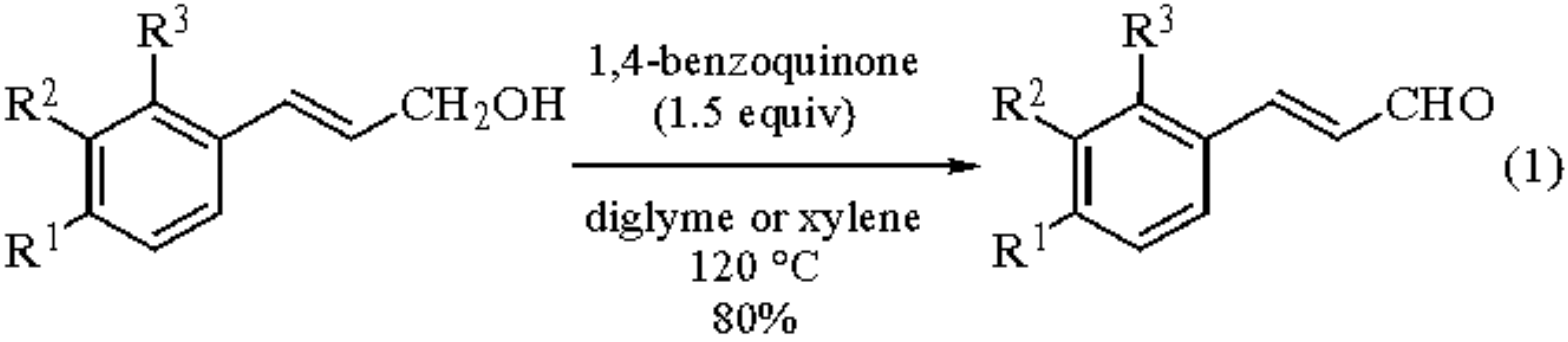

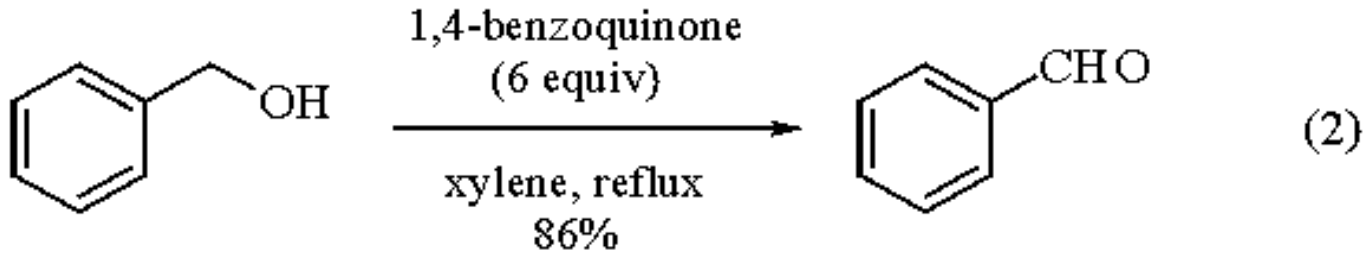

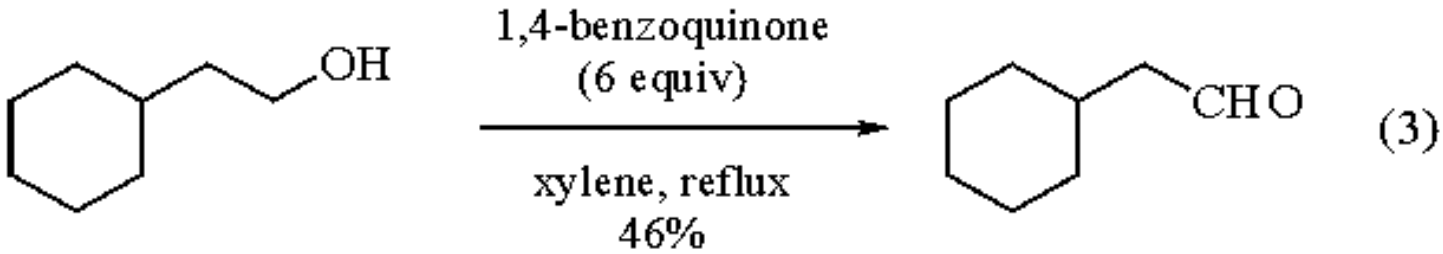

Nitrogenous compounds can be oxidized by 1,4-benzoquinone in refluxing benzene.[8,9] Aurich reported the conversion of hydroxyamine (**1**) to nitrone (**2**) through the reaction with 1,4-benzoquinone (eq 4).[9] Wiberg used 1,4-benzoquinone to transform tetrazene (**3**) into molecular nitrogen (eq 5).[10] Rossazza reported the oxidation of leurosine at the carbon α to nitrogen (eq 6).[11]

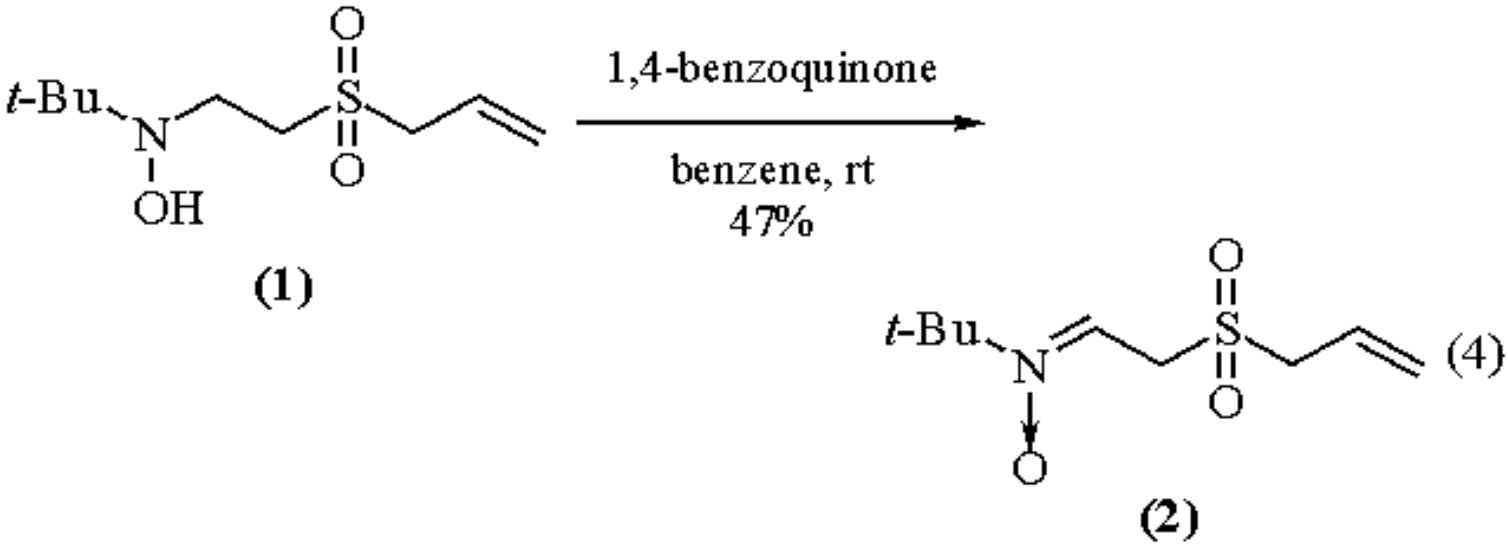

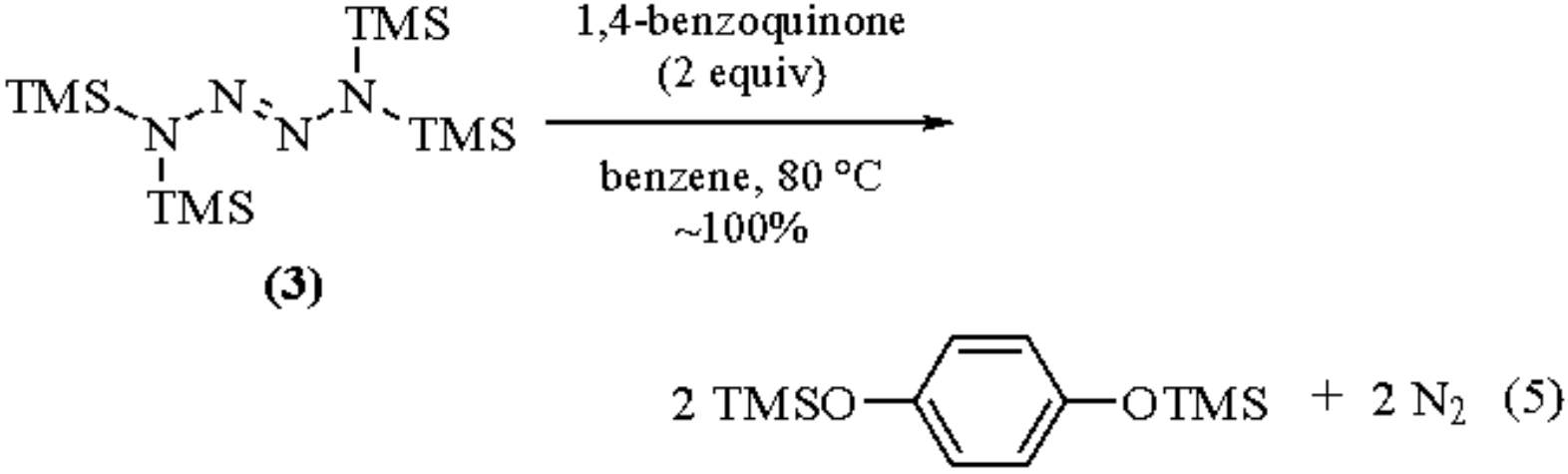

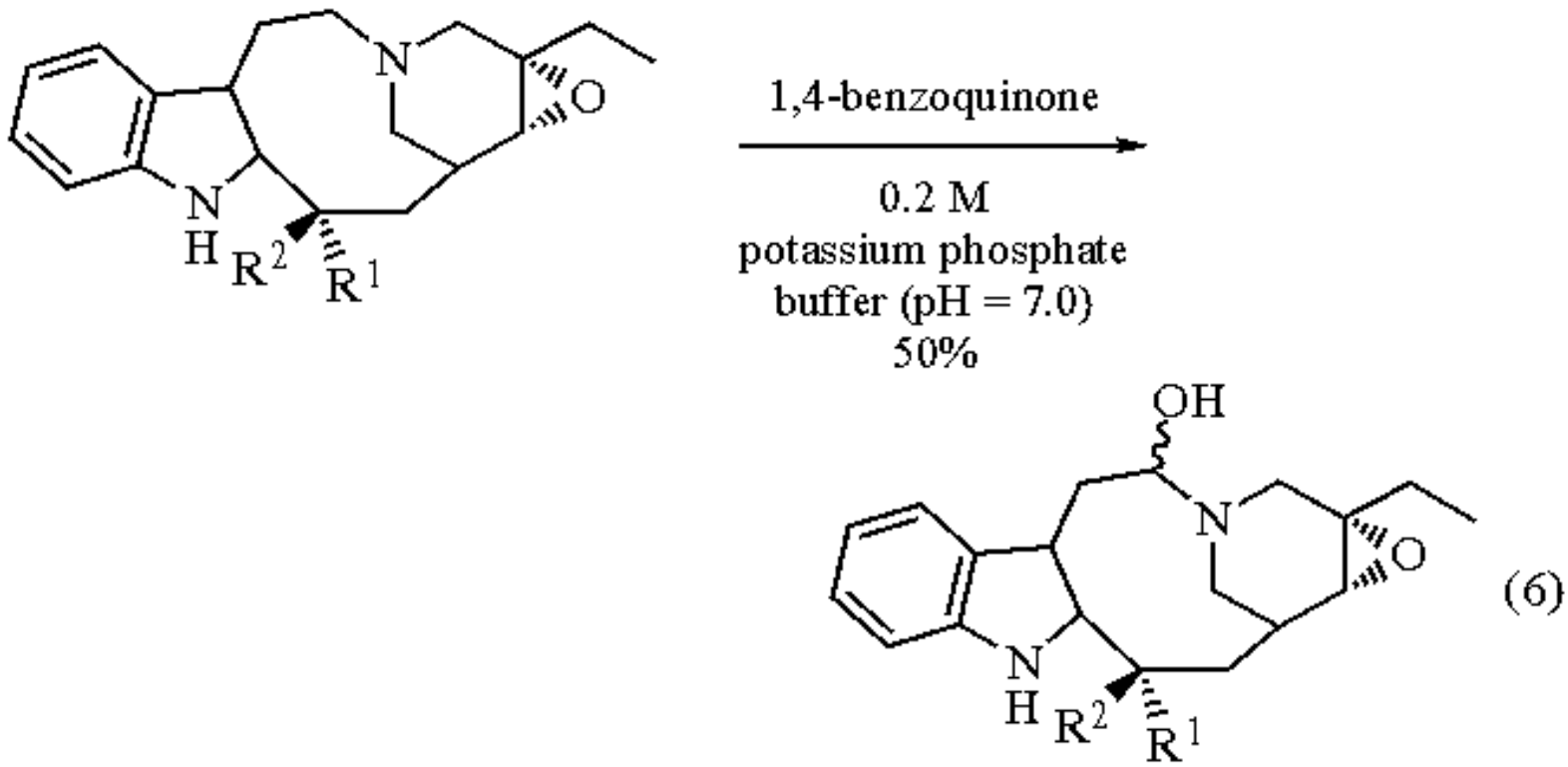

In the oxidation of alkenes with palladium(II) acetate, 1,4-benzoquinone serves as a cooxidant to reoxidize palladium(0) to palladium(II).[12,13] Davidson reported the oxidation of alkene (**4**) to a vinyl acetate with 0.1 equiv of palladium acetate and 1 equiv of 1,4-benzoquinone (eq 7).[14]

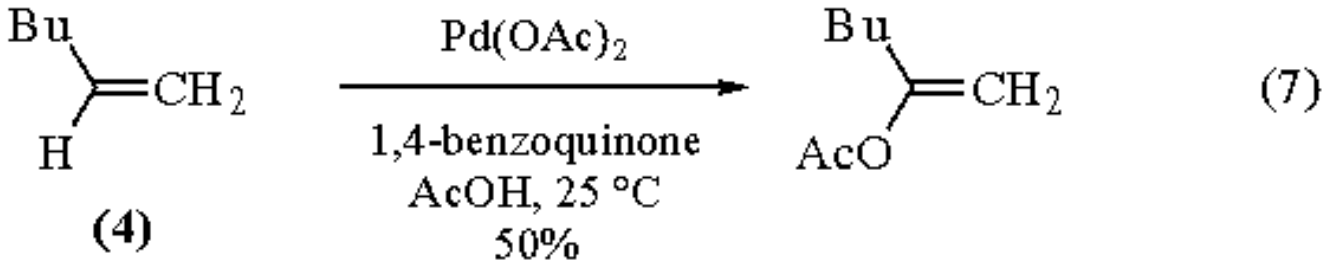

Backvall reported that the reaction of 1,3-cyclohexadiene with ***Palladium(II) Acetate*** and 1,4-benzoquinone gave 1,4-diacetoxy-2-cyclohexene in high yield. The stereochemistry of the products was influenced by additives. In the

presence of lithium acetate, the major *trans*-diacetate was obtained in 90% yield.[15] Without the addition of lithium acetate, a 1:1 mixture of *trans* and *cis* isomers was produced. However, the *cis*-diacetate was the major (>93%) product when both lithium acetate and lithium chloride were added (eq 8).[15] When the reaction was carried out in acetic acid containing trifluoroacetic acid and lithium trifluoroacetate, the *trans* isomer of 1-acetoxy-4-trifluoroacetoxy-2-cyclohexene was the major product in 67% yield (eq 9).[16] Similar oxidative 1,4-additions of other dienes, such as 1,3-butadiene, also can be accomplished in a regio- and stereoselective fashion (eq 10).[17] However, 1,4-benzoquinone has a high tendency to undergo Diels-Alder reactions when used as a cooxidant for $Pd(OAc)_2$ in such reactions. Many reactions of this type use only catalytic amounts of 1,4-benzoquinone and stoichiometric amounts of external oxidants, such as $Ce(SO_4)_2$, $Tl(OAc)_3$, and MnO_2.[18]

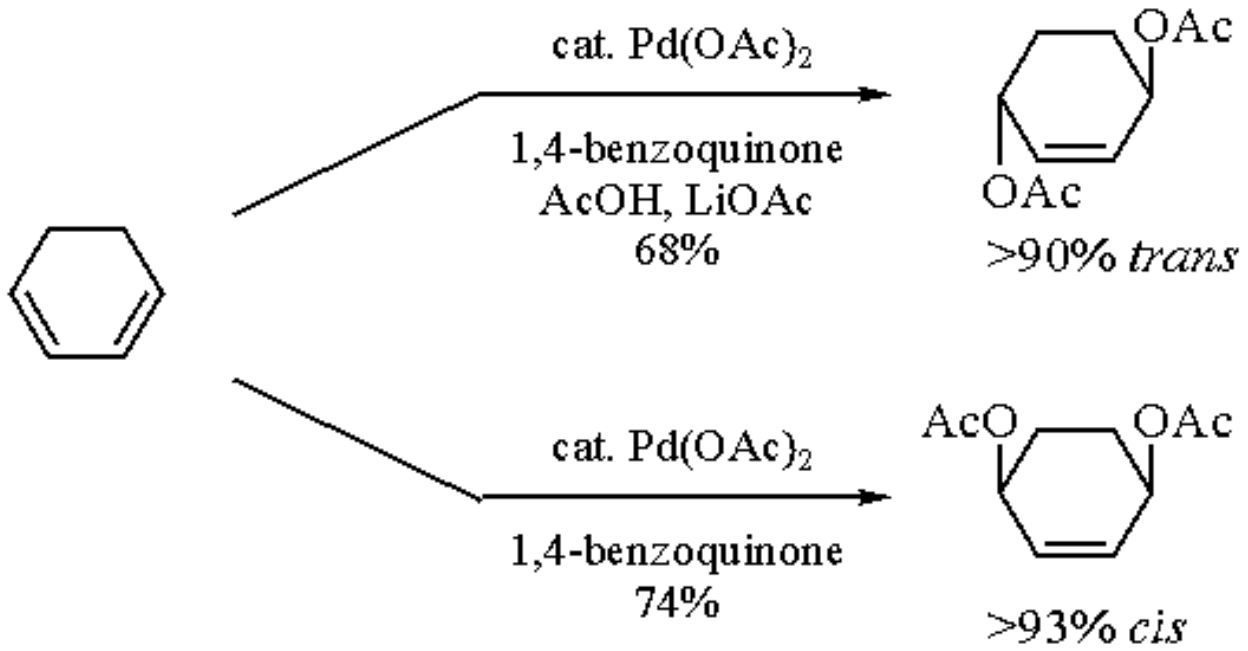

(8)

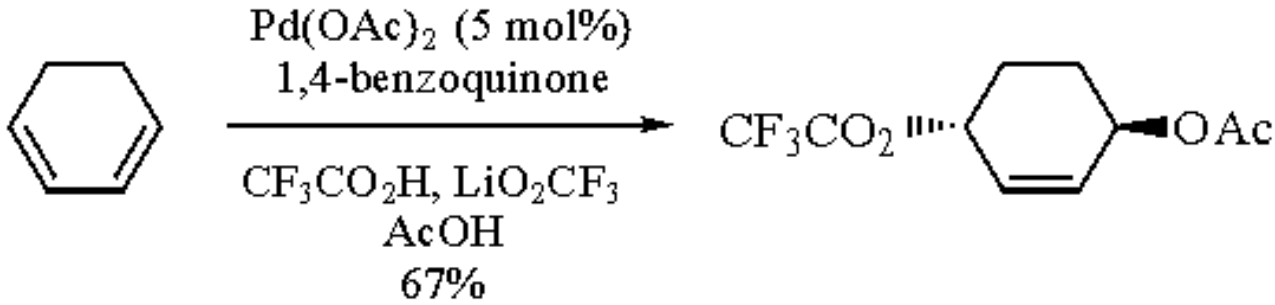

(9)

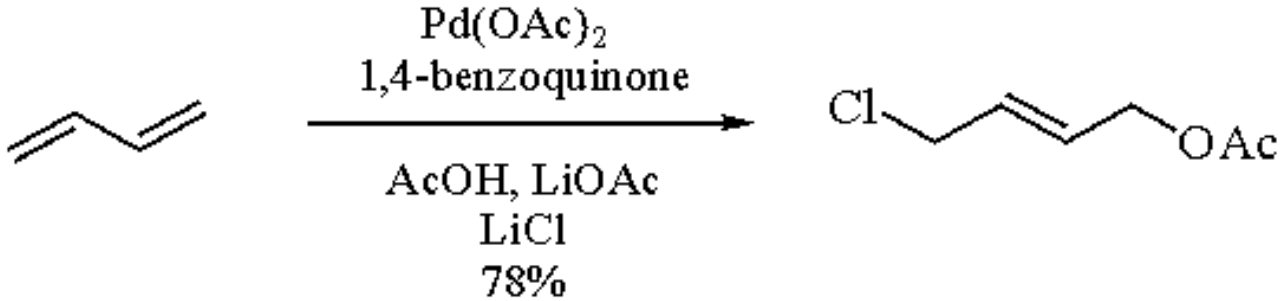

(10)

The combination of 1,4-benzoquinone and a catalytic amount of palladium acetate can transform silyl enol ethers into conjugated enones.[19] This reaction is not only regiospecific (eq 11) but also stereospecific to give the more stable *trans*

acyclic enone (eq 12).

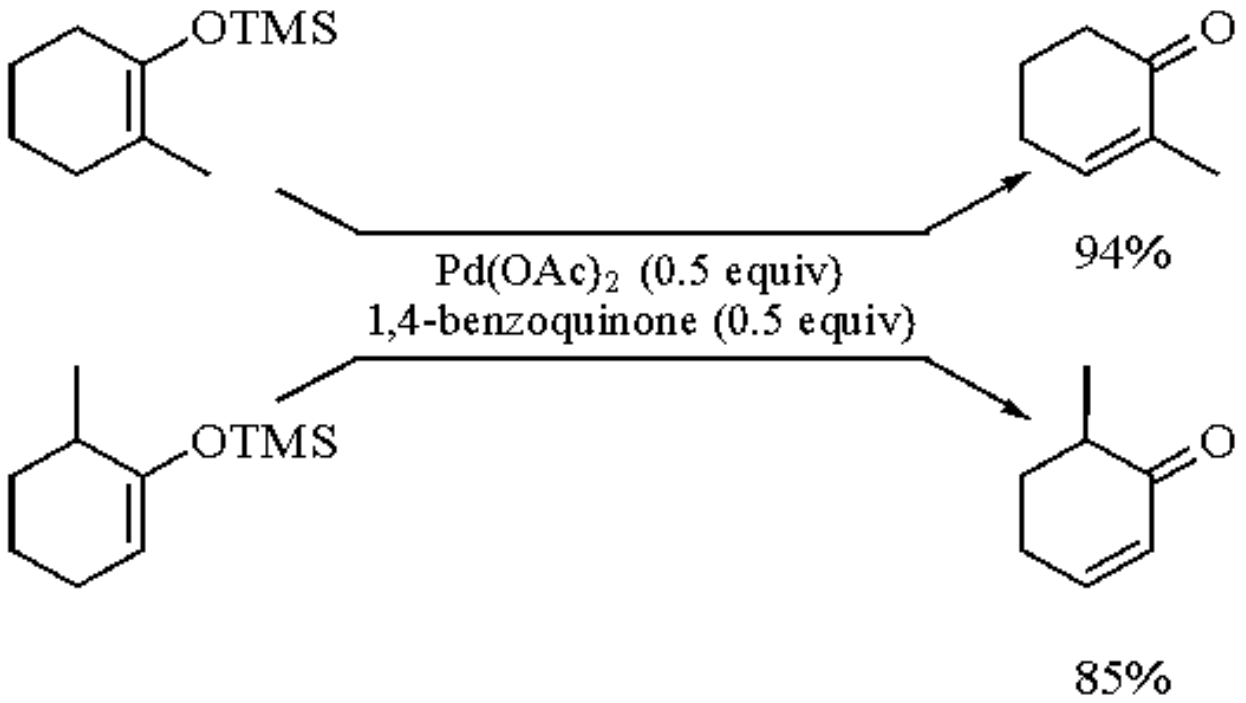

(11)

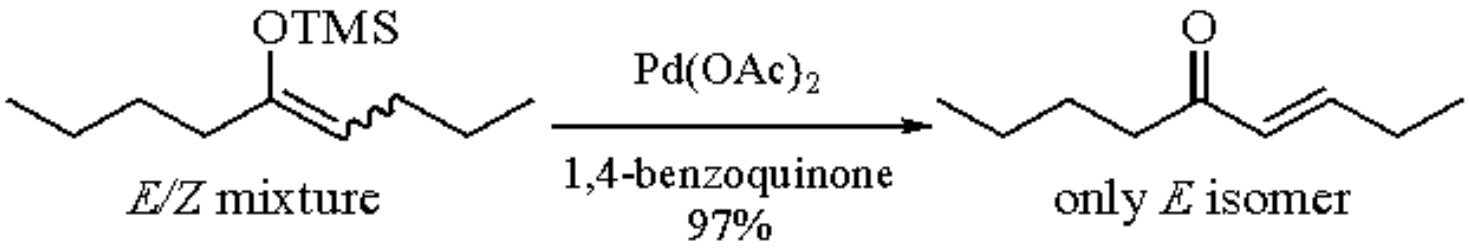

(12)

Antonsson used ***Manganese Dioxide*** as the oxidant and 0.05 equiv of palladium acetate and 0.20 equiv of 1,4-benzoquinone as catalyst for oxidative ring closure of 1,5-hexadienes to give cyclopentane derivatives in good yield (eq 13).[20] With 1,4-benzoquinone and 10 mol % of ***Palladium(II) Chloride***, a homoallylic alcohol underwent oxidative ring closure to give a γ-butyrolactol (eq 14).[21]

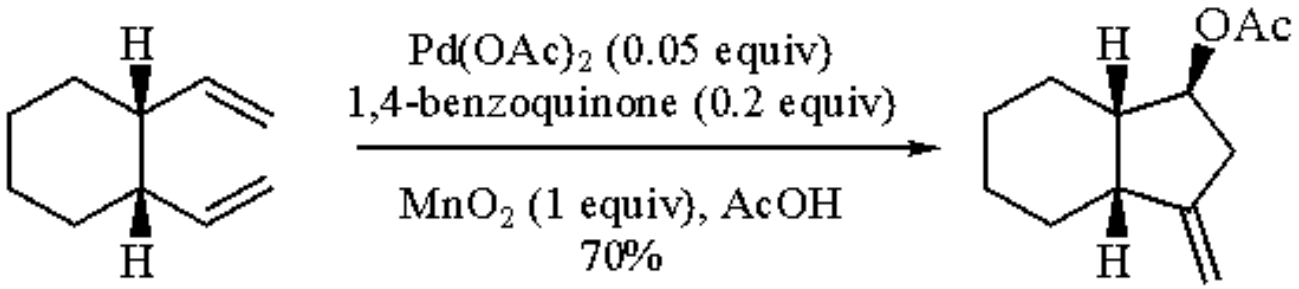

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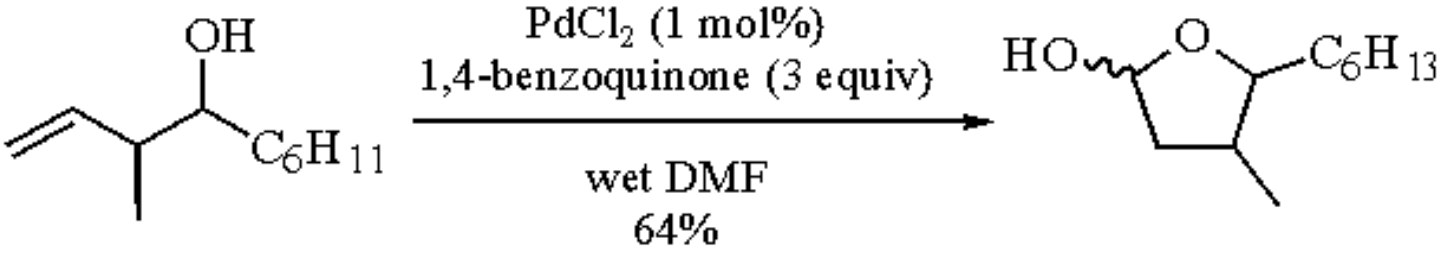

(14)

The combination of palladium acetate and 1,4-benzoquinone was used in the ring opening of an α,β-epoxysilane to give 19% of oct-2-enal in the presence of oxygen gas (eq 15).[22] Similar reagents are effective in the oxidative coupling of carbon monoxide in methanol to give methyl oxalate (eq 16).[12]

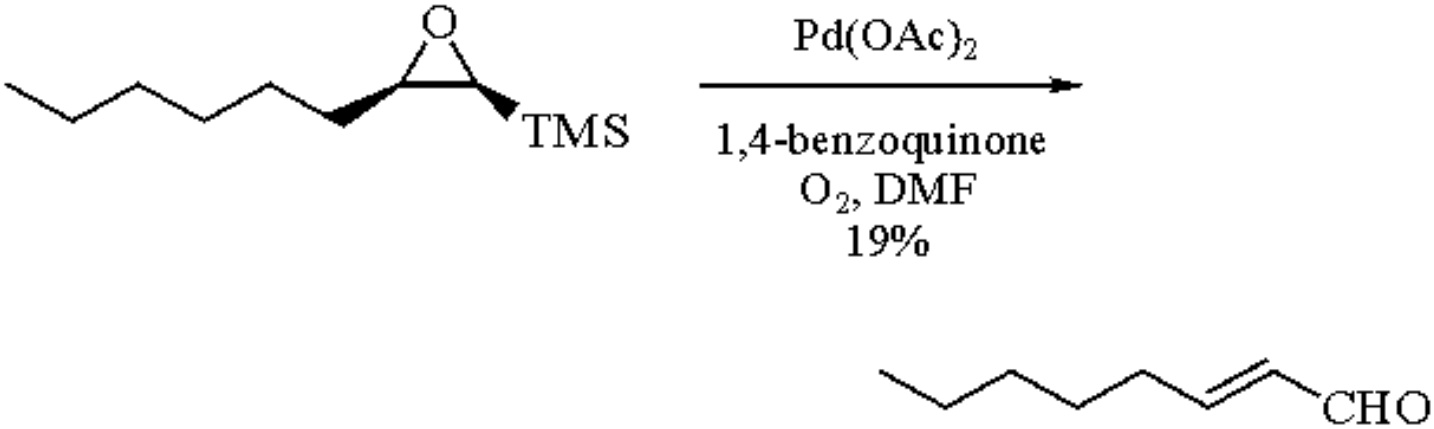

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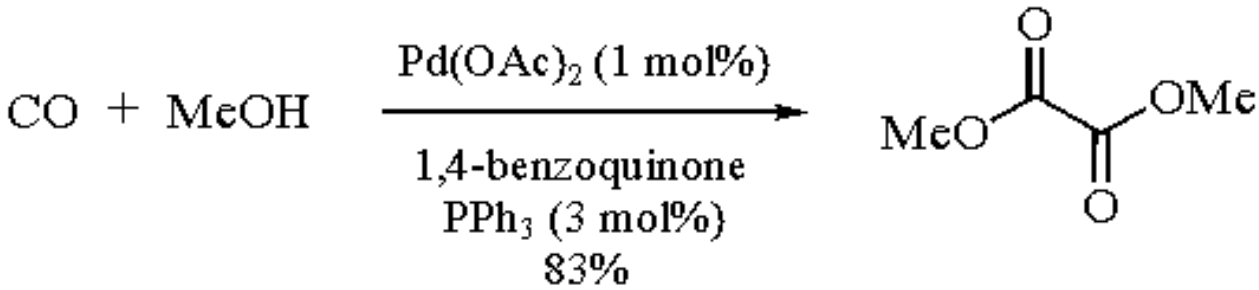

(16)

As Dienophile.

1,4-Benzoquinone is an excellent dienophile in the Diels-Alder reaction toward electron rich dienes.[23,24] The bicyclic cycloadducts of these reactions are frequently used as the starting materials for the synthesis of natural products. A typical example is demonstrated by Mehta in a total synthesis of capnellene, in which 1,4-benzoquinone is allowed to react with 1-methyl-1,3-cyclopentadiene to give compound (**5**) (eq 17).[25] The cycloaddition of 1,4-benzoquinone and another activated diene is shown in eq 18.[26]

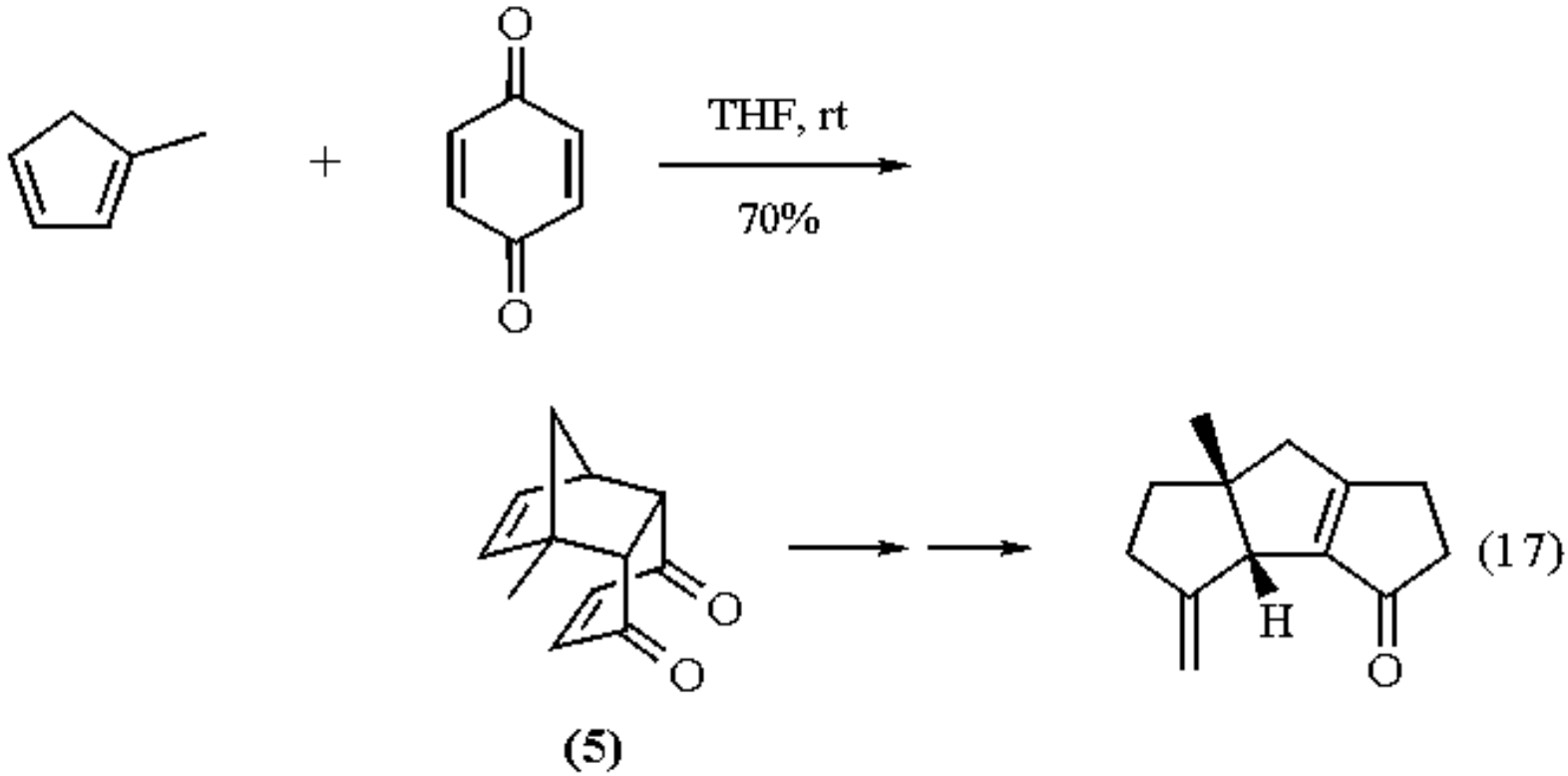

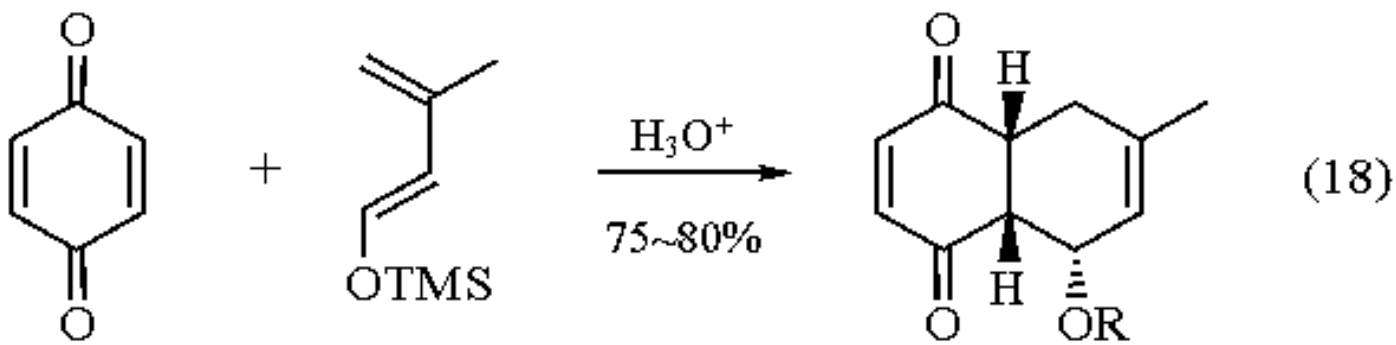

Asymmetric Diels-Alder reactions of 1,4-benzoquinone have been reported. Several examples are shown in eqs 19-21.[3,27,28]

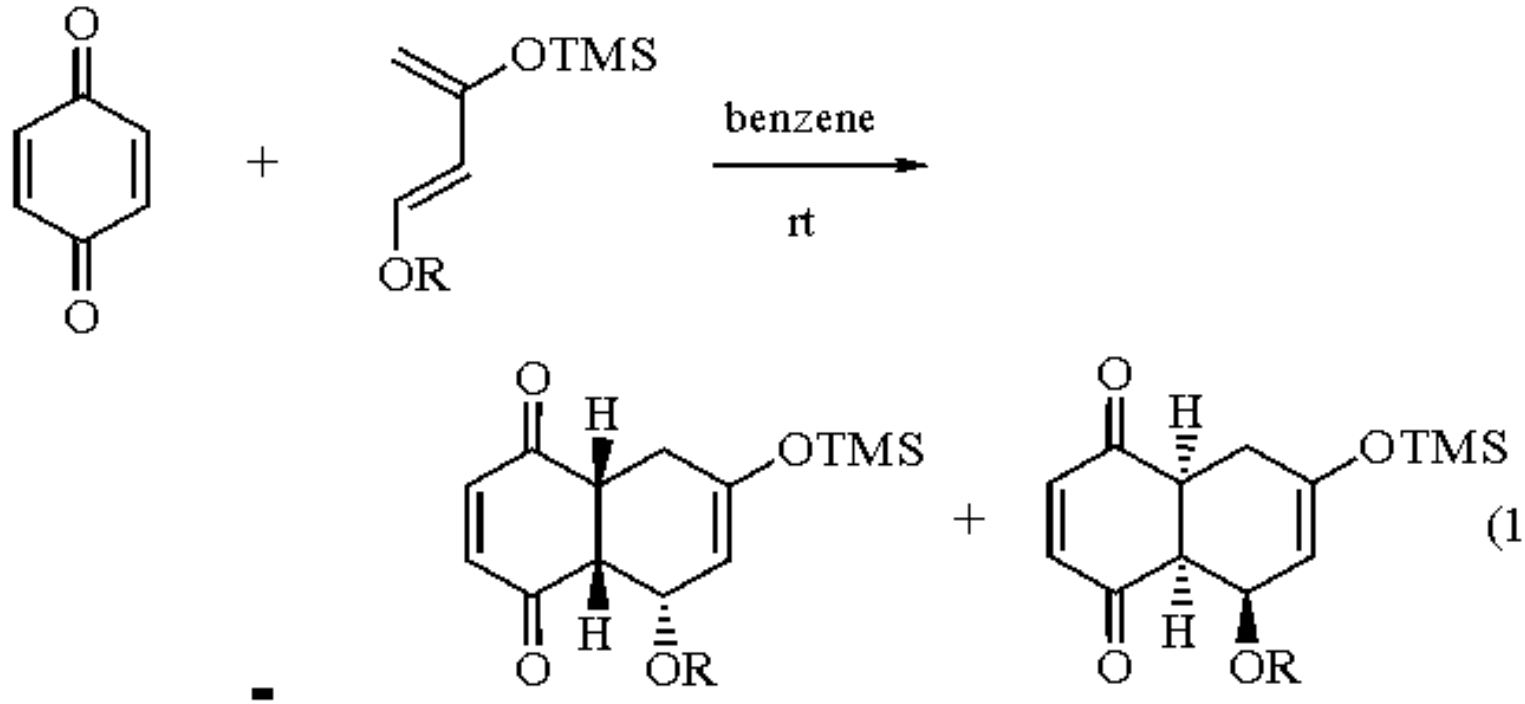

(19)

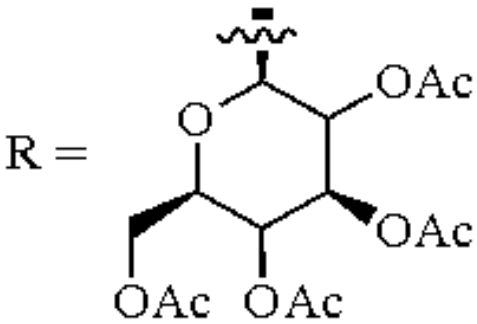

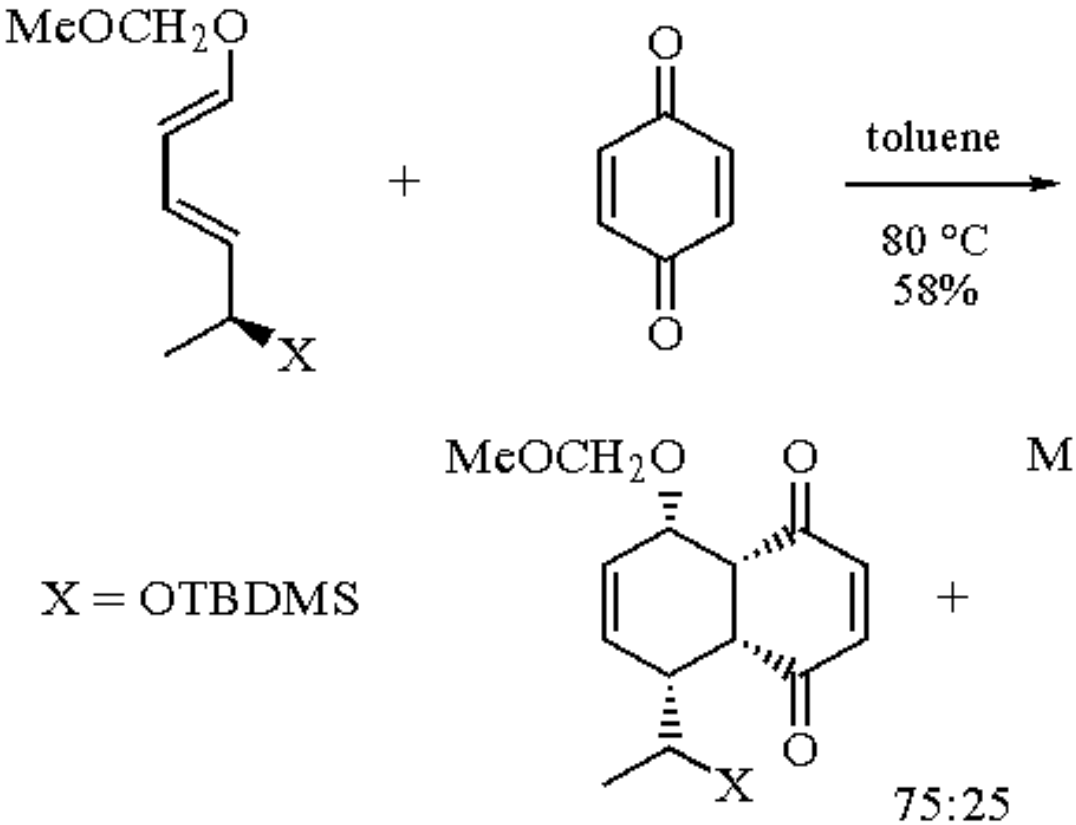

X = OTBDMS

(20)

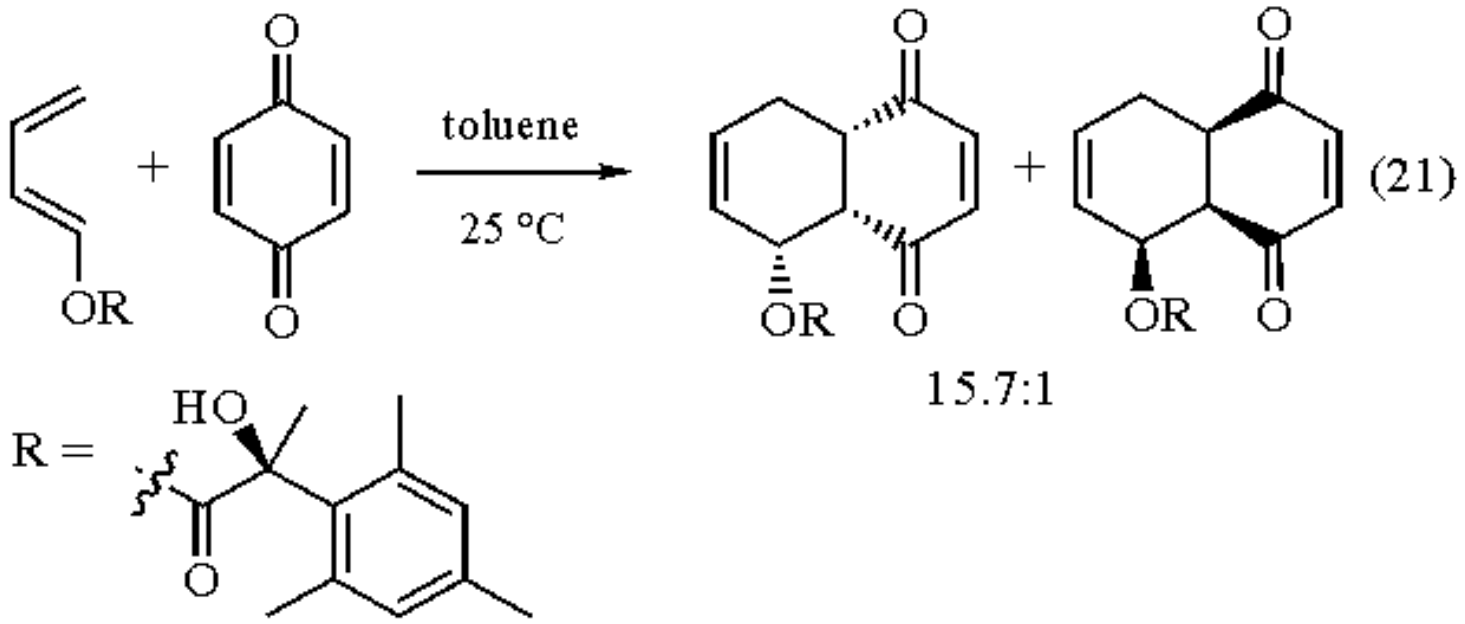

(21)

Under high pressure, even electron deficient dienes react with 1,4-benzoquinone. Dauben reported the asymmetric cycloaddition of a chiral dienic ester and 1,4-benzoquinone to produce chiral adducts with moderate enantioselectivity (eq 22).[29]

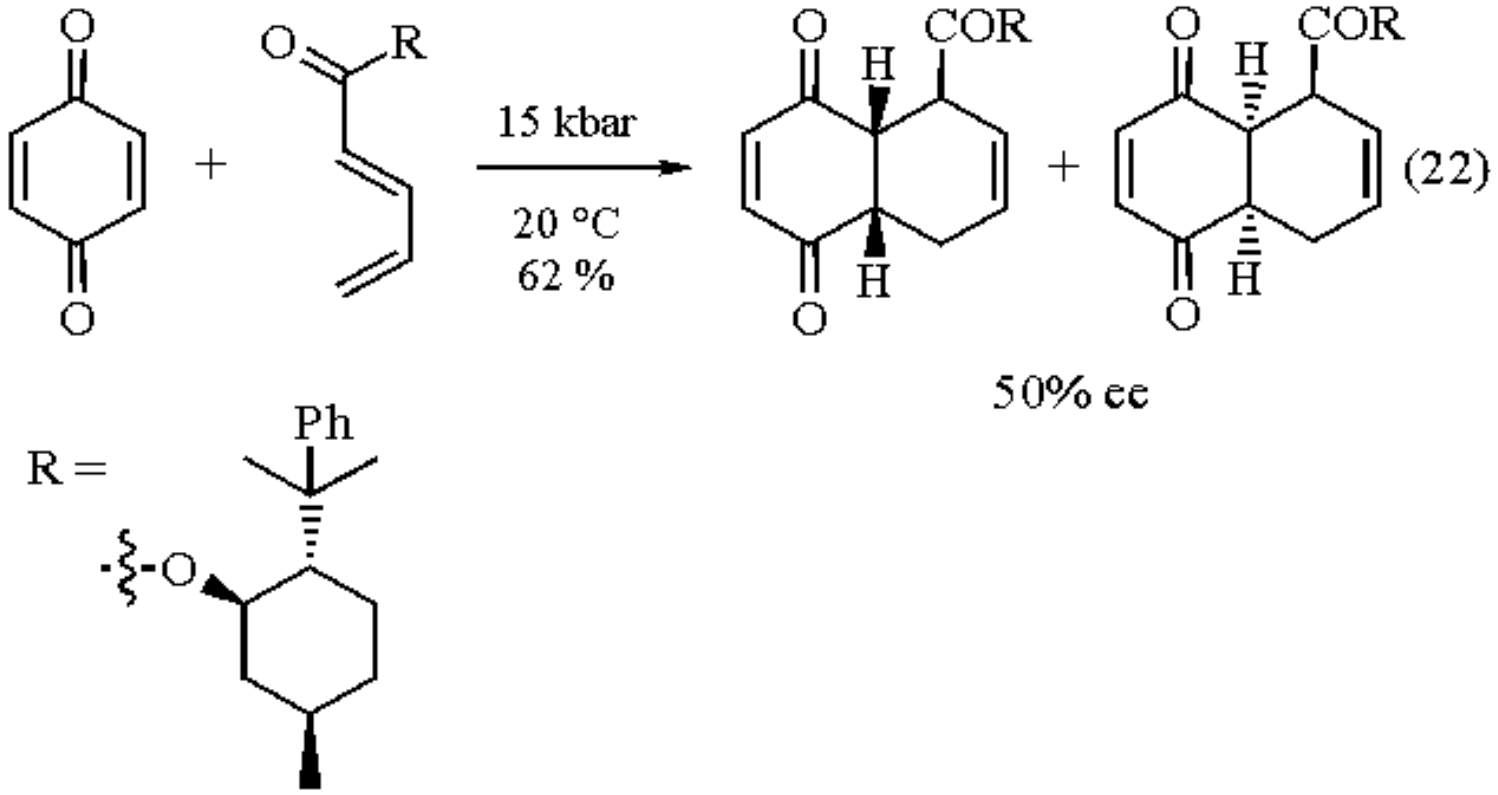

(22)

Preparation of 5-Hydroxyindoles.

The reaction of 1,4-benzoquinone with certain enamines has been used to prepare 5-hydroxyindole derivatives.[4,30] The first example was reported by Nenitzescu, in which he successfully prepared ethyl 5-hydroxy-2-methylindole-3-carboxylate from 1,4-benzoquinone and ethyl 3-aminocrotonate (eq 23).[4] The ease of the reaction and the availability

of the reactants have made it a popular method for indole synthesis. However, the yields of this type of reaction vary over a wide range (5-90%).

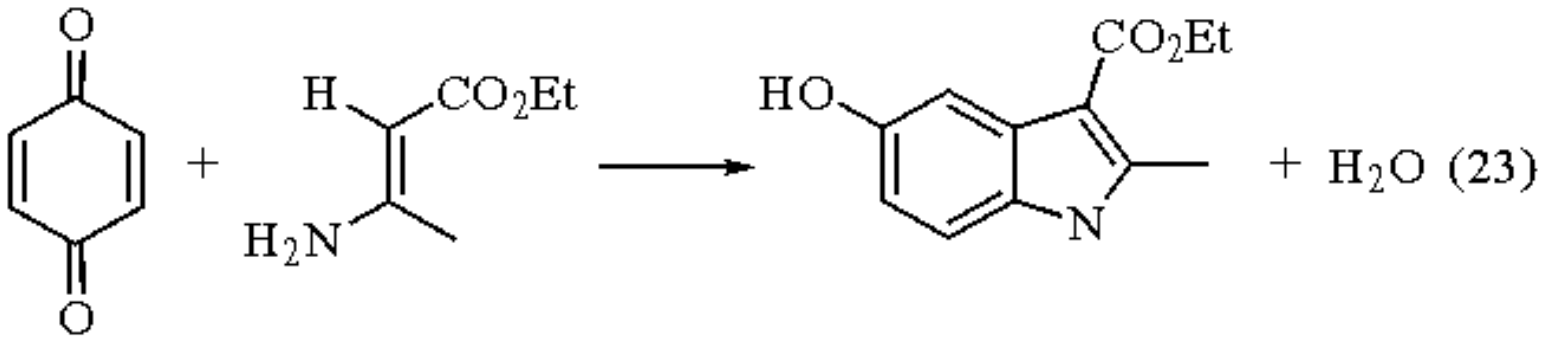

As Reaction Promoter.

In the hydrogenation of nitrobenzene with platinum catalyst in DMSO, addition of 1,4-benzoquinone accelerates the reaction rate.[31]

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1,2,3-Benzothiadiazole 1,1-Dioxide[1]

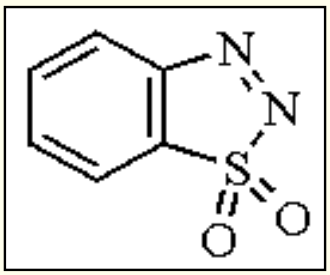

[37150-27-9] · $C_6H_4N_2O_2S$ · 1,2,3-Benzothiadiazole 1,1-Dioxide · (MW 168.17)

(benzyne precursor[1])

Solubility: sol ether.

Preparative Method: by diazotization of sodium 2-aminobenzenesulfinate, which is obtained in three steps from 2-nitroaniline.[2]

Handling, Storage, and Precautions: it can be isolated as yellow-brown needles, but slowly decomposes even at 0 °C and explodes between 45 and 60 °C. A safer alternative is to use it in solution, in which it decomposes smoothly at 10 °C. Preparation and handling should be carried out with good shielding.

Generation of Benzyne.[1]

Decomposition of 1,2,3-benzothiadiazole 1,1-dioxide in ether affords benzyne, nitrogen, and sulfur dioxide (eq 1).[2]

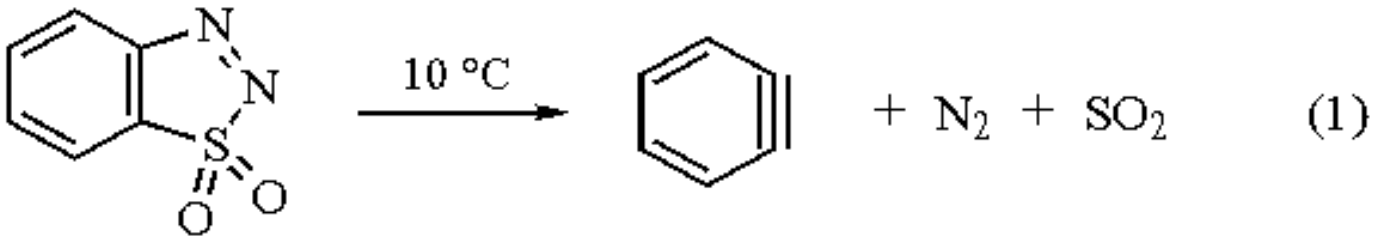

This is a very mild procedure (neutral, relatively low temperature) for the generation of benzyne. However, despite the examples which follow, the time-consuming preparation of 1,2,3-benzothiadiazole 1,1-dioxide has greatly limited its use in synthesis. Moderate yields have been obtained in the reactions of cyclic dienes with benzyne generated in situ from 1,2,3-benzothiadiazole 1,1-dioxide. Furan, for example, traps benzyne efficiently under these conditions to afford the adduct in 54% yield (eq 2).[3]

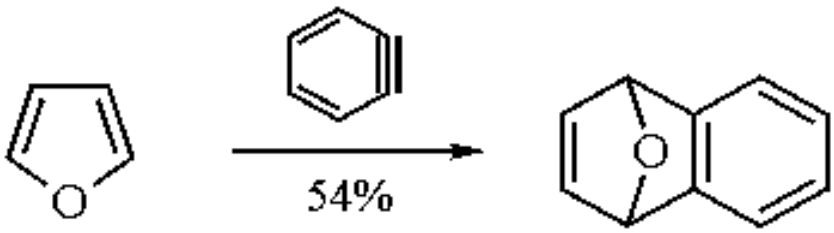

(2)

2-Pyrone reacts with benzyne to give a bicyclic adduct, which loses CO_2 by a retro-Diels-Alder reaction to afford naphthalene in 36% yield (eq 3).[3]

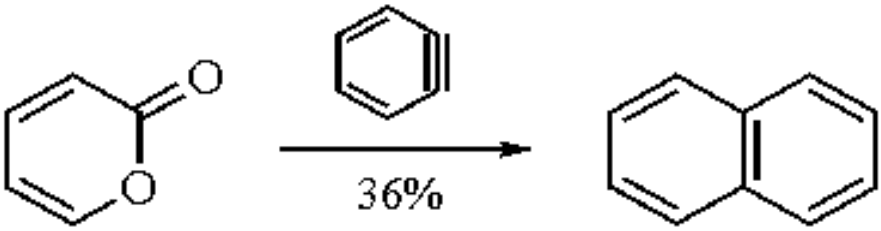

(3)

Cyclopentadiene derivatives react with benzyne to yield bridged compounds (eq 4).[4]

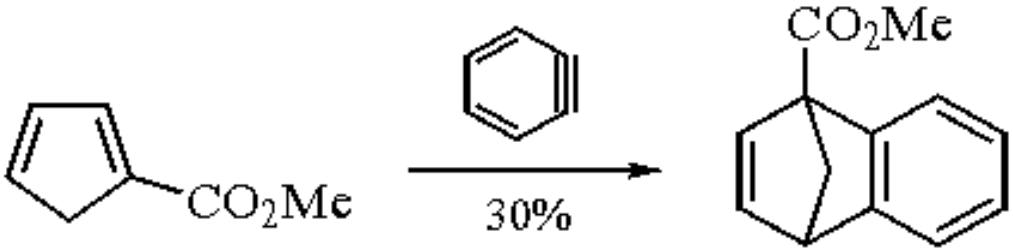

(4)

Due to the low decomposition temperature of 1,2,3-benzothiadiazole 1,1-dioxide, cycloaddition with less reactive dienes affords complex mixtures with poor yields of cycloadducts. For example, the decomposition of 1,2,3-benzothiadiazole 1,1-dioxide in thiophene leads to a complex mixture with less than a 5% yield of products derived from cycloaddition.[5]

The effect of silver(I) on the course of the reactions of benzyne with polyenes has also been reported.[6] When 1,2,3-benzothiadiazole 1,1-dioxide was decomposed in the presence of 1,3-cyclohexadiene, a complex mixture was obtained. Four products were characterized, giving a total yield of 28% (eq 5). When 1,2,3-benzothiadiazole 1,1-dioxide was added to a silver-diene complex, the yield and selectivity of the reaction were improved (eq 6).

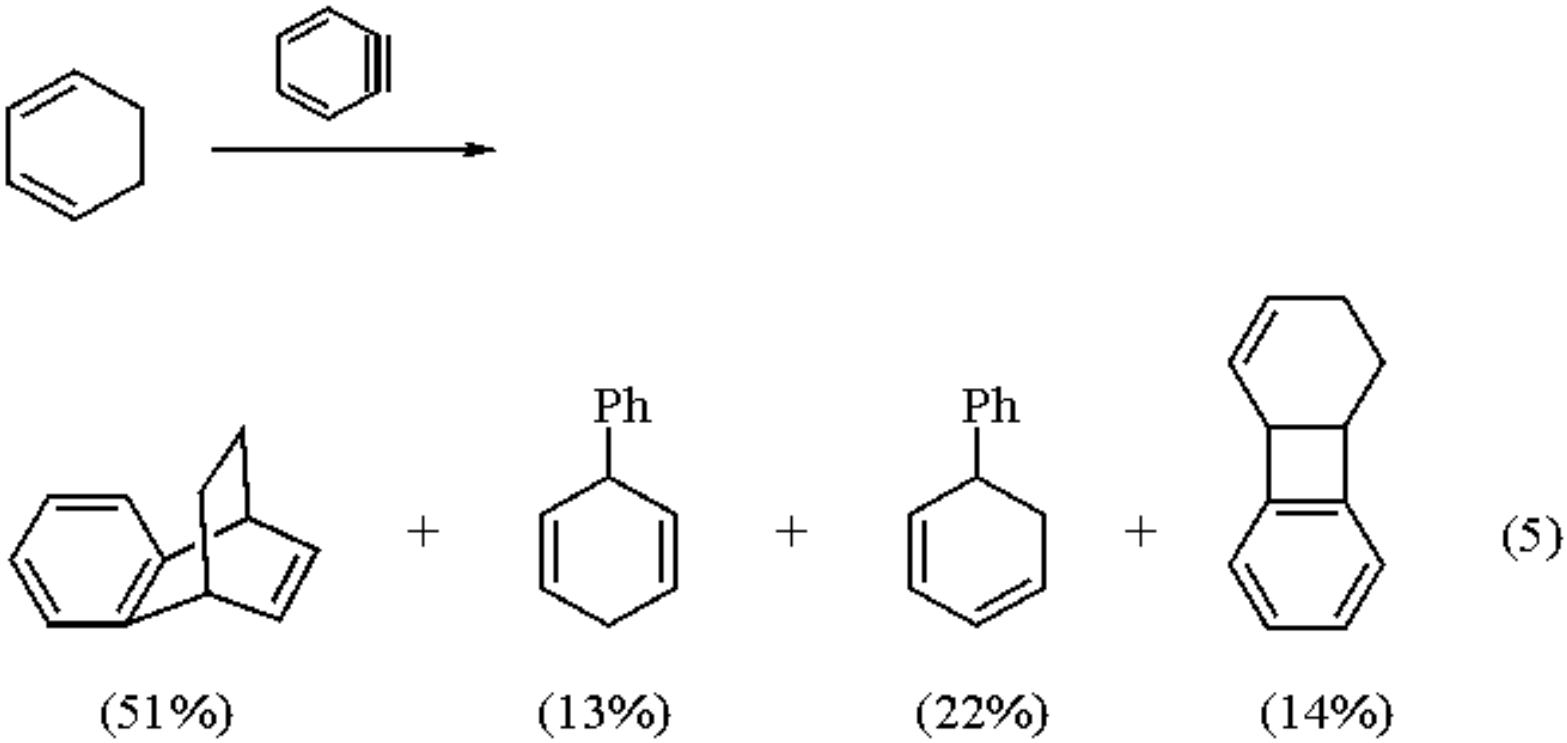

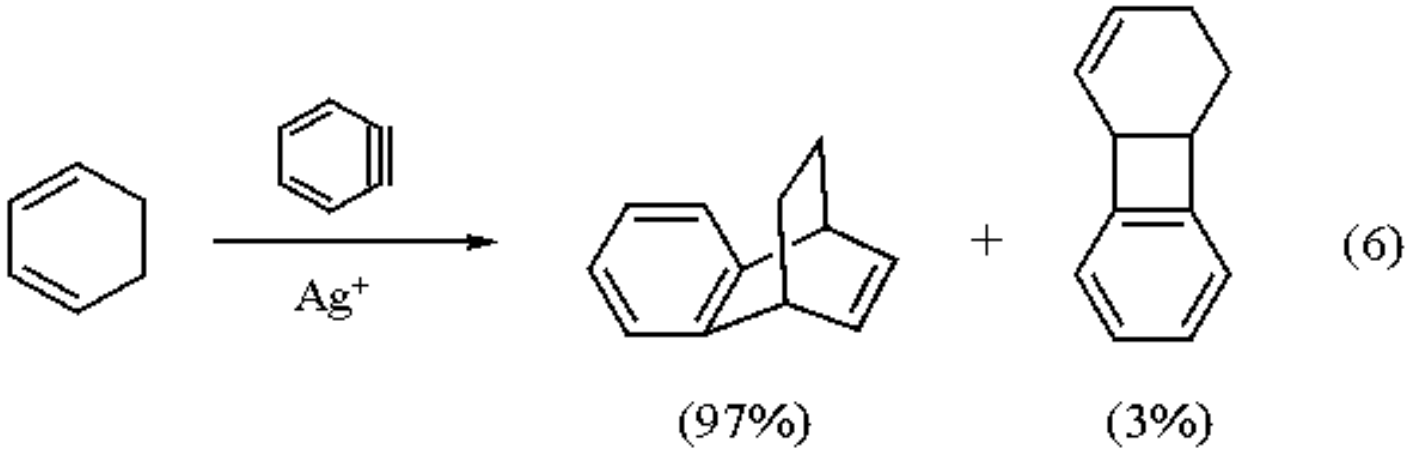

Related Reagents.

Benzenediazonium-2-carboxylate; ***Diphenyliodonium Carboxylate***.

---

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Luis Castedo & Enrique Guitián

Benzothiazole[1]

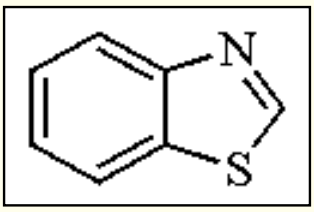

[95-16-9] · C_7H_5NS · Benzothiazole · (MW 135.18)

(formyl and acyl anion equivalent;[2] one-carbon homologation of aldehydes via the 2-trimethylsilyl derivative;[3] the *N*-methylbenzothiazolium ring system has been used as a leaving group[4])

Physical Data: mp 2 °C; bp 231 °C/765 mmHg; bp 131 °C/34 mmHg; *d* 1.246 g cm^{-3}; n_D 1.6379.

Solubility: slightly sol H_2O; sol acetone; very sol ethanol, diethyl ether, THF, CS_2.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^1H and ^{13}C NMR.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: use in a fume hood. Benzothiazole should be used freshly distilled for best results. Toxic by inhalation, in contact with skin, and if swallowed.

2-Lithiobenzothiazole.[5]

Benzothiazole (**1**) is easily metallated at the 2-position by employing 1.0 equiv of ***n-Butyllithium*** at -78 °C in diethyl ether as solvent.[2a,6] Chikashita et al.[2b] have found that better results can be achieved by adding a 10% excess of *n*-butyllithium and carrying out the reaction in THF as a solvent (eq 1). In fact, when diethyl ether is used as solvent or less than 2 mL THF/mmol benzothiazole, the lithium compound should precipitate and the corresponding suspension becomes very thick, making stirring difficult.

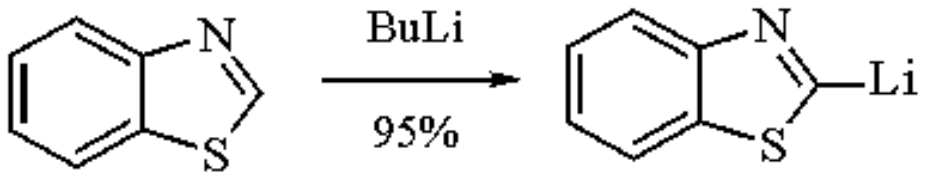

(1)

(1) **(2)**

2-Lithiobenzothiazole (**2**) is stable only below -50 °C. A solution of 2-Lithiobenzothiazole in THF gives rise to a clear orange-colored solution. At temperatures higher than -50 °C a dark-brown solution indicating decomposition of the organolithium compound is observed. Consequently, reactions with this reagent have to be carried out at temperatures lower than -50 °C. 2-Lithiobenzothiazole (**2**) reacts with various electrophiles[7] such as esters or nitriles (eq 2), α-halo ketones (eq 3), and carbonyl compounds[4] to give the intermediate carbinols which can be easily dehydrated to the corresponding alkenes (**3**) as described (eq 4).[2]

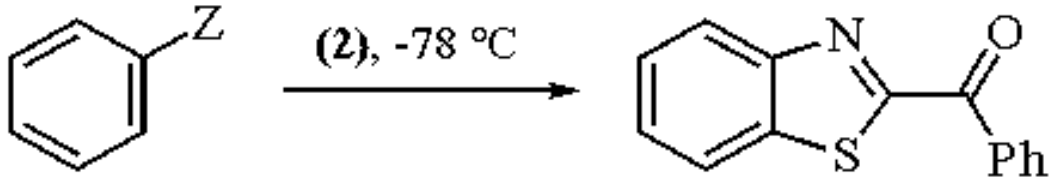

(2)

$Z = CO_2Et$, CN

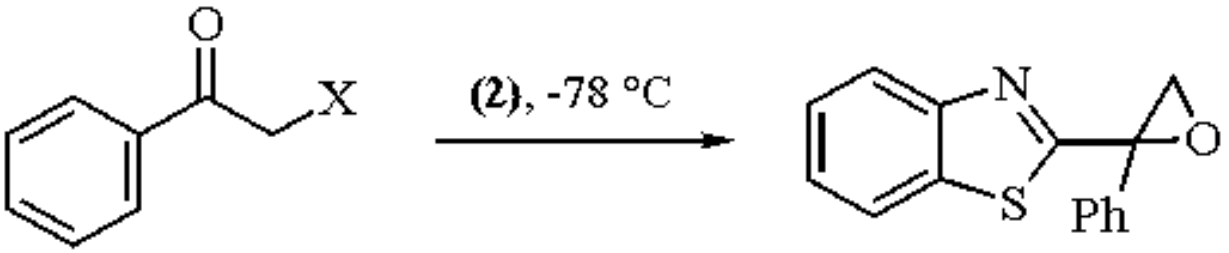

(3)

X = Br, Cl

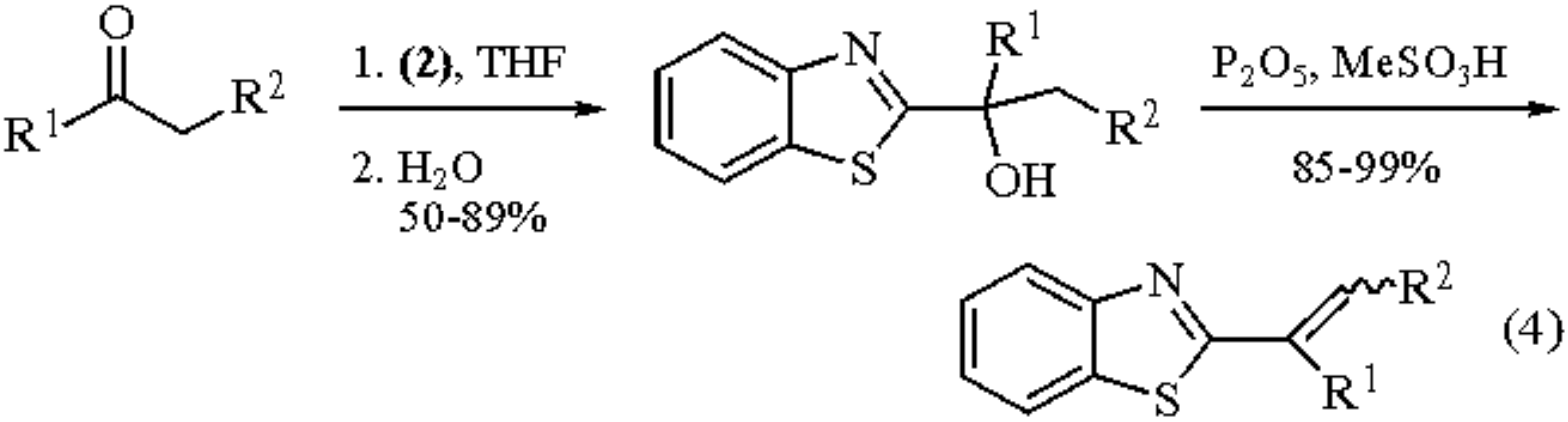

(4)

(3)

On the other hand, Chikashita et al.[7] suggest that 2-lithiobenzothiazole (**2**) does not react with alkyl halides.

The synthetic utility of the benzothiazole nucleus is demonstrated through the unmasking to the carbonyl function.[2] The methodology involves three steps: (a) methylation of 2-substituted benzothiazoles (**4**), (b) reduction of the resulting salts (**5**), and (c) hydrolysis under mild and neutral conditions to afford the aldehydes (**6**) (eq 5).[2,4] In several cases, however, the efficiency of this unmasking protocol and its compatibility with other protecting groups were not demonstrated.

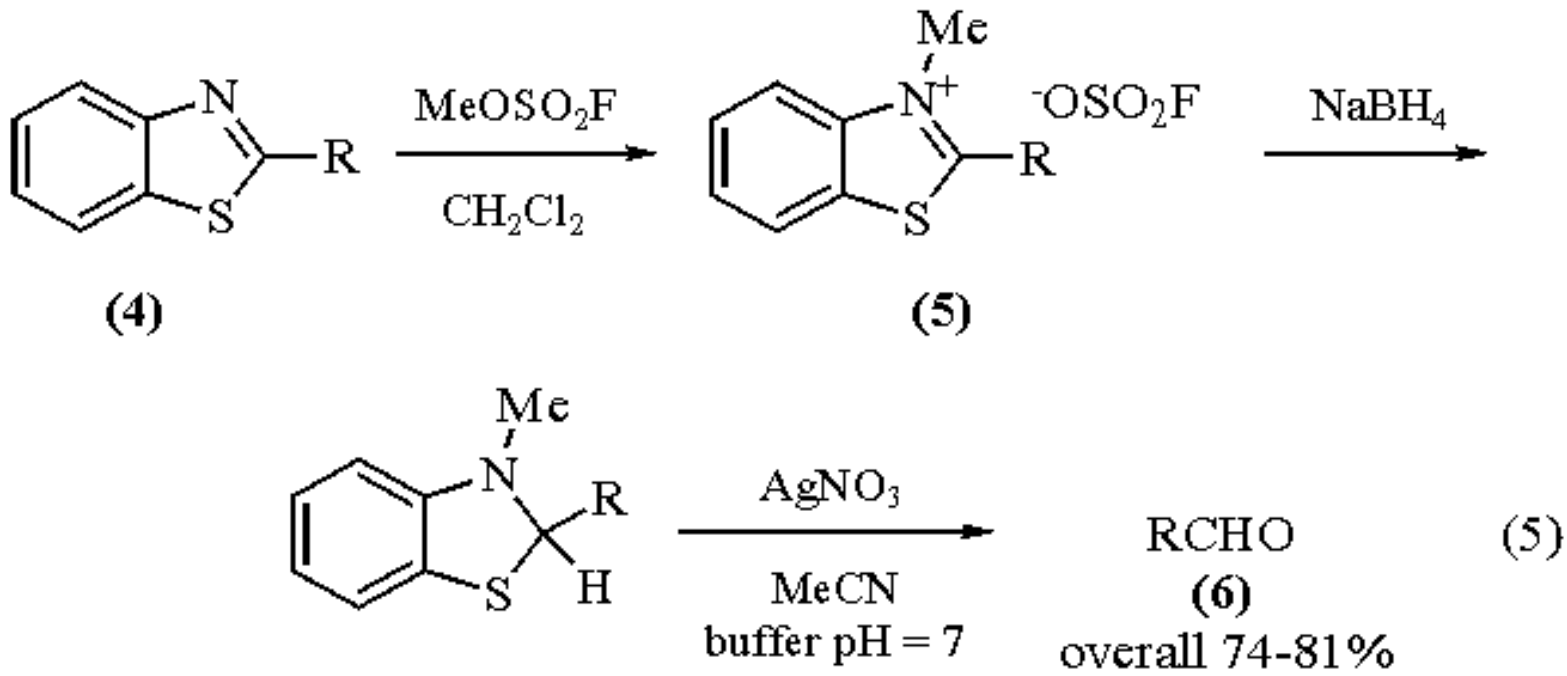

The *N*-methylbenzothiazolium salts (**5**) also react with organometallic reagents to give 2,2-disubstituted *N*-methylbenzothiazolines which after hydrolysis afford the corresponding ketones (**7**) (eq 6).[2,4]

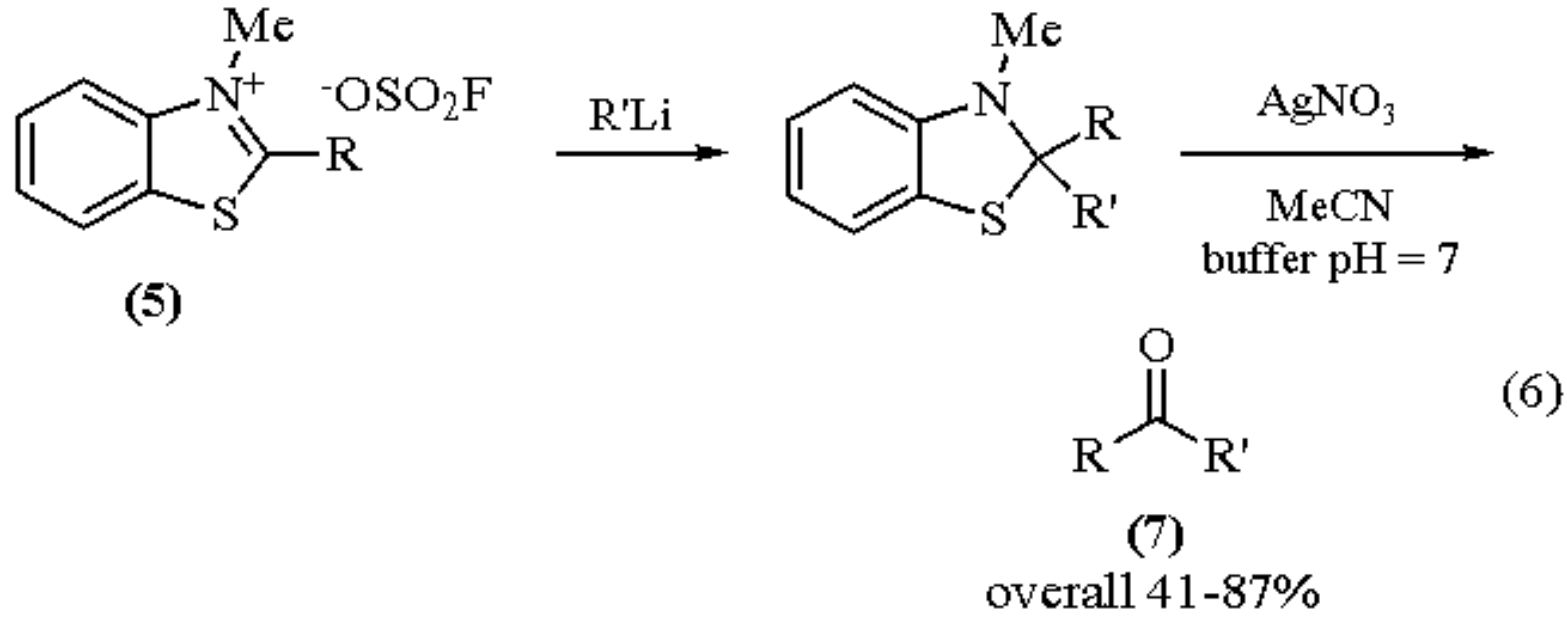

Corey and Boger have utilized this homologating methodology to devise new carbon-carbon bond-forming reactions[8]

and annulation processes for fused and spiro rings.[9] Another application of benzothiazole chemistry involves the use of the heterocyclic ring as a leaving group. The synthesis of carboxylic acid derivatives via the *N*-methylbenzothiazolium salts (**8**) and (**9**), as outlined in eq 7, takes advantage of this property.[4b]

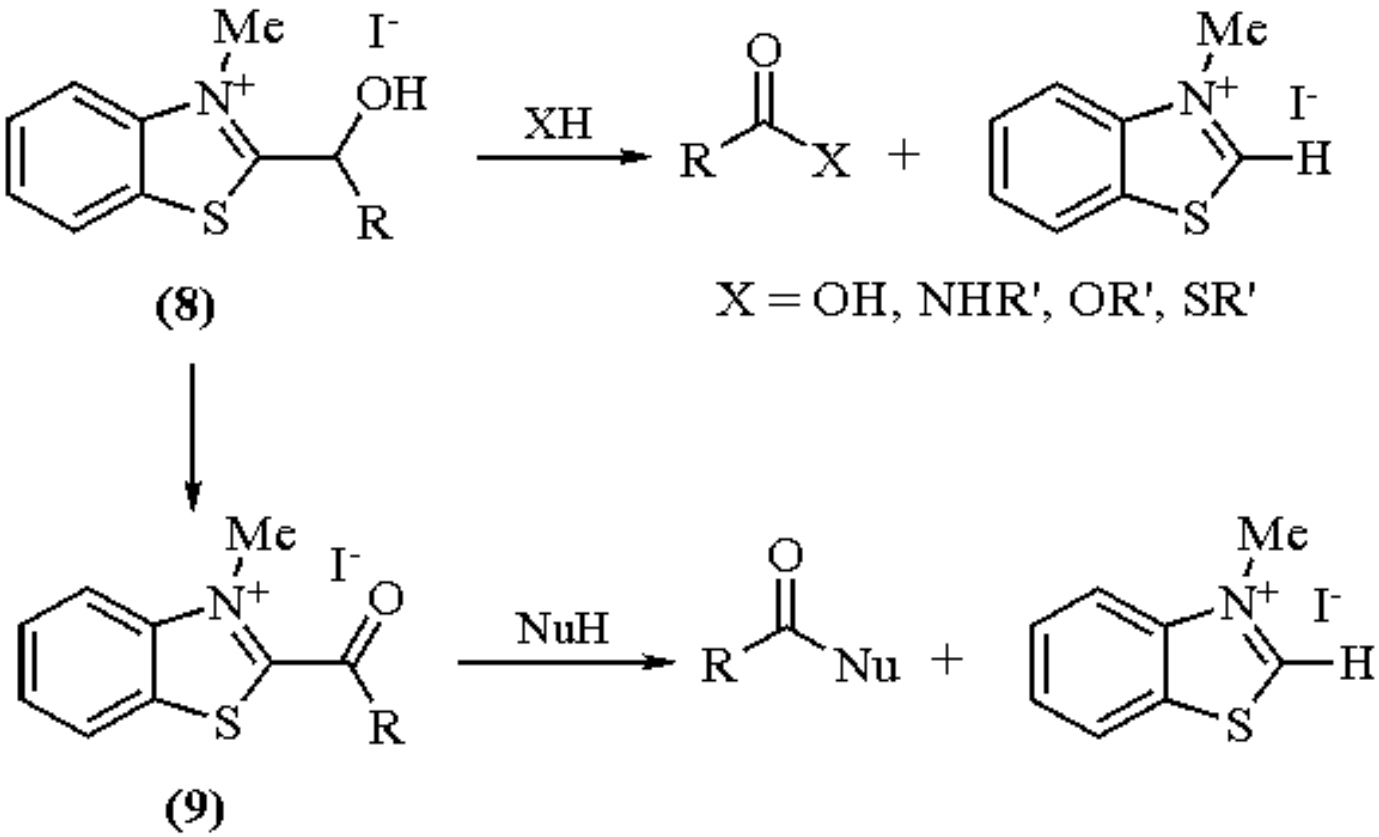

(7)

2-(Trimethylsilyl)benzothiazole.

This reagent can be prepared in high yield by addition of ***Chlorotrimethylsilane*** to 2-lithiobenzothiazole (**2**) at -78 °C with subsequent gradual warming to room temperature over a 4-5 h period (eq 8).[10]

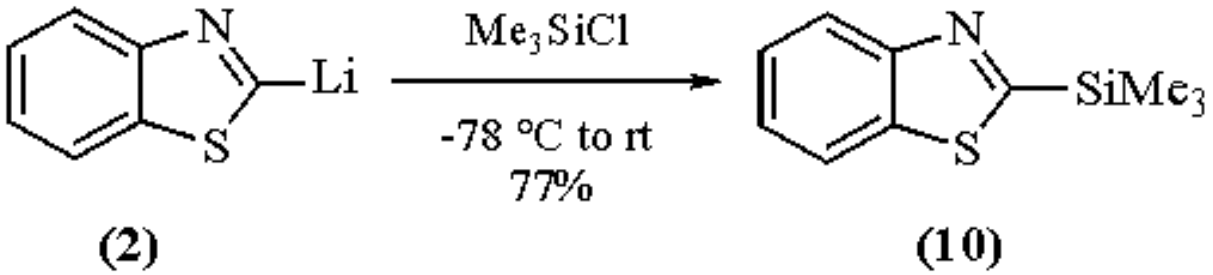

(8)

2-(Trimethylsilyl)benzothiazole (**10**) reacts with several electrophiles such as acid derivatives and carbonyl compounds in the absence[3a,10] (eq 9) or in the presence of ***Potassium t-Butoxide*** as catalyst[3b] (eq 10).

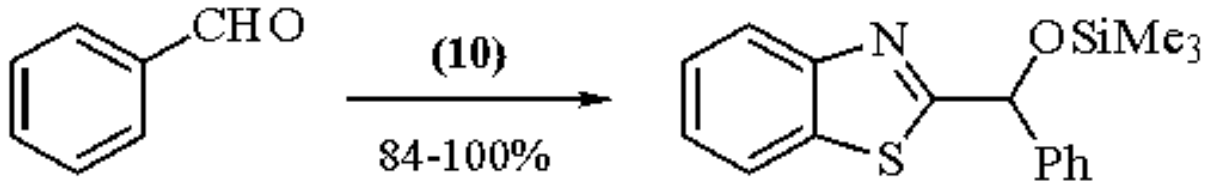

(9)

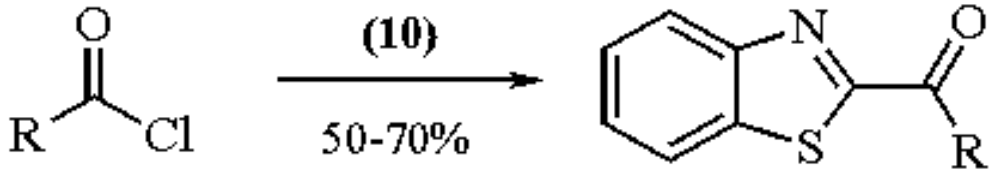

(10)

Only one addition of 2-(trimethylsilyl)benzothiazole (**10**) to a chiral aldehyde has been reported[3c] and significant diastereoselection was observed, in contrast to 2-lithiobenzothiazole (**2**) which showed a complete lack of stereoselectivity in the reaction with the same aldehyde (**11**) (eq 11).

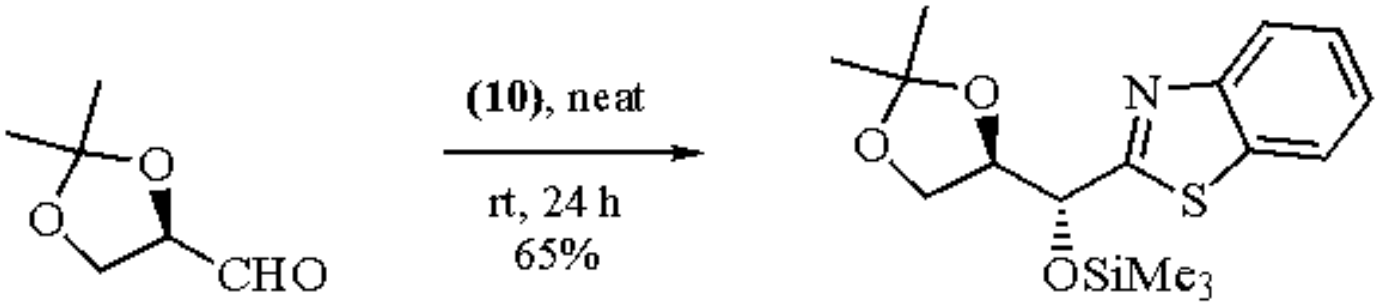

(11)

(11) ds = 80%

Since benzothiazole has been shown to be a formyl anion equivalent,[11] this reaction could represent a stereoselective homologation process. However, for this purpose ***2-(Trimethylsilyl)thiazole*** is a more convenient synthetic equivalent since higher stereoselectivity is obtained with this reagent, and the aldehyde release is easier with thiazole than benzothiazole.

2-(Trimethylsilyl)benzothiazole (**10**) has been also used in the synthesis of heteroaromatic phosphines[12] and mesomeric betaines.[13]

---

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1-Benzotriazolyl Diethyl Phosphate

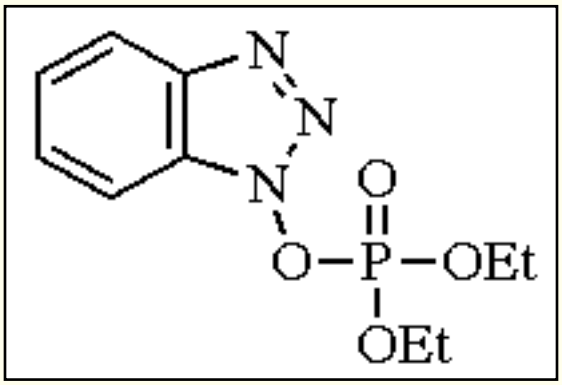

[96338-11-3] · $C_{10}H_{14}N_3O_4P$ · 1-Benzotriazolyl Diethyl Phosphate · (MW 271.21)

(coupling reagent for amides and peptide synthesis[1,2])

Alternate Name: BDP.

Solubility: sol MeCN, DMF, EtOAc, CH_2Cl_2, THF.

Form Supplied in: oil; not available from commercial sources.

Preparative Method: by reaction of diethyl chlorophosphate (1 equiv) and 1-hydroxybenzotriazole (1 equiv) in the presence of triethylamine (1 equiv) in dry THF at 0 °C for 30 min, with 90-95% yields.

Purification: by filtration through a short column of silica gel or cellulose.

Handling, Storage, and Precautions: the oil can be stored in a desiccator with drierite at 4 °C for several weeks without decomposition. Distillation in vacuo leads to decomposition.

1-Benzotriazolyl diethyl phosphate (BDP) has been used as a condensing reagent for the preparation of amides. Typically, equimolar amounts of carboxylic acids, amines, and 1-benzotriazolyl diethyl phosphate, in the presence of triethylamine (2.1 equiv) in a broad range of solvents (the relative coupling efficiency is DMF > MeCN = THF > CH_2Cl_2) react rapidly and cleanly with coupling times in the range of 10-60 min at 25 °C, yielding the corresponding amides in > 90% yields (eq 1).

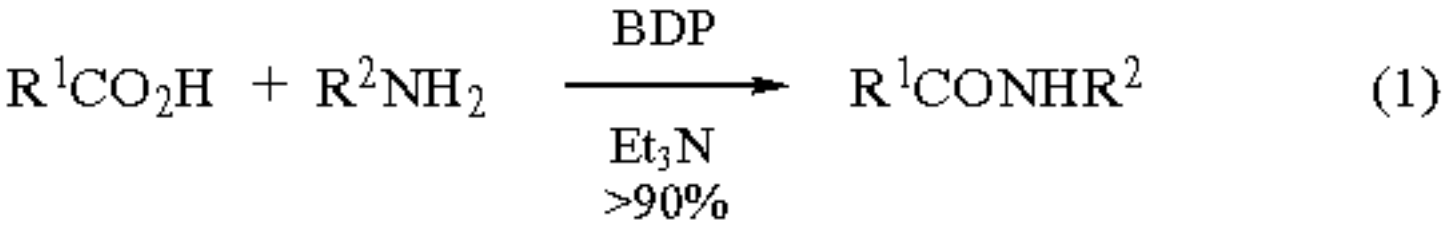

1-Benzotriazolyl diethyl phosphate is also suitable for hindered carboxylic acids and amines, as well as poorly nucleophilic amines. Thus *N*-cyclohexylbenzamide is obtained from benzoic acid and cyclohexylamine with the addition of 1-benzotriazolyl diethyl phosphate, whereas the use of ***1,3-Dicyclohexylcarbodiimide*** did not yield any trace of the target product. Benzoic acid is readily converted to the corresponding amides by the reaction with 1-benzotriazolyl diethyl phosphate and benzylamine or aniline. Similarly, reaction of acetic acid with sterically hindered *t*-butylamine yielded the corresponding acetamide. Finally, crotonic acid is cleanly converted to the corresponding amides without 1,4-addition side-products.

Additionally, 1-benzotriazolyl diethyl phosphate has been used for the preparation, in solution, of dipeptides and tripeptides. The reaction is carried out as described above with *N*-protected amino acids or dipeptides, and amino acid ester hydrochlorides, in DMF for 4 h, at 25 °C, with a yield superior to 75%. Racemization from 1-benzotriazolyl diethyl phosphate mediated couplings is checked by different methods. Young[3] and Anderson[4] tests gave low degree (<4%) of racemization when DMF is used as a solvent. Other solvents such as THF, EtOAc, and CH_2Cl_2 gave more racemization. Furthermore, the Shiori[5] test gave a higher degree of racemization even in DMF (18%). A related analog, 1-benzotriazolyl diphenyl phosphate, led to 39% of racemization, indicating that the degree of racemization is also dependent on the nature of organophosphate.

1-Benzotriazolyl diethyl phosphate has not been used in solid-phase peptide synthesis,[6] although other commercial triazole derivatives such as ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (BOP)[7] or ***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate*** (HBTU)[8] are commonly used in that strategy.

---

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Fernando Albericio & Steven A. Kates

Millipore Corporation, Bedford, MA, USA

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Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate[1]

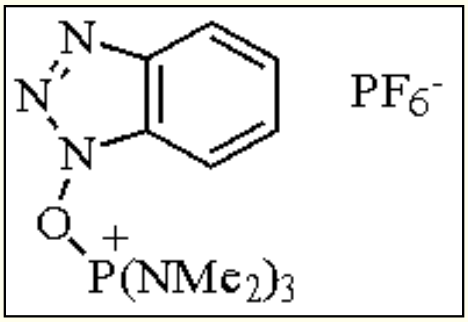

[566002-33-6] · $C_{12}H_{22}F_6N_6OP_2$ · Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate · (MW 442.29)

(peptide coupling agent providing high yield and low racemization levels;[1] promotes peptide cyclization[19] and other lactamization,[23] especially β-lactam formation;[24] used to effect various amidification reactions[25-29] and selective esterification;[31] reagent for nucleotidic coupling[32])

Alternate Names: BOP; Castro's reagent.

Physical Data: mp 138 °C (dec.).

Solubility: insol H_2O; sol THF, CH_2Cl_2, MeCN, acetone, DMF, NMP, DMSO.

Form Supplied in: white solid; commercially available. Purity 97-98%.

Analysis of Reagent Purity: ^{1}H NMR (acetone-d_6): 3.0 (d, 18H, J_{H-P} = 10 Hz, NMe_2), 7.9 (m, 4H, arom.). ^{31}P NMR (CH_2Cl_2): +43.7 (s, P^+), -144.2 (septet, PF_6^-). IR (KBr): 1010 (P-N), 840, 770, 560 (PF_6^-).

Preparative Methods: BOP reagent was initially obtained[2a] by reaction of ***Hexamethylphosphorous Triamide*** (tris(dimethylamino)phosphine, TDAP) with CCl_4 in the presence of HOBt (***1-Hydroxybenzotriazole***) followed by precipitation of the phosphonium salt by anion exchange with aqueous KPF_6 solution. It was then prepared[2b,c] by reaction of cheaper $(Me_2N)_3PO$ (HMPA) with $COCl_2$ (phosgene) to generate the chlorophosphonium chloride intermediate, with treatment of the latter with HOBt and base, and precipitation as below. $COCl_2$ was further replaced by $POCl_3$.[2d,e] The crude final product can, if necessary, be purified by recrystallization from a mixture of acetone-ether or CH_2Cl_2 (DCM)-ether.

Handling, Storage, and Precautions: irritant and harmful. Light sensitive. Incompatibility: strong oxidizing

agents. Avoid breathing dust; avoid contact with eyes, skin, and clothing. Keep container closed and store in the dark. Refrigerate. Although BOP is widely used, it is important to stress that the carcinogenic HMPA is a side product and the reagent must be handled with caution. All operations should be carried out in a fume hood.

Peptide Coupling Reagent.

First prepared with the aim to associate both the coupling agent (phosphonium salt as dehydrating agent) and the racemization suppressor (HOBt additive) in the same compound, the BOP reagent has since then been widely developed, mainly in peptide synthesis, as well as in other fields. Mechanistic studies on the probable intermediates (acyloxyphosphonium salt, active ester, symmetrical anhydride, oxazolone, eq 1) during the activation step of carboxylic acids with BOP have been made. Early investigations indicating the intermediacy of a benzotriazolyl active ester,[1a,2b,3] as in activation with the DCC/HOBt (see ***1,3-Dicyclohexylcarbodiimide***) reagent system, were later questioned[1c] in the light of better results obtained with BOP in a number of cases. After further studies, the direct formation of the acyloxyphosphonium salt, presumably through the cyclic complex (eq 1), was postulated as likely.[1c]

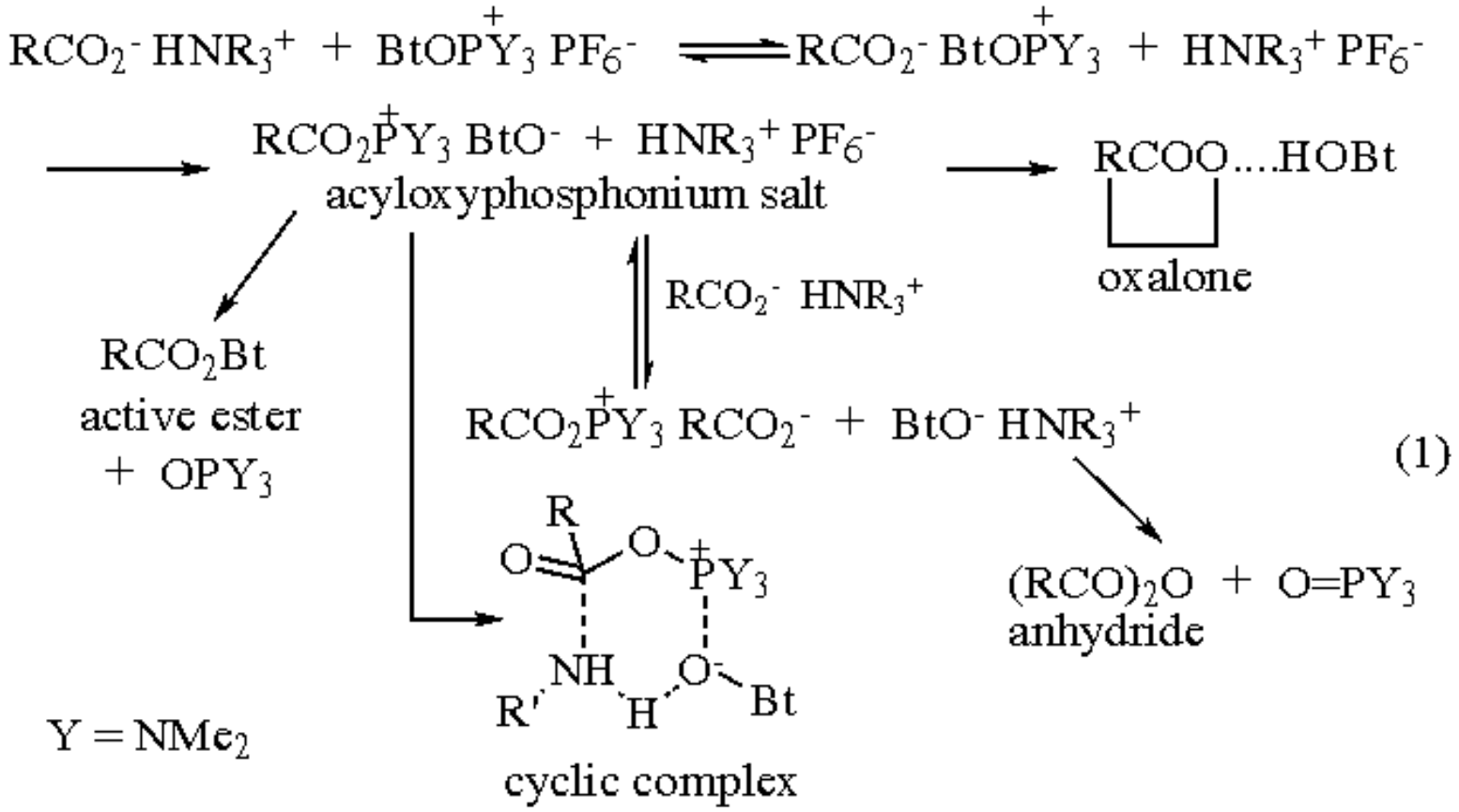

Unoptimized initial work in peptide coupling with BOP had already shown high yields and short reaction times, even with bulky amino acids (eq 2) and little if no side reactions with some sensitive amino acids bearing unprotected side chain functional groups.[2]

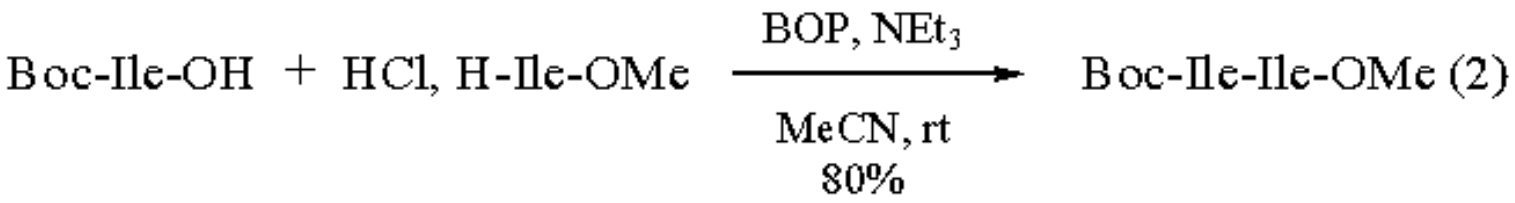

Unlike DCC, BOP reacts exclusively with carboxylate salts, with carboxylic acids remaining unchanged. The trifluoroacetate anion is not activated by BOP; therefore the trifluoroacetylation side reaction is never encountered.

In usual peptide synthesis (e.g. with the Boc/TFA deprotection strategy), a typical coupling step is conducted as follows: BOP is added to the mixture of the Boc-amino acid (or peptide acid segment) and the C-terminal-protected peptide salt (generally the TFA salt). The solvent can be THF, DCM, MeCN, DMF, or NMP, according to the solubility of the reaction partners, but using as high a concentration as possible. No reaction occurs until the tertiary base, *N*-methylmorpholine, ***Triethylamine***, or preferably ***Diisopropylethylamine*** (DIEA), is added. In every case the reaction mixture has to be kept rather basic in order to ensure a fast coupling. Three equiv of base are necessary to neutralize the carboxylic acid, the amine salt, and the acidic HOBt. In such conditions the coupling rate is so high that racemization is negligible in urethane-protected amino acid coupling and fairly low, albeit not negligible, in segment coupling (see eq 3).[4] The excess of acid and BOP is typically 1.1 mol equiv in solution synthesis.

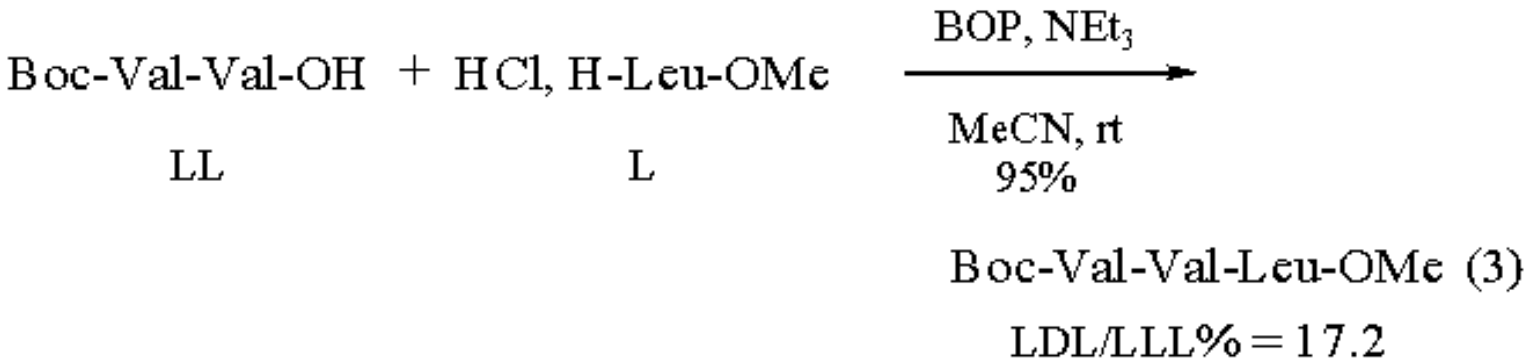

Racemization in segment coupling has been studied with realistic models[4a] in solution; it appears to be very small when nonhindered amino acids (Ala, Leu, Lys…) are activated, but coupling of segments terminated with bulky residues (Val, Ile, Thr…) are to be avoided (eq 3).[4b]

Segment condensation with BOP is generally peculiarly fast compared with conventional use of the classical DCC/HOBt method, as a few hours are enough to achieve coupling of equimolar quantities of both partners, provided the highest concentration is used (eq 4).[5]

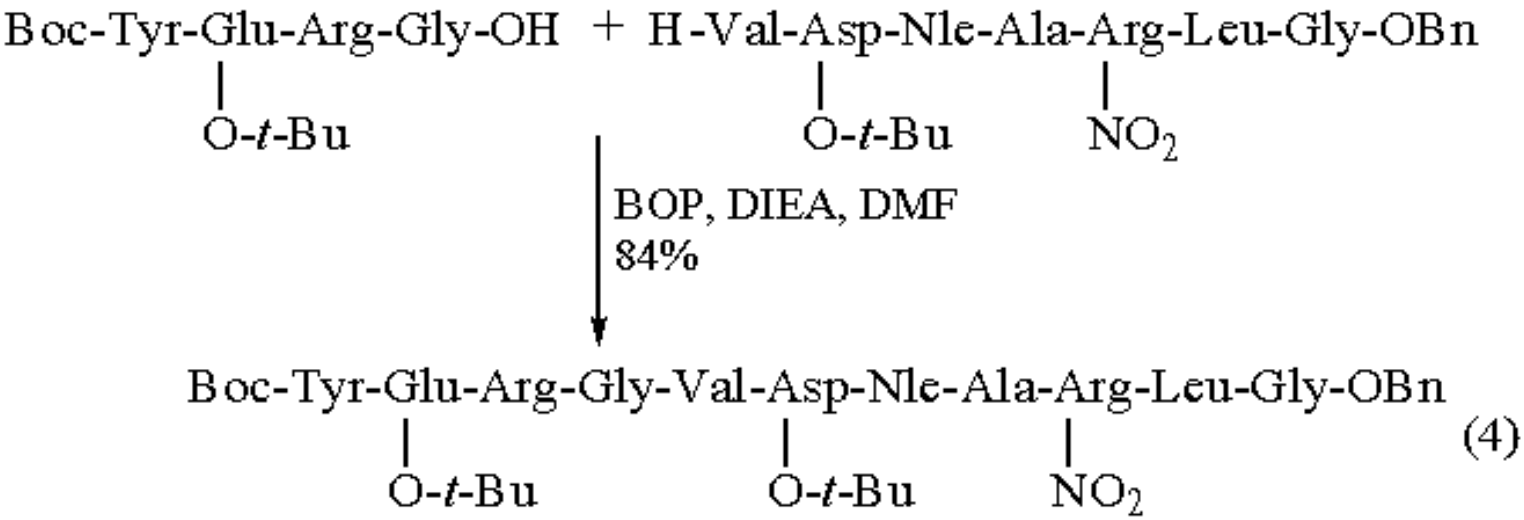

It is very characteristic that this procedure allows the skipping of a separate neutralization step, either in solution or in SPPS (solid phase peptide synthesis) using the Boc/TFA strategy. This is not only time-saving but also useful to minimize diketopiperazine formation during the third step of a synthesis.

The coupling reaction of Boc-Ile-OH with H-His-Pro-OMe . TFA is generally a very low yield reaction as the neutralization of the dipeptide salt is very readily followed by cyclization to cyclo(His-Pro) (eq 5). Using the BOP procedure allows the efficient in situ trapping of the dipeptide amine by the acylating reagent. This feature also makes strategies of segment coupling at a proline residue possible, which are very often restricted by the necessity of using prolyl *t*-butyl esters in order to avoid the cyclization reaction.

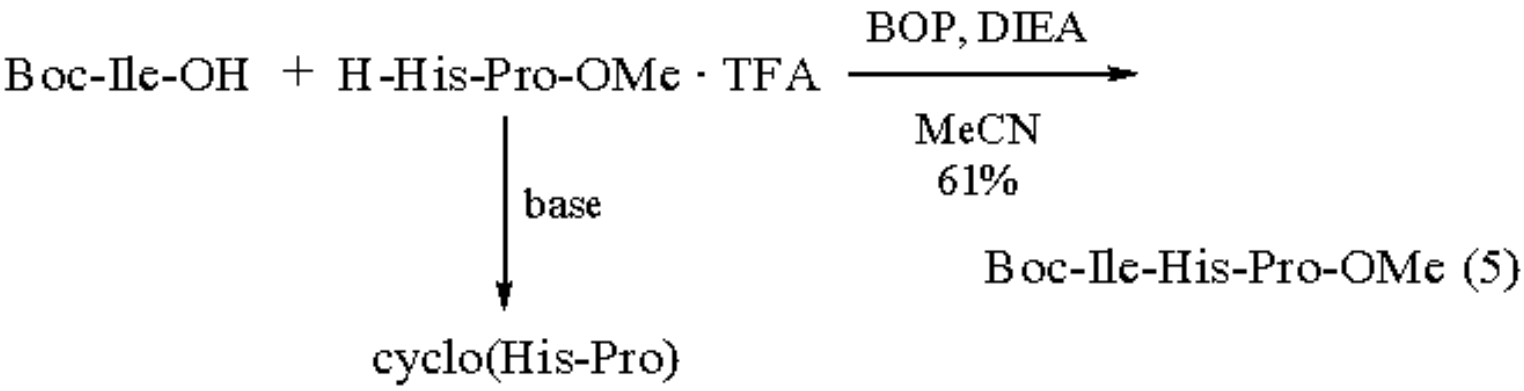

This specific ability of BOP for avoiding diketopiperazine formation is illustrated in liquid phase synthesis[5a] as well as in the SPPS.[5c,d,6,7b]

Another facility offered by BOP is the possibility to couple DCHA salts, due to the high rate ratio of amino acid coupling towards dicyclohexylamine (DCHA). This feature is especially useful in SPPS where the small amount of dicyclohexylamide formed is easily washed out. The main application of that procedure lies in the introduction of histidine as the cheap and easily acessible Boc-His(Boc)-OH both in liquid (eq 6)[5a] and solid[7b-d] phase synthesis.

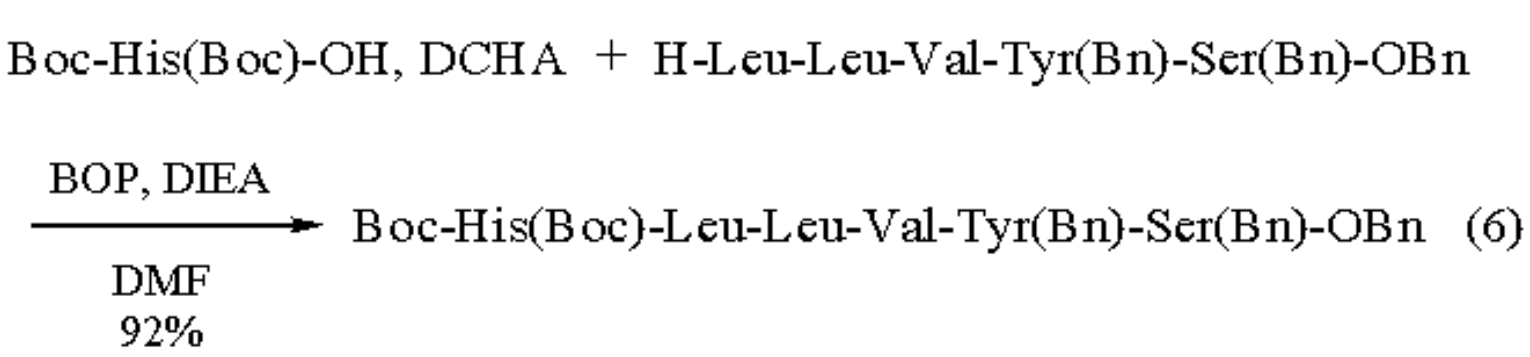

Many peptides have been synthesized in solution,[5a,b,8] stepwise or by segment coupling, using BOP as coupling agent.

In solid phase synthesis, BOP exhibits some distinct advantages, including the suppression of a separate neutralization step previously mentioned; indeed, after TFA treatment and washing, it is convenient to introduce the next Boc-amino acid and BOP as solids, with a minimal volume of solvent and, at last, DIEA. Coupling is generally completed after 15-30 min, with the pH maintained at 8 with excess of acylating reagents (1.5-3M). Finally, the water- and DCM-soluble byproducts, HMPA and HOBt, allow very easy washing of the reaction product, in contrast to DCC condensation where elimination of insoluble urea often remains a problem.

The use of BOP in SPPS, initially limited,[7] has since been widely developed, with Boc/TFA,[9,10] Boc/HF,[11] and mainly Fmoc/piperidine[12-15] deprotection systems. In most cases it compares favorably with other reagents such as DCC, DCC/HOBt, and symmetrical anhydride. As already observed in the liquid phase, some amino acids with side chain functional groups such as Tyr, Thr, Ser (hydroxy group),[2a,9b] or poorly soluble pGlu (γ-lactam)[7d,9c] can be used without protecting groups; other functional groups such as $CONH_2$ (Asn) can lead in some cases to partial dehydration (e.g. β-cyanoalanine)[11,14b,c] or cyclization (succinimide)[9a,30] and need to be protected; such classical dehydration reactions, not observed by others,[1a,2a,b] are sometimes dependent on reactions conditions (e.g. repeated coupling cycles) and must be carefully examined.

Peptide Cyclization.

Various results were provided[16-20] in peptide chain cyclization with BOP, arising either from the reaction conditions or from the ring size, and from the linear precursor conformation.

Better yields and purities are obtained[16] with less powerful coupling agents such as DPPA (***Diphenyl Phosphorazidate***) and NDPP (norborn-5-ene-2,3-dicarboxamidodiphenyl phosphate) in cyclization of tetra- and pentapeptide sequences, despite the need for longer reaction times than with BOP or HBTU (***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate***; 1,1,3,3-tetramethyluronium analog of BOP).

Comparable yields are given for Boc-γ-D-Glu-Tyr-Nle-D-Lys-Trp-OMe cyclizations[17] with BOP ($NaHCO_3$, 4 h, 76%) and MTPA (dimethylphosphinothioyl azide, NEt_3, 36 h, 79%), albeit in different reaction conditions; in this work the reported racemization associated with the use of BOP is not shown.

Cyclization, leading to Gly/Lys-containing peptide macrocycles,[18] has been investigated with a number of coupling reagents. Among them DEPC (***Diethyl Phosphorocyanidate***), DPPA, and BOP are the most effective ones, giving near-quantitative yields.

Macro ring closure of a partly proteinogenic sequence in the synthesis[19] of the cyclodepsipeptide Nordidemnin B was

carried out using BOP in heterogeneous conditions (eq 7).

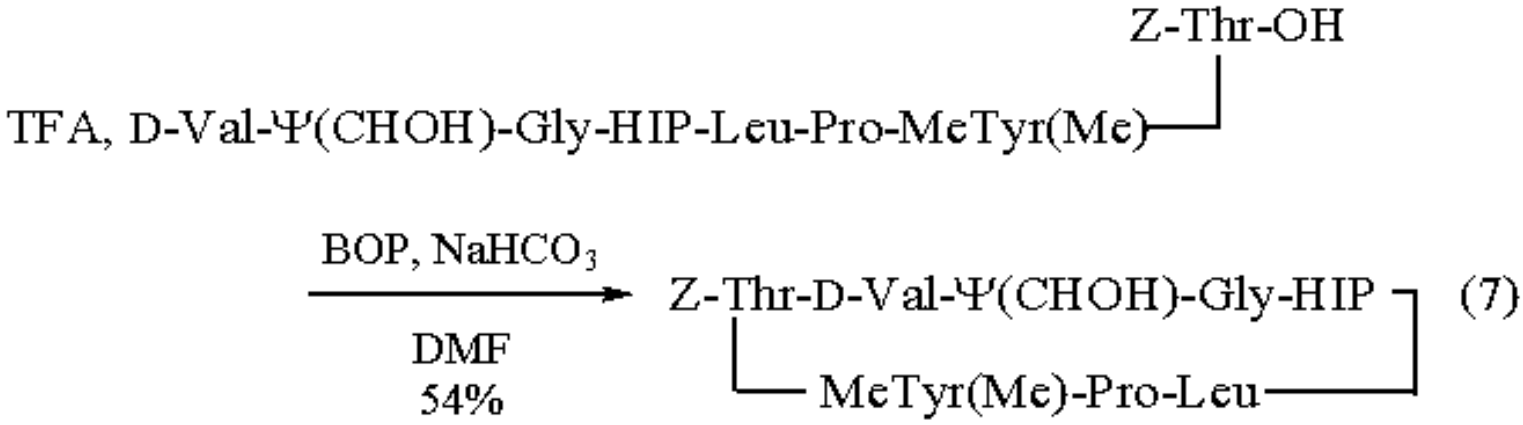

In SPPS, side chain to side chain cyclization by the BOP procedure not only proceeds more rapidly, but also gives a purer cyclic product than the DCC/HOBt procedure.[20]

The use of BOP has been reported in the final cyclization of cyclosporin,[21b] even if some racemization is observed. The very difficult coupling of *N*-methyl amino acids is achieved in the same work,[21] as in the preceding syntheses.[19] For the coupling of hindered *N*-methyl[22a] and α,α-dialkyl[22b] amino acids, new reagents[22] such as PyBroP, PyCloP, or PyClU seem to be more promising.

Besides the peptide field, cyclization leading to macrocyclic polyether tetralactams (crown ethers) have been carried out with BOP.[23]

β-Lactam Cyclization.

Cyclization of β-amino acids to β-lactams is efficiently effected by treatment with BOP (eq 8).[24a] The present method appears to be limited to the formation of β-lactams from *N*-unsubstituted β-amino acids ($R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$, yield 10%).

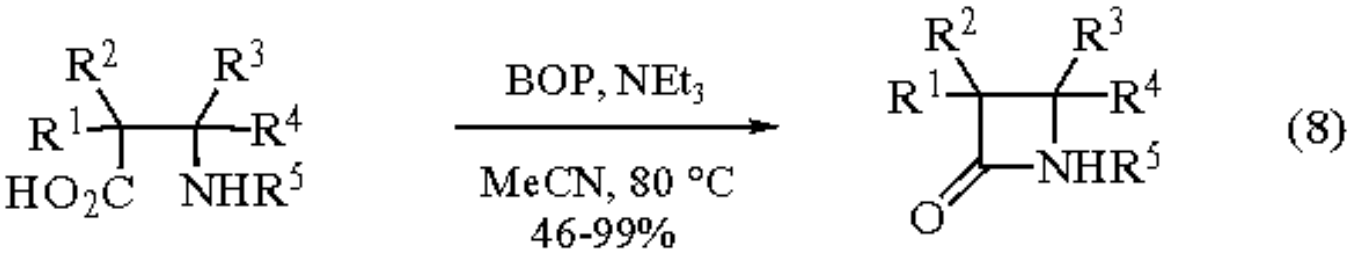

$R^1 = H, Me;\ R^2 = H, OPh;\ R^3 = H, Me, Ph;$
$R^4 = H, Me, n\text{-}Pr;\ R^5 = CH_2Ph,\ c\text{-}C_6H_{11},\ n\text{-}C_8H_{17}$

In the cephem series, cyclization yields of 80% are obtained with BOP, in DCM at rt, with retention of the initial chirality.[24b]

Amidation.

A number of other various amidation reactions have been conducted using BOP. Such preparations include *N*,*O*-dimethyl hydroxamates of amino acids[25a] and peptides[25b] (precursors of chiral peptidyl aldehydes), heterocyclic amide fragments in the synthesis of macrolide[26] and porphyrin models,[27] dansylglycine anhydride as a mixed sulfonic-carboxylic imide by dehydration-cyclization of dansylglycine,[28] and selective monoacylation of heterocyclic diamine in carbohydrate series (eq 9).[29]

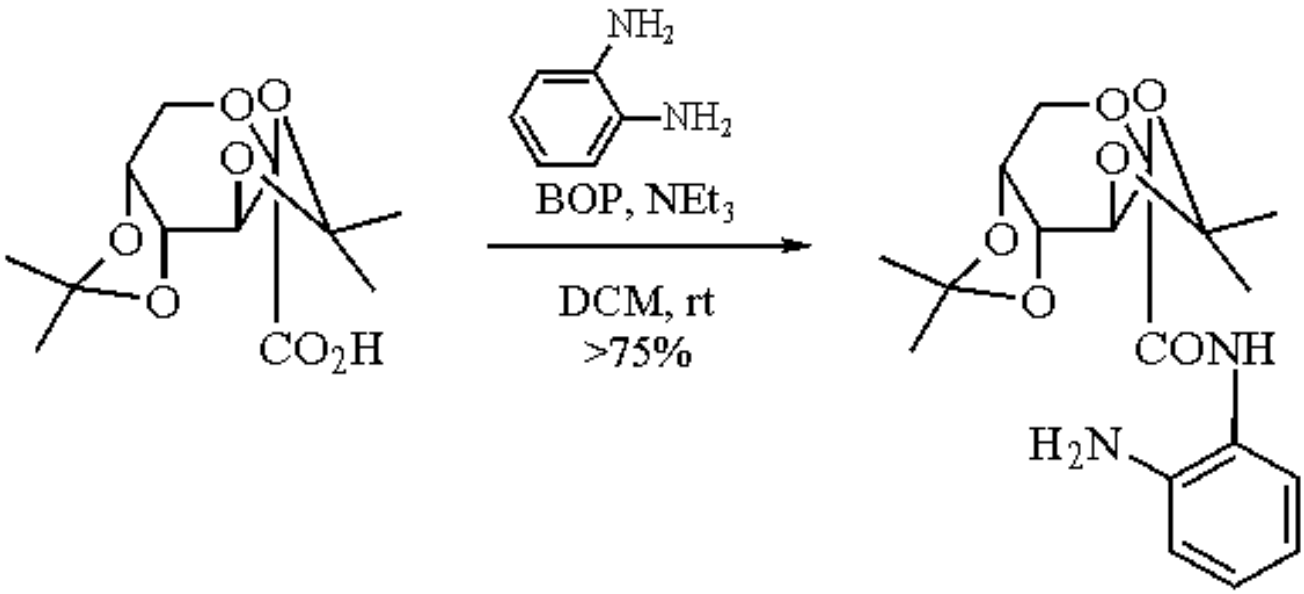

(9)

Esterification.

Treatment of N-protected amino acids with phenol, NEt_3, and BOP in the appropriate solvent (DCM, MeCN, DMF) affords the corresponding phenyl esters in good yield (eq 10).[30]

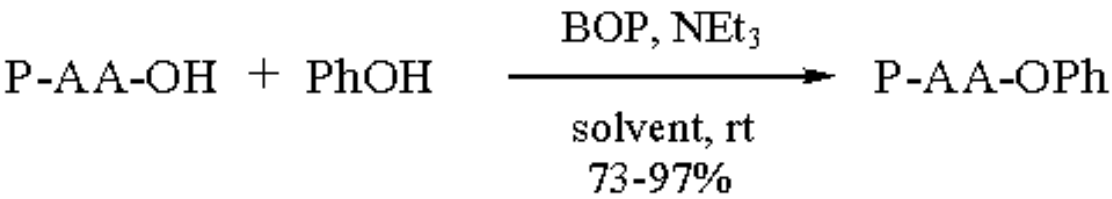

(10)

P = Boc, Z; AA = Ala, Ile, Phe, Trp, Pro, Ser, Met, Cys(SBn), Lys(εZ)

BOP in combination with ***Imidazole*** (ImH) as catalyst provides a very mild system for selective esterification of polyhydroxy compounds such as carbohydrates; thus trehalose is converted into mono-, di-, and tripalmitate mixtures, with the various quantities of each of them depending on the solvent and acid/alcohol ratio. Monoacylated compounds can be obtained selectively, albeit in moderate yield (31%).[31]

Nucleotidic Coupling and Related Reactions.

BOP has been used as a condensing agent to promote internucleotidic bond formation in phosphotriester

oligodeoxyribonucleotide synthesis.[32] ^{31}P NMR studies[32a] show that a benzotriazolyl phosphate derivative is involved as an active ester intermediate, as with carboxylic acids.[3]

The BOP procedure was applied to the preparation of undecanucleoside decaphosphate.[32b] The same type of activation with BOP is carried out for introducing a phosphonamide bond in dipeptide models[33] with good efficiency (&egt;60%); coupling reactions by activation of phosphinic acid derivatives[34] with BOP give poor yields.

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O-Benzotriazol-1-yl-*N,N,N´,N´*-tetramethyluronium Hexafluorophosphate

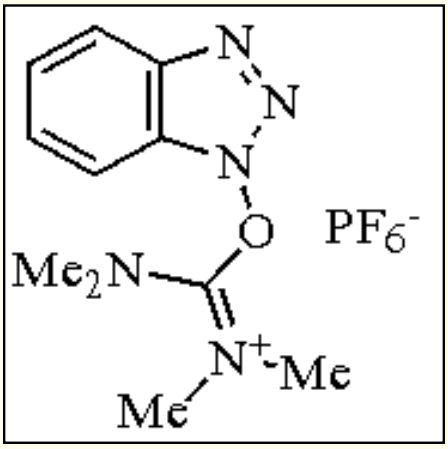

[94790-37-1] · $C_{11}H_{16}F_6N_5OP$ · *O*-Benzotriazol-1-yl-*N,N,N´,N´*-tetramethyluronium Hexafluorophosphate · (MW 379.29)

(coupling reagent for peptide synthesis[1])

Alternate Name: HBTU.

Physical Data: mp 206-207 °C (dec).

Solubility: sol DMF (0.5 mol L^{-1}). With the tetrafluoroborate counterion the corresponding salt (TBTU) is slightly more soluble (0.6 mol L^{-1}).

Form Supplied in: white solid; widely available.

Purification: by crystallization in a mixture of MeCN and CH_2Cl_2.

Handling, Storage, and Precautions: very stable, not hygroscopic, and can be stored indefinitely. Solutions in DMF (0.45 M) can be stored in an inert atmosphere for weeks. Syntheses of peptides carried out with freshly prepared, 6 and 13 week stored solutions show similar quality of the crude product.[3] Violent decomposition can occur when dried at elevated temperature.[4]

Both *O*-benzotriazol-1-yl-*N,N,N´,N´*-tetramethyluronium hexafluorophosphate (HBTU) and tetrafluoroborate (TBTU) salts have been used as condensing reagents for the preparation of peptides in both solution and solid-phase strategies.[1,4] In solution, reaction of α-amino protected amino acids or dipeptides with equimolar amounts of α-

carboxyl protected amino acids or dipeptides and ***Diisopropylethylamine*** (DIEA) (2 equiv) in DMF proceeds cleanly for 15 min at 0 °C, yielding the corresponding peptides in good yields (80-96%) (eq 1).[1,4]

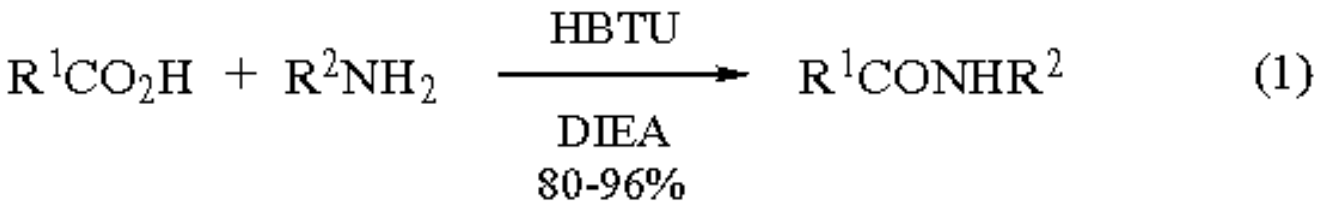

HBTU activation has been adapted for automated stepwise solid-phase peptide synthesis for both *t*-butoxycarbonyl (Boc) and fluorenylmethoxycarbonyl (Fmoc) strategies.[5] For the former, a simple, effective protocol has been developed, which involves simultaneous in situ neutralization with coupling (extra equivalents of base are required). This protocol is particularly suitable for assembling complex peptides, arising from sequence-dependent peptide chain aggregation. Since aggregation occurs when protonated α-ammonium peptide-resin intermediates are neutralized, simultaneous neutralization and acylation can help to overcome this phenomenon.[6] For Fmoc chemistry, efficient protocols are also available for both batch and continuous-flow systems.[3,7]

Various protected peptide segments have been coupled on solid-phase using a combination of TBTU, HOBt, and DIEA for the syntheses of several small proteins. Coupling yields, using threefold excess of peptide segment and coupling times of ~12 h, are greater than 95%.[8]

Racemization from uronium salt mediated couplings has been determined by analysis of the epimeric products by HPLC using different models. In all cases, racemization is similar or lower than that obtained with carbodiimide and benzotriazole based phosphonium salt methods.[1,2,4,9]

In the absence of the carboxylic component, HBTU reacts with amino groups leading to the formation of a Schiff base (eq 2).[10] Thus in syntheses conducted in solution, the excess of both HBTU and amino component should be avoided. In both solution and solid-phase strategies the sequence of reagent addition is critical. HBTU should be delivered to the carboxylic component for preactivation, prior to the addition of the amine. The Schiff base formation can also occur during slow reactions, such as the preparation of cyclic peptides, where both amino and carboxylic components are in equimolar amounts and an excess of the uronium salt can block the amino group.[11] For the synthesis of cyclic peptides the phosphonium derivatives ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (BOP)[12] and benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP),[13] can be more useful.

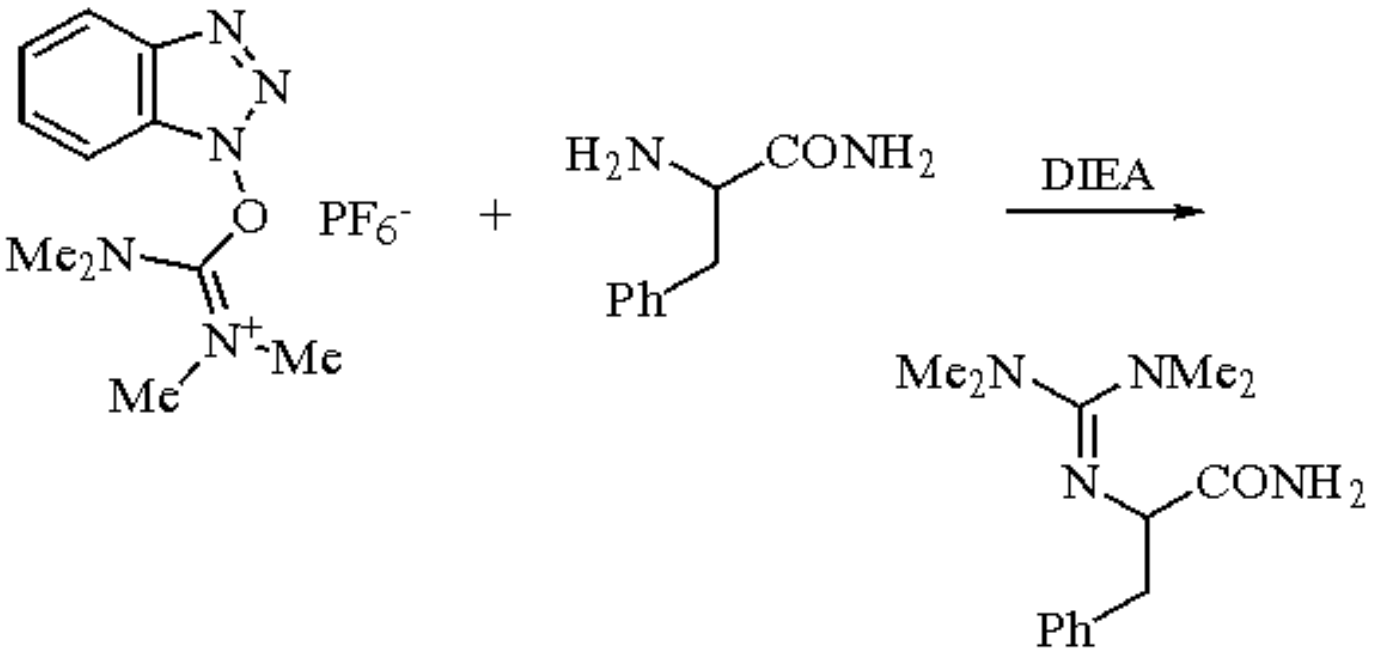

(2)

Uronium salts have been used for cyclization of linear peptides in both solution and solid-phase modes. Since this reaction is sequence dependent, there are no general conditions. Thus cyclization in solution with uronium salt methods give, for some peptides, better results than the classical reagent ***Diphenyl Phosphorazidate*** (DPPA),[14] but for another case the converse is true.[15] Furthermore, dehydration of *C*-terminal aspartylamide peptides during cyclization with HBTU has been described. This side-reaction can be prevented by the addition of one equivalent of HOBt.[16] Although good results have been obtained in the solid-phase,[17] guanidino formation side-reactions have also been reported.[11]

Recently, other uronium salts, such as *O*-(*N*-succinimidyl)-*N*,*N*,*N´*,*N´*-tetramethyluronium tetrafluoroborate (TSTU),[4,18] *O*-(*N*-5-norbornene-*endo*-2,3-dicarboximidyl)-*N*,*N*,*N´*,*N´*-tetramethyluronium tetrafluoroborate (TNTU),[4,18] *O*-(2-oxo-1(2*H*)-pyridyl)-*N*,*N*,*N´*,*N´*-bis(pentamethylene)uronium tetrafluoroborate (TOPPipU),[19] ***N-[(Dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium Hexafluorophosphate N-Oxide*** (HATU),[20] and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N´*,*N´*-bis(tetramethylene)uronium hexafluorophosphate (HAPyU)[21] have been described and are commerically available. The uronium salts derived from 7-aza-1-hydroxybenzotriazole (HATU and HAPyU) have been shown to be superior to their benzotriazole analogs in terms of coupling efficiency,[20,21] racemization,[22] and cyclization,[23] in both solution and solid-phase strategies.

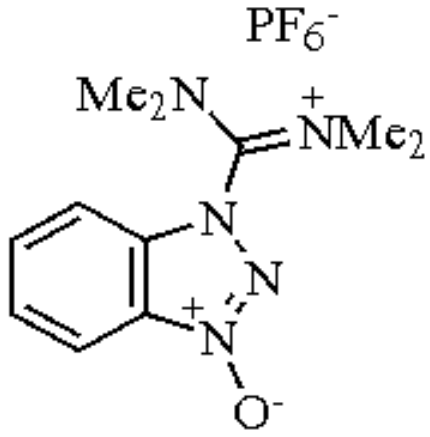

(3)

Finally, an X-ray structure determination of HBTU revealed that the solid-state structure differs considerably from the formulation commonly presented in the literature. The solid-state structure is not the *N,N,N´,N´*-tetramethyluronium salt but rather the guanidinium *N*-oxide (**3**).[24]

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Fernando Albericio & Steven A. Kates

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1-Benzoyl-2-*t*-butyl-3,5-dimethyl-4-imidazolidinone[1]

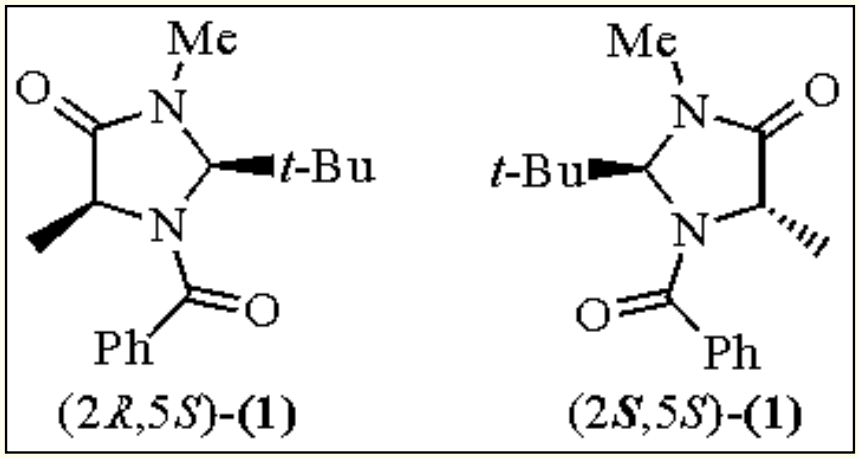

(2*R*,5*S*)

[97443-91-9] · $C_{16}H_{22}N_2O_2$ · 1-Benzoyl-2-*t*-butyl-3,5-dimethyl-4-imidazolidinone · (MW 274.36) (2*S*,5*S*)

[97443-88-4]

(imidazolidinones for generating the enantiomeric enolates derived from alanine;[2,3] reagents for the preparation of α-methylated amino acids through enolate alkylation, benzylation, and nitroalkene addition[3-5])

Physical Data: (2*R*,5*S*)-(**1**): mp 125 °C; [α]rtD = -47.7° (*c* = 1.04, $CHCl_3$); (2*S*,5*S*)-(**1**): mp 175 °C; [α]rtD = +44.5° (*c* = 1.0, $CHCl_3$).

Solubility: sol THF.

Preparative Method: the imine from (*S*)-alanine *N*-methylamide and pivalaldehyde is cyclized by heating with benzoic anhydride to give mainly *cis*-(**1**) [(2*R*,5*S*)-(**1**)] in modest yields; alternatively, the imine cyclizes to the *trans*-substituted heterocycle by treatment with HCl in MeOH, and subsequent benzoylation produces *trans*-(**1**) [(2*S*,5*S*)-(**1**)] in high yield (eq 1).[2]

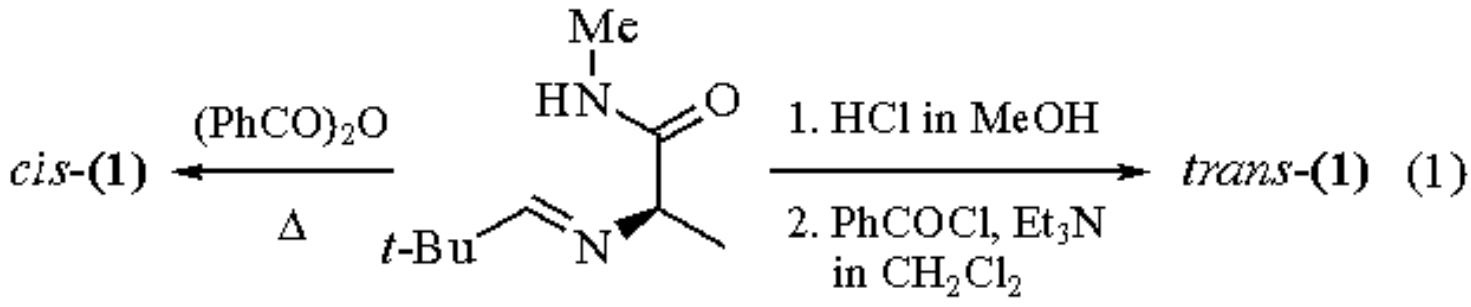

Handling, Storage, and Precautions: both diastereoisomers are readily crystallizable compounds which are stable at rt for years.

Alkylations of the Lithium Enolates.

Treatment of the reagents with ***Lithium Diisopropylamide*** (LDA) generates the enolates (**2**) or *ent*-(**2**) (crystal structure of *rac*-TBDMS-(**2**)[6]) which can be alkylated[3,5] to give, for instance, (*R*)-α-methyl-dopa (**3**) or triacetyl (*S*)-α-methyl-dopa.[3]

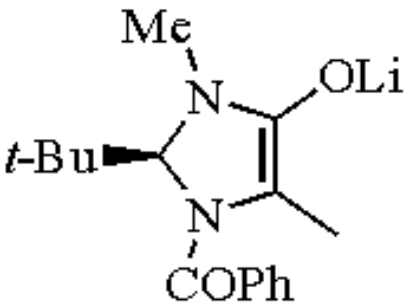

(2)

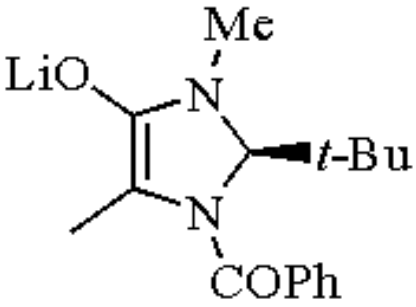

ent-**(2)**

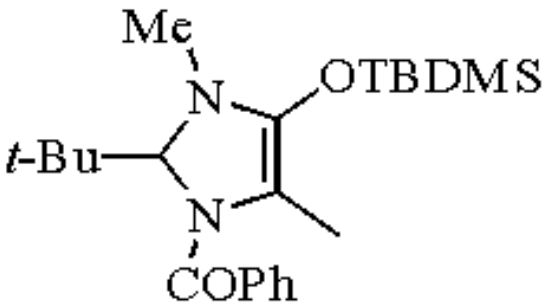

rac-TBDMS-**(2)**

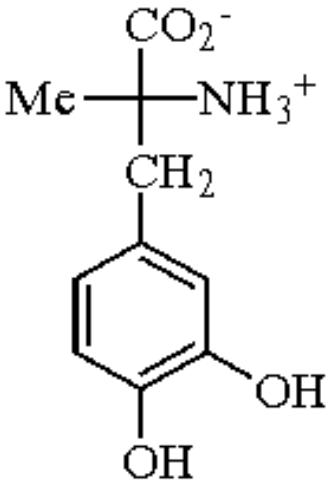

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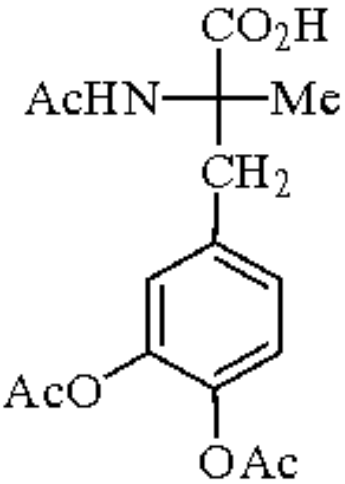

ent-(Ac)$_3$-**(3)**

Benzoylimidazolidinones of Other Amino Acids.

In a similar way, other proteinogenic and nonproteinogenic amino acids have been converted to imidazolidinones (**4**) and alkylated through enolates to give derivatives of α-branched α-amino acids. Examples of the R group in (**4**) are as follows: *i*-Pr,[2-4] Bn,[2] $(CH_2)_2SMe$,[2,7,8] $CH{=}CH_2$,[8] Ph,[2] $(CH_2)_3NHCO_2Bn$,[5] $(CH_2)_4NHCO_2Bn$,[5] CH_2CO_2H,[9] $(CH_2)_2CO_2H$.[9] The limitation of the method is given by the fact that certain amino acid *N*-methylamides, the intermediates on the way from the 3-methylimidazolidinones to free amino acids, are *very* difficult to hydrolyze.[10] Except for the procedure described here and for those methods involving enantioselective catalysis, all other syntheses of amino acids rest upon the use of a covalently attached chiral auxiliary which has to be discarded, recovered, or destroyed after use.[1c]

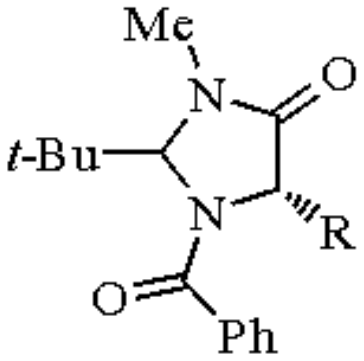

(4)

The Principle of Self-Regeneration of Stereogenic Centers.[1,11,12]

In the absence of additional chirality the generation of an enolate from a simple amino acid will lead to racemization.[13] There are two ways around this: (i) attachment of a chiral auxiliary, and (ii) diastereoselective generation of an additional stereogenic center which makes sure that the subsequently generated enolate is still chiral. In the case of alanine, described here, the acetal chirality center serves this purpose. The most general case is described in eq 2. Thus an α- or β-amino, -hydroxy-, and -mercaptocarboxylic acid may be converted to one of two diastereoisomeric acetals. The original stereogenic center can now be eliminated without forming an achiral species; subsequent reactions at the newly formed trigonal center should be diastereoselective, so that the product of acetal hydrolysis is nonracemic. The trigonal center at the site of the original stereogenic center may be part of an electrophilic or a nucleophilic double bond system, or may be a radical center. In the overall process, a substituent (mostly a hydrogen) at the one and only chirality center of the starting material is replaced by a new substituent stereoselectively. Since no chiral auxiliary is employed, this has been termed the principle of self-regeneration of the stereogenic center (SRSC). The auxiliary is actually the aldehyde, used for generating the second stereogenic center, and it is removed in the final hydrolysis step.

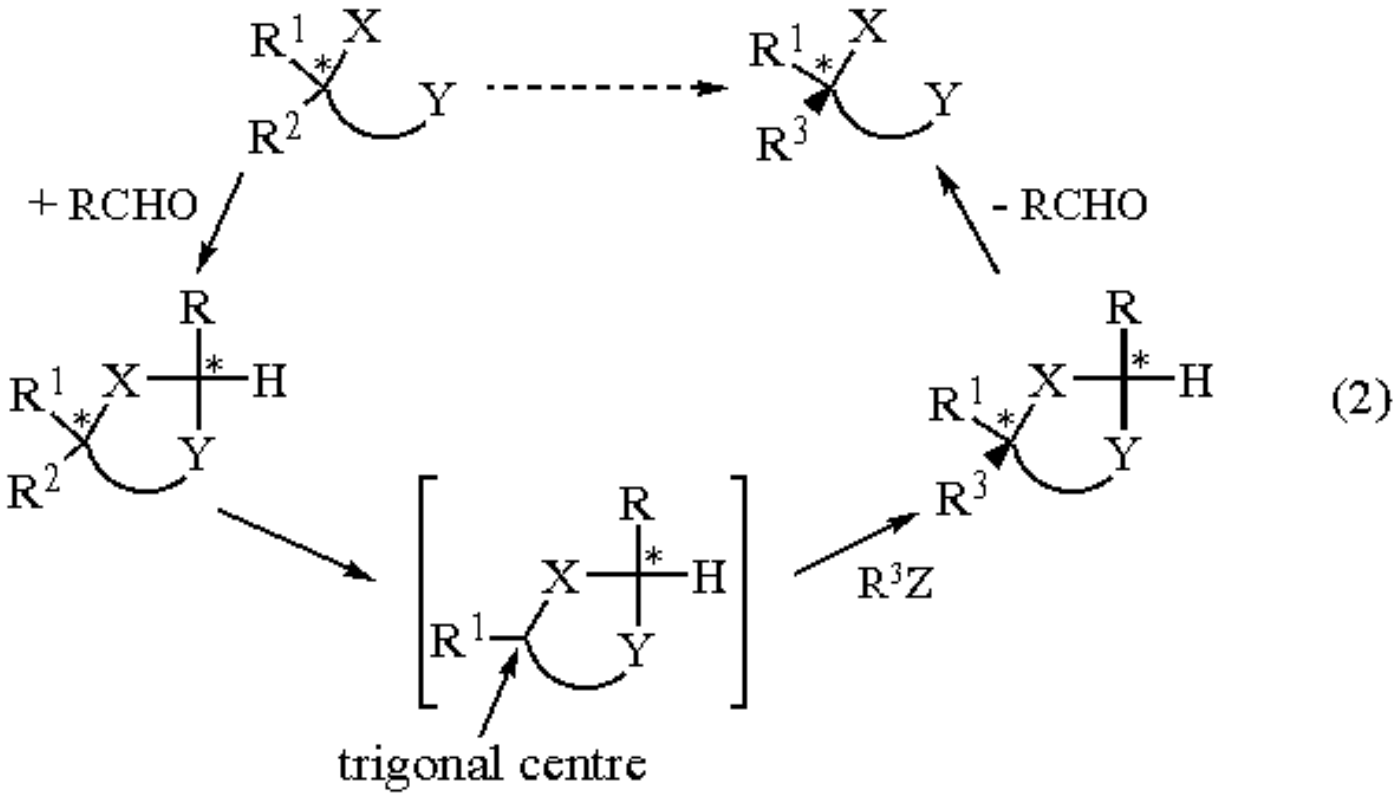

Oxazoline, oxazolidine, dihydropyrimidine, and 1,3-dioxine derivatives can also be used in this way.

Related Reagents.

(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one***; ***Diethyl Acetamidomalonate***; ***N-(Diphenylmethylene)aminoacetonitrile***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Ethyl Isocyanoacetate***; ***Methyl N-Benzylidenealaninate***; ***(R)-Methyl 2-t-Butyl-3(2H)-oxazolecarboxylate***.

---

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13. For three exceptions see the alkylations of an aspartic acid,13a of an aziridine carboxylic acid,13b and of a cysteine derivative.13c (a) Seebach, D.; Wasmuth, R. *AC(E)* **1981**, *20*, 971. (b) Häner, R.; Olano, B.; Seebach, D. *HCA* **1987**, *70*, 1676. (c) Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *CC* **1991**, 924.

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(2*S*,4*S*)-3-Benzoyl-2-*t*-butyl-4-methyl-1,3-oxazolidin-5-one[1]

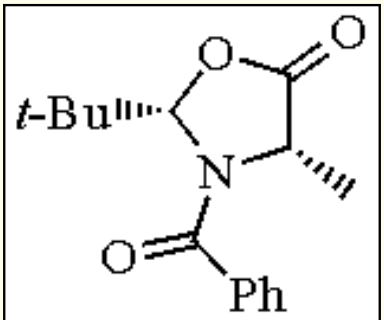

(1)

[104057-64-9] · $C_{15}H_{19}NO_3$ · (2*S*,4*S*)-3-Benzoyl-2-*t*-butyl-4-methyl-1,3-oxazolidin-5-one · (MW 261.32)

(cyclic acetal of *N*-benzoylalanine; reagent for the preparation of enantiopure α-methyl-α-aminocarboxylic acids;[2] precursor to the 4-methylidene derivative;[3a] a radicalophile;[3b] a Michael acceptor;[4] and an ene component for Diels-Alder additions,[5] with formation of more complex α-amino acids)

Physical Data: mp 94.2-94.5 °C; [α]rtD = -29.3° (*c* = 1.0, $CHCl_3$).

Solubility: sol THF, poorly sol hexane.

Preparative Methods: the sodium salt of the pivalaldehyde imine of (*S*)-alanine is cyclized to the oxazolidinone by reaction with PhCOCl in CH_2Cl_2 at low temperature; the *cis*/*trans* ratio in the crude product depends upon the exact reaction conditions, it is usually 4:1; purification by a combination of crystallization and chromatography gives the pure *cis* derivative in 60-70% yield.[2]

Handling, Storage, and Precautions: the solid material is stable for years when stored in a bottle.

Generation of the Enolate and Reactions with Electrophiles.

The enolate of the title reagent (**1**) is generated with lithium amide bases and reacts with electrophiles such as benzylic bromides or tricarbonyl(fluorobenzene)chromium to give the corresponding 4,4-disubstituted derivatives of type (**2**), which are hydrolyzed under acidic conditions[2,6-8] to, for instance, the amino acids[2,7] (**3**) and (**4**).

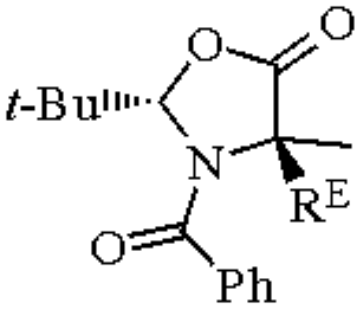

(2)

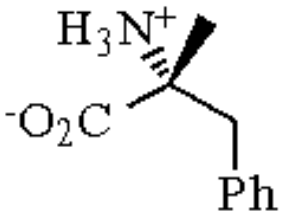

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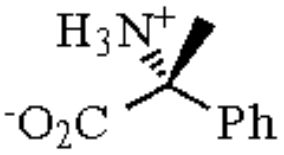

(4)

In the overall process the α-hydrogen of the alanine has been replaced by benzyl or phenyl stereoselectively (an application of the principle of self-regeneration of the stereogenic center). The analogous 2-*t*-butyl-3-benzoyloxazolidinones of valine,[2] phenylalanine,[2] methionine,[2,9] and lysine[6] have also been prepared and alkylated to give α-branched amino acids.

Other Oxazolidine as well as Thiazolidine Derivatives for Branching Amino Acids.

The cyclic derivative of alanine and other amino acids employed most frequently for α-alkylation is not (**1**) but rather the benzaldehyde acetal (**5**), either with a benzoyl[5,10] or with a Cbz[11] group on nitrogen. These compounds were used for the preparation of 2-methyl-2-aminobutanoic acid, α-methylphenylalanine, α-methyllysine, 2-methylaspartic acid, and 2-methylglutamic acid. Bicyclic compounds containing oxazolidinone rings such as (**6**) (from alanine, leucine, and phenylalanine)[12] and (**7**) (from azetidinecarboxylic acid,[13] proline,[14] hydroxyproline,[15] and cysteine[16]) have also been applied to the synthesis of branched amino acids.

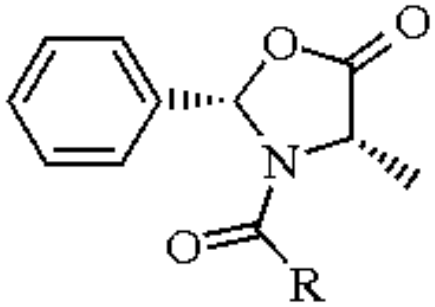

(5)

R = Ph, OBn

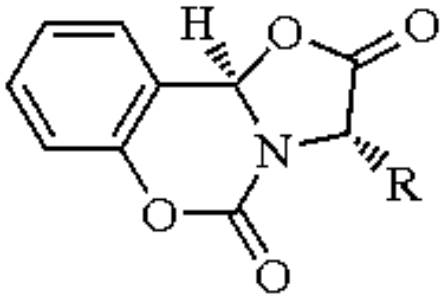

(6)

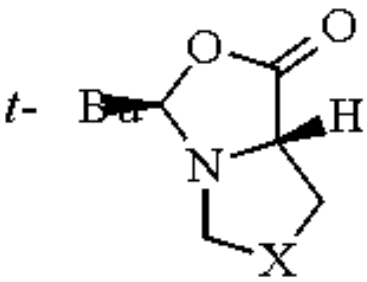

(7)

X = $(CH_2)_{0,\ 1}$
X = CHOR
X = S

Finally, the enolates (**8**), (**9**), and (**10**) of oxazolidine and thiazolidine carboxylates have been used for the synthesis of enantiopure α-substituted serine,[17] cysteine,[18] threonine,[17] *allo*-threonine,[17] and β-hydroxyleucine.[19]

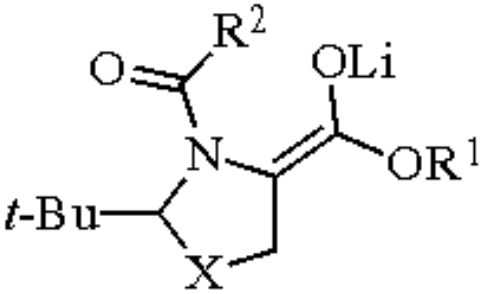

(8)

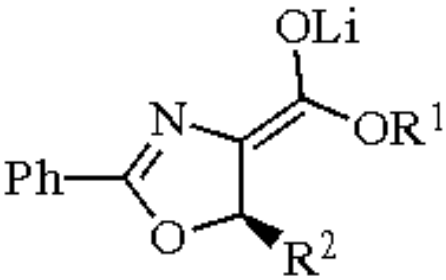

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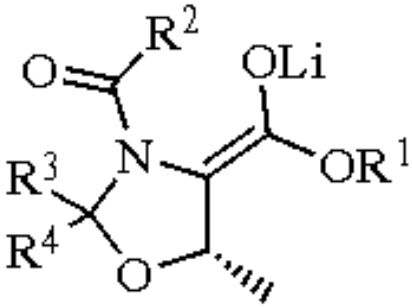

(10)

α-Bromination-dehydrobromination of oxazolidinone (**1**) (NBS, then DBU) or an alternative preparation starting from cysteine gives the methylene derivative (**11**) which combines with cyclopentadiene and cyclohexadiene in [4 + 2] cycloadditions; these reactions were used for the synthesis of (*R*) and (*S*)-2-aminobicyclo[2.2.1]heptane-2-carboxylic acids as shown in eq (1).[3-5]

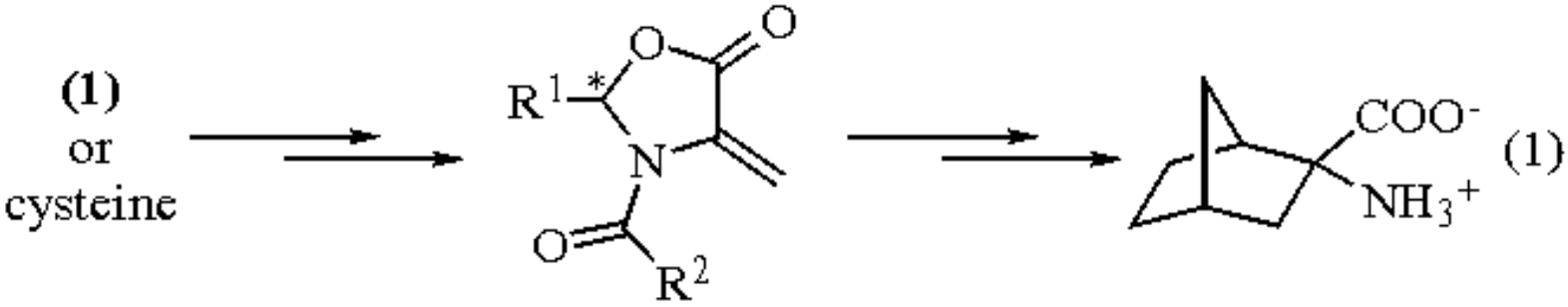

(11)

(*R*)- and (*S*)-2-*t*-Butyl-1,3-oxazolidin-5-ones: Chiral Glycine Derivatives.

Since the oxazolidinone enolates are good diastereoselective nucleophiles, and since the products are much more readily hydrolyzed to the free amino acids than those derived from imidazolidinones, it was also desirable to make available the corresponding glycine derivative (**12**). This was achieved by preparative HPLC resolution on Chiraspher, Chiracel OD, or Pirkle columns (up to 10 g per injection, separation factors α up to 2.35).[8,20] The enolate of the 2-*t*-butyl-substituted N-Cbz oxazolidinone was especially useful for the synthesis of a large variety of (*R*)- and (*S*)-threonines; see, for instance, the cyclosporin component MeBmt (**13**)[21] and the *p*-nitrophenylserine (**14**)[22] in eq (2).

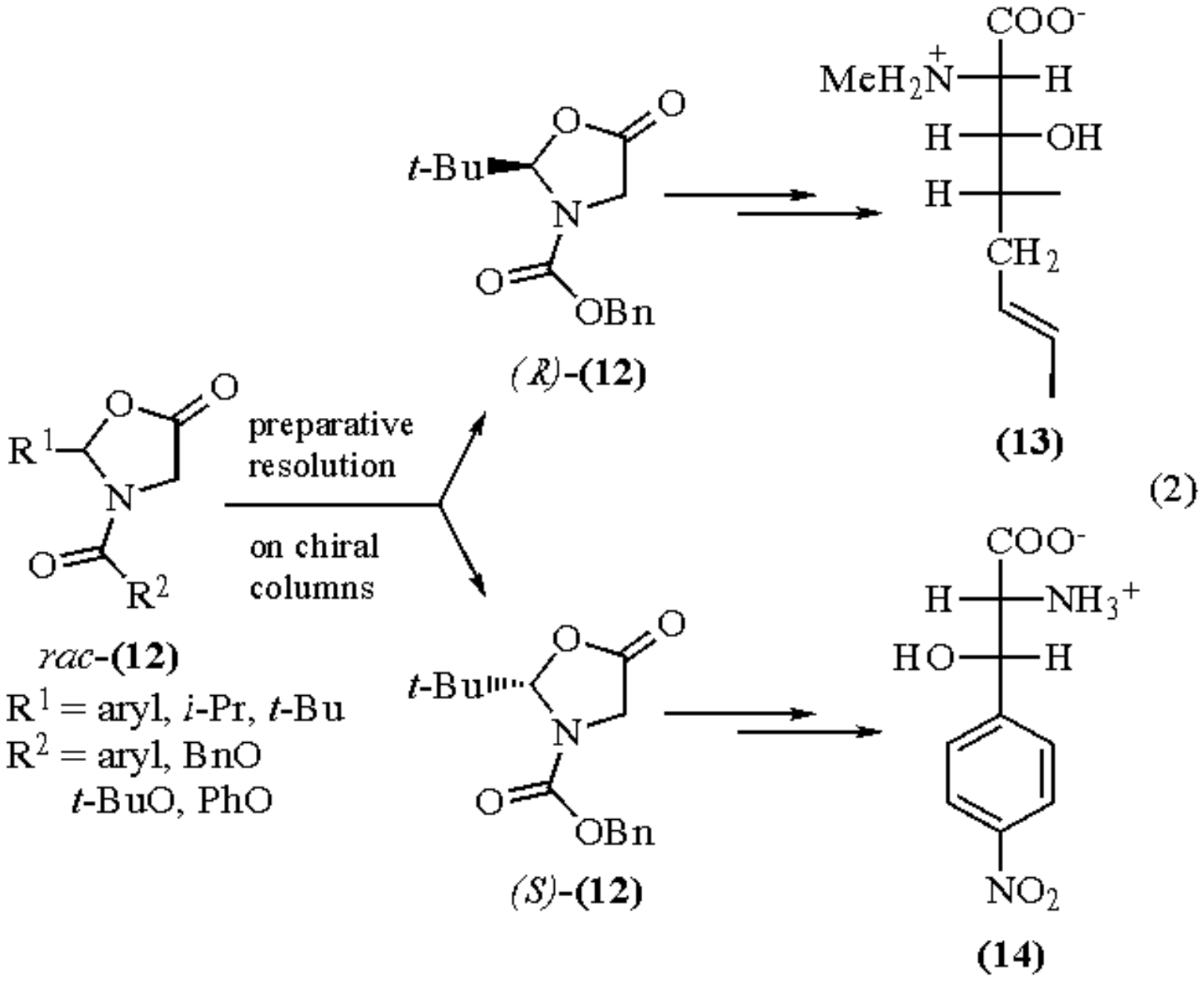

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one***; ***Diethyl Acetamidomalonate***; ***N-(Diphenylmethylene)aminoacetonitrile***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Methyl N-Benzylidenealaninate***.

---

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Benzoyl Chloride[1]

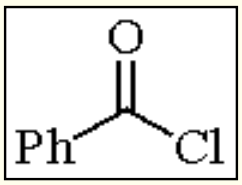

[98-88-4] · C_7H_5ClO · Benzoyl Chloride · (MW 140.57)

(useful acylating agent; preparation of ketones from organometallic compounds;[2,3] preparation of 1,3-dicarbonyl compounds from enolates or enols;[4,5] Friedel-Crafts acylation and related reactions[6] with aromatic and heterocyclic compounds,[7] alkenes,[8] alkynes,[9] enoxysilanes,[10] and silicon compounds;[11] acylation of enol ethers, ketene acetals,[12] and enamines;[13] protection of alcohols as benzoates;[14] protection of amines as benzamides[15])

Physical Data: bp 197.2 °C; mp -1 °C; *d* 1.21 g cm^{-3}.

Solubility: slowly decomposed by water and alcohols; sol most organic solvents.

Form Supplied in: colorless liquid; penetrating odor; widely available.

Purification: the good commercial grade of benzoyl chloride can be purified by distillation. The technical material must be purified as follows: a 50% solution of PhCOCl in ether or cyclohexane is washed with cold 5% aqueous sodium bicarbonate; after drying over $CaCl_2$ the solvent is eliminated under vacuo and the PhCOCl is distilled.[16]

Handling, Storage, and Precautions: use in a fume hood; lachrymatory, irritating to skin, eyes and mucous membranes; toxic by inhalation and ingestion.

Acylation of Organometallic Compounds.[2,3]

PhCOCl reacts with various organometallic reagents to give the corresponding phenyl ketones in variable yields. The first acylation reactions were performed with organocadmium and organozinc compounds (eqs 1 and 2).[3a,b] In THF, organozinc reagents give poor results; however, the yields are clearly improved in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** (eq 3).[3c]

$$\text{MeCdCl} + \text{PhCOCl} \xrightarrow[85\%]{\text{benzene, reflux}} \text{MeCOPh} \qquad (1)$$

$$\text{MeZnI} + \text{PhCOCl} \xrightarrow[80\%]{\text{benzene, 0 °C}} \text{MeCOPh} \qquad (2)$$

$$\text{MeZnCl} + \text{PhCOCl} \xrightarrow[25\ °\text{C}]{\text{THF}} \text{MeCOPh} \qquad (3)$$

no catalyst, 12 h: 10%
5% $Pd(PPh_3)_4$, 30 min: 80%

With the very reactive organomagnesium compounds, the acylation takes place in the presence of $Fe(acac)_3$[3d] or $MnCl_2$[3e] (eqs 4 and 5). It is worthy of note that the 1,2-addition, which is rapid under these reaction conditions (10-20 °C), is completely avoided.

$$\text{PhCOCl} + \text{MeMgCl} \xrightarrow[80\%]{3\%\ Fe(acac)_3,\ \text{THF, rt}} \text{MeCOPh} \qquad (4)$$

$$\text{PhCOCl} + \text{BuMgCl} \xrightarrow[90\%]{3\%\ MnCl_4Li_2,\ \text{THF, 0 °C, 45 min}} \text{BuCOPh} \qquad (5)$$

Organocopper (60% of PhCOMe from $MeCu.PBu_3$)[3f] and cuprate reagents (eq 6),[3g] which are now widely used, give only moderate yields of phenyl ketones. Better yields are obtained at low temperature by using a large excess of organocuprate[3h] or heterocuprate (eq 7).[3i]

$$Me_2CuLi + \text{PhCOCl} \xrightarrow[58\%]{\text{ether, -5 °C}} \text{MeCOPh} \qquad (6)$$

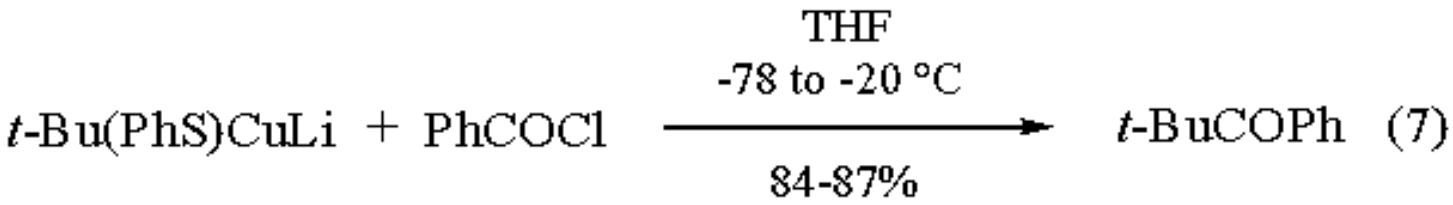

Organomanganese compounds afford excellent yields by the use of a stoichiometric amount of reagents under mild conditions (eq 8).[3j]

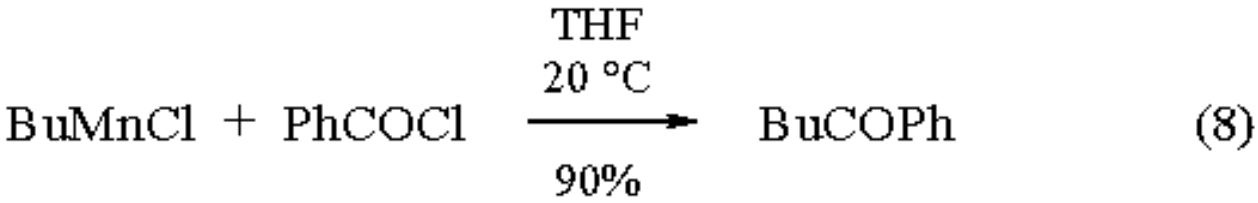

Acylation of Enolates, Enols, and Related Reactions.[4,5]

According to the reaction conditions, PhCOCl reacts with ketone enolates to lead to enol benzoates (*O*-acylation, kinetic product) or β-diketones (*C*-acylation, thermodynamic product) (eq 9).[5a]

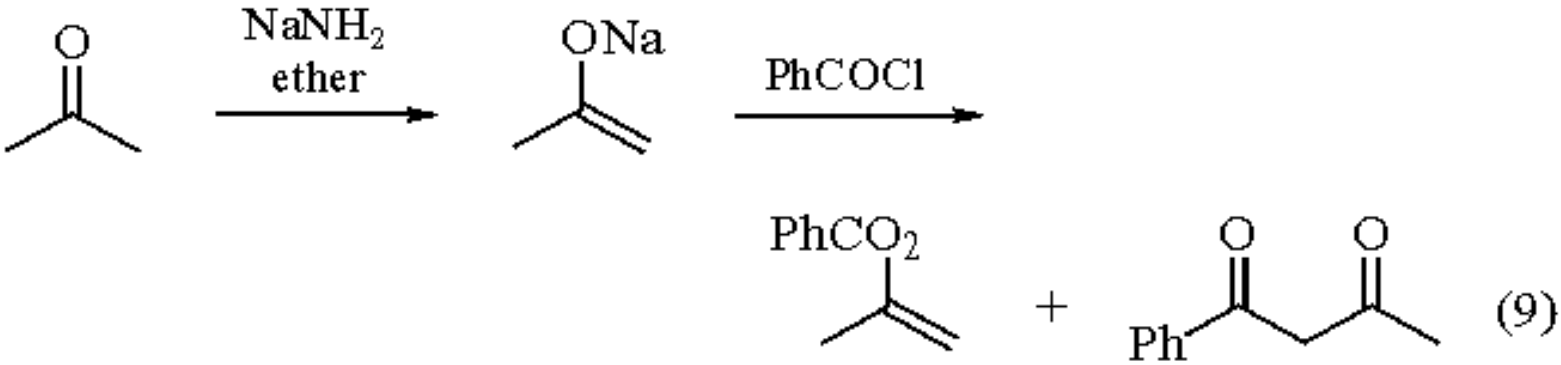

2 equiv of PhCOCl:	41%	6%
2 equiv of enolate:	9%	33%

PhCOCl very often gives a mixture of the *O*- and *C*-acylated products. To prepare the enol ester (kinetic conditions) a more reactive acylating agent such as ***Acetyl Chloride*** is generally used. Moreover, carboxylic acid anhydrides are generally preferred to acyl halides. Accordingly, PhCOCl is preferred to prepare 1,3-dicarbonyl compounds. Ketones (eq 10),[5b] esters (eq 11),[5c] and more commonly β-keto esters or related CH acidic compounds (eqs 12-15)[5d-g] can be *C*-acylated via the preformed enolate (eq 11) or directly under basic conditions (eq 13).[5e]

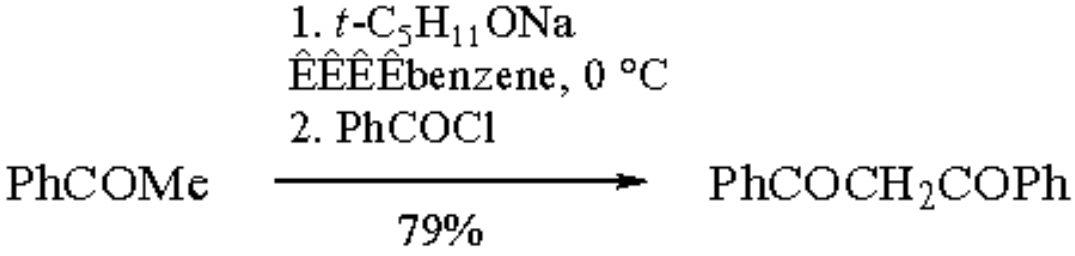

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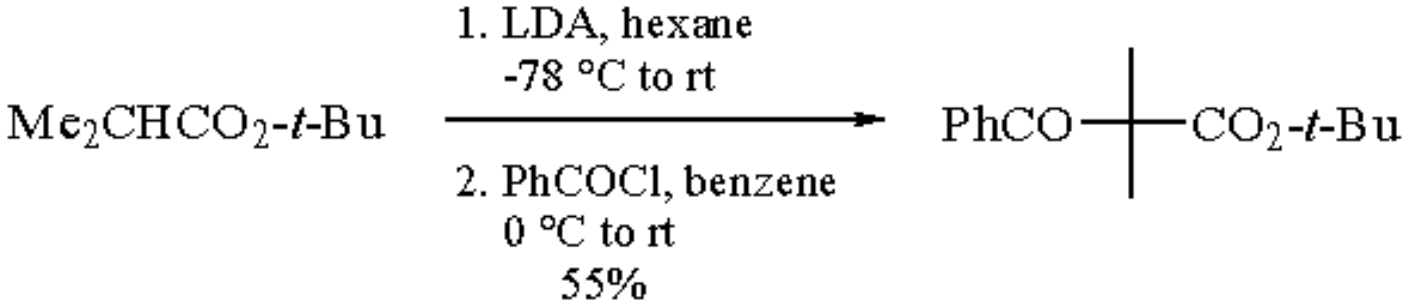

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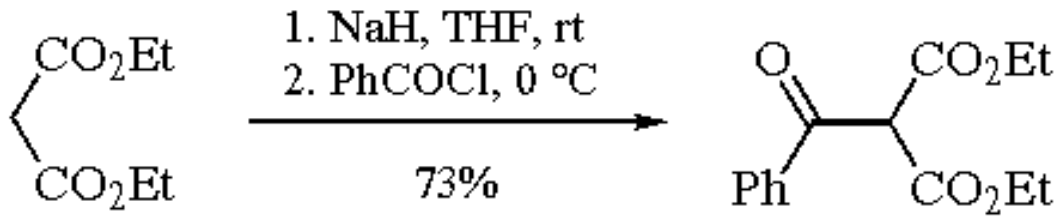

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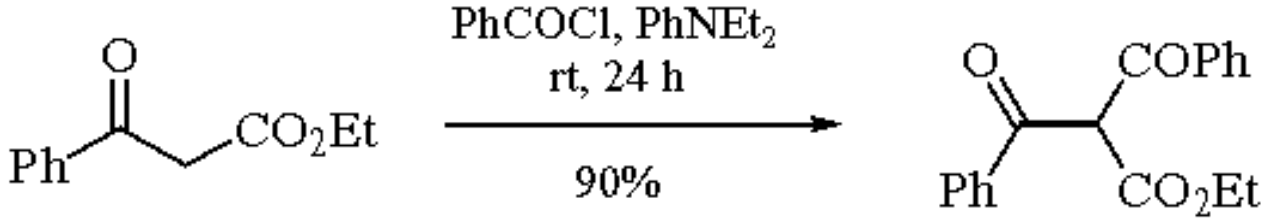

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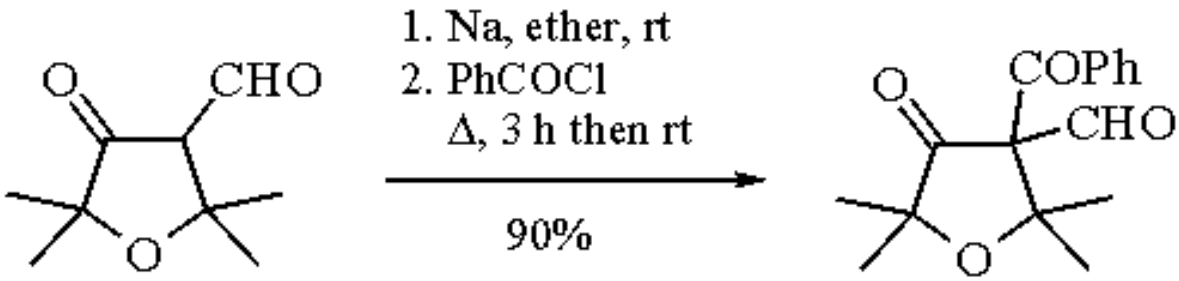

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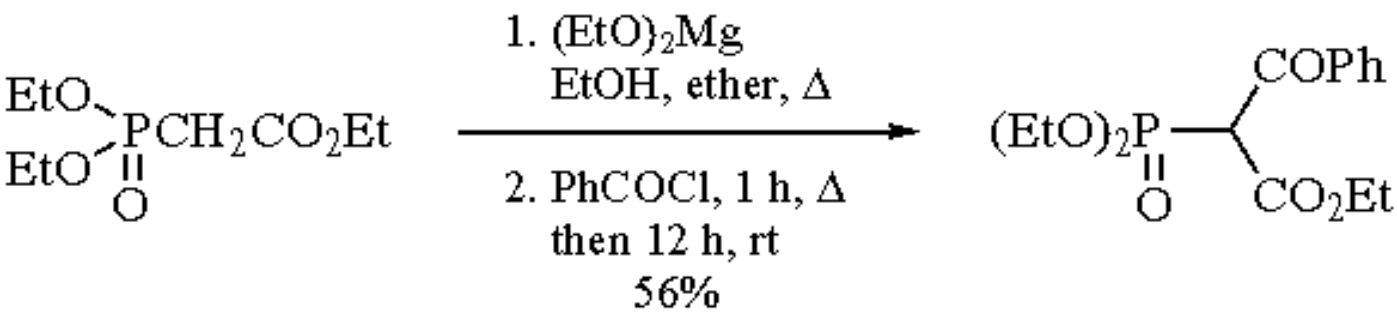

(15)

Friedel-Crafts Acylation and Related Reactions.[6,7]

Aromatic compounds (eqs 16 and 17)[7a,b] are acylated by PhCOCl in the presence of a Lewis acid such as $AlCl_3$, $TiCl_4$, BF_3, $SnCl_4$, $ZnCl_2$, or $FeCl_3$, or of a strong acid such as polyphosphoric acid or CF_3SO_3H.[6] Metallic Al or Fe and iodine (in situ formation of a Lewis acid) can also act as a catalyst.[6] Various solvents that have been used to perform this reaction are CS_2, CH_2Cl_2, 1,2-dichloroethane, nitrobenzene, and nitromethane.[6] PhCOCl is less reactive than aliphatic carboxylic acid chlorides (with benzene in nitromethane the relative reaction rates are PhCOCl:MeCOCl = 6:100).[7a] As for all electrophilic substitutions, the rate and the regioselectivity of the acylation closely depend on the nature and on the position of the substituents on the aromatic system[6] (eqs 16 and 18[7c]). The nature of the solvent can also exert a strong influence.[6]

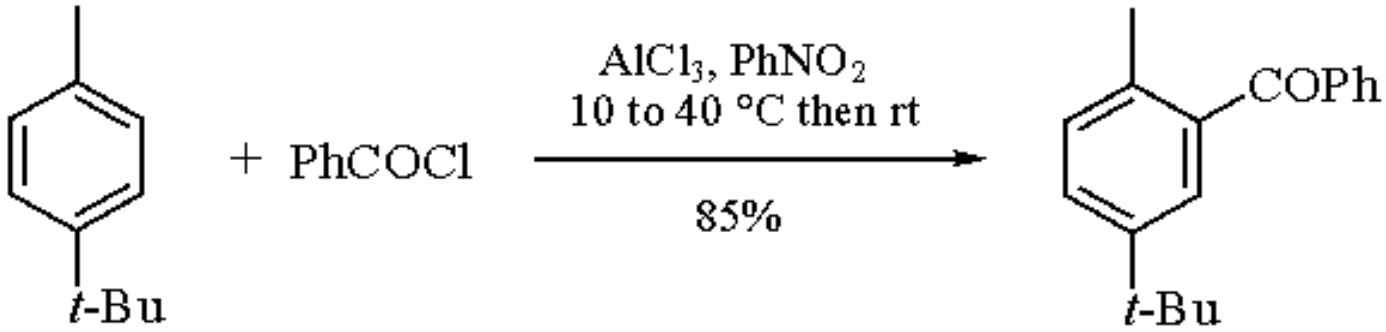

(16)

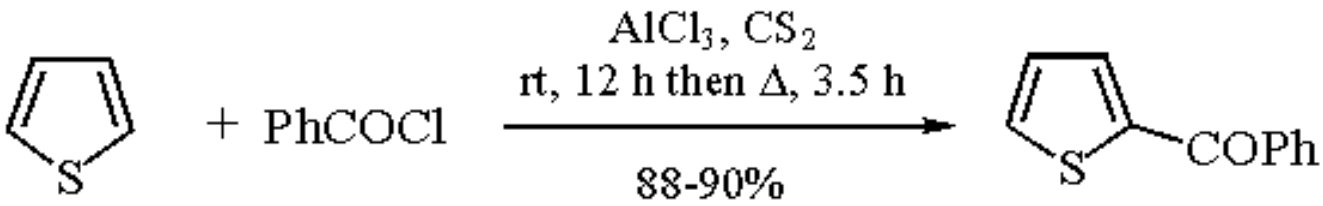

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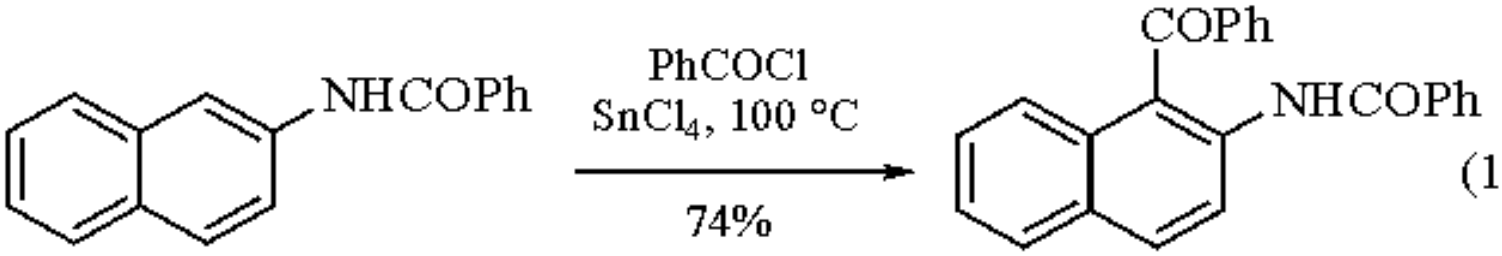

(18)

The electrophilic acylation of alkenes or alkynes is another example of Friedel-Crafts reactions and is carried out under similar conditions.[6,8,9] With PhCOCl, alkenes can lead to β-chloro alkyl ketones or, more frequently, to the corresponding α,β-ethylenic ketones (eq 19)[8b] according to the reaction conditions.[6,8a] PhCOCl also adds to triple bonds to give a β-chloro vinyl ketone[9] (eq 20).[9b]

$$H_2C{=}CH_2 + PhCOCl \xrightarrow[70\%]{AlCl_3,\ CHCl_2CHCl_2,\ 5\ °C} H_2C{=}CHCOPh \quad (19)$$

$$HC{\equiv}CH + PhCOCl \xrightarrow[\text{65-70\%}]{AlCl_3,\ ClCH_2CH_2Cl,\ 0\ ^\circ C} PhCOCH{=}CHCl \quad (20)$$

Under Friedel-Crafts conditions, PhCOCl reacts with various silicon compounds. Thus β-diketones are easily obtained from enoxysilanes[10a,b] (eq 21).[10c] Conversely, vinyl-, aryl-, and allylsilanes lead to the corresponding vinyl, aryl, and allyl ketones in good yields[11a-c] (eq 22[11d] and eq 23[11e]). Vinylsilanes can lead to a mixture of β-chloro alkyl ketones and conjugated enones; a basic treatment is then necessary to obtain only the enone (eq 23).

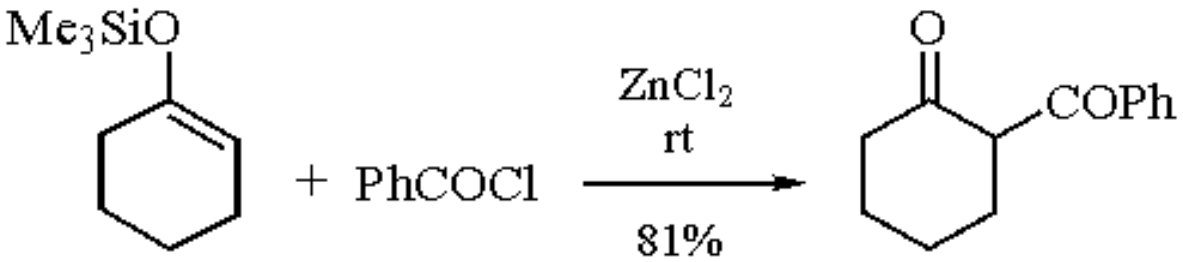

(21)

$$PhCH{=}CHSiMe_3 \xrightarrow[\text{2. } Et_3N,\ \text{ether},\ \Delta\ \ \text{73\%}]{\text{1. } PhCOCl,\ AlCl_3,\ \hat{E}\hat{E}CH_2Cl_2,\ 0\ ^\circ C} PhCH{=}CHCOPh \quad (22)$$

$$H_2C{=}CHCH_2SiMe_3 \xrightarrow[\text{90\%}]{PhCOCl,\ AlCl_3,\ CH_2Cl_2,\ -30\ ^\circ C} H_2C{=}CHCH_2COPh \quad (23)$$

Acylation of Enol Ethers, Ketene Acetals,[12] and Enamines.[13]

Enol ethers,[12a] ketene acetals (eq 24),[12b] and enamines (eq 25)[13g] react with PhCOCl to provide the corresponding β-acylated products (eq 24).[12b] The acylation of enamines has been extensively studied (eq 25);[13a-f] the resulting β-acyl enamine is generally hydrolyzed to give β-diketones (eq 25).

$$(MeO)_2C{=}CH_2 + PhCOCl \xrightarrow[\text{55\%}]{Et_3N,\ \text{ether},\ \Delta} (MeO)_2C{=}CHCOPh \quad (24)$$

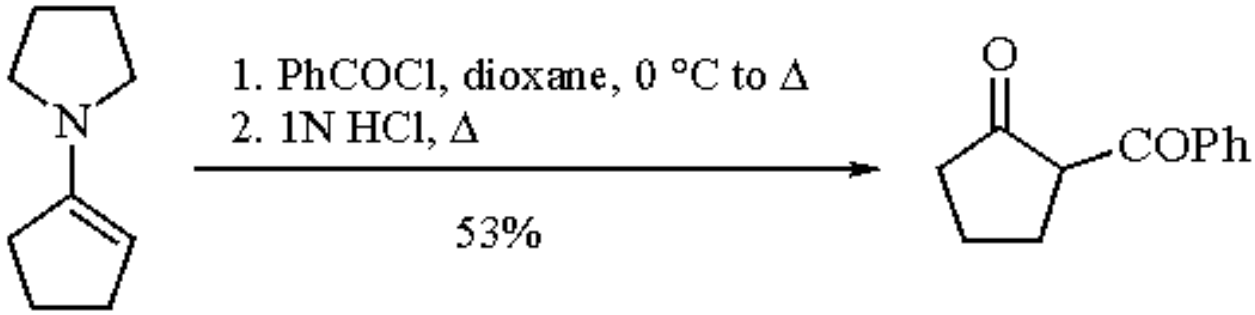

(25)

Protection of Alcohols as Benzoates[14] and of Amines as Benzamides.[15]

PhCOCl easily reacts with alcohols to give the corresponding benzoates in excellent yields.[14a] The acylation is performed in the presence of an amine, very often pyridine or triethylamine. CH_2Cl_2 or a large excess of amine is generally used as solvent (eq 26).[14d] The reaction has also been performed by phase transfer catalysis (PhCOCl, benzene, Bu_4NCl, 40% NaOH).[14e] Alternatively, the alcohol can be converted to lithium alcoholate (with BuLi), which readily reacts with PhCOCl to give quantitatively the corresponding benzoate (eq 27).[14f] Tributyltin ether prepared by treatment of the alcohol with ***Bis(tri-n-butyltin) Oxide*** has also been used as intermediate.[14g] Benzoates are very often prepared to protect alcohols[14b,c] because they are more stable than acetates and their tendency to migrate to adjacent hydroxyl groups is lower.[14h,i] In most cases the benzoylation of polyhydroxylated molecules is more selective than the acetylation.[14h,i] PhCOCl has also been used to monoprotect diols,[14f] and to acylate a primary alcohol in the presence of a secondary alcohol.[14j] Under similar conditions (pyridine), phenols are converted to aryl benzoates.[14a,k]

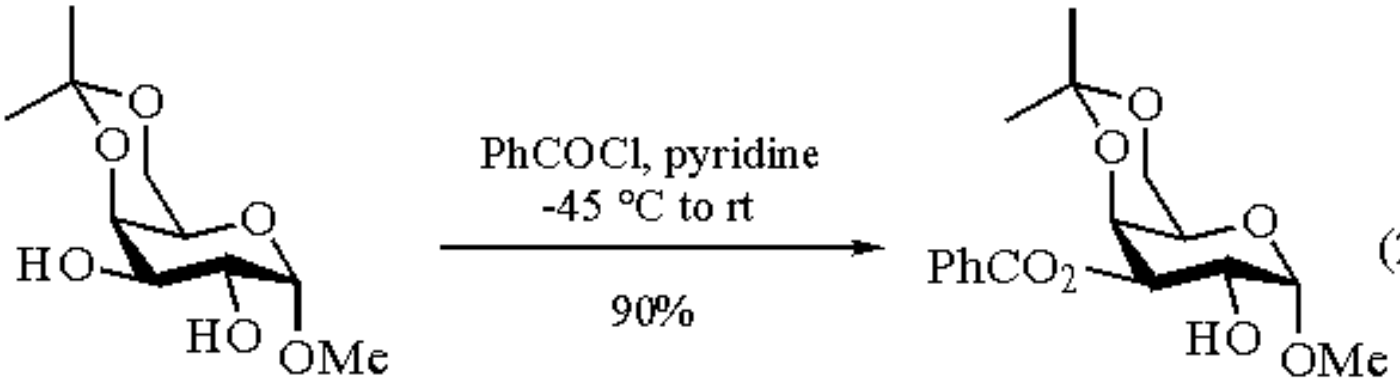

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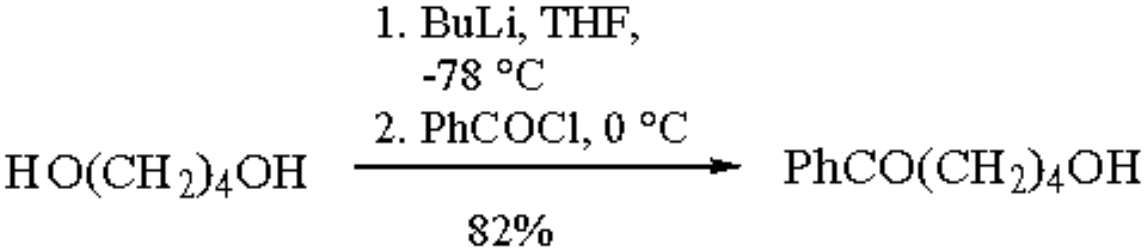

(27)

PhCOCl reacts also easily with primary or secondary amines in the presence of a base, aqueous alkali (Schotten-

Bauman procedure), or tertiary amines (pyridine or Et_3N), to afford the corresponding amides (eq 28).[15b] This reaction is used to protect amines.[15c]

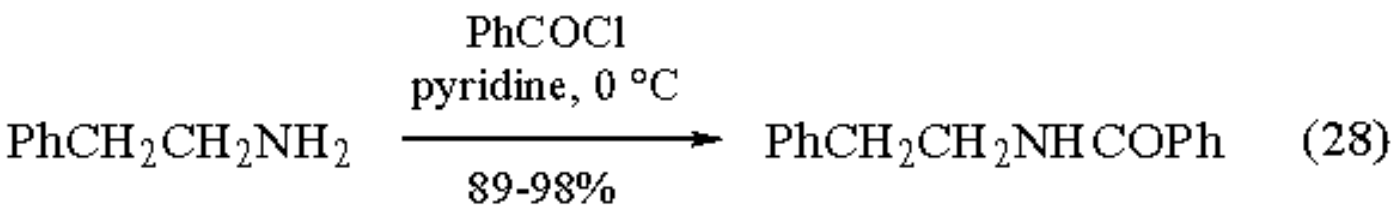

Miscellaneous Reactions.

PhCOCN (see ***Acetyl Cyanide***), which is used as acylating agent (for instance, to protect alcohols)[17a] can be prepared by reacting PhCOCl with ***Copper(I) Cyanide*** (60-65%).[17b,c] Diazoalkanes are readily acylated by PhCOCl to give diazo ketones.[18a,b] These compounds are interesting as intermediates[18c-e] to prepare α-halo ketones, α-hydroxy ketones or arylacetic acids (Arndt-Eistert reaction).[18e] PhCOCl has also been used to prepare volatile acyl chlorides (C_2 to C_6) from the corresponding carboxylic acids.[19] On the other hand, it reacts with sulfoxides to lead generally to the corresponding α-chloro sulfides (Pummerer rearrangement).[20]

Related Reagents.

Acetyl Chloride; ***Acetyl Cyanide***; ***Benzoic Anhydride***.

---

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16. See Ref. 17b, p 113, note 3.
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Benzoyl Isothiocyanate[1]

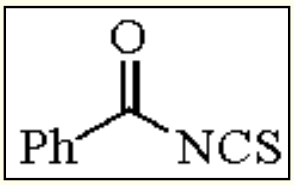

[532-55-8] · C_8H_5NOS · Benzoyl Isothiocyanate · (MW 163.19)

(reactive isothiocyanate for condensation and cyclization reactions to form thioamides, thioureas, and heterocycles)

Physical Data: bp 133-136 °C/18 mmHg; *d* 1.214 g cm^{-3}.

Solubility: freely sol most organic solvents.

Form Supplied in: liquid or prepared in situ from benzoyl chloride and ammonium thiocyanate.[2]

Purification: distillation in vacuo.

Handling, Storage, and Precautions: toxic; lachrymatory; handle in fume hood. Moisture sensitive; reacts exothermically with strong bases and amines.

Thiourea Synthesis.

The reaction of anilines and aromatic heterocyclic amines with benzoyl isothiocyanate affords the corresponding *N*-aryl-*N*´-benzoylthioureas, which can be hydrolyzed under basic conditions to give good to excellent yields of the *N*-arylthioureas (eq 1).[2,3]

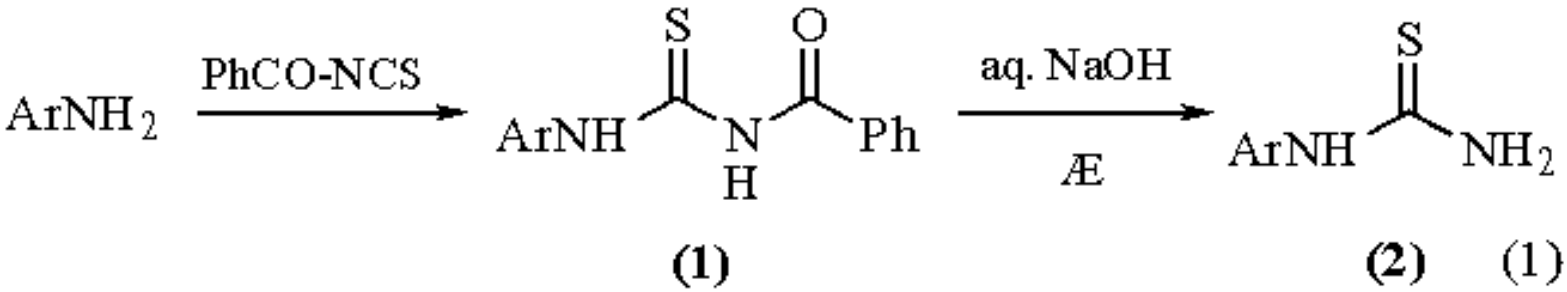

Ar	(1)	(2)
Ph	97%	84%
4-$CF_3C_6H_4$	95%	90%
4-$MeOC_6H_4$	83%	95%
4-$NO_2C_6H_4$	77%	46%

Reactions of benzoyl isothiocyanate with more basic amines or hydrazines often give mixtures of products derived from reaction at the carbonyl, thus giving rise to benzamide or benzhydrazide derivatives.[4]

Synthesis of Thioamides.

Benzoyl isothiocyanate reacts with active methylene compounds to give the expected thioamide derivatives. For example, reaction with ethyl cyanoacetate (as the sodium salt) affords thioamide (**3**) which was readily cyclized with hydrazine to partially protected heterocycle (**4**) in good yield (eq 2).[5] Adducts analogous to (**3**) are obtained starting with malonitrile (40%) and acetylacetone (55%).

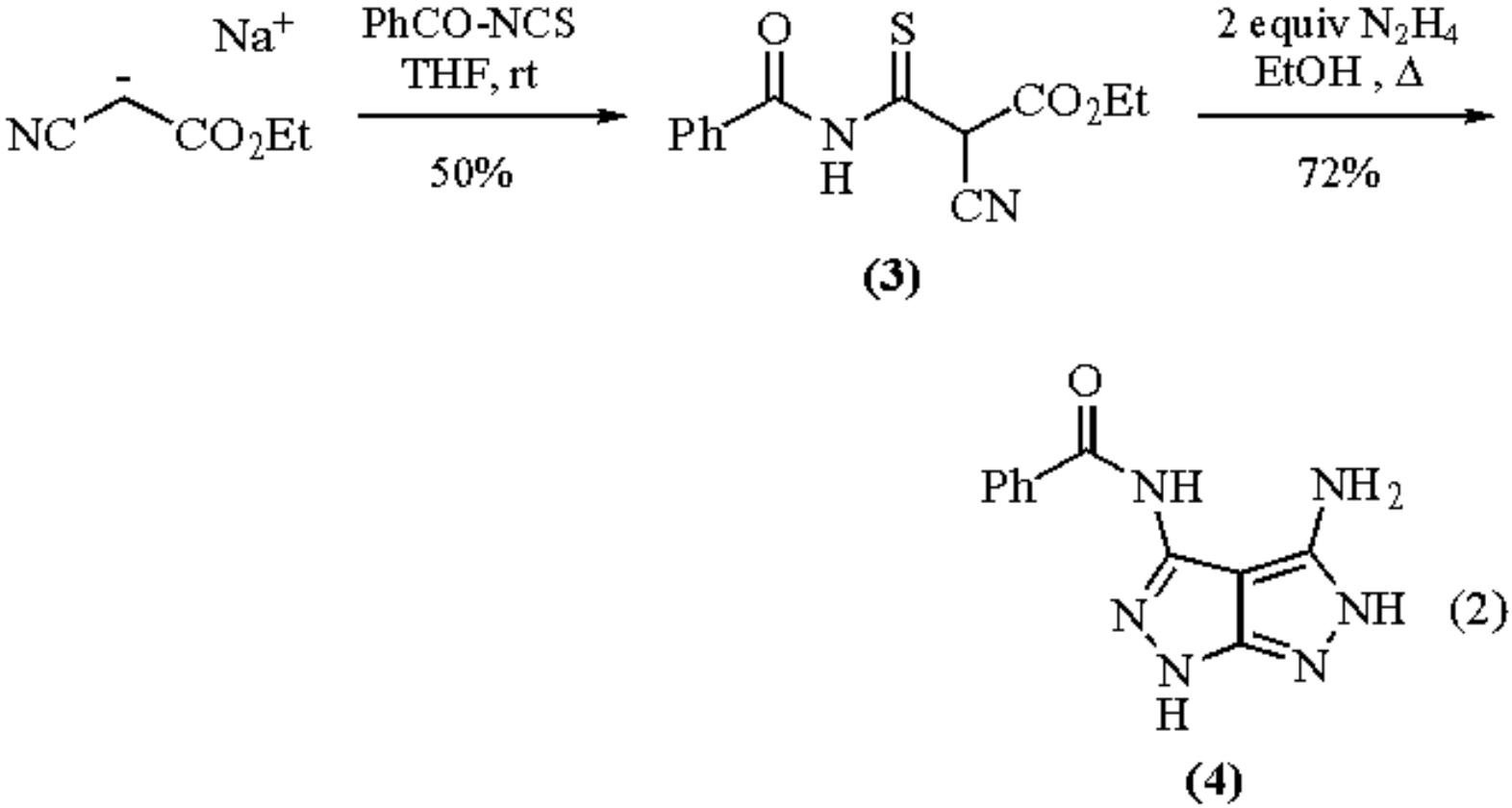

Synthesis of Heterocycles.

Benzoyl isothiocyanate is used in a concise synthesis of biologically active isoguanosine (**5**) (eq 3).[6] Other guanosine analogs can be prepared in similar fashion.[7]

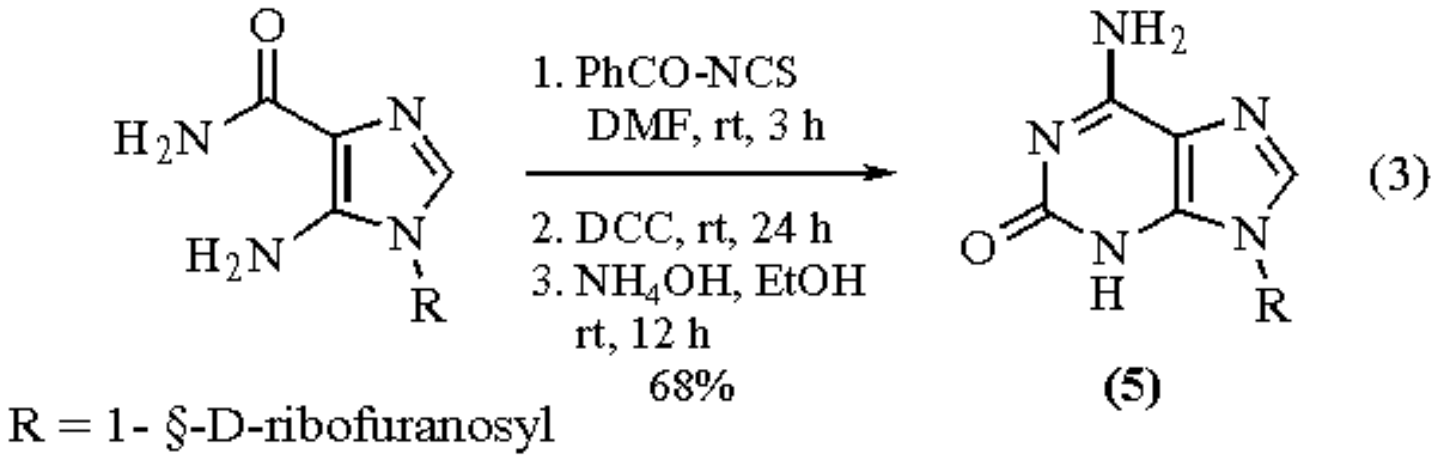

Aminoguanidine hydrochloride reacts preferentially at the hydrazino group with benzoyl isothiocyanate to give benzoylthiosemicarbazide (**6**). Cyclization of (**6**) to either thiadiazole (**7**) or to triazole (**8**) is dependent on reaction conditions (eq 4).[8]

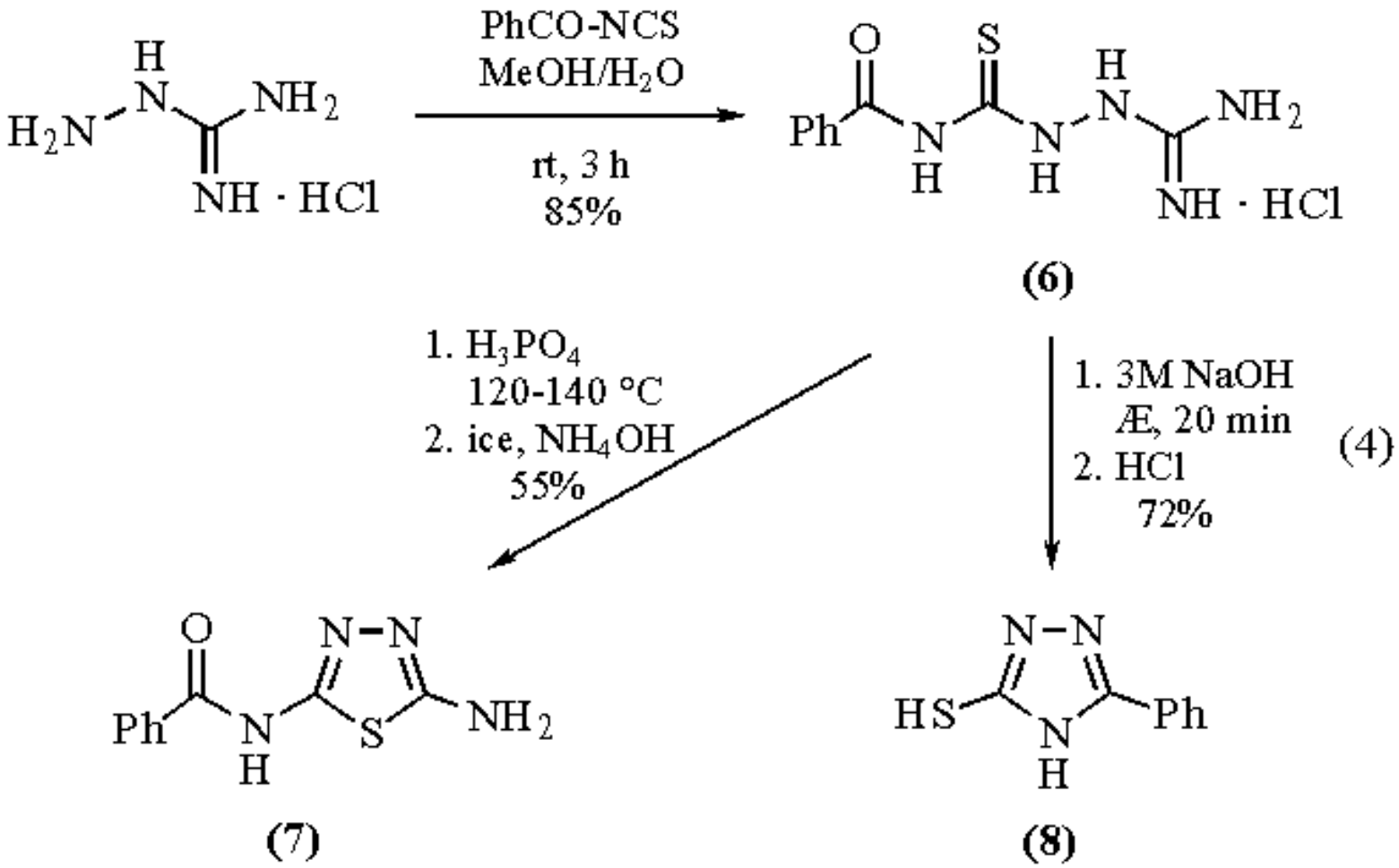

A number of pyrimidines can be synthesized employing benzoyl isothiocyanate as a key reagent. Condensation/cyclization reactions of benzoyl isothiocyanate with imidates[9] (eq 5), *S*,*N*- and *N*,*N*-ketene acetals,[10] activated enamines,[11] and acetonitriles[12,13] give rise to structurally diverse pyrimidine derivatives, in moderate to good yields.

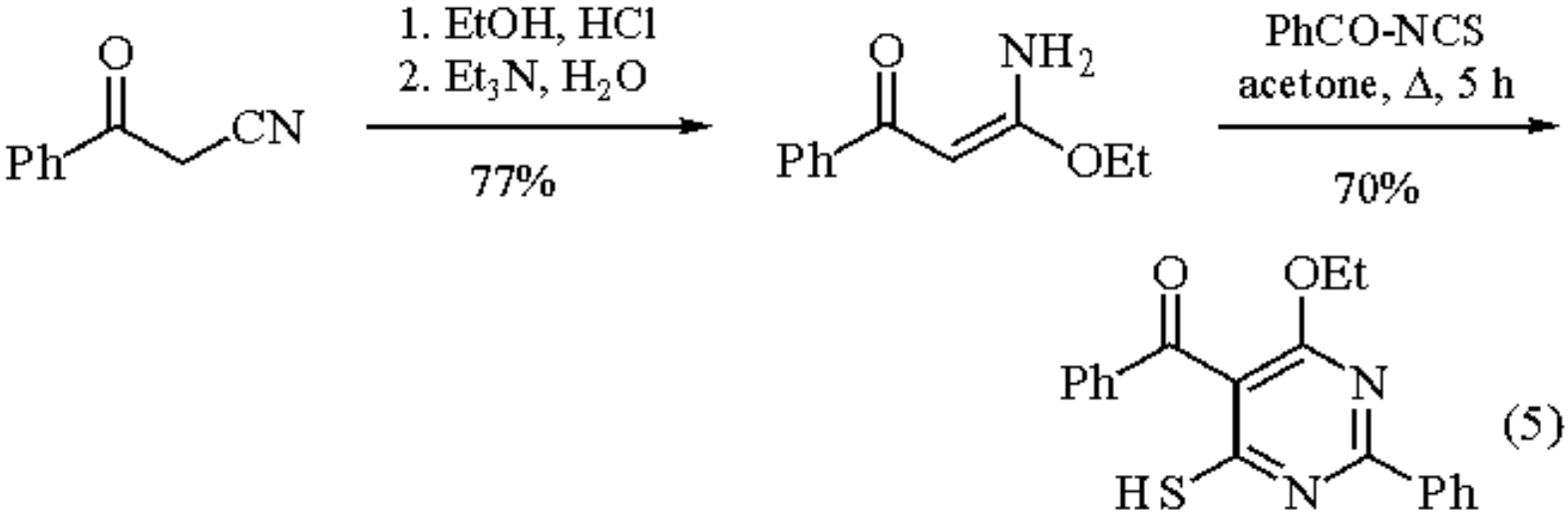

Related Reagents.

Ethoxycarbonyl Isothiocyanate; ***Methyl Isocyanate***.

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Benzoyl Nitrate[1]

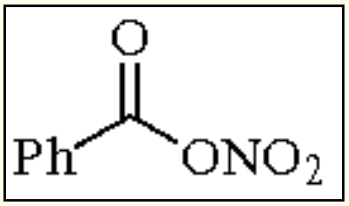

[6786-32-9] · $C_7H_5NO_4$ · Benzoyl Nitrate · (MW 167.12)

(nitrating agent for arenes and some other functionalities; benzoylation may also occur; oxidizes thiols to disulfides, thioethers to sulfoxides, and HCl to chlorine)

Physical Data: not known; presumably liquid at room temperature. *d* 1.3 g cm^{-3} at 0 °C.[2]

Solubility: miscible with common organic solvents.

Form Supplied in: not commercially available.

Preparative Methods: a standard approach is to add an equivalent amount of PhCOCl to a solution of freshly dried $AgNO_3$ in MeCN at -20 °C, and to filter off AgCl. The solution may be kept at -40 °C for some time, but develops a precipitate of benzoic acid.[3] CCl_4 may also be used as a solvent.[4] Alternatively, PhCOCl in MeCN is added dropwise to a rapidly stirred solution of $AgNO_3$ in MeCN plus the required substrate, such as PhR, to be nitrated; eventually this is done at reflux temperature.[3] This is likely to work satisfactorily only if the target reaction is sufficiently rapid.

Purification: kinetic and product studies (such as in the nitration of toluene[4] and also involving substituted analogs of the title reagent) yield an invariant isomer composition of the nitrotoluenes,[3] suggesting that the active ingredient may be N_2O_5, present in equilibrium with benzoic anhydride.

Handling, Storage, and Precautions: unstable above room temperature; stock solution may be stored in the cold,[3] but the use of freshly (or in situ) prepared reagents is recommended. This reagent should be handled in a fume hood.

Electrophilic Nitration (and Benzoylation).

Regular nitration of toluene typically gives a 50% yield of $MeC_6H_4NO_2$, with *o*:*m*:*p* = 62:4:34.[3] In the presence of Al-exchanged mordenite a 99% yield has been claimed, the isomer distribution now being 67:1:32;[5] with H-ZSM 11, selectivity to *para* was even 98%. Further examples include PhR with R = Et, *n*-Pr, *i*-Pr, *t*-Bu; *p*-terphenyl gave a 71% crude yield of $p\text{-}NO_2C_6H_4C_6H_4C_6H_4NO_2\text{-}p$. With *o*-xylene, 3- and 4-nitro-*o*-xylene (28% yield, ratio 32:68) *and* the corresponding benzoyloxy derivatives (16%, ratio 5:95) are formed; the benzoates apparently arise via *ipso* attack of nitronium ion, *p*- or *o*-addition of benzoate ion, and elimination of HNO_2.[6] Thiophene gives 2- and 3-nitrothiophene, in a ratio of ca. 6.[7] Secondary amines can be converted into the *N*-nitro derivative[8] (eq 1). Primary arylamines ($ArNH_2$), however, give ArNHOBz in high yield.[8] Indoles with a free 3-position are converted into their 3-nitro derivatives; 3-methylindole leads to 3-methyl-2-nitroindole, but yields in these reactions are modest (<35%).[9]

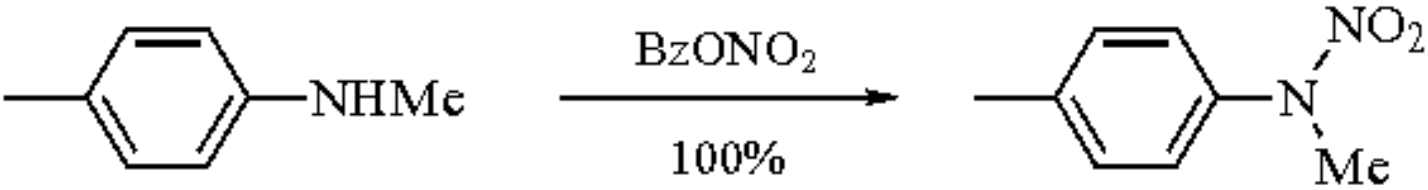

(1)

Oxidation.

Benzenethiol is quantitatively converted into PhSSPh.[2] Thiol ethers rapidly give sulfoxides in high yield, without further oxidation to sulfones, even well below 0 °C.[10]

Other Applications.

The oxidative power of the reagent can be directed to effect chlorination. In MeCN with aq. HCl it liberates Cl_2, and when performing the reaction in the presence of e.g. toluene, up to 1.7 mol of chlorotoluene (*o*:*p* = 54:46) per mol of benzoyl nitrate could be obtained.[11] Alcohols (ROH) are converted into $RONO_2$ and PhCOOH.[2]

Thermolysis.

Upon reflux in CCl_4 (9 h) PhCl, $PhCO_2H$, some $PhNO_2$, and CO_2 are produced.[12] In refluxing benzene, biphenyl, benzoic anhydride, $PhCO_2H$, and $PhNO_2$ arise. In both cases radical reactions occur.[13] Controlled gas-phase thermolysis at ca. 290 °C of RCO_2NO_2 can afford RNO_2 in ca. 50% yields.[14]

---

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Benzoyl Trifluoromethanesulfonate

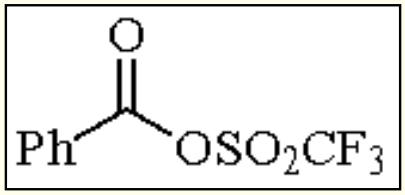

[36967-85-8] · $C_8H_5F_3O_4S$ · Benzoyl Trifluoromethanesulfonate · (MW 254.18)

(reagent for protection of hindered hydroxy groups as their benzoyl esters;[1] reagent effecting ring expansion of bridgehead carbaldehydes;[2,3] a highly reactive benzoylating reagent for Friedel-Crafts acylations[4])

Alternate Name: benzoyl triflate.

Physical Data: bp 92-94 °C/2.2 mmHg; *d* 1.51 g cm^{-3}

Solubility: generated and used in inert solvents such as dichloromethane, carbon tetrachloride, nitromethane, or carbon disulfide.

Preparative Methods: synthesized from ***Benzoyl Chloride*** and ***Trifluoromethanesulfonic Acid***.[1,5] Generation in situ has been achieved with benzoyl chloride and silver triflate,[5a,6] benzoic anyhdride and triflic acid,[5b,7] and reaction of *S*-methyl thiobenzoate with methyl triflate.[8]

Purification: the reagent can be distilled under reduced pressure.

Handling, Storage, and Precautions: very moisture sensitive and corrosive. Darkens on exposure to air, but can be stored at rt under dry nitrogen for several months without appreciable decomposition.

Benzoylation of Sterically Hindered Alcohols.

Benzoyl triflate is a reagent that has successfully been used for protecting sterically hindered alcohols as their benzoyl esters.[1] The reaction proceeds without base but in this case simple ketals and acetals undergo deprotection during the aqueous workup.[1a,b] If other Lewis acid-sensitive functional groups are present in the substrate, e.g. epoxides and spiroacetals, addition of pyridine is essential to prevent substantial decomposition.[1b] Nevertheless, some epoxide functions have been observed to undergo clean ring opening when the carbocation generated by the epoxide opening can be quenched by rearrangement (eq 1).[1a,b]

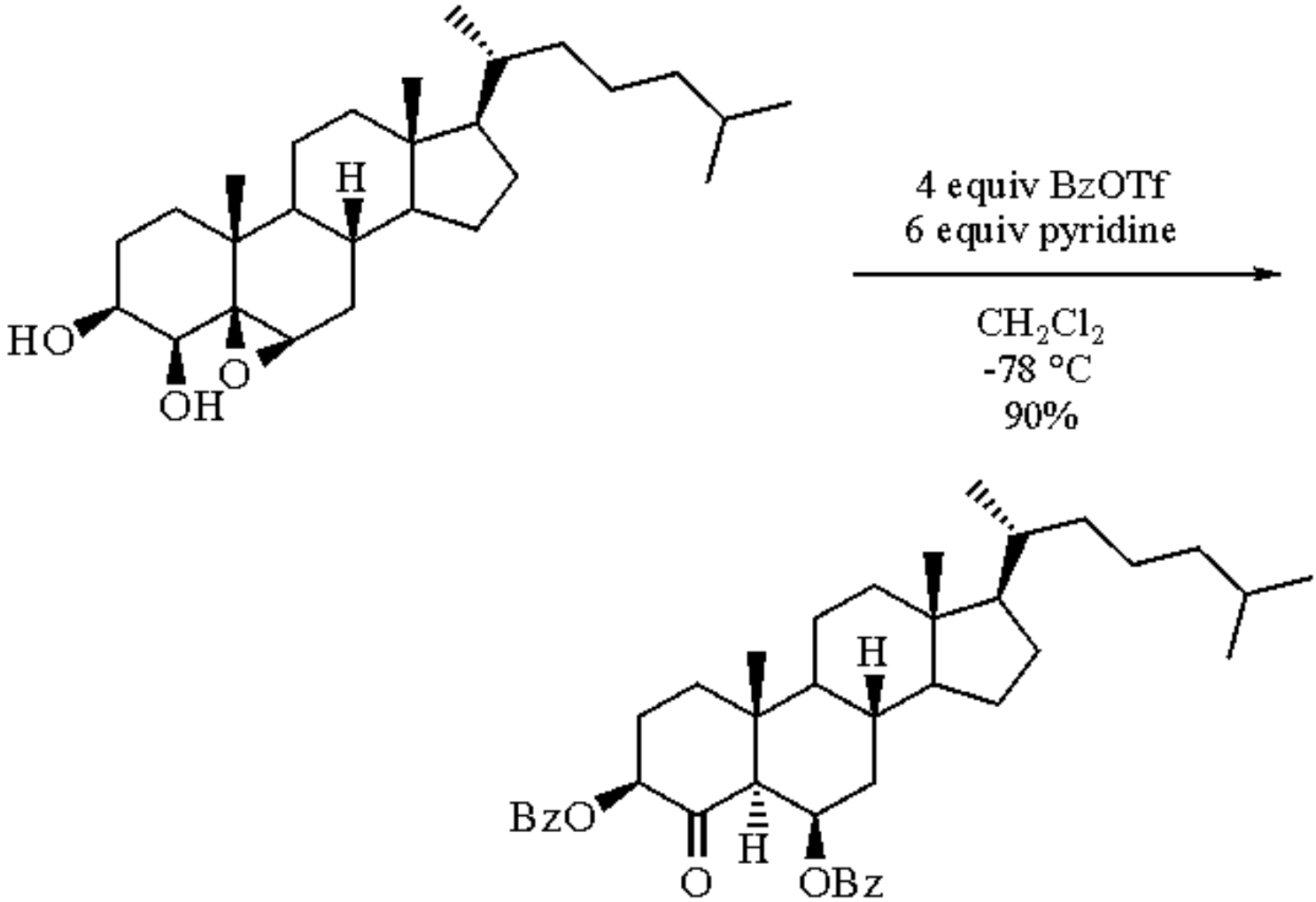

(1)

Ring Expansion of Bridgehead Carbaldehydes.

Bridgehead carbaldehydes react with benzoyl triflate and triflic acid to give ring-expanded 1,2-diol monobenzoyl esters (eq 2),[2,3] but other strong acids in place of triflic acid give greatly reduced yields.[2b] Unsymmetrical carbaldehydes react to give a mixture of the possible rearranged products,[2] and quenching the reaction with ***Tetra-n-butylammonium Iodide*** in place of water gives the corresponding tertiary iodo benzoate.[3]

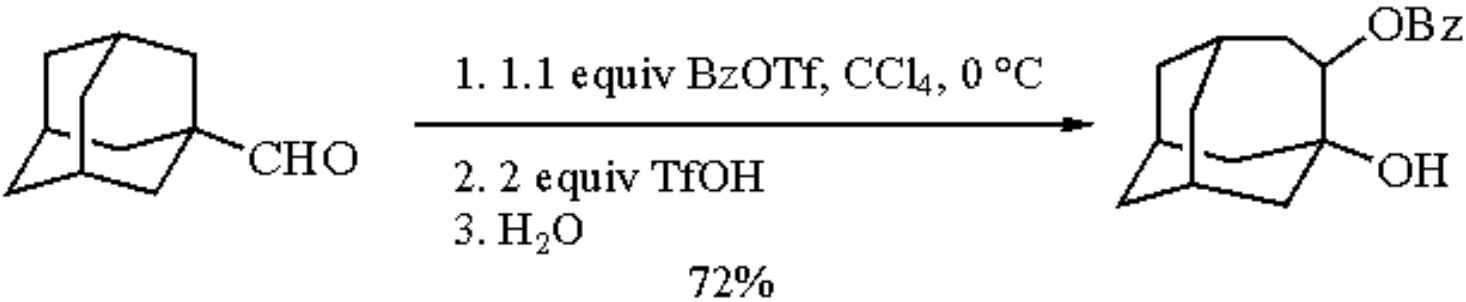

(2)

Friedel-Crafts Benzoylation.

Mixed carboxylic-triflic acid anhydrides are highly active Friedel-Crafts acylating agents.[4] Benzoyl triflate can

benzoylate benzene and deactivated chlorobenzene without the addition of a Friedel-Crafts catalyst,[5,6] whereas other sulfonic-carboxylic acid anhydrides fail to react at higher temperatures, even with activated arenes such as anisole. Friedel-Crafts benzoylation is possible in a catalytic cycle[5b,6,9] using benzoyl chloride or benzoic anhydride and 1-10 mol% of triflic acid, which is far superior to other Brønsted or Lewis acids.[5b,9] Substituted benzoyl triflates have been made also; for example, 4-nitro-,[5,6,8,10] 4-methyl-,[8] and 2,4,6-trimethylbenzoyl triflates.[8] Benzoyl triflate has also been used to benzoylate less common heteroaromatic substrates such as 1,3,5,2,4-trithiadiazepine.[7] Although this was low yielding, conventional Friedel-Crafts chemistry had failed completely.

Reaction mixtures of 2-(trifluoromethylsulfonyloxy)pyridine, benzoic acid, and trifluoroacetic acid have also been used to benzoylate arenes, and benzoyl triflate is one of the proposed acylating species in this mixture.[11]

Benzoylation of alkynes[12] has been reported using benzoyl triflate. Both *cis*- and *trans*-vinyl triflates as well as indenones are produced, with the distribution depending on ring and alkyne substituents (eq 3).

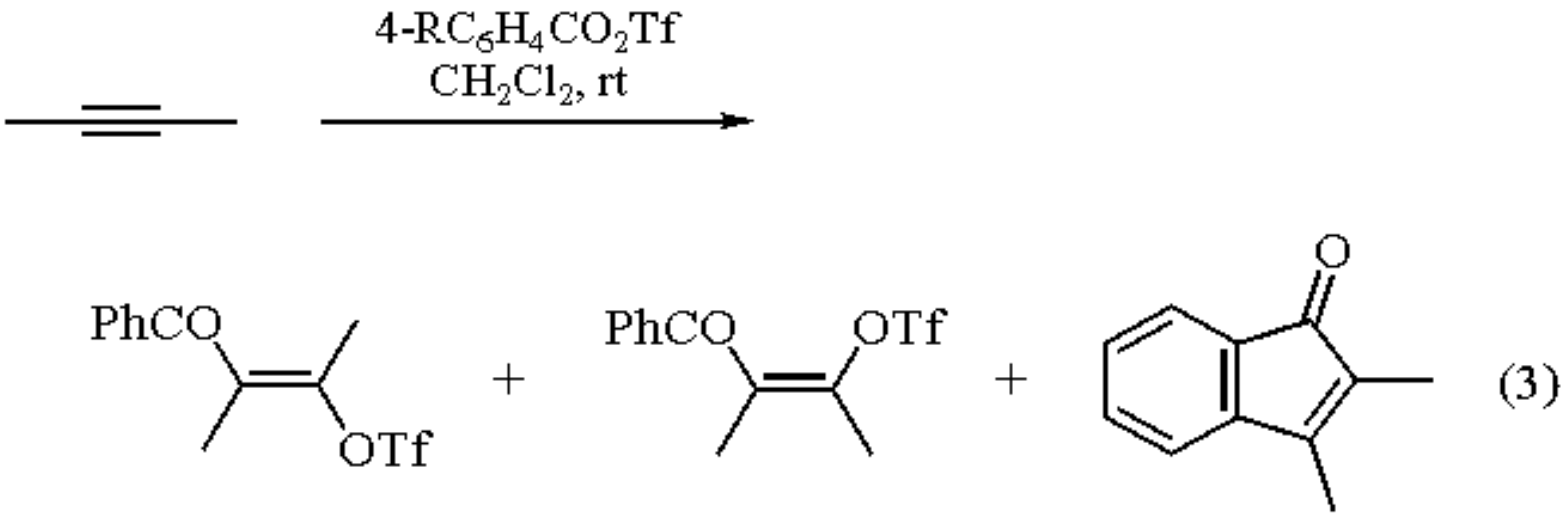

R = H	71.5	6.5	22.0
R = NO_2	40.0	60.0	0.0
R = OMe	82.0	1.5	16.5

Reaction with α-diazo ketones[13] was shown to proceed via *O*-benzoylation. Quenching of the reaction with an amine produced triazoles, whereas warming resulted in loss of nitrogen and formation of 1,3-dioxolium salts (eq 4).

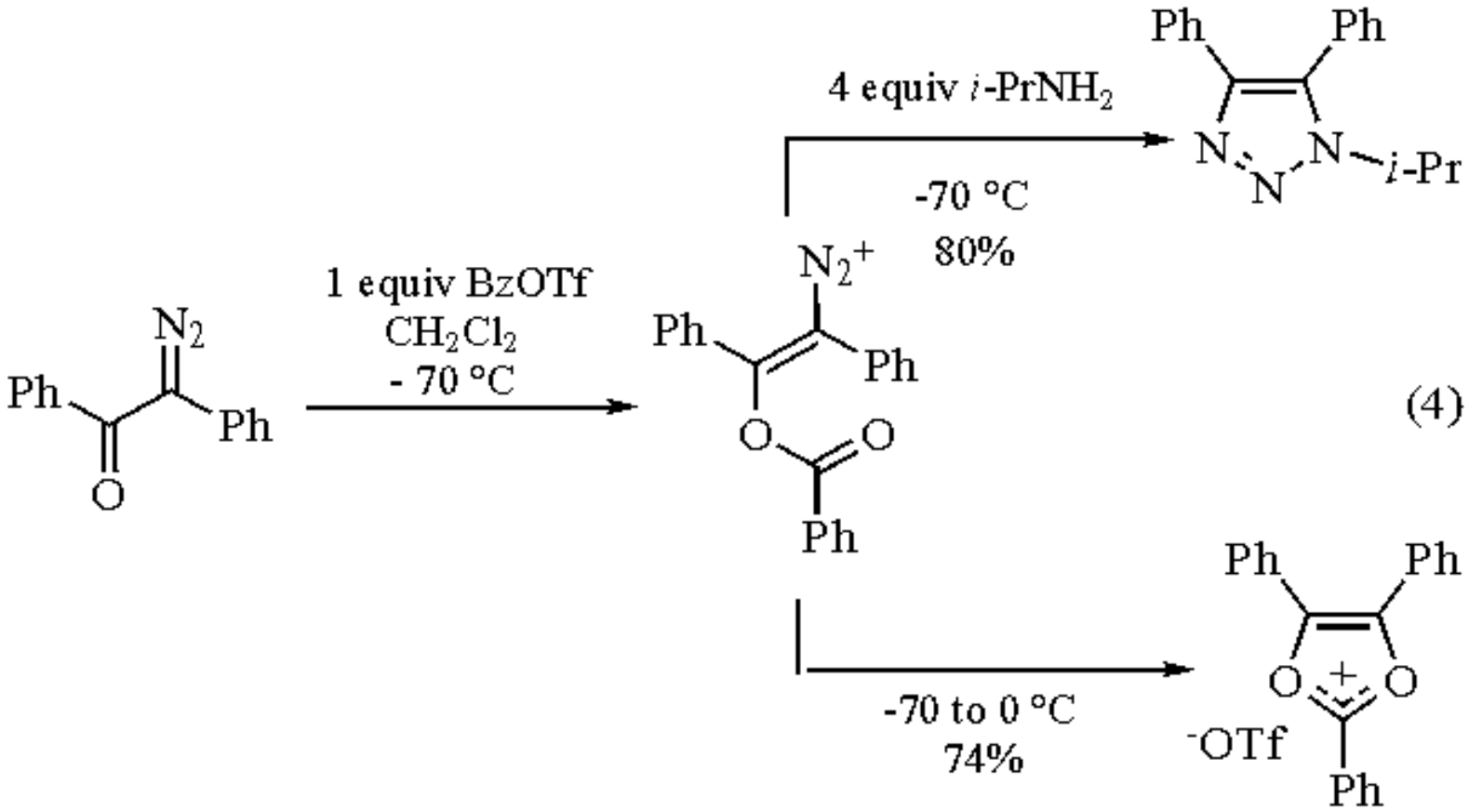

Mixed carboxylic-triflic acid anydrides for Friedel-Crafts acylations are not just restricted to aromatic carboxylic acids, and these can have advantages over conventional Friedel-Crafts systems when applied to sensitive substrates.[14] Aliphatic carboxyl triflates[4-8] and trifluoroacetyl triflate[15] have been made, and intramolecular Friedel-Crafts acylation has been achieved using an aromatic acid chloride with triflic acid catalysis.[16]

Related Reagents.

Acetyl Fluoride; ***Benzoyl Chloride***.

---

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Benzyl Bromide

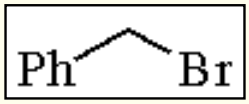

[100-39-0] · C_7H_7Br · Benzyl Bromide · (MW 171.04)

(benzylating agent for a variety of heteroatomic functional groups as well as carbon nucleophiles)

Physical Data: mp -3 to -1 °C; bp 198-199 °C; *d* 1.438 g cm^{-3}.

Solubility: sol ethereal, chlorinated, and dipolar aprotic solvents.

Form Supplied in: 98-99% pure liquid.

Handling, Storage, and Precautions: the reagent is a potent lachrymator and should be handled in a fume hood.

Benzylation of Heteroatomic Functional Groups.

Benzylation of various heteroatomic functional groups is readily achieved with this reagent under a variety of conditions and finds widespread application in organic synthesis, primarily as a protecting group.[1]

Alcohols and phenols are benzylated upon treatment with benzyl bromide under basic conditions. For example, treatment of alcohols with ***Sodium Hydride*** or ***Potassium Hydride*** in ethereal solvent[2] or DMF[3] generates alkoxides, which subsequently undergo Williamson reactions with benzyl bromide. Selective benzylation of a primary alcohol in the presence of a secondary alcohol has been accomplished in DMF at low temperature.[4]

Benzylation of alcohols using ***Potassium Fluoride-Alumina*** and benzyl bromide in acetonitrile at room temperature is effective.[5] Silver oxide in DMF is yet another base system.[6] Of particular interest in carbohydrate applications is the reaction of benzyl bromide with carbohydrate derivatives which have been pretreated with tin reagents. Thus it is possible to benzylate an equatorial alcohol in the presence of an axial alcohol (eq 1)[7] and also to selectively benzylate an anomeric hydroxy through ***Di-n-butyltin Oxide***.[8]

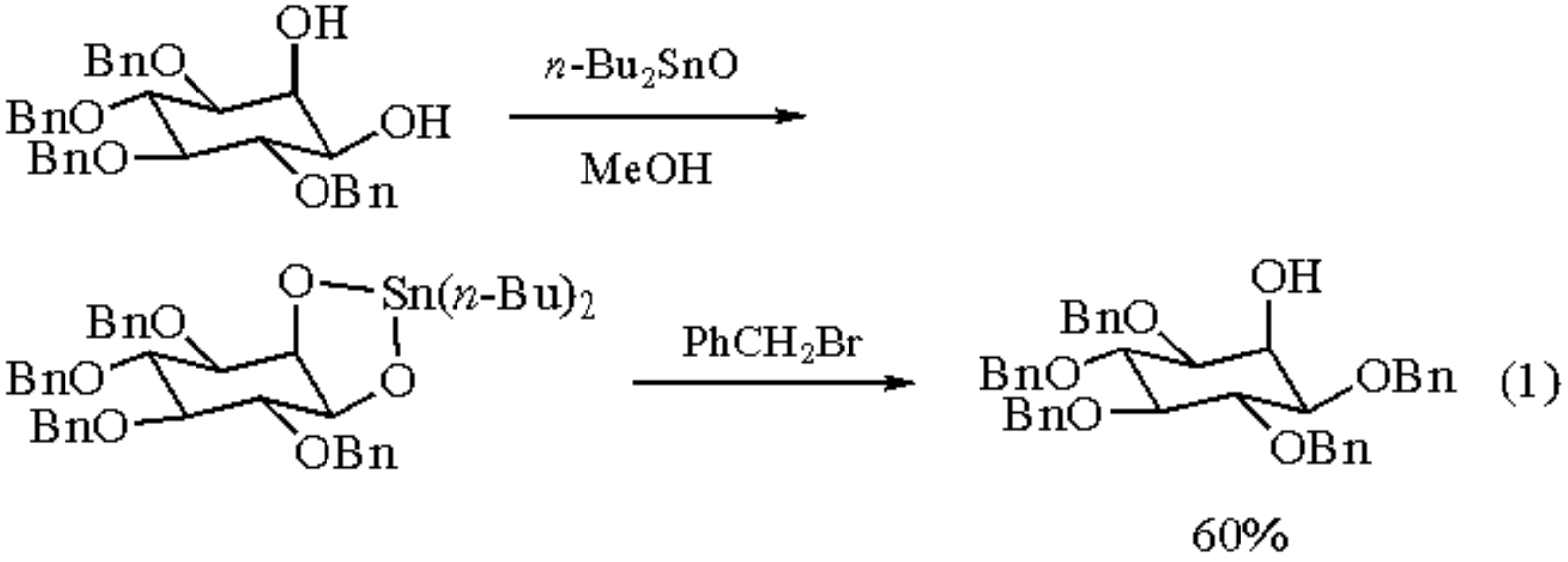

In some instances the sluggish reactivity of sterically hindered alcohols toward benzyl bromide may be overcome through addition of a catalytic iodide source such as ***Tetra-n-butylammonium Iodide***, which generates the more reactive benzyl iodide in situ (see ***Benzyl Iodide***). Benzylation of phenols proceeds well under the conditions described for aliphatic alcohols. Owing to the greater acidity of phenols it is possible to use weaker bases such as ***Potassium Carbonate*** for these reactions.[9]

Benzyl bromide will readily alkylate amino groups. Reactions are normally carried out in the presence of additional base and dibenzylation of primary amines is usually predominant.[10] Selective quaternization of a less hindered tertiary amine in the presence of a more hindered tertiary amine has been described.[11] Amide and lactam nitrogens can be benzylated under basic conditions,[12] as can those of sulfonamides[13] and nitrogen heterocycles.[14]

Thiols,[15] silyl thioethers,[16] and thiosaccharins[17] may be benzylated with benzyl bromide under basic conditions. Thus L-cysteine is *S*-benzylated under basic conditions (eq 2).[18] Benzylation of selenols is likewise possible.[19] A synthesis of benzylic sulfones is possible using ***Benzenesulfonyl Chloride*** and ***Sodium O,O-Diethyl Phosphorotelluroate*** with benzyl bromide.[20]

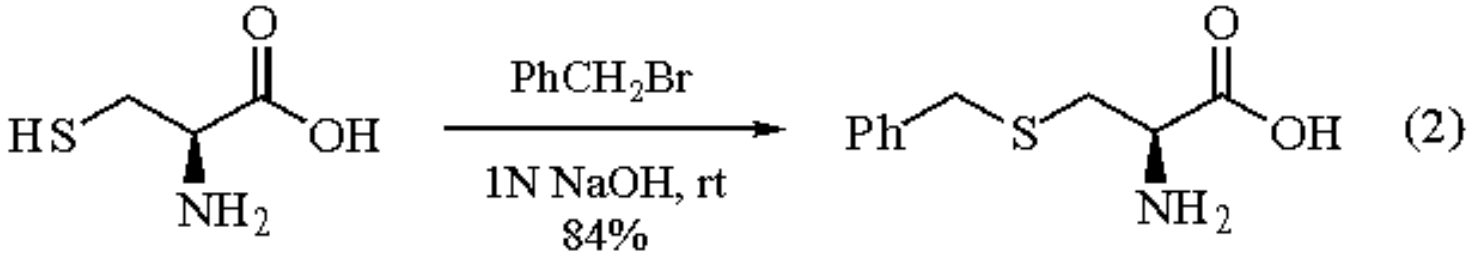

Although the preparation of benzyl carboxylate esters from benzyl bromide and carboxylate anions is not the most common route to these compounds, the reaction is possible when carried out in DMF[20] or using zinc carboxylates.[21]

Nucleophilic attack on benzyl bromide by cyanide and azide anions is feasible with ion-exchange resins or with the corresponding salts.[22]

Reactions with Active Methylene Compounds.

Enolates of ketones,[23] esters,[24] enediolates,[25] 1,3-dicarbonyl compounds,[26] amides and lactams,[27] as well as nitrile-stabilized carbanions,[28] can be alkylated with benzyl bromide. Cyclohexanone may be benzylated in 92% ee using a chiral amide base.[29] Amide bases as well as alkoxides have been employed in the case of nitrile alkylations.[28b] Benzylation of metalloenamines may be achieved[30a] and enantioselective reactions are possible using a chiral imine (eq 3).[30b] However, reactions between benzyl bromide and enamines proceed in low yield.[31] The benzylation of a ketone via its enol silyl ether, promoted by fluoride, has been observed.[32]

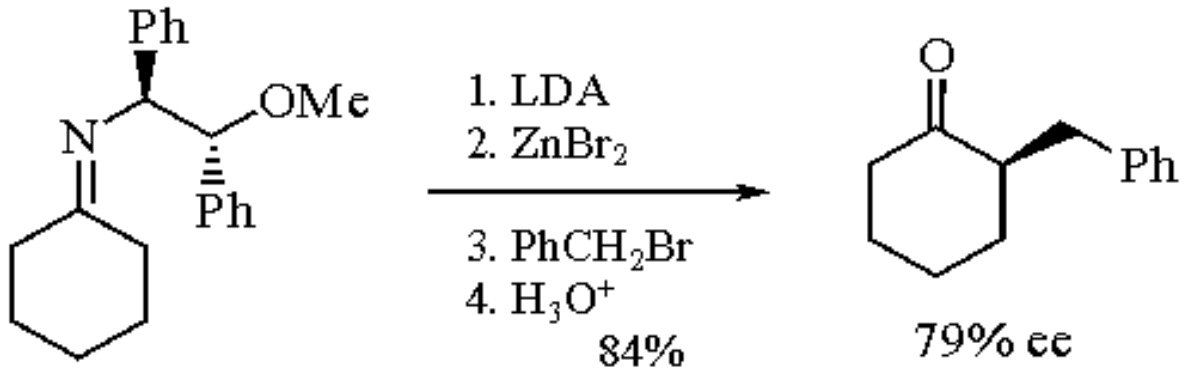

(3)

Reactions with Metals and Organometallics.

Difficulties encountered in the preparation of benzylic metal compounds with active metals are due primarily to the tendency of these compounds to undergo Wurtz coupling (self condensation).[33] Benzylmagnesium bromide may nevertheless be prepared from benzyl bromide and used under standard[34] or Barbier conditions.[35] Benzyllithium cannot be obtained practically from benzyl bromide. Benzylzinc bromide and the cyanocuprate BnCu(CN)ZnBr have both been prepared. The cuprate undergoes 1,2-additions with aldehydes and ketones.[36]

The propensity of benzyl bromide to undergo coupling with organometallic reagents may be used to advantage, as organolithiums,[37] Grignard reagents,[38] organocuprates,[39] organocadmiums,[40] organochromiums,[41] and organoiron reagents[42] are all known to give coupling products. An interesting coupling of benzyl bromide with *N*-methylphthalimide under dissolving metal conditions has been reported (eq 4).[43]

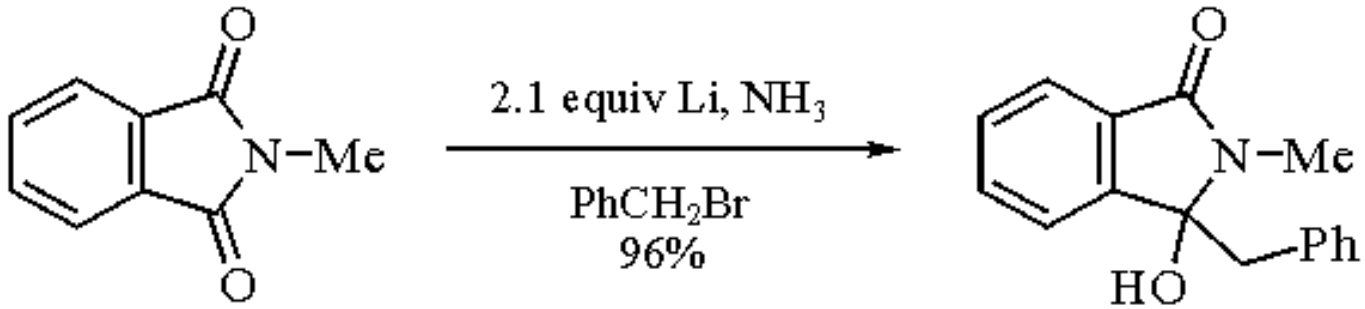

(4)

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Benzyl Bromomethyl Sulfide

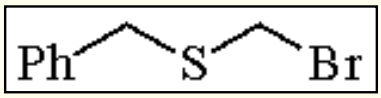

[15960-81-3] · C_8H_9BrS · Benzyl Bromomethyl Sulfide · (MW 217.12)

(introduction of protected mercaptomethyl group via enolate alkylation; synthesis of α-methylene ketones and carboxylic acids[2])

Physical Data: bp 65.5-67 °C/0.2 mmHg.

Solubility: sol CH_2Cl_2, THF.

Preparative Methods: from phenylmethanethiol, paraformaldehyde, and 48% HBr_2 or from benzyl chloromethyl sulfide and anhyd HBr.[3]

Handling, Storage, and Precautions: store cold; use in a fume hood.

Benzyl bromomethyl sulfide alkylates enolates derived from ketones,[2] carboxylic acids,[2] malonates,[3] oxazolidones,[4] and oxazolidyl carboximides,[1] often where ***Benzyl Chloromethyl Sulfide*** (see also ***Chloromethyl Methyl Sulfide*** and ***Chloromethyl Phenyl Sulfide***) proved unsuccessful (eq 1).[2] The alkylation products are debenzylated to give α-mercaptomethyl groups,[1,4] or converted to α-methylene compounds by oxidation to sulfoxides followed by thermolysis (see also ***Dimethyl Disulfide*** and ***Diphenyl Disulfide***).[2,5]

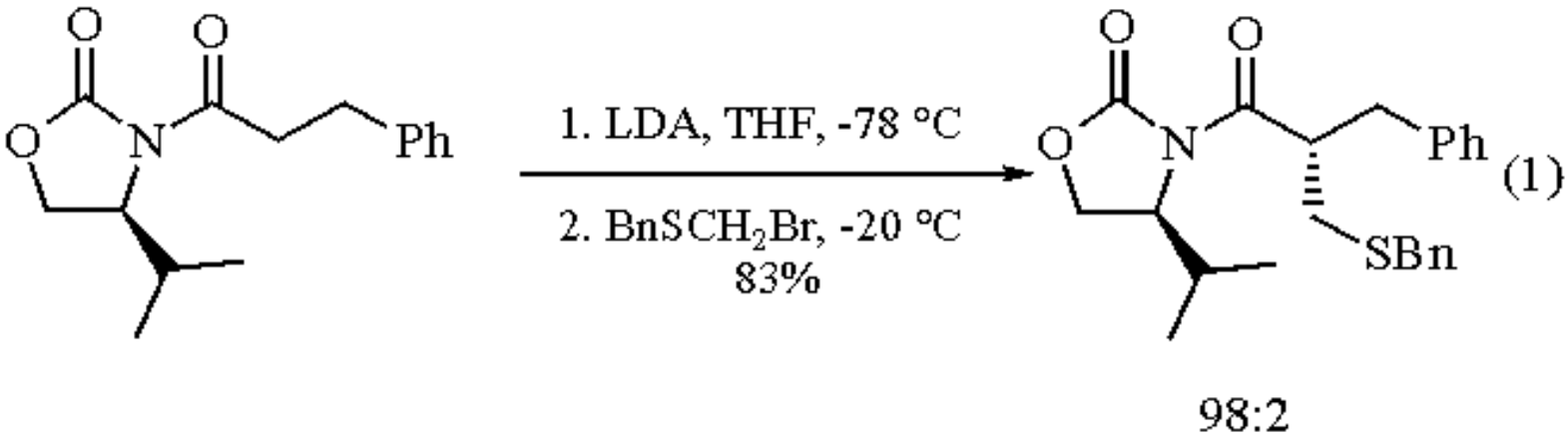

Although benzyl bromomethyl selenide reacts 18 times more slowly than benzyl bromomethyl sulfide, similar alkylation has been achieved with carboxylic acid and amide dianions, enolates of tertiary ketones, and protected amino acid esters (glycine, valine, and alanine).[2] Oxidative debenzylation with Br_2 or SO_2Cl_2 cleanly converts the

selenide to the selenenyl halide, which is conveniently reduced in situ to the diselenide (eq 2). Alternatively, oxidation of the selenide followed by selenoxide elimination mildly generates the alkene (eq 2).[2]

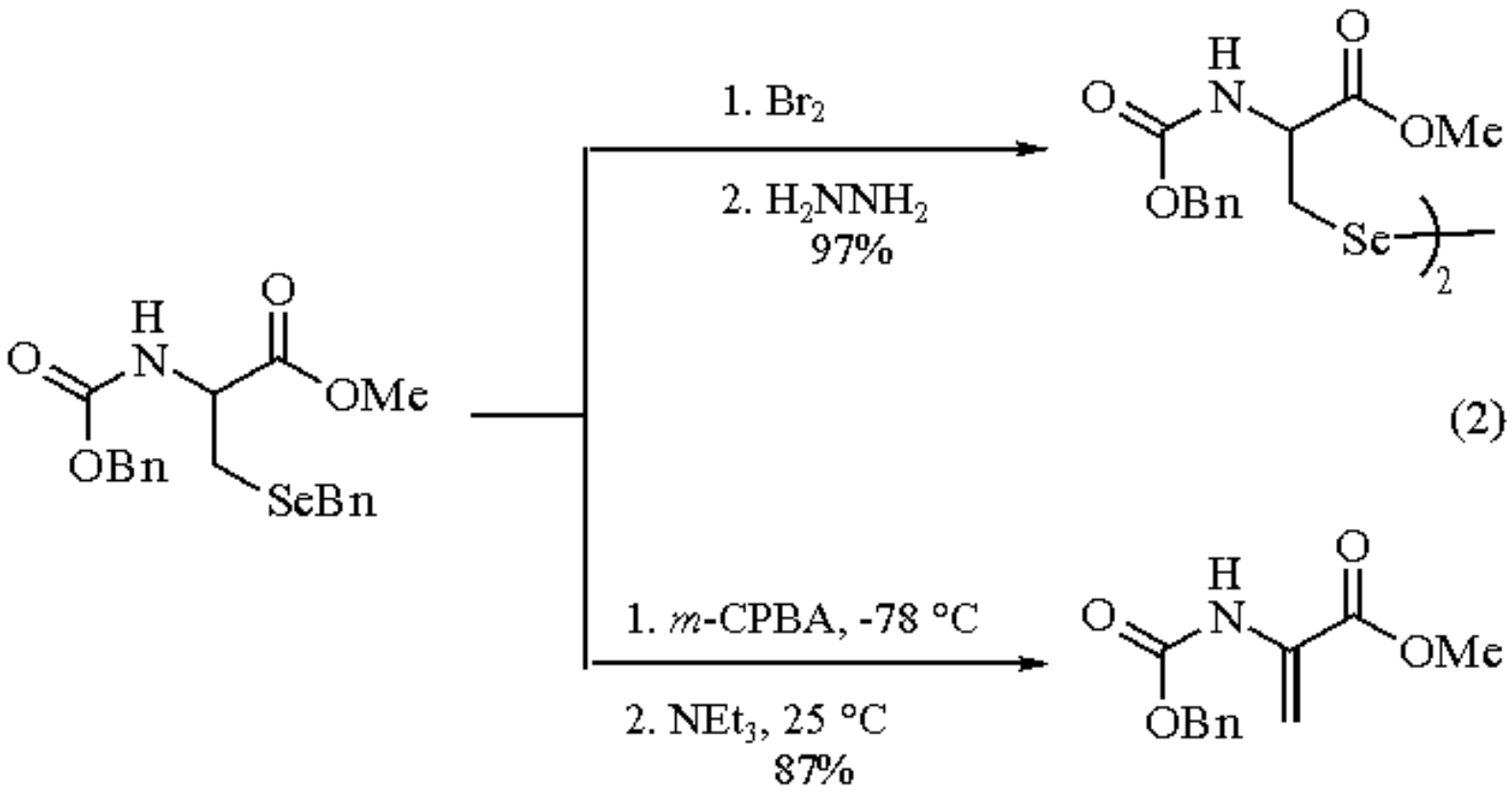

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Benzyl 1,3-Butadiene-1-carbamate

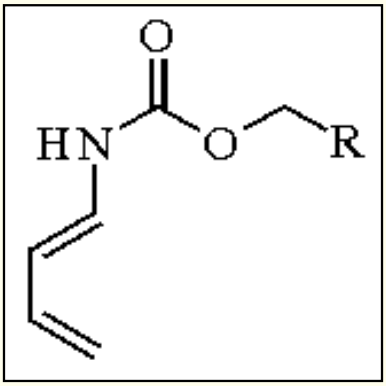

(**1**; R = Ph)

[65899-49-2] · $C_{12}H_{13}NO_2$ · Benzyl 1,3-Butadiene-1-carbamate · (MW 203.09) (**2**; R = Me)

[61759-61-3] · $C_7H_{11}NO_2$ · Ethyl 1,3-Butadiene-1-carbamate · (MW 141.08)

(1,3-dienes: useful aminobutadiene equivalents for Diels-Alder reaction,[1] regio- and stereoselective reactions even with poor dienophiles;[2] used in the synthesis of complex heterocyclic natural products[3] and aminoanthraquinones[4])

Physical Data: [5-7] (**1**) mp 74-75 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, Ph), 6.71 (br d, *J* = 9 Hz, =CHNH), 6.26 (dt, *J* = 10, 17 Hz, CH=CH_2), 5.4-5.8 (m, CH=CHNH and NH), 5.15 (s, CH_2Ph), 4.8-5.2 (m, =CH_2); ^{13}C NMR ($CDCl_3$) δ 127.2, 112.5, 134.6, 113.5, 128.3, 128.4, 128.7, 136.0, 153.7, 67.5. (**2**) mp 44-45 °C; ^{1}H NMR ($CDCl_3$) δ 7.7 (br d, NH), 5.3-6.9 (m, vinylic), 4.5-5.1 (m, =CH_2), 4.13 (q, *J* = 7 Hz, Me); ^{13}C NMR ($CDCl_3$) δ 127.6, 112.1, 134.8, 113.2, 14.5, 61.7, 154.1.[2,5]

Solubility: (**1**) readily sol dioxane and toluene; (**2**) sol dioxane.

Preparative Methods: The synthesis of various *N*-acyl-1-amino-1,3-dienes have been described in detail.[6-10] The following, which uses a Curtius rearrangement (eq 1),[7] illustrates the procedure commonly used in the synthesis of (**1**) and (**2**).

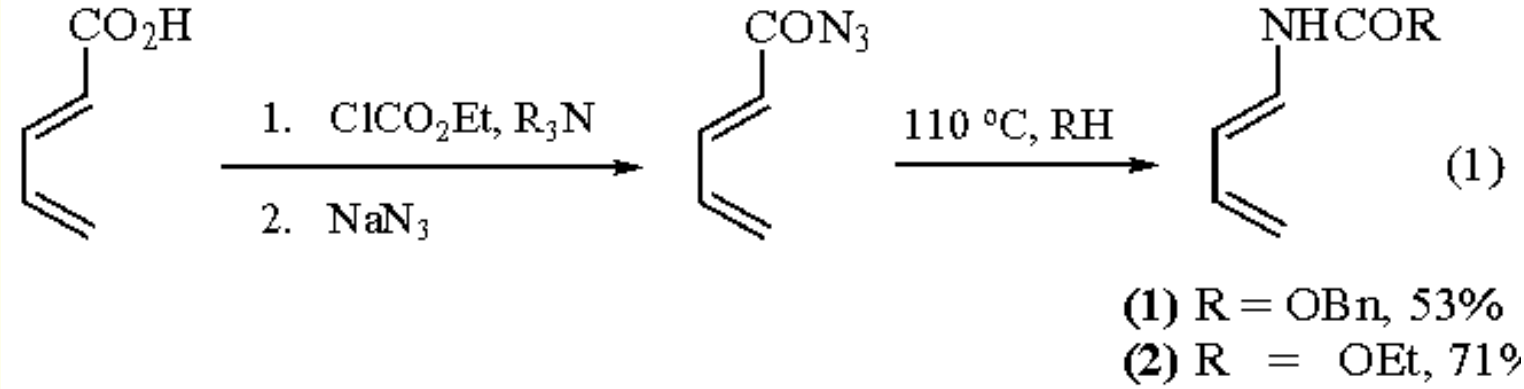

Handling, Storage, and Precautions: in general, acyl azides are potentially explosive. Therefore solutions containing acyl azides should not be evaporated to dryness.[5] Both (**1**) and (**2**) are stable solids, which can be stored in a freezer for several months. However, they are acid-sensitive and may be decomposed by traces of deuterium chloride present in chloroform-*d*.[5] In rigorously degassed (oxygen-free) solutions, these diene carbamates are stable for extended periods even at 140 °C and this has been a critical factor in their successful reactivity with poor dienophiles.[2]

Diels-Alder Reactions.

Both (**1**) and (**2**) react with a broad range of dienophiles, providing a variety of amino-functionalized cycloadducts in high yields. Reaction with methyl acrylate yields cyclohexenes with high regio- and stereoselectivity (*endo*) (eq 2).[6] In contrast, with the same dienophile, 2,4-pentanedienoic acid requires longer reaction times and gives a mixture of all the possible stereo- and regioisomers.[1]

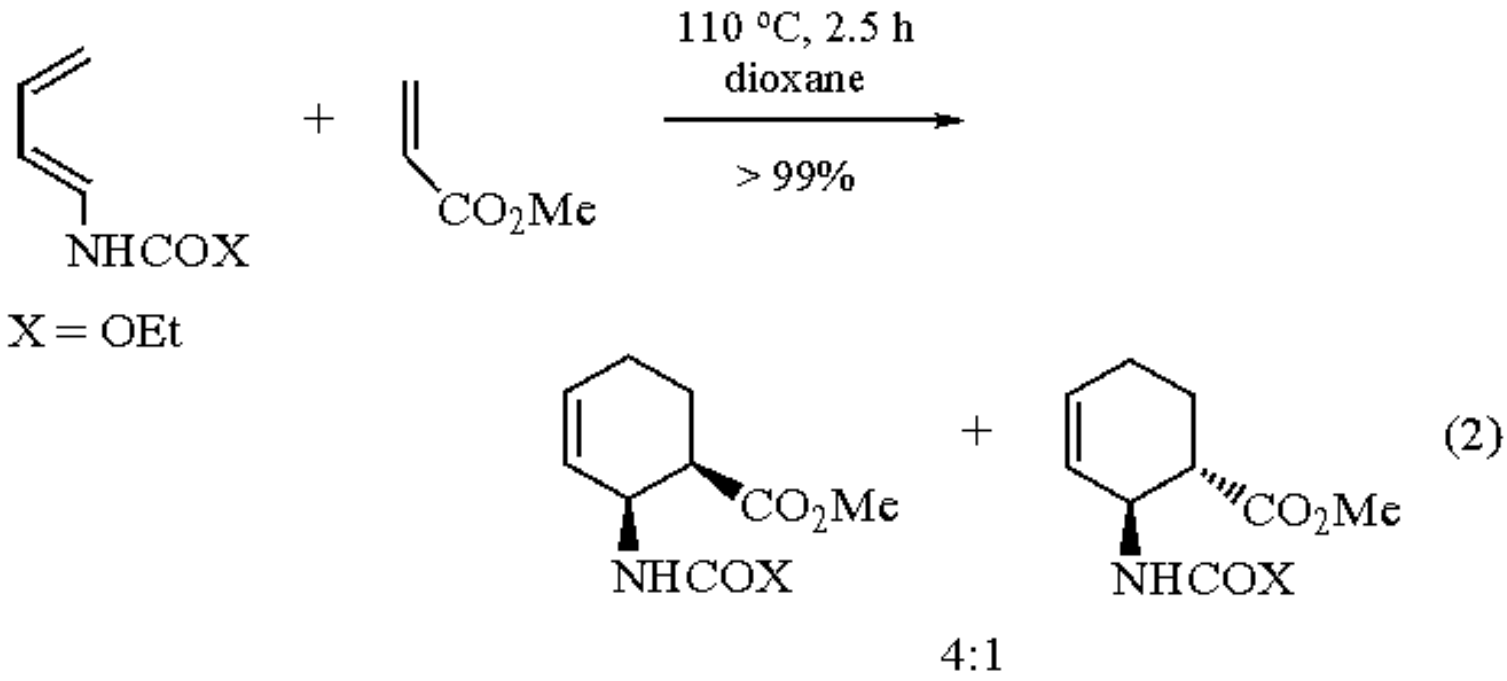

The ability to give *endo* selectivity, coupled with their higher reactivity, is, in part, responsible for the versatility of (**1**) and (**2**) in natural product synthesis. The construction of three of the chiral centers found in (±)-pumiliotoxin C was achieved in a single step (eq 3).[11,12] While other dienes exhibited lower stereoselectivities with *trans*-crotonaldehyde,[13,14] (**1**) and (**2**)

gave the *endo* products in 61 and 67% yields, respectively; these were key intermediates in the synthesis of (±)-pumiliotoxin C.[12] Additionally, use of a chiral dienophile, (5*R*)-5-hydroxy-6,6-dimethylhept-2-en-4-one, permitted the asymmetric synthesis of (+)-pumiliotoxin C.[15]

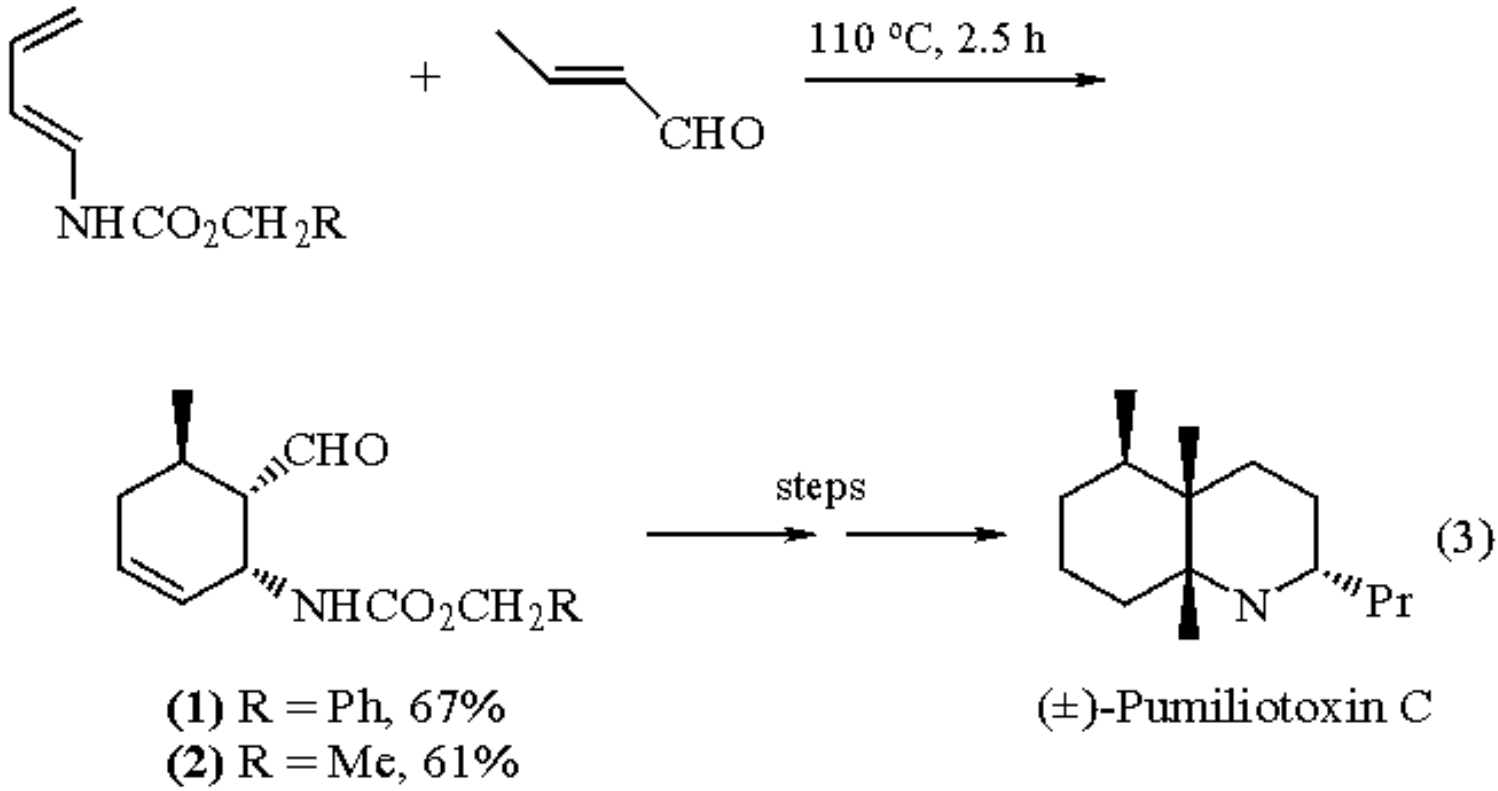

The cycloaddition of benzyl *trans*-1,3-butadiene-1-carbamate (**1**) and ethyl atropate affords the major product *endo*; this was a key intermediate in the synthesis of (±)-tilidine (eq 4).[16] Of significance is the opposite stereoselectivity exhibited by the related *trans*-1-(dialkylamino)-1,3-dienes ($R^1 = R^2 = Me$).[17,18]

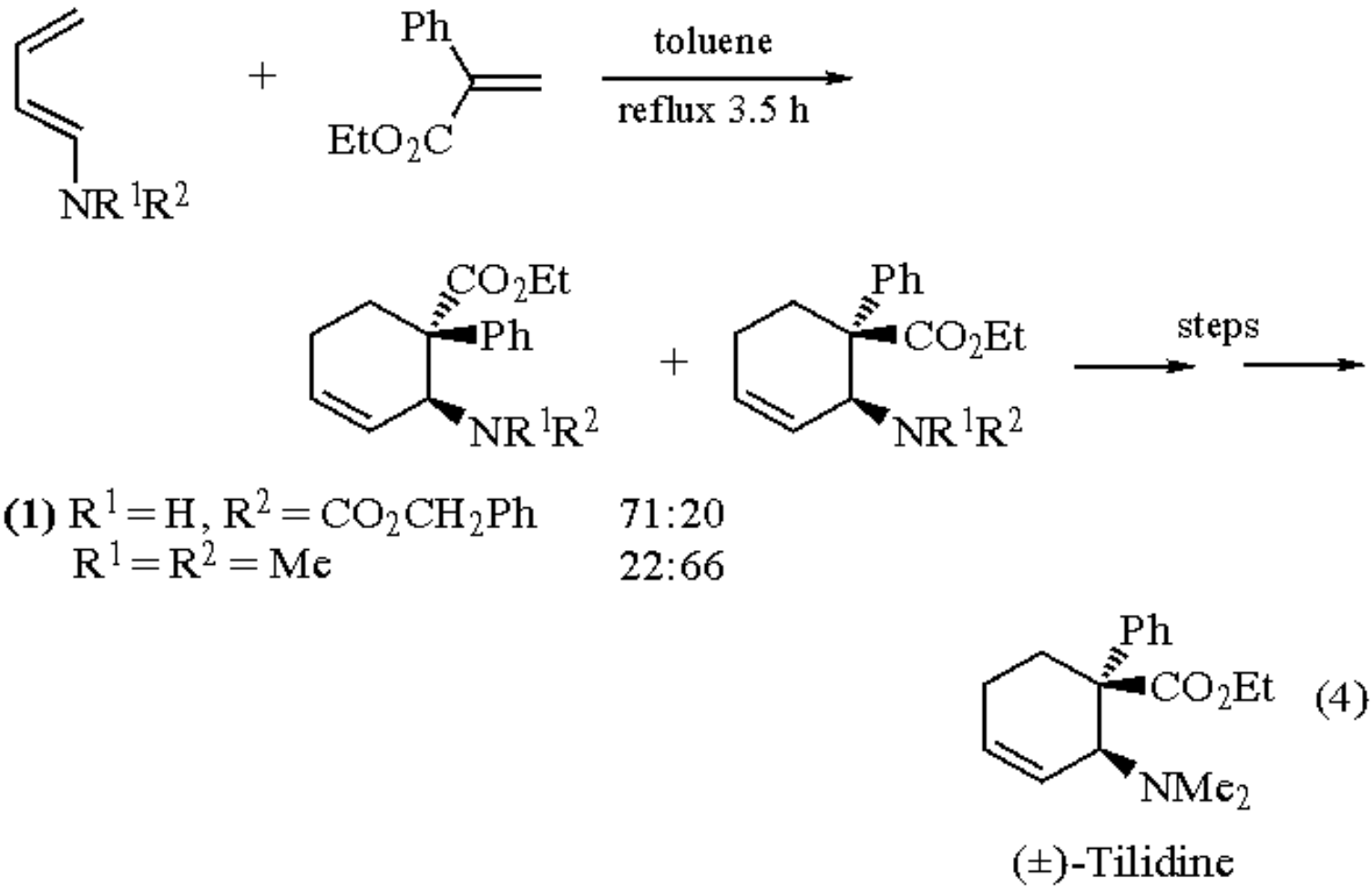

The most remarkable feature of dienes (**1**) and (**2**) is their ability to give *endo* cycloaddition products, in good yields, with extremely poor dienophiles such as methyl *trans*-crotonate, *trans*-crotonaldehyde, 2-cyclohexenone, styrene, and 3,4-methylenedioxystyrene.[2,11,19-24] The reaction of (**1**) with phenylacetylene (140 °C, 114 h),[2] however, led to a mixture of 13 products, suggesting an upper limit to the reactivity of these dienes.

To date, Diels-Alder reactions involving (**1**) and (**2**) have been the key step in syntheses of gephyrotoxin,[26] (±)-perhydrogephyrotoxin,[25] (+)-pumiliotoxin,[11,15] (±)-isogabaculine,[27] and (±)-tilidine.[16] In addition, substituted aminoanthraquinones have been synthesized by the regioselective cycloaddition of (**1**) to naphthoquinones followed by aromatization.[4,28] Also noteworthy is the synthesis of epimeric *cis*-decahydroquinoline-5-carboxylic acids, which involved the reaction of (**1**) with *trans*-3-acetylcrotonaldehyde.[29] Additionally, the presence of an easily modifiable phenyl group in (**1**) has led to the generation of a water-soluble diene (eq 5), which has been used in antibody-catalyzed Diels-Alder reactions.[30] Exclusive formation of either isomer (*endo* or *exo*) has been possible, depending on the transition state analog used for the elicitation of catalytic antibodies.[30]

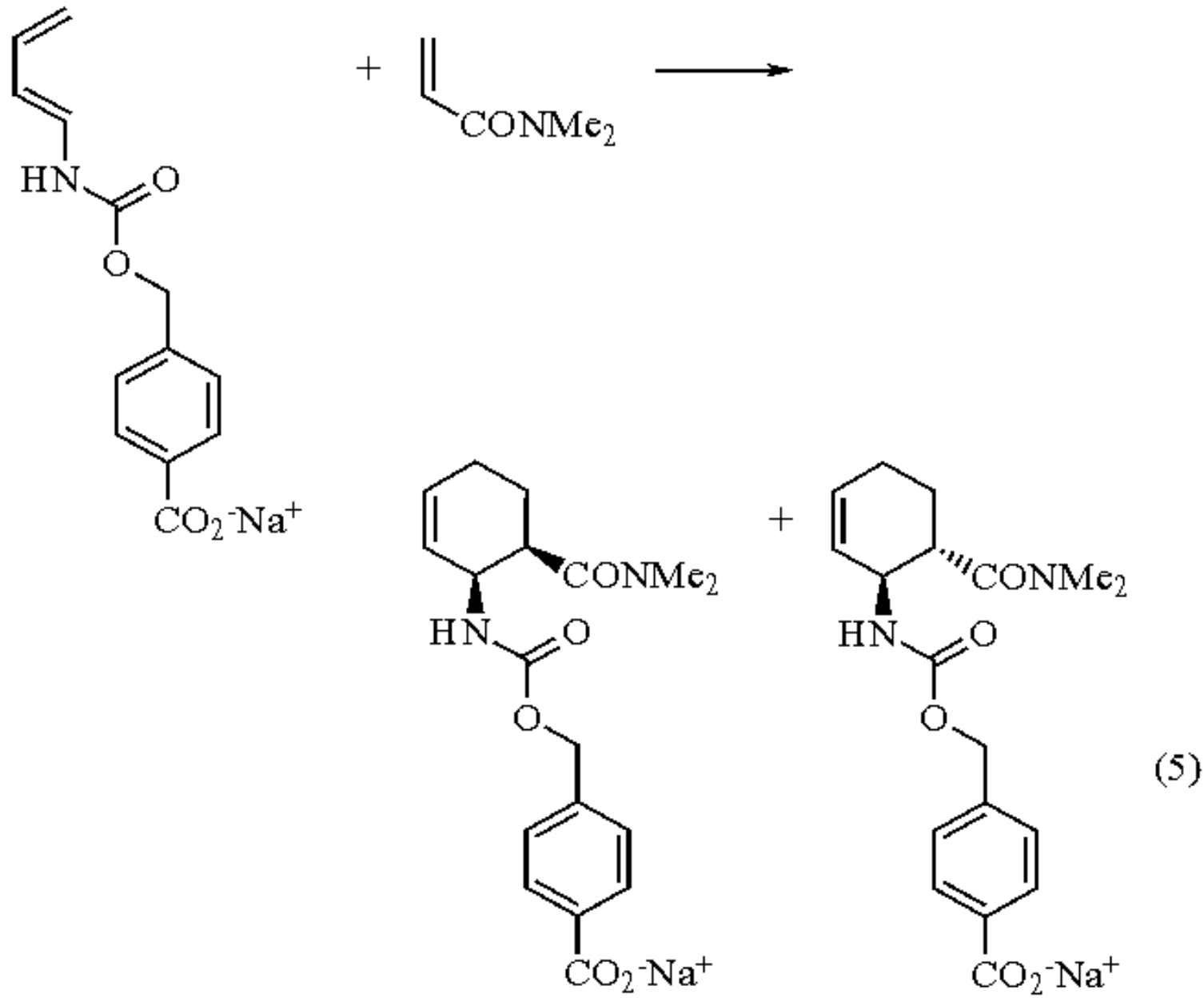

(i) buffer, 37 °C 85:15
(ii) antibody, buffer, 37 °C exclusive formation of either isomer

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Benzyl Chloride

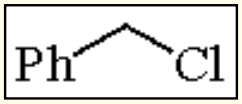

[100-44-7] · C_7H_7Cl · Benzyl Chloride · (MW 126.59)

(benzylating agent for a variety of heteroatom functional groups and carbon nucleophiles; precursor to benzyl organometallics)

Physical Data: bp 177-181 °C; *d* 1.100 g cm^{-3}.

Solubility: freely miscible in ethereal, chlorinated, and dipolar aprotic solvents.

Form Supplied in: 99% pure liquid.

Handling, Storage, and Precautions: the reagent is a mutagen and possibly a carcinogen. It should be used in a fume hood.

Benzylation of Heteroatom Functional Groups.

Benzyl chloride is a versatile benzylating agent for heteroatom functional groups and is commonly used to introduce this protecting group.[1] Benzylation of alcohols with this reagent is achieved under strongly basic conditions such as KOH, either in an alcoholic solvent[2] or under phase transfer conditions with *n*-Bu_4NHSO_4.[3] Silver oxide in DMF is also effective.[4] A procedure involving $Ni(acac)_2$ has also been reported.[5] Phenols may also be benzylated under basic conditions.[6]

Amino groups are readily benzylated when treated with benzyl chloride in the presence of carbonate or hydroxide base,[5] although dibenzylation of primary amines is a competing reaction.[7] Thiols are benzylated with sodium hydroxide or cesium carbonate in polar solvents such as ethanol or DMF.[8] Dibenzyl sulfide is produced by reaction of benzyl chloride with elemental sulfur and sodium triethylborohydride.[9]

Amides can be *N*-benzylated with this reagent under the influence of strong bases such as metal hydrides.[10] A benzyl carboxylate ester may be formed from benzyl chloride and the corresponding sodium salt of the acid in DMSO.[11]

Benzyl cyanide can be prepared from benzyl chloride and KCN with an ion exchange resin.[12] Benzyl azide is formed by reaction with trimethylsilyl azide in HMPA.[13]

Benzylation of Active Methylene Compounds.

The anions or dianions of β-ketoesters,[14] substituted malonate esters,[15] β-ketoaldehydes,[16] β-diketones,[17] β-ketoamides,[18] and β-ketonitriles[19] all react effectively with benzyl chloride to afford *C*-benzylated products. When the dianion of a β-ketoamide, β-ketoester, or β-diketone is generated and treated with benzyl chloride, benzylation is observed at the least acidic position. Nitrile-stabilized carbanions are readily benzylated in ethereal solvents, ammonia, or DMSO.[15,20] Benzyl chloride also reacts well with carbanions derived from ketones,[21] esters,[22] imines (metalloenamines),[23] oximes,[24] and hydrazones.[23] When benzalacetophenone is treated sequentially with 2 equiv of potassium in ammonia and then with benzyl chloride in ether, a formal conjugate addition of the benzyl group is observed (eq 1).[25] If a second equivalent of benzyl chloride is added, benzylation occurs at both the α- and β-positions.

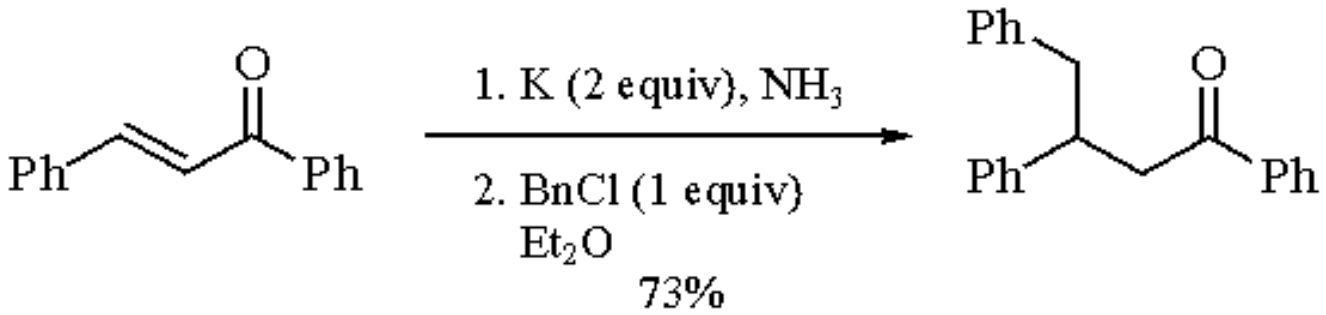

(1)

Reactions with Metals and Organometallics.

Benzylmagnesium chloride can be prepared satisfactorily by rapid addition of benzyl chloride to magnesium in ether.[26] Benzyl chloride is readily dimerized by lithium naphthalenide,[27] sodium and tetraphenylethane,[28] zinc in the presence of catalytic nickel(II) bromide,[29] with titanocene dichloride and diiodomethane,[30] $(PPh_3)_3CoCl$,[31] and by electrolysis.[32] The cross-coupling reactions of benzyl chloride with other organometallics is demonstrated by the benzylation of organolithiums,[33] as in the case of a directed lithiation product (eq 2),[32a] Grignard reagents,[34] and organocuprates.[35] Vinyl boranes, derived from the addition of boron tribromide to alkynes and subsequent alkylation with organozincs (eq 3),[35a] couple with benzyl chloride under palladium catalysis.[36] Benzyl chloride will add to an α-diketone in the presence of powdered nickel to give the α-ketol (eq 4).[37]

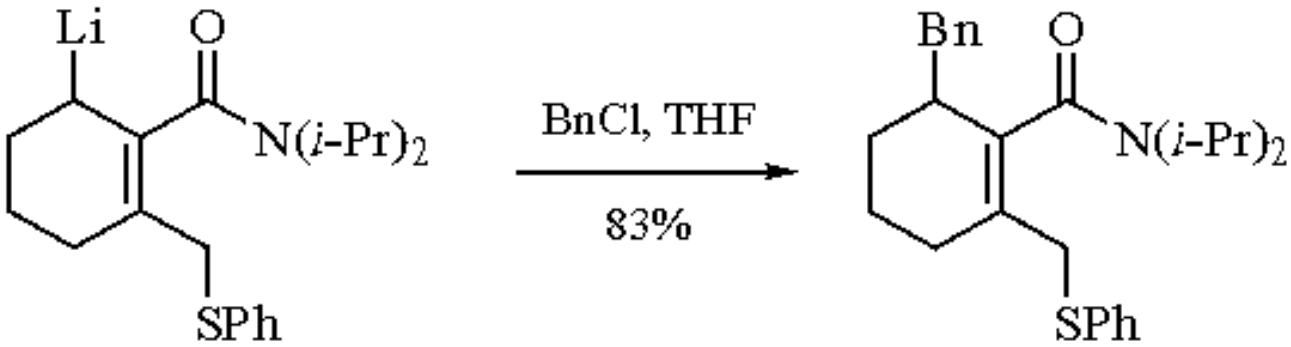

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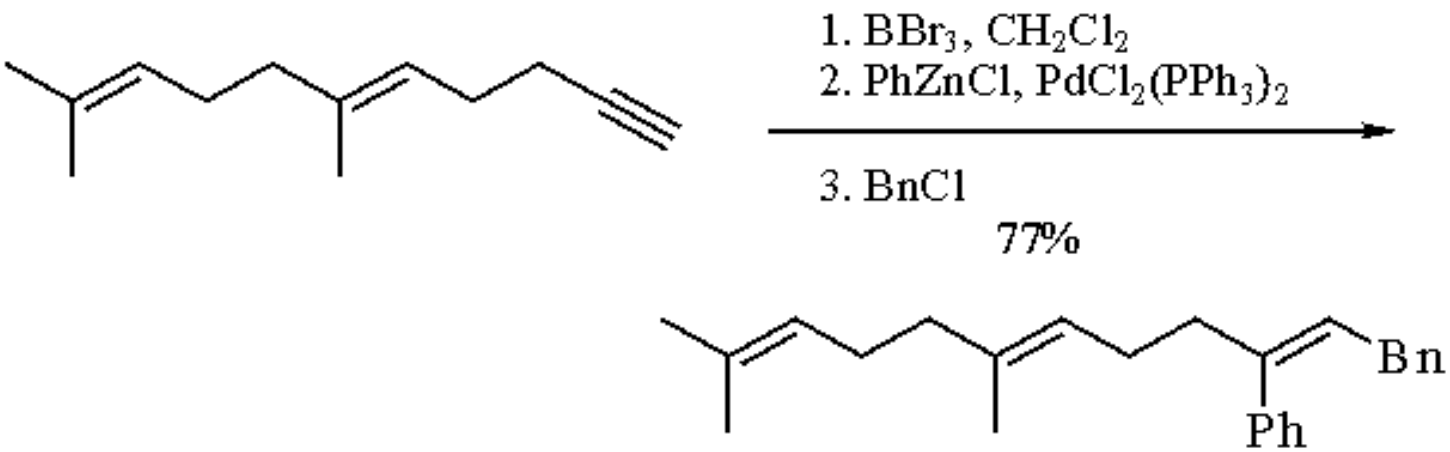

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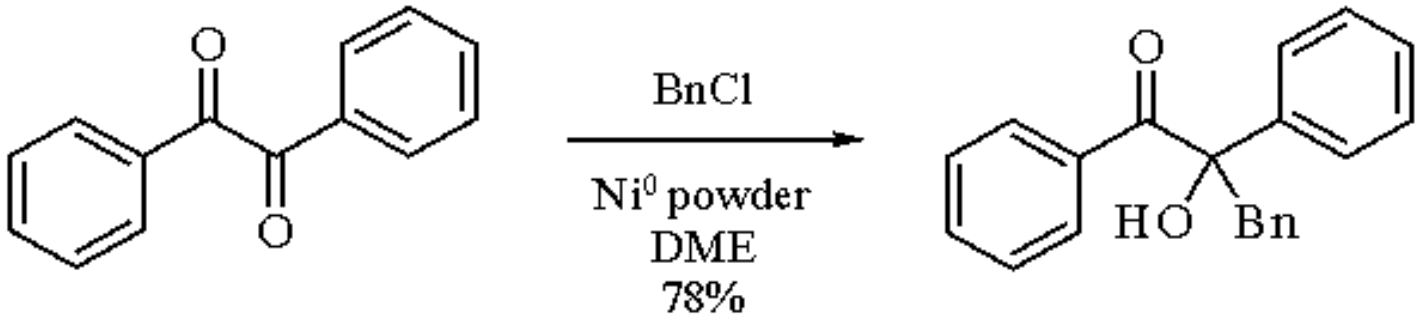

(4)

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Benzylchlorobis(triphenylphosphine)palladium(II)[1]

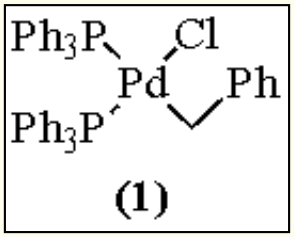

(1)

[22784-59-4] · $C_{43}H_{37}ClP_2Pd$ · Benzylchlorobis(triphenylphosphine)palladium(II) · (MW 757.59)

(catalyst for the cross coupling[1] of alkyl-, vinyl-, alkynyl-, and allylstannane groups with acyl chlorides,[2] allyl halides,[3] vinyl triflates, and iodides[4])

Physical Data: mp 166-170 °C.

Solubility: sol THF, benzene, and other organic solvents.

Form Supplied in: crystalline; commercially available.

Preparative Methods: may be prepared from benzyl chloride and $(Ph_3P)_4Pd$ in benzene at room temperature, washed with Et_2O, and dried under vacuum.[5]

Handling, Storage, and Precautions: is an air-stable solid and remains stable in solution. Irritant.

Cross Coupling Reactions with Organostannane Compounds.

Palladium catalysis of cross coupling reactions is well established in organic chemistry.[1] Benzylchlorobis(triphenylphosphine)palladium(II) (**1**), first reported in 1969,[2] is used extensively for these reactions. Other palladium complexes, such as dichlorobis(triphenylphosphine)palladium(II) and ***Tetrakis(triphenylphosphine)palladium(0)***, catalyze cross coupling reactions; however, the title compound generally provides higher yields in shorter reaction times. Most common is the coupling of an organotin compound with an acyl halide to produce ketone products (eq 1), which has many advantages over existing methods of preparing ketones from acyl chlorides. The yields are high, and in many cases, nearly quantitative. Both the organotin compound and the catalyst are air stable. The reaction tolerates a wide variety of functional groups; ester, alkene, nitro, nitrile, halo, methoxy, silyloxy, vinyl ether, and even aldehyde remain intact during the reaction. Sterically hindered acid chlorides will react, and conjugate addition with α,β-unsaturated acid chlorides does not occur. Further, if a vinyl-, aryl-, or alkynyl-trialkylstannane is used, only the vinyl, aryl, or alkynyl group is transferred. With stannanes as substituents on a stereogenic center, the reaction proceeds with stereochemical inversion of the stereogenic center.[6] Acylstannanes can be prepared by the coupling of acyl halides and distannyl species.[7]

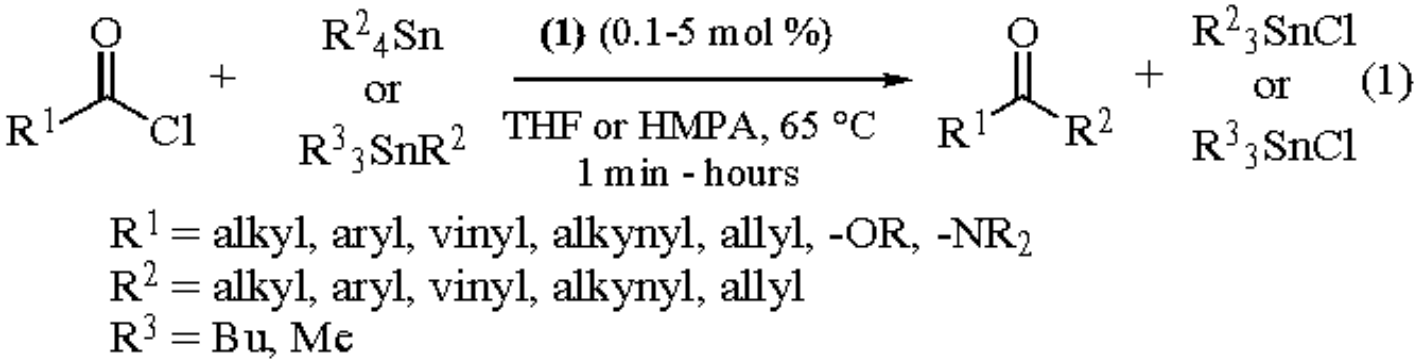

Aldehydes can be prepared from acid chlorides and ***Tri-n-butylstannane*** in the presence of (**1**).[8] While this reduction can be performed by mixing the substrate and Bu_3SnH, ester byproducts and other products resulting from radical reactions occur without the palladium catalyst. 1,2-Diketones can be made easily by the reaction of a 1-methoxyvinylstannane and an acid chloride, followed by hydrolysis (eq 2).[9] A similar 2-methoxyvinylstannane was employed in the synthesis of agglomerin A and (±)-carolinic acid.[10] Vinylstannanes and acyl chlorides have been coupled intramolecularly to provide 11-, 12-, 14-, 16-, and 20-membered macrocycles in 32-72% yields.[11]

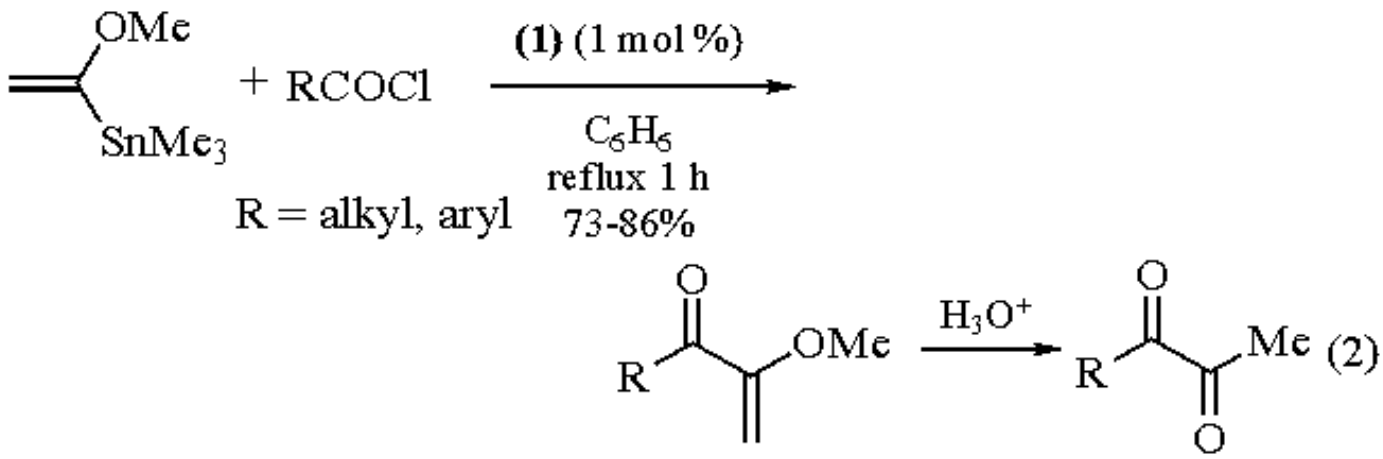

Allylic halides can be coupled with organostannanes without allylic transposition.[3b] The reaction takes place with inversion of stereochemistry at the allylic carbon, and double bond geometry remains intact for acyclic substrates (eq 3).[3c] In addition, carbon monoxide can be inserted during the course of the reaction to provide ketone products.[3a,12] Vinyl iodides couple in a similar fashion,[4a] and the coupling of vinyl triflates was used in the synthesis of pleraplysillin.[4b]

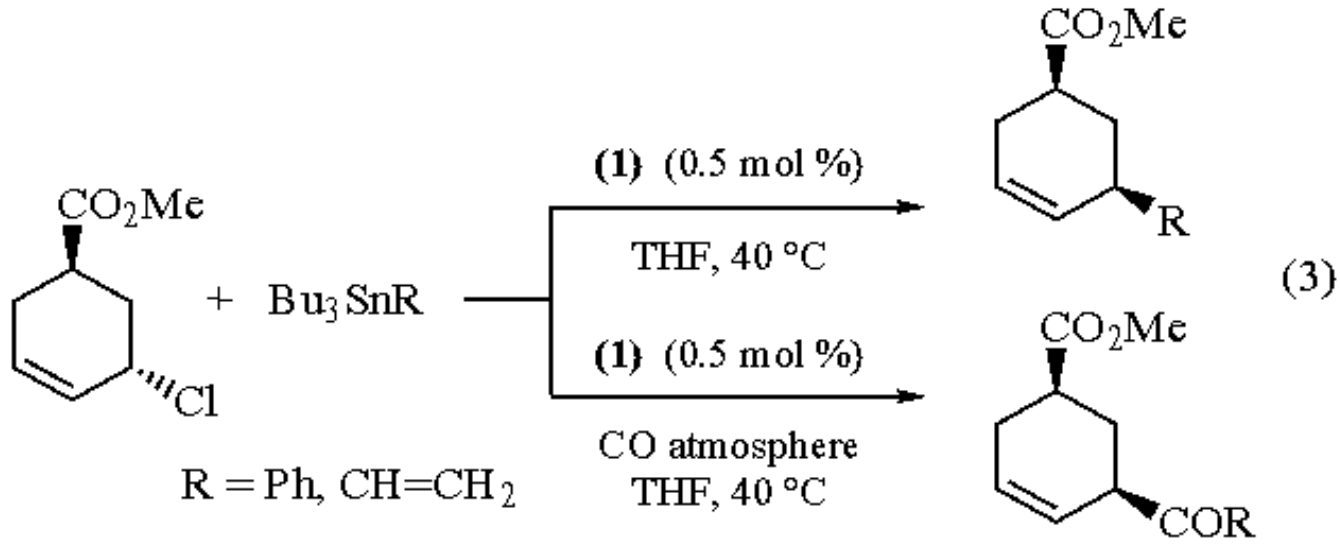

Ether Cleavage and Formation Reactions.

While the cross coupling reactions of organotin compounds in the presence of (**1**) tolerate a great deal of functionality, cyclic (5-membered or less), allylic and benzylic ethers can be cleaved upon reaction with an acid chloride catalyzed by the presence of trialkyltin chloride (eq 4).[13] Aliphatic and phenolic ethers are not consumed. Complementary to this method of ether substrate cleavage, epoxides, oxetanes, and tetrahydrofurans can be formed by the reaction of bromo ketones and allylic stannanes or α-ketostannanes (eq 5).[14] Other alkylstannanes fail to give cyclic ethers.

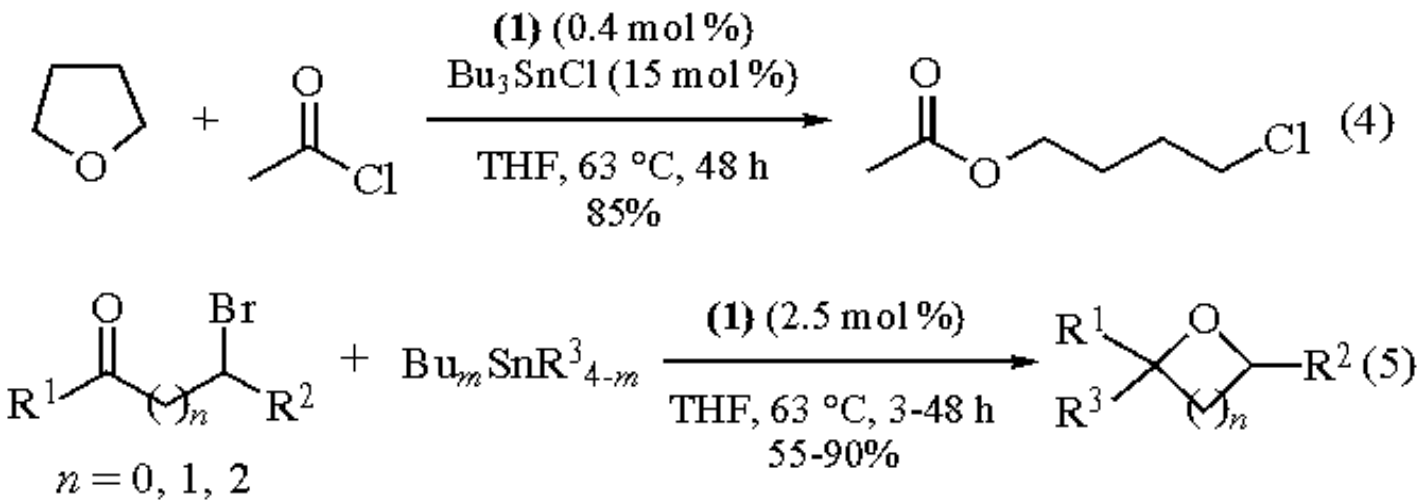

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Benzyl Chloroformate[1]

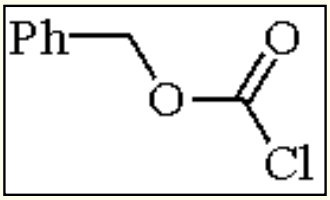

[501-53-1] · $C_8H_7ClO_2$ · Benzyl Chloroformate · (MW 170.60)

(protecting agent for many functional groups, especially for the N-protection of amino acids;[7] activates pyridine rings toward nucleophilic attack;[53] reagent for the preparation of other benzyloxycarbonylating agents[3])

Alternate Name: benzyloxycarbonyl chloride (CbzCl).

Physical Data: colorless oily liquid, bp 103 °C/20 mmHg (with slow decarboxylation to benzyl chloride at this temperature); bp 85-87 °C/7 mmHg; mp 0 °C; *d* (20 °C) 1.195 g cm^{-3}; *n*20D 1.5190.

Form Supplied in: widely available.

Preparative Methods: CbzCl can be readily prepared by the reaction of benzyl alcohol and phosgene, either in toluene solution[4] or neat.[1b,5,6] Purification of such freshly prepared CbzCl is often not necessary; indeed, ca. 25% residual toluene solvent does not interfere with derivatization reactions.[4]

Purification: commercial CbzCl is typically better than 95% pure and is often contaminated by benzyl chloride, benzyl alcohol, toluene, and HCl.[2,3] On storage it can undergo a slow HCl-catalyzed decomposition, even at low temperature.[1a,3] It has been recommended[1b,2] that CbzCl which has been stored for long periods be purified by flushing with a stream of dry air to remove dissolved CO_2 and HCl impurities. Filtration and storage over Na_2SO_4 may be followed by distillation; it is important that low temperatures (oil bath <=85 °C)[1b] and high vacuum be used to minimize thermal decomposition.[3]

Handling, Storage, and Precautions: CbzCl is highly toxic and is a cancer suspect agent; it is a lachrymator with an acrid odor and should be handled with caution in a fume hood.

Protection of Amines.

The most widespread application of CbzCl is in the protection of primary and secondary amines as the corresponding benzyl carbamates. These reactions are usually performed either under Schotten-Baumann conditions,[7] by using aq $NaHCO_3$ or aq Na_2CO_3 as base in an organic solvent (eq 1),[8] or in the presence of an organic base (typically Et_3N) in

CH_2Cl_2.[9] The isolation and/or crystallization of amines is often facilitated by Cbz derivatization of the crude amine generated in another reaction.[10] A wide variety of primary and secondary aliphatic amines, including aziridines,[11] azetidines,[12] and other sensitive[7,9] and electron-deficient[8c] amines, can be selectively protected in the presence of alcohol,[8b,13] phenol,[14] and thiol[15] functionality; however, the selective protection of hindered secondary amines over secondary alcohols has proved difficult.[16]

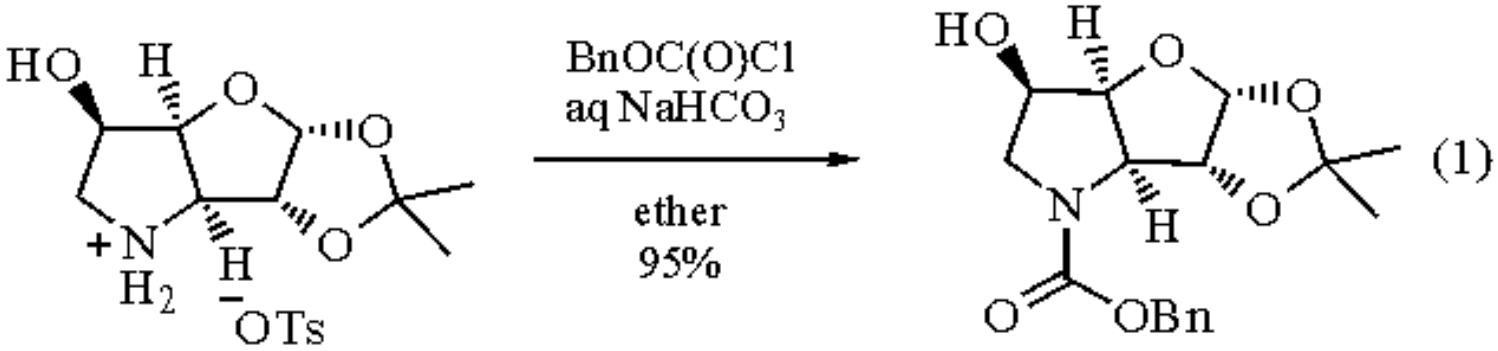

The N-protection of amino acids during peptide synthesis constitutes a major application of this methodology.[1,8a] References to the N-protection of individual amino acids using CbzCl have been tabulated.[1b,e] Use of the *N*-Cbz protecting group generally affords crystalline amino acid derivatives and suppresses racemization at the α-stereocenter during peptide bond formation. The *N*-Cbz group is stable to conditions used for the formation of peptide bonds. Benzyl carbamates are highly complementary to *t*-butyl (i.e. Boc) carbamates in peptide synthesis (see ***t-Butyl Azidoformate***). Schotten-Baumann conditions are most commonly employed for the preparation of *N*-Cbz amino acids (eq 2);[1b,4] racemization at the α stereocenter is suppressed under these basic conditions by the adjacent negatively charged carboxylate group. The use of a lower reaction temperature (-20 °C) has been shown in one case to afford a higher yield of pure *N*-Cbz derivative.[17] One disadvantage of the standard Schotten-Baumann protocol is the need for either the simultaneous addition of CbzCl and aq NaOH, or the sequential addition of small aliquots of these reagents, throughout the course of the reaction. A modified procedure[1b] using $NaHCO_3$ as the base[8d] avoids this inconvenience. A recent report indicates that *N*-Cbz derivatization of a range of α-amino acids can be conveniently achieved, albeit in only moderate yield, by refluxing with CbzCl in ethyl acetate without added base; interestingly, no racemization was observed.[18]

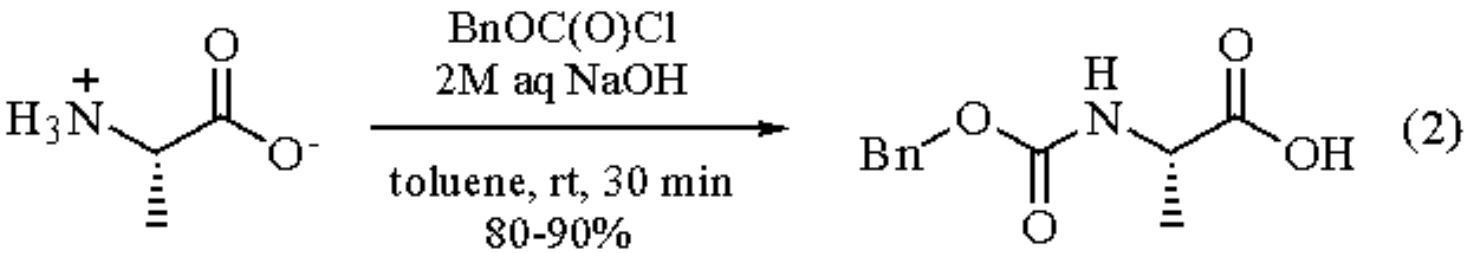

The selective protection of the o-amine in α,o-diamino acids can be achieved by chelation of the α-amino and α-carboxylate functionality by Cu^{II} ion (eq 3).[1b,f,18,19] The Cu^{II} chelate can be cleaved by H_2S,[1f] by thioacetamide,[19] or by use of a chelating ion-exchange resin.[17] Selective protection of the ε-amino group in lysine, the imidazole ring nitrogen in histidine, and the α-amino function in serine, can all be accomplished in homogeneous aqueous medium in the absence of added base using Cbz-imidazolium chloride, a water-soluble benzyloxycarbonylating agent which is prepared in situ from CbzCl and *N*-methylimidazole.[20] Benzyl succinimidyl carbonate, best prepared by reaction of the dicyclohexylammonium salt of *N*-hydroxysuccinimide with CbzCl,[21] is also useful for the *N*-Cbz protection of α-amino acids without the need for added base.

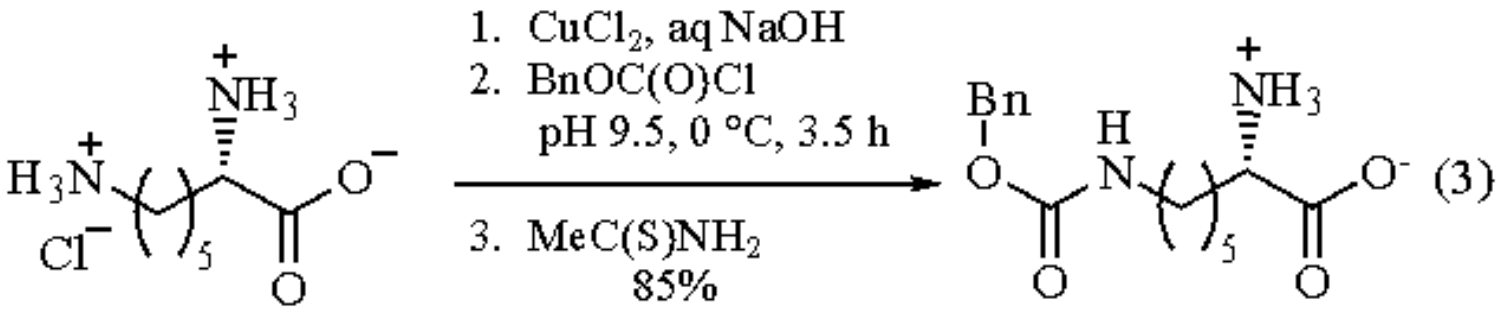

The *N*-Cbz group is stable to a variety of weakly acidic and basic conditions.[22] Benzyl carbamates are most commonly cleaved to the free amine by catalytic hydrogenolysis (H_2/Pd-C)[23] although a plethora of alternate reductive (e.g. transfer hydrogenolysis,[24] Li/liq NH_3[25]), strongly acidic (e.g. HBr/HOAc[26]), and neutral conditions have been employed.[1] The use of transfer hydrogenolysis (cyclohexadiene, 10% Pd-C) allows for the clean deprotection of *N*-Cbz pyrimidines without concomitant reduction of the 5,6-double bond that is observed under standard catalytic hydrogenolysis conditions.[27] The acid stability of the *N*-Cbz group can be manipulated by the introduction of electron-withdrawing or electron-donating substituents onto the phenyl ring. Selective deprotection of an *N*-Cbz group in the presence of an *S*-Cbz moiety can be achieved using HBr/HOAc at rt.[28]

Primary and secondary arylamines can also be *N*-carbamoylated using CbzCl, typically in the presence of aq Na_2CO_3 (eq 4)[29] or pyridine.[30] The protection of electron-deficient anilines can be accomplished using MgO in acetone.[31] Protection of a pyrrole nitrogen can be achieved by initial deprotonation to the potassium salt.[32]

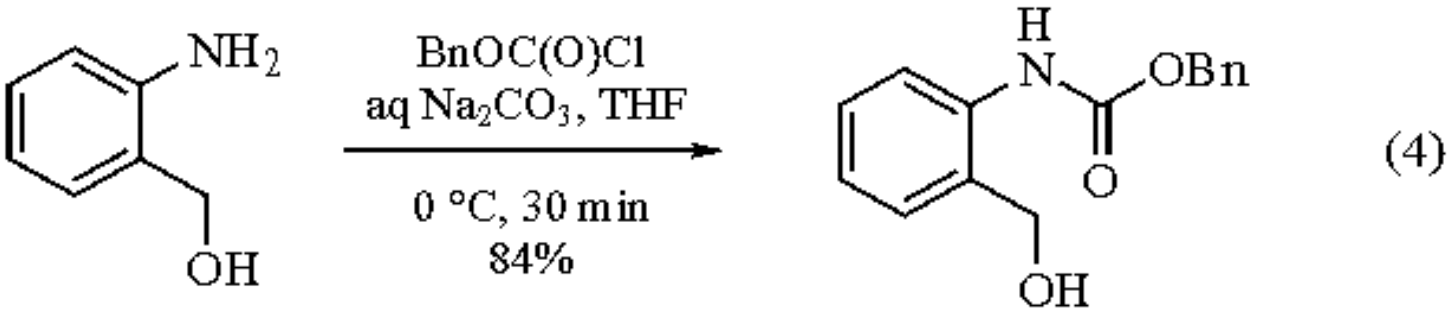

N-Benzyl carbamates prepared as outlined above can also serve as useful intermediates in the overall *N*-methylation of secondary amines, since $LiAlH_4$ reduction of a benzyl carbamate affords the corresponding tertiary *N*-methylamine (eq 5).[33]

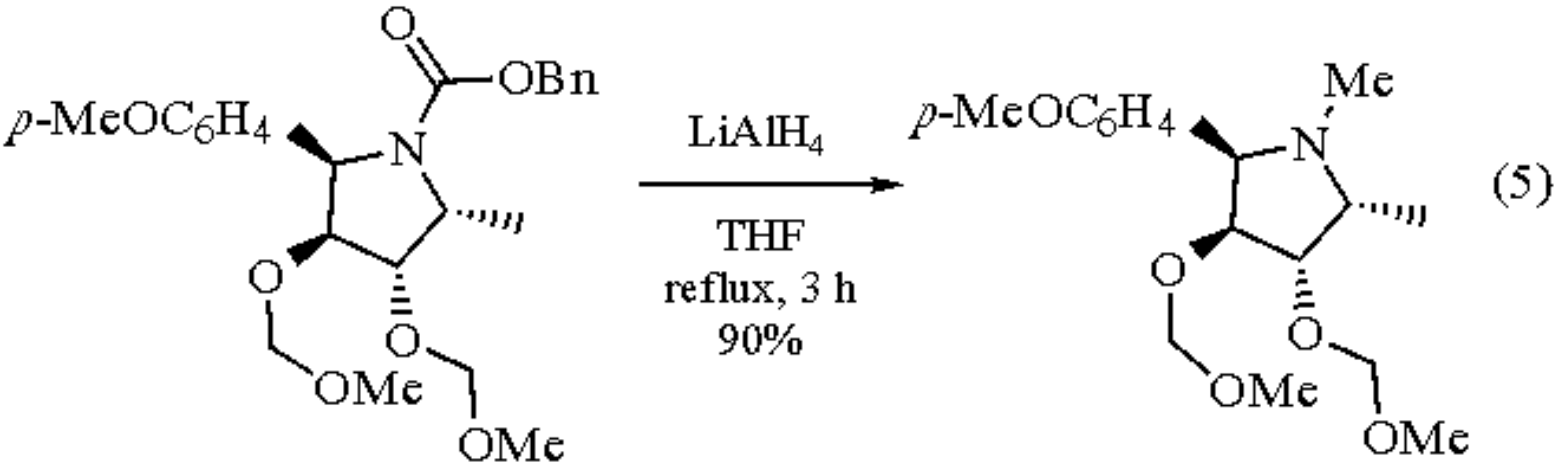

Other N-Protection Reactions.

The protection of an amide as its *N*-Cbz derivative can be achieved using CbzCl with Et_3N/DMAP,[34] or by initial deprotonation of the amide using BuLi or $(Me_3Si)_2NLi$.[35] The N-protection of nucleosides is usually ineffective with CbzCl but can be selectively and efficiently accomplished using *N*-Cbz imidazolium salts generated in situ from the reaction of CbzCl with *N*-alkylimidazoles (eq 6).[27,36]

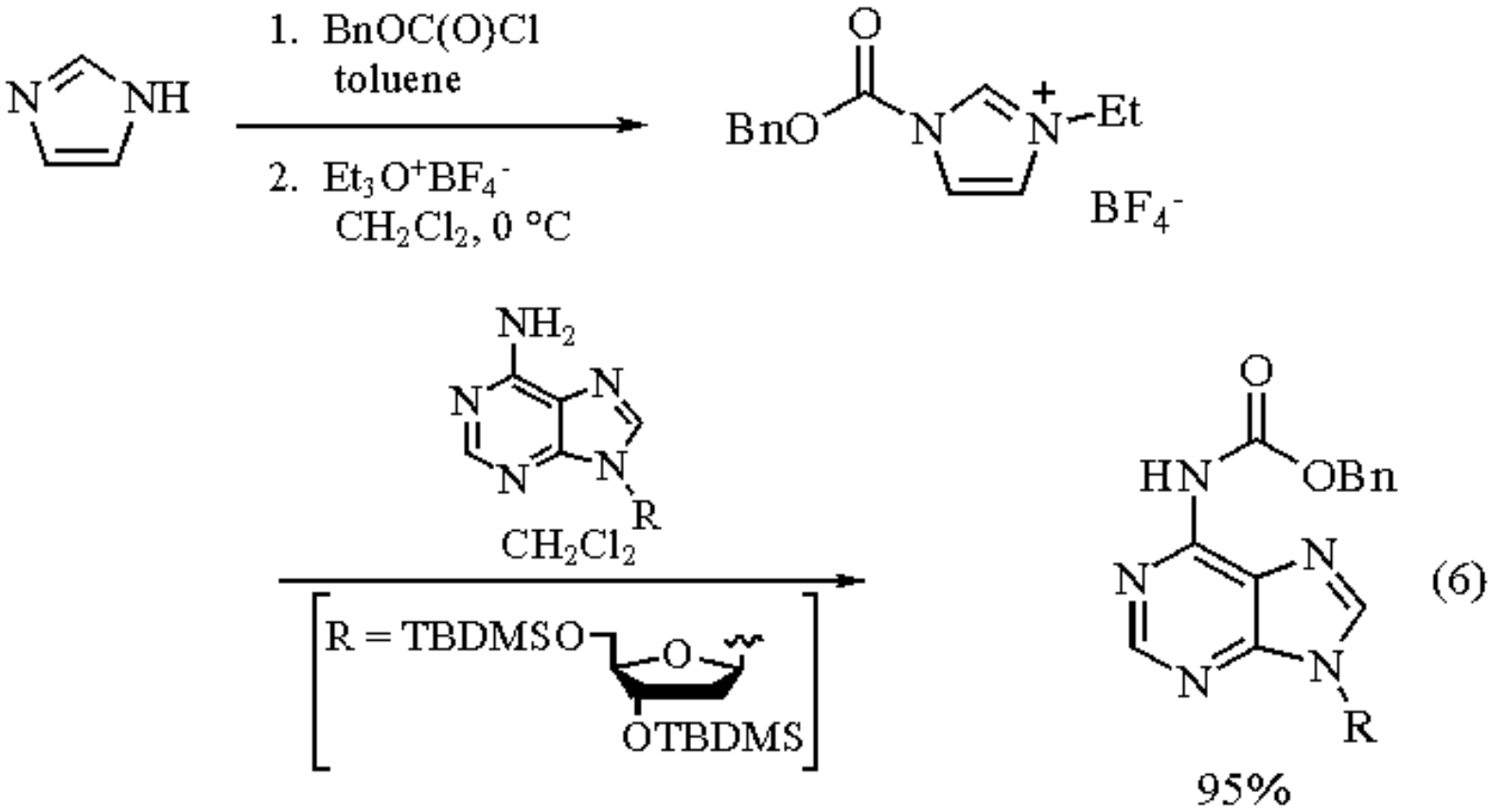

Protection of Alcohols and Phenols.

Protection of alcohols and phenols as the corresponding benzyl carbonates is typically achieved using CbzCl in the

presence of an organic base (e.g. Et_3N,[37] pyridine[38]) in CH_2Cl_2 or ether at low temperature (-20 °C to rt). The selective protection of one secondary alcohol in the presence of other secondary and tertiary alcohols has been accomplished using DMAP at very low temperatures (-40 to -20 °C) for 3 days (eq 7).[39]

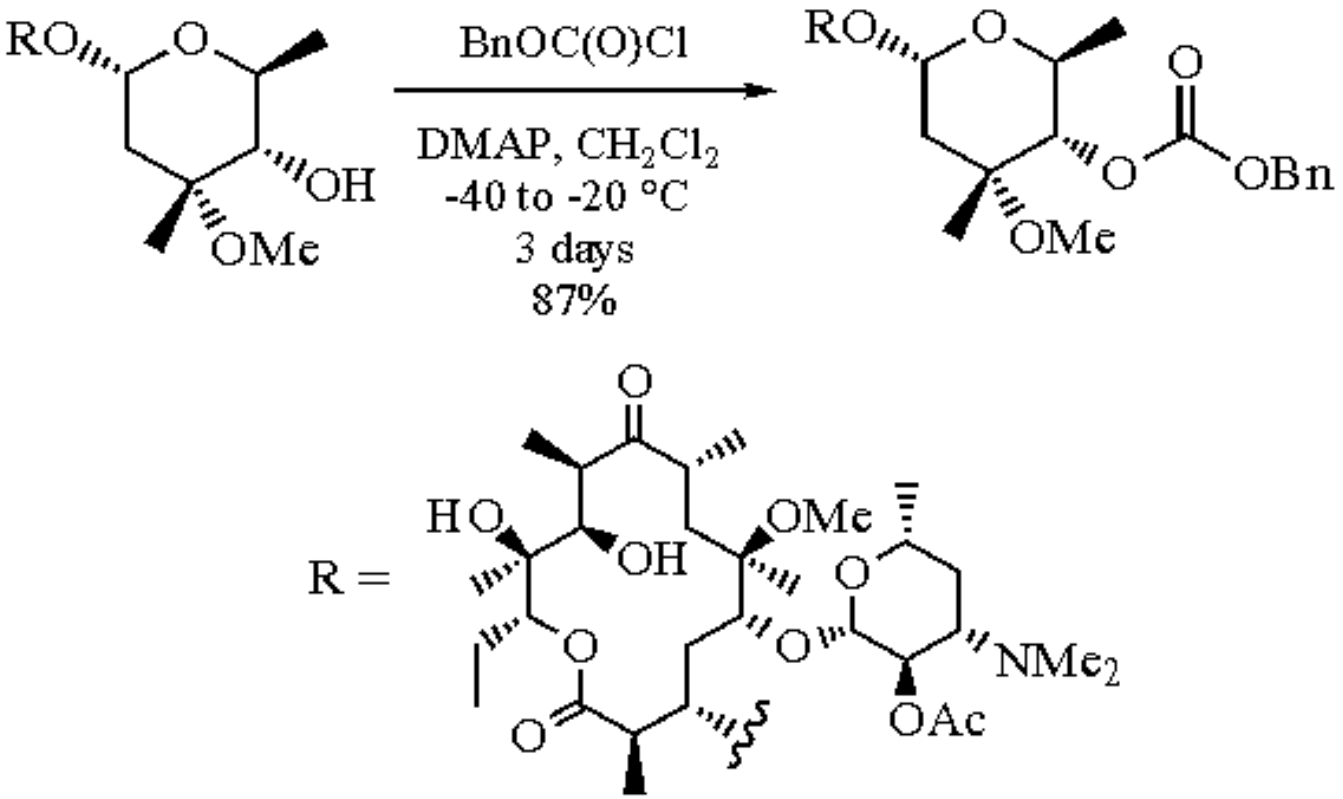

(7)

The use of NaH as base allows for the efficient protection of even hindered electron-deficient alcohols (eq 8).[40] A secondary alcohol can be selectively protected over an indole nitrogen.[41] 1-*O*-Methylated 2-deoxyribose sugars can be protected at the 3- and 5-hydroxyl groups[38] while the hemiacetal function is selectively protected over secondary alcohols in 1-unprotected sugars.[42] Both alcohol-[38,43] and phenol-derived[44] benzyl carbonates are efficiently deprotected by catalytic hydrogenolysis; benzyl carbonates are more readily cleaved under these conditions than benzyl ethers.[38] Removal of the *O*-Cbz group can also be achieved by electrolytic reduction.[45]

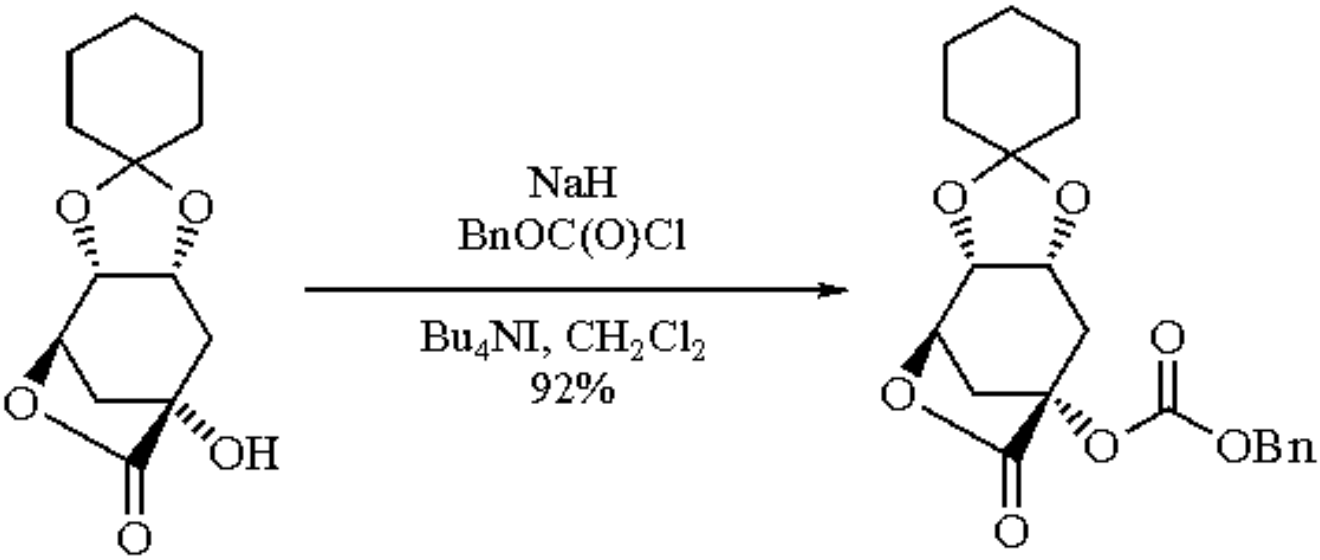

(8)

Protection of Thiols.

The protection of thiols using CbzCl can be achieved using Et_3N as base.[46] The use of aq $NaHCO_3$ as base allows for the selective protection of the SH group in cysteine (eq 9), while *N,S*-bisprotection is observed under Schotten-Baumann conditions (eq 10).[47] Selective protection of the cysteine SH moiety can also be achieved using Cbz-imidazolium chloride, a water-soluble benzyloxycarbonylating agent prepared in situ from CbzCl and *N*-methylimidazole.[20] Both *N*- and *S*-Cbz groups are deprotected using refluxing CF_3CO_2H[48] or by electrolytic reduction.[45] The use of NaOMe/MeOH at rt for 5-10 min allows for the selective cleavage of *S*-Cbz over *N*-Cbz groups.[28]

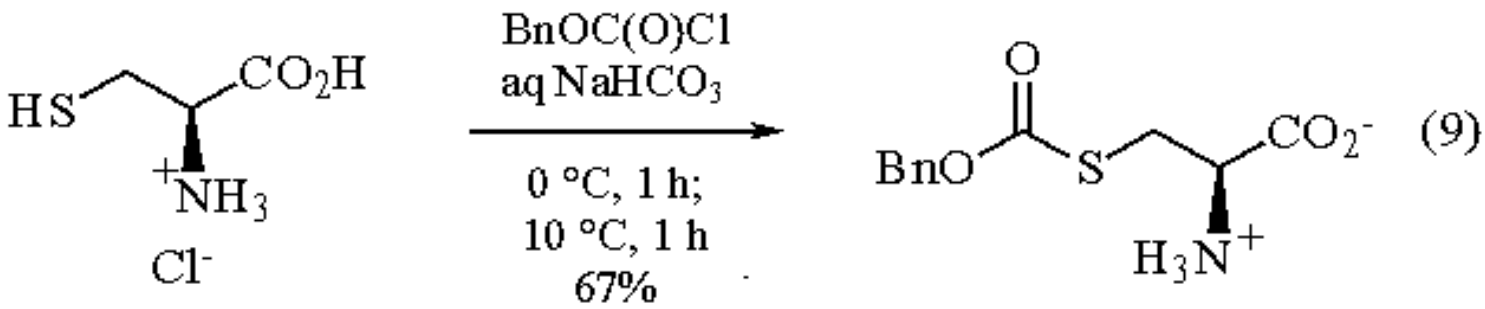

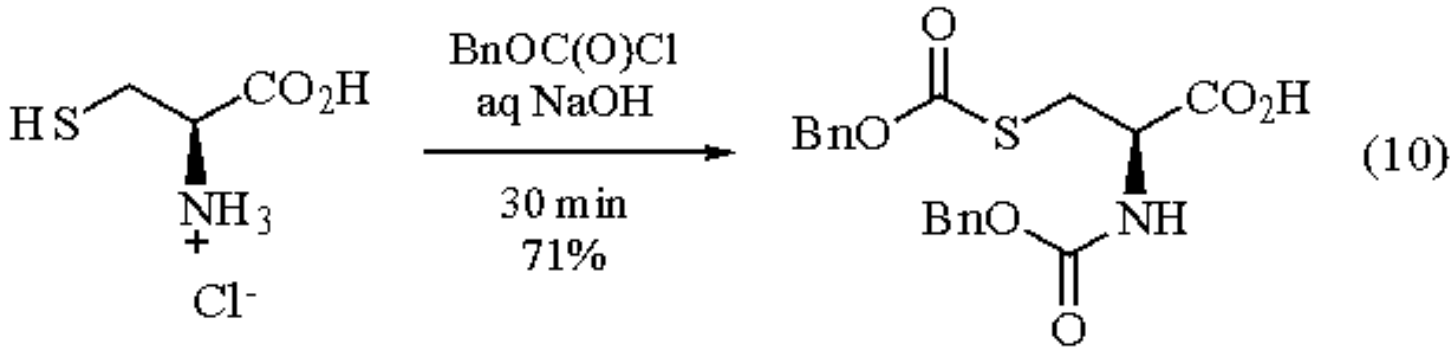

Decarboxylative Esterification of Carboxylic Acids.

The preparation of benzyl esters from sterically uncongested carboxylic acids,[49] including α-keto acids[37,50] and malonic acid half esters,[51] can be achieved using CbzCl in the presence of an organic base (Et_3N,[37,50,51] pyridine,[52] or Et_3N/DMAP[49] in CH_2Cl_2 or THF). The lack of reactivity of sterically crowded carboxylic acids[49] allows for the selective esterification of the less crowded of two acid moieties (eq 11).[52] A major attraction of the benzyl ester group is its susceptibility to cleavage to the free carboxylic acid by catalytic hydrogenolysis[1d,23] or transfer hydrogenolysis.[1d]

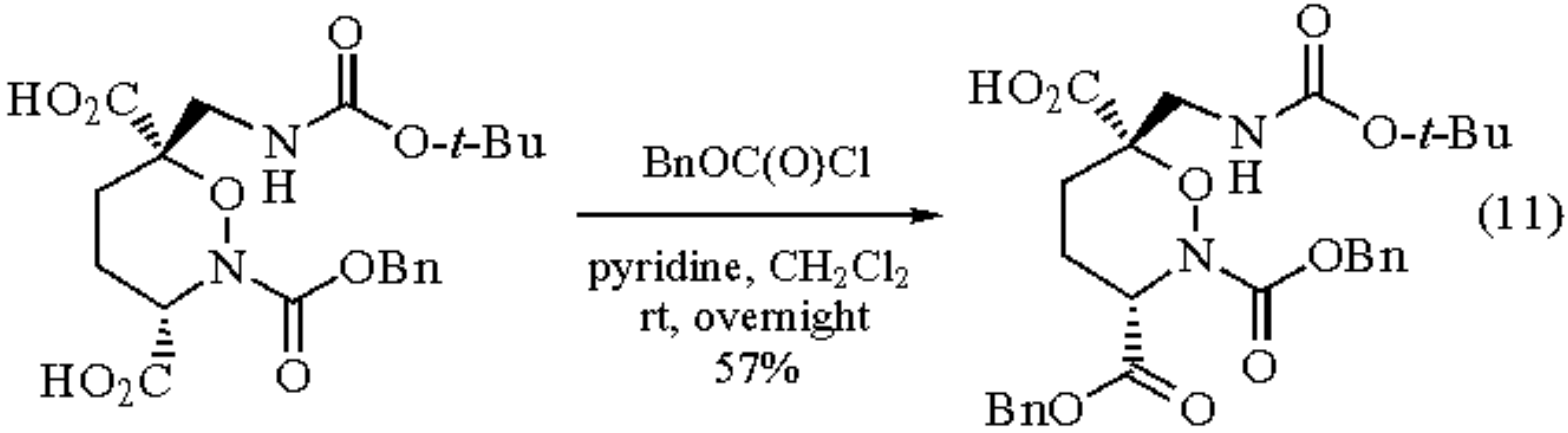

Activation of Pyridine Ring Towards Nucleophilic Attack.

Pyridine and various 4-substituted pyridines can be activated by CbzCl toward regioselective nucleophilic attack by $NaBH_4$[53] and by alkyl,[54] aryl,[55] and alkynyl[56] Grignard reagents, affording the corresponding 2-substituted 1,2-dihydropyridines (eq 12). Treatment of a 3-substituted pyridine with CbzCl and $NaBH_4$ can afford a mixture of 1,2- and 1,4-reduction products; however, reaction with CbzCl and Red-Al proceeds via regioselective 1,2-reduction at the less crowded α-carbon (eq 13).[57]

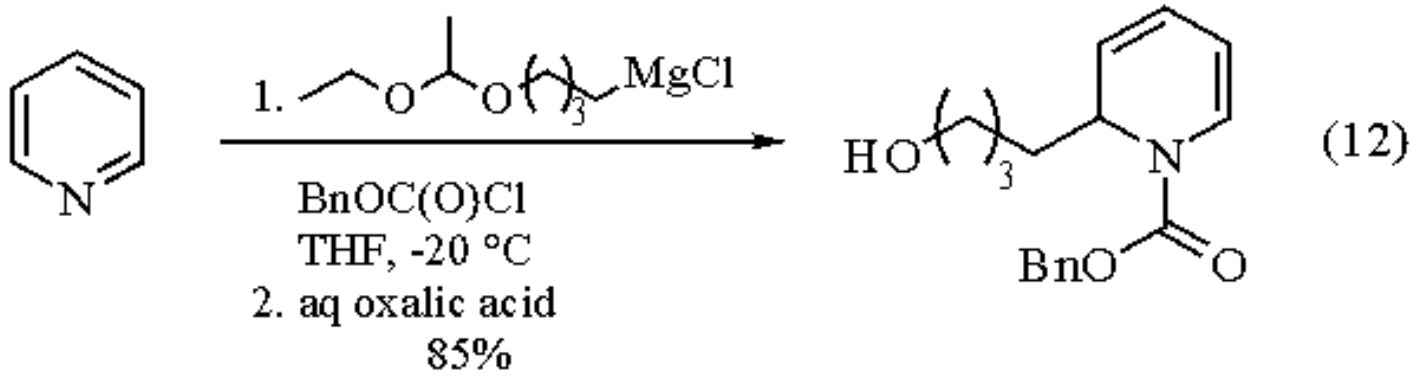

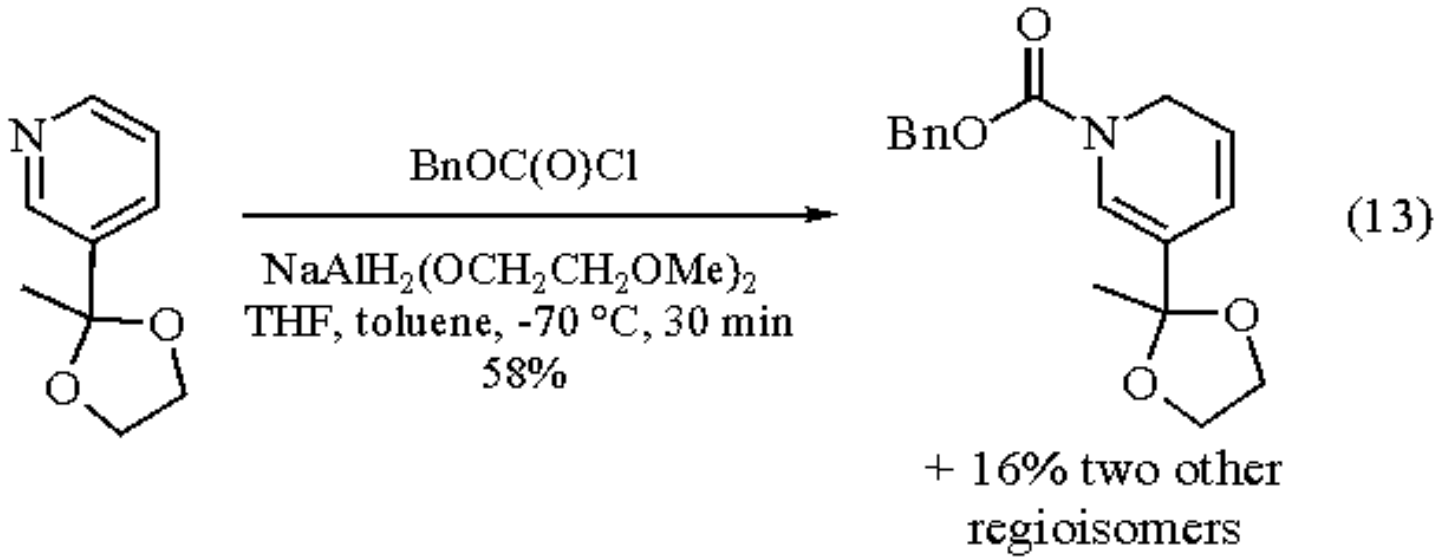

Generation of Other Benzyloxycarbonylating Agents.

A variety of other benzyloxycarbonylating agents can be prepared from CbzCl.[3] For example, reaction of CbzCl with sodium benzyl carbonate affords dibenzyl carbonate, a promising stable crystalline alternative to CbzCl for achieving clean and efficient *N*-benzyloxycarbonylation.[3] *N*-Cbz-imidazole, prepared from CbzCl and imidazole, has proved a suitable reagent for the selective protection of primary over secondary amines.[58]

Related Reagents.

4-Bromobenzyl Chloroformate; ***Methyl Chloroformate***; and ***2,2,2-Trichloroethyl Chloroformate***.

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Benzyl Chloromethyl Ether[1]

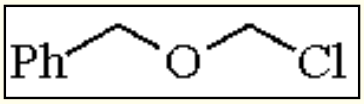

[3587-60-8] · C_8H_9ClO · Benzyl Chloromethyl Ether · (MW 156.61)

(protecting group for alcohols[2] and amines;[3] electrophile in alkylation of carbanions;[4] and source of nucleophilic benzyloxymethyl anion[5])

Physical Data: bp 53-56 °C/1.5 mmHg; 96-99 °C/11 mmHg; *d* 1.13 g cm^{-3}; n_D^{20} 1.5268-1.5279.

Solubility: sol THF, ether, dioxane, dichloromethane, chloroform, benzene, toluene, DMF, DMSO, and acetonitrile.

Form Supplied in: liquid.

Analysis of Reagent Purity: NMR, GC.

Preparative Methods: benzyl alcohol plus aqueous formaldehyde and hydrogen chloride gas;[1,6,7] reaction of benzyl methyl ether with boron trichloride;[8] cleavage of benzyloxymethyl methyl sulfide with sulfuryl chloride.[9]

Purification: distillation.

Handling, Storage, and Precautions: stable indefinitely when kept dry but destroyed by water and other nucleophilic reagents.

Alcohol Protecting Group.

The foremost use for this reagent is as a protecting group for the alcohol functional group. This can be illustrated in a step utilized in the total synthesis of kijanolide (eq 1).[10] An enantioselective synthesis of the taxol side chain used the benzyloxymethyl (BOM) ether for protection of an alcohol group (eq 2).[11]

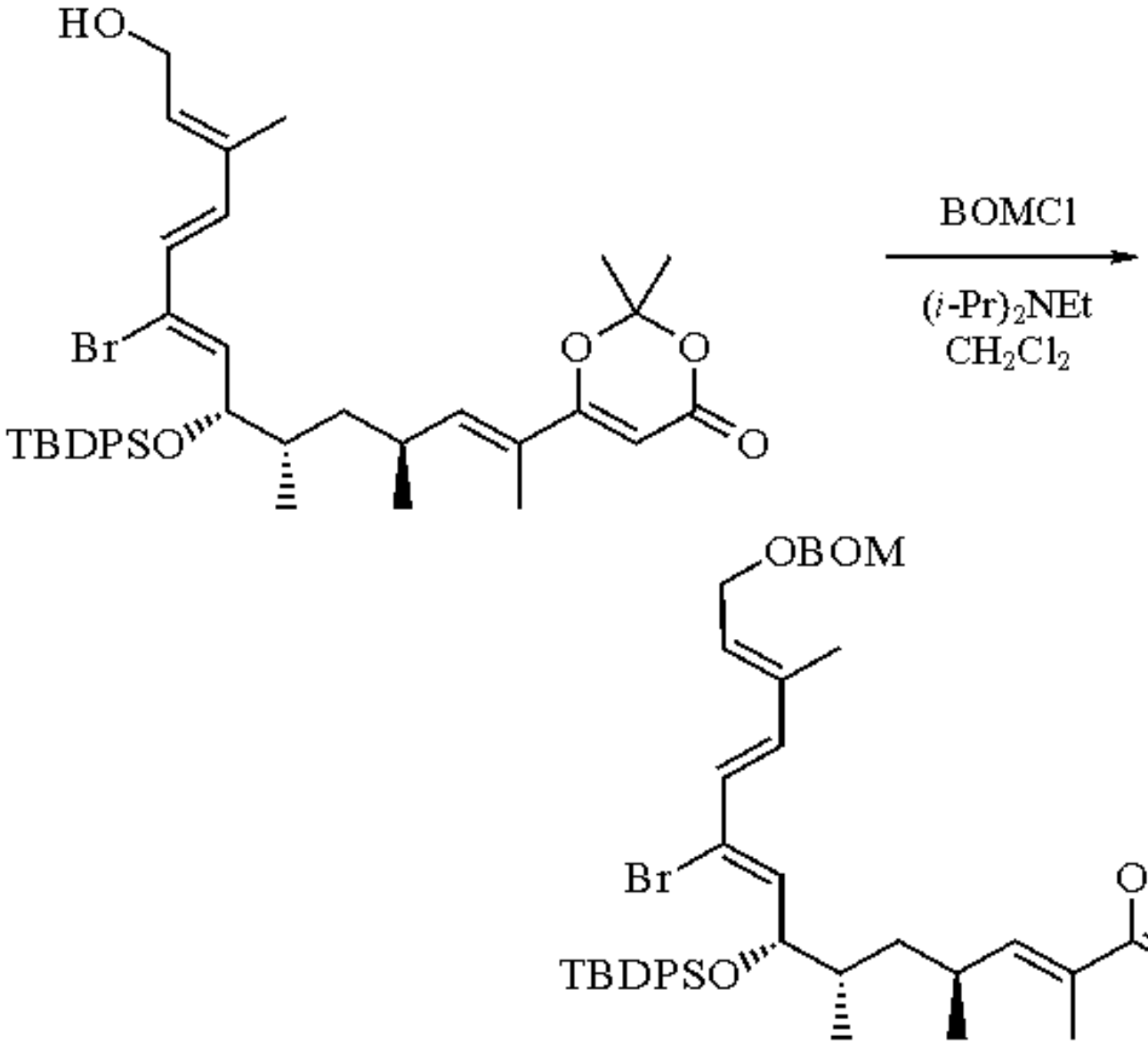

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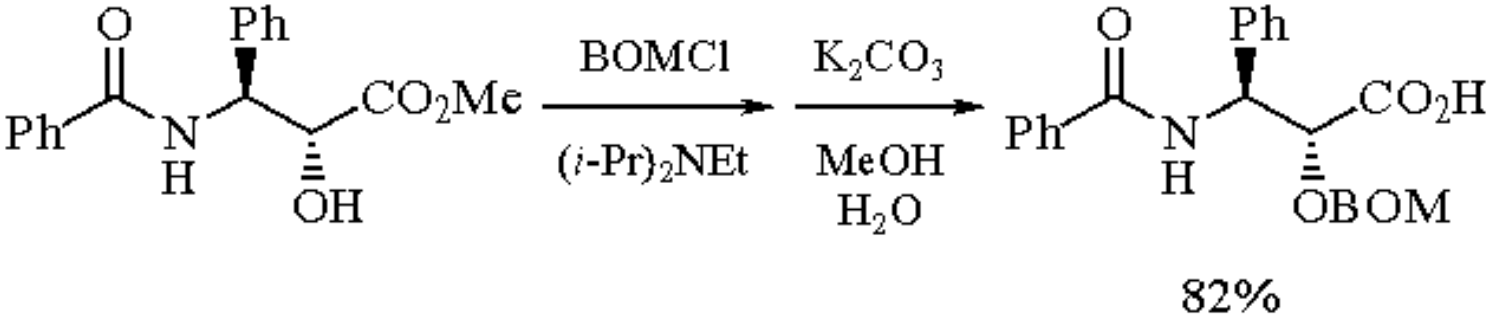

(2)

Ethyl lactate can be protected as a BOM ether for subsequent nucleophilic additions to the corresponding aldehyde with high diastereoselectivity.[12] A synthesis of zoapatanol used selective protection of a diol (eq 3).[13] Primary alcohols can be protected selectively in the presence of secondary hydroxy groups,[14] and secondary hydronyls react more quickly than tertiary ones with benzyl chloromethyl ether and base.[15] Removal of this protecting group can be carried out by hydrogenolysis over Pd.

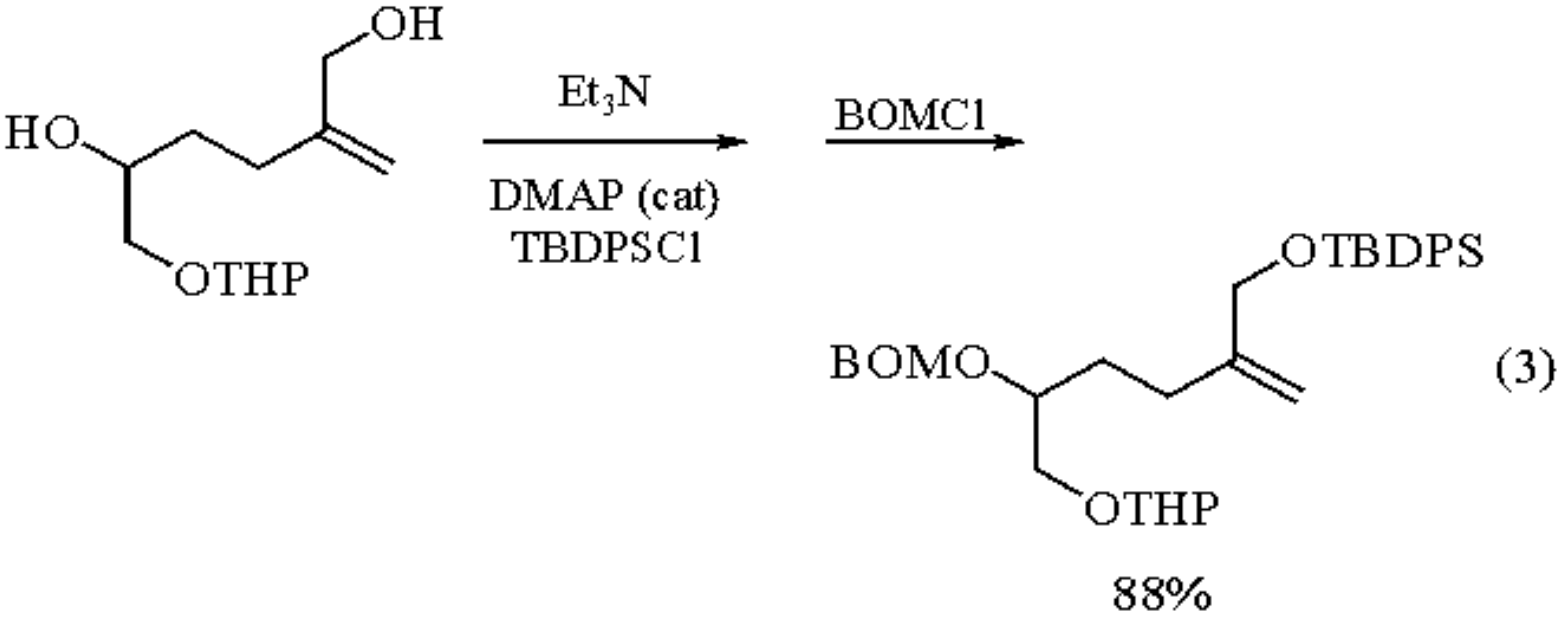

Amine Protecting Group.

2,3,5-Triiodoimidazole reacts with ***Potassium Carbonate*** in DMF followed by benzyl chloromethyl ether to give the 1-BOM derivative in 83% yield.[3] A substituted purine undergoes protection with benzyl chloromethyl ether and ***Sodium Hydride*** (eq 4).[16] Imide nitrogens can be protected in the presence of lactam nitrogens because of the difference in acidity.[17]

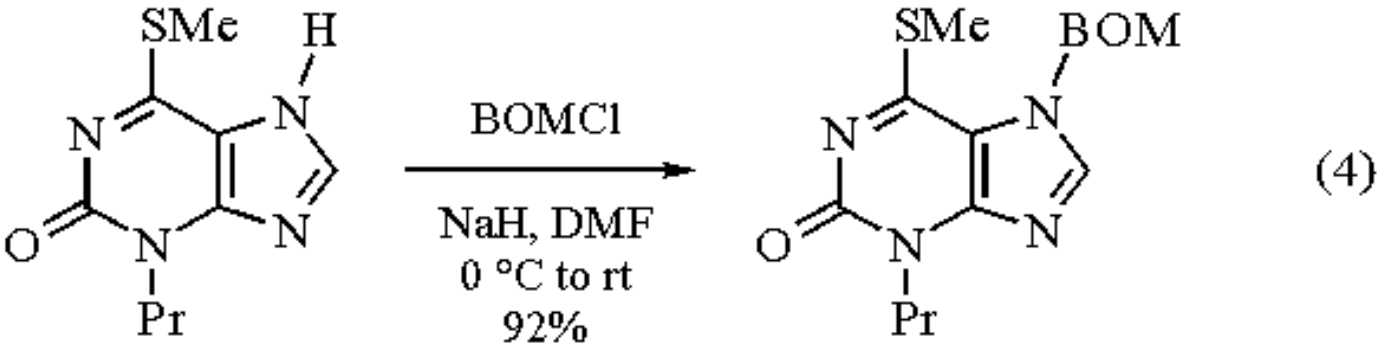

Alkylation of Carbanions.

Methyl 2-phenylpropionate can be deprotonated with LDA and alkylated on carbon with benzyl chloromethyl ether.[4] Introduction of the BOM group in both chiral amides (eq 5)[18] and dianions (eq 6)[19] gives good yields. Removal of the benzyl group by hydrogenolysis completes the hydroxymethylation process.

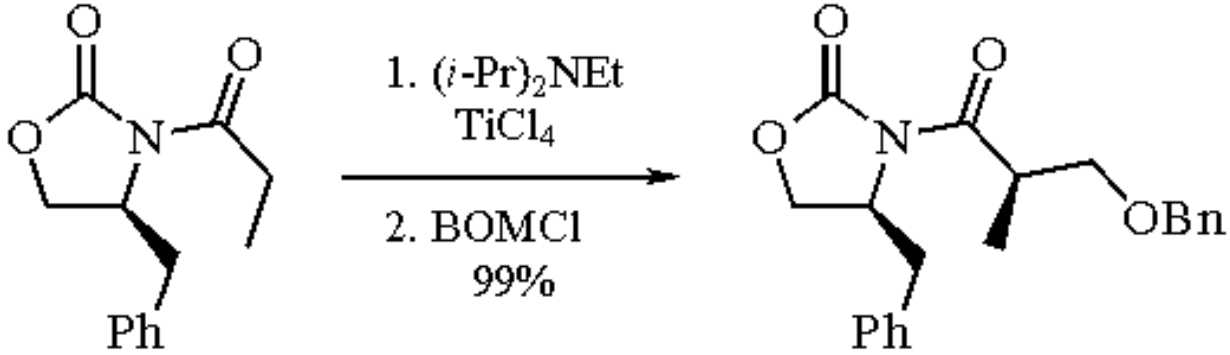

(5)

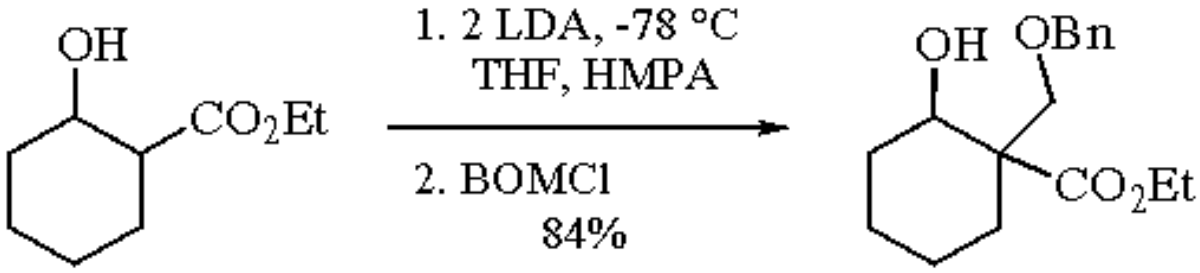

(6)

Benzyloxymethyl Anion.

Both Grignard and organolithium reagents of the benzyloxymethyl anion can be prepared. The Grignard reagent is formed by reaction with ***Magnesium***.[20] Trapping this species with ***Tri-n-butylchlorostannane*** and reaction of the stannane with ***n-Butyllithium*** gives the organolithium.[20] Addition to electrophiles is predictable (eq 7).[5] Removal of the benzyl group via hydrogenolysis reveals that the ether anion is a masked methanol dianion.

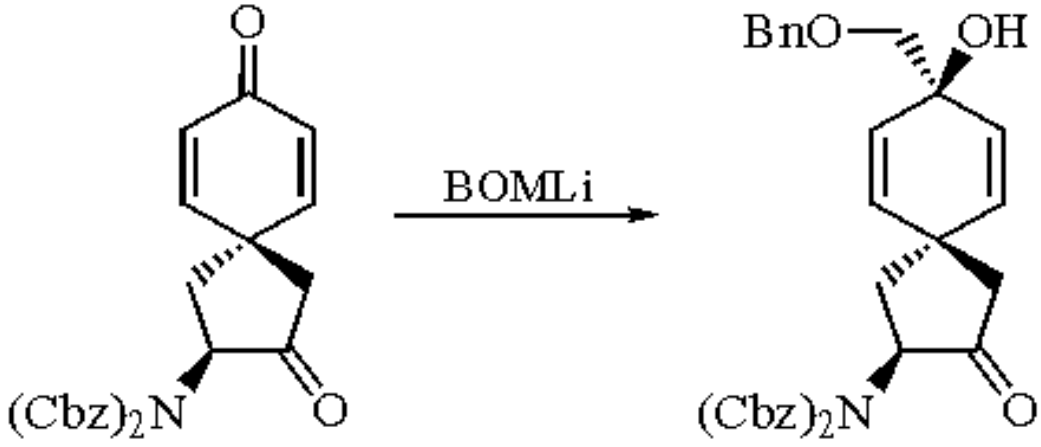

(7)

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Benzyl Chloromethyl Sulfide

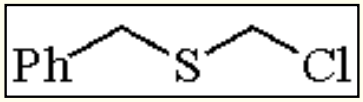

[3970-13-6] · C_8H_9ClS · Benzyl Chloromethyl Sulfide · (MW 172.67)

(protecting group in peptide synthesis,[5] palladium complexes,[10] biologically active iminium compounds,[13] sulfones, and sulfoximes[15])

Alternate Name: benzylthiomethyl chloride; chloromethyl benzyl sulfide; chloromethylthiomethylbenzene.

Physical Data: bp 78 °C/0.2 mmHg; bp 98-99 °C/2.5 mmHg; *n*25D 1.571-1.578.

Solubility: sol most organic solvents.

Preparative Method: the reagent is obtained following the procedure of Fancher.[1] Chloromethylation of phenylmethanethiol with paraformaldehyde in concentrated hydrochloric acid gives the desired benzyl chloromethyl sulfide. To paraformaldehyde (7.5 g) in 50 mL of benzene, 100 mL of concentrated HCl is added in 5 min with stirring. The mixture is kept at 40 °C for a while and phenylmethanethiol (33.75 g) in 50 mL of benzene is added slowly. The resulting mixture is maintained slightly above 40 °C for 2 h. After removing the solvent, the product is purified by distillation under reduced pressure. The unpleasant odor can be in large part suppressed by washing used apparatus immediately with alkaline permanganate. Other methods have been described elsewhere.[2]

Handling, Storage, and Precautions: should only be used in a fume hood.

Protecting Group in Peptide Synthesis.

Methods for the protection of the thiol group of cysteine during peptide synthesis have been prompted in part by evidence that the removal of the *S*-benzyl group from peptides containing *S*-benzylcysteine may be accompanied by side reactions, including fission of the peptide chain[3] and desulfuration.[4] The usefulness of the benzylthiomethyl group as an S-protecting group has been demonstrated by the synthesis of different peptides such as glutathione in pure form and near quantitative yield.[5] The benzylthiomethyl group is stable during the synthesis, and in the final stage can be cleanly removed under standard conditions (mercury(II) acetate in 80% formic acid at rt for 30 min).

Ligand in Mono- and Bimetallic Complexes.

Mono- and bimetallic complexes of short bite ligands such as bis(diphenylphosphino)methane (dppm),[6]

bis(diphenylarsino)methane (dpam),[7] (diphenylarsino)(diphenylphosphino)methane (dapm),[8] and 2-(diphenylphosphino)pyridine (Ph_2py)[9] have received considerable attention recently. These short bite ligands can act in monodentate, bidentate chelating, or bidentate bridging modes in complexes, depending on the nature of the ligand and metal center, and on the oxidation of the metal ion. Only a few bidentate ligands with different donor sites P and S have been reported. Sanger reported the synthesis of some complexes using (phenylthiomethyl)diphenylphosphine as a bridging ligand.[10] However, the coordinating ability of the phenylthiomethyl group seemed weak in bimetallic complexes lacking a metal-metal bond. Based on these observations, it was possible to form a palladium(I) complex containing a metal-metal bond and (benzylthiomethyl)diphenylphosphine as bridging ligand (eq 1).[11] In this case the benzyl group was introduced to enhance the donor ability in the sulfide moiety. Bidentate ligands incorporating a phosphine and a thioether are of interest for the following reasons: (1) when the phosphine and thioether functions are both coordinated to a platinum-group metal, the thioether is expected to be more labile than phosphine, generating a vacant site at the metal center; (2) the generation of heterodinuclear complexes due to preferential coordination of phosphine and thioether to different metals; and (3) the possibility of geometric and coordination isomerism in complexes of these ligands.

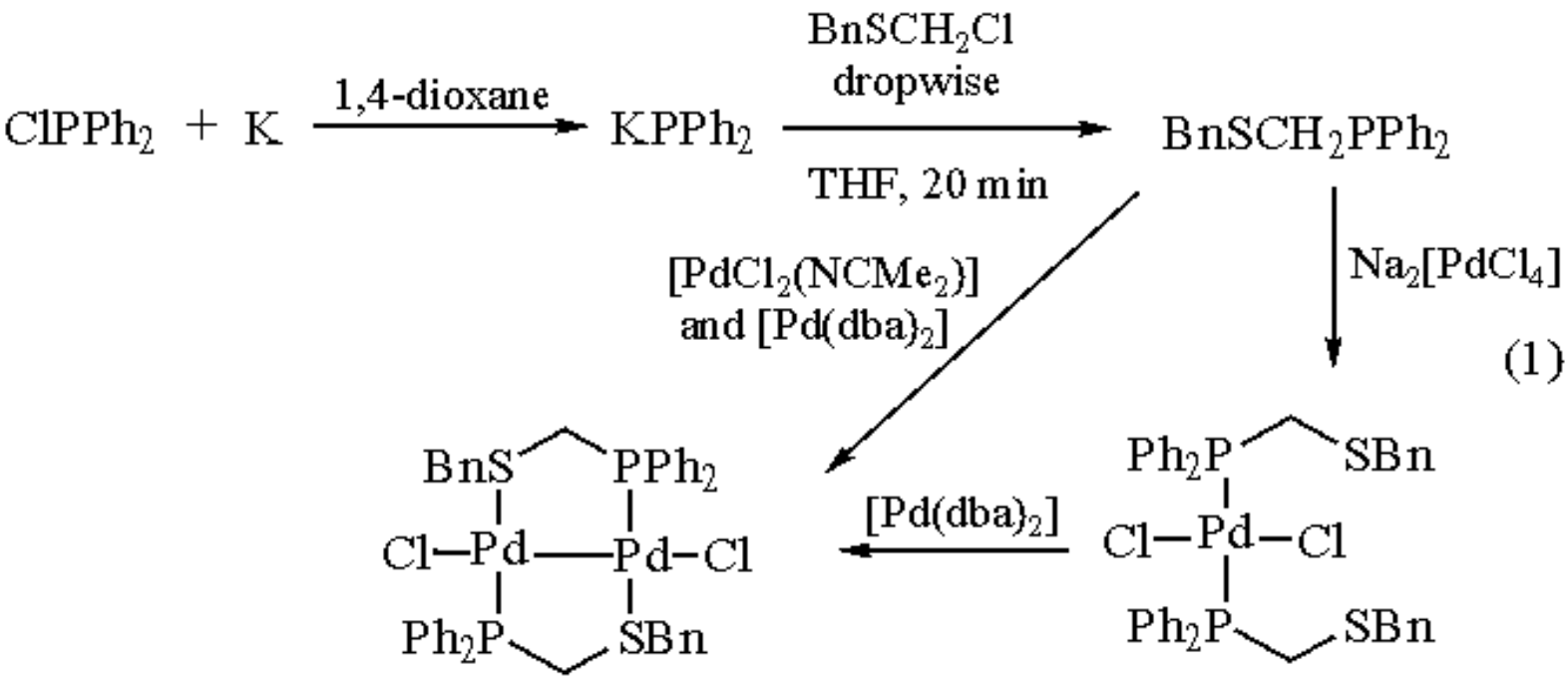

$[Pd_2Cl_2(m\text{-}PhCH_2SCH_2PPh_2)_2]$ can react with substituted alkynes (RC&tbond;CR´; R = Ph, R´ = H; R = CO_2Me, R´ = H; R = R´ = CO_2Me) to yield A-frame-type palladium(II) complexes $[Pd_2Cl_2(\mu\text{-}RC\&tbond;CR)(\mu\text{-}PhCH_2SCH_2PPh_2)_2]$ (eq 2).

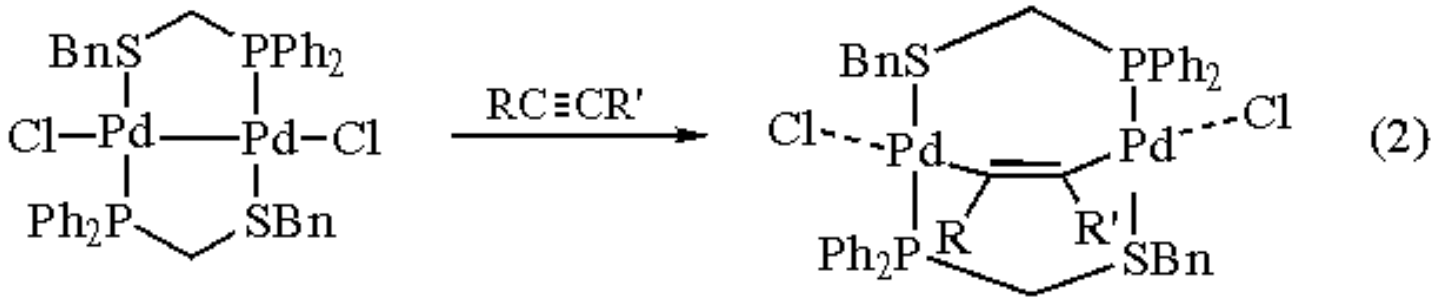

Complexes of the type $[CpFe(CO)(PPh_3)(CH_2SCH_2Ph)]$ were also synthesized (eq 3).[12] Conformational analyses of

iron complexes of the type $[CpFe(CO)(PPh_3)(CH_2XCH_2R)]$ (R = O, S) were conducted in order to investigate the dependence of conformation on solvent polarity.

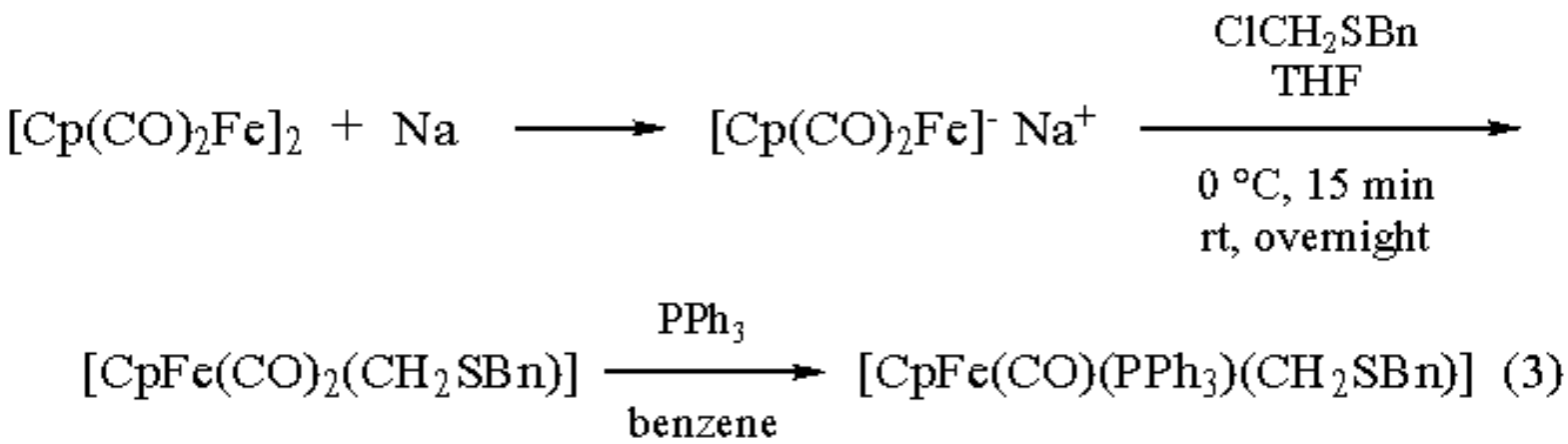

Synthesis of 1-*n*-Octyl-2-phenyl-3-(*n*-benzylthiomethyl)imidazolium Chloride.

Imidazolium compounds with alkoxymethyl or alkylthiomethyl groups are potent antimicrobial agents.[13] They can be easily prepared (eq 4).[14]

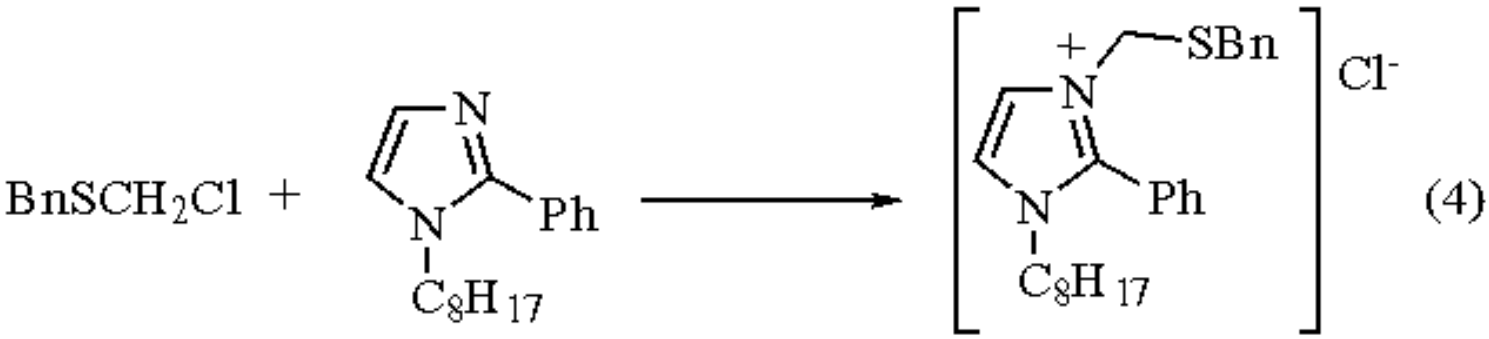

Preparation of the Sulfoxime Group.

The sulfoxime group (**1**) has a potential for incorporation into enzyme inhibitors. It can mimic the tetrahedral intermediate (**2**) in carboxamide addition reactions, notably with a metalloprotease.[15]

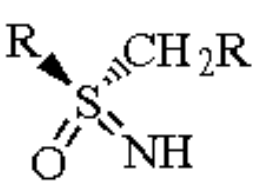

(1)

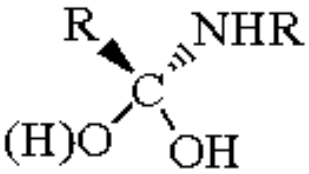

(2)

In the present case, chloromethyl phenylethyl sulfide serves as precursor for securing the desired β-sulfonimidoylpropionic acid.[16] Like benzyl chloromethyl sulfide, it can be prepared according to the procedure described by Böhme.[2b]

Preparation of Benzylsulfonylmethyl Styryl Sulfones.

Novel unsaturated sulfones have been obtained by the condensation of aryl- and benzylsulfonylmethylacetic acids and aryl aldehydes in the presence of catalytic amounts of benzylamine in glacial acetic acid (Knoevenagel condensation).[17] The products obtained are stable (*E*)-alkenes (eq 5), which are known intermediates in the synthesis of a number of carbocyclic[1b,18] and heterocyclic compounds.[19]

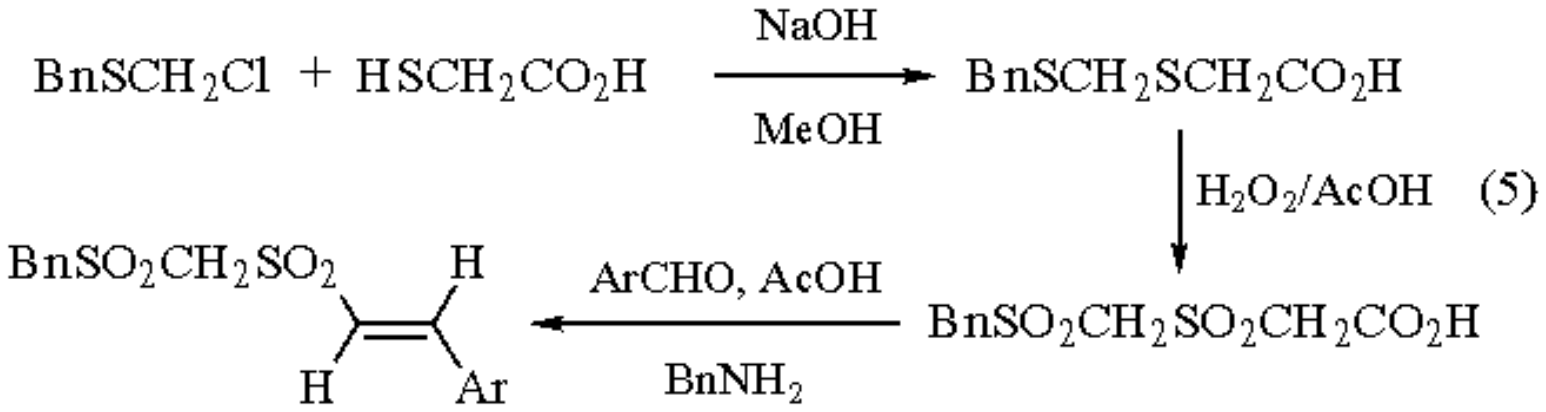

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3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride[1]

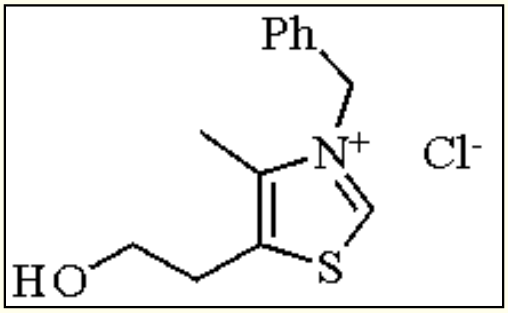

[4568-71-2] · $C_{13}H_{16}ClNOS$ · 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride · (MW 269.79)

(in the presence of bases, catalyst for the preparation of acyloins and benzoins[2] from aldehydes, and for addition of aldehydes to electrophilic double bonds[3])

Physical Data: mp 141-143 °C.

Solubility: sol H_2O, MeOH, EtOH; slightly sol cold MeCN; insol ether, pentane.

Form Supplied in: colorless crystals, widely available.

Analysis of Reagent Purity: ^{1}H NMR; mp.

Preparative Method: Organic Syntheses procedure.[2]

Handling, Storage, and Precautions: store dry.

Formation of Benzoins and Acyloins from Aldehydes.

Many thiazolium salts catalyze the formation of benzoins from aromatic aldehydes and of acyloins from aliphatic aldehydes in the presence of a base as shown in the preparation of furoin from furan-2-carbaldehyde (eq 1).[2]

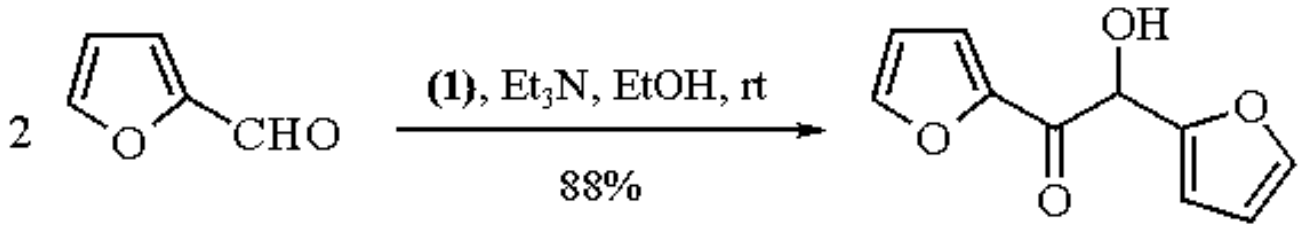

(1)

This catalytic reaction has long been known,[4] the most prominent salt being thiamine (vitamin B_1). Other azolium salts[5] and nucleophilic carbenes, or dimers thereof, also catalyze this reaction.[6] Chiral thiazolium salts have been used.[7] The reaction can be performed as a phase-transfer reaction at preparative scale in water.[8] The title reagent (**1**) has been used in the preparative large-scale formation of acyloins and benzoins in the presence of ***Triethylamine*** in ethanol under anhydrous conditions (eq 2).

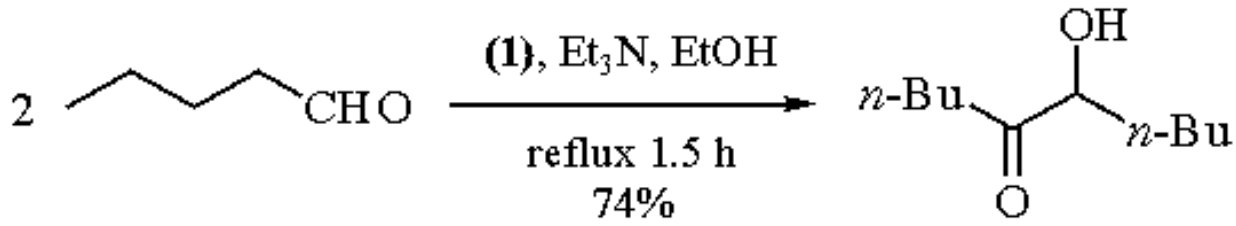

(2)

Simple aliphatic acyloins,[9] mixed aliphatic acyloins,[10] and acyloins containing other functional groups[11] have been prepared.

Formose Reaction.

A very special case of acyloin formation is observed when formaldehyde is used in that the construction of simple sugars occurs. Only some of the numerous possible products are found in the formose mixture.[12] A similar result has been reported with ethylbenzothiazolium bromide as catalyst.[13]

Addition of Aldehydes to Activated Double Bonds.

This reaction has been reviewed.[3] (**1**) in the presence of bases (e.g. Et_3N or NaOAc) catalyzes the addition of aliphatic and heterocyclic aldehydes to α,β-unsaturated ketones (to yield γ-diketones), esters (to yield γ-ketoesters), and nitriles (to yield γ-ketonitriles), for example (eq 3).[14] This further illustrates the umpolung effect of this reagent on the aldehyde carbonyl reactivity.

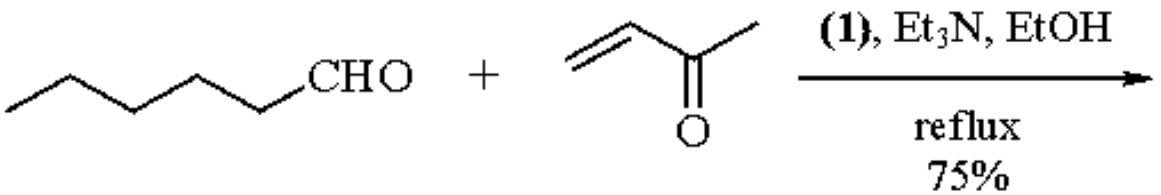

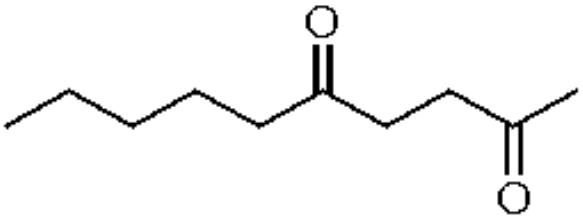

(3)

This reaction is used in the synthesis of tri- and polyketones,[15] cyano ketones,[16] 1,4-diketones,[17] and oxocarboxylic esters.[16b,18] Mannich bases (β-dialkylamino ketones) or their quaternary salts can replace the unsaturated ketones.[3] α-Keto carboxylic acids can replace the aldehydes, because these readily decarboxylate under the reaction conditions (eq 4).[19]

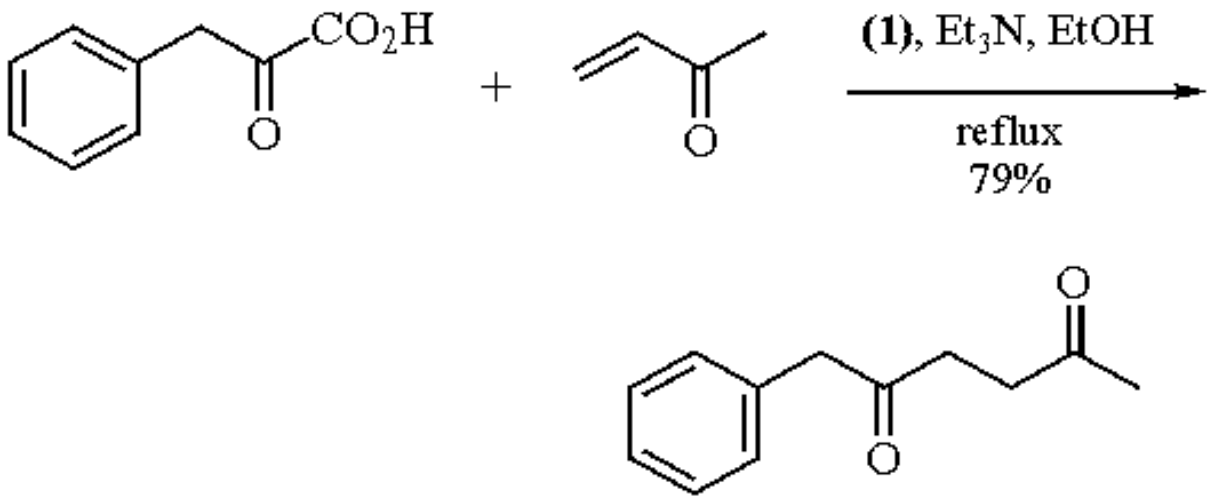

(4)

Addition of Aldehydes in Presence of Other Reagents.

The presence of ***Pentacarbonyliron*** changes the reaction pathway to afford different products (eq 5).

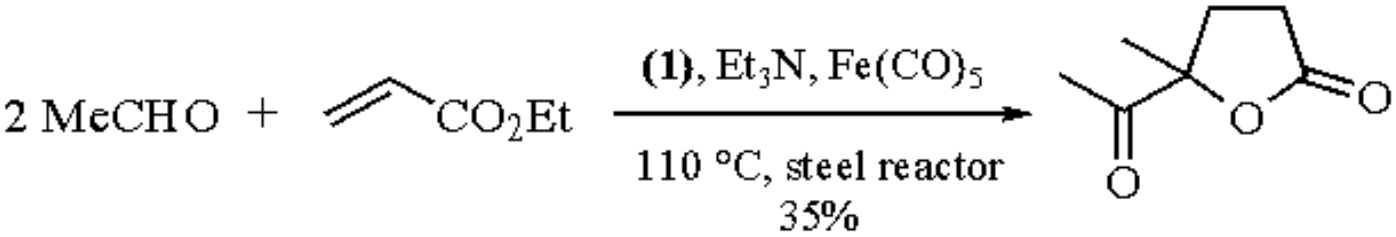

(5)

Michael addition of ethyl acrylate to acetoin and transesterification yields the product shown (35%) together with ethyl levulinate (10%).[20] For details on additions of aldehydes in presence of oxidants see ***3-Benzyl-4-methyl-1,3-thiazolium Chloride***.

Related Reagents.

Table 1 shows some widely used 1,3-thiazolium salts analogs of (**1**) that are especially well suited with aromatic aldehydes for the above benzoin preparations and for aldehyde additions to double bonds.[3]

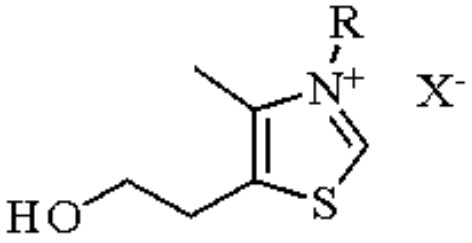

(2)

Table 1 Properties of Some Salts

R	X	CAS No.	MW	Mp (°C)	Empirical formula
Et[a,b]	Br	[54016-70-5]	252.17	84 86	$C_8H_{14}BrNOS$
Me[a,b,c]	I	[16311-69-6]	285.14	85 87	$C_7H_{12}INOS$

[a] Hygroscopic. [b] Widely available. [c] Light sensitive.

Other Reagents.

Sodium Cyanide or ***Potassium Cyanide*** are the classical catalysts for benzoin formation from aromatic aldehydes[21] and they can also be used for the addition of aromatic aldehydes to activated double-bonds.[3] Carboxylic esters and metals such as sodium are used in the classic acyloin condensation[22] and its modern variations.[23] Numerous other acyl anion equivalents have been described.[24]

---

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O-Benzylhydroxylamine Hydrochloride[1]

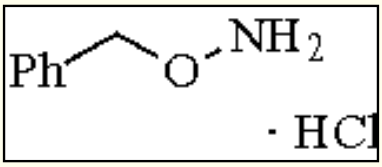

(base)

[622-33-3] · C_7H_9NO · *O*-Benzylhydroxylamine · (MW 123.15) (.HCl)

[2687-43-6] · $C_7H_{10}ClNO$ · *O*-Benzylhydroxylamine Hydrochloride · (MW 159.62)

(reagent for the preparation of *N*-hydroxyamides[2] (including *N*-hydroxy peptides[3] and *N*-hydroxy β-lactams[4]) and hydroxamic acids;[5] derivatizing agent for ketones,[6-8] aldehydes,[6] and carbohydrates[9])

Alternate Names: O-phenylmethylhydroxylamine hydrochloride; benzyloxyamine hydrochloride; benzyloxyammonium chloride.

Physical Data: white flakes, mp 234-238 °C (subl); hygroscopic.

Solubility: sol H_2O, pyridine; slightly sol alcohol; insol ether.

Analysis of Reagent Purity: ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 5.17 (s, 2H, CH_2), 7.42 (s, 5H, C_6H_5), 11 (br, ex NH_2).

Preparative Methods: the free base *O*-benzylhydroxylamine, a liquid of bp 115-119 °C/30 mmHg, is easily prepared from the commercially available hydrochloride salt.[10] For many reactions, however, it is preferable to generate the free base in situ from the salt.

Handling, Storage, and Precautions: store in a cool dry place to preclude contact with moisture and oxygen; may be harmful by inhalation, ingestion, or skin absorption; avoid contact with the eyes.

N-Hydroxyamides and Hydroxamic Acids.

The ease with which an *O*-benzyl moiety can be converted, often through catalytic hydrogenation, to the analogous alcohol allows this reagent to be used as an O-protected equivalent of hydroxylamine. For example, it is especially suited for the preparation of *N*-hydroxyamides (eq 1)[2] (including *N*-hydroxy peptides[3] and *N*-hydroxy β-lactams),[1,4,11] hydroxamic acids (eq 2),[5] and *N*-hydroxyimides (eq 3).[12]

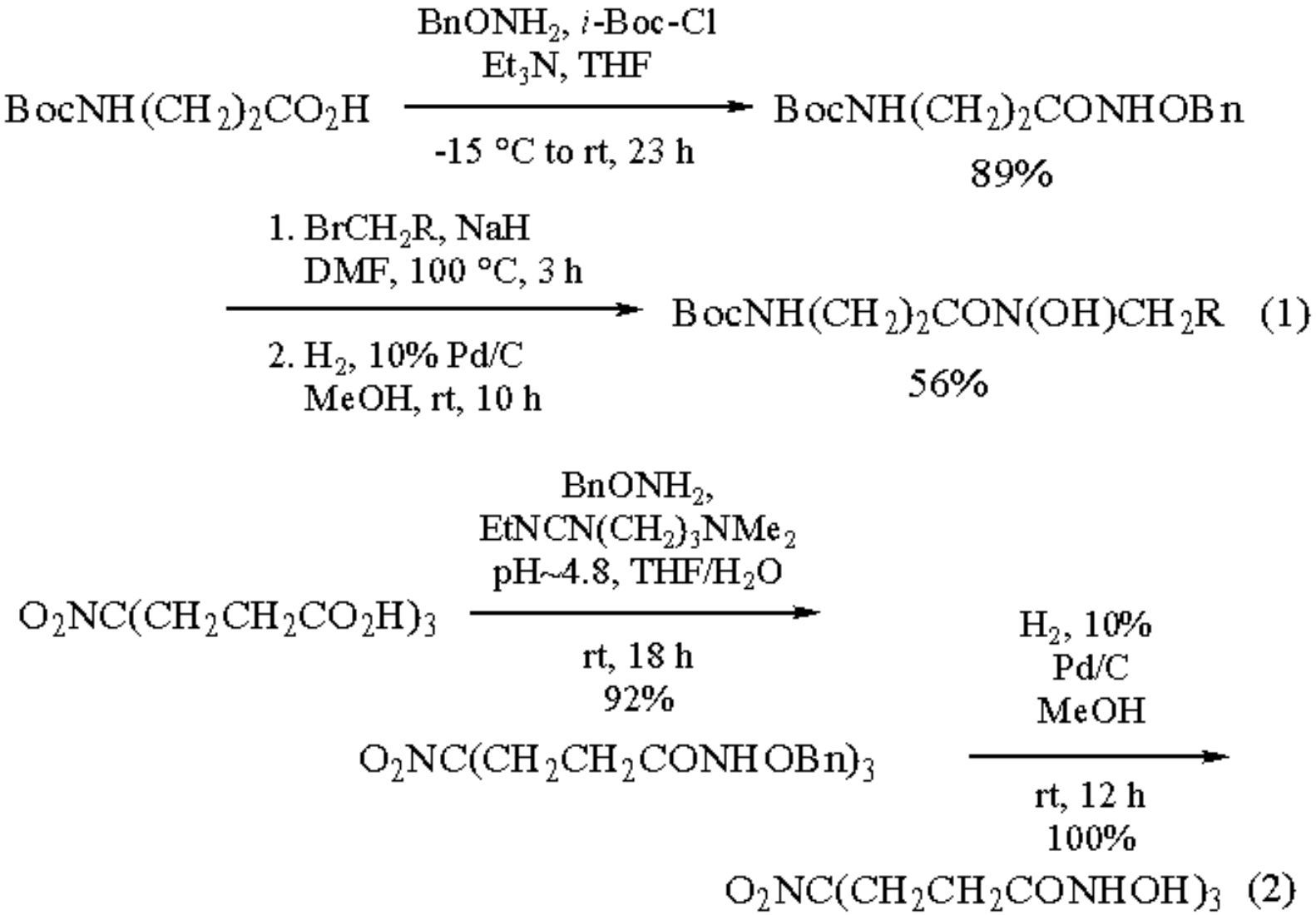

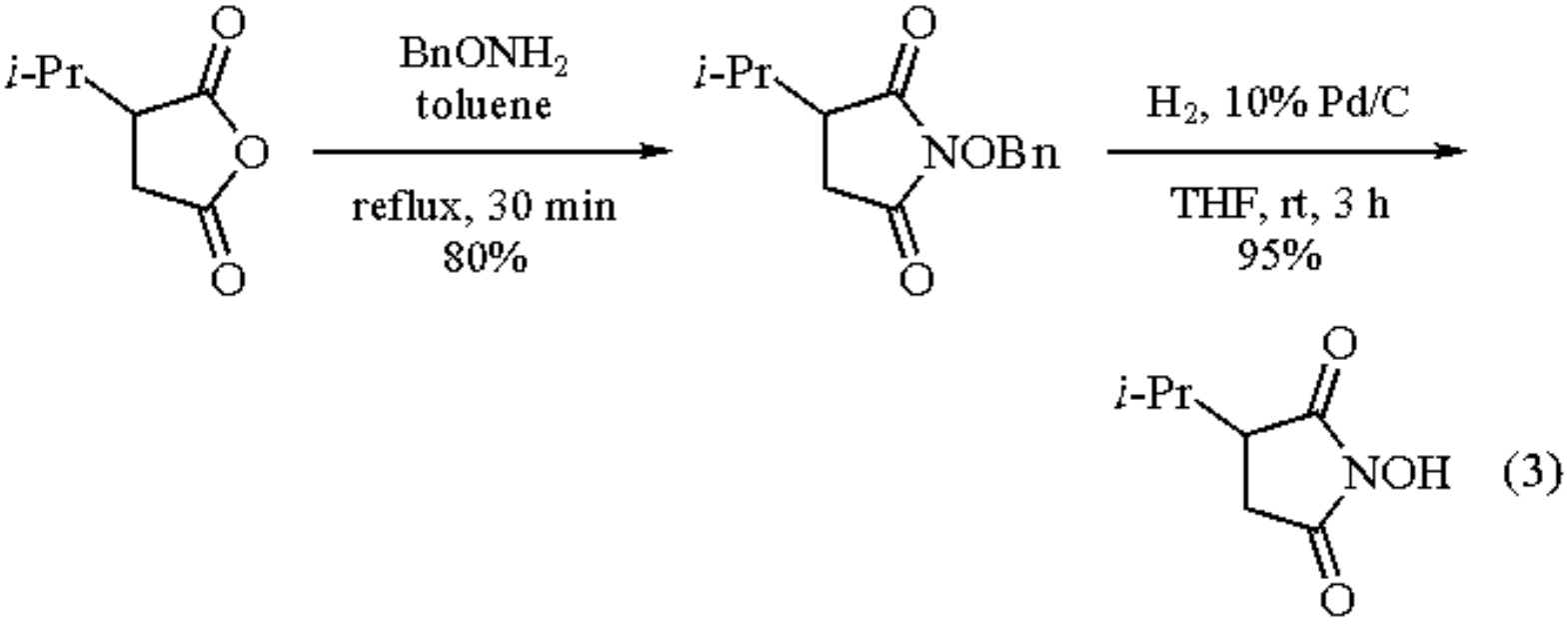

Other functional groups prepared by similar methodology include *N*-alkyl hydroxyureas, *N*-alkyl-*N*-hydroxycarbamates and *N*-alkylhydroxylamines.[13]

O-Benzyloximes.[1]

The reagent is used extensively as a derivatizing agent for preparation of *O*-benzyloximes of ketones,[6-8] aldehydes,[6] and carbohydrates (eq 4).[9] Usually both *syn* (*Z*) and *anti* (*E*) isomers are formed.

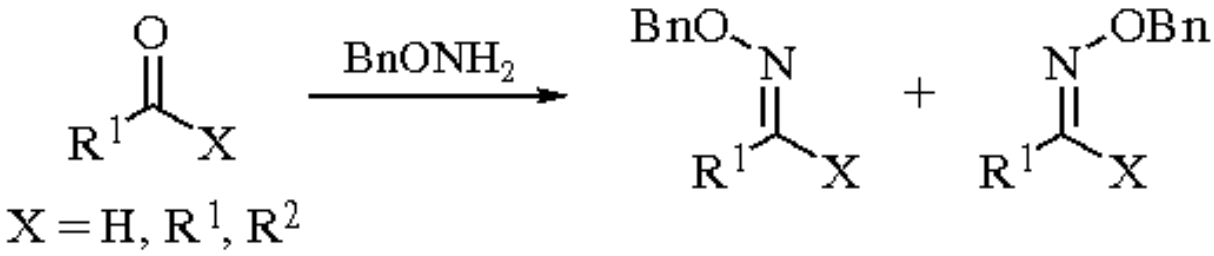

(4)

Reaction with *O*-alkyl thiocarboxylates affords alkyl *N*-benzyloxycarboximidates,[14] while enol esters may be converted in the presence of saturated ester functions to their respective ketoximes (eq 5).[15]

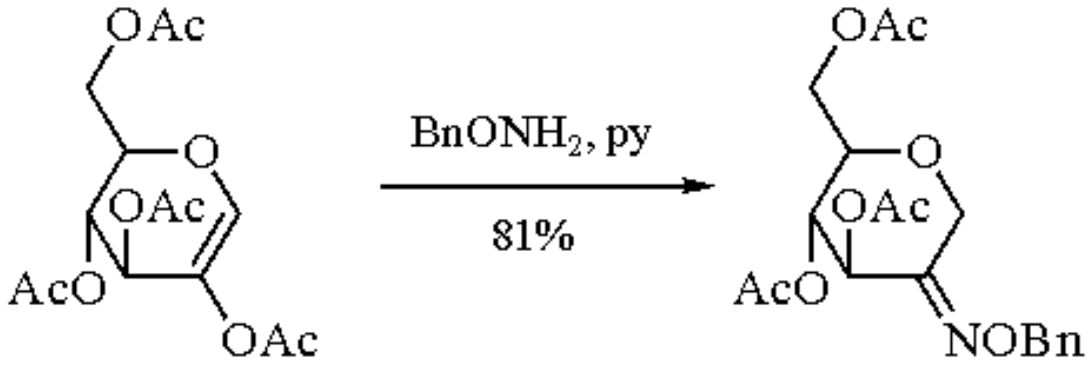

(5)

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David C. Rees & Niall M. Hamilton

N-Benzylhydroxylamine[1]

(base)

[622-30-0] · C_7H_9NO · *N*-Benzylhydroxylamine · (MW 123.15) (.HCl)

[29601-98-7] · $C_7H_{10}ClNO$ · *N*-Benzylhydroxylamine Hydrochloride · (MW 159.62)

(condenses with a wide variety of aldehydes to afford *N*-benzylnitrones;[2] hydroxylamination reagent for allyl esters under palladium(0) catalysis[3])

Physical Data: mp 57 °C; hydrochloride salt, mp 108-110 °C.

Form Supplied in: available commercially as the hydrochloride salt.

Preparative Methods: oxime reduction;[4-7] hydroxylamine alkylation;[8] isoxazole alkylation.[9]

Purification: sublimation.

Handling, Storage, and Precautions: hygroscopic. Use in a fume hood.

For a discussion of this reagent, see ***N-Cyclohexylhydroxylamine***.

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(η^4-Benzylideneacetone)tricarbonyliron[1]

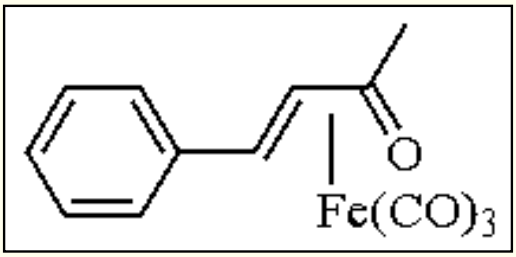

[38333-35-6] · $C_{13}H_{10}FeO_4$ · (η^4-Benzylideneacetone)tricarbonyliron · (MW 286.07)

(reagent for the complexation of 1,3-butadienes[5] and 1,3-cyclohexadienes[8] under mild reaction conditions)

Physical Data: mp 88-89 °C.

Solubility: sol hexane, benzene, toluene, diethyl ether, THF, 1,2-dimethoxyethane, chloroform, ethyl acetate.

Form Supplied in: red crystals.

Analysis of Reagent Purity: IR, NMR.

Preparative Methods: conveniently prepared by either thermal[2-4] or photochemical and thermal[1,5,8a] reaction of nonacarbonyldiiron with benzylideneacetone. The best procedure is heating a solution of benzylideneacetone in diethyl ether with an excess of nonacarbonyldiiron at reflux, which provides the (η^4-benzylideneacetone)tricarbonyliron complex $Fe(bda)(CO)_3$ in 81% yield (eq 1).[6,7]

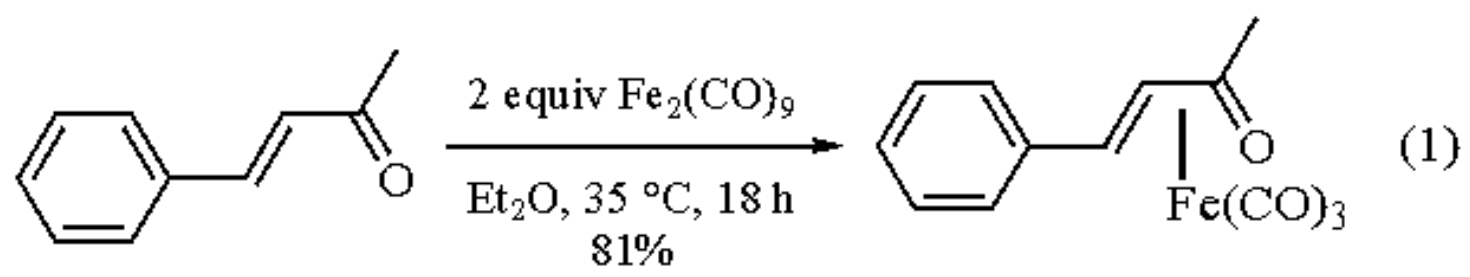

Purification: chromatography on silica gel (ethyl acetate/petroleum ether, 1:9); recrystallization from hexane.

Handling, Storage, and Precautions: should be handled and stored under an inert gas atmosphere of argon or nitrogen. Use in a fume hood.

The $Fe(bda)(CO)_3$ complex serves as a mild source of the tricarbonyliron fragment. The reaction of $Fe(bda)(CO)_3$ and 1,3-dienes occurs at ca. 60 °C with smooth transfer of the tricarbonyliron moiety onto the diene ligand and affords the corresponding tricarbonyl(η^4-1,3-diene)iron complexes in high yields (eq 2).[5]

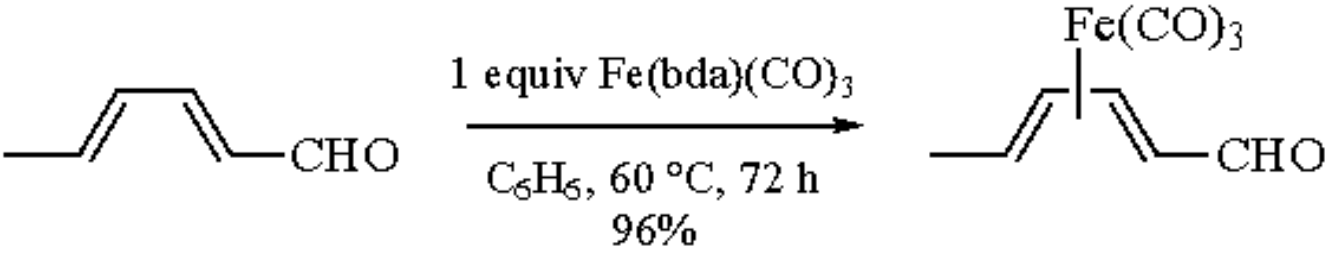

(2)

The standard procedure for the synthesis of tricarbonyl(η^4-diene)iron complexes involves thermal or photochemical reaction of the diene with ***Pentacarbonyliron***, ***Nonacarbonyldiiron***, or ***Dodecacarbonyltriiron***. Thus tricarbonyliron transfer reagents offer a useful synthetic alternative for the preparation of the tricarbonyliron complexes of dienes which are sensitive towards heat or UV irradiation. For example, tricarbonyl(η^4-8,8-diphenylheptafulvene)iron cannot be prepared by direct reaction of the free ligand with one of the carbonyliron compounds, but is obtained in high yield on transfer complexation with $Fe(bda)(CO)_3$ (eq 3).[2]

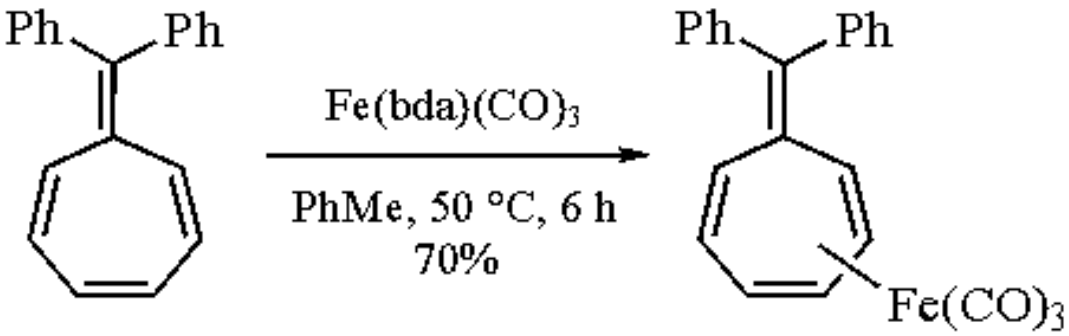

(3)

The tricarbonyliron unit can also be used for the protection of labile diene systems in order to achieve selective transformations at other double bonds present in the molecule. Protection of the steroid B-ring diene system of ergosterol derivatives by the tricarbonyliron fragment provides the corresponding diene complex, which has been used for selective reactions at the 22,23-double bond (eq 4).[8]

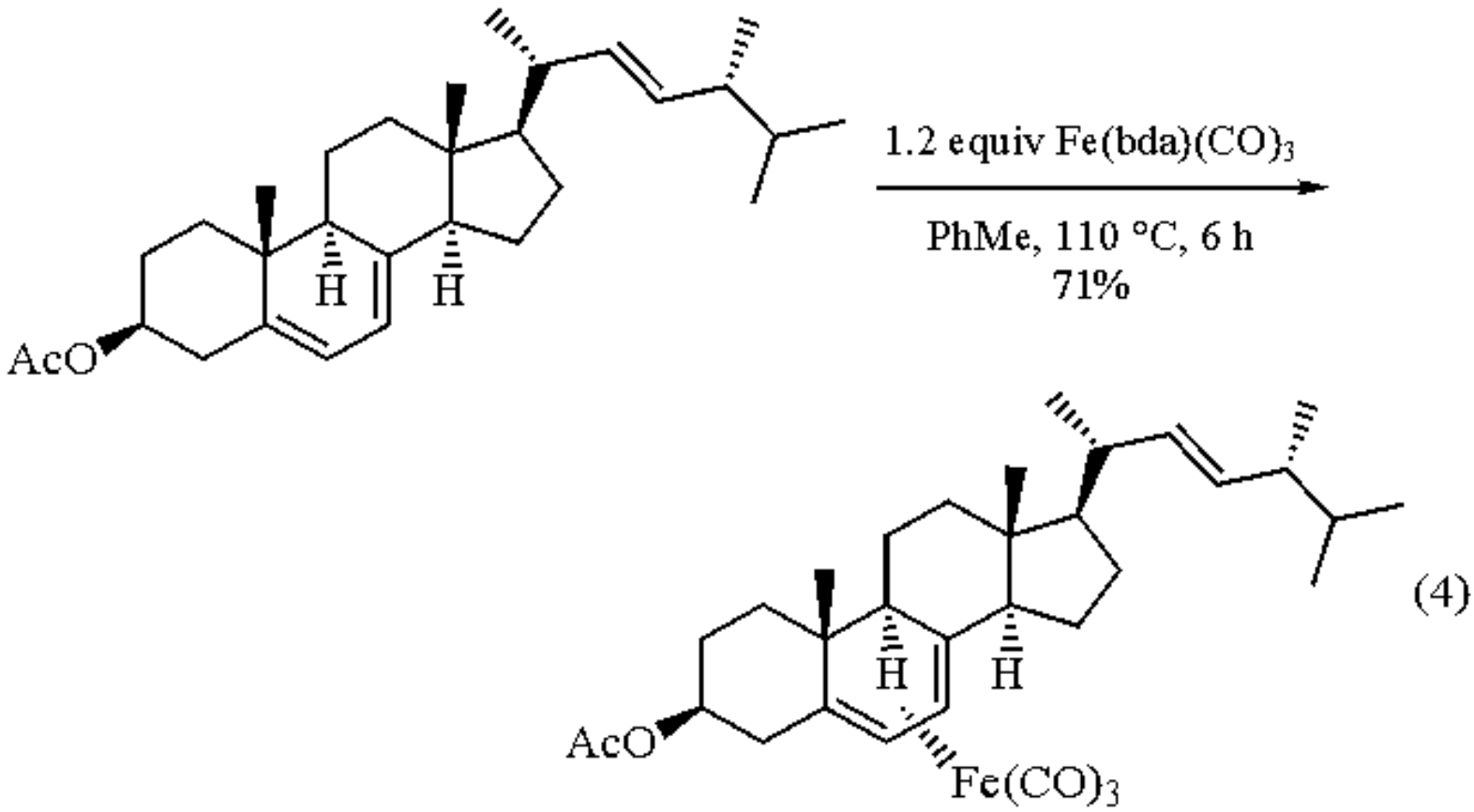

A broad range of labile diene systems can be complexed using the $Fe(bda)(CO)_3$ reagent and therefore stabilized by the tricarbonyliron fragment.[1,9] These transfer reactions of metal fragments to diene ligands involving the benzylideneacetone ligand have been extended to the $[Fe(CO)_2PPh_3]$ and the $[Fe(CO)_2P(OPh)_3]$ moieties. Using this method the corresponding cycloheptadiene complexes are conveniently prepared in high yields (eq 5).[4,10]

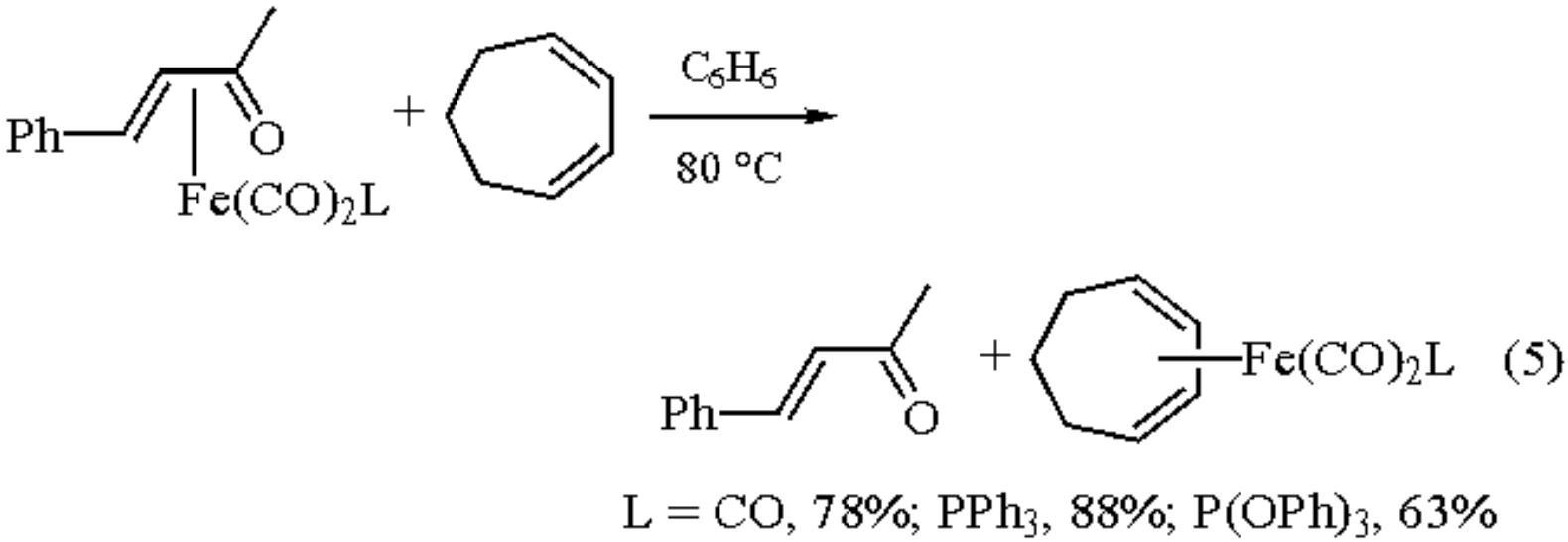

The mechanism of the tricarbonyliron transfer reaction using $Fe(bda)(CO)_3$ has been the subject of extensive investigations.[1,5,10b,11] Low asymmetric inductions (<40% ee) in the complexation of prochiral dienes using optically active $Fe(1\text{-oxadiene})(CO)_3$ complexes have been obtained.[12] Nucleophilic additions to $Fe(bda)(CO)_3$ have also been studied.[6,7,13]

Other Tricarbonyliron Transfer Reagent.

Tricarbonylbis(η^2-*cis*-cyclooctene)iron.

The photolytic reaction of pentacarbonyliron with an excess of *cis*-cyclooctene in hexane solution at -40 °C provides tricarbonylbis(η^2-*cis*-cyclooctene)iron (Grevel's reagent) in 56% yield (eq 6).[14]

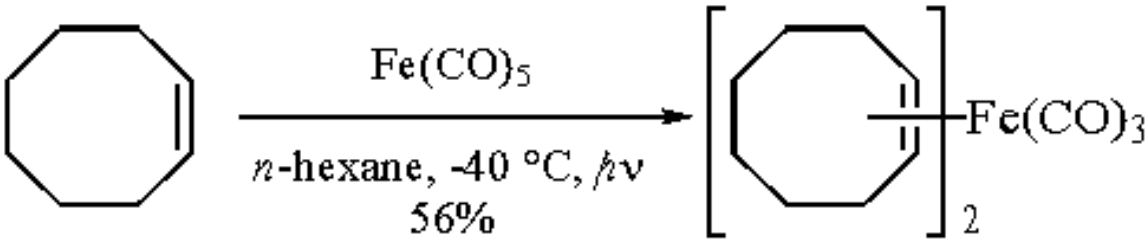

(6)

The solid compound can be handled at room temperature, but in solution the complex is labile at temperatures above -35 °C. The advantage of Grevel's reagent compared to $Fe(bda)(CO)_3$ is that the tricarbonyliron transfer reaction occurs under extremely mild conditions at temperatures below 0 °C. Moreover, in contrast to $Fe(bda)(CO)_3$,[5] 1,4-dienes can be complexed using Grevel's reagent with concomitant double bond migration to the conjugated diene system (eq 7).[14a] Useful applications of Grevel's reagent to organic synthesis have been described.[15]

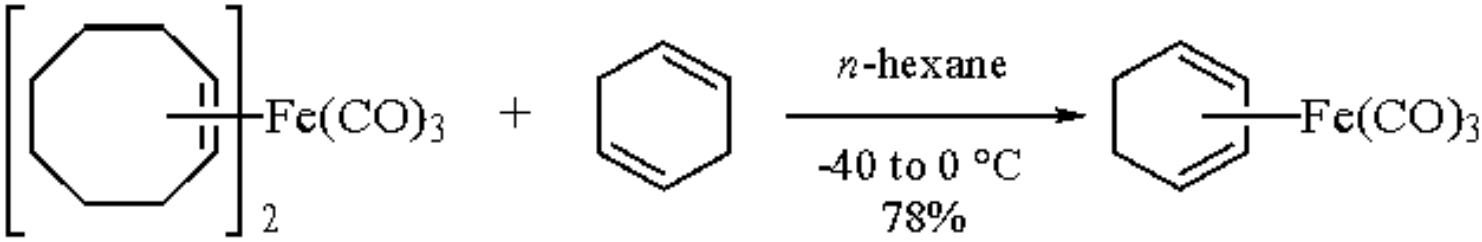

(7)

(η^4-1-Aza-1,3-butadiene)tricarbonyliron Complexes.

More recently, (η^4-1-aza-1,3-butadiene)tricarbonyliron complexes have been shown to represent very useful tricarbonyliron transfer reagents.[16] The tricarbonyliron complexes of the 1-aza-1,3-butadienes can be conveniently prepared by thermal reaction with nonacarbonyldiiron.[17,18] However, the yields of such complexes have been considerably increased by an ultrasound-promoted complexation of the 1-aza-1,3-butadienes at room temperature (e.g. 88% for the cinnamaldehyde/*p*-anisidine imine (eq 8).[16]

(eta-4-Benzylideneacetone)tricarbonyliron

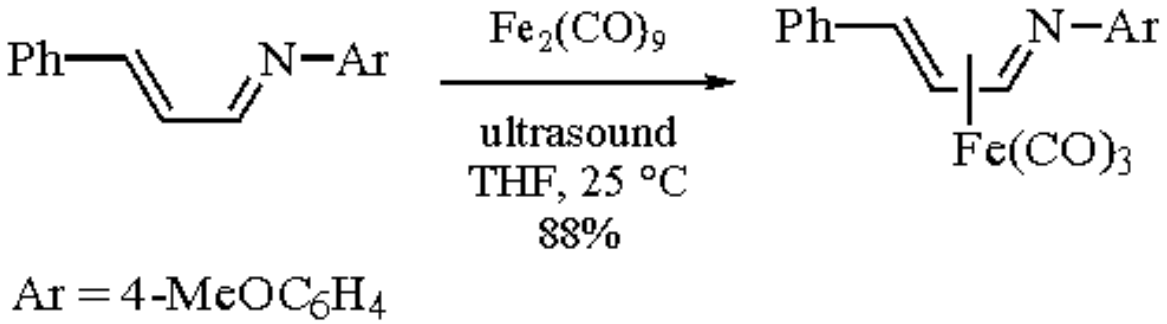

(8)

In contrast to the former reagents, the 1-azadiene complex is stable in the air for months. A smooth transfer of the tricarbonyliron fragment from the 1-azadiene complex to 1,3-dienes is effected in THF at reflux temperature and provides, for example, tricarbonyl(η^4-1,3-cyclohexadiene)iron in 95% yield (eq 9).[16] After the transfer the free 1-azadiene is recovered in more than 95% yield by crystallization.

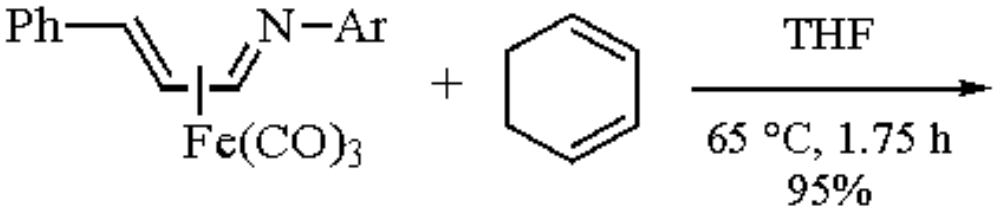

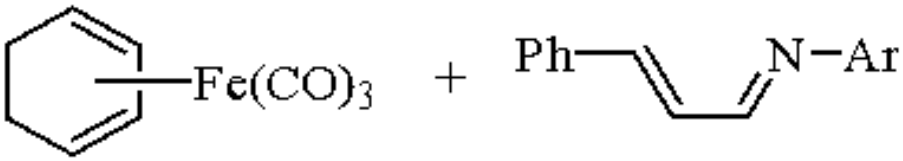

(9)

The major advantage of the 1-azadiene in comparison with the two former reagents is that the corresponding free ligand can be employed in catalytic amounts. Thus the 1-aza-1,3-butadiene is a useful catalyst for the complexation of 1,3-dienes by nonacarbonyldiiron or pentacarbonyliron. The yield for the 1-azadiene-catalyzed complexation of 1,3-cyclohexadiene is quantitative based on the iron carbonyl source (eq 10).[16]

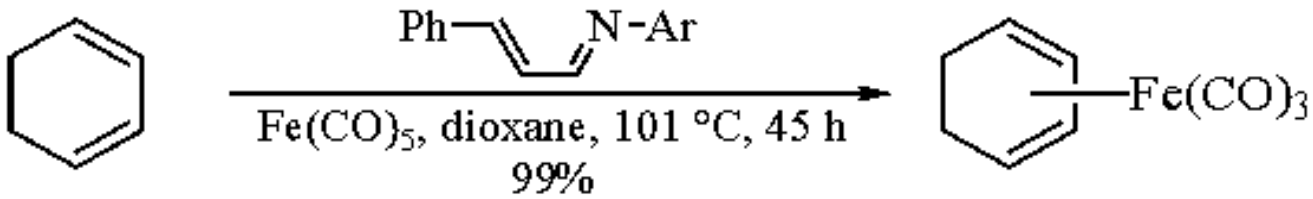

(10)

Immobilization of the 1-azadiene on a polystyrene resin provides a heterogeneous catalyst which is more easily separated from the reaction mixture and which can be resubmitted to the catalytic complexation.[16] The mechanism of the 1-azadiene-catalyzed complexation has been investigated and it was found that condensation of cinnamaldehyde with *o*-anisidines provides even more efficient catalysts.[19]

---

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Benzylidenetriphenylphosphorane[1]

$Ph_3P=CHPh$

[16721-45-2] · $C_{25}H_{21}P$ · Benzylidenetriphenylphosphorane · (MW 352.41)

(Wittig reagent for the conversion of aldehydes into alkenes[1])

Form Supplied in: usually, Wittig reagents are prepared in situ from the appropriate phosphonium salt. As such, benzyltriphenylphosphonium chloride is available as a white powder or as a mixture with sodium amide, $NaNH_2$.

Preparative Methods: benzylidenetriphenylphosphorane is prepared from benzyltriphenylphosphonium chloride by deprotonation with base.[1,2] Formation of the ylide from this salt has been accomplished with many different base and solvent combinations. In more recent preparations the salt typically is suspended in dry THF under an inert atmosphere and a solution of the base, either BuLi or KHMDS, is added by syringe.[3a,b] Alternatively, the salt and $NaNH_2$ are transferred to a flask in a dry box and then benzene is added.[4a] The ylide can also be generated with alkoxide bases in protic solvents[5] (such as NaOEt/EtOH) or under phase transfer conditions (CH_2Cl_2/H_2O with NaOH).[6]

Purification: benzyltriphenylphosphonium chloride can be recrystallized from absolute ethanol or $CHCl_3$/petroleum ether.

Handling, Storage, and Precautions: benzyltriphenylphosphonium chloride is a slightly hygroscopic solid. It can be dried efficiently under vacuum at elevated temperature (<10 Torr and 40 °C) overnight. Benzylidenetriphenylphosphorane is destroyed rapidly by exposure to oxygen or to moisture, and for this reason is usually prepared immediately before use. When protected from these materials, however, solutions of the ylide are stable for extended periods of time.[7]

Wittig Reagent for the Conversion of Aldehydes into Alkenes.

The reaction between benzylidenetriphenylphosphorane and an aldehyde to form an alkene and triphenylphosphine oxide is experimentally easy to carry out and proceeds under mild conditions at room temperature.[1a] A valuable feature of the Wittig procedure is that, in contrast to many elimination and pyrolytic reactions, it gives rise to alkenes in which the position of the double bond is established unambiguously.[1b] The aldehyde component may contain a wide variety of other functional groups such as hydroxyl, ether, ester, halogen, and terminal alkyne which generally do not interfere with the reaction.[1a,b] The utility of the Wittig reaction is shown by the fact that it has already been used in the synthesis of many alkenes, including a considerable number of natural products.[1b,c,d] Often, excellent selectivity for either the (*Z*)- (with a nonstabilized ylide) or (*E*)-alkene (with a stabilized ylide) can be obtained. In the case of benzylidenetriphenylphosphorane

(a moderated ylide), (*Z*):(*E*) selectivity is often poor,[1b] and apparently quite sensitive to experimental conditions (see Table 1).

Table 1 $Ph_3P{=}CHPh + PhCHO$ ® $PhCH{=}CHPh$

Entry	Base	Solvent	*Z*:*E*
1	PhLi	Et_2O	30:70[8]
2	BuLi	THF	60:40[5]
3	BuLi	C_6H_6	34:66[9]
4	$NaNH_2$	C_6H_6	44:56[4]
5	NaHMDS	C_6H_6	48:52[13]
6	NaOEt	EtOH	66:34[10]
7	NaOEt	EtOH	53:47[11]
8	NaOEt	DMF	74:26[11]
9	KO-*t*-Bu	*t*-BuOH	25:75[12]
10	NaOH	CH_2Cl_2/H_2O	59:41[6]

This ylide is historically important because its reactions with aromatic aldehydes were explored extensively during the first attempts to understand the mechanism of the Wittig reaction.[1a,c] Regrettably, the key reaction $Ph_3P{=}CHPh + PhCHO$ has proved to be the most difficult to control among all of the known Wittig systems. An inspection of Table 1 reveals inconsistencies in a number of the *Z*:*E* ratios for this reaction when the work of different groups is compared.[4-6,8-12] For example, the reported (*Z*) selectivity among the lithium-free entries varies from 25%[12] (entry 9) to 74%[11] (entry 8). Dramatic variations such as these were sometimes cited to support claims of reversal, cation effects, anion effects, electronic effects, or solvent effects in the mechanism of the Wittig reaction.[14] More recent studies are beginning to clarify these mechanistic questions and to explain the origin of selectivity in the Wittig reaction.[15]

Examples of Wittig reactions of benzylidenetriphenylphosphorane with aliphatic aldehydes are uncommon in the literature, and, as with aromatic aldehydes, the (*Z*):(*E*) selectivity is poor. However, if the structure of the substituents at phosphorus in the ylide are varied, then dramatic changes in the selectivity of the reaction are observed. A number of examples of this effect have been published. Two of the most striking examples are shown in eqs 1 and 2.[16]

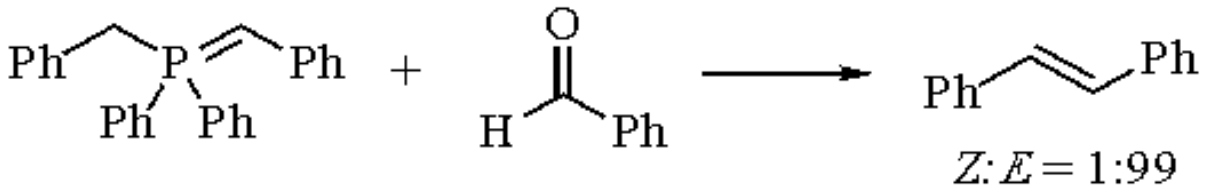

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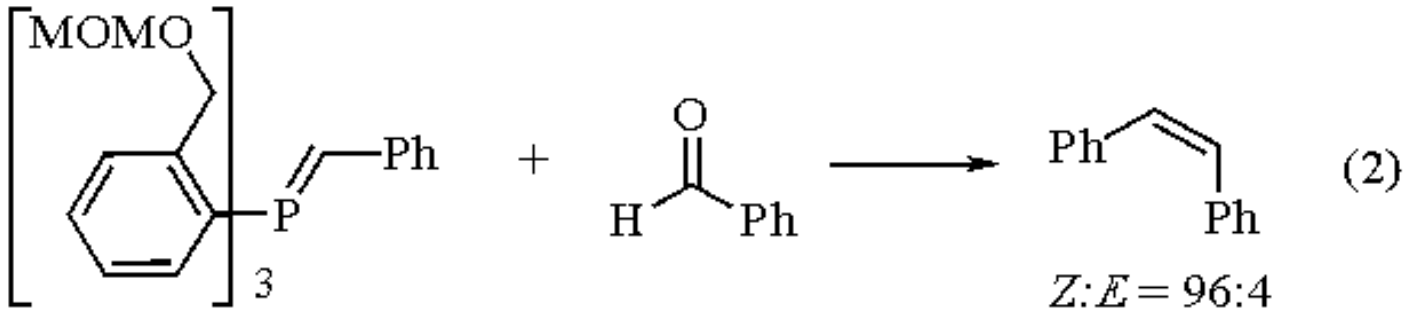

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16. (a) (*E*) selectivity: Bandmann, H.; Bartik, T.; Bauckloh, S.; Behler, A.; Brille, F.; Heimback, P.; Louven, J.-W.; Ndalut, P.; Preis, H.-G.; Zeppenfeld, E. *ZC* **1990**, *30*, 193. (b) (*Z*) selectivity: Tsukamoto, M.; Schlosser, M. *SL* **1990**, 605. Jeganathan, S.; Tsukamoto, M.; Schlosser, M. *S* **1990**, 109.

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Benzyl Iodide

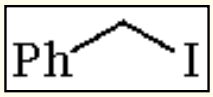

[620-05-3] · C_7H_7I · Benzyl Iodide · (MW 218.04)

(benzylating agent for heteroatomic functional groups and enolate anions; precursor to benzylic radicals)

Physical Data: bp 93 °C/10 mmHg; mp 24.5 °C; *d* 1.733 at 25 °C.

Solubility: sol alcohols, ether, and aromatic solvents.

Form Supplied in: 98% pure liquid.

Handling, Storage, and Precautions: potent lachrymator; should be handled in a fume hood.

Benzylation of Heteroatomic Functional Groups.

Benzyl iodide will react with alcohols under basic conditions to afford benzyl ethers and displays higher reactivity than other benzylating agents (see ***Benzyl Chloride***, ***Benzyl Bromide***, ***Benzyl p-Toluenesulfonate***). The reagent is frequently generated in situ, for example from benzyl bromide and tetrabutylammonium iodide in THF, and is useful for benzylation of sterically hindered alcohols.[1] Benzylation under less basic conditions is achieved with CsF and Bu_2SnO in DMF (eq 1).[2] The reagent can also be used to benzylate a phenolic hydroxyl group in the presence of silver oxide.[3] A benzyl penicillanate ester was prepared from the acid and benzyl iodide in the presence of triethylamine in acetone.[4] Benzylation of a thiopyrone in acetone to give the *S*-benzylated thiopyrylium salt has been reported.[5]

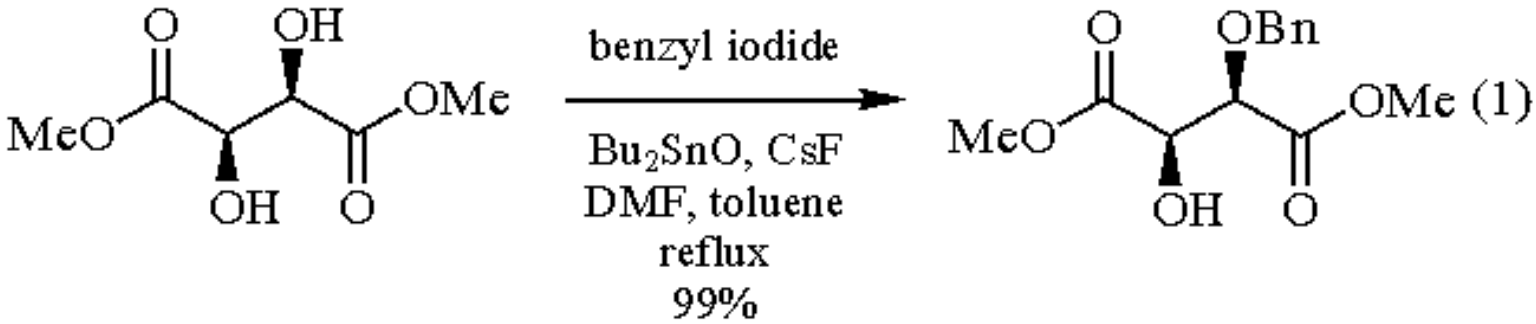

Benzylation of Active Methylene Compounds.

Benzyl iodide is reactive toward various enolate anions and has found use in the asymmetric benzylation of such

anions. For example, the enolate derived from a chiral 1,3-oxathiolan-5-one was benzylated to afford, after hydrolysis, a benzylated thioglycolic acid derivative (eq 2).[6]

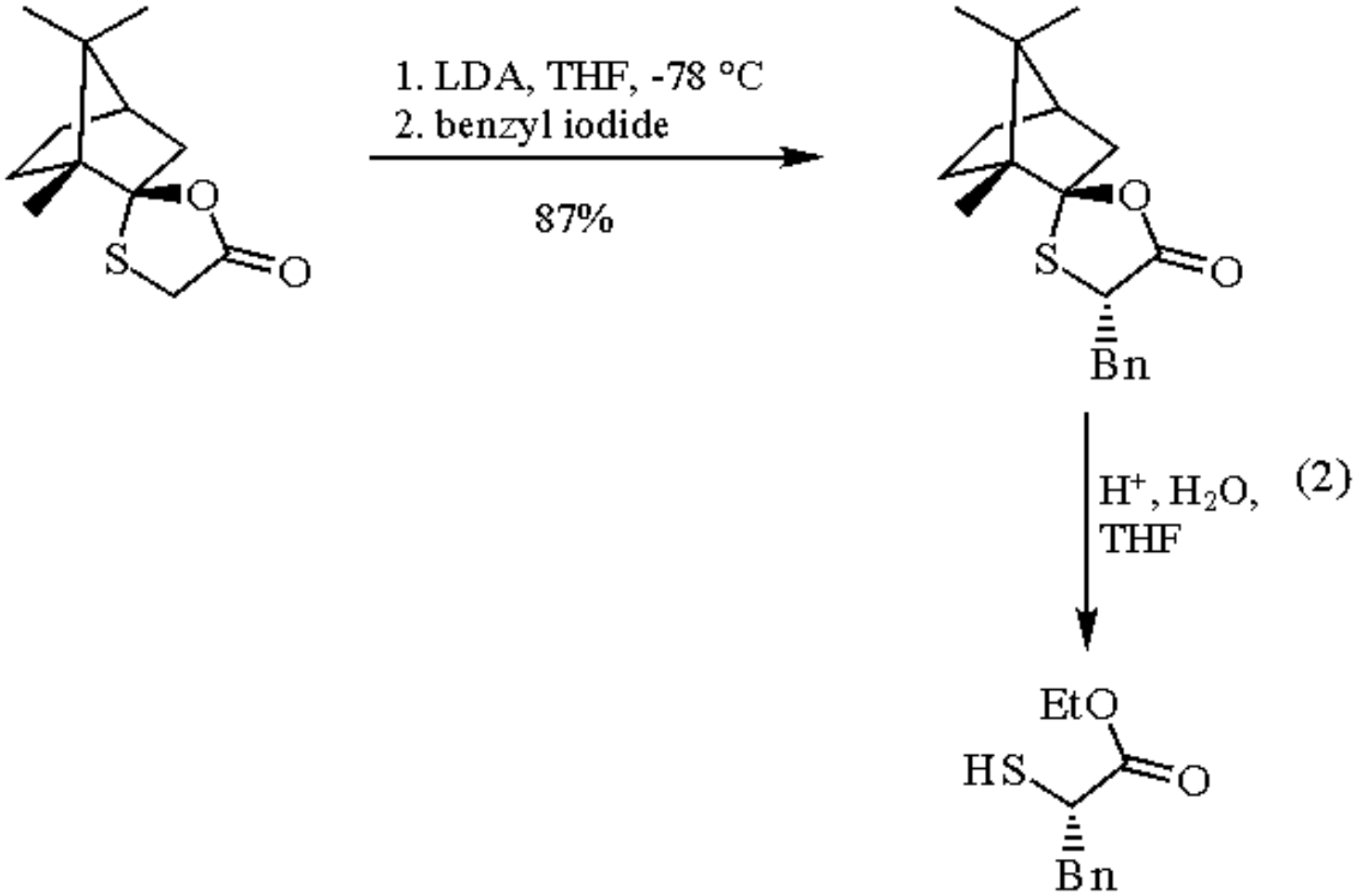

Chiral acylsultam enolates have been allylated with benzyl iodide with high diastereoselectivity in a route to protected amino acids.[7] An amide derived from ephedrine similarly affords benzylated acids and esters, and the corresponding methyl ketones are also available via this method.[8] Stereoselectivity in these reactions has been attributed to chelation of the metal by the chiral auxiliary. An enantioselective synthesis of L-[3-^{11}C]phenylalanine was achieved through a chiral glycine derivative, where an 8-phenylmenthol ester served as the chiral auxiliary under phase transfer catalysis conditions (eq 3).[9] Asymmetric benzylation of an aldehyde has also been reported using a chiral metalloenamine.[10]

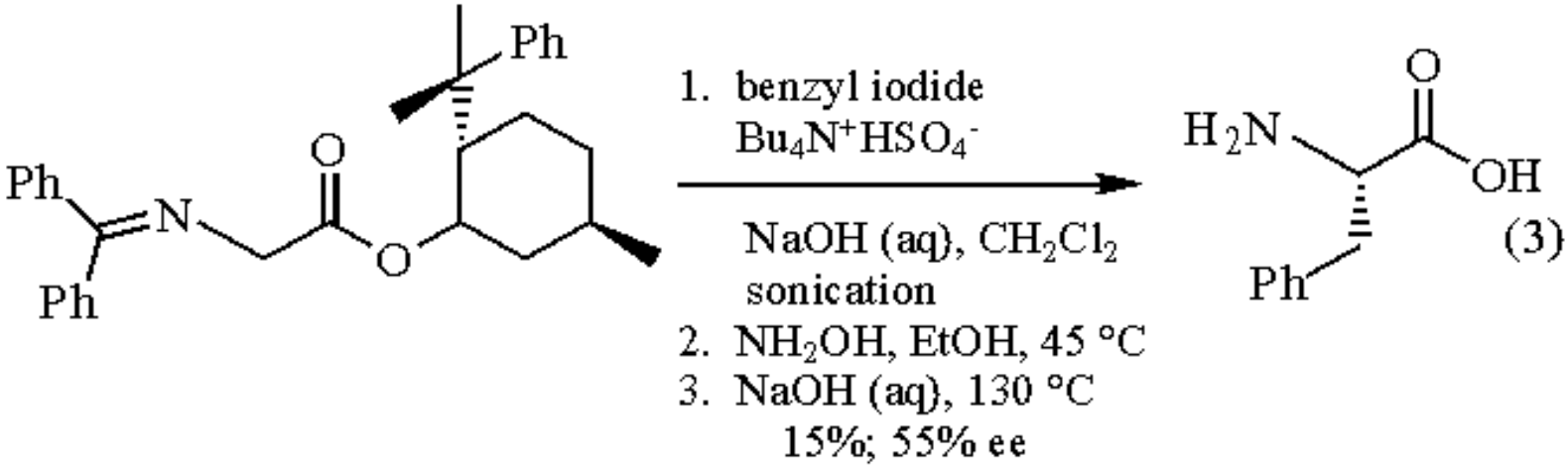

Sulfone stabilized carbanions also react with benzyl iodide.[11] This methodology has been applied to the preparation of polyenes. Likewise, formamidine stabilized carbanions allow access to α-benzylated amines with this reagent.[12]

Radical Reactions.

The benzyl radical has been generated from benzyl iodide and shown to undergo addition to unsaturated mono-[13] and dinitriles.[14] The resultant nitrile-stabilized radical may be further alkylated in the presence of ***Allyltributylstannane*** (eq 4). Oxidative coupling of benzyl iodide with excess ***Allyl Iodide*** in the presence of ***Triethylborane*** and oxygen has also been reported.[15]

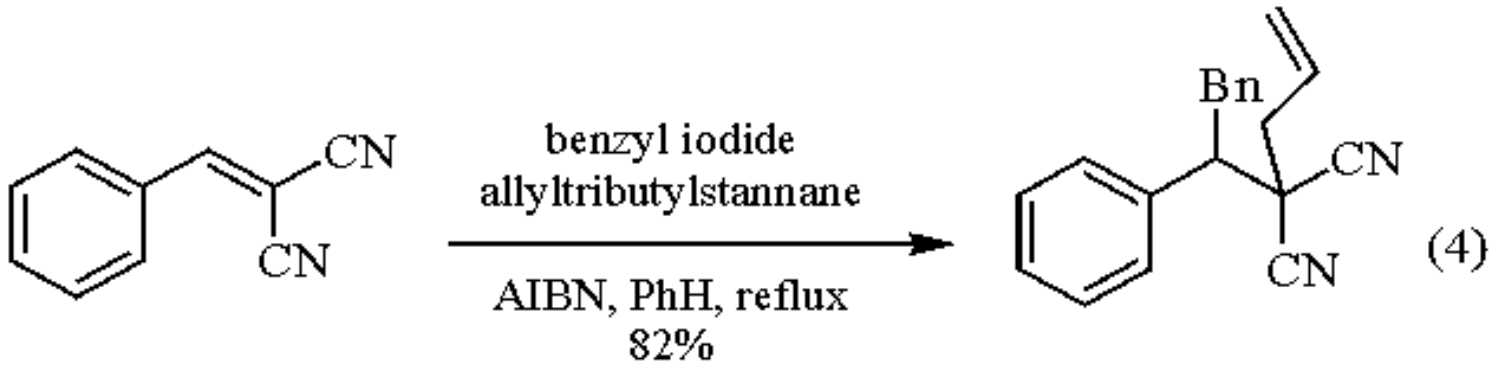

Reactions with Organometallics.

Dibenzyl ketone has been prepared in 95% yield by treatment of benzyl iodide with ***Tetracarbonylnickel*** in DMF.[16]

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Benzyl Isopropenyl Ether

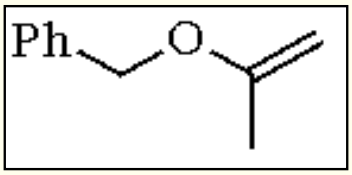

[32783-20-3] · $C_{10}H_{12}O$ · Benzyl Isopropenyl Ether · (MW 148.20)

(protecting group for compounds with multiple hydroxy groups;[1] acetone enolate equivalent[2])

Physical Data: bp 191-192 °C.[3]

Solubility: sol acetone, benzene.

Preparative Methods: the first reported synthesis of the reagent was accomplished by the pyrolytic decarboxylation of β-benzyloxycrotonic acid.[3] An alternate method for the preparation proceeds via dehydrohalogenation of 2-benzyloxy-1-chloropropane with potassium *t*-butoxide in DMSO (82% yield).[1]

Alcohol Protection.

Benzyl isopropenyl ether (**1**) has been shown to react with free hydroxy groups at rt in benzene in the presence of 10 mol % ***Dichloro(1,5-cyclooctadiene)palladium(II)*** to produce the corresponding mixed benzyl acetals in 85-98% isolated yield (eq 1).[1] The protecting group can also be introduced in comparable yields with catalytic ***Phosphorus Oxychloride*** or ***p-Toluenesulfonic Acid***. Cleavage of the mixed acetal took place at rt in the presence of catalytic 5% ***Palladium on Carbon*** under 1 atm of hydrogen in 92-99% yield. The protecting group was stable to hydride reducing agents (LAH, DIBAL), alkyllithium, and Grignard reagents, and was stable to alkaline hydrolysis conditions (1 M NaOH/THF, 1/1). Exposure to 1 M ***Acetic Acid*** in THF (1/1) effects cleavage of the protecting group.

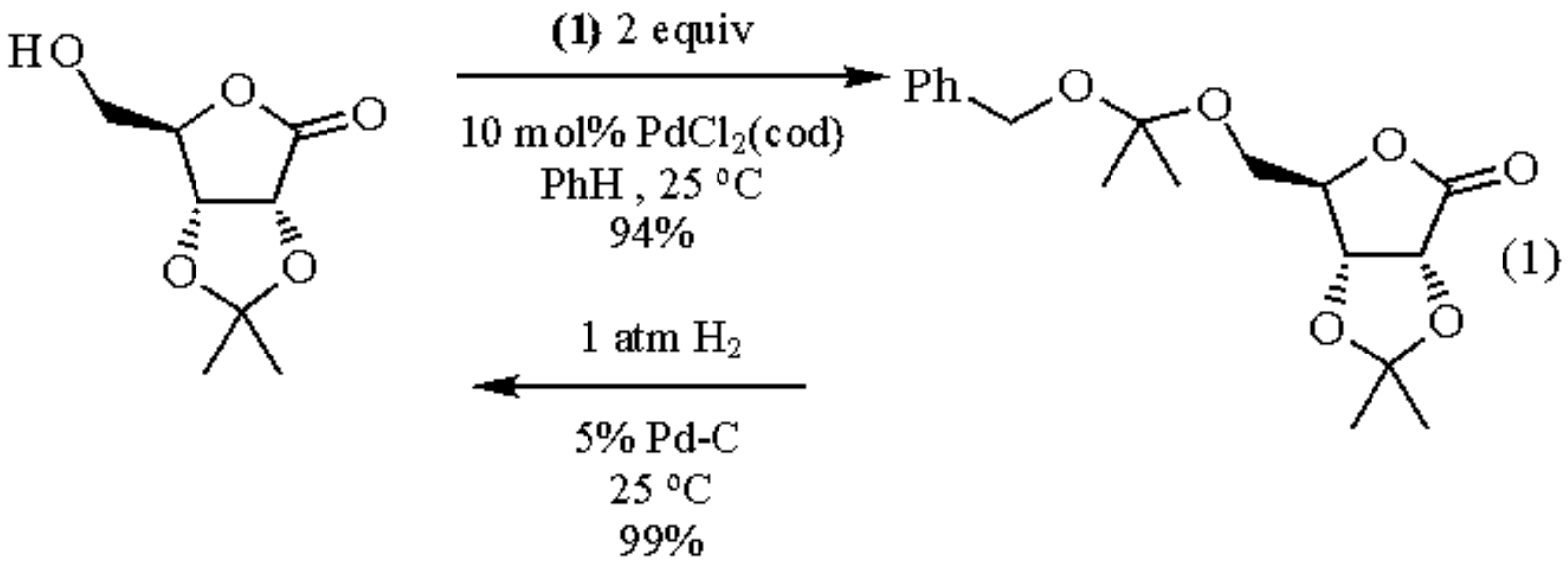

The primary advantage of this alcohol-protecting group over many similar reagents[4] is the neutral conditions used for its introduction and removal. An alternative method for protecting alcohols as mixed acetals makes use of catalytic ***Cobalt(II) Chloride*** in MeCN at rt.[5] The reported range of yields for this method was slightly lower (68-91%); however, the ready availability and low cost of the cobalt catalyst recommends its use.

A closely related reagent for alcohol protection is 2-phenoxypropene, which was easily prepared from phenyl acetate and Tebbe's reagent in 57% yield.[6] Conversion of alcohols to the corresponding phenyl mixed acetals took place with catalytic phosphorus trichloride. Hydrolytic cleavage with 0.1 M HCl and ether was complete in 30 s.

Acetone Enolate Equivalent.

An early application in which (**1**) was used as an acetone enolate equivalent in a Lewis acid-catalyzed condensation with ketones has been reported.[2] For example (eq 2), condensation of (**1**) with acetone in the presence of ***Boron Trifluoride Etherate*** produced 4-benzyloxy-4-methyl-2-pentanone in 52% yield. This early methodology has largely been eclipsed by advances involving the use of silyl enol ethers.

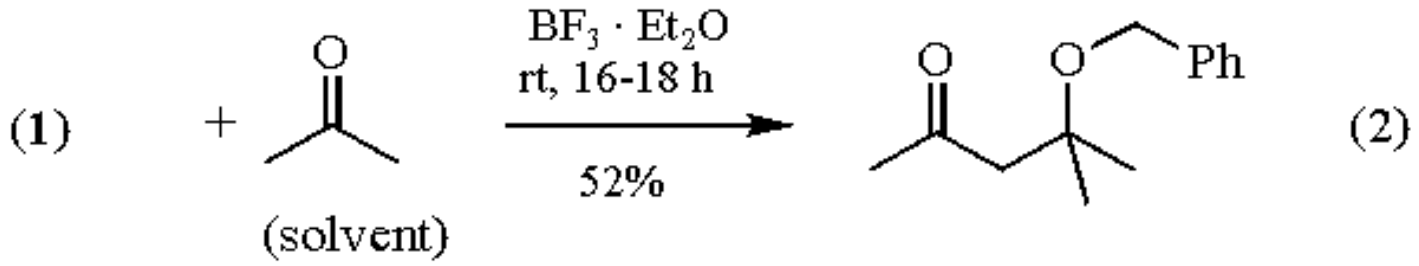

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Benzyllithium[1]

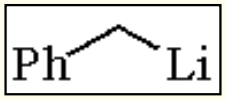

[766-04-1] · C_7H_7Li · Benzyllithium · (MW 98.07)

(benzylating agent in substitutions and additions at carbon; used to attach benzyl groups to other metals and nonmetals)

Physical Data: by X-ray, the DABCO complex forms contact ion pairs with Li over planar benzyl anions[2] and the THF-TMEDA complex has pyramidal benzylic carbon atoms.[3] UV[4] and ^{1}H,[5] ^{13}C,[6] and ^{7}Li[7] NMR studies have been reported.

Solubility: sol ethers; DABCO complex crystallizes from hexane as it forms.[8]

Form Supplied in: prepared in situ and used directly.

Preparative Methods: preparation from benzyl ethyl ether and ***Lithium*** in THF/ether is recommended on a large scale; toluene metalation for pure samples.[8] Metalation of toluene with ***n-Butyllithium***/TMEDA gives 90-91% yield, but contaminated with 5-6% *m*-tolyllithium and 2% each of *o*- and *p*-tolyllithium;[9] metalation of toluene with butyllithium/***Potassium t-Butoxide***, then reaction of the red solid benzylpotassium with LiBr in ether, gives purer product.[10] Preparations from organotin compounds by exchange may be contaminated with organotin compounds.[10] A method involving treatment of benzyl selenides with BuLi at -78 °C should be especially useful for benzyllithiums containing halogens or methoxyls.[11]

Handling, Storage, and Precautions: must be prepared and transferred under an inert gas to exclude oxygen and moisture.

Nucleophilic Substitutions at Carbon.

Resonance-stabilized Li reagents such as benzyllithium are stronger nucleophiles but weaker bases than alkyllithium reagents, permitting displacement of Br^- and I^- from cyclohexyl and cyclopentyl systems in Wurtz-type couplings (eq 1).[12] Optically active secondary halides react with clean inversion.[13]

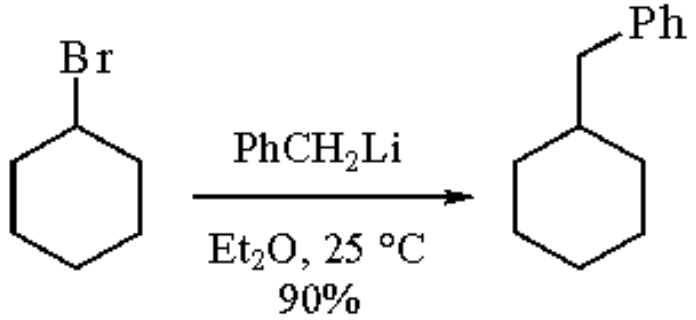

(1)

Nucleophilic Substitutions at Other Nonmetals.

Cinchonine (an optically active alcohol) can be displaced from phosphinites by benzyllithiums to give optically active phosphines with inversion of configuration (eq 2).[14] The stereoselectivity was much greater with sterically hindered benzyl derivatives.

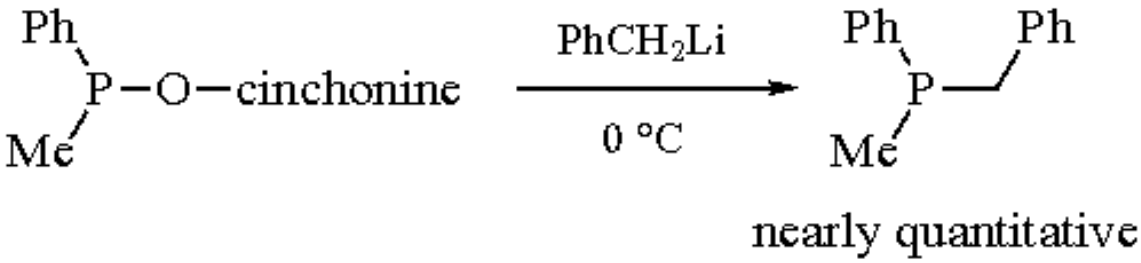

(2)

Vinyl azide acts as a NH_2^+ equivalent in reaction with benzyllithium (eq 3), providing a method for the amination of such compounds.[15]

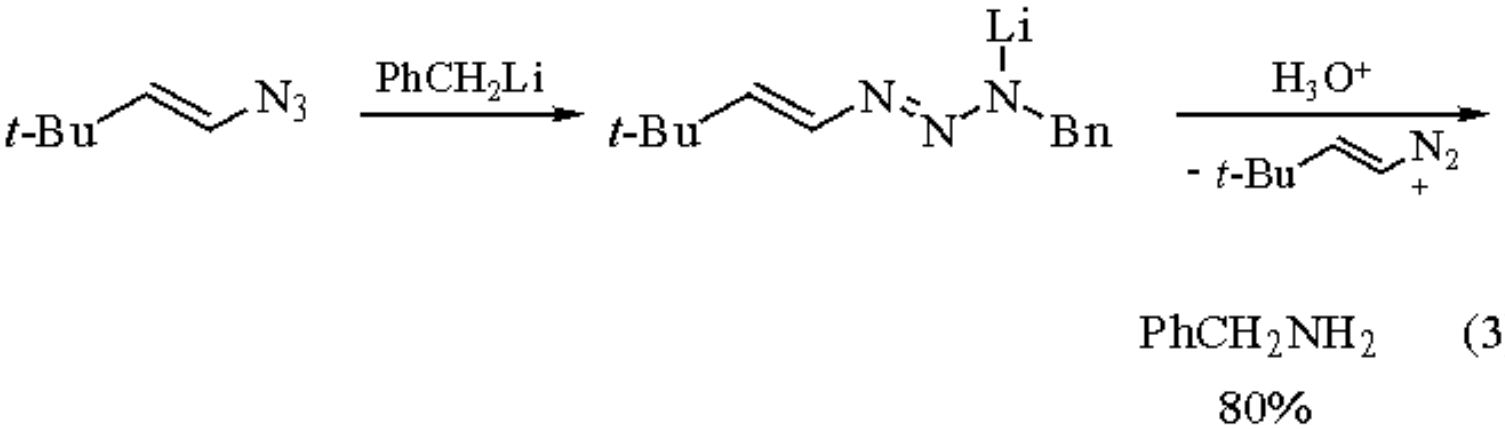

(3)

Additions to Double Bonds.

Besides the usual additions to aldehydes and ketones, benzyllithium adds to ketenes as shown in eq 4 to give regiospecific enolates which can be used in aldol condensations.[16] It also adds to a double bond of cyclooctatetraene and then acts as a base, leading to benzylcyclooctatetraene dianion (eq 5).[17]

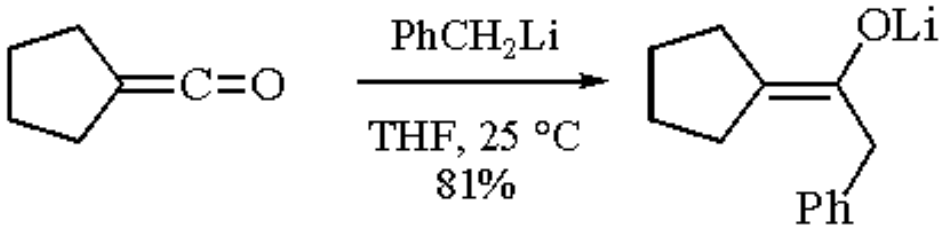

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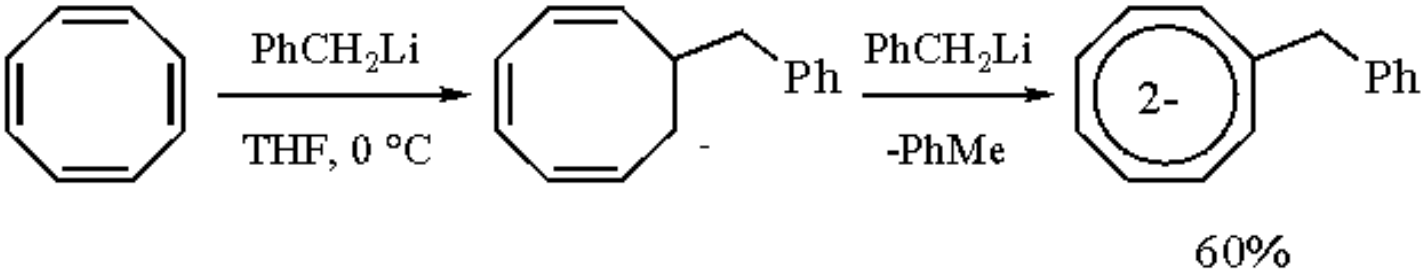

(5)

The direction of addition of benzyllithium to vinyl groups depends on the substituents. It adds to the more-substituted carbon of the double bond of allyl alcohol (eq 6),[18] but (in the presence of Cu^{I}) to the less-substituted carbon of the double bond in the epoxyalkene in eq 7.[19]

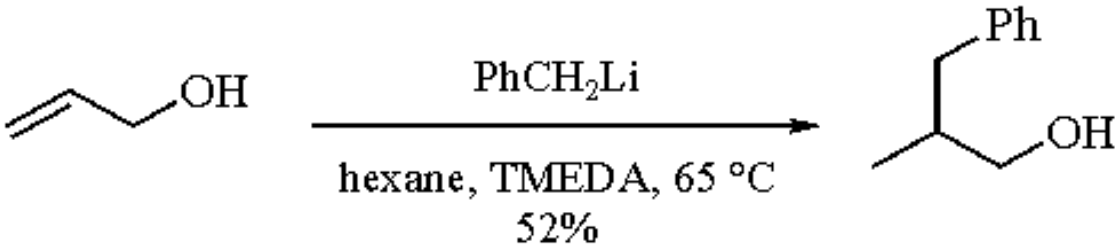

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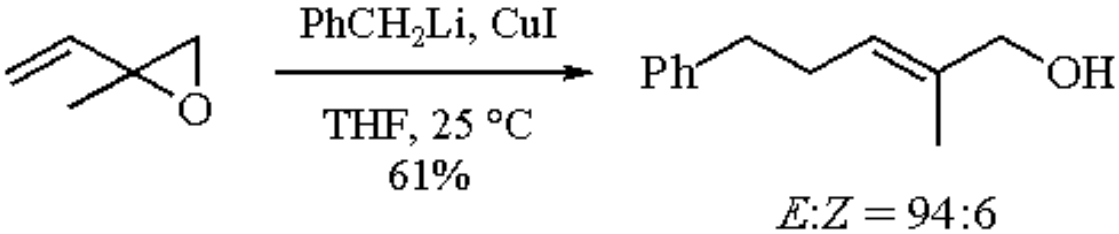

(7)

Metal Exchange.

Benzyllithium used in the presence of copper salts may react as lithium dibenzylcuprate.[19] Benzyllithium has been used to make benzylzinc[20] and rare earth benzyl derivatives.[21]

Related Reagents.

Table 1 lists some useful benzyllithium derivatives.[22-30] See also ***Benzylmagnesium Chloride***.

Table 1 Benzyllithium Derivatives

Structure	Name	Mol. form.

Structure	Name	Mol. form.
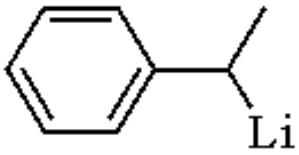	Ethane, 1-lithio-1-phenyl-	C_8H_9Li[22]
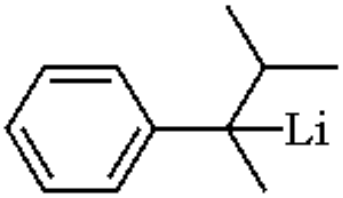	Butane, 2-lithio-2,3-dimethyl-	$C_{11}H_{15}Li$[23]
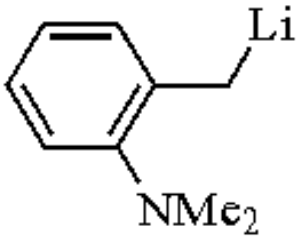	Benzene, 1-lithiomethyl-2-dimethylamino-	$C_9H_{12}LiN$[24]
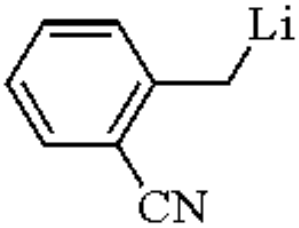	Benzene, 1-lithiomethyl-2-cyano-	C_8H_6LiN[25]
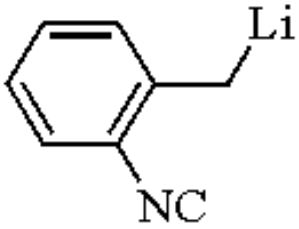	Benzene, 1-lithiomethyl-2-isocyano-	C_8H_6LiN[26]
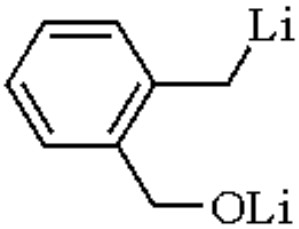	Benzene, 1-lithiomethyl-2-lithoxymethyl-	$C_8H_8Li_2O$[27]
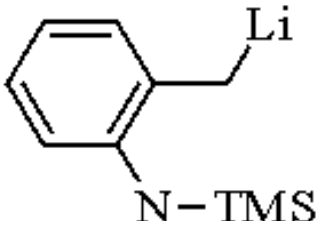	Aniline, 2-lithiomethyl-	$C_{10}H_{15}Li_2NSi$[28]

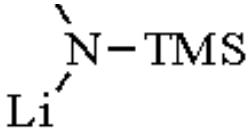

Aniline, 2-lithiomethyl-
N-lithio-*N*-trimethylsilyl-

$C_{10}H_{15}Li_2NSi$[28]

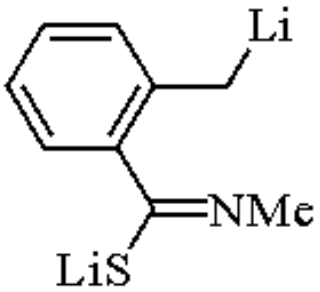

Benzene, 1-lithiomethyl-
2-(*N*-methyl-*S*-lithio-thiamido)-

$C_9H_9Li_2NS$[29]

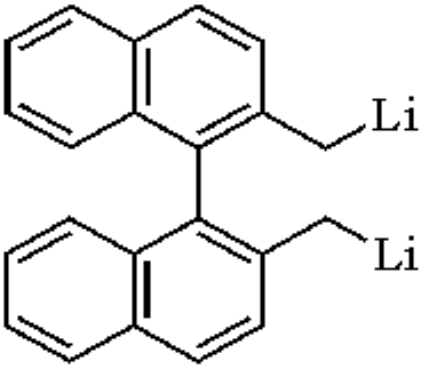

1,1'-Binaphthyl, 2,2'-
bis(lithiomethyl)-

$C_{22}H_{16}Li_2$[30]

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Benzylmagnesium Chloride

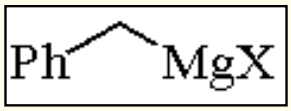

(X = Cl)

[6921-34-2] · C_7H_7ClMg · Benzylmagnesium Chloride · (MW 150.89) (X = Br)

[1589-82-8] · C_7H_7BrMg · Benzylmagnesium Bromide · (MW 195.34)

(adds to many unsaturated functional groups; benzyl can displace halide and like groups; can function as a strong base and a Lewis acid[1b-f])

Physical Data: usually prepared or purchased as a solution and used without isolation. Addition of HMPA to an Et_2O solution of BnMgCl causes significant changes in the UV spectrum that indicate ionization to benzyl anions.[2]

Solubility: BnMgCl and BnMgBr are soluble in Et_2O and THF, and insoluble in hydrocarbons.

Form Supplied in: solutions of BnMgCl in Et_2O and THF are commercially available.

Analysis of Reagent Purity: see ***Methylmagnesium Bromide***.

Preparative Methods: [1c,e,3] in spite of the commercial availability of BnMgCl solutions, BnMgCl[4] and BnMgBr are often prepared from reaction of a benzyl halide and Mg, usually in Et_2O or THF.

Handling, Storage, and Precautions: see ***Methylmagnesium Bromide***. Benzyl Grignard reagents do not significantly attack Et_2O or THF at normal reaction temperatures

Preparation.

Yields of routine BnMgCl and BnMgBr preparations often exceed 90%, but those of BnMgI preparations are lower due to competing formation of bibenzyl and other dimers. Yields of Grignard reagents from benzyl chlorides and bromides having α-substituents and certain aryl substituents also are lower. In such cases, yields often are significantly improved by using activated Mg that permits preparation at lower temperatures. A simple activation procedure involves stirring the Mg under nitrogen,[5] but other convenient procedures[6] are available (also see ***Phenylmagnesium Bromide***).

Representative Applications.[1b-f]

A benzyl Grignard reagent is used most frequently in reactions that result in attachment of its organic group to an electrophilic carbon atom of the substrate, most often of a carbonyl group, nitrile, or other unsaturated function. Some reactions[7] of benzyl Grignard reagents, with unhindered carbonyl compounds,[8,9] (eq 1) for example,[8] furnish *ortho*-substituted products. Further reaction of the triene (e.g. **2**) that probably forms initially can provide a product of double addition (**1**), sometimes significant even when excess Grignard reagent is used. *Ortho*- and sometimes small amounts of *para*-substituted products also are found in displacement reactions of benzyl Grignard reagents with reactive alkyl halides.[10] See also ***Benzyllithium*** and ***Methylmagnesium Bromide***.

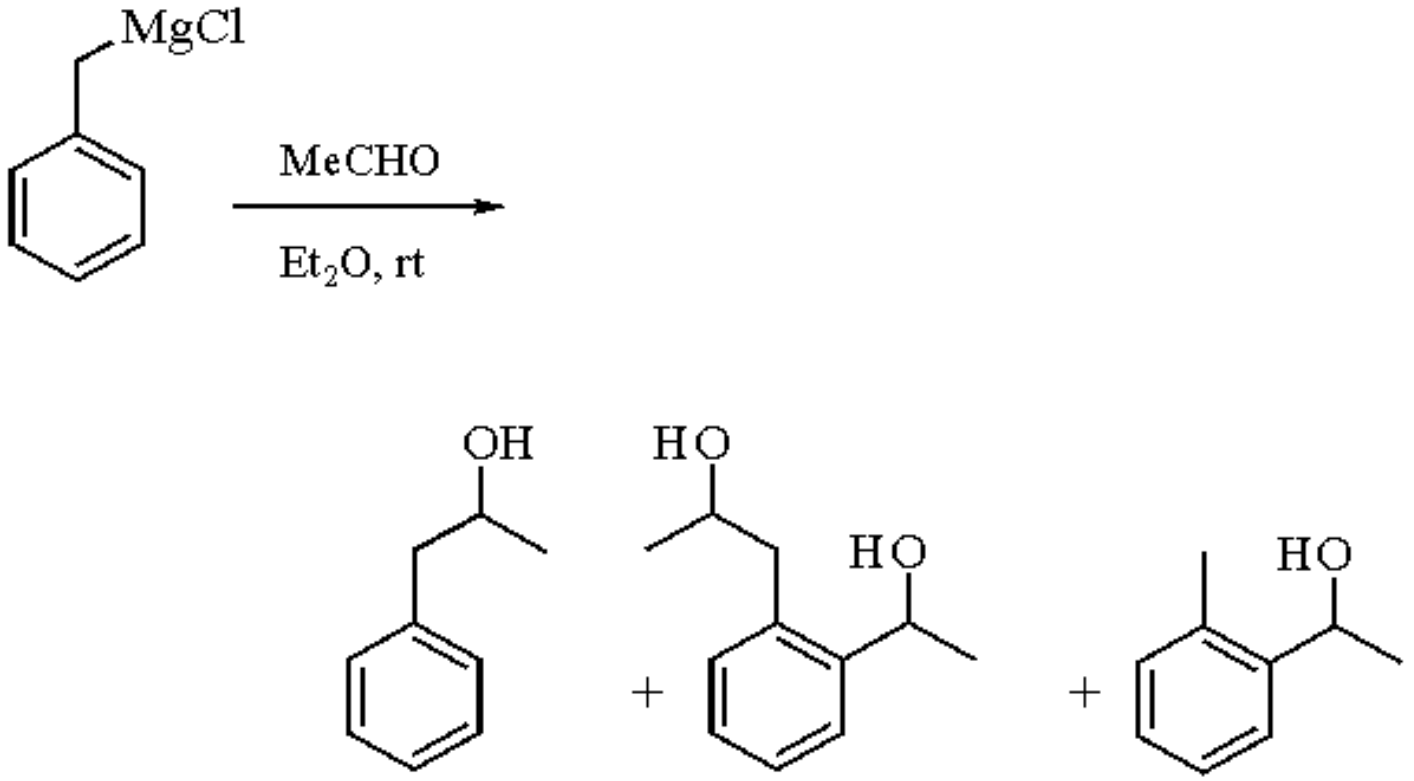

(1)

BnMgCl:MeCHO		(1)	
1:1	11%	76%	<1%
3:1	22%	30%	8%

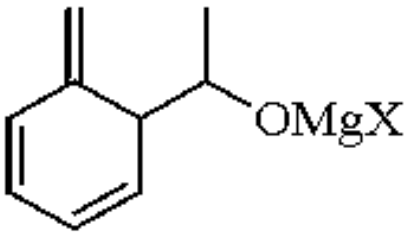

(2)

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Benzyl(methoxymethyl)methylamine

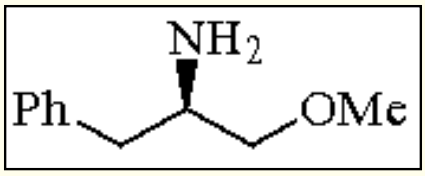

(*S*)

[64715-80-6] · $C_{10}H_{15}NO$ · Benzyl(methoxymethyl)methylamine · (MW 165.23) (*R*)

[59919-07-2]

(chiral auxiliary for the enantioselective alkylation of ketones[1] and aldehydes;[2] can form chiral cuprate reagents[3])

Physical Data: (*S*) bp 55-59 °C/0.1 mmHg; mp HCl salt 151-152 °C; $[\alpha]_D^{25}$ -14.4° (*c* 5.7, benzene); HCl salt $[\alpha]_D^{25}$ +19.7° (*c* 2.5, EtOH).

Preparative Method: these chiral methoxy amines are readily prepared from (*S*)- or (*R*)-phenylalanine via reduction followed by methylation.[2]

Handling, Storage, and Precautions: conversion of the freshly distilled amine to its hydrochloride salt is a convenient way to store and handle the compound. The free amine reacts with atmospheric carbon dioxide to produce the respective carbonate. The free amine should be stored tightly sealed under argon or nitrogen immediately after distillation to avoid CO_2 adsorption.

Enantioselective Alkylation.

Both antipodes of this chiral amine have been used in the enantioselective alkylation of ketones and aldehydes via their respective chiral, nonracemic lithioenamines (eq 1). The enantioselectivity in alkylation results from the induced rigidity of the lithioenamine upon chelation with the methoxy group, providing the bias necessary to influence the direction and rate of entry of the electrophile.

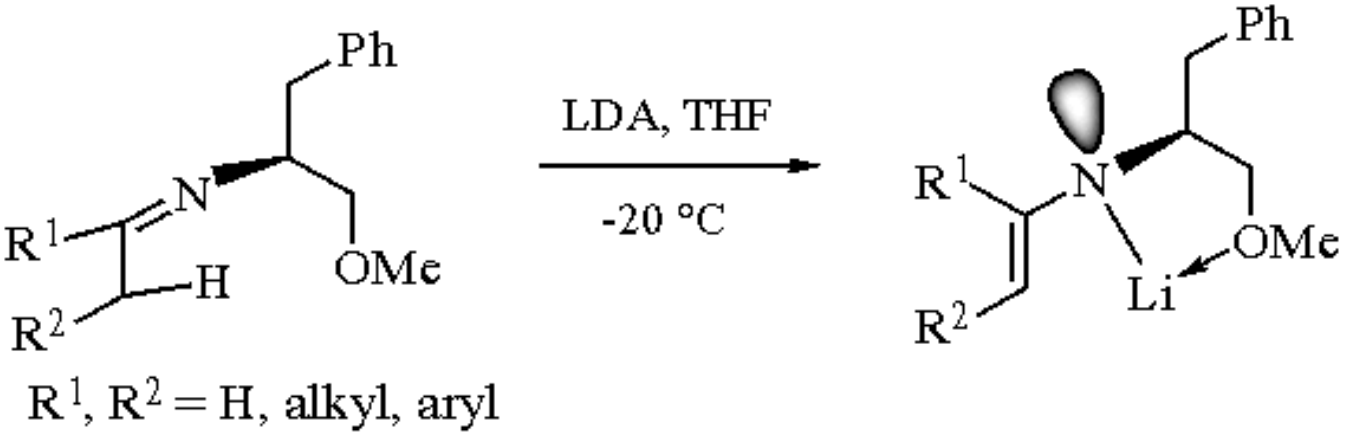

Medium-sized cyclic ketones have been enantioselectively alkylated via their chiral lithioenamines to yield 2-alkylcycloalkanones in 80-100% ee.[4] This procedure has also furnished α,α´-dialkyl cyclohexanones in good enantiomeric excess (eq 2).[4] Based on this protocol, regiospecific deuteration of 3-methylcyclohexanones has been achieved with good enantioselectivity.[5]

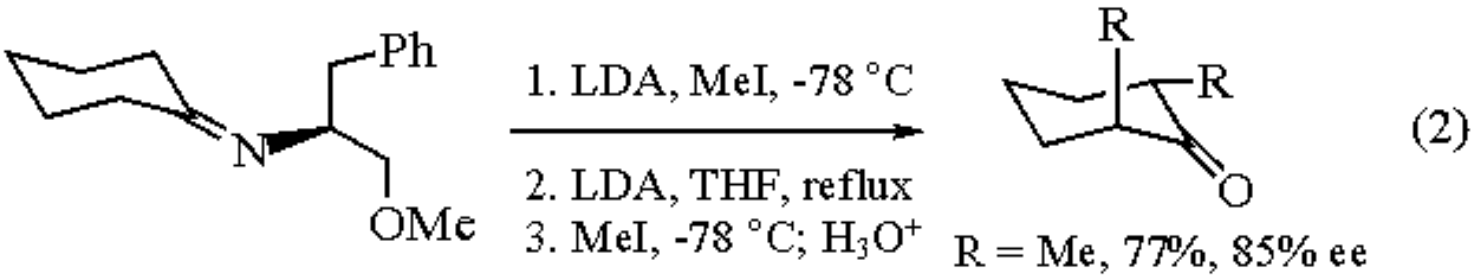

In contrast with medium-sized cyclic ketones, alkylation of macrocyclic ketones can afford either optical antipode depending on whether the lithioenamine is formed via kinetic (*E*-) or thermodynamic conditions (*Z*-enamine) (eq 3).[6] Optically active α-alkyl macrocyclic ketones have been formed in 30-82% enantiomeric excess, with chemical yields of 62-90%.

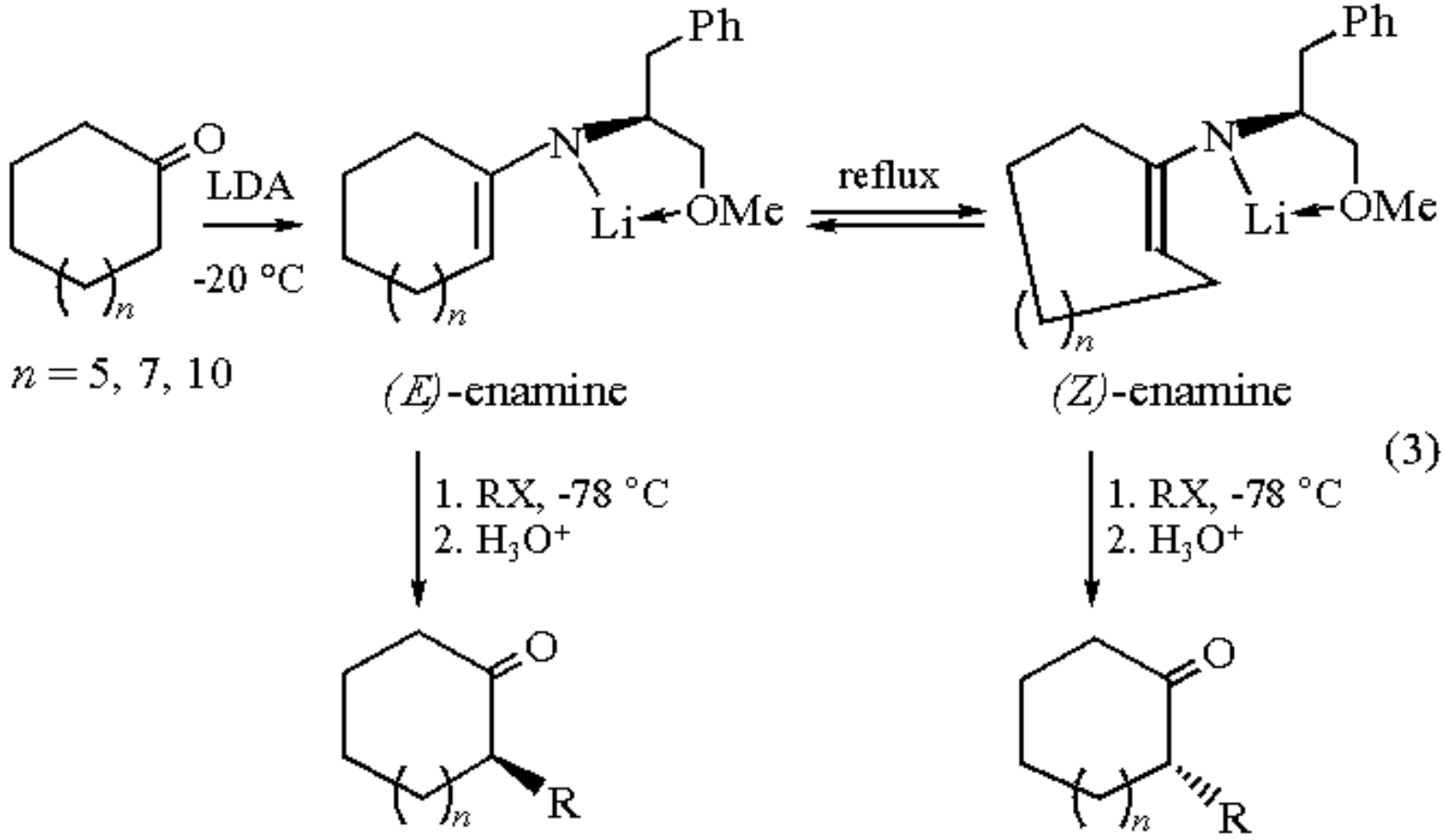

In a similar manner, aldehydes can also be enantioselectively alkylated by this procedure. However, the enantiomeric excess obtained is much lower (47%).[2] A special application of this method is the enantioselective alkylation of aldehydes for the construction of quaternary stereogenic centers. An example is the formation of the chiral quaternary carbon in 4-methyl-4-phenylcyclohex-2-en-1-one in high enantiomeric excess using this methodology (eq 4).[7]

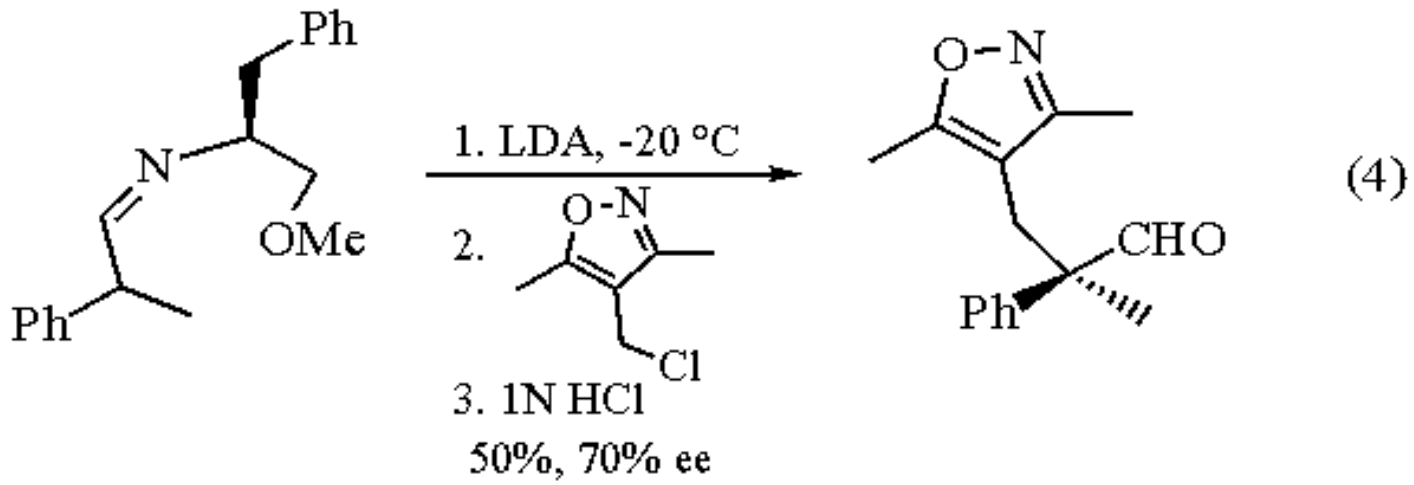

Chiral Cuprate Reagents.

This chiral amine has also found application in asymmetric conjugate addition of copper azaenolates to cyclic enones. Lithium azaenolates of optically active acetone imines have been used in the preparation of chiral cuprate reagents.

However, the asymmetric induction is low (17-28% ee) when this amine is employed (eq 5).[3]

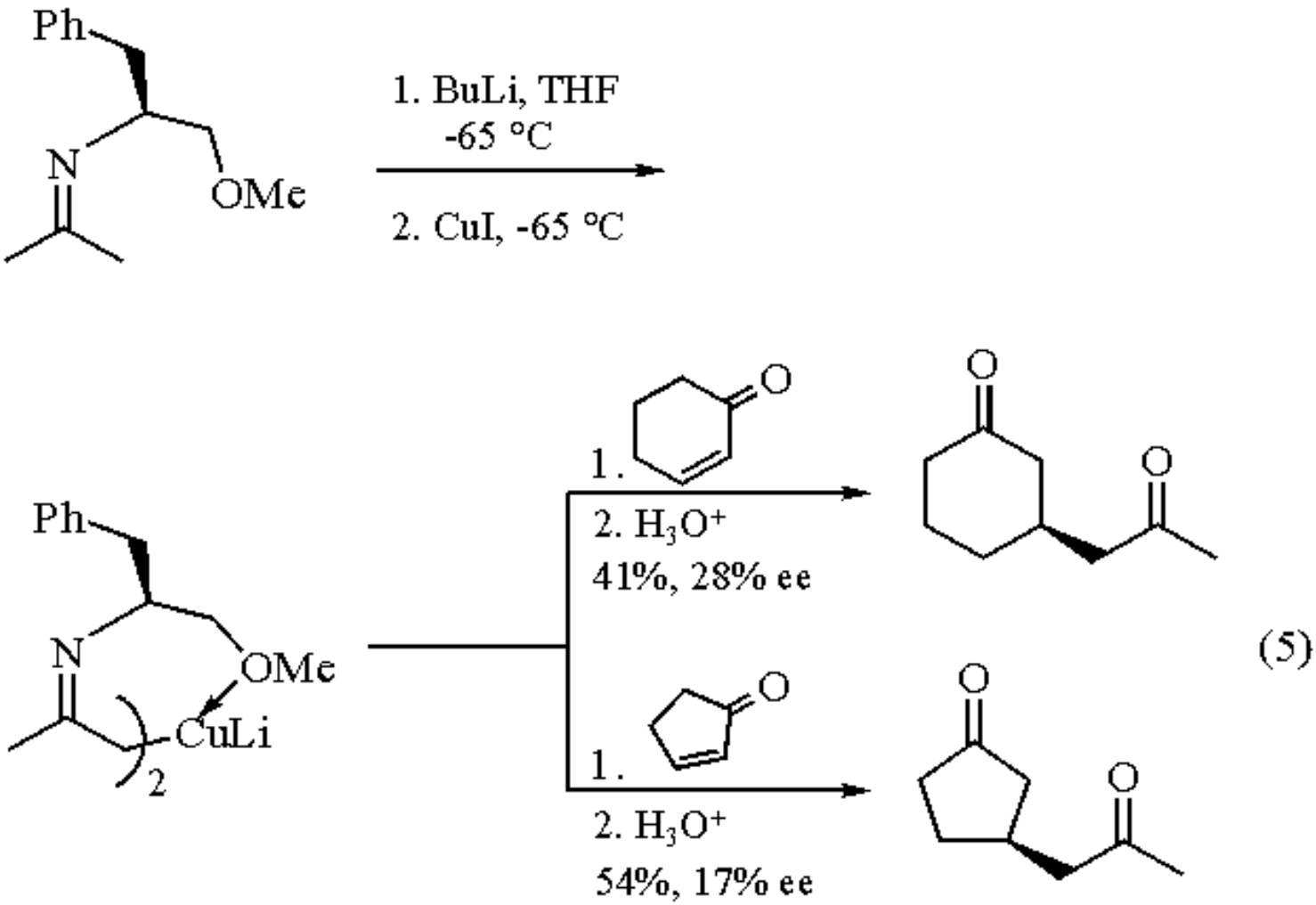

Enantioselective alkylation of aldehydes and ketones can also be accomplished using Enders' reagents SAMP and RAMP.[8] In contrast with Meyer's chiral auxiliary, the synthesis of Enders' reagents is lengthy and the recovery is inconvenient because cleavage of the auxiliary does not afford back the reagent. It also generates nitrosoamines (via ozonolysis) which are considered carcinogenic compounds. Therefore, the ease of preparation, availability of the starting material, and efficient cleavage and recovery of this chiral amine make it a convenient chiral auxiliary.

---

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Eduardo A. Véliz & Joseph P. Konopelski

N-Benzyl-*N*-(methoxymethyl)-*N*-trimethylsilylmethylamine[1]

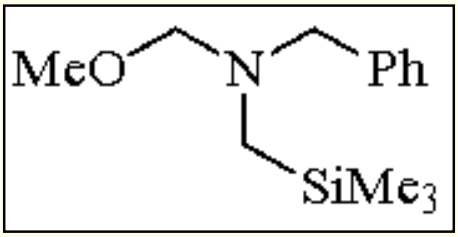

[93102-05-7] · $C_{13}H_{23}NOSi$ · *N*-Benzyl-*N*-(methoxymethyl)-*N*-trimethylsilylmethylamine · (MW 237.42)

(nonstabilized azomethine ylide precursor;[1] reacts with alkenes to give pyrrolidines;[2] alkynes give 3-pyrrolines;[2] carbonyl and thiocarbonyl groups afford 1,3-oxazolidines and 1,3-thiazolidines, respectively[3])

Physical Data: bp 77-80 °C/0.5 mmHg.

Preparative Methods: most conveniently prepared by treatment of benzylamine with chloromethyltrimethylsilane followed by formaldehyde and methanol.[4] Access to higher ether homologs is achieved by replacing methanol with the appropriate alcohol.[5] An alternate procedure involves alkylation of lithium *N*-benzyltrimethylsilymethylamide with methoxymethyl chloride.[2]

Purification: distillation under reduced pressure, although good yields can be obtained with undistilled reagent.

Handling, Storage, and Precautions: the reagent should be handled in a well ventilated fume hood.

1,3-Dipolar Cycloadditions.

N-Benzyl-*N*-(methoxymethyl)-*N*-trimethylsilylmethylamine (**1**) is a valuable reagent for in situ generation of the *N*-benzyl azomethine ylide (**2**). It is generally preferred over alternative silylmethylamine precursors[6-8] because of ease of handling and use. The ylide (**2**) is most conveniently generated from (**1**) using a catalytic amount of ***Trifluoroacetic Acid*** as described by Achiwa.[2] Alternative catalysts include LiF,[3,4] TBAF,[7] Me_3SiOTf-CsF,[5] or Me_3SiI-CsF.[5] Mechanistic studies provide evidence that the reactive intermediate generated from (**1**) with either CF_3CO_2H or F^- is a 1,3-dipolar species.[7,8] Reaction of (**2**) with alkenes provides an efficient convergent route to

pyrrolidine derivatives. Alkynes afford 3-pyrrolines[2] which can be converted into pyrroles.[6a] The ylide (**2**) reacts most readily with electron deficient alkenes and alkynes since this pairing results in a narrow dipole HOMO-dipolarophile LUMO energy gap.[9] Examples of suitable dipolarophiles include unsaturated esters,[2-5] ketones,[2] imides,[2,4] nitriles,[4] and sulfones.[3,4] Cycloaddition occurs with complete *cis* stereospecificity[2-4] (eq 1) which is consistent with a concerted mechanism. Dipolarophiles containing an endocyclic double bond afford fused bicyclic pyrrolidines,[10] whereas substrates with an exocyclic double bond provide access to spirocyclic systems.[11]

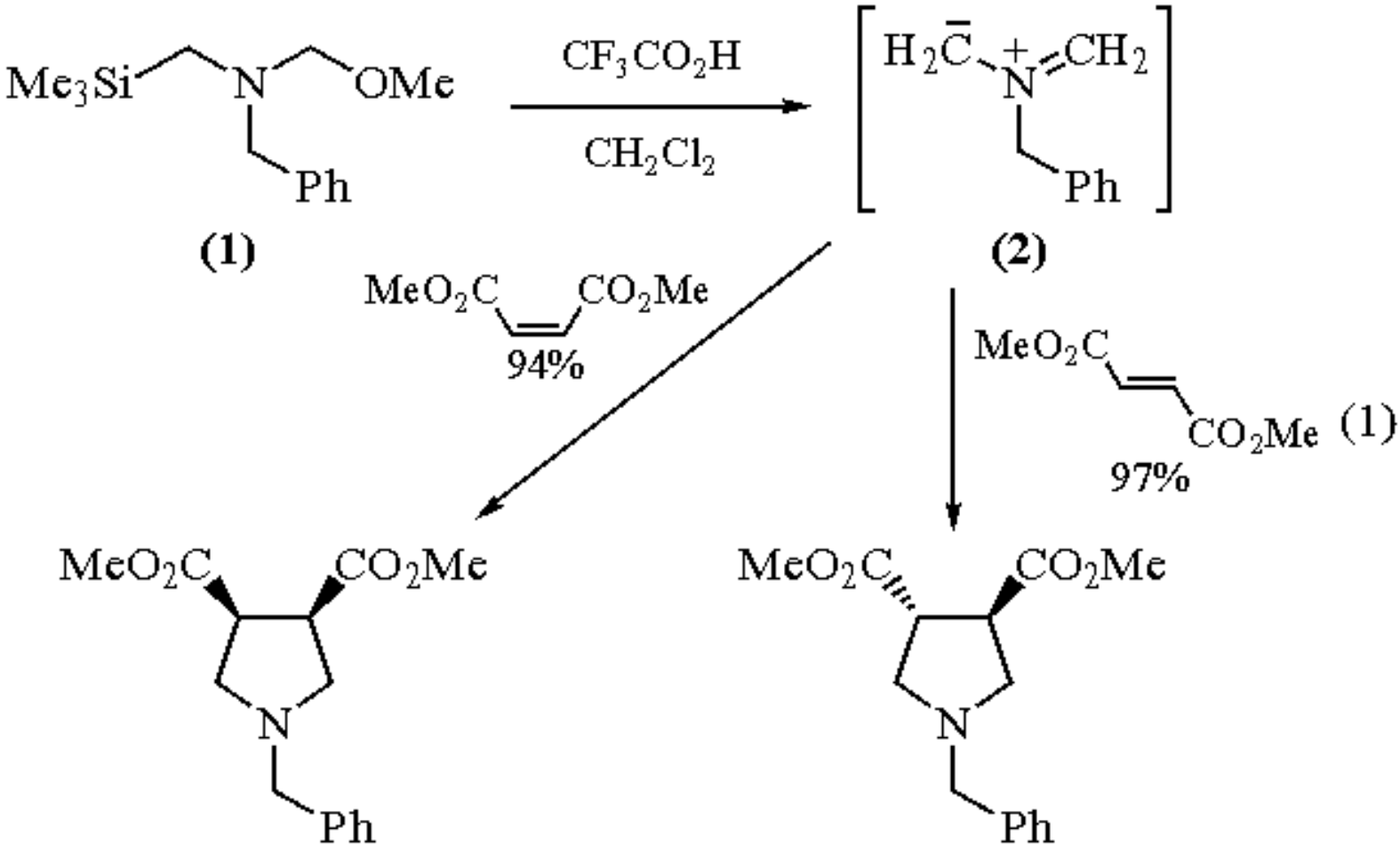

Styrenes bearing electron withdrawing aromatic substituents such as CN and NO_2 give high yields of 3-arylpyrrolidines (eq 2).[12] When electron withdrawing groups are absent yields tend to be poor. Vinylpyridines afford 3-pyridylpyrrolidines.[12] The reactivity of alkenes can be enhanced by the introduction of a CF_3 substituent. For example, α-trifluoromethylstyrene gives a high yield of cycloadduct whereas α-methylstyrene is unreactive.[13]

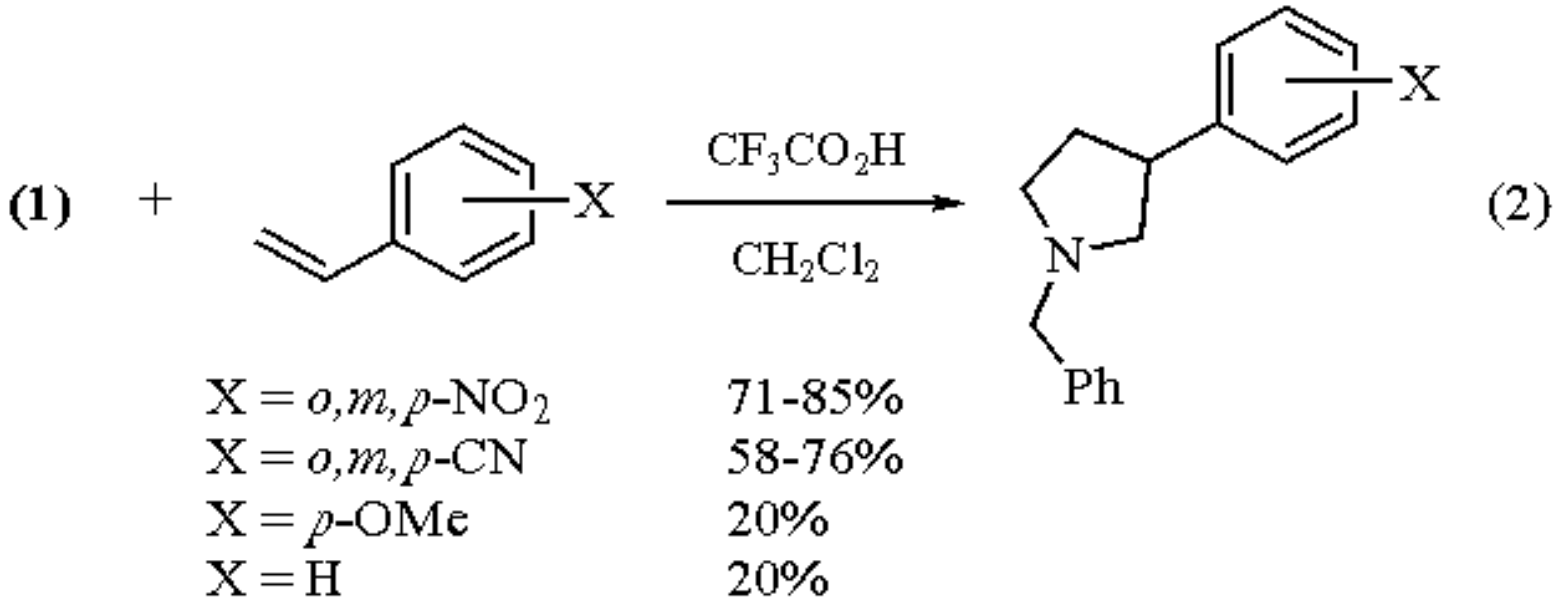

Cycloaddition reactions with aldehydes and ketones afford 1,3-oxazolidines while thioketones give 1,3-thiazolidines (eq 3).[3] Adducts derived from reaction at both the carbonyl and alkenic double bond have been observed with an α,β-unsaturated aldehyde.[3]

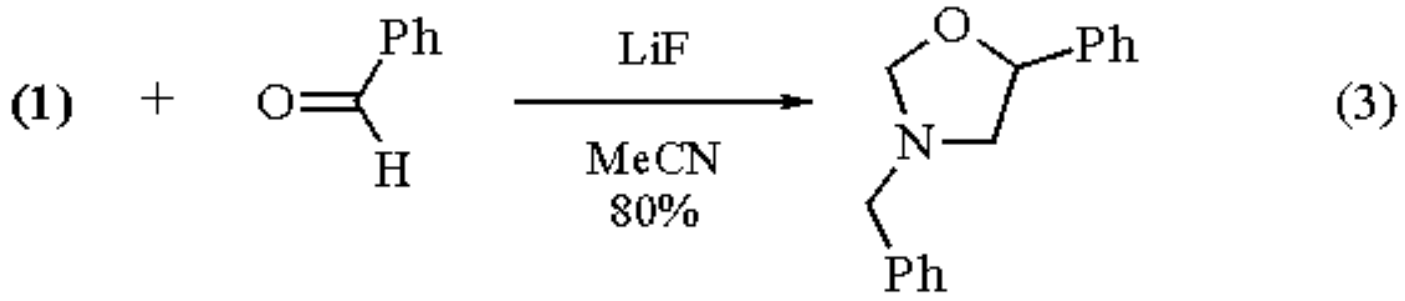

Diastereoselective 1,3-Dipolar Cycloadditions.

Several examples of high diastereofacial selectivity with homochiral dipolarophiles have been reported. Cycloaddition of (**1**) with the cyclic dipolarophile (**3**) occurs with complete π-facial selectivity as a result of addition from the side opposite the bulky silyloxymethyl group (eq 4).[14] The key step in an asymmetric synthesis of (*S*)-(-)-cucurbitine involves cycloaddition of (**1**) with the α,β-dehydrolactone (**4**) to give the pyrrolidine (**5**) as a single diastereomer (eq 5).[15]

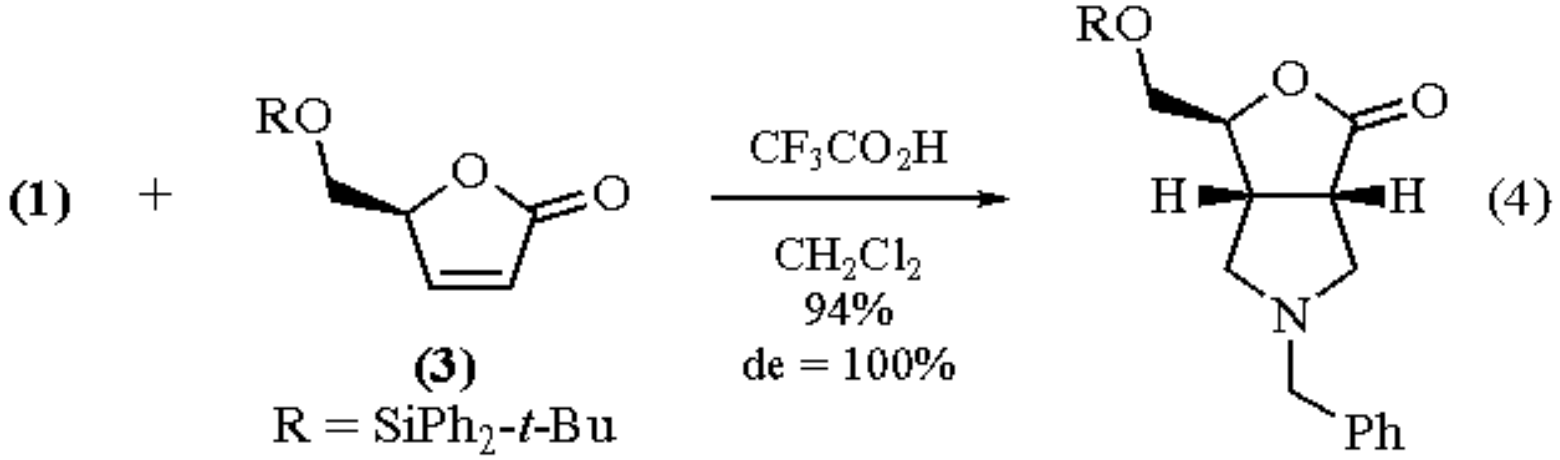

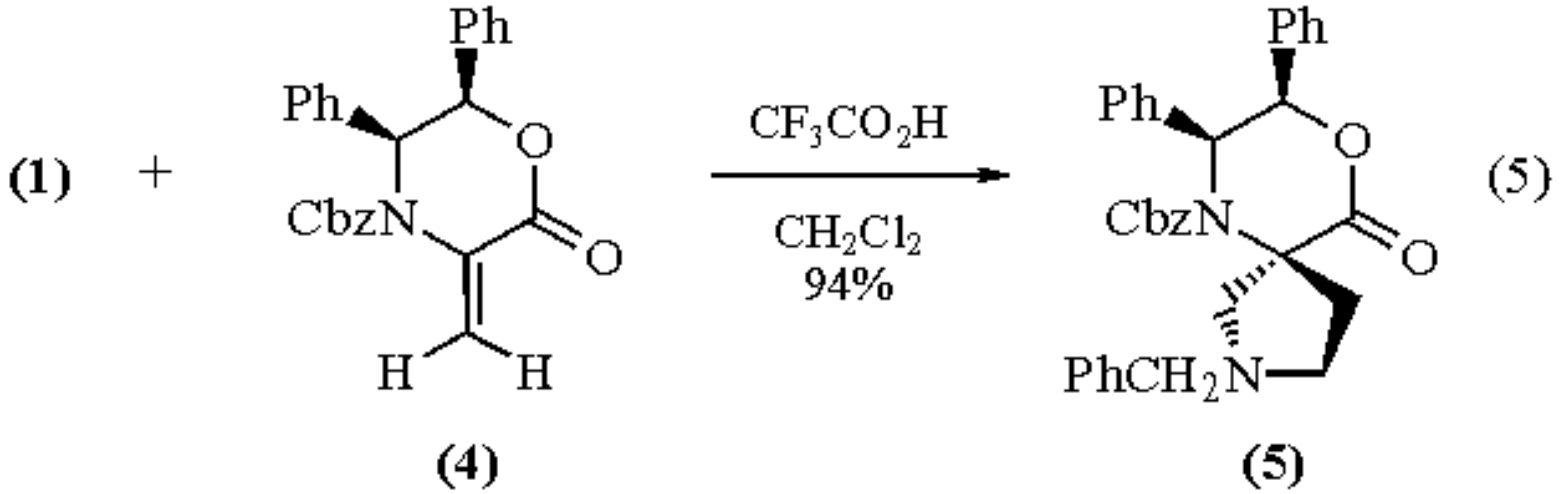

Double asymmetric induction employing a chiral *N*-α-methylbenzyl analog of (**1**) has been described.[16]

---

1. (a) Terao, Y.; Aono, M.; Achiwa, K. *H* **1988**, *27*, 981. (b) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231.
2. Terao, Y.; Kotaki, H,; Imai, N.; Achiwa, K. *CPB* **1985**, *33*, 2762.
3. Padwa, A.; Dent, W. *JOC* **1987**, *52*, 235.
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5. Hosomi, A.; Sakata, Y.; Sakurai, H. *CL* **1984**, 1117.
6. (a) Padwa, A.; Chen, Y. Y.; Dent, W.; Nimmesgern, H. *JOC* **1985**, *50*, 4006. (b) Pandey, G.; Lakshmaiah, G.; Kumaraswamy, G. *CC* **1992**, 1313.
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9. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *JACS* **1973**, *95*, 7301.
10. Orlek, B. S.; Wadsworth, H.; Wyman, P.; Hadley, M. S. *TL* **1991**, *32*, 1241.
11. Orlek, B. S.; Wadsworth, H.; Wyman, P.; King, F. D. *TL* **1991**, *32*, 1245.
12. Laborde, E. *TL* **1992**, *33*, 6607.
13. Begue, J. P.; Bonnet-Delpon, D.; Lequeux, T. *TL* **1993**, *34*, 3279.
14. Wee, A. G. H. *JCS(P1)* **1989**, 1363.

15. Williams, R. M.; Fegley, G. J. *TL* **1992**, *33*, 6755.
16. Fray, A. H.; Meyers, A. I. *TL* **1992**, *33*, 3575.

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3-Benzyl-4-methyl-1,3-thiazolium Chloride[1]

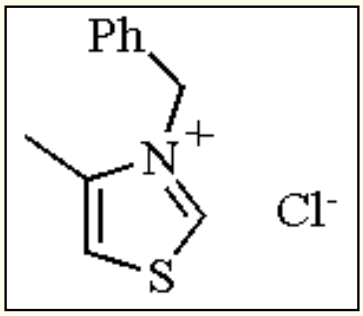

[4209-18-1] · $C_{11}H_{12}ClNS$ · 3-Benzyl-4-methyl-1,3-thiazolium Chloride · (MW 225.74)

(benzoin condensation catalyst; in the presence of bases, catalyzes the preparation of cyclic acyloins from dialdehydes, and of aromatic esters from aromatic aldehydes)

Physical Data: mp 188 °C; monohydrate 136 °C.[2]

Solubility: sol H_2O, MeOH, EtOH and related solvents; insol ether or pentane.

Analysis of Reagent Purity: ^{1}H NMR, mp.

Preparative Methods: colorless crystals prepared from 4-methyl-1,3-thiazole and benzyl chloride, or benzylthioformamide and chloroacetone.[2]

Handling, Storage, and Precautions: store dry.

Formation of Benzoins and Acyloins from Aldehydes.

Many thiazolium salts catalyze the formation of benzoins from aromatic aldehydes and of acyloins from aliphatic aldehydes, both in presence of bases (eq 1). This catalytic reaction has long been known,[3] the most prominent salt being thiamine (vitamin B_1). For details on the use of other salts, see ***3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride***. The title reagent is the only one known to catalyze the formation of five- and six-membered cyclic acyloins in the presence of a base (eq 2).[4]

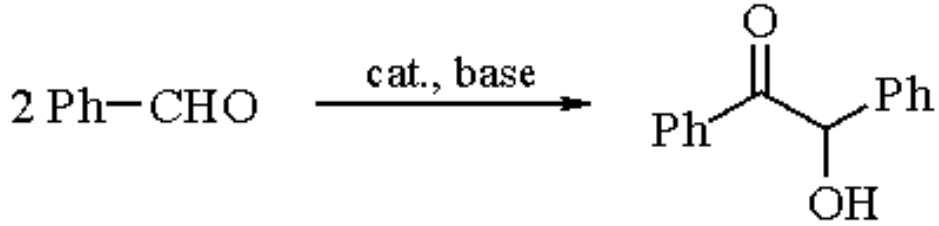

(1)

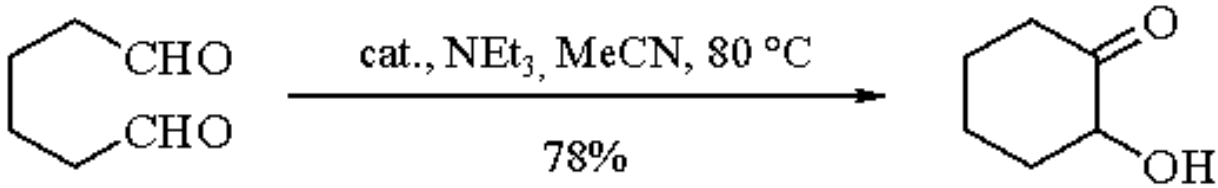

(2)

Oxidative Reactions.

Aromatic aldehydes in presence of a nitro compound, an alcohol, and a base react in a different way (eq 3). No formation of benzoins is observed, with only the carboxylic esters and nitrobenzene reduction products being formed.[5] Quinones react analogously to nitro compounds.[6] A test for the catalytic activity of azolium salts uses flavin as oxidant and indicator;[7a] details are given in a related bioorganic model study on the reaction of thiamine.[7b]

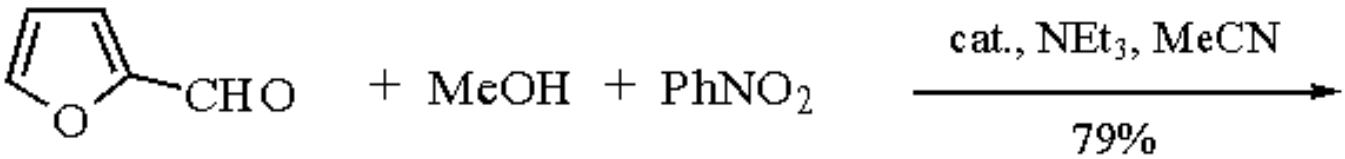

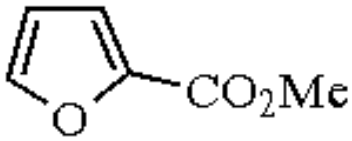

+ azobenzene + azoxybenzene (3)

Addition of Aldehydes to Electrophilic Double Bonds.[8]

Full details are given under the entry for ***3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride***. The reagent in the presence of bases catalyzes addition, but shows a tendency to form byproducts (eq 4). In this case the byproduct results from Michael addition to the benzoin instead of to the activated aldehyde.[9]

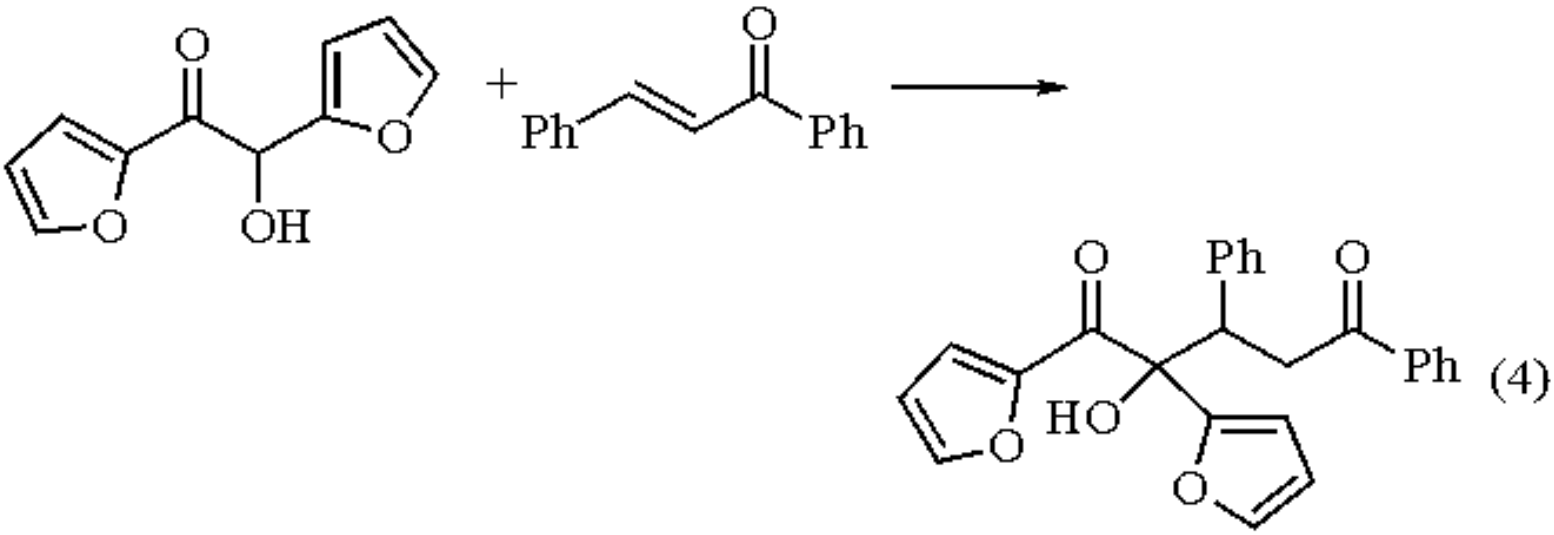

Reduction and Hydrolysis of the Reagent.

The reagent, like other thiazolium salts, is easily reduced by ***Sodium Borohydride***[10] to the thiazoline and the ring is easily cleaved by aqueous bases.[2b]

Other Reagents.

Acyloins are produced by the action of metals such as sodium on carboxylic esters;[11] benzoins are produced by the catalytic action of cyanides on aromatic aldehydes.[12]

Related Reagents.

3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride; ***3-Benzylthiazolium Bromide***.

---

1. (a) Fieser L. F.; Fieser M. *FF* **1979**, *7*, 18. (b) *Beilstein* **1983**, *27-III/IV*, 971.
2. (a) Karimullah *JCS* **1937**, 961. (b) Sykes P.; Todd A. R. *JCS* **1951**, 534.
3. Breslow R. *JACS* **1958**, *80*, 3719.
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5. (a) Castells J.; Llitjós H.; Moreno-Mañas M. *TL* **1977**, 205. (b) Castells J.; Pujol F.; Llitjós H.; Morena-Mañas M. *T* **1982**, *38*, 337. (c) Inoue H.; Higashiura *CC* **1980**, 549. (d) Shinkai S.; Yamashita T.; Kusano Y.; Manabe O. *JOC* **1980**, *45*, 4947.
6. Vovk A. I.; Murav'eva I. V.; Yasnikov A. A. *ZOB* **1985**, *55*, 1400 (*CA* **1985**, *103*, 214 513p).
7. (a) Yano Y.; Tsukagoshi Y. *JCR(S)* **1984**, 406. (b) Rastetter W. H.; Adams J. *JOC* **1981**, *46*, 1882.
8. Stetter H.; Kuhlmann H. *OR* **1991**, *40*, 407.
9. Castells J.; Duñach E.; Geijo F.; López-Calahorra F.; Prats M.; Sanahuja O.; Villanova L. *TL* **1980**, *21*, 2291.
10. Clarke G. M.; Sykes P. *JCS(C)* **1967**, 1269.
11. (a) McElvain S. M. *OR* **1948**, *4*, 256. (b) Bloomfield J. J.; Owsley D. C.; Nelke J. M. *OR* **1976**, *23*, 259. (c) Finley K. T. *CRV* **1964**, *64*, 573. (d) Rühlmann K. *S* **1971**, 236.
12. Ide W. S.; Buck J. S. *OR* **1948**, *4*, 269.

Benzyl 4-Nitrophenyl Carbonate

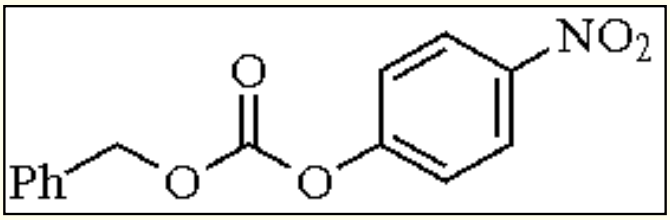

[13795-24-9] · $C_{14}H_{11}NO_5$ · Benzyl 4-Nitrophenyl Carbonate · (MW 273.24)

(reagent for protection of tryptophan nucleus[1])

Physical Data: mp 78-80 °C.

Solubility: sol ether, methanol, chloroform.

Form Supplied in: fibrous powder.

Tryptophan Protection.[1]

Protection of the indole ring on a tryptophan residue, as an acid-stable Cbz derivative, was required for the synthesis of a tetrapeptide target molecule. Thus reaction of a Boc-protected dipeptide fragment with the reagent (**1**) and ***Potassium Fluoride*** solubilized with ***18-Crown-6*** provided the Cbz-protected derivative (eq 1). The naked fluoride ion serves as the base to abstract a proton from the indole ring.

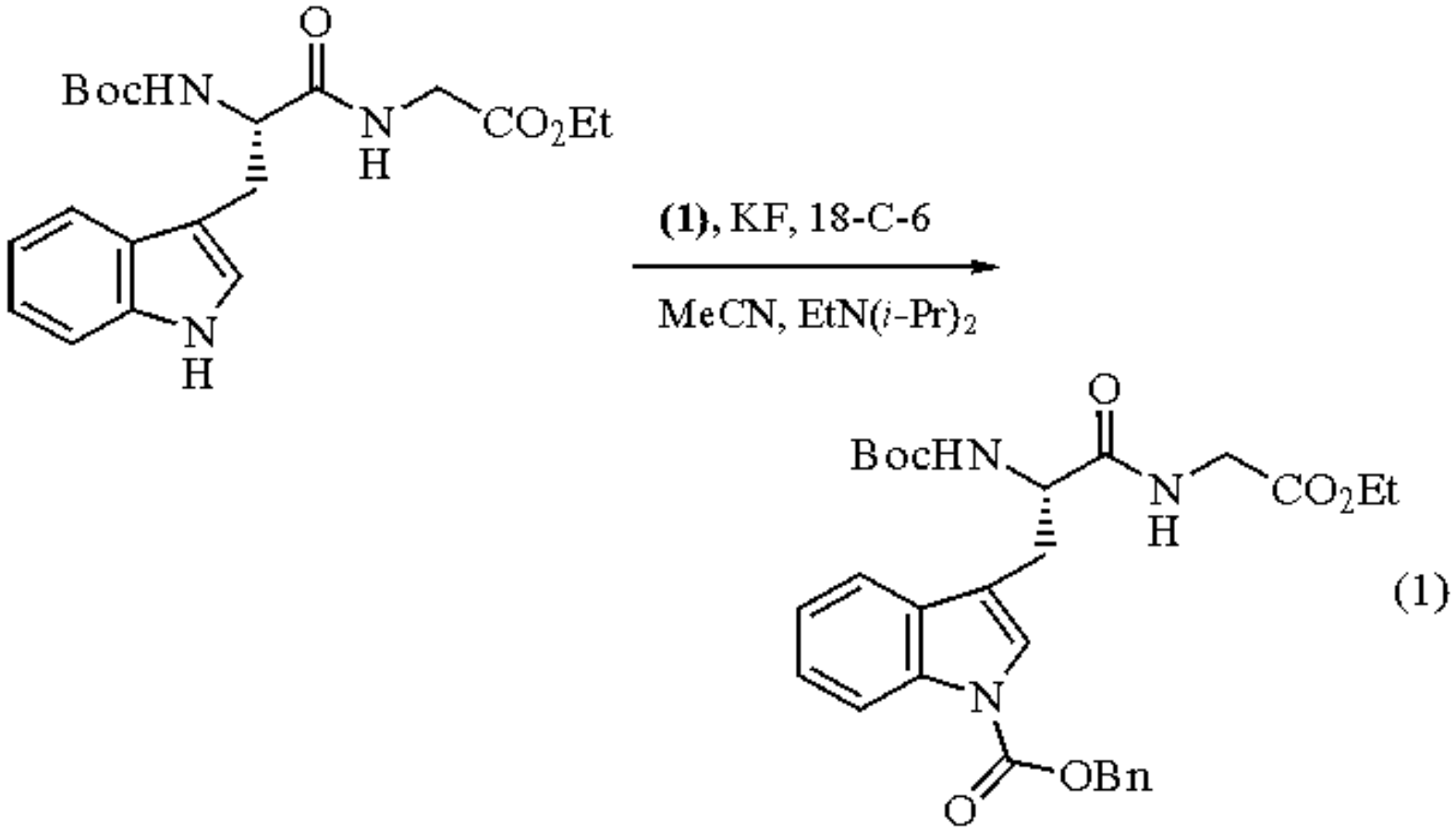

Related Reagents.

Benzyl Chloroformate.

---

1. Chorev, M.; Klausner, Y. S. *CC* **1976**, 596.

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Utah State University, Logan, UT, USA

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(*S*)-4-Benzyl-2-oxazolidinone

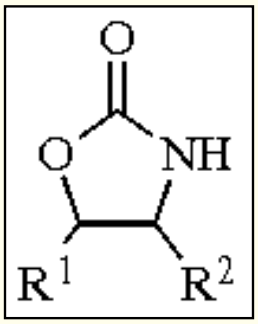

(**1**; R^1 = H, R^2 = &wbond;Bn) (*S*)

[90719-32-7] · $C_{10}H_{11}NO_2$ · (*S*)-4-Benzyl-2-oxazolidinone · (MW 177.20) (Li salt)

[123731-35-1] (**2**; R^1 = H, R^2 = &wlbond;Bn) (*R*)

[102029-44-7] · $C_{10}H_{11}NO_2$ · (*S*)-4-Benzyl-2-oxazolidinone · (MW 177.20) (Li salt)

[128677-61-2] (**3**; R^1 = H, R^2 = &wbond;*i*-Pr) (*S*)

[17016-83-0] · $C_6H_{11}NO_2$ · (*S*)-4-Isopropyl-2-oxazolidinone · (MW 129.16) (Li salt)

[96021-69-1] (**4**; R^1 = &wlbond;Ph, R^2 = &wlbond;Me) (4*R*,5*S*)

[77943-39-6] · $C_{10}H_{11}NO_2$ · (*S*)-4-Benzyl-2-oxazolidinone · (MW 177.20) (Li salt)

[92061-65-7] (**5**; R^1 = &wbond;Ph, R^2 = &wbond;Me) (4*S*,5*R*)

[16251-45-9] · $C_{10}H_{11}NO_2$ · (4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidinone · (MW 177.20) (Li salt)

[127882-97-7] (**6**; R^1 = H, R^2 = &wbond;Ph) (*S*)

[99395-88-7] · $C_9H_9NO_2$ · (*S*)-4-Phenyl-2-oxazolidinone · (MW 163.18) (**7**; R^1 = H, R^2 = &wlbond;Ph) (*R*)

[90319-52-1] · $C_9H_9NO_2$ · (*S*)-4-Benzyl-2-oxazolidinone · (MW 163.18) (**8**; R^1 = H, R^2 = &wbond;*t*-Bu) (*S*)

[54705-42-9] · $C_7H_{13}NO_2$ · (*S*)-4-*t*-Butyl-2-oxazolidinone · (MW 143.19)

(chiral auxiliaries used in asymmetric alkylations,[1] acylations,[2] halogenations,[3] aminations,[4] hydroxylations,[5] aldol reactions,[6] conjugate additions,[7,8] Diels-Alder reactions,[9] acyl transfer,[10] and sulfinyl transfer[11])

Physical Data: (**1**) mp 87-89 °C; (**2**) mp 85-87 °C; (**3**) mp 71-72 °C; (**4**) mp 118-121 °C; (**5**) mp 118-121 °C; (**6**) mp 130-132 °C; (**7**) mp 130-132 °C; (**8**) mp 118-120 °C.

Solubility: sol most polar organic solvents.

Form Supplied in: white crystalline solid; commercially available.

Analysis of Reagent Purity: 99% purity attainable by GLC.

Handling, Storage, and Precautions: no special handling or storage precautions are necessary. There is no known toxicity. It may be harmful by inhalation, ingestion, or skin absorption and may cause skin or eye irritation.

Synthesis of the Chiral Oxazolidinone Auxiliaries.

(*S*)-4-Benzyl- (**1**), (*R*)-4-benzyl- (**2**), (*S*)-4-*i*-propyl- (**3**), (4*R*,5*S*)-4-methyl-5-phenyl- (**4**), (*S*)-4-*t*-butyl- (**8**), and (*S*)-4-phenyl-2-oxazolidinones (**6**) are commercially available. Typical procedures to form these chiral auxiliaries involve the reduction of α-amino acids to the corresponding amino alcohols or the purchase of amino alcohols, followed by formation of the cyclic carbamate (eq 1). A number of high-yielding methods of reduction have been employed for this transformation, including ***Boron Trifluoride Etherate*/*Borane-Dimethyl Sulfide***,[12] ***Lithium Aluminum Hydride***,[1,6,13,14] ***Sodium Borohydride*/*Iodine***,[15] and ***Lithium Borohydride*/*Chlorotrimethylsilane***.[8] Selection among these methods is largely based upon cost of reagents and ease of performance. Reagents for effecting the second transformation include ***Diethyl Carbonate*/*Potassium Carbonate***[12] or ***Phosgene***,[16 -18] with the former being preferable for large-scale production. Ureas,[19,20] dioxolanones,[21] chloroformates,[22] trichloroacetate esters,[22,23] ***N,N´-Carbonyldiimidazole***,[24] and ***Carbon Monoxide*** with catalytic elemental ***Sulfur***[25] or ***Selenium***[26,27] provide alternatives for the transformation of amino alcohols to the derived oxazolidinones.

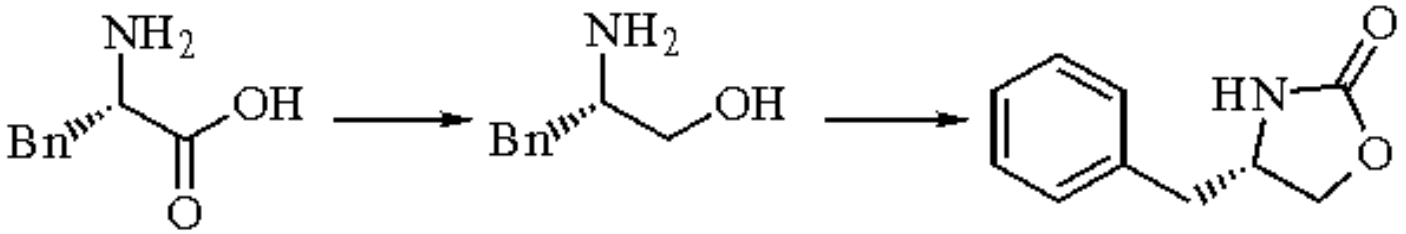

(1)

Conversion of the appropriate α-amino acids to oxazolidinones may also be performed as a one-pot procedure, obviating the need to isolate the intermediate amino alcohols (eqs 2 and 3).[28,29] Overall isolated yields for these procedures are 70-80%.

(S)-4-Benzyl-2-oxazolidinone

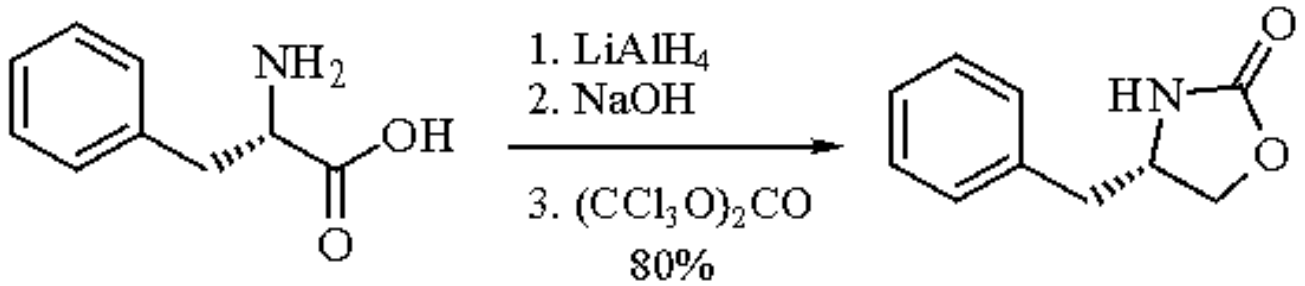

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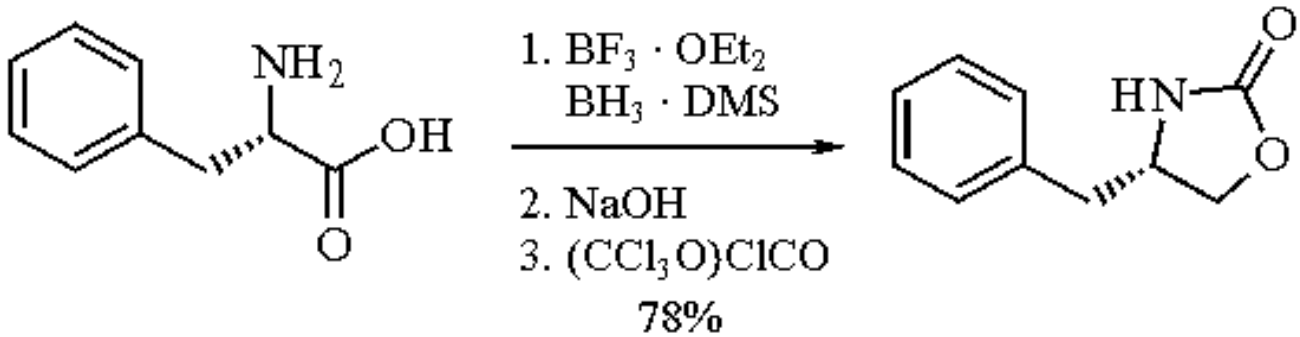

(3)

Carbamate-protected amino alcohols also yield oxazolidinones upon treatment with base (eq 4)[30,31] or ***p-Toluenesulfonyl Chloride*** (eq 5).[32] The latter reaction requires the protection of the amino group as the *N*-methylated carbamate for selective inversion of the hydroxyl-bearing center.

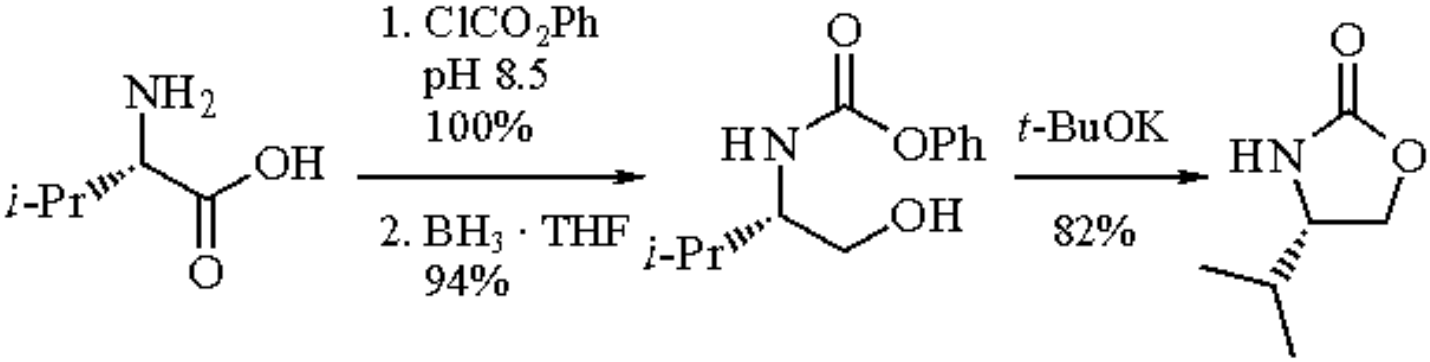

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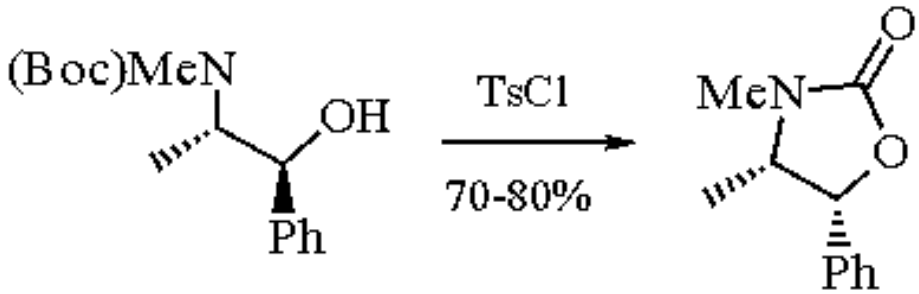

(5)

Resolution of racemic oxazolidinones affords either enantiomer of the auxiliary and provides a versatile route to unusually substituted derivatives (eq 6).[33]

(S)-4-Benzyl-2-oxazolidinone

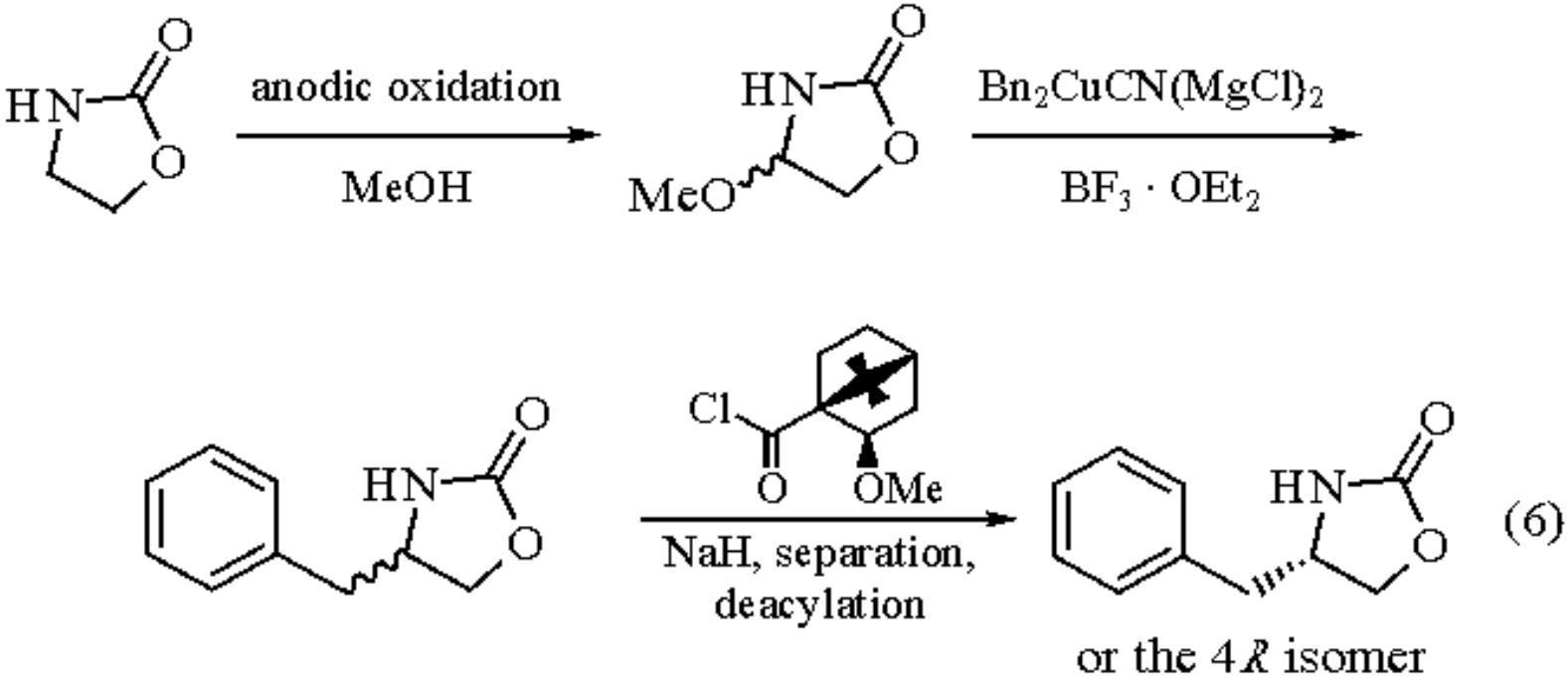

Methods of *N*-Acylation.

Lithiated oxazolidinones add to acid chlorides (eq 7)[6,34] and mixed anhydrides (eq 8)[35,36] in high yields to form the derived *N*-acyl imides. In the latter case the anhydride may be formed in situ with ***Trimethylacetyl Chloride***, and then condensed with the lithiated oxazolidinone selectively at the less hindered carbonyl moiety.

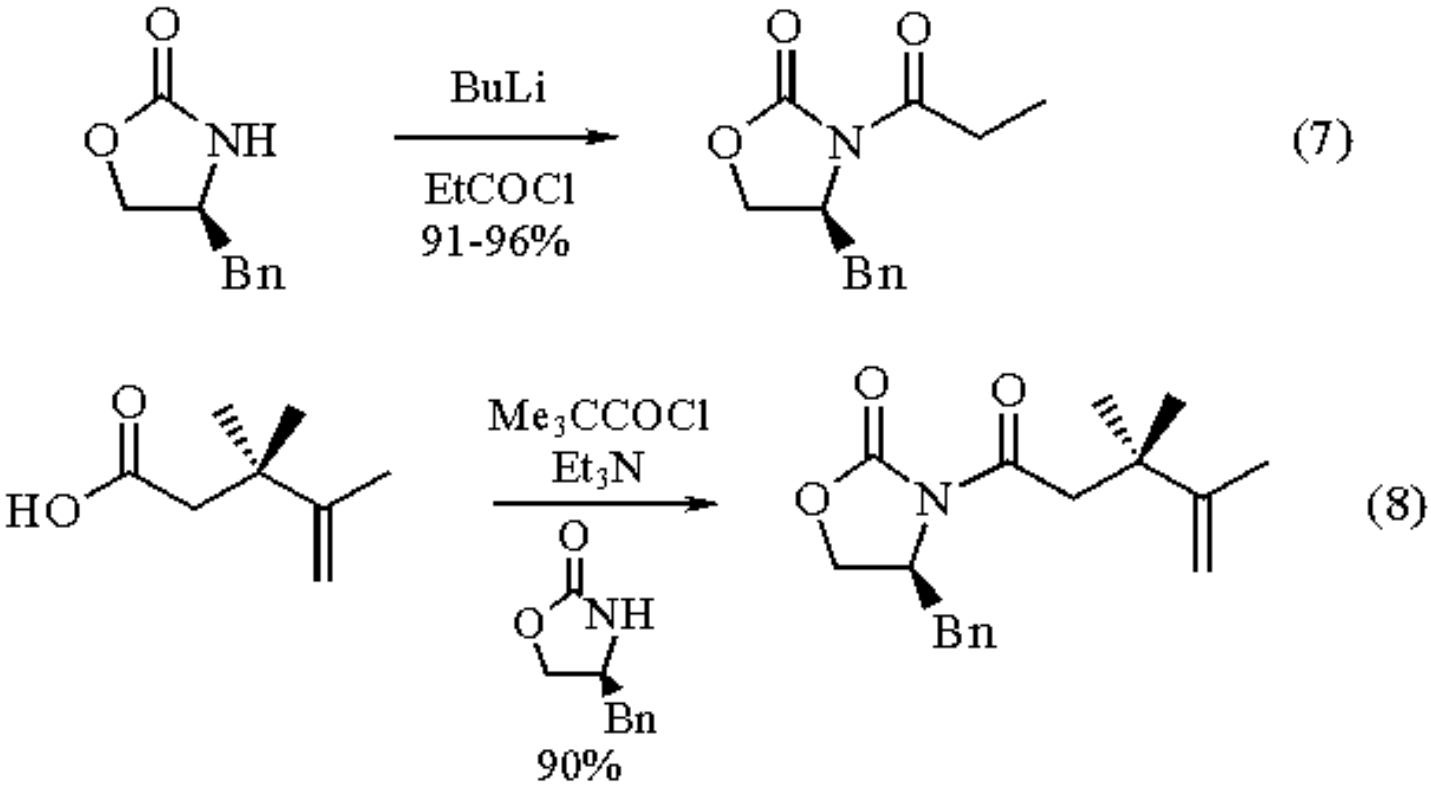

Acryloyl adducts cannot be formed through traditional acylation techniques due to their tendency to polymerize. These adducts may be obtained through reaction of acryloyl chloride with the bromomagnesium salt of the oxazolidinone

auxiliary[9,37] or the *N*-trimethylsilyl derivative in the presence of ***Copper(II) Chloride*** and ***Copper*** powder.[38] These methods yield products in the range of 50-70%.

Methods of *N*-Alkylation.

In analogy with acylation techniques, metalated oxazolidinones add to alkyl halides to afford the *N*-alkylated products in high yields.[39-42]

Enolization of *N*-Acyloxazolidinones.

Various methods have been developed to effect the enolization of chiral *N*-acyloxazolidinones. In alkylation reactions, both ***Lithium Diisopropylamide*** and ***Sodium Hexamethyldisilazide*** deprotonate these imides to provide the (*Z*)-enolates in >100:1 selectivity.[1]

Di-n-butylboryl Trifluoromethanesulfonate with a tertiary amine also provides the (*Z*)-enolates of chiral acyl oxazolidinones in >100:1 selectivity for use in subsequent aldol additions.[6,14] With ***Triethylamine***, ***Diisopropylethylamine*** (Hünig's base), or ***2,6-Lutidine*** the order of addition is of no consequence to enolization.[43] Triethylamine has traditionally seen the greatest utilization in these reactions based upon cost considerations; however, with certain sensitive aldehyde substrates, lutidine provides milder reaction conditions.[44]

The (*Z*)-enolate is also accessed exclusively using titanium enolization procedures.[45,47] Irreversible complexation of ***Titanium(IV) Chloride*** with tertiary amine bases demands complexation of the substrate with the Lewis acid prior to treatment with either triethylamine or Hünig's base. Reactions using Hünig's base occasionally display higher diastereoselectivities, particularly in Michael additions.[7,45] Of the alkoxy titanium species employed in imide enolization, only $TiCl_3$(O-*i*-Pr) is capable of quantitative enolate formation. In these reactions, order of addition of reagents is not significant. These enolates demonstrate enhanced nucleophilicity, albeit with somewhat diminished diastereoselectivity.

Other Lewis acids have been demonstrated to provide moderate levels of enolization, including ***Aluminum Chloride***, ***Magnesium Bromide***, and ***Tin(II) Trifluoromethanesulfonate***.[45,46] However, $SnCl_4$, Me_2AlCl, and $ZrCl_4$ failed to provide detectable enolization.[45]

Enolate Alkylation.

Alkylation of chiral *N*-acyloxazolidinones by simple alkyl and allylic halides occurs through the chelated lithiated (*Z*)-imide enolates to afford products in greater than 93:7 diastereoselectivities (eqs 9 and 10).[1] For small electrophiles such as ***Iodomethane*** and ***Ethyl Iodide***, NaHMDS proved to be the enolization base of choice. On selected substrates, alkyl triflates also demonstrate promise as alkylating agents.[34]

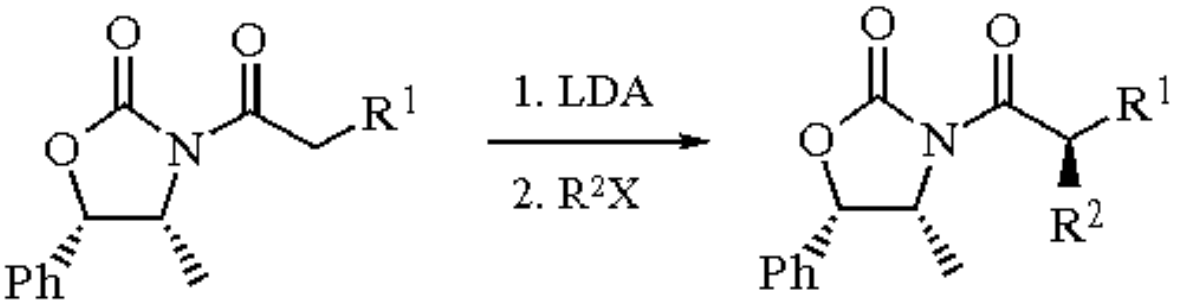

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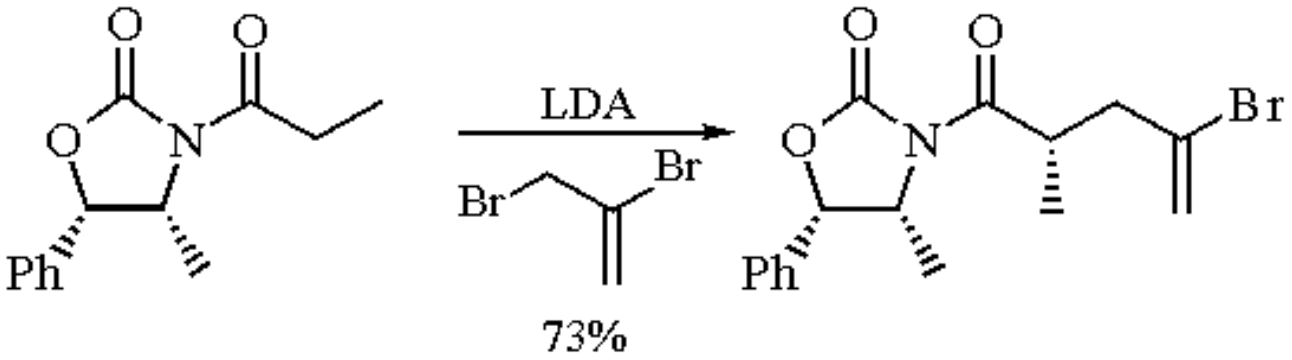

(10)

For benzyloxymethyl electrophiles, titanium enolates are superior to the corresponding lithium enolates in both yield and alkylation diastereoselectivity (eq 11). Unfortunately, the analogous *p*-methoxybenzyl-protected β-hydroxy adducts cannot be obtained by this method. In other cases the titanium methodology complements the corresponding reactions of the lithium and sodium enolates for S_N1-like electrophiles.[47] It is noteworthy that imides may be selectively enolized under all of the preceding conditions in the presence of esters (eq 12).

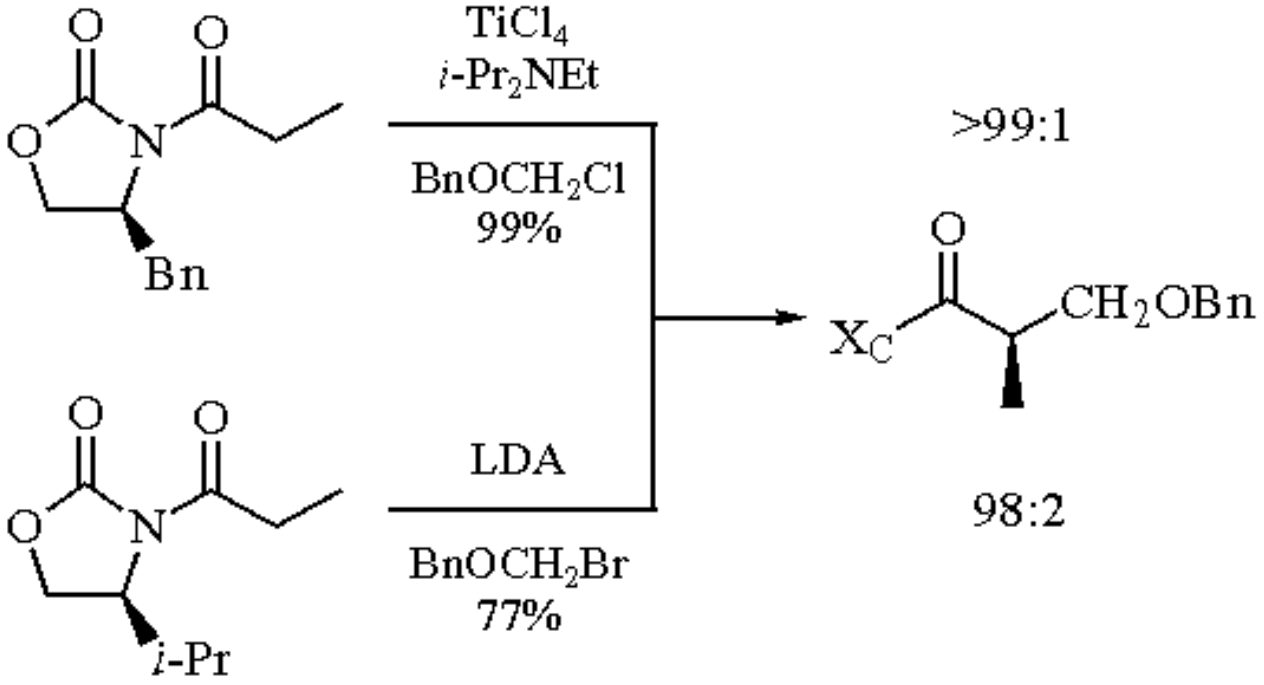

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(S)-4-Benzyl-2-oxazolidinone

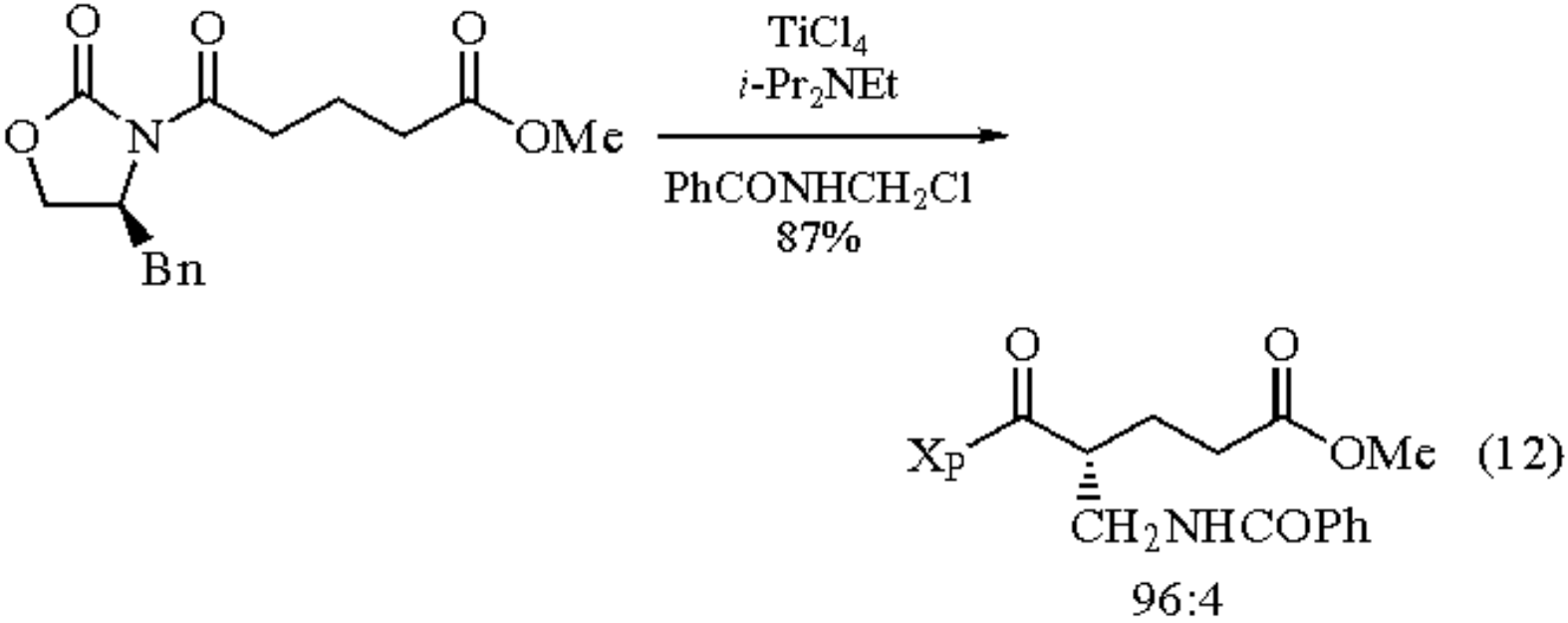

(12)

Treatment of the silyl enol ethers of *N*-acyloxazolidinones with selected electrophiles that do not require Lewis acid activation similarly results in high induction of the same enolate face (eq 13).[48] The facial bias of this conformationally mobile system improves with the steric bulk of the silyl group.

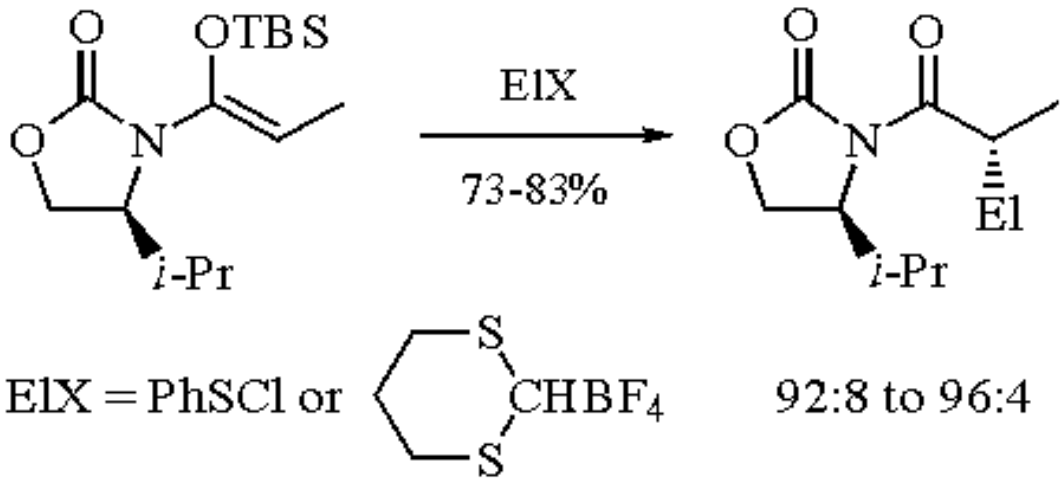

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Chiral oxazolidinones have also been used to induce chirality in $TiCl_4$-mediated allylsilane addition reactions to α-keto imides (eq 14).[49]

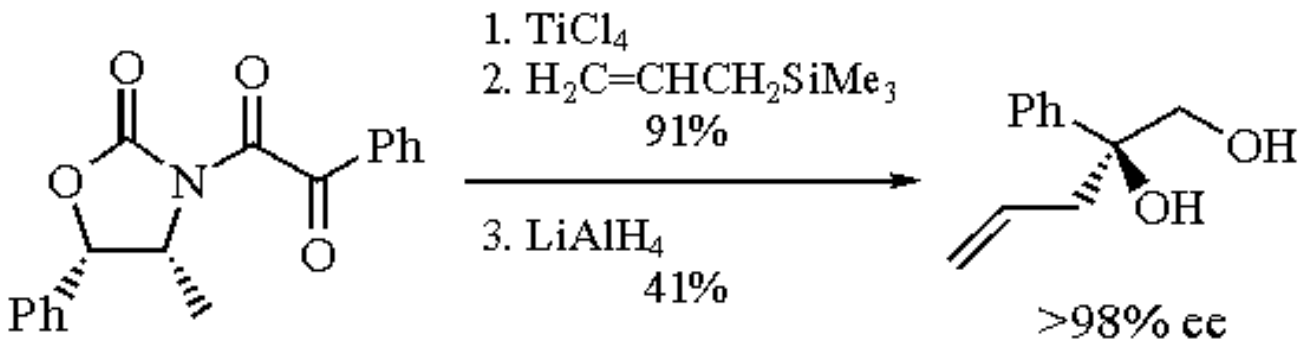

(14)

(S)-4-Benzyl-2-oxazolidinone

Enolate Alkylations with Transition Metal Coordinated Electrophiles.

Coordination of various transition metals to dienes and aromatic compounds sufficiently activates these compounds to nucleophilic addition, resulting in high asymmetric induction at the α-center. However, the manganese complexes of various benzene derivatives couple with lithium enolates in low selectivity at the nascent stereogenic center on the ring (eq 15).[50]

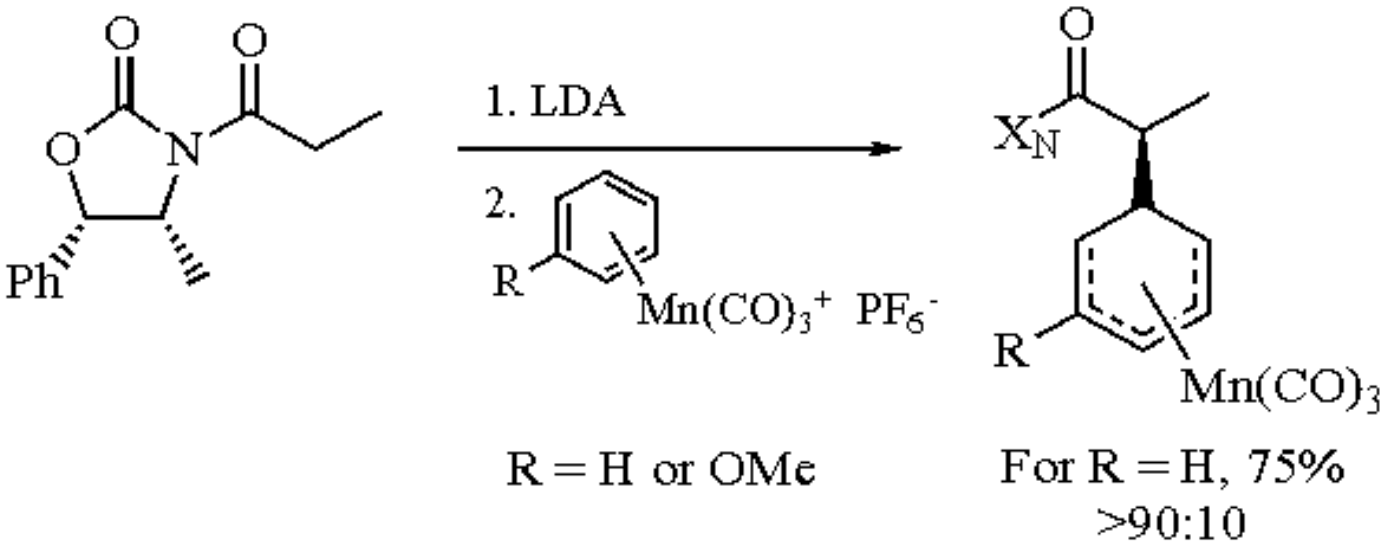

(15)

In contrast, molybdenum and iron diene complexes undergo the same type of reaction with chiral lithium imide enolates, with moderate to good induction at the β-position (eq 16).[51-53]

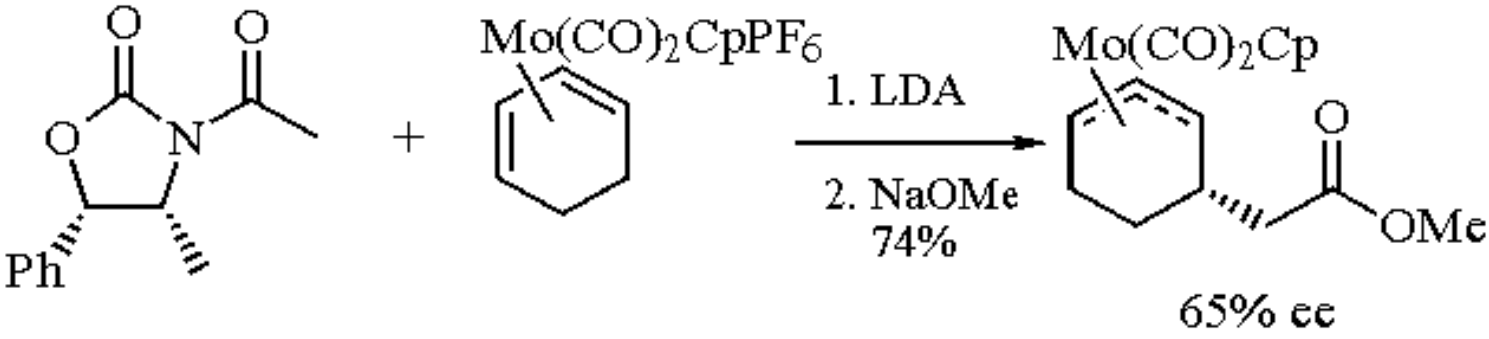

(16)

Dicobalt hexacarbonyl-coordinated propargyl ethers also combine with imide boron enolates through a kinetic resolution of the rapidly interconverting propargylic cation isomers to afford a 92:8 mixture of isomers at the β-center in 80% yield (eq 17). Stereocontrol of the α-center is 97:3.[54]

(S)-4-Benzyl-2-oxazolidinone

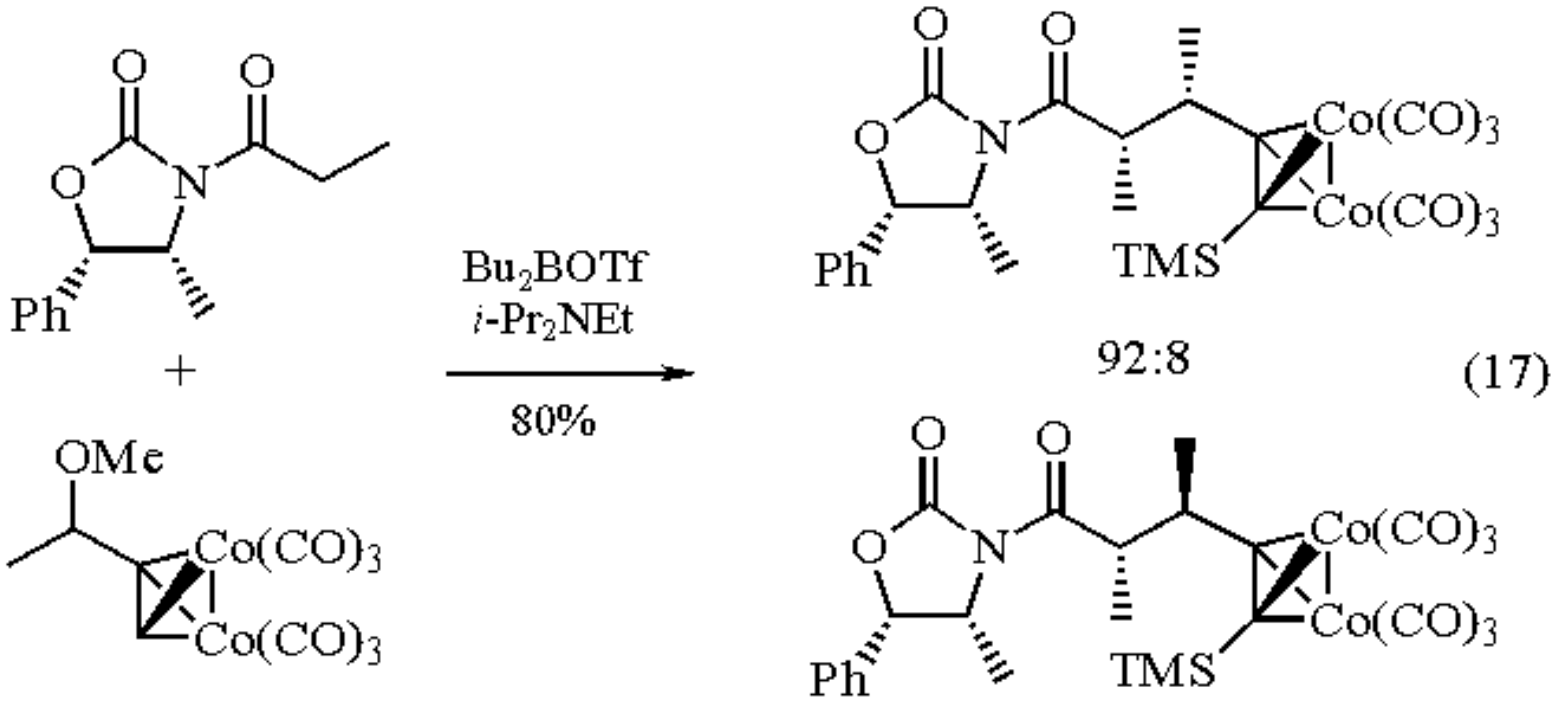

Enolate Acylation.

Acylation of these enolates provides a direct route to β-dicarbonyl systems. Acylations generally proceed with >95% diastereoselection in 83-95% yields, with the valine-derived auxiliary providing slightly higher selectivity (eq 18).[2] The sense of induction is consistent with reaction through the chelated lithium (*Z*)-enolate, and the newly generated stereocenter is retained through routine manipulations.

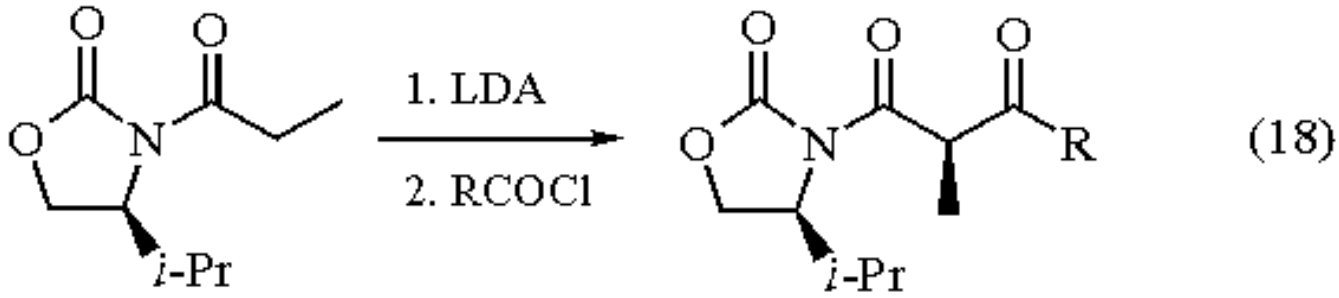

An alternate approach to these useful 1,3-dicarbonyl substrates may be achieved through enolate orthoester acylation. Titanium enolates have been employed to effect this transformation (eq 19).[45,47] Similarly, treatment of the titanium enolate of β-ketoimide with dioxolane orthoesters results in the formation of a masked tricarbonyl compound (eq 20). Trimethyl orthoacetate and ***Triethyl Orthoacetate*** are not appropriate partners in these coupling reactions.[45,47]

(S)-4-Benzyl-2-oxazolidinone

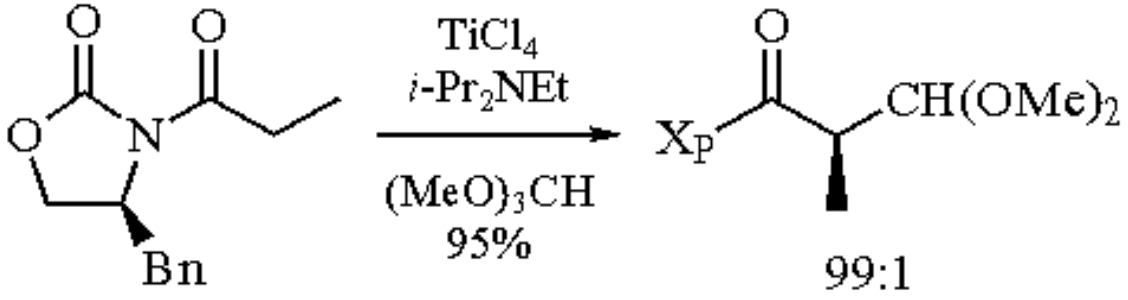

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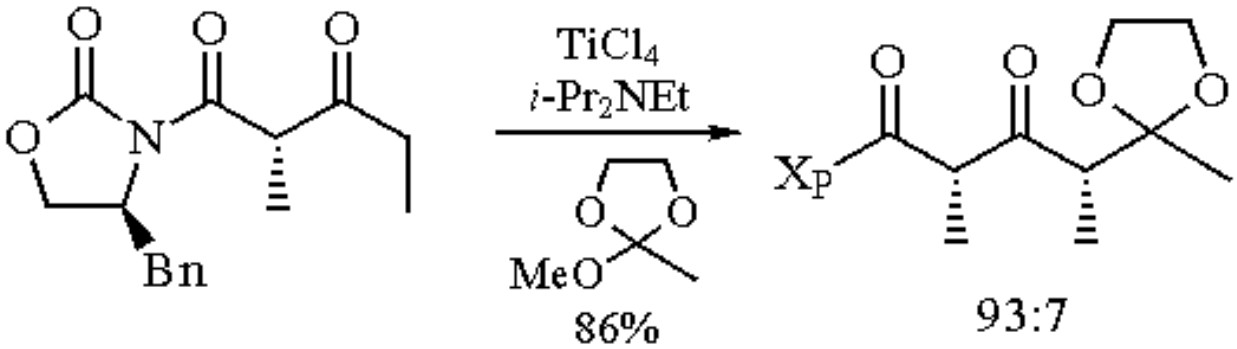

(20)

Michael Addition.

Titanium imide enolates are excellent nucleophiles in Michael reactions. Michael acceptors such as ethyl vinyl ketone, ***Methyl Acrylate***, ***Acrylonitrile***, and *t*-butyl acrylate react with excellent diastereoselection (eq 21).[7,45] Enolate chirality transfer is predicted by inspection of the chelated (*Z*)-enolate. For the less reactive unsaturated esters and nitriles, enolates generated from $TiCl_3$(O-*i*-Pr) afford superior yields, albeit with slightly lower selectivities. The scope of the reaction fails to encompass β-substituted, α,β-unsaturated ketones which demonstrate essentially no induction at the prochiral center. Furthermore, substituted unsaturated esters do not act as competent Michael acceptors at all under these conditions.

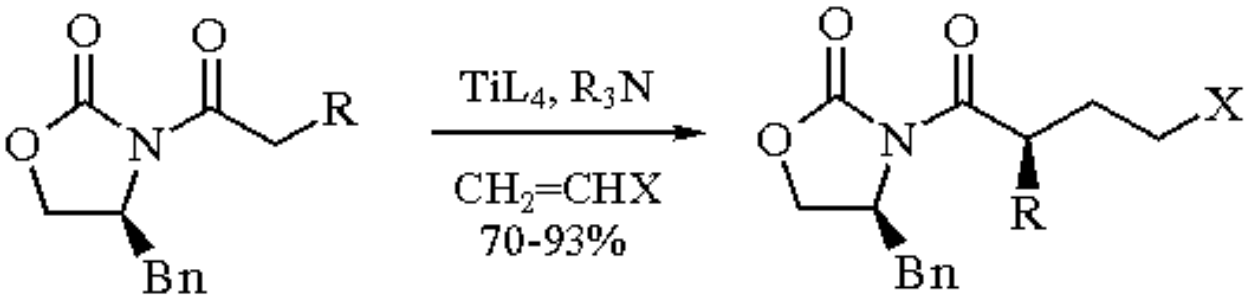

(21)

X = COEt, CO_2Me, CN >95:5

Various chelated lithium imide enolates have also served as nucleophiles in Michael additions to 3-trifluoromethyl acrylate, favoring the *anti* isomer (eq 22).[55]

(S)-4-Benzyl-2-oxazolidinone

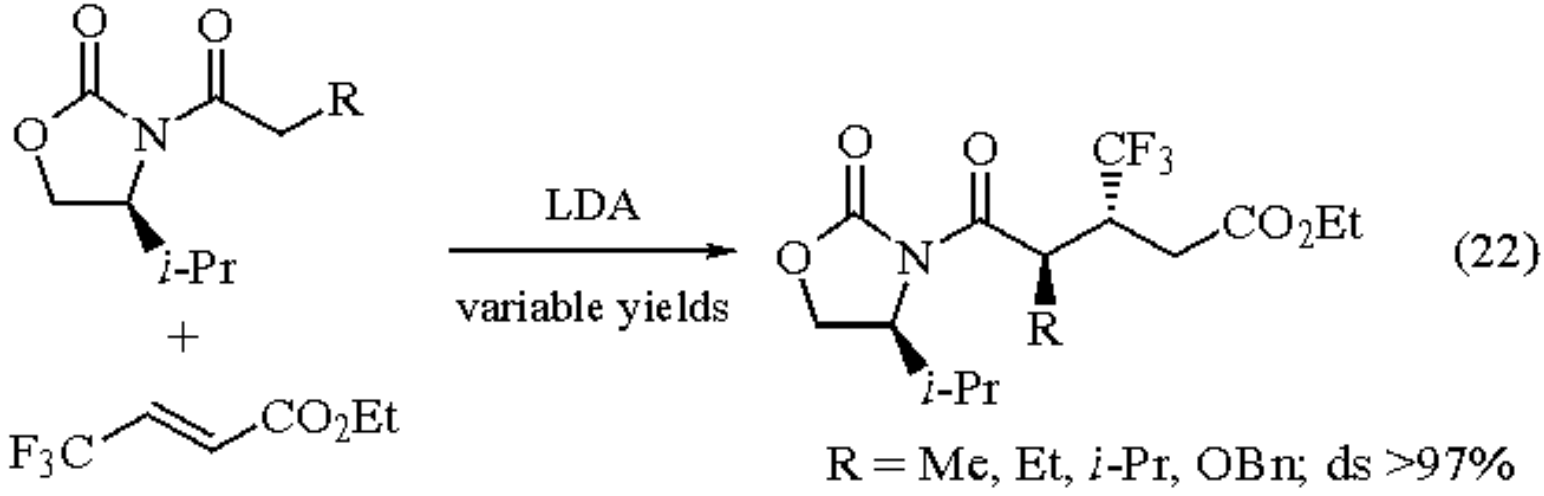

Enolate Hydroxylation.

Treatment of the sodium enolates with the Davis oxaziridine reagent affords the hydroxylated products with the same sense of induction as the alkylation products (eq 23).[5,35] Although high diastereoselectivity may be achieved with ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** (MoOPH), such reactions proceed in lower yields.

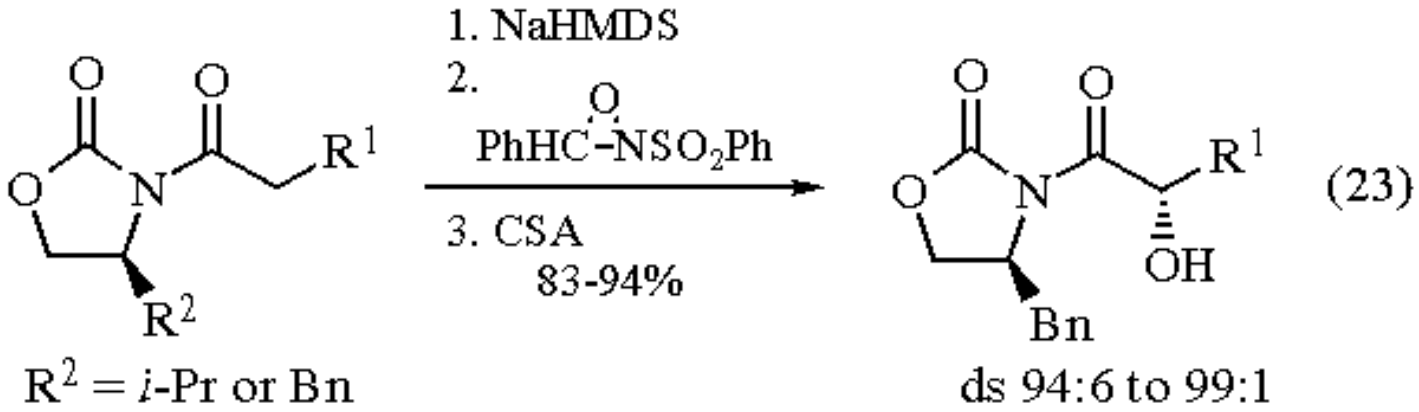

Enolate Amination.

Amination likewise can be effected using ***Di-t-butyl Azodicarboxylate*** (DBAD).[4,56] Despite the excellent yields and diastereoselectivity obtained using this methodology (eq 24), the harsh conditions required for further transformation of the resultant hydrazide adducts (***Trifluoroacetic Acid*** and hydrogenation at 500 psi over ***Raney Nickel*** catalyst) limit its synthetic utility.

(S)-4-Benzyl-2-oxazolidinone

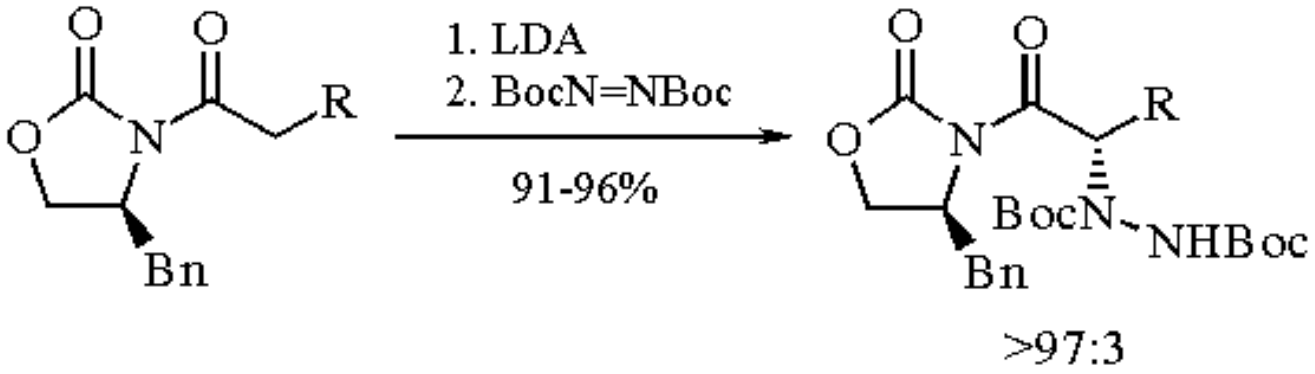

(24)

As a method for the synthesis of α-amino acids, the hydrazide methodology has now largely been supplanted by direct enolate azidation (eq 25).[4,57] These adducts are susceptible to mild chemical modification to afford *N*-protected α-amino acid derivatives. Under optimal conditions, yields range from 74-91% and selectivities from 91:9 to >99:1. Imide enolization can be carried out selectively in the presence of an enolizable *t*-butyl ester and suitably protected amino groups.

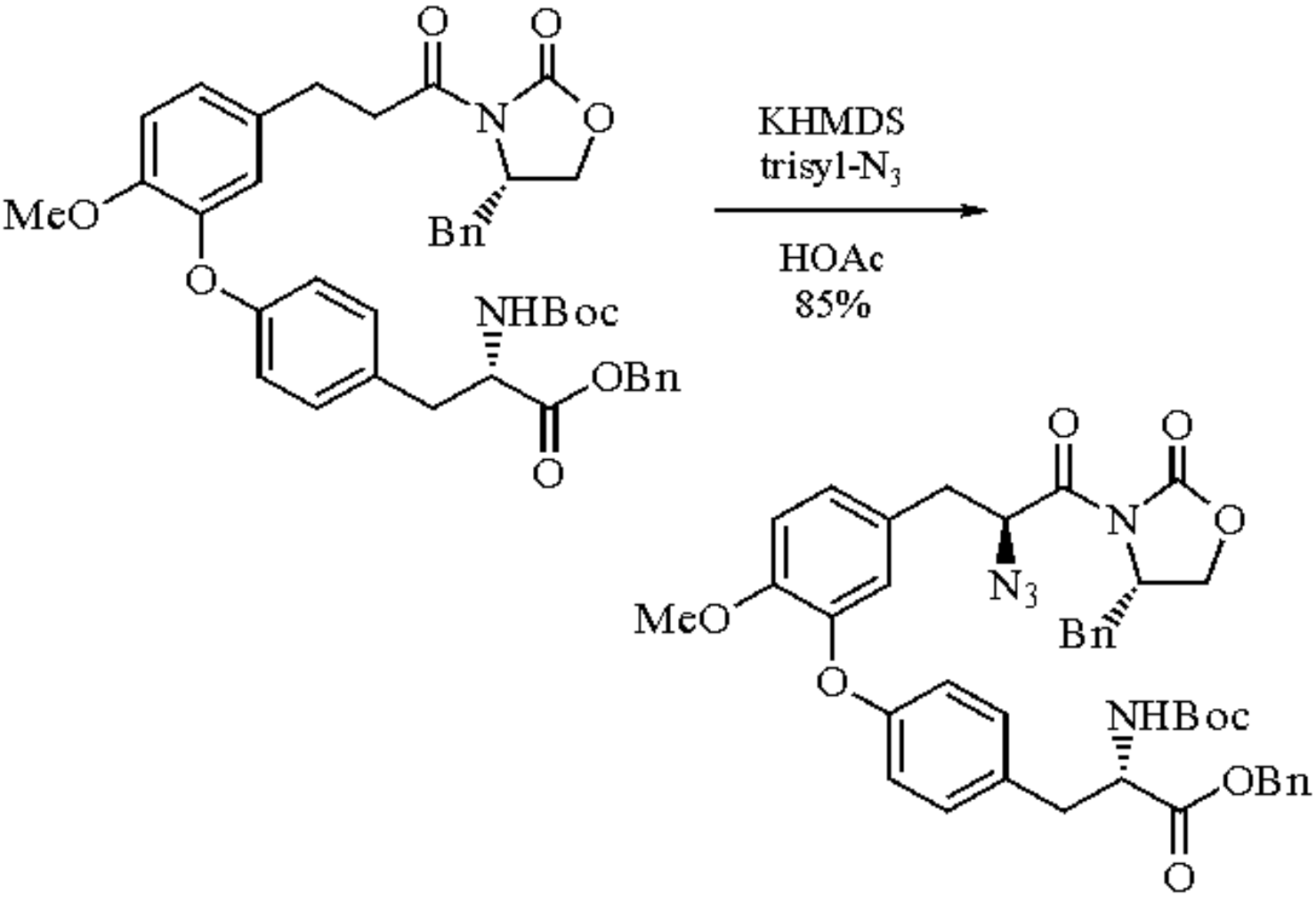

(25)

Hydrogenation of the azide moiety readily provides the amine using ***Palladium on Carbon*** and H_2 or ***Tin(II) Chloride***. This methodology has been extended to the synthesis of arylglycines (eq 26).[58]

(S)-4-Benzyl-2-oxazolidinone

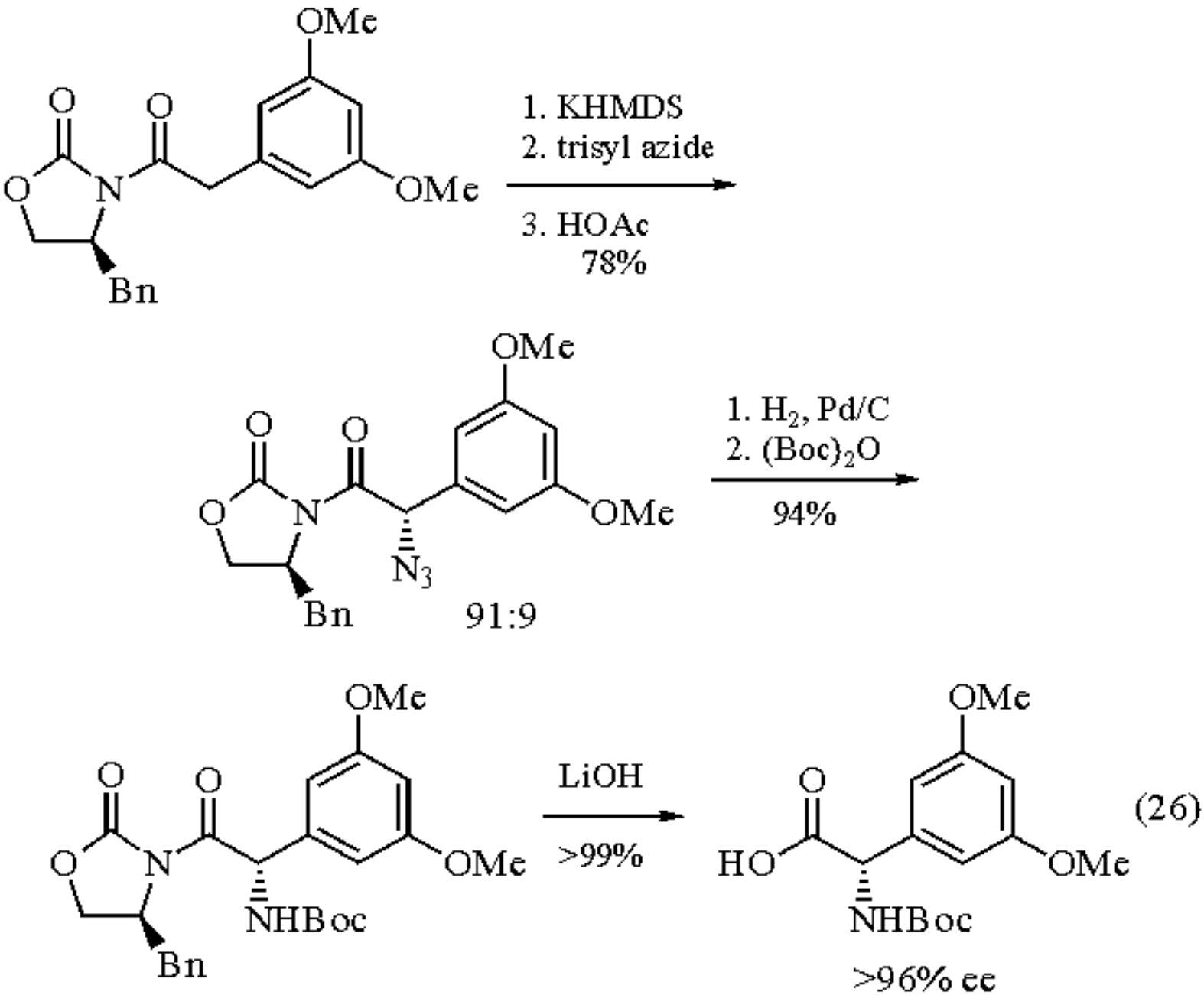

Failure to use ***2,4,6-Triisopropylbenzenesulfonyl Azide*** results in substantial diazo imide formation. However, optimization for the formation of the α-diazo imide compounds can be achieved with NaHMDS and *p*-nitrobenzenesulfonyl azide, followed by a neutral quench (eq 27).[4] These diazo compounds, however, have failed to demonstrate utility in asymmetric carbenoid chemistry.[59]

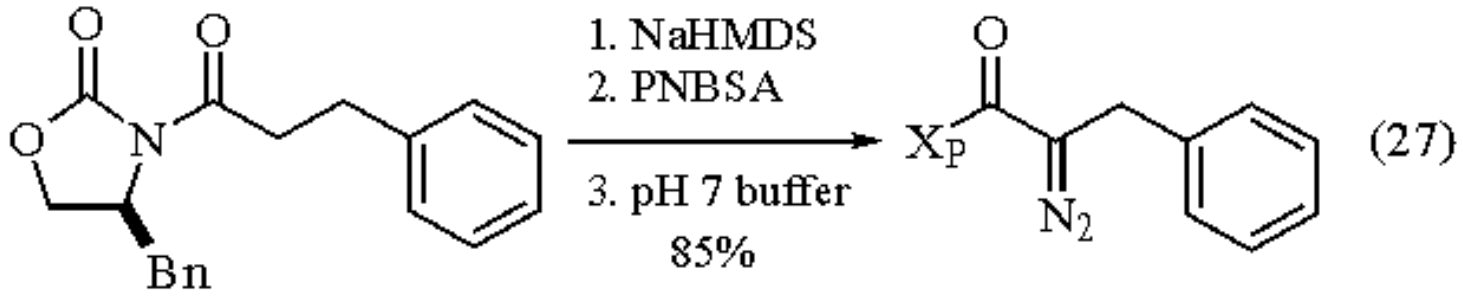

Enolate Halogenation.

Enolate halogenation is achieved by reaction of the boryl enolate with ***N-Bromosuccinimide***, affording configurationally stable α-bromo imides in >94:6 diastereoselectivity in 80-98% yield (eq 28).[3,4] The sense of induction suggests halogenation of the chelated (*Z*)-enolate. Introduction of an α-fluoro substituent can be effected by the treatment of imide enolates or α,β-unsaturated enolates with *N*-fluoro-*o*-benzenedisulfonimide (eq 29).[60]

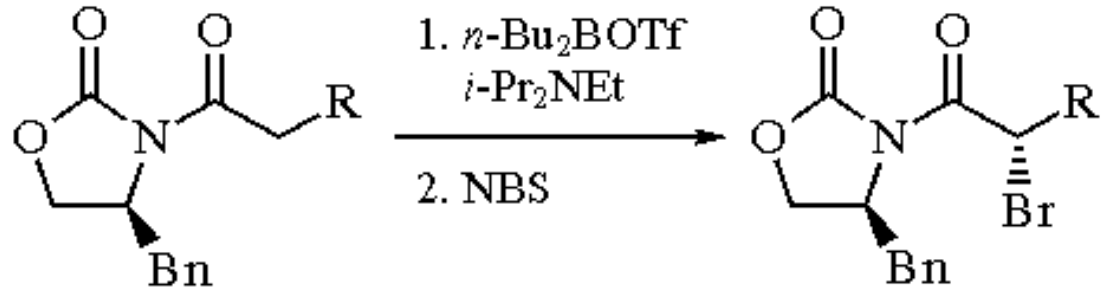

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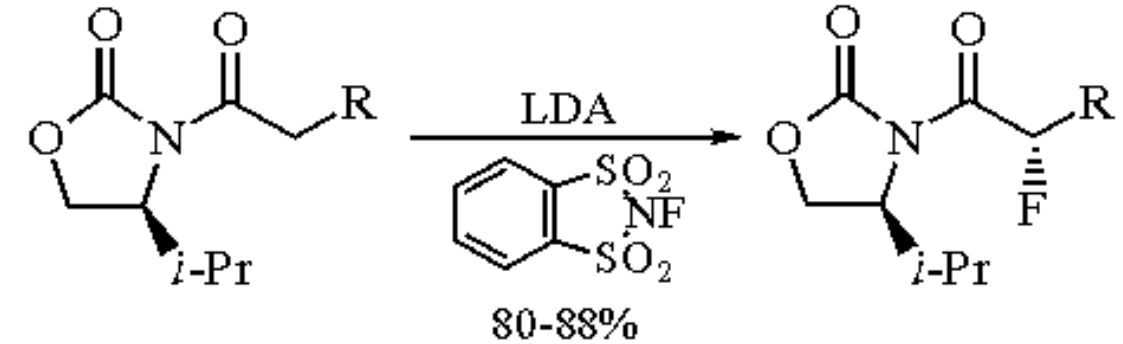

(29)

R = *n*-Bu, *t*-Bu, Bn, Ph 86-97% de

Displacement of a halide at the α-position with tetramethylguanidinium azide (TMGA) introduces nitrogen functionality with inversion of the original halide configuration and <1% epimerization (eq 30).[3,4]

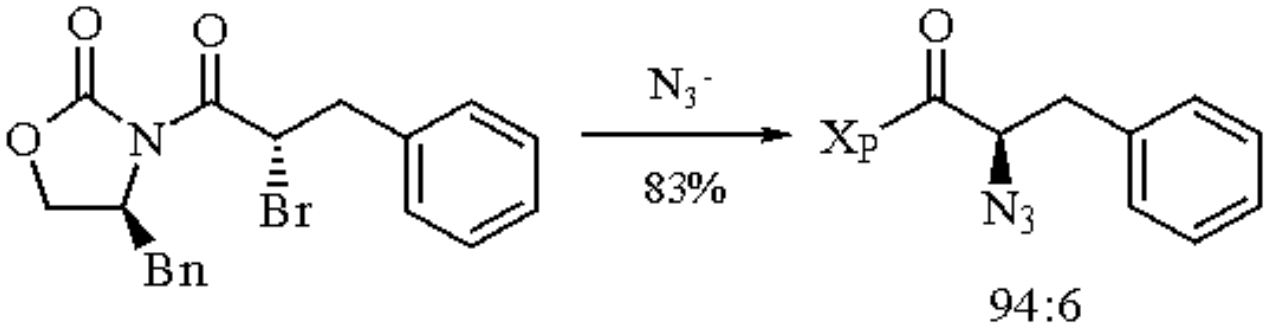

(30)

In those transformations where other stereogenic centers reside proximal to the prochiral center, auxiliary control is dominant in most cases (eq 31).[61]

(S)-4-Benzyl-2-oxazolidinone

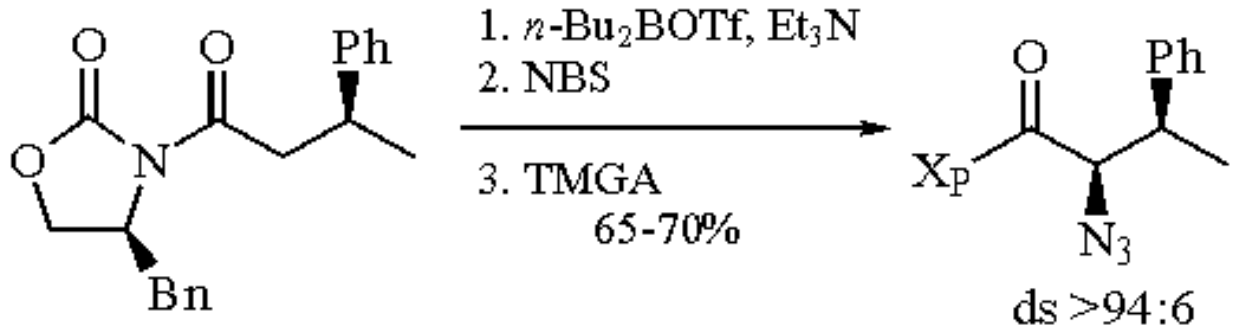

(31)

Aldol Reactions.

The dibutyl boryl enolates of chiral acyloxazolidinones react to afford the *syn*-aldol adducts with virtually complete stereocontrol (eq 32).[6,13,14,43,61-64] Notably, the sense of induction in these reactions is opposite to that predicted from the analogous alkylation reactions. This reaction is general for a wide range of aldehydes and imide enolates.[36,65-69] Enolate control overrides induction inherent to the aldehyde reaction partner.

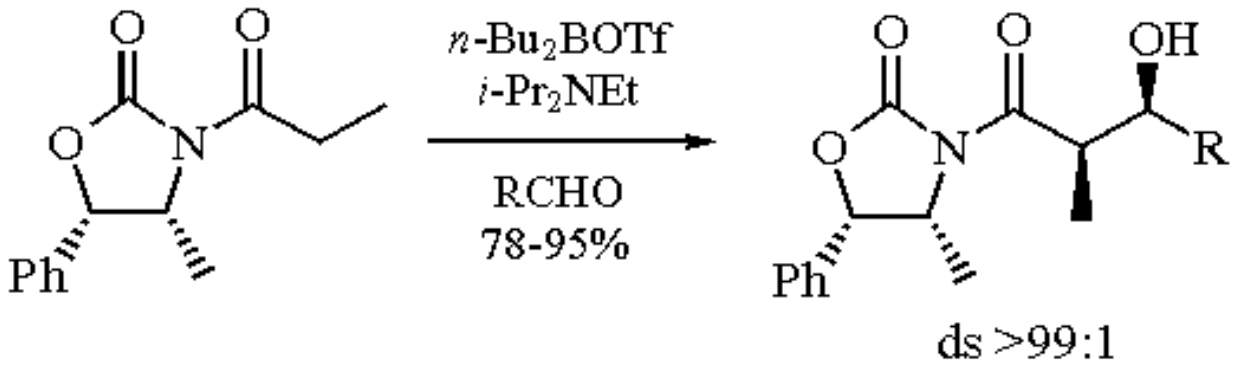

(32)

Titanium enolates of propionyloxazolidinones also undergo aldol reactions with the same sense of induction as the boryl counterparts, but require two or more equivalents of amine base to afford adducts in marginally higher yields but diminished selectivity (eq 33).[45]

(S)-4-Benzyl-2-oxazolidinone

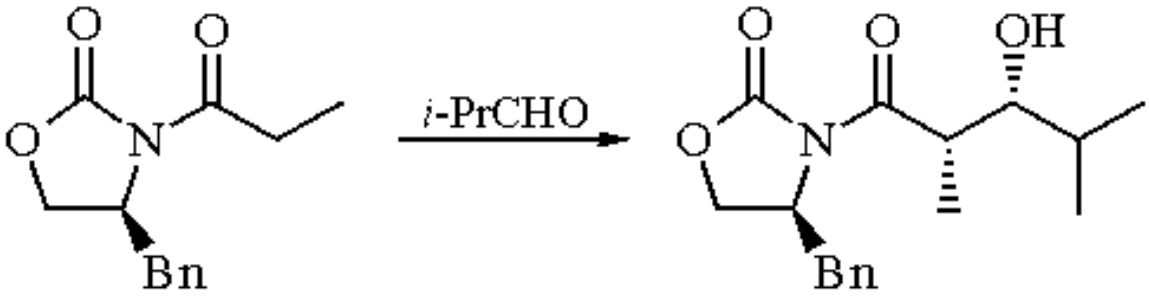

(33)

Enolization	Yield	Stereoselection
$TiCl_4$, i-Pr_2NEt	87%	94:6
$TiCl_4$, TMEDA	84%	98:2
n-Bu_2BOTf, Et_3N	83%	>99:1

A second entry to dicarbonyl substrates utilizes the aldol reaction to establish the α-methyl center prior to oxidation of the β-hydroxyl moiety. Commonly, this oxidation is performed using the ***Sulfur Trioxide-Pyridine*** complex, which results in <1% epimerization of the methyl-bearing center (eq 34).[2] Interestingly, this procedure procures the opposite methyl stereochemistry from that obtained through enolate acylation of the same enantiomer of oxazolidinone.

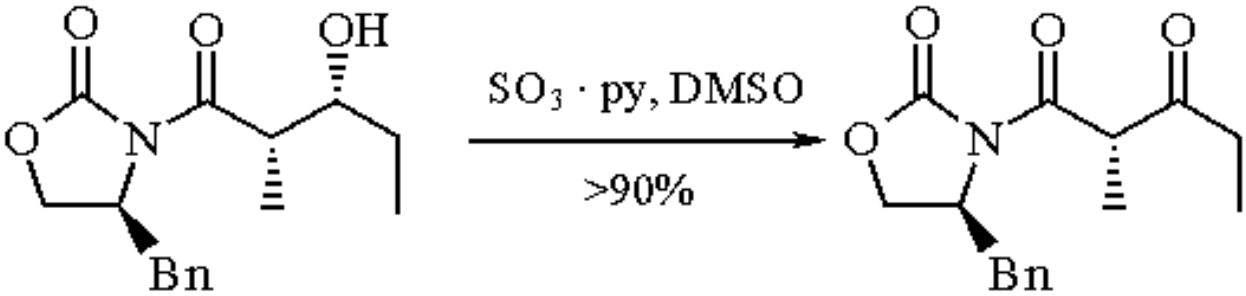

(34)

Non-Evans Aldol Reactions.

Either the *syn*- or *anti*-aldol adducts may be obtained from this family of imide-derived enolates, depending upon the specific conditions employed for the reaction. Although the illustrated boron enolate affords the illustrated *syn*-aldol adduct in high diastereoselectivity, the addition reactions between this enolate and Lewis acid-coordinated aldehydes afford different stereochemical outcomes depending on the Lewis acid employed (eq 35).[70] Open transition states have been proposed for the ***Diethylaluminum Chloride*** mediated, *anti*-selective reaction. These *anti*-aldol reactions have been used in kinetic resolutions of 2-phenylthio aldehydes.[71]

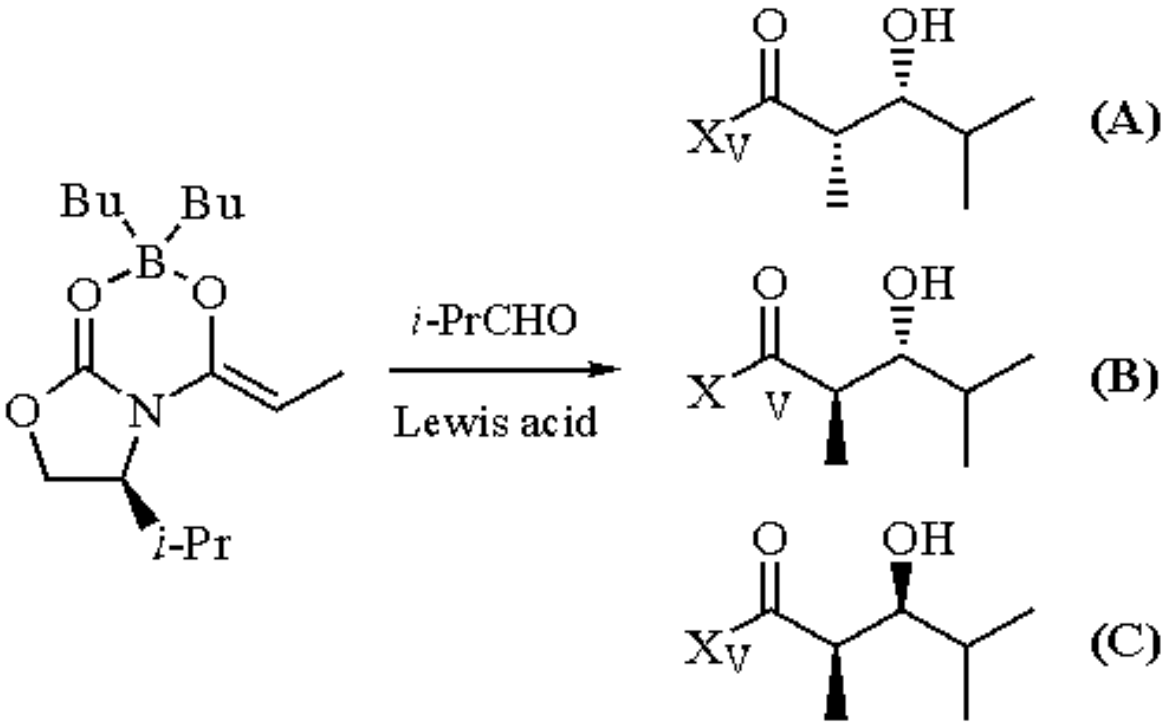

(35)

Lewis acid	Yield	A:B:C
$TiCl_4$ (2 equiv)	83%	0:16:84
$SnCl_4$ (2 equiv)	60%	0:13:87
Et_2AlCl (2 equiv)	63%	0:95:5

Enolates derived from α-haloimides also exhibit metal-dependent *syn/anti*-aldol diastereoselection. The derived Li, Sn^{IV}, and Zn enolates afford the *anti* isomer in reactions with aromatic aldehydes, while the corresponding B and Sn^{II} enolates lead to the conventional *syn* products.[72,73] The non-Evans *syn* adducts have also been observed in reactions organized by ***Chlorotitanium Triisopropoxide***.[74,75]

Crotonyl Enolate Aldol Reactions.

Boron enolates of the *N*-crotonyloxazolidinones have been shown to afford the expected *syn*-aldol adducts (eq 36).[76,77] The propensity for self-condensation during the enolization process is minimized by the use of triethylamine over less kinetically basic amines.

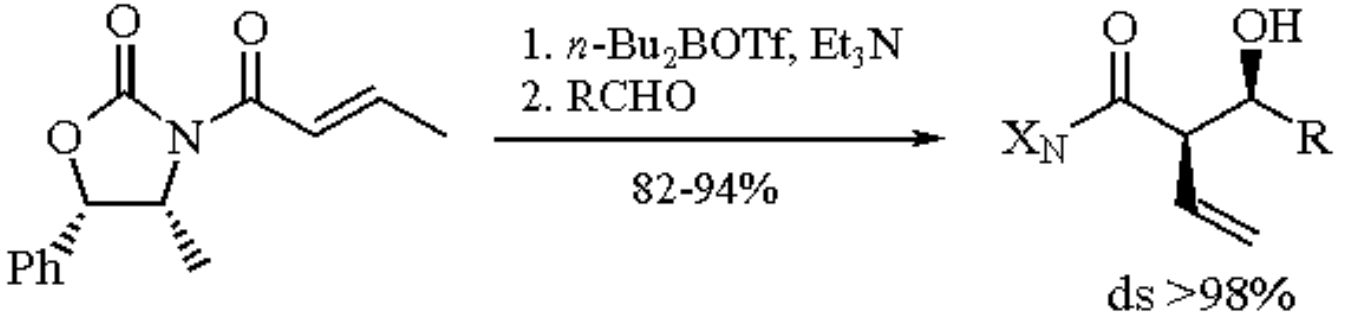

α-Alkoxyacetate Aldol Reactions.

The enolates derived from *N*-α-alkoxyacetyloxazolidinones also provide good yields of aldol adducts. Proper choice of reaction conditions leads to either the *syn* (eq 37)[78] or *anti* (eq 38)[46] adducts. In an application of this aldol reaction in the synthesis of cytovaricin, a complex chiral aldehyde was found to turnover the expected *syn* diastereoselectivity of the boron enolate.[66]

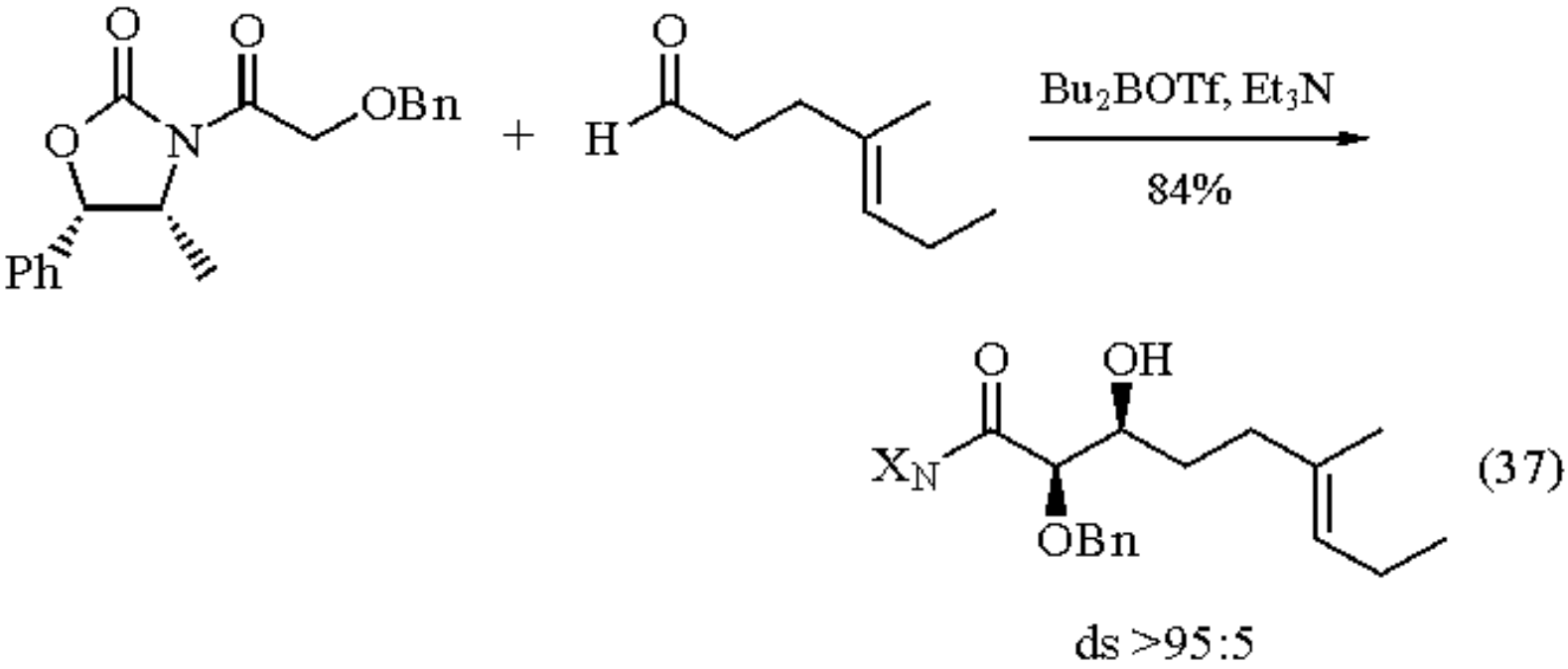

(S)-4-Benzyl-2-oxazolidinone

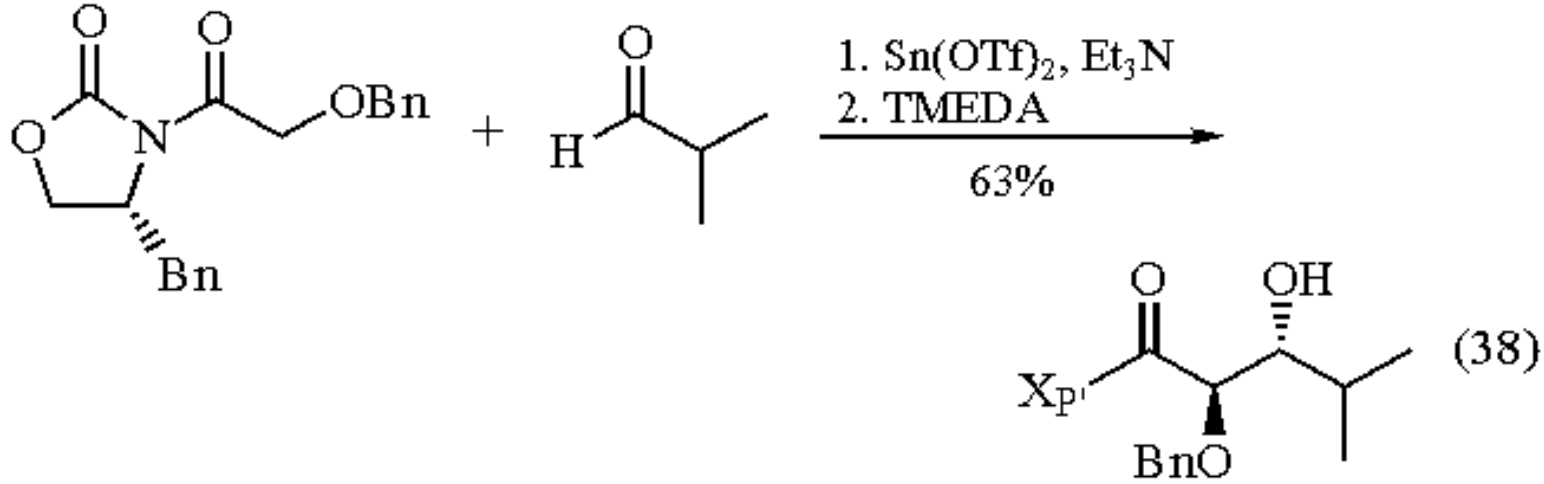

ds of desired to the total amount of other isomers = 77:23

N-Isothiocyanoacetyl Aldol Reactions.

Auxiliary-controlled masked glycine enolate aldol reactions afford the chiral oxazolidine-2-thiones which can be cleaved to provide the *syn*-aldol adducts regardless of aldehyde stereochemistry (eq 39).[79]

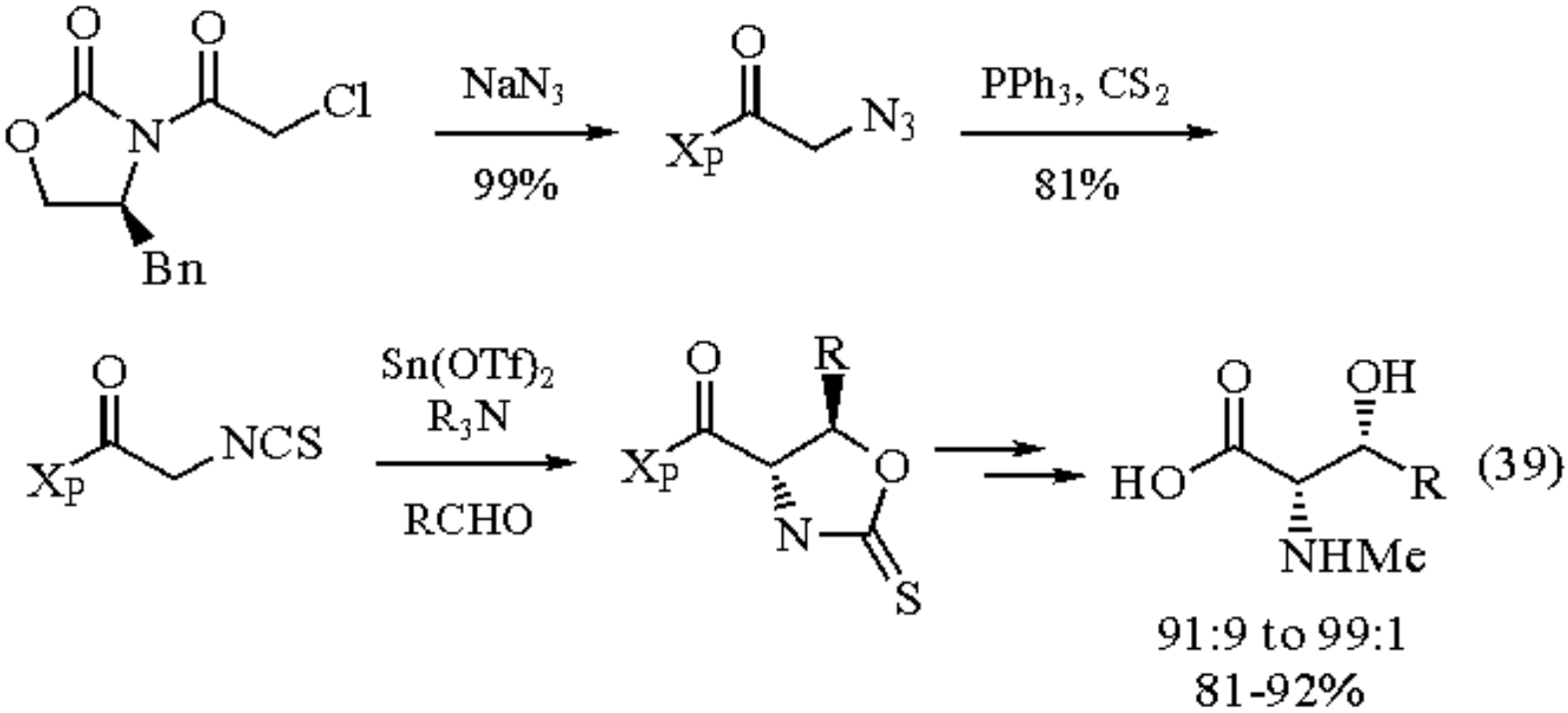

N-Haloacetyl Aldol Reactions.

N-Haloacetyloxazolidinones form suitable enolate partners in aldol reactions, although complete aldehyde conversion requires the use of a slight excess of imide (eq 40). The products can be chromatographed to diastereomeric purity.[4,80] Nucleophilic azide displacement of α-halo-β-hydroxy *syn* aldol adducts affords the corresponding *anti* α-amino-β-hydroxy compounds (eq 41).[4,80] Intramolecular displacement of the halogen to form the α-amino product is also

(S)-4-Benzyl-2-oxazolidinone

possible (eq 42).[80]

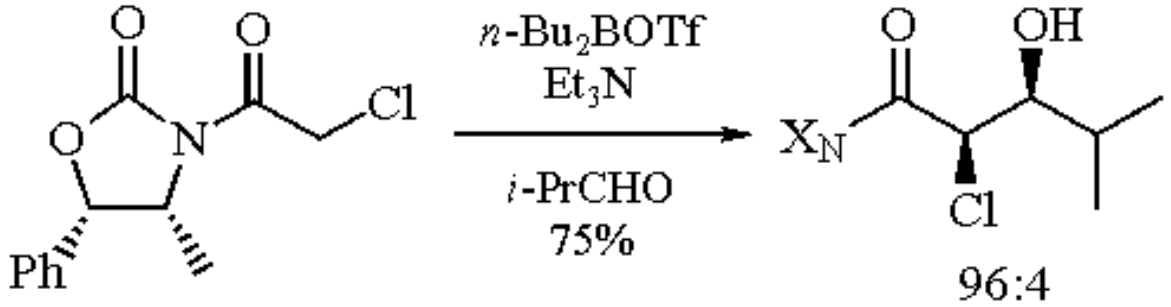

(40)

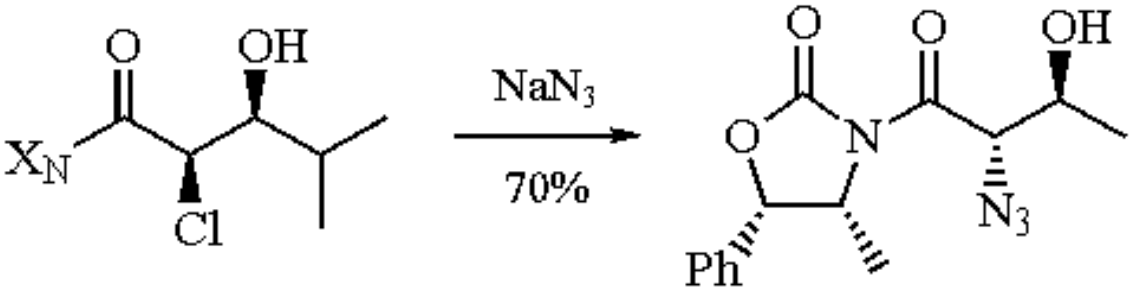

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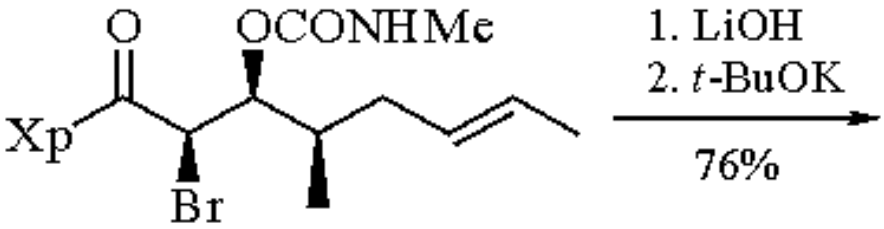

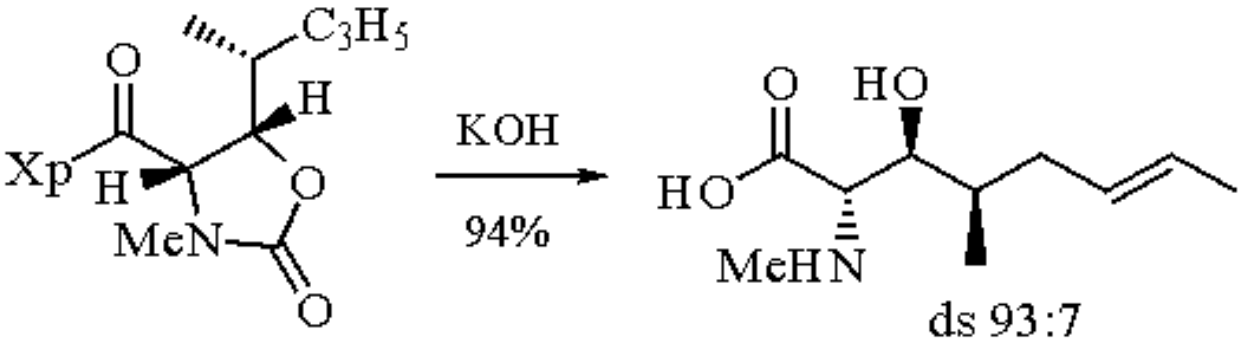

(42)

Acetate Aldol Equivalents.

In contrast to the reliably excellent selectivities of α-substituted dibutylboryl imide enolates, boron enolates derived from *N*-acetyloxazolidinones lead to a statistical mixture of aldol adducts under the same reaction conditions. Acetate enolate equivalents may be obtained from these enolates bearing a removable α-substituent. To this end, thiomethyl- or thioethylacetyloxazolidinones (eq 43)[13] as well as haloacetyloxazolidinones can be submitted to highly selective boron-mediated aldol reactions. Products can be transformed to the acetate aldol products via desulfurization with either Raney Ni[81] or ***Tri-n-butylstannane*** and ***Azobisisobutyronitrile***,[82] or via dehalogenation with ***Zinc-Acetic Acid*** (eq 44).[81] This latter procedure provides several advantages over the sulfur methodology, including ease of imide preparation and improved overall yields.

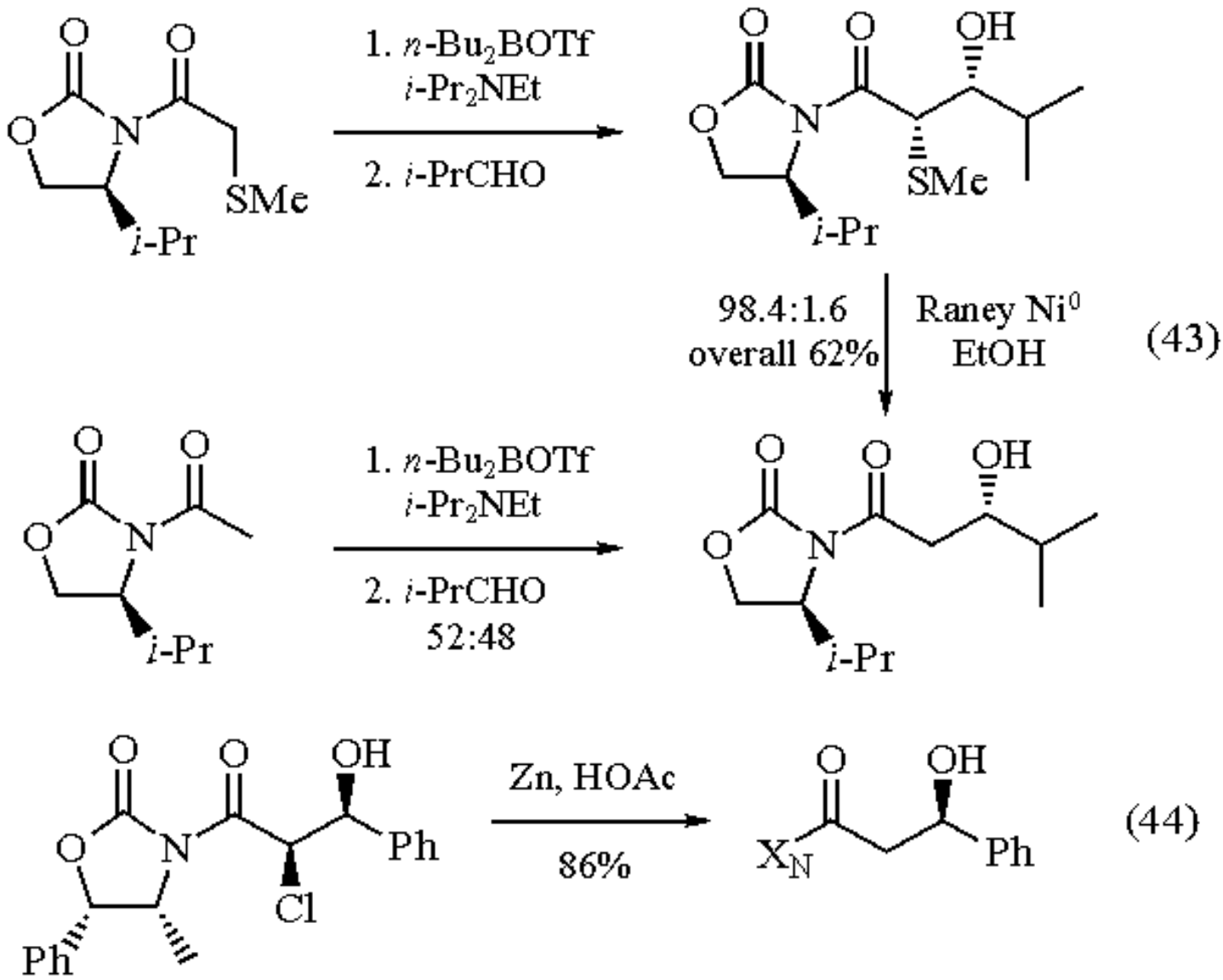

β-Ketoimide Aldol Reactions.

As has been demonstrated, chiral oxazolidinones provide a gateway into asymmetric β-ketoimides via either an aldol-oxidation sequence, or enolate acylation. These substrates can then undergo an iterative aldol reaction, where chirality is induced by the methyl-bearing α-center. To date, three of the four diastereomeric aldol adducts may be selectively obtained with a variety of aldehydes (eq 45).[36,83-86]

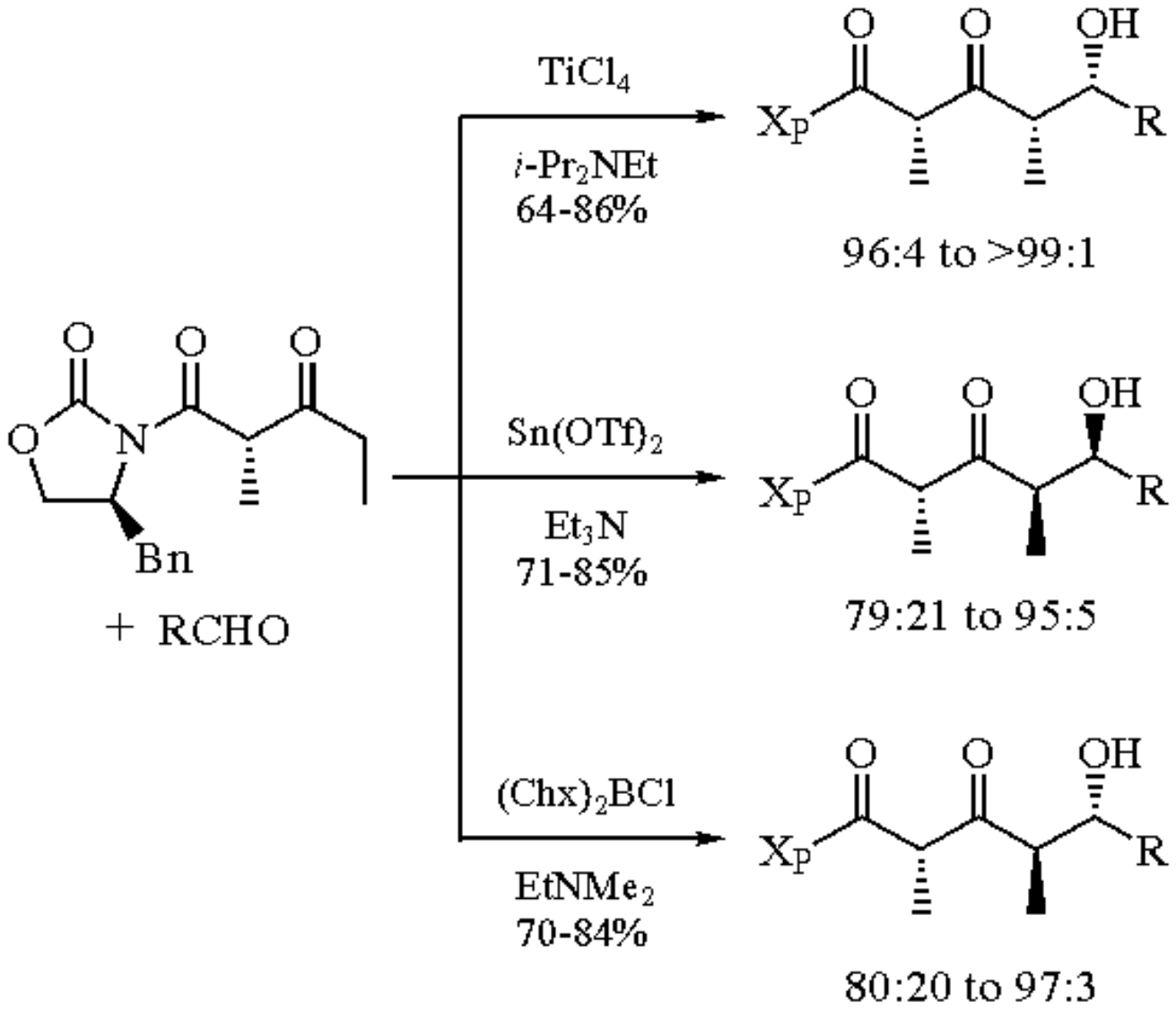

(45)

Reformatsky Reactions.

The Reformatsky reaction of α-halooxazolidinones provides an alternative to the more conventional aldol reaction. Although the traditional zinc-mediated Reformatsky using valine-derived compounds proceeds nonselectively,[87,88] the Sn^{II} modification with 2-bromo-2-methylpropionyloxazolidinone proceeds well (eq 46).[89,90] In this particular case, however, the geminal dialkyl substituents favor the endocyclic carbonyl acyl transfer of the auxiliary by the aldolate oxygen.

(S)-4-Benzyl-2-oxazolidinone

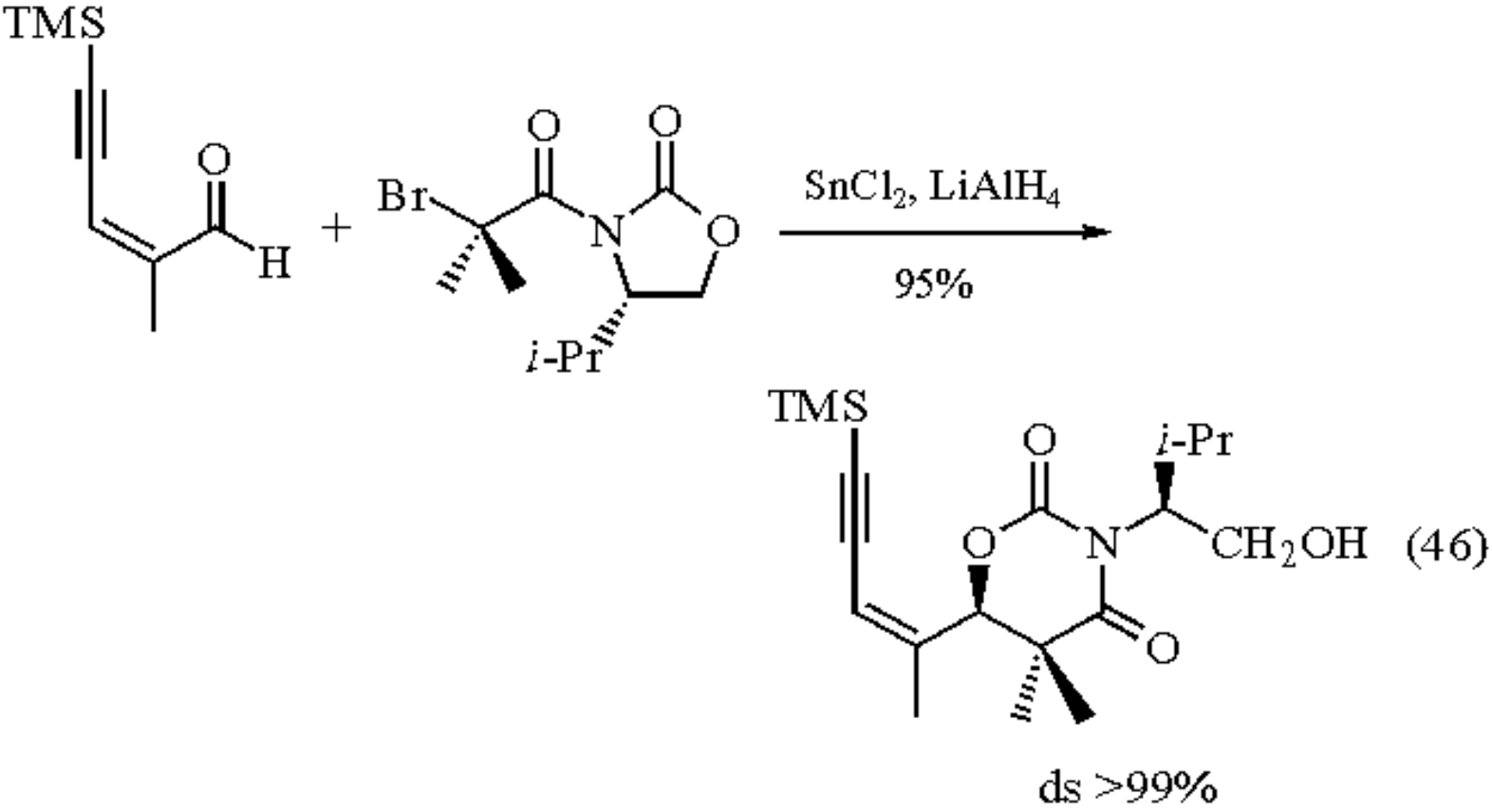

(46)

Acyl Transfer Reactions.

(*S*)-*N*-benzoyloxazolidinones have been used as acyl transfer reagents to effect the kinetic resolution of racemic alcohols.[10] The bromomagnesium alkoxides formed from phenyl *n*-alkyl alcohols selectively attack the exocyclic benzoyl moiety to afford recovered auxiliary and the derived (*R*)-benzoates in >90% ee and >90% yield (eq 47). The scope of this reaction seems to be limited to this class of substrates as selectivity drops with increasing the steric bulk of the alkyl group.

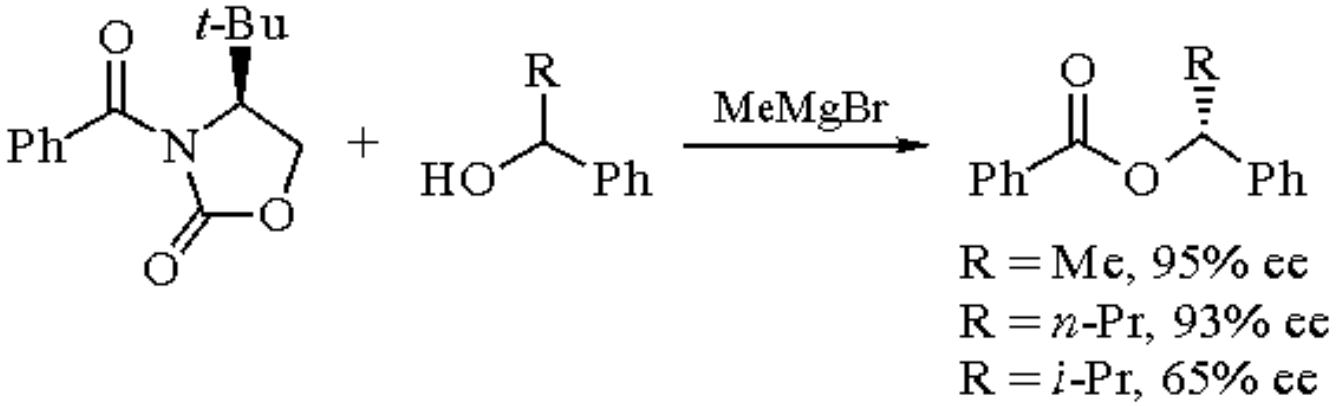

(47)

Sulfinyl Transfer Reactions.

Grignard reagents add to diastereomerically pure *N*-arylsulfinyloxazolidinones with inversion of configuration at sulfur to afford enantiopure dialkyl or aryl alkyl sulfoxides in excellent yields (eq 48).[11] Although broader in synthetic utility

than the menthyl sulfinate esters,[91,92] this methodology is comparable to Kagan's chiral sulfite substrates as a strategy for constructing chiral sulfoxides.[93,94]

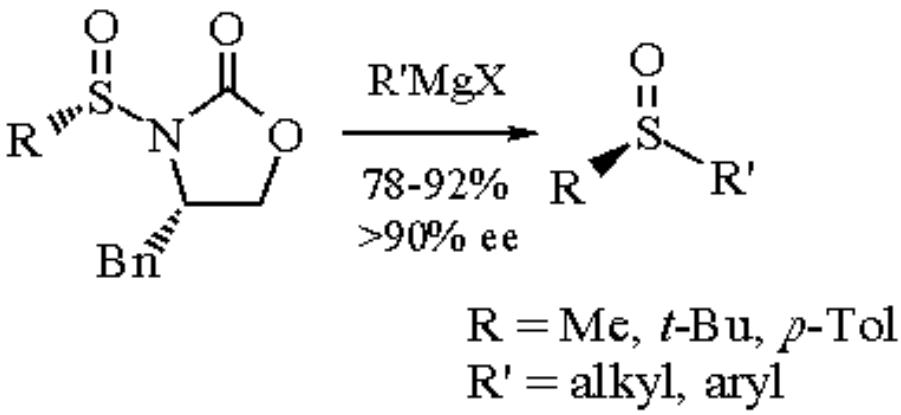

(48)

The *N*-arylsulfinyloxazolidinone methodology is readily extended to the formation of sulfinylacetates, sulfinates, and sulfinamides with >95% ee and high yields (eq 49).

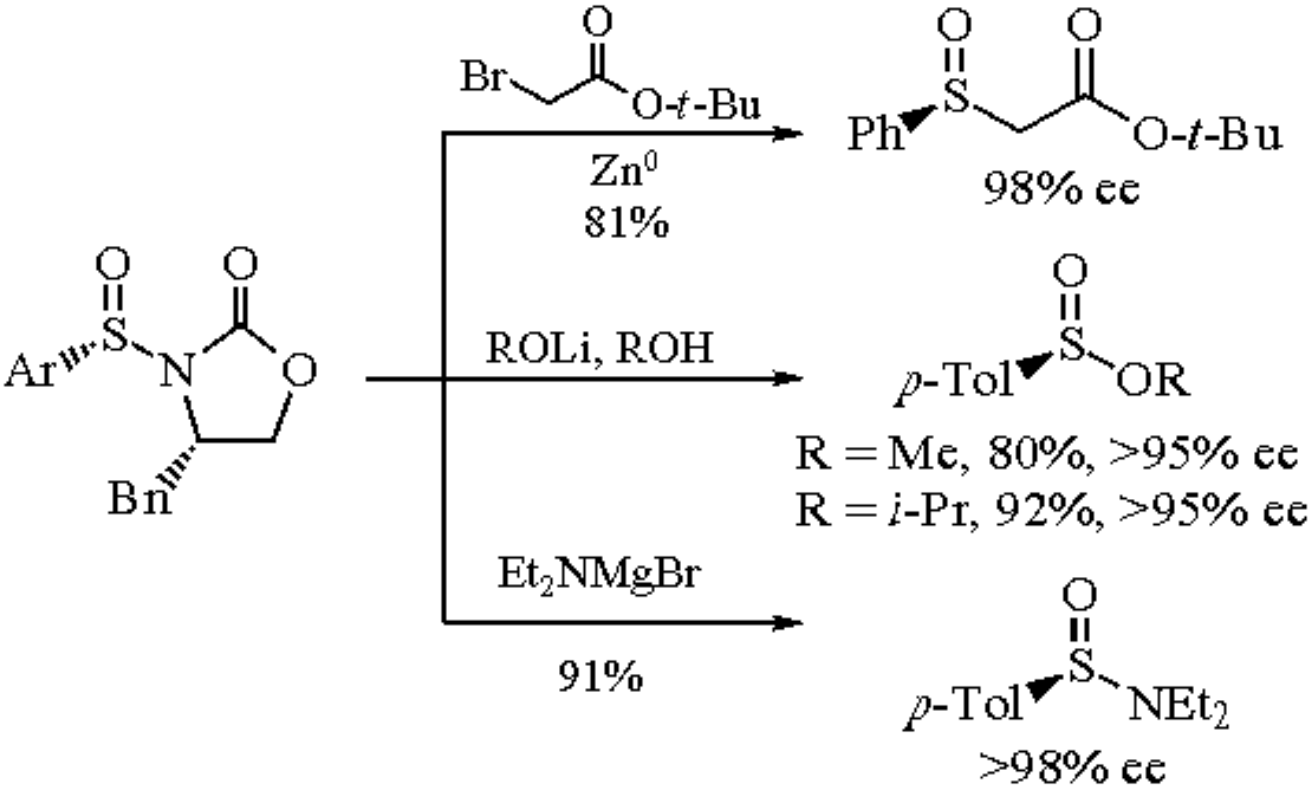

(49)

Diels-Alder Reactions.

Chiral α,β-unsaturated imides participate in Lewis acid-promoted Diels-Alder cycloaddition reactions to afford products in uniformly excellent *endo/exo* and *endo* diastereoselectivities (eqs 50 and 51).[9,37,95,96] Unfortunately, this reaction does not extend to certain dienophiles, including methacryloyl imides, β,β-dimethylacryloyl imides, or alkynic imides. Cycloadditions also occur with less reactive acyclic dienes with high diastereoselectivity (eq 52). Of the auxiliaries surveyed, the phenylalanine-derived oxazolidinones provided the highest diastereoselectivities. This methodology has been recently extended to complex intramolecular processes (eq 53).[68,95,97] In this case, use of the

unsubstituted achiral oxazolidinone favored the undesired diastereomer.

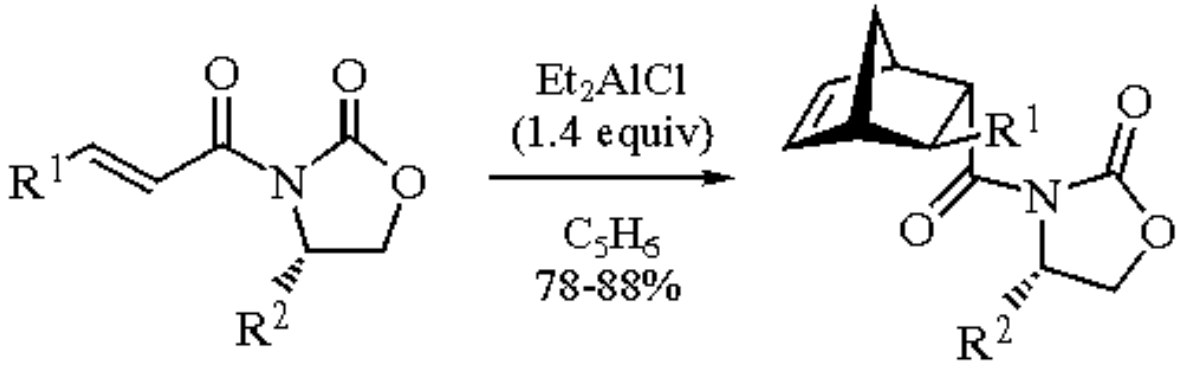

(50)

$R^1 = H$ or Me; $R^2 = i$-Pr or Bn

endo:*exo* >98:2
endo ds >95:5

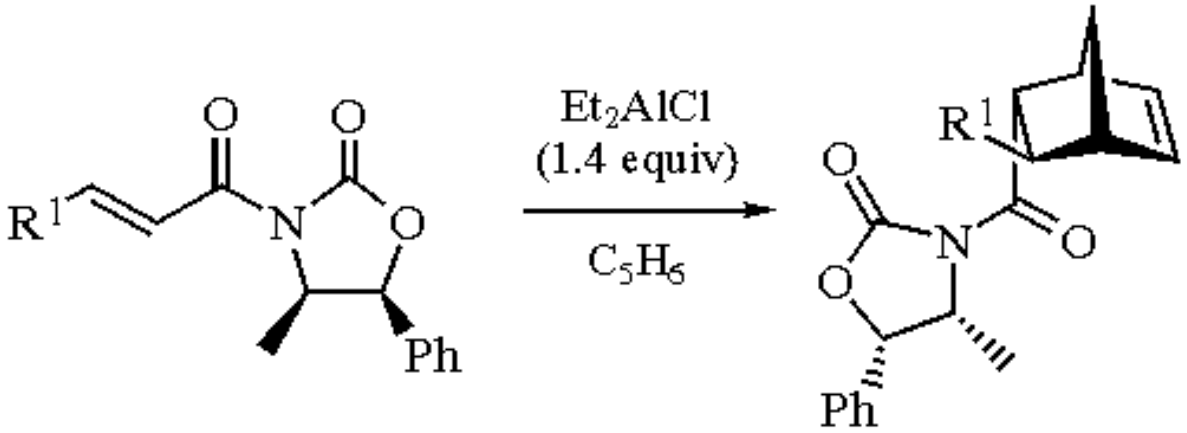

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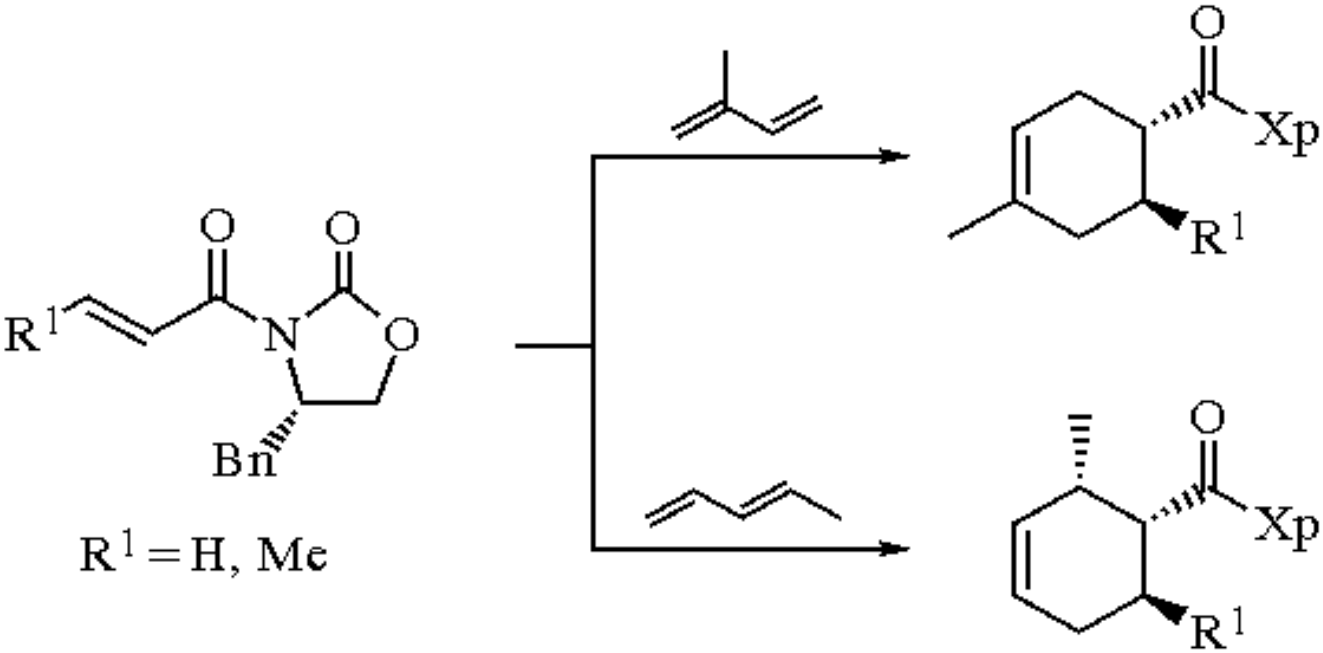

(52)

$R^1 = H$, Me

ds from 94:6 to >99:1
77-85%

(S)-4-Benzyl-2-oxazolidinone

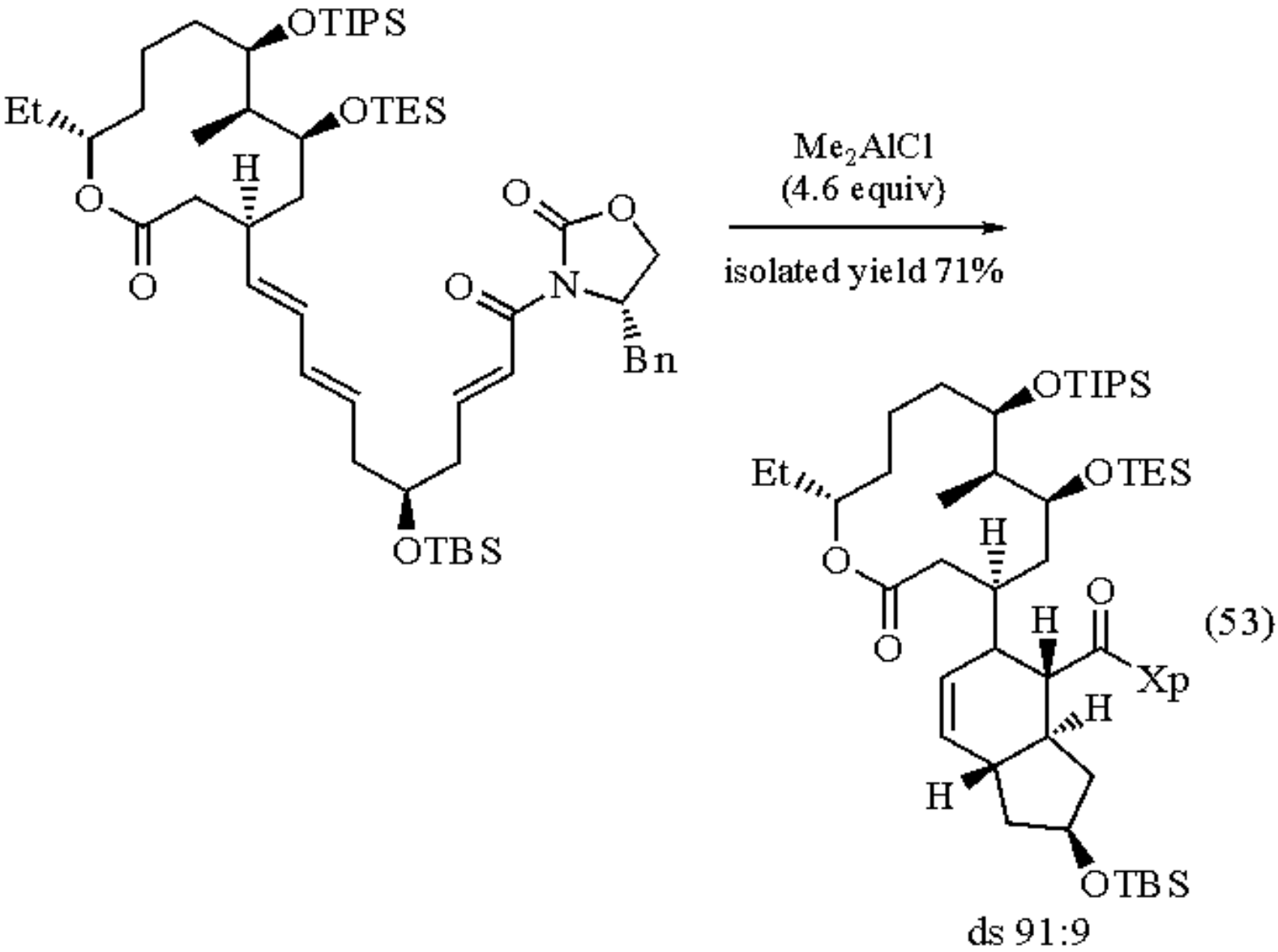

(53)

Staudinger Reactions.

Chiral oxazolidinones have been employed as the chiral control element in the Staudinger reaction as well as the ultimate source of the α-amino group in the formation of β-lactams.[41] Cycloaddition of ketene derived from 4-(*S*)-phenyloxazolidylacetyl chloride with conjugated imines affords the corresponding β-lactams in 80-90% yields with excellent diastereoselectivity (eq 54). The auxiliary can then be reduced under Birch conditions to reveal the α-amino group.

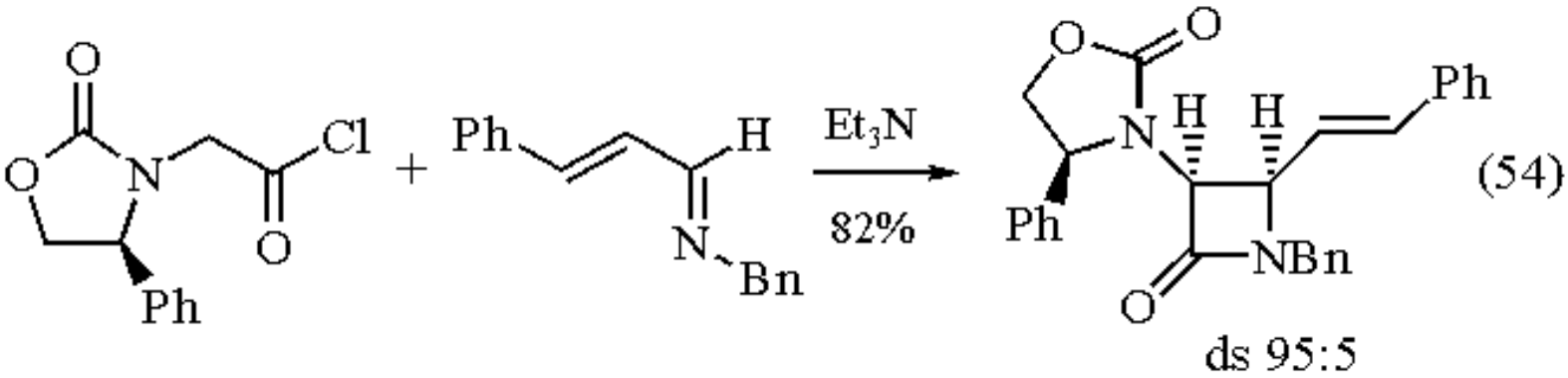

Conjugate Addition Reactions.

α,β-Unsaturated *N*-acyloxazolidinones have been implemented as Michael acceptors, inducing chirality in the same sense as in enolate alkylation reactions. Chiral α,β-unsaturated imides undergo 1,4-addition when treated with diethylaluminum chloride (eq 55). Photochemical initiation is required for the analogous reaction with ***Dimethylaluminum Chloride***.[96]

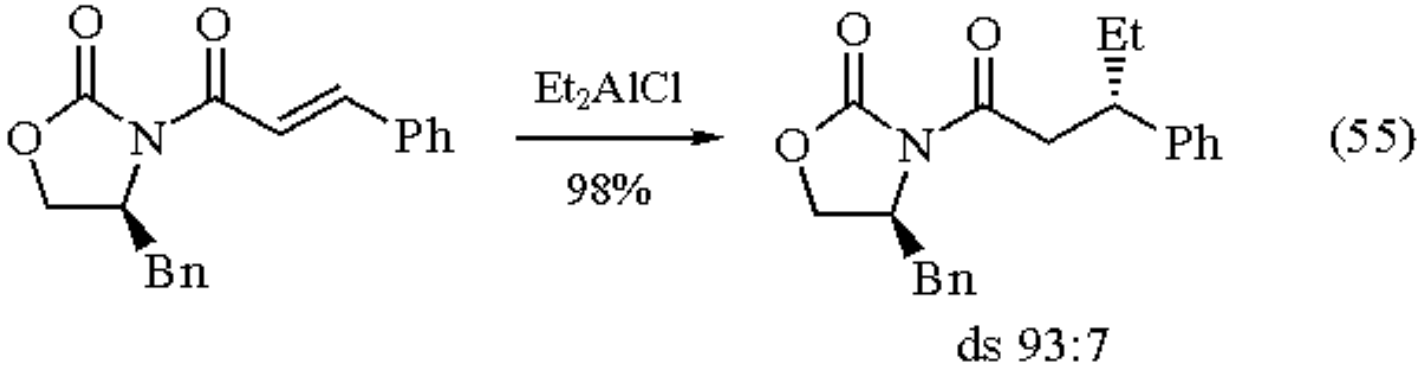

Organocuprates also undergo conjugate addition with chiral α,β-unsaturated imides.[98] Treatment of the imides derived from 4-phenyl-2-oxazolidinone with methyl- or arylmagnesium halides and CuBr affords conjugate addition products in yields over 80% with few exceptions (eq 56).[8] Reaction diastereoselectivity appears to be contingent upon the use of the 4-phenyloxazolidinone auxiliary. The preceding methodology has been applied to the synthesis of β-methyltryptophan (eq 57).[99]

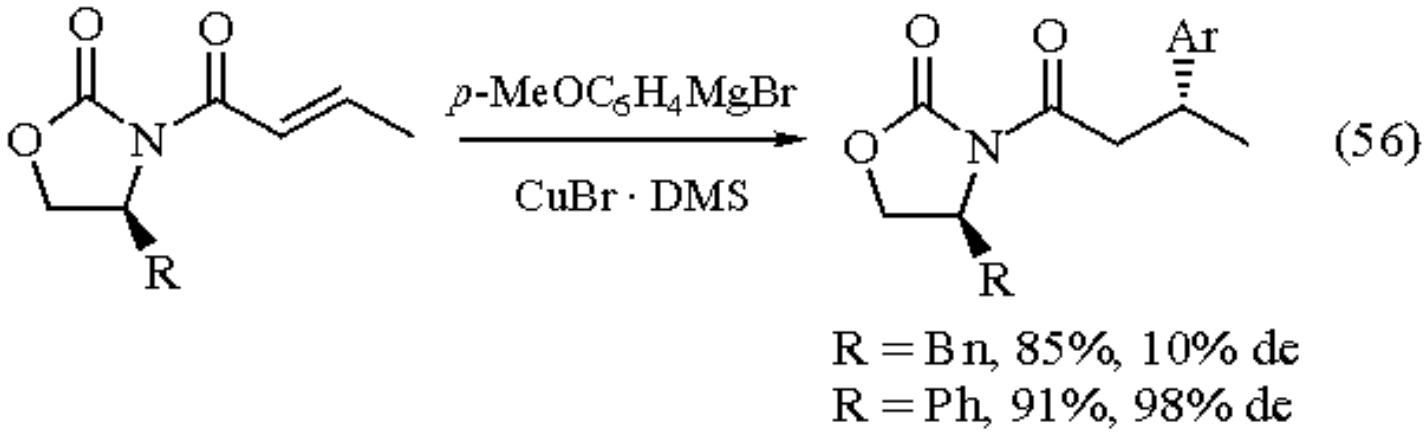

(S)-4-Benzyl-2-oxazolidinone

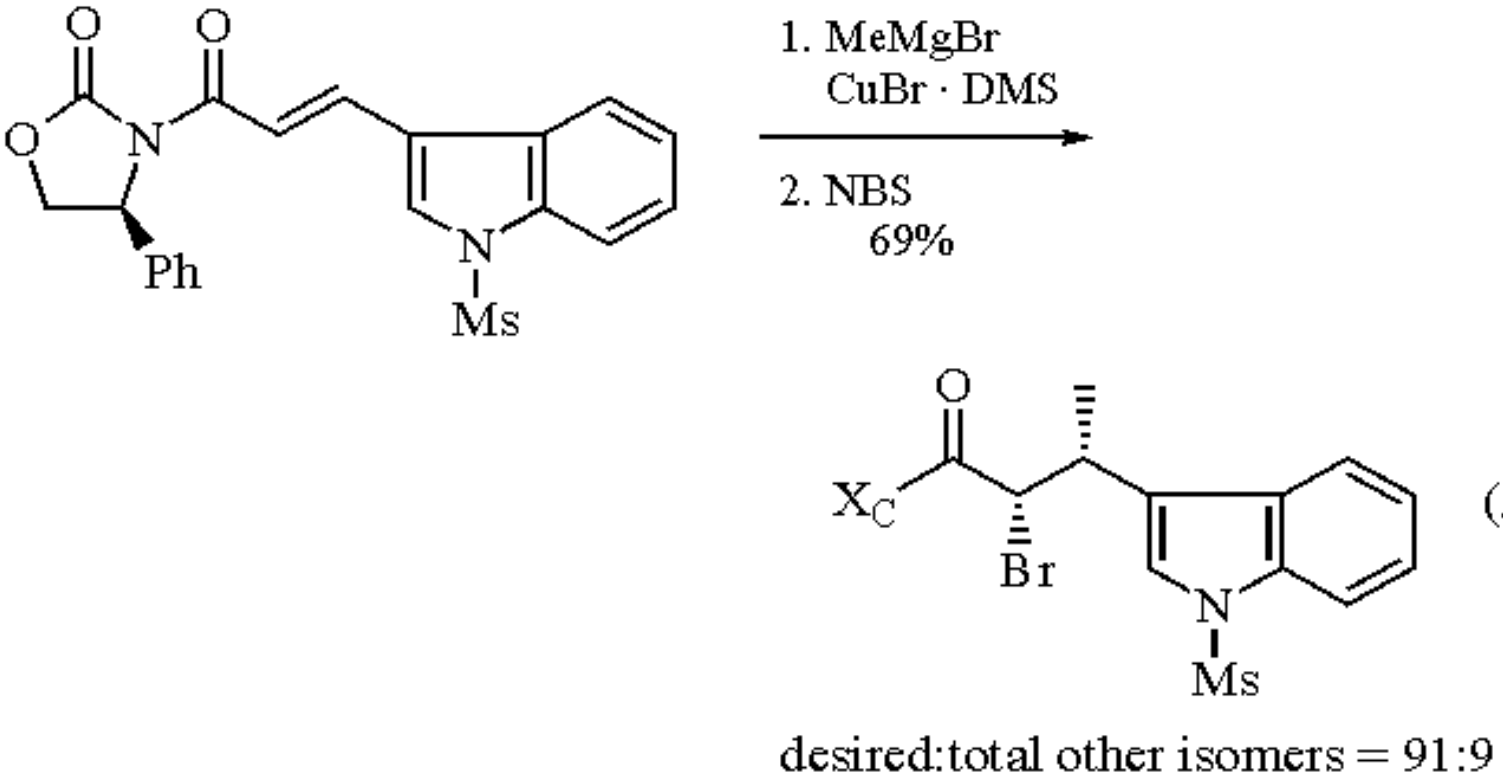

Similar chemistry using chiral sultam auxiliaries demonstrates superior yields and selectivities for specific cases of cuprate conjugate additions, but have not yet been extended to the more complex multistep transformation series illustrated above.[100,101] Moderate selectivities have been obtained in alkyl cuprate additions to γ-aminocrotonate equivalents where the nitrogen is derived from the oxazolidinone.[102]

The 4-phenyl-2-oxazolidinone auxiliary has also been employed in the $TiCl_4$-mediated conjugate additions of allylsilanes (eq 58).[103] Analogous reactions using the phenylalanine-derived auxiliary with dimethylaluminum chloride afforded lower selectivities.[104] In these reactions the oxazolidinones perform better than the sultams.

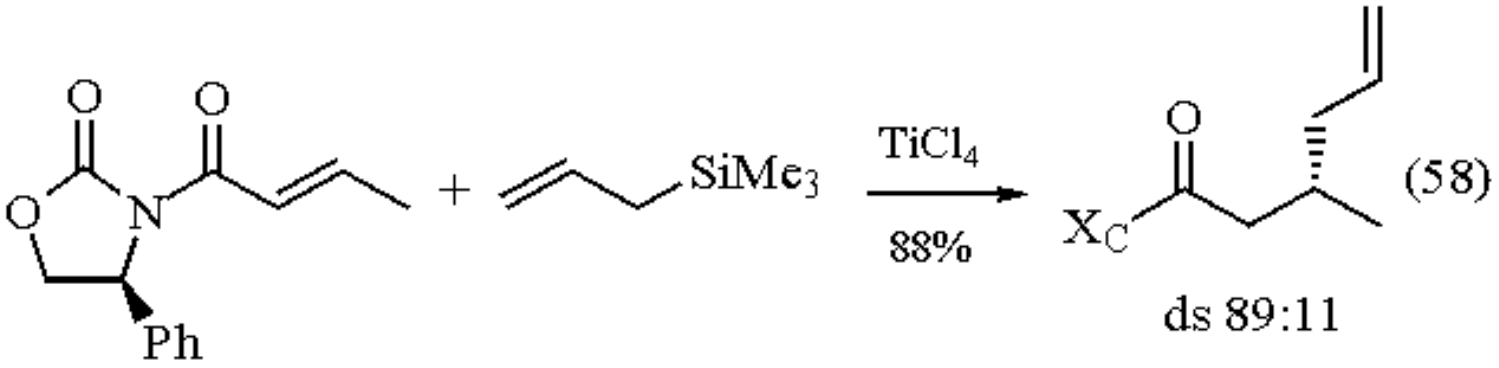

Nucleophilic addition of thiophenol to chiral tiglic acid-derived imides proceeds in excellent yields and diastereoselectivities (eq 59).[105] Complete turnover of both the α- and β-centers results from the use of the (*Z*) rather than (*E*) isomer. Poor β-induction was found with the imides derived from cinnamic acid.

(S)-4-Benzyl-2-oxazolidinone

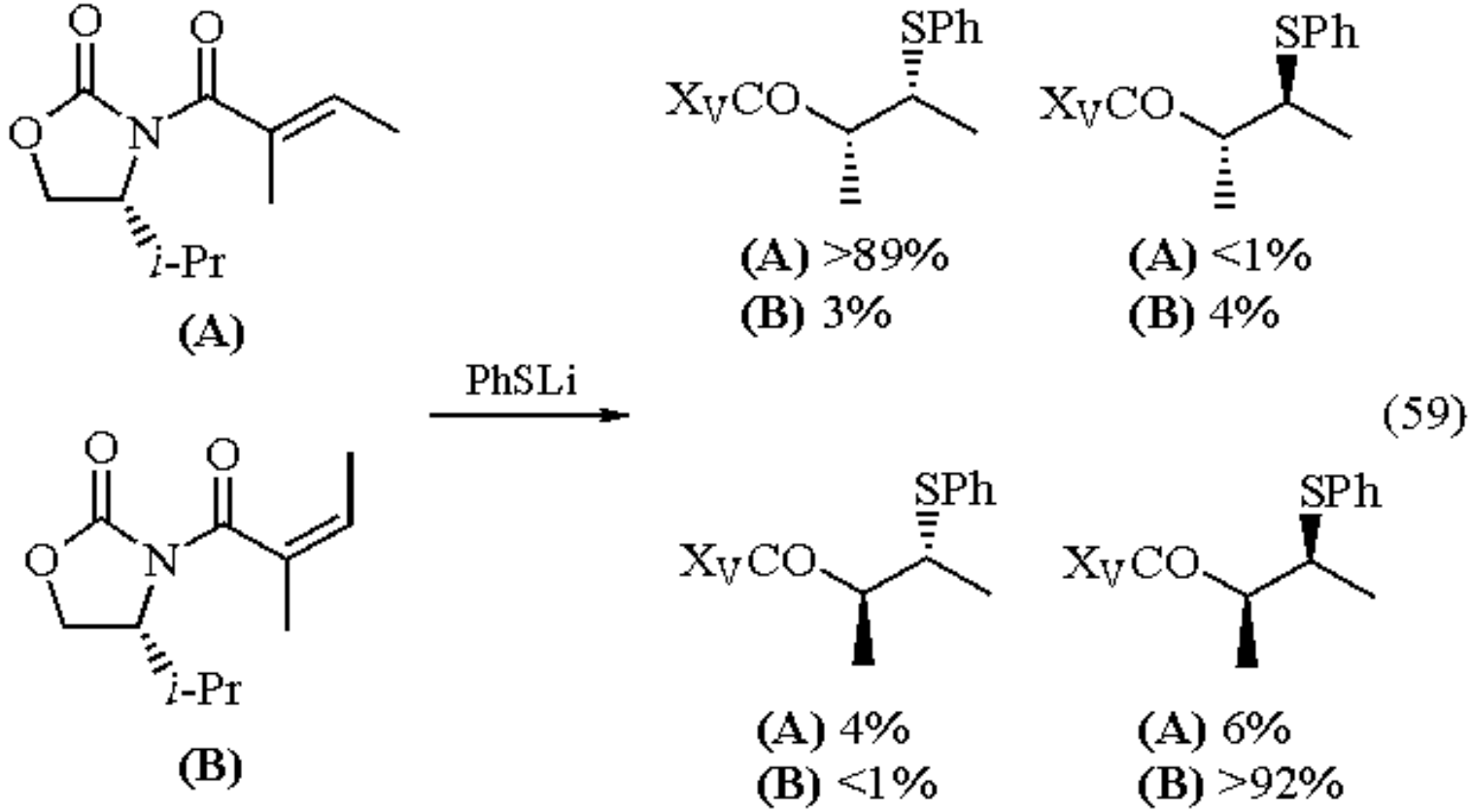

Dimethylaluminum chloride also catalyzes the ene reactions of chiral α,β-unsaturated imides with 1,1-disubstituted alkenes in moderate yields and selectivities.[104]

Oxazolidinone-Substituted Carbanions.

Oxazolidinone-substituted organostannanes readily undergo transmetalation with alkyllithium reagents to the organolithium derivatives which then can undergo nucleophilic addition reactions. *N*-Substituted oxazolidinones can act in this capacity as both a nitrogen source and source of chirality (eq 60). Although the α-stereoselection in these reactions is excellent, a greater variety of reactant alkylstannanes are available using chiral imidazolidinones in place of oxazolidinones.[39,40,42]

(S)-4-Benzyl-2-oxazolidinone

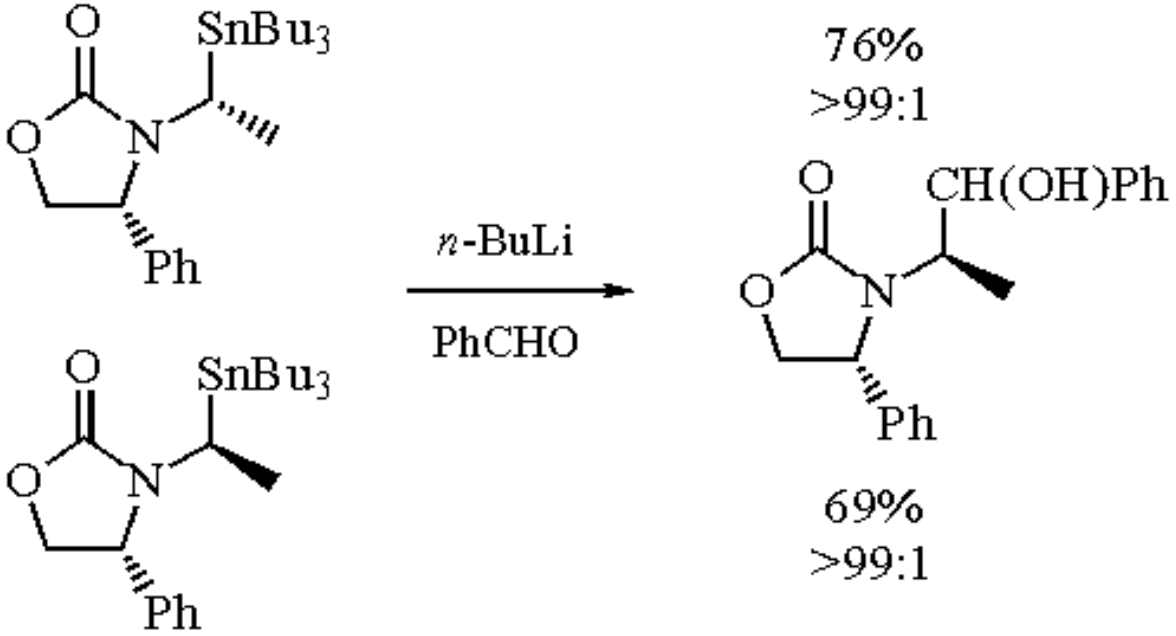

(60)

Synthesis of Cyclopropanes.

Chiral imide enolates which contain γ-halide substituents undergo intramolecular displacement to form cyclopropanes.[106] Halogenation of γ,δ-unsaturated acyl imides occurs at the γ-position in 85% yield with modest stereoinduction. The (*Z*) sodium enolates of these compounds then cyclize through an intramolecular double stereodifferentiating reaction (eq 61).

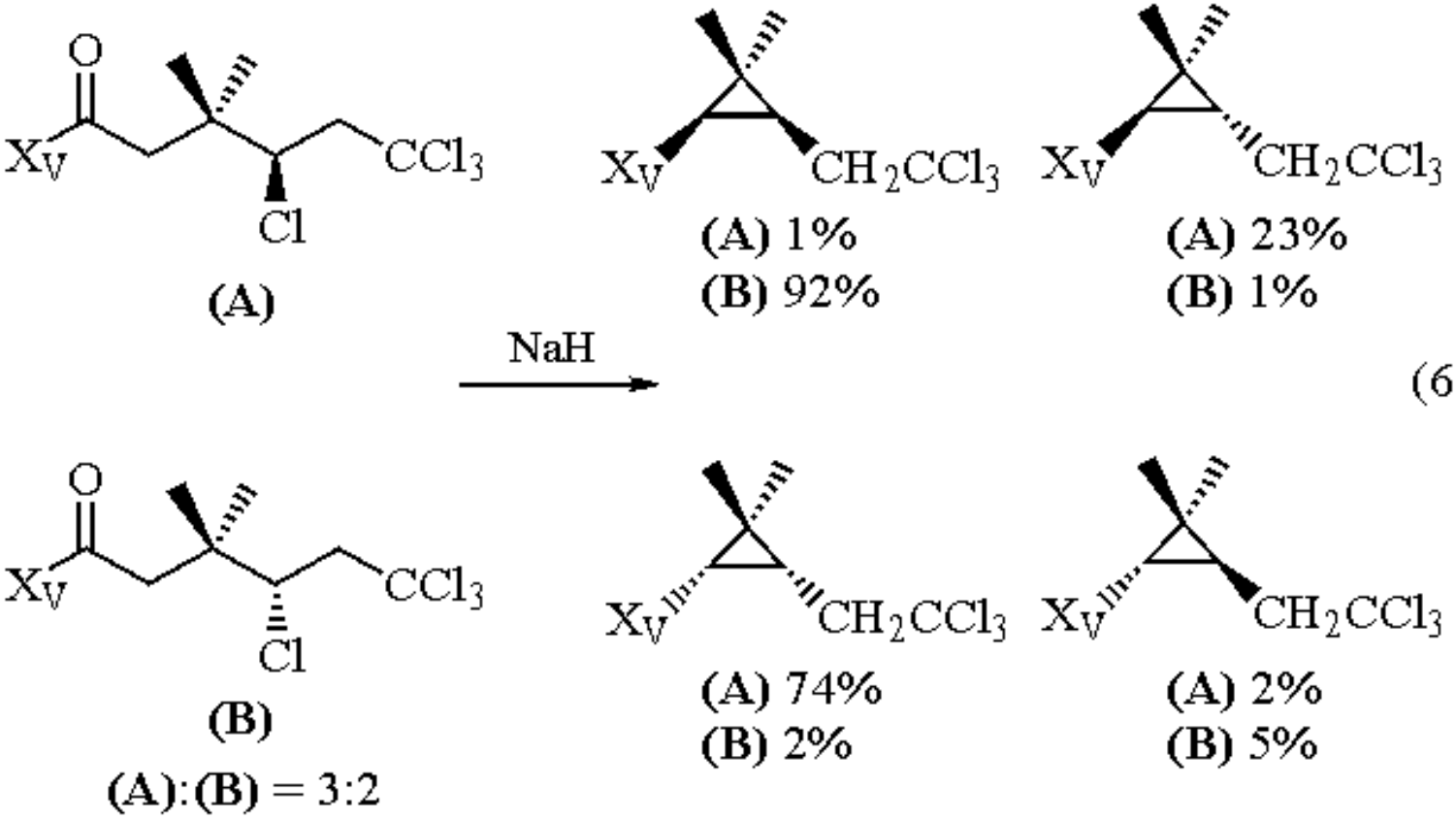

(61)

(S)-4-Benzyl-2-oxazolidinone

Stereoselective Cyclizations.

Sultams have been demonstrated to be superior sources of chirality in selected cases of iodolactonizations,[107] oxidative 1,5-diene cyclizations,[108] and Claisen-type rearrangements of β-acetoxyl substrates.[109]

Chiral Ligands.

Bidentate chelation of dirhodium(II) compounds by chiral oxazolidinones creates asymmetric sites on the metal, leading to induction in cyclopropanations and carbon-hydrogen insertion reactions. The oxazolidinones are less effective in this capacity than are the pyrrolidines.[110]

Removal of the Chiral Auxiliary.

In each of the following transformations, the oxazolidinone auxiliary is recovered in high yields (eq 62).

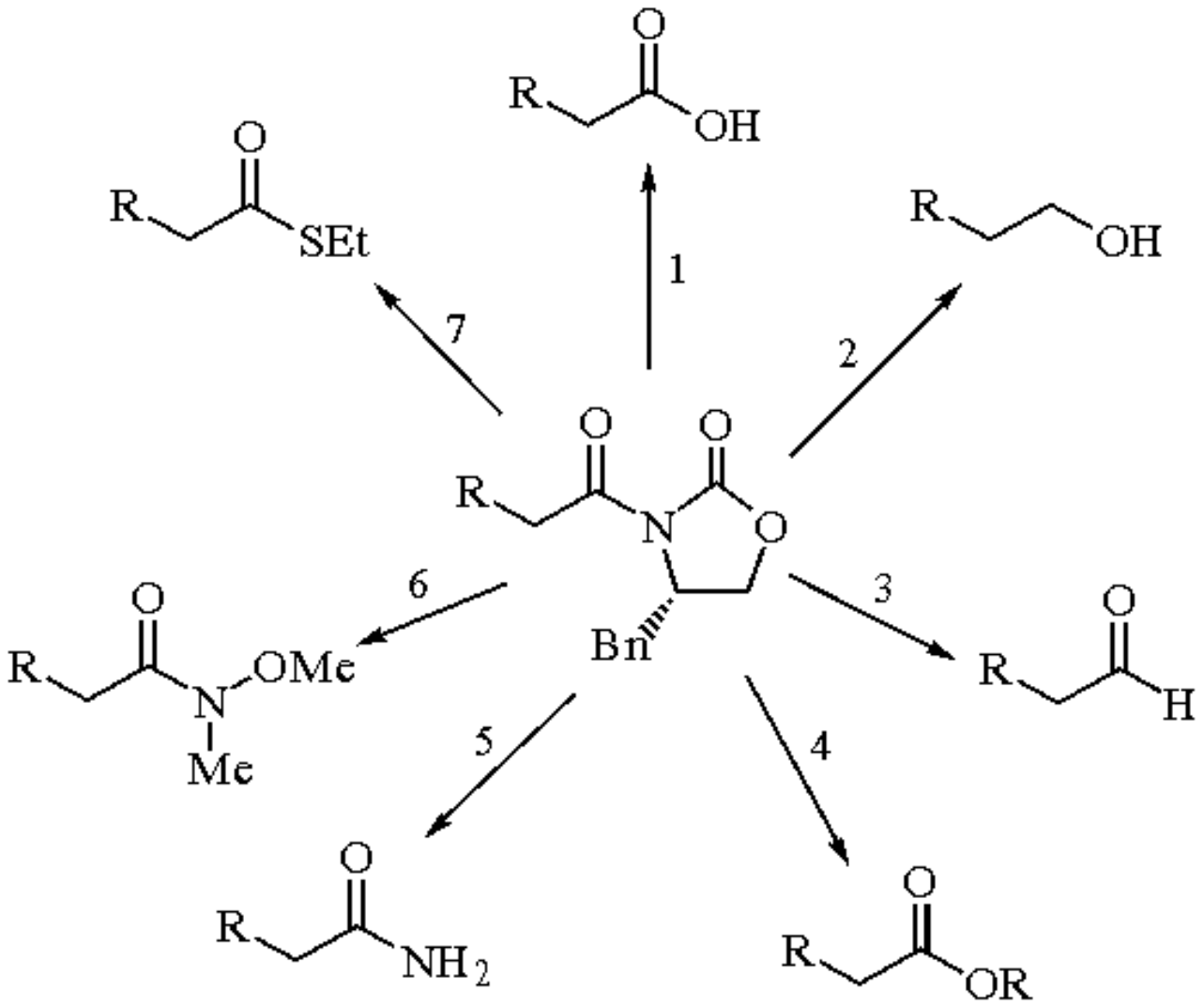

(62)

1a) KOH, MeOH; 1b) LiOH, MeOH or THF; 1c) LiOH, H_2O_2.
2a) $LiAlH_4$; 2b) $LiBH_4$; 2c) $LiBH_4$, H_2O; 2d) $LiBH_4$, MeOH;
2e) $LiAlH_4$, H_2 Lindlar cat., TFA; 2f) Bu_3B, HOAc, $LiBH_4$.

2e) $LiAlH_4$, H_2, Lindlar cat., TFA; 2f) Bu_3B, HOAc, $LiBH_4$.
3a) i) $LiBH_4$, H_2O; ii) DMSO, $(COCl)_2$, Et_3N;
3b) i) $Me_2AlN(OMe)Me$; ii) DIBAL;
3c) i) LiSEt; ii) Et_3SiH, Pd/C.
4a) LiOBn; 4b) $Ti(OBn)_4$; 4c) ROMgBr; 4d) NaOMe;
4e) $Ti(OEt)_4$.
5) i) N_2H_4; ii) isopentyl nitrite, NH_4Cl.
6) $Me_2AlN(OMe)Me$.
7) LiSEt.

Conversion to the Acid.

Hydroxide[6,111] and peroxide[112] conditions saponify acyl imides in excellent yields; however, with sterically hindered acyl groups endocyclic cleavage may predominate upon treatment with ***Lithium Hydroxide***. ***Lithium Hydroperoxide***, however, is highly selective for the exocyclic carbonyl moiety.

Conversion to the Alcohol.

Reduction of acyl imides to their corresponding alcohols is effected by a number of reagents, including ***Lithium Aluminum Hydride***,[1] ***Lithium Borohydride***,[1] $LiAlH_4/H_2$/Lindlar's cat./TFA,[113] $LiBH_4/H_2O/Et_2O$,[114] $LiBH_4$/MeOH/THF,[36] and Bu_3B/HOAc/$LiBH_4$.[77] Although the sole use of $LiAlH_4$ or $LiBH_4$ affords product often in low yields, the addition of an equivalent of H_2O or MeOH greatly enhances reaction efficiency. The MeOH/THF modification occasionally produces more consistent results. The last of the methods outlined above is effective in preventing retro-aldol cleavage in sensitive substrates such as crotyl or α-fluoro aldol adducts (eq 63).

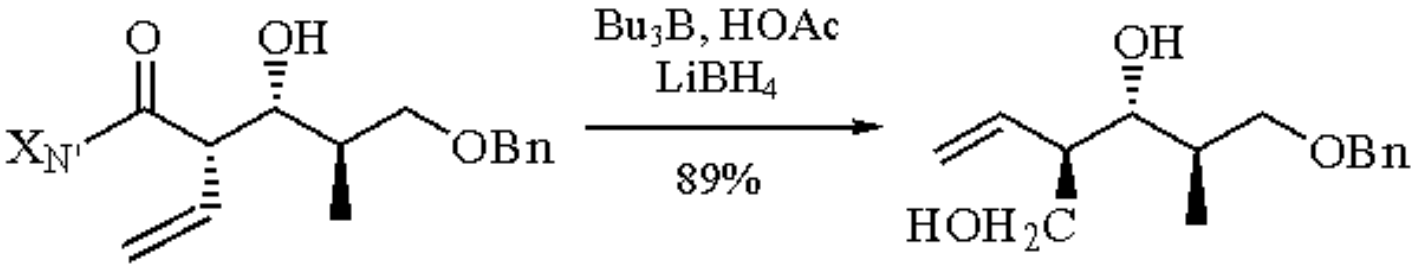

(63)

Conversion to the Aldehyde.

This transformation is accomplished through a two-step procedure. One such variant requires reduction to the alcohol (e.g. $LiAlH_4$, H_2O) and subsequent oxidation (e.g. Swern conditions).[36,85] Alternatively, Weinreb transamination[78,115-117] followed by ***Diisobutylaluminum Hydride***,[78] or conversion to the thioester (see below) and subsequent ***Triethylsilane*** reduction,[86] afford the desired aldehyde in excellent yields. Weinreb transamination proceeds with minimal endocyclic cleavage when there is a β-hydroxy moiety free for internal direction of the aluminum species.

(S)-4-Benzyl-2-oxazolidinone

Conversion to Esters.

Ester formation is readily achieved by conventional alcoholysis with alkoxides such as LiOBn,[1] NaOMe,[6] or ROMgBr (eq 64).[76,118] In hindered cases, endocyclic cleavage becomes competitive. Various titanium(IV) alkoxides have also been employed to effect this transformation.[4,119]

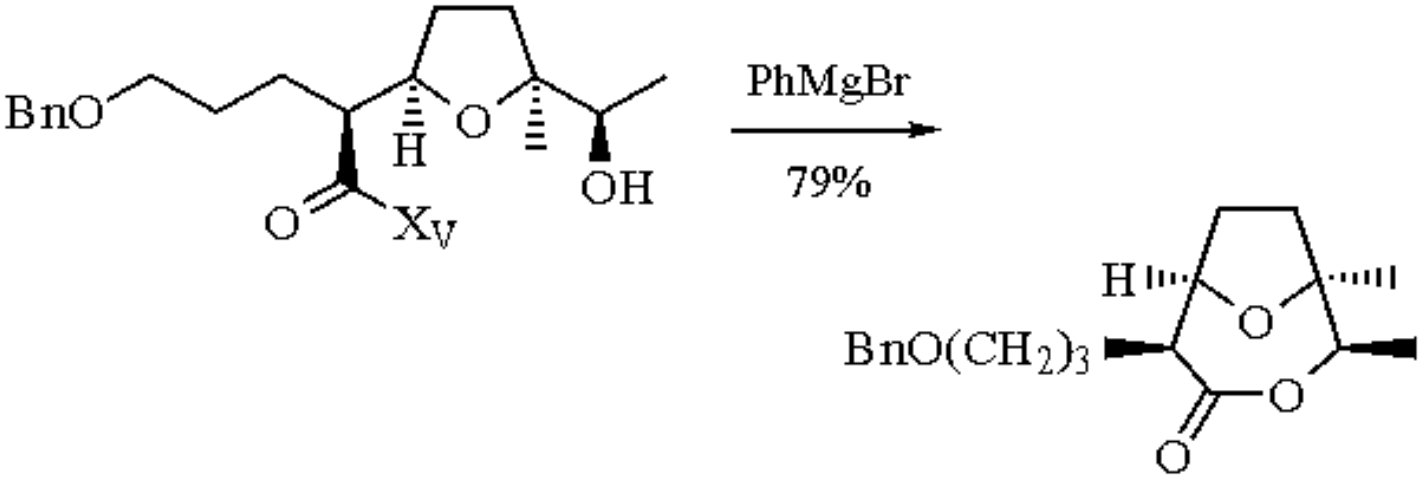

(64)

Conversion to Amides.

N-Acyloxazolidinones may be converted to the primary amide via the corresponding hydrazide.[120] Alternatively, trimethylaluminum/amine adducts form active transamination reagents,[36,117] providing amides of β-hydroxy acyloxazolidinones through intramolecular amine addition of the aminoaluminum species (eq 65).[105]

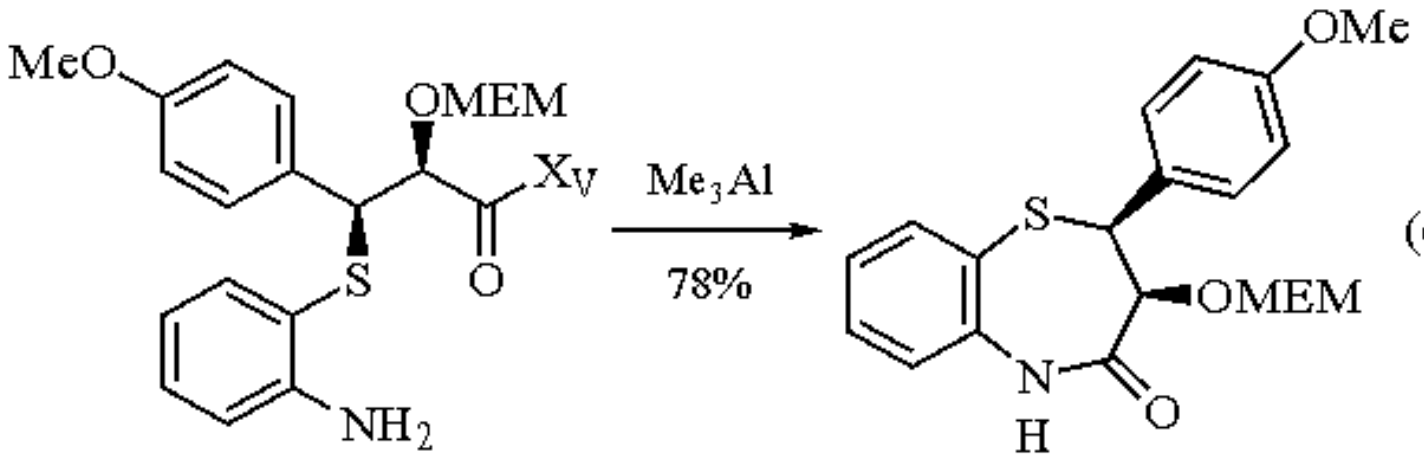

(65)

Conversion to Thioesters.

The transformation of *N*-acyl imides into thioesters with lithium thiolate reagents proceeds with exceptional selectivity for the *exo* carbonyl moiety even in exceptionally hindered cases.[121] A recent application of this reaction in a complex setting has been reported (eq 66).[68,97] This transformation is significant in that the normally reliable peroxide hydrolysis procedure proved to be nonselective. The recently reported high yield reduction of thioesters to aldehydes[86]

(S)-4-Benzyl-2-oxazolidinone

enhances the utility of these thioester intermediates.

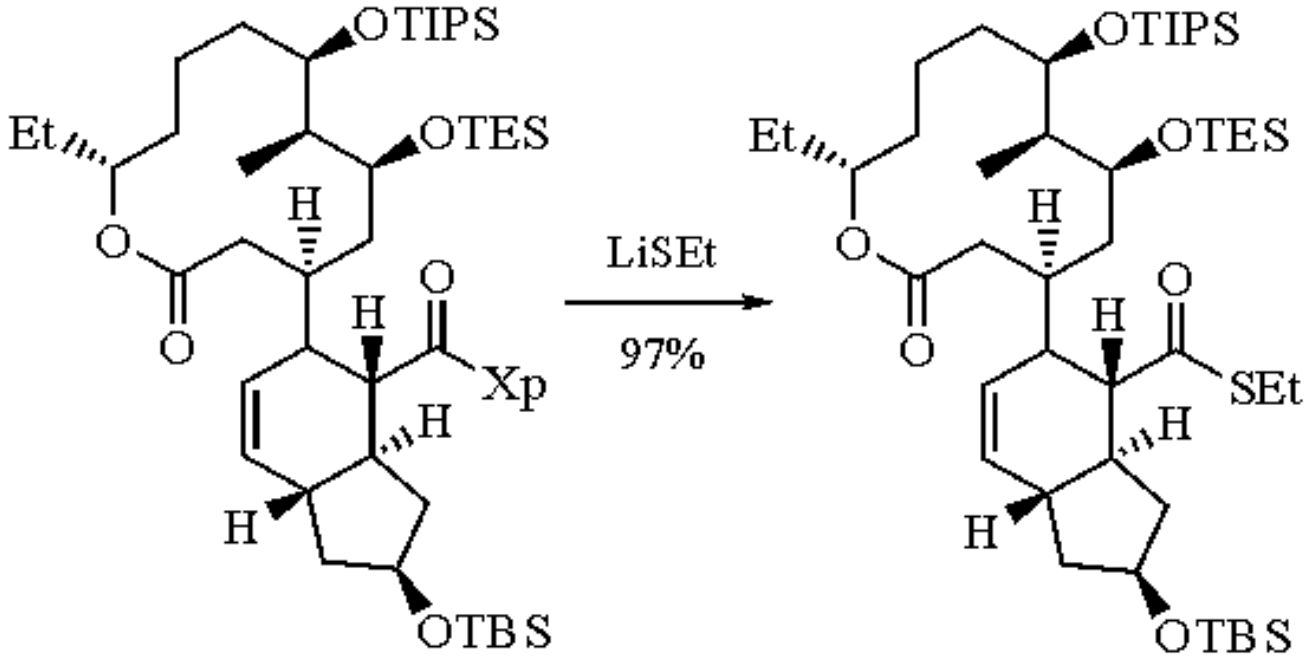

(66)

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David A. Evans &

3-(2-Benzyloxyacetyl)thiazolidine-2-thione[1]

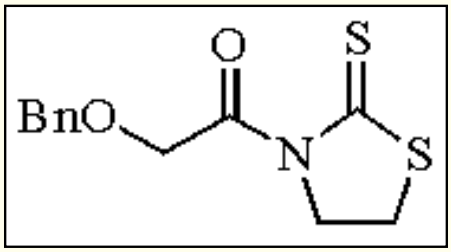

[92486-00-5] · $C_{12}H_{13}NO_2S_2$ · 3-(2-Benzyloxyacetyl)thiazolidine-2-thione · (MW 267.36)

(synthon for α-benzyloxy carboxylic esters, amides, or aldehydes;[2,3] enolate precursor for the diastereo- and enantioselective aldol reactions[4])

Physical Data: mp 81.0-82.0 °C.

Form Supplied in: slightly yellow crystals

Preparative Method: methyl 2-hydroxyacetate is converted to methyl 2-benzyloxyacetate (1, NaH; 2, BnBr, DMF, 0 °C to rt, 80%). The acetate is then treated with $LiOH.H_2O$ (1.25 equiv) in THF-H_2O at rt to give 2-benzyloxyacetic acid (99%). The acid is converted to the corresponding acid chloride (oxalyl chloride (2.7 equiv, 60 °C, 1.5 h), which is treated with thiazolidine-2-thione in the presence of triethylamine in dichloromethane to give the title reagent (**1**) (81% from the acid).

Handling, Storage, and Precautions: use in a fume hood.

Diastereo- and Enantioselective Aldol Reactions.

Optically active 1,2-diol units are widely distributed in natural products such as macrolides, polyethers, and carbohydrates, etc. The aldol reactions of the enolates derived from α-alkoxyacetic acid ester derivatives with aldehydes provide a useful way to construct 1,2-diols,[5] and several asymmetric reactions have been developed.

The tin(II) enolate prepared from (**1**), ***Tin(II) Trifluoromethanesulfonate***, and ***1-Ethylpiperidine*** reacts with aldehydes in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) to afford the *anti* aldol adducts in good yields with good selectivities (eq 1). Interestingly, *syn* selective reactions proceed in the absence of TMEDA. Optically active *anti* aldol adducts can be obtained in the presence of chiral diamine (**2**) instead of TMEDA.

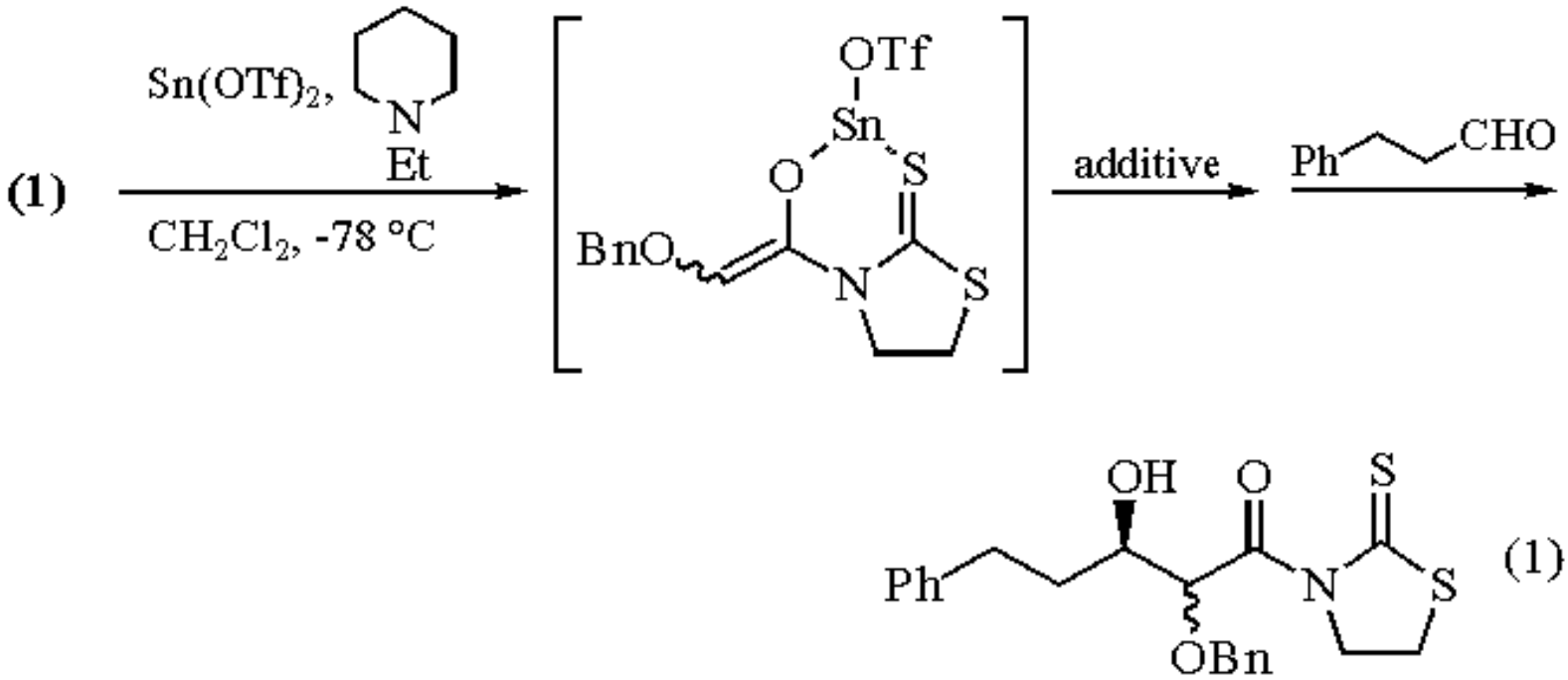

Additive	Yield (%)	*syn:anti*	ee (%) *(anti)*
none	62	74:26	-
TMEDA	70	15:85	-
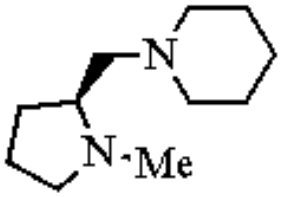 **(2)**	81	13:87	94

The tin(II) enolate of chiral oxazolidinone derivative (**3**) also works well in the presence of TMEDA to give the *anti* aldol in good yield.[6]

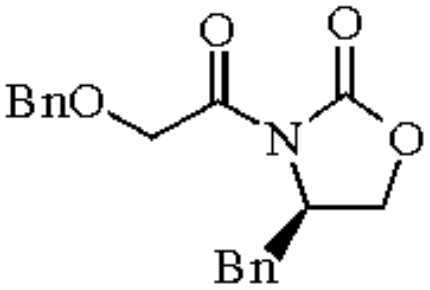

(3)

Optically active *syn* and *anti* diol units can be easily prepared by the asymmetric aldol reaction of aldehydes with silyl

enolates (**4**) and (**5**), respectively, under the influence of chiral tin(II) Lewis acid (**6**).[7,8] Diastereofacial selectivities are controlled simply by choosing the protective group of the α-alkoxy part of ketene silyl acetals (eqs 2 and 3).

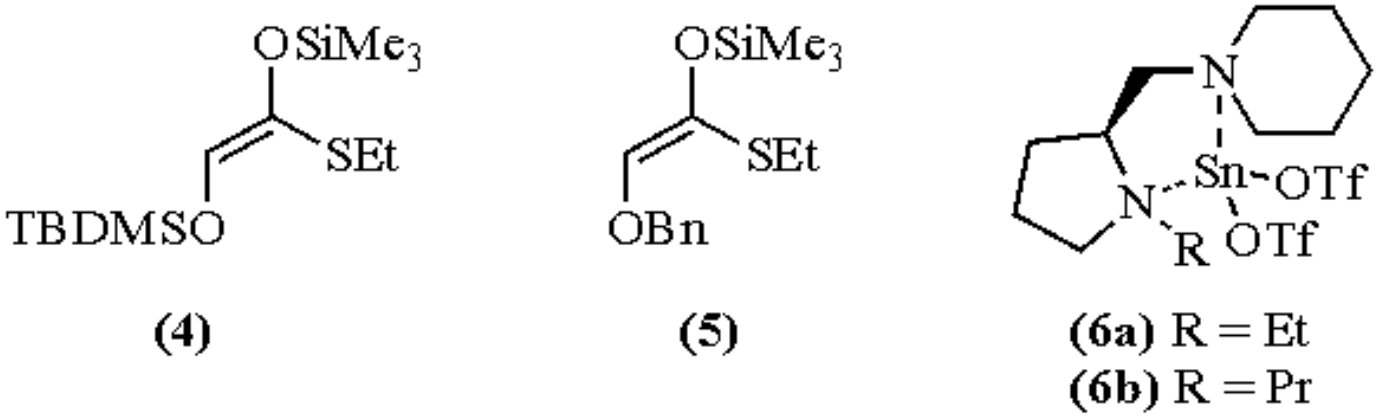

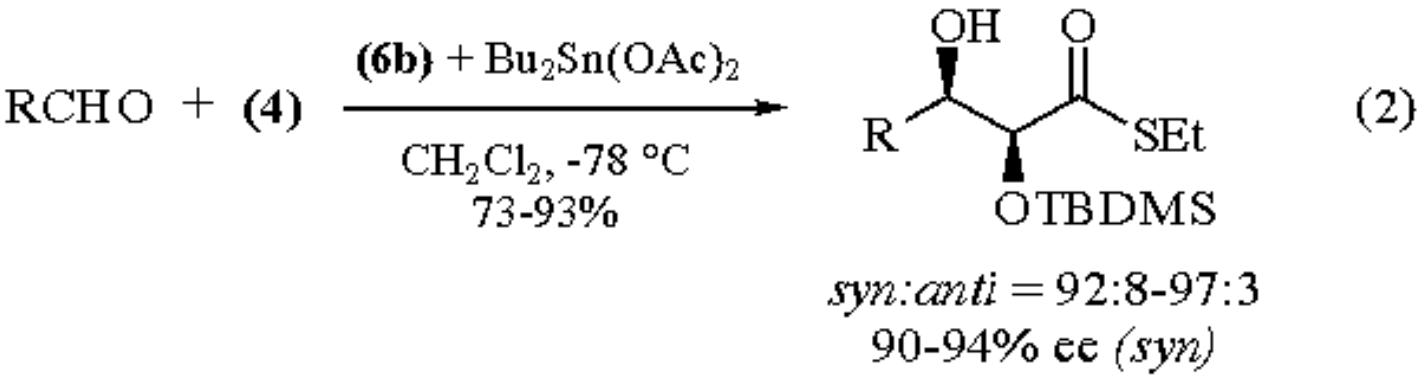

(2)

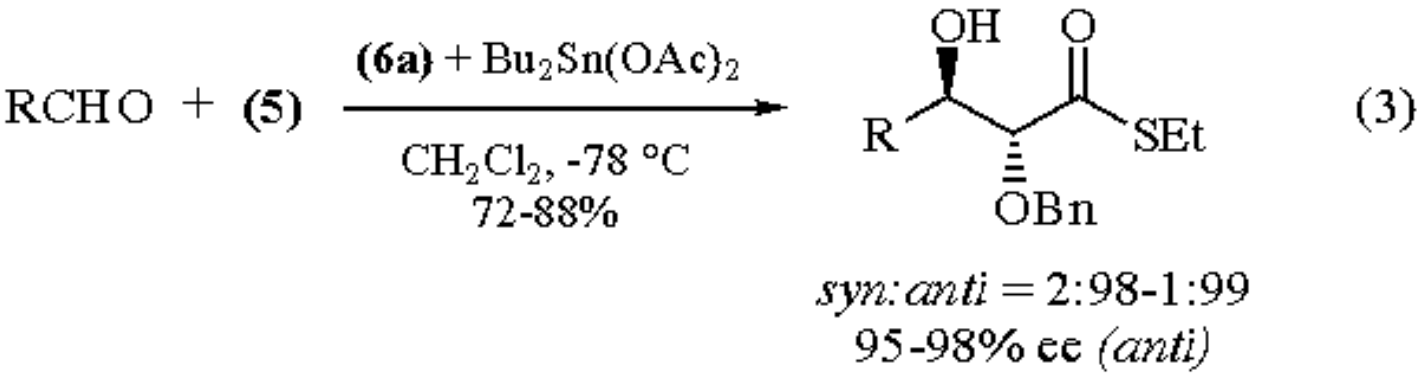

(3)

While stoichiometric amounts of chiral sources are required in the reaction of eqs 2 and 3, the truly catalytic asymmetric version is realized by using a novel catalyst system consisting of tin(II) triflate, chiral diamine (**7**), and tin(II) oxide (eq 4).[9]

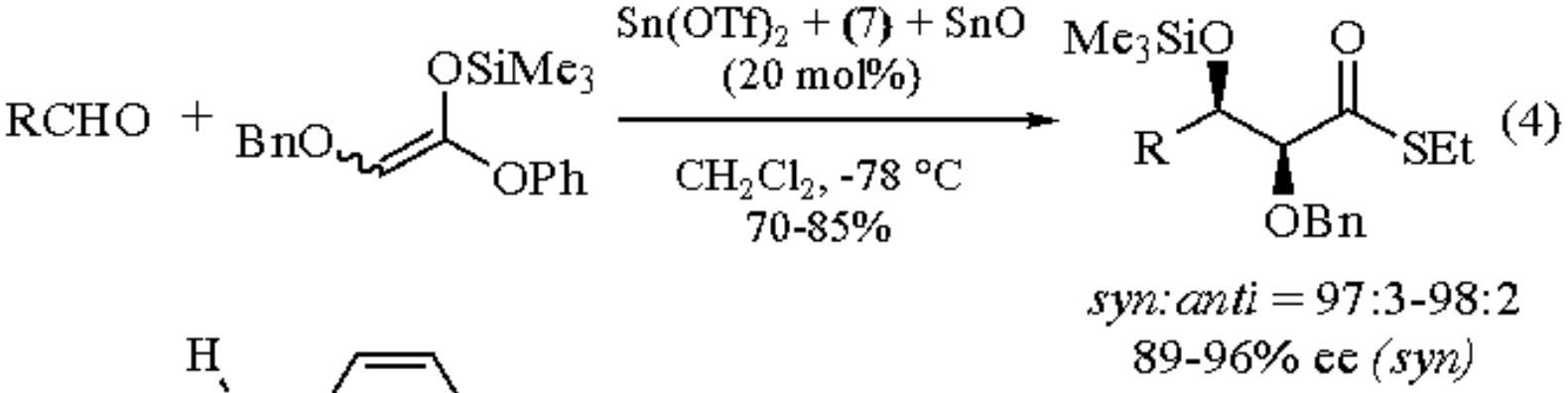

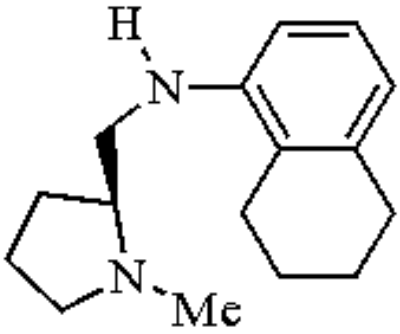

(7)

Related Reagents.

Ethyl Mandelate; ***Phenoxyacetic Acid***.

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Benzyloxycarbonylhydrazine

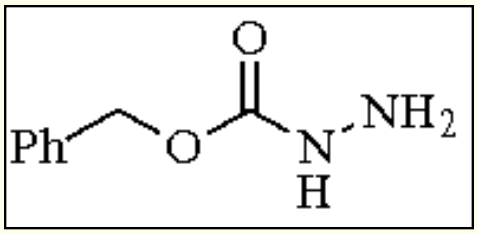

(base)

[5331-43-1] · $C_8H_{10}N_2O_2$ · Benzyloxycarbonylhydrazine · (MW 166.18) (.HCl)

[2540-62-7]

(preparation of hydrazides of amino acids for use in peptide synthesis[1])

Alternate Names: carbobenzoxyhydrazine; benzyl hydrazinocarboxylate.

Physical Data: mp 67-69 °C; hydrochloride salt, mp 170-170.5 °C

Preparative Method: prepared by reaction between ***Hydrazine*** and dibenzyl carbonate.[1]

Purification: recrystallization from ethyl acetate/hexane, or from ether.

Peptide Synthesis.

Benzyloxycarbonylhydrazine (**1**) has found use in the preparation of the hydrazides of amino acids and peptides.[1] (**1**) reacts with *N*-protected (phthaloyl or Boc) amino acid chlorides to give the benzyloxycarbonylhydrazide derivatives (**2**) (eq 1).[1] *N*-Deprotection (eq 2) leaves the N-terminus available for coupling to a suitable activated carboxylic acid derivative, giving (**4**) (eq 3); this stepwise elongation procedure may be continued until the desired peptide sequence is obtained. Hydrogenation then affords the peptide hydrazide (**5**) (eq 4). Preparation by this method, where the protected hydrazide is introduced early, at the amino acid stage, avoids the usual need to expose a complex or sensitive peptide ester to hydrazine. Indeed, the hydrazides of *N*-phthaloyl amino acids or peptides were previously inaccessible since hydrazine effects removal of the phthaloyl group rather than reacting with the ester. The hydrazide (**5**) can next be converted to the acyl azide (**6**) (eq 5) in readiness for coupling with an amino component.

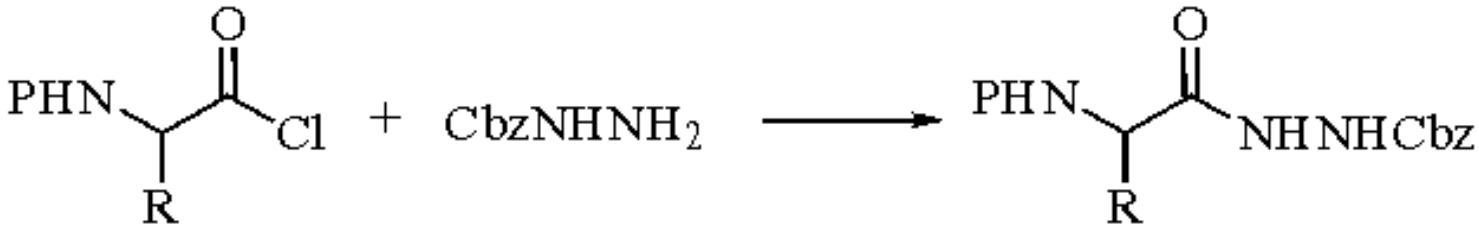

(1)

P = phthaloyl or Boc **(1)** **(2)**

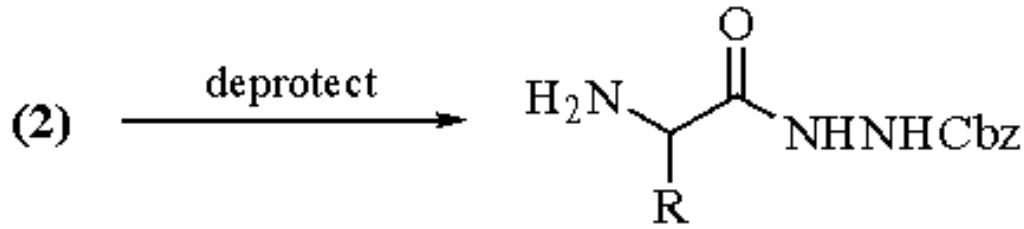

(2)

(3)

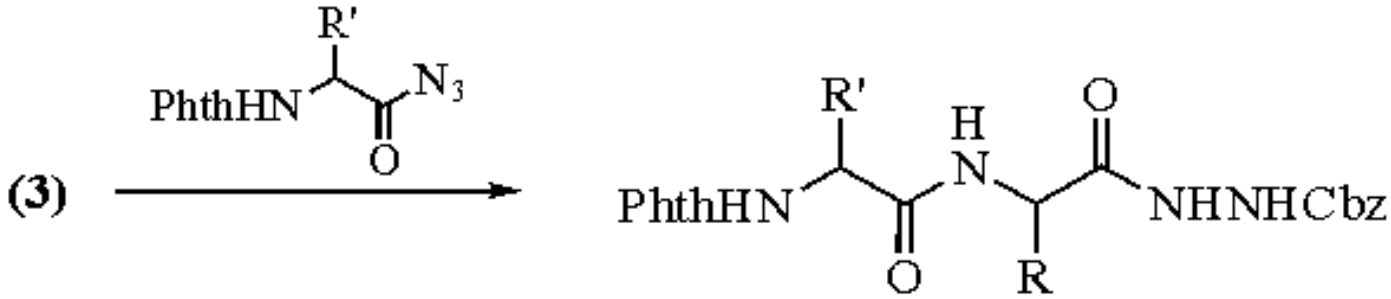

(3)

(4)

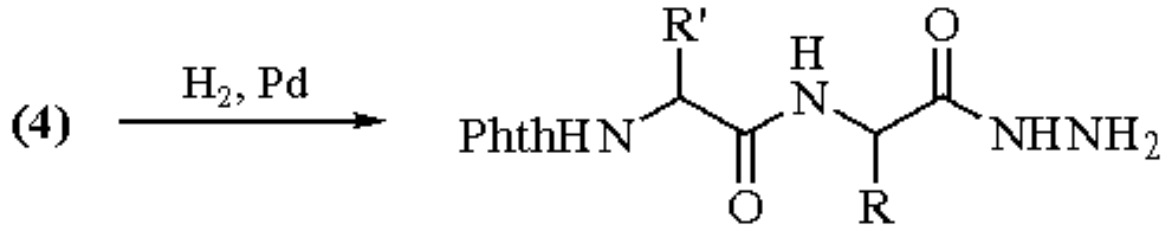

(4)

(5)

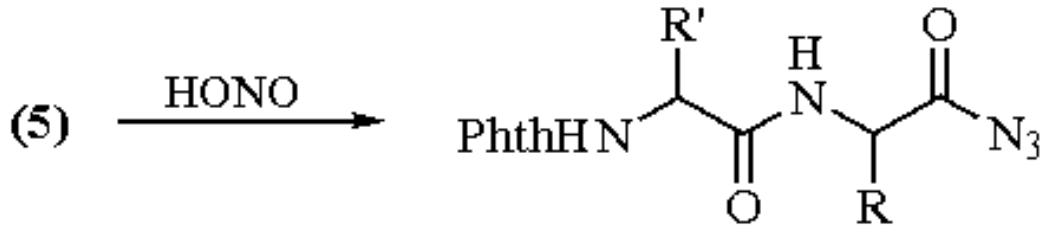

(5)

(6)

N-Benzyloxycarbonyl-L-serine β-Lactone

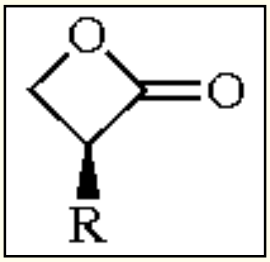

(R = NH-Cbz) (**1**)

[26054-60-4] · $C_{11}H_{11}NO_4$ · *N*-Benzyloxycarbonyl-L-serine β-Lactone · (MW 221.21) (R = NH-Boc) (**2**)

[98541-64-1] · $C_8H_{13}NO_4$ · *N-t*-Butoxycarbonyl-L-serine β-Lactone · (MW 187.20) (R = NH_3^+ OTs^-) (**3**)

[112839-95-9] · $C_{10}H_{13}NO_5S$ · L-Serine β-Lactone Tosylate · (MW 259.28)

(reagent for the synthesis of β-substituted alanines[1,2])

Alternate Name: (*S*)-3-(*N*-benzyloxycarbonyl)aminooxetan-2-one.

Physical Data: (**1**): mp 133-134 °C, [α]25D = -26.8° (*c* = 1, MeCN); (**2**): mp 119.5-120.5 °C, [α]25D = -26.2° (*c* = 1, MeCN, 24 °C); (**3**): mp 133-135 °C (darkening), dec. 173 °C, [α]25D = -15.9° (*c* = 2.2, DMF).

Solubility: (**1**) and (**2**) sol most organic solvents; (**3**) sol polar aprotic organic solvents and H_2O.

Form Supplied in: white solids.

Preparative Methods: (**1**) is easily made by cyclization of commercially available *N*-Cbz-L-serine (**4**) under modified Mitsunobu conditions, using a preformed complex of dimethyl azodicarboxylate (DMAD) and ***Triphenylphosphine*** (eq 1).[3] The reaction proceeds via hydroxy group activation, and labeling studies show that the 3-hydroxy group is lost in a 4-*exo-tet* cyclization mechanism.[5] The β-lactone must be separated quickly from the reaction mixture,[3] and a slight excess of DMAD improves the yield because unreacted triphenylphosphine can cause polymerization.[6] The Boc (*t*-

butoxycarbonyl) analog (**2**) is prepared similarly, and the *p*-toluenesulfonate (tosylate) salt (**3**) is synthesized from (**2**) by acidic cleavage.[4]

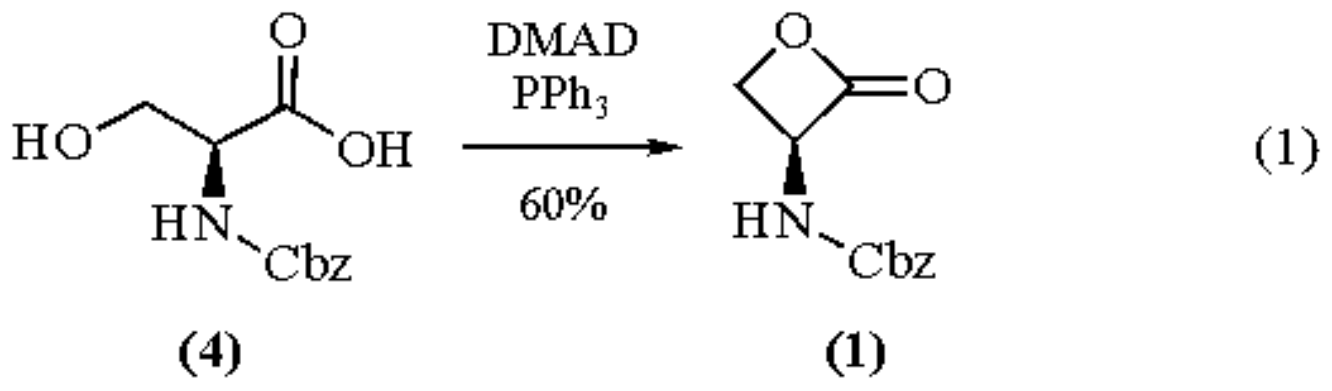

Purification: see Pansare et al.[3,4]

Handling, Storage, and Precautions: the β-lactones (**1**)-(**3**) are stable for many months at 4 °C in dry form. Neutral or slightly acidic solutions of (**1**) and (**2**) are stable for at least 1 day; (**3**) must be used in situ; basic and strongly acidic solutions rapidly decompose these β-lactones. They should be handled in a fume hood.

Ring-Opening Reactions.

N-Cbz-β-lactone (**1**) is a very useful tool for the synthesis of optically active α-amino acids. Unlike other well established procedures,[2] this method does not generate the chiral center at the α-carbon but rather homologates optically pure serine derivatives at the β-carbon. Although this review is limited to the use of *N*-Cbz-L-serine β-lactone to generate L-amino acids in most applications, the corresponding D-serine β-lactones are available analogously from inexpensive D-serine derivatives. Ring-opening of β-lactones can occur in two different modes. Soft nucleophiles (e.g. carboxylate, thiolate) usually attack the β-carbon, whereas hard nucleophiles (e.g. hydroxide, methoxide, organolithium compounds) tend to target the carbonyl group. In certain cases, altering the conditions (e.g. N-substituent, solvent) directs the mode of addition. For example, ammonia in THF at 0 °C attacks the β-position of (**1**) to give the protected α,β-diaminopropanoic acid (**6**), whereas the same nucleophile in acetonitrile reacts with acyl oxygen cleavage to produce serine amide (**5**) (eq 2).[7] However, acetonitrile enhances β-attack by ammonia in the case of the *N*-Boc lactone (**2**).[8]

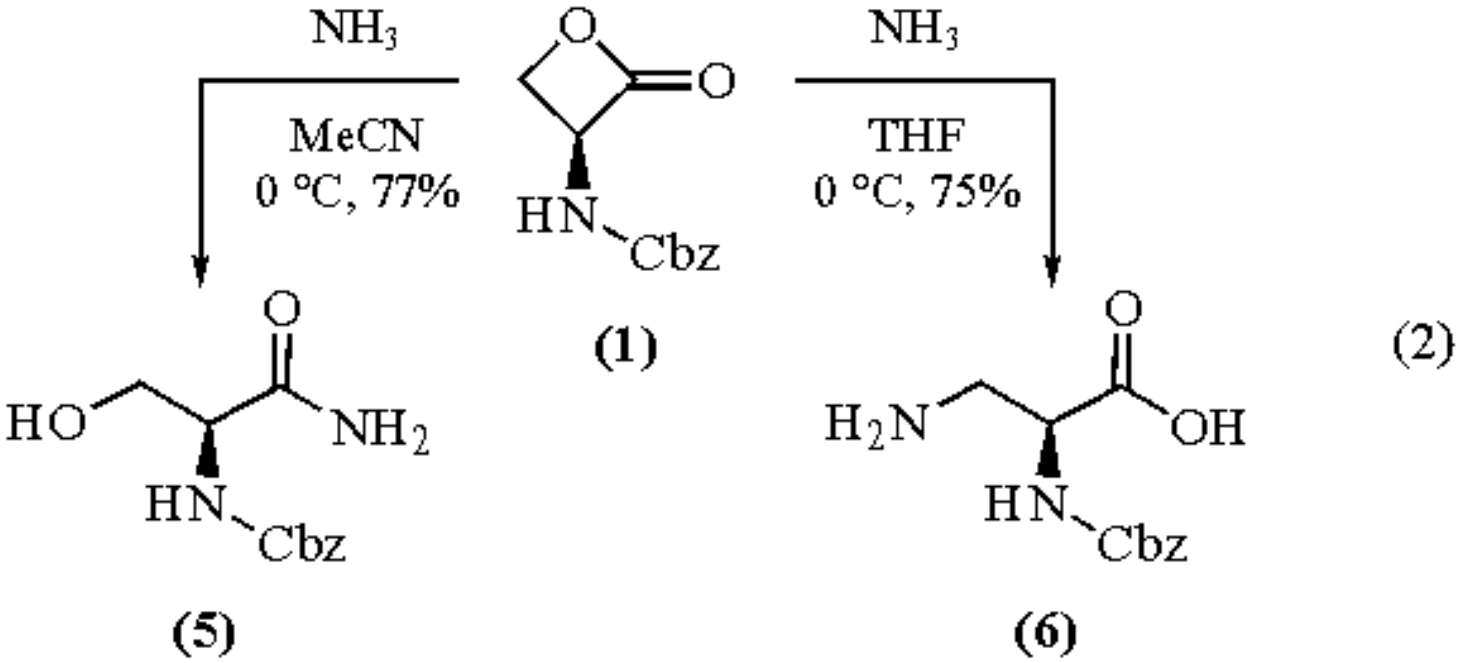

A variety of heteroatom nucleophiles have proven suitable for the desired ring-opening at the β-position (eq 3), such as Nu^- = NH_3, NMe_3, OAc^-, SBn^-, Cl^-, Br^-, pyrazole, and thiourea (S-attack).[7] Sulfur nucleophiles appear to require protic solvent for good results in this process.

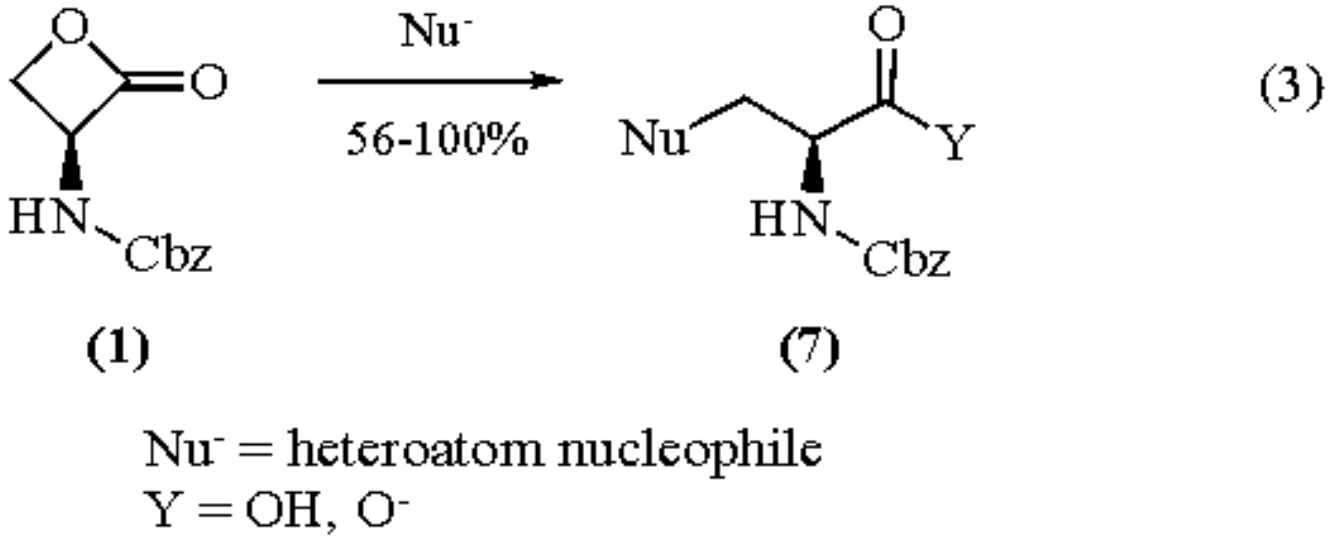

Carbon-carbon bond formation can be achieved with copper-catalyzed Grignard reagents (eq 4), or less cleanly with organolithium-derived cuprate reagents (R_2CuLi or $R_2Cu(CN)Li_2$).[9] Thus Cbz-serine β-lactones behave like chiral enone equivalents, with 1,4-attack of the carbanion at the β-position leading to amino acids and 1,2-attack leading to ketones or even alcohols. Hard organometallics, such as copper-free organolithium or Grignard reagents, react primarily at the carbonyl group, but the organocuprates add at the β-carbon to produce the desired amino acids (**8**) in good to moderate yields. The magnesium plays a key role in this reaction in terms of regioselectivity, optical purity (>99.4 % ee), and yield. The lithium cuprate reagents show less regioselectivity and in certain cases (e.g. R = Ph) can lead to some epimerization at the α-carbon. Temperature control (-23 °C is often ideal) is critical in reactions of (**1**) with organometallic reagents.

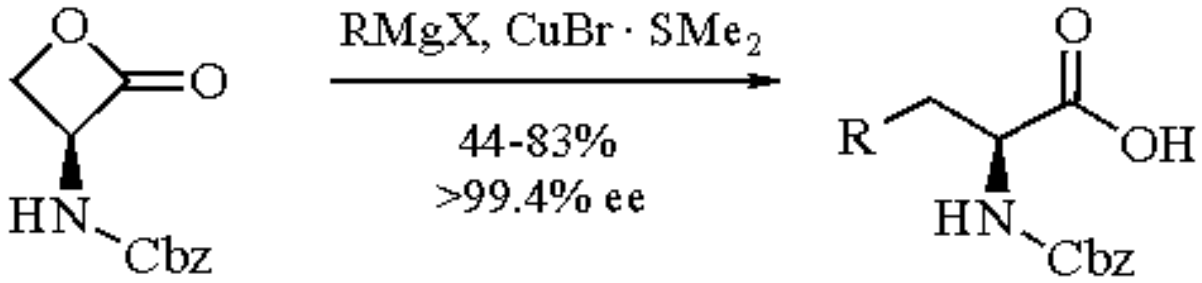

(4)

(1) R = alkyl, vinyl, Ph (8)

Acyl-oxygen cleavage of the serine β-lactone, although not desired in most cases, has been employed for the synthesis of (*S*)-2-methyl-4-benzyloxycarbonylaminopyrazolidine (**10**). Methylhydrazine in dichloromethane adds regioselectively to the carbonyl group of (**1**) to afford the hydrazide (**9**), which after several steps affords (**10**) (eq 5).[10]

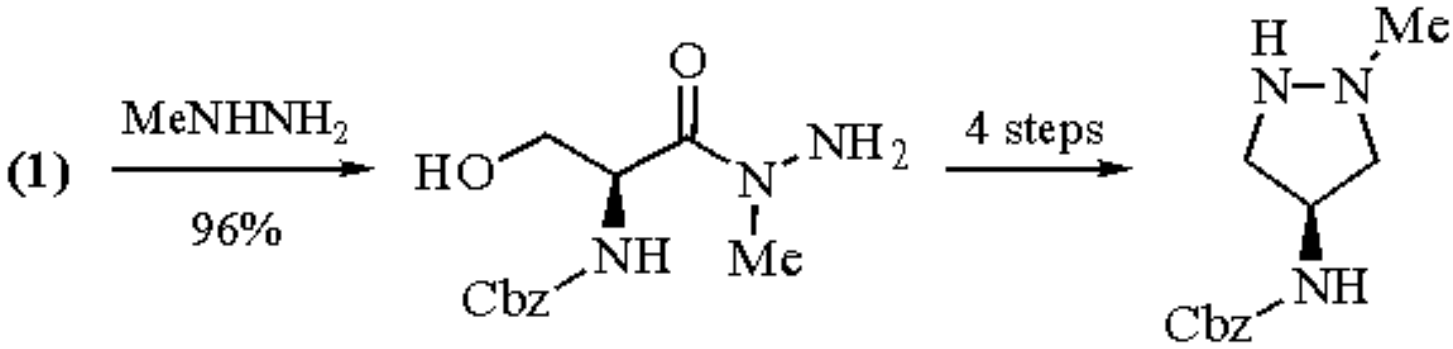

(5)

(9) (10)

The anionic polymerization of *N*-benzyloxycarbonyl-L-serine β-lactone leads to poly(*N*-acyl-L-serine ester) (M_w = ca. 40 000), from which poly(L-serine ester hydrochloride) can be obtained by hydrogenation.[11]

Other 3-Aminooxetanones.

Various other α-amino-β-lactones have been prepared and used in amino acid syntheses. The Boc derivative (**2**),[6-9,12-14] the tosylate salt (**3**),[4,15] and the recently published *N*-Fmoc-L-serine β-lactone[16] generally exhibit similar reactivity towards nucleophiles (e.g. phosphites[14,16]), and the choice of β-lactone can often be determined by requirements of subsequent synthetic steps. However, some differences have been observed. In addition to the ammonia reaction described above,[7,8] the condensation of β-mercaptoethylamine (**11**) with (**1**) results in nucleophilic attack by nitrogen leading to (**12**), whereas the same nucleophile attacks the tosylate salt (**3**) with reverse chemoselectivity giving the corresponding amino acid (**13**) (eq 6).[7,15] The salt (**3**) has the advantage of producing free amino acids in cases where deprotection of nitrogen may affect the β-substituent.

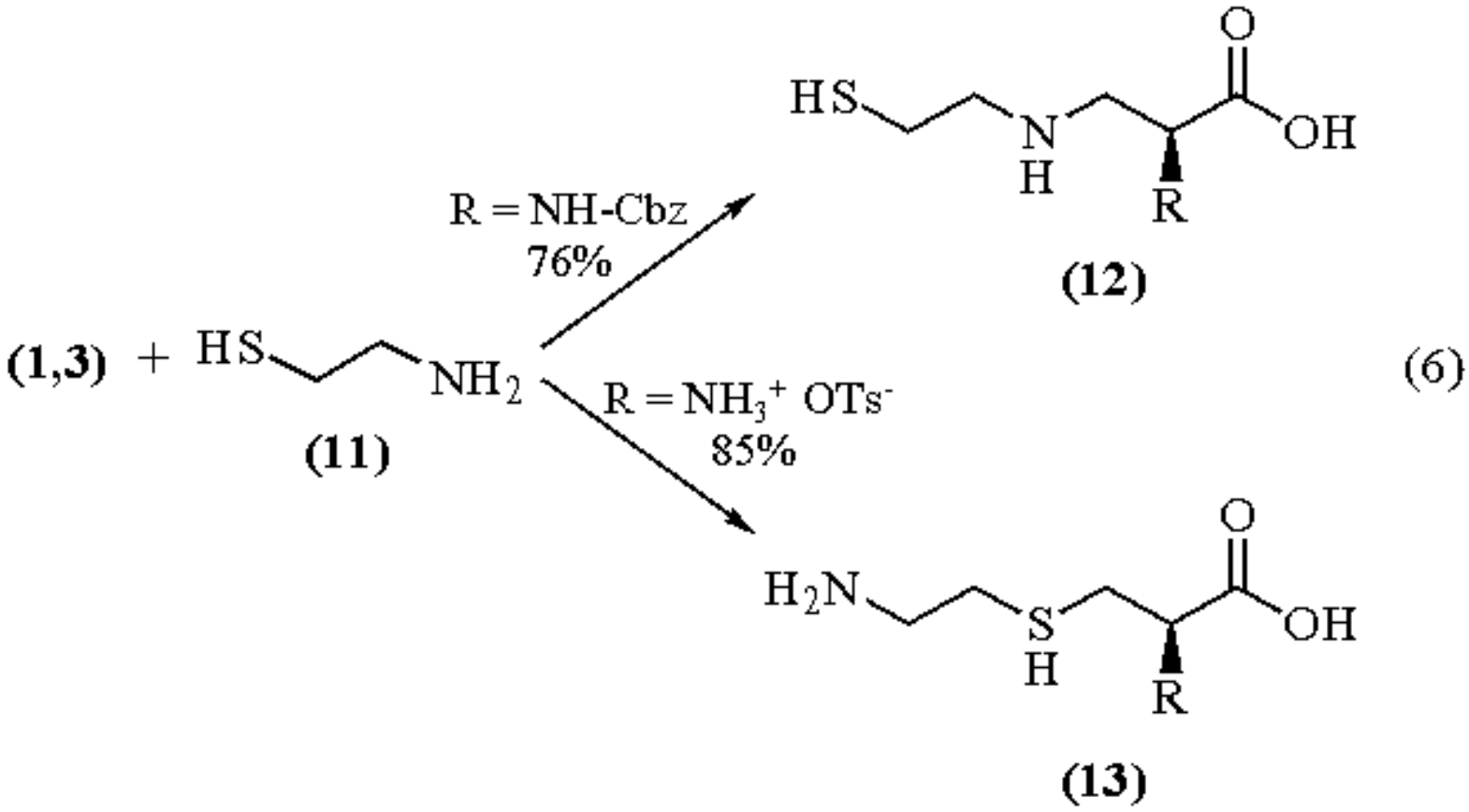

The L-threonine β-lactone (**14**), in contrast to the serine β-lactones, has been synthesized by carboxyl group activation (4-*exo*-*trig*).[17] Initial experiments have shown that ring opening of such β-substituted lactones tends to proceed by attack at the carbonyl except with certain nucleophiles (e.g. thiourea, halides). However, correct choice of N-protecting group allows the synthesis of a range of other β-substituted α-amino-β-lactones,[17b,c] such as the antiobiotic obaflourin (**15**).[18]

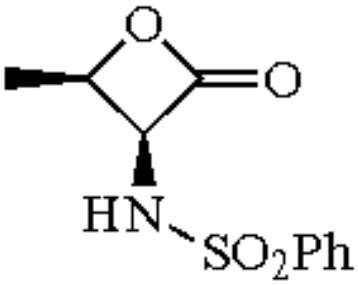

(14)

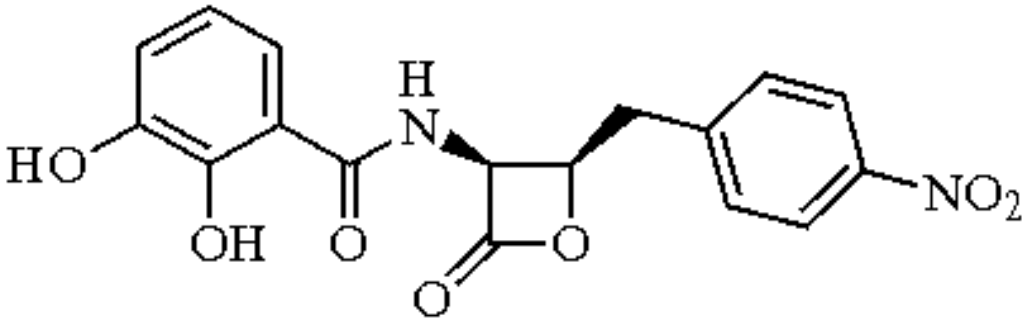

(15)

In summary, ring opening of serine-β-lactones is an attractive method for generating optically pure β-substituted alanines; the synthesis usually occurs with little or no epimerization.

Related Reagents.

Diketene; β-***Ethynyl***-β-***propiolactone***; β-***Methyl***-β-***propiolactone***; β-***Propiolactone***.

---

1. For a review on β-lactone chemistry, see: Pommier, A.; Pons, J.-M. *S* **1993**, 441.
2. For a review on amino acid synthesis, see: Williams, R. M. *Synthesis of Optically Active* α-*Amino Acids*; Pergamon: Oxford, 1989.
3. Pansare, S. V.; Huyer, G.; Arnold, L. D.; Vederas, J. C. *OS* **1991**, *70*, 1.
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5. Ramer, S. E.; Moore, R. N.; Vederas, J. C. *CJC* **1986**, *64*, 706.
6. Lodwig, S. N.; Unkefer, C. J. *J. Labelled Compds. Radiopharm.* **1991**, *31*, 95.
7. Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *JACS* **1985**, *107*, 7105. Ratemi, E. S.; Vederas, J. C. *TL* **1994**, *35*, 7605.
8. Kucharczyk, N.; Badet, B.; Le Goffic, F. *SC* **1989**, *19*, 1603.
9. Arnold, L. D.; Drover, J. C. G.; Vederas, J. C. *JACS* **1987**, *109*, 4649.
10. Kim, K. S.; Ryan, P. C. *H* **1990**, *31*, 79.
11. (a) Zhou, Q.-X.; Kohn, J. *Macromol.* **1990**, *23*, 3399. (b) Gelbin, M. E.; Kohn, J. *JACS* **1992**, *114*, 3962.
12. Soucy, F.; Wernic, D.; Beaulieu, P. *JCS(P1)* **1991**, 2885.
13. Rosenberg, S. H.; Spina, K. P.; Woods, K. W.; Polakowski, J.; Martin, D. L.; Yao, Z.; Stein, H. H.; Cohen, J.; Barlow, J. L.; Egan, D. A.; Tricarico, K. A.; Baker, W. R.; Kleinert, H. D. *JMC* **1993**, *36*, 449.
14. Smith, E. C. R.; McQuaid, L. A.; Paschal, J. W.; DeHoniesto, J. *JOC* **1990**, *55*, 4472.
15. Arnold, L. D.; May, R. G.; Vederas, J. C. *JACS* **1988**, *110*, 2237.
16. Hutchinson, J. P. E.; Parkes, K. E. B. *TL* **1992**, *33*, 7065.
17. (a) Pansare, S. V.; Vederas, J. C. *JOC* **1989**, *54*, 2311; (b) Pu, Y.; Martin, F. M.; Vederas, J. C. *JOC* **1991**, *56*, 1280. (c) Rao, M. N.; Holkar, A. G.; Ayyangar, N. R. *CC* **1991**, 1007.
18. Lowe, C.; Pu, Y.; Vederas, J. C. *JOC* **1992**, *57*, 10. Pu, Y.; Lowe, C.; Sailer, M.; Vederas, J. C. *JOC* **1994**, *59*, 3642.

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2-[2-[(Benzyloxy)ethyl]-6,6-dimethylbicyclo[3.3.1]-3-nonyl]-9-borabicyclo[3.3.1]nonane

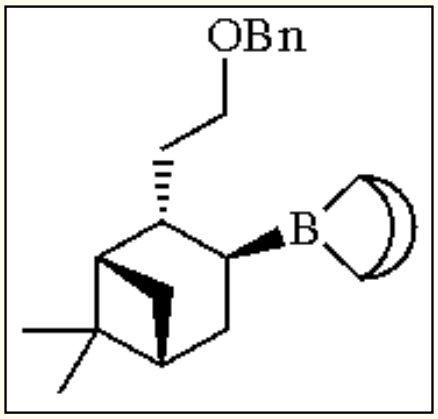

[81971-15-5] · $C_{26}H_{39}B$ · 2-[2-[(Benzyloxy)ethyl]-6,6-dimethylbicyclo[3.3.1]-3-nonyl]-9-borabicyclo[3.3.1]nonane · (MW 378.41)

(asymmetric reducing agent[1])

Alternate Name: NB-Enantrane®.

Solubility: sol most organic solvents.

Form Supplied in: 0.5M solution in THF; commercially available.

Preparative Methods: NB-Enantrane[2] may be prepared by hydroboration of nopol benzyl ether (commercially available, or from nopol and benzyl bromide[1a]) with ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) (eq 1).

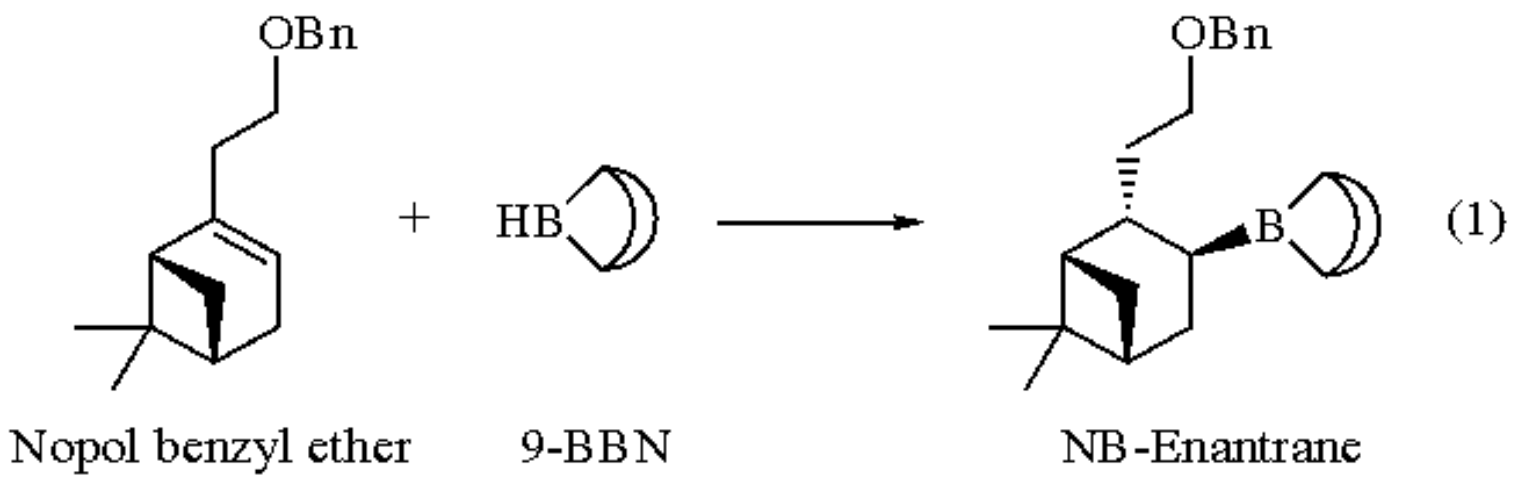

Handling, Storage, and Precautions: NB-Enantrane is an air-sensitive reagent and must be handled under an inert atmosphere. Use in a fume hood.

Asymmetric Reductions.

NB-Enantrane is an analog of ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane*** (Alpine-Borane[1b]). Since the absolute configuration of nopol is the opposite of (+)-α-pinene, the reagent provides the opposite mode of asymmetric induction. The reagent provides higher asymmetric induction than Alpine-Borane for cases where the two groups flanking the ketone are relatively small, such as methyl or ethyl alkynyl ketones (eq 2).

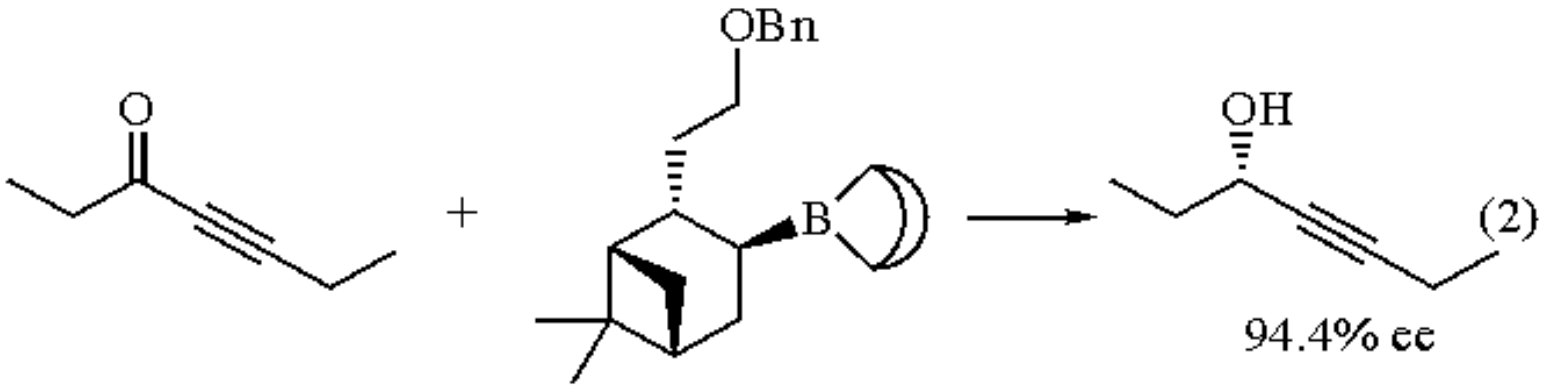

Reduction occurs via transfer of the tertiary hydride, which is β to the boron. Since this is the hydride added during the hydroboration process, labeled material may be obtained by using labeled 9-BBN in the initial preparation. The absolute configuration of the product may be predicted by using a simple six-membered ring model (**1a**) for the transition state. The larger group is placed away from the reagent in this arrangement.

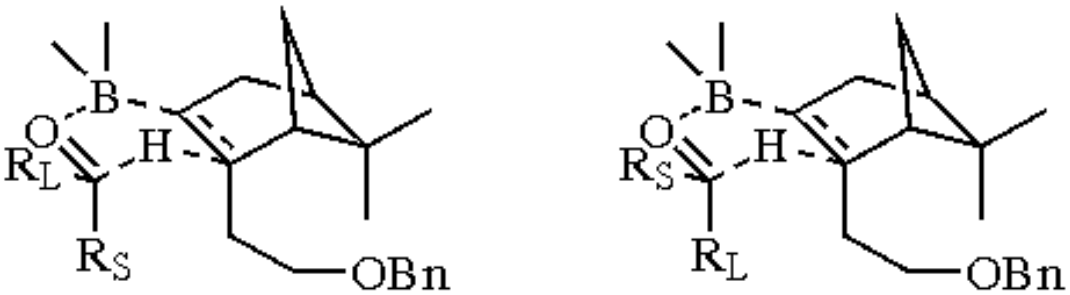

(1a) favored **(1b)** disfavored

The reagent presumably leads to higher asymmetric induction because of the increased size of the nopol side chain. Brown has shown that replacing the vinylic methyl group of α-pinene with larger groups also leads to higher asymmetric induction (eq 3).[3]

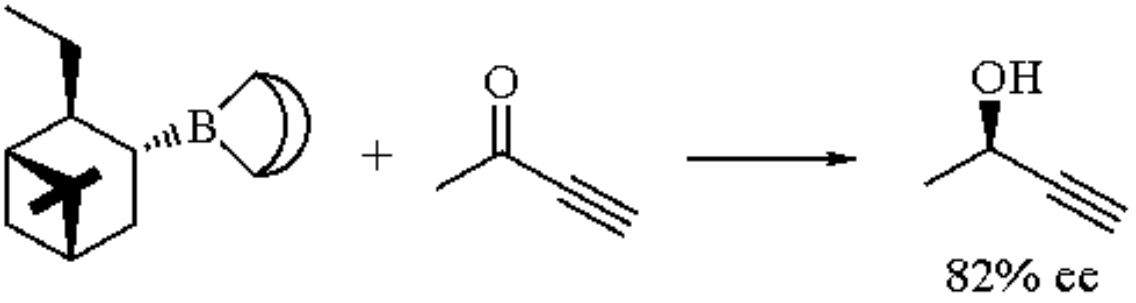

(3)

Borohydride Reagent.

Treatment of NB-enantrane with ***t-Butyllithium*** provides the lithium trialkylborohydride NB-Enantride® (eq 4).[4] This reagent is an effective asymmetric reducing agent for acetophenone and alkyl methyl ketones such as 2-octanone (eq 5). Few reagents show selectivity for such alkyl ketones.

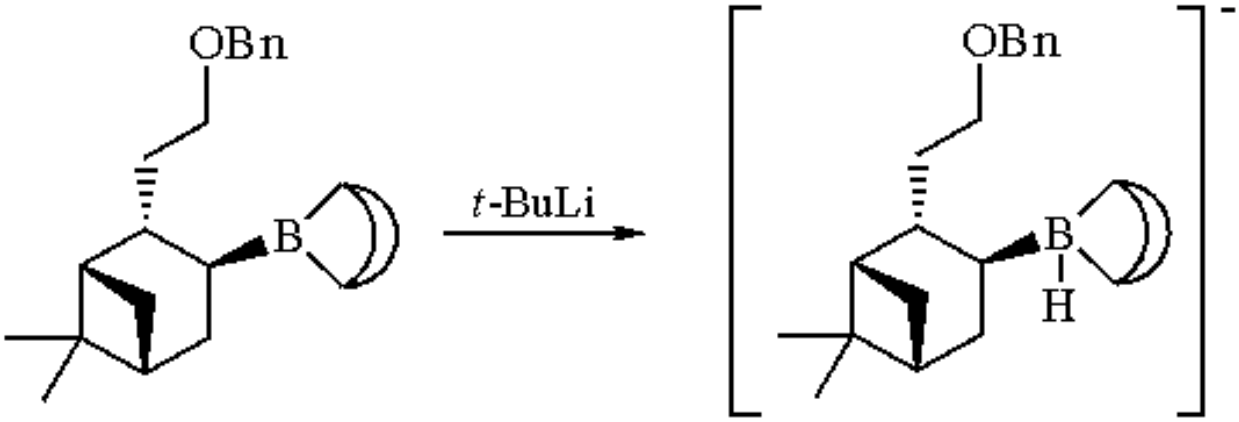

(4)

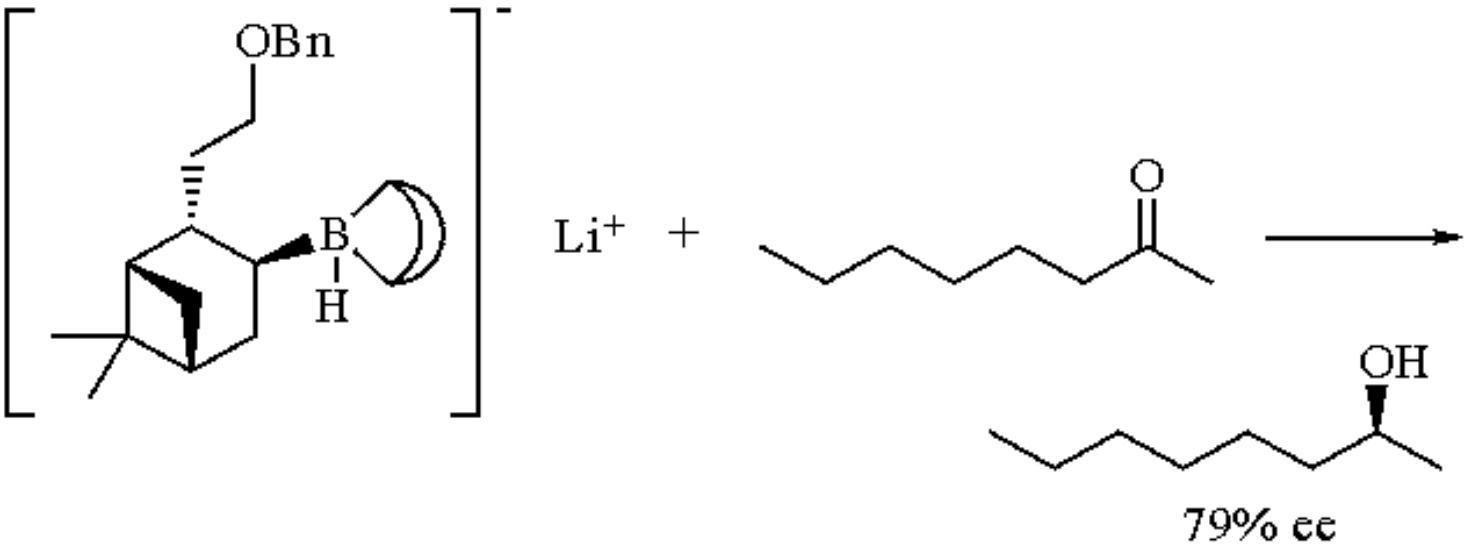

(5)

Related Reagents.

(+)-B-Chlorodiisopinocampheylborane; ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane***.

1. (a) Midland, M. M.; Kazubski, A. *JOC* **1982**, *47*, 2814. (b) Midland, M. M. *CRV* **1989**, *89*, 1553.
2. NB-Enantrane is a trademark of Aldrich Chemical Company.
3. Brown, H. C.; Ramachandran, P. V.; Weissman, S. A.; Swaminathan, S. J. *JOC* **1990**, *55*, 6328.
4. Midland, M. M.; Kazubski, A.; Woodling, R. E. *JOC* **1991**, *56*, 1068.

M. Mark Midland

University of California, Riverside, USA

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Benzyloxyhydroxamic Acid

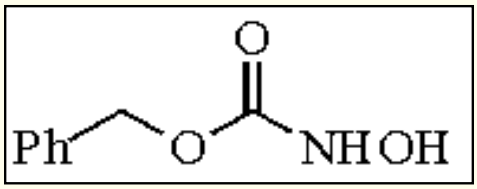

[3426-71-9] · $C_8H_9NO_3$ · Benzyloxyhydroxamic Acid · (MW 167.16)

(precursor to a benzyloxy nitroso carbonyl compound which can function as a dienophile in Diels-Alder reactions[1])

Physical Data: mp 65-70 °C.

Solubility: sol water; slightly sol organic solvents.

Form Supplied in: solid; widely available.

Benzyloxyhydroxamic acid generates benzyl nitrosoformate upon oxidation with a tetraalkylammonium periodate. Treatment of in situ generated benzyl nitrosoformate with dienes gives cyclic adducts in good yield. Baldwin and co-workers reported the first total synthesis of tabtoxin by utilizing the Diels-Alder reaction of a benzyl nitrosoformate with a suitable cyclohexadiene.[1] Thus ethyl cyclohexa-1,3-dienecarboxylate reacted with benzyl nitrosoformate (generated in situ from *N*-benzyloxyhydroxamic acid and tetraethylammonium periodate) to yield a single isomer (eq 1). The resulting adduct was then converted to tabtoxin in a few steps.

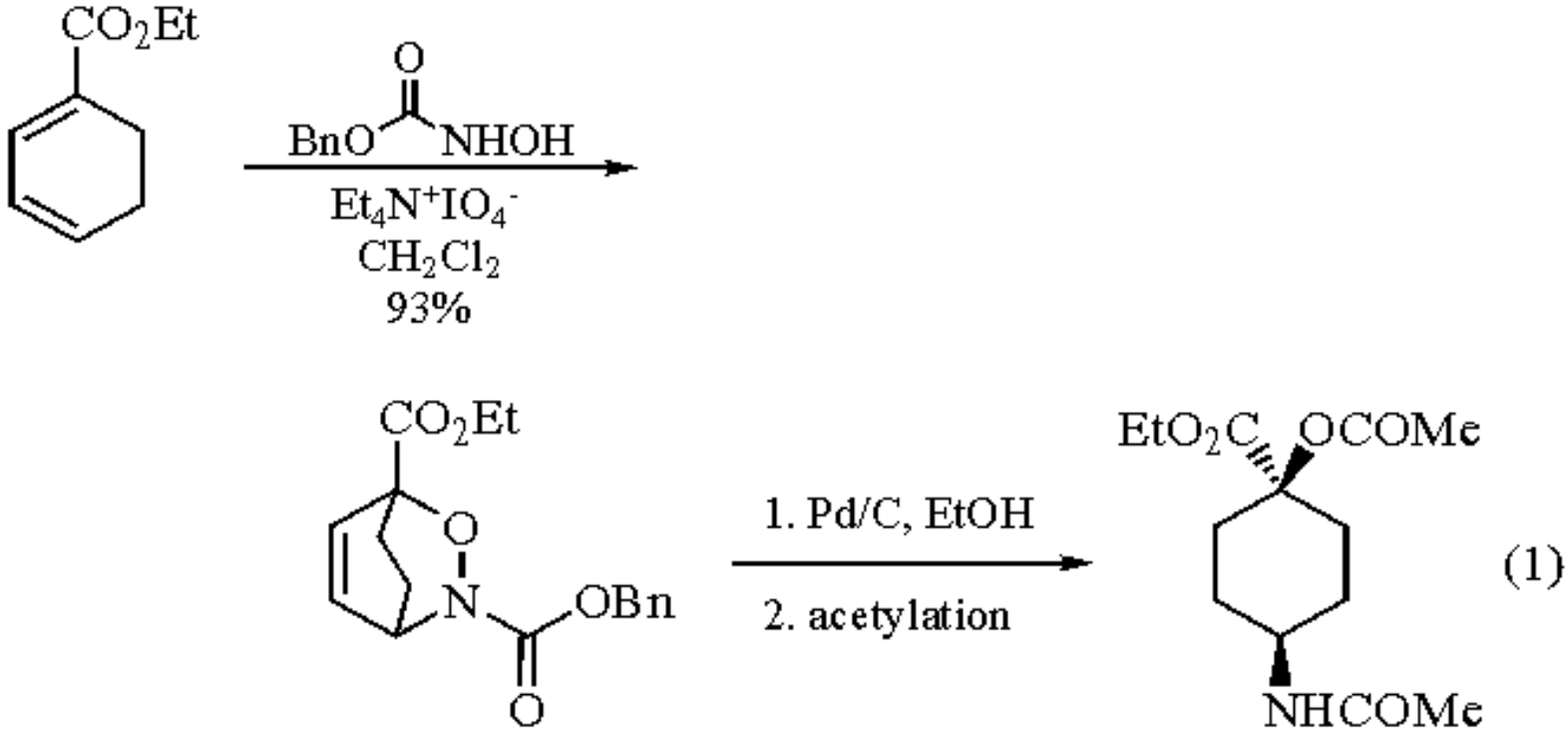

Recently, Hudlicky[2] and Martin[3] have successfully used [4 + 2] cycloaddition of benzyl nitrosoformate with a substituted cyclohexadiene in synthetic studies directed toward lycoricidine (eqs 2 and 3).

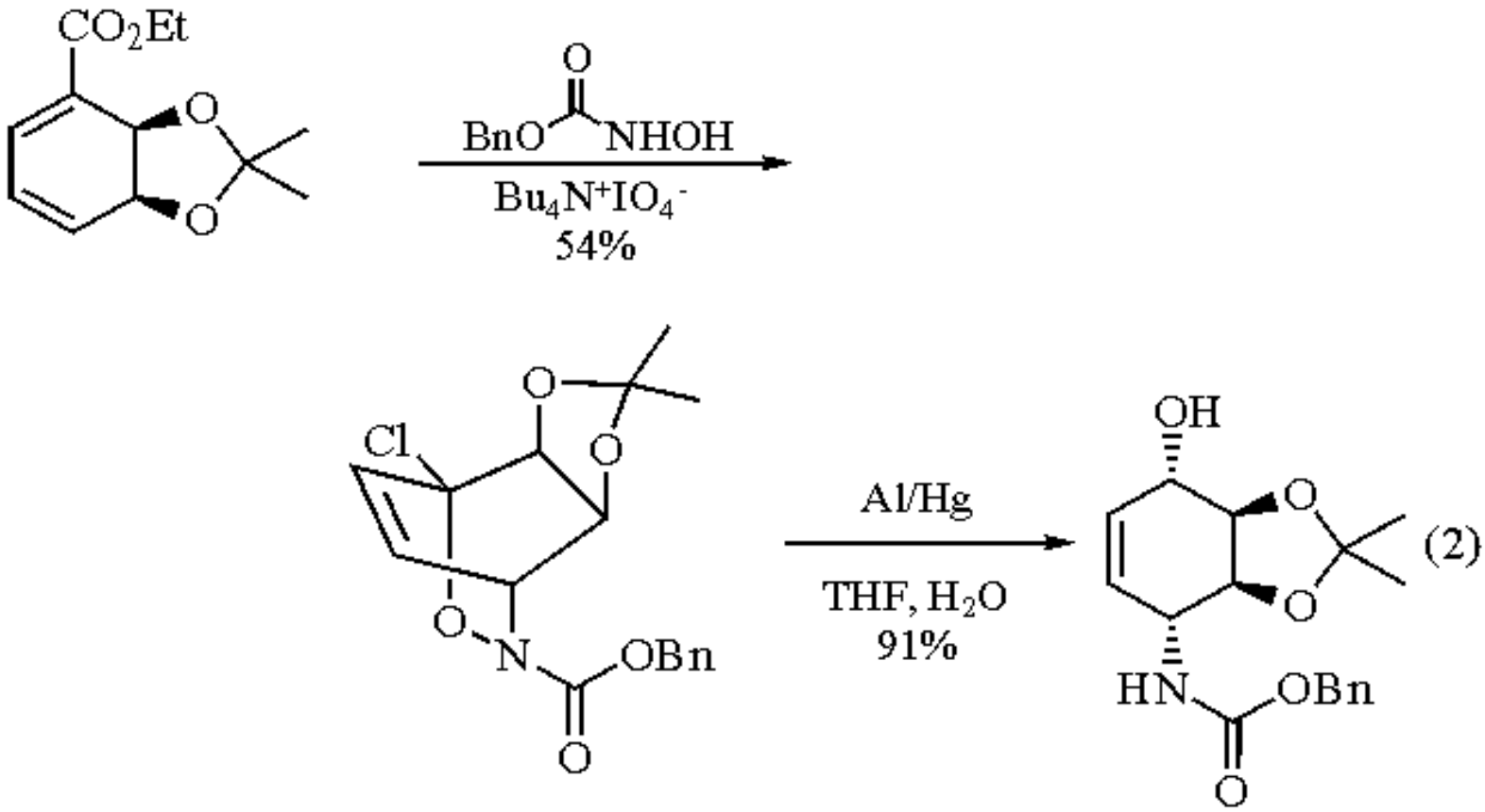

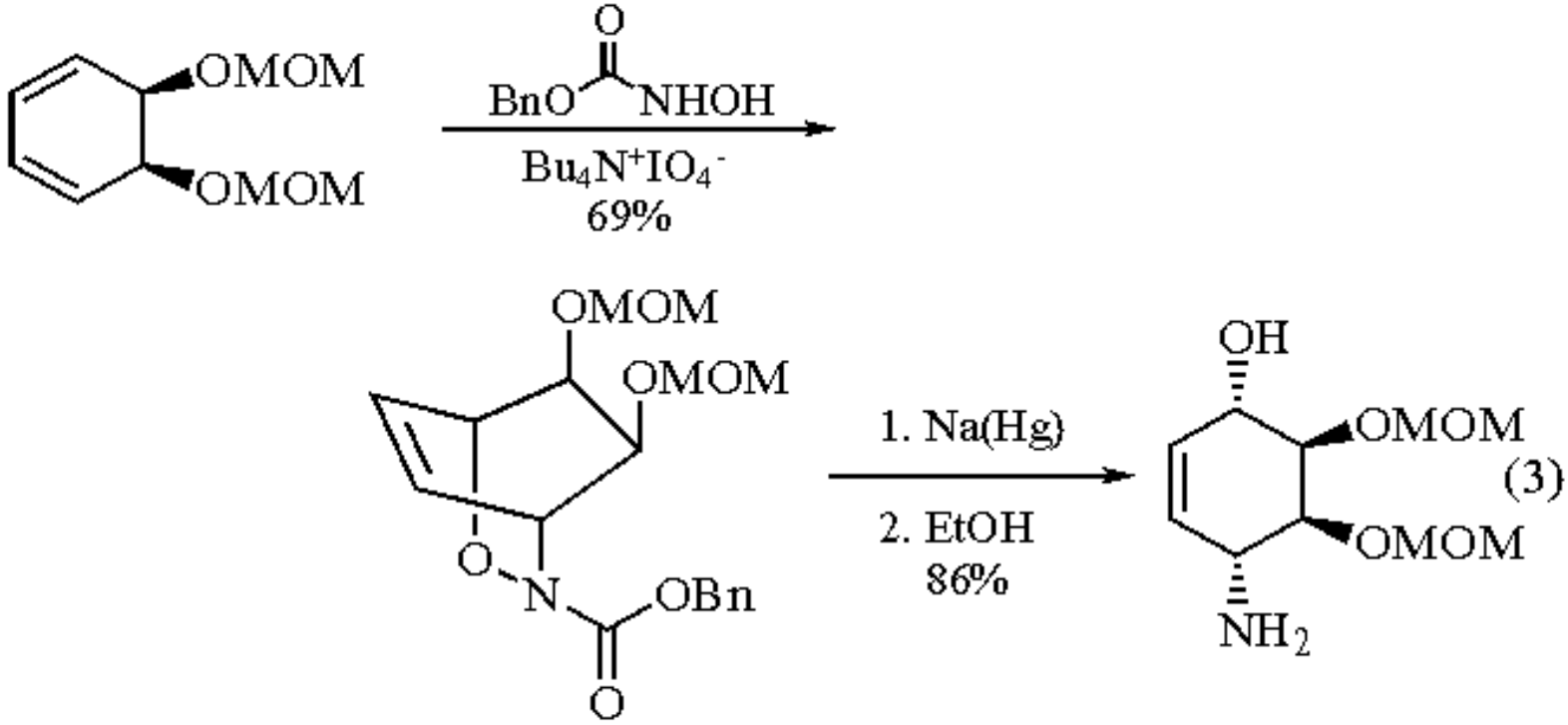

The dimethyl acetals of (*E*)-2,4-pentadienal and (*E*,*E*)- and (*E*,*Z*)-2,4-hexadienals undergo regio- and stereospecific cycloaddition reactions with benzyl nitrosoformate (eq 4).[4] Similarly, this reagent reacts with a 1-silyloxy diene to give regioisomeric cycloadducts in good yield (eq 5).[5]

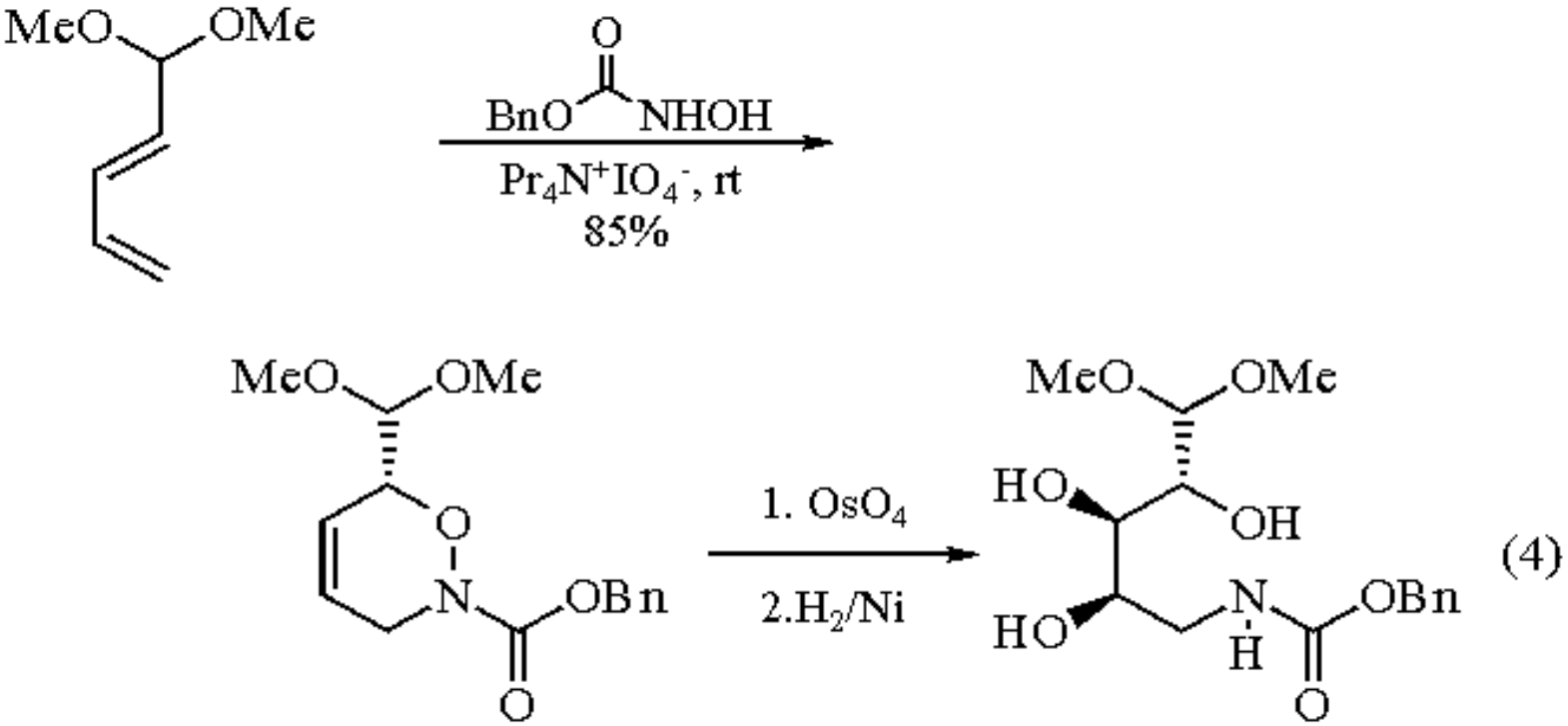

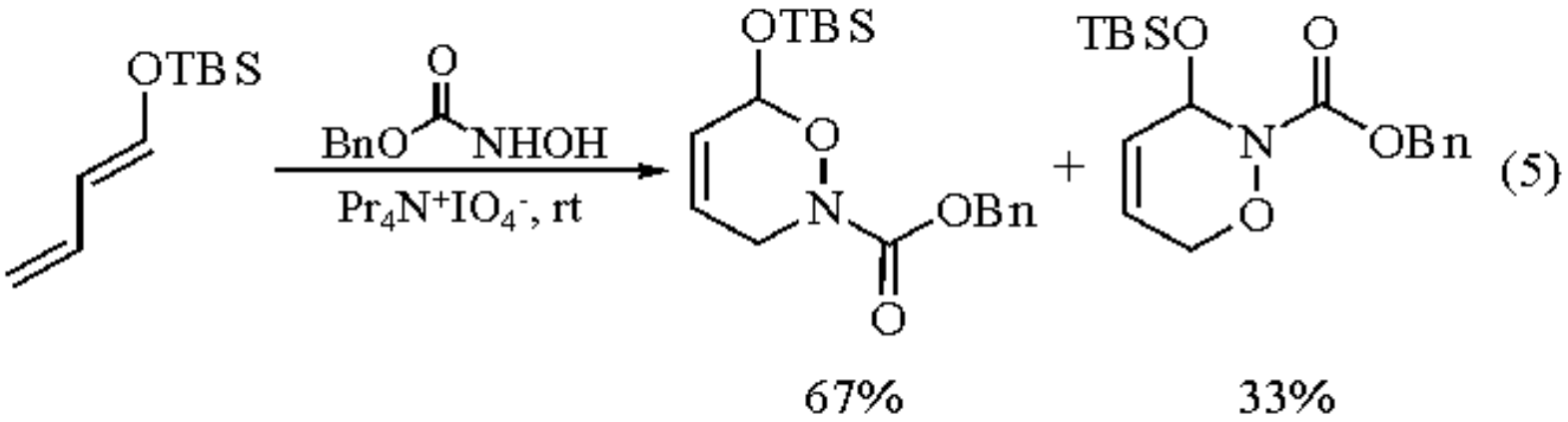

Martin has reported that benzyloxyhydroxamic acid, as well as other hydroxamic acids such as ***Benzohydroxamic Acid*** and phenylacetohydroxamic acid, is smoothly oxidized to the corresponding acylnitroso compound under Swern conditions ($(COCl)_2$, DMSO, CH_2Cl_2; then NEt_3) at -78 °C. This protocol has also been used to generate chiral nitroso carbamates, which afford [4 + 2] cycloadducts in excellent yield and with high diastereomeric excess (eq 6).[6]

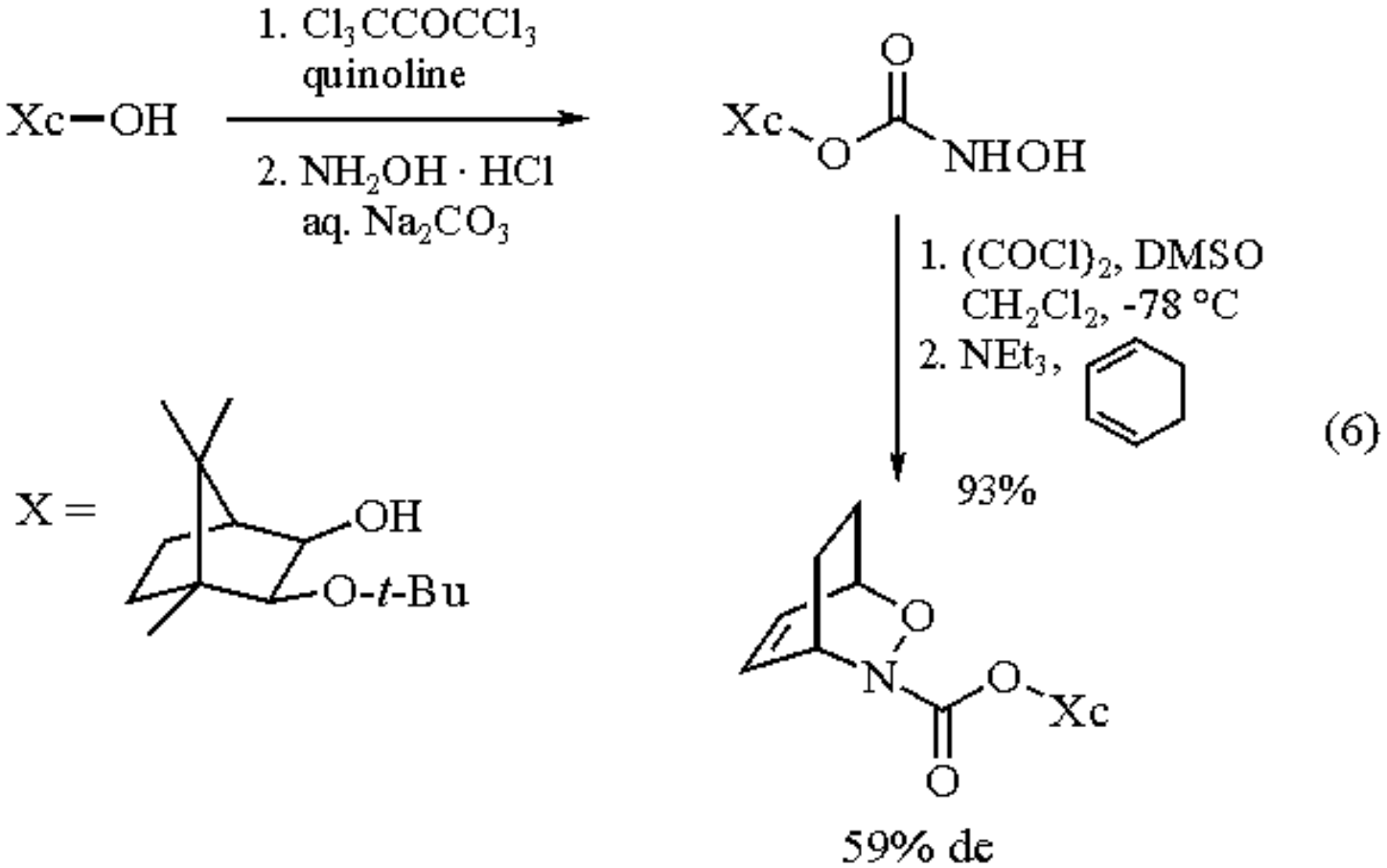

Related Reagents.

Benzohydroxamic Acid; ***Nitrosocarbonylmethane***.

1. Baldwin, J.; Patrick, D. B.; Gallacher, G.; Singleton, K. A.; Wallace, P. M. *CC* **1984**, *40*, 3695.
2. (a) Hudlicky, T.; Olivo, H. F. *TL* **1991**, *32*, 6077. (b) Hudlicky, T.; Olivo, H. F. *JACS* **1992**, *114*, 9694.
3. Tso, H.; Martin, S. F. *H* **1993**, *35*, 85.
4. Streith, J.; Geffroy, G.; Fritz, H.; Defoin, A. *HCA* **1988**, *71*, 1642.
5. Streith, J.; Defoin, A. *HCA* **1991**, *74*, 1653.
6. Martin, S. F.; Hartmann, M.; Josey, J. A. *TL* **1992**, *33*, 3583.

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1-(Benzyloxymethoxy)propyllithium

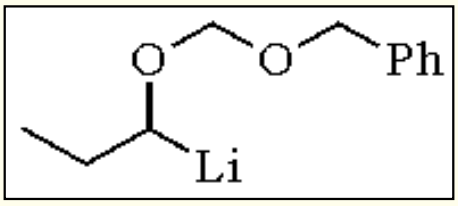

[83876-83-9] · $C_{11}H_{15}LiO_2$ · 1-(Benzyloxymethoxy)propyllithium · (MW 186.18)

(reagent for enantioselective nucleophilic α-hydroxyalkylation; example for several similar reagents)

Form Supplied in: in situ generation at low temperature in THF, ether, or hexane.

Preparative Method: the (preferentially enantioenriched) reagent is generated by tin-lithium exchange of [1-(benzyloxymethoxy)propyl]tributylstannane (eq 1)[1] which proceeds with stereoretention. The lithium carbanion is configurationally stable in THF below approx -40 °C. The nonracemic precursor is obtained by classic[1a] or enzymatic[2] resolution of the α-stannylalkanol, asymmetric reduction[3] of acylstannanes (eq 2), or from chiral (1-chloroalkyl)boronates.[4]

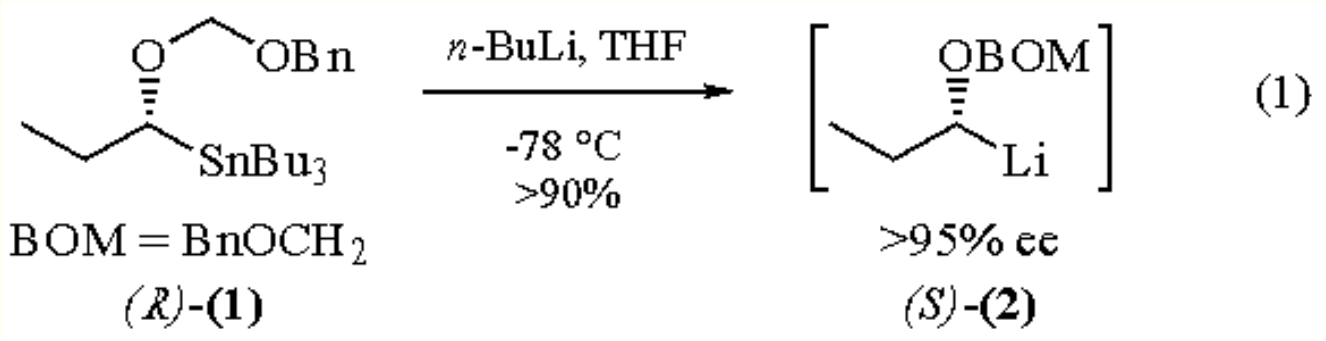

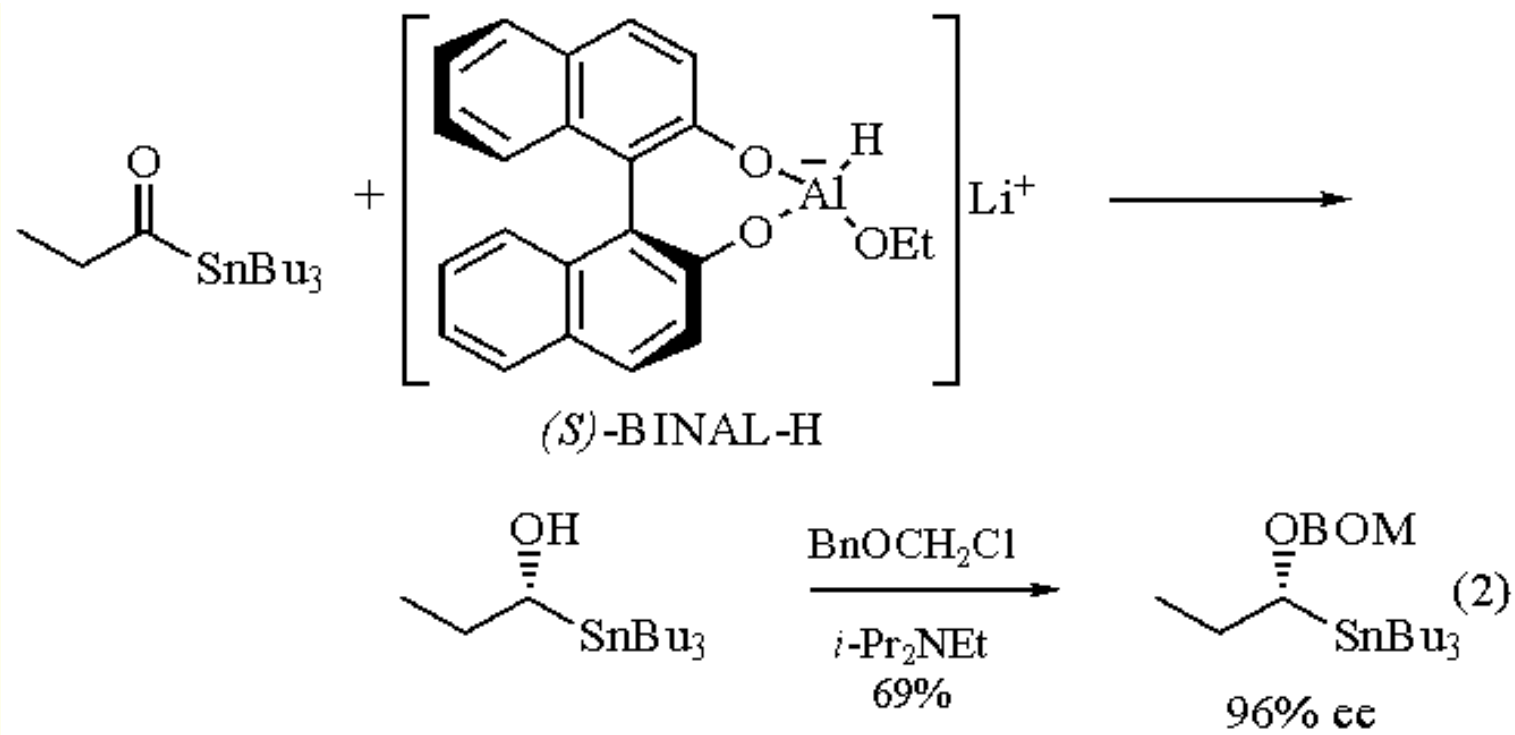

Handling, Storage, and Precautions: solution in THF must be kept under exclusion of air or moisture below -40 °C.

Reactions.

Alkylation[1a] with ***Dimethyl Sulfate*** and carboxylation[5] proceed with complete stereoretention to yield BOM-protected (*S*)-2-butanol[1a] or (*S*)- or (*R*)-2-hydroxybutanoic acid (eq 3).[5] Analogously prepared (*S*)-1-(methoxymethoxy)propyllithium undergoes clean Michael addition to *N*,*N*´,*N*´-trimethylacryloylhydrazide, and the product can be converted to (*S*)-4-hexanolide (eq 4).[6] The acylation of the (*R*) enantiomer by an *N*,*N*-dimethylalkanamide leads to an α-hydroxy ketone, which was converted to (+)-*endo*-brevicomin (eq 5).[7]

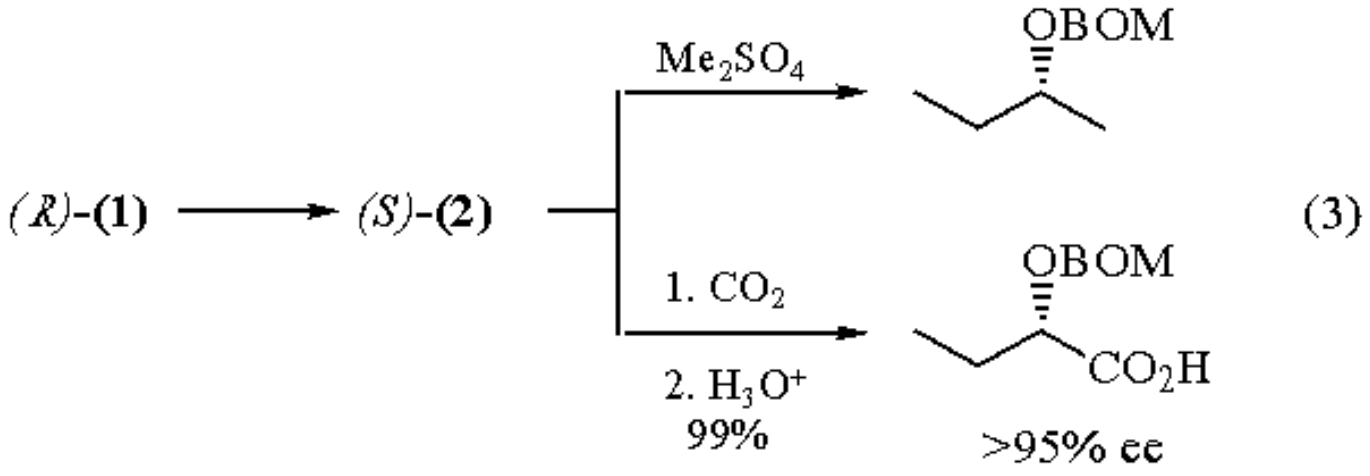

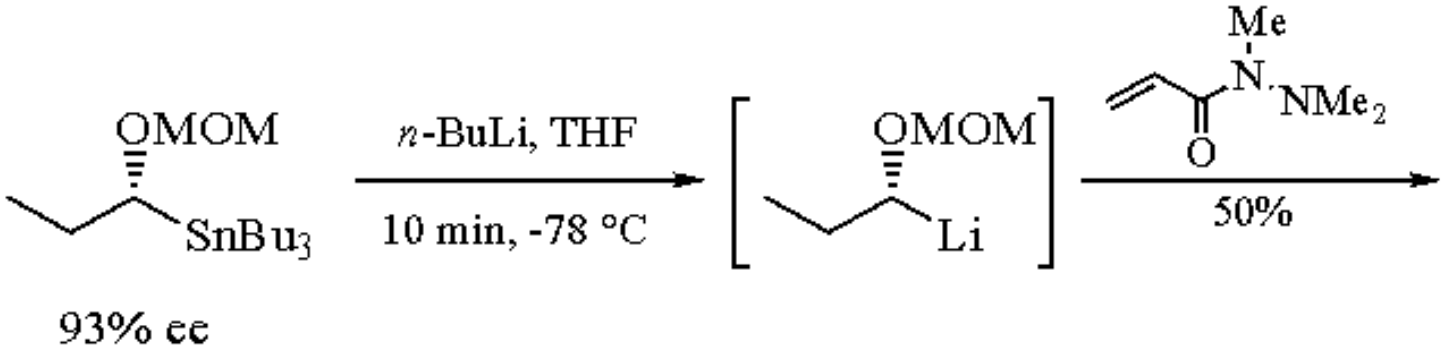

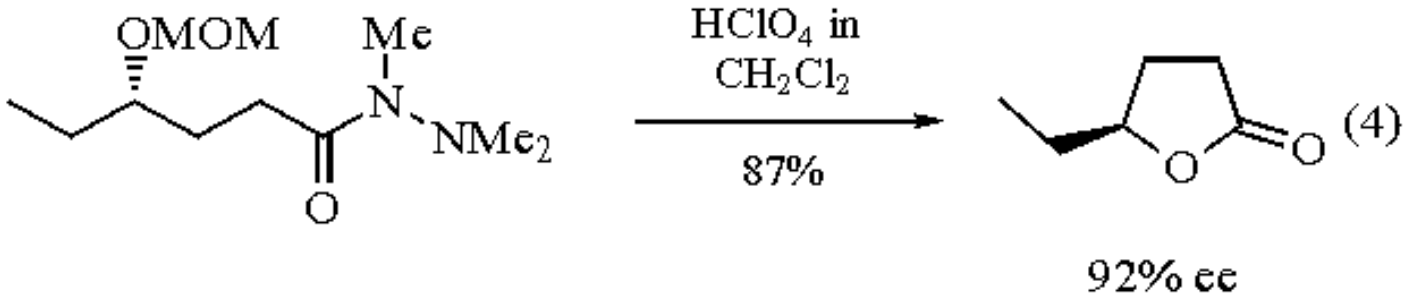

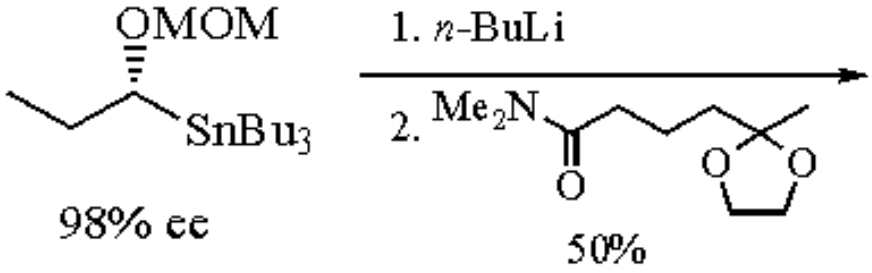

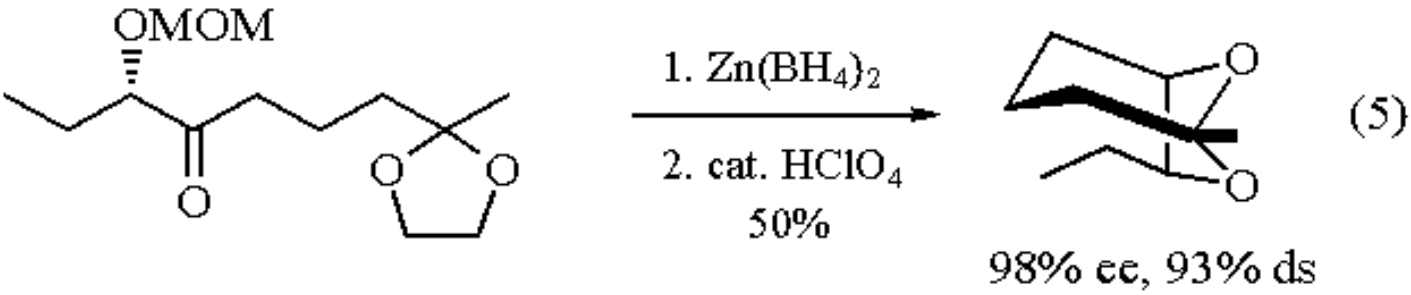

The addition of the lithium reagent to aldehydes gives monoprotected *syn*- and *anti*-*vic*-1,2-alkanediols with low diastereoselectivity (eq 6),[8] which is improved in favor of the *syn* diastereomers by lithium-magnesium exchange and by application of β-branched analogs.[8] Higher and opposite diastereoselectivity is achieved with the appropriate tributyltin or tributyllead reagents under Lewis acid catalysis; however, acetal O-protecting groups are not tolerated (eq 7).[9]

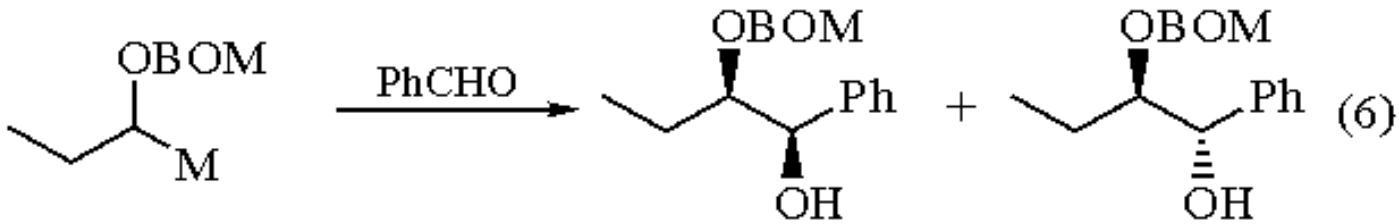

Racemates		
M = Li	53:47	75%
M = MgBr	63:37	77%

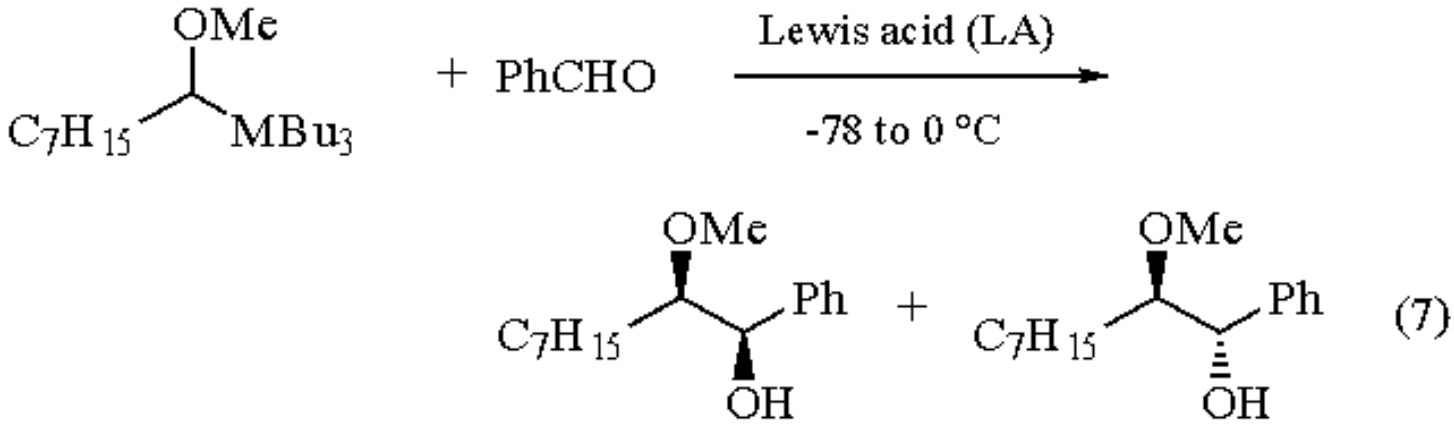

Racemates		
M = Sn, LA = $TiCl_4$	99:1	90%
M = Pb, LA = $BF_3 \cdot OEt_2$	20:80	54%

The cuprate reagents, derived from 1-(methoxymethoxy)alkyllithium, undergo 1,4-addition to enones[10] and to enals (in the presence of ***Chlorotrimethylsilane***) (eq 8).[11] Enantioenriched reagents racemize under these conditions.[12]

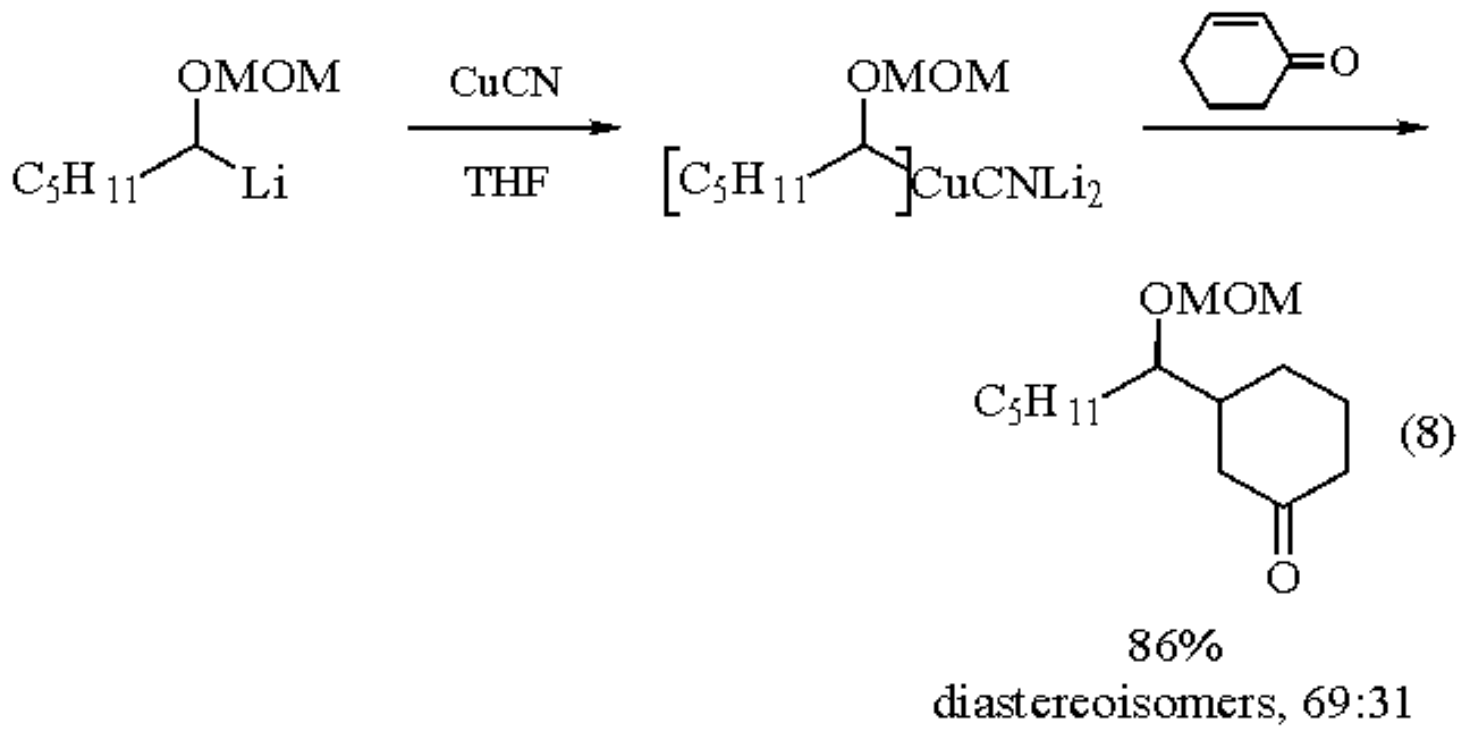

Related Reagents.

1-Lithioalkyl *N*,*N*-dialkylcarbamates are generally accessible by direct deprotonation of alkyl carbamates,[13] either in racemic form or highly enantiomerically enriched (see ***(-)-Sparteine***) (eq 9). Sterically blocked lithiated alkyl benzoates do not permit alkyl substitution at the carbanionic center.[14] Preexisting stereogenic centers in the precursor cause an efficient internal, kinetically controlled, chiral induction in the deprotonation step.[15] This was demonstrated by the synthesis of (2*S*,4*S*)-2-hydroxy-4-pentanolide (eq 10)[15a] from (*S*)-2,3-butanediol and of protected (2*S*,3*S*)-2-hydroxy-3-amino acids (eq 11)[15b] and the chain elongation of 2-amino alkanols.[15b]

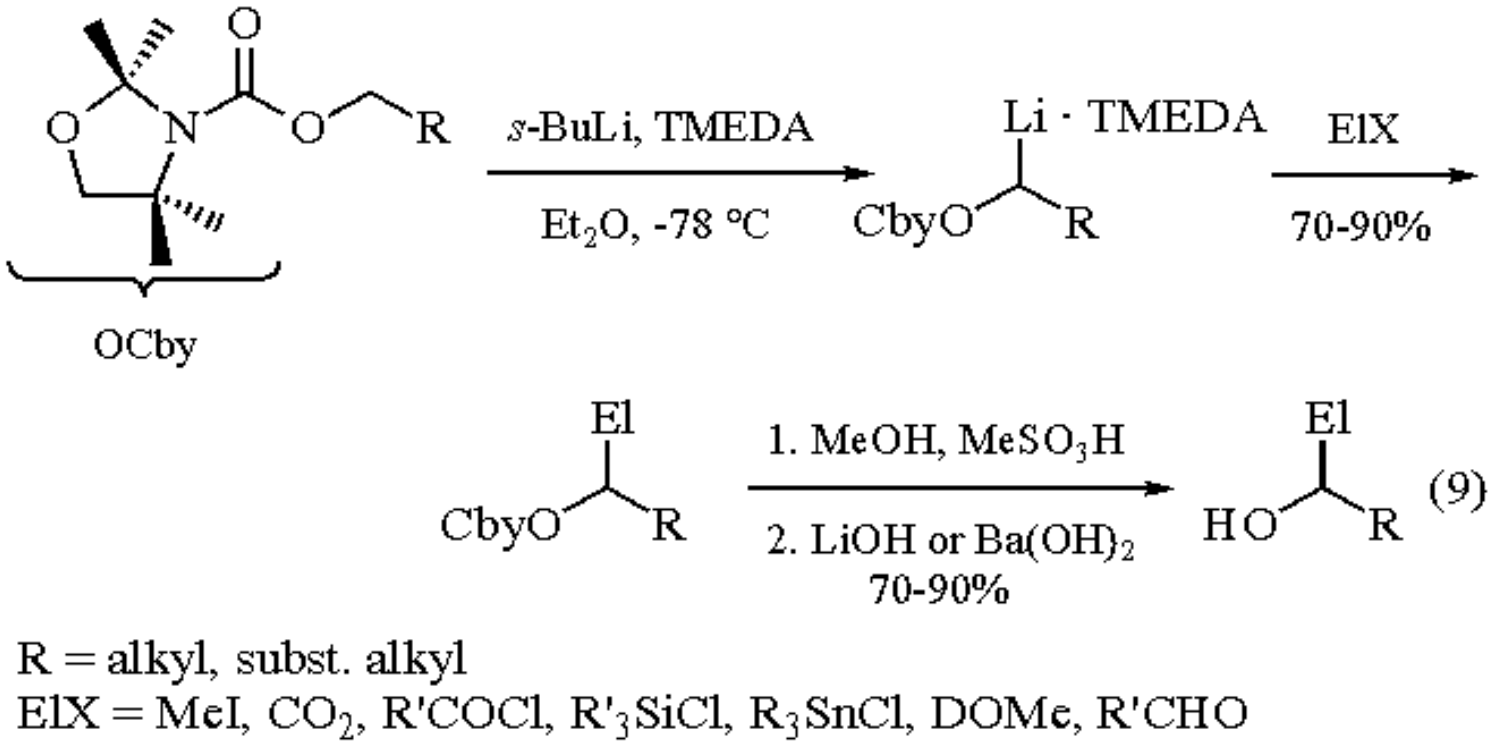

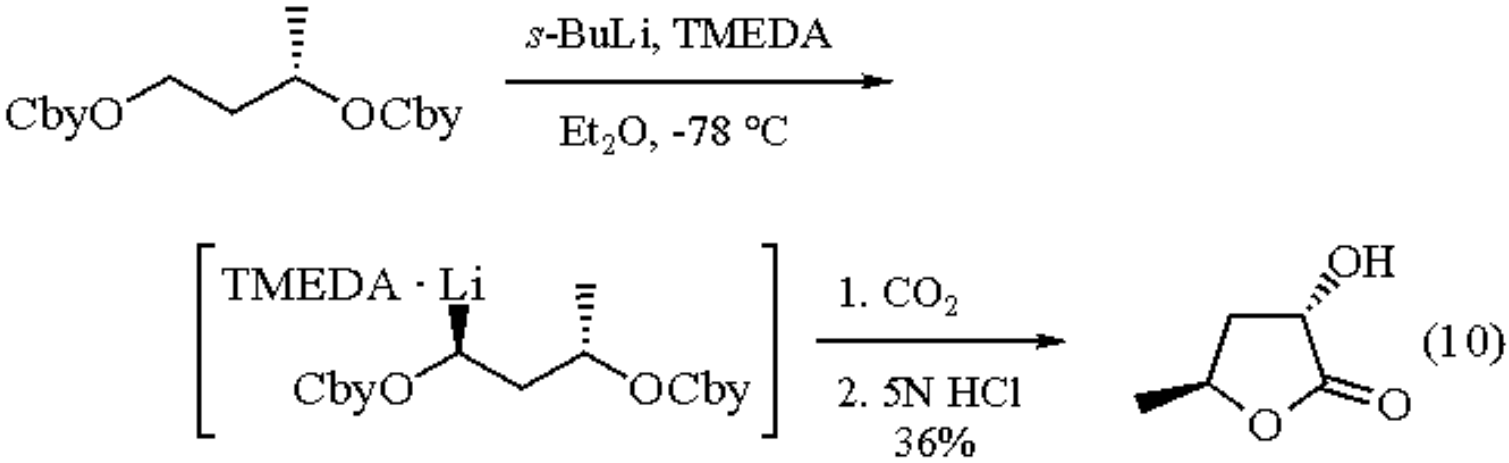

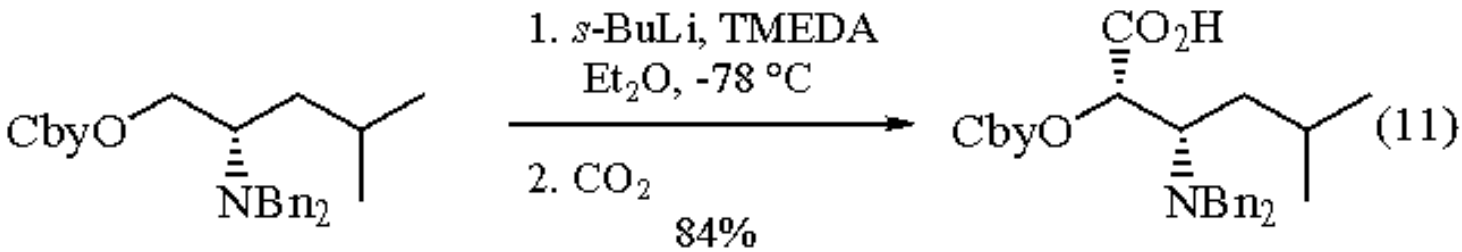

Racemic 1-methoxyalkyllithium[16] reagents are easily obtained from monothioacetals by reductive lithiation[17] with lithium salts of radical anions, such as ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN).[18] The method is particularly useful for the preparation of substituted 2-lithiotetrahydropyrans[19] and 2-lithiotetrahydrofurans.[19] The axial lithium compound is preferentially formed from the radical intermediate under kinetic control, irrespective of the relative configuration of the precursor; it epimerizes above -30 °C to form the more stable equatorial epimer (eq 12).[19,20]

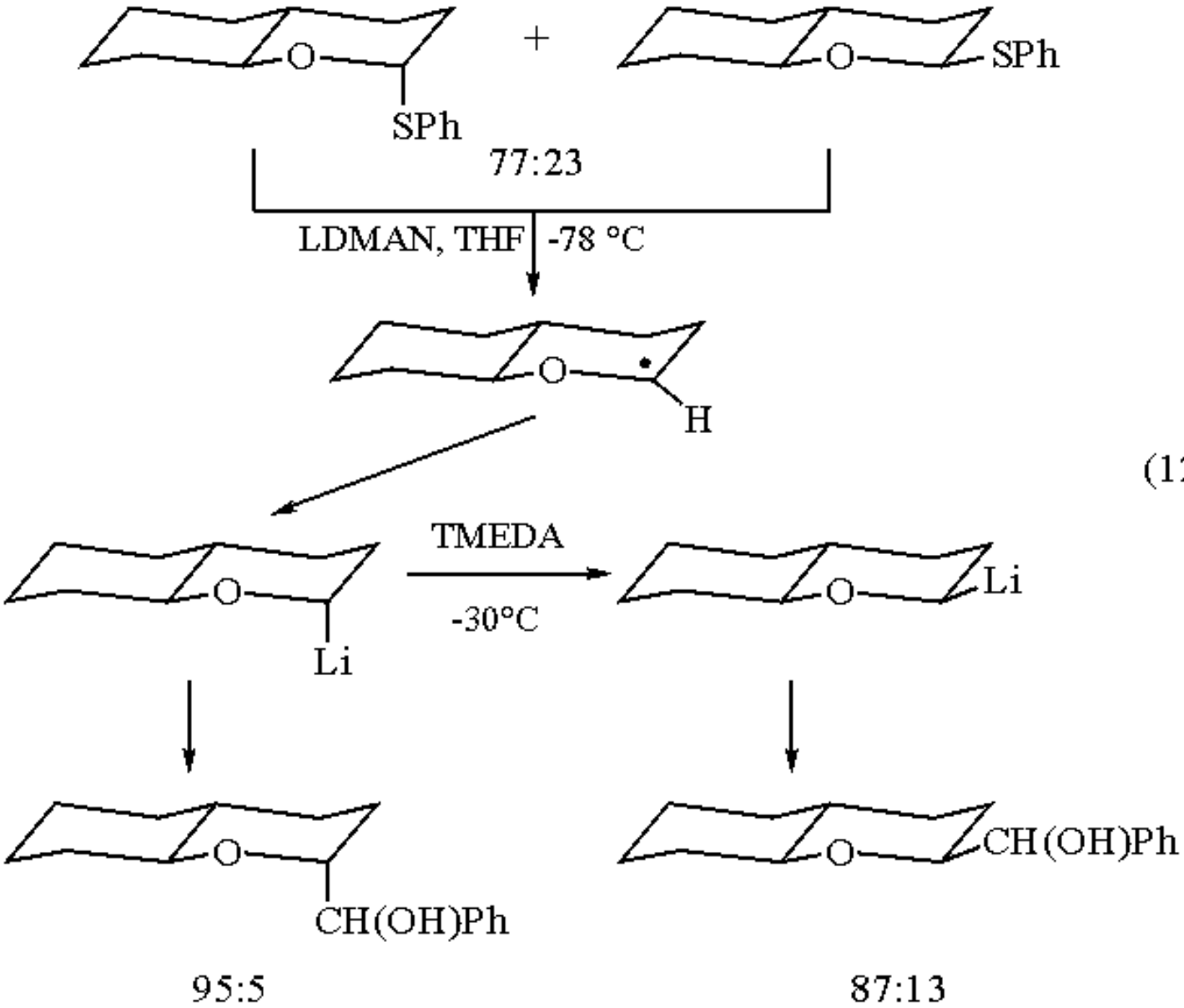

(12)

Protected phenylthio- and phenylsulfonyl-2-deoxypyranosides were also subjected to these conditions and substituted by electrophiles via the 1-lithiopyranosides.[21] Both α- and β-1-(3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosyl)cuprates, prepared by these methods, undergo highly stereoselective conjugate additions to enals and enones (eq 13).[22]

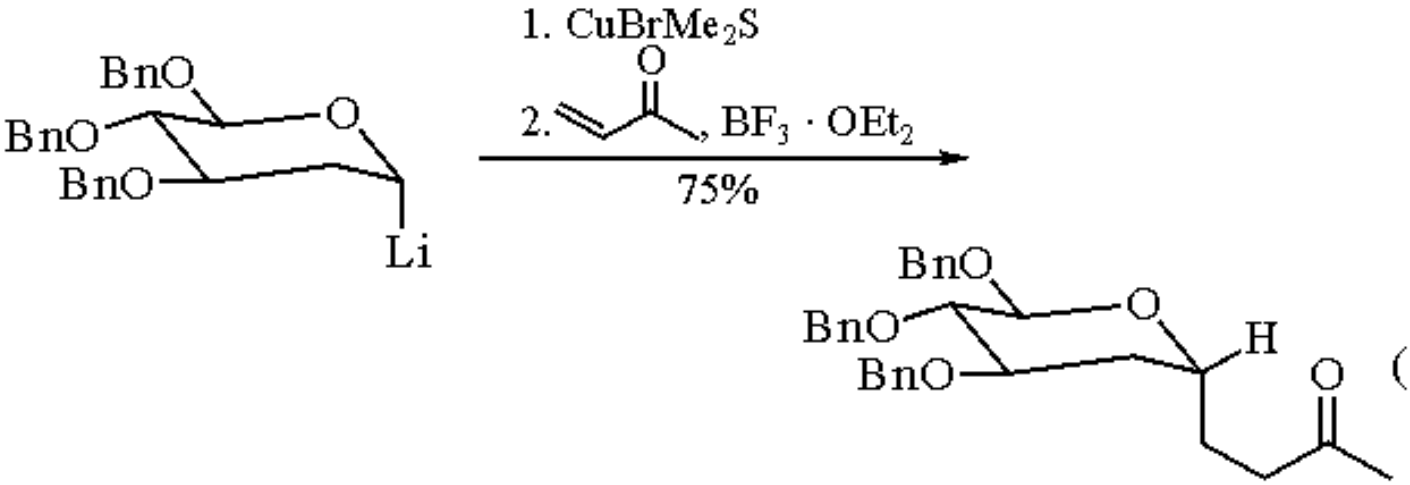

(13)

Even (3,4,6-tri-*O*-benzyl-2-*O*-lithio-α-D-glucopyranosyl)lithium can be generated and added to aldehydes (eq 14).[23]

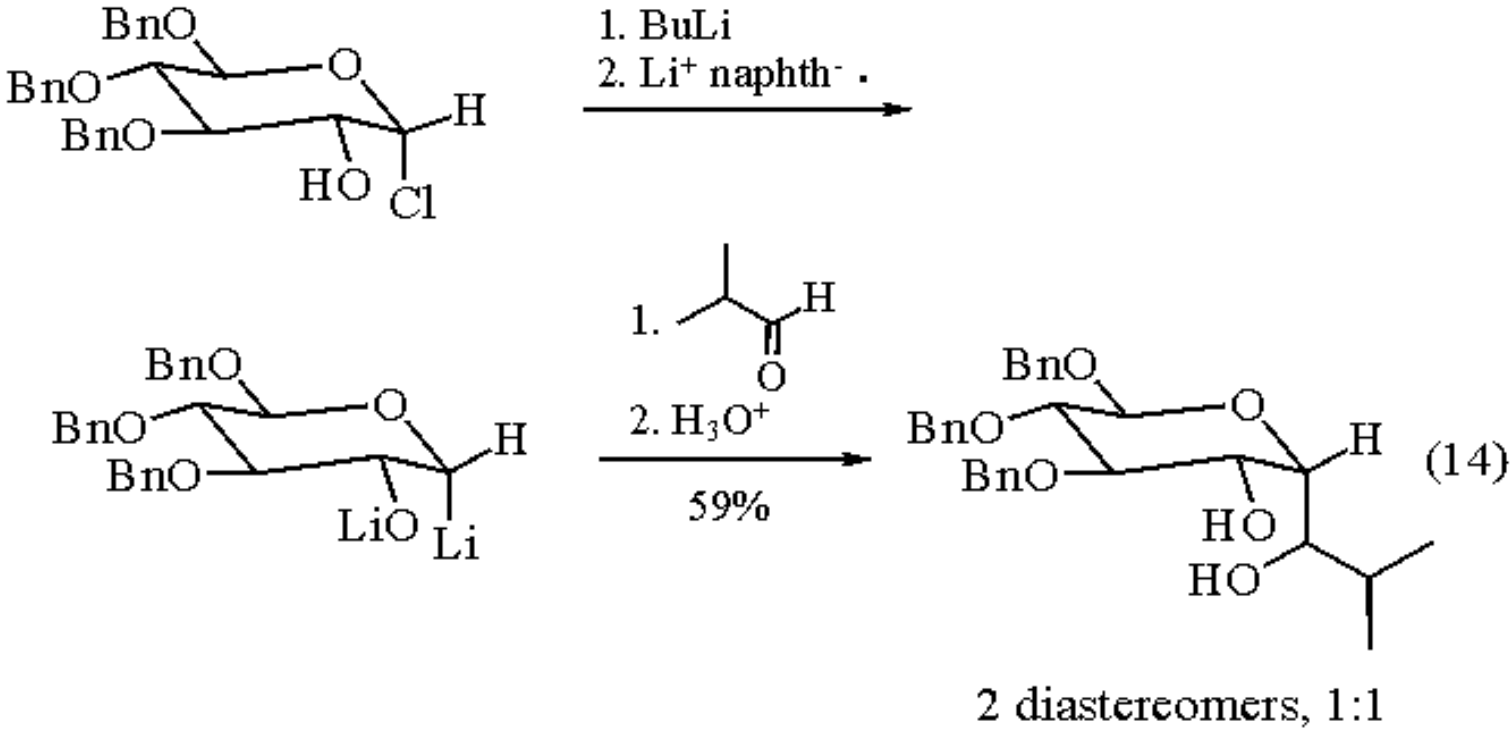

4-Lithio-1,3-dioxanes[19c,24] derived from chiral 1,3-diols are similarly generated and proved to be versatile building blocks in the stereoselective synthesis of polyols, such as 1,3,5,7,9,10-decanehexaol (eq 15).

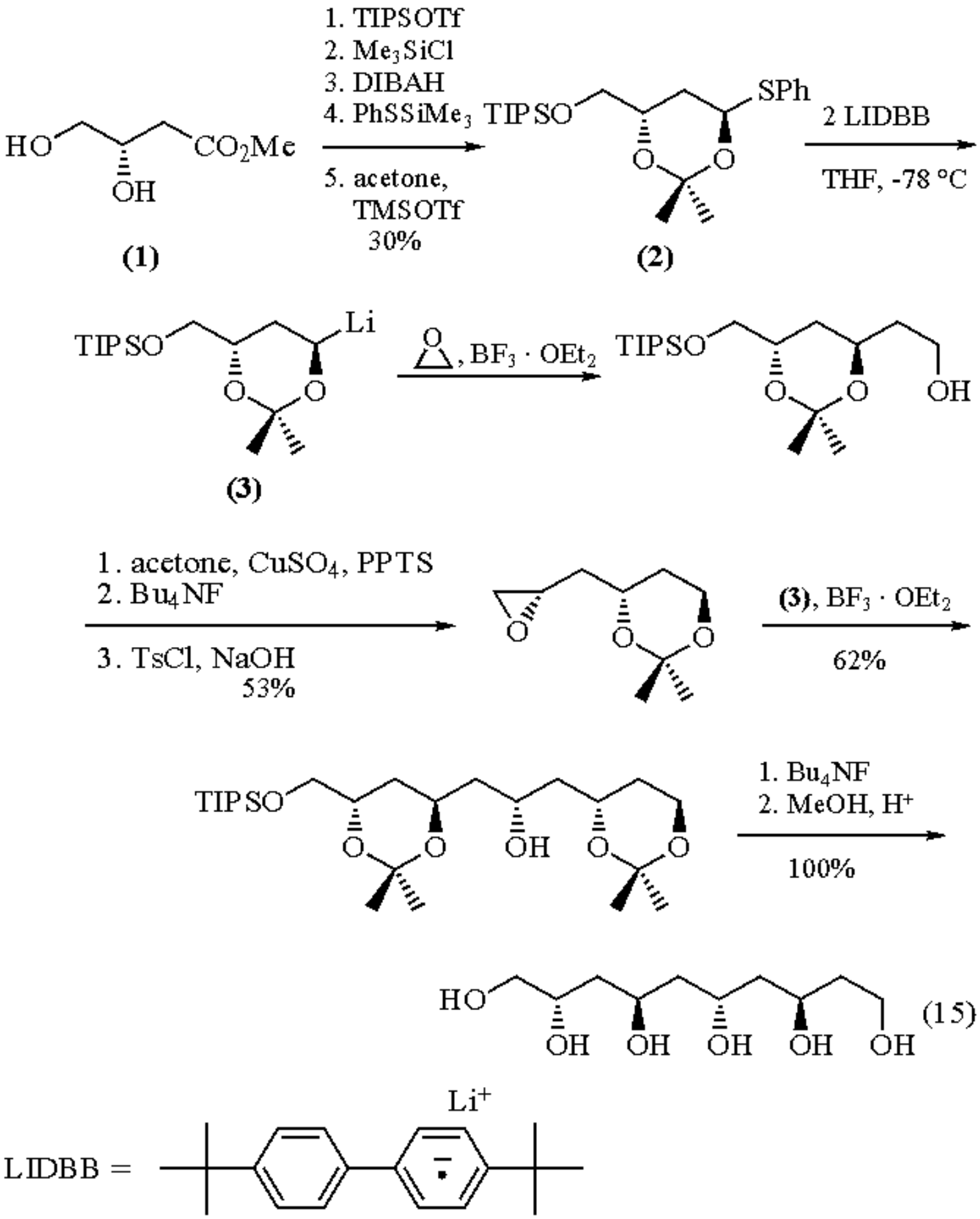
1. TIPSOTf
2. Me3SiCl
3. DIBAH
4. PhSSiMe3
5. acetone, TMSOTf
30%
HO
CO2Me
OH
(1)
TIPSO
SPh
(2)
2 LIDBB
THF, -78 °C
TIPSO
Li
(3)
, BF3 · OEt2
TIPSO
OH
1. acetone, CuSO4, PPTS
2. Bu4NF
3. TsCl, NaOH
53%
(3), BF3 · OEt2
62%
TIPSO
OH
1. Bu4NF
2. MeOH, H+
100%
HO
OH
(15)
Li+
LIDBB =

The zinc-copper reagents, obtained from 1-(acetoxyalkyl)zinc bromides,[25] are subjected to efficient alkylations, alkynylations, acylations, and Michael addition reactions (eq 16).

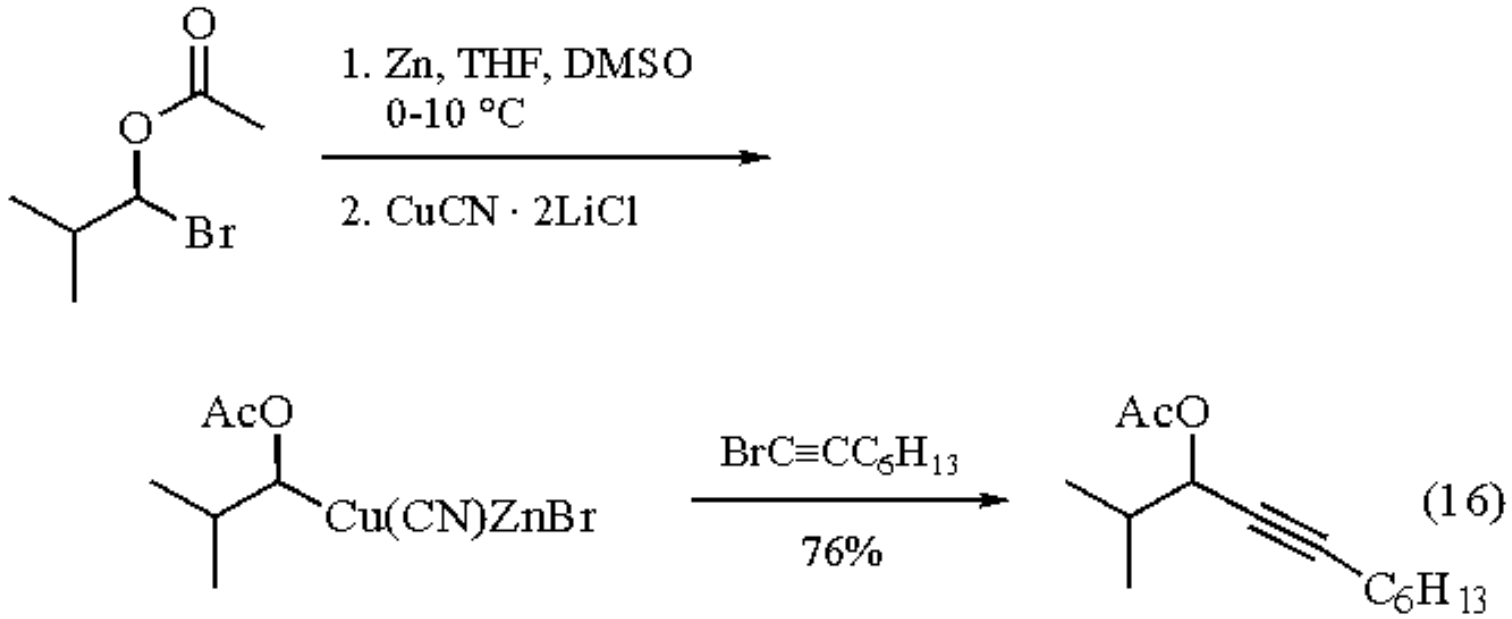

(16)

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(*SP*-4-4)-[(*S*)-[*o*-(1-Benzyl-2-pyrrolidinecarboxamido)-α-phenylbenzylidene]glycinato(2-)-*N,N´,N´´,O*[1]]nickel

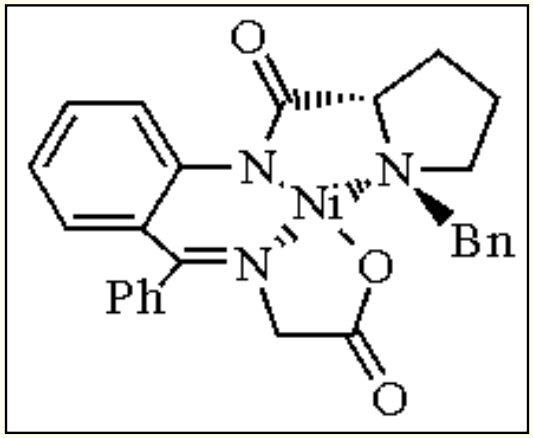

[96293-17-3] · $C_{27}H_{25}N_3NiO_3$ · (*SP*-4-4)-[(*S*)-[*o*-(1-Benzyl-2-pyrrolidinecarboxamido)-α-phenylbenzylidene]glycinato(2-)-*N,N´,N´´,O*[1]]nickel · (MW 498.20)

(used in asymmetric alkylations,[1] 1,2-additions,[2] and 1,4-additions[3] to prepare α-amino acids)

Alternate Name: nickel(II) nitrate-(*S*)-*o*-(benzylprolylamino)benzophenone-glycine

Physical Data: diamagnetic, mp 208-212 °C.

Solubility: sol $CHCl_3$; insol MeOH.

Form Supplied in: not commercially available; prepared as a red solid.[1]

Preparative Method: prepared by condensation of (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone (BBP) with glycine in the presence of nickel(II) nitrate in methanol.[1]

Purification: purified by sequential chromatography over silica gel and Sephadex LH-20, or by dry flash chromatography.[1]

Handling, Storage, and Precautions: care should be taken in applying samples to purified Sephadex. The addition of basic media can present an explosion hazard.

Alkylations.

The high kinetic stability of the Ni^{II}-BBP-glycine complex (**1**) permits alkylation and halogenation of its derived enolate. Alkylations mediated by powdered alkali in DMF, MeCN, or aqueous acetone have proven superior, though other methods are known (eq 1).[1] Substituents introduced in this fashion kinetically and thermodynamically prefer the face opposite the *N*-benzyl group. Consequently, the (*S*)-proline derived complex instills high (*S*) selectivity in alkylation products. Electrophilic bromination at this site licenses subsequent attack by nucleophiles (eq 2).[5] Electrophilic attack at nitrogen frequently precludes the use of free glycine in this synthesis. The title reagent solves this problem through protection of the amino group as its Schiff's base.[6] Chromatographic separation of the alkylated complexes followed by acidic hydrolysis liberates α-amino acids of high optical purity. As a consequence, (**1**) has been used as a chiral building block for fluorinated phenylalanines and pharmaceutically important radiolabeled amino acids.[1,7,8]

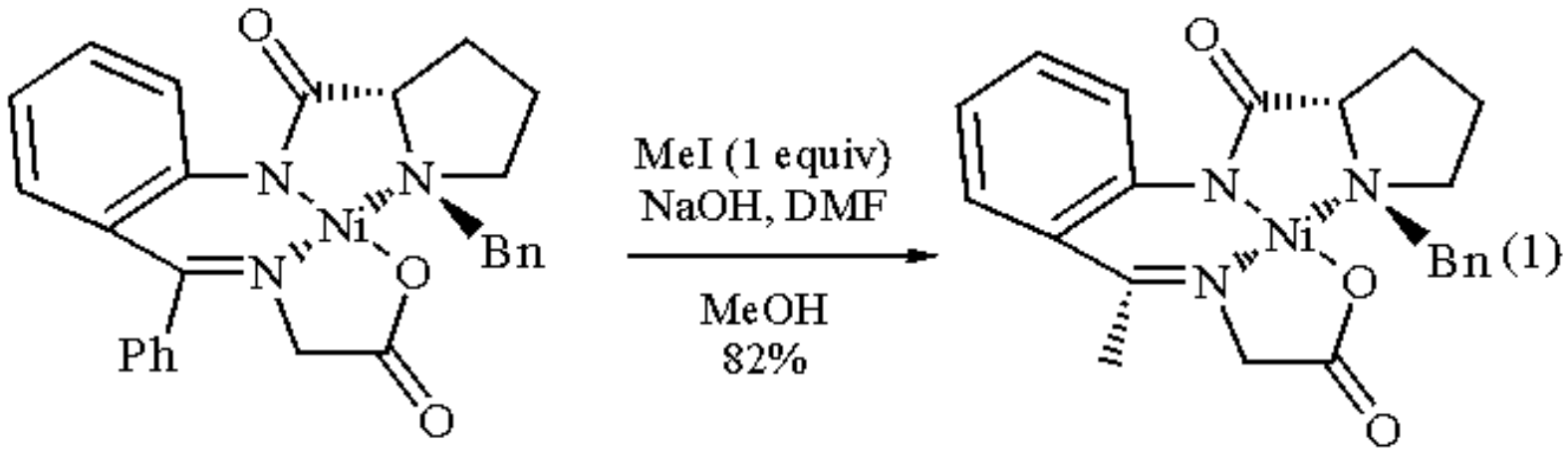

(1) α:β = 9:1

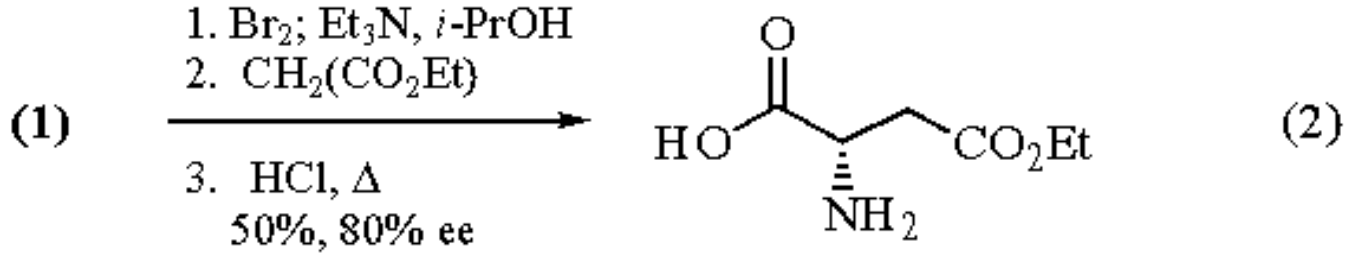

1,2-Additions.

Increased C-H acidity (pK_a = 18.8 in DMSO) facilitates condensation of the complex with aldehydes and ketones, while the use of free glycine is generally problematic.[9,10] The stereochemical outcome at the α-carbon parallels those of alkyl halide alkylations.[11] Thus the Ni^{II}-BBP-glycine complex provides a route to asymmetric aldols and *anti* β-substituted α-aminobutanoic acids (eqs 3 and 4).

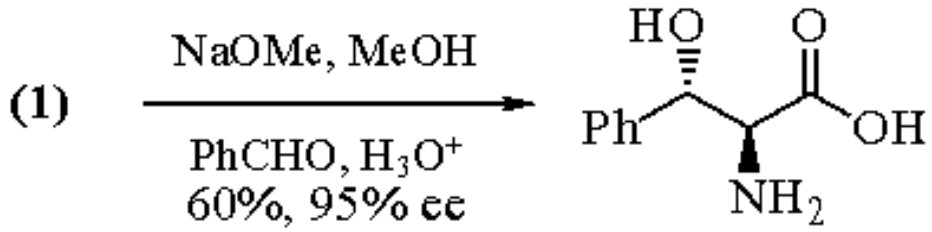

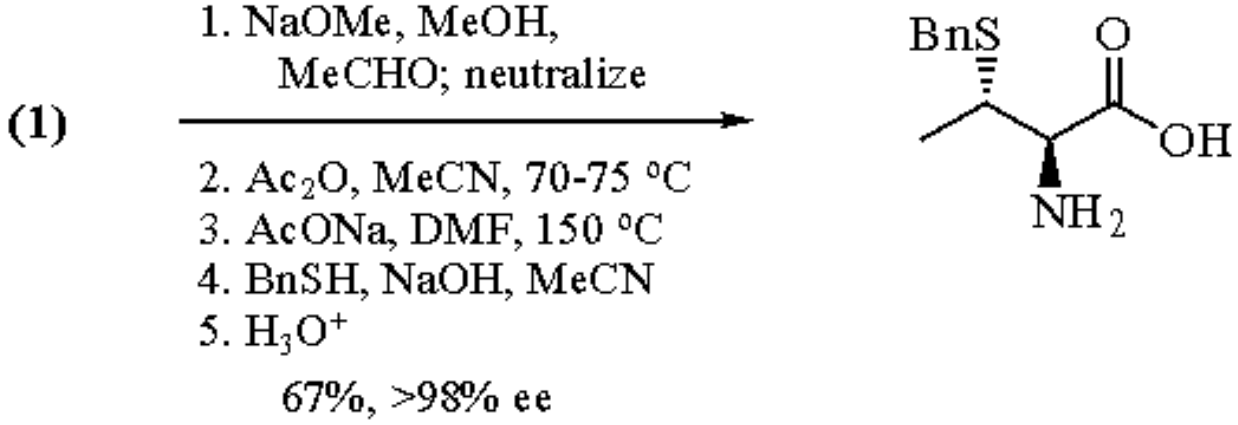

1,4-Additions.

Glycine complex (**1**) undergoes asymmetric conjugate addition to α,β-unsaturated esters, nitriles, aldehydes, and ketones.[3] Judicious selection of alkene leads to (*S*)-glutamic acids, though vigorous conditions (concd HCl, 100 °C) are employed for hydrolysis. The high levels of enantioselectivity achieved by this method have culminated in an asymmetric synthesis of proline derivatives (eq 5).[4]

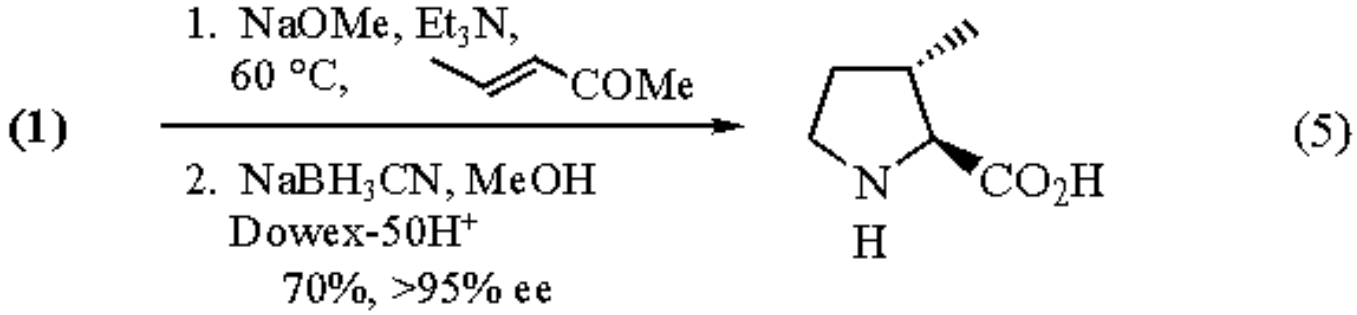

Related Reagents.

Other conceptually related materials used for asymmetric amino acid synthesis include benzophenone imines derived from α-amino esters, α-amino esters temporarily protected as the derived acetals, and bislactim ethers.[12]

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N-Benzylquininium Chloride

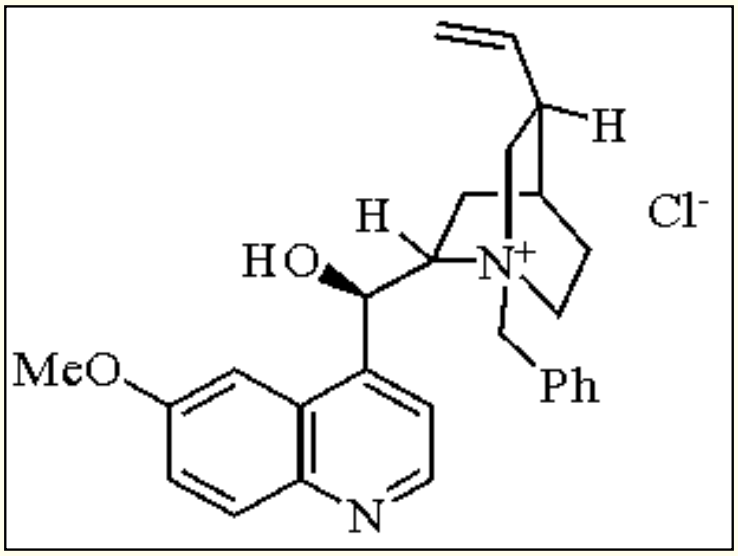

[67174-25-8] · $C_{27}H_{31}ClN_2O_2$ · *N*-Benzylquininium Chloride · (MW 451.01)

(chiral, nonracemic quaternary ammonium salt; catalyst for a variety of phase transfer reactions under basic conditions[1])

Alternate Names: Quibec; BQC.

Physical Data: mp 180-181 °C, [α]19D -235.5° (*c* = 1.5, H_2O);[2] monohydrate: mp 169-172 °C (dec), $[\alpha]_D$ -212.5° (*c* = 0.5, EtOH).[3]

Solubility: freely sol H_2O, alcohols, acetone; slightly sol EtOAc; sparingly sol $CHCl_3$.[4]

Form Supplied in: solid.

Purification: recrystallized from absolute EtOH.[3]

The combined use of catalytic amounts of *N*-benzylquininium chloride (**1**) with hydroxide bases (NaOH or KOH) has been explored for a variety of phase transfer reactions, including epoxidations, alkylations, and Michael reactions. The degree of stereoselectivity in product formation induced by the reagent can vary widely.[5]

BQC is derived from quinine, which is a member of the *cinchona* family of alkaloids. Ammonium salts derived from quinidine, a diastereomer of (**1**) at the hydroxyl substituent, have been used less frequently in catalysis than BQC. Quinidinium salts often give rise to products with enantioselectivity opposite to that from (**1**). Other related compounds, such as those derived from cinchonine and cinchonidine (which lack the methoxy substituent on the

quinoline nucleus), have found application in organic synthesis. The *cinchona* alkaloids, as well as salt derivatives in which the benzyl group bears various substituents, have also been studied.[6] Results from polymer-bound catalysts have not been promising.[7]

Benzylquininium chloride has shown good to excellent selectivity in the epoxidation of α,β-unsaturated ketones.[8] Oxidation of quinone (**2**) in the presence of (**1**) with aqueous ***t-Butyl Hydroperoxide*** and ***Sodium Hydroxide*** in toluene gave rise to a 95% chemical yield of epoxide (**3**) in 78% ee (eq 1).[2] Recrystallization improved the ee to 100% with 63% mass recovery. Aqueous ***Hydrogen Peroxide*** decreased both the yield (89%) and enantioselectivity (50% ee).

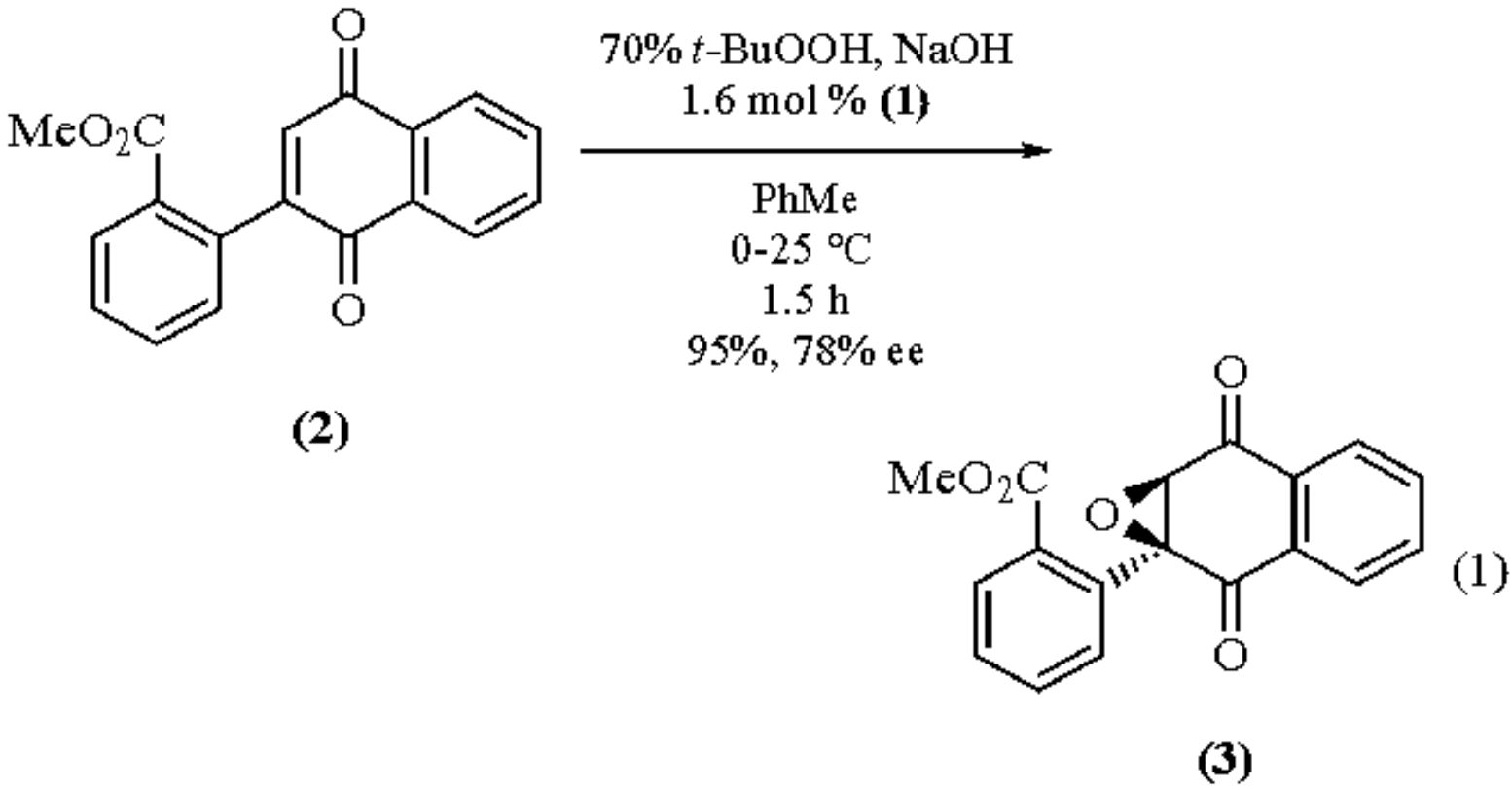

Enantiomerically enriched epoxides have also been generated using (**1**) in the Darzens reaction of α-chloro ketones with aldehydes, as well as through ring closure of racemic halohydrins.[9] The extent of enantioselectivity for both reactions is similar (optical purity 6-8% ±1), suggesting a moderate degree of kinetic resolution occurring in each case.

Benzylquininium chloride has been studied as a catalyst for the asymmetric Michael reaction. Reaction of amidomalonate (**5**) and chalcone (**4**) with catalytic base and a variety of chiral, nonracemic ammonium salts in the absence of solvent produced (**6**) in yields of 41-68% and 20-68% ee (eq 2).[10] The quinine-derived salt (**1**) was of intermediate effectiveness (38% ee, 47% yield) when compared to ephedrine-based catalysts. Although (**1**) was not specifically tested with regard to solvation effects, it is suggested that increased aggregation of reactive species under solid-liquid PTC conditions leads to enhanced organization and selectivity. Low levels of induction have been observed in other systems.[11] A study comparing various chiral alkaloid salts, bases, and reaction conditions on enantioselectivities in the conjugate addition of thiols and nitroalkanes to enones has been reported.[12] Remarkable results have also been obtained in the cinchonium/cinchonidinium-catalyzed reaction of an indanone with methyl vinyl ketone.[13] A direct comparison with a more efficient lanthanum-binaphthol complex has been reported.[14]

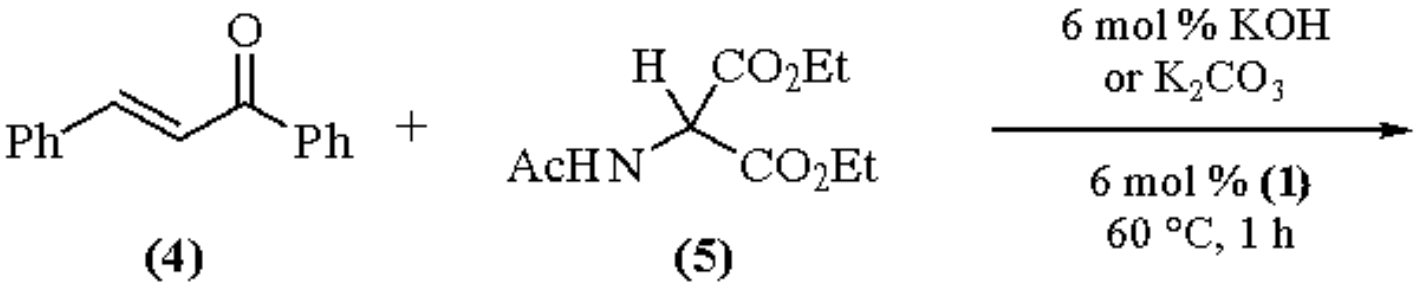

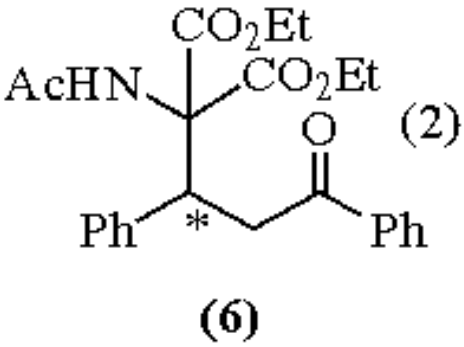

(2)

Phase-transfer alkylations have been studied using *cinchona* alkaloid derivatives; however, results have been more promising with the cinchonium/cinchonidinium series than with the quininium/quinidinium group.[15] For example, catalytic asymmetric alkylation in high yield and selectivity has been achieved with *N*-(*p*-trifluoromethylphenyl)cinchonium bromide (*p*-CF_3BCNB) (eq 3).[16] A systematic investigation of reaction variables (catalyst type, solvent, concentration, temperature, stirring rate, leaving group, etc.) has produced a general method to prepare α-amino acids in 44-62% ee.[17]

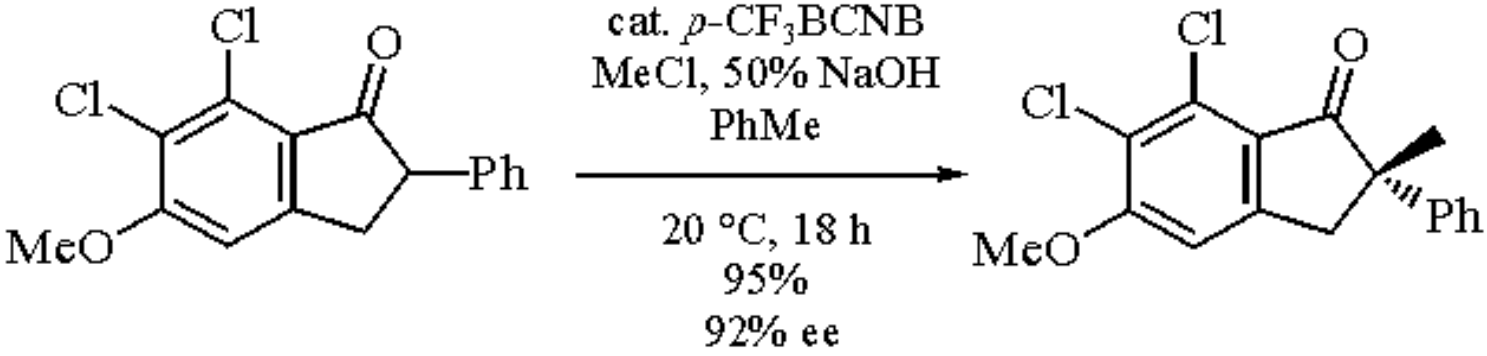

(3)

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Benzylsulfonyldiazomethane[1]

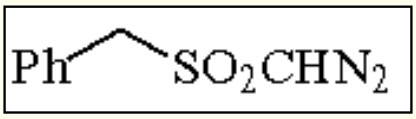

[1588-80-3] · $C_8H_8N_2O_2S$ · Benzylsulfonyldiazomethane · (MW 196.22)

(safe, nonexplosive, shelf-stable substitute for diazomethane;[2] performs similar reactions such as ring expansions[3] and Arndt-Eistert syntheses;[4] enables the preparation of various substituted benzyl sulfones)

Alternate Name: BSDM.

Physical Data: mp 98-99 °C; bright yellow solid.

Solubility: sol halogenated organic solvents.

Form Supplied in: not available commercially.

Preparative Methods: from the corresponding urethane via nitrosation with nitrosyl chloride followed by rearrangement on neutral alumina,[2] or via reaction of ethyl benzylsulfonylacetate with tosyl azide in the presence of triethylamine.[5]

Handling, Storage, and Precautions: no toxicological data available; nonexplosive; stable for over 4 months at -20 °C. Use in a fume hood.

Diazomethane Substitute Reactions.

Many reactions of benzylsulfonyldiazomethane (BSDM) are analogous to those of ***Diazomethane***, for which it was developed as a replacement. When treated with BSDM in the presence of ***Titanium(IV) Chloride***, cycloalkanones are converted to the corresponding ring-expanded α-benzylsulfonyl ketones. These are then converted to the synthetically useful vinyl sulfones upon bromination followed by exposure to silver ion (eq 1).[3] BSDM also serves well for the preparation of α-diazo α-sulfonyl ketones, which are Wolff rearrangement precursors (eq 2).[6] The α-benzylsulfonyl diazo ketones are also convertible to α-sulfonyl esters by treatment with alcohols (eq 3).[4]

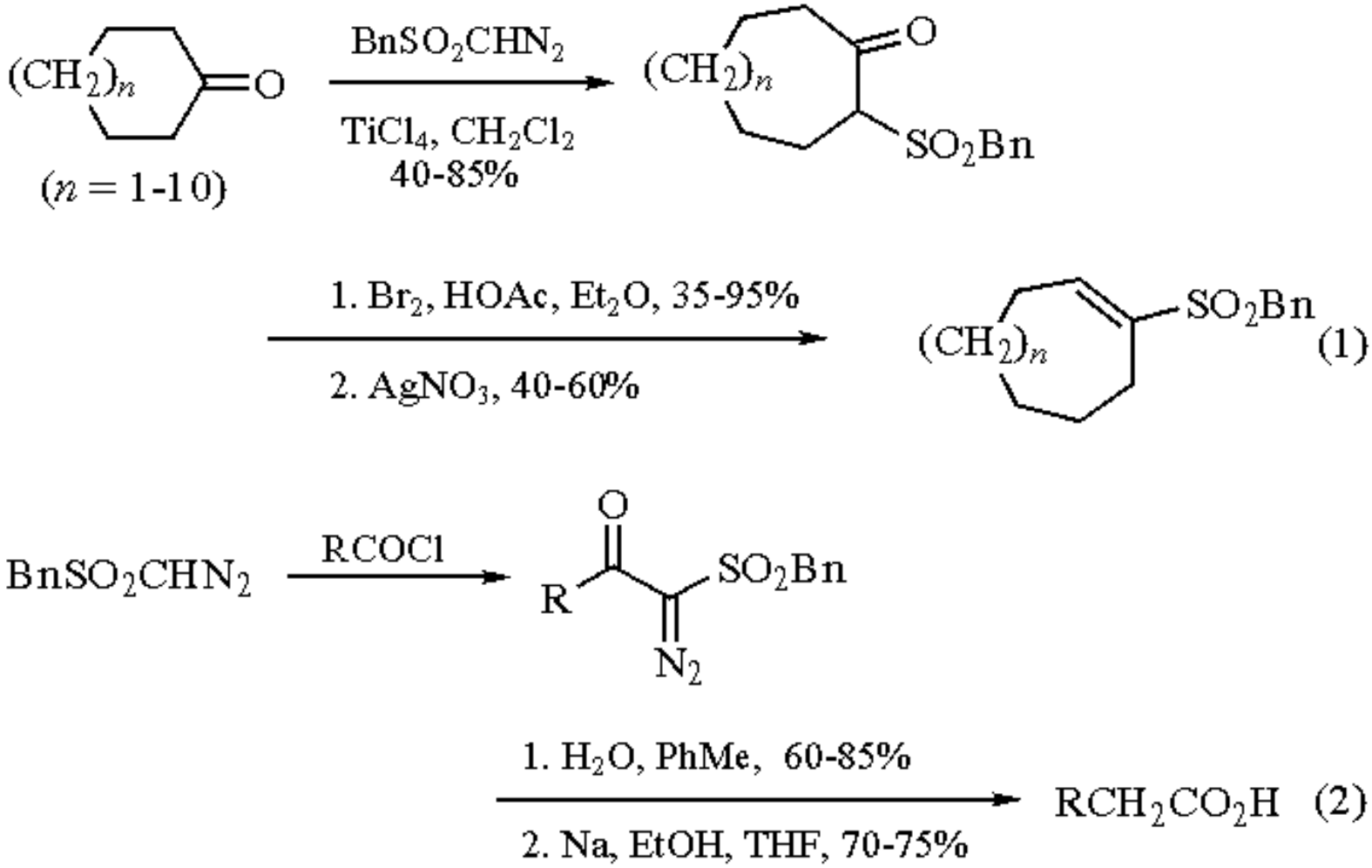

α-Substituted Sulfones.

When treated with ***Nitrosyl Chloride***, BSDM affords three products, the major one being the α-chloro sulfone. The oxime, also produced, is of interest as a precursor to nitrile oxides (eq 4).[1] Reaction with sulfenyl chlorides affords α-chloro α-sulfenyl sulfones (eq 5),[7] while ***t-Butyl Hypochlorite*** in alcohol solvent enables the synthesis of α-alkoxy α-chloro sulfones, wherein the alkoxy substituent is derived from the solvent (eq 6).[8] Finally, exposure of BSDM to ***p-Toluenesulfonic Acid*** provides the corresponding α-tosylate in 88% yield.[5]

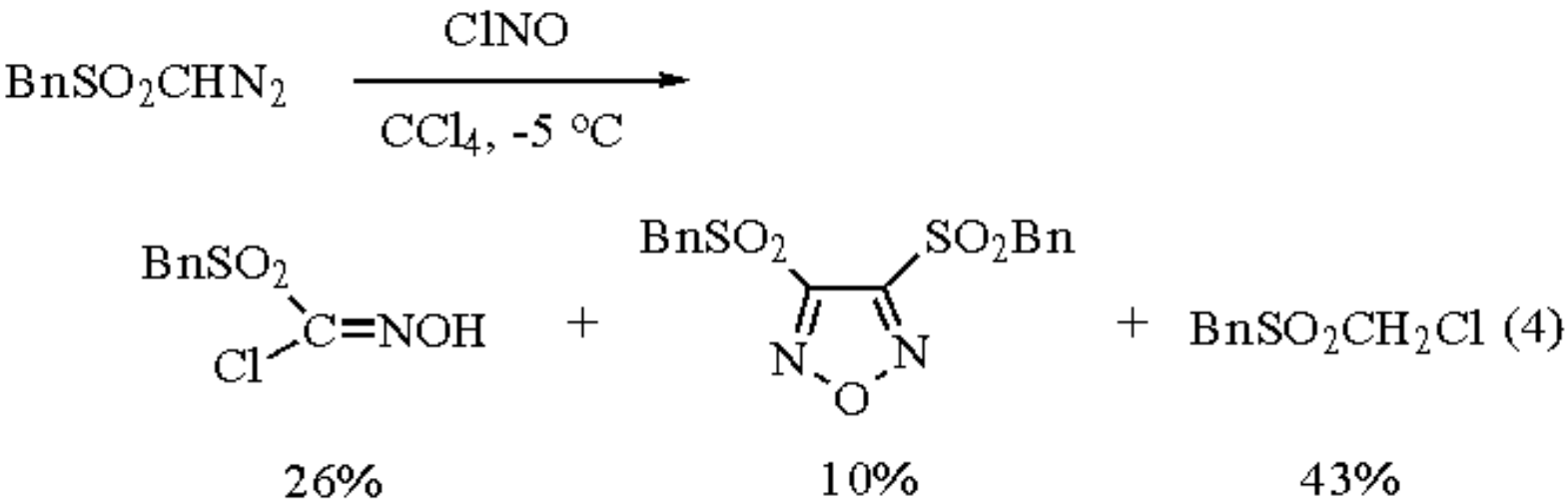

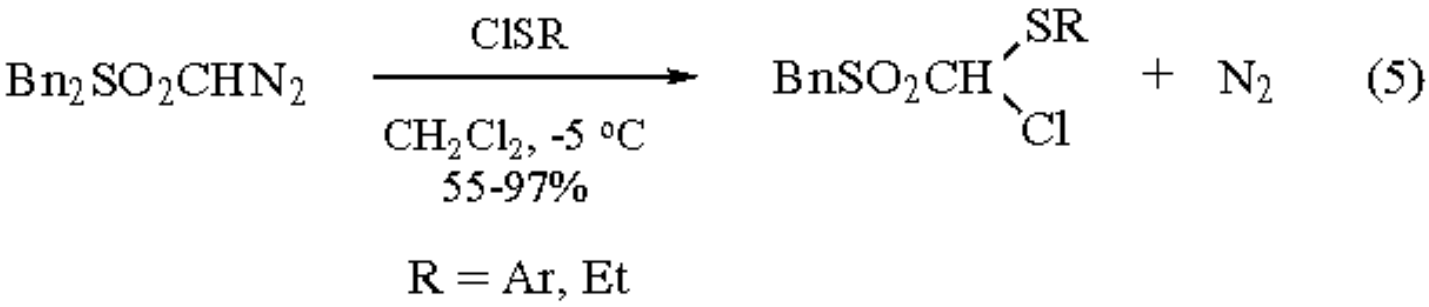

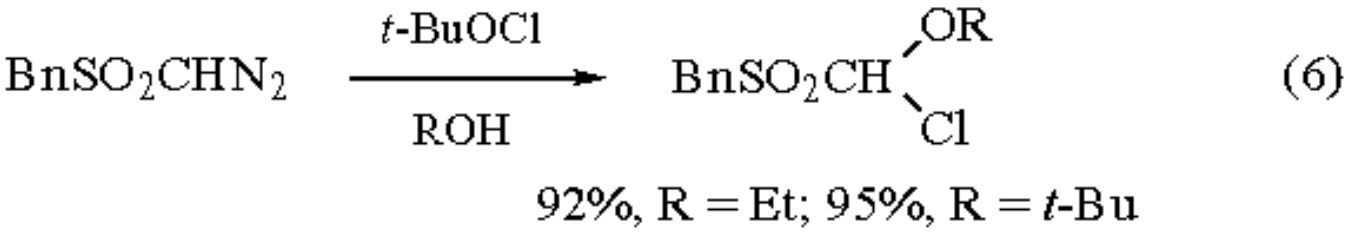

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(*S*)-4-Benzyl-2,2,5,5-tetramethyloxazolidine

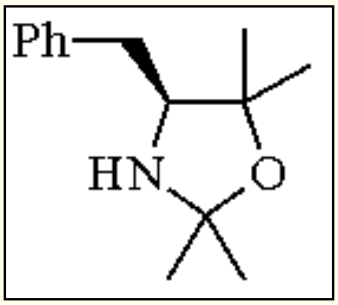

[144899-42-3] · $C_{14}H_{21}NO$ · (*S*)-4-Benzyl-2,2,5,5-tetramethyloxazolidine · (MW 219.33)

(chirality-controlling auxiliary[1])

Physical Data: colorless liquid; IR,[2] ^{1}H NMR,[1] and ^{13}C NMR[2] spectra are available.

Solubility: very sol in most organic solvents; decomposition occurs in protic solvents.

Handling, Storage, and Precautions: decomposes on silica gel column chromatography; recommended not to be stored for a long time.

Introduction.

(*S*)-4-Benzyl-2,2,5,5-tetramethyloxazolidine is used as a chirality-controlling auxiliary. Its amide derivatives preferentially occupy the *syn* conformation[1] so that one of the π-facial reaction sites of the amide moiety becomes sterically less hindered. This chiral auxiliary will be especially useful for the asymmetric reactions which have to be performed in the absence of metallic additives.

Preparation and Stability.

Since *N*-unsubstituted oxazolidines are labile to hydrolysis, they should be transformed immediately after preparation to amide derivatives, which show much higher stability. Thus reaction of (*S*)-3-amino-2-methyl-4-phenyl-2-butanol[3] with acetone in the presence of a catalytic amount of ***p-Toluenesulfonic Acid*** produces (*S*)-4-benzyl-2,2,5,5-tetramethyloxazolidine. *N*-Acylation using acryloyl, cinnamoyl, and propanoyl chloride (Et_3N, -78 °C) gives the corresponding amides. The *N*-crotonoyl derivative is better obtained by the crotonoylation of (*S*)-3-amino-2-methyl-4-phenyl-2-butanol followed by acetalization with $(Me)_2C(OMe)_2$.

Unsaturated Amides.

Cycloaddition of (*S*)-3-acryloyl-4-benzyl-2,2,5,5-tetramethyloxazolidine with ***Benzonitrile Oxide*** proceeds smoothly at 0 °C to provide the corresponding oxazolidine in a 93:7 diastereomer ratio (eq 1),[4] which is quantitatively reduced with ***Lithium Triethylborohydride*** to give the isoxazoline-5-methanol derivative without loss of enantiomeric purity. A single diastereomer of isoxazoline can be obtained when 3-acryloyl-2,2-dimethyl-4-diphenylmethyloxazolidine is employed.[4]

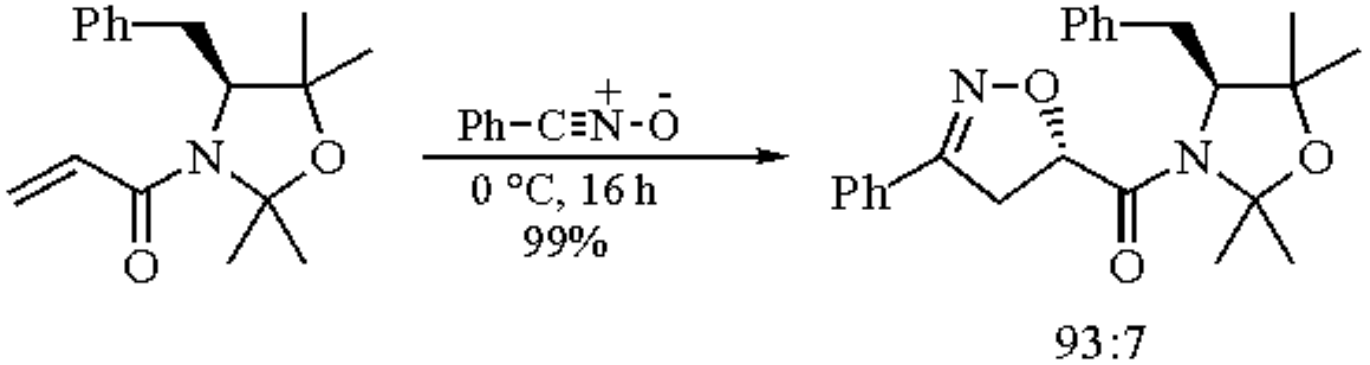

(1)

Conjugate additions of organocuprates to (*S*)-4-benzyl-3-crotonoyl-2,2,5,5-tetramethyloxazolidine in the presence of ***Chlorotrimethylsilane*** (1.2 equiv) also proceed in a highly diastereoselective manner (eq 2) to give, after the acid-catalyzed hydrolytic removal of the chiral auxiliary, optically pure carboxylic acids with β-chirality.[5]

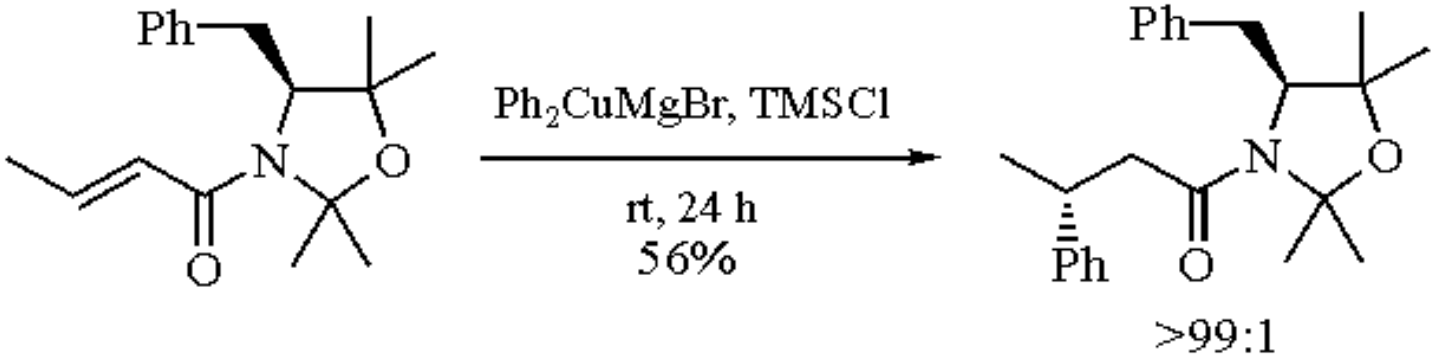

(2)

Amide Enolates.

The lithium (*Z*)-enolate can be generated from (*S*)-4-benzyl-3-propanoyl-2,2,5,5-tetramethyloxazolidine and ***Lithium Diisopropylamide*** in THF at -78 °C. Its alkylations[6] take place smoothly in the presence of ***Hexamethylphosphoric Triamide*** with high diastereoselectivity (eq 3), and its Michael additions[7] to α,β-unsaturated carbonyl compounds are also exclusively diastereoselective (eq 4). Synthetic applications have been made in the aldol reactions of the titanium (*Z*)-enolates of α-(alkylideneamino) esters.[8]

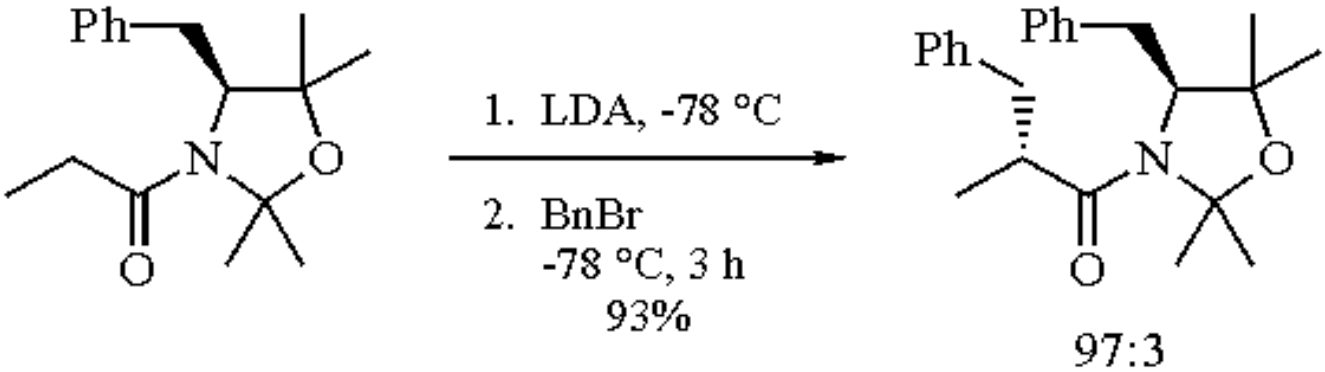

(3)

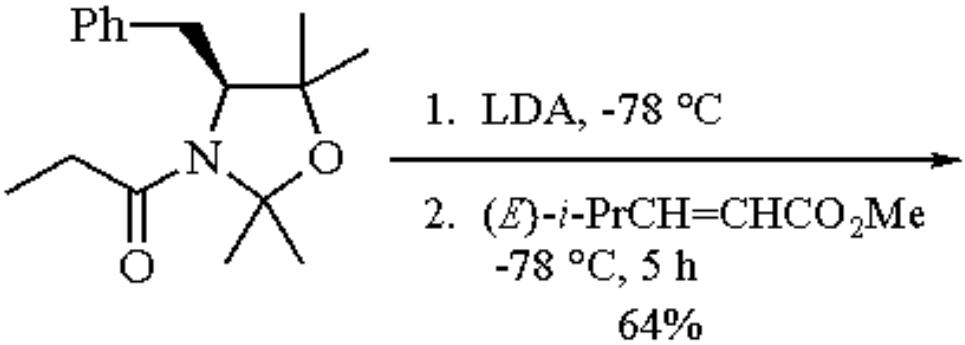

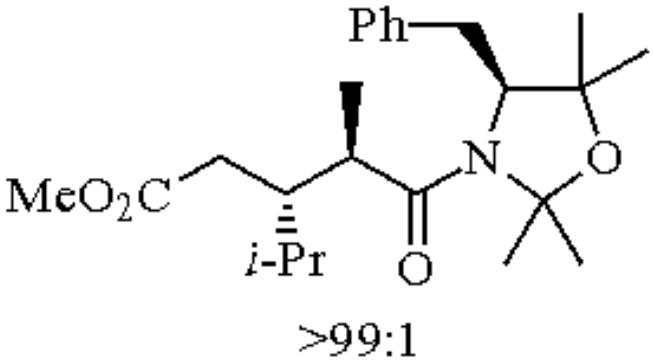

(4)

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2. IR (neat) 3350, 2950, 1410, 1360, 1100, and 800 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ = 23.21, 27.37, 28.52, 29.60, 35.95, 67.04, 80.66, 92.75, 128.48, 128.62, 128.71, and 139.00.
3. (*S*)-3-Amino-2-methyl-4-phenyl-2-butanol is available from (*S*)-phenylalanine and MeMgI (4 equiv): diethyl ether, rt, 5 h, 58%.
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3-Benzylthiazolium Bromide[1]

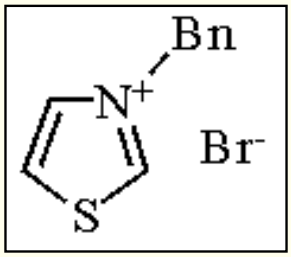

[75066-50-1] · $C_{10}H_{10}BrNS$ · 3-Benzylthiazolium Bromide · (MW 256.16)

(in combination with base is a redox catalyst for the oxidation of aldehydes coupled with the reduction of organic compounds[2])

Physical Data: mp 155-156 °C.

Solubility: freely sol methanol; sol ethanol, DMSO, and DMF; sparingly sol chloroform, dichloromethane, and acetone; insol THF, benzene, and ethyl acetate.

Form Supplied in: white columnar crystals.

Analysis of Reagent Purity: ^{1}H NMR (DMSO-d_6, 270 MHz) δ 5.82 (s, 2H, CH_2), 7.41-7.53 (m, 5H, C_6H_5), 8.37 (dd, 1H, H-5, *J* = 3.7 and 2.4 Hz), 8.61 (dd, 1H, H-4, *J*= 3.7 and 1.8 Hz); 10.40 (dd, 1H, H-2, *J* = 2.4 and 1.8 Hz).

Purification: recrystallized from 5:1 benzene/ethanol.

Handling, Storage, and Precautions: the reagent is somewhat hygroscopic and should be dried before use.

Oxidation of Aldehydes to Methyl Esters.

3-Benzylthiazolium bromide, in methanol containing ***Triethylamine***, catalyzes a redox reaction in which aldehydes are oxidized to methyl esters, and certain organic compounds such as acridine, phenazine, azobenzene, and nitrobenzene are reduced.[2] The redox reactions are carried out as follows. Triethylamine (5*n* mmol) and the substrate (4*n* mmol) are added to a frozen solution of a mixture of aldehyde (6*n* mmol) and 3-benzylthiazolium bromide (*n* mmol) in degassed methanol (10*n* mL). The solution, after melting, is stirred under argon at rt for a 20-h period. To increase the yield in the redox reaction, an excess of aldehyde is added. The presence of air in methanol results in the production of methyl esters by oxidation of aldehydes.

The mechanism of this process is outlined in eq 1. The thiazolium salt is first transformed into an ylide by the action of

triethylamine[3] and the ylide then reacts with the aldehyde to form an adduct (active aldehyde)[4] which undergoes a redox reaction with the organic substrate in methanol to give a methyl ester and the reduced form of the substrate (eq 1).

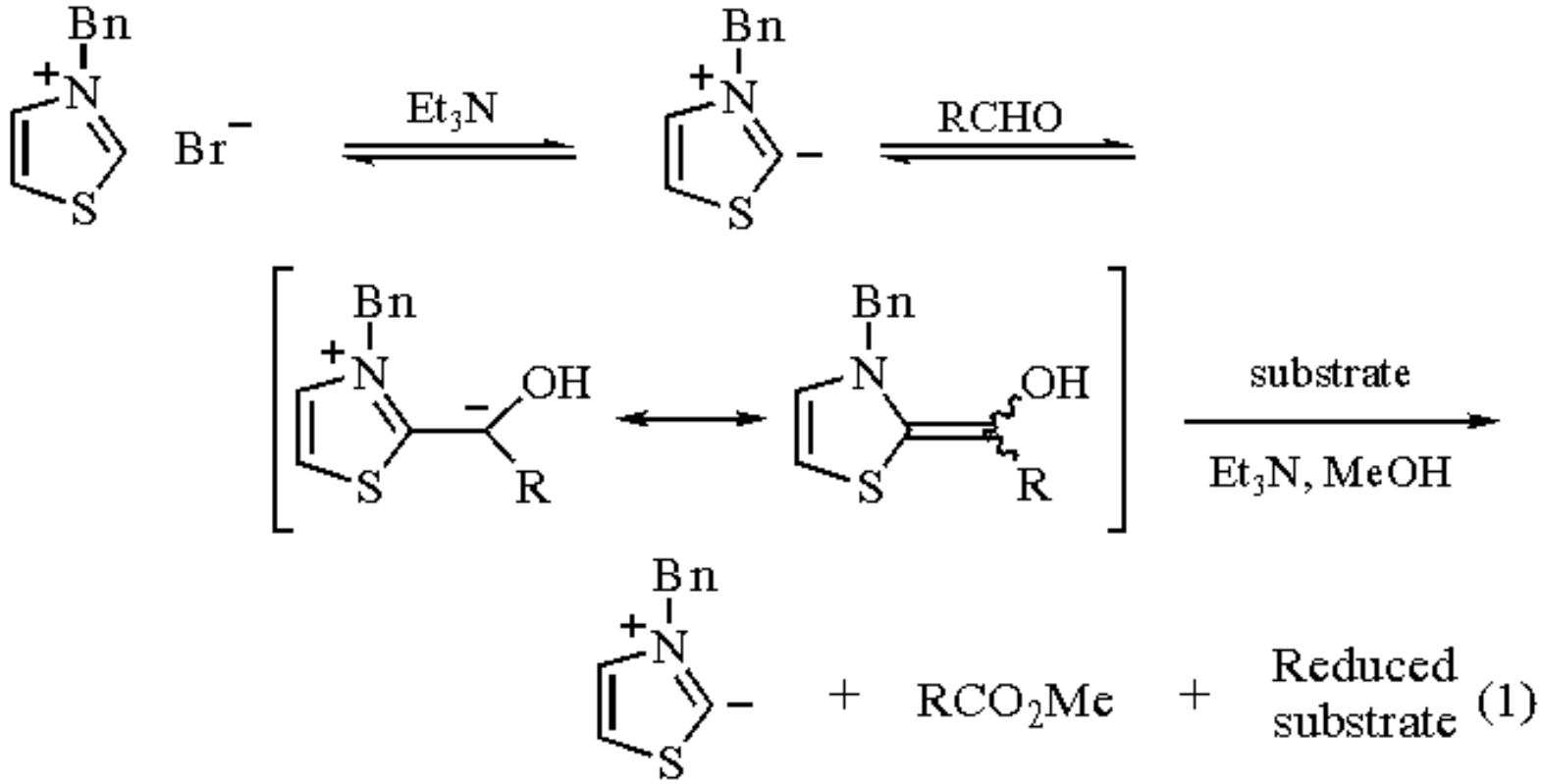

Acridine is reduced by benzaldehyde, 2-furaldehyde, and heptanal in the presence of 3-benzylthiazolium bromide and triethylamine in degassed methanol to give 9,9´-biacridan in satisfactory yields, while aldehydes are oxidized to the corresponding methyl esters (eq 2).[2] The excess aldehydes are converted into α-hydroxy ketones by benzoin condensation.[5] The redox reaction is thought to proceed via the transfer of electrons from the active aldehyde to acridine.

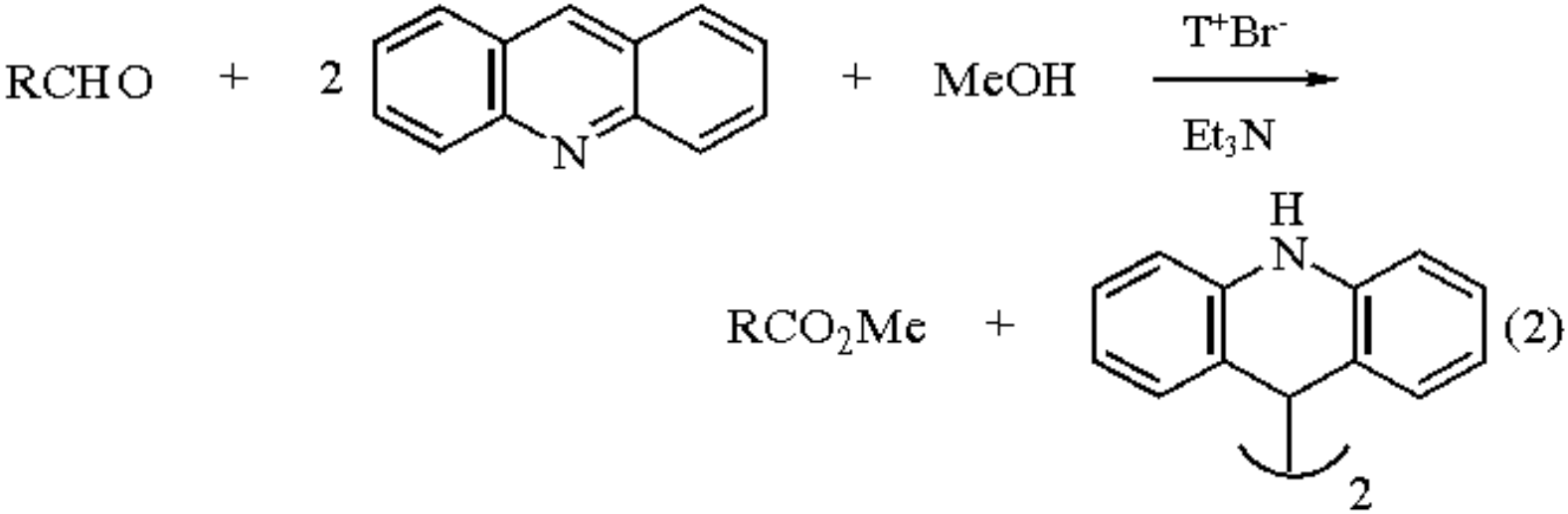

R = Ph	87%	93%
R = 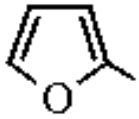	30%	40%
R = $Me(CH_2)_5$	67%	72%

T^+Br^- = 3-benzylthiazolium bromide

Phenazine and azobenzene are reduced, under similar conditions, to 5,10-dihydrophenazine (eq 3) and hydrazobenzene (eq 4), respectively; the latter is converted into benzidine on treatment with hydrochloric acid after the reaction.[2] Nitrobenzene is reduced to aniline and *N*-benzoyl-*N*-phenylhydroxylamine (eq 5).[2,6]

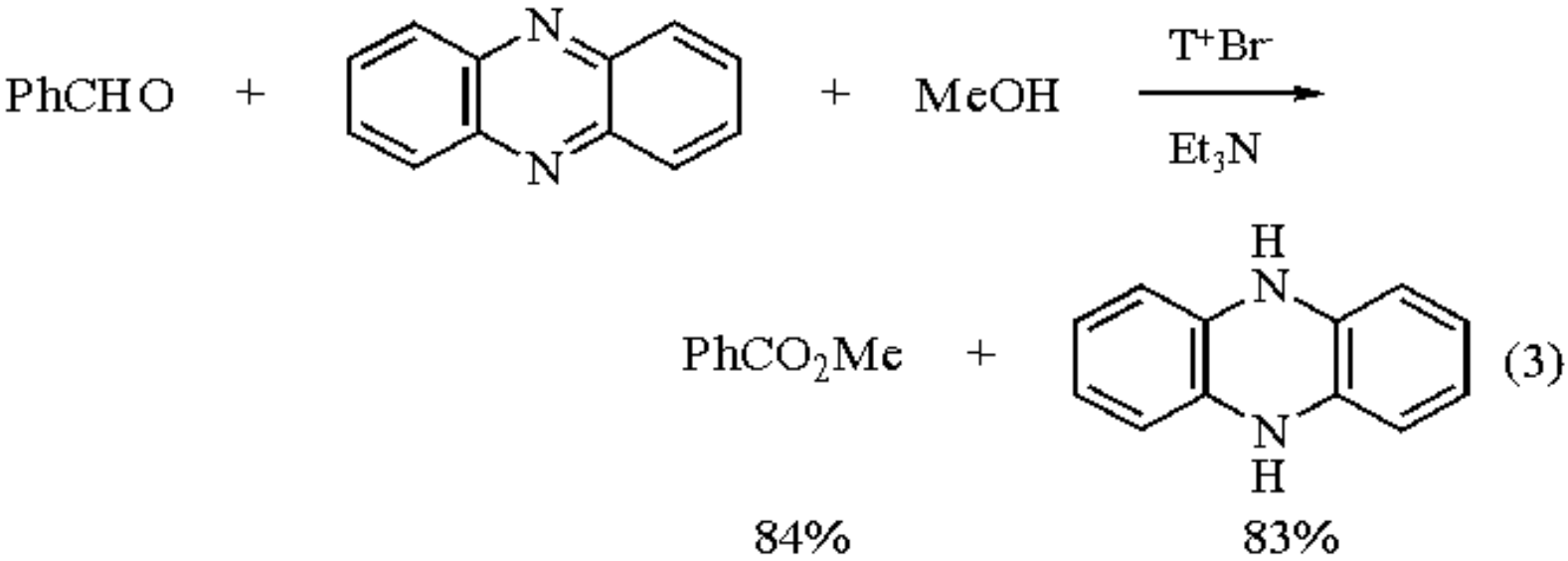

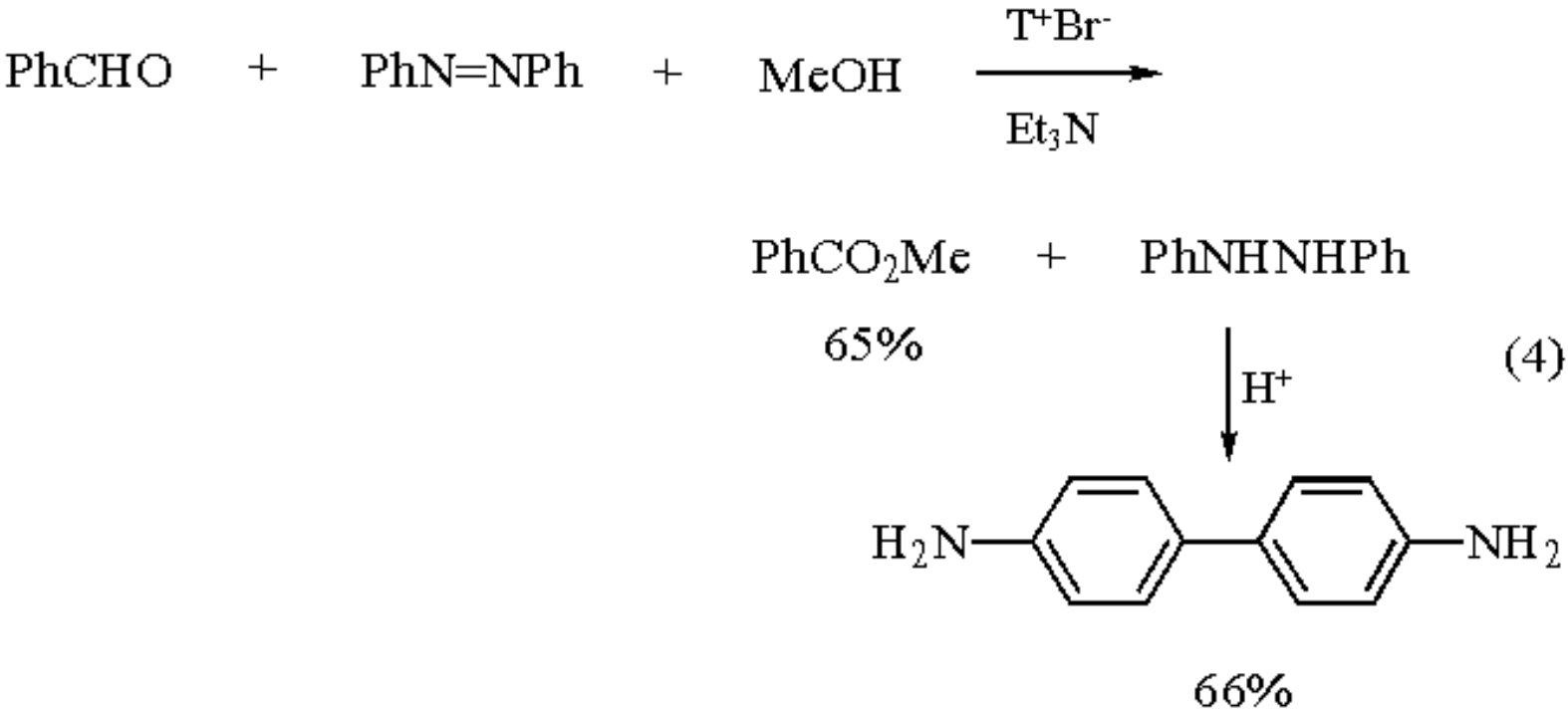

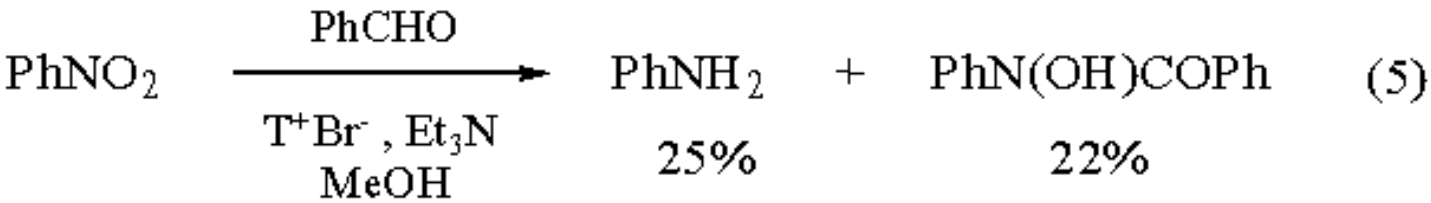

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Benzyl *p*-Toluenesulfonate

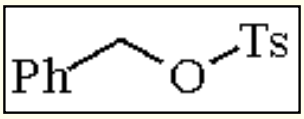

[1024-41-5] · $C_{14}H_{14}O_3S$ · Benzyl *p*-Toluenesulfonate · (MW 262.32)

(benzylating agent for heteroatomic functional groups and enolate anions)

Alternate Name: benzyl tosylate.

Physical Data: mp 58 °C.

Solubility: sol alcohols, ether, and aromatic solvents.

Preparative Method: typically prepared from tosyl chloride and benzyl alcohol.[1]

Handling, Storage, and Precautions: may be stored as a crude or purified solid at 0 °C for up to 3 months; potential vessicant. Use in a fume hood.

Benzylation of Heteroatomic Functional Groups.

Phenols are benzylated with this reagent under basic conditions. The regioselectivity, when more than one phenol is present in the substrate, favors the less sterically hindered hydroxy group (eq 1).[2] In the case of phenols where *C*-alkylation commonly accompanies *O*-alkylation, benzyl tosylate gives higher selectivity for *O*-alkylation than ***Benzyl Chloride***.[2] This is illustrated in the benzylation of a phloroglucinol derivative, where benzyl chloride afforded only 18% of the desired product under similar reaction conditions (eq 2).

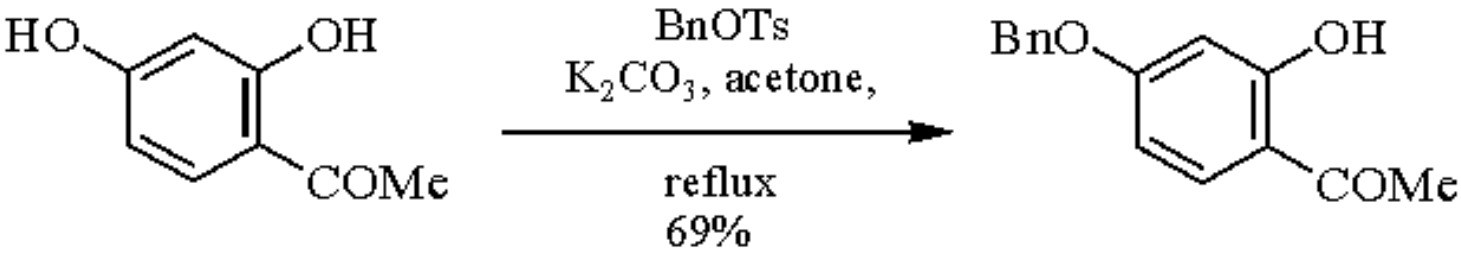

(1)

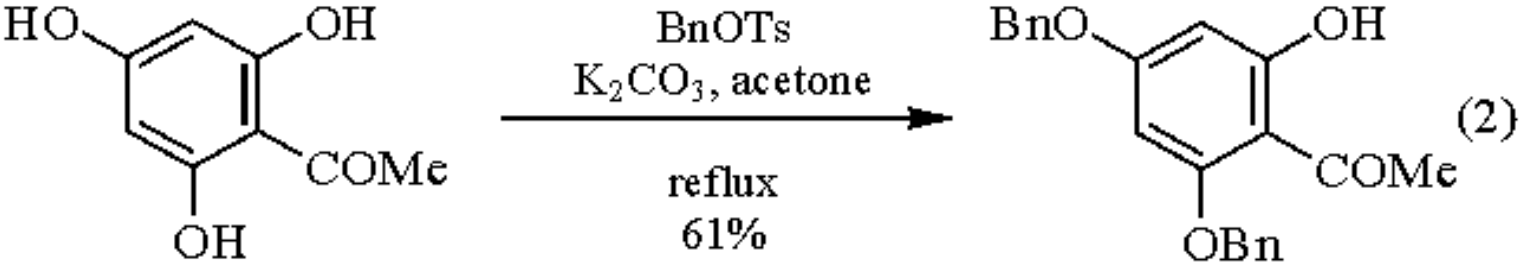

Lactams[3] and vinylogous amides[4] can be selectively *N*-benzylated under basic conditions with this reagent (eq 3). Methylamine affords benzylmethylamine when reacted in excess with benzyl tosylate in ether.[5]

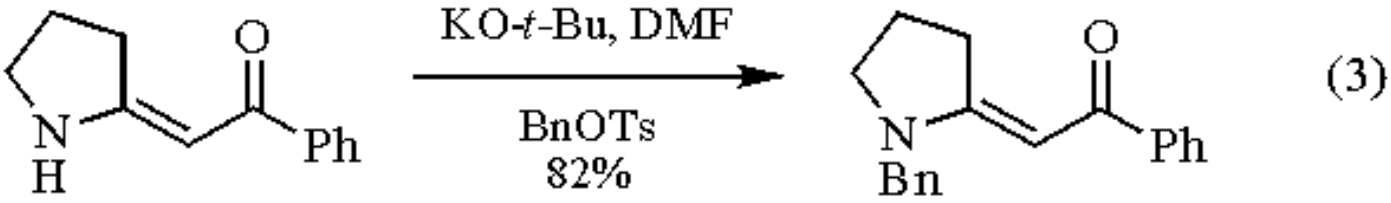

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Benzyl 3-(Tributylstannyl)acrylate

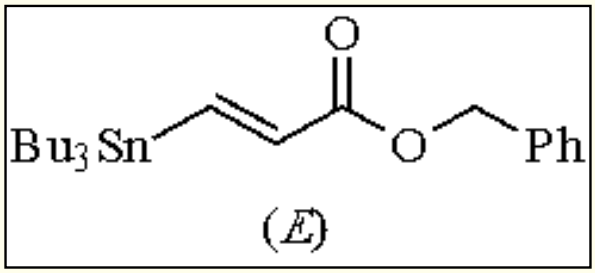

(*E*)

[86633-19-4] · $C_{22}H_{36}O_2Sn$ · Benzyl 3-(Tributylstannyl)acrylate · (MW 451.22) (*Z*)

[86633-18-3]

(this reagent, along with the corresponding ethyl and methyl esters, are useful partners for Pd^0-catalyzed coupling reactions with a variety of substrates including aryl triflates,[1-3] aryl bromides[4] and iodides,[5,6] vinyl triflates,[7,8] vinyl iodides,[9-13] allylic chlorides,[14] acyl chlorides,[15-17] and sulfonyl chlorides[18])

Physical Data: colorless oil.

Solubility: sol THF, $CHCl_3$.

Preparative Methods: the benzyl acrylates (**1**) and (**2**) can be obtained by nonstereoselective hydrostannylation of benzyl propynoate (eq 1).[15,20] Mixtures of substances (**3**) and (**4**)[10] and of (**5**) and (**6**)[13,21] have been prepared in similar fashion (eq 1). In each case the geometric isomers are chromatographically separable. The stereocontrolled synthesis of (**3**) can be achieved by sequential treatment of (*E*)-1,2-bis(tributylstannyl)ethene with an alkyllithium and $ClCO_2Et$.[22,23] On the other hand, stereospecific syntheses of (**5**) and (**6**) have been achieved by reaction of methyl (*E*)- and (*Z*)-3-chloro (or iodo)acrylates with Bu_3SnCu[24] (see ***Tri-n-butylstannylcopper***).

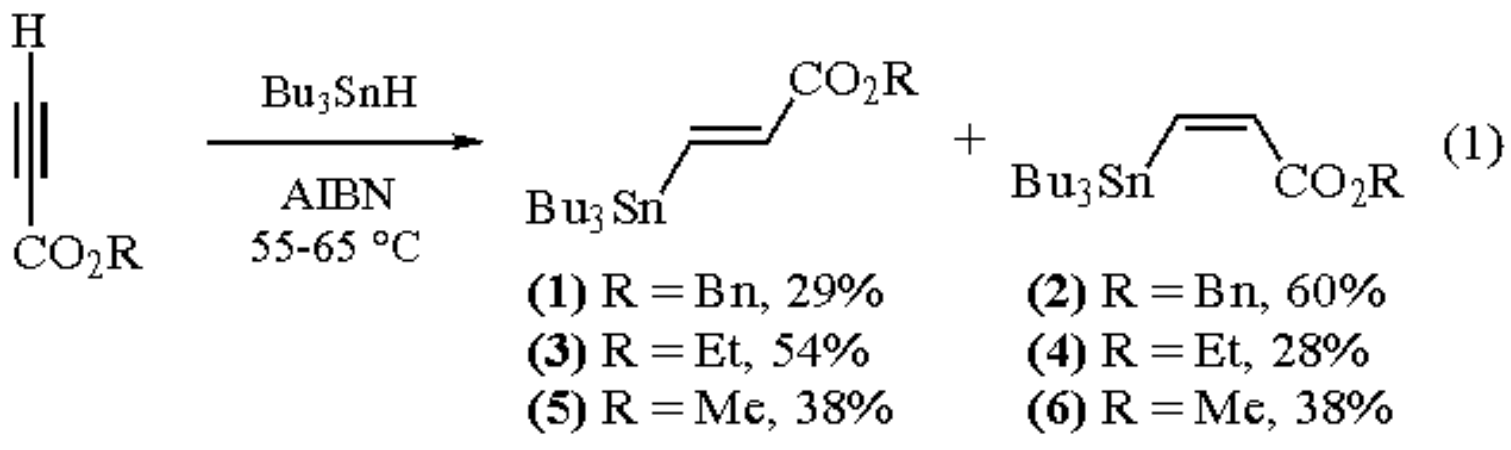

Handling, Storage, and Precautions: since organotin compounds are toxic,[19] reactions preparing and employing the reagent should be carried out and worked up in a fume hood.

Reaction with Aryl Triflates and Halides.

The Pd^0-catalyzed couplings of reagents (**1**)-(**6**) with aryl triflates[1-3] or halides[4-6] constitute a useful method for the direct incorporation of a 2-(alkyoxycarbonyl)vinyl moiety into aromatic systems. Examples are shown in eqs 2-4.[1,3,6] As indicated by eq 2, the couplings employing the (*Z*) reagents (**2**), (**4**), and (**6**) are generally more sluggish than those employing the corresponding (*E*) isomers. Furthermore, the reaction of (**7**) with (**2**) is not stereoselective.[1] On the other hand, the interesting cross-coupling reaction involving tricarbonyl(iodo-η^5-cyclopentadienyl)methyltungsten and the (*Z*) acrylate (**6**) (eq 4) proceeds in a completely stereoselective fashion, with retention of reagent stereochemistry.[6]

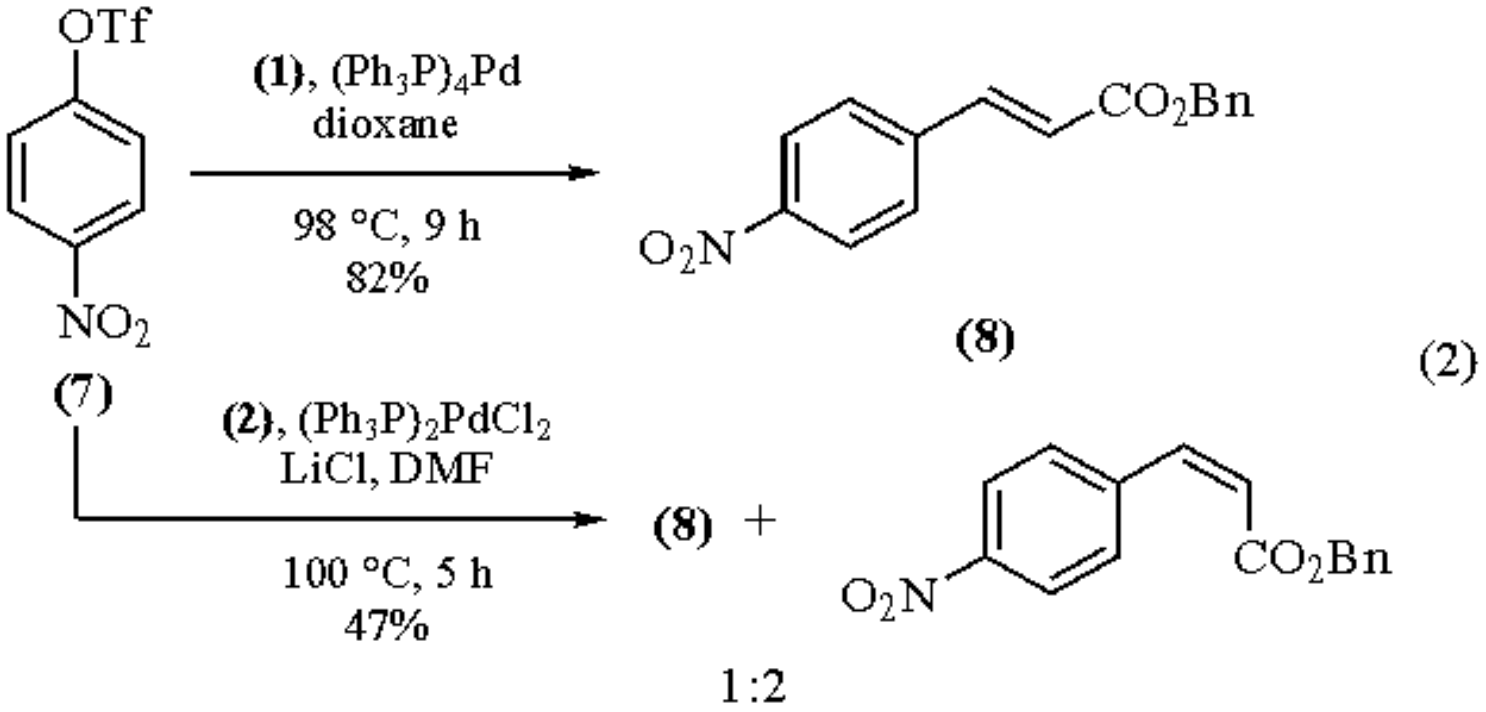

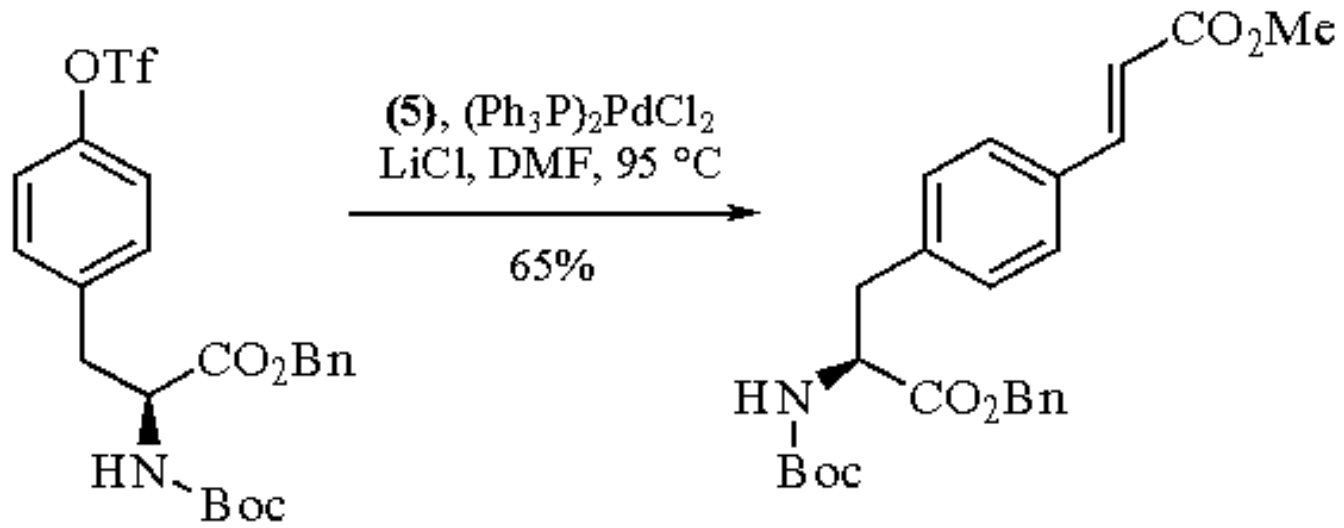

(3)

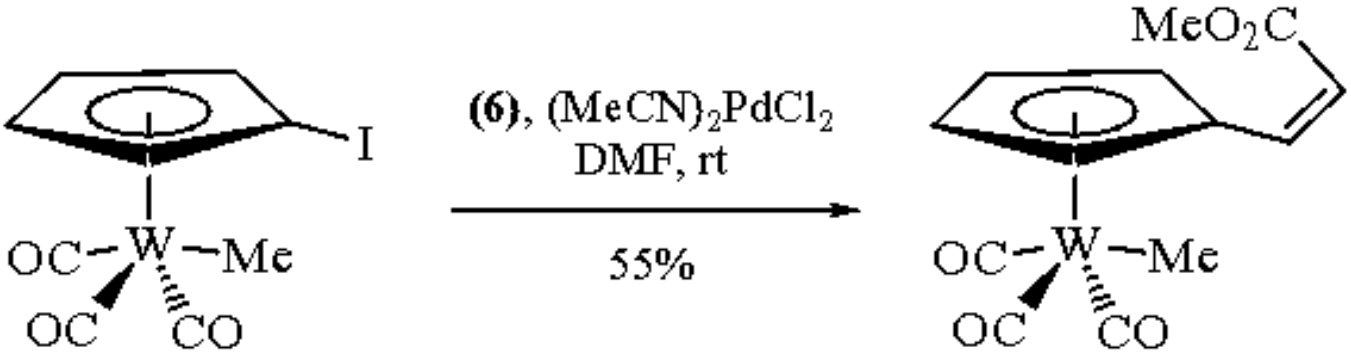

(4)

Reaction with Vinyl Triflates and Iodides.

The Pd^0-mediated couplings of reagents (**1**)-(**6**) with vinyl triflates[7,8] and iodides[10-13] produce a valuable method for the stereocontrolled synthesis of substituted alkyl 2,4-alkadienoates (eqs 5-8).[8,10,12] This carbon-carbon bond-forming process appears to be stereospecific (eqs 6-8). In contrast, formation of the unsymmetrical divinyl ketone (**9**) via cross-coupling of 1-iodocyclohexene with the (*Z*)-acrylate (**2**) in the presence of CO is not stereoselective (eq 9).[9] The mechanism of this process has been discussed in detail.[9]

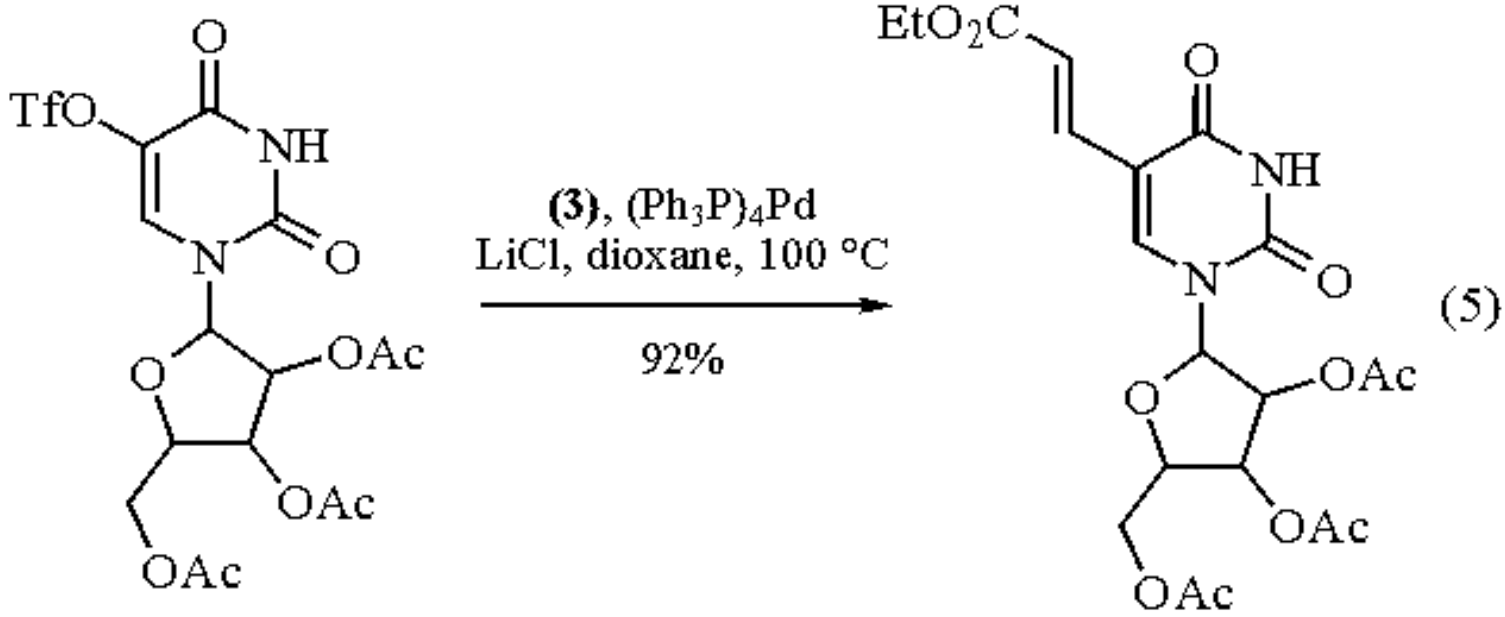
TfO
O
NH
N
O
OAc
OAc
OAc
(3), (Ph3P)4Pd
LiCl, dioxane, 100 °C
92%
EtO2C
O
NH
N
O
OAc
OAc
OAc
(5)

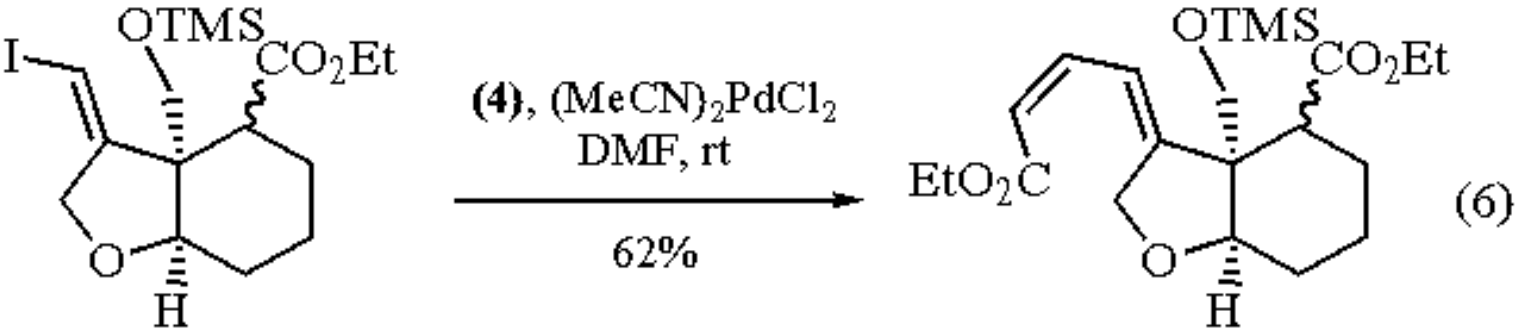
I
OTMS
CO2Et
O
H
(4), (MeCN)2PdCl2
DMF, rt
62%
OTMS
CO2Et
EtO2C
O
H
(6)

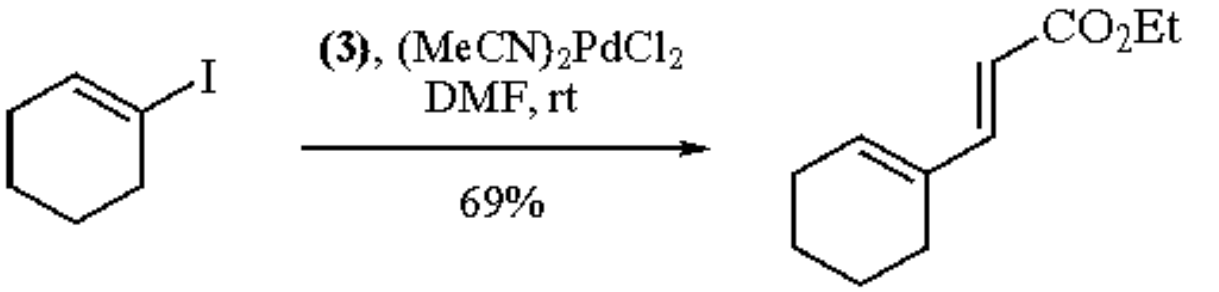
I
(3), (MeCN)2PdCl2
DMF, rt
69%
CO2Et
(7)

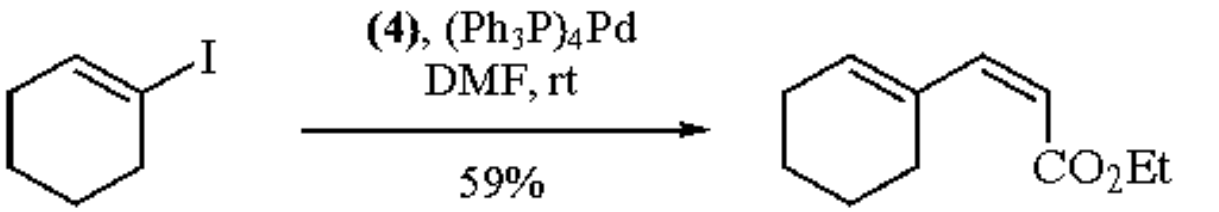
I
(4), (Ph3P)4Pd
DMF, rt
59%
CO2Et
(8)

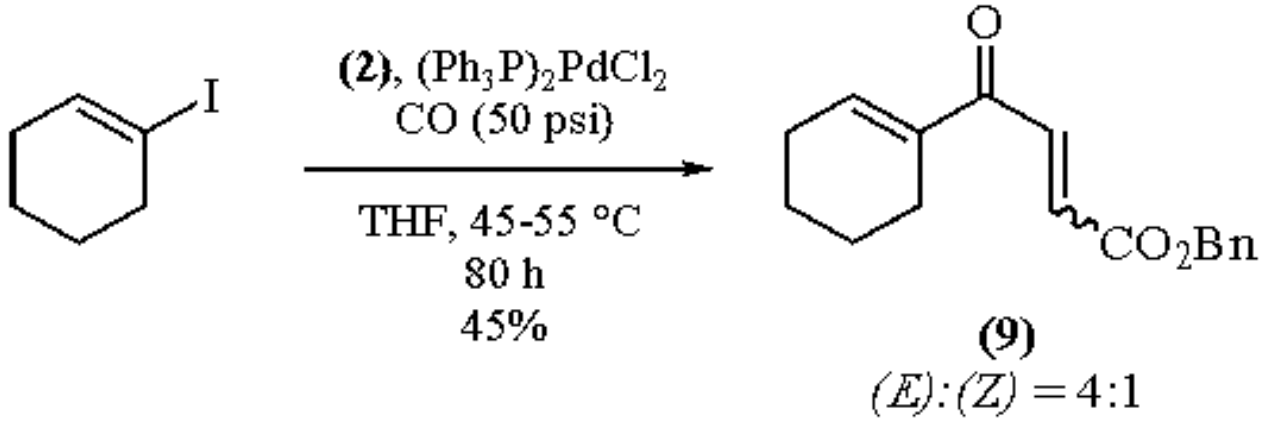

(9)

Reaction with Allylic Chlorides.

Reaction of allyl halides with vinylstannanes in the presence of a Pd^0 catalyst provides, efficiently, cross-coupled products. An example of this process involving the (*Z*)-acrylate (**2**) is shown in eq (10).[14] The substitution reaction takes place with overall inversion of configuration, while the stereochemistry of the acrylate moiety is retained.

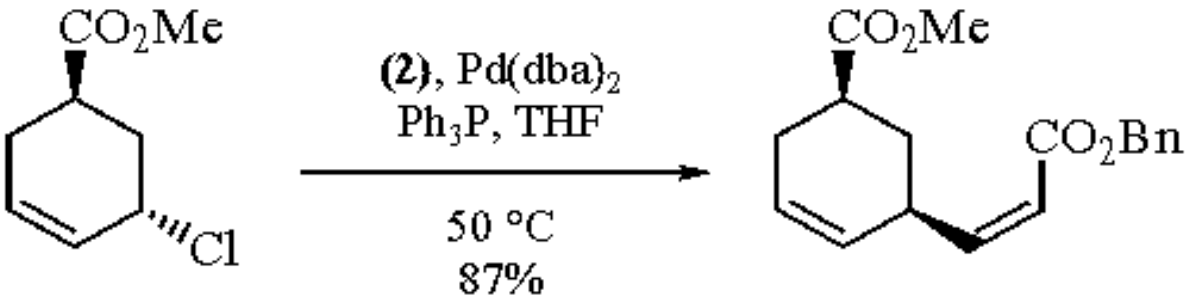

(10)

Reaction with Acyl and Sulfonyl Chlorides.

Acyl and sulfonyl chlorides react with 3-tributylstannylacrylates in the presence of Pd^0 to give alkyl 4-oxo-2-alkenoates[15-17] and β-alkoxycarbonyl-α,β-unsaturated sulfones,[18] respectively (eqs 11 and 12).[16,18] In each case the configuration of the product is (*E*), regardless of the stereochemistry of the acrylate reagent.[15,17,18] Intramolecular versions of the acyl chloride coupling process have been employed to prepare macrocyclic substances,[25] including the macrodiolide (*R*,*R*)-(-)-pyrenophorin.[25c]

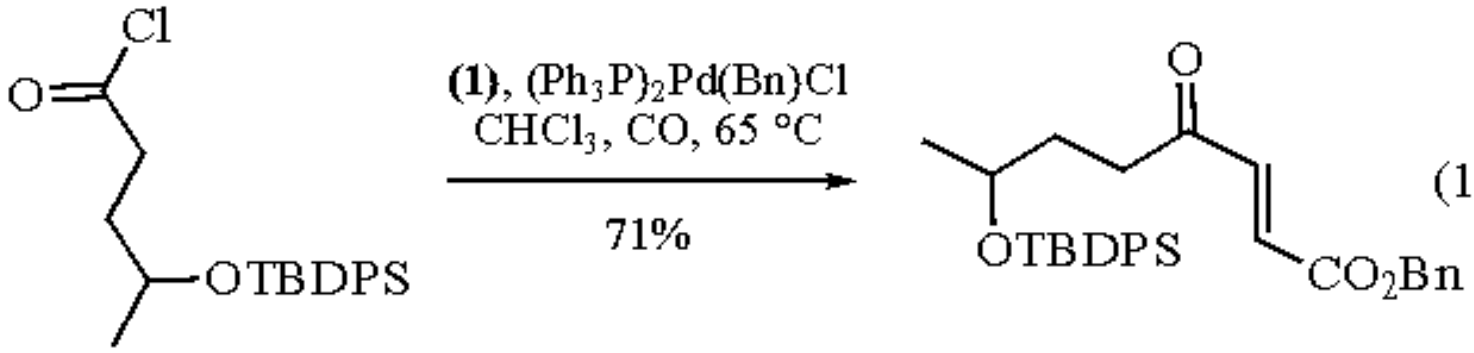

(11)

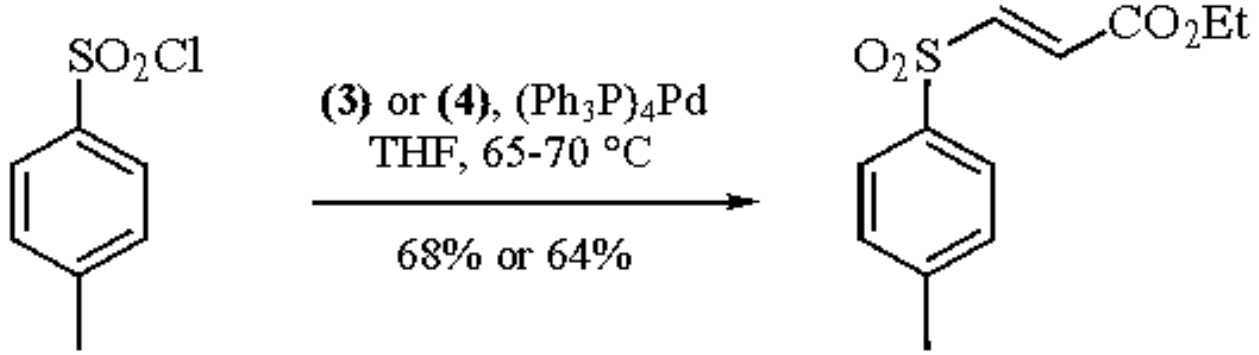

(12)

Miscellaneous Reactions.

Reagent (**3**) has been used as a dienophile in Diels-Alder reactions[22] and has been converted into the synthetically useful epoxide ethyl (*E*)-3-tributylstannyl-2,3-epoxypropanoate.[26] The methyl acrylates (**5**) and (**6**) have been employed in effecting a highly stereoselective radical substitution process (eq 13),[27] which played a key role in a total synthesis of the natural product bulgecin C.[27]

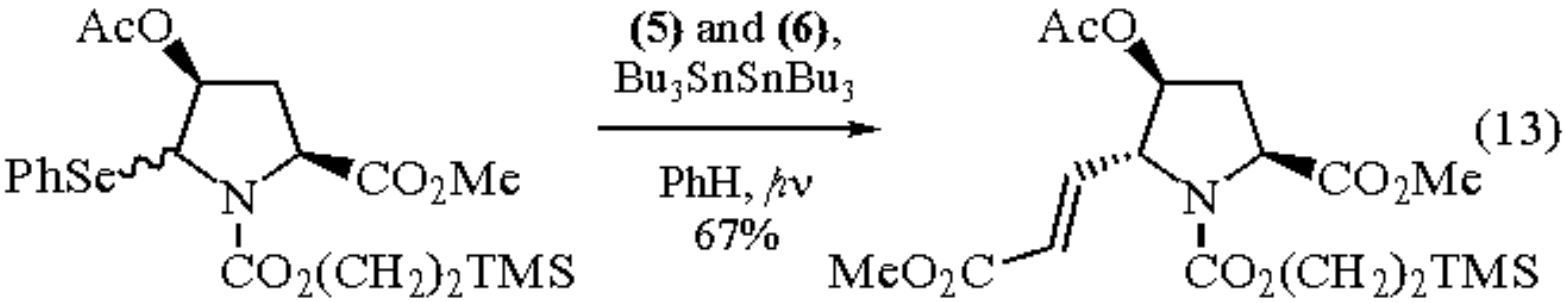

(13)

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Benzyl 2,2,2-Trichloroacetimidate

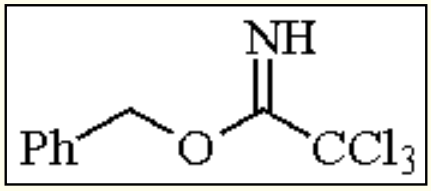

[81927-55-1] · $C_9H_8Cl_3NO$ · Benzyl 2,2,2-Trichloroacetimidate · (MW 252.53)

(reagent for protection of hydroxy groups as benzyl ethers under mildly acidic conditions[1])

Alternate Name: BTCA.

Physical Data: bp 106-114 °C/0.5 mmHg; *d* 1.359 g cm^{-3}

Solubility: reactions are most often carried out in a mixture of cyclohexane/dichloromethane;[1] decomposition by rearrangement to *N*-benzyl trichloroacetamide is accelerated in more polar solvents.

Form Supplied in: colorless oil.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: moisture sensitive.

Hydroxy Group Protection.

The benzyl ether is one of the most versatile and frequently used protecting groups in organic synthesis.[2] The most common way of introducing this group is with a strong base and ***Benzyl Bromide*** using the classical Williamson ether synthesis methodology. Recently, benzyl trichloroacetimidate[3] has found widespread use to protect hydroxy functionalities as their benzyl ethers under mildly acidic conditions,[1,4,5a] when the more conventional strong base-mediated methods either failed or gave lower yields due to side reactions and/or starting material decomposition.

The imidate can be prepared from the sodium alkoxide ion of benzyl alcohol and trichloroacetonitrile according to procedures based on those developed by Cramer[3] in the late 1950s. Substituted benzyl ethers have also been prepared this way, for example using 4-methoxybenzyl trichloroacetimidate,[5] 3,4-dimethoxybenzyl trichloroacetimidate,[6] and 2,6-dichlorobenzyl trichloroacetimidate,[7] and the method has also been applied for the synthesis of allyl[1b] and *t*-butyl ethers,[8] as well as for 2-phenylisopropyl esters[9] for peptide synthesis. The benzyl and 4-methoxybenzyl 2,2,2-trichloroacetimidates are available commercially.

The reaction is performed in nonpolar media to prevent rearrangement of the acetimidate to *N*-benzyl trichloroacetamide, and as an added advantage the solid trichloroacetamide byproduct can simply be removed by filtration. These constraints limit the substrate range to those molecules soluble in this type of solvent; for example, a sugar triol which was insoluble in dichloromethane, when reacted in DMSO yielded very little of the benzylated product desired.[10] It was also noted that differential (primary versus secondary) hydroxy protection in carbohydrates (eq 1) was poor,[10] and the ratio of the 6-OBn to 4-OBn products was at best 2:1.

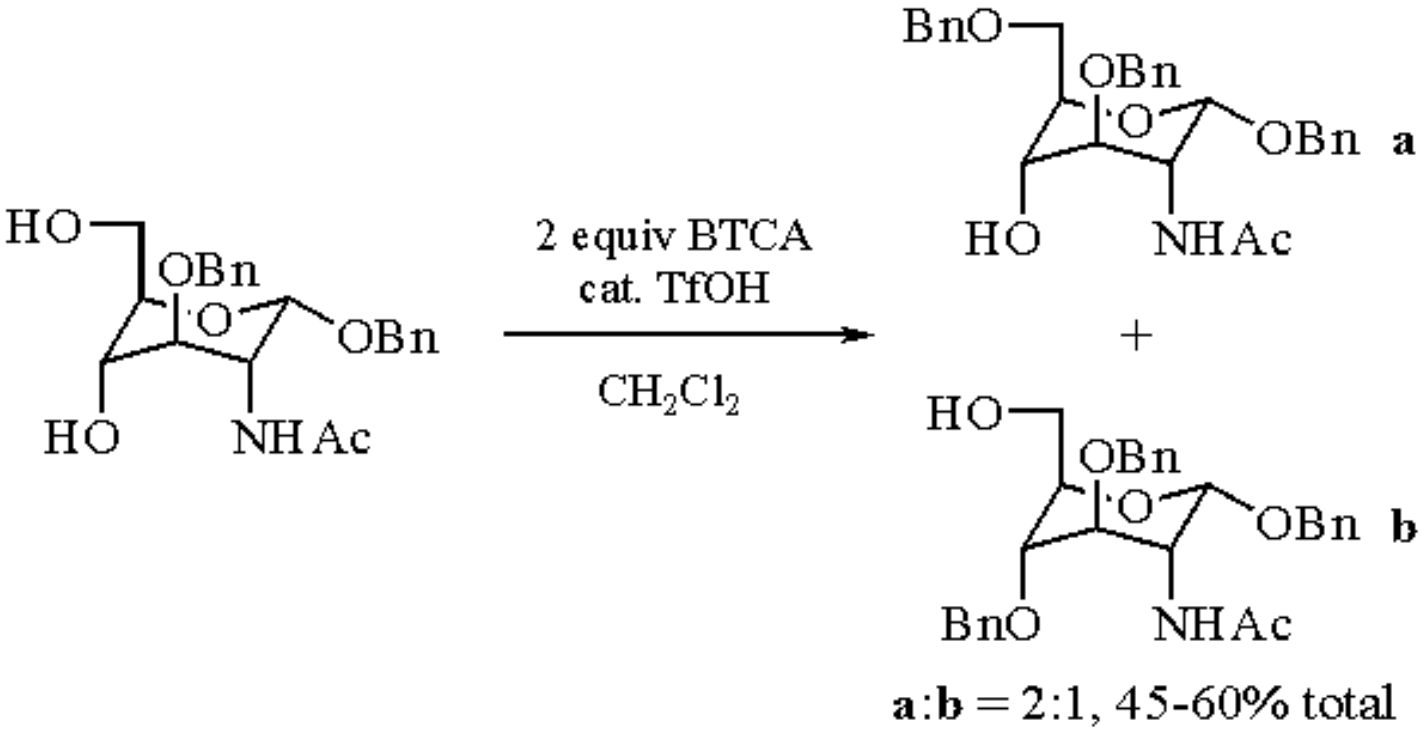

(1)

The reagent has been used widely in carbohydrate[1,10-14] chemistry. The method was found to be useful in cases where *O*-benzoyl group migration had been observed under basic conditions (eq 2),[11] and has also been applied to inositol derivatives,[15] when the same problem[15a] was encountered.

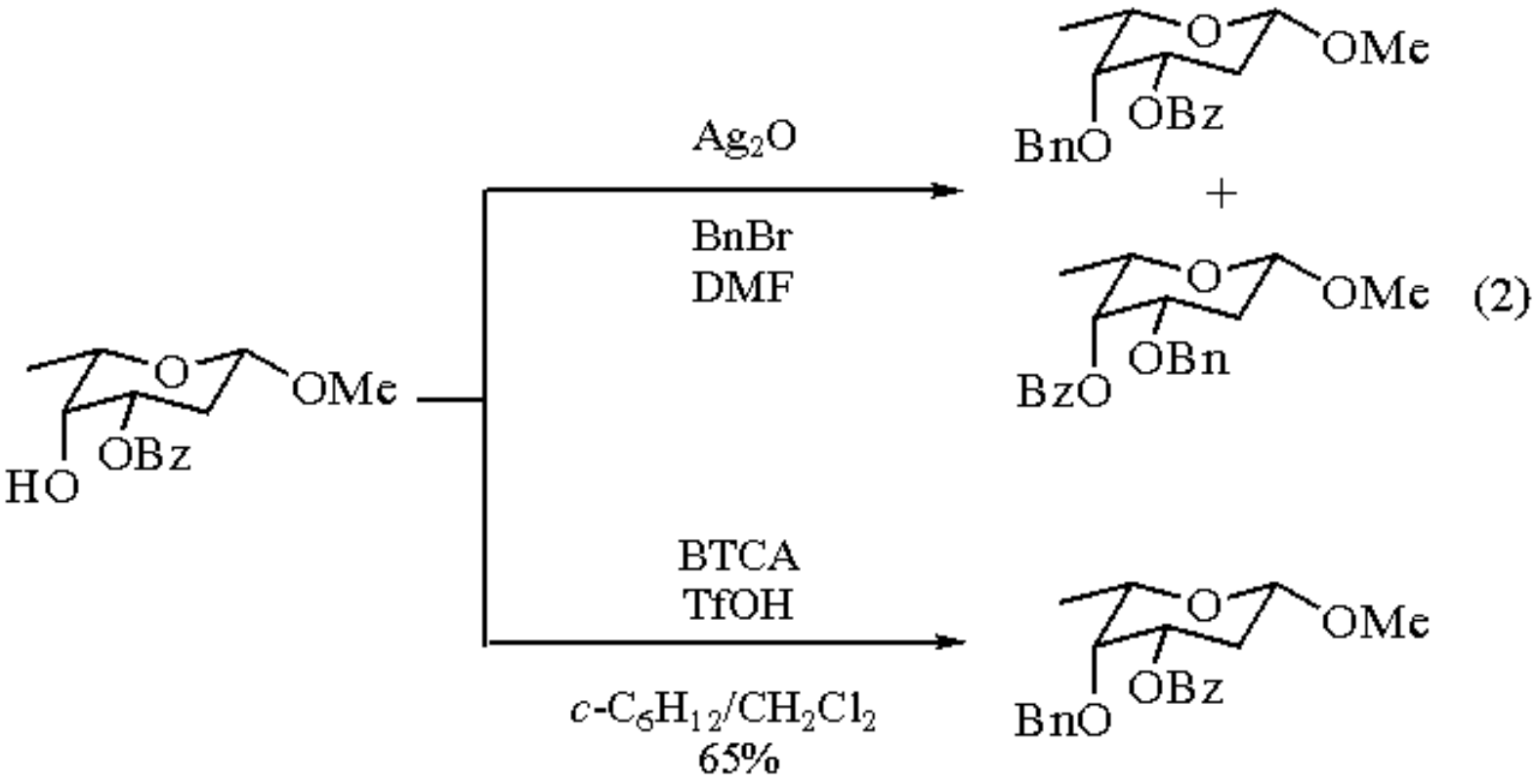

When *N*-acetyl-protected sugar amines were under investigation[1,12] the *N*-acetyl group was observed to undergo transformation to the *O*-benzyl imidate in competition with OH benzylation (eq 3). It appears for best yields at least 1 equiv of reagent per OH and NAc group is needed, and subsequent hydrolysis and reacetylation of the amine are necessary to obtain are the originally desired material. Similar problems were encountered with the morpholine derived lactams (eq 4),[16a] where mixed products were obtained, but with β-lactams[16b] with *N*-amide protection (eq 5), *O*-benzylation with benzyl trichloroacetimidate proceeded smoothly. BTCA has recently been used to convert diketopiperazines into their bis-benzyl imino ethers.[17]

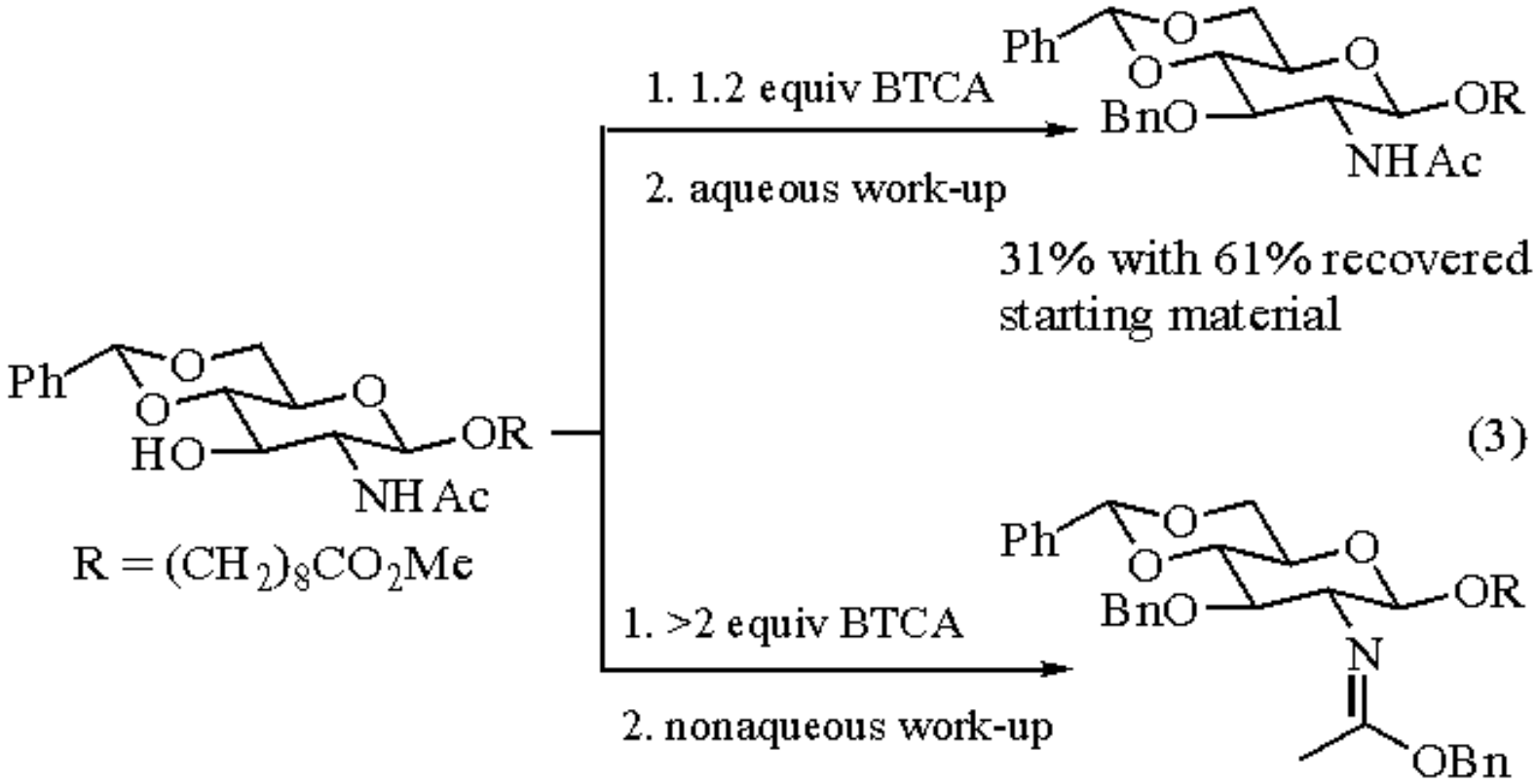
1. 1.2 equiv BTCA
2. aqueous work-up
31% with 61% recovered starting material
R = (CH2)8CO2Me
1. >2 equiv BTCA
2. nonaqueous work-up

(3)

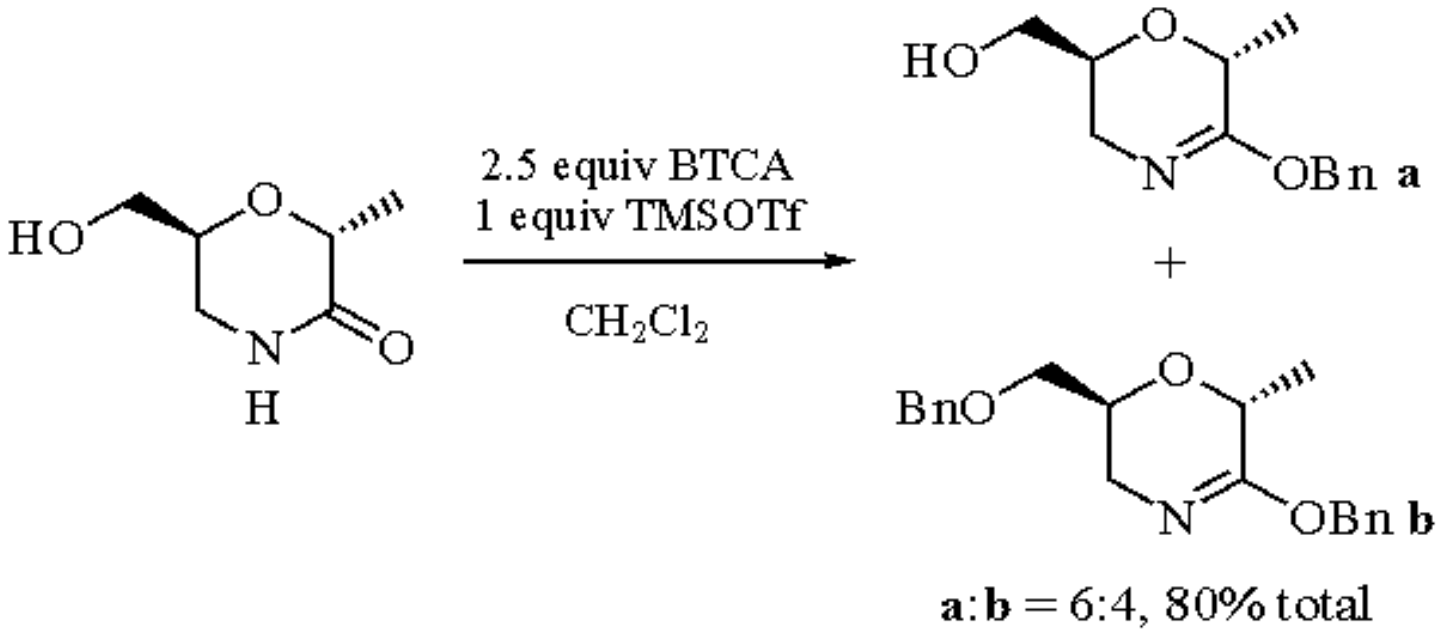
2.5 equiv BTCA
1 equiv TMSOTf
CH2Cl2
a
b
a:b = 6:4, 80% total

(4)

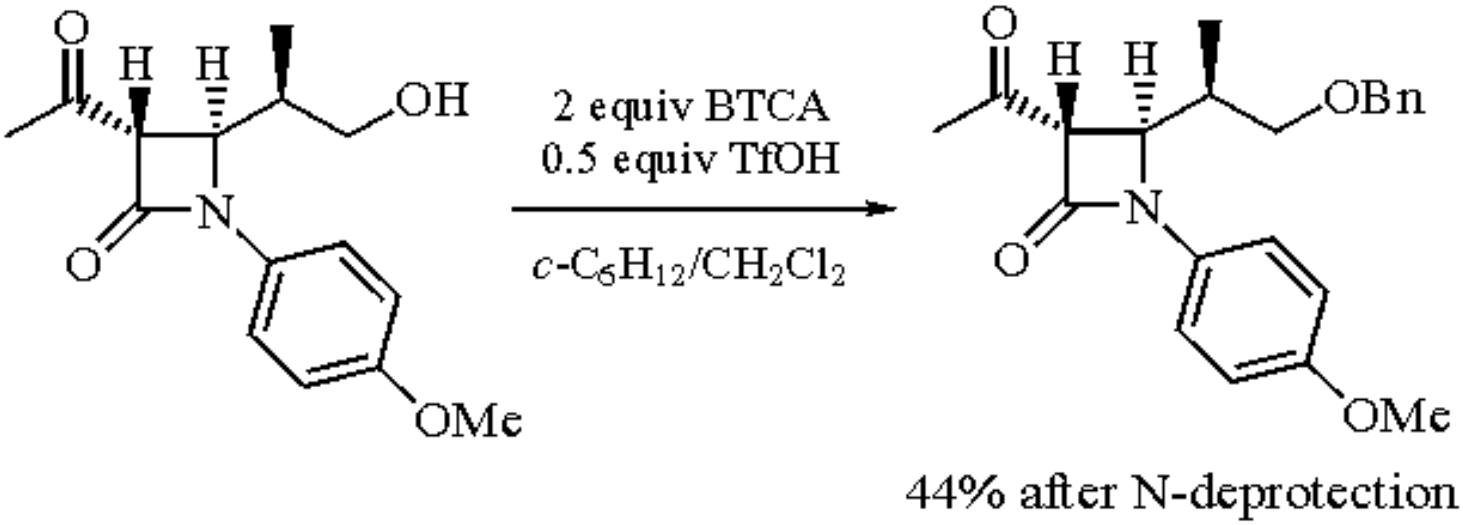

(5)

Other classes of molecules which have been benzylated using this reagent include hydroxy ketones,[4] hydroxy halides[4,7,18] and esters[19-23] such as tartrates,[19] hydroxy propionates or butanoates,[20] long alkyl chain hydroxy esters,[21] and hydroxy lactones.[4] Under basic conditions problems such as enolization, aldol reactions, elimination and epoxide formation can cause problems and when 2-substituted esters, such as ethyl (*S*)-lactate,[22] are required as homochiral starting materials, then protection using this method circumvents the considerable risk of racemization that accompanies the use of bases (eq 6).

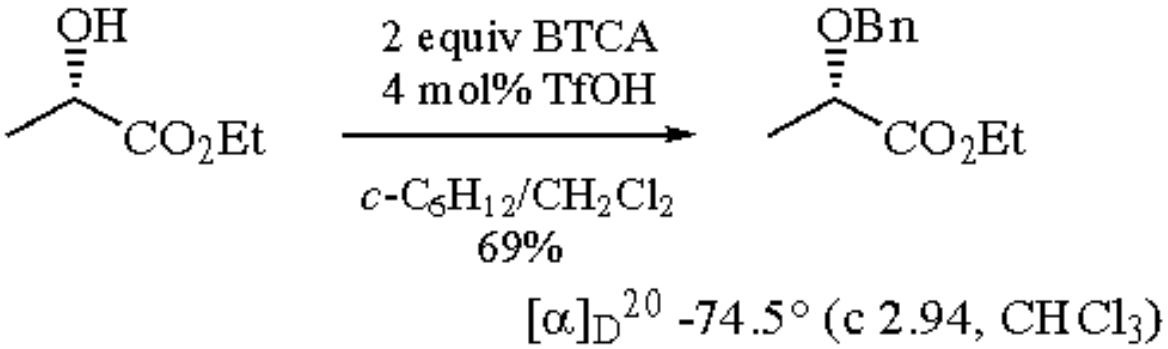

(6)

Under these benzylation reaction conditions, it has been shown that the *N*-*t*-butoxycarbonyl (N-Boc) (eq 7) and *N*-(2-trimethylsilyl)ethoxycarbonyl (*N*-TEOC) (eq 8) protected amino acid derivatives are converted into their *N*-benzyloxycarbonyl (N-Z) analogs.[24] In most cases yields were moderate, but surprisingly the *t*-butyldimethylsilyloxy and *t*-butyl ester functions are relatively unaffected by the acidic conditions.

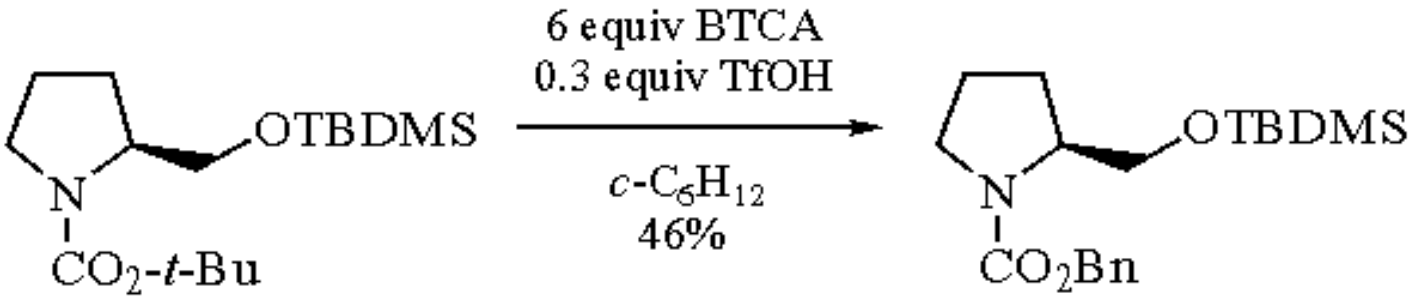

(7)

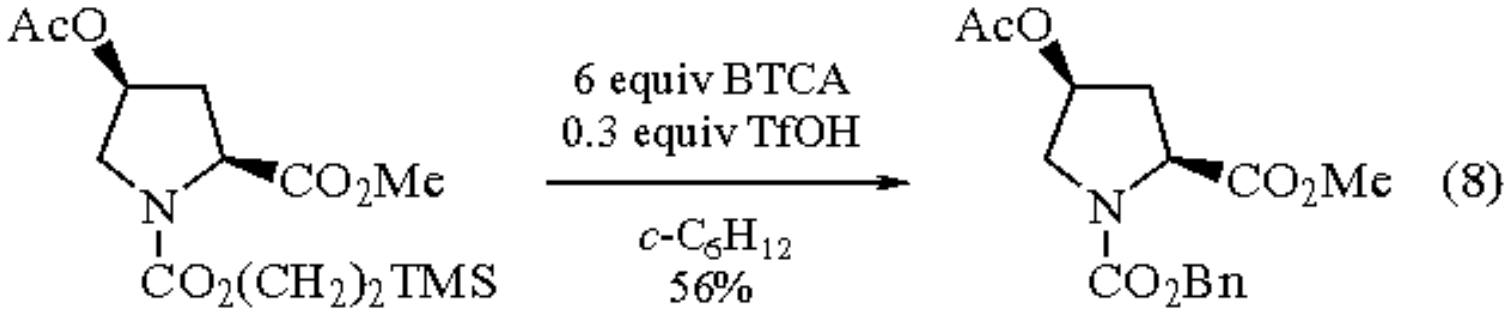

The most frequently employed acid catalyst is TfOH (***Trifluoromethanesulfonic Acid***, or triflic acid), but others that have been used include $BF_3.OEt_2$,[4,8] TMSOTf,[4,16] *p*-TsOH,[6] and TFA.[23,16] Camphorsulfonic acid, pyridinium *p*-toluenesulfonate, and trityl perchlorate have also been investigated in conjunction with the more reactive 4-methoxybenzyl trichloroacetimidate.[5a]

Functional groups sometimes sensitive to acidic conditions such as simple esters,[1,19-23] lactones,[4,5d] acetals,[1,5a,15] epoxides,[5a,13] 2-methoxyethyloxymethyl (MEM) groups,[6] *t*-butyldimethylsilyl ethers,[14,24-27] and orthoformates[15b] are generally unaffected by the catalytic amounts of acid used, although some tertiary alcohols[4] and 1-trimethylsilylalkynes[4] have been noted to give poor yields.

Related Reagents.

Benzyl Bromide; ***Benzyl Chloride***; ***Benzyl Iodide***; ***Benzyl Trifluoromethanesulfonate***; ***3,4-Dimethoxybenzyl Bromide***; ***4-Methoxybenzyl 2,2,2-Trichloroacetimidate***.

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Benzyltriethylammonium Chloride[1]

$BnNEt_3^+ Cl^-$

[56-37-1] · $C_{13}H_{22}ClN$ · Benzyltriethylammonium Chloride · (MW 227.81)

(phase transfer catalyst[1])

Alternate Names: TEBA; TEBAC.

Physical Data: mp 185 °C (dec).

Solubility: sol acetone, alcohol, H_2O, 1% aq. NaOH; insol ether, 20% aq. NaOH.

Form Supplied in: anhydrous white solid; monohydrate also available.

Analysis of Reagent Purity: tetraalkylammonium salts can be titrated with potassium 3,5-di-*t*-butyl-2-hydroxybenzenesulfonate and iron(III) chloride.[1a]

Preparative Method: via the reaction of ***Benzyl Chloride*** with ***Triethylamine*** in absolute ethanol.[2]

Purification: precipitation from acetone with ether.[2]

Handling, Storage, and Precautions: highly hygroscopic.

Introduction.

Benzyltriethylammonium chloride is one of many commonly used phase transfer catalysts. Although in specific reactions other phase transfer catalysts have proven superior,[3] TEBA remains the reagent of choice for many reactions.

Catalyst for C-C Bond Formation.

TEBA has been used extensively in the formation of carbenes in heterogeneous systems. Dichlorocarbene[2,4] is formed from ***Chloroform*** and aqueous ***Sodium Hydroxide*** in the presence of TEBA (eq 1).[4a] Dibromocarbenes can also be generated using TEBA.[4b,4d] TEBA has been used as a means of introducing hydroxide or carboxylate ion in alkylations of nitriles,[5] cyanohydrins,[6] Schiff bases,[7] sulfones,[8] malonates,[9] and benzyl ketones.[10] Michael addition reactions[11] have been catalyzed by TEBA, as well as the condensation of *O*-benzoyl cyanohydrins,[12] malonitrile,[13] and sulfones[14]

with benzaldehyde. Condensation of 3-methyl-5-pyrazolone with ***Carbon Disulfide*** and alkyl bromides was realized under phase transfer conditions using TEBA.[15]

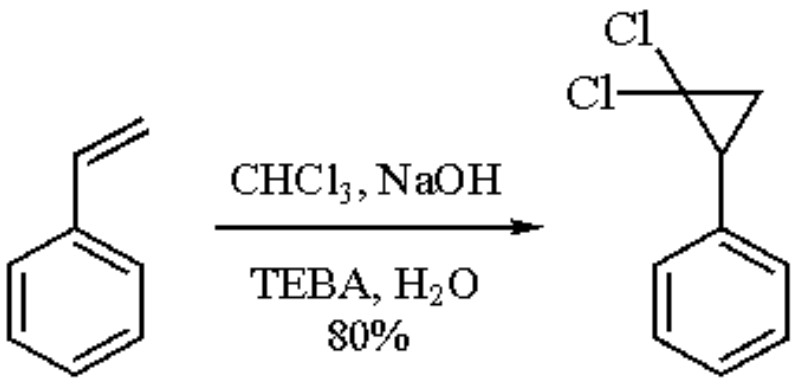

(1)

Catalyst for C-N Bond Formation.

TEBA has been used in the alkylation of trifluoroacetamide with α-bromo esters to form, after hydrolysis, α-amino acids (eq 2).[16] TEBA has also been used in the nitration of aromatics,[17] the alkylation of secondary amides,[18] and the dehydration of ureas to form carbodiimides.[19] Reaction of thioamides with dibromoethane and sodium hydroxide catalyzed by TEBA gives thiazolidines.[20]

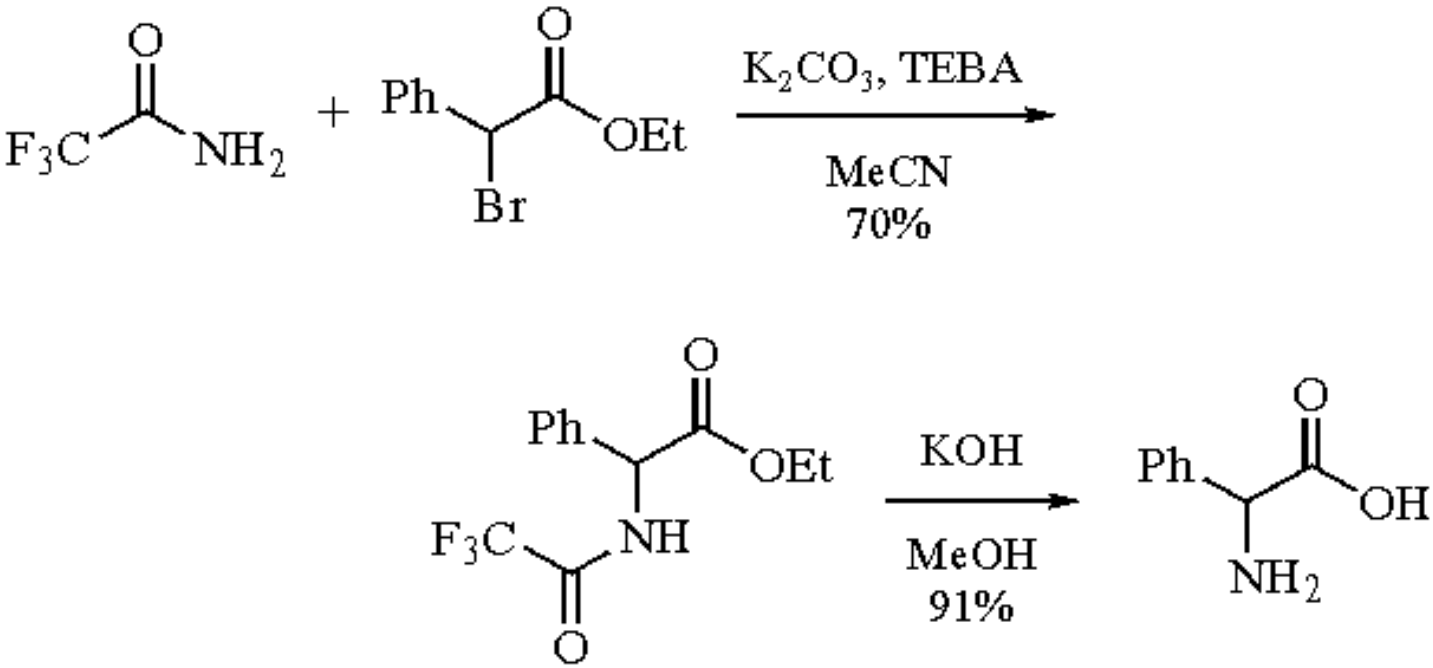

(2)

Catalyst for C-O Bond Formation.

Benzyl[21] ethers have been formed using TEBA catalysis. TEBA has been used in a variety of oxidation reactions, including permanganate oxidation of longifolene[22] and benzaldehyde,[23] α-hydroxylation of benzyl nitriles giving phenyl ketones,[24] and ***Ruthenium(VIII) Oxide*** catalyzed oxidations of secondary alcohols to ketones with ***Sodium Periodate***.[25]

Catalyst for Carboxylic Acid Functionalization.

TEBA facilitates the solubilization of organic acids, permitting formation of a diacid chloride from an insoluble diacid (eq 3).[26] Organic peroxy acids can also be prepared from the corresponding acid using TEBA and potassium persulfate.[27]

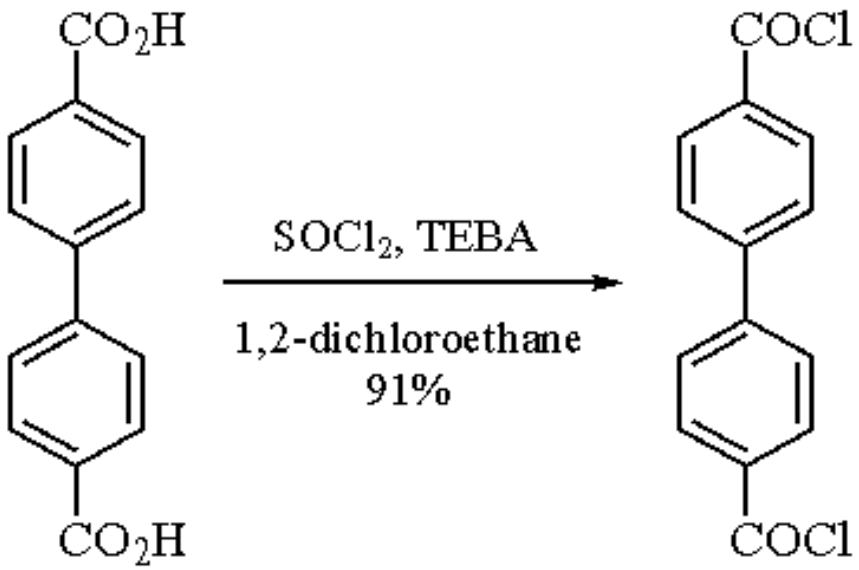

(3)

Catalyst for P-X Bond Formation.

TEBA has been used in the formation of phosphorodiamidates from bis(dimethylamino) phosphorochloridate[28] and phosphate esters[29] or phosphoramidates[30] from ***Diethyl Phosphonite***. Di-*t*-butyl phosphorohalidates have been prepared from di-*t*-butyl phosphite using TEBA, carbon tetrachloride and aq. NaOH.[31]

Miscellaneous Uses.

TEBA has proven very effective in the formation of metal hydrides under phase transfer conditions;[32] for example, $(Ph_3P)_3RuHCl$ and $(i\text{-}Pr_3P)_2IrHCl_2$ are converted to $(Ph_3P)_3RuH_2(H)_2$ and $(i\text{-}Pr_3P)_2IrH_5$,[32a] respectively, upon reaction with hydrogen and aq. NaOH/benzene with TEBA. In metal carbonyl chemistry, TEBA has been used as a phase transfer catalyst.[33] TEBA has also been used in the dibromination of alkenes[34] and azide transfer reactions.[35] Selective tosylation of adenosine has been achieved using ***Di-n-butyltin Oxide***, ***p-Toluenesulfonyl Chloride***, and TEBA (eq 4).[36]

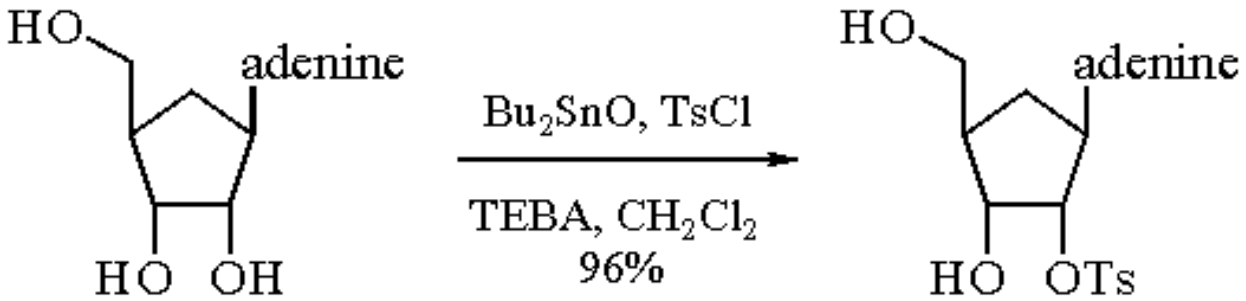

(4)

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Benzyltriethylammonium Chlorochromate[1]

$[PhCH_2NEt_3]^+[CrO_3Cl]^-$

[106542-73-8] · $C_{13}H_{22}ClCrNO_3$ · Benzyltriethylammonium Chlorochromate · (MW 327.77)

(a mild and neutral oxidizing agent for benzylic and allylic alcohols[1])

Physical Data: mp 89 °C.

Solubility: fairly sol common organic solvents.

Form Supplied in: orange crystalline solid; not commercially available.

Preparative Method: ***Chromic Acid*** (10 g, 0.1 mol) in 3 M HCl (200 mL) is added to an aqueous solution (250 mL) of ***Benzyltriethylammonium Chloride*** (22.7 g, 0.1 mol). The crude product precipitates and can be recrystallized from acetone-water; yield 86%. The reagent prepared according to this procedure was initially described as bis(benzyltriethylammonium dichromate).[2] Later, it was demonstrated that the compound obtained under these conditions is actually benzyltriethylammonium chlorochromate.[3]

Handling, Storage, and Precautions: the reagent is a stable orange crystalline solid. No data have been reported about storage and precautions. Chromium(VI) derivatives are reported to be toxic agents. The reagent should be handled in a fume hood.

Oxidation of Benzylic and Allylic Alcohols.

Benzyltriethylammonium chlorochromate can selectively oxidize benzylic and allylic alcohols to the corresponding carbonyl compounds in almost quantitative yield. Yields are low (30%) for primary alkanols and cycloalkanols. The reaction can be performed in HMPA at 60-80 °C for 4-6 h.[2] Alternatively, the oxidation can be carried out under phase-transfer conditions.[3a] Yields range from 75-

99%.

The reagent can be utilized for the selective oxidation of thiols to disulfides in high yield and this method has been applied to alkanethiols, arylalkanethiols, and arenethiols.[2]

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Benzyltriethylammonium Permanganate

$[PhCH_2NEt_3]^+[MnO_4]^-$

[68844-25-7] · $C_{13}H_{22}MnNO_4$ · Benzyltriethylammonium Permanganate · (MW 311.26)

(oxidant, used for the oxidation of alkanes and arenes to alcohols or ketones,[1,2] ethers to esters,[3] primary alcohols to methylene diesters,[4] secondary alcohols to ketones,[4] amines to amides,[5] aldehydes to carboxylic acids,[6] and sulfides or sulfoxides to sulfones[7])

Physical Data: [8] purple solid, decomposes at 101 °C (TDA), 127-129 °C (melting point tube).

Solubility: [8] 4.97 × 10^{-3} M in H_2O; 5.76 × 10^{-2} M in CH_2Cl_2; 4.6 × 10^{-3} M in $CHCl_3$; insol. CCl_4 and toluene.

Analysis of Reagent Purity: ε = 2530 ± 30 L mol^{-1} cm^{-1} at 526 nm[8] or iodometric titration.[1]

Preparative Methods: [1] a solution of ***Benzyltriethylammonium Chloride*** (227.8 g, 1.00 mol) in 200 mL of water is added slowly dropwise to a solution of ***Potassium Permanganate*** (158.0 g, 1.00 mol) in 4.7 L of water. Violet crystals are recovered by filtration and dried under vacuum at rt. Yield: 294.8 g (95%).

Handling, Storage, and Precautions: oxidant, store small amounts (10-100g) in glass vessels at or below rt. Decomposes violently when heated above 50 °C or subjected to shocks.[9,10] Room temperature should not be exceeded when drying under vacuum.[9]

Oxidation of Alkanes and Arenes.[1,2]

Certain alkanes and the benzylic carbon of alkyl-substituted arenes are oxidized by benzyltriethylammonium permanganate in methylene chloride or acetic acid to give alcohols or ketones. Good yields (based on unrecovered starting material) are obtained (25-98%), but the extent of conversion (based on the amount of hydrocarbon used as starting material) is quite low (11-44%). Some typical examples are shown in eqs 1-4.

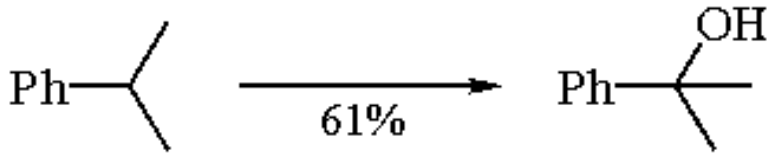

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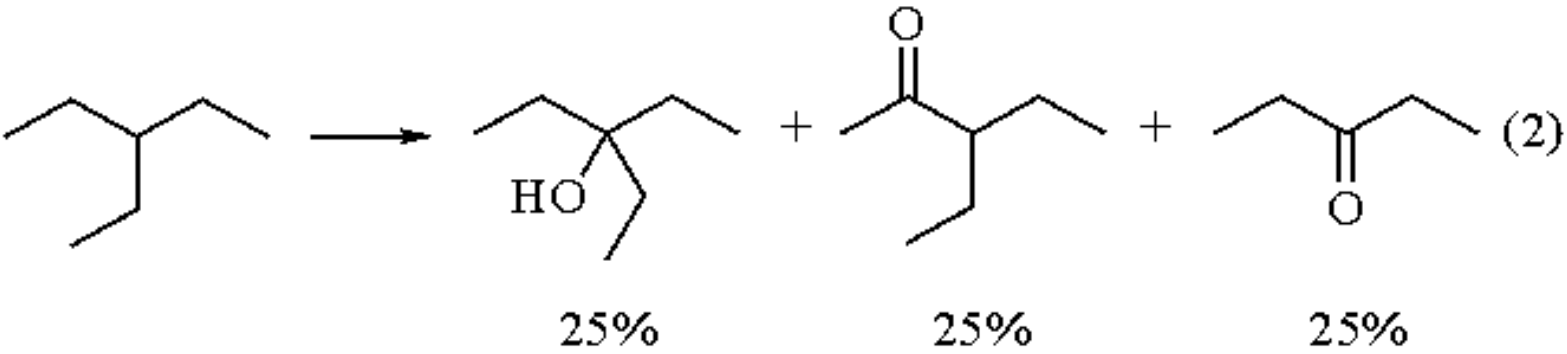

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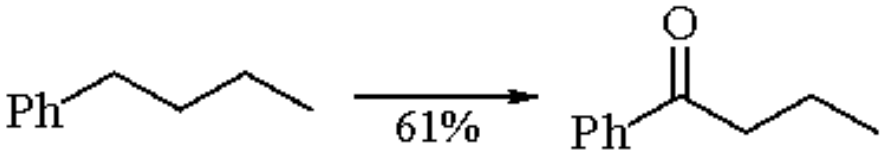

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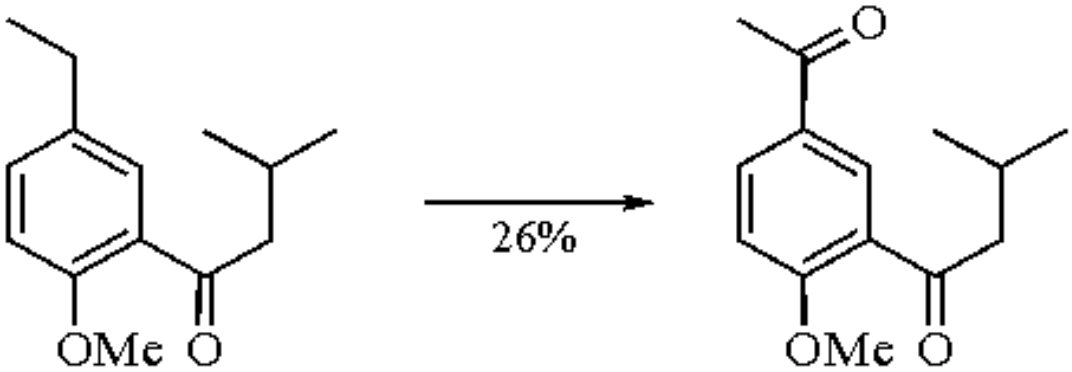

(4)

Oxidation of Ethers to Esters.[3]

Benzyltriethylammonium permanganate oxidizes ethers to esters in good yield under nonaqueous conditions in reactions that are reminiscent of those reported for ***Ruthenium(VIII) Oxide***. The advantage of using benzyltriethylammonium permanganate is that it does not result in the degradation of aromatic ethers. Examples reported include eqs 5-7.

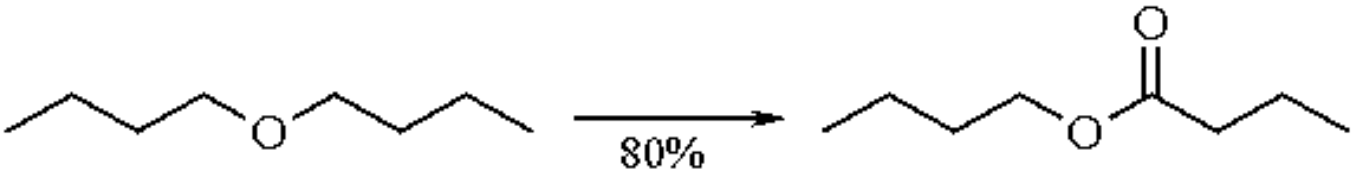

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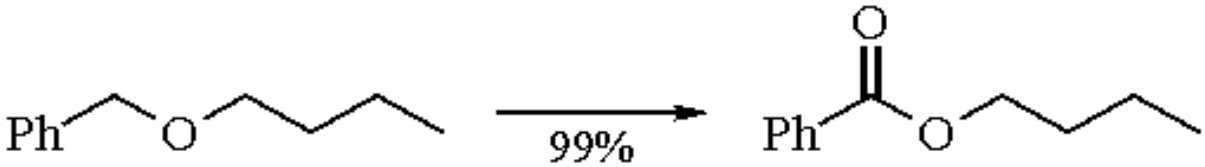

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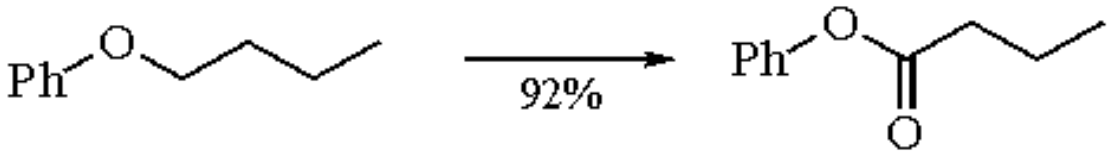

(7)

Oxidation of Alcohols.[4]

The oxidation of secondary alcohols to ketones with this reagent is accompanied by a certain amount of carbon-carbon bond cleavage. Primary alcohols are oxidized to carboxylates, which undergo further reaction with methylene chloride when it is used as the solvent. The principle products are methylene diesters. Examples include those shown in eqs 8-10.

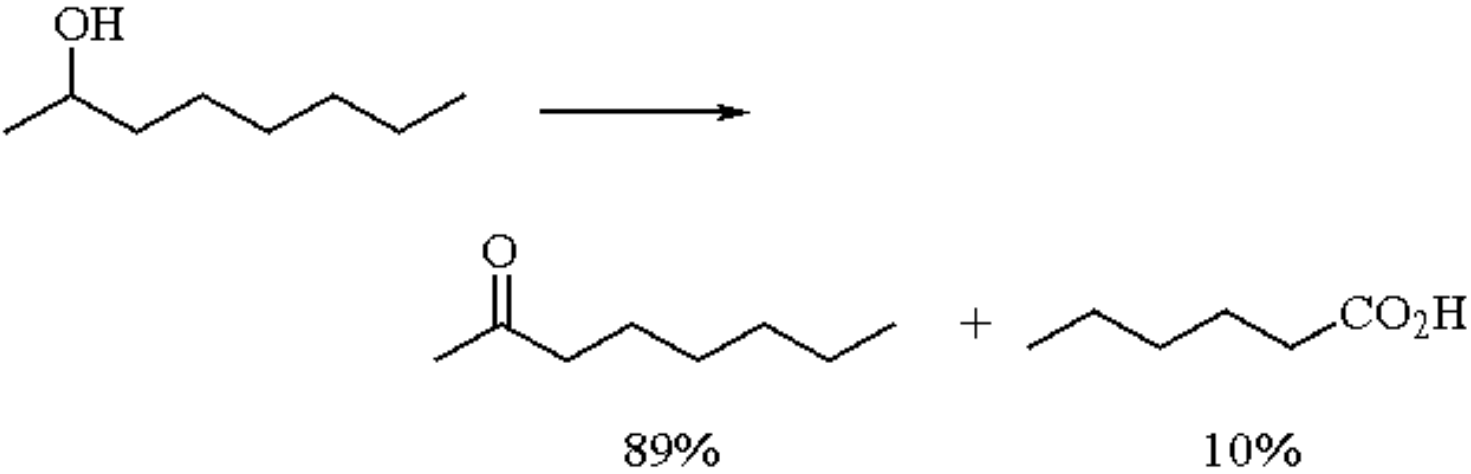

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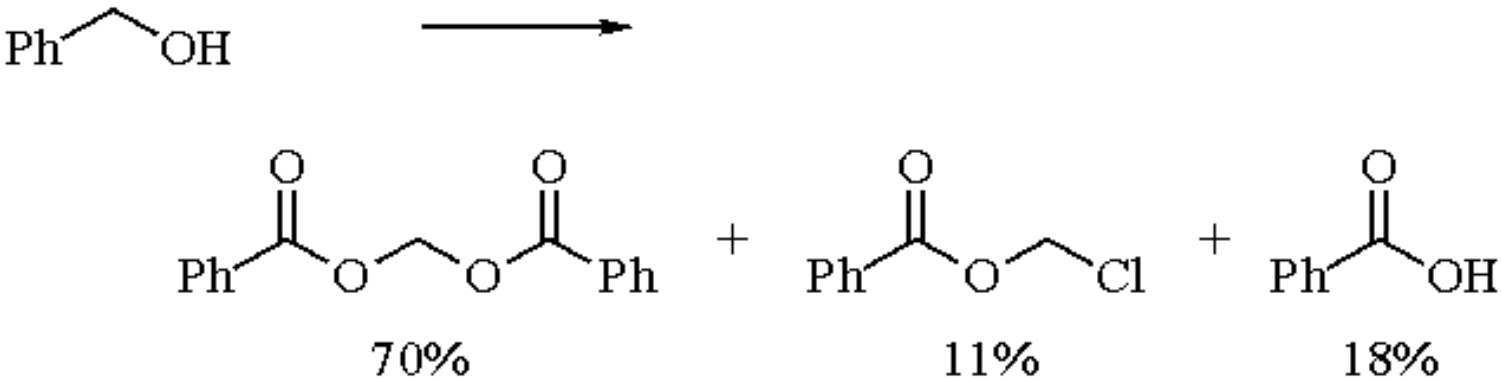

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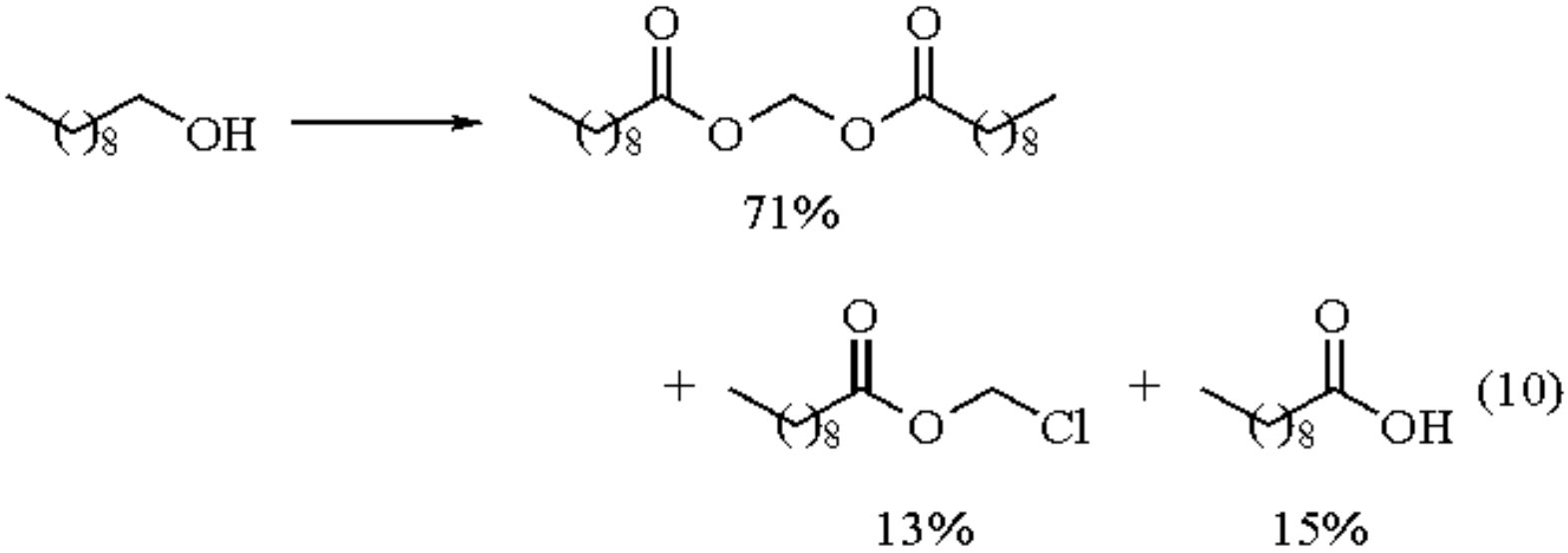

Oxidation of Amines.[5]

Tertiary amines are oxidized to *N*,*N*-dialkylamides in good yields. Primary and secondary amines are less selectively oxidized. Examples include eqs 11 and 12.

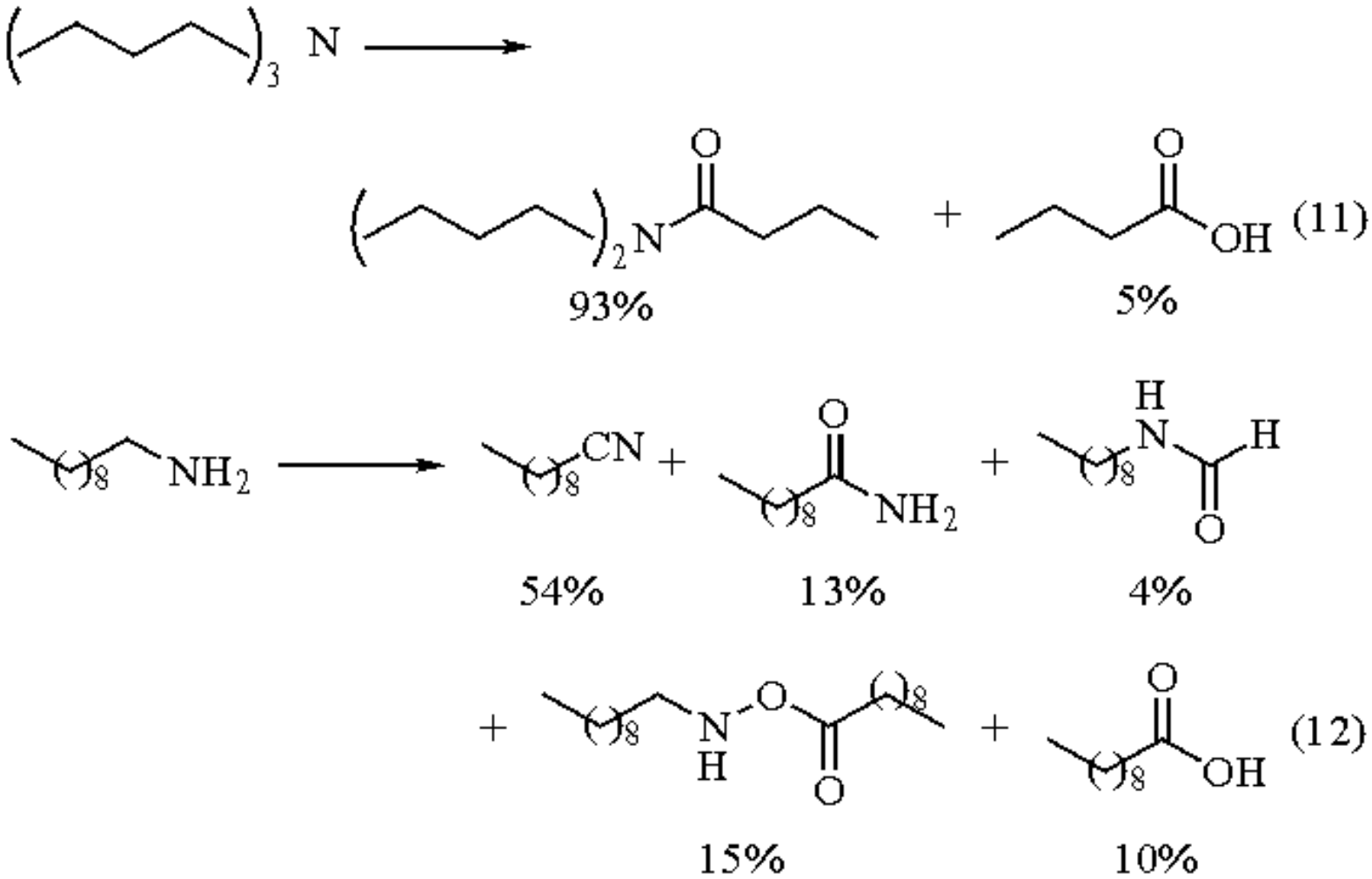

Oxidation of Aldehydes.[6]

Aldehydes are oxidized by benzyltriethylammonium permanganate to carboxylic acids in organic solvents at rt, e.g. eqs 13 and 14.

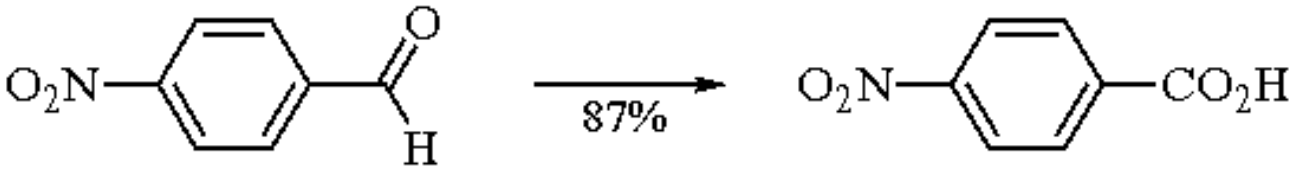

(13)

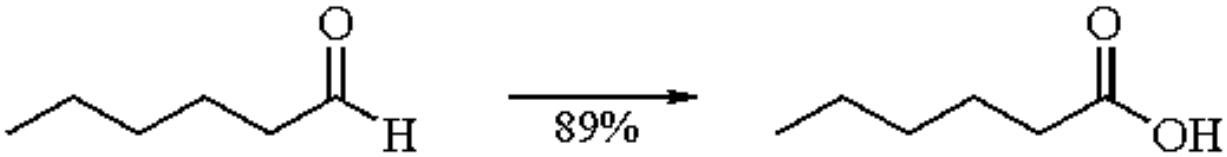

(14)

Oxidation of Sulfides and Sulfoxides.[7]

Sulfides and sulfoxides are oxidized cleanly to the corresponding sulfones by benzyltriethylammonium permanganate under nonaqueous conditions. Examples include eqs 15-18.

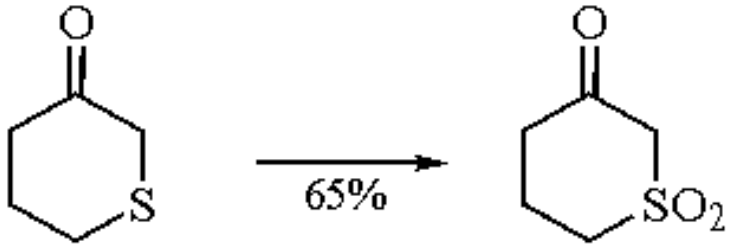

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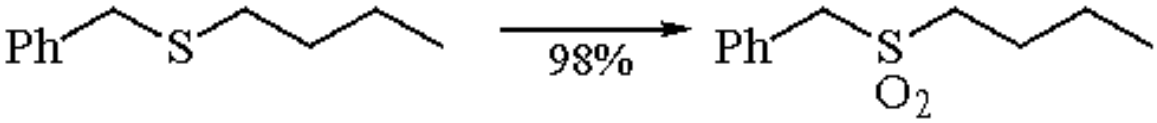

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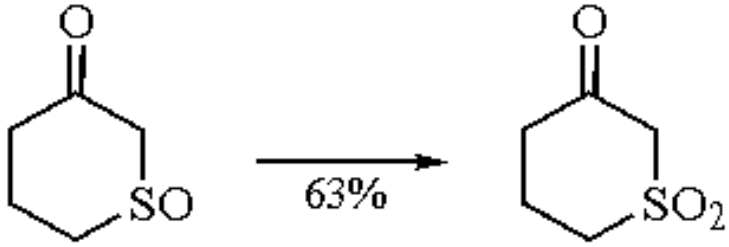

(17)

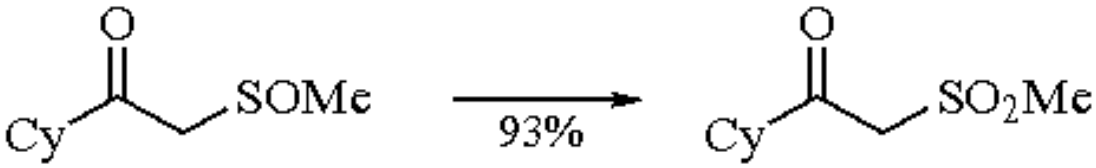

(18)

The reactions of benzyltriethylammonium permanganate are very similar to those of other quaternary ammonium and phosphonium permanganates such as ***Tetra-n-butylammonium Permanganate*** and ***Methyltriphenylphosphonium Permanganate***. Similar reactions can also be carried out more simply by use of phase transfer processes which are described under ***Potassium Permanganate***.

---

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Benzyl Trifluoromethanesulfonate[1]

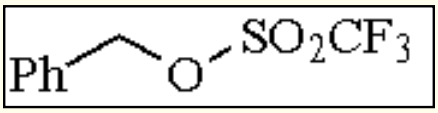

[17674-16-7] · $C_8H_7F_3O_3S$ · Benzyl Trifluoromethanesulfonate · (MW 240.18)

(a highly electrophilic alkylating agent used for the formation of benzyl ethers,[2-7] and for Friedel-Crafts benzylation[13-17])

Alternate Name: benzyl triflate.

Solubility: generated and used in situ in inert solvents such as CH_2Cl_2.

Preparative Methods: from benzyl alcohol, ***Trifluoromethanesulfonic Acid***, and ***2,6-Di-t-butylpyridine*** in CH_2Cl_2. When used in Friedel-Crafts alkylation reactions, it has been made from a benzyl halide and silver triflate.[15,16]

Handling, Storage, and Precautions: generated in situ and used immediately. The compound is extremely readily hydrolyzed. Use in a fume hood.

Introduction of the Benzyl Protecting Group.

Alkyl triflates, such as benzyl triflate, are extremely reactive alkylating agents.[1] Benzyl triflate has been used in carbohydrate chemistry[2-5] for the protection of hydroxy groups as their benzyl ethers, and is particularly useful for protecting the 2-hydroxy group in pyranosides.[2,3] Alkyl triflates have also been used to protect the 1-hydroxy group in sugar acetals without causing anomerization,[4] and the reagent is compatible with acetate,[2,3] isopropylidene,[3] azide,[5] and *t*-butyldimethylsilyl groups.[5] The reagent is also a useful alternative to the benzyl halide/base method for making ethers, when strongly basic conditions need to be avoided[5] (see also ***Benzyl 2,2,2-Trichloroacetimidate***). Benzyl triflate has been used with compounds other than carbohydrates,[6-9] and yields with some base-sensitive compounds can be excellent (eq 1).[6] 4-Nitrobenzyl ethers have also been made via the triflate,[8] as 4-nitrobenzyl bromide is known to be base-sensitive and so not fully compatible with the classical Williamson ether synthesis methodology.

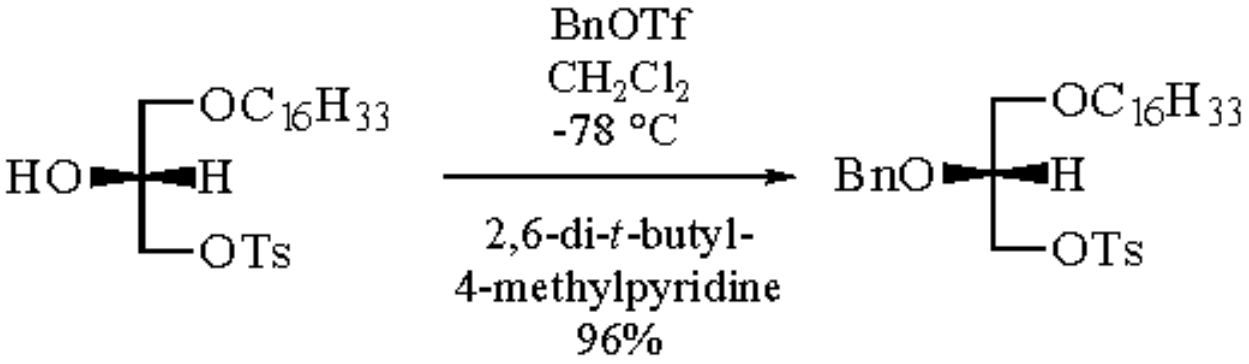

(1)

Problems can arise with the use of benzyl triflate when the substrate is a nitrogen-containing heteroaromatic compound, as significant *N*-alkylation is observed[8,9] (hence the use of the expensive, but highly hindered, 2,6-di-*t*-butylpyridine in the synthesis of the reagent[2,3]). However, *N*-benzylation is sometimes required and benzyl triflate has been used for the protection of the hindered, deactivated N^{im}-3 site in N^{im}-1-Boc protected histidines (eq 2).[10] Other methods for this derivatization need specialized blocking groups to prevent racemization of the substrate under the harsher conditions.

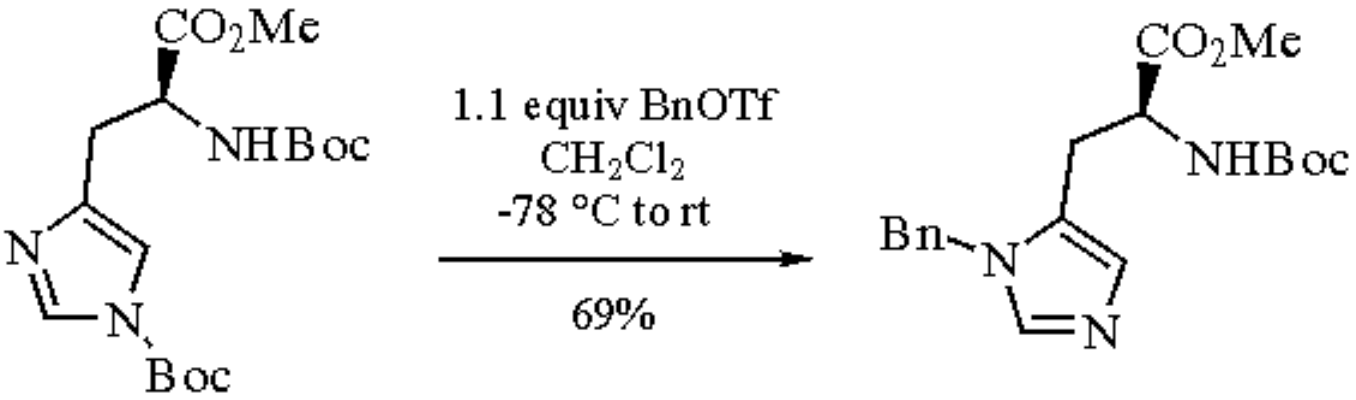

(2)

Benzyl triflate mediated benzylation of alcohols in sulfur-containing compounds such as ethylene dithioacetals can cause problems.[11] The highly electrophilic agent reacts at sulfur initially and causes ring opening of the protecting group (eq 3).

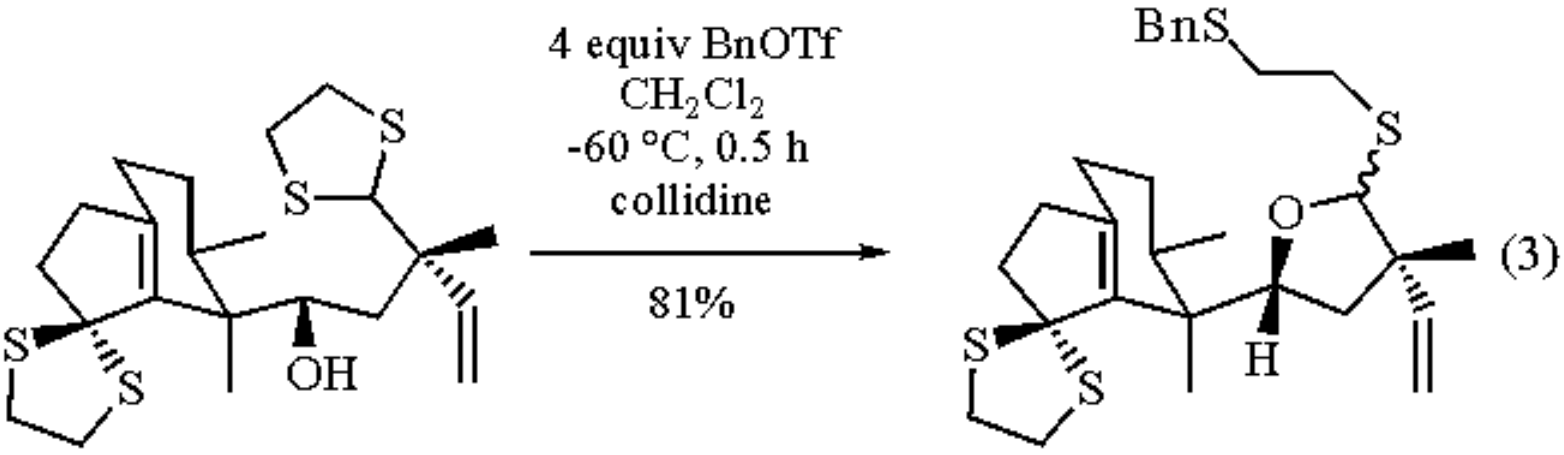

(3)

The thiophilicity of benzyl triflate does mean that thioethers can be conveniently protected as benzylsulfonium triflates (eq 4).[12] In this case, protection of the thioether is necessary to prevent concomitant sulfide-sulfone

oxidation during oxidation of the primary hydroxy group to a carboxylic acid.

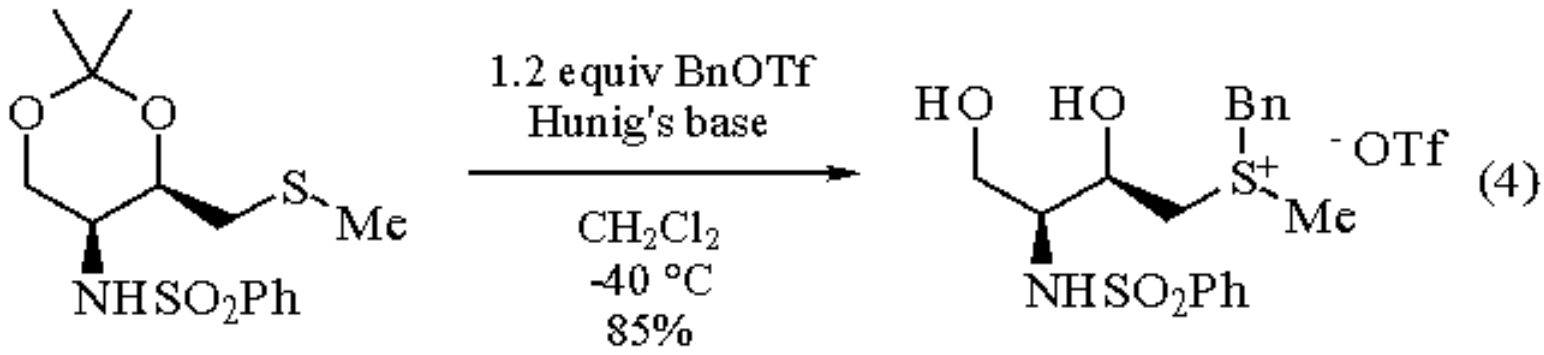

Friedel-Crafts Alkylation.

Benzyl triflate, like other alkyl triflates, is an active agent for Friedel-Crafts alkylation of arenes.[13-17] Benzyl triflate can be generated with a benzyl halide and silver triflate,[15,16] and then used to alkylate arenes such as alkylbenzenes,[15] anisoles,[16] and phenols.[16] Reaction occurs at rt without catalysis, but other alkyl triflates are generally less active, sometimes only reacting efficiently with a Lewis acid catalyst.[15] Recently, benzyl triflate has been reported as a decomposition product of *N*-nitroso-*N*-benzyltrifluoromethanesulfonamides, and if this reaction is done in arene solvents such as benzene then Friedel-Crafts alkylation products are obtained.[17]

---

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Benzyltrimethylammonium Dichloroiodate[1]

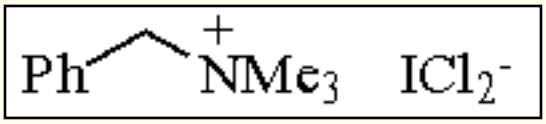

[114971-52-7] · $C_{10}H_{16}Cl_2IN$ · Benzyltrimethylammonium Dichloroiodate · (MW 348.05)

(iodinating agent for aromatic compounds;[1] chloroiodo addition to unsaturated bonds;[1] α-chlorination of acetyl derivatives[1])

Physical Data: mp 125-126 °C.

Solubility: sol CH_2Cl_2, MeCN, $MeNO_3$, DMSO, DMF; slightly sol MeOH, EtOH, AcOEt; insol C_6H_{14}, Et_2O, CCl_4, $CHCl_3$, C_6H_6, AcOH.

Form Supplied in: yellow needles.

Analysis of Reagent Purity: ^1H NMR (CD_3CN) δ 3.11 (s, 9H, 3 CH_3), 4.48 (s, 2H, CH_2), 7.50 (s, 5H, C_6H_5).

Preparative Methods: to a solution of ICl (16.2 g, 0.1 mol) in CH_2Cl_2 (200 mL) at room temperature is added dropwise over 30 min a solution of benzyltrimethylammonium chloride (18.6 g, 0.1 mol) in water (100 mL); yield 30 g (86%).[2]

Purification: recrystallize from CH_2Cl_2-Et_2O (3:1).

Handling, Storage, and Precautions: stable solid; gradually decomposes in water. This reagent should be handled in a fume hood.

Electrophilic Iodination of Aromatic Compounds.

This solid reagent (**1**) can be used stoichiometrically in place of viscous ***Iodine Monochloride*** to iodinate aromatic compounds (eq 1). The iodinating ability of (**1**) is considerably higher than that of molecular ***Iodine***.

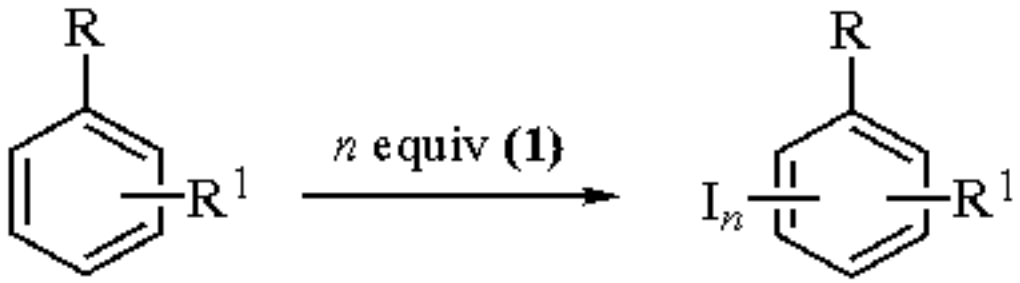

(1)

$R = OH, NH_2, OR^2, AcNH, R^2$

The reaction of phenols with (**1**) in CH_2Cl_2-MeOH in the presence of powdered ***Calcium Carbonate*** or $NaHCO_3$ for several hours at room temperature gives iodophenols in 63-96% yield. Because the presence of MeOH markedly facilitates the reaction, it is assumed that the active species is methyl hypoiodite (MeOI) produced from (**1**) and MeOH. $NaHCO_3$ is used for the iodination of phenols bearing electron-attracting substituents, and $CaCO_3$ is used for the iodination of phenols bearing electron-releasing groups.[2]

The reaction of aromatic amines with (**1**) in CH_2Cl_2-MeOH in the presence of $CaCO_3$ powder at room temperature gives iodo-substituted aromatic amines (73-96% yield). In these cases it is necessary to add $CaCO_3$ powder to remove the HCl generated.[3] The reaction of aromatic ethers with (**1**) in AcOH in the presence of ***Zinc Chloride*** at room temperature gives iodo-substituted aromatic ethers (87-98% yield). The reagent is insoluble in AcOH at room temperature, but the addition of $ZnCl_2$ increases its solubility, allowing the iodination of aromatic ethers to proceed smothly under mild conditions. An equimolar amount of $ZnCl_2$ with respect to (**1**) is required. Thus 2-methylanisole gives 97% yield of 4-iodo-2-methylanisole via the above iodination.[4]

The reaction of acetanilides with (**1**) in AcOH-$ZnCl_2$ at room temperature or at 70 °C gives iodo-substituted acetanilides (60-97% yield). Thus treating acetanilide with (**1**) in AcOH-$ZnCl_2$ at room temperature for 2 h gives a 77% yield of 4-iodoacetanilide.[5]

The reaction of simple arenes with (**1**) in AcOH-$ZnCl_2$ at room temperature or at 70 °C gives iodo-substituted products in 40-99% yield. Thus treating 1,4-dimethylbenzene with 1 equiv of (**1**) at room temperature for 16 h gives a 75% yield of 2-iodo-1,4-dimethylbenzene, and with 2 equiv of (**1**) at 70 °C for 72 h gives a 67% yield of 2,5-diiodo-1,4-dimethylbenzene.[6] The reaction of ethyl 4-aminobenzoate with 1 equiv of (**1**) in CH_2Cl_2-MeOH in the presence of $CaCO_3$ at room temperature for 48 h gives ethyl 4-amino-3-iodobenzoate in 97% yield.[7] The reaction of thiophenes with (**1**) in AcOH-$ZnCl_2$ under mild

conditions gives iodo-substituted thiophenes (39-98% yield). For example, the reaction of 3-methylthiophene with 2 equiv of (**1**) in AcOH in the presence of $ZnCl_2$ at room temperature for 4 h gives a 92% yield of 2,5-diiodo-3-methylthiophene.[8]

Chloroiodo Addition to Unsaturated Bonds.

The reaction of alkenes with (**1**) in CH_2Cl_2 at room temperature gives the chloroiodo adducts in an *anti* stereospecific and regioselective manner (eq 2); in methanol these adducts are obtained along with methanol-incorporated products.[9]

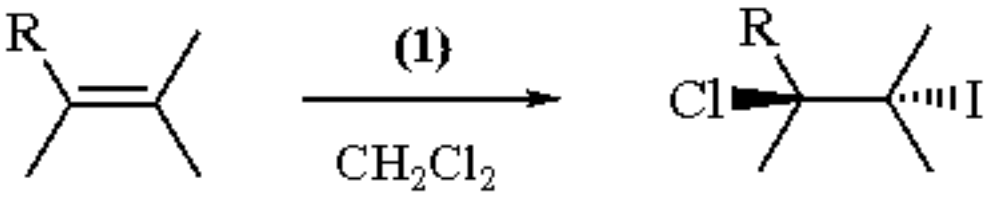

(2)

α-Chlorination of Acetyl Derivatives.

The reaction of aromatic acetyl derivatives with 2 equiv of (**1**) in an appropriate solvent give α-chloro acetyl derivatives (eq 3). Thus the reaction of acetophenone with (**1**) in refluxing $ClCH_2CH_2Cl$-MeOH for 3 h gives a 97% yield of α-chloroacetophenone,[10] and the reaction of 2-acetylpyrrole with (**1**) in THF at room temperature for 12 h gives 2-chloroacetylpyrrole in 85% yield.[11]

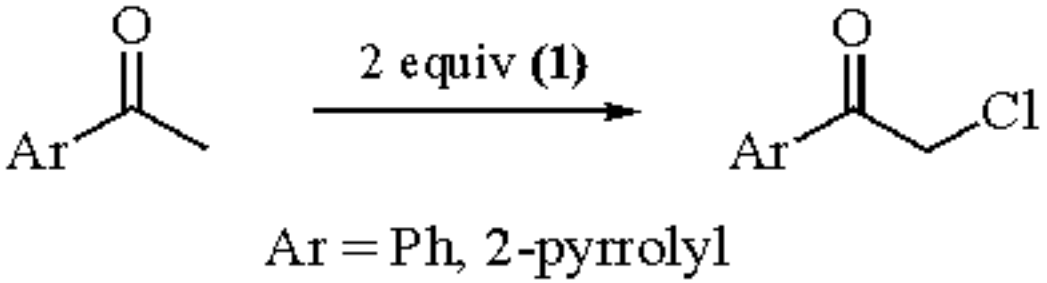

(3)

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Benzyltrimethylammonium Hydroxide

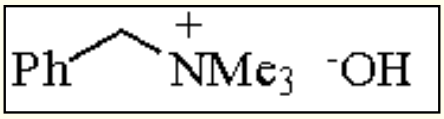

[100-85-6] · $C_{10}H_{17}NO$ · Benzyltrimethylammonium Hydroxide · (MW 167.25)

(quaternary ammonium salt; strong base; phase transfer catalyst[1])

Alternate Name: Triton® B.

Physical Data: none available (generally obtained in solution).

Solubility: sol water, alcohols, hydrocarbons, aromatic hydrocarbons, halogenated solvents.

Form Supplied in: 40 wt % in H_2O; 35-40 wt % in MeOH (Triton B). Typical impurities are amines or benzyl alcohol.

Purification: [2] methanol solution can be decolorized with charcoal, concentrated to a syrup, and dried under vacuum at 75 °C and 1 mmHg pressure. Anhydrous reagent is obtained by drying over P_2O_5 in a vacuum desiccator.

Handling, Storage, and Precautions: hygroscopic solutions; highly toxic; decomposition can occur on heating.[3]

Epoxidations.

Benzyltrimethylammonium hydroxide (**1**) is a common reagent in organic synthesis. It finds use as a catalytic base in the epoxidation of α,β-unsaturated ketones with ***t-Butyl Hydroperoxide***,[4] as demonstrated in a step toward the total synthesis of a complex anthracyclinone (eq 1).[5] The combination of Triton B and either *t*-BuOOH or ***Hydrogen Peroxide*** has been used to advantage in situations where conventional epoxidation conditions have proven either destructive[6] or ineffective.[7] Epoxidations of other α,β-unsaturated systems, such as sulfonates,[8] have also been reported.

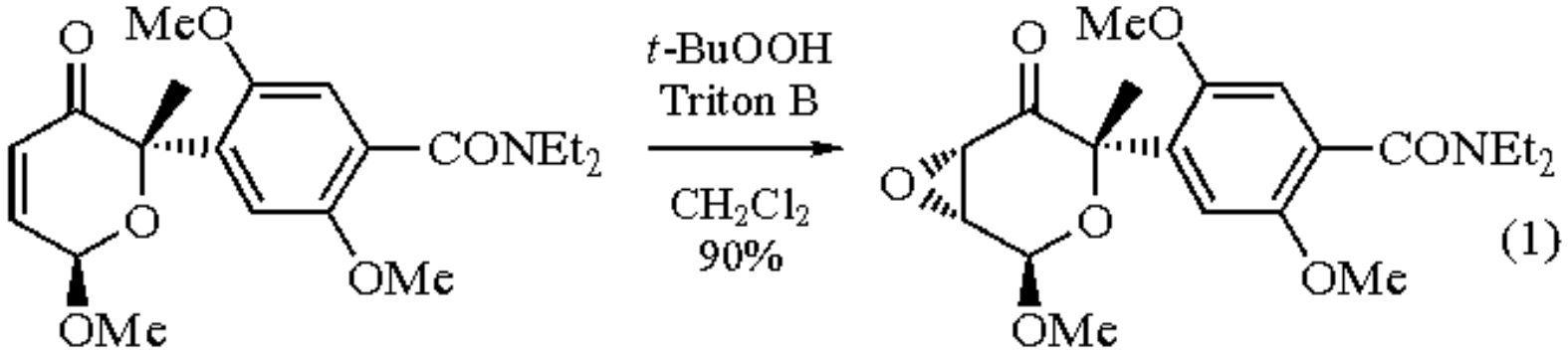

Oxidations at Activated Methylenes.

Benzyltrimethylammonium hydroxide has been used as a catalyst for the oxidation of methylene and/or methine groups. The oxidation of a tricyclic ketone to an anthraquinone was accomplished in good yield using this approach (eq 2).[9] Similarly, benzylic anions have been generated and efficiently trapped with air in DMSO.[10]

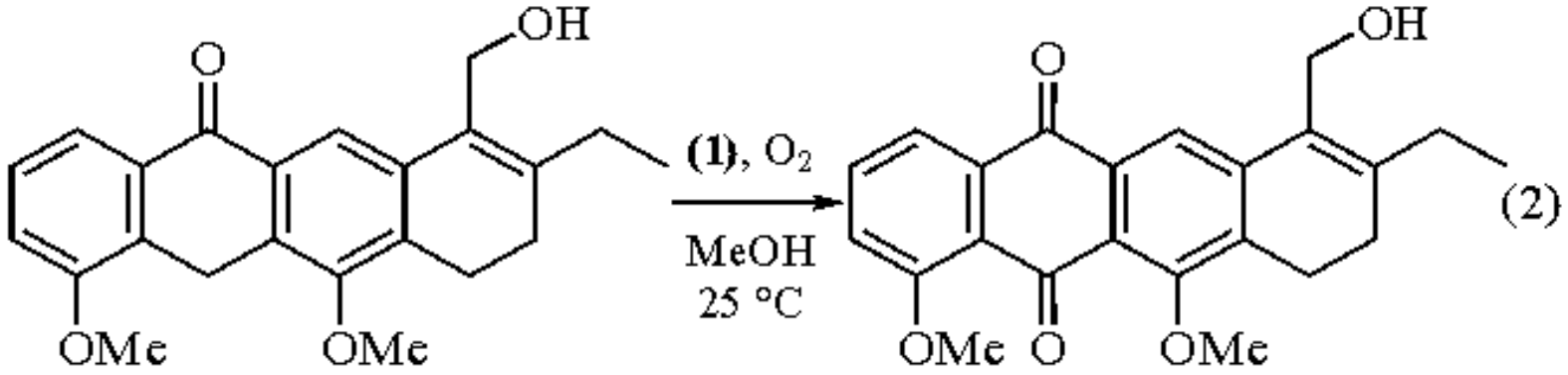

Dehydrohalogenation.

A variety of 1-bromoalkynes have been prepared through the action of Triton B on 1,1-dibromoalkenes.[11] Both aryl and alkyl substituents were examined, with recoveries ranging from 35 to 87%, and generally above 60% yield (eq 3).

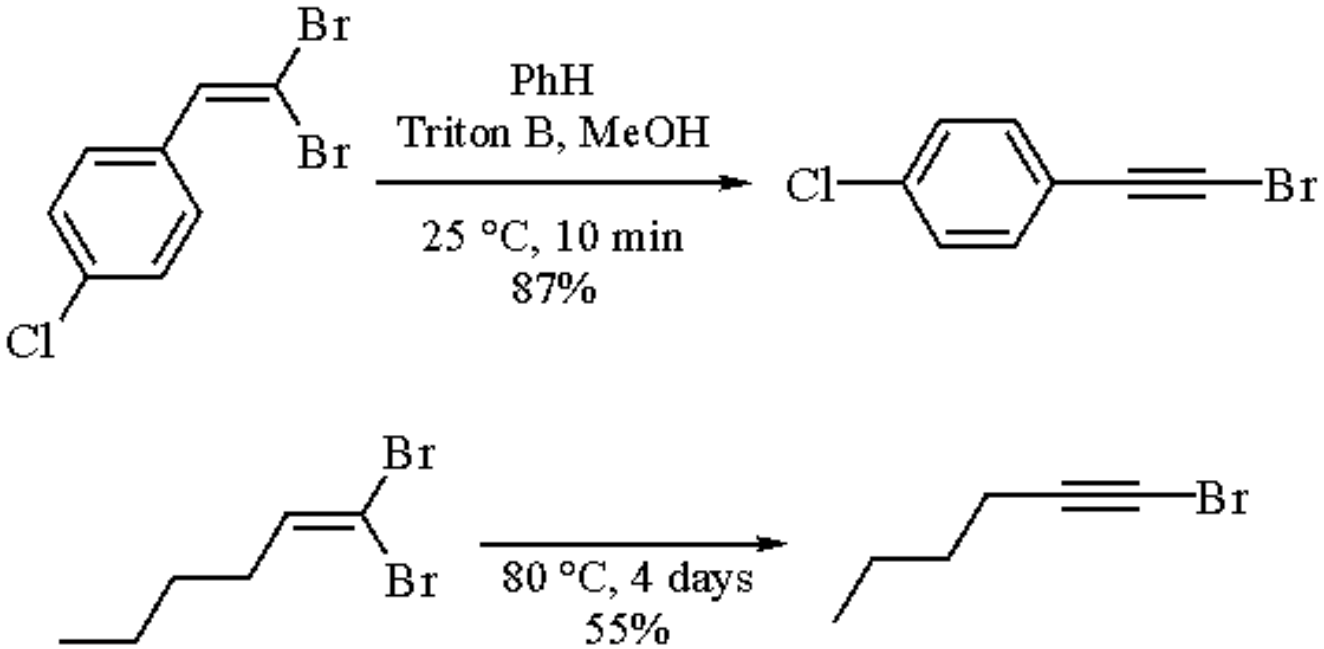

(3)

In an extension of this reaction, a synthesis of propargyl amines using Triton B was developed in which 1,1-dibromoalkenes were dehydrohalogenated, isomerized in situ to bromoallenes, and subjected to nucleophilic attack by primary or secondary amines (eq 4).[12] Yields ranged from 5 to 88%. Attack by methanol was also examined; however, yields were generally low.

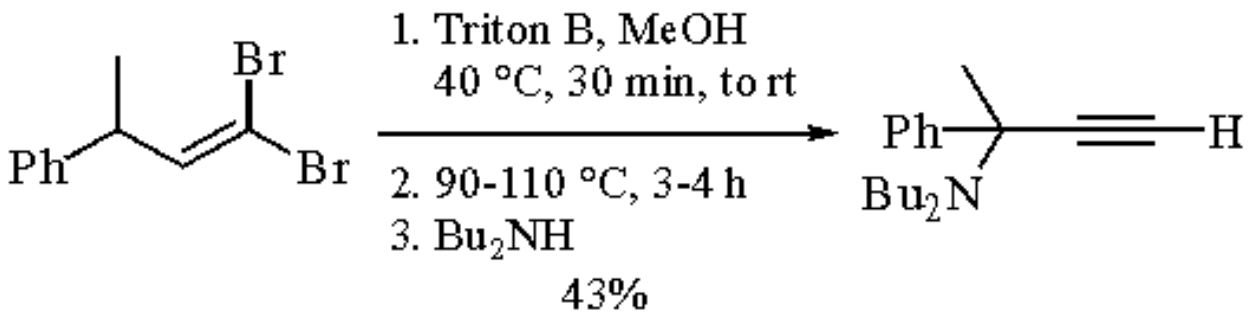

(4)

Aldol Condensations.

The aldol reaction has often been carried out with Triton B functioning as base. In the synthesis of a cytochalasin intermediate, a seven-membered ring was closed under the action of Triton B in excellent yield (eq 5).[13] The reagent can effect the double aldol condensation of dibenzyl ketone with benzil, producing tetraphenylcyclopentadienone in excellent yield (eq 6).[14]

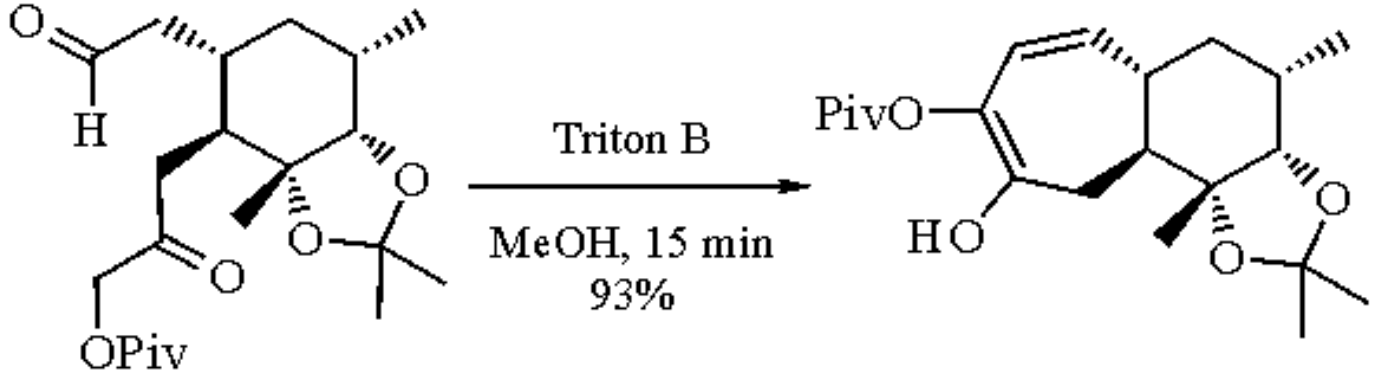

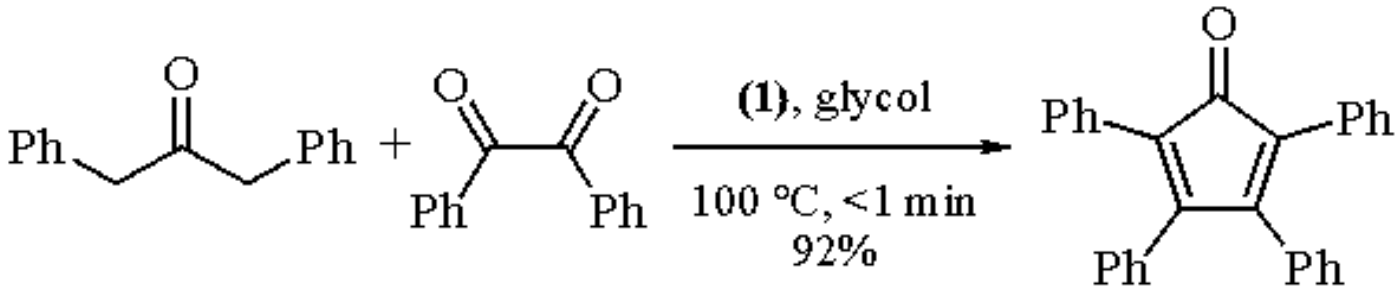

The action of Triton B has been used in the synthesis of 2-thiomethylindoles (eq 7).[15] Condensation of various 2-sulfonamido aldehydes with methyl methylsulfinylmethyl sulfide (55-88%) followed by treatment with H_2S and HCl gave rise to the indole products (62-80%).

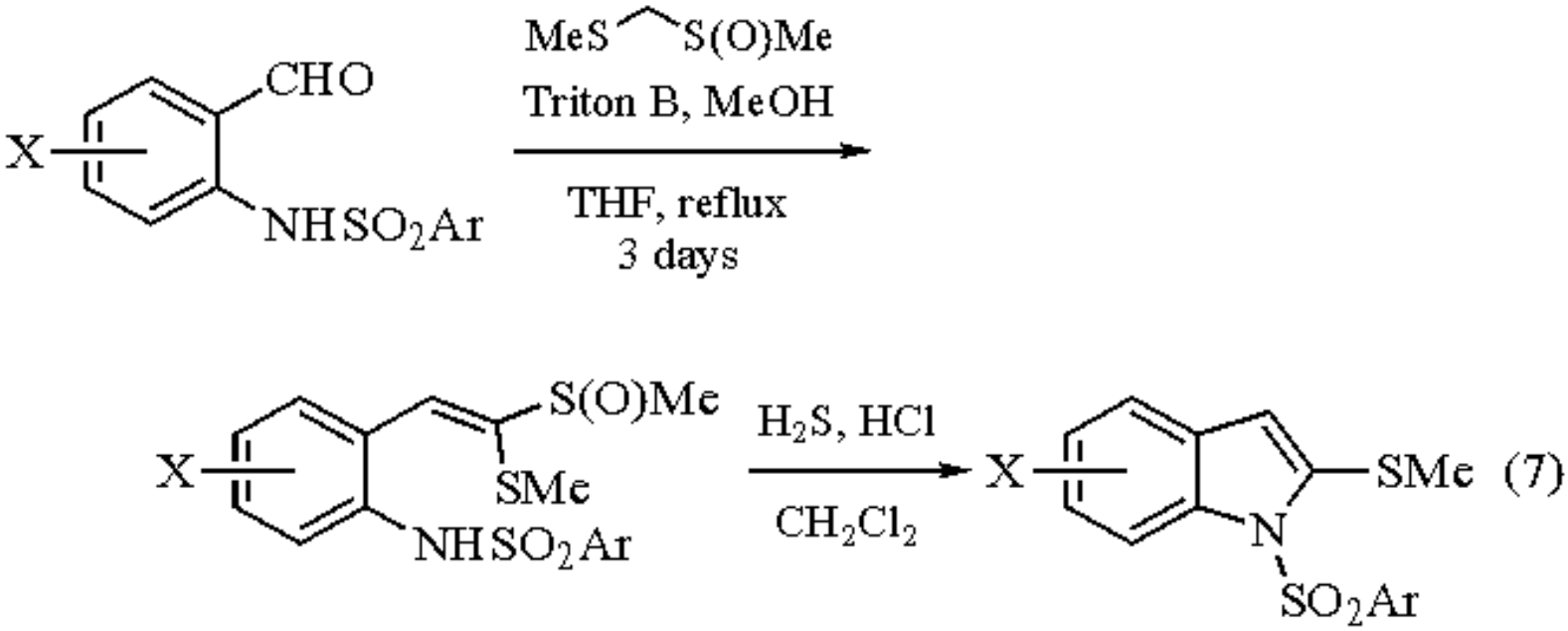

Conjugate Additions.

Triton B is an effective catalyst for the conjugate addition of carbon acids to Michael acceptors. Such is the case with the reaction of nitromethane and *t*-butyl acrylate mediated by a methanolic solution of (**1**) (eq 8).[16] In the given example, the triester formed was used in the preparation of dendritic macromolecules. Other bases were not as effective.[17] Nitroalkanes have also been added intramolecularly to alkynylamides[18] and intermolecularly to a variety of

unsaturated systems. The addition of a benzonitrile to methyl acrylate in a Michael fashion was reported to occur in excellent yield (eq 9).[19] Heteroatomic nucleophiles have also been added in a 1,4-fashion to conjugated systems.[20]

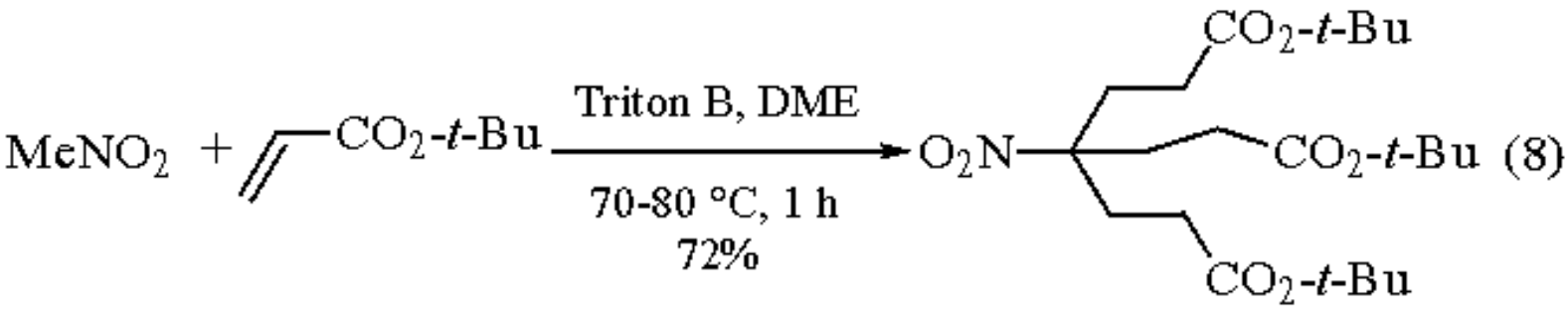

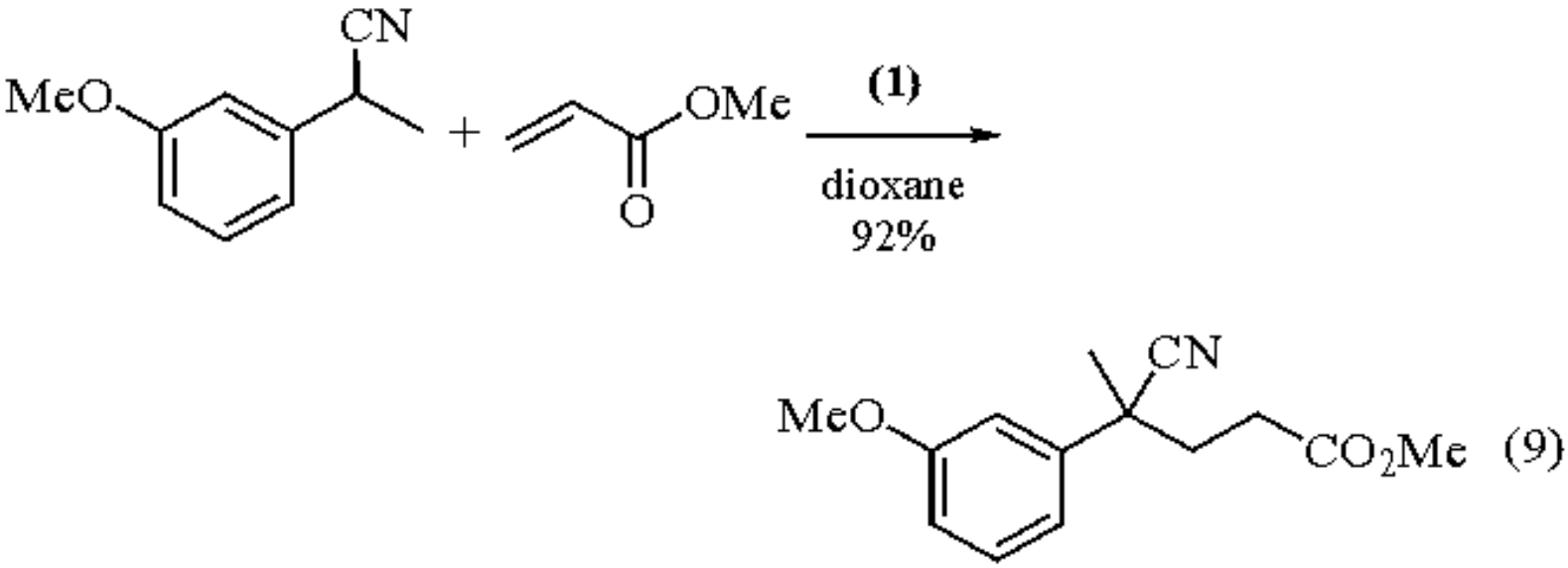

The addition of nucleophiles to vinylsiloxycyclopropanecarboxylates catalyzed by Triton B was reported to be an efficient method for the preparation of functionalized 4-oxoalkanoates (eq 10).[21] Other catalysts were not as effective.

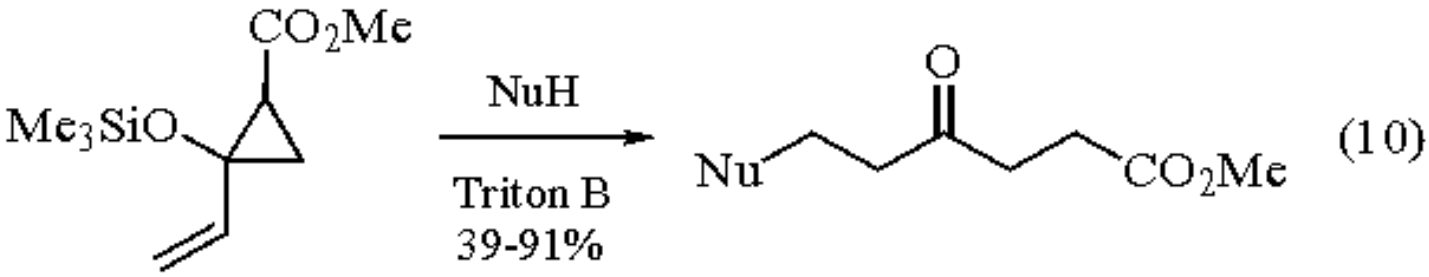

NuH = malonates, nitroalkanes, thiols

Benzyltrimethylammonium hydroxide also has been utilized in steroid syntheses through the Torgov reaction.[22] A cyclic 1,3-diketone can be *C*-alkylated through a formal S_N2' displacement of an ionizable tertiary hydroxy group (eq 11). Alkylation of 1,3-diketones with halides is also well known.[23]

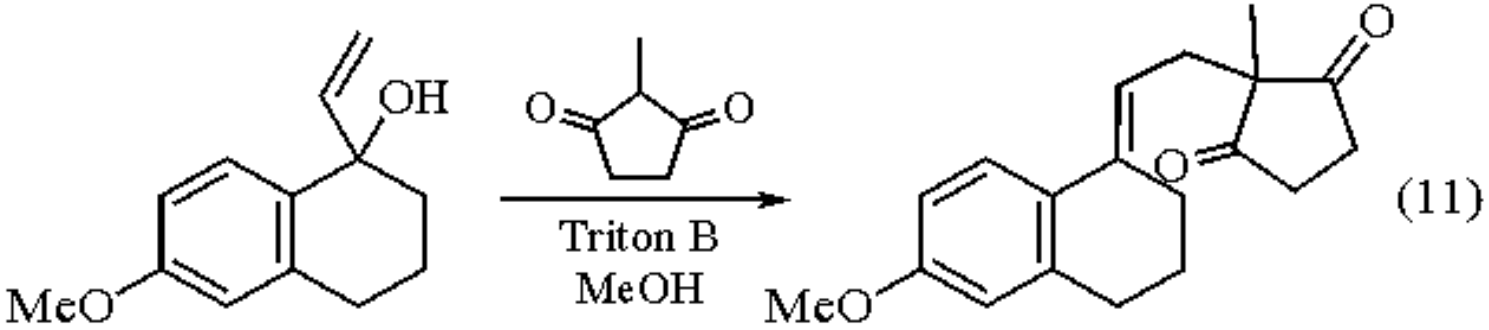

Eq 12 shows a novel photolytic reaction in which Triton B was used to improve the conversion of an amino enone into a bridged bicyclic compound.[24]

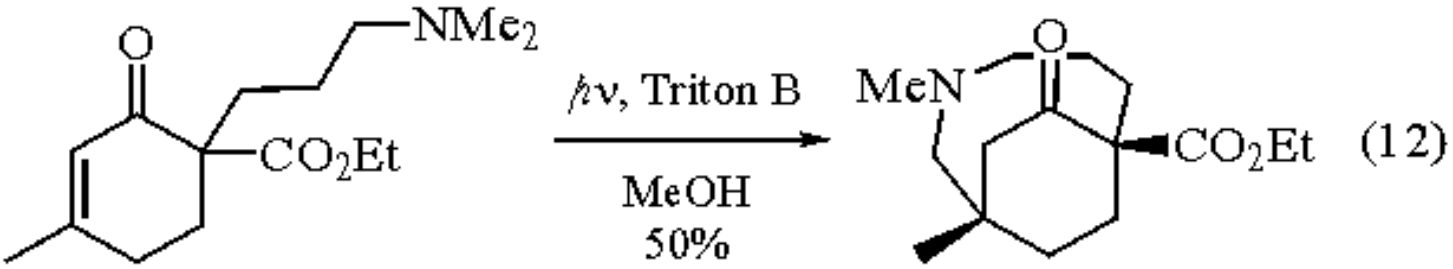

Benzyltrimethylammonium hydroxide has also been used in the conversion of an α-hydroxy-1,1-dichloride to an aldehyde, which was cyclized to generate the tetracyclic compound rhodomycinone (eq 13).[25]

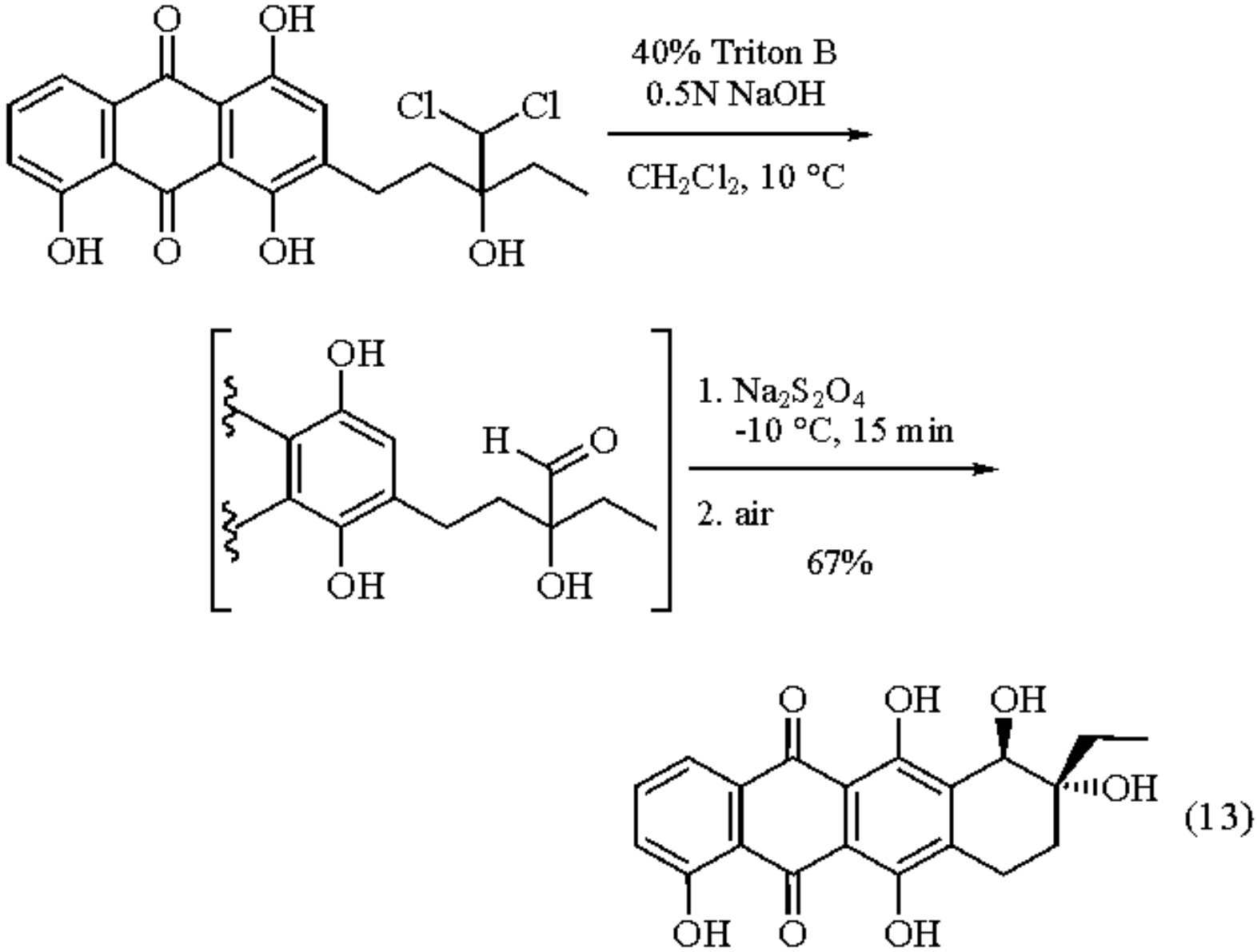

(13)

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Benzyltrimethylammonium Tetrachloroiodate[1]

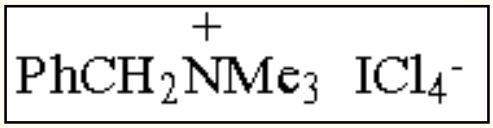

[121309-88-4] · $C_{10}H_{16}Cl_4IN$ · Benzyltrimethylammonium Tetrachloroiodate · (MW 418.96)

(chlorinating agent for aromatic compounds;[1] side-chain chlorination of aromatic compounds;[1] chlorine addition to alkenes[1])

Physical Data: mp 106-125 °C (sinters at 106-107 °C, and melts completely at 125 °C).

Solubility: sol MeCN, $MeNO_3$, DMSO, DMF; slightly sol MeOH, EtOH, AcOH, AcOEt, $CHCl_3$, CH_2Cl_2; insol C_6H_{14}, CCl_4, C_6H_6, H_2O.

Form Supplied in: yellow needles.

Analysis of Reagent Purity: ^{1}H NMR (CD_3CN) δ 3.07 (s, 9H, 3 CH_3), 4.40 (s, 2H, CH_2), 7.50 (s, 5H, C_6H_5).

Preparative Methods: chlorine gas is bubbled into a solution of benzyltrimethylammonium chloride (18.6 g, 0.1 mol) and iodine (12.7 g, 0.05 mol) in CH_2Cl_2 (300 mL) for 15 min; yield 40 g (95%).[2] For alternative methods, see Kajigaeshi et al.[3]

Handling, Storage, and Precautions: stable solid, but gradually decomposes with evolution of Cl_2 when in contact with air for a long time. This reagent should be handled in a fume hood.

Electrophilic Chlorination of Aromatic Compounds.

This solid reagent (**1**) is used to chlorinate aromatic compounds (eq 1) and is considerably safer and more convenient to use than toxic gaseous ***Chlorine***.

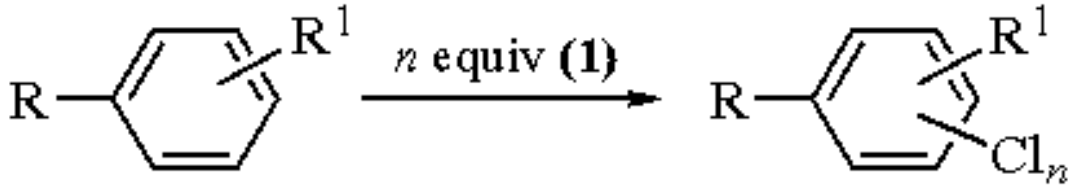

(1)

$R = OH, NH_2, OR^2, AcNH, R^2$

The reaction of phenols with (**1**) in CH_2Cl_2 at room temperature gives chloro-substituted phenols (66-91% yield). In these cases the chlorination of phenols having an electron-donating groups in the aromatic ring gives polychloro-substituted phenols; however, chlorination of phenols having electron-withdrawing groups can be controlled step by step.[4]

The reaction of aromatic amines with a calculated amount of (**1**) in AcOH at room temperature or at 70 °C gives chloro-substituted aromatic amines (66-99% yield). The active species in these chlorinations may be acetyl hypochlorite (AcOCl). In these cases, chlorination of amines having electron-withdrawing groups in the aromatic ring gives the desired chloro-substituted products, but chlorination of amines having electron-donating groups leads to oxidation products.[5]

The reaction of aromatic ethers with a calculated amount of (**1**) in AcOH or CH_2Cl_2 under mild conditions gives, selectively, chloro-substituted aromatic ethers (71-96% yield). Chlorination of nitroanisoles is unsuccessful.[6]

The reaction of acetanilides with a calculated amount of (**1**) in AcOH at room temperature or at 70 °C gives, selectively, the desired chloro-substituted acetanilides (81-93% yield). Chlorination of nitroacetanilides does not proceed.[7]

The reaction of arenes with a calculated amount of (**1**) in AcOH at room temperature or at 70 °C gives aromatic chlorides (40-99% yield). Thus treating 1,3,5-trimethylbenzene with 1, 2, and 3 equiv of (**1**) gives 1-chloro-, 1,3-dichloro-, and 1,3,5-trichloro-2,4,6-trimethylbenzene, respectively, in good yields.[8] The reaction of thiophenes with (**1**) in AcOH at room temperature or at 70 °C gives chloro-substituted thiophenes. For example, the reaction of 3-methylthiophene with 2 equiv of (**1**) gives 2,5-dichloro-3-methylthiophene in 81% yield.[9]

Side-Chain Chlorination of Aromatic Compounds.

The reaction of arenes with (**1**) in CCl_4 in the presence of AIBN under reflux gives α-chloro-substituted compounds. Thus the reaction of toluene with 1 equiv of (**1**) for 4 h gives benzyl chloride and benzylidene dichloride in 77% and 11% yield, respectively.[3] The reaction of acetophenones (eq 2) with 1 equiv of (**1**) in $ClCH_2CH_2Cl$-MeOH under reflux gives α-chloroacetyl derivatives (95-99% yield). Thus treating acetophenone with (**1**) for 3 h gives a 99% yield of α-chloroacetophenone.[2] The reaction of acetophenones

with 2 equiv of (**1**) in AcOH at 70 °C gives α,α-dichloroacetyl derivatives (66-99% yield). In this fashion, the chlorination of acetophenone with 2 equiv of (**1**) for 5 h gives 2,2-dichloro-1-phenylethanone in 90% yield.[10]

$$\text{Ar-COMe} \xrightarrow[\text{solvent, }\Delta]{n\text{ equiv }(\mathbf{1})} \text{Ar-COCH}_2\text{Cl or Ar-COCHCl}_2 \qquad (2)$$

solvent: $n = 1$, $ClCH_2CH_2Cl$-MeOH; $n = 2$, AcOH

Addition of Chlorine to Alkenes.

The reaction of alkenes with 1 equiv of (**1**) in CH_2Cl_2 at room temperature gives the expected chlorine adducts in a nonstereospecific manner (eq 3). In MeOH or AcOH this reaction produces chlorine adducts along with solvent-incorporated products in a regioselective manner.[11]

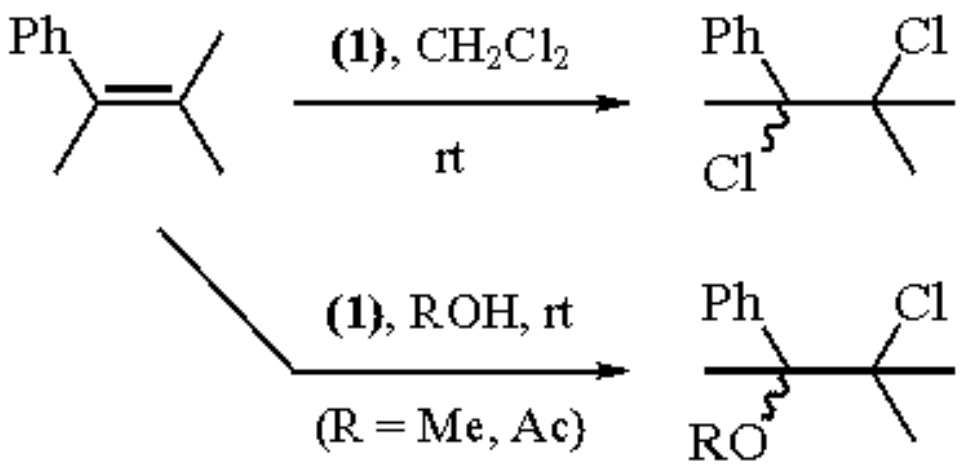

(3)

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Benzyltrimethylammonium Tribromide[1]

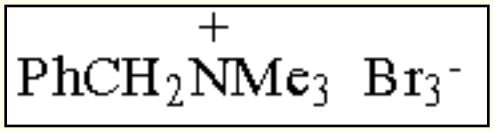

[111865-47-5] · $C_{10}H_{16}Br_3N$ · Benzyltrimethylammonium Tribromide · (MW 389.96)

(brominating agent for aromatic compounds;[1] side-chain bromination of aromatic compounds;[1] addition of bromine to π bonds;[1] mild oxidizing agent for many functional groups[1])

Physical Data: mp 100-101 °C.

Solubility: sol CH_2Cl_2, DMSO, DMF; slightly sol MeOH, AcOH, AcOEt, $CHCl_3$; insol hexane, benzene, CCl_4, H_2O.

Form Supplied in: orange-red needles.

Analysis of Reagent Purity: ^{1}H NMR (CD_3CN) δ 3.14 (s, 9H, 3 CH_3), 4.50 (s, 2H, CH_2), 7.52 (s, 5H, C_6H_5).

Preparative Methods: to a solution of benzyltrimethylam-monium chloride (11 g, 0.06 mol) and $NaBrO_3$ (4.5 g, 0.03 mol) in water (100 mL) is added aq. HBr (47%, 0.18 mol) under stirring at room temperature; yield 18.2 g (78%).[2] For an alternative method, see Kajigaeshi et al.[3]

Purification: recrystallize from CH_2Cl_2-Et_2O (10:1).

Handling, Storage, and Precautions: stable solid, but decomposes slightly upon standing for a long time in contact with air or water. This reagent should be handled in a fume hood.

Electrophilic Aromatic Substitution of Bromine.

This reagent (**1**) can be regarded as a solid form of ***Bromine***. The end points of its reactions can be detected by the decolorization of the reagent. Accordingly, the electrophilic bromo substitution of aromatic compounds with (**1**) has been extensively investigated (eq 1).

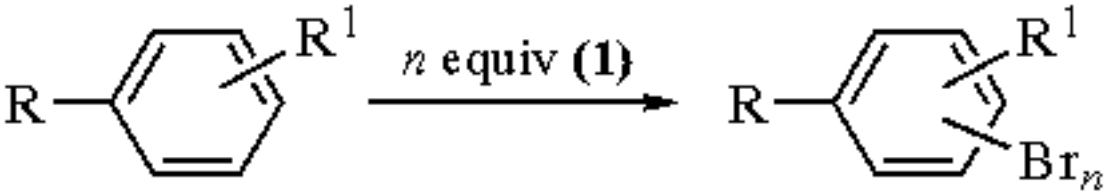

(1)

$$R = OH,\ NH_2,\ OR^2,\ AcNH,\ R^2$$

The reaction of phenols with a calculated amount of (**1**) in CH_2Cl_2-MeOH at room temperature gives mono-, di-, or tribromo-substituted phenols, selectively.[3] Because the presence of MeOH markedly facilitates the brominations, it can be assumed that the active species is methyl hypobromite (MeOBr) produced from the reaction of (**1**) with MeOH.[4] Polystyrene-bound (**1**) can also be used as the brominating reagent.[5]

The reaction of aromatic amines with (**1**) in CH_2Cl_2-MeOH containing ***Calcium Carbonate*** powder at room temperature gives bromo-substituted aromatic amines.[6] Polystyrene-bound (**1**) is also used for the preparation of polybromo-substituted aromatic amines.[7]

The reaction of aromatic ethers with a stoichiometric amount of (**1**) in CH_2Cl_2-MeOH or AcOH-$ZnCl_2$ under mild conditions gives, selectively, mono-, di-, or tribromo-substituted aromatic ethers.[8] The reagent is only slightly soluble in acetic acid at room temperature, but the addition of ***Zinc Chloride*** increases its solubility, allowing the bromination of aromatic ethers to proceed smoothly under mild conditions. An equimolar amount of $ZnCl_2$ with respect to (**1**) is required.[9]

Bromo-substituted acetanilides have been obtained from the reaction of acetanilides with (**1**) in CH_2Cl_2-MeOH[10] or AcOH-$ZnCl_2$.[11]

Arenes are brominated smoothly by (**1**) in AcOH with the aid of the Lewis acid $ZnCl_2$.[9] The reaction of thiophenes with (**1**) in AcOH-$ZnCl_2$ under mild conditions gives bromo-substituted thiophenes.[12]

Side-Chain Bromination of Aromatic Compounds.

The reaction of arenes with a calculated amount of (**1**) in refluxing benzene in the presence of AIBN gives α-bromo-substituted arenes.[13] The reaction of acetophenones with 1 equiv of (**1**) gives α-bromo-substituted acetophenones and with 2 equiv of (**1**) gives α,α-dibromo-substituted acetophenones.[2]

Addition to Alkenes.

The reaction of alkenes with (**1**) in aprotic solvents gives 1,2-dibromo adducts via a stereospecific *anti* addition; in protic solvents such as MeOH and AcOH it gives the corresponding dibromo adducts along with considerable amounts of solvent-incorporated products in a regioselective manner.[14]

Oxidation with (1).

This reagent has been conveniently used as a mild oxidizing agent in place of liquid bromine. Specifically, the oxidation of primary alcohols or ethers to dimeric esters,[15] α,o-diols or cyclic ethers to lactones,[15] secondary alcohols to ketones,[15] benzyl alcohols to benzaldehydes or benzoic acids,[16] 1,4-benzenediols to 2,5-cyclohexadiene-1,4-diones,[17] sulfides to sulfoxides[18] and thiols to disulfides[19] have been reported. By using (**1**), the haloform reaction of methyl ketones,[20] *N*-bromination of amides,[21] and Hofmann degradation of amides[22] have also been achieved.

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(Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate

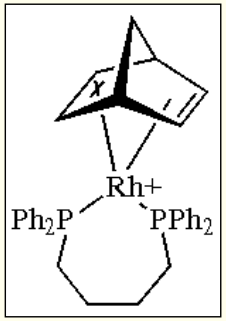

[82499-43-2] · $C_{35}H_{36}BF_4P_2Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate · (MW 708.4)

(reagent for catalytic hydrogenation;[9-11] hydrosilylation,[26] hydroboration,[27,28] and aldol condensation[32])

Physical Data: mp 211-212 °C (dec).

Solubility: insol Et_2O, pentane; sol CH_2Cl_2, MeOH, etc.

Form Supplied in: orange crystalline powder. *Drying:* used as supplied in anhydrous solvent.

Analysis of Reagent Purity: ^{31}P NMR indicates presence of free phosphine ligand and phosphine oxides; the characteristic ^{103}Rh coupled doublet (J_{RhP} = 155 Hz) demonstrates pure material.

Preparative Methods: a solution of [Rh(nbd)acac] in THF is treated with fluoroboric acid, followed by addition of 1,4-bis(diphenylphosphino)butane (dppb). The solution becomes deep red and ether is added to precipitate the catalyst, which is then isolated by filtration.[3a] The unpurified product is generally adequately pure for most applications. Recrystallization from methanol can be performed to obtain orange needles of [Rh(nbd)(dppb)]BF_4. Although air-sensitive in solution, the crystalline complex is indefinitely stable when prepared pure and stored under N_2 or Ar below 0 °C. A convenient preparation of the corresponding trifluoromethanesulfonate has been described.[3b] The cyclooctadiene (cod) analog has been characterized by X-ray crystallography,[4] and the dynamic solution structure of related systems has been studied by multinuclear NMR techniques.[5]

Handling, Storage, and Precautions: store under argon in freezer; stable as solid; solutions are air sensitive. Literature describes the use of perchlorate salts but their use cannot be recommended due to risk of detonation. Use in a fume hood.

Introduction.

Homogeneous catalytic hydrogenation with cationic rhodium catalysts has been extensively explored by Schrock and Osborn.[1] Use of these complexes in stereoselective organic synthesis has been a topic of more recent interest, and has been recently reviewed.[2] The reagent of choice for many of these directed hydrogenations has continued to be [Rh(nbd)(dppb)]BF_4 (**1**).

Directed Hydrogenation.

By far the most significant application of (**1**) has been in diastereoselective hydrogenation reactions. The ability of (**1**) to retain a significant level of Lewis acidity under conventional hydrogenation conditions has facilitated the development of directed hydrogenations in which (**1**) engages in prior coordination to heteroatoms situated proximal to the alkene functionality. Scheme 1 shows a general mechanistic scheme by which (**1**) may catalyze hydrogenation.[6] This scheme is derived by analogy to mechanistic steps elucidated in the context of the hydrogenation of *N*-acyl dehydroamino acids, which have been demonstrated to coordinate to (**1**) in a bidentate fashion.

(Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate

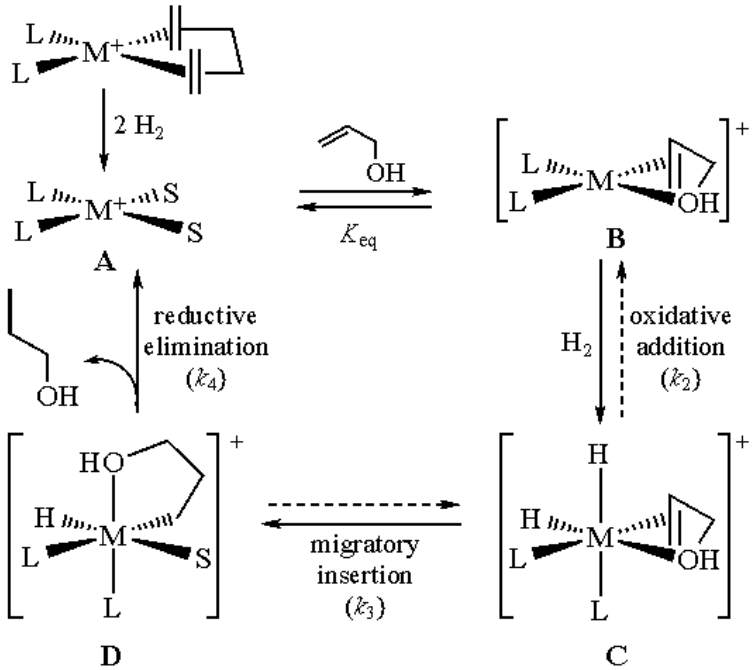

Scheme 1

Catalyst (**1**) readily absorbs 2 moles of H_2 to form complex A which may coordinate two solvent molecules.[7] The reversible binding of the substrate then occurs in a bidentate fashion to give complex B. Oxidative addition of dihydrogen then occurs to form the dihydride species C, which then undergoes migratory insertion to form the rhodium alkyl D. Although a primary Rh alkyl is shown in Scheme 1, a secondary Rh alkyl is possible as well. Finally, reductive elimination occurs to give the reduced product with concomitant regeneration of the active catalyst.

At low pressures the addition of hydrogen to a rhodium complex (schematically shown as B) is probably rate-determining, but at higher pressure, pre-equilibria (A to B) can contribute to the rate law. The effect of pressure on mechanism has important implications in the directed hydrogenation of substituted alkenes which can undergo double bond isomerization. This issue has been addressed in synthetic and mechanistic studies employing (**1**) (see below).

An early observation of directed hydrogenation was made by Thompson[8a] using $ClRh(PPh_3)_3$ with a cyclic homoallylic alcohol as reactant; the stereoselectivity of hydrogenation could be enhanced by base so that delivery of hydrogen to the alkene from an alkoxide-coordinated rhodium was postulated. Acyclic diastereoselection was observed in hydrogenation of allylic alcohols with complex (**1**)[8b] and a high level of stereochemical control observed for hydrogenations catalyzed by ***(1,5-Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate*** (**2**).[8c,8d] The ensuing discussion will concentrate on catalysis by complex (**1**).

Cyclic Alkenes.

The directing effect of alcohol substituents is perhaps most dramatically demonstrated with cyclic alkenes in which products are formed via hydrogenation from the more hindered face (Table 1). Entries 1-3 serve to illustrate that the directing alcohol may reside in either the allylic, homoallylic, or bis(homoallylic) position relative to the alkene undergoing hydrogenation, while synthetically useful levels of selectivity are retained.[9] Entry 4 is included to illustrate the dramatic steric congestion which can be overcome in directed hydrogenation reactions employing (**1**). Entries 5[10] and 6[11] illustrate the compatibility of (**1**) with protected amine functionality. In addition, when the alkenes in entry 5 or 6 are reduced under heterogeneous, nondirecting conditions, the other face of each alkene is reduced with high selectivity. Finally, entry 7 demonstrates that hydroxyl directivity in the [2.2.2] bicyclic system is also possible.[12]

Table 1 Hydroxyl-Directed Reductions with Catalyst **(1)**

Entry	Substrate	Major product	Mol % **(1)**	H_2 pressure (psi)	Selectivity
1	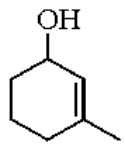	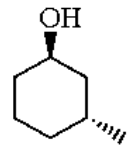	3.5	375	>200:1
2, 3	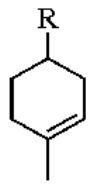	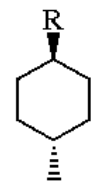	10	1000	R = OH 64:1 R = CH_2OH 19:1
4	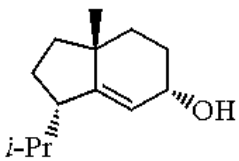	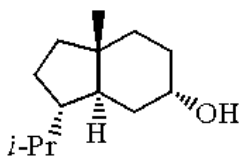	10	800	70:1
5	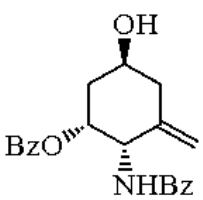	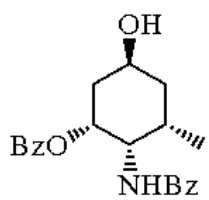	35	15	>19:1
6	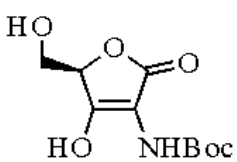	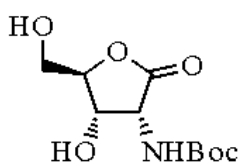	10	1400	91:9
7	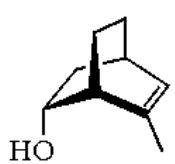	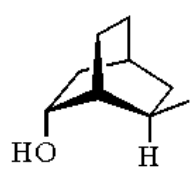	20	20	>99:1

Other Oxygen Directing Groups.

The Lewis acidity of (**1**) is manifested in coordination to other heteroatom-based functional groups which can direct hydrogenation. Table 2 demonstrates that (**1**) has a sufficient affinity for ethers[11] and esters[13] so that directed hydrogenations can be achieved when these functional groups are proximal to alkenes, although the rates and selectivities are somewhat lower than with the corresponding alcohols. While ketones, acetals, carboxylic acids, and amides have been demonstrated to direct catalytic

hydrogenation with the corresponding Ir^+ catalyst (**2**),[14] these functional groups do not provide good results when (**1**) is employed with cyclic alkenes. The lack of directivity from amides with (**1**) is particularly intriguing given the dramatic coordination properties of this moiety in the Rh^I catalyzed hydrogenation of *N*-acyl dehydroamino acids.[15]

Table 2 Oxygen Heteroatom-Directed Reductions with Catalyst **(1)**

Entry	Substrate	Major product	Mol %	Selectivity
1	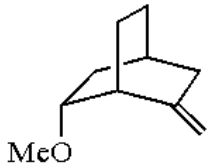	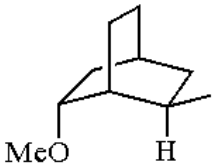	2	7:1
2	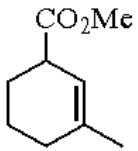	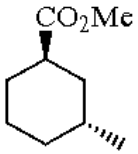	2	32:1
3	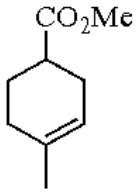	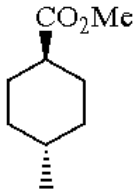	2	7:1
4	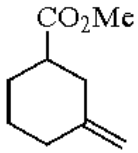	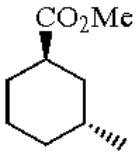	2	4:1

Acyclic Alkenes.

Acyclic alkenes also undergo stereoselective hydrogenation with catalysis by (**1**) (Table 3). It is significant to note that, in entry 1,[8b] although high selectivity is observed for the *anti* isomer, about 20% of the product is obtained as the corresponding methyl ketone, indicating that alkene isomerization is a competitive process. Entries 2 and 3 illustrate that either the *syn* or *anti* isomer can be obtained depending on the substitution pattern on the starting alkene.[8] In addition, this study established that alkene isomerization can be effectively suppressed at higher pressures. Entries 4-6 establish the efficiency of (**1**) for the reduction of unsaturated hydroxy esters,[16,17] which are not effectively reduced by (**2**). A model rationalizing the stereochemical outcome of these reductions has been proposed.[18] In this model, simultaneous coordination of the hydroxyl group and the alkene differentiates the diastereotopic faces. This analysis also explains the fact that alkene isomerization at low H_2 pressures contributes to diminished diastereoselectivities. This explanation has been confirmed by independent mechanistic experiments in which entries 2 and 3 were studied employing (**1**) and D_2.[19]

Table 3 Reduction of Acyclic Allylic Alcohols with Catalyst **(1)**

Entry	Substrate	Major product	Mol % **(1)**	H_2 pressure (psi)	Selectivity
1	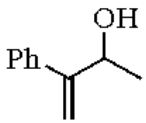	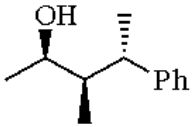	2	15	32:1
2	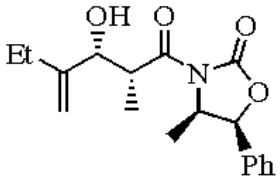	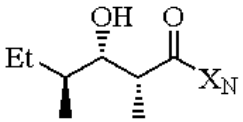	17.5	640	13:1
3	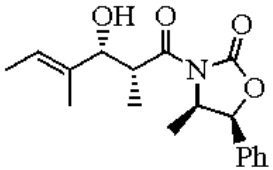	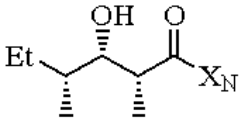	17.5	640	10:1
4	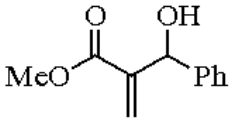	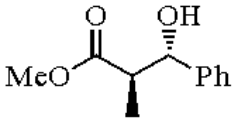	0.5	15	99:1
5	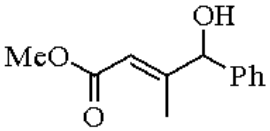	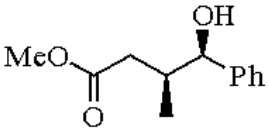	10	15	32:1
6	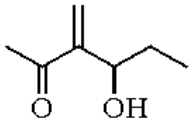	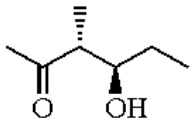	5	15	9:1

Catalyst (**1**) is effective in the directed reduction of homoallylic alcohols as well (Table 4). Entries 1-3 indicate that 1,1-disubstituted alkenes exhibit reasonable levels of diastereoselectivity in directed hydrogenations, although this level depends greatly on substitution pattern.[15,20] Entries 4-8 illustrate homoallylic trisubstituted alkenes undergo directed hydrogenation under catalysis by (**1**) with very high levels of selectivity, and that the configuration of the allylic substituent plays a significant role in modulating the level of selectivity. This study includes a rationale to explain the observed diastereoselectivities based on the principles of allylic strain.[1a,21]

Table 4 Reduction of Acyclic Homoallylic Alcohols with Catalyst **(1)**

Entry	Substrate	Major product	Mol % **(1)**	H_2 pressure (psi)	Selectivity
1	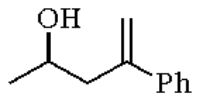	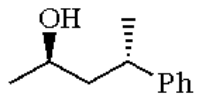	2	15	7:1
2	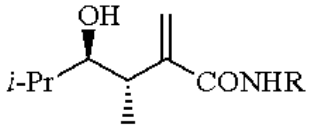	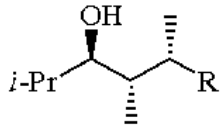	5	15	10:1
3	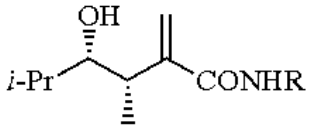	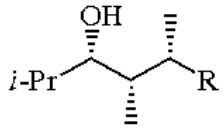	5	15	2:1
4	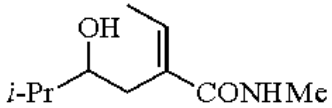	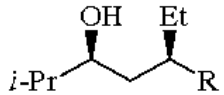	5	15	8:1
5	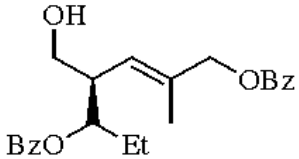	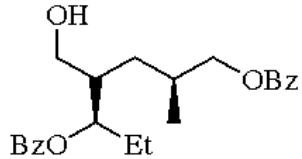	20	15	32:1
6	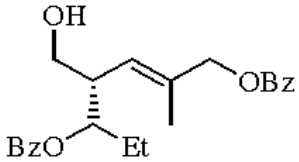	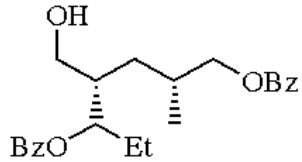	20	15	99:1
7	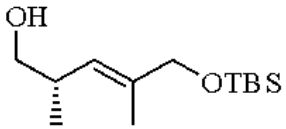	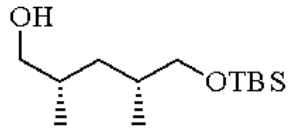	3	15	19:1
8	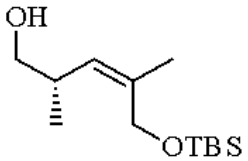	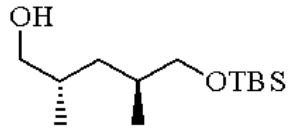	3	15	10:1

As with cyclic alkenes, nonhydroxylic directing groups can be used in the directed hydrogenation of acyclic alkenes. The selective reductions of 3-substituted itaconate esters illustrate the directing capacity of esters (Table 5). It appears that the presence of coordinating allylic substituents can effect the level of selectivity.[22]

Table 5 Directed Reduction Of Unsaturated Esters

Entry	Substrate	Major product	Mol %	Selectivity
1	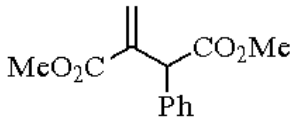	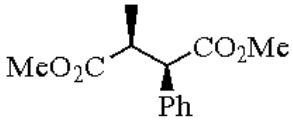	2	200:1
2	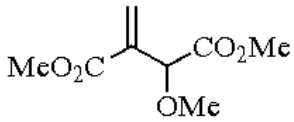	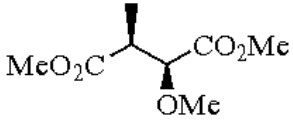	2	49:1
3	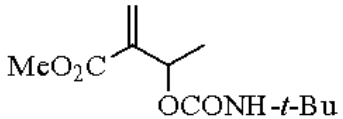	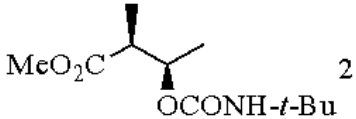	2	17:1
4	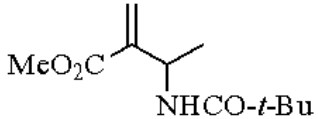	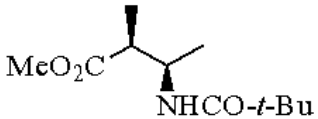	5	99:1
5	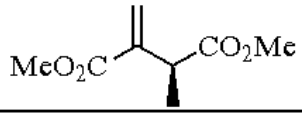	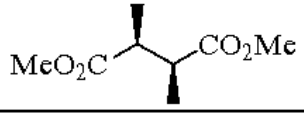	5	250:1

Applications in Total Synthesis.

Two recent examples of directed hydrogenations employing (**1**) in the total synthesis of complex molecules are illustrated. In eq 1 a simultaneous diastereoselective reduction of the trisubstituted alkene and the α,β-unsaturated ester afforded the illustrated advanced intermediate in the asymmetric total synthesis of ionomycin.[23] In addition, a two-directional application has been utilized in an asymmetric synthesis FK-506 (eq 2).[24]

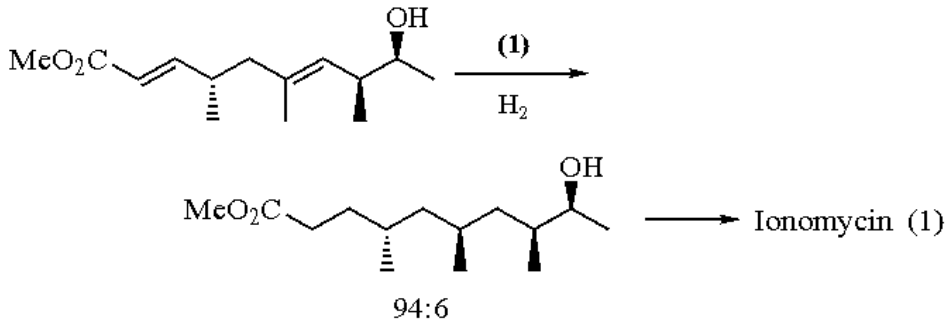

(Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate

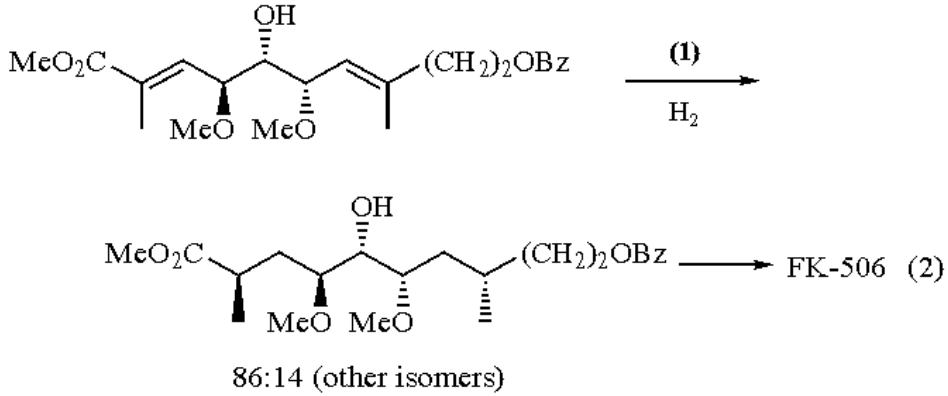

Miscellaneous Applications.

The hydroxyl directed hydrogenation of vinylstannanes and -silanes has been demonstrated to proceed efficiently.[25] The authors present a transition state model which rationalizes the observed results (eqs 3 and 4).

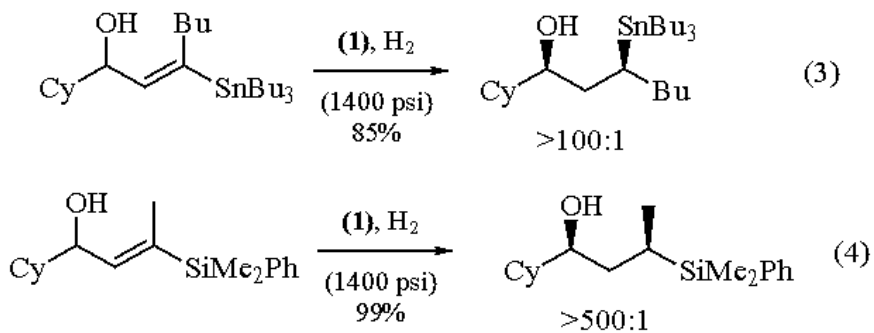

Hydrosilylation.

Rhodium(I) complexes catalyze the asymmetric hydrosilylation of prochiral ketones (eq 5), in the presence of (-)-sparteine.[26] Secondary alcohols are obtained in up to 30% optical yield by this method.

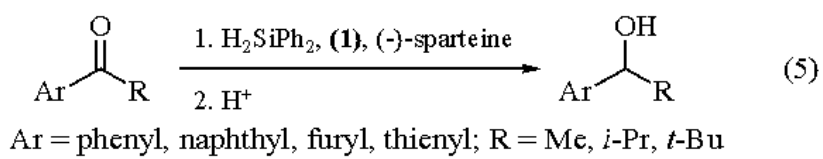

Hydroboration.

[Rh(cod)(dppb)]BF_4 is an efficient catalyst for the hydroboration of a range of vinylarenes.[27,28] Addition of ***Catecholborane*** to various styrene derivatives in the presence of 2 mol % catalyst gives, after oxidative workup, >99% secondary alcohol; in contrast, the corresponding uncatalyzed reaction gives the primary alcohol as the major product (eq 6).

(Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate

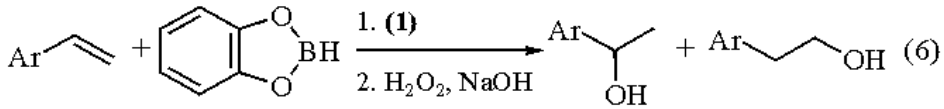

Ar = phenyl, 4-F, 4-Cl, 4-Me, 4-MeO, 3-F, 3-Cl
2-Cl, 2-$MeOC_6H_4$, naphthyl

This high regioselectivity is restricted to monosubstituted alkenes, indene, and (*E*)-1-phenylpropene. Analogous reactions with terminal aliphatic alkenes generally lead to primary alcohols as the major product, although alkene isomerization and BH_3-derived products arising from catalyst degradation can be problematic. 1,1-Disubstituted alkenes require longer reaction times, 1,2-disubstituted alkenes are still less reactive, and trisubstituted alkenes are essentially unreactive. This allows preferential hydroboration at the less hindered double bond in limonene (eq 7).[29]

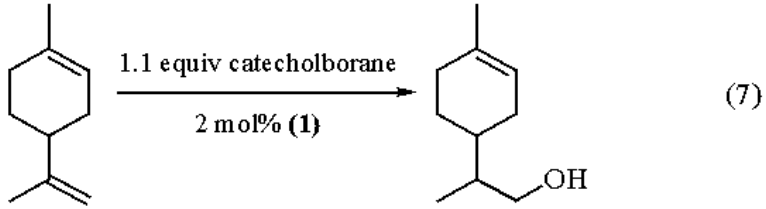

Asymmetric hydroboration of styrenes with the boranes derived from ephedrine and pseudoephedrine catalyzed by [Rh(nbd)(dppb)]OTf gives excellent regioselectivity, but poor enantioselectivity (eq 8). Better optical yields are obtained using rhodium complexes with more rigid [ferrocenyl]diphosphines.[30]

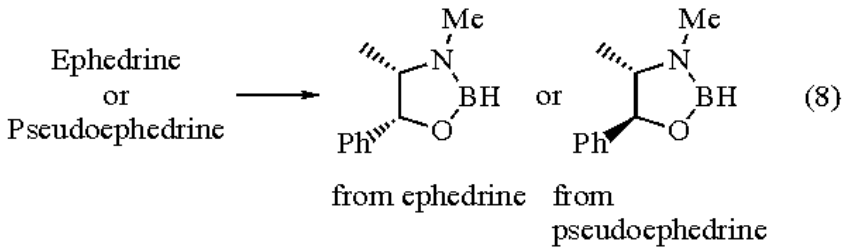

Diastereoselective rhodium-catalyzed hydroborations of allylic alcohol derivatives give results complementary to those observed in the uncatalyzed reaction with ***9-Borabicyclo[3.3.1]nonane***. The *syn* selectivity of the catalyzed reaction increases as the bulk of the R group increases (*syn*:*anti* = 79:21 for R = TBDPS) (eq 9).[29]

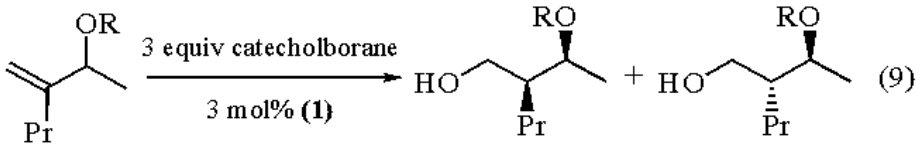

R = H, Bn, TBDMS, TBDPS

Exocyclic 1,1-disubstituted alkenes also give complementary selectivity (*syn*:*anti* = 93:7 for R = TBDMS) (eq 10) to that observed with 9-BBN.[29]

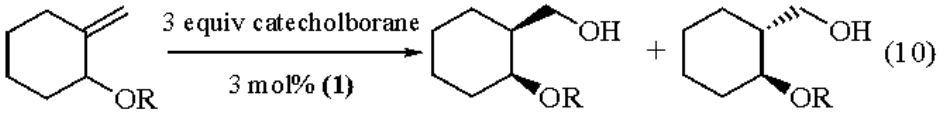

R = H, TBDMS

Aldol Condensations.

(Bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis(diphenylphosphino)butane]rhodium(I) Tetrafluoroborate

The rhodium complex has been utilized as a catalyst in aldol condensation of silyl enol ethers and aldehydes[31] or aldehyde equivalents (eqs 11 and 12).[32]

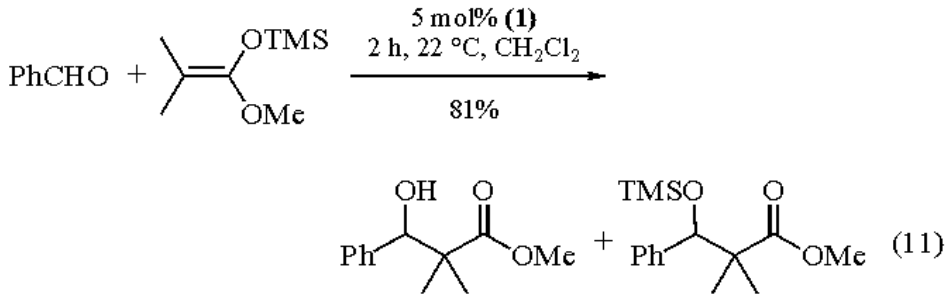

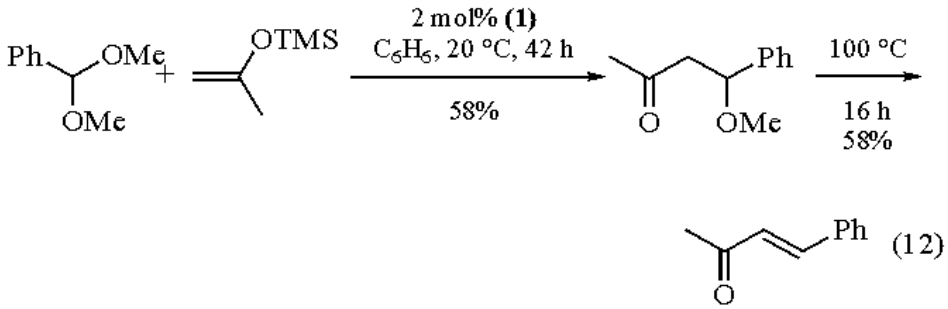

Although this rhodium complex has been studied in hydrocarbonylation and alkene isomerization, other rhodium catalysts give much higher yields and/or offer greater selectivity.

Finally, the ability of (**1**) to induce the isomerization of alkenes has been exploited in synthesis.[33] In the absence of H_2, the dominant product of the isomerization of the illustrated homoallylic silane is the allylic silane shown (eq 13). The reaction is presumably driven by the β-silicon effect.[34]

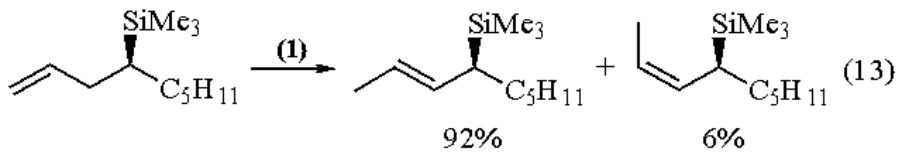

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(Bicyclo[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis(diphenylphosphino)butane]rhodium Perchlorate[1]

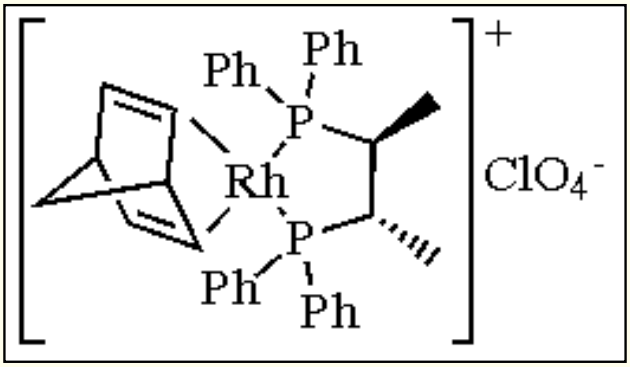

(ClO_4^-)

[65012-74-0] · $C_{35}H_{36}ClO_4P_2Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis(diphenylphosphino)butane]rhodium Perchlorate · (MW 720.97) (BF_4^-)

[79790-89-9] · $C_{35}H_{36}BF_4P_2Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis(diphenylphosphino)butane]rhodium Tetrafluoroborate · (MW 708.33) (PF_6^-)

[99340-29-1] · $C_{35}H_{36}F_6P_3Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(2*S*,3*S*)-bis(diphenylphosphino)butane]rhodium Hexafluorophosphate · (MW 766.49)

(catalyst precursor used in the asymmetric hydrogenation of amino acid precursors, as well as in transfer hydrogenation and hydrosilation reactions[2a,b])

Alternate Name: (bicyclo[2.2.1]hepta-2,5-diene)(chiraphos)rhodium perchlorate; (norbornadiene)(chiraphos)rhodium perchlorate.

Physical Data: $^{31}P\{^1H\}$ NMR (CD_3OD) δ 58.4 ppm, J_{Rh-P} = 154 Hz.

Solubility: sol CH_2Cl_2, MeOH, THF/MeOH, and H_2O/MeOH mixtures; sparingly sol THF; insol Et_2O.

Form Supplied in: cationic rhodium-chiraphos complexes are usually prepared in situ or from the procedure given below. In reactions employing the various rhodium-chiraphos complexes, the diene ligand is frequently hydrogenated prior to catalysis to afford the active solvated catalyst precursors $[RhS_2(chiraphos)]^+$.

Preparative Method: ***Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate*** (0.290 g) and (*S*,*S*)-chiraphos[1,3] (0.308 g) (see ***2,3-Bis(diphenylphosphino)butane***) are dissolved in methylene chloride (5 mL) and THF (5 mL) under nitrogen. Hexane (6 mL) is then added and, after the mixture is allowed to stand at 25 °C for 1 h and then for 2 h at 5 °C, orange-red crystals of [Rh(nbd)(*S*,*S*-chiraphos)]ClO_4 are collected (0.43 g).

Handling, Storage, and Precautions: cationic rhodium-chiraphos complexes are air-sensitive and should be handled and stored under an inert atmosphere.

Hydrogenation.

Rhodium(I) complexes containing chiral phosphine ligands are extremely useful in the preparation of enantiometrically pure amino acids.[2,4] Asymmetric hydrogenation of α-(*N*-acylamino)acrylic acids proceeds in high chemical yields (95-100%) with essentially complete optical purity (eq 1). For example, DOPA, alanine, and tyrosine are obtained from asymmetric hydrogenations catalyzed by rhodium(I)-chiraphos cations with optical yields of 83, 91, and 92% respectively.[2,4,5] Catalyzed hydrogenations of the analogous aliphatic compounds are somewhat less enantioselective.[6] Indeed, hydrogenation of the (*E*) isomers gives products with even lower optical yields (eq 2).

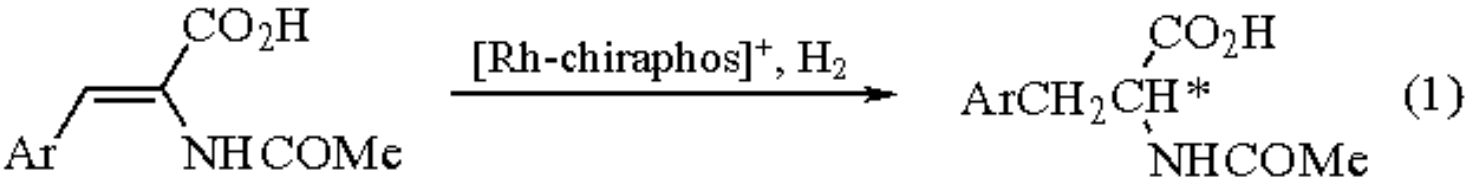

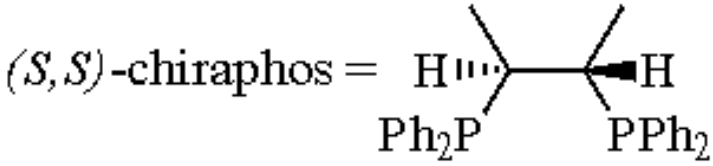

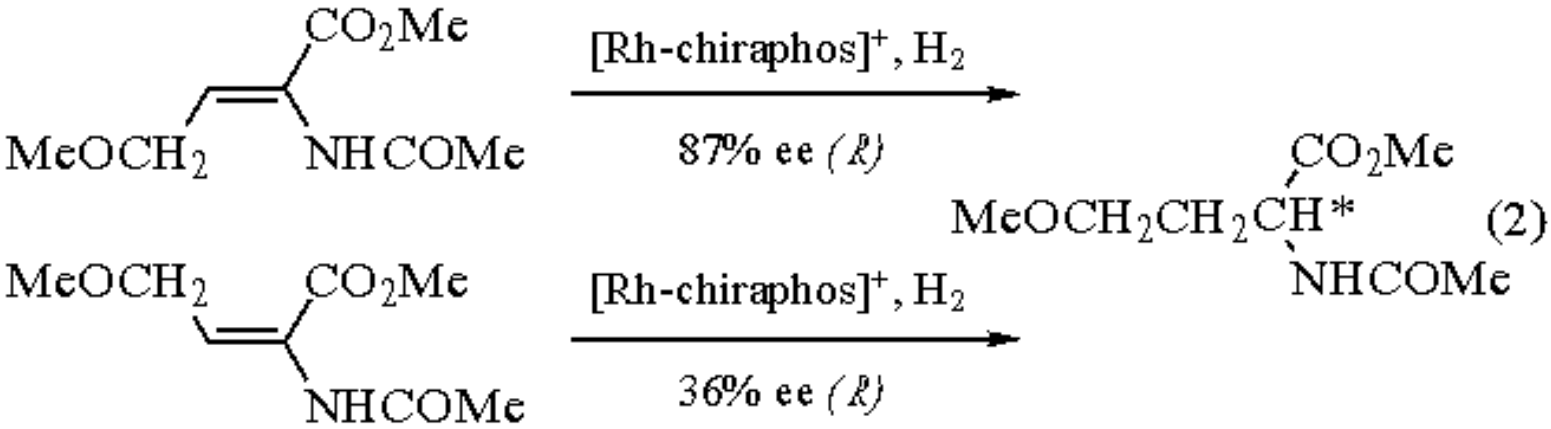

The active herbicidal agent L-phosphinothricin[7] is obtained with enantiomeric excesses up to 91% from the asymmetric hydrogenation of α-acylamidoacrylate precursors (eq 3). While yields of the primary hydrogenation products are quantitative, enantiomeric excesses increase slightly in reactions run in a H_2O/MeOH mixture. Adverse

effects are observed in reactions carried out in THF/MeOH.

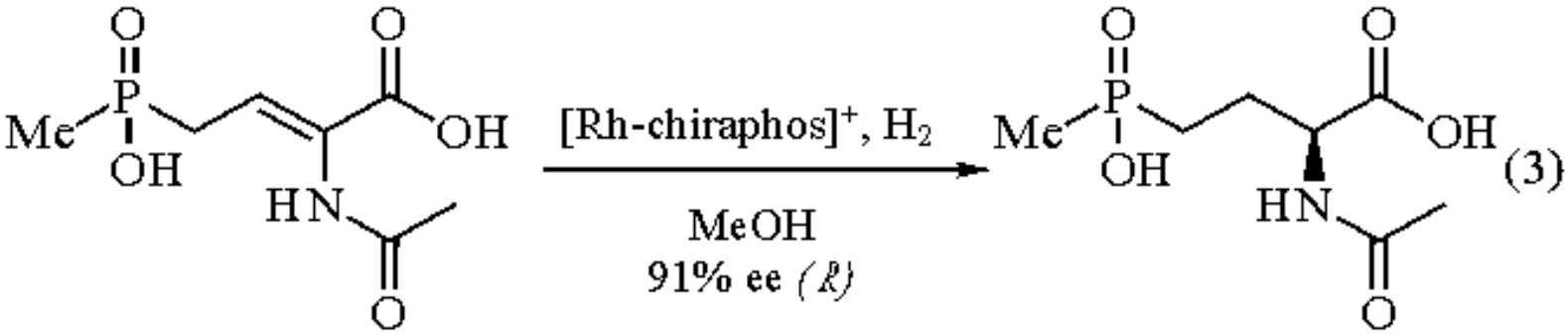

Reactions with 1,1,1-trifluoro-2-(acetyloxy)-2-propene provide the first example of a vinyl acetate with a fully saturated substituent geminal to the heteroatom to be hydrogenated asymmetrically with high efficiency (eq 4).[8] Rhodium-chiraphos cations also hydrogenate ketone[9] and epoxide[10] functionalities, albeit with low optical yields, and are, therefore, not synthetically useful. While this rhodium system seems somewhat limited to the preparation of amino acids, other rhodium[11] and ruthenium[12] catalyst precursors are currently available which show enhanced activity and selectivity for a much broader group of hydrogenation substrates.

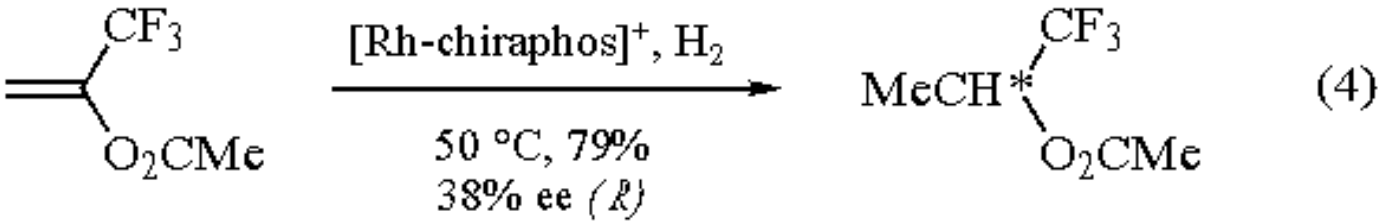

Transfer Hydrogenation.

Transfer hydrogenation invokes the use of alcohols as a source of hydrogen for the reduction of organic functionalities. While rhodium-chiraphos cations catalyze the asymmetric transfer hydrogenation of acetophenone with high conversion (76%), optical yields are low (8.3%).[13] Slightly higher enantiomeric excesses are obtained for the asymmetric reduction of ethyl phenyl ketone to give the corresponding alcohol (eq 5).[14]

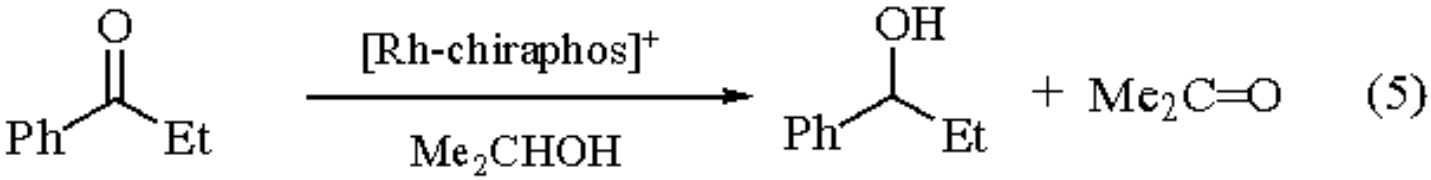

Miscellaneous.

Intramolecular hydrosilation of internally substituted alkenes proceeds rapidly (t = 6 min) in the presence of rhodium-chiraphos cations to give cyclic siloxanes in high yields (eq 6).[15] Basic workup proceeds with retention of configuration converting allylic alcohol derivatives to chiral 1,3-diols. Higher optical yields are obtained for analogous aryl alkenes. Hydroboration of vinylarenes with catecholborane employing cationic rhodium-chiraphos complexes affords secondary alcohols, upon oxidative workup, in high yields but with low optical purity. Much higher

enantiomeric excesses are obtained in reactions using analogous rhodium-BINAP catalyst precursors.[16]

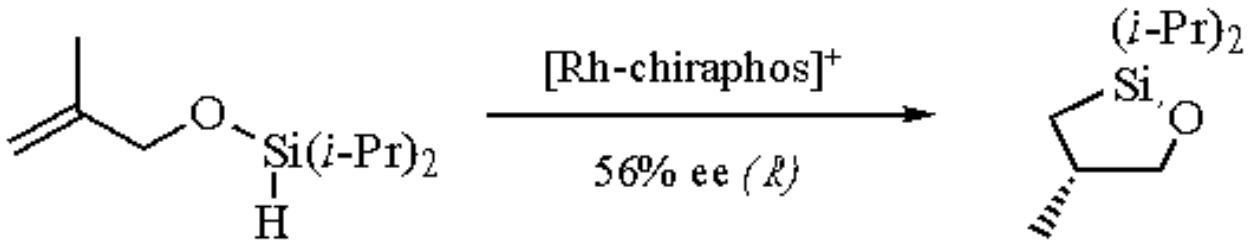

(6)

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(Bicyclo[2.2.1]hepta-2,5-diene)[(*R,R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]rhodium Tetrafluoroborate[1]

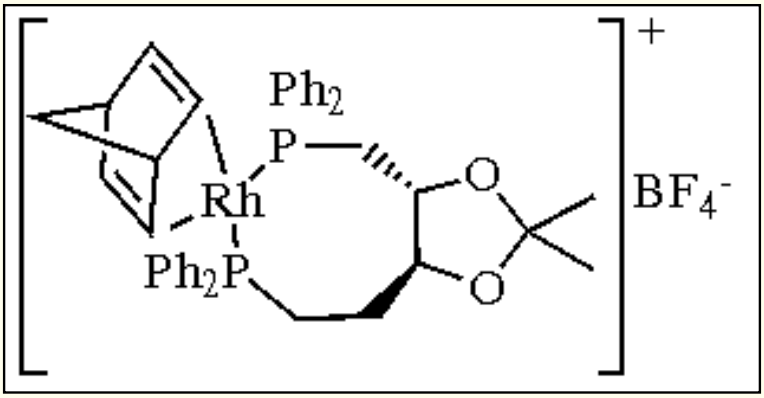

(BF_4^-)

[67650-23-1] · $C_{38}H_{40}BF_4O_2P_2Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(*R,R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]rhodium Tetrafluoroborate · (MW 780.39) (ClO_4^-)

[81445-14-9] · $C_{38}H_{40}ClO_6P_2Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(*R,R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]rhodium Perchlorate · (MW 793.04) (PF_6^-)

[132014-70-1] · $C_{38}H_{40}F_6O_2P_3Rh$ · (Bicyclo[2.2.1]hepta-2,5-diene)[(*R,R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]rhodium Hexafluorophosphate · (MW 838.55)

(chiral catalyst precursor for the asymmetric hydrogenation of amino acid precursors as well as for hydrosilations, hydroborations, hydroformylations, alkene migration, and hydrogen transfer reactions[2])

Alternate Name: (bicyclo[2.2.1]hepta-2,5-diene)(DIOP)rhodium tetrafluoroborate; (norbornadiene)(DIOP)rhodium tetrafluoroborate.

Physical Data: while physical data for the title complex are sparse, the analogous cod complex has been characterized fully. Physical data for [Rh(1,5-cod)(DIOP)]ClO_4: mp 183-184 °C (dec); ^1H NMR ($CDCl_3$) δ 1.09 (s, 6H, CH_3), 2.37 (m, 8H, CH_2), 2.71 (m, 4H, CH_2), 3.67 (m, 2H, CH), 4.54 (m, 4H, CH=), 5.26-8.00 (m, 20H, Ph) ppm.

Solubility: sol EtOH, MeOH, CH_2Cl_2; sparingly sol THF; insol Et_2O.

Form Supplied in: cationic rhodium-DIOP complexes are usually prepared in situ or from the procedure given below. In reactions employing the various rhodium-DIOP complexes, the diene ligand is frequently hydrogenated prior to catalysis to afford the active solvated catalyst precursors $[RhS_2(DIOP)]^+$.

Preparative Method: to an acetone (30 mL) solution of $[Rh(1,5\text{-cod})Cl]_2$ (0.27 g, 0.55 mmol) is added ***Silver(I) Perchlorate*** (0.233, 1.15 mmol) and the mixture is allowed to stir for 1 h at ambient temperature. Colorless precipitates are removed by filtration through filter paper and washed with dry acetone. To the pale yellow filtrate and washings is added DIOP (***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane***)[1,3] (0.50 g, 1.15 mmol) in acetone. The crude complex is recrystallized from an acetone-ether mixture to give deep-orange crystals (0.37 g, 45%).[4]

Handling, Storage, and Precautions: cationic rhodium-DIOP complexes are air-sensitive and should be handled and stored under an inert atmosphere.

Hydrogenation.

Asymmetric hydrogenation catalyzed by chiral transition metal complexes is an active research area of synthetic organic chemistry, largely owing to its utilization in Monsanto's L-DOPA synthesis.[2b] Rhodium(I) complexes containing chiral phosphine ligands are used extensively; the standard for evaluating the efficiency of these catalyst precursors is the asymmetric hydrogenation of α-(*N*-acylamino)acrylates.[5] Using the cationic rhodium-DIOP systems, hydrogenation of various precursors of alanine, phenylalanine, tyrosine, DOPA and leucine proceed almost quantitatively with optical yields approaching 95% ee.[6-8] For example, hydrogenation of prochiral thienyl-substituted acylaminoacrylates gives the corresponding saturated propanoic acid derivatives as shown in eq 1.[9]

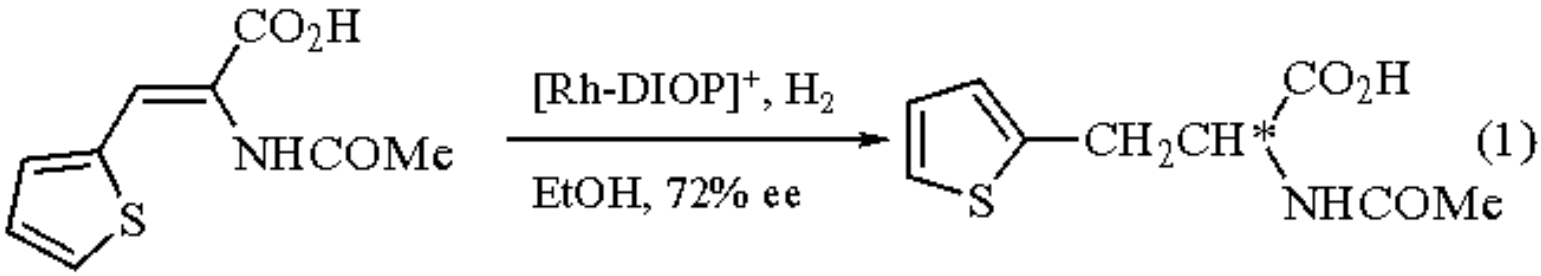

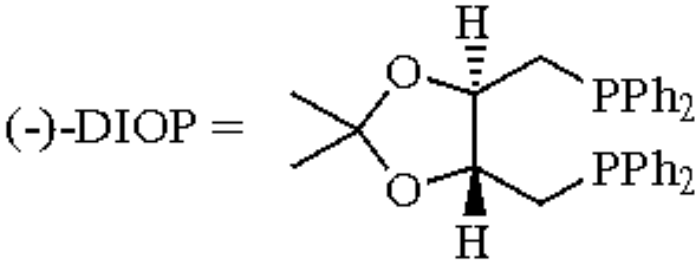

The naturally occurring amino acid phosphinothricin can be prepared by the asymmetric hydrogenation of α-acylamidoacrylate precursors with enantiomeric excesses reaching 70%.[10] Likewise, Leu-enkephalins and other small peptides can be prepared from asymmetric hydrogenations, although the reactions are only moderately stereoselective (23% ee) using cationic rhodium-DIOP complexes.[11] Although carbonyl functionalities can be stereoselectively reduced to the corresponding alcohols, optical yields are generally much lower than analogous reactions employing

neutral rhodium-DIOP complexes.[12] For instance, methyl 2-acetamido-3-oxobutyrate is hydrogenated en route to an enantioselective synthesis of D- and L-threonine in 90% yield but with enantiomeric excesses of only 18-25% when using cationic rhodium-DIOP systems (eq 2).[13]

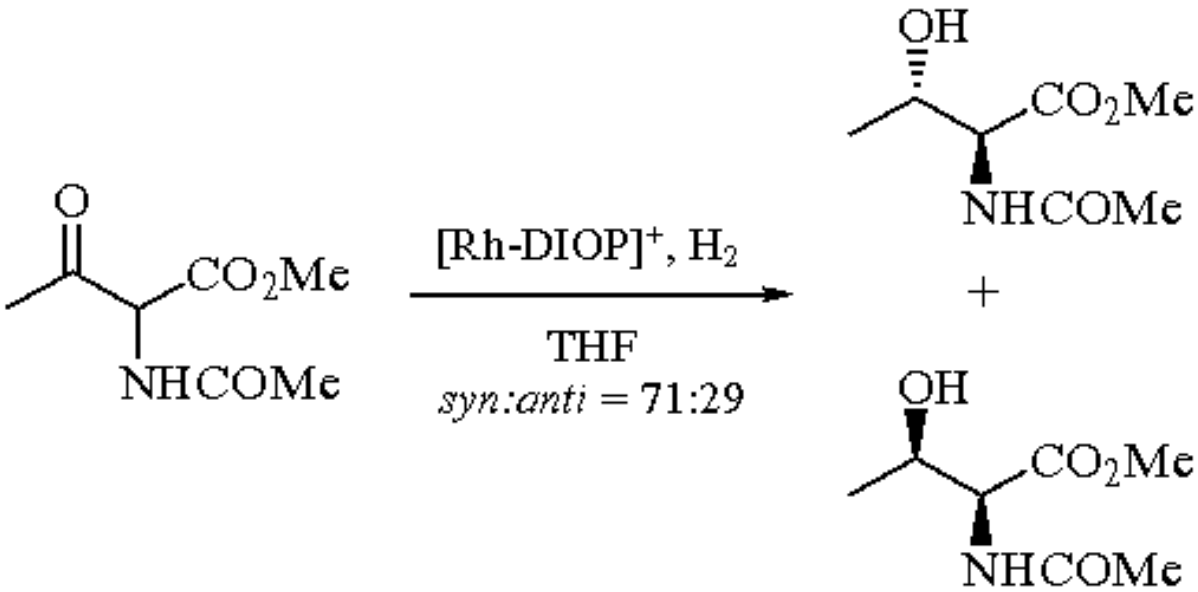

(2)

The asymmetric catalytic hydrogenolysis of epoxides can also be accomplished with chiral rhodium complexes. Unfortunately, optical yields using cationic DIOP complexes are low (30%) and epoxides without carboxy functionalities are not hydrogenated under similar conditions.[14] The addition of amines to the catalyst system has been found to enhance yields in the catalyzed hydrogenation of certain prochiral alkenes. Drastic increases in optical yields are observed in the asymmetric hydrogenation of 3-phenyl-3-butenoic acid upon addition of catalytic ***Triethylamine*** (eq 3).[15] Finally, as is generally the case for all asymmetric catalyzed hydrogenations, optical yields are disappointingly low for the reduction of simple alkenes (ca. 15%).[16]

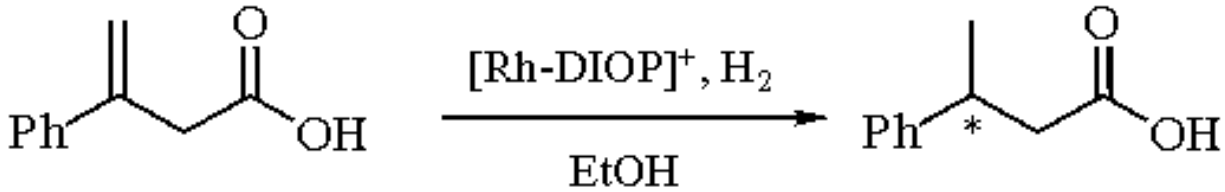

(3)

Amine	Yield (%)	ee (%)
None	6	16.7 *(S)*
Et_3N	78	70.3 *(S)*

Modified DIOP Ligands.

Alkylated[17] and sulfonated[18] analogs of the DIOP ligand, as well as amine[19] and boron[20] derivatives, have been

prepared recently. The corresponding cationic rhodium complexes are active catalysts for the asymmetric hydrogenation of amino acid precursors, generally proceeding with higher optical yields than reactions employing parent catalyst systems.

Alkene Migration.

Cationic rhodium-DIOP complexes are moderately effective for allylic hydrogen migration of secondary and tertiary allylamines to give the corresponding imines and (*E*)-enamines respectively (eq 4).[4] Higher yields are found, however, in reactions employing neutral rhodium systems containing different chiral phosphine ligands.

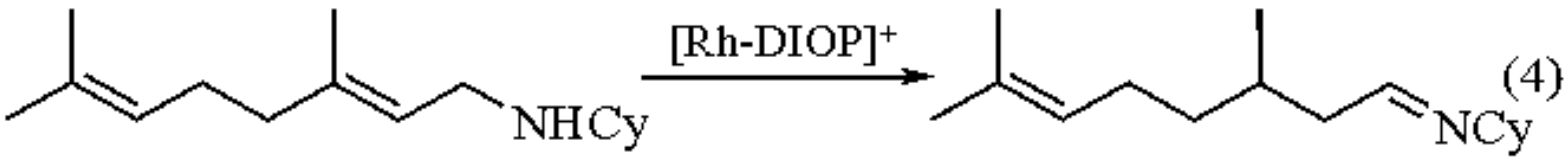

Miscellaneous.

Cationic rhodium-DIOP complexes are active catalyst precursors for a number of asymmetric reactions including hydrosilation,[21] hydroformylation,[22] hydrogen transfer,[23] and hydroboration (eq 5).[24] Optical yields, however, are generally much lower than reactions employing other chiral phosphines (or their neutral phosphinorhodium counterparts) and are, therefore, not synthetically useful.

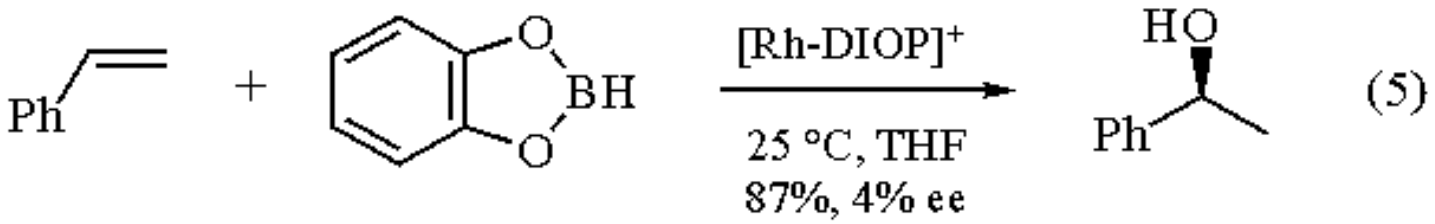

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1,1´-Binaphthalene-2,2´-dithiol[1]

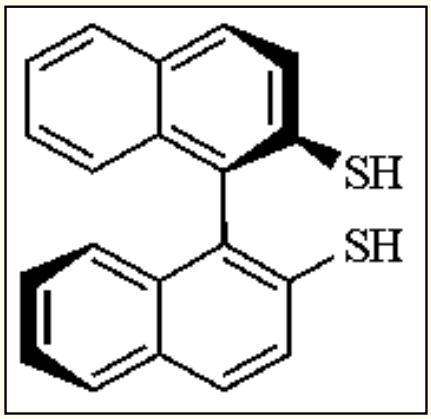

[102555-71-5] · $C_{20}H_{14}S_2$ · 1,1´-Binaphthalene-2,2´-dithiol · (MW 318.45) (-)

[124414-36-4] (±)

[55441-99-1]

(reagent for the preparation of chiral, atropisomeric organosulfur reagents of C_2 symmetry;[1] used as chiral ligand and in the preparation of chiral crown ethers)

Physical Data: mp 150-151 °C (benzene); (*R*)-(-): [α]22D -85.9°; [α]22546 -103.8° (*c* = 1, $CHCl_3$).

Analysis of Reagent Purity: the presence of the disulfide can be checked by TLC on silica gel, eluting with dichloromethane.

Preparative Methods: the original procedure used Ullman coupling of 1-bromo-2-naphthalenesulfonic acid.[2a] The intermediate 1,1´-binaphthalene-2,2´-sulfonic acid can be resolved with strychnine.[2b] Lithiation of 2,2´-dibromo-1,1´-binaphthalene with *t*-butyllithium, quenching with sulfur,[2c] and reduction of the resulting disulfide is an alternative preparation of the racemic dithiol. More practical procedures entail Newman-Kwart rearrangement of the thioester derived from binaphthol and dimethylthiocarbamoyl chloride, followed by hydrolysis.[3-5] Use of enantiomerically pure binaphthol as starting material gives the enantiomerically pure reagent.[4] Another resolution procedure involves enantioselective oxidation of sulfides which can be further transformed into the dithiol.[6]

Handling, Storage, and Precautions: the reagent oxidizes easily to the disulfide and should be stored under inert atmosphere. Use in a fume hood.

Binaphthalene-2,2´-dithiol is the starting material for the preparation of a number of sulfur-containing heterocycles of

synthetic utility. The basic principle lies in the generation of C_2 symmetric chiral variants of reagents that contain two sulfur atoms. For example, the achiral bis(phenylthio)methane becomes the chiral 1,3-dithiepine (eq 1), still maintaining similar structural features to the acyclic reagent.[7] This dithiepine belongs to the class of reagents that function as formyl anion synthons. The C_2 symmetry is also shared by the bisoxide (it forms stereoselectively as a single pseudoequatorial isomer) and the bis-sulfone. Reaction of the anion of the dithiepine with benzaldehyde gives an 8:2 mixture of diastereoisomers (eq 2).[7]

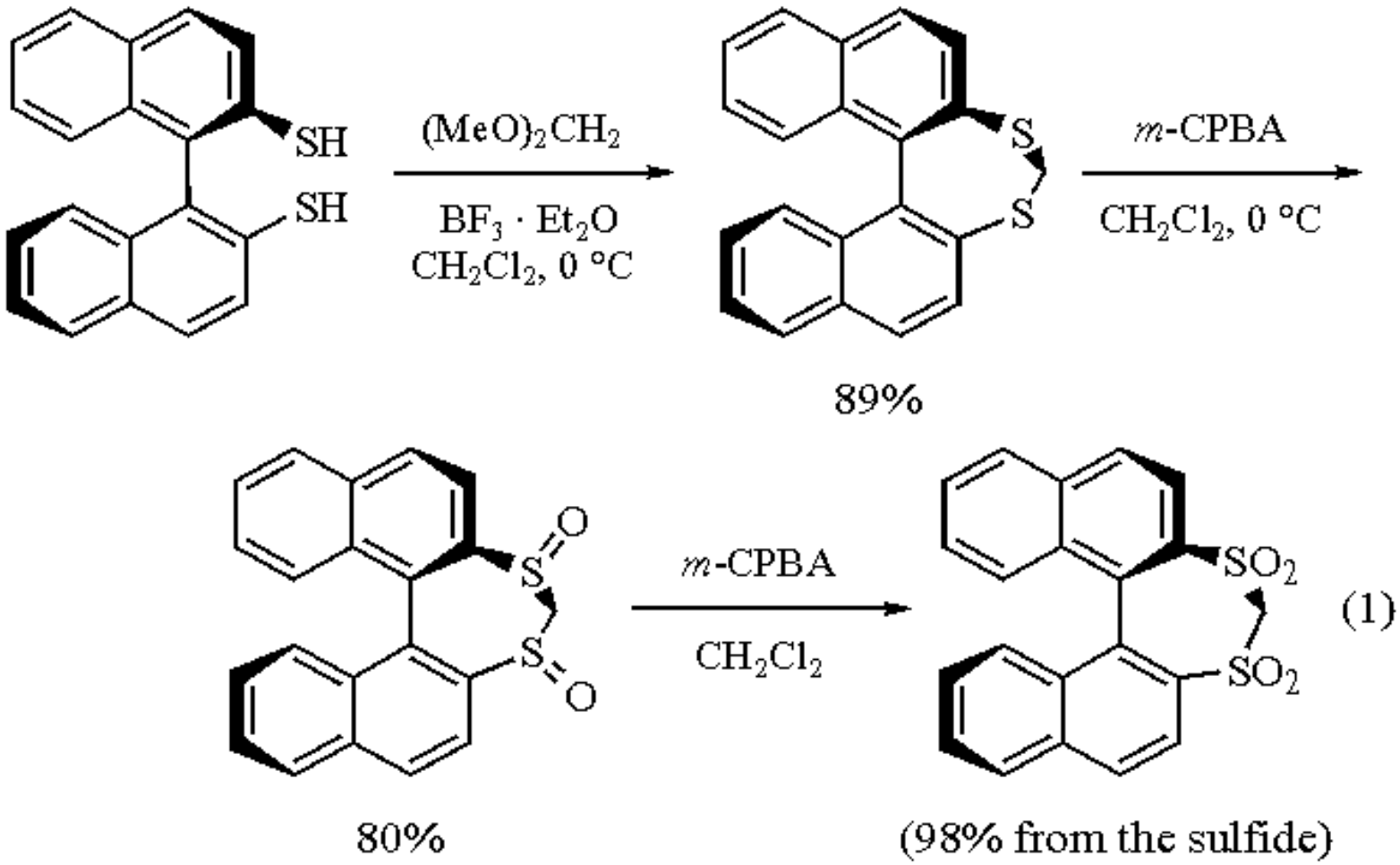

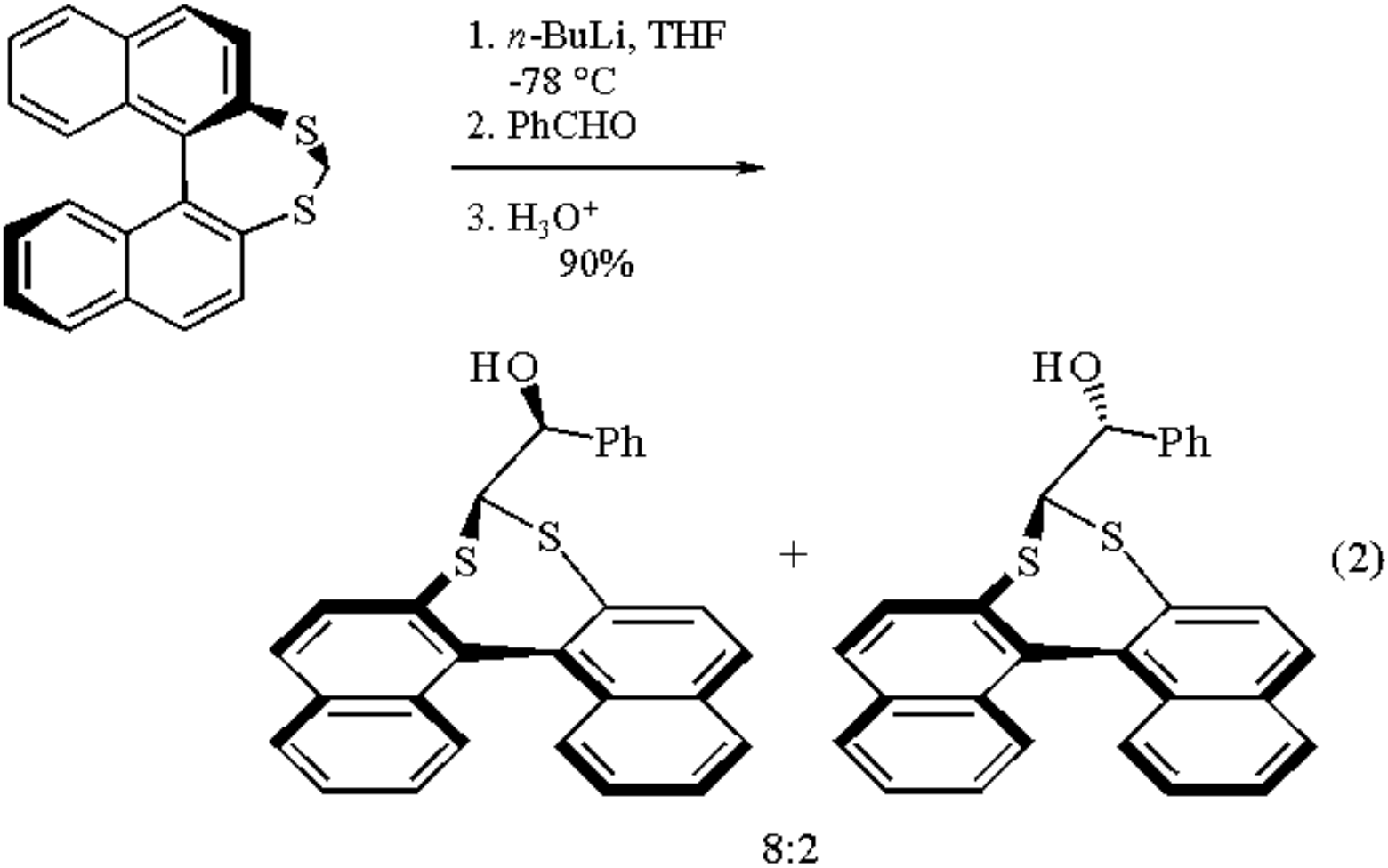

A single diastereoisomer is obtained in the reduction of the ketone with ***Lithium Aluminum Hydride*** as illustrated in eq 3.[8] The addition of other nucleophiles such as methylmagnesium iodide also gives single adducts.

1,1´-Binaphthalene-2,2´-dithiol

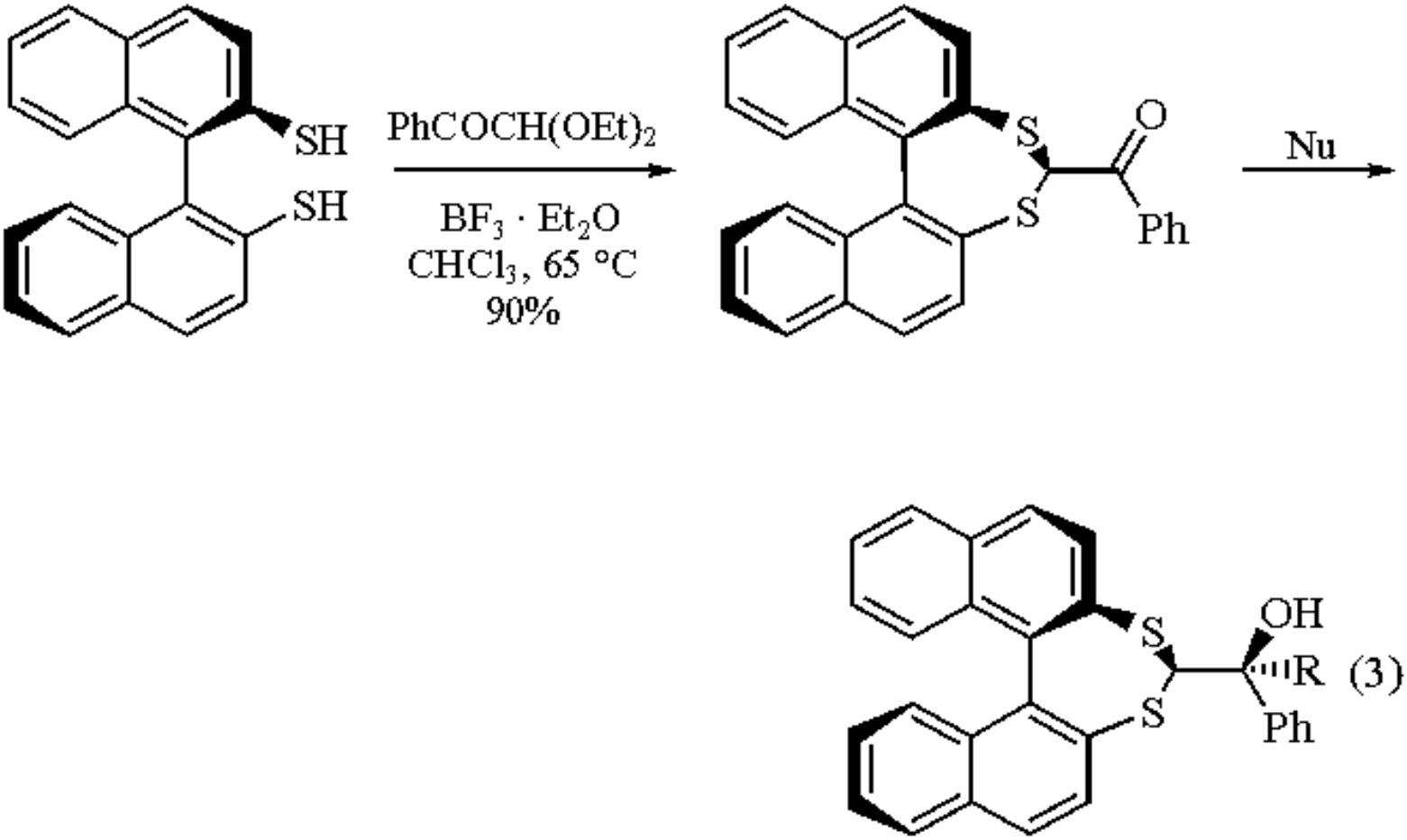

Nucleophile (Nu)	R	Reaction conditions	Diastereomeric ratio	Yield (%)
$LiAlH_4$	H	Et_2O, -78 °C, 45 min	100:0	98
$NaBH_4$	H	EtOH, H_2O, Et_3N, 20 °C, 4 h	86:14	99
MeMgI	Me	THF, Et_2O, 0 °C, 40 min	100:0	98

Monoxidation of the dithiepine gives single diastereomeric sulfoxides with pseudoequatorial configuration (eq 4).[7] In general, the oxides exhibit increased diastereoselectivity with respect to the unoxidized substrates, as in the examples of eq 5.[7]

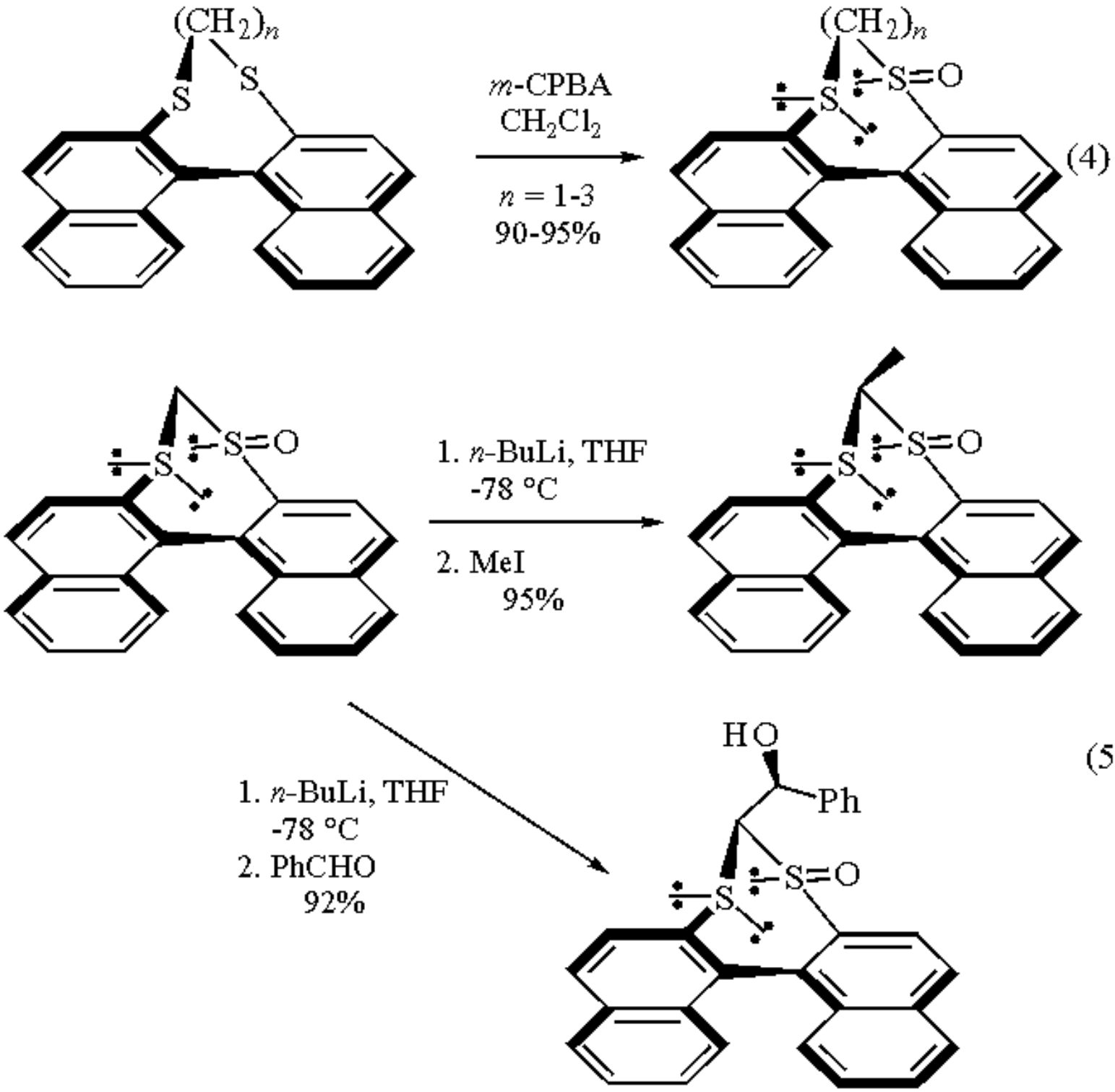

C_2 symmetric, chiral ketene dithioacetals containing the binaphthyl moiety can be prepared by Peterson alkenation of the title reagent (eq 6).[9] The corresponding bis-sulfone affords one *exo* and one *endo* adduct with cyclopentadiene (eq 7) which, once separated and desulfonylated, give the corresponding norbornenes (see ***1,1-Bis(phenylsulfonyl)ethylene***).[10]

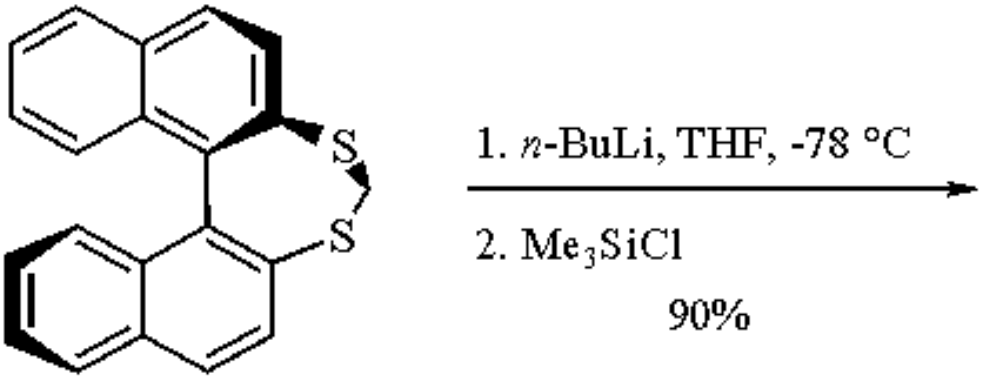
S
S
1. n-BuLi, THF, -78 °C
2. Me3SiCl
90%

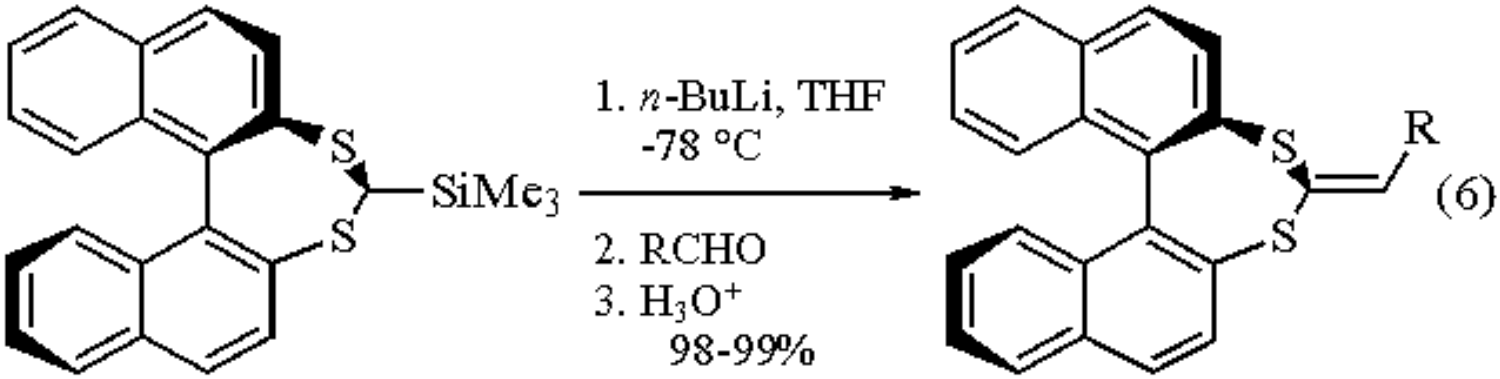
S
S
SiMe3
1. n-BuLi, THF
-78 °C
2. RCHO
3. H3O+
98-99%
S
S
R

(6)

R = H, Me, Ph

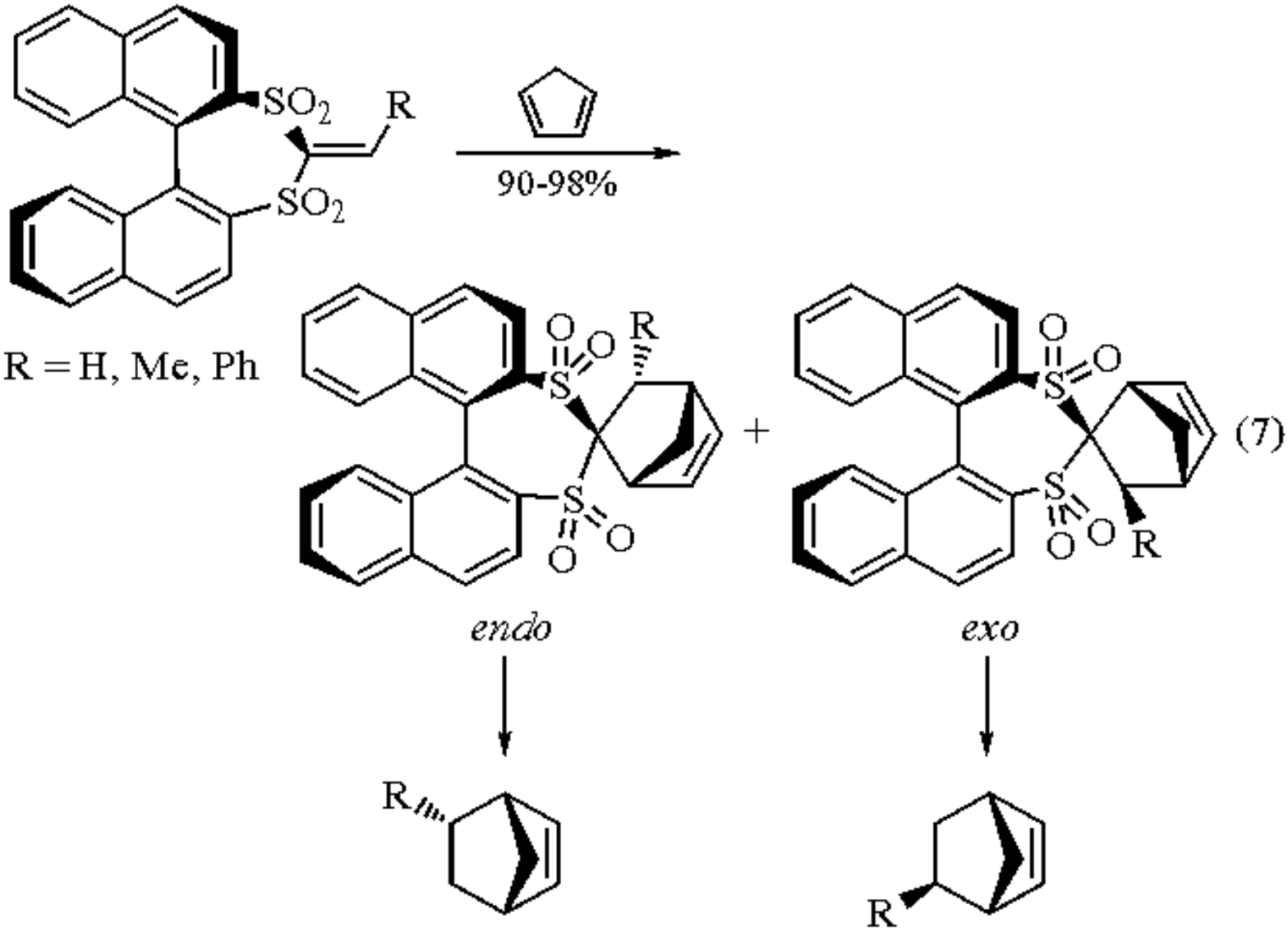

The dithiocine tetraoxide derived from cyclocondensation of binaphthodithiol with dichloroethylene and oxidation (eq 8) is a chiral version of the bis(phenylsulfonyl)ethylenes.[11] These compounds are useful acetylene equivalents in cycloaddition reactions (see ***1,2-Bis(phenylsulfonyl)ethylene***).[9] Indeed, a chiral acetylene equivalent allows the preparation of optically active hydrocarbons which would be difficult to prepare by classical methods. The dithiocine tetroxide reacts with nonsymmetric dienes to give a single crystalline diastereomeric adduct in most cases. Adducts (**1**) and (**2**) were obtained from acyclic and cyclic dienes.

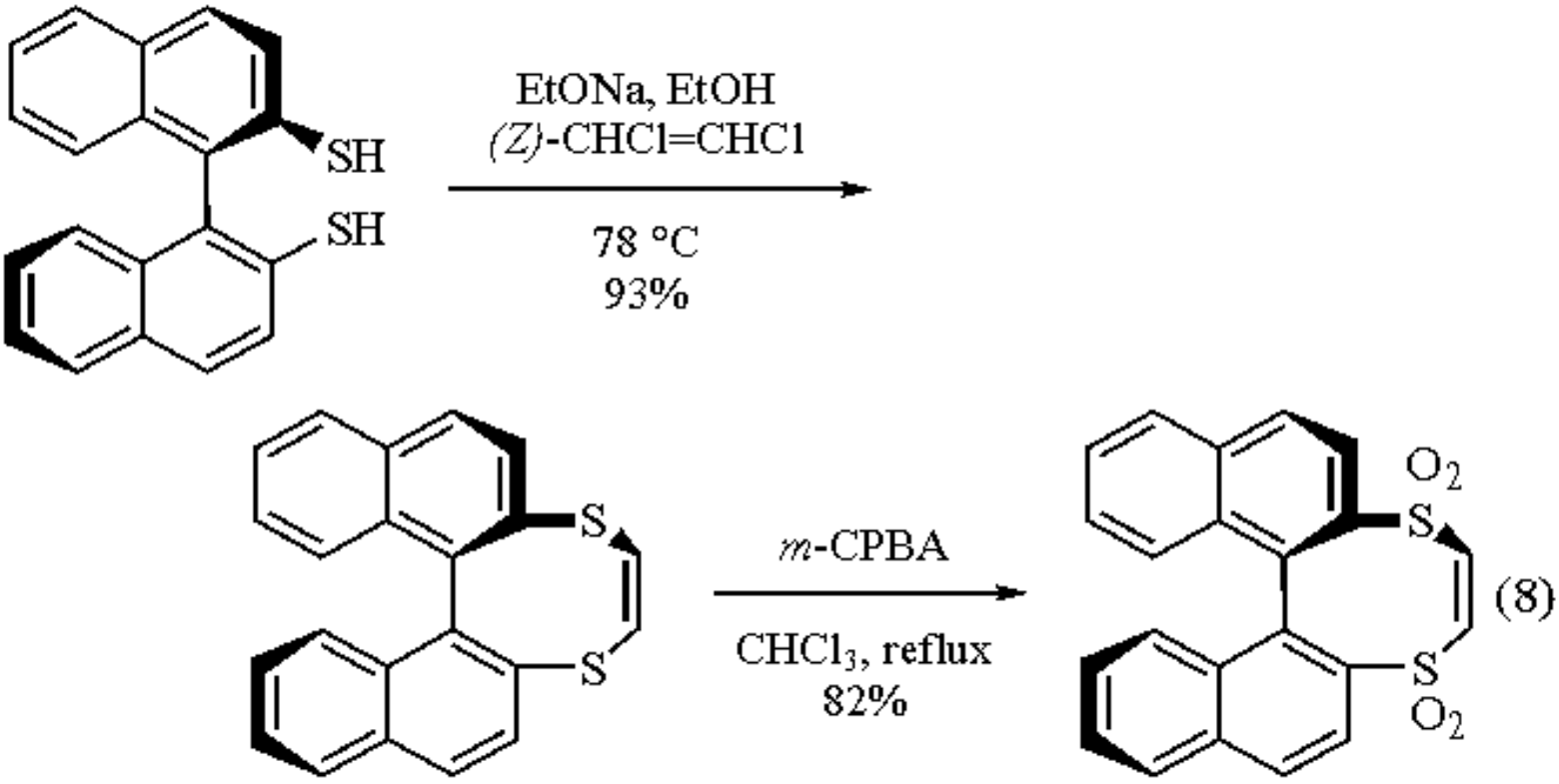

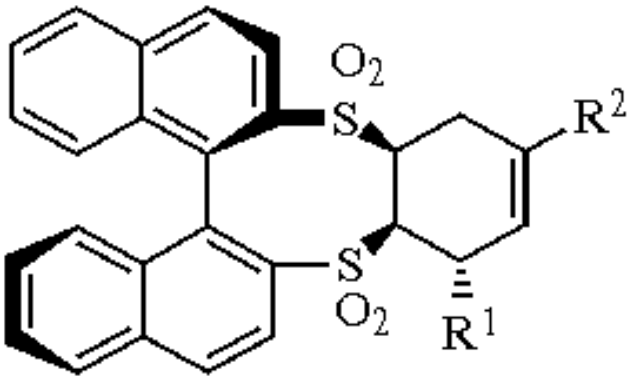

(1)

$R^1 = OMe, R^2 = OTMS$
$R^1 = OMe, R^2 = H$
$R^1 = OTMS, R^2 = H$
$R^1 = Me, R^2 = H$
$R^1 = H, R^2 = OTMS$
$R^1 = H, R^2 = Me$ (8:2 mixture)

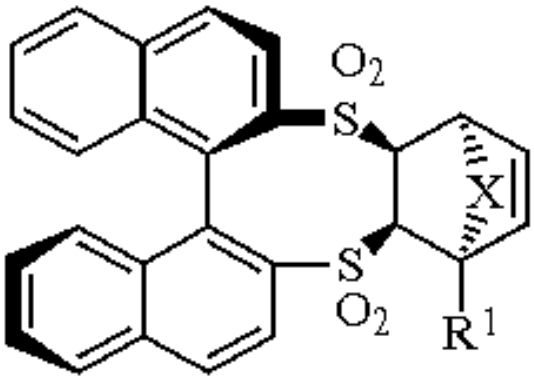

(2)

$R^1 = OMe, X = O$
$R^1 = OMe, X = -(CH_2)_2-$

The addition provides only one stereoisomer out of the four possible ones. ***Sodium Amalgam*** reduction in buffered methanol removes the binaphthyl residue to afford the hydrocarbon and recovered starting dithiol.[11]

Finally, it is notable that the title reagent has been used to prepare even larger ring systems such as chiral crown ethers,[3]

and the use of 1,1´-binaphthalene-2,2´-dithiol as ligand for rhodium(I) in the asymmetric hydroformylation of styrene has been described.[12]

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(*R*)-1,1´-Bi-2,2´-naphthol[1]

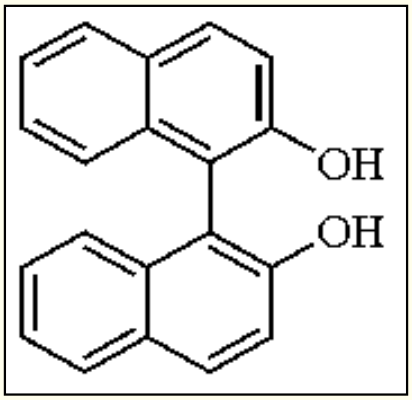

[18531-94-7] · $C_{20}H_{14}O_2$ · (*R*)-1,1´-Bi-2,2´-naphthol · (MW 286.33)

(chiral ligand and auxiliary[1])

Alternate Name: BINOL.

Physical Data: mp 208-210 °C; $[\alpha]^{21}$ +34° (*c* = 1, THF).

Solubility: sol toluene, CH_2Cl_2, $EtNO_2$.

Form Supplied in: white solid; widely available.

Preparative Methods: racemic 1,1´-bi-2,2´-naphthol (BINOL) is most conveniently prepared by the oxidative coupling reaction of 2-naphthol in the presence of transition metal complexes (eq 1).[2] The resolution of racemic BINOL with cinchonine may be performed via the cyclic phosphate (eq 2).[3] An alternative procedure to provide directly optically active BINOL is the oxidative coupling of 2-naphthol catalyzed by Cu^{II} salt in the presence of chiral amines (eq 3).[4] The best procedure uses (+)-amphetamine as the chiral ligand and provides BINOL in 98% yield and 96% ee. Above 25 °C the Cu^{II}/(+)-amphetamine/(*S*)-BINOL complex precipitates while the more soluble Cu^{II}/(+)-amphetamine/(*R*)-BINOL complex is slowly transformed into the former complex. 9,9´-Biphenanthrene-10,10´-diol has also been prepared in 86% yield and with 98% ee by a similar asymmetric oxidative coupling of 9-phenanthrol in the presence of (*R*)-1,2-diphenylethylamine.[5]

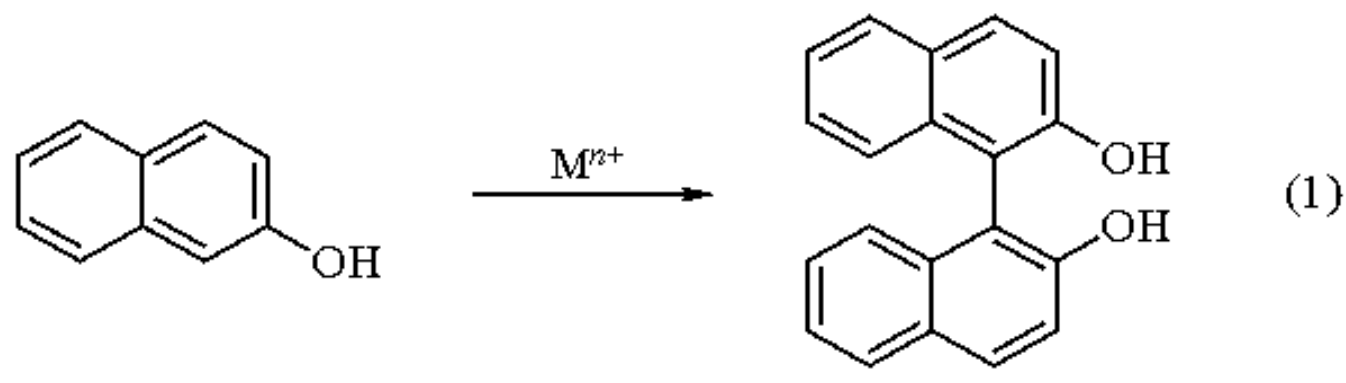
OH
M^{n+}
OH
OH

(1)

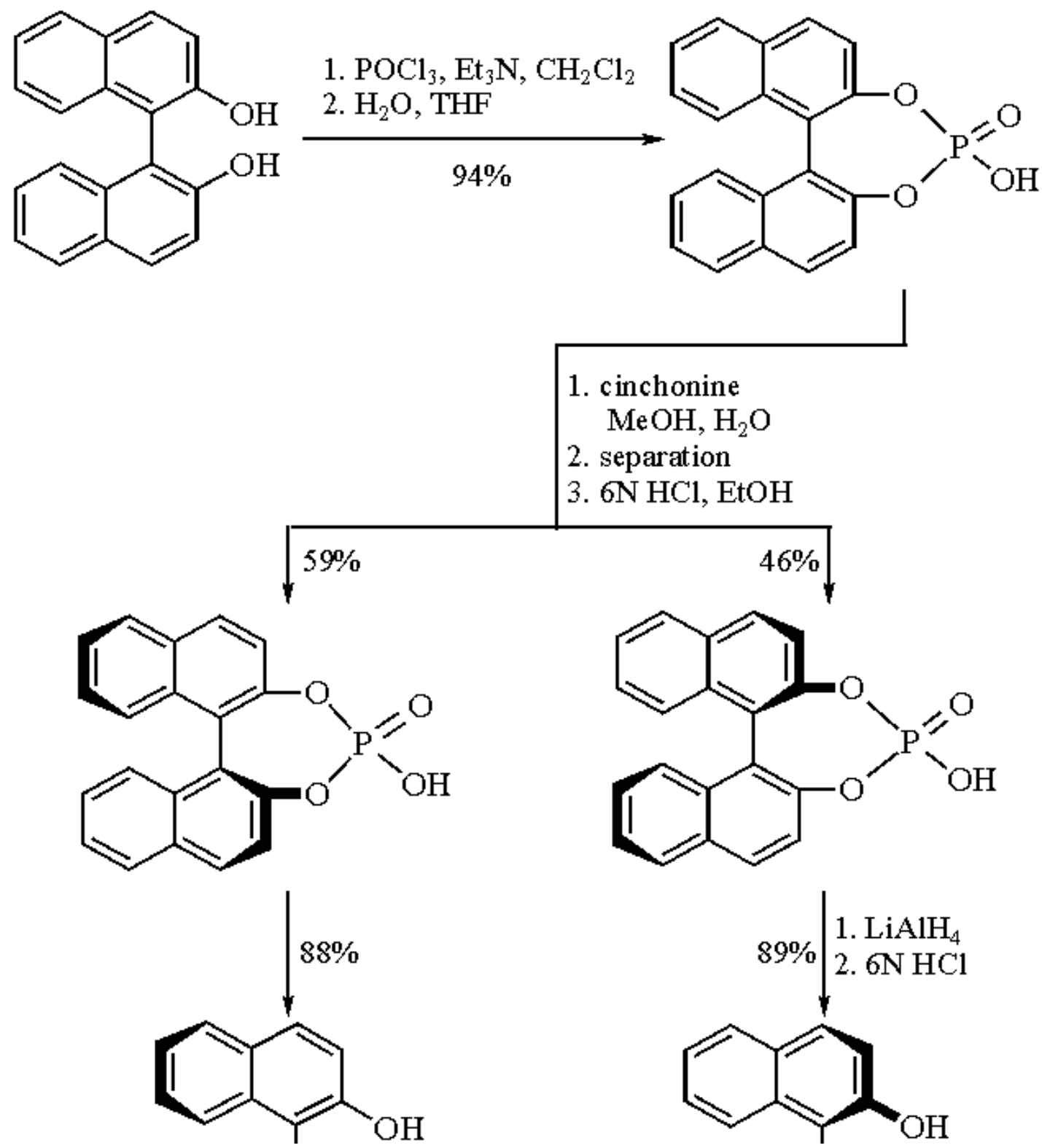
OH
OH
1. $POCl_3$, Et_3N, CH_2Cl_2
2. H_2O, THF
94%
O
O
P
O
OH
1. cinchonine
MeOH, H_2O
2. separation
3. 6N HCl, EtOH
59%
46%
88%
89%
1. $LiAlH_4$
2. 6N HCl
OH
OH

(R)-1,1´-Bi-2,2´-naphthol

(2)

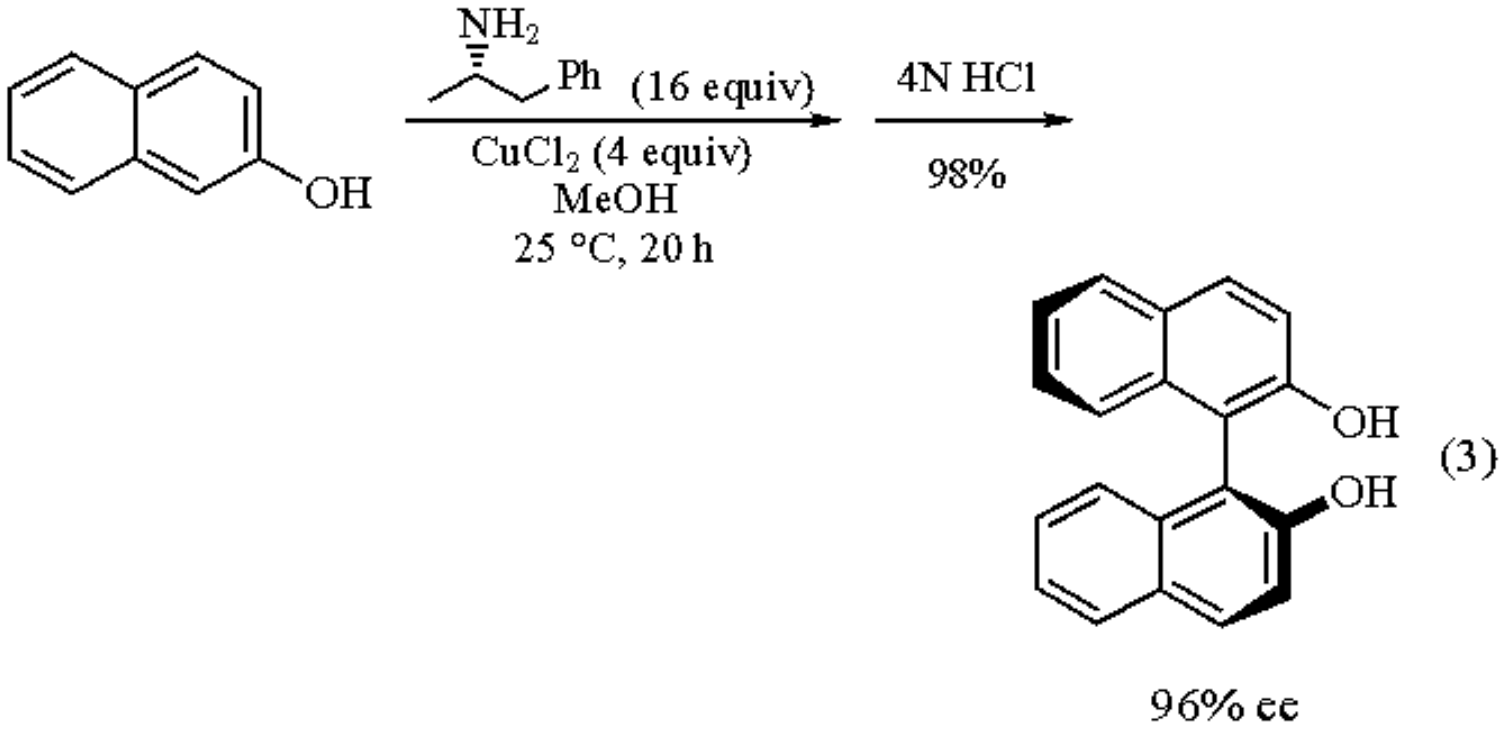

(3)

Handling, Storage, and Precautions: keep tightly closed, store in a cool dark place; on heating in butanol at 118 °C for 24 h, BINOL lost ~1% of its optical rotation; at 100 °C for 24 h in dioxane-1.2 N HCl, BINOL lost 56% of its rotation; after 24 h at 118 °C in butanol-0.7 N KOH, BINOL lost 20% of its rotation.

Hydrocarboxylation.

The cyclic phosphate resolved according to eq 2 can be used as the chiral ligand in the palladium(II) catalyzed asymmetric hydrocarboxylation of arylethylenes.[6] The 1-arylpropanoic acid is obtained regiospecifically with high enantioselectivity (91% ee) (eq 4).

(R)-1,1´-Bi-2,2´-naphthol

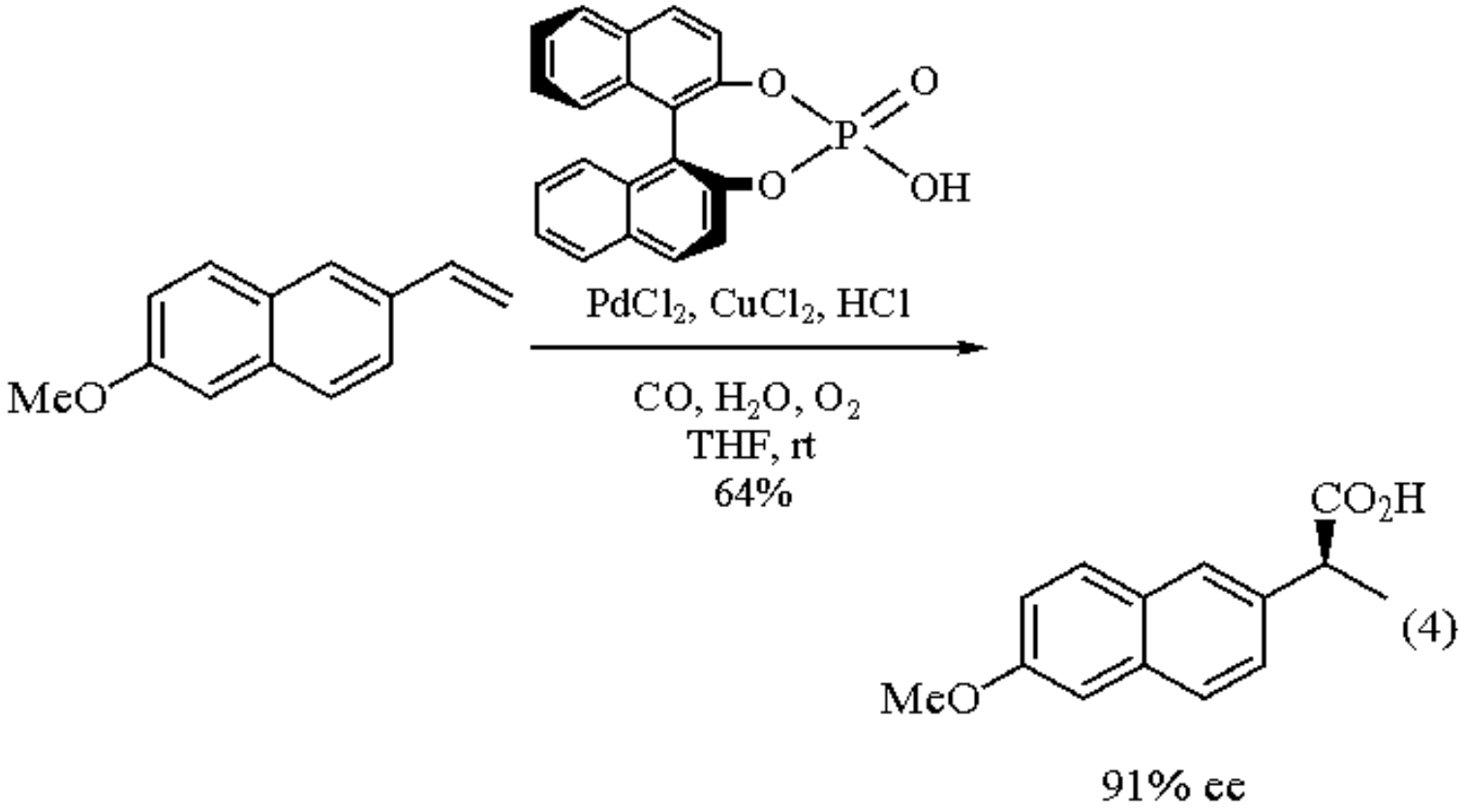

Crown Ethers.

BINOL-derived crown ethers have been reported.[7] Crown ethers containing 3,3´-disubstituted BINOL derivatives are particularly effective for asymmetric synthesis. Thus complexes of these crown ethers (e.g. ***18-Crown-6***) with ***Potassium Amide*** or ***Potassium t-Butoxide*** catalyze asymmetric Michael additions. The reaction of methyl 1-oxo-2-indancarboxylate with methyl vinyl ketone with the 3,3´-dimethyl-BINOL-crown ether/KO-*t*-Bu complex gives the Michael product in 48% yield and with 99% ee (eq 5).[8]

(R)-1,1´-Bi-2,2´-naphthol

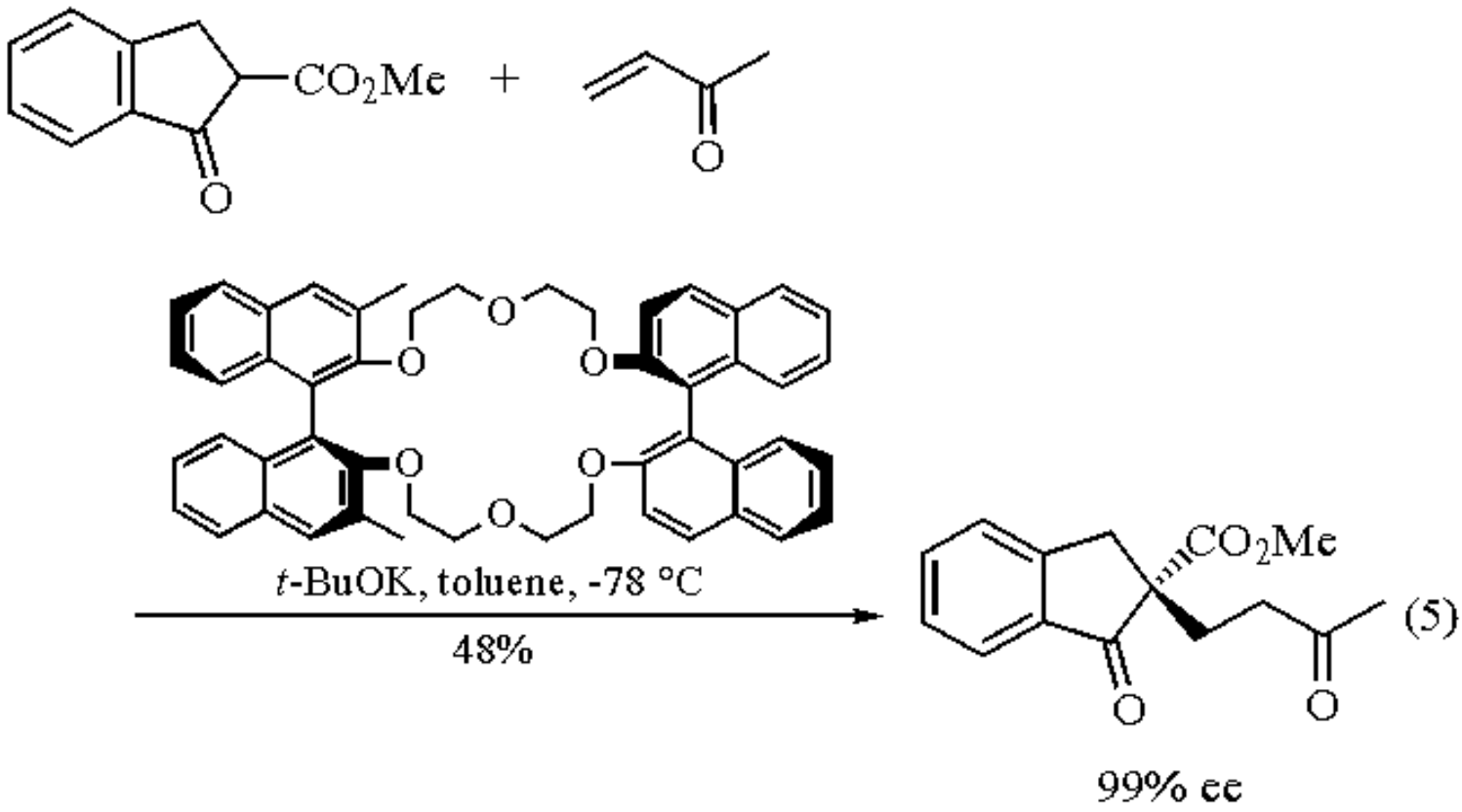

Polymerization.

Complexes of BINOL-derived crown ethers with KO-*t*-Bu or BuLi have been used as initiators in the asymmetric polymerization of methacrylates.[9] Thus optically active polymers are obtained with 80-90% isotacticity. Complexes of BINOL with ***Diethylzinc*** or $CdMe_2$ also initiate the asymmetric polymerization of heterocyclic monomers.[10] The chiral initiators selectively polymerize one enantiomer to give an optically active polymer. The unreacted monomer is recovered with 92% ee at 67% conversion in the polymerization of methylthiirane with (*S*)-BINOL/Et_2Zn.

Ullmann Coupling Reaction.

Axially dissymmetric biaryls have been synthesized via an intramolecular Ullmann coupling reaction of BINOL-derived aryl diesters (eq 6).[11] In the example shown, the functionalized binaphthyl is obtained with high ee after hydrolysis of the intermediate 12-membered cyclic diester.

(R)-1,1´-Bi-2,2´-naphthol

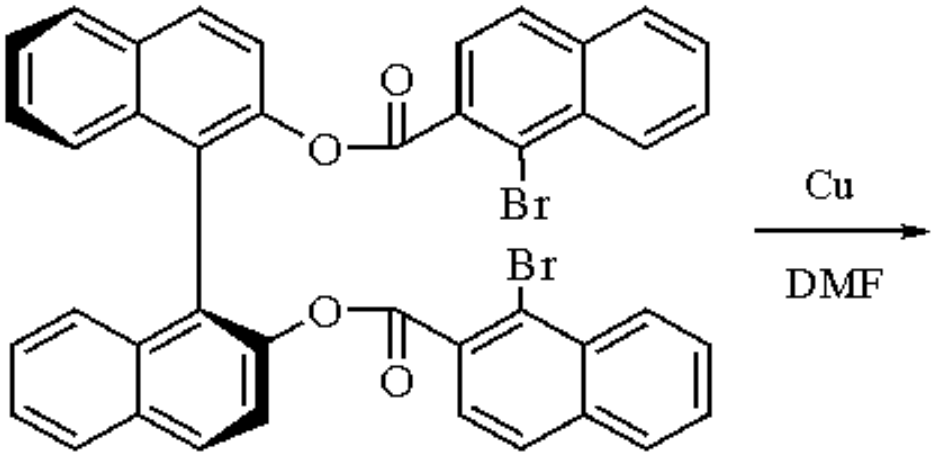

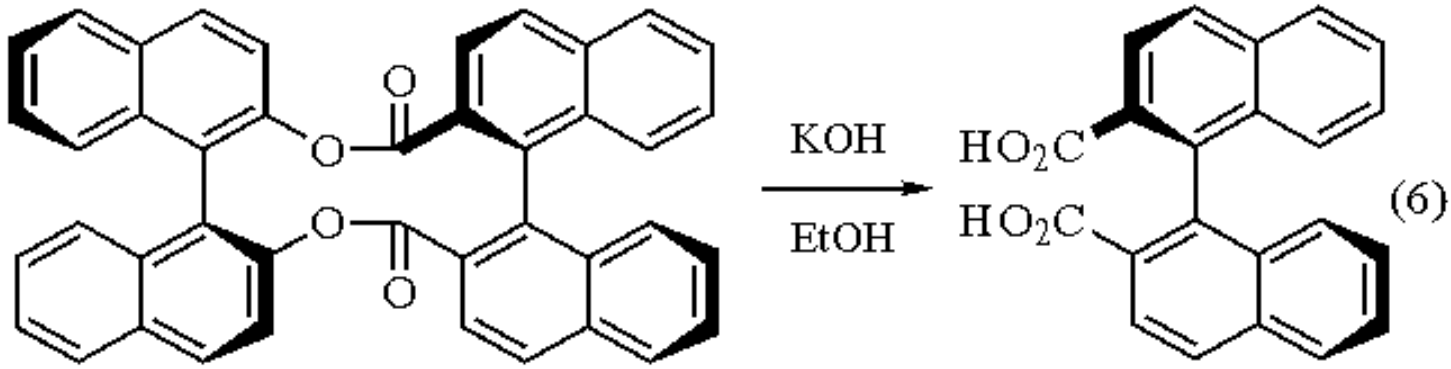

100% de

Reduction of Prochiral Ketones.

BINOL has been used as the chiral ligand of the reagent BINAL-H (see ***Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl***) for asymmetric reduction.[12] The reagent reduces prochiral unsaturated ketones to the corresponding secondary alcohols in up to 90% yield and >90% ee (eq 7); (*R*)-BINAL-H leads to the (*R*)-alcohols while (*S*)-BINAL-H gives the (*S*)-alcohols.

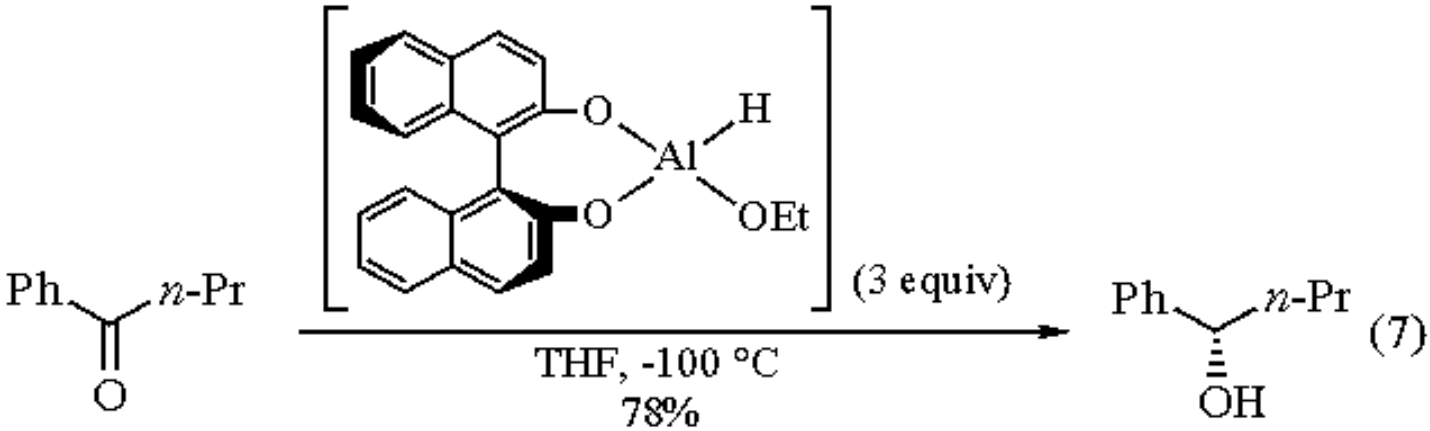

~100% ee

(R)-1,1´-Bi-2,2´-naphthol

Addition Reactions of Chiral Titanium Reagents to Aldehydes.

The preparation and use of the BINOL-derived titanium complexes in the enantioselective synthesis of some benzhydrols (>90% ee) have been reported (eq 8).[13]

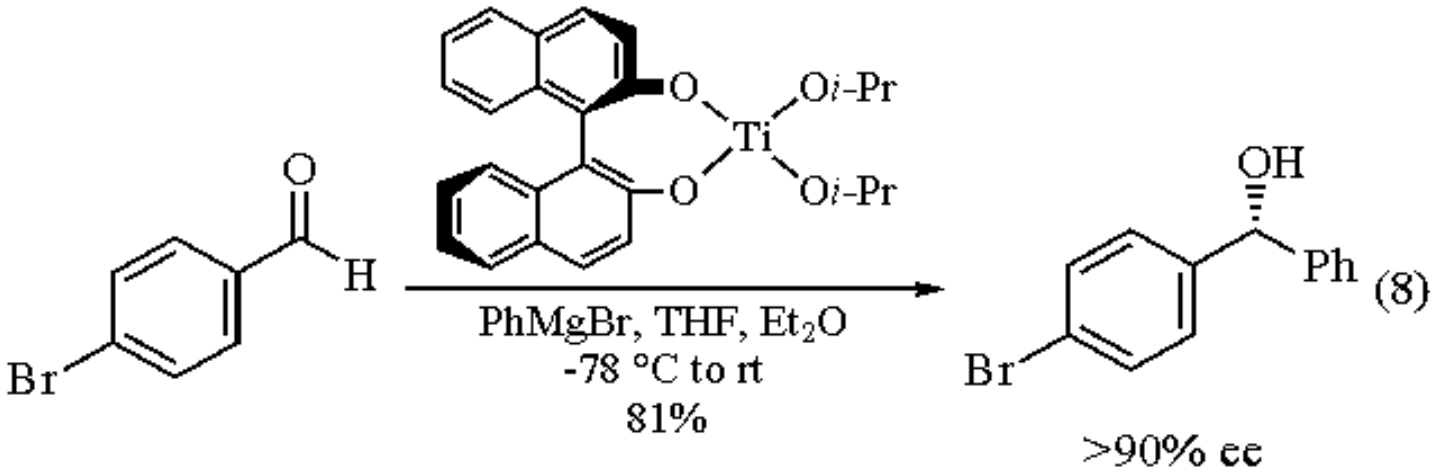

(8)

Cyanosilylation.

The chiral titanium reagent, prepared from the lithium salt of BINOL with $TiCl_4$, has been used as a catalyst for the asymmetric addition of cyanotrimethylsilane to aldehydes.[14] In the example shown, the cyanohydrin is obtained with <=82% ee (eq 9).

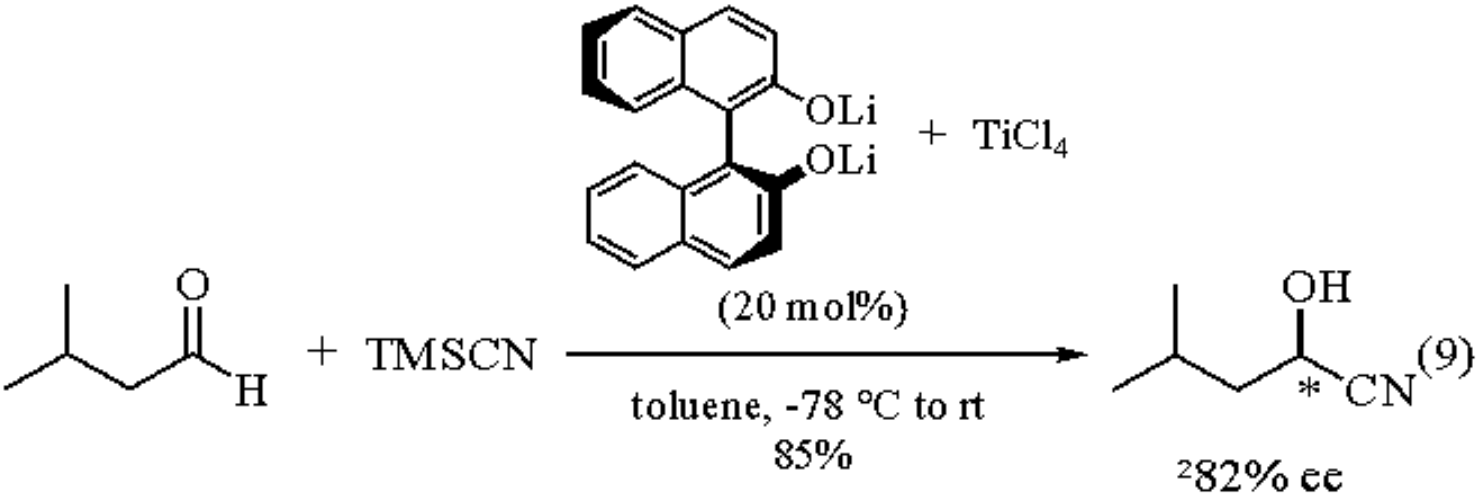

(9)

Diels-Alder Reactions.

BINOL and its derivatives are used as the chiral ligand of chiral Lewis acid complexes for enantioselective Diels-Alder cycloadditions. BINOL-$TiCl_2$, prepared from the lithium salt of BINOL with ***Titanium(IV) Chloride***, also catalyzes the enantioselective Diels-Alder reaction of cyclopentadiene with methacrolein (eq 10)[14,15] The *exo* adduct is obtained as the major product (56% yield), but with low enantioselectivity (16% ee). More recently, BINOL-TiX_2 (X = Br or Cl) have been

(R)-1,1´-Bi-2,2´-naphthol

prepared in situ from diisopropoxytitanium dihalides ($(i\text{-PrO})_2TiX_2$, X = Br[16] or Cl[17]) with BINOL in the presence of molecular sieves (MS 4A).[16] The Diels-Alder reaction of methacrolein with 1,3-dienol derivatives can be catalyzed by BINOL-TiX_2. The *endo* adducts are obtained in high enantioselectivity (eq 11).[18] Asymmetric catalytic Diels-Alder reaction of naphthoquinone derivatives as the dienophile (eq 12)[18] can in principle provide an efficient entry to the asymmetric synthesis of anthracyclinone aglycones. The reaction of the 5-hydroxynaphthoquinone with 1-acetoxy-1,3-diene in the presence of MS-free BINOL-$TiCl_2$ (10 mol%) provides the corresponding Diels-Alder product in high chemical yield and with high enantioselectivity (76-96% ee).[18b] The Diels-Alder product is also obtained by the use of 1 equiv of 3,3´-diphenyl-BINOL/borane complex (eq 13); the structure of the intermediate has been proposed.[19]

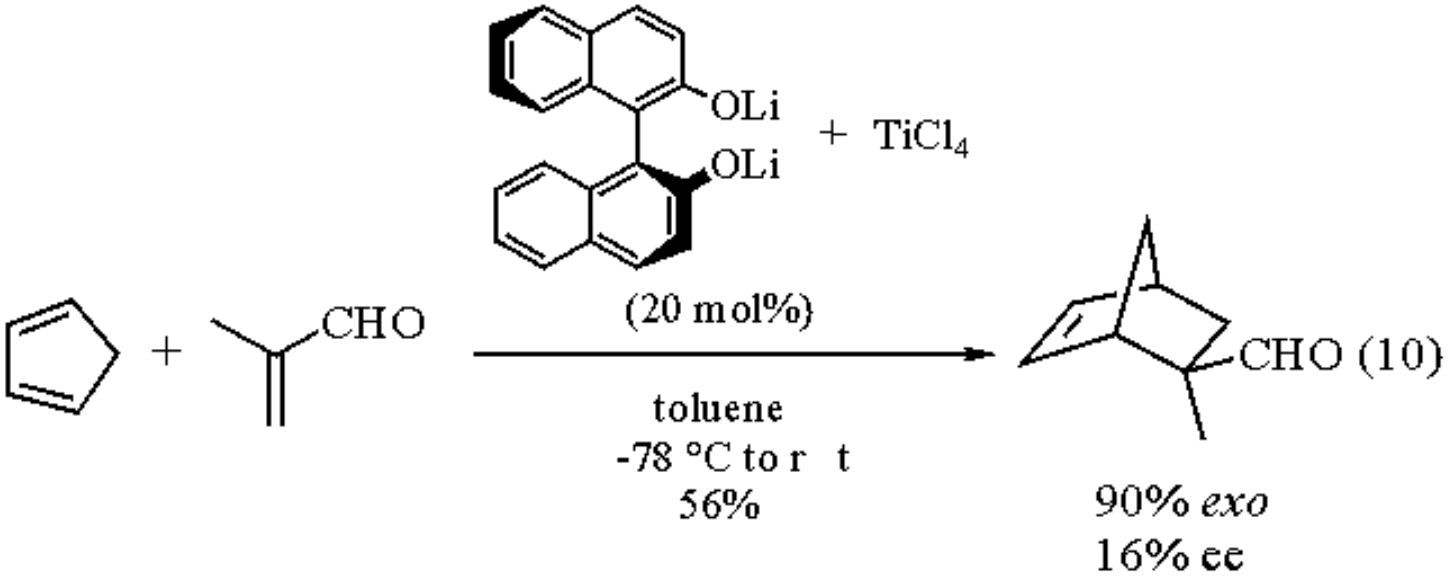

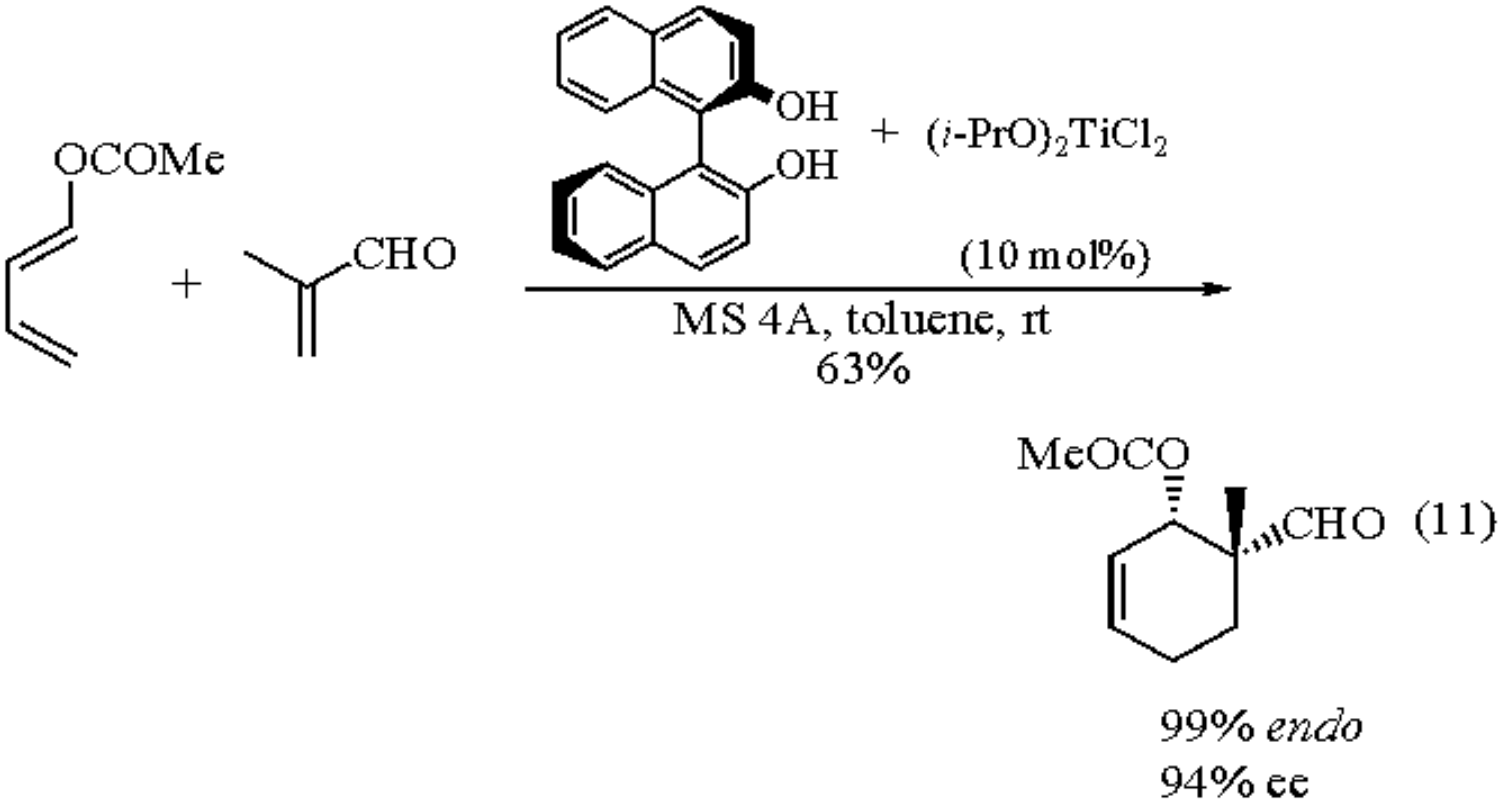

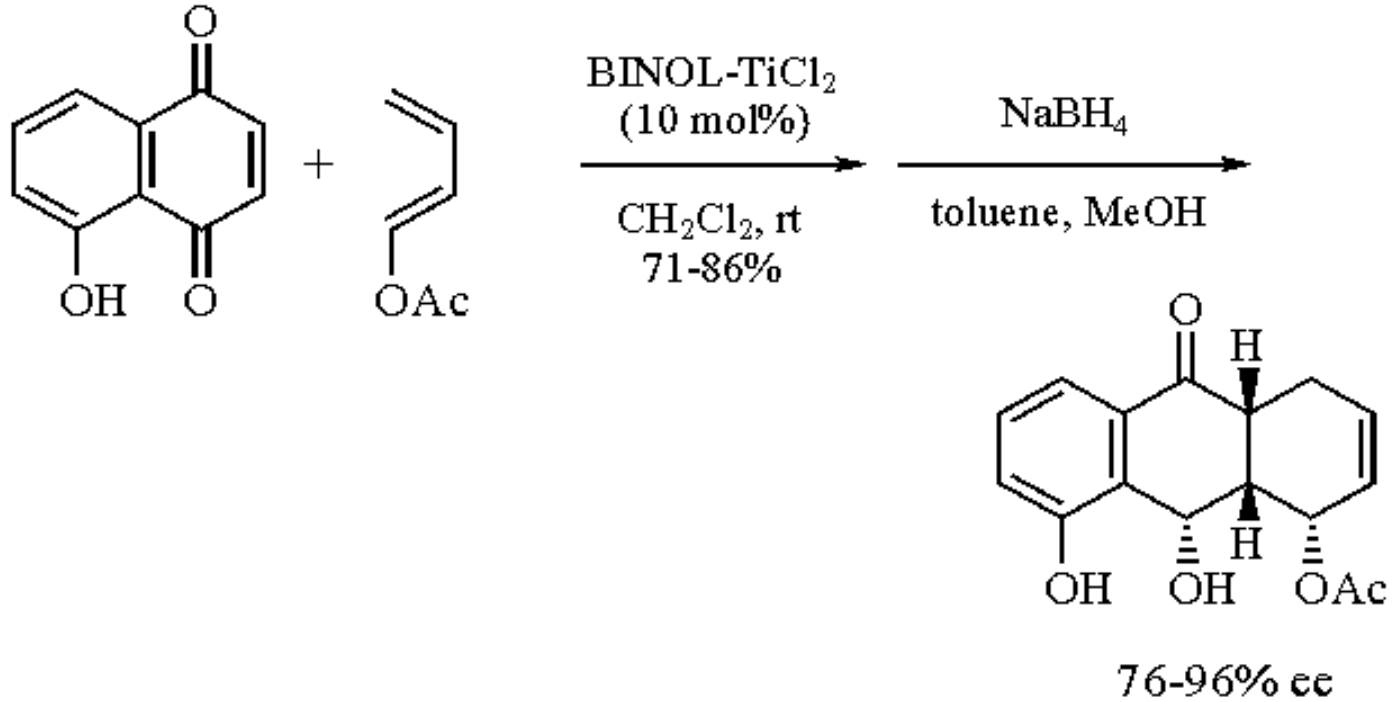
BINOL-TiCl2
(10 mol%)
CH2Cl2, rt
71-86%
NaBH4
toluene, MeOH
76-96% ee

(12)

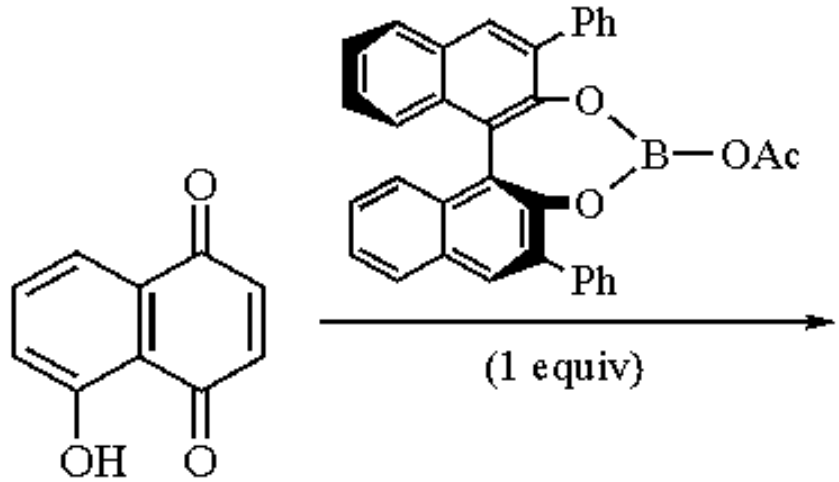
(1 equiv)

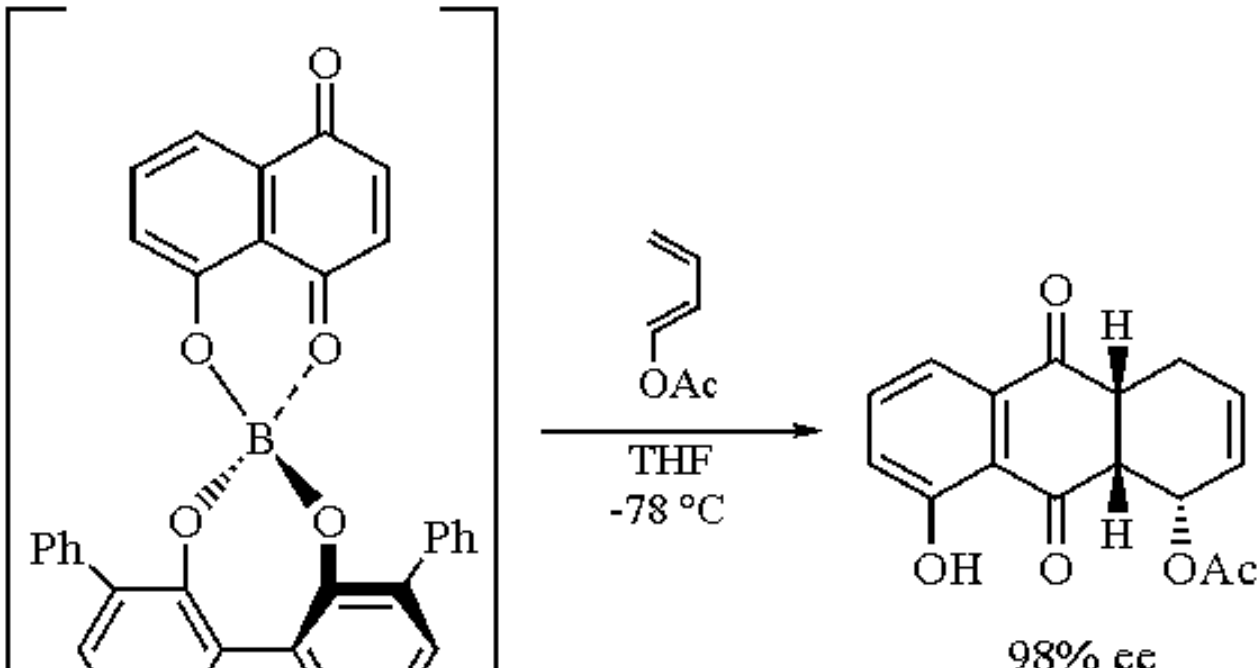
THF
-78 °C
98% ee

(13)

(R)-1,1´-Bi-2,2´-naphthol

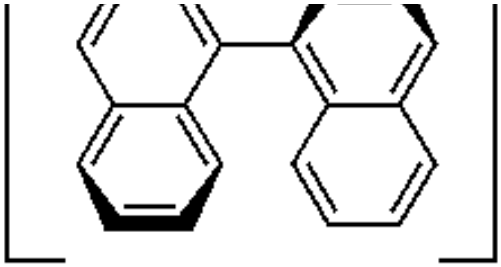

98% ee

3,3´-Diphenyl-BINOL-derived chiral aluminum reagents are prepared in situ by addition of ***Ethylaluminum Dichloride*** or ***Diethylaluminum Chloride*** to 3,3´-diphenyl-BINOL. These chiral aluminum reagents promote the enantioselective Diels-Alder reaction of cyclopentadiene with the oxazolidone dienophile (eq 14).[20] *Endo* products are obtained with a high level of asymmetric induction (>90% ee); however, a stoichiometric amount of the Lewis acid is required. The preparation and use of a C_3 symmetric BINOL-derived boronate has been reported (eq 15).[21] BINOL-B$(OAr)_3$ complexes have recently been developed for the asymmetric Diels-Alder reaction with imines (eq 16).[22]

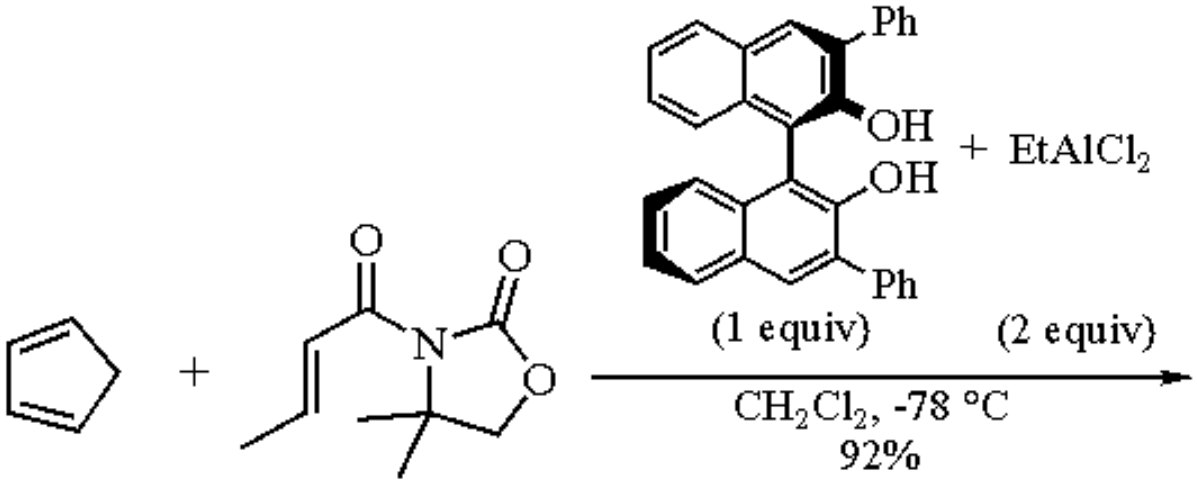

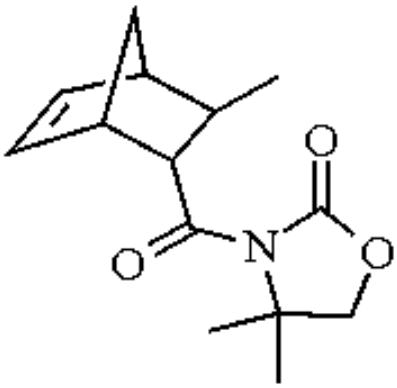

(14)

76% *endo*
95% ee

(R)-1,1´-Bi-2,2´-naphthol

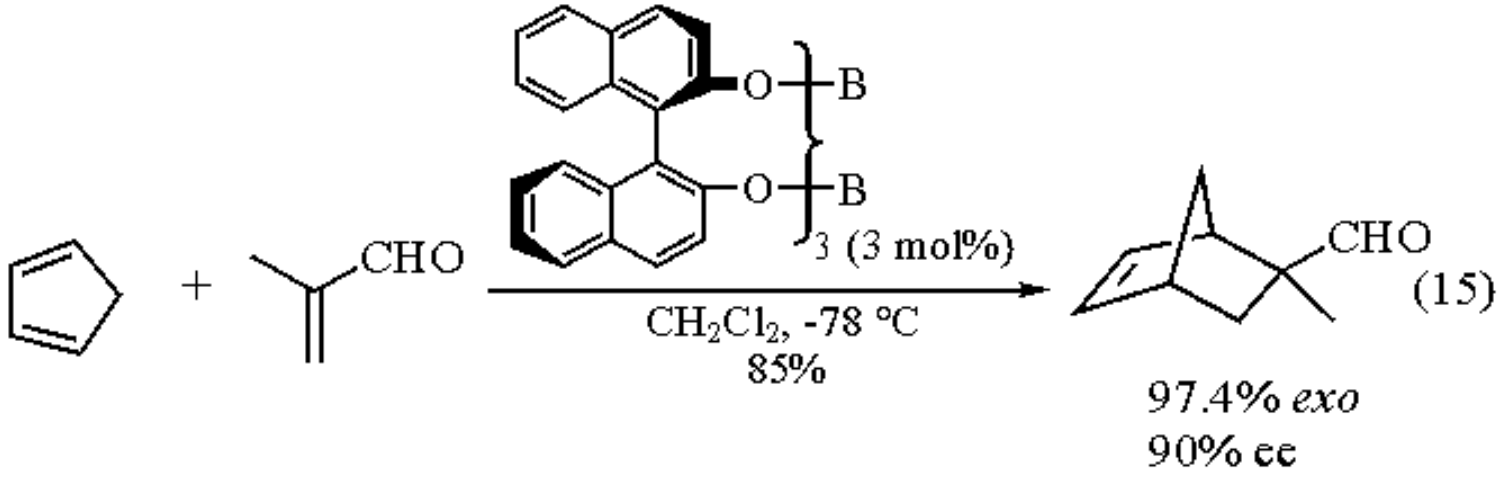

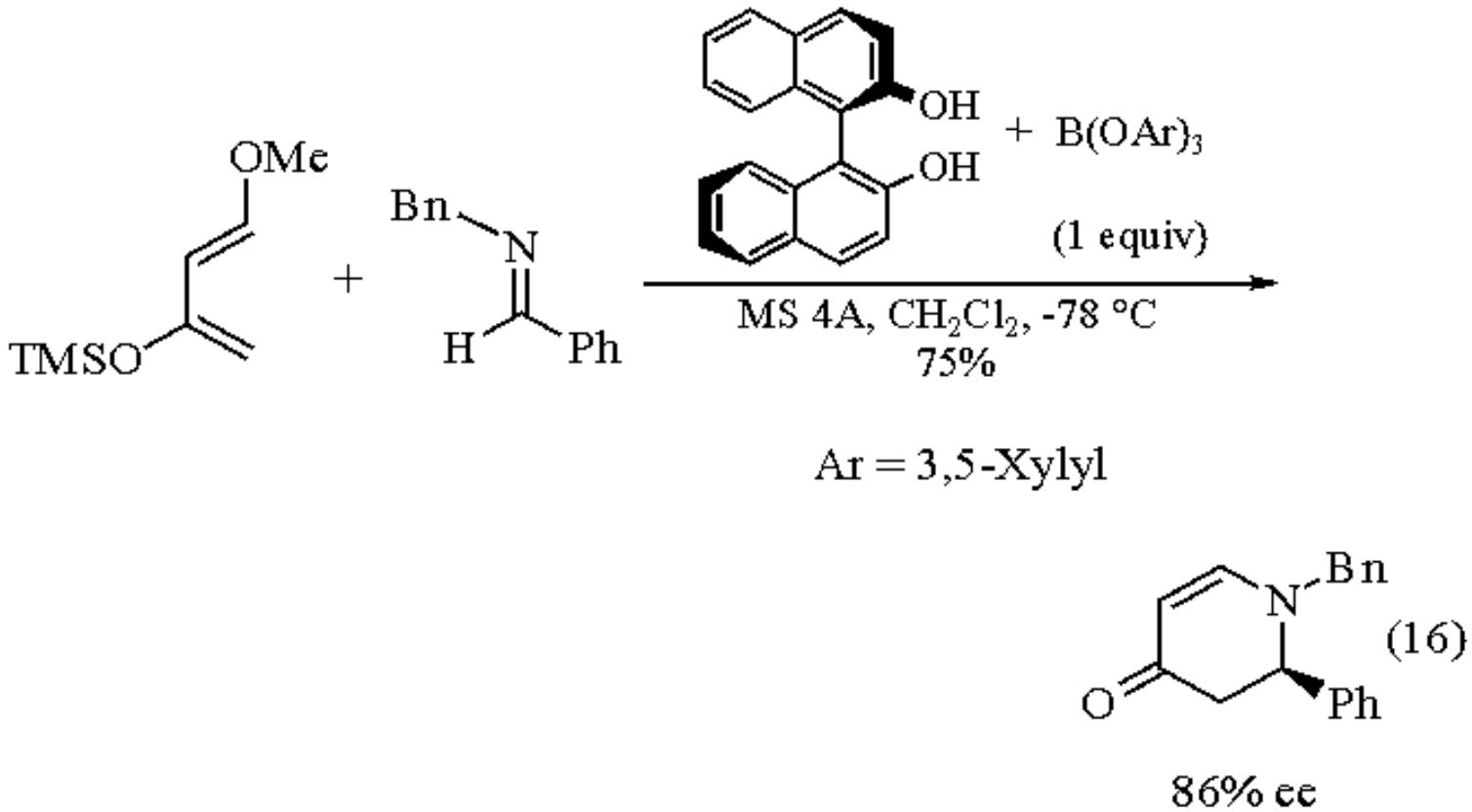

Hetero Diels-Alder Reaction.

Modified BINOL-derived organoaluminum reagents have been used in the asymmetric hetero Diels-Alder reaction of aldehydes (eq 17). The dihydropyrones are obtained with high *cis* diastereoselectivity and enantioselectivity.[23] The hetero Diels-Alder reaction of glyoxylates proceeds smoothly with methoxydienes using BINOL-$TiCl_2$ as a catalyst to give the *cis* product in high enantiomeric excess (eq 18).[18b,24] The hetero Diels-Alder product thus obtained can be readily converted to the lactone portion of HMG-CoA inhibitors such as mevinolin or compactin.

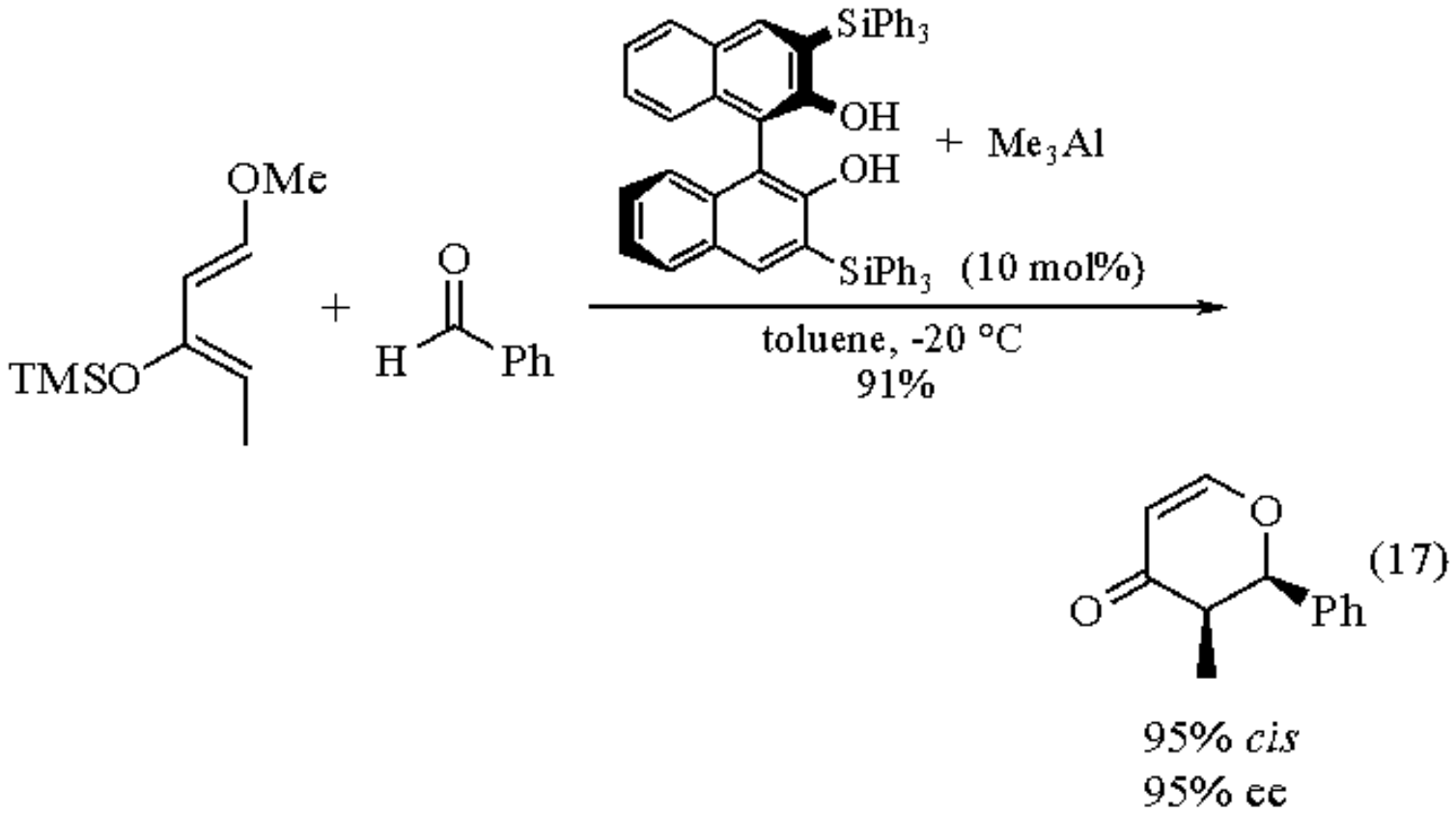

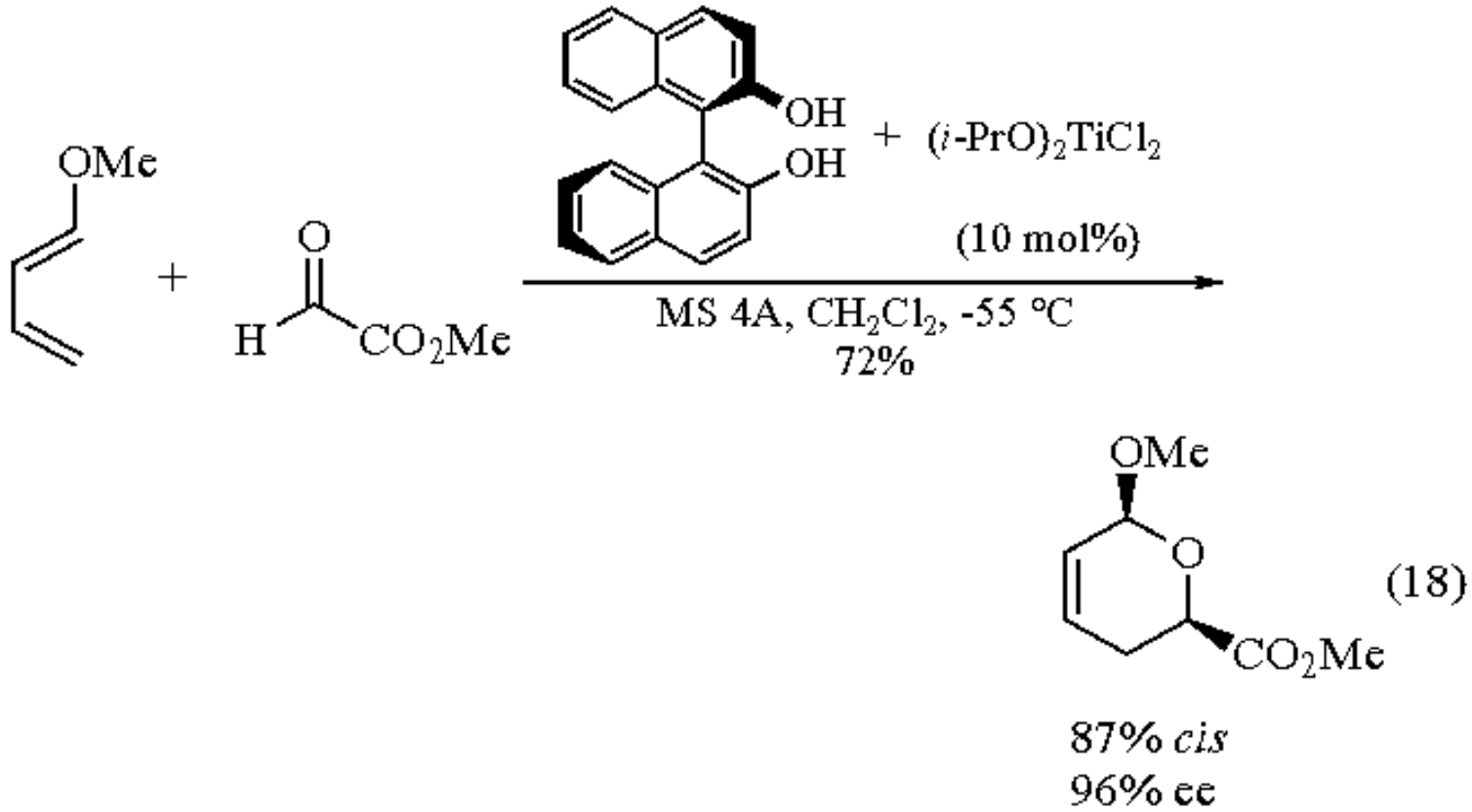

Carbonyl-Ene Reaction.

BINOL-TiX_2 reagent exhibits a remarkable level of asymmetric catalysis in the carbonyl-ene reaction of prochiral

(R)-1,1´-Bi-2,2´-naphthol

glyoxylates, thereby providing practical access to α-hydroxy esters.[16,25] These reactions exhibit a remarkable positive nonlinear effect (asymmetric amplification) that is of practical and mechanistic importance (eq 19).[26] The desymmetrization of prochiral ene substrates with planar symmetry by the enantiofacial selective carbonyl-ene reaction provides an efficient solution to remote internal asymmetric induction (eq 20).[27] The kinetic resolution of a racemic allylic ether by the glyoxylate-ene reaction also provides efficient access to remote but relative asymmetric induction (eq 21).[27] Both the dibromide and dichloride catalysts provide the (2*R*,5*S*)-*syn* product with 97% diastereoselectivity and &egt;95% ee.

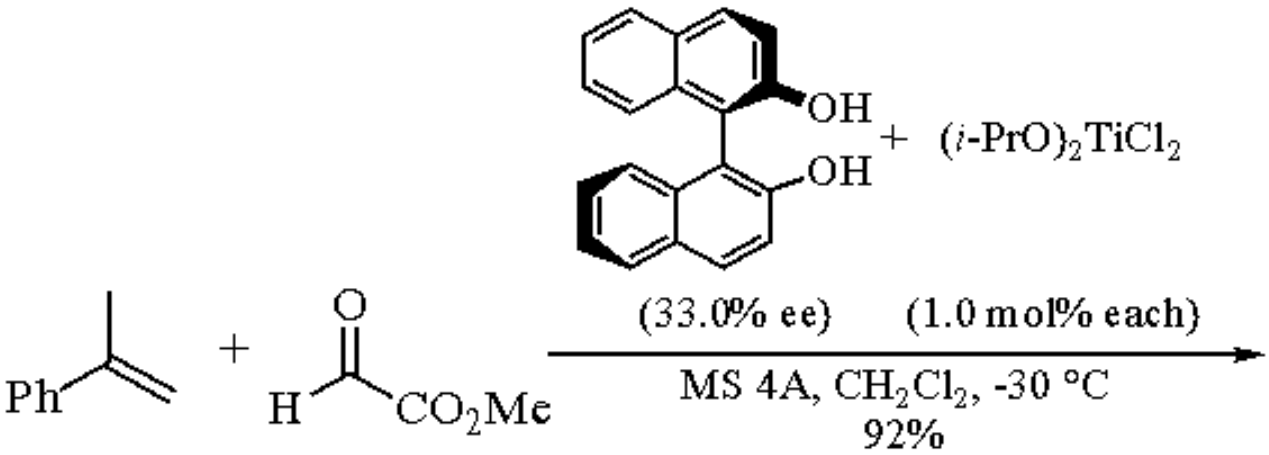

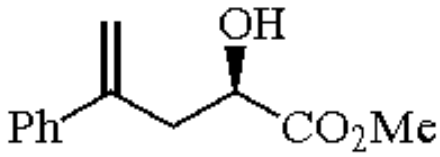

(19)

91.4% ee

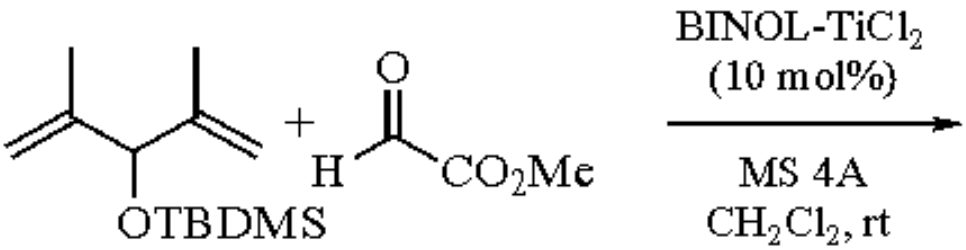

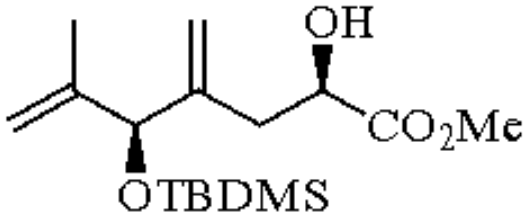

(20)

>99% *syn*
97% ee

(R)-1,1´-Bi-2,2´-naphthol

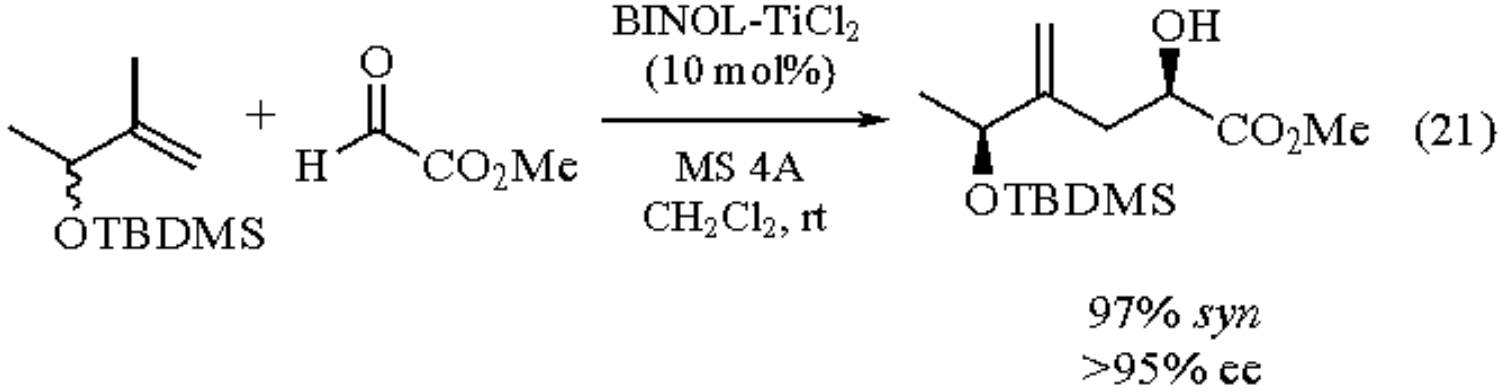

Ene Cyclization.

An intramolecular (3,4)-ene reaction of unsaturated aldehydes has been accomplished with the BINOL-derived zinc reagent.[28] Cyclization of 3-methylcitronellal with at least 3 equiv of BINOL-Zn reagent afforded the *trans*-cyclohexanol in 86% yield and 88% ee (eq 22). Asymmetric ene cyclizations of type (2,4) are also catalyzed by the BINOL-derived titanium complexes ((*R*)-BINOL-TiX_2, X = ClO_4 or OTf), modified by the perchlorate or trifluoromethanesulfonate ligand. The 7-membered cyclization of type 7-(2,4) gives the oxepane in high ee (eq 23).

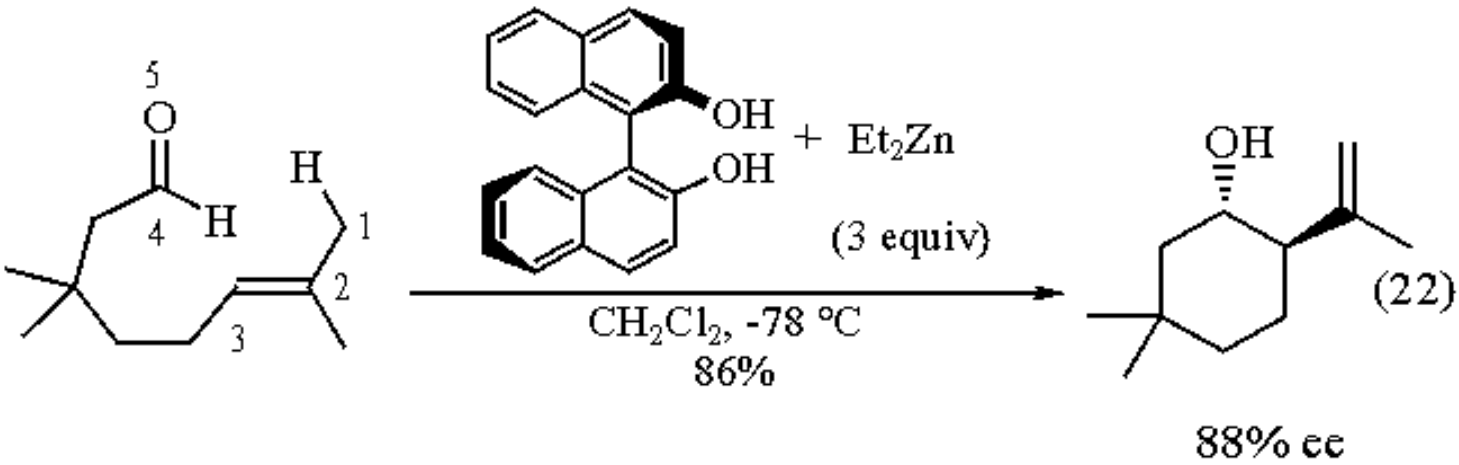

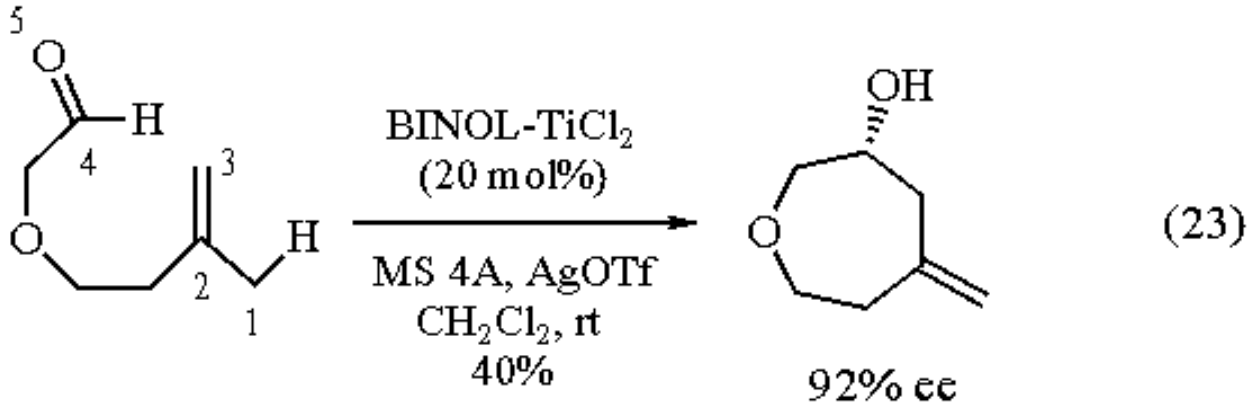

Cationic Cyclization.

A cationic cyclization of BINOL-derived neryl ether has been accomplished with an organoaluminum triflate catalyst.[29] Limonene is obtained in 54% yield and 77% ee (eq 24).

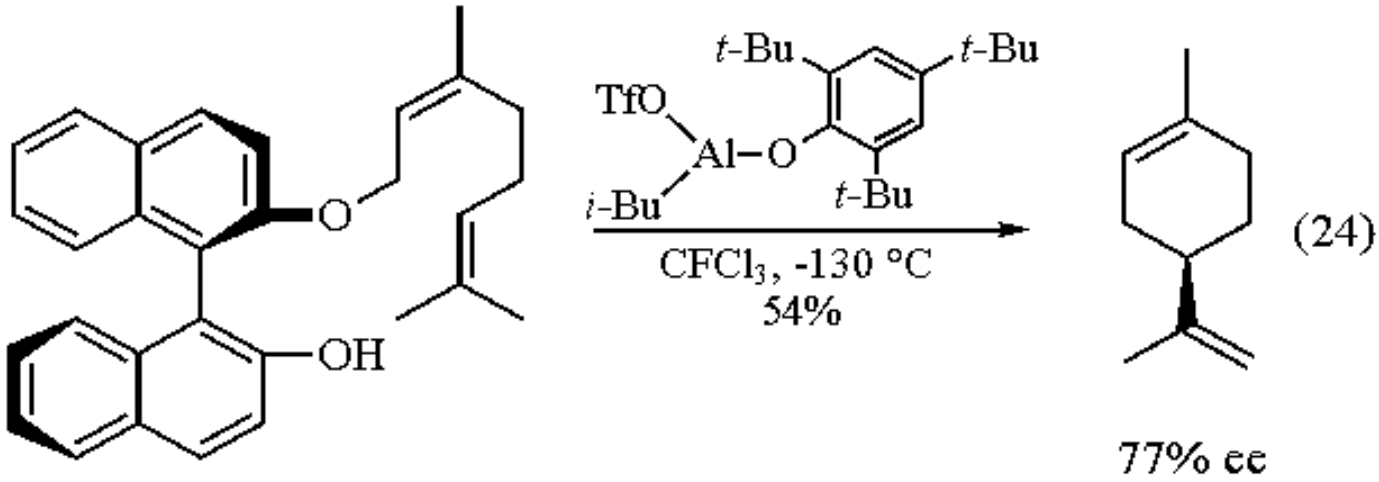

Mukaiyama Aldol Condensation.

The BINOL-derived titanium complex BINOL-$TiCl_2$ is an efficient catalyst for the Mukaiyama-type aldol reaction. Not only ketone silyl enol ether (eq 25),[30] but also ketene silyl acetals (eq 26)[31] can be used to give the aldol-type products with control of absolute and relative stereochemistry.

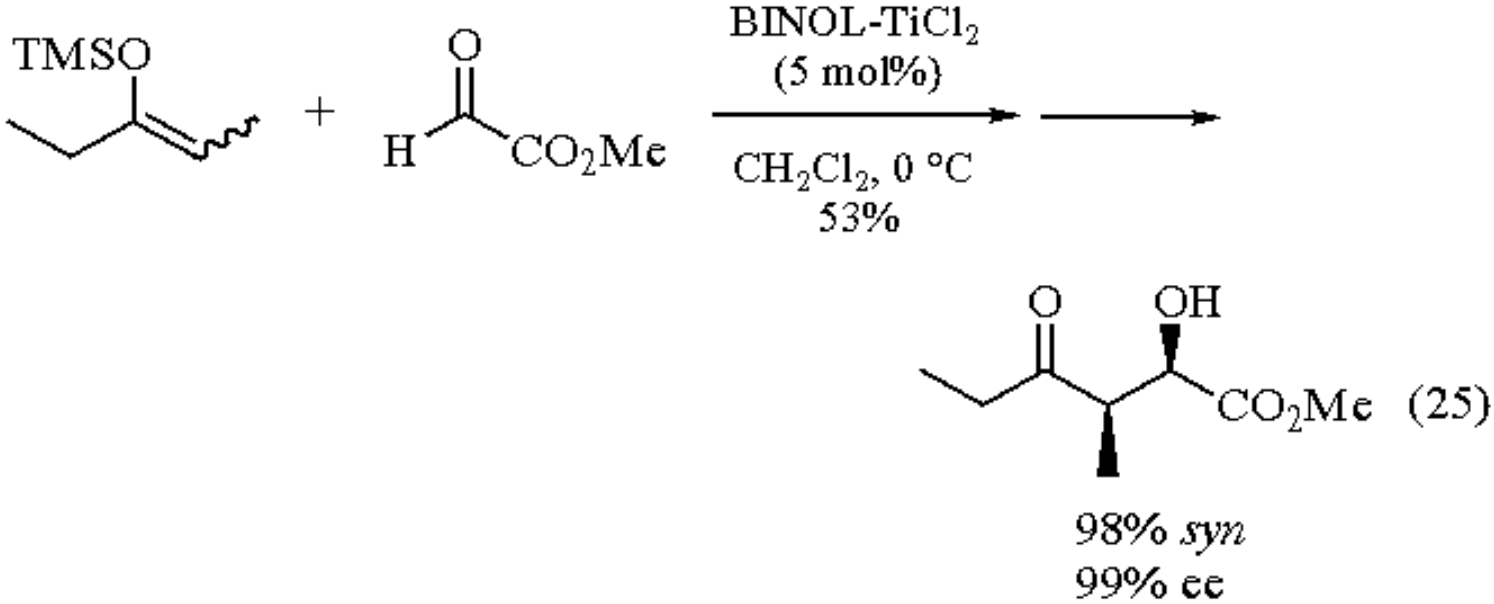

(R)-1,1´-Bi-2,2´-naphthol

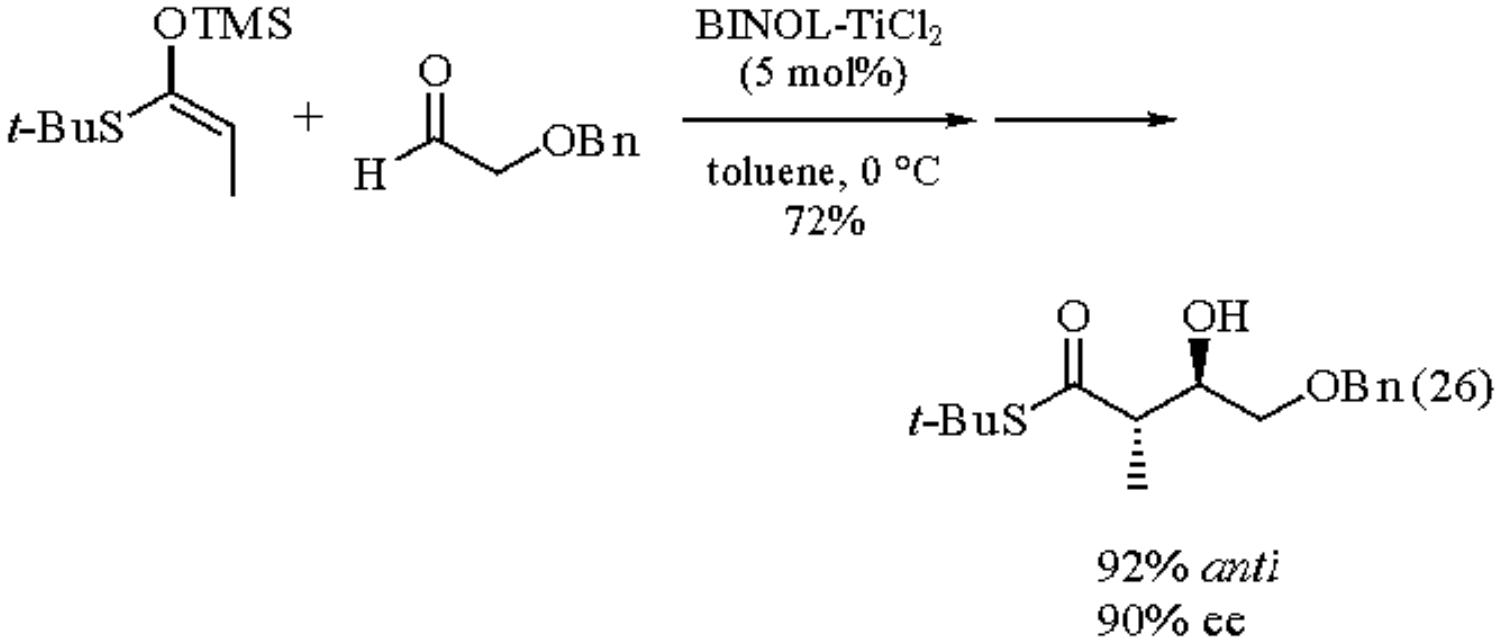

Nitro-Aldol Condensation.

A BINOL-derived lanthanide complex has been used as an efficient catalyst for the nitro-aldol reaction (eq 27).[32] Interestingly enough, the presence of water and LiCl in the reaction mixture is essential to obtain the high level of asymmetric induction and chemical yield.

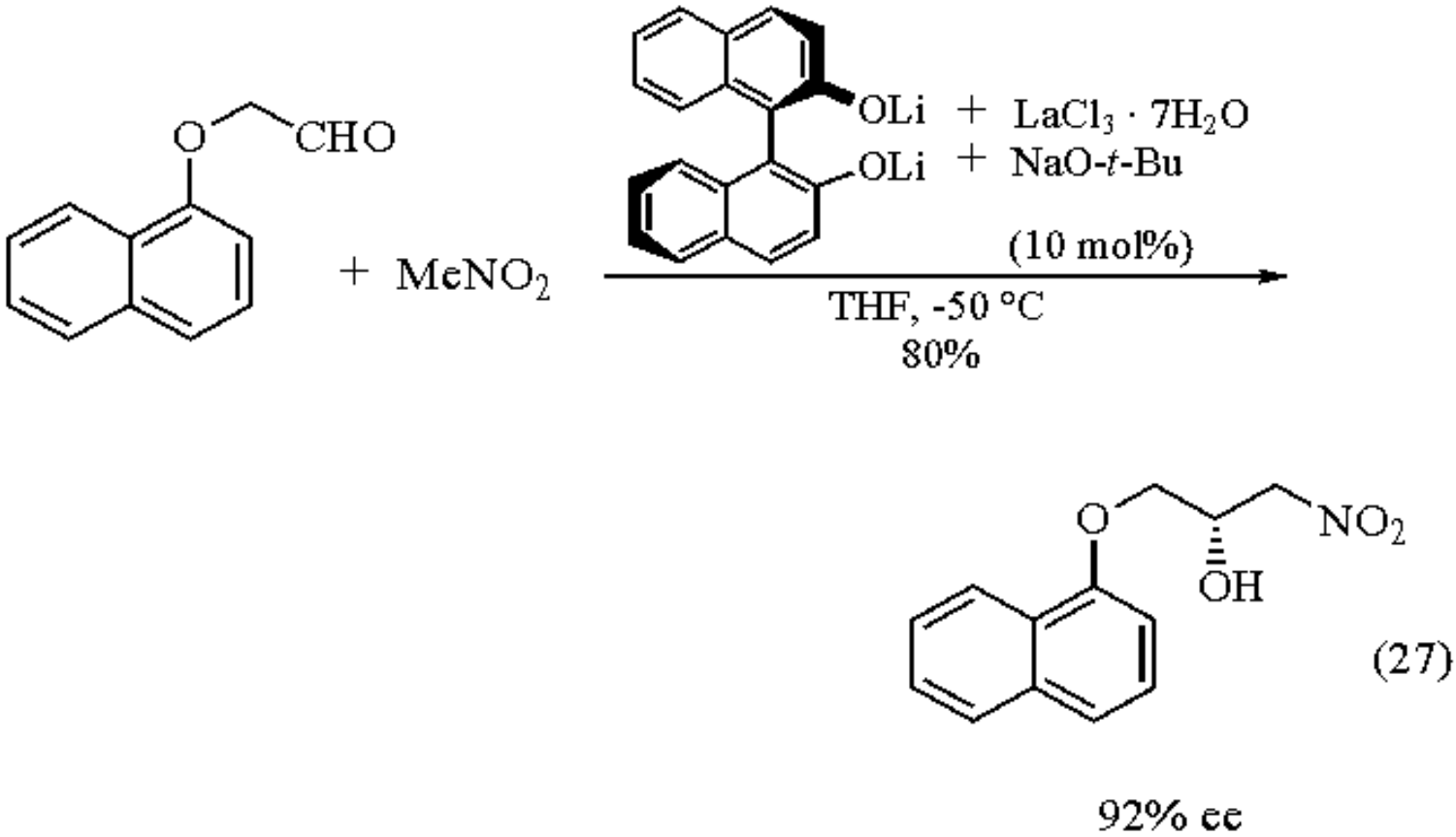

Carbonyl Addition of Allylic Silanes and Stannanes.

(R)-1,1´-Bi-2,2´-naphthol

BINOL-$TiCl_2$ reagent also catalyzes the asymmetric carbonyl addition reaction of allylic silanes and stannanes.[33] Thus the addition reaction of glyoxylate with (*E*)-2-butenylsilane and -stannane proceeds smoothly to give the *syn* product in high enantiomeric excess (eq 28). The reaction of aliphatic and aromatic aldehydes with allylstannane is also catalyzed by BINOL-$TiCl_2$ or BINOL-Ti(O-*i*-Pr)$_2$ to give remarkably high enantioselectivity.[34]

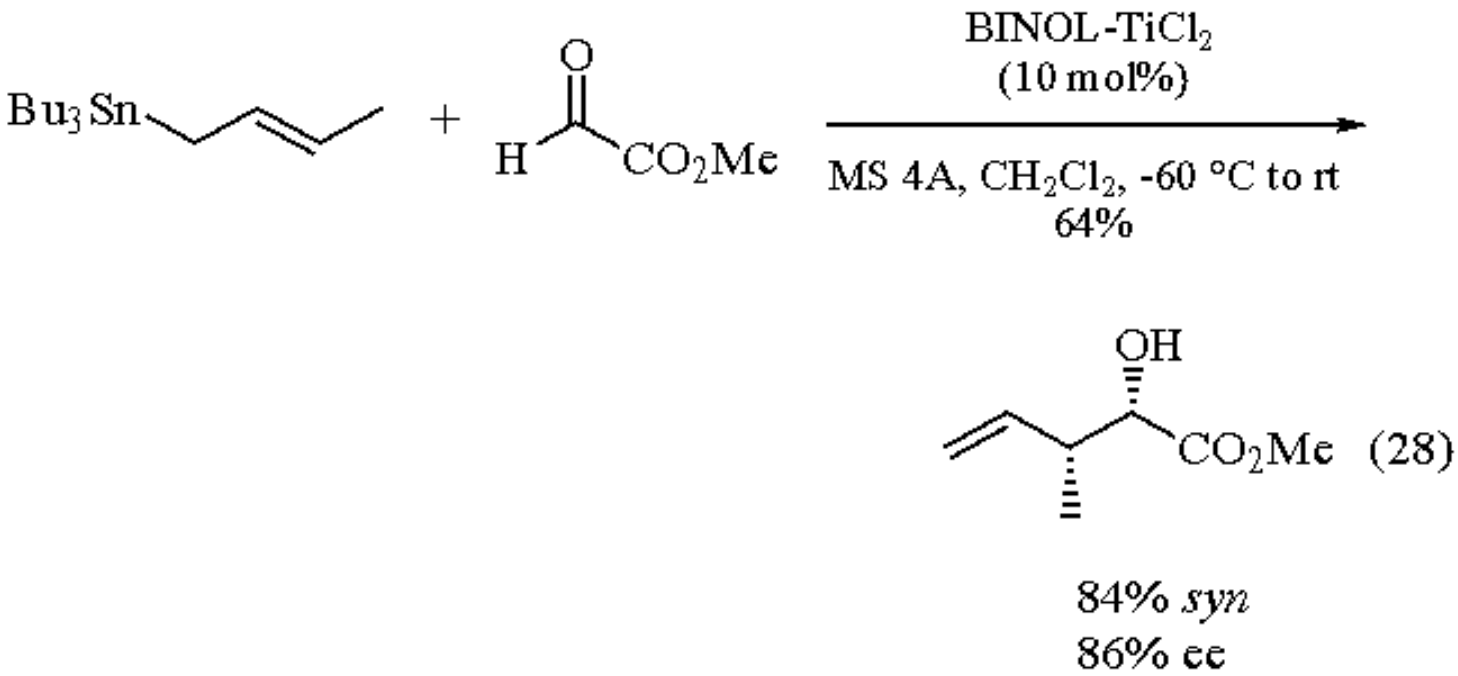

Claisen Rearrangements.

A modified BINOL-derived aluminum reagent is an effective chiral catalyst for asymmetric Claisen rearrangement of allylic vinyl ethers (eq 29).[35] The use of vinyl ethers with sterically demanding C-3 substituents is necessary for the high level of asymmetric induction.

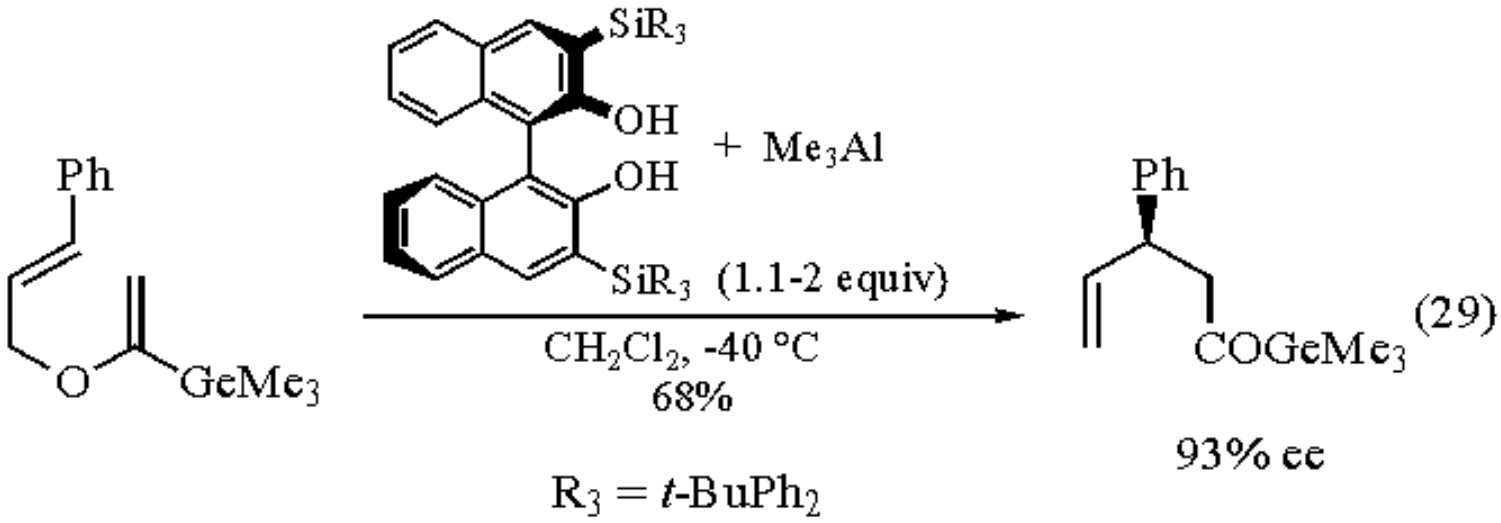

Alkylation of BINOL-Derived Ester Enolates.

The diastereoselective alkylation of BINOL-derived arylacetates affords the optically active 2-arylalkanoic acids (eq 30).[36]

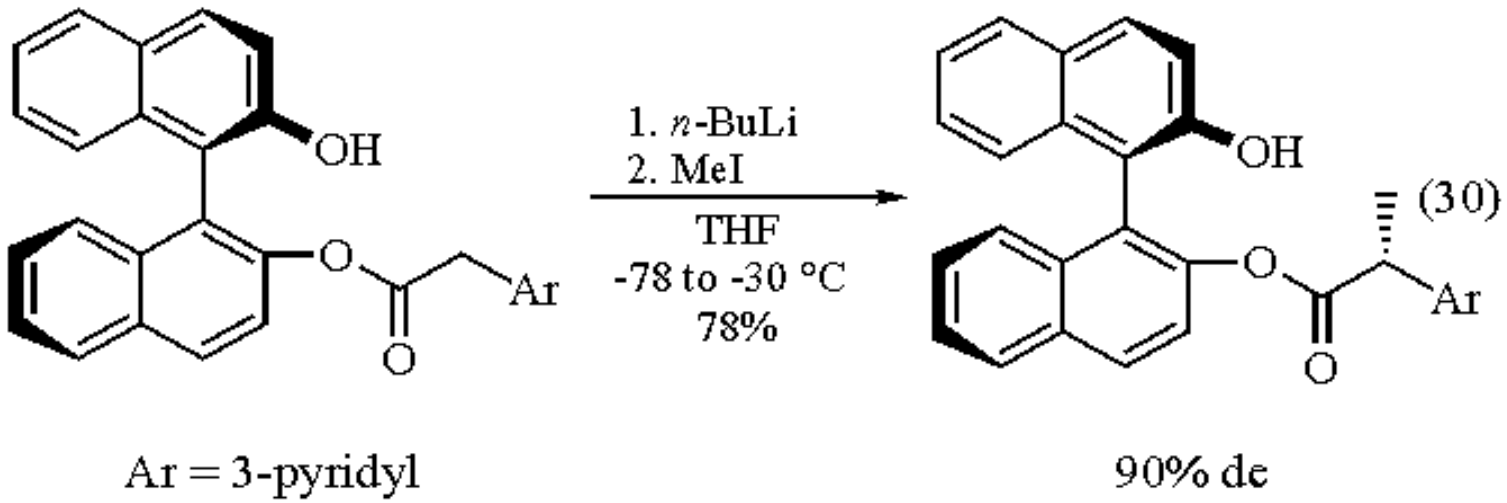

Related Reagents.

(R)-1,1´-Bi-2,2´-naphthotitanium Dichloride; ***(R)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide***; ***(R,R)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]titanium (R)-1,1´-Bi-2,2´-naphtholate***; ***(-)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]zirconium (R)-1,1´-Bi-2,2´-naphtholate***; ***Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl***.

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(*R*)-1,1´-Bi-2,2´-naphthotitanium Dichloride[1]

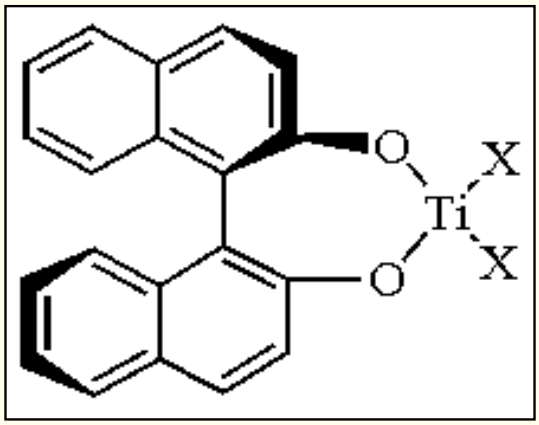

(X = Cl)

[116051-73-1] · $C_{20}H_{12}Cl_2O_2Ti$ · (*R*)-1,1´-Bi-2,2´-naphthotitanium Dichloride · (MW 403.10) (X = Br)

[128030-80-8] · $C_{20}H_{12}Br_2O_2Ti$ · (*R*)-1,1´-Bi-2,2´-naphthotitanium Dibromide · (MW 492.00) (X = ClO_4)

[138645-47-3] · $C_{20}H_{12}Cl_2O_{10}Ti$ · (*R*)-1,1´-Bi-2,2´-naphthotitanium Diperchlorate · (MW 531.09) (X = OSO_2CF_3)

[139327-61-0] · $C_{22}H_{12}F_6O_8S_2Ti$ · (*R*)-1,1´-Bi-2,2´-naphthotitanium Ditriflate · (MW 630.32)

(chiral Lewis acid for ene reactions,[2] Mukaiyama aldol reactions,[16] Diels-Alder reactions,[24] and cyanosilylations[27])

Alternate Name: BINOL-TiX_2.

Solubility: insol propionitrile; sol toluene, dichloromethane, and nitroethane.

Handling, Storage, and Precautions: titanium is reputed to be of low toxicity.

Introduction.

The (*R*)-1,1´-bi-2,2´-naphthotitanium dihalides (BINOL-TiX_2; X = Br or Cl) are most conveniently prepared in situ from the reaction of diisopropoxytitanium dihalides $(i\text{-PrO})_2TiX_2$; X = Br[2] or Cl[3]) with ***(R)-1,1´-Bi-2,2´-naphthol***

(BINOL) in the presence of molecular sieves (MS 4A) (eq 1).[2] When BINOL is mixed with ***Dichlorotitanium Diisopropoxide*** in the absence of MS 4A, almost no change is observed on the hydroxy-carbon signal of BINOL in the ^{13}C NMR spectrum. However, the addition of MS 4A to the solution of BINOL and $(i\text{-PrO})_2TiCl_2$ leads to a downfield shift of the hydroxy-carbon signal, indicating the formation of the BINOL-derived chiral catalyst. MS (zeolite) serves as an acid/base catalyst[4] and significantly facilitates the alkoxy ligand exchange in the in situ preparation of the chiral catalyst, BINOL-TiX_2. A 1:1 mixture of $(i\text{-PrO})_2TiX_2$ and (*R*)-BINOL in the presence of MS 4A in dichloromethane provides a red-brown solution. The molecularity of BINOL-TiX_2 in dichloromethane is ca. 2.0, depending on the concentration, particularly of homochiral (*R*)(*R*)- or (*S*)(*S*)-dimer which tends to dissociate to the monomer in lower concentration.[5]

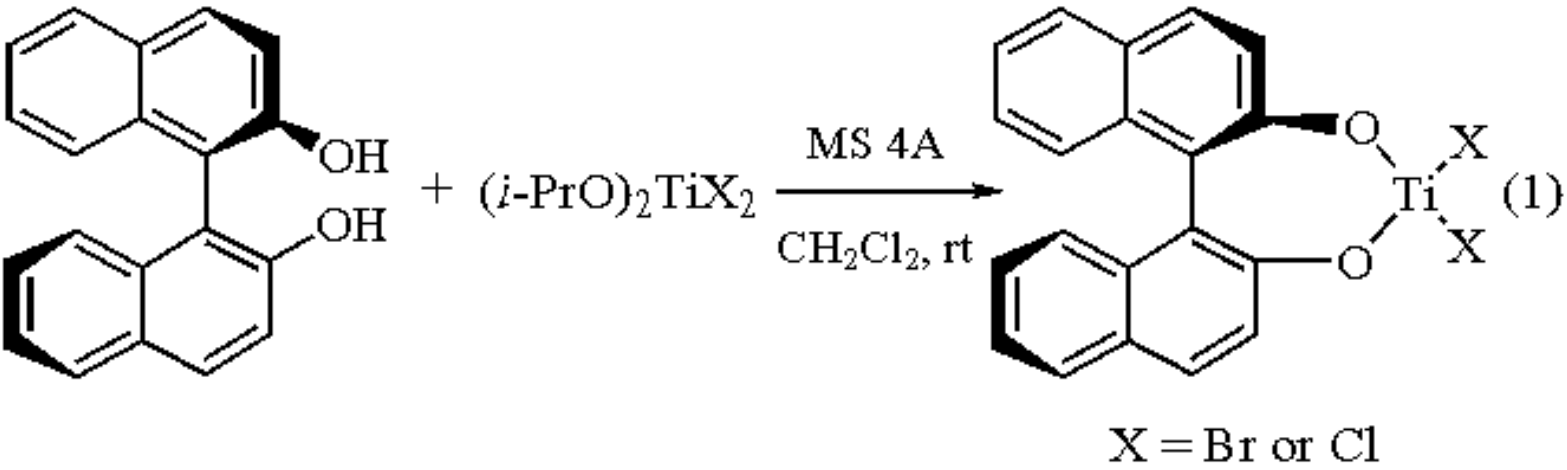

The chiral titanium complexes modified by the perchlorate or trifluoromethanesulfonate ligand such as (*R*)-1,1´-bi-2,2´-naphthotitanium diperchlorate (BINOL-$Ti(ClO_4)_2$) or (*R*)-1,1´-bi-2,2´-naphthotitanium ditriflate ((*R*)-BINOL-$Ti(OTf)_2$) can easily be prepared by the addition of ***Silver(I) Perchlorate*** or ***Silver(I) Trifluoromethanesulfonate*** (2 equiv) to BINOL-$TiCl_2$ (eq 2).[6]

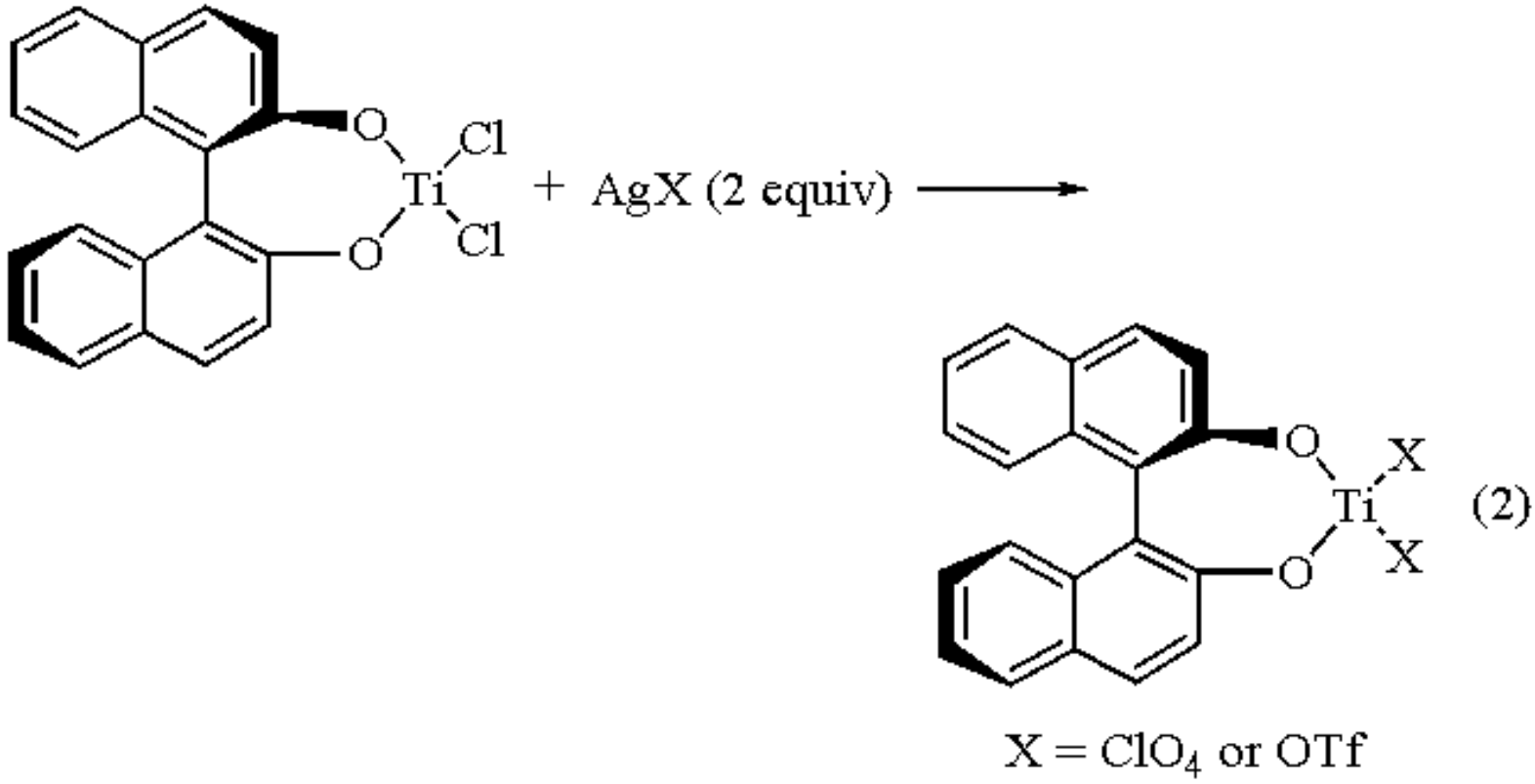

Asymmetric Catalysis of Carbonyl-Ene Reaction.

(*R*)-1,1´-Bi-2,2´-naphthotitanium dihalides exhibit a remarkable level of asymmetric induction in the carbonyl-ene reaction of prochiral glyoxylate to provide practical access to α-hydroxy esters, a class of compounds of biological and synthetic importance[7] (eq 3).[2] The catalyst derived from (*R*)-BINOL leads consistently to the (*R*)-alcohol product, whereas the catalyst derived from (*S*)-BINOL affords the (*S*)-enantiomer. Generally speaking, the dibromide is superior to the dichloride in both reactivity and enantioselectivity for the reactions involving a methylene hydrogen shift in particular. On the other hand, the dichloride is lower in reactivity but superior in enantioselectivity for certain reactions involving methyl hydrogen shift. The present asymmetric catalysis is applicable to a variety of 1,1-disubstituted alkenes to provide the ene products in extremely high enantiomeric excess by judicious choice of the dibromo or dichloro catalyst. The reactions of mono- and 1,2-disubstituted alkenes afford no ene product. However, vinylic sulfides and selenides serve as alternatives to mono- and 1,2-disubstituted alkenes, giving the ene products with virtually complete enantioselectivity along with high diastereoselectivity (eq 4).[8] The synthetic advantage of vinylic sulfides and selenides is exemplified by the synthesis of enantiomerically pure (*R*)-(-)-ipsdienol, an insect aggregation pheromone.

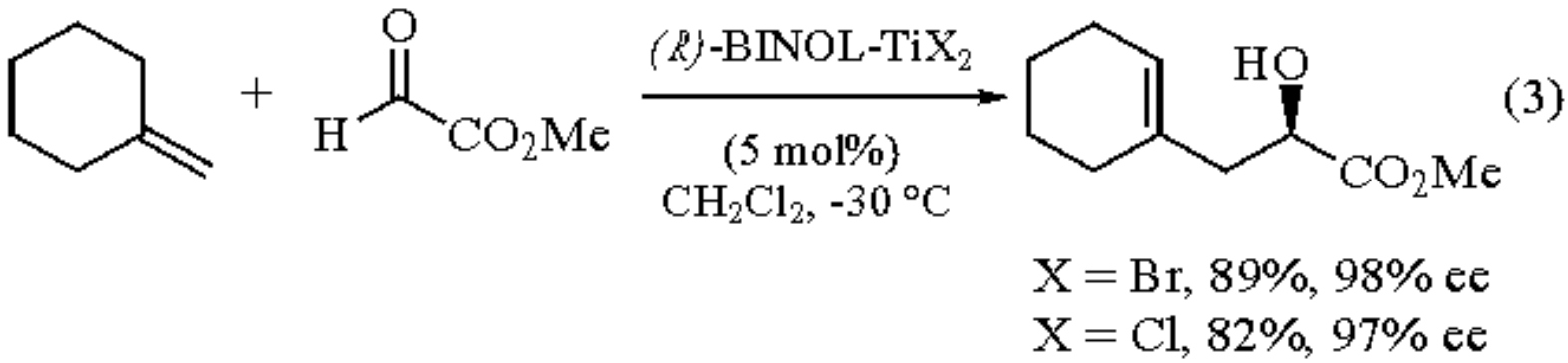

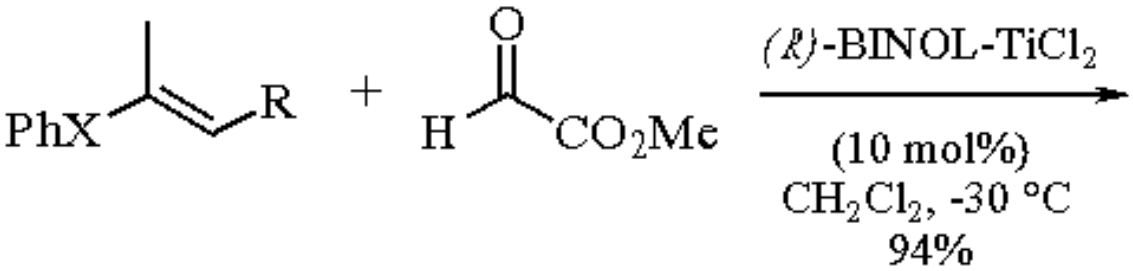

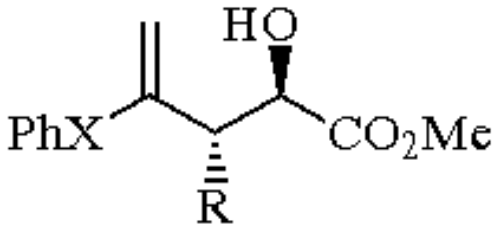

(4)

X = S, R = *i*-Bu, 95% *anti*, >99% ee

Positive Nonlinear Effect[5] (Asymmetric Amplification[9]).

A nonclassical phenomenon of asymmetric catalysis by the chiral BINOL-derived titanium complex is the remarkable positive nonlinear effect observed, which is of practical and mechanistic importance.[5] Convex deviation is observed from the usually assumed linear relationship between the enantiomeric purity of the BINOL ligand and the optical yield of the product. The glyoxylate-ene reaction catalyzed by the chiral titanium complex derived from a partially-resolved BINOL of 33.0% ee, for instance, provides the ene product with 91.4% ee in 92% chemical yield (eq 5). The optical yield thus obtained with a partially resolved BINOL ligand is not only much higher than the % ee of BINOL employed but is also very close to the value of 94.6% ee obtained using the enantiomerically pure BINOL. Thus the use of 35-40% ee of BINOL is sufficient to provide the equally high (>90% ee) level obtained with enantiomerically pure BINOL.

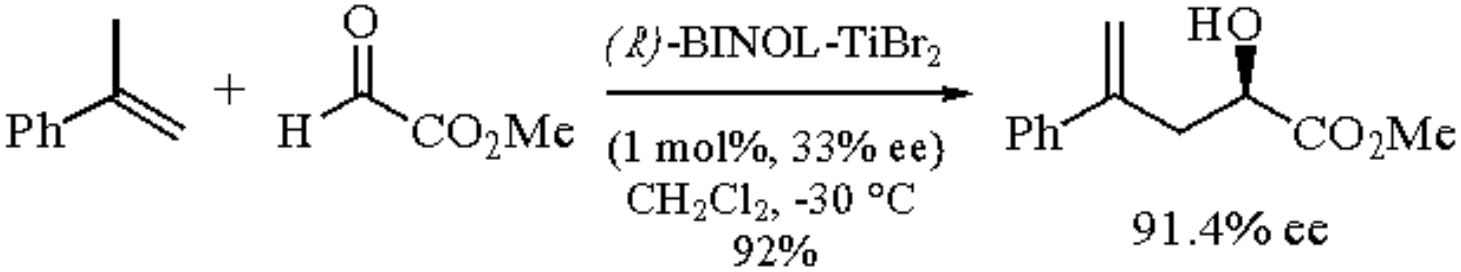

(5)

Asymmetric Desymmetrization.[10]

Desymmetrization of an achiral, symmetrical molecule is a potentially powerful but relatively unexplored concept for the asymmetric catalysis of carbon-carbon bond formation. While the ability of enzymes to differentiate between enantiotopic functional groups is well known,[11] little is known about the similar ability of nonenzymatic catalysts to effect carbon-carbon bond formation. The desymmetrization by the enantiofacial selective carbonyl-ene reaction of prochiral ene substrates with planar symmetry provides an efficient access to remote internal[12] asymmetric induction which is otherwise difficult to attain (eq 6).[10] The (2*R*,5*S*)-*syn* product is obtained in >99% ee along with more than

99% diastereoselectivity. The desymmetrized product thus obtained can be transformed stereoselectively by a more classical diastereoselective reaction (e.g. hydroboration).

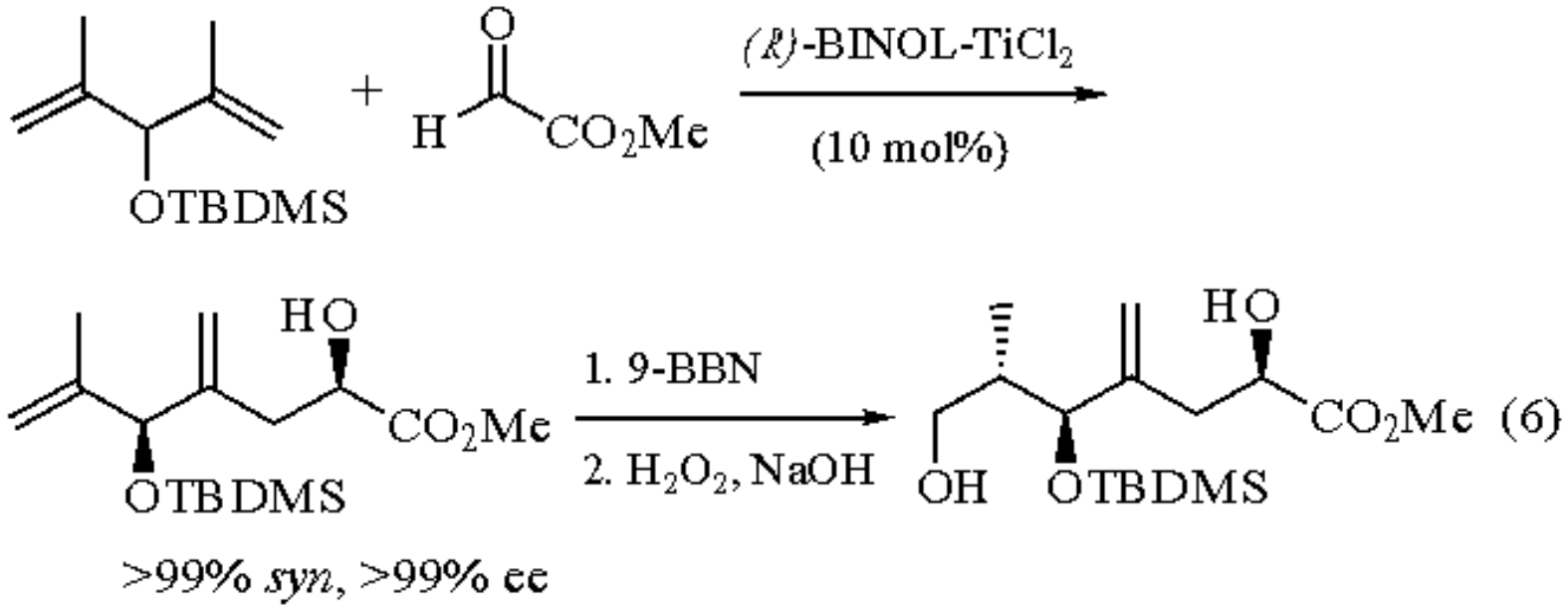

Kinetic Resolution.[13]

On the basis of the desymmetrization concept, the kinetic resolution of a racemic substrate might be recognized as an intermolecular desymmetrization.[10] The kinetic resolution of a racemic allylic ether by the glyoxylate-ene reaction also provides an efficient access to remote relative[12] asymmetric induction. Both the dibromide and dichloride catalysts provide the (2*R*,5*S*)-*syn* product with >99% diastereoselectivity along with more than 95% ee (eq 7). The high diastereoselectivity, coupled with the high % ee, strongly suggests that the catalyst/glyoxylate complex efficiently discriminates between the two enantiomeric substrates to accomplish effective kinetic resolution. In fact, the relative rates with racemic ethers are quite large, ca. 60 and 700, respectively. As expected, the reaction of (*S*)-ene using the catalyst (*R*)-BINOL-$TiCl_2$ (matched catalytic system) provides complete (>99%) 1,4-*syn* diastereoselectivity in high chemical yield, whereas the reaction of (*R*)-ene using (*R*)-BINOL-$TiCl_2$ (mismatched catalytic system) affords a diastereomeric mixture in quite low yield (eq 8).

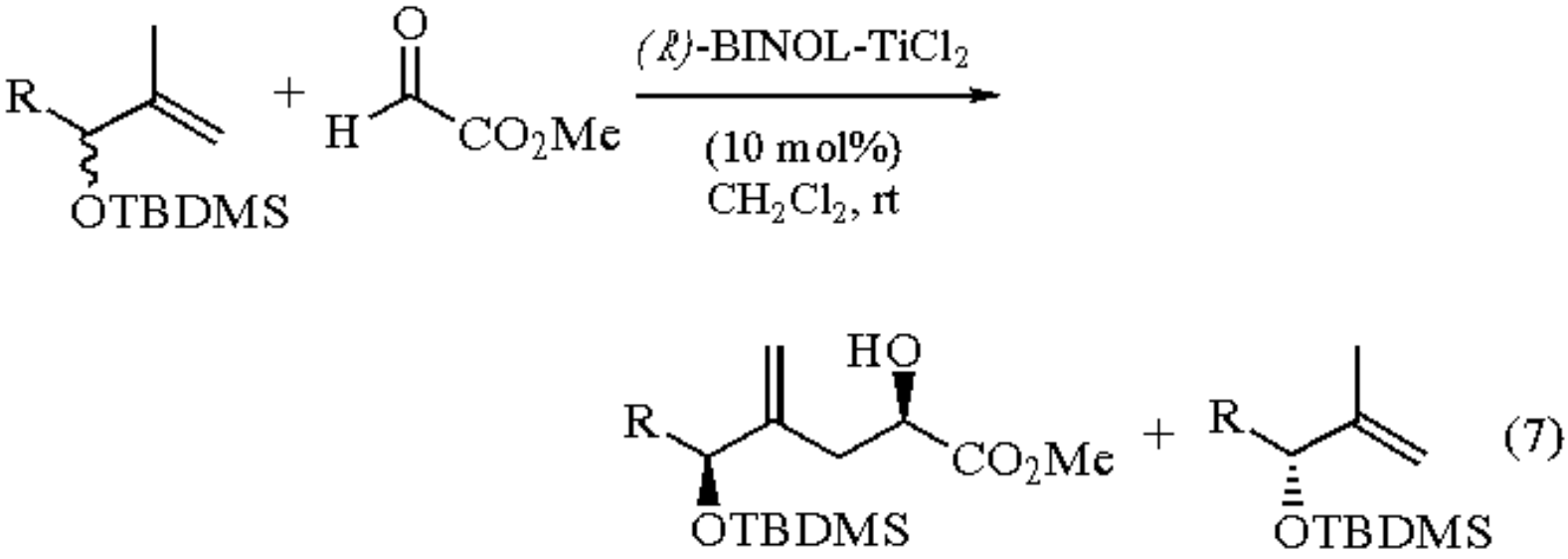

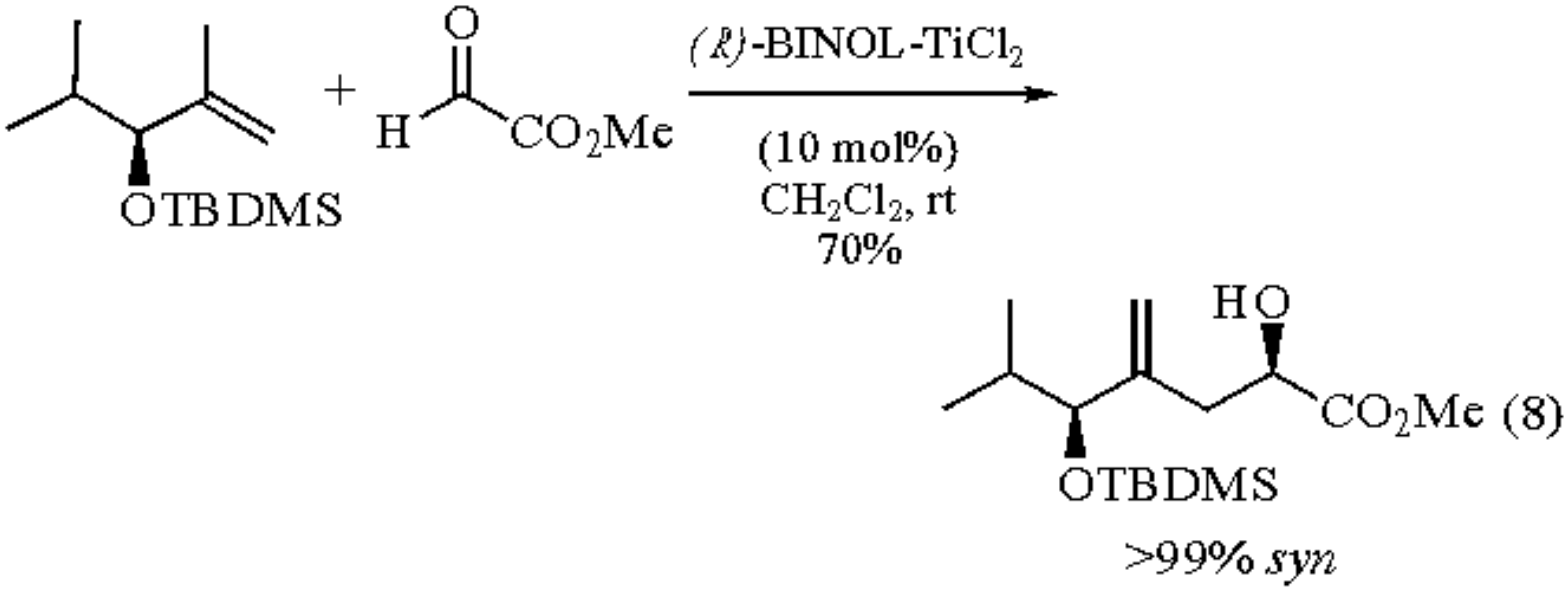

Ene Cyclization.[14]

The asymmetric catalysis of the intramolecular carbonyl-ene reaction not only of type (3,4) but also (2,4) employs the BINOL-derived titanium complexes ((*R*)-BINOL-TiX_2; X = ClO_4 or OTf), modified by the perchlorate and trifluoromethanesulfonate ligands.[6] The *trans*-tetrahydropyran is thus preferentially obtained in 84% ee (eq 9). The seven-membered cyclization of type 7-(2,4) gives the oxepane in high ee, where the *gem*-dimethyl groups are unnecessary (eq 10).

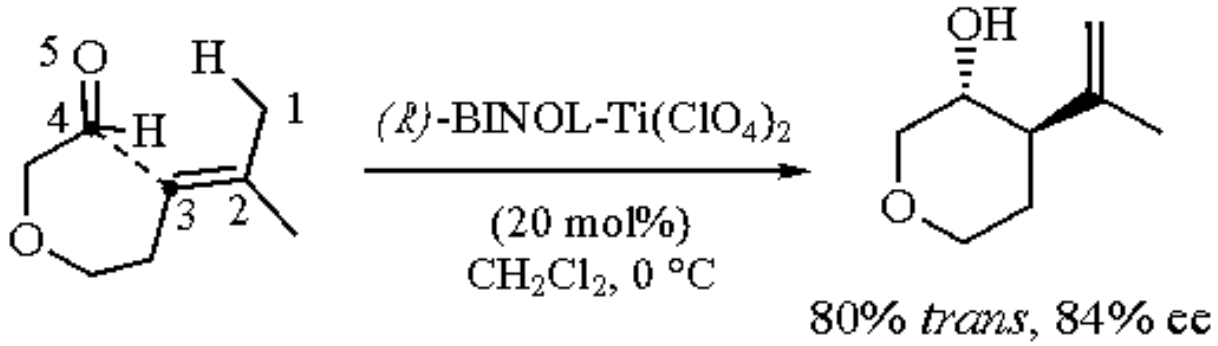

(9)

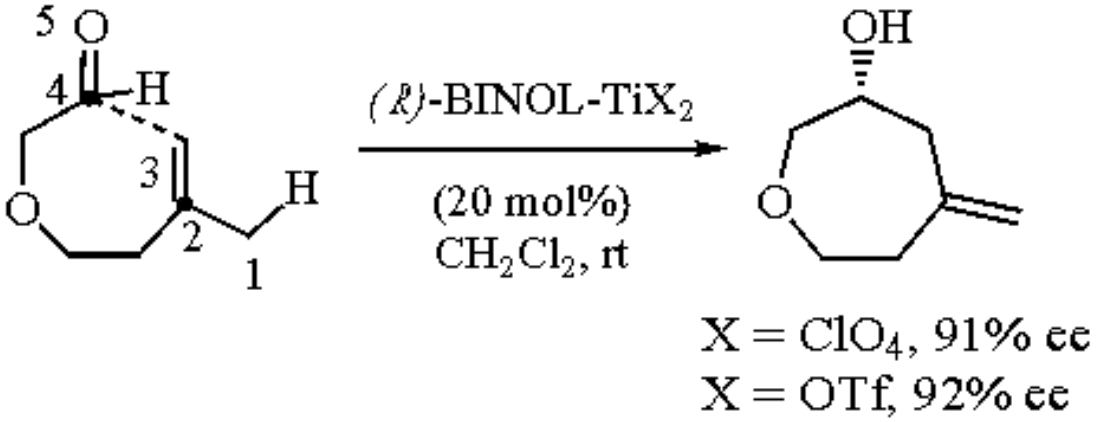

(10)

Mukaiyama Aldol Condensation.

As expected, the chiral titanium complex is also effective for a variety of carbon-carbon bond forming processes such as the aldol and the Diels-Alder reactions. The aldol process constitutes one of the most fundamental bond constructions in organic synthesis.[15] Therefore the development of chiral catalysts that promote asymmetic aldol reactions in a highly stereocontrolled and truly catalytic fashion has attracted much attention, for which the silyl enol ethers of ketones or esters have been used as a storable enolate component (Mukaiyama aldol condensation). The BINOL-derived titanium complex BINOL-$TiCl_2$ can be used as an efficient catalyst for the Mukaiyama-type aldol reaction of not only ketone silyl enol ethers but also ester silyl enol ethers with control of absolute and relative stereochemistry (eq 11).[16]

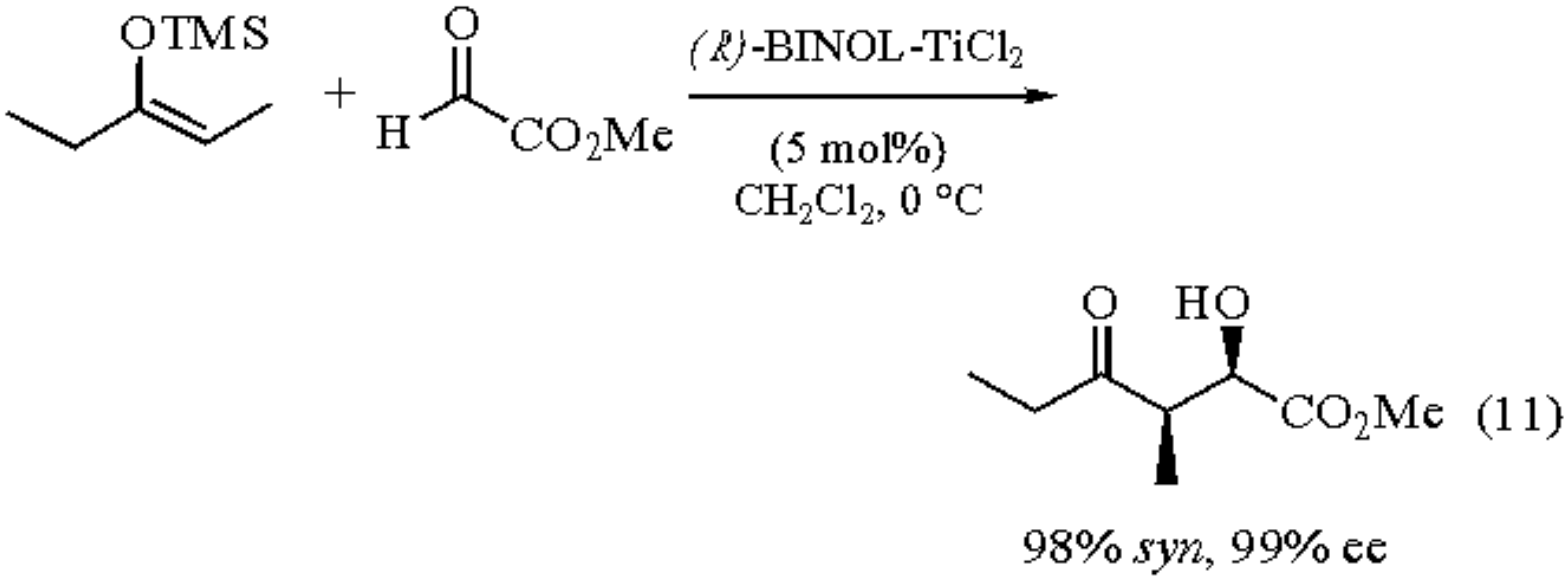

Carbonyl Addition of Allylic Silanes and Stannanes.[17]

The chiral titanium complex BINOL-$TiCl_2$ also catalyzes the asymmetric carbonyl addition reaction of allylic silanes and stannanes.[18] Thus the addition reaction of glyoxylate with (*E*)-2-butenylsilane and -stannane proceeds smoothly to give the *syn* product in high enantiomeric excess (eq 12). The *syn* product thus obtained can be readily converted to the lactone portion of verrucaline A. The reaction of aliphatic and aromatic aldehydes with allylstannane is also catalyzed by BINOL-$TiCl_2$ to give remarkably high enantioselectivity (eq 13).[19]

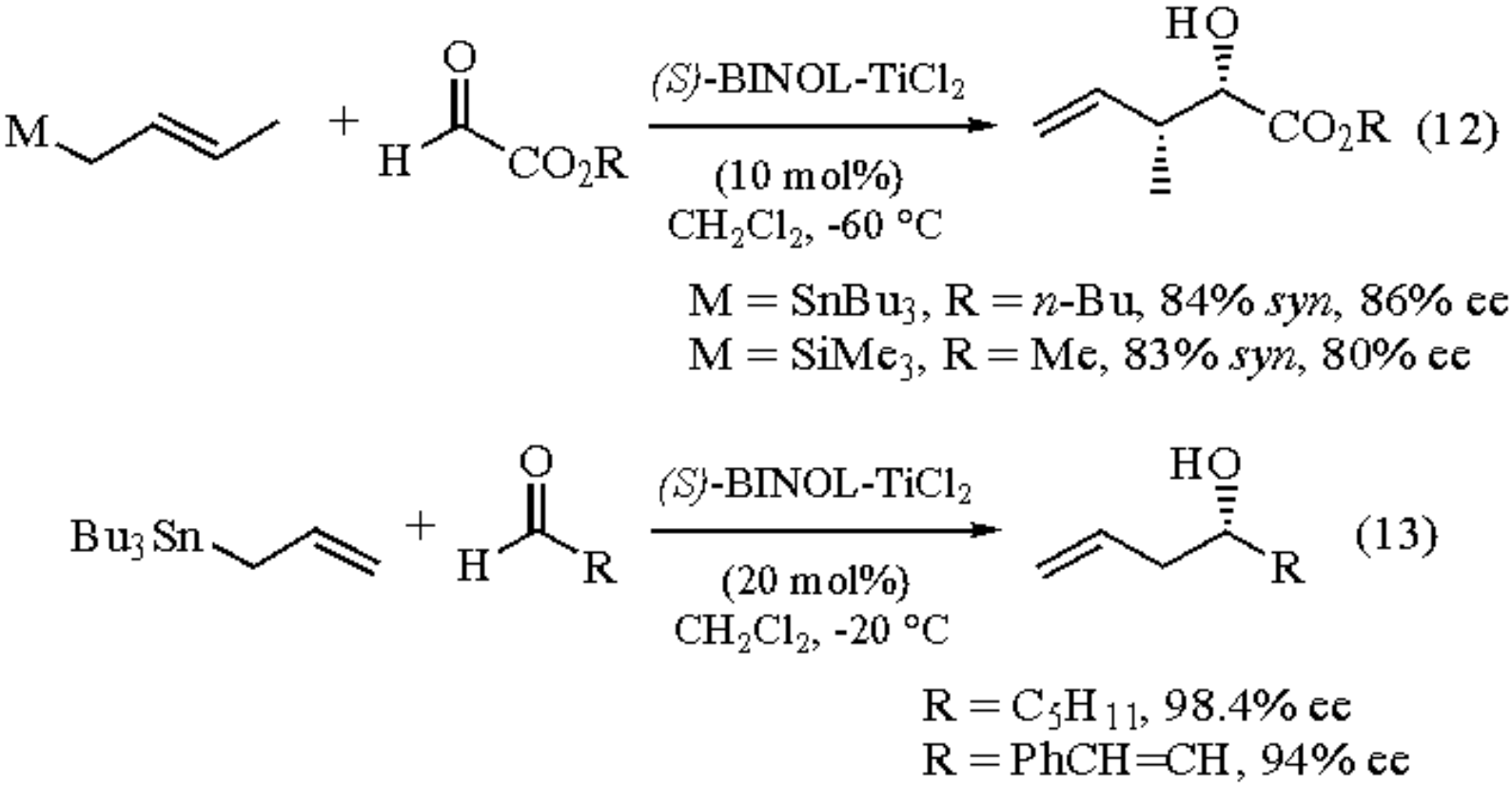

Hetero Diels-Alder Reaction.[20]

The hetero-Diels-Alder reaction involving glyoxylate as the dienophile provides an efficient access to the asymmetric synthesis of monosaccharides.[21] The hetero Diels-Alder reaction with methoxydienes proceeds smoothly with catalysis by BINOL-$TiCl_2$ to give the *cis* product in high enantiomeric excess (eq 14).[22] The dibromide affords a higher *cis* selectivity, however, with a lower enantioselectivity, particularly in the *trans* adduct. The product thus obtained can be readily converted to the lactone portion of HMG-CoA inhibitors such as mevinolin or compactin.[23]

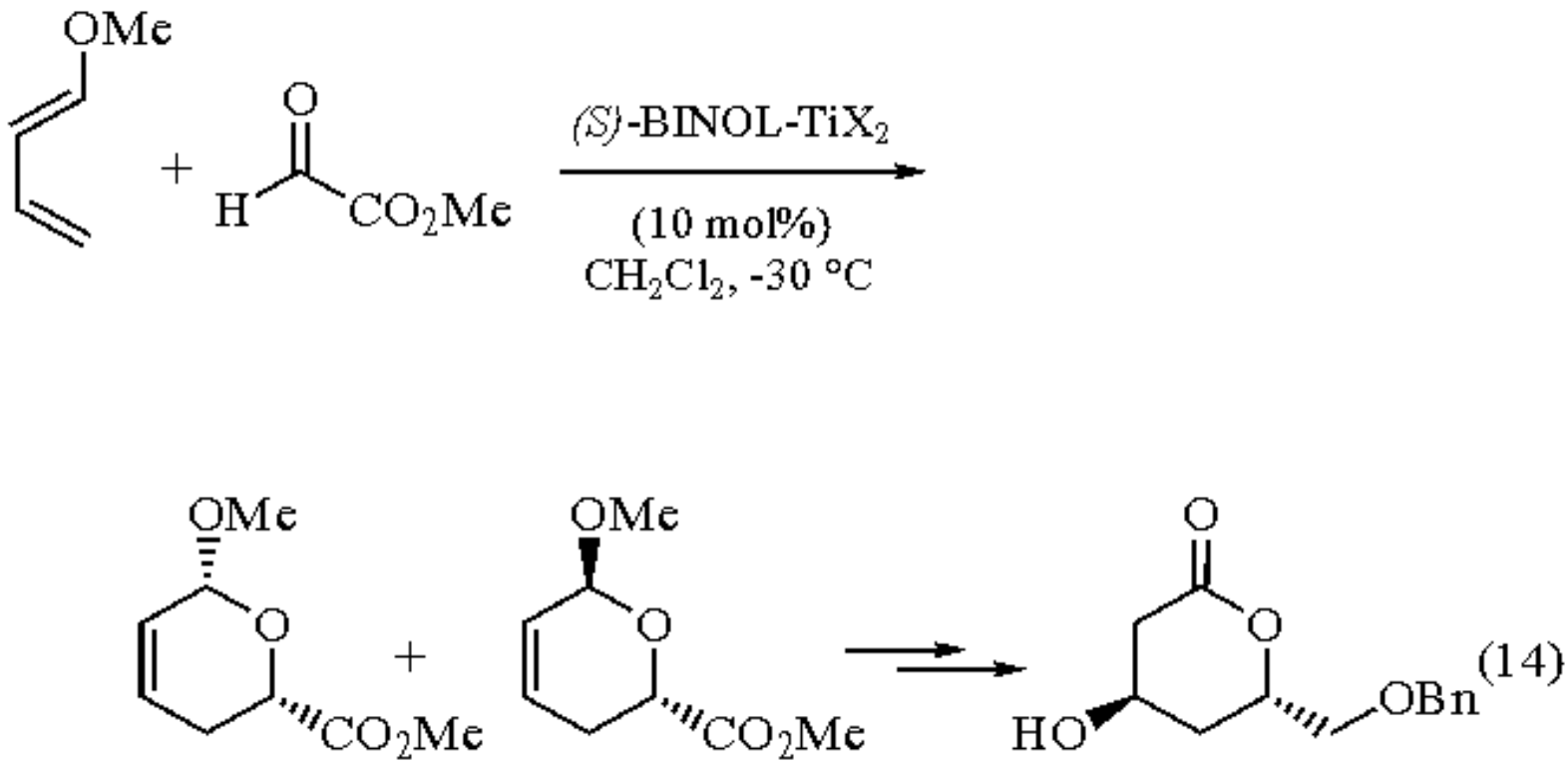

X = Cl ,78 (94% ee):22 (>90% ee)
X = Br, 84 (92% ee):16 (50% ee)

Diels-Alder Reaction.[24]

The Diels-Alder reaction of methacrolein with 1,3-dienol derivatives can also be catalyzed by the chiral BINOL-derived titanium complex BINOL-$TiCl_2$. The *endo* adduct was obtained in high enantioselectivity (eq 15).[22a,25] The sense of asymmetric induction is exactly the same as observed for the asymmetric catalytic reactions shown above. Asymmetric catalytic Diels-Alder reactions with naphthoquinone derivatives as the dienophile provide an efficient entry to the asymmetric synthesis of anthracyclinone aglycones (eq 16).[26]

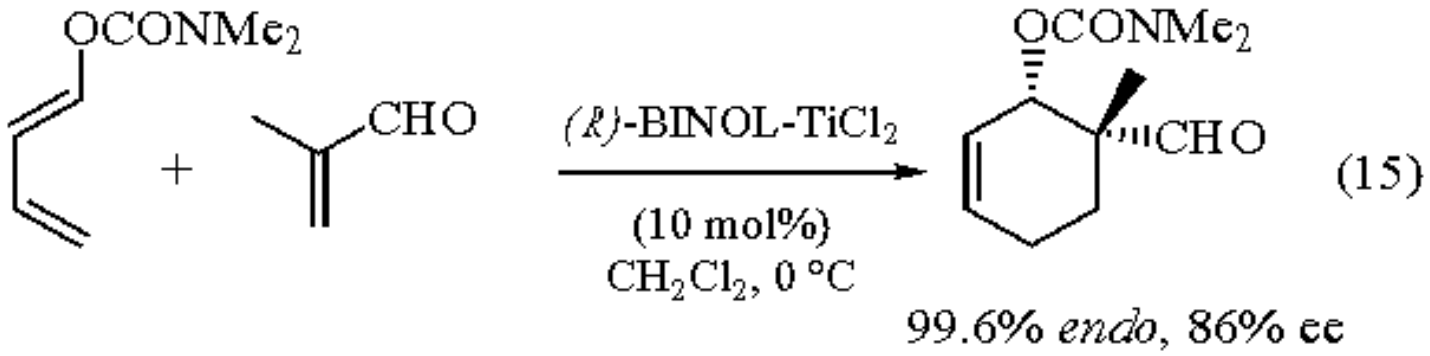

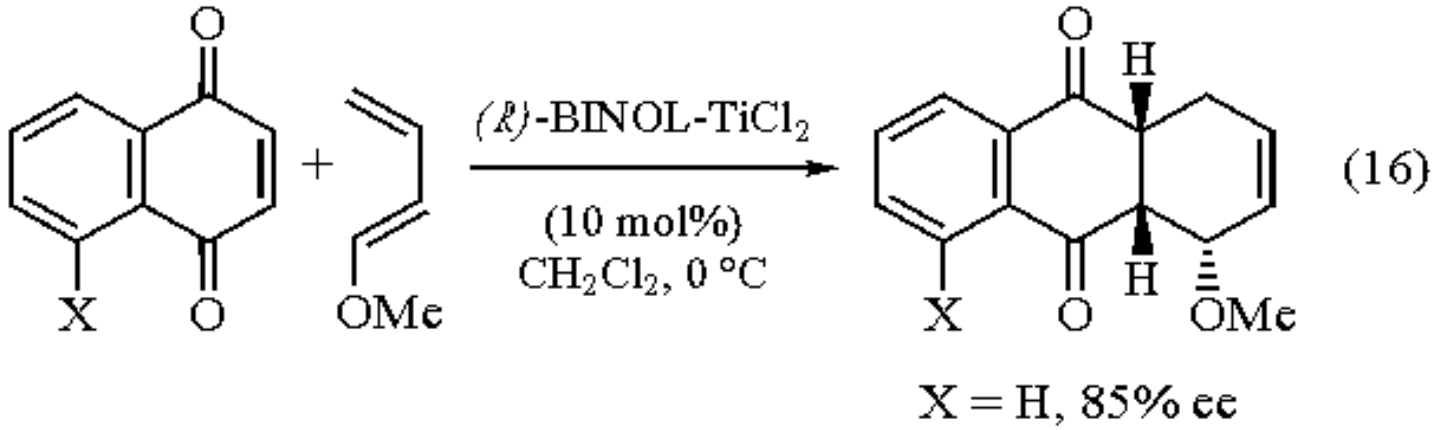

Cyanosilylation.[27]

Another preparative procedure of BINOL-$TiCl_2$ and the use thereof was reported in the asymmetric catalysis of the addition reaction of cyanotrimethylsilane to aldehydes.[28] The dilithium salt of BINOL in ether was treated with ***Titanium(IV) Chloride***, the red-brown mixture was warmed to room temperature, and the ether removed in vacuo. Dry benzene was added and the nondissolved solid was separated via filtration under nitrogen. Removal of the solvent delivered 50% of a sensitive red-brown solid which showed a single set of ^{13}C NMR signals (eq 17). The BINOL-$TiCl_2$ thus obtained was utilized to prepare the cyanohydrin of 3-methylbutanal in <82% ee (eq 18).

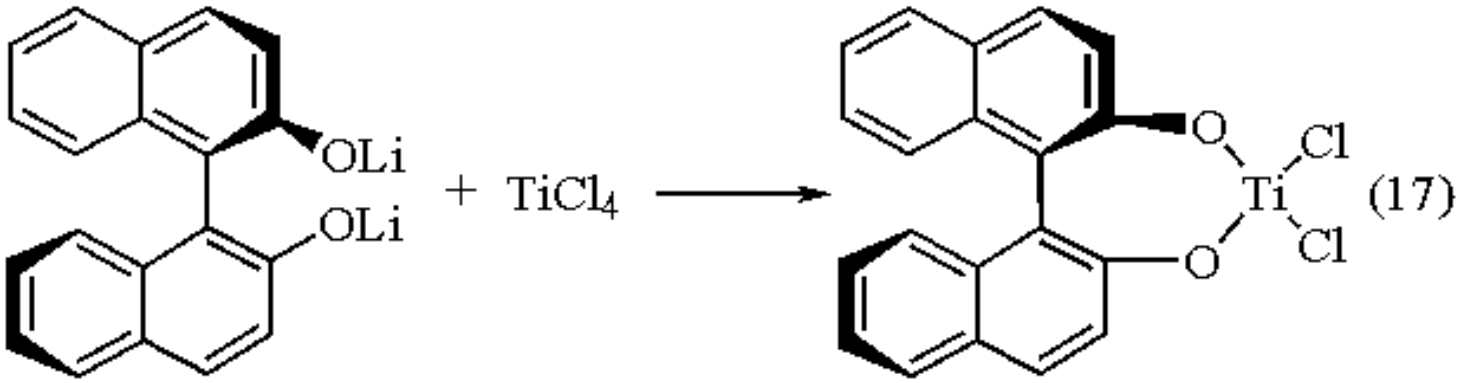

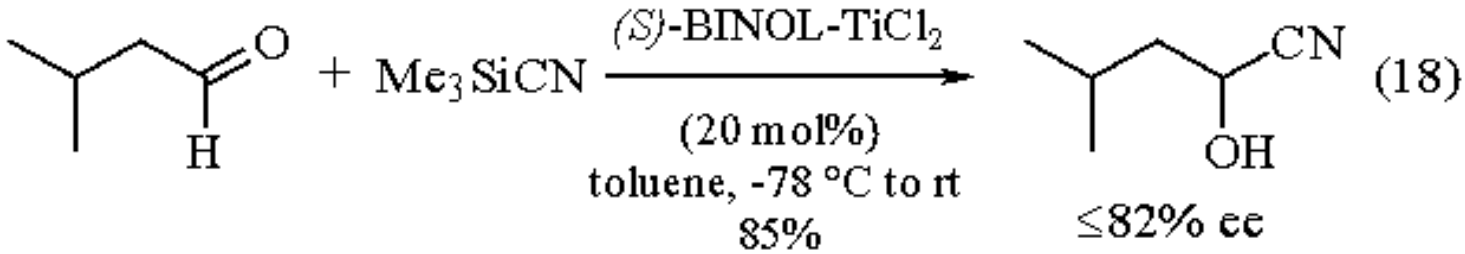

Related Reagents.

(R)-1,1´-Bi-2,2´-naphthol; ***(R)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide***; ***Titanium(IV) Chloride***.

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(*R*)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide[1]

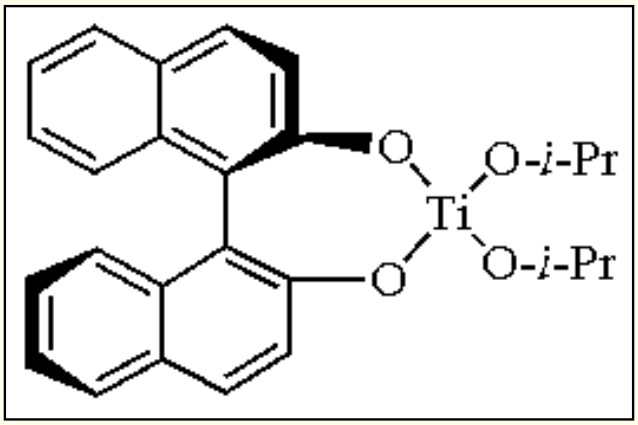

[123436-17-9] · $C_{26}H_{26}O_4Ti$ · (*R*)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide · (MW 450.37)

(mild Lewis acid catalyst for asymmetric oxidations[1,2] and allylations[7])

Physical Data: mp 127 °C (dec) (pentane/ether).

Solubility: sol dichloromethane, toluene, and ether.

Handling, Storage, and Precautions: titanium is reputed to be of low toxicity.

(*R*)-1,1´-Bi-2,2´-naphthotitanium diisopropoxide (BINOL-Ti(O-*i*-Pr)$_2$) (**1**), most conveniently prepared by the reaction of ***Titanium Tetraisopropoxide*** with ***(R)-1,1´-Bi-2,2´-naphthol*** through the azeotropic removal of isopropanol, is oxophilic (eq 1). A 1:1 mixture of Ti(O-*i*-Pr)$_4$ and (*R*)-BINOL in dichloromethane provides an orange-yellow solution and on removal of solvent gives a pale yellow solid. The molecularity of the 1:1 titanium-binaphthol species has been determined to be 2.3. However, the X-ray crystal structure is trimeric, containing a C_2 axis of symmetry.[3] This 1:1 complex provides, however, only low enantiomeric excess (ee) in the asymmetric epoxidation of allylic alcohols (eq 2).[1,3] However, the oxidation of sulfides to sulfoxides by ***t-Butyl Hydroperoxide*** proceeds catalytically with (**1**) to afford higher enantioselectivity than Kagan's catalytic method using diethyl tartrate as a chiral ligand (eq 3).[4] As Kagan has already reported, the amount of water added exhibits a significant effect upon ee value. A high ee is obtained when 0.5-3.0 equiv of H_2O was added to the sulfide, while a decrease of ee is observed when less than 0.5 equiv or more than 3.0 equiv of H_2O is used. In the absence of H_2O, only a low ee is obtained. Addition of water to (**1**) provides binaphthol-titanium oxide (BINOL-Ti=O; **2**) (eq 4),[5] which has been reported to serve as an asymmetric catalyst for the Mukaiyama aldol reaction (eq 5).[6]

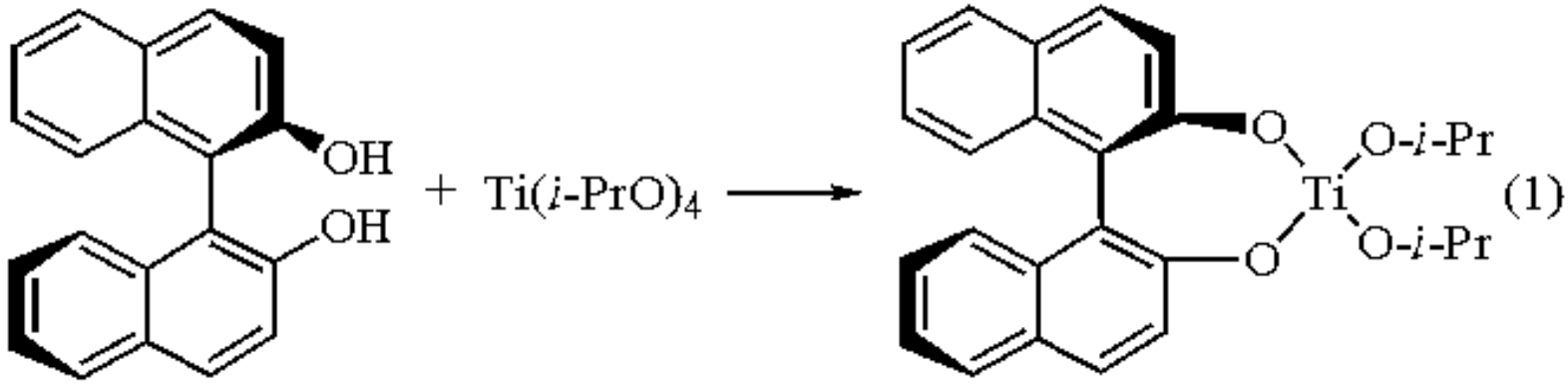

(1)

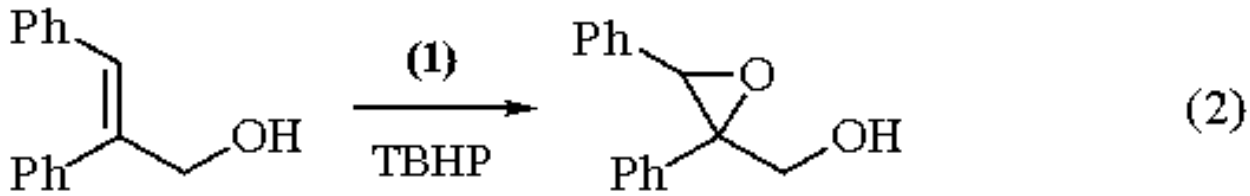

9% ee

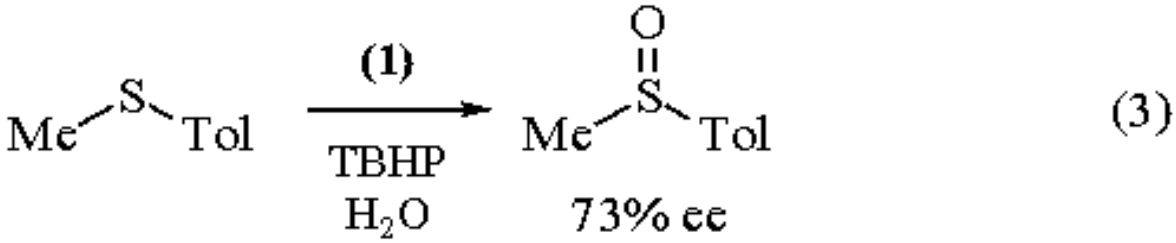

73% ee

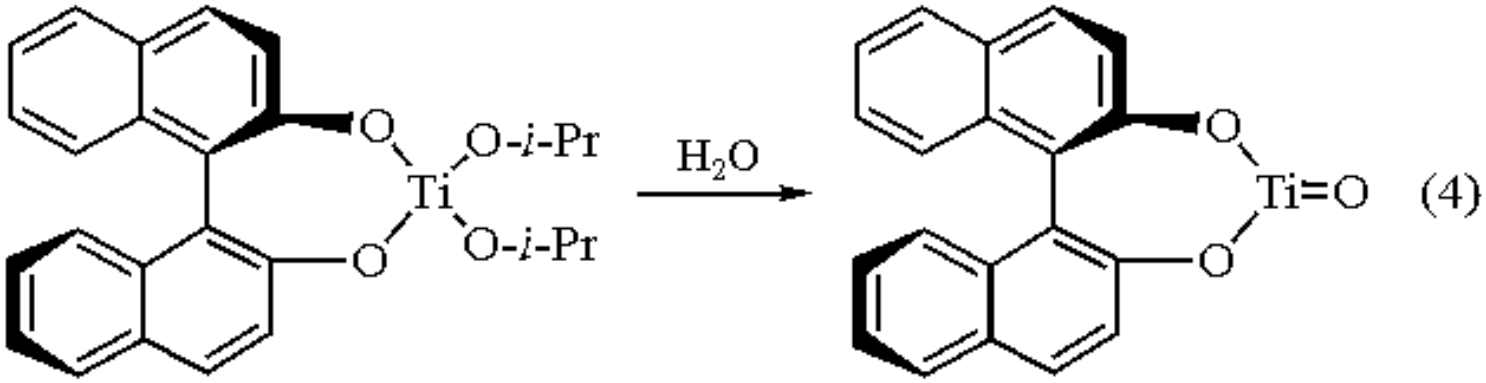

(2)

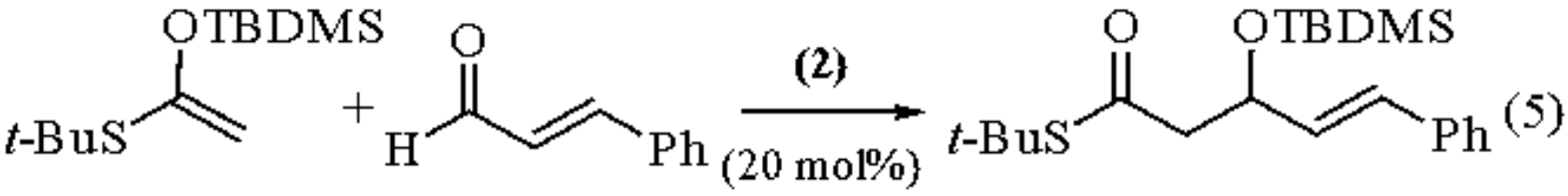

85% ee

Related Reagents.

(R)-1,1´-Bi-2,2´-naphthol; ***(R)-1,1´-Bi-2,2´-naphthotitanium Dichloride***; ***Titanium(IV) Chloride***.

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1,1´-Binaphthyl-2,2´-diyl Hydrogen Phosphate[1]

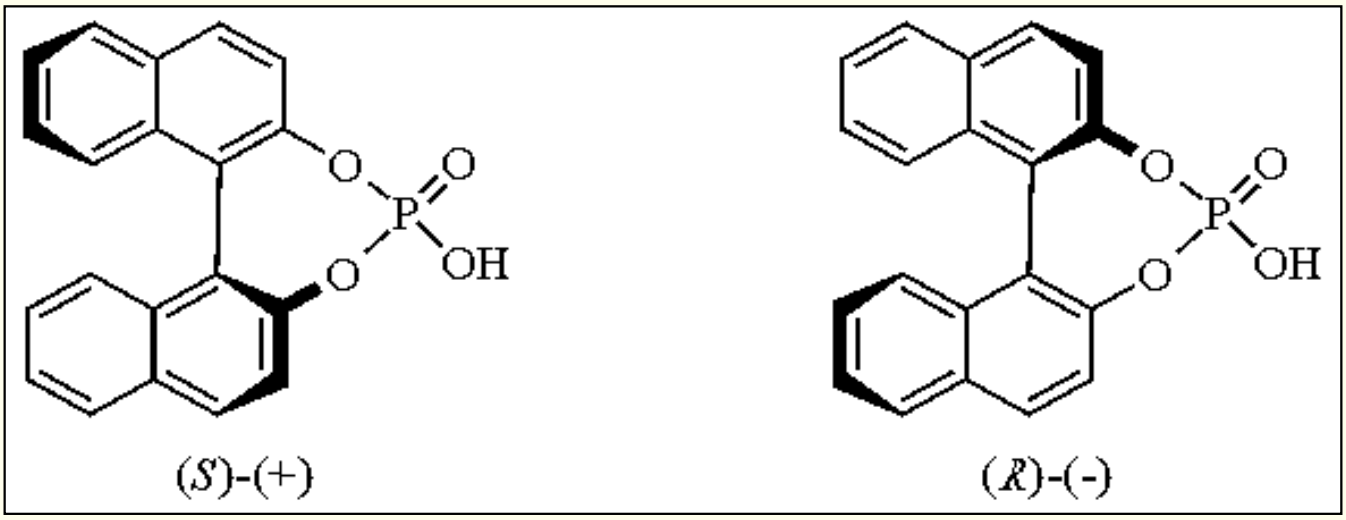

(*S*)-(+)

[35193-64-7] · $C_{20}H_{13}O_4P$ · 1,1´-Binaphthyl-2,2´-diyl Hydrogen Phosphate · (MW 348.30) (*R*)-(-)

[39648-67-4] (±)

[50574-52-2]

(reagent for optical resolution of a variety of organic bases[2] and helicenes;[3] NMR shift reagent for determining the enantiomeric purity of secondary and tertiary amines;[4] chiral ligand for homogeneous asymmetric catalysts[5,6])

Alternate Name: BNPPA.

Physical Data: (*S*)-(+)-BNPPA: $[\alpha]_D^{20}$ +605° (*c* 1.35, MeOH). (*R*)-(-)-BNPPA: $[\alpha]_D^{20}$ -605° (*c* 1.35, MeOH). Decomposes without melting at ca. 300 °C.

Solubility: racemate: sol ethanol (10 g/100 mL), sol methanol (3 g/100 mL), slightly sol water and other organic solvents. Enantiomer: sol ethanol (6 g/100 mL), sol methanol (2 g/100 mL), slightly sol water and other organic solvents.

Form Supplied in: white solid; racemic and optically active BNPPA are commercially available.

Preparative Methods: racemic BNPPA is obtained by condensation of (±)-binaphthol (see ***(R)-1,1´-Bi-2,2´-naphthol***) and ***Phosphorus Oxychloride*** followed by hydrolysis (eq 1).[1] Racemic BNPPA can be resolved by recrystallization of its cinchonine salt.[1]

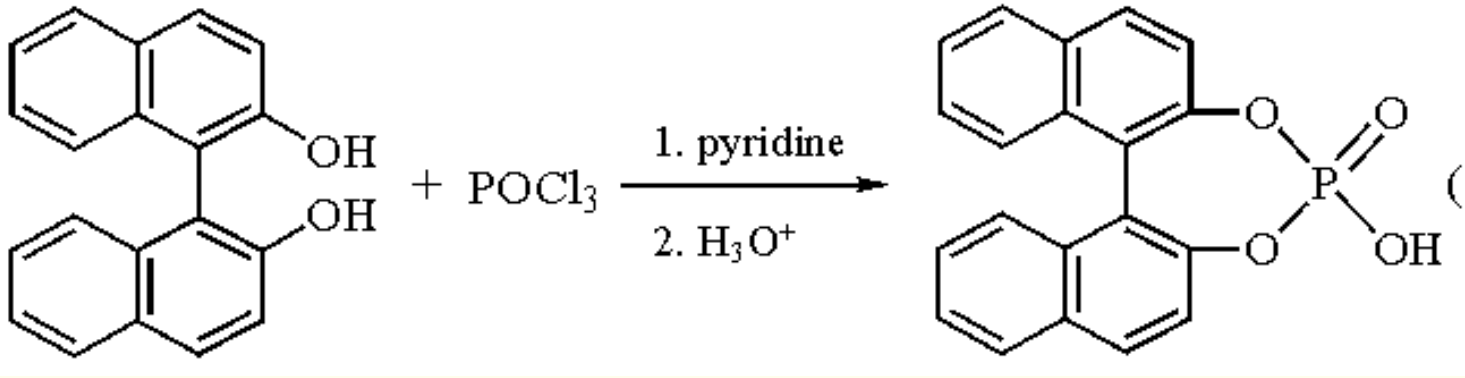

Chiral Ligand for Asymmetric Catalysts.

(*S*)-(+)- and (*R*)-(-)-BNPPA are efficient chiral ligands for the Pd-catalyzed hydrocarboxylation of alkenes.[5] Naproxen can be obtained regioselectively in 91% ee (eq 2).

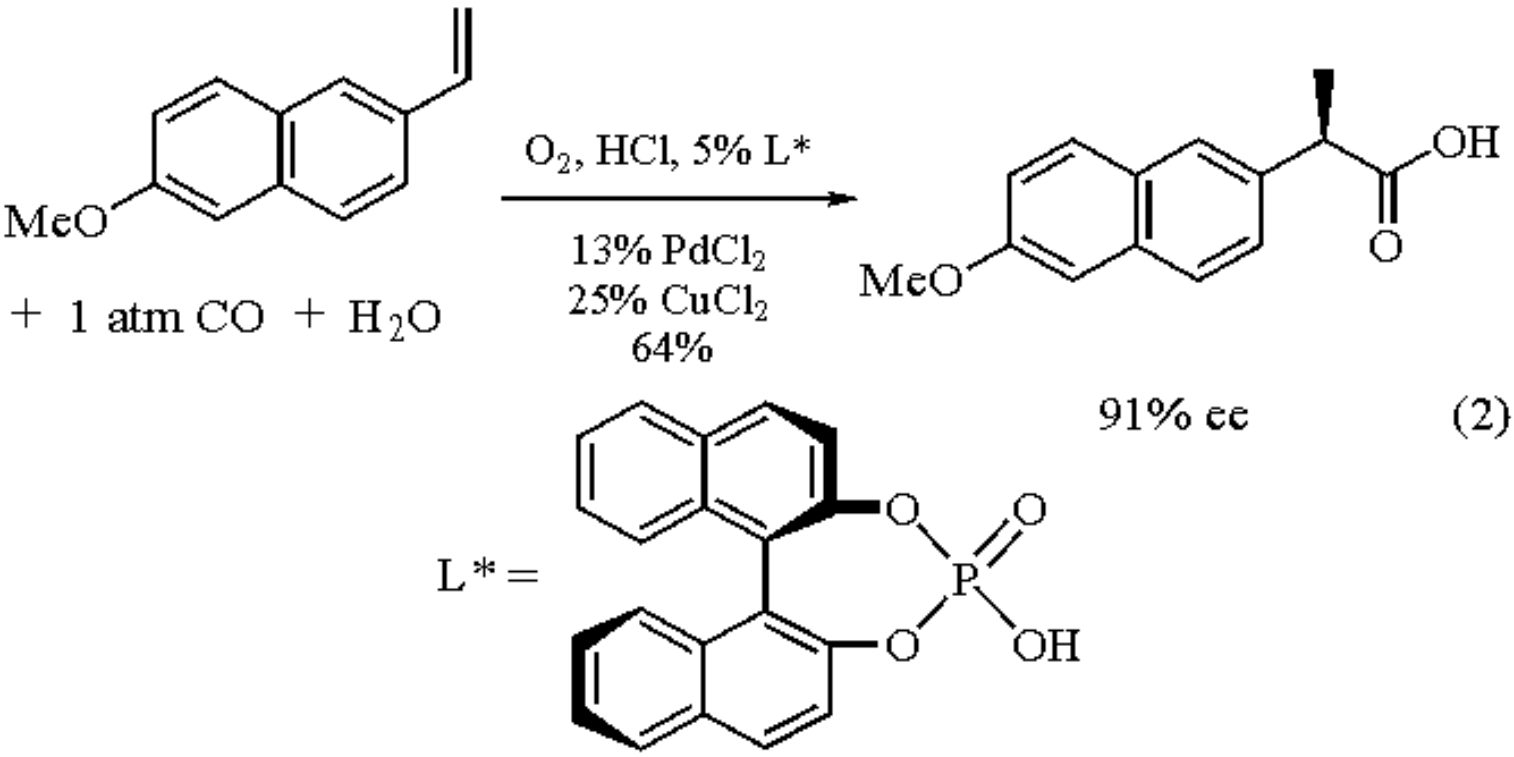

Dinuclear Rh complexes modified with optically active BNPPA catalyze asymmetric carbene reactions with moderate enantioselectivity (eqs 3 and 4).[6]

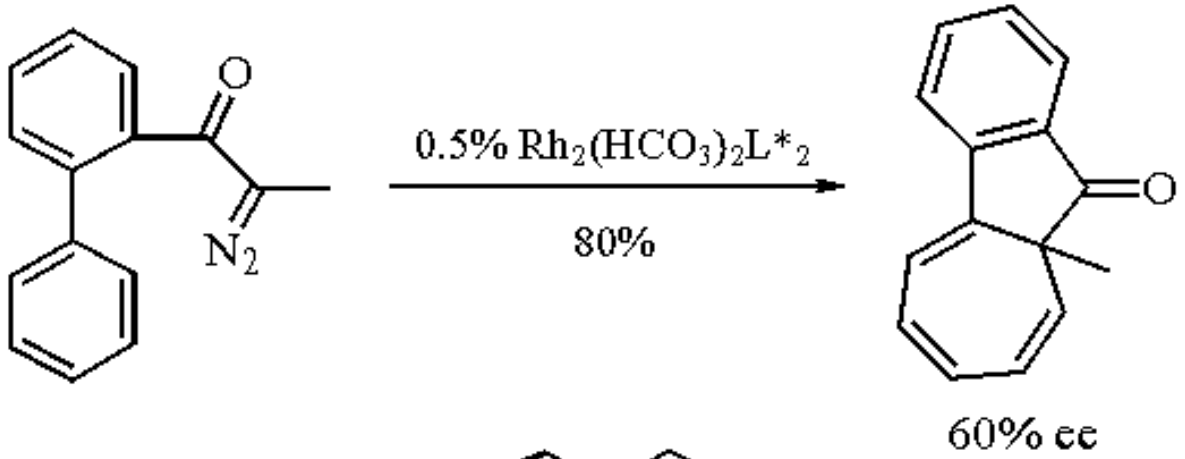

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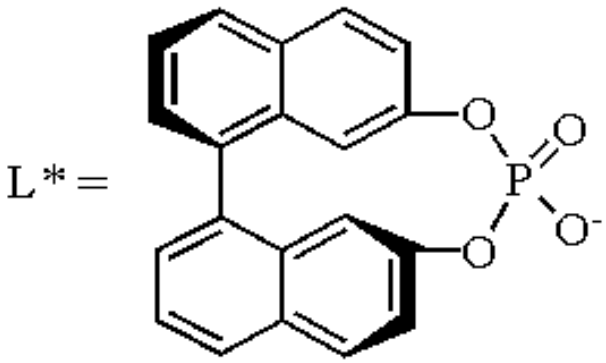

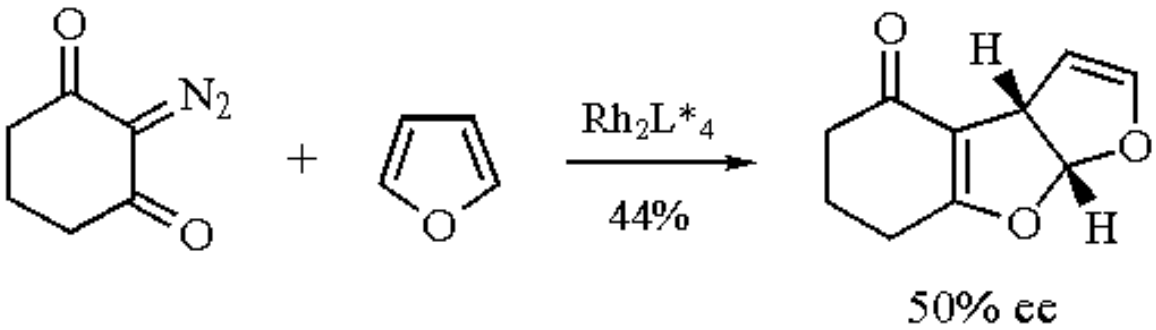

(4)

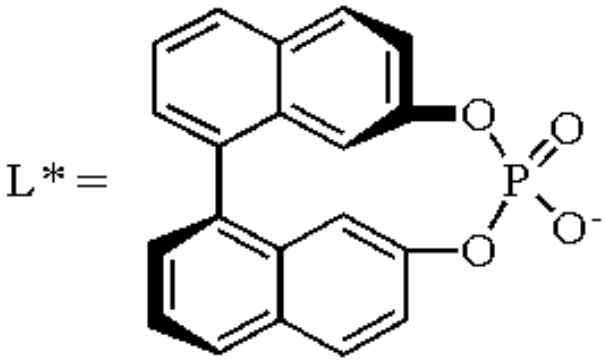

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2,2´-Bipyridinium Chlorochromate[1]

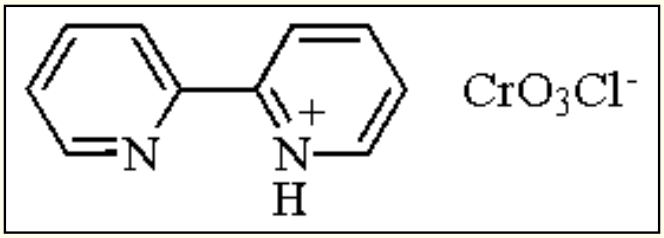

[76899-34-8] · $C_{10}H_9ClCrN_2O_3$ · 2,2´-Bipyridinium Chlorochromate · (MW 292.64)

(mild and selective oxidizing agent for primary and secondary alcohols;[2] can oxidize benzylic methylenes[11])

Alternate Name: BPCC.

Physical Data: mp not available.

Solubility: insol dichloromethane; sol acetone.

Form Supplied in: yellow crystalline solid; widely available.

Handling, Storage, and Precautions: the dry reagent is an air-stable and nonhygroscopic solid; it can be stored for extended periods protected from light and over calcium chloride. Solvents must be anhydrous and free of reducing impurities. 2,2´-Bipyridinium chlorochromate is reputed to be a toxic agent. The reagent should be handled in a fume hood.

Oxidation of Primary and Secondary Alcohols.

2,2´-Bipyridinium chlorochromate (BPCC) is a synthetically useful variant of ***Pyridinium Chlorochromate*** (PCC), in which the presence of the 2,2´-bipyridyl cationic ligand seems to offer special advantages in certain instances. Treatment of primary and secondary alcohols with BPCC in dichloromethane or acetone at rt for 2-4 h affords aldehydes and ketones in good yield (eqs 1-3).[2]

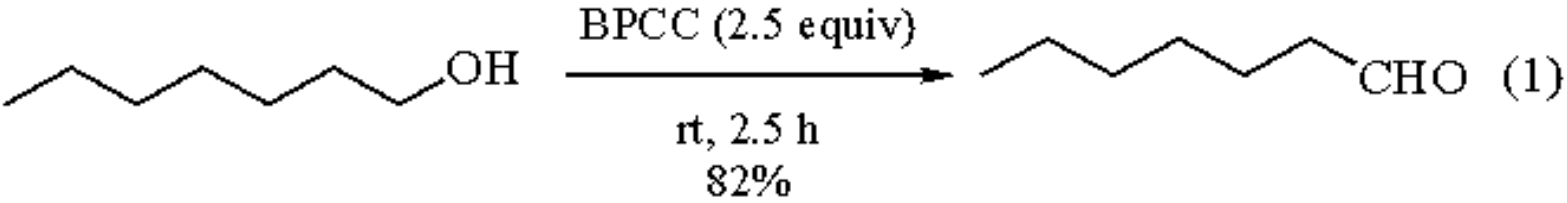

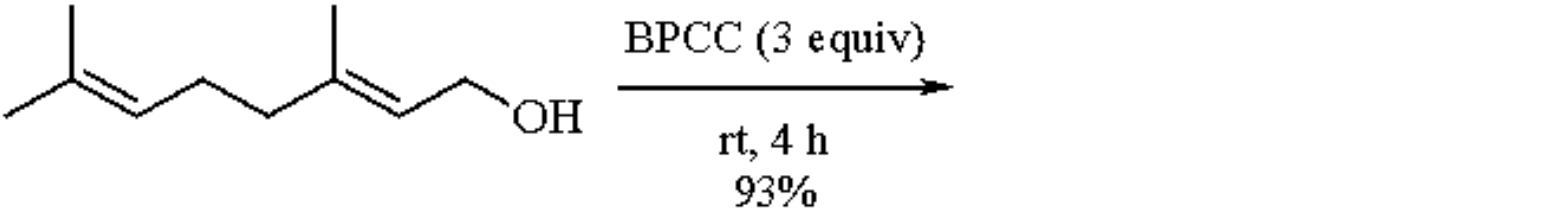

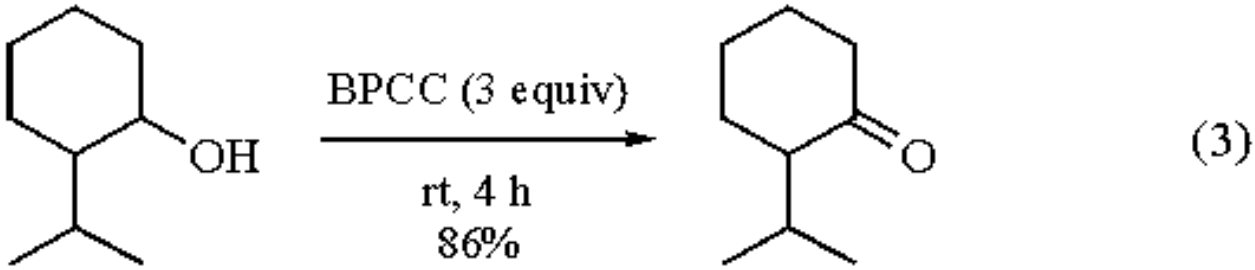

No overoxidation of aldehydes to carboxylic acids has been observed. BPCC is weaker than PCC, and thus 2-4 equiv are required for good yields.[3] However, the use of this reagent greatly simplifies purification of reaction products, since the chromium-containing byproducts are water-soluble granular materials, which can easily be removed by filtration through Celite. BPCC has proven to be efficient for the oxidation of alcohols in molecules containing acid-sensitive groups, due to the buffering effect of the 2,2´-bipyridyl system. Oxidation of citronellol gives citronellal in 89% yield without the cationic cyclization that occurs when unbuffered pyridinium chlorochromate is used.[4] BPCC can also be buffered with sodium acetate, and this is especially useful for oxidations in systems prone to epimerization (eq 4).[5,6]

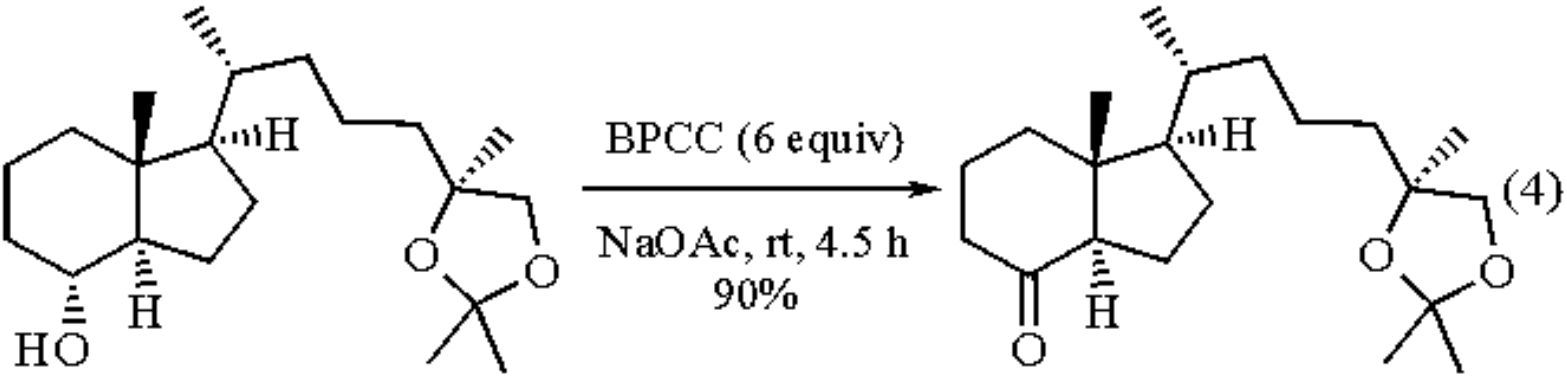

BPCC can be utilized for the oxidation of unsaturated primary alcohols in polyenes. Thus (2*E*,4*Z*)-2,4,11-dodecatrien-1-ol is smoothly oxidized in dichloromethane at rt to the corresponding unsaturated aldehyde without *E*/*Z* isomerization (eq 5).[7]

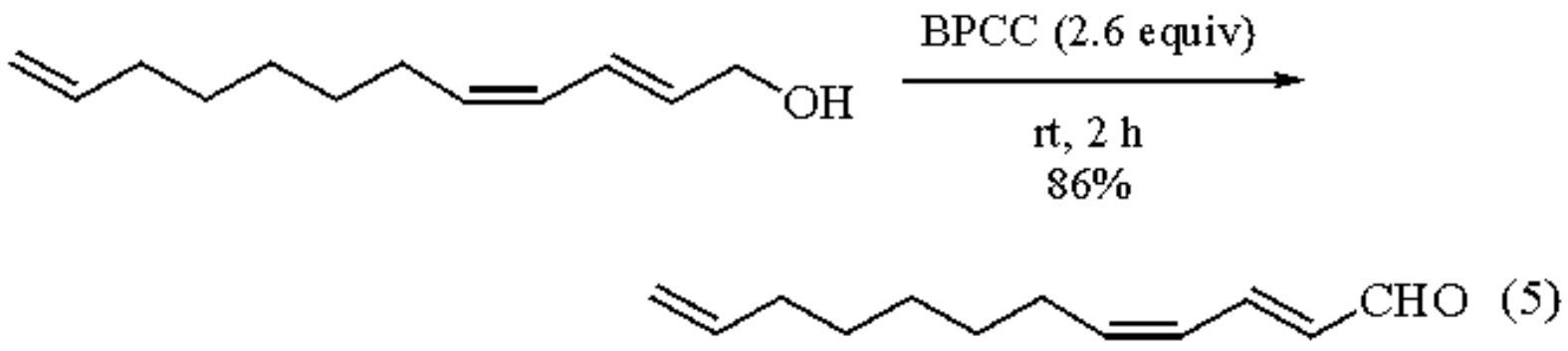

A particularly mild oxidant can be obtained by combination of BPCC with neutral ***Alumina***. 1,2-Diols undergo oxidative carbon-carbon cleavage to aldehydes when treated with BPCC alone,[8] but BPCC/alumina (1:1) converts the same 1,2-diol into an α-hydroxy ketone, albeit in moderate yield (eq 6).[9]

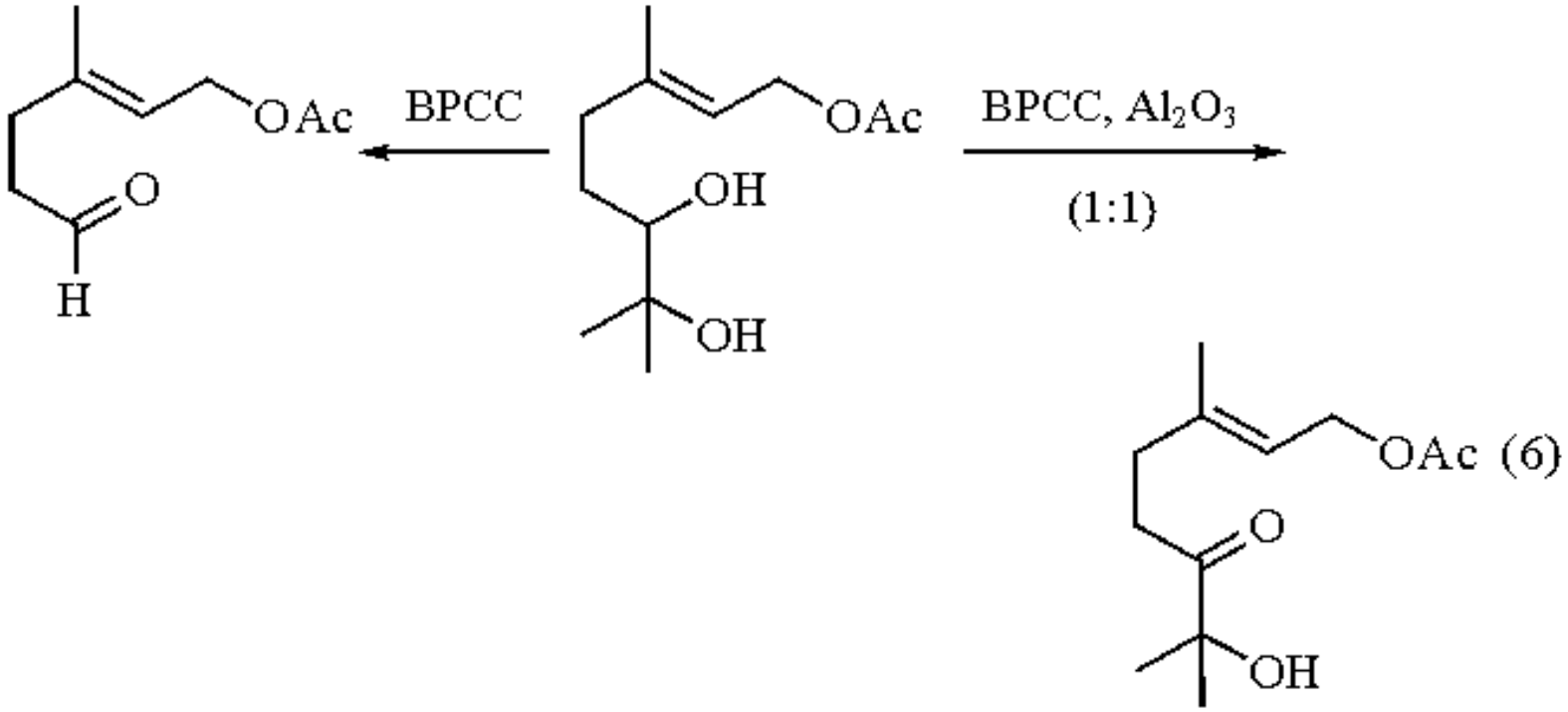

BPCC in conjuction with alumina as a buffering agent is effective in oxidizing a primary alcohol in the presence of a silyl ether protecting group (the acidic PCC reagent attacks silyl ethers). 5-(Benzyloxy)-3-[(*t*-butyldiphenylsilyl)oxy]pentan-1-ol is thus converted into the corresponding aldehyde in almost quantitative yield (eq 7).[10]

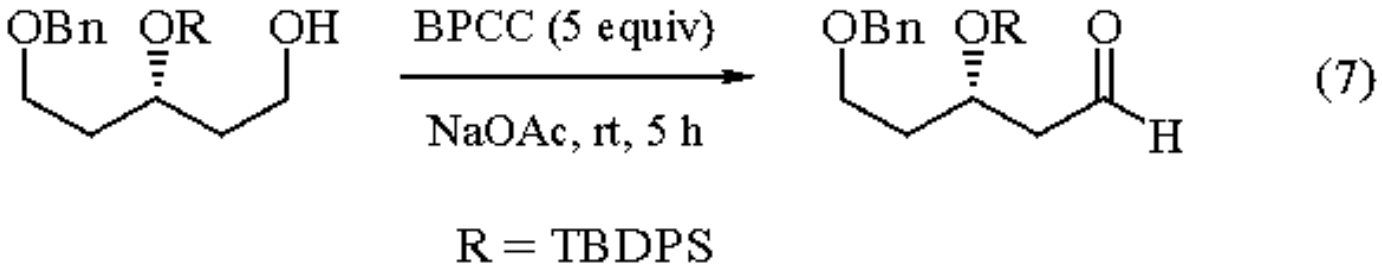

Oxidation of Benzylic Methylene.

BPCC in acetone is able to perform benzylic oxidation of hydrocarbons to aryl ketones. A large excess of oxidant must be used (16 equiv) and these reactions require 24-28 h (eqs 8 and 9).[11] PCC is also effective for these types of benzylic oxidation.

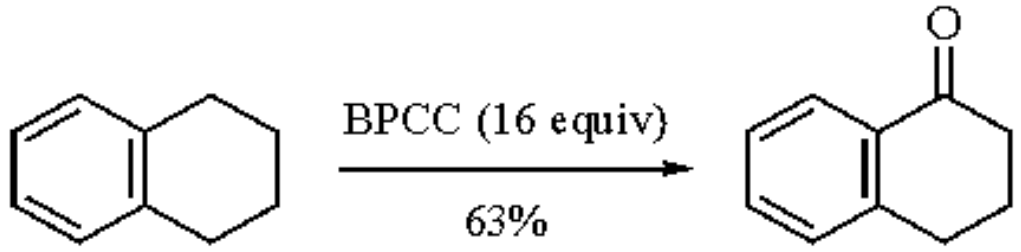

(8)

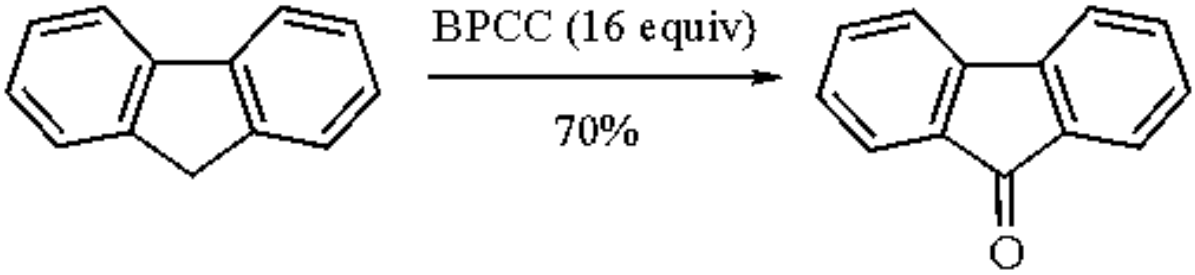

(9)

Oxidative Ring Opening of Furan.

PCC is a useful reagent in oxidative ring opening of several furans, but the reagent is less effective in the reactions of reactive furans, such as 5-methoxy derivatives. By contrast, treatment of the same substrate with BPCC effects a smooth cleavage to an α,β-unsaturated γ-keto ester (eq 10).[12]

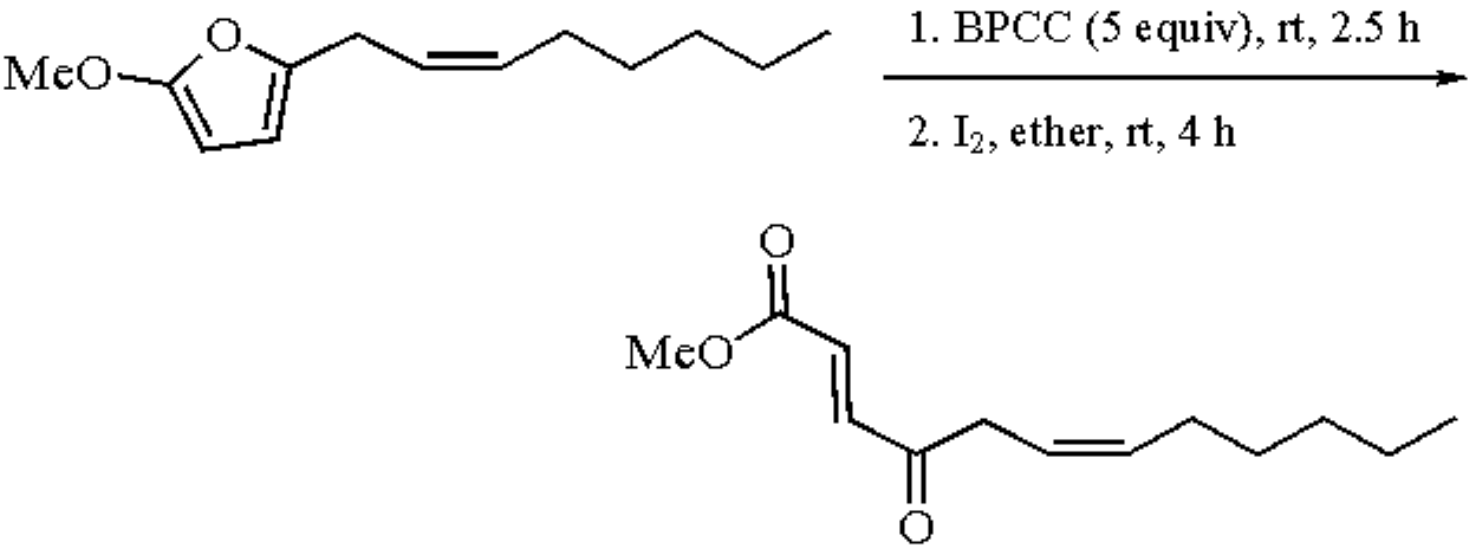

(10)

Oxidation of Sulfur-Containing Molecules.

BPCC (1 equiv) at rt can oxidize dialkyl sulfides to the corresponding sulfoxides (68-87% yield). However, dialkyl sulfones may be present as a byproduct, especially with primary alkyls (eq 11).[4]

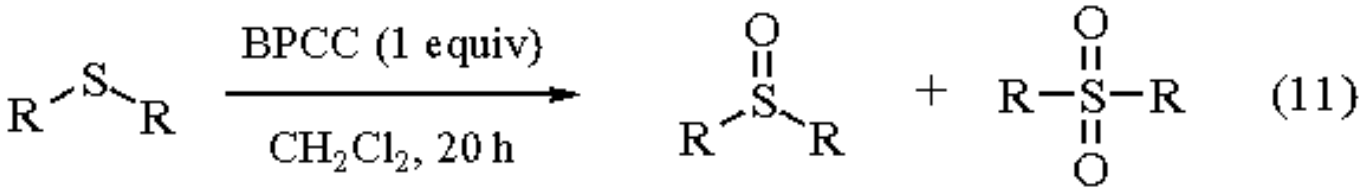

R = *n*-Pr	80%	19%
R = *n*-Bu	87%	2.8%
R = *t*-Bu	68%	0%

---

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Bis(acetonitrile)chloronitropalladium(II)[1]

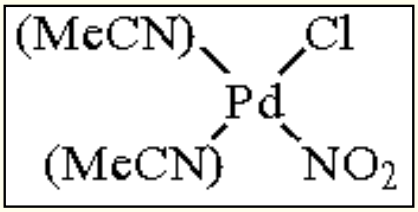

[77933-52-9] · $C_4H_6ClN_3O_2Pd$ · Bis(acetonitrile)chloronitropalladium(II) · (MW 269.98)

(reagent capable of catalyzing the oxidation of alkenes to ketones,[2] aldehydes,[3] or epoxides[4])

Physical Data: yellow solid, mp 107-109 °C.[2]

Solubility: sol chloroform, benzene, acetonitrile.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) 2.19 (s).[2]

Preparative Method: prepared from the reaction of $Pd(MeCN)_2Cl_2$ (formed from ***Palladium(II) Chloride*** and acetonitrile) with 1 equiv of ***Silver(I) Nitrite*** in ***Acetonitrile***.[2] Removal of the silver chloride after 1 h by filtration and evaporation of the solvent gives the required complex in quantitative yield.

Handling, Storage, and Precautions: the complex should be stored under an inert atmosphere. Palladium compounds are reported to be mildly toxic. Acetonitrile is highly flammable and lachrymatory.

Reactions of Alkenes.

Bis(acetonitrile)chloronitropalladium(II) can act as an efficient catalyst for the oxidation of alkenes to ketones.[2] The reaction frequently gives good yields and high selectivity, even for acid sensitive substrates such as 2-methyl-3-buten-2-ol (eq 1).[5]

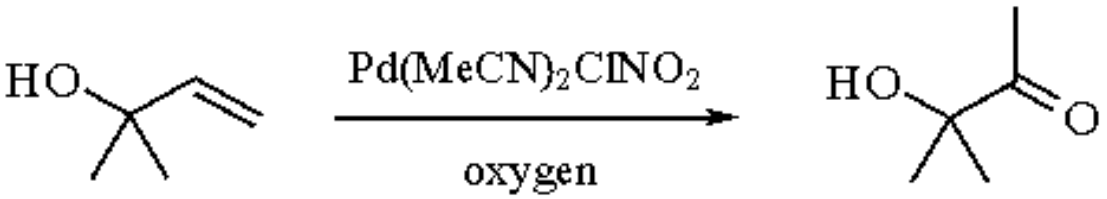

(1)

Occasionally the rate for the reaction can be too low. In such situations the rate can be dramatically increased by making the catalyst a cationic palladium complex.[6] This can be achieved by the addition of a silver salt. For instance, if

Silver(I) Hexafluoroantimonate is added to the palladium complex the rate of oxidation of oct-1-ene to octan-2-one in THF shows a 20-fold rate increase over the neutral palladium species. Under these conditions and over longer periods of time, the resultant ketone can undergo oxydehydrogenation to give the α,β-unsaturated ketone. In the case of cyclohexene the reaction can proceed even further to form phenol (eq 2).

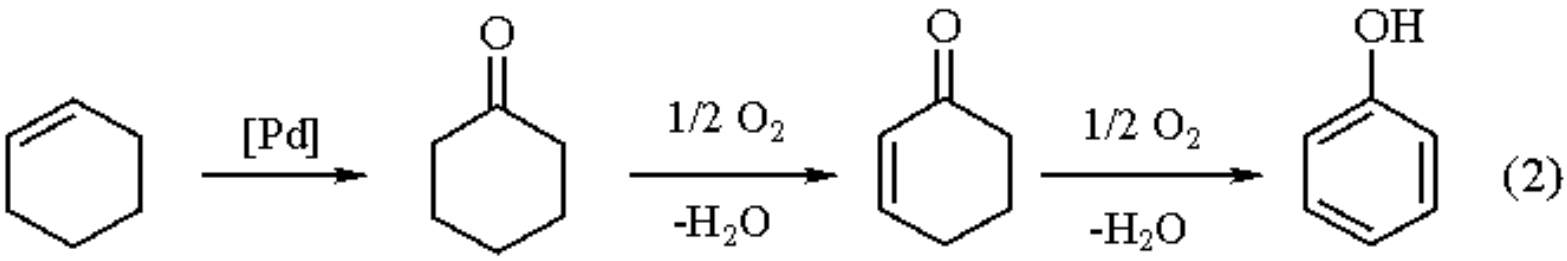

If bis(acetonitrile)chloronitropalladium(II) is treated with ***Copper(II) Chloride*** in *t*-butanol at 55 °C, a new catalyst is formed which will catalyze the oxidation of terminal alkenes to aldehydes (60-70% yields) with reasonable selectivity (eq 3).[3]

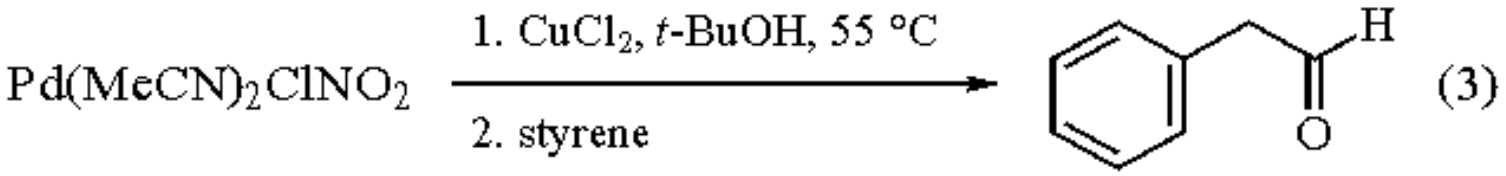

These conditions also enhance the rate of reaction and by carrying out the reaction in a 1:1 mixture of *t*-butanol and *N*,*N*-diethylpivaloylamide,[7] instead of just *t*-butanol, the selectivity can be changed to favor formation of the ketone (generally with >90% selectivity).

If the alkene being oxidized is more sterically constrained, the hydrogen migration necessary to produce the ketone becomes disfavored and an epoxide is formed instead (eq 4).[8] For this reaction to be efficient, the transformation must be carried out at low-to-moderate concentration. If the epoxidation of norbornene is attempted at high concentration, dimerization occurs to give a tetrahydrofuran adduct.[9]

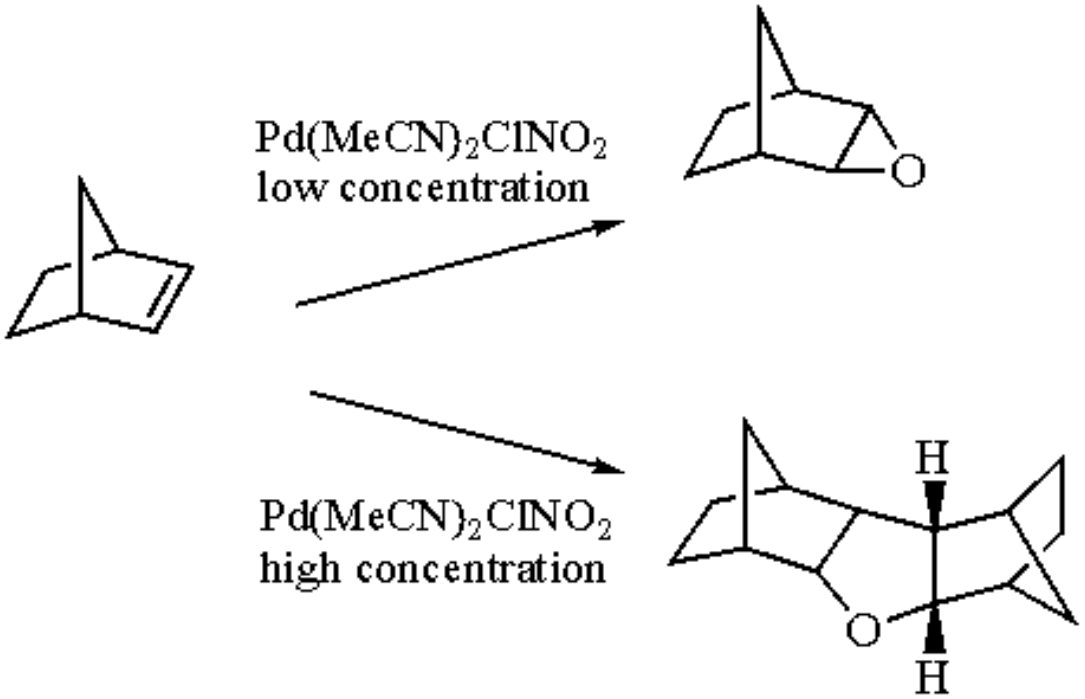

(4)

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Bis(acetonitrile)dinitropalladium(II)[1]

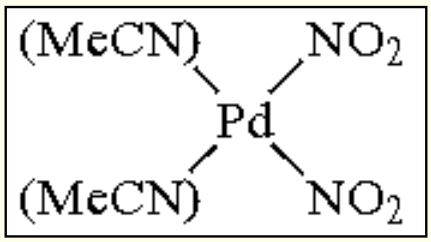

[77933-53-0] · $C_4H_6N_4O_4Pd$ · Bis(acetonitrile)dinitropalladium(II) · (MW 280.54)

(reagent capable of catalyzing the oxidation of alkenes to ketones[2,3] and the nitration of alkenes[3])

Physical Data: yellow solid.

Solubility: sol acetone, dichloromethane, acetonitrile; sparingly sol toluene.

Analysis of Reagent Purity: ^{1}H NMR (acetone-d_6): 2.16 ppm (s).[3]

Preparative Method: prepared from the reaction of $Pd(MeCN)_2Cl_2$ (formed from the reaction of ***Palladium(II) Chloride*** and ***Acetonitrile***) with 2 equiv of ***Silver(I) Nitrite*** in acetonitrile. Removal of silver chloride by filtration after 1 h and evaporation of the solvent gives the complex as a yellow solid in quantitative yield.[3]

Handling, Storage, and Precautions: darkening of the complex occurs on extended drying under vacuum or upon recrystallization from acetonitrile and toluene. The complex should be stored under an inert atmosphere. Palladium compounds are reported to be slightly toxic and acetonitrile is highly flammable and lachrymatory.

Oxidation and Nitration of Alkenes.

Bis(acetonitrile)dinitropalladium(II) has been shown to be effective for the catalytic oxidation of alkenes to ketones[2,3] or for the nitration of alkenes.[3] Which of the possible products is obtained is primarily dependent on the choice of solvent.[2] If the reaction is carried out in acetone, formation of the ketone is favored, but if toluene is used the nitration product predominates (eq 1).

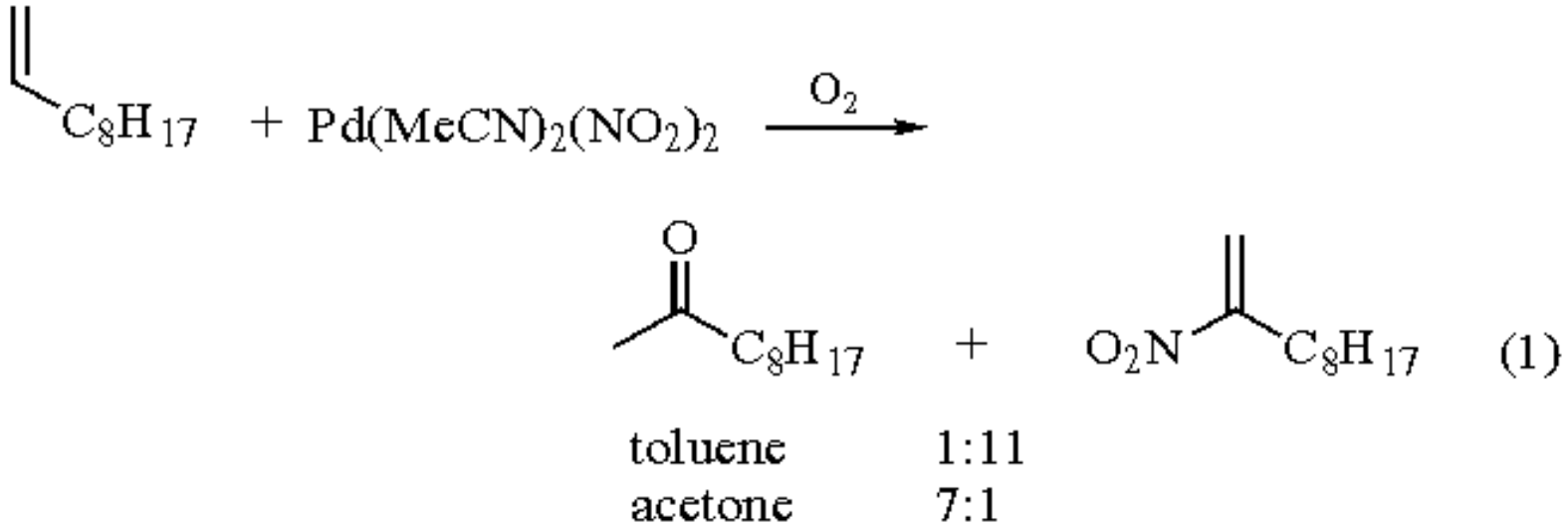

The reaction in toluene, however, takes over a week to go to completion because of the sparing solubility of the palladium complex. A more recent study has shown that the same yields and selectivity can be obtained in 5 h by carrying out the reaction in refluxing dichloromethane.[3] It should be noted that nitration with this complex is limited to terminal alkenes. Internal (such as *cis*-2-butene) and cyclic (such as cyclohexene) alkenes react with the complex to give primarily oxidized products.

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Bis(acetylacetonato)zinc(II)

$Zn(MeCOCHCOMe)_2(H_2O)$

[14024-63-6] · $C_{10}H_{16}O_5Zn$ · Bis(acetylacetonato)zinc(II) · (MW 263.60)

(catalyst for the coupling of aryl substituted allylic alcohols with β-dicarbonyl compounds,[1] and of organoboranes with organohalides;[2] selective *C*-alkylation of β-diketones;[3] preparation of amino acid derivatives, aminomaleimides,[4] and β-trichloromethyleneamino diones[5])

Alternate Name: $Zn(acac)_2$.

Physical Data: mp: anhydrous: 127 °C; monohydrate: 135-138 °C.

Solubility: dissolves readily in most organic solvents.

Form Supplied in: crystalline; widely available.

Preparative Method: from the reaction of $ZnSO_4.7H_2O$ with acetylacetone (2,4-pentanedione) and NaOH.[6]

Purification: anhydrous: sublimation, 110 °C (0.1 mmHg), recrystallized from *n*-hexane;[6] monohydrate: recrystallized from ethyl acetate.[6]

Handling, Storage, and Precautions: hygroscopic; irritating to eyes, respiratory system and skin. The monohydrate is unstable toward heat, and forms byproducts on dissolution of the hydrate. The anhydrous zinc complex is stable toward heat.

Introduction.

$Zn(acac)_2$ is a widely available catalyst which is prepared through the reaction of $ZnSO_4$, acetylacetone and NaOH, to give either the hydrate or the anhydrous zinc complex.[5] $Zn(acac)_2$ can perform two general types of reactions: (1) stoichiometric reaction at the nucleophilic carbon of the zinc acetylacetonate, and (2) catalytic reaction at the nucleophilic carbon of other β-dicarbonyl substrates.

Stoichiometric Coupling Reactions.

$Zn(acac)_2$ efficiently forms a carbon-carbon bond through the coupling of aryl substituted allylic alcohols with the

nucleophilic central carbon of the acetoacetonate ligand (eq 1).[1] Starting with either (*E*) or (*Z*) allylic alcohols, these reactions give (*E*)-γ,δ-unsaturated ketones through *syn-anti* isomerization of the intermediate π-allyl palladium species. The ***Titanium Tetraisopropoxide*** serves to (1) activate the allylic alcohol toward π-allyl complex formation via an allyl titanate, and (2) activate the coupled dicarbonyl species toward deacylation. An intractable mixture of products occurs when alkyl rather than aryl substituted allylic alcohols are used.[1] Of the various palladium catalysts investigated for this reaction, ***Tetrakis(triphenylphosphine)palladium(0)*** is effective while $PdCl_2$, $Pd(OAc)_2$, and $PdCl_2(PhCN)_2$ are not. $Zn(acac)_2$ can also be prepared in situ by mixing ***Zinc Chloride*** and acetylacetone in the presence of ***Triethylamine***, and can then be used to perform transformations similar to those previously described. This in situ preparation can also be employed to couple allylic alcohols with the zinc enolate of β-keto esters and β-diesters as well as other β-diketones (eq 2).[1]

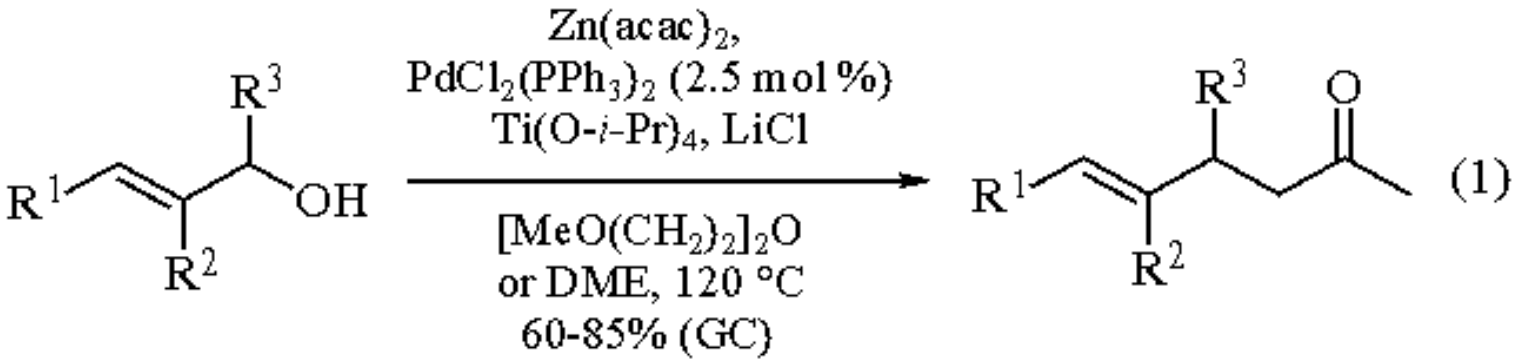

R^1 = 2-naphthyl, $R^2 = R^3 = H$; $R^1 = R^3 = H$, R^2 = Ph; $R^1 = R^2 = H$, R^3 = Ph

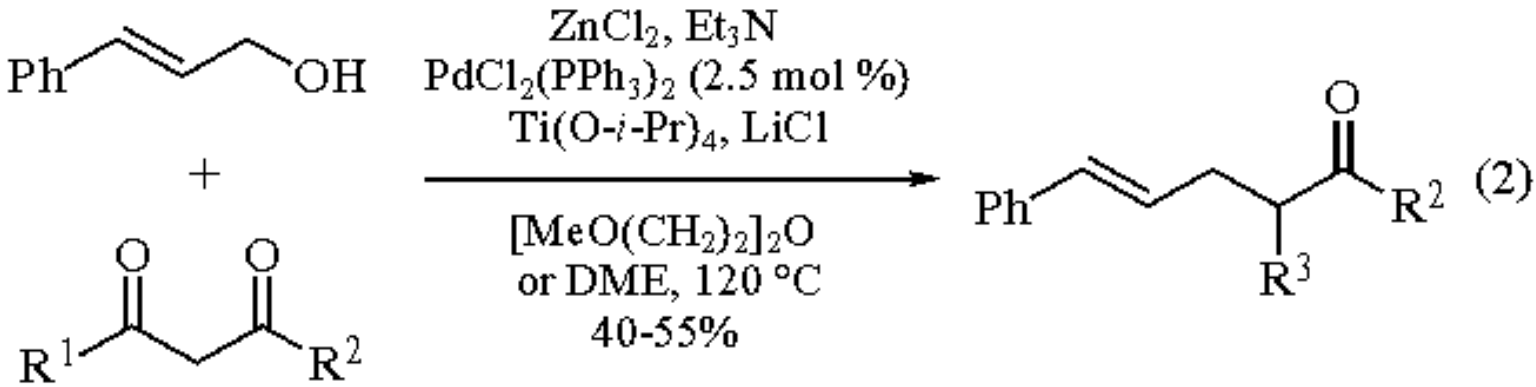

$R^1 = R^2$ = Me, $R^3 = H$; $R^1 = R^2$ = Ph, $R^3 = H$;
R^1 = Ph, R^2 = OEt, $R^3 = H$; $R^1 = R^2$ = OEt, $R^3 = CO_2Et$

Unsymmetrical ketones are produced through the carbonylative cross-coupling reaction of aryl iodides or benzyl halides with trialkylboranes mediated by $Zn(acac)_2$ and $PdCl_2(PPh_3)_2$. Typically, yields for this coupling process range from 43-82%.[2] The use of either Et_3B or *B*-alkyl-9BBN derivatives proved to be efficient in the transfer of the desired alkyl group (eq 3).[2] For activation of these coupling reactions, $Zn(acac)_2$ is superior to the acetoacetonate complexes of various other metals (i.e. Li, Mg, Al, Ca, Ti, Mn, Fe, Co, Cu, Mo, and Sn).

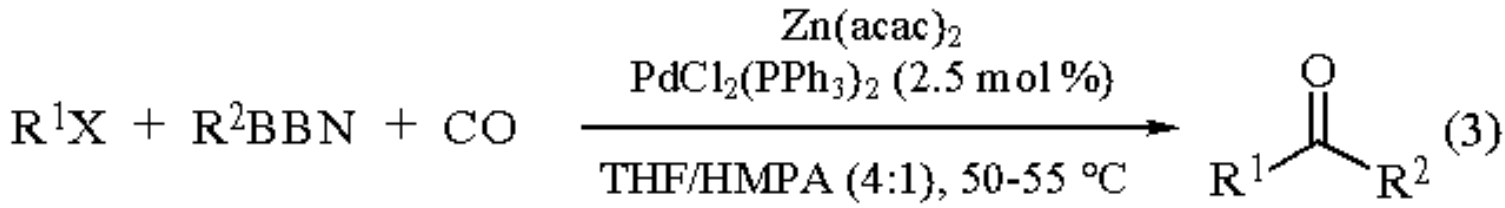

$R^1X = PhI, PhCH_2Cl; R^2 = \text{primary or secondary alkyl}$

Selective *C*-alkylation occurs through the addition of various S_N1-type organohalides to the nucleophilic carbon of the $Zn(acac)_2$ (eq 4).[3] This transformation provides yields comparable to those obtained with $Co(acac)_2$, but overall these reagents are less effective than $Co(acac)_3$.[3]

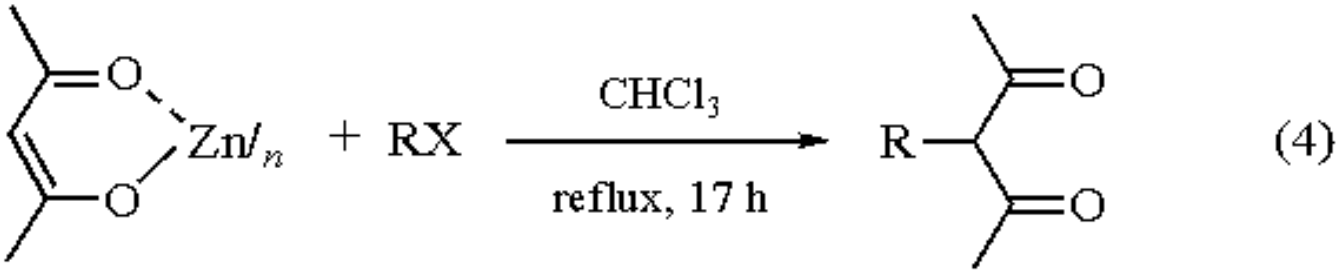

$RX = PhCH_2Br, PhCH(Me)Br, Ph_2CHBr, Ph_3CCl$, 1-bromoadamantane

Catalytic Reactions with β-Dicarbonyl Compounds.

Unsaturated α-amino acid derivatives are obtained through the $Zn(acac)_2$ catalyzed reaction of ethyl cyanoformate with β-diketones, β-keto esters, and β-diesters (eq 5).[4] Similar reactions with β-keto amides result in the formation of cyclic aminomaleimides (eq 6).[4]

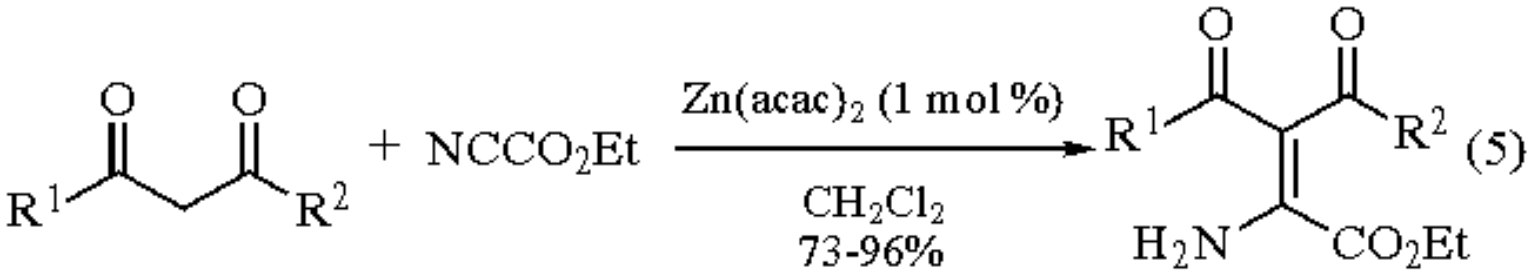

$R^1 = R^2 = Me; R^1 = R^2 = Ph; R^1 = Me, R^2 = OEt; R^1 = R^2 = OEt$

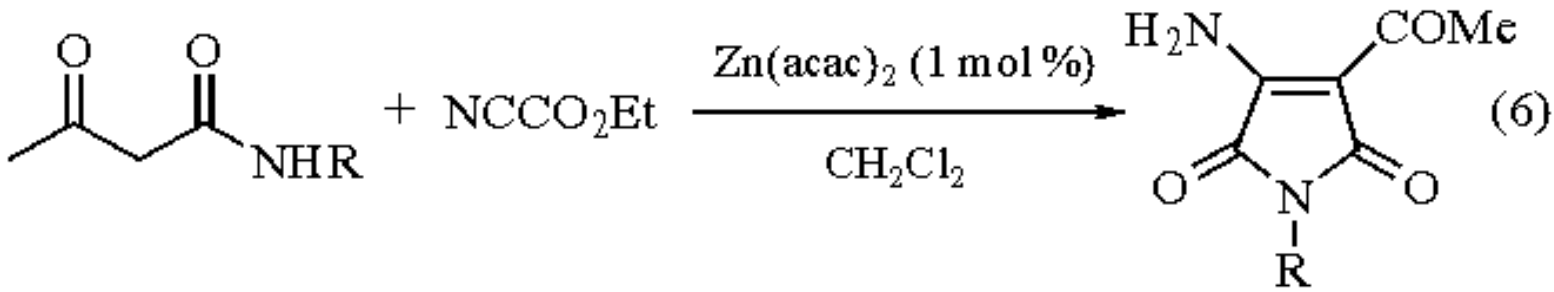

R = H, 52%; R = Bn, 90%

$Zn(acac)_2$ also effectively promotes the addition of β-diketones or β-keto esters to trichloroacetonitrile, giving β-trichloromethyleneamino diones in 40-90% yields.[5] The addition of β-dicarbonyl compounds to cyanogen can be achieved with the use of either $Cu(acac)_2$ or $Zn(acac)_2$ (eq 7). These metal catalyzed reactions of cyanogen with β-keto amides give different regioselectivity when compared to catalysis by the ethoxide ion.[7]

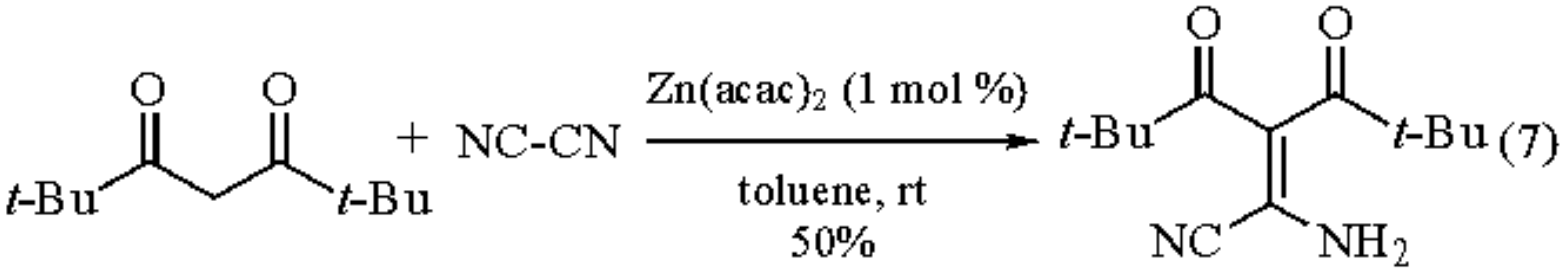

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Bis(acrylonitrile)nickel(0)[1]

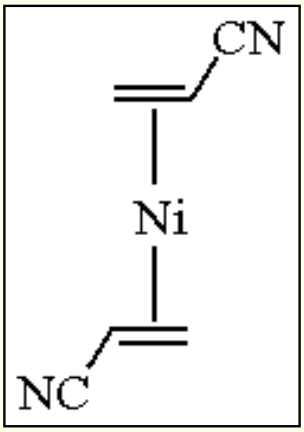

[12266-58-9] · $C_6H_6N_2Ni$ · Bis(acrylonitrile)nickel(0) · (MW 164.82)

(source of nickel(0) useful for the oligomerization of strained alkanes and alkenes,[2] and the cyclooligomerization of alkynes[3])

Alternate Name: $Ni(AN)_2$.

Physical Data: mp 105 °C dec (N_2). The structure of this complex has been thoroughly investigated.[4]

Solubility: sol pyridine, *n*-butylamine. Only sparingly sol most other organic solvents.

Analysis of Reagent Purity: IR: ν_{CN} 2200, $\nu_{C=C}$ 1446 cm^{-1}.[1]

Preparative Methods: under a CO_2 condenser, 2.6 g ***Tetracarbonylnickel*** (caution: extremely toxic, volatile) was refluxed with 25 mL of freshly distilled ***Acrylonitrile*** for 4 h with collection of evolved CO gas. The resultant bright red solid was collected under N_2, washed with methanol and ether, and dried.[5]

Handling, Storage, and Precautions: highly oxygen sensitive: pyrophoric. Special inert-atmosphere techniques must be used.[6] Should be stored at 0 °C.

Oligomerization of Strained Alkanes and Alkenes.

$Ni(AN)_2$ has been shown to react with strained alkanes by oxidative addition of nickel(0) to C-C bonds. These organometallic complexes can go on to form new C-C bonds in the presence of electron-deficient alkenes. Bicyclo[2.1.0]pentane reacts with a catalytic amount of $Ni(AN)_2$ in the presence of acrylonitrile or methyl acrylate to give mixtures of norbornane products and a cyclopentene (eq 1).[7] The norbornane products are formed by insertion of

the activated alkene into the initially formed organometallic complex, followed by reductive elimination of a bridged nickelacyclohexane intermediate. β-Hydride elimination of this intermediate leads instead to the cyclopentene product. Bicyclo[1.1.0]butanes also react to give allylcyclopropanes (see also ***Bis(1,5-cyclooctadiene)nickel(0)***).[8] In addition, the highly-strained 1,8-bishomocubane system has been isomerized in the presence of this catalyst.[9]

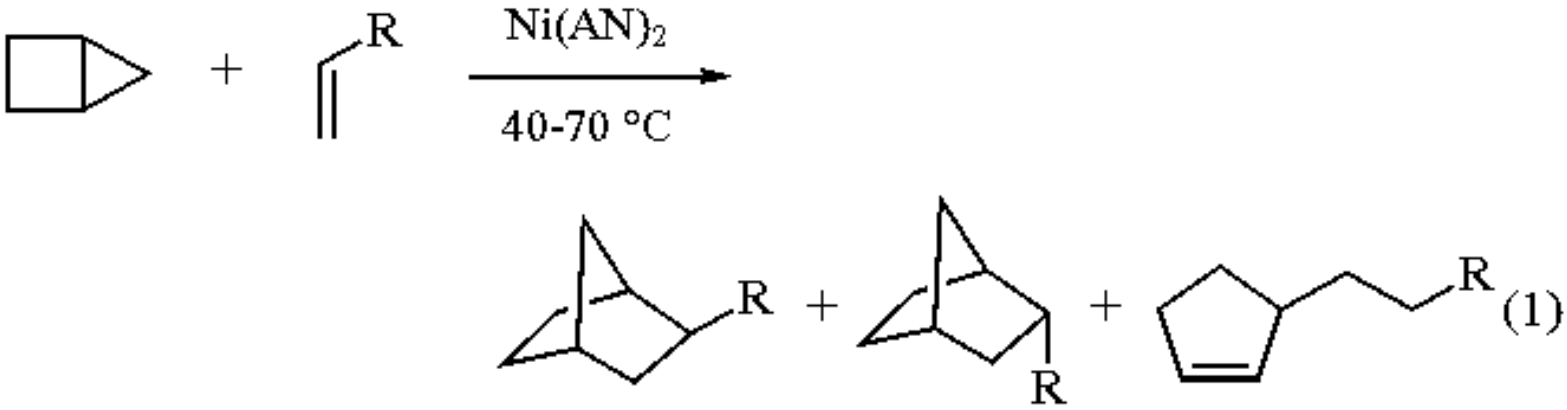

R = CN	47%	28%	16%
R = CO_2Me	33%	33%	22%

Quadricyclane (**1**) is isomerized to norbornadiene (**3**) in the presence of $Ni(AN)_2$ in 87% yield (eq 2).[10] The reaction proceeds through organonickel intermediate (**2**), and indeed, addition of an electron-deficient alkene to pure samples of either (**1**) or (**3**) along with the nickel catalyst gives rise to the same adduct (**4**). This [2 + 2 + 2] cycloaddition of norbornadiene is facilitated by the addition of phosphorus ligands, and the steric properties of these ligands influence the stereoselectivity of the reaction (see also ***Dicyanobis(triphenylphosphine)nickel(II)***).[11] Norbornene derivatives can be induced to participate in [2 + 2] cycloadditions,[12] and methylenecyclopropanes react with alkenes to give methylenecyclopentanes (see also ***Bis(1,5-cyclooctadiene)nickel(0)***).[13]

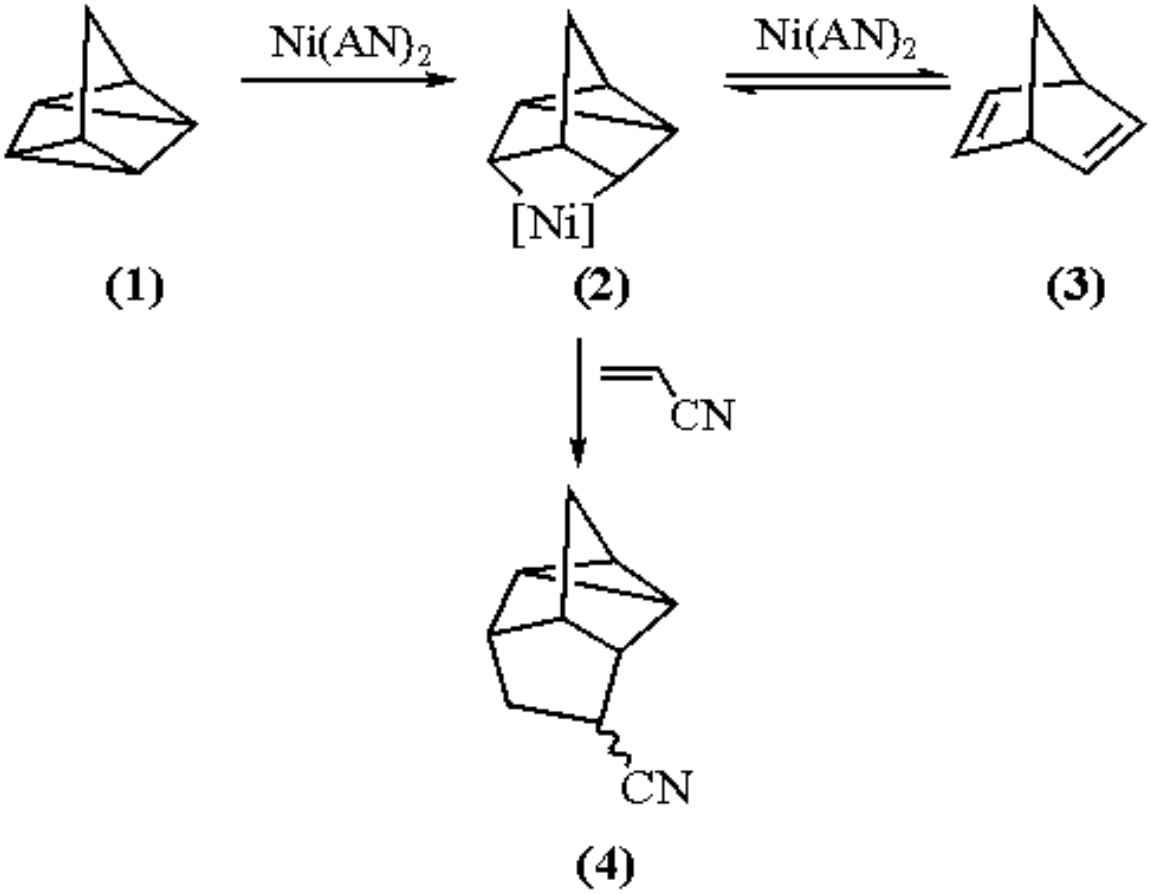

(2)

Cyclooligomerization of Alkynes.

In the presence of a catalytic amount of $Ni(AN)_2$, alkynes can be cyclotrimerized to give benzene derivatives (see also ***Bis(1,5-cyclooctadiene)nickel(0)***).[14] Labeling studies have shown that the [2 + 2 + 2] cyclotrimerization of 2-butyne does not take place through a cyclobutadiene intermediate, but probably occurs via a nickelacyclopentadiene species.[15] When acetylene is used in this reaction, cyclotetramerization occurs to give cyclooctatetraene (see also ***Tetrakis(trichlorophosphine)nickel(0)***).

Other Uses.

This complex can also be used to catalyze the Meerwein arylation reaction[16] between activated alkenes and arenediazonium salts.[17] Acrylonitrile may be selectively dimerized to form 1,4-dicyanobutenes when phosphorus ligands are present.[18] Nitriles are converted into methyl ketones using $Ni(AN)_2$ and ***Trimethylaluminum***.[19]

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Bis(allyl)di-μ-bromodinickel

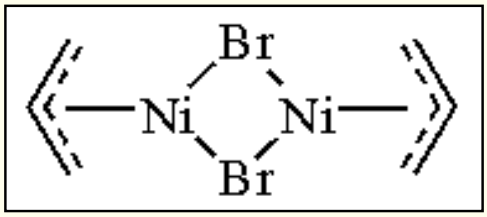

[12012-90-7] · $C_6H_{10}Br_2Ni_2$ · Bis(allyl)di-μ-bromodinickel · (MW 359.33)

(reacts with organic halides by a nickel-radical chain reaction; couples allyl groups, forming macrocycles; generates alcohols from carbonyls)

Physical Data: red solid; sublimation point 80 °C; dipole moment 1.31 D.[1]

Solubility: sol benzene, DMF, and other organic solvents.

Preparative Method: the reagent may be prepared from allyl bromide and $Ni(CO)_4$ or $Ni(cod)_2$ as described below.

Purification: by sublimation.

Handling, Storage, and Precautions: is air and moisture sensitive. It is generally prepared and used in situ. See entries for ***Allyl Bromide***, ***Tetracarbonylnickel***, and ***Bis(1,5-cyclooctadiene)nickel(0)*** for further information.

Synthesis and General Considerations.

The reagent was originally generated from the reaction of $Ni(CO)_4$ with allyl bromide (eq 1).[1] Later, it was found that $Ni(cod)_2$ also works well as the nickel source in the synthesis of (allyl)nickel halides.[2]

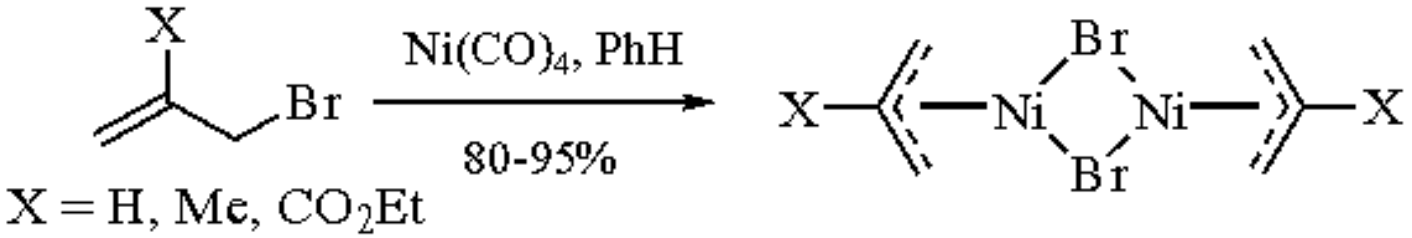

(1)

The geometry of the complex consists of two allyl groups bonded through their π-systems to the nickel atoms. Because the center core of Ni_2Br_2 is planar, there are two possible geometries for the complex. In one, the center carbons of the allyl groups are on the same side (*cis*) of the Ni_2Br_2 plane, and in the other, they are on opposite sides (*trans*). Typically, the mixture of these two complexes is used for all subsequent reactions.

The synthesis of the allylnickel halide complex is not restricted to allyl bromide itself. A variety of methyl substituted and cyclic allyl derivatives will form complexes. In contrast to the better known allylpalladium complexes, which are electrophilic, these allylnickel halide complexes are nucleophilic. With unsymmetrically substituted allyl complexes, it is usually the less substituted of the carbons which forms the bond to the electrophile.[3]

Reactions with Alkyl, Aryl, and Vinyl Halides.

Allylnickel halide complexes react with a large variety of organic halides, including primary, secondary, tertiary, vinyl, and aryl compounds, and will do so smoothly, even in the presence of many common functional groups, including alcohols and esters (eq 2). The reactivity order for the X group is I > Br >> Cl. These reactions work only in polar coordinating solvents such as DMF or HMPA.[3-6]

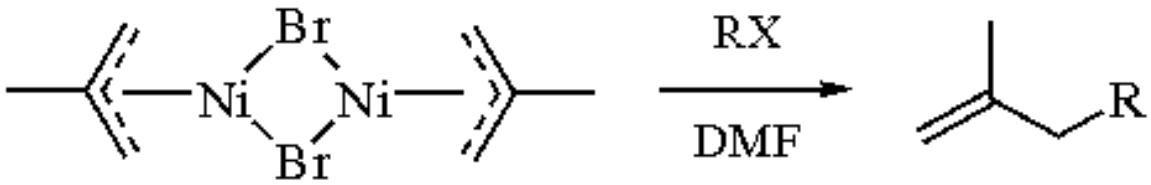

(2)

RX = $PhCH_2Br$, 91%; cyclohexyl iodide, 91%; $H_2C{=}CHBr$, 70%; PhI, 98%

Initially it was believed that a coordinating solvent was needed because the first step is cleavage of the dimer, with the solvent filling-in the now vacant coordination site. Subsequent steps of this reaction are oxidative addition to the RX bond, which proceeds smoothly regardless of the substitution pattern of the R group, followed by reductive elimination of the R-allyl product.[3]

More recently, it has been shown that the mechanism is much more complicated.[7] The reaction goes by a radical chain process; however, it is a nickel and not a carbon radical which is the chain carrying species. This mechanism nicely explains the observed initiation by light, heat, or a reducing agent, the inhibition by an electron acceptor, the reactivity of a large variety of different organic halides, and the racemization observed for secondary halides.

Reaction with Allyl Halides.

One of the more common reactions of an allylnickel halide complex is with an allyl halide to generate a 1,5-hexadiene. A variation of this reaction has been used to couple two allyl groups together to form a macrocyclic ring system (eq 3).[8] This method has proven successful for rings as large as 18. In addition, the reaction

conditions are compatible with a large variety of substitution patterns and functional groups.

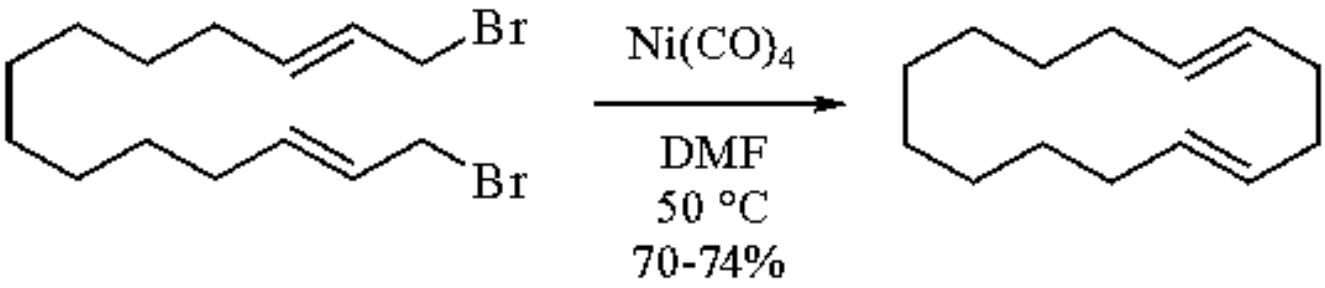

(3)

Reaction with Carbonyls.

The allylnickel halide complex will attack an aldehyde or a ketone to generate an alcohol (eqs 4 and 5).[9] However, it will not attack an ester or nitrile. The reaction with a quinone generates an allyl-substituted quinone product, through an initial Michael addition to the α,β-unsaturated system.[10]

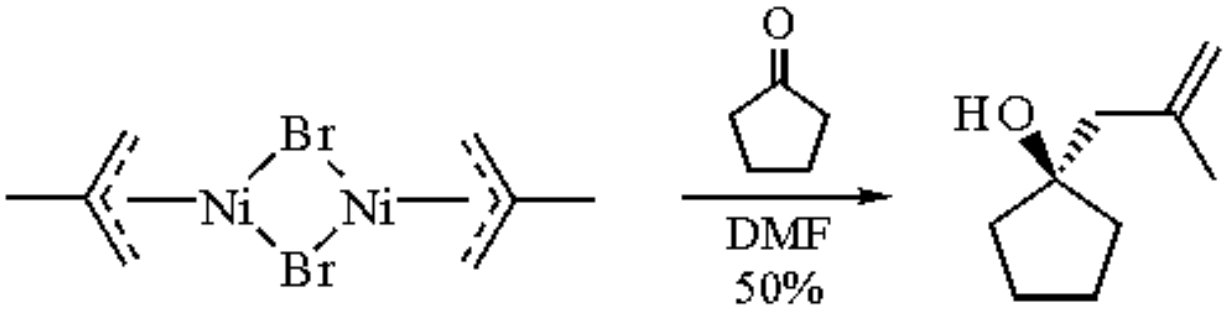

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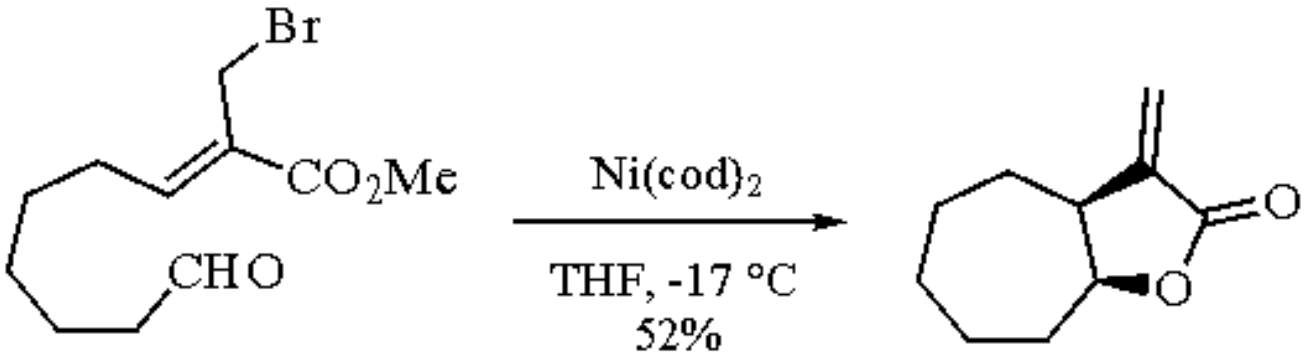

(5)

(via π-allylnickel complex)

Other Reactions.

Tetracarbonylnickel, an allyl bromide derivative, and an alkyne react to generate a cyclopentenone derivative (eq 6).[11,12] It is believed that these reactions go through an allylnickel halide complex as an intermediate.

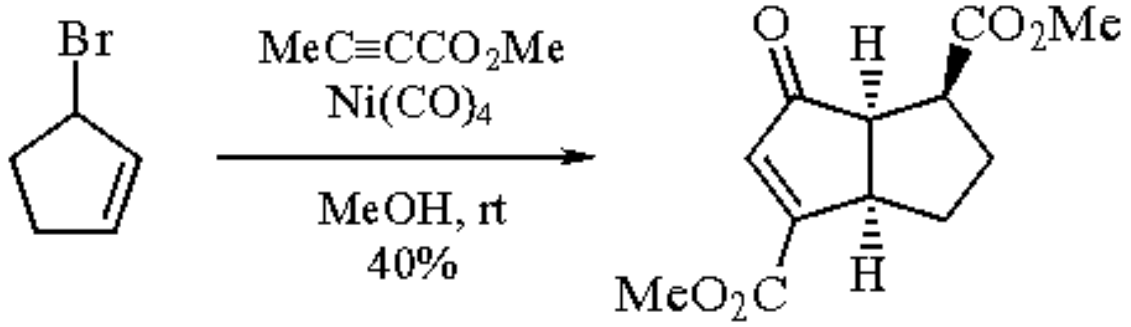

(6)

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Bis(allyl)di-μ-chlorodipalladium[1]

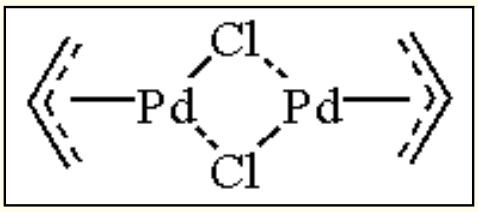

[12012-95-2] · $C_6H_{10}Cl_2Pd_2$ · Bis(allyl)di-μ-chlorodipalladium · (MW 365.89)

(prototype substrate for π-allylpalladium reactions,[1] catalyst precursor for allylic alkylations,[1] cross-coupling reactions,[1] diene dimerization,[2] addition of nucleophiles to dienes,[3] conversion of allyl amines to dienes,[4] siloxycyclopropane cleavage,[5] and decomposition of diazo compounds[6])

Physical Data: mp 160 °C.

Solubility: sol benzene, $CHCl_3$, acetone, methanol.

Form Supplied in: pale yellow crystals; widely available.

Analysis of Reagent Purity: IR;[7] MS;[8] ^{13}C NMR;[9] ^{1}H NMR.[10]

Preparative Methods: numerous routes are available.[1] Preferred methods are: reaction of propene with ***Palladium(II) Trifluoroacetate***, followed by counterion exchange with chloride;[11] reaction of ***Potassium Tetrachloropalladate(II)*** with ***Allyl Chloride*** in water;[12] reaction of Na_2PdCl_4, allyl chloride, and CO in water.[13]

Prototype Substrate for π-Allylpalladium Reactions.

Examples of the addition of nucleophiles to bis(allyl)di-μ-chlorodipalladium (**1**) and the homologous unsymmetrical di-μ-chlorobis(crotyl)dipalladium (**2**) are shown below. The latter is included to illustrate aspects of the regiochemistry of nucleophilic attack. The addition of ligands, typically phosphines, is generally required to enhance the electrophilicity of these reagents.[14]

Carbon nucleophiles of pK_a 10-20 have been most studied and often work best with these substrates (eq 1),[1,15] but enamines,[1] cyclopentadiene anions,[1q] enolates (eq 2),[1,16] organotin, -thallium, -zinc, -aluminum, -lithium, and -zirconiums,[1q] as well as Grignards (eq 3)[1,17] and borates,[18] also add to π-allylpalladium complexes. Heteroatom nucleophiles also add successfully; these include amines (eq 4),[1,19] amides,[1q] azides,[1q] magnesium amides,[1q]

sulfonamides,[1q] alcohols,[1q] acids (eq 5),[1,20] nitrites,[1q] sulfinic acids,[1q] thiols,[1q] phosphines,[1q] and phosphites.[1q] Limited use of transition metal nucleophiles is also known.[21]

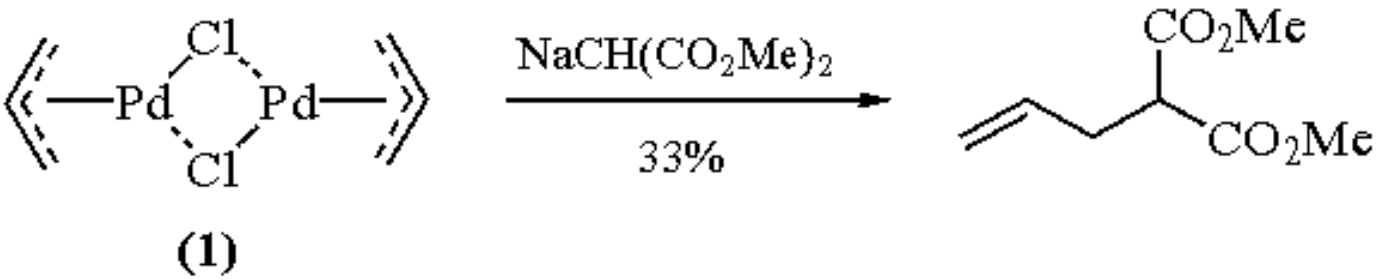

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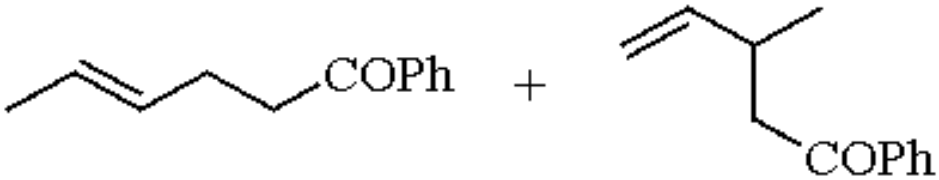

51% 20% (2)

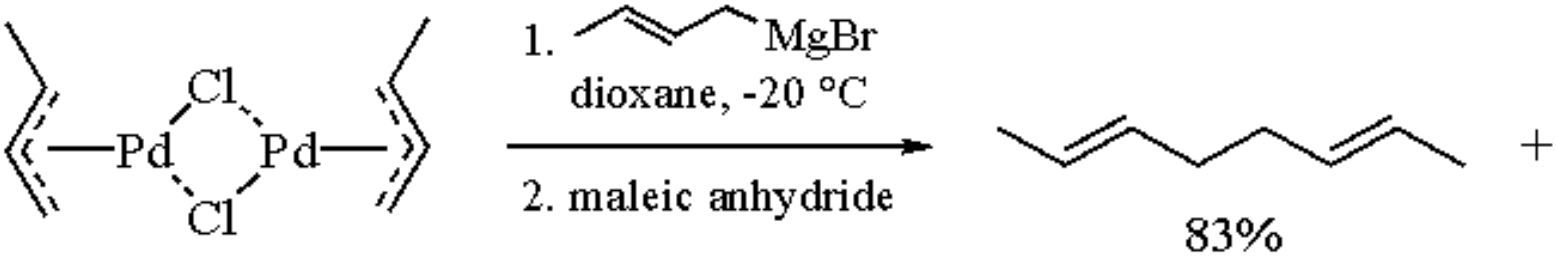

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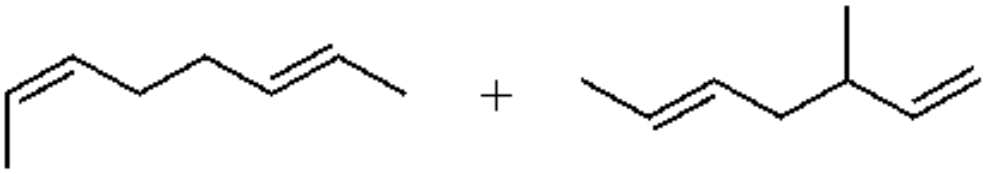

14% 2% (3)

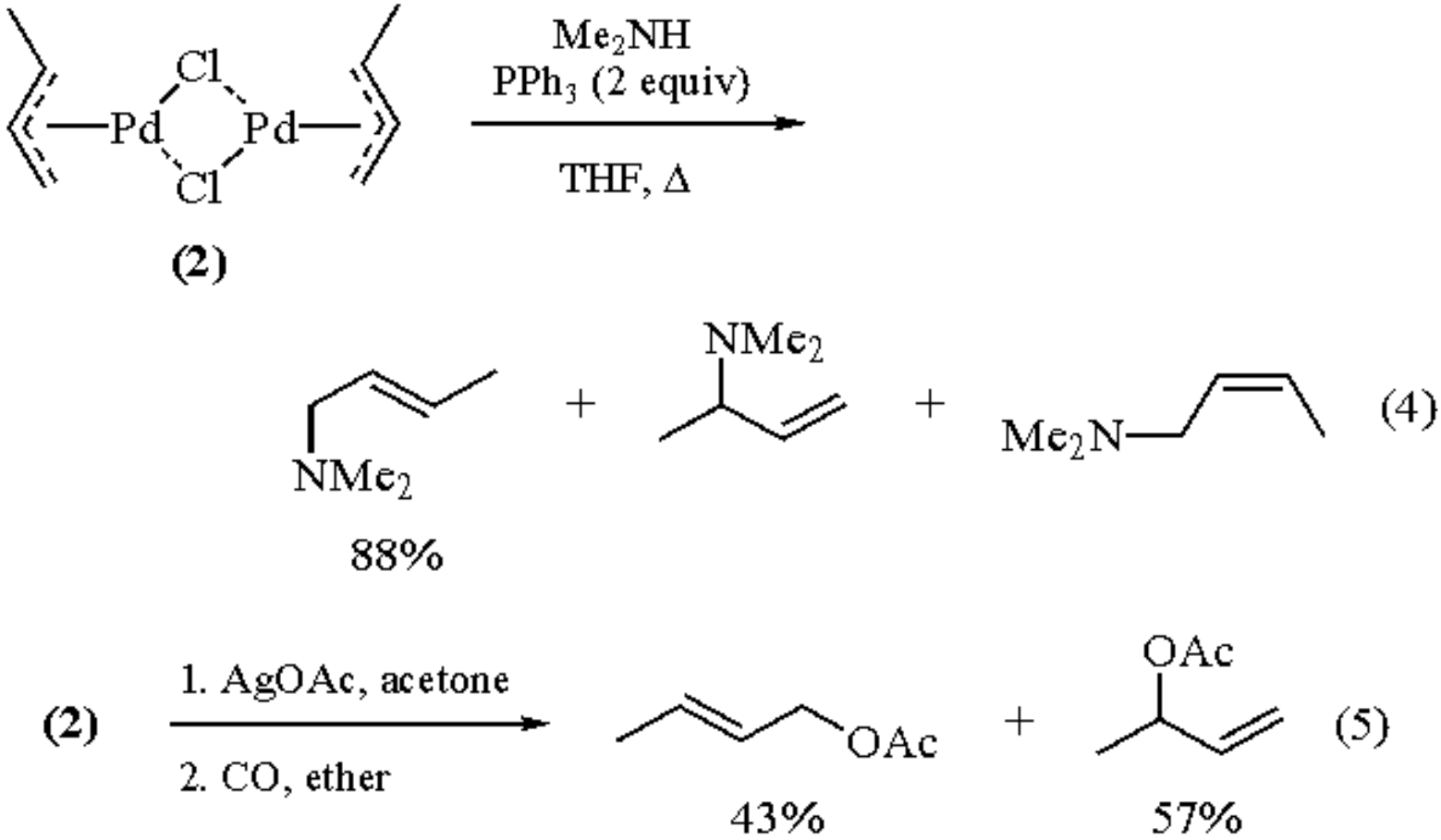

The use of ***Hexamethylphosphoric Triamide*** and ***Triethylamine*** as ligands in place of the usual phosphines in the addition of ester enolates to (**1**) results in the formation of cyclopropanes via the unusual initial attack at the central carbon atom (eq 6).[22] The process is very limited with respect to nucleophile, however, as only branched ester enolates produce a cyclopropane. ***N,N,N´,N´-Tetramethylethylenediamine*** and ***Carbon Monoxide*** as ligands also promote central carbon attack by ester enolates.[23]

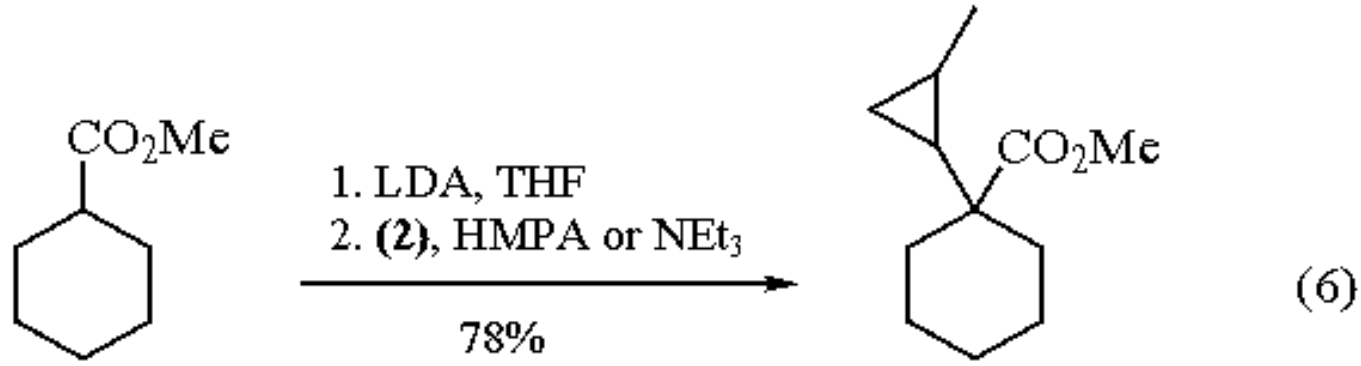

The attack by nucleophiles on π-allylpalladium complexes is generally a stereospecific process, but whether the reaction occurs with retention or inversion with respect to the metal is a complex issue, and strongly depends on the nature of the nucleophile employed.[24]

Insertion Reactions.

CO can be inserted into π-allylpalladium dimers to prepare various β,γ-unsaturated carboxylic acid derivatives (eq 7).[25,26] This process is greatly facilitated by the presence of carboxylate anions. The bridged acetato complex (**3**) works equally as well as (**2**) in this reaction. Similarly, isocyanides,[27,28] CO_2,[29] and SO_2[1q] can also be inserted into these complexes.

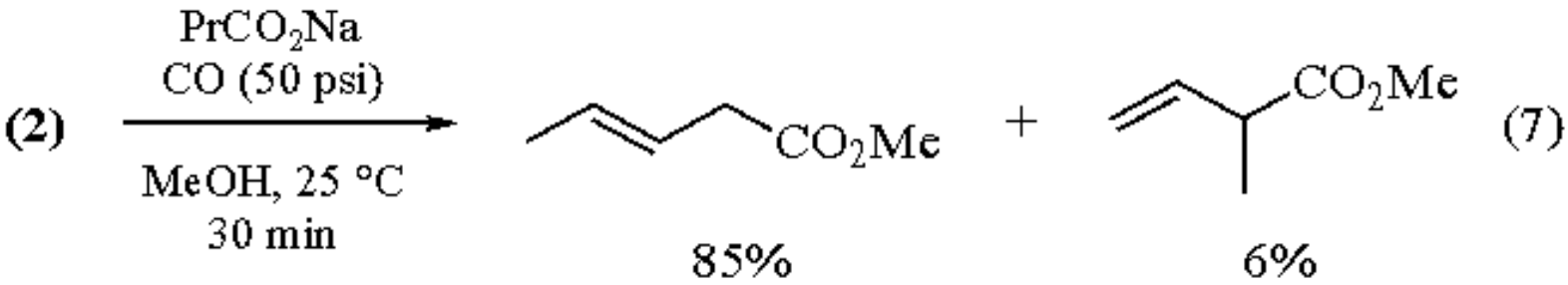

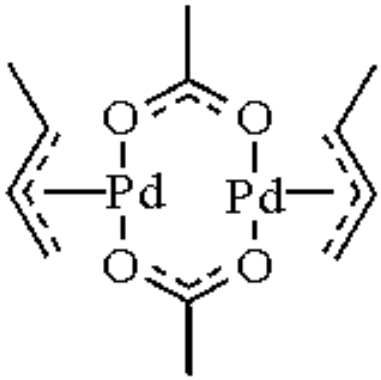

(3)

π-Allylpalladium dimers can also react with alkenes (eq 8),[30] dienes,[31] and allenes[1] by an insertion process.

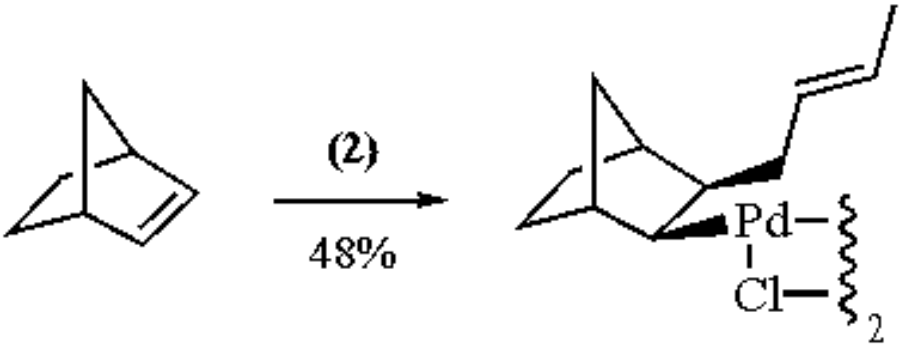

(8)

Reduction.

A variety of metal hydride reducing agents can be employed to reduce π-allylpalladium dimers. These include ***Sodium Borohydride***, ***Sodium Cyanoborohydride***, ***Lithium Triethylborohydride***, ***Lithium Aluminum Hydride***, ***Lithium Tri-t-butoxyaluminum Hydride***, polymethylhydrosiloxane, and R_3SiH (eq 9).[1q,32] Formic acids and formate salts also reduce π-allylpalladium complexes to the corresponding alkenes by the liberation of CO_2 and the in situ formation of a Pd hydride.

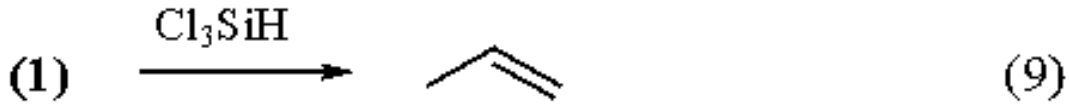

The use of stoichiometrically generated π-allylpalladium dimers such as (**1**), (**2**), and (**3**) has largely been obviated by the discovery that the crucial allyl intermediate can be generated catalytically from PdL_4 and an allyl-X compound, where X is a wide variety of leaving groups (see ***Tetrakis(triphenylphosphine)palladium(0)*** for example).[1]

Use as a Catalyst Precursor. Allylic alkylations.

The allylpalladium chloride dimer (**1**) is a particularly useful catalyst precursor for a variety of Pd-mediated processes and possesses a number of significant advantages over PdL_4 complexes. For example, the dimer (**1**) can be employed in conjunction with a ligand L and be subjected to designed in situ reduction to yield a Pd^0-L catalyst. A catalyst generated in this fashion allows rapid access to a great spectrum of Pd^0-L species by obviating the need for individual syntheses of each PdL_4 complex. In addition, the ratio of Pd/L, which is often crucial in defining catalyst performance, can be simply varied. Such variation is obviously not possible with a PdL_4 complex.

The use of (**1**) as a catalyst precursor in a classic π-allyl alkylation is shown in eq 10 as a key step in the preparation of a carbanucleoside, carbovir.[33]

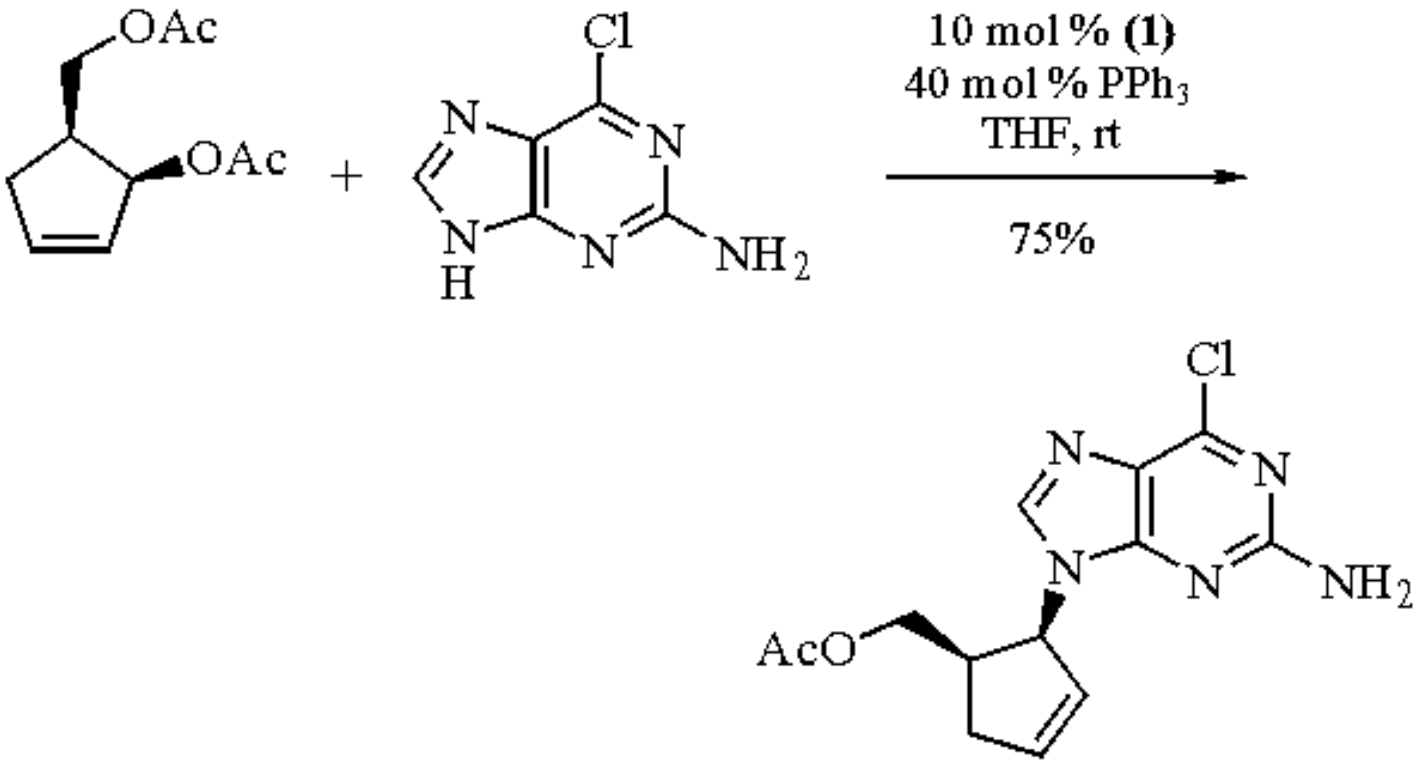

(10)

Significant use of (**1**) as a Pd^0 catalyst precursor has come in the area of asymmetric π-allylpalladium alkylations.[34] A large number of optically active ligands, L*, have been screened in the palladium-catalyzed alkylation step. Particularly promising L* ligands for this reaction include: phosphinoaryldihydrooxazoles (eq 11);[35] ferrocenylphosphines appended with a side chain designed to interact with the incoming nucleophile (eq 12);[36]

phosphinooxazoles;[37] thienyloxazoles;[38] bis-oxazoles;[39] 5-aza-semicorrins;[40] and BINAP.[41]

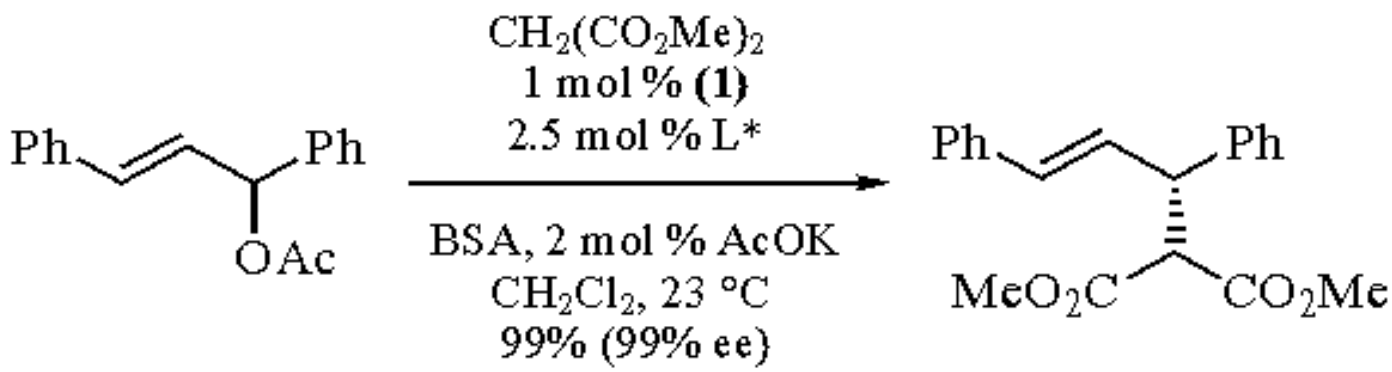

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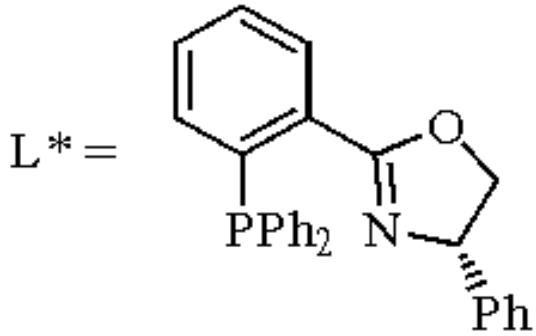

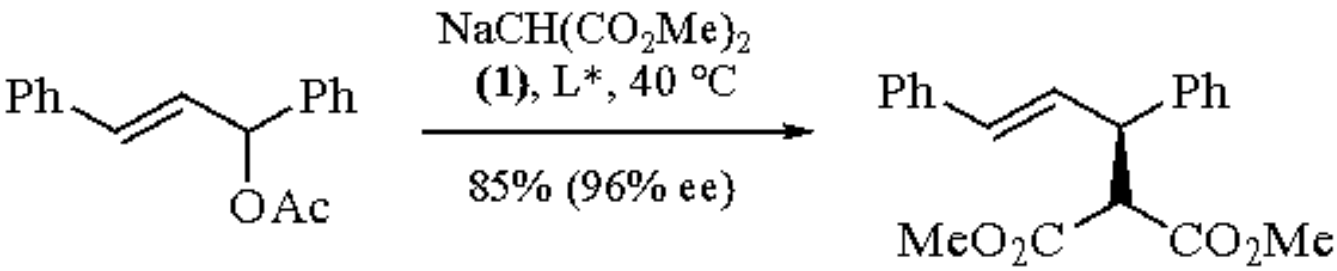

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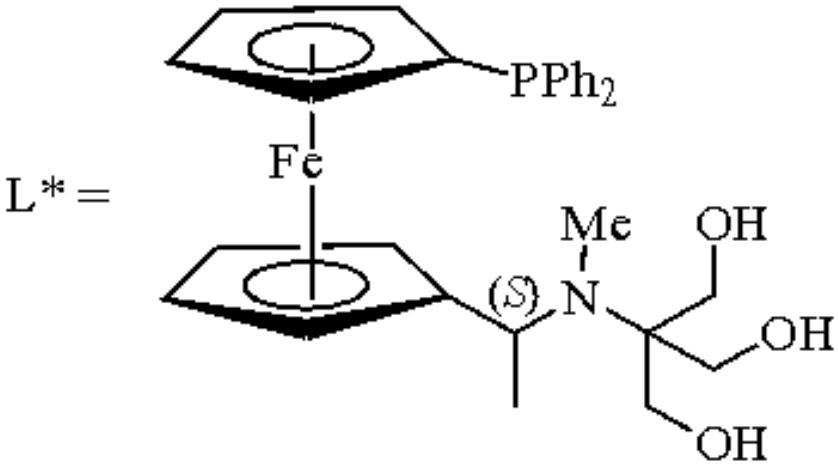

The chloro dimer (**1**) has also been employed in Pd-catalyzed asymmetric hydrosilation of alkenes (eq 13).[42]

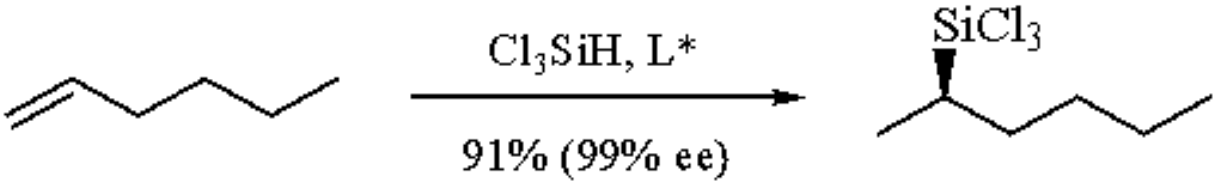

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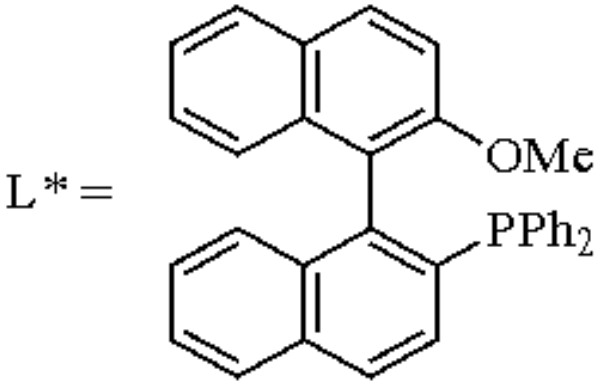

(*S*)

Cross-Coupling Reactions.

The transition metal catalyzed cross-coupling reaction of an organometallic nucleophile and an organic halide constitutes an important carbon-carbon bond forming process. Organometallic compounds of zinc, aluminum, boron, zirconium, magnesium, mercury, copper, tin, silicon, and palladium have all been employed as coupling partners. The dimer (**1**) has served as an excellent catalyst for this process, as illustrated below. The coupling of organotin (eq 14)[43,44] and -zirconium (eq 15)[45] reagents with allyl halides has employed a combination of (**1**) and maleic anhydride to effect cross coupling. The fluoride promoted, Pd-catalyzed, cross coupling of organosilanes and organohalides appears to be a particularly mild and selective way to achieve this reaction. This process allows coupling of alkenylsilanes with alkenyl and allyl halides (eq 16),[46,47] aryl- and heteroarylsilanes with aryl and heteroaryl iodides (eq 17),[48,49] alkyl silicates with aryl halides (eq 18),[50] and ethynyl- and allylsilanes with vinyl, aryl, and allyl halides.[51]

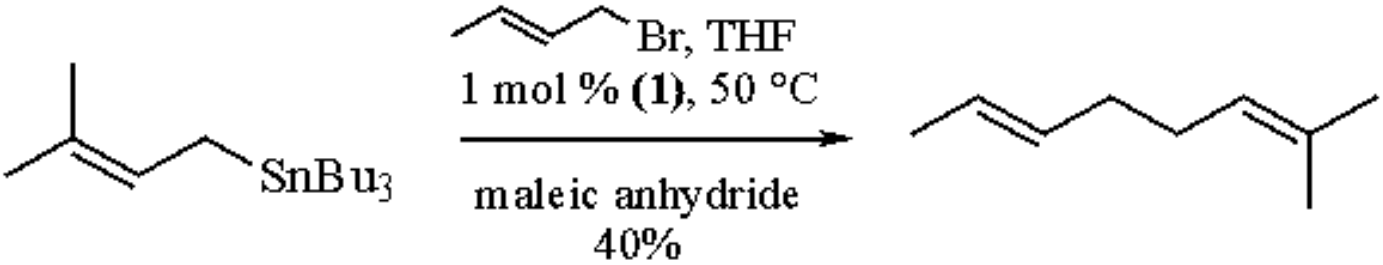

(14)

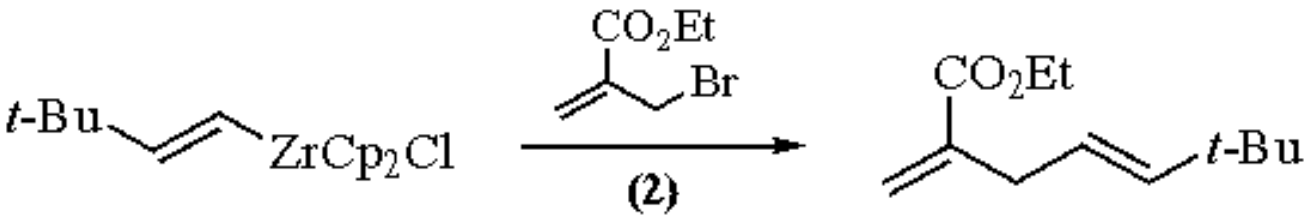

(15)

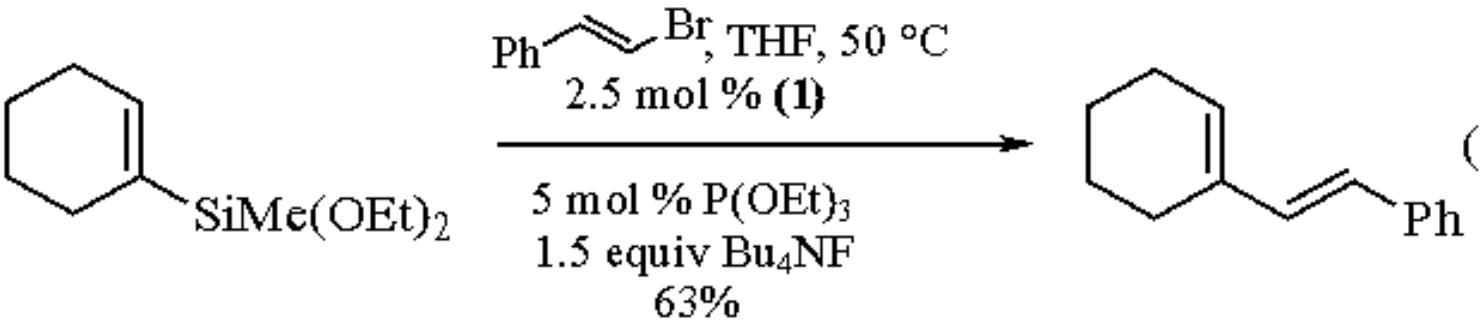

(16)

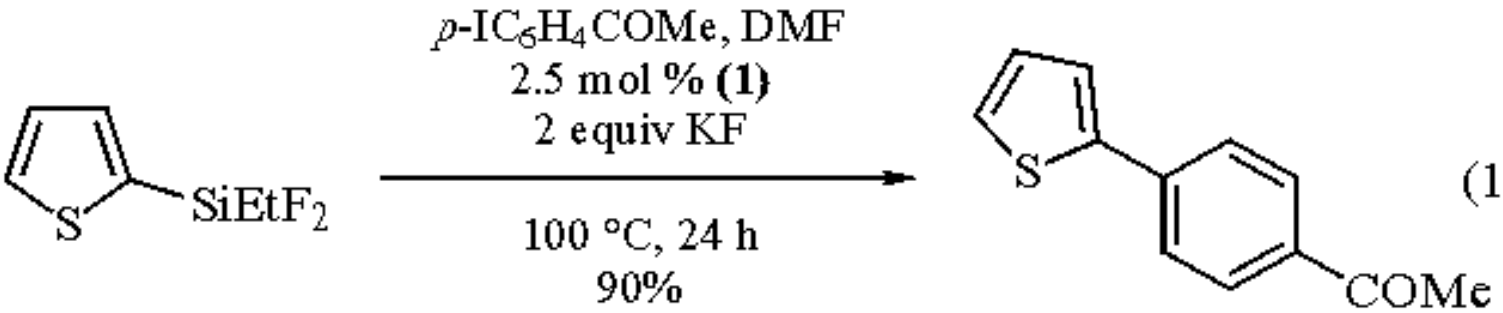

(17)

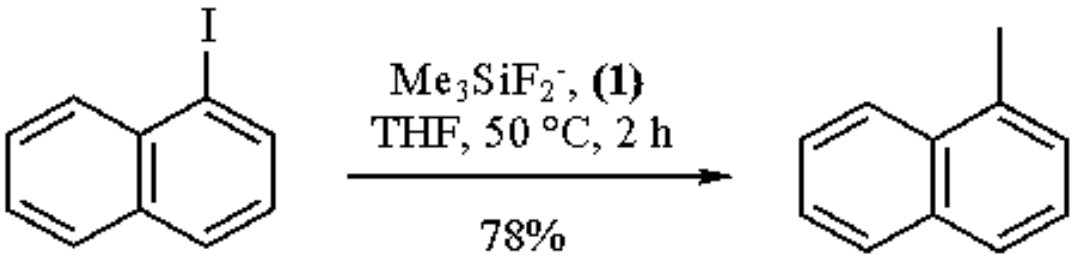

(18)

In the presence of CO these fluoride-promoted Pd-catalyzed cross-coupling reactions provide unsymmetrical ketones (eq 19),[52,53] including polyaryl ketones.[54]

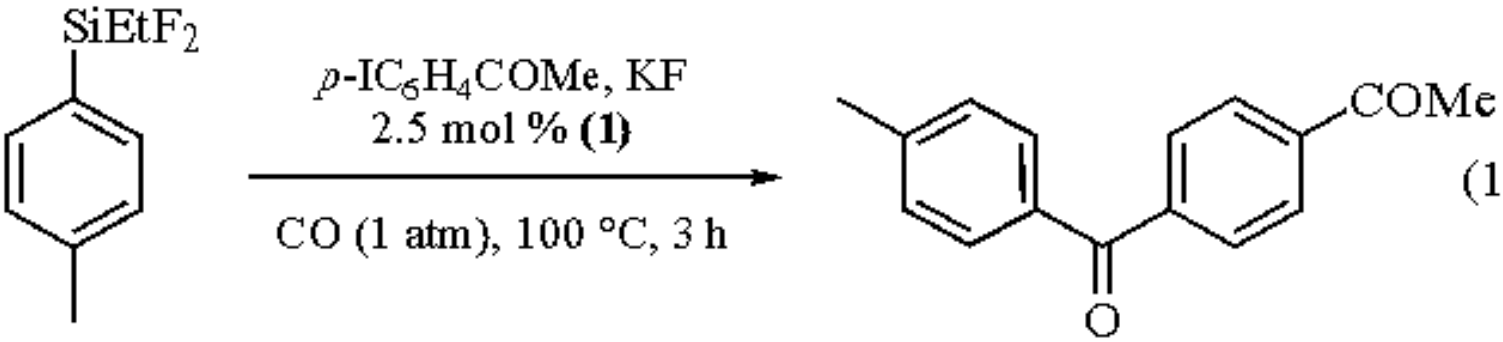

(19)

The title reagent can also catalyze the stannylation (eq 20)[55,56] and silylation[57,58] of organic halides via cross coupling.

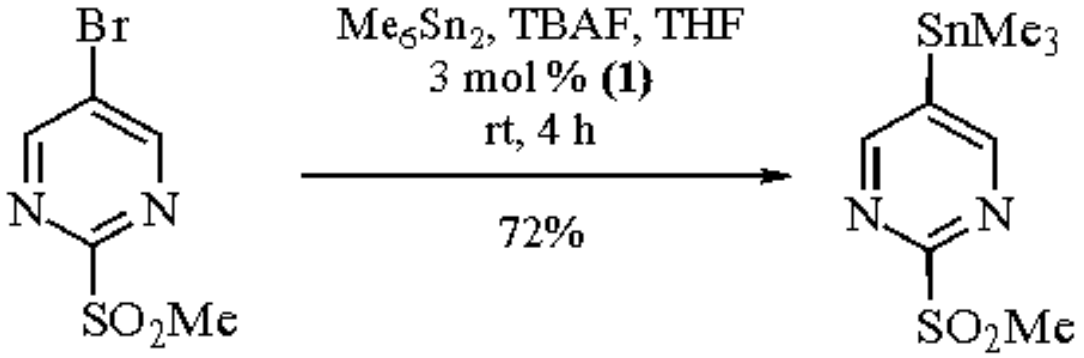

(20)

Diene Dimerization.

The reductive dimerization of isoprene to its head-to-tail dimer has been achieved in high yield using di-μ-acetatobis(allyl)dipalladium (**4**) as the catalyst in combination with phosphine ligands.[2] To achieve optimal selectivity for the desired dimers, a large number of phosphines have been examined in this reaction. Use of the complex (**4**) with the phosphine allows rapid access to each of the desired catalysts, as well as maximum flexibility with respect to Pd/L ratio (eq 21).[2]

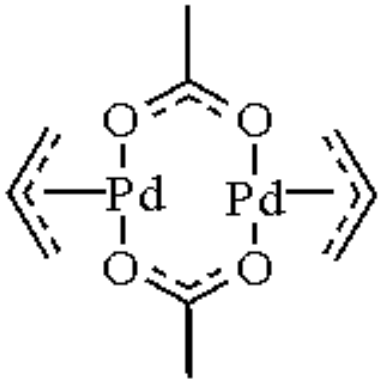

(4)

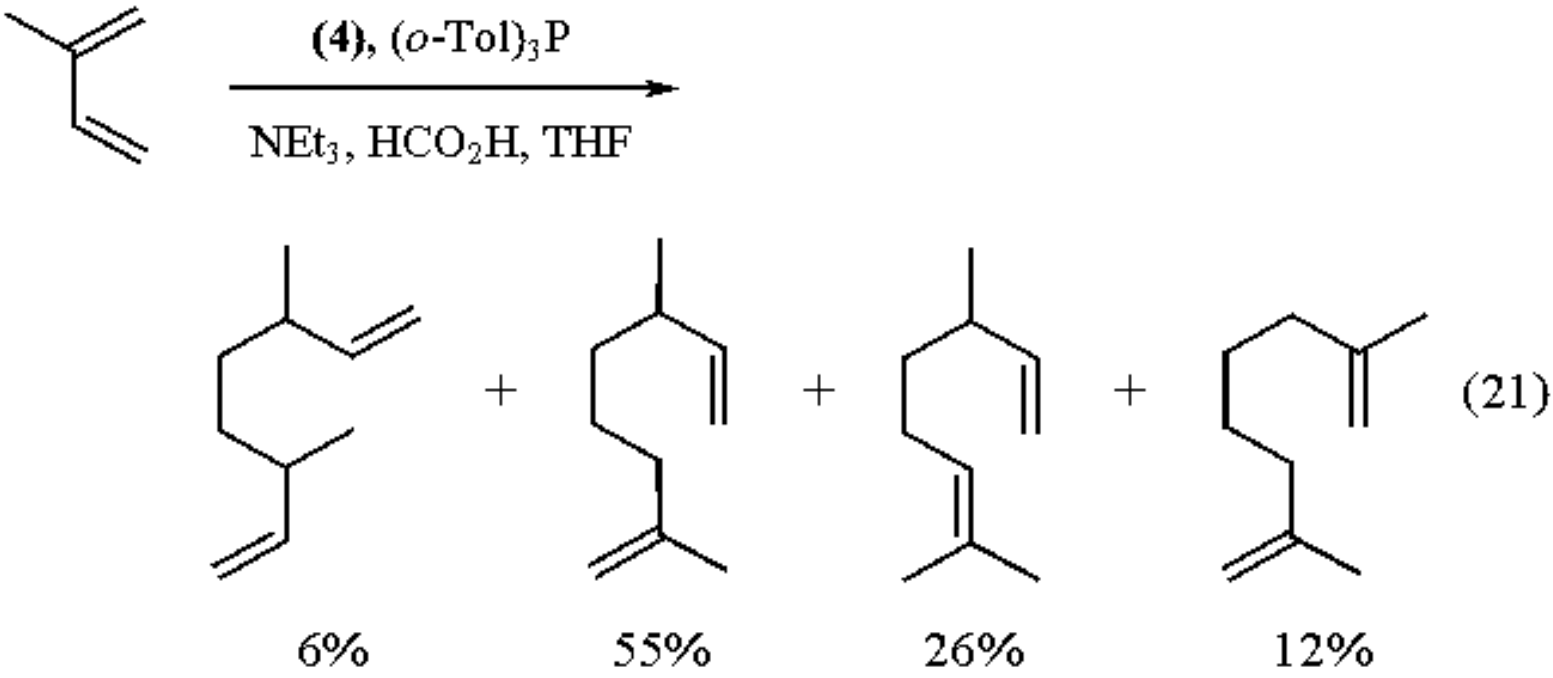

(21)

The organopalladium intermediates in the diene dimerization can also be intercepted by reagents such as ROH,[2] R_3SiSiR_3,[59] and CO_2 (eq 22).[60]

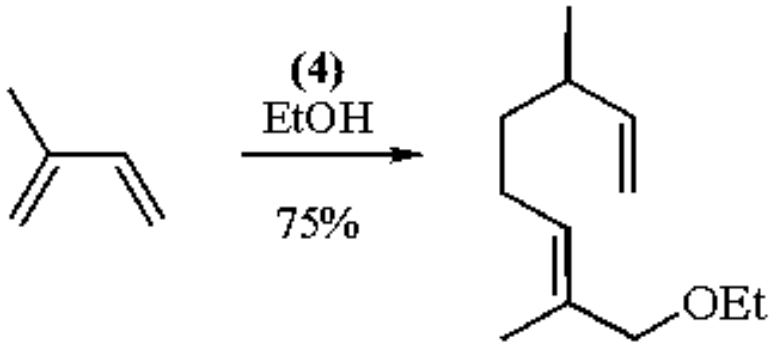

(22)

Codimerization of dienes and alkenes is also possible (eq 23). In this case, (**1**) and Ph_3P-BF_3 are employed as cocatalysts.[61] Complex (**1**) has also been used in the polymerization of butadiene.[62]

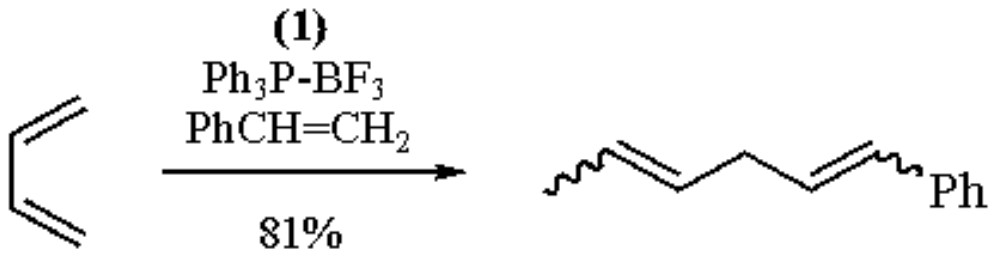

(23)

Addition of Nucleophiles to Dienes.

The use of (**1**) with bidentate phosphine ligands and NaOMe to effect in situ Pd reduction allows the selective addition of nucleophiles to 1,3-dienes, including isoprene, without significant competing diene dimerization (eq 24).[3]

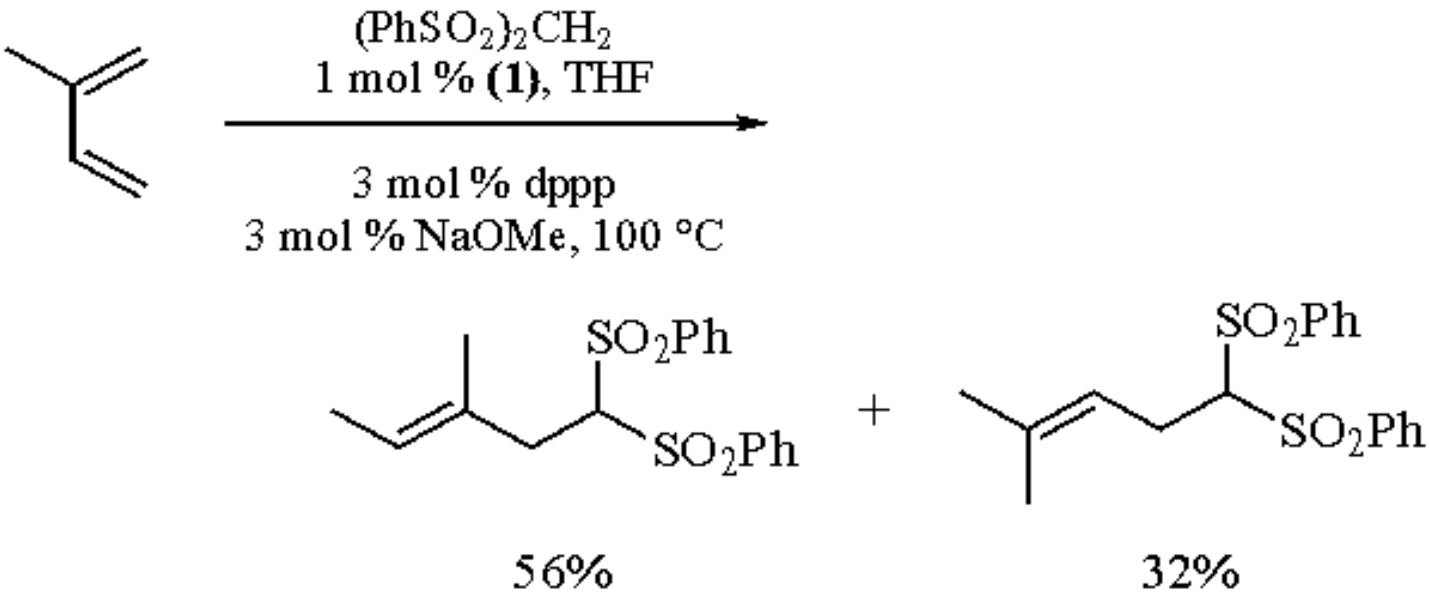

(24)

Arenesulfinic acids have also been reported to add to 1,3-dienes in the presence of (**1**) and Ph_3P to yield allylic sulfones (eq 25).[63]

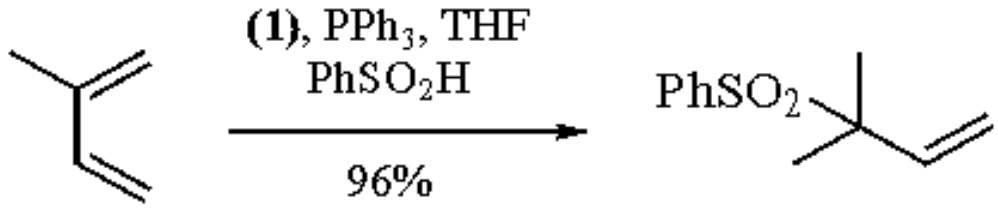

(25)

Preparation of Dienes from Allylic Amines.

Treatment of allylic amines with a catalyst generated from the reaction of (**1**) with $Ph_2P(CH_2)_4PPh_2$ (dppb) and $NaClO_4$ gave the corresponding diene (eq 26).[4] Interestingly, the catalyst generated in this fashion was found to be superior to $Pd(dppb)_2$.

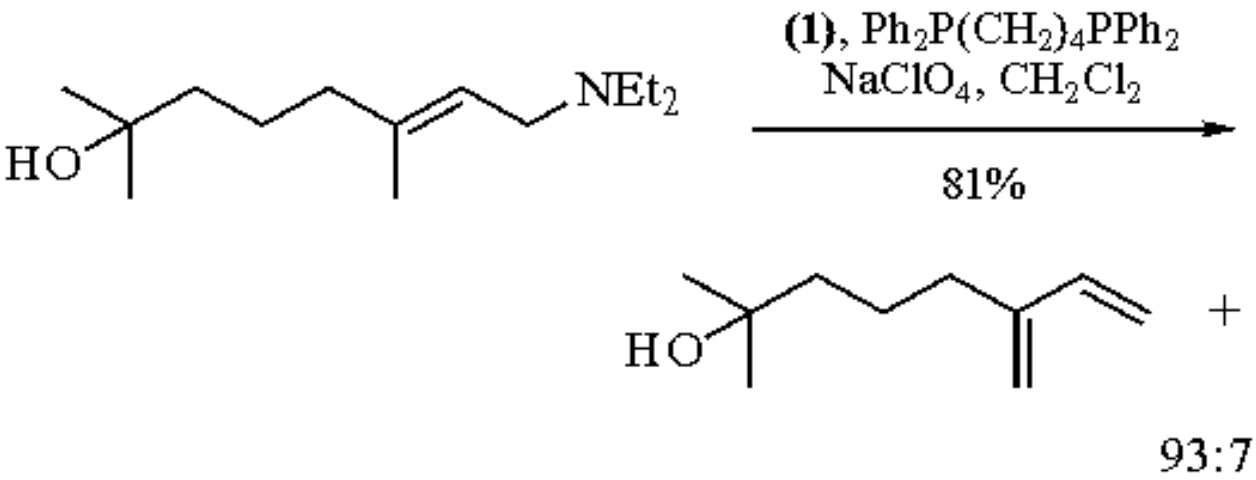

(26)

Siloxycyclopropane Cleavage.

Siloxycyclopropanes undergo C-C bond cleavage and coupling to aryl triflates (eq 27)[5a,b] and acid chlorides (eq 28)[5a,c] in the presence of (**1**) and a phosphine or phosphite ligand. In this fashion, the siloxycyclopropanes serve as synthetically useful homoenolate anions.

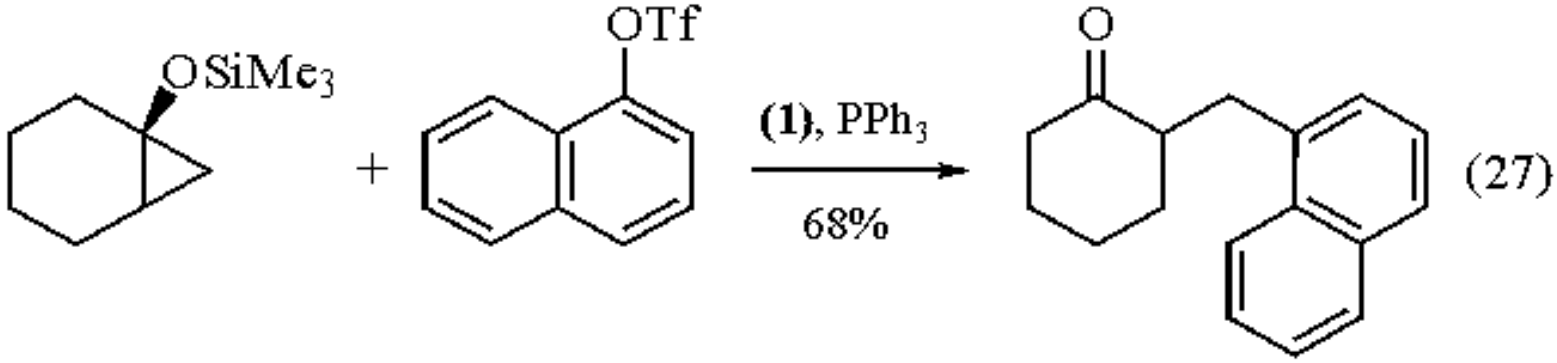

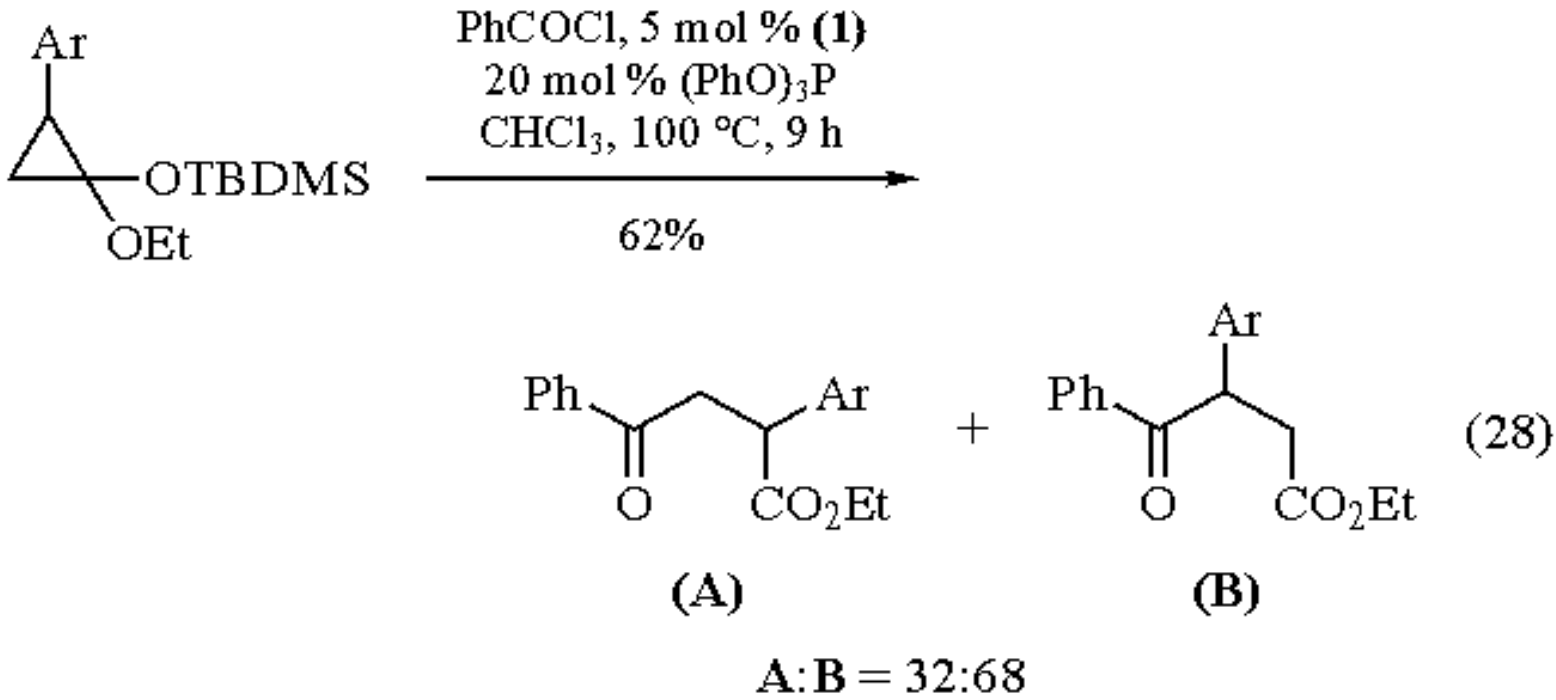

Decomposition of Diazo Compounds.

The title reagent decomposes ethyl diazoacetate to the corresponding carbene under mild conditions.[6a] If the decomposition is conducted in the presence of an alkene, a cyclopropane is produced (eq 29).[6a]

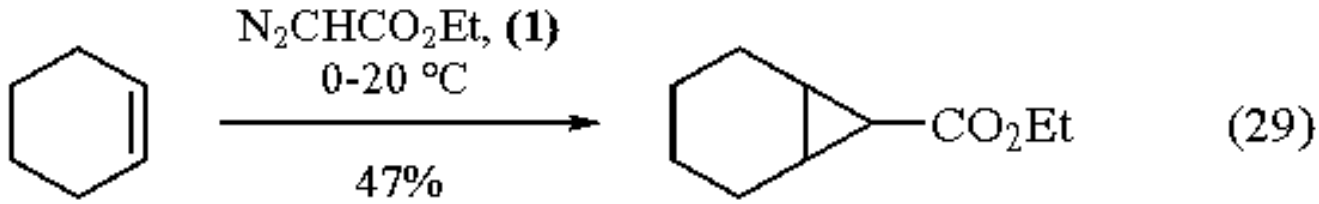

Diazo ester (**5**) undergoes ring enlargement via a carbene intermediate with (**1**) as the catalyst (eq 30).[6b]

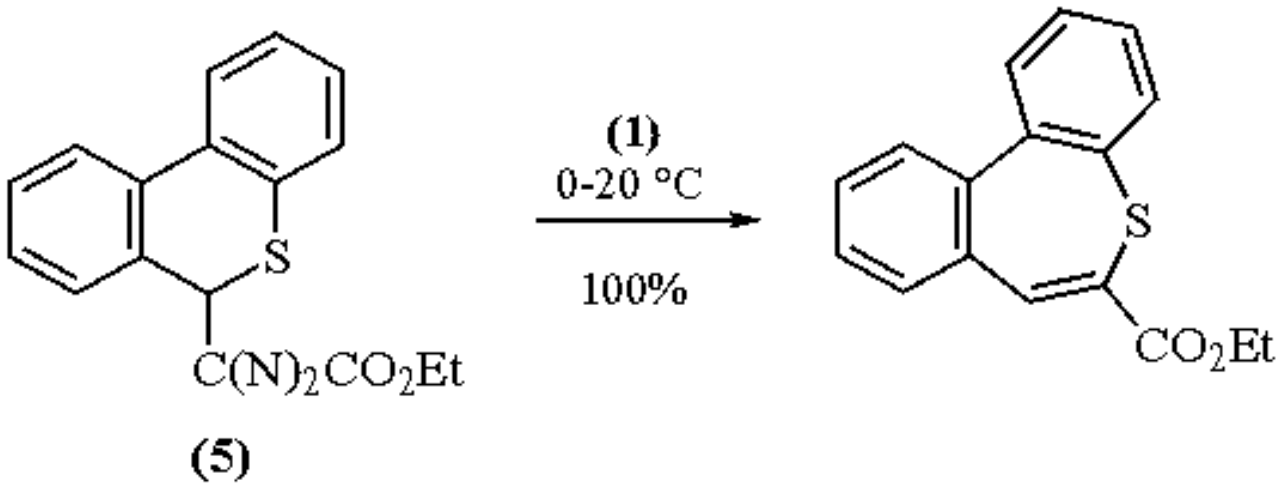

(30)

Diazo ester (**6**) follows different decomposition pathways depending on the transition metal catalyst employed.[6c] $Rh_2(OAc)_4$ yielded (**7**), while (**1**) gave (**8**) (eq 31).

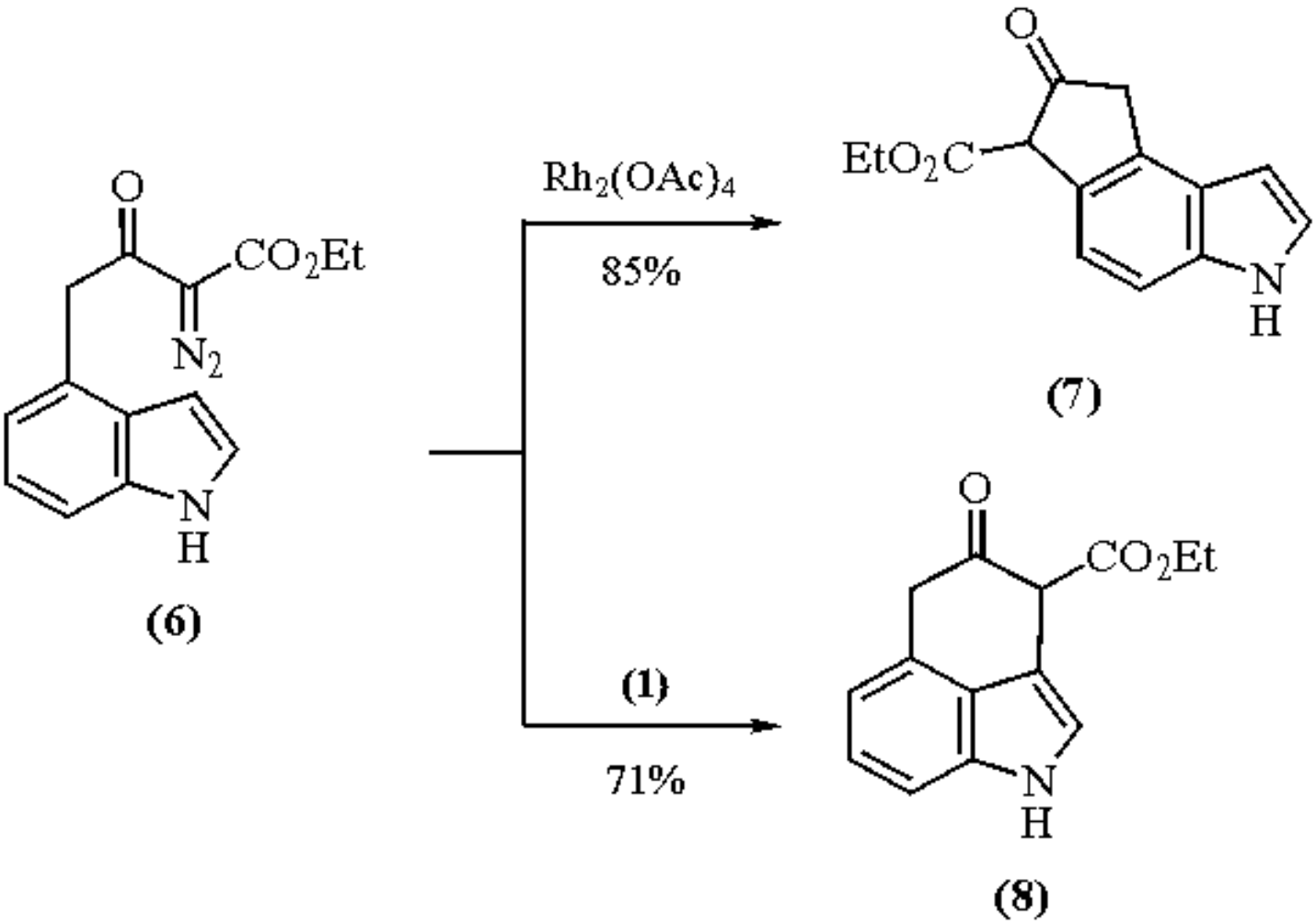

(31)

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4,4´-Bis(2-amino-6-methylpyrimidyl) Disulfide

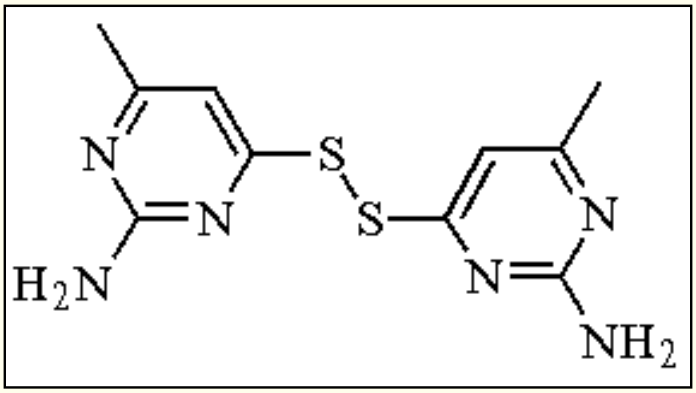

[69945-13-7] · $C_{10}H_{12}N_6S_2$ · 4,4´-Bis(2-amino-6-methylpyrimidyl) Disulfide · (MW 280.37)

(in combination with phosphines, induces lactonization of o-hydroxy acids[1])

Physical Data: mp 207-209 °C.

Solubility: sol benzene, acetonitrile.

Form Supplied in: not available from commercial sources.

Preparative Methods: readily prepared from commercially available 2-amino-4-chloro-6-methylpyrimidine, which is treated with $NaS.H_2O$ (5 equiv) in degassed propylene glycol at 140 °C for 3 h. The solution is diluted with H_2O and neutralized with acetic acid. The collected precipitate is recrystallized from ethanol, giving pure 2-amino-4-mercapto-6-methylpyrimidine, which is dimerized with iodine in boiling methanol containing potassium carbonate.

Purification: by crystallization from ethanol or chromatography on silica gel (chloroform-ethanol, 1:1).

4,4´-Bis(2-amino-6-methylpyrimidyl) disulfide and ***Triphenylphosphine*** form the corresponding thioesters of o-hydroxy acids, which under high dilution conditions and in the presence of ***Silver(I) Perchlorate*** as a thiol scavenger give the corresponding macrolides (eq 1). Optimal conditions involve 1.5 equiv of both the disulfide and the phosphine, and 1.1 equiv of the silver salt, in refluxing dry benzene for 5 h.[1]

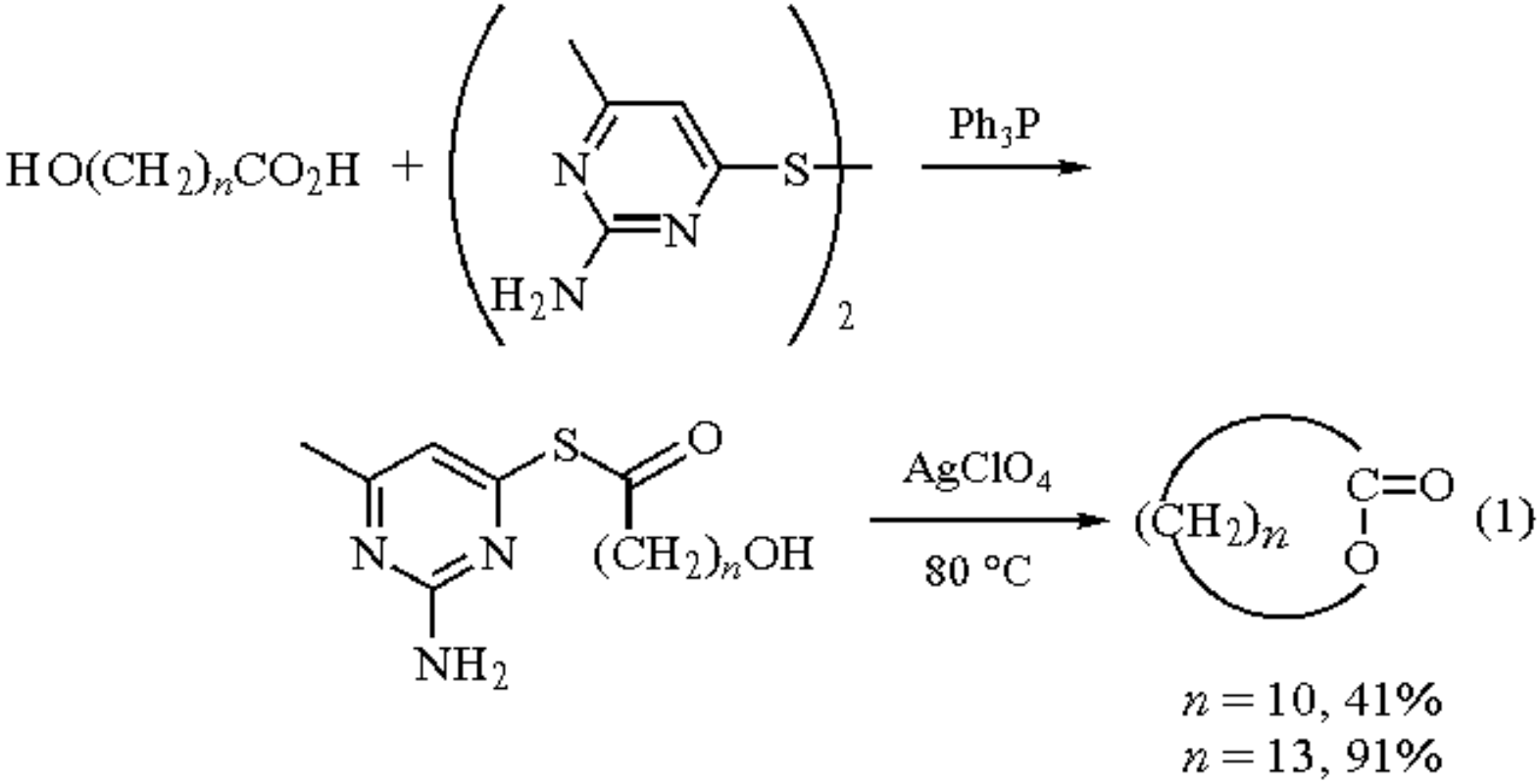

2,2´-Dipyridyl Disulfide and related compounds have also been used as a method for macrolide formation; the addition of thiophilic metal cations and/or pyridine derivatives has been found to assist this process.[2]

This oxidation-reduction condensation,[3] using 2,2´-dipyridyl disulfide, constitutes an excellent strategy for the solid-phase synthesis of peptides. This method does not affect amino acids sensitive to oxidation, proceeds under mild conditions without the requirement of basic or acid catalysts, and has the advantages of minimizing both racemization of carboxyl component and side-reactions of certain amino acids.[4] Furthermore, it has been successfully applied to phosphorylation reactions, such as the synthesis of coenzyme A,[5] oligothymidilates, and nucleotide cyclic phosphates,[6] and nucleotides from O^2,2´-cyclouridine.[7]

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Fernando Albericio & Steven A. Kates

Bis(benzonitrile)dibromopalladium(II)

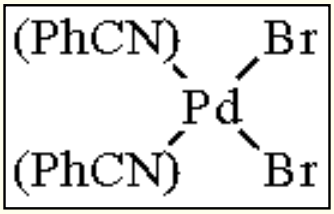

[15003-43-7] · $C_{14}H_{10}Br_2N_2Pd$ · Bis(benzonitrile)dibromopalladium(II) · (MW 472.47)

(palladium catalyst used in the codimerization of alkynes and allyl halides;[1-3] synthesis of α-(*Z*)-halomethylene-γ-butyrolactone derivatives;[4-6] isomerization of alkenes[7,8])

Physical Data: dark brown crystals.

Solubility: sol benzene, methanol.

Form Supplied in: not commercially available.

Preparative Method: prepared in 90% yield by reacting $PdBr_2$ in PhCN with prolonged heating at 100 °C. The reaction mixture is filtered while hot and the filtrate cooled to give a brown precipitate. Additional product is obtained by precipitation with cyclohexane.

Purification: recrystallize from low-boiling petroleum ether.

Handling, Storage, and Precautions: usually prepared just prior to use.

Codimerization of Alkynes and Allyl Halides.

The title reagent (**1**) catalyzes the codimerization of alkynes and allyl halides under mild conditions to yield substituted 1,4-pentadienes in one step. This provides a very convenient synthetic method for the preparation of halogen substituted mono- and/or dialkenes (eqs 1 and 2).[1-3]

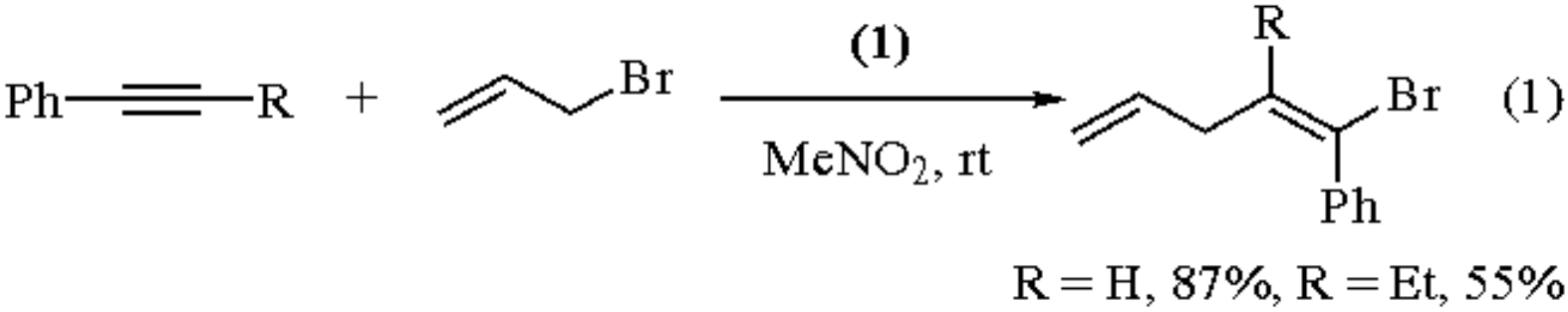

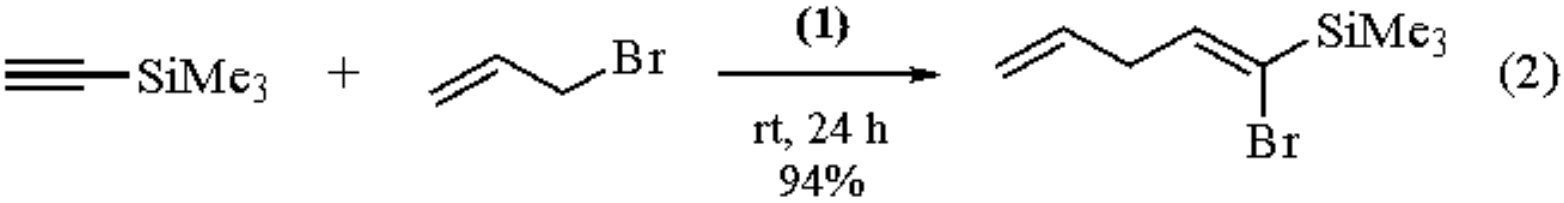

Metalated (*Z*)-1-bromo-1-trimethylsilyl-1,4-pentadiene, a 4-pentenoyl anion equivalent, has been prepared by this method. This compound shows great utility in the transformation of alkynylsilanes into carbonyl compounds.

Butyrolactone Synthesis.

Butyrolactones are prepared conveniently by intramolecular cyclizations mediated by bis(benzonitrile)dibromopalladium(II), as shown in eq 3.[4-6]

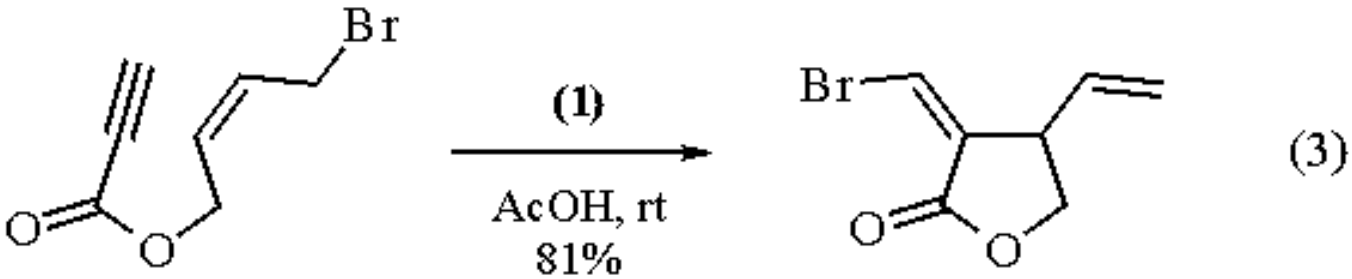

Isomerization of Alkenes and Addition of Amines to Terminal Alkenes.

Isomerization of alkenes by the title reagent is specific for double-bond migration with no detectable skeletal rearrangement (eq 4).

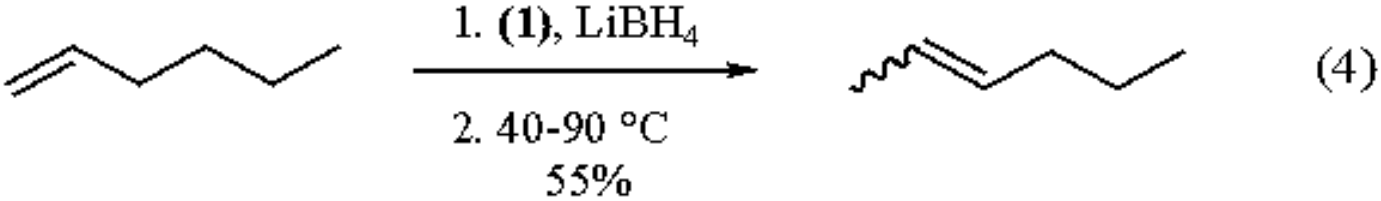

Bis(benzonitrile)dibromopalladium(II) promotes amination of terminal alkenes to give, after reduction, high yields of

amines (eq 5).[8] Internal alkenes may also be aminated, but the yields are moderate to low. The yield of the amination is strongly temperature dependent and, as the temperature increases, there is a steady decrease in the yield.

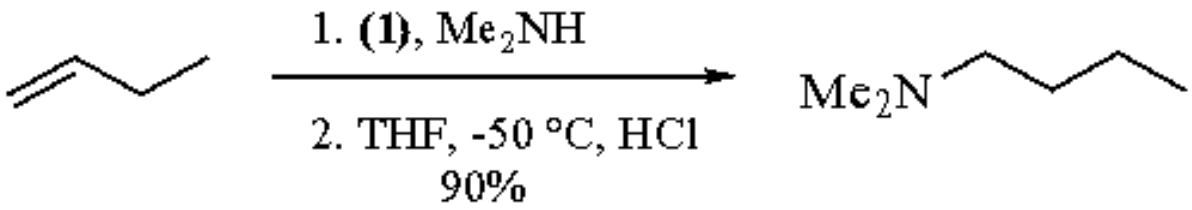

(5)

Related Reagents.

Bis(benzonitrile)dichloropalladium(II) is similar to reagent (**1**). They are interchangeable in almost all reactions. The former is more reactive.[9]

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Bis(benzonitrile)dichloropalladium(II)

$Pd(PhCN)_2Cl_2$

[14220-64-5] · $C_{14}H_{10}Cl_2N_2Pd$ · Bis(benzonitrile)dichloropalladium(II) · (MW 383.57)

(used as an organic solvent-soluble form of $PdCl_2$ and as a Pd^{II} catalyst)

Alternate Name: bis(benzonitrile)palladium chloride.

Physical Data: mp 129-130 °C.

Solubility: sol chloroform, dichloromethane, benzene, toluene.

Form Supplied in: commercially available as an orange-yellow powder.

Handling, Storage, and Precautions: air-stable, not hygroscopic.

General Considerations.

The title reagent is most often used as a soluble source of palladium chloride. Reactions of this and other palladium chloride derivatives are described in the article on ***Palladium(II) Chloride***.

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Okayama University of Science, Japan

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Bis(benzonitrile)dichloroplatinum(II)

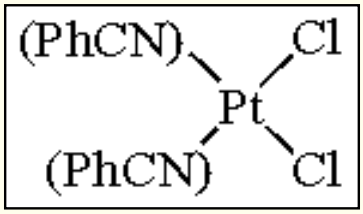

[14873-63-3] · $C_{14}H_{10}Cl_2N_2Pt$ · Bis(benzonitrile)dichloroplatinum(II) · (MW 472.25) (*cis*)

[15617-19-3] (*trans*)

[51921-56-3]

(catalyst for hydrogenation of nitro compounds[5,7a] and hydroformylation of alkenes;[13] versatile starting material for complexes of platinum[3])

Physical Data: mp 224 °C (dec).

Solubility: sol dichloromethane.

Form Supplied in: yellow crystalline solid.

Preparative Methods: prepared as a mixture of *cis* and *trans* complexes. The reaction of ***Palladium(II) Chloride*** in benzonitrile at room temperature for 7 h yields a mixture that can be separated chromatographically to yield 26% *trans*- and 58% *cis*-$PtCl_2(PhCN)_2$.[1] An alternate route requires stoichiometric amounts of potassium tetrachloroplatinate(II) and benzonitrile stirred at room temperature for one week. Trituration of the product with hot benzene yields pure *cis*-$PtCl_2(PhCN)_2$ in 60% yield; the cooled benzene solution yields pure *trans*-$PtCl_2(PhCN)_2$ in 20% yield.[2a,b]

Purification: chromatography on silica gel with dichloromethane as eluant,[1] or trituration with hot benzene.[2a,b]

Introduction.

The title reagent is frequently used as the starting material for preparation of organometallic complexes of platinum.[3] The labile ligand, PhCN, can be easily displaced with various phosphorus(III) ligands, thereby modifying or improving the activity of the catalyst. Polymer-supported platinum catalysts are prepared by treating phosphole-containing copolymers with the title reagent. The resulting heterogeneous catalyst can be used in the presence of

Tin(II) Chloride dihydrate to catalyze the hydroformylation of a variety of alkenic substrates.[4]

Hydrogenations.

The homogeneous hydrogenation of aliphatic nitro compounds is catalyzed by platinum metal phosphine complexes. These complexes are formed in situ by treating the title reagent, which possesses the labile ligand PhCN, with a phosphine reagent, for example ***(R)-N,N-Dimethyl-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethylamine*** (PPFA) at 1000 psi (eq 1).[5]

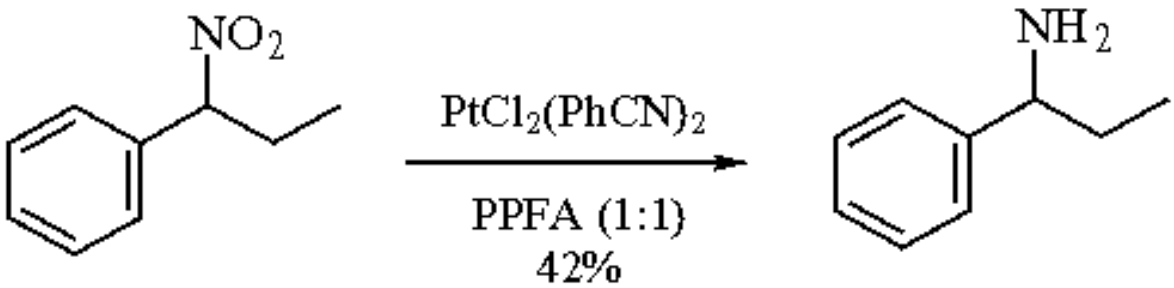

(1)

Platinum catalysts have also been utilized in the reductive *N*-acylation of nitro compounds. The catalyst system requires the platinum catalyst, carbon monoxide, a Lewis acid (***Tin(IV) Chloride***), and a phosphorus(III) ligand. For example, the title reagent, when used in conjunction with ***Triphenylphosphine***, $SnCl_4$, acetic acid, and CO at 60 atm, yields acetanilide in 89% yield from nitrobenzene (eq 2).[7a] When ethanol is used in place of the acetic acid, the resulting product is the carbamate.[7b]

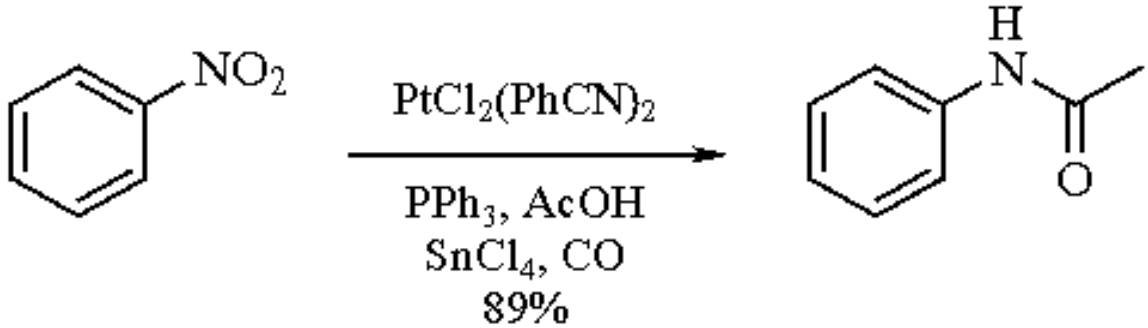

(2)

Carbonylations, Rearrangements, and *N*-Alkylations.

Platinum catalysts have been used for the carbonylation of alkyl, alkenyl, and alkynyl iodides under carbon monoxide pressure. The title reagent, when used in the presence of ***Tri-n-butylphosphine*** and ***Triethylamine***, shows good catalytic activity in the methoxycarbonylation of 1-iodo-1-octyne (eq 3).[6]

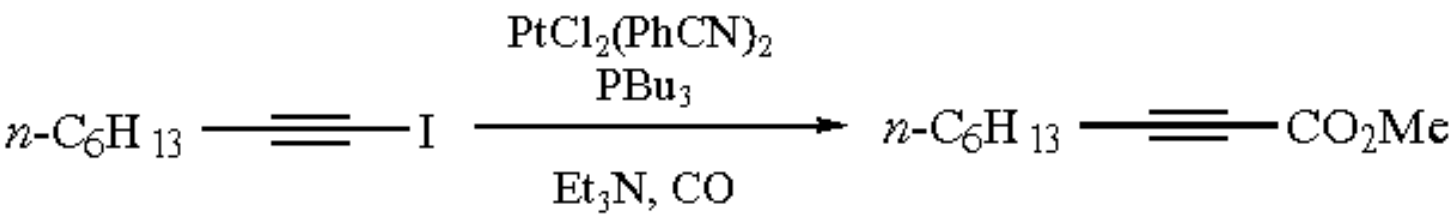

(3)

The transformation of a primary amine to a secondary amine has also been catalyzed by the title reagent.[8] Similar transformations have been reported with ruthenium[9a,b] and palladium[10] catalysts. The title reagent, in the presence of the Lewis acid $SnCl_2.2H_2O$ (Sn:Pt = 2.5:1), catalyzes the reaction of *n*-butylamine to give *N*,*N*-dibutylamine in 65% yield (eq 4). Other Lewis acids such as $SnCl_4$, $FeCl_3$, $AlCl_3$ are not effective in this reaction.

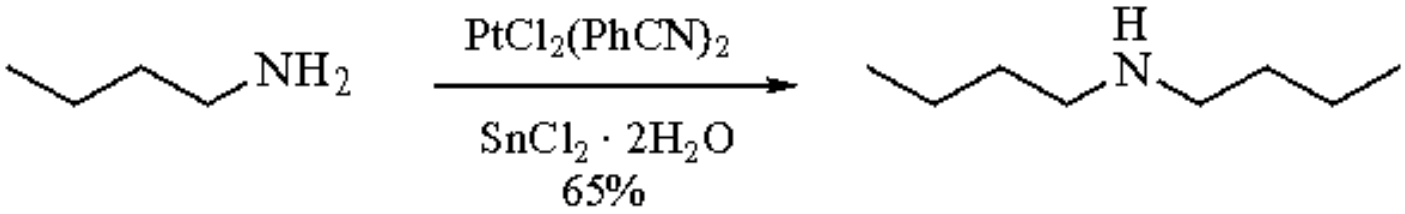

(4)

Rearrangements of oxocyclopropanes to vinyl ethers can be accomplished using the title reagent.[12a,b] The rearrangement of cyclopropanes containing the combination of vicinal alkoxy and alkoxy-carbonyl substituents is facile when using $PtCl_2(PhCN)_2$ as the catalyst (eq 5). Other transition metal complexes, e.g. ***Tetracarbonyl(di-μ-chloro)dirhodium*** and $[Ru(CO)_3Cl_2]_2$, are also active catalysts in this system, as are ***Copper Bronze*** and ***Copper(I) Chloride***.

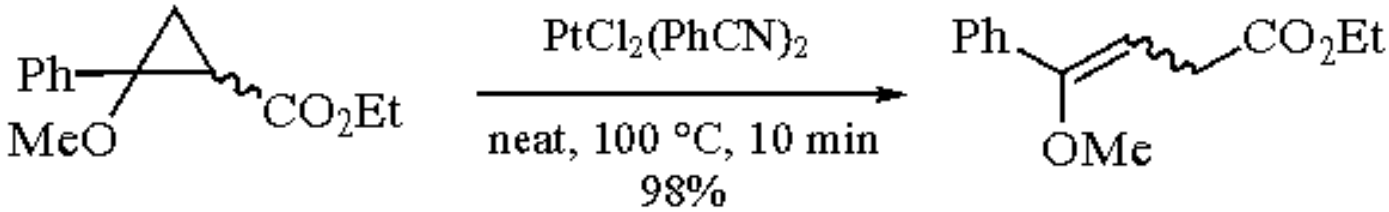

(5)

N-Alkylation and *N*-allylation can be catalyzed by the title reagent in conjunction with $SnCl_2.2H_2O$.[11] Reaction of aniline with an allylic alcohol gives *N*-allylated products (eq 6). The platinum catalyst does not catalyze isomerization of the allylic alcohol to the corresponding aldehyde.

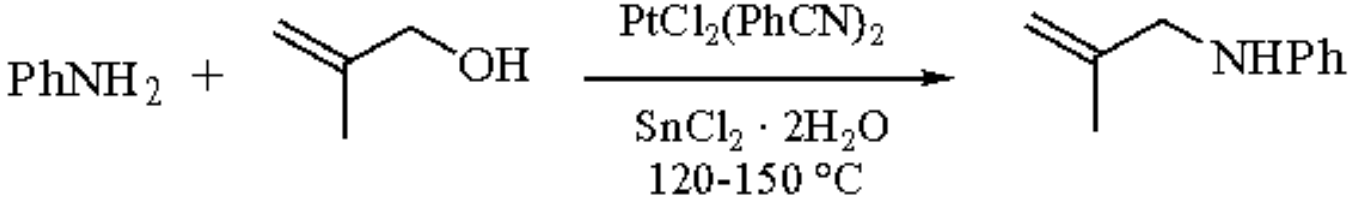

(6)

The hydroformylation of 1-pentene is catalyzed by the title reagent, $SnCl_2.2H_2O$, and a bidentate phosphine ligand under carbon monoxide pressure. When the bidentate ligand is (-)-DIOP (***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane***) the reaction proceeds in 5 h at 100 °C, yielding 75% hexanal, 9% pentane, and 16% 2-pentene.[13]

---

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Bis(benzoyloxy)borane[1]

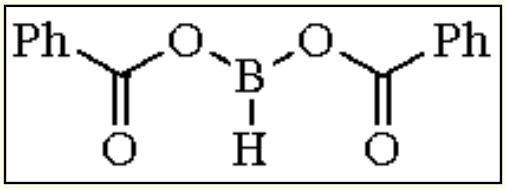

[94596-93-7] · $C_{14}H_{11}BO_4$ · Bis(benzoyloxy)borane · (MW 254.05)

(reagent for the reduction of tosylhydrazones of aldehydes, ketones, and enones to the corresponding methylene derivatives[1,2])

Physical Data: mp 166-168 °C

Solubility: sol chloroform, THF, and pentane; reacts readily with water and other protic solvents.

Form Supplied in: white crystalline solid

Analysis of Reagent Purity: the technical bulletin *Quantitative Analysis of Active Boron Hydrides*, available upon request from the Aldrich Chemical Company, Milwaukee, WI, USA, describes methodology to determine reagent purity by hydrogen gas evolution.

Preparative Methods: available via the controlled addition of borane-THF complex to benzoic acid at 0 °C.[1a,b] Preparation using borane-dimethyl sulfide complex involves much milder reaction conditions (25 °C).[2]

Handling, Storage, and Precautions: shows good stability that results from adduct formation with solvent (THF or DMS). Solutions of the reagent in THF have shown little decomposition after storage at 0 °C for 10 days.[1b]

Reduction of Tosylhydrazones of Aldehydes, Ketones, and α,β-Unsaturated Aldehydes and Ketones.

Bis(benzoyloxy)borane has been used for the reduction of tosylhydrazones to the corresponding methylene derivatives. This method offers a mild alternative to the classical Wolff-Kishner and Clemmensen reduction procedures which preclude the presence of sensitive functional groups.[3] This reagent is comparable in reactivity to ***Catecholborane***, which had previously been demonstrated to be a very efficient reagent for the reduction of tosylhydrazones.[4] Regiospecific alkene migration occurs during the reduction of α,β-unsaturated derivatives,[5] and allenes result from the reduction of alkynic substrates.[6] Given the commercial availability of catecholborane, it is probably the reagent of

choice for tosylhydrazone reduction. Representative tosylhydrazone reductions employing bis(benzoyloxy)borane are given in eqs 1-4. The reactions are typically complete in 0.5 to 2 h. As with catecholborane a regiospecific and stereospecific rearrangement occurs in the reduction of α,β-unsaturated tosylhydrazones, permitting the preparation of thermodynamically unstable alkenes.[5,6] The related ***Bis(trifluoroacetoxy)borane*** has been used in the reduction of indoles to indolines.[7]

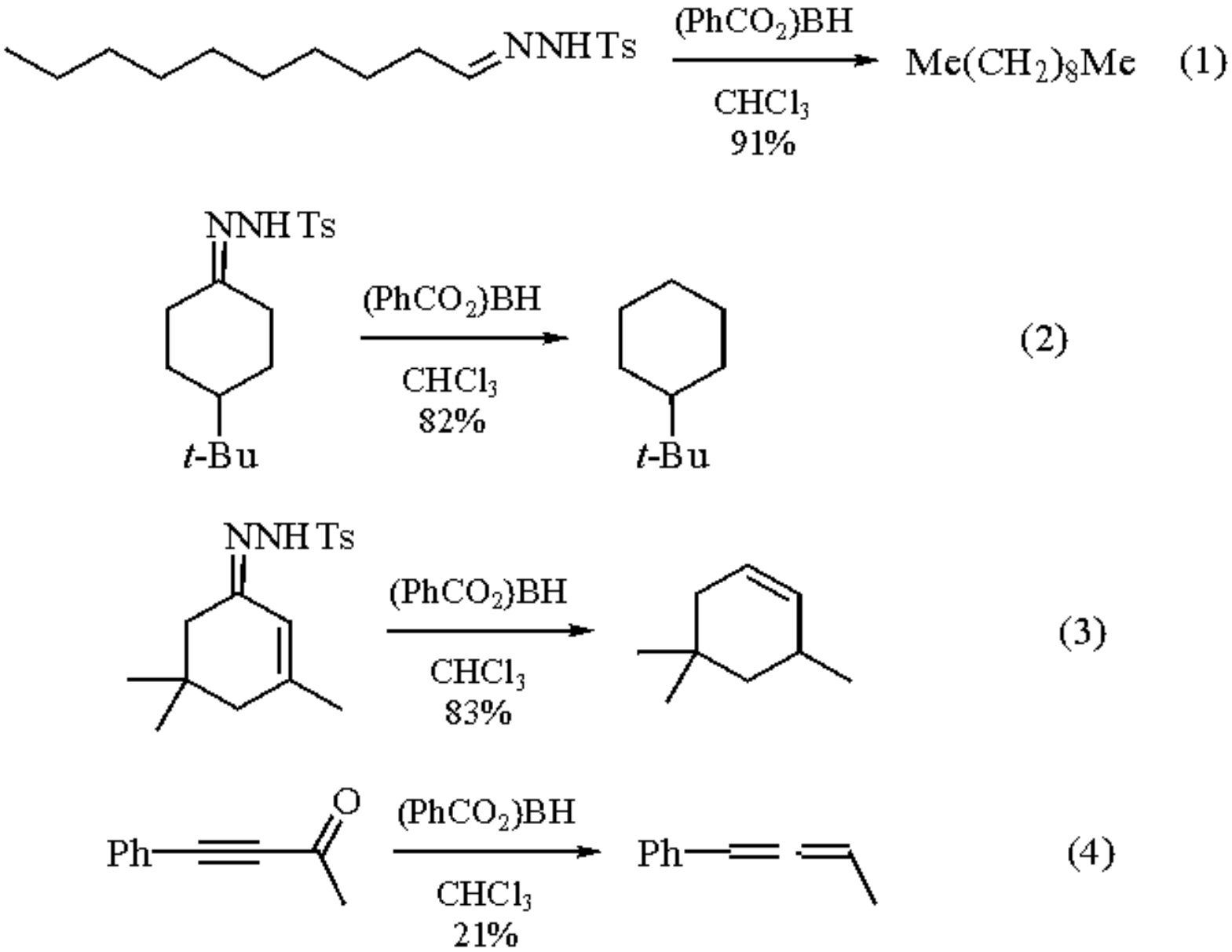

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Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium[1]

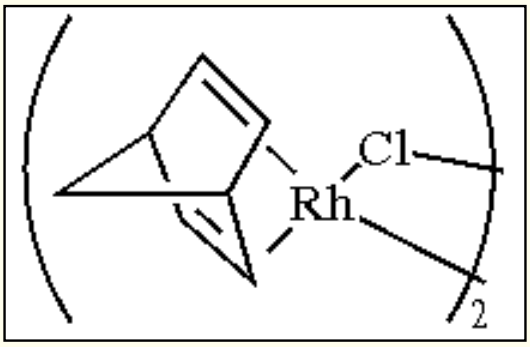

[12257-42-0] · $C_{14}H_{16}Cl_2Rh_2$ · Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium · (MW 461.00)

(catalyst for valence isomerization[2] and N-heterocyclization;[3] in combination with phosphorus ligands are catalysts for hydrogenation of many functional groups[5,6] and hydroformylation; with chiral ligands are catalysts for asymmetric hydrogenation[7-11])

Alternate Name: dichlorobis(norbornadiene)dirhodium.

Physical Data: mp 240 °C dec.

Solubility: sol chloroform and benzene; insol ether and light petroleum.

Form Supplied in: yellow crystals.

Preparative Methods: ***Rhodium(III) Chloride*** and bicyclo[2.2.1]hepta-2,5-diene in aq ethanol, when shaken for 2 days, give a yellow deposit.

Purification: recrystallized from chloroform and light petroleum.

Handling, Storage, and Precautions: air stable up to 240 °C.

Catalytic Activity.

The rhodium chloride dimer is easily prepared from rhodium trichloride and the diene has been well used as a catalyst for valence isomerization of quadricyclanes to bicyclo[2.2.1]hepta-2,5-dienes (eq 1).[2]

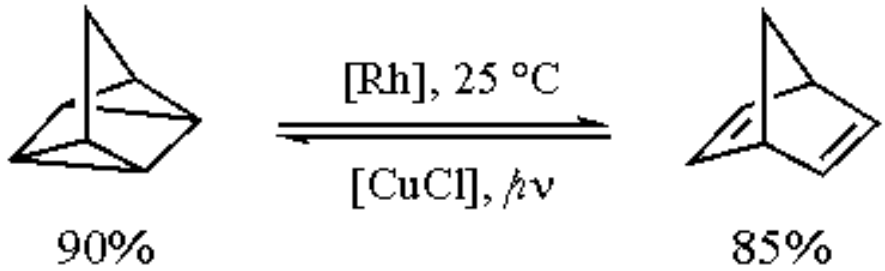

(1)

The reverse isomerization is catalyzed by ***Copper(I) Chloride*** under irradiation.[2c] This cycle has attracted much attention as a solar energy storage system. The rhodium dimer catalyzes the reaction between aminoarenes and alkanals to give quinolines (eq 2).[3] The rhodium dimer is easily transformed into a monomeric neutral form in combination with neutral donor ligands, which turns into a cationic form in the presence of such salts as ***Potassium Hexafluorophosphate*** and $NaClO_4$ (eq 3).

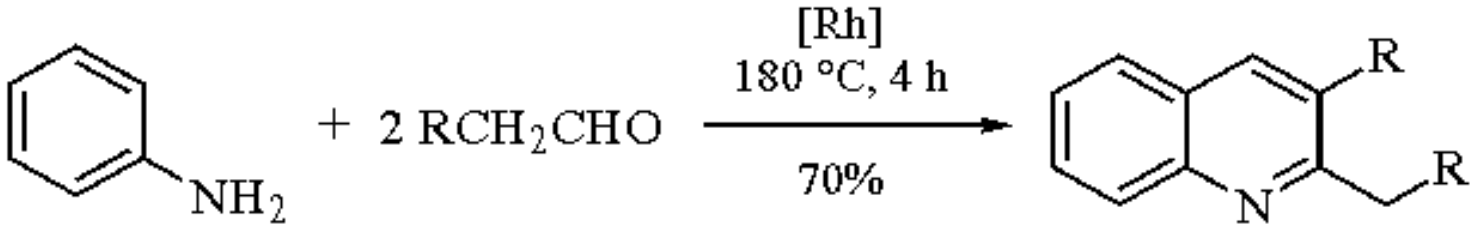

(2)

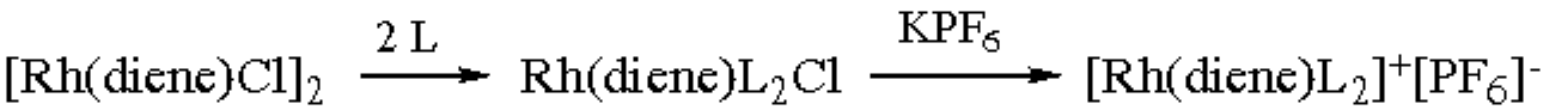

(3)

These rhodium complexes of two types show high catalytic activities for hydrogenation of many unsaturated groups[5-11] such as C=C, C&tbond;C, C=O, and C=N. In particular, cationic rhodium complexes are efficient under mild conditions (at ambient temperature and 1 atm of H_2).[5] The original rhodium dimer is readily modified into a selection of active catalysts by use of a wide range of phosphorus ligands including chiral,[7-11,13] polymer-supported,[14] and water-soluble types.[15,16]

With a variety of chiral ligands, such substrates as alkenes,[7] ketones,[8] α-keto amides,[9] α-keto esters,[10] and imines[11] are hydrogenated highly enantioselectively (eqs 4-7).

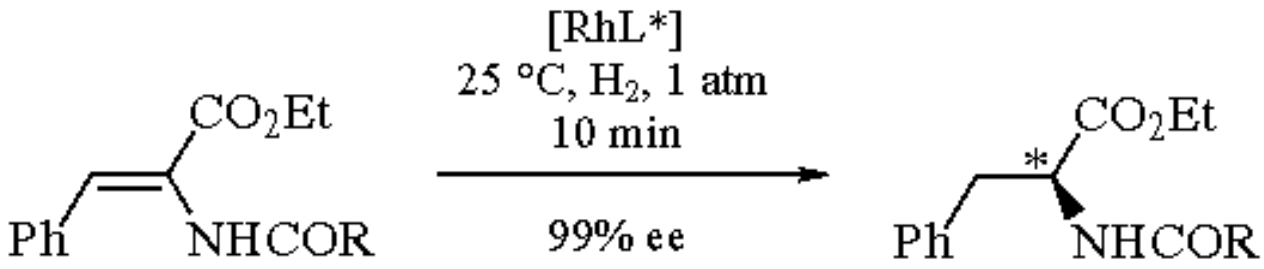

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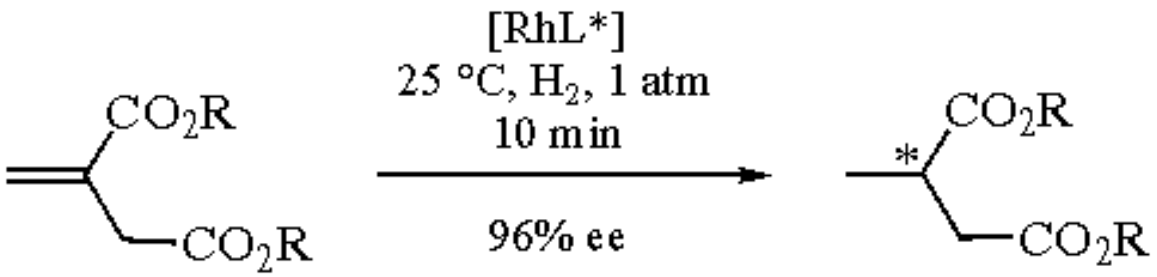

(5)

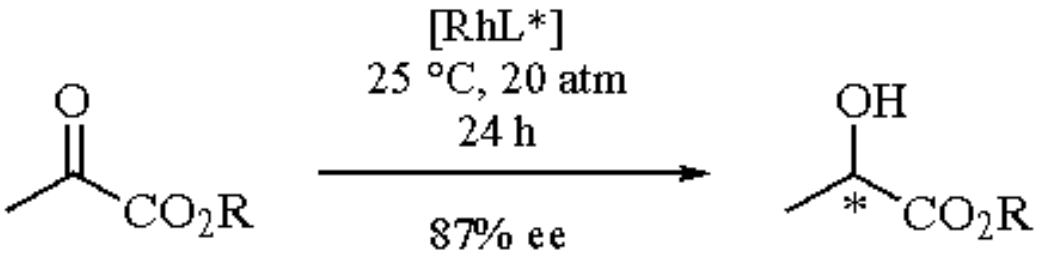

(6)

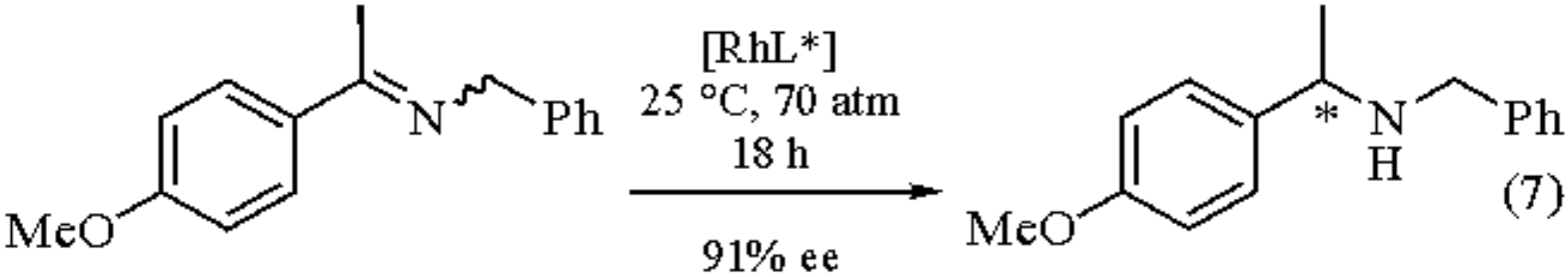

(7)

Hydroformylation of alkenes proceeds with a rhodium catalyst,[12] even asymmetrically.[13] A polymer-supported rhodium catalyst is efficient for hydrogenation of benzenes to cyclohexanes.[14] Water-soluble phosphine ligands are applicable for asymmetric hydrogenation of alkenes[15] and hydroformylation of alkenes.[16]

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate; ***Chlorotris(triphenylphosphine)rhodium(I)***.

---

1. Abel, E. W.; Bennett, M. A.; Wilkinson, G. *JCS* **1959**, 3178.
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Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate[1]

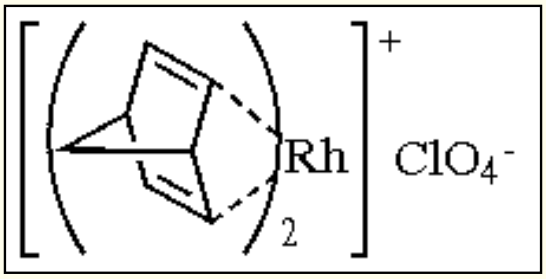

[60576-58-1] · $C_{14}H_{16}ClO_4Rh$ · Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate · (MW 386.64)

(precursor for various cationic rhodium complexes,[2] which are used as catalysts for hydrogenation,[3] allylic hydrogen migration,[4] hydrosilation,[5] and hydroacylation[6])

Alternate Name: $[Rh(nbd)_2]ClO_4$.

Solubility: sol CH_2Cl_2; insol THF, hexane.

Form Supplied in: rust-brown crystals containing 1 mol THF solvent of crystallization.

Preparative Methods: to a mixture of bicyclo[2.2.1]hepta-2,5-diene (nbd, 0.14 g, 1.5 mmol) and ***Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium*** (0.35 g, 0.75 mmol) in CH_2Cl_2 (15 mL) at room temperature is added ***Silver(I) Perchlorate*** (0.315 g, 1.5 mmol) under nitrogen. After stirring for 1 h, precipitated AgCl is filtered off to give a CH_2Cl_2 solution of $[Rh(nbd)_2]ClO_4$. This solution can be directly used for the next reaction,[7] or diluted by THF (15 mL) followed by evaporation of CH_2Cl_2 under vacuum to separate orange needles of $[Rh(nbd)_2]ClO_4$, which are collected and washed with cold THF and then dried in vacuo to afford rust-brown crystals (0.5 g).[8] For another preparation from $[RhCl(C_2H_4)_2]$, see Fairlie and Bosnich.[6]

Handling, Storage, and Precautions: explosive when heated.

Preparation of Cationic Rhodium Complexes.

Cationic rhodium complexes are useful homogeneous catalysts in organic synthesis. In particular, many selective reactions have been accomplished by use of cationic rhodium complexes with various ligands, i.e. phosphines, pyridine derivatives, and bidentate phosphines. These complexes are expeditiously prepared from $[Rh(diene)_2]^+X^-$ by ligand

exchange, where only one diene is replaced by two monodentate ligands or a single bidentate ligand (eq 1).[9] The complexes thus obtained are used as catalysts, or further treated with molecular hydrogen to afford diene-free complexes, which can also be employed as catalysts (eq 2).[2]

$$[Rh(nbd)_2]^+ ClO_4^- \xrightarrow{(S,S)\text{-CHIRAPHOS}} [Rh(nbd)\{(S,S)\text{-CHIRAPHOS}\}]^+ ClO_4^- \quad (1)$$

$$[Rh(nbd)\{(R)\text{-BINAP}\}]^+ ClO_4^- \xrightarrow[\text{MeOH}]{H_2} [Rh\{(R)\text{-BINAP}\}(MeOH)_2]^+ ClO_4^- \quad (2)$$

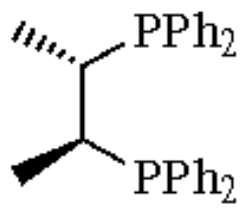

(*S*,*S*)-CHIRAPHOS

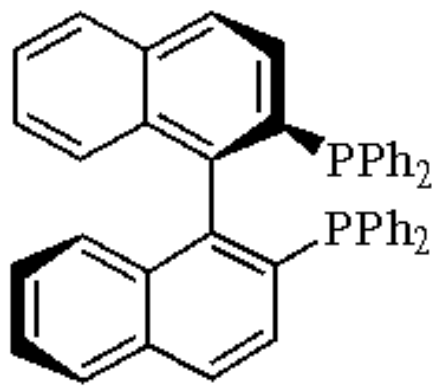

(*R*)-BINAP

Hydrogenation Catalysts.

The cationic rhodium complexes effectively catalyze hydrogenation of carbon-carbon[9] as well as carbon-oxygen[10] multiple bonds. Bidentate phosphine ligands are most frequently used, and certain chiral ligands induce high enantioselectivities.

Asymmetric hydrogenation of dehydroamino acids to optically active α-amino acids has been studied most extensively. The high optical yields (>90% ee) are attained with BINAP,[3] CHIRAPHOS,[8] CAPP,[11] SKEWPHOS,[12] etc. as ligands in hydrogenation of α-(acylamino)cinnamic acid derivatives (eq 3). Itaconic acid is also hydrogenated in the presence of a (*S*,*S*)-CAPP-Rh complex to afford (*R*)-methylsuccinic acid in 95% ee.[11]

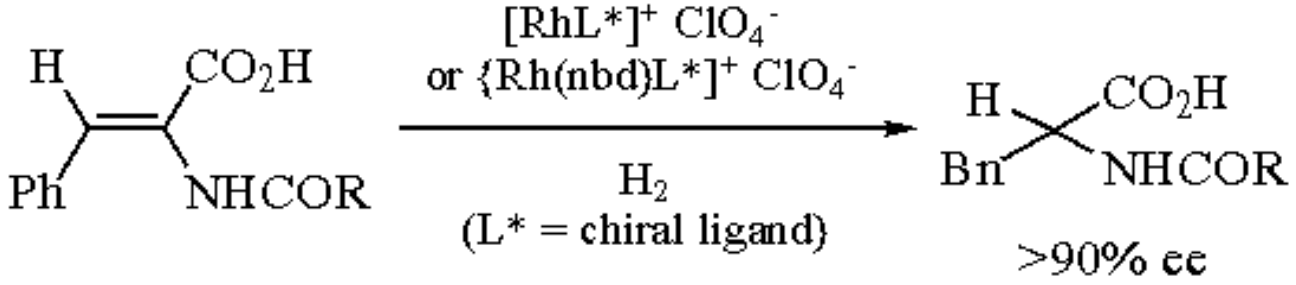

(3)

Hydrogenation of ketones is effectively catalyzed by cationic rhodium complexes with phosphine ligands having alkyl substituents on the phosphorus atom, while arylphosphine-rhodium complexes show only a low catalytic activity.[10,13] Another kind of remarkable catalyst is the cationic rhodium complex with (*R*)-(*S*)-BPPFOH, which catalyzes hydrogenation of 3,4-dihydroxyphenyl (*N*-methylamino)methyl ketone hydrochloride in 95% ee to afford the corresponding 2-amino alcohol, e.g. epinephrine (eq 4).[14]

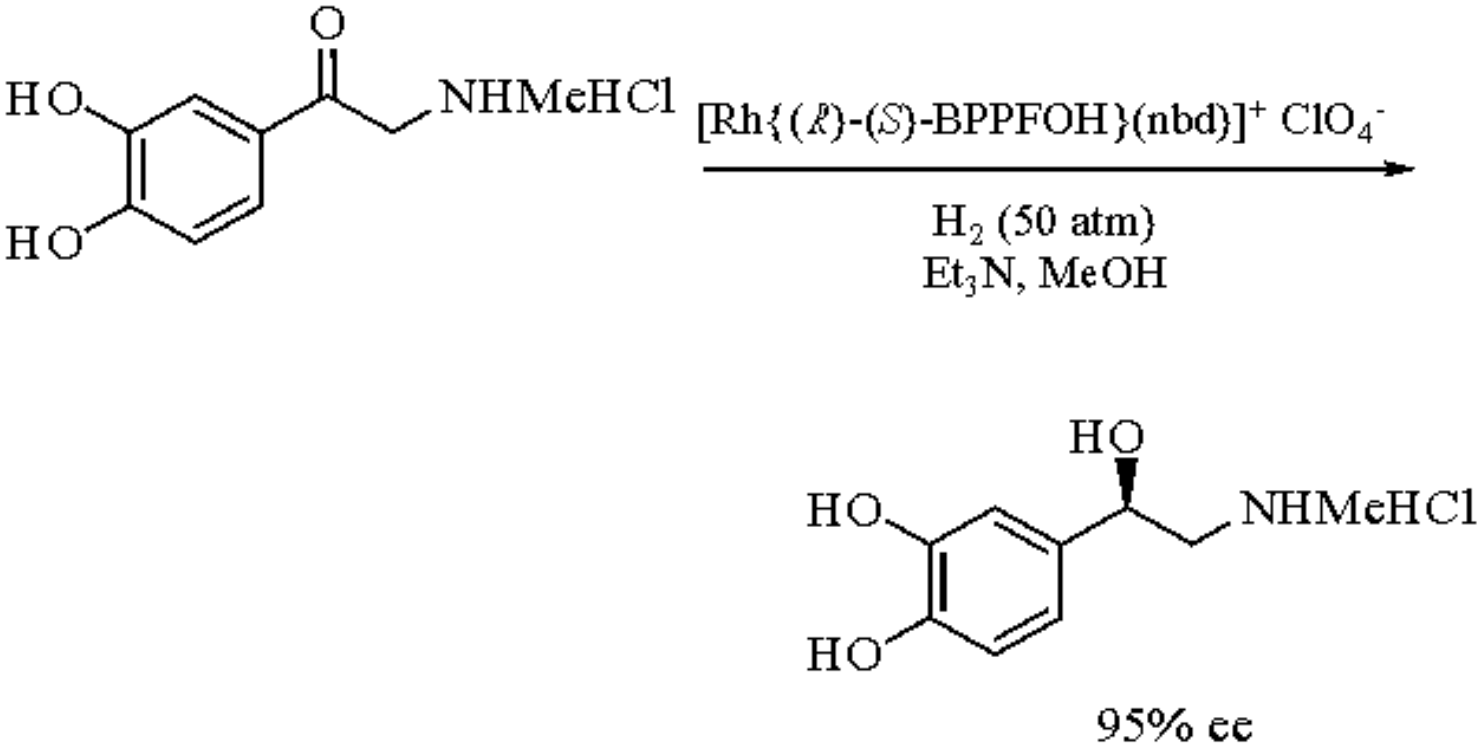

(4)

Isomerization of Allylamines to Enamines.

Allylic hydrogen migration is catalyzed by cationic rhodium complexes. With optically active bidentate phosphines, i.e. BINAP, achiral allylamines isomerize to optically active enamines in high enantiomeric excess (eq 5).[4]

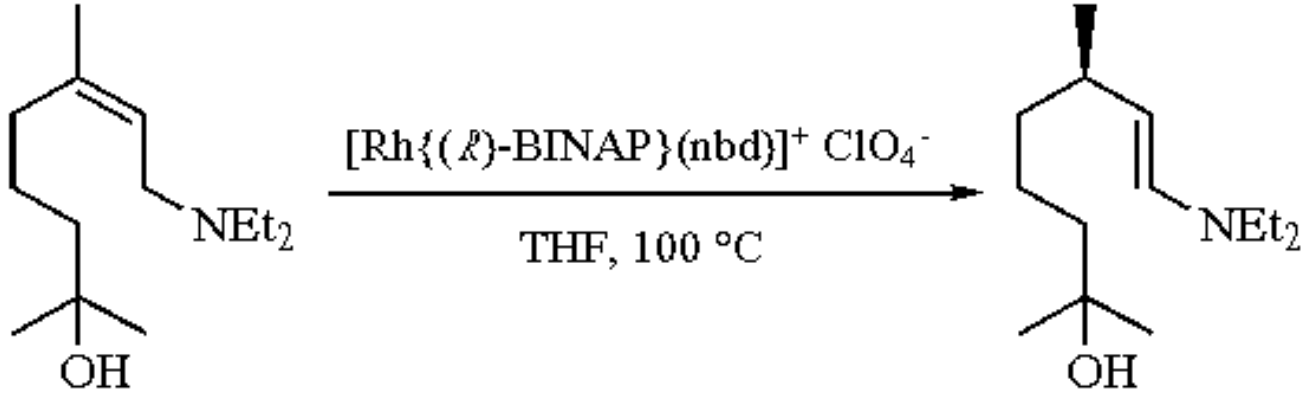

(5)

Hydrosilation.

Asymmetric hydrosilation of prochiral ketones is promoted by cationic rhodium complexes with AMPHOS[15] as well as DIOP[16] to afford the corresponding alcohols in modest to good enantioselectivities. Carbon-carbon double bonds in allylic alcohols are intramolecularly hydrosilated in a highly enantioselective manner. Subsequent H_2O_2 oxidation affords optically active 1,3-diols (eq 6).[5]

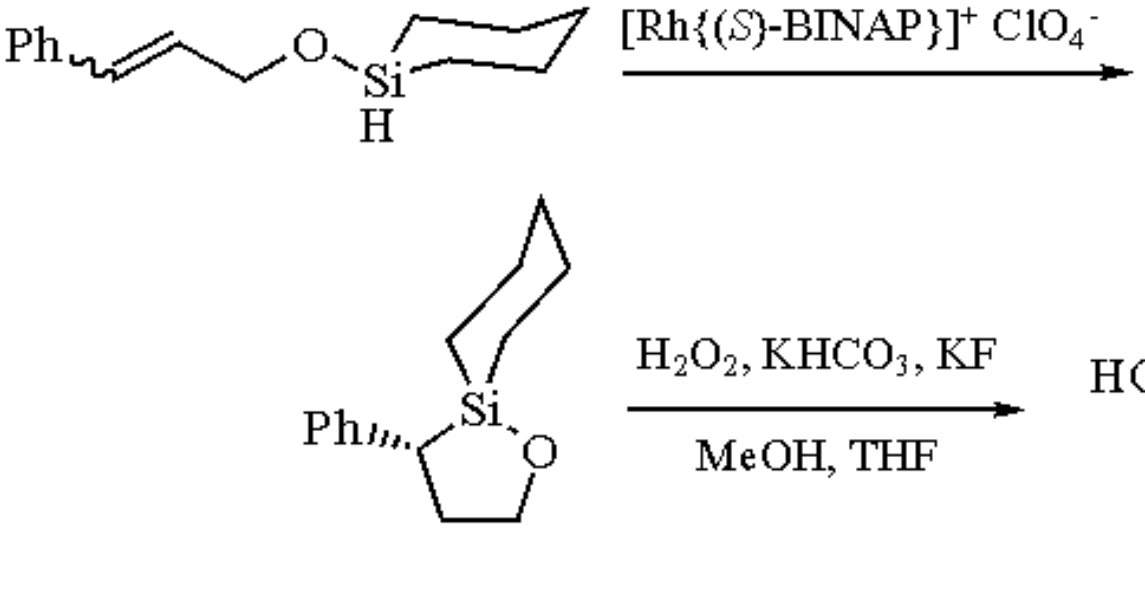

(6)

Hydroacylation.

Cationic rhodium complexes which have bidentate phosphine ligands mediate the hydroacylation of substituted 4-pentenals to cyclopentanones (eq 7).[6] Cationic catalysts are superior in activity to neutral ones such as Wilkinson's catalyst.[17]

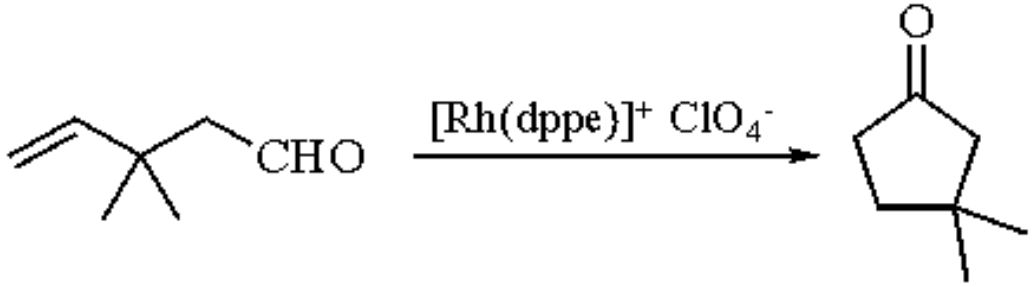

(7)

For a more detailed discussion of catalytic asymmetric syntheses via rhodium complexes, see those entries that deal specifically with rhodium complexes/optically active ligand combinations.

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(R)-1-(S)-1´,2-Bis(diphenylphosphino)ferrocenylethanol; ***Bis(1,5-cyclooctadiene)rhodium Tetrafluoroborate-(R)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***; ***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***; ***(E)-(3-Chloro-1-methyl-1-propenyl)trimethylsilane***; ***(1,5-Cyclooctadiene)[(3R,4R)-3,4-bis(diphenylphosphino)-1-methylpyrrolidine]rhodium Tetrafluoroborate***; ***Chlorotris(triphenylphosphine)rhodium(I)***.

---

1. (a) Harada, K.; Munegumi, T. *COS* **1991**, *8*, Chapter 1.6. (b) Takaya, H.; Noyori, R. *COS* **1991**, *8*, Chapter 3.2. (c) Smith, K.; Pelter, A. *COS* **1991**, *8*, Chapter 3.10. (d) Hiyama, T.; Kusumoto, T. *COS* **1991**, *8*, Chapter 3.12. (e) *Comprehensive Organometallic Chemistry*; Wilkinson, G., ed.; Pergamon: Oxford 1982; Vol. 8.
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11. *N*-(*N´*-Substituted carbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidines: Ojima, I.; Yoda, N. *TL* **1980**, *21*, 1051.
12. (*S,S*)- or (*R,R*)-2,4-bis(diphenylphosphino)pentane: MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *JACS* **1981**, *103*, 2273.
13. Tani, K.; Suwa, K.; Tanigawa, E.; Yoshida, T.; Okano, T.; Otsuka, S. *CL* **1982**, 261.
14. (*R*)-1-(*S*)-1´,2-Bis(diphenylphosphino)ferrocenylethanol: Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *TL* **1979**, 425.
15. *N,N*-Dimethyl-1-{*o*-(diphenylphosphino)phenyl}ethylamine: Payne, N. C.; Stephan, D. W. *IC* **1982**, *21*, 182.
16. 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane: Hayashi, T.; Yamamoto, K.; Kasuga, K.; Omizu, H.; Kumada, M. *JOM* **1976**, *113*, 127.
17. Larock, R. C.; Oertle, K.; Potter, G. F. *JACS* **1980**, *102*, 190.

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Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(*R*)-1-(*S*)-1´,2-Bis(diphenylphosphino)ferrocenylethanol[1]

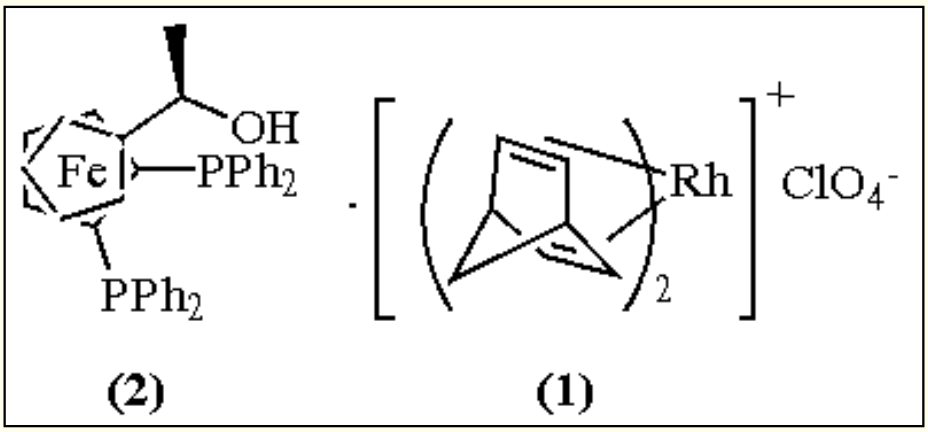

(**1**)

[60576-58-1] · $C_{14}H_{16}ClO_4Rh$ · Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(*R*)-1-(*S*)-1´,2-Bis(diphenylphosphino)ferrocenylethanol · (MW 386.64) (**2**)

[71049-99-5] · $C_{36}H_{32}FeOP_2$ · Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(*R*)-1-(*S*)-1´,2-Bis(diphenylphosphino)ferrocenylethanol · (MW 598.44)

(catalyst for asymmetric hydrogenation of functionalized carbonyl compounds[2,3] and enol phosphinates[4])

Alternate Name: (**1**): $[Rh(nbd)_2]ClO_4$; (**2**): (*R*)-(*S*)-BPPFOH.

Physical Data: (*R*)-(*S*)-BPPFOH: [α]25D -285° (*c* 0.5, $CHCl_3$); mp 154-155 °C.

Solubility: $[Rh(nbd)_2]ClO_4$: sol CH_2Cl_2; insol THF, hexane.

Form Supplied in: $[Rh(nbd)_2]ClO_4$: rust-brown crystals containing 1 mol THF solvent of recrystallization.

Preparative Method: (*R*)-(*S*)-BPPFOH is prepared from optically resolved (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine (**3**) as shown in eq 1.[5] Dilithiation of (*R*)-(**3**) with ***n-Butyllithium*** followed by treatment with ***Chlorodiphenylphosphine*** affords (*R*)-(*S*)-BPPFA stereoselectively. It is treated with an excess of ***Acetic Anhydride*** at 100 °C to give (*R*)-(*S*)-BPPFOAc with retention of configuration. Finally, treatment with BuLi followed by hydrolysis affords (*R*)-(*S*)-BPPFOH in enantiomerically pure form.

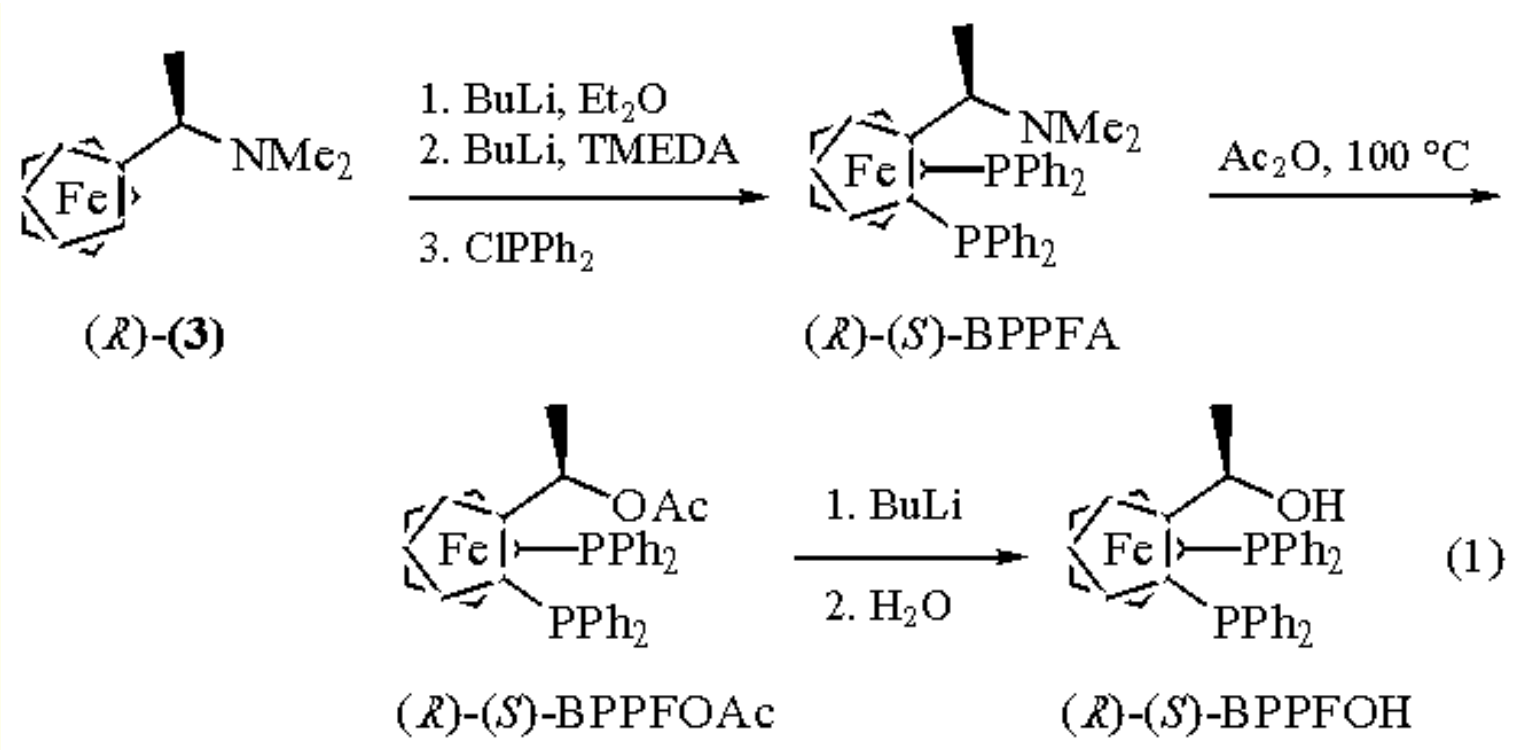

Purification: (*R*)-(*S*)-BPPFOH: chromatography on alumina (EtOAc) followed by recrystallization from ethanol.

Handling, Storage, and Precautions: $[Rh(nbd)_2]ClO_4$: ***explosive*** when heated.

Asymmetric Hydrogenation of Functionalized Carbonyl Compounds.

(*R*)-(*S*)-BPPFOH is designed to have a secondary interaction with a carbonyl substrate through the hydroxy group on the side chain of the ferrocene ring. This additional interaction enables a substrate to coordinate to the metal center with preferential recognition of one prochiral face. In addition to the title combination reagent, $[Rh(cod)_2]ClO_4$ and (*R*)-(*S*)-BPPFOH and the isolated complex, [Rh{(*R*)-(*S*)-BPPFOH}(diene)]ClO_4, will be considered together below.

A high optical yield is attained with [Rh{(*R*)-(*S*)-BPPFOH}(cod)]ClO_4 in the hydrogenation of pyruvic acid to afford (*R*)-2-hydroxypropionic acid (eq 2).[2] Addition of 1 equiv of ***Triethylamine*** is necessary to obtain optimal enantioselectivity. The beneficial effect of the hydroxy group on the side chain of the ferrocene ring is demonstrated by the fact that use of (*R*)-1-(*S*)-1´,2-bis(diphenylphosphino)ferrocenylethyldimethylamine ((*R*)-(*S*)-BPPFA), which is analogous to (*R*)-(*S*)-BPPFOH but lacks the hydroxy group, gives a much inferior result. In the case of a simple ketone, e.g. acetophenone or methyl *t*-butyl ketone, the enantioselectivity is around 40-50% ee.

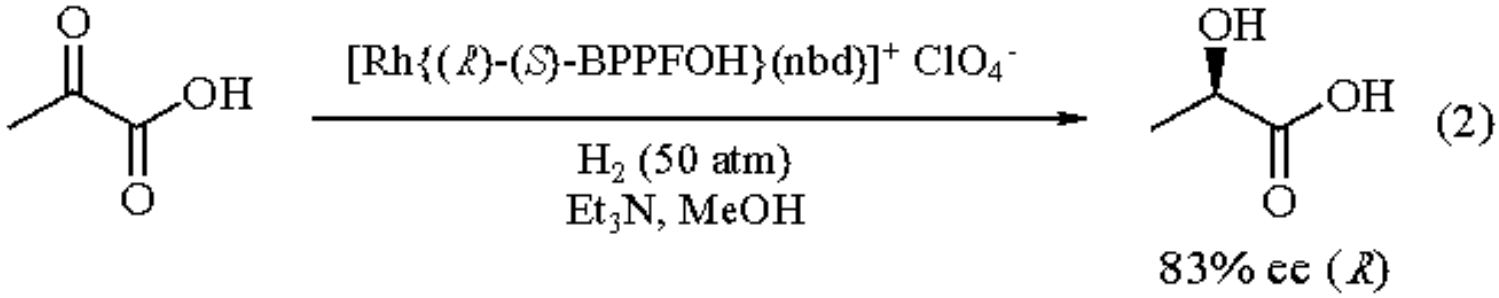

Hydrogenation of aminomethyl aryl ketone hydrochlorides is also catalyzed by [Rh{(*R*)-(*S*)-BPPFOH}(nbd)]ClO_4 to give (*R*)-2-amino-1-arylethanol hydrochlorides in high ee in the presence of triethylamine (eq 3).[3] 3,4-Disubstitution on the aromatic ring by hydroxy or alkoxy groups affords higher selectivity. The principal sympathomimetic hormone, epinephrine, especially is produced in enantiometrically pure form from (*N*-methylamino)methyl 3,4-dihydroxyphenyl ketone hydrochloride.

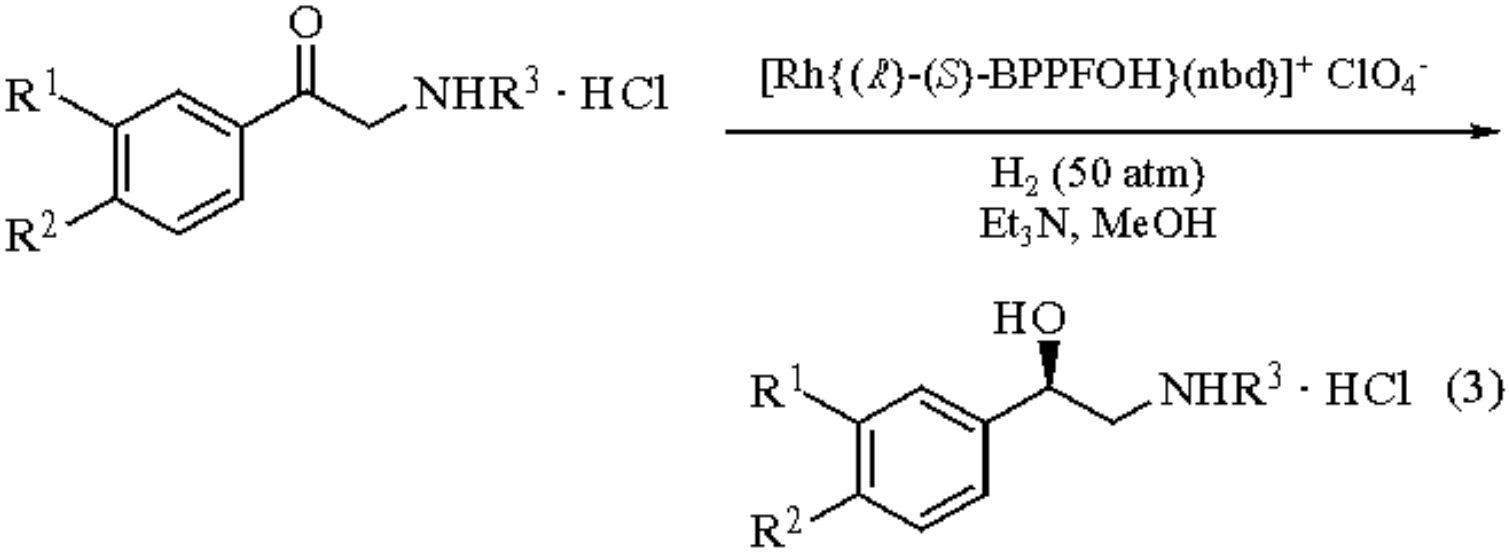

$R^1 = R^2 = OMe$, $R^3 = H$	86% ee
$R^1 = R^2 = OH$, $R^3 = Me$	95% ee
$R^1 = R^2 = R^3 = H$	52% ee
$R^1 = H$, $R^2 = OH$, $R^3 = Me$	69% ee

Asymmetric Hydrogenation of Enol Phosphinates.

Catalytic asymmetric synthesis of secondary alkyl alcohols in up to 78% ee is accomplished by asymmetric hydrogenation of enol diphenylphosphinates followed by hydrolysis (eq 4).[4] The highest enantioselectivity is obtained in the hydrogenation of 1-phenylvinyldiphenylphosphinate, though in the case of phosphinates derived from dialkyl ketones, selectivities are rather low. Substitution of the diphenylphosphinyl group for other phosphorus-containing functional groups lowers the stereoselectivity. Since enol phosphinates are easily prepared from prochiral ketones, this sequence provides an alternative method for the asymmetric hydrogenation of prochiral ketones.

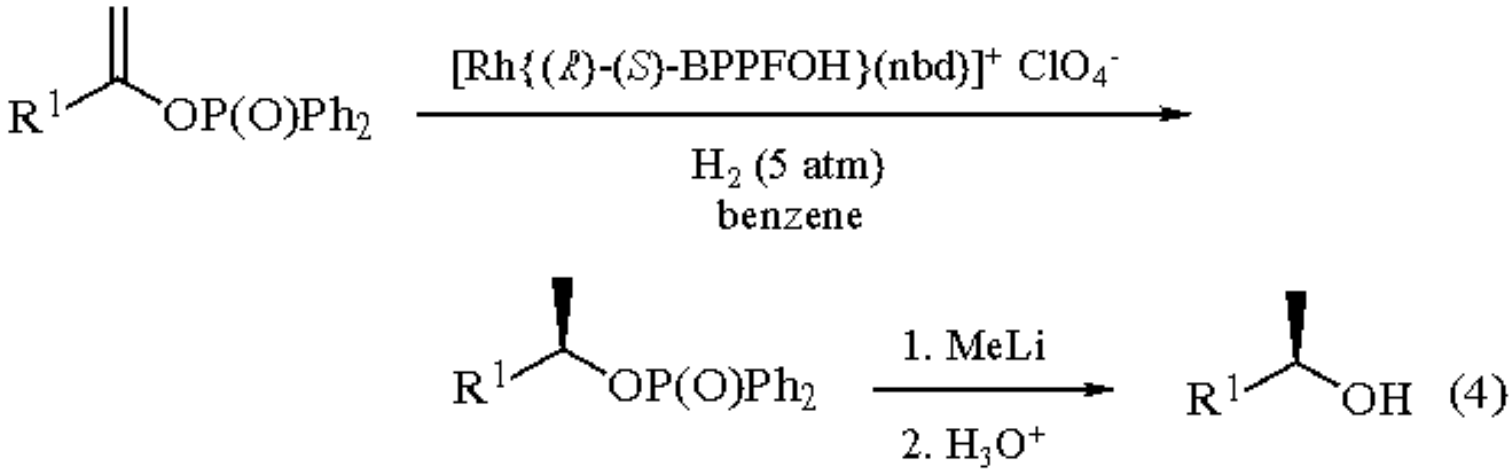

$R^1 = Ph$, 78% ee (*R*); $R^1 = i$-Pr, 60% ee (*R*); $R^1 = t$-Bu, 39% ee (*S*)

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate.

---

1. Harada, K.; Munegumi, T. *COS* **1991**, *8*, Chapter 1.6.
2. Hayashi, T.; Mise, T.; Kumada, M. *TL* **1976**, 4351
3. Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *TL* **1979**, 425.
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Bis(2,2´-bipyridyl)copper(II) Permanganate

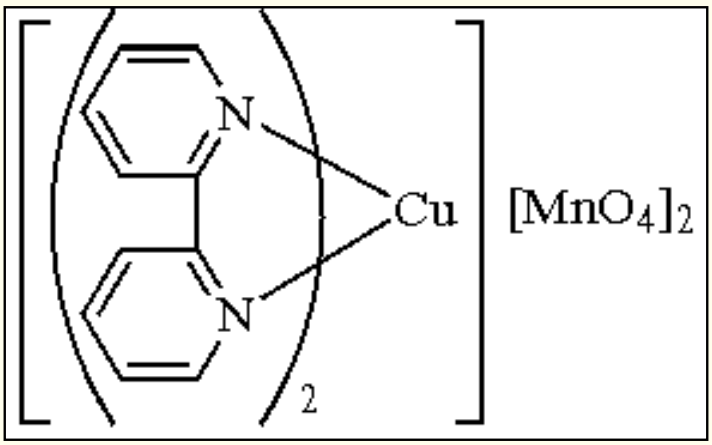

[86609-17-8] · $C_{20}H_{16}CuMn_2N_4O_8$ · Bis(2,2´-bipyridyl)copper(II) Permanganate · (MW 613.79)

(oxidant, used for the oxidation of thiols to disulfides,[1] benzylic alcohols to carbonyl compounds,[2] aromatic amines to azo compounds,[2] benzylamine and oximes to the corresponding carbonyl compounds[2])

Alternate Name: bis(2,2-bipyridine-*N,N´*)copper(2+) permanganate.

Physical Data: purple solid; decomposes at 105-110 °C.[2]

Solubility: sol water, acetone, and methylene chloride.[2]

Analysis of Reagent Purity: λ_{max} (log ε) (H_2O): 290 nm (4.50), 296 (4.59), 306 (4.58), 458, (3.23), 474 (3.28), 491 (3.38), 510 (3.49), 529 (3.57), 552 (3.54), 576 (3.35).

Preparative Methods: ***Potassium Permanganate*** (0.01 mol) dissolved in a minimum of water is added to bis(2,2´-bipyridyl)copper(II) chloride (0.02 mol) in water (25 mL). On cooling a purple precipitate is collected and air dried.[2] The yield is 95%.

Handling, Storage, and Precautions: oxidant, store in a glass vessel at or below rt. The reagent should be filtered and dried on a filter paper, not on a sintered glass funnel. It should be transferred with nonmetallic spatulas; if metallic spatulas are used the reagent may burst into flame.[1]

Oxidation of Thiols to Disulfides.[1]

Bis(2,2´-bipyridyl)copper(II) permanganate can be used to prepare disulfides from the corresponding sulfides. The reactions are carried out in methylene chloride at rt, times range from 5-45 min (eqs 1 and 2).

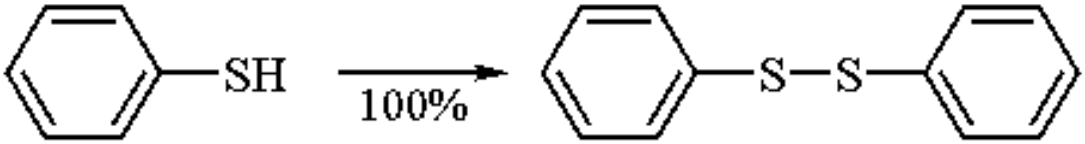

(1)

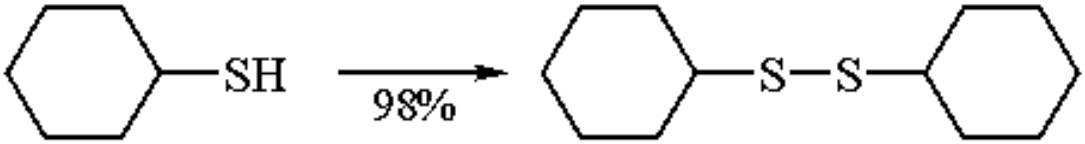

(2)

Oxidation of Aromatic Amines to Azo Compounds.[2]

In a somewhat similar reaction, aromatic amines are oxidatively coupled to give azo compounds. The reactions are carried out in refluxing methylene chloride. Some examples are shown in eqs 3 and 4.

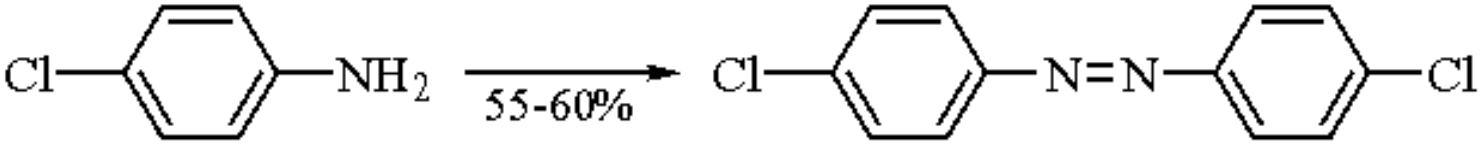

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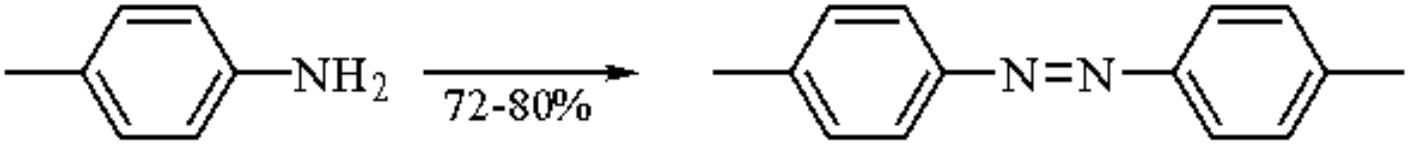

(4)

Oxidation of Benzylic Secondary Alcohols.[2]

Benzyl and cinnamyl alcohols are oxidized to the corresponding aldehydes by this reagent. Of particular interest is the observation that benzylic secondary alcohols are selectively oxidized, as in eq 5.

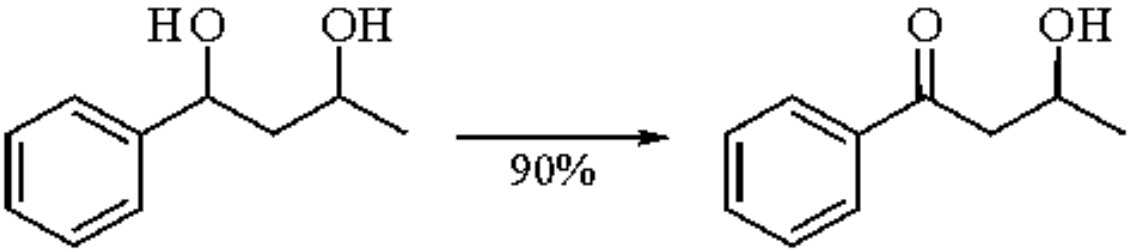

(5)

Oxidation of Alkenes.[2]

When acetone is used as the solvent, carbon-carbon double bonds adjacent to an aromatic ring are cleaved, as in eq 6.

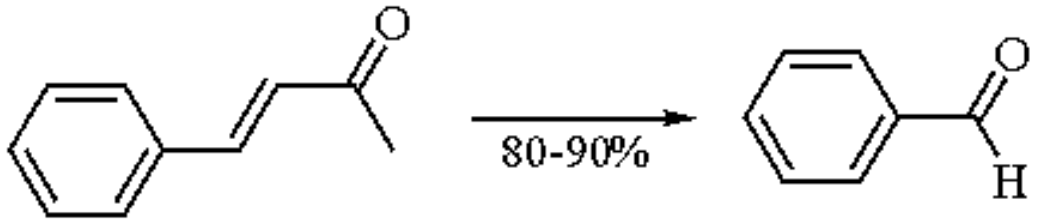

(6)

Conversion of Oximes to Carbonyl Compounds.

Oximes are converted into the corresponding carbonyl compounds when treated with this reagent (eq 7).

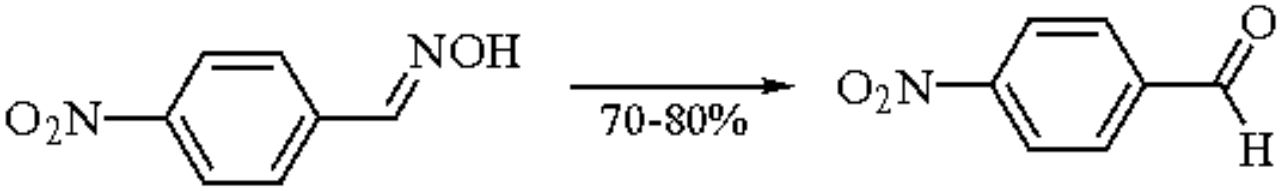

(7)

The reactions of bis(2,2´-bipyridyl)copper(II) permanganate are very similar to those of ***Bis(pyridine)silver(I) Permanganate***. Kinetic studies of the oxidation of aliphatic aldehydes[3] and thioacids[4] by bis(2,2´-bipyridyl)copper(II) permanganate have been reported.

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Bis[1,2-bis(diphenylphosphino)ethane]palladium(0)[1]

$(Ph_2PCH_2CH_2PPh_2)_2Pd$

[31277-98-2] · $C_{52}H_{48}P_4Pd$ · Bis[1,2-bis(diphenylphosphino)ethane]palladium(0) · (MW 903.26)

(homogeneous catalyst most widely used in allylic substitution reactions;[5] good catalyst for bulky substrates;[1] slowly dissociating ligand that gives good stereoselectivity[5])

Alternate Names: 1,2-ethylenebis(diphenylphosphine)palladium; bis(diphenylphosphinoethane)palladium(0); ethanediylbisdiphenylphosphinepalladium(0).

Physical Data: mp 234 °C.[2]

Solubility: sol nonprotic solvents.

Form Supplied in: yellow solid.

Analysis of Reagent Purity: ^{31}P and ^{1}H NMR in $CDCl_3$ and ^{31}P NMR in benzene.[3]

Preparative Methods: by reduction of palladium(II) with $NaBH_4$,[2] DIBAL-H, hydrazine, KOH/phosphine,[4] or F^-.[3] Most conveniently prepared in situ from $Pd(dba)_2$ or $Pd(OAc)_2$.[5,6]

Purification: recrystallized from benzene-ethanol[2] or ethanol.[5]

Handling, Storage, and Precautions: air and light sensitive. If stored under nitrogen or argon it is stable for about one month. Avoid inhalation. Use in a fume hood.

General Considerations.

$Pd(dppe)_2$ is a homogeneous catalyst, commercially available but usually prepared in situ because of its sensitivity to oxygen.[5,6] It is often used as a catalyst in allylic substitution reactions. This reaction proceeds via formation of a (π-allyl)palladium(II) complex by oxidative addition of palladium(0) to an allylic substrate. Subsequent nucleophilic attack on the π-allyl gives the product and liberates a palladium(0) complex. The latter complex can then activate a new substrate and this makes the reaction catalytic. The reaction is stereoselective and net retention is generally

observed as a result of a double inversion (eq 1).

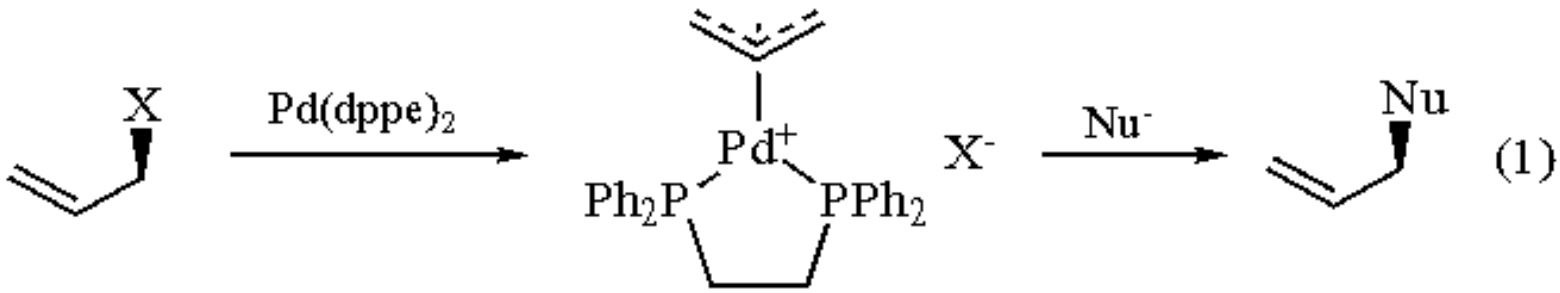

With the exception of $Pd(dppe)_2$[1b] there are few zerovalent palladium complexes that offer any advantage over the widely used ***Tetrakis(triphenylphosphine)palladium(0)***. Dppe is a bidentate ligand and therefore sterically less demanding than PPh_3. It is used for bulky substrates and in reactions where it is important to have a stable initial alkene-metal complex.[1a,7]

In allylic substitution reactions, dppe forms a stable (π-allyl)palladium complex and the stability of the complex makes geometrical isomerization possible prior to nucleophilic attack (eq 2).[8,9] If the starting material is *cis*, the *trans* product can be obtained if appropriate reaction conditions are used.[8]

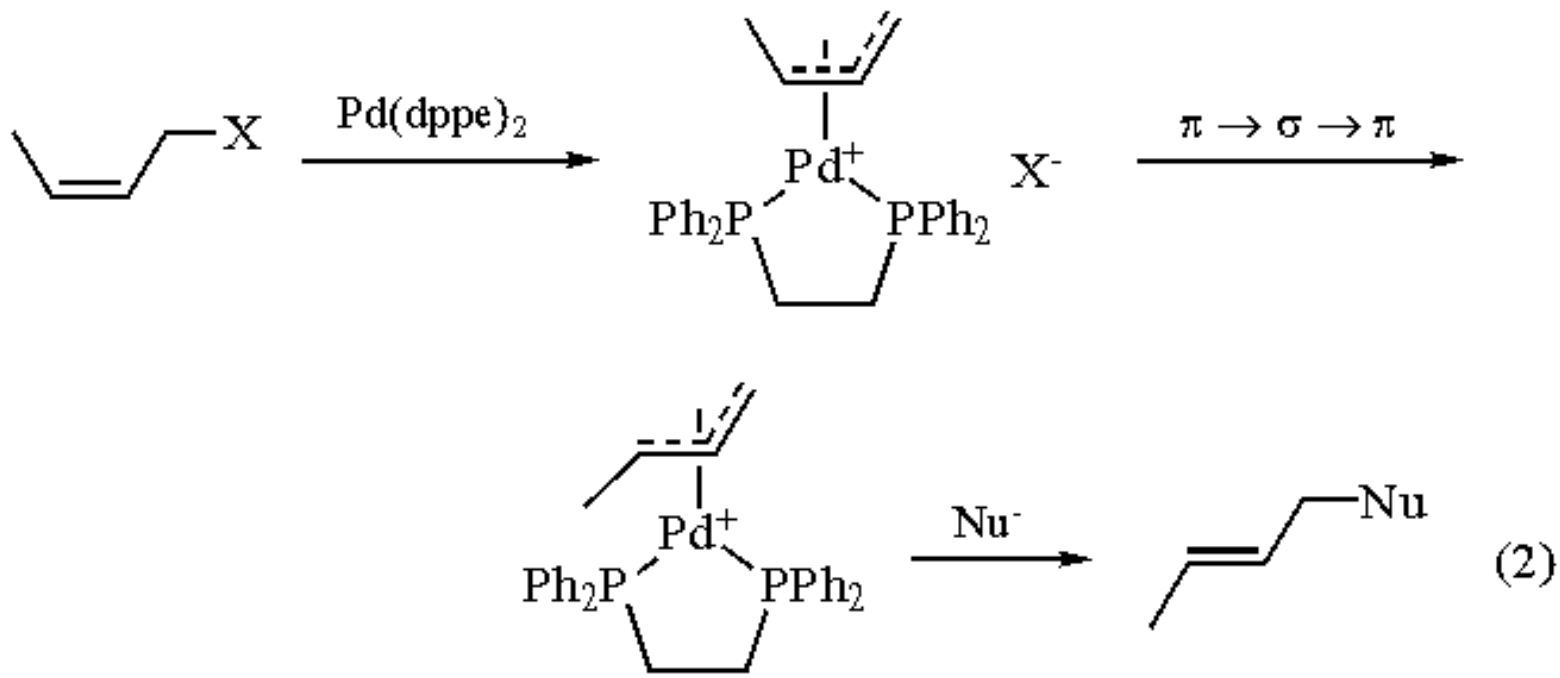

Dppe is used in stereoselective allylic substitution reactions.[10] Because of its slow dissociation from palladium in $Pd(dppe)_2$, only a little Pd(dppe) is present in the solution. This is important because PdL_2 is more nucleophilic than PdL_4[11a] and can displace Pd in (π-allyl)palladium complexes and cause a loss of stereoselectivity (eq 3).[10,11]

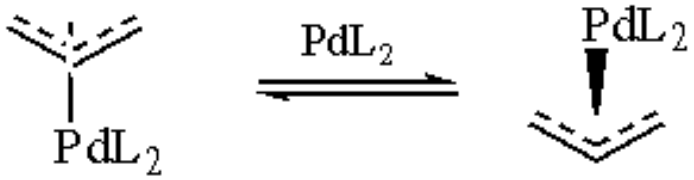

(3)

Different ligands afford different products in Pd^0-mediated allylic substitutions.[12] For example, dialkylpalladium complexes with chelating bidentate or monodentate phosphine ligands, respectively, react via different pathways. If a bidentate ligand with a carbon chain of 2-4 carbons between the phosphorus atoms is used, a *cis* complex is obtained.[13] If instead a monodentate ligand or a bidentate ligand with a longer carbon chain is used, a *trans* complex is formed.[14] These different complexes give rise to different products.[15] Dppe favors reductive elimination whereas monodentate ligands favor β-elimination (eq 4). Variations in the carbon backbone can also affect the chelating power of the bidentate ligand and give rise to different product distributions.[12i]

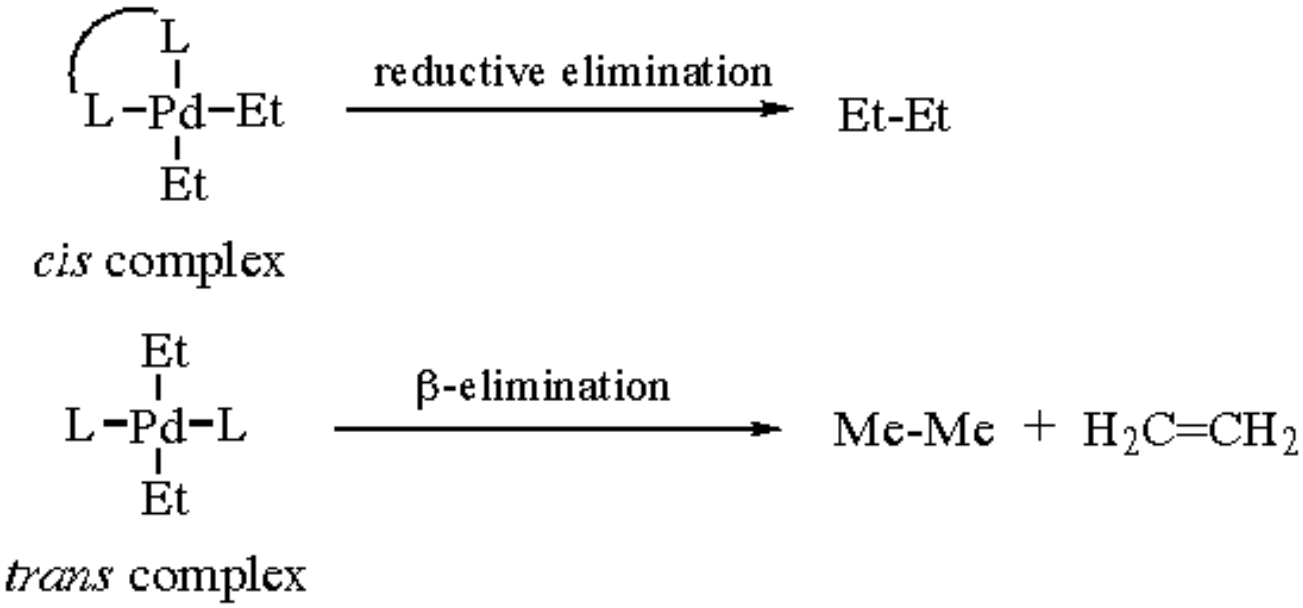

(4)

In general, reactions catalyzed by $Pd(dppe)_2$ are sensitive to the reaction conditions.[16] By varying the temperature,[12j] solvent,[7,16d,17] phosphine to palladium ratio,[5,6,15] the source of $Pd(dppe)_2$,[5,6] or added bases,[18] different products may be obtained.

Reactions with $Pd(dppe)_2$ as the Catalyst.

There are some reactions where it is essential to use $Pd(dppe)_2$ as the catalyst to obtain good results. For example, allylic substitution reactions where primary or secondary amines,[8] Schiff bases,[6,9a] or carbanions[9-19] act as nucleophiles give highest yields using the title reagent. One example is the cyclopropane forming reaction shown in eq 5.[5,12f,20] Another example can be found in an annulation reaction used in a synthesis of alloyohimbone.[21]

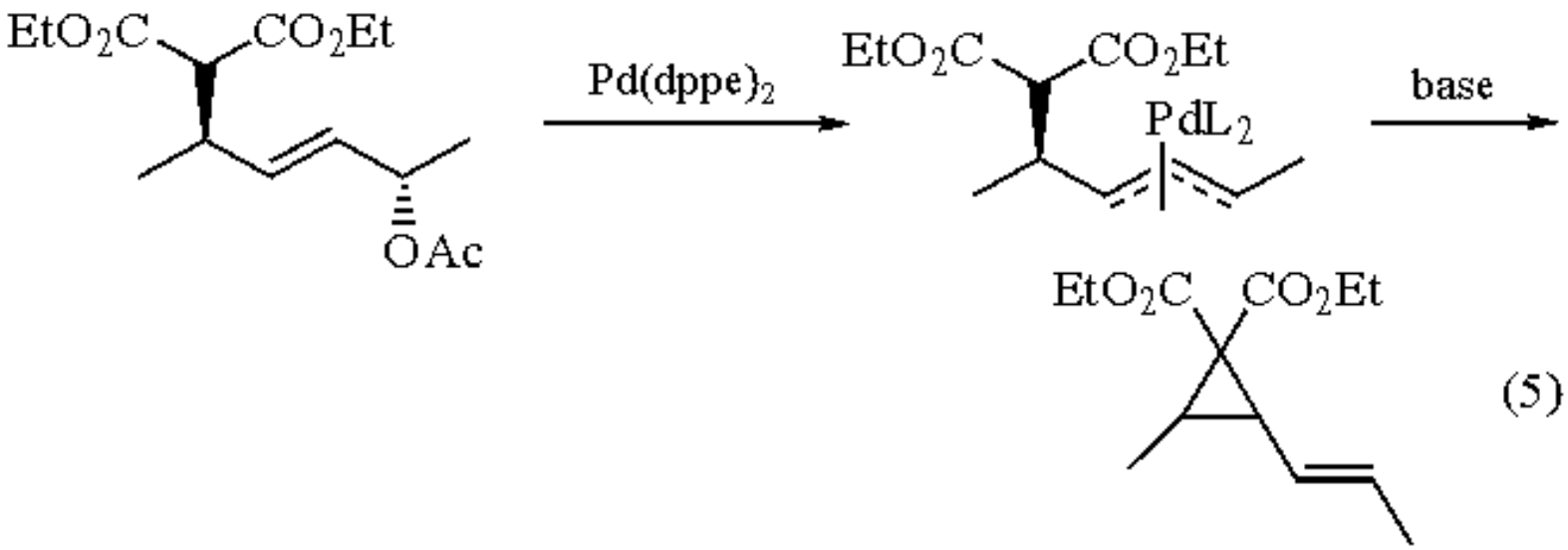

$Pd(dppe)_2$ is the best reagent for oxidation of cyclohexene,[22] for CO insertion reactions,[23] in some reactions employing CO_2,[12h,24] for the rearrangement of tetrahydrofurans to cyclopentanones,[7] in the synthesis of 1,3-dienes by elimination of HOAc in an allylic acetate,[5] and for the formation of α,β-unsaturated ketones from allyl enol carbonates.[25] There are other reactions where $Pd(dppe)_2$ can be used but is not always the best catalyst. The title reagent has been used for coupling reactions,[16f,26] in homogenous hydrogenation,[4b] in oxidative homologation,[27] and as a promotor for isomerizations of α-iodocarbonyls involving radical rather than organometallic intermediates.[28]

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Bis[1,3-bis(diphenylphosphino)propane]rhodium Tetrafluoroborate[1]

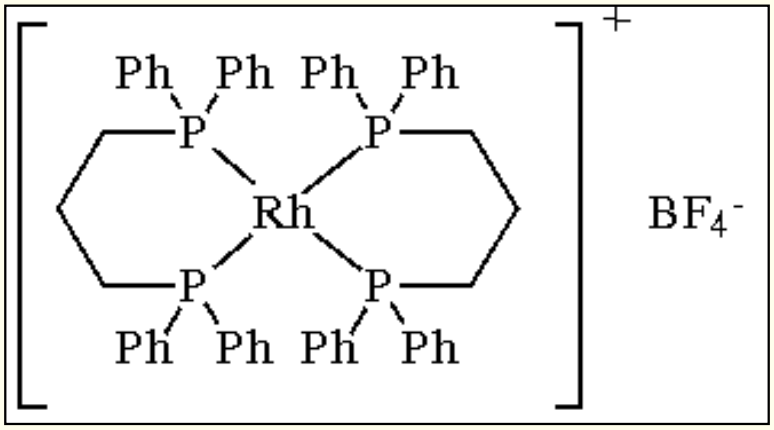

[70196-21-3] · $C_{54}H_{52}BF_4P_4Rh$ · Bis[1,3-bis(diphenylphosphino)propane]rhodium Tetrafluoroborate · (MW 1014.61)

(catalytic decarbonylation of aldehydes[2,3])

Solubility: sol CH_2Cl_2, acetone, MeCN, *m*-xylene, toluene; slightly sol MeOH; insol diethyl ether.

Analysis of Reagent Purity: ^{31}P NMR: δ = 6.4, J_{Rh-P} = 132 Hz (ambient temp, acetone-d_6, downfield from 85% H_3PO_4). Electronic absorption spectroscopy: λ_{max}, nm (log ε$_{max}$) 406 (3.49).

Preparative Method: all manipulations are carried out under a nitrogen atmosphere with use of standard Schlenk techniques. Rh_2Cl_2(1,5-cyclooctadiene)$_2$ (400 mg, 1.63 mmol) is dissolved in 50 mL of degassed acetone to which ***Silver(I) Tetrafluoroborate*** (337 mg, 1.73 mmol) is added to precipitate AgCl. The mixture is stirred for 1 h and filtered. The filtrate is added to an acetone solution of dppp (***1,3-Bis(diphenylphosphino)propane***) (1.58 g, 3.84 mmol). The acetone is partially evaporated under vacuum leaving a precipitate of orange-yellow flakes of $[Rh(dppp)_2]BF_4$ in high yield.

Purification: the product $[Rh(dppp)_2]BF_4$ is recrystallized from a solvent mixture of CH_2Cl_2 and Et_2O by a standard layering technique. The orange-yellow flakes of $[Rh(dppp)_2]BF_4$ are dissolved in a minimum amount of CH_2Cl_2 in a Schlenk tube equipped with a rubber septum. A volume of Et_2O (ca. 3 times the CH_2Cl_2 volume) is carefully layered on top with use of a syringe or cannular tube. The solvents are allowed to slowly diffuse, and large red crystals are isolated. The red crystals are washed with Et_2O and dried under vacuum.[4]

Handling, Storage, and Precautions: the catalyst is air stable in the solid state. However, it is recommended that it be stored under N_2. Decarbonylation reactions *must* be carried out in the absence of oxygen.

Aldehyde Decarbonylation.

The catalyst $[Rh(dppp)_2]BF_4$ decarbonylates aldehydes in a homogeneous solution phase with rates that are more than two orders of magnitude faster than the stoichiometric reagent ***Chlorotris(triphenylphosphine)rhodium(I)***, or the catalytic reagent ***Carbonyl(chloro)bis(triphenylphosphine)rhodium(I)***. A wide variety of aldehydes can be decarbonylated under mild thermal conditions, as shown in Table 1.[5] This decarbonylation reaction occurs with high product yields (based on aldehydes), and total turnovers in excess of 100 000 have been achieved. The catalyst is stable for days, and the reactions are highly selective. A typical reaction with benzaldehyde or heptanal is carried out with approx. 20 mg of $[Rh(dppp)_2]BF_4$ dissolved under an N_2 atmosphere in 30 mL of either neat aldehyde or about 2 mL of aldehyde in *m*-xylene or toluene. The homogeneous solution is stirred at constant temperature and continuously purged with N_2 gas. The products can be collected continuously in a cold trap connected to a reflux condenser.

Table 1 Yield and Conversion for the Decarbonylation of Various Aldehydes[a]

Aldehyde (mmol)	Time (day)	Temp. (°C)	Product	Yield[b] (%)	Conversion (%)[b]
Benzaldehyde (2.45)	2.0	140	Benzene	79	100
Cinnamaldehyde (4.00)	2.0	118	Styrene	95	100
2-Phenylpropanal (64.0)	1.5	175	Ethylbenzene	83	93
Heptanal (1.85)[c]	2.0	118	Hexane	39	46
2-Ethylbutanal (60.8)[c]	1.5	110	Pentane	15	43

[a] 0.02 to 0.05 mmol $[Rh(dppp)_2]BF_4$ catalyst in *m*-xylene or a-methylnaphthalene solvent. [b] The % yield = [(moles decarbonylation product)/(moles aldehyde added)] ´ 100; % conversion = [(moles decarbonylation product)/(moles aldehyde consumed)] ´ 100. [c] These aldehydes are decarbonylated in lower yield (still good activities, Table 2) due to thermal instability.

The activity of the catalyst is dependent on the steric size and electronic inductive properties of the aldehyde substrate.

Compared to other catalysts, $[Rh(dppp)_2]BF_4$ is significantly more active for the decarbonylation of benzaldehyde. $Rh(PPh_3)_3Cl$[6] at 150 °C demonstrates a catalytic activity of 0.60 moles benzene (mol catalyst)$^{-1}$ h^{-1} while the catalytic activity of $[Rh(dppp)_2]BF_4$ at the same temperature is 1.0×10^2. Focusing on the steric size of the substrate, there is a significant rate decrease when the α-carbon atom of the aldehydes is substituted (Table 2). The decarbonylation of tertiary aldehydes is of no synthetic utility as it occurs very slowly, even at 180 °C. *Para* substitution on benzaldehyde (either with electron-withdrawing or electron-donating groups) decreases the catalytic activity. This is in contrast to that observed using $Rh(PPh_3)_3Cl$ (stoichiometric reaction at 100 °C), where a linear Hammet plot was obtained with a positive ρ value.[7]

Table 2 Steric and Electronic Effects of Aldehydes and Catalyst Selectivity

Aldehyde	Only volatile product	Temp (°C)	Catalytic activity (turnover h^{-1})
Heptanal	Hexane	115, 150	31, 330
Benzaldehyde	Benzene	115, 150	11, 90
p-Methylbenzaldehyde	Toluene	115, 150	3.0, 34
p-Methoxybenzaldehyde	Anisole	150	10
p-Chlorobenzaldehyde	Chlorobenzene	150	1.0
2-Ethylbutanal	Pentane	115	5.0
2-Phenyl-2-methylbutanal	2-Phenylbutane	180	1.3
2-Phenylpropanal	Ethylbenzene	115, 150	16, 67
Cinnamaldehyde	Styrene	150	135
a-Methylcinnamaldehyde	*cis*-b-Methylstyrene	150	16

An important characteristic of $[Rh(dppp)_2]BF_4$ is its excellent selectivity. For example, the yield for benzene production from benzaldehyde is 100%. Note that 1-heptanal is converted into 86% hexane and 14% 1-hexene by $Rh(PPh_3)_3Cl$ (stoichiometric reaction, 25 °C); while using $[Rh(dppp)_2]BF_4$ as the catalyst, the only volatile product is hexane.

Additionally, only ethylbenzene is produced from 2-phenylpropanal although the possible unsaturated product, styrene, is very stable. $Rh(PPh_3)_3Cl$ is also known to isomerize double bonds during decarbonylation.[8] For example, α-methylcinnamaldehyde is converted into 91% *cis*- and 9% *trans*-β-methylstyrene at 140 °C. No *trans* isomer is produced using $[Rh(dppp)_2]BF_4$ at 150 °C.

The effect of added reagents on the catalytic activity of $[Rh(dppp)_2]BF_4$ is worth noting. The catalyst will tolerate molar concentrations of ketones, acids, alkenes, and chlorinated aromatics with only a moderate decrease in activity.[1] In general, reagents that can compete for a coordination site on the rhodium atom (i.e. CO, nitriles, phosphines, acid chlorides) will effectively retard the reaction rate. Most importantly, the presence of O_2 irreversibly decomposes the catalyst in solution. Thus all decarbonylations must be carried out under an inert atmosphere such as N_2 gas.

There have been several reports of catalytic aldehyde decarbonylation systems based on Ru^{II} and Fe^{II} tetraphenylporphyrin compounds.[9,10] These catalysts are thought to involve radical pathways and offer an alternative to $[Rh(dppp)_2]BF_4$.

---

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Bis[*N,N*-bis(trimethylsilyl)amino]tin(II)[1]

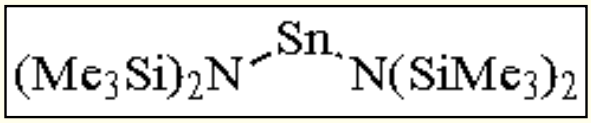

[59863-13-7] · $C_{12}H_{36}N_2Si_4Sn$ · Bis[*N,N*-bis(trimethylsilyl)amino]tin(II) · (MW 439.46)

(stannylene precursor; reduction of azides to primary amines; insertion with alkyl and aryl halides; enamine synthesis; conversion of esters and carboxylic acids to secondary and tertiary amides)

Alternate Name: tin(II) bis[bis(trimethylsilyl)amide].

Physical Data: mp 37-38 °C, ^{1}H NMR(C_6D_6) δ 0.30; ^{119}Sn NMR(C_6D_6) δ 770.

Solubility: sol hexane, benzene, Et_2O, THF, acetonitrile.

Preparative Methods: a 500 mL round bottomed flask equipped with a nitrogen inlet was charged with 65 mL of dioxane and 40.1 g of anhydrous ***Tin(II) Chloride*** (0.21 mol). This suspension was allowed to stir for 30 min at rt, and was then treated with 71.0 g of ***Lithium Hexamethyldisilazide*** (0.43 mol) in several small portions. During the addition of $LiN(TMS)_2$ the reaction mixture became warm and turned dark red-orange in color. A Vigreux column and vacuum distillation apparutus were attached to the flask, and it was heated at 35 °C for 45 min. The apparatus was then placed under vacuum (0.5 mmHg) and the bath warmed to 85 °C. The forerun, mainly dioxane, was collected with the help of a dry ice acetone bath. Bis[*N,N*-bis(trimethylsilyl)amino]tin(II) distilled as a bright red oil between 105-115 °C (80.4 g, 86%); this material solidified upon standing at rt.[2]

Handling, Storage, and Precautions: is nonpyrophoric but should be handled under a nitrogen atmosphere, and stored in a refrigerator. Since the solid is very soluble in hexane, it is convenient to prepare a hexane solution which may then be transferred via conventional syringe techniques. It readily hydrolyzes to tin(II) oxide, which is of reputed low toxicity. Use in a fume hood.

Stannylene Precursor.

The two silazane ligands on $Sn[N(TMS)_2]_2$ undergo facile metathesis reactions with amines, alcohols, amides, carboxylic acids, amine hydrochloride salts, and related compounds.[1] For example, addition of 2 equiv of piperidine to $Sn[N(TMS)_2]_2$ gives bis(piperidinyl)tin(II) (**1**) as a bridging dimer (eq 1). Subsequent addition of 1 equiv of *t*-BuOH to (**1**) yields tin(II) alkoxyamide (**2**), also as a dimer. Primary amines react with $Sn[N(TMS)_2]_2$ to give tin(II) amines with a cubic structure.[1]

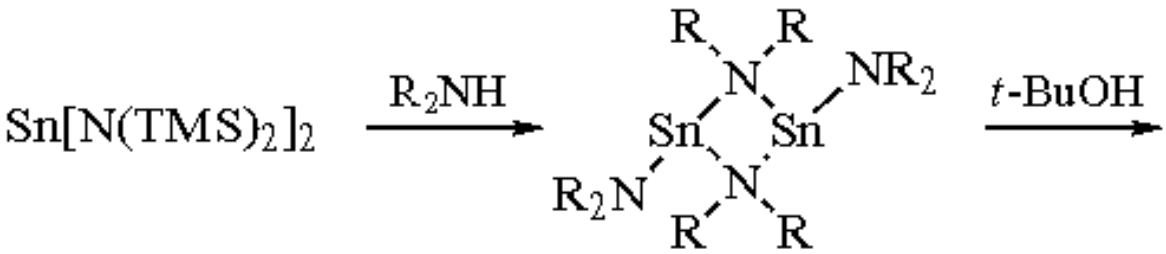

(1)

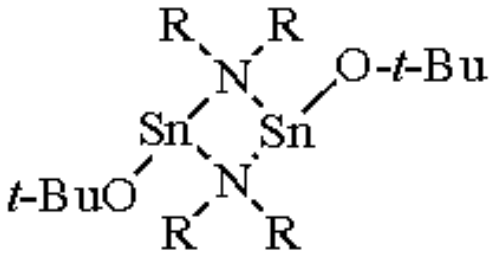

(1)

(2)

Reduction/Insertion Chemistry.

$Sn[N(TMS)_2]_2$ has been used for the reduction of azides to primary amines.[3] It undergoes insertion reactions with both alkyl and aryl halides, especially bromides and iodides (eq 2).[4]

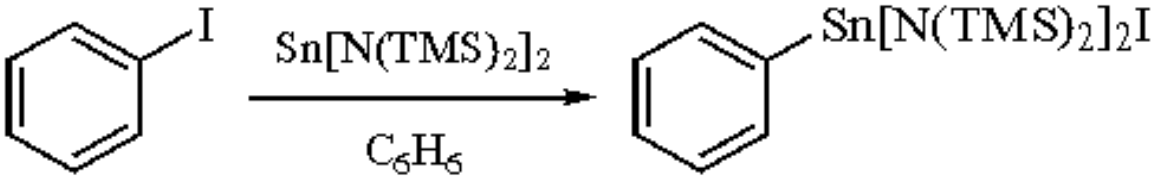

(2)

Enamine Synthesis.

$Sn[N(TMS)_2]_2$ converts α-unsubstituted aldehydes to *trans*-*N*,*N*-bis(trimethylsilyl)enamines in 22-40% isolated yield (eq 3).[5] It does not react with more hindered α-substituted aldehydes, nor with ketones, esters, nitriles, acetals, terminal alkynes, alkenes, epoxides, or ethers. Addition of a secondary alkylamine to $Sn[N(TMS)_2]_2$ prior to addition of either an aldehyde or a ketone results in formation of a *N*,*N*-dialkylenamine (eq 4).[6]

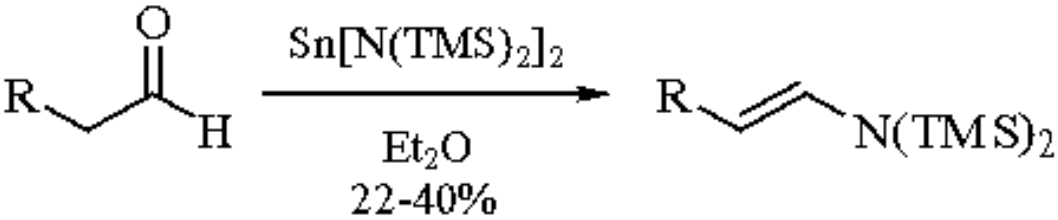

(3)

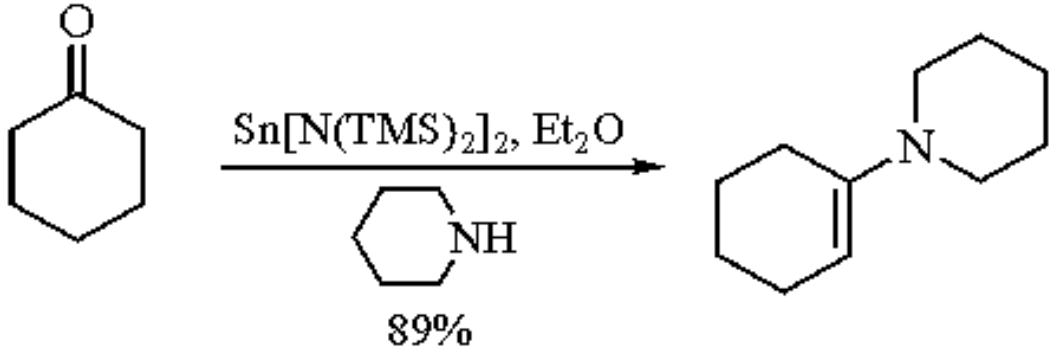

(4)

Esters to Tertiary Amides.

Esters can be converted to tertiary amides using reagents derived in situ from $Sn[N(TMS)_2]_2$ (see ***Dimethylaluminum Amide***). For example, addition of 1 equiv of piperidine to $Sn[N(TMS)_2]_2$ generates an unsymmetrical tin(II) amine, which converts methyl 2-phenylacetate to an amide in 74% yield (eq 5).[7] Similarly, addition of both piperidine and *N-t*-butylacetamide to $Sn[N(TMS)_2]_2$ generates a new tin(II) amine via metathesis of both silazane ligands; this reagent converts methyl 2-phenylacetate to its piperidine amide in 93% yield.

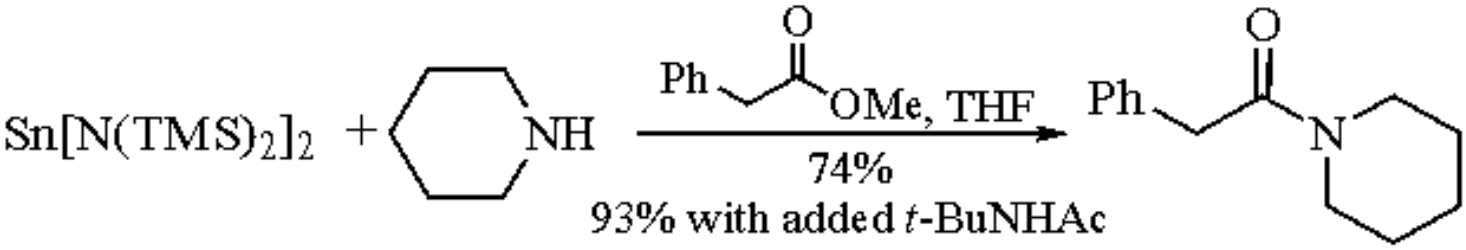

(5)

An intramolecular variant of this methodology can be used for the preparation of β-lactams from β-amino esters. Nonsterically encumbered β-amino esters are readily cyclized to β-lactams simply with $Sn[N(TMS)_2]_2$ (eq 6).[8] Substrates with bulky groups on nitrogen or at the β-position of the amino ester are converted to β-lactams in high yield using unsymmetrical tin(II) amines.

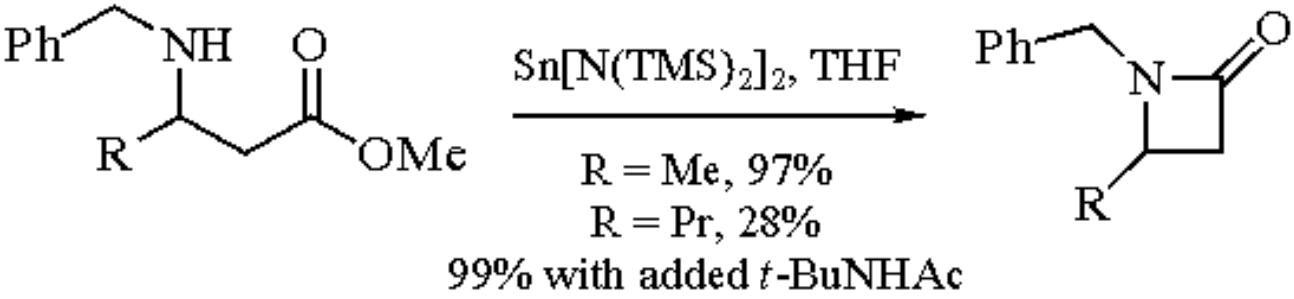

(6)

Finally, the ester to tertiary amide transformation can also be effected using the amine hydrochloride salts of volatile amines. Addition of $Sn[N(TMS)_2]_2$ to dimethylamine hydrochloride generates a tin(II) amido chloride, which efficiently converts α-unsubstituted esters to amides (eq 7).[9]

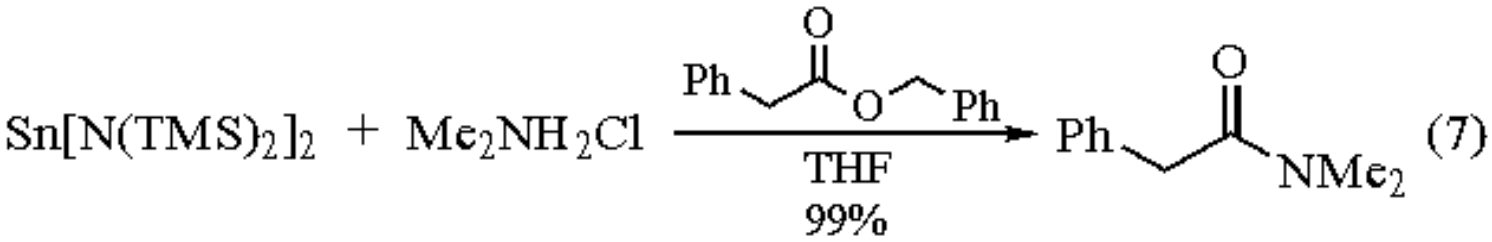

Esters to Secondary Amides.

Tin(II) amines with a cubic structure are formed in the reaction of $Sn[N(TMS)_2]_2$ with primary amines. These tetrameric tin(II) amines are less reactive towards esters than the dimeric tin(II) amines formed from $Sn[N(TMS)_2]_2$ and secondary amines. This lack of reactivity can be circumvented via two procedures, one of which is substrate based and the other, reagent based.[10] In the substrate based approach, a glycol ester reacts with $Sn[N(TMS)_2]_2$ and a primary amine to give an intermediate tin(II) alkoxyamine. Intramolecular delivery of the amino group to the ester provides the secondary amide in high yield (eq 8). In the second approach, simple methyl esters can be converted to secondary amides using a reagent derived from $Sn[N(TMS)_2]_2$, *N*,*N*-dimethylethanolamine, and a primary amine (eq 9). Incorporation of *N*,*N*-dimethylethanolamine as the auxillary ligand appears to retard formation of cubic tetramers and help promote transfer of the primary amino group.

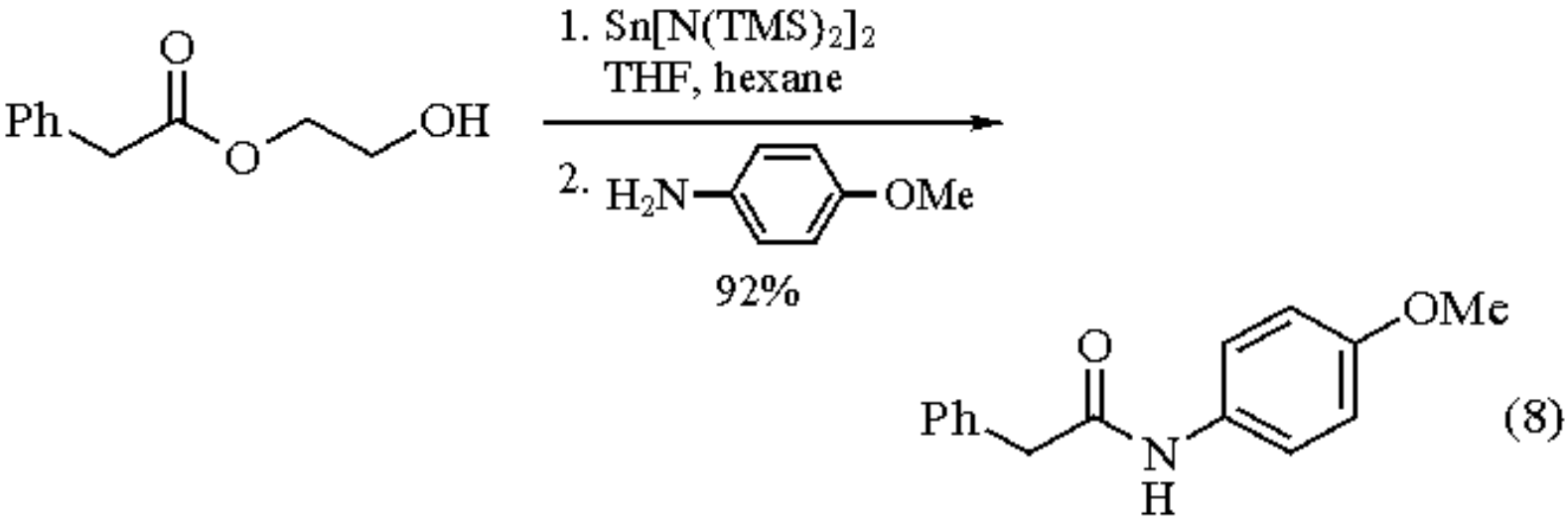

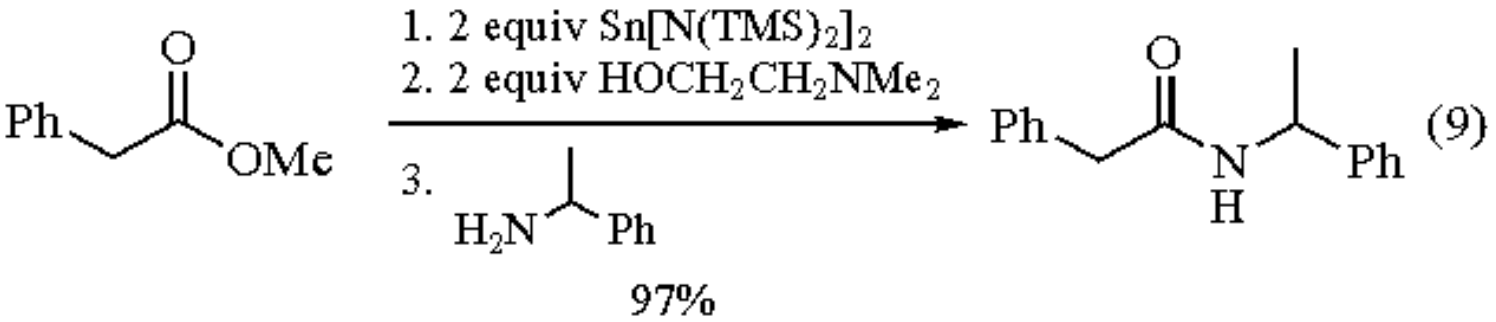

Carboxylic Acids to Secondary or Tertiary Amides.

Carboxylic acids that are less sterically encumbered than pivalic acid can be converted to amides using

$Sn[N(TMS)_2]_2$.[11] For example, reaction of 2-(*t*-butyldimethylsiloxy)-2-phenylacetic acid with $Sn[N(TMS)_2]_2$ and either a primary or secondary amine generates a tin(II) carboxyamine (eq 10). This intermediate is smoothly converted to an amide without racemization of the α-chiral center when heated at reflux for 1 h or stirred at rt overnight.

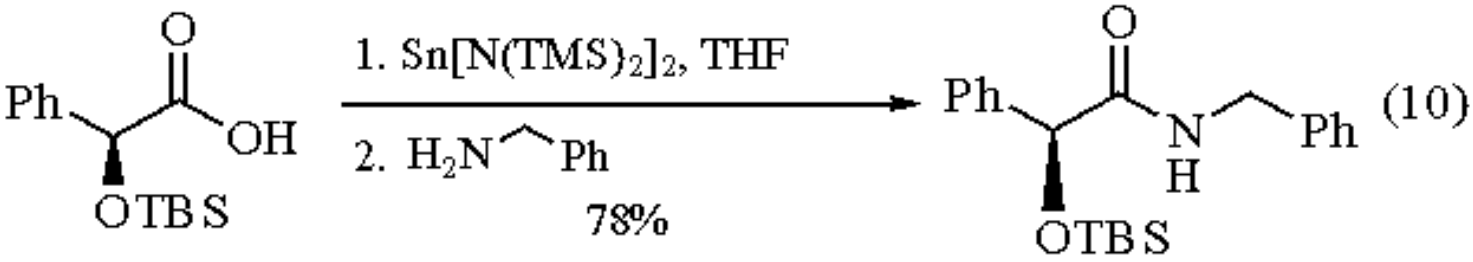

Related Reagents.

Dimethylaluminum Amide; ***Hexamethyldisilazane***; ***Lithium Hexamethyldisilazide***; ***Piperidine***; ***Tin(II) Chloride***; ***Titanium(IV) Chloride***.

---

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1,4-Bis(bromomagnesio)butane[1]

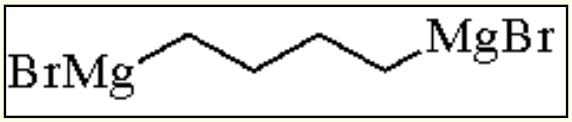

[23708-48-7] · $C_4H_8Br_2Mg_2$ · 1,4-Bis(bromomagnesio)butane · (MW 264.53)

(constructing block agent: transformation of many functional groups into cyclopentane, spiro[4.4]nonane, and spiro[4.5]decane synthetic intermediates, and metallacycles)

Solubility: sol THF, ether, and toluene.

Form Supplied in: generally prepared in THF.

Analysis of Reagent Purity: titration.[2]

Preparative Methods: the following preparative method was found to be of general use for the preparation of various 1,*n*-bis(bromomagnesio)alkanes (*n* = 4-6), as well as for primary, secondary, and unsaturated di-Grignard reagents, from the corresponding dibromides.[3] ***1,4-Dibromobutane*** (69 mmol) dissolved in anhydrous THF (150 mL) is added dropwise to ***Magnesium*** turnings (150 mmol) covered with a few mL of the dibromide solution. The exothermic reaction starts within a few minutes and is controlled by the rate of addition of the dibromide, avoiding excessive heating. After an additional 2 to 6 h period, the formation of the reagent is completed (yield ~90%) (eq 1). However, for 1,3-bis(bromomagnesio)propane, this procedure is not suitable, as the elimination product is mostly formed. Therefore, one should refer to the appropriate literature for that particular case.[4]

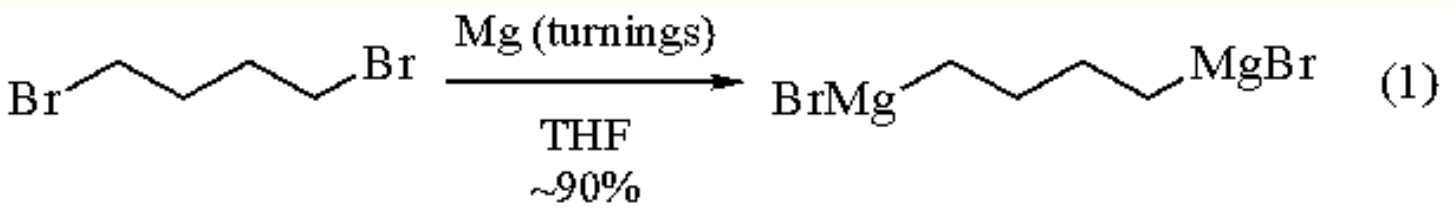

Handling, Storage, and Precautions: solutions are highly flammable; must be stored in the absence of proton sources, carbon acids, and oxygen. Flasks and Schlenk tubes should be flushed with dry Ar or N_2. Handle with standard syringe technique to prevent contact of the solutions with oxygen and moisture. Solutions can be stored at 0 °C for months.

Synthetic Applications.

1,4-Bis(bromomagnesio)butane is a remarkable annulation reagent. It carries out annulation readily, unlike the pentane or propane analogs. 1,3-Bis(bromomagnesio)propane undergoes hydride transfer and/or addition reaction with electrophiles, furnishing reduction products, α,o-diadducts, and cyclobutane derivatives.[4] With 1,6-bis(bromomagnesio)hexane, 1,6-diaddition compounds are obtained in good yield, while the annulation with carboxylic acid derivatives produces modest yields.

Cyclopentane Derivatives.

The reaction of 1,4-bis(bromomagnesio)butane with esters leads to the formation of cyclopentanols.[5] The application of this annulation process is important for the synthesis of cyclopentanol derivatives substituted with functionalized alkyl groups (eq 2) that are difficult to obtain from the corresponding Grignard reagent and cyclopentanone.[6]

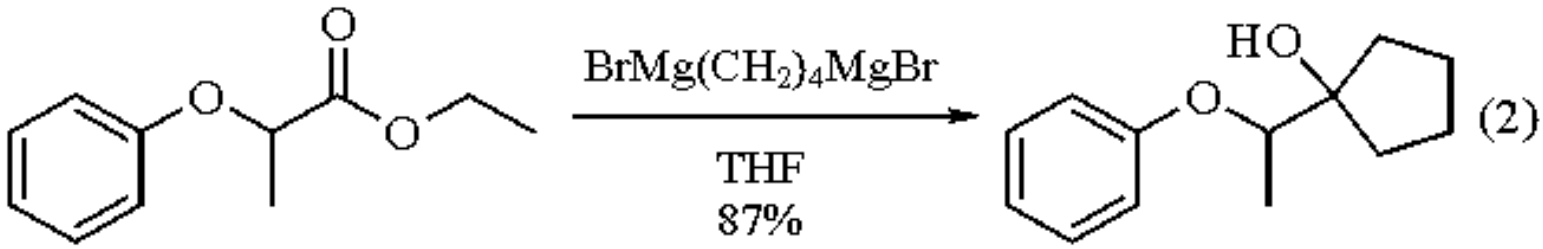

Another advantage of this methodology is the production of *trans*-1,2-disubstituted cyclopentanols with 1,4-bis(bromomagnesio)pentane (eq 3).[3b] This stereoselection is complementary to that obtained by direct addition of an alkyl Grignard to 2-methylcyclopentanone, which gives mainly *cis*-1,2-disubstituted cyclopentanols.[7]

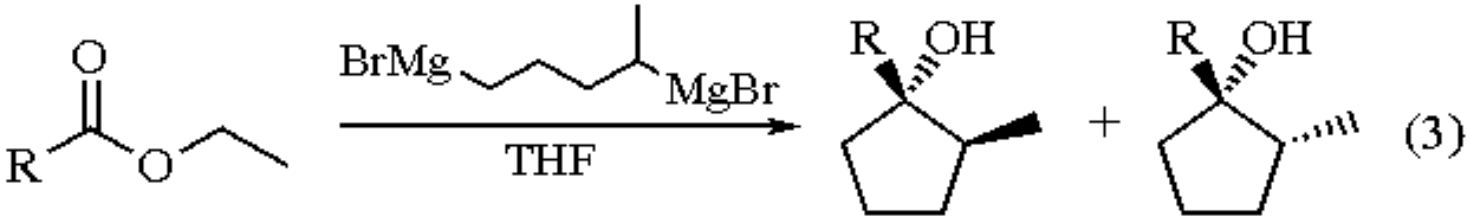

R =	H	77 : 23
	Me	96 : 4
	Cy	95 : 5
	Ph	89 : 11

Lactones undergo the annulation process with 1,4-bis(bromomagnesio)butane.[8] Eq 4 shows annulation on dihydrocoumarin.[9] Yields are higher than observed with ***1,5-Bis(bromomagnesio)pentane***, which also forms products of intermolecular attack and hydride transfer.

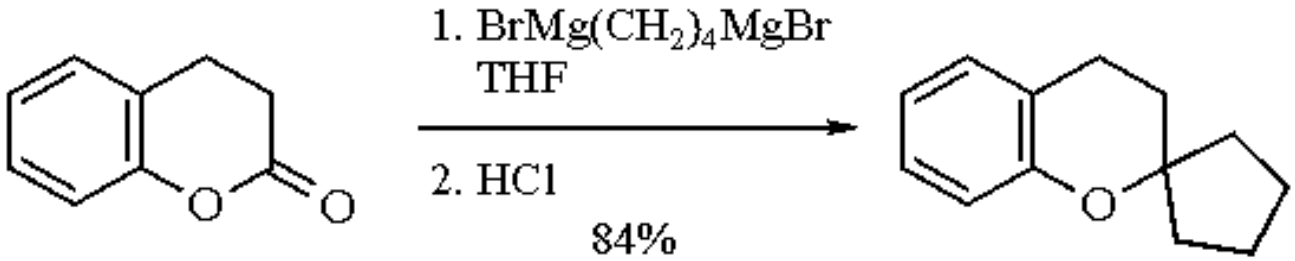

(4)

Oximes of 3-alkyl-3-(1-hydroxycyclopentyl)alkan-2-ones were prepared in high yields from 4,4-dialkylisoxazol-5-ones and 1,4-bis(bromomagnesio)butane (eq 5).[3a,10] These results contrast with those obtained for primary Grignard reagents, which produce only the corresponding 5-hydroxy-2-isoxazolines (eq 6).[11]

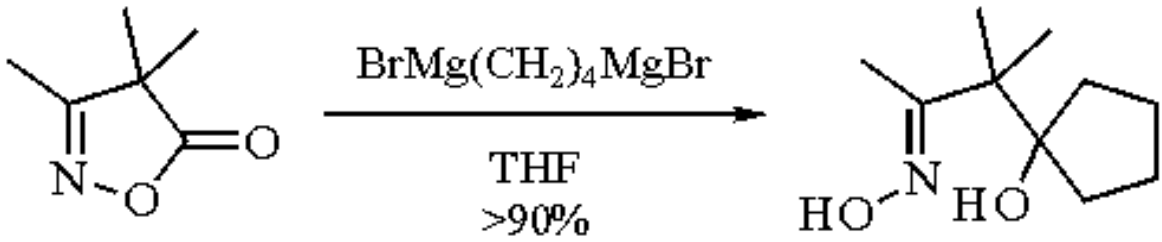

(5)

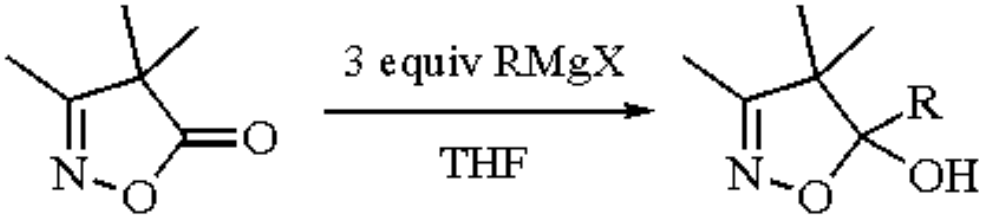

(6)

Symmetrically and unsymmetrically substituted cyclic anhydrides are converted in good yield to spirolactones.[12] For unsymmetrical cyclic anhydrides, preferential attack takes place on the more accessible carbonyl group, followed by a second nucleophilic addition to the intermediate ketone, leading to five-carbon annulation (eq 7).[12b] This methodology was successfully used for the construction of linearly fused polyquinane, a class of fused ring compounds containing only cyclopentane rings.[13]

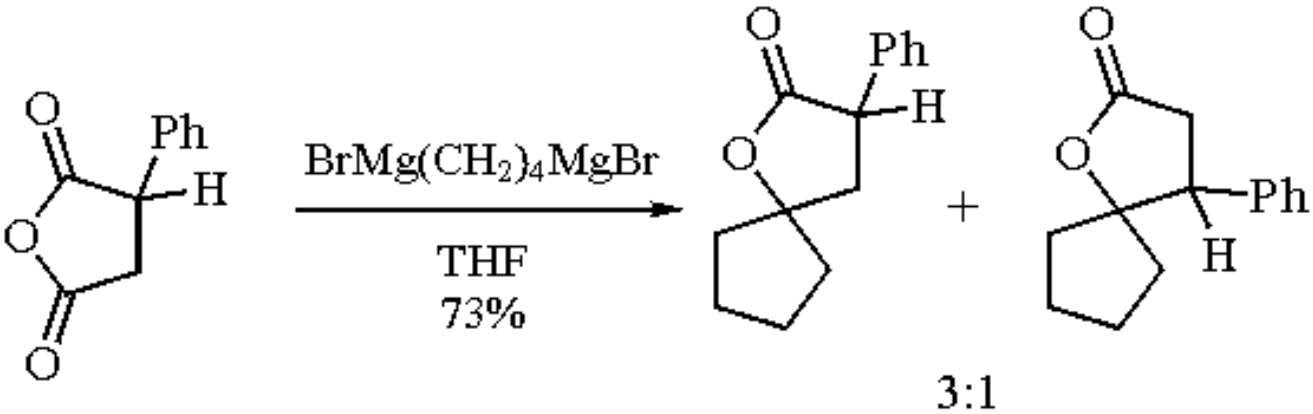

(7)

Organobiscuprates.

In the presence of the ***Copper(I) Bromide***-dimethyl sulfide complex, 1,4-bis(bromomagnesio)butane reacts with 3-

halocycloalk-2-en-1-ones to afford spiro ketones.[14] This annulation methodology was applied, for example, to 1,4-bis(bromomagnesio)pentane and 3-bromocyclopent-2-en-1-one to form *cis*-1-methylspiro[4.4]nonan-2-one (eq 8) (see also ***1,5-Bis(bromomagnesio)pentane***).

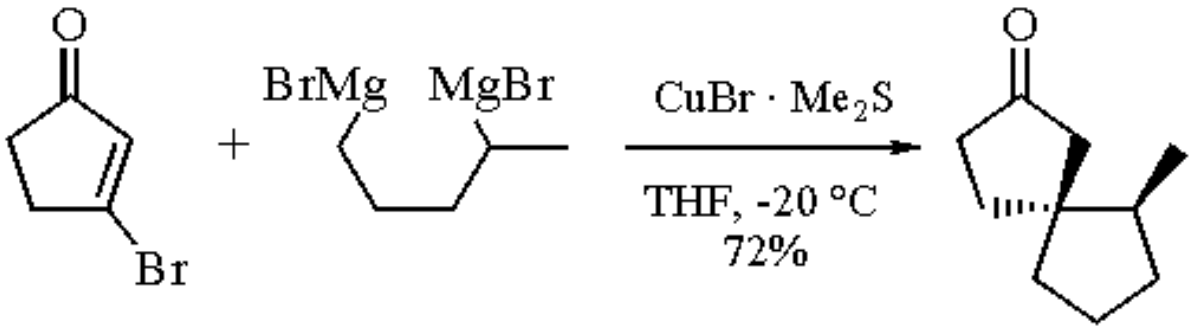

(8)

Metallacyclopentanes.

The synthesis of various metallacyclopentanes from metal dihalides and 1,4-bis(bromomagnesio)butane constitutes a useful application of the di-Grignard reagent.[15] These metallacycles may then be used in synthetic applications (see ***1,4-Dilithiobutane***). The formation of chiral 2,5-dimethylborolane illustrates such an approach (eq 9).[16]

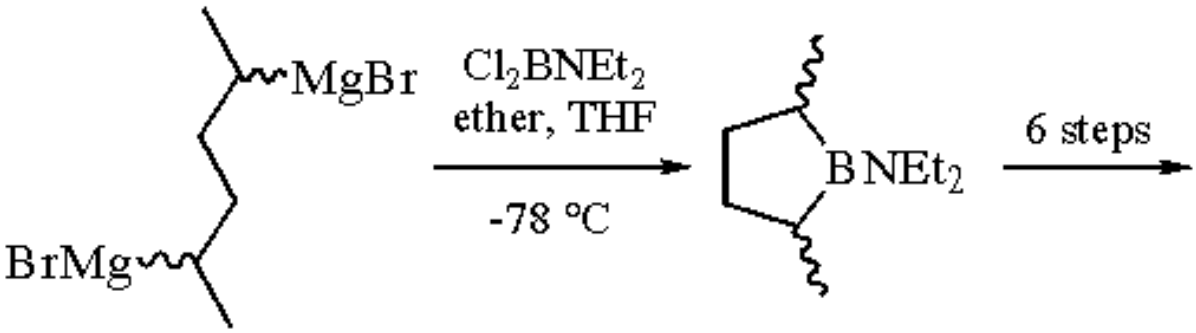

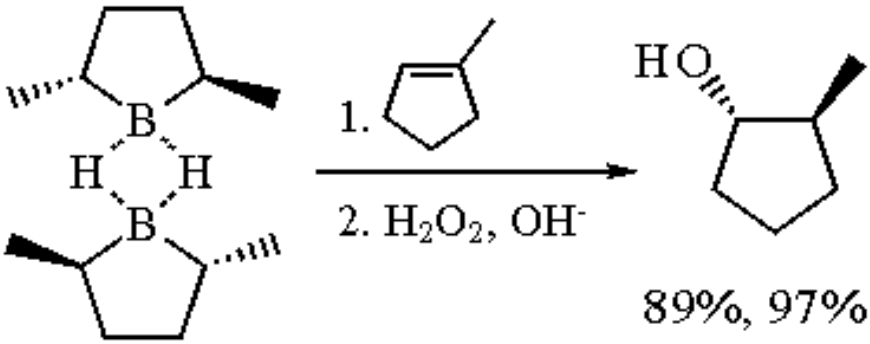

(9)

89%, 97% ee

Related Reagents.

1,5-Bis(bromomagnesio)pentane; ***1,4-Dilithiobutane***; ***1,5-Dilithiopentane***.

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1. (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954; pp. 769-772; (b) Lindsell, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; vol. 1, Chapter 4.
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1,5-Bis(bromomagnesio)pentane[1]

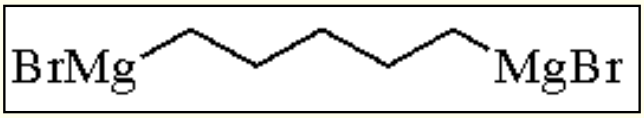

[23708-48-7] · $C_5H_{10}Br_2Mg_2$ · 1,5-Bis(bromomagnesio)pentane · (MW 278.55)

(constructing block agent: transformation of many functional groups into cyclohexane, spiro[4.5]decane, and spiro[5.5]undecane synthetic intermediates, and α,o-difunctional compounds)

Physical Data: d 0.999 g cm^{-3}.

Solubility: sol THF, ether, and toluene.

Form Supplied in: the reagent is available in THF (0.5 M).

Analysis of Reagent Purity: titration.[2]

Handling, Storage, and Precautions: solutions are highly flammable; must be stored in the absence of proton sources, carbon acids, and oxygen. Flasks should be flushed with dry Ar or N_2. Handle with standard syringe technique to prevent contact of the solutions with oxygen and moisture.

Structure.

The observation of the existence of Schlenk's equilibrium was first confirmed in the preparation of magnesiocycloalkanes.[3,4] During the preparation and use of 1,5-bis(bromomagnesio)pentane at low temperature, $MgBr_2$ precipitates from THF solution (eq 1).[5]

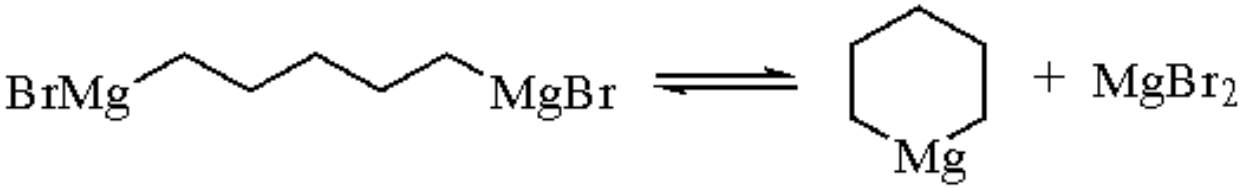

(1)

Synthetic Applications.

Bis(bromomagnesio)pentane mainly undergoes carbon-carbon bond formation with carbon electrophiles to provide α,o-difunctional[6-8] and cyclohexane derivatives.[9-11] However, in the presence of hindered electrophiles, the addition is

accompanied by a reduction process which leads also to the formation of monoaddition adducts.

Reaction with Esters.

The earliest uses of 1,5-bis(bromomagnesio)pentane were as an annulation reagent with carboxylic esters.[9] Reactions with hindered substituted esters form some products derived from intramolecular reduction (eq 2), in contrast to ***1,4-Bis(bromomagnesio)butane***.[12]

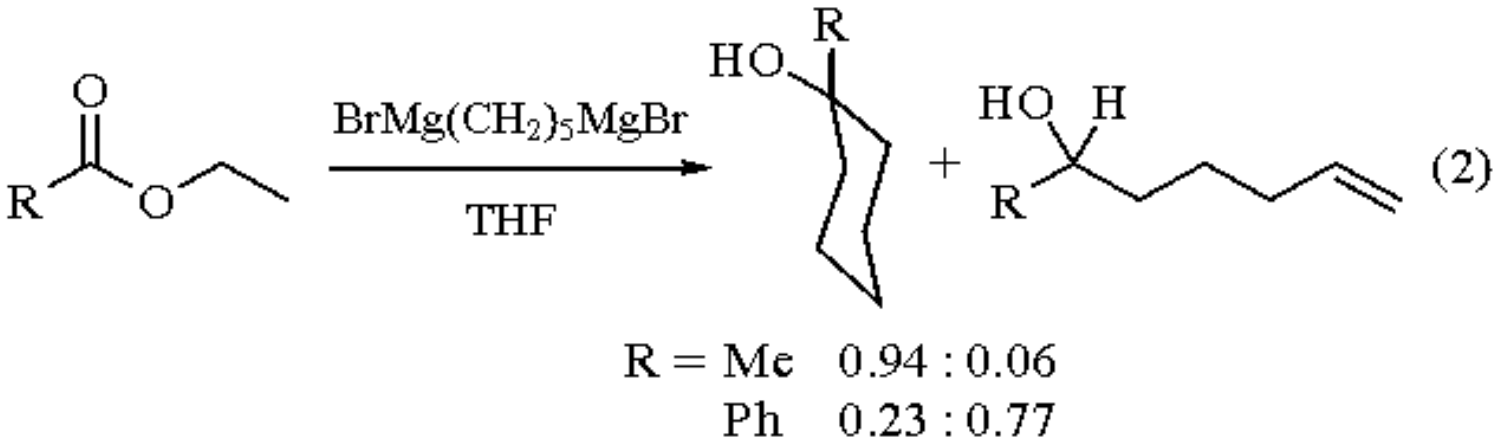

(2)

Reaction with Lactones.

Similarly, this reagent led to a general one-pot synthesis of (hydroxyalkyl)cyclohexanols by a double nucleophilic addition to the carbonyl group of lactones. The obtained diols were converted, by appropriate transformations, into spirolactones and spiro ethers (eq 3).[13]

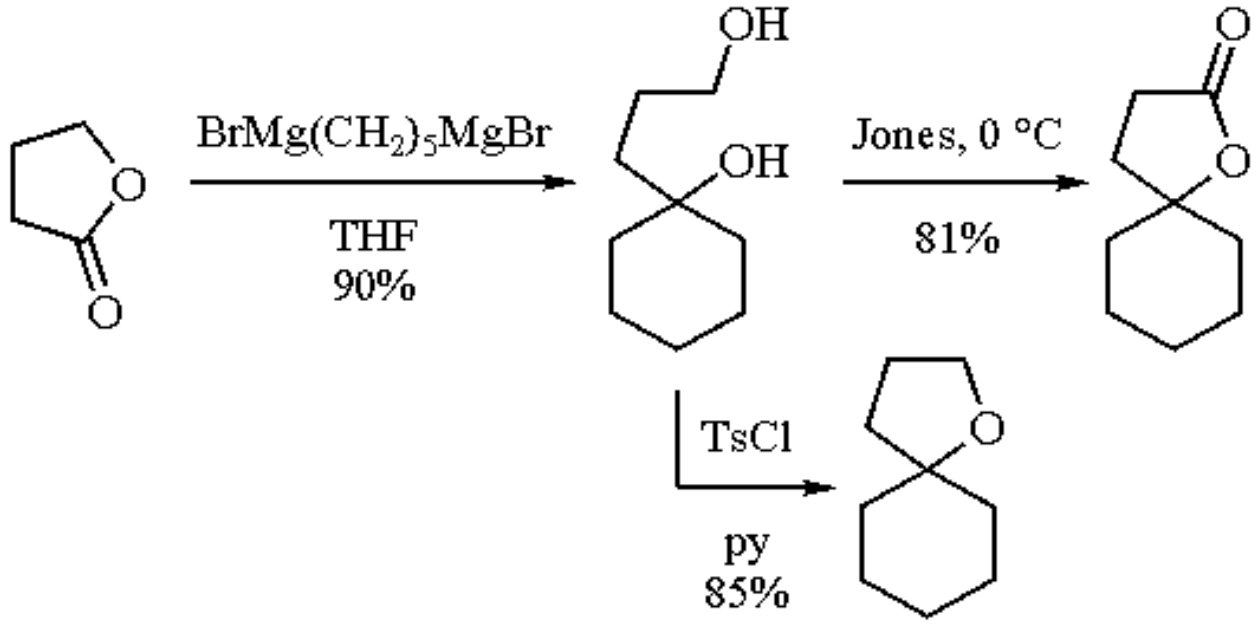

(3)

Seven-carbon annulation using 1,6-bis(bromomagnesio)hexane was achieved with various carboxylic acid derivatives and coumarins. A typical example is given with the synthesis of 3,4-dihydrospiro[2*H*]-1-benzopyran-2,1´-cycloheptane, a spirochroman (eq 4).[14]

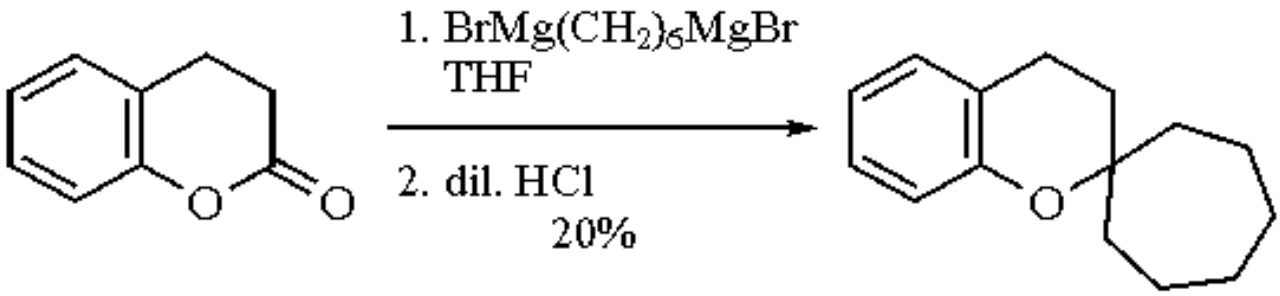

(4)

Reaction with Carboxylic Anhydrides.

The reaction of 1,5-bis(bromomagnesio)pentane with cyclic anhydrides gives spirolactones.[5,15] The intermediate carboxylate diminishes the formation of reduction products so that intramolecular Grignard addition takes place almost exclusively (eq 5).

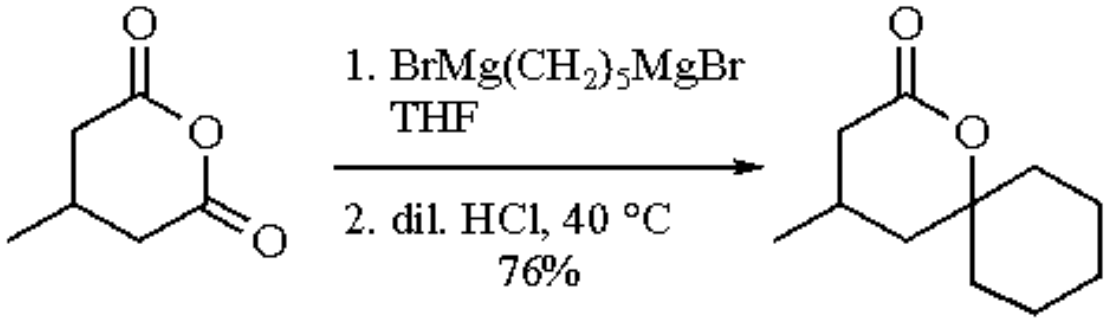

(5)

The reaction of the di-Grignard reagent with bridged bicyclic anhydrides gives good to excellent yields if a stoichiometric or excess amount of reagent is used.[16] The reaction is chemoselective and, for unsymmetrical anhydrides, takes place at the less hindered carbonyl group. Thus reaction of 1,5-bis(bromomagnesio)pentane with *endo*- and *exo*-furan and cyclopentadiene adducts produces bridged bicyclic spirolactones in 80-100% yields. The furan adducts lead, by subsequent distillation, via a retro Diels-Alder reaction, to a convenient synthesis of spirobutenolides (eq 6).[17] This reaction can also be used with primary Grignard reagents and ***1,4-Bis(bromomagnesio)butane***

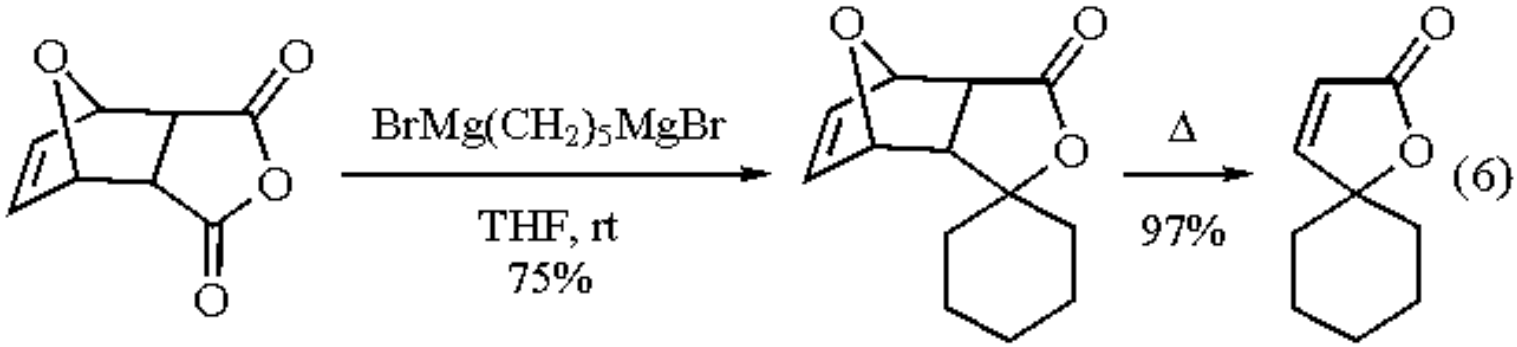

(6)

The spiroannulation process also works well with heterocyclic anhydrides.[18] Examples are regioselective cyclizations with pyridinecarboxylic, isatoic, and azaisatoic anhydrides (eq 7).

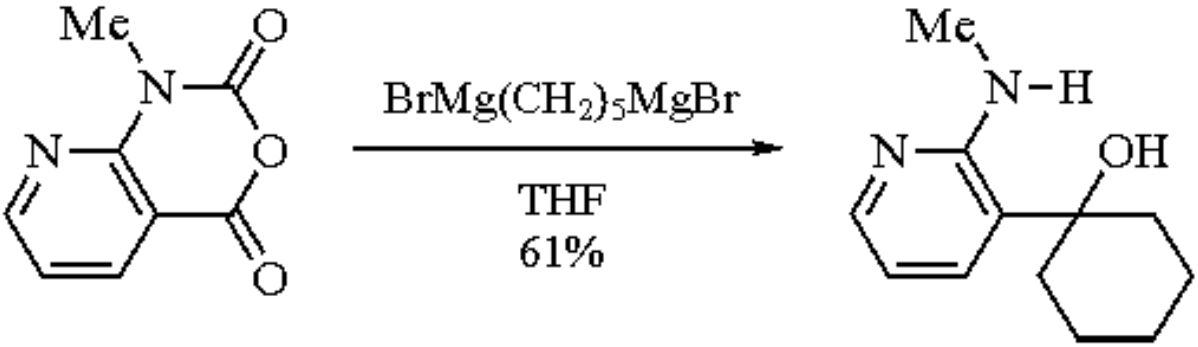

(7)

Reaction with 3-Halocycloalk-2-en-1-ones.

Spiro ketones are formed when the di-Grignard reagent is used, in the presence of CuBr.MeS, with 3-halocycloalk-2-en-1-ones (eq 8).[19] Replacement of the di-Grignard reagent with 1,*n*-dilithioalkane and 2 equiv of copper(I) thiophenoxide leads to more side products.

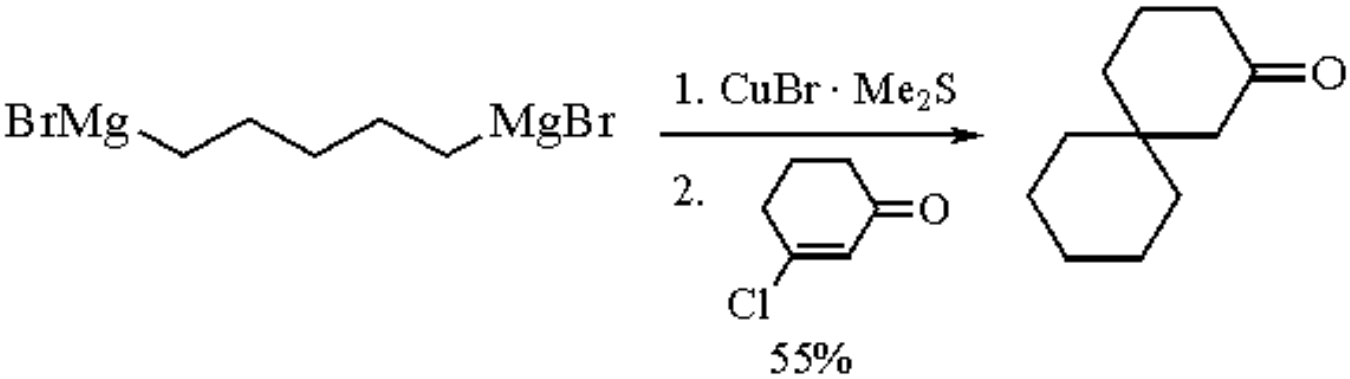

(8)

This methodology was successfully extended to an unsaturated di-Grignard in a synthesis of the spirosesquiterpene β-vetivone (eq 9).

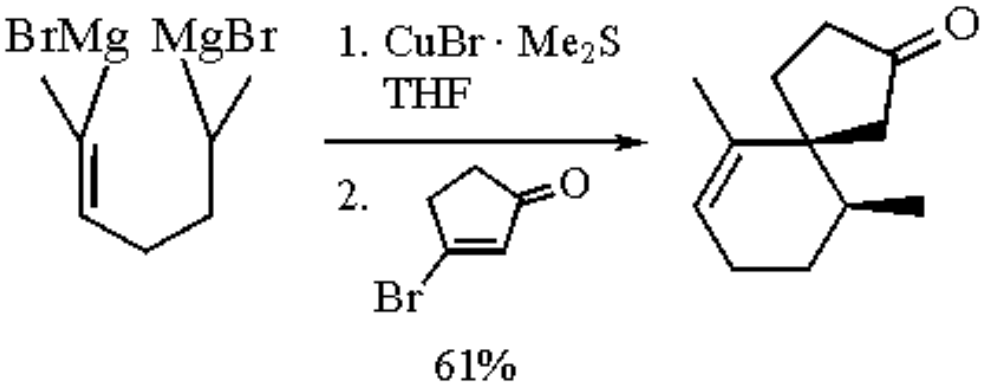

(9)

1,5-Bis(bromomagnesio)pentane-CuI was also used with alkylidenecyanoacetates. Quaternary-substituted hydrocarbons were obtained, but in very low yields.[20]

α,ο-Difunctional Compounds.

1,5-Bis(bromomagnesio)pentane has been widely used for the preparation of α,o-difunctional compounds. Carbon dioxide, aldehydes, and ketones were usually selected as electrophiles. This procedure is typified by the reaction with cyclohexanone (eq 10).[7b,8,21]

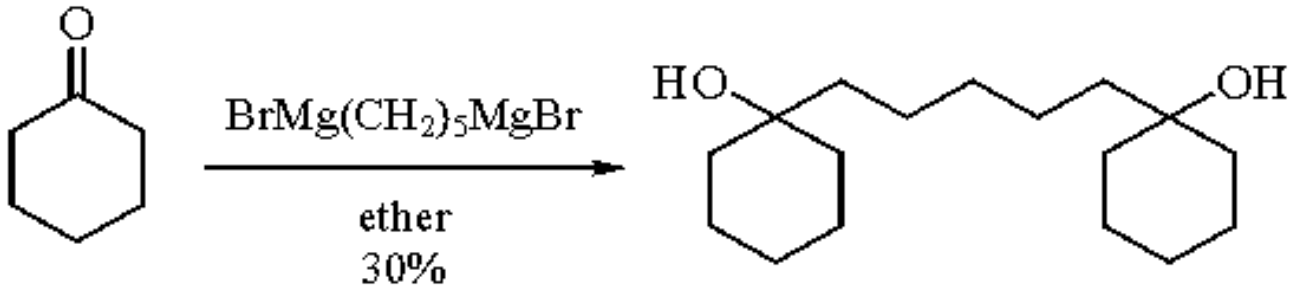

(10)

Reaction with Trialkylboranes.

The reaction of 1,5-bis(bromomagnesio)pentane with trialkylboranes in benzene gives selective boron-magnesium transmetalation to alkylmagnesium bromides (eq 11). The transformation proceeds fast in benzene and toluene, relatively fast in ether, but extremely slowly in THF.[22]

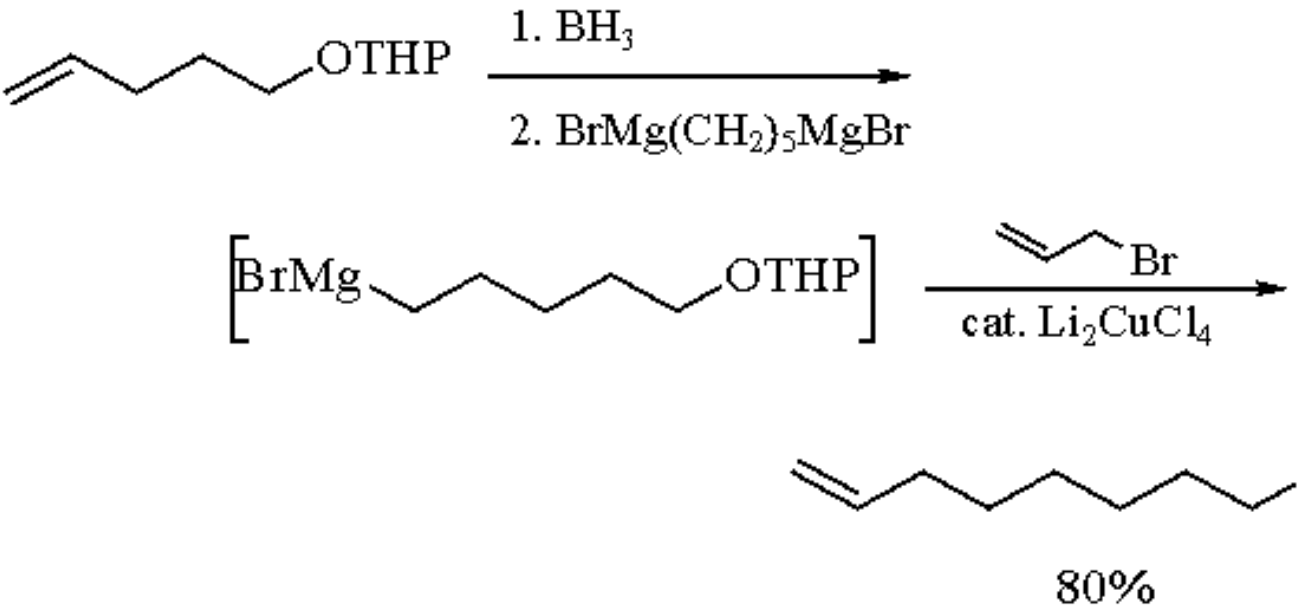

(11)

Related Reagents.

1,4-Bis(bromomagnesio)butane; ***1,4-Dilithiobutane***; ***1,5-Dilithiopentane***.

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1. (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954; pp 769-772. (b) Lindsell, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 1 Chapter 4.
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2,3-Bis(bromomethyl)-1,3-butadiene

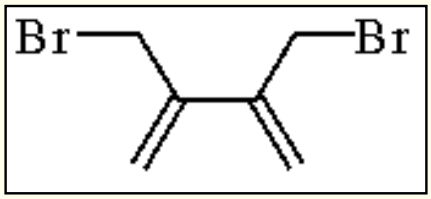

[18214-55-6] · $C_6H_8Br_2$ · 2,3-Bis(bromomethyl)-1,3-butadiene · (MW 239.94)

(Diels-Alder diene;[1] preparation of other 2,3-disubstituted 1,3-dienes[2])

Physical Data: mp 57-58 °C.

Solubility: sol pentane, THF.

Form Supplied in: white solid.

Preparative Methods: Zn-Cu[1] or Sn-Cu[3] mediated dehalogenation of tetrakis(bromomethyl)ethylene; thermolysis of a precursor sulfone;[3] and through reaction of allene with $PdBr_2$.[4,5]

Purification: recrystallization from pentane,[1] hexane,[6] or hexane-ethyl acetate.[5]

Handling, Storage, and Precautions: light sensitive; tends to polymerize at room temperature. Stable for months when stored as a solid or as a solution in ether in the dark at 0 °C.

Diels-Alder Diene.

The primary synthetic uses of 2,3-bis(bromomethyl)-1,3-butadiene (**1**) are in Diels-Alder chemistry, in preparation of heterocycles, in the preparation of π-allyl organometallic complexes,[7] and in polymer chemistry. The reactivity of (**1**) is not unlike that of other 1,3-dienes and allylic halides. Diels-Alder reaction of (**1**) with benzoquinone leads to dihydronaphthoquinone (**2**) in 69% yield (eq 1).[8]

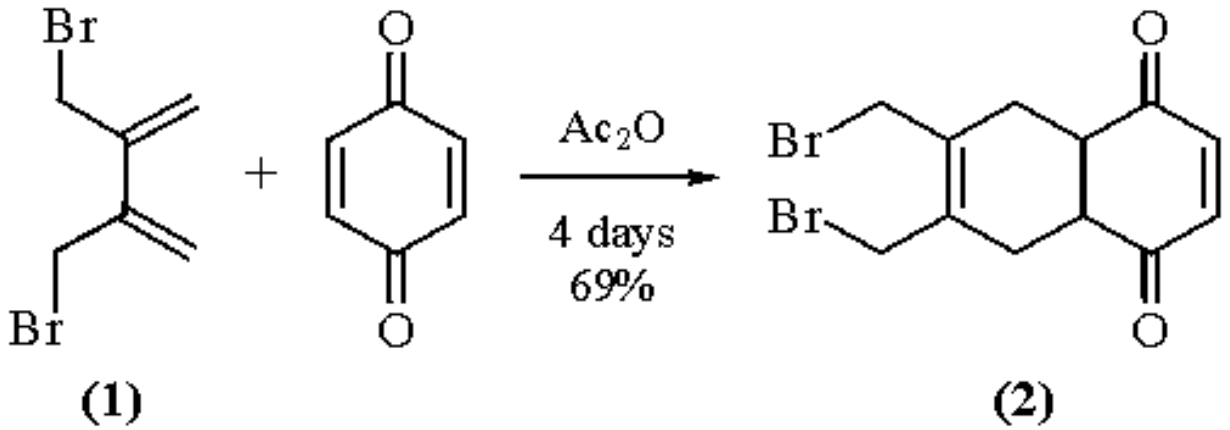

(1)

Electron deficient alkynes and diazo compounds are also active Diels-Alder partners (eq 2).[2] Diels-Alder reaction of (**1**) with ***Diethyl Azodicarboxylate*** (DEAD) leads to (**3**). Similarly, treatment of (**1**) with ***Dimethyl Acetylenedicarboxylate*** (DMAD) leads to (**4**).[1] Debromination of these allylic bromides with zinc-copper couple results in the formation of new 1,3-dienes that can be used in additional Diels-Alder reactions.[1]

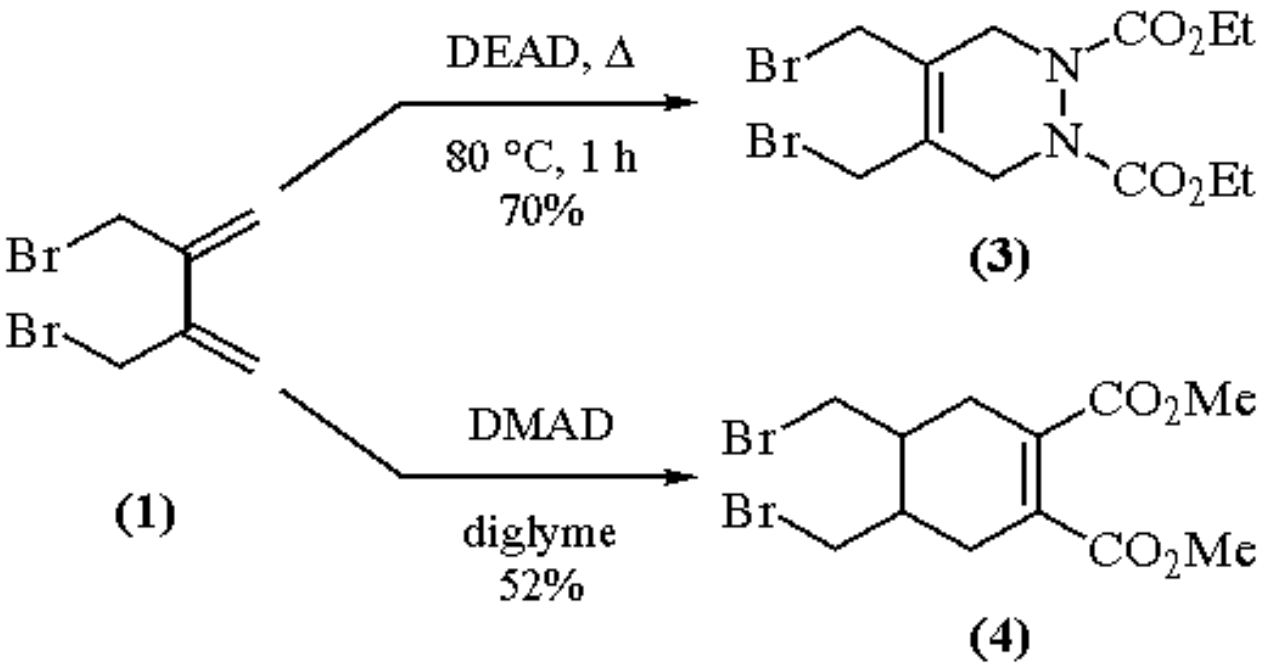

(2)

2,3-Disubstituted 1,3-Dienes.

Treatment of (**1**) with a variety of nucleophiles leads to mono- or dialkylation (eq 3). Symmetrical 2,3-disubstituted butadienes (**5**) result[1,9] from reaction of (**1**) with NaOMe, NaOAc, NaN_3, or KCN, and further elaboration of these dienes has been accomplished. Addition of unstabilized carbon nucleophiles such as vinylmagnesium chloride leads to polyenes.[1]

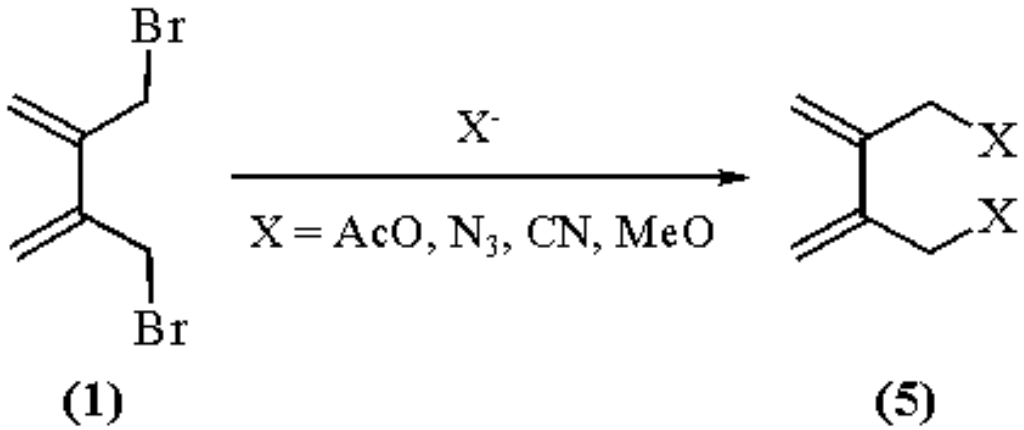

(3)

Treatment of tertiary diamines leads to the formation of polyelectrolytes (eq 4).[6]

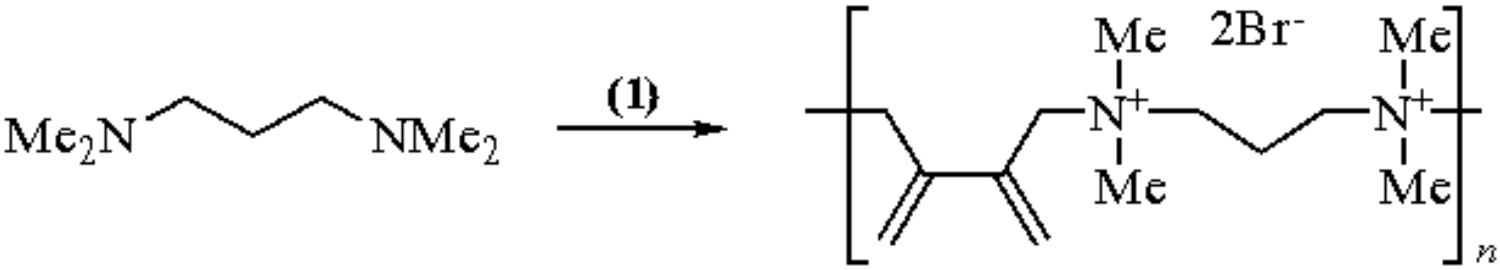

(4)

Heterocycles.

Treatment of (**1**) with other anions such as Na_2S,[10] NaOH in DMSO,[9] Na_2Se,[11] RNH_2 (R = alkyl or aryl),[9] or stabilized carbanions[2] produces bis(methylene) heterocycles (**6**) (eq 5). There are examples of heterocycles resulting from the treatment of (**1**) with diamines.[12]

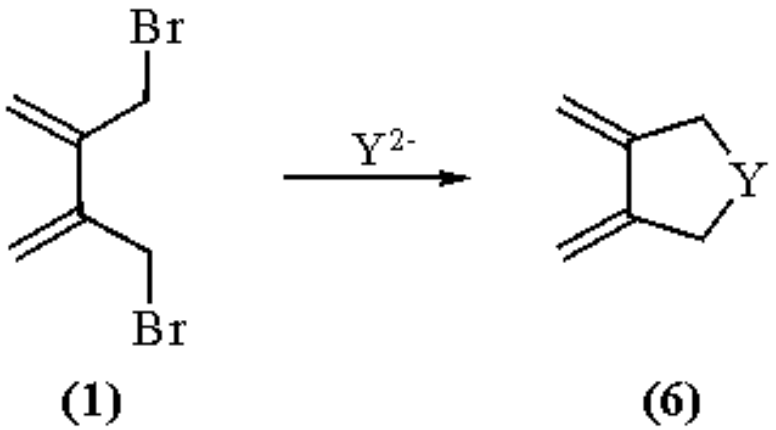

(5)

Heterocycles (**6**) participate in Diels-Alder reactions,[2] as well as undergoing (in some cases) intramolecular photochemical [2 + 2] reactions to form [3.2.0]bicyclic systems.[1] Several of the 3,4-dimethylenepyrrolidine compounds have been used as monomers in the synthesis of polypyrroles.[13,14]

1. Gaoni, Y.; Sadeh, S. *JOC* **1980**, *45*, 870.
2. Commerçon, A.; Ponsinet, G. *TL* **1985**, *26*, 4093.
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(1*S*,9*S*)-1,9-Bis{[(*t*-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin[1]

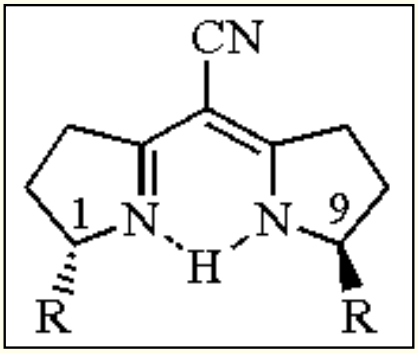

(**1**; R = CH_2OSiMe_2-*t*-Bu)

[105251-52-3] · $C_{24}H_{45}N_3O_2Si_2$ · (1*S*,9*S*)-1,9-Bis{[(*t*-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin · (MW 463.81) (**2**; R = CMe_2OH)

[105251-53-4] · $C_{16}H_{25}N_3O_2$ · (1*S*,9*S*)-1,9-Bis[(1-hydroxy-1-methyl)ethyl]-5-cyanosemicorrin · (MW 291.39) (**3**; R = CO_2Me)

[105251-49-8] · $C_{14}H_{17}N_3O_4$ · Dimethyl (1*S*,9*S*)-5-cyanosemicorrin-1,9-dicarboxylate · (MW 291.31)

(chiral ligands for enantiocontrol of metal-catalyzed reactions such as cobalt-catalyzed conjugate reduction of α,β-unsaturated carboxylic esters and amides or copper-catalyzed cyclopropanation of alkenes)[1]

Physical Data: (**1**) mp 75-76 °C, $[\alpha]_D$ -64.7° (*c* 1.0, $CHCl_3$ at rt); (**2**) mp 162 °C, $[\alpha]_D$ -82.0°; (**3**) mp 78-79 °C, $[\alpha]_D$ -145°.

Solubility: insol H_2O; (**1**) sol in all common organic solvents, including *n*-hexane; (**2**) and (**3**) sol CH_2Cl_2, alcohol, THF, and EtOAc, insol hexane, slightly sol diethyl ether.

Form Supplied in: white crystalline solid; (**1**) and (**3**) are commercially available.

Handling, Storage, and Precautions: as crystalline solids, semicorrins of this type are stable at ambient temperature; for longer periods, storage at -20 °C is recommended.

Preparation of Semicorrin Ligands and Metal Complexes.

The crystalline diesters (*S*,*S*)-(-)-(**3**) and (*R*,*R*)-(+)-(**3**) are readily synthesized in enantiomerically pure form starting from L-pyroglutamic acid (-)-(**4**) or its enantiomer (eq 1).[2] By selective transformation of the ester groups, a wide range of semicorrin derivatives with different substituents at the stereogenic centers is accessible.[2,3] Among the various derivatives that have been prepared, semicorrins (**1**) and (**2**) proved to be the most versatile ligands for the stereocontrol of metal-catalyzed reactions.

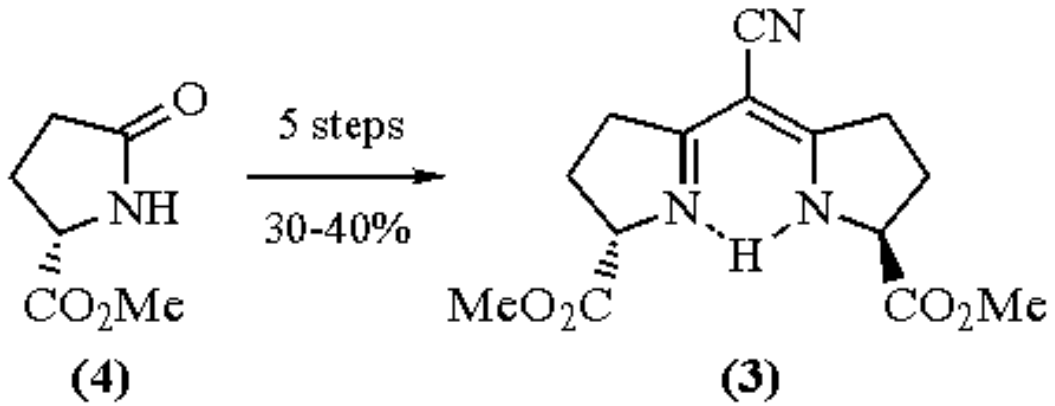

(1)

Semicorrins form stable chelate complexes with a variety of metal ions such as Co^{II}, Rh^{I}, Pd^{II}, or Cu^{II}. Depending on the metal ion, the ligand structure, and the reaction conditions, mono- or bis(semicorrinato) complexes are obtained.[2,3]

Enantioselective Conjugate Reduction of α,β-Unsaturated Carboxylic Esters and Amides.

Cobalt semicorrin complexes are highly efficient catalysts for the reduction of electrophilic C=C bonds, using ***Sodium Borohydride*** as reducing agent.[1] In the presence of 0.1-1 mol % of catalyst, formed in situ from ***Cobalt(II) Chloride*** and ligand (**1**), esters of β-disubstituted α,β-unsaturated carboxylic acids are cleanly reduced to the corresponding saturated esters in essentially quantitative yield and with high enantioselectivity.[1,3b,4] The best results are obtained in a mixture of ethanol and a polar aprotic solvent such as DMF or diglyme under careful exclusion of oxygen. The reduction of ethyl geranate (eq 2) and the corresponding (*Z*) isomer (eq 3) are typical examples. Both reactions lead to ethyl citronellate with 94% ee. Depending on the double bond geometry, either the (*R*) or (*S*) enantiomer is obtained. The isolated double bond is inert under these conditions. During aqueous workup, the chiral ligand (**3**) forms a catalytically inactive bis(semicorrinato)cobalt(II) complex, and can be recovered by decomplexation with acetic acid.

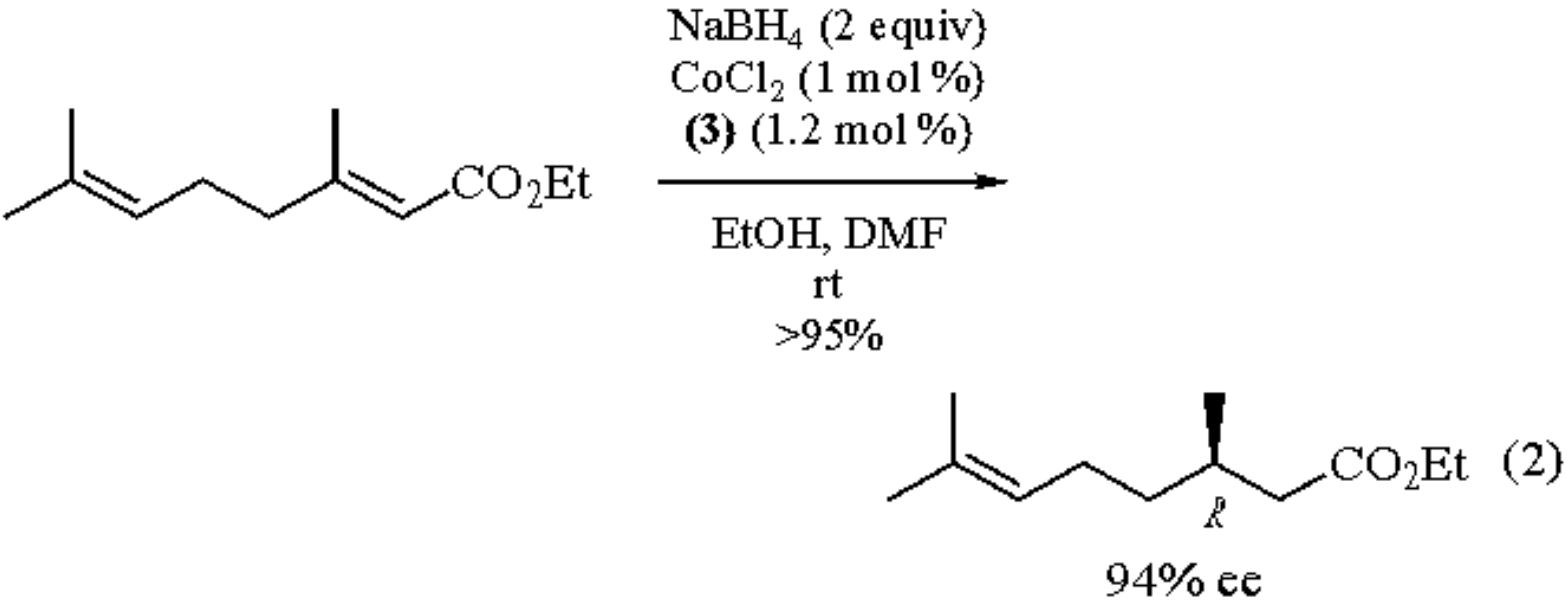

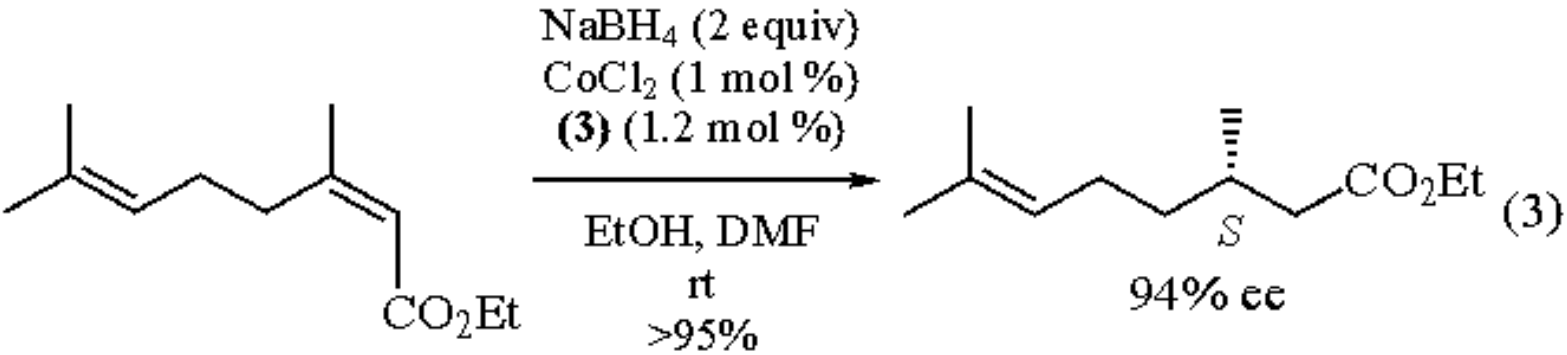

Even higher selectivities approaching 99% ee have been obtained with primary and secondary carboxamides (eqs 4 and 5).[5] With substrates of this type, the catalyst system can undergo more than 5000 turnovers without significant loss of selectivity. An analogous diene-carboxamide was found to react with high regio- and enantioselectivity to give the corresponding γ,δ-unsaturated amide with a preference of >95:5 over the α,β-unsaturated isomer (eq 5). Tertiary carboxamides react rather sluggishly and with distinctly lower selectivity. The method cannot be applied to α,β-unsaturated ketones because the uncatalyzed nonstereoselective reaction with $NaBH_4$ proceeds at a similar rate as the cobalt-catalyzed process.

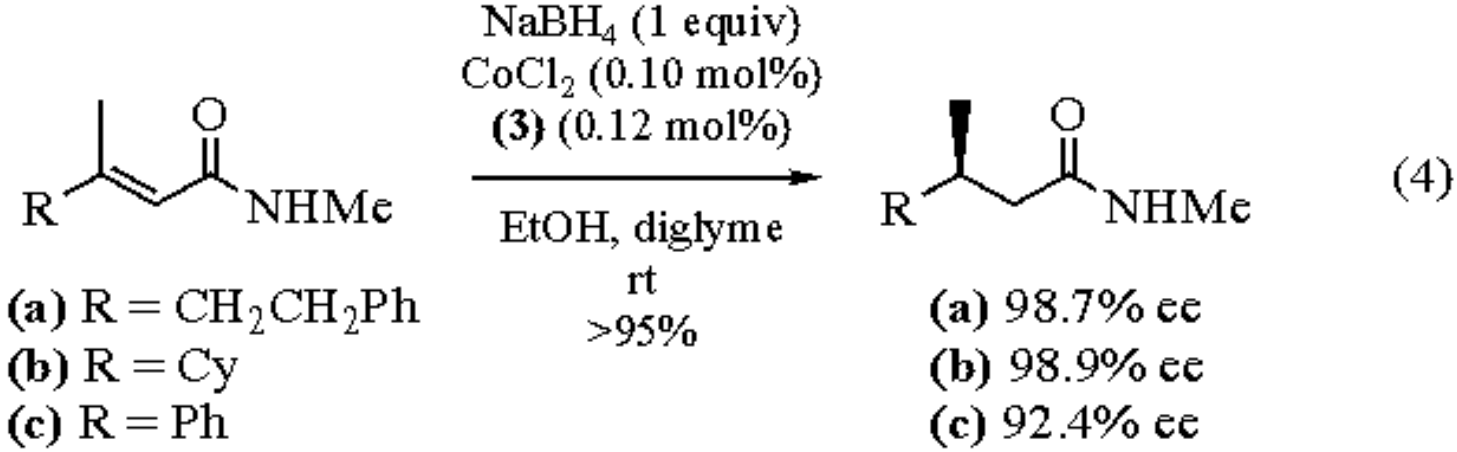

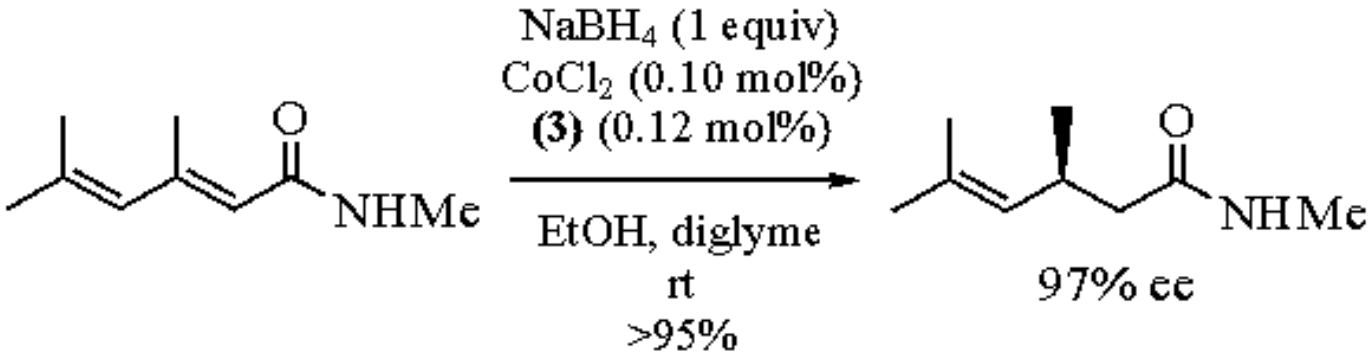

(5)

Deuteration experiments showed that the β-H atom in the product stems from borohydride whereas the α-H atom is introduced by proton transfer from ethanol.[3b] Formation of the α-(C-H) bond is nonstereoselective; accordingly, the reduction of analogous substrates with an α- instead of a β-disubstituted double bond leads to racemic products (a mechanistic model rationalizing the stereoselectivity of (semicorrinato)cobalt catalysts is available[1]).

Enantioselective Cyclopropanation of Alkenes.

Semicorrin copper complexes catalyze the reaction of diazo compounds with alkenes leading to optically active cyclopropanes.[1,6] The highest enantiomeric excesses have been obtained with the bulky ligand (**2**). The stable crystalline bis(semicorrinato)copper(II) complex (**5**) serves as a convenient catalyst precursor. The actual catalyst, which is presumed to be a mono(semicorrinato)copper(I) complex, is generated in situ by heating in the presence of the diazo compound or by reduction with ***Phenylhydrazine*** at rt. Alternatively, the catalyst can be prepared from the free ligand and ***Copper(I) t-Butoxide***. Reactions are usually carried out at rt in an apolar solvent such as dichloroethane using 1 mol % of catalyst. The best results are obtained with terminal alkenes or dienes and certain 1,2-disubstituted alkenes which react with alkyl diazoacetates to give the corresponding cyclopropanecarboxylates with high enantioselectivity (eqs 6-8). The relatively poor *trans*/*cis* selectivity is a general problem which is also encountered with other catalysts.[7] Recently, even higher enantiomeric excesses have been achieved with substrates of this type, using cationic Cu^{I} complexes of C_2-symmetric bis(oxazolines) (**6**) (see ***(S,S)-2,2´-(Dimethylmethylene)bis(4-t-butyl-2-oxazoline)***) or 5-aza-semicorrins (**7**).[1,8]

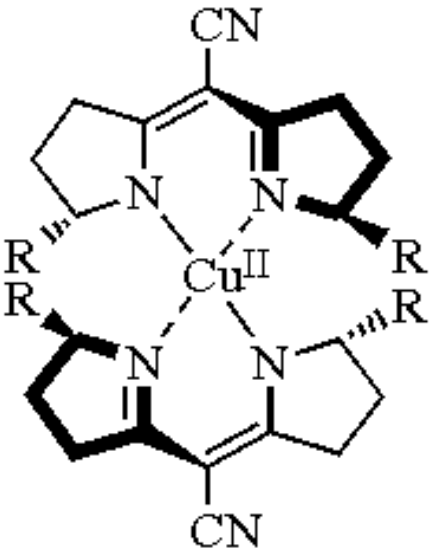

(5) R = CMe_2-*t*-Bu

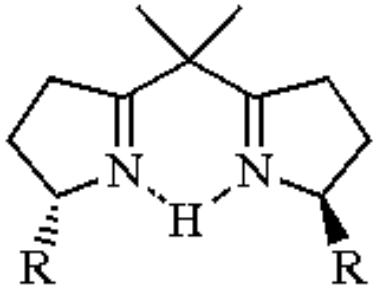

(6) R = *t*-Bu

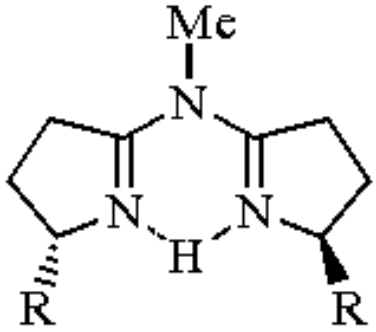

(7) R = $CMe_2OSiR'_3$

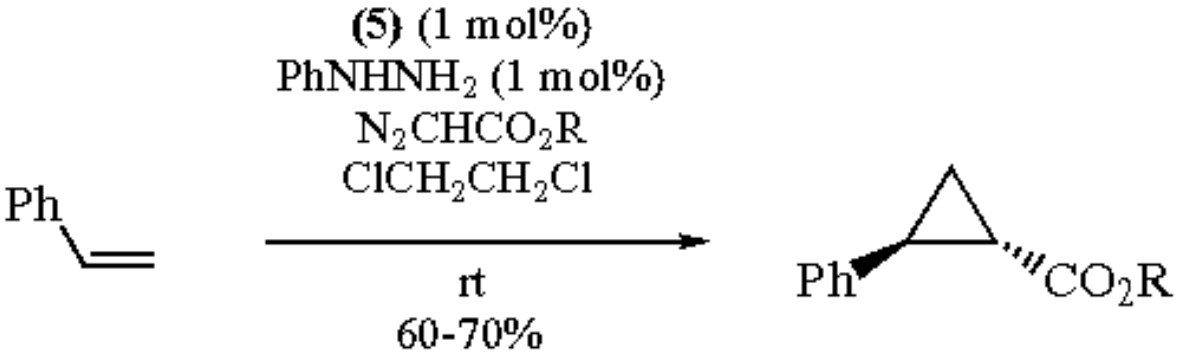

(6)

R = Et, 92% ee; *trans*:*cis* = 73:27
R = (+)-menthyl, 97% ee; *trans*:*cis* = 82:18

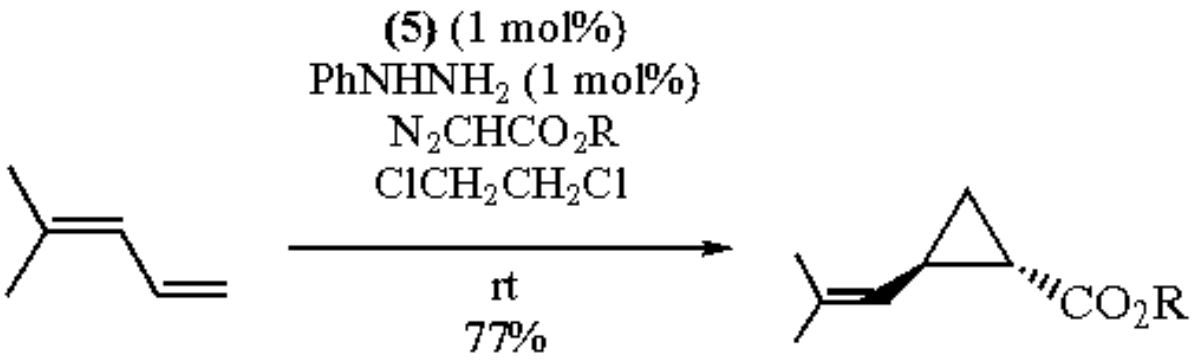

(7)

R = (+)-menthyl, 97% ee
trans:*cis* = 63:37

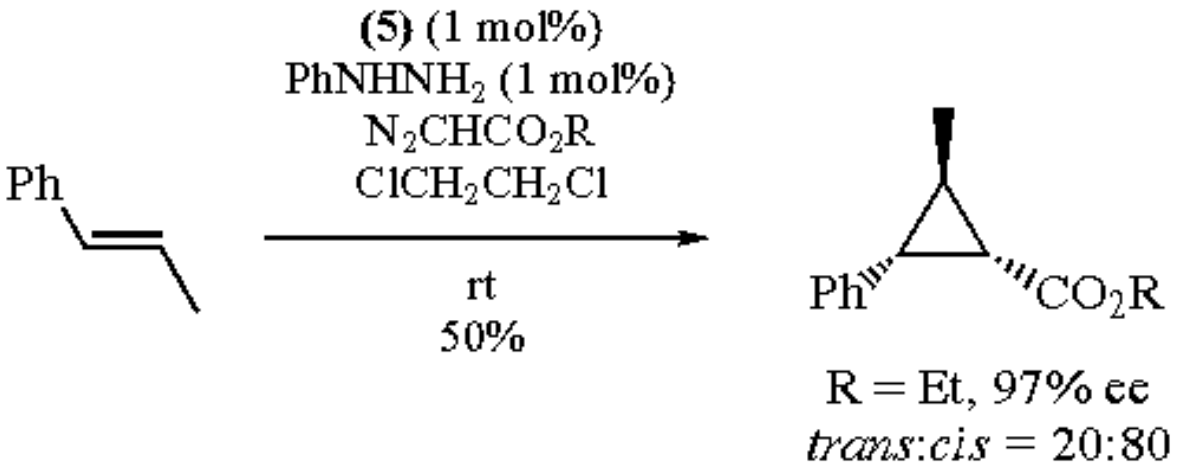

(8)

(Semicorrinato)copper catalysts have also been used for intramolecular cyclopropanation reactions of alkenyl diazo ketones (eqs 9 and 10).[9] In this case the (semicorrinato)copper catalyst derived from complex (**5**) proved to be superior to related methylene-bis(oxazoline)copper complexes. Interestingly, analogous allyl diazoacetates react with markedly lower enantioselectivity under these conditions, in contrast to the results obtained with chiral Rh^{II} complexes which are excellent catalysts for intramolecular cyclopropanations of allyl diazoacetates but give poor enantioselectivities with alkenyl diazo ketones (see ***Dirhodium(II) Tetrakis(methyl 2-pyrrolidone-5(S)-carboxylate)***).[7] Moderate enantioselectivities in the reactions shown in eqs 9 and 10 have been reported for (salicylaldiminato)copper catalysts (77% and 34% ee, respectively).[10]

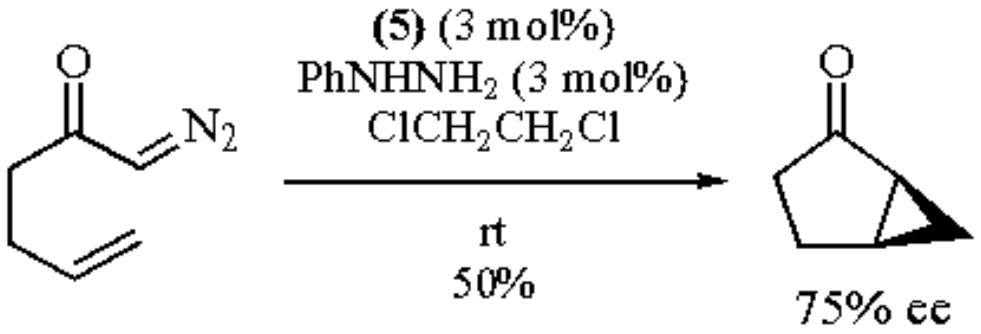

(9)

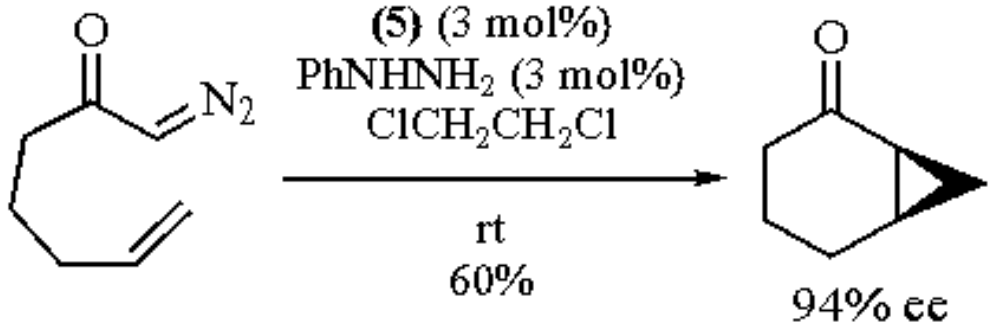

(10)

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Bis(α-camphorquinone dioximato)cobalt

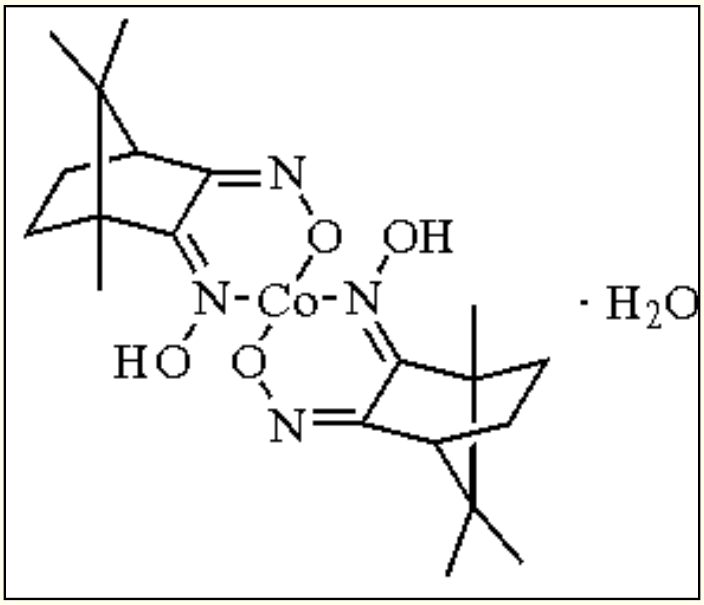

[67770-21-2] · $C_{20}H_{32}CoN_4O_5$ · Bis(α-camphorquinone dioximato)cobalt · (MW 467.43)

(catalyst for asymmetric cyclopropanation, especially for styrene, butadiene, and conjugated alkenes such as acrylates)

Physical Data: mp 240 °C (under nitrogen).

Solubility: sol hydrocarbons or similar organic solvents.

Form Supplied in: ligand may be available but the catalyst is sensitive to air and must be prepared just before use.

Analysis of Reagent Purity: a change in color from brown to pale brown or yellow indicates decomposition. Only the soluble part should be used.

Preparative Method: $Co(\alpha\text{-cqd})_2$ is prepared from ***Cobalt(II) Chloride*** hexahydrate and the corresponding isomer of camphorquinone dioxime (cqd) (from optically active natural camphor) in ethanol with addition of an aqueous solution of NaOH under nitrogen or argon.[1] This complex is best when freshly prepared before use under nitrogen or preferably under argon. The starting material, L-camphor, is easily obtained in optically pure form.

Handling, Storage, and Precautions: the dry solid must be kept under nitrogen or argon, preferably in the cold. The solution of the catalyst in organic solvents such as benzene, acetone, ethyl acetate, hexanes, or acetophenone deteriorates on standing even under nitrogen. Therefore use just after preparation is recommended.

Although many chiral cyclopropanation catalysts are known, this class of complexes is superior for the alkenes containing vinyl, phenyl, or alkoxycarbonyl groups. Some relevant examples are shown in eqs 1-5. In eq 5, the enantiomeric excess of the product is not known due to the absence of enantiomerically pure isomer. The absolute configuration is not known.

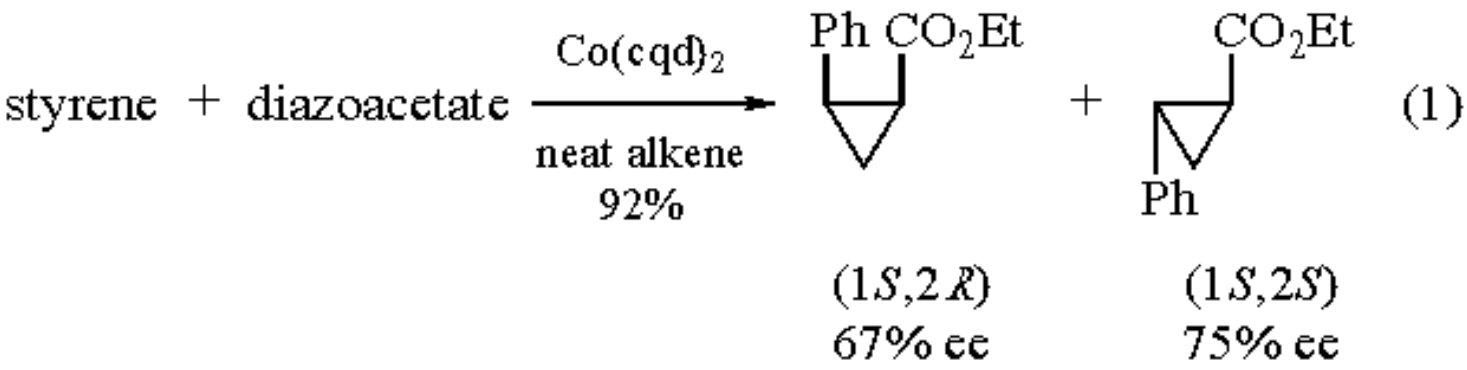

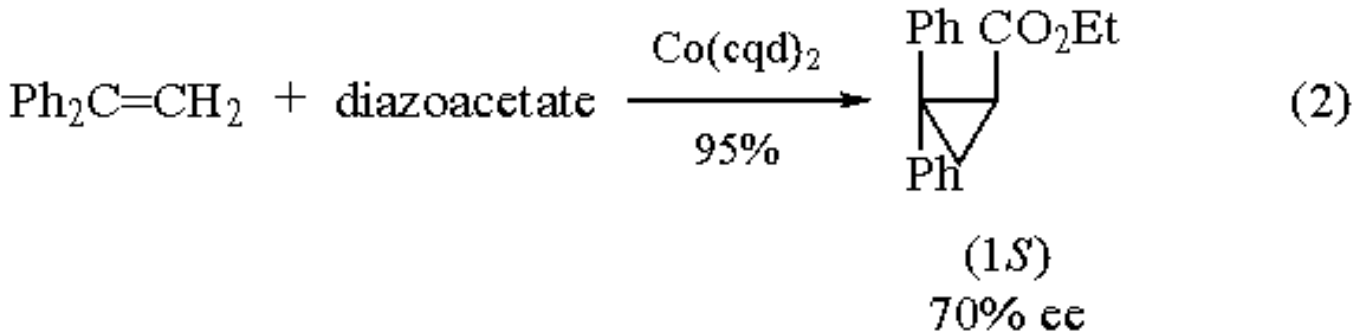

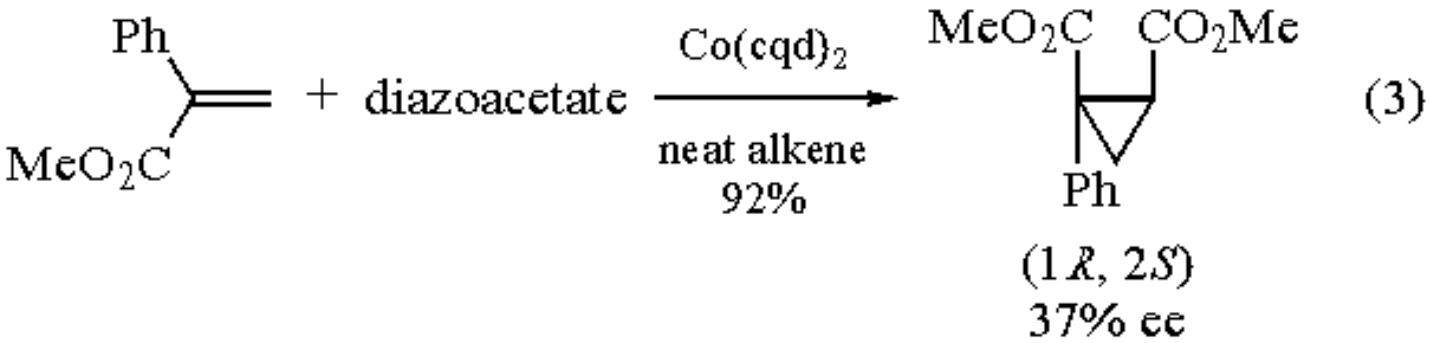

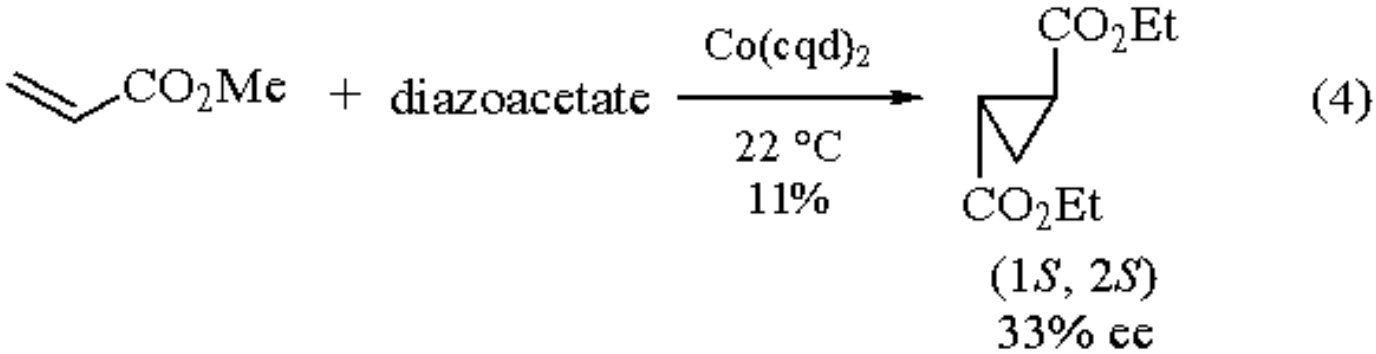

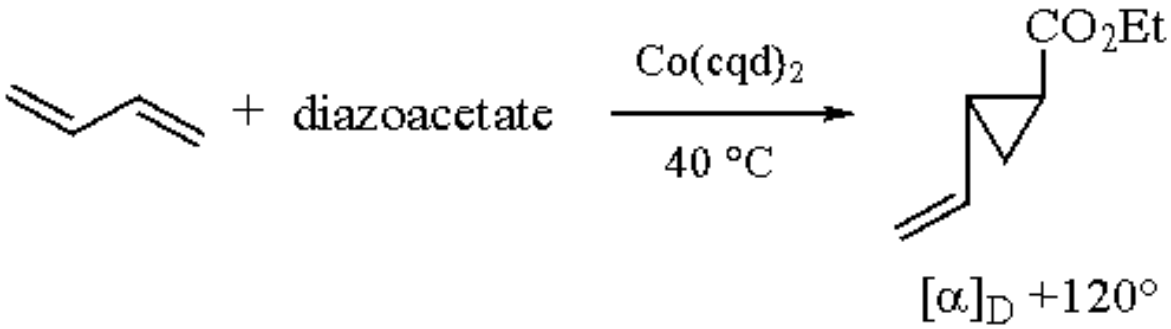

(5)

The related vicinal dioximatocobalt(II) complexes such as $Co(dmg)_2$ and $Co(nqd)_2$ (dmg = dimethylglyoximato, nqd = nopinoquinone dioximato), are also catalytically active but the enantioselectivity varies with the structure of the alkenes.

The steric bulk of the ester alkyl group generally enhances the ee values (eqs 6-8). Thus, the neopentyl ester of diazoacetate gives the highest ee value (88%) for the reaction with styrene (eq 6).

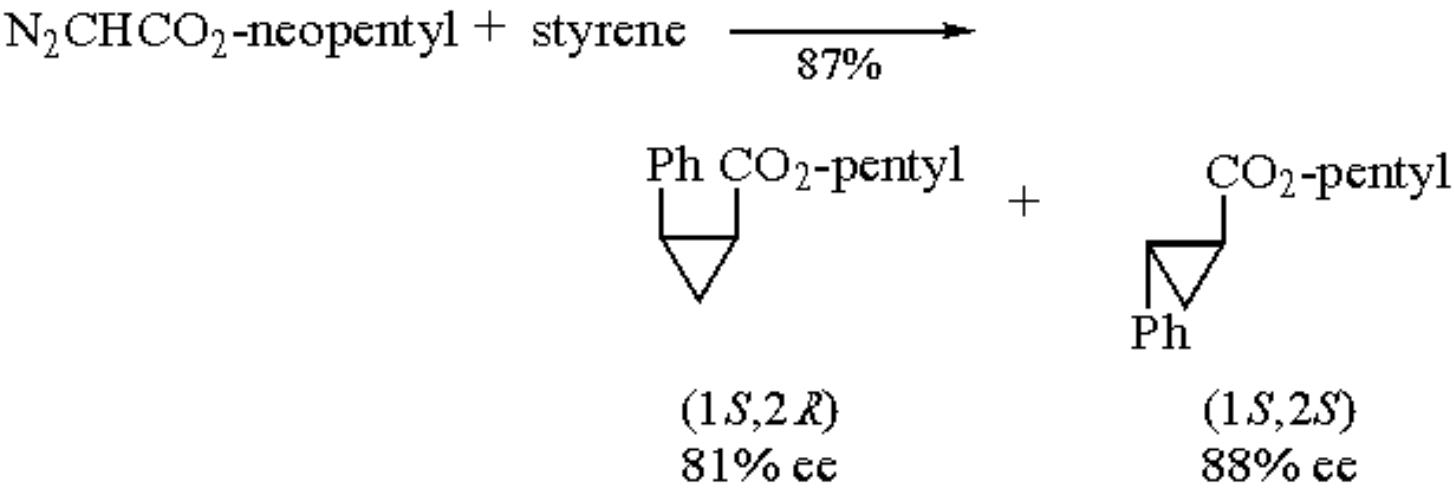

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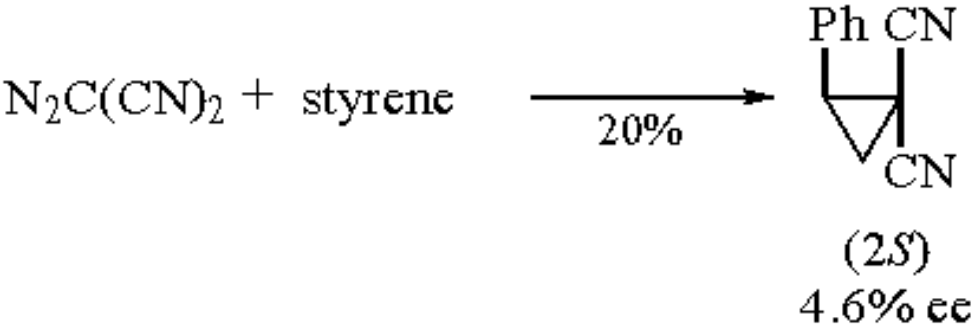

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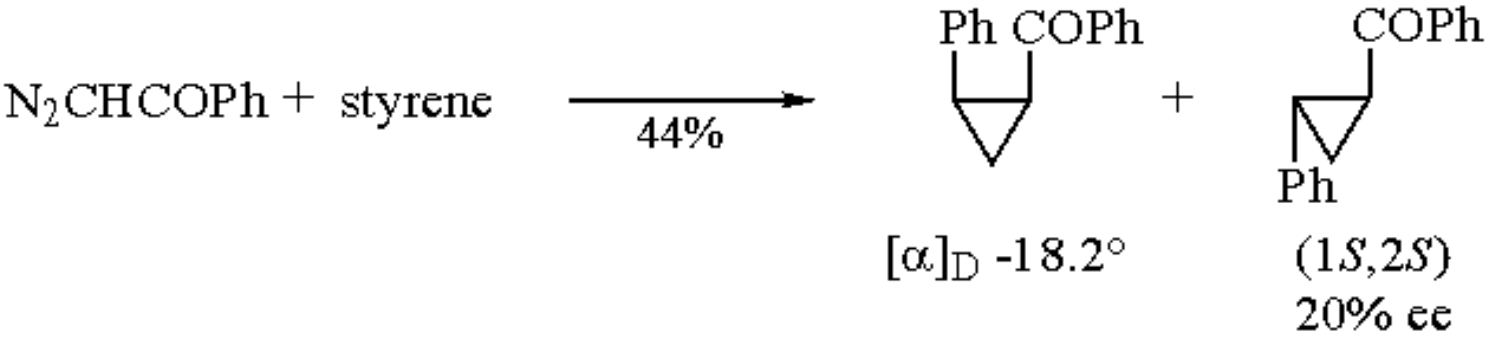

(8)

Other than diazoacetates, diazoacetophenone and diazodicyanomethane may also be used for cyclopropanation. The ee values are, however, lower than those obtained for diazoacetates.

Various organic solvents can be used, e.g. benzene, toluene, hexanes, acetone, acetophenone, diethyl ether. However, the substrate must be in large excess to the diazo compounds. The effect of additives has been examined. Pyridine or similar donor molecules retard the catalytic rates and decrease the optical yields.[3]

The enantioselectivity increases upon decreasing temperature. Thus the reaction between 0 and about -30 °C gives the best enantioselectivity in neat alkene.

Related chiral dioximato ligands have also been prepared. Isomeric nopinoquinone dioximato ligands (β- and δ-nqd) are prepared from 1-pinene.[4] The δ-isomer has been found to work to give an enantiomerically opposite isomer relative to the isomer obtainable with cqd by the cyclopropanation.

The enantiomeric purity of the chiral cyclopropanes may be enhanced by recrystallization of the acid obtained after mild alkaline hydrolysis of the chiral ester when the ee values are over 60%.

Related Reagents.

(S,S)-2,2´-(Dimethylmethylene)bis(4-t-butyl-2-oxazoline); ***Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)***; ***Copper(II) Trifluoromethanesulfonate***; ***(1S,9S)-1,9-Bis{[(t-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin***; ***(S)-2-[2-(Diphenylphosphino)phenyl]-4-phenyloxazoline***; ***Ethyl Diazoacetate***.

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1,2-Bis(chlorodimethylsilyl)ethane[1]

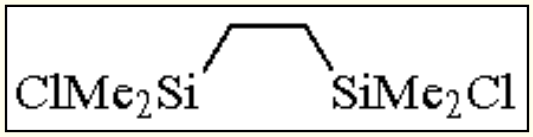

[13528-93-3] · $C_6H_{16}Cl_2Si_2$ · 1,2-Bis(chlorodimethylsilyl)ethane · (MW 215.27)

(reagent for the protection of primary amines as their tetramethyldisilylazacyclopentane or Stabase adducts; used in combination with zinc to form organozinc carbenoids; electrophilic silylating reagent)

Physical Data: mp 36-41 °C; bp 198 °C/734 mmHg.

Form Supplied in: white, waxy solid with a sharp acid odor; 96% pure.

Handling, Storage, and Precautions: the dry solid reacts with moisture to produce hydrogen chloride. Incompatible with strong acids, alcohols, strong bases and strong oxidizers; may be ignited by static electricity; causes severe irritation to the respiratory tract. The reagent therefore should be used in a well ventilated hood.

Protection of Primary Amines.

Few protecting groups exist for the N,N-diprotection of primary amines (see ***1,4-Bis(dimethylamino)-1,1,4,4-tetramethyldisilethylene***). The tetramethyldisilylazacyclopentane or Stabase adduct (**3**) is particularly attractive for this purpose due to its ease of preparation, base stability and facile removal. This cyclic disilane is easily prepared (eq 1) from the commercially available title reagent (**1**).[2] For primary amines with pK_a values between 10 and 11, typical reaction conditions involve the treatment of a dichloromethane solution of the amine with (**1**) in the presence of two equivalents of triethylamine at room temperature. Subsequent workup with aqueous dihydrogen phosphate provides (**3**) in excellent yields.[1] Stabase adducts are quite stable to strongly basic conditions such as ***n-Butyllithium*** and ***s-Butyllithium*** (at -25 °C), ***Lithium Diisopropylamide***, and Grignard reagents making it a superb candidate for use in the alkylation of substrates bearing a primary amine. For example, protected amino acid derivatives are easily alkylated (eq 2).[1,3] After formation of the lithium enolate of the protected ethyl glycinate (**4**) under standard conditions, exposure to various alkyl halides or aldehydes yields alkylation products such as (**5**).[1]

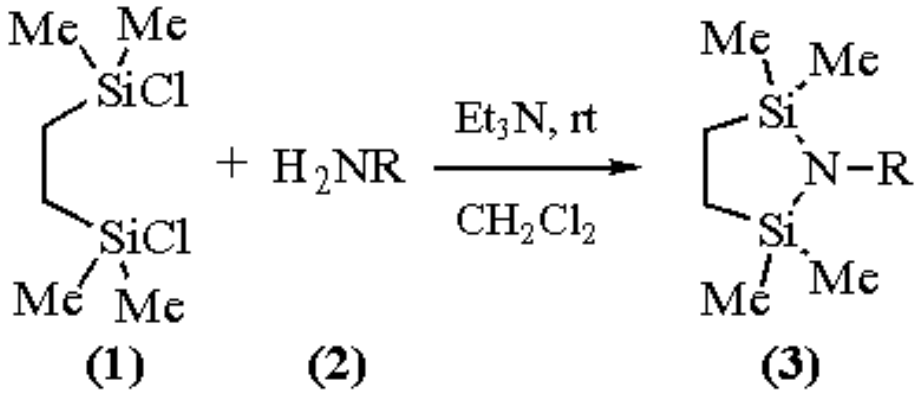

(1)

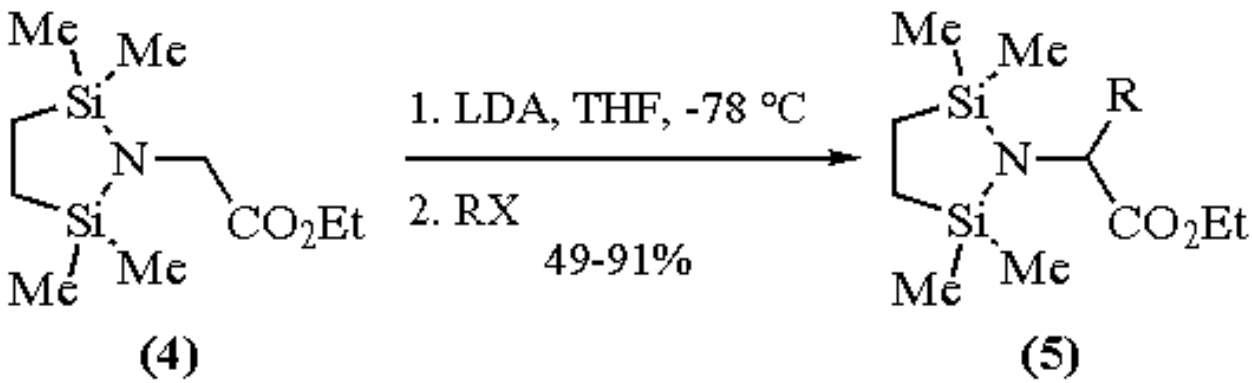

(2)

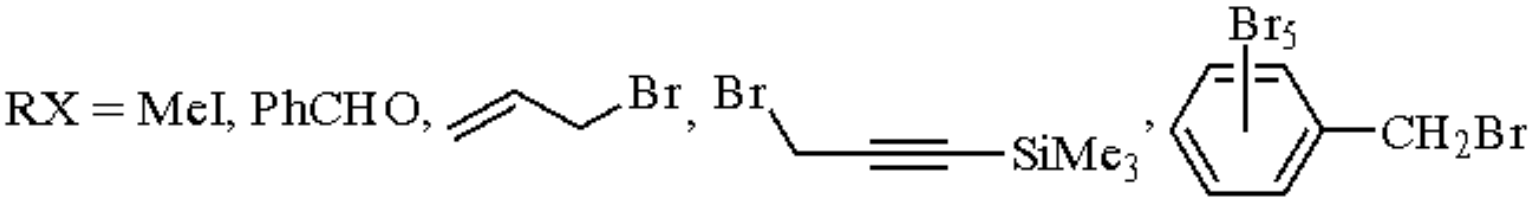

In addition to its base stability, this protecting group is readily cleaved under acidic conditions; often upon workup. After quenching the metallated dihydropyridine in eq 3 with the Stabase-protected aminoethyl disulfide (**7**), simple in situ treatment with saturated aqueous ammonium chloride liberates the regioisomeric free amines (**8a**) and (**8b**).[4] However, more vigorous conditions are sometimes required. For example, allylic amine (**11**) was produced by exposure of the crude coupling product of (**9**) and (**10**) to an excess of ethanolic HCl at 0 °C (eq 4).[5] Alternatively, Stabase deprotection can be achieved by reaction with ethanolic ***Sodium Borohydride***, as demonstrated in eq 5. The tertiary alcohol resulting from Grignard addition to aromatic ketone (**12**) was thus deprotected by treatment with $NaBH_4$ in ethanol to afford amino alcohol (**13**).[6]

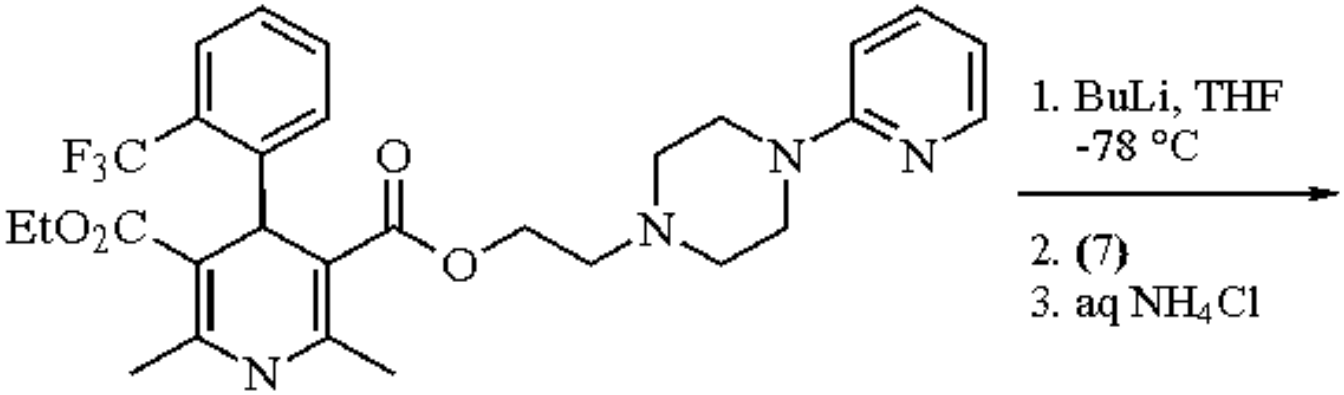

(6)

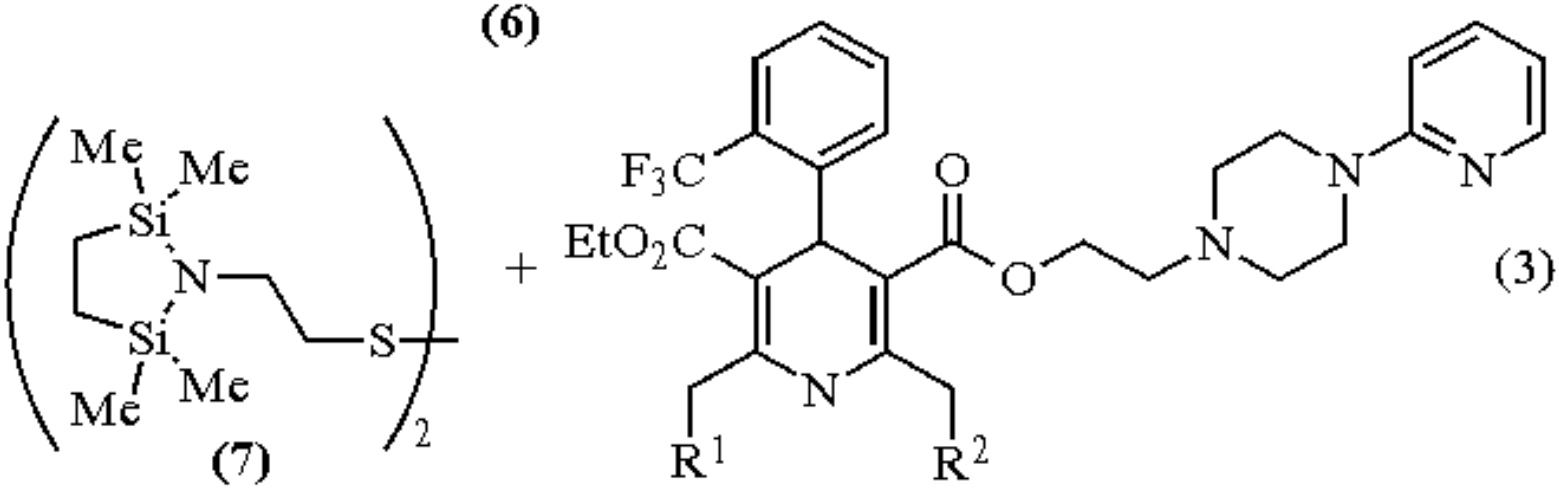

(7) + **(3)**

(8a) $R^1 = H$; $R^2 = SCH_2CH_2NH_2$; 16%
(8b) $R^1 = SCH_2CH_2NH_2$; $R^2 = H$; 18%

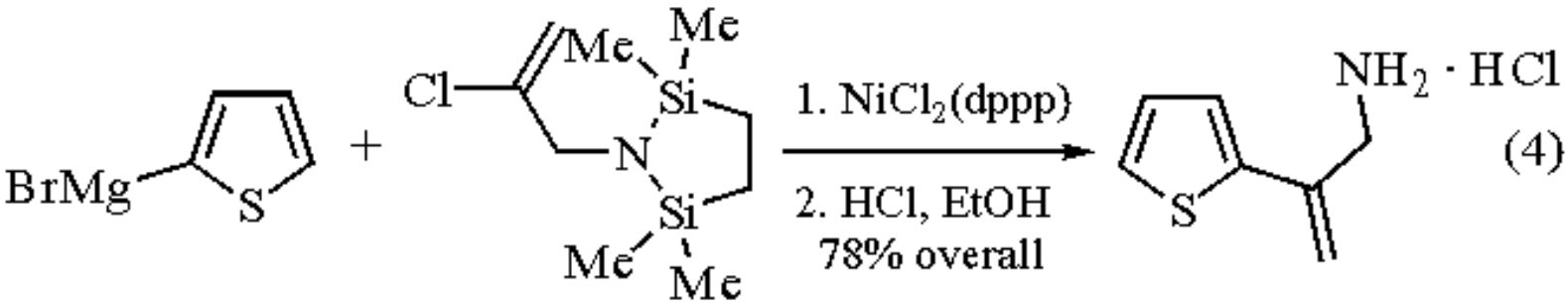

(9) + **(10)** → **(11)** (4)

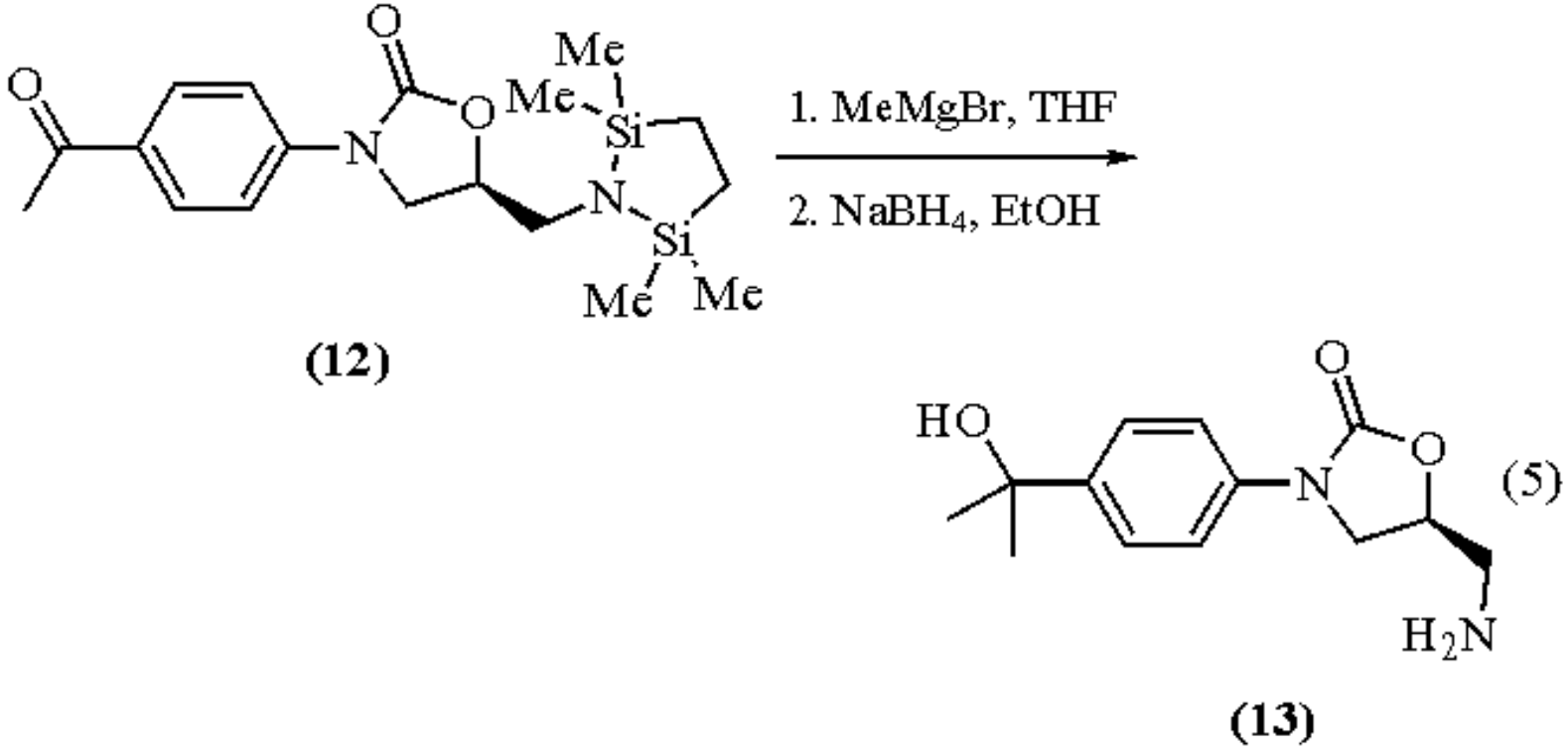

Cleavage of Stabase adducts reveals a reactive primary amine that can be utilized in further transformations. Several groups have engineered one-pot, multistep processes that exploit both the protecting power and the acid lability of the cyclic disilane to generate amines in situ. An elegant example of such a transformation is illustrated in the general synthesis of 2-substituted pyrrolidines (**17**) which otherwise are difficult to synthesize (eq 6). Addition of the Stabase-protected Grignard (**14**) to an *N*-methoxy-*N*-methyl amide is followed by treatment of the reaction mixture with ethanolic HCl. Collapse of the intermediate hemiaminal is followed by Stabase cleavage and concomitant cyclization to the imine (**16**) in a single operation. The substituent R may vary from aliphatic to a wide variety of heterocyclic compounds.[7]

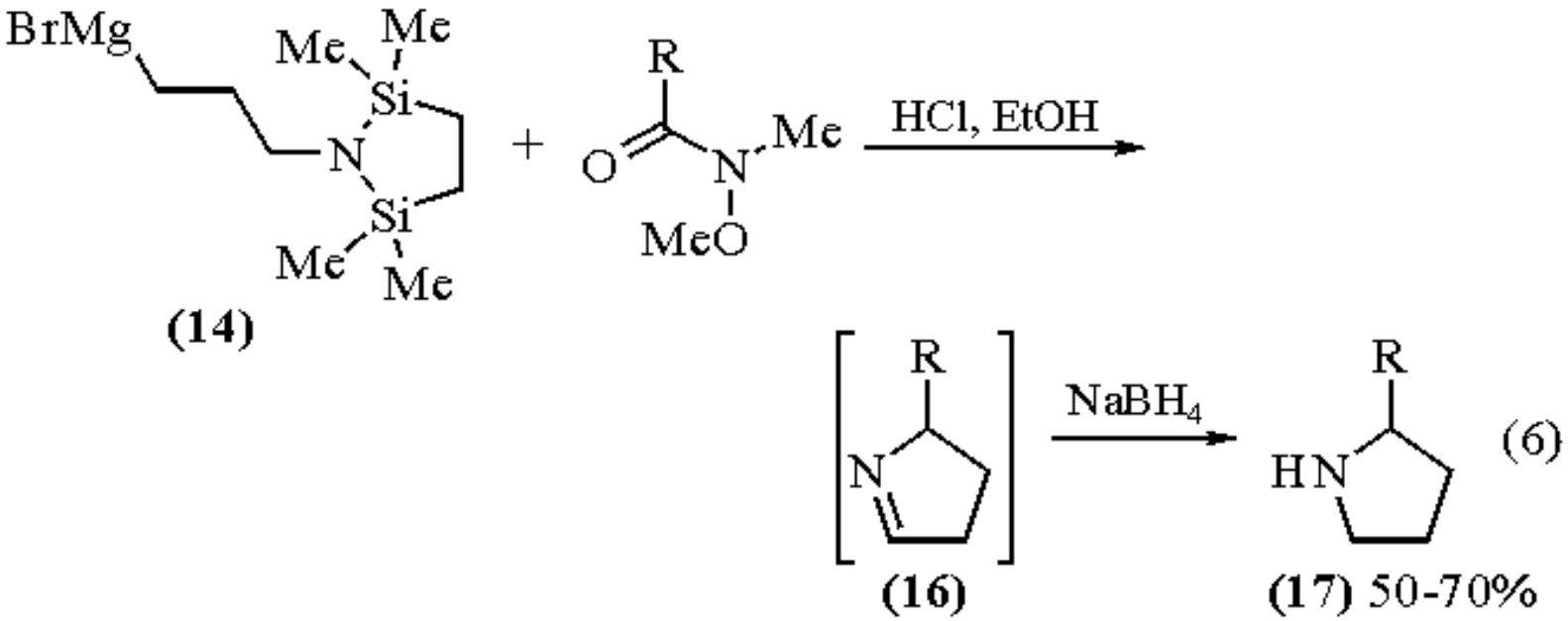

A further extension of this concept is shown in the 6-substituted 3-pyridinol synthesis described in eq 7. Treatment of condensation product (**19**) with 1 M HCl initiates Stabase deprotection that is followed by acid-catalyzed

rearrangement of the resulting amino alcohol to pyridine (**20**).[8]

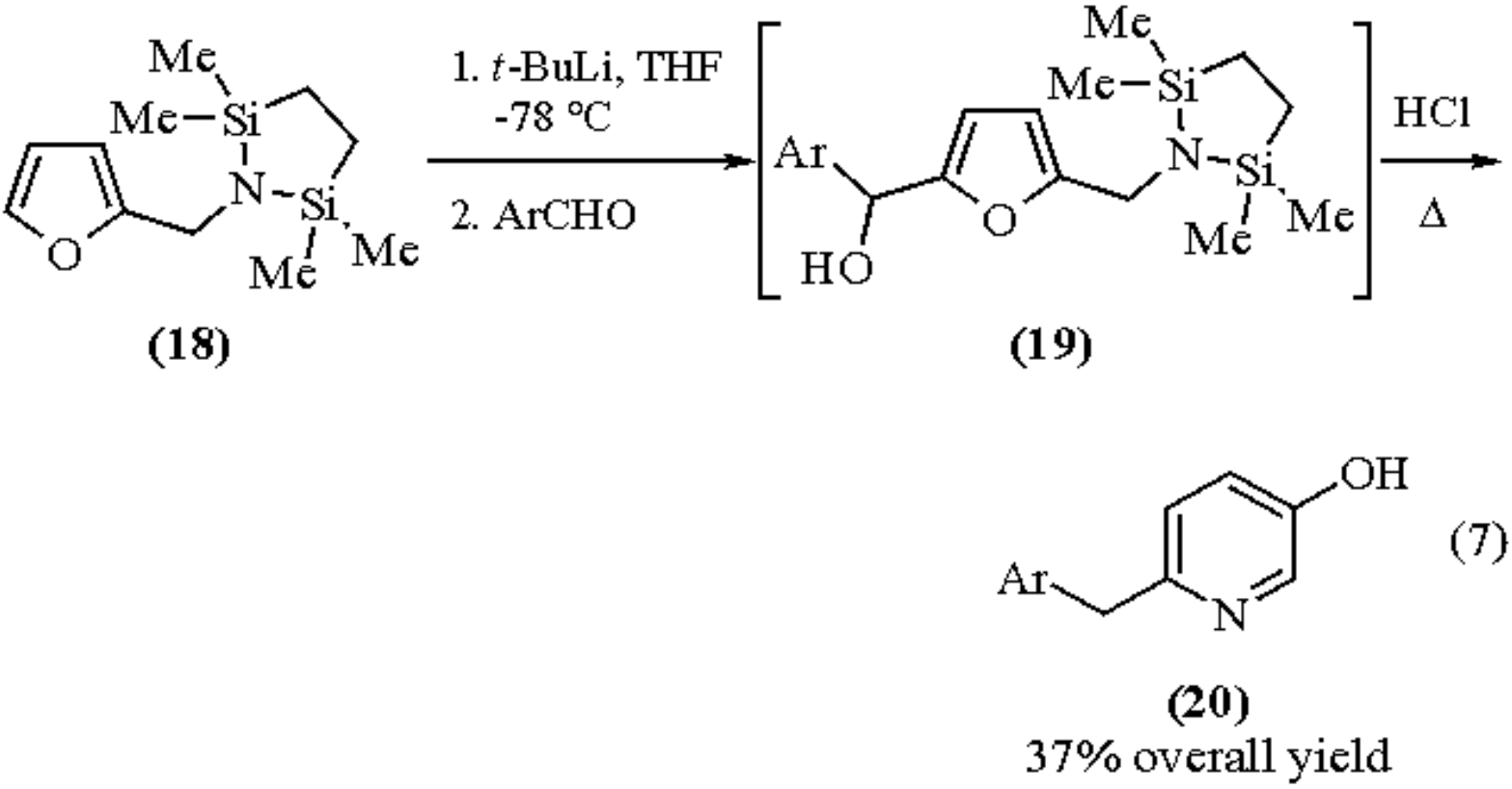

Formation of Organozinc Carbenoids.

When aromatic aldehydes and certain α,β-unsaturated carbonyl compounds are treated with zinc and 1,2-bis(chlorodimethylsilyl)ethane, an organozinc carbenoid results. This two-electron process is postulated to occur as depicted in eq 8. Sequential reaction of the two silicon atoms with the zinc carbonyl complex and subsequent extrusion of the cyclic siloxane (**23**) gives rise to the putative organozinc carbenoid (**24**). When generated in the presence of an alkene, cyclopropanes (**25**) are produced in good yields as in eq 9.[9] When 2 equiv of carbonyl compound are employed, the organozinc carbenoid is trapped by excess carbonyl compound, and the intermediate epoxide is deoxygenated to yield products (**26**) of symmetrical dicarbonyl coupling (eq 10).[10]

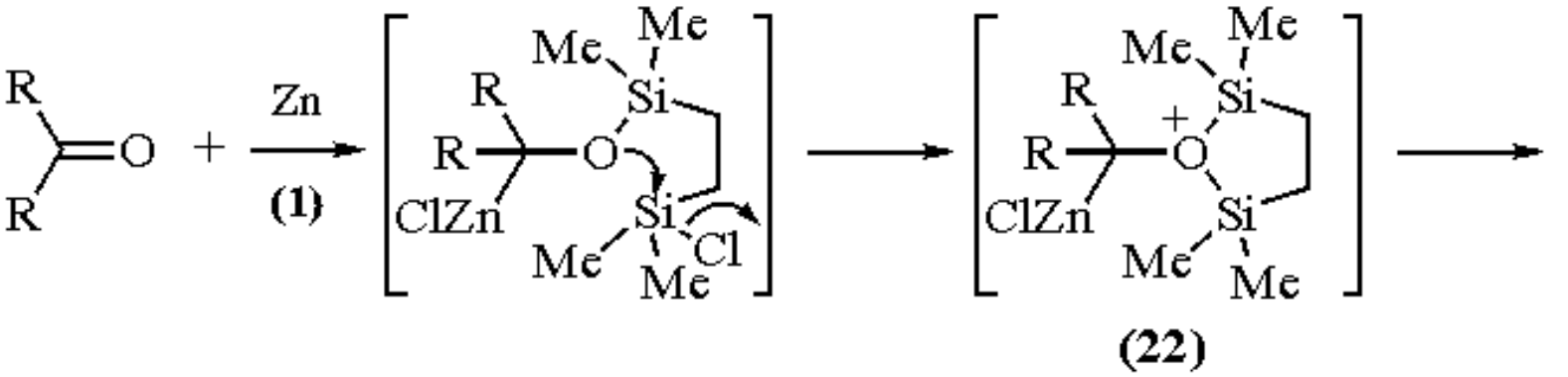

(22)

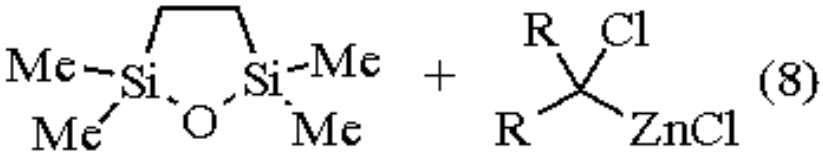

(8)

(23) (24)

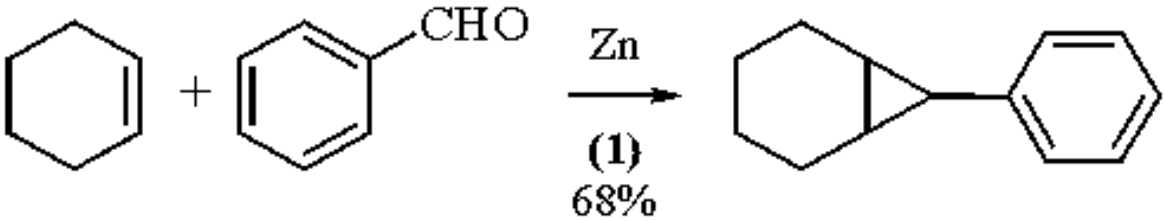

(9)

(25)

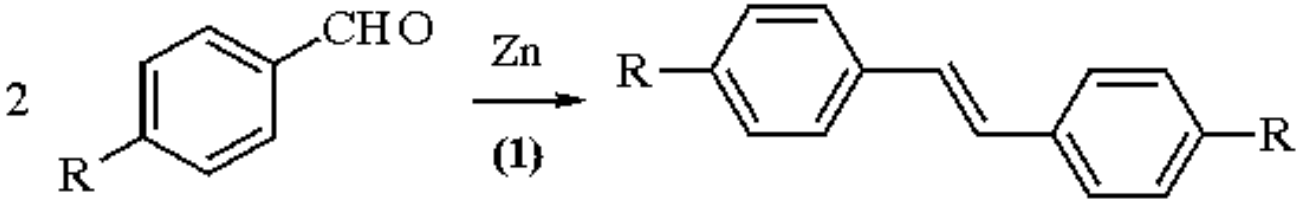

(10)

(26) R = Me, 86%

Electrophilic Silylation Reagent.

1,2-Bis(chlorodimethylsilyl)ethane is not only an effective amine silylating reagent, but can also be employed in reactions with other anions. For example, when treated with the silver sulfonate salt as in eq 11, the nonafluorobutanesulfonic acid silyl ester (**27**), an extremely powerful silylating reagent, results.[11] Carbanions are also effectively trapped by (**1**). A series of rigid butadiene Diels-Alder precursors such as (**28**) have been prepared in this fashion as outlined in eq 12.[12]

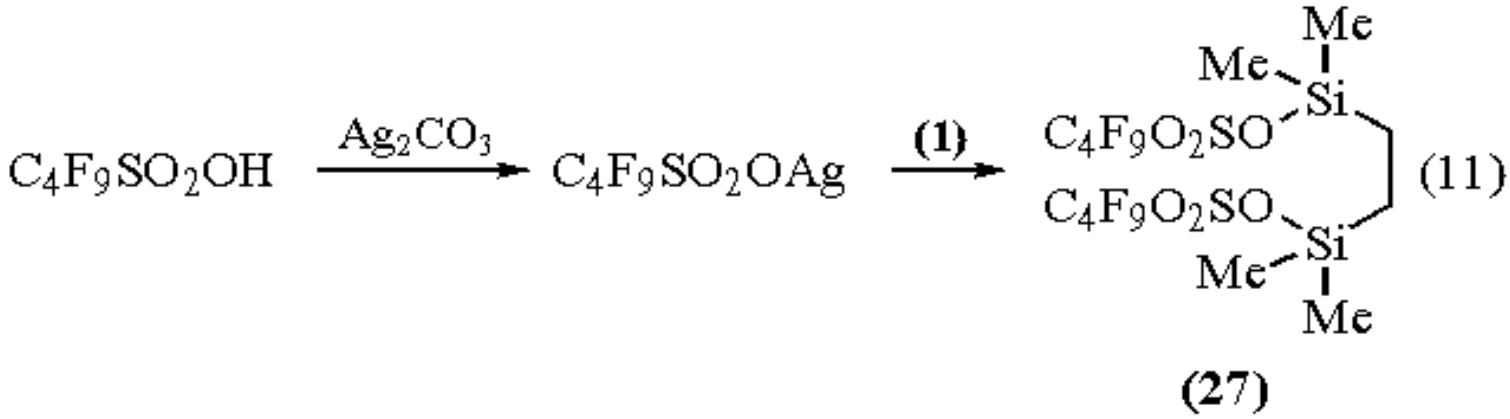

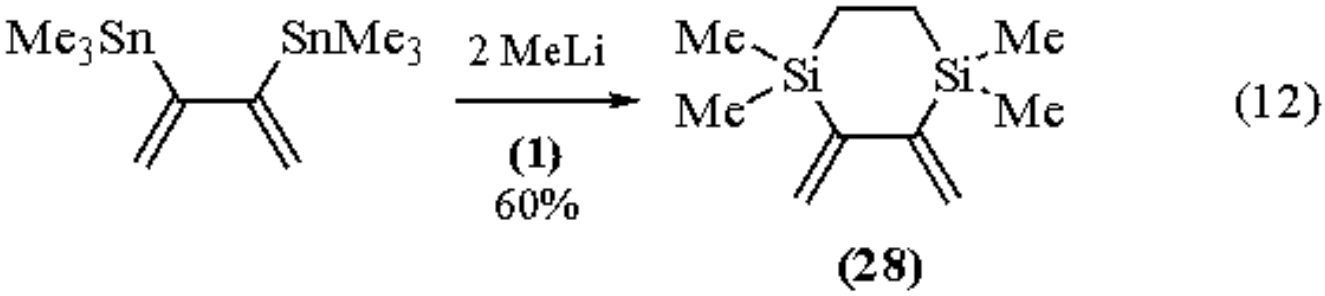

Related Reagents.

1,4-Bis(dimethylamino)-1,1,4,4-tetramethyldisilethylene.

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Bis(chloromethyl) Ether

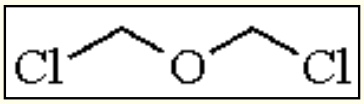

[542-88-1] · $C_2H_4Cl_2O$ · Bis(chloromethyl) Ether · (MW 114.96)

(useful reagent for the chloromethylation of aromatic moieties[1] and for the preparation of oxygen-containing heterocycles[2])

Alternate Names: BCME; α,α´-dichloromethyl ether; 1,1´-dichloromethyl ether; chloromethyl ether; oxybis(chloromethane); *sym*-dichloromethyl ether.

Physical Data: bp 106 °C; mp -41.5 °C; *d* 1.315 g cm^{-3}.

Preparative Method: the large-scale preparation of bis(chloromethyl) ether using paraformaldehyde, hydrogen chloride, and chlorosulfonic acid has been reported by Buc as an *Organic Synthesis* preparation.[3]

Handling, Storage, and Precautions: this agent is a strong irritant to the eyes and respiratory tract and is a known carcinogen.[4] All procedures using this reagent should be carried out in a fume hood.

Aromatic Chloromethylation.

Bis(chloromethyl) ether is an effective reagent for the direct chloromethylation of a variety of aromatic substrates. The reaction occurs via electrophilic aromatic substitution of the oxonium ion generated upon treatment of the reagent with acid catalyst. For example, chloromethylation of *p*-nitroanisole using BCME and ***Zinc Chloride*** in dimethyl sulfide afforded 4-nitro-2-chloromethylanisole in 74% yield (eq 1).[1] The procedure was reported to be superior to chloromethylation using paraformaldehyde and hydrogen chloride, which afforded only poor yields of the desired anisole. A variation of this process using ***Chlorosulfonic Acid*** as the catalyst chloromethylated *p*-nitrotoluene to give 2-chloromethyl-4-nitrotoluene in quantitative yield (eq 2).[5]

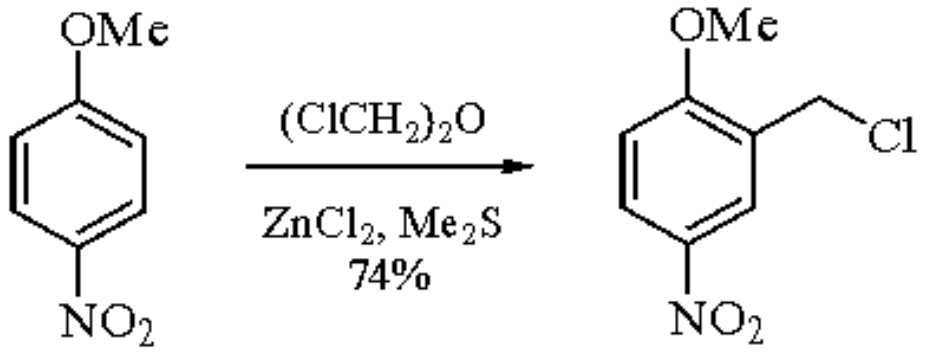

(1)

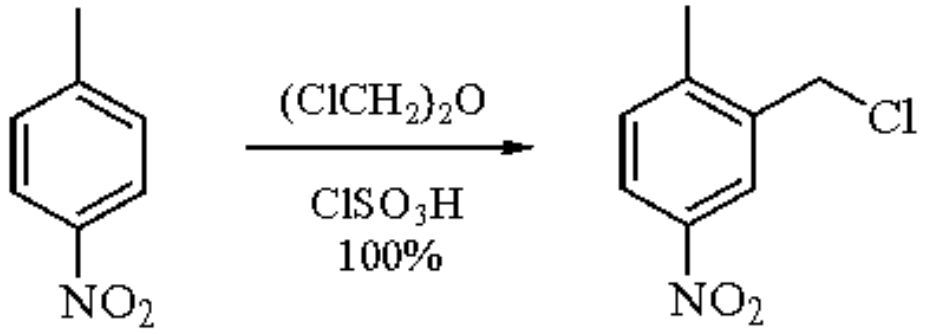

(2)

The chloromethylation of aromatic heterocycles has also been reported. For example, 3,5-dimethylisoxazole was chloromethylated to give 4-chloromethyl-3,5-dimethylisoxazole (eq 3).[6] The synthesis of 5-(halomethyl)-2-pyranones for use as α-chymotrypsin inhibitors have also employed this chloromethylation procedure. Thus treatment of 5-(trifluoromethyl)-2-pyranone with BCME and sulfuric acid gave 3-(chloromethyl)-5-(trifluoromethyl)-2-pyranone in 50% yield (eq 4).[7]

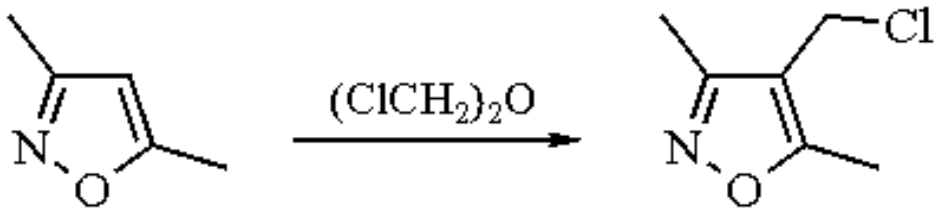

(3)

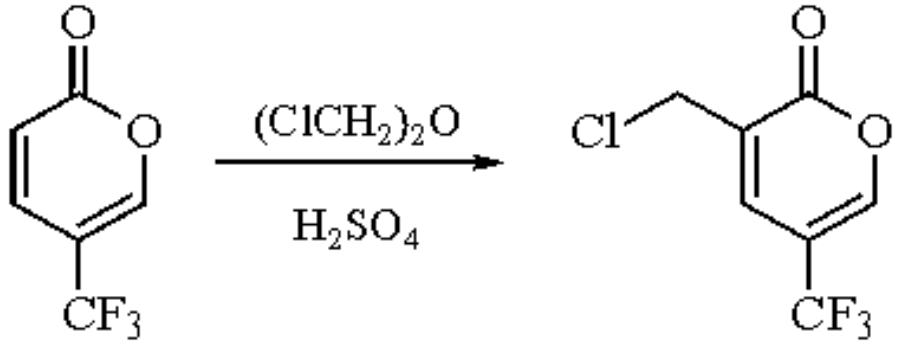

(4)

Alkylation and Heterocycle Formation.

Oxygen-containing heterocycles have also been prepared using BCME. For example, tetrahydrofurans have been prepared via cyclocondensation of simple alkenes with chloromethoxymethyllithium (eq 5), an agent derived from BCME.[2] Other examples include the preparation of macrocyclic heterocycles. For example, 18-crown-6 coronands have been prepared for use as ionophores via condensation of a bipyrazole with BCME (eq 6).[8]

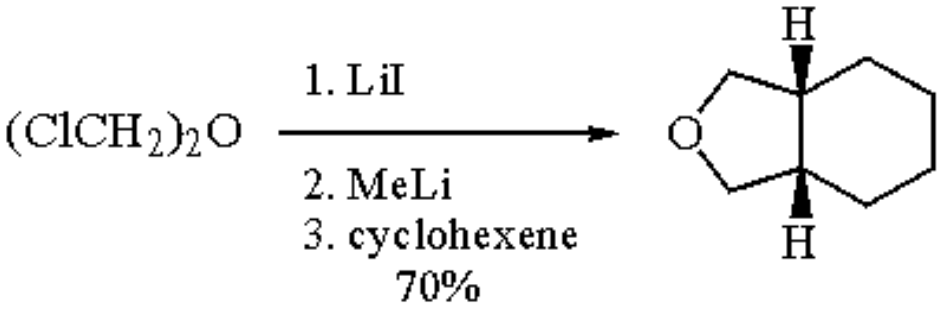

(5)

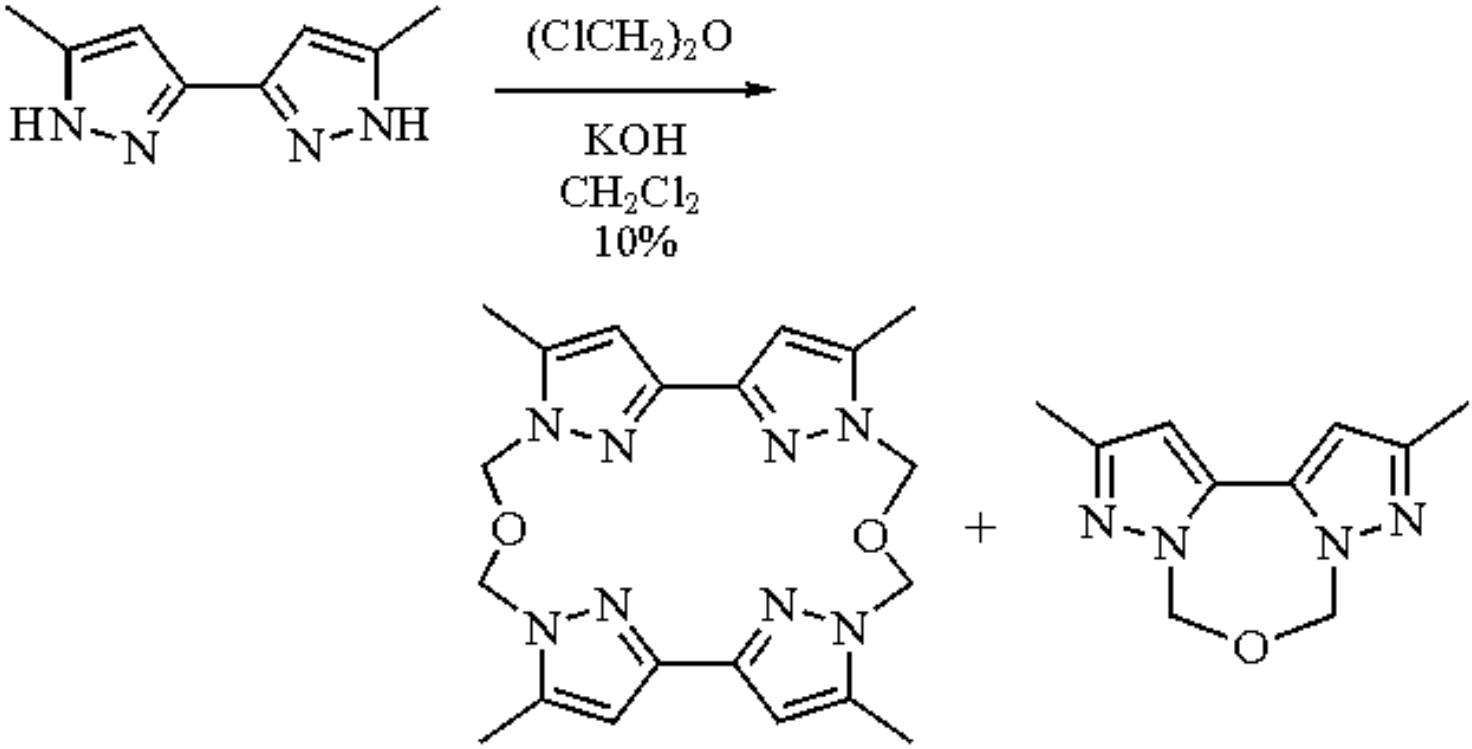

(6)

BCME has also been employed in the preparation of symmetrical and unsymmetrical dimethyl ether derivatives (eq 7). Bis(pyridinium and imidazolium) quaternary salts, useful as reversible acetylcholinesterase inhibitors, were prepared via stepwise condensation of the requisite pyridine or imidazole with BCME followed by a second equivalent of amine heterocycle.[9] Likewise, symmetrical dineopentyl ethers have been prepared by Refomatsky reaction using ethyl α-bromo esters, BCME, and zinc (eq 8).[10]

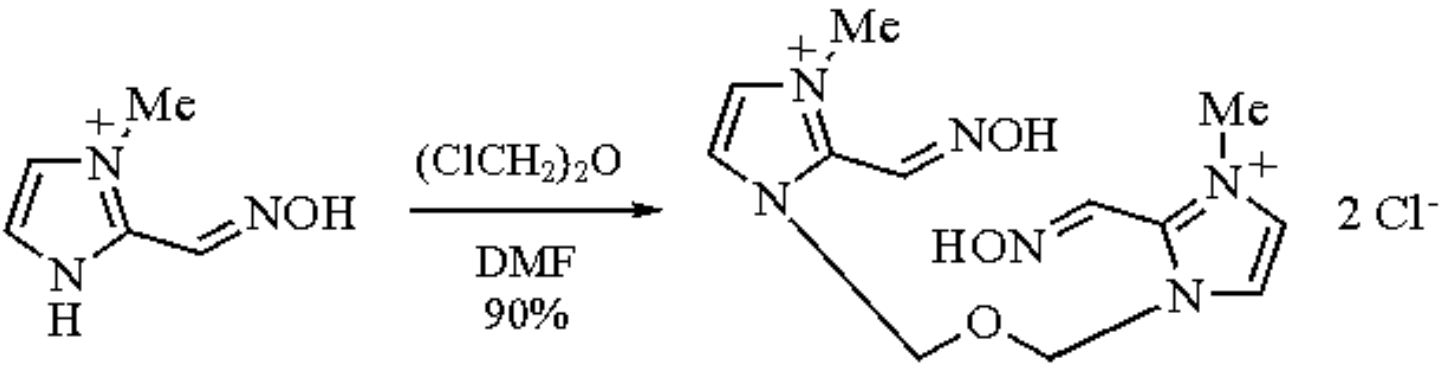

(7)

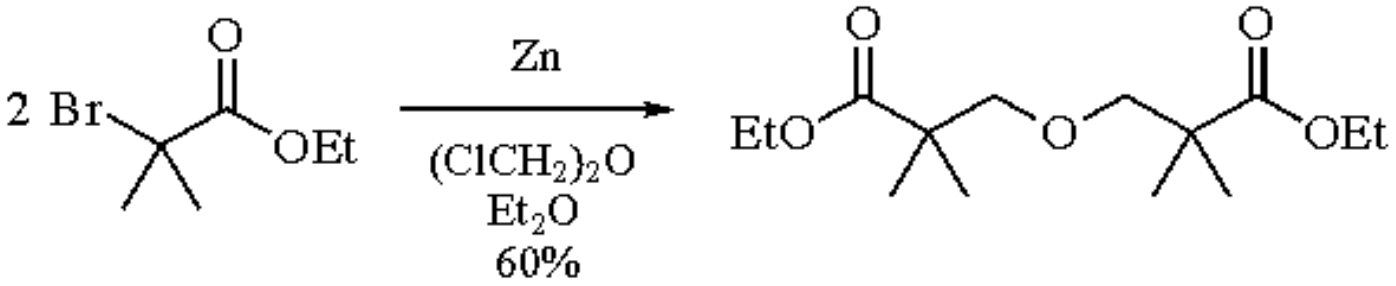

(8)

Phenols, thiols, phosphines, and pyridines have also been used as nucleophiles with BCME for the synthesis of symmetrical ethers. For example, 4-chlorophenol,[11] 2,5-dimethylbenzenethiol,[12] pyridine,[13] and triphenylphosphine[14] gave, respectively, 90%, 72%, 48%, and 69% yields of the corresponding bis-alkylation products.

---

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Bis(cyclohexyl isocyanide)gold(I) Tetrafluoroborate-(*R*)-*N*-[2-(*N,N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine[1]

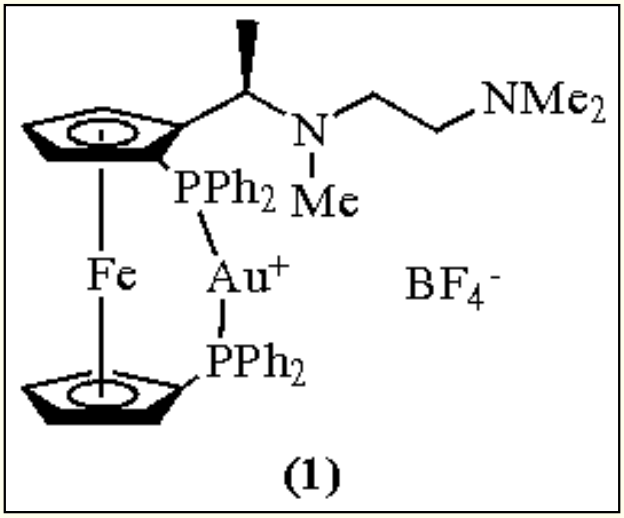

[-] · $C_{41}H_{44}AuBF_4FeN_2P_2$ · Bis(cyclohexyl isocyanide)gold(I) Tetrafluoroborate-(*R*)-*N*-[2-(*N,N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine · (MW 966.38) (gold component)

[43067-36-3] · $C_{14}H_{22}AuBF_4N_2$ · Bis(cyclohexyl isocyanide)gold(I) Tetrafluoroborate-(*R*)-*N*-[2-(*N,N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine · (MW 502.14) (ferrocene component)

[119477-31-5] · $C_{41}H_{44}FeN_2P_2$ · Bis(cyclohexyl isocyanide)gold(I) Tetrafluoroborate-(*R*)-*N*-[2-(*N,N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine · (MW 682.62)

(chiral catalyst for asymmetric aldol reactions giving high diastereo- and enantioselectivity;[2] enantioselective synthesis of β-hydroxy-α-aminophosphonates;[3] asymmetric allylation[4])

Solubility: sol dichloromethane, 1,2-dichloroethane, and diethylene glycol dimethyl ether; insol diethyl ether and pentane.

Preparative Method: the complex is prepared in situ by the reaction of bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate[5] with ***(R)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(S)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine***,[6] typically in dichloromethane.[7]

Handling, Storage, and Precautions: prepare under anhydrous conditions and use under a dry inert atmosphere

of nitrogen.

Enantioselective Aldol Reactions.

The development of synthetic methodology for the diastereoselective and enantioselective formation of C-C bonds through the use of catalytic quantities of chiral transition-metal catalysts is a topic of fundamental importance. In 1986, Ito and Hayashi reported an elegant asymmetric synthesis of dihydrooxazolines by the gold(I)-catalyzed aldol reaction (more correctly a Knoevenagel reaction) of an aldehyde with an isocyanoacetate ester in the presence of a chiral ferrocenylamine ligand.[7] The chiral catalyst (*R*)-(*S*)-(**1**) is conveniently prepared in situ as described above.[5,6] The dihydrooxazolines obtained provide a convenient precursor to enantiomerically pure β-hydroxy-α-amino acid derivatives. The *trans* (4*S*,5*R*)-oxazoline in high ee is obtained predominantly in the reaction of aldehydes with α-isocyanoacetate esters catalyzed by (*R*)-(*S*)-(**1**) (eqs 1-3).[7-9] High stereoselectivity is retained with alkyl-substituted α-isocyanoacetate esters (eq 4), although reduced diastereoselectivity and enantioselectivity is often obtained with large α-substituents.[10]

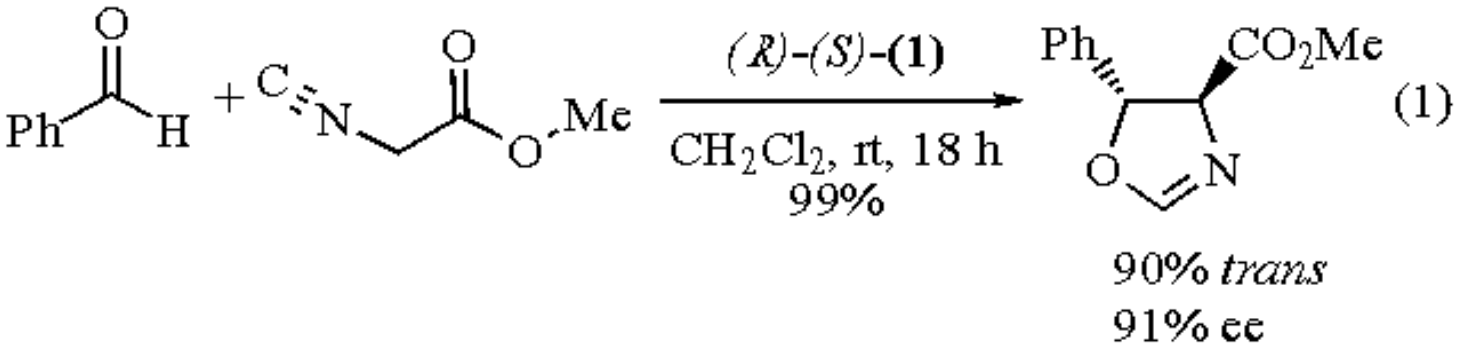

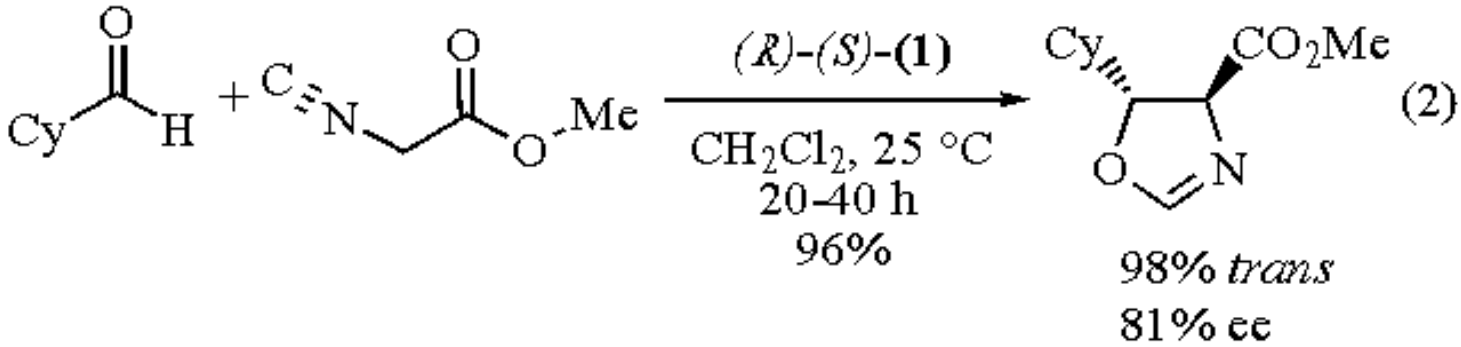

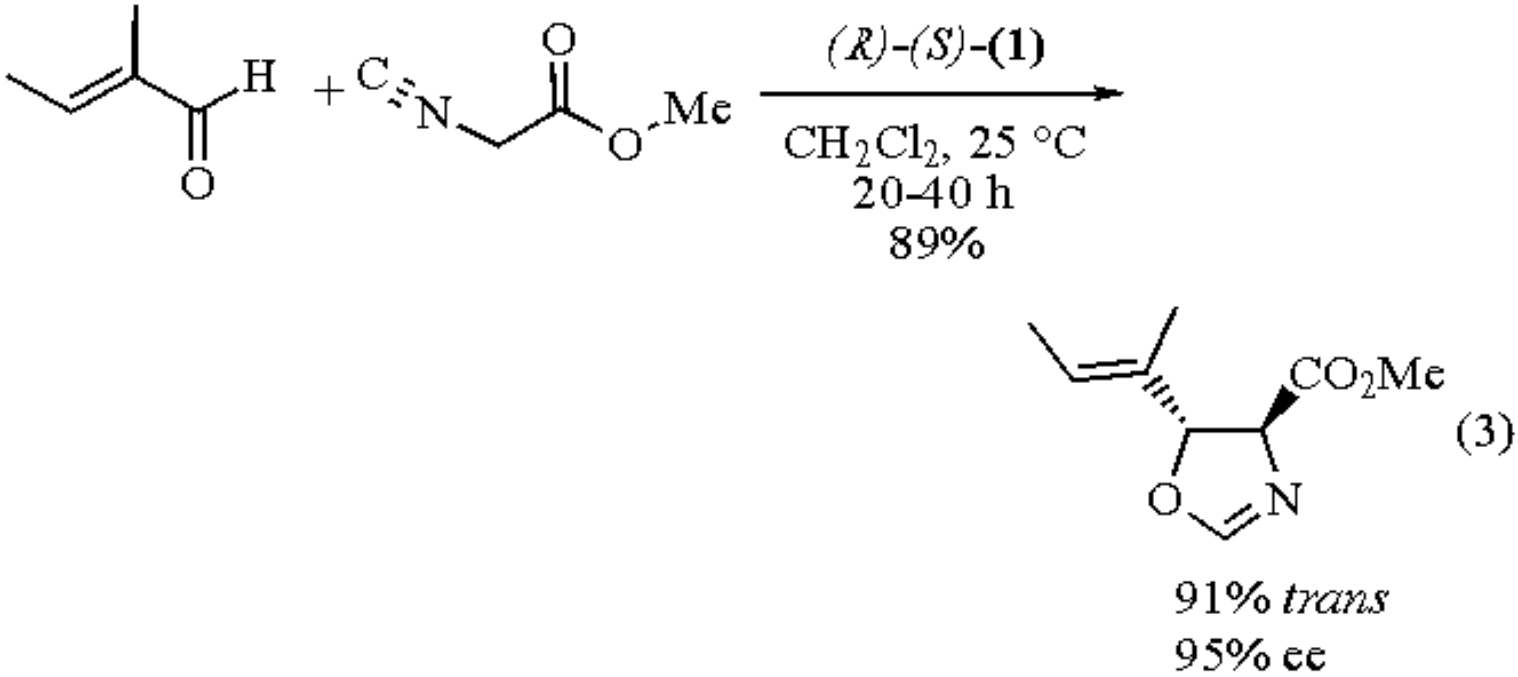

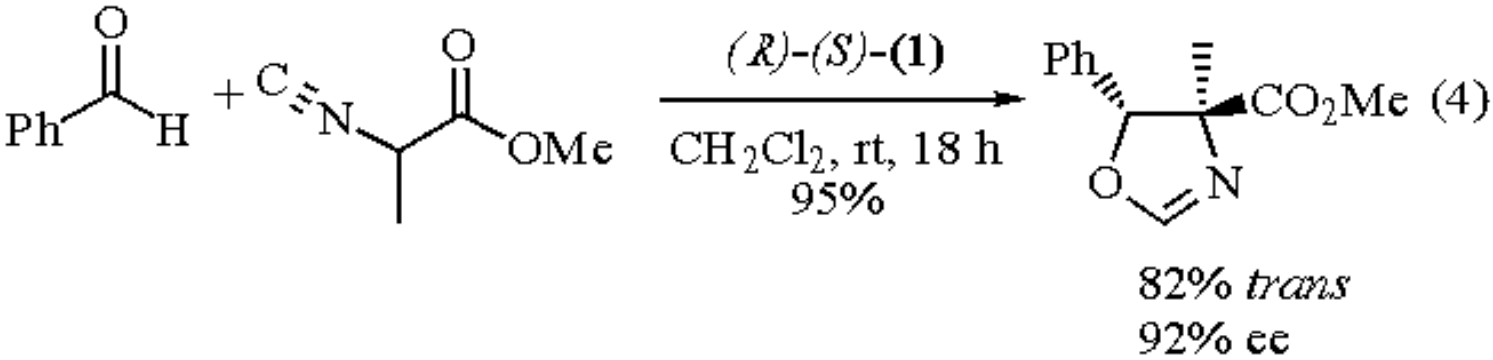

A wide variety of ester functionalities are tolerated (eq 5).[11] A single stereocenter is formed in high ee when formaldeyde is utilized as a reaction component, which leads to an efficient asymmetric synthesis of α-alkylserines (eq 6).[12] The utilization of α-keto esters provides a facile route to β-alkyl-β-hydroxyaspartic acid. Higher diastereo- and enantioselectivity are obtained by the reaction of the α-keto ester with the corresponding *N*,*N*-dimethyl-α-isocyanoacetamide (eq 7).[13] In certain cases, the use of α-isocyanoacetamides is advantageous for improving stereoselectivity in the corresponding reaction with aldehydes.[14] The presence of α-heteroatoms or certain electronegative groups in the aldehyde component of the reaction may lead to dramatic changes in diastereo- and enantioselectivity.[8,11] Opposite product chirality can be obtained in the gold(I)-catalyzed aldol reaction by using the (*S*)-(*R*) enantiomer of (**1**).

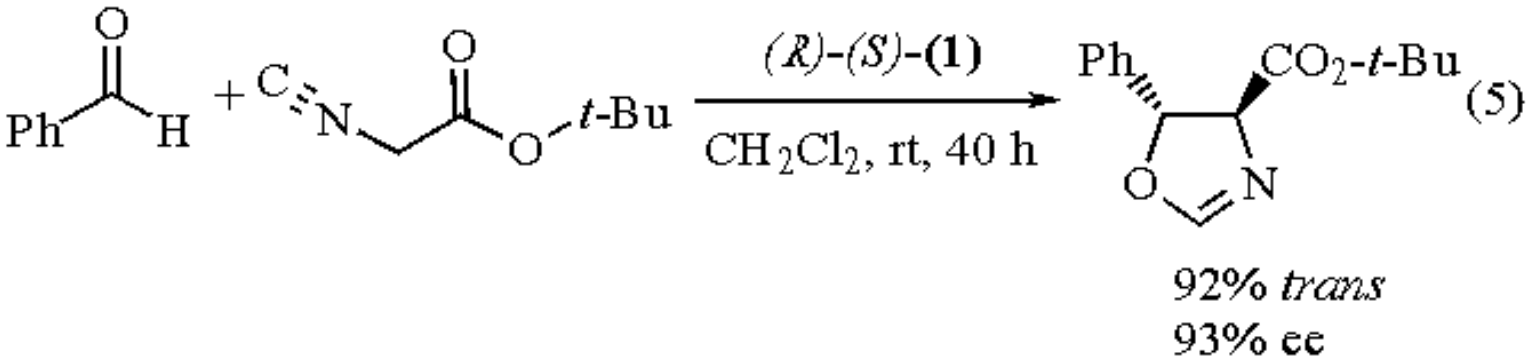

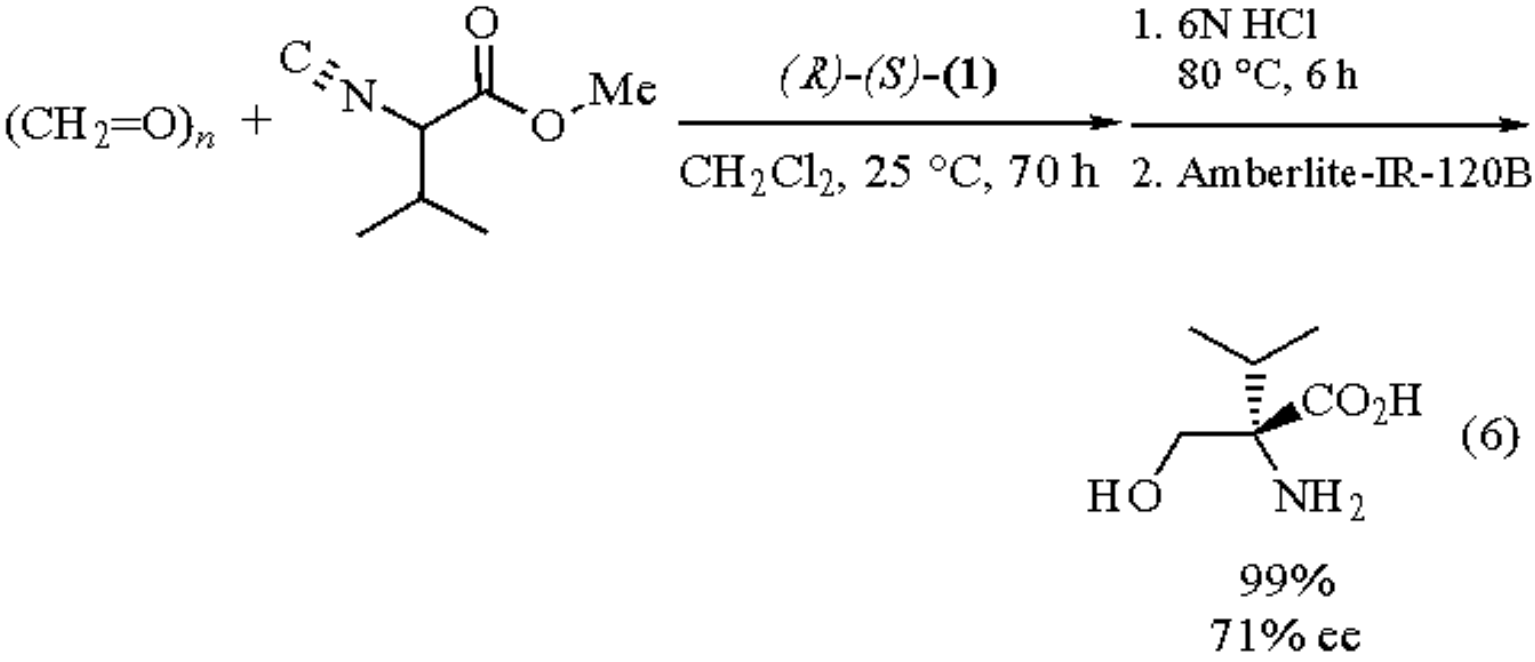

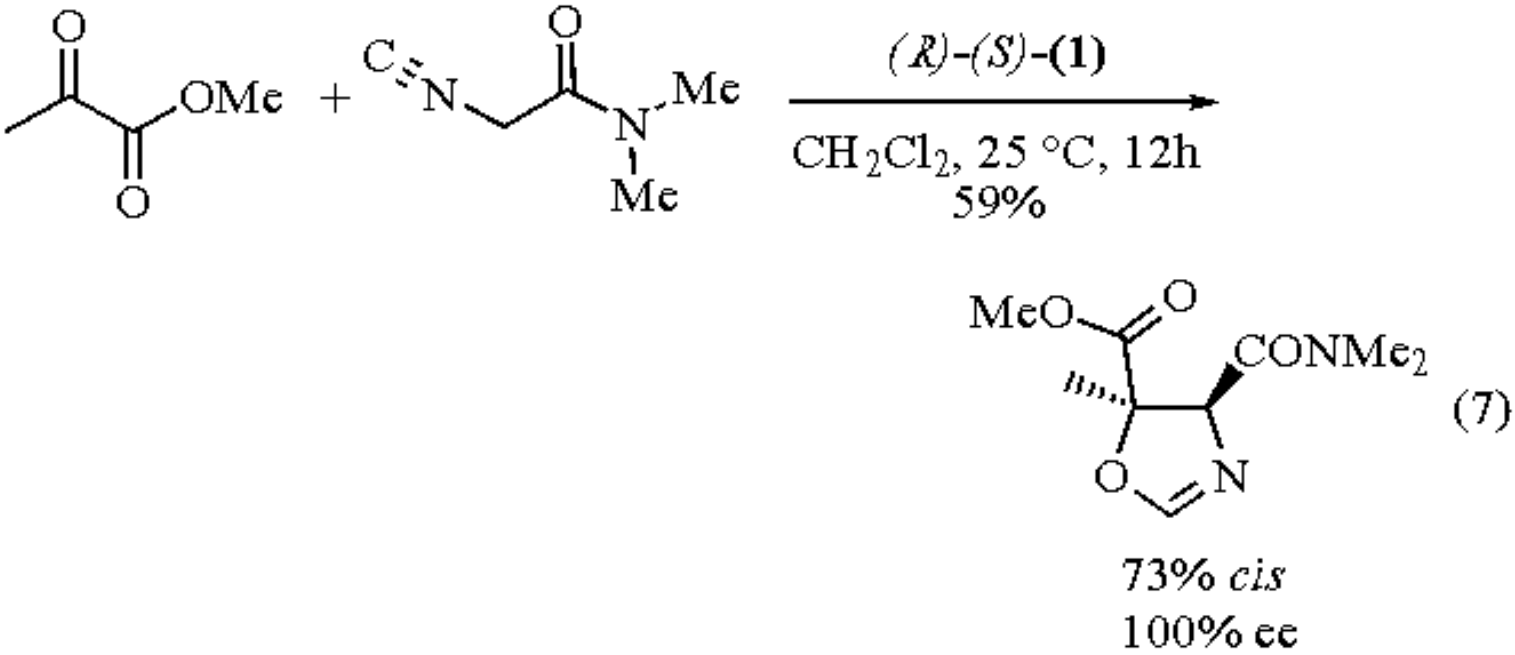

Double stereodifferentiation (double asymmetric induction) between a chiral substrate and the chiral ferrocenylamine ligand has been demonstrated (eq 8).[11] The stereocenter (central chirality) as well as the stereoaxis (axial chirality) affects both product diastereoselectivity and enantioselectivity.[15] Chiral cooperativity (or internal cooperativity) refers to individual chirotopic segments of the ligand molecule acting in a cooperative manner to promote a particular diastereo- and enantioselectivity in the product.[8,15-18] The effects of distant stereocenters in ligands analogous to (*R*)-(*S*)-(**1**) upon the stereoselectivity of the gold(I)-catalyzed aldol reaction has been studied.[19,20] Improvements in stereoselectivity can be obtained in certain cases by modification of the terminal *N*,*N*-dimethylamino substituent in the side chain of (*R*)-(*S*)-(**1**),[2,9,10,12,21] (compare eqs 4 and 9) as well as the aryl substituents on phosphorus.[22] Several recent studies have appeared dealing with the elucidation of the stereoselective transition-state geometry.[8,23-25] An elegant study of aldol stereochemistry has important implications on the stereoselective transition-state geometry for the gold(I)-catalyzed aldol reaction.[26] A report has appeared describing the use of a neutral gold(I) ferrocenylamine catalyst for asymmetric aldol reactions, albeit in lower diastereo- and enantioselectivity.[27]

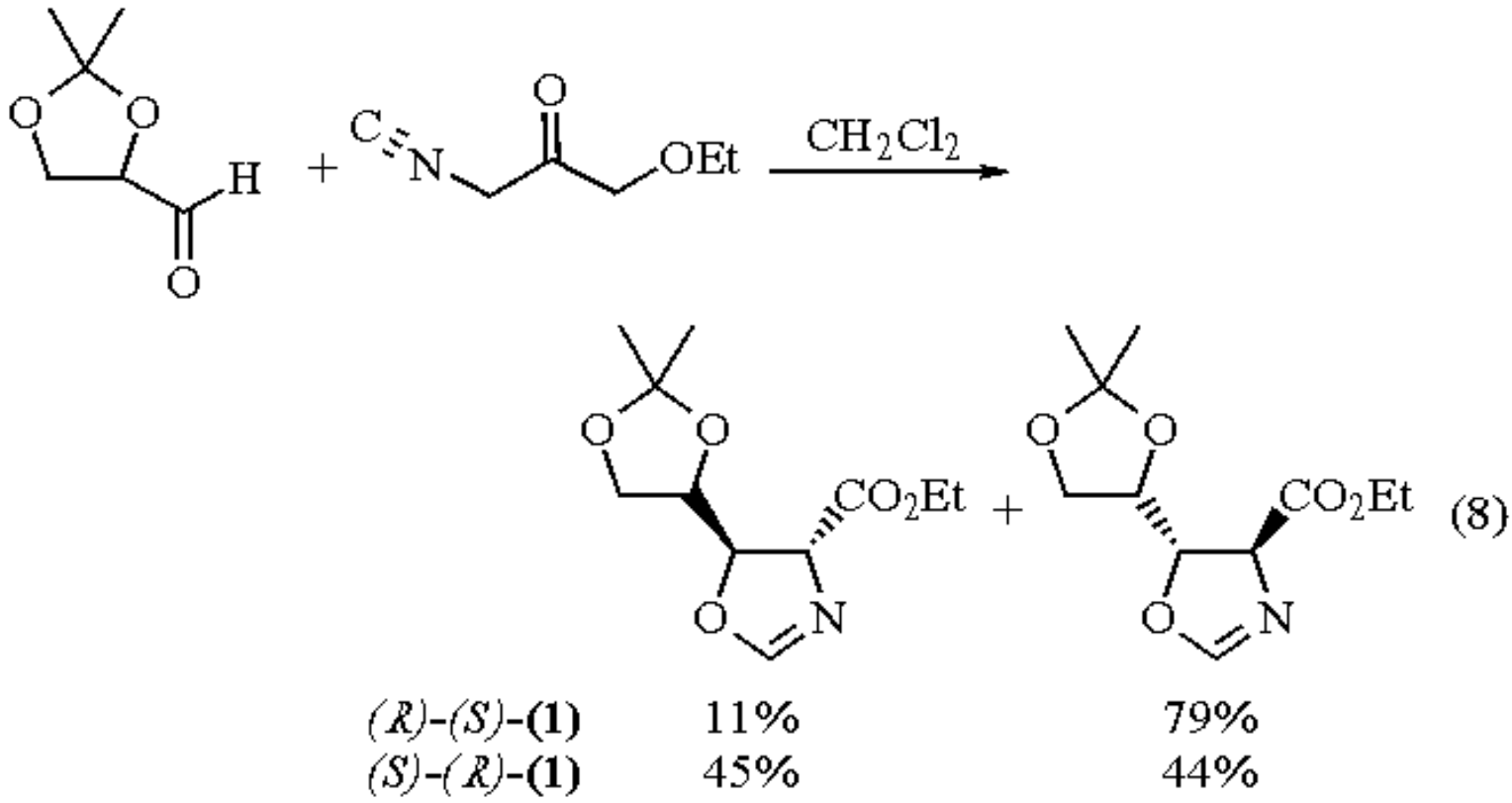

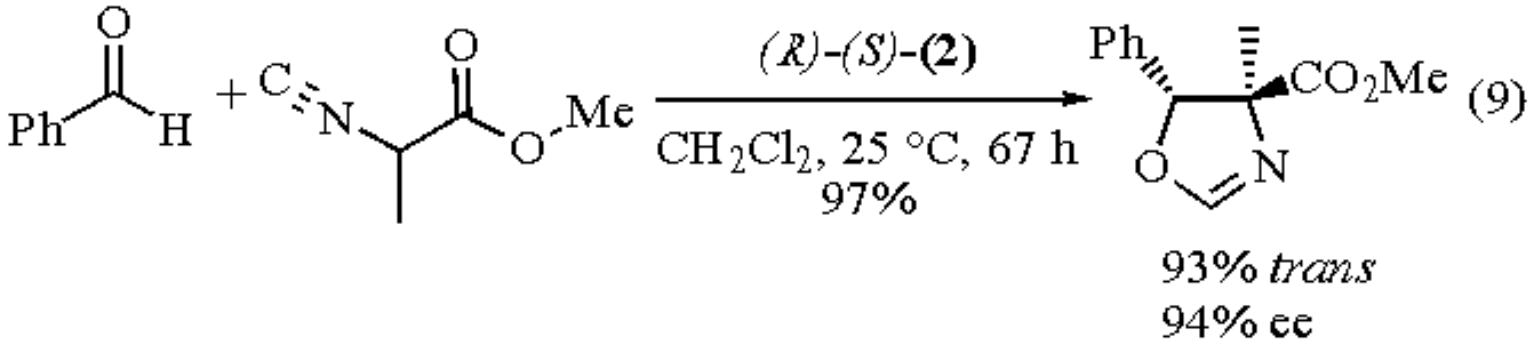

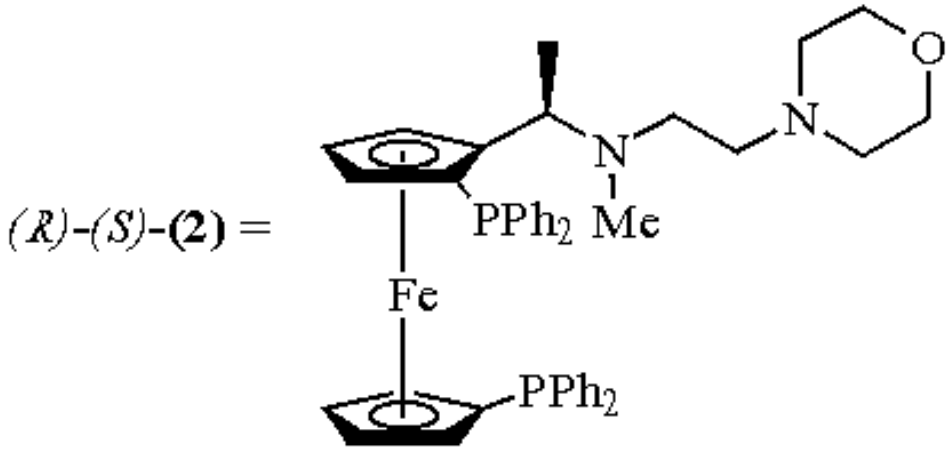

The gold(I)-catalyzed aldol reaction has been applied to the synthesis of several natural products including cyclosporin's unusual amino acid MeBmt, in which two of the three product stereocenters were generated by the reaction of 2-(*R*)-methyl-4-hexenal with ethyl α-isocyanoacetate (eq 10).[28] Although either enantiomer of the *trans*-dihydrooxazole can be obtained by using (*R*)-(*S*)-(**1**) or (*S*)-(*R*)-(**1**), a modest effect due to matching and mismatching of substrate and ligand chirality is

apparent (double stereodifferentiation).[29] Methylation of the *trans*-dihydrooxazole with ***Trimethyloxonium Tetrafluoroborate*** followed by aqueous sodium bicarbonate hydrolysis gives the formamido ester enantiomerically pure after crystallization. The absolute configuration of the two stereocenters formed was confirmed by X-ray crystallography. Careful hydrolysis of the formamido ester to avoid skeletal rearrangement yields MeBmt. In this kilogram scale synthesis, the catalyst can be recovered by precipitation with either diethyl ether or pentane, and can be recycled a number of times without any loss of activity or selectivity.

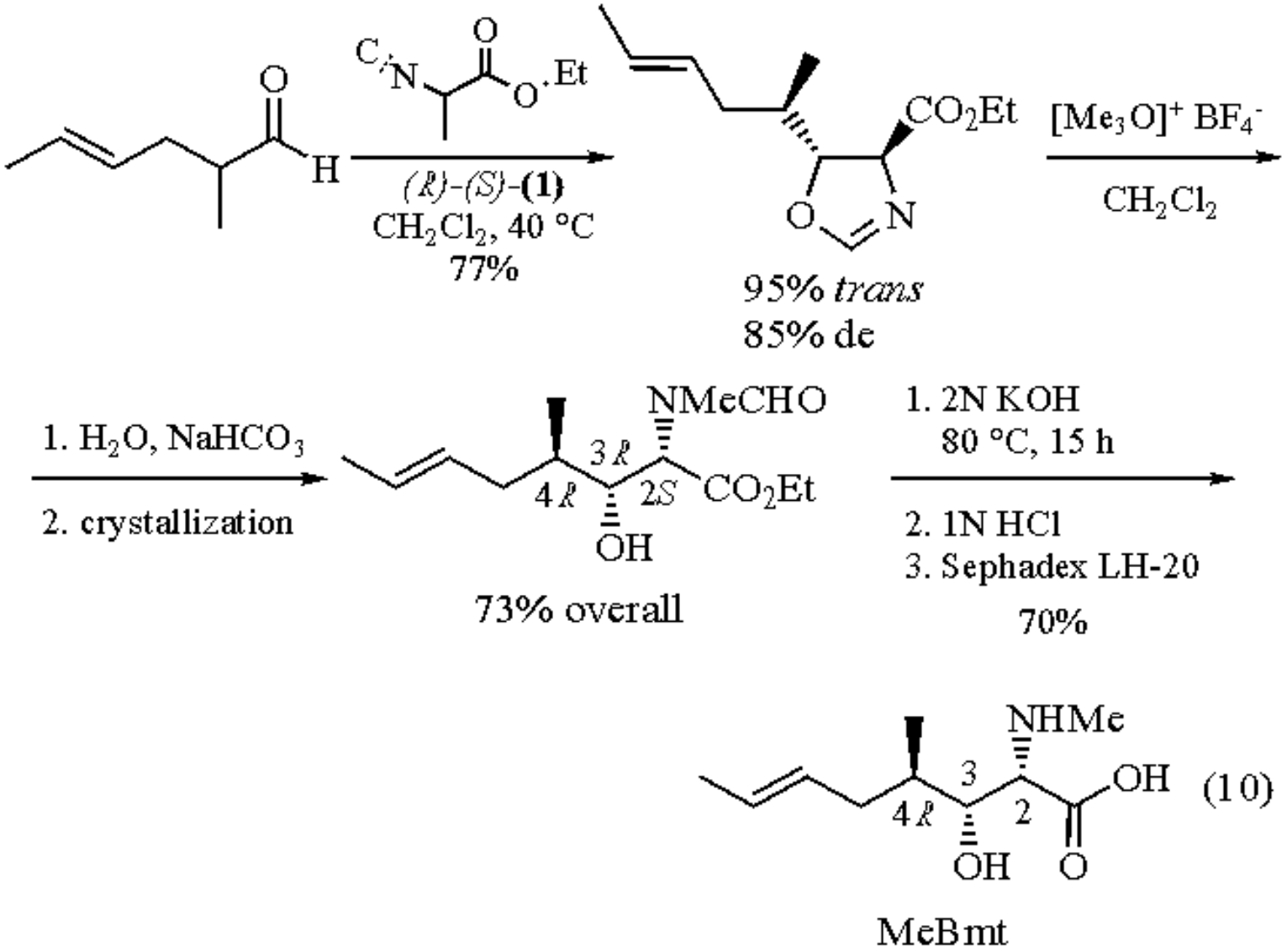

(10)

The gold(I)-catalyzed asymmetric aldol reaction with the chiral ligand (*R*)-(*S*)-(**2**) has been applied in the synthesis of D-*erythro*- and *threo*-sphingosines (eq 11).[30] The D-*erythro*-sphingosine can be prepared from the *threo* isomer by inversion of the C-3 hydroxyl group.

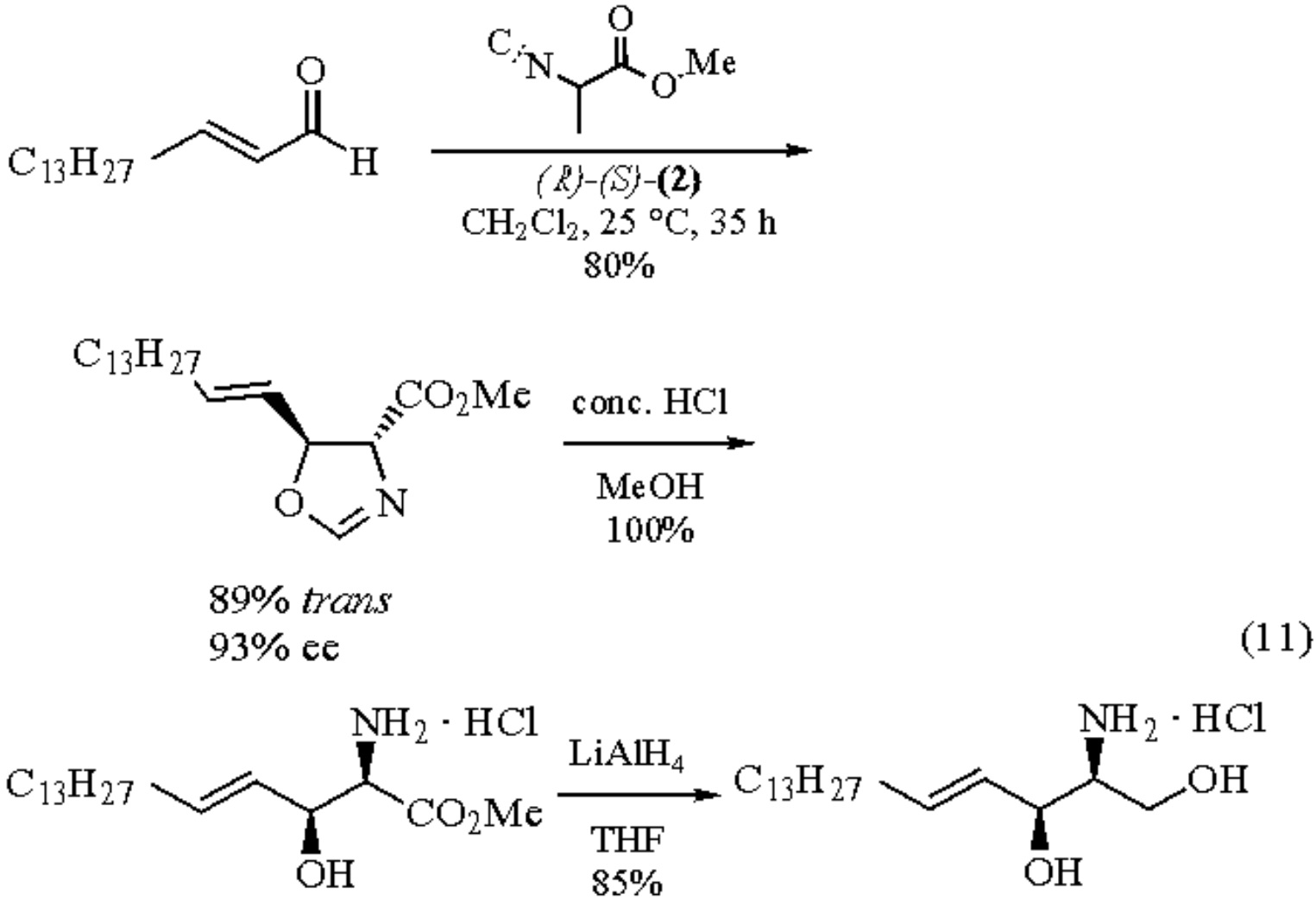

Chiral β-Hydroxy-α-Aminophosphonic Acids.

An enantioselective synthesis of substituted dihydrooxazolin-4-yl phosphonates was reported by the reaction of an aldehyde with α-isocyanomethylphosphonate ester catalyzed by (*R*)-(*S*)-(**1**) (eq 12).[31] The enantiomeric purity of the product was determined by $^{31}P\{^{1}H\}$ NMR spectroscopy using the chiral solvating reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Independently, an asymmetric synthesis of α-aminophosphonic acids was reported using the chiral ferrocenylamine catalyst (*R*)-(*S*)-(**3**) (eq 13).[32]

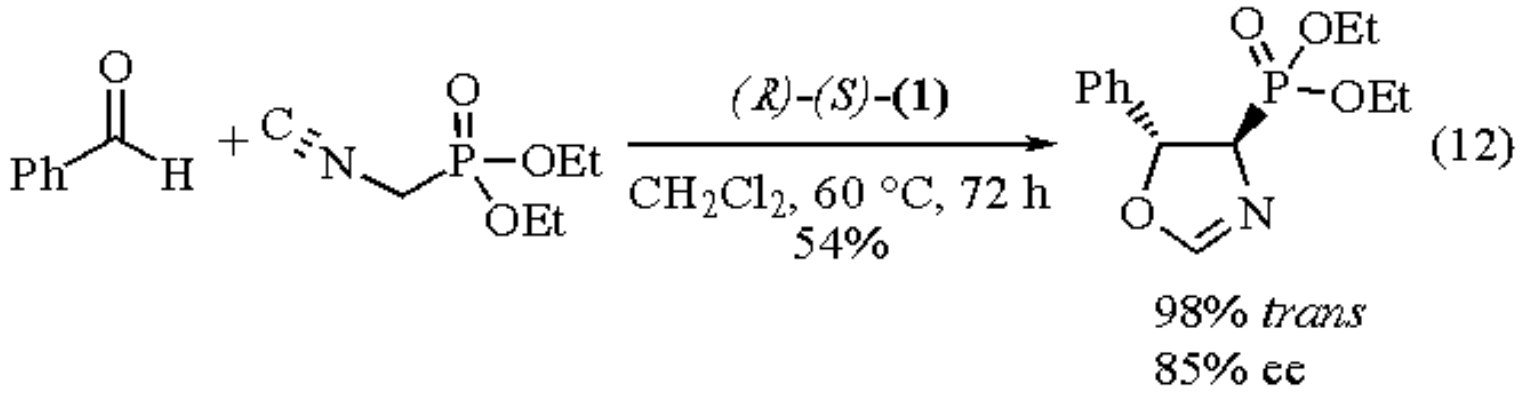

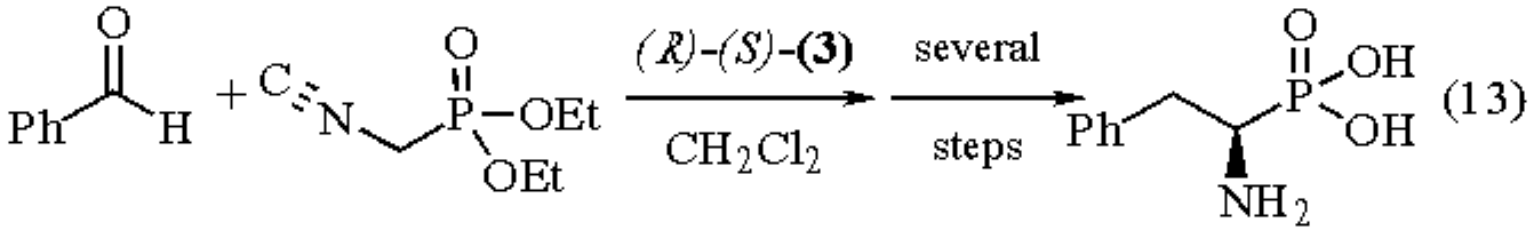

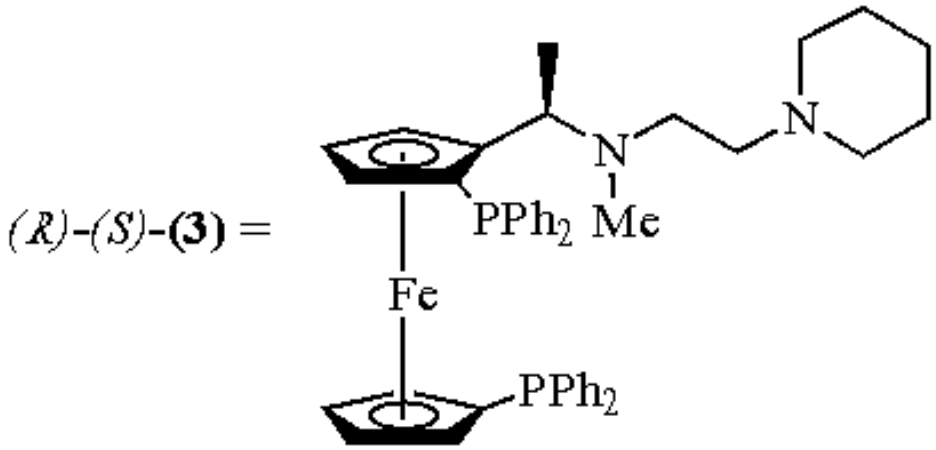

Asymmetric Allylation.

Asymmetric allylation of β-diketones using the palladium analog of (**1**) has been described.[4] Higher enantioselectivity can be achieved in this case using ferrocenylamines with a modified alkyl side chain.[4] For synthetically useful ferrocenylamine complexes of other metals, see ***(R)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(S)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine***.

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Stephen D. Pastor

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Bis(1,5-cyclooctadiene)nickel(0)[1]

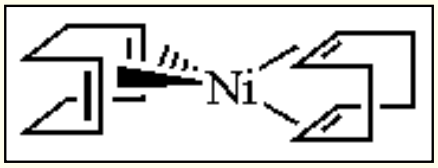

[1295-35-8] · $C_{16}H_{24}Ni$ · Bis(1,5-cyclooctadiene)nickel(0) · (MW 275.08)

($Ni(cod)_2$ is a source of nickel(0) useful for the preparation of π-allylnickel halides,[2] for coupling of aryl and alkenyl halides,[3] and for the oligomerization and cycloaddition of strained alkenes,[4] of alkynes,[5] and of 1,3-dienes[6])

Physical Data: mp 60 °C dec (N_2).

Solubility: sol benzene, toluene, THF, ether, DMF, HMPA, *N*-methylpyrrolidinone.

Form Supplied in: yellow-orange crystals of 98+% purity.

Analysis of Reagent Purity: ^{1}H NMR: δ 4.31 (br, =CH), 2.08 (br, CH_2).[1]

Preparative Methods: the standard preparation[2b] is a modification of the original procedure by Wilke and co-workers[7] and involves the reduction of ***Nickel(II) Acetylacetonate***, $Ni(acac)_2$, with ***Triethylaluminum*** in the presence of 1,5-cyclooctadiene (cod) and 1,3-butadiene in toluene. A more convenient preparation utilizes ***Diisobutylaluminum Hydride*** (DIBAL) as the reducing agent.[8] In a typical reaction, 45.4 mL of a 1.0 M THF solution of DIBAL was added to a 250 mL Schlenk flask containing 4.67 g of $Ni(acac)_2$, and 7.93 g cod in THF solution under a nitrogen atmosphere at -78 °C. The resulting dark, reddish-brown solution was warmed to 0 °C and treated with diethyl ether to give a light yellow precipitate. Filtration under nitrogen gave a 72% yield of $Ni(cod)_2$ which was suitable for immediate use. Optional recrystallization from toluene under inert atmosphere gave bright yellow-orange needles with 40% recovery.

Handling, Storage, and Precautions: highly oxygen sensitive. Special inert-atmosphere techniques must be used.[9] Should be stored at 0 °C.

π-Allylnickel Halides.

π-Allylnickel halide complexes are prepared by reaction of allylic halides with $Ni(cod)_2$ in a nonpolar solvent (eq 1).[10] The resulting dimeric species, isolated as a red solid, can be purified by crystallization, stored in the absence of air, and weighed out for reaction like any other moderately air-sensitive compound.[2b] $Ni(cod)_2$ is preferred over

Tetracarbonylnickel for this transformation due to the mildness of conditions required, the extreme toxicity and thermal instability of $Ni(CO)_4$, and the absence of byproducts caused by CO insertion.

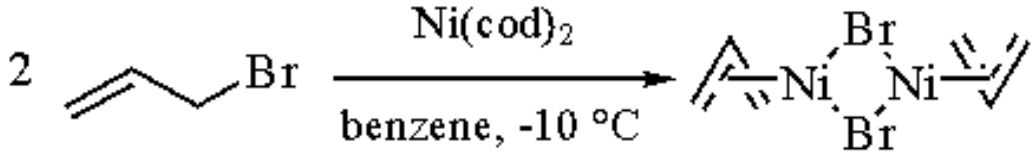

(1)

In polar, coordinating solvents such as DMF, HMPA, and *N*-methylpyrrolidinone, π-allylnickel halide complexes react with a wide range of alkyl, alkenyl, and aryl halides[11] to replace a halogen with the allyl group, as shown by the reactivity of π-(2-methallyl)nickel bromide (**1**) (eq 2).[12] These complexes also react with aldehydes and ketones to give homoallylic alcohols,[13] with quinones to produce allylquinones,[14] and with 2-pyridylcarboxylates to give β,γ-unsaturated ketones.[15] However, they do not react readily with esters, acid chlorides, amides, nitriles, or alcohols. Due to this significantly lower reactivity in these reactions, they offer a greater degree of selectivity over their allyllithium, -magnesium, and -zinc counterparts.[16] Mechanistic aspects of the coupling reaction between organic halides and π-allylnickel halides have been investigated and a radical-chain pathway has been proposed.[17]

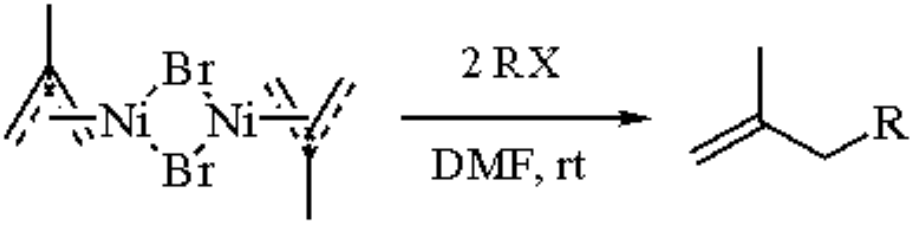

(2)

(1)

The π-allylnickel halide formation reaction (eq 1) is tolerant to substitution on the allyl halide starting material. 1,1-Dimethylallyl,[13] 2-ethoxycarbonylallyl,[13] 2-methoxyallyl,[18] and 2-trimethylsilylmethyl[19] nickel halide complexes, to name a few, have all been synthesized and utilized in subsequent coupling reactions. Alkene-containing allyl halides have been also used to form dienes.[20] Allyl iodides are more reactive than allyl bromides for the generation of π-allylnickel halides and allyl chlorides are unreactive. Allyl mesylates and trifluoroacetates do not work as well as bromides due to extensive homocoupling of the substrates.[19] α,β-Unsaturated aldehydes and ketones react with $Ni(cod)_2$ in the presence of a trialkylsilyl chloride to give [1-[(trialkylsilyl)oxy]allyl]nickel chloride dimers (**2**) (eq 3).[21] These complexes couple to alkyl halides at the γ-position upon irradiation under a sun lamp to give silyl enol ethers (**3**), making the overall transformation a useful reversed-polarity complement to organocuprate conjugate addition chemistry. Chiral allyl acetals (**4**) have also been utilized to form chiral (*E*)-enol ethers (**5**) which serve as homoenolate equivalents of a new type (eq 4).[22]

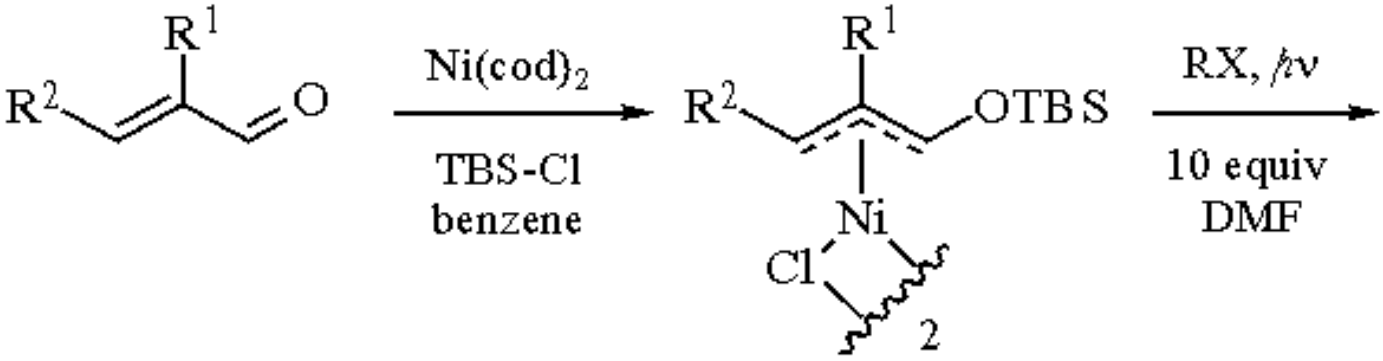

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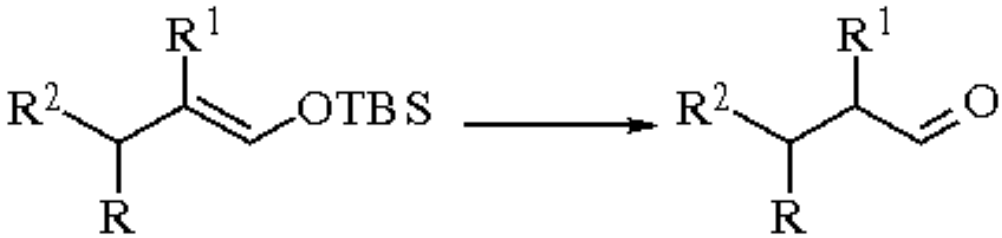

(3)

(3)
60-80% overall

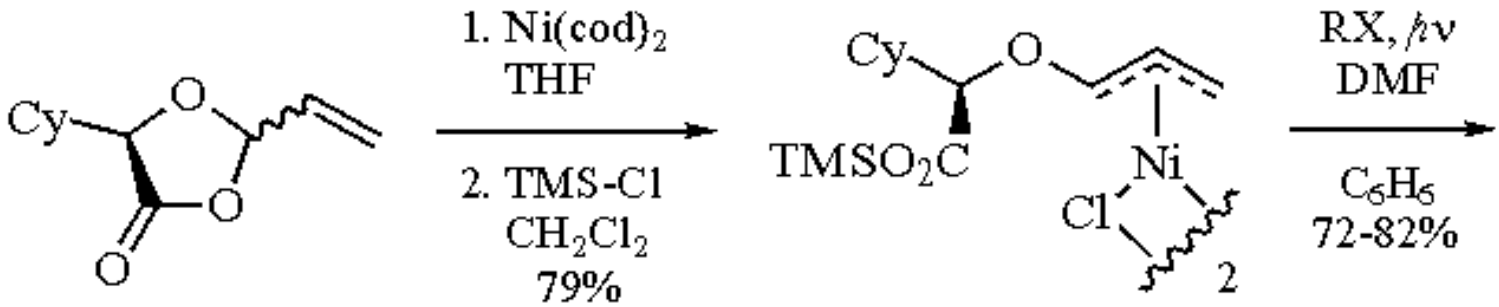

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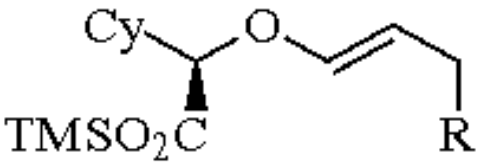

(4)

(5)

Complexes having π-allylnickel halide-like reactivity may also be used as transient intermediates in polar media without the need for isolation. This type of reactivity is especially important for the intramolecular coupling of allyl groups (see ***Tetracarbonylnickel***). In these cases, allylic tosylates and carboxylates may also be used for the initial oxidative addition of the allyl substrate to nickel.[23] In one interesting group of reactions (eq 5),[24] a π-allyl intermediate undergoes an intramolecular alkene insertion to form a ring followed by β-hydride elimination to give diene (**6**). If carbon monoxide and methanol are included in the reaction mixture, CO insertion, followed by intramolecular insertion of the newly-formed double bond, followed by a final methoxycarbonylation gives rise to keto ester (**7**). The palladium

catalyst ***Bis(dibenzylideneacetone)palladium(0)*** also catalyzes these reactions, but with poor diastereoselectivity. An allylic sulfonium ion (**8**) has shown a similar reactivity and has been utilized in the total synthesis of confertin.[25] Intramolecular coupling with an aldehyde followed by spontaneous lactonization yielded the tricyclic α-methylene-γ-lactone (**9**) (eq 6). Insertion of terminal alkynes into π-allylnickel complexes derived from allylic esters (**10**) has led to a catalytic synthesis of nonconjugated alkenynes (**11**) (eq 7).[26]

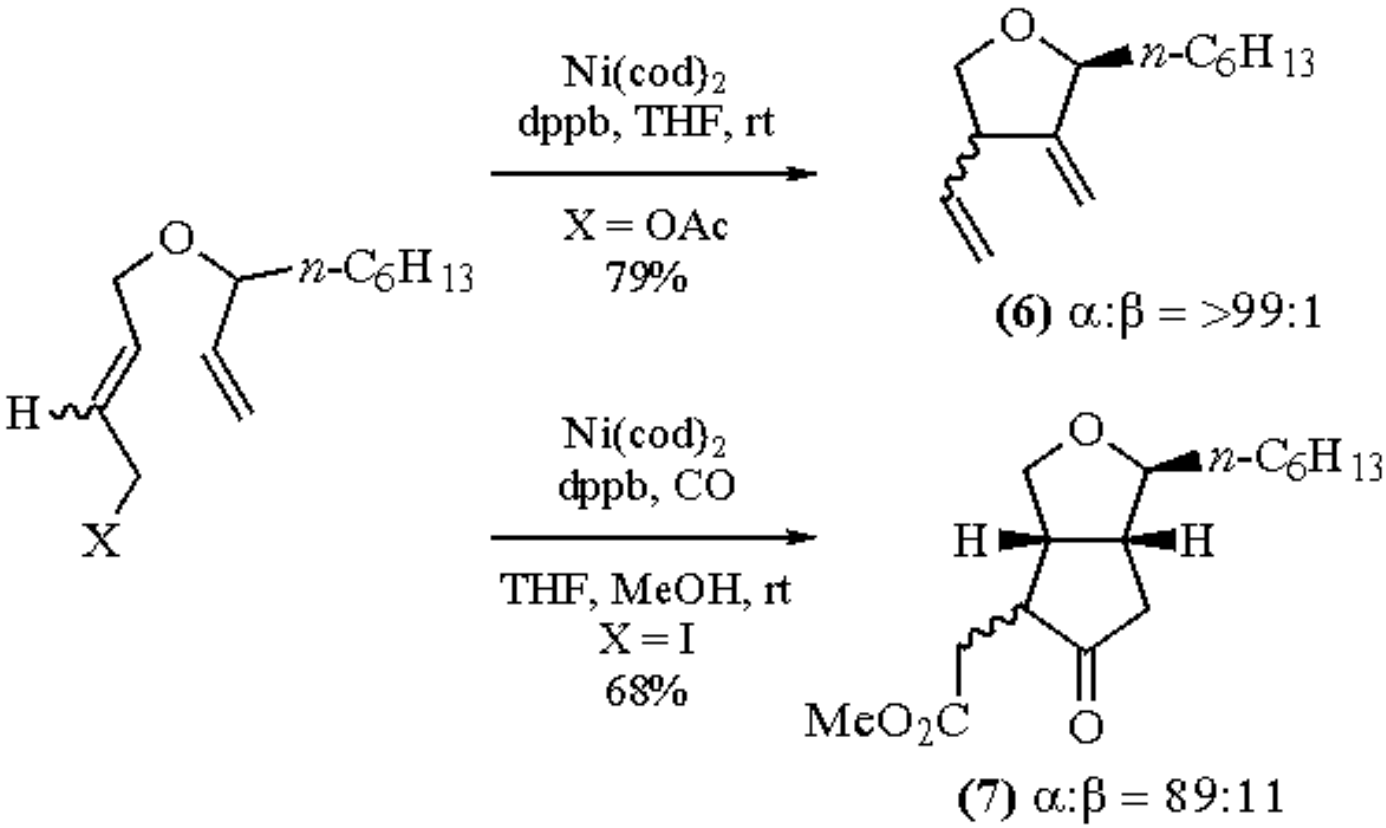

(5)

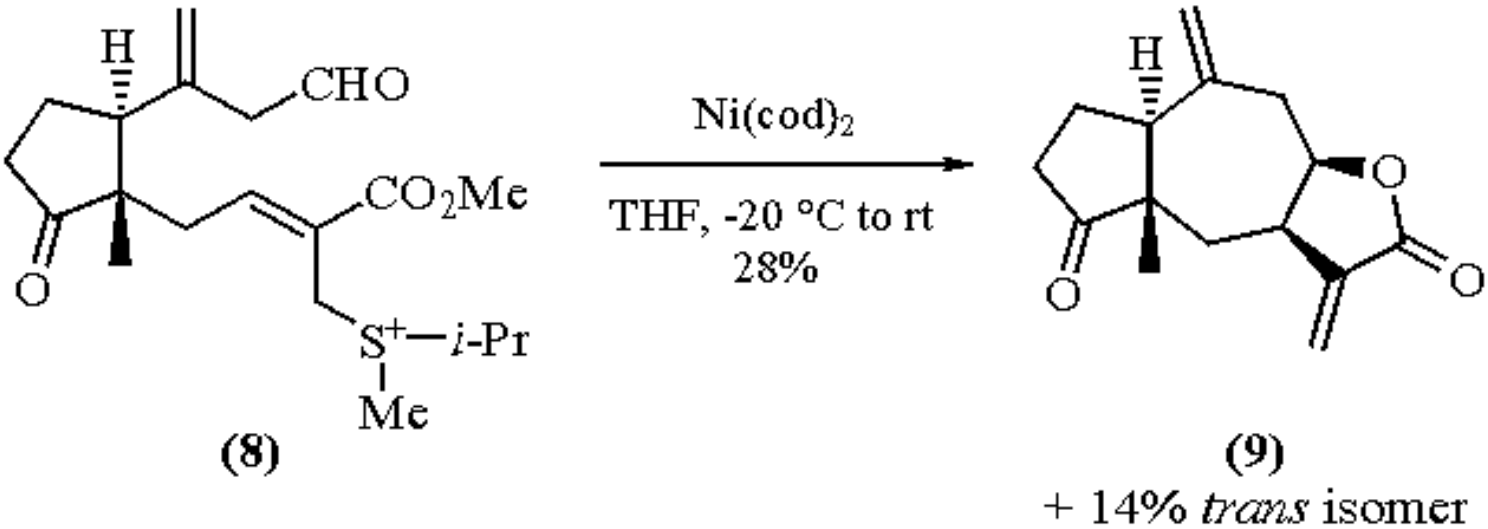

(6)

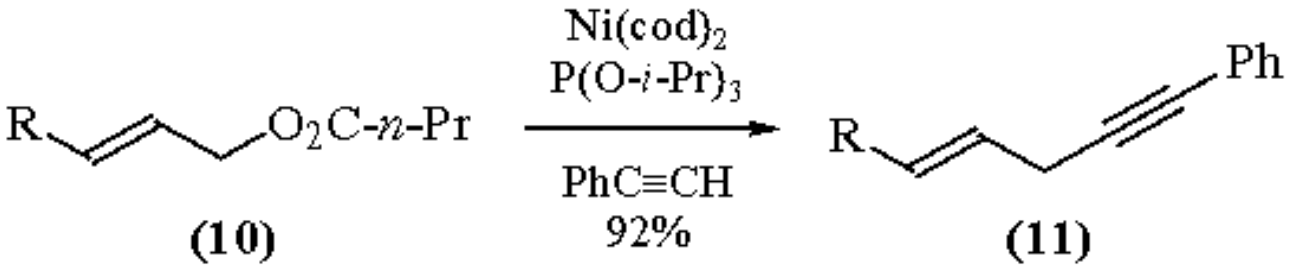

(7)

Coupling of Aryl Halides.

$Ni(cod)_2$ reacts with a variety of aryl halides in DMF to give diaryl compounds in generally high yields (80-90%) (eq 8).[27]

$$2\ ArX + Ni(cod)_2 \xrightarrow[25\text{-}40\ ^\circ C]{DMF} Ar_2 + NiX_2 + cod \qquad (8)$$

Ortho substituents on the aryl halide drastically reduce the rate of the reaction and an increase in temperature leads only to decomposition of the nickel catalyst. The reaction is tolerant of most functional groups with both electron-donating and electron-withdrawing substituents allowing efficient coupling. Nitro groups, however, destroy the catalytic activity of the nickel complexes.[28] Acidic functionalities such as alcohols, phenols, or carboxylic acids cause reduction of the aryl halide in preference to coupling. The order of reactivity of substrates is I > Br > Cl with phenol *p*-toluenesulfonate esters being completely unreactive. This reaction may be contrasted with the copper-catalyzed Ullmann reaction,[29] which typically requires high temperatures (&egt;200 °C), or a two-step coupling procedure requiring intermediate arylmagnesium or -lithium reagents which are incompatible with many functional groups.

Attempted cross-coupling usually leads to mixtures of products due to extensive symmetrical coupling. Nevertheless, this strategy was utilized in the synthesis of a 2-benzazepine.[30] Intramolecular coupling reactions,[3,31] on the other hand, are generally quite efficient (eq 9)[32] and often benefit from added phosphine ligand (see also ***Tetrakis(triphenylphosphine)nickel(0)***).

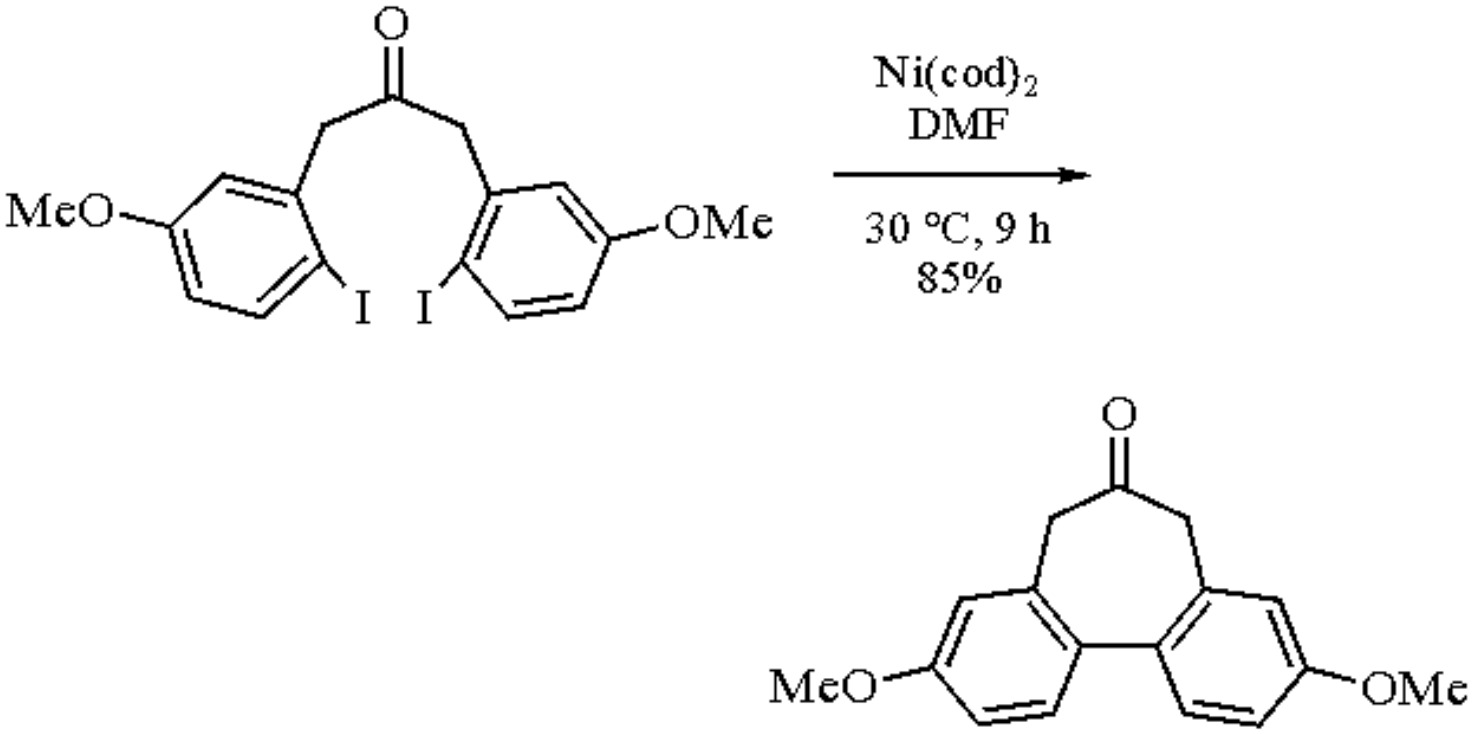

(9)

Coupling of Alkenyl Halides.

$Ni(cod)_2$ reacts with alkenyl halides to produce symmetrical 1,3-dienes.[33] These reactions may be carried out in DMF, or in ether with an added ligand such as Ph_3P. Coupling of simple alkenyl halides gives only moderate yields (48-70%) with mixtures of geometrical isomers. Reactions of alkenyl halides bearing electron-withdrawing substituents such as α- and β-haloacrylates, however, are more efficient and highly stereoselective (eq 10).[3] The intramolecular coupling of a simple diiodide has also been shown to be effective (eq 11).[3] Finally, there is one example of the intramolecular coupling of alkyl halides in which α,o-dihaloalkanes are cyclocoupled to give cycloalkanes by a $Ni(cod)_2$-bipyridyl complex.[34]

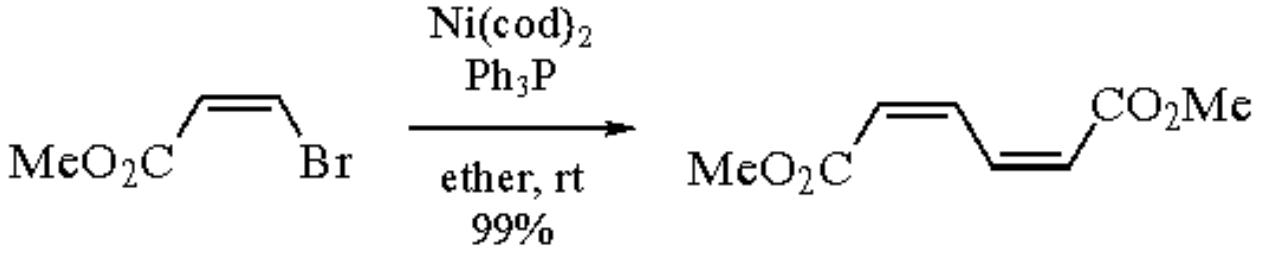

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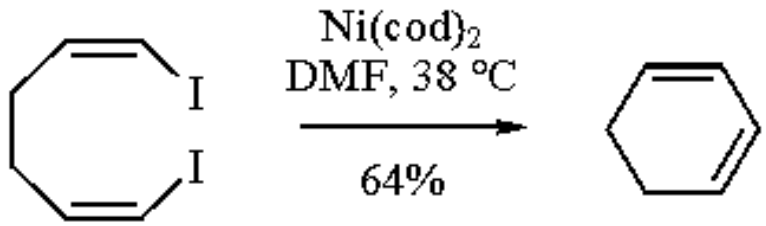

(11)

Oligomerization of Strained Alkenes and Alkanes.

3,3-Disubstituted cyclopropenes are known to react with electron-deficient alkenes in the presence of catalytic $Ni(cod)_2$ to give vinylcyclopropanes (eq 12).[35] The mechanism of the reaction begins with oxidative addition of Ni^0 into the C-1-C-3 bond, but there is some dispute as to whether a carbenoid intermediate is involved.[4] Methyl, phenyl, and methoxy groups have all been used as geminal substituents on the cyclopropene; however, the stereochemistry of the starting alkene is not preserved when methoxy is used.[36] Alkyl group substitution on the electron-deficient alkene disfavors this reaction pathway and leads to [2 + 2] cyclodimerization of the cyclopropene.[37] Addition of ligands has also been shown to affect the distribution of products. When the catalyst is modified by the bulky $P(i\text{-Pr})_2(t\text{-Bu})$, a [2 + 2 + 2] cycloaddition is observed (eq 13).[38]

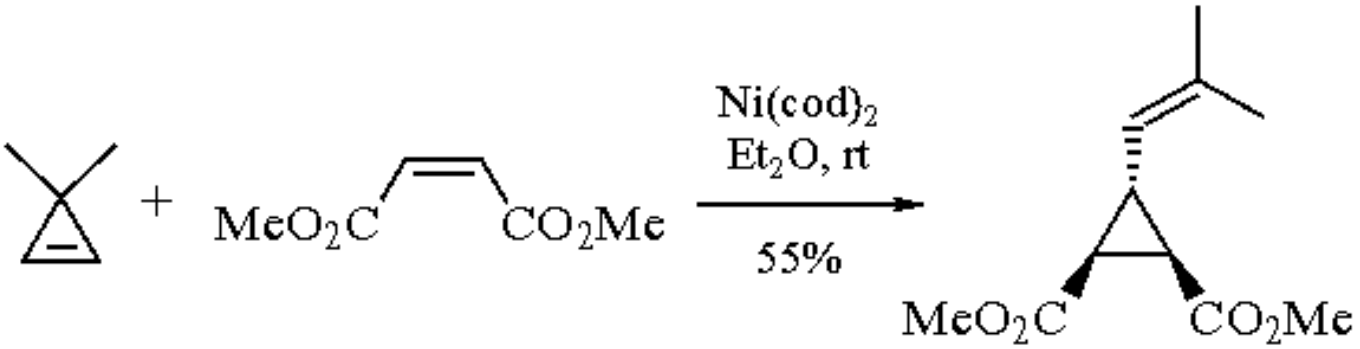

(12)

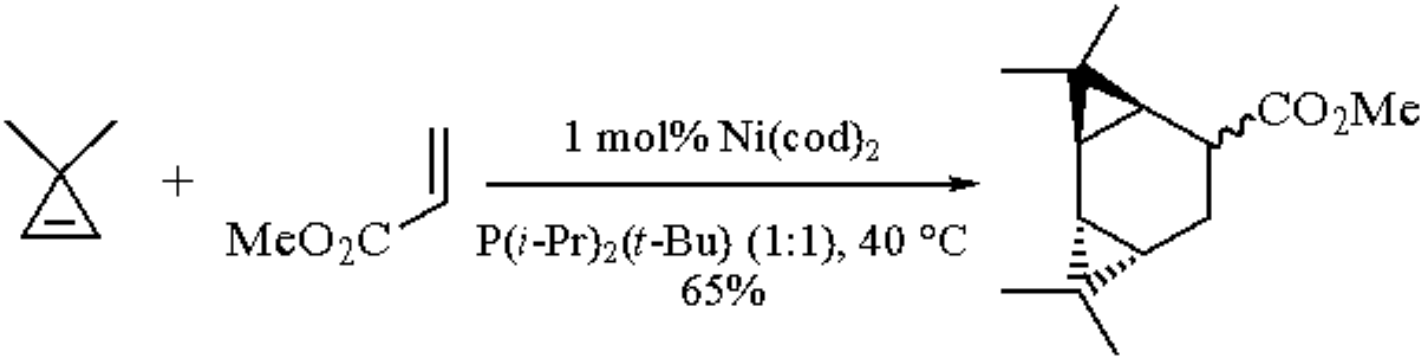

(13)

Cyclobutenones react with alkynes in the presence of $Ni(cod)_2$ to give substituted phenols. Many substituents are tolerated, but regioselectivity is poor (eq 14). The reaction proceeds by oxidative addition of nickel at the C-1-C-4 bond followed by insertion of the alkyne.[39] Cyclopropenones react to form benzoquinones.[40] This mechanism may involve a nickel-catalyzed [2 + 2] cyclodimerization followed by a thermal isomerization or an alkene methathesis.

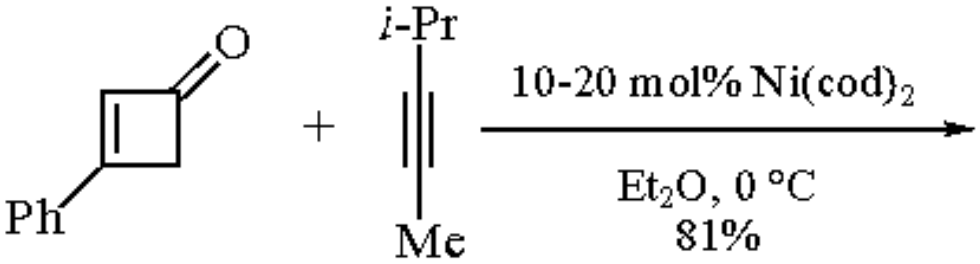

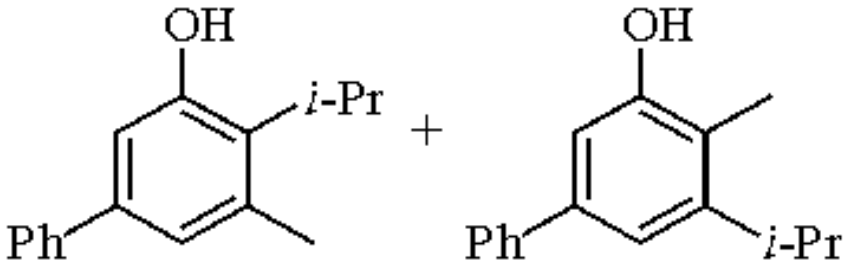

(14)

1:1

Norbornene derivatives[41] and cyclobutenes[42] have also been shown to react with alkenes under the influence of $Ni(cod)_2$ catalyst to give [2 + 2] cycloadducts. Norbornadiene substrates can react with electron-deficient alkenes in a [2 + 2 + 2] cycloaddition pathway to give homo-Diels-Alder products (eq 15) (see also ***Bis(acrylonitrile)nickel(0)***).[43] Norbornadiene also forms [2 + 2] cycloadducts with the exceptionally reactive methylene cyclopropane.[44] When this reaction was carried out in the presence of a chiral phosphine ligand, the product was obtained in an enantiomerically enriched form.

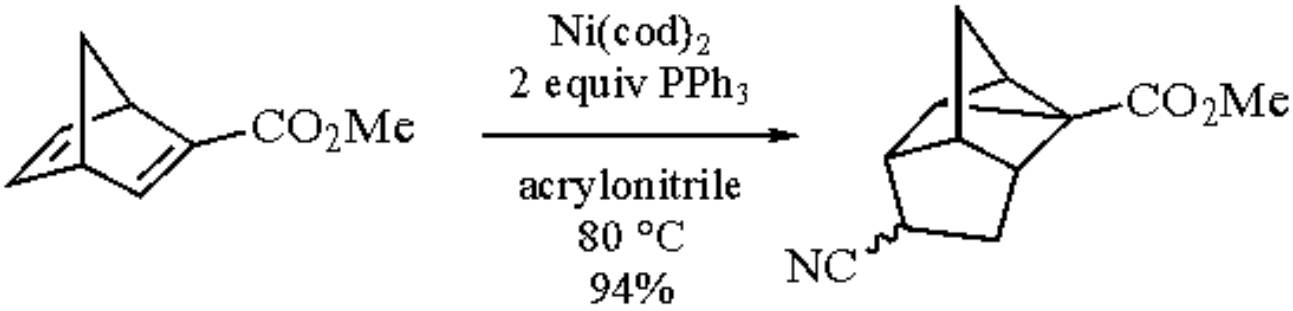

(15)

exo:*endo* = 1:2.3

In addition to the ability to undergo [2 + 2] cycloadditions, methylenecyclopropanes have two additional and more useful [3 + 2] modes of reactivity available under nickel catalysis. As shown for the cycloaddition of methylenecyclopropane with an alkene (eq 16), distal ring opening by nickel leads to products of Type A, whereas Type B products are not a direct result of proximal ring opening, but are formed indirectly via reductive dimerization of two alkene units to give a metallacyclopentane followed by a cyclopropylmethyl/3-butenyl rearrangement. The course of the reaction is determined by many factors including the stoichiometry and physical properties of the ligands bonded to nickel, the number, type, and position of substituents on the methylenecyclopropane, and the nature of the substituents on the participating alkene. Because of these many contributing effects, it is difficult to predict which reaction pathway will be followed under any given condition; however, some general reactivity patterns can be deduced.[4]

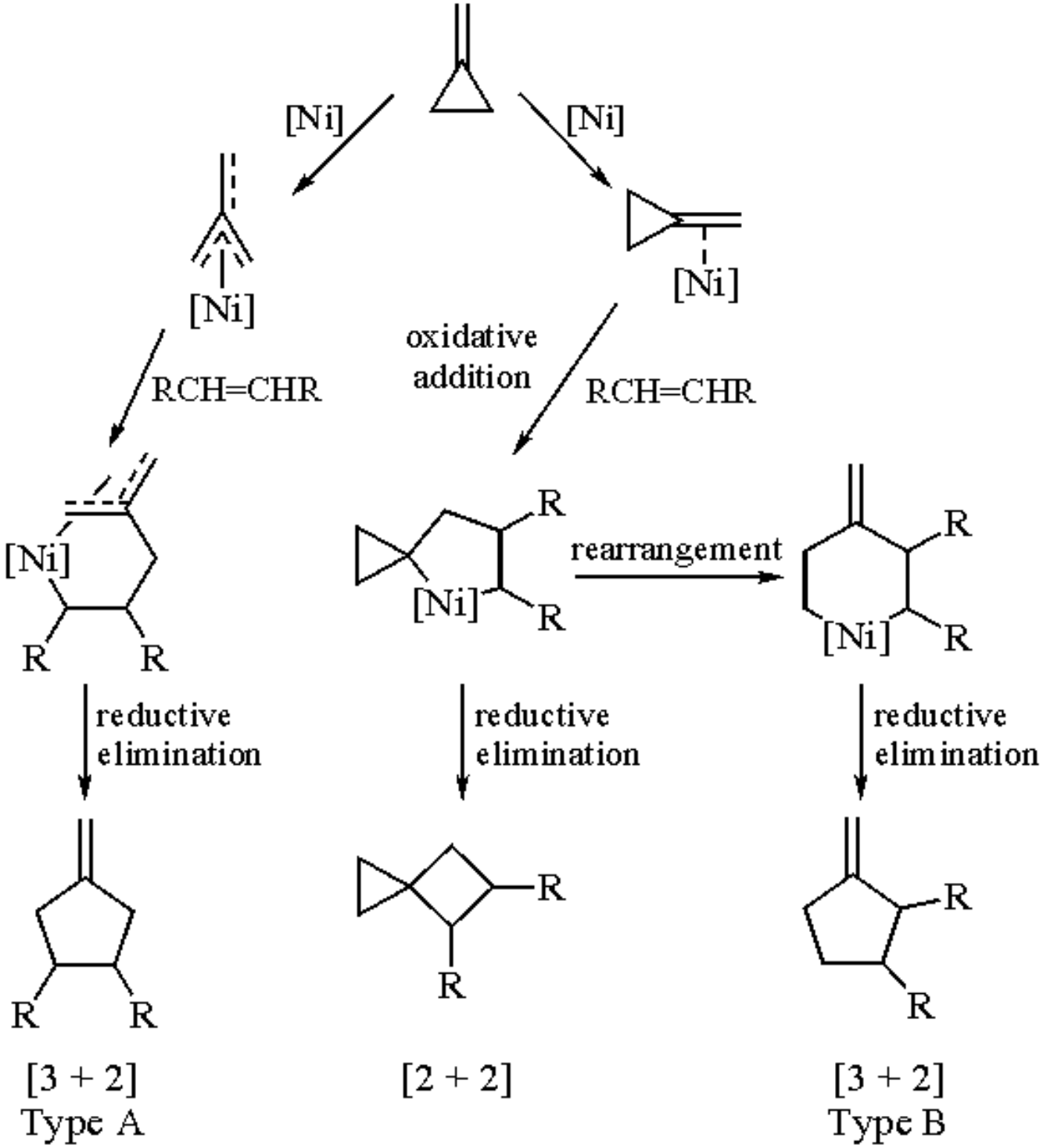

(16)

While the dimerization and trimerization of methylenecyclopropanes have been investigated,[45] these reactions are not useful from a synthetic standpoint. For this reason the present treatment will consider only the cycloadditions between methylenecyclopropanes and alkenes. The use of low valent nickel complexes, which have the ability to catalyze reactions of both Type A and Type B should be contrasted with the use of palladium(0) catalysts such as ***Bis(dibenzylideneacetone)palladium(0)***[46] or $Pd(\eta^3\text{-}C_3H_5)(\eta^5\text{-}C_5H_5)$[47] which lead exclusively to products of Type A.[4b]

Unsubstituted methylene cyclopropane can form 1:1 adducts with acrylates, crotonates, and maleates to give Type B cycloaddition products in high yields (eq 17)[48] (see also ***Bis(acrylonitrile)nickel(0)***). The use of enantiomerically pure alkyl acrylates in this type of reaction gave products with up to 64% de.[49] Addition of ligands requires higher reaction

temperatures and results in decreased stereoselectivity.[50] Ligand addition also leads to Type A cycloadducts when highly electron-deficient alkenes such as dialkyl fumarates and maleates are used. It is clear that the outcome of these reactions is highly dependent upon the electronic properties of catalyst and substrate.

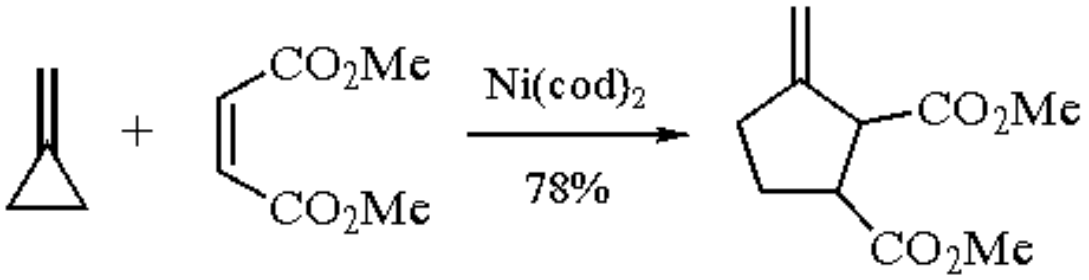

(17)

cis:*trans* = 9:1

Substitution at the three-membered ring generally gives rise to cycloadducts of Type B.[4b] When (-)-camphorsulfamylacrylate was reacted with 2,2-dimethylmethylenecyclopropane, a methylenecyclopentane was obtained with a diastereomeric excess of 98% (eq 18).[51] When the substituents are phenyl groups, however, Type A cycloaddition results.[4]

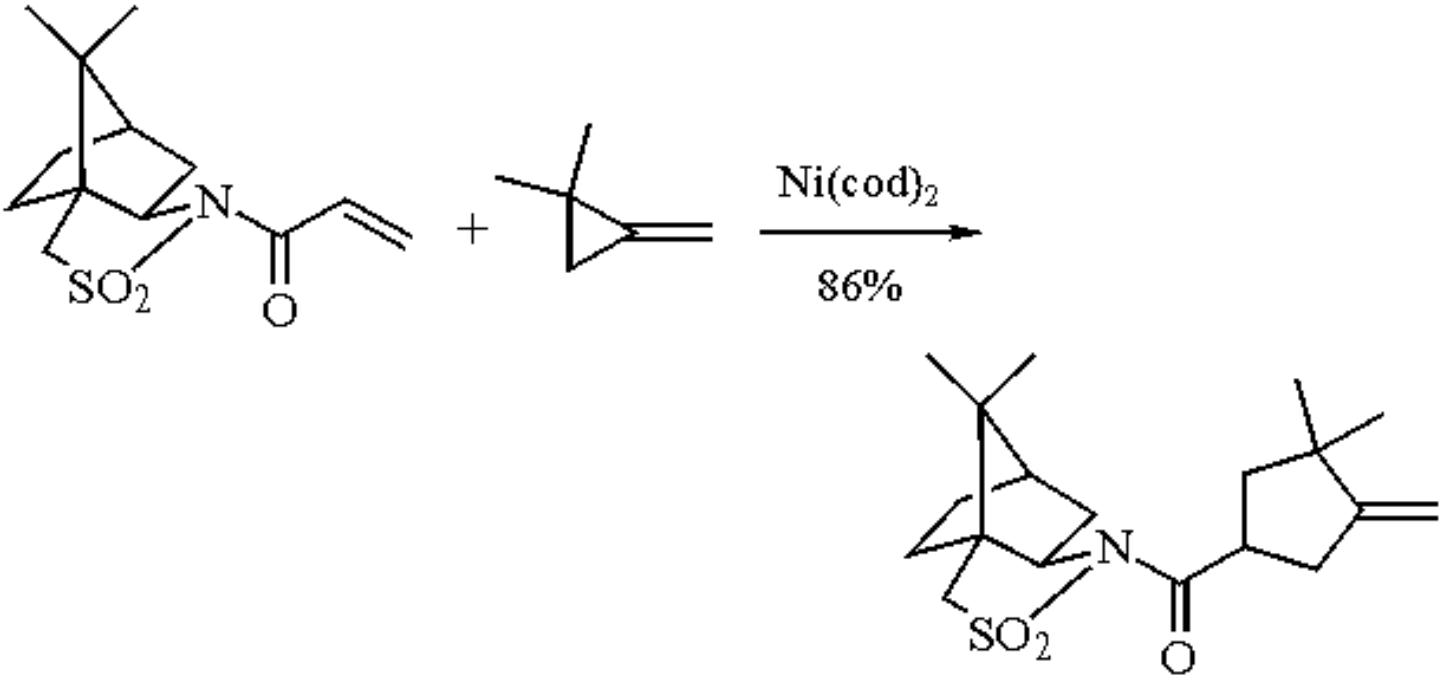

(18)

98% de

Substitution at the double bond almost always leads to cycloaddition of Type A. In these reactions there is an added complication of regioselectivity brought about by the intermediacy of a trimethylenemethane-like species. Thus ethyl crotonate reacts with isopropylidenecyclopropane to give a mixture of the alkylidenecyclopentane (**12**) and the 2-substituted methylenecyclopentane (**13**) (eq 19).[52] The use of bulky phosphite ligands and a high ligand:metal ratio favors the formation of 2-substituted methylenecyclopentanes. Alkenes without electron-withdrawing groups favor the formation of alkylidenecyclopentanes.[4,53] The use of triisopropylphosphine/palladium(0) catalysts also leads to this type of product.[4,54] Disubstituted alkynes can also be used in the cycloaddition to produce alkylidenecyclopentenes.[55] When ***Triethylborane*** was added along with the catalyst, systems that normally reacted along a Type A pathway were

induced to react via Type B.[56] An interesting transannular cycloaddition was utilized to prepare a [3.3.3]propellane, although a palladium catalyst was found to be more suitable than nickel (eq 20).[57] Allene can also be oligomerized by $Ni(cod)_2$.[5a,58]

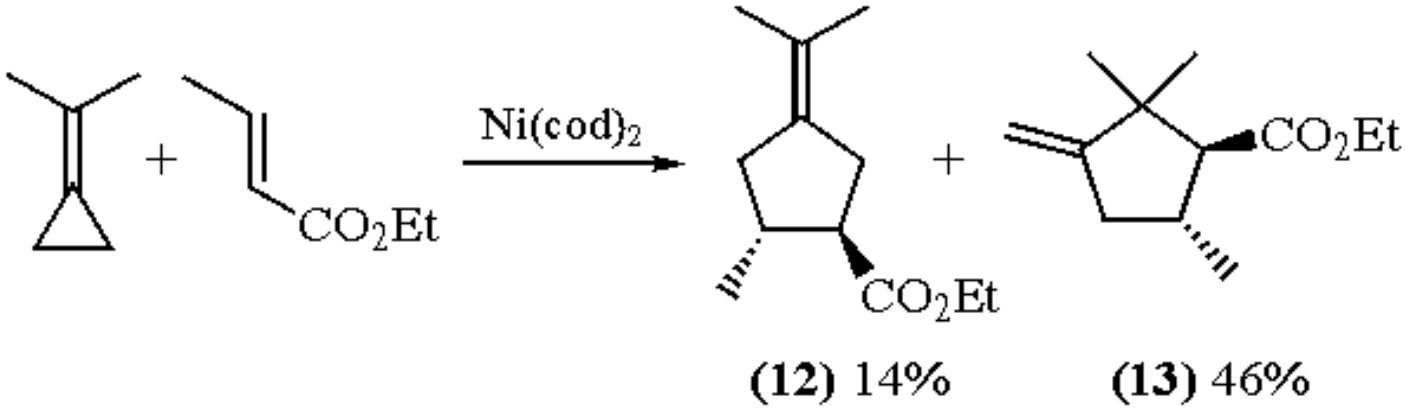

(19)

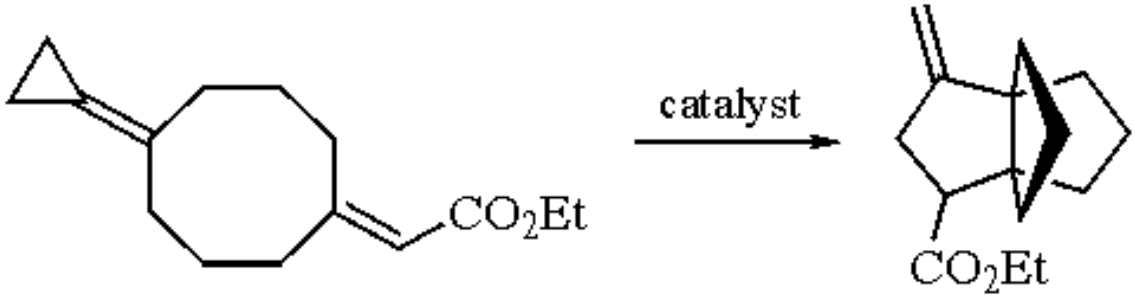

(20)

20 mol% $Ni(cod)_2/PPh_3$, 110 °C 74%
10 mol% $PdCl_2(PPh_3)_2$/DIBAL, 130 °C 98%

Finally, some strained alkanes are known to undergo oligomerization in the presence of Ni^0 catalysts (see also ***Bis(acrylonitrile)nickel(0)***). Bicyclo[1.1.0]butanes react by suffering a geminal two-bond cleavage to form an allylcarbene intermediate which may be trapped stereoselectively by an electron-deficient alkene (eq 21).[59] Additionally, a nickel-catalyzed asymmetric vinylcyclopropane-cyclopentene rearrangement has been reported using $Ni(cod)_2$ with chiral phosphine ligands.[60]

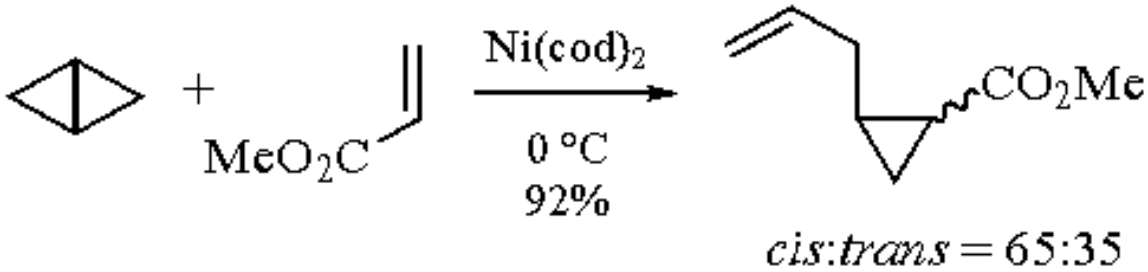

(21)

Oligomerization of Alkynes.

The nickel catalyzed intermolecular oligomerizations of alkynes are some of the oldest and best-studied reactions in

organometallic chemistry.[1,5a] Tetramerization and trimerization lead to cyclooctatetraenes and aromatic molecules, respectively. The cycloaddition of two equivalents of alkyne with one equivalent of alkene provides an interesting route to cyclohexadienes.[61] Addition of isocyanides leads to iminocyclopentadienes,[62] insertion of CO_2 gives pyrones,[63] and insertion of isocyanates yields 2-oxo-1,2-dihydropyridines.[64] Finally, hydroacylation of monoalkynes with aldehydes yields α,β-enones.[65]

The synthetic utility of these reactions is greatly increased when they are used intramolecularly with tethered alkynes since more than one ring can be formed and regiochemical problems are drastically reduced.[5b] Tethered diynes react with $Ni(cod)_2$ and CO_2 in the presence of trialkylphosphine ligands to give bicyclic α-pyrones (eq 22).[66] The reaction is catalytic in nickel and works well with three- and four-atom tethers, but the yield suffers when the tether length is raised to five. Tricyclohexylphosphine was found to be the best choice of ligand. When other ligands were used, dimerization of the starting material was observed. It is believed that an electron-donating ligand may be required for strong CO_2 coordination. The reaction is tolerant of many groups on the alkyne terminus including alkyl, hydrogen, and trimethylsilyl. The choice of these groups helps determine the regiochemistry of the CO_2 addition.[67] The use of aldehydes in the reaction allows for the catalytic generation of bicyclic α-pyrans (eq 23).[68] In these cases the structure of the added phosphine ligand does not play a crucial role; however, the length of the tether and the choice of alkyne substituents exert a great influence on the outcome of the reaction. Other products from this reaction such as oxoalkyl-substituted cyclopentenes are explained by various hydrogen transfer isomerizations of a strained 1,2-bis(alkylidene)cycloalkane intermediate.

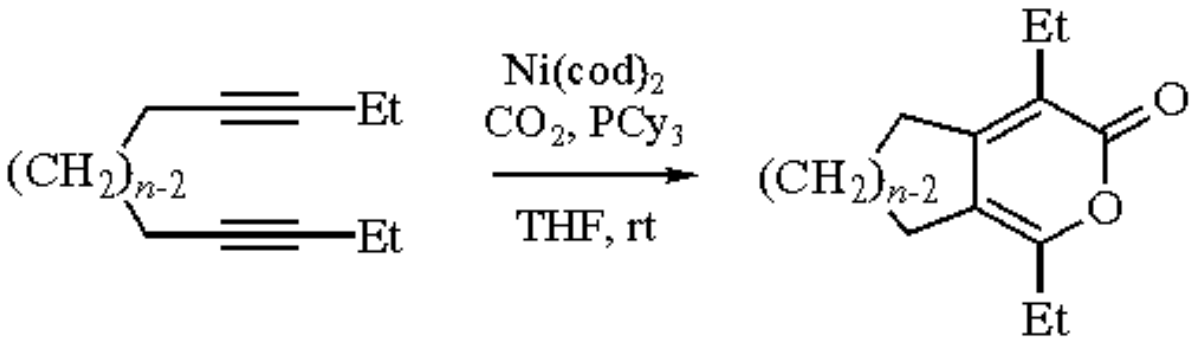

(22)

$n = 3$	88%
$n = 4$	90%
$n = 5$	19%

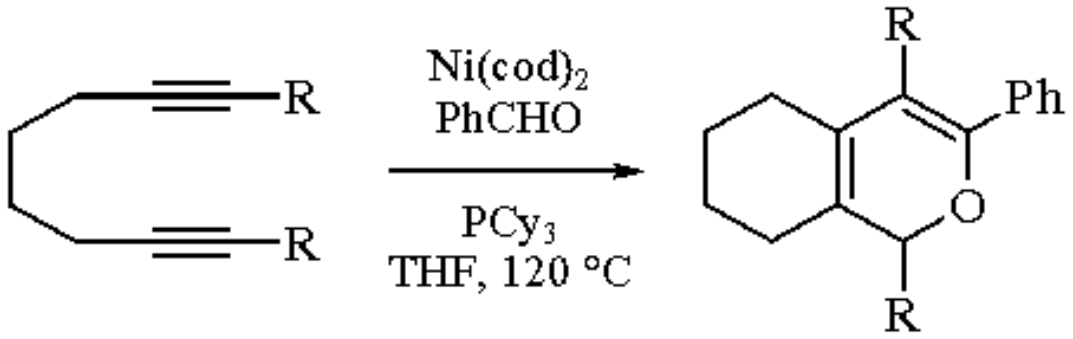

(23)

R = Me	39%
R = Et	79%
R = *n*-Bu	78%

Diynes undergo cyclization with 2,6-dimethylphenyl isocyanide in the presence of a stoichiometric amount of $Ni(cod)_2$ to yield polycyclic iminocyclopentadienes.[69] In contrast to the previous cycloadditions, this reaction does not require a phosphine ligand, and seven-membered rings can be formed in moderate yields (47%). The products of these reactions could be hydrolyzed to the corresponding cyclopentadienones by ***10-Camphorsulfonic Acid***, used as diene moieties in Diels-Alder reactions, or stereoselectively substituted at the angular position by a 1,4-addition of an alkyllithium reagent.[5b] Enynes may also take part in this reaction to produce iminocyclopentenes with significant diastereoselectivity (eq 24).[70] No reaction occurs when carbon monoxide is used as the cyclization partner; however, there are titanium, zirconium, and cobalt catalysts that are able to carry out such a transformation directly.[71]

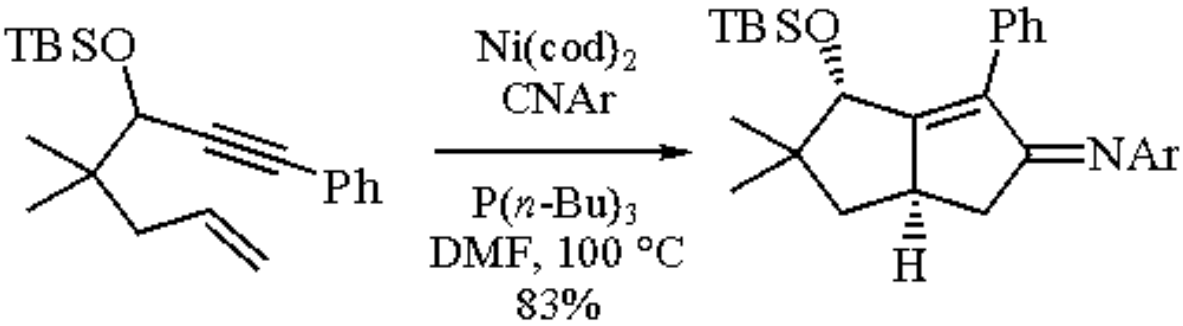

(24)

Oligomerization of 1,3-Dienes.

Extensive studies of the catalytic cyclooligomerization of butadiene have shown that many different products can be obtained from the reaction, depending upon the conditions chosen.[6] These products result from the variety of σ- and π-allylnickel intermediates that can be formed during the catalytic cycle (eq 25).[72] Low-temperature NMR studies of the reaction of butadiene with stoichiometric amounts of $Ni(cod)_2$ have shown that the η^1,η^3-octadienyl complex (**14**) is formed after reductive coupling of the two diene units.[73] This intermediate, which is probably important in the catalytic reaction as well, can isomerize to the bis-π-allyl complex (**15**). Reductive elimination to regenerate a nickel(0) species from these and other allylnickel(II) complexes can lead to 4-vinylcyclohexanes (VCH), 1,2-divinylcyclobutanes (DVCB), or 1,5-cyclooctadienes (cod). Insertion of alkenes or dienes into these intermediates leads to larger ring systems.[6a] These intermediates can also be induced to react with carbonyl compounds, but they are much less nucleophilic than π-allylhalide-like complexes.[74]

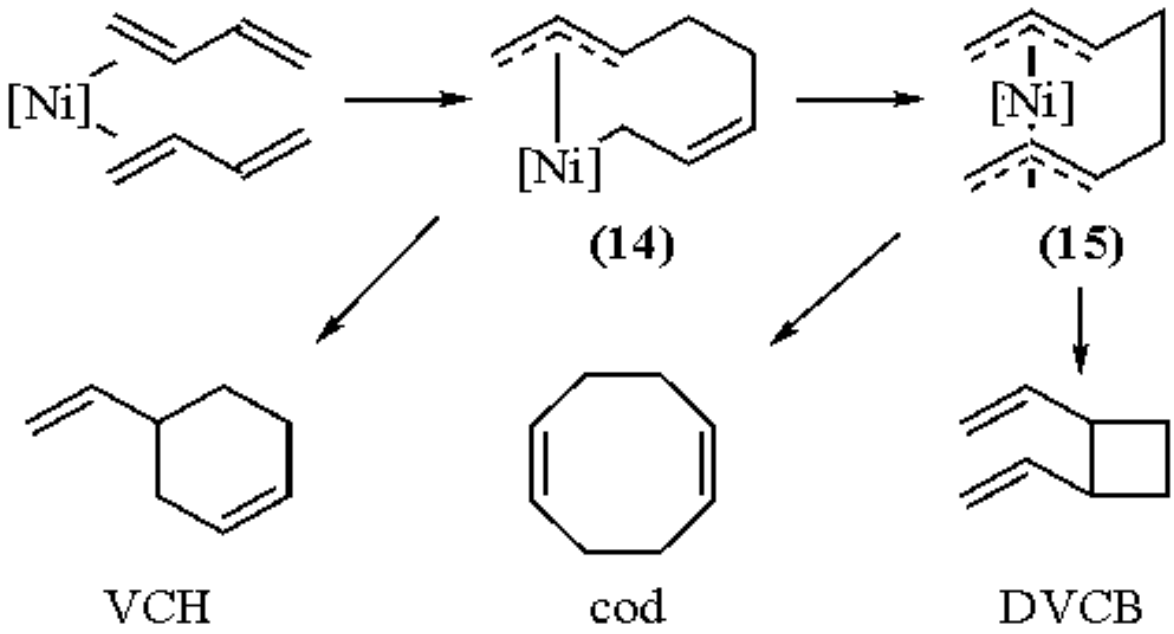

(25)

Due to the lack of general methods for the production of medium-sized rings, the synthetic value of these reactions lies especially in their ability to generate cyclooctane ring systems. Control of the cyclodimerization of 1,3-dienes to give cyclooctadiene products preferentially is contingent upon the substitution of the diene as well as the composition of the catalyst system, with both of these factors being mutually dependent. The choice of modifying ligand is extremely important in the selectivity of the reaction, with both electronic and steric parameters being important.[75] It has also been shown for some functionalized dienes that the method of generation of the Ni^0 catalyst is important to this selectivity. Catalysts generated from the reduction of nickel(II) salts such as $Ni(acac)_2$ with alkylaluminum derivatives favor formation of VCH derivatives, while aluminum-free reagents such as $Ni(cod)_2$ give preference to the cod products.[76] Several iron and cobalt catalysts have been reported to selectively catalyze cod production, while titanium, iron, and manganese catalysts have led to VCH products. Palladium catalysts, on the other hand, give DVCB products.[5a]

When [4 + 4] cycloadditions occur, simple alkyl substituents on the diene usually give 1,5-disubstituted cod products as a result of initial head-to-tail linking, but mixtures of products are inevitable.[1] Functional groups that can coordinate to nickel act as internal ligands to guide the reaction. Thus methyl 2,4-pentadienoate cyclodimerizes regio- and stereoselectively to give a *trans*-1,2-disubstituted cyclooctadiene (eq 26).[77] While ester and silyl ether substituents worked well in this reaction, amino and amido groups were not tolerated.

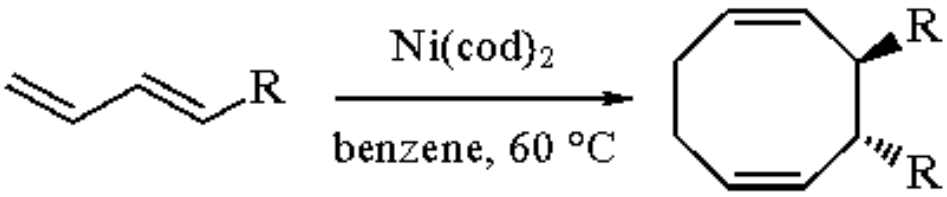

(26)

$R = OSiMe_3$, 90%
$R = CO_2Me$, 83%

The synthetic utility of these reactions is significantly enhanced when the cycloadditions are carried out intramolecularly. When the diene units are connected by a tether, the production of byproducts can be essentially

eliminated.[78] Terminally linked dienes undergo Type I [4 + 4] cycloadditions, giving rise to *cis*-fused bicycles when the tether length is three atoms, and *trans*-fused systems when the tether length is increased to four atoms. Diastereoselectivity is observed in these cycloadditions when substitution is made at an allylic position, and the degree of selectivity is related to the size of the substituent (eq 27).[79] A nickel catalyzed intramolecular [4 + 4] cycloaddition was used as the key step in the synthesis of (+)-asteriscanolide (eq 28).[80] Furthermore, when one of the diene fragments is connected at an internal position, bridged ring-systems can be assembled (eq 29).[81] This Type II class of cycloaddition was used in an approach to the taxane skeleton.[82] When trisubstituted dienes are used as substrates for the reaction, angularly substituted bicycles can be obtained.

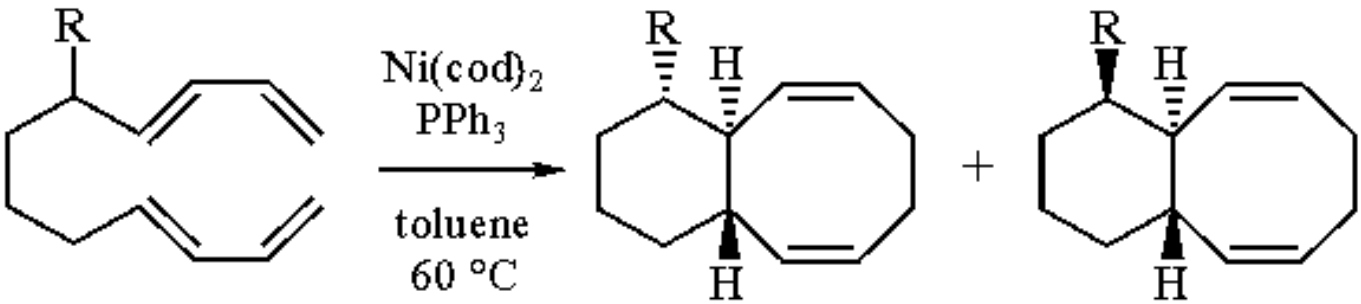

(27)

R	Yield	Ratio (α:β)
CN	66%	1.6:1
Me	88%	20:1
CH_2OAc	93%	22:1
CO_2Me	65%	65:1

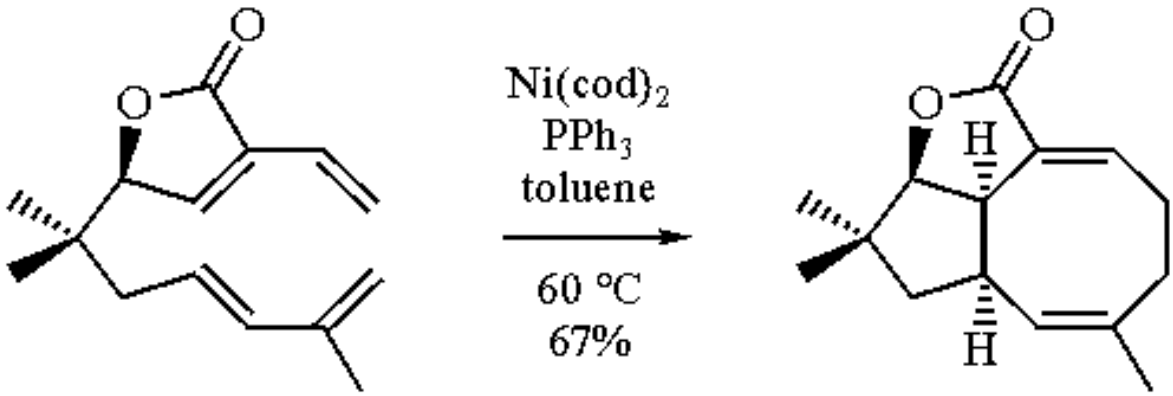

(28)

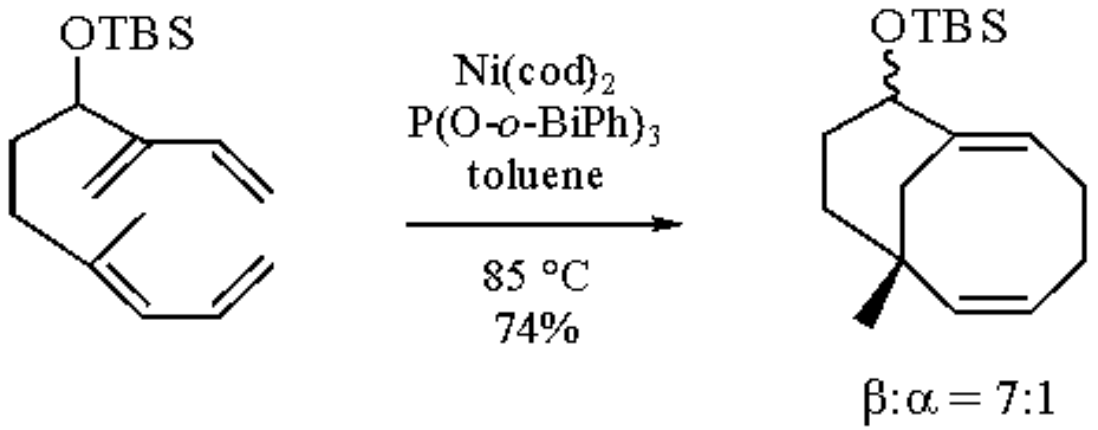

(29)

These reactions can also be tailored to give 1,4-cyclohexadiene products if an alkyne is tethered to the diene (eq 30).[83] These catalytic [4 + 2] cycloaddition reactions are an attractive alternative to the Diels-Alder reaction because they are very mild, tolerant of a wide array of functional groups, and are exempt from the restrictive electronic substitution requirements of the thermally activated reaction. If the alkyne portion of the molecule is replaced by an alkene, however, a rhodium catalyst must be used.[84] When an allene is used the regiochemistry of the cycloaddition can be controlled by the choice of catalyst (eq 31).[85]

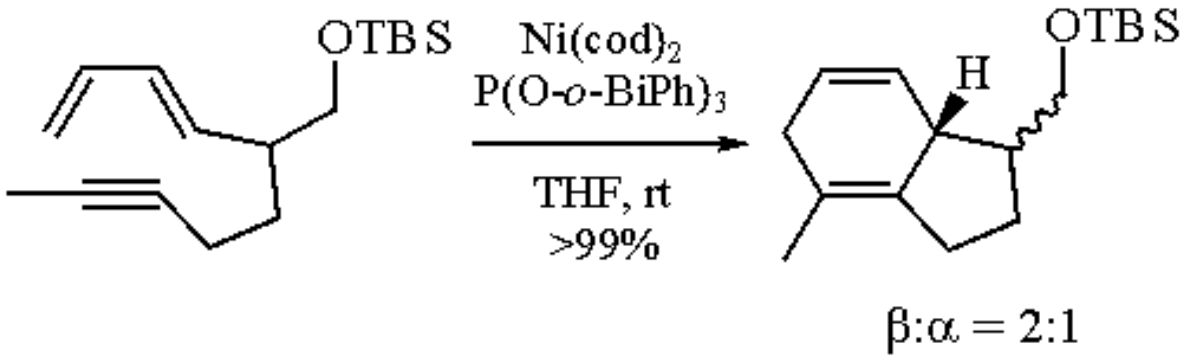

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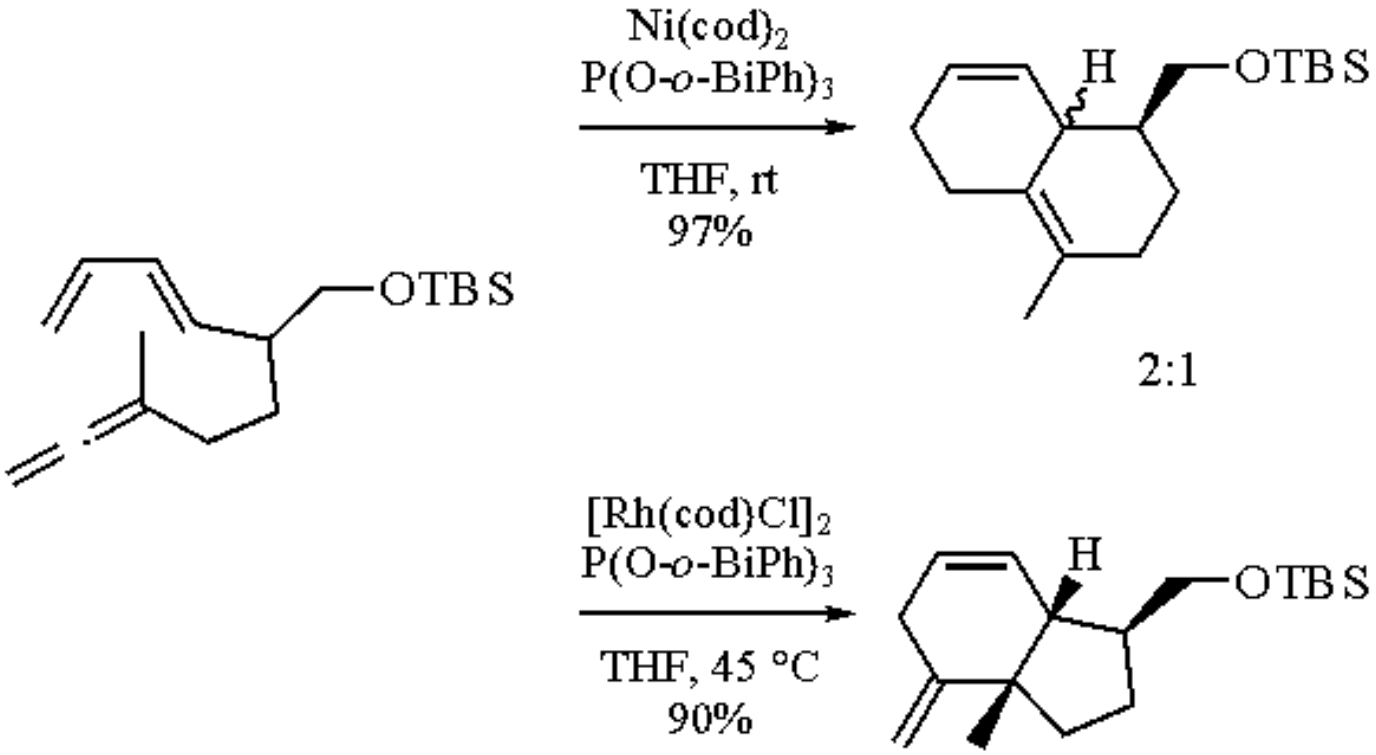

(31)

Linear dimerizations of 1,3-dienes may be induced by the addition of a hydrogen donor such as an amine, alcohol, or an aminophosphinate ligand to the catalyst.[5a,86] When a chiral aminophosphinate ligand was used, piperylene was dimerized to a 21:70 ratio of the two head-to-head 1,3,6-octatriene isomers having ~90% and 35% ee, respectively.[87]

Other Uses.

Sulfur heterocycles can undergo hydrodesulfurization and ring contraction in the presence of nickel(0) complexes.[88] Symmetrical aromatic ketones may be prepared from aromatic carboxylic acids through the coupling of their *S*-(2-pyridyl) derivatives.[89] Alkenes can be formed from 1,2-diols by the stereospecific cleavage of thionocarbonates.[90] Alkane- and alkenecarboxylic acids can be generated from the reaction of alkenes with a nickel(0) catalyst and CO_2.[91] Geminal dihalides react with nickel(0) catalysts and electron deficient alkenes to give cyclopropanes.[92]

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Bis(1,5-cyclooctadiene)rhodium Tetrafluoroborate-(*R*)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl[1]

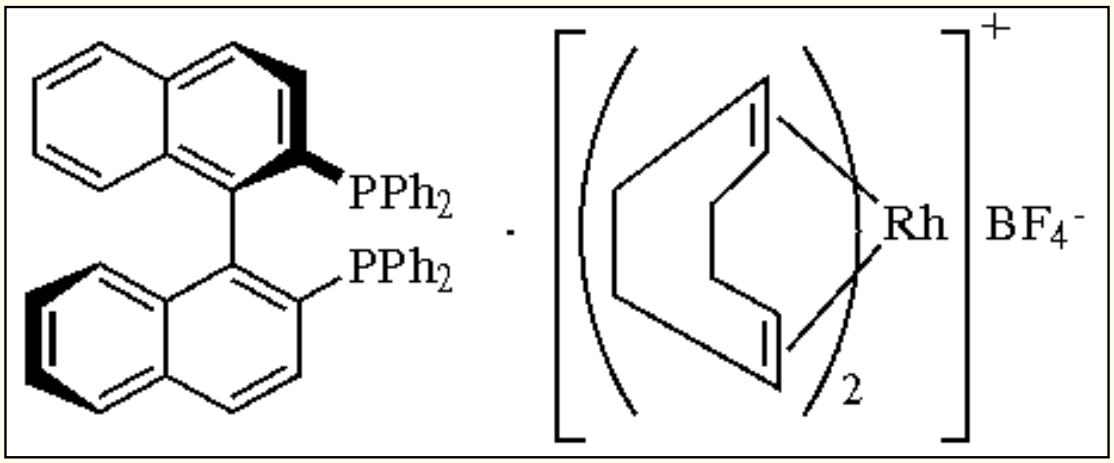

([Rh(cod)$_2$]BF$_4$)

[35138-22-8] · $C_{16}H_{24}BF_4Rh$ · Bis(1,5-cyclooctadiene)rhodium Tetrafluoroborate-(*R*)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl · (MW 406.07) ((*R*)-BINAP)

[76189-55-4] · $C_{44}H_{32}P_2$ · Bis(1,5-cyclooctadiene)rhodium Tetrafluoroborate-(*R*)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl · (MW 622.68)

(catalyst for asymmetric hydrogenation,[2] isomerization,[3] hydroboration,[4] and intramolecular hydrosilation[5] of alkenes)

Physical Data: [Rh(cod)$_2$]BF$_4$: mp 206-8 °C; (*R*)-BINAP: mp 240-241 °C; [α]25D + 229° (*c* = 0.32, benzene).

Form Supplied in: [Rh(cod)$_2$]BF$_4$: orange-red crystals; (*R*)-BINAP: colorless crystals.

Analysis of Reagent Purity: (*R*)-BINAP: ^{31}P NMR (4:1 C_6D_6-CD_3OD): δ -12.8 (s); mp and optical rotation shown above are also useful for analysis of the purity.

Purification: [Rh(cod)$_2$]BF$_4$: recrystallization from CH_2Cl_2 and ether; (*R*)-BINAP: recrystallization from a mixture of toluene and EtOH.

Handling, Storage, and Precautions: [Rh(cod)$_2$]BF$_4$: hygroscopic; corrosive.

Asymmetric Hydrogenation.

The diene-free cationic rhodium complex of (*R*)-BINAP catalyzes the enantioselective hydrogenation of dehydroamino acids. α-(Benzoylamino)acrylic acid is hydrogenated at rt to afford (*S*)-*N*-benzoylphenylalanine in 100% ee (eq 1).[2] To obtain maximal stereoselectivity the reaction should be carried out under a low concentration of substrate (100% in 0.013 M vs. 62% in 0.15 M) and low initial hydrogen pressure (100% at 1 atm, but 71% at 50 atm).

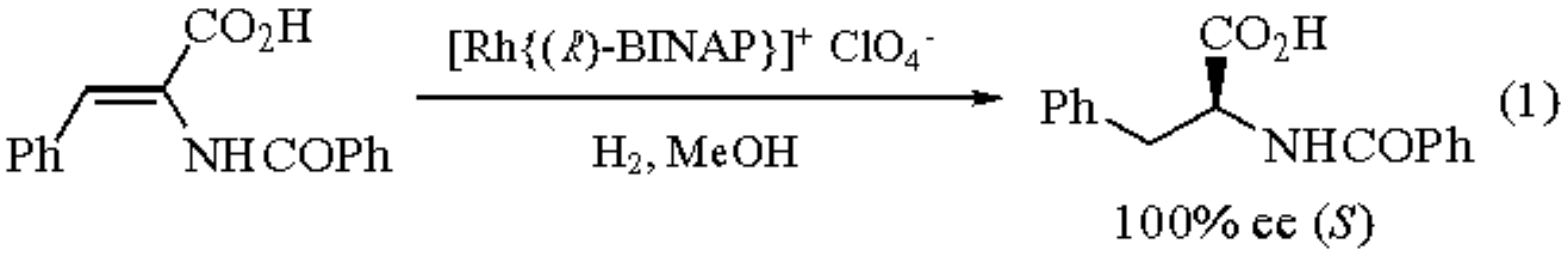

Optically active homoallylic alcohols are hydrogenated with differentiation of the diastereofaces (eq 2).[6] Use of the matched ligand, i.e. (*R*)-BINAP, gives a product of 96% de, while the mismatched (*S*)-ligand affords low selectivity.

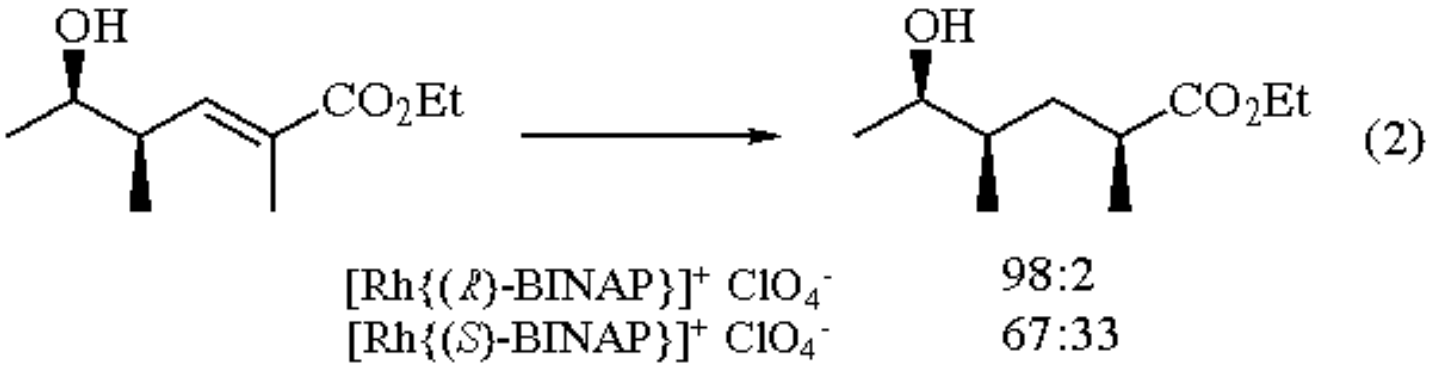

Allylic Hydrogen Migration.

Cationic Rh^I diphosphine complexes are very active catalysts for allylic hydrogen migration of tertiary and secondary allylamines to give the corresponding (*E*)-enamines and imines, respectively. Highly enantioselective isomerization is accomplished by use of (*R*)-BINAP as a diphosphine ligand.[3] Diethylnerylamine, which has (*Z*) geometry, gives (*R*)-(*E*)-diethylcitronellenamine in 95% ee in the presence of 1 mol % of [Rh{(*R*)-BINAP}(cod)]ClO_4, while the isomeric diethylgeranylamine gives (*S*)-(*E*)-diethylcitronellenamine in 96% ee (eq 3). Thus the method presented above offers a desired enantiomer by proper choice of alkene geometry and chirality of BINAP.

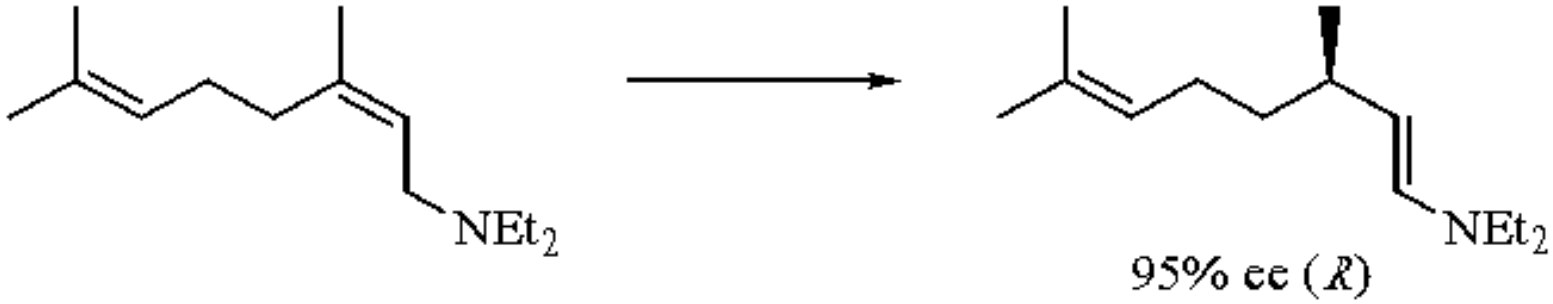

$[Rh\{(R)\text{-BINAP}\}(cod)]^+ ClO_4^-$ (3)

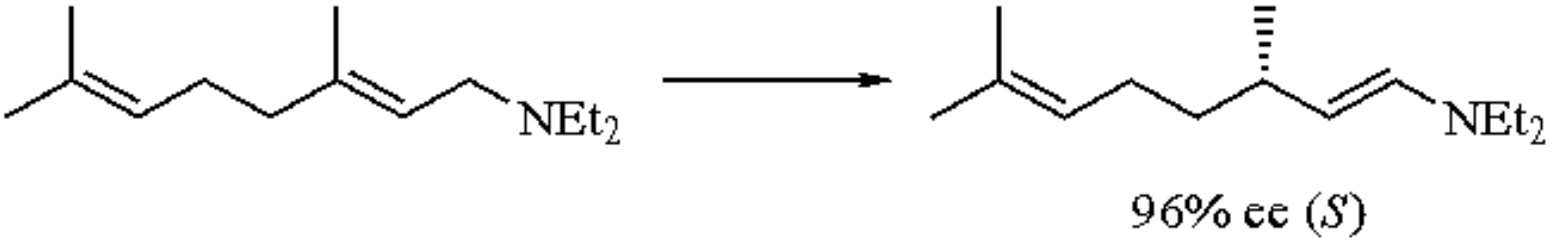

Cationic Rh-(*R*)-BINAP complexes also catalyze the allylic hydrogen migration of racemic 4-hydroxy-2-cyclopentenone to 1,3-cyclopentanedione with 5:1 enantiomeric discrimination. The racemate is kinetically resolved to (*R*)-4-hydroxy-2-cyclopentenone of 91% ee at 72% conversion at 0 °C (eq 4).[7]

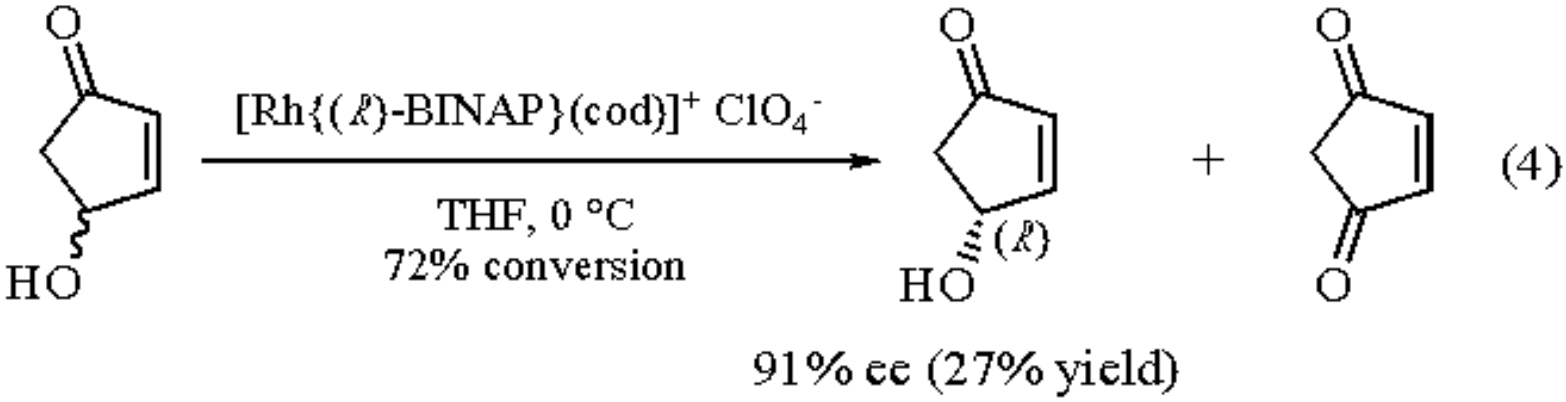

Asymmetric Hydroboration.

Rhodium complexes are known to catalyze hydroboration of alkenes with unreactive borane derivatives, e.g. catecholborane and oxaborolidine.[8] This reaction proceeds enantioselectively by use of BINAP as a ligand for neutral[9-11] or cationic[4,12] rhodium complexes. Reaction of styrene with catecholborane followed by oxidation affords (*R*)-1-phenylethanol in 96% ee in the presence of (*R*)-BINAP and $[Rh(cod)_2]BF_4$ (eq 5).[4]

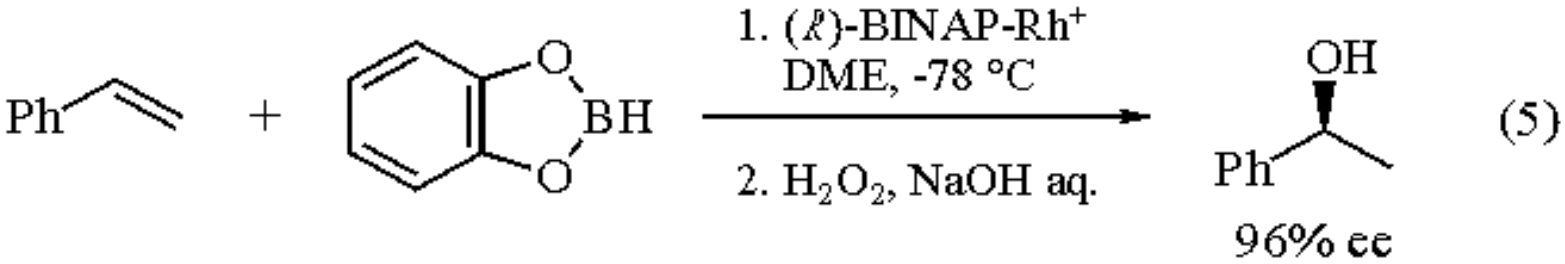

Asymmetric Intramolecular Hydrosilation.

Intramolecular hydrosilation of allylic alcohols followed by oxidation is a convenient method for the stereoselective preparation of 1,3-diols.[13] An enantioselective version is achieved by use of diene-free BINAP-Rh$^+$ (eq 6).[5] Both silyl ethers derived from cinnamyl alcohol and its *cis* isomer give (*R*)-1-phenylpropane-1,3-diol in high ee regardless of alkene geometry.

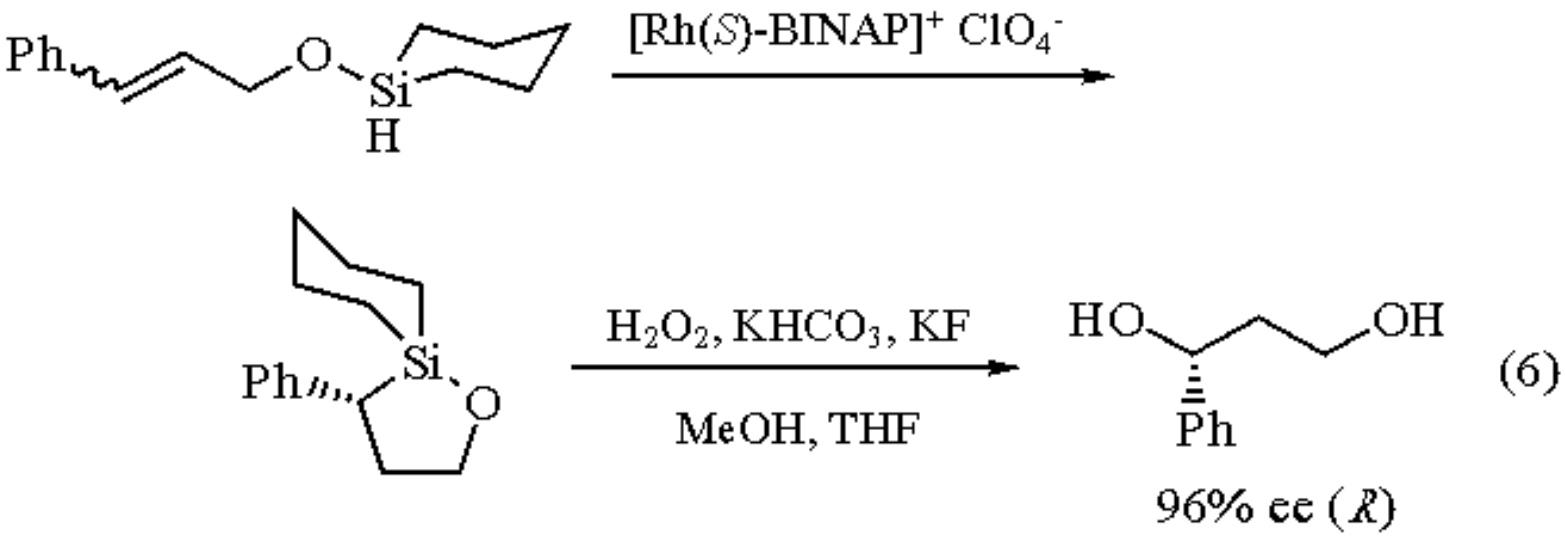

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate; ***Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(R)-1-(S)-1´,2-Bis(diphenylphosphino)ferrocenylethanol***; ***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***; ***Chlorotris(triphenylphosphine)rhodium(I)***.

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Bis(cyclopentadienyl)cobalt

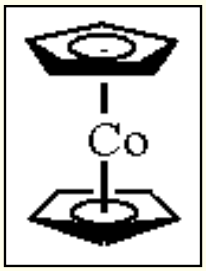

[1277-43-6] · $C_{10}H_{10}Co$ · Bis(cyclopentadienyl)cobalt · (MW 189.12)

(reducing agent; catalyst; source of other organocobalt complexes and of substituted cyclopentanes or cyclopentadienes)

Alternate Name: cobaltocene.

Physical Data: mp 173-174 °C; sublimes 40 °C/0.1 mmHg; paramagnetic.

Solubility: sol petrol and other common org solvents, but reacts with chlorocarbons and oxidizing agents (e.g. nitromethane).

Form Supplied in: black-purple cryst; commercially available; readily synthesized from Co^{II} salts [preferably $Co(NH_3)_6Cl_2$] + CpNa in THF.[1]

Handling, Storage, and Precautions: highly air- and somewhat moisture-sensitive and light-sensitive; indefinitely stable in vacuo or under dry inert atmosphere (N_2, Ar) in the dark; storage in the cold is recommended; toxic.

Catalytic Reactions.

As well as its very facile oxidation to cobaltocenium salts (see ***Bis(cyclopentadienyl)cobalt Hexafluorophosphate***), cobaltocene is a source of $CpCoL_2$ complexes, e.g. the dicarbonyl (L = CO) (eq 1)[2] (see ***Dicarbonyl(cyclopentadienyl)cobalt(I)***) and the bis(ethylene) complex (L = C_2H_4) (eq 2)[3] (see also ***(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)***). Like these diamagnetic complexes ($CpCoL_2$), it catalyzes the reaction of alkynes with nitriles to give 2-substituted pyridines (eq 3),[4] related reactions with isocyanates (eq 4) and carbodiimides,[5] and the closely related alkyne cyclotrimerization.[6] It also catalyzes hydroformylation of alkenes, e.g. 1-octene (eq 5),[7] and is comparable in activity as catalyst to both ***Dicarbonyl(cyclopentadienyl)cobalt(I)*** and ***Octacarbonyldicobalt***, but the last one gives a higher *n*:*i*-nonanal ratio in this reaction.

$$Cp_2Co + CO \longrightarrow CpCo(CO)_2 \qquad (1)$$

$$Cp_2Co + K + 2\,C_2H_4 \xrightarrow[0\ ^\circ C]{Et_2O} CpCo(C_2H_4)_2 + C_5H_5K \qquad (2)$$

RCN + 2 C_2H_2 ⟶ 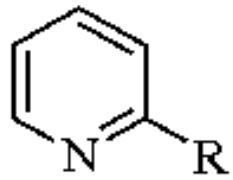

(3)

$$PhC{\equiv}CCO_2Me + PhNC{=}O \xrightarrow[\substack{135\ ^\circ C \\ 19\ h}]{Cp_2Co}$$

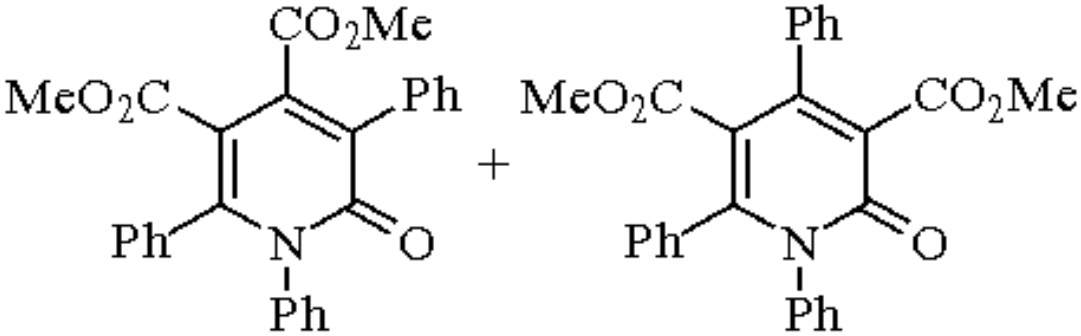

(4)

$$C_6H_{13}CH{=}CH_2 + CO + H_2 \xrightarrow[\substack{\text{or } CpCo(CO)_2 \\ \text{or } Co_2(CO)_8}]{Cp_2Co}$$

$$C_8H_{17}CHO + C_6H_{13}CHMeCHO \qquad (5)$$

In the presence of base, cobaltocene catalyzes the efficient addition of carbon dioxide to 2-methylbut-3-yn-2-ol (eq 6).[8] In conjunction with copper chelates, it is reported to catalyze polymerization and block copolymerization of methyl methacrylate.[9]

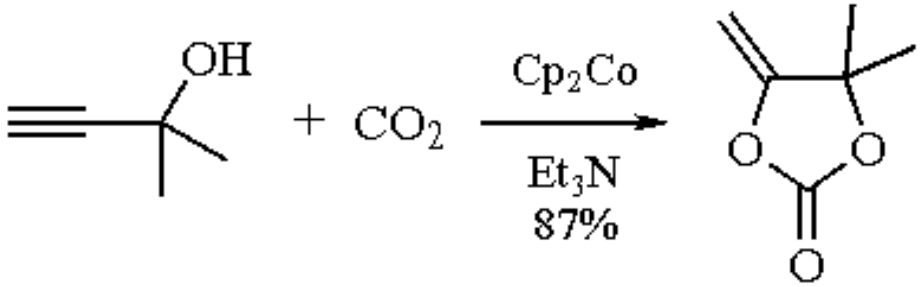

(6)

Stoichiometric Reactions.

As a 19-electron complex, cobaltocene acts as a powerful one-electron reducing agent. Its use as such has been largely confined to the reduction of a wide range of organometallic substrates. Little is known about its ability to reduce metal-free organic substrates apart from its reactions with alkyl halides, including polyhalides, which proceed according to eq 7 and possibly by the steps in eqs 8 and 9. The last step (eq 9) finds support from the addition of the radical &bdot;CMe_2CN, generated from AIBN.[10] The general reaction (eq 7) occurs efficiently with halomethanes and with allylic, benzylic, and propargylic halides, with α-halo esters and ketones and with benzoyl chloride.[11] A related reaction occurs with active hydrogen compounds (e.g. C*H*Cl_3, *H*C_2Ph, *H*CH_2CN, *H*CH_2COMe) in the presence of O_2, apparently via an oxygen adduct of cobaltocene, e.g. eq 10.[12] Interaction of cobaltocene with organomercury[13] and -cadmium[14] reagents also leads to 5-*exo*-substituted cyclopentadiene(cyclopentadienyl)cobalt (eq 11) accompanied by products suggesting radicals (for another route to these 5-*exo*-substituted complexes and some aspects of their behavior, see ***Bis(cyclopentadienyl)cobalt Hexafluorophosphate***).

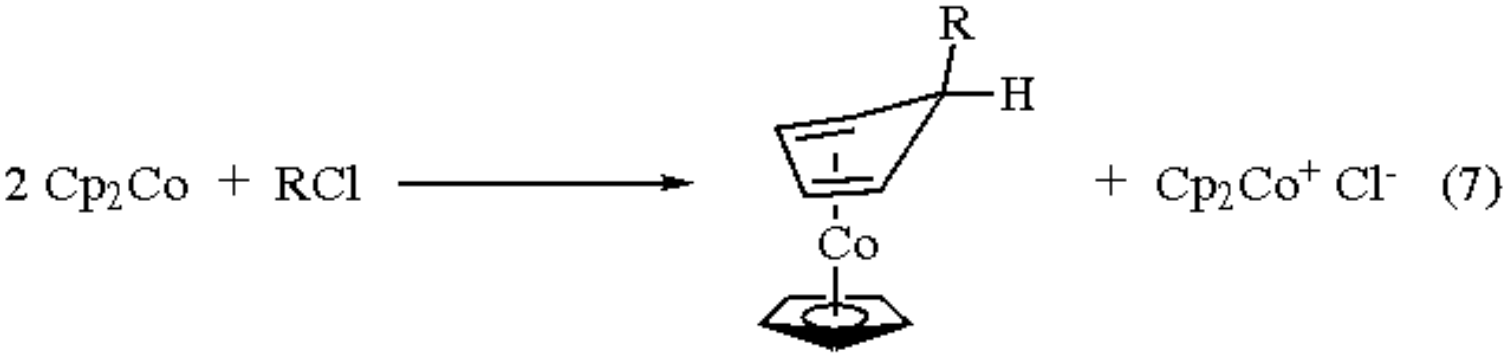

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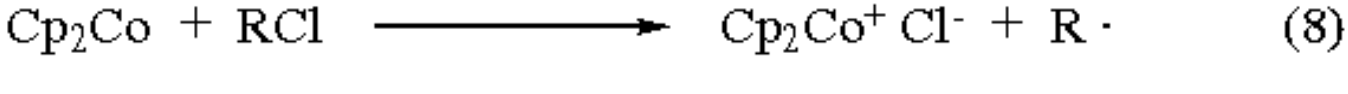

(8)

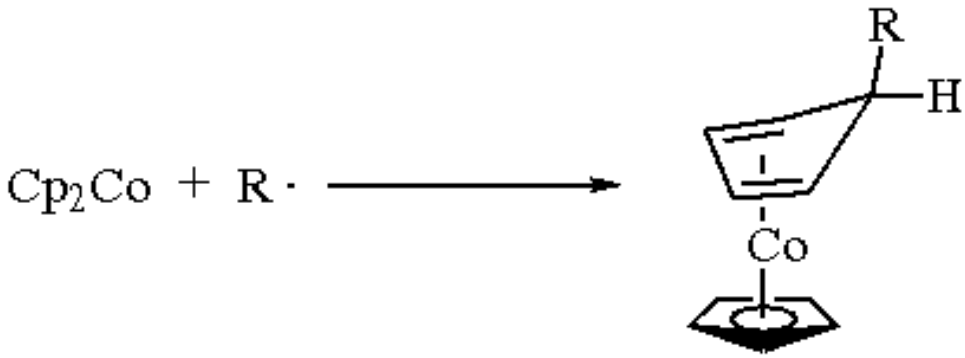

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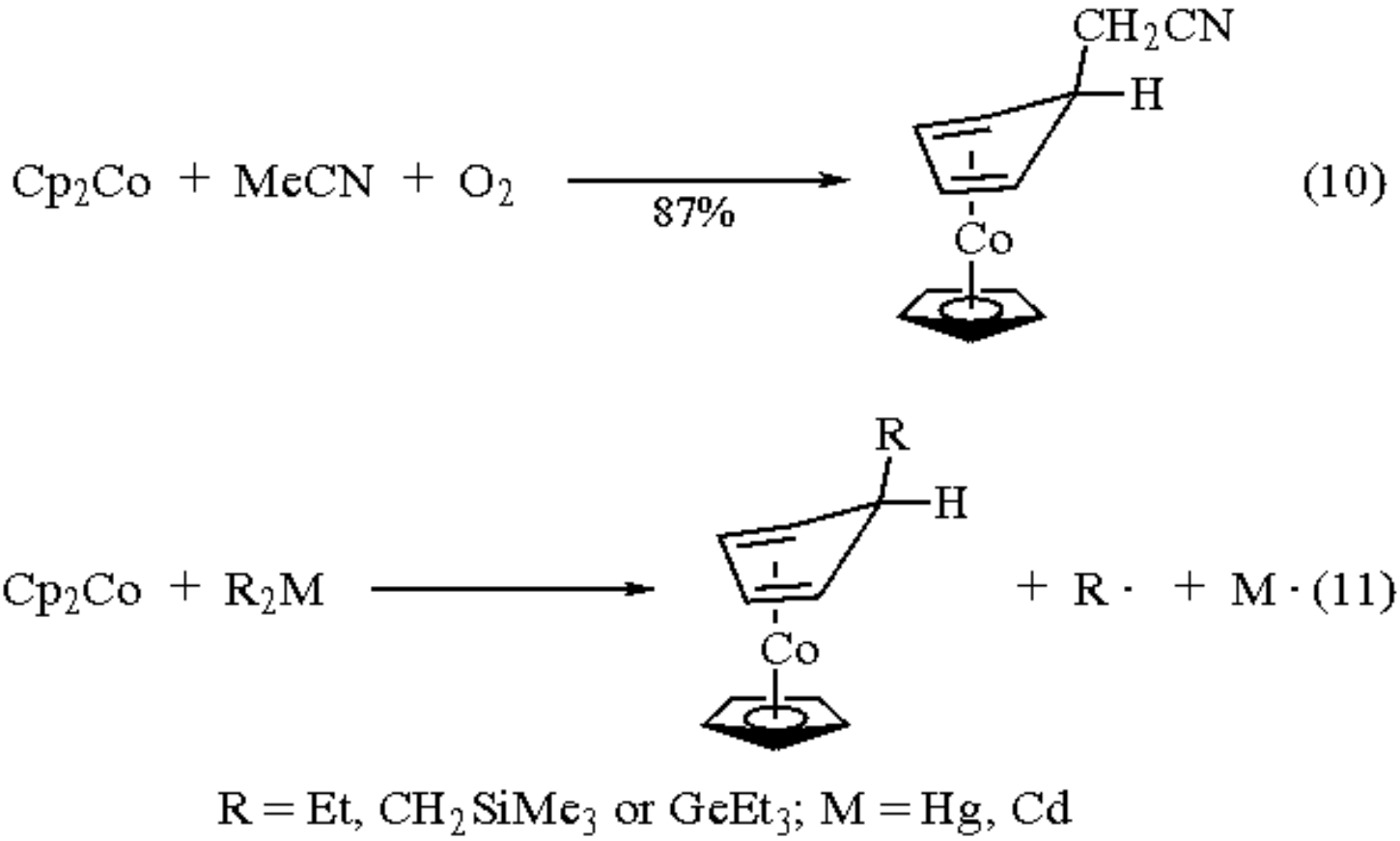

All such complexes are potential sources of substituted cyclopentadienes, but little attention has been paid to such use. (Trichloromethyl)cyclopentadiene has been liberated by iodine oxidation (eq 12) of the complex prepared from Cp_2Co with CCl_4 or with $CHCl_3/O_2$.[15] However, reactions in which the diene moiety is displaced by other ligands (e.g. Me_2S in the presence of HBF_4[16] or PhC_2Ph[17]) have been carried out without isolation of the metal-free product(s).

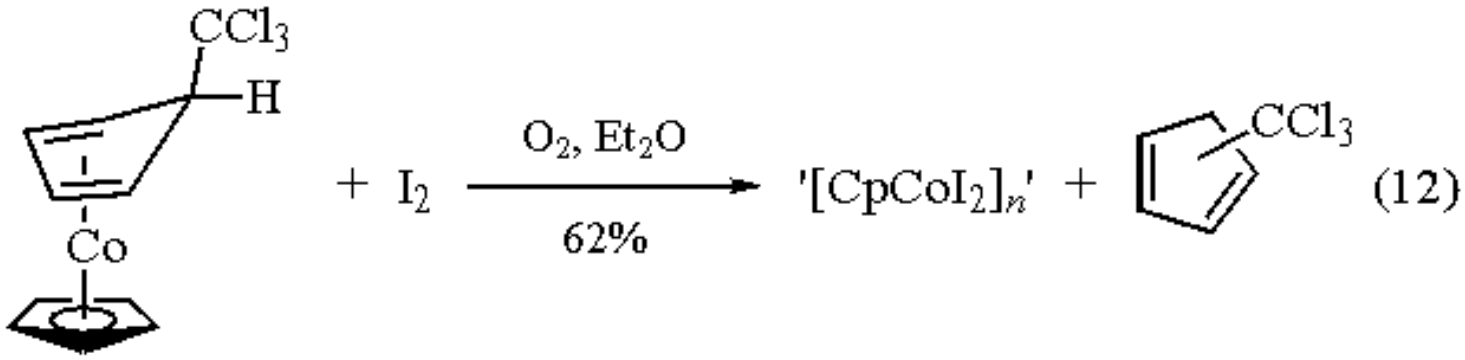

The complexes with 5-*exo*-haloalkyl groups undergo ring enlargement on solvolysis (eq 13).[18] In a closely analogous sequence, cobaltocene adds dihaloboranes, e.g. eq 14, to give products which undergo ring enlargement (eq 15) on hydrolysis or on treatment with Lewis acids.[19]

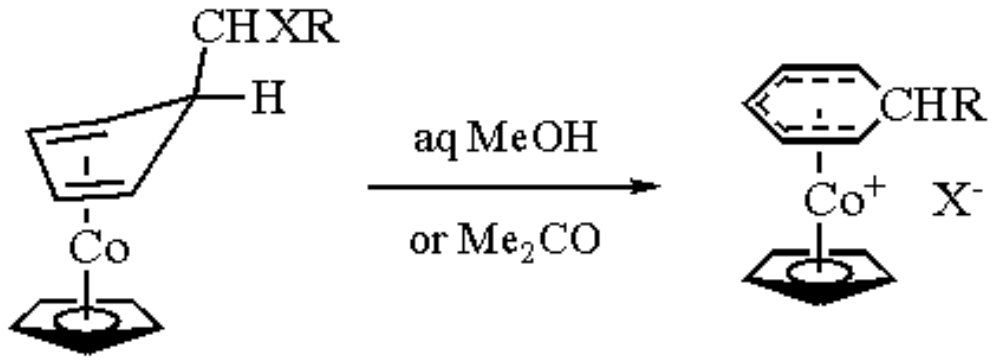

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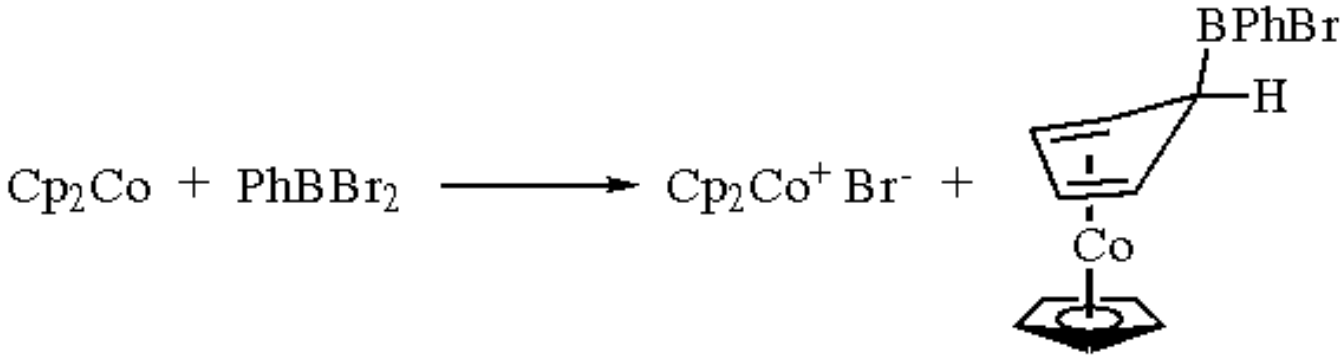

(14)

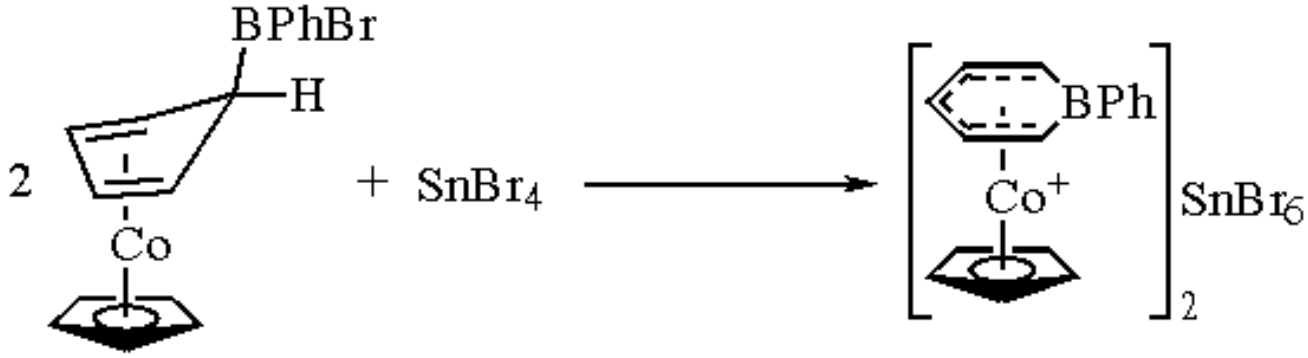

(15)

A one-step synthesis of azulene from cobaltocene is reported to proceed in 12-21% yield according to eq 16.[20]

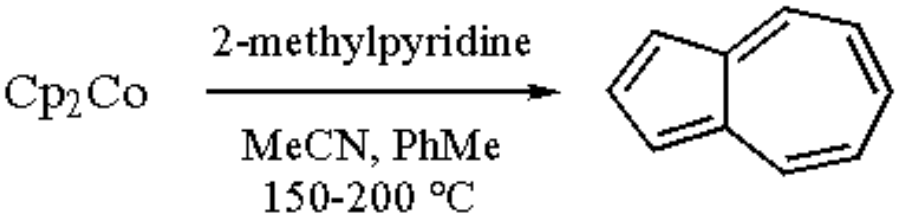

(16)

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Bis(cyclopentadienyl)cobalt Hexafluorophosphate

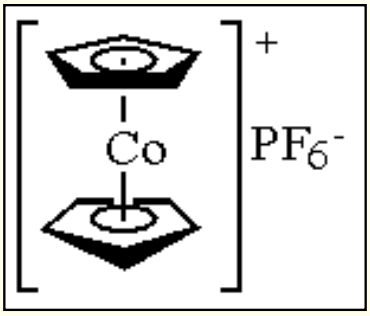

[12427-42-8] · $C_{10}H_{10}CoF_6P$ · Bis(cyclopentadienyl)cobalt Hexafluorophosphate · (MW 334.09)

(source of (cyclopentadiene)(cyclopentadienyl)cobalt and its substitution products and, hence, of substituted cyclopentadienes and cyclopentanes)

Alternate Name: cobaltocenium hexafluorophosphate.

Solubility: sol acetone, hot ethanol; sparingly sol ether, water.

Form Supplied in: yellow crystalline solid; available commercially.

Preparative Method: readily synthesized from cobalt(II) salts + CpNa, followed by air + HPF_6 or NH_4PF_6. Salts with a wide range of other counterions may be obtained similarly. The cobaltocenium ion[1] may be precipitated from aqueous solution by a variety of large anions. In addition to PF_6^-, convenient counterions include Br_3^- and I_3^-. The simple halides are hygroscopic, but may be obtained in anhydrous form by removal of water under vacuum.

Handling, Storage, and Precautions: very stable; irritant.

The potential synthetic value of cobaltocenium salts depends on the facile addition of hydride (eq 1)[2] and of (unstabilized) carbon nucleophiles (eq 2)[3] to give (cyclopentadiene)(cyclopentadienyl)cobalt(I) complexes. The unsubstituted $(C_5H_5)Co(C_5H_6)$ is similar in reactivity to ***(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)***. *Exo* substituted derivatives of the type formed in eq 2 are also available from ***Bis(cyclopentadienyl)cobalt***.

They react sluggishly or not at all (depending on R) with triphenylmethyl cations, which in general only abstract *exo*-but in some cases also abstract *endo*-H.[5] However, in many of the cases where they fail it has been found that the products of eq 2 may be converted to substituted cobaltocenium salts by the action of ***N-Bromosuccinimide*** (eq 3)[4] or strong ***Sulfuric Acid***.[5c] Alternatively, thermolysis causes 1,5-H migration (eq 4),[5a,b] making possible subsequent *exo*-H

abstraction (eq 5). However, any further carbanion addition to the resultant monosubstituted cobaltocenium salts will result in isomer mixtures and hence becomes less attractive as a route to disubstituted cyclopentadienes.

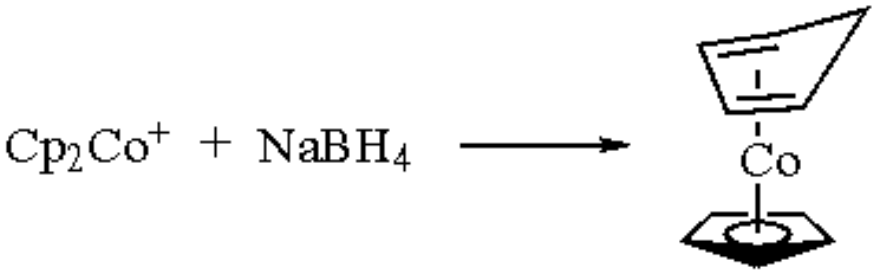

(1)

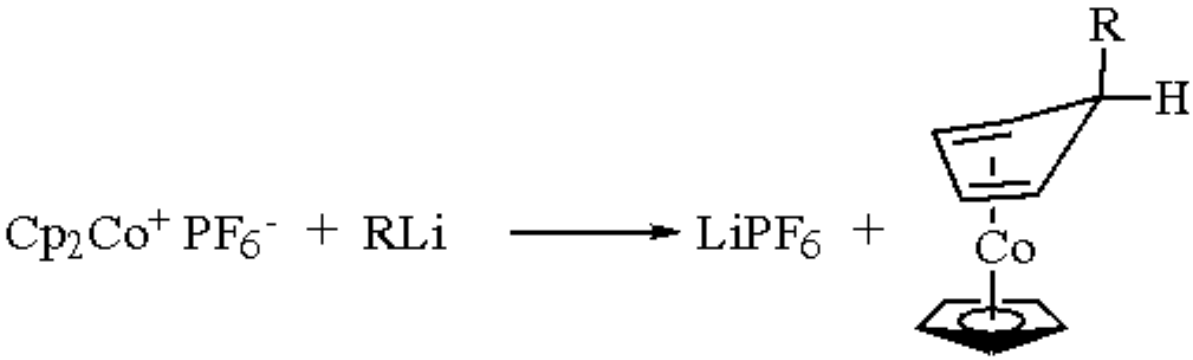

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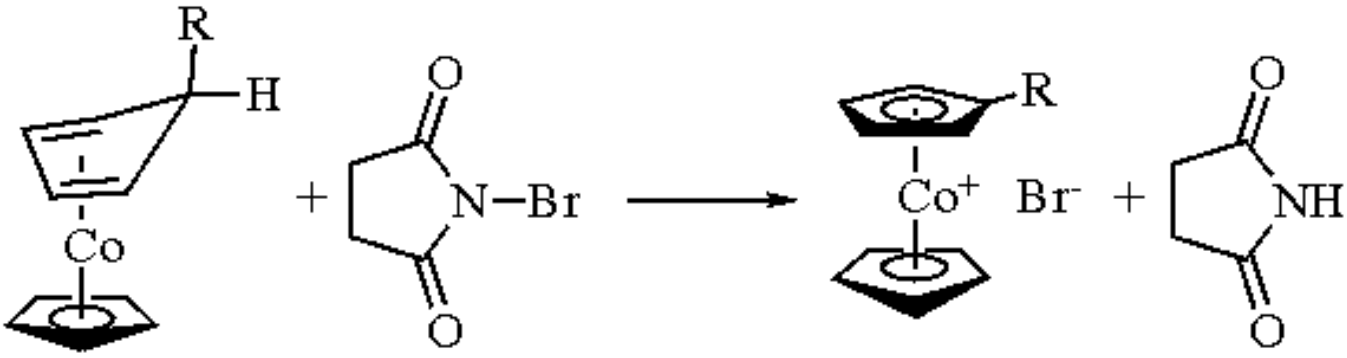

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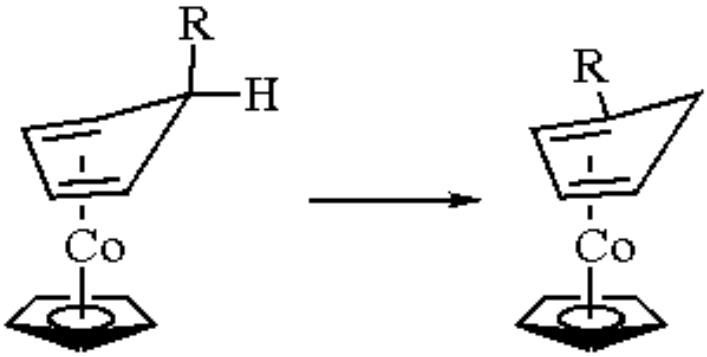

(4)

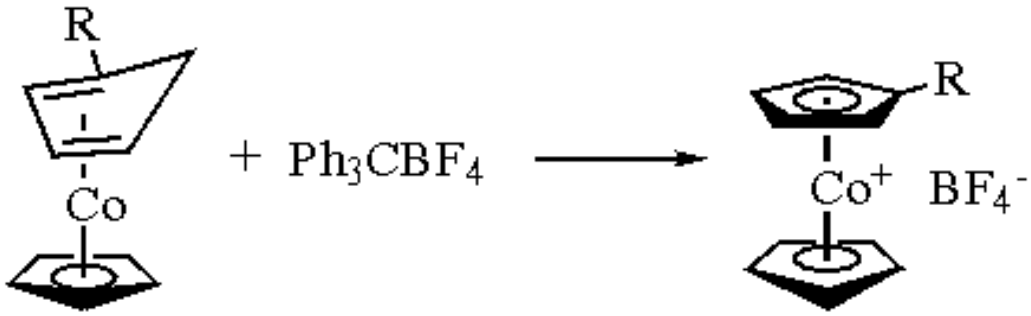

(5)

Methyl and 1,1´-dimethyl derivatives of the cobaltocenium ion are smoothly oxidized by strong oxidants, e.g. ***Potassium Permanganate***, to the corresponding mono- and dicarboxylic acids.[6] The latter, in turn, have been converted to the diacid chlorides,[6b,d] a source of polymers;[7] further conversion by Curtius degradation yields the 1,1´-diaminocobaltocenium ion, itself oxidizable to the dinitro compound.[6b,d] Oxidation of 1,1´-diethylcobaltocenium yields the 1,1´-diacetyl substituted cation[8] and the 1,1´,2,2´-tetracarboxylic acid is formed by oxidation of the dibenzocobaltocenium [bis(indenyl)cobalt(III)] salt with $KMnO_4$.[6a] Such processes are a potential source of substituted cyclopentadienes, as are transformations utilizing the enhanced acidity of α-CH groups. The principle is illustrated by the polysubstitution shown in eq 6.[9]

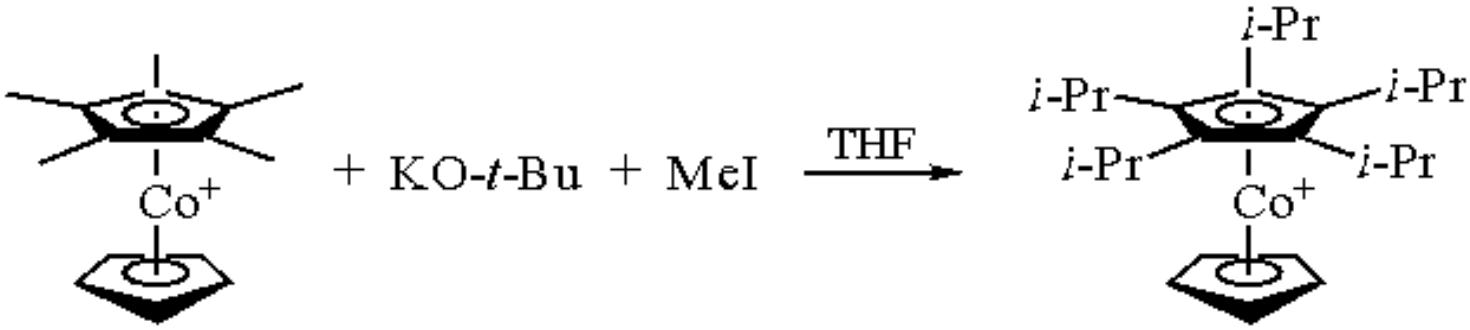

(6)

A rather remarkable, but low yield, synthesis of azulene is achieved in one step when cobaltocenium hexafluorophosphate is heated with ***Sodium Hydroxide*** (or ***Sodium Amide***), probably via the intermediates included in eq 7.[10]

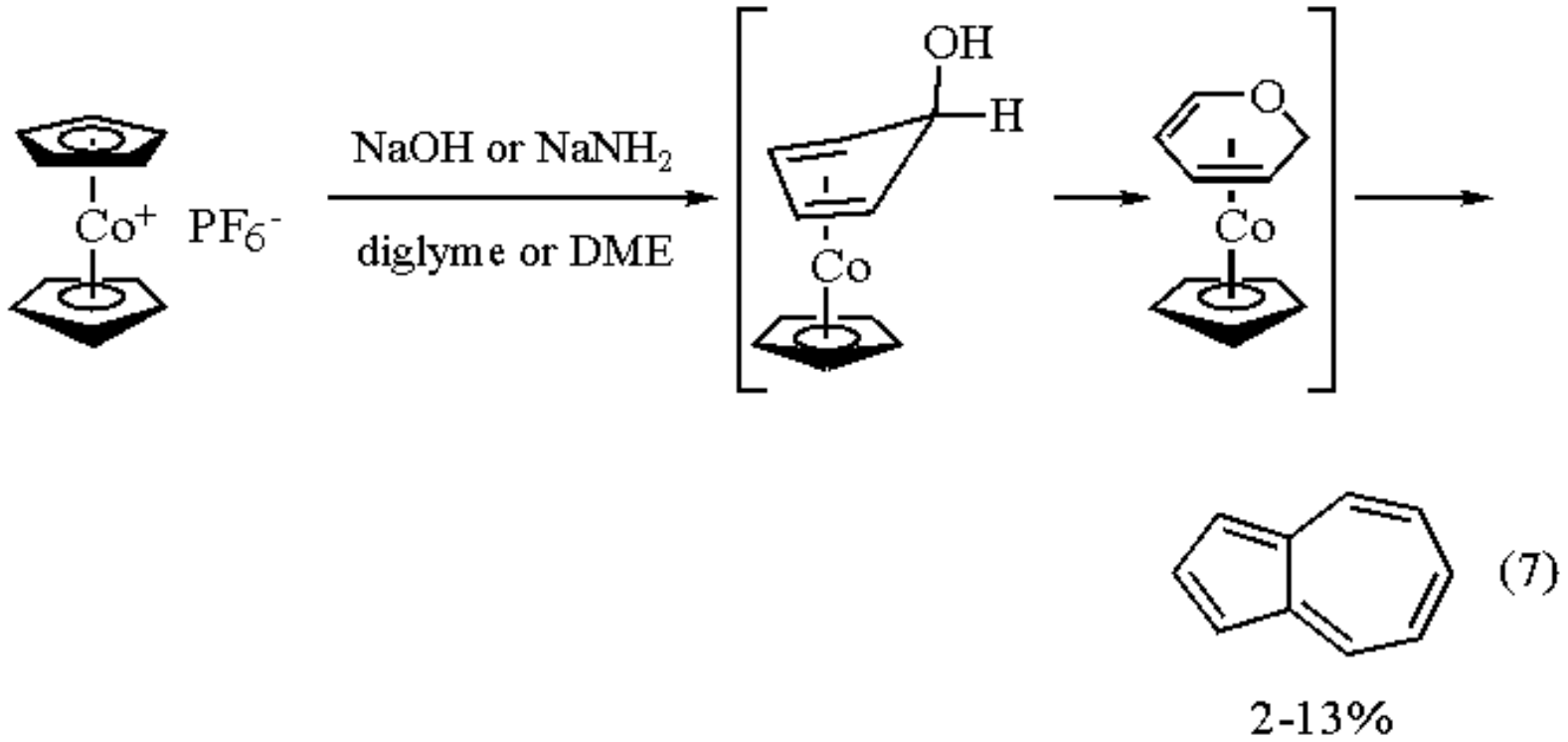

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Bis(η^5-cyclopentadienyl)dihydridozirconium[1]

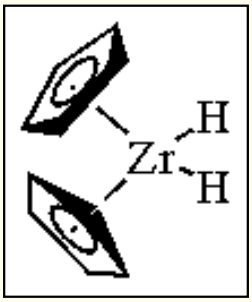

[37342-98-6] · $C_{10}H_{12}Zr$ · Bis(η^5-cyclopentadienyl)dihydridozirconium · (MW 223.42)

(catalyst for hydrogenation of alkenes and alkynes in combination with hydrogen;[2] catalyst for Meerwein-Ponndorf-Verley type reduction and Oppenauer type oxidation;[3] catalyst for crossed-aldol condensation;[4] catalyst for Tishchenko reaction;[5] reducing agent for organohalogen compounds[6])

Physical Data: polymeric in solid and dimeric $[Cp_2ZrH(\mu\text{-}H)]_2$ in benzene or toluene.[7] The polymeric nature of $[Cp_2ZrH_2]_n$ is suggested by its involatility, insolubility, and insusceptibility to reaction in air. The presence of a Zr-H-Zr bridging system is inferred from the intense broad IR absorption band at 1520 cm^{-1}.[8]

Solubility: insol common solvents.

Form Supplied in: white solid.

Analysis of Reagent Purity: ash (ZrO_2), 55.5%; hydrolyzable H_2, 1.99 g atm mol^{-1}; ^1H NMR (C_6D_6)[7] δ 5.75 (C_5H_5), 3.85 (J = 7.3 Hz), -3.45 (J = 7.3 Hz); IR (KBr disk)[8] 1520, 1300 cm^{-1} (Zr-H).

Preparative Methods: the following method is convenient for the preparation of Cp_2ZrH_2. μ-Oxobis[chlorobis(η^5-cyclopentadienyl)zirconium] ($[Cp_2ZrCl]_2O$) is prepared by the reaction of ***Dichlorobis(cyclopentadienyl)zirconium*** (Cp_2ZrCl_2), available from commercial sources, in dichloromethane and water in aniline.[9] To a solution of $[Cp_2ZrCl]_2O$ in THF is added dropwise ***Lithium Aluminum Hydride*** in THF with stirring under an argon atmosphere. The reaction mixture is stirred for ca. 8 h at rt, filtered, and then washed with THF to give the Cp_2ZrH_2 complex as a white solid (eq 1).[9]

$$2\ Cp_2ZrCl_2 + H_2O \longrightarrow [Cp_2ZrCl]_2O + 2\ HCl$$

$$[Cp_2ZrCl]_2O + LiAlH_4 \longrightarrow 2\ Cp_2ZrH_2 + LiCl + 1/2\ (AlOCl)_2 \qquad (1)$$

Handling, Storage, and Precautions: photosensitive and hydrolyzed by water; should be stored in the dark under

an argon atmosphere.

Reaction with Alkenes.

Alkyl zirconium derivatives, which can be prepared by the addition of Cp_2ZrH_2 to alkenes (hydrozirconation), are easily decomposed by hydrogenolysis to give the corresponding alkanes under mild conditions.[2,10] As a consequence, Cp_2ZrH_2 can be used as a catalyst for the hydrogenation of alkenes to alkanes (eq 2).[2]

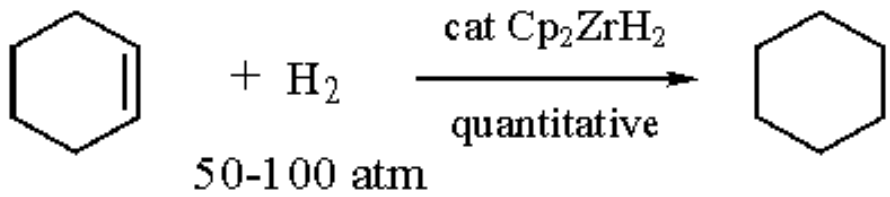

(2)

Reaction with Alkynes.

Cp_2ZrH_2-catalyzed hydrogenation of alkynes is also attained (eq 3).[2] Cp_2ZrH_2 reacts with monosubstituted acetylenes to give di-*trans*-alkenyl zirconium complexes, but with diarylacetylene, tetraarylbutadiene complexes are formed (eqs 4 and 5).[11]

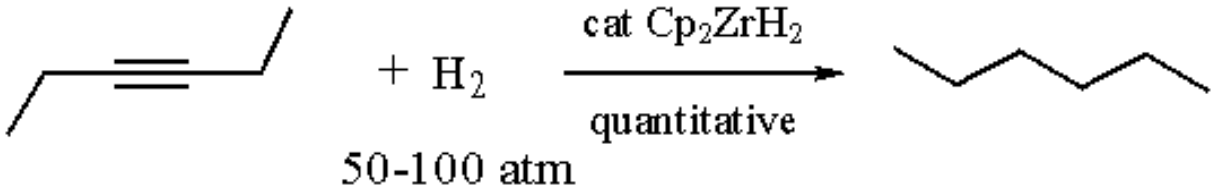

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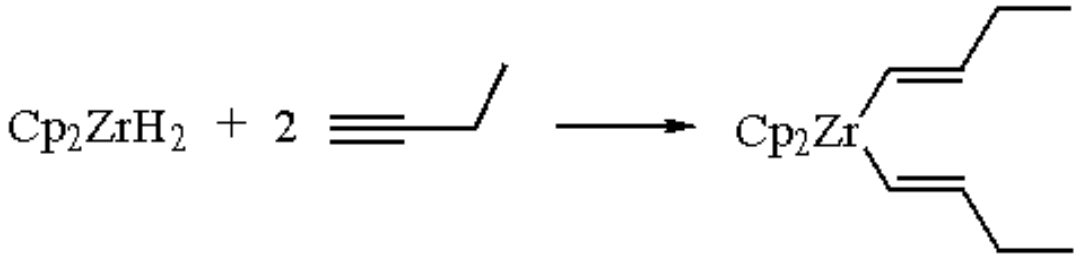

(4)

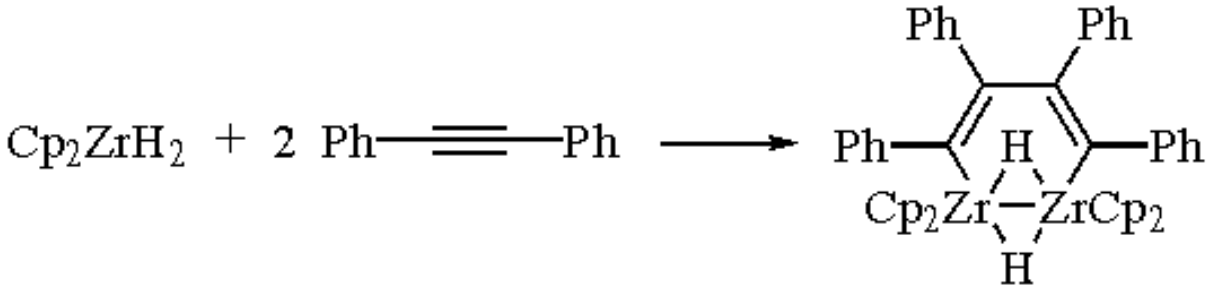

(5)

Meerwein-Ponndorf-Verley Type Reduction.

Cp_2ZrH_2 catalyzes hydrogen transfer reaction from alcohols to carbonyl compounds.[3] The regioselective 1,2-reduction of α,β-unsaturated carbonyl compounds to allylic alcohols is accomplished in the presence of 2-propanol (eq 6).[12,13] The reagent mediates the chemoselective reduction of keto aldehydes to hydroxy ketones (eq 7).[13] Steroidal diketones, e.g. androst-4-ene-3,17-dione, are reduced to the 17-hydroxy enones with high chemoselectivity (eq 8).[13]

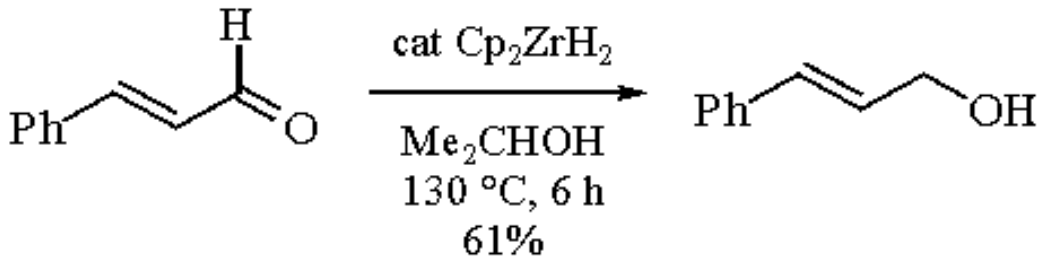

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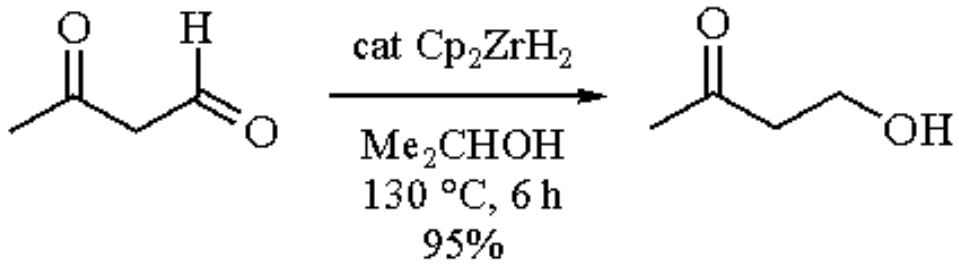

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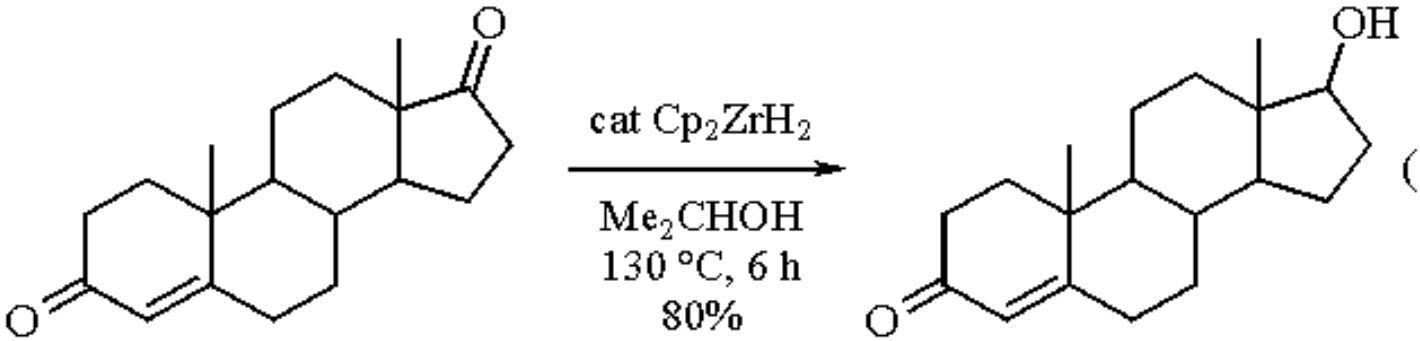

(8)

Oppenauer Type Oxidation.

The above discovery (Meerwein-Ponndorf-Verley type reduction) has been extended to the Oppenauer type oxidation.[3] Simple terpenoids, such as geraniol and nerol, are oxidized with retention of stereochemistry of the carbon-carbon double bond to form the corresponding α,β-unsaturated aldehydes (eq 9).[14]

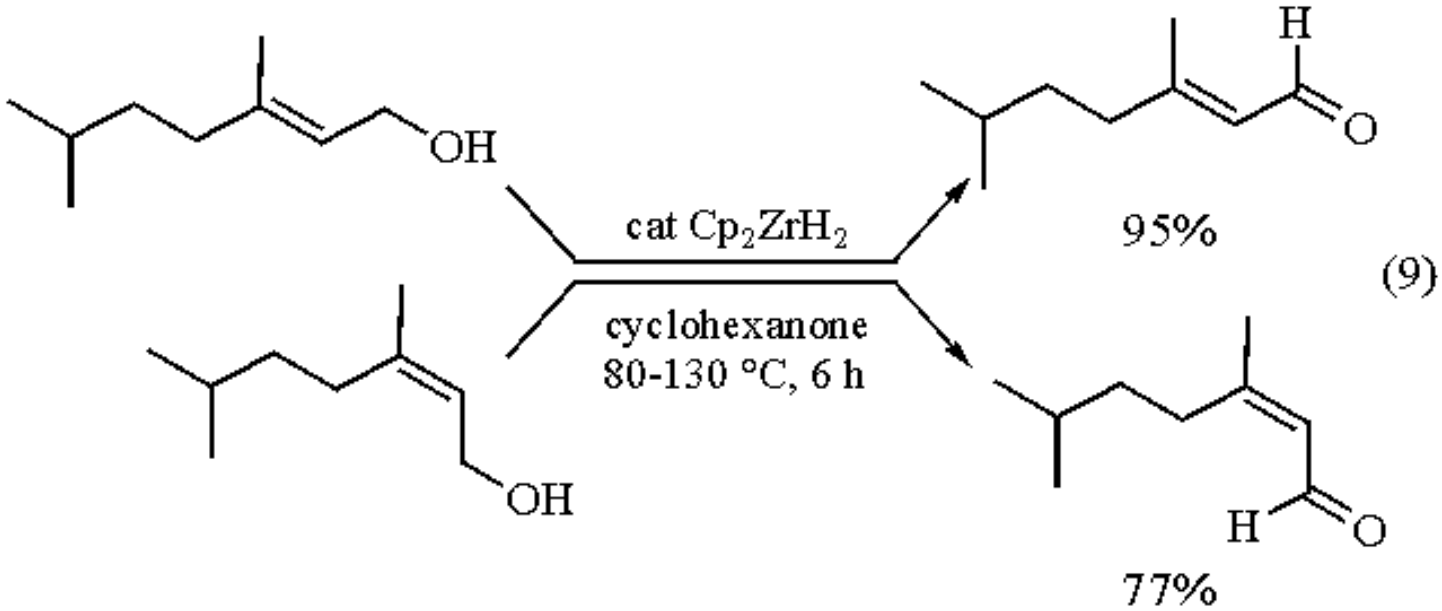

Crossed Aldol Condensation.

Cp_2ZrH_2 catalyzes the selective crossed aldol condensation between alicyclic ketones and aliphatic aldehydes to form the corresponding 2-alkylidenecycloalkanones (eq 10).[4] The reaction of alicyclic ketones with primary alcohols gives 2-alkyl-2-cycloalken-1-ones via the Oppenauer type oxidation followed by crossed aldol condensation (eq 11).[4]

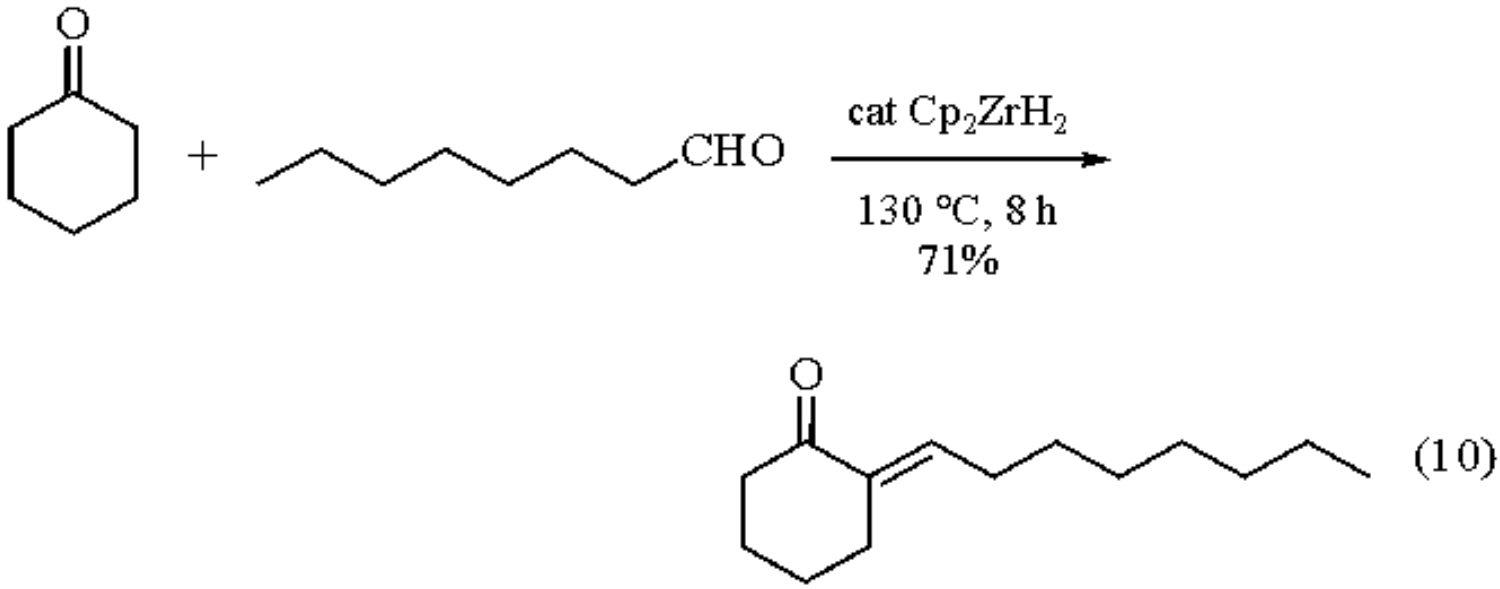

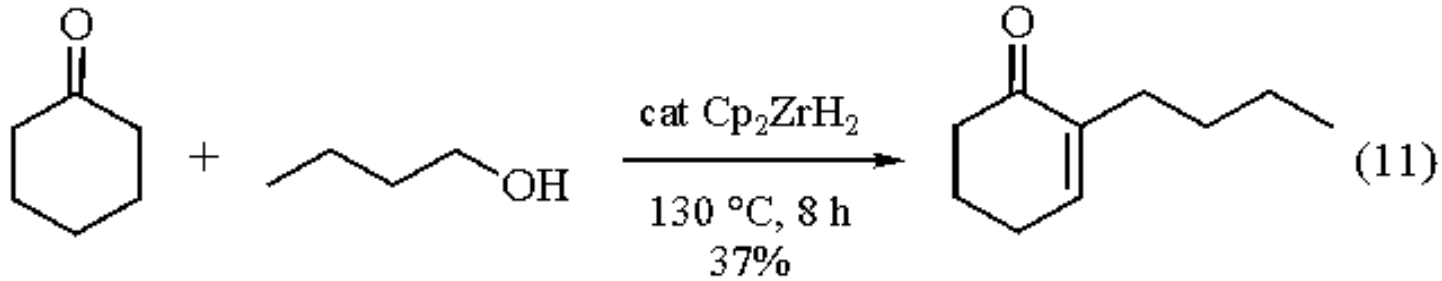

Tishchenko Reaction.

Cp_2ZrH_2 efficiently catalyzes the selective dimerization of aldehydes to esters under mild conditions (eq 12). The crossed dimerization of different kinds of aldehydes is also achieved (eq 13).[5]

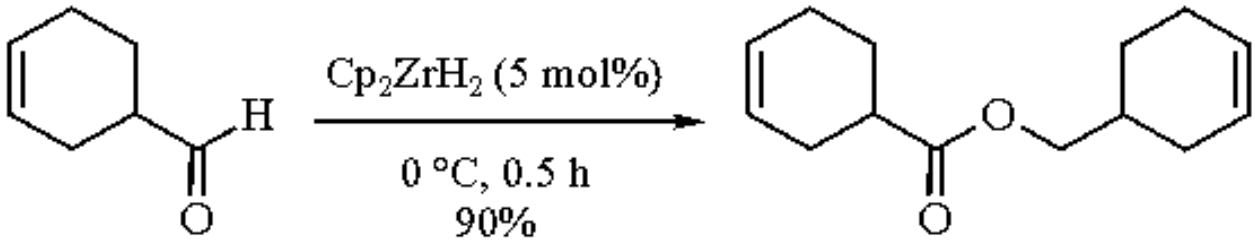

(12)

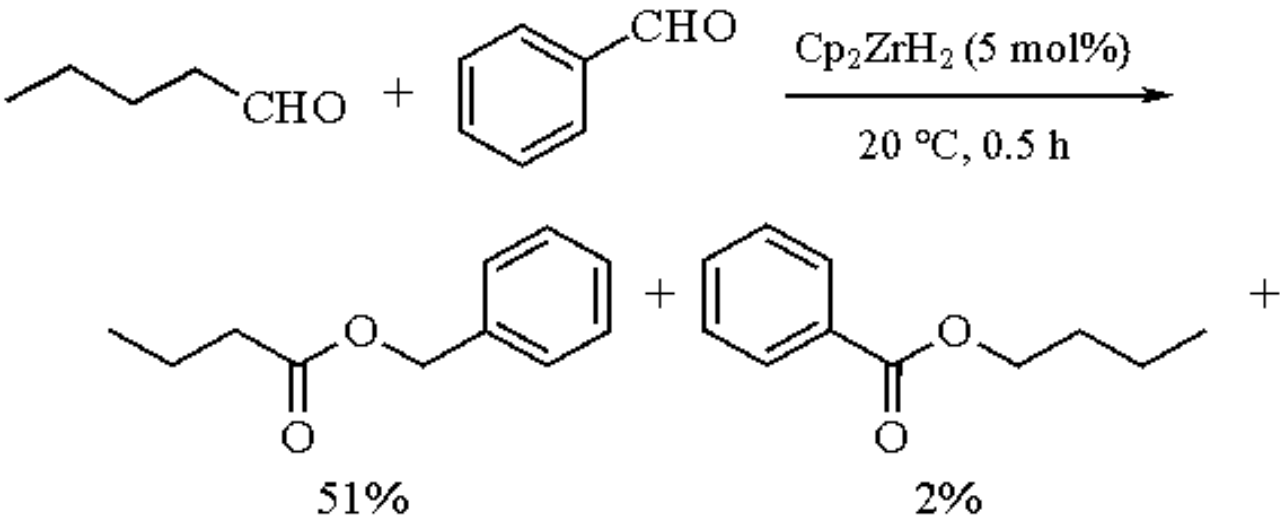

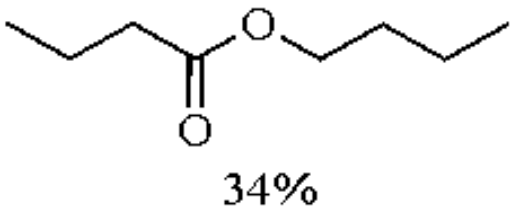

(13)

Dehalogenation of Organohalogen Compounds.

Reductive dehalogenation of organohalogen compounds is achieved by the action of Cp_2ZrH_2.[6] Replacement of hydride in Cp_2ZrH_2 by chloride occurs readily. Thus the reaction of Cp_2ZrH_2 with dichloromethane gives Cp_2ZrCl_2 quantitatively (eq 14).[15]

$$CH_2Cl_2 + Cp_2ZrH_2 \longrightarrow CH_4 + Cp_2ZrCl_2 \qquad (14)$$

Reaction with Alcohols.

Cp_2ZrH_2 readily reacts with alcohols to form the corresponding alkoxy complexes (eq 15).[16]

$$Cp_2ZrH_2 + 2\,ROH \longrightarrow Cp_2Zr(OR)_2 + Zr(OR)_4 \qquad (15)$$

Reaction with Carboxylic Acid and Acetone.

The addition of Cp_2ZrH_2 to excess glacial acetic acid in THF affords $Cp_2Zr(OAc)_2$ (eq 16).[16] Similarly, the slow addition of acetone to a suspension of Cp_2ZrH_2 in THF forms $Cp_2Zr(O\text{-}i\text{-}Pr)_2$ (eq 17).[17]

$$Cp_2ZrH_2 + MeCO_2H \xrightarrow{THF} Cp_2Zr(OAc)_2 \qquad (16)$$

$$Cp_2ZrH_2 + MeCOMe \xrightarrow{THF} Cp_2Zr(O\text{-}i\text{-}Pr)_2 \qquad (17)$$

Reaction with Carbon Monoxide.

The carbonylation of Cp_2ZrH_2 occurs at room temperature to yield an η-formaldehyde-zirconocene complex in a low yield (eq 18).[18] This η-acyl zirconium complex reacts with Cp_2ZrH_2 to form a dinuclear μ-aldehyde-zirconocene hydride complex (eq 19).[18]

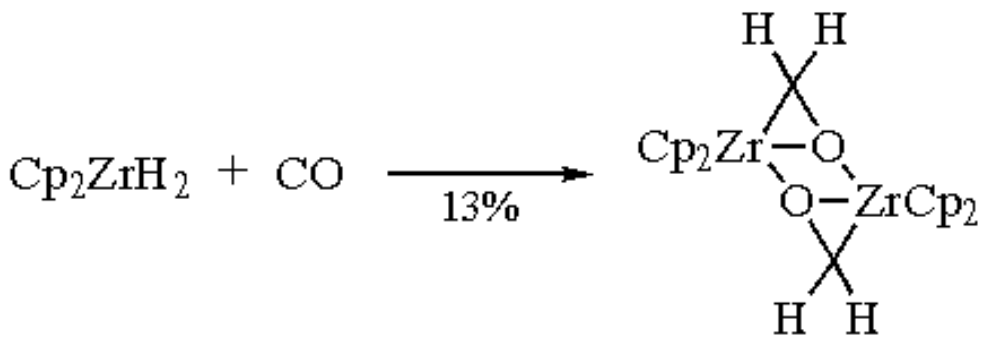

(18)

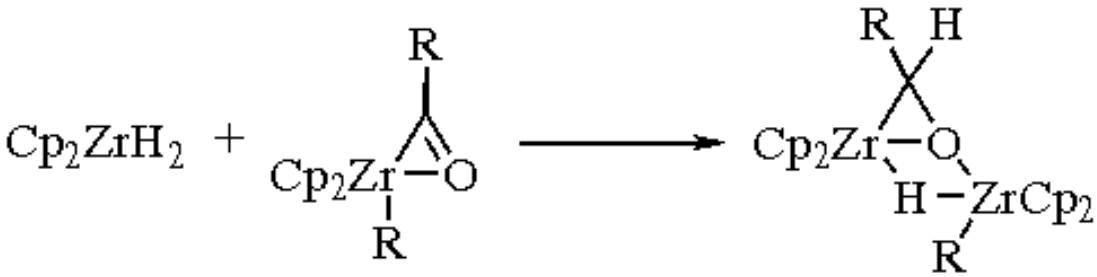

(19)

R = Me, 34%; Ph, 57%

Reaction with Organoborane and Aluminum Complexes.

Cp_2ZrH_2 with ***Borane-Tetrahydrofuran*** or ***Catecholborane*** affords quantitatively $Cp_2Zr(BH_4)_2$ (eqs 20 and 21).[16] When Cp_2ZrH_2 is treated with ***Triethylaluminum*** pale blue product, which is not stable in solution, is obtained. The dinuclear structure is proposed on the basis of ^1H NMR and IR spectra (eq 22).[19]

$$Cp_2ZrH_2 + 2\,H_3B \cdot THF \longrightarrow Cp_2Zr(BH_4)_2 \qquad (20)$$

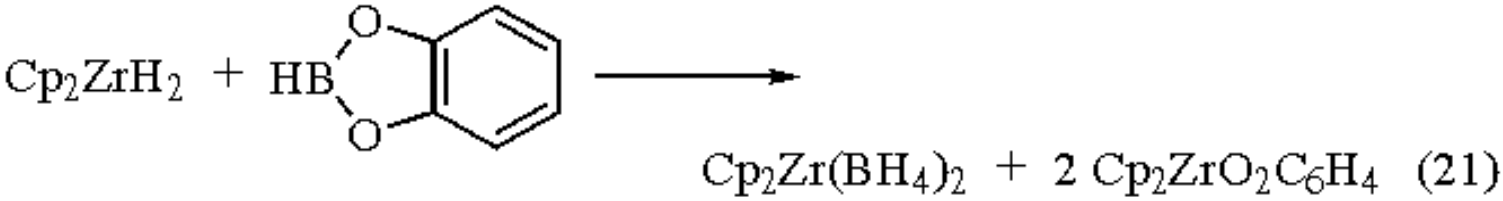

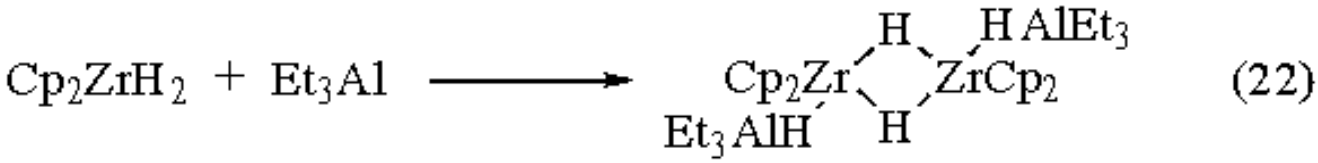

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Kansai University, Osaka, Japan

Bis(η^5-cyclopentadienyl)(diiodozinc)(μ-methylene)titanium[1]

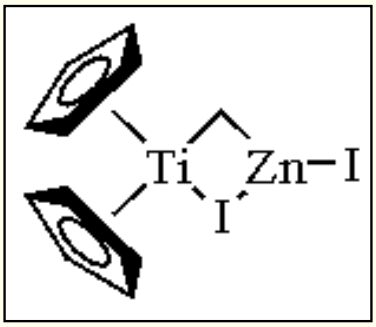

[87370-10-3] · $C_{11}H_{12}I_2TiZn$ · Bis(η^5-cyclopentadienyl)(diiodozinc)(μ-methylene)titanium · (MW 511.28)

(reagent for methylenation of ketones; methylation of nitriles and alkynes; coupling reagent for conversion of benzyl halides to bibenzyl)

Physical Data: δ_H (toluene-d_8) 8.37 (2H), 5.92 (10H).

Solubility: sol THF and toluene at rt; precipitates from THF at -78 °C to give a deep-red $Cp_2TiCH_2.ZnI_2.(THF)_x$ complex.

Analysis of Reagent Purity: concentration can be determined by reaction of originally prepared THF solution with benzophenone to form 1,1-diphenylethylene.

Preparative Methods: $Cp_2TiCH_2.ZnI_2$ is readily generated by the reaction of Cp_2TiCl_2 with $CH_2(ZnI)_2$ in THF.[1]

Handling, Storage, and Precautions: moisture sensitive; must be manipulated under a nitrogen atmosphere; presumably pyrophoric.

Methylenation and Other Reactions.[1]

$Cp_2TiCH_2.ZnI_2$ has been compared[1,2] to the structurally related Tebbe reagent (***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***) and reacts in an analogous way with both cyclic and acyclic ketones to give the corresponding alkene (eqs 1 and 2).

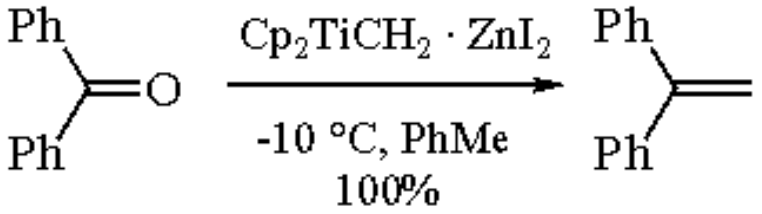

(1)

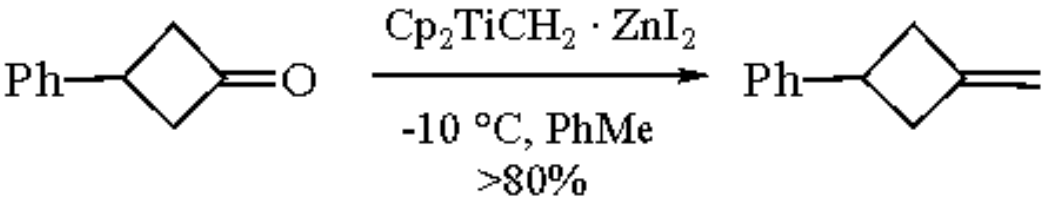

(2)

However, unlike the Tebbe reagent, $Cp_2TiCH_2.ZnI_2$ does not appear to form the methyl ketone, to any significant extent, when it reacts with acid chlorides. For example, reaction of the title reagent with benzoyl chloride affords only small amounts (ca. 20%) of acetophenone, the main product arising from ring-opening of the complexed THF which yields the benzoate of 4-chloro-1-butanol (eq 3). The reagent effects the reductive coupling, presumably via an electron transfer process, of active halides such as benzyl bromide or chloride, and bibenzyls are produced (eq 4).

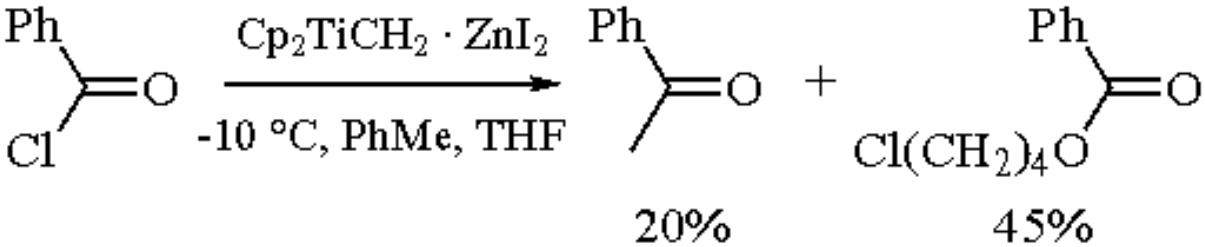

(3)

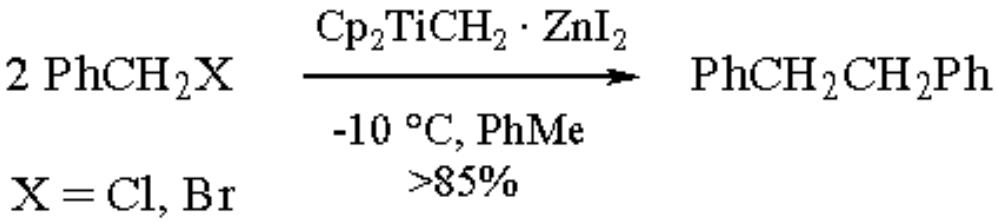

(4)

While $Cp_2TiCH_2.ZnI_2$ fails to react with imines, treatment of the reagent with benzonitrile gives acetophenone upon aqueous workup. The observation that α-deuteroacetophenone is formed when D_2O is used in the quenching step supports the intermediacy of a metallocycle (eq 5) in this process.

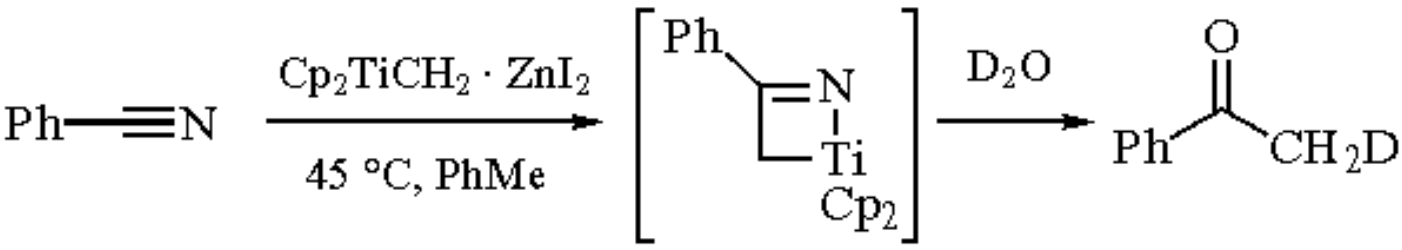

(5)

Analogous metallocycles are formed when the reagent is allowed to react with alkynes, and hydrolytic cleavage of such intermediates then leads to net *syn* addition of the elements of methane across the original triple bond. The reaction of phenylacetylene with $Cp_2TiCH_2.ZnI_2$ then D_2O is representative (eq 6). However, methylenative dimerization is the

major reaction pathway, and this process involves initial self-condensation of the metallocycle to produce a second intermediate which upon reaction with D_2O affords, when phenylacetylene is used as substrate, a 3:1 mixture of diphenyl-1,5-hexadienes (eq 6).

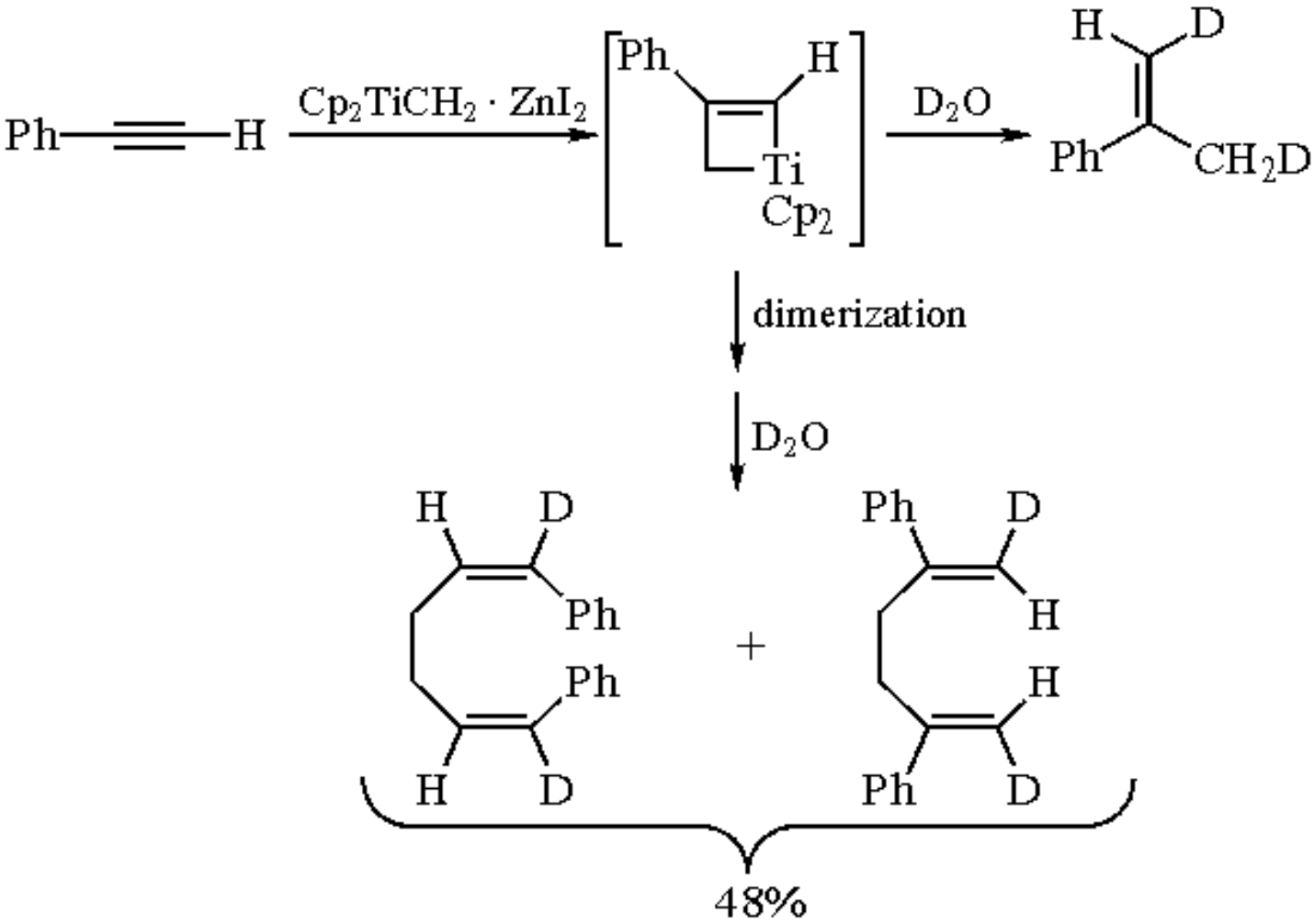

(6)

The reaction of 1-trimethylsilyl-1-octyne with $Cp_2TiCH_2.ZnI_2$ (eq 7) differs in two respects from that of the preceding alkyne in that: (i) small amounts of an allene are formed (presumably by a β-hydride elimination) and (ii) the principal methylenated dimers have the structures shown, and these probably arise by a process involving insertion into an allylic C-Zn bond. Deuterium-labeling studies are consistent with such mechanistic proposals which involve the intermediacy of a common metallocycle. Some 32% of the product mixture consisted of the same methylated vinylsilane as formed from reaction of the substrate with Cp_2TiCl_2 and $MeAlCl_2$.

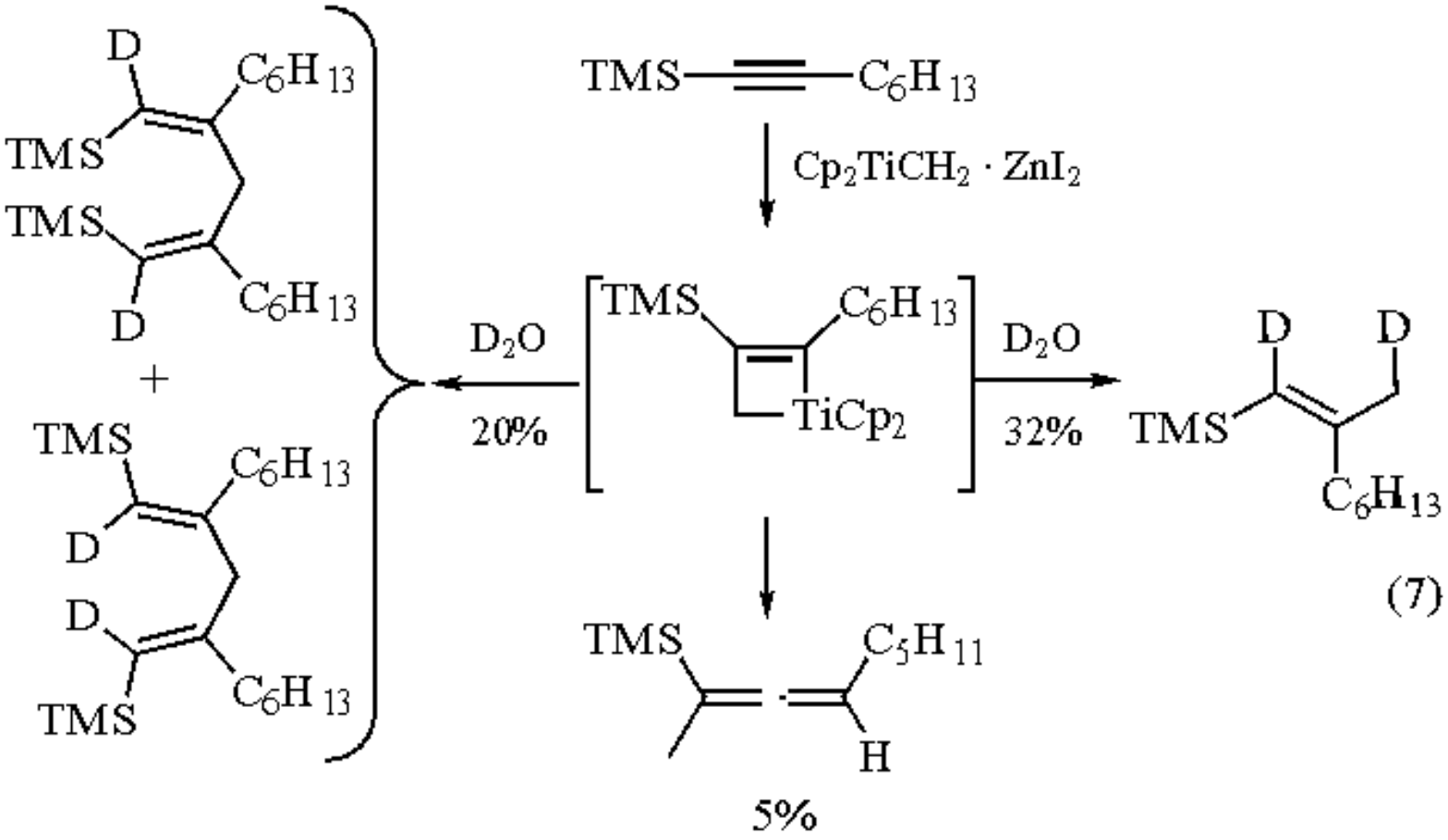

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Bis(cyclopentadienyl)dimethyltitanium[1]

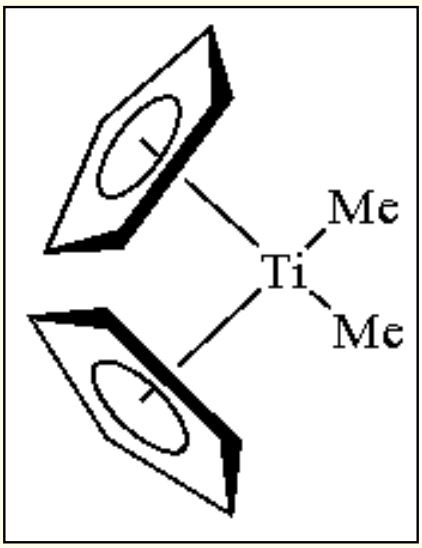

[1271-66-5] · $C_{12}H_{16}Ti$ · Bis(cyclopentadienyl)dimethyltitanium · (MW 208.14)

(reagent of low basicity and acidity, useful for the methylenation of carbonyl compounds;[2] methylenates highly enolizable ketones,[2] esters[2] and lactones,[2] including aldonolactones[3] and acid-labile substrates;[4] homologs of the reagent perform carbonyl alkylidenations;[5-7] reacts with alkynes[8,9] and nitriles[8-10] and can initiate the ring-opening metathesis polymerization of strained cyclic alkenes;[11] it is a useful precursor for Ziegler-Natta polymerization catalysts,[12] a cocatalyst for alkene metathesis[13] and a catalyst for alkene hydrogenation[14] and the dehydrogenative coupling of silanes[15,16])

Alternate Name: dimethyltitanocene.

Physical Data: mp >90 °C dec.

Solubility: sol most aprotic organic solvents, e.g. Et_2O, THF, CH_2Cl_2, toluene, hexanes.

Form Supplied in: orange crystals; not available commercially.

Analysis of Reagent Purity: ^{1}H NMR (250 MHz, C_6D_6) δ 0.04 (s, 6H), 5.69 (s, 10H).

Preparative Method: [17] a solution of ***Methyllithium*** (2.1 equiv) in Et_2O is added dropwise to a suspension of ***Dichlorobis(cyclopentadienyl)titanium*** in Et_2O (3-5 mL mmol^{-1}) cooled in an ice bath. After 1 h the reaction mixture is quenched with ice water, the ether layer is separated, dried over $MgSO_4$, filtered and evaporated. The resulting bright orange crystals of the reagent, obtained in 95% yield, are dissolved in THF or toluene and stored in the dark, in the refrigerator or freezer.

Handling, Storage, and Precautions: sensitive to oxygen and light, but can be briefly exposed to air and water. In the solid state the reagent is not stable for more than a few hours at rt, but it can be stored for months in the dark as a THF or toluene solution. Although it is stable in solution at rt, the reagent is best stored in a refrigerator.

Methylenation of Carbonyl Compounds.[2]

Although the Wittig reagent[18] $CH_2{=}PPh_3$ (see ***Methylenetriphenylphosphorane***) and several other P-, Si-, or S-stabilized methylene anions[19] are commonly used for the methylenation of aldehydes and ketones, these reagents have several synthetic limitations due to their inherent basicity. Wittig-type alkenations generally fail with readily enolizable carbonyls or substrates that undergo a facile nucleophilic addition or elimination. Furthermore, sterically hindered substrates are often methylenated in low yields, while the alkenation of esters and lactones is usually not possible with these methods. Several Ti-based methylenation procedures[1c] have been developed that avoid most of the problems encountered with Wittig-type processes. The combination of ***Dibromomethane-Zinc-Titanium(IV) Chloride***,[20] particularly Lombardo's reagent,[21] is useful for the methylenation of sterically hindered and highly enolizable aldehydes and ketones. The similar reagent CH_2I_2-Zn-$TiCl_4$[22] is also used for this purpose, while two other variations, CH_2I_2-Zn-Ti(O-*i*-Pr)$_4$ and CH_2I_2-Zn-Me_3Al, allow the chemoselective methylenation of aldehydes in the presence of ketones.[23] Another widely used reagent is the Tebbe reagent (see ***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***),[1b,1c,24,25] which is useful for the methylenation of a variety of carbonyls, including aldehydes, enolizable ketones, esters and lactones. This reagent, however, is not suitable for highly acid-labile substrates and requires stringent inert atmosphere techniques due to its high sensitivity to air and water.

Dimethyltitanocene is an experimentally convenient alternative to the Tebbe reagent.[2] It is easier to prepare and handle and is suitable for the methylenation of aldehydes, ketones, esters, and lactones, including highly enolizable and acid-labile substrates. Heating a solution of a carbonyl compound and Cp_2TiMe_2 (1-3 equiv) in the dark at 60-80 °C, in a sealed flask or under argon, results in a clean and efficient methylenation. Unlike the reactions of the Tebbe reagent, this procedure does not require aqueous workup. The product can be isolated by precipitation of the yellow titanium oxide byproduct, filtration and purification by chromatography or distillation. Although the yields for the methylenation of aldehydes are moderate (eq 1),[2] the reaction works well for alkyl and aryl ketones (eq 2),[2] as well as for cyclic ketones (eq 3).[26]

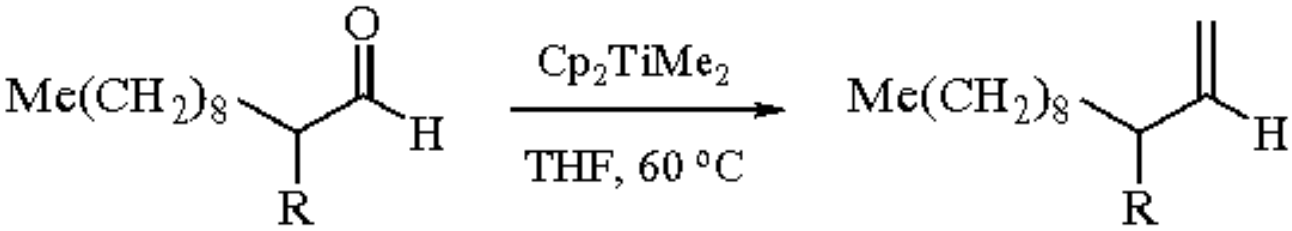

(1)

R = H 48%
R = Me 62%

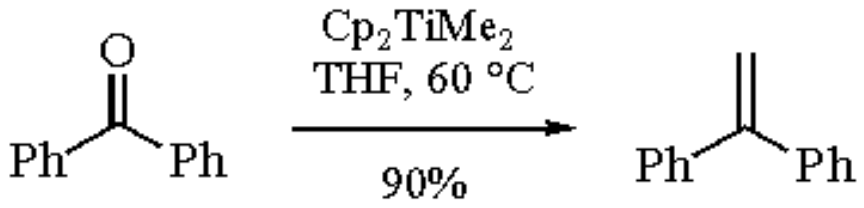

(2)

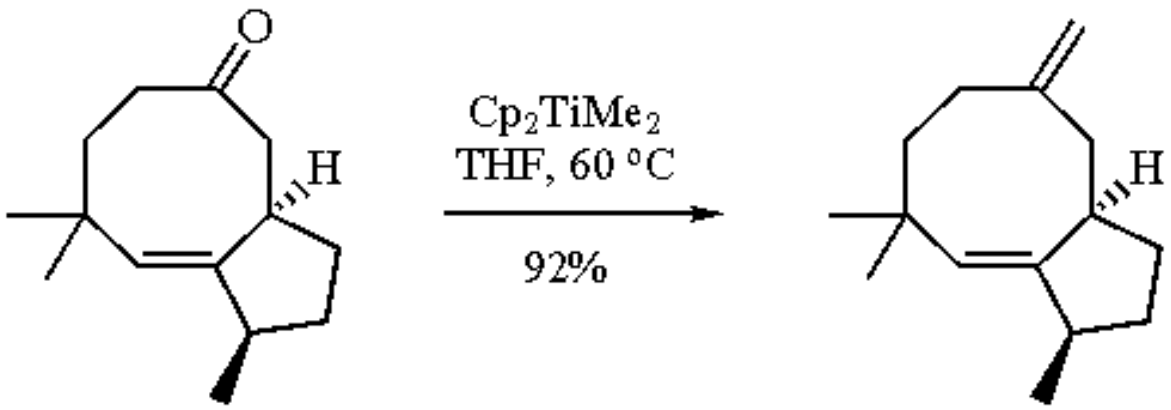

(3)

Aldehydes (eq 4)[27] and ketones (eq 5)[2] are methylenated faster than esters or lactones. Due to its suppressed basicity and similarity to the Tebbe reagent[28] and Takai's procedure,[22] Cp_2TiMe_2 also methylenates highly enolizable ketones (eq 6).[2]

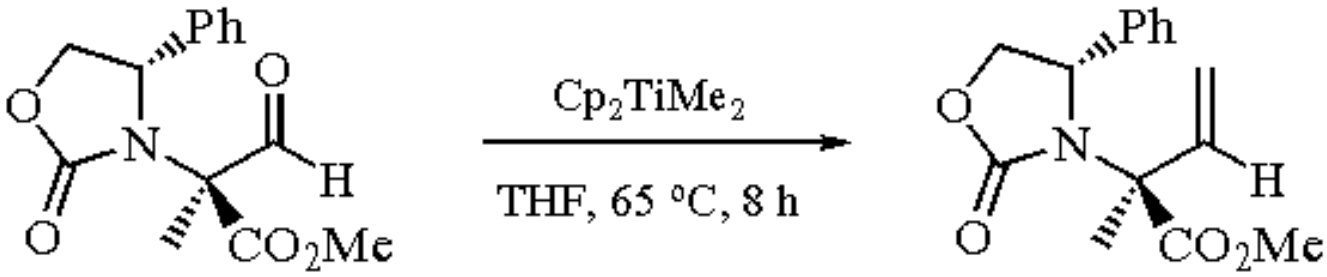

(4)

52% @ 62% completion

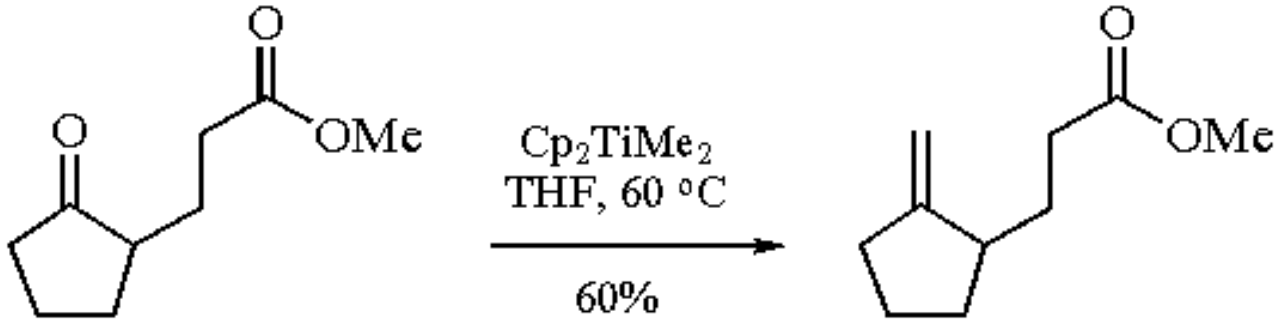

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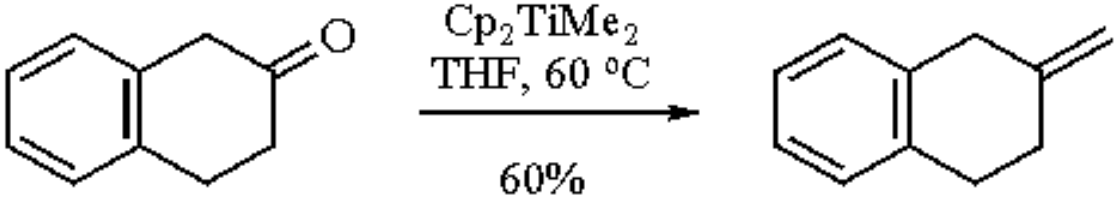

(6)

Esters (eq 7)[2] and lactones (eq 8),[29] including aldonolactones (eq 9),[3] are efficiently methylenated with this reagent. Since the resulting enol ether products undergo facile acid-catalyzed hydrolysis, their isolation and purification should be done under basic conditions. Highly acid-sensitive substrates, such as spiroketal lactones (eq 10)[4] which decompose with the Tebbe reagent, can be readily methylenated with Cp_2TiMe_2.

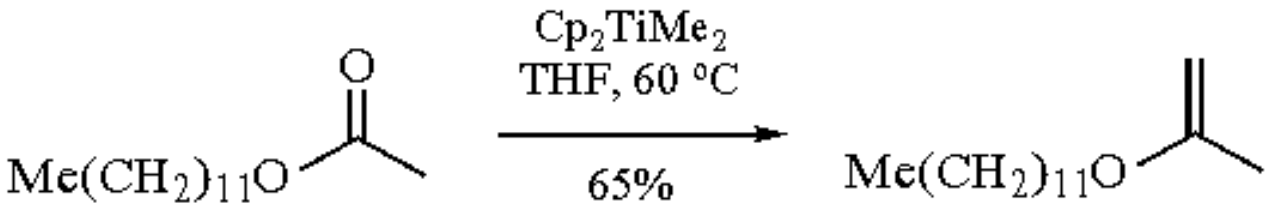

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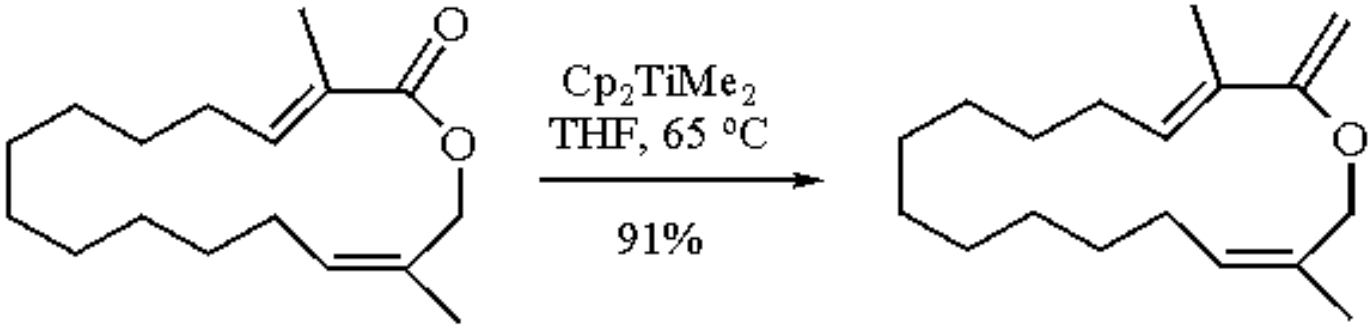

(8)

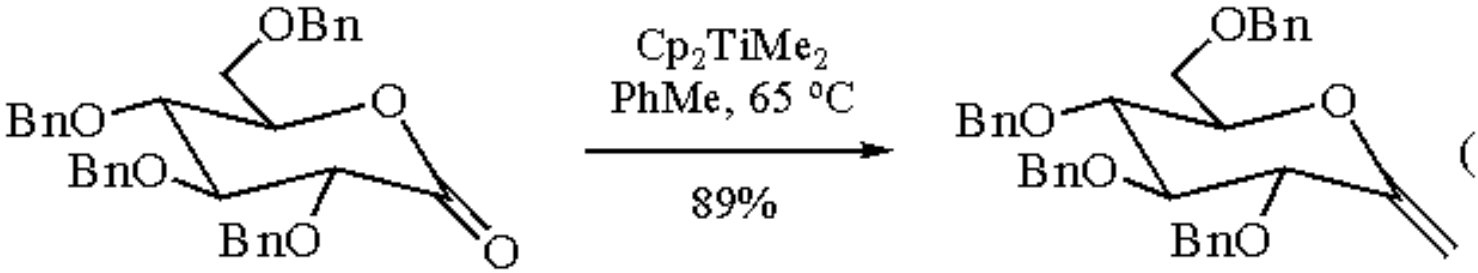

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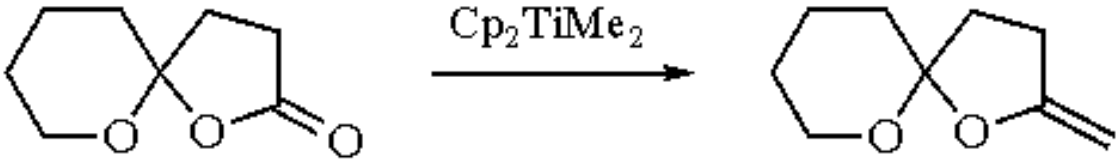

(10)

Alkylidenations of Carbonyl Compounds.

While homologs of the Tebbe reagent are difficult to prepare, the corresponding dialkyltitanocene derivatives are readily prepared from Cp_2TiCl_2 and alkyllithium or Grignard reagents. With the exception of compounds that undergo facile β-hydride elimination, dialkyltitanocenes are adequately stable for isolation in a pure form. Thermolysis of such derivatives in the presence of aldehydes, ketones, esters, lactones, or amides, results in carbonyl alkylidenation. Thus dibenzyltitanocene gives benzylidenation products (eq 11),[5] bis(trimethylsilylmethyl)titanocene forms vinylsilanes (eq 12),[6] while bis(cyclopropyl)titanocene forms cyclopropylidenes (eq 13).[7]

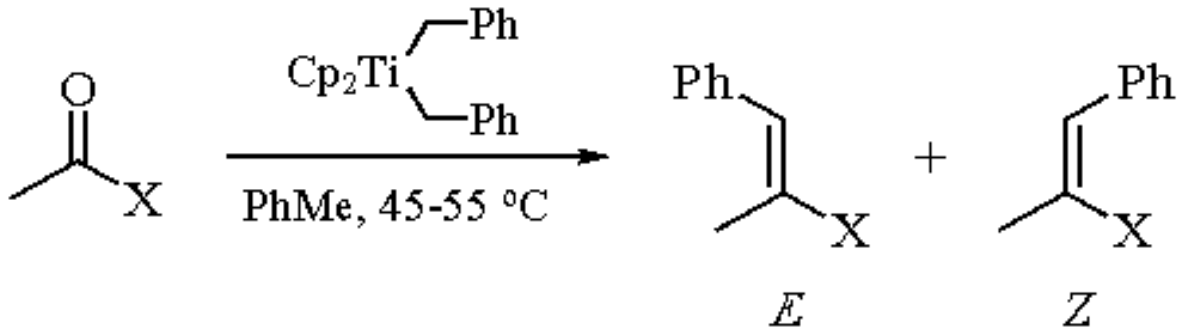

(11)

X = O(CH$_2$)$_{11}$Me	80%	60:40
X = NMe$_2$	45%	71:29

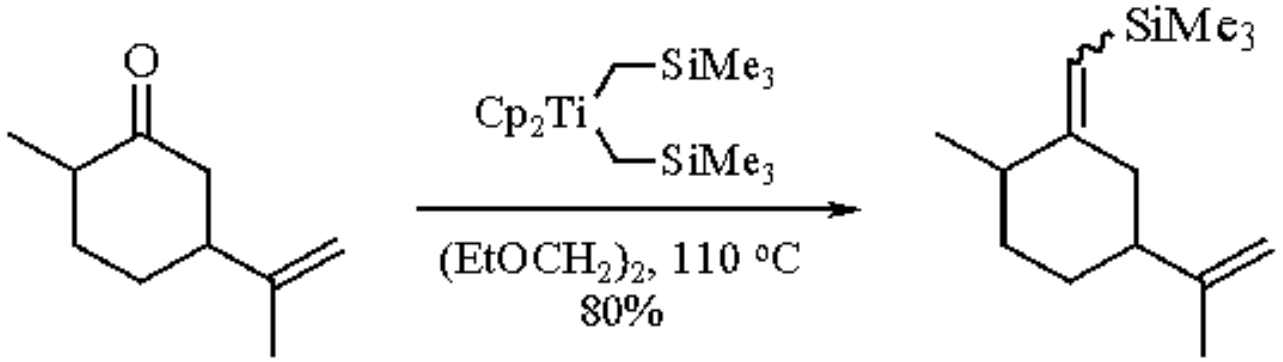

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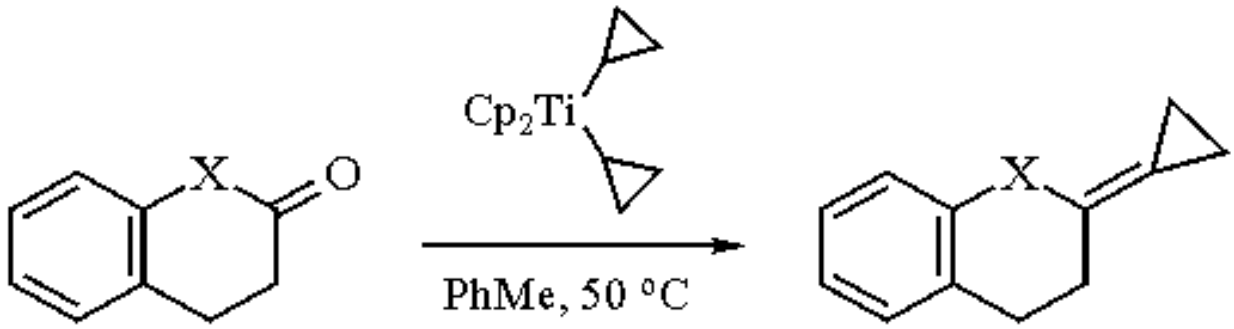

(13)

X = CH$_2$	70%
X = O	67%

Formation of Titanium Enolates with $(C_5Me_5)_2TiMe_2$.

The pentamethyl-Cp derivative $(C_5Me_5)_2TiMe_2$ behaves differently from Cp_2TiMe_2. Upon thermolysis it forms a reactive titanium methylidene species which undergoes insertion into one of the Cp methyl groups.[30] Rather than carrying out methylenations, $(C_5Me_5)_2TiMe_2$ reacts with ketones to form titanium enolates with a high degree of regio- and stereocontrol (eq 14).[31] It also forms similar enolates from epoxides (eq 15).[32]

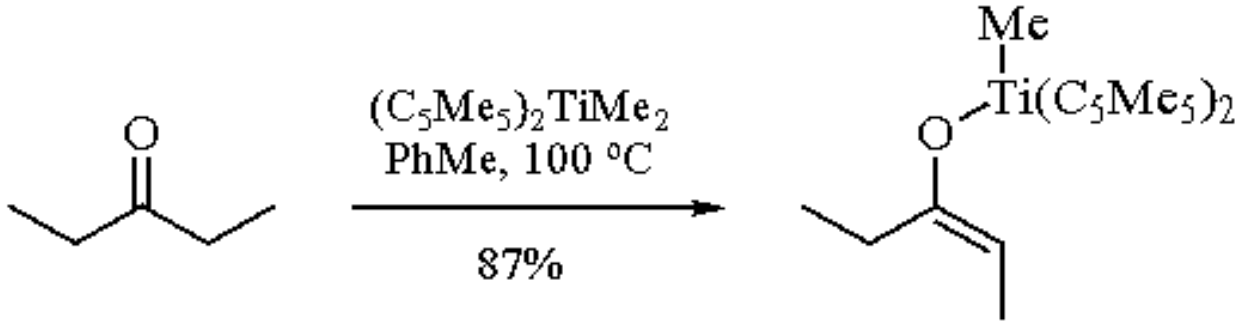

(14)

$E:Z = 180:1$

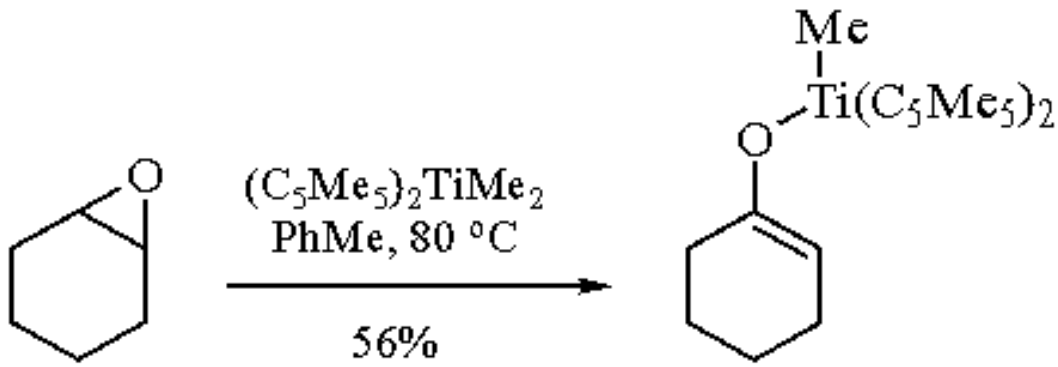

(15)

Reactions with Alkynes.

Although addition-elimination pathways are also possible,[2,8,9] it is likely that the thermolysis of Cp_2TiMe_2 generates the highly reactive intermediate $Cp_2Ti{=}CH_2$, which can be trapped by various substrates. In the case of alkynes, clean quantitative conversions to the corresponding titanacyclobutenes take place.[8,9] Titanacyclobutenes[33] can also be prepared with the Tebbe reagent, and they react with aldehydes, ketones, nitriles, and other electrophiles to give a variety of titanium-free products (eq 16).[8] Interestingly, the reaction of Cp_2TiMe_2 with alkynes under photolytic conditions forms titanacyclopentadienyl derivatives,[34] presumably via a titanocene (Cp_2Ti) intermediate.

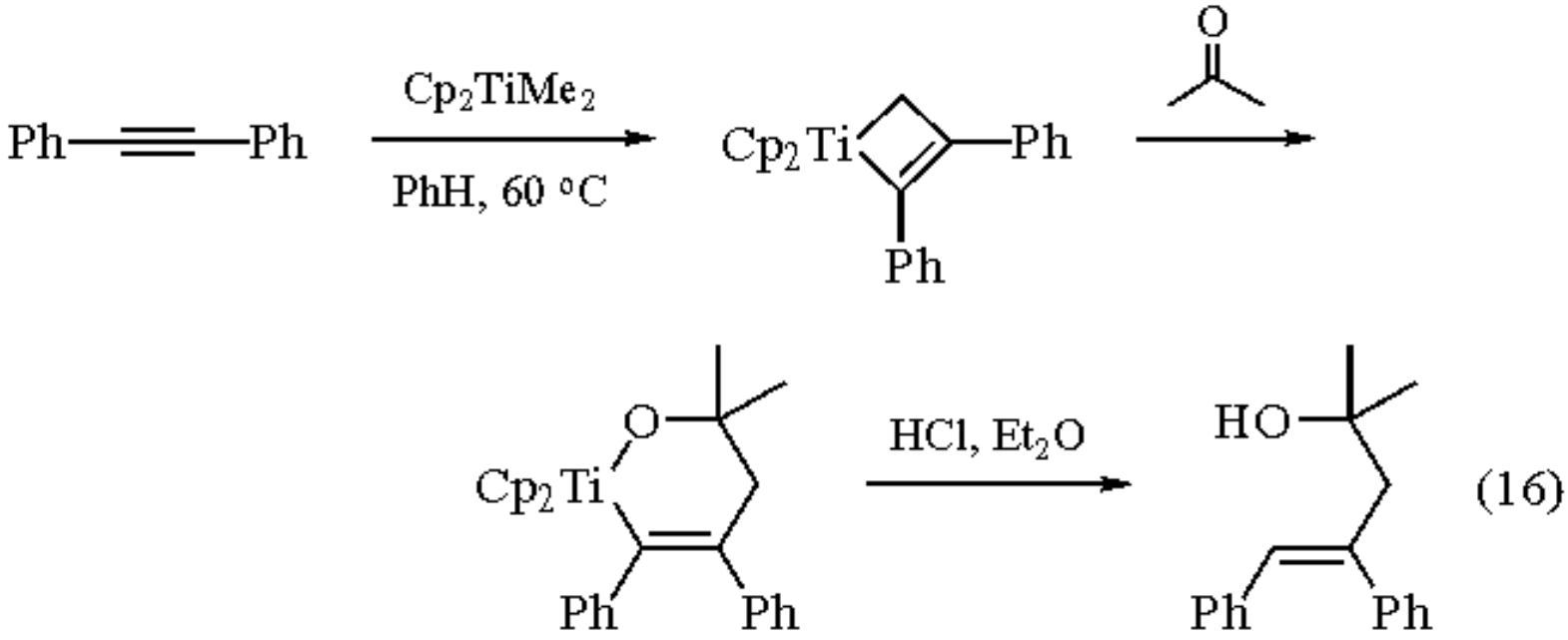

Reactions with Nitriles.

Thermolysis of Cp_2TiMe_2 in the presence of nitriles (2 equiv) generates 1,3-diazatitanacycles,[8-10] which can be hydrolyzed to 4-amino-1-azadienes (eq 17).[10]

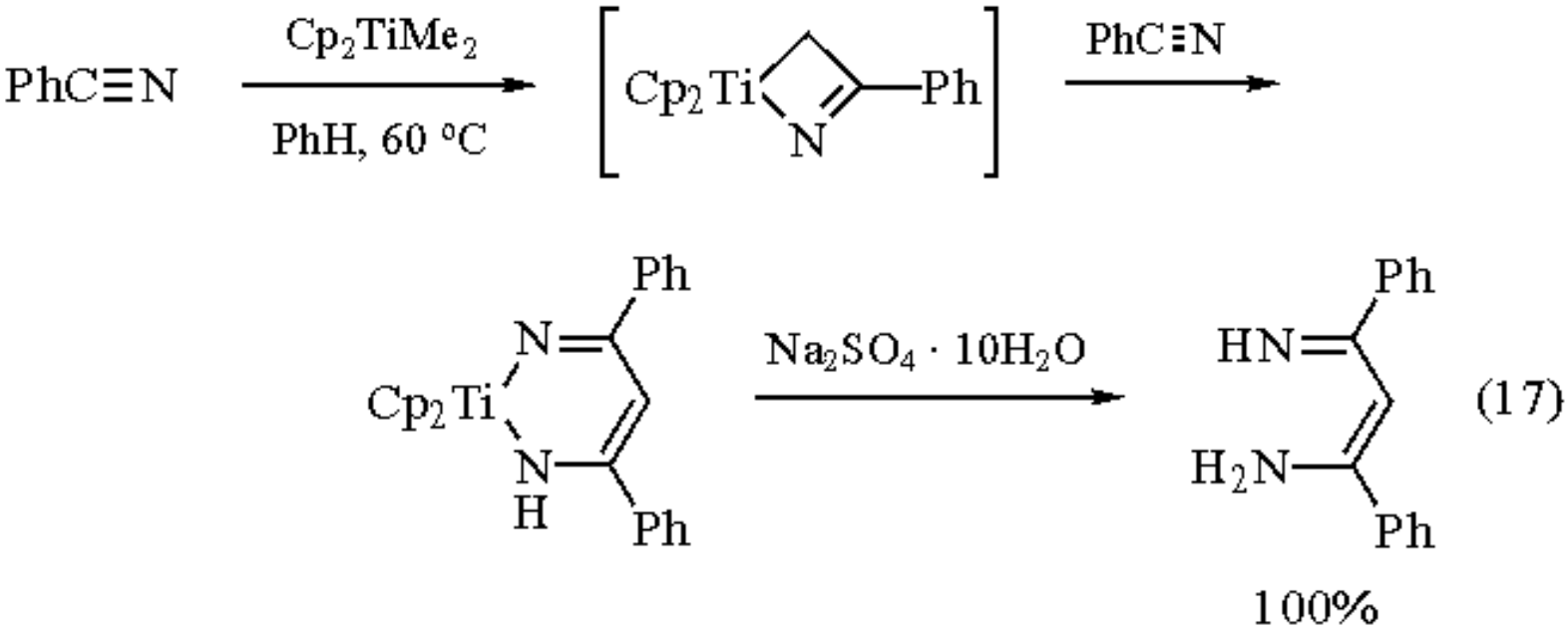

Ring-Opening Metathesis Polymerization.

Norbornene readily undergoes ROMP with Cp_2TiMe_2 and other dialkyltitanocenes (eq 18).[11]

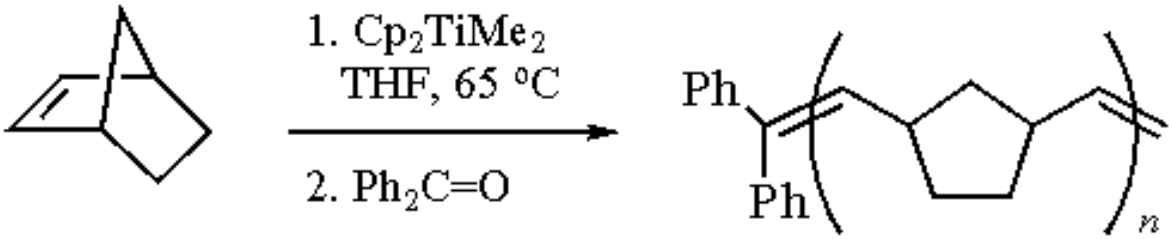

(18)

Alkene Metathesis.

Among other related systems, the combination of Cp_2TiMe_2 with $WOCl_4$ shows the best catalytic activity for alkene metathesis (eq 19).[13]

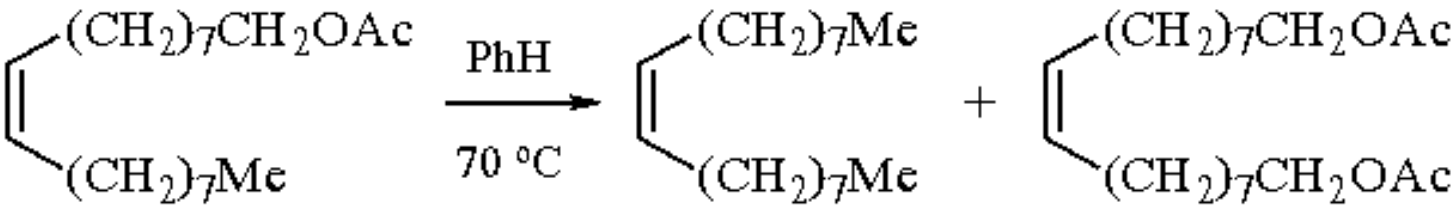

(19)

Cp_2TiMe_2, $WOCl_4$	43%	45%
$Cp_2TiClMe$, $WOCl_4$	41%	39%
Cp_2ZrMe_2, WCl_6	30%	36%
Cp_2TiMe_2, WCl_6	39%	16%

Ziegler-Natta Polymerization of Alkenes.

In combination with Al compounds or other acids,[35] dialkyltitanocenes generate cationic titanocene complexes[12] which catalyze the Ziegler-Natta polymerization of alkenes (eq 20).[36-38]

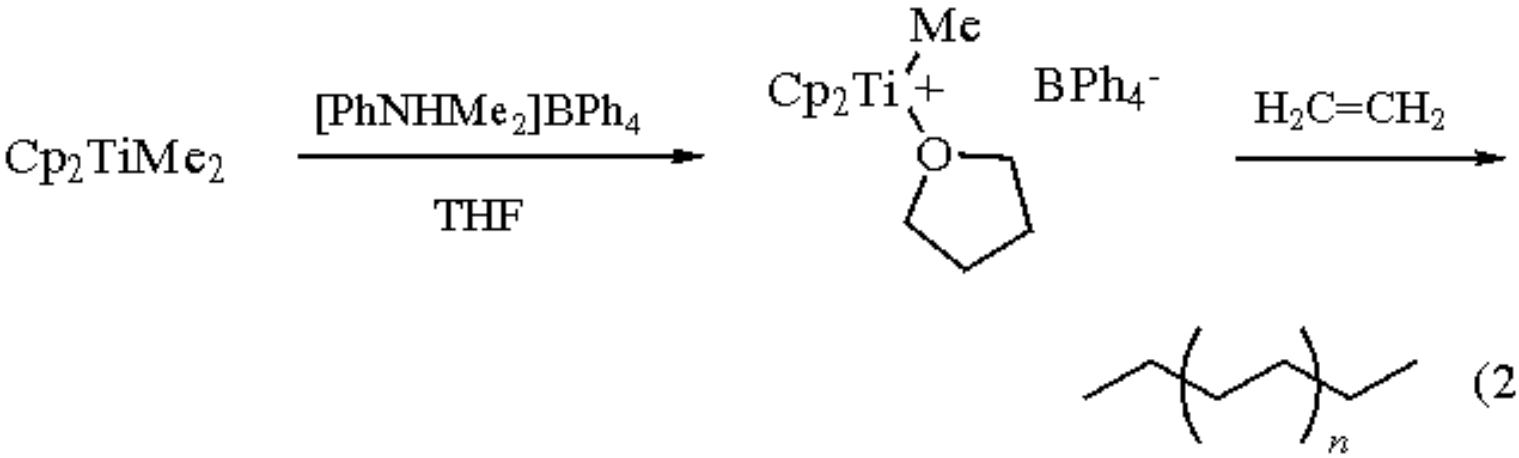

(20)

Hydrogenation of Alkenes.

A variety of dicyclopentadienyl Ti derivatives, including Cp_2TiMe_2, can catalyze the hydrogenation of alkenes, presumably via a Ti-H species (eq 21).[14]

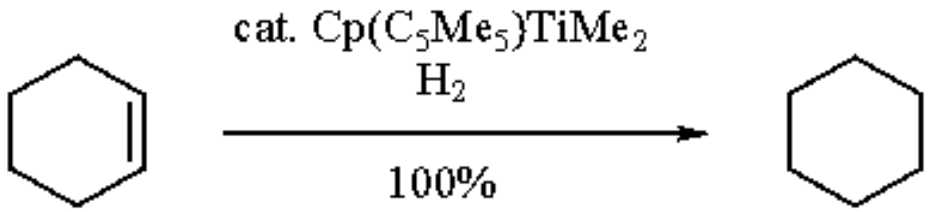

(21)

Reactions with Silanes.

In the presence of catalytic amounts of Cp_2TiMe_2[15] or other similar derivatives,[16,39] hydrosilanes undergo dehydrogenative coupling to form oligomers and polymers (eq 22).[15] Alkene hydrogenation, isomerization, or hydrosilylation occurs when an alkene is present,[40,41] while in ammonia a different type of dehydrocoupling takes place (eq 23).[42]

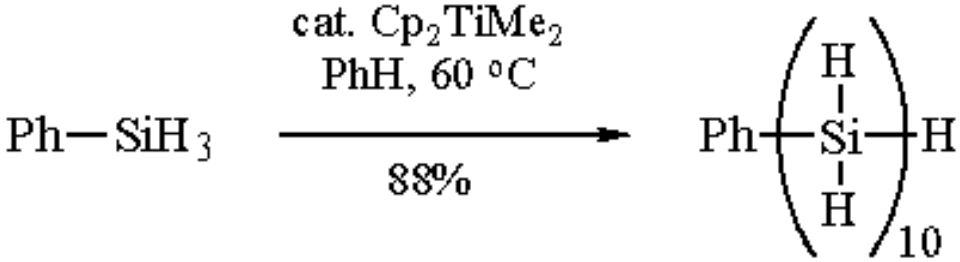

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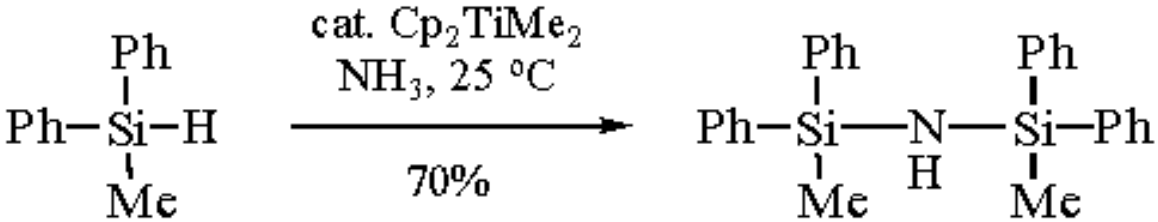

(23)

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Bis(cyclopentadienyl)-3,3-dimethyltitanacyclobutane[1]

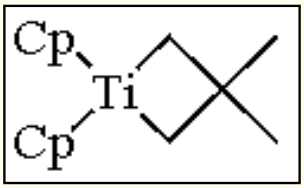

[80122-07-2] · $C_{15}H_{20}Ti$ · Bis(cyclopentadienyl)-3,3-dimethyltitanacyclobutane · (MW 248.20)

(methylenating agent for alkenation of carbonyl compounds, particularly esters, ketones, and aldehydes;[1a,c] of low basicity and functions without epimerization at α-chiral centers; catalyst precursor in living ring-opening metathesis polymerization[1b])

Solubility: very sol dichloromethane, diethyl ether, and toluene; moderately sol pentane.[2]

Form Supplied in: red crystalline solid.

Analysis of Reagent Purity: by ^{1}H NMR (toluene-d_8, -10 °C)[3] or by bromination in ether at -20 °C followed by quantitation of the 1,3-dibromo-2,2-dimethylpropane product by GC.[4]

Preparative Methods: most often prepared from the Tebbe reagent (**1**) by reaction with isobutene and 4-dimethylaminopyridine in dichloromethane.[3] Alternatively, may be formed in 89% yield from Cp_2TiCl_2 and a 1,3-di-Grignard reagent, which is in turn obtained from 1,3-dibromo-2,2-dimethylpropane in 18% yield.[4,5]

Purification: may be recrystallized by slow cooling of a toluene solution from 0 °C to -78 °C under an inert atmosphere. Recrystallization from diethyl ether is also effective.

Handling, Storage, and Precautions: the title reagent (**2a**) may be stored indefinitely under nitrogen atmosphere, preferably in the dark. Although this titanacycle is moderately air- and water-sensitive, it may be handled in air for brief periods. In solution this complex is labile and will decompose to give the purple dimer $[Cp_2Ti(\mu\text{-}CH_2)]_2$,[6] as well as isobutene and other uncharacterized products. Solutions should be prepared at 0 °C and used immediately.[2]

Reactivity of Titanacyclobutanes.

A number of titanacyclobutane complexes (e.g. (**2a-e**)) have been efficiently prepared from Tebbe reagent (**1**) (***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***)[1c,2,7-9] and studied in significant detail (eq

1).[1] Typically pyridine bases are used; ether or tetrahydrofuran as bases give equilibrium concentrations of (**1**) and (**2**).[10] Certain titanacyclobutanes may be prepared in variable yields from 1,3-di-Grignard reagents;[4,5,11] a few examples are shown in eq 2. Very recently a route to titanacyclobutanes via cationic π-allyl species was demonstrated.[12] Also, titanacyclobutanes may be prepared by reaction of alkenes with less stable titanacyclobutanes.[3,8,9] These metallacycles cleave to afford $Cp_2Ti{=}CH_2$ (as the free methylidene or, more likely, an alkene complex[13]) as shown in the ester to vinyl ether conversion of eq 3.[1a,1c,14]

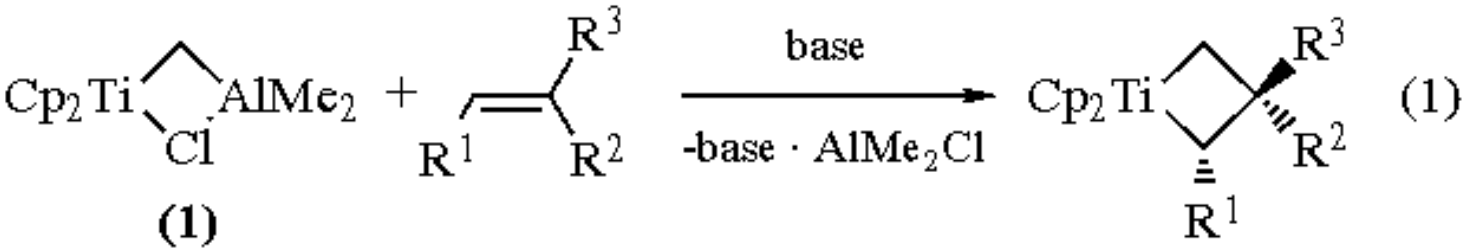

(2a) $R^1 = H$; $R^2, R^3 = Me$
(2b) $R^1 = H$; $R^2 = Me$; $R^3 = n\text{-Pr}$
(2c) $R^1, R^2 = H$; $R^3 = t\text{-Bu}$
(2d) $R^1, R^2 = H$; $R^3 = i\text{-Pr}$
(2e) $R^1, R^2 = (CH_2)_3$; $R^3 = H$

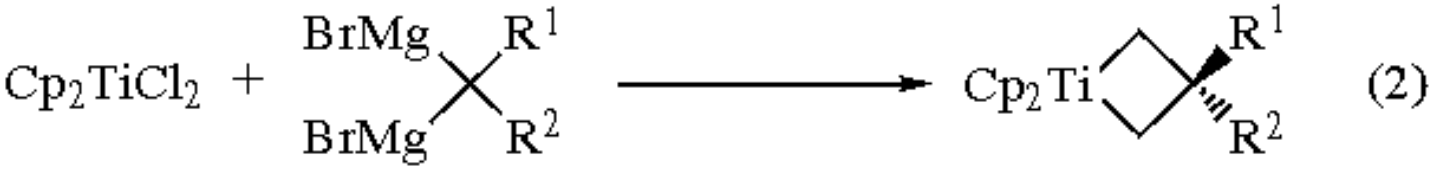

(2)

(2a) $R^1 = R^2 = Me$
(2c) $R^1 = H$; $R^2 = t\text{-Bu}$
(2f) $R^1 = R^2 = H$
(2g) $R^1 = H$; $R^2 = Me$

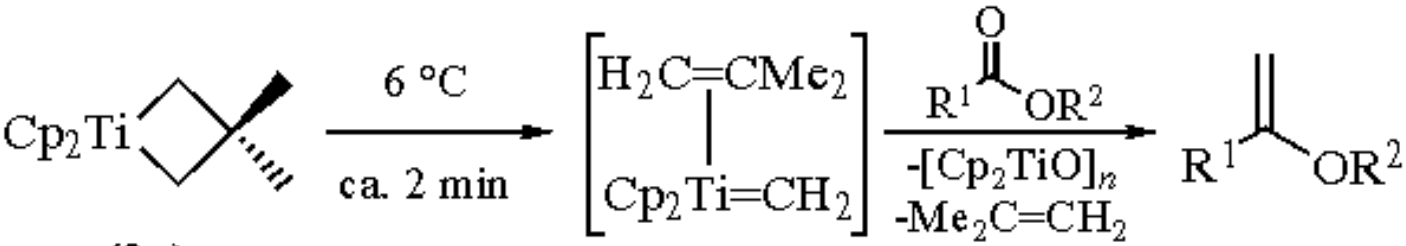

(3)

The titanacyclobutanes may thus serve as aluminum-free alternatives to the Tebbe reagent for methylenation of a range of carbonyl compounds. Another application which involves retro 2 + 2 cleavage of metallacycles is the ring-opening metathesis polymerization (ROMP) of strained cycloalkenes via substituted methylidene intermediates (see below).[1b] As methylidene sources the titanacyclobutanes offer advantages over (**1**); primarily in avoidance of side reactions due

to acidic aluminum species, ease of workup, and lesser air sensitivity. However, titanacyclobutanes have not been as widely employed because they are not commercially available and preparation requires Schlenk line and glovebox techniques.

The titanacyclobutanes undergo a number of potentially useful reactions in which the carbon skeleton of the ring remains intact in products such as alkanes, 1,3-dibromides, cyclopropanes, and acyloins. These products may be conveniently obtained from titanacycles formed in situ from (**1**).[1a]

Titanacyclobutanes as Methylidene Precursors.

Most titanacyclobutanes, including (**2a-e**), thermally cleave by a retro 2 + 2 process to liberate alkene and afford the reactive methylidene species $Cp_2Ti{=}CH_2$, or an alkene complex thereof, as shown in eq 3.[1f,13,14] Thus much of the chemistry of these metallacycles is qualitatively similar to that of the Tebbe reagent (**1**).[1c] For example, the titanium methylidene so produced affords vinyl ethers from a wide range of esters (eq 3), a conversion which is not possible using Wittig alkylidene phosphorane reagents.[15] Aldehydes and ketones are likewise methylenated and reaction takes place without epimerization at α-chiral centers,[1a] a frequent problem when using highly basic Wittig conditions.[16] Yields in these methylenations are generally good to excellent. The intermediate titanaoxacyclobutanes are not observed in these transformations, although stable analogs having β-alkylidene substitution have been characterized.[17] This methylenation chemistry has been the subject of a recent comprehensive review.[1c]

Different reactivity is observed for the titanacycles with acid chlorides as shown in eq 4.[18] The titanium enolates of methyl ketones which result do not undergo double-bond isomerization, and are useful in the aldol reaction. Although the Tebbe reagent shows similar reactivity, yields are much lower.[19] Reaction of the titanacyclobutanes with sterically hindered ketones also affords titanium enolate complexes; however, these are not active in the aldol reaction.[20] Reaction with anhydrides also gives enolate complexes which are not active in the aldol reaction. By contrast, unhindered imides may be methylenated in good yield with excellent selectivity in unsymmetrical cases.[21]

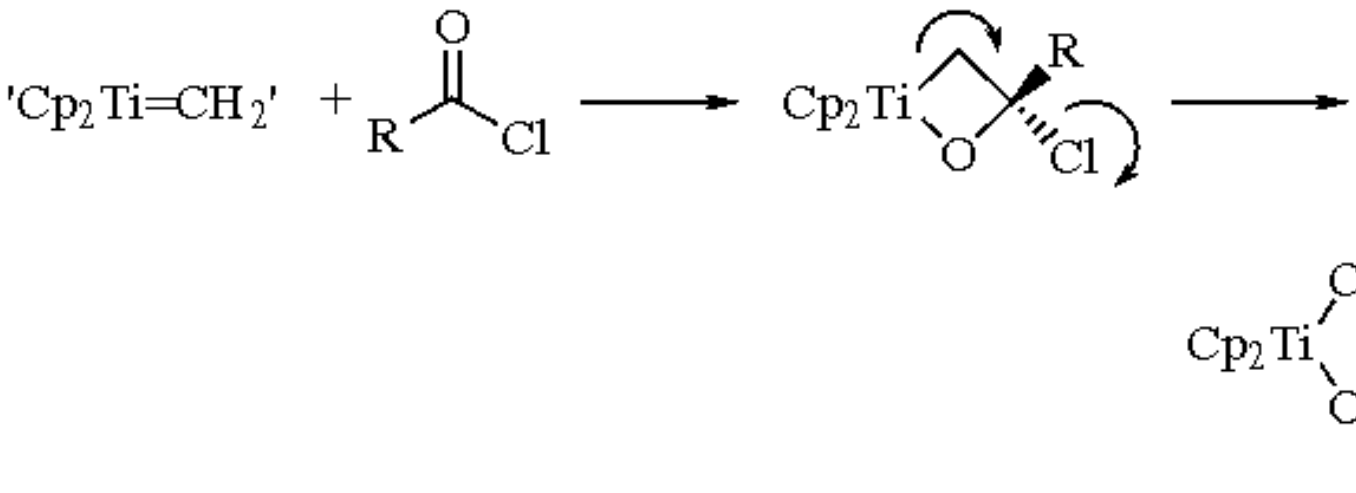

(4)

Reaction with certain alkyl halides occurs to give titanocene alkyl halides $[Cp_2Ti(Cl)CH_2R]$ via a radical mechanism.[22]

Although α-alkyl substituted titanacyclobutanes (e.g. **2h**, see eq 6) are thermally unstable,[10] α-alkylidene substitution is favorable[23-25] and leads to a versatile synthesis (via titanium vinylidene intermediates) of substituted allenes from ketones as shown in eq 5.[26]

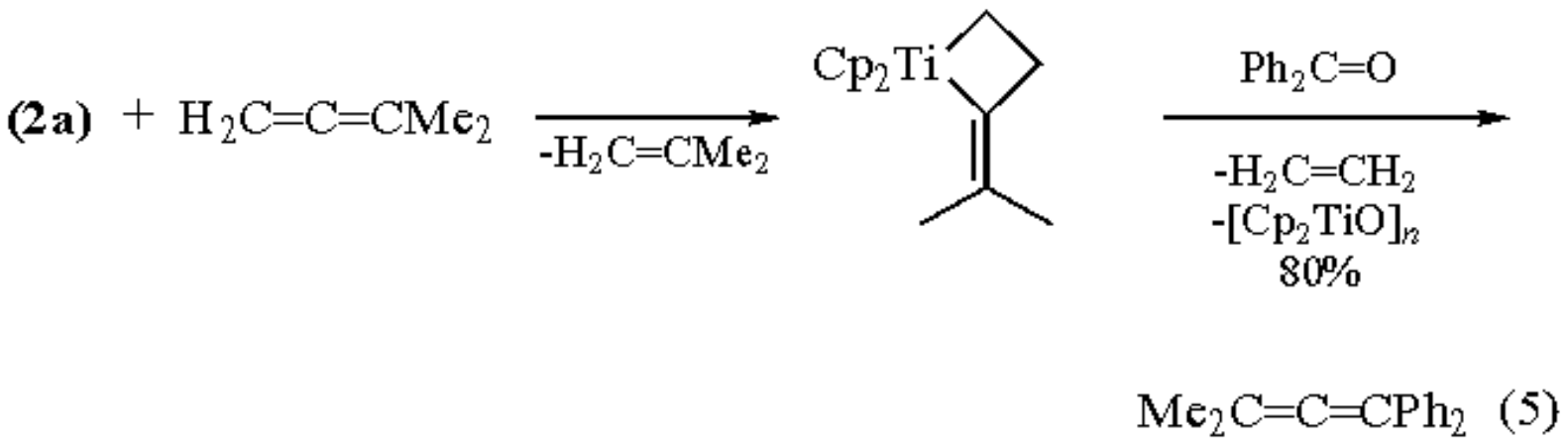

The titanacyclobutanes have also served as precursors in the synthesis of various interesting heterobimetallic μ-methylene complexes[27] and other organometallic species,[28] including titanium methylidene phosphine complexes.[29]

Choice of metallacycle is dictated by reaction conditions and ease of preparation. β-Substituted metallacycles such as (**2c** and **2d**) are especially stable and react at 50-60 °C, whereas β,β-disubstituted titanacycles such as (**2a** and **b**) react at about 0 °C.[1a,13] By contrast, the Tebbe reagent may be used at -40 °C. Titanacyclobutane (**2a**) is particularly convenient for NMR studies due to the simplicity of its spectrum, while (**2b**) is prepared by the same general method using a liquid alkene which is easier to handle than isobutene.

It should be noted that alternate methods for formation of active titanium methylidene species have been developed.[1c] A widely used system for methylenation of ketones[30] is the still undefined mixture formed from $Zn/CH_2X_2/TiCl_4$. Also, thermolysis of Cp_2TiMe_2 provides a clean aluminum-free source of $Cp_2Ti{=}CH_2$ and shows considerable synthetic promise.[31] Except in the case of titanacyclobutanes prepared from strained cycloalkenes (see below), or α-alkylidene substituted cases (see above), the titanacyclobutanes are efficient precursors only for the unsubstituted methylidene species; several approaches to substituted methylidene equivalents of titanium or zirconium have been devised,[1c,32] including a preparation of titanocene vinylcarbene complexes from cyclopropenes.[33]

Reactions Involving Substituted Alkylidene Intermediates: Ring-Opening Metathesis Polymerization (ROMP).[1b]

The titanacyclobutanes were the first metallacycles to demonstrate the requisite reactivity for catalysis of alkene metathesis via alkylidene complex intermediates.[34] However, these species are not useful catalysts for productive metathesis of acyclic alkenes. This is due to the propensity of α-substituted titanacyclobutanes such as (2h) to cleave to the unsubstituted methylidene, as

illustrated by eq 6.[10]

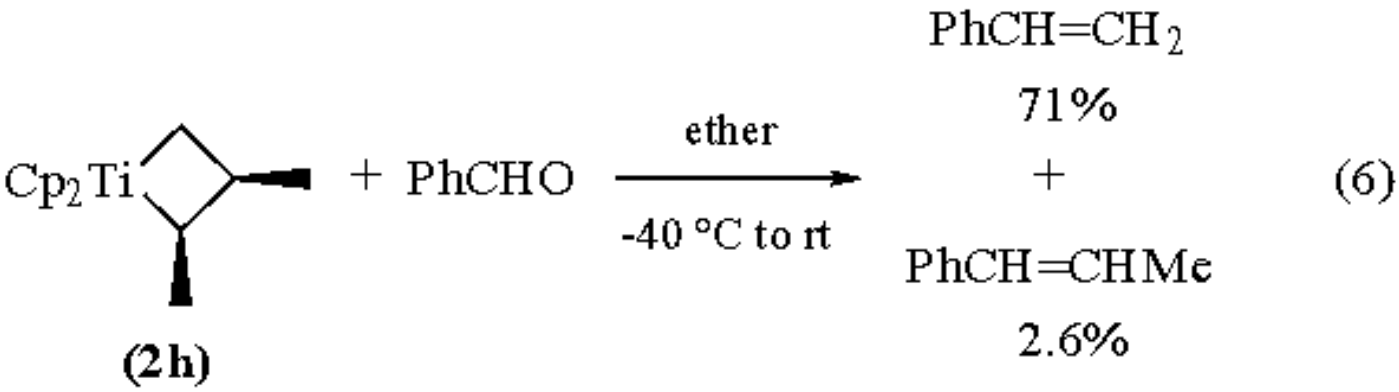

However, titanacyclobutanes formed from strained cycloalkenes will ring open to afford substituted methylidenes. This useful mode of reactivity is illustrated for complex (2i), formed from 3,3-dimethylcyclopropene, which yields titanium alkylidene phosphine complex (3), as shown in eq 7.[9]

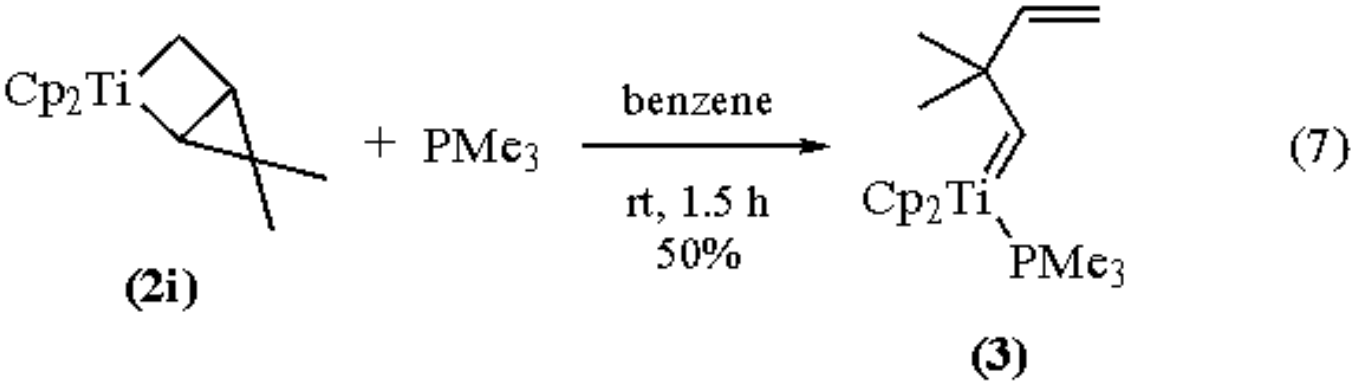

Likewise, (2i) reacts with benzophenone to afford 3,3-dimethyl-1,1-diphenyl-1,4-pentadiene.[9] Norbornene affords the extremely stable titanacyclobutane (2j) upon reaction with (1) or even the quite stable titanacycle (2d) under suitable conditions, and this species reacts further with norbornene (benzene solution, 65 °C) to produce ring-opened polynorbornene (*cis*:*trans* ratio 38:62) as

illustrated in eq 8.[35] Because rates of chain transfer and chain termination are very slow relative to initiation and propagation in this system, a living polymerization process occurs. The low polydispersity (below 1.1) of the polynorbornene and the linear increase in molecular weight with time are consistent with this. Another entry into this chemistry involves thermolysis of dimethyltitanonocene.[31b] The living nature of this system allows for end capping of the polymer chains by Wittig-type reactions with, for example, benzophenone[36] or acetone,[37] and also, by sequential addition of different monomers, for the production of block copolymers.[37,38] Other monomer units employed include benzonorbornadiene, 6-methylbenzonorbornadiene, and *endo*- and *exo*-dicyclopentadiene, which have been used to synthesize diblock and triblock copolymers of low polydispersity as illustrated in eq 9.[37] It has been possible to end-cap ROMP polymers with an aldehyde group and to use aldol-group-transfer polymerization to make diblock polymers with poly(vinyl alcohol) or poly(silyl vinyl ether) segments.[38a] ROMP chemistry using titanium methylidene sources has also been used to produce the novel cross-conjugated poly(3,4-isopropylidenecyclobutene) shown in eq 10, which becomes conducting upon oxidative doping.[39]

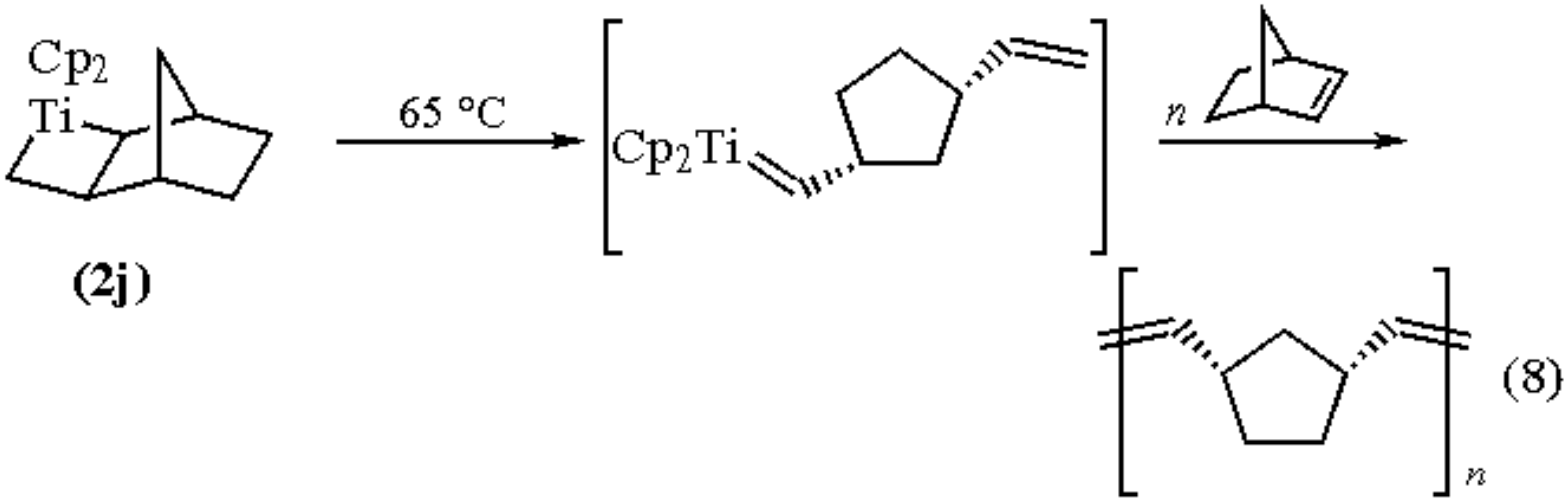

(2j)

(8)

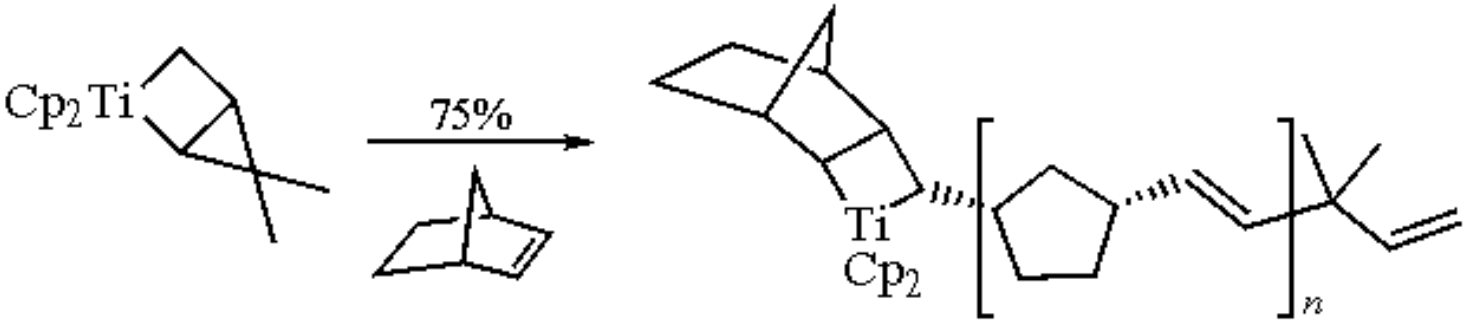

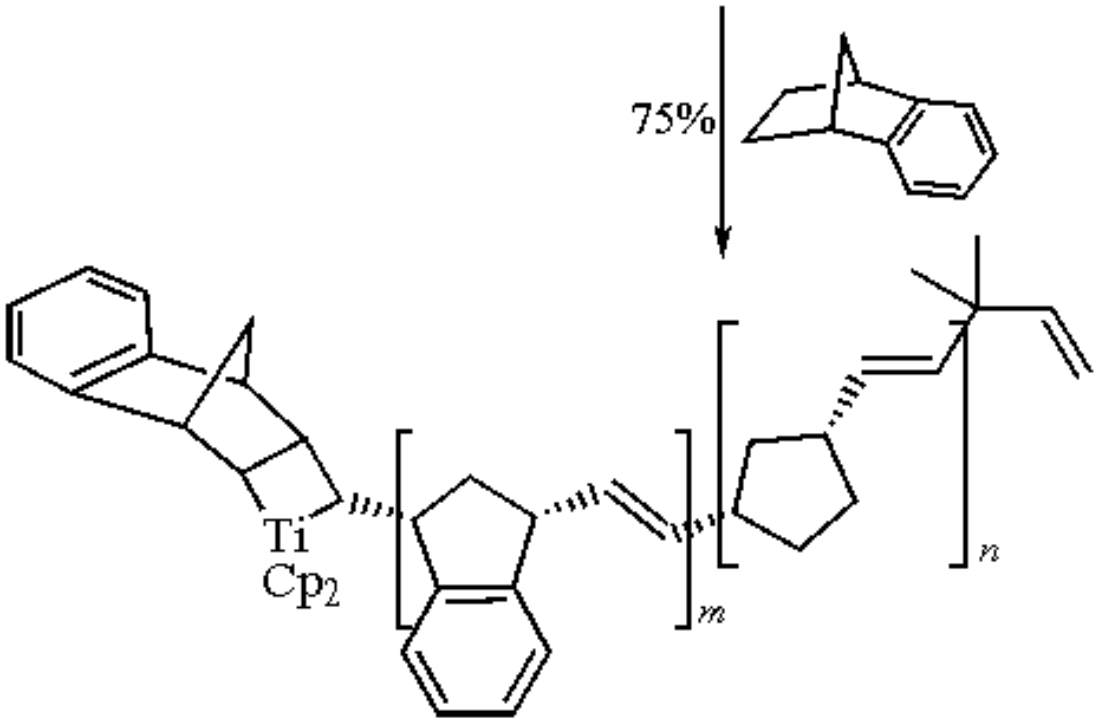

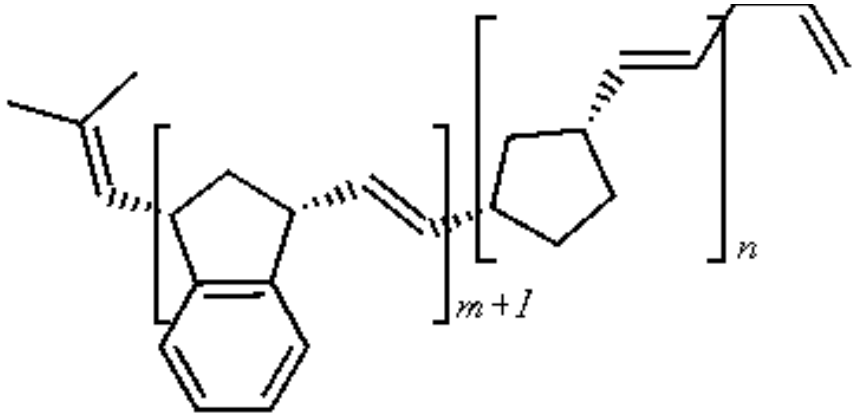

(9)

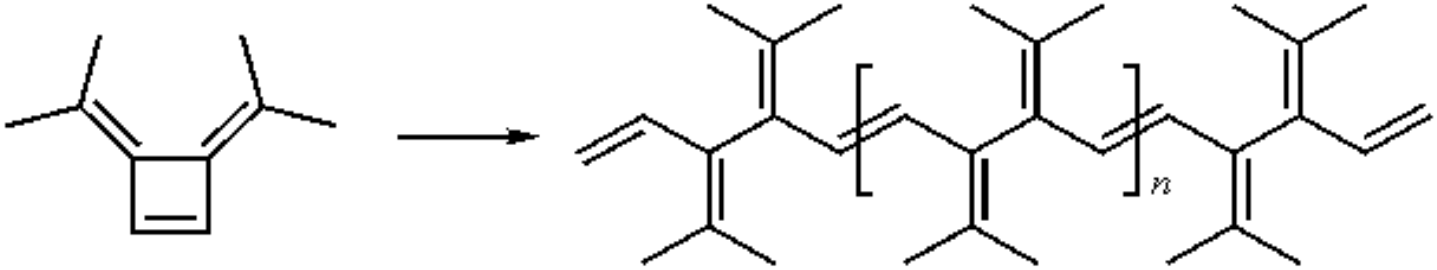

(10)

Numerous other ROMP catalysts have been developed,[1d,40] some of which are stable to air and water and are active at room temperature.[41]

It should be noted that in situ formation of a derivative of (2j), which cleaves to give a substituted methylidene, was employed in the synthesis of $\Delta^{9,12}$-capnellene.[42] Certain molybdenum alkylidenes show considerable promise for the stoichiometric[43] or catalytic[44] preparation of cycloalkenes, from unsaturated ketones or dienes, respectively, via metallacyclobutanes which cleave to afford substituted methylidenes.

Reactions Not Involving Methylidene Species.

Alkanes are produced upon acidolysis;[34,45] for example (2a) affords neopentane.[1a] Titanacyclobutanes may be

directly halogenated to afford 1,3-dibromides[1a] as shown in eq 11.[2a] This reaction is typically quantitative, and has been used to assay the titanacyclobutanes.[4]

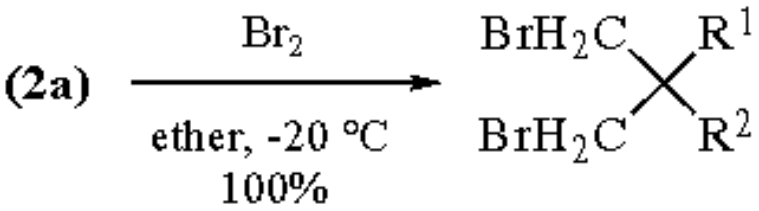

(11)

By contrast, iodination leads to cyclopropane formation in good yield,[1a] as shown in eq 12, a process which was demonstrated to proceed stepwise with retention of stereochemistry at one carbon and inversion at the other.[46] The titanacycles may be photolyzed, as in eq 13, to afford cyclopropanes via a 1,4-biradical intermediate.[47] Reaction with chemical oxidants such as tetrakis(trifluoromethyl)cyclopentadienone or ferricinium salts also affords cyclopropanes by reductive elimination.[48] Carbonylation leads to reductive coupling of two carbon monoxide units to afford a stable enediolate complex of titanocene which may be converted to a cyclic acyloin upon acidolysis; in the one-pot process of eq 14, metallacycle (2c) is generated in situ from the Tebbe reagent.[1a,2a]

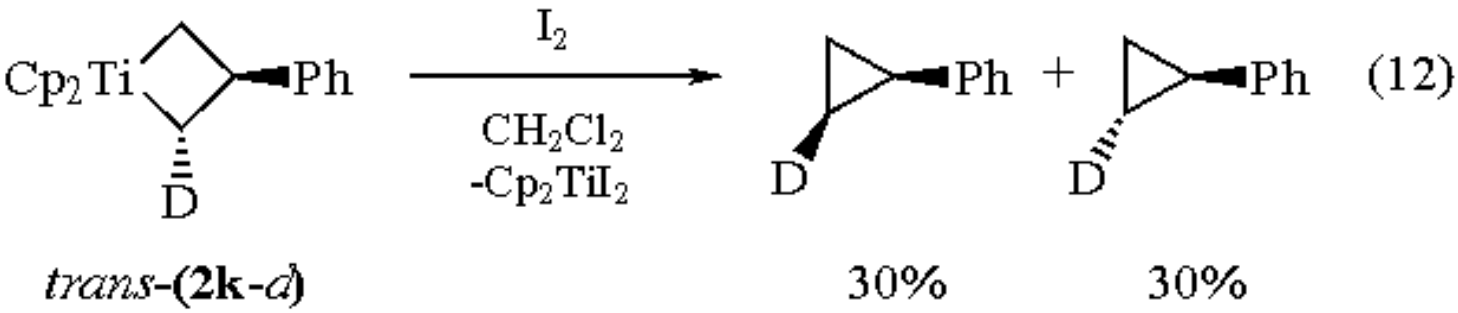

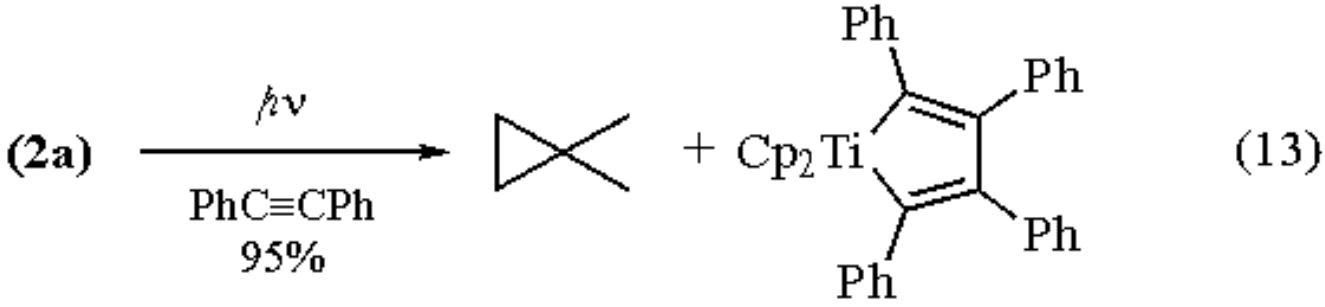

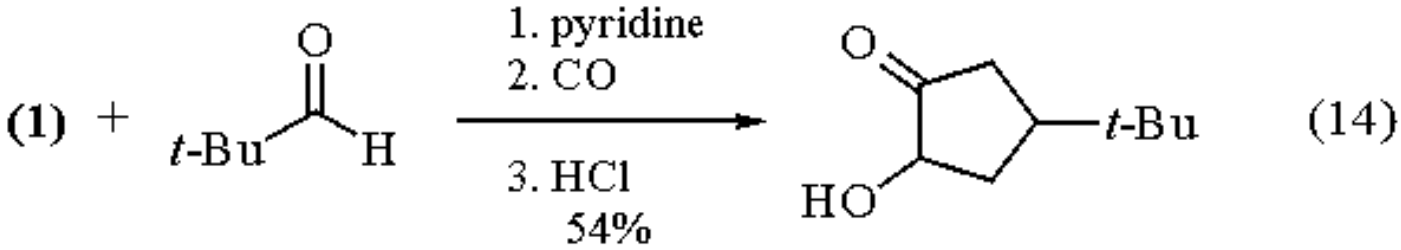

Related Reagents.

***Bis(cyclopentadienyl)dimethyltitanium*; *Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane*; μ-*Chlorobis(cyclopentadienyl)(dimethylaluminum)*-μ-*methylenetitanium*; *Dibromomethane-Zinc-Titanium(IV) Chloride*.**

---

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Bis(cyclopentadienyl)diphenyltitanium[1]

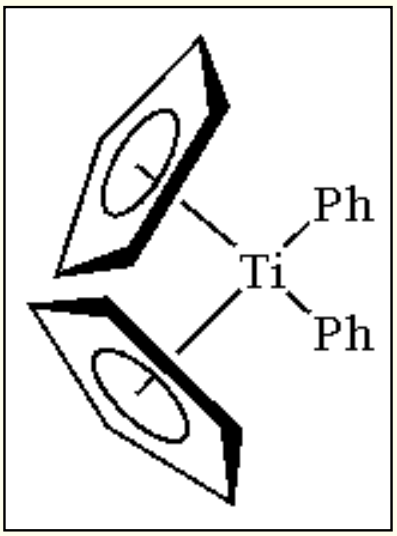

[1273-09-2] · $C_{22}H_{20}Ti$ · Bis(cyclopentadienyl)diphenyltitanium · (MW 332.28)

(reagent for the preparation of aryl derivatives via thermolysis and trapping with electrophiles;[2] catalyst for the hydrogenation of alkenes,[3] the polymerization of alkenes,[4,5] the polymerization of silanes,[6] the hydrosilylation of ketones,[7] the silylation of alcohols[8] and aldol condensation[9])

Alternate Name: diphenyltitanocene.

Physical Data: mp 146-148 °C dec.

Solubility: sol most aprotic organic solvents, e.g. Et_2O, THF, CH_2Cl_2, toluene, hexanes.

Form Supplied in: orange-yellow crystals; not available commercially.

Preparative Method: [10,11] a solution of ***Phenyllithium*** (2 equiv) in Et_2O is added dropwise to a suspension of ***Dichlorobis(cyclopentadienyl)titanium*** in Et_2O (3-5 mL $mmol^{-1}$) stirred at rt under N_2. After 1 h, the reaction mixture is cooled to -30 °C and quenched with methanol. Evaporation of the solvents upon warming to rt, addition of Et_2O, filtration, evaporation, and recrystallization from CH_2Cl_2/pentane gives 95% of orange-yellow crystals of Cp_2TiPh_2.

Handling, Storage, and Precautions: sensitive to oxygen and light but can be briefly exposed to air and water; not stable for more than a few days at rt, and decomposes more rapidly in solution; can be stored in the dark in a refrigerator.

Bis(cyclopentadienyl)titanium Derivatives.

The presence of π-bonded cyclopentadienyl substituents on titanium results in a lower Lewis acidity and enhanced thermal stability.[1] A variety of bis(cyclopentadienyl)titanium (Cp_2Ti, titanocene) complexes can be easily prepared from Cp_2TiCl_2, which is commercially available and inexpensive. Among the most widely used *C*-substituted compounds are the dimethyl (see ***Bis(cyclopentadienyl)dimethyltitanium***) and diphenyl derivatives. In general, diaryltitanocenes are less reactive and more thermally stable than the corresponding dimethyl compounds.

Thermolytic Reactions.

Upon heating at high temperatures, diaryltitanocenes undergo extrusion of benzene and formation of a titanocene-benzyne complex, which reacts with alkynes[2,12] to form a benzotitanole adduct. Subsequent reaction of this intermediate with electrophiles gives various titanium-free products (eq 1).[2] Analogous chemistry occurs with the more synthetically versatile zirconocene complexes,[13] while different products are obtained under photochemical conditions.[14] The titanocene-benzyne complex can also be trapped with dinitrogen to form anilines in low yields,[15,16] as well as with carbon dioxide to form benzoic esters upon methanolysis (eq 2).[17]

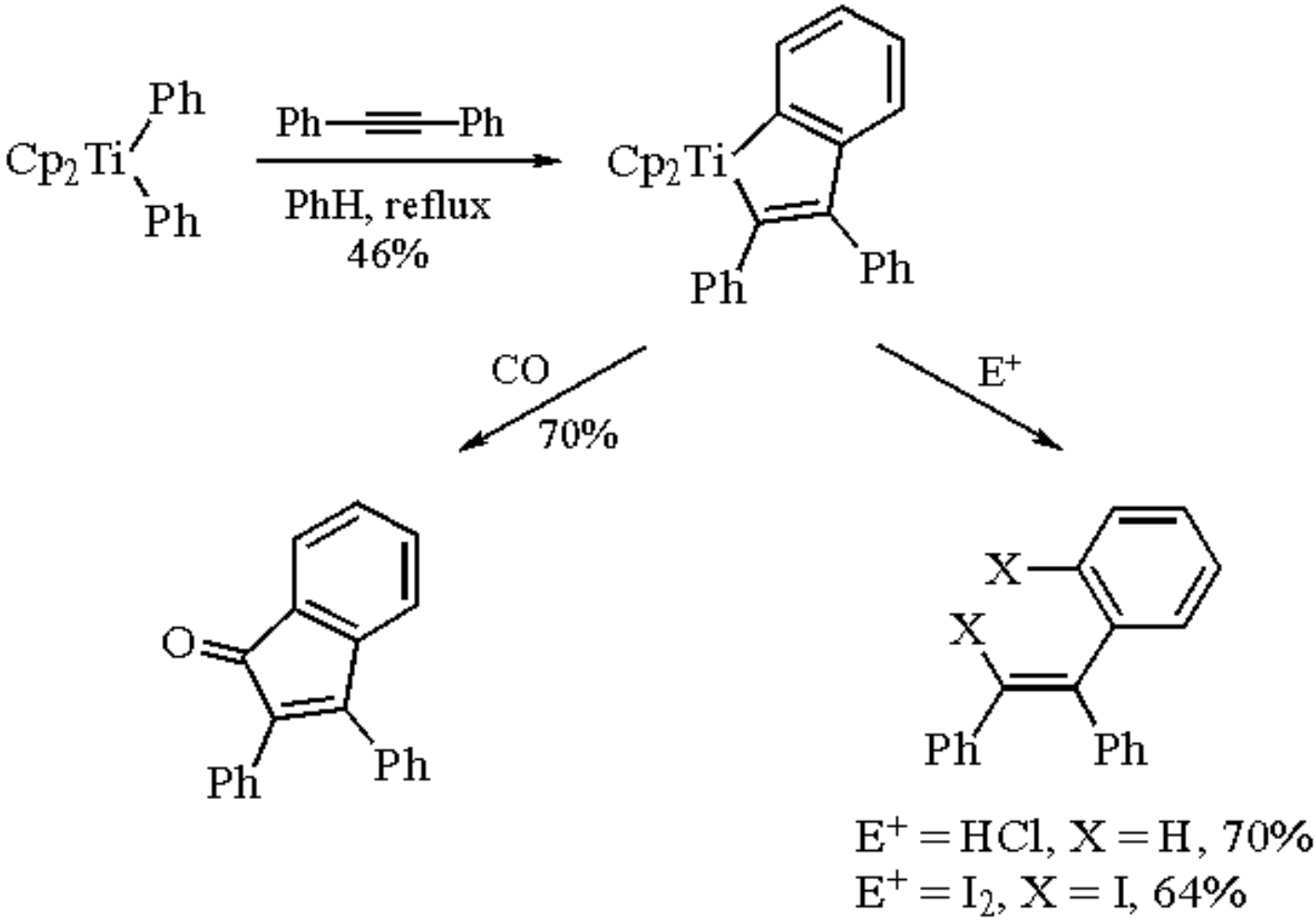

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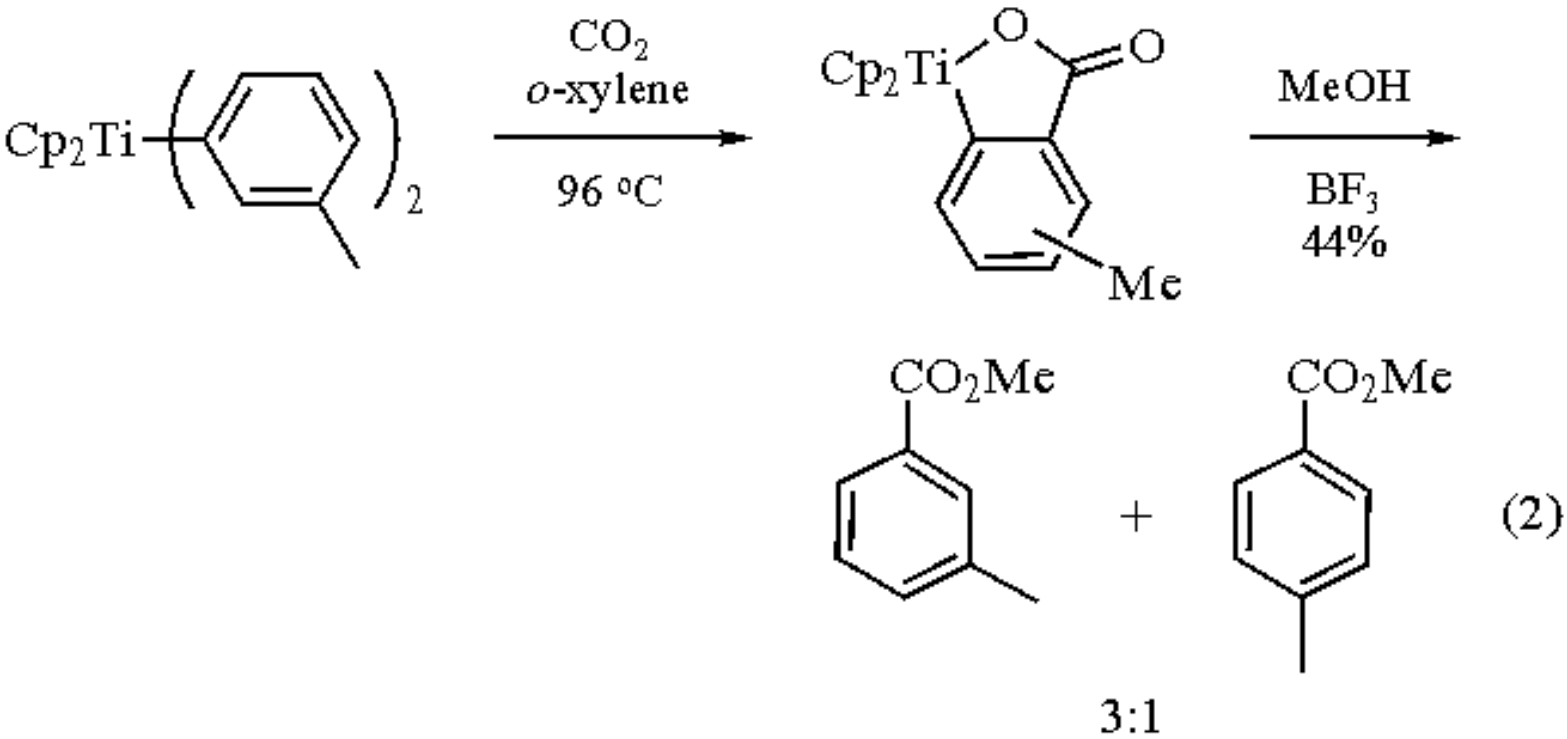

Reactions with Alkenes.

Diaryl titanocenes, like their dimethyl analogs, can serve as catalysts for the hydrogenation of alkenes under thermal[3] or photochemical[18] conditions. Also, the parent compound, (Cp_2TiPh_2),[4,5] as well as various analogs with other Cp ligands,[5,19] are useful catalyst components for the isotactic polymerization of propene (eq 3).[5]

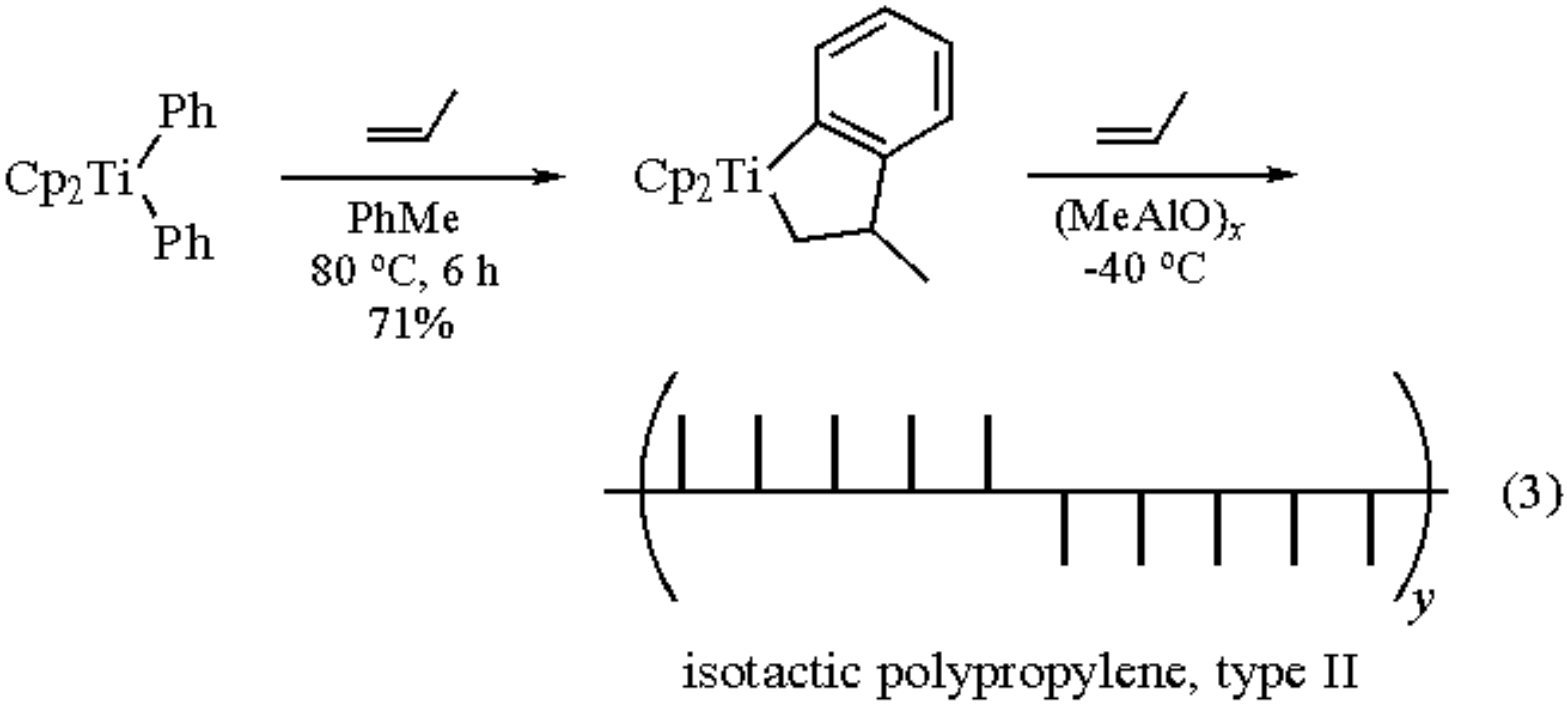

Reactions with Silanes.

Similarly to Cp_2TiMe_2 and other related derivatives,[20] Cp_2TiPh_2 catalyzes the dehydrogenative polymerization of hydrosilanes (eq 4).[6] It also catalyzes the hydrosilylation of ketones (eq 5)[7] and the silylation of alcohols (eq 6) and diols (eq 7).[8]

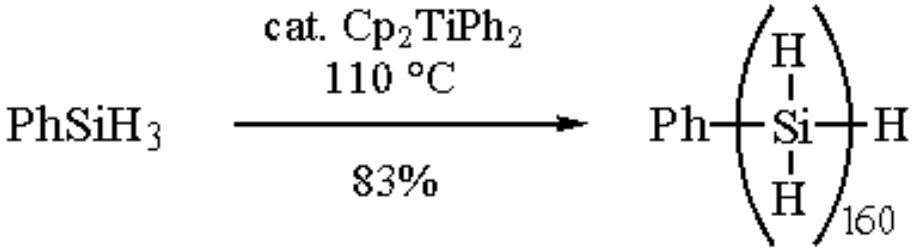

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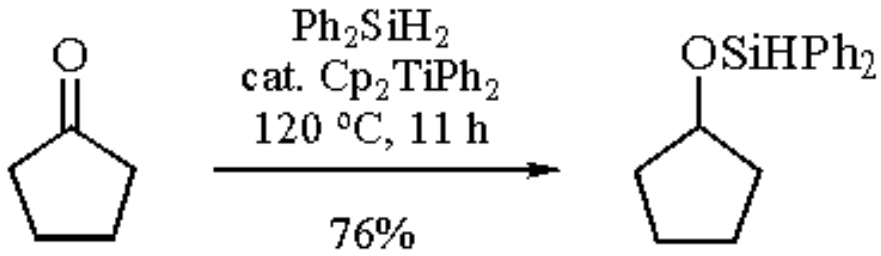

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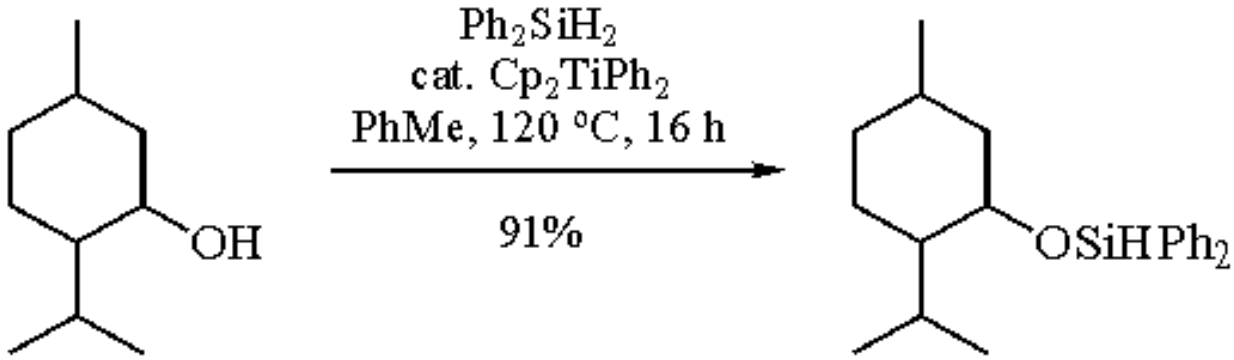

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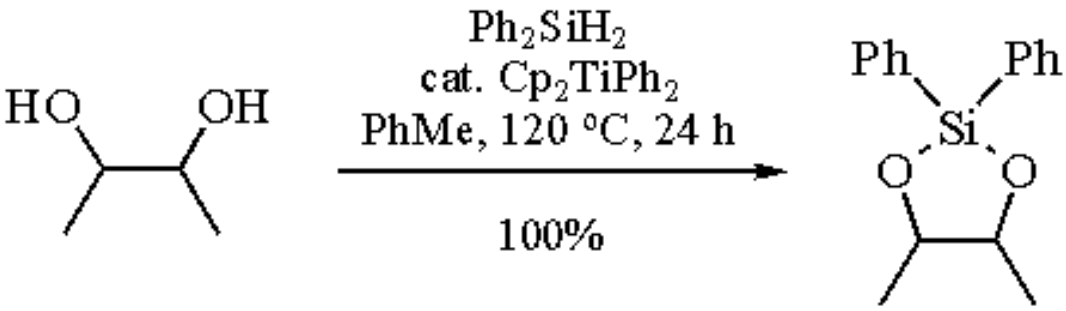

(7)

Aldol Condensation.

Cp_2TiPh_2 is a good catalyst for the self-condensation of aliphatic aldehydes and the mixed aldol condensation of acetophenones with aromatic aldehydes (eq 8).[9]

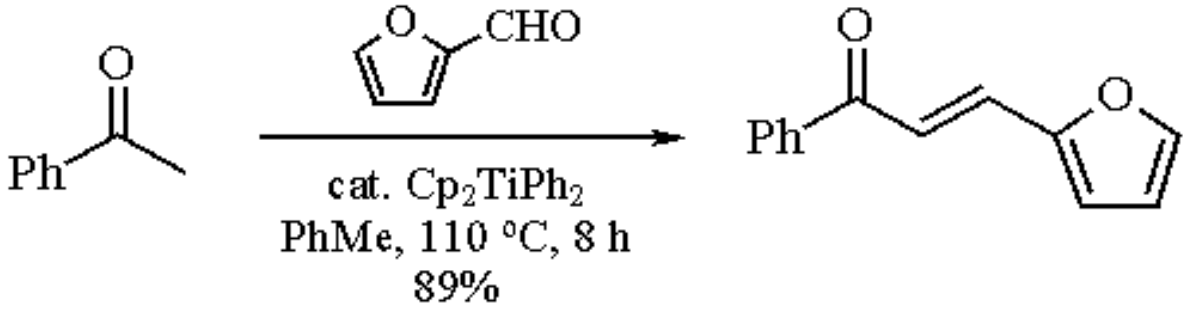

(8)

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Bis(cyclopentadienyl)diphenylzirconium[1]

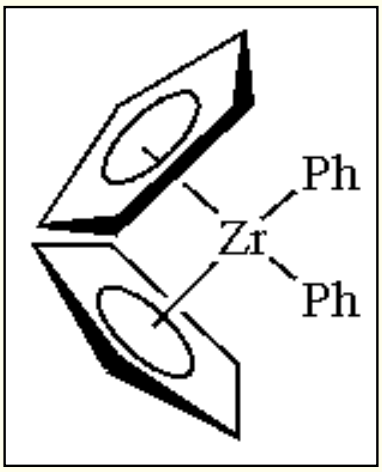

[51177-89-0] · $C_{22}H_{20}Zr$ · Bis(cyclopentadienyl)diphenylzirconium · (MW 375.62)

(precursor of Cp_2Zr;[3,4] precursor of zirconium-benzyne complex[8,9]; insertion reaction into Zr-Ph bond[20])

Alternate Name: diphenylzirconocene.

Physical Data: mp 140 °C dec.

Solubility: sol THF, CS_2; appears to react with $CHCl_3$; reacts with protic solvents.

Analysis of Reagent Purity: IR (nujol cm^{-1}) 1405(m), 1240(w), 1050(m), 1005(m), 980(m), 827(w), 820(s), 775(s), 698(s); ^1H NMR (CS_2) δ: 6.10(s), 6.8-7.3(m); (THF-d_8) δ: 6.18, 6.93(m), 7.23 (m).

Preparative Method: the reaction is conducted under an atmosphere of argon. A suspension of 1.0 g (3.4 mmol) of ***Dichlorobis(cyclopentadienyl)zirconium*** in 20 mL of diethyl ether is cooled to -40 °C. ***Phenyllithium*** (3.0 mL, 2.3 M) is subsequently added dropwise via a syringe over a 45 min period with magnetic stirring, during which time a white crystalline solid separates from solution. Stirring is continued at -40 °C for 1 h and the temperature is slowly allowed to rise to 0 °C. The solvent is then evaporated under reduced pressure and the solid residue is washed with pentane and decanted. The remaining residue is extracted with diethyl ether and the extracts are filtered under nitrogen. Concentration of the filtrate yields 1.0 g (80%) of white crystalline Cp_2ZrPh_2.[2]

Purification: recrystallization at low temperature from diethyl ether; cannot be sublimed.

Handling, Storage, and Precautions: appears to be more stable than the dimethyl analog toward air and moisture. Use in a fume hood.

Precursor of Cp_2Zr.

Reductive elimination of biphenyl from diphenylzirconocene is induced photochemically and gives a zirconocene Cp_2Zr species which has not been characterized but which reacts with various reagents. In the presence of dienes, zirconocene-diene complexes are obtained as stable complexes (eq 1).[3] With alkynes, a dimerization occurs to give zirconacyclopentadienes (eq 2).[4] Reaction of vinylzirconocene with Cp_2Zr affords a dinuclear (alkene)zirconocene complex (eq 3).[5] Coupling of phenyl groups on zirconium is also achieved by the reaction of Cp_2ZrPh_2 with an oxidant such as tetrakis(trifluoromethyl)cyclopentadienone (eq 4).[6]

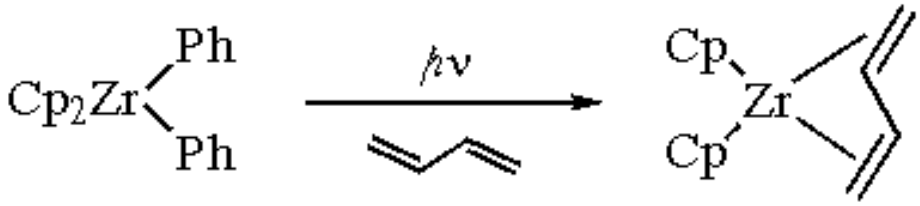

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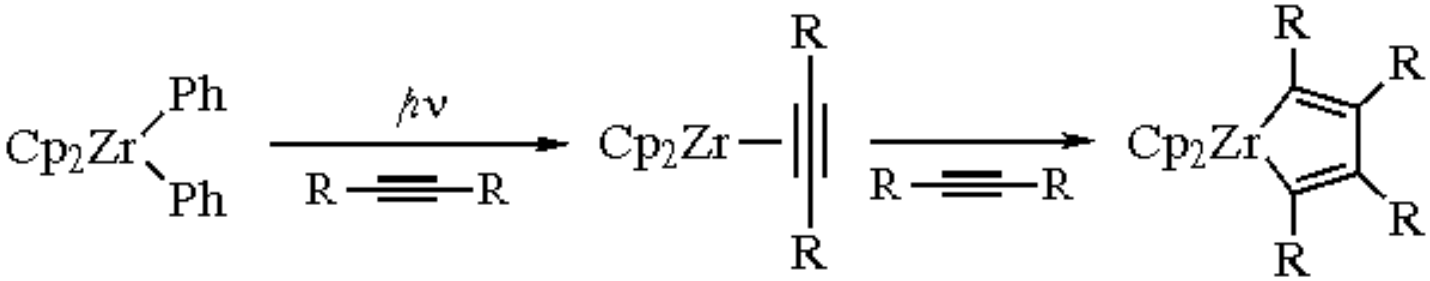

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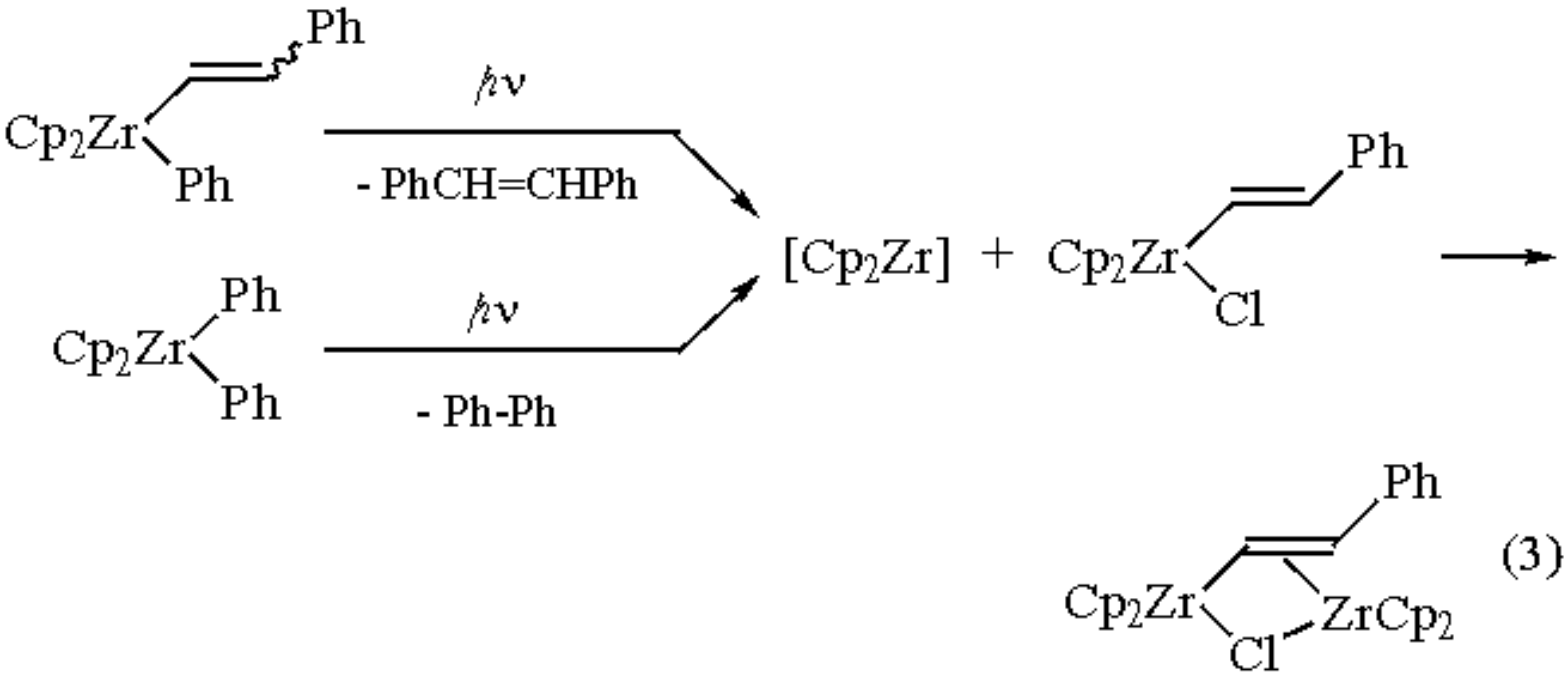

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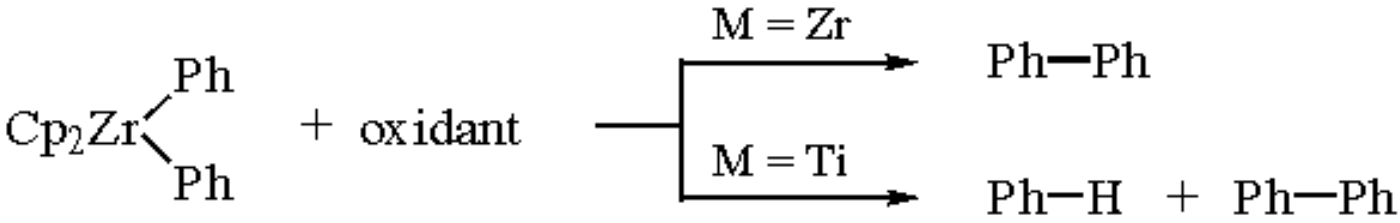

(4)

Precursor of Zirconium-Benzyne Complex.

Thermolysis of diarylzirconocenes shows a different aspect of their reactivity. When a solution of di-*p*-tolylzirconocene is stirred in degassed absolute benzene at 70 °C for 3 h and treated with bromine, *m*-bromotoluene and bromobenzene are formed in addition to the expected products such as zirconocene dibromide and *p*-bromotoluene.[7] This is due to the formation of phenyltolylzirconocene (eq 5).[7]

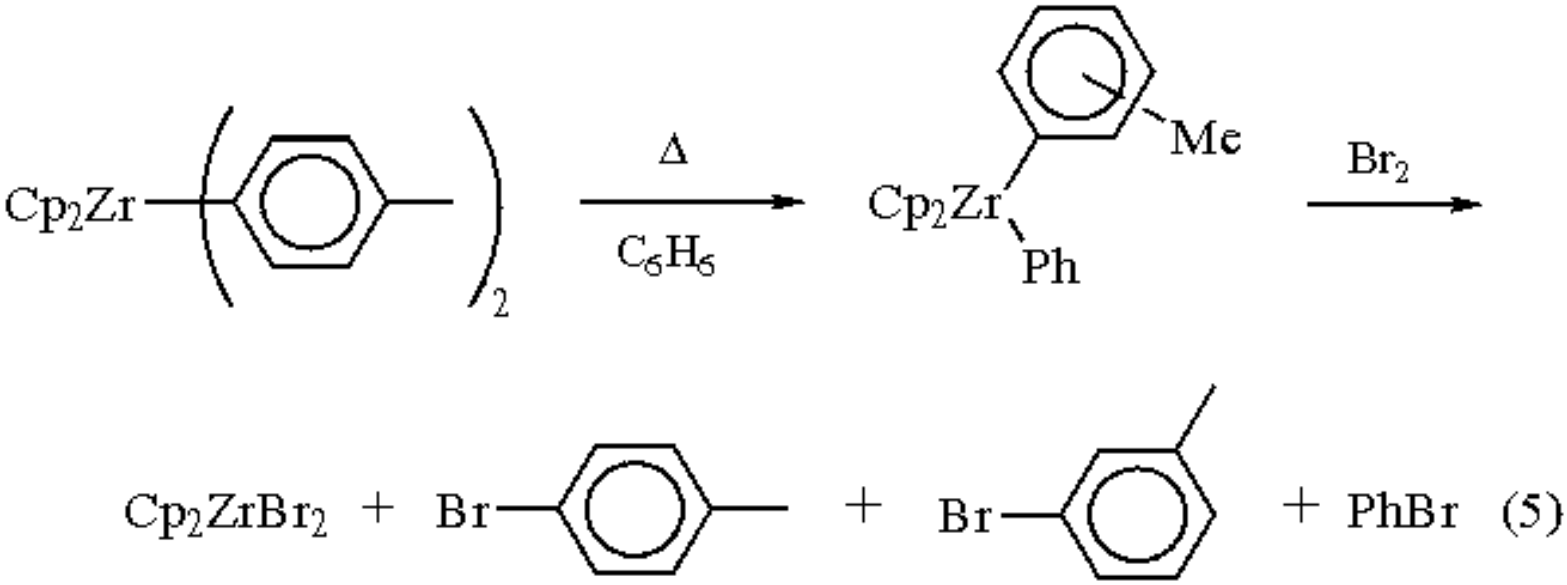

(5)

When thermolysis of diphenylzirconocene is carried out at 70 °C under ethylene (20 bar), zirconaindan is formed in excellent yield (eq 6).[8] The zirconaindan compounds can be used for further reactions, e.g. carbonylation (eq 7).[9] The zirconaindan is formed by the coupling reaction of benzyne with ethylene. The coupling reaction with substituted alkenes is highly regioselective (&egt;95%) and stereospecific (eq 8).[10] The alkene moiety of zirconaindans can be replaced by other alkenes as shown in eq 9.[8]

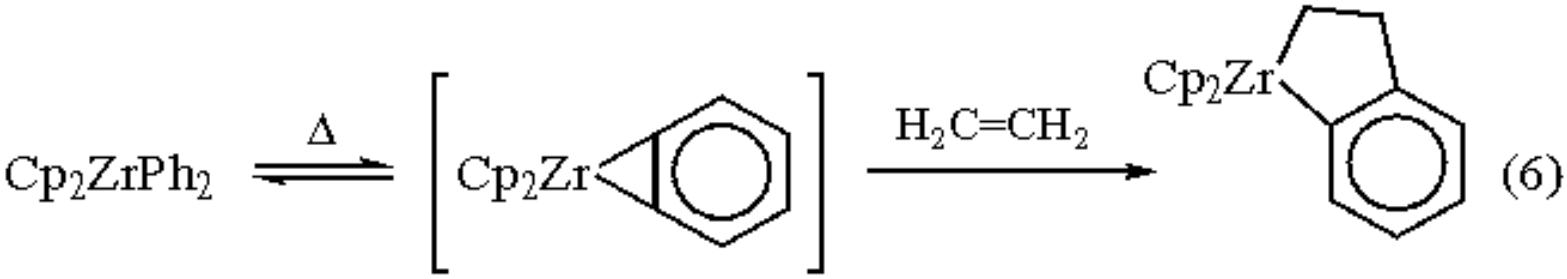

(6)

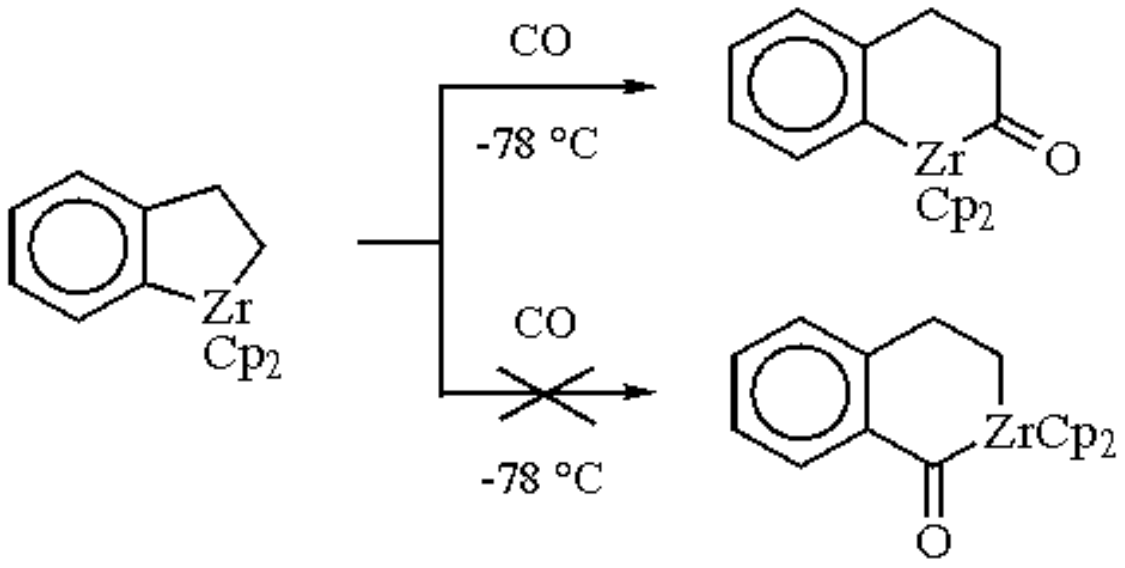
CO
-78 °C
Zr
Cp2
O
CO
-78 °C
ZrCp2
O

(7)

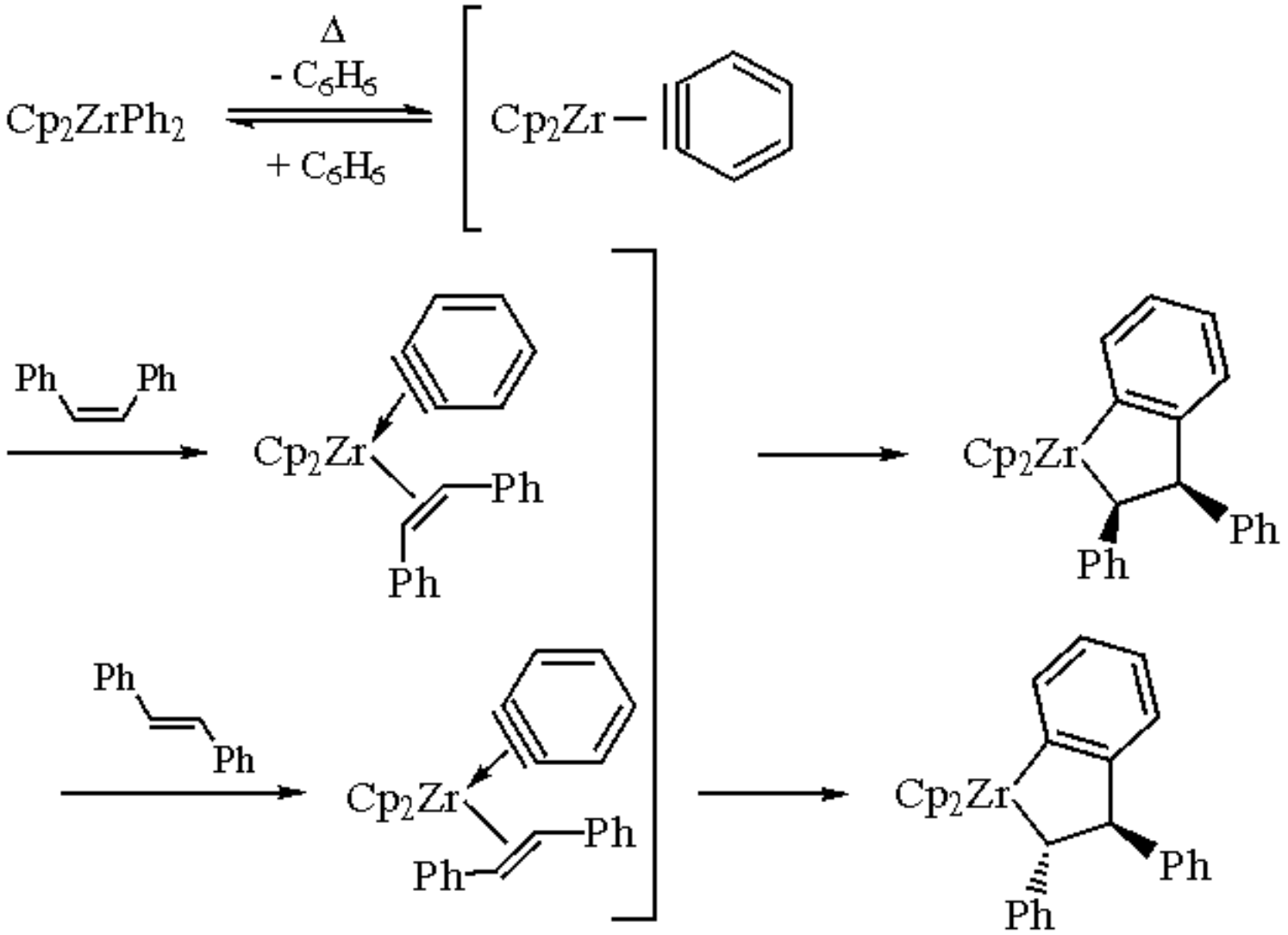
Cp2ZrPh2
Δ
- C6H6
+ C6H6
Cp2Zr
Ph
Ph
Cp2Zr
Ph
Ph
Cp2Zr
Ph
Ph
Ph
Ph
Cp2Zr
Ph
Ph
Cp2Zr
Ph
Ph

(8)

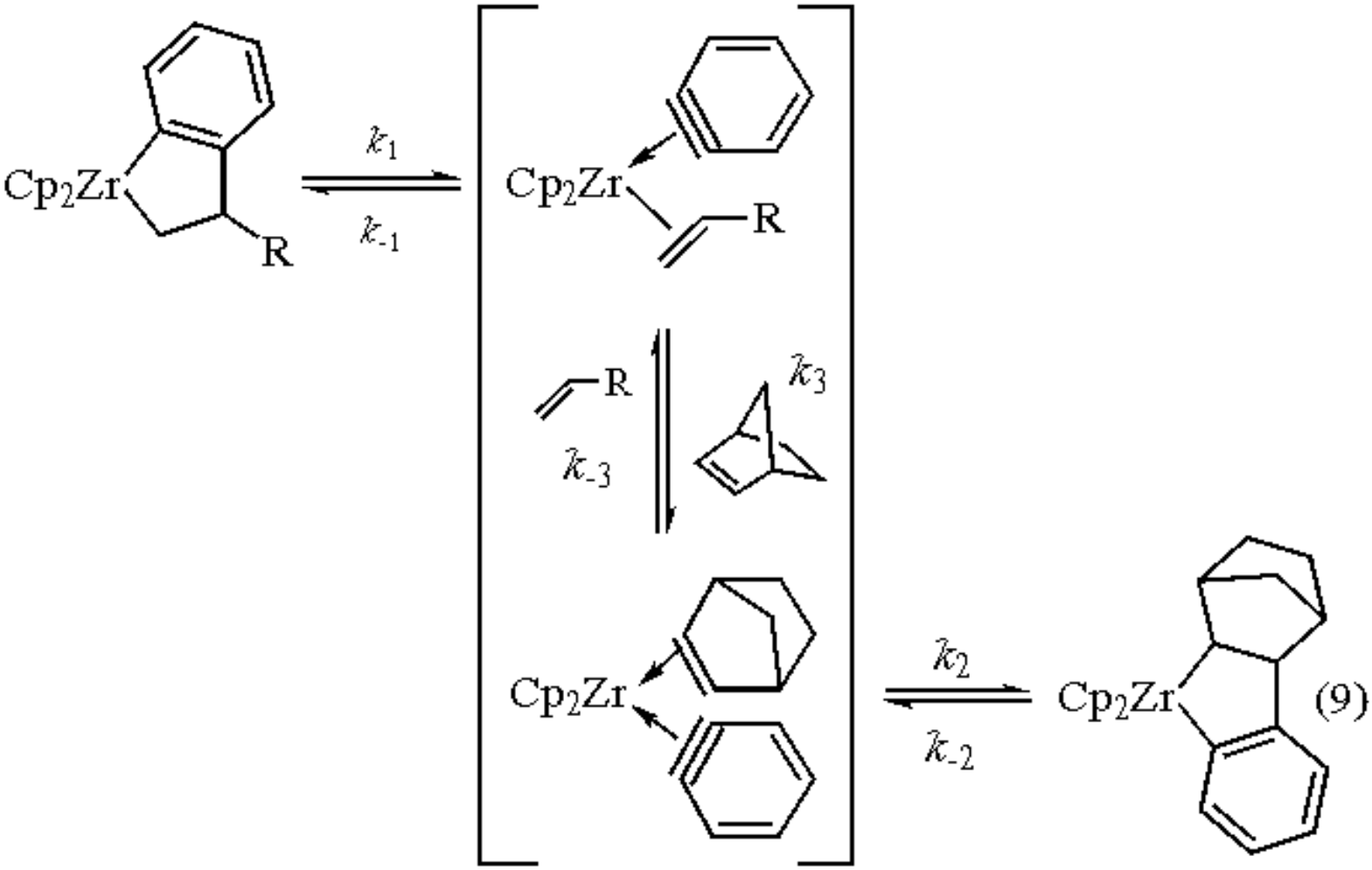

Carbon monoxide coordinated to a transition metal also reacts with benzyne formed in situ to afford a cyclic carbene complex (eq 10).[11] The zirconocene-benzyne complex can be trapped with PMe_3 to form a crystalline complex (eq 11).[12] The benzyne complex reacts with various unsaturated compounds such as nitriles,[12,13] alkynes,[12] ketones,[12] and phosphaacetylene[14] to form five-membered zirconacycles (eqs 12 and 13). Coupling products with alkynes can be converted into heterocycles such as benzothiophene (eq 14).[15] Organic compounds which have an acidic hydrogen react with benzyne to give monophenyl(organo)zirconocene compounds. When the benzyne complex reacts with an ylide or furan, the corresponding monophenyl(organo)zirconocene gives six-membered zirconacycles (eq 15).[16]

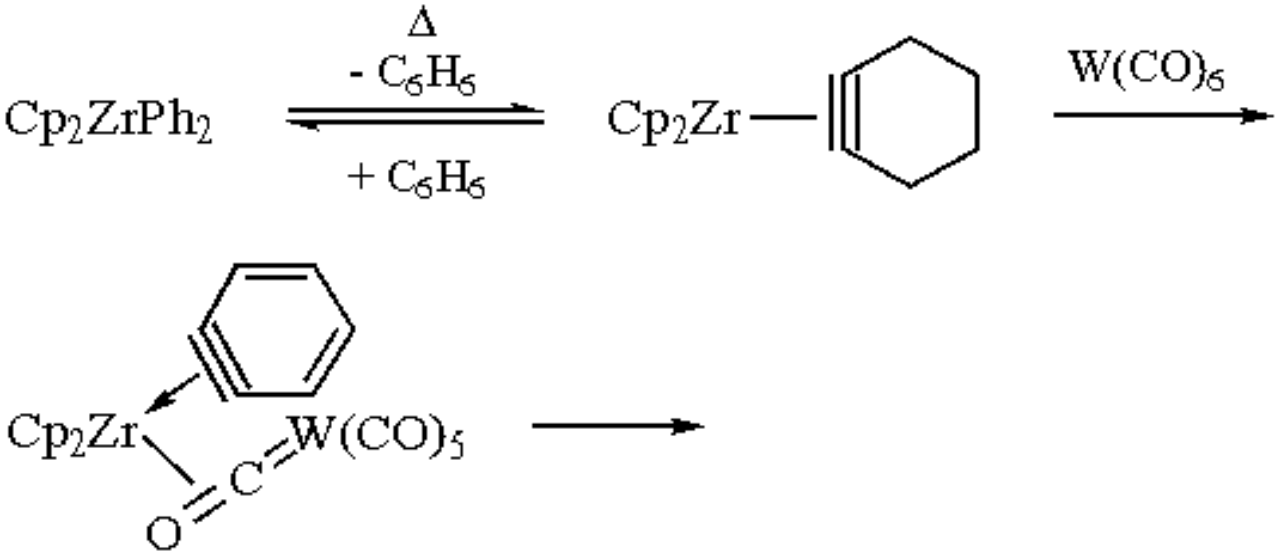
Cp2ZrPh2
Δ
- C6H6
+ C6H6
Cp2Zr
W(CO)6
Cp2Zr
W(CO)5
O
C

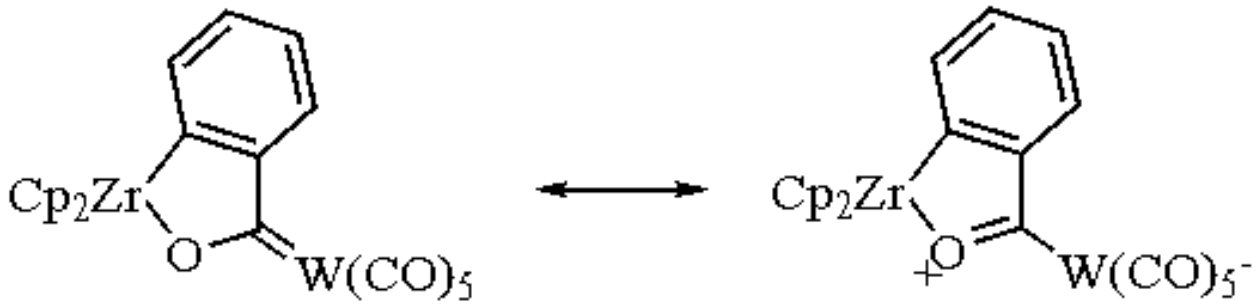
Cp2Zr
O
W(CO)5
Cp2Zr
+O
W(CO)5-

(10)

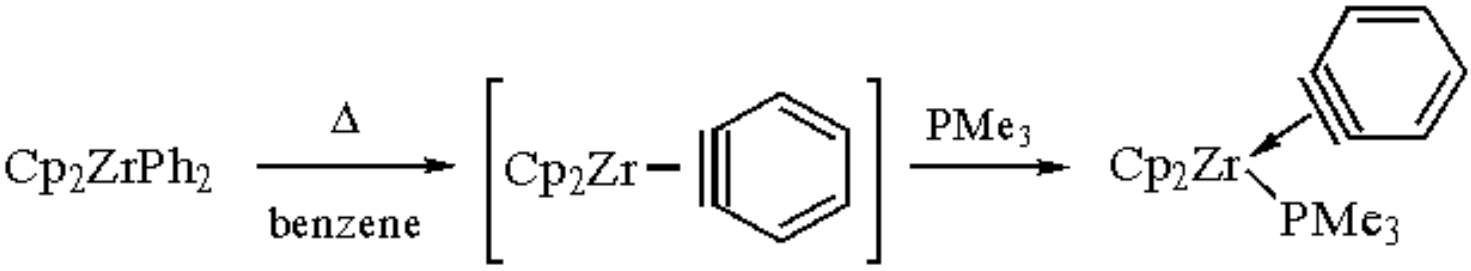
Cp2ZrPh2
Δ
benzene
Cp2Zr
PMe3
Cp2Zr
PMe3

(11)

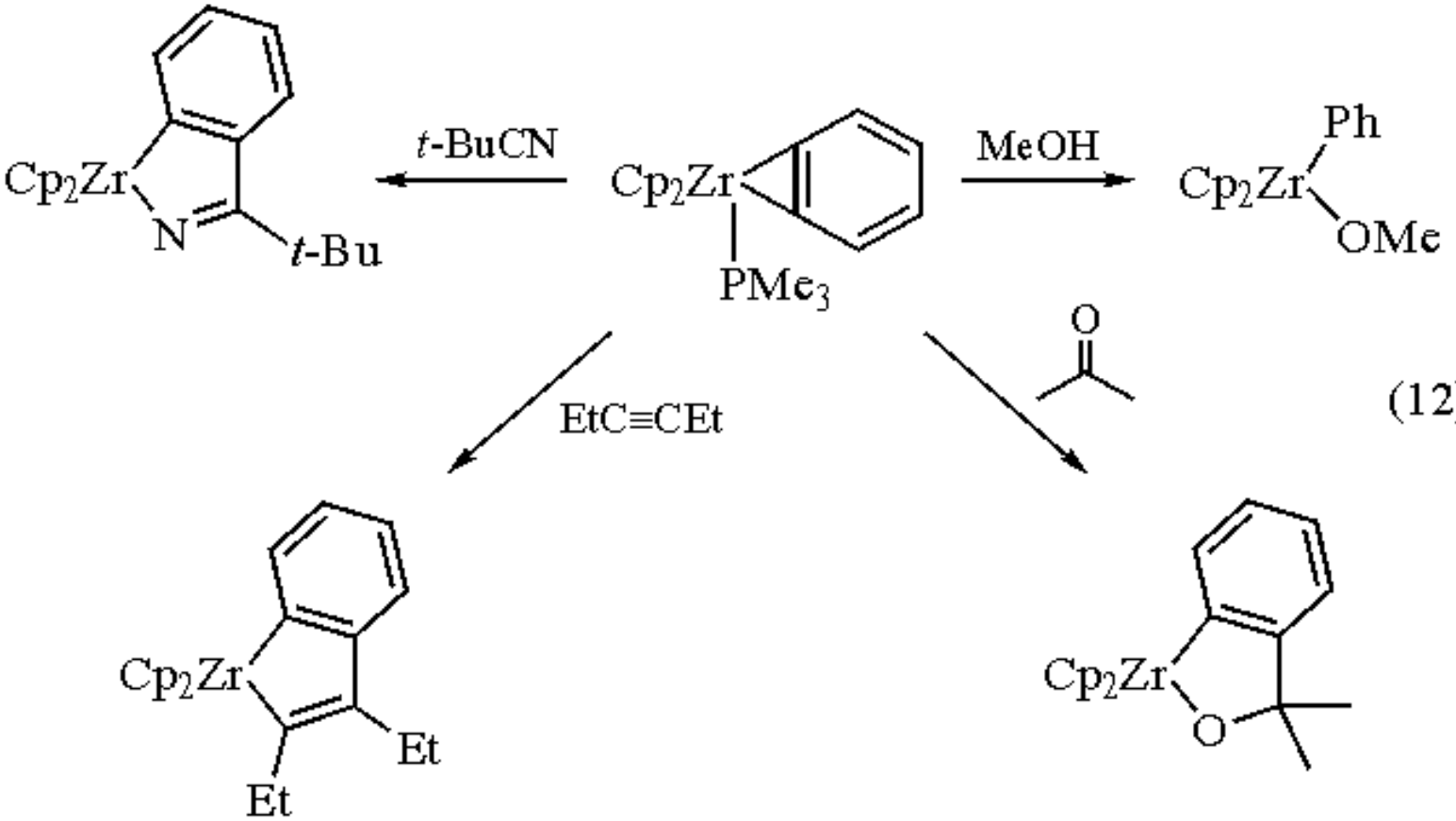
Cp2Zr
N
t-Bu
t-BuCN
Cp2Zr
PMe3
MeOH
Ph
Cp2Zr
OMe
EtC≡CEt
O
Cp2Zr
Et
Et
Cp2Zr
O

(12)

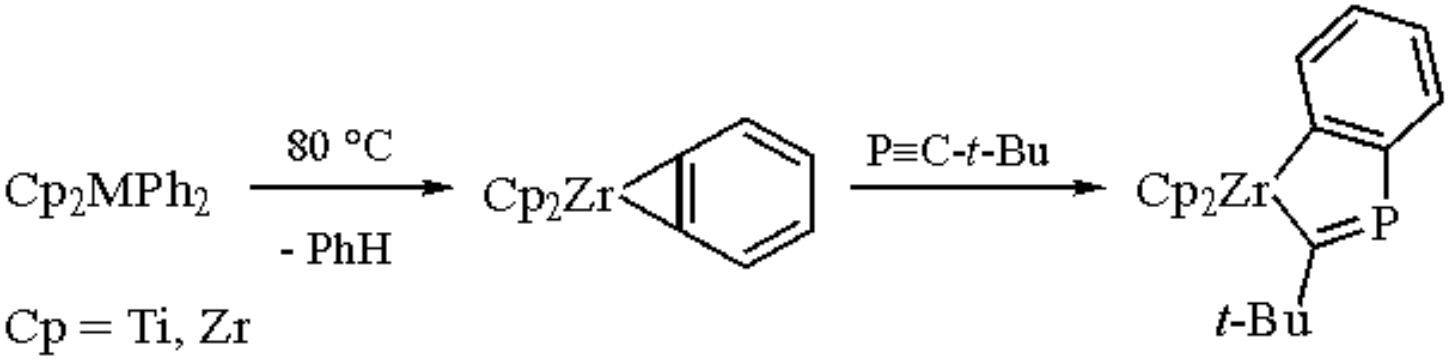
Cp2MPh2
80 °C
- PhH
Cp2Zr
P≡C-t-Bu
Cp2Zr
P
t-Bu
Cp = Ti, Zr

(13)

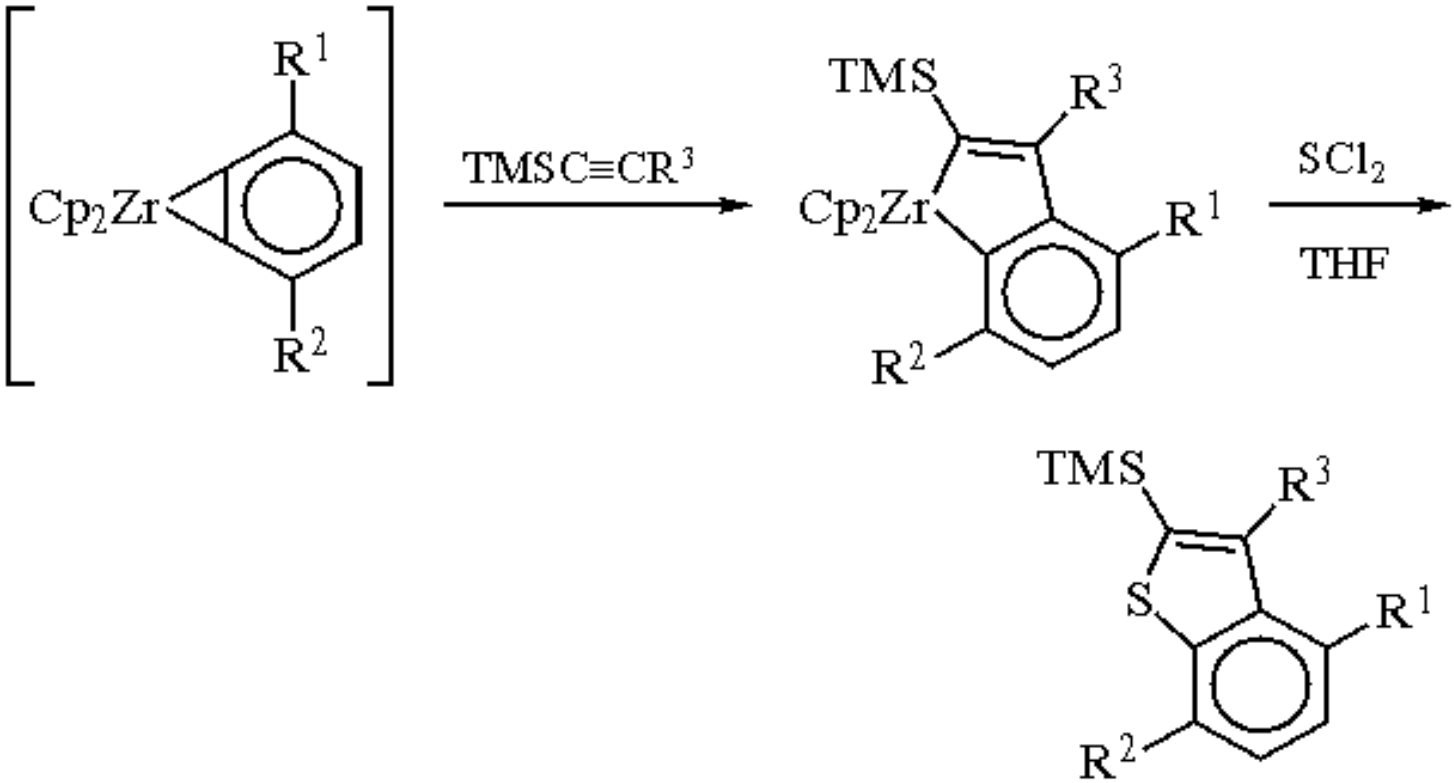

(14)

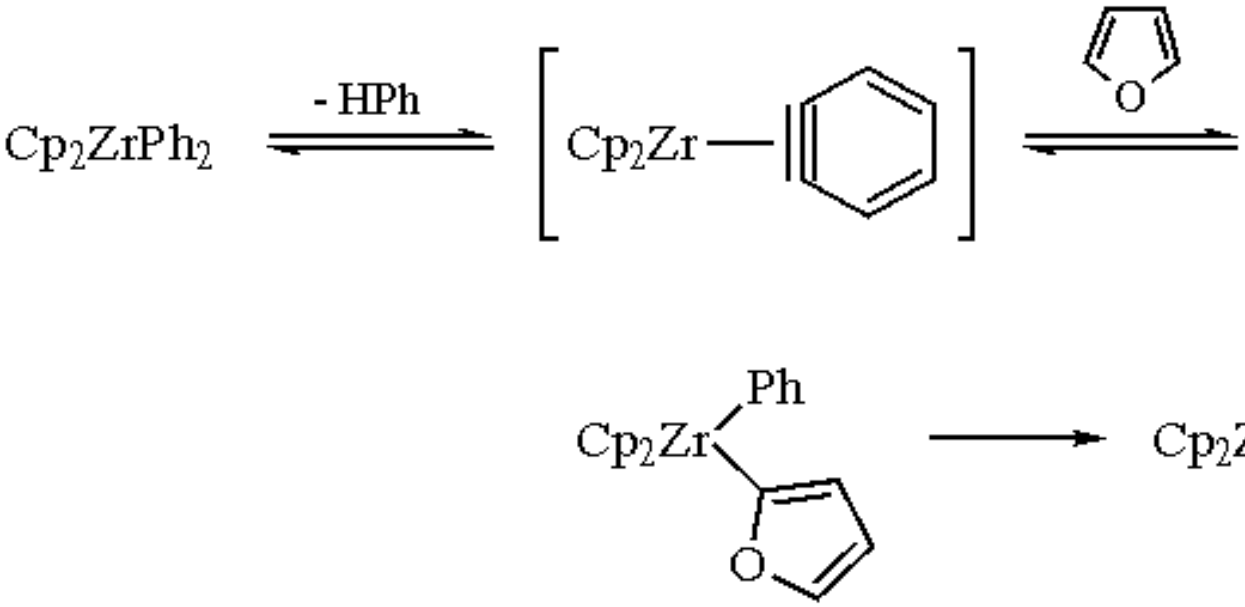

(15)

Insertion or Migration Reaction of Cp_2ZrPh_2.

Carbonylation of Cp_2ZrPh_2 at atmospheric pressure occurs rapidly even at -70 °C to give the benzoyl complex $Cp_2Zr(COPh)(Ph)$ in ca. 80% yield (eq 16).[17] The complex formed under kinetic control has a benzoyl oxygen bound to a lateral coordination site, an O-outside complex. This complex isomerizes above -50 °C to the thermodynamically favored O-inside complex.[18] At 70 °C, 1,2-migration of the remaining σ-bonded aryl ligand of the benzoyl complex from zirconium to the acyl-carbon occurs to form a side-on coordinated benzophenone ligand (eq 17).[19] Insertion reactions of diphenylketene, aryl isocyanates, and *p*-tolylcarbodiimide into the Zr-Ph bond are also observed.[20] However, carbon dioxide does not react with Cp_2ZrPh_2 at room temperature at atmospheric pressure. Insertion of NO

gas into the Zr-Ph bond produces a zirconium complex containing the $[ON(Ph)NO]^-$ ligand.[21]

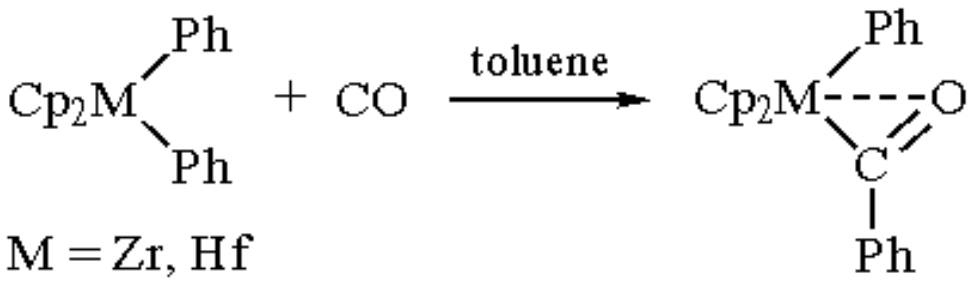

(16)

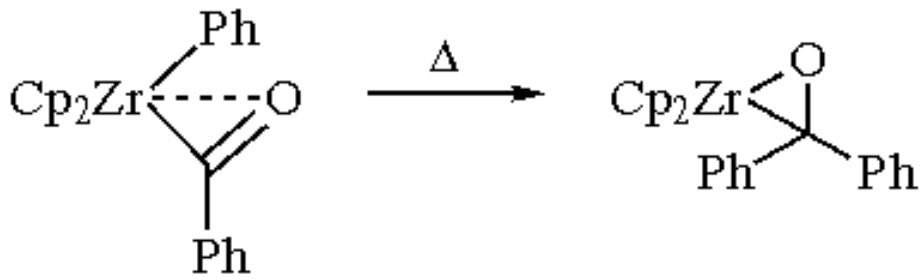

(17)

Treatment of Cp_2ZrPh_2 with alkynyllithium compounds, RCCLi, affords, after hydrolysis with 3N HCl or iodonolysis with an excess of I_2, migration products, PhCCR, in good yields (eq 18).[22] Insertion reaction of acetonitrile into the Zr-Ph bond is achieved with oxidants such as Ag^+ or Cp_2Fe^+ (eq 19).[23]

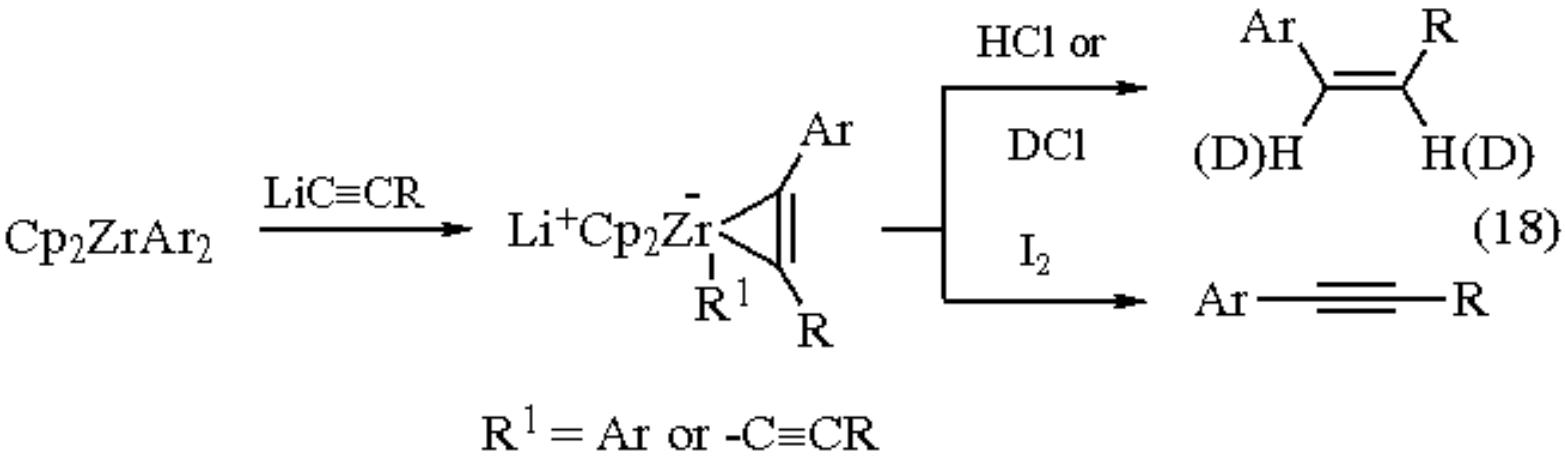

(18)

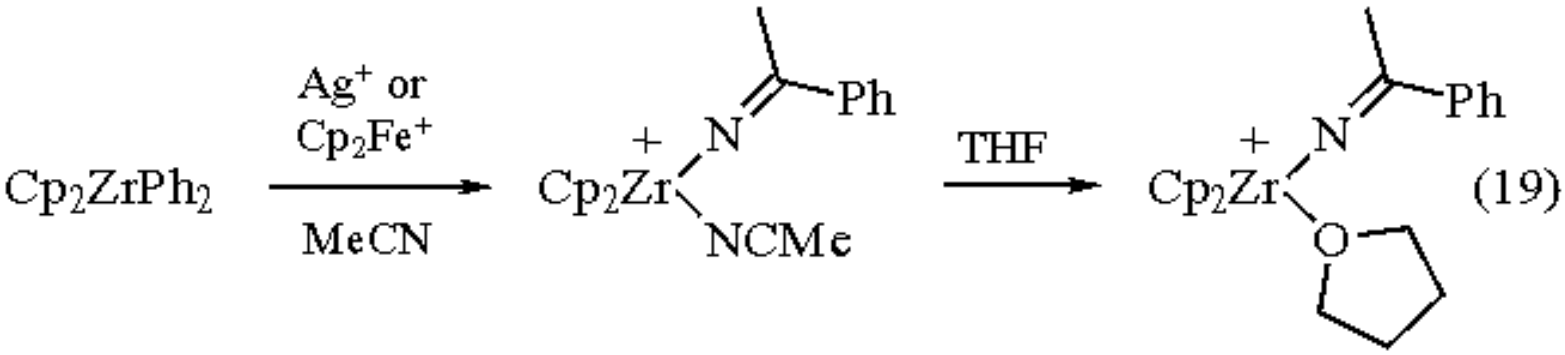

(19)

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Bis(cyclopentadienyl)methylzirconium Tetraphenylborate-Tetrahydrofuran[1]

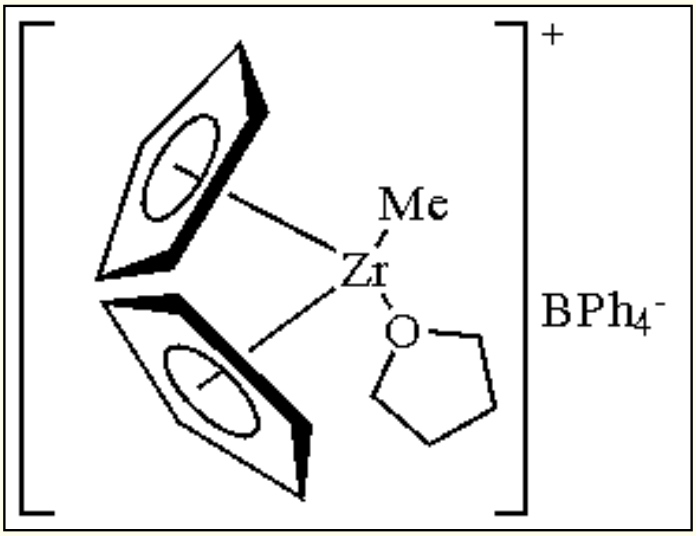

[100909-50-0] · $C_{39}H_{41}BOZr$ · Bis(cyclopentadienyl)methylzirconium Tetraphenylborate-Tetrahydrofuran · (MW 627.78)

(alkene polymerization agent;[2] can insert carbon monoxide, nitriles, and alkynes;[3] can function as a Lewis acid[4])

Solubility: sol CH_2Cl_2 and 1,2-dichloroethane; reacts with protic solvents.

Analysis of Reagent Purity: ^{1}H NMR (CD_2Cl_2) δ 7.6-6.7 (m, 20H, BPh_4^-), 6.31 (s, 10H), 3.44 (m, 4H, THF), 1.80 (m, 4H, THF), 0.74 (s, 3H).

Preparative Methods: treatment of Cp_2ZrMe_2 with 1 equiv of $AgBPh_4$ in MeCN followed by recrystallization from THF gives $Cp_2ZrMe(THF)^+BPh_4^-$.[3a] Alternatively, it can be obtained directly by treating Cp_2ZrMe_2 with $[HNBu_3][BPh_4]$ or $[Cp'_2Fe][BPh_4]$ ($Cp' = C_5H_4Me$) in THF.[5]

Purification: recrystallization from hot THF gives a relatively stable pale yellow crystalline solid.

Handling, Storage, and Precautions: the dry solid is highly sensitive to moisture and oxygen and should be stored in a dry box; a coordinating solvent, such as MeCN, causes ligand exchange.

Ligand.

Although complexes having ligands other than THF are known,[3a] most descriptions focus on the Lewis acidic THF complex due to there being abundant examples of its use in organic synthesis. The THF-free species Cp_2ZrMe^+, generated as a transient intermediate in CH_2Cl_2 solution, decomposes, principally to Cp_2MeCl.[2a] The THF ligand is labile and generally undergoes rapid exchange with nitriles, small phosphines, pyridine, and other heterocycles. In general, the cationic $Cp_2ZrMe(THF)^+$ complex is more reactive than neutral $Cp_2ZrMeCl$ or Cp_2ZrMe_2 complexes as a result of the increased unsaturation and charge.

Insertion Reaction.

The high insertion reactivity of this complex has been noted and representative insertions are summarized in eqs 1-4.

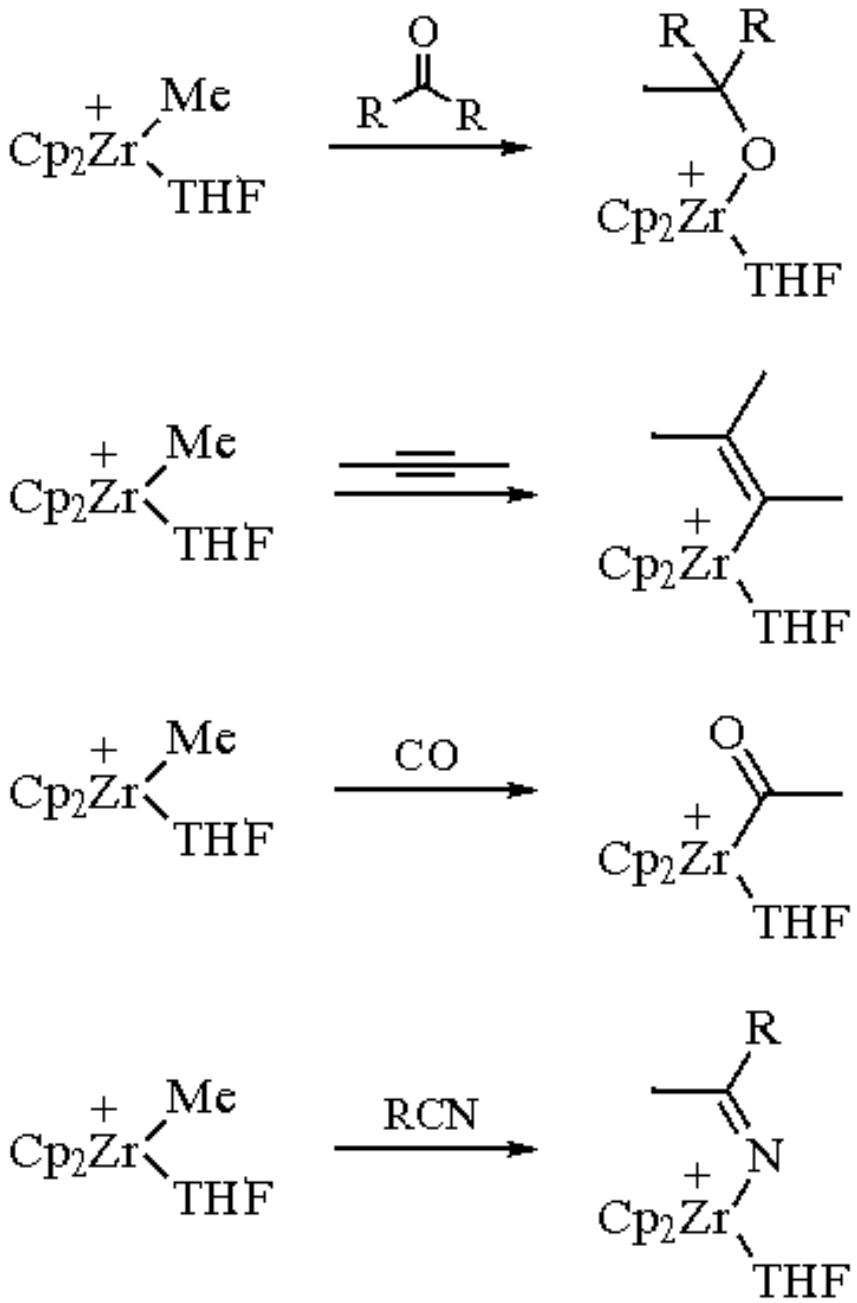

(1)

(2)

(3)

(4)

The Zr-CH_3 bond of this complex in THF can be cleaved by H_2 to yield the insoluble hydride $Cp_2Zr(H)(THF)^+BPh_4^-$.[6]

The reaction of the cationic methyl complex with stoichiometric amounts of α-picoline yields the η^2-pyridyl complex, $Cp_2Zr(\eta^2\text{-}N,C\text{-picolyl})(THF)^+$, via initial ligand substitution followed by rapid C-H activation/CH_4 elimination ($t_{1/2}$ 6 min, 23 °C, CH_2Cl_2) (eq 5).[7]

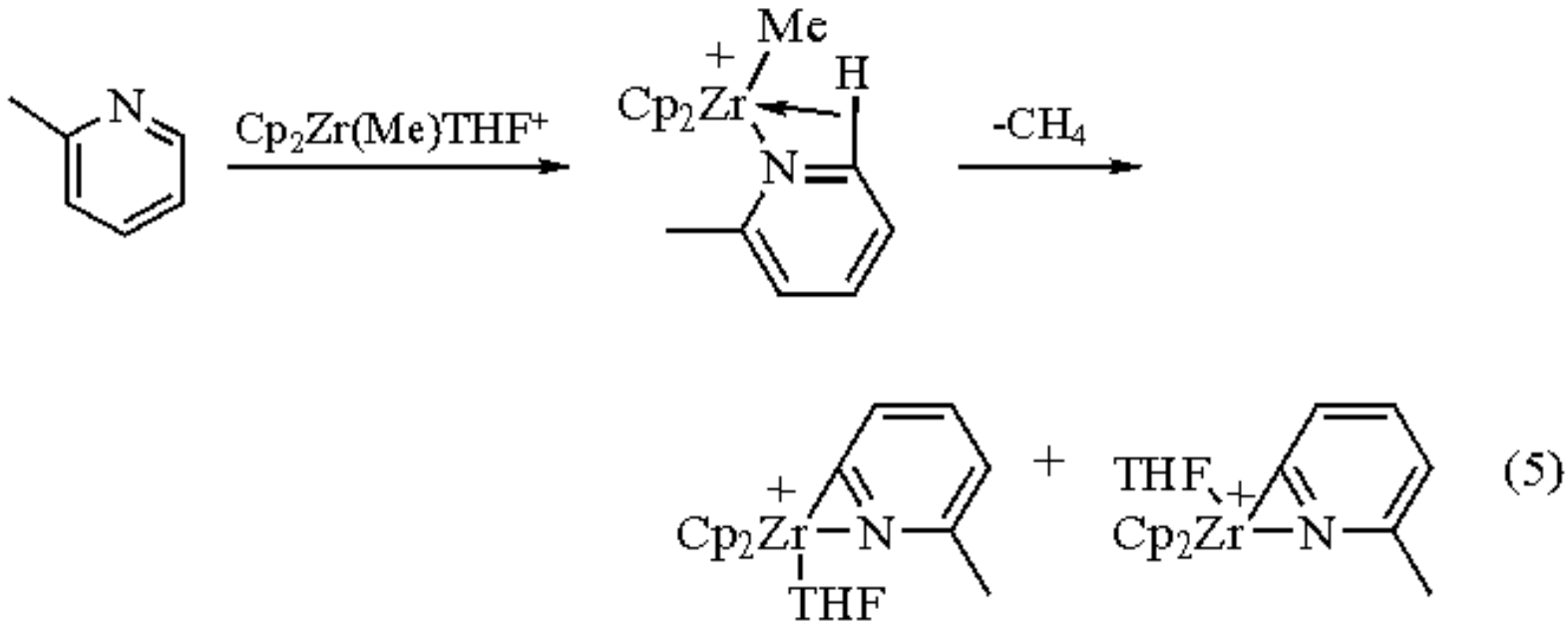

Interestingly, use of pyridine itself causes a much slower reaction (hours, 50 °C, CH_2Cl_2). The acceleration of C-H activation by the α-methyl group of α-picoline is considered to be due to steric crowding which enhances the overlap of the *ortho* C-H bond with the Zr LUMO.[8] The C-H activation of a variety of N-heterocyclic compounds[9] can be achieved in CH_2Cl_2 as shown in eqs 6-8. These metallacycles react with alkenes and alkynes to give stable five- or six-membered metallacycles which can be converted to α-substituted heterocycles upon hydrolysis (eqs 9-11).[7a,9,10] The formation of these metallacycles was suggested to be both kinetically and thermodynamically favored.[10a] More importantly, alkenes and *ortho*-substituted pyridines are coupled by catalytic amounts of $Cp_2Zr(Me)^+$ in 1,2-dichloroethane under an H_2 atmosphere (eq 12).[7b]

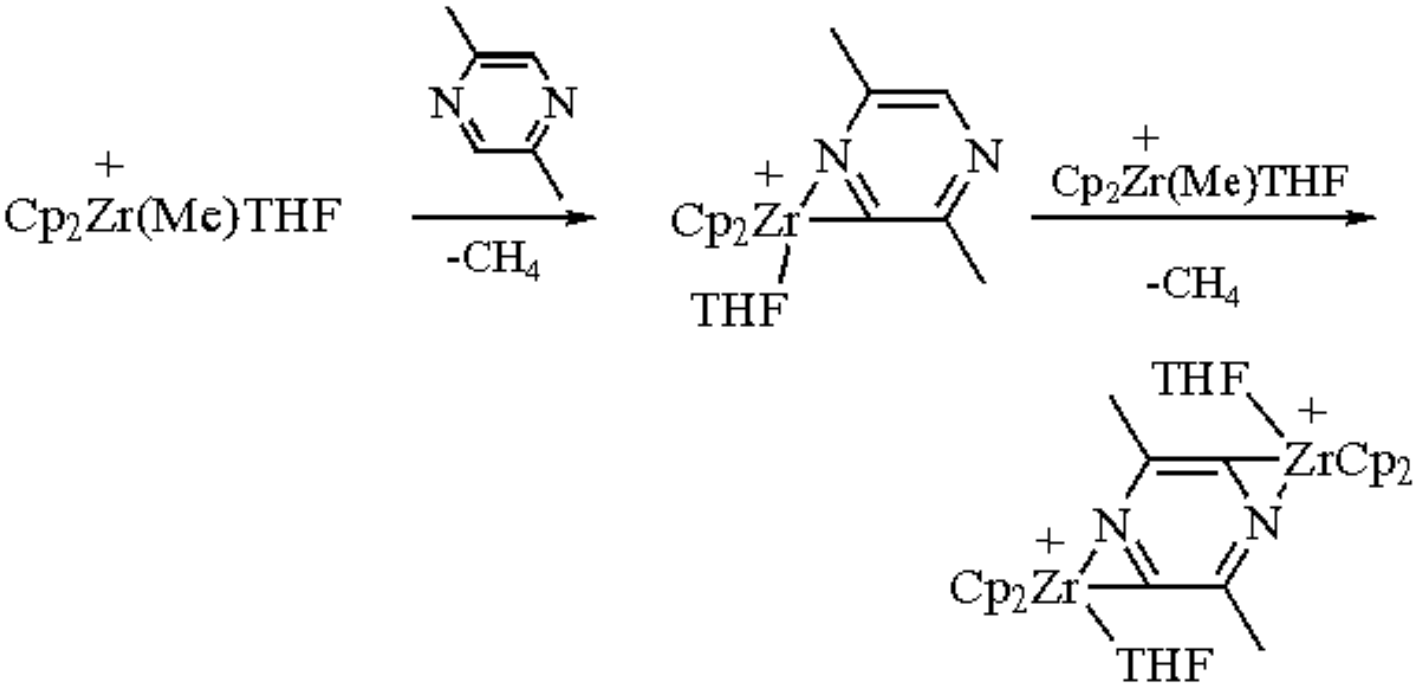
Cp2Zr(Me)THF
-CH4
Cp2Zr
THF
Cp2Zr(Me)THF
-CH4
THF
ZrCp2
Cp2Zr
THF

(6)

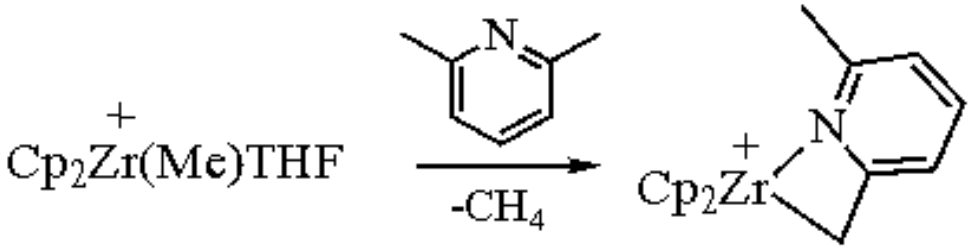
Cp2Zr(Me)THF
-CH4
Cp2Zr

(7)

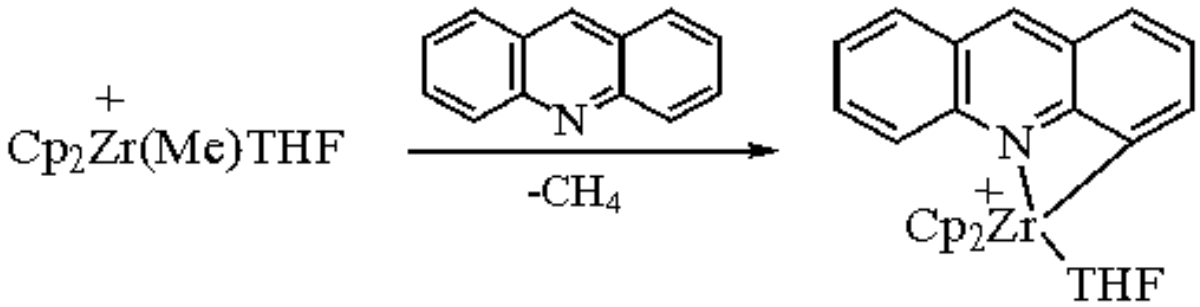
Cp2Zr(Me)THF
-CH4
Cp2Zr
THF

(8)

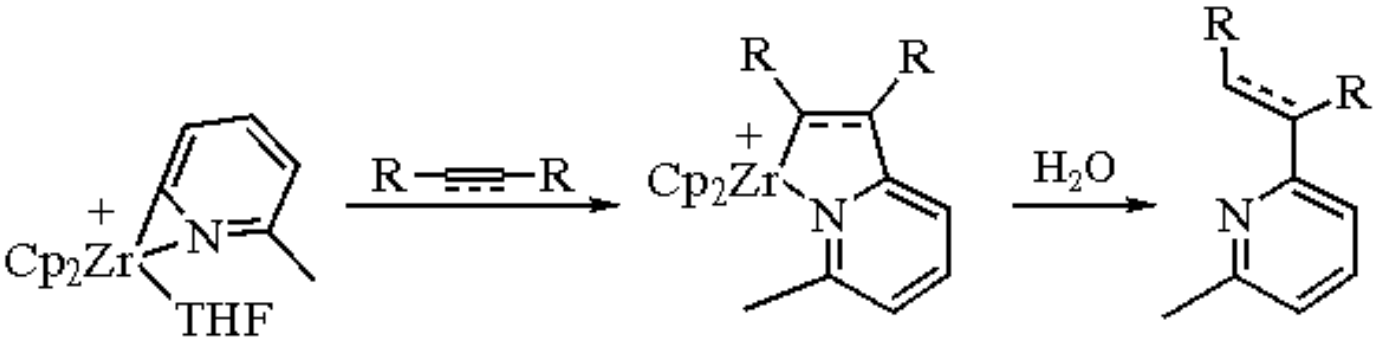
Cp2Zr
THF
R
R
Cp2Zr
H2O
R
R

(9)

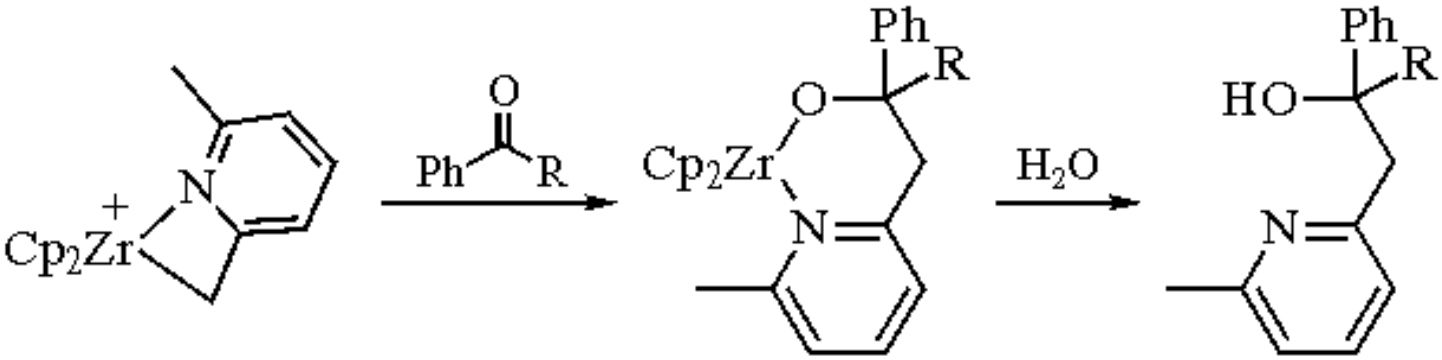

(10)

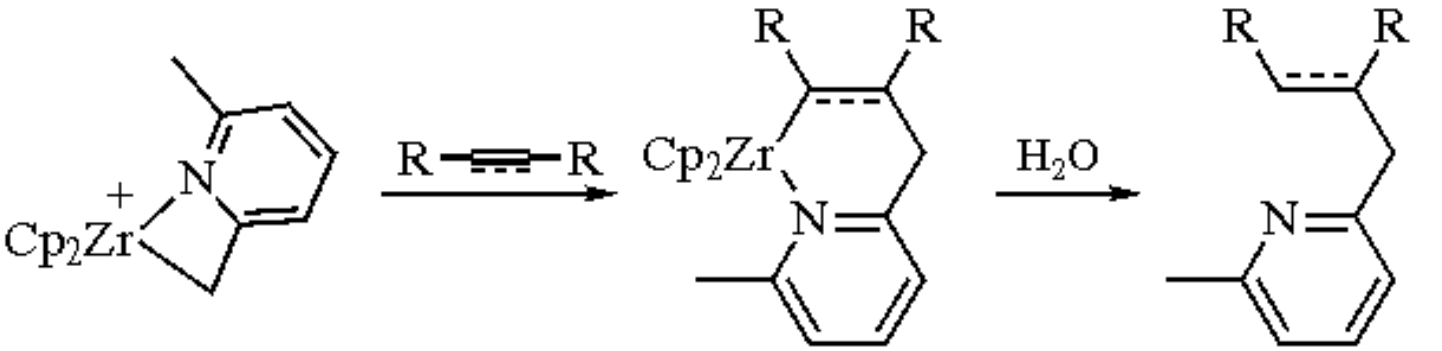

(11)

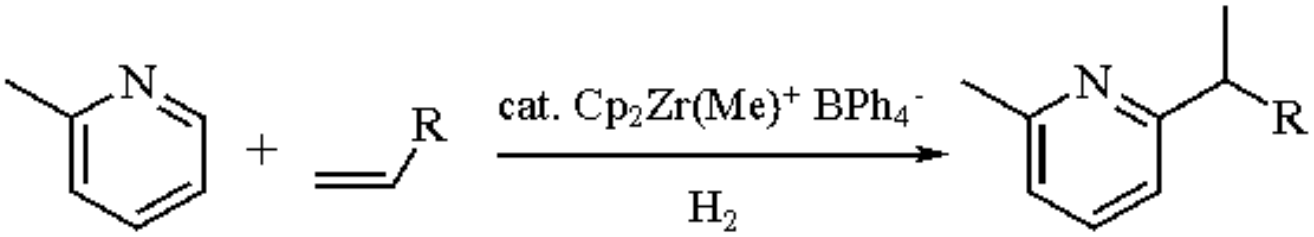

(12)

Lewis Acid Catalyst.

Treatment of $Cp_2Zr(Me)(THF)^+BPh_4^-$ with *t*-BuOH gives $Cp_2Zr(O\text{-}t\text{-}Bu)(THF)^+$ (eq 13), which is an effective catalyst in the Diels-Alder (eq 14) and Mukaiyama aldol reactions (eq 15).[4]

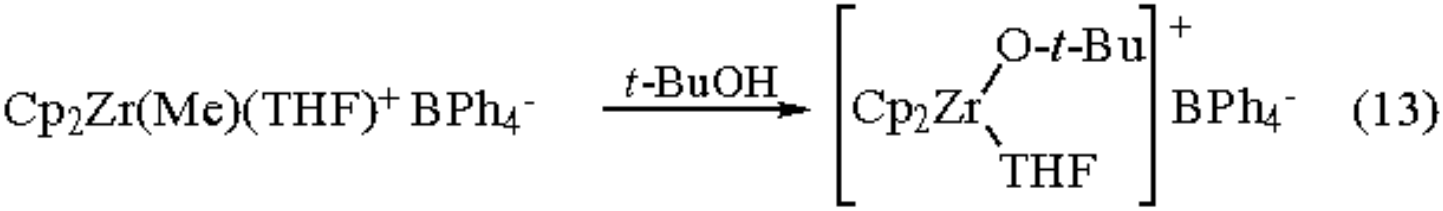

(13)

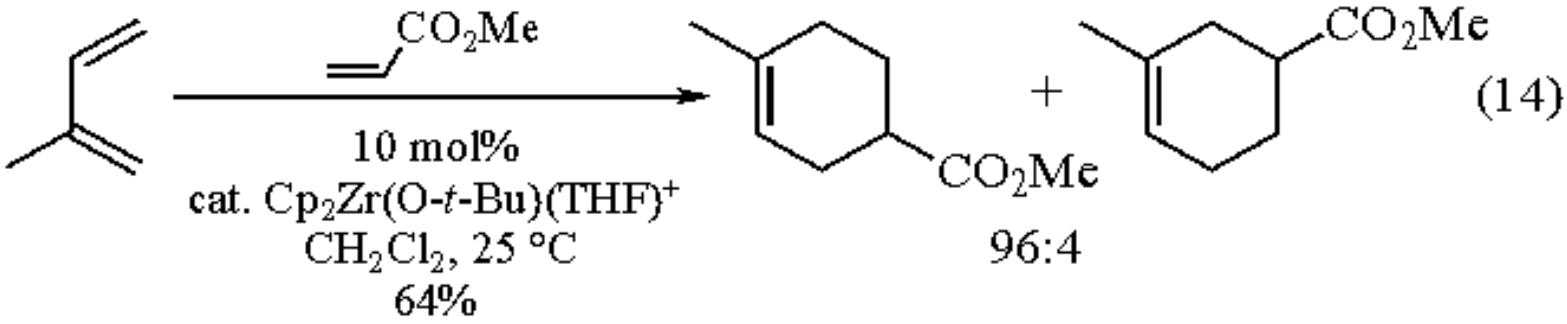

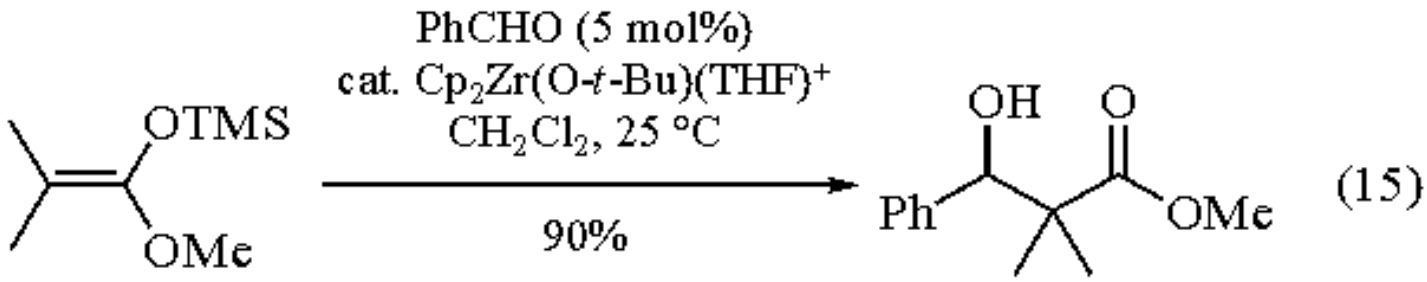

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Bis[(η^5-cyclopentadienyl)(μ-nitrosyl)cobalt](*Co -Co*)

Bis[(η^5-cyclopentadienyl)(μ-nitrosyl)cobalt]

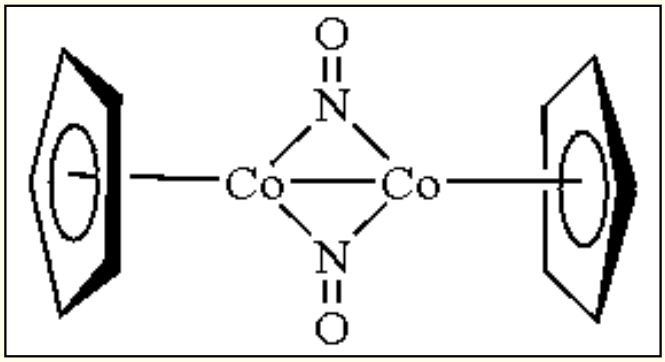

[51862-20-5] · $C_{10}H_{10}Co_2N_2O_2$ · Bis[(η^5-cyclopentadienyl)(μ-nitrosyl)cobalt](*Co -Co*) · (MW 308.08)

(starting material for the synthesis of Co(Cp)[1] and Co(NO)[2-4] containing compounds; also used in the preparation of dinitrosoalkane derivatives[12-14] and 1,2-diamines[15,16])

Physical Data: IR (KBr): 1585 s, 1525 ss, br [ν(NO)] cm^{-1}. ^1H NMR (C_6D_6, int. TMS): δ 4.77 [s, C_5H_5].

Form Supplied in: black, air-stable crystals.

Solubility: sol toluene and CH_2Cl_2.

Preparative Methods: ***Dicarbonyl(cyclopentadienyl)cobalt(I)*** (18 g, 0.1 mol) is dissolved in 150 mL of hexane using the Schlenk technique to exclude air. A weak stream of dry NO is passed through the solution. The NO gas can be prepared in a Kipp apparatus from $NaNO_2$ and concentrated sulfuric acid/water (1:1). Traces of NO_2 are removed by a trap kept at -40 °C and by KOH. After 2 h, the color of the reaction mixture turns from red to brown. A black solid is formed. The suspension is brought to a Kieselgel column (30 × 3 cm) and eluted with petroleum ether until the nonreacted red $Co(Cp)(CO)_2$ is completely eluted. The product elutes with CH_2Cl_2 as a dark brown band. The solution is concentrated until crystallization starts. The product is precipitated by addition of petroleum ether, filtered, washed several times with petroleum ether and dried. Yield: 10-10.5 g (65-70%) (see eq 1).[1]

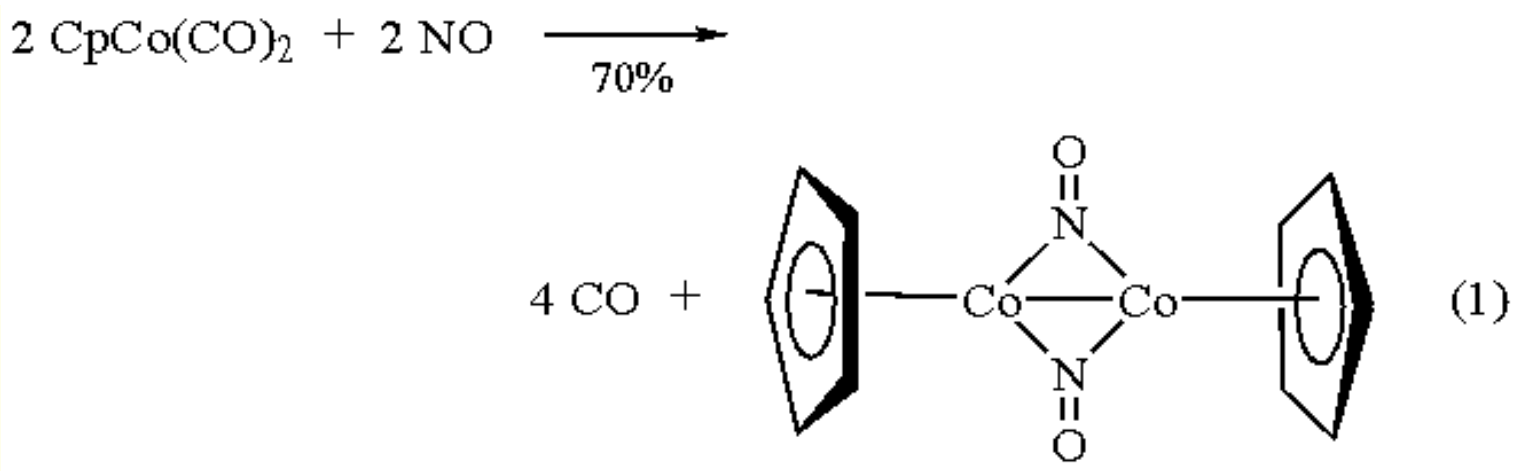

Handling, Storage, and Precautions: solutions of $[Co(Cp)NO]_2$ in toluene or CH_2Cl_2 are air-sensitive. Solid $[Co(Cp)NO]_2$ can be stored without decomposition. Can be sublimed with partial decomposition in high vacuum at 90-100 °C. Handle in a fume hood.

$[Co(Cp)NO]_2$ as the Starting Material for Other CpCo Containing Compounds.

The Co-Co bond in $[Co(Cp)NO]_2$ can be cleaved to give the compounds [(Cp)Co(NO)R],[2] [(Cp)Co(NO)Cl],[3] $[(Cp)Co(NO)GeR_3]$,[4] and $[(Cp)Co(NO)SnR_3]$.[4] $[Co(Cp)NO]_2$ can also be used for the preparation of other compounds such as $[(Cp)CoH]_4$[5] and $[(Cp)Co]_3(NO)_2$.[6] The NO bridges in $[Co(Cp)NO]_2$ can be replaced by carbonyl bridges,[6-8] by methylene bridges,[9] by amido bridges,[10] and by phenylthiolato and diphenylphosphido bridges.[11]

An interesting reaction takes place if $[Co(Cp)NO]_2$ is treated with NO in the presence of alkenes such as norbornene. A unique chelating bis(nitrosoalkane) ligand system is formed in this three-component synthesis (see **1**),[12-14] which can be used for the synthesis of 1,2-diamines.[15,16] Detailed mechanistic studies have been reported.[17-19]

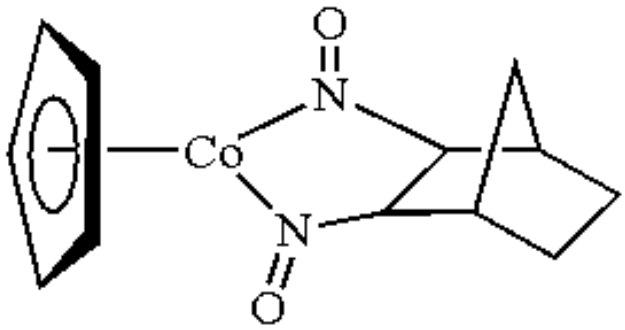

(1)

Chemical[20-22] and electrochemical[23] oxidations as well as chemical[3] and electrochemical[23] reductions of $[Co(Cp)NO]_2$ have been reported. The pentamethylcyclopentadienyl analog $[Co(\eta^5\text{-}C_5Me_5)NO]_2$[3] and the pentaphenylcyclopentadienyl analog $[Co(\eta^5\text{-}C_5Ph_5)NO]_2$[24] of $[Co(Cp)NO]_2$ have been prepared. The structure of $[Co(Cp)NO]_2$ was determined by X-

ray crystallography.[8] Spectroscopic measurements and calculations concerning the electronic structure of $[Co(Cp)NO]_2$ have been reported.[25-33]

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Bis(cyclopentadienyl)titanium Bis(trifluoromethanesulfonate)[1]

($Cp_2Ti(OSO_2CF_3)_2$) (**1**)

[76262-87-8] · $C_{12}H_{10}F_6O_6S_2Ti$ · Bis(cyclopentadienyl)titanium Bis(trifluoromethanesulfonate) · (MW 476.20) ($Cp_2Zr(OSO_2CF_3)_2$) (**2**)

[94728-52-6] · $C_{12}H_{10}F_6O_6S_2Zr$ · Bis(cyclopentadienyl)zirconium Bis(trifluoromethanesulfonate) · (MW 519.54) ($Cp^*_2Ti(OH_2)_2^{2+}$) (**3**)

[121266-23-7] · $C_{20}H_{34}O_2Ti$ · Bis(pentamethylcyclopentadienyl)diaquatitanium · (MW 354.37)

(catalyst for Diels-Alder reaction, Mukaiyama crossed-aldol reaction, and Sakurai reaction)

Physical Data: (**1**) red crystals; ^1H NMR (CD_3NO_2) δ 7.06 (s). An X-ray crystal structure has been reported.[2]

Solubility: sol CH_2Cl_2, $MeNO_2$; insol benzene, hexane.

Analysis of Reagent Purity: NMR, elemental analysis.

Preparative Method: [1,2] $Cp_2Ti(OSO_2CF_3)_2$ is prepared by treatment of a 0.06 M THF solution of ***Dichlorobis(cyclopentadienyl)titanium*** with 5.5 equiv of a 0.19 M THF solution of ***Silver(I) Trifluoromethanesulfonate***. After stirring for 15 min the reaction mixture is filtered, the red filtrate is layered with hexane, and the resulting red crystals are collected. Recrystallization from CH_2Cl_2/pentane or THF/hexane affords $Cp_2Ti(OSO_2CF_3)_2$ (25-30%) as red needles. The precursors (Cp_2TiCl_2 and $AgOSO_2CF_3$) are widely available.

Handling, Storage, and Precautions: $Cp_2Ti(OSO_2CF_3)_2$ and $Cp_2Zr(OSO_2CF_3)_2$ can be handled for short periods of time in air, but are best handled and stored in a glove box. Both can be prepared in situ. The pentamethylcyclopentadienyl analog $Cp^*_2Ti(OH_2)_2^{2+}$ is air and water stable. Titanium(IV) is reputed to be

of low toxicity.

General.

The triflate analog of titanocene dichloride, $Cp_2Ti(OSO_2CF_3)_2$, was first prepared in 1980.[2] The trifluoromethanesulfonate ligands were found to be covalently bound to the titanium center in the solid state[2] and in CD_2Cl_2 solution,[1,3] but are easily displaced by various neutral ligands such as water,[4] methyl vinyl ketone (MVK), and nitromethane.[1,3] Recent interest in $Cp_2Ti(OSO_2CF_3)_2$ (**1**), its zirconium analog $Cp_2Zr(OSO_2CF_3)_2$ (**2**), and in the pentamethylcyclopentadienyl diaqua complex $Cp^*_2Ti(OH_2)_2^{2+}$ (**3**),[4] has focused on the ability of these species to function as Lewis acids in various organic transformations.[1,3,5-7] It has been found that very low catalyst loadings are required (0.01-1 mol %) for many transformations which typically require stoichiometric Lewis acids. Although most of the work reported to date has concerned simple substrates and NMR scale reactions, isolated yields are noted to be in the 65-90% range for many of these transformations. The generality of the ability of (**1**)-(**3**) to mediate reactions of more complex molecules remains to be determined.

NMR studies of the interaction of $Cp_2Ti(OSO_2CF_3)_2$ with MVK indicate that the ketone can displace triflate from the titanium center, affording a number of different species including cationic complexes such as $Cp_2Ti(OSO_2CF_3)(MVK)^+$ and $Cp_2Ti(MVK)_2^{2+}$. These cationic complexes are formed reversibly and rapidly, and are believed to account for the observed catalytic activity.[3] In addition, the zirconium complex (**2**), when prepared in THF, is isolated as a THF solvate (**2**.THF).

Diels-Alder Reactions.[1,3,5]

The Diels-Alder cycloaddition between simple 1,3-dienes such as cyclopentadiene and isoprene with α,β-unsaturated carbonyl compounds such as MVK and acrolein is efficiently catalyzed by (**1**)-(**3**) (eqs 1-3). As is typical of Lewis acid-catalyzed Diels-Alder reactions, enhanced *endo* selectivity is observed compared to the thermal reactions. An advantage of these catalysts over other Lewis acids such as ***Titanium(IV) Chloride*** or ***Tin(IV) Chloride*** is that strictly anhydrous conditions need not be maintained, and catalyst loadings of 1 mol % are sufficient to drive the reaction to completion in a reasonable time period (<24 h) for most substrates.[1,3] The addition of up to 10 equiv (vs. catalyst) of water to reactions mediated by the diaqua complex (**3**) has no observed effect on the rate of reaction, nor do the products inhibit catalytic activity.[5]

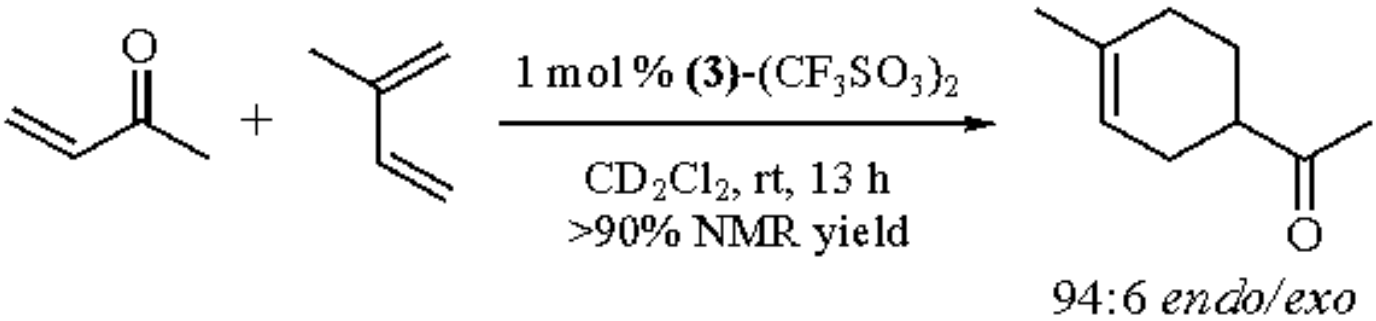

(1)

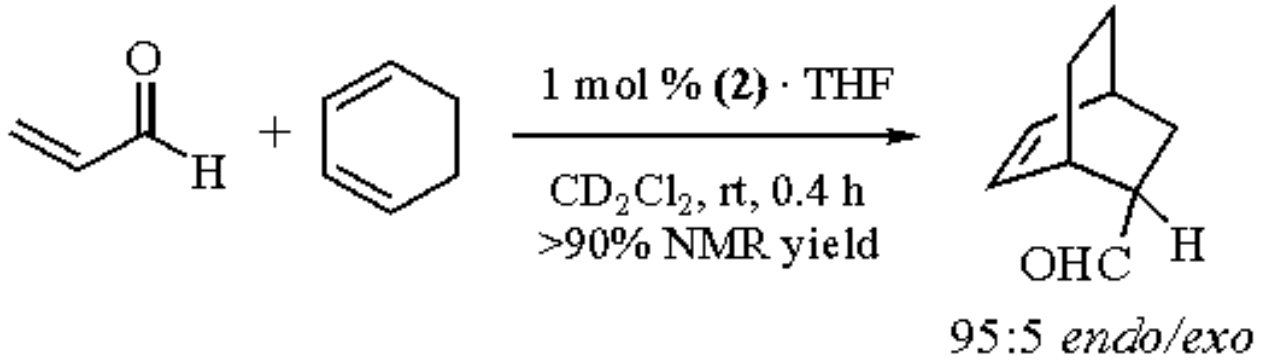

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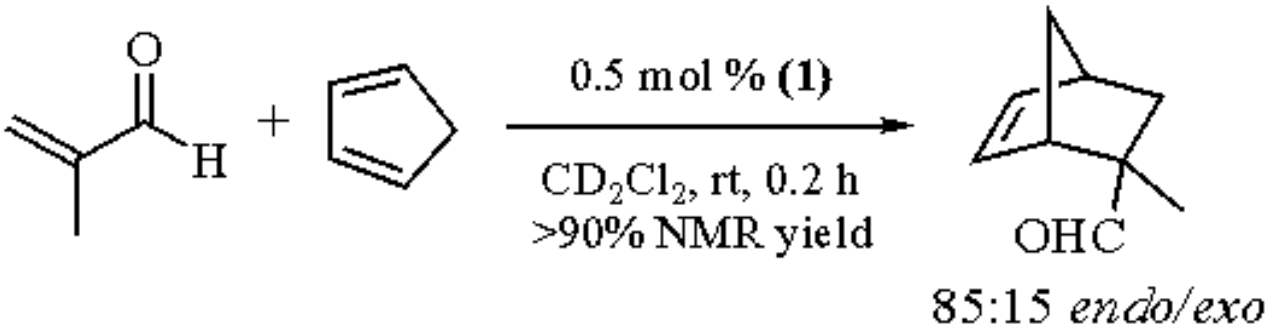

(3)

Mukaiyama Crossed-Aldol Reactions.[1,6]

Catalysts (**1**) and (**2**).THF have also been shown to catalyze the reaction between silyl enol ethers and carbonyls (eqs 4 and 5) (i.e. the Mukaiyama crossed-aldol reaction[8]). Catalyst loadings of 0.5% are sufficient except for highly hindered substrates such as pinacolone, and pivaldehyde reacts only slowly under the typical reaction conditions with a 2,2-dimethylsilyl ketene acetal. The primary advantages of (**1**) and (**2**).THF over other typical Lewis acids such as $TiCl_4$ and ***Boron Trifluoride*** are decreased susceptibility to inhibition by water, and the smooth reaction of silyl enol ethers at low catalyst loadings.

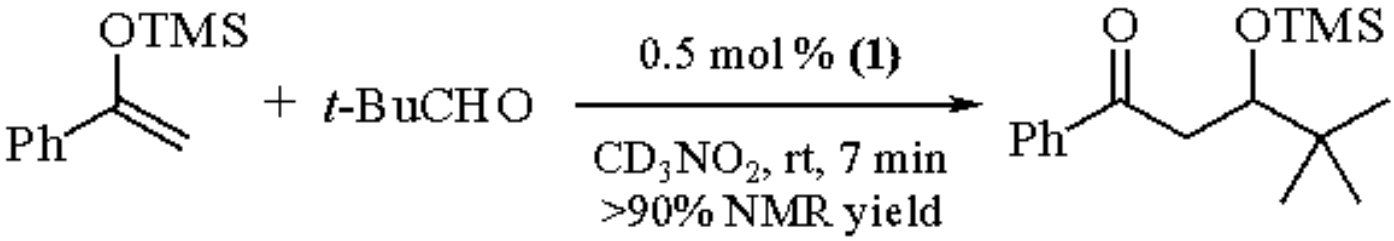

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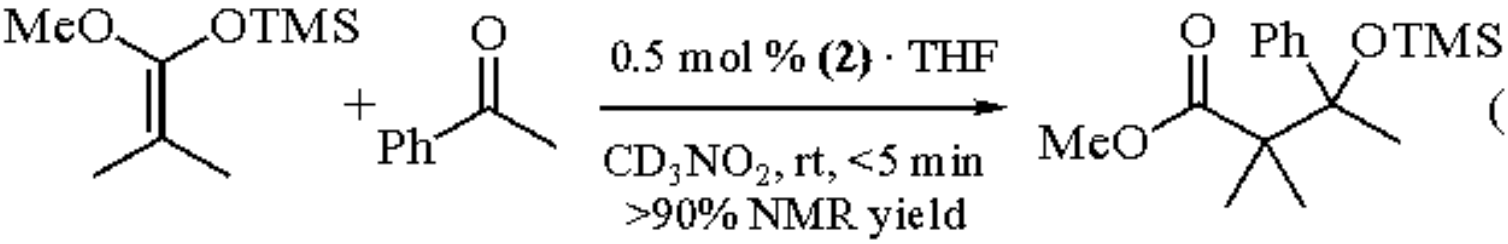

(5)

Sakurai Reactions.[1,7]

The reaction of allylsilanes with ketones and acetals (the Sakurai reaction[9]) is catalyzed efficiently by (**1**) and (**2**).THF (eqs 6 and 7). As with the Diels-Alder and Mukayama reactions discussed above, very low catalyst loadings are required. In addition to ketones and acetals (eqs 6 and 7), a limited number of orthoesters also react with allylsilanes when catalyzed by (**1**) (eq 8).

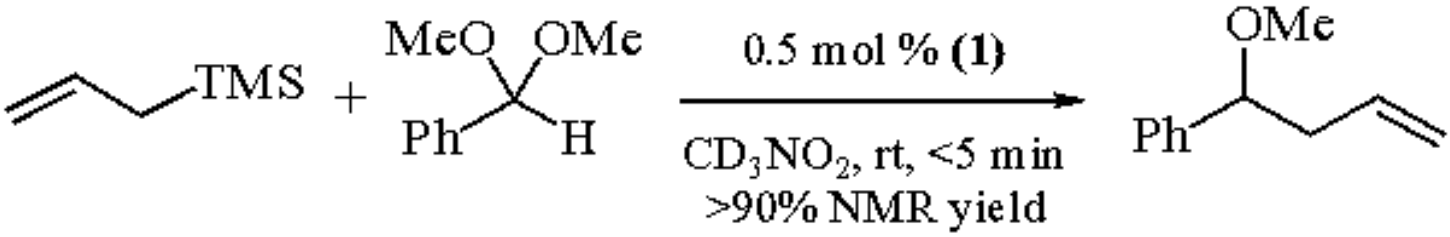

(6)

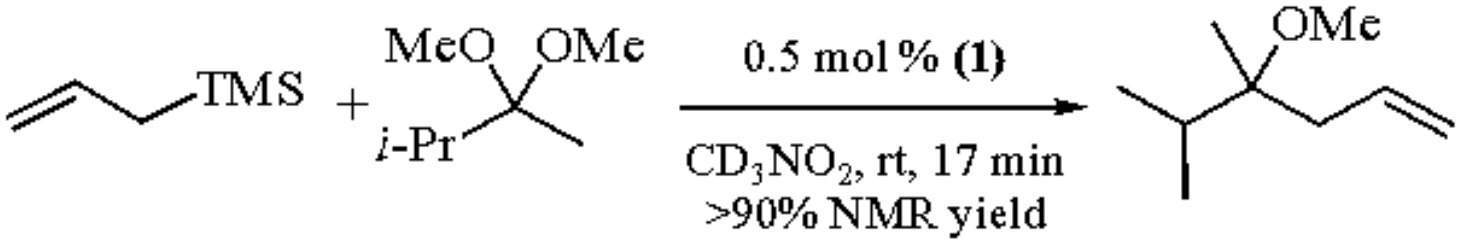

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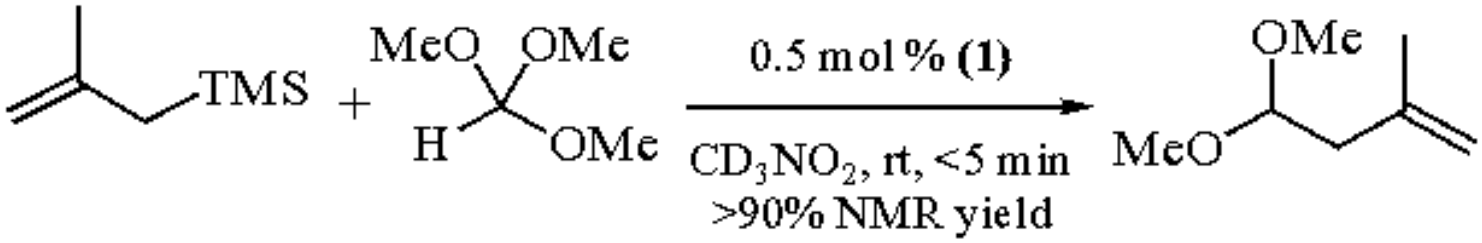

(8)

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1. Hollis, T. K.; Odenkirk, W.; Robinson, N. P.; Whelan, J.; Bosnich, B. *T* **1993**, *49*, 5415.
2. Thewalt, U.; Klein, H. P. *Z. Kristallogr*. **1980**, *153*, 307.
3. Hollis, T. K.; Robinson, N. P.; Bosnich, B. *OM* **1992**, *11*, 2745.
4. Thewalt, U.; Honold, B. *JOM* **1988**, *348*, 291.
5. Hollis, T. K.; Robinson, N. P.; Bosnich, B. *JACS* **1992**, *114*, 5464.
6. Hollis, T. K.; Robinson, N. P.; Bosnich, B. *TL* **1992**, *33*, 6423.
7. Hollis, T. K.; Robinson, N. P.; Whelan, J.; Bosnich, B. *TL* **1993**, *34*, 4309.
8. Reviews: (a) Mukaiyama, T. *OR* **1982**, *28*, 203. (b) Mukaiyama, T.; Murakami, M. *S* **1987**, 1043.
9. Reviews: (a) Sakurai, H. *PAC* **1982**, *54*, 1. (b) Fleming, I.; Dunogués, J.; Smithers, R. *OR* **1989**, *37*, 57.

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Bis(cyclopentadienyl)bis(2,6-dimethylphenylamino)zirconium

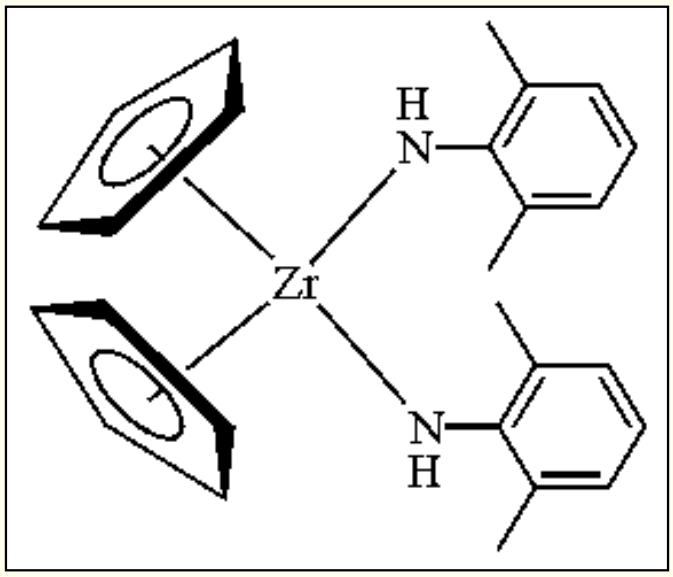

[117939] · $C_{26}H_{30}N_2Zr$ · Bis(cyclopentadienyl)bis(2,6-dimethylphenylamino)zirconium · (MW 461.76)

(hydroamination catalyst, precursor to the reactive imido intermediate $Cp_2Zr{=}NAr$)

Alternate Name: bis(cyclopentadienyl)zirconium bis(2,6-dimethylphenyl)amide.

Solubility: insol *n*-hexane and ether; sol toluene and THF.

Preparative Methods: $Cp_2Zr(NHAr)_2$ (**1**) can be prepared by heating Cp_2ZrMe_2 with 2,6-dimethylaniline or by addition of Cp_2ZrCl_2 to a solution containing 2 equiv LiNHAr (eq 1).[1]

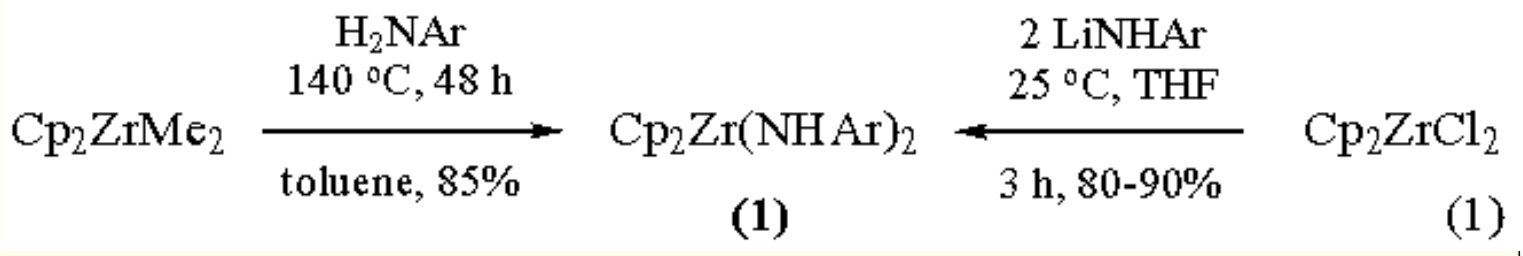

Purification: recrystallization from toluene layered with *n*-hexane.

Handling, Storage, and Precautions: $Cp_2Zr(NHAr)_2$ is water sensitive and should be handled and stored under a nitrogen atmosphere in a dry box or using standard Schlenk techniques. Solvents should be free of traces of air and moisture. Zirconium is believed to be of low toxicity; 2,6-dimethylaniline is toxic. Use in a fume hood.

Reactivity.

Thermolysis of (**1**) at 95-110 °C in toluene results in the α-elimination of 1 equiv of 2,6-dimethylaniline and generation of the transient intermediate $Cp_2Zr{=}NAr$.[1,2] This intermediate has been trapped as its ligand adduct $Cp_2Zr(=NAr)(L)$ (L = THF, $OPPh_3$) with Lewis bases, and it reacts with alkynes to give azametallacyclobutenes (**2**) (eq 2). Cycloadditions with a variety of alkynes have been observed and were found to be reversible near 95 °C.

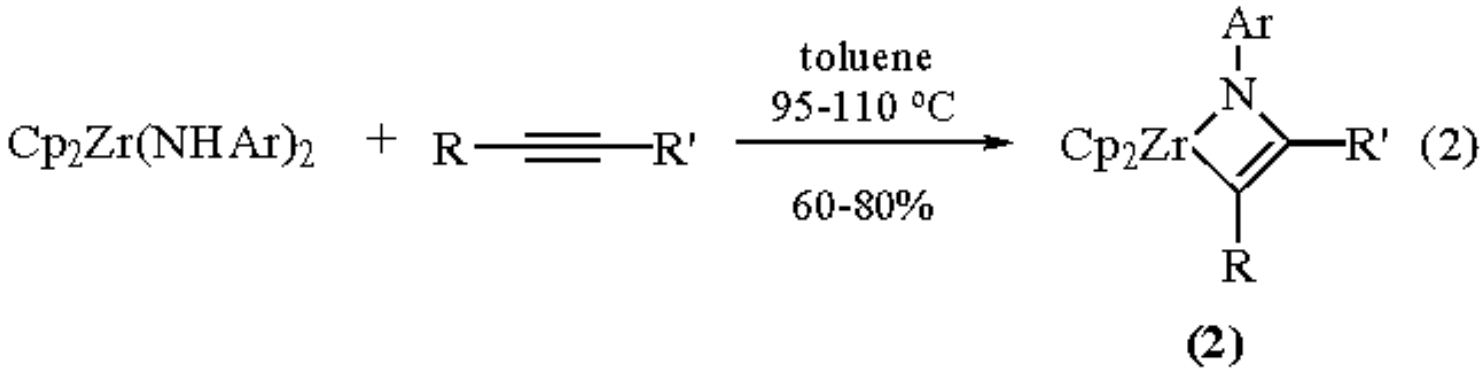

(2)

Catalytic Hydroamination of Alkynes and Allene.

(**1**) also serves as a catalyst for the hydroamination of alkynes.[1,3] For example, heating a toluene solution containing equal amounts of 2,6-dimethylaniline and diphenylacetylene in the presence of 3 mol % of (**1**) to 95-110 °C results in the formation of the *N*-(2,6-dimethylphenyl)enamine (**3**) (eq 3). The rate of production of enamine is slow under these conditions; however, if the reaction is conducted with the exclusion of air and water, complete conversion to the enamine is observed. Additionally, heating allene and 2,6-dimethylaniline with 3 mol % of (**1**) to 90 °C for 6 days results in the formation of the anti-Markovnikov addition product, the 2,6-dimethylphenylimine of acetone.[3] When (**1**) and 2,6-dimethylaniline are heated in the presence of ethylene, allylbenzene, or norbornene, no addition of the amine to the alkene occurs.

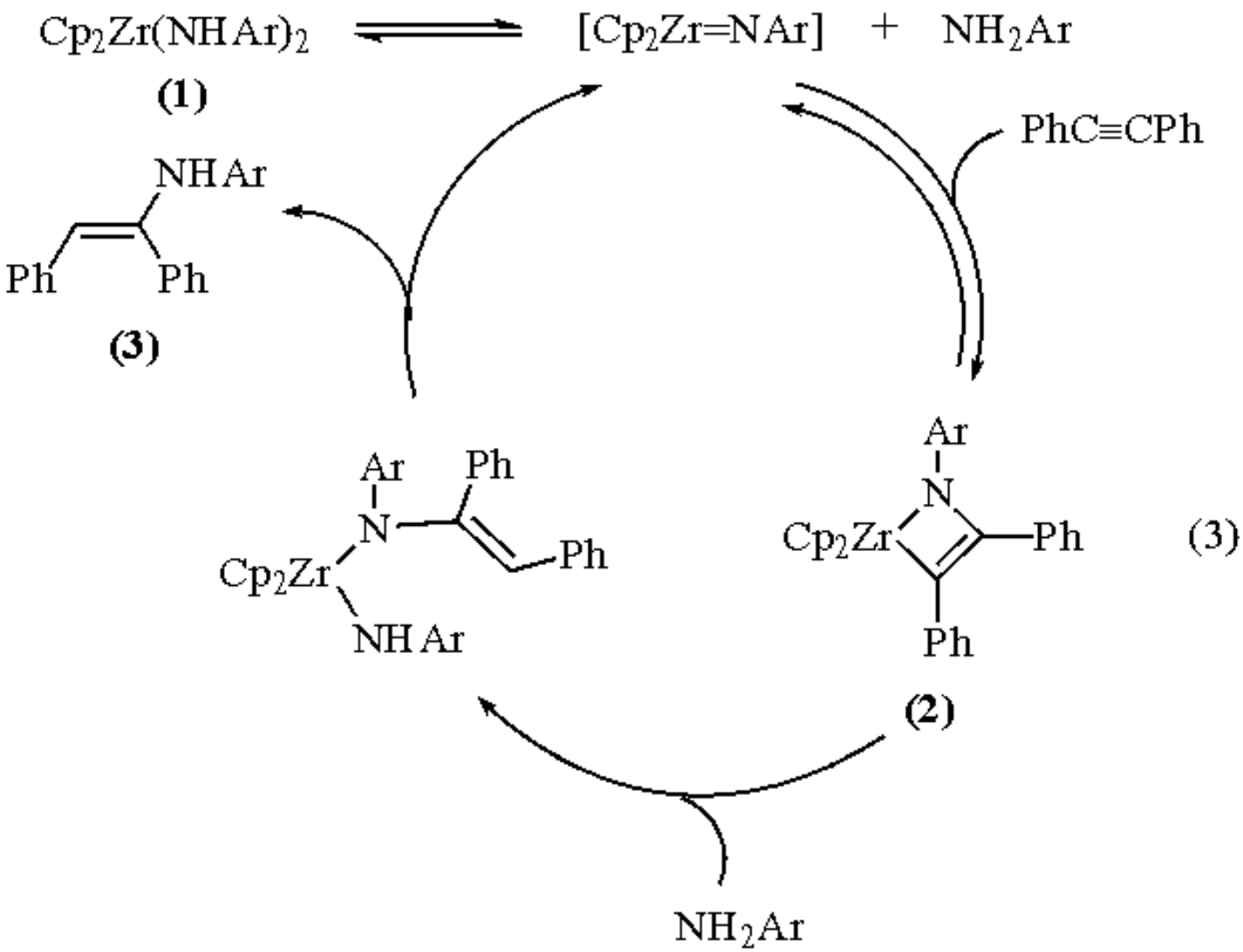

Regiochemistry of Additions.

Stoichiometric generation of the reactive imido intermediate $Cp_2Zr{=}NAr$ in the presence of unsymmetrical alkynes results in formation of two regioisomeric azametallacyclobutenes.[3] Regioselectivity comparable to that of the hydroborating reagents disiamylborane and dicyclohexylborane has been observed.[4] The larger substituent on the alkyne exhibits a strong preference to be α to the zirconium center leading primarily to the anti-Markovnikov products after hydrolysis of the metallacycles. The origin of this selectivity is believed to be dictated by the steric interactions between the large nitrogen bound group and the substituent on the alkyne. Generation of $Cp_2Zr{=}NAr$ from (**1**) under catalytic conditions results in an erosion in the regiospecificity of the hydroamination product. This is due to the reversibility of the cycloaddition and the difference in relative rates of protonation of the regioisomeric metallacycles by 2,6-dimethylaniline (which favors protonation of the minor regioisomer for steric reasons).

Formation of α,β-Unsaturated Imines.

(**1**) can be used in a two-step process for the synthesis of α,β-unsaturated imines as illustrated in eq 4.[5] The first step involves synthesis of the azametallacyclobutene. Addition of benzaldehyde or isobutyraldehyde initially gives the addition product which, upon warming, undergoes a [2 + 4] cycloreversion to provide the α,β-unsaturated imine.

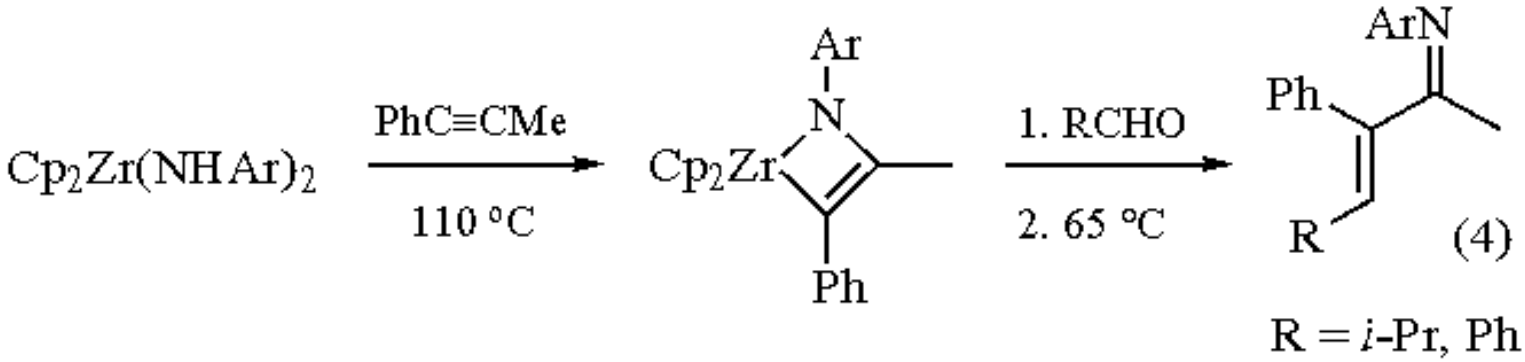

Related Reagents.

Chloro(cyclopentadienyl)dimethyltitanium.

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1. Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *JACS* **1992**, *114*, 1708.
2. Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *JACS* **1988**, *110*, 8729.
3. Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *JACS* **1993**, *115*, 2753.
4. Brown, H. C.; Campbell, J. B., Jr. *Aldrichim. Acta* **1981**, *14*, 3.
5. (a) Baranger, A. M. Ph.D. Thesis, University of California, Berkeley, 1993. (b) Hanna, T. A.; Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *JACS* **1995**, *117*, submitted for publication.

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Bis(dibenzylideneacetone)palladium(0)

$(PhCH{=}CHCOCH{=}CHPh)_2Pd$

[32005-36-0] · $C_{34}H_{28}O_2Pd$ · Bis(dibenzylideneacetone)palladium(0) · (MW 575.01)

(catalyst for allylation of stabilized anions,[1] cross coupling of allyl, alkenyl, and aryl halides with organostannanes,[2] cross coupling of vinyl halides with alkenyl zinc species,[3] cyclization reactions,[4] and carbonylation of alkenyl and aryl halides[5])

Physical Data: mp 135 °C (dec).

Form Supplied in: solid.

Preparative Method: prepared by adding sodium acetate to a hot methanolic solution of dibenzylideneacetone and $Na_2[Pd_2Cl_6]$, cooling, filtering, washing with MeOH, and air drying.[6]

Handling, Storage, and Precautions: moderately air stable in the solid state; slowly decomposes in solution to metallic palladium and dibenzylideneacetone.

Allylation of Stabilized Anions.

$Pd(dba)_2$ is an effective catalyst for the coupling of electrophiles and nucleophiles, and has found extensive use in organic synthesis (for a similar complex with distinctive reactivities, see also ***Tris(dibenzylideneacetone)dipalladium***). Addition of a catalytic amount of $Pd(dba)_2$ activates allylic species, such as allylic acetates or carbonate derivatives, toward nucleophilic attack.[1] The intermediate organometallic complex, a π-allylpalladium species, is formed by backside displacement of the allylic leaving group, and stereochemical inversion of the original allylic position results. Subsequent nucleophilic attack on the external face of the allyl ligand displaces the palladium in this double inversion process to regenerate the original stereochemical orientation (eq 1).[7] The allylpalladium intermediate can also be generated from a variety of other substrates, such as allyl sulfones,[8] allenes,[9] vinyl epoxides,[10] or α-allenic phosphates.[11] In general, the efficiency of $Pd(dba)_2$ catalysis is optimized through the addition of either ***Triphenylphosphine*** or ***1,2-Bis(diphenylphosphino)ethane*** (dppe).

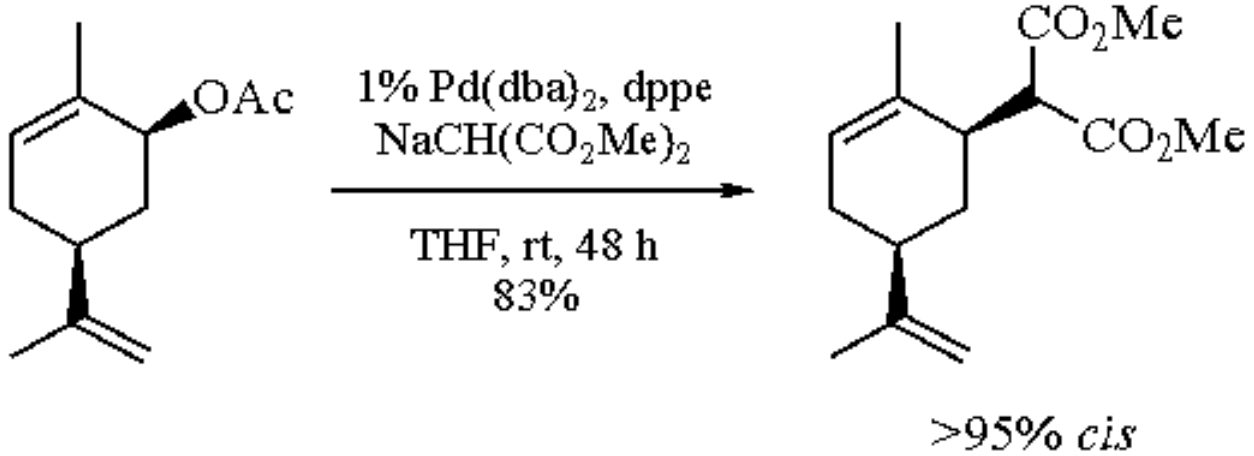

(1)

The anions of malonate esters,[12] cyclopentadiene,[12] β-keto esters,[13] ketones,[13,14] aldehydes,[14] α-nitroacetate esters,[15] Meldrum's acid,[15] diethylaminophosphonate Schiff bases,[16] β-diketones,[17] β-sulfonyl ketones and esters,[17] and polyketides[18,19] represent the wide variety of carbon nucleophiles effective in this reaction. Generation of the stabilized anions normally is accomplished by addition of ***Sodium Hydride***, ***Potassium Hydride***, or basic ***Alumina***.[15] However, when allyl substrates such as allylisoureas,[14] allyl oxime carbonates,[17] or allyl imidates[20] are used, the allylation reaction proceeds without added base. Nitrogen nucleophiles, such as azide[10] and nucleotide[21] anions, are useful as well.

The coupling reaction generally proceeds regioselectively with attack by the nucleophile at the least hindered terminus of the allyl moiety,[22] accompanied by retention of alkene geometry (eq 2). Even electron-rich enol ethers can be used as the allylic moiety when an allylic trifluoroacetyl leaving group is present.[23] When steric constraints of substrates are equivalent, attack will occur at the more electron rich site.[19] Although this reaction is usually performed in THF, higher yields and greater selectivity are observed for some systems with the use of DME, DMF, or DMSO.[14,16,20] Alternatively, $Pd(dba)_2$ can promote efficient substitution of allylic substrates in a two-phase aqueous-organic medium through the use of $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ as a phase transfer ligand.[24]

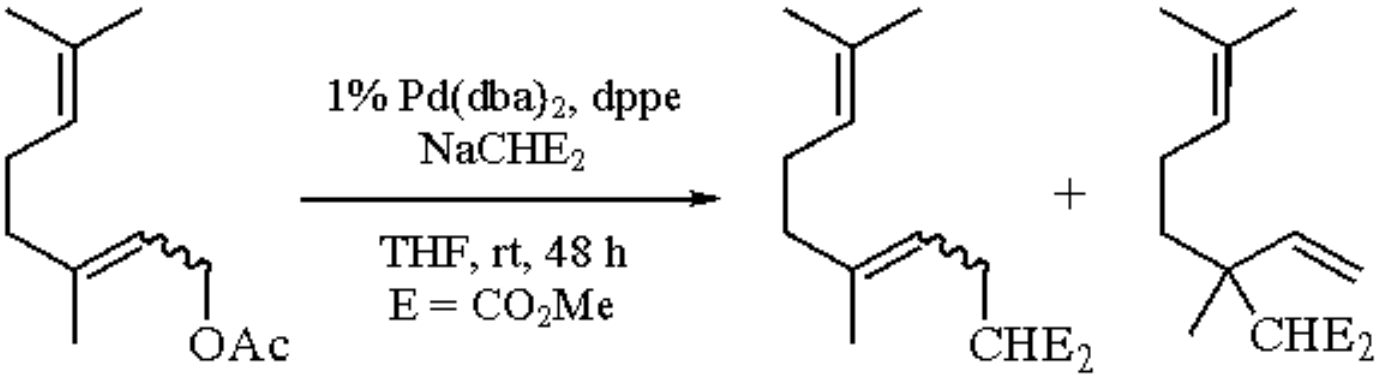

(2)

(*E*) isomer	47%	95 (*E* only):5
(*Z*) isomer	62%	76 (*Z* only):23

Intramolecular reaction of a β-dicarbonyl functionality with a π-allyl species can selectively produce three-,[25] five-,[25] or six-membered[26] rings (eq 3).

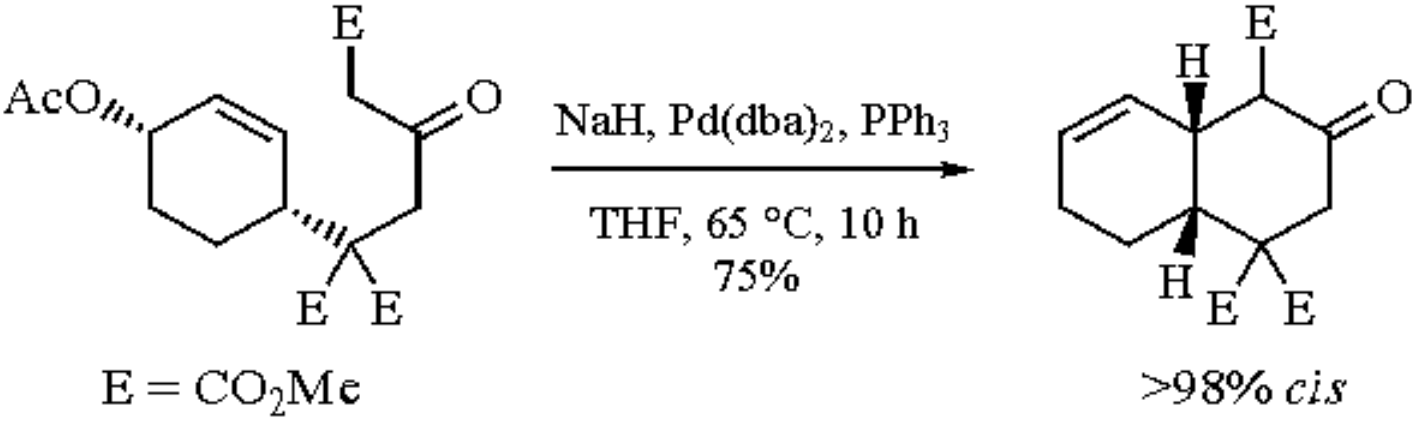

(3)

Asymmetric Allylation Reactions.

Employing chiral bidentate phosphine ligands in conjunction with $Pd(dba)_2$ promotes allylation reactions with moderate to good enantioselectivities, which are dependent upon the solvent,[27] counterion,[28] and nature of the allylic leaving group.[27] Chiral phosphine ligands have been used for the asymmetric allylation of α-hydroxy acids (5-30% ee),[29] the preparation of optically active methylenecyclopropane derivatives (52% ee),[22] and chiral 3-alkylidenebicyclo[3.3.0]octane and 1-alkylidenecyclohexane systems (49-90% ee).[27] Allylation of a glycine derivative provides a route to optically active α-amino acid esters (eq 4).[28] The intramolecular reaction can produce up to 69% ee when vicinal stereocenters are generated during bond formation (eq 5).[30]

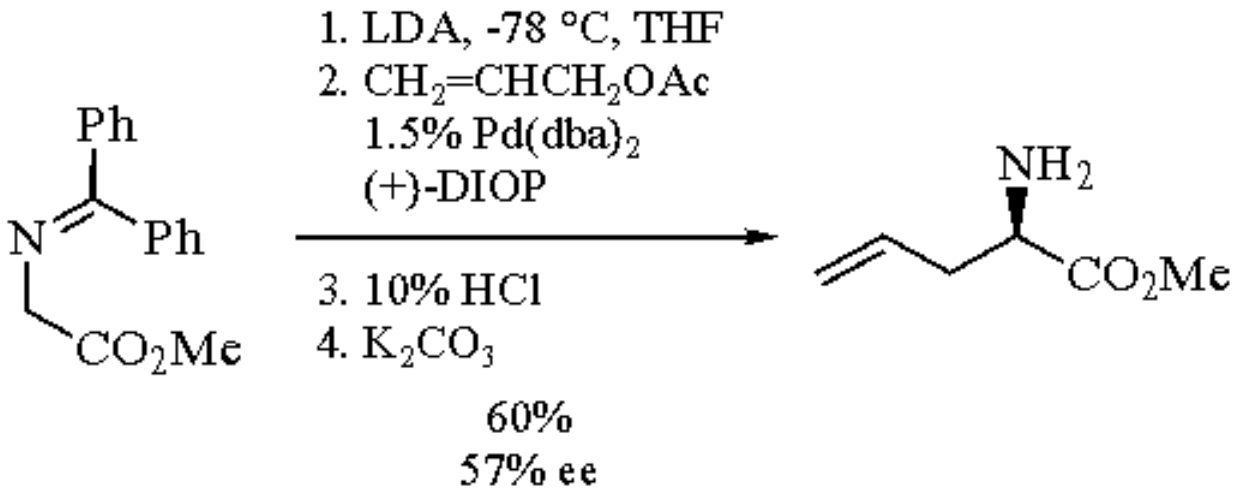

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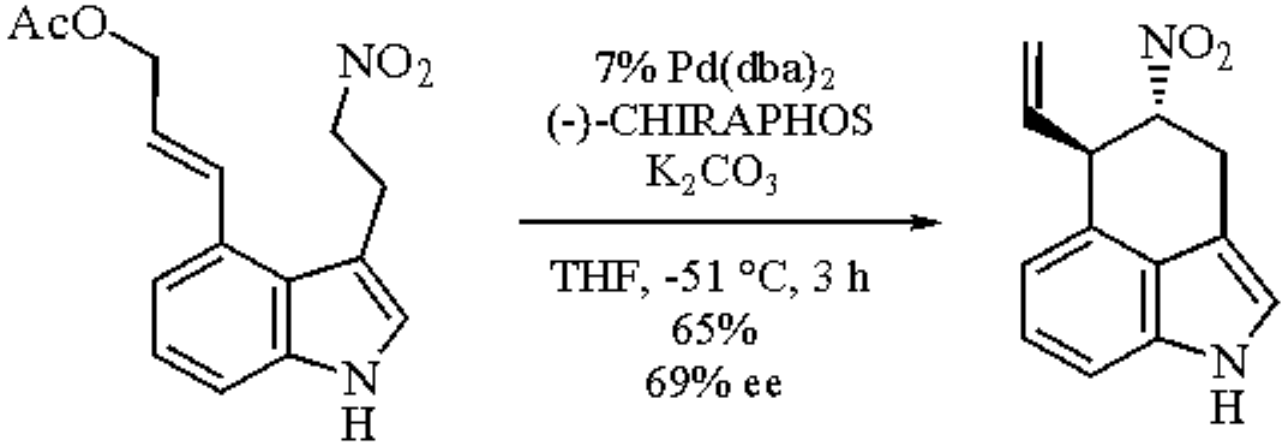

(5)

Cross-Coupling Reactions.

Allylic halides,[5,31] aryl diazonium salts,[32] allylic acetates,[33] and vinyl epoxides[34] are excellent substrates for $Pd(dba)_2$ catalyzed selective cross-coupling reactions with alkenyl-, aryl-, and allylstannanes. The reaction of an allylic halide or acetate proceeds through a π-allyl intermediate with inversion of sp^3 stereochemistry, and transmetalation with the organostannane followed by reductive elimination results in coupling from the palladium face of the allyl ligand. Coupling produces overall inversion of allylic stereochemistry, a preference for reaction at the least substituted carbon of the allyl framework, and retention of allylic alkene geometry. In addition, the alkene geometry of alkenylstannane reagents is conserved (eq 6). Functional group compatibility is extensive, and includes the presence of CO_2Bn, OH, OR, CHO, OTHP, β-lactams, and CN functionality.

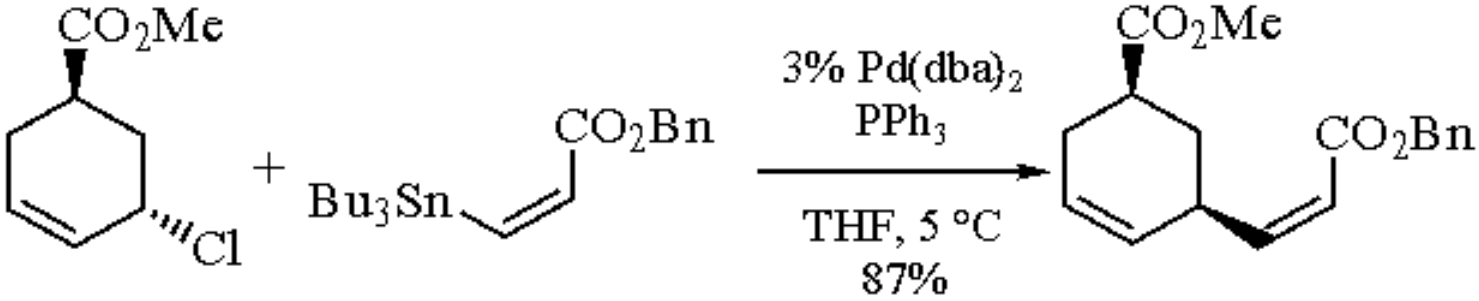

(6)

Similar methodology is used for the coupling of alkenyl halides and triflates with 1) alkenyl-, aryl-, or alkynylstannanes,[35] 2) alkenylzinc species,[3,36] or 3) arylboron species.[37] This methodology is applied in the synthesis of cephalosporin derivatives (eq 7),[35] and can be used for the introduction of acyl[3,36] and vinylogous acyl[3] equivalents (eq 8).

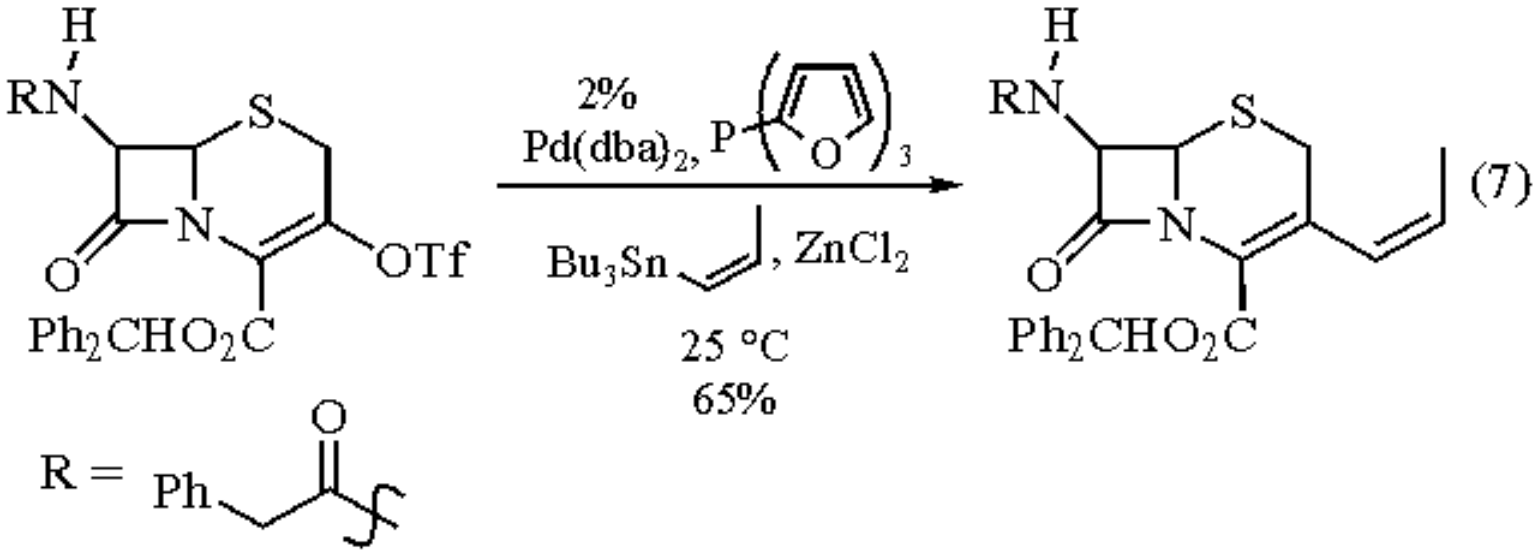

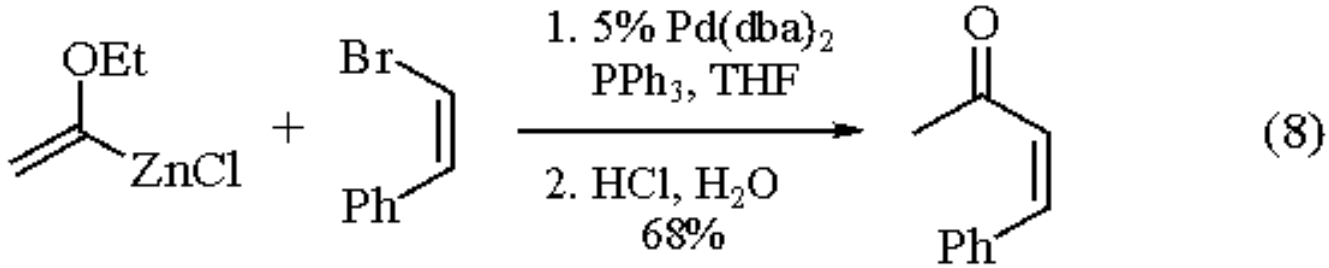

Intramolecular Reaction with Alkenes.

Palladium π-allyl complexes can undergo intramolecular insertion reactions with alkenes to produce five- and six-membered rings through a metallo-ene-type cyclization.[4] This reaction produces good stereoselectivity when resident chirality is vicinal to a newly formed stereogenic center (eq 9), and can be used to form tricyclic and tetracyclic ring systems through tandem insertion reactions.[38] In the presence of $Pd(dba)_2$ and triisopropyl phosphate, α,β-alkynic esters and α,β-unsaturated enones undergo intramolecular [3 + 2] cycloaddition reactions when tethered to methylenecyclopropane to give a bicyclo[3.3.0]octane ring system (eq 10).[39]

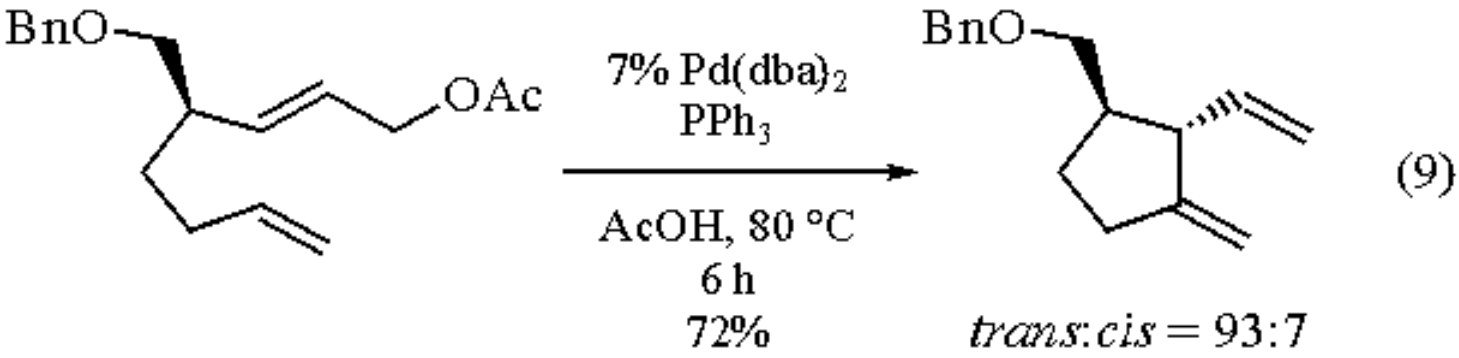

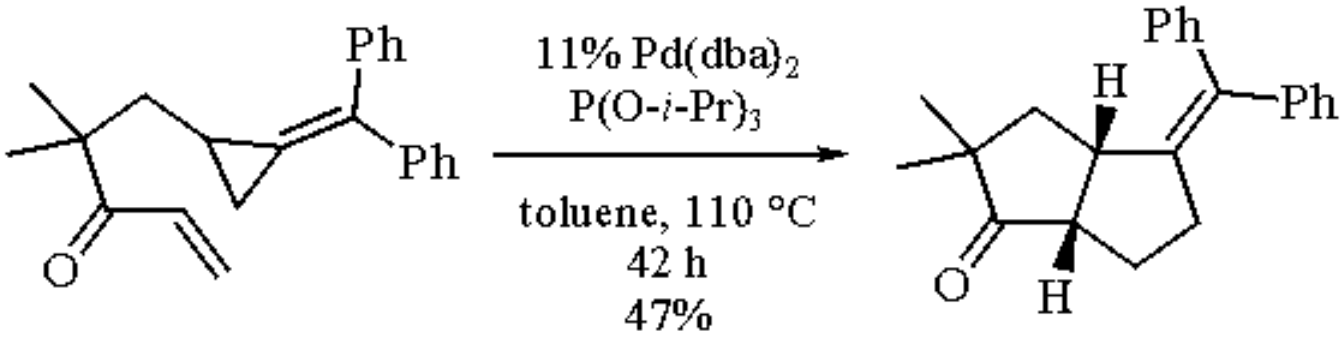

(10)

Carbonylation Reactions.

In the presence of CO and $Pd(dba)_2$, unsaturated carbonyl derivatives can also be prepared through carbonylative coupling reactions. Variations of this reaction include the initial coupling of allyl halides with carbon monoxide, followed by a second coupling with either alkenyl- or arylstannanes (eq 11).[5] This reaction proceeds with overall inversion of allylic sp^3 stereochemistry, and retains the alkene geometry of both the allyl species and the stannyl group. Similarly, aryl and alkenyl halides will undergo carbonylative coupling to generate intermediate acylpalladium complexes. Intermolecular reaction of these acyl complexes with $HSnBu_3$ produces aldehydes,[35,40] while reaction with MeOH or amines generates the corresponding carboxylic acid methyl ester[41] or amides, respectively.[42]

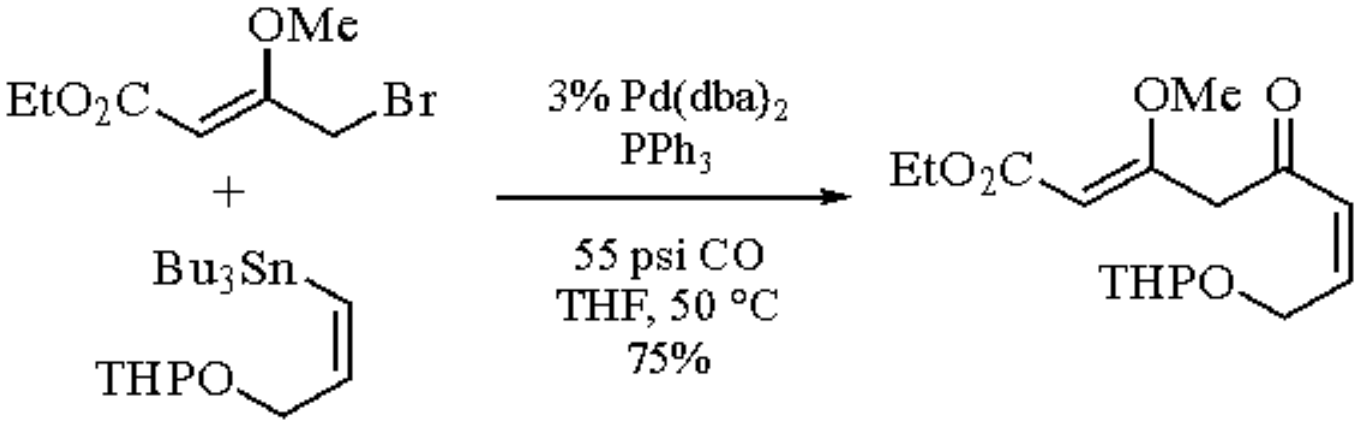

(11)

Palladium acyl species can also undergo intramolecular acylpalladation with alkenes to form five- and six-membered ring γ-keto esters through exocyclic alkene insertion (eq 12).[43] The carbonylative coupling of *o*-iodoaryl alkenyl ketones is also promoted by $Pd(dba)_2$ to give bicyclic and polycyclic quinones through endocyclization followed by β-H elimination.[44] Sequential carbonylation and intramolecular insertion of propargylic and allylic alcohols provides a route to γ-butyrolactones (eq 13).[45]

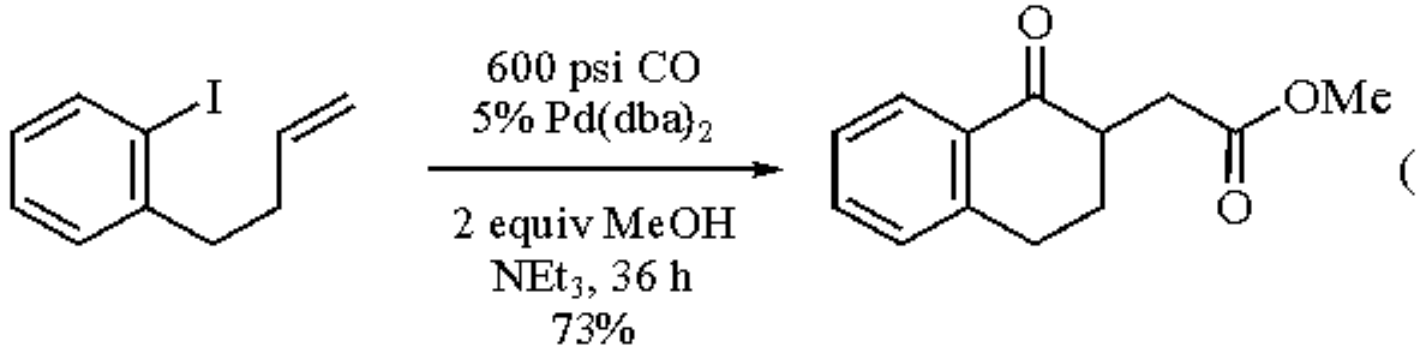

(12)

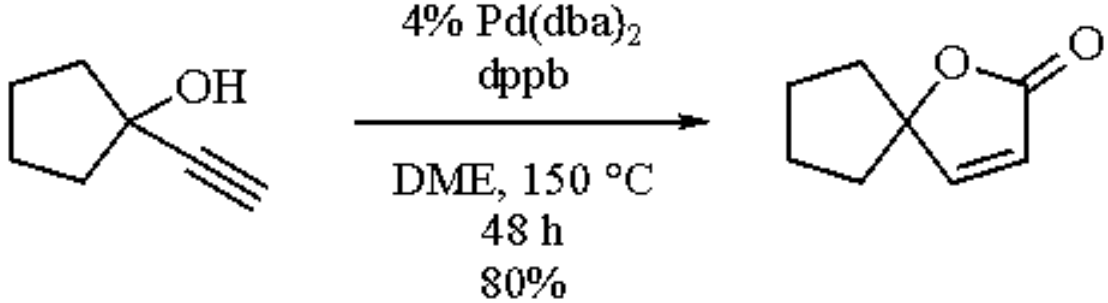

(13)

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Bis(dicarbonylcyclopentadienyliron)[1]

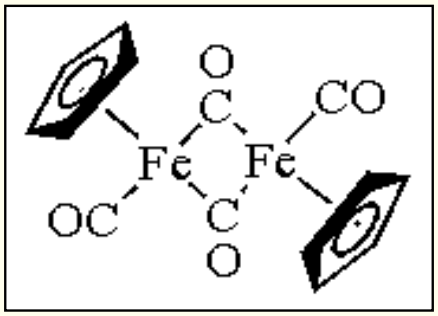

[12154-95-9] · $C_{14}H_{10}Fe_2O_4$ · Bis(dicarbonylcyclopentadienyliron) · (MW 353.92)

(dinuclear metal carbonyl catalyst for a variety of carbon-carbon bond forming reactions;[3,7] radical initiator;[19] precursor to alkyl- and acyliron complexes useful in organic synthesis[20])

Physical Data: mp 194 °C (dec); *d* 1.77 g cm^{-3}.

Solubility: very sol $CHCl_3$, pyridine, and alcohol; sol CCl_4 and CS_2; slightly sol pentane; insol H_2O.

Form Supplied in: dark reddish-purple solid; purity >97% widely available.

Handling, Storage, and Precautions: the reagent is stable to air, unaffected by H_2O, and can be stored for long periods of time. Reputed to be very toxic by inhalation and ingestion; avoid breathing of particles or vapors. Use in a fume hood.

Catalysis.

The catalytic properties of bis(dicarbonylcyclopentadienyliron) (Fp_2) are well established.[2] The hydroformylation of alkenes at moderate temperatures (125-175 °C) and pressures of H_2 and CO (50-100 atm) employing catalytic amounts of Fp_2 produces saturated aldehydes.[3,4] Aldehyde formation is regioselective, favoring the formation of branched *iso*-aldehydes over *n*-aldehydes. The reagent catalyzes isomerization of internal alkenes to terminal alkenes; the products are the *iso*- and *n*-aldehydes (eqs 1 and 2).[3] Oxo reactions catalyzed by the dinuclear metal carbonyls of Co or Ru give rise to considerable amounts of alcohols and/or higher aldehydes via aldol condensation or hydrogenation of the aldehyde.[4] Reactions catalyzed by Fp_2 are clean and selective, a result of the considerably weaker acidity and hydrogenating ability of the active metal hydride species.[5] The catalytic activity of the reagent is lower than the other dinuclear metal carbonyl species; thus longer reaction times are necessary.[3] The range of optimum temperatures is narrow. Best results have been observed at 150 °C.

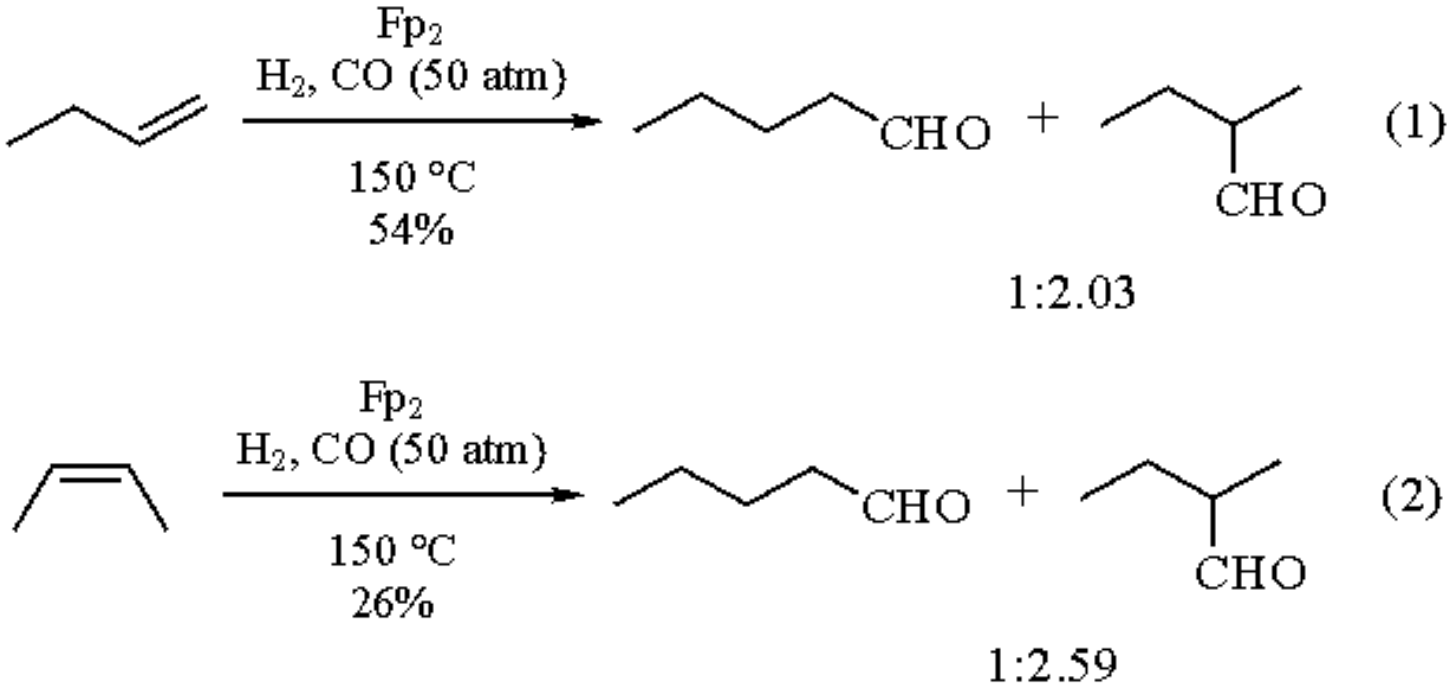

The reagent catalyzes the reaction of cycloalkanes with CCl_4 to give cycloalkyl halides in good yield.[6] The simple addition of CCl_4 to terminal alkenes at moderate temperatures is catalyzed by Fp_2, and results in good yields of 1,1,1,3-tetrachloroalkanes.[7] Similar reactions promoted by mononuclear metal carbonyl catalysts give mixtures of telomer homologs,[8] which are not formed when Fp_2 is employed.[7a] The reaction is completely regiospecific in that CCl_3 is added exclusively at the terminal carbon of the alkene. The reagent also effects the regioselective carbonylation of terminal alkenes in the presence of CCl_4 and CO, offering a convenient regioselective route to 2-alkyl-4,4,4-trichlorobutanoyl chlorides (eq 3).[7a,9] In alcohol solvents the corresponding ester is obtained in nearly the same yield.[7a] Whereas the peroxide catalyzed reaction of ethylene, CO, and CCl_4 results in a telomeric mixture,[10] the Fp_2 catalyzed reaction gives only the 1:1 adduct.[7a] The Fp_2 catalyzed reactions of methyl trichloroacetate with terminal alkenes give good yields of 4-alkyl-2,2-dichloro-γ-butyrolactones (eq 4).[11] The reagent also promotes intramolecular cyclization of allyl trichloroacetate to trichlorinated γ-lactones, albeit in lower yield than when Cu^I salts are employed.[12] The reaction of benzylamine with CCl_4 at moderate temperatures (120-130 °C), using Fp_2 as catalyst, provides a useful route to 2,4,5-triphenylimidazoline derivatives (eq 5).[13] While this reaction is promoted by other catalysts,[14] Fp_2 is the cleanest and most reactive. Perfluoroalkyl-substituted acetals are obtained in excellent yield by the Fp_2 catalyzed coupling of perfluoroalkyl iodides, enol ethers, and alcohols (eq 6).[15]

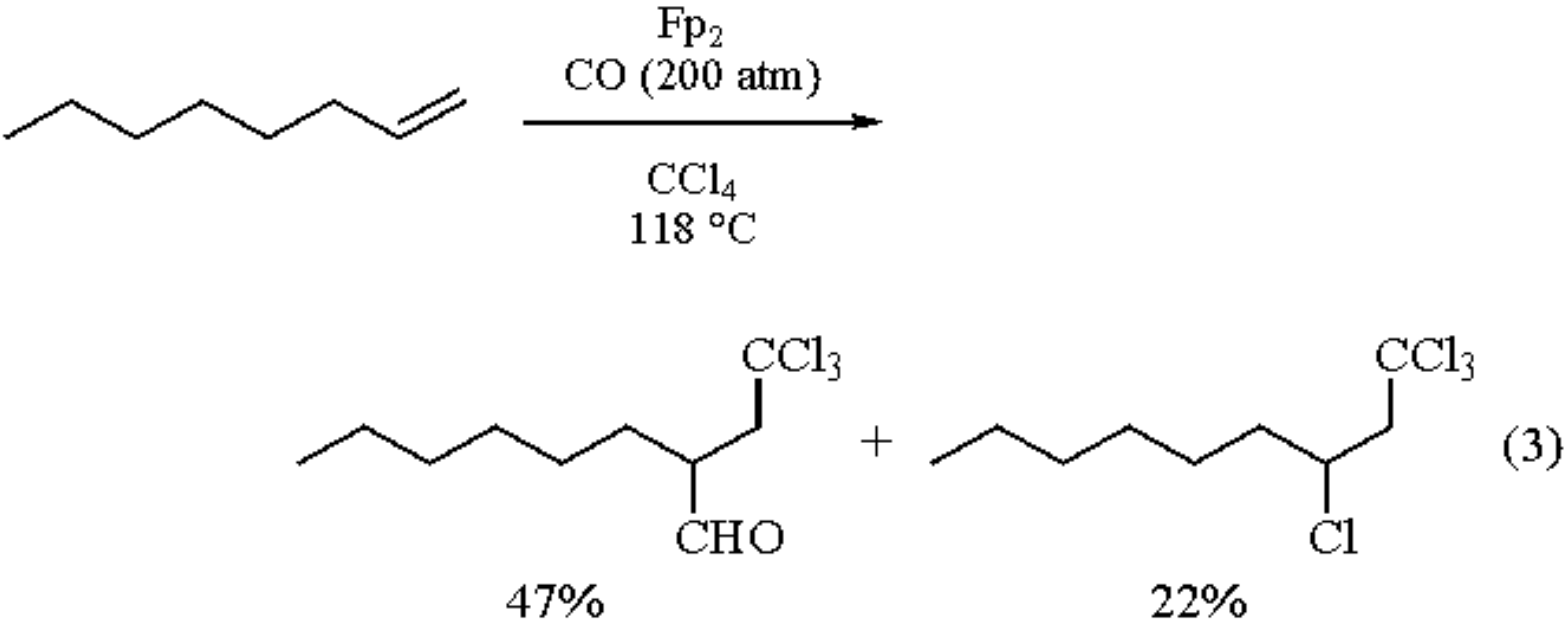
Fp2
CO (200 atm)
CCl4
118 °C
CCl3
CHO
47%
CCl3
Cl
22%
(3)

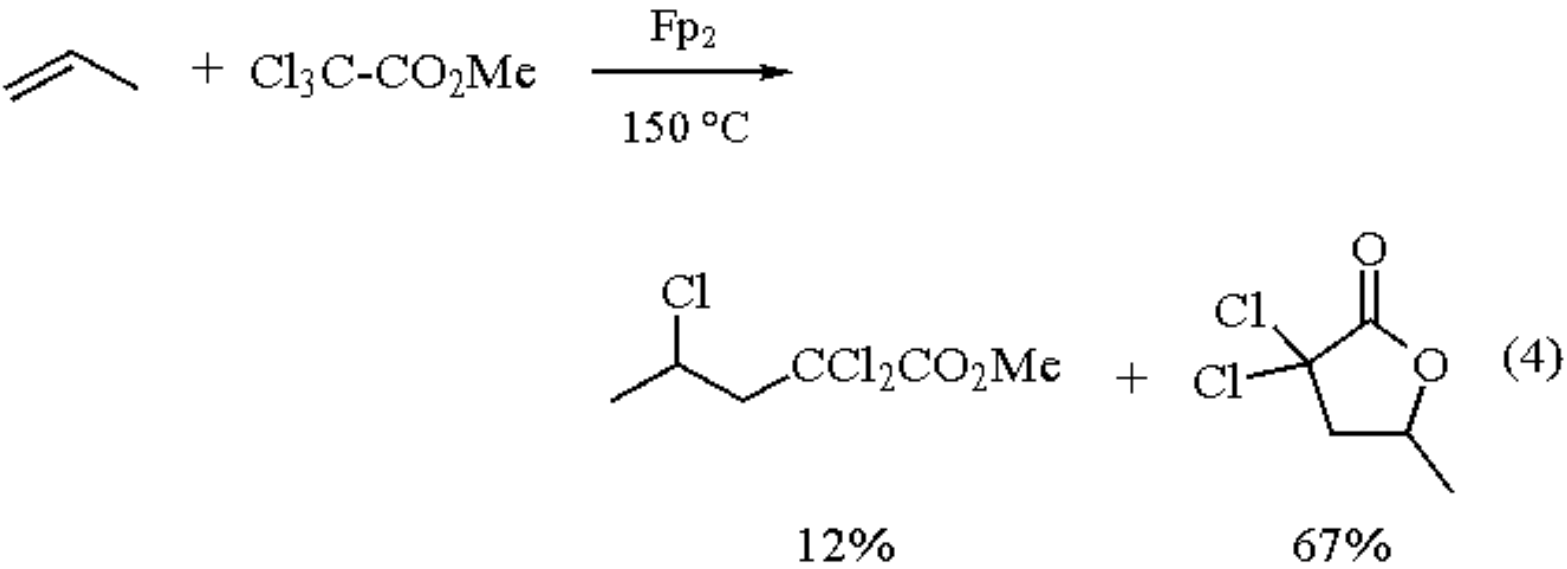
Cl3C-CO2Me
Fp2
150 °C
Cl
CCl2CO2Me
12%
O
Cl
Cl
O
67%
(4)

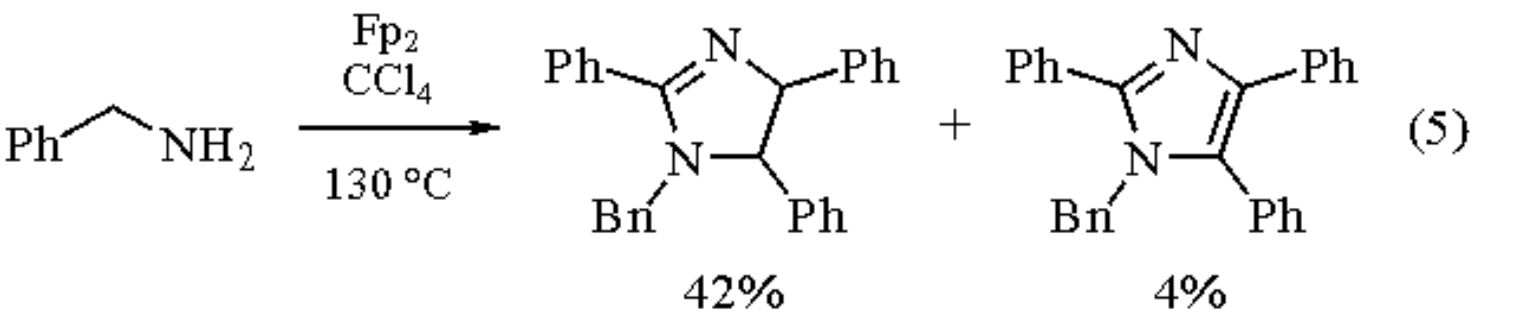
Ph
NH2
Fp2
CCl4
130 °C
Ph
N
Ph
N
Bn
Ph
42%
Ph
N
Ph
N
Bn
Ph
4%
(5)

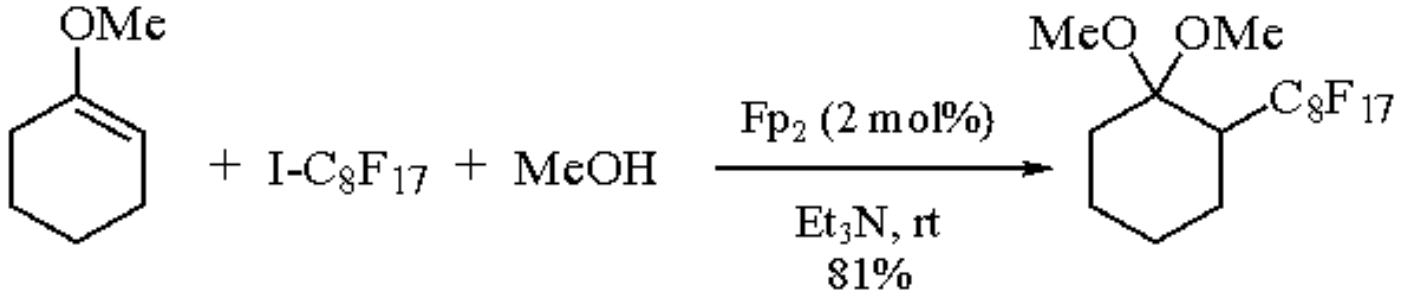

(6)

The reagent catalyzes the cyclotrimerization of disubstituted acetylenes to benzenes at high temperatures.[16] Butadiene and isoprene are rapidly and selectively cyclodimerized to 4-vinyl-cyclohexenes by the action of Fp_2.[17] Aromatic and aliphatic thioketones are desulfurized and converted to substituted ethylenes by the action of Fp_2 in refluxing benzene.[18]

Radical Promoter.

Fp_2 is an efficient promoter of radical reactions in the manner of organotin compounds. Irradiation of alkyl halides in the presence of a stoichiometric equivalent of Fp_2 leads to C-centered radicals via halogen abstraction by the initially formed 17-electron metal-centered $CpFe(CO)_2$ radical. These carbon radicals can be trapped by alkenes, leading to saturated addition products. Unsaturated addition products can be obtained in the absence of electron-withdrawing substituents on the alkene (eq 7).[19] If no alkenes are present, hydrogen abstraction from solvent leads to alkanes in high yield.

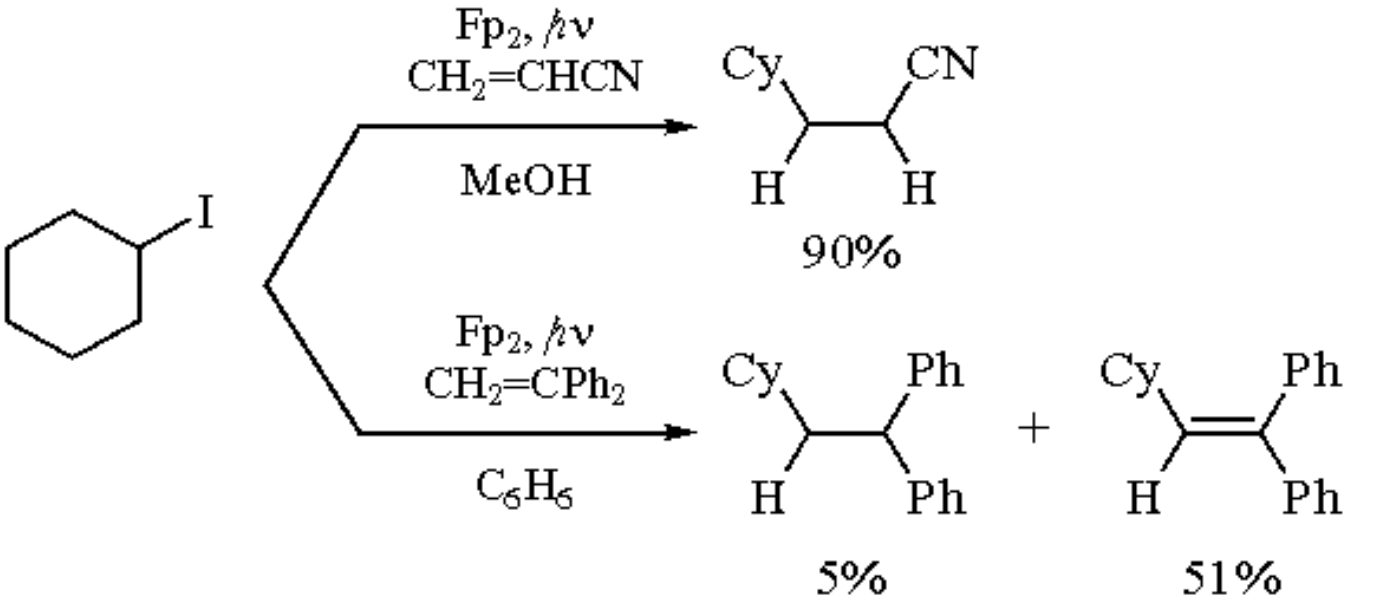

(7)

Alkyl- and Acyliron Complexes.

Treatment of Fp_2 with ***Sodium Amalgam*** generates the $CpFe(CO)_2^-$ anion (Fp^-), a powerful nucleophile which reacts with a variety of electrophilic carbon species.[20] Alkyl- and acyliron (Fp-R and Fp-COR) complexes are readily available on a large scale and have found extensive use in organic synthesis.[21] One-electron oxidants demetalate the alkyl or acyl ligand and lead to a variety of carbonyl compounds,[22] e.g. esters,[23] acids,[23a,24] and amides.[23a,25]

Decomplexation occurs with a high degree of stereoselectivity (eq 8).[26]

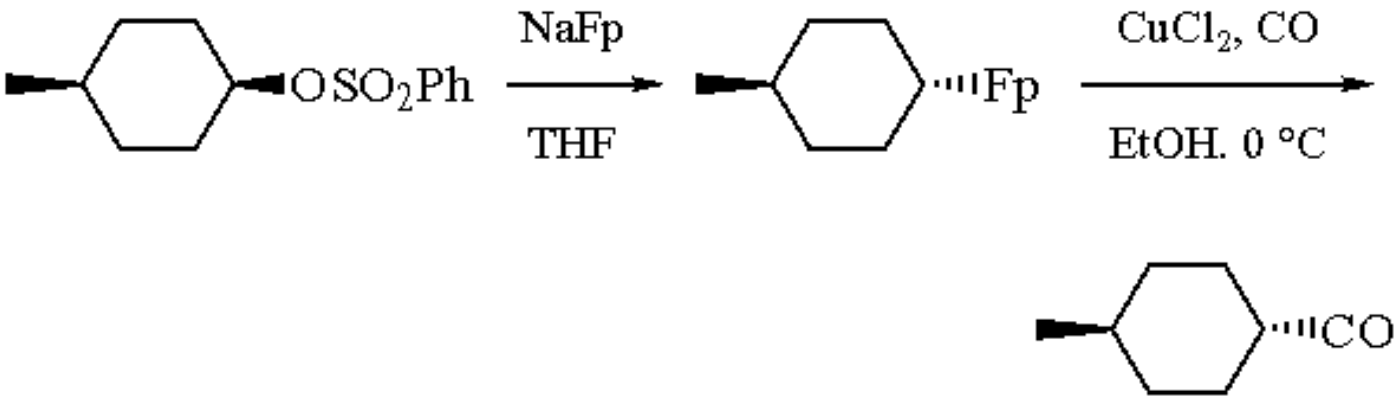

(8)

Treatment of alkyliron complexes with ***Triphenylcarbenium Tetrafluoroborate*** results in β-hydride abstraction to give cationic Fp(alkene) complexes.[27] Subsequent liberation of the alkene gives products with a high degree of regio- and stereoselectivity. 2-Alkyliron complexes usually give only the terminal alkene, and 3-alkyliron complexes give only the (*Z*)-alkene (eq 9).[28] Cationic Fp(alkene) complexes, prepared from alkyliron complexes,[27,28] or other routes,[29] react smoothly with lithium enolates and enamines, to give high yields of alkylated products.[30] However, the reactions often show poor regioselectivity. Complexes derived from α,β-unsaturated carbonyl compounds are both highly reactive and highly regioselective with a wide variety of nucleophiles.[31] Vinyl ether complexes, likewise highly reactive and regioselective, are useful vinyl cation equivalents for the vinylation of enolates (eq 10).[31b,32]

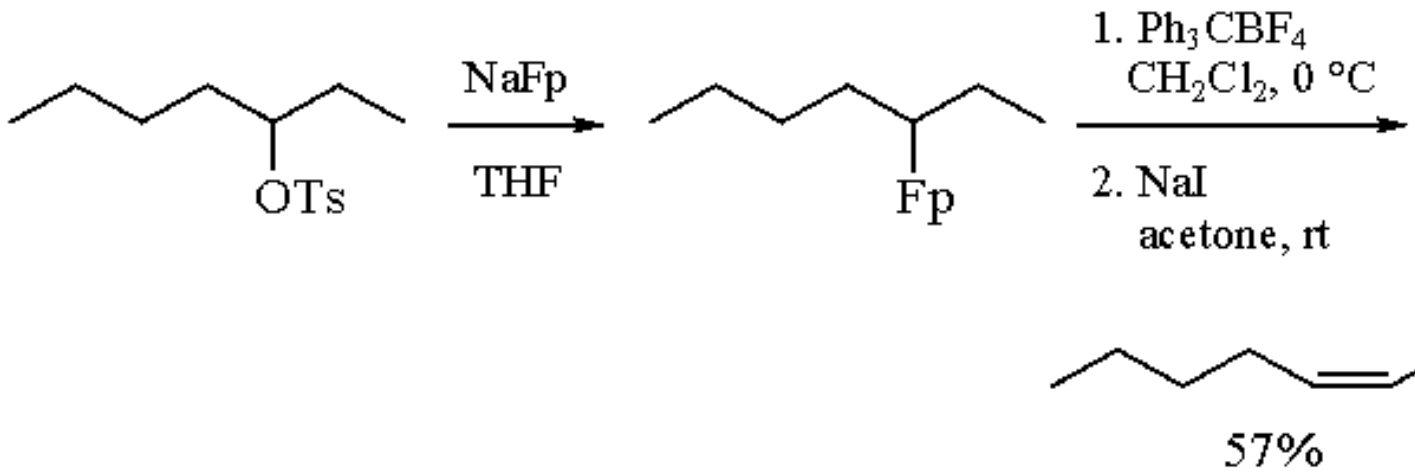

(9)

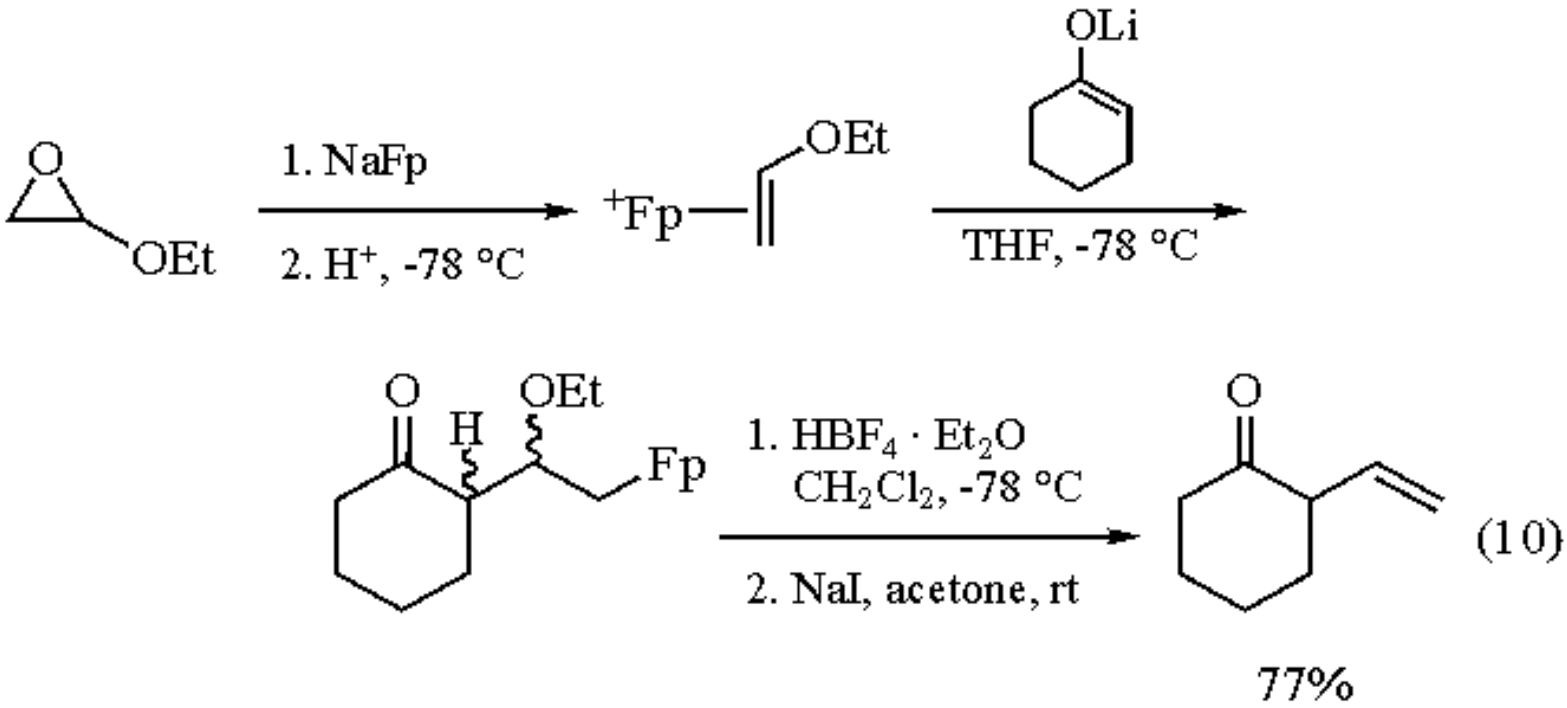

Electrophilic transition metal alkylidene complexes of the type $Cp(CO)_2Fe{=}CRR'^{+}$ ($Fp{=}CRR'^{+}$) smoothly effect the cyclopropanation of alkenes.[33] These iron-carbene complexes are readily prepared by ionization of a leaving group located at the α-position of the alkyliron complex.[34] In particular, the dimethylsulfonium salts offer a chemically mild route to the carbene.[34c,d] Because of the electrophilic nature of the carbene, cyclopropanation is selective for electron rich alkenes (eq 11).[35] High stereoselectivity can be achieved; carbene transfers usually favor higher energy, sterically crowded *cis* products (eq 12).[34d,e,36] Enantioselective cyclopropanations are possible through the use of phosphine substituted iron-carbene complexes possessing a chiral metal center. Optically pure complexes of the type $Cp(CO)(PR_3)Fe{=}CRR'^{+}$ are efficiently prepared from the acyliron complex.[37] While enantioselectivities observed for methylene are low (10-38% ee),[38] ethylidene transfers to various alkenes occur with high selectivity (70-97% ee) (eq 13).[37,39]

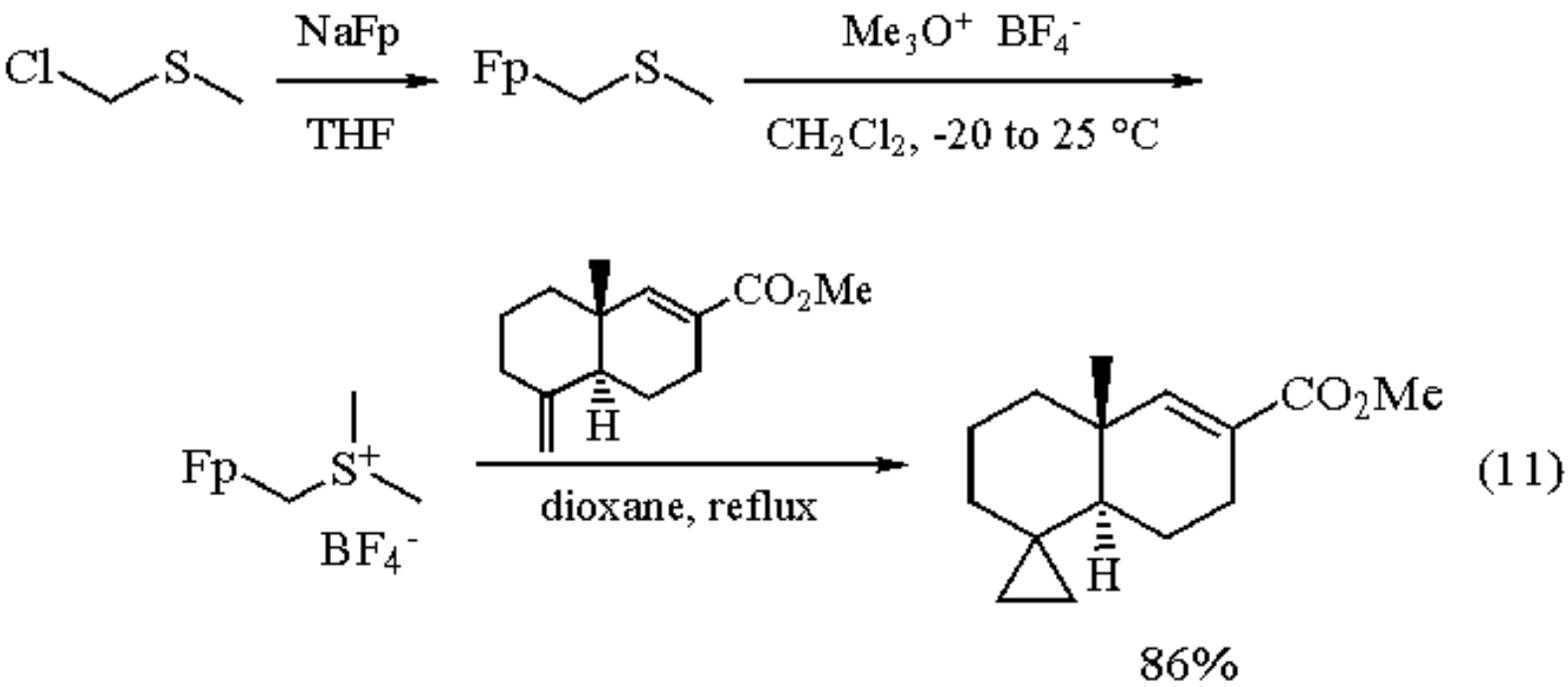

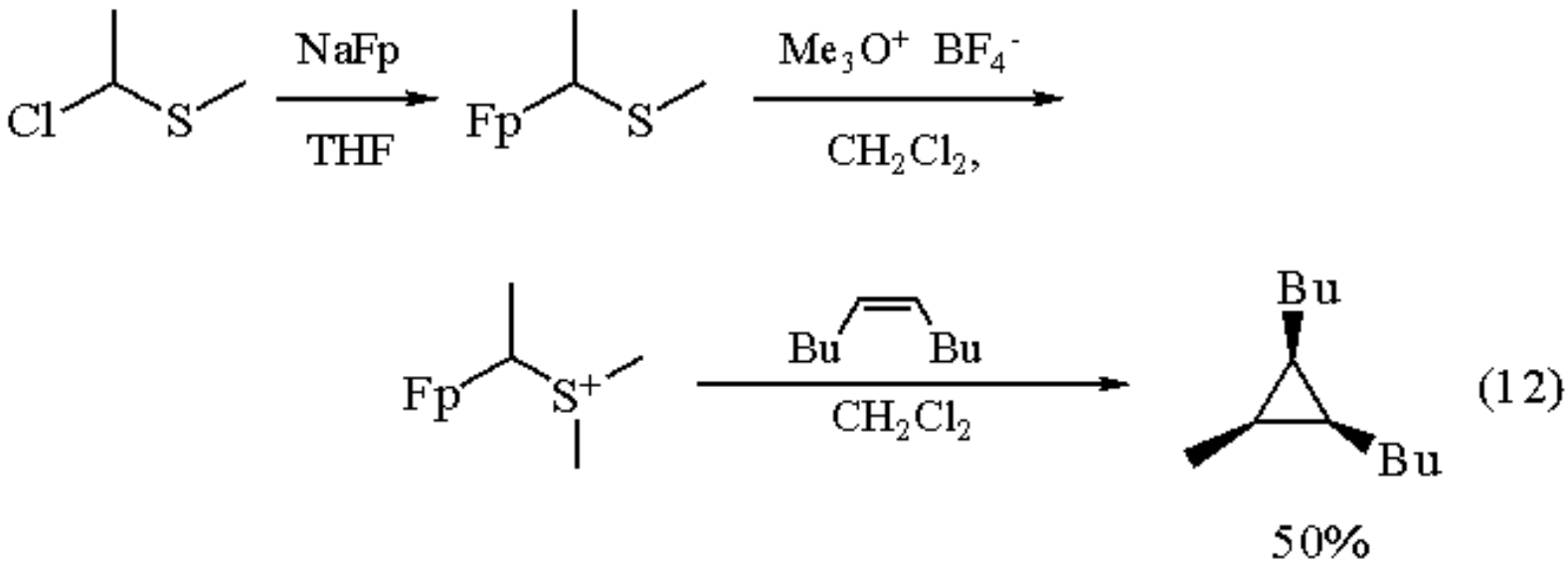

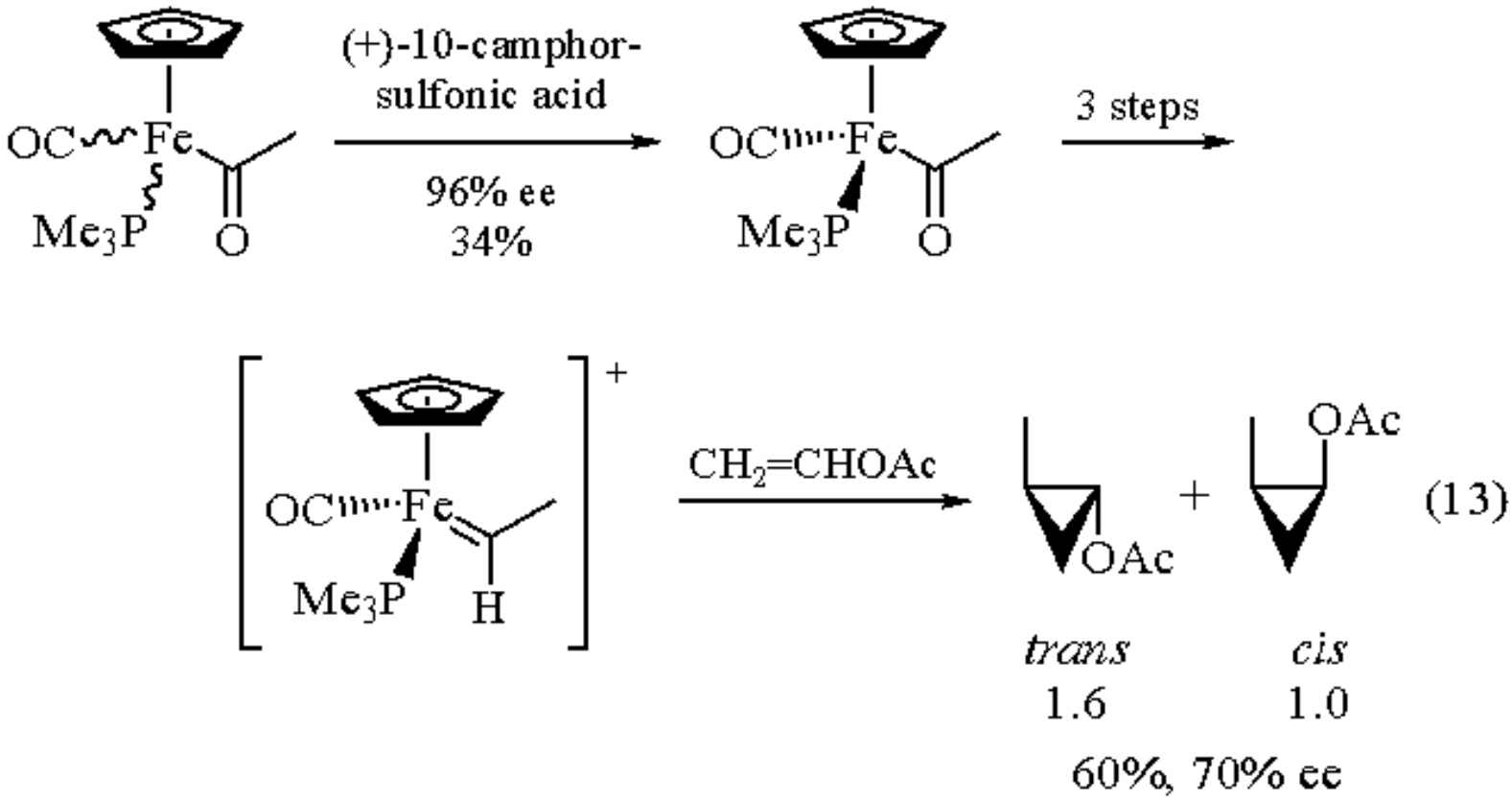

Related Reagents.

Dicarbonyl(cyclopentadienyl)(isobutene)iron Tetrafluoroborate; ***Sodium Dicarbonylcyclopentadienylferrate***.

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Bis(dichlorotrimethylsilylmethyl)mercury[1]

$Hg(CCl_2SiMe_3)_2$

[18903-82-7] · $C_8H_{18}Cl_4HgSi_2$ · Bis(dichlorotrimethylsilylmethyl)mercury · (MW 512.80)

(by thermal treatment formally transfers **:**$CClSiMe_3$ to alkenes, resulting in cyclopropane formation,[2] and to silanes, inserting into Si-H bond[2])

Physical Data: mp 143-146 °C.

Solubility: sol hexane, benzene, chlorobenzene.

Preparative Methods: reaction of Me_3SiCCl_2Li[3] with $HgBr_2$ at -135 °C in a solvent mixture containing THF, Et_2O, and pentane furnishes the title reagent in 35% yield.[2,4] For this class of silicon-containing organomercurials, the above approach has proven superior to the more classical *t*-BuOK procedure[1] (see also ***Phenyl(trichloromethyl)mercury***).

Purification: recrystallization from hexane.

Handling, Storage, and Precautions: flame-dried glassware and an atmosphere of dry nitrogen are used for the reactions. Organomercury compounds should be carefully handled, and skin contact and inhalation should be particularly avoided. All reactions must be conducted in a well-ventilated hood.

Cyclopropanation of Alkenes.

The synthetic relevance of α-haloorganomercury compounds stems mainly from their utility in preparing cyclopropanes (see also ***Phenyl(trichloromethyl)mercury***) by carbene transfer to simple alkenes. In this respect, bis(dichlorotrimethylsilylmethyl)mercury is quite stable thermally and does not transfer divalent carbon under mild conditions; for example, it was recovered unaltered after heating with cyclohexene at 83 °C for 7 days. However, addition of 1 equiv of ***Diphenylmercury*** results in activation of the reagent with respect to the α-haloorganomercurial.[2,5] The $Hg(CCl_2SiMe_3)_2$-$HgPh_2$ system cyclopropanates cyclooctene at 125 °C under nitrogen (eq 1).[2]

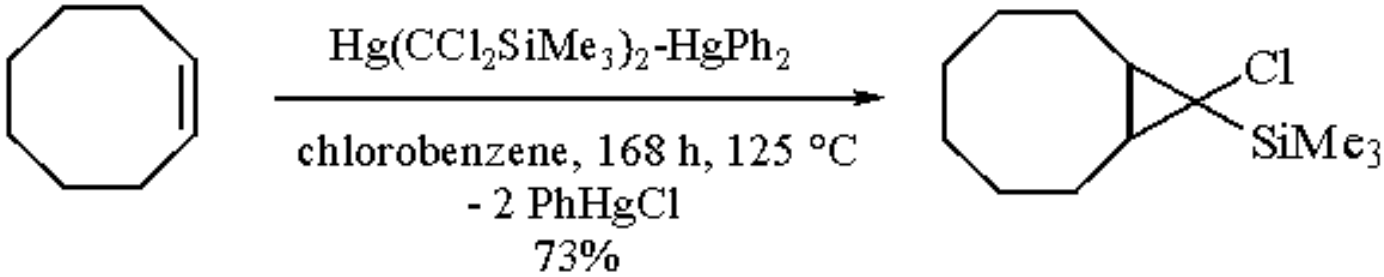

(1)

Insertion into Si-H Bond.

Another common feature of the reactivity of α-haloorganomercurials is their easy reaction with Si-H bonds. Thus insertion of the functional carbene **:**$CClSiMe_3$ into the Si-H bond takes place when a 1:1 mixture of $Hg(CCl_2SiMe_3)_2$-$HgPh_2$ is reacted with an excess of triethylsilane (eq 2).[2] The PhHgCl byproduct was not isolated, but it reacts with the excess of silane under the reaction conditions, furnishing mercury and diphenylmercury.

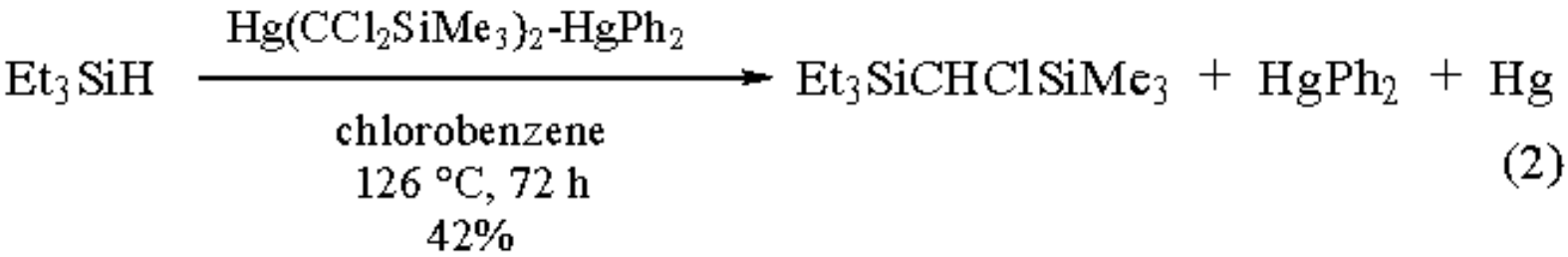

(2)

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1. (a) Seyferth, D. *PAC* **1970**, *23*, 391. (b) Seyferth, D. *ACR* **1972**, *5*, 65. (c) Zeller, K.-P.; Straub, H. *MOC* **1974**, *13/2b*, 351. (d) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985; Chapter X, pp 327-413.
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Bis(diethylaluminum) Sulfate

$(Et_2Al)_2SO_4$

[13747-43-8] · $C_8H_{20}Al_2O_4S$ · Bis(diethylaluminum) Sulfate · (MW 266.27)

(a Lewis acid catalyst for alkene polymerization[1-4] and for promotion of allylstannane additions to various carbon electrophiles[5,6])

Physical Data: none reported.

Solubility: sol hexanes, benzene, and *n*-heptane.

Form Supplied in: white solid; not widely available.

Analysis of Reagent Purity: by elemental analysis.

Preparative Method: the following procedure has proven most efficacious:[3] a flask containing dry pulverized Na_2SO_4 is charged with a solution of ***Diethylaluminum Chloride*** (2 equiv) in *n*-heptane (or benzene). The stirred mixture is heated at reflux for 1 day. The liquid phase is removed by syringe and concentrated under reduced pressure to afford bis(diethylaluminum) sulfate as a white solid.

Handling, Storage, and Precautions: decomposes in air and reacts violently with moisture with evolution of ethane.[3] Use in a fume hood.

Catalyst for Alkene Polymerization.

Bis(diethylaluminum) sulfate has been used in combination with other organometallic complexes to catalyze different types of alkene polymerizations.[1-4] A 1:2 combination of this catalyst and cobalt(II) thiocyanate-bis(triphenylphosphine) effectively polymerizes 1,3-butadiene (and isoprene) to 1,2-syndiotactic polyisobutadiene.[1] A three-component catalyst system containing bis(diethylaluminum) sulfate, ***Tris(acetylacetonato)iron(III)*** and ***Triphenylphosphine*** promotes the production of linear dimers of butadiene.[2] The title reagent has also proven effective as a powerful activator of ***Titanium(III) Chloride*** in the polymerization of propylene.[4]

Catalyst for Allylstannane Addition.

Bis(diethylaluminum) sulfate is a good Lewis acid catalyst for promoting the coupling of allylstannanes with various

electrophiles. For example, it catalyzes the addition of an allyl unit to acetals (eq 1), carbonyl compounds (eq 2), and α,β-unsaturated ketones (eq 3).[5]

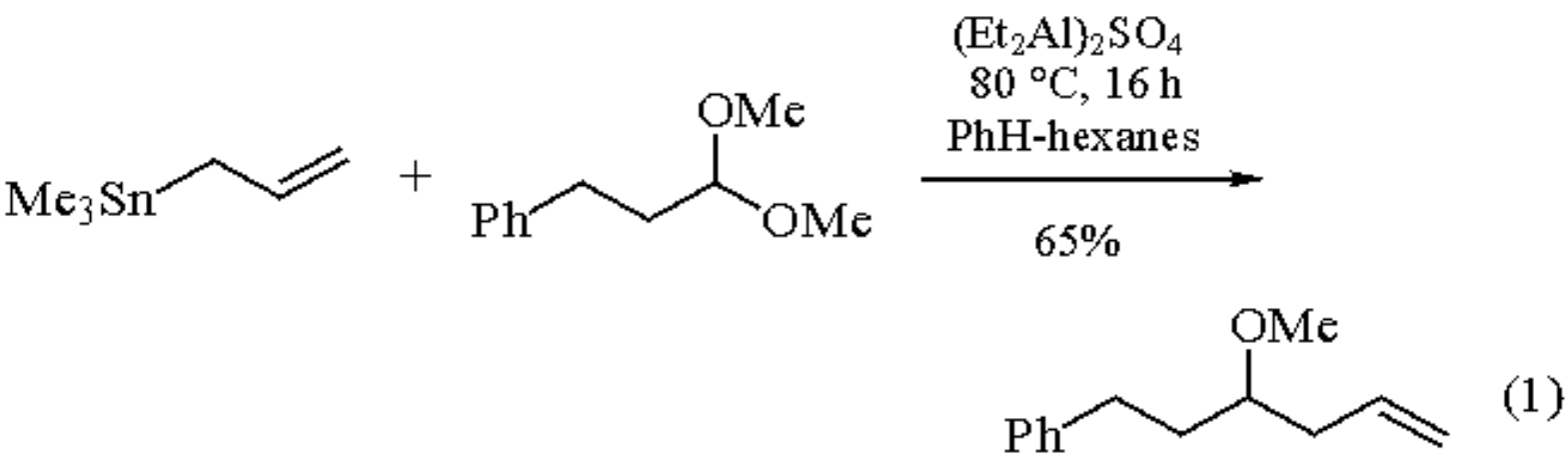

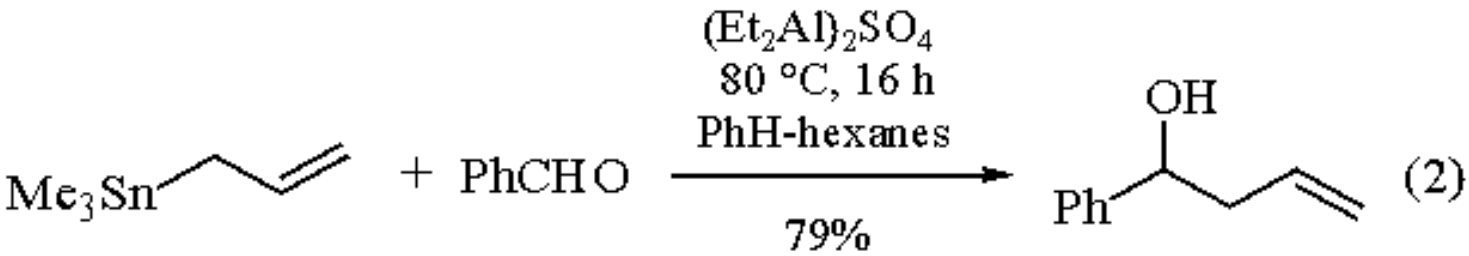

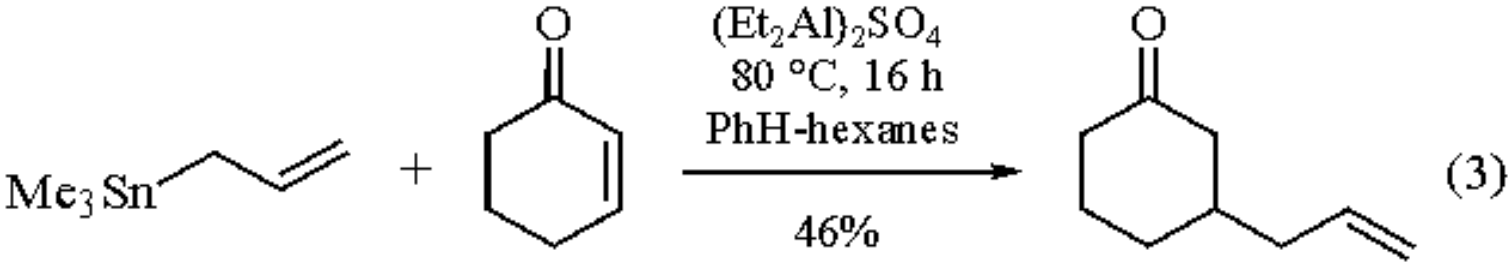

Bis(diethylaluminum) sulfate also promotes the coupling of allylstannanes with various allylic species, such as allylic halides (eq 4), ethers (eq 5), and acetates (eq 6).[6] The 1,5-diene products are obtained in good yield, albeit with modest regioselectivity. Many of these allylations are also catalyzed by ***Boron Trifluoride Etherate***, but the yields are generally lower.[5,6]

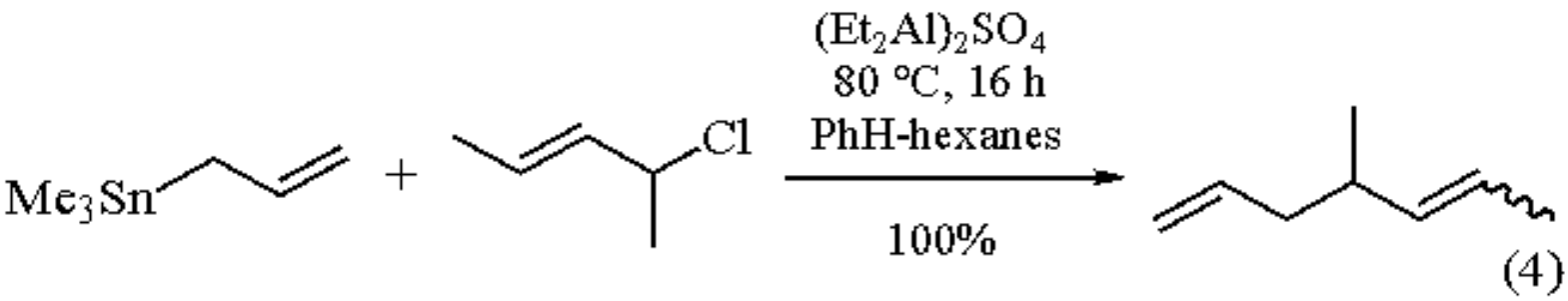

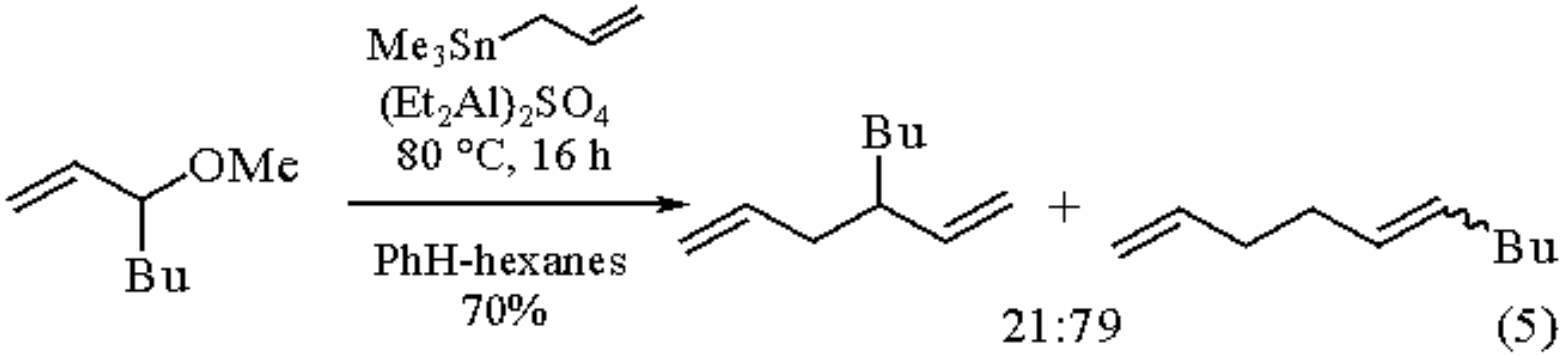

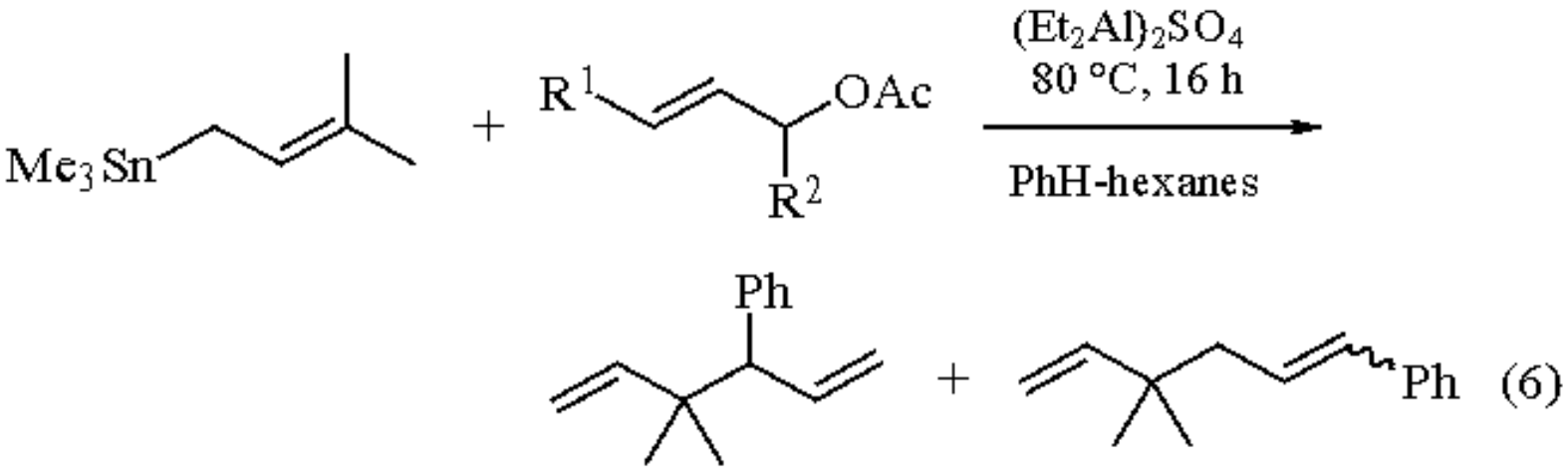

$R^1 = Ph, R^2 = H, 67\%$ 47:53
$R^1 = H, R^2 = Ph, 94\%$ 47:53

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1,2-Bis(2,5-diethylphospholano)benzene

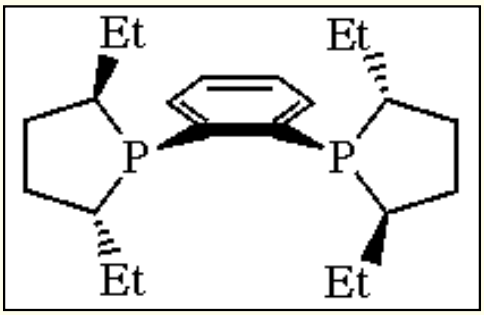

[136705-64-1] · $C_{22}H_{36}P_2$ · 1,2-Bis(2,5-diethylphospholano)benzene · (MW 362.47)

(ligand for asymmetric catalysis;[1] rhodium complexes are efficient catalyst precursors for highly enantioselective hydrogenation of α-(*N*-acylamino)acrylates,[1,2] enol acetates,[1] and *N*-acylhydrazones[3,4])

Alternate Name: (*R*,*R*)- and (*S*,*S*)-Ethyl-DuPHOS.

Physical Data: bp 138-143 °C/0.045 mmHg; (*R*,*R*)-Ethyl-DuPHOS, [α]25D = -265° (*c* 1, hexane).

Form Supplied in: colorless viscous liquid; both enantiomers available commercially.

Analysis of Reagent Purity: optical rotation, ^{1}H NMR, ^{31}P NMR, ^{13}C NMR.

Preparative Methods: preparation of (*R*,*R*)-Ethyl-DuPHOS requires the use of (3*S*,6*S*)-3,6-octanediol.[1,2] Enantiomerically pure (3*S*,6*S*)-octanediol is obtained in 35-45% overall yields via a simple three-step procedure[5,6] involving the Ru-(*S*)-BINAP-catalyzed asymmetric hydrogenation[7] of methyl propionylacetate to methyl (3*S*)-3-hydroxypentanoate (95% yield, 99% ee), followed by quantitative hydrolysis to the corresponding β-hydroxy acid, and subsequent electrochemical Kolbe coupling (eq 1). This sequence has been used for the synthesis of multigram quantities of (3*S*,6*S*)-octanediol, as well as a series of related chiral 1,4-diols.[2,6] Antipodal (3*R*,6*R*)-octanediol was prepared in a similar fashion by employing the (*R*)-BINAP-Ru catalyst in the first step.[6]

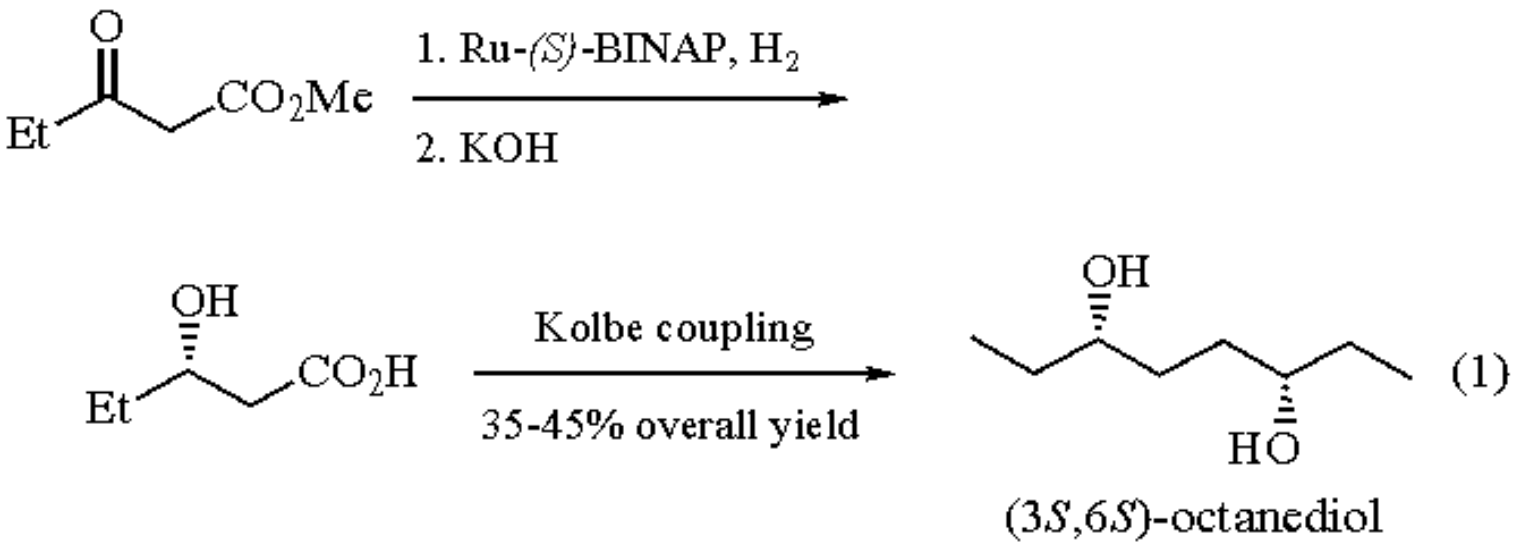

The crystalline (3*S*,6*S*)-octanediol (mp 51-52 °C; [α]25D = +22.8° (*c* 1, $CHCl_3$)) is next converted to the corresponding (3*S*,6*S*)-octanediol cyclic sulfate (mp 80-81 °C; [α]25D = +28.6° (*c* 1, $CHCl_3$)) through reaction with ***Thionyl Chloride***, followed by oxidation with ***Sodium Periodate*** and a catalytic amount (0.1 mol%) of ***Ruthenium(III) Chloride*** (eq 2).[2] The final step involves successively treating 1,2-bis(phosphino)benzene[8] with ***n-Butyllithium*** (2 equiv 1.6 M in hexane), followed by (3*S*,6*S*)-octanediol cyclic sulfate (2 equiv), and then *n*-BuLi (2.2 equiv) to provide the product (*R*,*R*)-Ethyl-DuPHOS in 78% yield after purification by distillation (eq 2). The use of (3*R*,6*R*)-octanediol cyclic sulfate in eq 2 allows the analogous preparation of (*S*,*S*)-Ethyl-DuPHOS. In addition to Ethyl-DuPHOS (R = Et), a series of other DuPHOS derivatives (R = Me, Pr, *i*-Pr, Cy, Bn) have been prepared in this manner.[1,2]

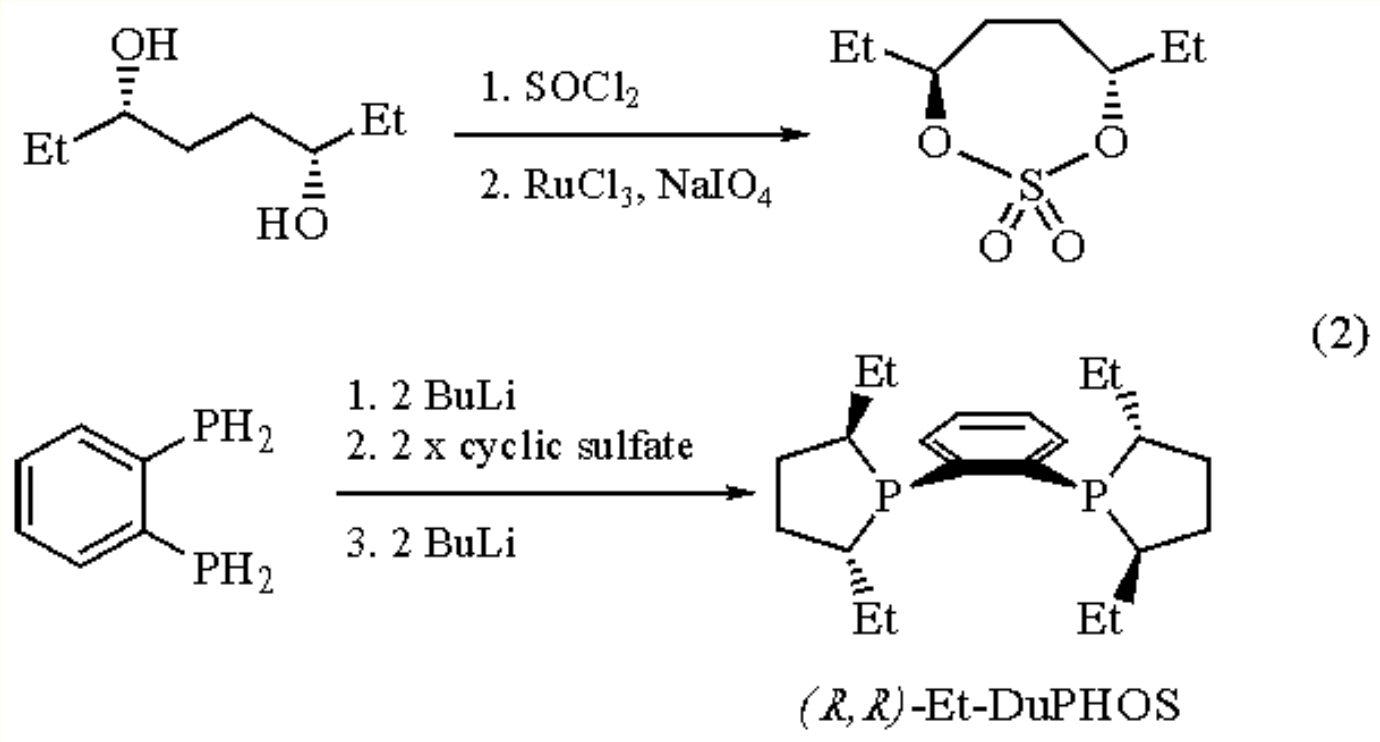

Handling, Storage, and Precautions: somewhat air sensitive and should be handled and stored in a nitrogen or argon atmosphere. Metal complexes generally are sensitive to oxygen in solution. Use in a fume hood.

Catalyst Precursors: Rhodium Complexes.

The cationic rhodium complexes [(cod)Rh(Ethyl-DuPHOS)]$^+$X$^-$ (X = OTf, PF_6, BF_4, SbF_6) serve as efficient catalyst precursors for both enantioselective hydrogenation[1-6] and intramolecular hydrosilylation[9] reactions. These complexes are most conveniently prepared by reacting the ligand, either (*R*,*R*)-Ethyl-DuPHOS or (*S*,*S*)-Ethyl-DuPHOS, with the complexes [$(cod)_2$Rh]$^+$X$^-$ in THF.[2,10] Since the solid rhodium catalysts are less air-senstive than the ligands, they may be weighed quickly in air, although storage under nitrogen or argon is recommended.

Enantioselective Hydrogenations.

α-(*N*-Acylamino)acrylates.

The cationic Ethyl-DuPHOS-Rh catalysts are particularly well-suited for highly enantioselective hydrogenation of α-(*N*-acylamino)acrylates to α-amino acid derivatives (eq 3).[1,2]

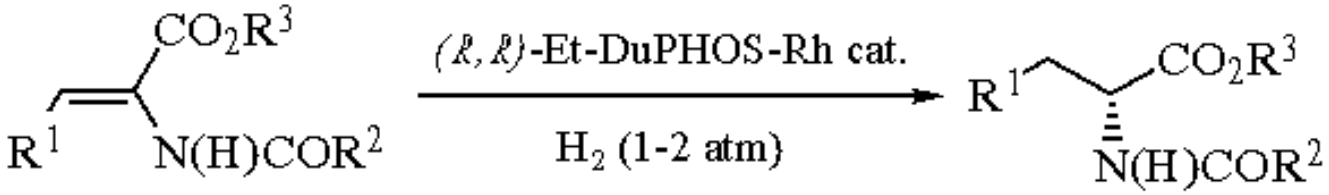

(3)

The reactions proceed under mild conditions (1 atm H_2, 25 °C, MeOH) and are extremely efficient (substrate-to-catalyst ratios S/C up to 50 000 have been demonstrated). The breadth of the Ethyl-DuPHOS-Rh catalyst is noteworthy; extremely high enantioselectivities (&egt;99% ee) are achieved over a broad range of substrates (Table 1). Accordingly, the Ethyl-DuPHOS-Rh catalysts can provide practical access to a wide variety of natural, unnatural, nonproteinaceous, and labeled α-amino acids. The absolute configurations of the products are very predictable; (*R*,*R*)-Ethyl-DuPHOS-Rh complexes consistently afford products of (*R*) absolute configuration, while (*S*,*S*)-Ethyl-DuPHOS-Rh complexes provide (*S*)-α-amino acid derivatives. Similarly high ees are obtained with the corresponding carboxylic acid substrates (R^3 = H), as well as with *N*-benzoyl (R^2 = Ph) and *N*-Cbz (R^2 = OBn) α-(*N*-acylamino)acrylates. Significantly, the Ethyl-DuPHOS-Rh catalysts allow hydrogenation of both (*Z*) and (*E*) isomeric α-(*N*-acetylamino)acrylates in high enantiomeric excess (>99% ee) to afford products with the same absolute configuration. Many desirable α-(*N*-acylamino)acrylates are unavoidably synthesized as a mixture of (*E*) and (*Z*) isomers, and a separation step generally is required prior to hydrogenation. When using the Ethyl-DuPHOS-Rh catalysts, however, the need to separate isomeric substrates is often eliminated, thus providing a practical route to many amino acid derivatives.

Table 1 Asymmetric Hydrogenation of a-(*N*-acetamido)acrylates (R^2,R^3 = Me) with Ethyl-DuPHOS Rh Catalyst

R^1	% ee
H	99.8
Me	99.6
Et	99.7
Pr	99.6
i-Pr	99.4
t-Bu	96.2
Ph	>99
1-Naphthyl	>99
2-Naphthyl	>99
2-Thienyl	>99
Ferrocenyl	>99

Enol Acetates.

Several enol acetates are hydrogenated with high enantioselectivities using the Ethyl-DuPHOS-Rh catalysts (eqs 4 and 5).[1] The selectivities are significantly higher than any previously reported for these substrates.[11] The scope of these reactions and substrates bearing β-substituents have not yet been examined.

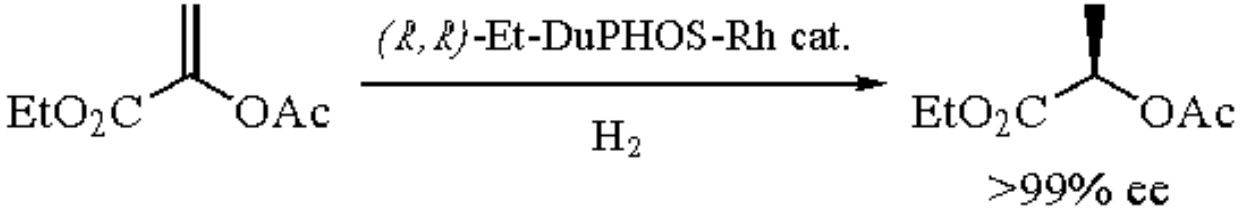

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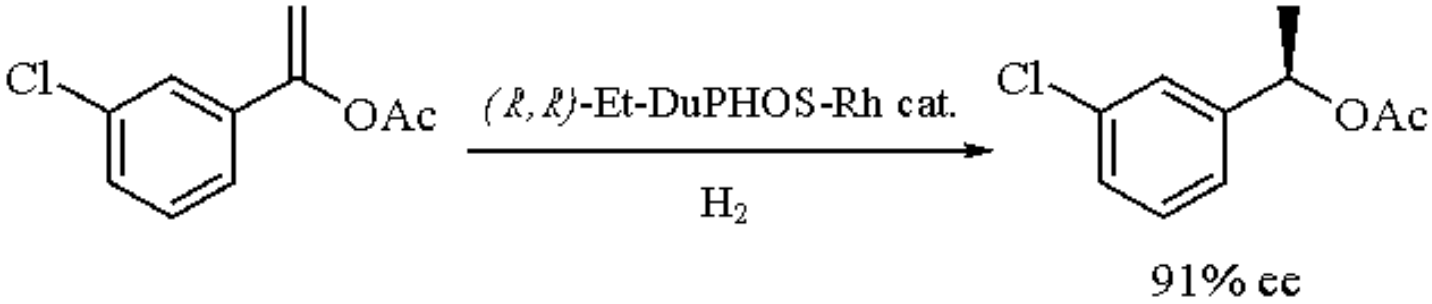

(5)

N-Benzoylhydrazones.

The C=N double bond of *N*-benzoylhydrazones may be hydrogenated with high enantioselectivities using the Ethyl-DuPHOS-Rh catalyst systems (eq 6).[3,4]

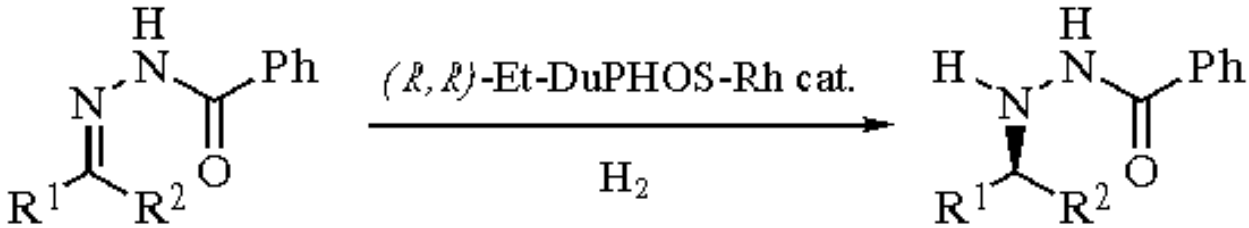

(6)

Under optimized conditions (0 °C, 60 psi H_2, *i*-PrOH, S/C 500), the (*R*,*R*)-Et-DuPHOS-Rh catalyst predictably provides a variety of *N*-benzoylhydrazine products in high enantiomeric excess and with (*S*) absolute configuration (Table 2).

Table 2 Asymmetric Hydrogenation of *N*-Benzoylhydrazones with Ethyl-DuPHOS Rh Catalyst

R^1	R^2	% ee
Ph	Me	95
Ph	CH_2Ph	84
p-$NO_2C_6H_4$	Me	97
p-BrC_6H_4	Me	96
2-Naphthyl	Me	95
CO_2Et	Me	89
CO_2Me	Et	91
CO_2Me	Ph	90
$P(O)(OEt)_2$	Ph	90
Cy	Me	72
Et	Me	43

An interesting and potentially useful property of the Et-DuPHOS-Rh catalyst system is the high level of chemoselectivity exhibited in the hydrogenation of *N*-benzoylhydrazones. Little or no reduction of various functional groups including alkenes, alkynes, ketones, aldehydes, nitriles, imines, carbon-halogen, and nitro groups is observed under conditions required for complete reduction of the hydrazones.

Enantioselective hydrogenation of *N*-benzoylhydrazones represents a key transformation in a three-step asymmetric catalytic reductive amination process that involves: (1) treating a ketone with benzoic acid hydrazide; (2) Ethyl-DuPHOS-Rh-catalyzed hydrogenation of the *N*-benzoylhydrazone; and (3) hydrolysis of the product *N*-benzoyl group (3 M HCl) to provide the corresponding hydrazine, or reductive cleavage of the product N-N bond with ***Samarium(II) Iodide*** to directly afford the corresponding amine (eq 7).[4]

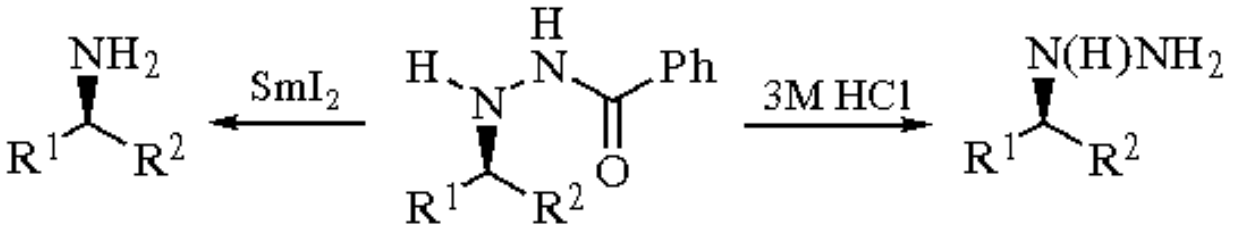

(7)

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Bis(diisopropylamino)aluminum Hydride

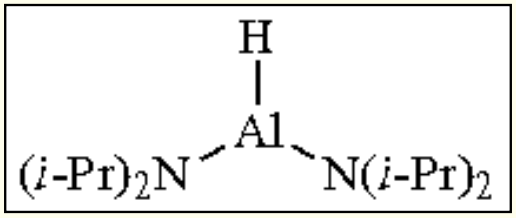

[2826-40-6] · $C_{12}H_{29}AlN_2$ · Bis(diisopropylamino)aluminum Hydride · (MW 228.36)

(reducing agent useful for regioselective conjugate reduction of enones;[1] can hydroaluminate double and triple bonds;[2] can reduce carbonyl compounds to alcohols[2b])

Solubility: sol THF, ether, hydrocarbons.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: Al-H stretching frequency (1820 cm^{-1}); aluminum content by titration with EDTA and back titration with $Zn(OAc)_2$; hydrogen content by gas evolution analysis.[2a,2b]

Preparative Methods: easily prepared by the addition of *i*-Pr_2NH to AlH_3 (from reaction of 100% H_2SO_4 with $LiAlH_4$)[3] in THF in a 2:1 molar ratio. H_2 is evolved during the addition. Reaction is complete after 3 h.[3] Highly pure reagent can be made by the reaction of Al metal and *i*-Pr_2NH (1:2 molar ratio) in benzene at 140 °C under 2000 psi H_2 pressure.[4]

Handling, Storage, and Precautions: moisture sensitive.

Regioselective Conjugate Reduction of Enones.

Excellent regioselectivity in the conjugate reduction of some α,β-unsaturated ketones using $(i\text{-}Pr_2N)_2AlH$ has been reported.[1] The 1,4-reduction product is formed almost exclusively for ketones of the type $R^1CH{=}CR^2COR^3$ (R^1 = Me, *t*-Bu, or Ph; R^2 = H or Me; R^3 = Me, *t*-Bu, or Ph) and yields are near quantitative (eq 1). Reactions are typically run in THF at 0 °C (2-4:1 molar ratio hydride:enone) and are complete within 15 min to 1 h. However, the reagent appears to have limited generality. Poor regioselectivities occur in the reductions of methyl vinyl ketone and cyclohexenone. When the enone system is disubstituted at the 4-position (e.g. $Me_2C{=}CHCOMe$ or isophorone), little or no reaction occurs. On the other hand, cyclopentenone undergoes smooth reduction to give the 1,4-product with only traces of the 1,2-product. Similar extents of regioselectivity are obtainable with HBI_2, but this reagent requires elevated temperatures, extended reaction times (9-20 h), a larger excess of hydride (8:1), and gives very poor yields with cyclic ketones.

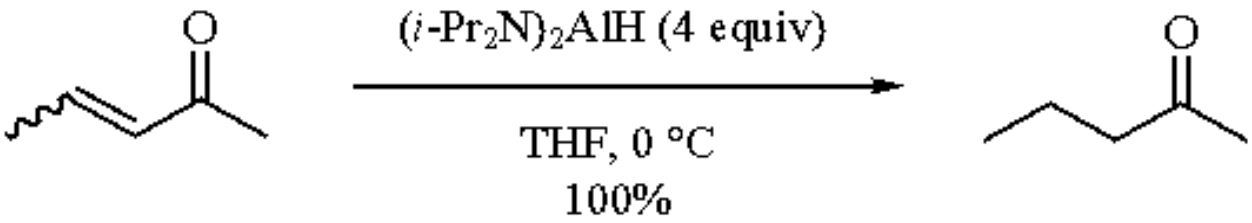

(1)

Hydrometalation.

Hydroalumination of alkynes by (i-$Pr_2N)_2AlH$ in the presence of a transition metal catalyst (typically 5 mol % ***Dichlorobis(cyclopentadienyl)titanium***) readily takes place to give high yields of the hydrometalated compound.[2] This organometallic species can be further functionalized by quenching the alanate with D_2O or I_2 to give the corresponding deutero or iodo product (eq 2).

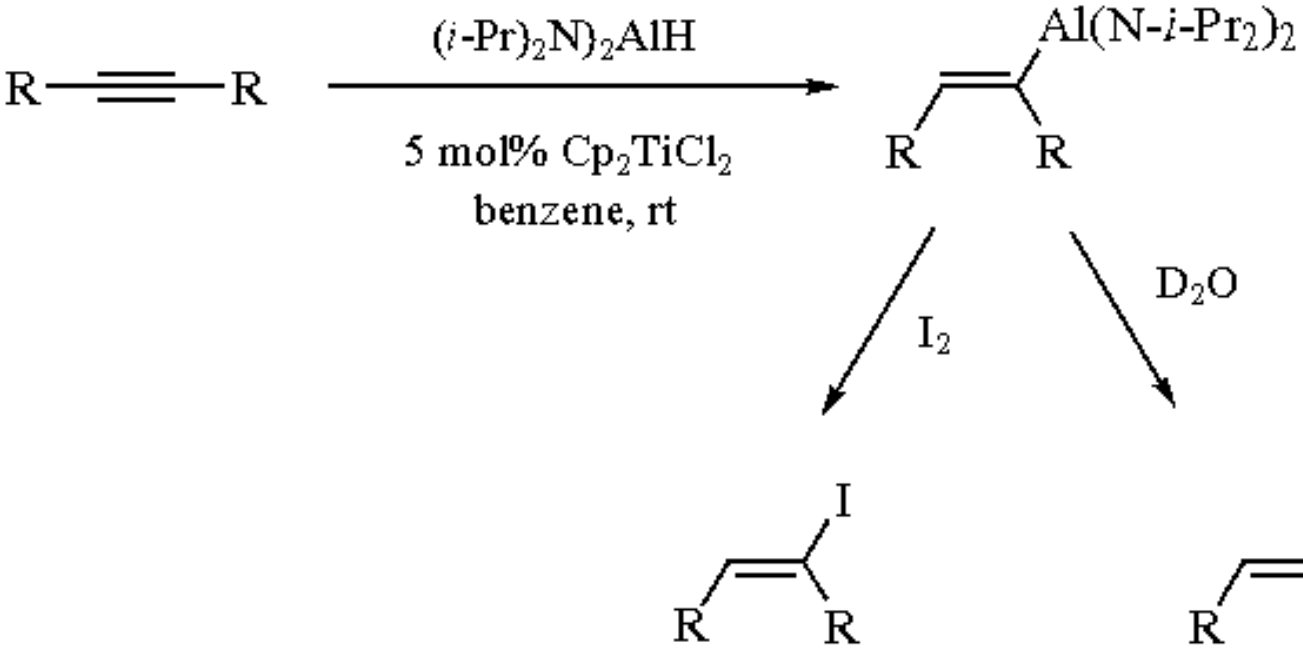

(2)

The reaction with alkynes is a stereospecific *syn* addition, giving alkenylaluminum intermediates.[2a,c] Internal alkynes provide high yields (82-95%) of the *cis*-alkene. No trace of the *trans* isomer is observed when the reaction is carried out at 0 °C. A considerable amount of the *trans*-alkene is formed when the temperature is raised to 25 °C at longer reaction times. Terminal alkynes yield a significant amount of alkane (49-54%) along with the alkene after hydrolysis of the alanate. In the case of unsymmetrical alkynes, regiochemistry is likely determined in the formation of the intermediate alkynyltitanium complex, with the subsequent transmetalation being the slow step of this process (eq 3).[2a] The transition metal adds preferentially to form the less sterically hindered complex.

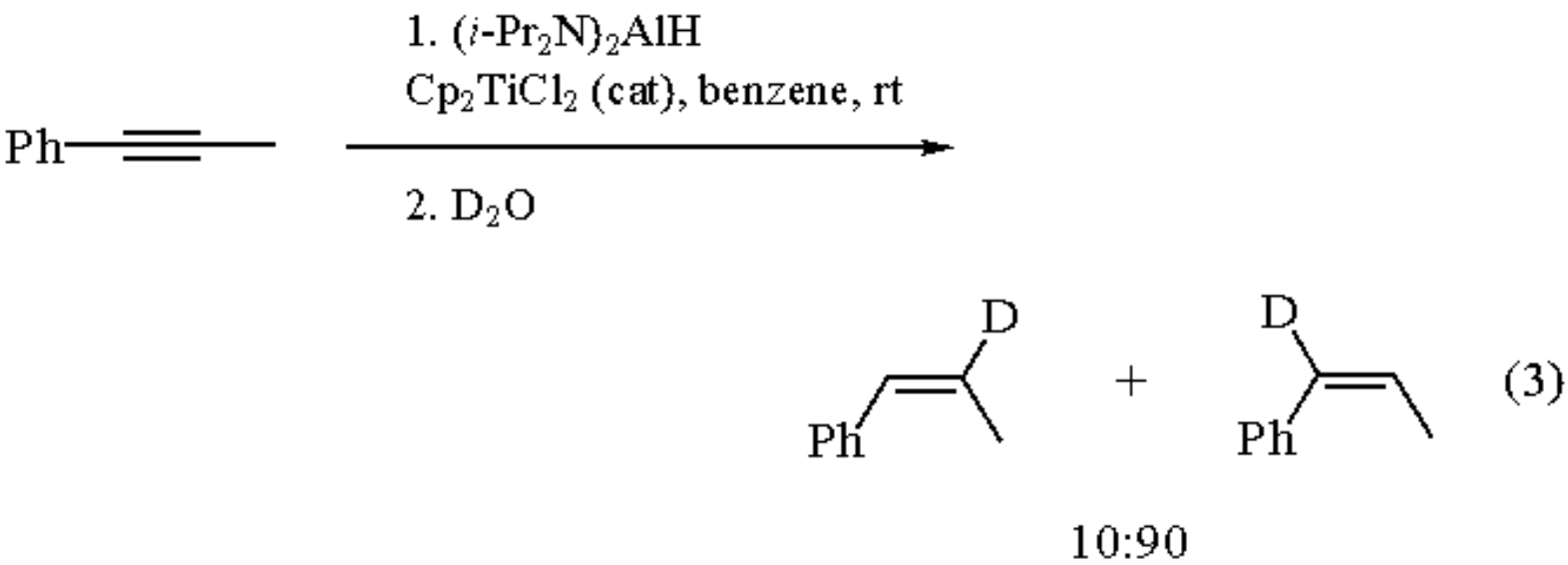

Mono- and disubstituted alkenes are hydrometalated in nearly quantitative yields to provide the alkane upon hydrolytic workup. Tri- and tetrasubstituted alkenes give little or no reaction.[2c] Conjugated dienes react with (i-$Pr_2N)_2AlH$ (1:2 molar ratio) to give mixtures of 1,2- and 1,4-addition products in fair yields (55-60%). An interesting solvent effect was reported in the reaction of 1,5-hexadiene. In THF an 8:1 mixture of alkane and monoene products is formed in 90% yield, whereas cyclization occurs in benzene to give methylcyclopentane (90%).

Nonenolizable carbonyl compounds are quantitatively reduced to the corresponding alcohols (eq 4).[2b] Enolizable ketones are reduced in moderate yields (40-45%) employing a 2:1 molar ratio of (i-$Pr_2N)_2AlH$ to ketone. Stereoselectivity in the reduction of 4-t-butylcyclohexanone decreases when the solvent is changed from THF (92:8 eq:ax alcohols) to benzene (70:30 eq:ax alcohols).

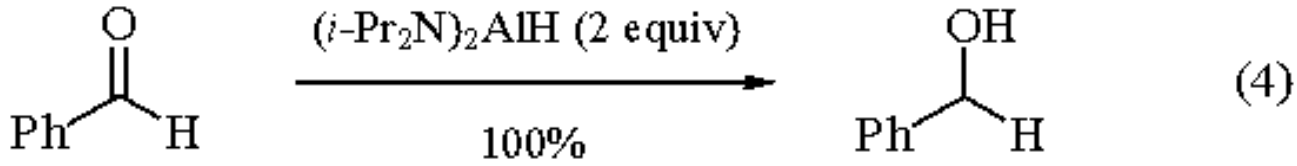

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Melinda Gugelchuk

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Bis(dimethylamino)methane[1]

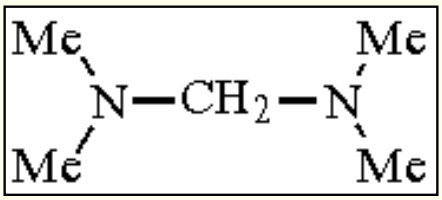

[51-80-9] · $C_5H_{14}N_2$ · Bis(dimethylamino)methane · (MW 102.18)

(precursor for the preparation or in situ generation of *N*,*N*-dimethyl(methylene)ammonium salts;[2,3] used for dimethylaminomethylation of active methylene compounds,[1,4] arylstannanes,[5] and electron-rich heterocycles;[6] useful for the preparation of α,β-unsaturated ketones[7])

Alternate Names: N,N,N´,N´-tetramethylmethanediamine; dimethyl(dimethylamino)methylamine; formaldehyde bis(*N*,*N*-dimethylaminal).

Physical Data: bp 85 °C; *d* 0.749 g cm^{-3}; fp -12 °C.

Solubility: sol H_2O, ether.

Form Supplied in: colorless liquid; widely available.

Purification: dried over potassium hydroxide pellets and distilled.

Handling, Storage, and Precautions: highly flammable. Potent lachrymator. Emits toxic fumes under fire conditions. Handle with gloves in a well-ventilated fume hood. Incompatible with acids, acid chlorides, strong oxidizing agents, and carbon dioxide.

Bis(dimethylamino)methane (**1**) can be used for the dimethylaminomethylation of active methylene compounds. Acidic conditions such as ***Trifluoroacetic Acid*** (TFA) (eq 1)[4] or ***Phosphoric Acid*** in ***Acetic Acid*** (eq 2)[8] catalyze the elimination of dimethylamine from (**1**), resulting in the formation of *N*,*N*-dimethyl(methylene)ammonium salts. The in situ use of these salts in the Mannich reaction is usually more convenient than the direct use of the preformed *N*,*N*-dimethyl(methylene)ammonium salts, since the latter are typically hygroscopic and difficult to handle.

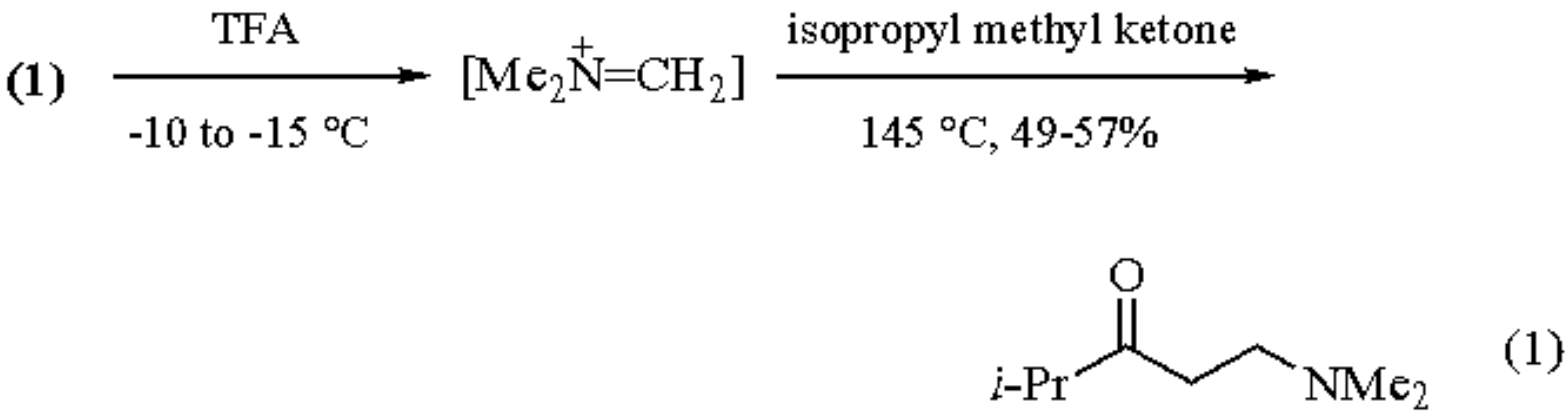

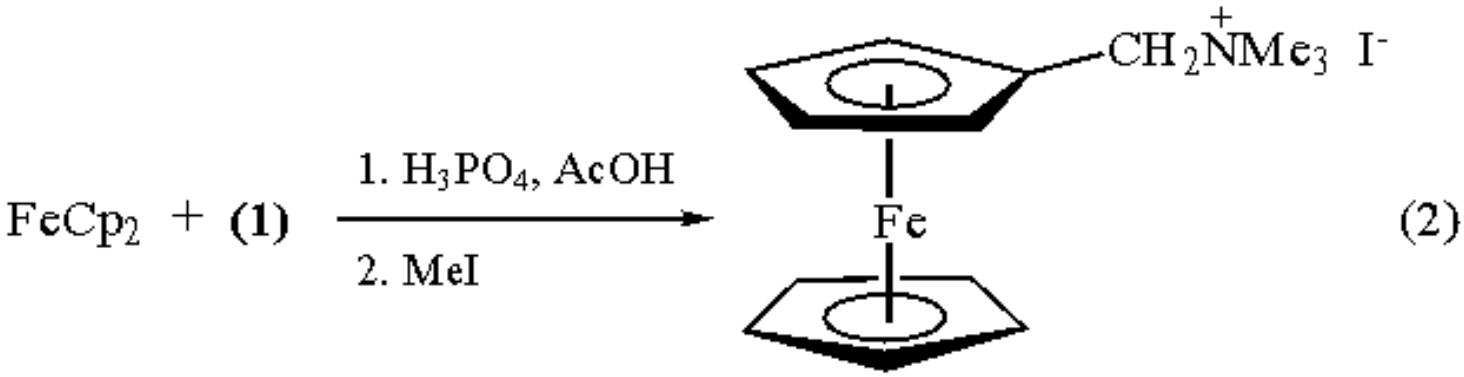

Acyl chlorides or ***Chloroiodomethane*** can also be used in combination with (**1**) to accomplish dimethylaminomethylation of activated methylene compounds (eq 3)[9] and silyl enol ethers (eq 4),[10] respectively. The resulting tertiary amine may in some instances be eliminated to produce the corresponding terminal alkene (eq 5).[11] Reagent (**1**) was shown by de Solms[7] to be superior to the classical Mannich base for the preparation of α,β-unsaturated ketones (eq 6).

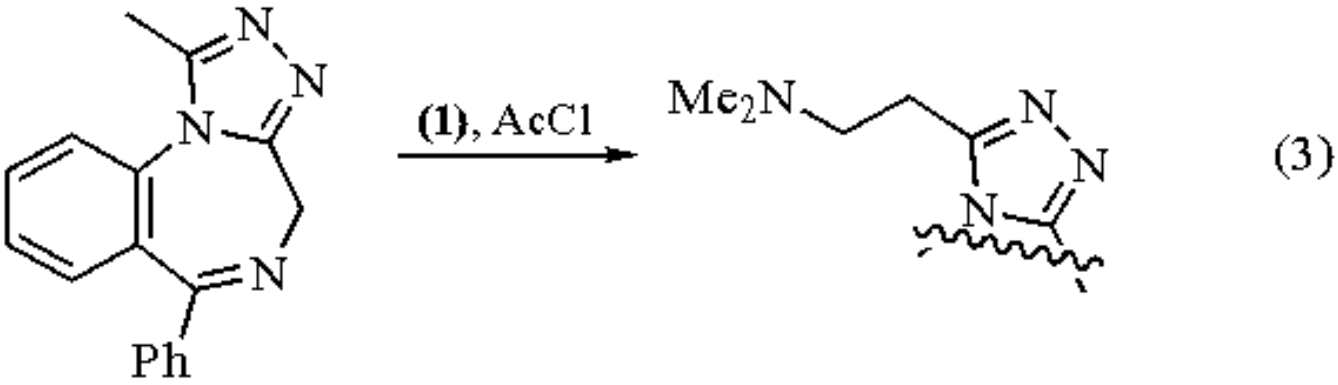

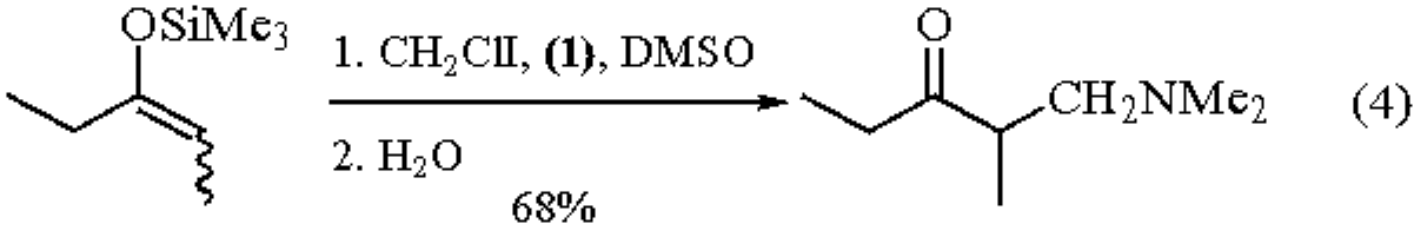

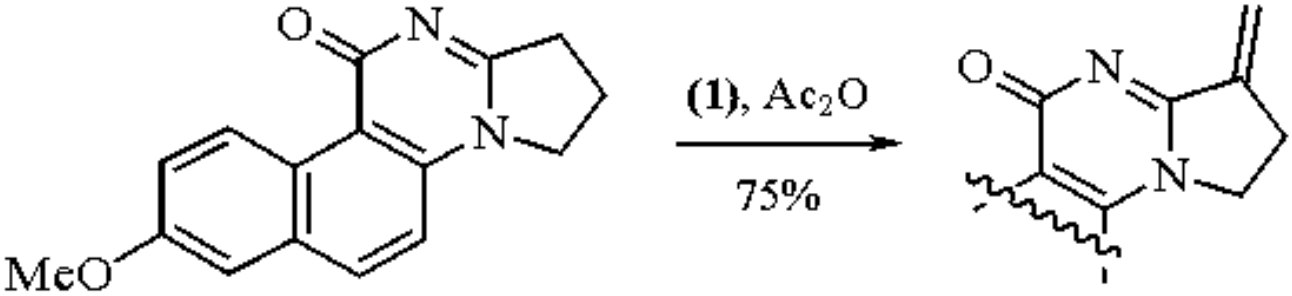

(5)

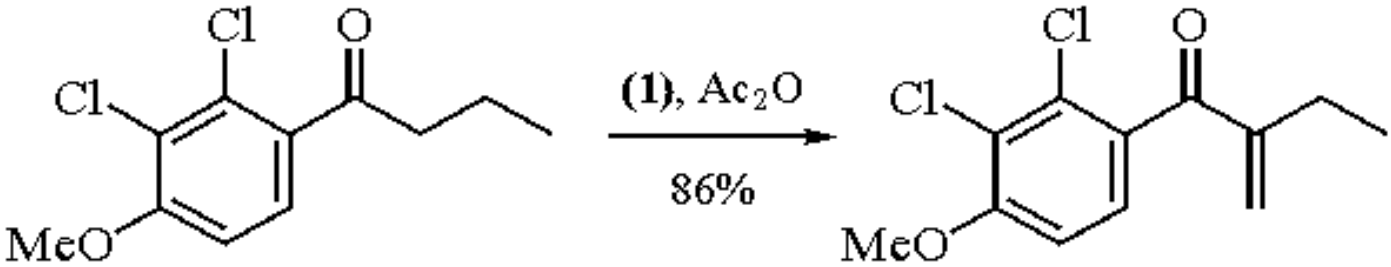

(6)

N,*N*-Dimethyl(methylene)ammonium chloride and iodide can be prepared and isolated from the reaction of (**1**) with ***Acetyl Chloride*** (eq 7)[2] or ***Iodotrimethylsilane*** (eq 8),[3] respectively. However, in the reaction of (**1**) with ***Chlorotrimethylsilane***, the formation of *N*,*N*-dimethyl(methylene)ammonium chloride is not observed.[12] Thus in dimethylaminomethylation reactions employing (**1**) and TMSCl, the reactive intermediate is most likely to be the quarternary silylammonium salt (eq 9).

$$\textbf{(1)} \xrightarrow[0\ ^{\circ}C]{AcCl,\ Et_2O} Me_2\overset{+}{N}{=}CH_2\ Cl^- \qquad (7)$$

$$\textbf{(1)} + TMSI \longrightarrow Me_2\overset{+}{N}(SiMe_3)-CH_2-NMe_2\ I^- \longrightarrow Me_2\overset{+}{N}{=}CH_2\ I^- \qquad (8)$$

$$\textbf{(1)} + TMSCl \rightleftharpoons Me_2\overset{+}{N}(SiMe_3)-CH_2-NMe_2\ Cl^- \not\longrightarrow Me_2\overset{+}{N}{=}CH_2\ Cl^- \qquad (9)$$

$$\downarrow \text{indole} \longrightarrow ArCH_2NMe_2 + HCl + Me_2NSiMe_3$$

Dimethylaminomethylations of aryltrialkylstannanes with (**1**) in the presence of silyl chlorides have been reported (eq 10).[5] Reagent (**1**) also reacts with heterocyclic compounds such as *N*-methylpyrroles (eq 11) and indoles (eq 12) in the presence of acetyl chloride or excess ***Sulfur Dioxide*** to provide the corresponding Mannich products.[6]

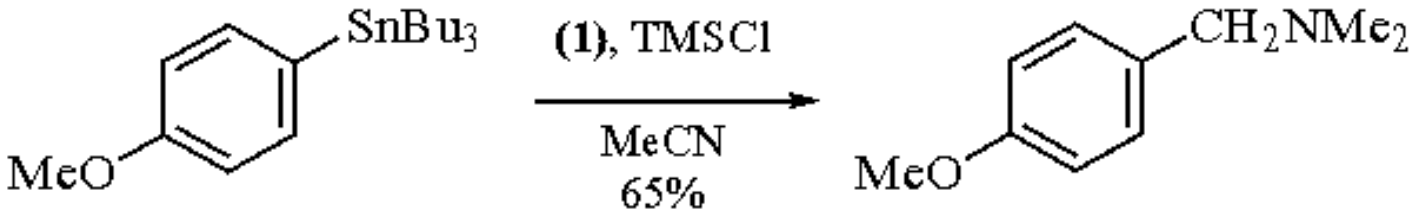

(10)

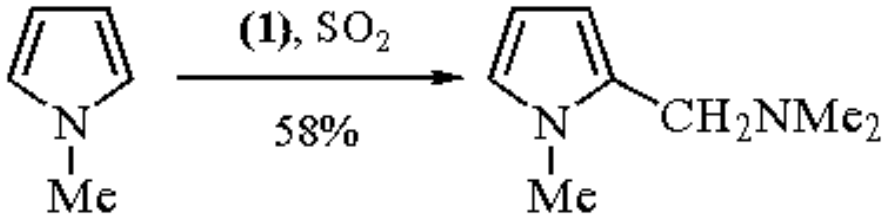

(11)

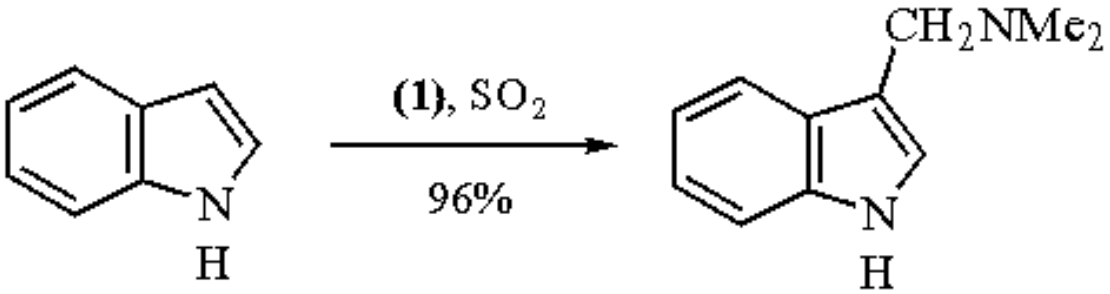

(12)

Related Reagents.

(Dimethylamino)methyl Methyl Ether; ***Dimethyl(methylene)ammonium Iodide***; ***Formaldehyde-Dimethylamine***; ***(Methoxymethyl)bis(trimethylsilyl)amine***; ***N-(Methylthiomethyl)piperidine***; ***Tris(dimethylamino)methane***; ***Tris(formylamino)methane***.

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Pfizer Central Research, Groton, CT, USA

1,8-Bis(dimethylamino)naphthalene[1,2]

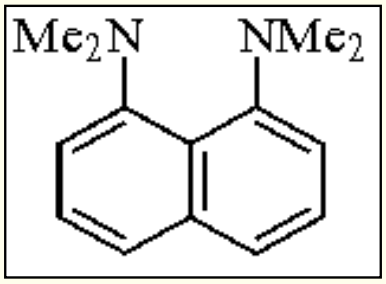

[20734-58-1] · $C_{14}H_{18}N_2$ · 1,8-Bis(dimethylamino)naphthalene · (MW 214.31)

(used as weakly nucleophilic strong base)

Alternate Name: Proton Sponge®.

Physical Data: mp 49-51 °C (45-46 °C).[3]

Solubility: sol most organic solvents.

Form Supplied in: yellow-tan crystals.

Preparative Method: prepared in 82% yield from 1,8-diaminonaphthalene, dimethyl sulfate, and sodium hydride.[3]

Purification: recrystallized from petroleum ether.[3]

Handling, Storage, and Precautions: irritant.

Strong Base.

The strong basic properties of 1,8-bis(dimethylamino)naphthalene (**1**) are attributed to a combination of dipole-dipole repulsions (nitrogen lone pairs), van der Waals repulsions, and steric inhibition of resonance.[4] Relief of strain imposed by the close proximity of the nitrogen lone pairs occurs upon protonation, giving this base one of the highest pK_a values of the aromatic amines (pK_a 12.1; pK_a of *N*,*N*-dimethylaniline 5.1). A variety of stronger Proton Sponge-like aromatic amine bases, such as the 2,7-dimethoxy derivatives (**2**) and (**3**)[5] and the bis(dimethylamino)fluorenyl system (**4**),[6] have been prepared and exhibit pK_a values of 16.1, 16.3, and 13.5, respectively. However, it is observed in these types of systems that the rates of proton transfer to and from the amine base are very slow.[7]

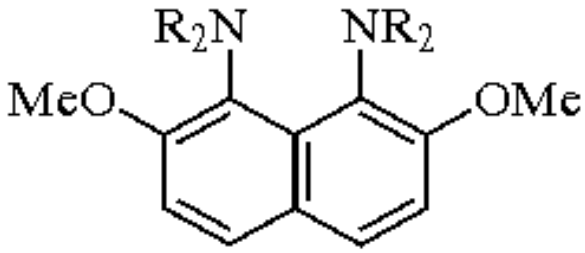

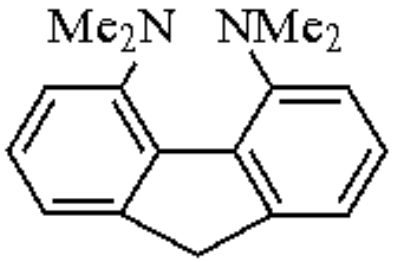

(2) R = Me
(3) R = Et

(4)

The weak nucleophilic character of (**1**) makes this reagent useful for applications involving the neutralization of acid in systems sensitive to Lewis basic reagents. In the phosphorylation of 5-vinyl- and 5-ethynyl-2´-deoxyuridines to the corresponding 5´-triphosphates (eq 1),[8] Proton Sponge effectively promotes formation of the intermediate phosphorodichloridate whereas other bases (TEA, *i*-Pr_2EtN, collidine, DBU, DBN) are ineffective. A phosgene-free synthesis of highly pure isocyanates from carboxylic acids and ***Diphenyl Phosphorazidate*** occurs in good yields only with (**1**) as base (eq 2).[9] Other tertiary amine bases give lower yields and contaminate the product after distillation. The oxidative decarboxylation-deoxygenation of 3-hydroxycarboxylic acids to tri- and tetrasubstituted alkenes (eq 3) makes use of Proton Sponge to eliminate acid-catalyzed alkene isomerization or degradation of the products,[10,11] and the ***Tin(II) Trifluoromethanesulfonate***-promoted addition of aliphatic 1-alkynes to aldehydes (eq 4) proceeds best when performed with this nonnucleophilic base.[12]

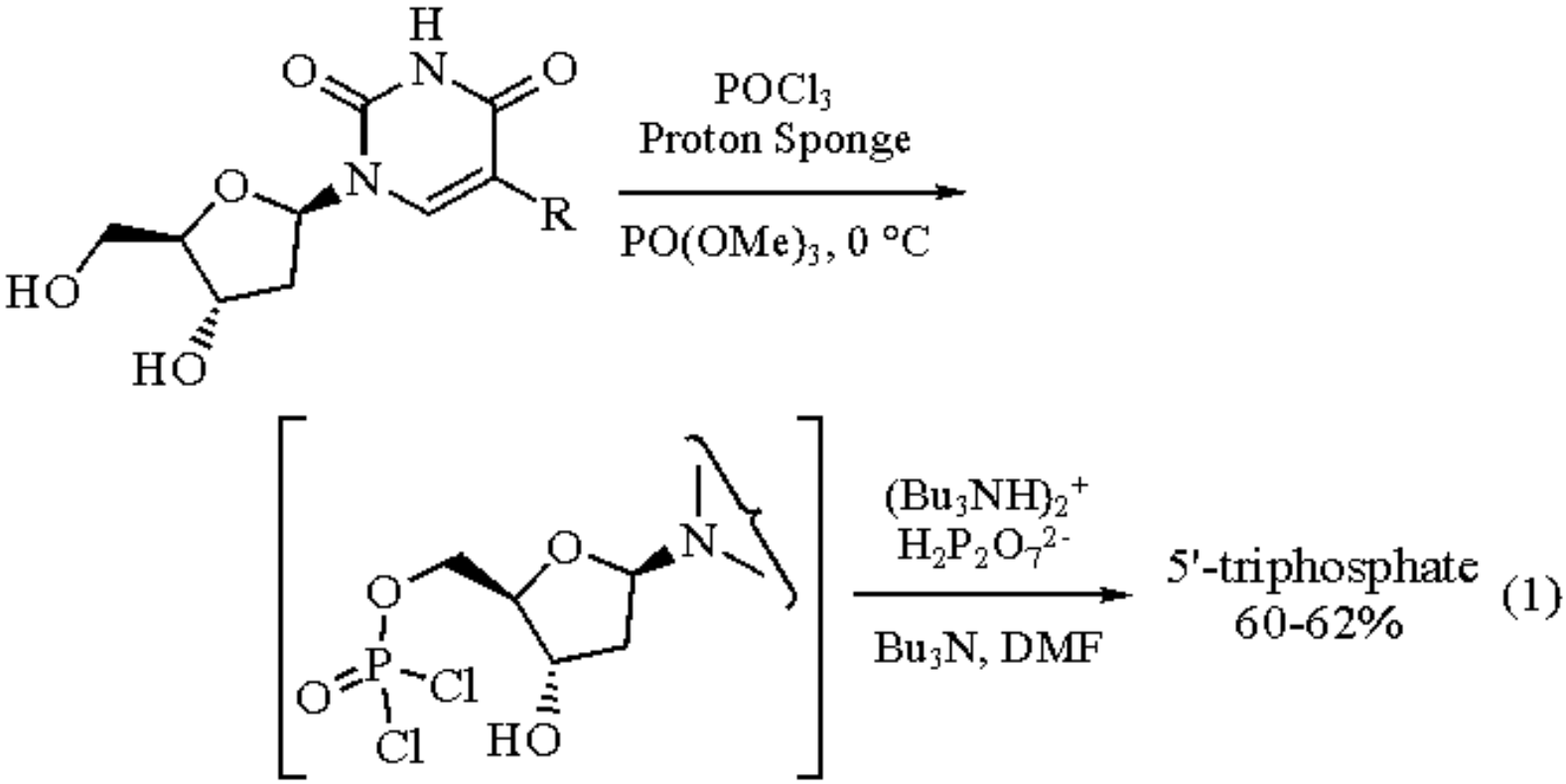

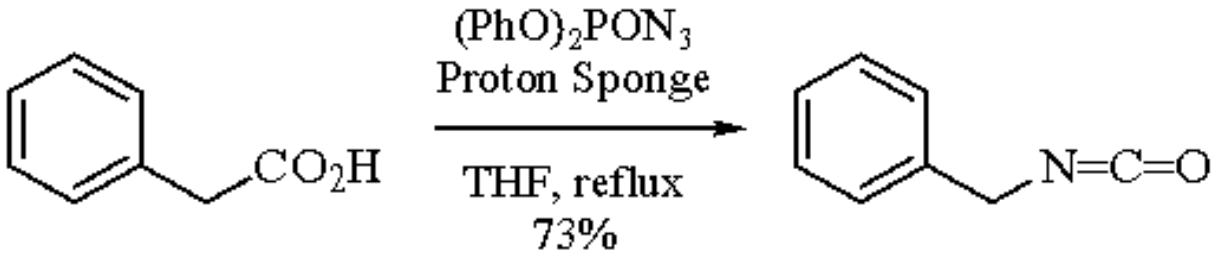

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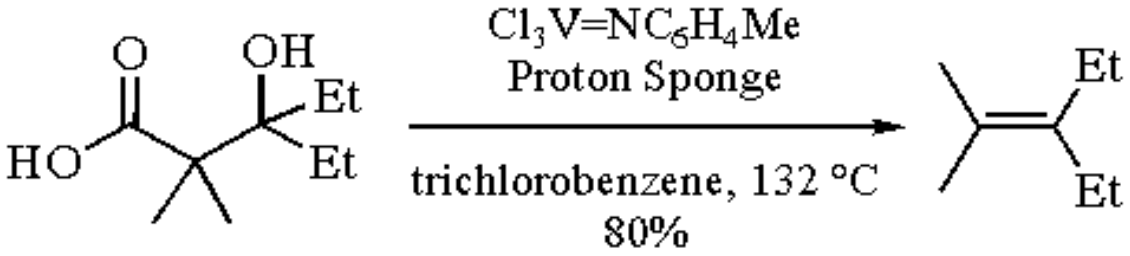

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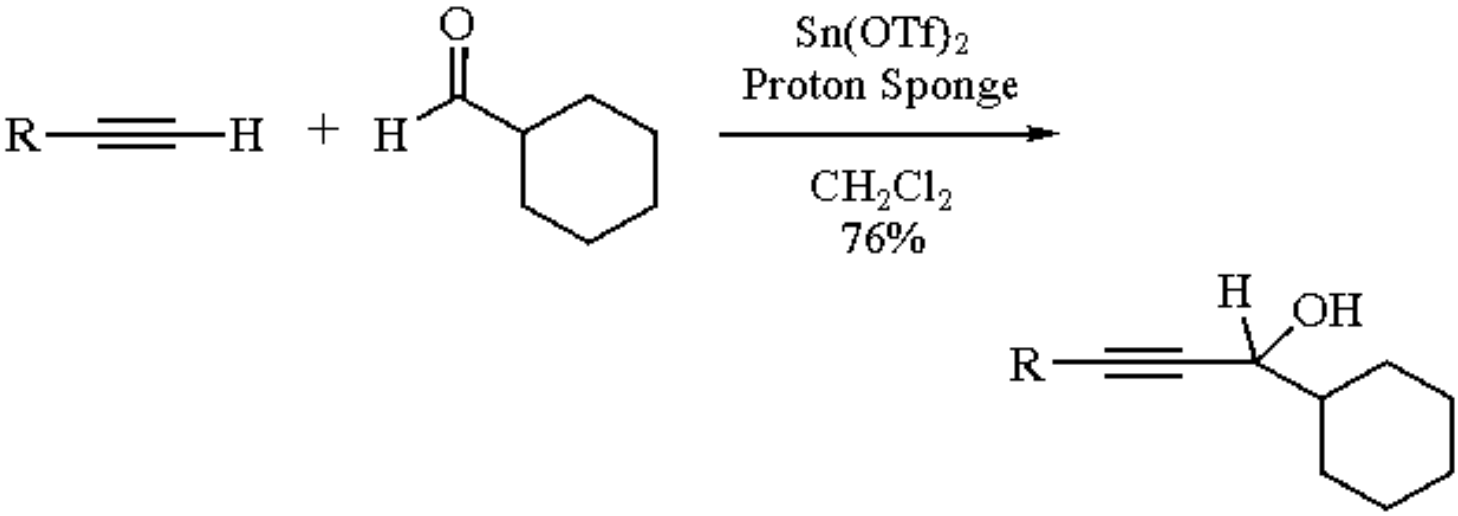

(4)

1,8-Bis(dimethylamino)naphthalene has particular value in applications involving the use of transition metal catalysts. Its use in palladium-catalyzed arylations (eq 5),[13,14] alkoxycarbonylation (eq 6),[15] and intramolecular cyclizations[16] is noteworthy, giving superior yields compared to other more nucleophilic bases.

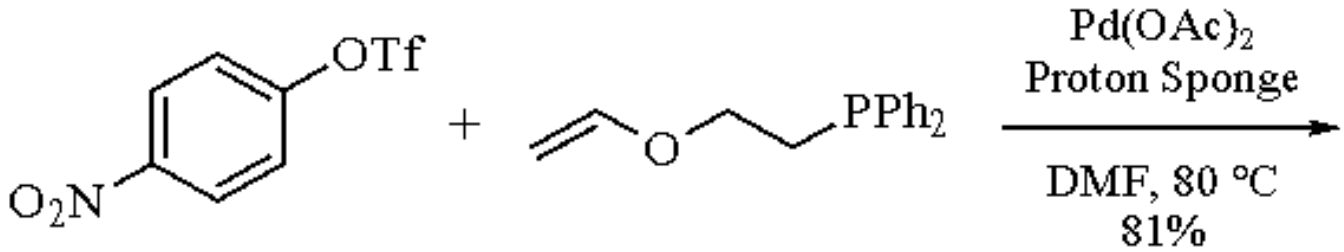

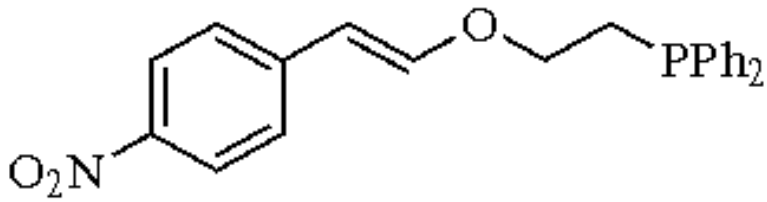

(5)

$E:Z = 1:1$

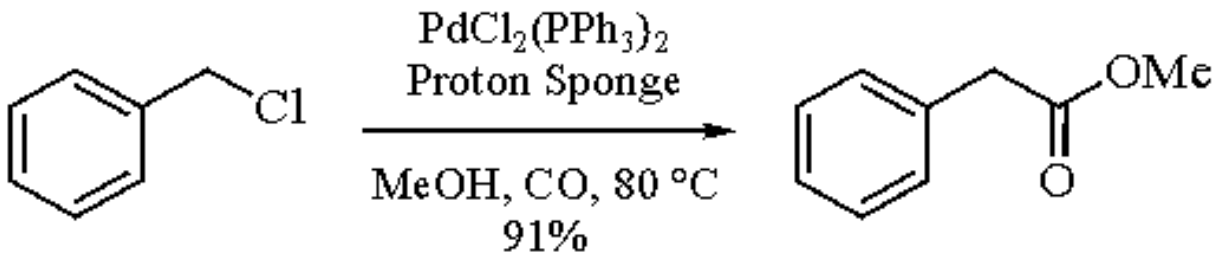

(6)

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Bis(dimethylamino) Phosphorochloridate

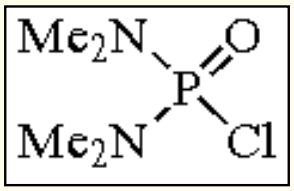

[1605-65-8] · $C_4H_{12}ClN_2OP$ · Bis(dimethylamino) Phosphorochloridate · (MW 170.58)

(reagent for protection of alcohols,[1] ketones,[2] thiols[3] and amines;[4] reductive deoxygenation of alcohols and ketones[2])

Physical Data: fp >230 °C; *d* 1.152 g cm^{-3}.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: moisture sensitive; store in a dry, cool environment. Handle in a well-ventilated fume hood.

Protection and/or Reductive Deoxygenation of Alcohols and Ketones.

Bis(dimethylamino) phosphorochloridate constitutes a useful protecting reagent for hydroxyls,[1] thiols[3] and for ketones (i.e. enols).[2] The phosphorodiamidates, prepared by phosphorylation of the corresponding alcoholate or enolate, are stable to various conditions and deprotection is accomplished under mild conditions in nearly quantitative yield.[5]

The phosphorodiamidates of alcoholates are readily reduced in high yield by lithium-ethylamine solution (eq 1).[2] The two-step reductive deoxygenation of ketones (RCOR´ -> RCHOHR´ -> RCH_2R´) has unique advantages over the traditional Wolff-Kishner reduction if the substrate is particularly sensitive to acid/base conditions or if the substrate exhibits severe steric congestion in the vicinity of the carbonyl moiety (eq 2). Bis(dimethylamino) phosphorochloridate[6] (and diethyl phosphate)[7] have been used to trap the kinetic enolate of enediones (e.g. analogs of the Wieland-Miescher ketones) prior to reduction to corresponding alkene.[8]

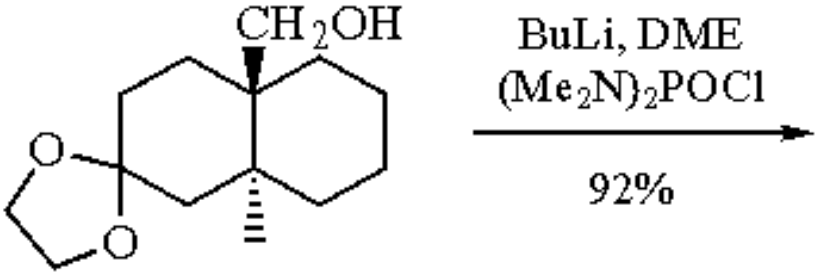

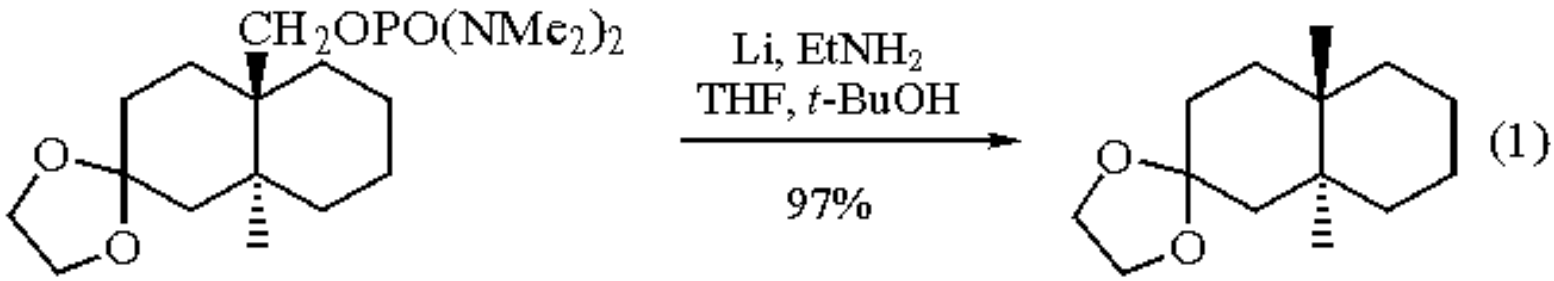

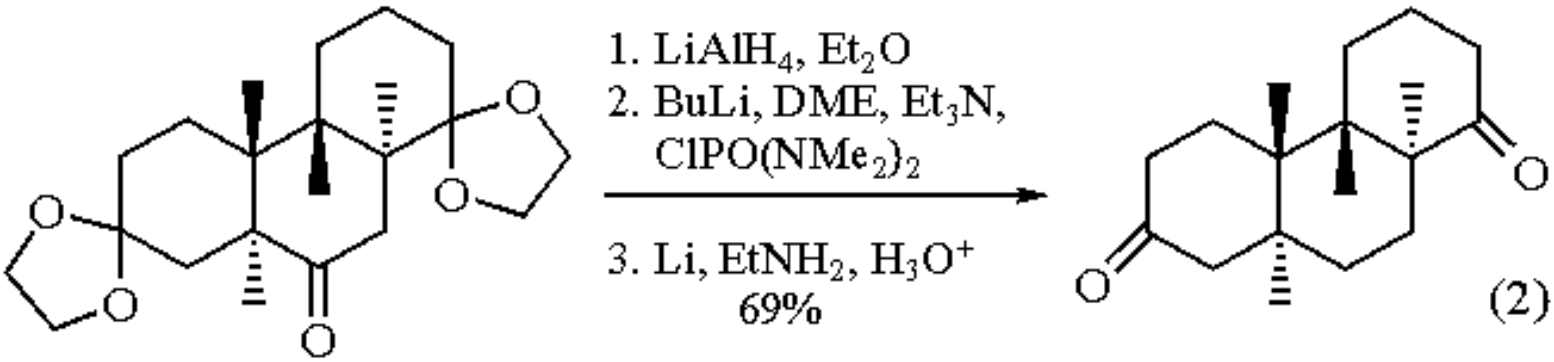

Glycopyranosyl *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidates appear to promote highly stereoselective 1,2-*trans*-β-glycosidation reactions.[9] When comparison is made with other phosphorus-containing reagents[10] that promote glycosidations (specifically, the diphenyl phosphate method,[10a] which affords similar reactivity and stereoselectivity), the glycosyl phosphorodiamidates have the advantage of being shelf-stable glycosyl donors (eq 3).[9]

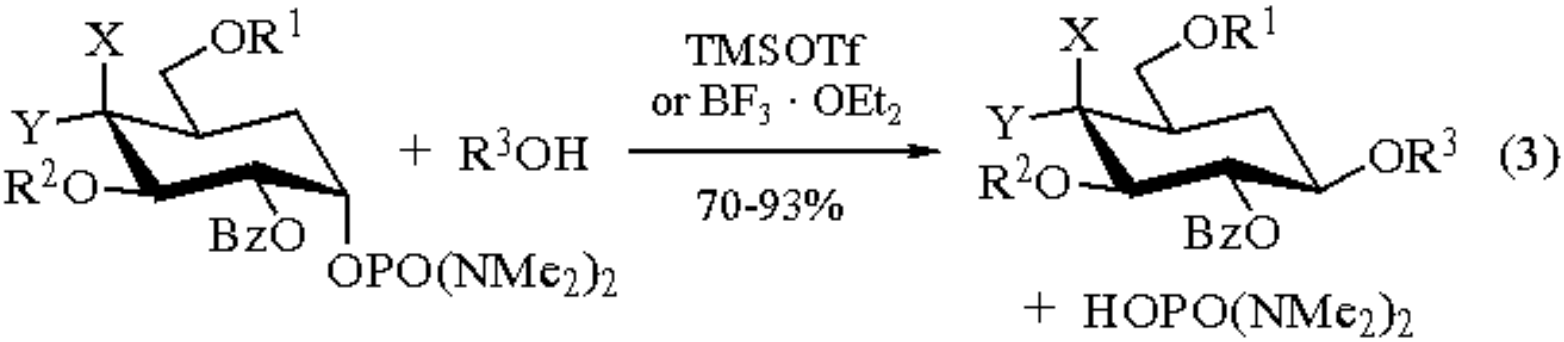

$R^1 = R^2 = Y = Bn, X = H$; $R^1 = R^2 = X = Bn, Y = H$;
$R^1 = R^2 = Y = Bz, X = H$; $R^1 = R^2 = X = Bn, Y = H$;
R^3 = steroidal alcohols

Bis(dimethylamino)phosphorodiamidate has been employed as a directing agent for the α-lithiation of tetrahydroisoquinolines,[11] the 3-lithiation of 2-furanol,[12] and for the *ortho*-lithiation of phenols[13] and naphthols.[13b] In the case of phenols, the *ortho*-lithiated species prepared by reaction of the derived phosphorodiamidates with ***s-Butyllithium*** at -105 °C can be subsequently trapped (ca. -105 °C) with a variety of electrophiles to afford *ortho*-substituted phosphorodiamidates (eq 4).

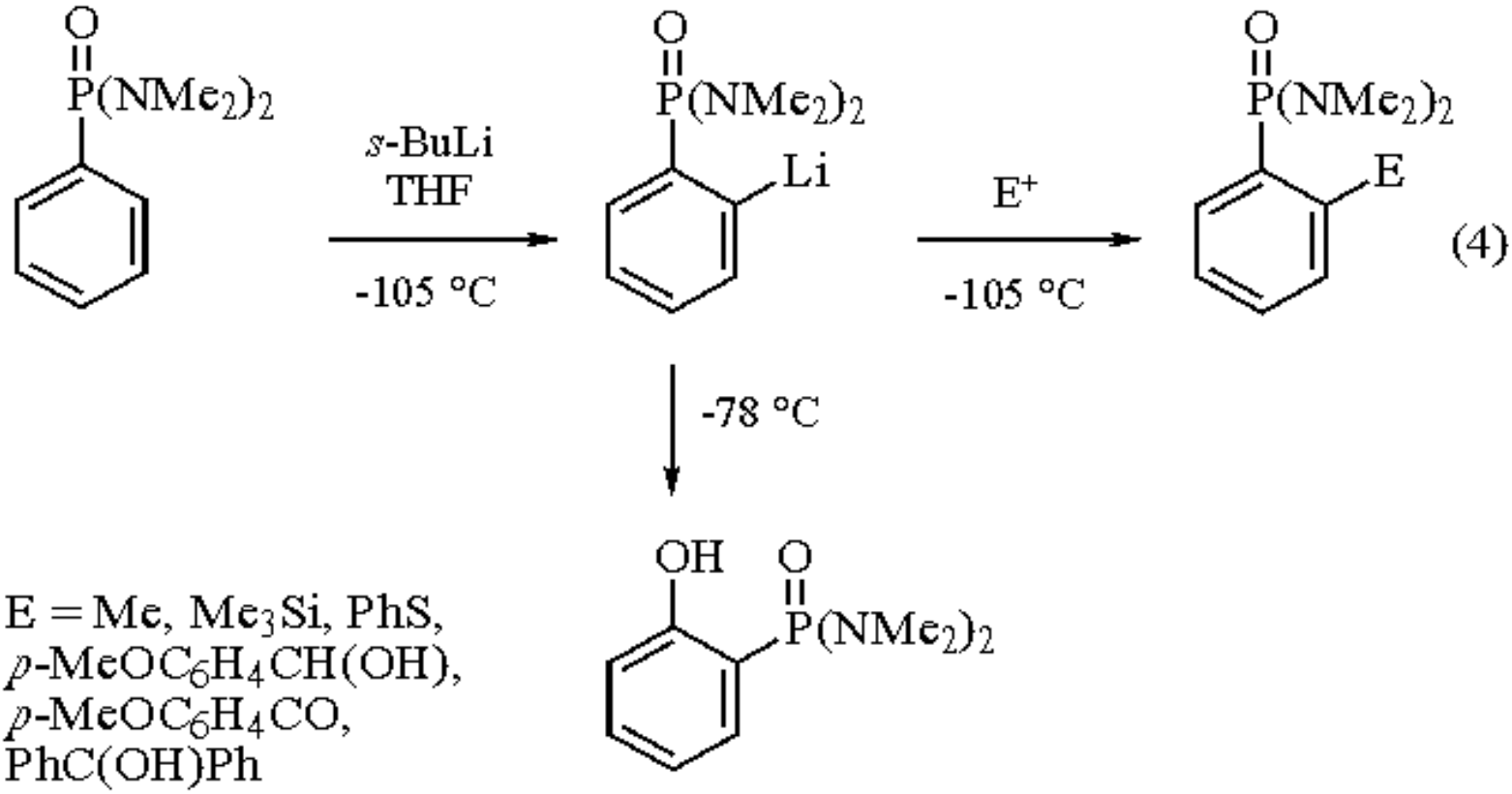

(4)

Protection of Primary Amines.

Protection of primary aliphatic amines employing the bis(dimethylamino)phosphoryl group gives *N*-alkylphosphoramides[4] which can be subsequently substituted to afford *N*,*N*´-dialkyl or propargylic phosphoramides (eq 5).[14]

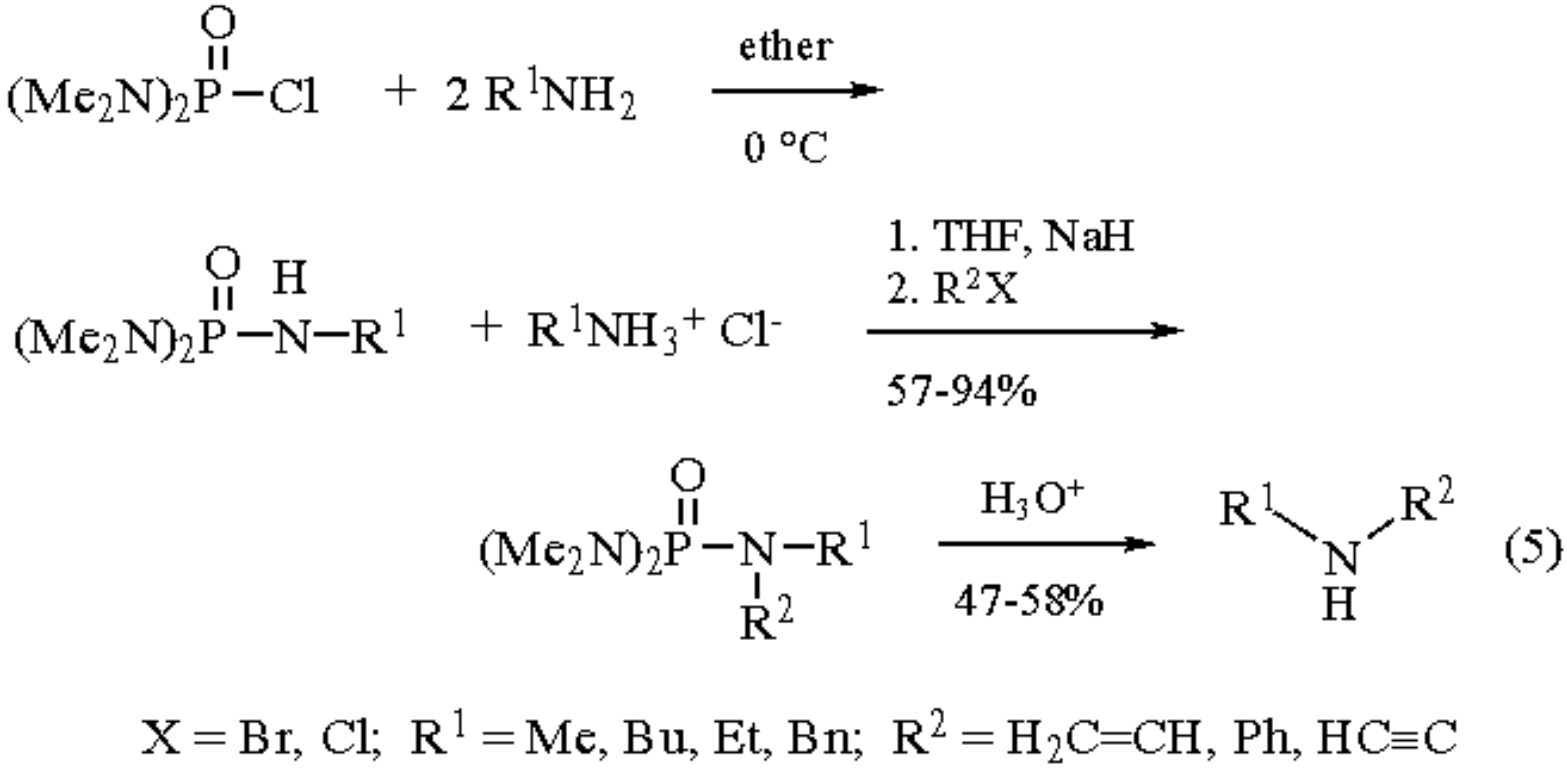

Hydroboration of *N*-alkylpropargylic phosphoramides occurs without nitrogen-boron complexation and with a regioselectivity and stereospecificity similar to that observed with alkynes,[4] while substituted propargylic amines and ethylenic amino ketones are easily prepared from the corresponding phosphoramides.[15]

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Isabel Mathieu-Pelta & Slayton A. Evans, Jr.

1,4-Bis(dimethylamino)-1,1,4,4-tetramethyldisilethylene[1]

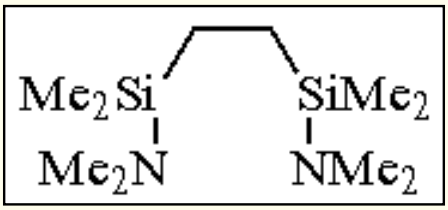

[91166-50-6] · $C_{10}H_{28}N_2Si_2$ · 1,4-Bis(dimethylamino)-1,1,4,4-tetramethyldisilethylene · (MW 232.52)

(reagent for the protection of primary amines with lower pK_a values, such as substituted anilines, as their tetramethyldisilylazacyclopentane or Stabase adduct; precursor of tetramethyldisilylthiacyclopentane, a sulfur transfer reagent)

Physical Data: bp 100-103 °C/13 mmHg; *d* 0.824 g cm^{-3}.

Preparative Method: the reagent is prepared as a colorless liquid in 90% yield by treating commercially available bis(chlorodimethylsilyl)ethane with 5 equiv of dimethylamine in ether at 0 °C for 5 h.

Handling, Storage, and Precautions: the liquid vapors are heavier than air and may travel a considerable distance to a source of ignition. Vapor-air mixtures are explosive above the flash point of 14 °C. Use in a fume hood.

Protection of Primary Aromatic Amines.[1]

The title reagent is used for the preparation of Stabase derivatives of primary amines, and is particularly useful for the protection of primary aromatic amines with pK_a values of 10-11 (see ***1,2-Bis(chlorodimethylsilyl)ethane***). The protection of substituted anilines is achieved by heating equimolar amounts of the title compound and the anilines in the presence of ***Zinc Iodide*** (0.5 mol %) under a slow stream of nitrogen at 140 °C for 5 h. In many cases the products can be purified by vacuum distillation. Cleavage of the Stabase adducts to the corresponding primary amines can be performed in ether in the presence of 2 equiv of methanol and a small amount of *p*-toluenesulfonic acid monohydrate (0.2 mol %). The tetramethyldisilylazacyclopentane or Stabase adduct (**3**) is a particularly attractive protecting group due to its ease of preparation, base stability, and facile removal (eq 1).

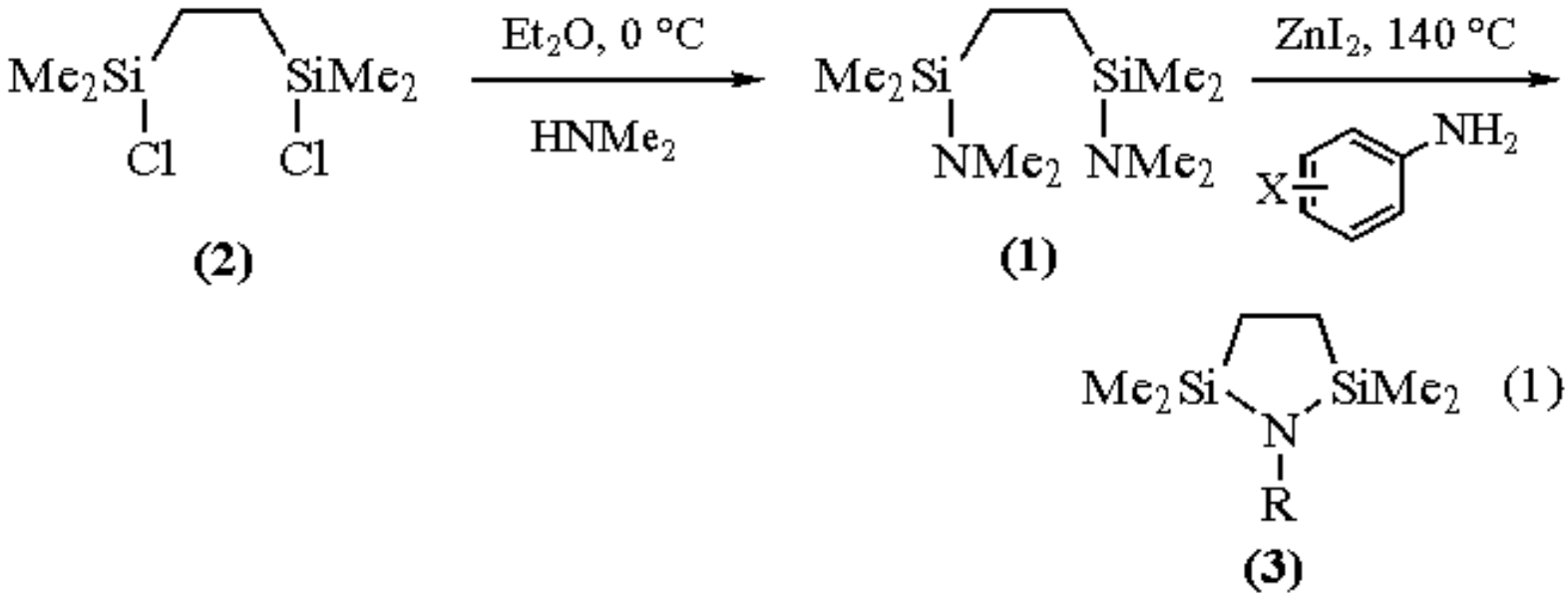

The title compound was utilized to protect 2-amino-6-bromopyridine (**4**) in 72% yield in a sequence to prepare helicopodant (**7**) (eq 2).[2]

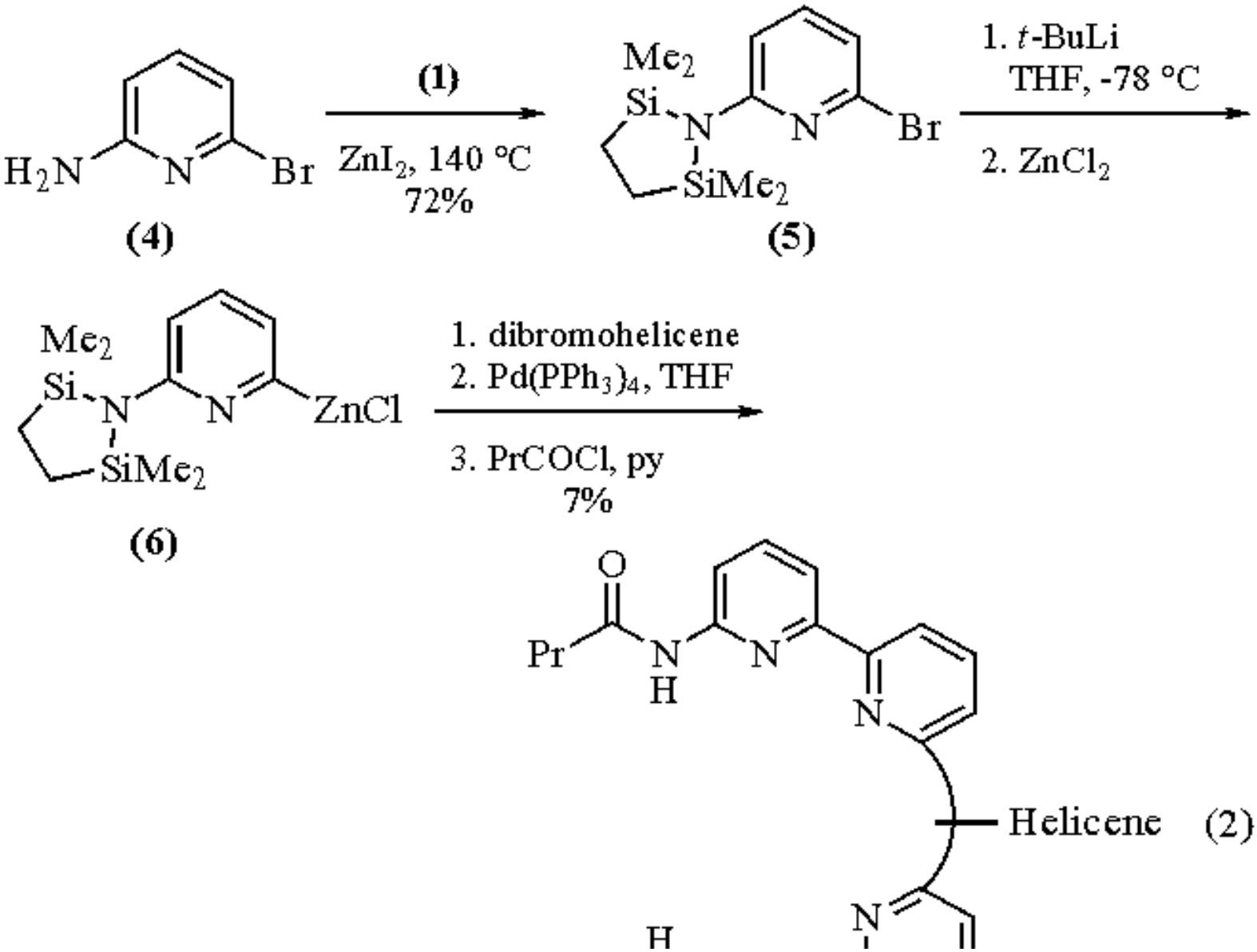

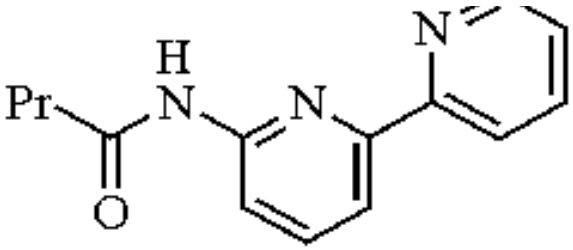

(7)

Sulfur Transfer Reagent.

The reagent was used to prepare 2,2,5,5-tetramethyl-2,5-disila-1-thiacyclopentane (**8**) which acts as a sulfur transfer reagent. An example of this reaction is shown in eq 3.[3]

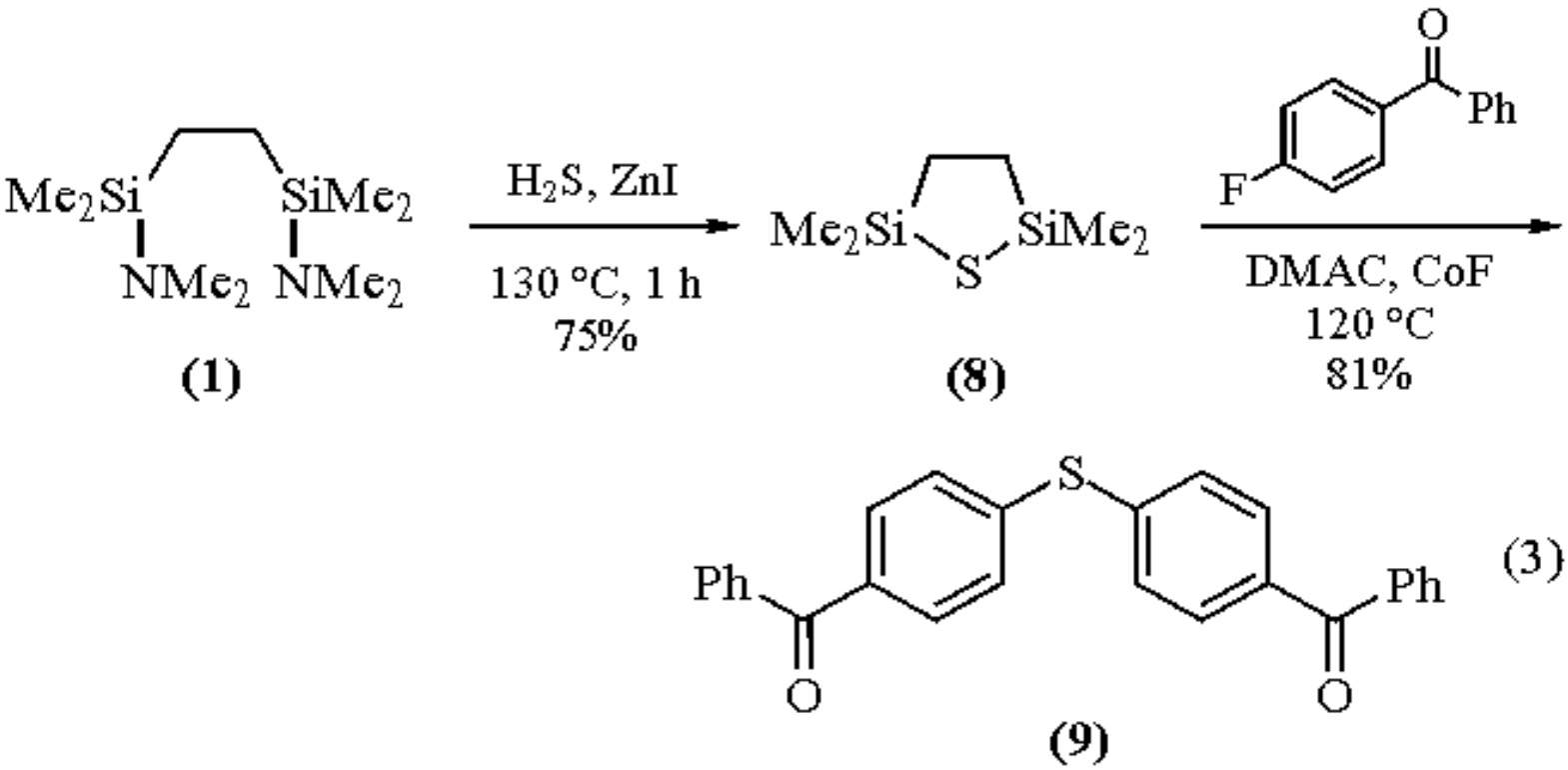

(3)

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Bis(*N,N*-dimethylformamido)oxodiperoxomolybdenum(VI)

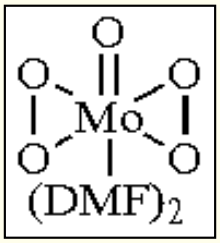

[23319-73-5] · $C_6H_{14}MoN_2O_7$ · Bis(*N,N*-dimethylformamido)oxodiperoxomolybdenum(VI) · (MW 322.13)

(useful as an aprotic oxidant in the oxidation of trimethylsilylated amides to the corresponding hydroxamic acids;[1] catalyst for the epoxidation of alkenes[2,3])

Physical Data: mp 100-102 °C.

Solubility: sol water, $CHCl_3$, CH_2Cl_2; insol ether.

Form Supplied in: yellow powder. *Drying:* the hydrated complex is dried in vacuo over P_2O_5.

Preparative Method: molybdic acid (20 g, 0.15 mol) is dissolved in 30% hydrogen peroxide (100 mL) at 35 °C. The yellow solution is cooled to 15 °C and DMF (21.9 g, 0.3 mol) added. The aqueous solution is partially evaporated under reduced pressure, maintaining the temperature below 35 °C. The resultant yellow crystals are collected by filtration, and washed thoroughly with ether and a small volume of methanol (2 × 25 mL).

Handling, Storage, and Precautions: the complex is stable under storage.

Hydroxamic Acids.

A variety of natural products containing hydroxamic acid functions possess a wide range of biological activities, including the important role of hydroxamic acids in certain iron-transporting systems.[4] Trimethylsilylation of secondary amides activates them towards oxidation to hydroxamic acids by the peroxo-molybdenum complex MoO_5.HMPA.[5] The trimethylsilylation of amides is a well documented process.[6] The derivatives are sensitive to water and protic solvents, being solvolyzed to the parent amide. In order to oxidize trimethylsilylated amides, aprotic oxidants are required. Since molybdenum is known to form stable complexes with hydroxamic acids, there existed the possibility that, after oxidation, the product hydroxamic acid would become complexed with the molybdenum ion, thus avoiding further overoxidation during the reaction. Molybdenum pentoxide complexes are stable, covalent diperoxo species.[7] Several such complexes are known. Two useful ones are MoO_5.HMPA and MoO_5.py.HMPA (see ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)***). These HMPA complexes are more easily prepared because they are insoluble in water, but released HMPA can interfere with workup. The bis(dimethylformamide) complex is the preferred oxidant. It is water soluble and more stable on storage and there is no residual water ligand to interfere with the subsequent oxidation. Furthermore the released DMF ligands interfere less in the workup procedure than HMPA. Since oxidations with these peroxo complexes are thought to involve substrate-molybdenum complex formation,[8] competing strong donor ligands

or very polar solvents competitively inhibit the reaction and oxidations are best carried out in chloroform or, routinely, dichloromethane solutions. Liberation of the uncomplexed hydroxamic acids is accomplished by extraction of the molybdenum ion with warm EDTA at pH 9. Since many of the hydroxamic acids are water soluble, their efficient recovery requires continuous extraction with either chloroform or dichloromethane after adjustment of the pH of the solution to 7.5. Although the yield on oxidation of silylated secondary aliphatic amides is usually only moderate (15-40%), hydroxylation of acetanilides proceeds consistently with yields of 40-50%. The reaction is efficient for oxidation of benzoxazinones (eq 1). The products are useful herbicides because of inhibition of auxin.

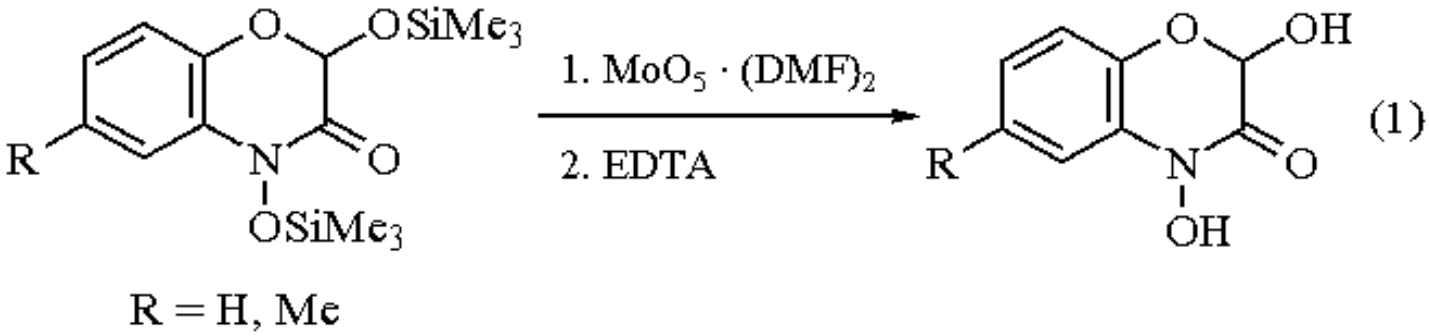

Some other substrates are 2-(trimethylsilyloxy)pyridine (eq 2) and 4-quinolone (eq 3) as its trimethylsilyl derivative, giving the corresponding hydroxamic acids in 90% and 55% yield, respectively. In contrast, silylated ureas and carbamates fail to give the desired oxidation products.

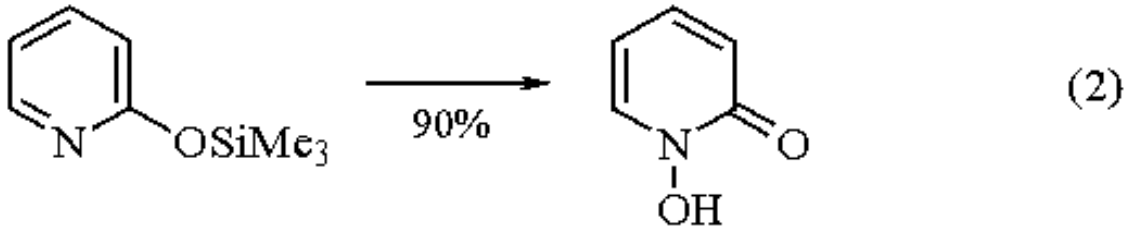

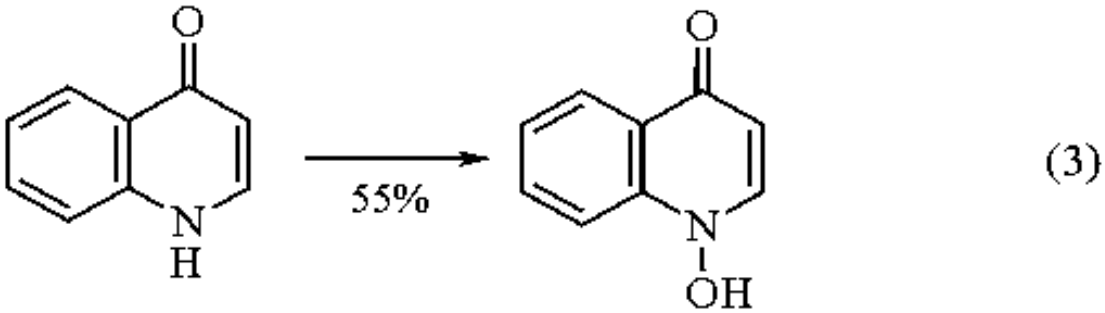

Epoxidation Catalyst.[2,3]

A UV and IR examination of the epoxidation of cyclohexene by ***1,1-Di-t-butyl Peroxide***, catalyzed by the complexes of MoO_5 with DMF or HMPA, showed that the mechanism involves the initial, rapid, reaction of the catalyst with *t*-BuOOH to give the Mo peroxo complex which then epoxidizes the alkene via an O transfer. This latter step involves the formation and subsequent cleavage of a fused molybdenadioxacyclopentane ring.

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Tapan Ray

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Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)[1]

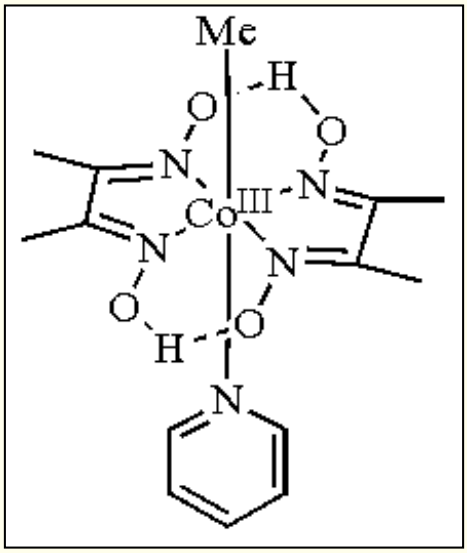

[61754-28-7] · $C_{14}H_{22}CoN_5O_4$ · Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III) · (MW 383.29)

(prototype of alkylcobaloximes and model compound for methylcobalamine[1])

Alternate Names: methyl(pyridine)cobaloxime(III); $MeCo^{III}(dmgH)_2py$.

Physical Data: mp 215-220 °C (dec); *d* 1.42 g cm^{-3}; polarographic half-wave potentials (acetonitrile solution, vs $Ag/AgNO_3$ electrode): -1.75, -2.44, -3.01 V; λ_{max} = 438 nm (log ε = 3.17); ^1H, ^{13}C, ^{59}Co NMR, and ESR data,[2] FT-IR and Raman spectroscopy,[3] polarographic properties (dropping mercury electrode),[4] photochemical and radiolytic C-Co bond cleavage,[5] thermal decomposition,[6] and X-ray crystallography[7] have been described.

Solubility: sol many organic solvents (acetone, methanol, methylene chloride); slightly sol THF, benzene, ethyl acetate; almost insol water.

Preparative Method: orange crystals readily available from cobalt(II) chloride, butane-2,3-dione dioxime (dimethylglyoxime, $dmgH_2$), pyridine (py), and dimethyl sulfate or methyl iodide.[8]

Handling, Storage, and Precautions: requires no special handling procedures. It is less light-sensitive than its solutions, which tend to decompose with loss of methyl and formation of cobaloxime(II), but should be stored in amber colored vials under nitrogen. For some reactions the 4-*t*-butylpyridine derivative of methyl(pyridine)cobaloxime(III), i.e. methyl(4-*t*-butylpyridine)cobaloxime(III), is easier to handle especially when column chromatography on silica gel (ethyl acetate, orange band, R_f = 0.4) is required, or in applications which require higher concentrations of alkylcobaloxime(III) in solution or use of nonpolar solvents. Samples have been purified with reversed phase HPLC on a chromsil C_{18} column.[9]
Methyl(pyridine)cobaloxime is readily recrystallized from methanol/water mixtures under a nitrogen atmosphere.

General Preparation of Organocobalt(dmgH)$_2$ Complexes.

Organo-$Co^{III}(dmgH)_2$ complexes were originally developed by Schrauzer as vitamin B_{12} analogs[9,10,11] (see also ***Cobalt Salen Complexes***

and ***Cobalt Salophen Complexes***), and extensive mechanistic studies into their reactions have been carried out.[10,12] The preparation of $RCo^{III}(dmgH)_2$ complexes can be accomplished by reacting $Co^{I}(dmgH)_2$, $Co^{II}(dmgH)_2$, or $Co^{III}(dmgH)_2$ reagents with electrophiles, radicals, and nucleophiles respectively.[10] The most common method for the preparation of $RCo^{III}(dmgH)_2$ reagents is via displacement reactions using supernucleophilic $Co^{I}(dmgH)_2$. $Co^{I}(dmgH)_2$ can be prepared in situ from the readily available $Co^{II}(dmgH)_2$ or $ClCo^{III}(dmgH)_2py$ by reduction with ***Sodium Borohydride***[8,13] or hydrogen gas,[14] electrochemically,[15] or by disproportionation.[16] The reduced $Co^{I}(dm\ gH)_2$ reacts with a variety of substrates including alkyl halides, acyl halides, vinyl halides,[17] alkynyl halides,[18] activated aryl halides,[19] alkyl tosylates, alkyl sulfates, alkyl phosphates,[20] and oxiranes.[21] Allylic halides and propargylic halides may undergo both S_N2 and S_N2' substitution, with steric factors largely determining the course of the reaction (eq 1).[22] For base sensitive substrates, $Co^{II}(dmgH)_2$ can be used in conjunction with Zn metal and an alkylating agent (eq 2).[23]

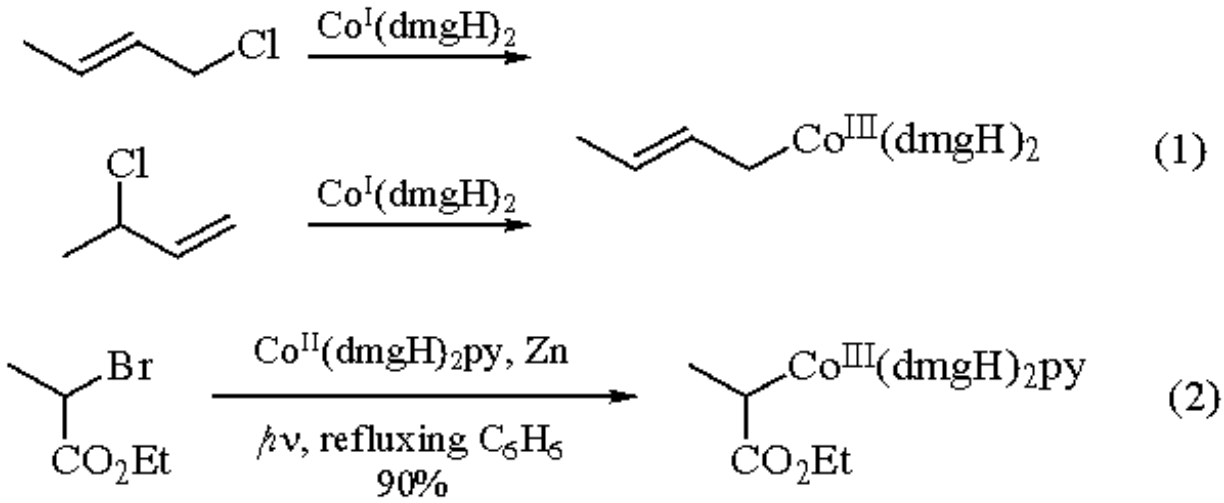

$Co^{I}(dmgH)_2$ adds to activated alkenes and alkynes, e.g. styrene and acrylonitrile, in alkaline protic solvents to give β-substituted products arising from *trans* addition of the metal ion and a proton from the solvent (eq 3). Under neutral or acidic conditions, $Co^{I}(dmgH)_2$ exists as the protonated hydrido $HCo^{III}(dmgH)_2$ species, and α-substituted products arising from a *cis* addition are isolated (eq 4).[17] 1,3-Dienes that do not possess terminal substituents react to give $allylCo^{III}(dmgH)_2$ complexes (eq 5).[24]

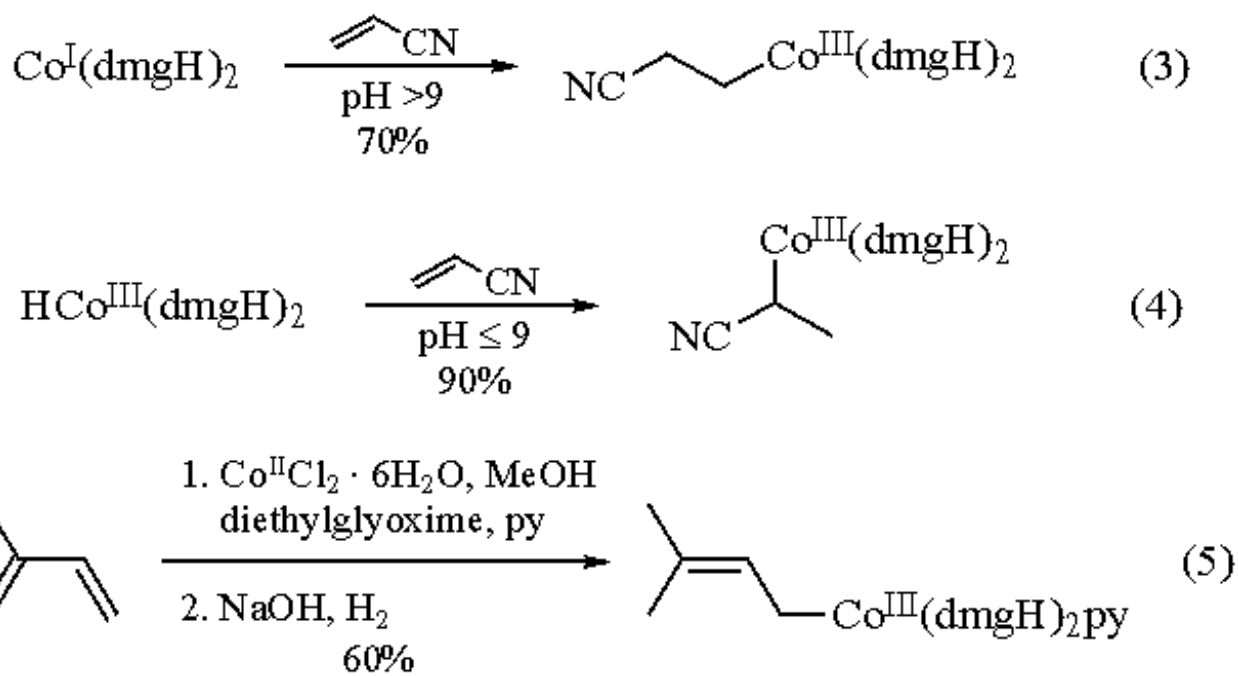

$ClCo^{III}(dmgH)_2py$ reacts with alkyl metals such as Grignard reagents,[25] alkyllithiums, alkylborons, and alkylaluminums, leading to the corresponding organo-$Co^{III}(dmgH)_2$ complexes (eq 6).[26] A one-pot procedure whereby $Co^{I}(dmgH)_2$ is formed in situ from a cobalt(II)

salt, pyridine, and dimethylglyoxime under reducing conditions, followed by the addition of an alkylating agent, can be employed (eq 7).[8]

$$\mathrm{ClCo^{III}(dmgH)_2py} \xrightarrow[79\%]{\text{3 equiv EtMgBr, THF}} \mathrm{EtCo^{III}(dmgH)_2py} \quad (6)$$

$$\mathrm{Co^{II}Cl_2} \xrightarrow[\text{3. } Me_2SO_4 \quad 99\%]{\text{1. 2 equiv } (dmgH)_2\text{, MeOH, py; 2. NaOH}} \mathrm{MeCo^{III}(dmgH)_2py} \quad (7)$$

Methylation.

Methyl(pyridine)cobaloxime(III) is a methylating agent. Due to its covalent nature, the carbon-cobalt bond can be cleaved with nucleophiles, radicals, and electrophiles. For some transformations, photochemical, thermal, or oxidative activation of the carbon-cobalt bond may be required. Thiolates are methylated at room temperature (eq 8).

$$\mathrm{Me[Co^{III}]} + \mathrm{MeS^-Na^+} \xrightarrow[25\ ^\circ\mathrm{C}]{\text{MeOH, dark}} \mathrm{MeSMe} \quad (8)$$

$$[\mathrm{Co}] = \mathrm{Co(dmgH)_2py}$$

Thus in vitro methylation of coenzyme M with abiotic methyl(pyridine)cobaloxime(III) in basic alcoholic solutions and in the presence of cell extracts of *Methanobacillus omelianskii* yields methane, forming a model for methane biosynthesis.[27] Likewise, nucleophiles such as SCN^-, I^-, CN^-, and phosphines readily yield the corresponding methylated products. Electrophilic cleavage of the methyl carbon bond in methyl(pyridine)cobaloxime(III) occurs in the presence of ***Mercury(II) Acetate***, ***Thallium(III) Acetate***, and anhydrous acids, such as ***Trifluoroacetic Acid*** and ***Hydrochloric Acid***.[28] The former reaction mimics environmental formation of methylmercury via methylcobalamine in wastewater of heavily polluted industrial sites (eq 9).

$$\mathrm{Me[Co^{III}]} + \mathrm{Hg(OAc)_2} \xrightarrow[\substack{20\ ^\circ\mathrm{C} \\ 70\text{-}90\%}]{\text{pH 2-5}} \mathrm{[Co^{III}(OAc)]} + \mathrm{MeHgOAc} \quad (9)$$

Efficient and selective methyl transfer reactions from methyl(pyridine)cobaloxime(III) to α,β-unsaturated carbonyl compounds require assistance of palladium salts. Thus 1,4-benzoquinone is monomethylated in 70% yield in the presence of $LiPdCl_4$ (eq 10). Terminal alkenes such as styrene, 1-octene, or acrylates form the corresponding chain elongated (*E*)-alkenes. Substitution of an alkyl group by hydrogen occurs at the sterically less hindered alkenic carbon atom (eq 11).[29]

Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)

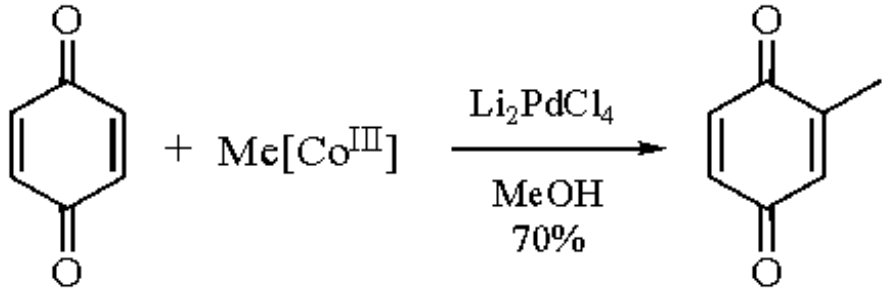

(10)

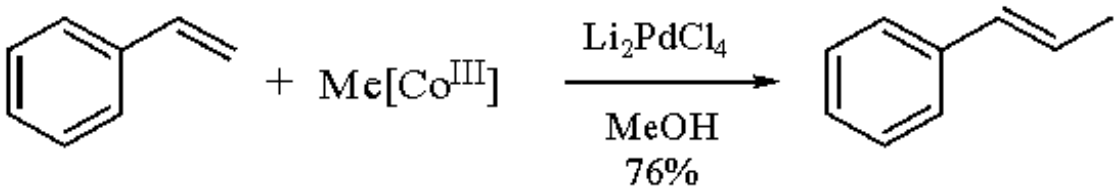

(11)

Cleavage of alkyl-cobalt bonds with solutions of bromine in the dark has proven to be a useful tool for dealkylation of cobaloximes in both mechanistic and preparative studies.[30] Due to the decreased oxidative power of iodine, alkylcobaloximes are converted to alkyl iodides only when the reaction mixtures are photolyzed.[31] Cobalt(IV) species have been discovered by ESR spectroscopy to be the primary products of photolytic iodination of alkylcobaloximes, and these then fragment to yield alkyl iodides (eq 12).

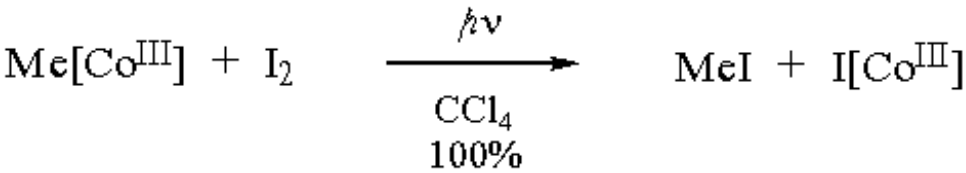

(12)

Insertion Reactions of Organocobalt(dmgH)$_2$) Complexes.

$RCo^{III}(dmgH)_2$ complexes undergo insertion of molecular oxygen under thermal or photochemical conditions to give alkylperoxycobaloximes ($ROOCo^{III}(dmgH)_2$).[32] The reaction is accompanied by racemization with chiral organocobaloximes.[33] $ROOCo^{III}(dmgH)_2$ complexes can be reduced using $NaBH_4$ or $LiAlH_4$, leading to the corresponding alcohols (eq 13),[15] and can act as sources of oxygen centered radicals.[24] Similarly, sulfur dioxide inserts readily into both primary and secondary alkyl $RCo^{III}(dmgH)_2$ complexes (eq 14). However, phenyl, vinyl, and styryl complexes have been shown to be inert to O_2 and SO_2.[34] Homolysis of $RCo^{III}(dmgH)_2$ complexes in the presence of carbon monoxide does not normally lead to acylcobalt complexes. If the reaction is carried out in an alcoholic solvent, however, then alkoxycarbonyl$Co^{III}(dmgH)_2$ ($ROCOCo^{III}(dmgH)_2$) complexes are formed, where the alkoxy group is derived from the solvent (eq 15).[35]

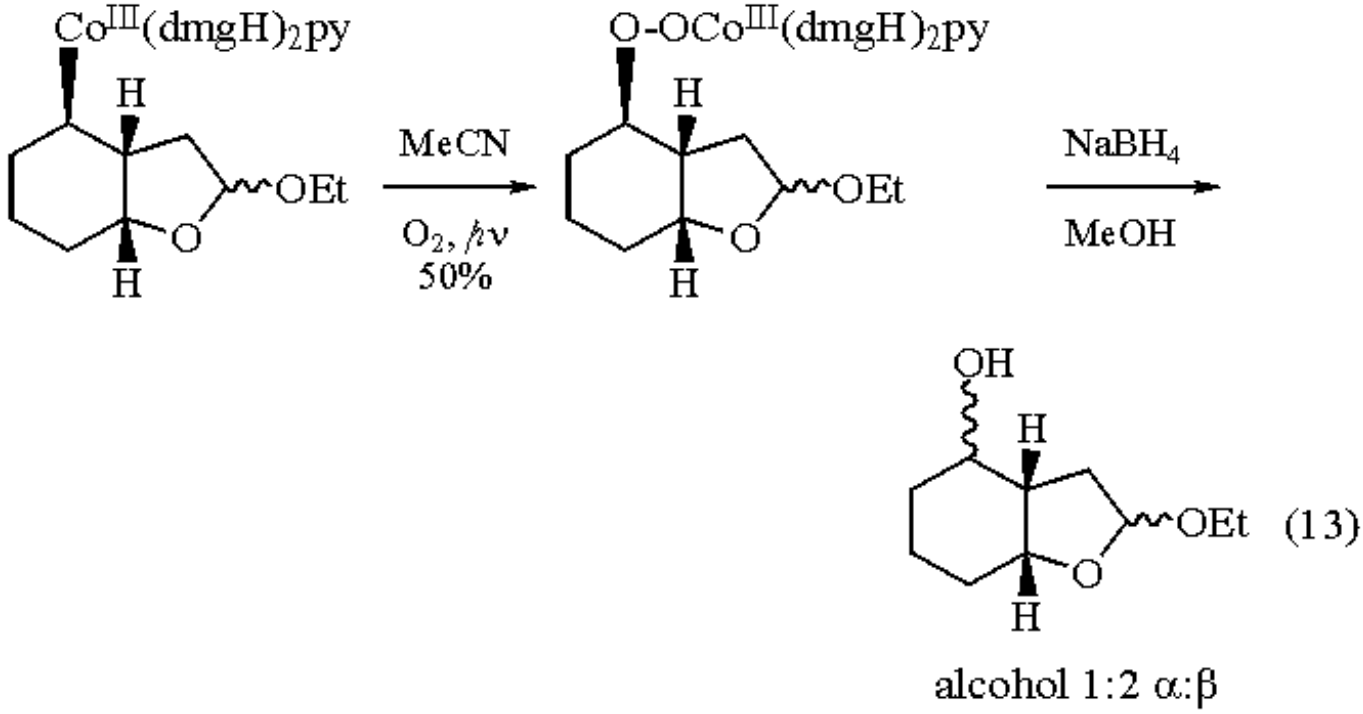

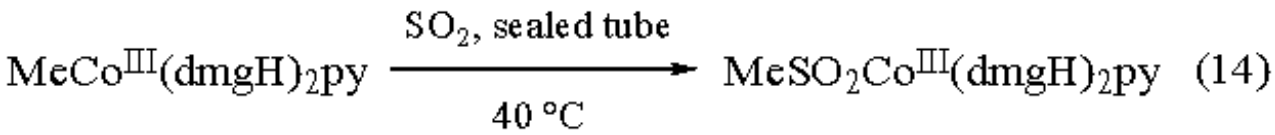

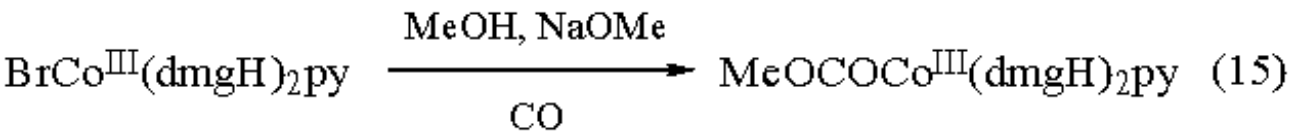

Homolytic cleavage of $RCo^{III}(dmgH)_2$ complexes in the presence of nitric oxide has been demonstrated. Thus mannosyl bromide yields the corresponding oxime via the mannosylcobaloxime (eq 16).[36] However, either alkyl oximes or nitrates and alcohols can be formed, depending upon the structure of the alkylcobaloximes.[37]

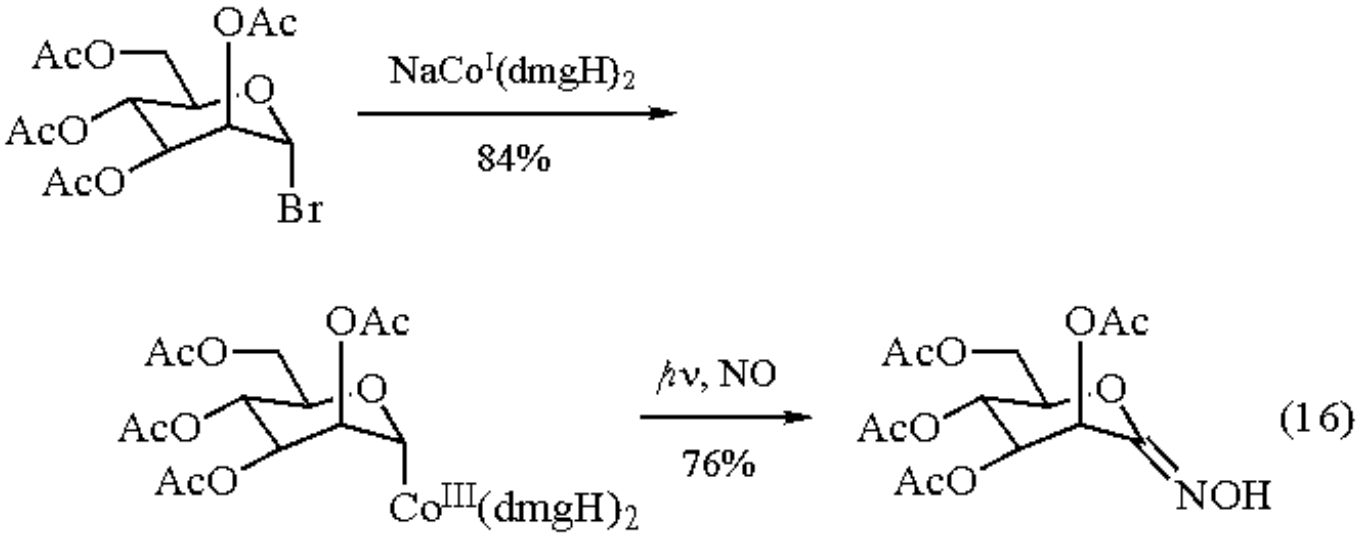

Photolysis of methyl(pyridine)cobaloxime(III) in the presence of alkyl methacrylates leads to selective formation of a dimer.[38] The primary step of this reaction is the formation of the methyl radical, which has been quenched with spin traps such as nitrosodurene or phenyl *t*-butyl nitrone.[39] Methyl radicals add to the β-position of alkyl methacrylates. The persistent cobaloxime(II) radical which is

present in solution traps the adduct radical and regenerates the unsaturation in the product via hydridocobaloxime formation. Hydridocobaloxime is the original catalyst for the dimerization of alkyl methacrylates, adding to the electron deficient acrylate and then formally inserting a second molecule of methacrylate via a radical-generation-alkene-trap-cobaloxime(II)-quench pathway. Subsequent hydridocobaloxime elimination regenerates the catalyst and expels the dimer (eq 17). General radical reactions are discussed in the following sections.

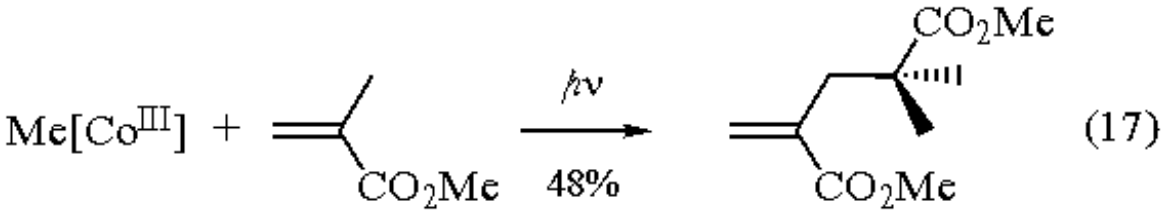

Radical Substitution Reactions.

Reactions between allylCo^{III}(dmgH)$_2$ complexes and organic radicals generally proceed via a S_H2' mechanism. Reactions between nitrogen, sulfur, and carbon centered radicals and allylCo^{III}(dmgH)$_2$ complexes lead to a range of 3-substituted propenes (eq 18).[40] Reaction of organic radicals with the terminal unsaturated carbon in but-3-enylCo^{III}(dmgH)$_2$ complexes gives rise to functionalized cyclopropanes via an intramolecular homolytic displacement (eq 19).[40] Alkyl-, allyl-, and benzylCo^{III}(dmgH)$_2$ complexes have been photolyzed in the presence of sulfur and selenium radical traps to provide the corresponding functionalized products in good yield (eq 20).[41]

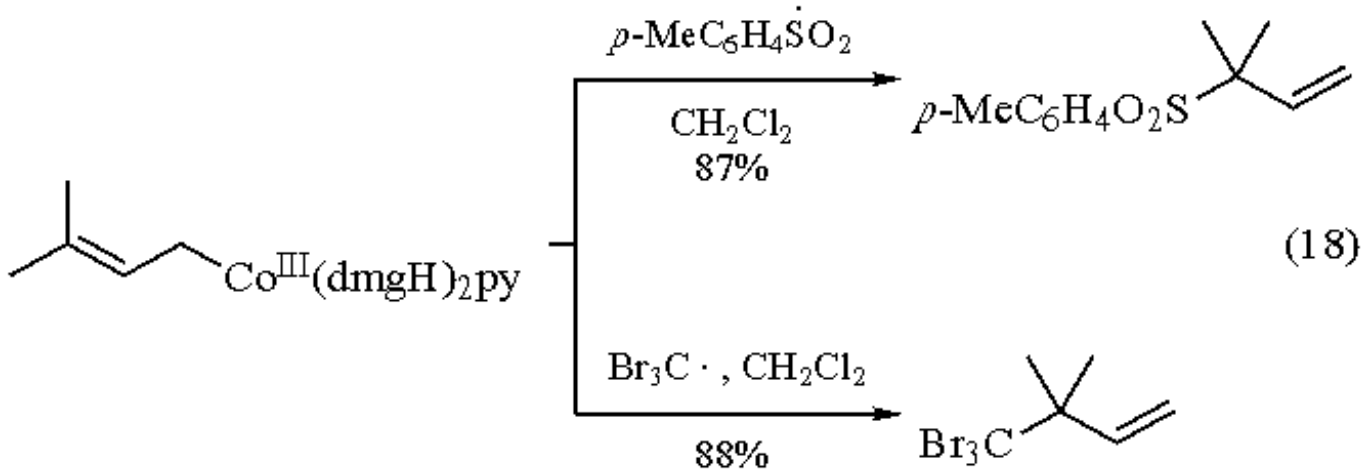

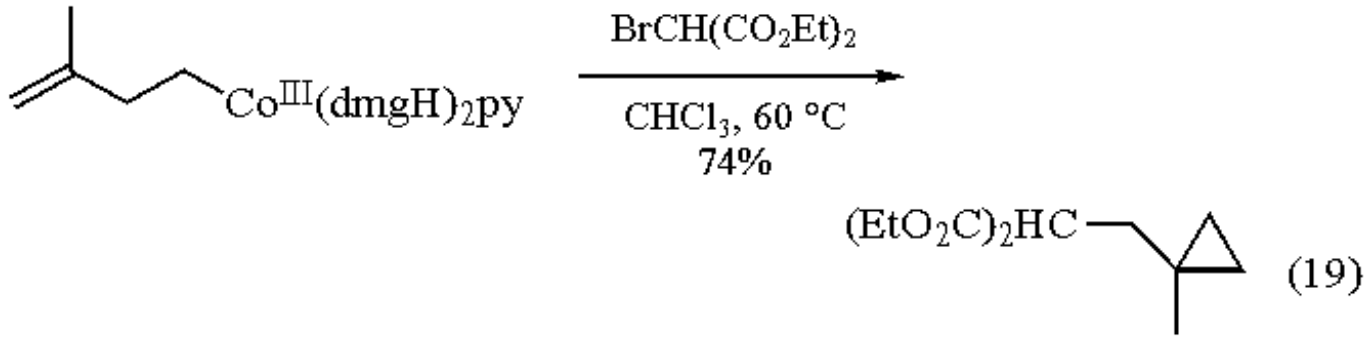

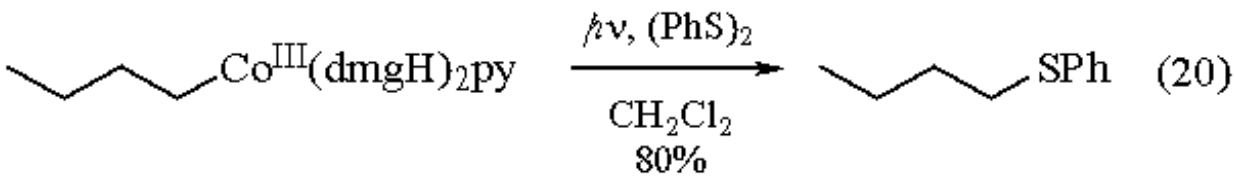

Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)

The allylic $Co^{III}(dmgH)_2$ complex prepared from hydrocobaltation of myrcene undergoes trapping by TEMPO (***2,2,6,6-Tetramethylpiperidin-1-oxyl***) upon irradiation in toluene. The resulting hydroxylamine can then be reduced to both nerol and geraniol (eq 21).[24] This conversion of a 1,3-diene to an allylic alcohol via the hydrocobaltation-oxidation sequence compares favorably with the related method of Suzuki utilizing ***Palladium(II) Chloride***.

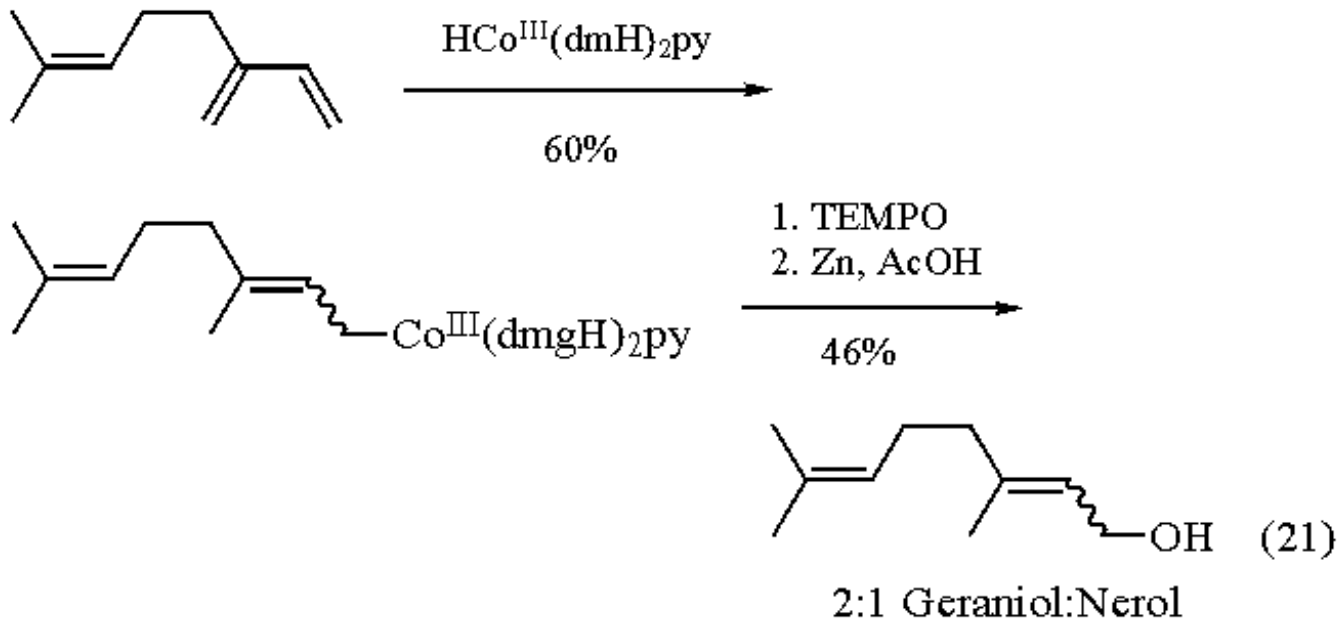

Radical Cyclization Reactions.

The ease of homolysis of the Co^{III}-carbon bond can be used to good effect in generating carbon centered radicals which can undergo inter- or intramolecular oxidative addition processes. Various 2-allyloxyethyl halides and tosylates react with $Co^{I}(dmgH)_2$ to give the corresponding tetrahydro-3-furanylmethylcobaloximes, which upon irradiation in benzene lead to products arising from β-elimination (eq 22).[42] $Co^{I}(dmgH)_2$ generated electrochemically catalyzes the cyclization of bromoacetal alkenes to give ring-fused tetrahydrofurans (eq 23).[43] In this case, as well as in other catalytic processes, the cyclizations are terminated reductively. An oxidative process has been developed to produce unsaturated β-oxy-γ-butyrolactones via a $Co^{I}(dmgH)_2$ mediated cyclization of the corresponding vinyl ether bromoacetal (eq 24),[44] and used in an approach to kainic acid (eq 25).[45] Tandem radical cyclizations mediated by $Co^{I}(dmgH)_2$ are also possible, with the option that the process can be intercepted after the first cyclization if desired (eq 26).[46]

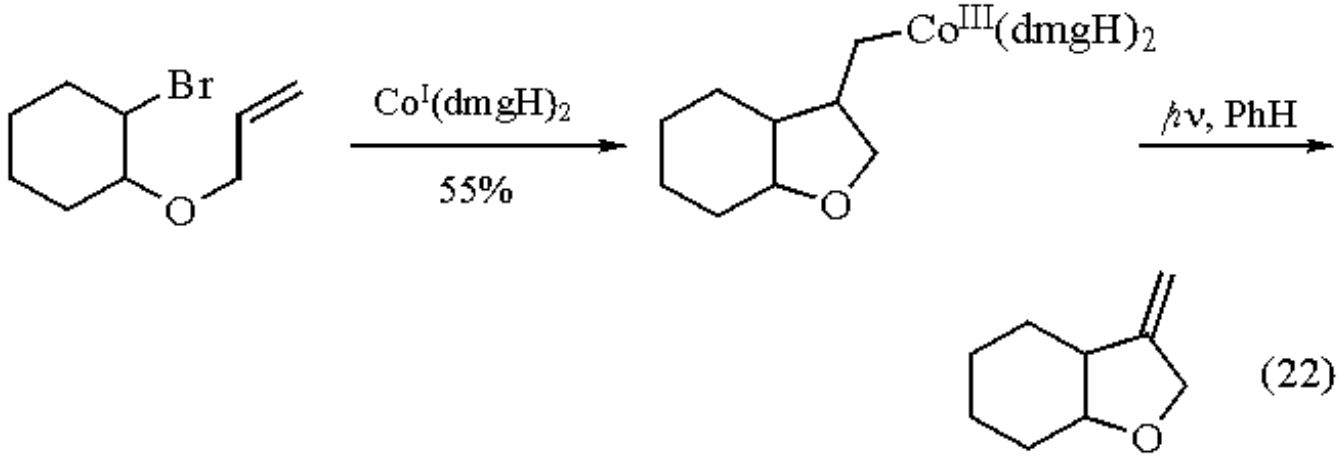

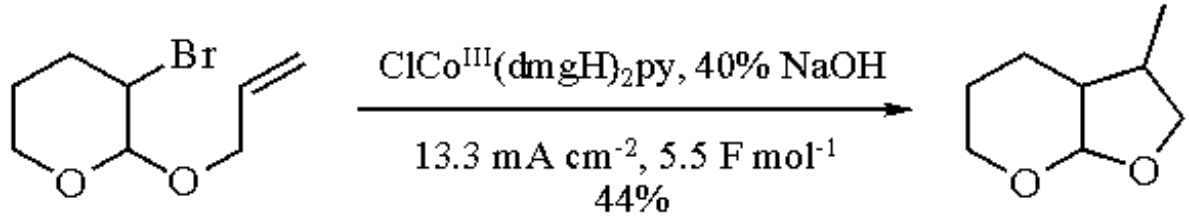

(23)

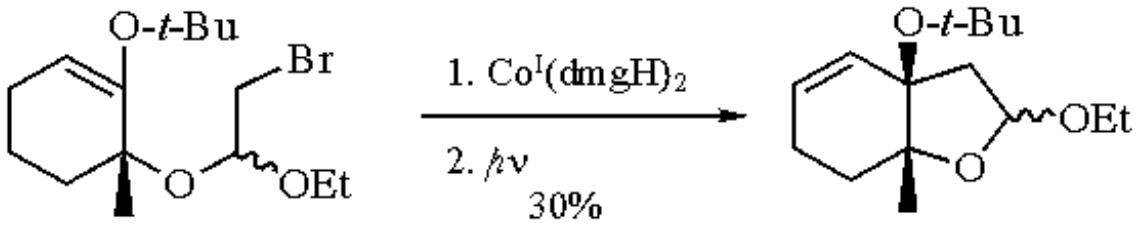

(24)

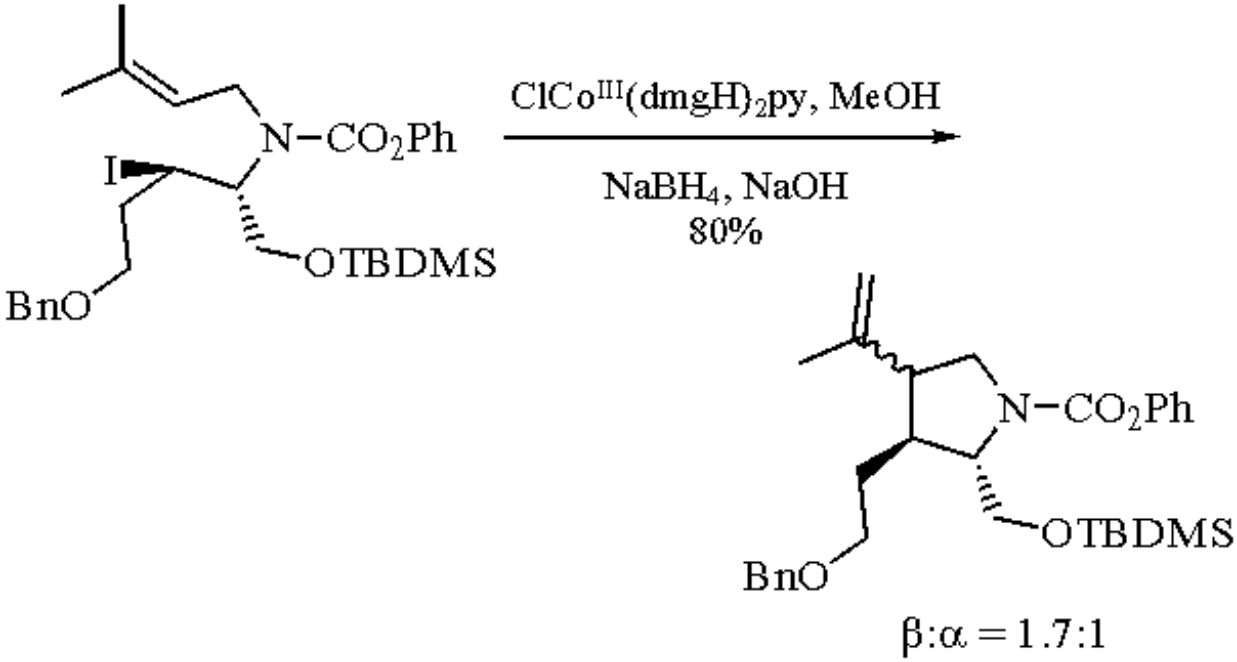

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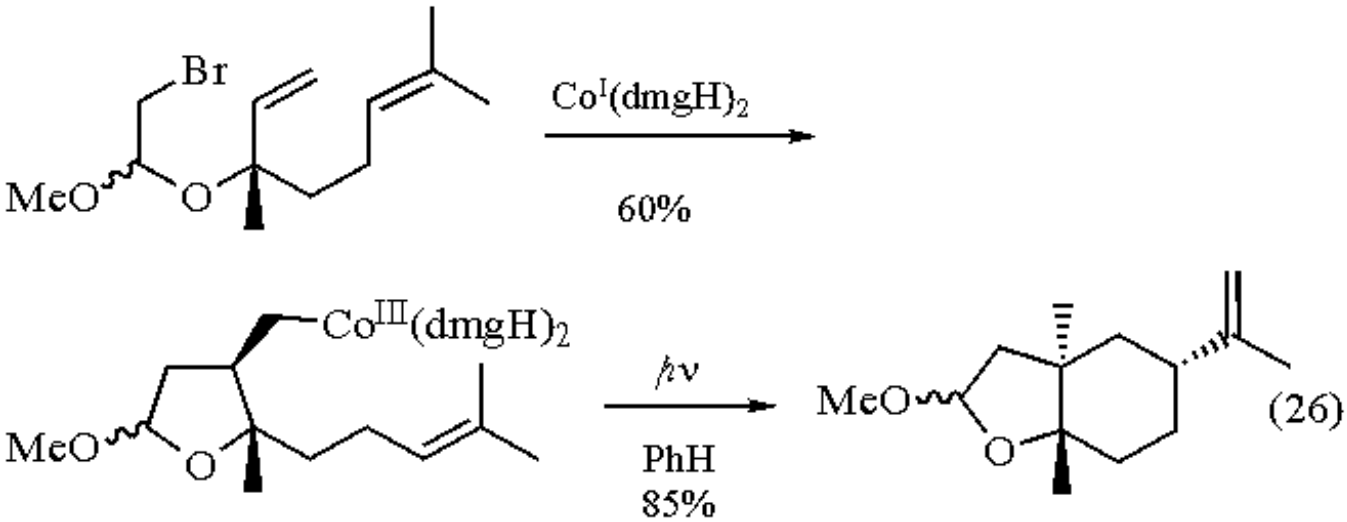

(26)

Radical cyclizations have also been initiated via the addition of $Co^{I}(dmgH)_2$ to oxiranes. In this case, irradiation of the intermediate β-hydroxycobaloximes with a sunlamp leads to efficient 6-*exo*-trig cyclizations followed by elimination of $HCo^{III}(dmgH)_2$ (eq 27).[47]

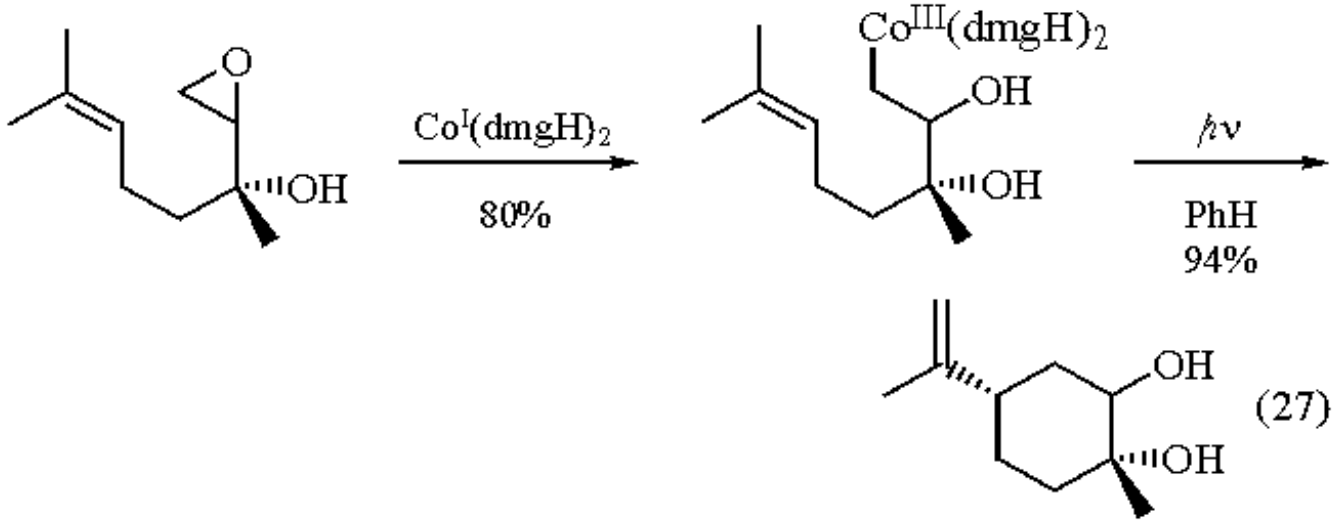

(27)

Intermolecular Radical Addition Reactions.

Alkyl radicals produced from the homolysis of alkyl$Co^{III}(dmgH)_2$ complexes can be trapped in an intermolecular fashion by activated alkenes (eq 28).[48] In these cases the unsaturated products are produced via the β-elimination of cobalt and hydrogen (dehydrocobaltation) from the intermediate cobaloxime. The sp^2-sp^2 coupling reaction between alkenes, involving a novel combination of hydrocobaltation-dehydrocobaltation reactions to and from alkenes, has been demonstrated.[49] This overall transformation is a useful alternative to the Heck reaction which cannot be employed in the case of alkyl halides. Irradiation of glycosylcobaloximes in the presence of various activated alkenes has been shown to give rise to either addition or substitution products depending upon the electronic nature of the substitutents on the alkene substrate (eq 29).[50] Nitroalkyl anions have also been employed in cross-coupling reactions giving rise to the corresponding nitro compounds in good yields (eq 30).[51]

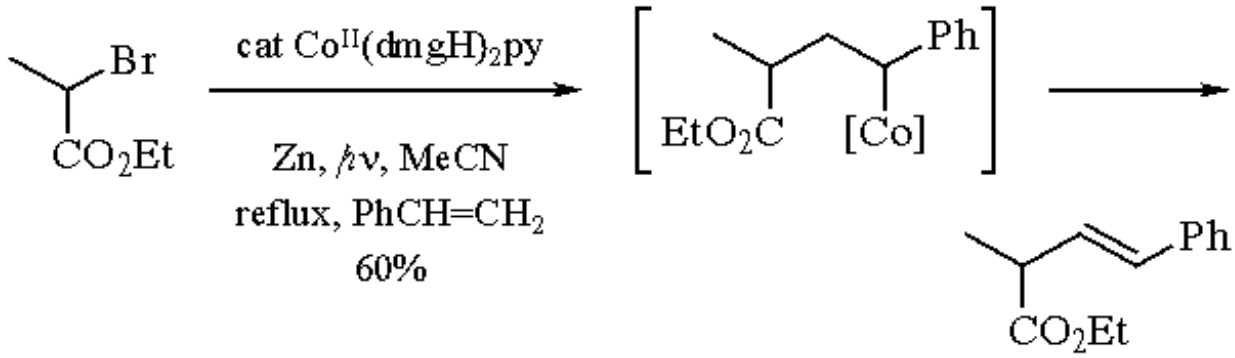

(28)

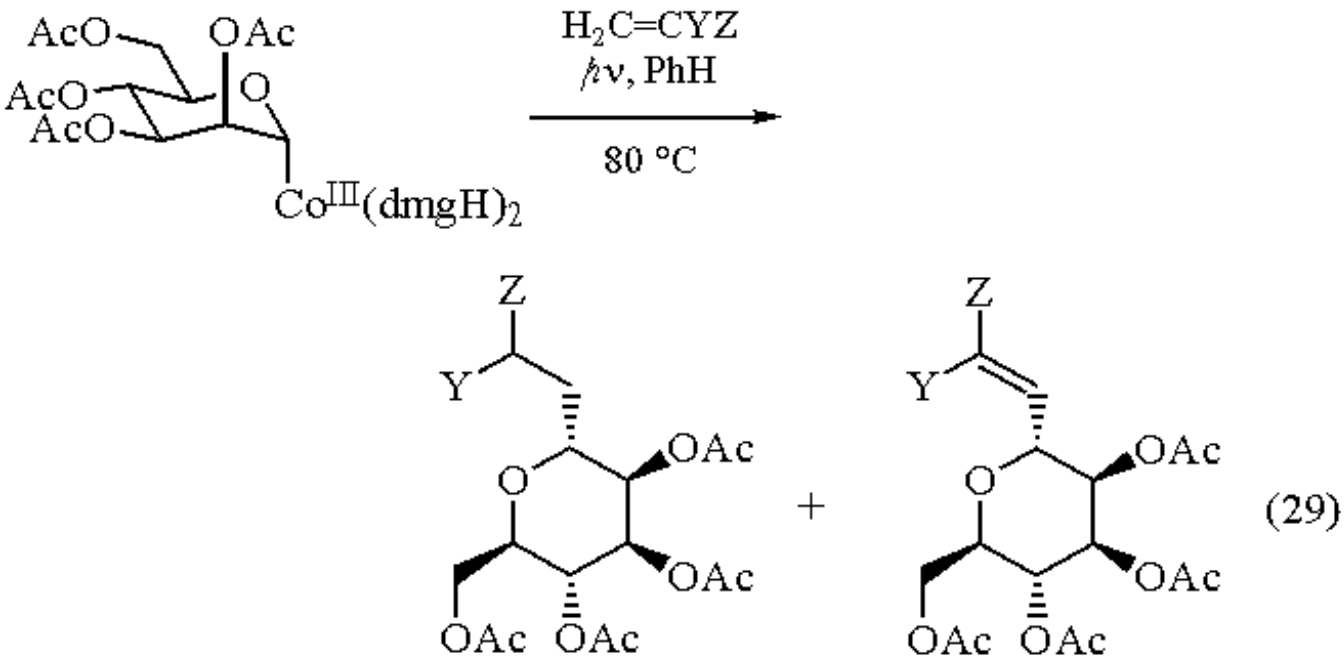

Y = H, Z = CN, 75%, 98:2
Y = OEt, Z = CN, 60%, 2:98

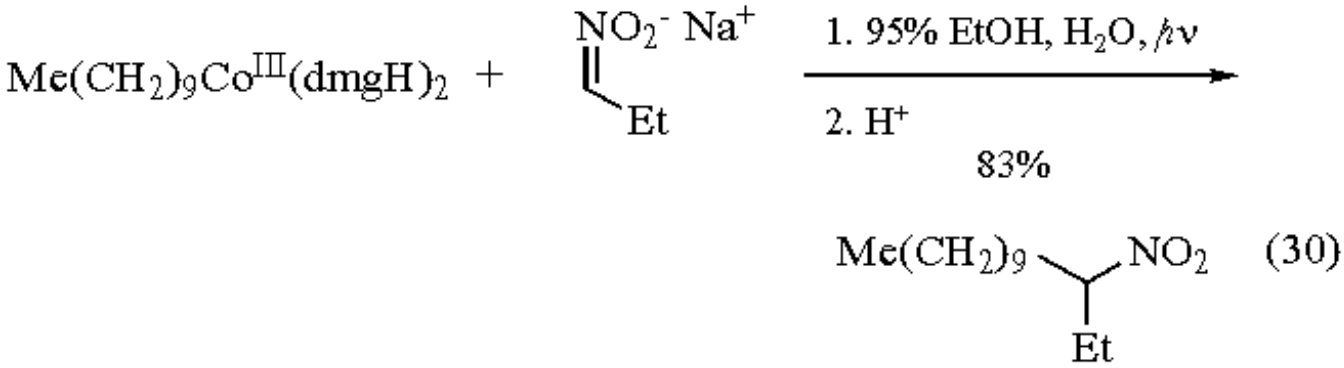

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University of Nottingham, UK

Bis(4,5-dimethyl-2-oxo-1,3,2-dioxaphospholenyl) Oxide[1]

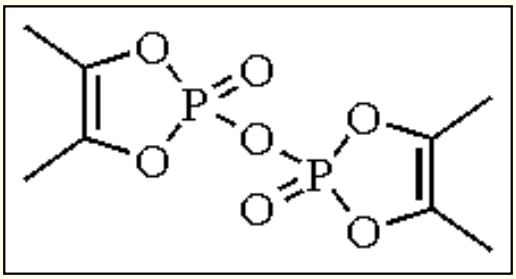

[55894-94-5] · $C_8H_{12}O_7P_2$ · Bis(4,5-dimethyl-2-oxo-1,3,2-dioxaphospholenyl) Oxide · (MW 282.13)

(phosphorylating agent; selective for primary alcohols over secondary alcohols, especially in the presence of triethylamine; used for the preparation of various unsymmetrical phosphodiesters; precursor of the more reactive phosphorylating agents 4,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphole and 4,5-dimethyl-2-(1´-imidazolyl)-2-oxo-1,3,2-dioxaphosphole)

Alternate Names: bis(1,2-dimethylethylene)pyrophosphate; acetoin enediol cyclopyrophosphate.

Physical Data: mp 84-86 °C.

Solubility: widely sol organic solvents.

Preparative Methods: prepared from 4,5-dimethyl-2-methoxy-2-oxo-1,3,2-dioxaphosphole (**1**) by treatment with pyridine in benzene to form the salt (**2**), followed by reaction with phosgene in benzene (eq 1). The solid (**3**) is recrystallized from CH_2Cl_2/hexanes.[2]

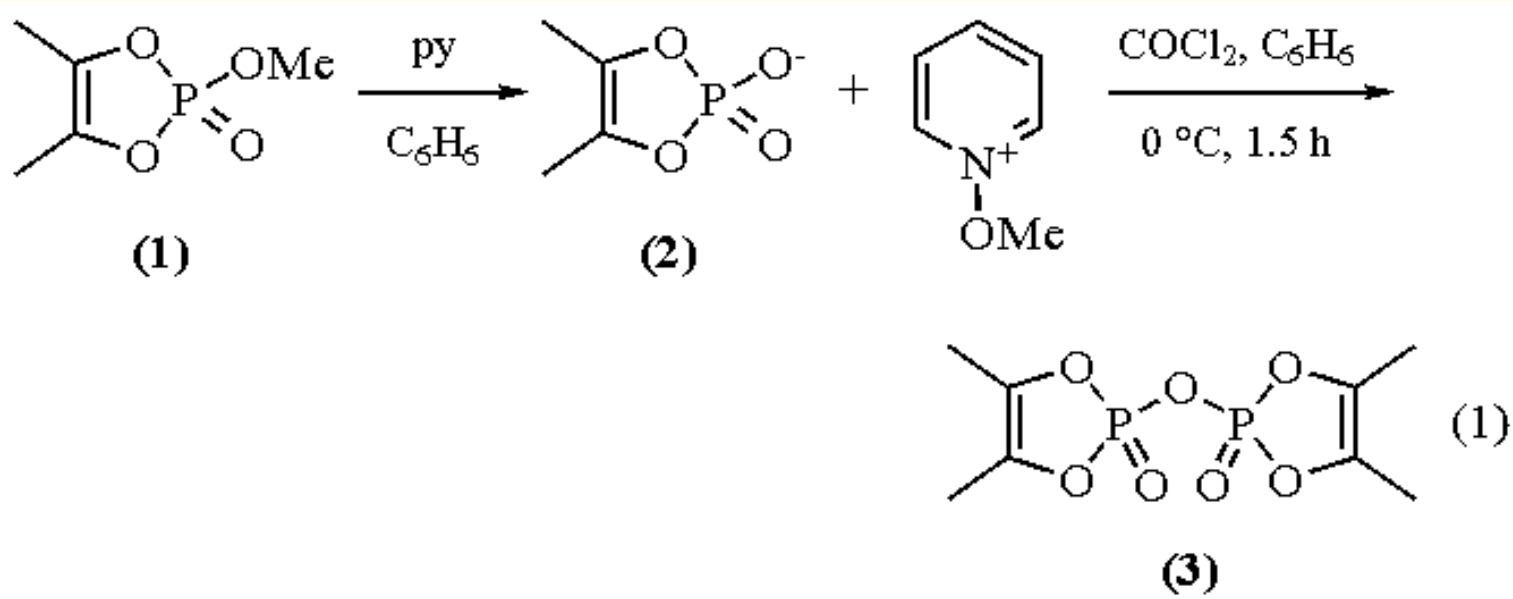

(1)

Handling, Storage, and Precautions: the reagent is hydrolyzed by water.

Phosphorylative Coupling of Two Different Alcohols.

The pyrophosphate (**3**) is used for the preparation of unsymmetrical phosphodiesters in a one-pot operation with no additional activation required. The primary alcohol of a diol can be phosphorylated selectively in the presence of an unprotected secondary alcohol.[3] This selectivity is catalyzed by ***Triethylamine***. Thus the reaction of the monoester (**4**) (derived from the reaction of (**3**) with cyclopentanol) with *trans*-2-hydroxymethylcyclopentanol produces the diesters (**6**) and (**7**) in a 98:2 ratio in the presence of triethylamine (eq 2). With no added base, this ratio is 90:10, while in the presence of imidazole the ratio drops to 80:20.[4] The preparation of unsymmetrical phosphodiesters works best if the first alcohol used is the more hindered of the two alcohols to be utilized. As expected, the triethylamine-induced rate enhancement of phosphorylation of a primary alcohol decreases with increasing steric requirements of the alkyl group in the phosphomonoester (**4**). The byproduct salts (**5**) can be reconverted into the pyrophosphate (**3**) by treatment with phosgene.[3]

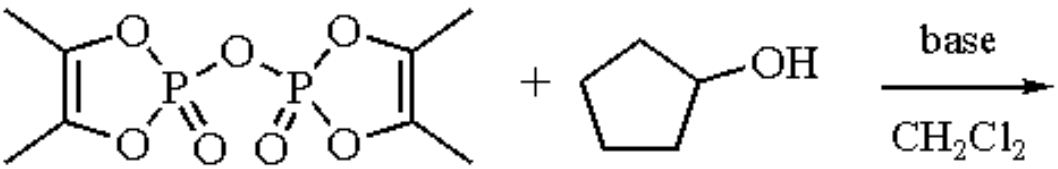

(3)

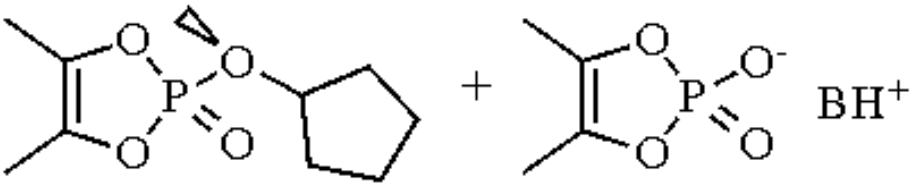

(4) **(5)**

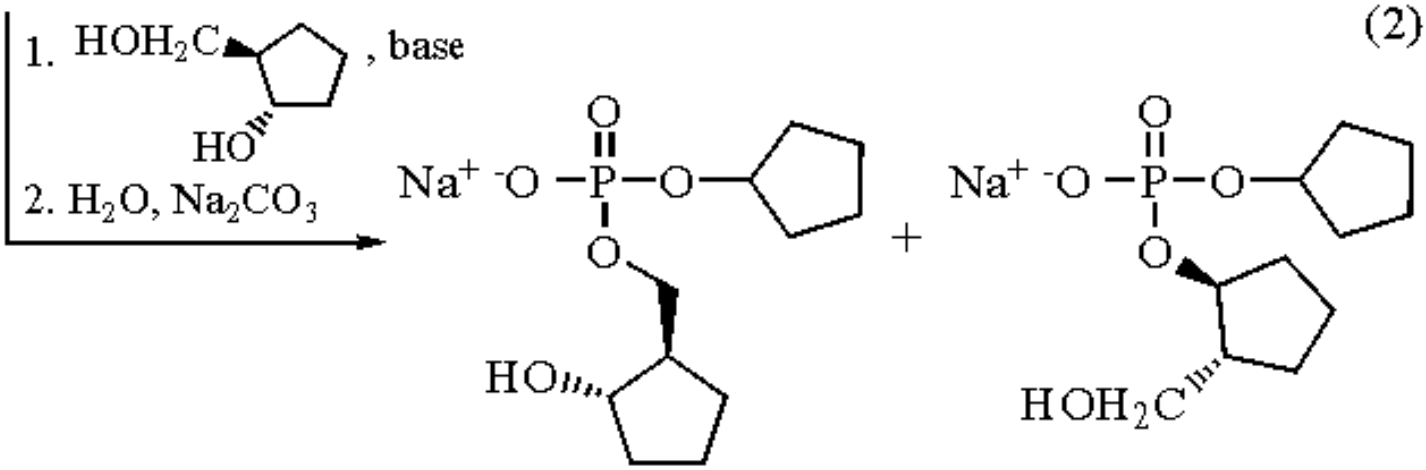

(2)

(6) **(7)**

Aminoethanol derivatives can be effectively phosphorylated and coupled with other alcohols (eq 3).[5] The two

phosphotriesters (**8**) and (**9**) were formed in a ratio of 5:1, and could be separated via chromatography.

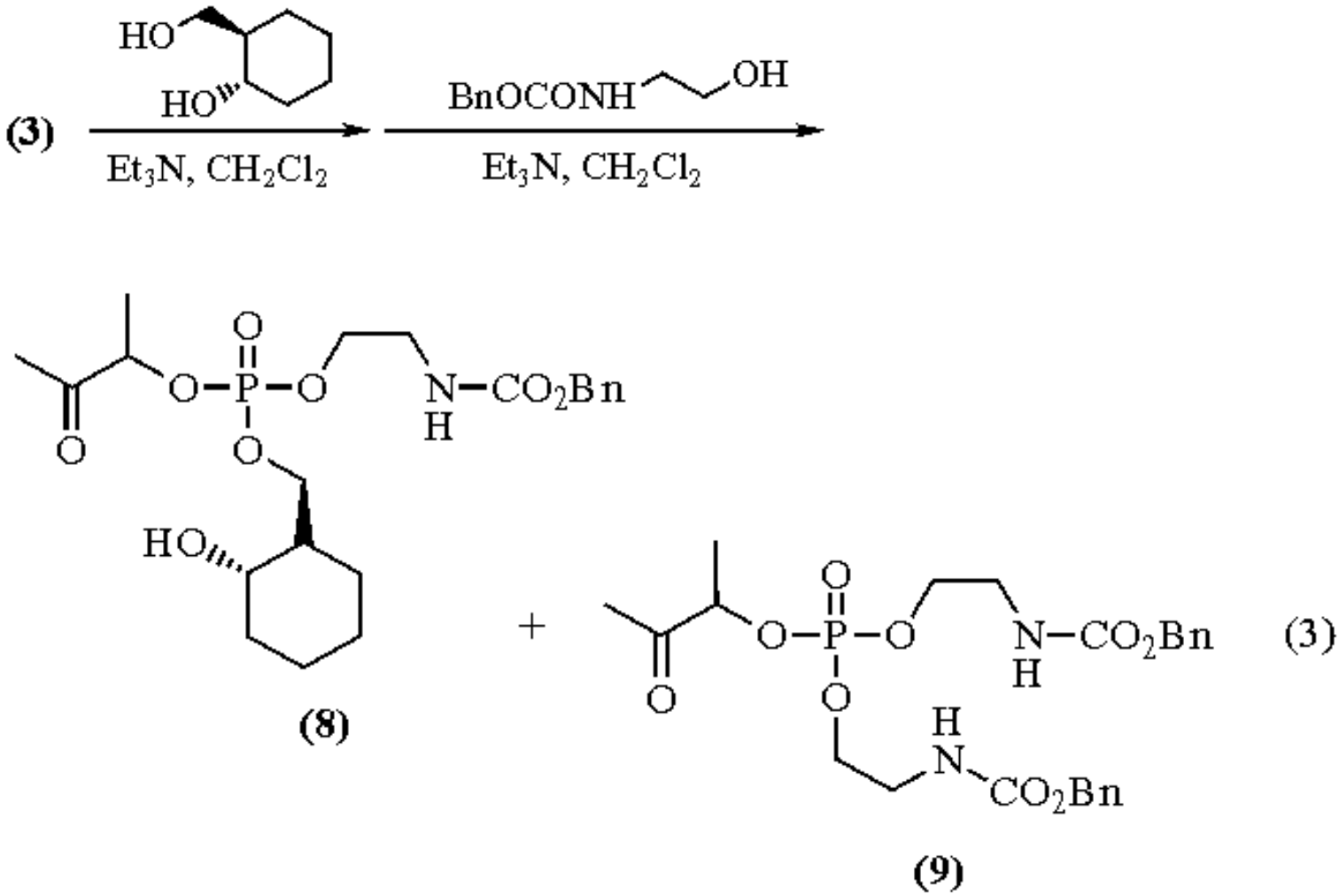

Phospholipid Derivatives.

Phosphatidyl-6-D-glucose analogs (**13**) can be prepared from the pyrophosphate (**3**) via initial reaction with diacylglycerol (**10**) to form the phosphomonoester (**11**). Subsequent treatment of (**11**) with a suitably protected glucose derivative (**12**) gave (**13**) in 30-50% overall yield (eq 4).[6] Better yields (55-60%) of the final product were obtained with the triprotected glucose (**12a**). Reaction of the initial adduct (**11**) with 0.5 equiv of 2-(*t*-butyldimethyl-siloxy)glycerol forms the basis of the synthesis of diphosphatidylglycerols (cardiolipins).[7]

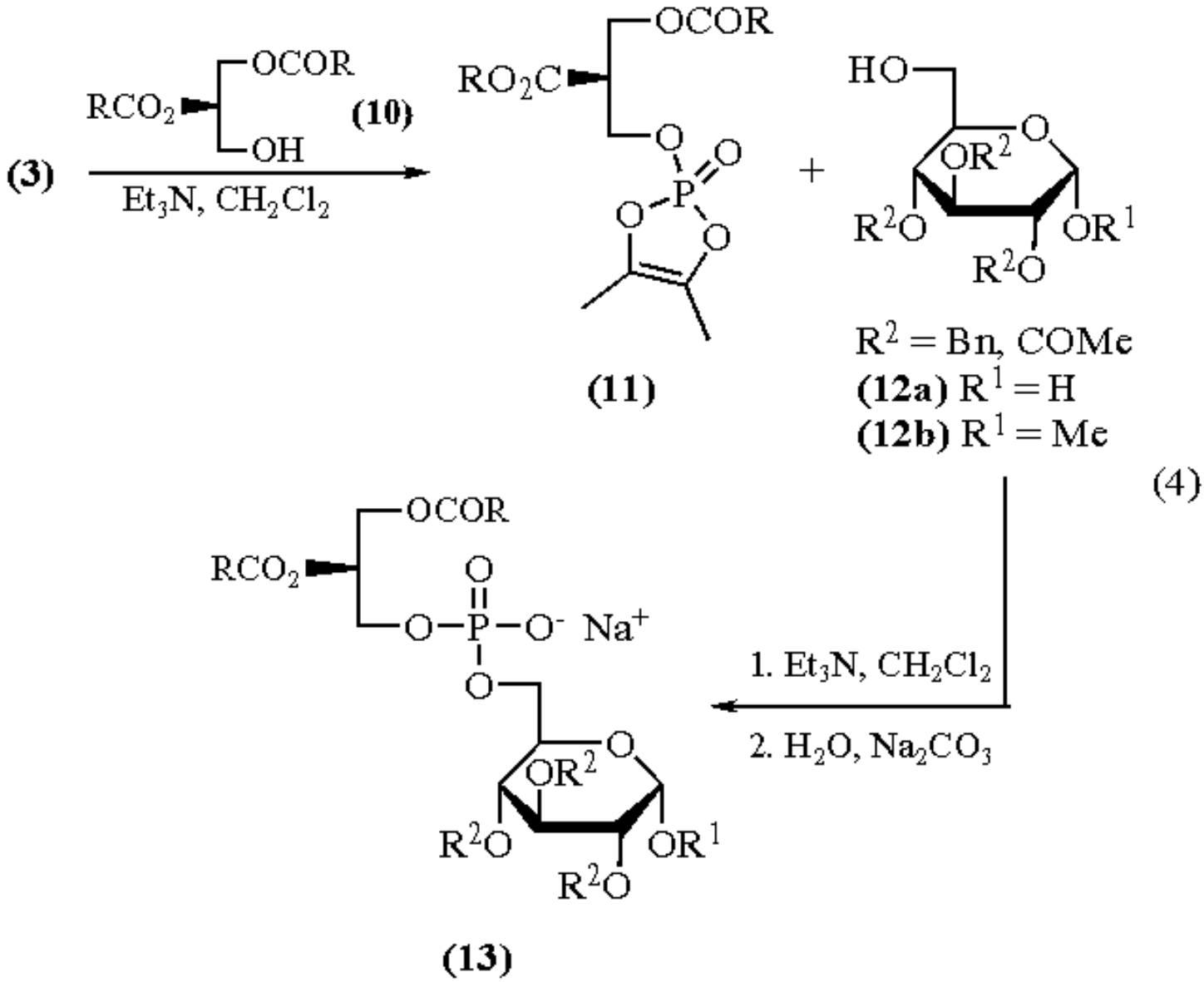

Nucleotides.

This phosphorylative method has been applied to the syntheses of di- and tetradeoxynucleotides,[8] as well as phospholiponucleotides (**14**) (eq 5).[9]

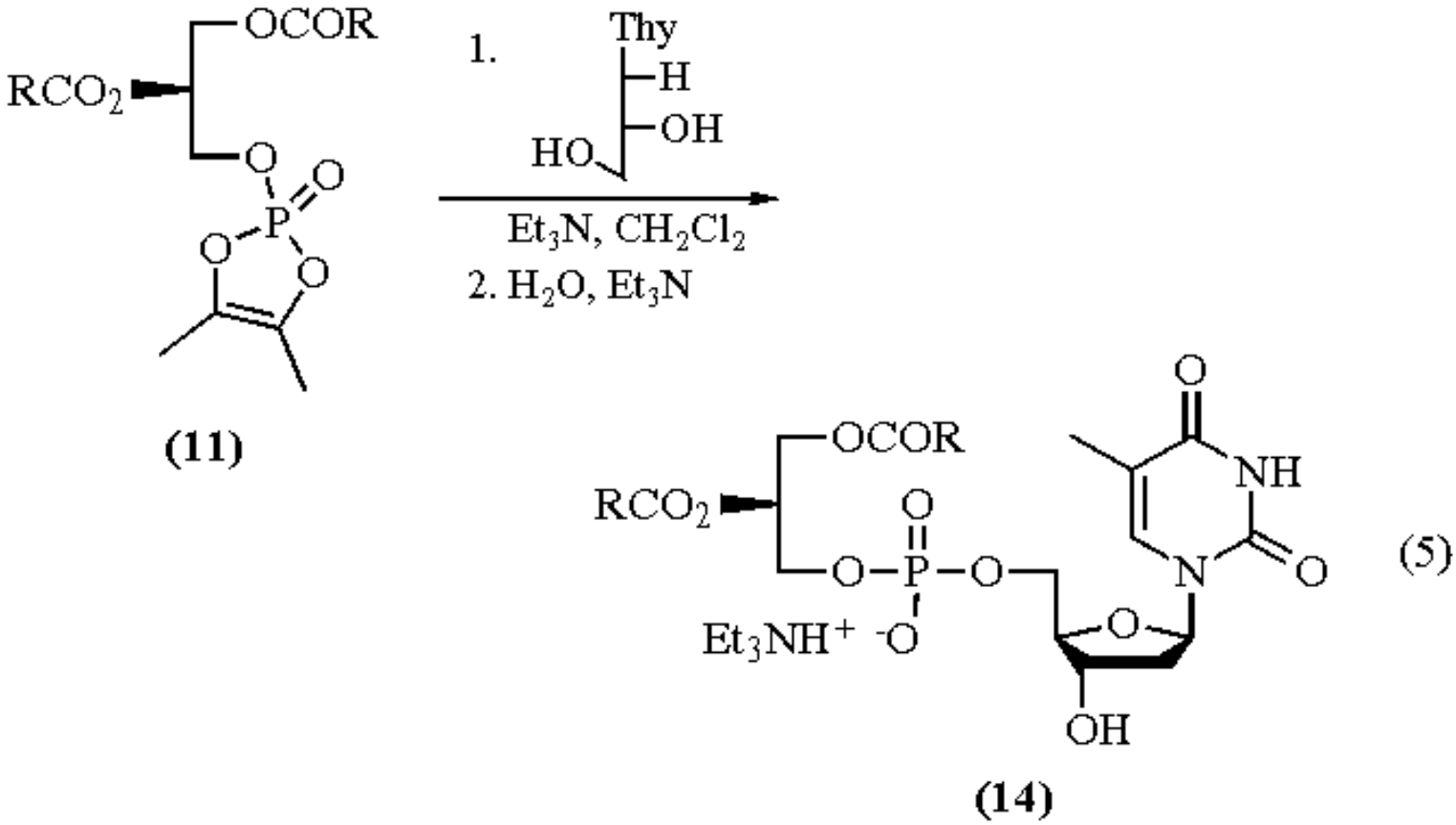

Preparation of Other Phosphorylating Agents Derived from (3).

Two more reactive (and less selective) phosphorylating agents can be easily derived from the pyrophosphate (**3**). The phosphochloridate (**15**) is formed from the reaction of (**3**) with phosgene (eq 6).[2] This highly reactive phosphorylating reagent reacts well with poorly nucleophilic or sensitive alcohols in high yields in the presence of triethylamine or pyridine.[10] The second derivative (**16**) is formed from the reaction of either the pyrophosphate (**3**) or the phosphorchloridate (**13**) with imidazole.[2] This reagent, while more reactive than (**3**), exhibits less selectivity than (**3**) in the reactions of primary vs. secondary alcohols. ***Imidazole*** has also been found to catalyze the reaction between alcohols (including secondary) and phosphomonoesters such as (**4**).[4]

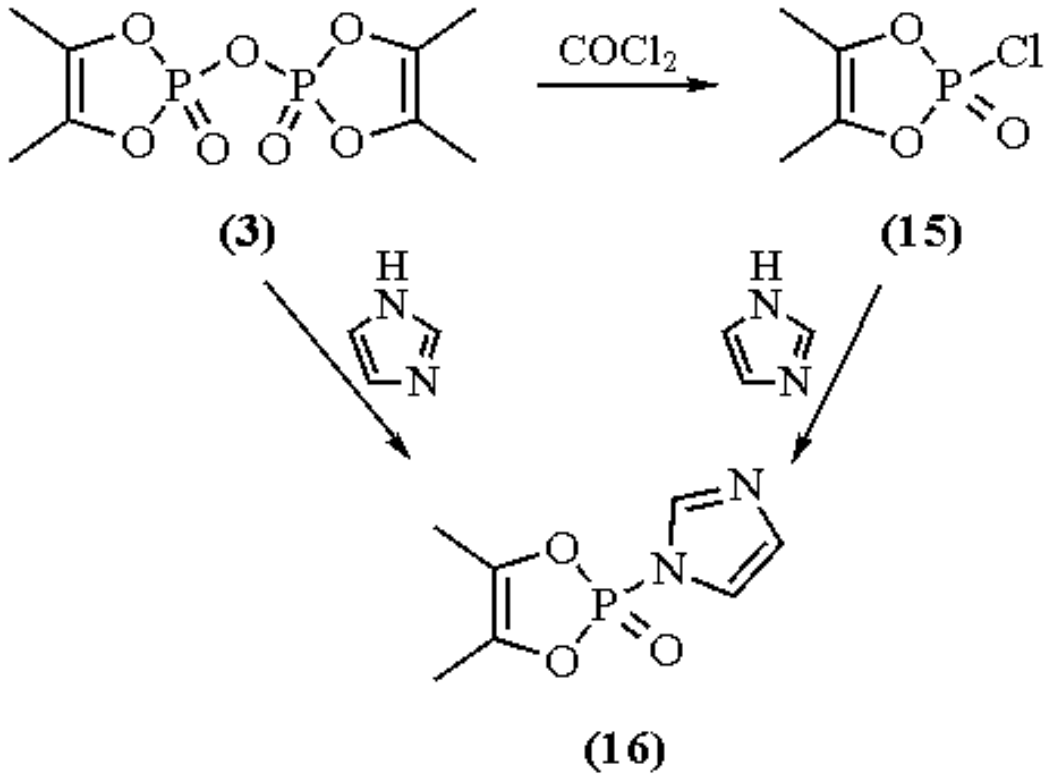

(6)

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10. Ramirez, F; Okazaki, H.; Marecek, J. F. *S* **1975**, 637.

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Bis(2,4-dinitrophenyl) Carbonate[1]

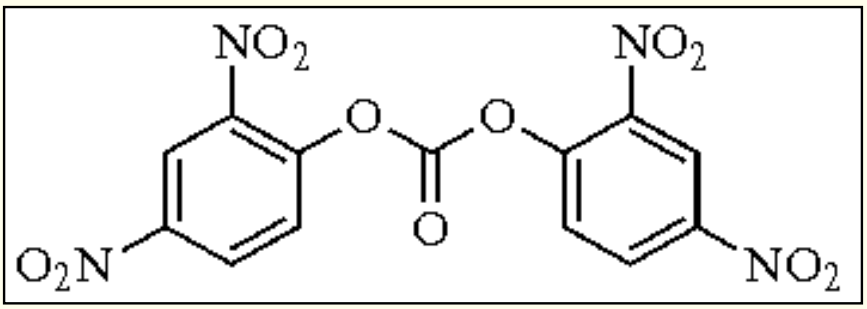

[7497-12-3] · $C_{13}H_6N_4O_{11}$ · Bis(2,4-dinitrophenyl) Carbonate · (MW 394.21)

(peptide and azapeptide coupling reagent that functions by activating amines, forming derivatives suitable for condensation with N-protected amino acids;[1-4] converts carboxylic acids to activated esters[2])

Alternate Names: carbonic acid bis(2,4-dinitrophenyl) ester; 2,4-dinitrophenyl 2,4-dinitrophenoxyformate.

Physical Data: yellow solid, mp 130-131 °C,[5] mp 148 °C;[2] hygroscopic; X-ray structure.[6]

Solubility: sol EtOAc, pyridine, DMF, $CHCl_3$; moderately sol benzene; insol hexane; dec hot H_2O, EtOH.

Preparative Method: diphenyl carbonate (20 g) is added to a stirred mixture of conc HNO_3 (100 mL) and conc H_2SO_4 (120 mL) at 50-55 °C over 1 h. The resulting suspension is stirred at 50 °C for 3 h, left at rt for 90 h and poured onto ice. The precipitate is washed with iced water and dried in vacuo over P_2O_5. This affords bis(2,4-dinitrophenyl) carbonate (31.2 g, 85%) which recrystallizes from hexane/benzene giving crystals, mp 144-146 °C.[3]

Handling, Storage, and Precautions: store in a cool dry place to preclude contact with moisture; the hazardous and toxicological properties have not been investigated; may explode if heated rapidly.

Peptide and Azapeptide Coupling.

The reagent is used to activate amino groups (eq 1) for subsequent coupling with N-protected amino acids and hydrazides, affording peptide (eq 2) and azapeptide (eq 3) derivatives, respectively.[1-4] Cbz-protected amino acids are coupled without racemization but *N*-acylated amino acids lose all optical activity.[2]

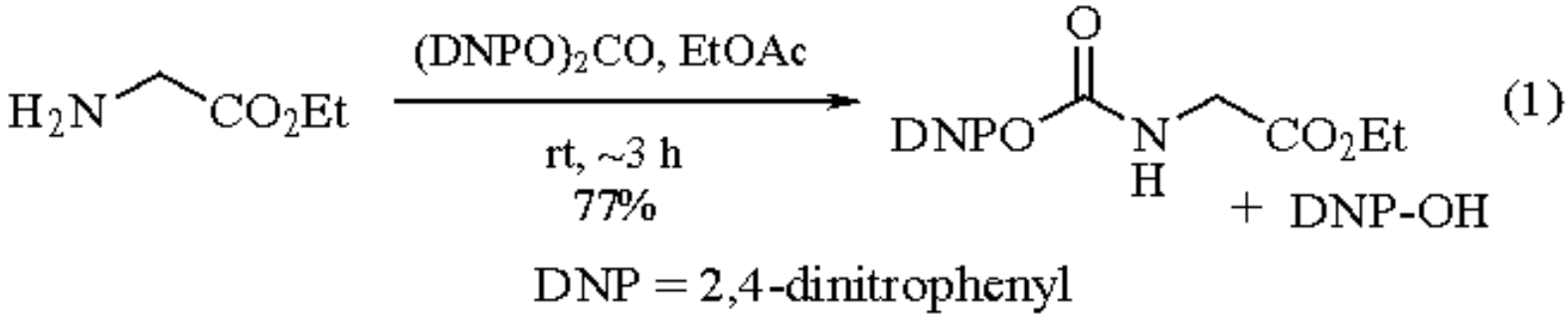

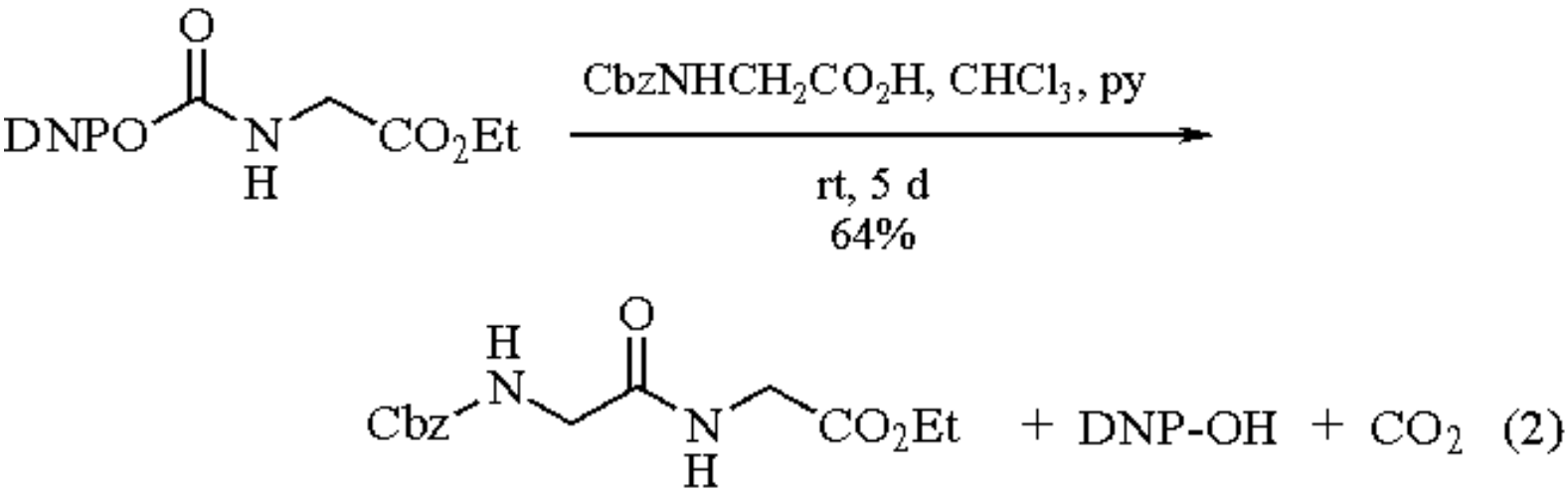

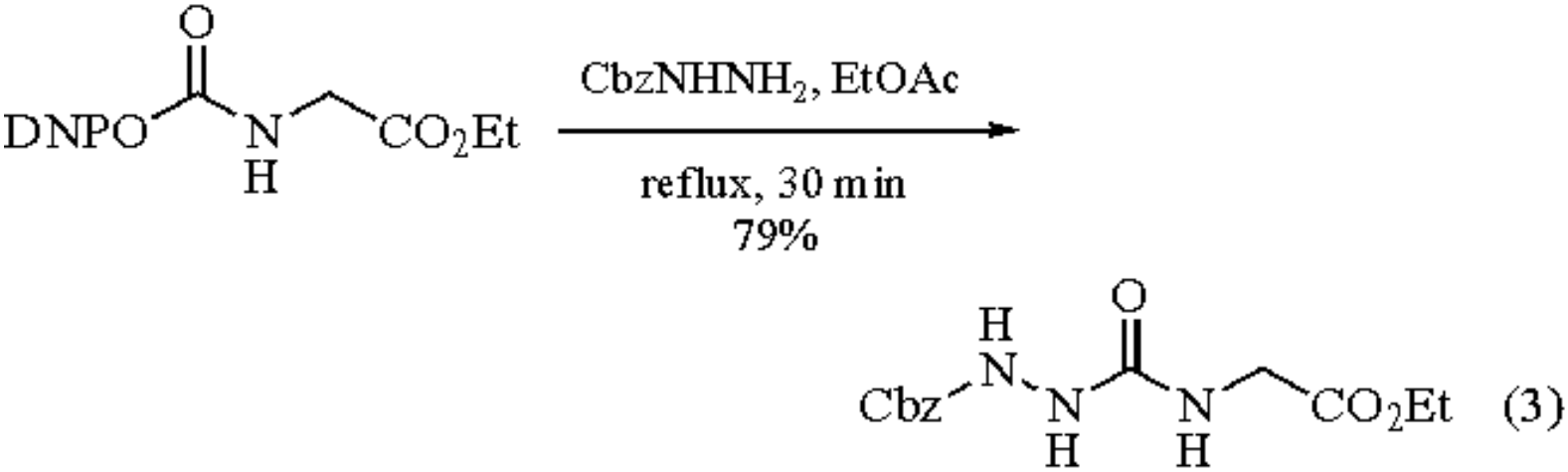

Attempts to prepare azapeptides by activating hydrazides have proved unsuccessful because of the propensity of the intermediate to undergo base-catalyzed cyclization and elimination to stable oxadiazolones (eq 4).[3]

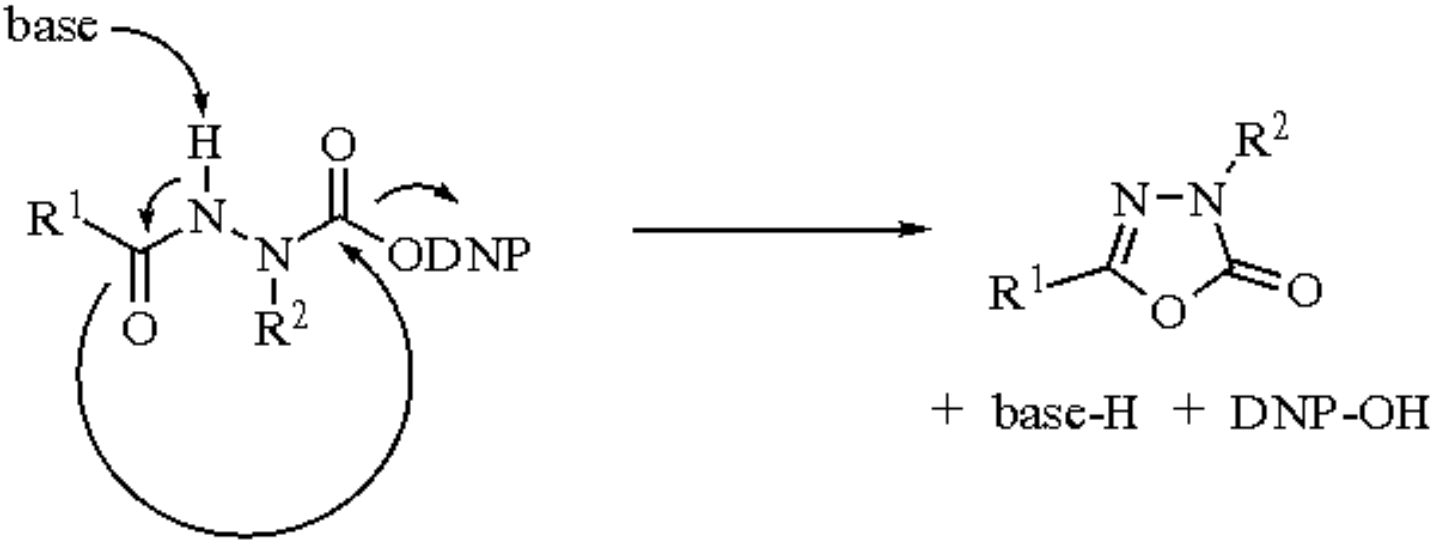

(4)

Activated Esters from Carboxylic Acids.

The reagent is attacked by carboxylate ions, forming unstable intermediates which spontaneously decarboxylate to dinitrophenyl esters (eq 5).[2] These activated esters are good acylating agents and undergo transesterification on reaction with alkoxide or aryloxide ions (eq 6).[2] The mild conditions under which these activated dinitrophenyl esters can be formed makes them preferable intermediates to the analogous 4-mononitrophenyl esters which are less active towards nucleophiles; also 2,4-dinitrophenol is more acidic than 4-nitrophenol and consequently may be easier to separate from the desired reaction product during workup.

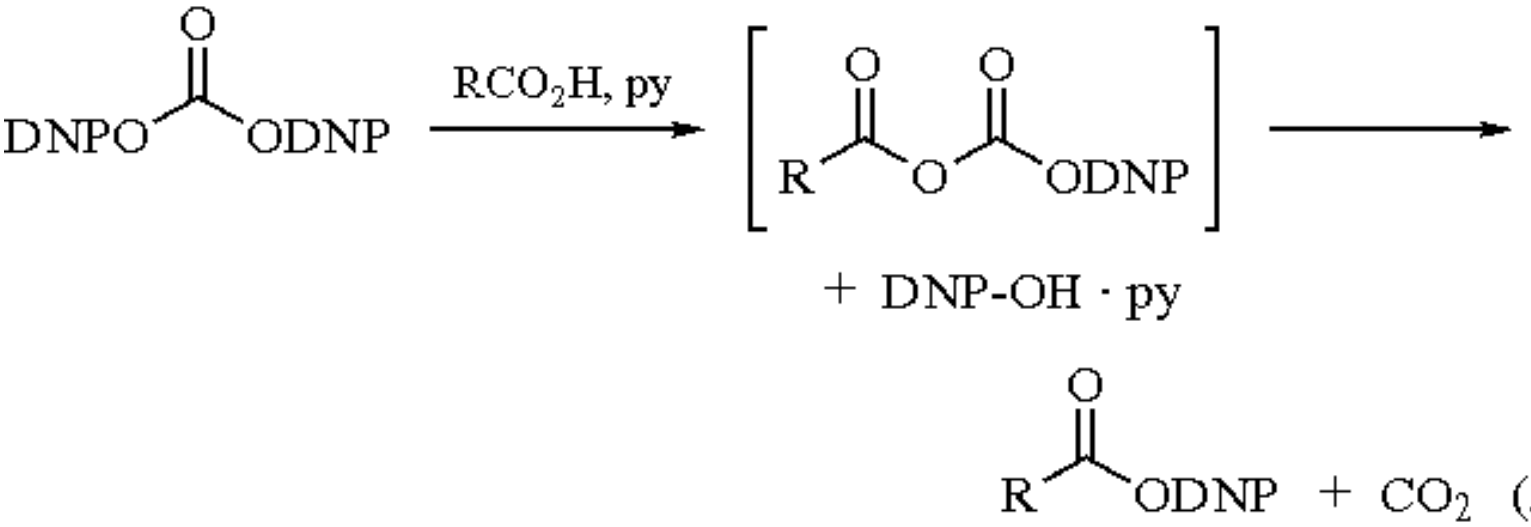

(5)

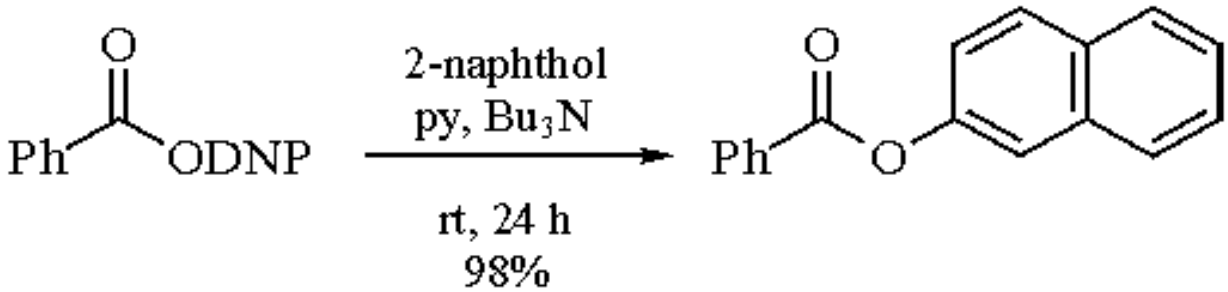

(6)

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1,4-Bis(diphenylhydrosilyl)benzene

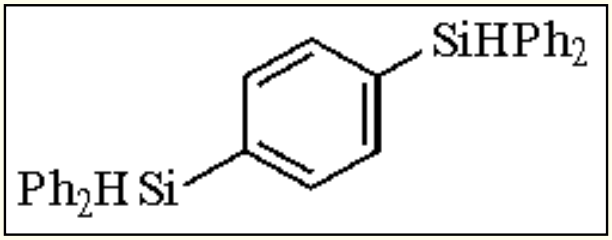

[3520-15-8] · $C_{30}H_{26}Si_2$ · 1,4-Bis(diphenylhydrosilyl)benzene · (MW 442.71)

(reducing reagent for esters under radical conditions)

Physical Data: mp 108 °C.

Solubility: sol benzene and THF.

Form Supplied in: white solid.

Preparative Methods: easily prepared by the Grignard reaction of ***Chlorodiphenylsilane*** with *p*-dibromobenzene (eq 1).

Handling, Storage, and Precautions: this reagent is stable in air. Because the toxicological properties are unknown, it should be handled in a well-ventilated hood.

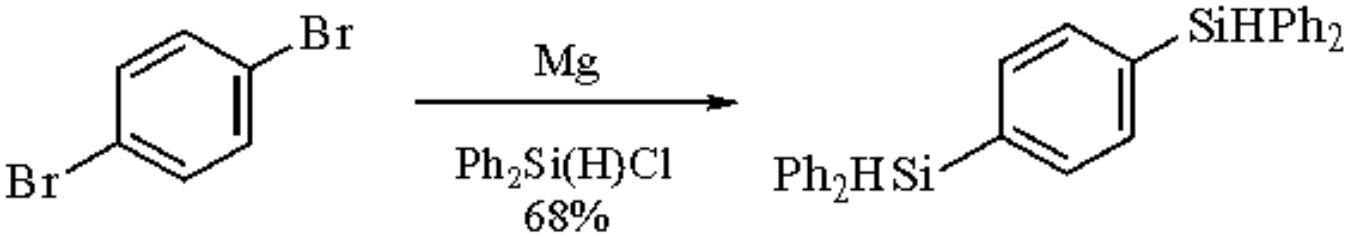

(1)

1,4-Bis(diphenylhydrosilyl)benzene is a useful deoxygenating reagent for esters under radical conditions. Thus the reagent reacts with acetates in the presence of the radical generator ***1,1-Di-t-butyl Peroxide*** (DTBP) at 140 °C to give the corresponding hydrocarbons (eq 2). Acetates derived from primary, secondary, and tertiary alcohols are reduced in high yield.[1] Use of this reagent is preferred compared to monosilanes like ***Triphenylsilane***,[2] since the silicon-containing byproducts are higher boiling and more polar. Consequently, alkane products are easily isolated from reductions with this reagent.

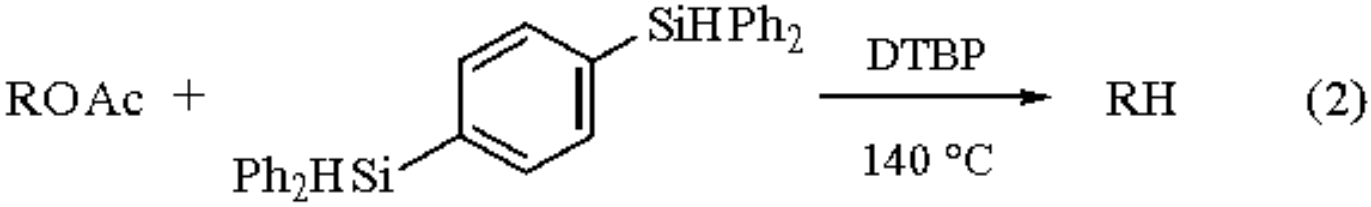

This reduction can be applied to deoxygenation of carbohydrates. Both *O*-acetylfuranoses and pyranoses are converted to the corresponding deoxy sugars (Table 1).[3] Acetylated derivatives of sugars which have an anomeric hydroxy group and *vic*-diols are also deoxygenated without any side reactions.[4]

Table 1

Acetylated sugar	Deoxy sugar	Yield (%)
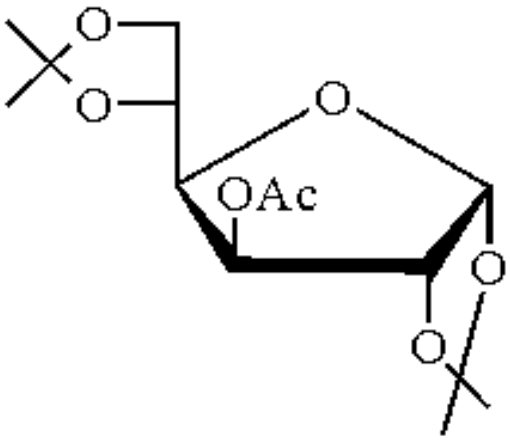	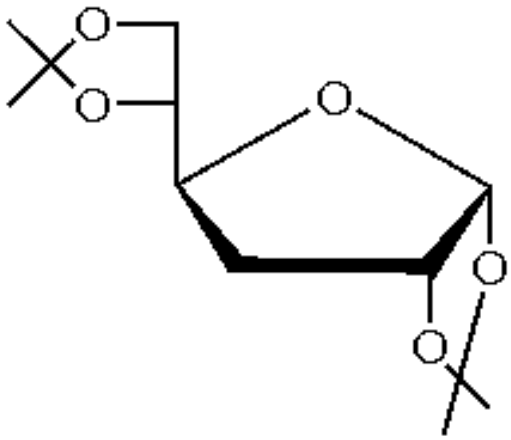	74
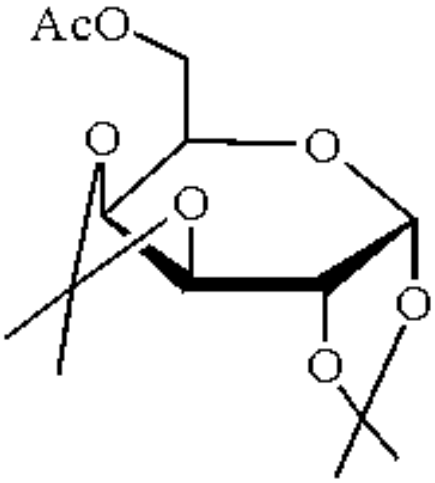	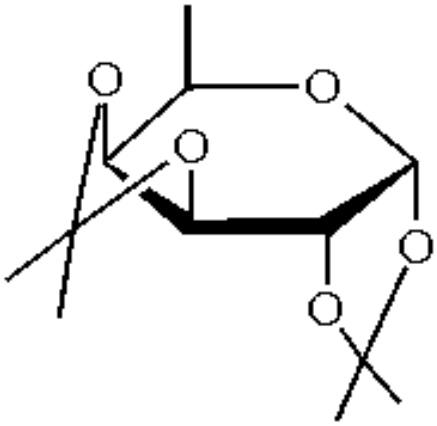	70
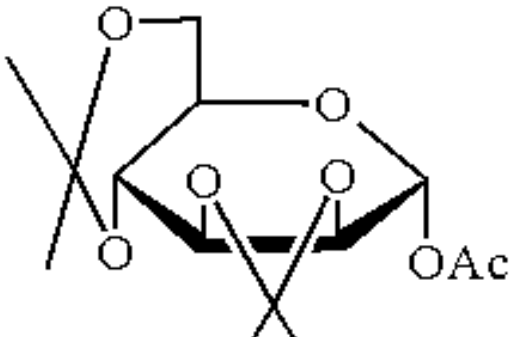	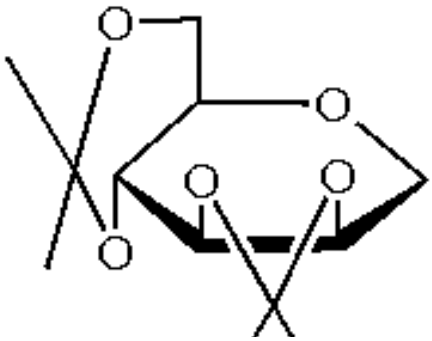	77

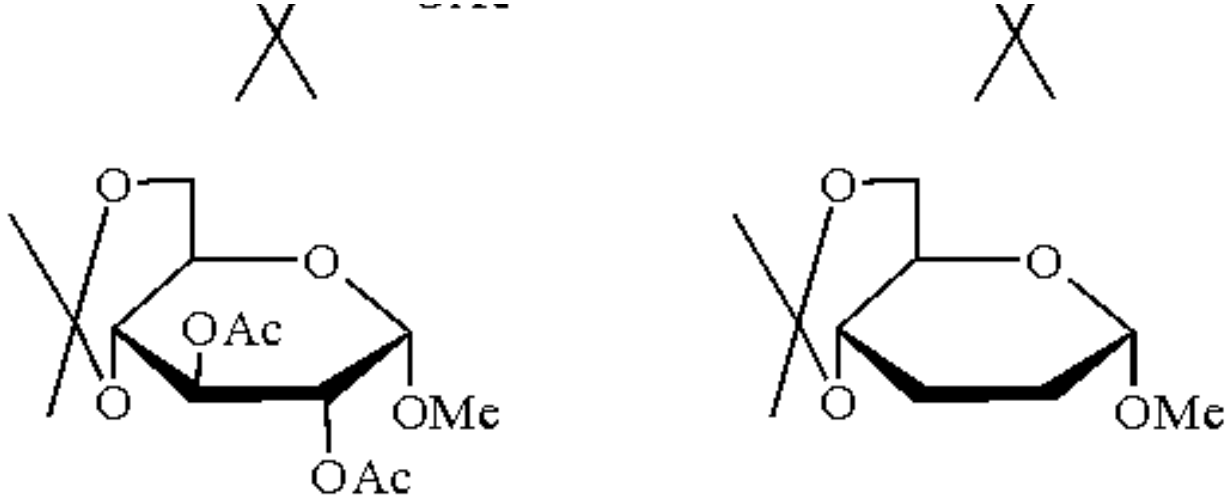

70

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2. (a) Sano, H.; Ogata, M.; Migita, T. *CL* **1986**, 77. (b) Sano, H.; Takeda, T.; Migita, T. *S* **1988**, 402.
3. Sano, H.; Takeda, T.; Migita, T. to be published.
4. (a) Photodeoxygenation of the anomeric acetate gives free anomeric hydroxy compound: Pete, J.-P.; Portella, C.; Monneret, C.; Florent, J.-C.; Khuong-Huu, Q. *S* **1977**, 774. (b) Deoxygenation of 1,2-diols via bis-xanthates using diphenylsilane gives alkenic compounds: Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *T* **1993**, *49*, 7193.

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Bis(1,3-diphenyl-2-imidazolidinylidene)[1]

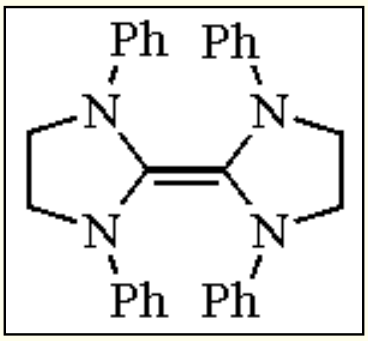

[2179-89-7] · $C_{30}H_{28}N_4$ · Bis(1,3-diphenyl-2-imidazolidinylidene) · (MW 444.58)

(electron-rich alkene; useful for formylation of arenes[1])

Physical Data: mp 285 °C (dec).

Form Supplied in: prepared from 1,2-dianilinoethane and triethyl orthoformate.[2]

Handling, Storage, and Precautions: easily autoxidized; reagent that has oxidized may be upgraded by washing with CH_2Cl_2;[2] store under dry nitrogen; reagent readily reacts with protic solvents, e.g. MeOH,[1] and hydrolyzes in the presence of weak acid[3] or basic[1] media.

Arene Formylation.

Phenols treated with bis(1,3-diphenyl-2-imidazolidinylidene) in refluxing DMF give *para*-substituted cyclic aminals, which upon acid-catalyzed hydrolysis yield the corresponding aldehyde (eq 1).[4,5] Multiple substitution can take place when an additional hydroxy or an acetamido moiety is present (eq 2).[6] The reaction tolerates additional substituents on the phenolic ring, including alkyl, cycloalkyl, dialkylamino, chloro, acetamido, 2*H*-1,2,3-triazolyl, phenyl, and alkoxy groups;[4-6] 8-hydroxyquinoline-7-carbaldehyde was prepared in 52% yield.[6]

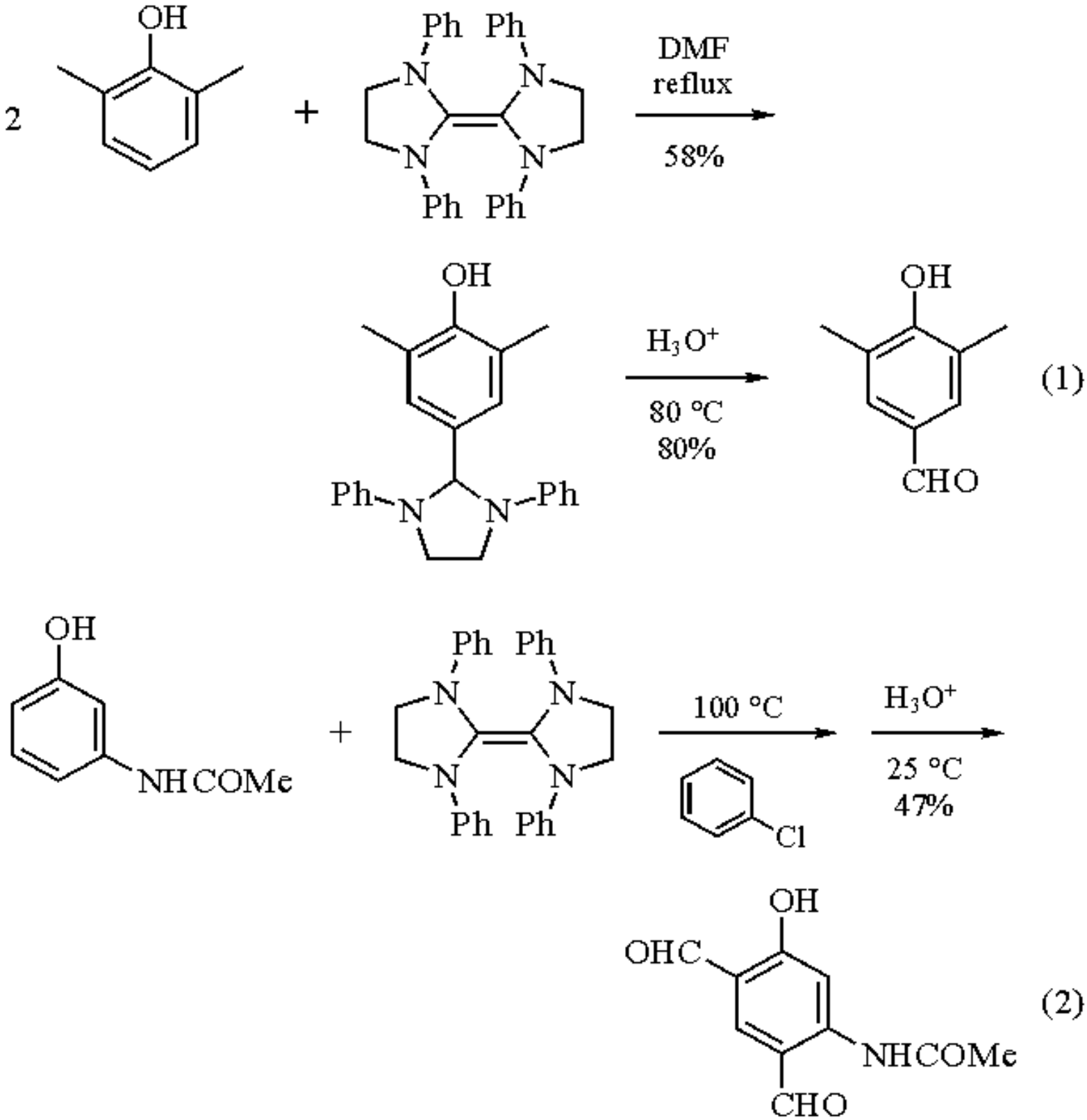

α-Substituted Aldehydes.

Addition of CH acidic compounds (e.g. $PhCH_2CO_2Et$ or cyclopentanone) to bis(1,3-diphenyl-2-imidazolidinylidene) gives the α-substituted aminals, which upon hydrolysis provide entry into α-substituted aldehydes (eq 3).[1,7]

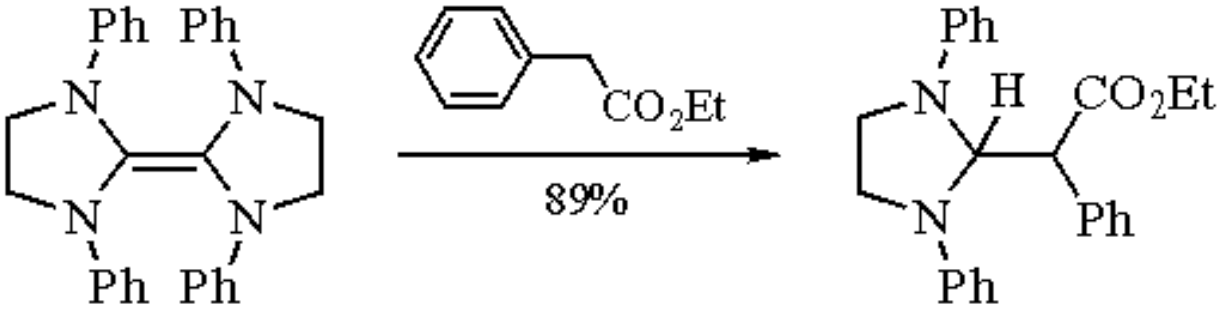

(3)

Aminoamidines.

Treatment of a primary amine with bis(1,3-diphenyl-2-imidazolidinylidene) gives the aminoamidine,[8] while dialkylamines and carboxamides react to give the 2-aminoimidazolidine[8] or *N*-(2-imidazolidinyl)carboxamides,[9] respectively (eq 4). Sulfonyl amides or phosphoric amides react to give either sulfonylamidines (78-95%) or phosphorylformamidines (83-100%).[10]

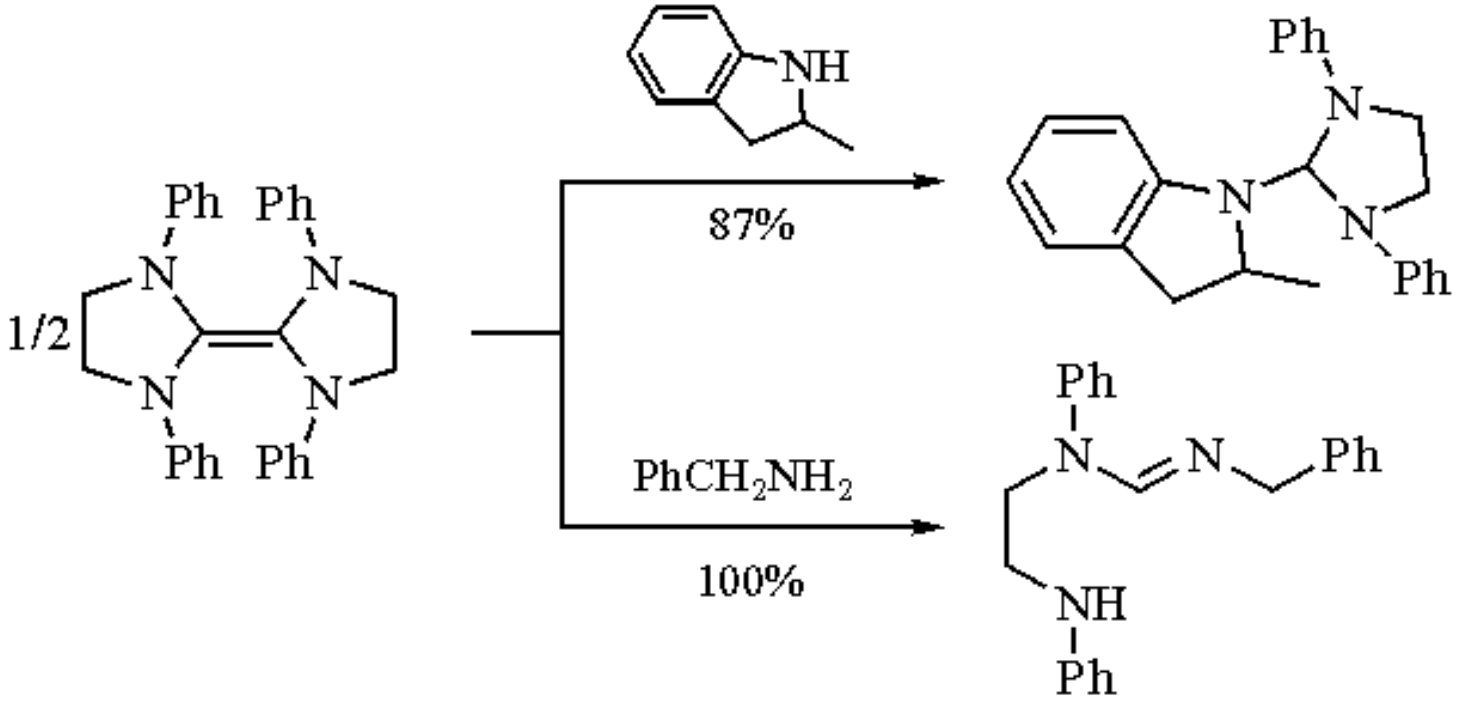

(4)

Homologs of 1,3-Diphenyl-2-imidazolidinone.

Treatment of solutions of bis(1,3-diphenyl-2-imidazolidinylidene) with O_2, S_8, or Se^0 gives, respectively, the imidazolidinone (90%),[7] thioimidazolidinone (85%),[11] or the imidazolidineselenone (62%)[12] (eq 5).

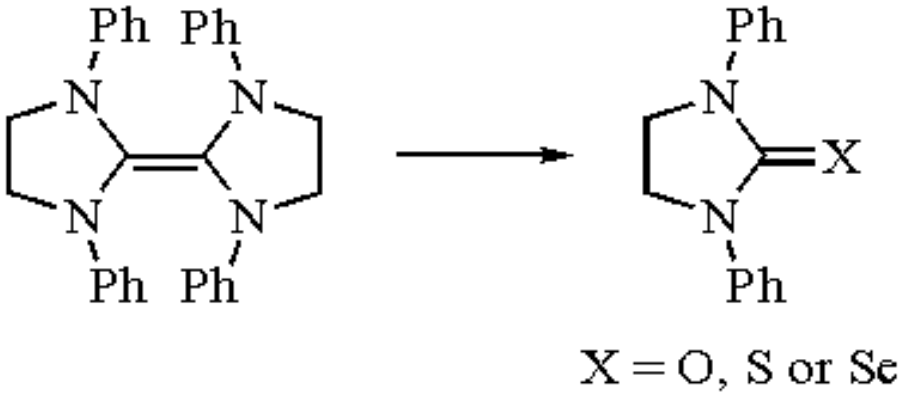

(5)

Carbene Complexes.

Palladium(II)[13,14] and platinum(II)[13] carbene complexes (*trans*) have been prepared from bis(1,3-diphenyl-2-imidazolidinylidene), as illustrated in eq 6.

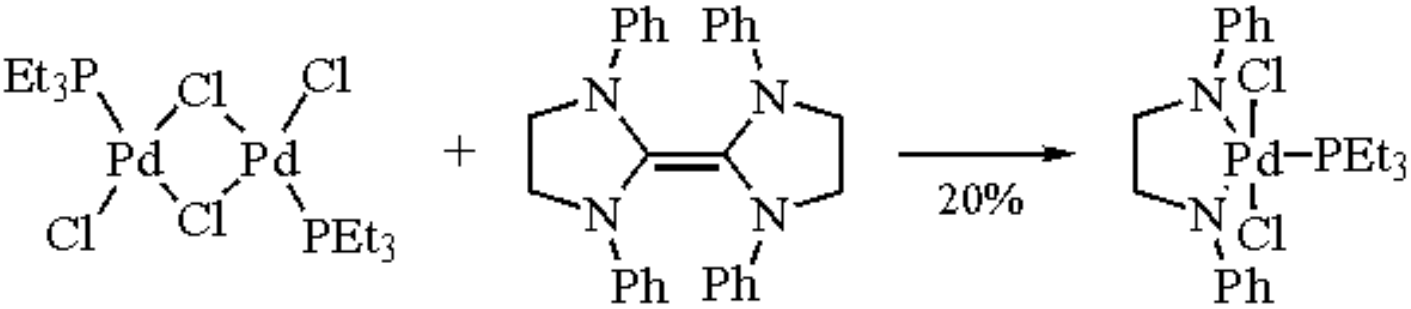

(6)

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(+)-*trans*-(2*S*,3*S*)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene[1]

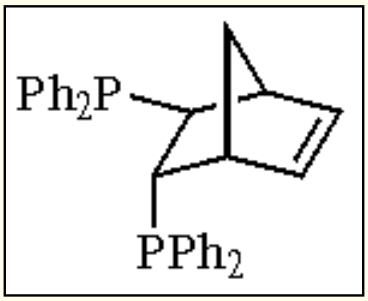

(+)

[71042-54-1] · $C_{31}H_{28}P_2$ · (+)-*trans*-(2*S*,3*S*)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene · (MW 462.51) (-)

[71042-55-1] (±)

[76740-45-9]

(ligand for transition metal catalyzed asymmetric hydrogenation of alkenes,[2] α-keto esters,[3] imines,[4] and β-keto esters;[5] homo-Diels-Alder reactions;[6] hydroarylation[7])

Alternate Name: (+)-NORPHOS.

Physical Data: mp 129-130 °C; [α]20D = +45° (*c* = 1.0, $CHCl_3$).

Preparative Method: trans-(2*S*,3*S*)-bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene (*R*,*R*-NORPHOS) has been prepared by reduction (***Trichlorosilane***) of the phosphine oxide, which was resolved with (-)-dibenzoyltartaric acid.[2]

Handling, Storage, and Precautions: NORPHOS is readily oxidized to the phosphine oxide and should be handled under N_2 or Ar. Use in a fume hood.

Asymmetric Hydrogenation.

Numerous optically active phosphines have been utilized for enantioselective hydrogenations of prochiral substrates.[1] In particular, transition metal complexes of (+)-NORPHOS have found particularly widespread use in asymmetric hydrogenations of a variety of unsaturated functional groups. Rhodium catalysts, prepared in situ from the reaction of $[Rh(diene)Cl]_2$ complexes and (+)-NORPHOS, have been reported for use in asymmetric hydrogenations.[2] The use of 80% ***Formic Acid*** as an alternative to hydrogen gas for catalytic alkene hydrogenations has been described.[8] Reduction of the bicyclo[2.2.1]hept-5-ene backbone of (+)-NORPHOS rapidly occurs under catalytic hydrogenation conditions to give the reduced diphosphine which is the actual ligand involved in catalysis (eq 1).[9] Asymmetric hydrogenation of (*Z*)-α-acetylaminocinnamic acid using a Rh complex of (+)-NORPHOS gave (*S*)-$PhCH_2CH(NHAc)CO_2H$ in quantitative yield and 92% ee (eq 2).[2] Similarly, hydrogenation of (*Z*)-α-acetylamino-2-butenoic acid occurred with 91.4% ee.[10] An additional example of the asymmetric hydrogenation of α-acetylaminoacrylic esters was reported in a synthesis of phosphinothricin in 91% ee (eq 3).[11] High enantiomeric excesses for alkene hydrogenation with (+)-NORPHOS are limited to α-acetylaminoacrylates which are capable of forming a chelate structure involving rhodium, the alkenic double bond, and the acetylamino functional group.

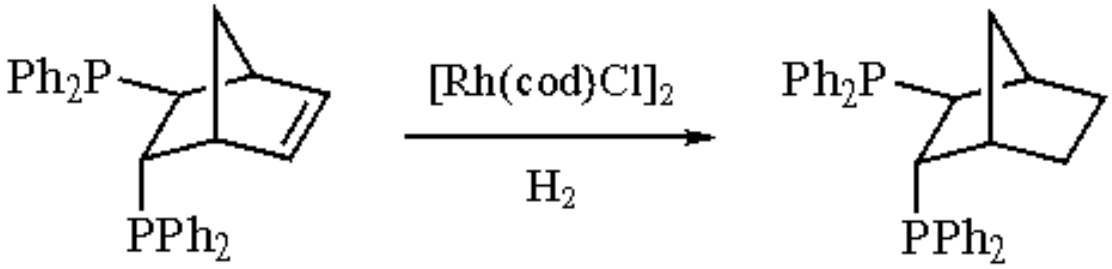

(1)

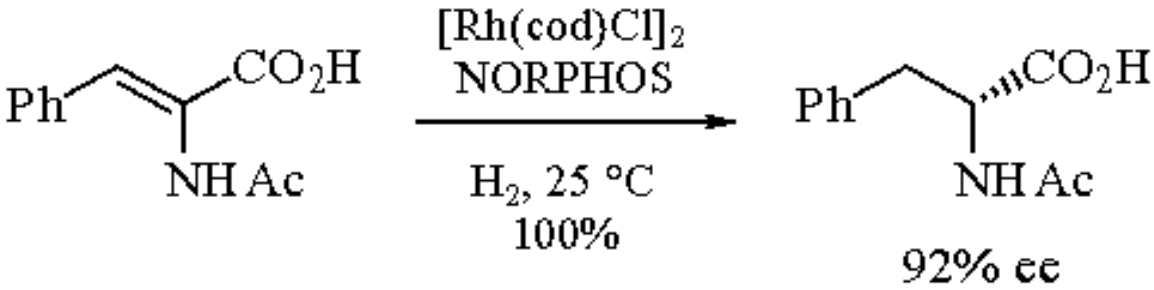

(2)

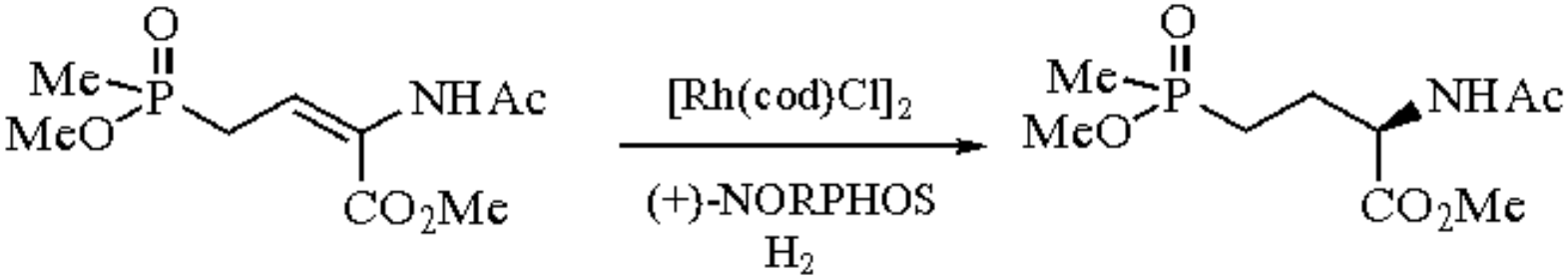

(3)

Rhodium complexes of (+)-NORPHOS have also been used for enantioselective hydrogenation of carbon-oxygen and carbon-nitrogen double bonds. Hydrogenation of $PhCH_2CH_2COCO_2Et$ with a catalyst prepared from ***Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium*** and (+)-NORPHOS gave a quantitative yield of $PhCH_2CH_2CH(OH)CO_2Et$ with 96% ee (eq 4).[3] Kinetic resolutions of racemic β-keto esters have been performed using asymmetric hydrogenation in the synthesis of (+)- and (-)-threonine.[5] Enantioselective hydrogenation of imines using a Rh complex of (+)-NORPHOS has been reported. Hydrogenation of $ArN{=}C(Me)CH_2OMe$ occurred with 61%

ee (eq 5).[4] The product enantioselectivity using NORPHOS was comparable to that observed using other diphosphine ligands.

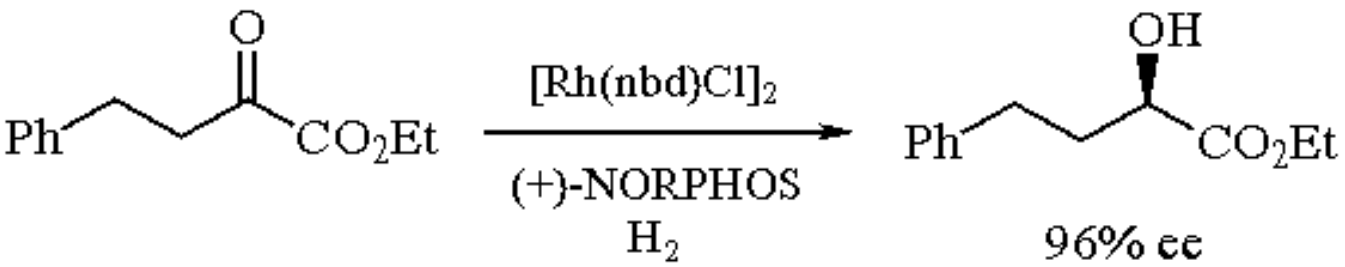

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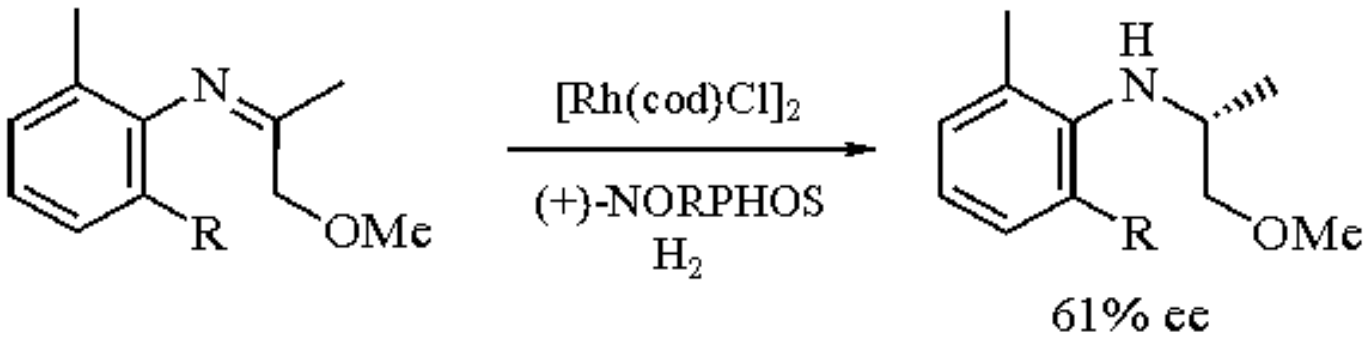

(5)

Homo-Diels-Alder Reactions.

The enantioselective synthesis of deltacyclenes from norbornadiene and monosubstituted alkynes has been catalyzed by a cobalt catalyst prepared from ***Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS***. 4-Phenyldeltacyclene was obtained in quantitative yield with >98% ee (eq 6).[6]

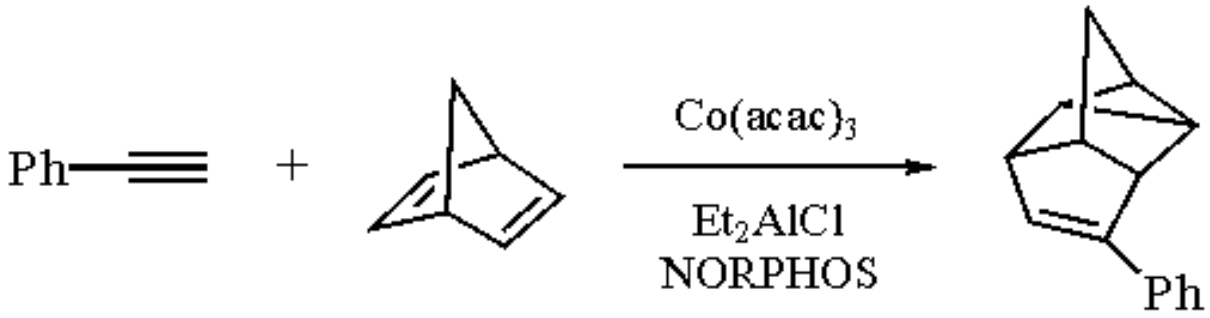

(6)

Asymmetric Alkene Hydroarylation.

The enantioselective addition of aryl iodides to norbornene has been reported using a palladium(II) complex of (+)-NORPHOS.[7] The reaction of norbornadiene with 4-methoxyiodobenzene proceeded with 40.6% ee (eq 7).

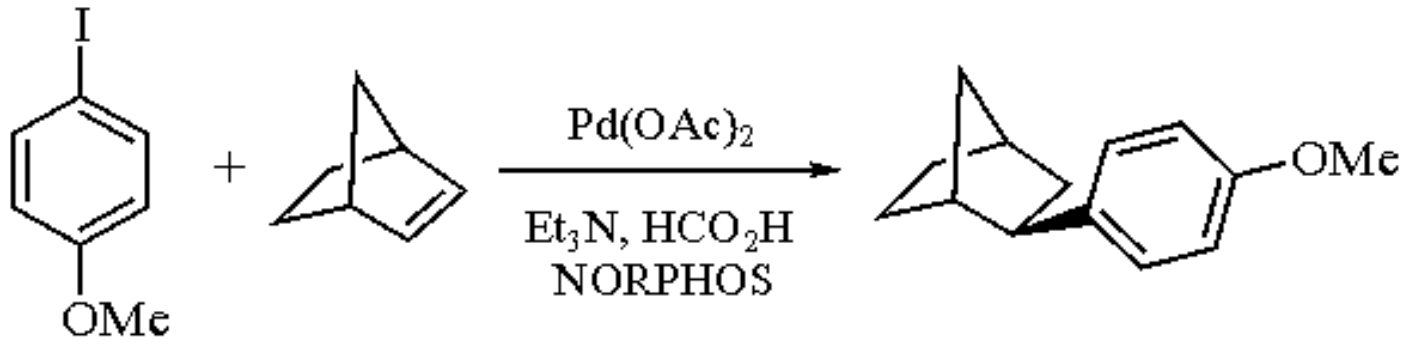

(7)

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(*R*)- & (*S*)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl[1]

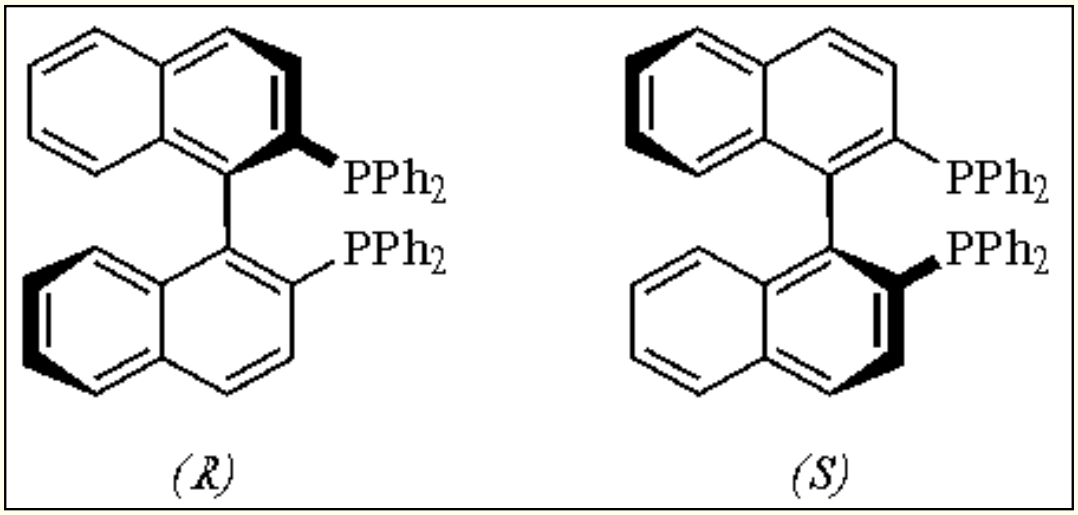

[76189-55-4] · $C_{44}H_{32}P_2$ · 2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl · (MW 622.70)

(chiral diphosphine ligand for transition metals;[2] the complexes show high enantioselectivity and reactivity in a variety of organic reactions)

Alternate Name: BINAP.

Physical Data: mp 241-242 °C; [α]25D -229° (*c* = 0.312, benzene) for (*S*)-BINAP.[3]

Solubility: sol THF, benzene, dichloromethane; modestly sol ether, methanol, ethanol; insol water.

Form Supplied in: colorless solid.

Analysis of Reagent Purity: GLC analysis (OV-101, capillary column, 5 m, 200-280 °C) and TLC analysis (E. Merck Kieselgel 60 PF_{254}, 1:19 methanol-chloroform); R_f 0.42 (BINAPO, dioxide of BINAP), 0.67 (monoxide of BINAP), and 0.83 (BINAP). The optical purity of BINAP is analyzed after oxidizing to BINAPO by HPLC using a Pirkle column (Baker bond II) and a hexane/ethanol mixture as eluent.[3]

Preparative Methods: enantiomerically pure BINAP is obtained by resolution of the racemic dioxide, BINAPO, with camphorsulfonic acid or 2,3-di-*O*-benzoyltartaric acid followed by deoxygenation with ***Trichlorosilane*** in the presence of ***Triethylamine***.[3]

Handling, Storage, and Precautions: solid BINAP is substantially stable to air, but bottles of BINAP should be flushed with N_2 or Ar and kept tightly closed for prolonged storage. BINAP is slowly air oxidized to the monoxide in solution.

BINAP-Ru^{II} Catalyzed Asymmetric Reactions.

Halogen-containing BINAP-Ru complexes are most simply prepared by reaction of $[RuCl_2(cod)]_n$ or $[RuX_2(arene)]_2$ (X = Cl, Br, or I) with BINAP.[4] Sequential treatment of $[RuCl_2(benzene)]_2$ with BINAP and sodium carboxylates affords Ru(carboxylate)$_2$(BINAP) complexes. The dicarboxylate complexes, upon treatment with strong acid HX,[5] can be converted to a series of Ru complexes empirically formulated as RuX_2(BINAP). These Ru^{II} complexes act as catalysts for asymmetric hydrogenation of various achiral and chiral unsaturated compounds.

α,β-Unsaturated carboxylic acids are hydrogenated in the presence of a small amount of Ru(OAc)$_2$(BINAP) to give the corresponding optically active saturated products in quantitative yields.[6] The reaction is carried out in methanol at ambient temperature with a substrate:catalyst (S:C) ratio of 100-600:1. The sense and degree of the enantioface differentiation are profoundly affected by hydrogen pressure and the substitution pattern of the substrates. Tiglic acid is hydrogenated quantitatively with a high enantioselectivity under a low hydrogen pressure (eq 1), whereas naproxen, a commercial anti-inflammatory agent, is obtained in 97% ee under high pressure (eq 2).[6a]

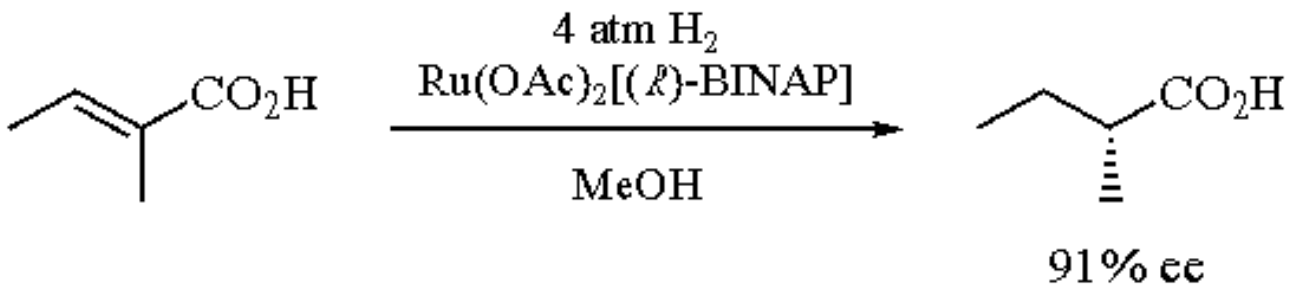

(1)

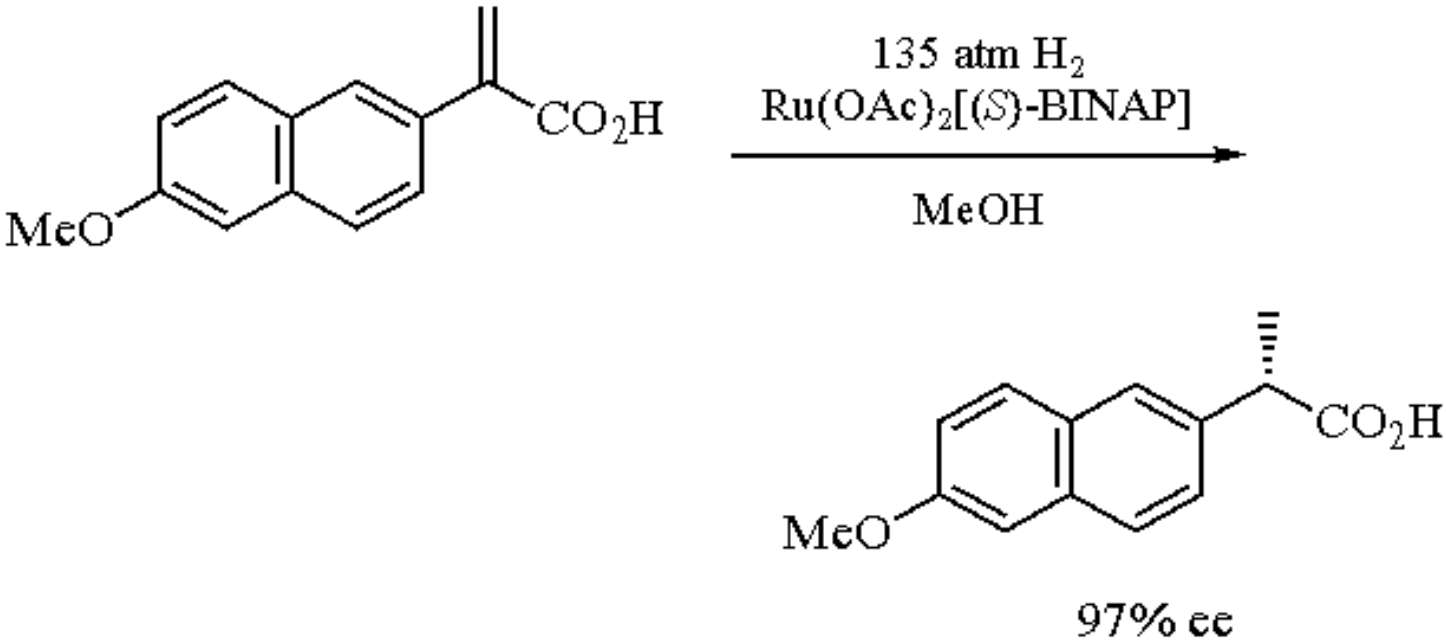

(2)

Enantioselective hydrogenation of certain α- and β-(acylamino)acrylic acids or esters in alcohols under 1-4 atm H_2 affords the protected α- and β-amino acids, respectively (eqs 3 and 4).[2a,7] Reaction of *N*-acylated 1-alkylidene-1,2,3,4-

tetrahydroisoquinolines provides the 1*R*- or 1*S*-alkylated products. This method allows a general asymmetric synthesis of isoquinoline alkaloids (eq 5).[8]

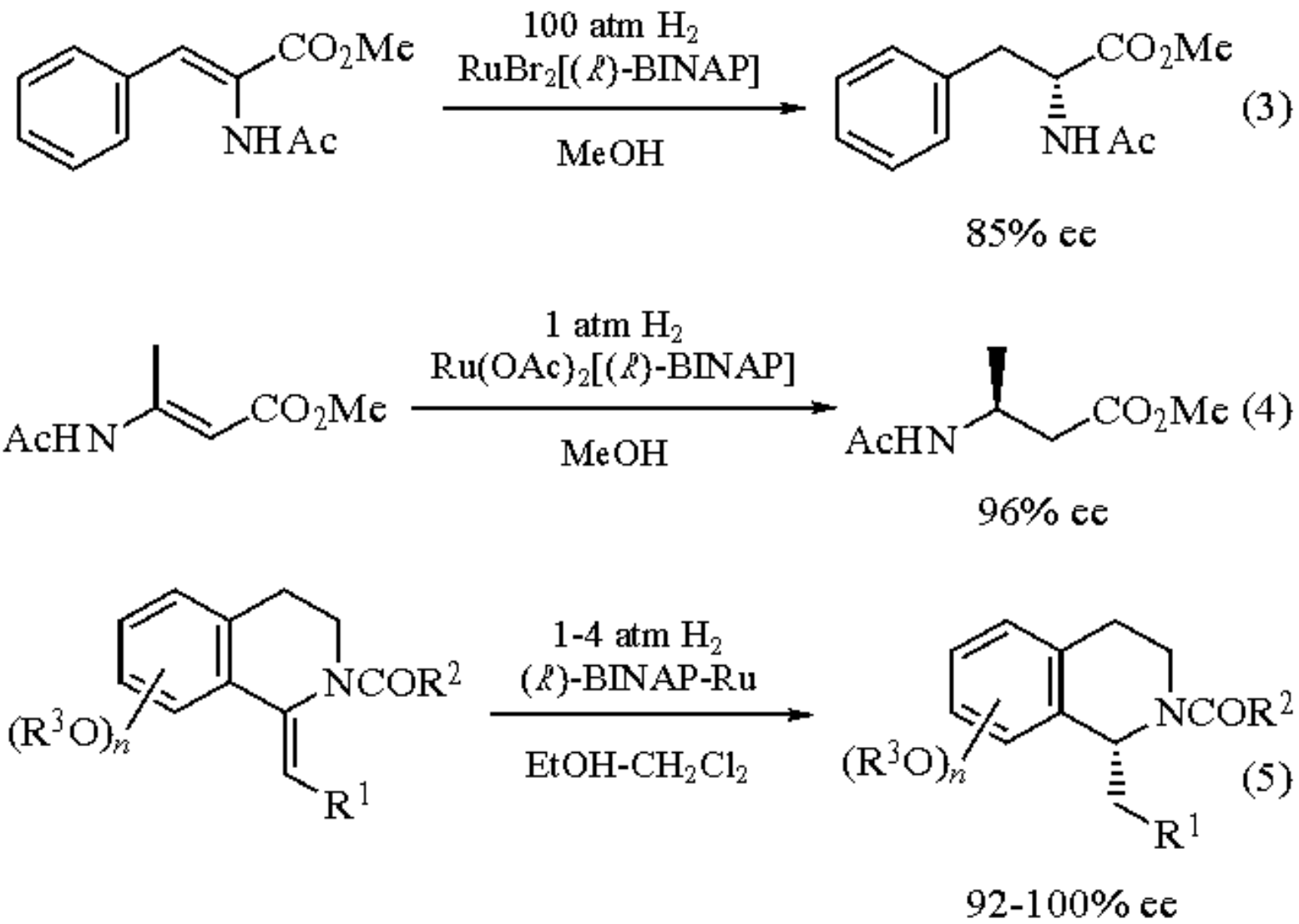

Geraniol or nerol can be converted to citronellol in 96-99% ee in quantitative yield without saturation of the C(6)-C(7) double bond (eq 6).[9] The S:C ratio approaches 50 000. The use of alcoholic solvents such as methanol or ethanol and initial H_2 pressure greater than 30 atm is required to obtain high enantioselectivity. Diastereoselective hydrogenation of the enantiomerically pure allylic alcohol with an azetidinone skeleton proceeds at atmospheric pressure in the presence of an (*R*)-BINAP-Ru complex to afford the β-methyl product, a precursor of 1β-methylcarbapenem antibiotics (eq 7).[10] Racemic allylic alcohols such as 3-methyl-2-cyclohexenol and 4-hydroxy-2-cyclopentenone can be effectively resolved by the BINAP-Ru-catalyzed hydrogenation (eq 8).[11]

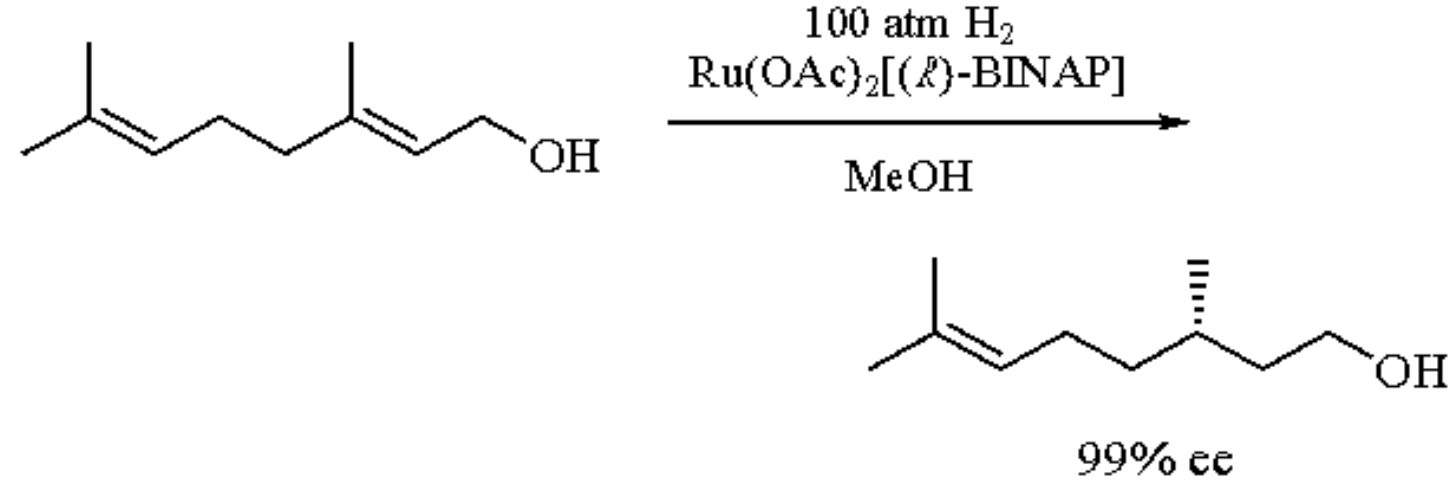

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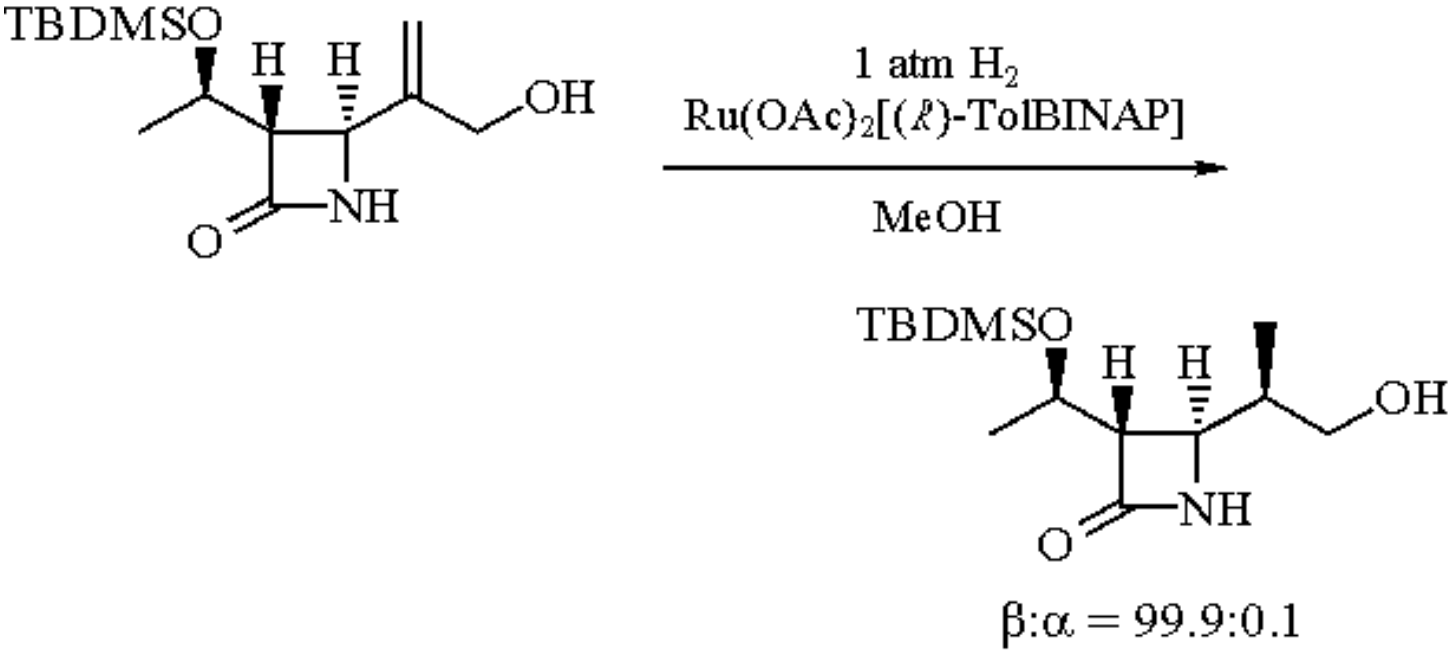

(7)

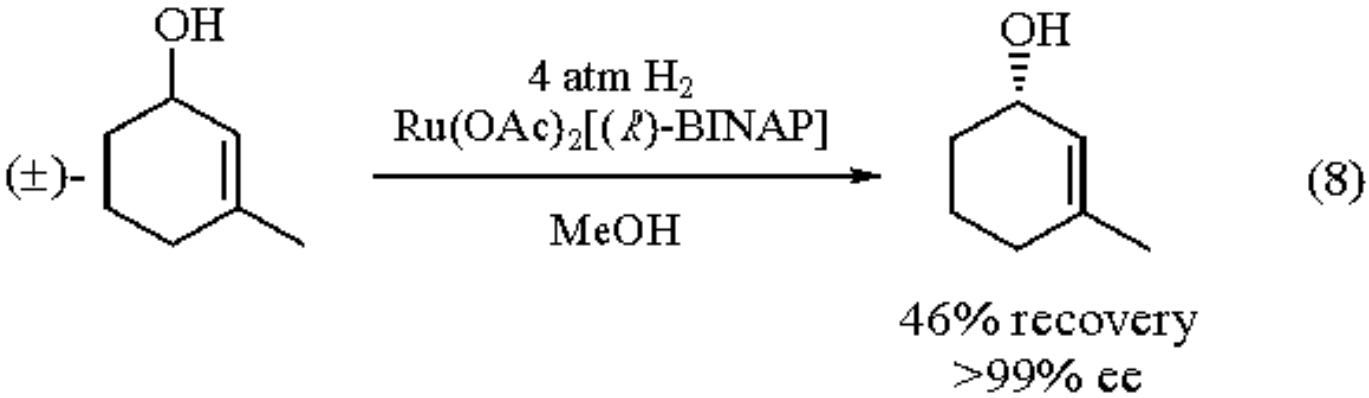

(8)

Diketene is quantitatively hydrogenated to 3-methyl-3-propanolide in 92% ee (eq 9). Certain 4-methylene- and 2-alkylidene-4-butanolides as well as 2-alkylidenecyclopentanone are also hydrogenated with high enantioselectivity.[12]

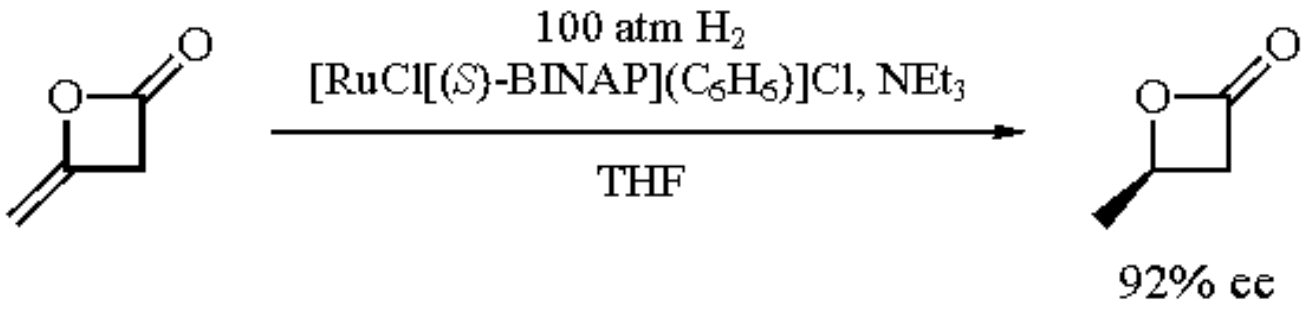

(9)

Hydrogenation with halogen-containing BINAP-Ru complexes can convert a wide range of functionalized prochiral ketones to stereo-defined secondary alcohols with high enantiomeric purity (eq 10).[13] 3-Oxocarboxylates are among the most appropriate substrates.[13a,4d] For example, the enantioselective hydrogenation of methyl 3-oxobutanoate proceeds quantitatively in methanol with an S:C ratio of 1000-10 000 to give the hydroxy ester product in nearly 100% ee (eq 11). Halogen-containing complexes RuX_2(BINAP) (X = Cl, Br, or I; polymeric form) or $[RuCl_2(BINAP)]_2NEt_3$ are used as the catalysts. Alcohols are the solvents of choice, but aprotic solvents such as dichloromethane can also be used. At room temperature the reaction requires an initial H_2 pressure of 20-100 atm, but at 80-100 °C the reaction proceeds smoothly at 4 atm H_2.[4c,4d]

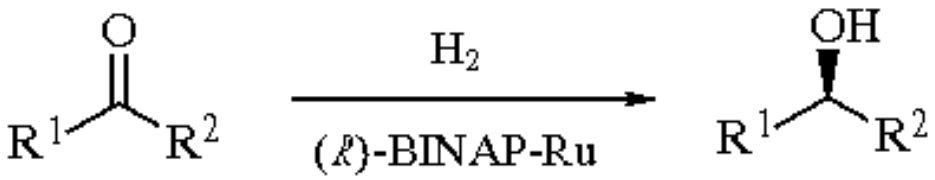

(10)

R^1 = alkyl, aryl; R^2 = CH_2OH, CH_2NMe_2, CH_2CH_2OH, CH_2Ac, CH_2CO_2R, CH_2COSR, CH_2CONR_2, $CH_2CH_2CO_2R$, etc.

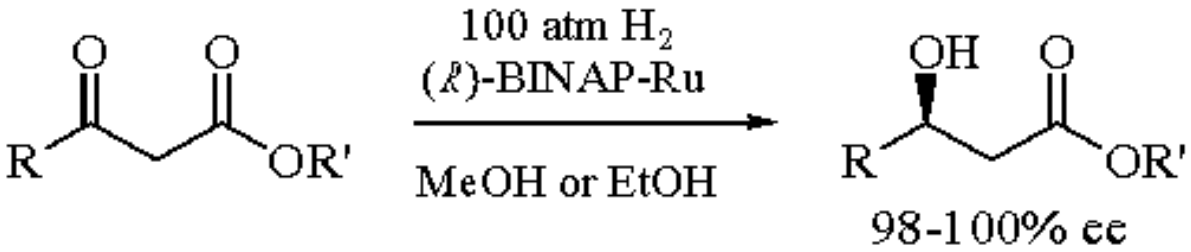

(11)

R = Me, Et, Bu, *i*-Pr; R′ = Me, Et, *i*-Pr, *t*-Bu

3-Oxocarboxylates possessing an additional functional group can also be hydrogenated with high enantioselectivity by choosing appropriate reaction conditions or by suitable functional group modification (eq 12).[13b,13c]

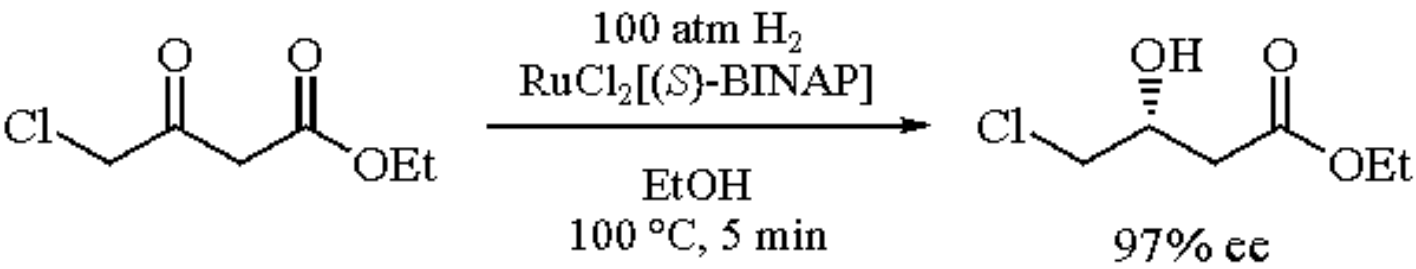

(12)

The pre-existing stereogenic center in the chiral substrates profoundly affects the stereoselectivity. The (*R*)-BINAP-Ru-catalyzed reaction of (*S*)-4-(alkoxycarbonylamino)-3-oxocarboxylates give the statine series with (3*S*,4*S*) configuration almost exclusively (eq 13).[14]

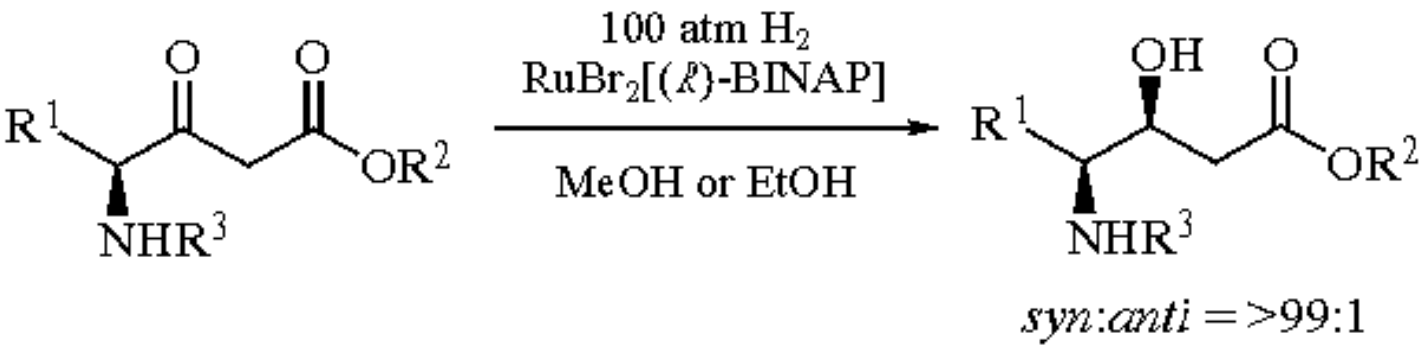

(13)

Hydrogenation of certain racemic 2-substituted 3-oxocarboxylates occurs with high diastereo- and enantioselectivity via dynamic kinetic resolution involving in situ racemization of the substrates.[15] The (*R*)-BINAP-Ru-catalyzed reaction of 2-acylamino-3-oxocarboxylates in dichloromethane allows preparation of threonine and DOPS (anti-Parkinsonian agent) (eq 14).[16] In addition, a common intermediate for the synthesis of carbapenem antibiotics is prepared stereoselectively on an industrial scale from a 3-oxobutyric ester (**1**) with an acylaminomethyl substituent at the C(2) position.[16a] The second-order stereoselective hydrogenation of 2-ethoxycarbonylcycloalkanones gives predominantly the *trans* hydroxy esters (**2**) in high ee, whereas 2-acetyl-4-butanolide is hydrogenated to give the *syn* diastereomer (**3**).[17]

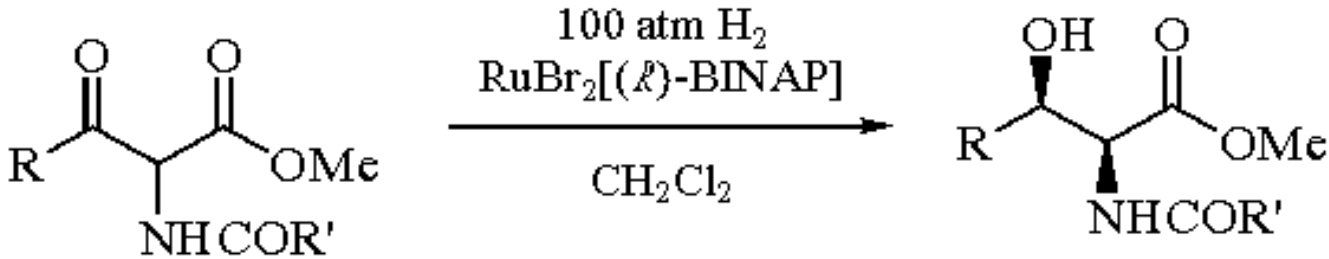

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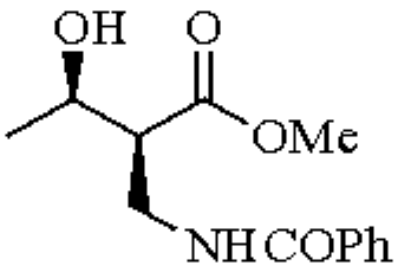

(1)
syn:*anti* = 94:6
98% ee

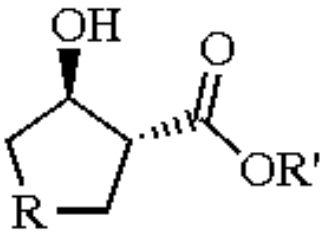

(2)
R = CH_2, $(CH_2)_2$, $(CH_2)_3$
trans:*cis* = 93:7-99:1
90-93% ee

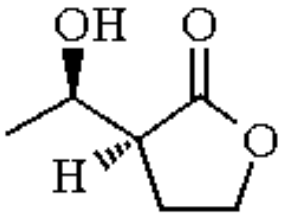

(3)
syn:*anti* = 98:2
94% ee

Certain 1,2- and 1,3-diketones are doubly hydrogenated to give stereoisomeric diols. 2,4-Pentanedione, for instance, affords (*R*,*R*)- or (*S*,*S*)-2,4-pentanediol in nearly 100% ee accompanied by 1% of the *meso* diol.[13b]

A BINAP-Ru complex can hydrogenate a C=N double bond in a special cyclic sulfonimide to the sultam with >99% ee.[18]

The asymmetric transfer hydrogenation of the unsaturated carboxylic acids using formic acid or alcohols as the hydrogen source is catalyzed by Ru(acac-F_6)(η^3-C_3H_5)(BINAP) or [RuH(BINAP)$_2$]PF_6 to produce the saturated acids in up to 97% ee (eq 15).[19]

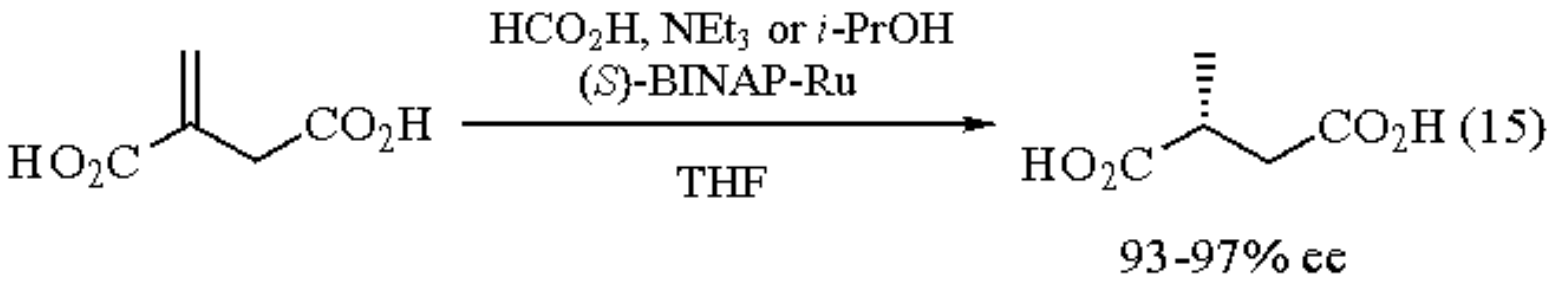

BINAP-Ru complexes promote addition of arenesulfonyl chlorides to alkenes in 25-40% optical yield.[20]

BINAP-Rh^I Catalyzed Asymmetric Reactions.

The rhodium(I) complexes [Rh(BINAP)(cod)]ClO_4, [Rh(BINAP)(nbd)]ClO_4, and [Rh(BINAP)$_2$]ClO_4, are prepared from [RhCl(cod)]$_2$ or ***Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium*** and BINAP in the presence of $AgClO_4$.[21] [Rh(BINAP)S_2]ClO_4 is prepared by reaction of [Rh(BINAP)(cod or nbd)]ClO_4 with atmospheric pressure of hydrogen in an appropriate solvent, S.[21a] BINAP-Rh complexes catalyze a variety of asymmetric reactions.[2]

Prochiral α-(acylamino)acrylic acids or esters are hydrogenated under an initial hydrogen pressure of 3-4 atm to give the protected amino acids in up to 100% ee (eq 16).[21a] The BINAP-Rh catalyst was used for highly diastereoselective hydrogenation of a chiral homoallylic alcohol to give a fragment of the ionophore ionomycin.[22]

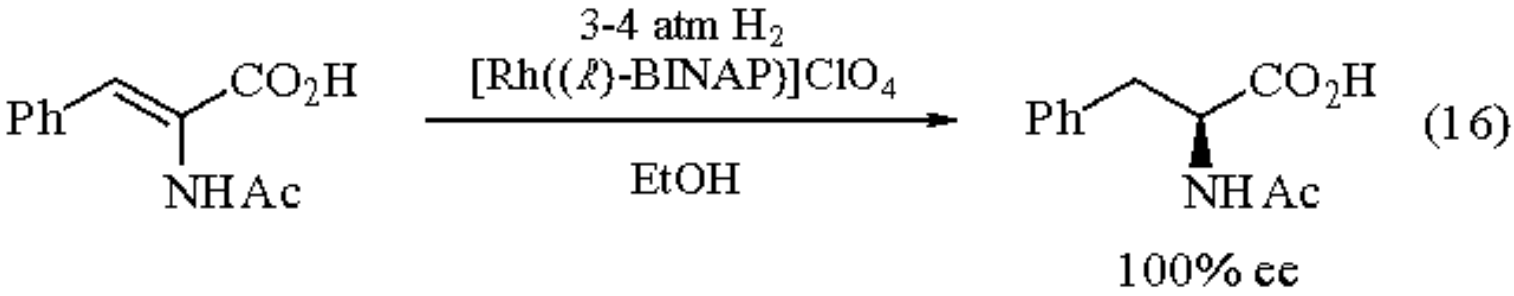

The cationic BINAP-Rh complexes catalyze asymmetric 1,3-hydrogen shifts of certain alkenes. Diethylgeranylamine can be quantitatively isomerized in THF or acetone to citronellal diethylenamine in 96-99% ee (eq 17).[23] This process is the key step in the industrial production of (-)-menthol. In the presence of a cationic (*R*)-BINAP-Rh complex, (*S*)-4-hydroxy-2-cyclopentenone is isomerized five times faster than the (*R*) enantiomer, giving a chiral intermediate of

prostaglandin synthesis.[24]

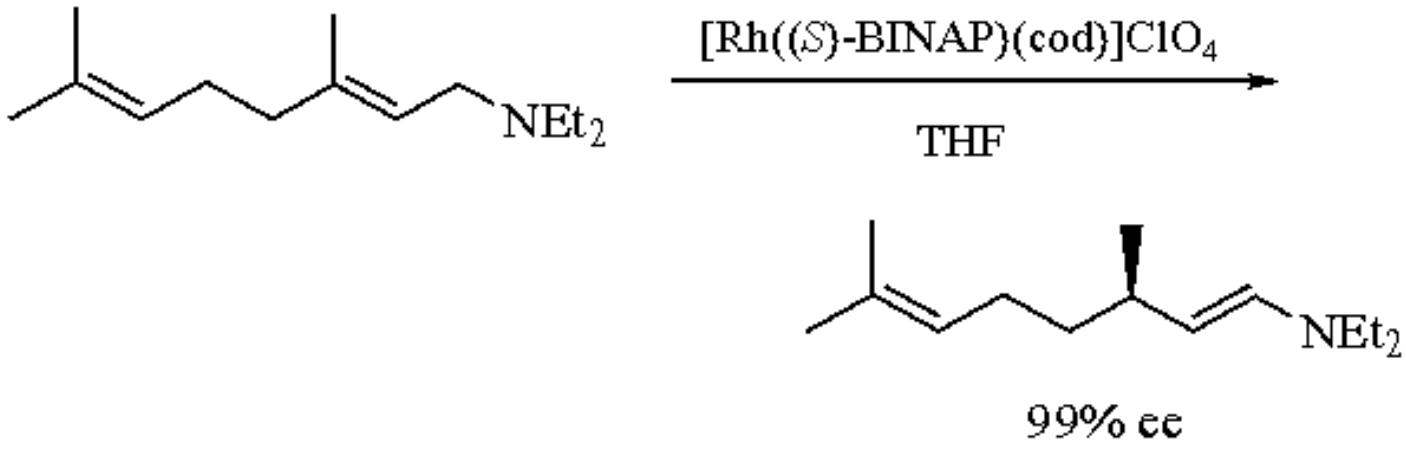

(17)

Enantioselective cyclization of 4-substituted 4-pentenals to 3-substituted cyclopentanones in >99% ee is achieved with a cationic BINAP-Rh complex (eq 18).[25]

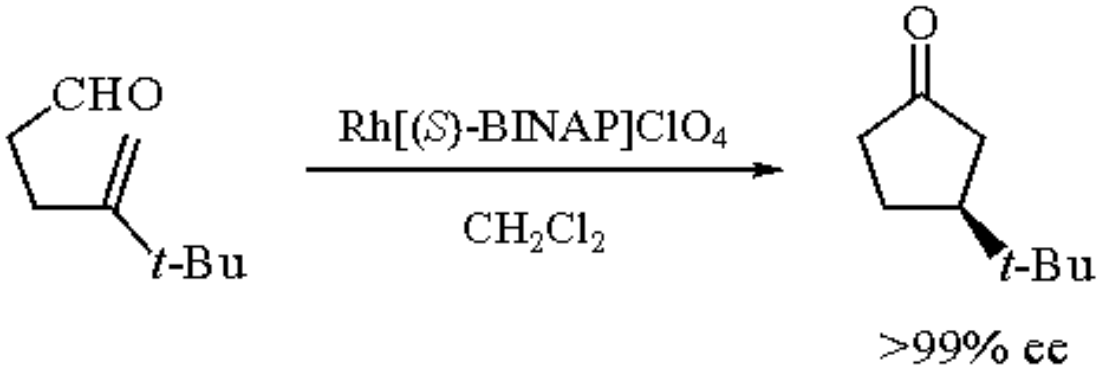

(18)

Reaction of styrene and catecholborane in the presence of a BINAP-Rh complex at low temperature forms, after oxidative workup, 1-phenylethyl alcohol in 96% ee (eq 19).[26]

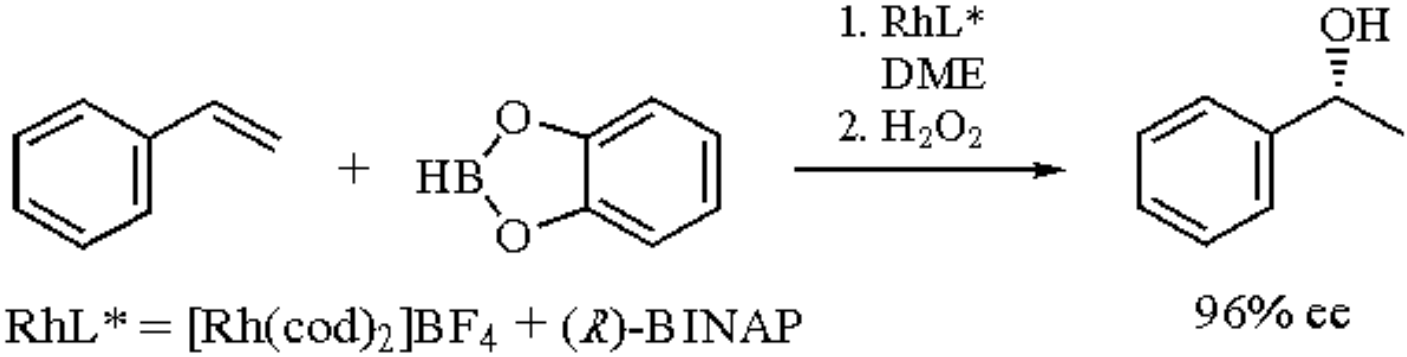

(19)

Neutral BINAP-Rh complexes catalyze intramolecular hydrosilylation of alkenes. Subsequent ***Hydrogen Peroxide*** oxidation produces the optically active 1,3-diol in up to 97% ee (eq 20).[27]

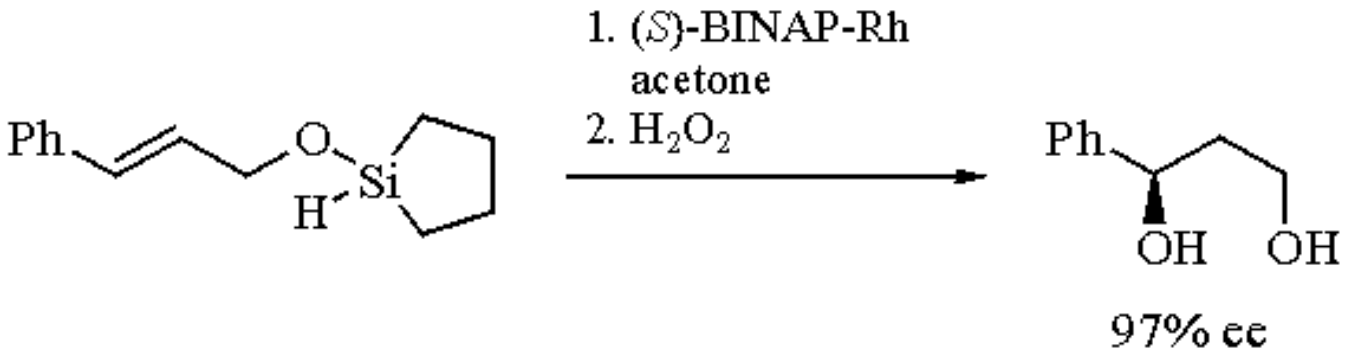

(20)

BINAP-Pd Catalyzed Asymmetric Reactions.

BINAP-Pd^0 complexes are prepared in situ from ***Bis(dibenzylideneacetone)palladium(0)*** or $Pd_2(dba)_3.CHCl_3$ and BINAP.[28] BINAP-Pd^{II} complexes are formed from ***Bis(allyl)di-μ-chlorodipalladium***, ***Palladium(II) Acetate***, or $PdCl_2(MeCN)_2$ and BINAP.[29-31]

A BINAP-Pd complex brings about enantioselective 1,4-disilylation of α,β-unsaturated ketones with chlorinated disilanes, giving enol silyl ethers in 74-92% ee (eq 21).[29]

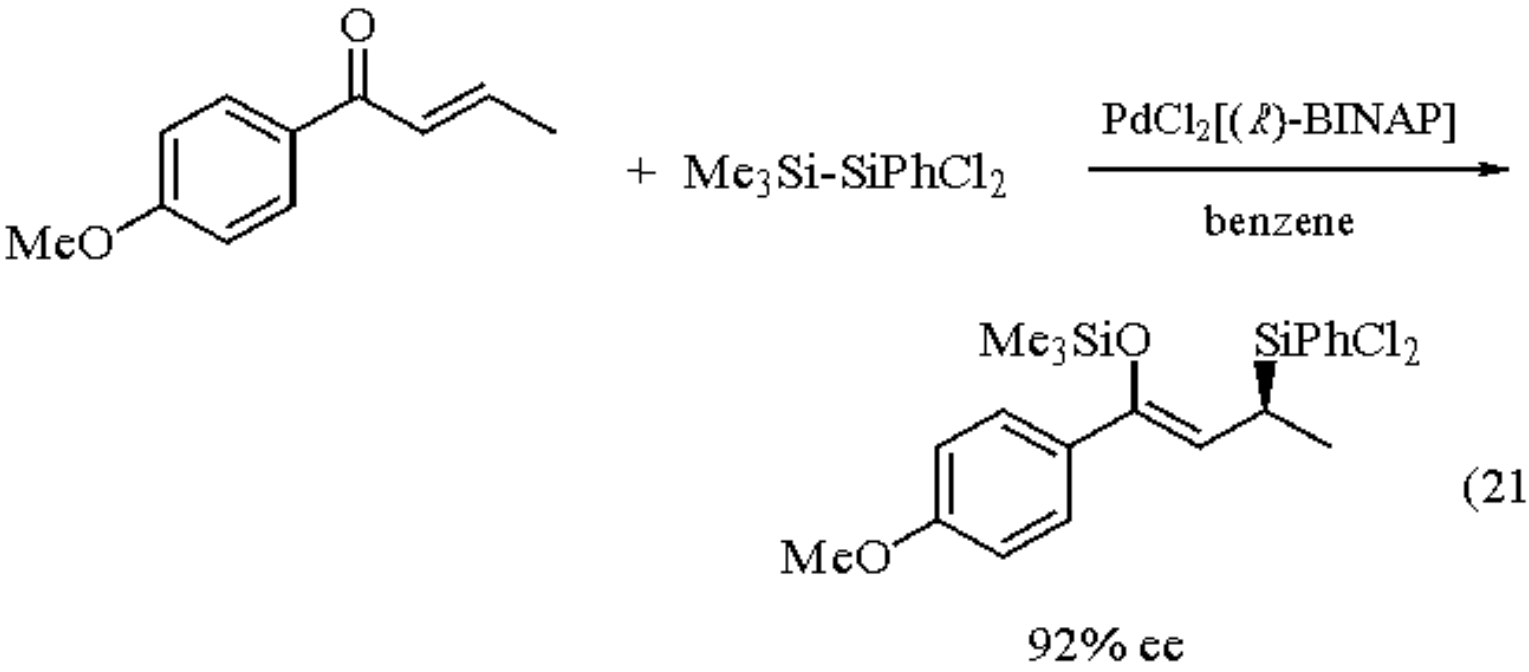

(21)

A BINAP-Pd^{II} complex catalyzes a highly enantioselective C-C bond formation between an aryl triflate and 2,3-dihydrofuran (eq 22).[30] The intramolecular version of the reaction using an alkenyl iodide in the presence of $PdCl_2$[(*R*)-BINAP] and ***Silver(I) Phosphate*** allows enantioselective formation of a bicyclic ring system (eq 23).[31]

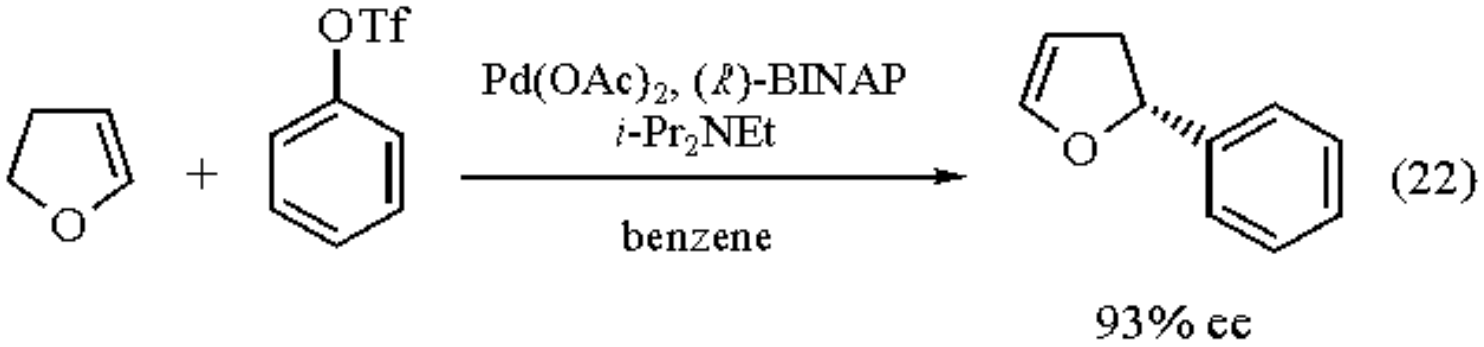

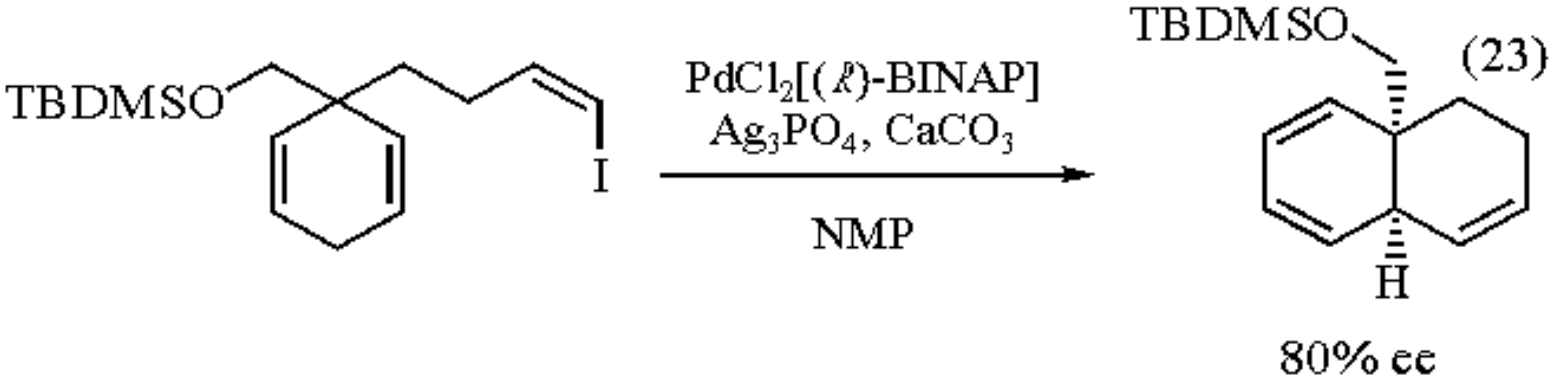

Enantioselective electrophilic allylation of 2-acetamidomalonate esters is effected by a BINAP-Pd^0 complex (eq 24).[32]

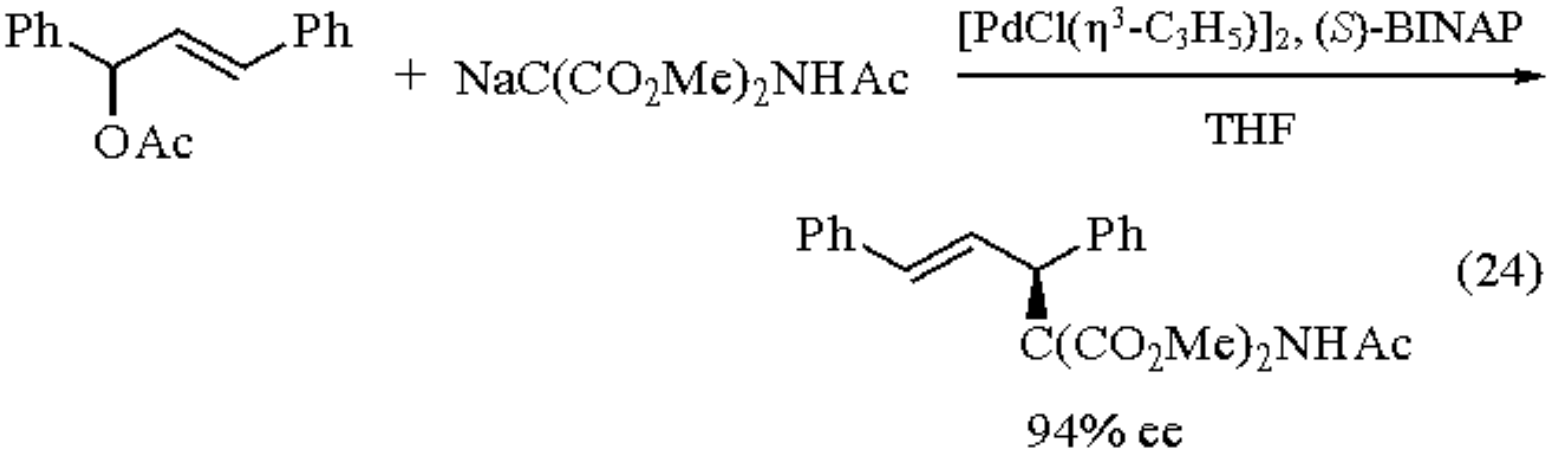

A BINAP-Pd^0 complex catalyzes hydrocyanation of norbornene to the *exo* nitrile with up to 40% ee.[28]

BINAP-Ir^I Catalyzed Asymmetric Reactions.

[Ir(BINAP)(cod)]BF_4 is prepared from [Ir(cod)(MeCN)$_2$]BF_4 and BINAP in THF.[33]

A combined system of the BINAP-Ir complex and bis(*o*-dimethylaminophenyl)phenylphosphine or (*o*-dimethylaminophenyl)diphenylphosphine catalyzes hydrogenation of benzylideneacetone[33a] and cyclic aromatic ketones[33b] with modest to high enantioselectivities (eq 25).

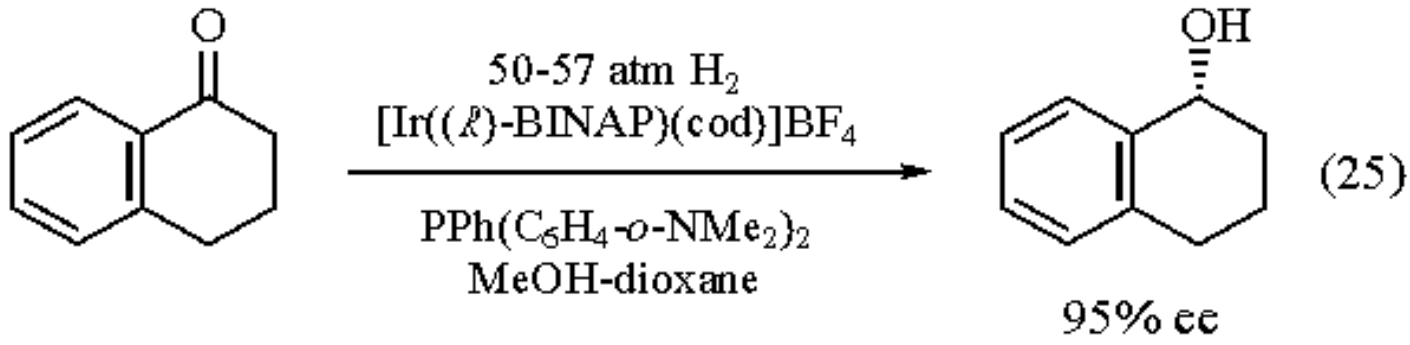

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Nagoya University, Japan

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1,4-Bis(diphenylphosphino)butane

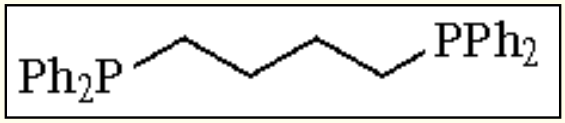

[7688-25-7] · $C_{28}H_{28}P_2$ · 1,4-Bis(diphenylphosphino)butane · (MW 426.48)

(ligand for metal-catalyzed lactonization of unsaturated alcohols;[1] allylic substitution;[2] cyclization reactions;[3] carbonylations;[4] alkyne isomerization;[5] alkyne-CO_2 coupling[6])

Alternate Name: dppb.

Physical Data: mp 135-137 °C.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: readily oxidized in solution to the phosphine oxide and should be handled under N_2 or Ar. The compound is air-stable in the solid state.

Lactonization of Unsaturated Alcohols.

Allylic and propargylic alcohols can be converted to lactones by carbonylation using a catalyst prepared from ***Tris(dibenzylideneacetone)dipalladium*** and dppb (eq 1).[1] Lactones are formed with secondary and tertiary alcohols. Primary allylic alcohols give α,β-unsaturated carboxylic acids (eq 2).

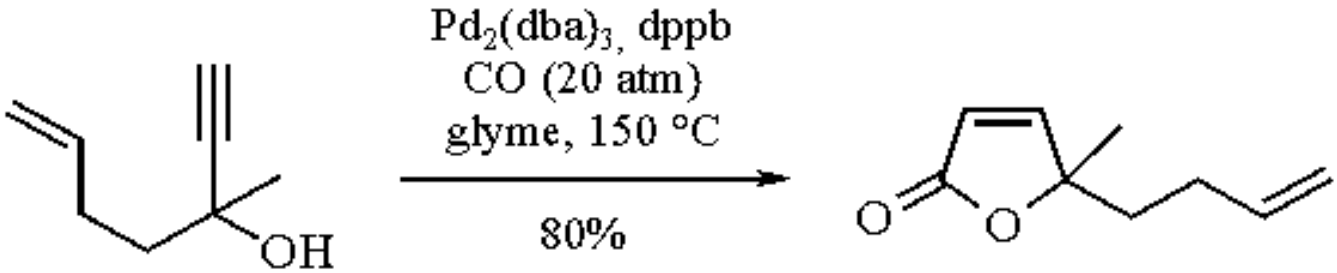

(1)

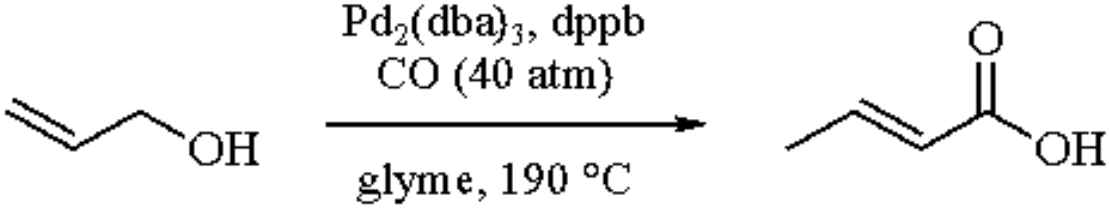

(2)

Allylic Substitution.

Alkylation of allyl acetates by dimethyl malonate derivatives is catalyzed by ***Palladium(II) Acetate***-dppb (eq 3).[2] Alkylation of the Pd(π-allyl) intermediate occurs exclusively at the terminal position. Regioselective addition to the internal position can be accomplished with $(MeCN)_3W(CO)_3$ in pyridine. Allylic azides can be prepared by reaction of ***Sodium Azide*** with allyl acetates using a catalyst prepared from $Pd_2(dba)_3$ and dppb (eq 4).[7] Addition of dimethyl sodiomalonate to 1-chloro-1-vinylcyclopropanes results in methylenecyclopropanes (eq 5).[8]

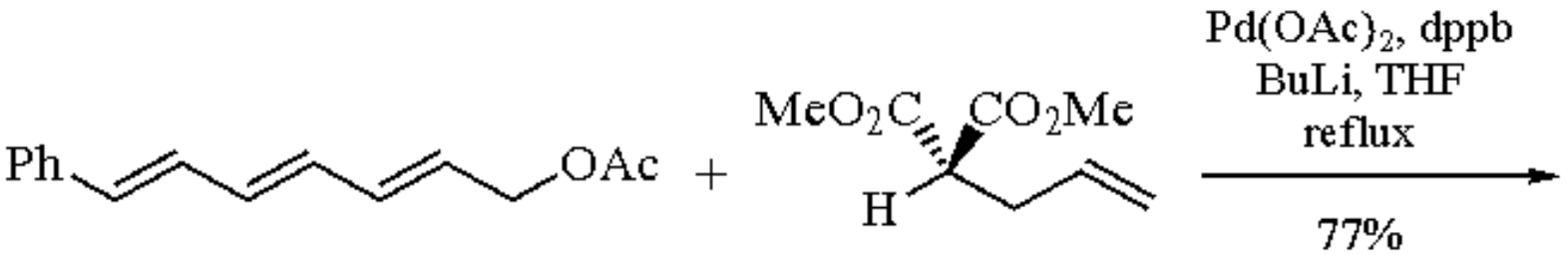

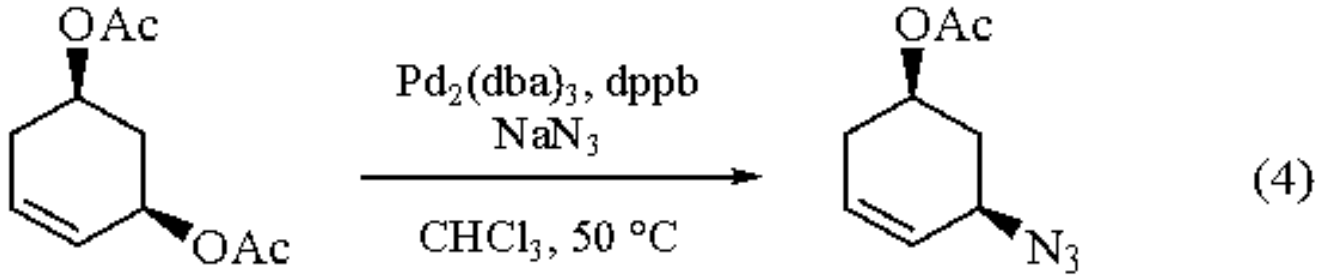

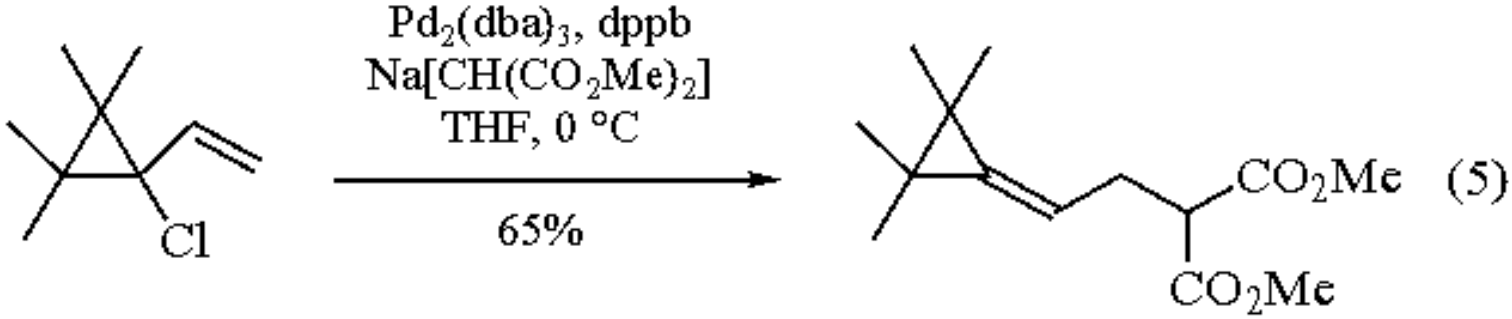

Cyclization Reactions.

Synthesis of pyrrolidines and furans by intramolecular allylation of alkenes is catalyzed by ***Bis(1,5-cyclooctadiene)nickel(0)***-dppb (eq 6).[3] Macrocyclization to give the 21-membered ring was catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)***-dppb (eq 7).[9]

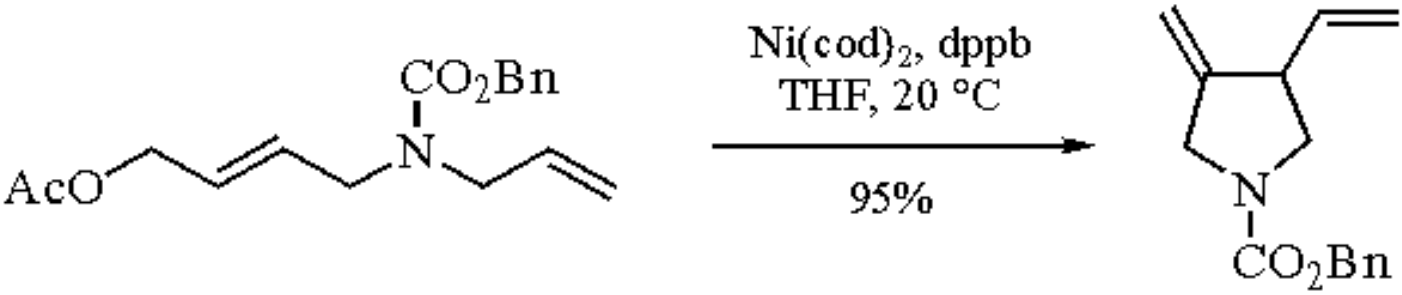

(6)

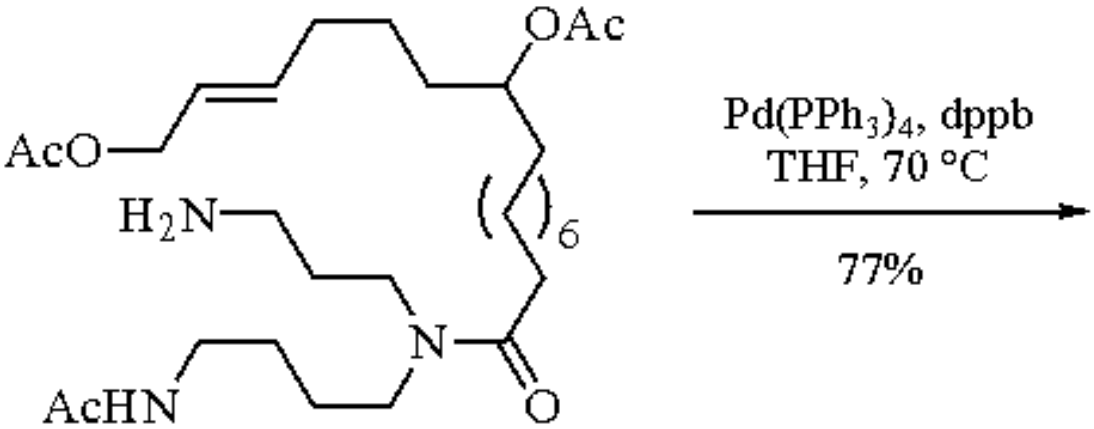

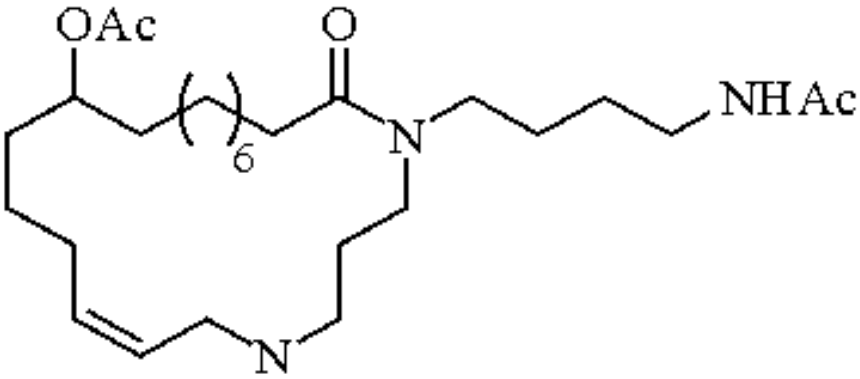

(7)

Hydroacylation Reactions.

Carbonylation of vinylarenes with formate esters is catalyzed by $Pd(PPh_3)_4$-dppb under CO. A mixture of linear and branched esters is formed from the reaction of *p*-methylstyrene and *n*-butyl formate (eq 8).[4] Hydroformylation of unsaturated amides is catalyzed by $Rh(PPh_3)_3(CO)H$ and dppb to give nitrogen heterocycles (eq 9).[10]

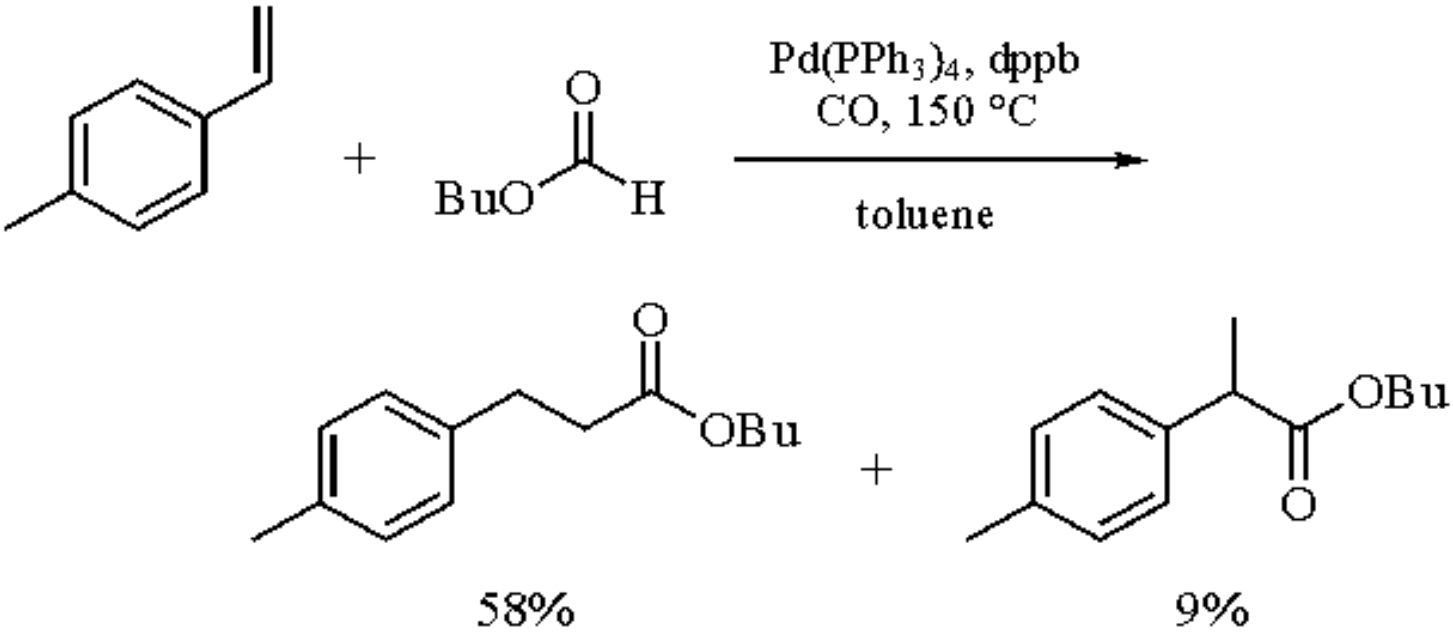

(8)

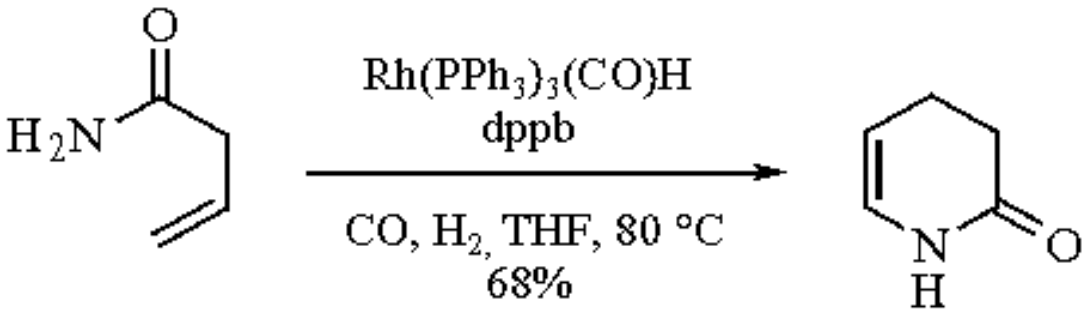

(9)

Alkyne Isomerizations.

Isomerization of alkynones to dienones was catalyzed by $Pd(OAc)_2$-dppb (eq 10).[5] The (*E*,*E*)-diene was stereoselectively formed.

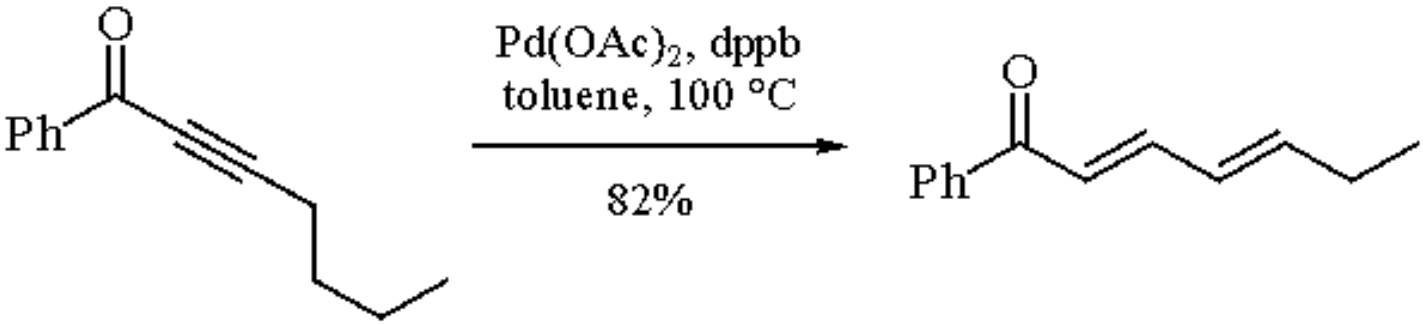

(10)

Alkyne-CO_2 Coupling.

Nickel(0) complexes of dppb catalyze the coupling of alkynes with carbon dioxide to give pyrones (eq 11).[6] Bicyclic products can be formed by coupling of CO_2 with diynes.[11]

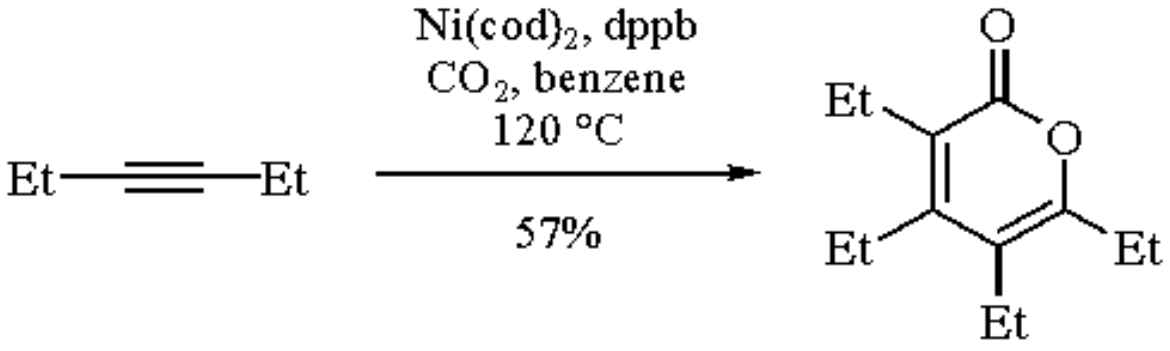

(11)

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(2*R*,3*R*)-2,3-Bis(diphenylphosphino)butane[1]

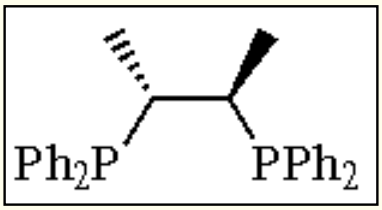

(2*R*,3*R*)

[74839-84-2] · $C_{28}H_{28}P_2$ · 2,3-Bis(diphenylphosphino)butane · (MW 426.48) (2*S*,3*S*)

[64896-28-2]

(ligand for asymmetric hydrogenation of alkenes[2] and β-keto esters;[3] allylic alkylation;[4] hydroarylation[5])

Alternate Name: (*R*,*R*)-CHIRAPHOS.

Physical Data: mp 107-109 °C; [α]20D +195° (*c* = 1.5, $CHCl_3$).

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: is indefinitely stable in air in the solid state. Solutions of CHIRAPHOS are readily oxidized to the phosphine oxide and should be handled under N_2 or Ar.[2]

Asymmetric Hydrogenation.

CHIRAPHOS has been employed in the enantioselective hydrogenation of a variety of unsaturated functional groups. The asymmetric hydrogenation of cinnamic acid derivatives has been extensively studied due to its relevance to the commercial synthesis of amino acids, such as L-Dopa.[1] Hydrogenation of (*Z*)-α-benzoylaminocinnamic acid is catalyzed in quantitative yield and 98% ee by a cationic rhodium complex prepared from $[Rh(cod)_2](ClO_4)$ and (*S*,*S*)-CHIRAPHOS (eq 1).[2] Asymmetric hydrogenations have also been performed using racemic CHIRAPHOS which has been resolved in situ by a substrate-induced kinetic resolution.[6] When racemic CHIRAPHOS (2 equiv) was reacted with complex (**1**) (R = (-)-menthyl), (*S*,*S*)-CHIRAPHOS selectively coordinated to Ir. This resulting (*S*,*S*)-CHIRAPHOS-Ir complex is catalytically inactive for alkene hydrogenation under typical conditions. In the presence of this Ir complex the remaining uncoordinated (*R*,*R*)-CHIRAPHOS is then utilized for rhodium-catalyzed hydrogenation of methyl (*Z*)-α-acetylaminocinnamate (eq 2). The enantiomeric excess using this route is identical to

that observed with authentic (*R*,*R*)-CHIRAPHOS.

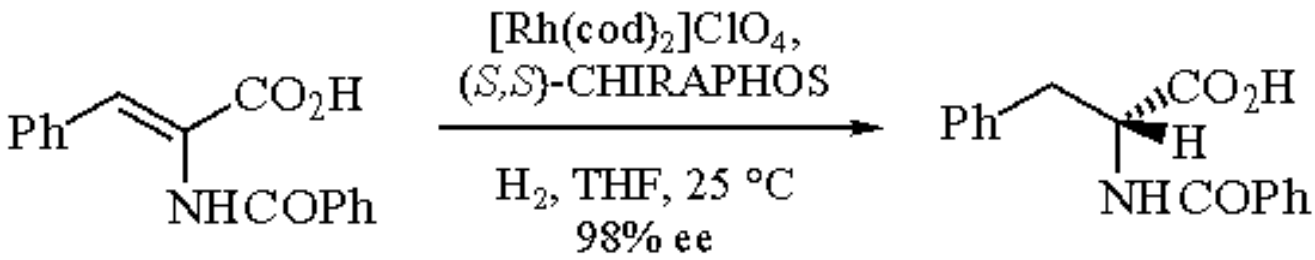

(1)

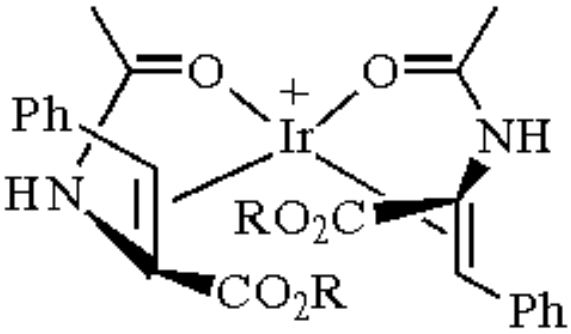

(1)

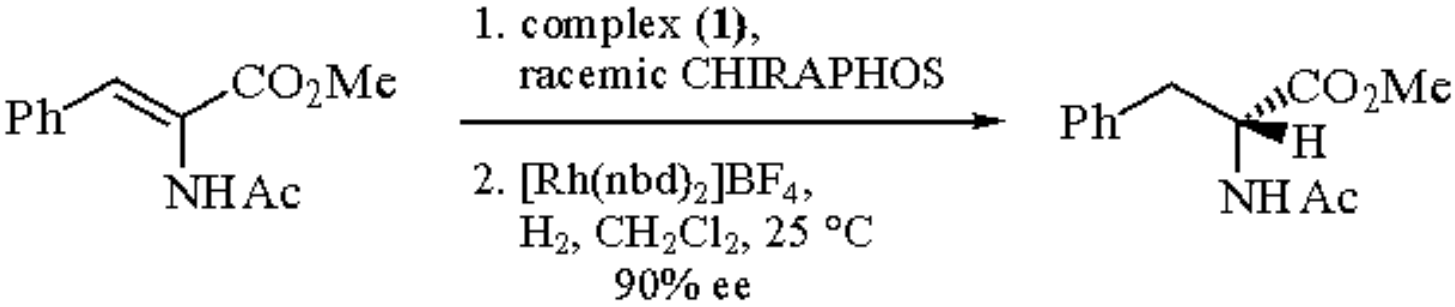

(2)

Rhodium and ruthenium complexes of CHIRAPHOS are also useful for the asymmetric hydrogenation of β-keto esters. Dynamic kinetic resolution of racemic 2-acylamino-3-oxobutyrates was performed by hydrogenation using ((*S*,*S*)-CHIRAPHOS)$RuBr_2$ (eq 3).[3] The product yields and enantiomeric excesses were dependent upon solvent, ligand, and the ratio of substrate to catalyst. Under optimum conditions a 97:3 mixture of *syn* and *anti* β-hydroxy esters was formed, which was converted to D-threonine (85% ee) and D-allothreonine (99% ee) by hydrolysis and reaction with propylene oxide.

(2R,3R)-2,3-Bis(diphenylphosphino)butane

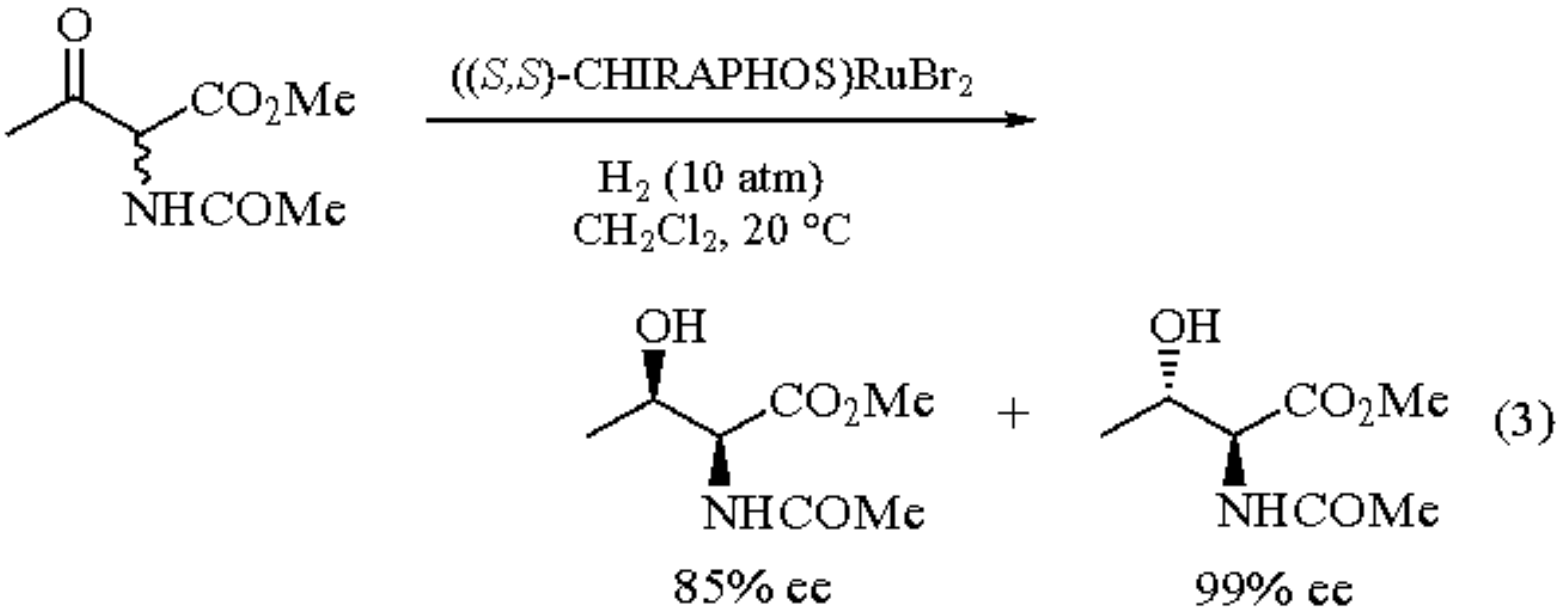

Allylic Alkylation.

The palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl sodiomalonate produces (**2**) in 86% yield and 90% ee (eq 4).[4] CHIRAPHOS was found to give higher enantioselectivity than both ***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl*** (BINAP) and ***(+)-trans-(2S,3S)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene*** (NORPHOS). Alkylation using other malonic acid derivatives gave similar optical yields. The product enantiomeric excess was reported to be greatly dependent upon the method of catalyst preparation.

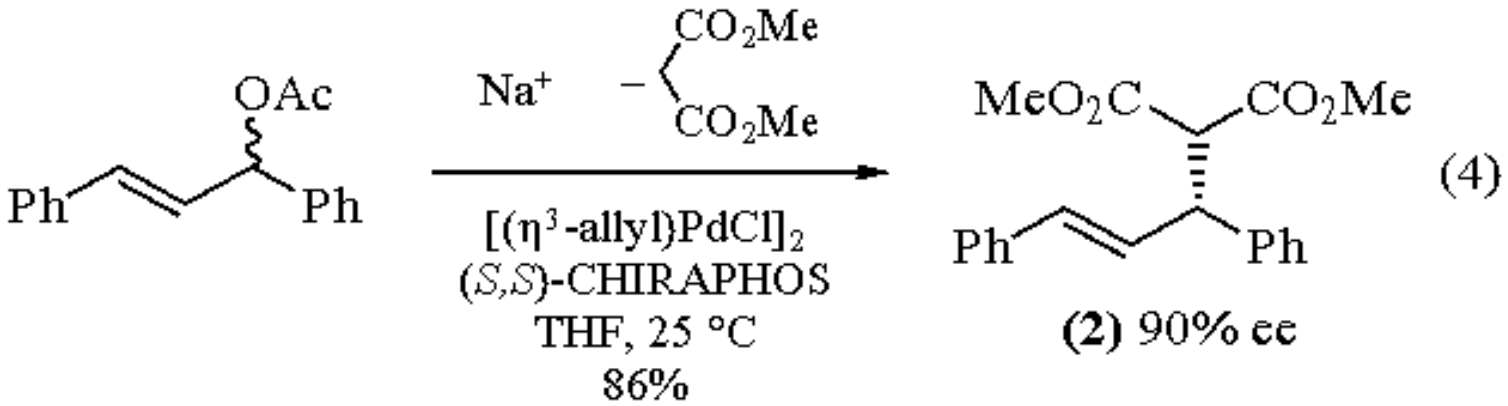

Alkene Hydroarylation.

The enantioselective addition of aryl iodides to norbornene has been reported using a palladium(II) complex of (*S*,*S*)-CHIRAPHOS. The reaction of norbornadiene with 4-methoxyiodobenzene proceeded with 30% ee (eq 5).[5] Enantioselectivities were dependent upon phosphine structure (see ***(+)-trans-(2S,3S)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene***).

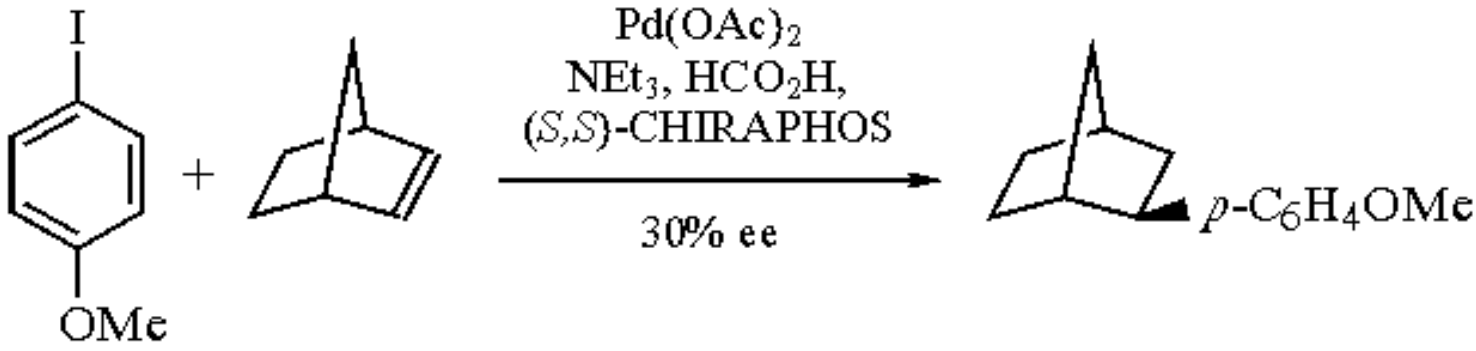

(5)

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1,2-Bis(diphenylphosphino)ethane

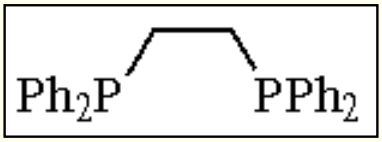

[1663-45-2] · $C_{26}H_{24}P_2$ · 1,2-Bis(diphenylphosphino)ethane · (MW 398.42)

(ligand for metal-catalyzed allylic alkylation;[1] decarboxylation of allylic esters;[2] 1,3-diene synthesis;[3] cycloaddition reactions;[4] carbonylation reactions[5])

Alternate Name: DIPHOS; dppe.

Physical Data: mp 140-142 °C.

Solubility: sol THF, $CHCl_3$, CH_2Cl_2, Et_2O, and other organic solvents.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: solutions are readily oxidized to the phosphine oxide and should be handled under N_2 or Ar. Solid samples can be handled in air. DIPHOS exhibits cytotoxic activity.

Allylation.

DIPHOS has been extensively used for palladium-catalyzed addition of nucleophiles to allylic substrates. Addition of enolates to allylic acetates provides a convenient method for the allylation of ketones (eq 1).[1] A variety of nitrogen[6] and sulfur[7] nucleophiles can also be utilized. Addition of diethyl sodiomalonate to vinylcyclopropyl tosylates produces methylenecyclopropanes (eq 2).[8] Regioselective alkylation of allylic dicarbonates occurs at the primary carbonate followed by conversion to vinylcyclopropanes (eq 3).[9] Addition of nucleophiles to propargyl carbonates is also catalyzed by palladium complexes of DIPHOS.[10] β-Keto esters with only one active hydrogen give double alkylation products (eq 4). The reaction of propargylic carbonates with β-dicarbonyl compounds which contain two active hydrogens results in monosubstitution followed by intramolecular *O*-alkylation to form 4-methylene-4,5-dihydrofurans (eq 5).

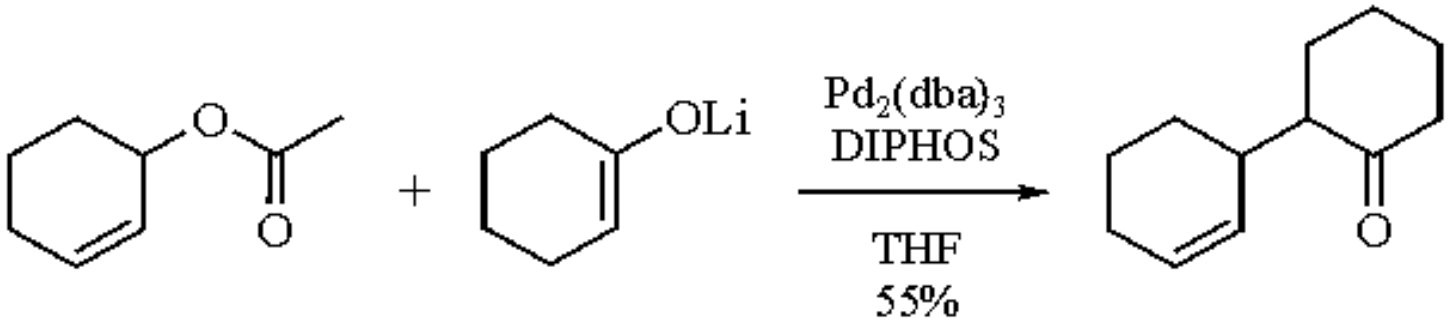
O
O
+
OLi
Pd2(dba)3
DIPHOS
THF
55%
O

(1)

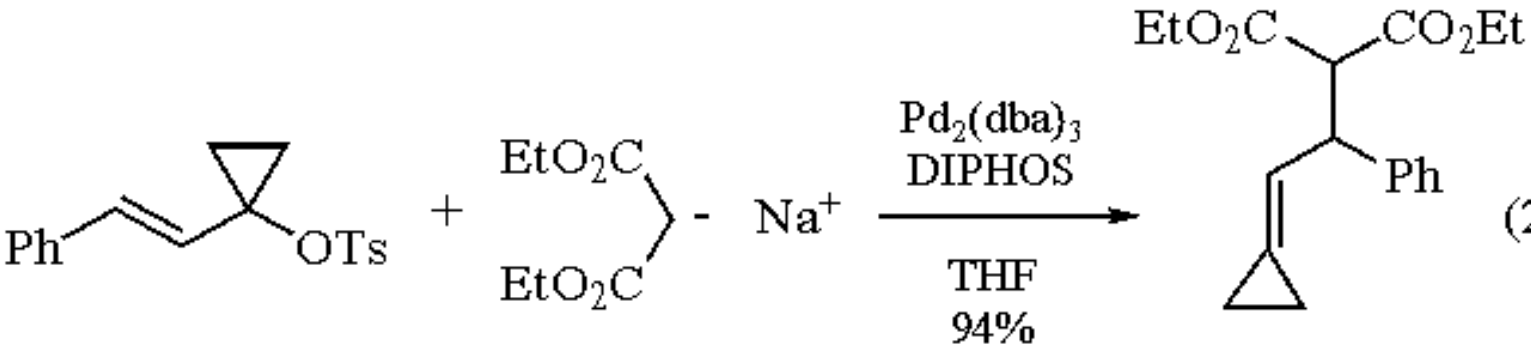
Ph
OTs
+
EtO2C
EtO2C
- Na+
Pd2(dba)3
DIPHOS
THF
94%
EtO2C
CO2Et
Ph

(2)

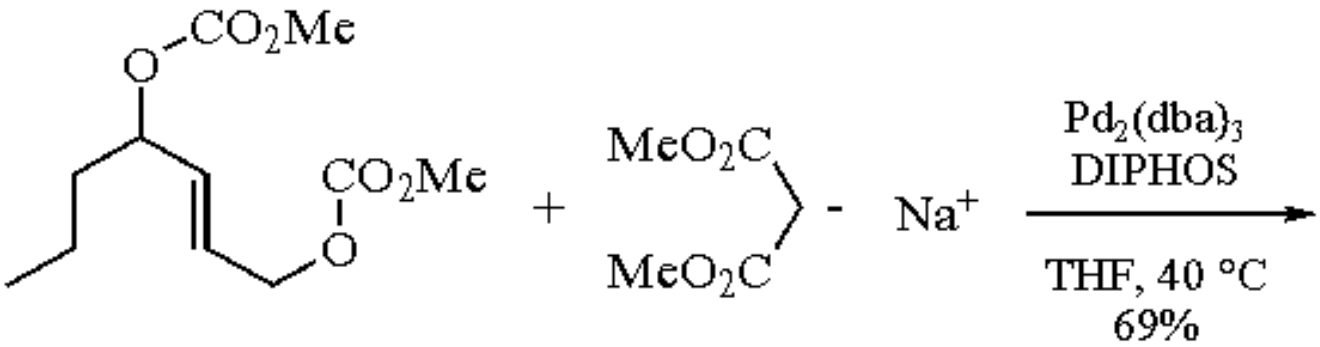
O
CO2Me
CO2Me
O
+
MeO2C
MeO2C
- Na+
Pd2(dba)3
DIPHOS
THF, 40 °C
69%

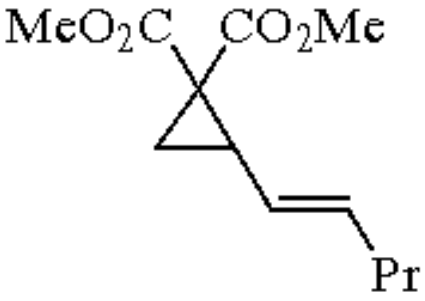
MeO2C
CO2Me
Pr

(3)

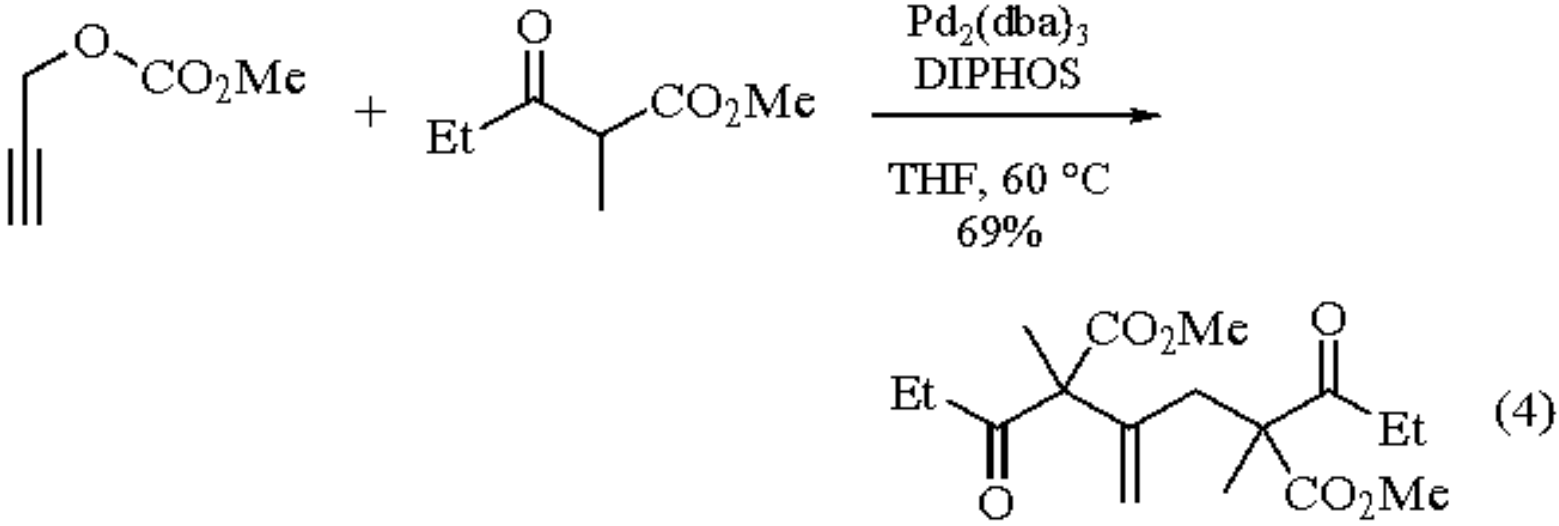

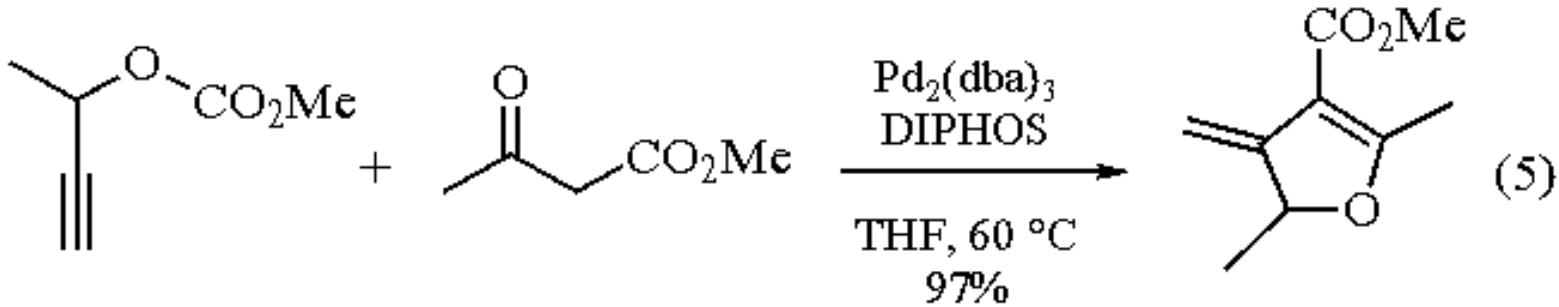

Decarboxylation of Allylic Esters.

Palladium-DIPHOS catalyzes the decarboxylation of allyl esters (eq 6).[2] *O*-Allyl dithiocarbonates undergo loss of COS with palladium(0)-DIPHOS to give thioethers.[11] Allyl carbonates and *S*-allyl dithiocarbonates fail to react under similar conditions.

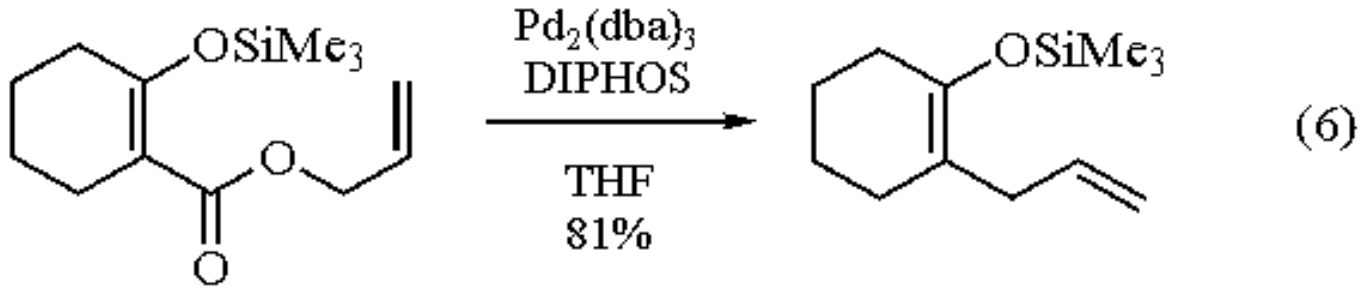

1,3-Diene Synthesis.

Palladium-DIPHOS complexes catalyze the formation of 1,3-dienes from the reaction of allenes, vinyl halides, and nucleophiles (eq 7).[3] Use of benzylic halides leads to substituted vinylarenes.

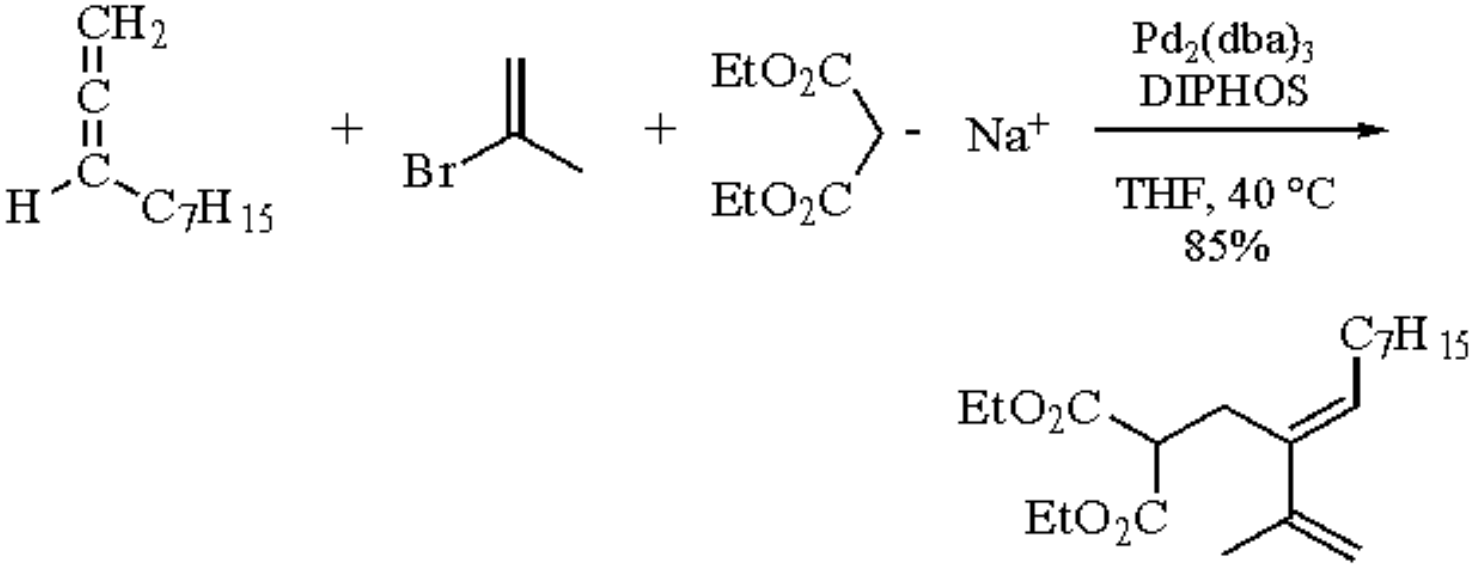

(7)

Cycloaddition Reactions.

The [3 + 2] cycloaddition of Pd-trimethylenemethane intermediates with alkenes provides access to methylenecyclopentanes (eq 8). Electron-deficient alkenes with ester, nitrile, and sulfone substituents readily undergo reaction. The homo-Diels-Alder cycloaddition of norbornadiene with alkynes is catalyzed by a cobalt-DIPHOS complex (eq 9).[12] Use of optically active phosphines produces deltacyclenes in high enantiomeric excesses (see ***(+)-trans-(2S,3S)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene*** (NORPHOS)).

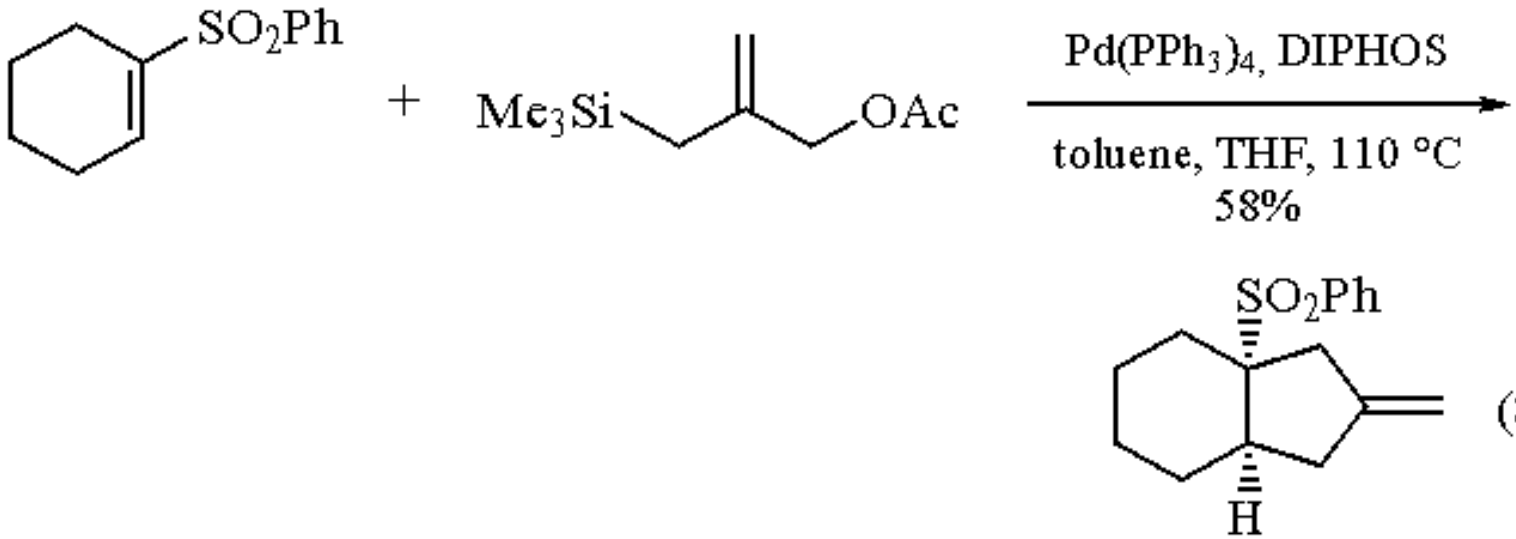

(8)

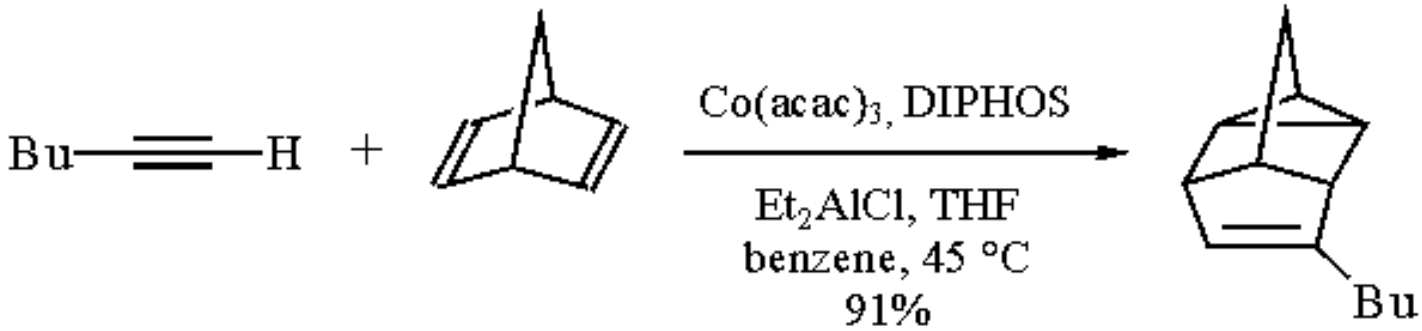

(9)

Carbonylation Reactions.

Palladium-DIPHOS catalyzes the alkoxycarbonylation of 3-chlorobutene in ethanol at 1 atm to give ethyl 3-pentenoate.[5] Carbonylation of propargyl carbonates at 15 atm produces dienoic esters (eq 10).[13]

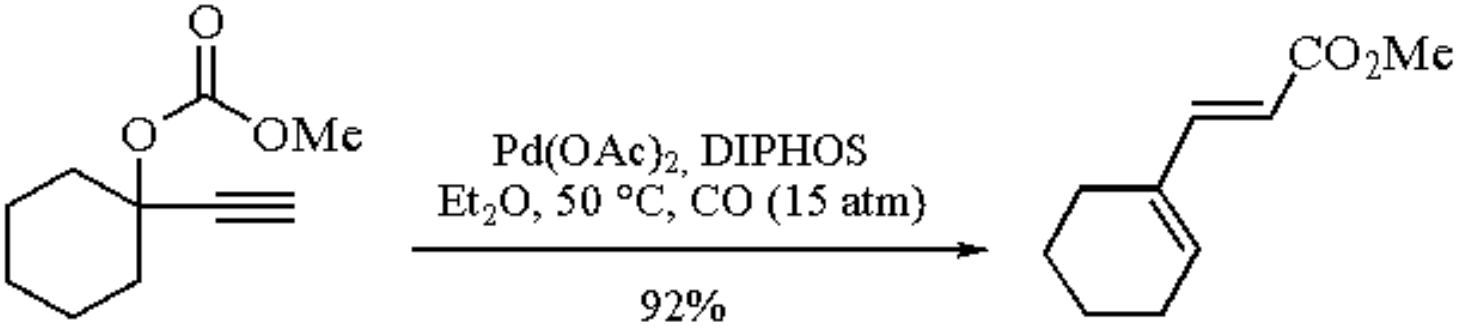

(10)

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1,2-Bis(diphenylphosphino)ethane Tetrabromide[1]

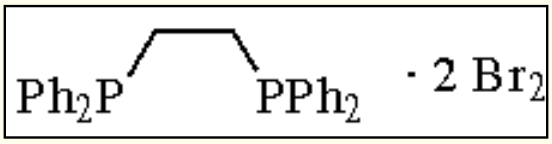

[7726-95-6] · $C_{26}H_{24}Br_4P_2$ · 1,2-Bis(diphenylphosphino)ethane Tetrabromide · (MW 718.04)

(reagent capable of effecting the conversion of alcohols and tetrahydropyranyl ethers into bromides rapidly and efficiently in the presence of other sensitive functional groups[1])

Solubility: sol CH_2Cl_2.

Preparative Method: generated in situ by treatment of 1,2-bis(triphenylphosphino)ethane with 2 equiv of bromine in dry dichloromethane at 0 °C under an inert atmosphere.[1]

Handling, Storage, and Precautions: the usual care should be taken to avoid contact of the skin with liquid bromine.

Conversion of Alcohols and THP Ethers to Bromides.

A frequently required synthetic transformation is the conversion of alcohols or protected forms thereof into the corresponding bromides or iodides. Although a myriad of reagents are available for performing this interconversion,[2] many are too harsh to operate successfully on highly sensitive molecules. Some time ago, ***Triphenylphosphine Dibromide*** was recognized to be capable of effecting the formation of bromides directly from tetrahydropyranyl ethers.[3,4] More spectacular still is the ability of 1,2-bis(diphenylphosphino)ethane tetrabromide to effect either of the preceding chemical changes in rapid fashion under extraordinarily mild conditions (eqs 1-3).[1] As can be seen in these examples, double and triple bonds, *t*-butyldimethylsilyl ethers, and carboxylate esters are stable in the presence of this reagent.

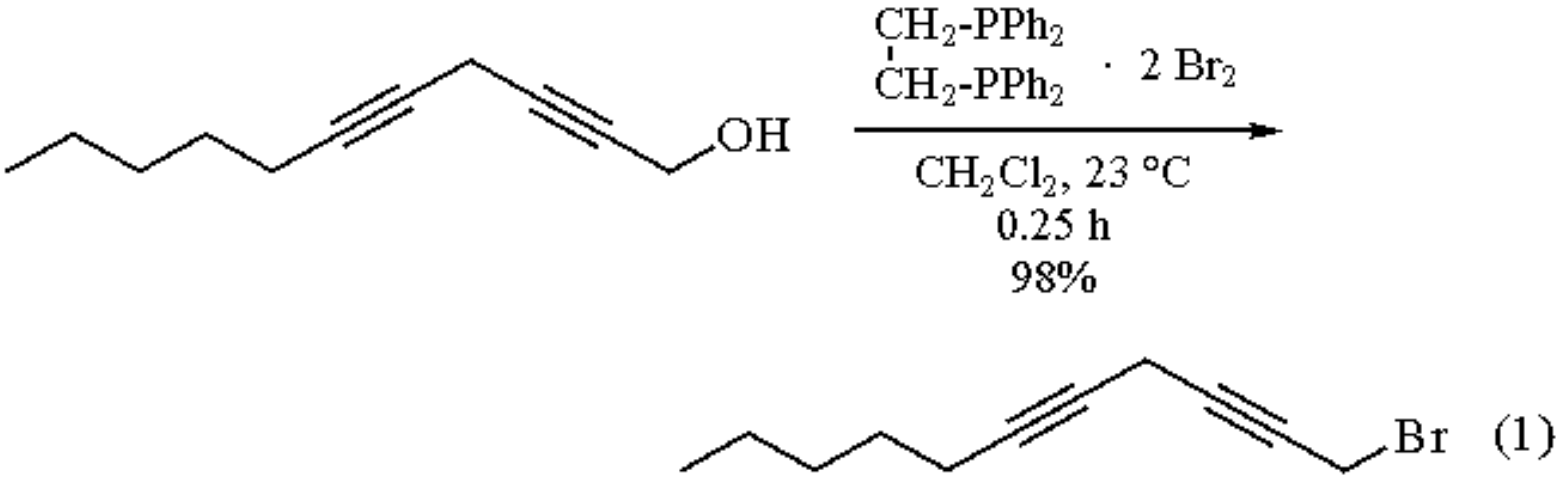

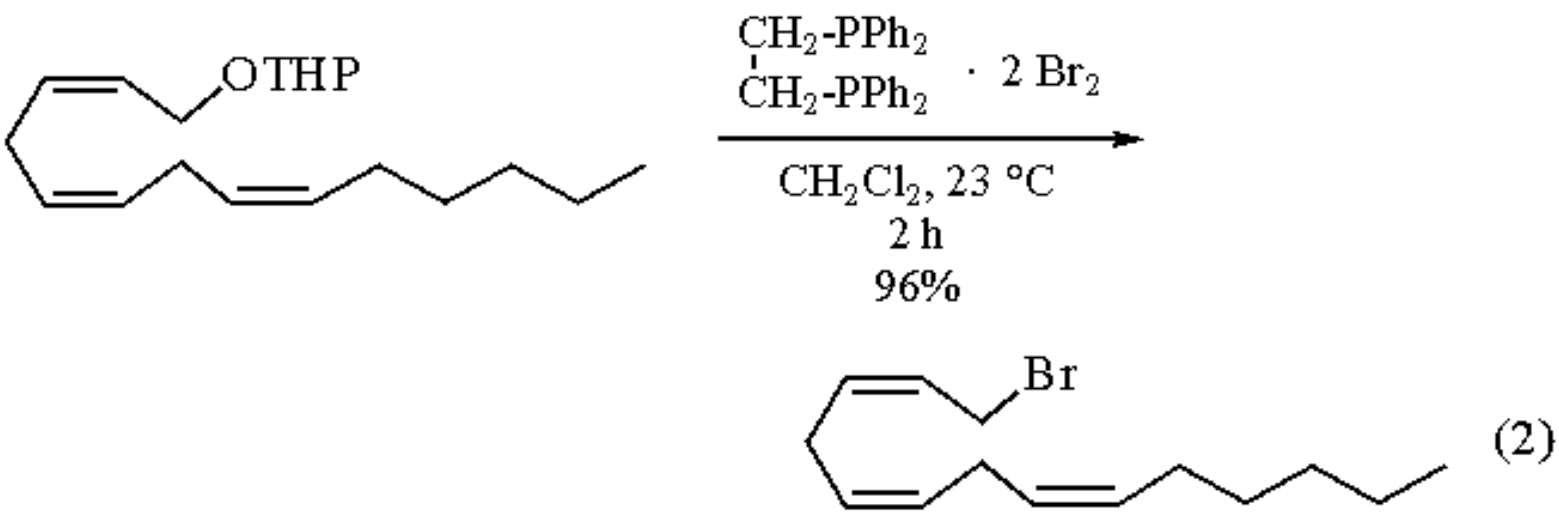

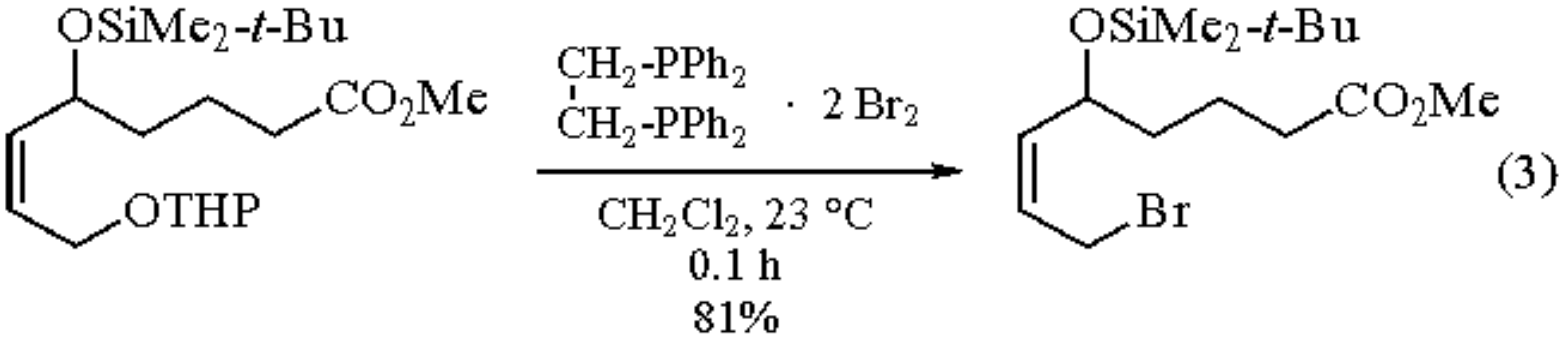

Usefully, the phosphorus-containing byproducts of this halogenation are not soluble in a solvent system composed of pentane/ether/dichloromethane (2:1:0.5). In the instances where the bromide product dissolves in this mixture, simple dilution and filtration suffice for isolation purposes.[1]

Although the inertness of the allylic silyl ether moiety demonstrated in eq 3 is noteworthy, the extraordinary mildness of this brominating agent is best reflected in its capability to function as advertized on the sensitive furanocembranoid precursors exemplified in eqs 4 and 5.[5,6] Comparable efficiency was not at all closely approximated by other means.

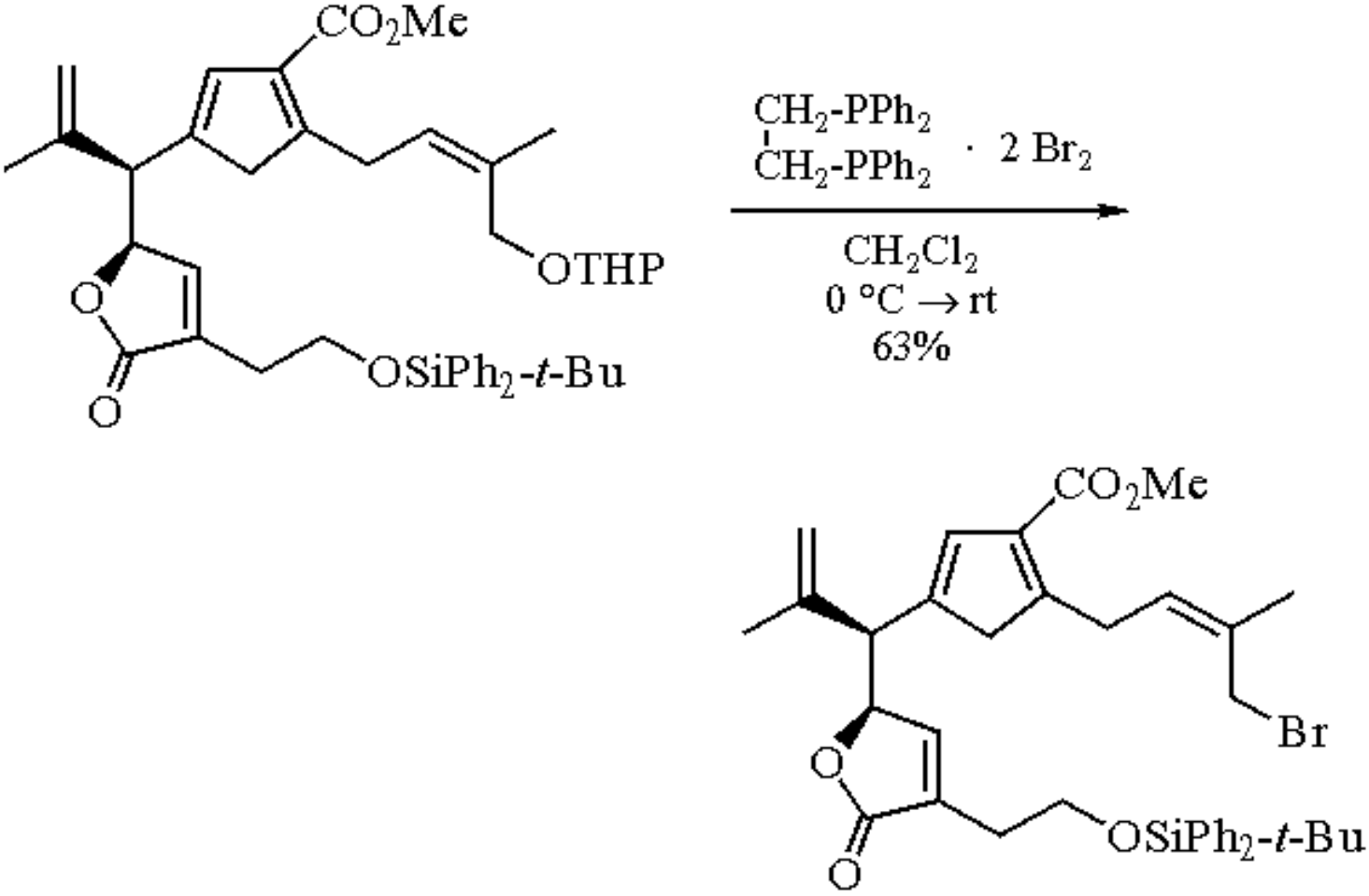
CO2Me
OTHP
OSiPh2-t-Bu
O
O
CH2-PPh2
CH2-PPh2
· 2 Br2
CH2Cl2
0 °C → rt
63%
CO2Me
Br
OSiPh2-t-Bu
O
O

(4)

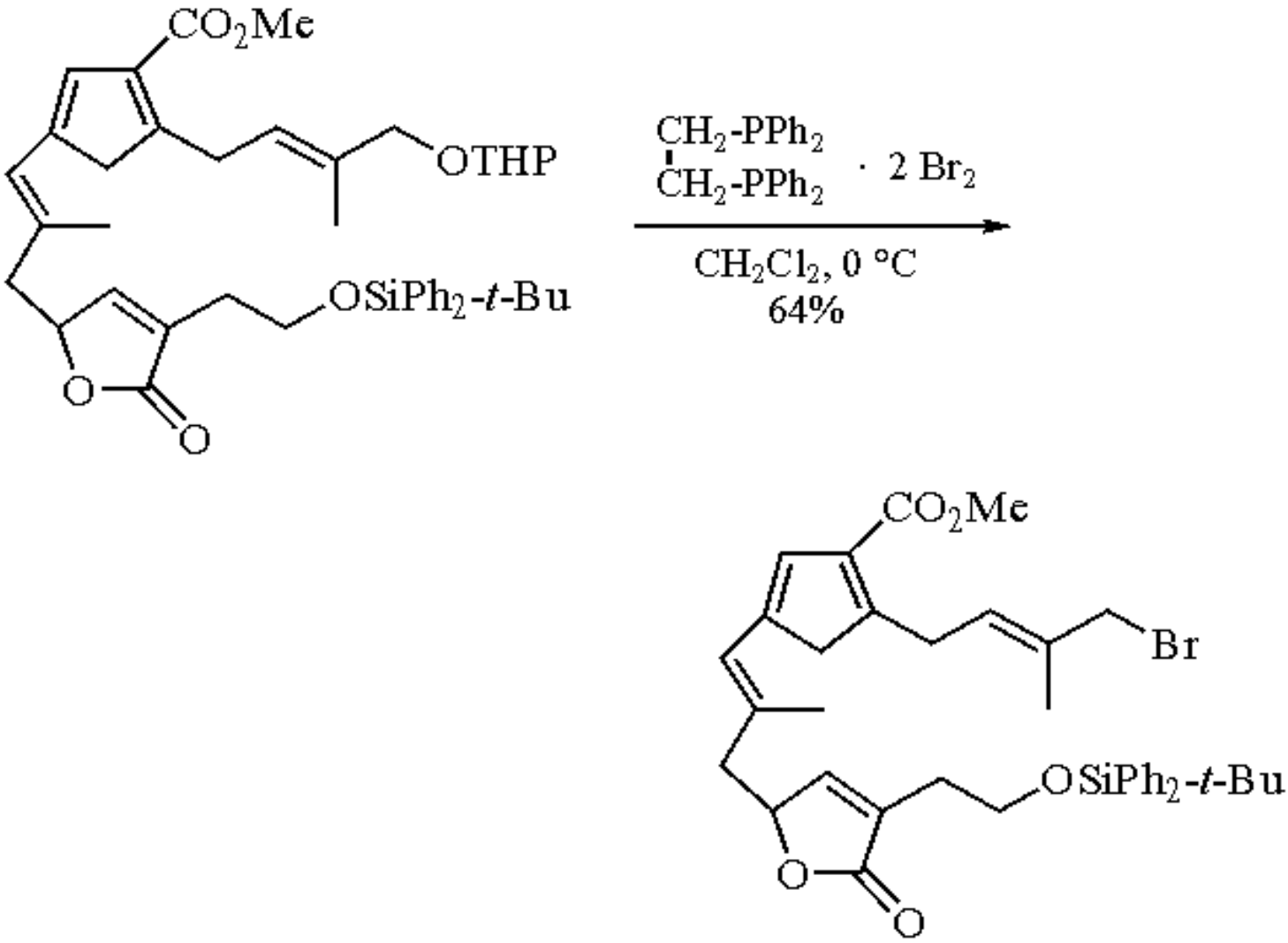

(5)

If bromine is replaced by iodine, 1,2-bis(diphenylphosphino)ethane tetraiodide is generated in situ. This reagent has given indication of being equally effective in delivering iodides (eqs 6 and 7).[1]

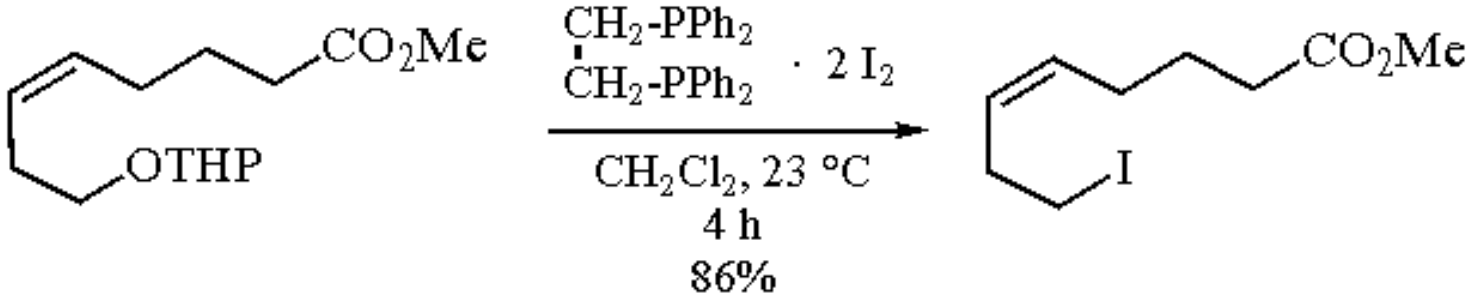

(6)

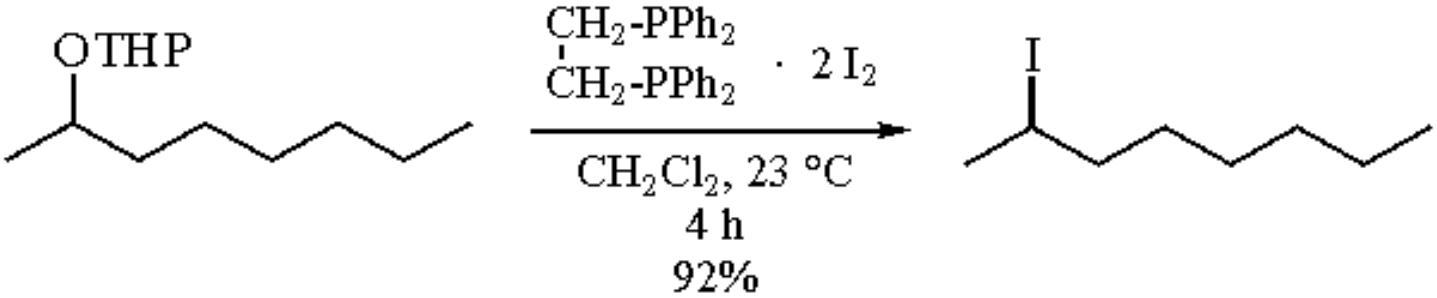

(7)

Inversion of configuration has been shown to operate in these interconversions, (*R*)-(-)-2-octanol giving rise to (*S*)-(-)-2-bromooctane of high optical purity.[1]

---

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1,1´-Bis(diphenylphosphino)ferrocene[1]

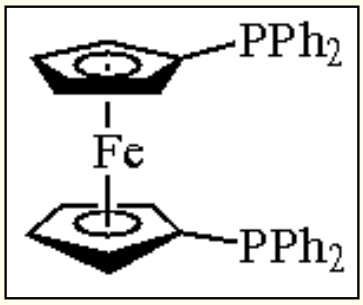

[12150-46-8] · $C_{34}H_{28}FeP_2$ · 1,1´-Bis(diphenylphosphino)ferrocene · (MW 554.39)

(chelating ligand capable of supporting hydroformylations,[2] cross coupling,[7] allylation,[20] carbonylative coupling,[23] and other catalytic processes employing Group 9 and 10 transition metals)

Alternate Name: dppf.

Physical Data: mp 183-184 °C dec.

Solubility: very sol $CHCl_3$, CH_2Cl_2, and alcohol; sol pentane; insol H_2O.

Form Supplied in: white solid, <97% purity, widely available.

Handling, Storage, and Precautions: the reagent is stable to air, unaffected by H_2O and can be stored for long periods of time. The toxic properties are not known.

Homogeneous Catalysis.

The reagent is an effective supporting ligand for a wide variety of catalytic reactions involving Group 9 and 10 metals. Rhodium-catalyzed hydroformylations of alkenes employing dppf result in higher regioselectivity for the linear aldehyde than when monophosphines are used.[2] The *cis* chelating nature of the ligand, compared to monophosphines, also allows lower ligand/metal ratios. The use of dppf in the rhodium-catalyzed hydroformylation of allyl alcohol, which is a convenient route to 1,4-butanediol, gives higher linear/branched selectivities than ***Triphenylphosphine*** under equivalent conditions (eq 1).[3] Likewise, slightly enhanced regioselectivities favoring the linear product are observed in the dppf supported hydroformylations of methyl acrylate and methyl methacrylate, a useful route to 1,3- and 1,4-difunctional compounds.[4] The dppf ligand demonstrates a very high degree of regioselectivity when employed in the palladium-catalyzed hydroesterification and hydrocarboxylation of perfluoroalkyl and perfluoroaryl alkenes (eq 2). With its use, linear/branched ratios of close to 100 have been observed.[5]

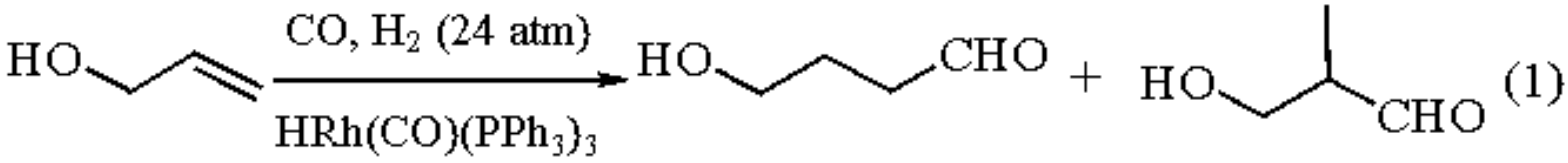

dppf:Rh ratio 8.5	87.9	12.1
PPh_3:Rh ratio 8.5	63.4	36.6

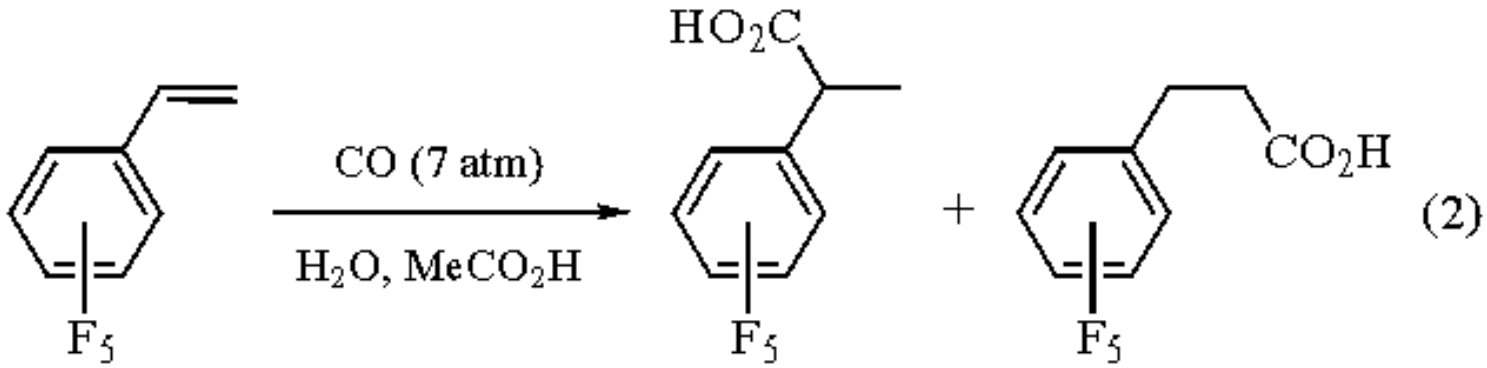

$PdCl_2(PPh_3)_2$	27	73
$PdCl_2$(dppf)	1	99

Nickel and palladium phosphine complexes catalyze cross-coupling reactions of organic electrophiles (R-X) and organometallic reagents (R´-M), demonstrating a very high degree of selectivity in product formation (R-R´).[6] This process has been most extensively used in coupling reactions of reagents which lack β-hydrogens, and are not susceptible to β-hydride eliminations. However, the palladium-dppf complex, ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***, cleanly and selectively catalyzes cross couplings of secondary alkyl organometallic reagents without the usual side reactions of isomerization and reduction observed with other phosphines (eq 3).[7] Likewise, the nickel complex, $NiCl_2$(dppf), is the most selective catalyst for the cross coupling of tertiary alkyl Grignard reagents with vinyl halides.[8] The unprecedented effectiveness of the dppf complexes in catalyzing carbon-carbon bond formation is attributed to the large value of the P-Pd-P bond angle in these rigid ligands.[7b]

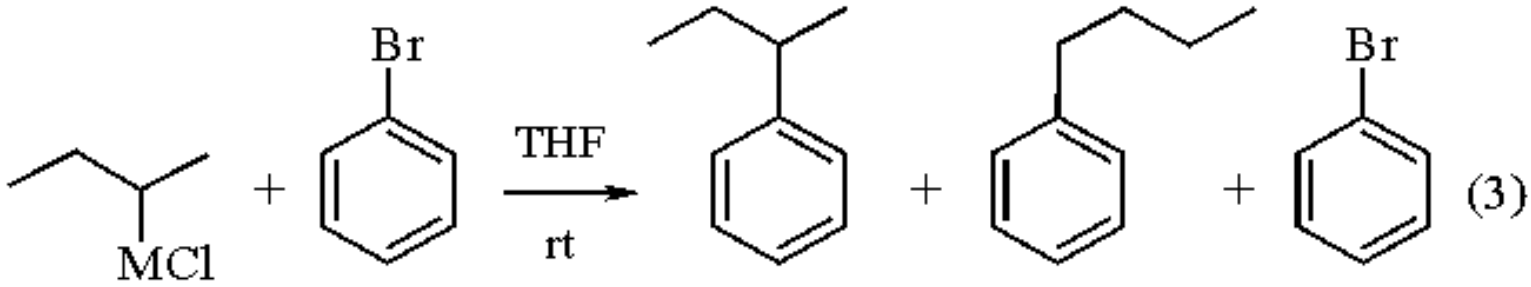

M = Mg, $PdCl_2(PPh_3)_2$, 24 h	4%	6%	31%
$PdCl_2$(dppf), 1 h	95%	0%	0%
M = Zn, $PdCl_2(PPh_3)_2$, 24 h	1%	2%	78%
$PdCl_2$(dppf), 20 h	100%	0%	0%

Cross-coupling reactions of organic halides with vinyl Grignards,[9] copper acetylides,[10] and organotin compounds[11] are most efficiently promoted by Pd^{II} dppf complexes, giving high yields, under mild conditions, with little or no homocoupling. The $PdCl_2$(dppf)-catalyzed coupling of dihaloaromatic compounds with ***Bis(1-methoxy-2-methyl-1-propenyloxy)dimethylsilane*** affords a new, simple, high-yield route to conducting polyarenediylvinylenes (eq 4).[12] The direct cyanation of nonactivated aryl halides and triflates with ***Potassium Cyanide*** is catalyzed by various nickel and palladium phosphine catalysts.[13] Again, the bis-chelating ligand dppf has been demonstrated to be the most effective ligand for this reaction, giving high yields of nitriles in a variety of solvents.[13b]

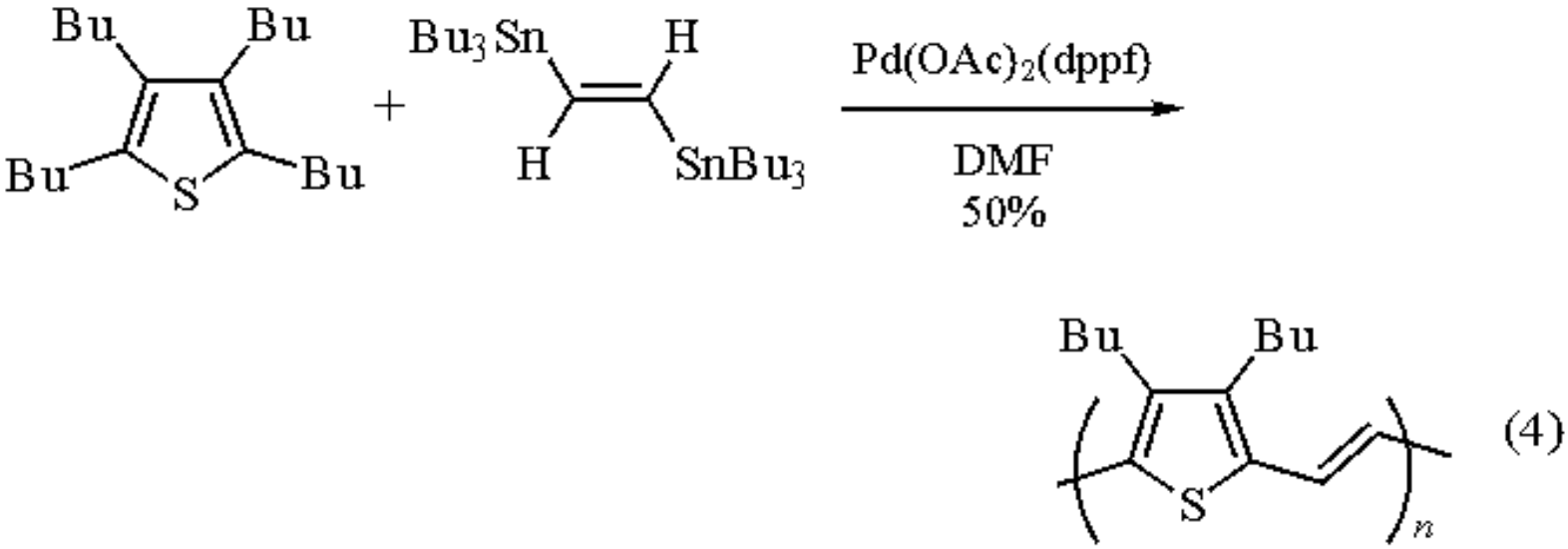

Diphosphine Ni^{II} or Pd^{II} complexes are the most effective catalysts for the preparation of alkylated heterocycles.[14] The $PdCl_2$(dppf)-catalyzed coupling of 2-(methylthio)oxazoles and -oxazolines with organometallic reagents results in high yields of the synthetically useful 2-alkyl or 2-aryl substituted heterocycles (eq 5).[15]

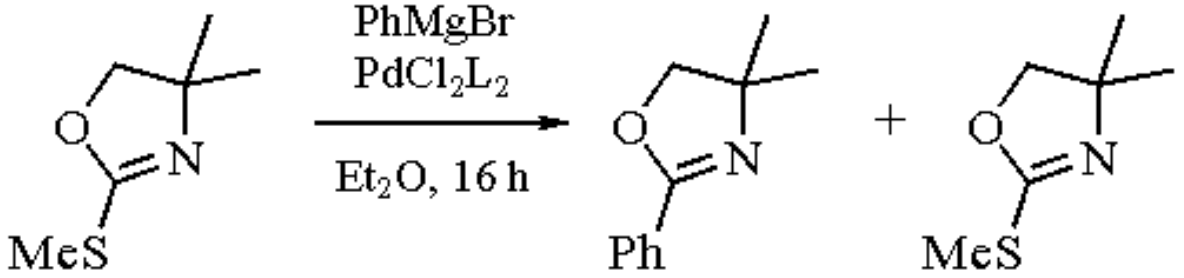

(5)

$L_2 = (PPh_3)_2$	24%	26%
dppf	99%	

The palladium-dppf-catalyzed cross coupling of organoboron compounds with organic halides is a useful method for carbon-carbon bond formation.[16] The hydroboration of haloalkyldienes, followed by intramolecular coupling, affords five- and six-membered rings in high yield.[17] The potential versatility of this process is demonstrated by the ready formation of stereodefined exocyclic alkenes (eq 6). Bipyridines are readily prepared by the palladium-dppf-catalyzed coupling of pyridine boronic acids with substituted halopyridines.[18]

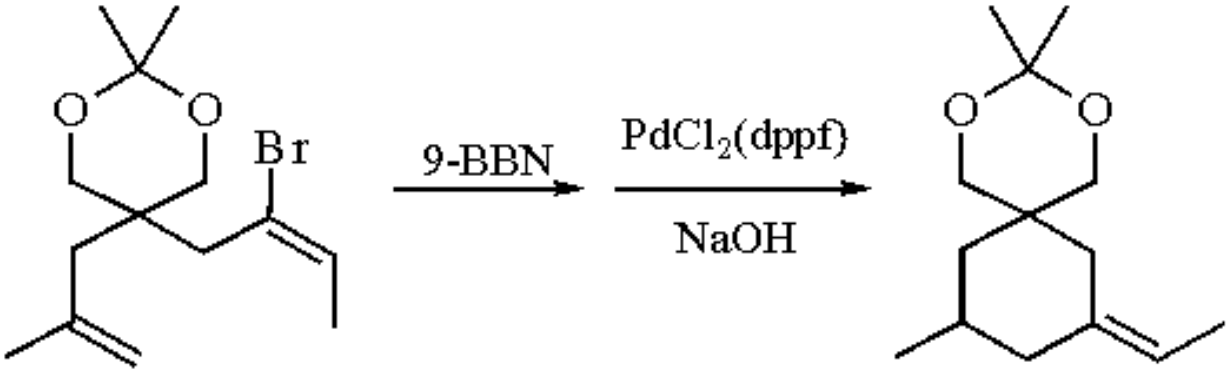

(6)

75%

A particularly useful synthetic process is the catalyzed nucleophilic substitution of allylic compounds.[19] The cross coupling of allylic ethers with Grignard reagents is efficiently catalyzed by the use of nickel and palladium complexes with dppf.[20] The two metals exhibit a useful regioselective divergence (eq 7).[20b] The nickel catalyst leads to carbon-carbon bond formation at the more substituted position while carbon-carbon bond formation occurs at the less substituted position with the palladium catalyst. The use of phosphine ligands other than dppf significantly degrades both the regioselectivity and efficiency of the catalyst. The fact that the isomeric silyl ethers (**1**) and (**2**) give identical product ratios argues strongly for a common π-allylmetal intermediate.

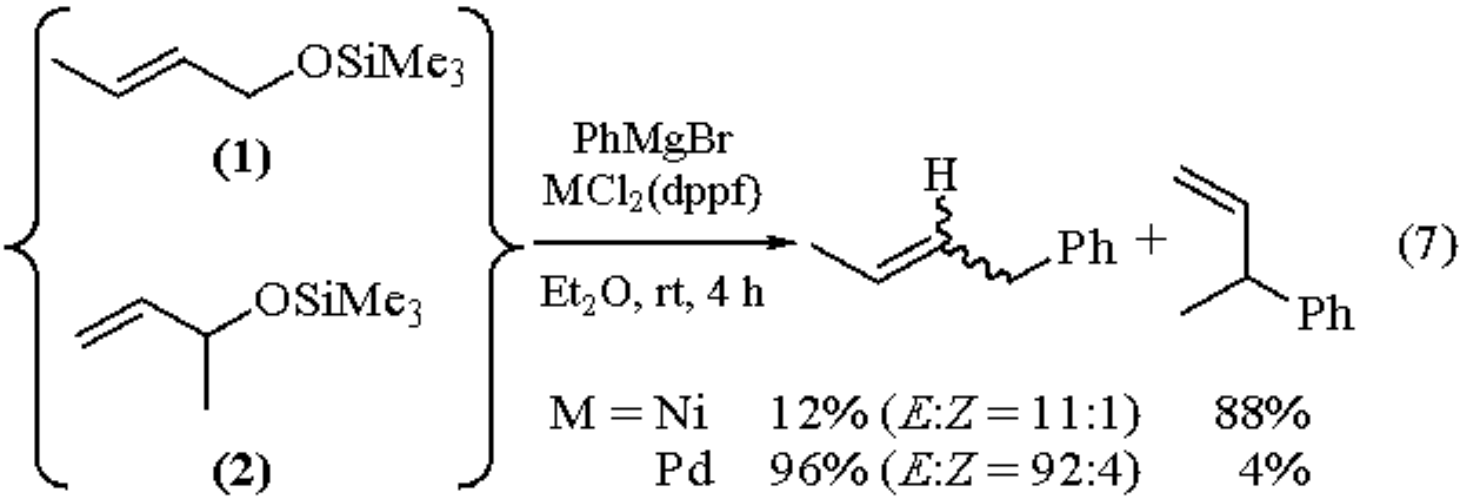

The stereochemical course of the reaction depends on the nature of the carbon nucleophile.[20b,21] A nonstabilized nucleophile such as an alkyl, aryl, or vinyl organometallic gives products with overall inversion of configuration, whereas a resonance stabilized nucleophile such as a malonate yields products with overall retention of configuration (eq 8).

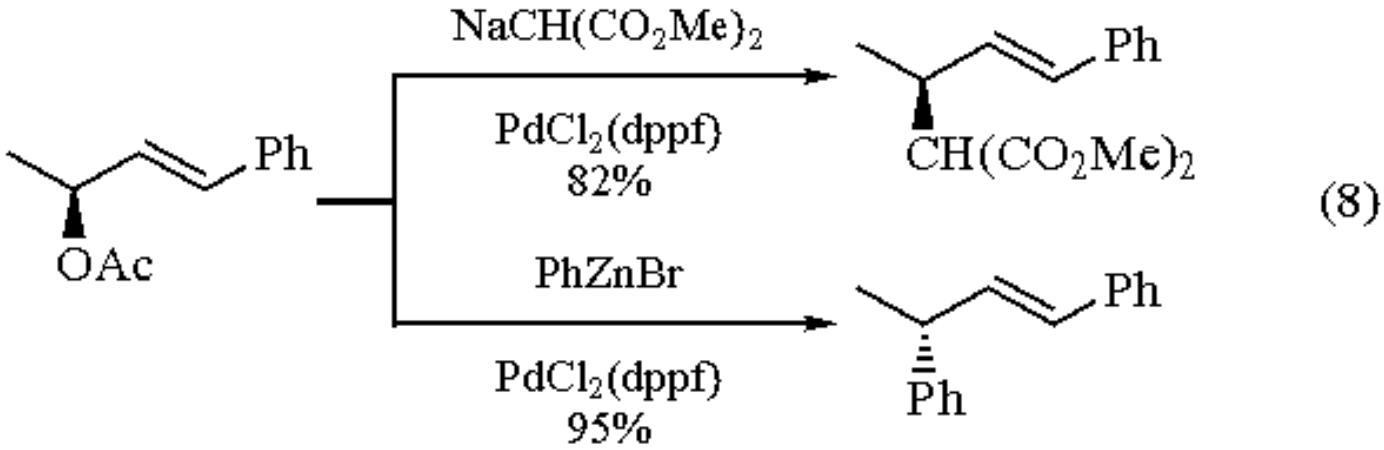

2-Butenylene dicarbamates readily undergo cyclization in the presence of phosphine-palladium(0) catalysts to produce 4-vinyl-2-oxazolidones in high yields.[22] The use of bis-chelating phosphines such as dppf increases the regioselectivity of the reaction, favoring attack of the Pd^0 species on the allylic substrate at the sterically less hindered carbon (eq 9).

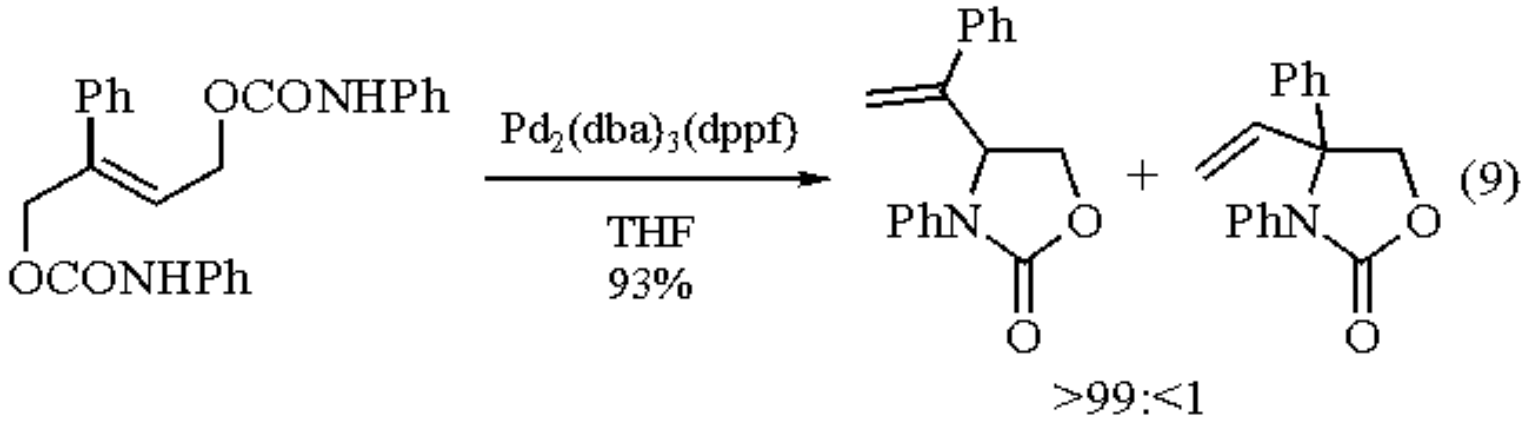

The palladium-catalyzed carbonylative coupling of organic halides with terminal alkynes offers a mild, simple, and

selective synthesis of unsymmetrical alkynic ketones.[23] In most cases, $PdCl_2$(dppf) is the best catalyst among a wide range of Pd^{II}-phosphine or Pd^{II}-arsine complexes. The dppf ligand profoundly increases the reactivity of the catalyst, such that selective ketone formation is possible at atmospheric pressures of carbon monoxide. Palladium-catalyzed carbonylative coupling of *o*-iodophenol with phenylacetylene, followed by in situ cyclization, provides a direct entry to the basic skeletons of the biologically active isoflavanones (**3**) and aurones (**4**) (eq 10).[24] The regiochemical outcome of the reaction can be altered by the addition of base to the reaction.

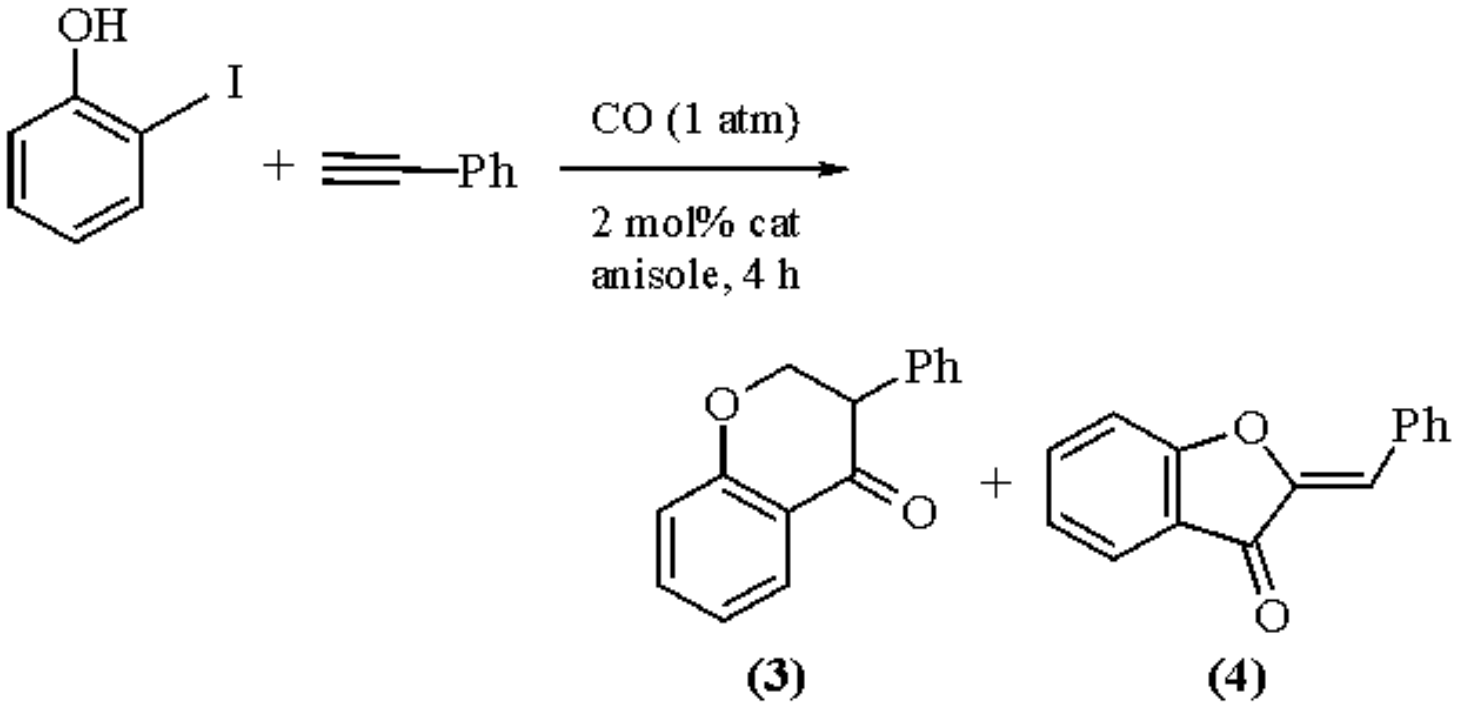

(10)

	(3)	(4)
$Pd(PPh_3)_3$	0%	68%
$Pd(OAc)_2$(dppf)	0%	100%
$Pd(OAc)_2$(dppf), DBU	92%	8%

Macrocyclic lactones having from 12 to 16 members are synthesized by the Pd-phosphine-catalyzed carbonylative coupling of esters having vinylstannane and vinyl triflate termini.[25] These couplings occur under mild conditions, tolerate a range of functional groups, are regiospecific, and are insensitive to ring size. However, formation of linear oligomers results in modest yields of lactone. A polystyrene supported dppf ligand system has been synthesized by copolymerization of styrene, *p*-divinylbenzene, and bis(diphenylphosphino)vinylferrocene.[26] Palladium catalysts supported on this polymer are more selective for large ring lactones, and linear oligomerization is suppressed (eq 11).

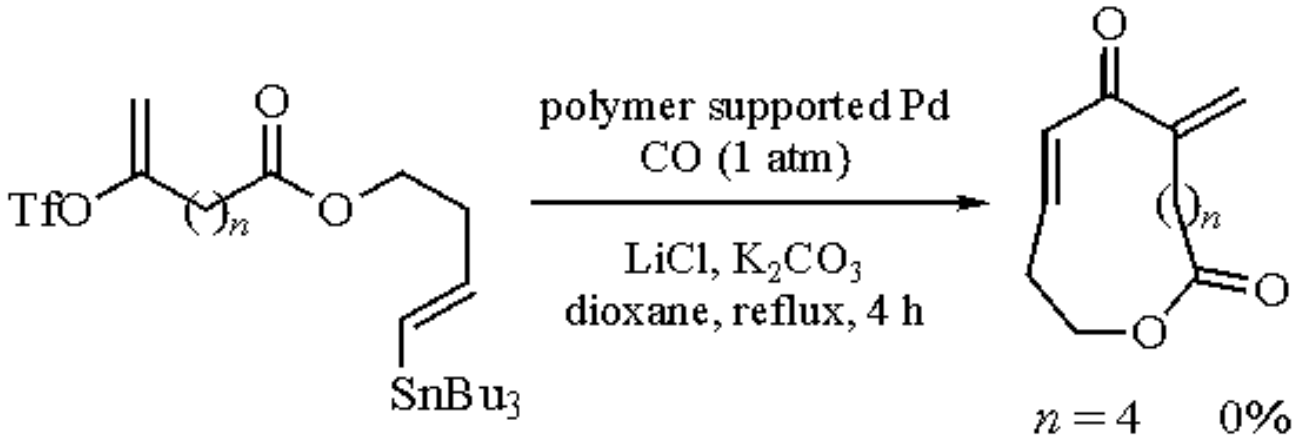

(11)

$n = 4$	0%
5	28%
6	78%
7	76%
8	72%

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1,3-Bis(diphenylphosphino)propane

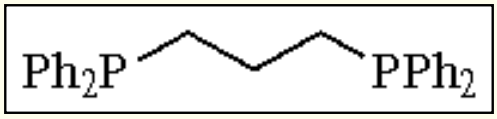

[6737-42-4] · $C_{27}H_{26}P_2$ · 1,3-Bis(diphenylphosphino)propane · (MW 412.45)

(ligand for metal-catalyzed substitution reactions of aryl and vinyl triflates,[1] halides,[2] and carbonates;[3] carbonylation reactions;[4] Grignard coupling;[5] diene alkylation;[6] macrocycle synthesis[7])

Alternate Name: dppp.

Physical Data: mp 63-65 °C.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: solutions are readily oxidized to the phosphine oxide and should be handled under N_2 or Ar. Solid samples of dppp are air stable.

Substitution Reactions.

Metal complexes of dppp catalyze the substitution of aryl triflates with a variety of reagents. A palladium complex of dppp catalyzes the deoxygenation of phenols via the corresponding triflate (eq 1).[1] A variety of functional groups can be introduced, including acetyl,[2] vinyl,[8] and phosphoryl[9] substituents. These reagents also catalyze the substitution reaction of aryl bromides with vinyl ethers (eq 2).[2] A palladium-dppp complex has been used for the conversion of allylic carbonates to sulfides (eq 3).[3]

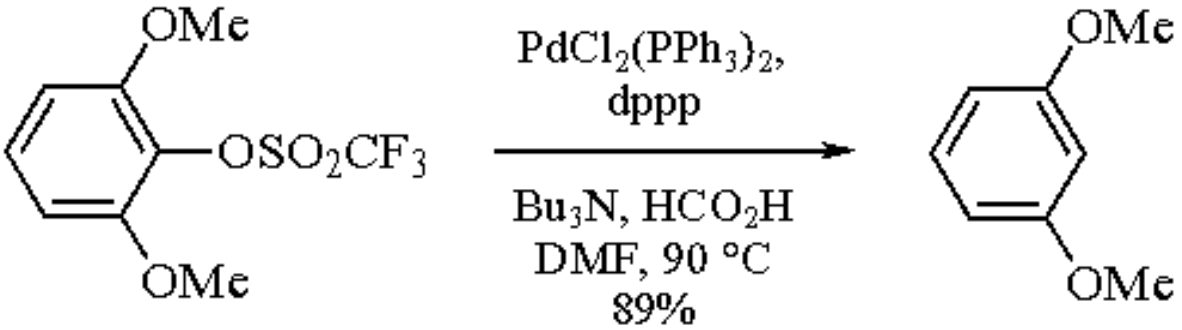

(1)

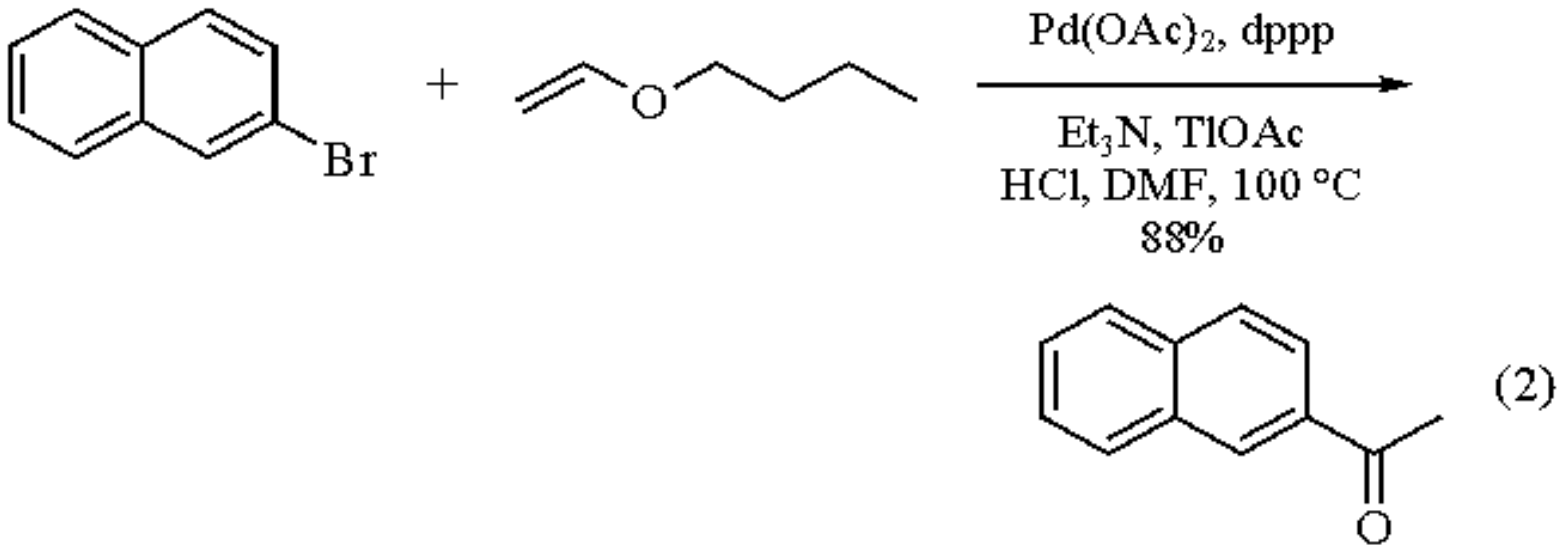

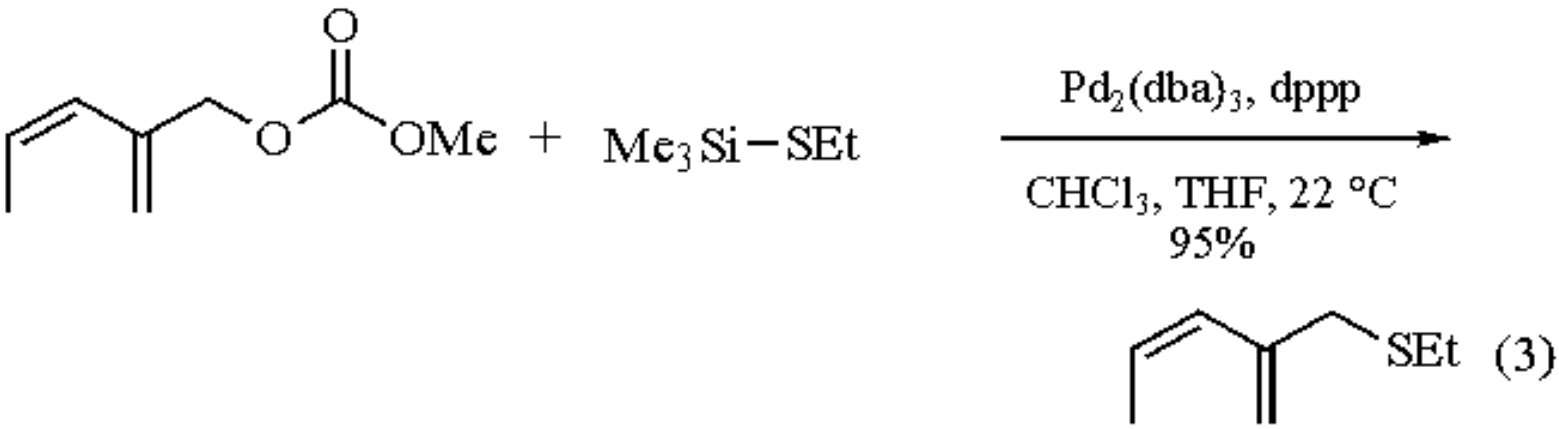

Carbonylation Reactions.

Palladium-dppp complexes catalyze the high-pressure carbonylation of allylic amines to give the corresponding amides (eq 4).[4] Aryl triflates undergo carbonylation in MeOH with the formation of the methyl ester (eq 5).[10] In the presence of alkynes, vinyl triflates are carbonylated to produce alkynyl vinyl ketones.[11] Aldehydes are decarbonylated in high yield by dppp in the presence of ***Carbonyl(chloro)bis(triphenylphosphine)rhodium(I)*** (eq 6).[12]

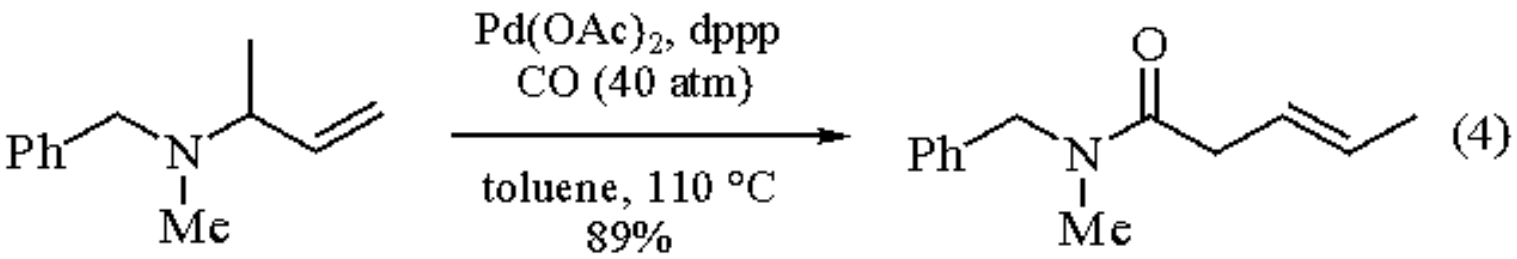

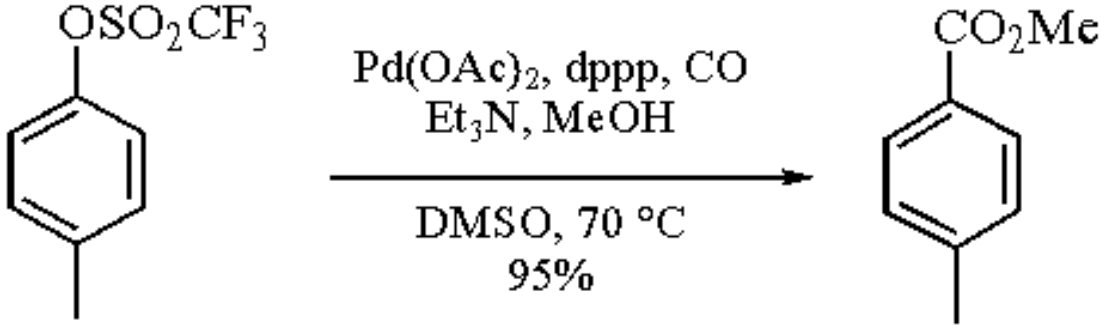

(5)

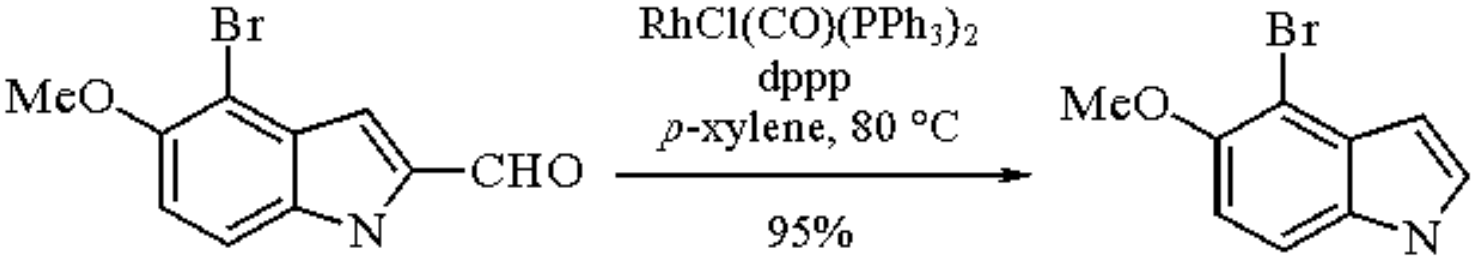

(6)

Grignard Coupling Reactions.

The coupling of aryl and alkyl halides with Grignard reagents is efficiently catalyzed by Ni complexes of dppp (eq 7).[5] The substitution of vinyl sulfides with ***Methylmagnesium Bromide*** in the presence of ***Dichlorobis(triphenylphosphine)nickel(II)*** and dppp leads to alkenes.[13]

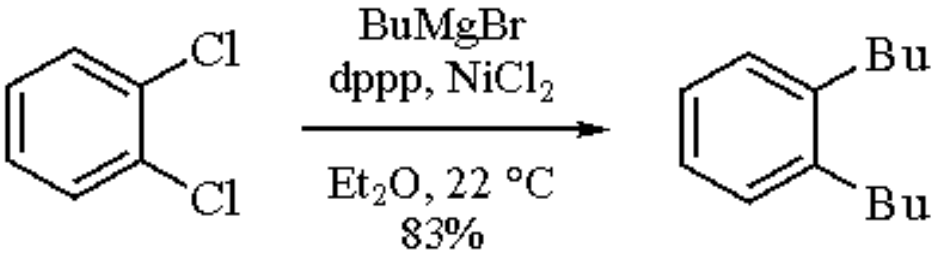

(7)

Diene Alkylation.

Nucleophilic addition of β-dicarbonyl enolates to dienes is catalyzed by Pd-dppp and NaOMe (eq 8).[6]

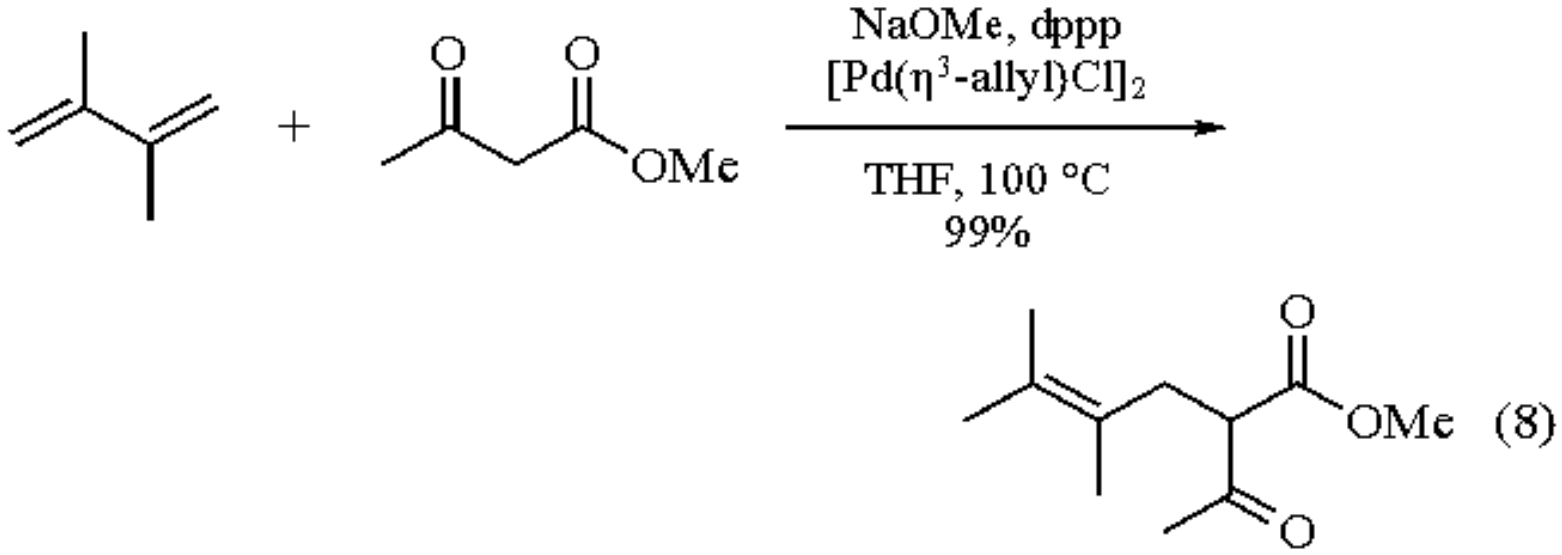

Macrocycle Synthesis.

The intramolecular, palladium-catalyzed reaction of allylic carbonates with substituted ethers produces macrocycles in high yield (eq 9).[7] The formation of 11- and 14-membered rings has been reported using dppp in combination with ***Tetrakis(triphenylphosphine)palladium(0)***.[7,14] Intermolecular reactions have also been reported.

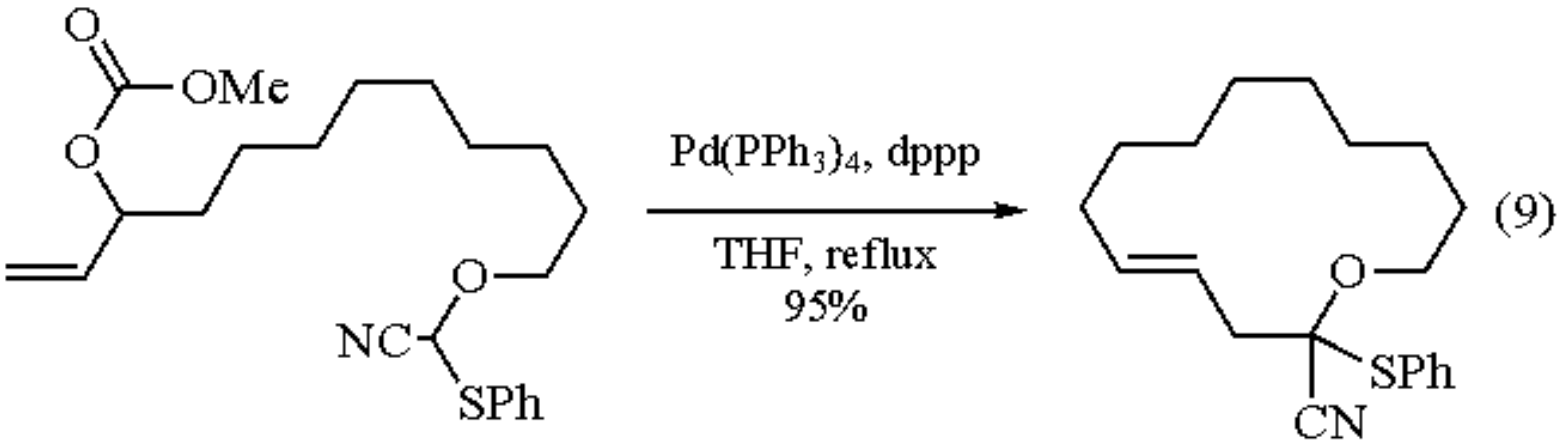

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Bis(2,2´-bipyridyl)silver(II) Peroxydisulfate

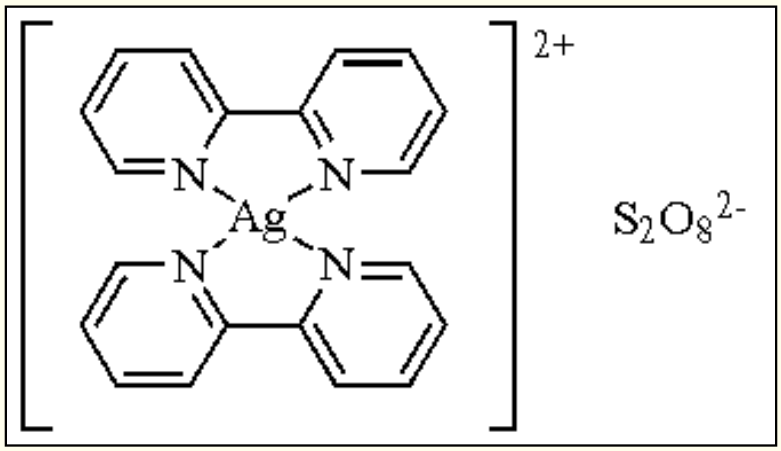

[47386-36-7] · $C_{20}H_{16}AgN_4O_8S_2$ · Bis(2,2´-bipyridyl)silver(II) Peroxydisulfate · (MW 612.36)

(one-electron oxidant capable of oxidizing electron-rich aromatic compounds in nucleophilic solvents)

Physical Data: mp 137 °C (dec).

Solubility: slightly sol acetic acid; increased by increasing concentration of acetate ions.

Analysis of Reagent Purity: contents of Ag^{II} can be assayed conveniently by addition of potassium iodide followed by iodometric titration.

Preparative Methods: oxidation of an aqueous suspension of silver nitrate in the presence of 2 equiv of 2,2´-bipyridyl by potassium peroxydisulfate.[1]

Handling, Storage, and Precautions: should be protected from light.

Aromatic Nuclear Substitution.

Electron-rich aromatic derivatives react with this reagent in acetic acid containing 0.5 M KOAc to give aryl acetates. Some examples of this stoichiometric reaction are given in Table 1. The reaction closely resembles the electrochemical oxidation of aromatic compounds; isomer distributions are quite similar. Of particular interest is the fact that, in many cases, yields higher than 100% were observed. This was explained by assuming Ag^{II} as the primary oxidant of the aromatic compound followed by reoxidation of the formed Ag^{I} by the counterion peroxydisulfate.[2]

Table 1 Nuclear Acetoxylation of Arenes using $Ag^{II}(bipy)_2S_2O_8$ in HOAc/0.5 M KOAc

Substrate	Isomer distribution			Yield (%)
	2-OAc	3-OAc	4-OAc	
Anisole	68	0.6	31	63
Biphenyl	21	0	79	18
Naphthalene[a]	95	5		63
4-Bromoanisole	100	0	0	35
4-Fluoroanisole	0	0	100	35
4-*t*-Butylanisole	100	0	0	63

[a]Isomer distribution refers to 1-acetoxy- and 2-acetoxynaphthalene, respectively.

Aromatic Side-Chain Substitution.

In the case of oxidation of methyl-substituted electron-rich aromatics, benzylic oxidation was observed. For example, 4-methoxytoluene gave, on oxidation in acetic acid/0.5 M KOAc, a mixture of 4-methoxybenzyl acetate and 4-methoxybenzyl alcohol in high yield.[2]

Catalytic Oxidations.

As indicated above, the counterion peroxydisulfate can act as a reoxidant for Ag^{I}. This was used in a catalytic version of the above reactions. Thus using a catalytic amount of either the Ag^{II} complex or AgOAc/2,2´-bipyridyl in acetic acid/0.5 M NaOAc and potassium peroxydisulfate as the oxidant, both nuclear and side-chain substitution can be achieved. The addition of barium acetate is important for a high turnover of the catalyst. For some examples, see Table 2.[2]

Table 2 Catalytic Acetoxylations of Some Aromatic Compounds

Substrate	Product	Yield (%)	Catalyst turnover
1,4-Dimethoxy-benzene	2-Acetoxy-1,4-dimethoxy-benzene	33	87
Anisole	Acetoxyanisoles	39	60
4-Bromoanisole	2-Acetoxy-4-bromoanisole	40	56
4-Methoxy-toluene	4-Methoxybenzyl-acetate	35[a]	75

[a] The byproduct 4-methoxybenzaldehyde, formed when using the pre-formed silver(II) complex as the catalyst, can be avoided by using AgOAc and 2,2¢bipyridyl instead.

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1,2-Bis(hydroxymethyl)benzene

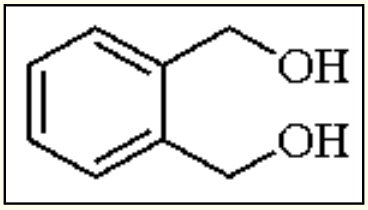

[612-14-6] · $C_8H_{10}O_2$ · 1,2-Bis(hydroxymethyl)benzene · (MW 138.17)

(reagent for the protection of carbonyl groups as benzodioxepin acetals)

Alternate Name: 1,2-benzenedimethanol.

Physical Data: mp 64-65 °C.

Solubility: sol most organic solvents.

Preparative Methods: commercially available.

Protection of Carbonyl Derivatives.

The title reagent (**1**) has been used as a protecting group for ketones and aldehydes by their conversion to the corresponding benzodioxepin. It offers the advantage of being removable under neutral conditions by hydrogenation, as opposed to other acetal protecting groups which are typically removed under acidic conditions. With simple ketones the diol is not effective in the formation of the acetals using common acids as catalysts as the yields are low. However, conversion of the diol to the corresponding orthoformate followed by treatment of the orthoformate with acid in the presence of a ketone or aldehyde provides the acetal in good to excellent yield (eq 1).[1] This reaction works with a wide variety of substrates, except very hindered ketones such as camphor.

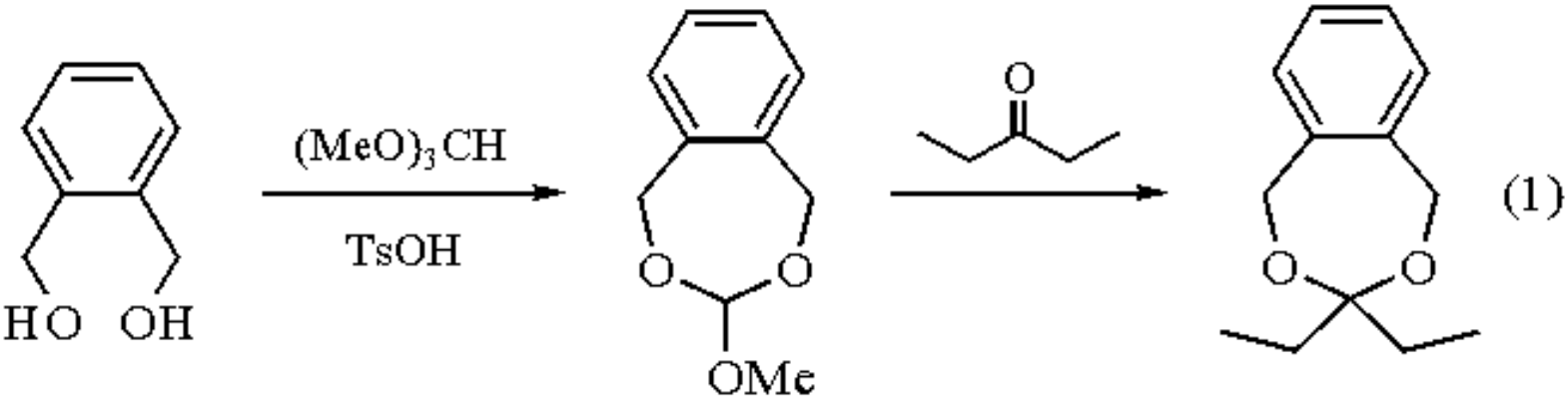

Alternatively, the use of sulfonated charcoal has been shown to be effective with the diol as a starting material (eq 2).[2]

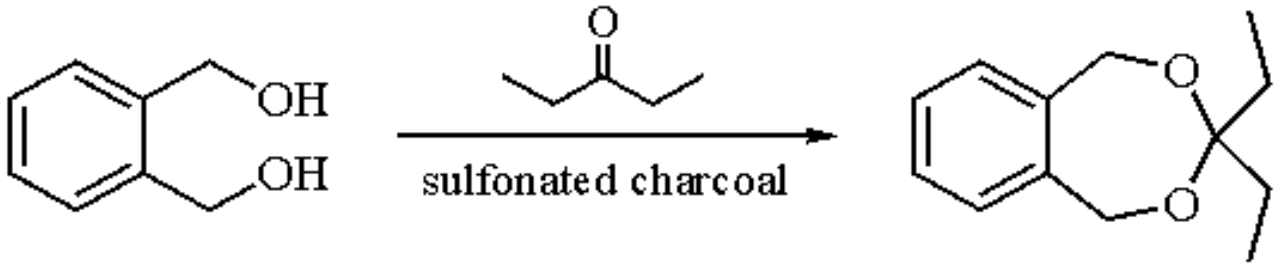

(2)

This reagent has been used as a protecting group for diethyl β-oxoglutarate, which was used in the synthesis of semivioxanthin (eq 3).[3] Other protecting groups failed due to difficulties encountered in their cleavage. Interestingly, in this case the authors chose to use the diol and tosic acid to obtain the acetal, but in poor yield (36%).

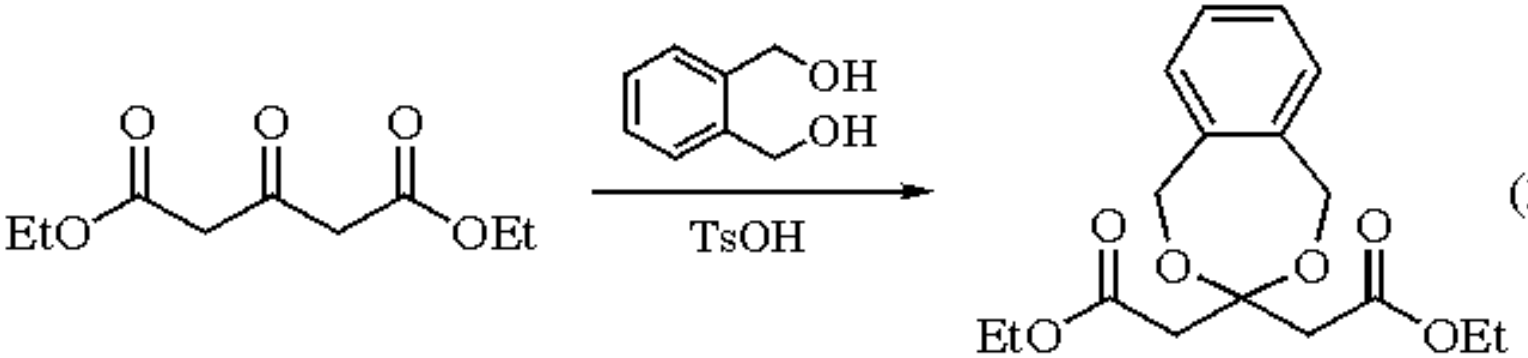

(3)

In the synthesis of an analog of *myo*-inositol 1,4,5-triphosphate, this group was used as a protecting group for a ketone as well as for a phosphoramidite. Thus treatment of the Birch reduction product of anisole with acetic acid and (**1**) provided the protected ketone (eq 4) which was converted to the requisite triol. This was coupled with the phosphoramidite derived from (**1**) and oxidized to the corresponding phosphotriester which was then cleaved to the desired phosphate (eq 5).[4]

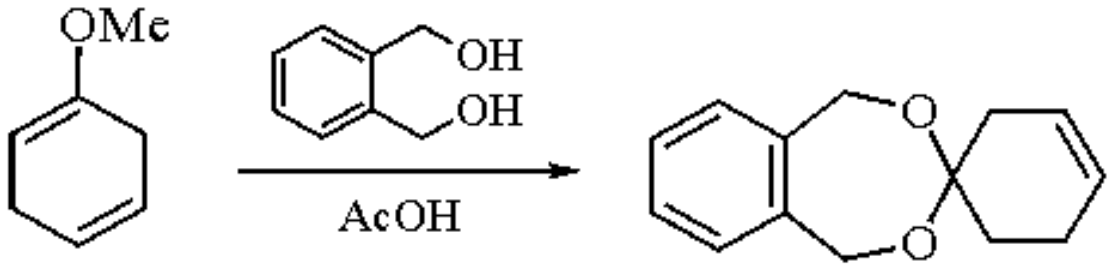

(4)

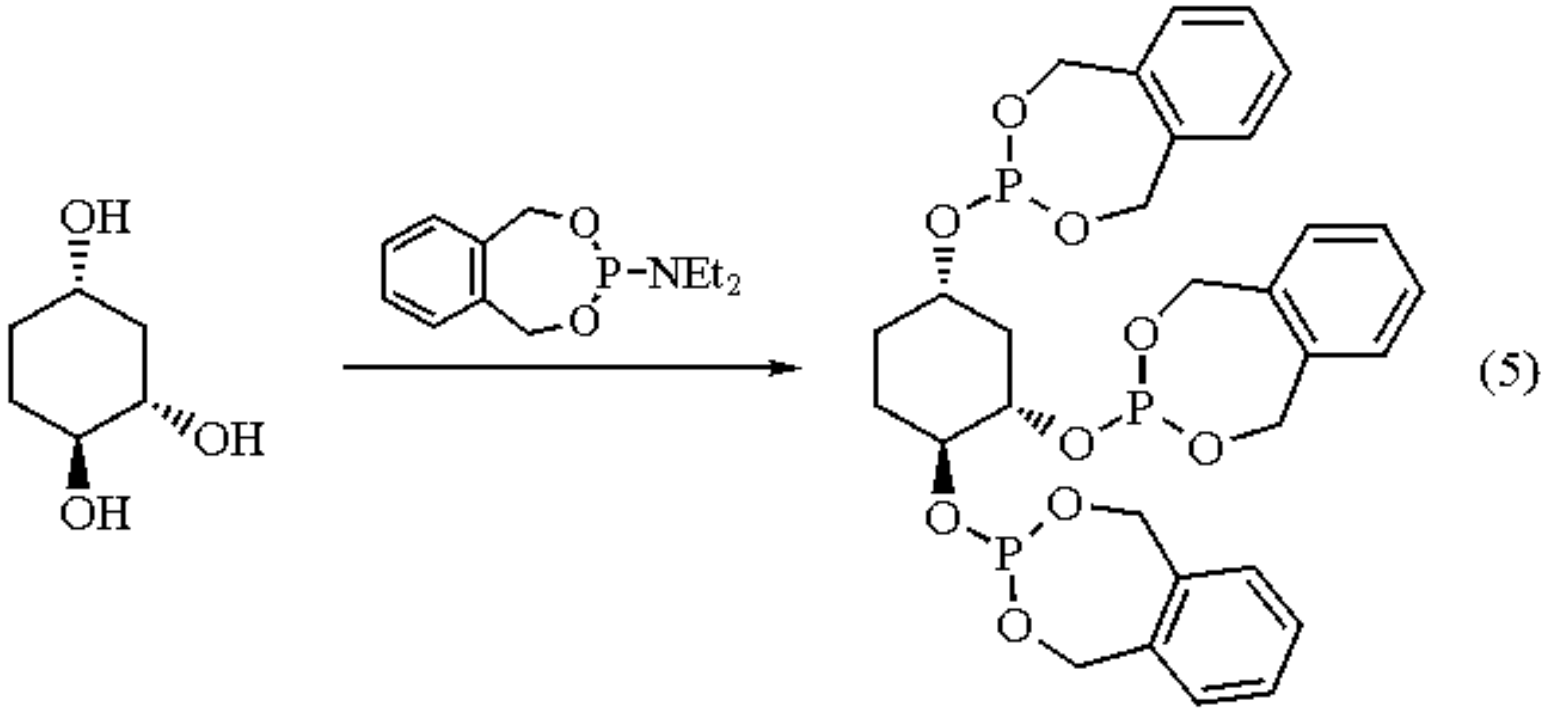

The earliest use of this reagent as a protecting group was in the synthesis of cyclopropanone hydrate. The synthesis required the use of a protecting group that could be removed under neutral conditions. Thus transacetalization of the diethyl acetal derived from bromoacetaldehyde with (**1**) provided the benzodioxepin which was converted to the desired cyclopropane derivative (eq 6).[5]

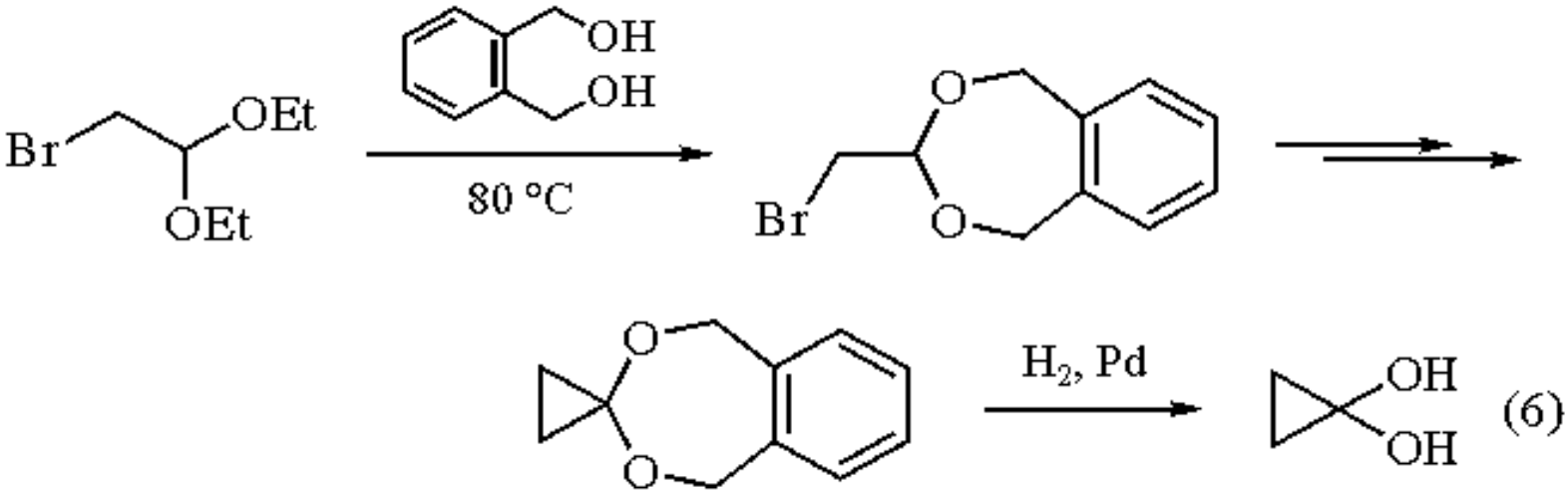

Related Reagents.

3-Bromo-1,2-propanediol; ***Ethylene Glycol***; ***1,3-Propanediol***.

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(η^5,η^5-1*S*,2*R*,4*S*,5*R*-1,4-Bis(indenyl)-2,5-diisopropylcyclohexane)titanium Dichloride

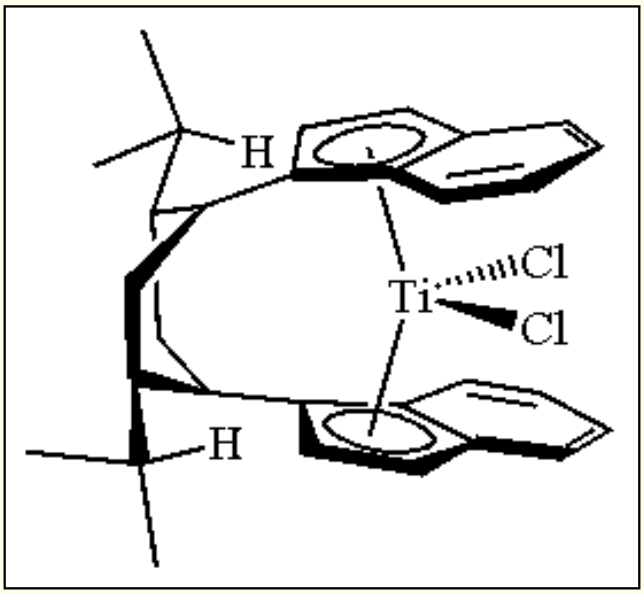

[139561-09-4] · $C_{30}H_{34}Cl_2Ti$ · (η^5,η^5-1*S*,2*R*,4*S*,5*R*-1,4-Bis(indenyl)-2,5-diisopropylcyclohexane)titanium Dichloride · (MW 513.38)

(alkene isomerization; titanium;[4] *ansa*-bis(indenyl) ligand; chiral ligand; C_2 symmetric ligand; asymmetric catalysis[8-10])

Physical Data: mp 264-265 °C (dec 240 °C); *d* 1.339 g cm^{-3}. Dark green crystals from hexane-CH_2Cl_2. [α]23D = +2900° (*c* 0.0202, CH_2Cl_2).

Solubility: sol $CHCl_3$ and CH_2Cl_2; insol hexane.

Preparative Methods: [1] the enantiomerically pure, chiral ligand (**2**) is prepared in two steps from the known (1*S*,2*R*,4*S*,5*R*)-2,5-diisopropylcyclohexane-1,4-diol (**3**) (eq 1).[2,3] It is obtained in 60% yield as a mixture of alkene regioisomers. The chiral titanocene reagent (**1**) is prepared by treatment of (**2**) with 2 equiv of ***n-Butyllithium*** followed by reaction with ***Titanium(III) Chloride*** and subsequent oxidation (HCl/air in $CHCl_3$) of the product (eq 2). It is obtained in 80% yield as a single stereoisomer.

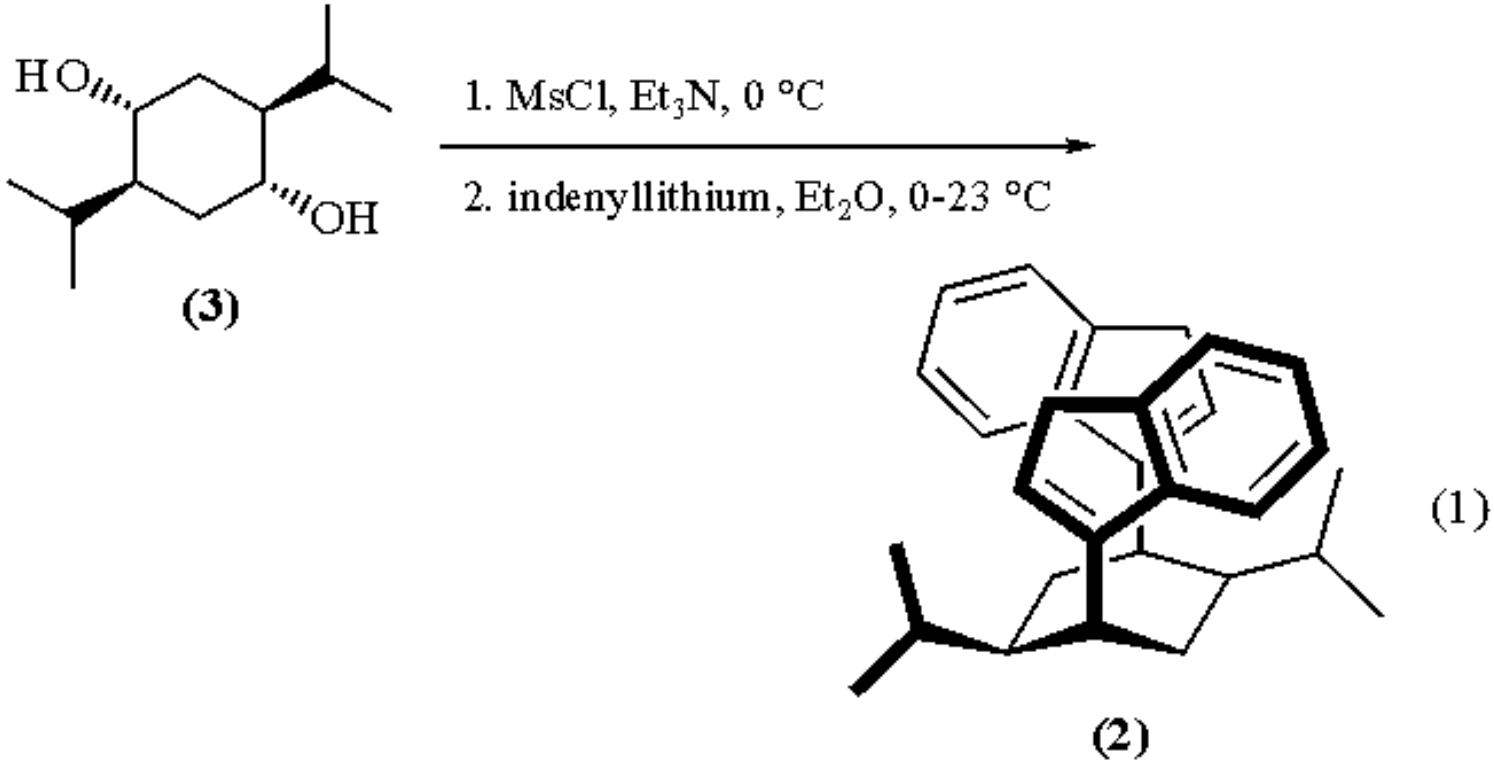
HO
OH
(3)
1. MsCl, Et3N, 0 °C
2. indenyllithium, Et2O, 0-23 °C
(2)
(1)

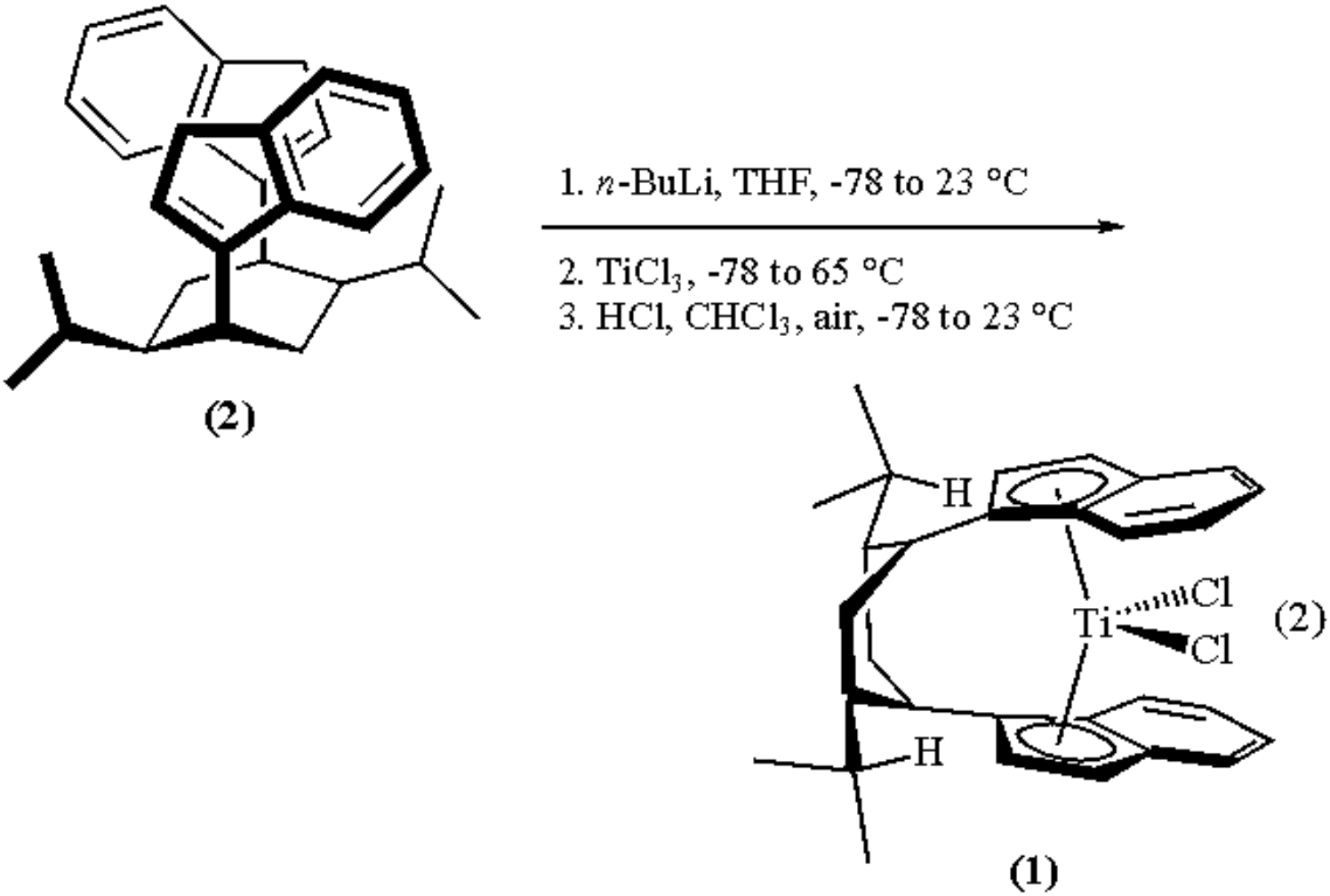
(2)
1. n-BuLi, THF, -78 to 23 °C
2. TiCl3, -78 to 65 °C
3. HCl, CHCl3, air, -78 to 23 °C
H
Ti
Cl
Cl
H
(1)
(2)

Asymmetric Alkene Isomerization.[1]

The chiral titanocene reagent (**1**) serves as precatalyst for the isomerization of alkene (**4**) (eq 3). Active isomerization catalyst is obtained by in situ reduction of (**1**) with ***Lithium Aluminum Hydride*** (164 °C, 30 min). Treatment of the achiral substrate (**4**) with 2 mol % catalyst produced axially dissymmetric product (*S*)-(**5**) in 44-76% ee (100% yield). The reaction is slow at room temperature (120 h required for complete reaction); faster rates are obtained at higher temperatures, but at the expense of lower product enantiomeric purity.

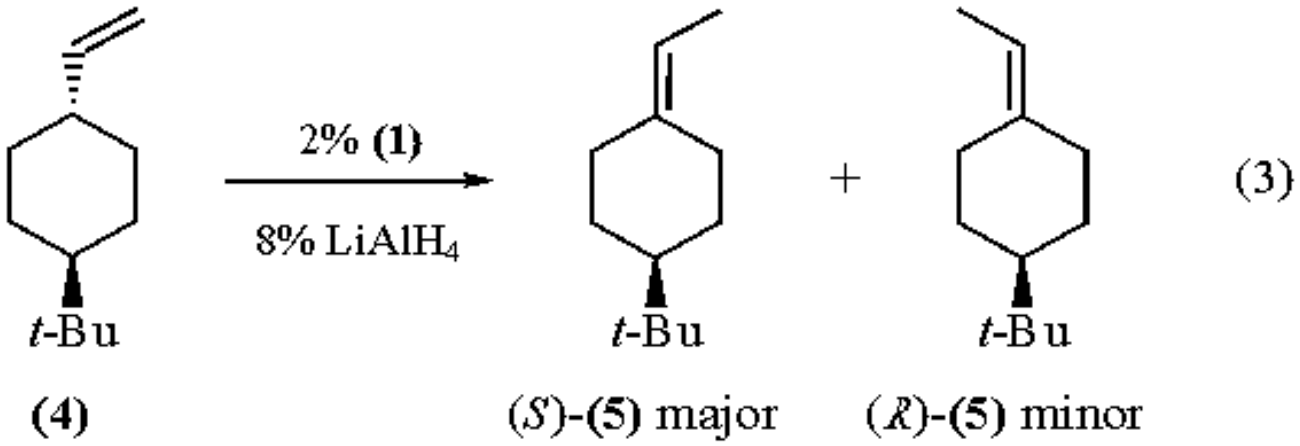

Other Chiral Cyclopentadienylmetal Complexes.

The chemistry of chiral cyclopentadienylmetal complexes is covered in a review by Halterman.[4] Brintzinger's 1,2-ethylenebis(1-indenyl) ligand is the one most commonly used in the preparation of chiral early metal metallocene catalysts.[5,6] Compared to Brintzinger's ligand, (**2**) has the advantage of producing chiral metallocene complexes as single stereoisomers. A related chiral bis(1-indenyl) ligand developed by Burk and Halterman, possessing the same advantages as (**2**), incorporates a binaphthyl unit as the chiral, enantiomerically pure bridging group.[7]

Other Reactions of Chiral Titanocene Derivatives.

Buchwald has recently reported the catalytic asymmetric hydrogenation of imines[8,9] and unfunctionalized alkenes[10] using chiral titanocene catalysts.

---

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2,6-Bis[(*S*)-4´-isopropyloxazolin-2´-yl](pyridine)rhodium Trichloride[1]

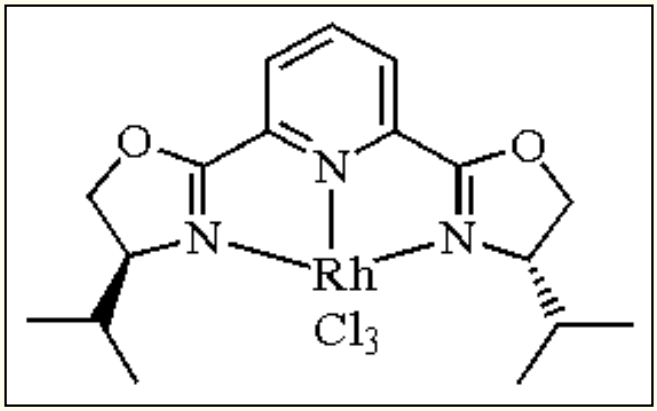

([Pybox-(*S*,*S*)-ip]$RhCl_3$)

[119038-51-6] · $C_{17}H_{23}Cl_3N_3O_2Rh$ · 2,6-Bis[(*S*)-4´-isopropyloxazolin-2´-yl](pyridine)rhodium Trichloride · (MW 510.65) (Pybox-(*S*,*S*)-ip)

[118949-61-4] · $C_{17}H_{23}N_3O_2$ · 2,6-Bis[(*S*)-4´-isopropyloxazolin-2´-yl]pyridine · (MW 301.39)

(highly enantioselective catalyst for hydrosilylative reduction of methyl ketones in combination with Ph_2SiH_2 and $AgBF_4$[5,6])

Alternate Name: [Pybox-(*S*,*S*)-ip]$RhCl_3$.

Physical Data: [Pybox-(*S*,*S*)-ip]$RhCl_3$: mp 279 °C (dec); [α]20D = +543° (*c* 1.09, CH_2Cl_2); Pybox-(*S*,*S*)-ip: white solid, mp 152-153 °C, [α]26D = -116.8° (*c* 1.0, CH_2Cl_2).[6]

Solubility: sol CH_2Cl_2, $CHCl_3$, and alcohols; slightly sol THF and ethyl acetate; insol diethyl ether, benzene, and H_2O.

Form Supplied in: orange solid; synthesized with $RhCl_3(H_2O)_3$ and Pybox-(*S*,*S*)-ip in ethanol at reflux for 3 h. The crude solid was purified by silica gel column chromatography with ethyl acetate and methanol as eluents; TLC R_f = 0.45 (ethyl acetate/methanol = 5:1, Merck Art 5715). *Drying:* although the rhodium compound is nonhygroscopic, it contains some quantity of water or solvents after the purification by chromatography. It should be dried under vacuum (< ca. 1 Torr) for 1 day at 20-60 °C before use.

Handling, Storage, and Precautions: stable in air and moisture.

Enantioselective Reduction of Ketones.

Hydrosilylation of ketones with chiral metal catalysts and hydrosilanes followed by hydrolysis provides optically active secondary alcohols from ketones. Most of the enantioselective hydrosilylations of ketones have been carried out with rhodium catalysts and chiral phosphine ligands. These systems give a middle range of enantioselectivities, especially with diphenylsilane and 1-naphthylsilane.[2] In the 1980s, many splendid results of more than 90% ee were reported with rhodium catalysts of chiral nitrogen-containing ligands such as pyridinethiazolidine[3] and pyridineoxazoline-*t*-Bu,[4,5] which are easily accessible from readily available, optically active amino acids and amino alcohols.

The 2,6-bis(oxazolinyl)pyridine ligand [Pybox-(*S*,*S*)-ip] was also developed as a chiral adjuvant for the asymmetric hydrosilylation of ketones. The Pybox ligand can be synthesized in large scale as a white crystalline solid by condensation of (*S*)-valinol and pyridine-2,6-dicarboxylic acid.[6] Heating of the ethanol solution of Pybox-(*S*,*S*)-ip and ***Rhodium(III) Chloride*** trihydrate gave the stable complex [Pybox-(*S*,*S*)-ip]$RhCl_3$ in 70% yield. Diphenylsilane and the catalytic amount of the Pybox-rhodium(III) complex with the aid of ***Silver(I) Tetrafluoroborate*** reduced aromatic and aliphatic methyl ketones in THF solution at -5 to 25 °C. After hydrolysis of the product silyl ethers in acidic methanol at 0 °C, optically active secondary alcohols were obtained in high yields and high enantioselectivities, e.g. from acetophenone to 1-phenylethanol in 91% yield and 94% ee (*S*) (eq 1; Table 1).[6]

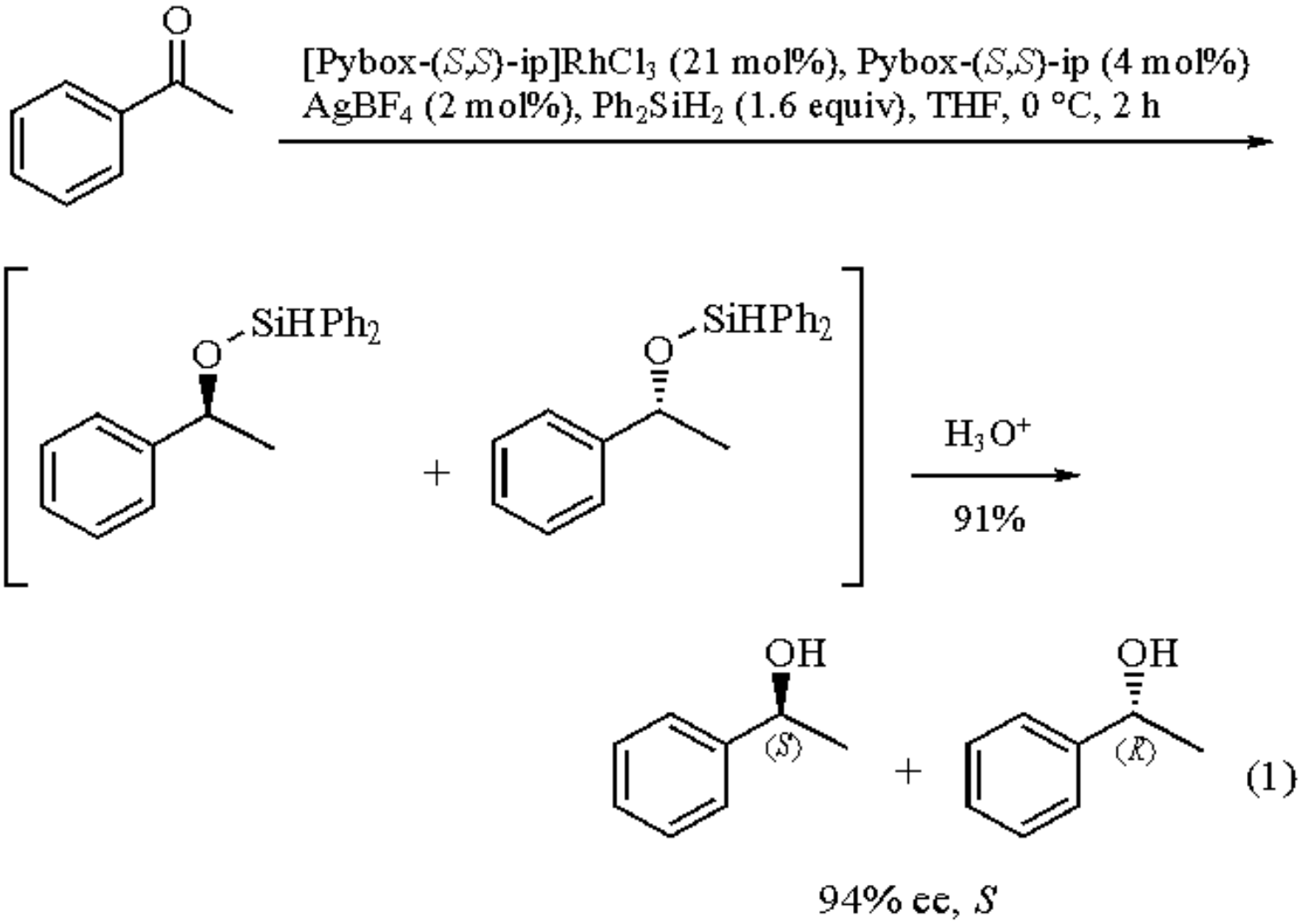

Table 1 Hydrosilylative Reduction of Methyl Ketones with [Pybox-(*S*,*S*)-ip]$RhCl_3$ and Diphenylsilane

(*S*,*S*)-ip]$RhCl_3$ and Diphenylsilane

Ketones	Product (85-93% yield)	ee (%)
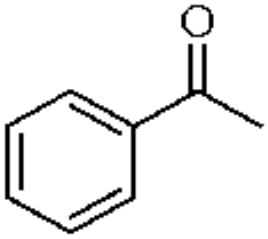	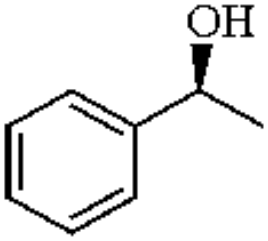	94
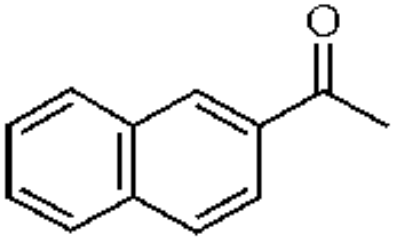	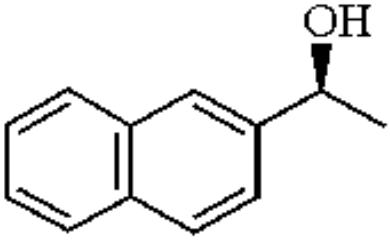	93
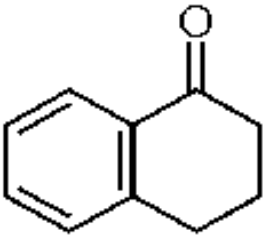	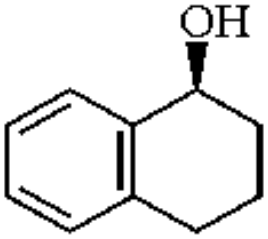	99
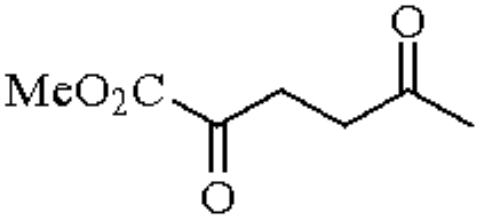	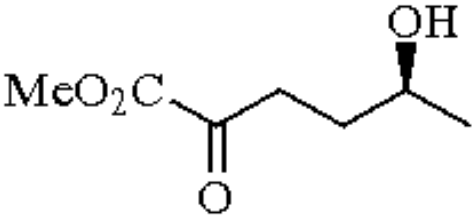	95
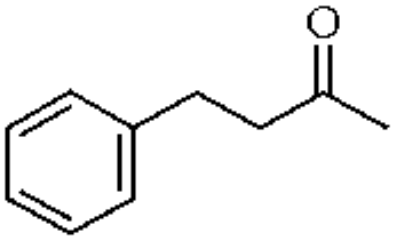	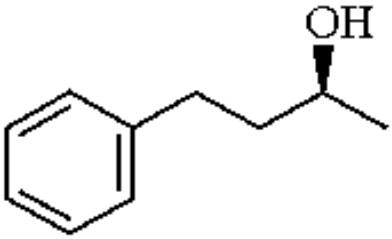	66
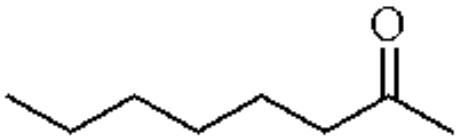	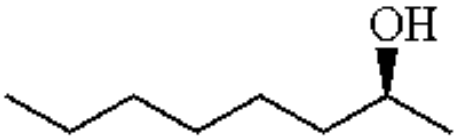	63

The stereoselectivity of the reduction of 4-*t*-butylcyclohexanone has been shown to give high proportions (>90%) of the *cis* (equatorial) alcohol in hydrogenations with heterogeneous rhodium catalysts or in transfer hydrogenations with homogeneous rhodium or iridium catalysts.[7] However, the Pybox-rhodium catalyst gave a ratio of 67:33 of the *trans*/*cis* alcohol,[8] similar to that obtained with the Wilkinson catalyst (eq 2).[9] Despite the low axial/equatorial selectivity, the enantioselectivities of the reduction of 2-phenyl- and 2-methoxycarbonylmethylcyclohexanone were extremely high (eqs 3 and 4).[8] Chalcone was also reduced to the allylic alcohol in 71% ee (eq 5).[6]

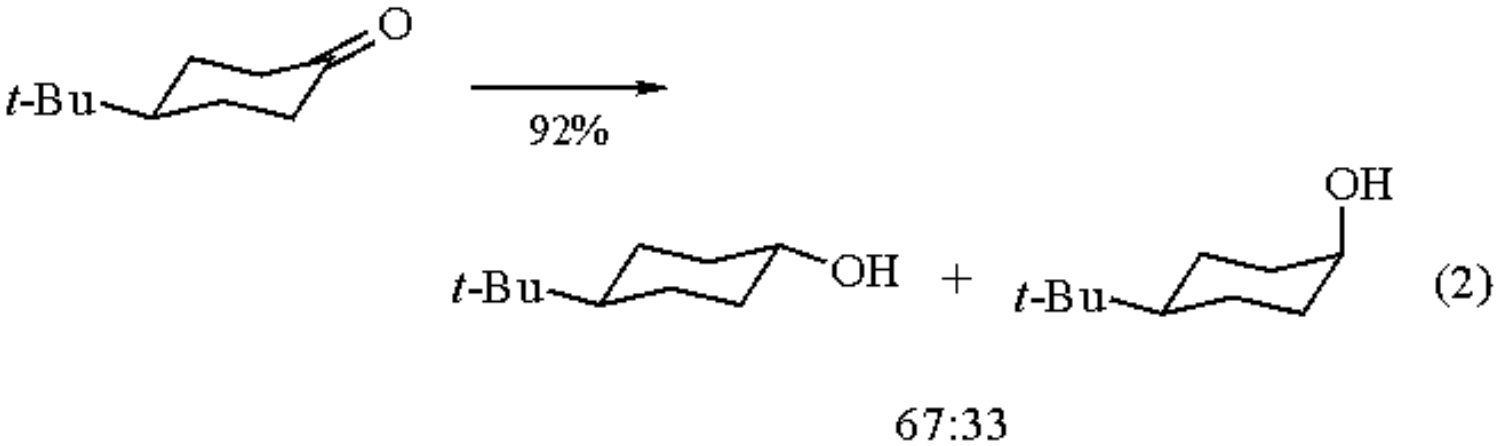

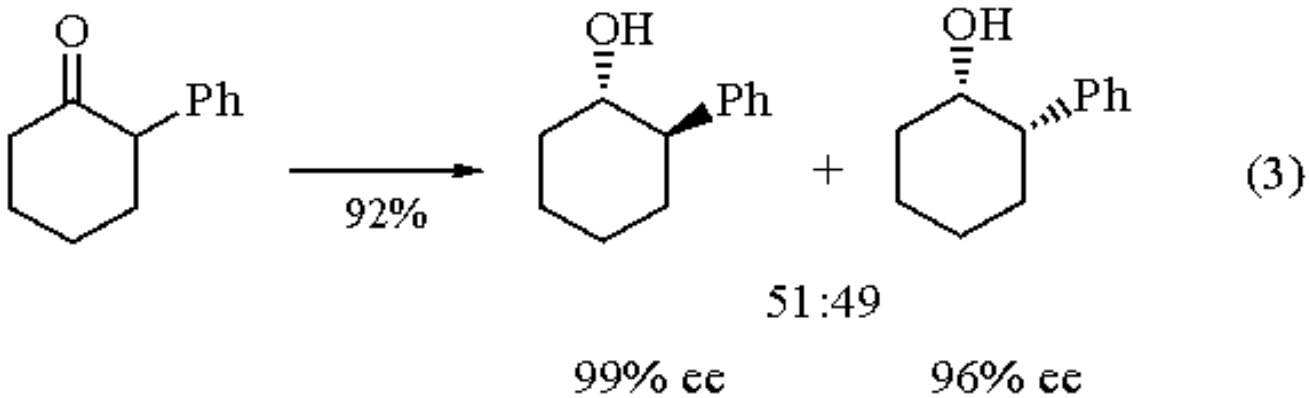

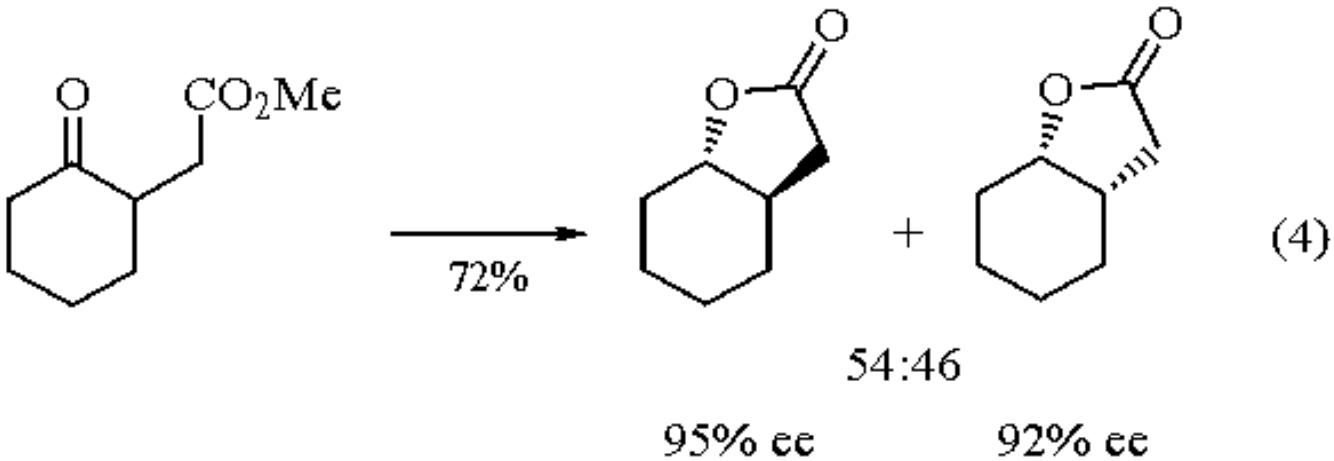

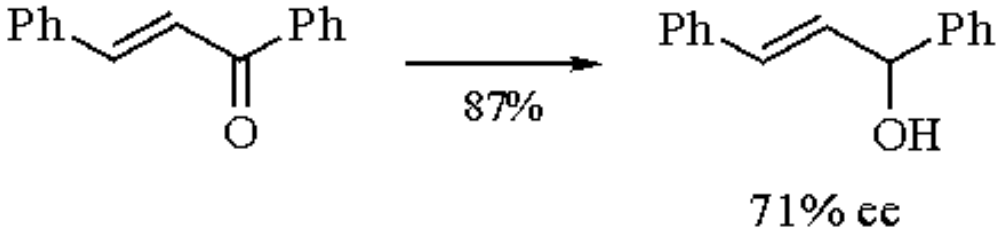

(5)

In place of diphenylsilane, 1,2-bis(dimethylsilyl)ethane was applied to the reduction of several ketones by the combination of the Pybox-rhodium complex and ***Silver(I) Trifluoromethanesulfonate*** to give the corresponding silyl enol ether exclusively (eq 6).[10]

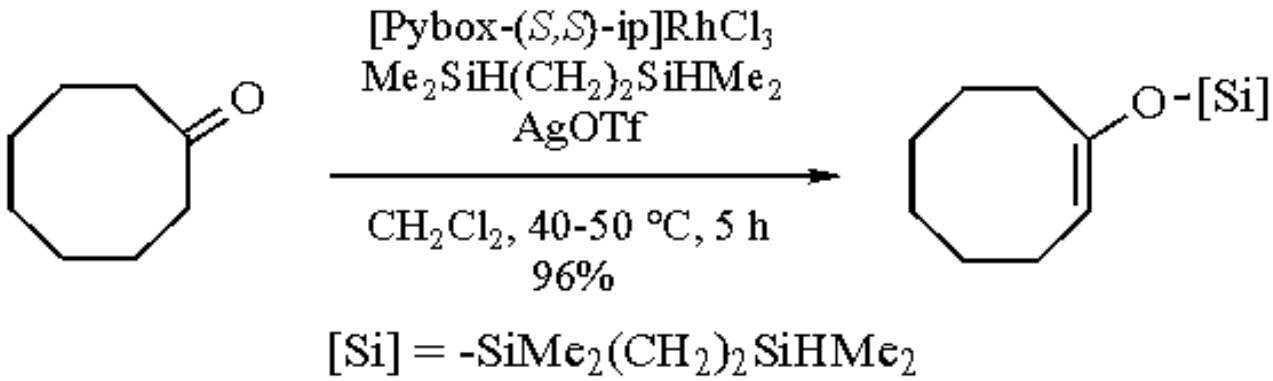

(6)

Chiral 4-substituted Pybox derivatives (**1**) were synthesized as chiral adjuvants to study remote electronic effects of the substituents in the asymmetric hydrosilylation.[11] The 4-Cl-Pybox-(*S*,*S*)-ip-Rh catalyst afforded the highest result (80% ee (*S*)) for the reduction of 2-octanone to 2-octanol in 88% yield.

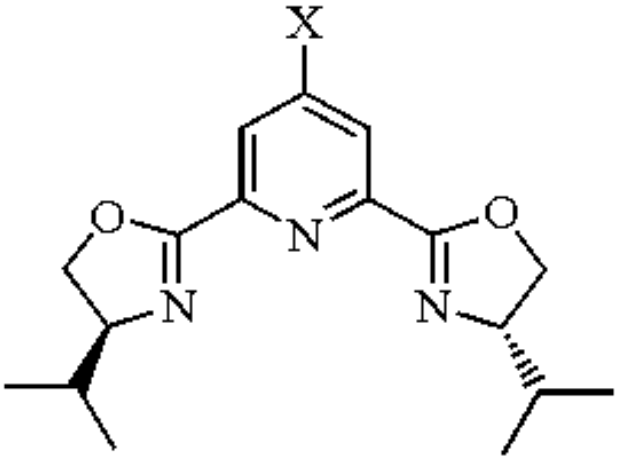

(1) 4-X-Pybox-(*S*,*S*)-ip

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2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone[1]

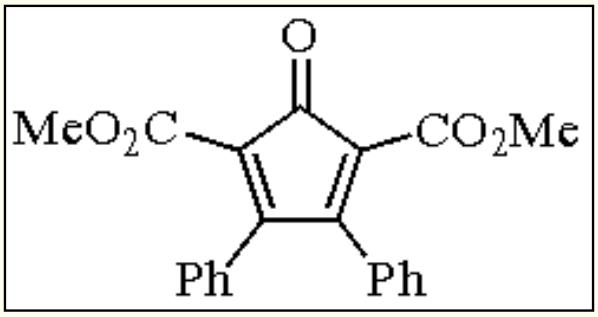

[16691-79-5] · $C_{21}H_{16}O_5$ · 2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone · (MW 348.35)

(reagent for cycloaddition reactions[1])

Physical Data: mp 169, 175 °C (from pet ether),[1a] 173 °C,[1b] 162-164 °C (from Ac_2O).[1c]

Form Supplied in: orange solid; may contain Diels-Alder dimer as impurity.[1]

Analysis of Reagent Purity: ^{1}H NMR.[1c]

Preparative Method: equimolar amounts of benzil and dimethyl 2-propanone-1,3-dicarboxylate in MeOH or EtOH with OH^- are allowed to react at 25 °C for 1 day to give the intermediate dimethyl 3,4-diphenyl-4-hydroxycyclopent-2-enone-2,5-dicarboxylate in 70-96% yield. Treatment of the intermediate with acid in benzene[1a] or in Ac_2O[1c] with heating gives the dienone in 98% yield containing 3% of the Diels-Alder dimer.[1c]

Cycloaddition Reactions.

As with other cyclopentadienones,[2] the reagent reacts readily in cycloaddition reactions with a variety of dienophiles. Dimerization upon heating to 200 °C has been reported,[1a] but the monomeric reagent is stable at rt. Reactions with dienophiles are typically conducted at temperatures between 20-120 °C. Reactions have been run neat or in inert solvents such as benzene and 1,2-dichloroethane. In the presence of excess dienophile, the reactions are allowed to proceed until the characteristic orange color of the dienone is discharged.

Reactions with dienophiles generally give [4 + 2] cycloaddition (Diels-Alder) products. Additions to substituted styrenes occur with modest to good *endo* stereoselectivity (eq 1), but cycloadditions with electron deficient dienophiles such as ***Maleic Anhydride*** give only the *endo* product.[3] Cycloadditions with *trans*-stilbene, ***Dimethyl Maleate***, and

Dimethyl Fumarate show that the reactions are stereospecific.[4] Kinetic studies of reactions with substituted styrenes gave negative ρ values,[3,5] leading to the classification of reverse electron demand cycloadditions. Cycloadditions with alkenes generally give bicyclic products such as shown in eq 1, but the first-formed products from cycloadditions with alkynes such as ***Dimethyl Acetylenedicarboxylate*** decarbonylate to give aromatic products (eq 2).[1a,3]

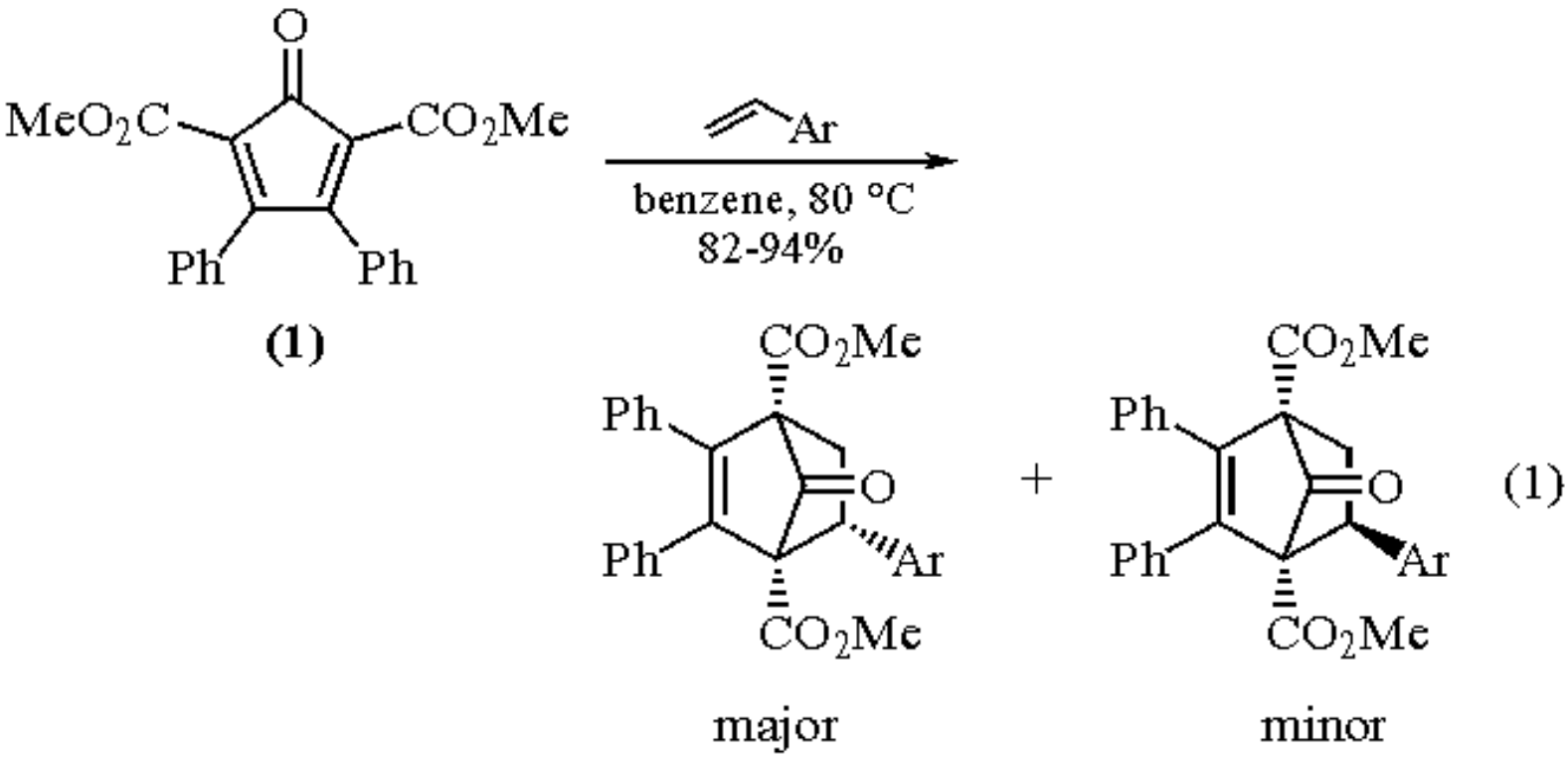

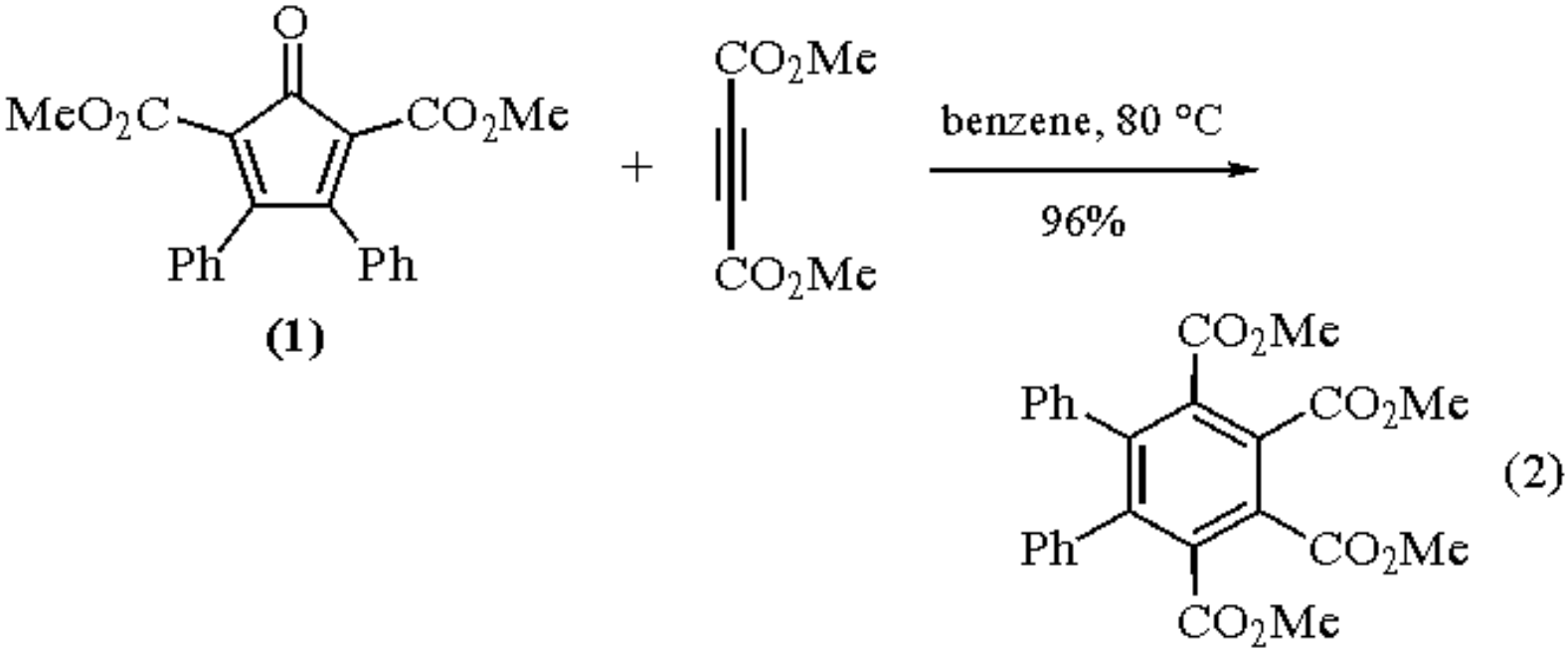

Because the dienone is monomeric and highly reactive in [4 + 2] cycloadditions, it has been used to trap intermediate alkene products that are unstable to the reaction conditions. For example, oxidation of the benzadiyne equivalent precursor in eq 3 in the presence of the dienone gives the substituted anthracene shown.[6]

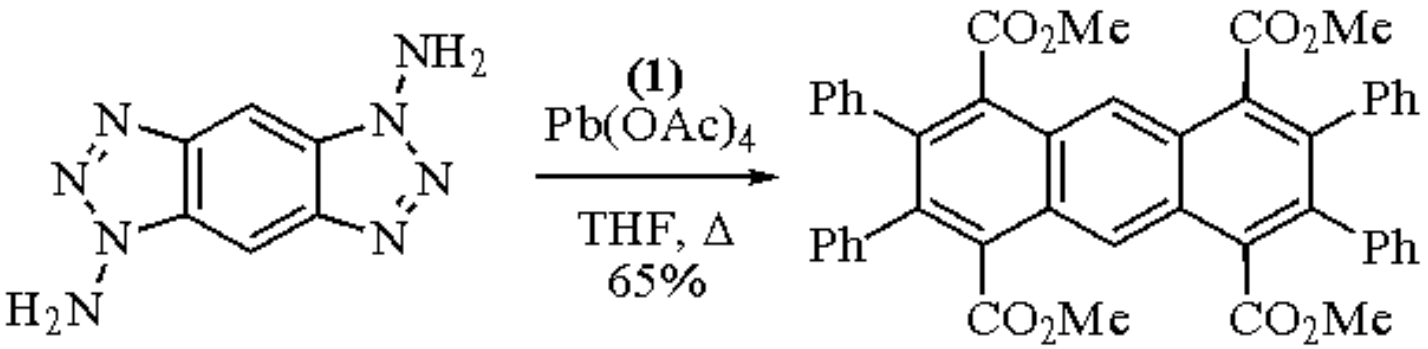

(3)

Mixtures of [4 + 6] and [4 + 2] cycloadducts are obtained in reactions of the dienone with oxepin[7] (eq 4), a 1*H*-azepin,[8] and 1,3,5,7-cyclooctatetraene.[9] Reaction of the dienone with tropone gives [4 + 6] addition products.[3]

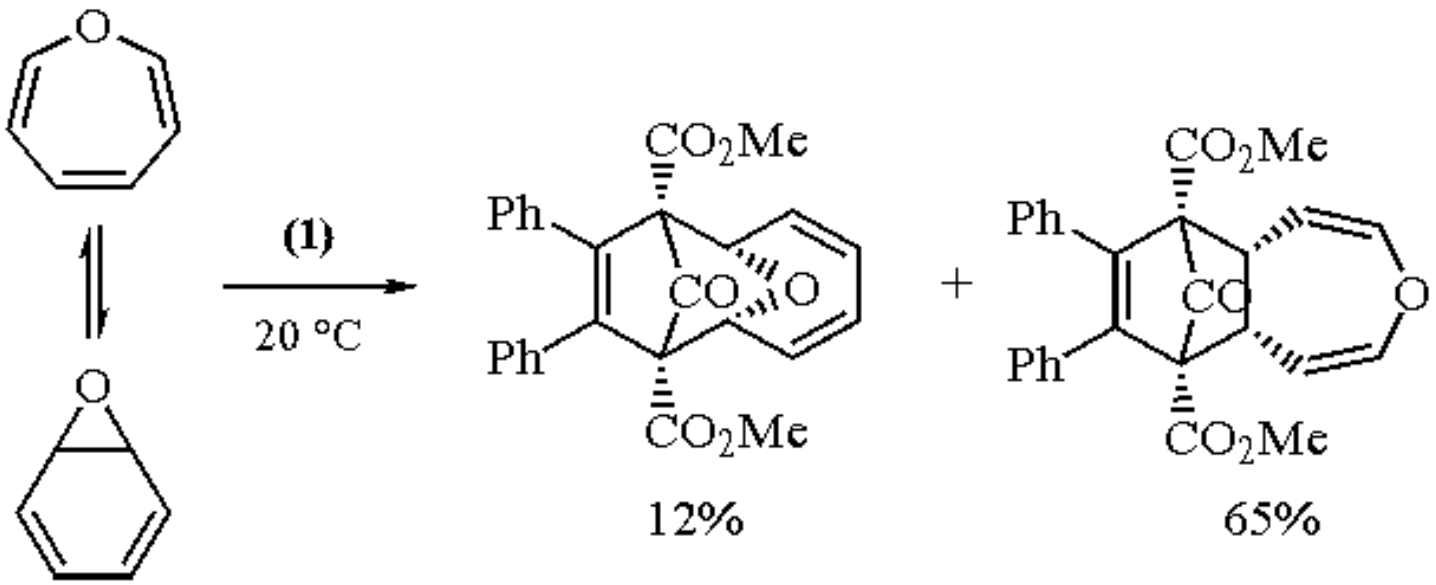

(4)

Dipolar cycloadditions as in reactions with diazoalkanes[1b] and with nitrile *N*-oxides[10] give [2 + 3] cycloadducts (eq 5).

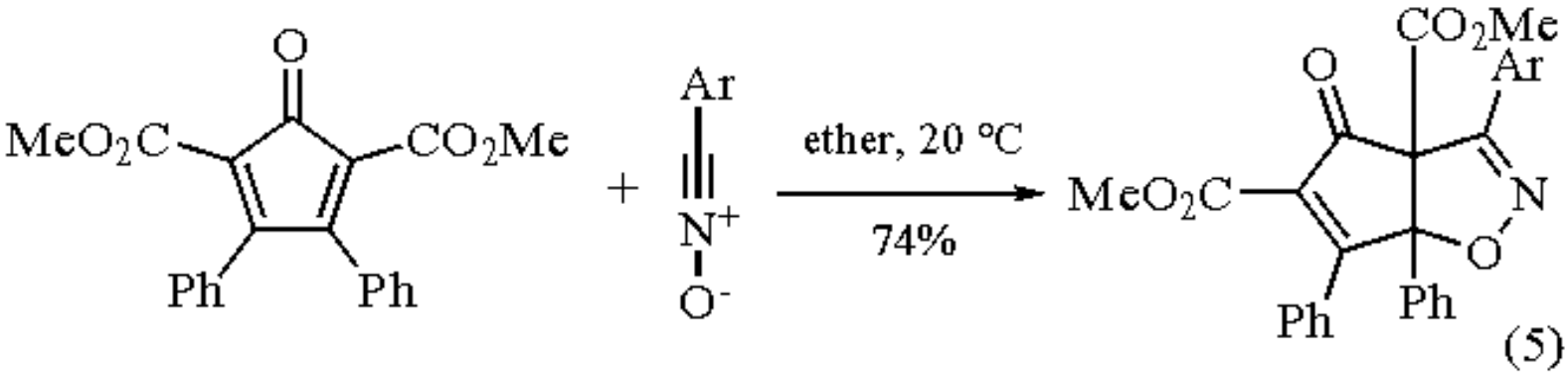

(5)

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Bis(1-methoxy-2-methyl-1-propenyloxy)dimethylsilane[1]

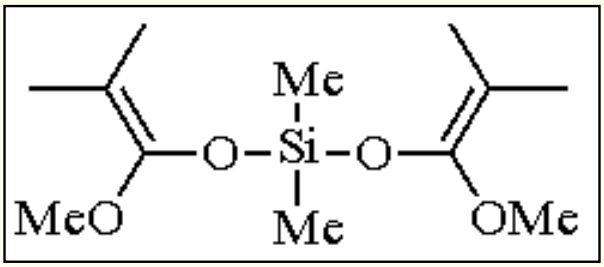

[86934-32-9] · $C_{12}H_{24}O_4Si$ · Bis(1-methoxy-2-methyl-1-propenyloxy)dimethylsilane · (MW 260.40)

(very useful bifunctional protecting agent for various types of H-acidic materials under mild conditions)

Physical Data: 89-90 °C/6.5 mmHg.

Form Supplied in: colorless liquid; not commercially available.

Preparative Method: prepared by treating 2 equiv of methyl lithioisobutyrate with 1 equiv of dichlorodimethylsilane at low temperature in dry THF, followed by distillation of the colorless liquid.

Handling, Storage, and Precautions: moisture sensitive; should be stored under nitrogen in a refrigerator.

The Dialkylsilylene Protecting Group.

Bifunctional compounds containing alcohol, thiol, acid, and amine units may be protected as cyclic dimethylsilylene derivatives, which are analogous to isopropylidene derivatives, by treatment with the title reagent (**1**).[2] Cleavage of the silylene protective group is easily achieved by hydrolysis or solvolysis. It should be noted that the dimethylsilylene group is highly sensitive to hydrolysis and is unstable to column chromatography.

Silylene derivatives have become very useful in synthetic organic chemistry. For example, the cyclic dimethylsilylene derivative (**2**) of *o*-hydroxyacetophenone is useful for [4 + 2] cycloadditions (eq 1).[3] A glycosyl donor and acceptor have been linked as the dimethylsilylene derivative (**3**) and used for stereoselective glycosylation (eq 2).[4] Also, an efficient and stereocontrolled aldol reaction of silylene enolate (**4**) with aldehydes has been reported (eq 3).[5]

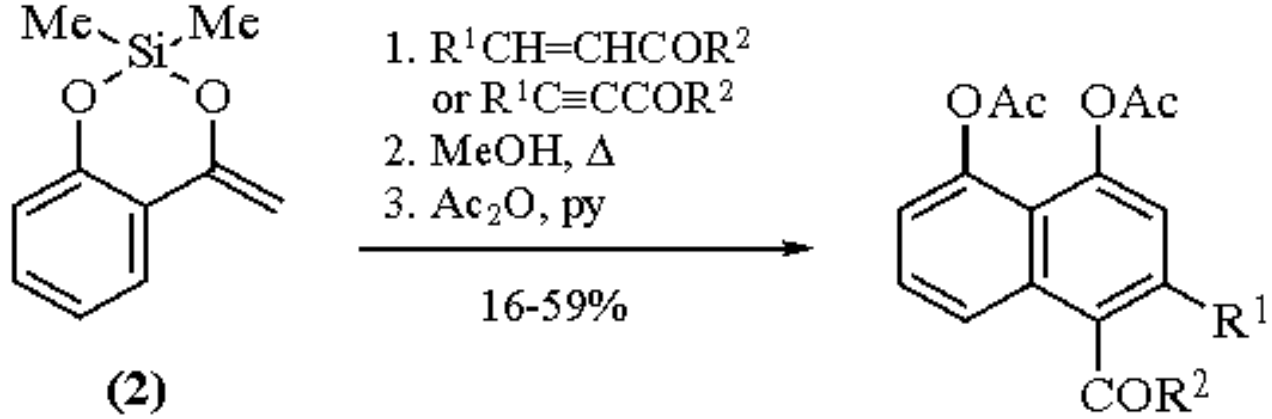

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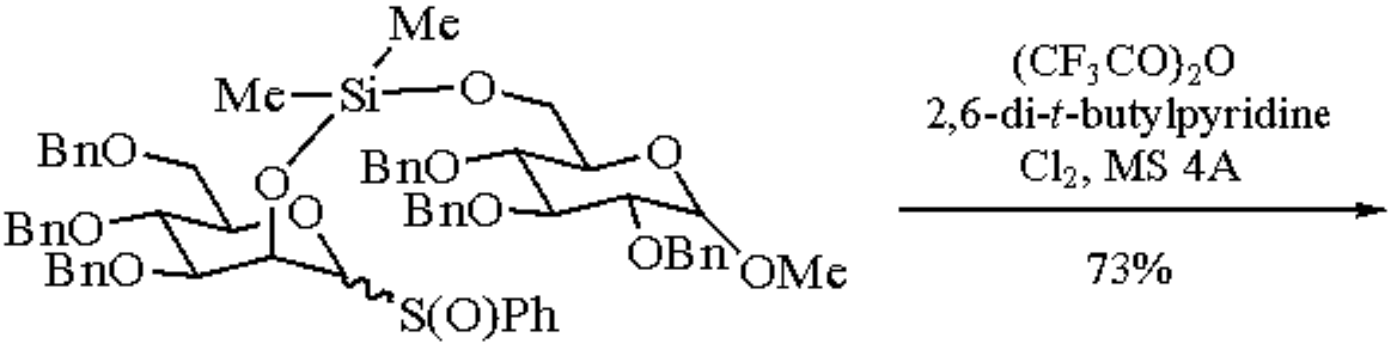

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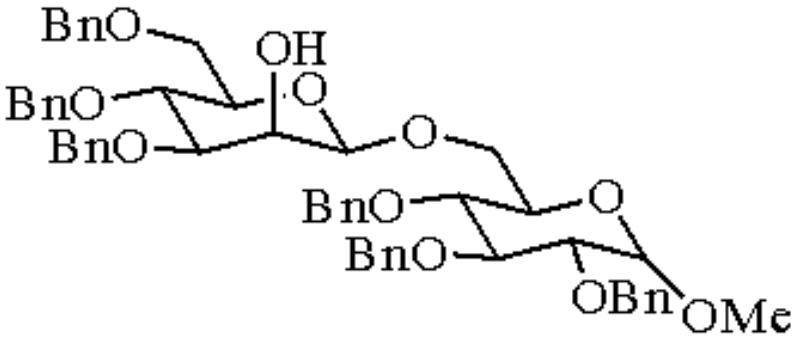

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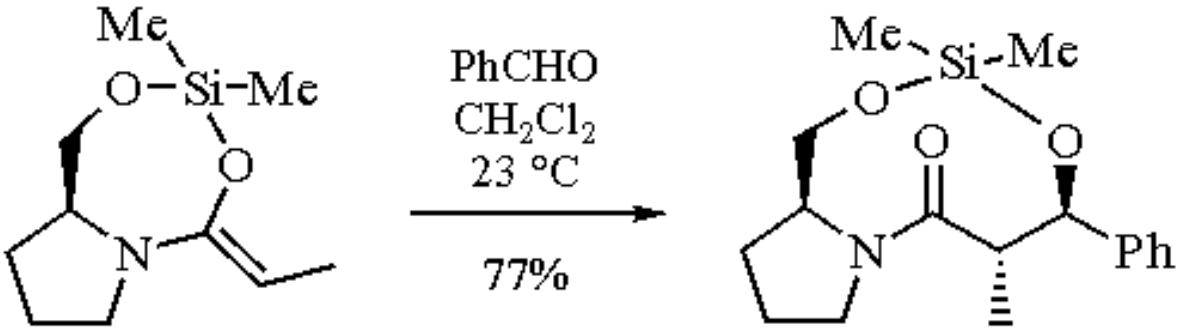

(4) (3)

Advantages of Bis(1-methoxy-2-methyl-1-propenyloxy)dimethylsilane.

Dichlorosilanes,[6] bis(trifluoromethanesulfonyl)silanes,[7] and dimethoxysilanes[8] have been used for the synthesis of dialkylsilylene derivatives. These methods, however, have some disadvantages: (i) a strong base or acid catalyst is required; (ii) forcing reaction conditions (high temperature for a long period) are sometimes required; (iii) large amounts of side-products such as inorganic salts, or amine or acid salts, are produced that must be separated from the moisture-sensitive silylene derivatives; and (iv) the yields of the products are not always high. Reagent (**1**), which is much more reactive than other difunctional silyl reagents, allows the ready silylenation of H-acidic materials in the absence of base, and allows isolation of pure products in almost quantitative yields without aqueous workup. The only reaction side-product is methyl isobutyrate, which is volatile.

Bifunctional Protection of H-Acidic Materials.[1,9]

The reaction of (**1**) with H-acidic materials is generally carried out by employing a slight excess of the reagent in an inert solvent such as CH_2Cl_2 or MeCN and usually gives a high yield of the corresponding silylene derivatives. Furthermore, addition of catalytic amounts of dichlorodimethylsilane induces a slightly exothermal reaction, leading to the rapid formation of the silylenes. A wide range of 1,2-, 1,3-, and 1,4-difunctional compounds give the corresponding silylenes in high yields (eqs 4-8). Monofunctional alcohols and carboxylic acids can also be linked via the dimethylsilylene group forming dialkoxy- and diacyloxydimethylsilane, respectively (eqs 9 and 10).

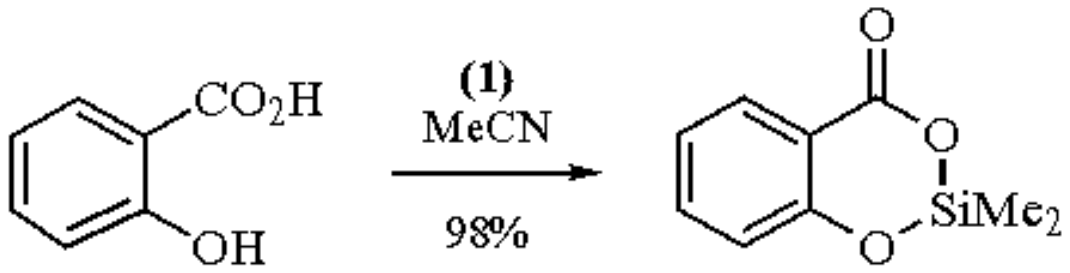

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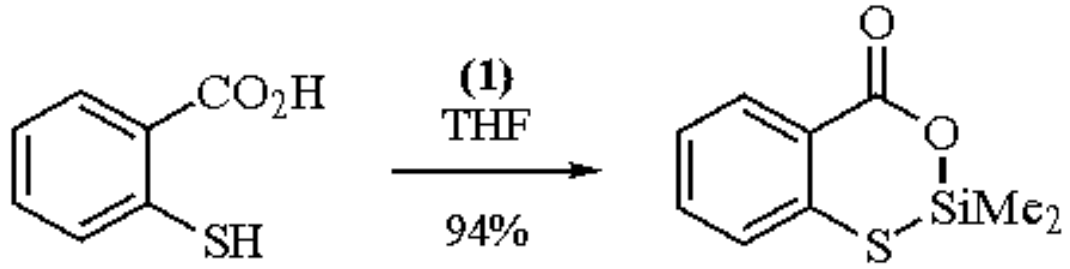

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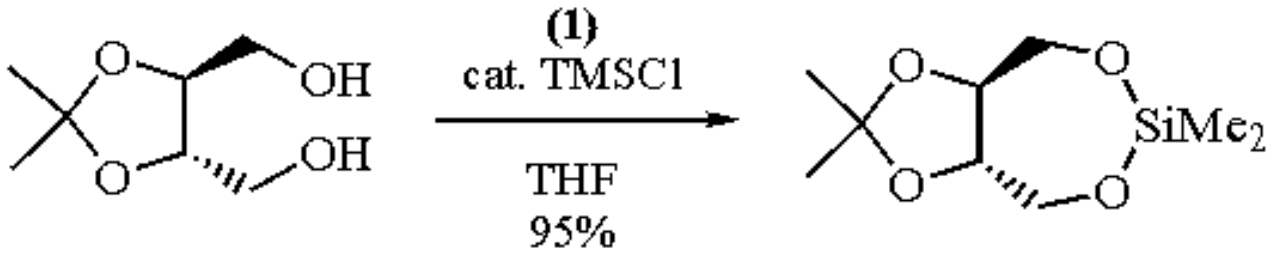

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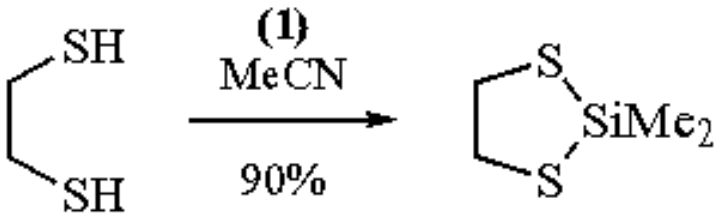

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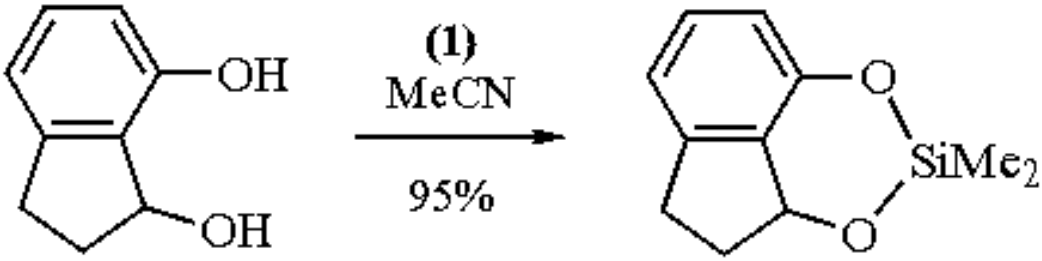

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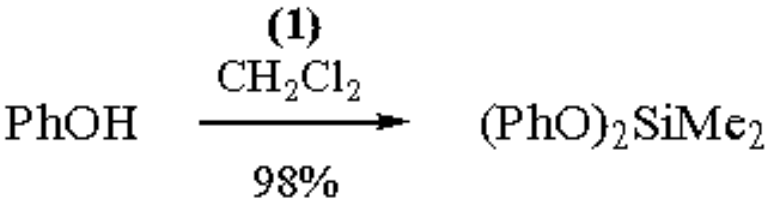

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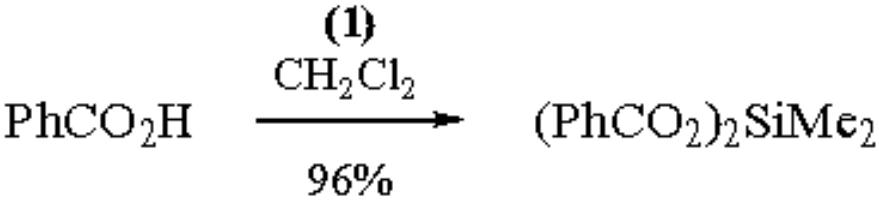

(10)

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trans-2,5-Bis(methoxymethyl)pyrrolidine

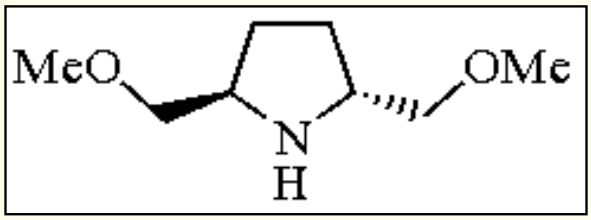

(±)

[144993-81-7] · $C_8H_{17}NO_2$ · *trans*-2,5-Bis(methoxymethyl)pyrrolidine · (MW 159.23) (*S*,*S*)-(+)

[93621-94-4] (*R*,*R*)-(-)

[90290-05-4]

(chiral auxiliary with C_2 symmetry;[1] used as a chiral auxiliary for alkylations, acylations, reductions, cycloadditions, and radical additions)

Physical Data: colorless oil; bp 110-115 °C/15 mmHg; for *S*,*S*-form, $[\alpha]_D$ = +7.8° (*c* = 3.0, EtOH).

Solubility: sol methylene chloride, chloroform, ethanol.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: ^{13}C NMR (δ 27.7, 56.7, 58.8, 76.1 ppm).

Handling, Storage, and Precautions: irritant; use only in a fume hood.

Chiral Amines with C_2 Symmetry.

trans-2,5-Dimethylpyrrolidine (**1**)[2] was the first chiral amine possessing C_2 symmetry used as a chiral auxiliary in asymmetric synthesis.[1,2a] Since that time a number of related systems have been developed including the title compound (**2**) and (**4**).[1] These amines were developed as C_2-symmetric analogs to the commercially available prolinol derivative (**5**). While proline-derived chiral auxiliaries have been widely used in asymmetric synthesis,[3] the C_2-symmetric chiral auxiliaries often give enhanced stereoselectivity when compared directly to the prolinol derivatives. Unfortunately the preparation of the C_2-symmetric compounds is more tedious and, at the time of writing, none are commercially available. For example, the standard route to chiral pyrrolidines (**2**) and (**3**) involves the resolution of *trans*-*N*-benzylpyrrolidine-2,5-dicarboxylic acid,[4] although other preparations have been reported.[5] In general,

pyrrolidines (**2**) and (**3**) have been used interchangeably and will be the primary focus of this entry.

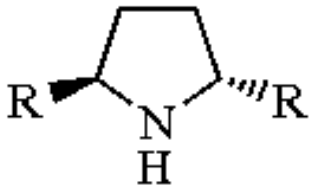

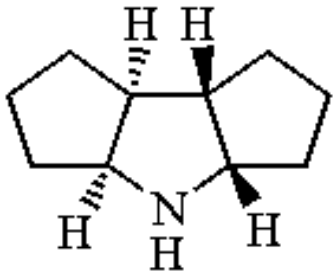

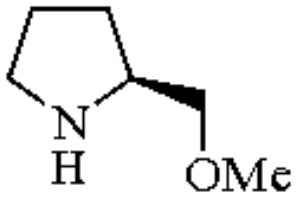

(1) R = Me
(2) R = CH_2OMe
(3) R = $[CH_2O]_2Me$

(4)

(5)

Alkylation of Amides Derived from *C*$_2$-Symmetric Pyrrolidines.

Alkylation of amides derived from either pyrrolidine (**2**) or (**3**) are highly stereoselective (eq 1).[4a] The reaction is successful for a large variety of amide derivatives[4a,6] and alkylating agents.[7] Upon hydrolysis of the amide, chiral acids are produced (eq 2). This method has been used to prepare α-amino[6d] and α-hydroxy acids.[6a] The diastereoselectivity observed is greater than for amides derived from prolinol (**5**).[3] While the degree of the stereoselectivity is almost identical for amides derived from either (**2**) or (**3**), the method for removal of the chiral auxiliary does differ (eq 2). In keeping with earlier results from the prolinol-derived amides,[3] the hydrolysis is best effected via the hydroxymethyl derivative (**10**). For derivative (**8**) this means that the methyl ether is first cleaved with either ***Boron Trichloride***[4a] or ***Boron Tribromide***.[8] In the case of the methoxymethyl derivative (**9**), refluxing in aqueous acid simultaneously effects both cleavage of the methoxymethyl ether and hydrolysis to the chiral acid.

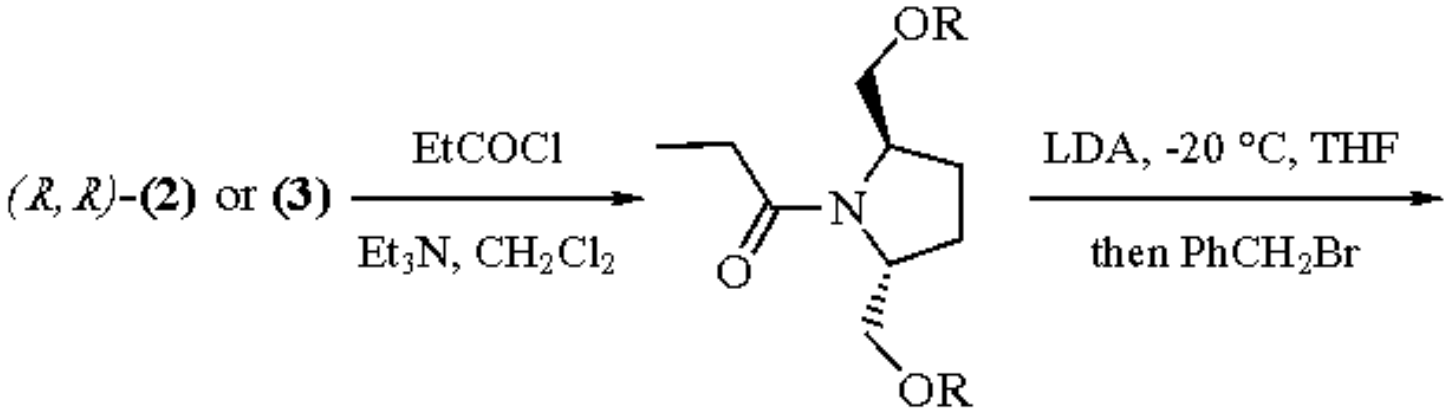

(6) R = Me
(7) R = CH_2OMe

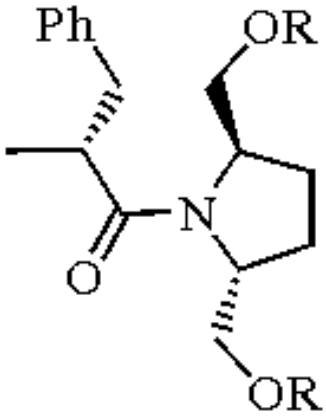

(1)

(8) R = Me, >95% de
(9) R = CH_2OMe, >95% de

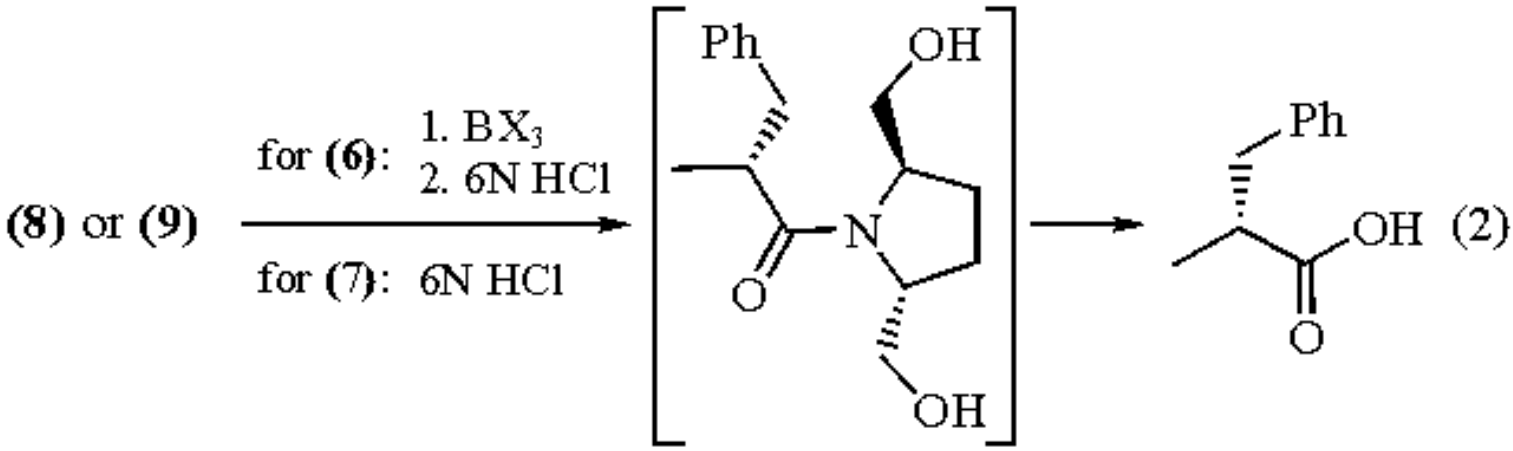

(2)

(10)

Reduction of α- and β-Ketoamides Derived from C_2-Symmetric Pyrrolidines.

By analogy to the alkylation reaction discussed above, acylation of the enolate derived from amide (**8**) produces the β-ketoamide (**11**) as a single diastereomer (eq 3).[9] Subsequent reduction of the ketone produces either the *syn*[9] or *anti*[10] β-hydroxyamides with high diastereoselectivity (eqs 4 and 5). Pyrrolidine-derived α-ketoamides have also been shown to react stereospecifically with reducing agents,[11] as well as with other organometallic reagents.[12]

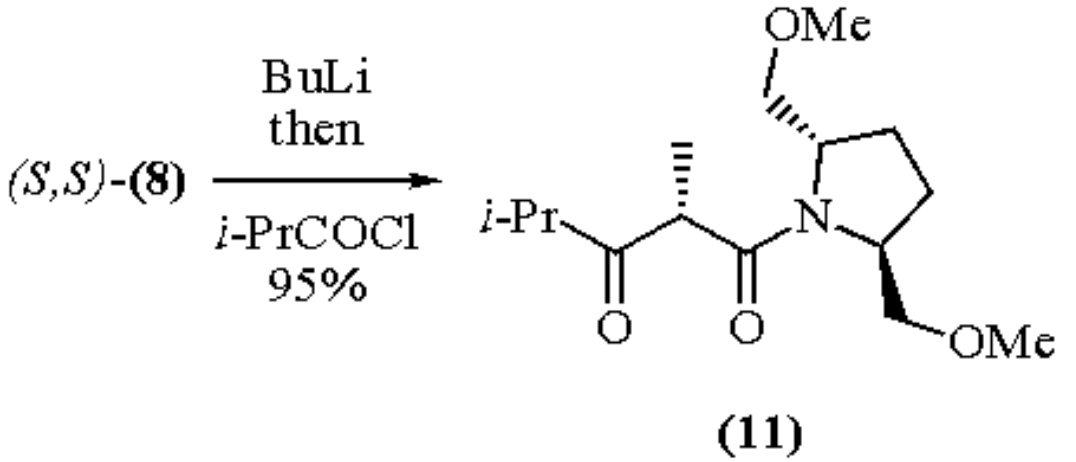

(3)

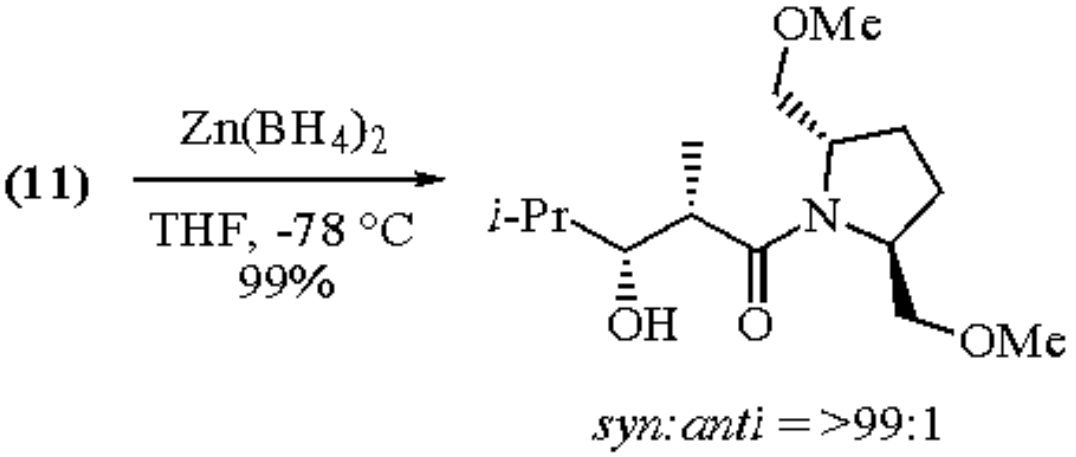

(4)

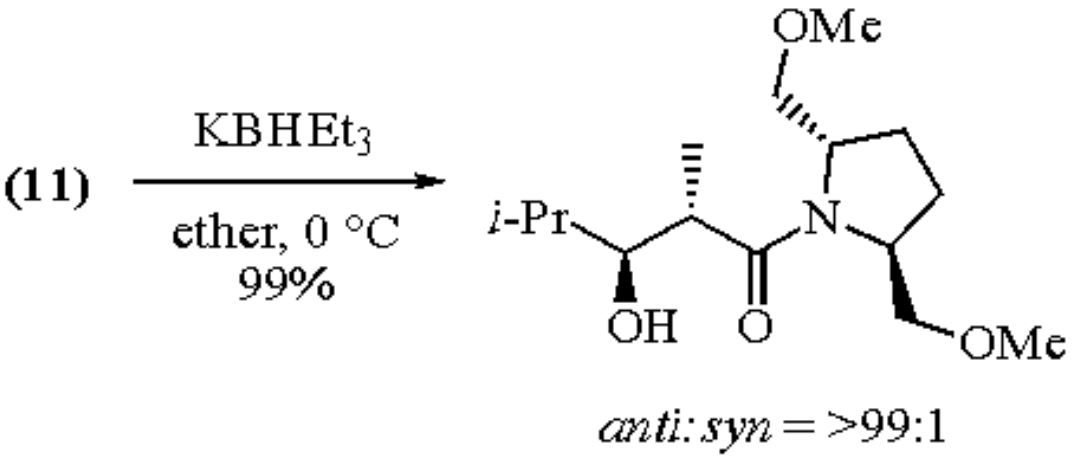

(5)

Cycloaddition Reactions.

Chiral acrylamides derived from pyrrolidines (**2**) or (**3**) undergo stereoselective [4 + 2] cycloaddition reactions with a

variety of cyclic dienes.[8a,13] Similarly, nitroso compounds derivatized with pyrrolidine (**2**) and generated in situ give cycloadducts with a high degree of stereoselectivity (eq 6).[8a,14] Intramolecular [2 + 2] cycloadditions involving pyrrolidine-derived keteniminium salts have been shown to produce chiral cyclobutanones.[4b]

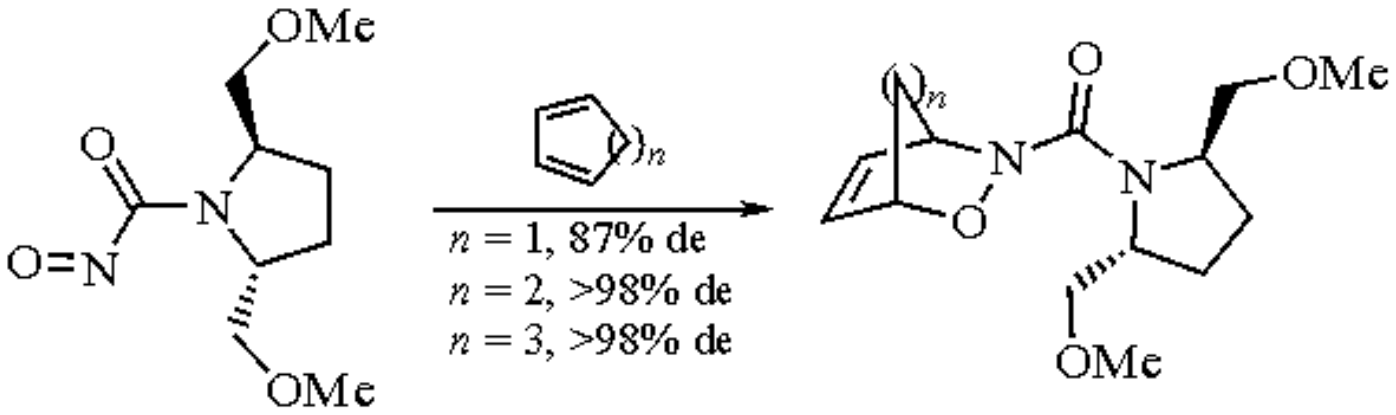

(6)

Other Reactions.

Other reactions in which pyrrolidines (**2**) and (**3**) have been used as chiral auxiliaries include radical additions,[8b] electrocyclizations,[15] and Wittig rearrangements.[7b]

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13. Kawanami, Y.; Katsuki, T.; Yamaguchi, M. *BCJ* **1987**, *60*, 4190.
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Patrick G. McDougal

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide[1]

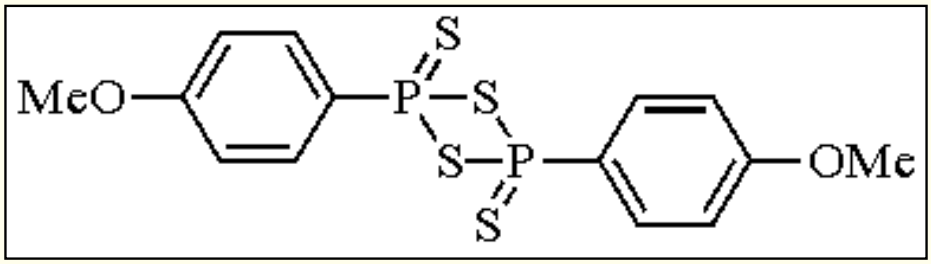

[19172-47-5] · $C_{14}H_{14}O_2P_2S_4$ · 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide · (MW 404.45)

(reagent for the conversion of carbonyl into thiocarbonyl groups[1])

Alternate Name: Lawesson's reagent.

Physical Data: mp 228-229 °C.

Solubility: modestly sol boiling organic solvents such as toluene, chlorobenzene, anisole, dimethoxyethane.

Form Supplied in: yellowish evil-smelling crystals; typical impurity is P_4S_{10}.

Analysis of Reagent Purity: FTIR spectrum.[1c]

Preparative Methods: reaction of P_4S_{10} with anisole in excess refluxing anisole.[2]

Purification: recrystallization from boiling toluene.

Handling, Storage, and Precautions: can be stored for months at rt if moisture is excluded. Prolonged heating in solution causes decomposition (polymerization). It is toxic and should be handled under a fume hood since hazardous H_2S is easily liberated with moisture.

Thionation of Carbonyl Compounds.

Lawesson's reagent (LR) is a most powerful reagent for the thionation of a wide variety of carbonyl compounds. Ketones, enones, carboxylic esters, thiolocarboxylic esters, amides, and related substrates are conveniently transformed into the corresponding thiocarbonyl compounds.[1] In some cases, follow-up products are isolated since certain thiones

are labile under the reaction conditions. Compared with P_4S_{10}, from which it is easily prepared,[2] LR exhibits several advantages. Its reactivity is significantly higher and it is sufficiently soluble in hot organic solvents, allowing homogeneous reaction conditions to be applied. Therefore many carbonyl compounds can be successfully thionated with LR but not with P_4S_{10}, or at least thionated in higher yields. Several reagents with structures similar to LR, which are even more reactive or more selective than LR, have been developed and are used in particularly difficult cases (see ***2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide***). The workup procedure depends on the reaction conditions applied, in particular on the solvent, and the products formed. If DME is used, the reaction mixture can be poured into water and the product extracted as usual. Low boiling hydrocarbons are best evaporated and the residue, which contains the product together with 2,4,6-tris(4-methoxyphenyl)cyclotriphosphoxane 2,4,6-trisulfide, is subjected to column chromatography. High boiling solvents such as tetralin or trichlorobenzene should be removed by flash chromatography in order to avoid thermal decomposition of the labile thiones.

Thioketones.

Thioketones of different types have been obtained from the corresponding ketones. Lawesson, who discovered LR to be a powerful reagent for the conversion of C=O into C=S groups, described the preparation of diaryl thioketones.[3] Substituents such as Me, Br, NO_2, or NMe_2 do not affect the good yields of up to 98% (eq 1).

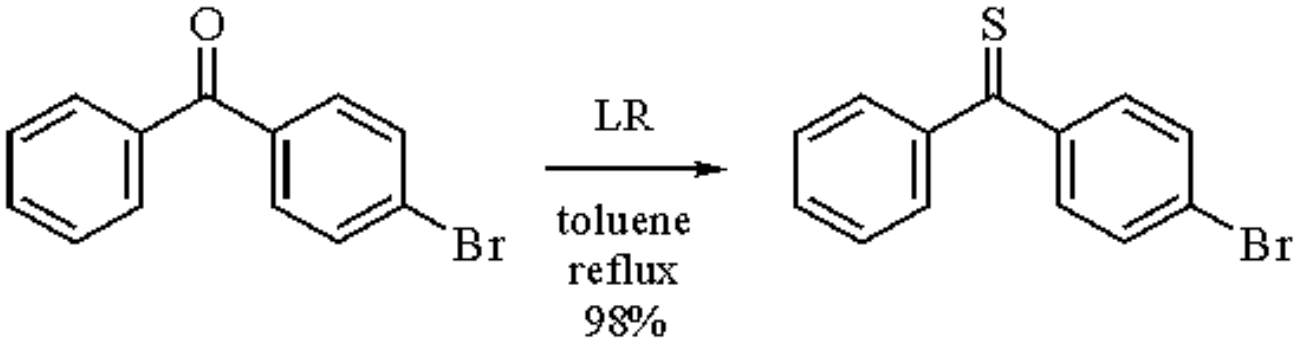

(1)

Recently, the diferrocenyl thioketones (**1**) and (**2**) were prepared from the corresponding ketones.[4] Alkyl aryl and dialkyl thioketones (**3**),[3] (**4**),[5] (**5**)[6] are formed in good yields if enethiolization is unfavored or impossible, whereas mainly enethiols are obtained from cycloalkanones (eq 2).[7]

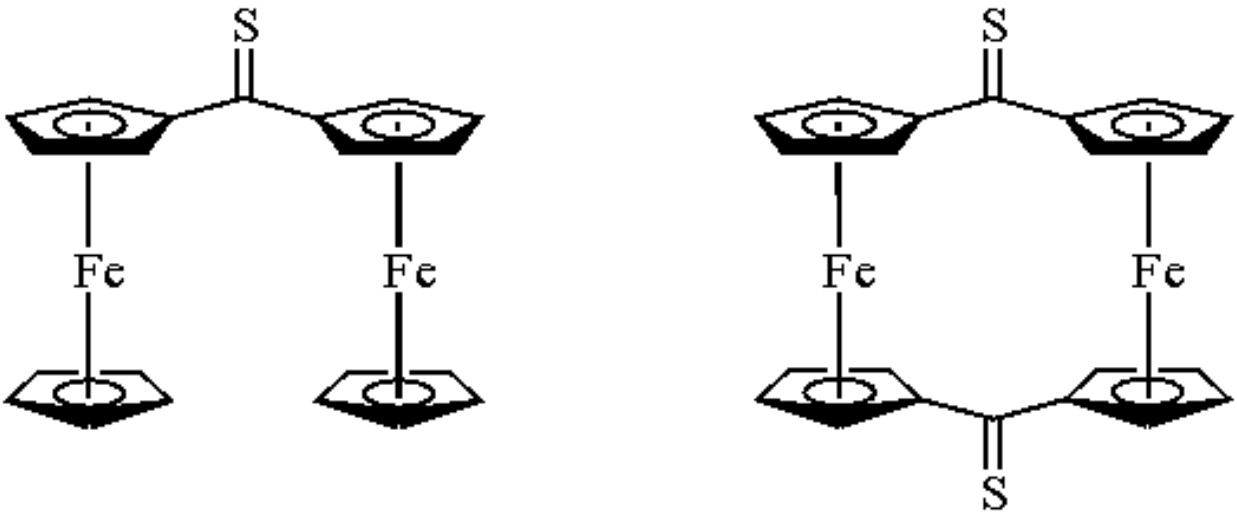

(1) 71% **(2)** 90%

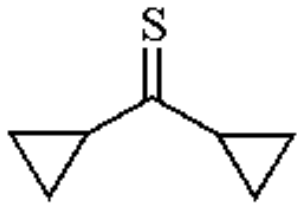

(3) 83%

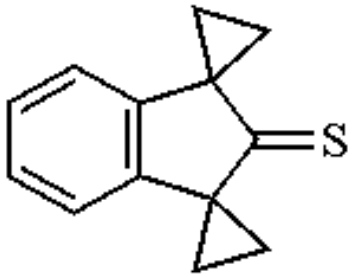

(4) 85%

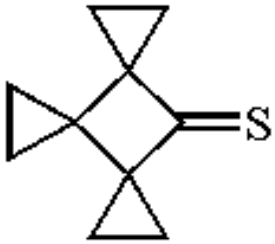

(5) 85%

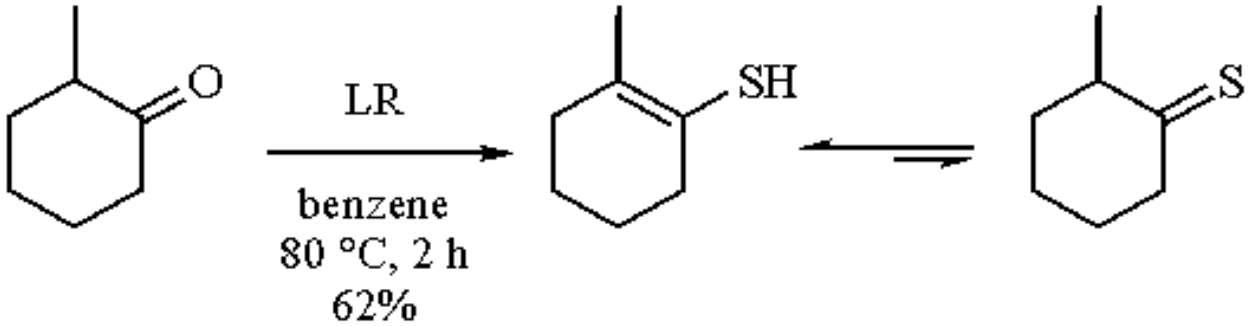

(2)

2-Cyclohexenones are thionated with LR (eq 3),[7] but only the vinylogous dithioester (**6**) is a stable compound. Acyclic enones (chalcones) give on reaction with LR the enethione dimers (eq 4).[8]

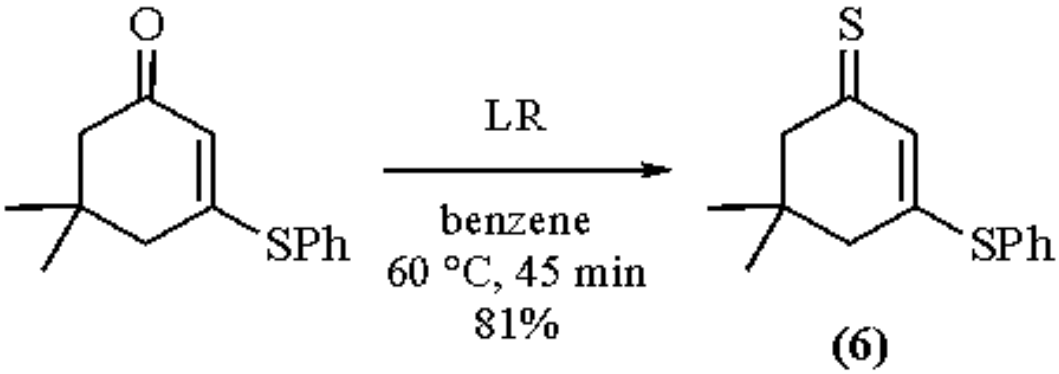

(6)

(3)

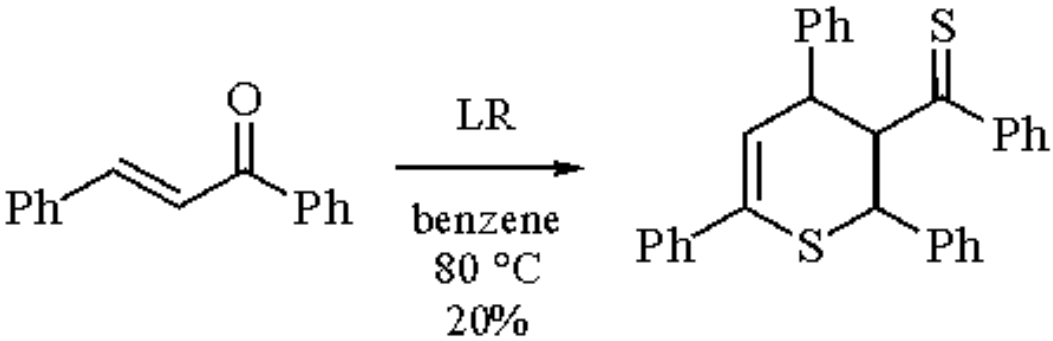

(4)

Again, stable enethiones are formed if an electron donating substituent (e.g. NR_2) is present in the β-position (eq 5).[9] Certain isolable 2,5-cyclohexadienethiones can be further transformed into bicyclohexadienylidenes (eq 6).[10]

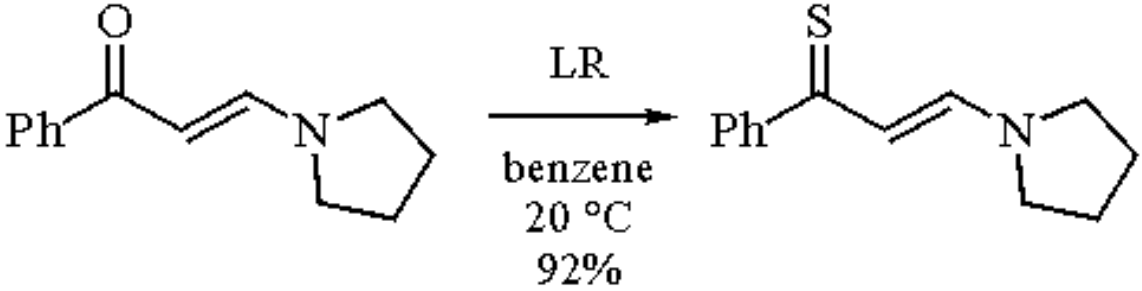

(5)

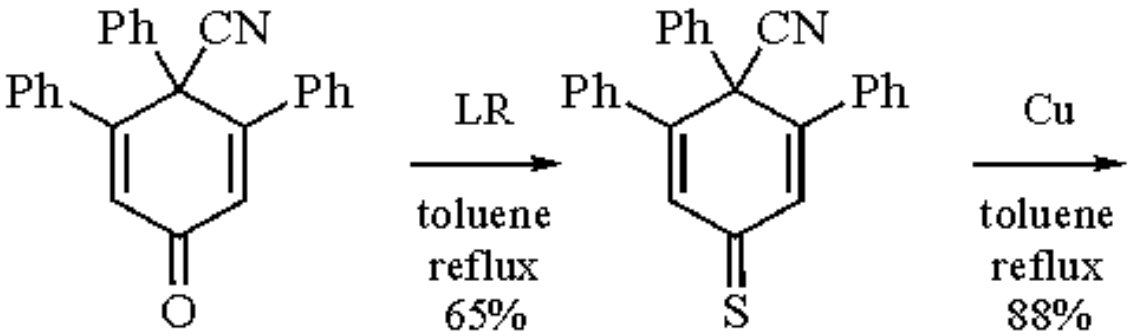

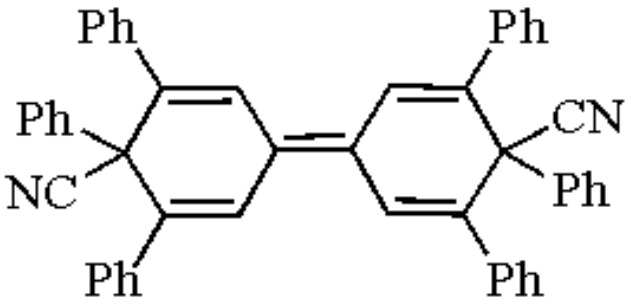

(6)

The thioanalogs of natural products such as the steroid (**7**)[11] or the colchicine alkaloid (**8**)[12] have also been prepared by use of LR.

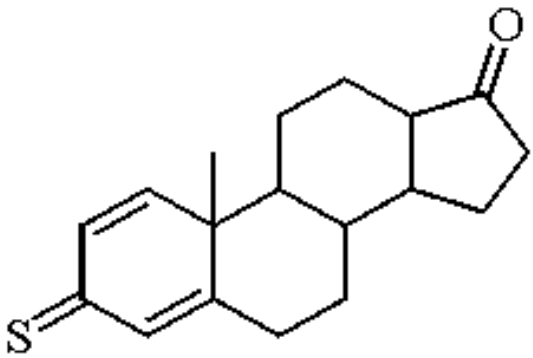

(7) 96%

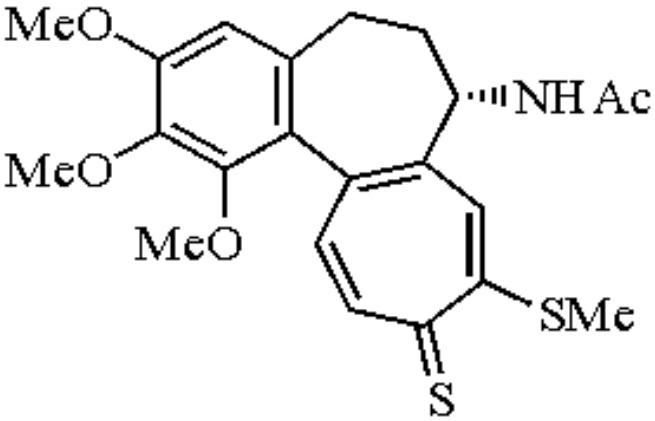

(8) 33%

Thio Analogs of Dicarbonyl Compounds.

In general, the most labile thiono analogs of α-dicarbonyl compounds cannot be prepared by any thionation procedure. However, thioacenaphthoquinone (**9**) as well as thioanthraquinone (**10**) were obtained from the quinones and LR.[13] Even α-thioxo thioamides are available (eq 7),[14] whereas 2,2,5,5-tetramethyl-4-thioxo-3-hexanone, which itself cannot be prepared from the corresponding diketone, reacts with LR to yield 3,4-di-*t*-butyl-1,2-dithiete, the valence isomer of the open-chain dithione (eq 8).[15]

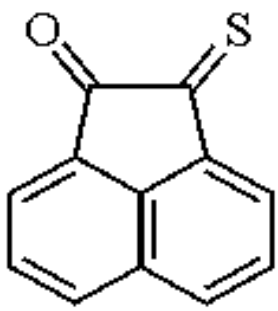

(9) 70%

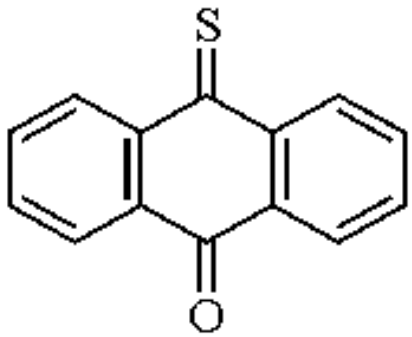

(10) 65%

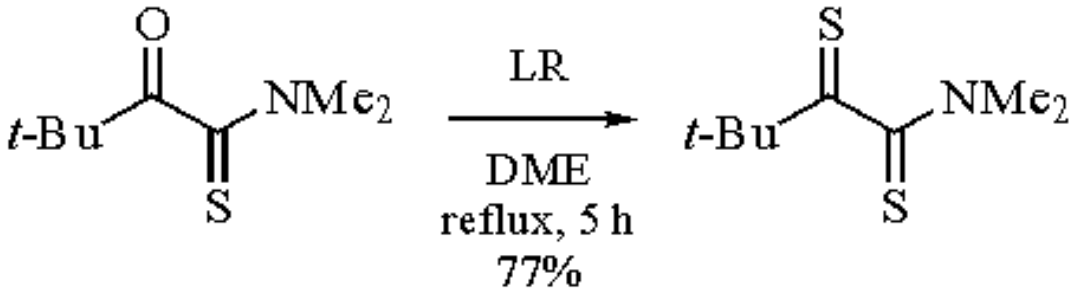

(7)

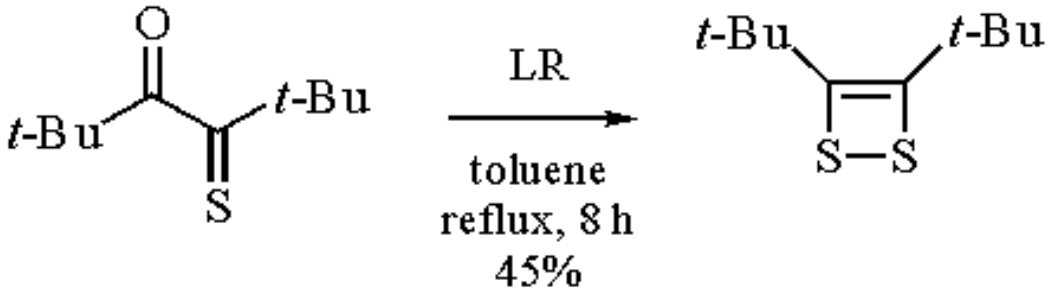

(8)

Thioketones with pronounced steric hindrance are obtained on reaction of cyclobutane-1,3-diones with LR (eq 9).[16]

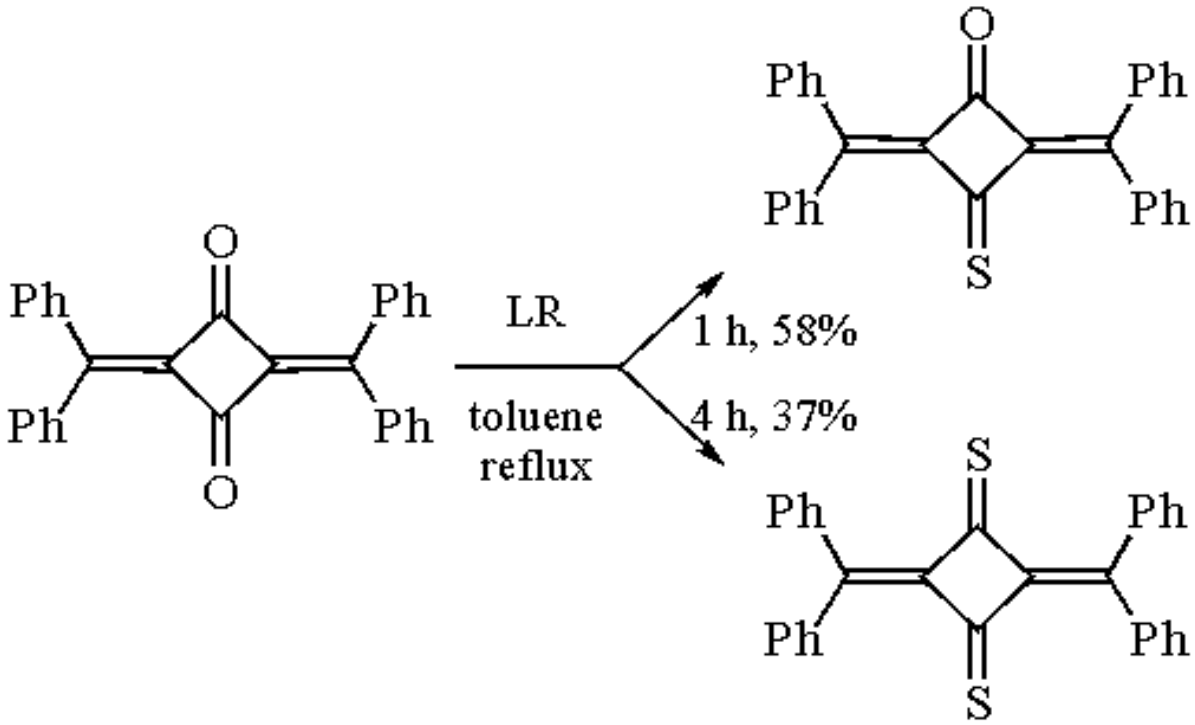

(9)

Diketones with remote C=O groups can be transformed by LR into the mono- or dithiones.[17]

Thiono Esters and Lactones.

Although thiono esters can be conveniently prepared via imidates,[18] the introduction of LR for the thionation of esters[3] represents a great advance in synthetic methodology since ordinary esters are used as educts and P_4S_{10} only reacts with esters if enforced reaction conditions are applied, under which many thiono esters decompose. Facile conversion of aliphatic and aromatic esters (eq 10),[3,19] α,β-unsaturated esters,[20] and lactones[21] to the corresponding thiono derivatives is effected in high yields (eqs 11 and 12).[22,23]

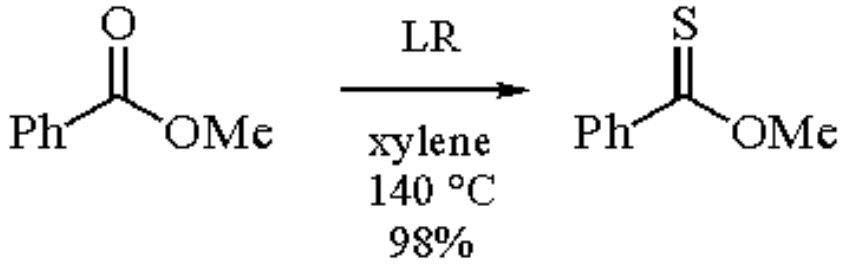

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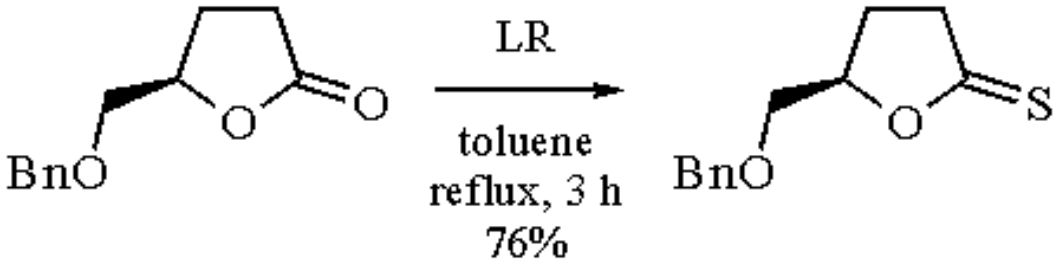

(11)

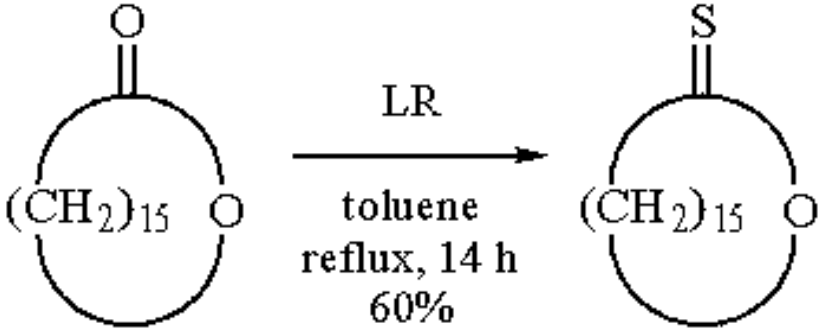

(12)

Thiono esters and lactones are important intermediates in modern organic synthesis since they easily undergo useful follow-up reactions. Ethers are formed on reduction with ***Raney Nickel***[24] or ***Tri-n-butylstannane*** (eq 13).[25]

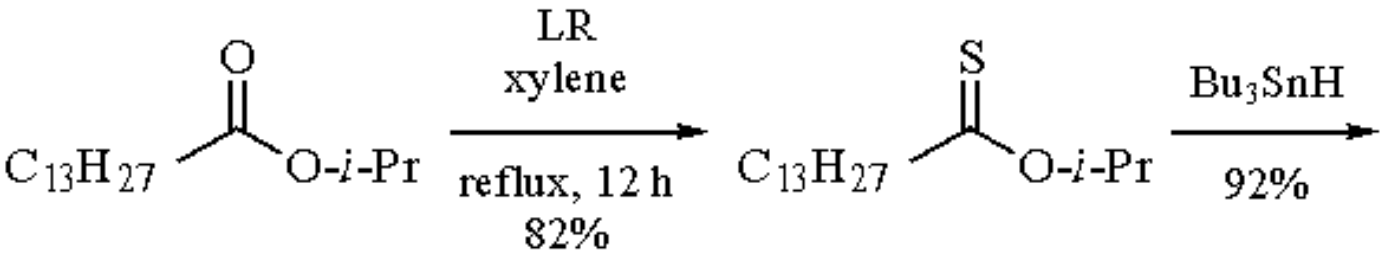

(13)

Macrocyclic bis-thionolactones have been prepared with LR. These were converted by reduction with ***Sodium Naphthalenide*** into the radical anions, which gave bicyclic systems through radical dimerization and subsequent methylation (eq 14).[26] This method was successfully applied by Nicolaou et al.[27] in the total synthesis of hemibrevetoxin B. One of the crucial steps of the synthesis was the preparation of the bis-thiono ester (**11**), which was achieved by using LR together with tetramethylthiourea in xylene at 175 °C.[27]

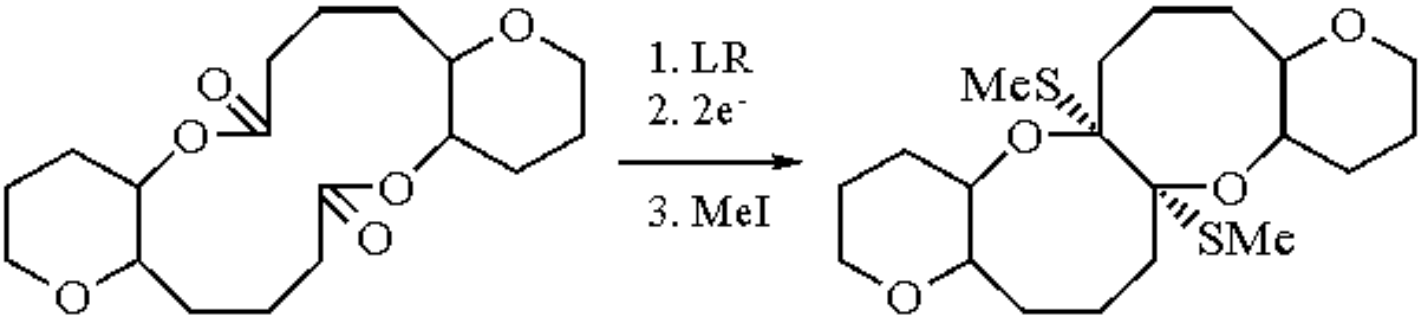

(14)

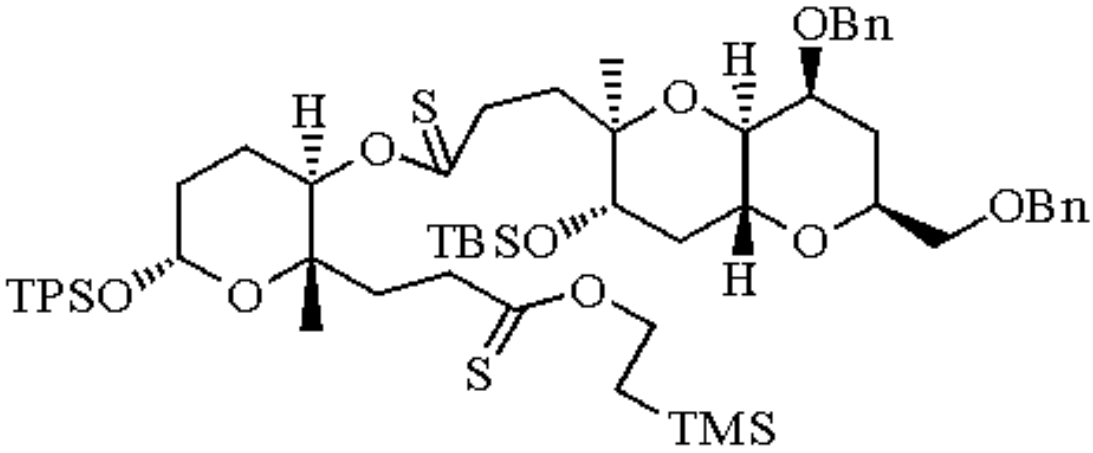

(11) 49%

Dithioesters and Related Compounds.

Thioesters are transformed into the corresponding dithioesters on reaction with LR.[3,20,28] Again the yields are nearly quantitative even if steric hindrance can be expected (eq 15).[3]

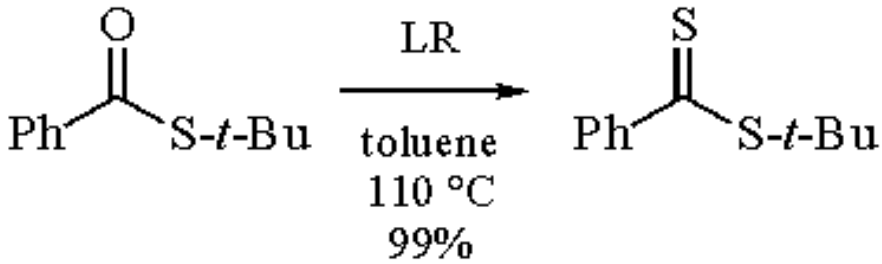

(15)

The reaction is completed within 5-15 min if tetralin at 210 °C is used as solvent.[28] Also, dithio-γ-lactones,[21,28] including dithiophthalides[29] and dithio-α-pyrones,[30] are formed smoothly whereas the hitherto unknown simple β- or δ-dithiolactones cannot be prepared, neither with LR nor by any other method. Interestingly, dithiopilocarpine is formed as a mixture of diastereomers on reaction of pilocarpine with LR (eq 16), i.e. both oxygen atoms of (**12**) are replaced by sulfur.[31] In an interesting sequence of thionation and rearrangement reactions, three different thiono analogs of 1,8-naphthalic anhydride were prepared (eq 17).[32]

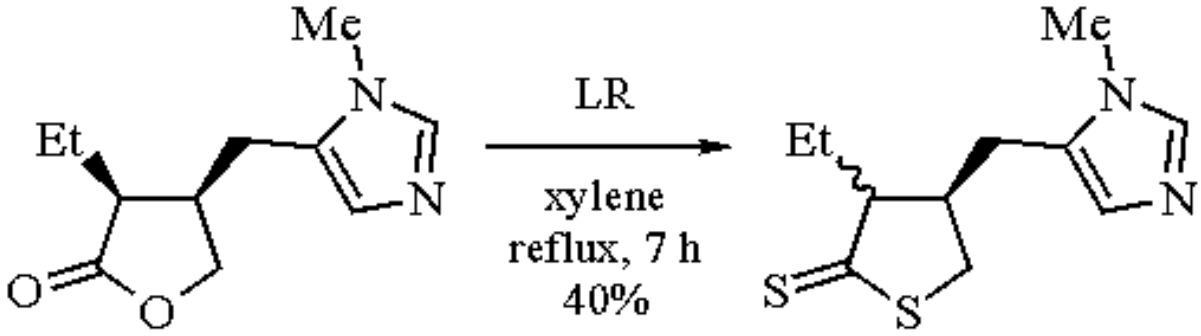

(16)

(12)

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide

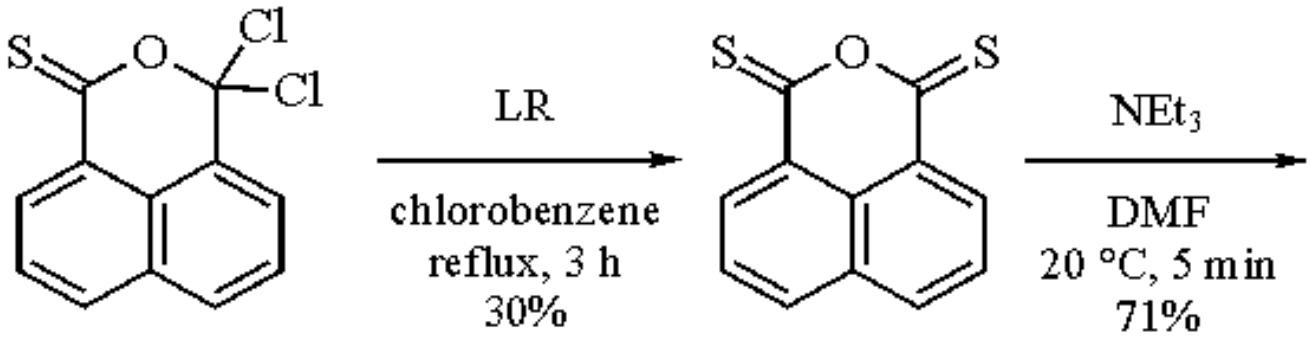

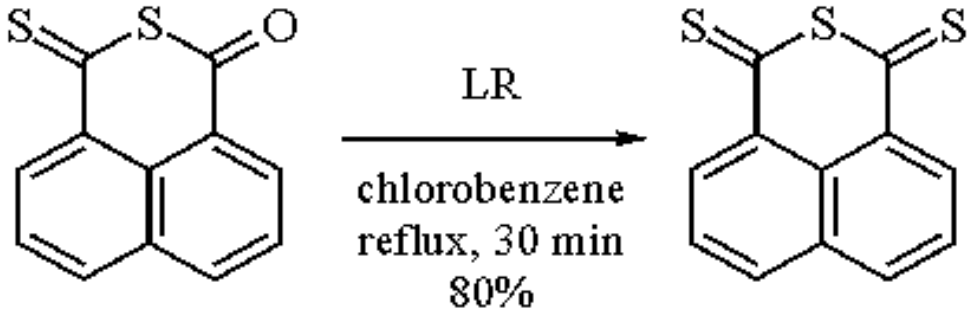

(17)

Thioamides and Related Compounds.

Thioamides are the most stable thiocarbonyl compounds and have been prepared, for a century, from amides and P_4S_{10} under rather drastic conditions. However, even for this purpose LR has turned out to be a superior reagent. High yields are obtained for all types of thioamides[1,33] and -lactams[1,33,34] including the elusive unsubstituted acrylothioamide (eq 18)[35] and thioformamides or thioamides bearing sensitive substituents such as NO_2, Z-NH,[36] or OH (eq 19).[33]

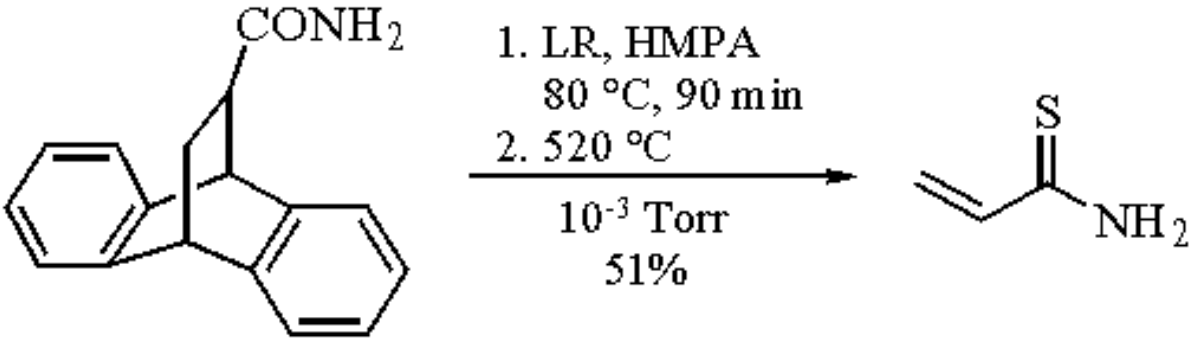

(18)

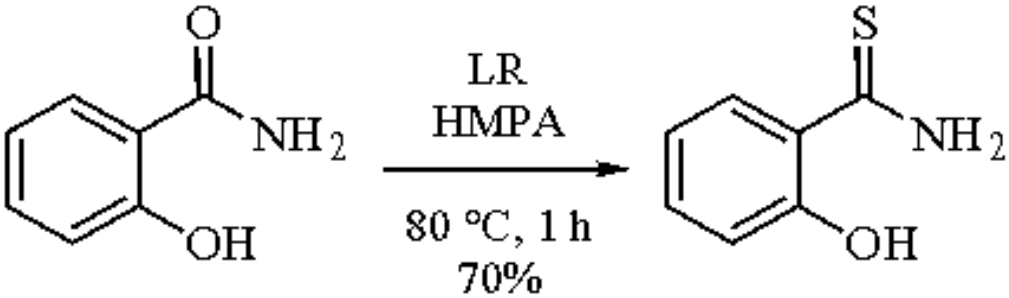

(19)

β-Lactams are also smoothly transformed[34] (eq 20),[37] which is important for the preparation of thio analogs of β-lactam antibiotics or azetidines. Furthermore, endothio oligopeptides became conveniently available only after LR had been introduced as reagent[1,38,39] (eq 21).[40]

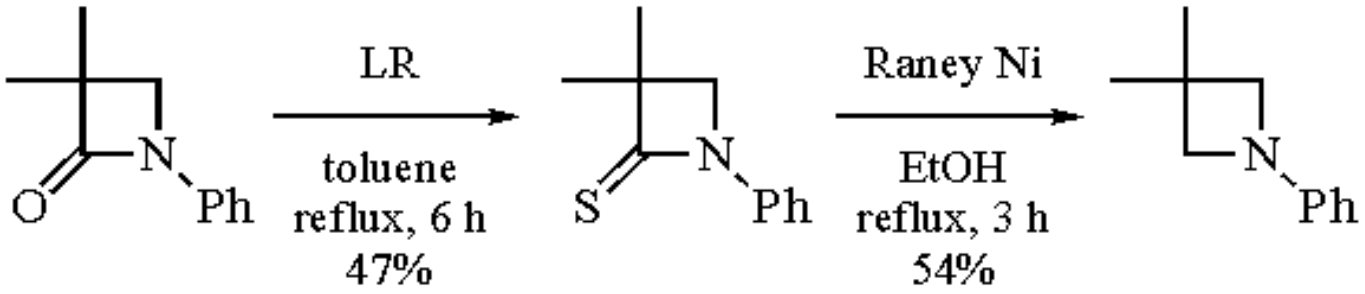

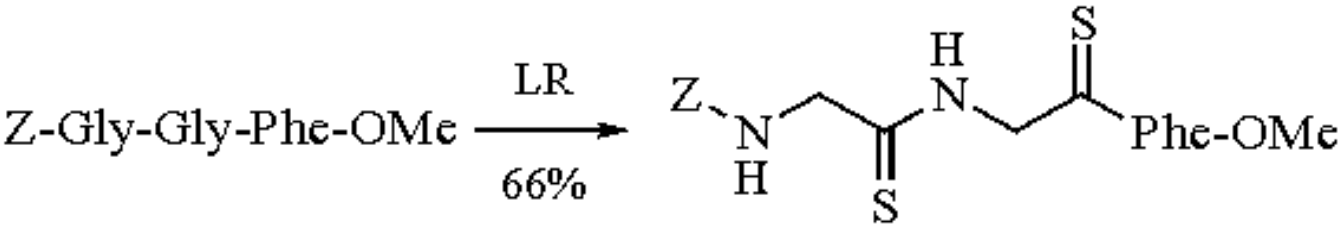

Recently the cyclopeptide [D-cysteine]^{8}cyclosporin has been prepared from [D-serine]^{8}cyclosporin via selective thionation with LR at the 7-position followed by intramolecular sulfur transfer.[41]

Miscellaneous Reactions of LR.

Under particular conditions, certain carbonyl compounds and other substrates react with LR to form thiophosphonates or heterocycles, which fact throws some light on the mechanism of thionation reactions with LR.[1] Carbinols undergo nucleophilic substitution with LR to form the corresponding thiols.[42] The redox properties of LR can be utilized to prepare dithiolactones from dialdehydes (eq 22),[43] α-oxo thioamides from nitro ketones (eq 23),[44] or sulfides from sulfoxides.[45]

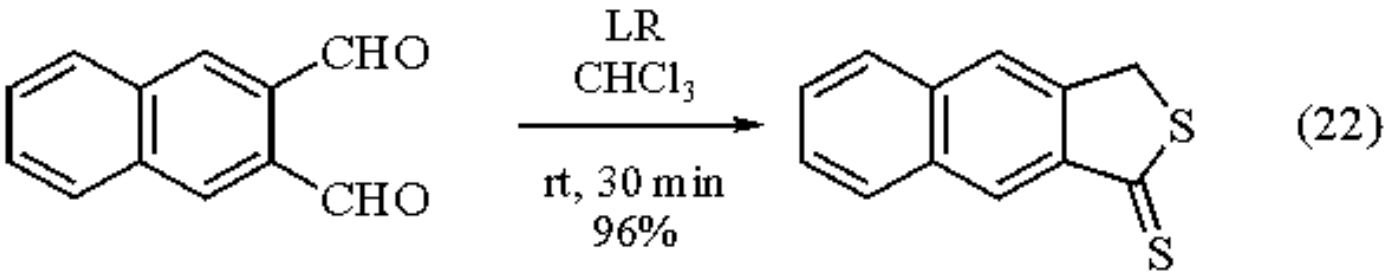

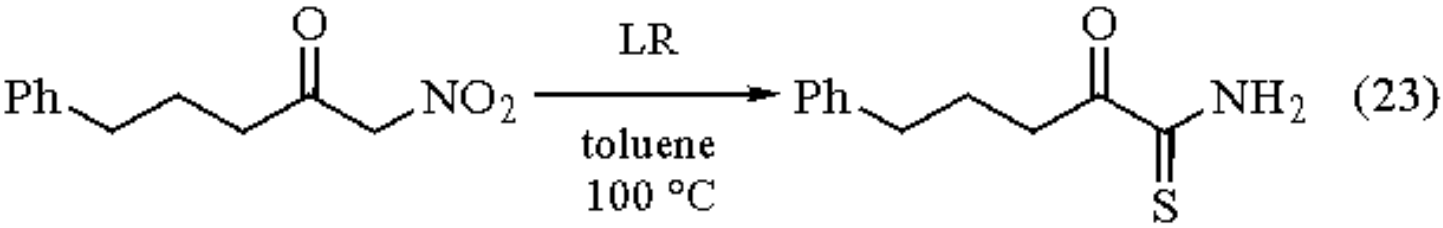

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Bis(*N*-methylsalicylaldimine)nickel[1]

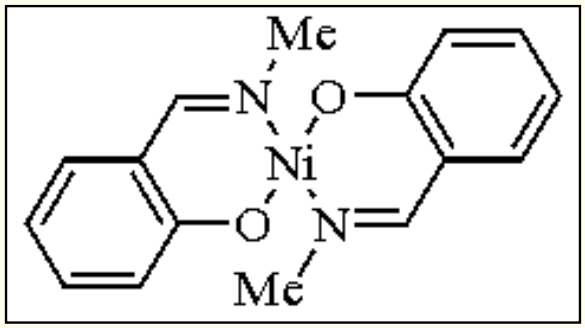

[14322-02-2] · $C_{16}H_{16}N_2NiO_2$ · Bis(*N*-methylsalicylaldimine)nickel · (MW 327.00)

(used in conjunction with triisobutylaluminum for alkyne coupling,[2] allene synthesis,[3] and conjugate reduction of α,β-enones[5])

Alternate Name: $Ni(mesal)_2$.

Physical Data: mp 195-198 °C, *d* 1.45 g cm^{-3}, λ_{max} 354 nm (solid).

Solubility: sol alcohol, ether, benzene, $CHCl_3$; slightly sol hexane.

Form Supplied in: olive-green solid, not commercially available.

Preparative Method: easily prepared from a 2:2:1 mixture of salicylaldehyde, methylamine, and nickel acetate in alcohol solution at 60 °C for 1 h. The green solid can be recrystallized from alcohol or from chloroform/petroleum ether.[1]

Handling, Storage, and Precautions: stable, nonhygroscopic; nickel compounds are cancer suspect agents.

Triisobutylaluminum-Bis(*N*-methylsalicylaldimine)nickel.

$Ni(mesal)_2$ modifies reactions of ***Triisobutylaluminum***, allowing for greater selectivity in reactions of alkynes. The two reagents are premixed, typically in a 50:1 Al:Ni molar ratio, in the reaction vessel before addition of substrates, but no isolation of the combined reagent is necessary. Note that most reactions are carried out in the absence of solvent.[2] Caution: triisobutylaluminum is pyrophoric and moisture sensitive.

Alkyne Coupling.

By itself, (i-Bu)$_3$Al promotes the coupling of 1-alkynes to give a complex mixture of i-butylalkenes, 1,3-dienes, and trisubstituted benzenes (eq 1). Catalytic amounts of Ni(mesal)$_2$ accelerate the reaction and show a preference for formation of head-to-tail dimers and benzene products (eq 2).[2] Nickel metallacyclopentadienes are proposed intermediates.

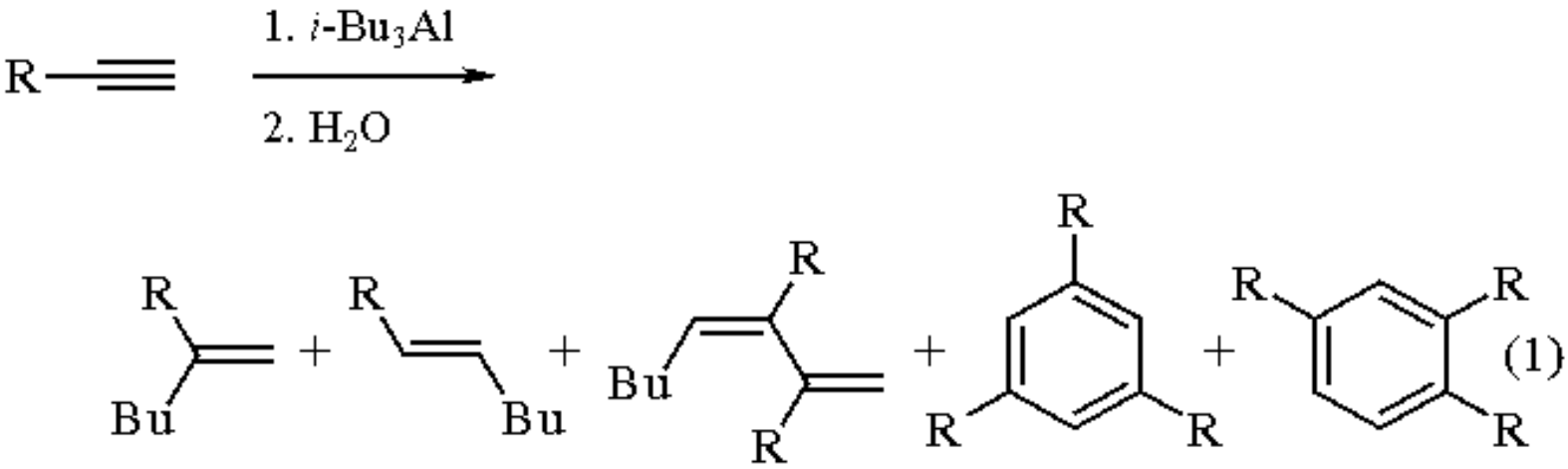

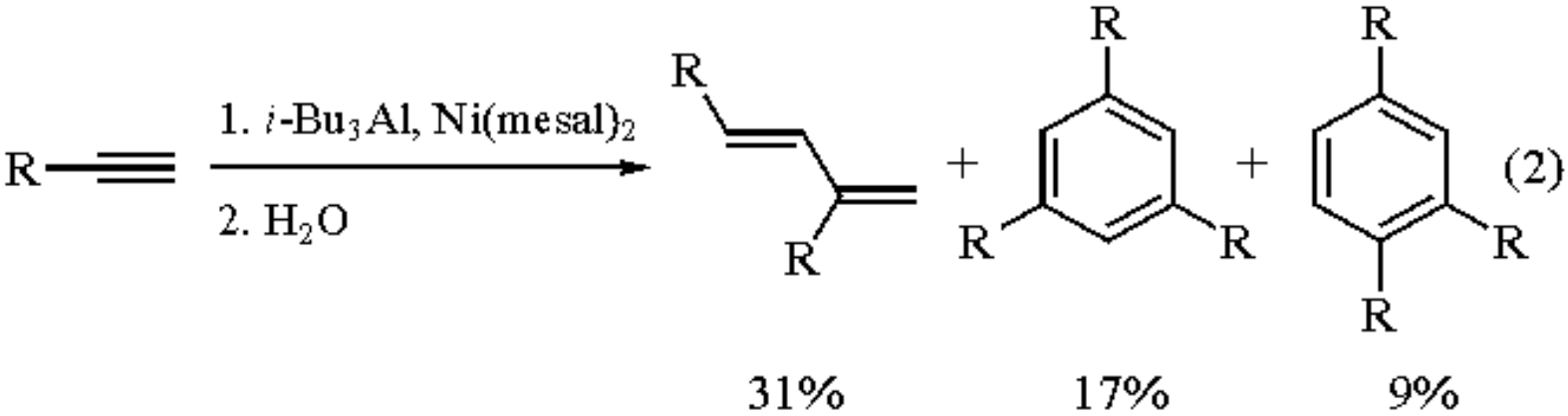

Allene Synthesis.

Ni(mesal)$_2$ catalyzes the cross-coupling reaction of allenic bromides with trialkylaluminum or Grignard reagents (eq 3).[3] The method is fairly general. Triisobutylaluminum was used in two-fold molar excess to the allene and 1 mol % Ni(mesal)$_2$ catalyst was added. When an enantiomerically enriched sample of the bromoallene was used as substrate, the reaction was found to occur with predominant retention of configuration in the allenyl moiety.[4]

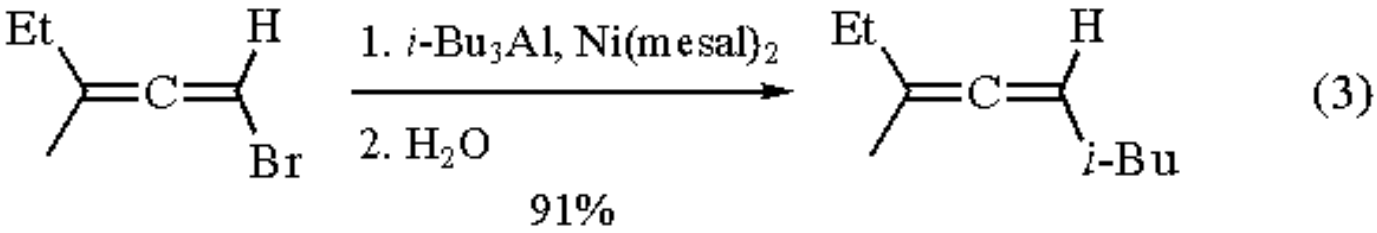

Reduction of α,β-Unsaturated Ketones.

Triisobutylaluminum alone leads to both 1,2-reduction products and 1,2-addition products on reaction with α,β-unsaturated ketones. In contrast, the same reaction catalyzed by 3 mol % $Ni(mesal)_2$ leads predominantly to reduction of the C-C double bond (eq 4).[5] The reaction is carried out in pentane at rt using a 1:1 molar ratio of enone and *i*-Bu_3Al.

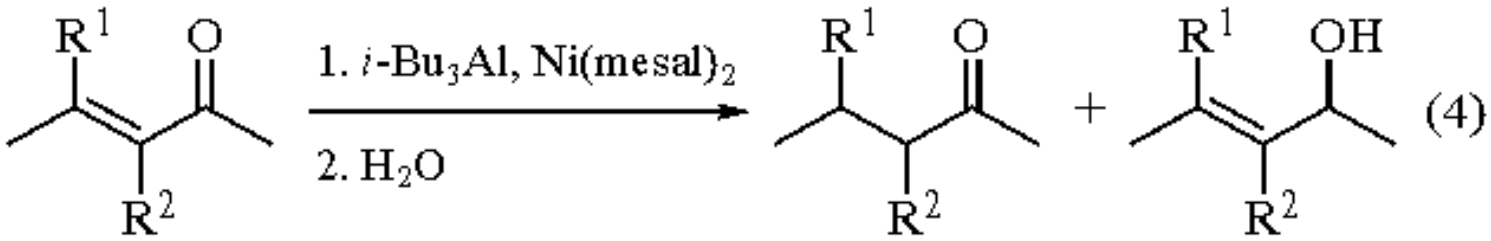

$R^1 = Me, R^2 = H$	96%	0%
$R^1 = H, R^2 = Me$	77%	23%

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2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide

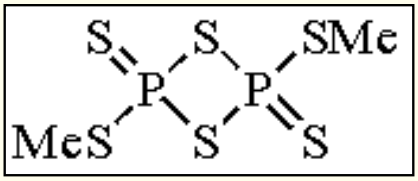

[82737-61-9] · $C_2H_6P_2S_6$ · 2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide · (MW 284.38)

(reagent for the conversion of carboxylic acids into dithioesters and carbonyl groups into thiocarbonyl groups)

Alternate Name: Davy's reagent.

Physical Data: mp 125-136 °C.

Solubility: sol hot aromatic hydrocarbons, chlorobenzene.

Form Supplied in: pale yellow, evil-smelling crystals.

Analysis of Reagent Purity: ^{1}H NMR spectrum: δ = 2.86 (d, J = 20 Hz, CH_3).

Preparative Method: reaction of P_4S_{10} with methanethiol or methanol.[1]

Purification: washing with cyclohexane.

Handling, Storage, and Precautions: should be stored in the cold with exclusion of moisture. It is very toxic and must be handled under a hood or in glove-boxes due to its intolerable odor and the hazardous methanethiol which is easily liberated with moisture.

Introduction.

2,4-Bis(methylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide as well as the analogous ethylthio, isopropylthio, and benzylthio derivatives have been introduced as reagents for syntheses by Davy and Metzner. These compounds (Davy's reagent, DR) can be used in the same way as Lawesson's reagent, LR (see ***2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide***), for the thionation of carbonyl groups. DR is, however, considerably more reactive and in many cases more selective than LR. Furthermore, it exhibits the unique ability to transform carboxylic acids into dithiocarboxylic esters in one step. Similar dithiadiphosphetane disulfides with arylthio substituents have been

designed in order to achieve an even improved effectiveness in thionation reactions and also to produce a more conveniently handled reagent compared with the obnoxious DR. The so-called Japanese reagent (JR), 2,4-bis(phenylthio)-1,3,2,4-dithiadiphosphetane 2,4-disulfide,[3] has recently found considerable synthetic application.

Transformation of Carboxylic Acids into Dithiocarboxylic Esters.[2,4]

Dithioesters bearing functional groups such as C=C double bonds,[2] halogen,[2,5] nitro,[6] or phenoxy groups[2] are obtained with yields of up to 68% on reaction of aliphatic (eq 1)[2b] or aromatic (eq 2)[5b] carboxylic acids with DR in boiling chlorobenzene. Acid chlorides can also be used as starting material.[2b,4] Isolation and handling of pure DR can be avoided by using a one-pot procedure (eq 3),[7] which consists of first reacting methanol or ethanol with P_4S_{10} followed by addition of the carboxylic acid and further P_4S_{10}. The above mentioned JR enables one to prepare phenyl dithiocarboxylates in extremely short reaction times (eq 4).[3]

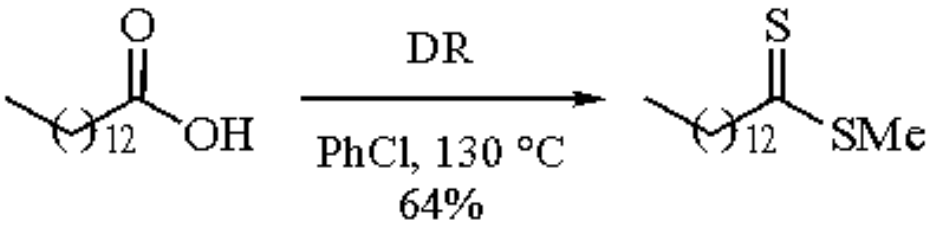

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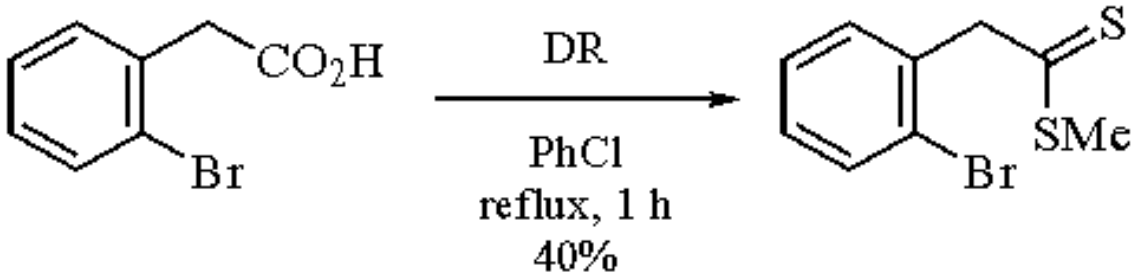

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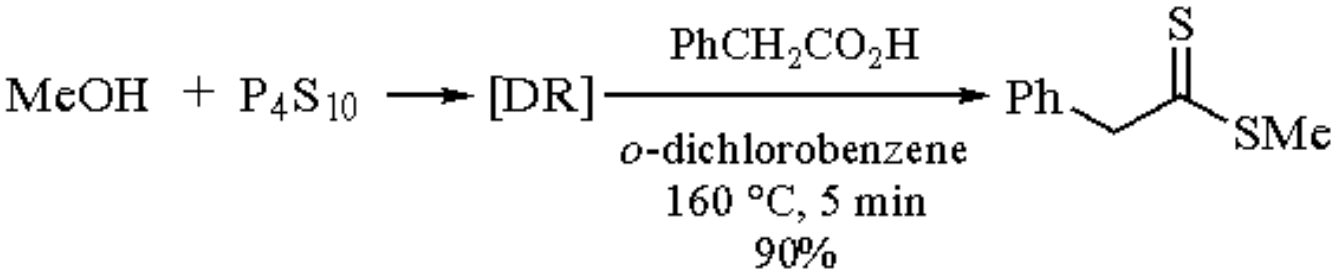

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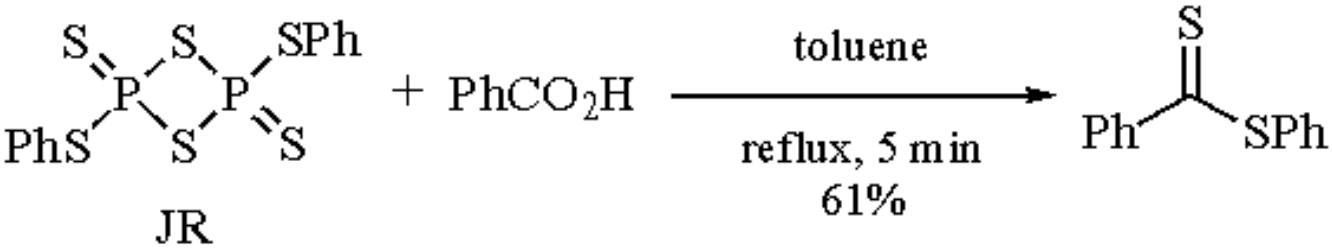

(4)

Thionation of Carbonyl Compounds.

Diaryl thioketones[8] and 2,4-bis(diphenylmethylene)cyclobutane-1,3-dithione[9] were obtained on reaction of the corresponding ketones with DR. On the other hand, JR was utilized to thionate selectively the carbonyl group of benzil monophenylimine.[10] If carboxylic esters or lactones are reacted with DR, dithiocarboxylic esters[4] or dithiolactones[4,8] are formed, i.e. the carbonyl group is thionated and the alkoxy group is substituted by an alkylthio group. Bis(5-methyl-2-thienyl) disulfide is produced in this way from a butenolide (eq 5).[4]

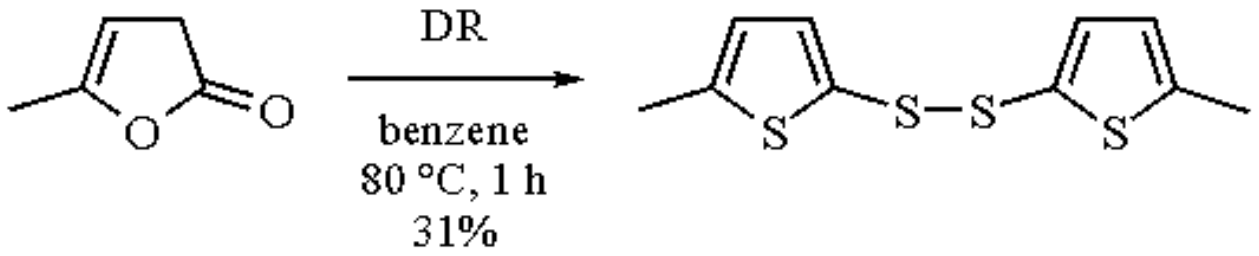

(5)

A systematic study on the thionation reactions of primary, secondary, and tertiary amides and lactams with DR compared with LR and 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, the so-called Belleau's reagent (BR),[11] has been performed.[12] Generally, good yields are obtained with whichever reagent is used, but each reagent may exhibit advantages in a special case. DR has been mainly utilized for the preparation of simple thioamides (eq 6).[8]

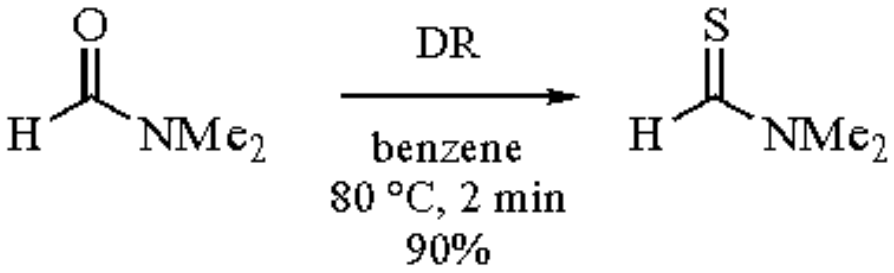

(6)

JR has found application in endothiopeptide synthesis.[3,13,14] One carbonyl group of a cyclohexapeptide is selectively thionated with JR (eq 7).[15] The cyclic thiopeptide exhibits enhanced effectiveness as an inhibitor of triosephosphate isomerase (TIM). This results from the pronounced alteration of the backbone conformation which is due to different hydrogen bridges. Belleau's reagent, BR, can be used similarly to JR to prepare thiooligopeptides selectively[16,17] or thiono esters of the carbohydrate series (eq 8).[18]

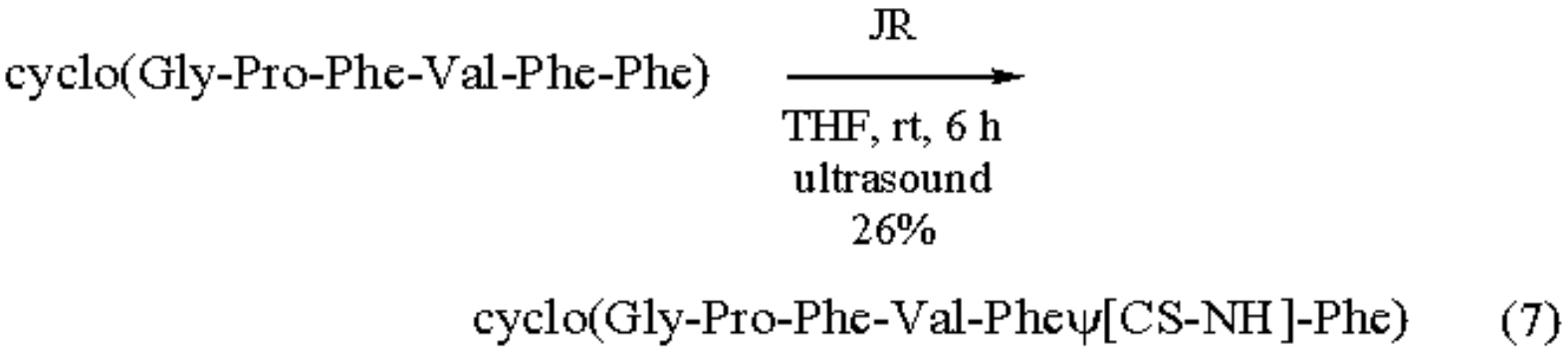

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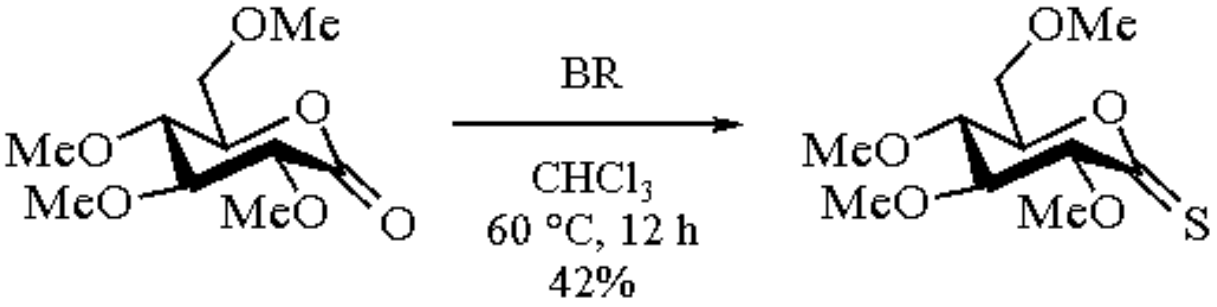

(8)

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Bis(methylthio)(trimethylsilyl)methane

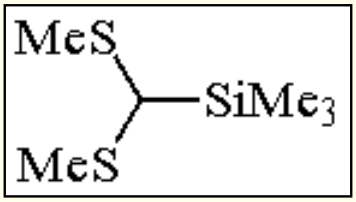

[37891-79-5] · $C_6H_{16}S_2Si$ · Bis(methylthio)(trimethylsilyl)methane · (MW 180.40)

(reagent used for synthesis of bis(methylthio)ketene acetals from aldehydes and ketones;[1] acyl anion synthon for conjugate additions to enones and enoates;[2] useful for one-carbon homologations[3])

Physical Data: bp 67-70 °C/10 mmHg.

Solubility: insol H_2O; sol organic solvents.

Preparative Methods: prepared from lithiobis(methylthio)methane by silylation with chlorotrimethylsilane (eq 1).[1] Both bis(methylthio)methane and ***Chlorotrimethylsilane*** are commercially available.

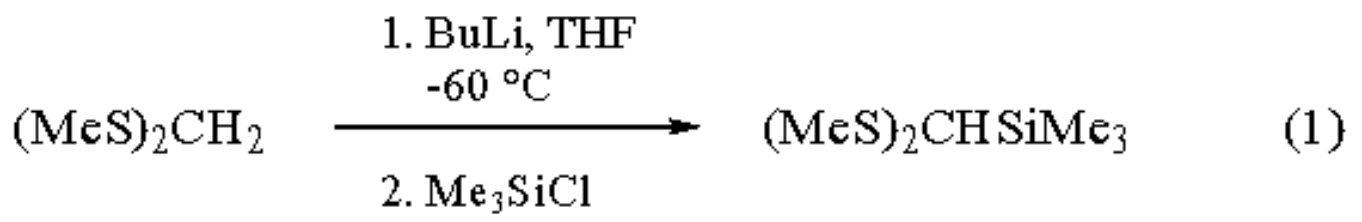

Handling, Storage, and Precautions: use in a fume hood.

Lithiobis(methylthio)(trimethylsilyl)methane.

The anion is generated by treatment of the title compound with ***n-Butyllithium*** in THF at -60 °C (eq 2). This species is well-behaved at low temperature. Useful reactions of this anion are discussed in the following sections.

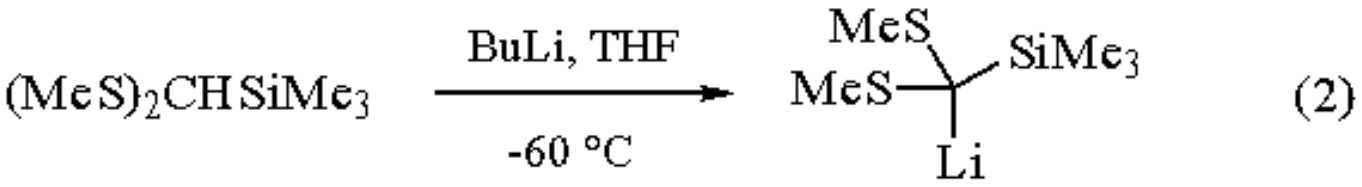

Thioketene Acetals.

The lithio reagent readily converts aldehydes and ketones into the corresponding bis(methylthio)ketene acetals via a Peterson alkenation sequence.[1] Aromatic aldehydes give excellent yields under these conditions (eq 3), and certain enolizable ketones such as acetophenone and cyclohexanone also react accordingly (eq 4). Alternative methods for preparing these acetals include a Horner-Wittig process that uses phosphonate derivatives[4] and an alkylative process involving CS_2 and MeI.[5] Relative to these alternatives, the title reagent offers advantages of ease of reagent preparation and control of regioselectivity. The phosphonate reagents are more nucleophilic, however, and avoid competitive deprotonation.

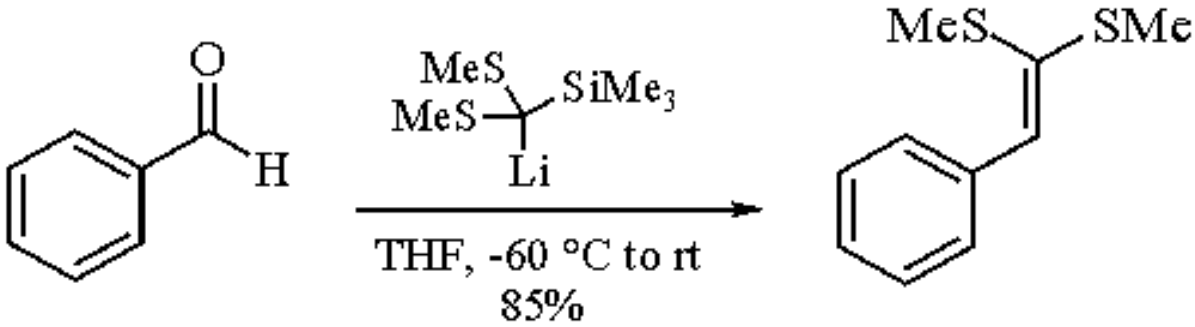

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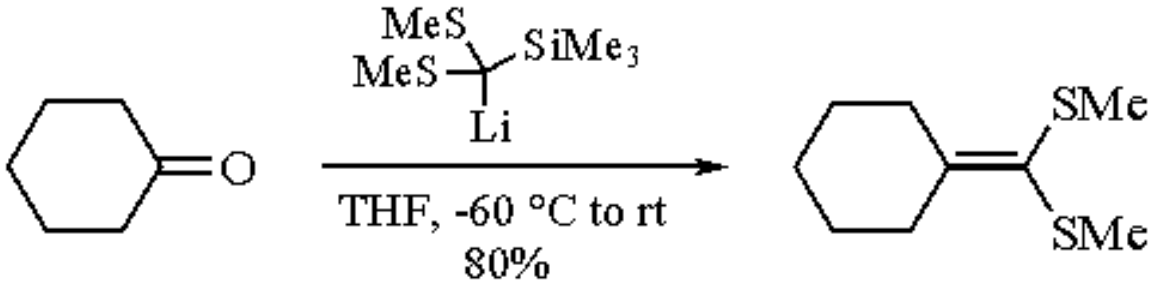

(4)

Reaction of the lithio species with α-oxo ketones and aldehydes allows the formation of β,β-disubstituted enones, useful intermediates for the preparation of unsaturated 1,5-diketones (eq 5).[6]

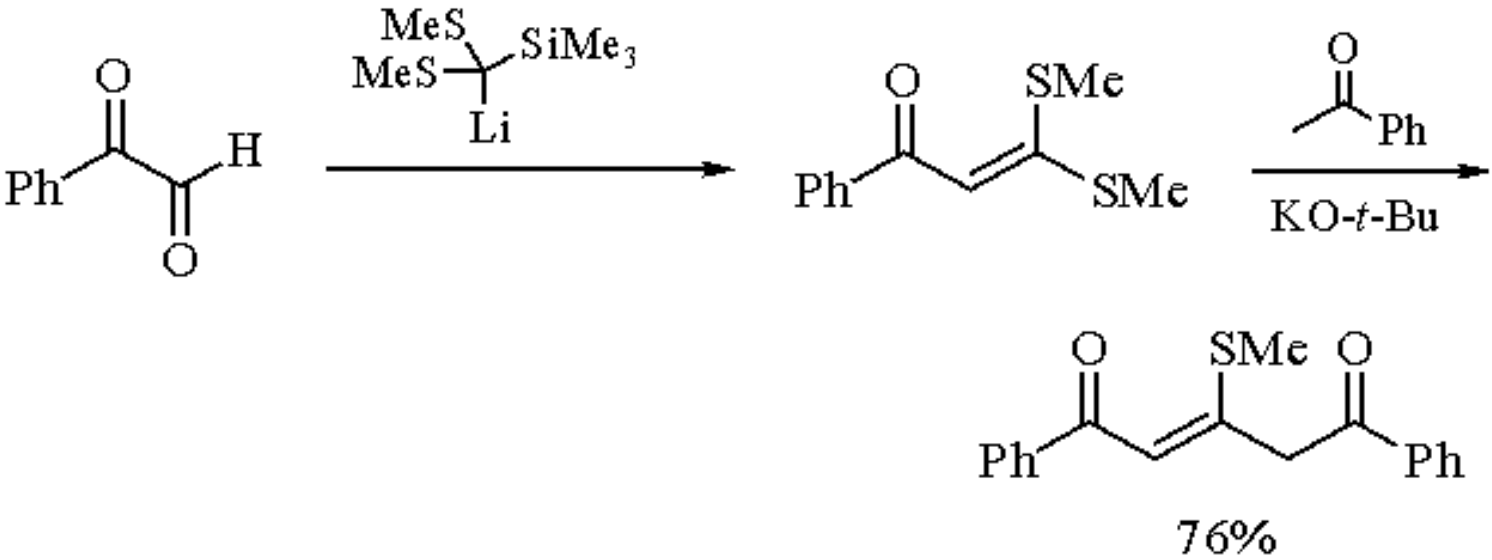

(5)

Acyl Anion Conjugate Additions.

The lithio reagent readily undergoes 1,4-addition to unsaturated substrates (eq 6), in direct contrast to the corresponding ***RL031-***, which is a poor Michael donor.[2] The initial Michael adducts can also be alkylated to provide highly functionalized products. Very good levels of diastereoselectivity have been observed in the 1,4-addition and enolate alkylations of cyclic enoates (eq 7)[7] and acyclic enones (eq 8).[8]

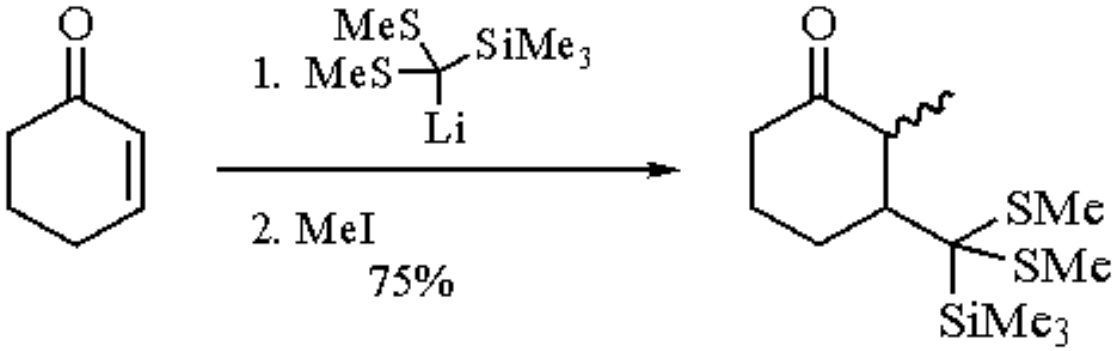

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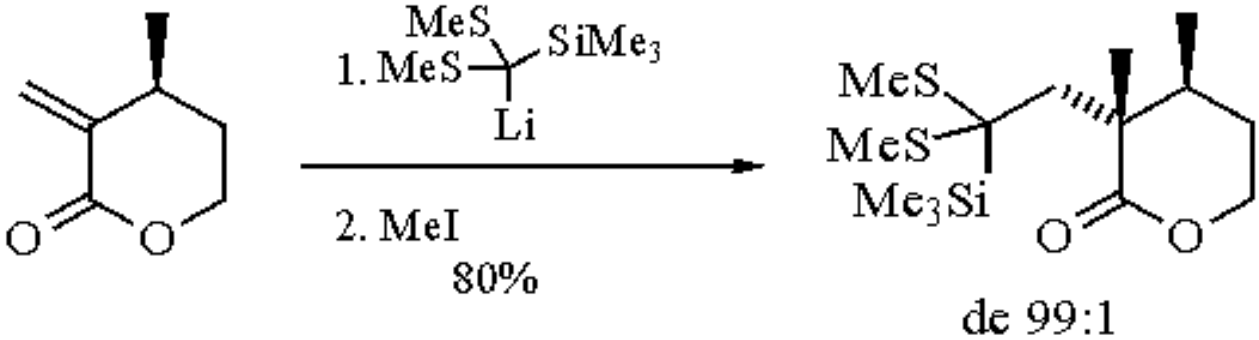

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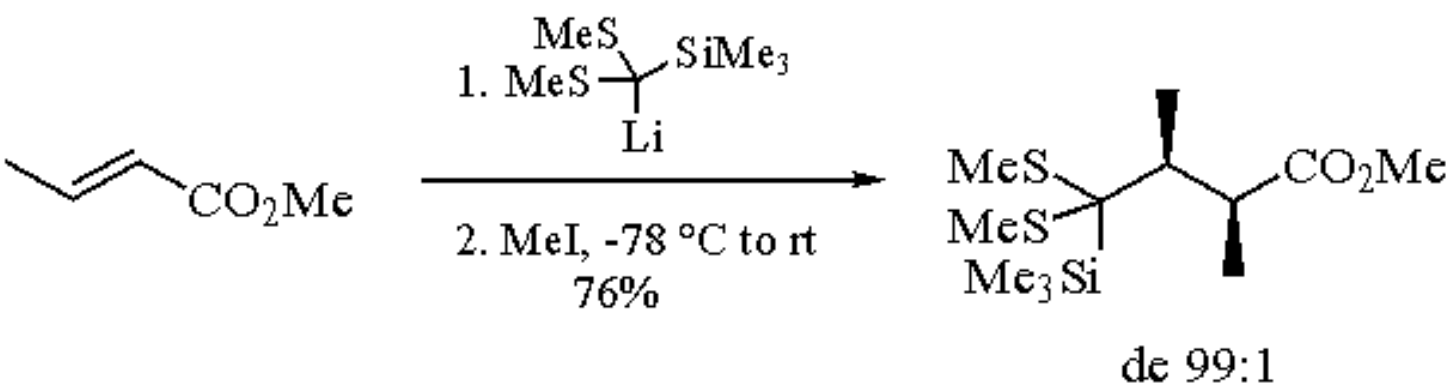

(8)

Other effective Michael donors of this type include lithiobis(phenylthio)(trimethylsilyl)methane,[9] lithio(methoxy)(phenylthio)(trimethylsilyl)methane,[10] and lithio(methylthio)(methylsulfoxido)methane.[11] The isolated yields with lithiobis(phenylthio)(trimethylsilyl)methane are generally superior to those with the title reagent, but the latter compound is more readily available and easier to handle than those listed above.

One-Carbon Homologations.[3]

The bis(methylthio)ketene acetals are useful synthetic intermediates because they are readily converted into *S*-methyl

thioesters (eq 9)[12] or the corresponding carboxylic acids and esters.[13a]

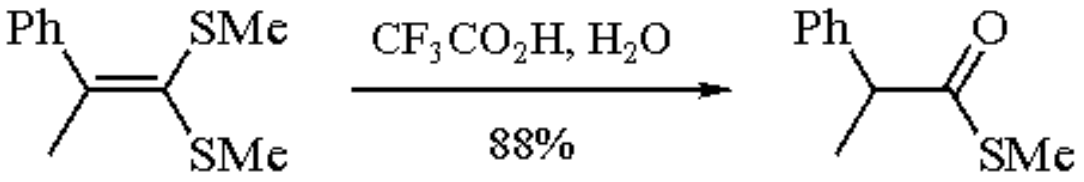

(9)

This acetal methodology was used for a 1,3-carbonyl transposition in a synthesis of (±)-myodesmone (eq 10),[13b] and for a one-carbon homologation en route to vitamin B_{12} (eq 11).[14]

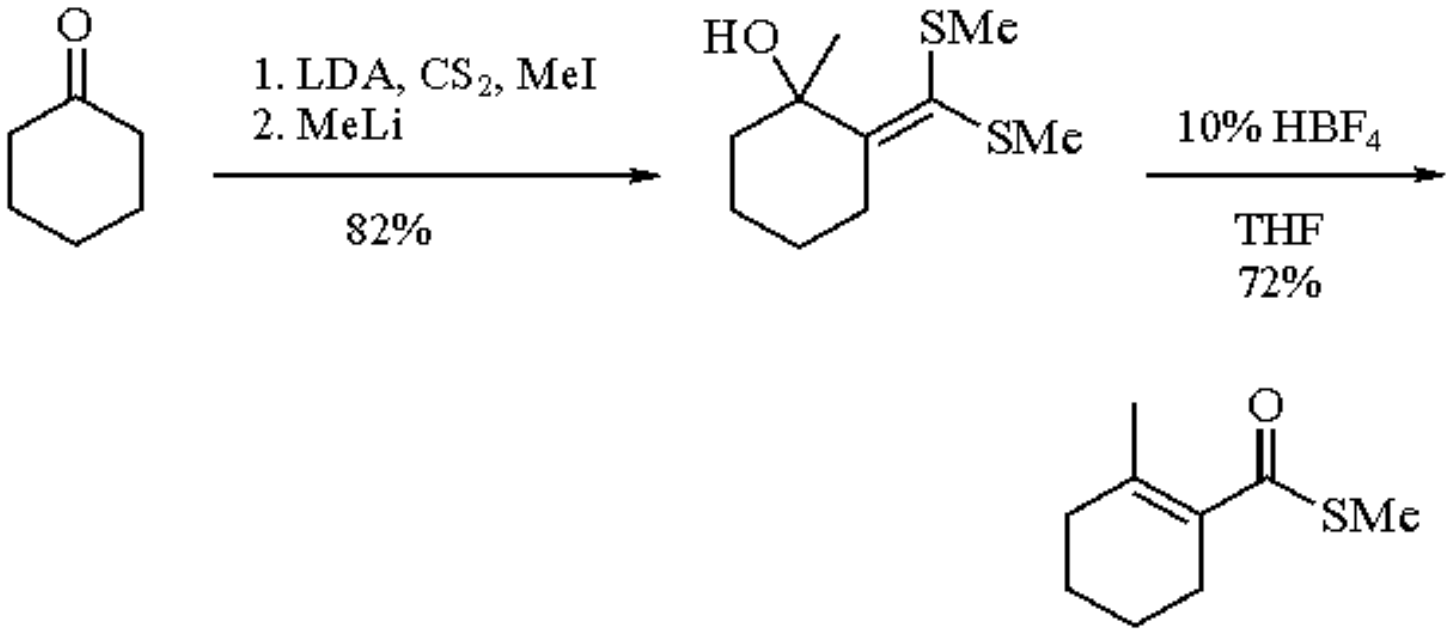

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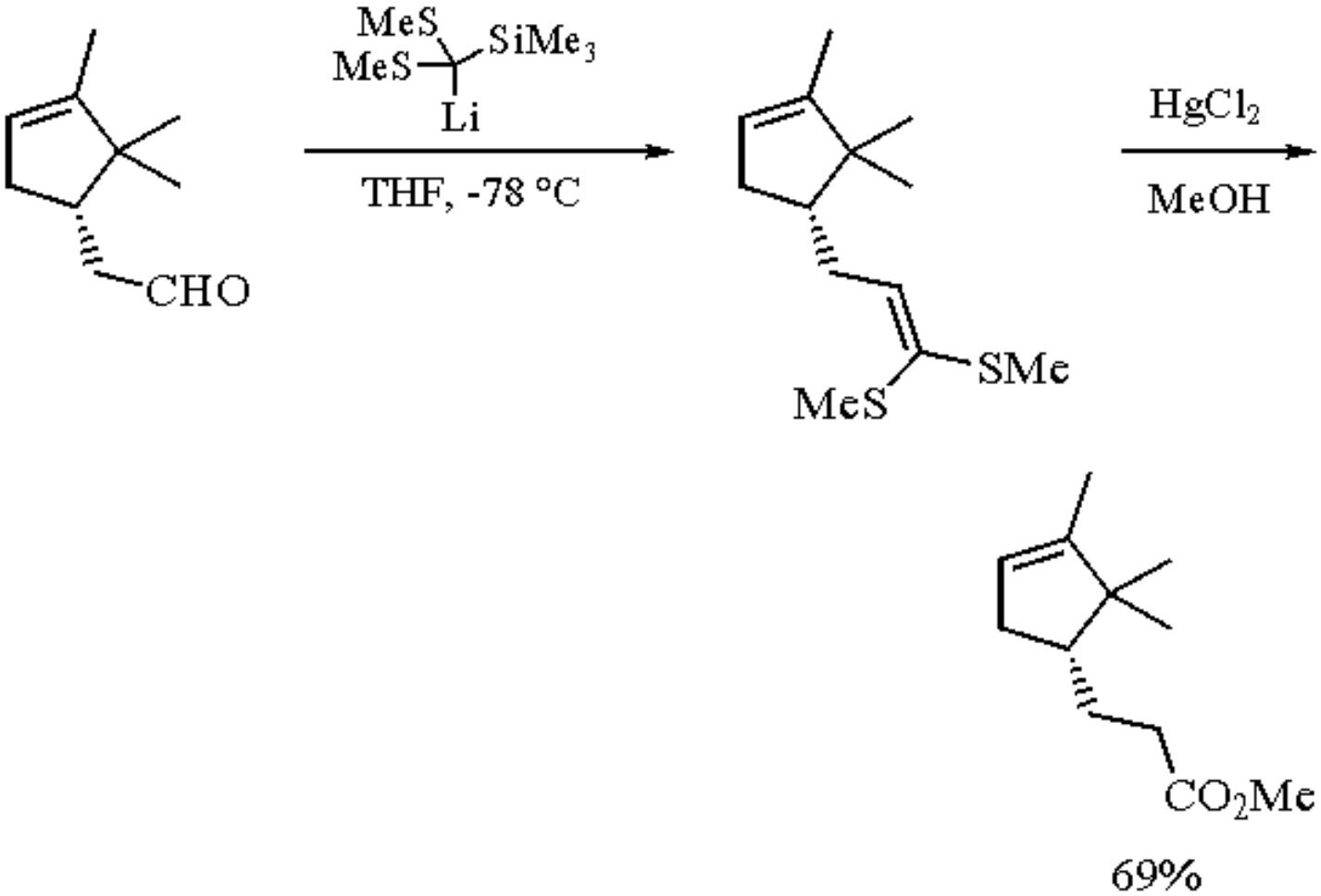

(11)

A particularly useful transformation is the fluoride-induced removal of the trimethylsilyl group to provide a mixed *O*,*S*-acetal that is easily converted into the corresponding aldehyde (eq 12).[10]

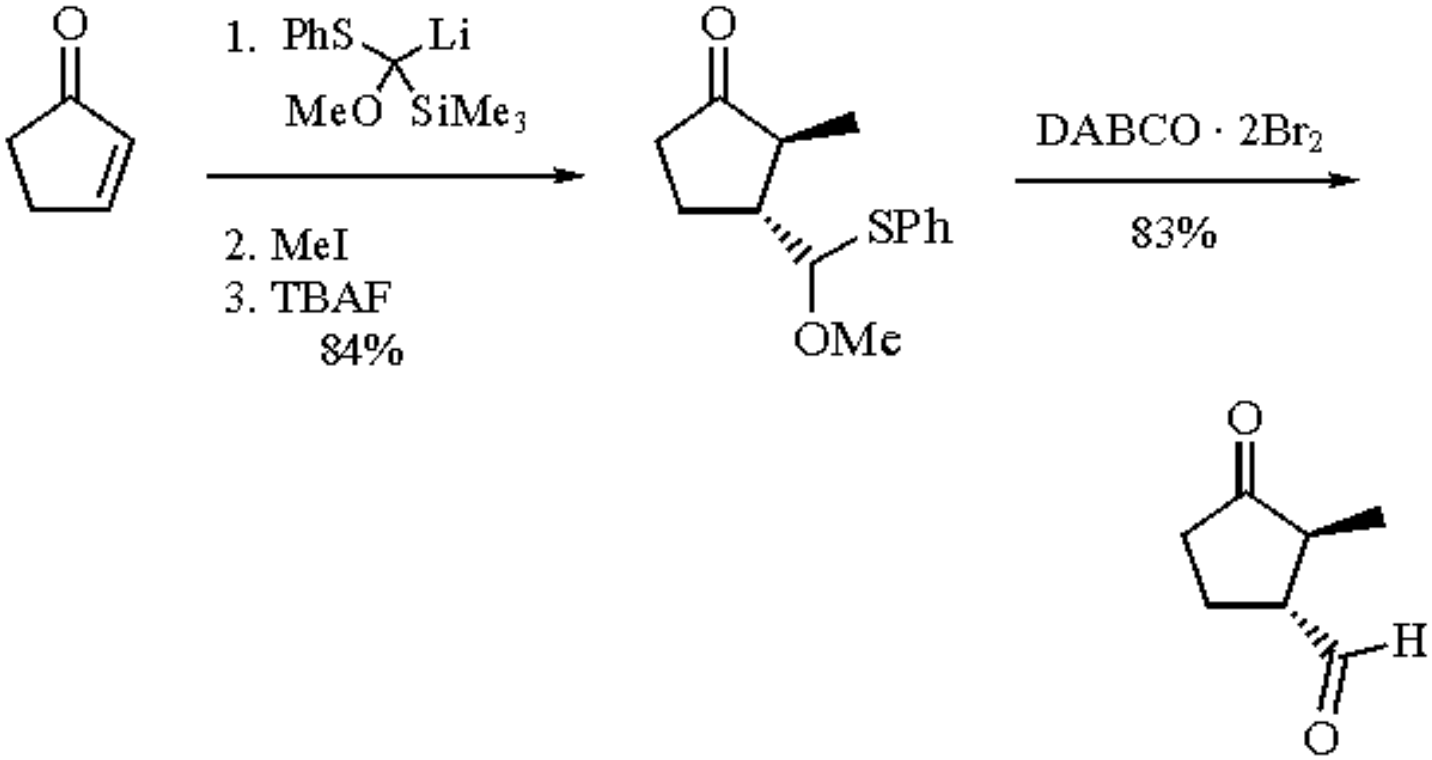

(12)

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Bis(methylthio)(trimethylstannyl)methane

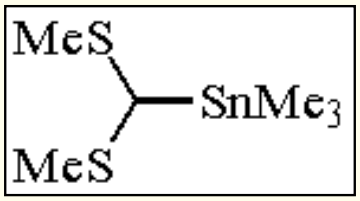

[62762-48-5] · $C_6H_{16}S_2Sn$ · Bis(methylthio)(trimethylstannyl)methane · (MW 271.00)

(precursor to acyl anion equivalent with 1,4-addition selectivity; dianion equivalent[1])

Physical Data: bp (distillation) 93-95 °C/7 mmHg; *n*20D 1.5548.

Preparative Methods: commercially available bis(methylthio)methane is deprotonated by ***n-Butyllithium*** in THF/hexane at -60 to 0 °C. The resulting lithio derivative is quenched at -40 °C with 1 equiv of ***Chlorotrimethylstannane***. An aqueous workup followed by vacuum distillation affords the bis(methylthio)(trimethylstannyl)methane reagent in 82% yield.[2] The analogous ***Bis(methylthio)(trimethylsilyl)methane*** can be prepared by a similar procedure.[3]

Handling, Storage, and Precautions: organotin compounds should be considered toxic and should be handled with appropriate care. Use in a fume hood.

1,4-Additions.

In contrast to lithiated 1,3-dithianes and related dithioacetals which undergo only 1,2-addition reactions with cyclic enones, lithiated bis(methylthio)(trimethylstannyl)methane furnishes 1,4-addition products in good yield. The reagent is metalated with ***Lithium Diisopropylamide*** in THF/HMPA at -78 to -30 °C; conjugate addition reactions (eq 1) are carried out from -78 to 25 °C. If the intermediate enolates are alkylated in situ with alkyl iodides, the products are predominantly the *trans*-2,3-disubstituted cycloalkanones (eq 2). The ***Bis(methylthio)(trimethylsilyl)methane*** reagent behaves similarly under these conjugate addition and alkylation reaction conditions.

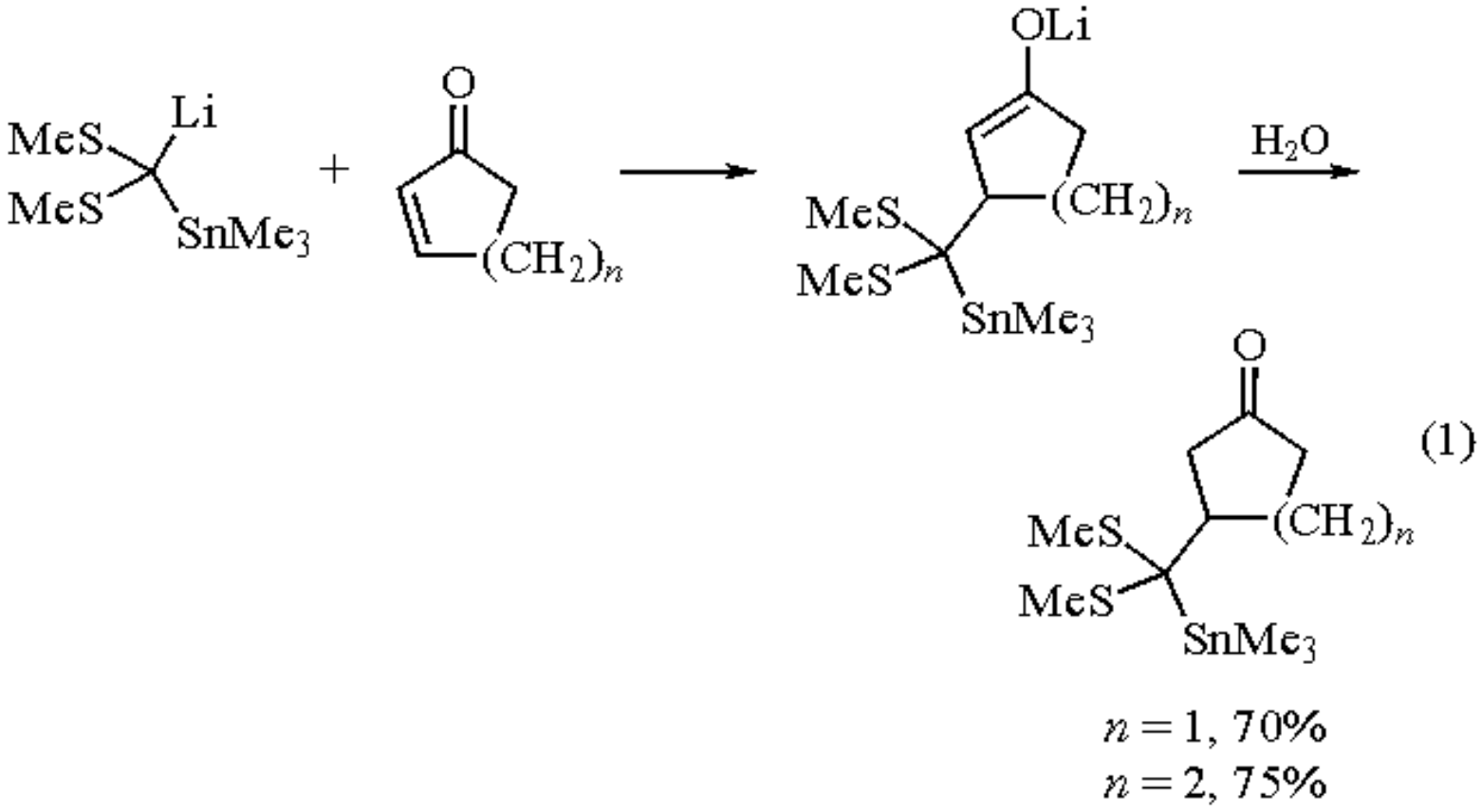

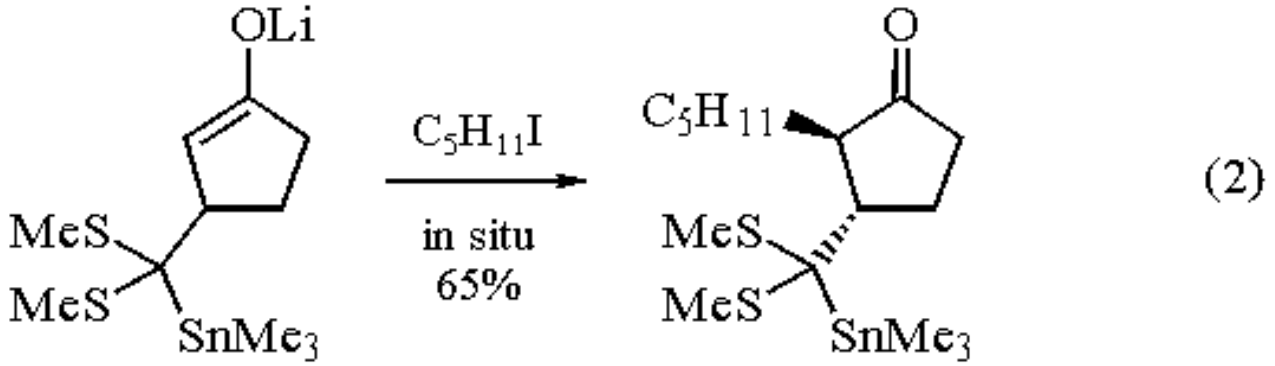

Dianions.

The intermediate enolates can also be converted to dilithium derivatives by transmetalation (***Methyllithium***, THF, -100 °C) after removal of the diisopropylamine. The dilithium species can then be treated sequentially with electrophiles (eq 3). The dithioacetal anion is the more reactive nucleophile.

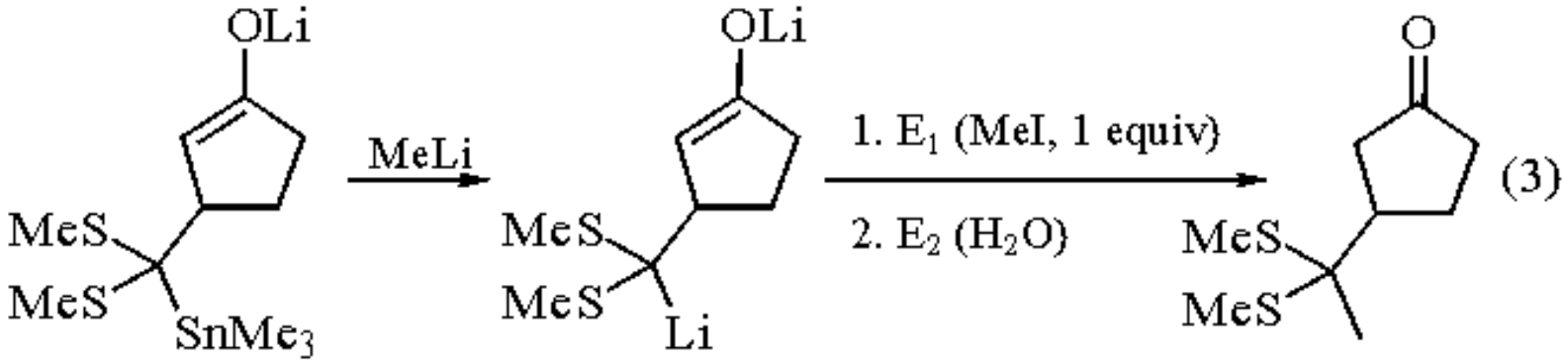

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2. Bürstinghaus, R.; Seebach, D. *CB* **1977**, *110*, 841 (*CA* **1977**, *87*, 6118n).
3. Seebach, D.; Kolb, M.; Gröbel, B.-T. *CB* **1973**, *106*, 2277 (*CA* **1974**, *80*, 27 320t).

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Bismuth(III) Oxide[1]

Bi_2O_3

[1304-76-3] · Bi_2O_3 · Bismuth(III) Oxide · (MW 465.96)

(oxidizing agent specific for conversion of α-hydroxy ketones to diketones[1])

Physical Data: mp 820 °C; *d* 8.9 g cm^{-3}.

Solubility: insol water and organic solvents; sol acids.

Form Supplied in: amorphous yellow powder.

Handling, Storage, and Precautions: no special precautions.

Oxidation of α-Hydroxy Ketones to 1,2-Diketones.

Bismuth(III) oxide is a specific reagent for the oxidation of α-hydroxy ketones to the corresponding diketones.[2,3] The oxidation is generally carried out in acetic acid at about 100 °C. Bismuth(III) oxide is soluble in acetic acid under these conditions and forms bismuth triacetate, the active oxidizing agent, which becomes reduced to metallic bismuth. Oxidation of simple α-hydroxy ketones is rapid, but more highly substituted compounds may require several days for complete reaction. Reaction of bismuth(III) oxide with α-hydroxy ketones is confined to examples possessing an α-hydrogen atom. It has been suggested that the oxidation proceeds via an enediol intermediate. Bismuth triacetate may act as an acylating agent towards alcohols and amines. This reaction occurs only at high temperatures (200 °C no solvent) and would not normally interfere with the oxidation of α-hydroxy ketones.

In a typical procedure the α-hydroxy ketone, dissolved in acetic acid, is heated on a steam bath with 1.2 equiv of bismuth(III) oxide. During the course of the reaction black metallic bismuth precipitates. Unhindered substrates are normally oxidized in under an hour under these conditions. The reaction mixture is filtered to remove bismuth and excess reagent; water is added and the product is extracted into ether. Yields of greater than 90% may be obtained. Sugars are not oxidized by the reagent and neither is

ascorbic acid. The presence in the reaction mixture of certain polyhydroxy compounds, such as glucose and catechol, inhibits the oxidation of α-hydroxy ketones owing to the formation of bismuth-containing compounds with these materials.[1]

---

1. Kitchin, J. P. In *Organic Synthesis by Oxidation with Metal Compounds*; Mijs, W. J.; de Jonge, C. R. H. I., Eds.; Plenum: New York, 1986; p 817.
2. Rigby, W. *JCS* **1951**, 793.
3. Djerassi, C.; Ringold, H. J.; Rosenkranz, G. *JACS* **1954**, *76*, 5533.

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Bis(4-nitrophenyl) Carbonate

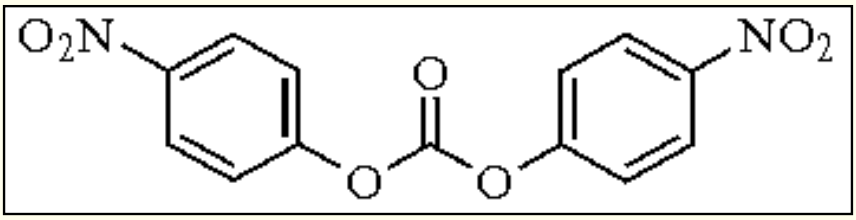

[5070-13-3] · $C_{13}H_8N_2O_7$ · Bis(4-nitrophenyl) Carbonate · (MW 304.22)

(peptide coupling reagent;[1] reagent for formation of carbamate linked cytosines[2])

Physical Data: mp 144-145 °C.

Solubility: sol chloroform and THF.

Form Supplied in: off-white powder.

Peptide Coupling Reagent.

N-Protected amino acids can be converted into activated 4-nitrophenyl esters suitable for peptide coupling reactions. Reaction of the N-protected amino acid in acetic acid and pyridine with 1.5 equiv of the reagent under reflux for 3 h affords the activated ester following loss of CO_2 from the intermediate mixed anhydride (eq 1).[1]

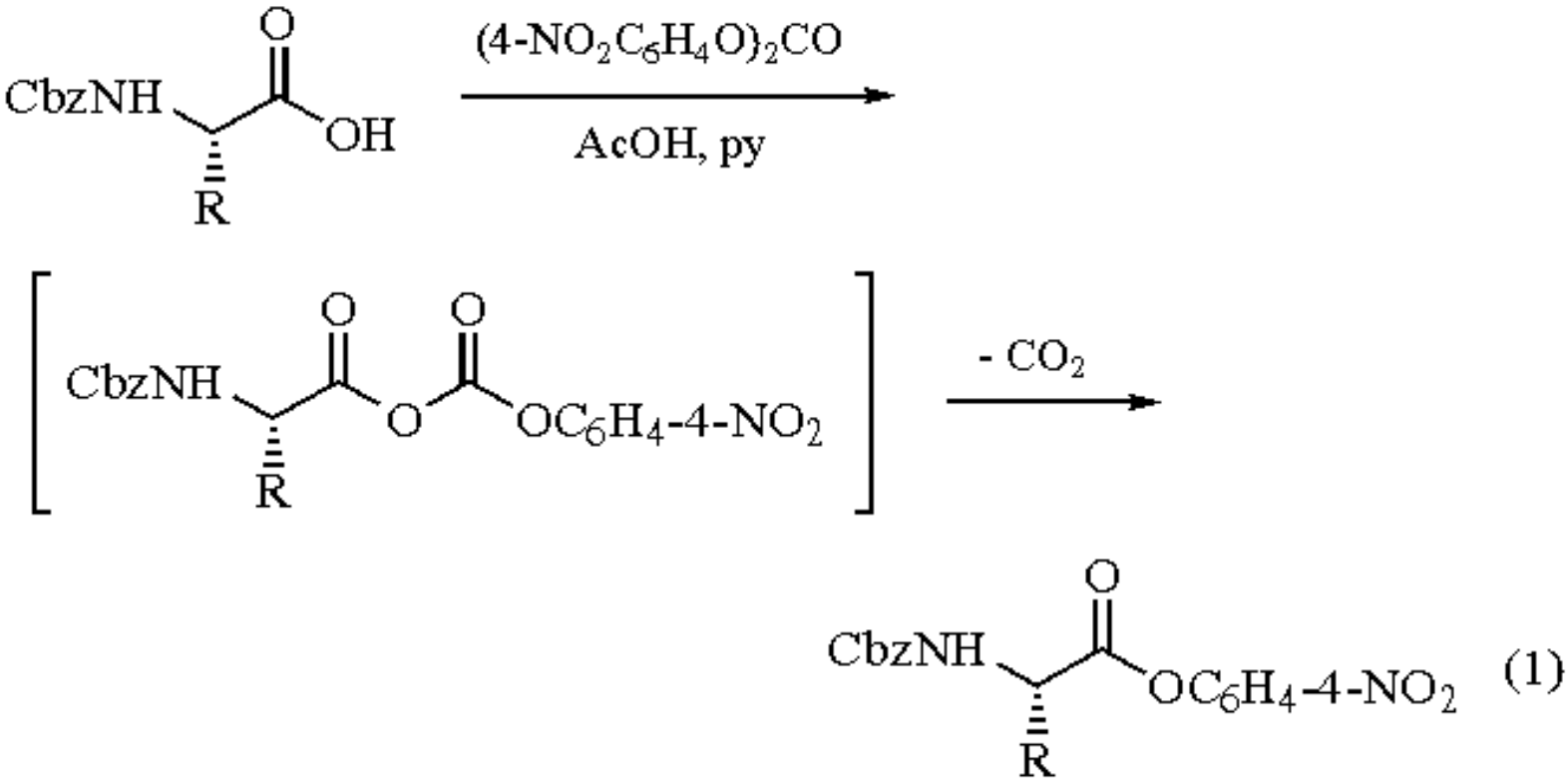

Formation of Carbamate-Linked Cytosine Oligomers.[2]

Reaction of the 5´-protected aminocytosine derivative (**1a**) with the reagent in DMF and Et_3N afforded an activated 4-nitrophenyl carbonate derivative. Following purification, reaction of this compound with another monomer unit, (**1b**), provided the linked dimer (**2**) (eq 2). This compound was elaborated further into a carbamate-linked hexameric cytosine oligomer which was found to conjugate strongly to native DNA strands.

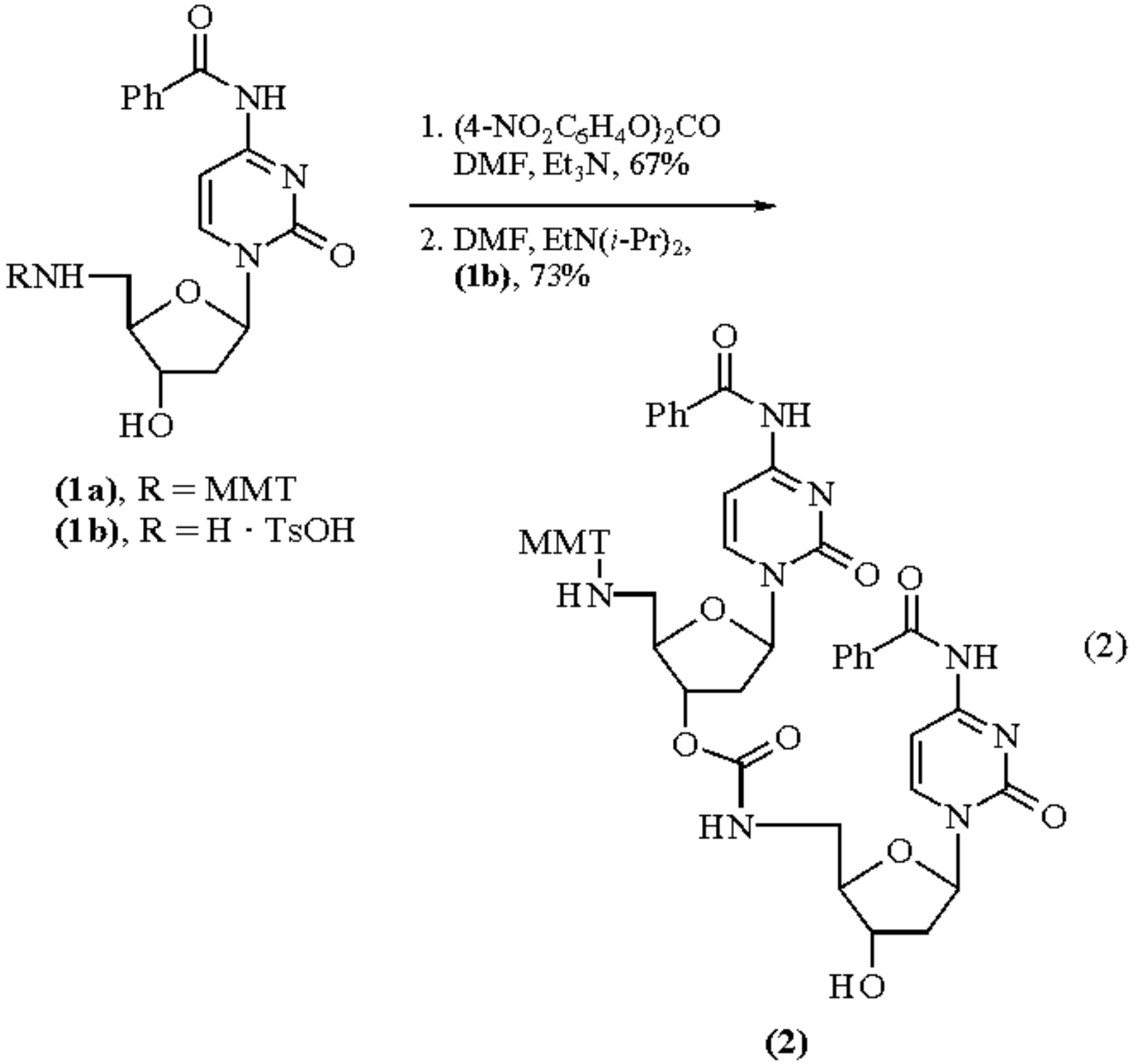

Formation of Ureido Sugars.[3]

A variety of 2-amino sugars can be converted into ureido derivatives in reasonable yields (50-83% for two steps). For example, methyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside is first reacted with the reagent to afford a 4-nitrophenyl carbamate intermediate which, upon further reaction with a variety of secondary amines in CH_2Cl_2 at room temperature for 5-24 h, provides the ureido sugar. In a similar manner, symmetrical and unsymmetrical *N*,*N*´-disubstituted ureas can be prepared by the sequential addition of amines to the reagent.[4]

1. (a) Wieland, T.; Heinke, B.; Vogeler, K.; Morimoto, H. *LA* **1962**, *655*, 189. (b) Glatthard, R.; Matter, M. *HCA* **1963**, *46*, 795.
2. Stirchak, E. P.; Summerton, J. E.; Weller, D. D. *JOC* **1987**, *52*, 4202.
3. Piekarska-Bartoszewicz, B.; Temeriusz, A. *Carbohydr. Res.* **1990** *203*, 302.
4. Izdebski, J.; Pawlak, D. *S* **1989**, 423.

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Bis(*p*-nitrophenyl) Hydrogen Phosphate

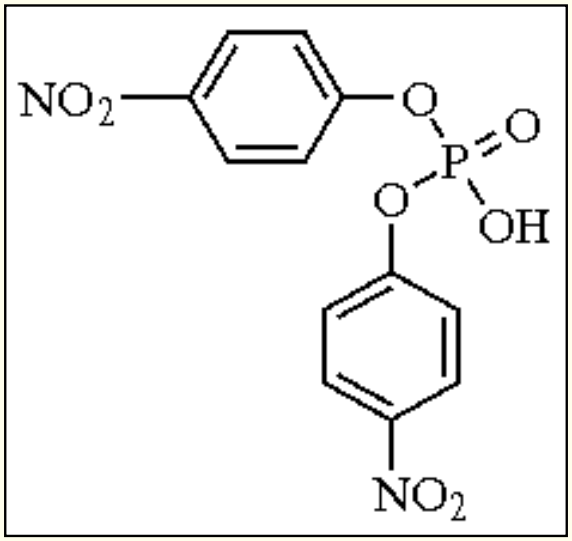

[645-15-8] · $C_{12}H_9N_2O_8P$ · Bis(*p*-nitrophenyl) Hydrogen Phosphate · (MW 340.19)

(acid catalyst[1,2] for preparation of nucleosides[3,4] and nucleoside acetals[1,5])

Physical Data: mp 175-175.5 °C;[6] pK_a 2.79 (H_2O),[7] pK_a 1.7 (50% EtOH).[8]

Form Supplied in: yellow crystals.

Preparative Methods: treat freshly distilled $POCl_3$ with finely powdered sodium *p*-nitrophenoxide, followed by partial alkaline hydrolysis of the corresponding tris(*p*-nitrophenyl) phosphate;[6] *p*-nitrophenol treated with $POCl_3$ in acetonitrile.[9]

Purification: recrystallization from H_2O to yield white needles.[6]

Nucleoside Synthesis.

Effective catalytic reagent for the preparation of nucleosides by fusion of purines with fully *O*-acetylated sugars.[3] This is superior to ***p-Toluenesulfonic Acid*** (except for synthesis of phenylborate nucleosides[10]), ethyl polyphosphate, or ***Zinc Chloride***. An example of the method[4] is the fusion of purine (**1**) with tetra-*O*-acetyl-D-ribofuranose (**2**), at 170-180 °C for 15 min under reduced pressure (water pump), to yield two nucleosides (**3**) and (**4**) (eq 1). The major product (**3**) is the triacetyl derivative of a naturally occurring nucleoside antibiotic nebularine.

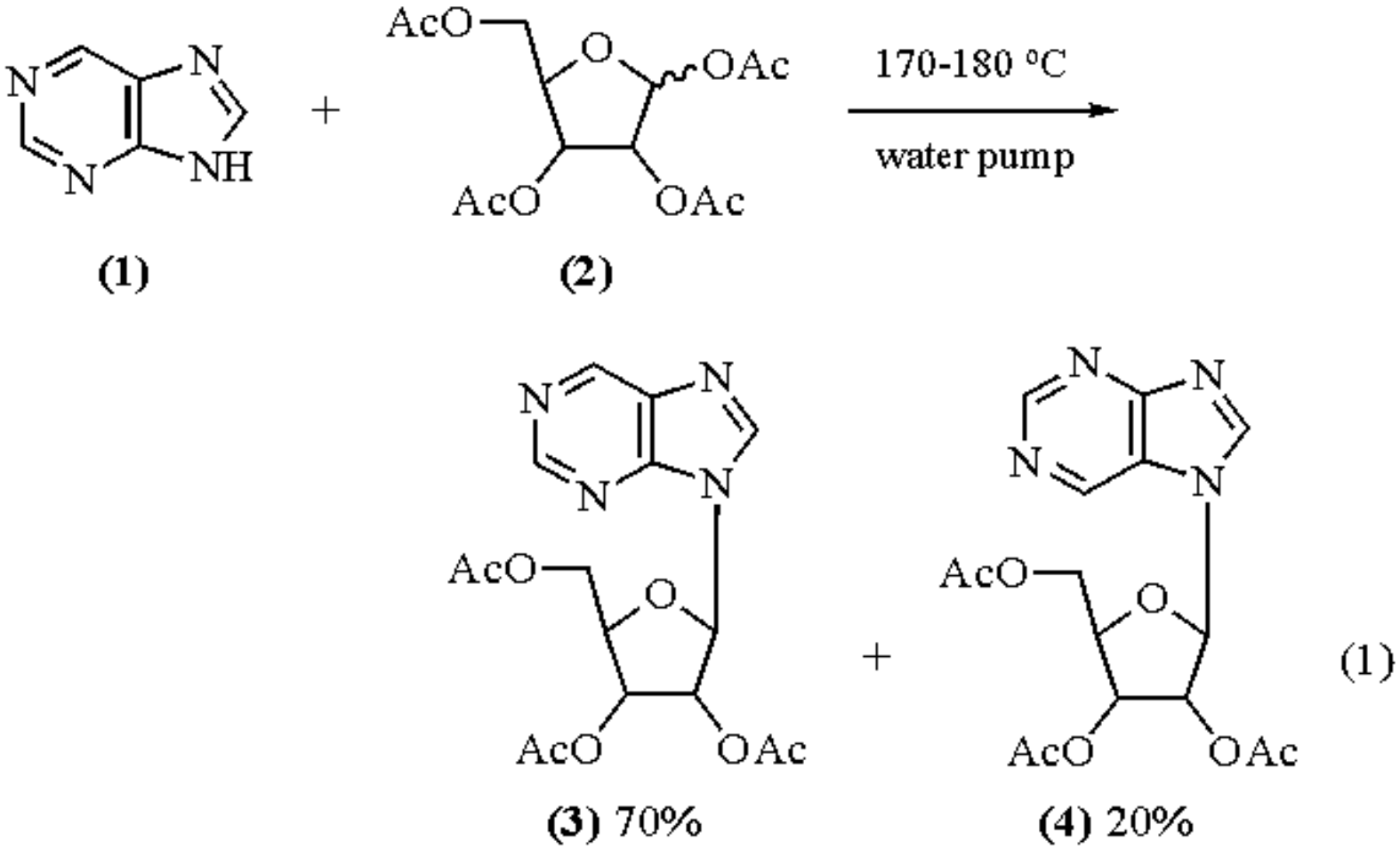

Acetal Synthesis.

The reagent is used as an acid catalyst for the conversion of purines and pyrimidine ribonucleosides to their corresponding 2´,3´-*O*-isopropylidene (acetonide) derivatives, in the presence of 2,2-dimethoxypropane (effective for maintaining the anhydrous conditions necessary of such conversions). An example of the method[1] is the preparation of 2´,3´-*O*-isopropylidene uridine (eq 2).

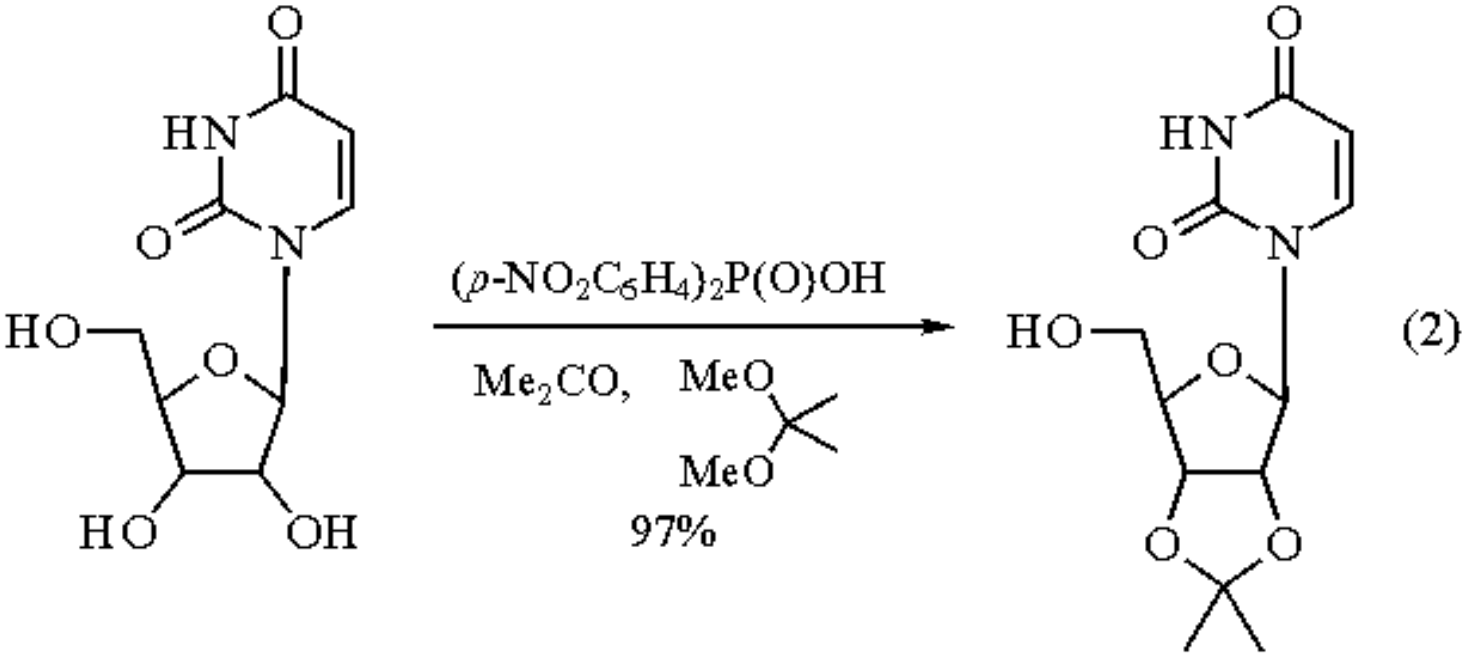

Bis(*p*-nitrophenyl) hydrogen phosphate is superior to ***p-Toluenesulfonic Acid*** as a catalyst for the reaction because it has twice the lipophilic area, making its salts with nucleosides correspondingly more soluble in acetone. This procedure has been extended to a range of acetals other than isopropylidene, with greater or lesser stability to acid.[5]

---

1. Hampton, A. *JACS* **1961**, *83*, 3640.
2. Hampton, A. *Biochem. Prep.* **1963**, *10*, 91.
3. Hashizume, T.; Iwamura, H. *T* **1965**, *35*, 3095.
4. Iwamura, H.; Hashizume, T. *JOC* **1968**, *33*, 1796.
5. Hampton, A.; Frakantoni, J. C.; Caroll, P. M.; Wang, S. *JACS* **1965**, *87*, 5481.
6. Moffat, J. G.; Khorana, H. G. *JACS* **1957**, *79*, 3741.
7. *Dictionary of Organophosphorus Compounds*; Chapman and Hall: New York, 1988; p 86.
8. Corby, N. S.; Kenner, G. W.; Todd, A. R. *JCS* **1952**, 1234.
9. Hashizume, T. Jpn. Patent 18 132, 1964 (*CA* **1965**, *62*, 6432).
10. McCormick, J. E.; McElhinney, R. S. *JCS(P1)* **1975**, 500.

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Bis(*o*-nitrophenyl) Phenylphosphonate

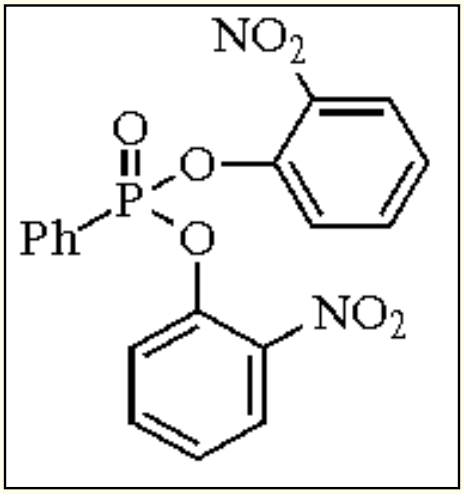

[73404-18-9] · $C_{18}H_{13}N_2O_7P$ · Bis(*o*-nitrophenyl) Phenylphosphonate · (MW 400.28)

(coupling reagent for peptide[1,2] and carboxamide synthesis[3])

Preparative Method: readily prepared from *o*-nitrophenol and phenylphosphonic dichloride ($PhP(O)Cl_2$).[1]

Peptide and Carboxamide Synthesis.

Condensation of the tetrabutylammonium salt of *N*-benzoyl-L-leucine with glycine ethyl ester, the components in the Young's test,[4] in DMF in the presence of bis(*o*-nitrophenyl) phenylphosphonate proceeds to give the corresponding dipeptide in 82-93% yield without racemization.[1] Employment of quarternary ammonium salts[5] enables the reaction to proceed smoothly because of increased solubility[6] and nucleophilicity of the carboxyl component. The coproducts are *o*-nitrophenol and the phosphonate ammonium salt, which means that no free base such as tertiary amines need to be utilized, which often cause serious problems such as racemization during condensation (eq 1).[4] This method has been efficiently applied to more complex hexaglycine and leucine-enkephalin (L-Tyr-Gly-Gly-L-Phe-L-Leu) peptides.[2]

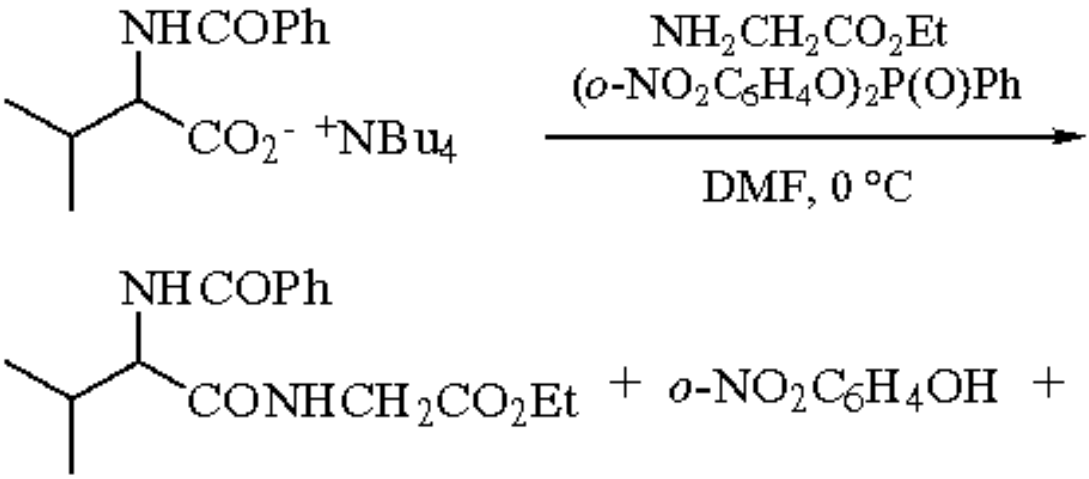

(1)

Preparation of both peptides and carboxamides have been simplified by the use of phase-transfer conditions in which the tetrabutylammonium carboxylic acid salts are formed in situ.[3] Thus treatment of free acids and amines in aqueous CH_2Cl_2 (or aqueous THF) with bis(*o*-nitrophenyl) phenylphosphonate in the presence of *n*-$Bn_4N^+HSO_4^-$ (or *n*-$Bn_4N^+Br^-$) gave corresponding carboxamides and peptides. An example of the method[3] is the preparation of an arylamide in quantative yield (eq 2).

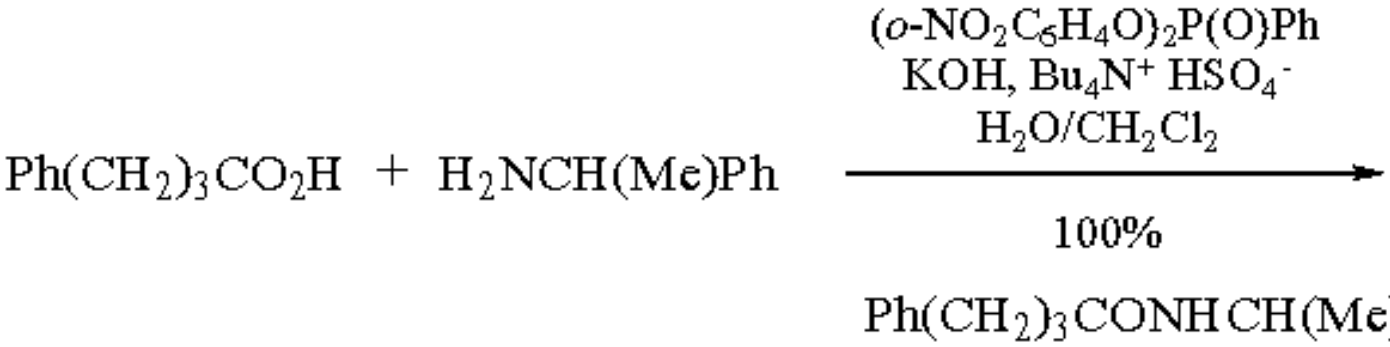

(2)

Related Reagents.

Bis(p-nitrophenyl) Phenylphosphonate.

---

1. Mukaiyama, T.; Morito, N.; Watanabe, Y. *CL* **1979**, *11*, 1305.
2. Watanabe, Y.; Morito, N.; Kamekawa, K.; Mukaiyama, T. *CL* **1981**, *1*, 65.
3. Watanabe, Y.; Mukaiyama, T. *CL* **1981**, *3*, 285.
4. Williams, M. W.; Young, G. T. *JCS* **1963**, 881.
5. Wakselman, M.; Acher, F. *TL* **1980**, *21*, 2705.
6. Luisi, P. L.; Bonner, F. J.; Pellegrini, A.; Wiget, P.; Wolf, R. *HCA* **1979**, *62*, 740.

Harjinder S. Bansal

Bis(*p*-nitrophenyl) Phenylphosphonate

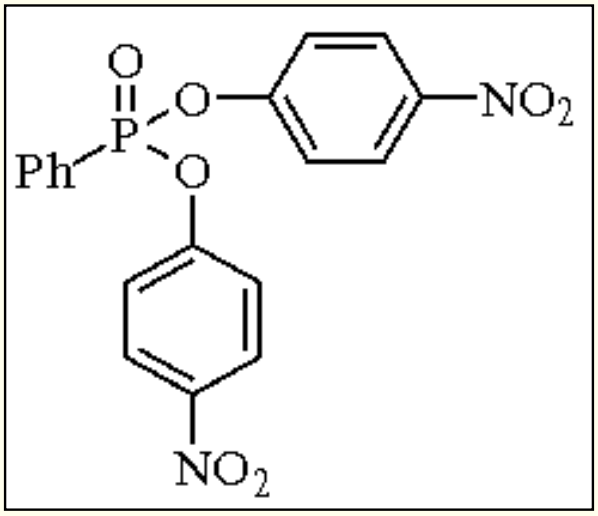

[38873-91-5] · $C_{18}H_{13}N_2O_7P$ · Bis(*p*-nitrophenyl) Phenylphosphonate · (MW 400.28)

(efficient peptide coupling agent causing little racemization[1,2])

Physical Data: mp 99-101 °C.[3]

Form Supplied in: off-white to tan granules.[3]

Preparative Method: heat phenylphosphonic dichloride ($PhP(O)Cl_2$) with 2 equiv of 4-nitrophenol at 160 °C for 4 h.[4]

Purification: recrystallize from CCl_4 (mp 94-96 °C).[4]

Handling, Storage, and Precautions: hygroscopic; store in a cool dry place. Incompatible with strong oxidizing agents, acids, and bases.[3]

Peptide Synthesis.

Bis(*p*-nitrophenyl) phenylphosphonate (see also ***Bis(o-nitrophenyl) Phenylphosphonate***) has been used as a coupling reagent in the condensation of the tetrabutylammonium salt of *N*-benzoyl-L-leucine with glycine ethyl ester. These are the reactants used in the Young's test,[5] which is known as the most severe racemization test. The most favorable solvent used in the coupling was DMF and the reaction proceeded to the corresponding dipeptide in 93% yield, at below 0 °C with little racemization (95-97% L-isomer) (eq 1).

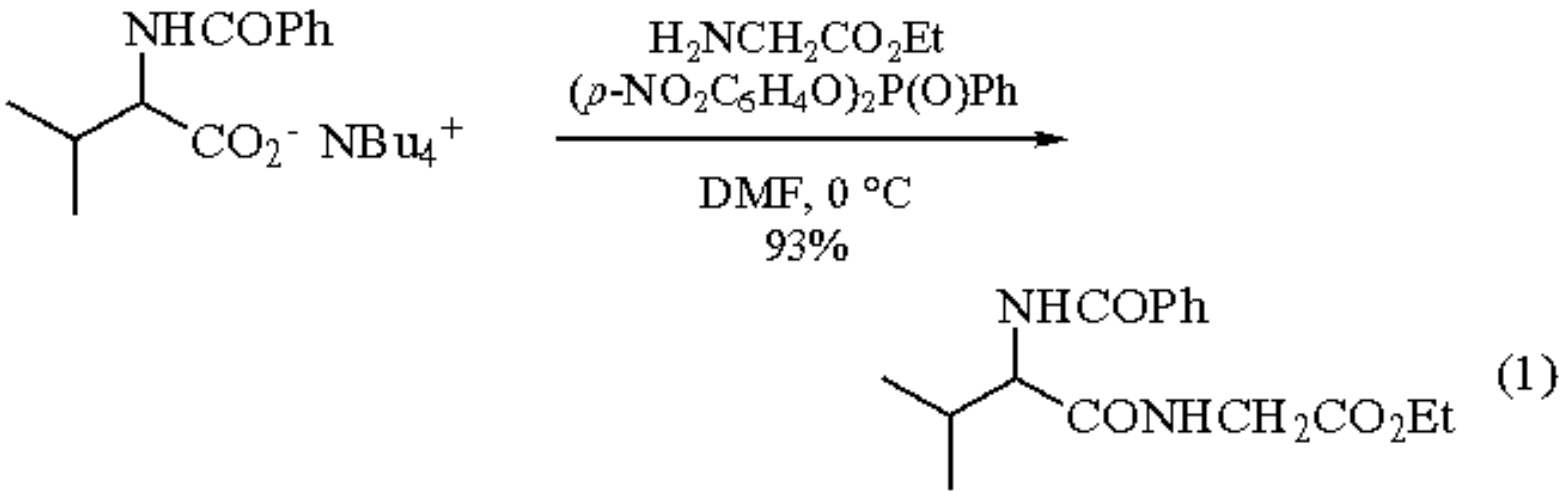

The advantage of using the tetrabutylammonium salt in the coupling reaction was that it increased both solubility[6] and nucleophilicity of the carboxylic component, enabling the reaction to take place without using tertiary amines, which play a major role in causing racemization. The quarternary ammonium salts were prepared by the reaction of alkaline *n*-$Bn_4N^+HSO_4^-$ or Bu_4N^+ OH^- on the carboxylic acid.[1]

This method has also been efficiently applied to the synthesis of opioid agonist leucine-enkephalin[2] (L-Tyr-Gly-Gly-L-Ppe-L-Leu) without protection of the phenolic hydroxy group in the tyrosine residue.[2]

---

1. Mukaiyama, T.; Morito, N.; Watanabe, Y. *CL* **1979**, *11*, 1305.
2. Watanabe, T.; Morito, N.; Kamekawa, K.; Mukaiyama, T. *CL* **1981**, *1*, 65.
3. *The Sigma-Aldrich Library of Chemical Safety Data*, 2nd ed.; Vol 1, p 443.
4. Loran, J. S.; Naylor, R. A.; Williams, A. *JCS(P2)* **1977**, 418.
5. Williams, M. W.; Young, G. T. *JCS* **1963**, 881.
6. Luisi, P. L.; Bonner, F. J.; Pellegrini, A.; Wiget, P.; Wolf, R. *HCA* **1979**, *62*, 740.

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Bis(*p*-nitrophenyl) Sulfite

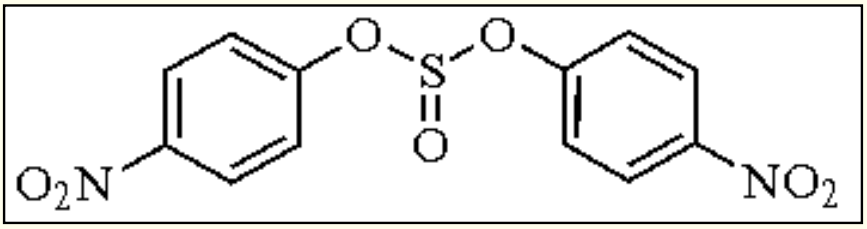

[35887-81-4] · $C_{12}H_8N_2O_7S$ · Bis(*p*-nitrophenyl) Sulfite · (MW 324.29)

(preparation of *p*-nitrophenyl esters for use in peptide synthesis)

Physical Data: mp 98-100 °C; bp 172-174 °C/11 mmHg.

Solubility: sol MeCN.

Preparative Method: by the reaction of ***p-Nitrophenol*** with ***Thionyl Chloride*** in the presence of ***Pyridine*** in benzene at 0 °C.[7]

Purification: recrystallization from chloroform/hexane. Several recrystallizations are required to obtain the reagent in a pure form.

Handling, Storage, and Precautions: may be stored as a solution in acetonitrile at -30 °C; under these conditions, decomposition occurs only slowly. Decomposition and reaction products are *p*-nitrophenol and sulfur dioxide. Handle with gloves and in a fume hood.

Bis(*p*-nitrophenyl) sulfite is used to prepare activated *p*-nitrophenol esters.[1-5] These esters have found exclusive application as a method for carboxyl activation. The *p*-nitrophenol activated esters are stable and their major application is in the synthesis of peptide bonds. The activated ester is prepared by the reaction of a peptide or *N*-protected amino acid in pyridine with bis(*p*-nitrophenyl) sulfite (eq 1).

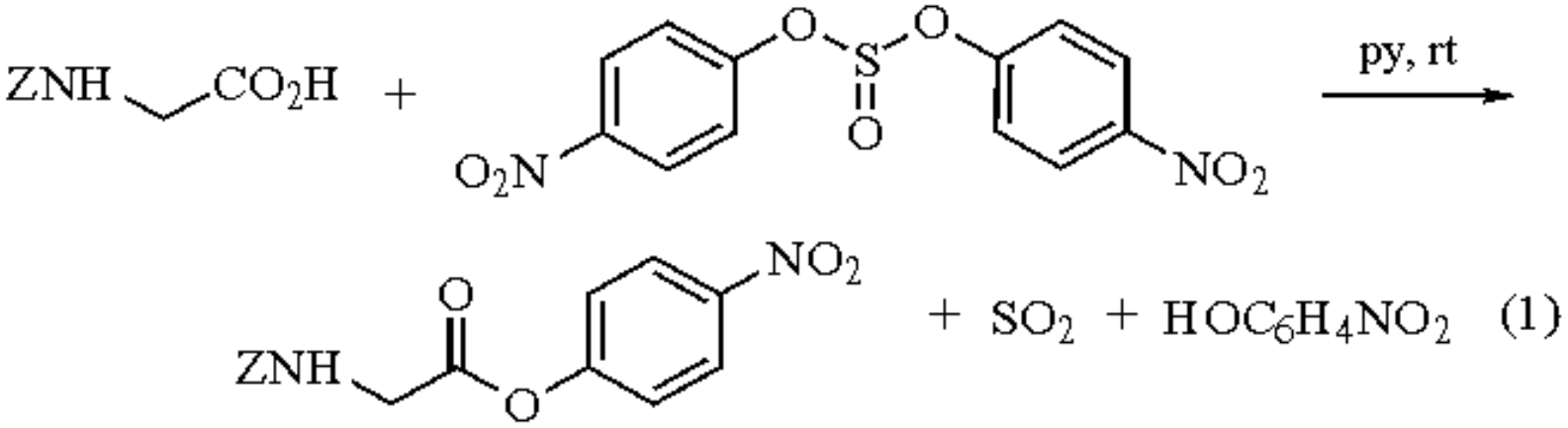

Some racemization has been observed where the amino acid is not a glycine or proline residue. An example of the use of this reagent is in the preparation of a cyclic peptide (eq 2).[4]

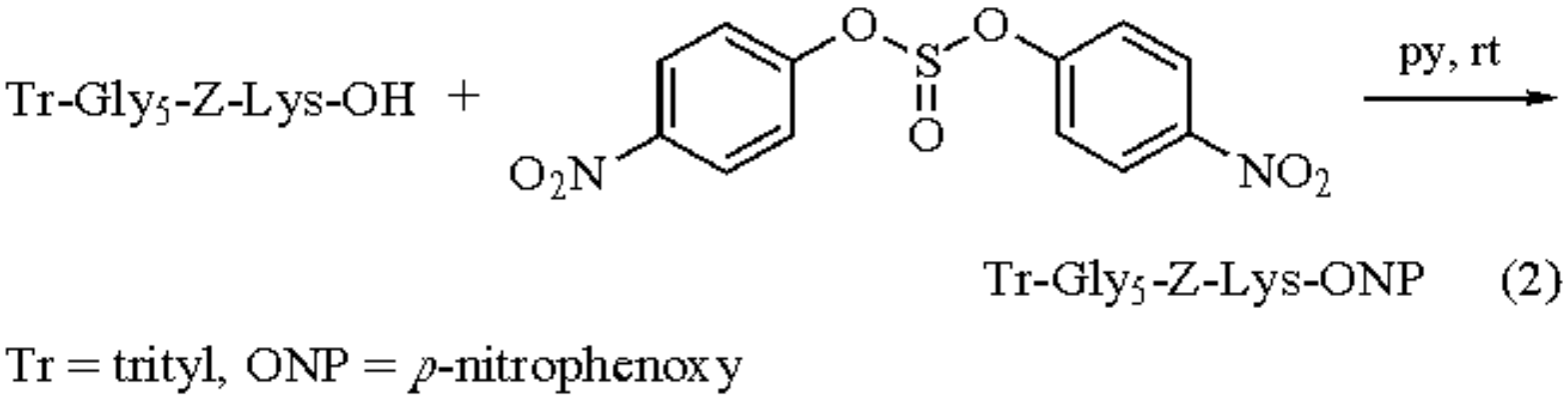

The *p*-nitrophenol esters are stable to acid (such as anhydrous TFA) but are moisture sensitive. Therefore, some hydrolysis of the ester occurs in the amine deprotection (eq 3). Following amine deprotection, further treatment with a base such as pyridine results in amide formation, to give the corresponding peptide (eq 4).

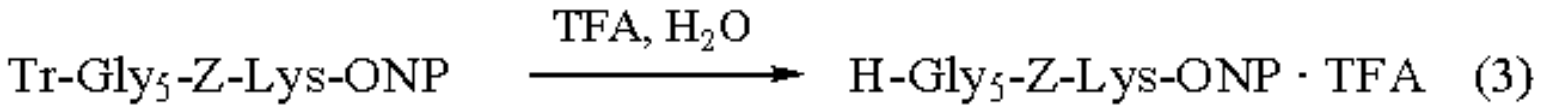

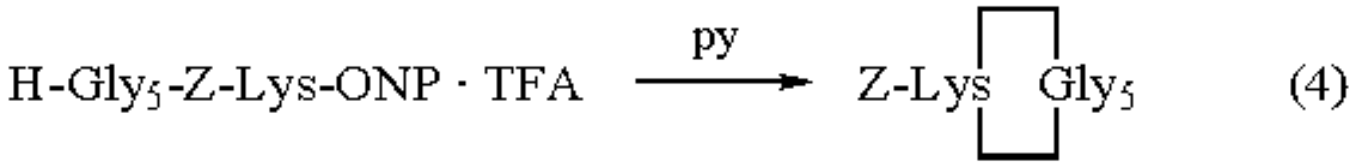

Carboxyl activation by other aryl esters based on halogen-substituted phenols has been investigated. Those derived from 2,4,5-trichlorophenol have found the widest application.[6] Pentafluorophenyl esters have also been prepared and react preferentially in the presence of *p*-nitrophenol esters.[8] Where the hydrogenolysis of benzyloxycarbonyl groups is required in the presence of acyl esters, the halogen-substituted acyl esters are preferred, as traces of unremoved *p*-nitrophenol can give rise to reactive *p*-aminophenol. It is also possible to prepare *p*-nitrophenol esters from *p*-nitrophenol and ***1,3-Dicyclohexylcarbodiimide***[9] or tris-*p*-nitrophenyl phosphite.[10]

1. Iselin, B.; Rittel, W.; Sieber, P.; Schwyzer, R. *HCA* **1957**, *40*, 373.
2. Iselin, B.; Schwyzer, R. *HCA* **1960**, *43*, 1760.
3. Studer, R.; Lergier, W. *HCA* **1965**, *48*, 460.
4. Montonori, O.; Izumiya, N. *BCJ* **1965**, *38*, 1831.
5. Aoyagi, H.; Izumiya, N. *BCJ* **1966**, *39*, 1747.
6. Pless, J.; Boissonnas, R. *HCA* **1963**, *46*, 1609.
7. May, S.; Kaiser, E. *JACS* **1969**, *91*, 6491.
8. Kisfaludy, L.; Roberts, J.; Johnson, R.; Mayers, G.; Kovacs, J. *JOC* **1970**, *35*, 3563.
9. Rothe, M.; Kunitz, F. *LA* **1957**, *609*, 88.
10. Farrington, J.; Hextall, P.; Kenner, G.; Turner, J. *JCS* **1957**, 1407.

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Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride[1]

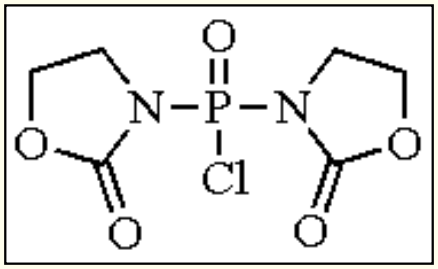

[68641-49-6] · $C_6H_8ClN_2O_5P$ · Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride · (MW 254.57)

(reagent for activating carboxyl groups,[1] converting acids to esters[2] (including thioesters[3] and phosphoesters[4]), amides[5] (including peptides[6-8] and β-lactams[9,10]), and anhydrides;[11] reagent for kinetic resolution of racemic carboxylic acids and alcohols[12])

Alternate Names: *N,N*-bis(2-oxo-3-oxazolidinyl)phosphordiamidic chloride; *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride; phosphoric acid bis(2-oxooxazolidide)chloride; BOP-Cl; BOPDCl.

Physical Data: white powder, mp 195-198 °C; hygroscopic.

Solubility: slightly sol CH_2Cl_2, MeCN, THF, DMF; dec H_2O.

Form Supplied in: white to off-white powder, typically 97% pure.

Analysis of Reagent Purity: IR (KBr): 1775 (C=O), 765 (P-Cl) cm^{-1}.

Purification: the outcome of reactions can be greatly affected by the purity of the reagent; commercial samples may require to be washed with cold water and recrystallized from MeCN prior to use.[13]

Handling, Storage, and Precautions: store in a cool dry place under nitrogen to preclude contact with moisture and oxygen. Use only in a chemical fume hood. Wear suitable protective clothing and eye/face protection. Causes burns and is harmful if swallowed, inhaled, or absorbed through skin.

Carboxyl Group Activator.

BOP-Cl[1] is used for a direct, one-pot conversion of carboxylic acids into esters (eq 1)[2] (including thioesters[3] and phosphoesters[4]), amides (eq 2),[5] and anhydrides (eq 3).[11] Conditions for minimizing side reactions and optimizing yields of both esters and amides are reported.[2,5] Advantages offered over previously used reagents, such as ***N,N´-Carbonyldiimidazole***, carbodiimides, and unsymmetrical anhydrides, include good yields (typically >80%), mild reaction

conditions, and tolerance of both steric bulk and a wide range of functional groups.

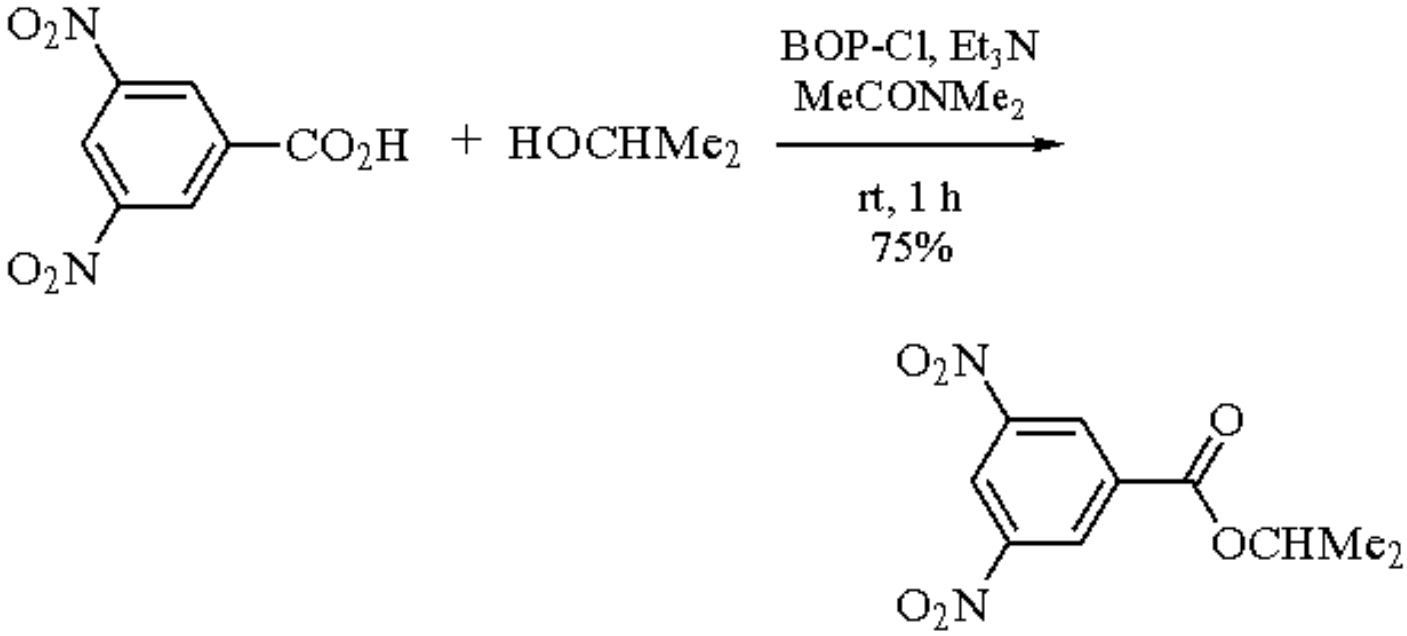

(1)

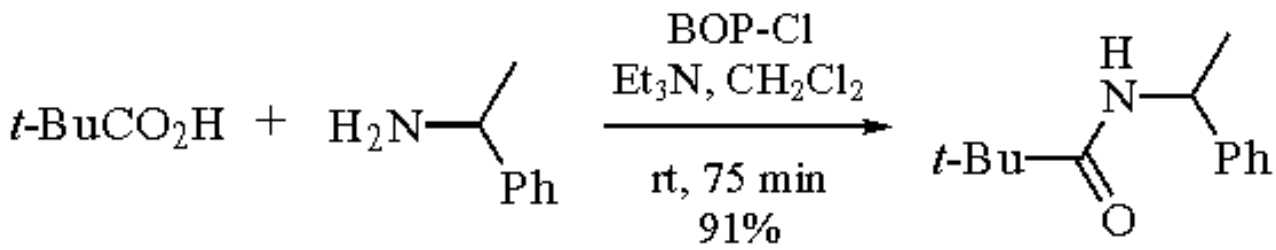

(2)

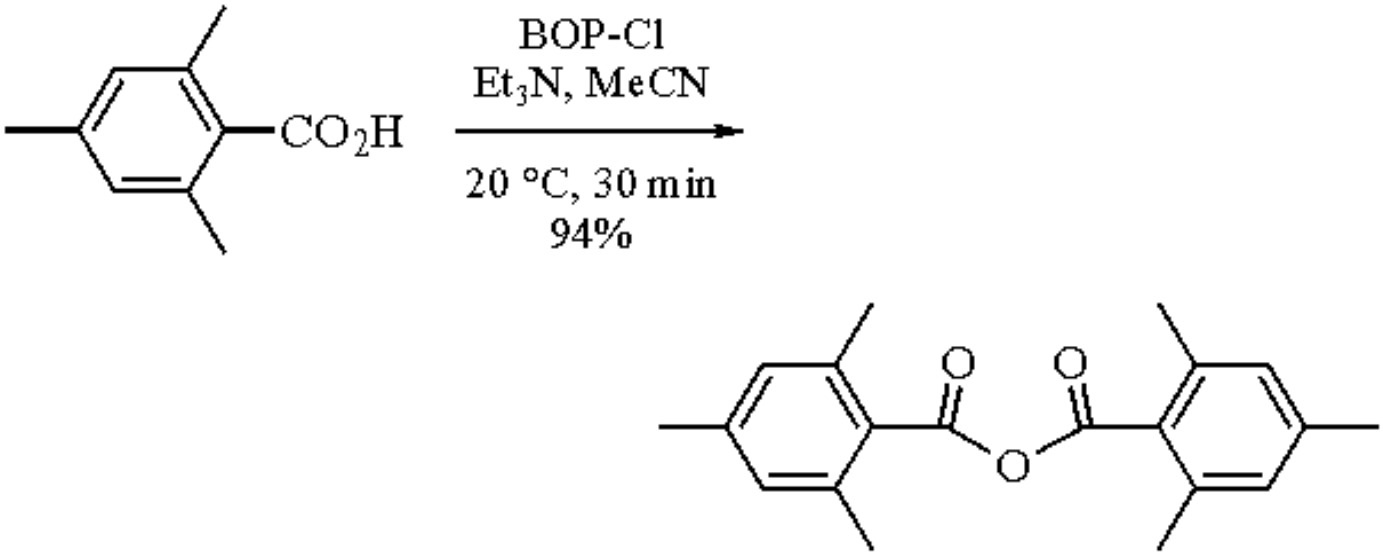

(3)

The mechanism of these reactions is assumed to involve displacement of chloride by the carboxylate anion to give a phosphorodiamidate (eq 4). Subsequent nucleophilic attack of an alcohol, amine, or a carboxylate anion affords phosphorodiamidic acid and esters, amides, and anhydrides, respectively (eq 5).

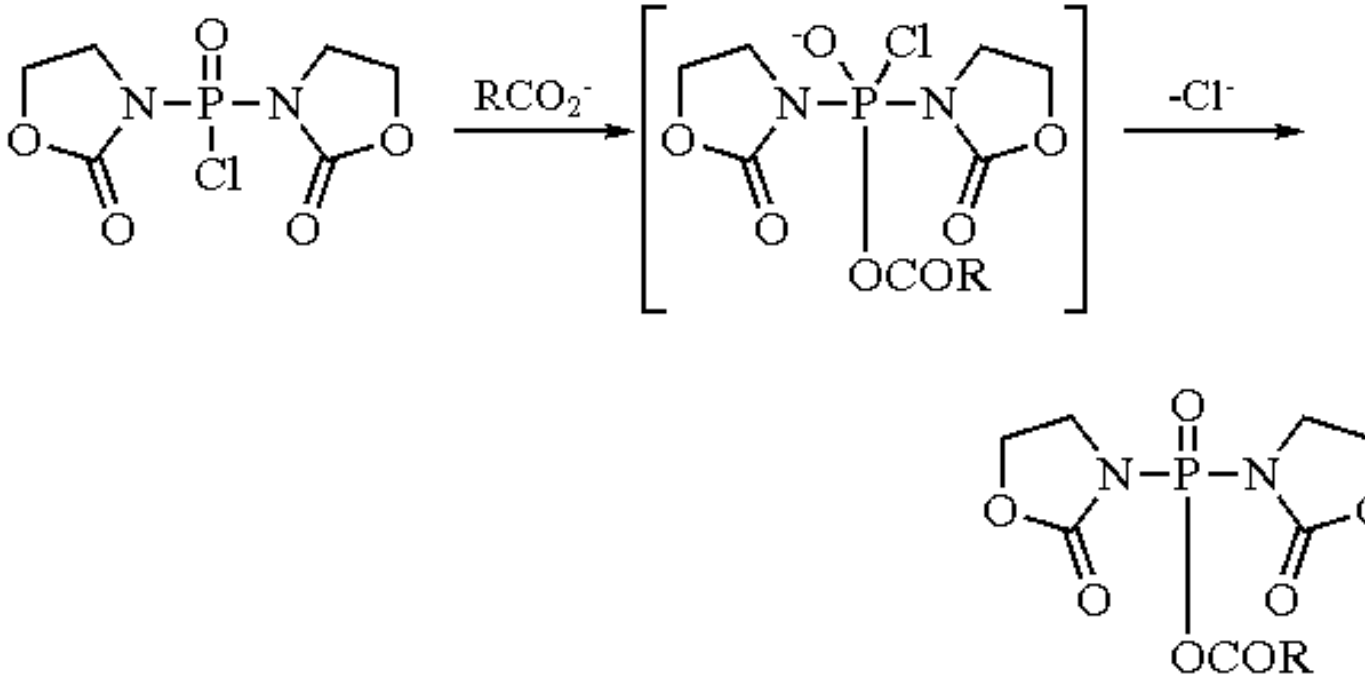

(4)

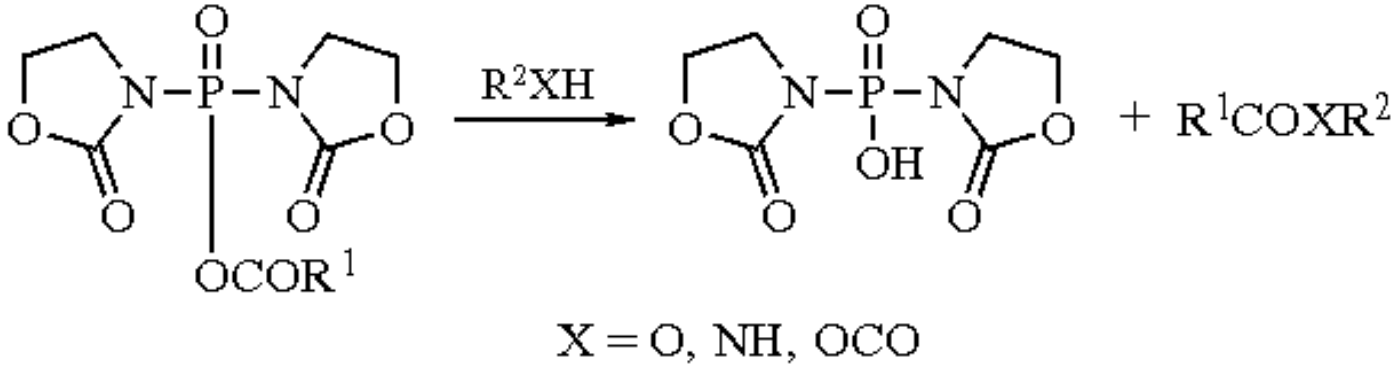

(5)

For lactonization (eq 6),[14] including the synthesis of macrolactones,[15] BOP-Cl is a useful reagent.

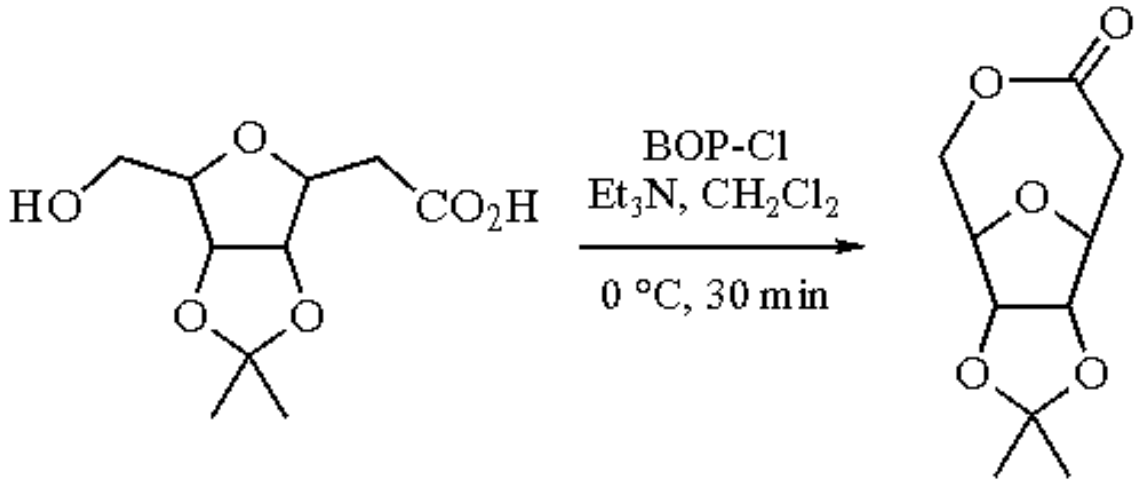

(6)

Chemo- and regioselective acylation with BOP-Cl is illustrated by the formation of 5´-benzoyldeoxyadenosine in good yield (eq 7).[16]

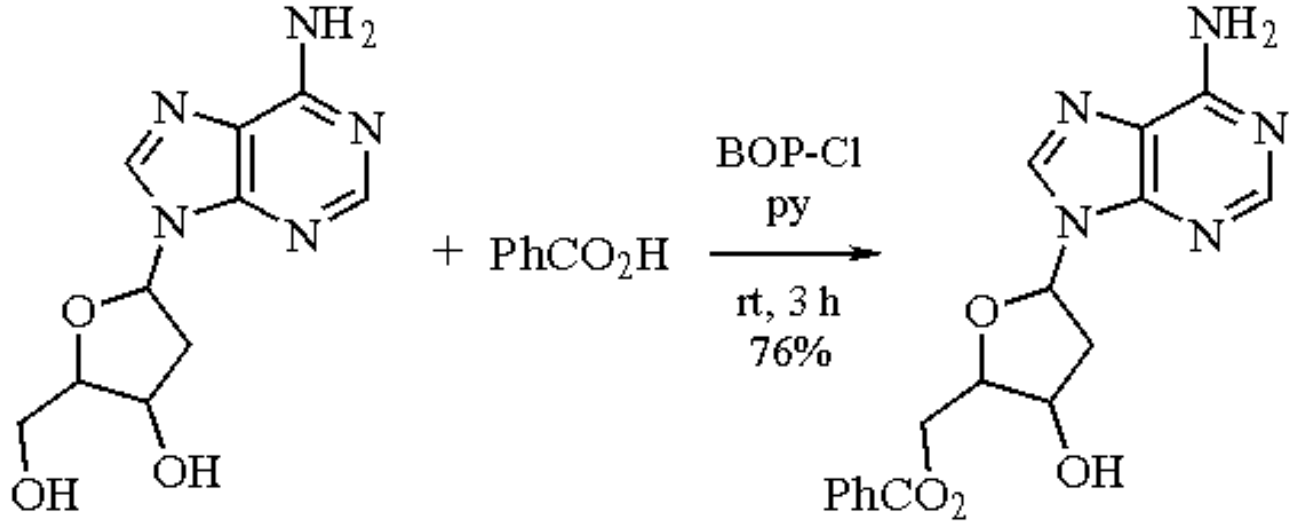

(7)

For the synthesis of oligonucleotides, BOP-Cl is an effective coupling reagent, allowing phosphotriesters to be prepared in high yields without detectable side reactions (eq 8).[17]

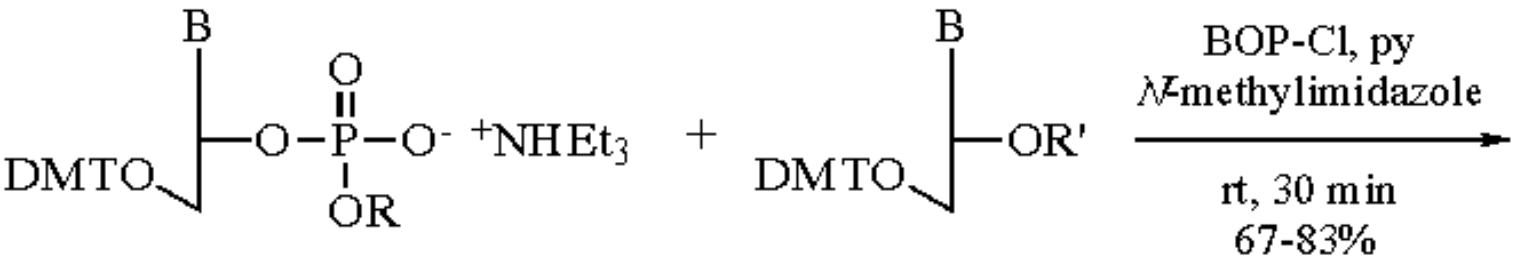

DMT = 4,4'-dimethoxytrityl

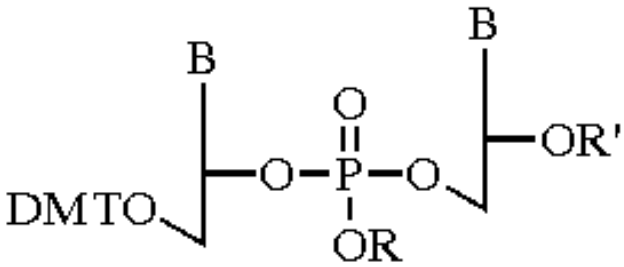

(8)

β-Lactams may be prepared either by condensation of imines with carboxylic acids (eq 9)[9] or by cyclization of β-amino acids (eq 10).[10]

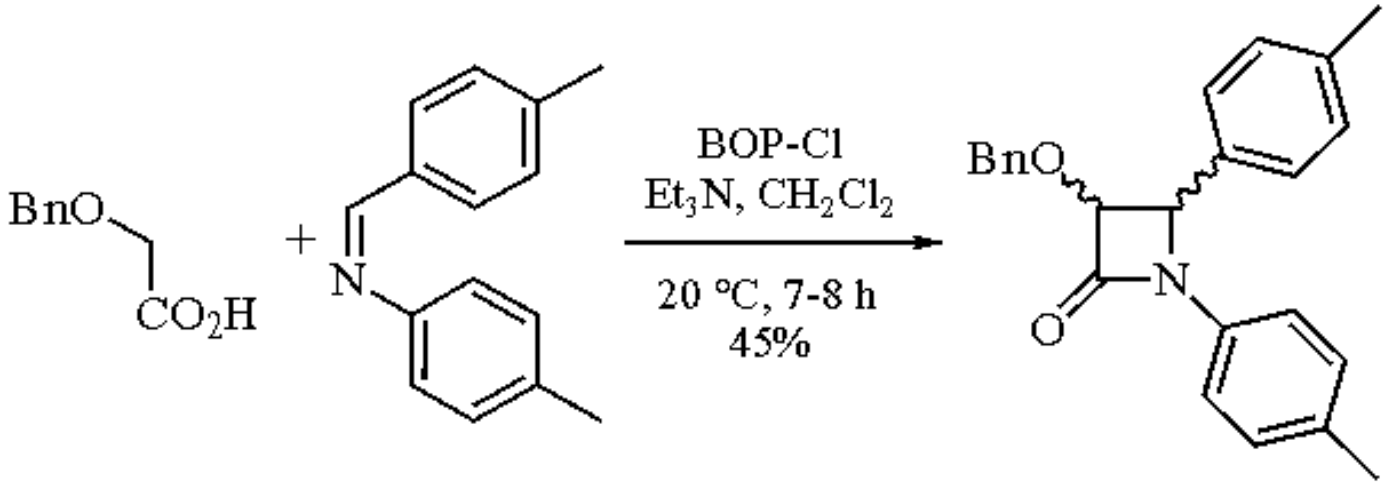

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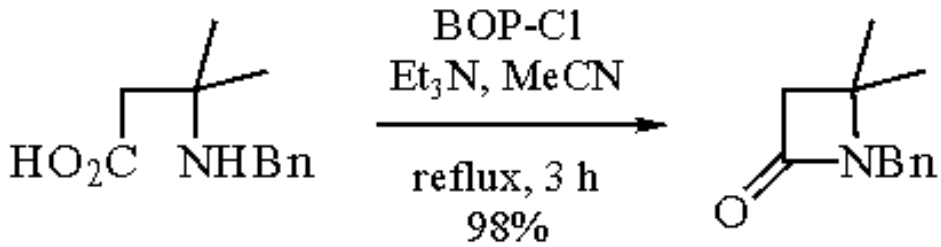

(10)

BOP-Cl has been used quite extensively for the synthesis of peptides.[6-8] It is particularly useful for coupling *N*-alkyl-α-amino acids with minimal racemization (eq 11),[18,19] although the quality of BOP-Cl employed in these reactions can significantly affect yields,[13] and the analogous azide, BOP-N_3, has been proposed as an alternative reagent.[20] Racemization can sometimes be suppressed by inclusion of additives such as ***1-Hydroxybenzotriazole*** (HOBt) or ***Imidazole*** (eq 12),[21] although under certain conditions HOBt can induce epimerization.[22]

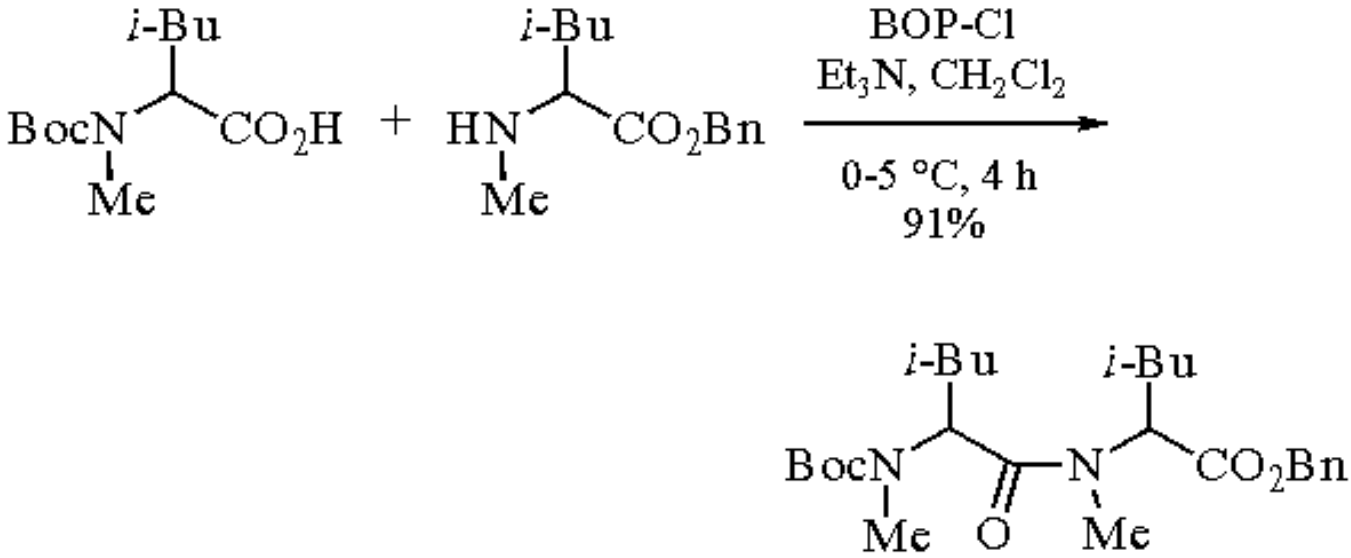

(11)

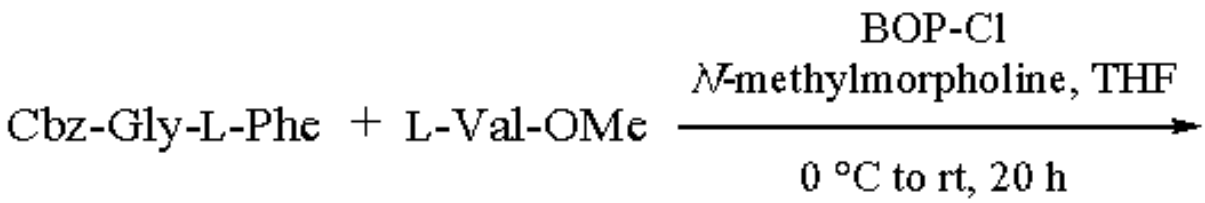

Cbz-Gly-D/L-Phe-L-Val-OMe (12)

	Yield (%)	Epimerization (%)
with HO-*t*-Bu	88	0.0
with imidazole	96	0.8
without HO-*t*-Bu or imidazole	78	5.6

Problems, notably racemization and poor yields due to oxazolone formation, are encountered when coupling *N*-acyl amino acids with BOP-Cl;[6] ***1,3-Dicyclohexylcarbodiimide*** (DCC) is a better reagent to use in such cases. Some limitations of BOP-Cl for peptide couplings have been discussed;[7] it is not recommended for β-branched α-amino acids (e.g. Boc-Val) or for couplings in which the nucleophile is a primary amine.[8]

Kinetic Resolution.

BOP-Cl is a condensation agent for the kinetic resolution of racemic carboxylic acids and alcohols with chiral alcohols (eq 13) and carboxylic acids, respectively.[12]

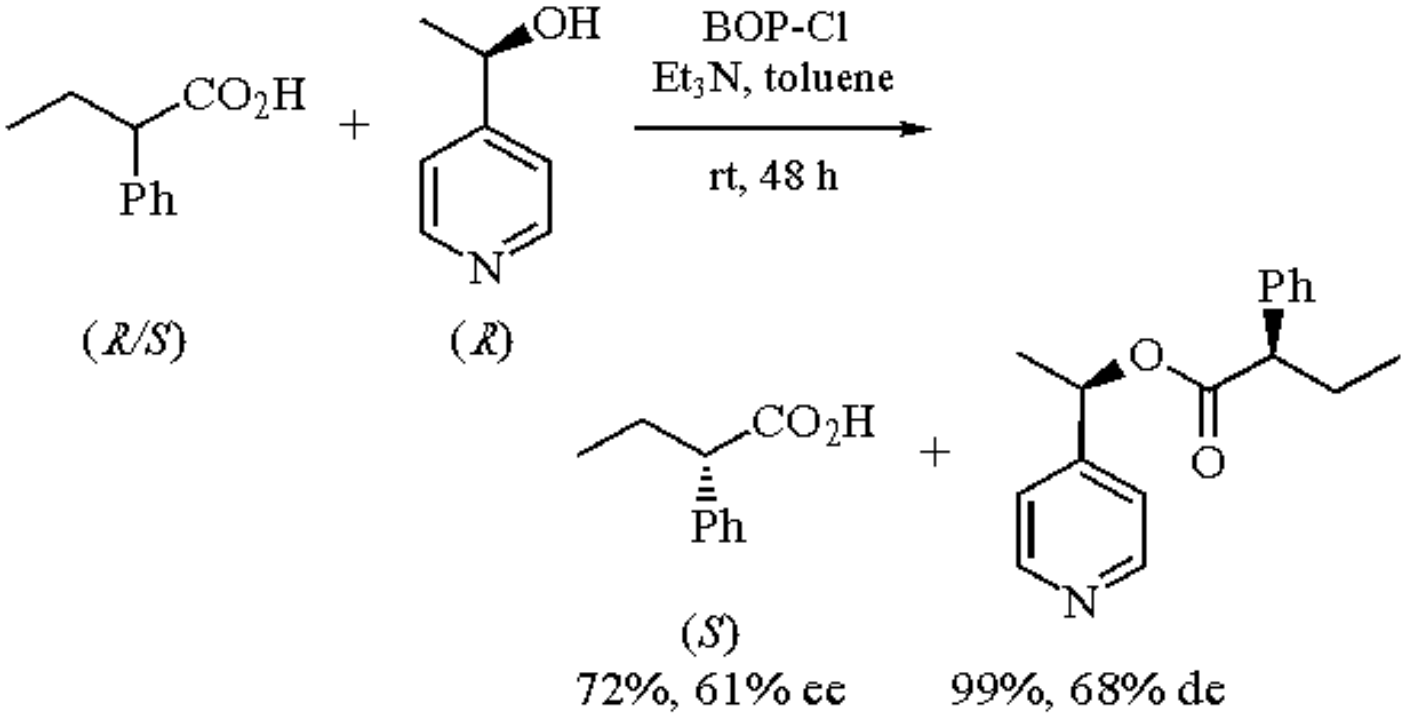

(13)

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Bis(*o*-phenylene) Pyrophosphite

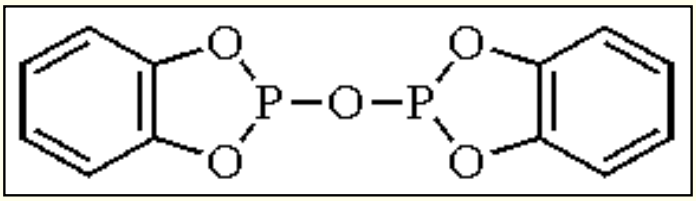

[16421-86-6] · $C_{12}H_8O_5P_2$ · Bis(*o*-phenylene) Pyrophosphite · (MW 294.14)

(reagent for peptide synthesis[1])

Physical Data: mp 72 °C; bp 156 °C/0.25 mmHg; *n*20D 1.5090 (supercooled liquid).

Preparative Method: reaction of ***Catechol*** with ***Phosphorus(III) Chloride*** gives *o*-phenylene phosphorochloridite, which upon hydrolysis affords bis(*o*-phenylene) pyrophosphite (**1**).[2]

Purification: purified by distillation at reduced pressure.

Handling, Storage, and Precautions: may be stored indefinitely in a stoppered bottle.

Peptide Synthesis.

The reagent (**1**) was introduced as a substitute in peptide synthesis for the widely used, but less easily prepared, ***Tetraethyl Pyrophosphate***. Heating a mixture of an *N*-protected (Cbz or phthaloyl) amino acid and an amino acid or peptide ester with 1.1 equiv of (**1**) in pyridine effects amide bond formation (eq 1).[1] The amino acid or peptide ester may be used as its hydrohalide or tosylate salt. The method is experimentally simple and has the additional advantage that the crude product is generally of sufficient purity for preparative purposes. Prereaction of (**1**) with either coupling partner to give the active ester or the phosphoramidite intermediate is possible but offers no advantage.

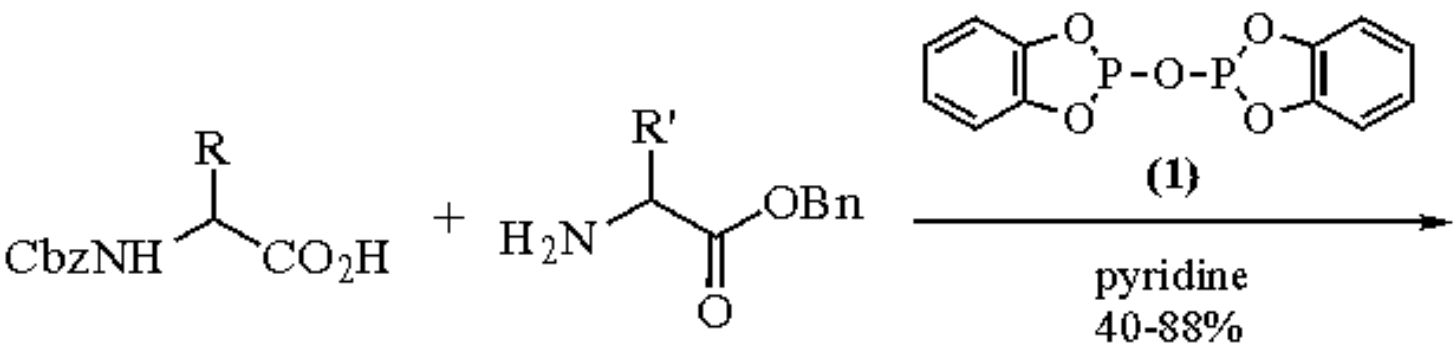

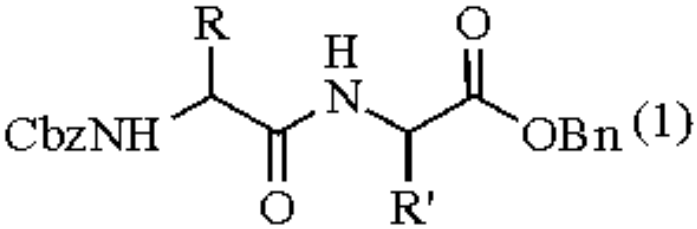

While no racemization was detected in couplings involving *N*-Cbz-protected amino acids, use of *N*-protected dipeptides as carboxyl components resulted in extensive racemization, presumably by the oxazolone mechanism. The method is also unsuitable for the synthesis of tyrosine peptides without prior protection of the phenolic hydroxy group, since *O*-phosphorylation may occur.

Synthesis of cyclic peptides using (**1**) was studied by Miller and Smith.[3] Use of diethyl phosphite as solvent rather than pyridine was found to be necessary; the method gave better results than ***1,3-Dicyclohexylcarbodiimide*** (DCC) for cyclization of penta- and hexapeptides, but was not suitable for cyclization of tripeptides.

---

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Alan Armstrong

University of Bath, UK

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1,2-Bis(phenylsulfonyl)ethylene[1]

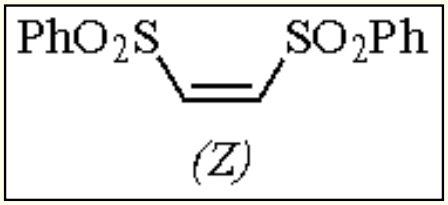

(*Z*)

[963-15-5] · $C_{14}H_{12}O_4S_2$ · 1,2-Bis(phenylsulfonyl)ethylene · (MW 308.37) (*E*)

[963-16-6]

(powerful dienophiles and synthetic equivalents of acetylene and ethylene in Diels-Alder cycloadditions;[2] react as Michael acceptors with substitution of a phenylsulfonyl group[3])

Alternate Name: BPSE.

Physical Data: (*Z*) mp 100-101 °C; (*E*) mp 219.5 °C.

Solubility: the (*Z*)-isomer is more soluble than the (*E*)-isomer in most solvents. In Diels-Alder cycloadditions conducted in dichloromethane, the (*Z*)-isomer affords quite insoluble adducts; conversely, the (*E*)-compound leads to more soluble products.

Form Supplied in: colorless solids; commercially available.

Analysis of Reagent Purity: purity with respect to one another can be checked by ^{1}H NMR. The vinyl protons of the (*Z*)-isomer appear at 6.82 ppm and those of the (*E*)-isomer at 7.37 ppm in $CDCl_3$.

Preparative Methods: (*Z*)-1,2-bis(phenylsulfonyl)ethylene is prepared by oxidation of the corresponding thioether,[2] which is prepared from (*Z*)-1,2-dichloroethylene[4] or, for large quantities, from 1,1-dichloroethylene.[4b] A mixture of the (*Z*)- and (*E*)-1,2-dichloroethylenes can also be used, but the (*E*)-isomer is unreactive under standard conditions.[4b] Under more drastic reaction conditions (DMF, 70-90 °C), (*E*)-1,2-dichloroethylene also affords the substitution product [57% (*E*), 14% (*Z*)].[4c] The preparation of the (*E*)-isomer is accomplished by sunlight-iodine catalyzed isomerization of the (*Z*)-isomer.[2]

Handling, Storage, and Precautions: the (*Z*)-isomer should be stored protected from direct light because it isomerizes to the (*E*)-form.

Cycloadditions.

1,2-Bis(phenylsulfonyl)ethylenes [(*Z*)- and (*E*)-BPSE] are most commonly used as synthetic equivalents of acetylene in cycloaddition reactions (eq 1).[2,5] A number of dienes have been prepared via this route which are otherwise not readily accessible.[6]

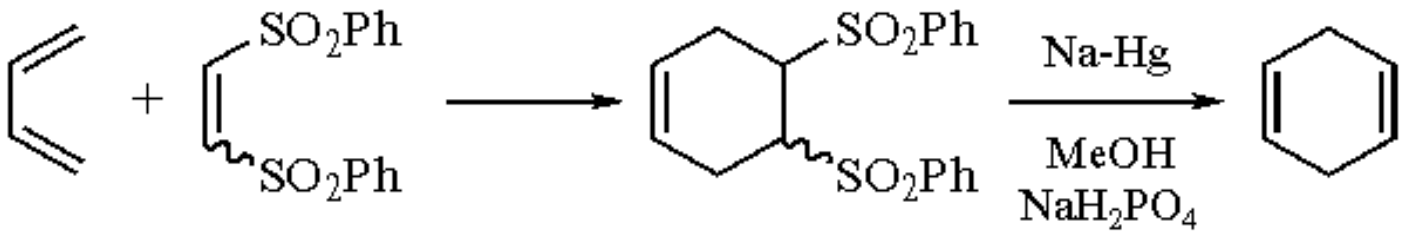

(1)

The preparation of both the *syn*- and the *anti*-sesquinorbornatrienes was possible because of the different stereochemistry by which the (*Z*)- and (*E*)-isomers add to 8,9-dehydroisodicyclopentadiene (eq 2).[7] Further studies on these molecules have been reported, including the preparation of deutero derivatives via the deuterated (*Z*)-BPSE.[8] Use of (*E*)-BPSE in the preparation of a natural product is described in eq 3.[9]

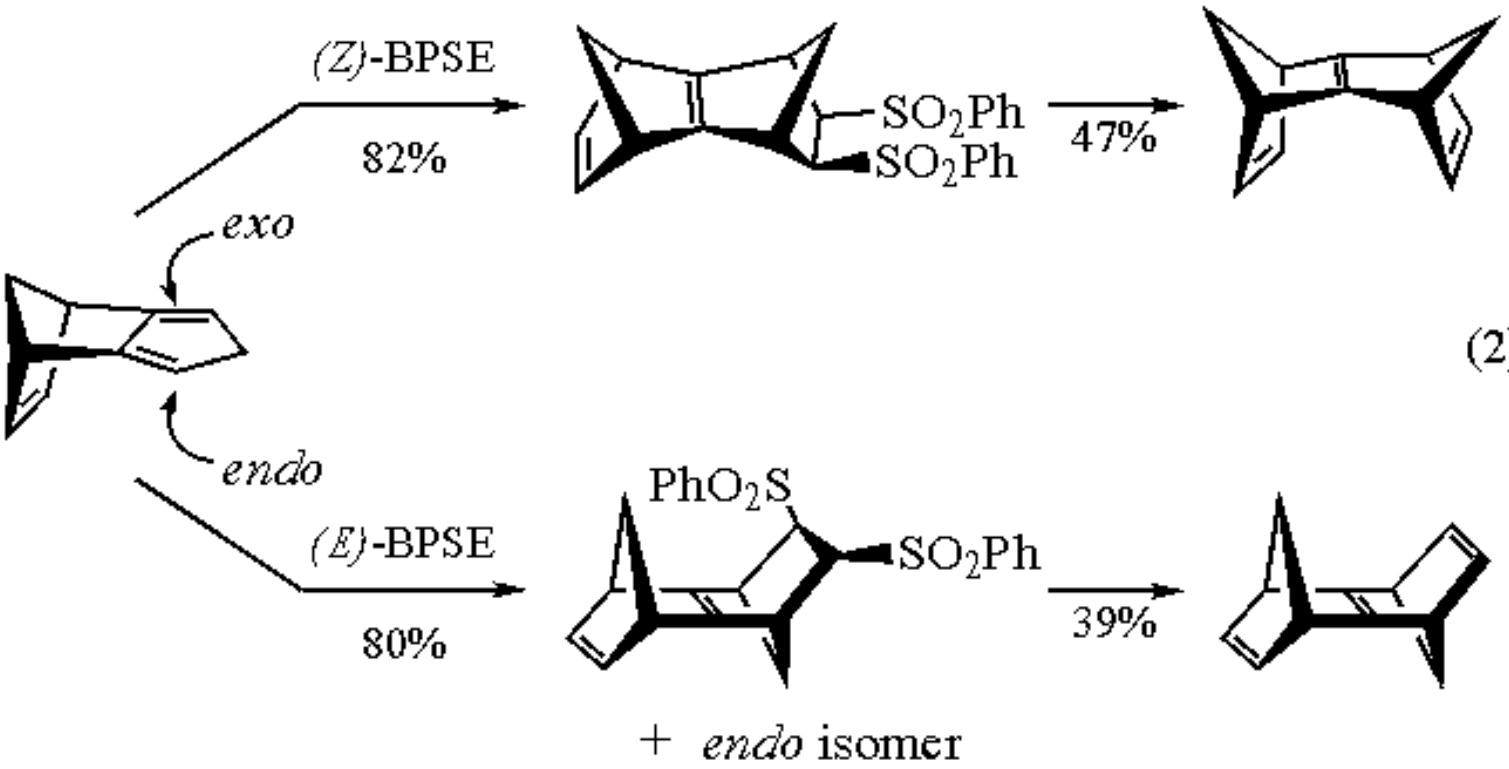

(2)

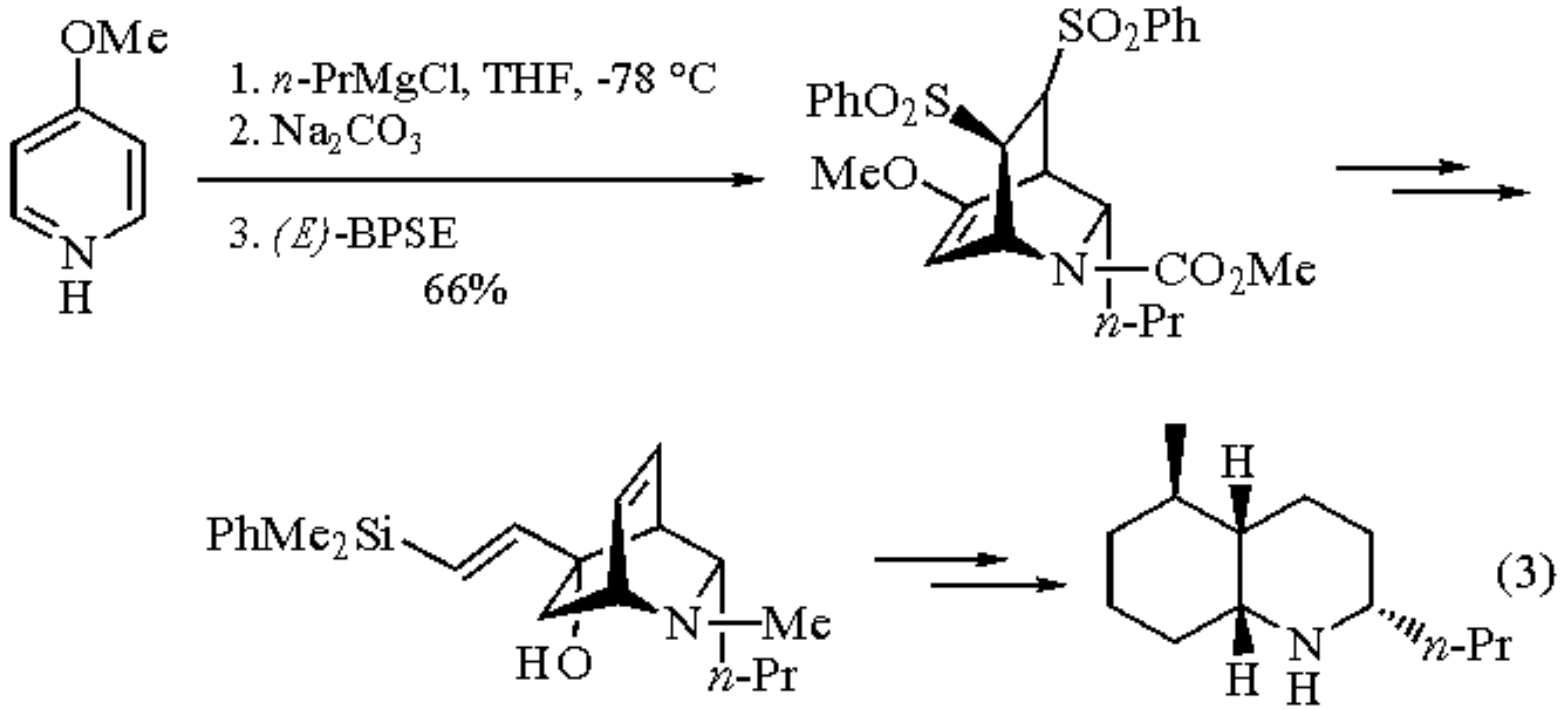

The choice of the solvent for cycloadditions is often crucial. While both reagents are not reactive towards furan in refluxing benzene,[10] they react smoothly at rt in quantitative yields in dichloromethane.[2,11]

Generally, the (*E*)-isomer is more reactive in cycloadditions than the (*Z*)-isomer. For example, the reaction of (*E*)-BPSE with cyclopentadiene in dioxane is 100 times faster than that of the (*Z*)-isomer.[12] A few dienes (1,3-cycloheptadiene and cyclooctatetraene are examples) react only with the former. With cyclopentadiene in dioxane, (*E*)-BPSE is twice as reactive as ***Maleic Anhydride***,[12] but cases have been reported where (*E*)-BPSE failed to react while maleic anhydride did react. Styrene, homobarrelene, and other polycyclic dienes are examples.[13] High pressure (10-12 kbar) can be used to increase reactivity.[14] Examples are the preparations of derivatives of *syn*-sesquinorbornatriene[14a] and of the C_{4v} [4]peristylane tetraketone (eq 4).[14c]

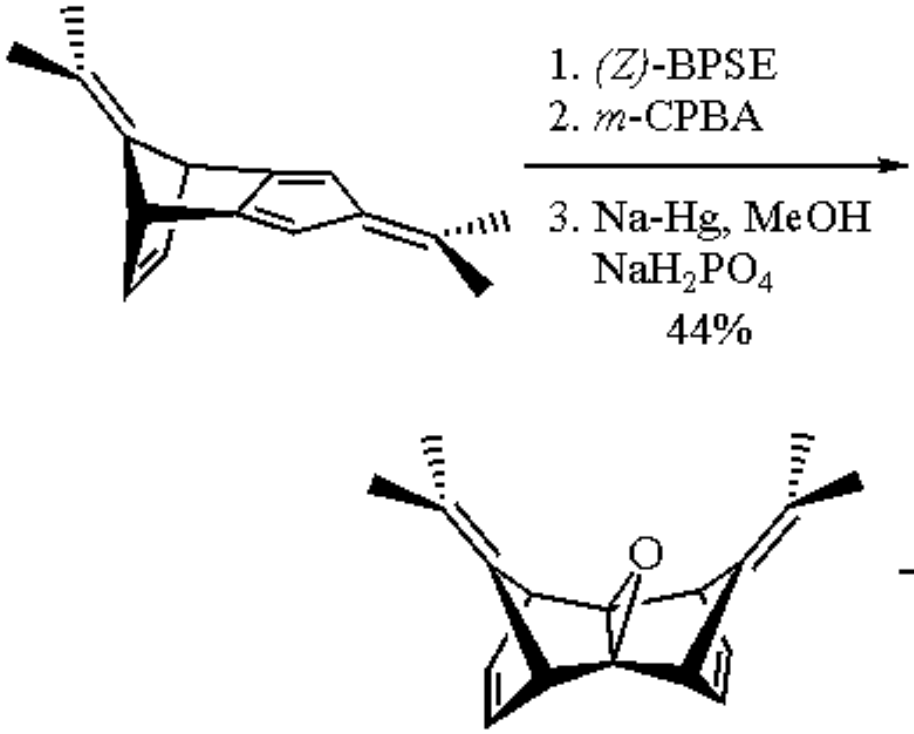

(4)

The desulfonylation of cycloadducts can be performed with ***Sodium Amalgam*** (1.5-6%) in methanol buffered with suspended sodium dihydrogen phosphate.[2] Because the reaction is heterogeneous, sonication has been proved beneficial.[13a] ***Samarium(II) Iodide*** in HMPA has also been used.[15] Other reducing agents and reaction conditions, such as ***Magnesium-Methanol***,[16] afford mixtures of saturated and unsaturated hydrocarbons. ***Lithium*** or ***Sodium*** metal in liquid ammonia effectively gives solely the saturated adduct, making the title reagent equivalent to ethylene in cycloaddition reactions.[17]

When treated with base, the Diels-Alder adducts give vinyl sulfones. In one example, the vinyl sulfone was further reacted with nucleophiles in a synthesis of ibogamine (eq 5).[18]

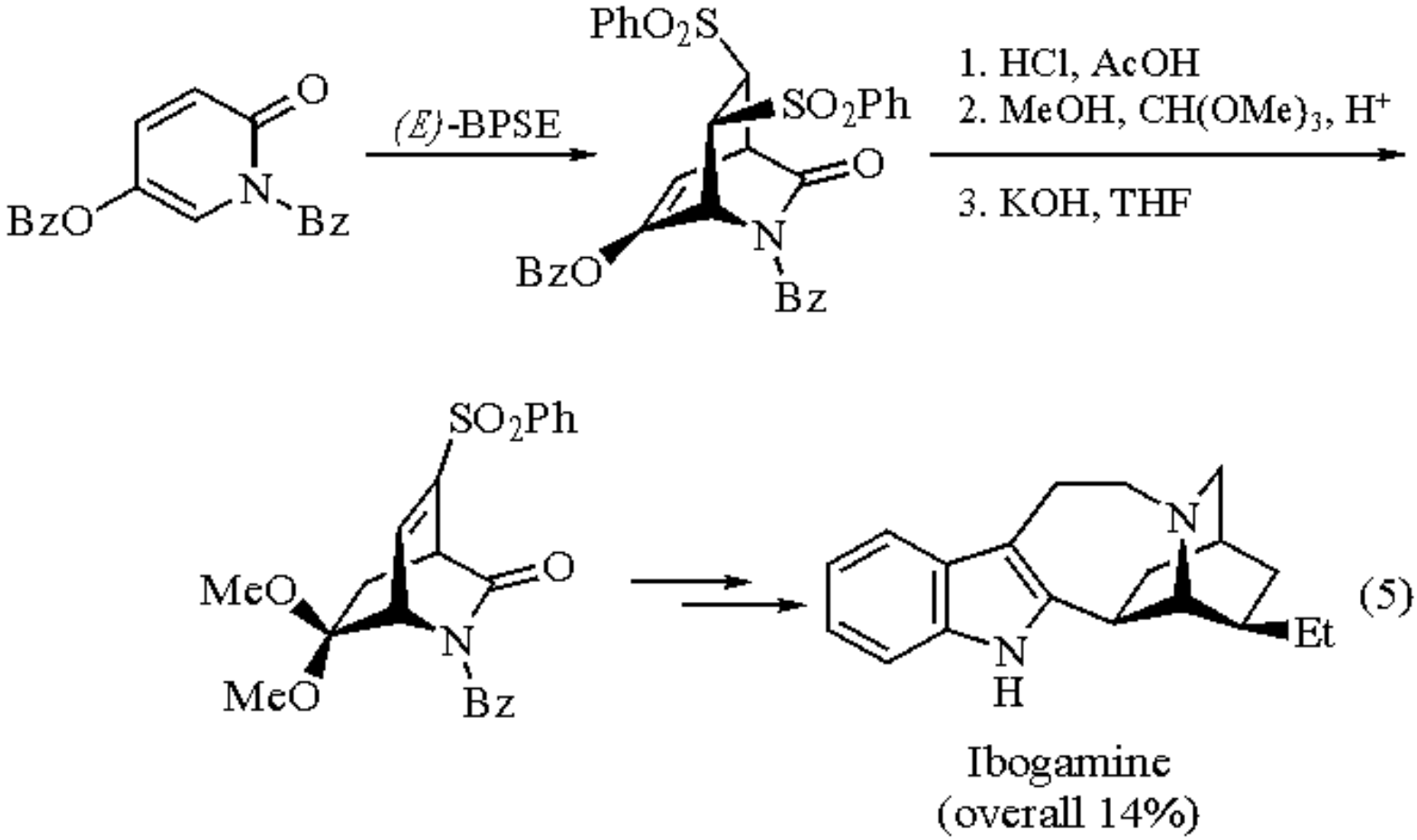

(5)

Substitution of one vinyl hydrogen with chlorine gives reagents that can be considered equivalents of the unstable bis(arylsulfonyl)alkynes (eq 6).[19]

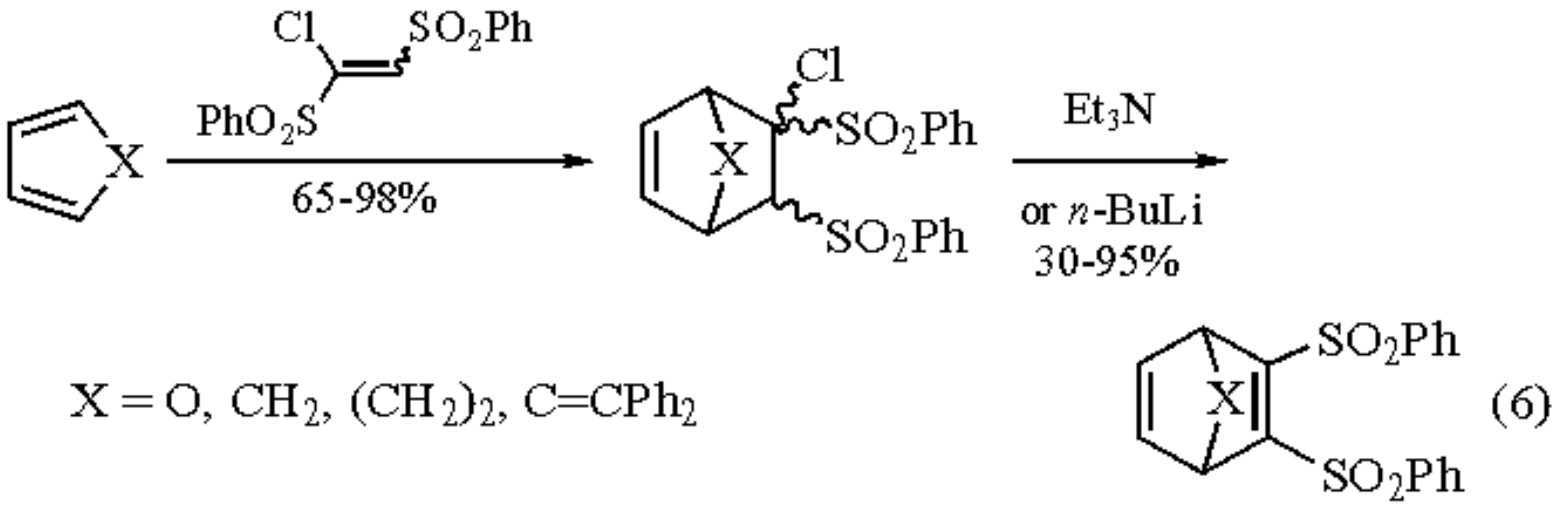

(6)

The parent and substituted bis(arylsulfonyl)alkenes, such as the one prepared in eq 6, are good Michael acceptors[20] and react with heteroatomic nucleophiles and Grignard reagents.[3,21] The products correspond to the formal substitution of one of the phenylsulfonyl groups. In eq 7, the product of the Michael addition cyclizes to a dihydrofuran upon deprotonation with ***Lithium Diisopropylamide***.[21a]

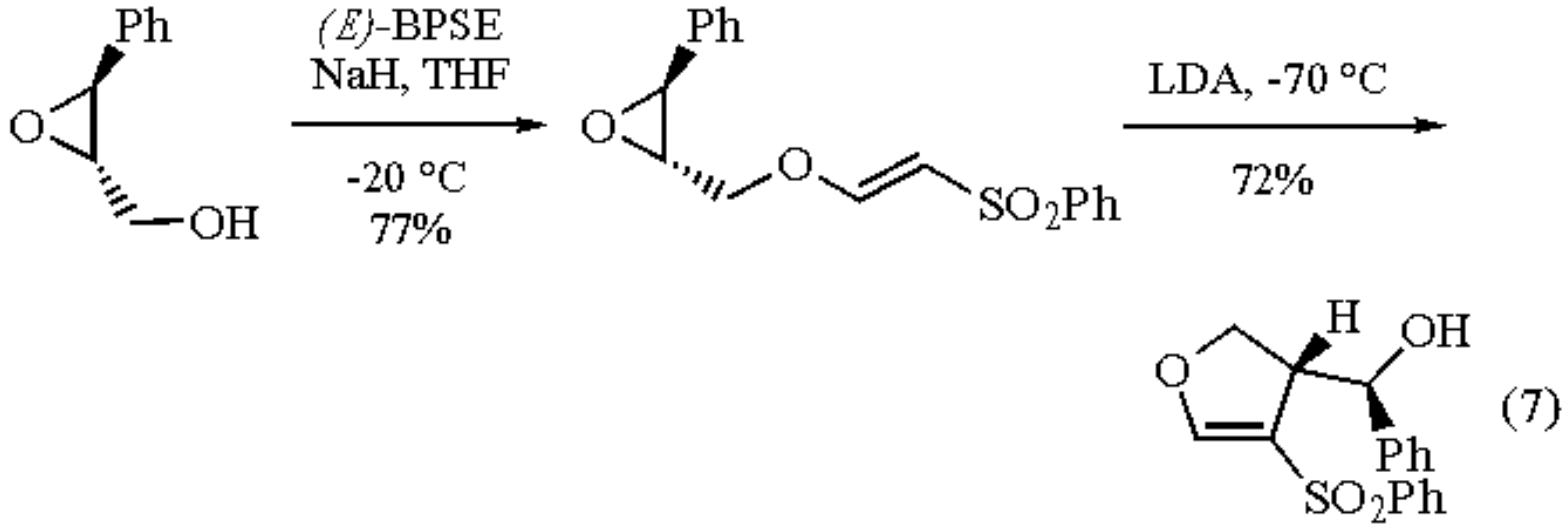

Both isomeric reagents are also reactive dipolarophiles.[22] For example, they react with azomethine ylides,[22a,b] nitrones,[22c] and diazoalkanes (eq 8).[22d]

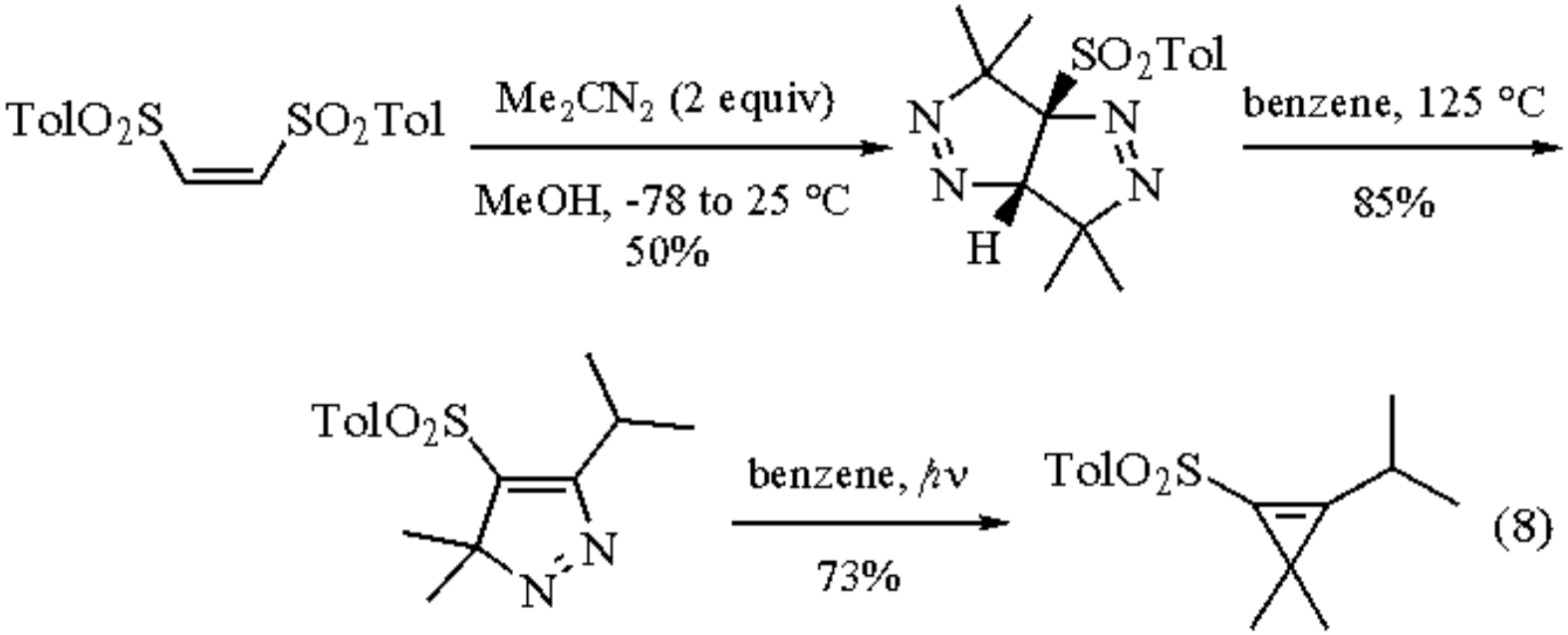

C_2-Symmetrical chiral versions of these reagents (**1**) and (**2**), which maintain the chemical properties associated with the achiral reagents, are available (see ***1,1´-Binaphthalene-2,2´-dithiol***).[23]

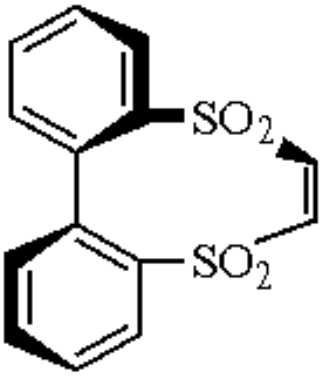

(1)

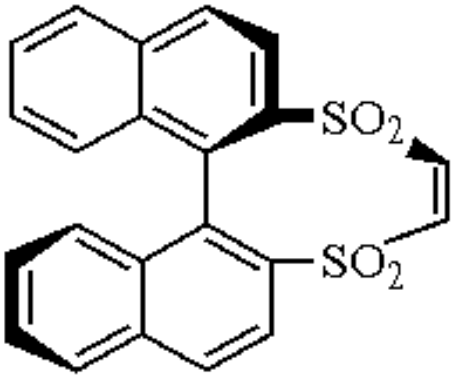

(2)

These reagents are stable towards racemization and are readily available from the respective dibenzo- or dinaphtho-2,2´-dithiols. In cycloadditions with nonsymmetrical dienes they afford a single diastereoisomer in most cases.

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1,1-Bis(phenylsulfonyl)ethylene[1]

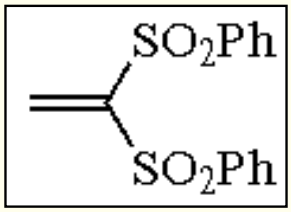

[39082-53-6] · $C_{14}H_{12}O_4S_2$ · 1,1-Bis(phenylsulfonyl)ethylene · (MW 308.37)

(powerful Michael acceptor and dienophile; reagent for two-carbon homologation of ketones; synthetic equivalent of ethylene in Diels-Alder reactions and of ethylene 1,2-dipole in cycloadditions)[1]

Alternate Name: 1,1-BPSE.

Physical Data: mp 124-126 °C.

Form Supplied in: colorless solid.

Analysis of Reagent Purity: depending upon the method of preparation, it may contain bis(phenylsulfonyl)methane and 1,1,3,3-tetrakis(phenylsulfonyl)propane as impurities. In a few cases, isomerization to (*E*)-1,2-bis(phenylsulfonyl)ethylene has been observed.[2,3a] The chemical shift of the vinyl protons is 7.19 ppm ($CDCl_3$).

Preparative Methods: the reagent can be prepared via careful oxidation of the corresponding ketene dithioacetal[3a] or via Mannich condensation of bis(phenylsulfonyl)methane with paraformaldehyde and a secondary amine followed by elimination with acids.[3]

Handling, Storage, and Precautions: keep dry and refrigerated; potential alkylating agent; use in a fume hood.

Addition Reactions.

The two geminal phenylsulfonyl groups impart to the double bond of 1,1-BPSE a strong electrophilic nature which manifests most evidently in Michael additions.[1b] Heteroatomic nucleophiles such as amines, alcohols, and thiols add in nonpolar solvents even without added base.[1b,3a] Water, either under acid or base catalysis, and strong nucleophiles in protic solvents can cleave the double bond with eventual formation of 1,1,3,3-tetrakis(phenylsulfonyl)propane.[1b,4] 1,1-BPSE adds to carbon nucleophiles generated from active methylene compounds using different bases[5] (eq 1),[5d] including fluoride ions,[5d] or under Lewis acid catalysis.[5a] Neutral carbon nucleophiles[6] such as enol ethers (eq 2)[6c] and enamines[6a] also add smoothly with no need of extra activation. Enantiomerically pure enamino esters give, after

hydrolysis, ketones which display stereochemistry opposite to that obtained with ***Phenylsulfonylethylene*** (eq 3).[6d] Ynamines react similarly, but in this case the likely zwitterionic intermediate cyclizes to a [2 + 2] cycloadduct (eq 4).[7]

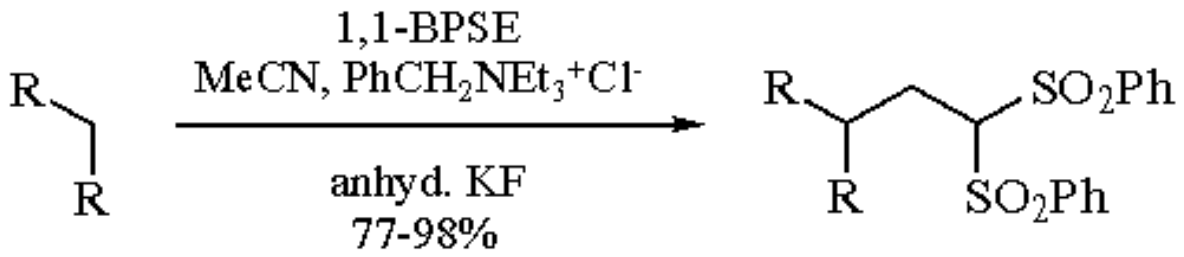

(1)

R = COMe, COPh, SO_2Ph, NO_2, etc.

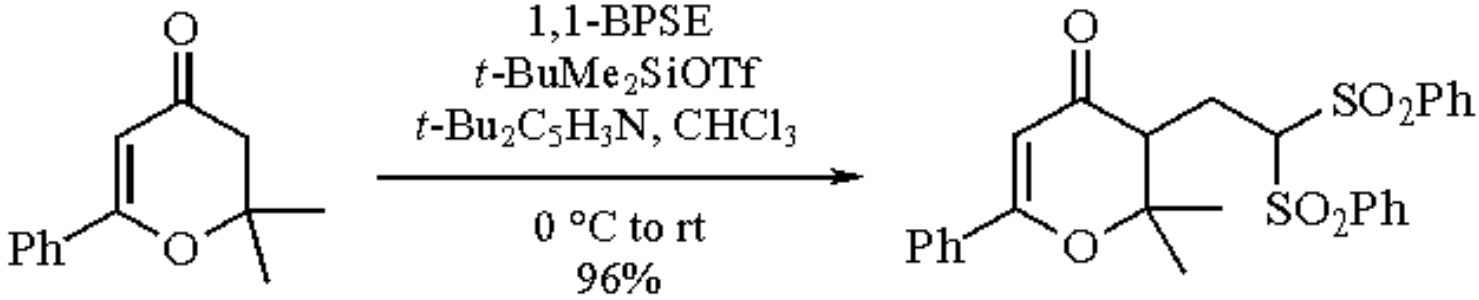

(2)

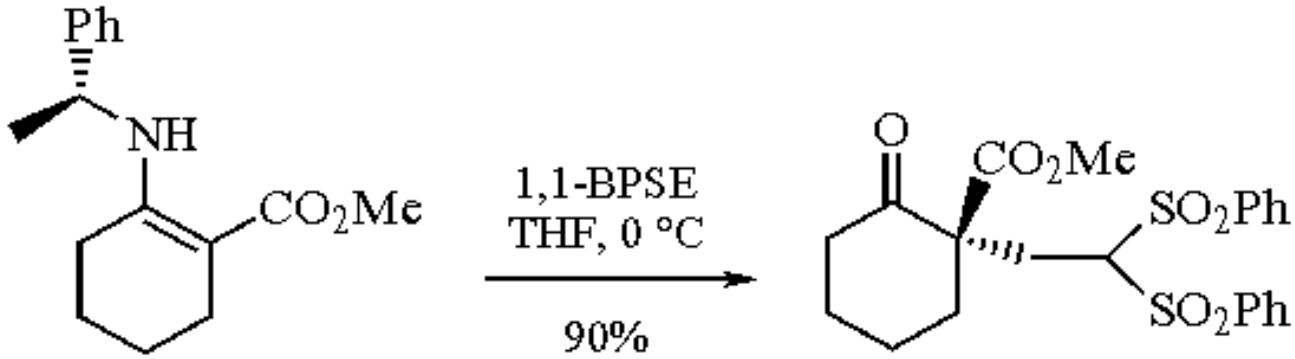

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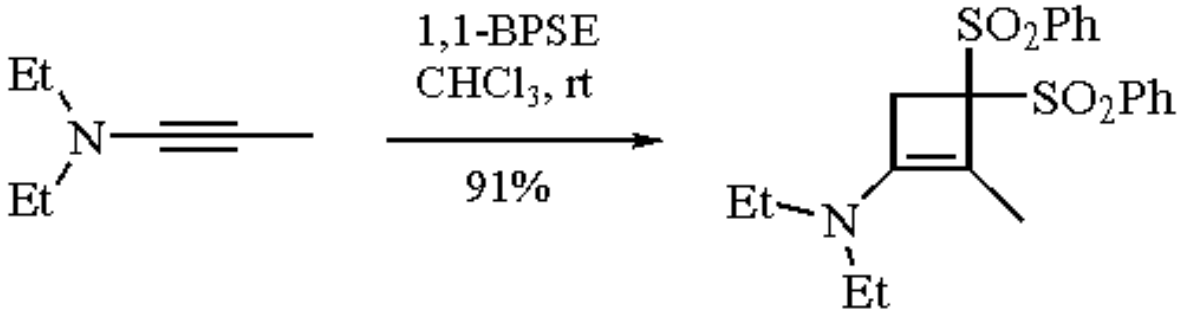

(4)

Enolizable ketones and imines also react with 1,1-BPSE even without base catalysis.[6] Since the nucleophile is presumably the enol, the regiochemistry of the addition is opposite to that obtained with enolates (eq 5).[6b]

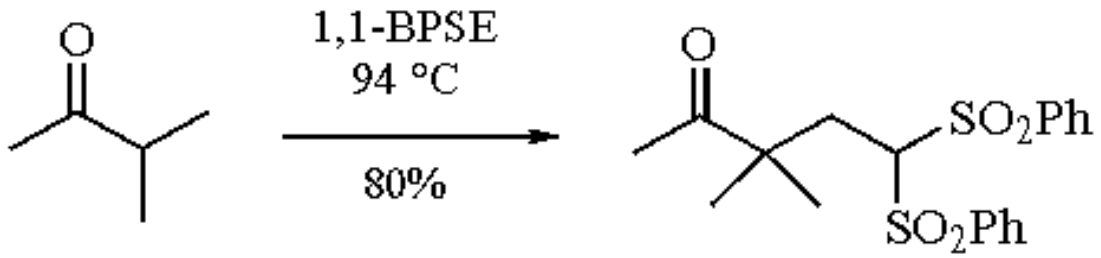

(5)

Cycloadditions.

The title reagent forms Diels-Alder adducts with dienes such as 1,3-cyclohexadiene (**1**),[8a,b] cycloheptatriene (**2**),[8a] norbornadiene (**3**),[6a,8c] quadricyclane (**4**),[6a,8a,c] 2-acetoxy-1,3-cyclopentadiene (**5**),[8a] and *N*-benzoylindole-2,3-quinodimethane (**6**).[8d] In cases where two regioisomers can form, the results are in accordance with the stereochemistry expected on the basis of orbital coefficients.[8a,d]

(1)

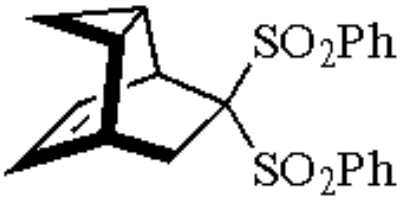

(2)

(3)

(4)

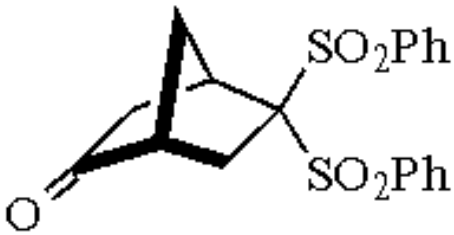

(5)

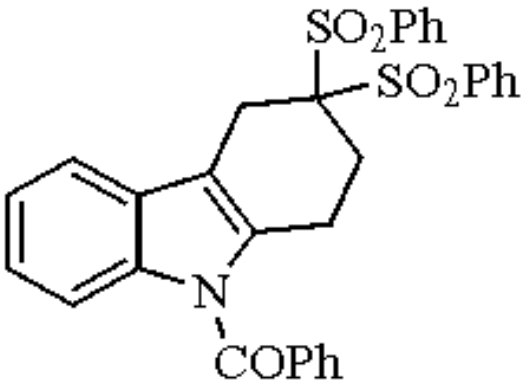

(6)

Due to the polarization of the reagent, [2 + 2] cycloadducts and products arising from dipolar rearrangements have been observed in reactions with strained alkenes. Benzonorbornadiene is an example (eq 6).[6a] The desulfonylation reaction can be performed with ***Aluminum Amalgam*** or ***Sodium Amalgam*** in such a way as to obtain sequential mono- and bisdesulfonylation (see also ***1,2-Bis(phenylsulfonyl)ethylene***).

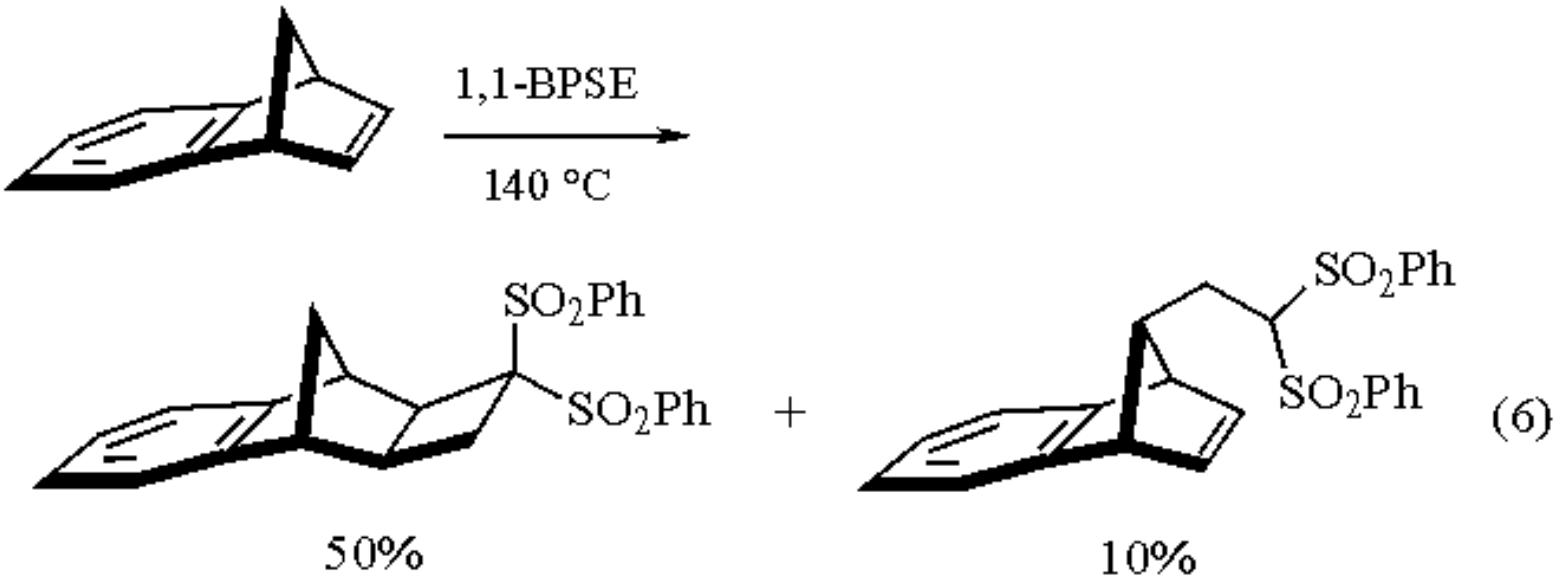

Chiral variants of the title reagent having a 2,2´-binaphthyl residue in the place of the two phenyl rings have been proposed (see ***1,1´-Binaphthalene-2,2´-dithiol***).[9]

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Bis(phenylthio)methane[1]

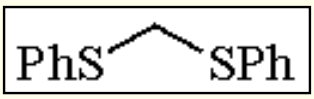

[3561-67-9] · $C_{13}H_{12}S_2$ · Bis(phenylthio)methane · (MW 232.36)

(lithio derivative is formyl anion equivalent[2] but chief uses are in synthesis of phenyl vinyl sulfides[3] and α-(phenylthio) ketones[4])

Physical Data: mp 38 °C.

Solubility: sol THF, diethyl ether; insol H_2O.

Form Supplied in: yellow crystals (white when pure).

Preparative Methods: all methods begin with benzenethiol (***Thiophenol***, PhSH). An early approach involved reaction of ***Diiodomethane*** with PhSNa (generated from PhSH and NaOH in ethanol).[2] Dichloromethane (CH_2Cl_2) has replaced the more expensive CH_2I_2 in more recent methods either in the presence of triethylamine[3] or under phase-transfer conditions with ***Potassium Carbonate*** and ***Benzyltriethylammonium Chloride***.[5] The hydrogen chloride-catalyzed reaction of benzenethiol with ***Dimethoxymethane*** is an effective procedure.[6]

Purification: recrystallize from petroleum ether.

Handling, Storage, and Precautions: irritating to mucous membranes and upper respiratory tract. Precautions should be followed to avoid inhalation, ingestion, contact with the eyes, or absorption through the skin. Stench. Store in a cool dry place. The toxicological properties appear not to have been thoroughly investigated but exposure can cause nausea, headache, and vomiting.

Introduction.

As reagents for nucleophilic acylation, bis(phenylthio)methane (**1**) and ***1,3-Dithiane*** were introduced into synthetic methodology at about the same time. Application of (**1**) to the synthesis of aldehydes involves a sequence of steps (eqs 1-3) analogous to those of 1,3-dithiane. In practice, however, the sequence beginning with 1,3-dithiane is the standard method for nucleophilic acylation while that based on (**1**) is rarely employed. Nevertheless, there are a number of novel transformations involving derivatives of (**1**) and it is the applications of these reactions that comprise the major portion of the present account. Before examining these reactions, a brief discussion of the metalation of (**1**) (eq 1) and the reactions of its lithio derivative (**2**) is in order.

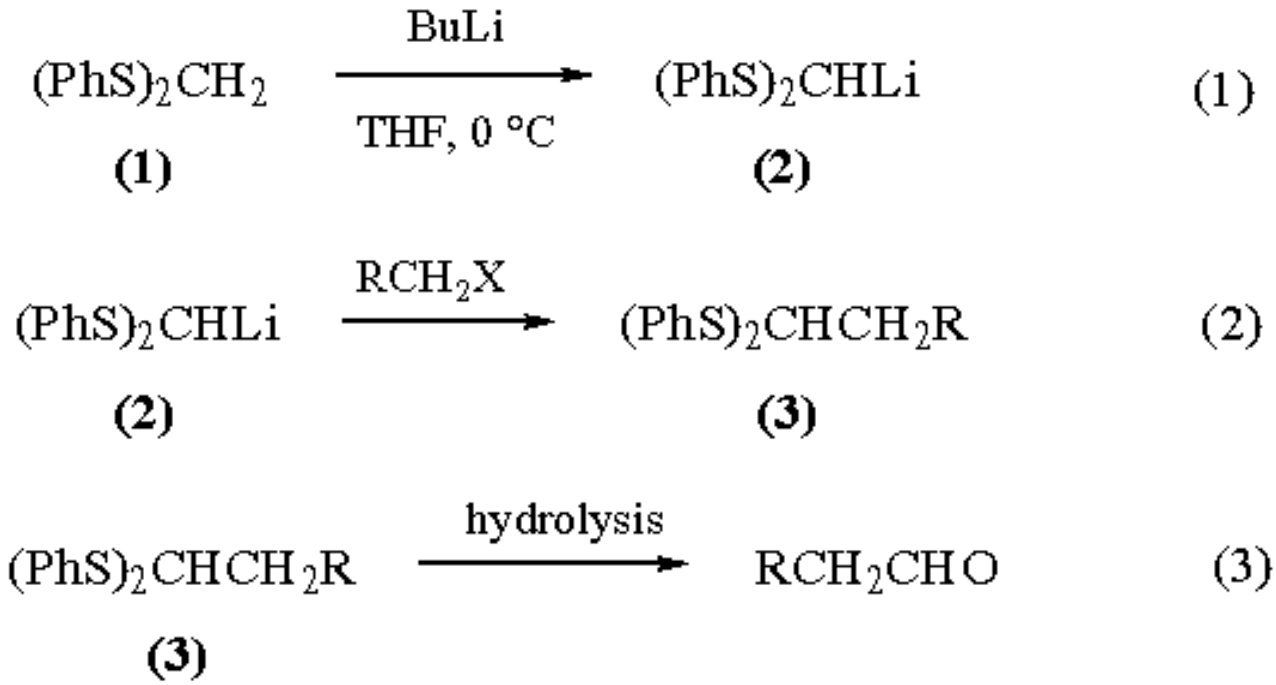

Metalation of (1) and Nucleophilic Reactivity of (2).

With a pK_a of 30.8 (in DMSO),[7] (**1**) is a somewhat stronger acid than 1,3-dithiane (pK_a = ca. 39 in DMSO) and is readily metalated with ***n-Butyllithium*** in THF (eq 1).[2,3] The resulting clear yellow solution of bis(phenylthio)methyllithium (**2**) is stable at 0 °C for at least 12 h. Early studies in which sodium amide in liquid ammonia was used in the metalation step gave lower yields of subsequent alkylation products.[8] Reaction of (**2**) with primary alkyl halides gives high yields of phenyl thioacetal derivatives of aldehydes (**3**) (eq 2).[2,9,10] Secondary alkyl halides are less effective alkylating agents but 3-chloro-1-butene, which is a relatively unhindered secondary allylic halide, gives the desired alkylation product in almost quantitative yield and without allylic rearrangement (eq 4).[11]

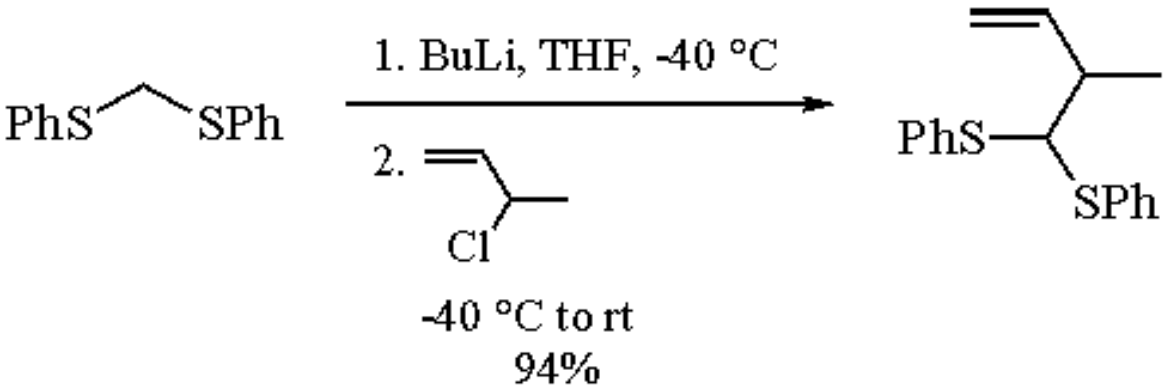

(4)

Dialkylation is difficult and requires the presence of metal-complexing agents to enhance the reactivity of the organometallic in the second alkylation step. Thus metalation of 1,1-bis(phenylthio)ethane (**4**)[12] in hexane containing TMEDA, followed by addition of a variety of primary alkyl halides, produced compounds of type (**5**) in synthetically useful yields (eq 5).[13] Similar results were obtained using a procedure in which ***Sodium Amide*** was added to a THF-HMPA solution of (**4**) and a primary alkyl halide.[14]

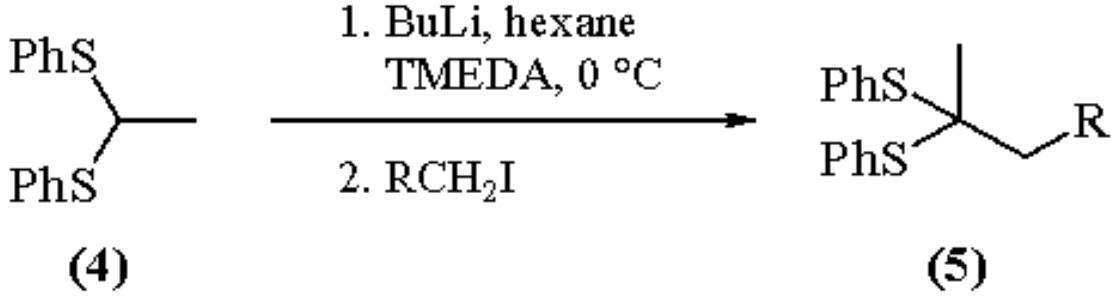

(5)

Bis(phenylthio)methyllithium (**2**) reacts with ethylene oxide to give the product of nucleophilic ring opening (eq 6).[15] Lithio derivative (**2**) reacts with epibromohydrin by displacement of halogen, leaving the epoxide ring intact.[10]

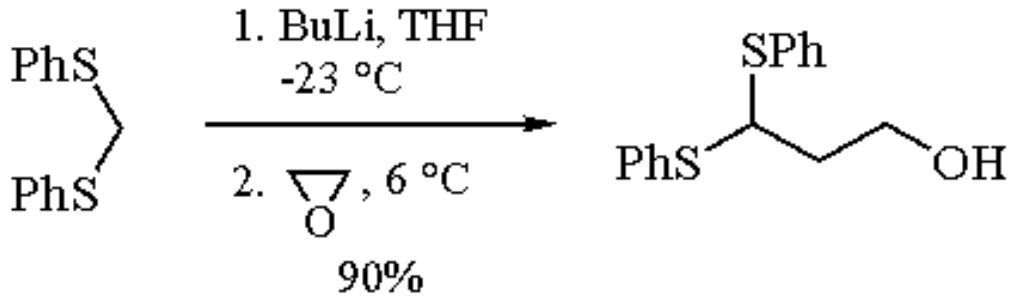

(6)

A number of studies directed toward synthetic applications of (**1**) have described reactions of lithio derivative (**2**) with aldehydes and ketones as a key step.[2-4,16,17] As exemplified in (eq 7), such reactions proceed readily.[9a] Addition of (**2**) to α,β-unsaturated aldehydes seems to be exclusively 1,2[3,18] but a mixture of 1,2- and 1,4-addition products are observed with α,β-unsaturated ketones. The tendency toward 1,4-addition is more pronounced with (**2**) than with ***2-Lithio-1,3-dithiane*** and is increased in the presence of HMPA (eq 8).[19] 1,4-Addition predominates in reactions of the cuprate reagent derived from (**2**).[20]

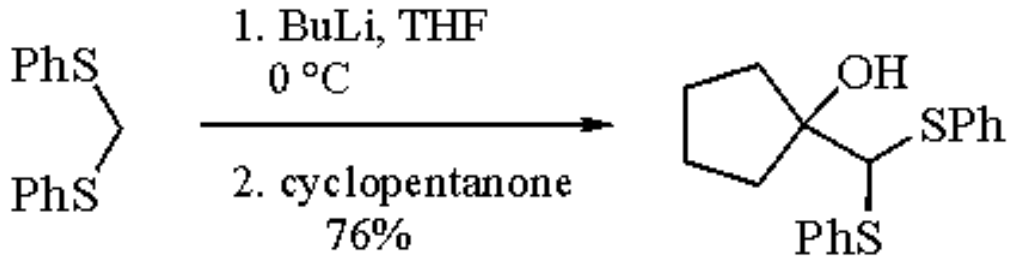

(7)

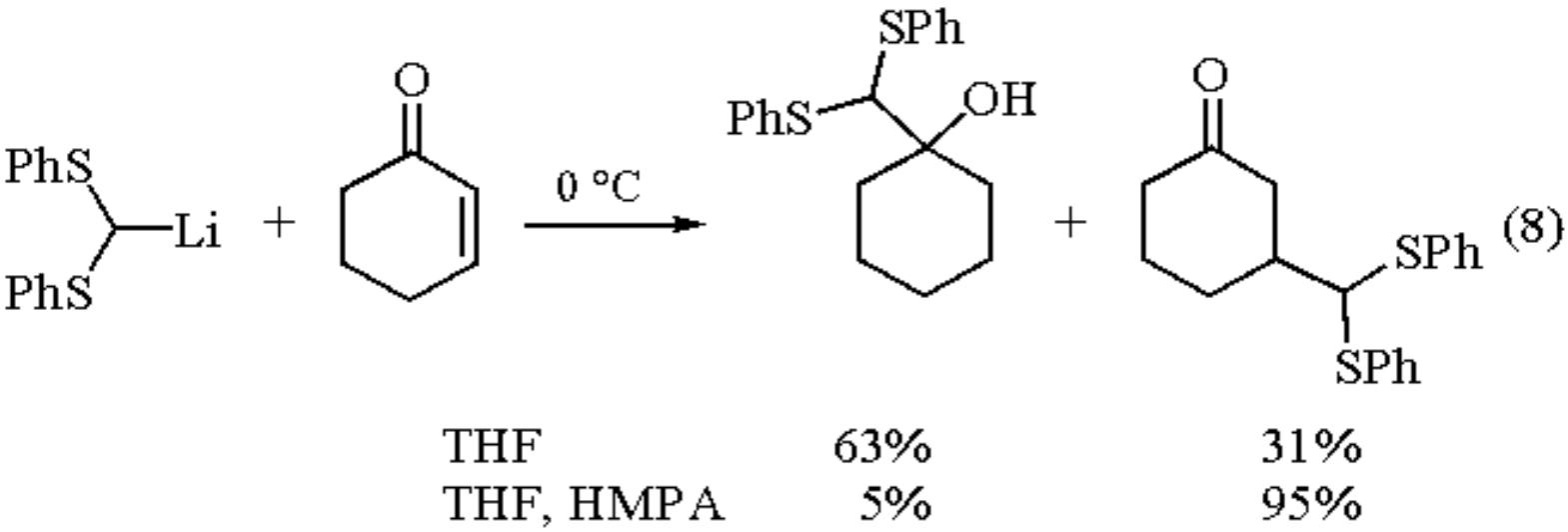

Preparation of Phenyl Vinyl Sulfides.

Copper(I) Trifluoromethanesulfonate (triflate) is an effective reagent for promoting carbocation formation by cleavage of a phenylthio substituent from bis(phenylthio) acetals (eq 9).[21] Deprotonation of the resulting α-phenylthio carbocation yields a phenyl vinyl sulfide. Reaction conditions have been developed for the effective synthesis of phenyl vinyl sulfides by alkylation of (**1**) followed by copper(I) triflate-induced elimination (eq 10).[3]

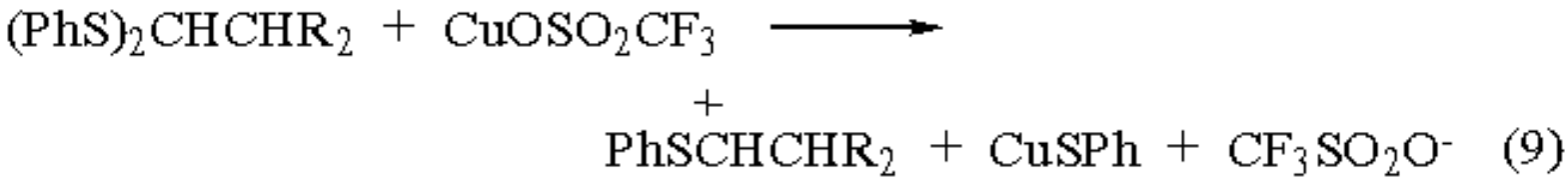

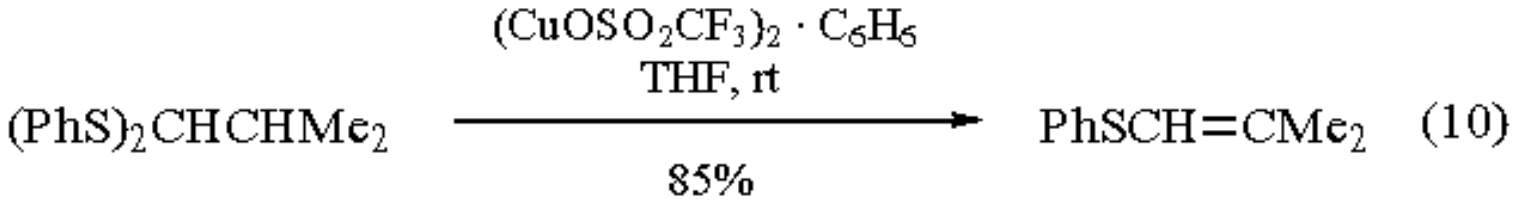

A novel fragmentation occurs when (**6**) (derived from (**2**) and 1,2-epoxycyclohexane) as its lithium alkoxide is treated with excess (4 equiv) of copper(I) triflate.[22] The product is a phenyl vinyl sulfide (eq 11).

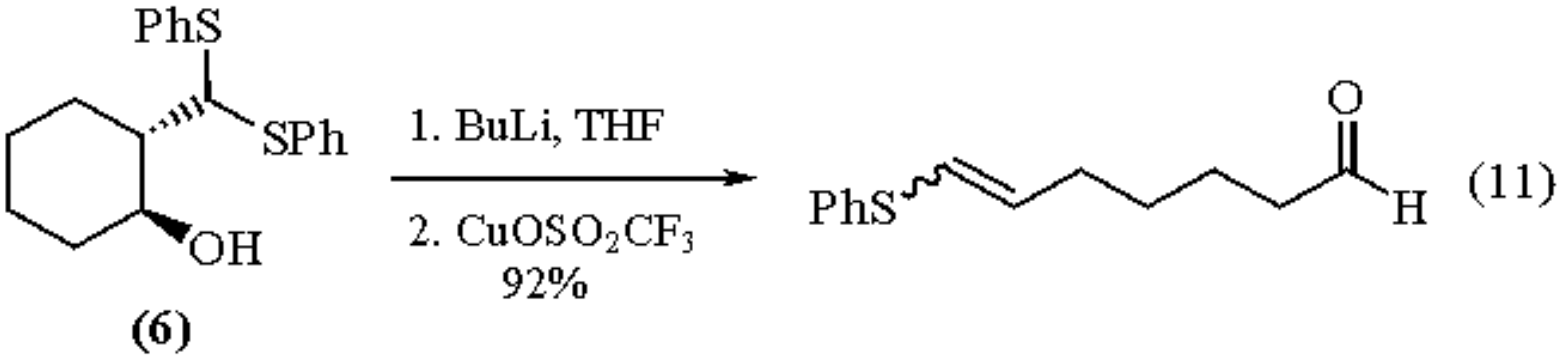

Preparation of α-(Phenylthio) Ketones.

The adducts of (**2**) with aldehydes and ketones give α-(phenylthio) ketones on treatment with copper(I) triflate in refluxing benzene containing *N*-ethyl-*N*,*N*-diisopropylamine (eq 12).[4] The adducts of cyclic ketones yield ring-expanded α-(phenylthio) ketones as illustrated by the example in eq 13. The reaction is believed to proceed by Cu^{I}-promoted ionization of one of the phenylthio substituents, followed by epoxide formation, then hydride or alkyl group migration.

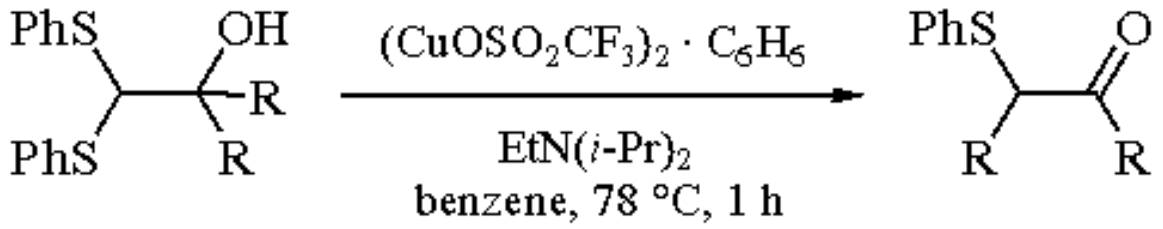

(12)

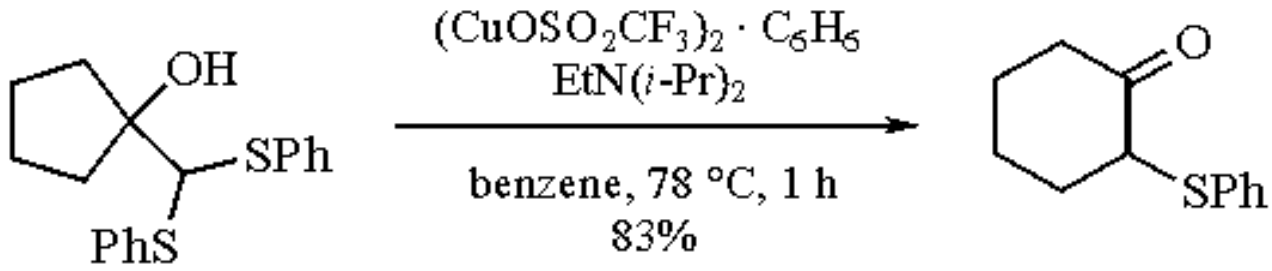

(13)

A similar transformation occurs when adducts of (**2**) with aldehydes and ketones are treated with ***p-Toluenesulfonic Acid*** in refluxing benzene.[9a] The adducts of (**2**) with cyclic ketones undergo an analogous rearrangement via a carbenoid mechanism when converted to their dianions by reaction with two equivalents of ***Methyllithium*** or ***s-Butyllithium*** in THF at 0 °C.[23] The α-(phenylthio) ketones formed by this procedure can serve as precursors to enones (by oxidation and thermal elimination of the resulting sulfoxide)[9b] and α-(phenylthio) enones (by Pummerer rearrangement).[16]

Bis(methylthio)methane as an Analogous Reagent.

Deprotonation of bis(methylthio)methane with *n*-butyllithium affords bis(methylthio)methyllithium, which has been used several times as a formyl anion equivalent. Addition of bis(methylthio)methyllithium to cyclic vinylogous esters[24] affords, after aqueous acid hydrolysis, 3-bis(methylthio)methylcyclohexenones (eq 14).[25] Thioacetal hydrolysis provides the 3-formylcyclohexenone.

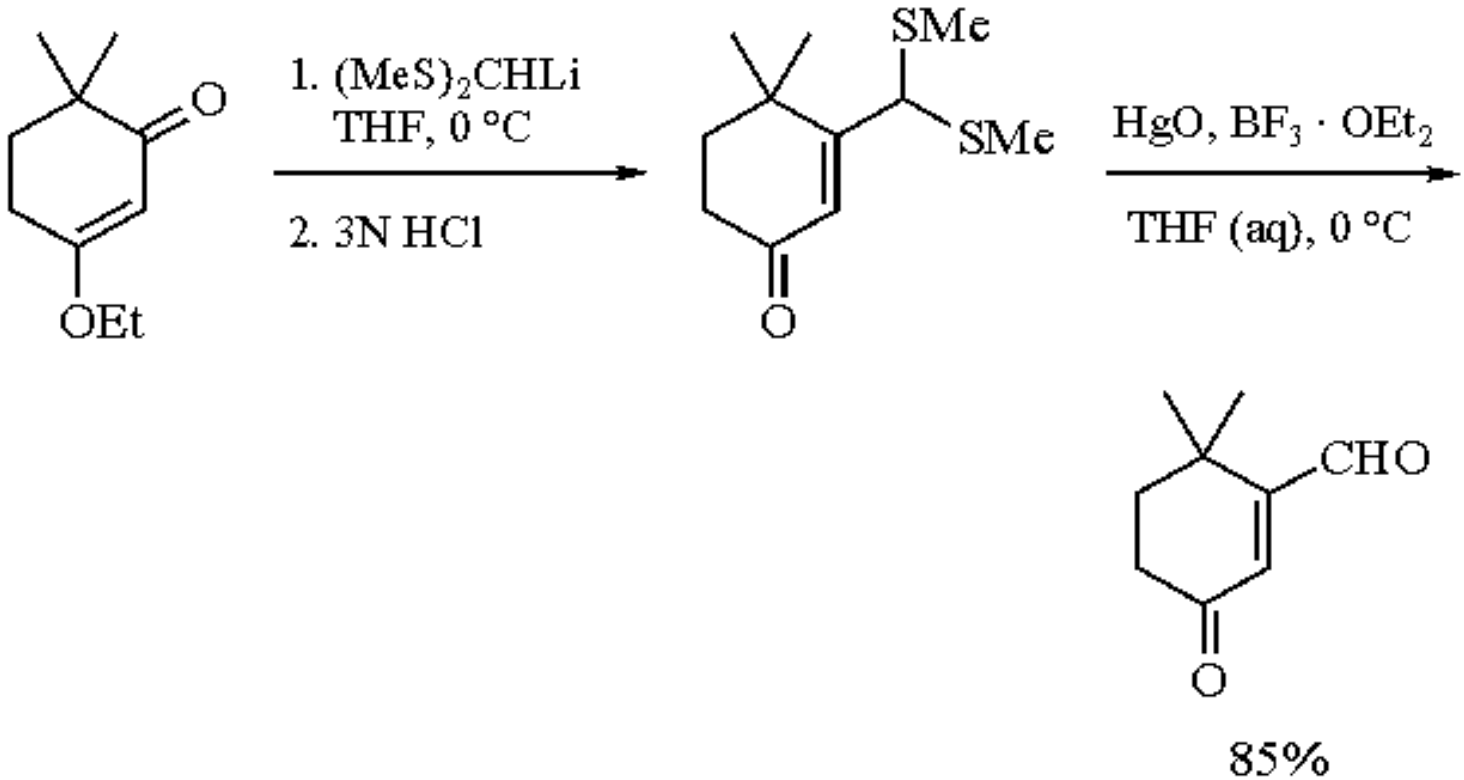

(14)

Epoxide opening by bis(methylthio)methyllithium, tosylate formation, deprotonation and intramolecular tosylate displacement affords cyclopropanone thioacetals in good yields via a one-pot procedure (eq 15).[26] Reaction of a carbohydrate *N*-acetylaziridine with bis(methylthio)methane and acetic acid gave in high yield the *S*-alkylation product (eq 16) via the presumed pathway shown. Clean inversion of configuration at C(7) was observed.[27]

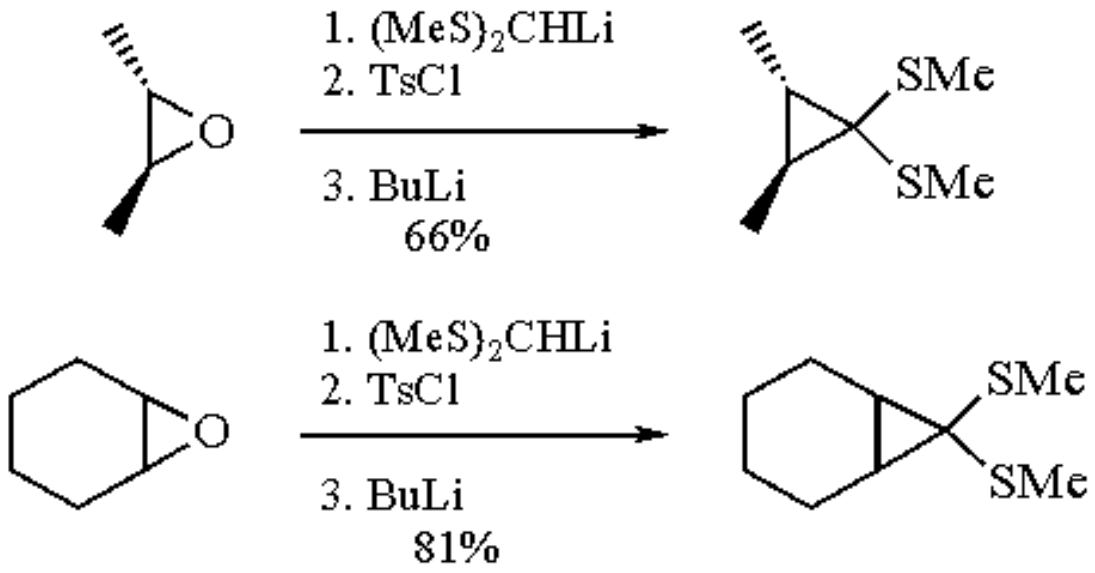

(15)

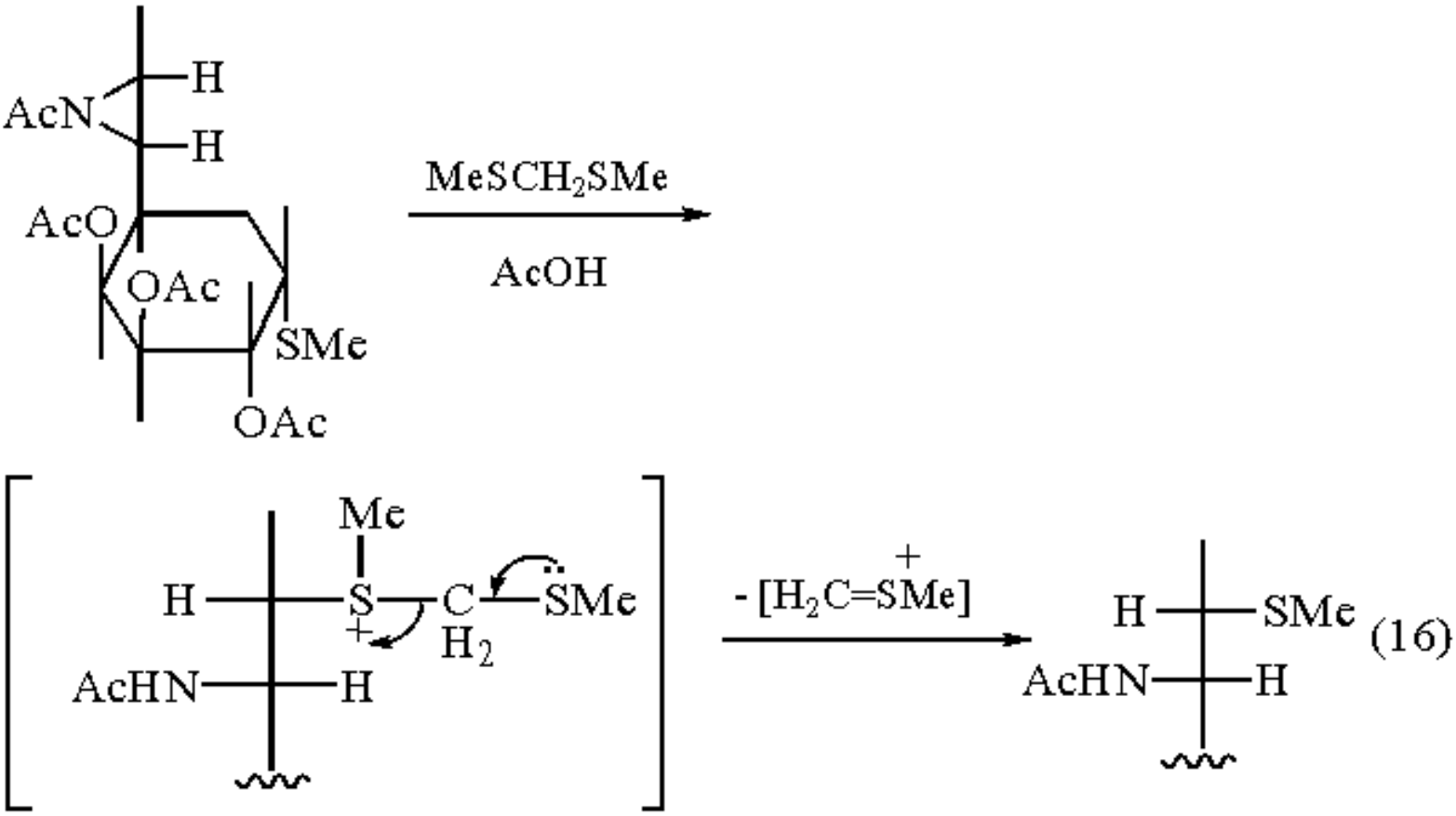

Electrophilic thionium ion intermediates have been accessed via thioacetals derived from bis(methylthio)methane.[28] Successive deprotonation/alkylation steps lead to the cyclization substrates in eqs 17 and 18. In the former, the bracketed thionium ion arises from treatment of the thioacetal with ***p-Toluenesulfinic Acid*** in warm acetonitrile. Cyclization and elimination steps yielded the 4-substituted indole.[28a] Treatment of the thioacetal in eq 18 with ***Dimethyl(methylthio)sulfonium Tetrafluoroborate*** provides the spirocyclic enone shown via initial thionium ion trapping by the vinylsilane, followed by allylic sulfide activation and cyclization involving the enol silyl ether.[28b] These applications highlight the nucleophilic *and* electrophilic behavior of the thioacetal linkage.

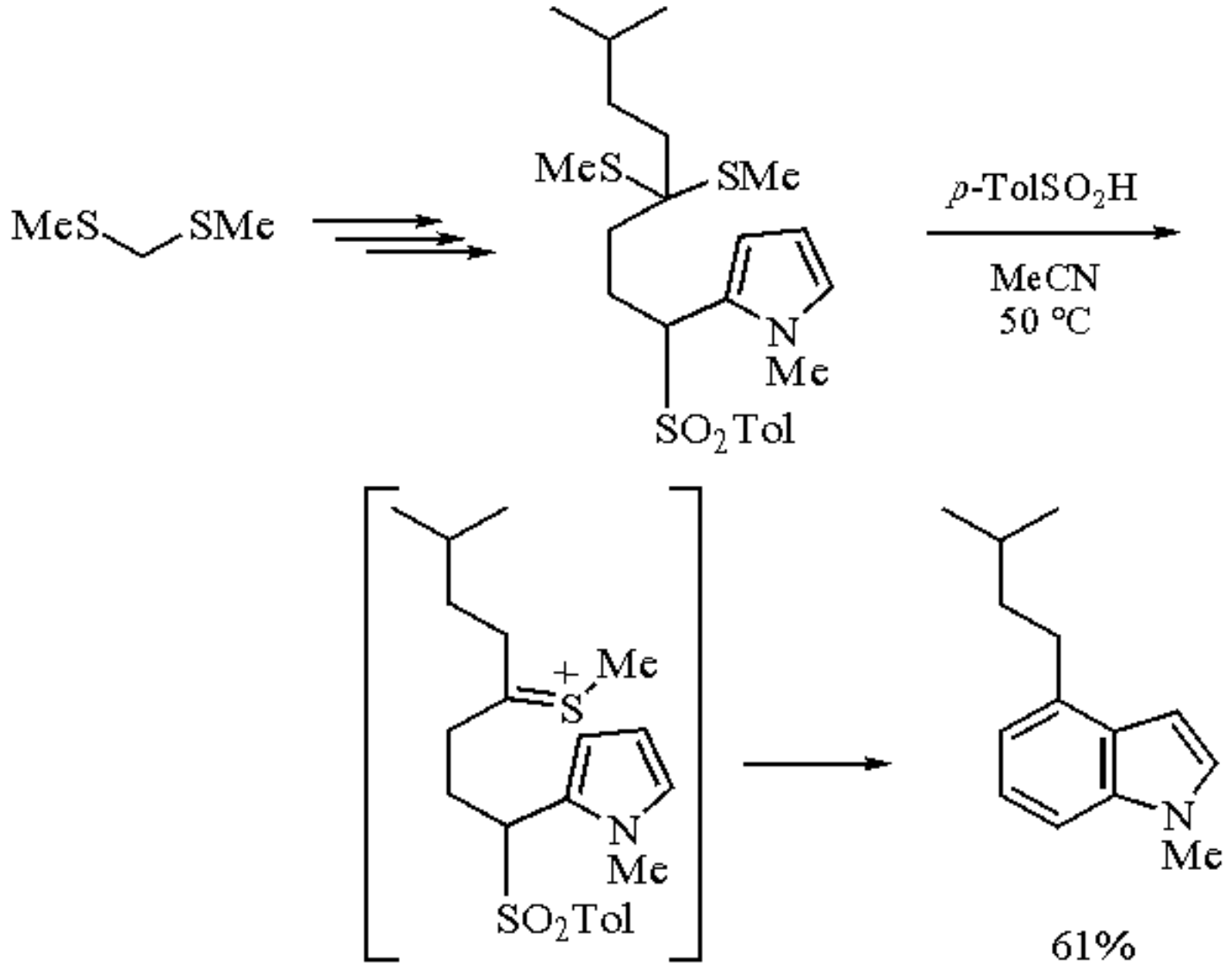
MeS
SMe
MeS
SMe
N
Me
SO2Tol
p-TolSO2H
MeCN
50 °C
+
Me
S
N
Me
SO2Tol
N
Me
61%

(17)

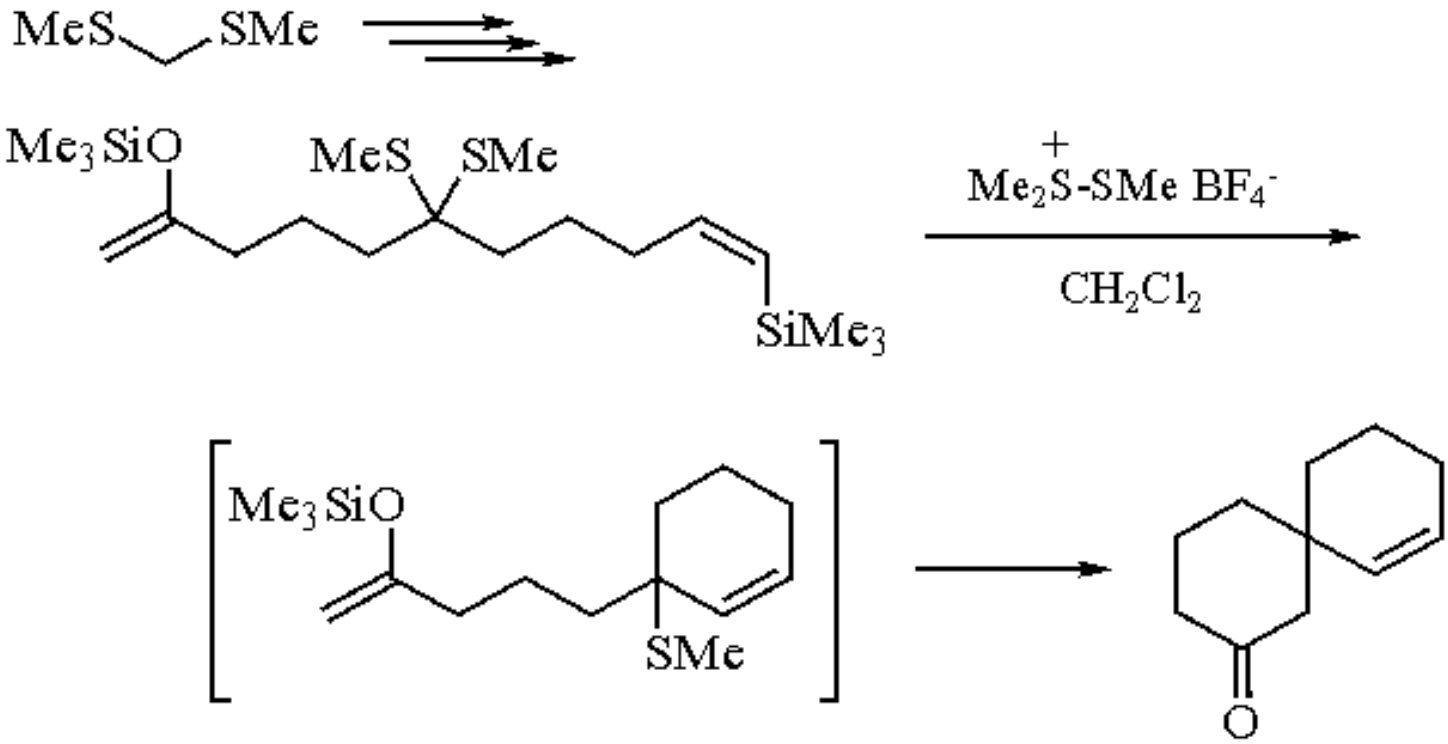
MeS
SMe
Me3SiO
MeS
SMe
SiMe3
+
Me2S-SMe BF4-
CH2Cl2
Me3SiO
SMe
O

(18)

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Bis(*N*-propylsalicylideneaminato)copper(II)

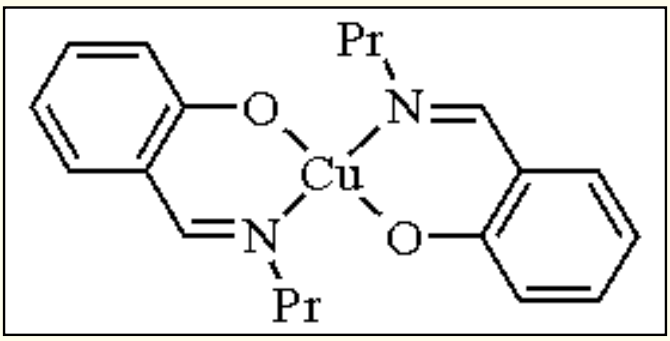

[14077-15-7] · $C_{20}H_{24}CuN_2O_2$ · Bis(*N*-propylsalicylideneaminato)copper(II) · (MW 387.97)

(catalyzes decomposition of diazo ketones to carbenoids;[2] promotes electron transfer reactions[4])

Alternate Name: bis[2-(*N*-propylformimidoyl)phenolato]copper.

Physical Data: green or greenish-brown needles; mp 127-128 °C.

Solubility: sol alcohol, dioxane, chloroform, and benzene; insol water, pet ether.

Preparative Method: by one-pot reaction of *n*-propylamine with the bis(salicylaldehato)copper complex prepared from copper(II) acetate and salicylaldehyde.[1]

Purification: recrystallization from cyclohexane or chloroform-ethanol.[1]

Handling, Storage, and Precautions: irritant. The copper chelate can be stored at rt in the absence of moisture.

Diazo Ketone Decomposition.

In the synthesis of the natural sesquiterpene (±)-α-chamigrene, construction of the spirocyclic skeleton involved an intramolecular ketocarbenoid addition via thermal copper-catalyzed diazo ketone decomposition, followed by dissolving-metal reduction of the cyclopropane ring in the product (eq 1).[2,3]

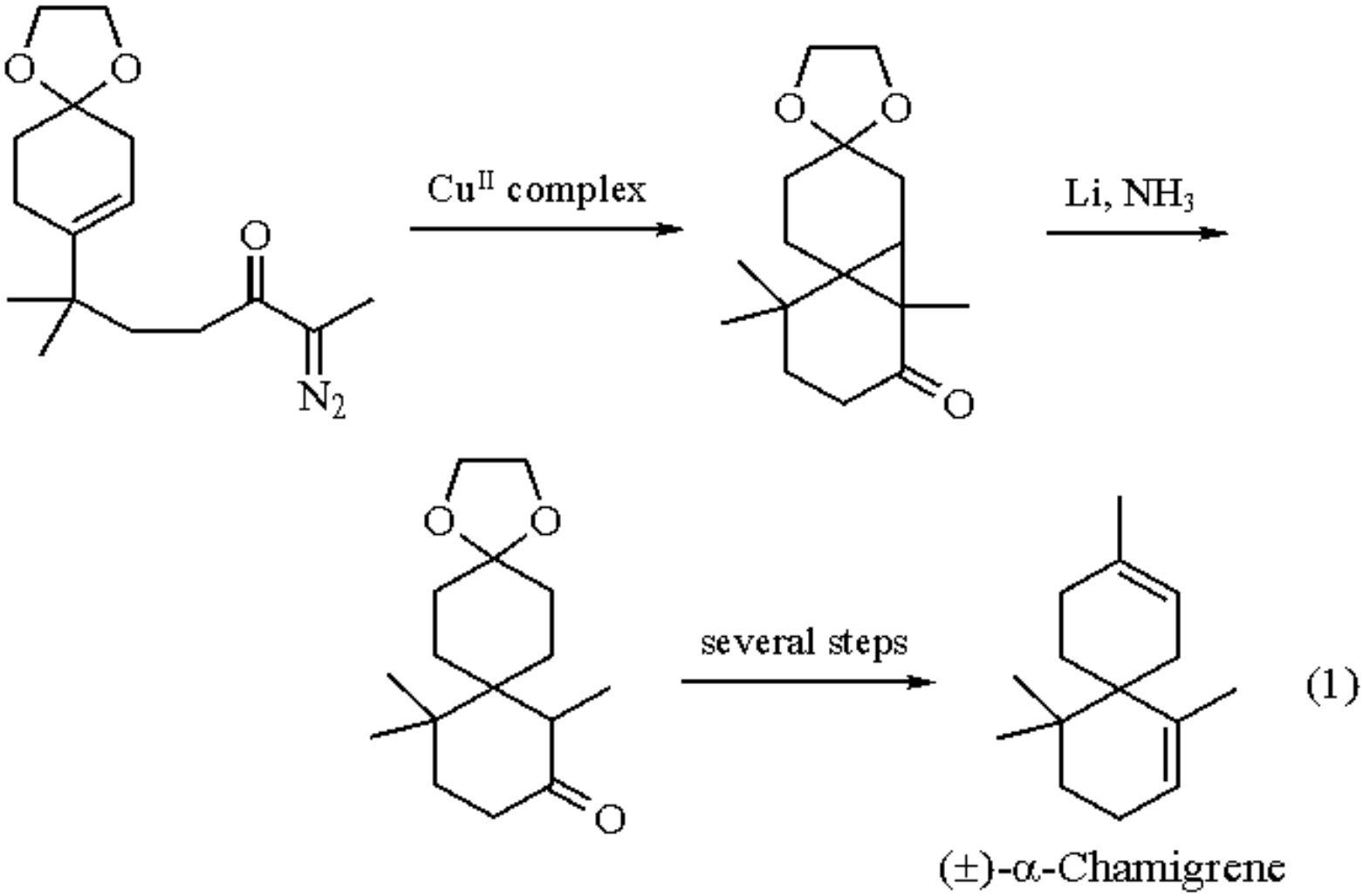

It was discovered that insoluble copper salts typically employed for such decompositions, e.g. ***Copper(II) Acetate*** and ***Copper(I) Chloride***, reacted instead with the acetal protecting group. Use of the more soluble copper chelate avoided this problem, giving the tricycloketone intermediate in 66% yield.[3] With relatively nonfunctionalized systems (eq 3), the more traditional copper salt catalysts are as effective as the title reagent; thus ***Copper*** powder could be employed in a similar diazo ketone decomposition which ultimately led to the spirocyclic (-)-acorenone B (eq 2).[3,5]

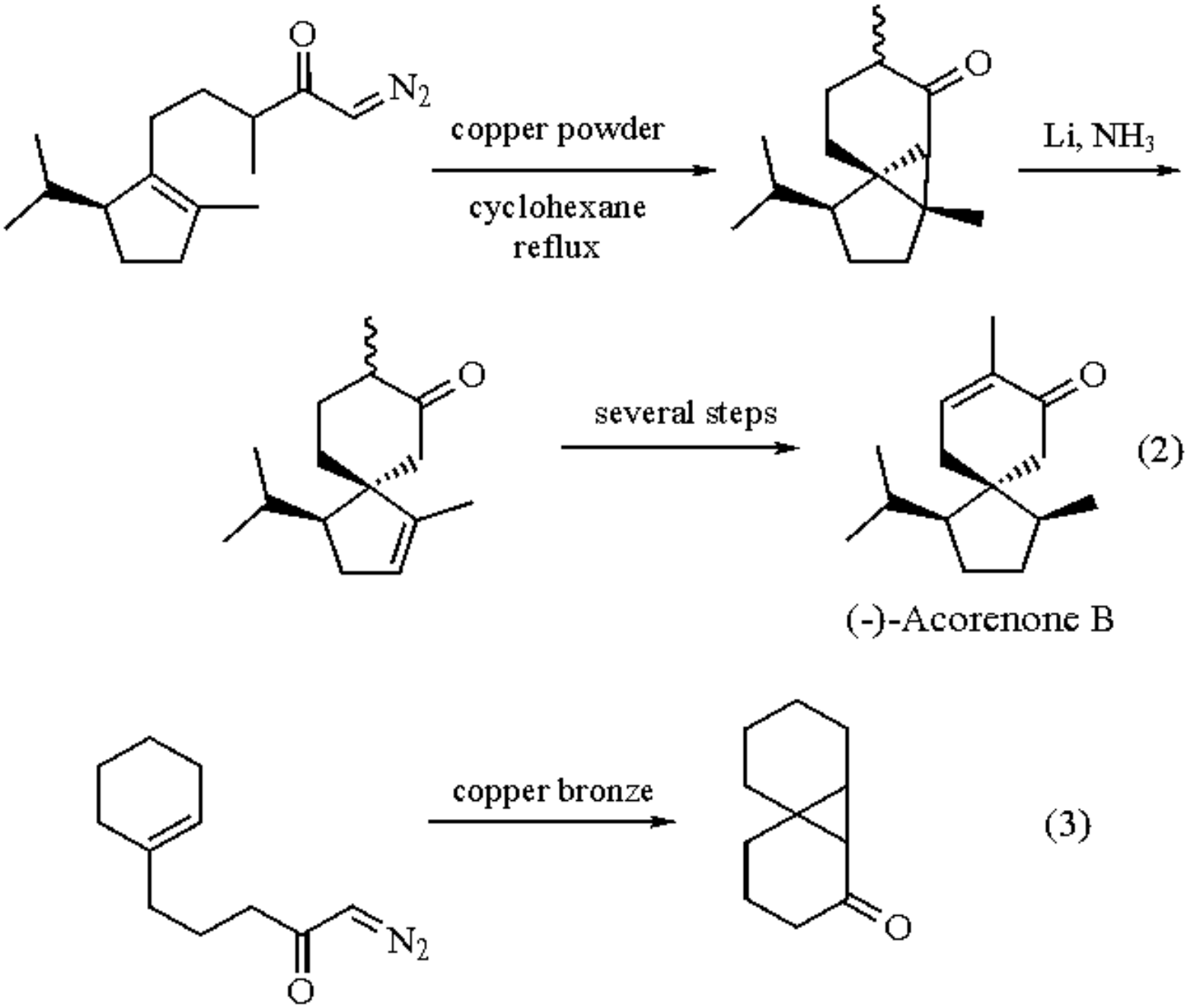

Electron Transfer Reaction.

The reagent, and other similar chelated copper(II) complexes, catalyzes the oxidation of 3,5-di-*t*-butylcatechol by O_2. The catalytic behavior is related to the electron transfer reactions between the complex and two-electron donors such as catechols and ascorbic acid (eq 4).[4]

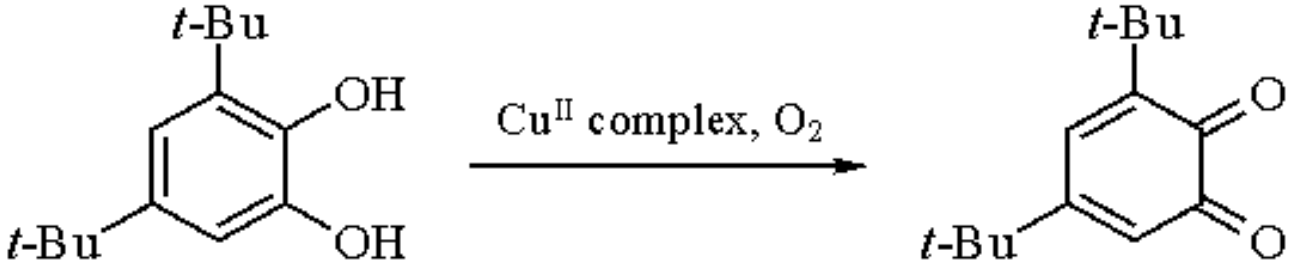

(4)

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Bis(*N*-propylsalicylideneaminato)cobalt(II)

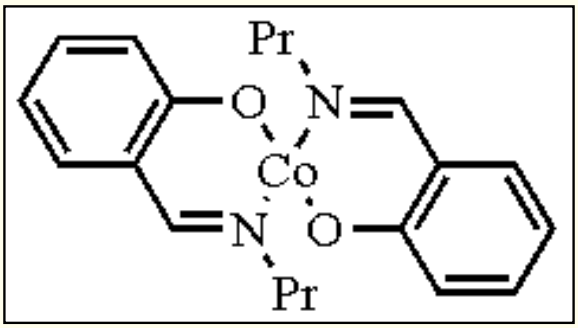

(R = *n*-Pr)

[100031-33-2] · $C_{20}H_{24}CoN_2O_2$ · Bis(*N*-propylsalicylideneaminato)cobalt(II) · (MW 383.35) (R = *i*-Pr)

[41754-09-0]

(catalyst for the conversion of arylglyoxals to α-aryl-α-hydroxyacetic esters[1])

Physical Data: mp 226-234 °C (R = *i*-Pr).[2]

Solubility: sol $CHCl_3$, benzene, and dioxane; slightly sol ethanol and cyclohexane; insol petroleum ether.

Form Supplied in: red crystals.

Preparative Methods: a solution of bis(salicylaldehyde)cobalt(II) dihydrate and a slight excess of propylamine in methanol is heated at reflux in the presence of a trace amount of formaldehyde for 10 to 40 min.[3] As the mixture is cooled, red crystals separate out. The crystals are filtered quickly and dried in vacuo.

Purification: recrystallization from *i*-PrOH/$CHCl_3$ (*i*-Pr).[4]

Handling, Storage, and Precautions: unlike the *N*-*i*-propylsalicylidene Co^{II} complex, the *N*-*n*-propylsalicylidene Co^{II} complex is readily oxidized by oxygen in the atmosphere.[3] It is thus necessary to carry out the above procedure in an oxygen-free atmosphere.

α-Phenyl-α-hydroxyacetic Ester.

Bis(*N*-*n*-propylsalicylideneaminato)cobalt(II) catalyzes the highly selective transformation of phenylglyoxal to α-phenyl-α-hydroxyacetic ester (eq 1).[1] After a solution of phenylglyoxal (**1**) (1.0 mmol) and *N*-*n*-propylsalicylidene

Co^{II} complex (**2a**) (0.2 mmol) in a mixture of *i*-PrOH (40 mL) and 1,2-dichloroethane (20 mL) was heated at 60 °C for 8 h under oxygen atmosphere, the metal complex was separated, and the solvent was evaporated to afford a 97:3 mixture of *i*-propyl mandelate (**3**) and *i*-propylphenyl glyoxylate (**4**) in 93% yield. *N*-*i*-Propylsalicylidene Co^{II} complex (**2b**) also catalyzes this transformation; however, a lower yield (31%) of *i*-propyl mandelate (**3**) was obtained. The hydroxocobalt(III) complex, $Co^{III}(OH)$,[5] which is generated from irreversible oxidation of the Co^{II} complex in alcoholic solvents, is believed to be the reactive catalytic species.

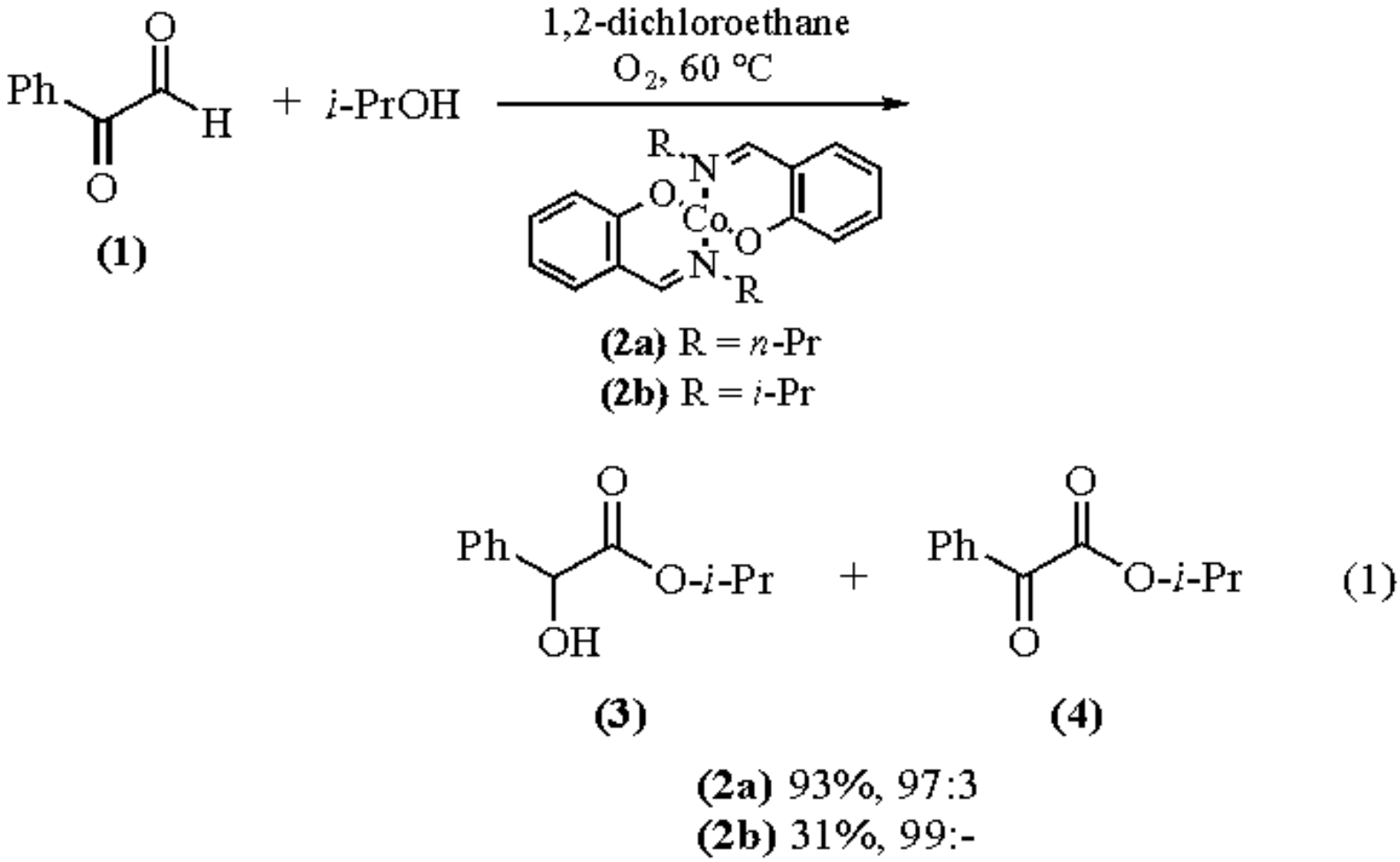

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Myong Ji University, Kyung Ki Do, Korea

Bis(pyridine)iodonium(I) Tetrafluoroborate[1]

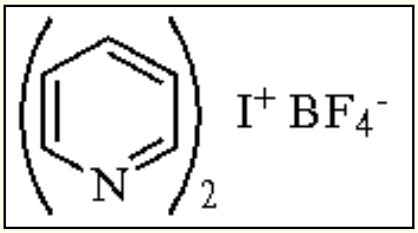

[15656-28-7] · $C_{10}H_{10}BF_4IN_2$ · Bis(pyridine)iodonium(I) Tetrafluoroborate · (MW 371.91)

(iodinating agent for the selective functionalization of unsaturated compounds;[2-4] can also mediate C-C bond formation[5])

Physical Data: mp 149-151 °C (dec).[6]

Solubility: sol CH_2Cl_2, DMSO, MeCN, pyridine, DMF; modestly sol $CHCl_3$; insol ether, THF, hexane.

Analysis of Reagent Purity: spectroscopic data: IR,[6] NMR (^1H, ^{13}C).[6]

Preparative Method: prepared by the reaction of HgO/HBF_4-SiO_2[7] with iodine and pyridine in dry CH_2Cl_2 at rt.[2,6] Solids are filtered off, and the reagent is isolated by precipitation from CH_2Cl_2 solution by addition of cold ether, repeating the operation several times until a negative test for mercury(II) is obtained (i.e. absence of precipitation of mercury by treatment of an aliquot with $NaBH_4$/NaOH).[2]

Purification: recrystallization from CH_2Cl_2-$CHCl_3$ (white solid).

Handling, Storage, and Precautions: can be safely stored under a nitrogen atmosphere (in the dark at 4 °C) for long periods of time (up to 3 months has been observed) without changing either properties or physical appearance.

Reaction with Alkenes.

Ipy_2BF_4 reacts readily with alkenes in CH_2Cl_2 to afford 1,2-disubstituted products arising from addition of iodine and pyridine.[6] Synthetically more important is the reaction of alkenes with Ipy_2BF_4 in the presence of nucleophiles, which provides a general method for the vicinal iodofunctionalization of alkenes. In this regard, HBF_4 (used as commercially available 54% ethereal soultion) is usually added to the reaction mixture to avoid the competitive formation of products

from pyridine acting as nucleophile (eq 1).[6] ***Tetrafluoroboric Acid*** was selected to neutralize pyridine on the basis of its low nucleophilic character. As an alternative, the use of ***Boron Trifluoride Etherate*** has been reported.

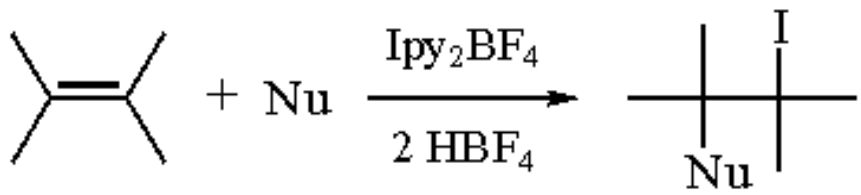

(1)

A variety of nucleophiles participate in this reaction, and the nature of the nucleophile is important in determining the experimental protocol. Typical inorganic salts (e.g. Br^-) behave as efficient nucleophiles in this reaction using dioxane:water (10:1 v/v) as solvent, so that addition of HBF_4 is not required. A different and representative procedure can be followed for nucleophiles that can be used as solvents; for instance, MeCN reacts at -30 °C with alkenes and Ipy_2BF_4-HBF_4 (1:2 molar ratio), furnishing 2-iodoamides after hydrolysis. On some occasions, CH_2Cl_2 can be employed as the solvent, allowing a reduction in the amount of nucleophile. Oxygenated compounds (for instance methanol) and arenes can also be employed as nucleophiles following the latter approach.

Remarkably, reaction of alkenes with Ipy_2BF_4-HBF_4 in CH_2Cl_2 (-60 °C, 30 min) in the absence of nucleophile produces iodofluorinated compounds in high yield. The regioselectivity of the process is illustrated in the reaction of 1-hexene (eq 2).[3] Regarding the stereochemistry of the reaction, it was found that cyclohexene leads exclusively to *trans*-1-fluoro-2-iodocyclohexane in 89% yield. This mild iodofluorination process is quite general with respect to the structure of the alkene and has been nicely adapted to fluoroiodinate the less reactive esters of acrylic acid. The regio- and stereoselectivity shown together with other features of this process are compatible with an initial electrophilic attack of iodine to the alkene followed by ring opening of the resulting iodonium ion via nucleophilic attack of one fluoride ion liberated by BF_4^-.[8]

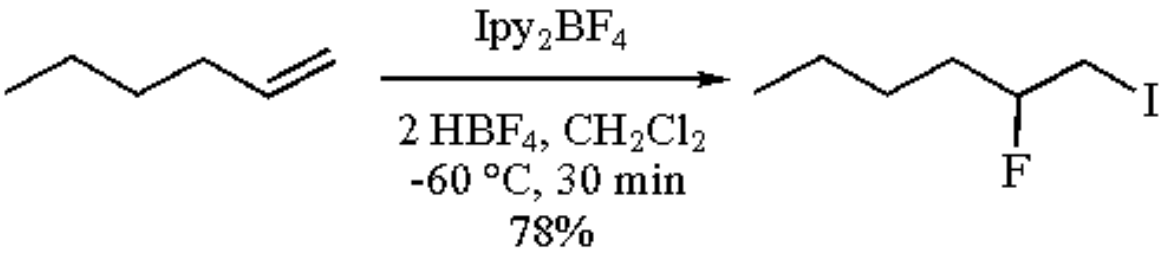

(2)

Carbon-carbon bond formation can also be mediated by the title reagent, providing routes to carbocycles. Reaction of difunctional α,δ-arylalkenes with Ipy_2BF_4-HBF_4 results in a diastereoselective and high-yield intramolecular six-membered ring construction (eq 3).[9] The regio- and stereochemistry found can be rationalized in terms of a chairlike transition state for the attack of electrophilic iodine to the difunctional compound, in agreement with the Stork-Eschenmoser hypothesis.[10] The reaction of 1,5- and 1,6-dienes took place in a related manner. It was found that, besides intramolecular carbon-carbon bond formation, concomitant fluorine incorporation into the cyclized products took place (e.g. 1,5-hexadiene gives 1-fluoro-4-iodocyclohexane as the major reaction product). Interestingly, cyclizations also occur when using ***Trifluoromethanesulfonic Acid*** instead of HBF_4; thus 1,5-hexadiene furnishes 4-iodocyclohexene in 70% yield.

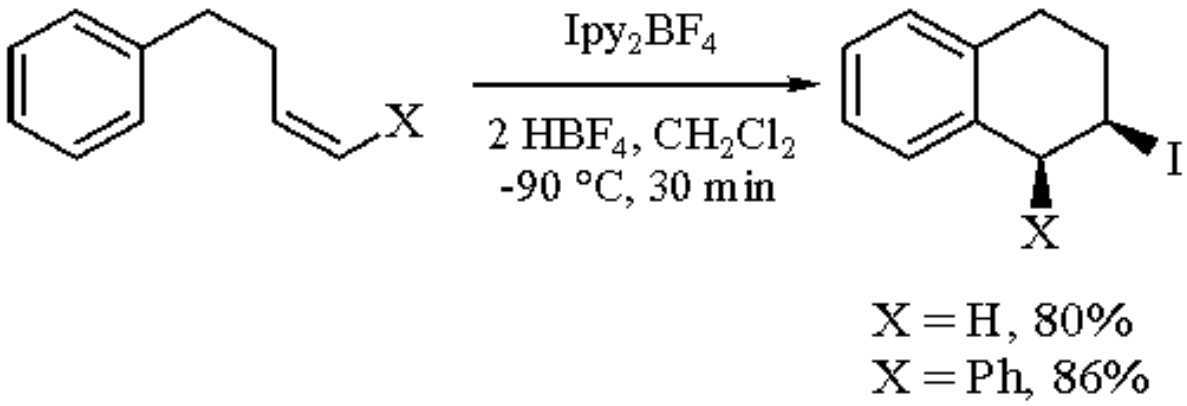

(3)

Reaction with 1,3-Dienes.

Nucleophiles react with conjugated dienes in the presence of Ipy_2BF_4-HBF_4, furnishing products derived from 1,2- and/or 1,4-addition.[11,12] The structure of the starting diene and, in some cases, the reaction temperature were decisive factors in determining the addition pattern. Terminal dienes (i.e. 1,3-butadiene, isoprene, 2,3-dimethyl-1,3-butadiene) cleanly afford 1,2-addition products (eq 4).[11] Exceptions to this trend were found when working with C_6H_6 and MeCN as nucleophiles, where 1,4-addition products were observed.[12]

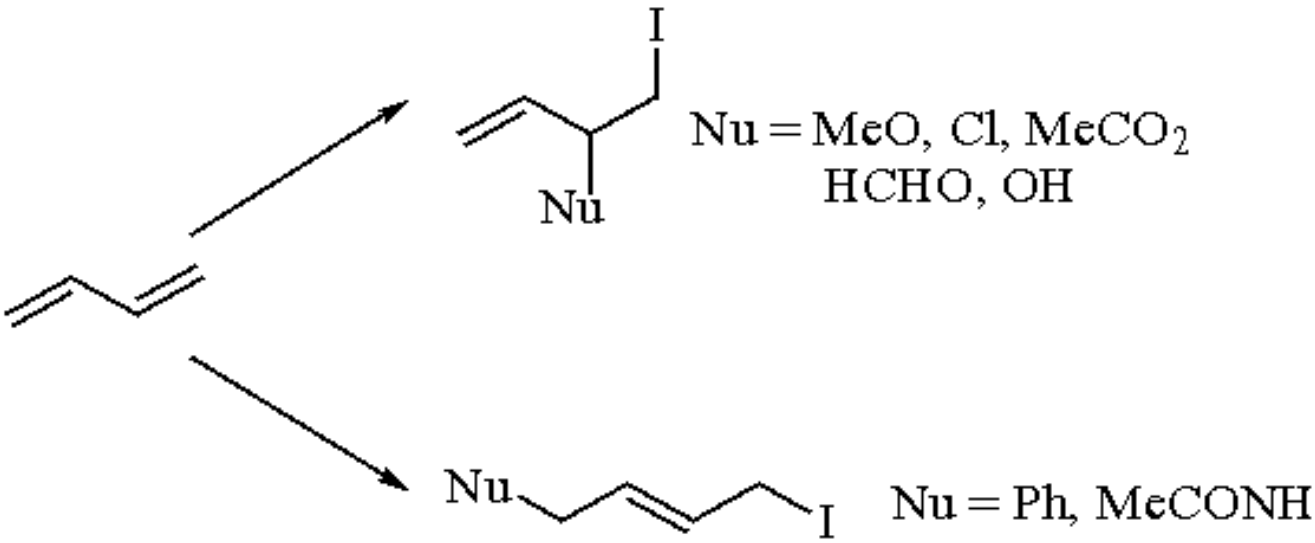

(4)

Thus reaction of 1,3-butadiene with Ipy_2BF_4-HBF_4 in MeOH at -40 °C furnished CH_2=CH-CH(OMe)CH_2I in 86% yield. Similar behavior was noticed for 2,3-dimethyl-1,3-butadiene (78% yield of the 1,2-addition product) without evidence for the formation of the 1,4-regioisomer. Internal dienes, such as 1,3-cyclooctadiene and 2,4-hexadiene, were found to undergo exclusively 1,4-addition irrespective of the nature of the nucleophile (Nu: Cl, OCHO (from DMF), MeCONH (from MeCN); NO_2^-).[11] In fact, 1,3-cyclooctadiene reacted with MeOH, under related conditions to those described for 1,3-butadiene, affording the 1,4-regioisomer in 58% yield. Experimental conditions were also described to isomerize 1,2-addition products (kinetic control) to their 1,4-regioisomers (thermodynamic control).[12]

Reaction with Alkynes.

This process has been studied in some detail. Alkynes react with Ipy_2BF_4 and nucleophiles (i.e. RCO_2H, Cl^-, py, ArH,

Br^-, I^-) to give 1,2-iodofunctionalized alkenes in moderate to good yield.[2,13,14] Addition products are generally formed as single regio- and stereoisomers; this fact enhances the synthetic utility of this reaction. The regiochemistry can be predicted by taking into account polar effects exerted by the substituents onto the triple bond; PhC&tbond;CH, *n*-BuC&tbond;CH, and PhC&tbond;CMe thus incorporated nucleophiles at the underlined carbon atom. With respect to stereoselectivity, the situation is somewhat more complicated but still some helpful generalizations are possible. Thus terminal alkynes furnished products derived from an *anti* addition of iodine and the nucleophile. For internal acetylenes the outcome was affected by the nature of the nucleophile; *syn* addition occurs for the strong nucleophile I^-, whereas weaker nucleophiles (RCO_2H, Cl^-, py, ArH) give rise to *anti* addition products.[2,14] Competition between *anti* and *syn* addition was noticed for borderline nucleophiles like Br^-. The same observation was made for reactions of weaker nucleophiles (RCO_2H) with internal alkynes bearing a bulky substituent on the sp carbon (PhC&tbond;C-*t*-Bu).[2] An ionic mechanism that involves participation of a vinyleneiodonium ion was proposed to account for the observed selectivity.

Taking advantage of their reactivity towards the reactive Ipy_2BF_4-HBF_4 in CH_2Cl_2 solution, alkynes were successfully employed to alkylate aromatic compounds. This type of Friedel-Crafts alkylation reaction had been rarely observed before (eq 5).[14] Efficient nucleophiles that take part in this alkylation include C_6H_6, C_6D_6, alkylbenzenes, anisole, and naphthalene. Bromobenzene gives only a modest yield (20%) of adduct on reaction with phenylacetylene. The alkyne component can be modified (*n*-BuC&tbond;CH; PhC&tbond;CMe), maintaining the same regioselectivity pattern in the addition. The intramolecular version of the process is also known.[9]

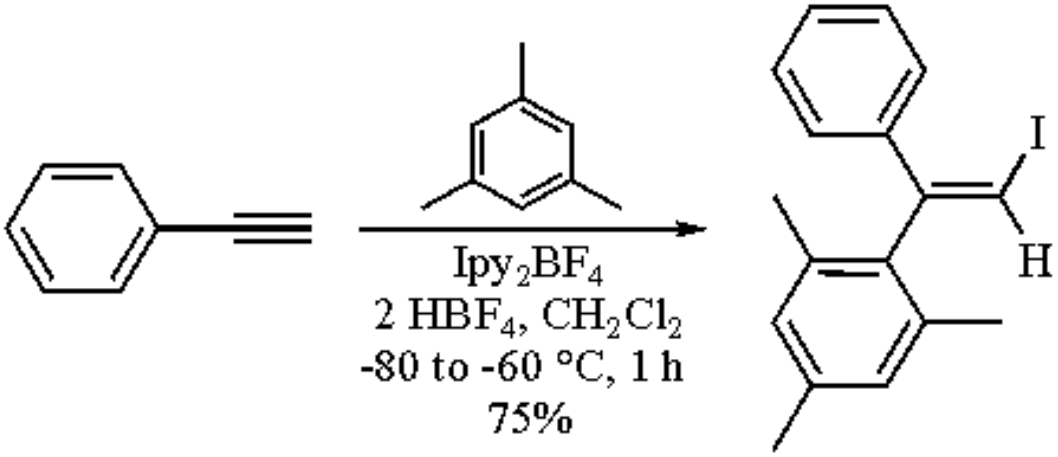

(5)

The influence of polar effects of the substituents to control the regiochemistry was clearly shown when alkynyl sulfides were used as starting materials (eq 6).[15]

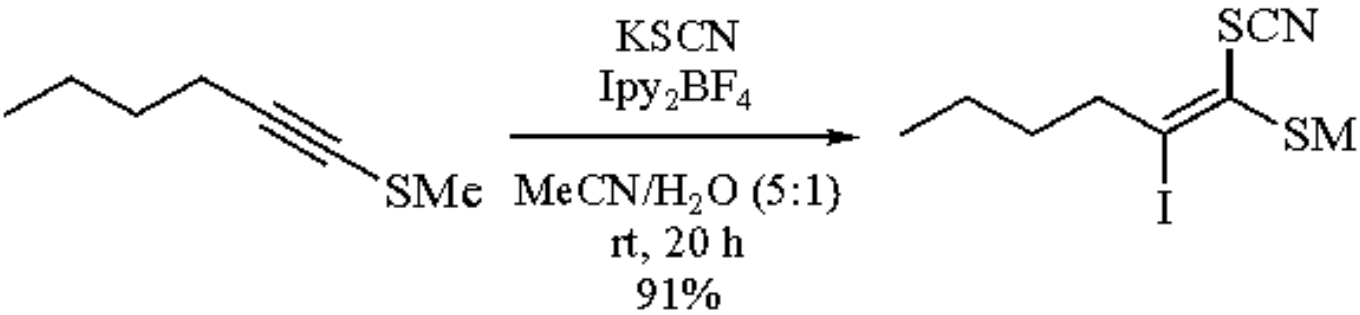

(6)

Based on this special reactivity of Ipy_2BF_4, a new one-pot procedure to prepare iodinated alkynes from alkynes was reported.[16] Room temperature reaction of both components, alkyne and Ipy_2BF_4, in the presence of MeONa-MeOH

affords good yields of products. This process is very clean and is compatible with the presence of several functional groups on the alkyne molecule. The iodoalkynes thus obtained undergo a number of interesting addition reactions; among these the iodofunctionalized product arising from incorporation of isopropanol as nucleophile is of particular interest (eq 7).[17]

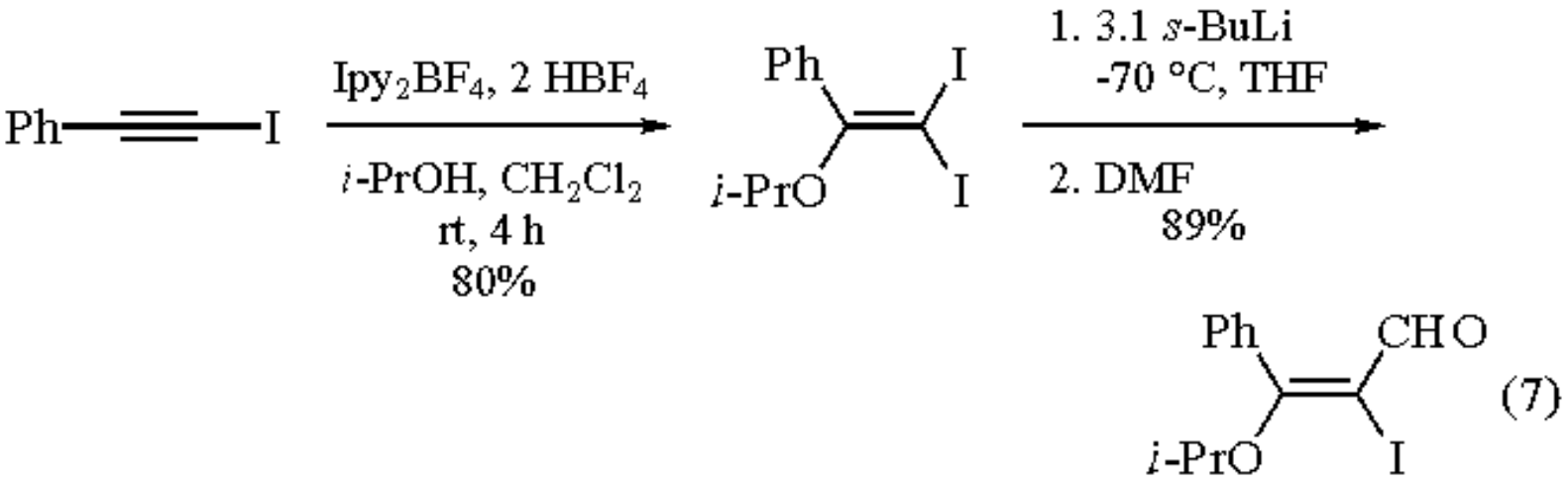

As depicted, treatment of Ph(*i*-PrO)C=CI_2 with excess ***s-Butyllithium*** followed by reaction of the metalated intermediate with an electrophile established an easy approach to the stereoselective elaboration of highly functionalized tetrasubstituted alkenes. The nature of the incorporated electrophile can be widely modified (H, D, allyl, MeS, Me, MeCHOH), leading always to the formation of a sole stereoisomer, that showing a *trans* relationship for the electrophile and the *i*-PrO group. The intermediate carbenoid species displayed unusual thermal stability in THF up to -20 °C and, remarkably, could be coupled in the presence of ***Copper(I) Chloride*** (THF, -60 °C), furnishing 1,4-diisopropoxy-1,4-diphenyl-1,2,3-butatriene in quantitative yield.[17] From a synthetic point of view, the second iodine atom can also be replaced. This can be done in a stepwise manner (eq 8)[17] or in a one-pot procedure (eq 8).[18] The former allows the preparation of functionalized enol ethers with defined stereochemistry.

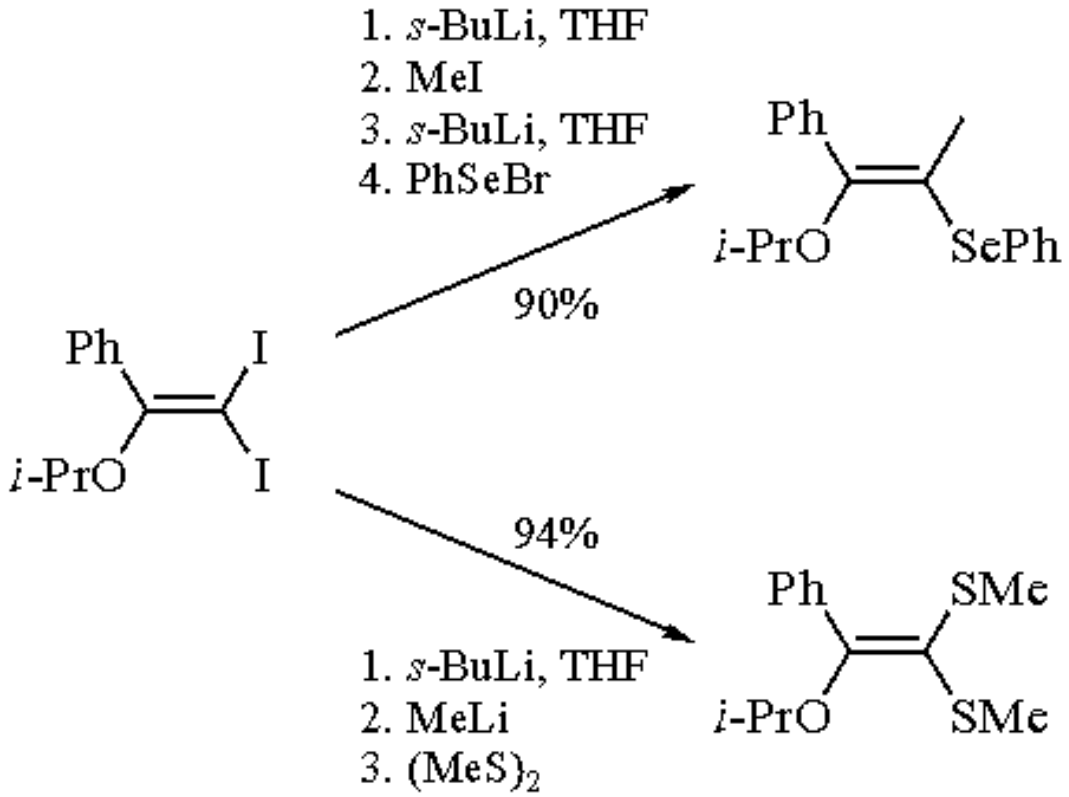

(8)

To enlarge the scope of the reactions of addition to 1-haloalkynes, the corresponding chloro and bromo derivatives were brought to react with Ipy_2BF_4 in the presence of different nucleophiles to afford stereoselectively the related 1-halo-1-iodo-1-alkenes.[19,20]

A distinctive feature of the reactivity of 1-iodoalkynes has recently been reported. It was shown that these iodoalkynes react with catalytic amounts of Ipy_2BF_4-HBF_4 to yield head-to-tail dimers through an unprecedented coupling reaction (eq 9).[5] The reaction works well either when R is an aryl group or when it contains a conjugated carbon-carbon double bond. Also, it was found that the reaction involving *p*-substituted arylalkynes is quite sensitive to the nature of substituent, and the observed trend of reactivity suggests an electrophilic mechanism. Under the reported reaction condition, no evidence for further oligomerization was found.

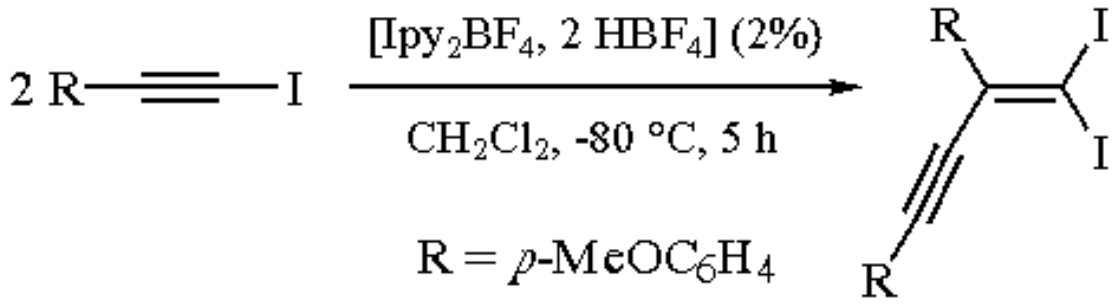

(9)

Reaction with Aromatic Compounds.

Ipy_2BF_4 has proven to be an excellent reagent to achieve the iodination of aromatic compounds.[4,21] The structure of the iodinated products can be predicted according to aromatic electrophilic substitution rules. The reaction of Ipy_2BF_4 with arenes takes place at room temperature in the presence of HBF_4 or CF_3SO_3H in CH_2Cl_2, furnishing monoiodo

derivatives with great regioselectivity and high yield. One of the major merits of the procedure lies in its ability to iodinate a wide range of arenes, from very activated compounds such as 1,3,5-trimethoxybenzene to deactivated systems such as nitrobenzene (almost all previously reported iodinating agents failed to react with nitrobenzene) (eq 10),[4] as well as heteroarenes such as indole, for which only catalytic amounts of acid are required. Use of either acid gives comparable results when the starting aromatic compound is activated (eq 11), whereas triflic acid is the acid of choice to iodinate deactivated aromatics.

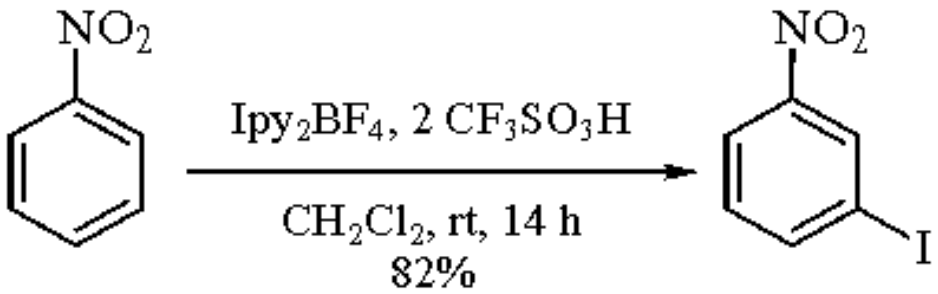

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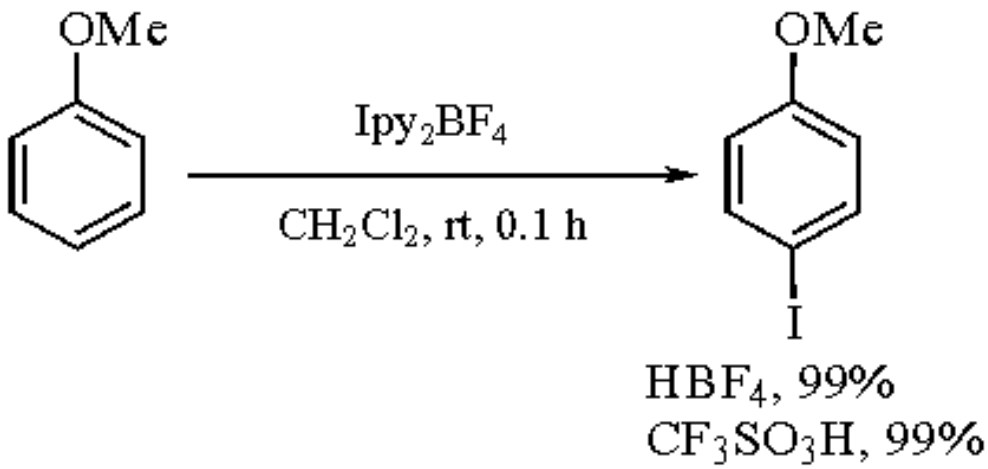

(11)

Benzaldehyde is also efficiently iodinated in 80% yield under similar conditions to those reported for nitrobenzene, without formation of oxidation products. In summary, the reported 21 examples[4] demonstrate that this is a general and reliable procedure which overcomes the well documented limited scope of aromatic iodination. Moreover, conditions were optimized to regioselectively prepare polyiodinated compounds at room temperature. In particular, reaction of Ipy_2BF_4 with C_6H_6 and CF_3SO_3H in CH_2Cl_2 provides an easy synthetic entry into a complete set of rarely accessible benzene derivatives (eq 12).[22]

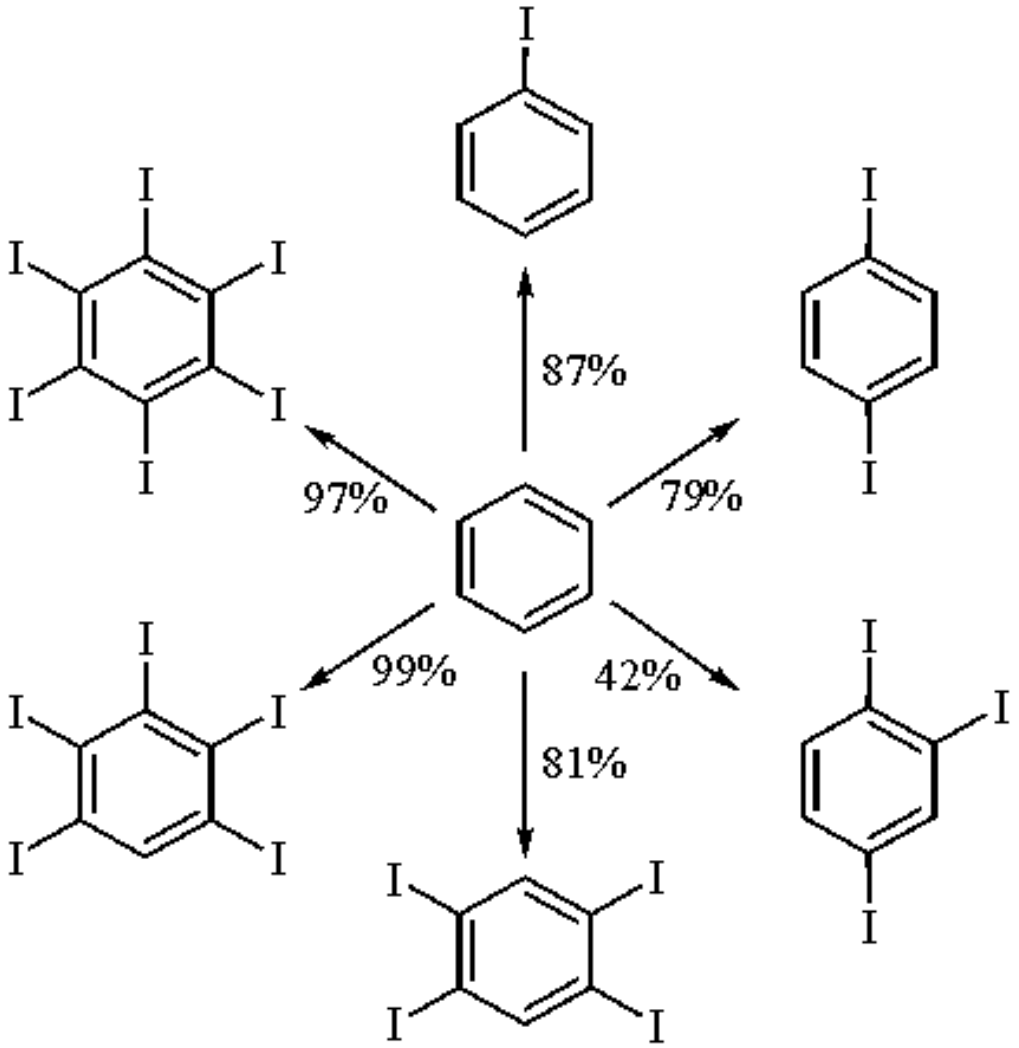

(12)

Finally, Ipy_2BF_4 is the reagent of choice to prepare 3,5-diamino-4-iodopyrazole through direct iodination of the corresponding pyrazole.[23]

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Bis(pyridine)silver(I) Permanganate

[82503-38-6] · $C_{10}H_{10}AgMnN_2O_4$ · Bis(pyridine)silver(I) Permanganate · (MW 385.01)

(oxidant, useful for the oxidation of polycyclic aromatics and alkynes to diketones,[1] primary benzylic alcohols to aldehydes,[2] secondary alcohols to ketones;[2] for the oxidative coupling of amines;[3] and the deoximation of oximes[3])

Physical Data: purple solid, decomposes at 104-105 °C.[2]

Solubility: sol acetone, chloroform and dichloromethane; sparingly sol benzene and pyridine.[2]

Analysis of Reagent Purity: elemental analysis.[2]

Preparative Method: pyridine (3 mol) is added to $KMnO_4$ (1 mol) dissolved in a minimum of distilled water followed by $AgNO_3$ (1 mol) in 1.7 L of distilled water. The purple precipitate (90%) is washed with water and then benzene. After drying over $CaCl_2$ it is recrystallized from acetone/benzene.[2] The visible spectrum resembles that of potassium permanganate and the IR displays a strong band at 900 cm^{-1}.

Handling, Storage, and Precautions: slowly reduced by polar solvents such as acetone, chloroform, and dichloromethane; less soluble, but more stable in benzene and pyridine;[2] insensitive to hammer blows, but ignites above 80 °C;[2] store small amounts (10-50 g) in glass vessels at or below rt.

Oxidation of Polycyclic Aromatic Hydrocarbons.[1]

Polycyclic aromatic hydrocarbons such as naphthalene, anthracene, and phenanthrene are converted into diketones when oxidized by bis(pyridine)silver permanganate as illustrated in eqs 1 and 2. The conditions employed are mild (rt in CH_2Cl_2) and the yields are uniformly high.

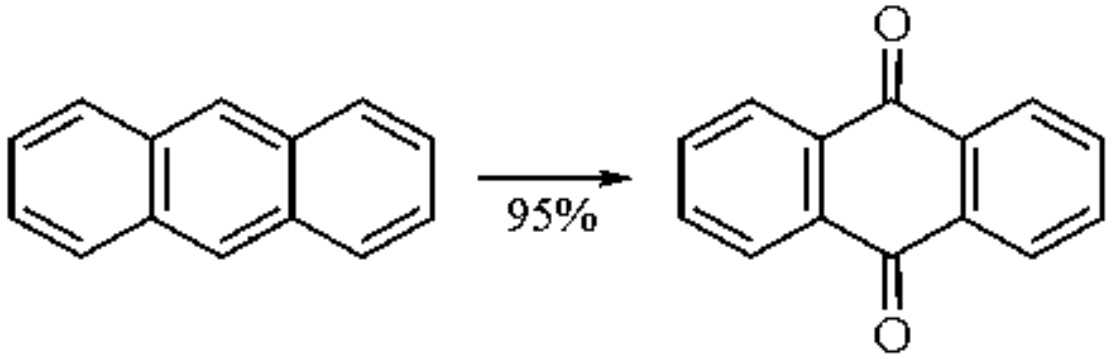

(1)

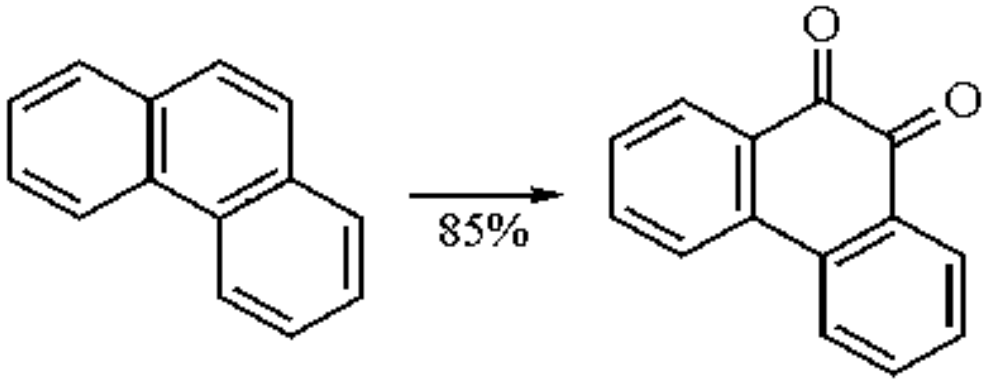

(2)

Oxidation of Alkynes.[2]

Nonterminal alkynes are also oxidized to diketones, while terminal alkynes undergo coupling, as illustrated in eqs 3 and 4. The conversion of benzocyclobutadienes into diketones is accompanied by carbon-carbon bond cleavage (eq 5).[2]

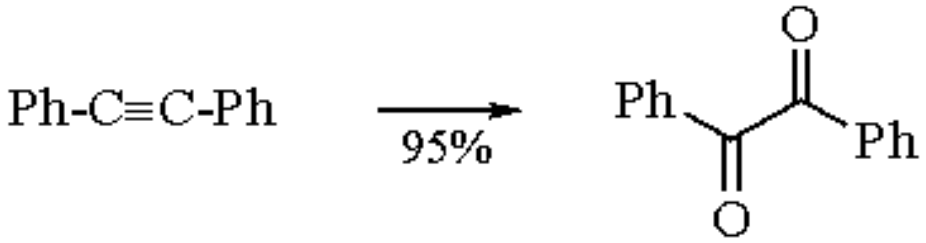

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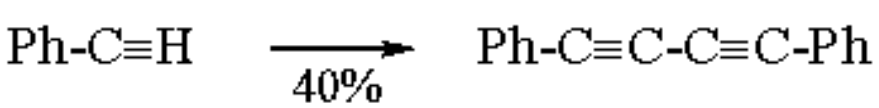

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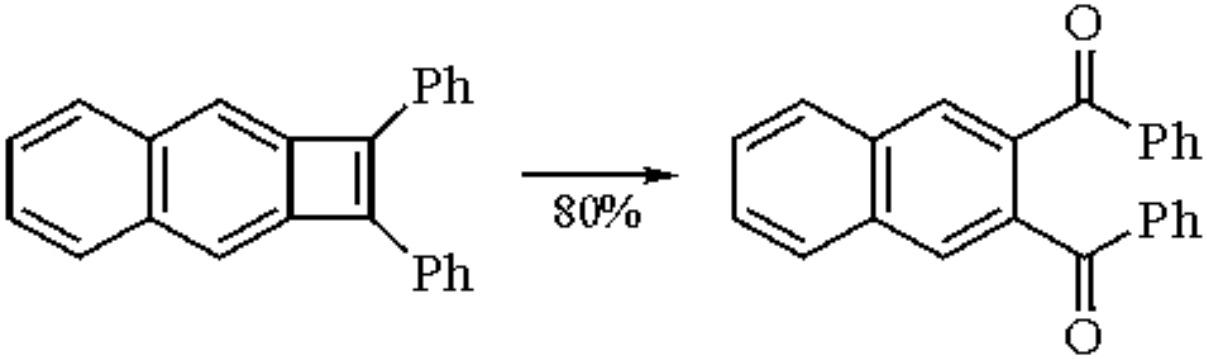

(5)

Oxidation of Primary Alcohols.[2]

Primary benzylic alcohols are converted into the corresponding aldehydes in good yield when oxidized by bis(pyridine)silver permanganate in benzene (eqs 6 and 7).

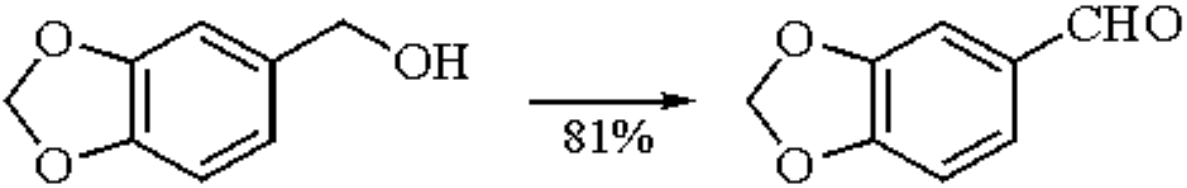

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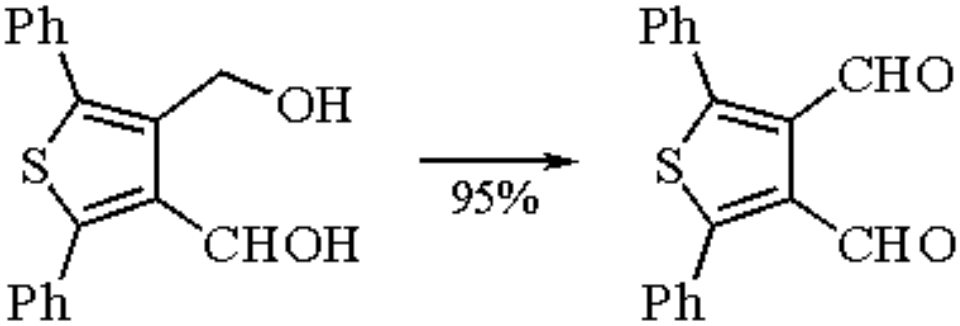

(7)

Oxidation of Secondary Alcohols.[2]

Secondary alcohols are converted into the corresponding ketones by use of this reagent (eqs 8 and 9).

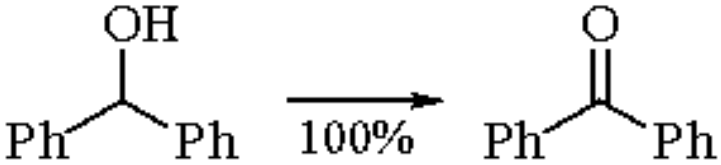

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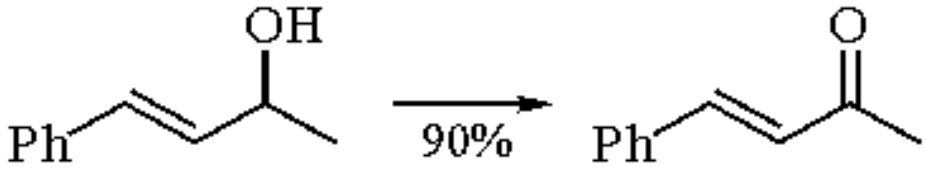

(9)

Oxidative Coupling of Amines.[2]

When treated with this oxidant, substituted anilines undergo a coupling reaction (eqs 10 and 11). Other primary amines are oxidized to aldehydes. For example, benzylamine gives benzaldehyde in 95% yield.

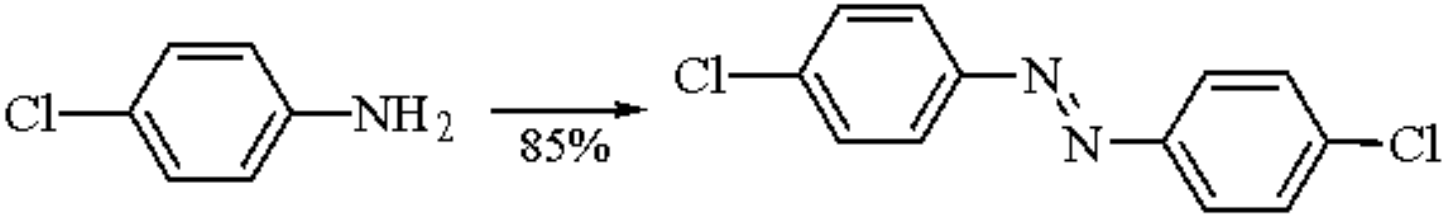

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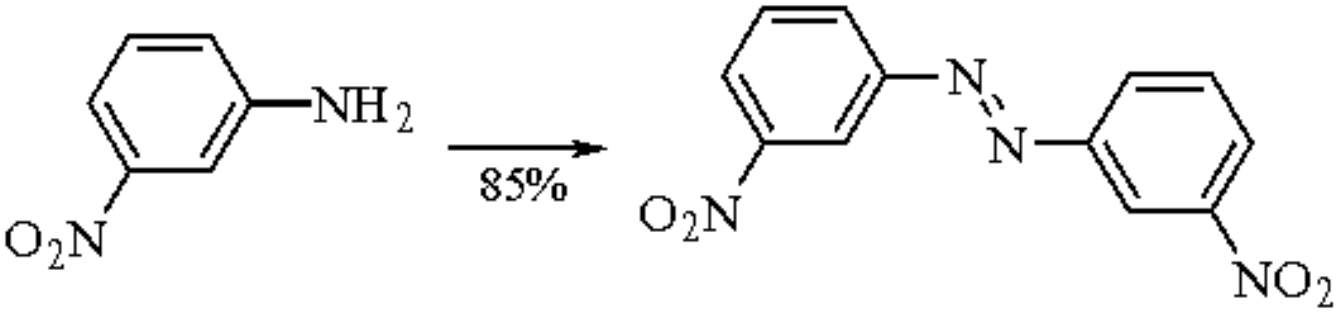

(11)

Oxidation of Oximes.[3]

Oximes are converted by bis(pyridine)silver permanganate into the corresponding aldehydes or ketones (eqs 12 and 13).

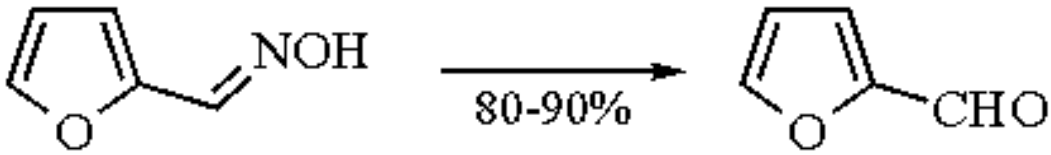

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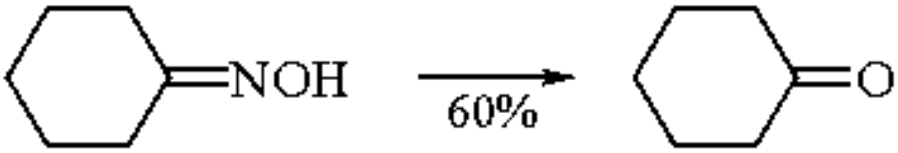

(13)

In most respects the reactions of bis(pyridine)silver permanganate are very similar to those of ***Bis(2,2´-***

bipyridyl)copper(II) Permanganate. The latter has, however, been reported to be more stable and easier to handle.[4]

---

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Bis(3-salicylideneaminopropyl)aminecobalt(II)[1]

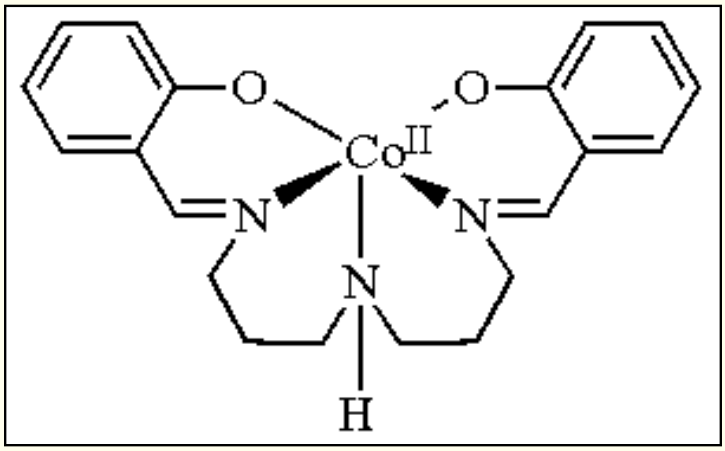

[15306-22-6] · $C_{20}H_{23}CoN_3O_2$ · Bis(3-salicylideneaminopropyl)aminecobalt(II) · (MW 396.36)

(catalyst for the homogeneous oxygenation of phenols with dioxygen in organic media)

Alternate Name: Co(Salpr).

Solubility: sol MeOH, CH_2Cl_2, $CHCl_3$, C_6H_6, THF, C_5H_5N and DMF.

Form Supplied in: green crystals.

Preparative Method: prepared under nitrogen from bis(salicylaldehydehydato)cobalt(II) dihydrate and bis(3-aminopropyl)amine.[2,3] The long green prisms are collected by suction, washed with cold methanol, and dried in a vacuum desiccator.

Purification: may be recrystallized from methanol if necessary; normally used without further purification.

Handling, Storage, and Precautions: store in a sealed container under an inert atmosphere.

Oxidation of 4-Substituted 2,6-Di-*t*-butylphenols to Quinols.

Co(Salpr), which binds dioxygen reversibly (1 O_2:2 Co), catalyzes the regioselective oxidation of 4-substituted 2,6-di-*t*-butylphenols in methanol to *p*-quinols, via alkylperoxycobalt(III) complexes and hydroperoxy intermediates, in high

yields (eq 1).[2,4-10] The peroxy complexes give the quinols quantitatively upon treatment with silica gel.[2] Either the complex or intermediate may be isolated. The regioselectivity of dioxygen incorporation depends on the nature of the substituent in the 4-position of the phenols.[9] In methanol, with 4-alkyl substituents, the oxygenation takes place in the 4-position (eq 1), and with 4-aryl substitution, oxygenation occurs exclusively at the 2-position (eq 2).[2,9] Complex product mixtures are obtained in benzene or chloroform.

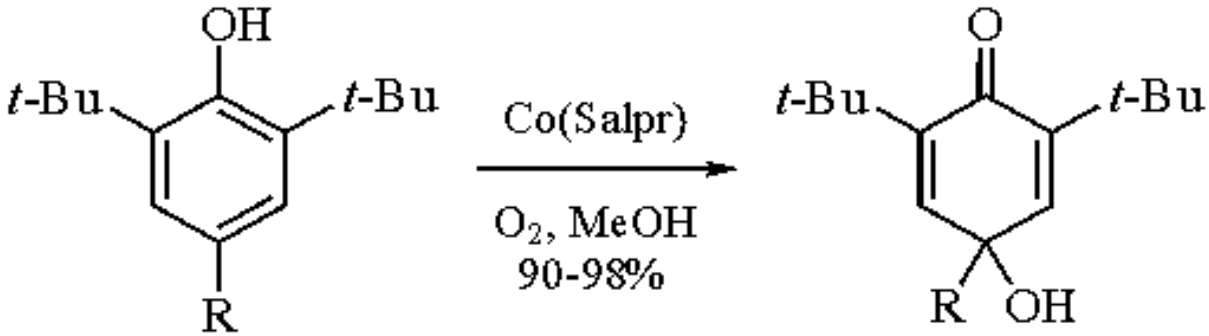

(1)

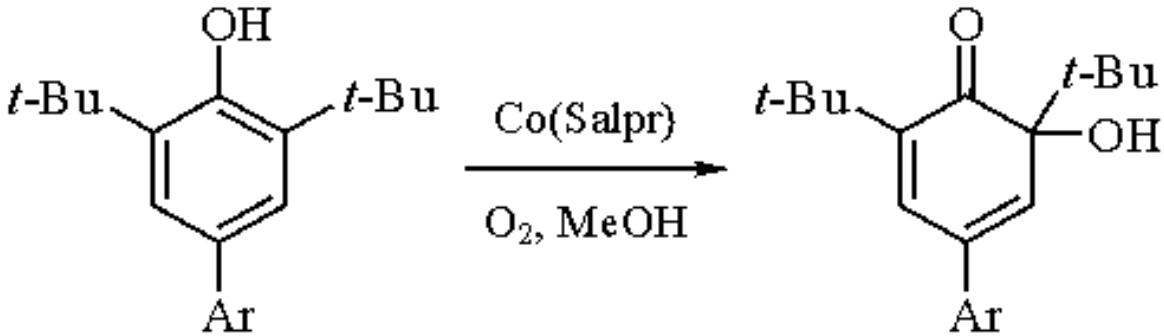

(2)

4-Alkyl-2,6-di-*t*-butylphenols give *p*-quinols in alkaline ethanol (cf. eq 1) and epoxy-*p*-quinols in DMF containing *t*-BuOK (eq 3).[10] The 4-aryl-substituted phenols afford *o*-quinols at low temperature (cf. eq 2), epoxy-*o*-quinols at 40 °C, and cyclopentadienones at 70 °C (eq 4).[10]

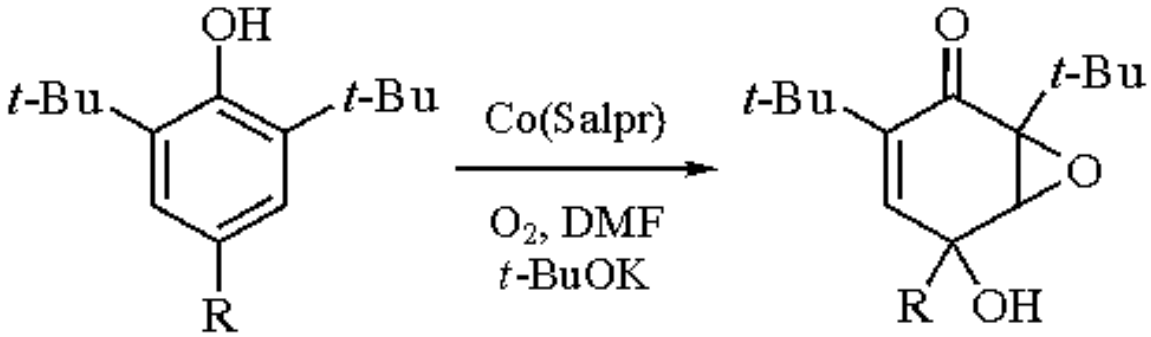

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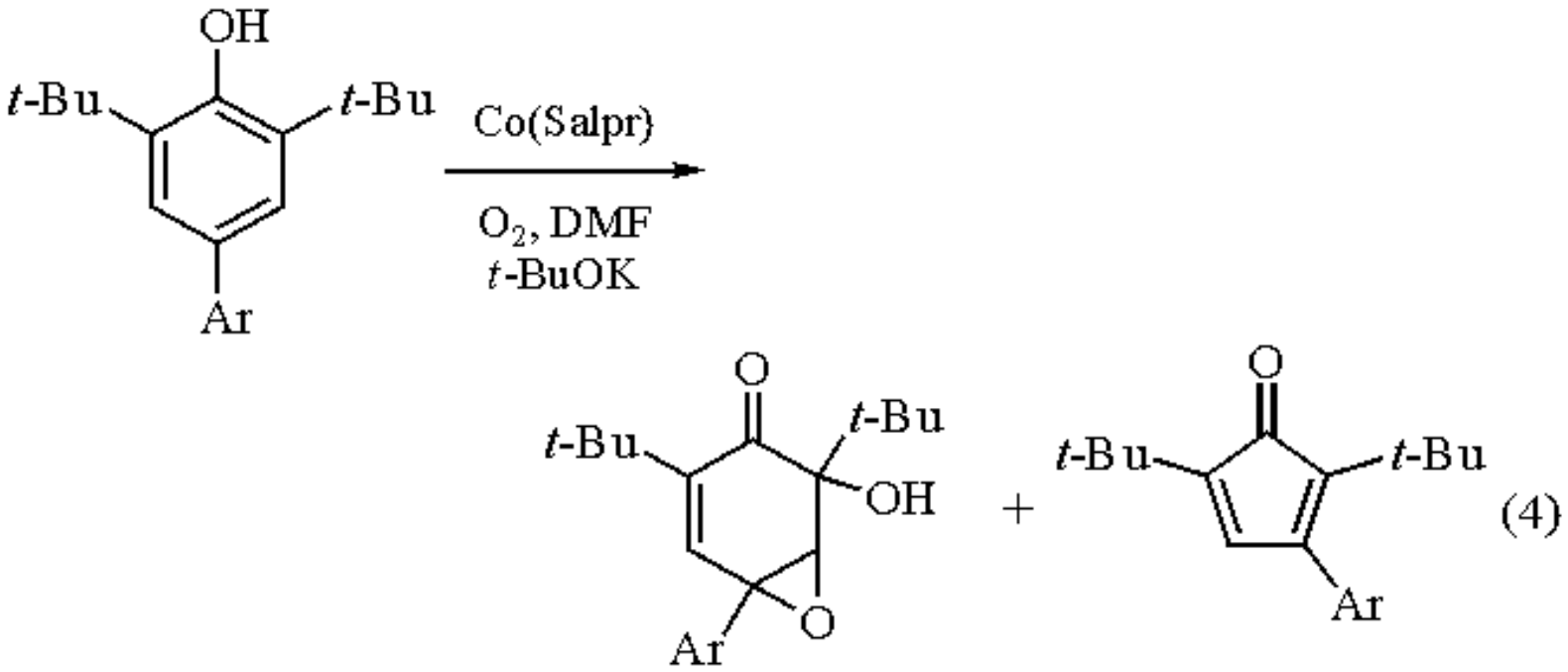

2,6-Di-*t*-butylphenols bearing electron-withdrawing groups at the 4-position are oxygenated exclusively at the 2 position with Co(Salpr) in CH_2Cl_2, to give the corresponding 3,5-di-*t*-butyl-6-hydroperoxy-2,4-cyclohexadienone derivatives (cf. eq 2; Ar = COR; CN; C=NR; C(R)=NOMe).[11,12] The 4-cyanophenol ultimately affords 3-cyano-2,5-di-*t*-butylcyclopentadienone (eq 5), and the imines also yield products resulting from intramolecular decomposition of the peroxy-*o*-quinolato Co^{III}(Salpr) intermediates (eq 6).[12]

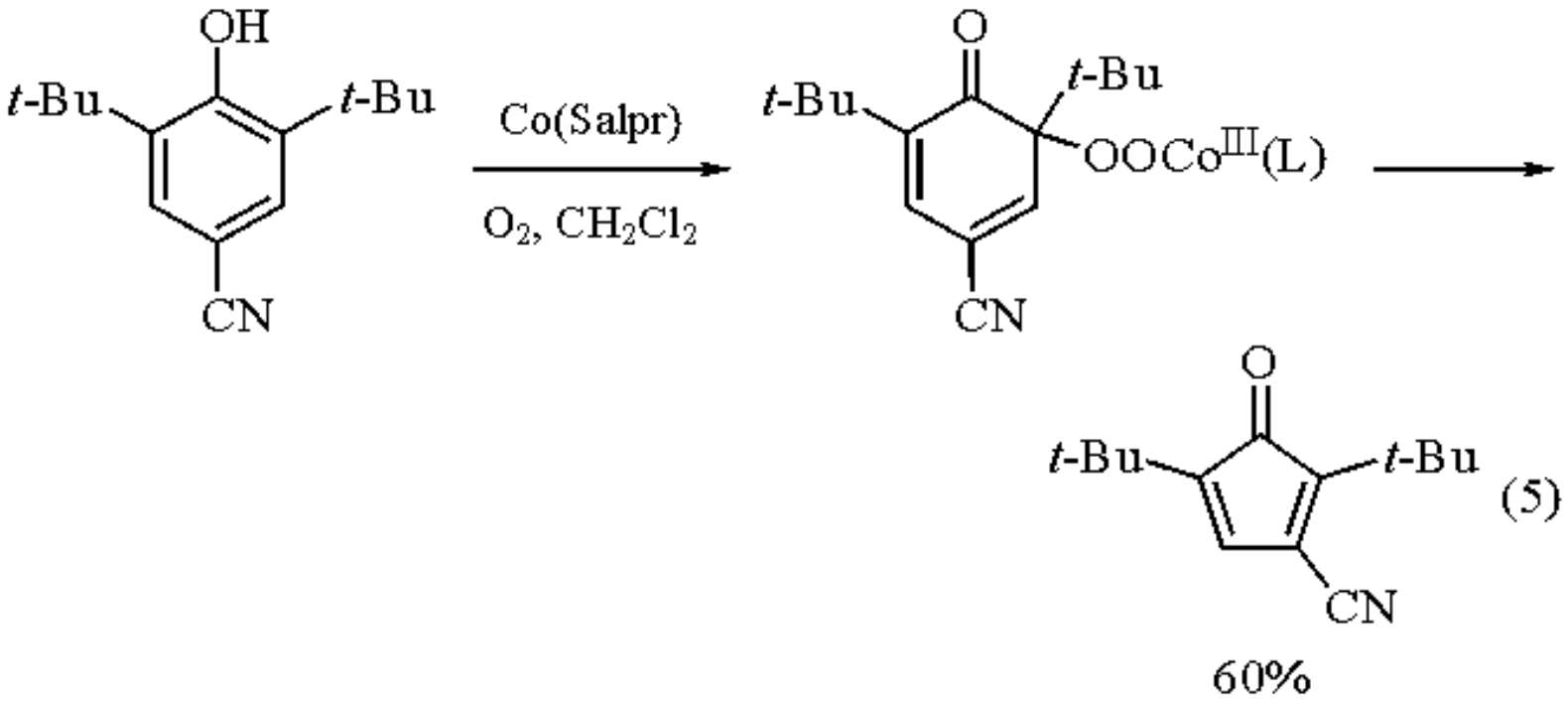

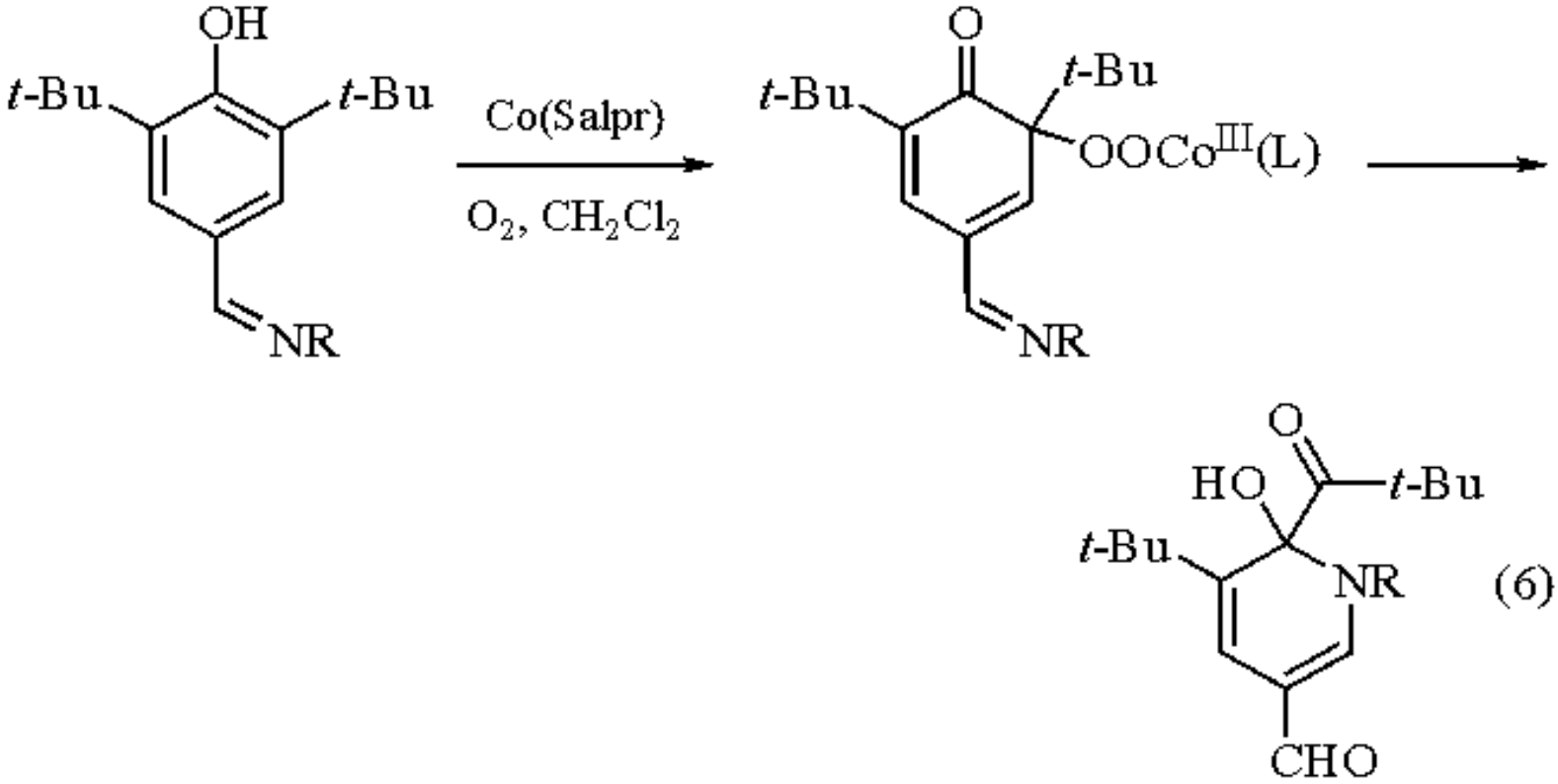

Oxidation of Alkyl Substituted Phenols to *p*-Benzoquinones.

Oxygenation of alkyl substituted phenols without a substituent *para* to the oxygen functionality in the presence of Co(Salpr) affords *p*-benzoquinone derivatives.[13-15]

Oxygenation of *t*-Butylphenols with an Unsaturated Side Chain.

The oxygenation of 4-alkenyl-2,6-di-*t*-butylphenols with Co(Salpr) in dichloromethane followed by filtration through a short column of silica gel affords the intermediate hydroperoxyquinone methides and *p*-acylphenols (eq 7).[9] The yields of the products depend on the nature of the alkenyl substituent. With 2-alkenyl-4,6-di-*t*-butylphenols, cleavage of the double bond to form only 2-acyl-4,6-di-*t*-butylphenols is observed.[9] These results indicate that dioxygen is incorporated exclusively into the alkenyl side chain. Each sp hybridized carbon atom is oxidized to a carbonyl group (1,2-dione) during the oxygenation of 4-alkynyl-2,6-di-*t*-butylphenols.[9,16]

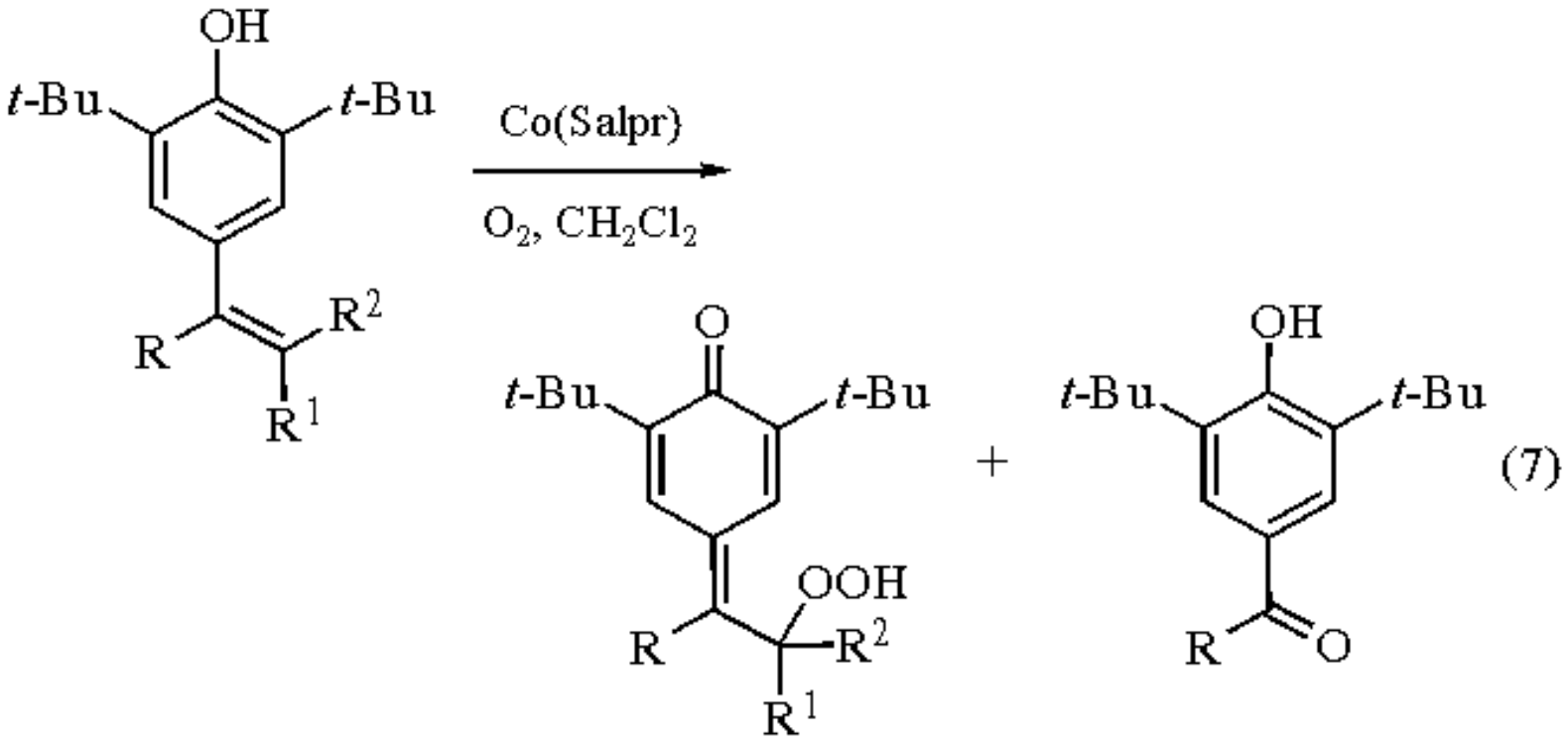

Oxidative Phenolic Coupling.

Carpanone, a lignan with five contiguous asymmetric centers, is synthesized in excellent yield by the Co(Salpr) catalyzed oxidation of *trans*-2-(1-propenyl)-4,5-methylenedioxyphenol (eq 8).[17] Co(Salpr) and Co(Salen) (***Salcomine***) are more effective catalysts than either Fe(Salen) or Mn(Salen).

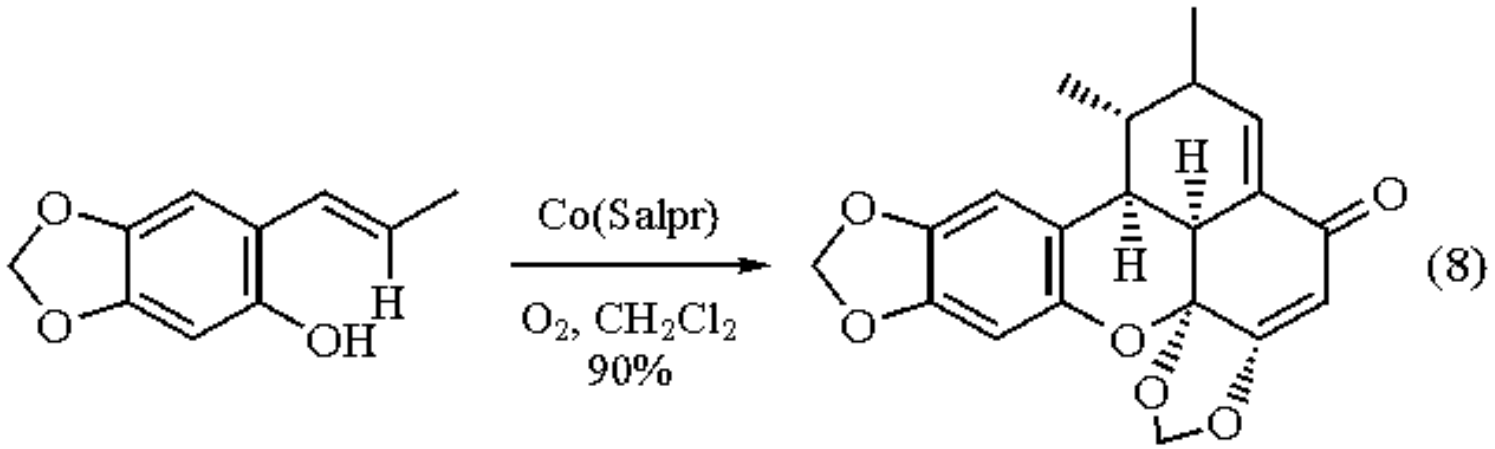

Oxidative Cyclization to Flavanones and 1,3-Benzodioxoles.

Co(Salpr) in methanol under nitrogen promotes the conversion of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones to retro-Claisen reaction products and flavanones.[18] Similarly, 2´-hydroxychalcones are also converted to flavanones (eq 9).[19] Substituted 2´-hydroxyacetophenone 4-bromophenylhydrazones are oxygenated readily in the presence of Co(Salpr) in ethanol to give 2-(4-bromophenylazo)-1,3-benzodioxoles in good yield (eq 10).[20]

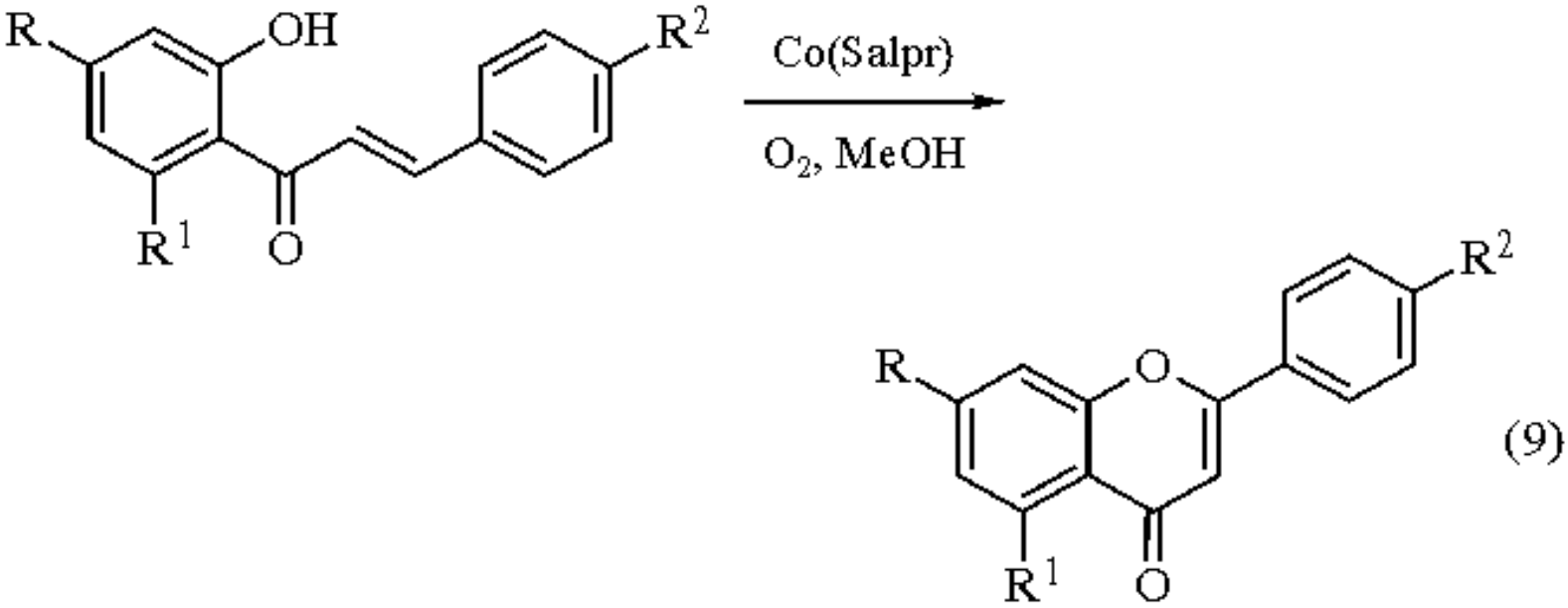

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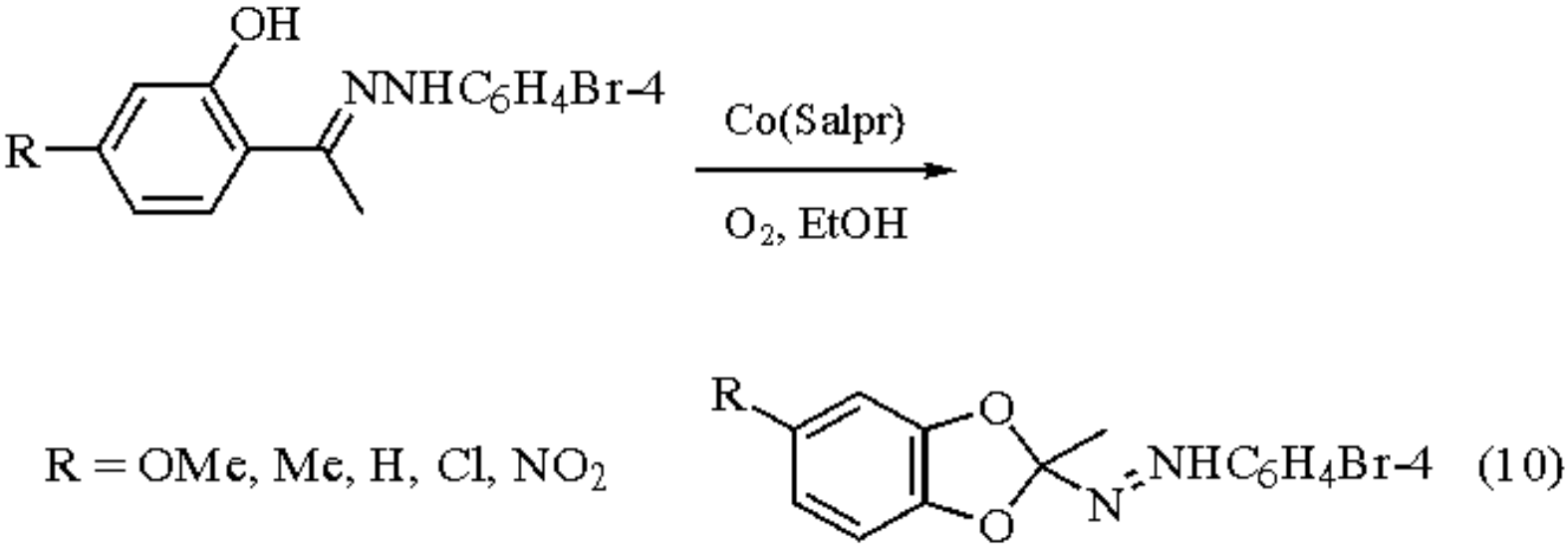

(10)

Other Applications.

Co(Salpr) and other cobalt-Schiff base complexes, in primary or secondary alcohols under dioxygen, catalyze the oxygenation of alkenes substituted with an aromatic or an electron-withdrawing group to ketones without double bond cleavage (eq 11).[21]

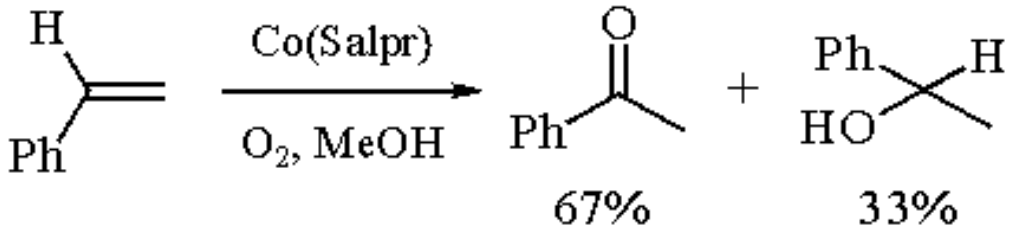

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N,N´-Bis(salicylidene)ethylenediaminenickel(II)[1]

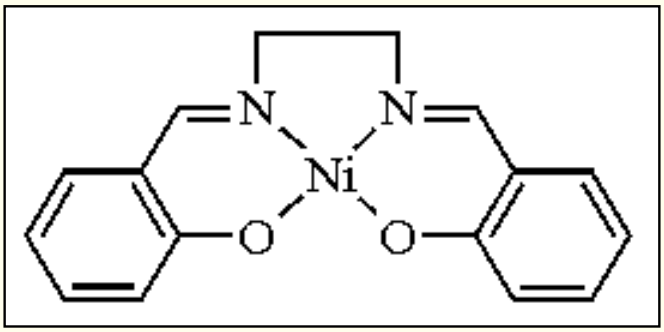

[14167-20-5] · $C_{16}H_{14}N_2NiO_2$ · *N,N´*-Bis(salicylidene)ethylenediaminenickel(II) · (MW 324.99)

(catalyst for alkane chlorination,[2] alkene epoxidation,[4] DNA oxidation,[5] Michael addition,[7] and radical cyclization[8])

Alternate Name: Ni(salen).

Physical Data: mp 337 °C, *d* 1.325 g cm^{-3}.

Solubility: insol H_2O; slightly sol benzene and ether; sol acetone, acetic acid, pyridine, $CHCl_3$, and CH_2Cl_2.

Form Supplied in: commercially available as an orange powder.

Preparative Method: easily and cheaply prepared from ethylenediamine, salicylaldehyde, and $Ni(OAc)_2$.[1]

Handling, Storage, and Precautions: low sensitivity to air and water; cancer suspect agent; handle with care.

Alkane Chlorination.

Ni(salen) catalyzes the chlorination of saturated hydrocarbons, such as adamantane and cyclohexane, and the benzylic position of arenes.[2] Reactions are carried out under phase-transfer conditions using aqueous ***Sodium Hypochlorite*** adjusted to pH 11 and CH_2Cl_2 solutions of the alkane (0.4 M) and catalyst (0.01 M). An 8.5:1 preference for chlorination at tertiary compared to secondary positions has been observed. Small amounts of ketone side products arise from hydrolysis of *gem*-dichloro compounds.

Alkene Epoxidation.

Ni(salen) is a highly efficient catalyst for alkene epoxidation using aqueous NaOCl adjusted to pH 9.3 under phase-transfer conditions (eq 1).[3,4] As little as 0.013 mol % catalyst can be used with respect to alkene. The reaction is highly sensitive to pH. Epoxidation and alkene chlorination are both enhanced at lower pH, and pH 9.3 was found to give an optimal epoxidation rate while minimizing chlorination.[4] Arylalkenes (styrenes, stilbenes) are the best substrates for this reaction, giving virtually quantitative conversion to epoxides, while alkylalkenes give relatively large percentages of chlorinated products. Use of optically active salen analogs fails to give enantioselectivity in epoxidation.[3]

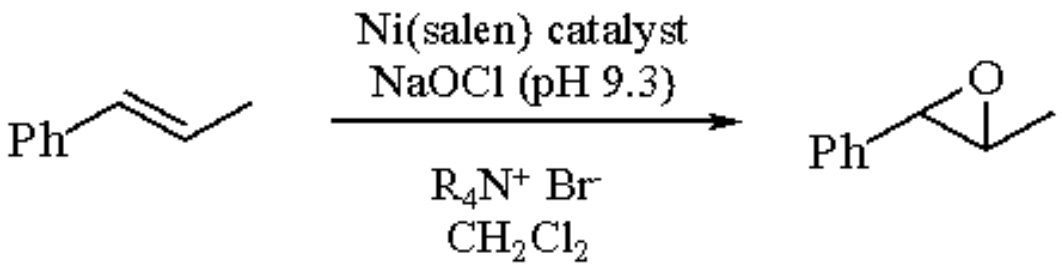

(1)

DNA Oxidation.

Ni(salen) is among the most active of a series of nickel(II) complexes as a catalyst for DNA oxidation. Form I supercoiled plasmid DNA is readily converted to Form II nicked DNA by single-strand cleavage in the presence of ***Iodosylbenzene*** or magnesium monoperoxyphthalate (MMPP).[5] Reactions typically involve use of 100 µM Ni(salen) and 1 mM oxidant at pH 6.8-7.0 for 5 min (PhIO) to 2.5 h (MMPP) at 25 °C.

A derivative of Ni(salen) bearing water-solubilizing groups (**1**) is an excellent reagent for oxidative alkylation of guanine residues in accessible sites of DNA structures.[6] In the presence of $KHSO_5$ as oxidant, a hairpin deoxyoligonucleotide showed specific reactivity at the G's located in the hairpin. The alkylation reaction gives rise to site-specific strand scission upon treatment with piperidine. Since the cleavage reaction is presumed to give clean phosphate ends, this method can be used for site-specific cleavage and synthesis of altered oligonucleotides.

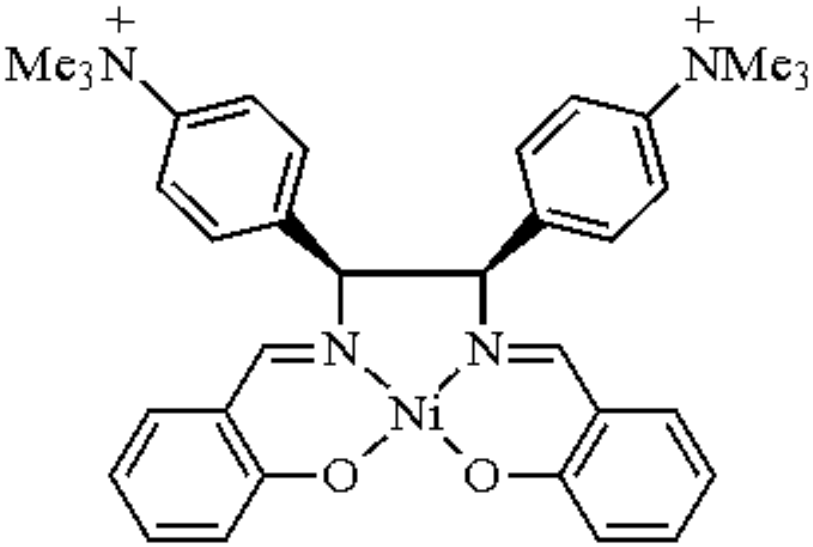

(1)

Michael Addition.

Ni(salen) and related Schiff base complexes catalyze the Michael addition of β-keto esters to methyl vinyl ketone.[7] For example, use of 1 mol % nickel catalyst in benzene gave excellent yields (84-96 %) of addition products when methyl vinyl ketone was used as the enone with various β-dicarbonyl compounds (eq 2). However, other Michael acceptors such as cyclohexenone gave considerably lower yields. Use of optically active Schiff base ligands gave low enantioselectivity (6% ee).

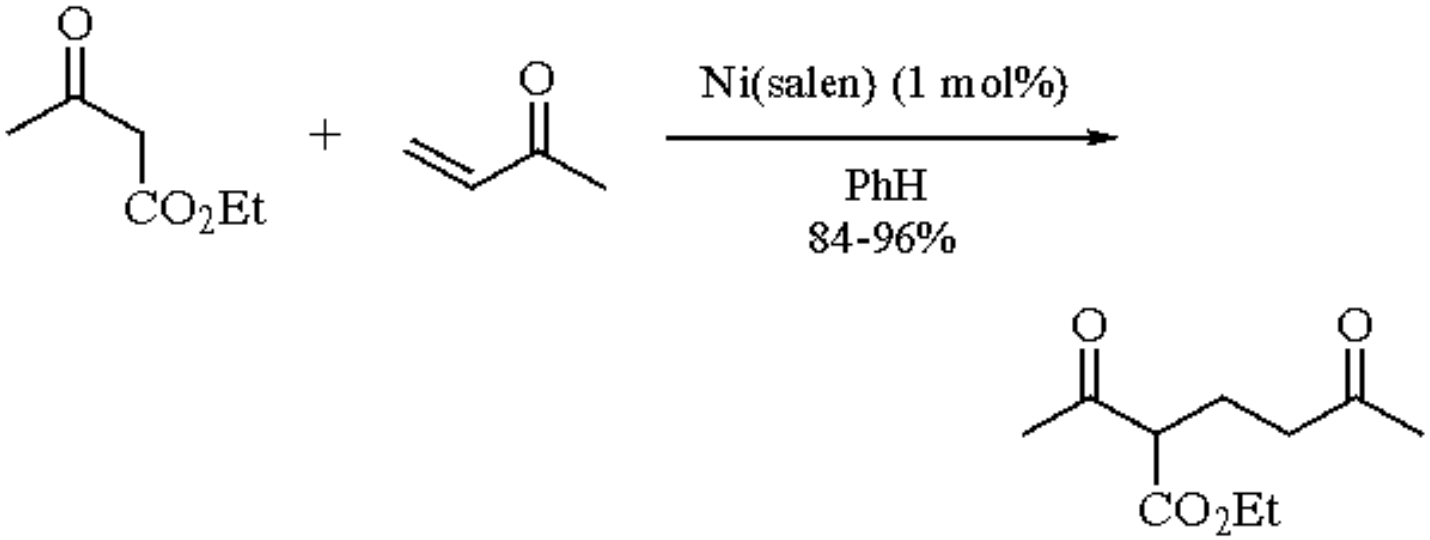

(2)

Radical Cyclization.

Ni^{II}(salen) undergoes reversible reduction to a nickel(I) species at a carbon cathode in DMF at a potential where 6-halo-1-hexynes are not electroactive. Thus Ni(salen) can be used as an electrocatalyst for the intramolecular cyclization of haloalkynes.[8] Reactions are carried out in DMF with 0.1 M tetraethylammonium perchlorate as electrolyte. Controlled potential electrolysis at -1.00 V gave excellent conversions of 6-halo-1-phenyl-1-hexyne to the

corresponding benzylidenecyclopentane (eq 3). Halide reduction was a minor competing process (6-17%).

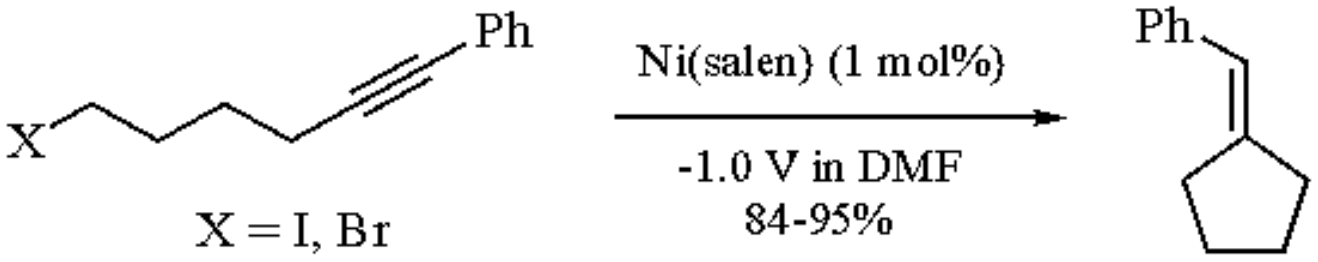

(3)

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Bis(tetrabutylammonium) Dichromate[1]

(n-$Bu_4N)_2Cr_2O_7$

[56660-19-6] · $C_{32}H_{72}Cr_2N_2O_7$ · Bis(tetrabutylammonium) Dichromate · (MW 700.92)

(mild selective oxidizing agent for benzylic and allylic alcohols;[2] can oxidize carbon-halogen bonds[3])

Alternate Name: TBADC.

Physical Data: mp 139-143 °C.

Solubility: sol dichloromethane, chloroform.

Form Supplied in: orange crystalline solid; widely available.

Preparative Method: a concentrated aqueous solution (300 mL) of ***Potassium Dichromate*** (29.4 g, 0.1 mol) is added to a saturated aqueous solution (300 mL) of ***Tetra-n-butylammonium Bromide*** (64.4 g, 0.2 mol). TBADC precipitates and can be removed by filtration (62.8 g, 90% yield).

Handling, Storage, and Precautions: reported to be a toxic agent. The reagent should be handled in a fume hood.

Oxidation of Benzylic and Allylic Alcohols.

TBADC is a neutral and mild oxidizing reagent, soluble in organic solvents. It can be used for the selective oxidation of benzylic and allylic alcohols to the corresponding carbonyl compounds. The reactions are performed in refluxing dichloromethane for 1-3 h with a stoichiometric amount of oxidant; yields range from 78 to 90% (eqs 1 and 2);[2] (*E*)/(*Z*) isomerization is observed in the oxidation of allylic alcohols.

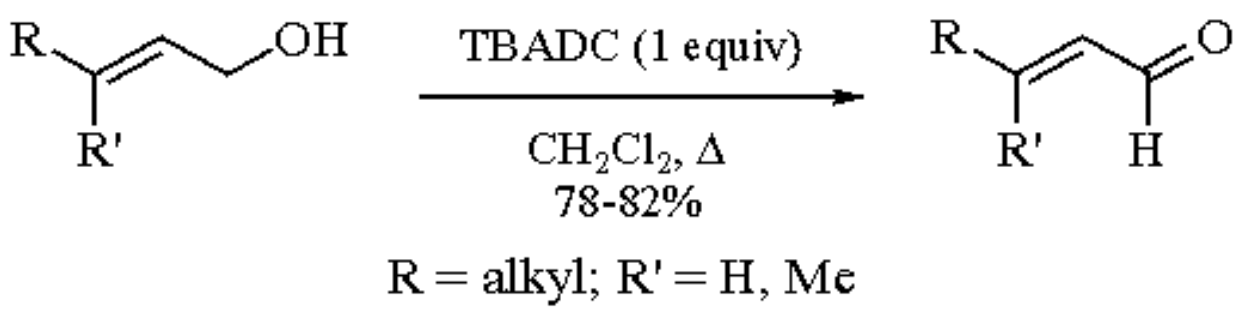

(1)

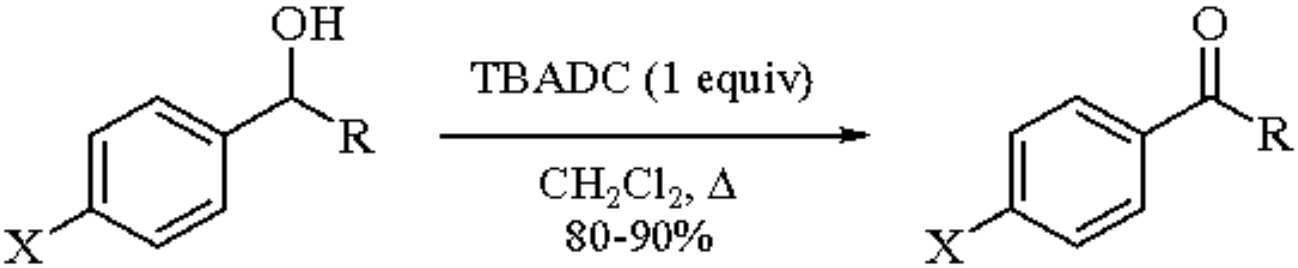

(2)

$X = H, Cl, OMe, NO_2; R = H, Me, CO_2Et$

Unactivated alcohols resist attack by the oxidant, being only slightly oxidized (10-20%) after 24 h at reflux.[2a]

Oxidation of Carbon-Halogen Bonds.

TBADC, acting as an oxidizing nucleophile, efficiently converts benzylic and allylic halides into the corresponding carbonyl compounds in boiling chloroform. The yields are generally excellent (eq 3).[3,4] The reactions are faster for bromides than for chlorides, and in the presence of an excess of oxidant.[3]

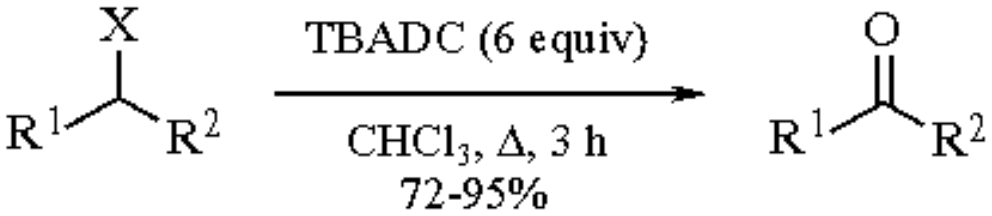

(3)

$R^1 = alkyl, aryl; R^2 = H, Me; X = Cl, Br$

Secondary alkyl bromides afford ketones in high yields, while primary alkyl bromides give a mixture of products with the corresponding aldehydes formed in very low yield.[3] Methyl 3,5-bromomethylbenzoate undergoes selective oxidation at one of two benzylic bromomethyl groups to form the corresponding aldehyde upon treatment with TBADC (0.66 equiv) in refluxing chloroform for 1 h, albeit in a moderate yield. The dialdehyde is obtained as a byproduct (eq 4).[4]

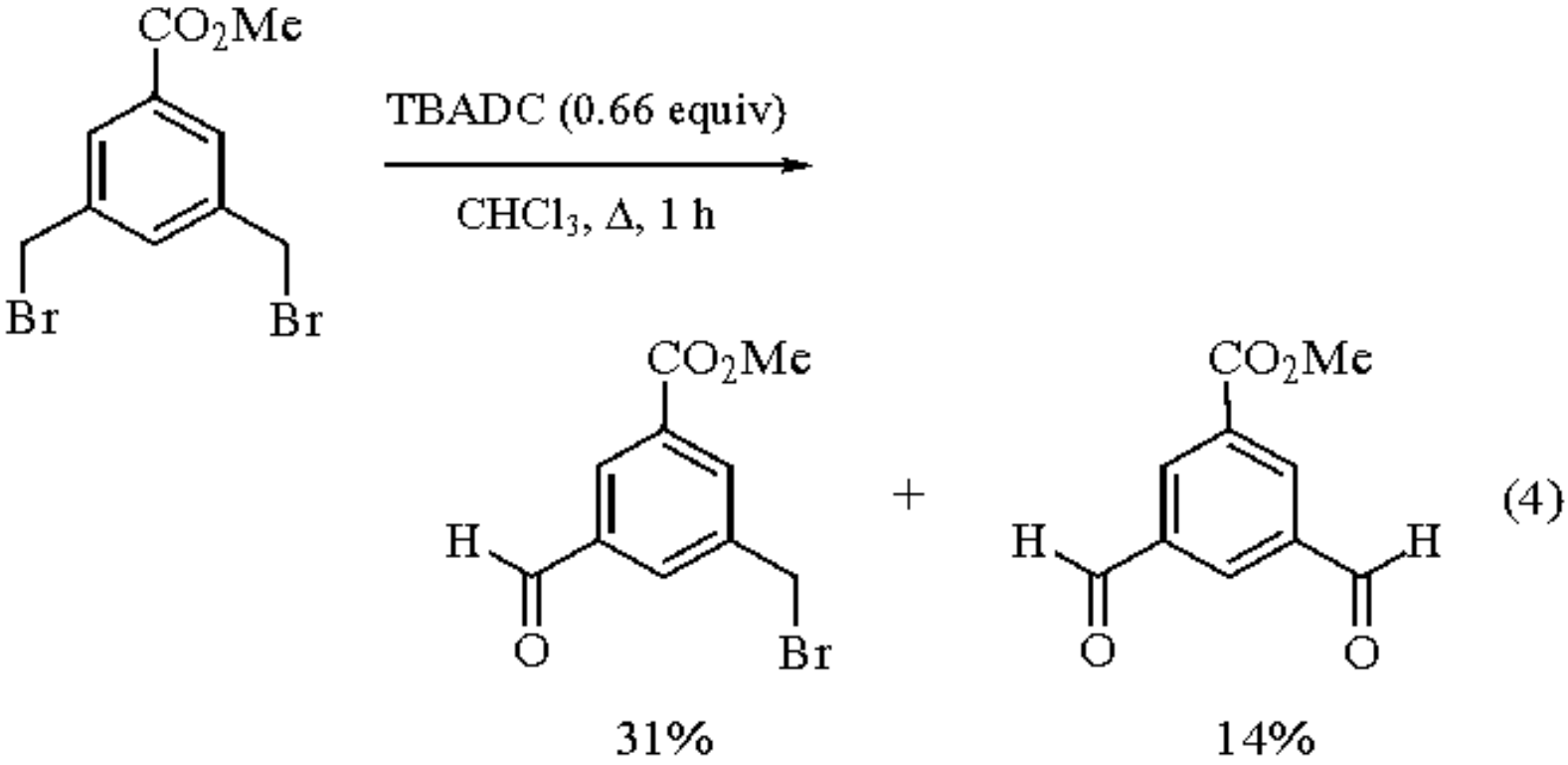

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Bis[*N*-(*p*-toluenesulfonyl)]selenodiimide

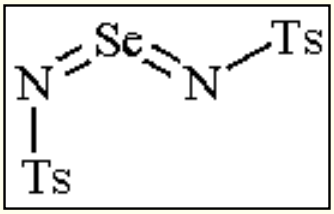

[60123-29-7] · $C_{14}H_{14}N_2O_4S_2Se$ · Bis[*N*-(*p*-toluenesulfonyl)]selenodiimide · (MW 417.36)

(allylic amination of alkenes and alkynes,[1] 1,2-diamination of 1,3-dienes[2])

Physical Data: mp 115-117 °C.

Preparative Methods: ***Selenium*** metal is allowed to react with 2 equiv of anhydrous ***Chloramine-T*** (TsNClNa) in $CHCl_2$ under N_2 for 24 h.[1] Also prepared by adding an ether solution of *N*,*N*-bis(trimethylsilyl)-*p*-toluenesulfonamide to an ether solution of selenyl chloride and stirring for 3 h.[3]

Handling, Storage, and Precautions: readily hydrolyzed by water; must be kept rigorously dry.

Allylic Amination and Diamination.

The title compound (**1**) effects allylic amination of alkenes (eq 1)[1] and alkynes (eq 2).[1] The reaction occurs via an initial ene reaction to form (**2**) followed by a [2,3]-sigmatropic rearrangement. Nitrogen insertion takes place without net rearrangement of the double bond and generally occurs at the most substituted allylic position (eq 3).[1]

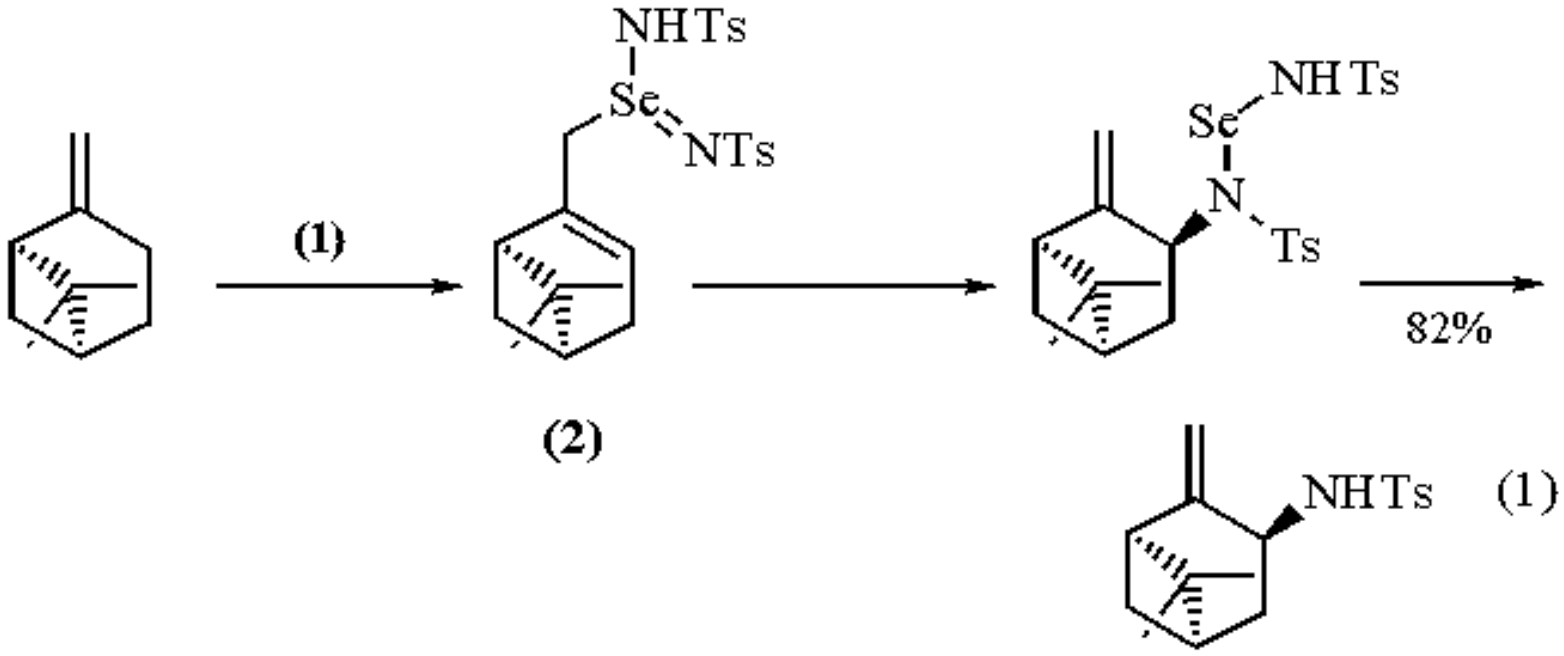

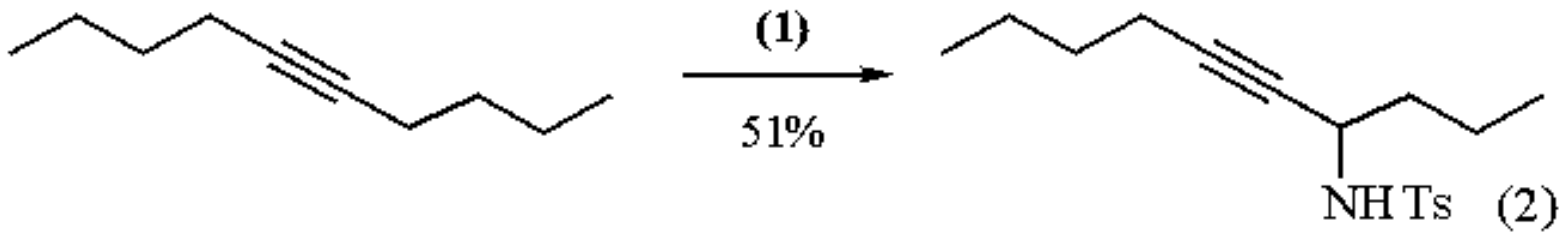

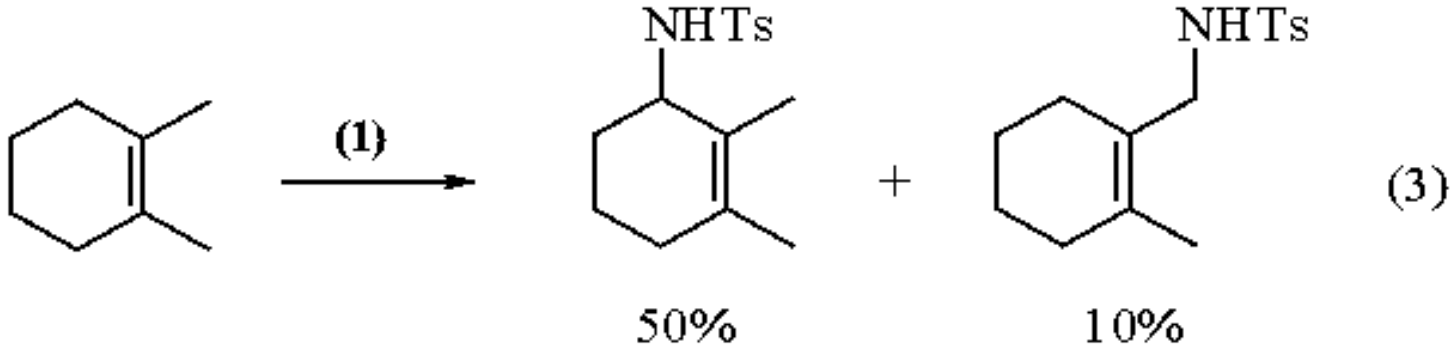

Compound (**1**) has been utilized in the total synthesis of gabaculine (**6**).[4] Upon treatment with (**1**), alkene (**3**) afforded a mixture of allylic amine derivatives (**4**) and (**5**) in 45% yield (eq 4). Compound (**1**) has also been used effectively in the syntheses of both β-apopicropodophyllin analogs[5] and daunosamine analogs.[6]

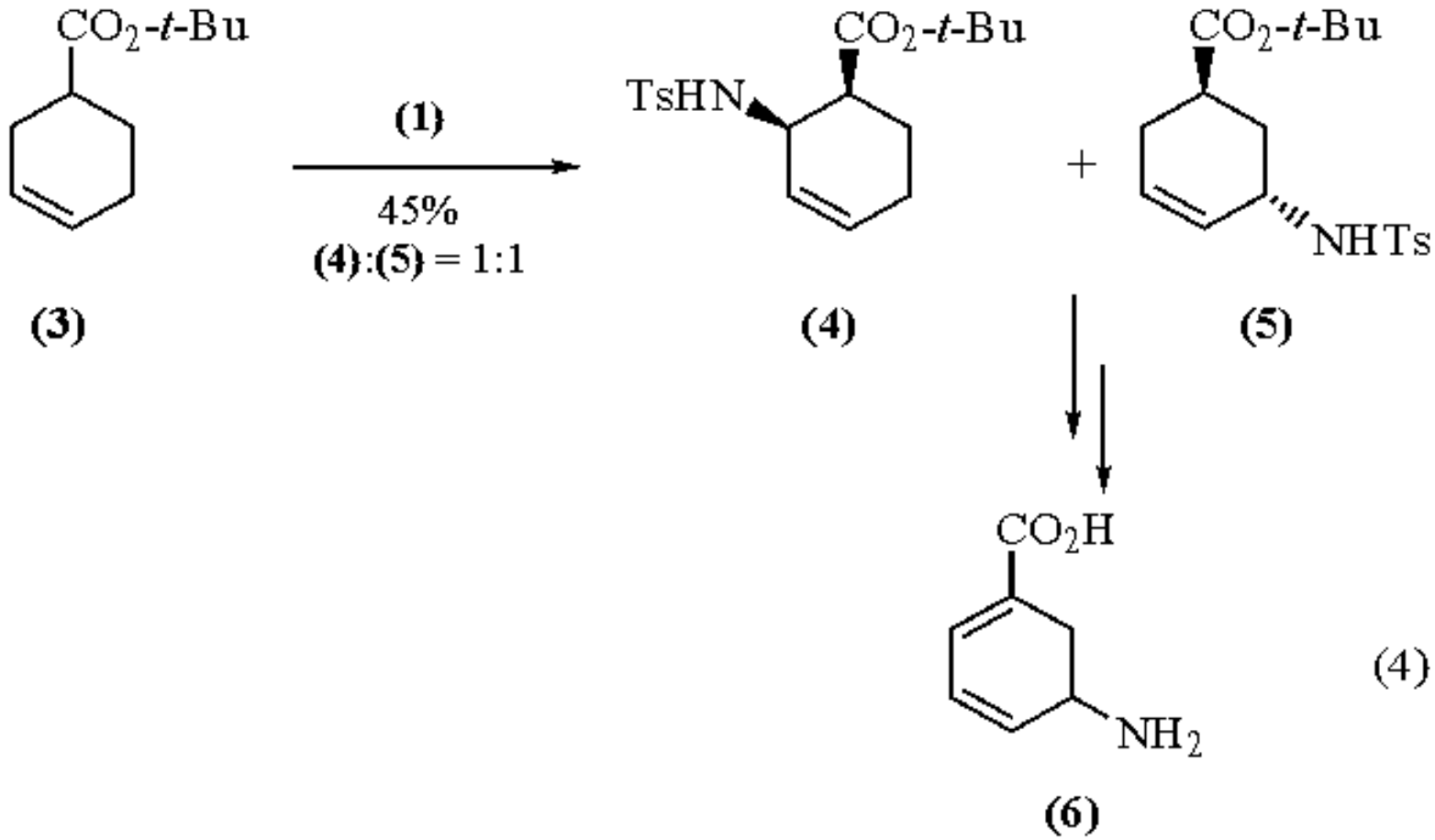

(4)

Trialkylsilyl enol ethers have also been aminated by (**1**), providing access to α-amino ketone derivatives (eq 5).[7] The products of the amination have the NHTs group in an axial orientation due to interactions between the π orbital and the σ* orbital of the C-N bond.[8] Compound (**1**) was used to aminate silyl enol ether (**7**) in the synthesis of the benzomorphanone core structure (**8**) (eq 6).[9]

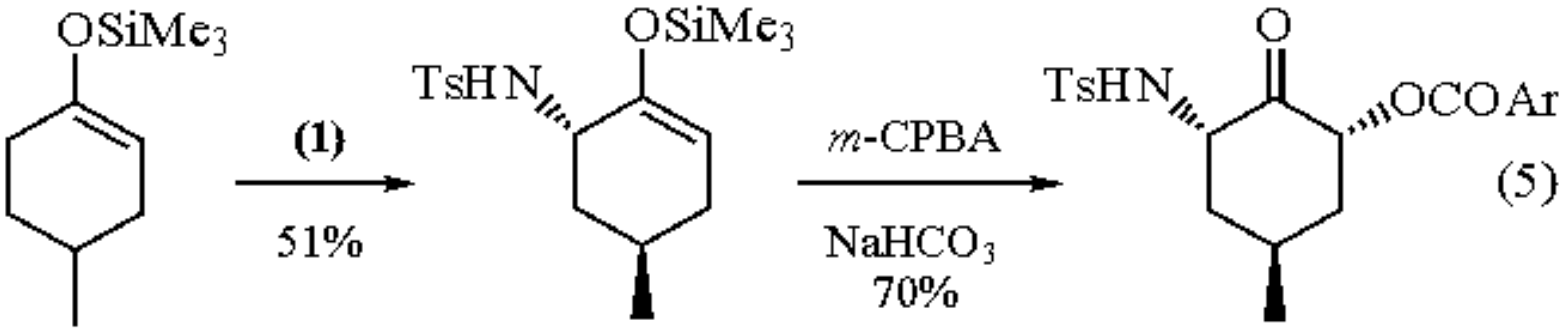

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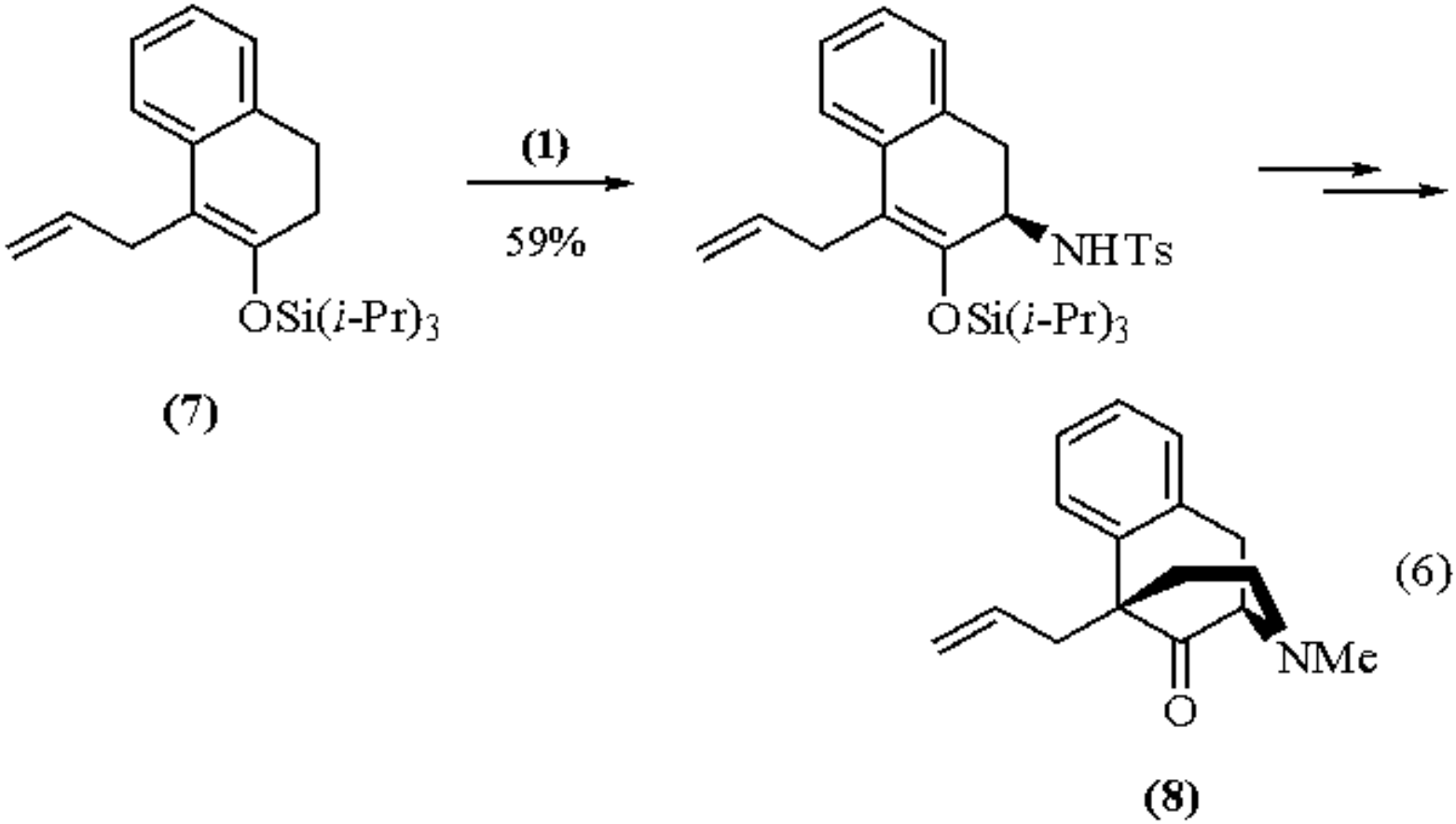

Compound (**1**), prepared from selenium oxychloride (**9**) and *N*,*N*-bis(trimethylsilyl)toluenesulfonamide (**10**) (eq 7), has been isolated and utilized in [4 + 2] cycloaddition reactions with dienes.[3] For example (**1**) reacts regioselectively with isoprene to yield 3,6-dihydro-1,2-selenazine (**11**) (eq 8).[3]

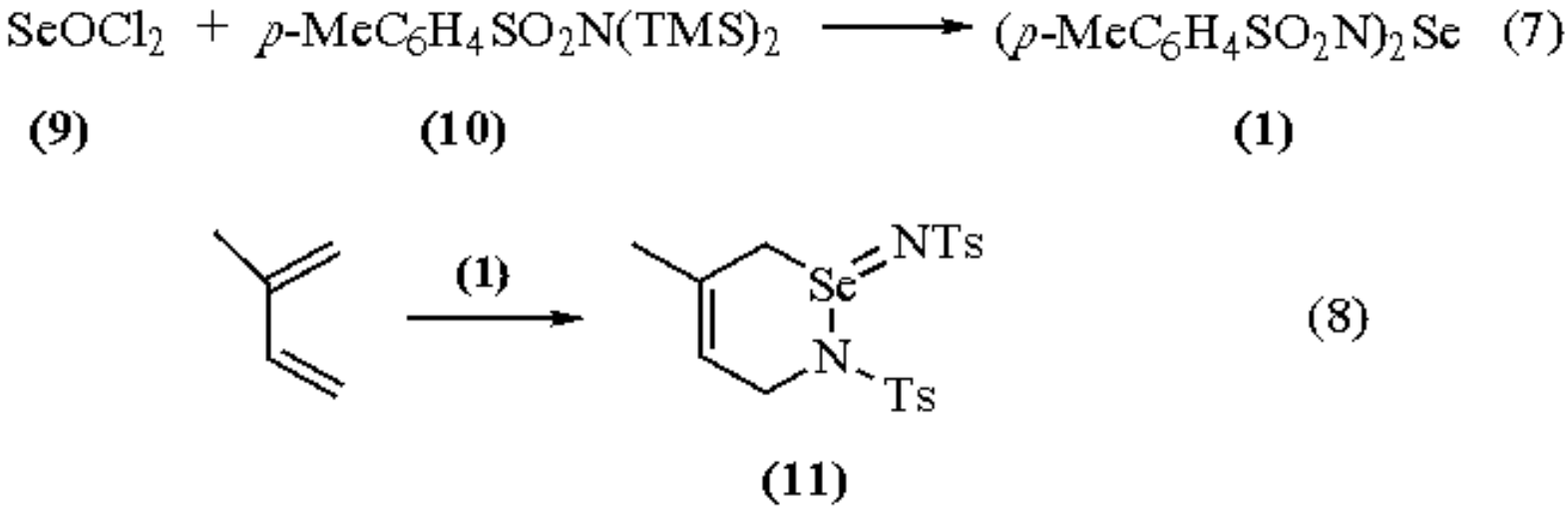

In cases where (**1**) is prepared from chloramine T, the reaction with 1,3-dienes directly produces 1,2-disulfonamides (eq 9)[2] rather than Diels-Alder adducts. Initially, the [4 + 2] adduct (**12**) is probably formed, which is then cleaved by traces of *p*-toluenesulfonamide to afford (**13**). This intermediate subsequently undergoes [2,3]-sigmatropic rearrangement to (**14**), which hydrolyzes in situ to yield disulfonamide (**15**). It has been suggested that the reagent prepared from selenium and chloramine T is actually $(TsNNa)_2SeCl_2$.[10] Cyclic dienes afford exclusively the *cis*-1,2-disulfonamides (eq 10).[2]

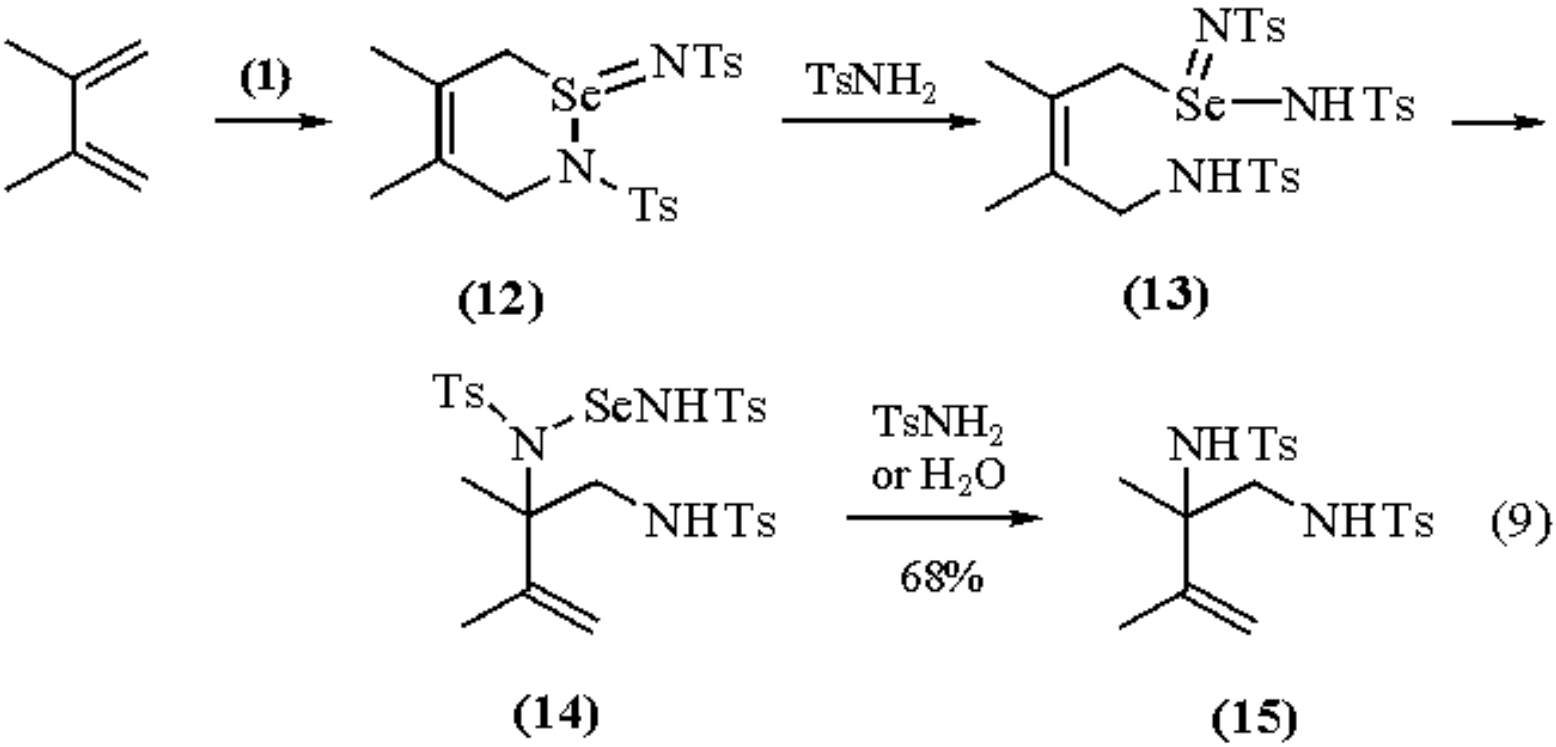

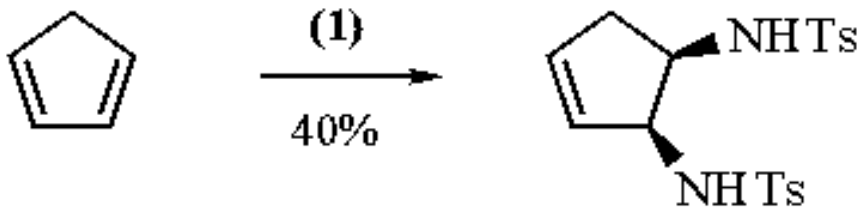

(10)

Compound (**1**) has been used to prepare 3-vinyl-1,2,5-selenadiazole (**17**) from 1,2-diamine (**16**) via a cyclocondensation reaction (eq 11).[11]

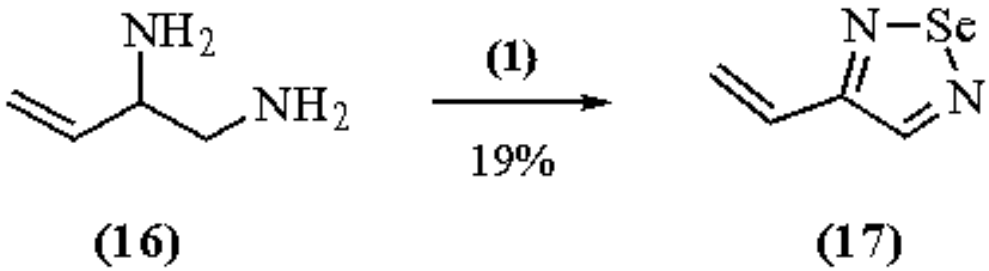

(11)

Related Reagents.

Bis[N-(p-toluenesulfonyl)]sulfodiimide.

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1. Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *JACS* **1976**, *98*, 269.
2. Sharpless, K. B.; Singer, S. P. *JOC* **1976**, *41*, 2504.

3. Barashenkov, G. G.; Derkach, N. Ya. *JOU* **1986**, *22*, 1069.
4. Singer, S. P.; Sharpless, K. B. *JOC* **1978**, *43*, 1448.
5. Anjanamurthy, C.; Rai, K. M. L. *IJC(B)* **1985**, *24*, 505.
6. Dyong, I.; Wiemann, R. *AG(E)* **1978**, *17*, 682.
7. Magnus, P.; Mugrage, B. *JACS* **1990**, *112*, 462.
8. Magnus, P.; Lacour, J.; Bauta, W.; Mugrage, B.; Lynch, V. *CC* **1991**, 1362.
9. Magnus, P.; Coldham, I. *JACS* **1991**, *113*, 672.
10. Derkach, N. Ya.; Levchenko, E. S. *RCR* **1989**, *58*, 507.
11. Bertini, V.; Lucchesini, F. *S* **1979**, 979.

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The Pennsylvania State University, University Park, PA, USA

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Bis[*N*-(*p*-toluenesulfonyl)]sulfodiimide[1]

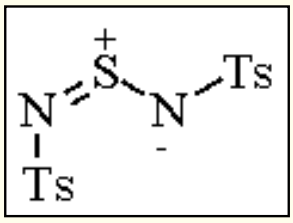

[851-06-9] · $C_{14}H_{14}N_2O_4S_3$ · Bis[*N*-(*p*-toluenesulfonyl)]sulfodiimide · (MW 370.46)

(can act as an enophile in ene reactions[4-6] and as a dienophile in Diels-Alder reactions;[2,10-12] participates in [2 + 2][4] and [3 + 2][15,16] cycloaddition reactions; cycloadds to ynamines[17])

Physical Data: bright yellow solid; mp 48-50 °C.

Solubility: sol benzene, toluene, chloroform, and methylene chloride.

Preparative Methods: a convenient in situ method for the synthesis of bis[*N*-(*p*-toluenesulfonyl)]sulfodiimide (**1a**) is by treating ***N-Sulfinyl-p-toluenesulfonamide*** with dry ***Pyridine*** in benzene (eq 1).[2] An alternative procedure is the reaction of SCl_2 or S_2Cl_2 with *p*-toluenesulfonamide in the presence of a base such as pyridine or triethylamine (eq 2).[3]

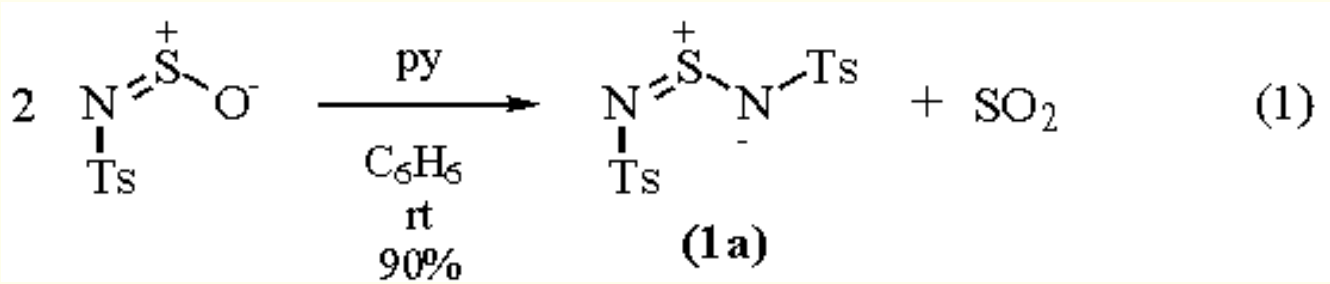

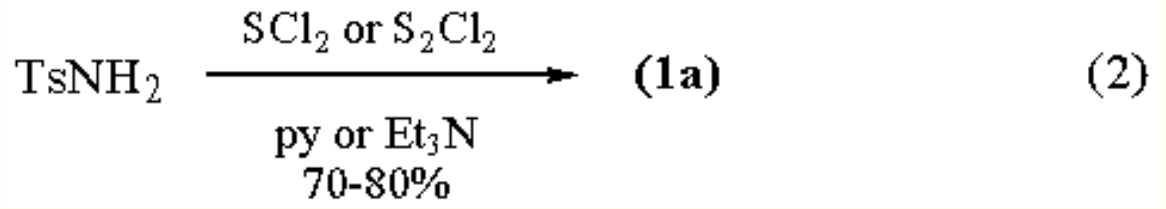

Handling, Storage, and Precautions: extremely sensitive to moisture and should be stored in a desiccator and handled only in a dry box or glove bag. Typically the title compound is generated and used in situ.

Ene Reaction or Allylic Amination.

Some years ago it was discovered that sulfur diimide (**1a**) is a highly reactive enophile, converting a wide variety of alkenes into sulfinamides under mild conditions. For example, (**1a**) reacts with allylbenzene at 10 °C to afford sulfinamide (**3**) in 91% yield (eq 3).[4,5] This reactive intermediate spontaneously undergoes a [2,3]-sigmatropic rearrangement to produce the diaminosulfane (**4**). It was also shown that the N-S-N bond is readily cleaved using Na_2SO_3 to give the allylic sulfonamide (**5**) in excellent yield.[5a]

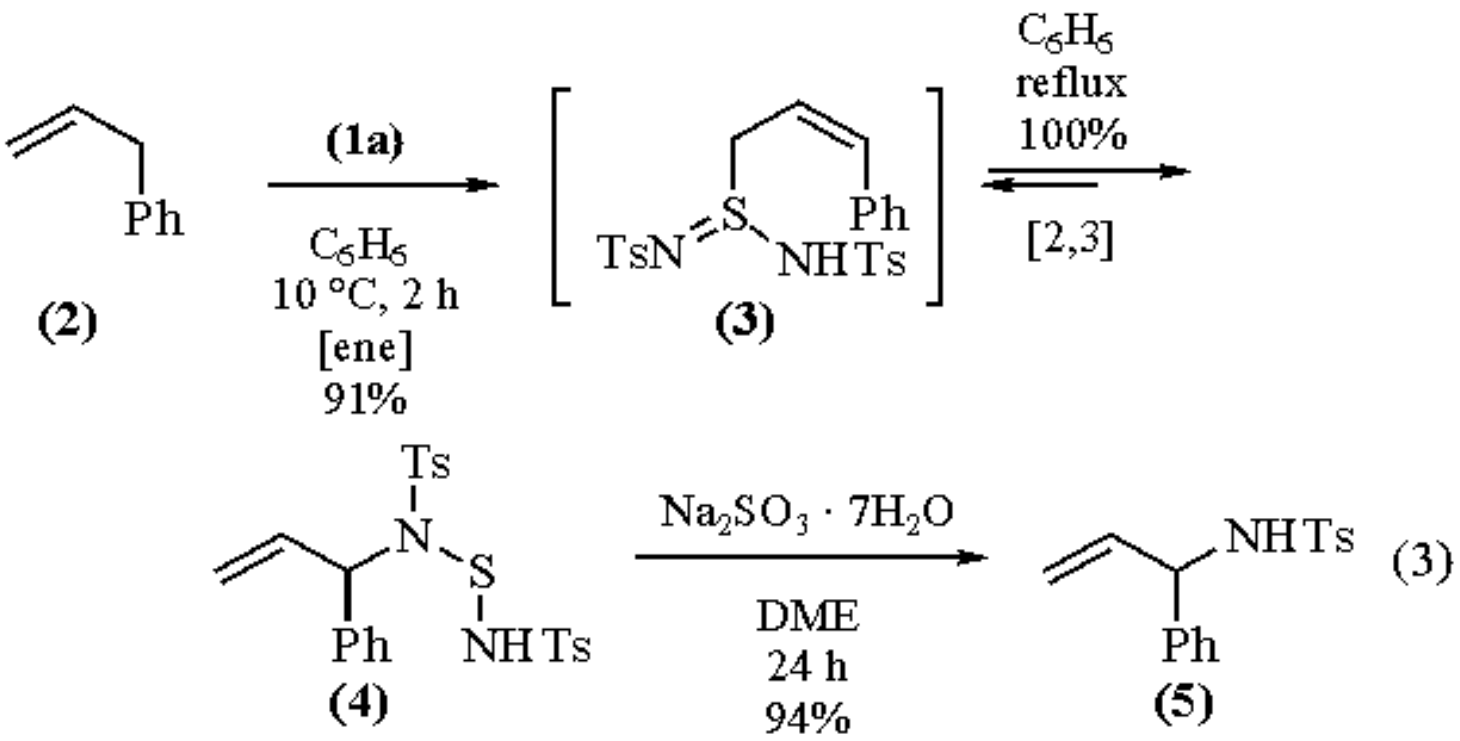

In a similar study, cyclic compounds, such as methylenecyclohexane, were shown to react with sulfur diimide (**1a**) to give principally disulfenamide (**7**) and initial ene product (**6**) as a minor component (eq 4).[6] These sulfenamide intermediates are slowly hydrolyzed with K_2CO_3 to the corresponding allylic sulfonamides.

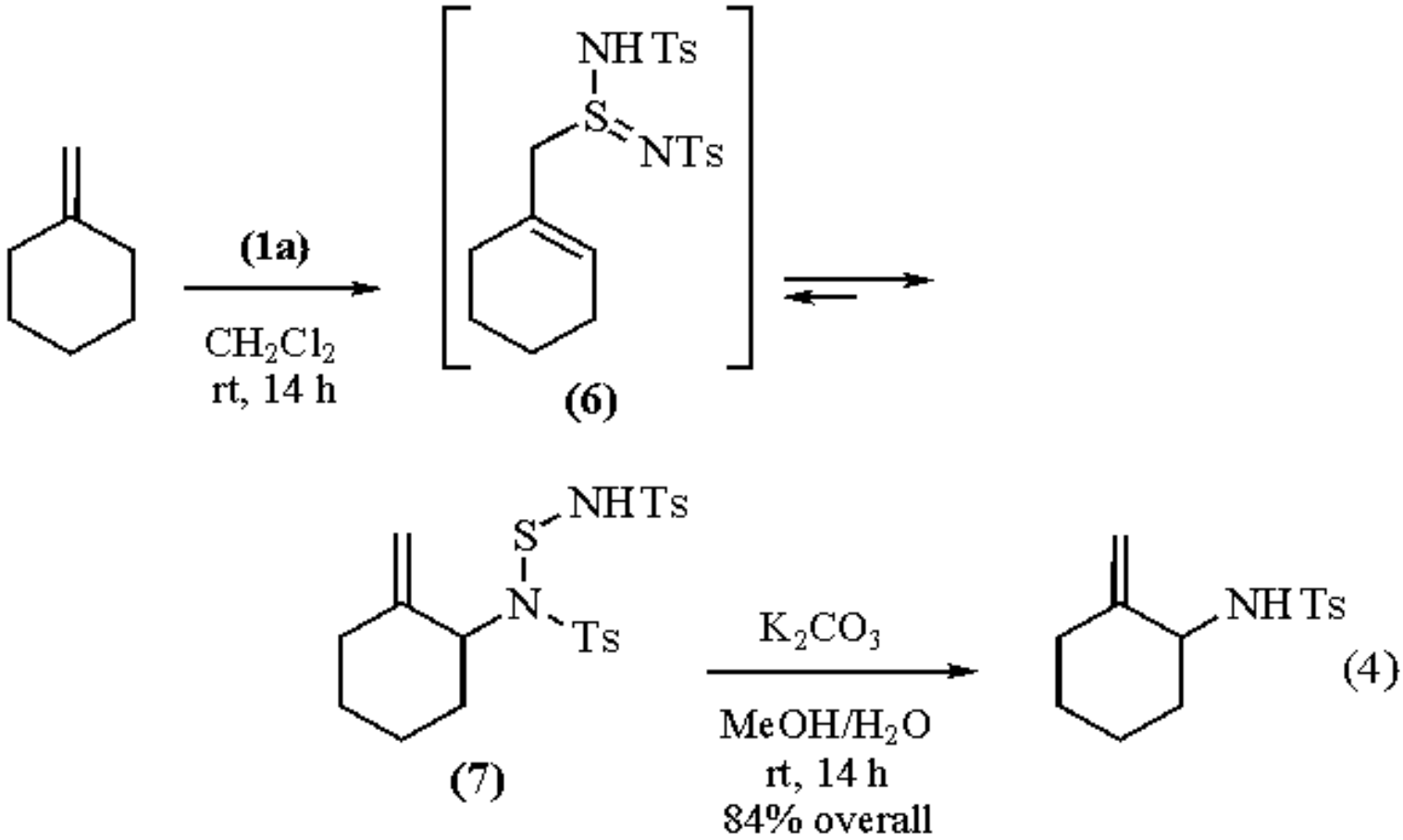

The allylic amination sequence has been applied to an elegant total synthesis of racemic gabaculine (**11**).[7] Treatment of cyclohexenyl derivative (**8**) with (**1a**) followed by basic hydrolysis affords predominantly allylic sulfonamide (**9**) (eq 5).

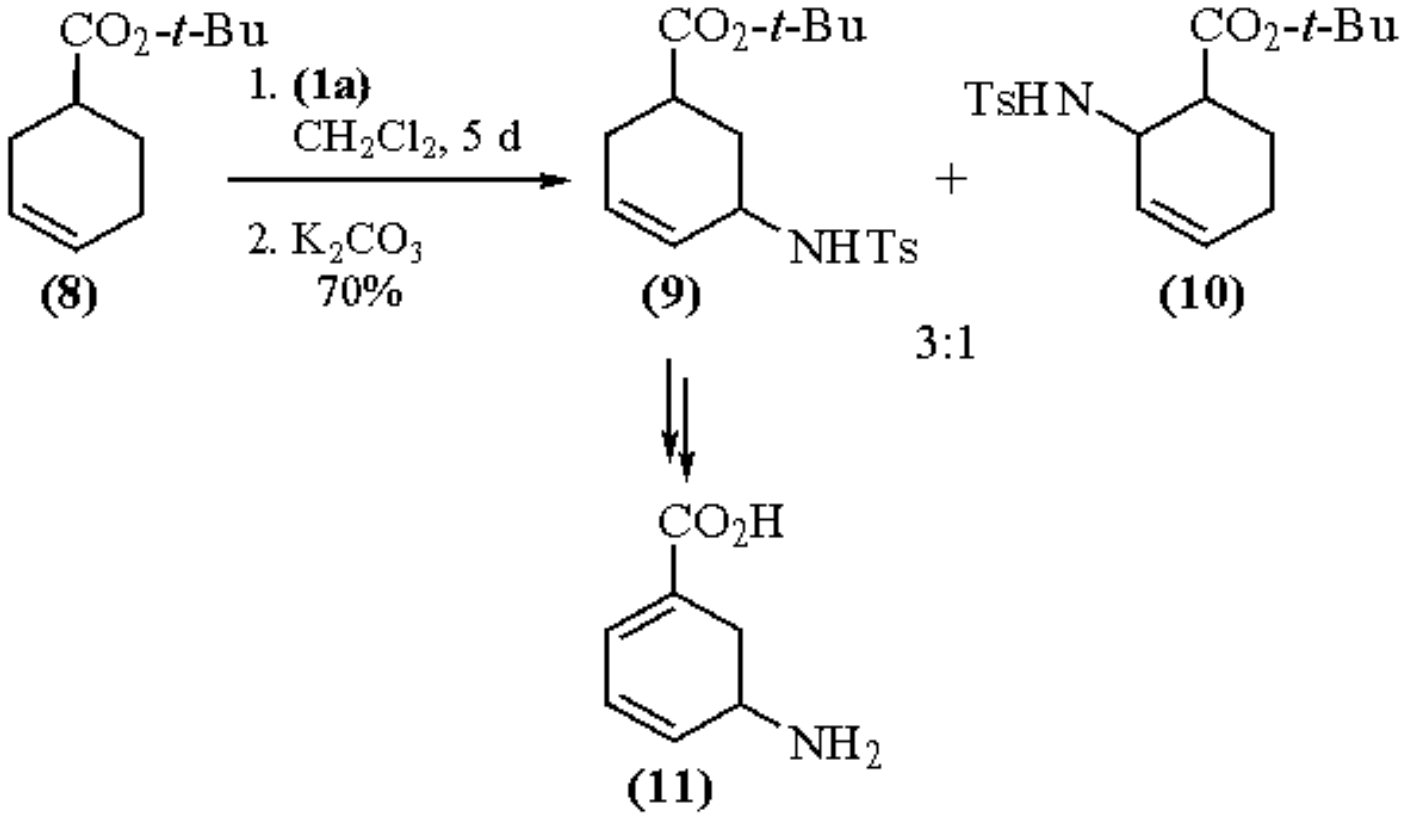

(5)

In similar fashion, the allylic sulfonamide moiety was also introduced in a synthesis of *N*-tosyldaunosamine (**12**), a derivative of the carbohydrate daunosamine (eq 6).[8]

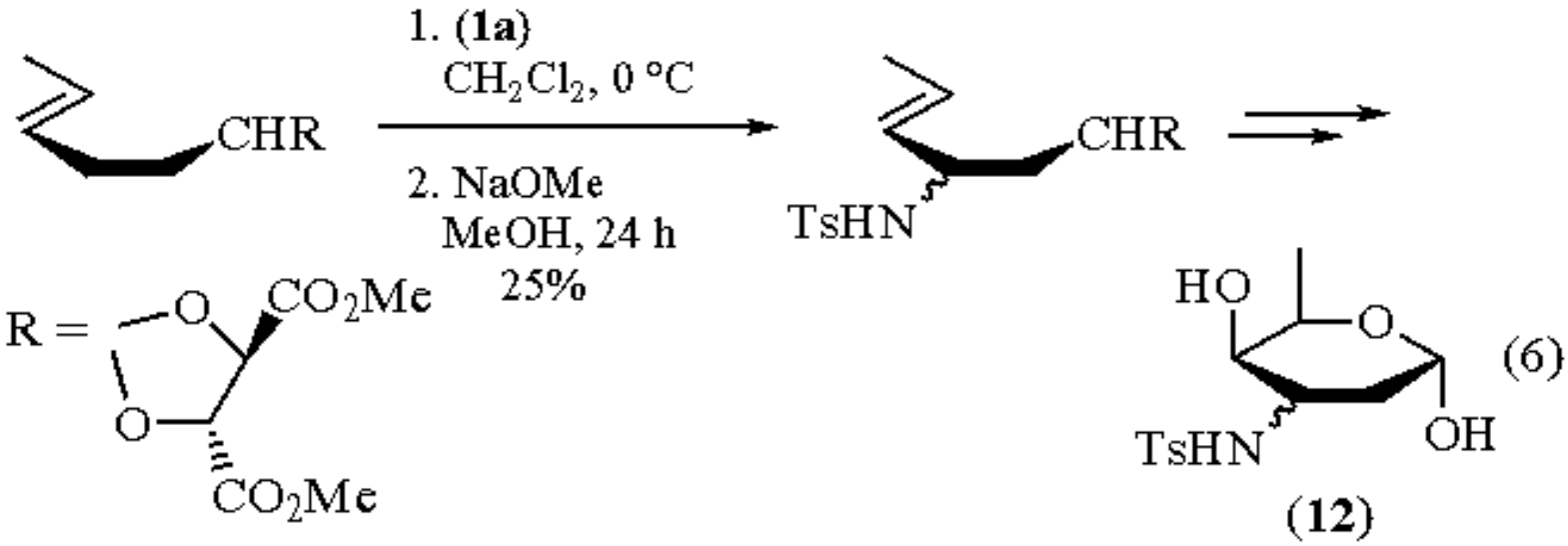

(6)

In a unique synthesis of functionalized 1,2,5-selenadiazole rings, homoallylic sulfonamide (**13**) was combined with (**1a**) to give bis(sulfonamide) (**14**) in 50% yield (eq 7).[9] This sequence represents an extension of the methodology of Sharpless and Kresze to an alkenic substrate which already contains a sulfonamide group on the homoallylic carbon (see above).

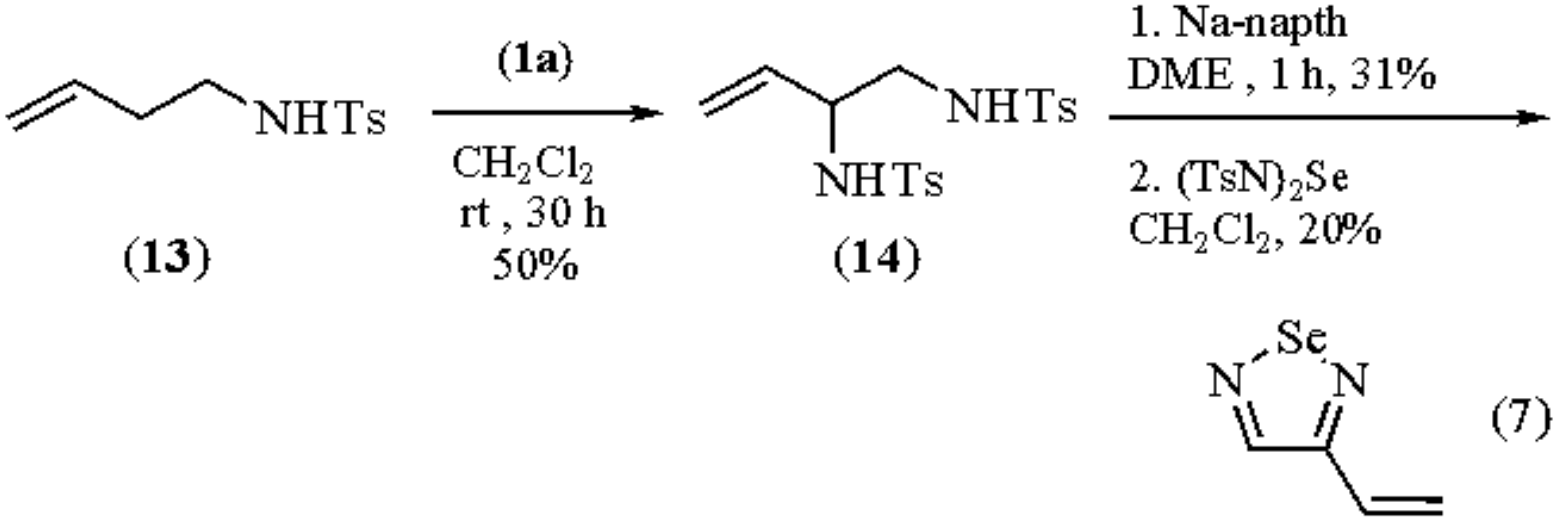

Diels-Alder Reactions.

Sulfur diimide (**1a**) is a highly reactive dienophile in regioselective [4 + 2] cycloadditions of unsymmetrical dienes.[1b,2,10] For instance, the Diels-Alder reaction of (**1a**) with (*E*)-piperylene (eq 8) and isoprene (eq 9) afforded C-3 and C-5 substituted 3,6-dihydrothiazin-1-imines, respectively, while chloroprene gave the 5-substituted cycloadduct (eq 10).[11]

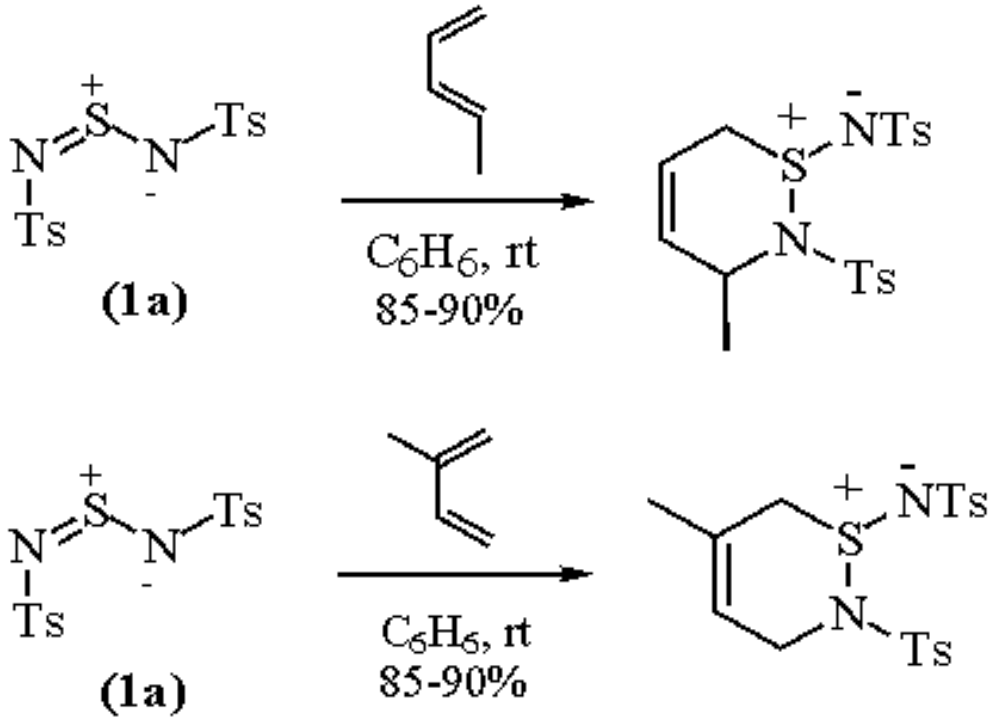

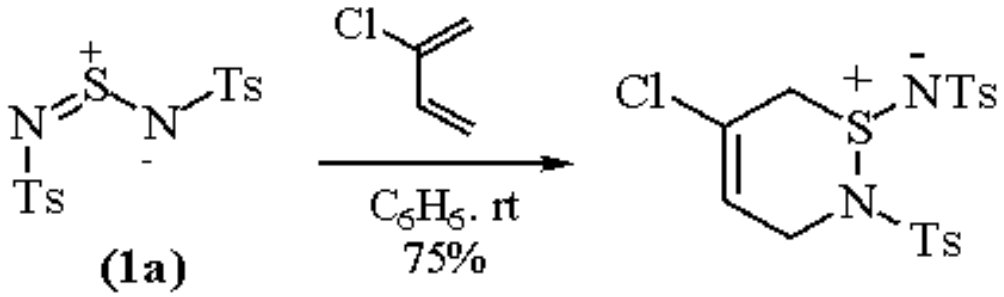

(10)

As an application of this methodology, (*E*,*E*)-2,4-hexadiene and (**1a**) react in benzene to produce a separable mixture of 3,6-dihydrothiazin-1-imines (**15a**) and (**16a**) (91%) in a 1.1:1 ratio,[12] while the cycloaddition with the bis(carbamate) (**1b**) afforded a 1:8 mixture of adducts (**15b**) and (**16b**), respectively (eq 11).[13] This Diels-Alder strategy was also applied to isomeric (*E*,*Z*)-2,4-hexadiene. Reaction of this diene with (**1a**) gave a 1:7 mixture of cycloadducts (**17a**) and (**18a**) (75%), while addition of bis(carbamate) (**1b**) to (*E*,*Z*)-2,4-hexadiene yielded 2.4:1 mixture of adducts (**17b**) and (**18b**) (65%) (eq 12).

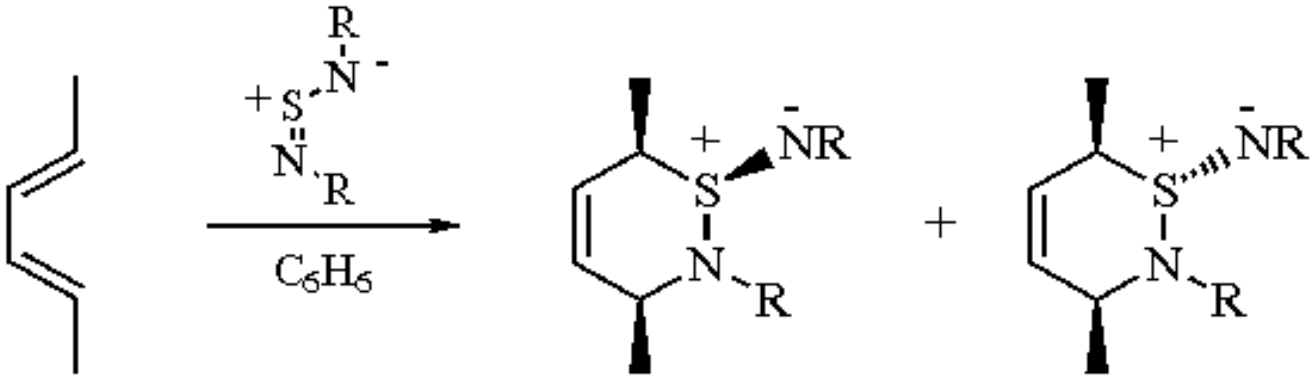

(11)

(**15**) (**16**)

R:	**a** = Ts	91%	1.1:1
	b = CO_2Me	71%	1:8

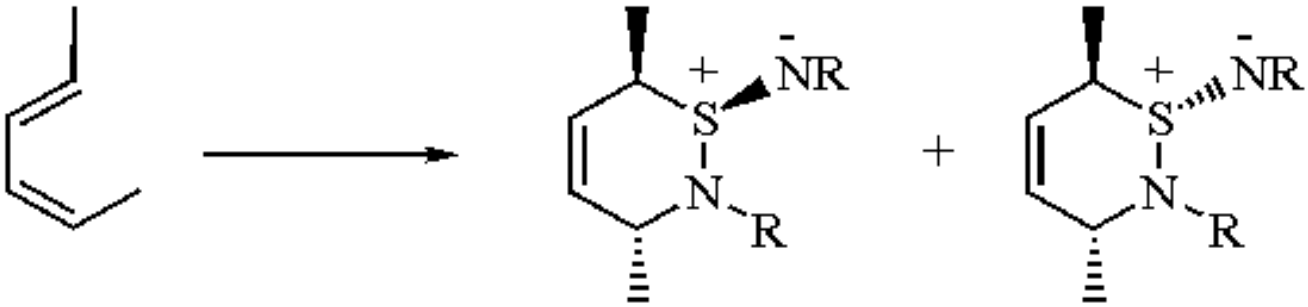

(12)

(**17**) (**18**)

R:	**a** = Ts	75%	1:7
	b = CO_2Me	65%	2.4:1

The 3,6-dihydrothiazin-1-imines generated from these hetero Diels-Alder processes were shown to be valuable intermediates in the stereocontrolled synthesis of unsaturated vicinal diamines.[12] Refluxing *cis*-dihydrothiazine-1-imines (**15**) and (**17**) (in either the sulfur diimide series or the bis(carbamate) series) in benzene stereoselectively produced stable thiadiazolidines (**19**) and (**21**) (eqs 13 and 14), respectively, via a novel transannular [2,3]-sigmatropic process.[13] Reduction of (**19**) and (**21**) with ***Sodium Borohydride*** gave (*E*)-*threo* vicinal diamine derivative (**20**) and (*E*)-*erythro* compound (**22**), respectively, in excellent yields.

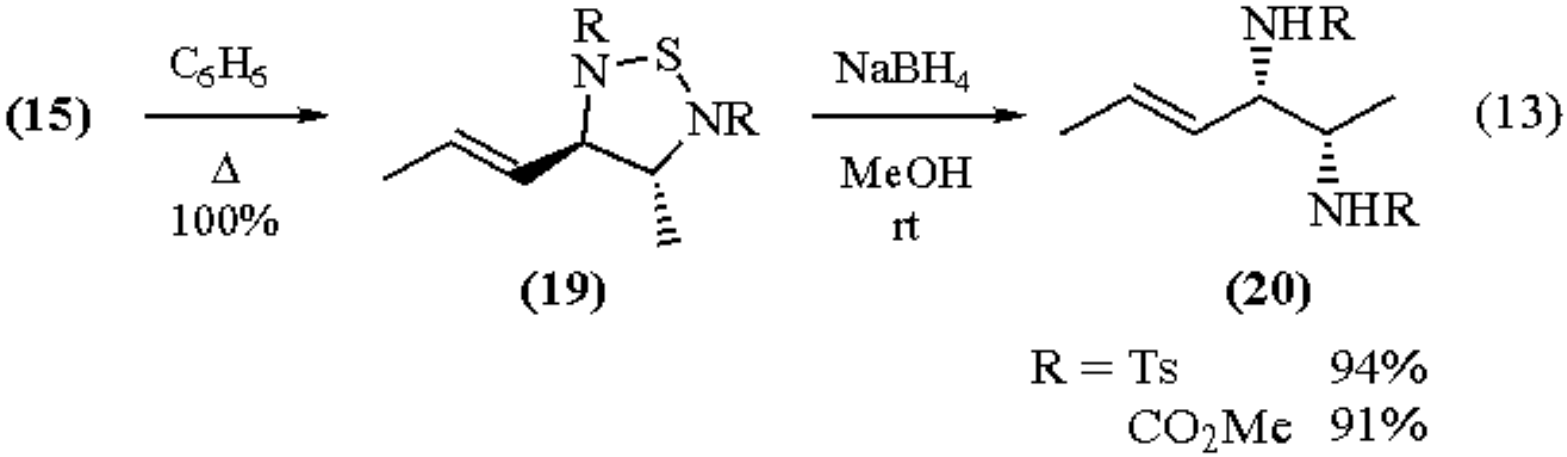

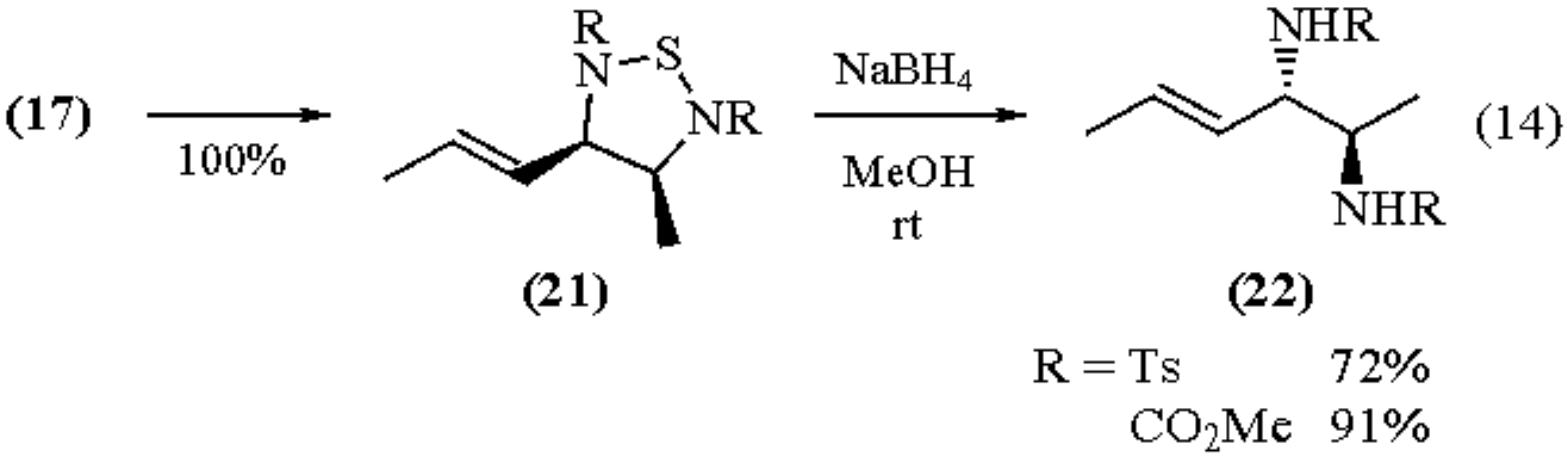

In contrast, *trans*-dihydrothiazin-1-imines (**16**) and (**18**) (in both the sulfur diimide and bis(carbamate) series) reacted with ***Phenylmagnesium Bromide*** to give initial allylic sulfinimine products which underwent facile [2,3]-sigmatropic rearrangement through an envelope-like transition state to afford sulfenamides (**23**) and (**24**) (eqs 15 and 16), respectively.[13] Desulfurization of sulfenamides (**23**) and (**24**) with ***Trimethyl Phosphite*** cleanly afforded the corresponding protected diamines in good yields.

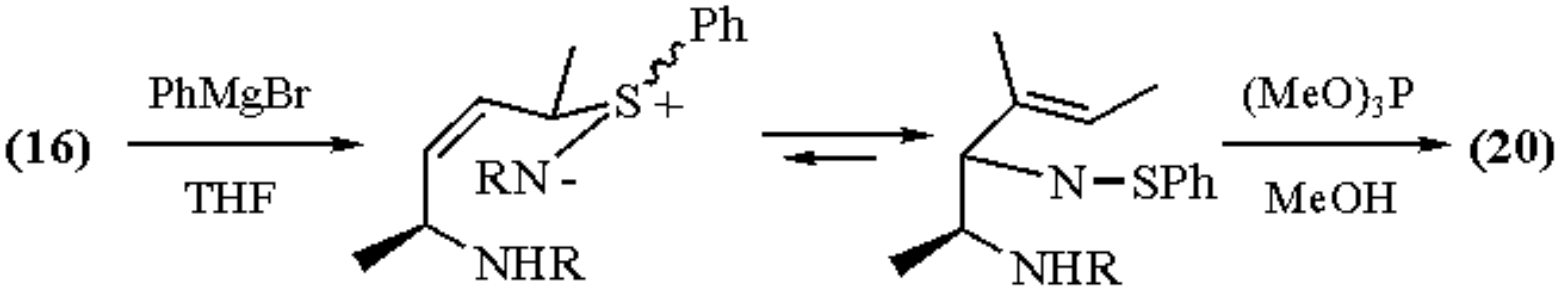

(23) R = Ts 83%
CO_2Me 92%

(15)

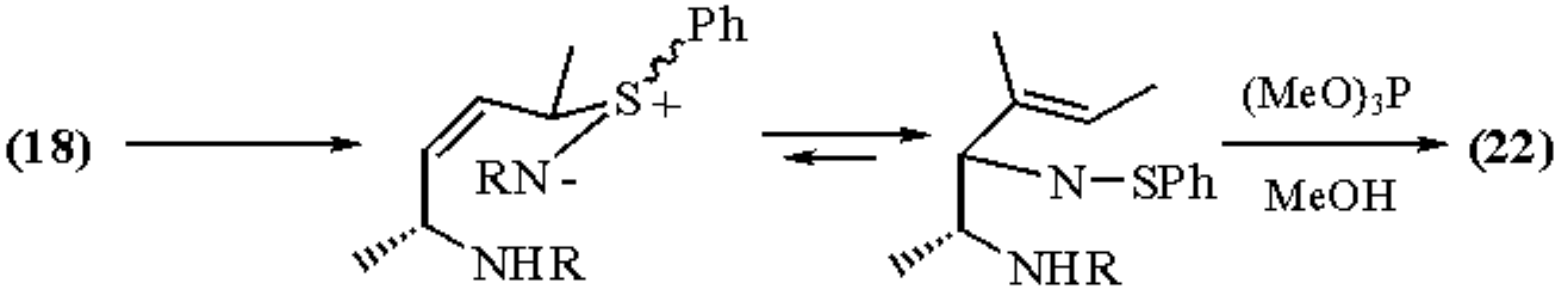

(24) R = Ts 71%
CO_2Me 94%

(16)

The methodology for the stereoselective synthesis of unsaturated vicinal diamines was also applied in an attempted total synthesis of biotin (**25**).[14] The Diels-Alder cycloaddition of (*E*,*E*)-diene (**26**) with (**1b**) occurred in high yield to produce a 7.7:1 mixture of epimeric 3,6-dihydrothiazin-1-imines (**27**) and (**28**) (eq 17). Heating adducts (**27**) and (**28**) in toluene induced the [2,3]-sigmatropic rearrangement, giving thiadiazolidines (**29**) and (**30**) in quantitative yield (eq 18). The mixture was readily separated and thiadiazolidine (**29**) was reduced, cyclized, and protected to afford urea (**31**) which unfortunately could not be converted to biotin.

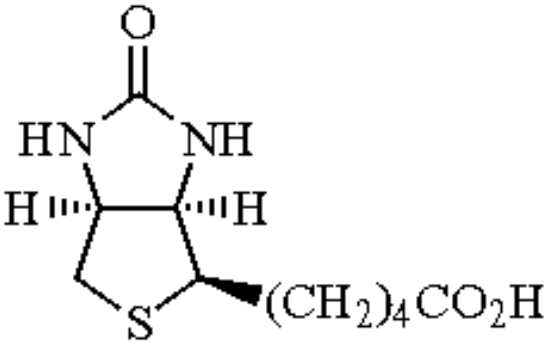

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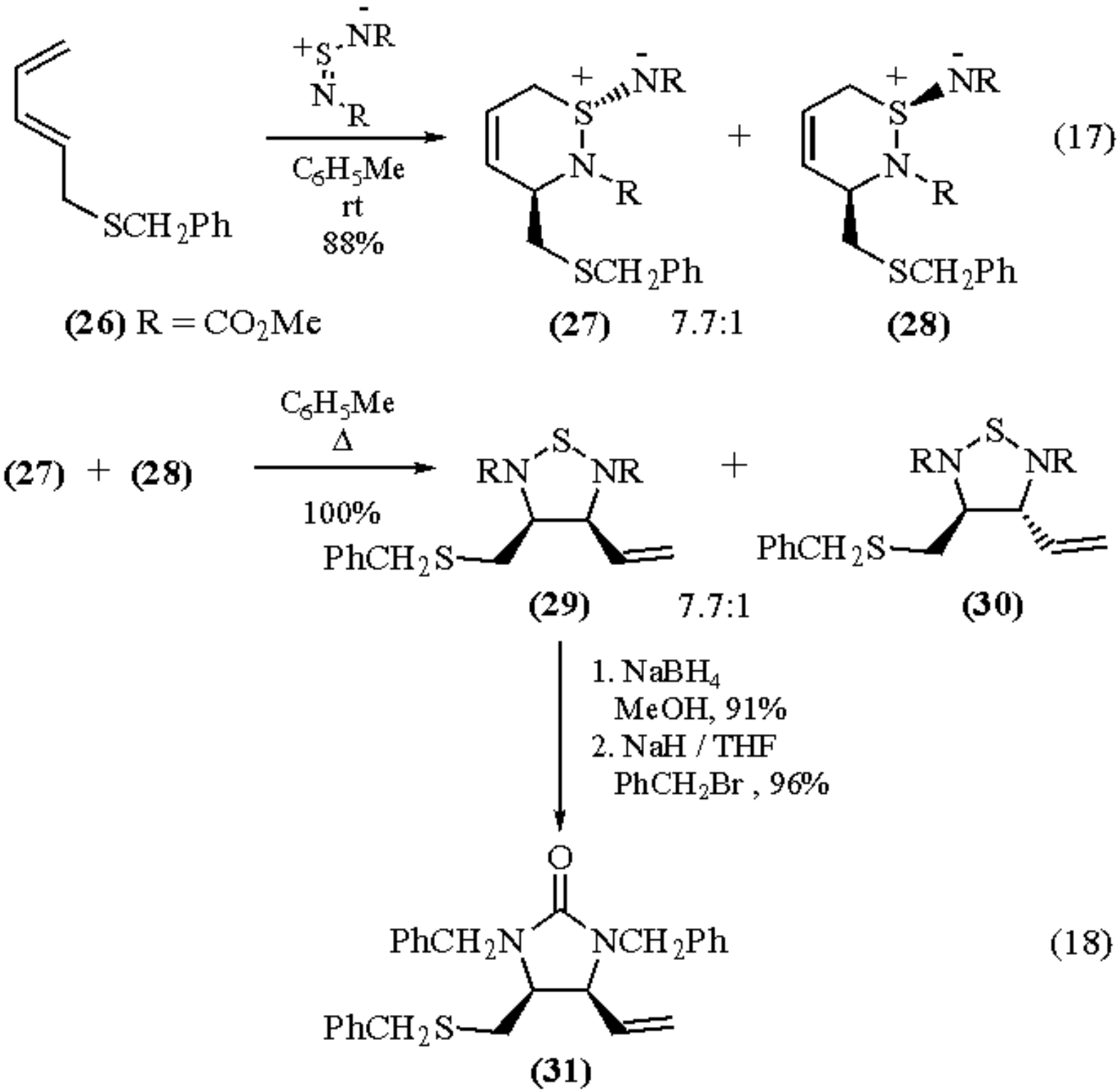

Other Cycloaddition Reactions.

Sulfur diimide (**1a**) and vinyl ether (**32**) combine to afford an unstable [2 + 2] cycloadduct which spontaneously undergoes a [1,5]-hydrogen shift to produce substituted diaminosulfane (**33**) (eq 19).[4]

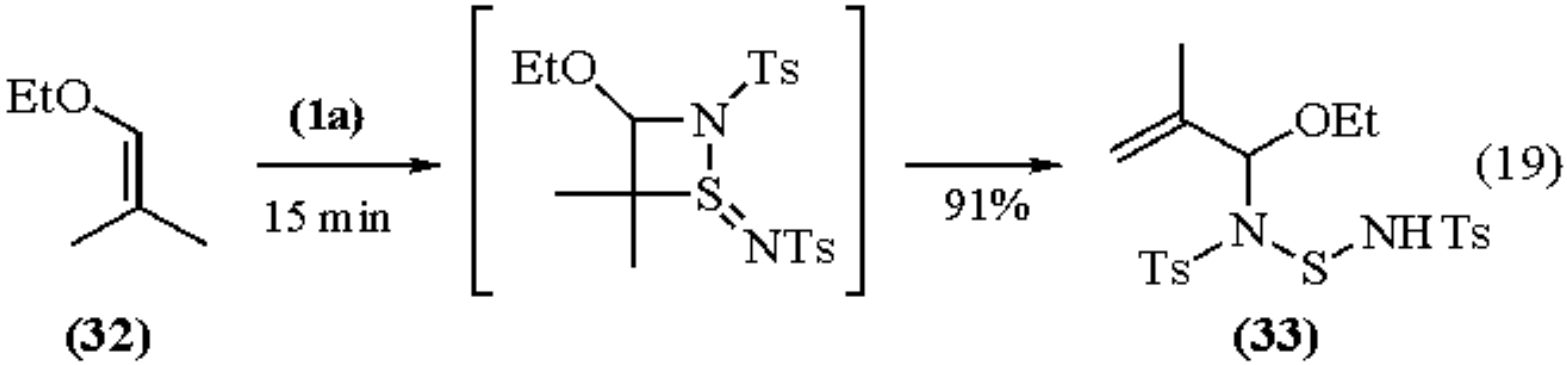

It has been shown that the periselectivity between ene reactions and [2 + 2] cycloadditions is delicately influenced by alkene geometry and stereoelectronic effects of the substituents.[1a] However, the periselectivity between a [2 + 2] and a [3 + 2] cycloaddition pathway was found to be dependent on the reaction temperature. For instance, if (**1a**) is added to diphenylketene at -15 °C, a reversible [2 + 2] cycloaddition takes place (eq 20), but at higher temperatures a [3 + 2] cycloaddition was observed (eq 21).[15]

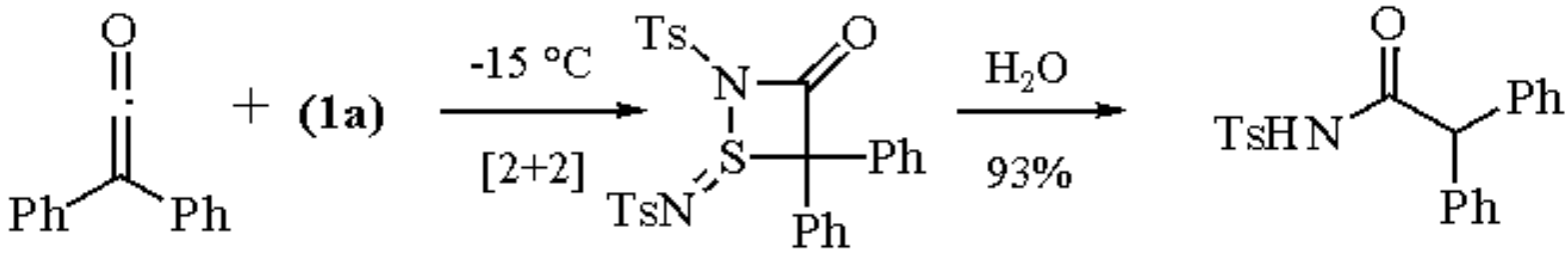

(20)

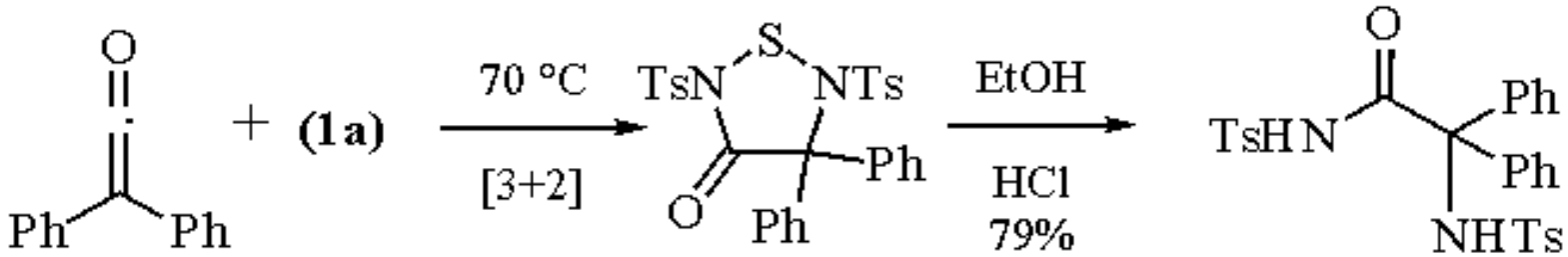

(21)

Another illustration of a rare [3 + 2] cycloaddition of (**1a**) is the reaction with diphenylfulvene to give cycloadduct (**34**), albeit in only 30% yield (eq 22).[16]

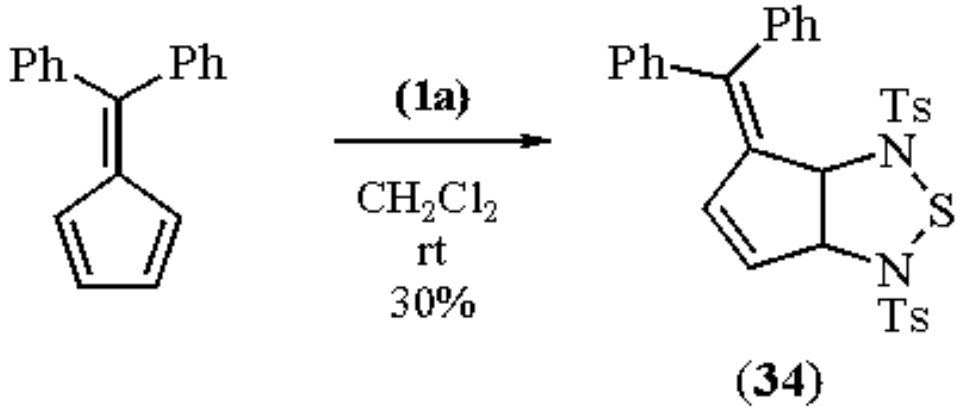

(22)

Sulfur diimide (**1a**) also cycloadds to ynamines in a [2 + 2] process in a novel synthesis of 1,4-diaza-1,3-butadienes (eq 23).[17]

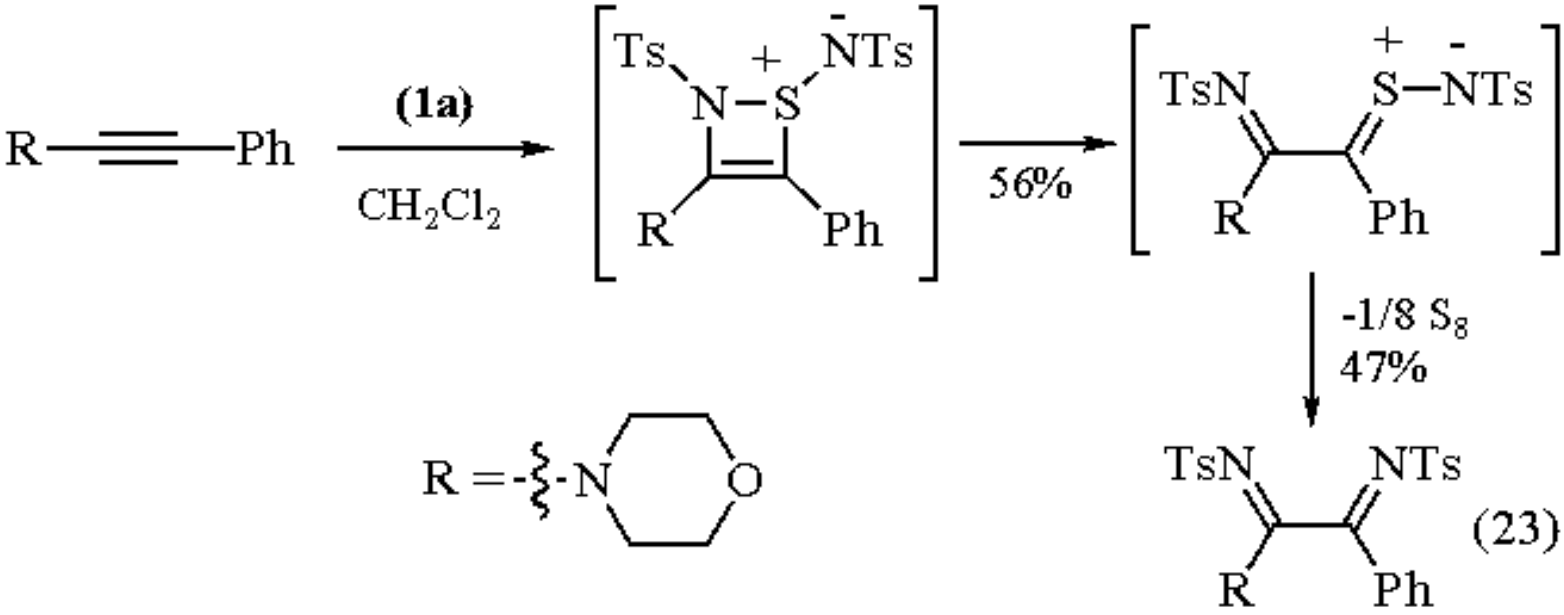

(23)

N,N´-Ditosyltellurodiimide.

Sulfur diimide (**1a**) and the corresponding selenodiimide (see ***Bis[N-(p-toluenesulfonyl)]selenodiimide***) have been utilized to synthesize *N*-tosylimines, but both procedures can occasionally suffer a lack of chemoselectivity since these reagents both also undergo Diels-Alder and ene reactions. Trost has developed an analogous procedure using tellurodiimide (**36**) (eq 24)[18] which does not undergo these undesired side reactions. Tellurodiimide (**36**), generated from ***Tellurium*** metal and ***Chloramine-T***, was combined with aldehyde (**35**) to afford *N*-tosylimine (**38**), presumably via a cycloaddition to a four-membered ring (**37**) followed by cycloreversion (eq 24).

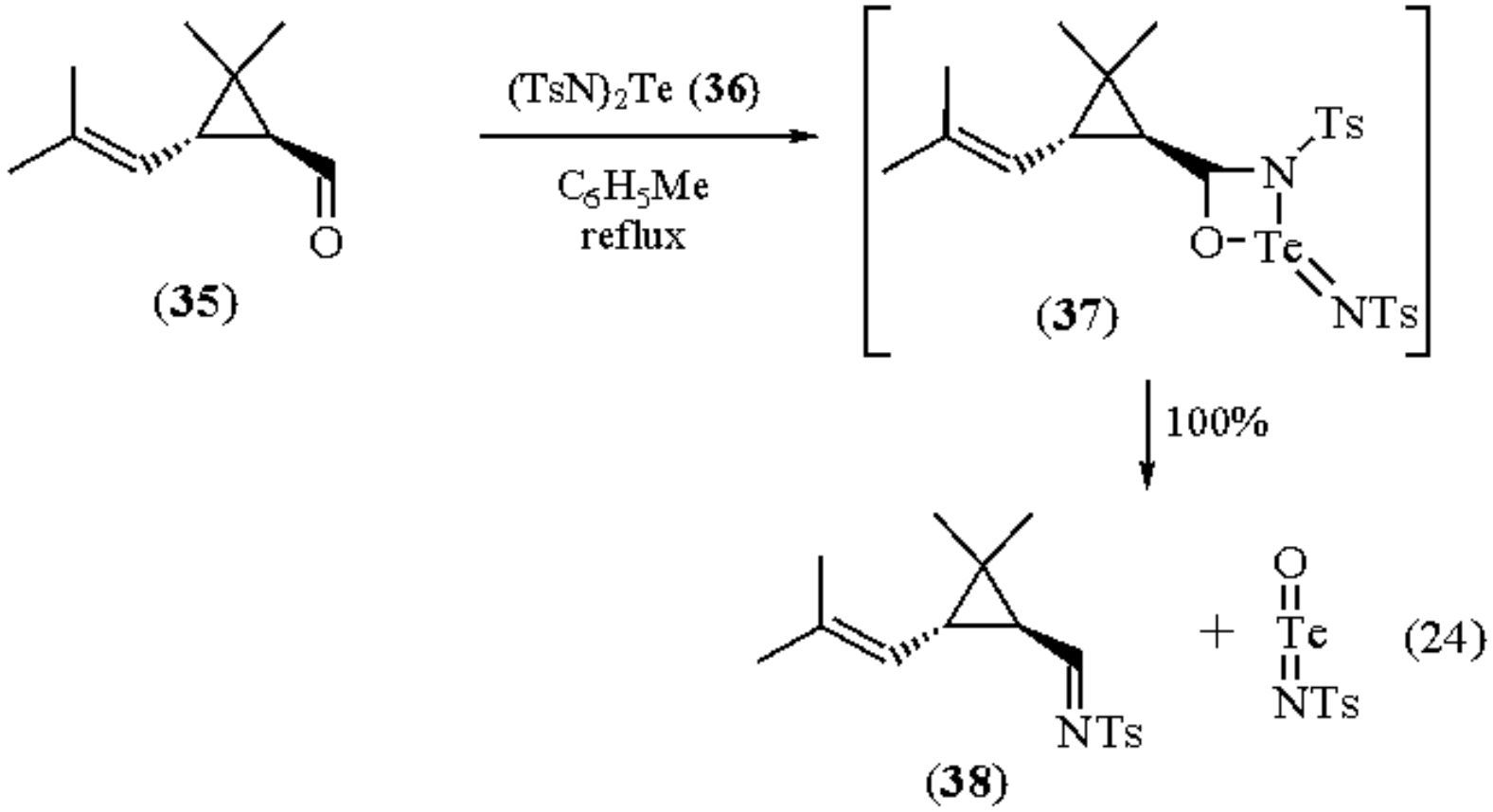

Related Reagents.

Bis[N-(p-toluenesulfonyl)]selenodiimide; ***N-Sulfinyl-p-toluenesulfonamide***.

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trans-1,2-Bis(tributylstannyl)ethylene[1]

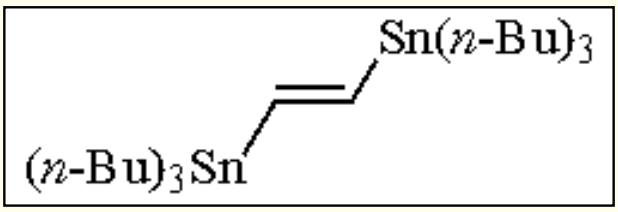

[14275-61-7] · $C_{26}H_{56}Sn_2$ · *trans*-1,2-Bis(tributylstannyl)ethylene · (MW 606.11)

(versatile vinyl anion synthon: efficiently monotransmetalated by alkyllithium reagents[2] and higher order organocuprates;[7,8] palladium-catalyzed coupling with a variety of electrophilic partners affords substituted vinylstannanes)

Physical Data: bp 170-86 °C/0.3 mmHg;[3a] colorless oil; ^{1}H NMR,[3a] IR.[3a]

Solubility: sol THF, DMF.

Analysis of Reagent Purity: TLC.[4]

Preparative Method: prepared in high yield by the reductive hydrostannation of tributylstannylacetylene with ***Tri-n-butylstannane*** and catalytic ***Azobisisobutyronitrile***.[2,3a,5]

Purification: can be purified by distillation[3] or by preparative reverse-phase chromatography.[4]

Handling, Storage, and Precautions: organostannane reagents are potentially toxic.[6] Their preparation and use must therefore be conducted, wearing appropriate protective clothing, in a well ventilated fume hood. The reagent should be stored under an inert atmosphere and protected from light.

Transmetalation.

Alkyllithium reagents efficiently transmetalate (*E*)-1,2-(bistributylstannyl)ethylene (**1**) to afford (*E*)-1-lithio-2-(tributylstannyl)ethylene, which exhibits reactivity typical of vinyllithium reagents.[2,3]

Higher order cyanocuprates ($Me_2CuCNLi_2$ and $Me(2\text{-Th})CuCNLi_2$) rapidly transmetalate (*E*)-1,2-(bistributylstannyl)ethylene in high yield at ambient temperature to afford the corresponding vinylcuprates ($n\text{-}Bu_3SnCH{=}CH)(Me)Cu(CN)Li_2$[7] and ($n\text{-}Bu_3SnCH{=}CH)(2\text{-Th})Cu(CN)Li_2$,[8] thus providing a very convient method for the preparation these useful reagents.[7-9]

Cross-Coupling Reactions.

Stille et al. pioneered the palladium-catalyzed cross-coupling reaction of organostannanes with a variety of electrophilic partners. These reactions proceed under mild conditions which are often compatable with typically sensitive functional groups.[1]

Palladium-catalyzed coupling of (*E*)-1,2-(bistributylstannyl)ethylene with appropriate electrophiles can afford either mono- or disubstituted products. The product distribution is readily and predictably controlled by the stoichiometry of the reactants. Coupling of (**1**) with 1 equiv of an allylic (eq 1),[10a] aromatic,[11] or vinyl halide[12] provides the corresponding substituted vinylstannane. Symmetrical stilbenes are prepared when 2 equiv of aryl halide are used.[13]

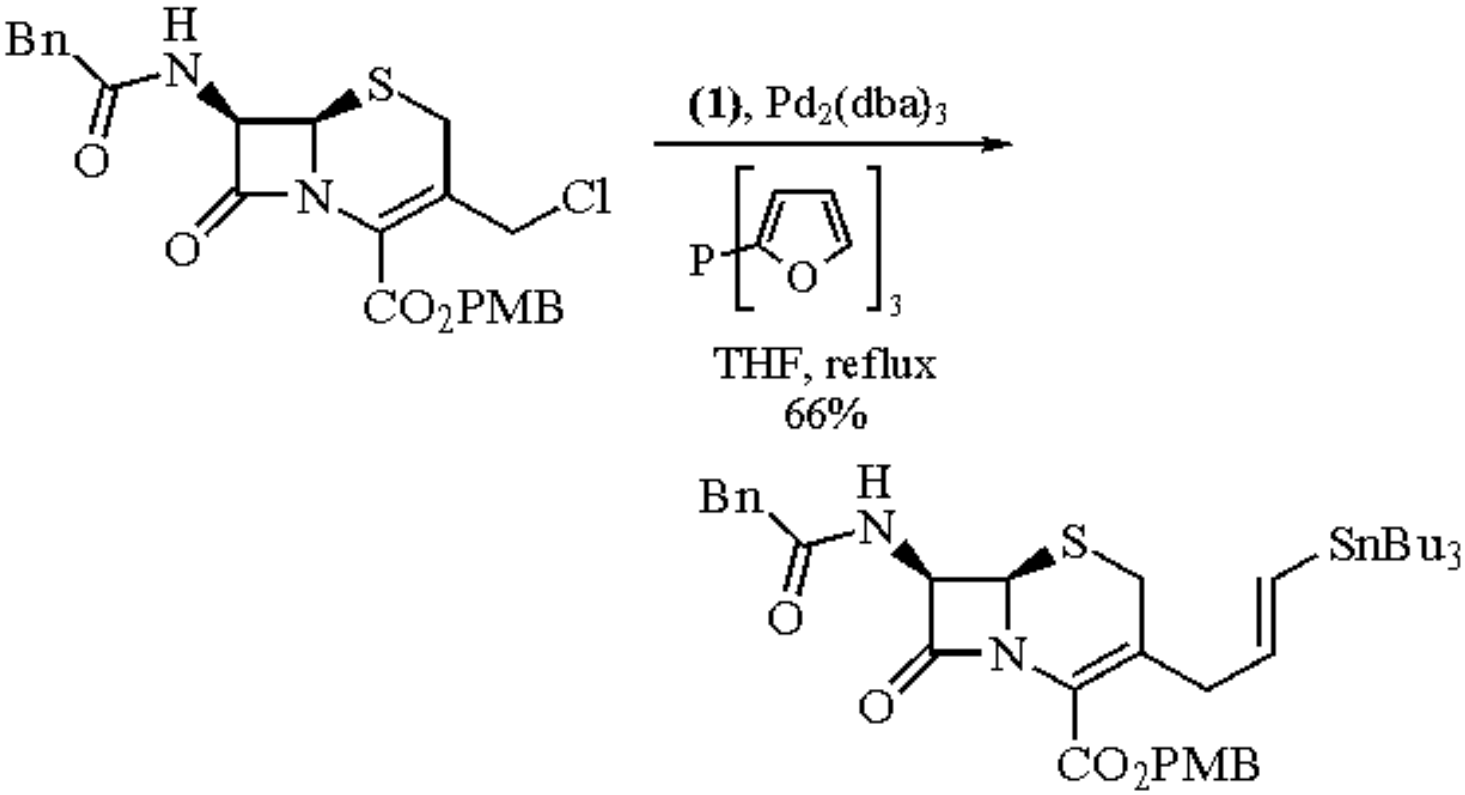

(1)

Macrocylization of the highly functionalized divinyl diiodide (**2**) (eq 2)[14] to rapamycin (**3**) is an elegant and unique example of the use of this reagent.

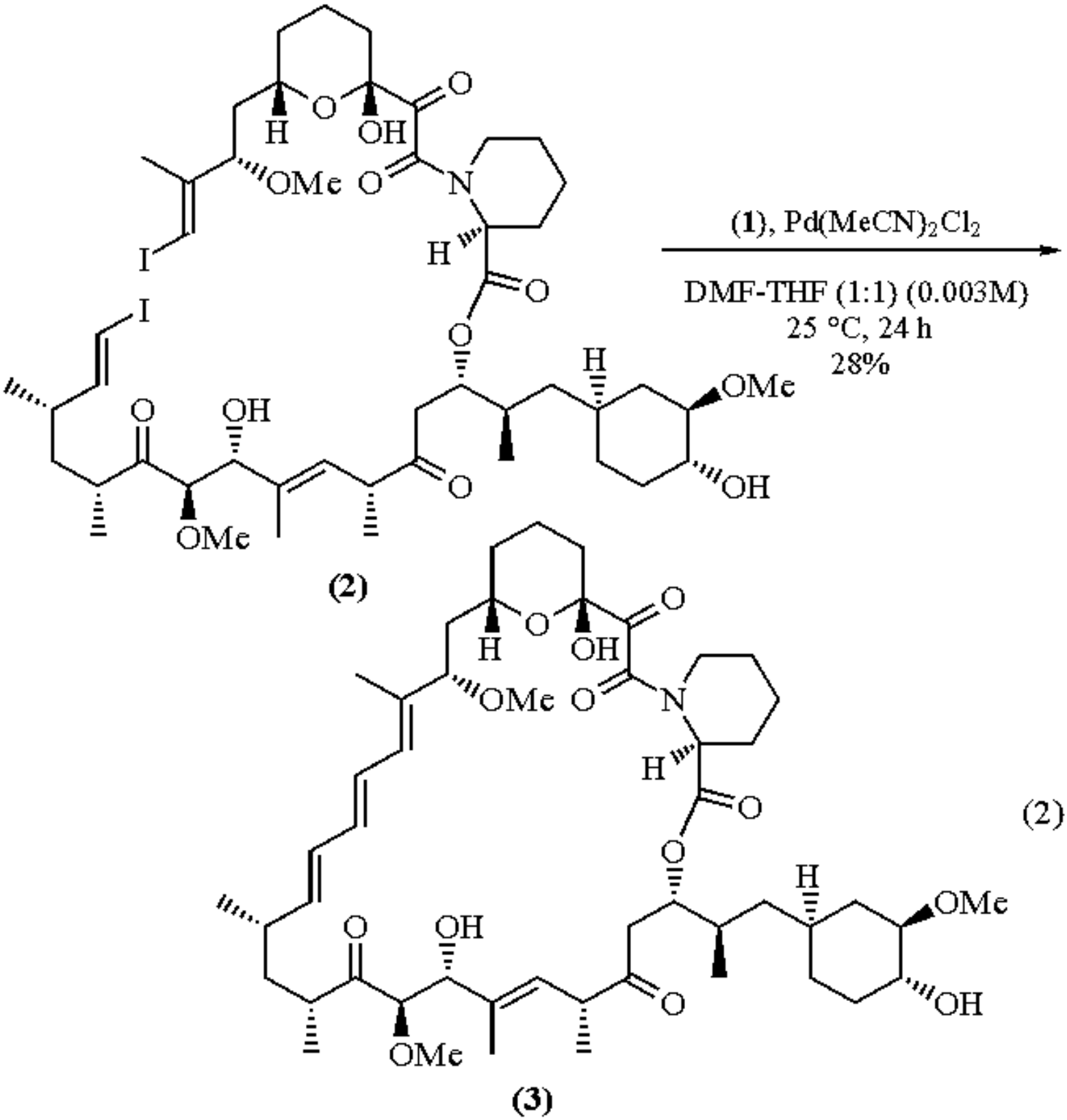

(2)

β-Stannyl enones are prepared in moderate yield by the palladium-catalyzed coupling of (*E*)-1,2-(bistributylstannyl)ethylene with acyl chlorides (eq 3).[15] Coupling of the product with a second acyl chloride provides a route to unsymmetrical 1,4-butanediones. The intermediate 1,4-butenediones are efficiently reduced in situ by a palladium hydride species generated during the course of the reaction.[15] Symmetrical 1,4-butanediones are prepared directly when 2 equiv of acid chloride are used.[15]

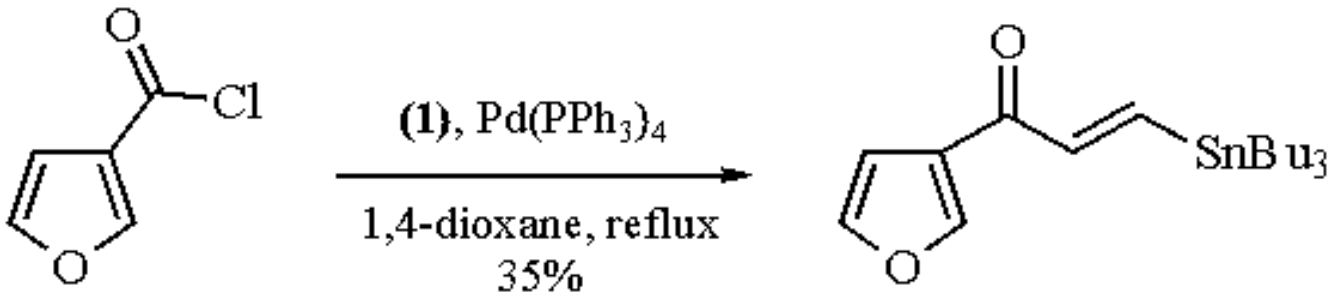

(3)

Aluminum Chloride-promoted coupling of (*E*)-1,2-bis(tributylstannyl)ethylene with acid chlorides provides an alternate, and often higher yielding, route to β-stannyl enones.[3b,16]

---

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Bis(tri-*n*-butyltin) Oxide

$(n\text{-}Bu_3Sn)_2O$

[56-35-9] · $C_{24}H_{54}OSn_2$ · Bis(tri-*n*-butyltin) Oxide · (MW 596.20)

promotes the oxidation of secondary alcohols and sulfides with Br_2; O- and N-activations; dehydrosulfurizations; hydrolysis catalyst)

Physical Data: bp 180 °C/2 mmHg; *d* 1.170 g cm^{-3}.

Solubility: sol ether and hexane.

Form Supplied in: colorless oil.

Handling, Storage, and Precautions: $(Bu_3Sn)_2O$ should be stored in the absence of moisture. Owing to the toxicity of organostannanes, this reagent should be handled in a well-ventilated fume hood. Contact with the eyes and skin should be avoided.

Oxidations.

Benzylic, allylic, and secondary alcohols are oxidized to the corresponding carbonyl compounds by using $(Bu_3Sn)_2O$-***Bromine***.[1] This procedure is quite useful for selective oxidation of secondary alcohols in the presence of primary alcohols, which are inert under these conditions (eqs 1-3).[2] $(Bu_3Sn)_2O$-***N-Bromosuccinimide*** can also be applied to the selective oxidation of secondary alcohols (eq 4).[3]

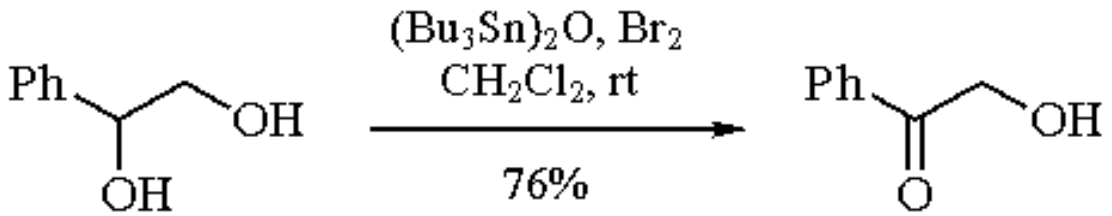

(1)

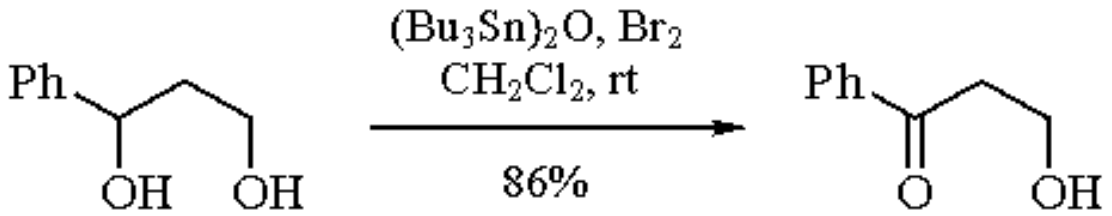

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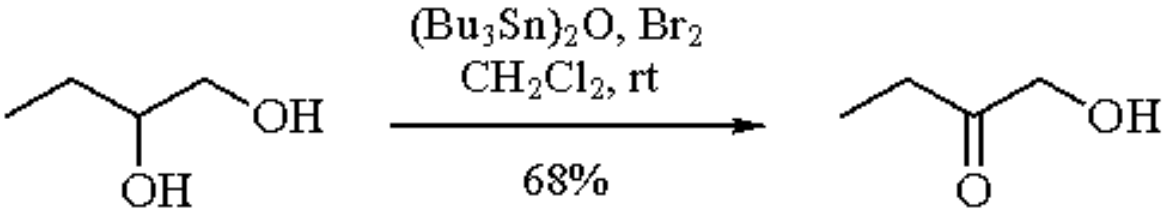

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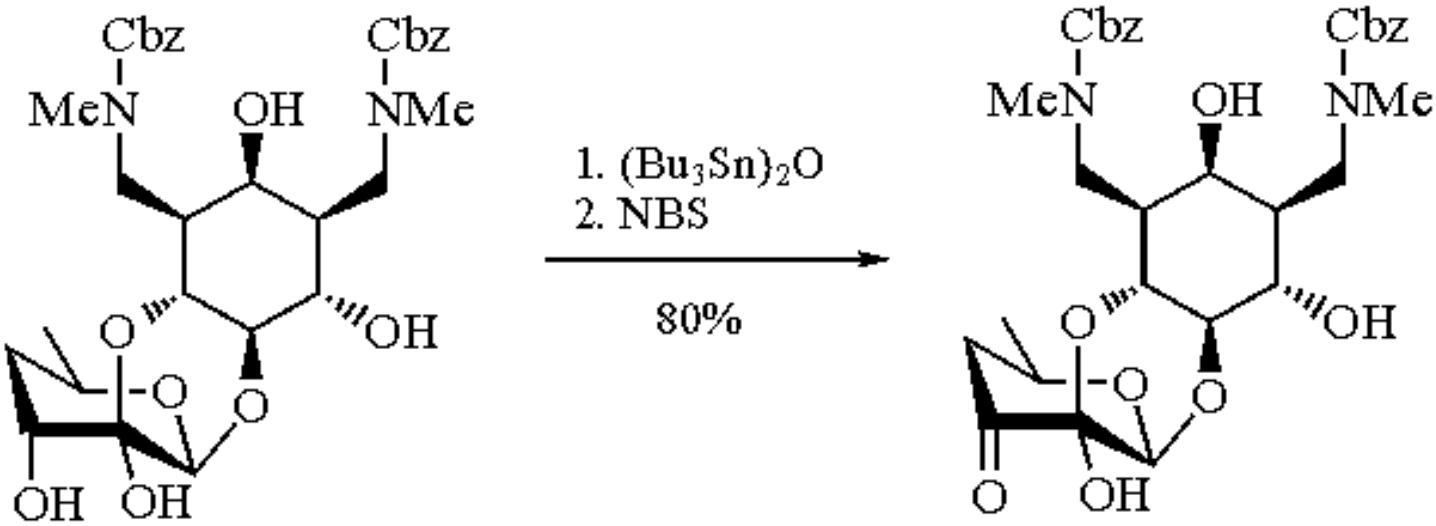

(4)

$(Bu_3Sn)_2O$-Br_2 oxidizes sulfides to sulfoxides in CH_2Cl_2 without further oxidation to sulfones, even in the presence of excess reagent (eq 5).[4] This procedure is especially useful for sulfides having long, hydrophobic alkyl chains, for which solubility problems are often encountered in the ***Sodium Periodate*** oxidation in aqueous organic solvents. Oxidation of sulfenamides to sulfinamides can be achieved without formation of sulfonamides using the reagent (eq 6).[4]

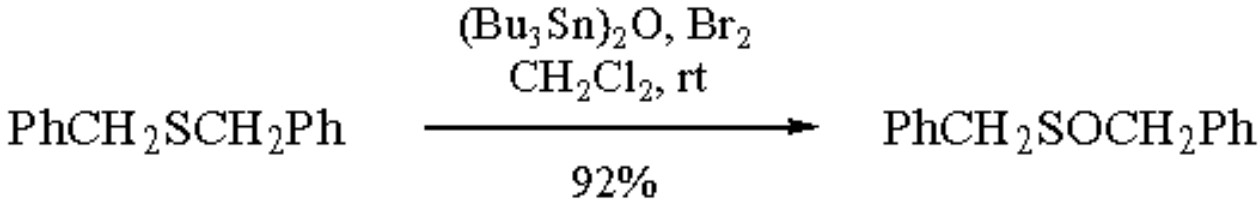

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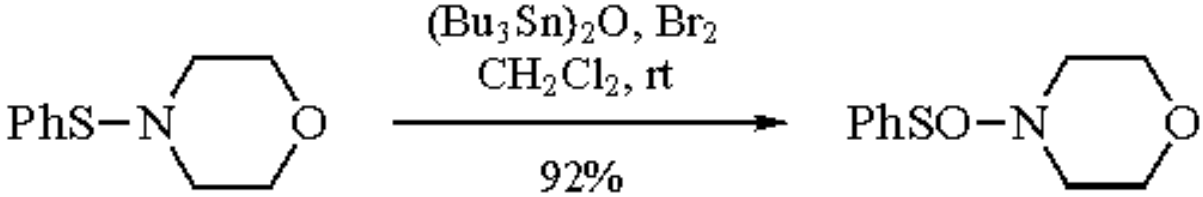

(6)

$(Bu_3Sn)_2O$-Br_2-***Diphenyl Diselenide*** in refluxing $CHCl_3$ transforms alkenes into α-seleno ketones (eq 7).[5]

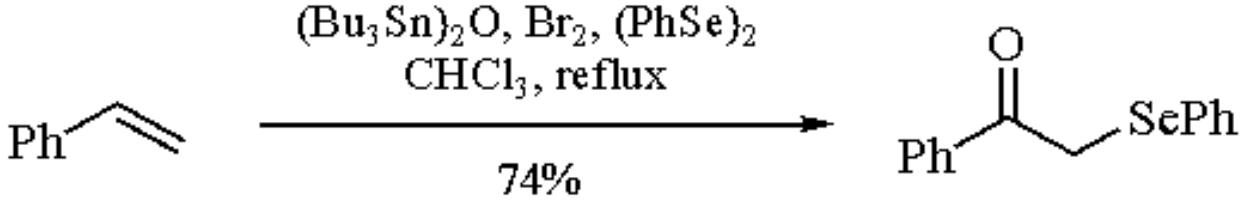

(7)

O- and N-activations.

$(Bu_3Sn)_2O$ has been used in the activation of hydroxy groups toward sulfamoylations, acylations, carbamoylations, and alkylations because conversion of alcohols to stannyl ethers enhances the oxygen nucleophilicity. Tributylstannyl ethers are easily prepared by heating the alcohol and $(Bu_3Sn)_2O$, with azeotropic removal of water. Sulfamoylation of alcohols can be achieved via tributyltin derivatives in high yields, whereas direct sulfamoylation gives low yields (eq 8).[6] This activation can be used for selective acylation of vicinal diols (eq 9).[7] In carbohydrate chemistry this approach is extremely useful for the regioselective acylation without the use of a blocking-deblocking technique (eq 10).[8] The order of the activation of hydroxy groups on carbohydrates has been investigated, and is shown in partial structures (**1**), (**2**), and (**3**).[9] Regioselective carbamoylation can also be accomplished by changing experimental conditions (eq 11).[10] On the other hand, alkylations of the tin derivatives are sluggish and less selective than acylations under similar conditions. Regioselective alkylation of sugar compounds, however, can be carried out in high yield by conversion to a tributyltin ether followed by addition of alkylating agent and quaternary ammonium halide catalysts (eq 12).[11]

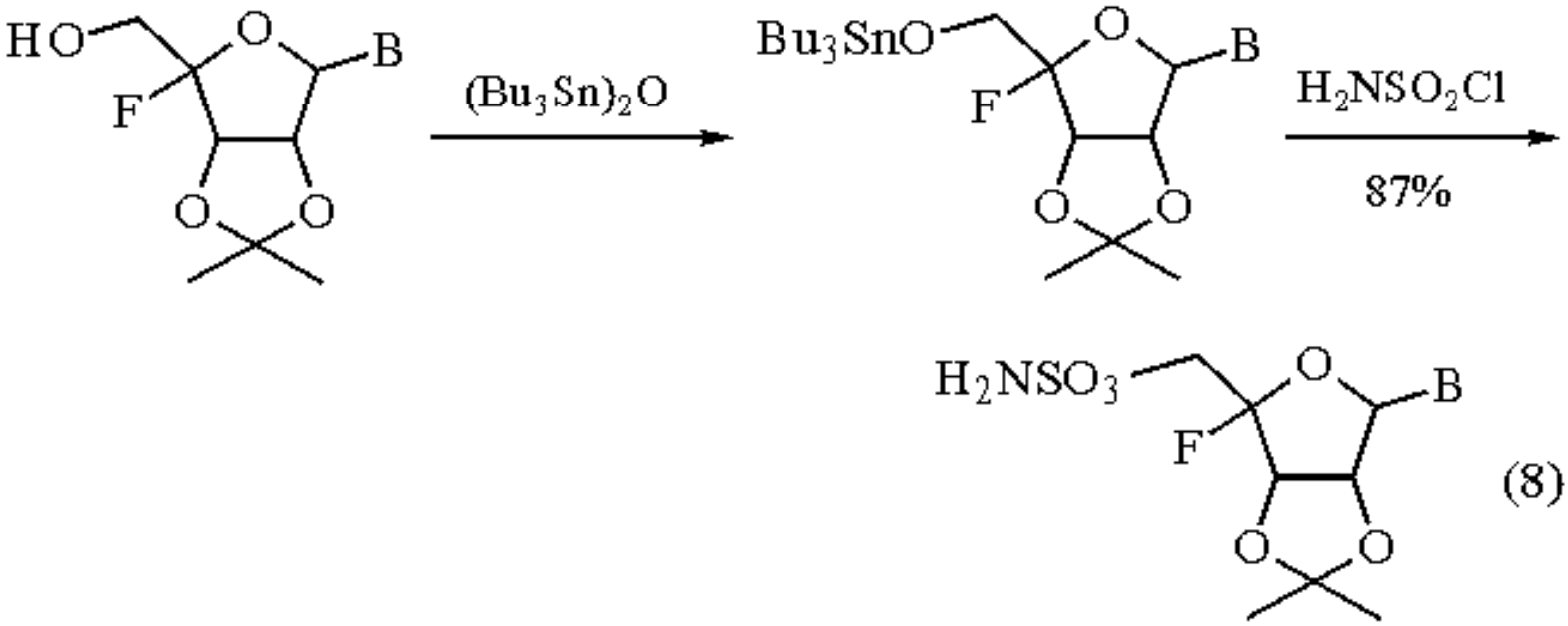

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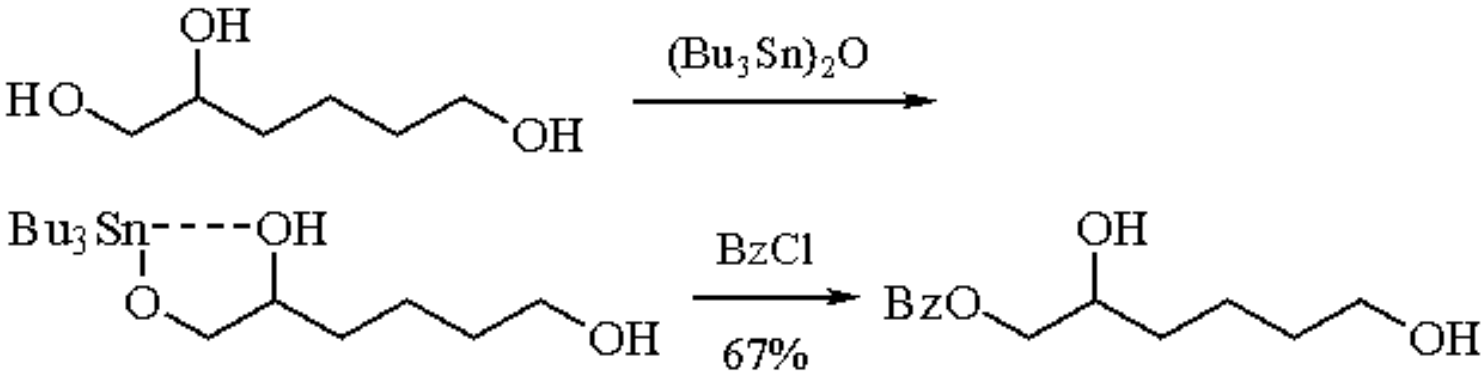

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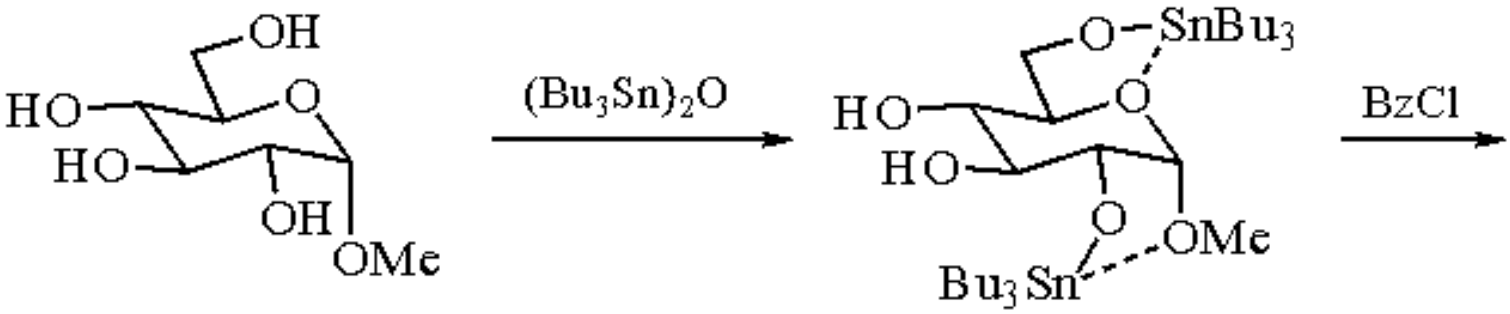

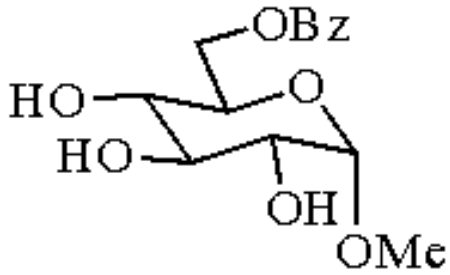

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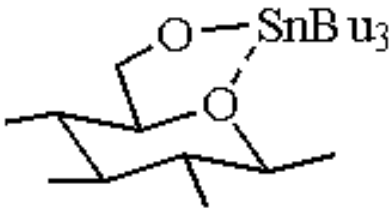

(1)
most reactive

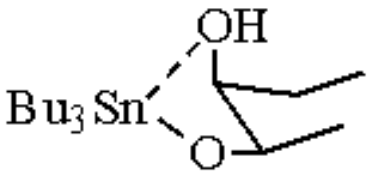

(2)
next most reactive

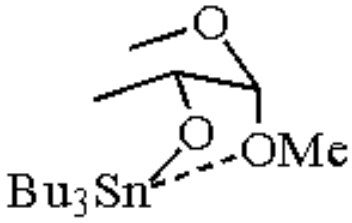

(3)
least reactive

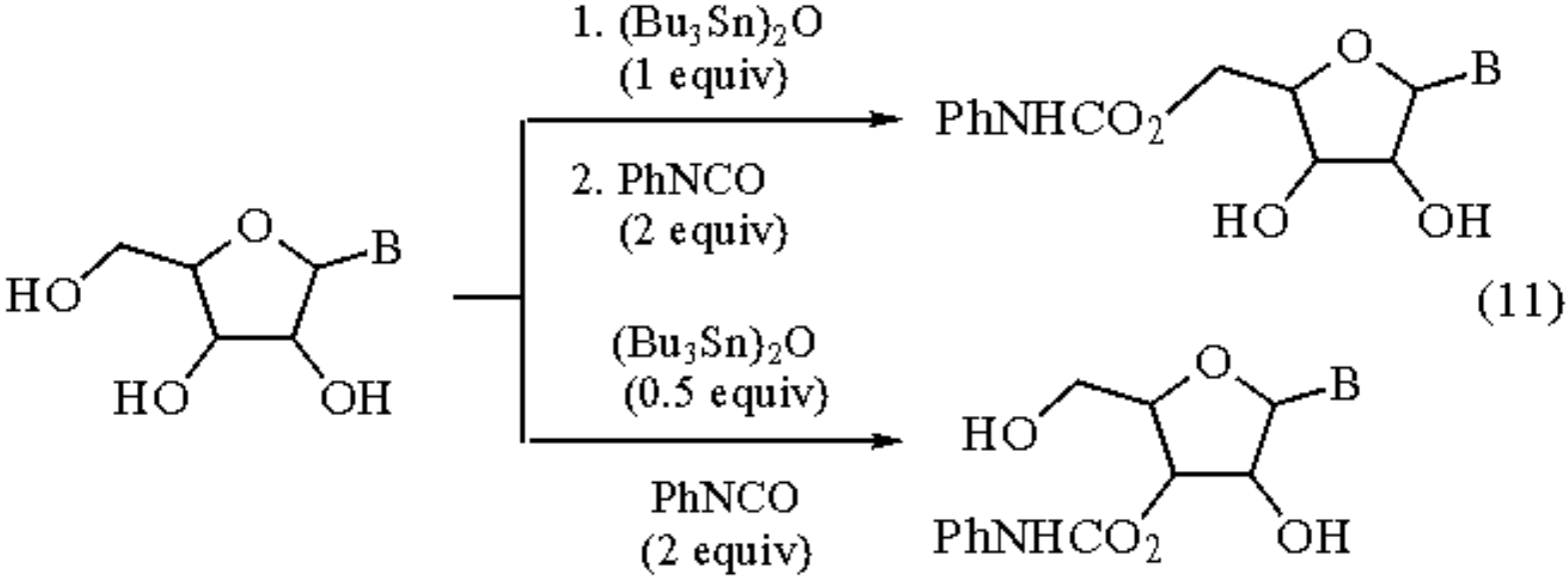

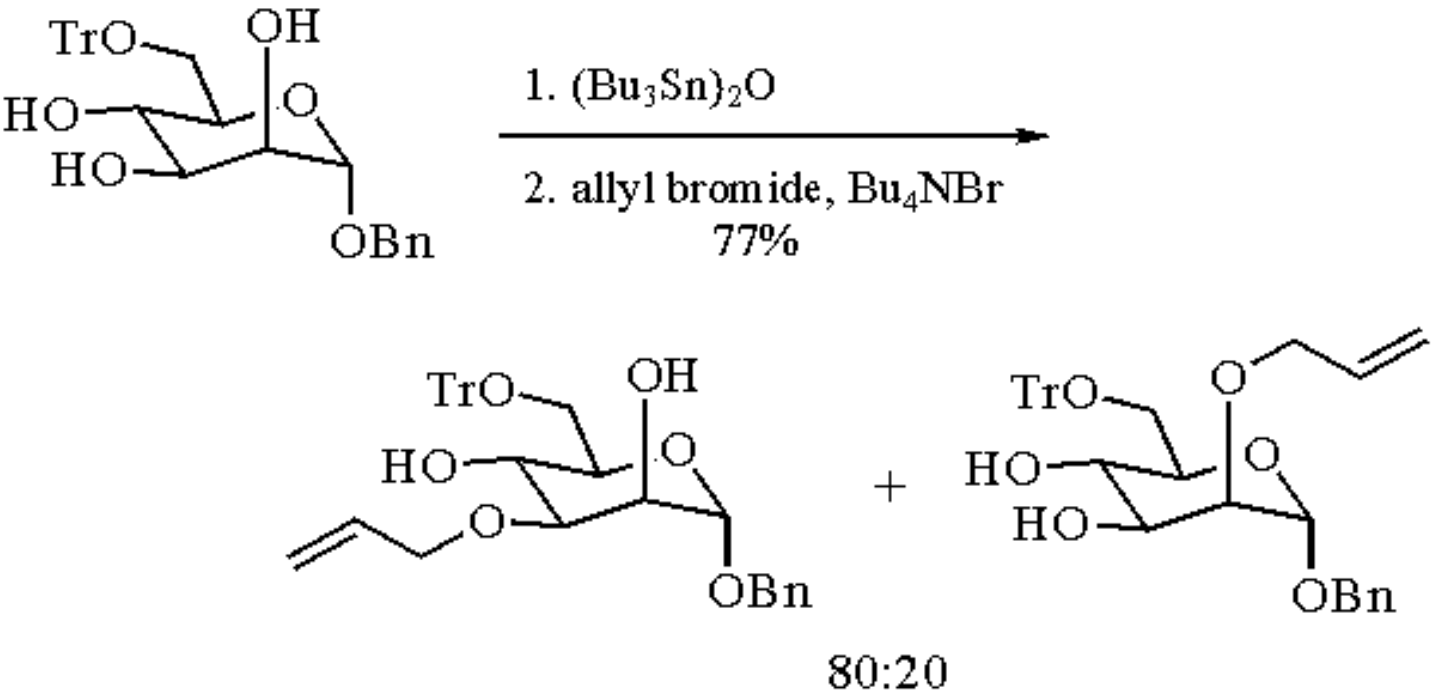

This O-activation is also effective for intramolecular alkylations such as oxetane synthesis (eq 13).[12] Similar N-activation has been used in the synthesis of pyrimidine nucleosides (eq 14).[13]

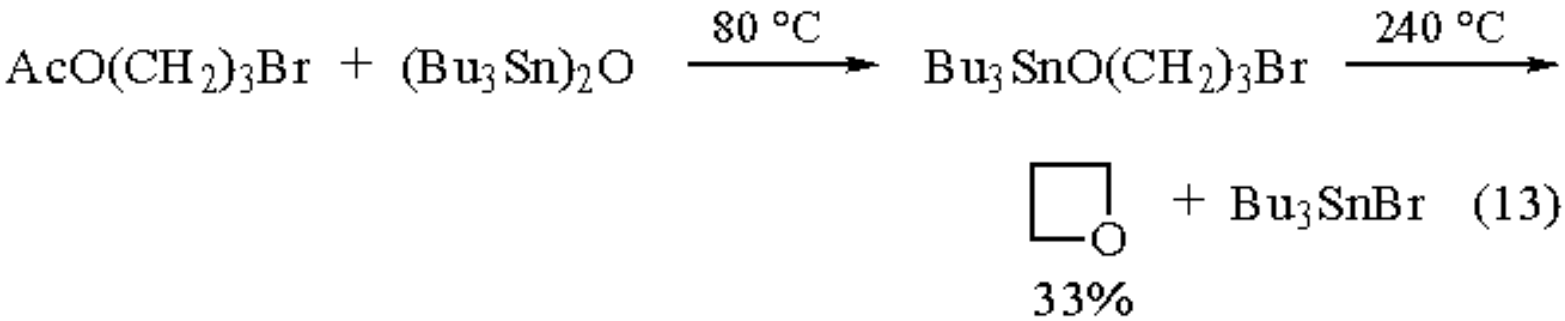

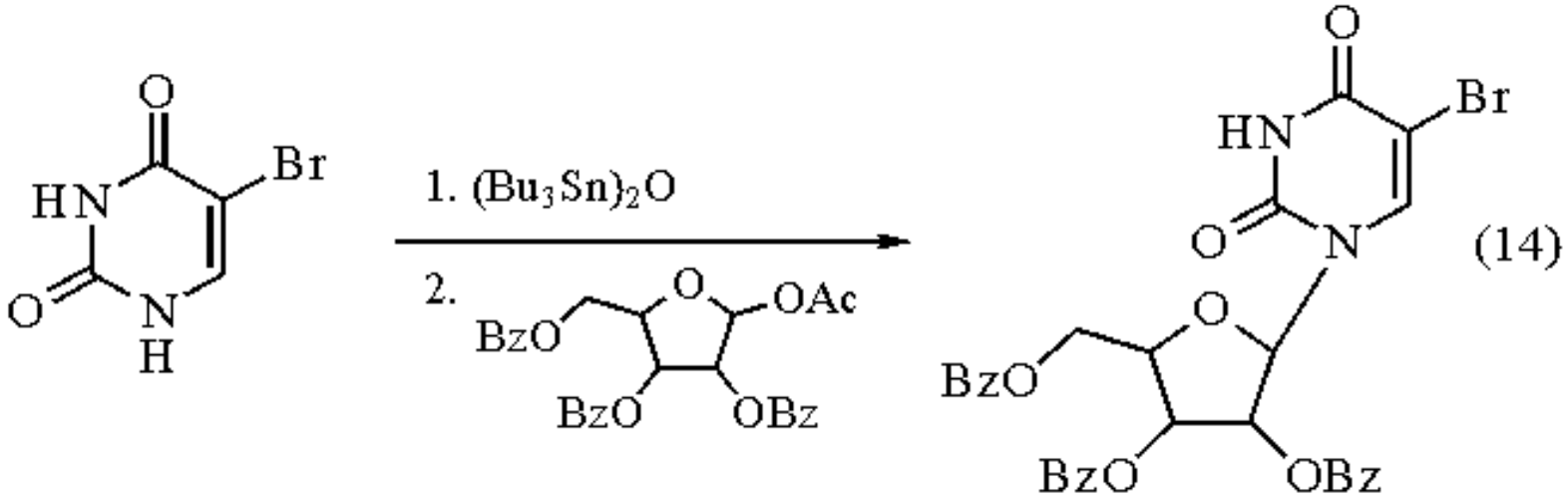

Dehydrosulfurizations.

The thiophilicity of tin compounds is often utilized in functional group transformations. Thus conversion of aromatic and aliphatic thioamides to the corresponding nitriles can be accomplished by using $(Bu_3Sn)_2O$ in boiling benzene under azeotropic conditions (eq 15).[14]

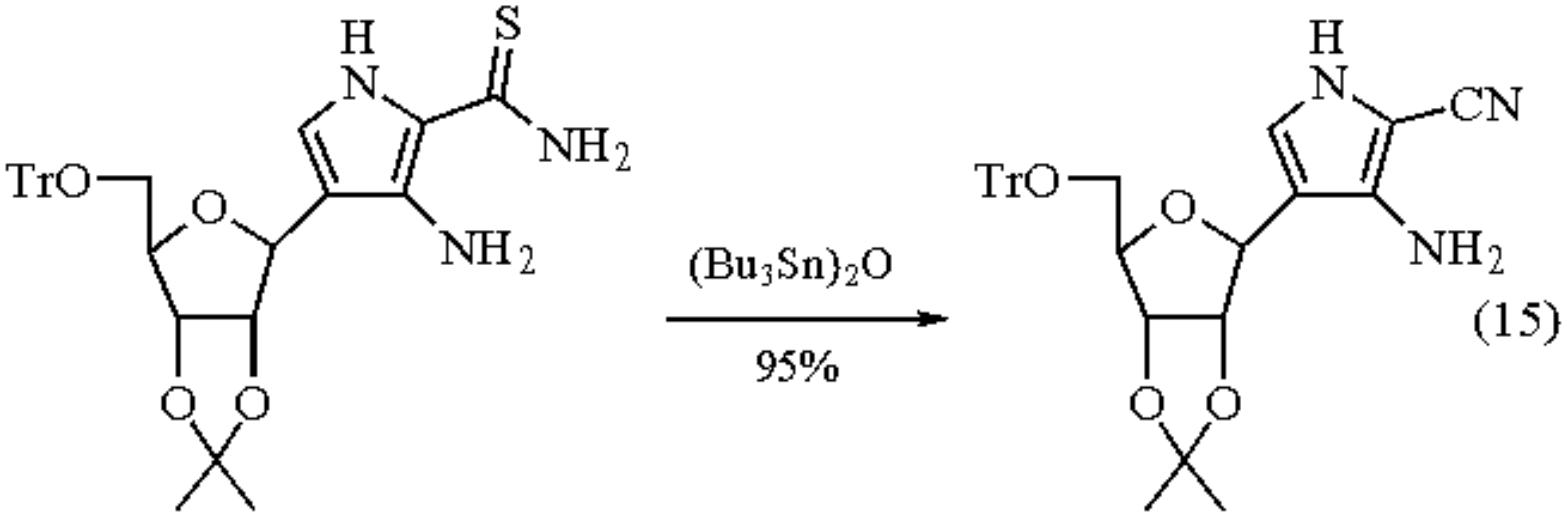

Hydrolysis.

Esters are efficiently hydrolyzed with $(Bu_3Sn)_2O$ under mild conditions (eq 16).[15]

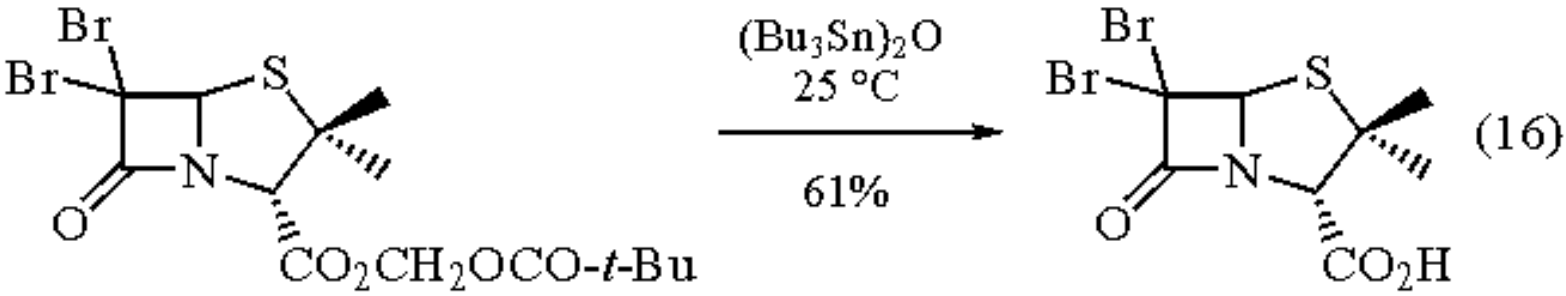

Transformation of primary alkyl bromides or iodides to the corresponding primary alcohols is achieved in good yield by using $(Bu_3Sn)_2O$-***Silver(I) Nitrate*** (or ***Silver(I) p-Toluenesulfonate***) (eq 17),[16] whereas this method is not applicable to secondary halides due to elimination.

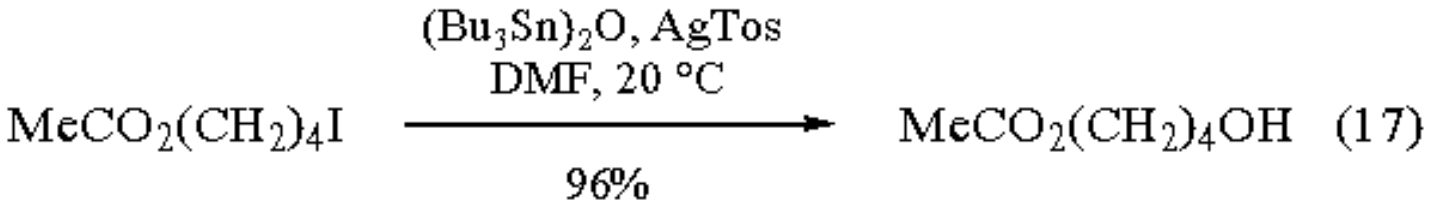

$(Bu_3Sn)_2O$ is a useful starting material for the preparation of tributyltin hydride, which is a convenient radical reducing reagent in organic synthesis. Thus ***Tri-n-butylstannane*** is easily prepared by using exchange reactions of $(Bu_3Sn)_2O$ with polysiloxanes (eq 18).[17]

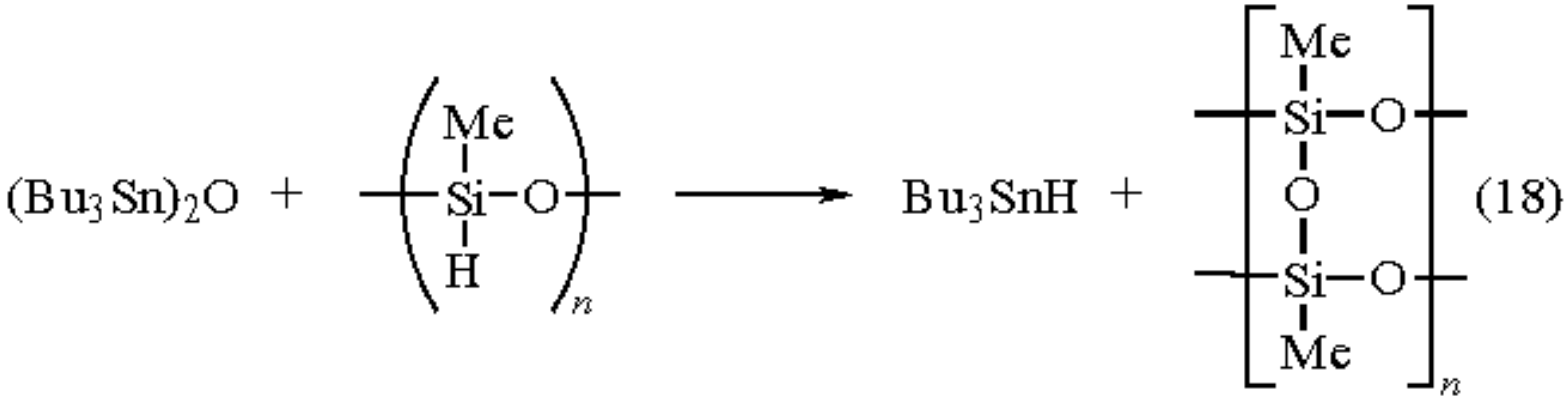

Related Reagents.

Tri-n-butyl(methoxy)stannane.

---

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Bis(tributyltin) Peroxide[1]

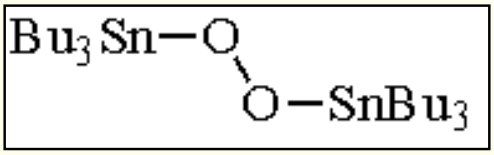

[63256-88-2] · $C_{24}H_{54}O_2Sn_2$ · Bis(tributyltin) Peroxide · (MW 612.07)

(mild nonalkaline source of dinucleophilic peroxide; reacts with alkyl triflates to deliver dialkyl peroxides, often in higher yields than obtained from the reaction of alkyl mesylates with hydrogen peroxide and a base)

Physical Data: unstable liquid.

Solubility: sol CH_2Cl_2.

Form Supplied in: must be freshly prepared.

Preparative Method: addition of ***Tri-n-butyl(methoxy)stannane*** to an ether-methanol solution of anhydrous ***Hydrogen Peroxide*** at 0 °C followed by removal of ether and methanol in vacuo at 0 °C.[1]

Purification: attempted purification by rapid column chromatography on silica gel or Florisil led to decomposition.

Handling, Storage, and Precautions: thermally unstable, but can be stored for 1 day neat at -20 °C. The reagent is presumed to be a strong oxidizing agent and, as with organic peroxides in general, there is a potential for explosion. The use of a safety shield is mandatory during preparation and use. Reaction with water releases anhydrous H_2O_2 that is hazardous.

Peroxide Transfer.

$Bu_3SnOOSnBu_3$ reacts with alkyl triflates to generate dialkyl peroxides in good yields. In many cases, as in the reaction with isopropyl triflate (eq 1), dialkyl ethers are formed as byproducts. Other syntheses of secondary dialkyl peroxides give significantly lower yields. For example, base-catalyzed alkylation of hydrogen peroxide with isopropyl mesylate gives diisopropyl peroxide in low yield (eq 2).[2] ***Silver(I) Trifluoroacetate***-assisted alkylation of 2-butyl hydroperoxide with 2-butyl bromide gives a low yield of dialkyl peroxide (eq 3).[3]

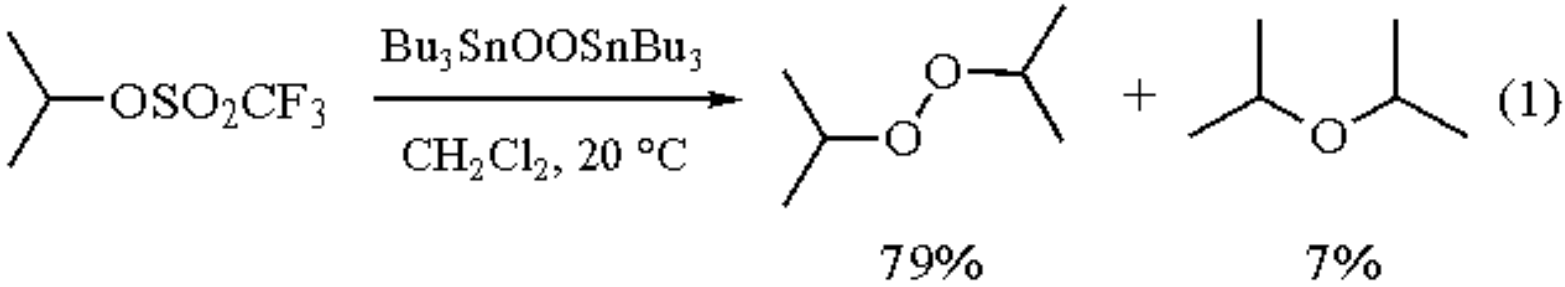

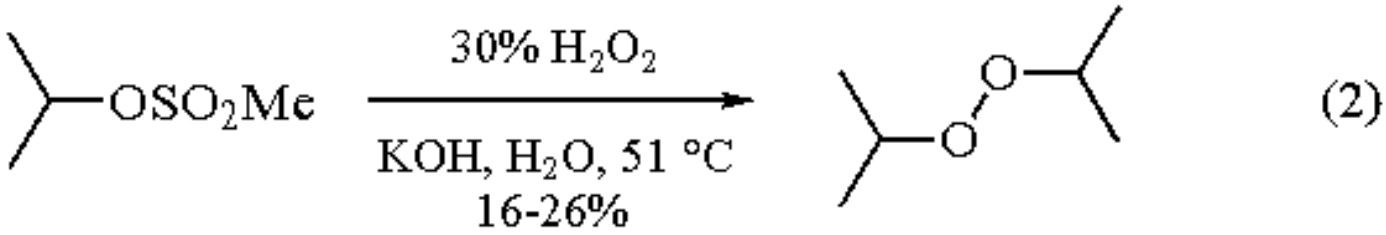

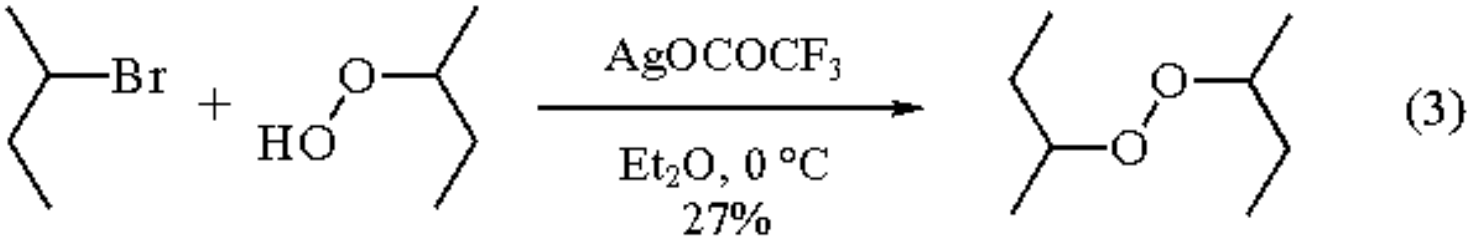

Cyclic dialkyl peroxides are obtained from the reaction of alkyl ditriflates with $Bu_3SnOOSnBu_3$ (eq 4). For volatile dialkyl peroxides, isolation is simplified and yields improved by using 1,2,4-trichlorobenzene as solvent. The reaction is conducted in vacuo, and the product is efficiently removed from the reaction mixture and collected in a cold trap (-78 °C). This protocol is essential for the preparation of 2,3-dioxabicyclo[2.2.1]heptane, the strained nucleus of prostaglandin endoperoxides, because this peroxide is unusually reactive (eq 5). It is noteworthy that pure 2,3-dioxabicyclo[2.2.1]heptane, mp 63-64 °C, is stable toward bis(tri-*n*-butyltin) peroxide.

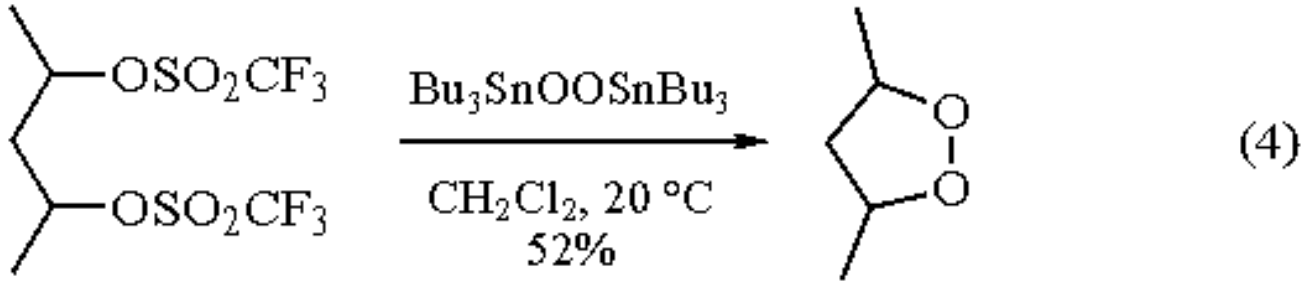

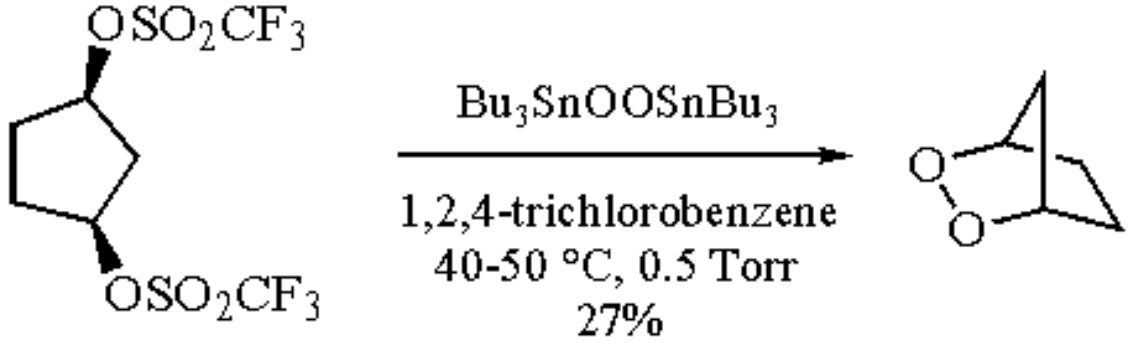

(5)

An ether, tetrahydropyran, is the major product of the reaction of $Bu_3SnOOSnBu_3$ with pentane 1,5-bistriflate. The relative preference for cyclic ether formation in the reaction of bistriflates is 5, 6 > 7 > 8-membered rings while that for cyclic peroxide formation is 4 &LLt; 5, 6 > 7-membered rings. The product ratios of cyclic peroxide versus cyclic ether indicate an important role for stereoelectronic preferences in the kinetically controlled partitioning of a monoalkylperoxytin precursor between two oxonium ion intermediates (eq 6).[4]

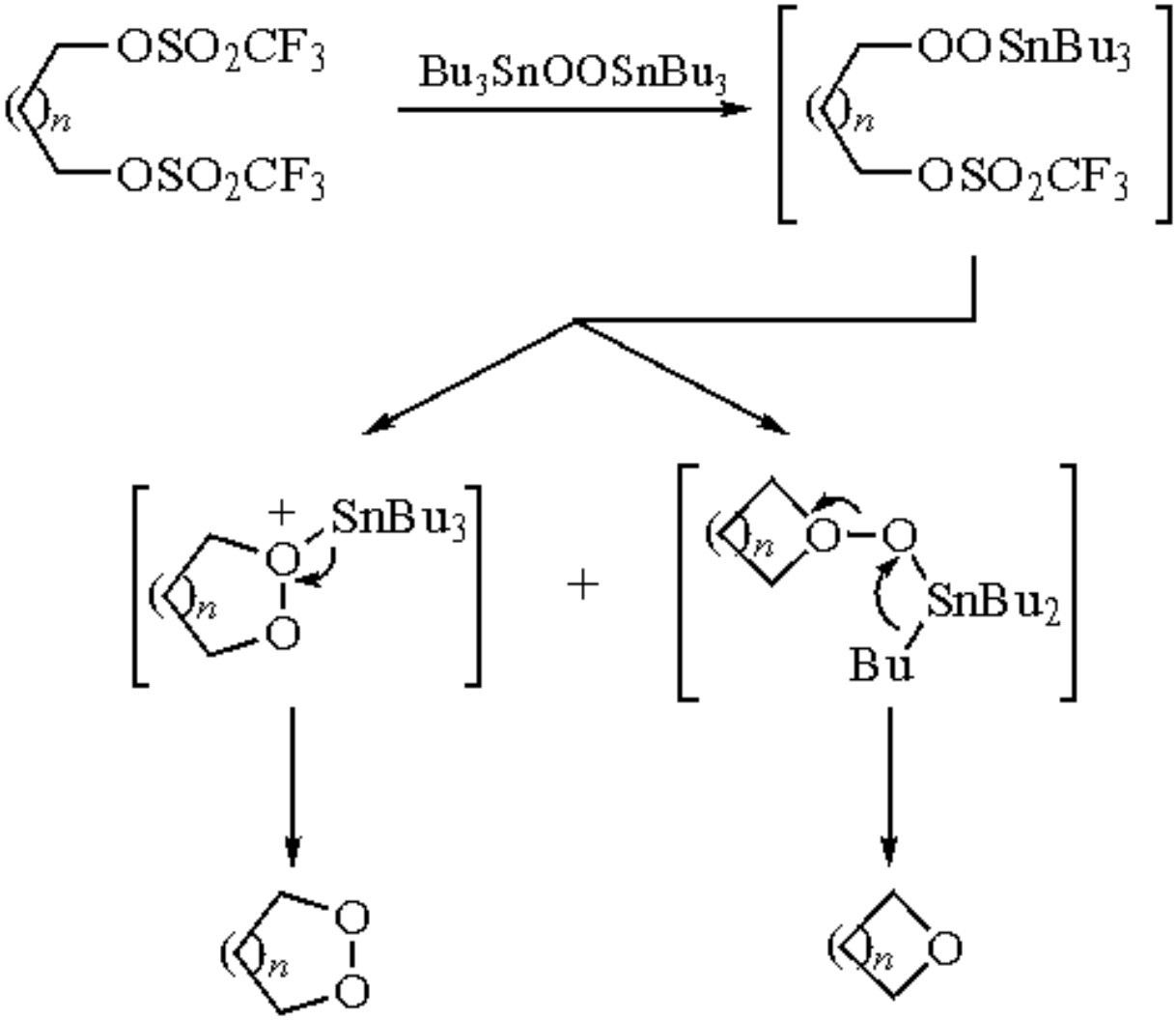

(6)

68%	$n = 1$	0%
65%	$n = 2$	24%
37%	$n = 3$	42%
23%	$n = 4$	6%

23% $n = 4$ 6%

---

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Bis(2,2,2-trichloro-1,1-dimethylethyl) Phosphorochloridate

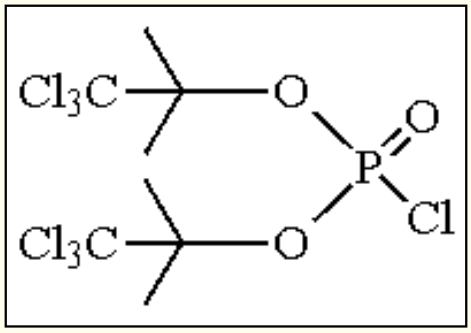

[17677-92-8] · $C_8H_{12}Cl_7O_3P$ · Bis(2,2,2-trichloro-1,1-dimethylethyl) Phosphorochloridate · (MW 435.33)

(phosphorylating reagent)

Physical Data: mp 81-82 °C.

Solubility: crystallized from pentane.

Form Supplied in: colorless solid.

Preparative Methods: the reagent[1] is conveniently prepared by the reaction of 2-trichloromethyl-2-propanol with PCl_3 in pyridine solvent to afford bis(2,2,2-trichloro-1,1-dimethylethyl) chlorophosphite (71%). The chlorophosphite is oxidized with ***(Diacetoxyiodo)benzene*** to give 65% of the desired phosphorochloridate (eq 1). This overall procedure represents an improved synthesis of the phosphorochloridate when compared to the different methods reported in the literature, which give mixtures of bis(2,2,2-trichloro-1,1-dimethylethyl) chlorophosphite and 2,2,2-trichloro-1,1-dimethylethyl dichlorophosphite.[2,3]

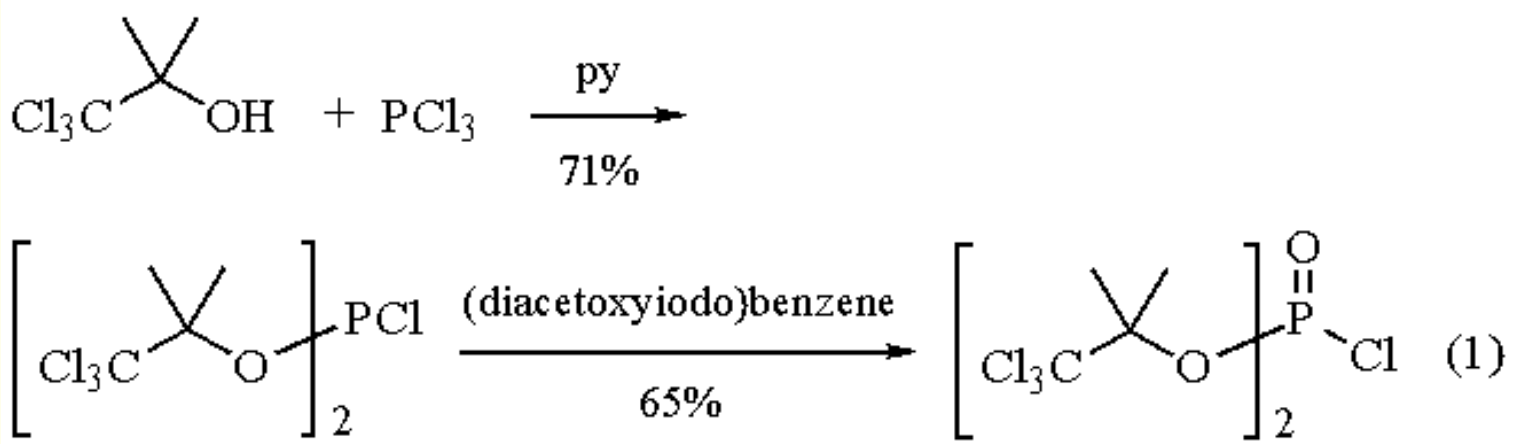

Handling, Storage, and Precautions: moisture sensitive; store in a cool, dry environment. Handle in a well-ventilated fume hood.

Phosphorylating Reagent.

Nucleoside derivatives are selectively phosphorylated and protected at the 5´-OH group using bis(2,2,2-trichloro-1,1-dimethylethyl) phosphorochloridate.[4] The chemospecificity favors the 5´-phosphorylated oligonucleotides which are formed exclusively, in presence of a free 3´-OH group (eq 2).[5] Compared to those of other alkylmono- and dichlorophosphate reagents,[6] the 2,2,2-trichloro-1,1-dimethylethyl group exhibits unusual stability towards acids and bases, which is a distinct advantage, especially when considering the different transformations required for effective oligonucleotide synthesis.[7,8] The bis(2,2,2-trichloro-1,1-dimethylethyl) group can be readily removed by the supernucleophilic cobalt(I) phthalocyanine anion $[Co^1Pc]^-$.[9]

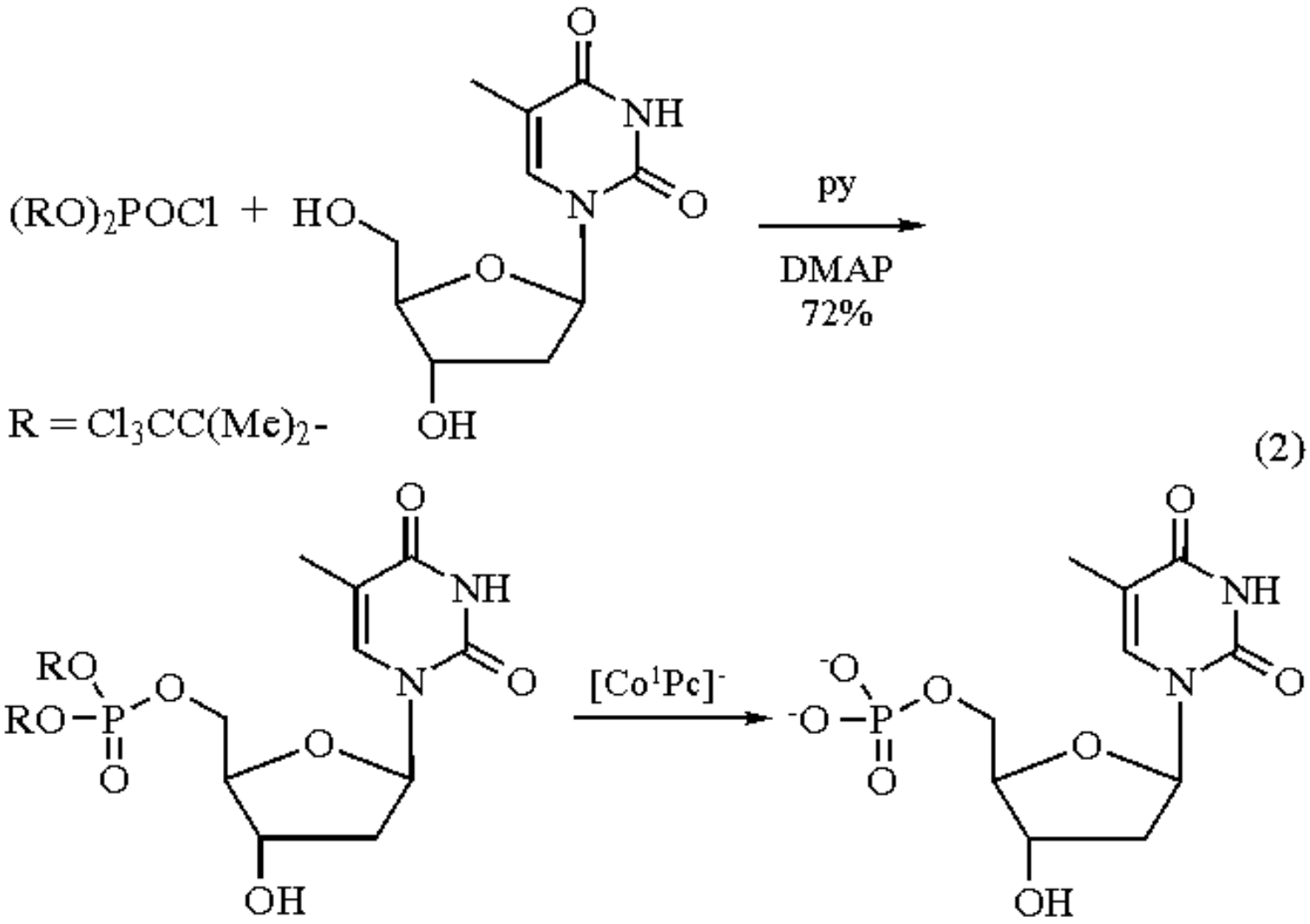

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Bis(2,2,2-trichloroethyl) Azodicarboxylate

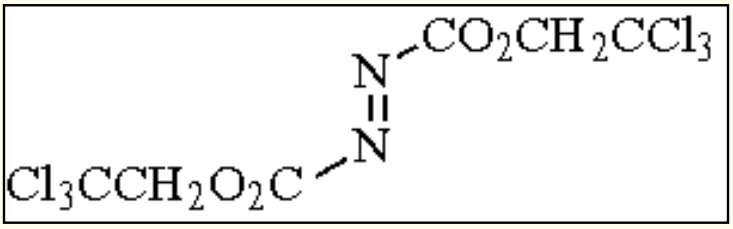

[38857-88-4] · $C_6H_4Cl_6N_2O_4$ · Bis(2,2,2-trichloroethyl) Azodicarboxylate · (MW 380.83)

(a reactive dienophile,[2] diene,[7] and enophile[8])

Physical Data: mp 110-111 °C.

Solubility: sol in a wide range of organic solvents.

Form Supplied in: slightly yellow plates.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) displays a singlet at δ 5.05.

Preparative Method: commercially available.[1]

Purification: recrystallize from pentane.

Handling, Storage, and Precautions: as with all azo compounds, caution should be exercised to avoid exposure of the material to heat. Store in a brown bottle.

Reaction as a Diels-Alder Dienophile.

Bis(2,2,2-trichloroethyl) azodicarboxylate (**1**) is most often used as a Diels-Alder dienophile.[2] Its relatively high reactivity occasionally makes it preferable to the less reactive diethyl or dimethyl analogs, since the times and temperatures needed to achieve reaction are often reduced. For example, the Diels-Alder reaction illustrated (eq 1) required 5 days to reach completion when dimethyl azodicarboxylate was used, in contrast to just 1 h with (**1**).[2]

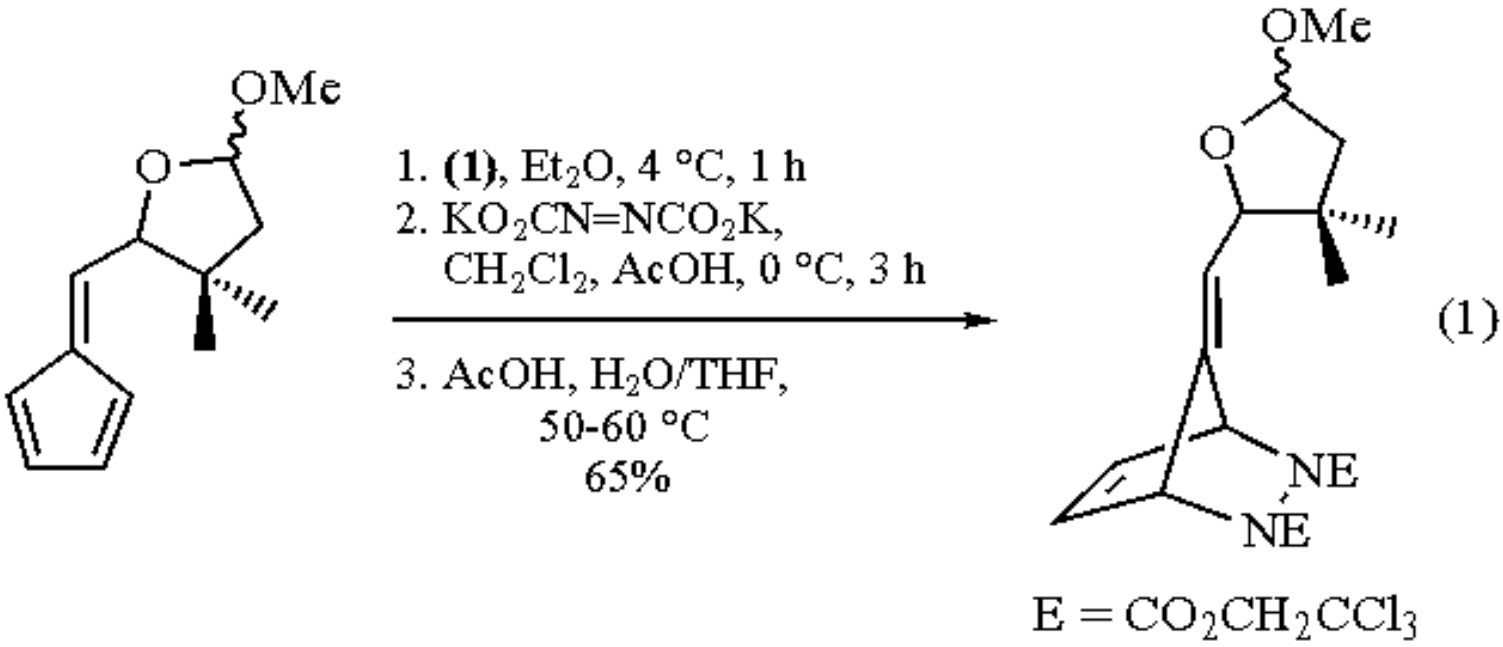

The bis(carbamate) cycloadducts are often highly viscous materials. Attempts to characterize them by ^{1}H NMR can be difficult by virtue of the several dynamic processes which occur on the NMR timescale.[3] To obtain a well-resolved spectrum requires that it be recorded at an elevated temperature.[3]

Most often, bis(carbamates) serve as precursors to azo compounds and the latter, in turn, to a host of theoretically interesting materials, reactive intermediates, and precursors to natural products.[2,4] While hydrolytic methods can also be used, the trichloroethoxy group is most often cleaved reductively, usually with ***Zinc-Acetic Acid***,[5] or with a ***Zinc/Copper Couple*** in the presence of a proton donating solvent,[2b,4] or via an electroreductive process.[6] The presence of a proton donor leads to the formation of an intermediate hydrazo compound, which requires further oxidation to generate the azo linkage. Occasionally, the azo compound is initially isolated as a copper complex and then freed by making the solution basic, often by using aqueous ammonia.[5] In the absence of a proton donor, the hydrazo compound is bypassed. In this case, oxidation of the intermediate dicarboxylate salt leads directly to the azo functionality.[2,6] Regardless of the method, yields are sometimes variable, and experimentation is often required to achieve optimal conversion.

Reaction as a Diene.

Interestingly, (**1**) can also serve as a diene. Thus when irradiated (eq 2) (350 nm), a novel [4 + 2] cycloaddition occurs between (**1**) and a variety of glycals.[7] Reaction times are quite long (e.g. 18 h to 2 weeks), but the yields are uniformly good (73-85%). Once again, the increased reactivity of (**1**) relative to other commonly used azodicarboxylates is apparent. For example, while the photoreaction (eq 2) requires 1.5 weeks, it fails to occur using dibenzyl azodicarboxylate. Treatment of the adducts with a catalytic amount of *p*-TsOH in methanol affords the corresponding methyl glycosides which, when exposed to zinc dust in acetic acid and acetone, followed by acetic anhydride/pyridine, generate 2-amino glycosides in good to excellent yields (60-97%; 75% for the case shown).

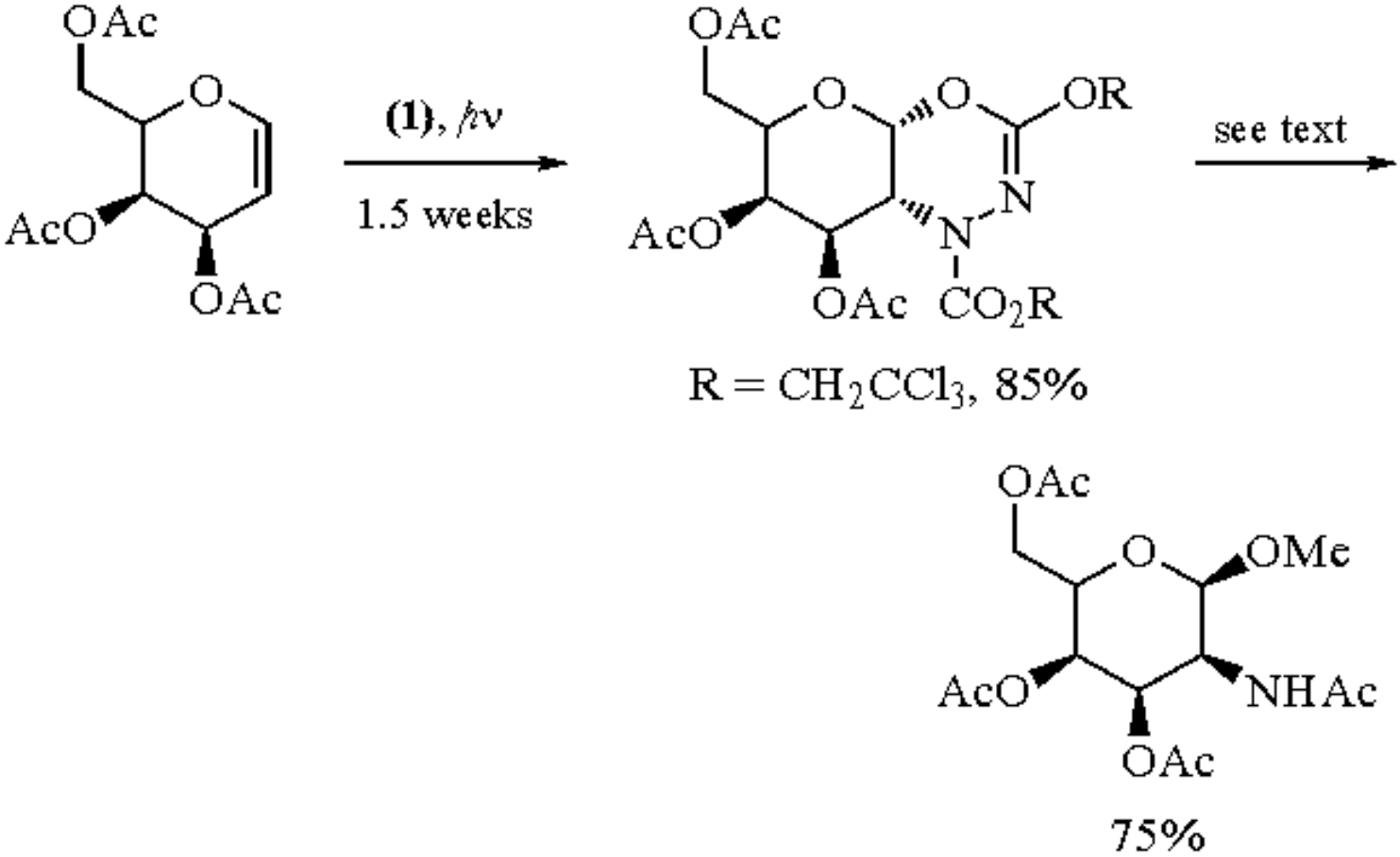

(2)

Reaction as an Enophile.

When used as an enophile, (**1**) provides a novel route to allylic amines.[8] Ene reactions with diethyl and dimethyl azodicarboxylate have also been reported, but the yields are low. In contrast, use of the trichloroethyl derivative affords ene adducts in 60-88% yield and allows generation of both cyclic and acyclic *N*-acylamines under mild conditions (eq 3).

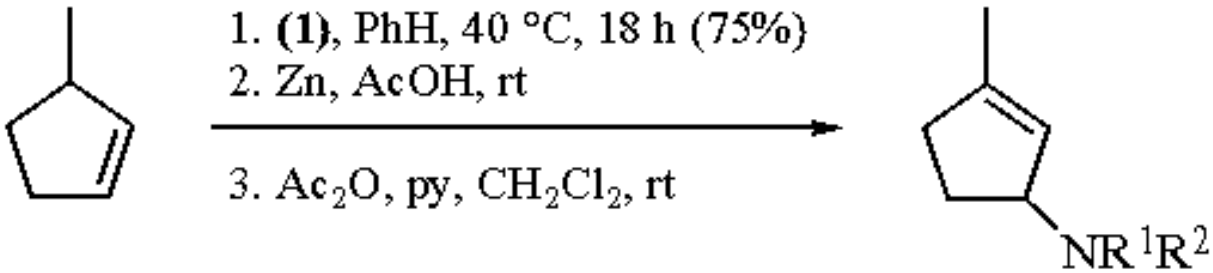

(3)

a, $R^1 = CO_2CH_2CCl_3$, $R^2 = NHCO_2CH_2CCl_3$
b, $R^1 = H$, $R^2 = Ac$, 88%

Related Reagents.

Di-t-butyl Azodicarboxylate; ***Diethyl Azodicarboxylate***.

---

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7. Leblanc, Y.; Fitzsimmons, B. J. *TL* **1989**, *30*, 2889.
8. Leblanc, Y.; Zamboni, R.; Bernstein, M. A. *JOC* **1991**, *56*, 1971.

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Bis(2,2,2-trichloroethyl) Phosphorochloridate

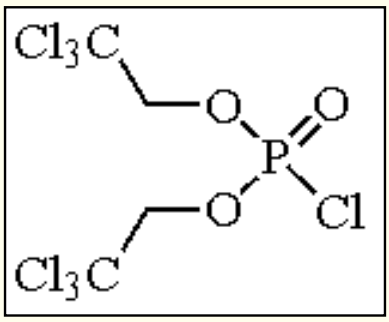

[17172-53-6] · $C_4H_4Cl_7O_3P$ · Bis(2,2,2-trichloroethyl) Phosphorochloridate · (MW 379.22)

(phosphorylating reagent)

Physical Data: mp 45-47 °C.

Form Supplied in: colorless solid.

Handling, Storage, and Precautions: may decompose on exposure to air or water. Store in a dry, cool environment. Corrosive material and it should be handled in a well-ventilated fume hood.

Phosphorylating Reagent.

Phosphorochlorides have been widely used for the direct introduction of a phosphate group in hydroxy amino acids.[1] The use of the 2,2,2-trichloroethyl group for the phosphate protection[2] in phosphoserine derivatives[3] constitutes an efficient method for effective phosphopeptide synthesis.[4] Nucleotides are selectively protected as the 5´-OH phosphate ester derivatives[5,6] with bis(2,2,2-trichloroethyl) phosphorochloridate (eq 1).[7]

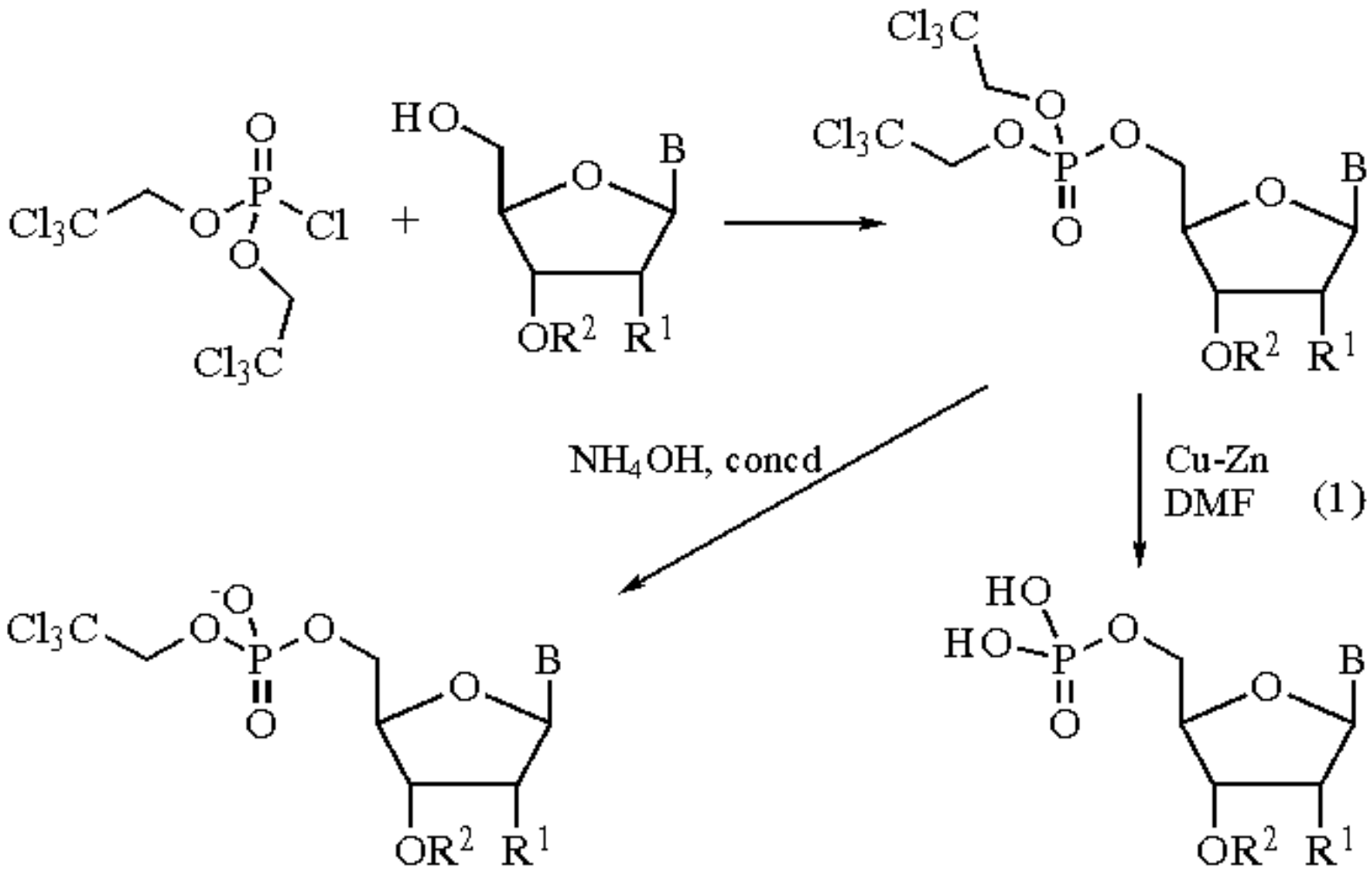

B = thymine, 4-thiothymine, and uracyl; R^1 = H, OH; R^2 = H, COMe, COPh

The isolated esters are stable in alkaline medium,[8] and selective cleavage of the 2,2,2-trichloroethyl group to afford the phosphate nucleotides occurs upon treatment with ***Zinc*** metal[9,10] (in DMF or acetic acid media) in presence of other protecting groups.[11] Bis(2,2,2-trichloroethyl) phosphorochloridate has also been successfully used as a phosphorylating agent for carbohydrates (eq 2),[12,13] and for the preparation of forskolin derivatives.[14]

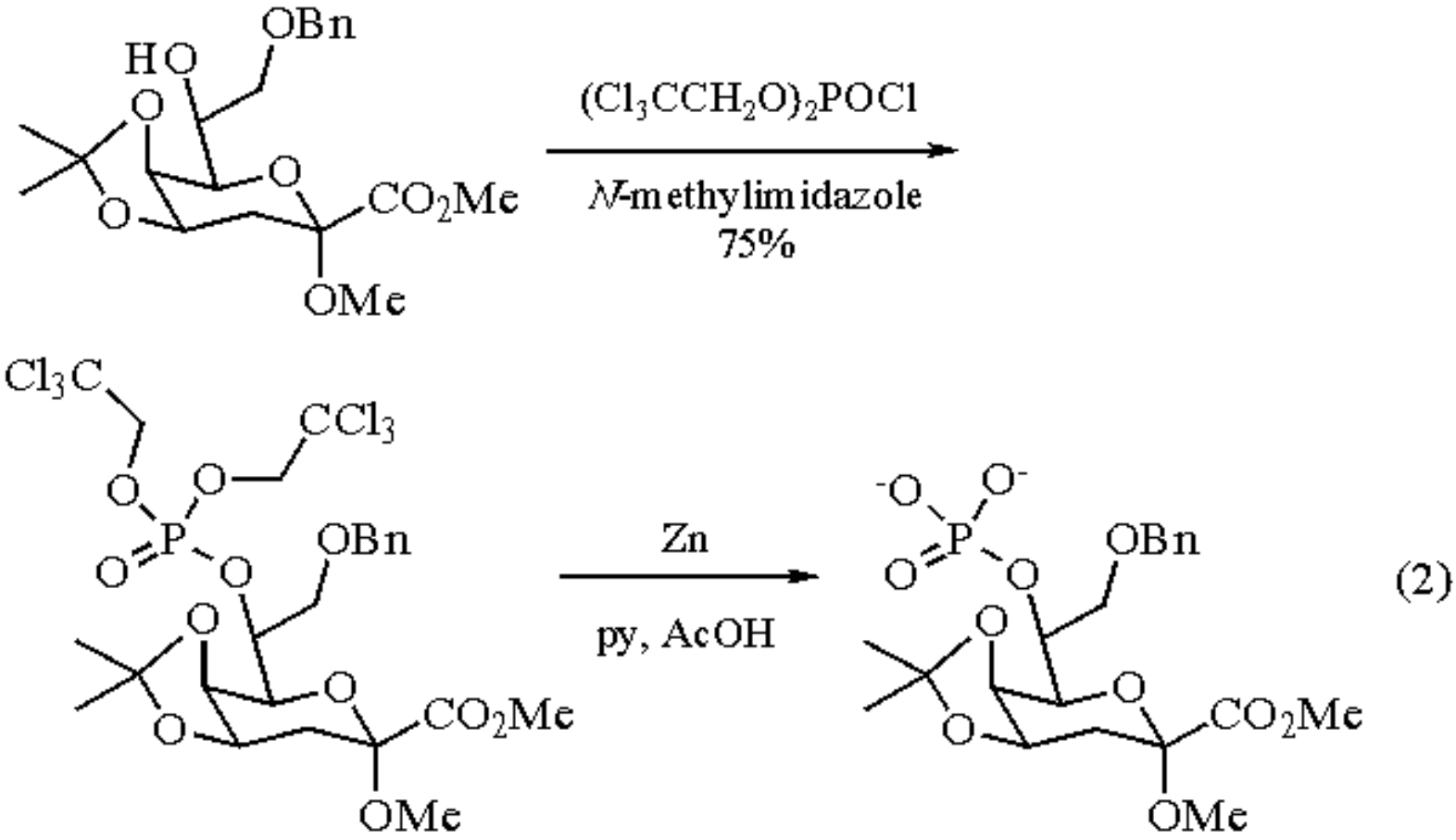

Preparation of Mixed Trialkyl Phosphates.

In a general transesterification method designed to prepare mixed trialkyl phosphates,[15] reactions of bis(2,2,2-trichloroethyl) phosphorochloridate with different alcohols, in pyridine solvent, and in presence of fluoride ion (***Cesium Fluoride*** or ***Tetra-n-butylammonium Fluoride***), afford the mixed trialkyl phosphates (eq 3).[16] Reactions with diols give cyclic phosphates (eq 4).[16] The 2,2,2-trichloroethyl group has been also conveniently used for the preparation of mixed triesters of nucleotides.[17]

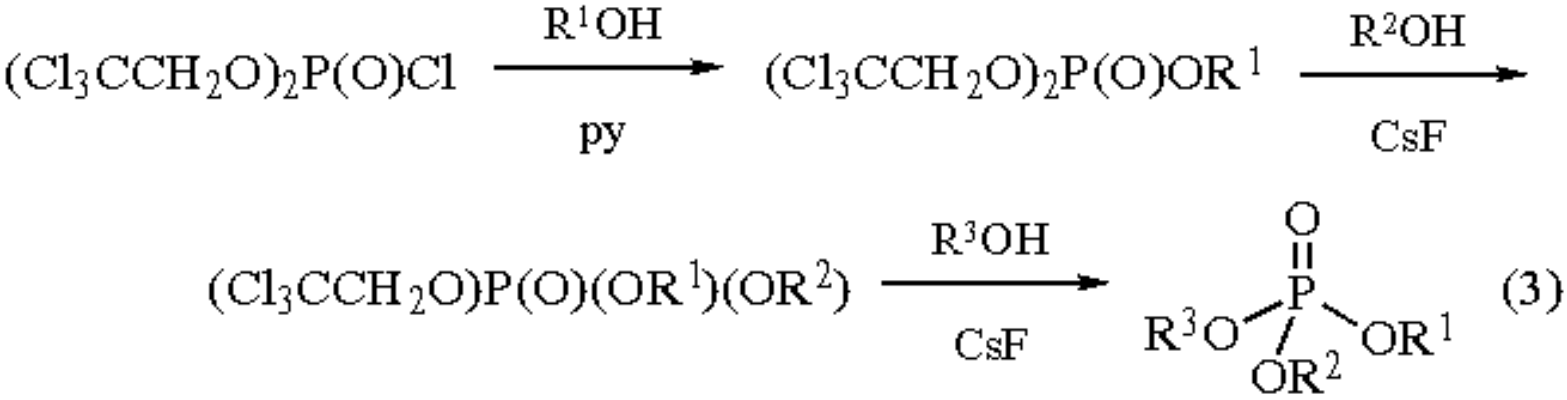

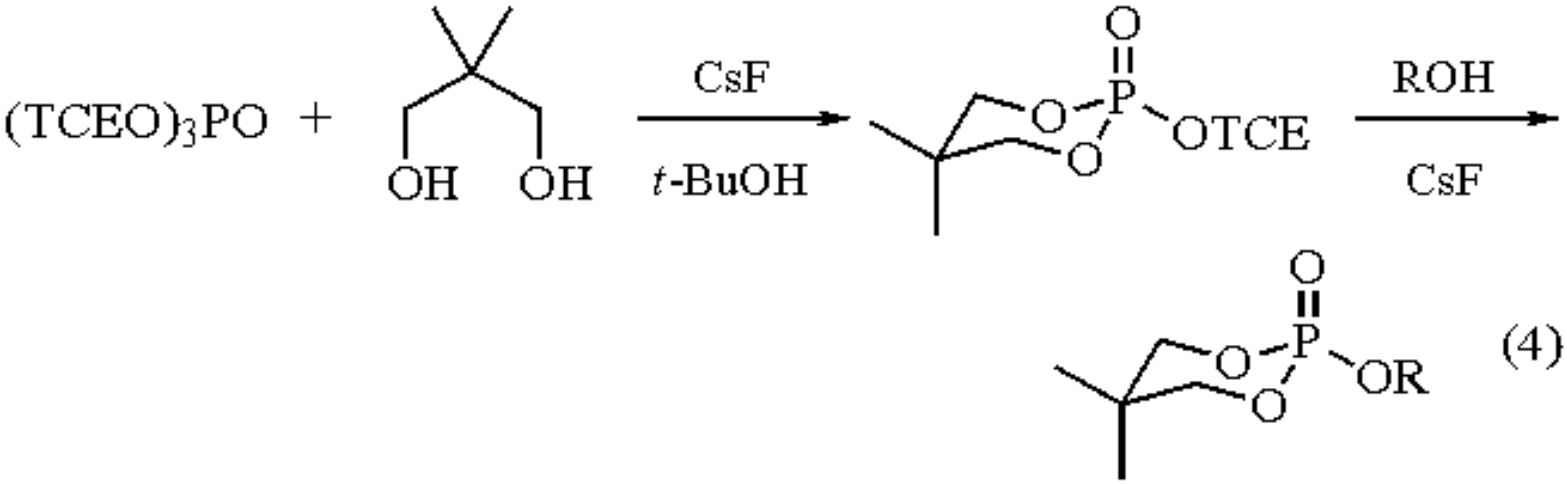

TCE = Cl_3CCH_2-; R = Me, Et, *i*-Pr

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Bis(trichloromethyl) Carbonate[1]

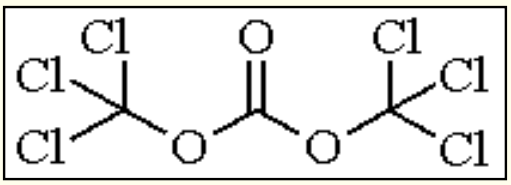

[32315-10-9] · $C_3Cl_6O_3$ · Bis(trichloromethyl) Carbonate · (MW 296.73)

(a phosgene surrogate)

Alternate Name: triphosgene.

Physical Data: mp 81-83 °C; bp 203-206 °C.

Solubility: sol methanol, ethanol, benzene, diethyl ether, hexane, THF, ethyl acetate; dec slowly in cold water.

Form Supplied in: white crystalline solid

Handling, Storage, and Precautions: the reagent is somewhat moisture sensitive, but scrupulously anhydrous conditions are not necessary. Rapid handling of the reagent in open air, in the absence of a glove bag or dry box, is usually satisfactory. This reagent should only be handled in a fume hood.

Introduction.

Phosgene gas is a versatile reagent for organic synthesis, which has been used in carbonylation, chloroformylation, chlorination, and dehydration reactions, to name a few.[1] However, because of the high toxicity of ***Phosgene***, it has not been used widely. Surrogates for phosgene have long been sought. ***Trichloromethyl Chloroformate*** (diphosgene) was introduced as one such phosgene substitute.[2] To the extent that diphosgene is a highly toxic, hygroscopic, and noxious liquid, it is not a fully satisfactory phosgene substitute. On the other hand, bis(trichloromethyl) carbonate (triphosgene; **1**) is a crystalline solid compound, is not very hygroscopic, and can substitute for phosgene in a plethora of chemical reactions. Triphosgene has been known since 1880,[3] but its synthetic utility had not been exploited until recently.

Carbonylation.

The formation of oxazoles,[4] quinazolinediones (eq 1),[5] carbonates (eq 2),[6] urea analogs,[7] and isocyanates (eq 3)[1] have been reported with triphosgene. The reactions give good to excellent yields and often require only 1/3 equiv of

triphosgene.

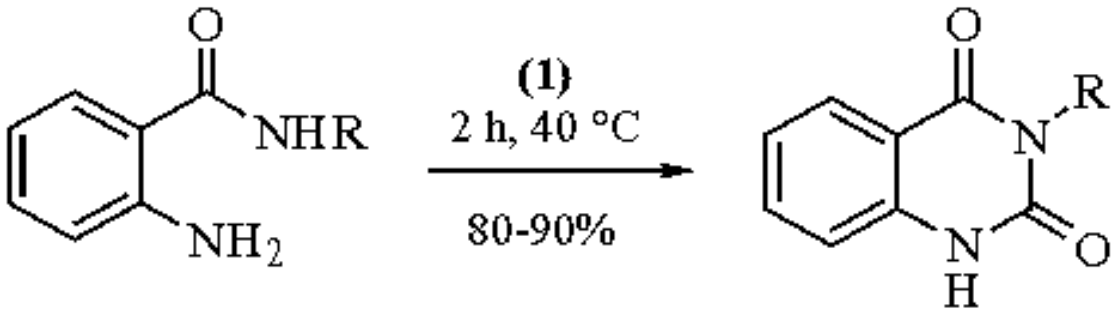

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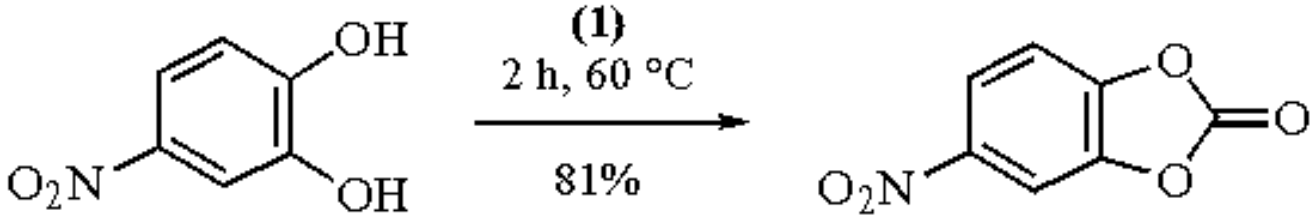

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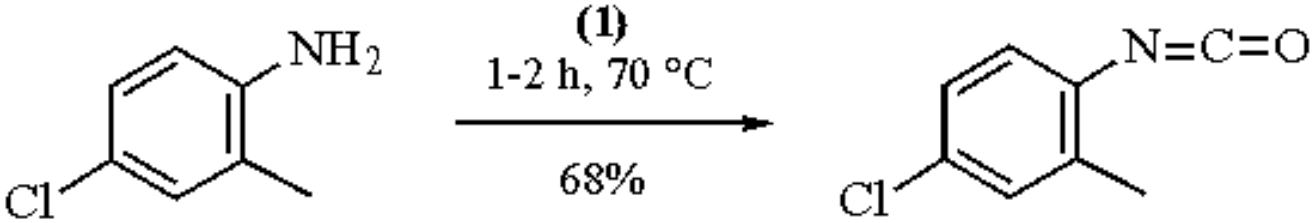

(3)

Chloroformylation.

The use of triphosgene in the formation of chloroformates with both hydroxy compounds (eq 4) and substituted amines (eq 5) has been reported.[1]

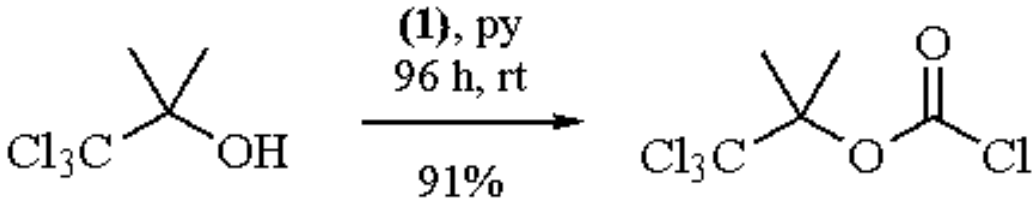

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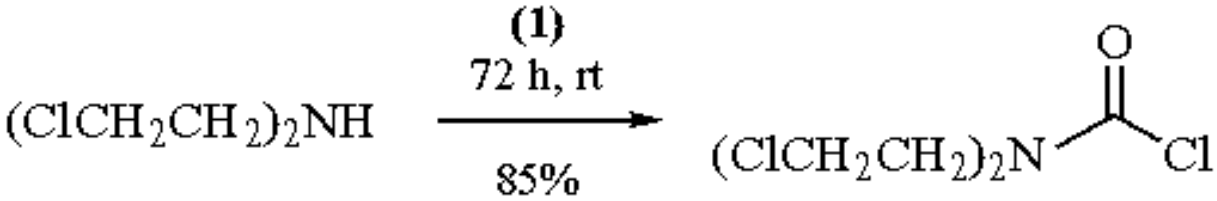

(5)

Dehydration.

Synthesis of isocyanides from formamides (eq 6) is the only example of a dehydration reaction reported for

triphosgene to date.[1]

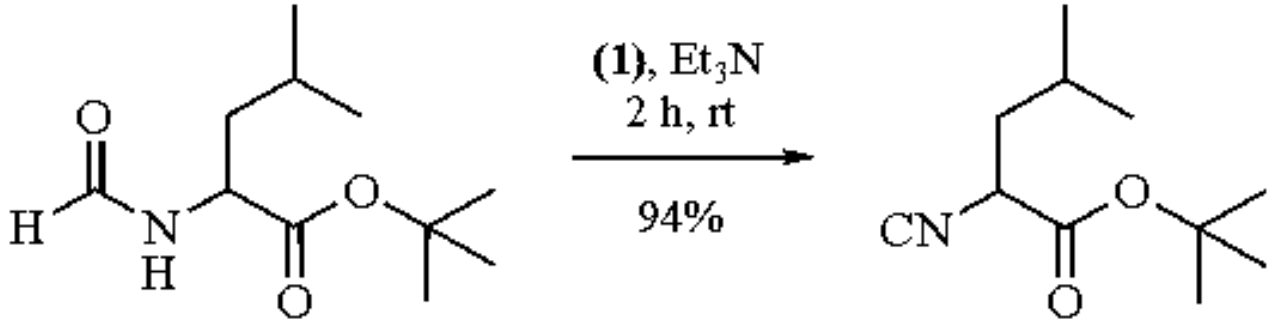

N-Carboxyamino Acid Anhydrides.

Synthesis of *N*-carboxyamino acid anhydrides (NCAs) is accomplished by the reaction of the zwitterionic unprotected amino acid with triphosgene at elevated temperatures (eq 7).[8] Wilder and Mobashery reported a milder version of this reaction, utilizing *N*-*t*-butoxycarbonyl-α-amino acids; in the presence of a stoichiometric quantity of ***Triethylamine*** and 1/3 equiv of triphosgene (eq 8) the reaction is believed to proceed via a chloroformic *N*-*t*-butoxycarbonyl-α-amino acid anhydride intermediate to give the corresponding NCA.[9] There are many synthetic routes to NCAs;[10] however, the use of triphosgene in the preparation of NCAs provides a facile, safe, mild, and practical entry to these important molecules.

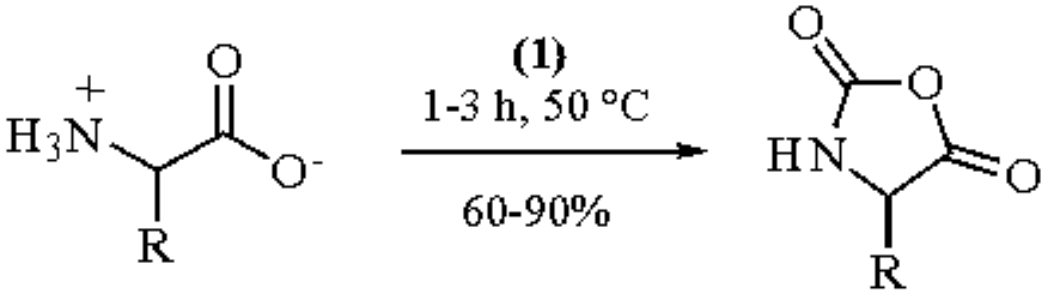

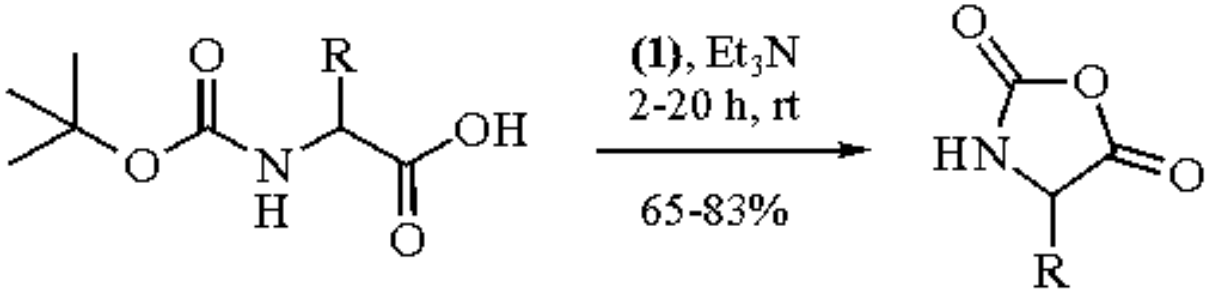

Chlorination.

Triphosgene has been used in the synthesis of acyl chlorides (eq 9).[1] Also, it has been shown to react with a variety of aldehydes to give α-chloro chloroformates (eq 10).[11] Goren et al. have shown that triphosgene mediates chloride substitution reactions on activated alcohols (eq 11);[12] this reaction involves the formation of an intermediary chloroformate species en route to the chlorinated product. The generality of the reaction was shown for benzylic (eq

12), allylic, and propargylic systems. This reaction proceeds primarily via S_N2, with some contribution by S_N1 and/or S_Ni mechanisms.[12] Chlorination with triphosgene is considerably milder than the typical chlorination reactions with ***Thionyl Chloride***, ***Phosphorus(III) Chloride***, ***Phosphorus(V) Chloride***, ***Oxalyl Chloride***, and the like; for example, acid-labile functionalities, such as *t*-butyl carbamate (BOC), benzhydryl, and *p*-methoxybenzyl groups, can be tolerated in the triphosgene-mediated reactions, whereas they do not normally survive reactions with other chlorination reagents.

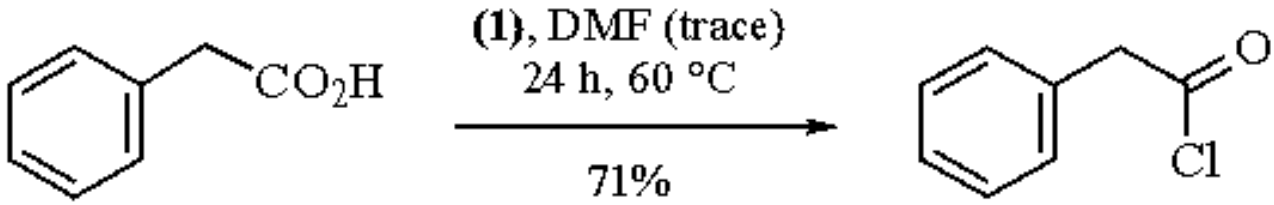

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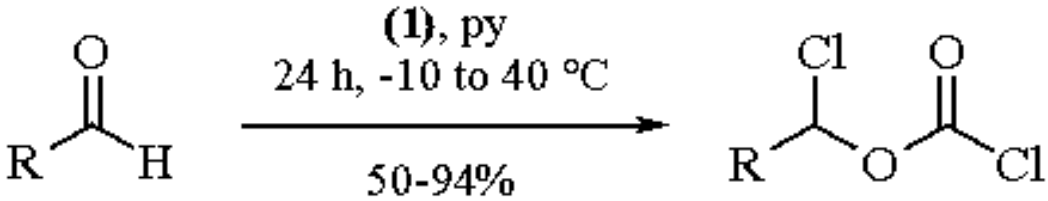

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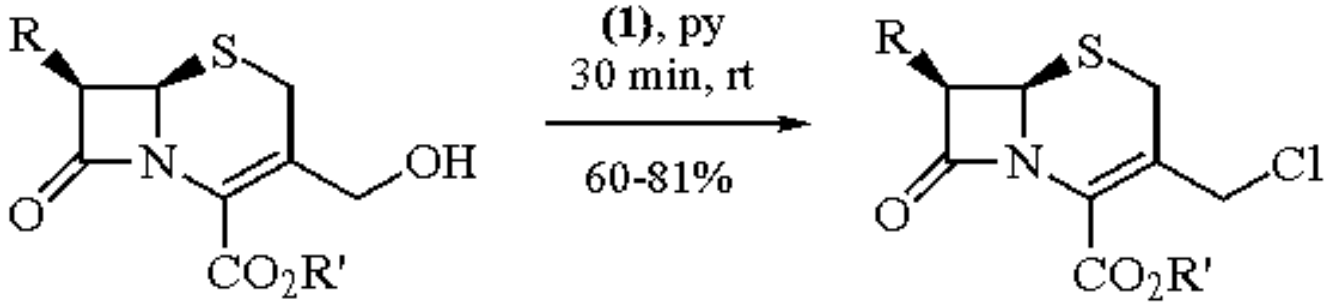

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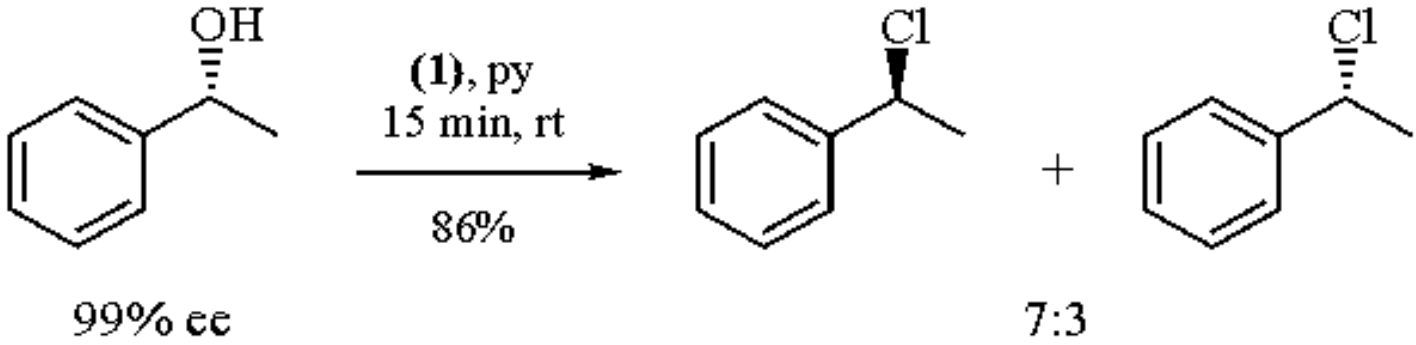

(12)

Oxidation.

Palomo et al. have demonstrated that primary and secondary alcohols are readily oxidized by triphosgene in the presence of ***Dimethyl Sulfoxide*** (DMSO) in good to excellent yields;[13a] the reaction is applicable to both activated (eq 13) and unactivated alcohols (eq 14). This reaction is a variation of the one reported by Barton with phosgene gas,[14] and it is an excellent alternative to Swern-type oxidations. Indeed, in some respects, oxidation of alcohols by triphosgene is superior to the widely used Swern oxidation. The triphosgene reaction tolerates acid-labile functionalities and is not as sensitive to residual moisture as oxalyl chloride used in the Swern oxidation. An

additional advantage of the method of Palomo et al. is the ease of handling of triphosgene, and the fact that the reaction is amenable to large-scale synthesis. The breadth and scope of this reaction have been investigated with a large variety of alcohol substrates.[13b] See also ***Dimethyl Sulfoxide-Triphosgene***.

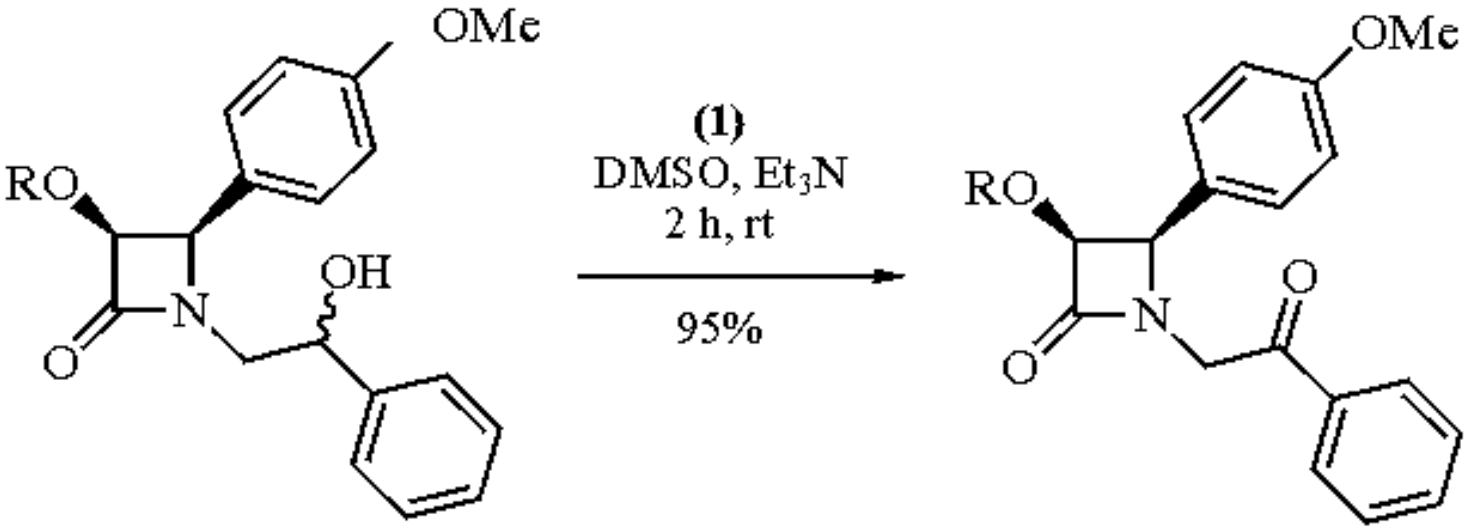

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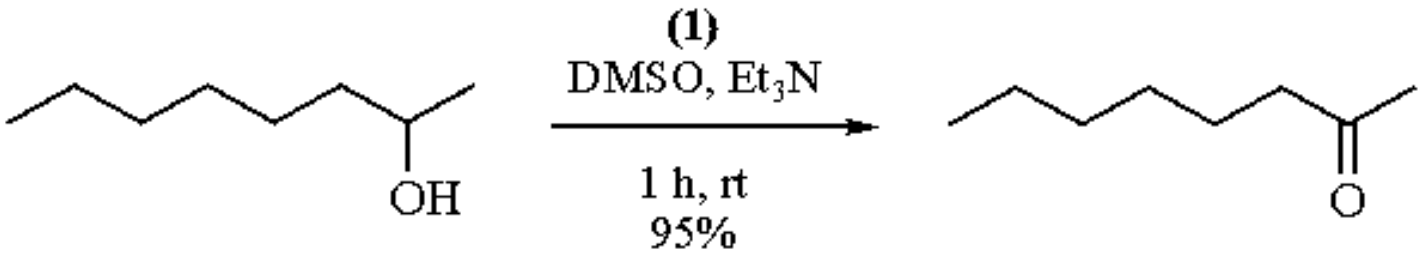

(14)

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Bis(trichloromethyl)mercury[1]

$Hg(CCl_3)_2$

[6795-81-9] · C_2Cl_6Hg · Bis(trichloromethyl)mercury · (MW 437.33)

(source of **:**CCl_2 by thermal treatment;[2,3] furnishes cyclopropanes by reaction with alkenes[4])

Physical Data: mp 141 °C.

Solubility: sol ether, THF, $CHCl_3$; insol cold H_2O, petroleum ether.

Analysis of Reagent Purity: IR,[5] Raman,[5] NMR (^{13}C and ^{119}Hg),[6] and NQR (^{35}Cl).[7]

Preparative Method: reaction of ***Mercury(II) Chloride*** ($HgBr_2$ has proven to be unreactive) with ***Sodium Trichloroacetate*** (1:2 molar ratio) in dry monoglyme at reflux for 1 h affords $Hg(CCl_3)_2$ as a crystalline solid after purification.

Purification: recrystallization from $CHCl_3$.

Handling, Storage, and Precautions: flame-dried glassware and an atmosphere of dry nitrogen are used for the reactions. Organomercury(II) compounds should be carefully handled and skin contact and inhalation should be particularly avoided. All reactions must be conducted in a well-ventilated hood.

Pyrolysis.

Gas phase pyrolysis of $Hg(CCl_3)_2$ at 350 °C gave mainly C_2Cl_4 and minor amounts of C_2Cl_6.[2,3] Similar pyrolysis in the presence of excess cyclopentadiene yields chlorobenzene, originated from addition of **:**CCl_2 to the C=C bond of the diene. Further and compelling evidence for carbene generation under pyrolytic conditions arises from investigations by matrix isolation techniques after the gas phase pyrolysis, allowing characterization of the intermediate species.[2,3]

Cyclopropanation of Alkenes.

A major reaction of some α-haloorganomercurials is their ability to cyclopropanate alkenes.[1] When dealing with $Hg(CCl_3)_2$, the reaction takes place at elevated temperatures and gives only modest yields (eq 1).[4] Yields can be slightly improved by raising the temperature. Thus, for example, running the reaction in an autoclave for 15 min, cyclohexene yields 25% of cyclopropanation at 200 °C, but 36% at 250 °C.[4]

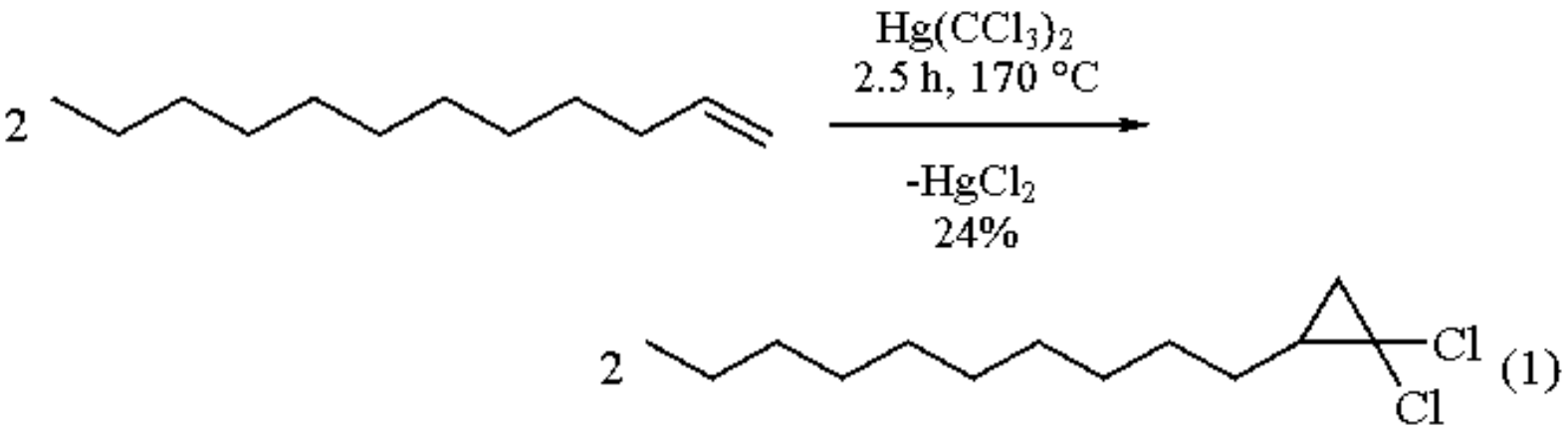

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Bis(2,4,6-trichlorophenyl) Malonate

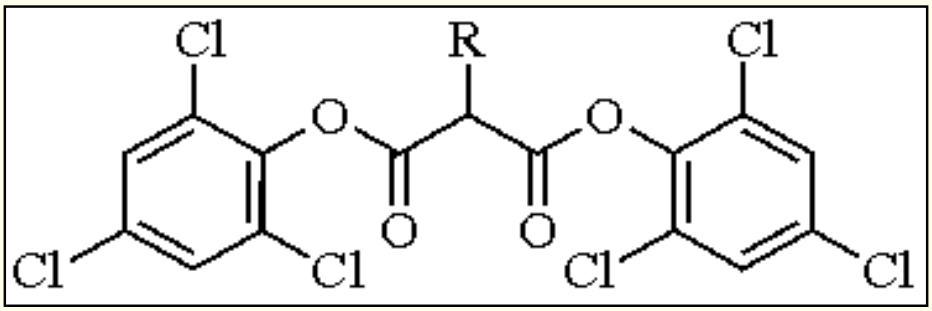

(R = H)

[15781-70-1] · $C_{15}H_6Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Malonate · (MW 462.93) (R = Me)

[15781-71-2] · $C_{16}H_8Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Methylmalonate · (MW 476.95) (R = Et)

[15781-72-3] · $C_{17}H_{10}Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Ethylmalonate · (MW 490.98) (R = *i*-Pr)

[15897-80-0] · $C_{18}H_{12}Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Isopropylmalonate · (MW 505.01) (R = *t*-Bu)

[-] · $C_{19}H_{14}Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) *t*-Butylmalonate · (MW 519.04) (R = Ph)

[15781-73-4] · $C_{21}H_{10}Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Phenylmalonate · (MW 539.03) (R = Bn)

[15781-74-5] · $C_{22}H_{12}Cl_6O_4$ · Bis(2,4,6-trichlorophenyl) Benzylmalonate · (MW 553.05)

(1,3-dielectrophile used mainly for the synthesis of five-, six-, and seven-membered heterocycles functionalized with oxo and hydroxy groups in the 1,3-position)

Alternate Names: active malonates (AMEs); magic malonates.

Physical Data: mp: R = H, 152-153 °C (toluene);[1,2] R = Me, 84-85 °C (EtOH);[1] R = Et, 101-102 °C (EtOH);[1] R = *i*-Pr, 95-96 °C (EtOH);[1] R = *t*-Bu, 132 °C (*n*-PrOH);[3] R = Ph, 97-98 °C (*n*-BuOH);[1] R = Bn, 106-107 °C (*i*-PrOH).[1] Other analogs: R = *n*-Pr,[4,5] *n*-Bu,[4,6] *s*-Bu,[7] *i*-Bu,[7] 4-methoxyphenyl,[8] 4-chlorobenzene,[7] 4-methoxybenzyl,[7] hexyl,[9] and 3-thienyl.[9]

Preparative Method: from the corresponding malonic acid and 2,4,6-trichlorophenol in the presence of phosphorus oxychloride. The reaction is preferably carried out with an excess of malonic acid (molar

ratio 1:1.6). The free malonic acids are readily obtained in about 90% yield by a modified saponification procedure[10] from the diethyl malonates (most of them are commercially available).[1,5]

Handling, Storage, and Precautions: the crude esters are quite unstable and should be used within 2 weeks. Crystallized material can be stored for 6-12 months (depending on the purity).

Reactions.

The vast majority of substrates which have been reacted with active malonic esters (AMEs, magic malonates) represent 1,3-dinucleophiles leading to six-membered heterocycles. Most of these condensations have been carried out thermally, by fusion at 150-250 °C, depending on the reactivity of the substrate. In some cases, bromobenzene, anisole or diphenyl ether have been used as solvents. However, for some substrates (mostly *N,N´*-dinucleophiles) a cold method exists which is useful for compounds which undergo transformations at higher temperature.

The reaction of acyclic and cyclic ketones leads to 4-hydoxy-2-pyrones. Thus the reaction of diethyl ketone with benzyl-AME yields the 3-benzyl-6-ethyl-5-methyl derivative which can be debenzylated with $AlCl_3$ at 150 °C (eq 1).[11] This is the starting material for the synthesis of two natural products (edulitin and obtusifolin). This compound cannot be obtained by using the unsubstituted AME, since (as a phenolic compound) it will react with further AME. Also the *t*-butyl group can be removed with $AlCl_3$; however, the corresponding *t*-butyl-AME gives lower yields with various substrates, and its preparation requires more steps.[3]

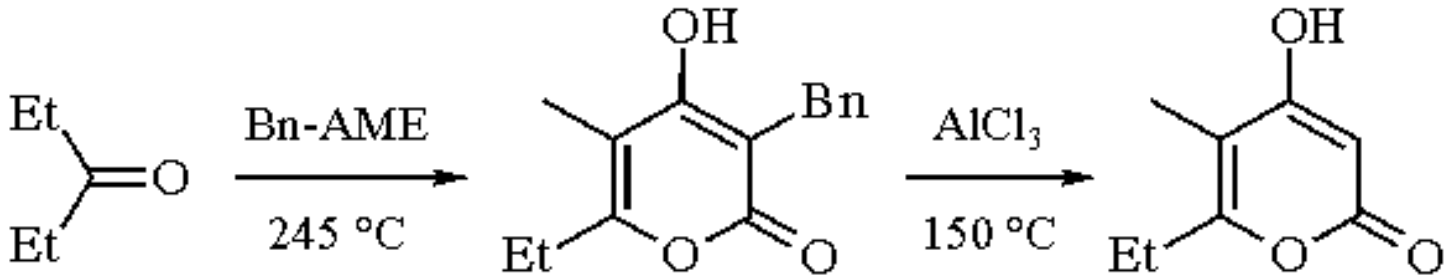

(1)

Phenols react with AMEs to yield 4-hydroxycoumarins.[12] The reaction of 3-methoxyphenol with 4-methoxyphenyl-AME (eq 2) affords a coumarin which on cyclodehydrogenation leads directly to coumestrol dimethyl ether.

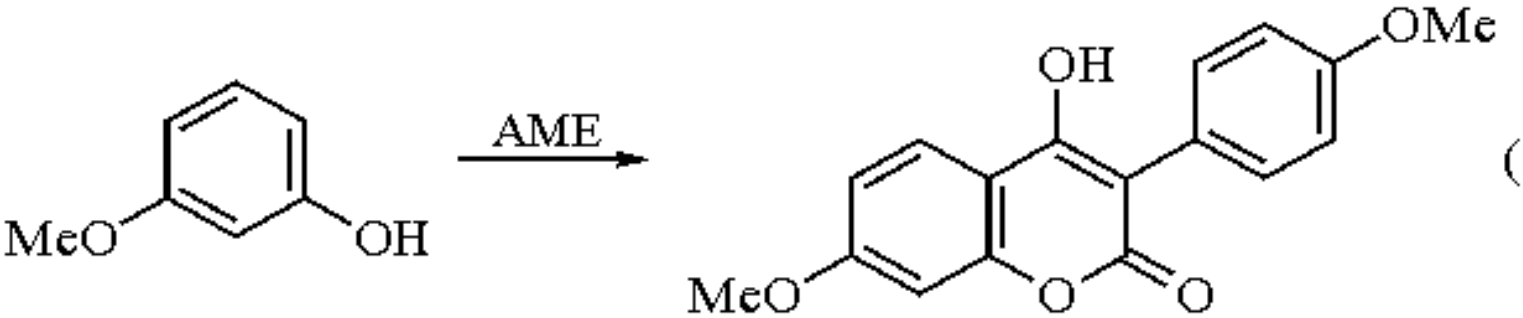

(2)

Enamines or azomethines react to yield 4-hydroxy-2-pyridones (eq 3).[13] The reaction temperature is strongly dependent on the structure of the substrate: a β-enamino ester ($R^1 = CO_2Et$) will react in refluxing bromobenzene, while acetophenone anil requires 240-250 °C. Cyclic substrates afford bicyclic hydroxypyridones (eq 4).[14]

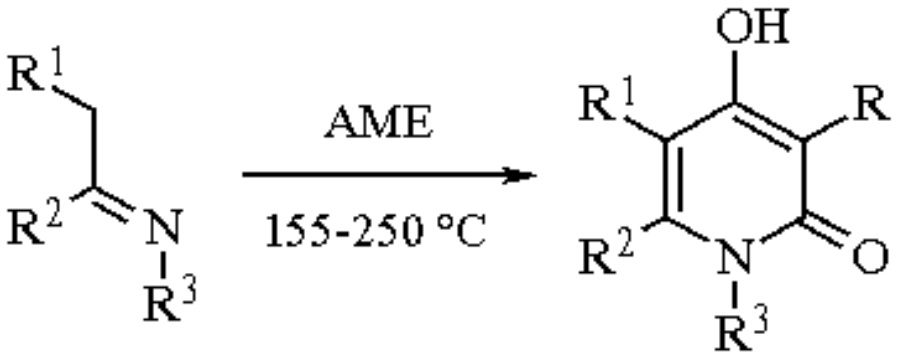

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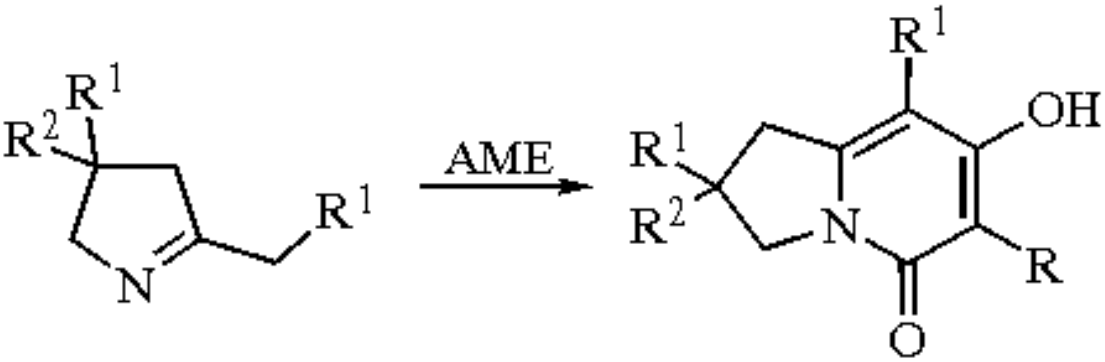

(4)

Even 2-alkylpyridines react with AMEs to give 2-hydroxy-4-quinolizines (eq 5).[1] The presence of an activating group in the side chain ($R^1 = CO_2Et$, CN, COR) is helpful, but not necessary. Many five- or six-membered heteroaromatic systems bearing a 2-alkyl side chain react in this way.[15]

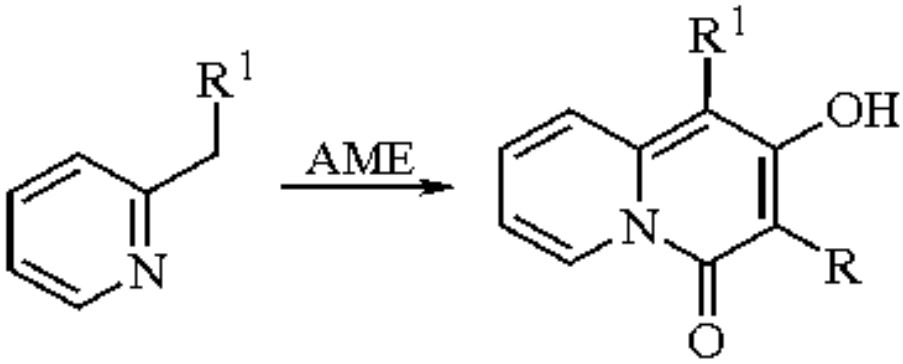

(5)

2-Aminopyridine is very reactive and gives pyridopyrimidines even with diethyl malonates if heated to 200 °C. However, in the presence of a substituent in position 6 the reaction requires higher temperatures and leads to formation of naphthyridine derivatives. With AMEs the reaction proceeds at rt to pyridopyrimidines which can then be rearranged quantitatively to naphthyridines (eq 6).[16]

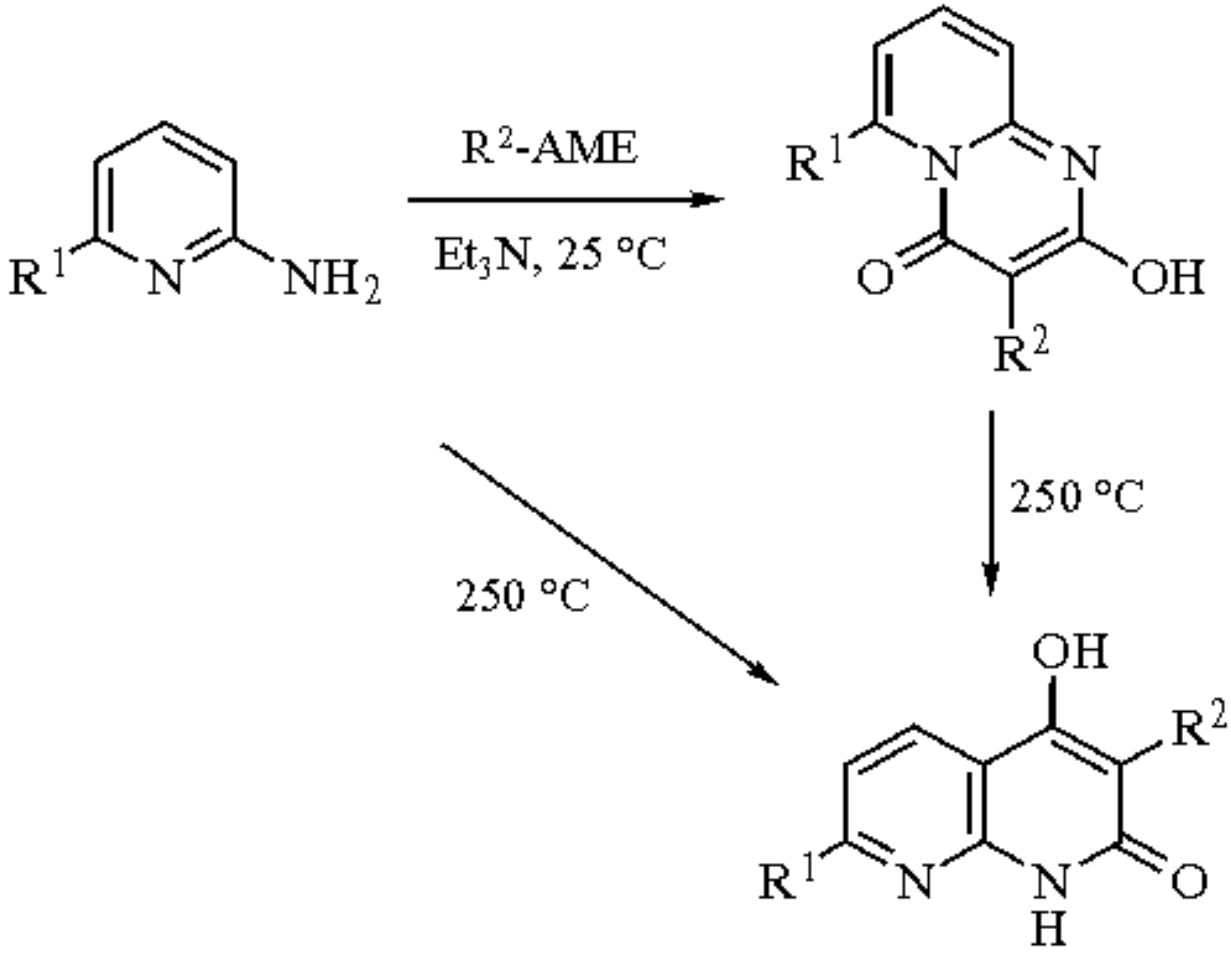

(6)

N,*N*´-Disubstituted amidines (and similar substrates which bear only one removable hydrogen atom) condense with AMEs to give cross-conjugated mesomeric betaines (eq 7).[17] The reaction has been extended to cyclic amidines (e.g. 2-alkylaminopyridines), leading to bicyclic compounds (**1**) and (**2**).[18] The reaction with five-membered 2-amino heterocycles has been studied extensively by Glennon et al.[5,7,19,20] Because of the biological activity found in this series, about 150 derivatives have been synthesized since 1973,[19] including those bearing a sugar moiety (R^1) at the nitrogen.[20]

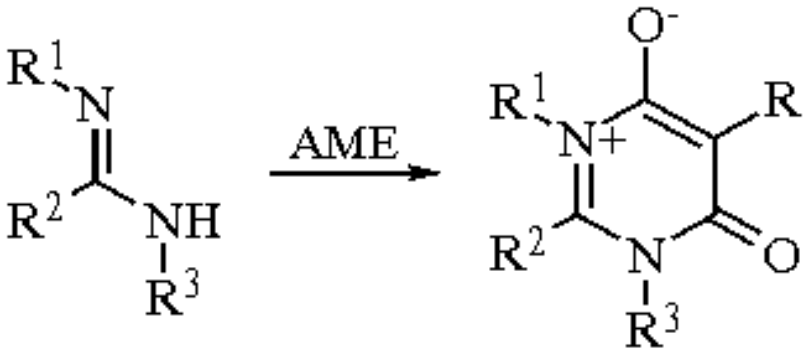

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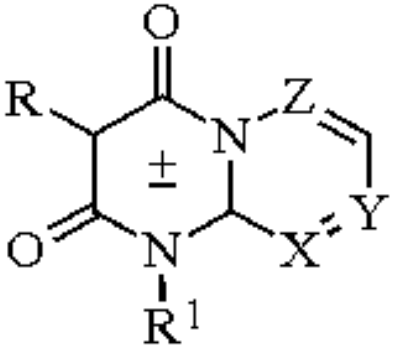

X, Y, Z = CH, CR, N

(1)

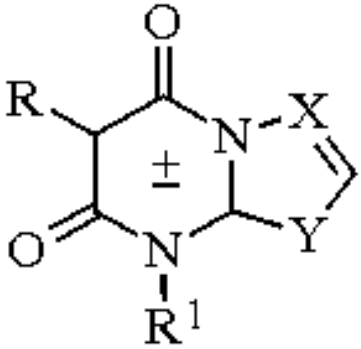

X = CH, CR, N
Y = O, S

(2)

Alternatives.

α-Carbonyl acid chlorides (ketene carbonyl chlorides) represent an effective alternative to AMEs; however, the number of described derivatives is limited. One of their advantages is their much lower molecular weight. On the other hand, the liberation of HCl sometimes brings problems. Bis(pentachlorophenyl) malonates have been proposed as an alternative.[21] However, they are less reactive, and very insoluble, and the liberated pentachlorophenol is more difficult to remove. Attempts to prepare mixed anhydrides from malonic acids, ethyl chloroformate, and triethylamine result in the formation of diethyl malonates.[22] An explanation for this unusual reaction has been described.[23]

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Carbon Suboxide***; ***(Chlorocarbonyl)ethylketene***; ***Diethyl Malonate***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***; ***Malonic Acid***; ***Malonyl Chloride***.

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Bis(tricyclohexyltin) Sulfide-Boron Trichloride

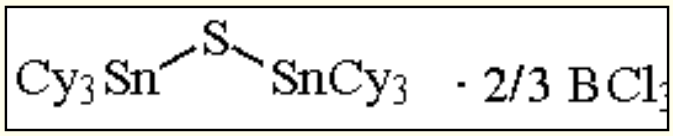

[13121-76-1] · $C_{36}H_{66}SSn_2$ · Bis(tricyclohexyltin) Sulfide-Boron Trichloride · (MW 768.36)

[10294-34-5] · BCl_3 · Bis(tricyclohexyltin) Sulfide-Boron Trichloride · (MW 117.17)

(functions as a conveniently prepared in situ form of boron trisulfide; a powerful sulfurating agent for the conversion of carbonyl units into their corresponding thiono carbonyl analogs, e.g. thioaldehydes, thioketones, β-thiolactams, thiolactams;[1] thiophenes;[2] the analogous bis(tricyclohexyltin) selenide-boron trichloride reagent is useful for selenation of carbonyl compounds to selenoaldehydes and selenoketones[1])

Physical Data: bis(tricyclohexyltin) sulfide: mp 130-132 °C; BCl_3: mp -107 °C; bp 12.5 °C.

Solubility: bis(tricyclohexyltin) sulfide: insol water; highly sol nonpolar organic liquids; less sol alcohol. Boron trichloride: Lewis acid, partially dissolves in aprotic organic liquids.

Form Supplied in: bis(tricyclohexyltin) sulfide: solid >97% pure; boron trichloride: gas (lecture bottle) 99.95% pure; more conveniently as a 1.0 M solution in dichloromethane, heptane, hexanes, or *p*-xylene.

Preparative Method: bis(tricyclohexyltin) sulfide: prepared in quantitative yield by treating tricyclohexyltin chloride with $Na_2S.9H_2O$ in refluxing ethanol (95%) for 2 h; recrystallization from CH_2Cl_2/MeOH affords pure material, mp 130-132 °C.[1]

Purification: bis(tricyclohexyltin) sulfide: by recrystallization.

Handling, Storage, and Precautions: bis(tricyclohexyltin) sulfide: irritant; stable solid. Boron trichloride (dichloromethane solution): corrosive; moisture sensitive; stored in nitrogen-filled pressure bottles kept cold in a refrigerator.

Chemistry.

Treating the tin sulfide reagent with a dichloromethane (or other) solution of ***Boron Trichloride*** in anhydrous toluene, at reflux, produces a highly reactive in situ form of boron trisulfide (eq 1). A potent form of boron triselenide is similarly derived from the corresponding tin selenide reagent (eq 2). [Bis(tricyclohexyltin) selenide is prepared in quantitative yield by treating tricyclohexyltin chloride with Na_2Se in anhydrous THF for 2 h. Recrystallization from CH_2Cl_2/MeOH affords pure material, mp 130-132 °C.][1] Other Group 14 organometallic sulfides[1] have been used as the chalcogen source with comparable efficacy (eq 3) and variations of the technique continue to be developed.[3-5]

$$3\ (Cy_3Sn)_2S + 2\ BCl_3 \longrightarrow 6\ Cy_3SnCl + 'B_2S_3' \qquad (1)$$

$$3\ (Cy_3Sn)_2Se + 2\ BCl_3 \longrightarrow 6\ Cy_3SnCl + 'B_2Se_3' \qquad (2)$$

$$3\ [R_3M]_2S + 2\ BCl_3 \longrightarrow 6\ R_3MCl + 'B_2S_3' \qquad (3)$$

R = Me, Ph; M = Si, Sn
R = *n*-Bu; M = Sn

If the in situ form of boron trisulfide is prepared in the presence of carbonyl-containing substrates, the carbonyl units are converted into their corresponding thiono analogs (eq 4); esters and lactones, however, generally are not converted in the process.

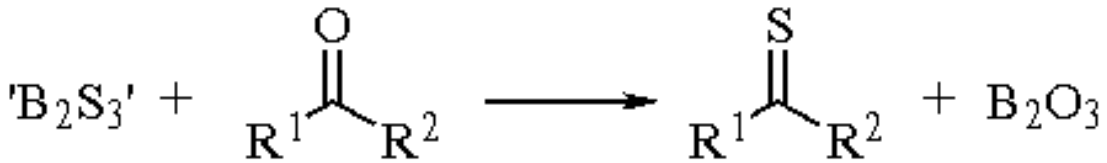

(4)

R^1, R^2	
nonenolizable aldehydes	65%
enolizable aldehydes	80% (as trimers)
nonenolizable ketones	85%
β-lactams, lactams	90%
lactones, esters	generally unreactive

The selenium analogs are similarly prepared, though isolation of the selenones, due to their inherent instability, is limited to hindered nonenolizable derivatives such as fenchone (eq 5).

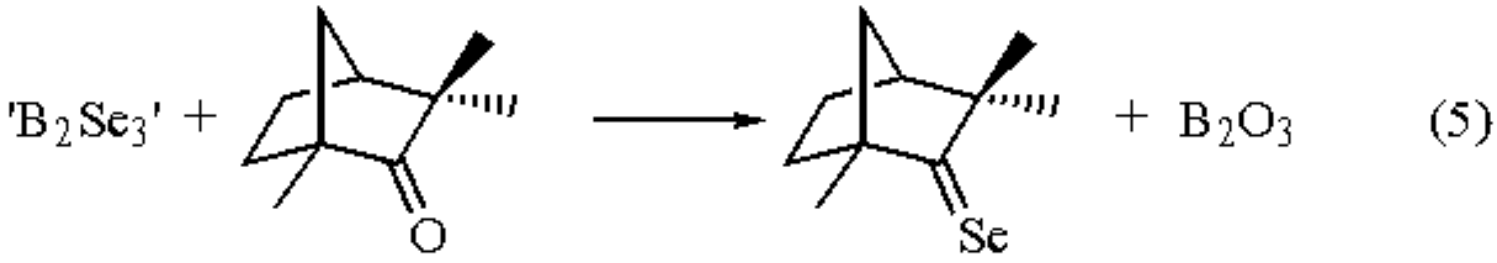

With some diketones such as 1,4-diones, thiophenes are the products (eq 6).[2] Though no mechanism is presented, a thione intermediate that enolizes, cylizes, and then dehydrates to the aromatic system might be possible.

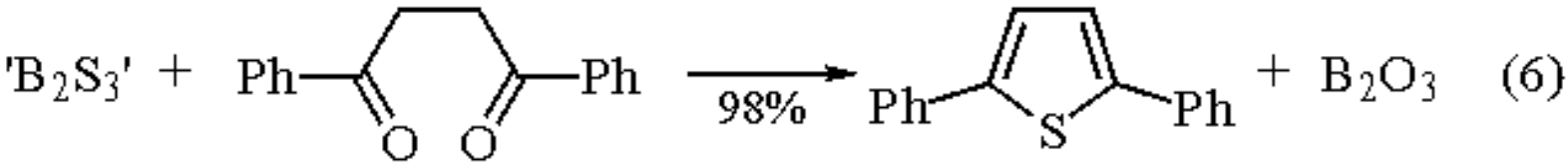

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Bis(trifluoroacetoxy)borane

$(CF_3CO_2)_2BH$

[-] · $C_4HBF_6O_4$ · Bis(trifluoroacetoxy)borane · (MW 237.85) (THF complex)

[75626-03-8] · $C_8H_9BF_6O_5$ · Bis(trifluoroacetoxy)borane · (MW 309.96)

(useful as a selective reducing agent, especially in the presence of strong acids)

Preparative Method: involves treatment of certain complexes of borane, such as ***Borane-Tetrahydrofuran***, ***Borane-Dimethyl Sulfide***, or ***Borane-Pyridine***, with ***Trifluoroacetic Acid*** in a suitable solvent such as tetrahydrofuran (THF), dichloromethane, or trifluoroacetic acid. Excess trifluoroacetic acid can be present because the title reagent is stable to protonolysis of the B-H bond.[1]

Handling, Storage, and Precautions: generated and employed in situ; normally not isolated and stored.[1,2] Hydrogen is evolved during reagent generation. The reagent causes the cleavage and oligomerization of THF.[1-3] Thus the use of borane-THF for reagent generation, or the use of THF as solvent, is not recommended for reactions at temperatures above 25 °C.[2] Use in a fume hood.

General Information.

Reductions of organic compounds with borohydride reagents in carboxylic acid media have been recognized for many years for diverse applications.[4] However, reductions with borane complexes in carboxylic acid media have received considerably less attention. Because the title reagent is stable to strong acids, such as trifluoroacetic acid, reductions can be performed in acidic media without the need for a large excess of boron hydride reagent.[1,2] The title reagent, which has been explored in some detail,[2] is applicable to a narrow class of reductions.

Reduction of Indoles to Indolines.

The reduction of indoles to indolines by use of hydride reagents is facilitated by activation of the indole, usually by protonation. The species reduced is actually the 3*H*-indolenium ion. Bis(trifluoroacetoxy)borane in trifluoroacetic acid,[1,2] and certain borane complexes (borane-THF,[1,2,5-8] borane-dimethyl sulfide,[1,2,6,9] and borane-pyridine[1,6,10]) in trifluoroacetic acid, offer a rapid, mild, convenient, high-yield method for this conversion. The benefits of this method are particularly realized in the reduction of indoles bearing basic amine groups.[1,2,5-8] High stereochemical control for the *cis* indoline can be obtained for the reduction of indoles bearing a 2,3-fused ring;[1,2,5-8] however, under certain conditions other stereochemical results can be obtained.[6,7] The mild, rapid reduction of tryptophan derivatives[10a,b] permits the selective reduction of Trp residues within peptides and proteins.[10b-d] Some representative examples are

depicted in eq 1,[1] eq 2,[9] eq 3,[5] and eq 4.[10a]

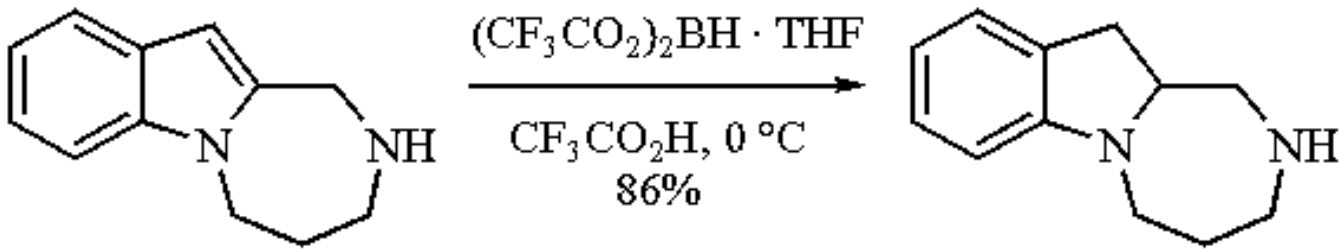

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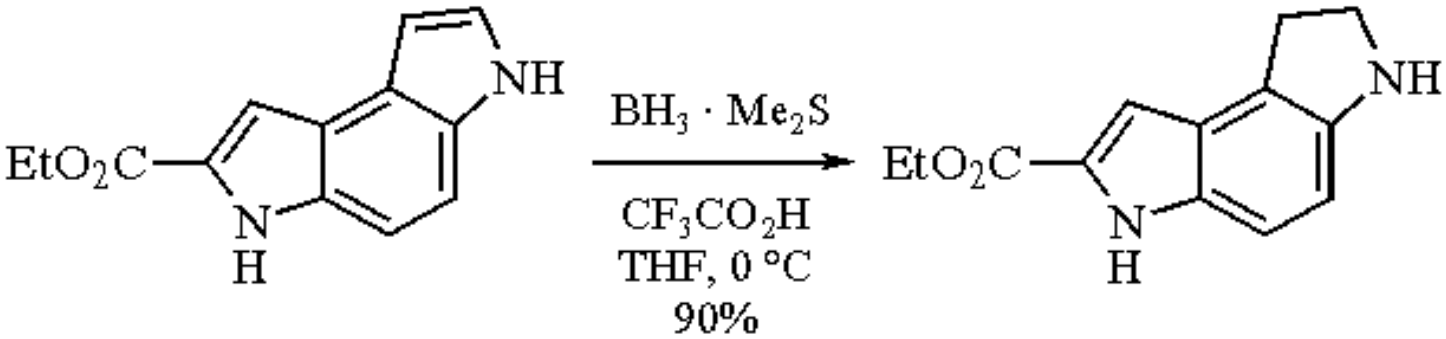

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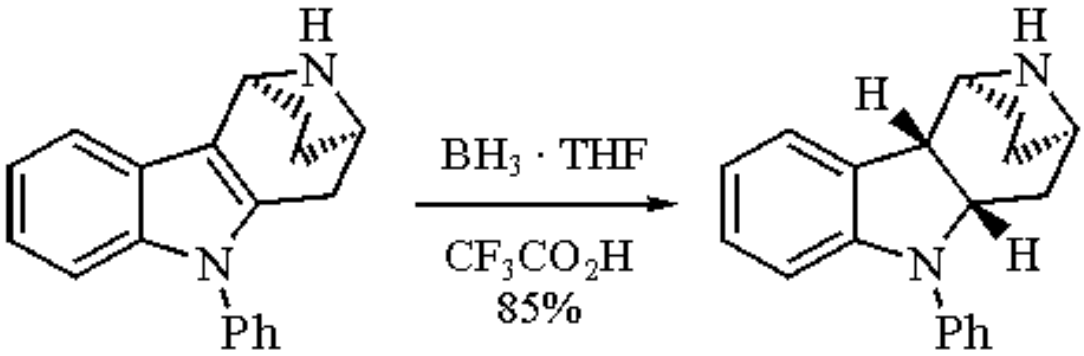

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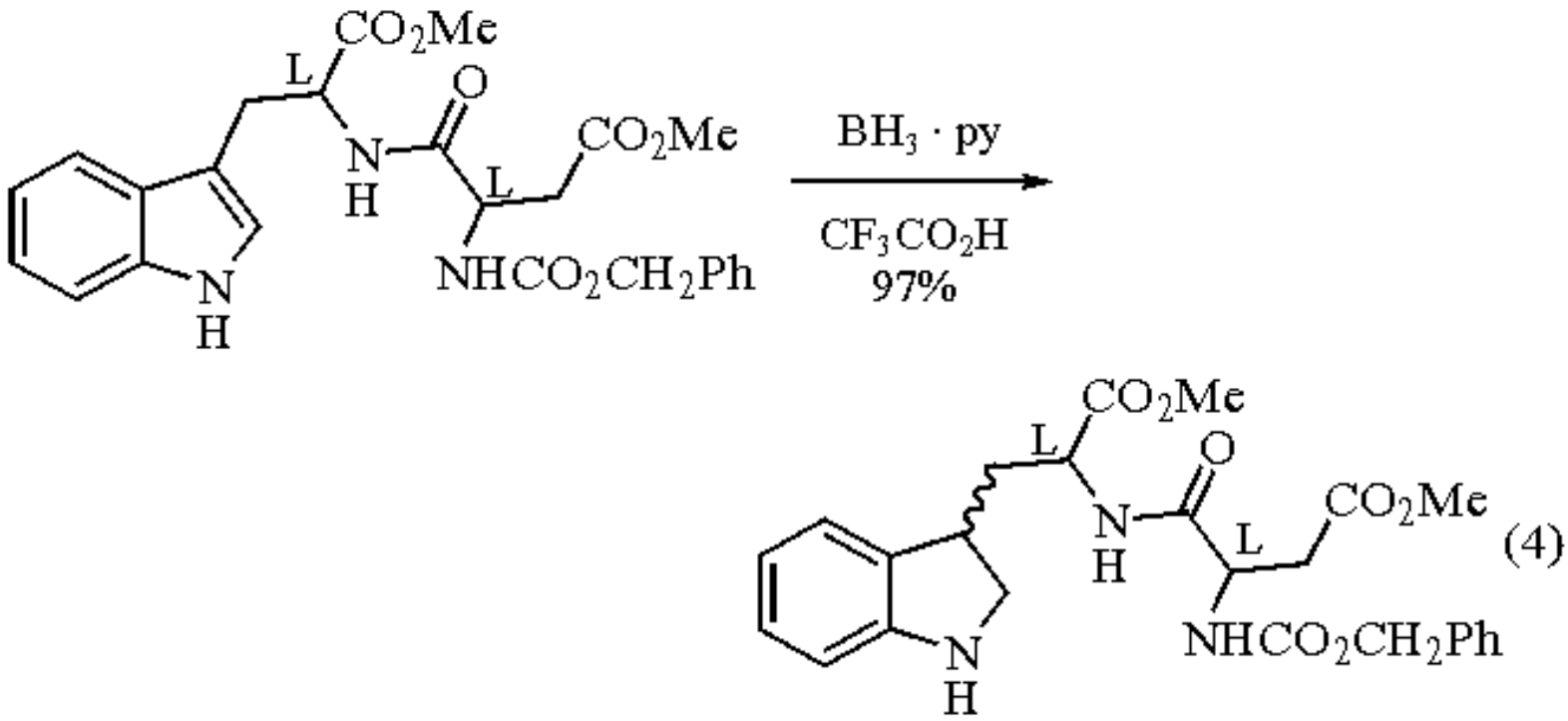

Reductive Deoxygenation of Carbinols.

Diaryl and triaryl carbinols are reduced to the corresponding hydrocarbon species by bis(trifluoroacetoxy)borane in trifluoroacetic acid, rapidly and in good yields (eqs 5 and 6).[2,11] In certain β-aryl-β-hydroxy tertiary amines, an enammonium-iminium rearrangement mechanism occurs, which can afford surprisingly effective stereochemical control (eq 6).[11] Diaryl ketones are directly deoxygenated to the corresponding diaryl hydrocarbons, via carbinol intermediates.[2,12] It is also possible with borane-pyridine and trifluoroacetic acid to deoxygenate monoaryl carbinols and ketones (eq 7).[12] Similarly, alkynic carbinols, in the form of dicobalt hexacarbonyl complexes, are reductively deoxygenated by using borane-dimethyl sulfide in trifluoroacetic acid; yields are moderate to good for the three steps of complex formation, reduction, and decomplexation (eq 8).[13] Ethers prone to forming carbocations in trifluoroacetic acid, such as trimethyl orthobenzoate and acyliminium ion precursors (eq 9), are also readily reduced.[2] By the same token, adducts from aldehydes or ketones and thiols are reduced to sulfides by using pyridine-borane and trifluoroacetic acid (eq 10).[14]

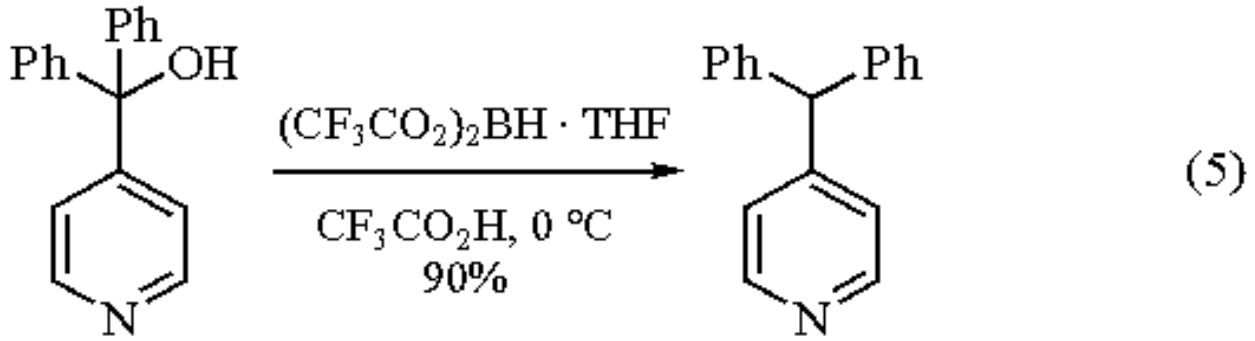

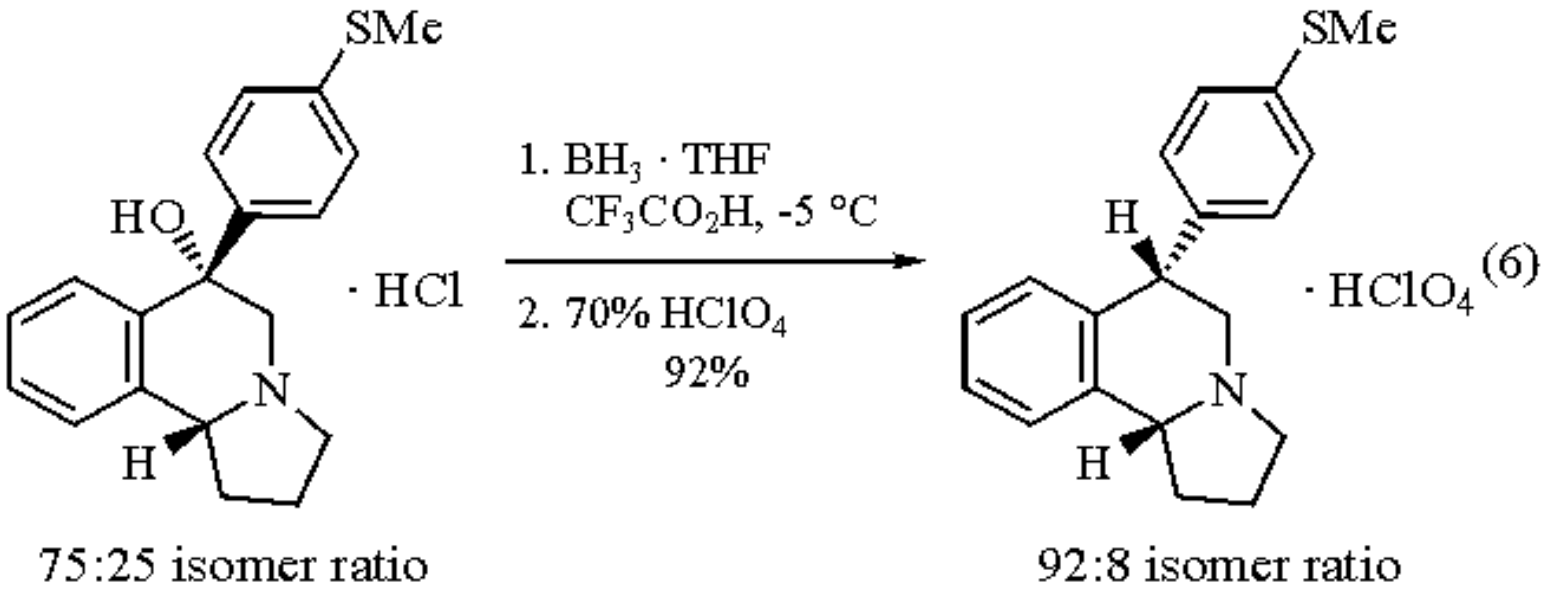

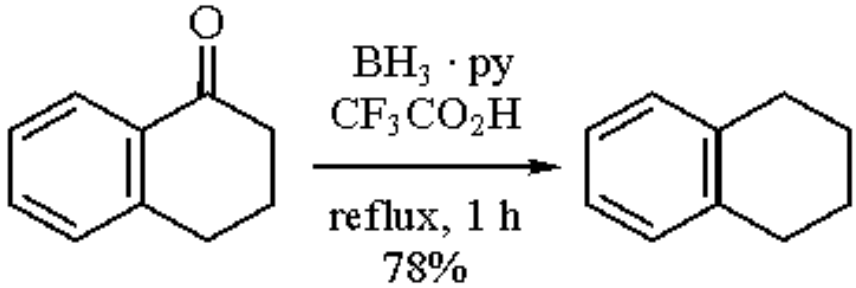

(7)

$$Me(CH_2)_7C{\equiv}CCH_2OH \xrightarrow[\text{3. } Fe(NO_2)_3 \cdot 9H_2O,\ 62\%]{\text{1. } Co_2(CO)_8,\ CH_2Cl_2;\ \text{2. } BH_3 \cdot Me_2S,\ CF_3CO_2H,\ 0\ ^\circ C} Me(CH_2)_7C{\equiv}CMe \quad (8)$$

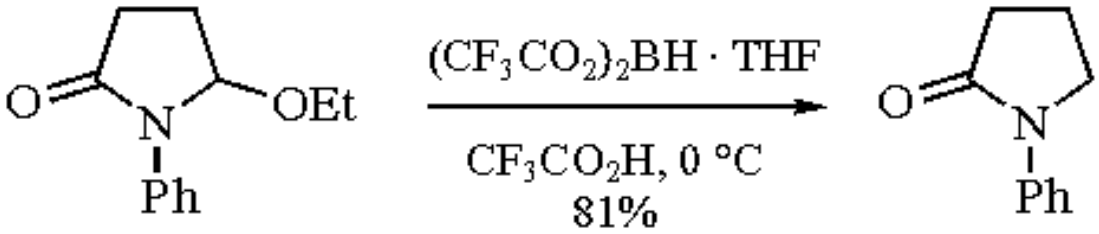

(9)

$$Ph(CH_2)_2CHO + BuSH \xrightarrow[CF_3CO_2H,\ 74\%]{BH_3 \cdot py} Ph(CH_2)_3S(CH_2)_3Me \quad (10)$$

Reduction of Other Functional Groups.

As suggested above, the title reagent readily reduces aldehydes and ketones to alcohols.[2] Imines are also readily reduced to amines (eq 11).[2,15] Cyclohexanone oxime is reduced to the hydroxylamine in 70% yield;[2] another example is shown in eq 12.[16] Tosylhydrazones are reduced to tosylhydrazines (eq 13) or the corresponding hydrocarbon (eq 14).[2] Certain diaza heterocycles, such as quinoxaline and quinazoline, are reduced (eq 15).[2] Many other functional groups and organic moieties are relatively inert to the reducing conditions: nitro, aryl/benzyl ether, nitrile, ester, carboxamide, acid, acid chloride, amidine, imide, alkene, alkyne, sulfoxide, disulfide, quinoline, isoquinoline, pyrrole, and benzofuran.[2,10]

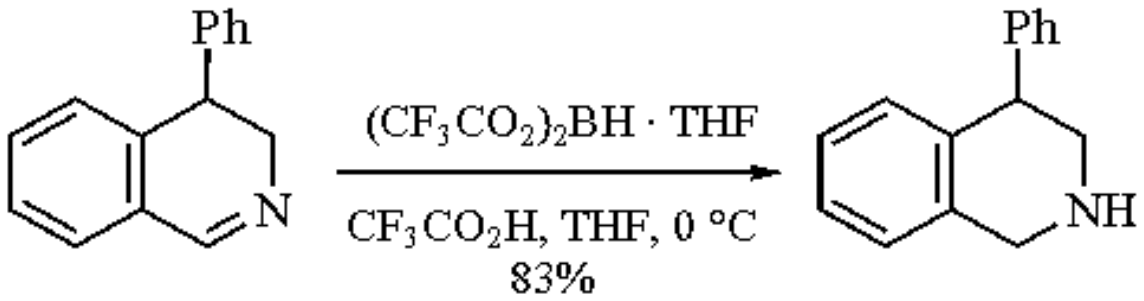

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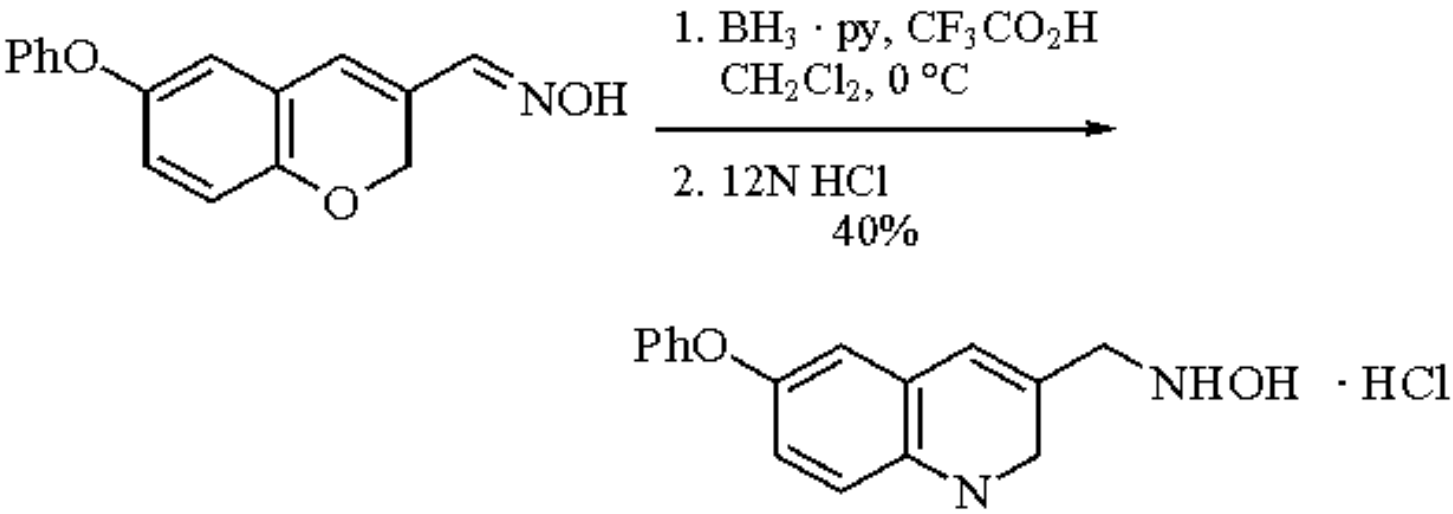

(12)

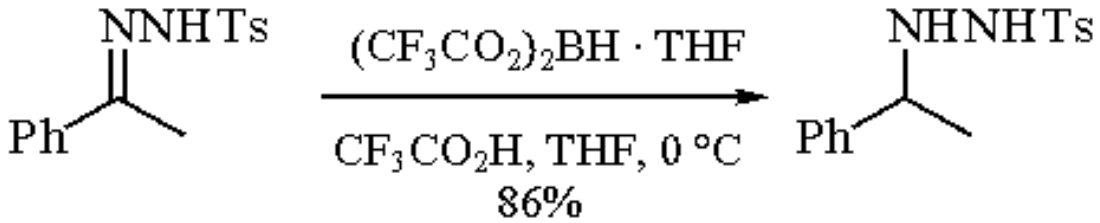

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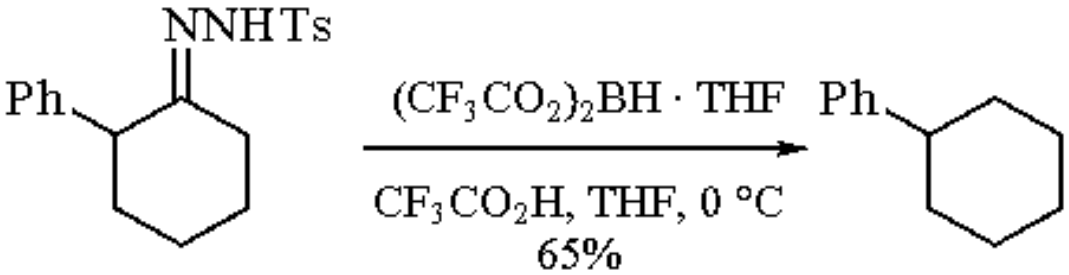

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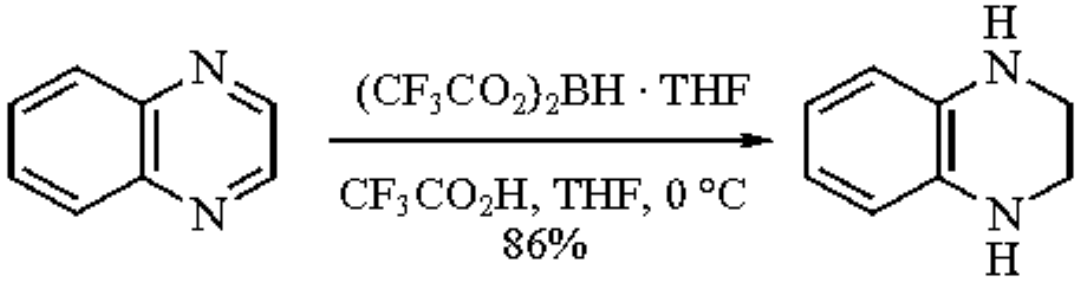

(15)

Related Reagents.

Bis(benzoyloxy)borane; ***Catecholborane***; ***Sodium Borohydride***; ***Sodium Tris(trifluoroacetoxy)borohydride***.

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N,O-Bis(trifluoroacetyl)hydroxylamine

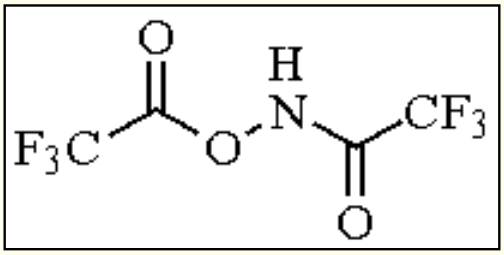

[684-78-6] · $C_4HF_6NO_3$ · *N,O*-Bis(trifluoroacetyl)hydroxylamine · (MW 225.05)

(conversion of aldehydes to nitriles[1])

Physical Data: mp 62 °C (subl, sealed tube; transition 50 °C);[1] mp 40-50 °C.[2]

Solubility: sol ether, benzene, hot CH_2Cl_2; insol cold CH_2Cl_2.

Analysis of Reagent Purity: ^{19}F NMR (δ -73.7 (s), -74.5 (s)); IR (1848, 1706 cm^{-1}); elemental analysis.

Preparative Method: addition of ***Trifluoroacetic Anhydride*** (2.2 equiv) to ***Hydroxylamine*** hydrochloride.

Purification: recrystallized from CH_2Cl_2.

Handling, Storage, and Precautions: hygroscopic; should be dried in a vacuum desiccator.

Conversion of Aldehydes to Nitriles.

In 1959, Pomeroy and Craig reported a new method for direct conversion of aldehydes to nitriles using pyridine and either trifluoroacetohydroxamic acid or *N,O*-bis(trifluoroacetyl)hydroxylamine, with the latter reagent providing higher yields of products (eq 1).[1] The reagent was prepared by refluxing $HONH_2.HCl$ with excess TFAA, followed by removal of volatiles and recrystallization from CH_2Cl_2. More recently, a modification of this procedure has been reported.[2] A mechanism proceeding through a cyclic, four-membered intermediate has been proposed.[3]

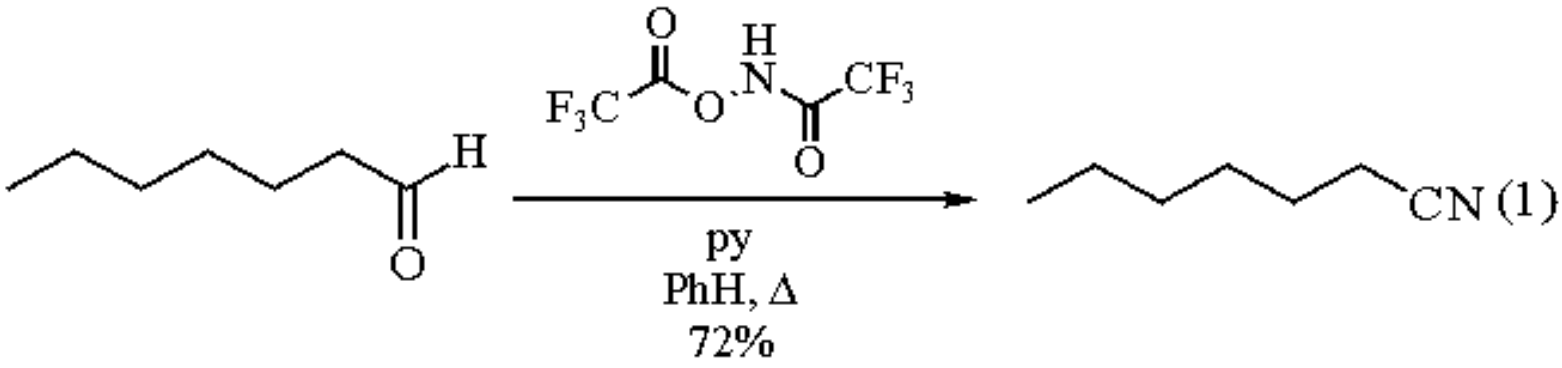

Since its first report, this reagent has been used extensively for the aldehyde to nitrile transformation in several complex substrates. Early examples included steroidal systems and mitomycin derivatives.[4] *N,O*-Bis(trifluoroacetyl)hydroxylamine can also be applied to the conversion of α-formyl ketones to the corresponding ketonitriles (eq 2).[5]

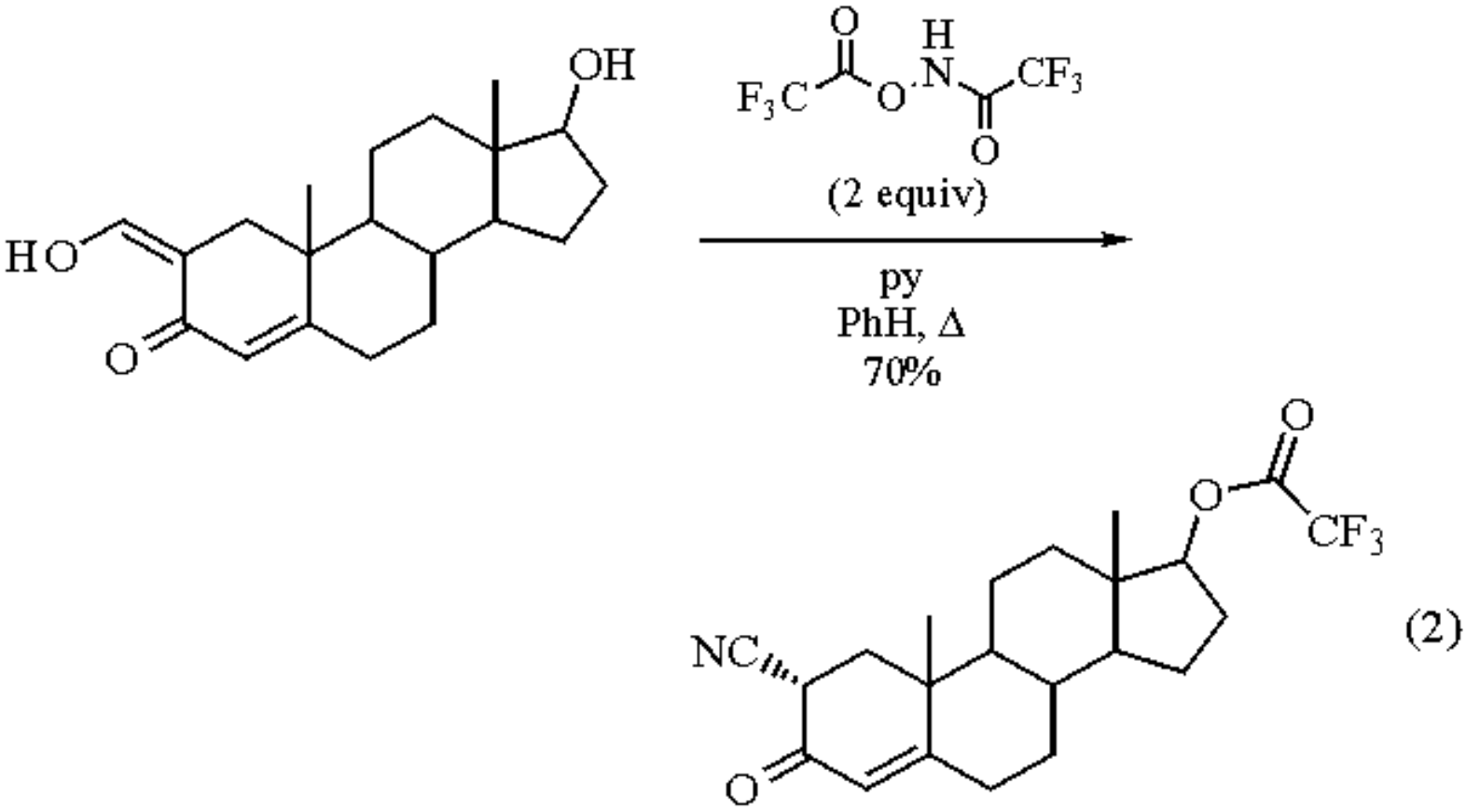

Other examples have demonstrated the compatibility of *N,O*-bis(trifluoroacetyl)hydroxylamine with a variety of potentially sensitive functional groups. An optically active cyclobutanecarbaldehyde was converted to the corresponding nitrile with no apparent epimerization.[6] α,β-Unsaturated aldehydes attached to thiazine or dihydrothiazine rings are also amenable to conversion into the corresponding α,β-unsaturated nitriles.[7] The reaction can be carried out in the presence of ester groups,[7,8] as exemplified by an early step in the synthesis of steganacine (eq 3).[8] Unsaturated aldehydes at the terminus of conjugated polyene systems have also been successfully converted to nitriles.[9] 1,3-Dithiane-2-carbaldehyde has been converted into the corresponding cyano-1,3-dithiane (eq 4).[10]

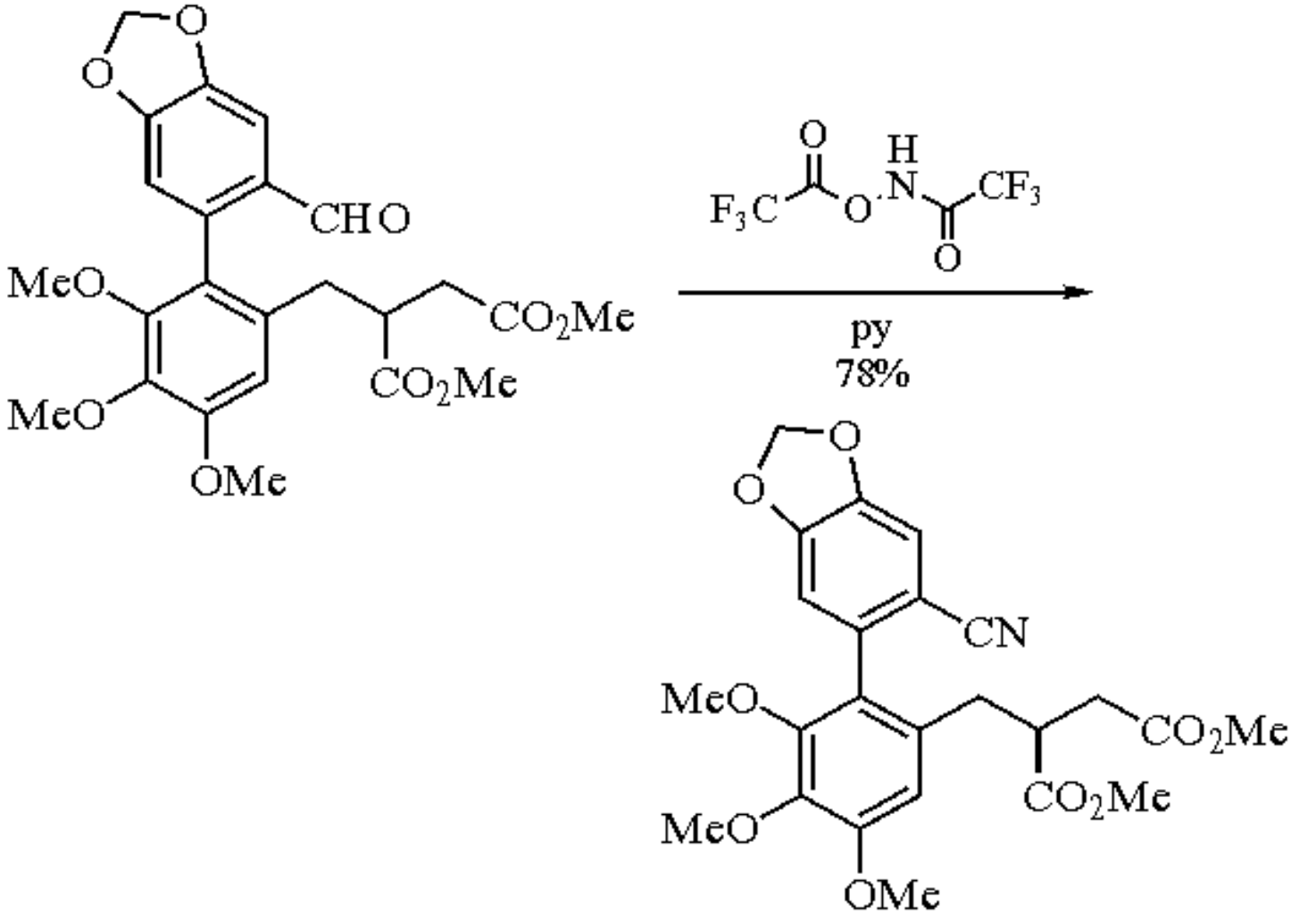

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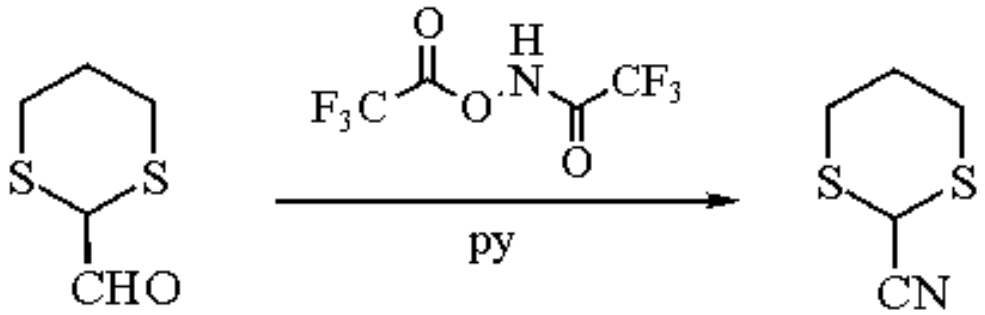

(4)

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1,3-Bis(triisopropylsilyl)propyne

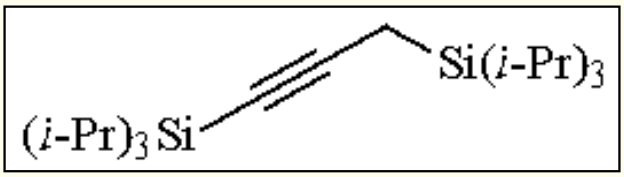

[82192-59-4] · $C_{21}H_{44}Si_2$ · 1,3-Bis(triisopropylsilyl)propyne · (MW 352.75)

(precursor of a stereoselective bulky C_3 nucleophile, functionalized Peterson reagent[1])

Alternate Name: 1,3-bis(TIPS)propyne.

Physical Data: bp 130-135 °C/0.08 mmHg; *d* 0.846 g cm^{-3}.

Solubility: both the reagent and its lithio derivative are soluble in ether or THF.

Analysis of Reagent Purity: GC at 210 °C on a glass capillary column coated with OV-17; TLC on silica (hexanes, R_f 0.75). ^1H NMR ($CDCl_3$, 80 MHz): δ = 1.63 (s, CH_2), 1.3-0.9 (m, 2 TIPS).

Preparative Method: 1,3-bis(TIPS)propyne is prepared in quantitative yield by silylation of ***3-Lithio-1-triisopropylsilyl-1-propyne*** with ***Triisopropylsilyl Trifluoromethanesulfonate***.[2]

Purification: by distillation or chromatography.

Handling, Storage, and Precautions: no special precautions required; the reagent is not changed when stored for several months at ambient temperature. The Li derivative is handled under inert gas using simple syringe equipment.

Generation of Lithio-1,3-bis(triisopropylsilyl)propyne.

The main use of the title reagent is as a precursor of the lithium derivative. 1,3-Bis(triisopropylsilyl)propyne is cleanly lithiated by treatment with 1 equiv of ***n-Butyllithium*** in THF at -20 °C (15 min) to what is probably an equilibrium mixture of propargylic and allenic species (**1**) and (**2**) (eq 1).[3] The bulky triisopropylsilyl (TIPS) group serves as a controlling group in the addition of (**1**/**2**) to electrophiles.

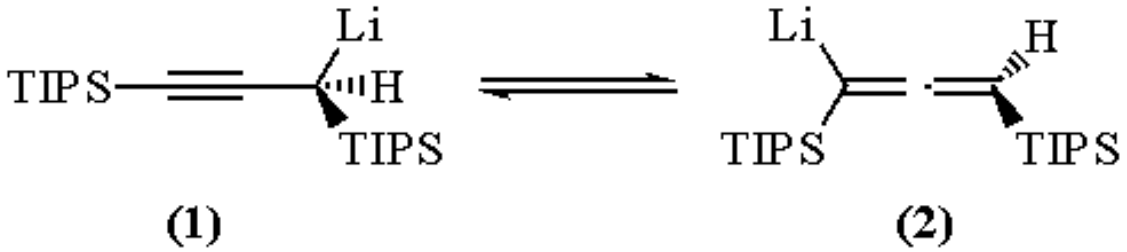

(1)

Formation of (*Z*)-enynes.

The lithio derivative reacts with aliphatic aldehydes (RCHO, -78 °C -> rt, few h) to form the (*Z*)-enynes R-CH=CH-C&tbond;C-TIPS (**3**) in good yield (57-79%) and high isomeric purity (*Z*:*E* &AApprox; 20:1, eq 2). The intermediate addition product formed by attack of (**2**) on the aldehyde has *erythro* configuration[2] and undergoes *syn* elimination of silanolate to give (**3**) by the pathway generally observed in Peterson reactions in alkaline media.[4]

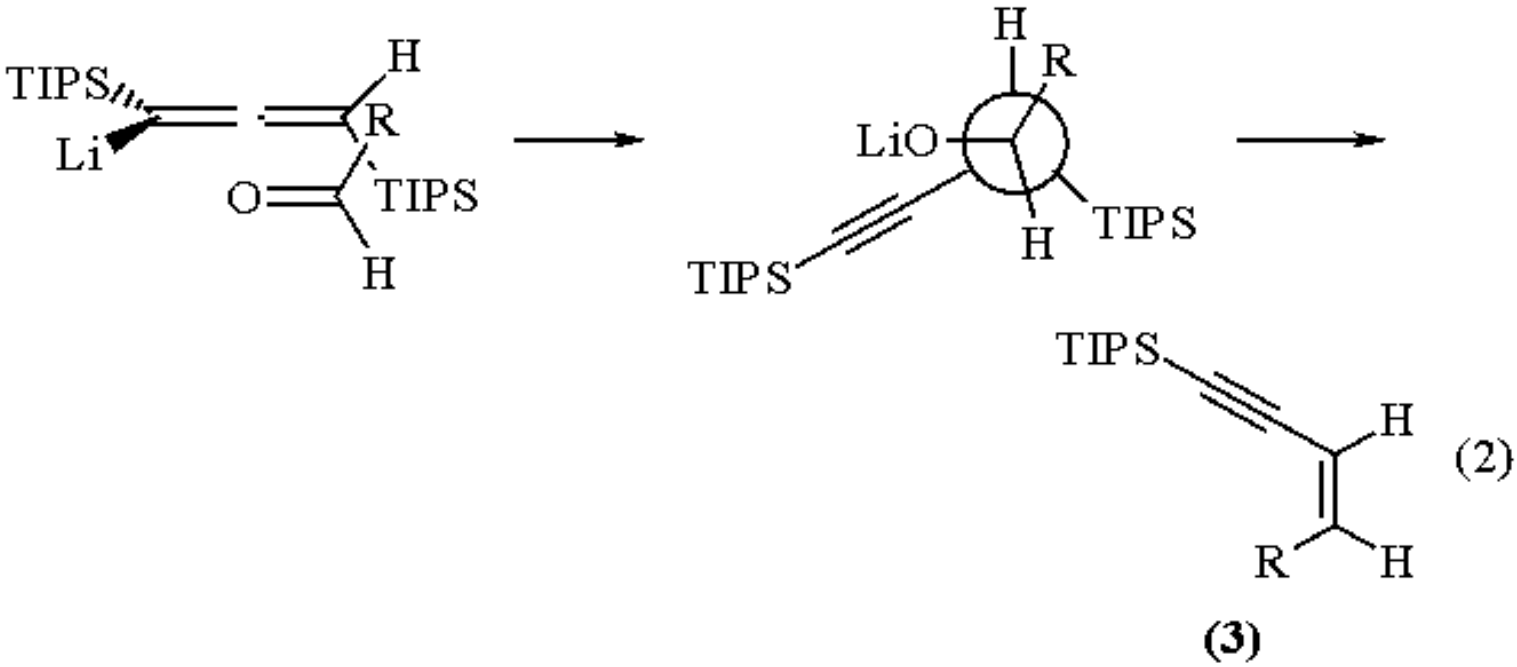

The method was used for attachment of the *cis* enyne side chain in a synthesis of gephyrotoxin,[5] and for the preparation of (*Z*)-non-3-en-1-yne, a building block in the synthesis of prostaglandins and of 11-HETE methyl ester.[6]

Formation of (*E*)-Enynes.

The stereoselectivity of the reaction can be reversed simply by adding 5 equiv ***Hexamethylphosphoric Triamide*** to the solution of (**1**/**2**) prior to addition of the aldehyde. Under these conditions the reaction is complete within a few seconds at -78 °C, and (*E*)-enynes (**4**) are isolated in 60-65% yield with high *E*:*Z* selectivity (20:1 to 10:1, eq 3). Evidence has been presented that the action of HMPA is exerted in the addition to the aldehyde, not in the elimination step.[2] A *threo* propargylic intermediate is presumably formed by attack of an ion pair similar to (**1**) onto the aldehyde. The method was used for the introduction of the *trans* enyne side chain in a synthesis of laurenyne.[7]

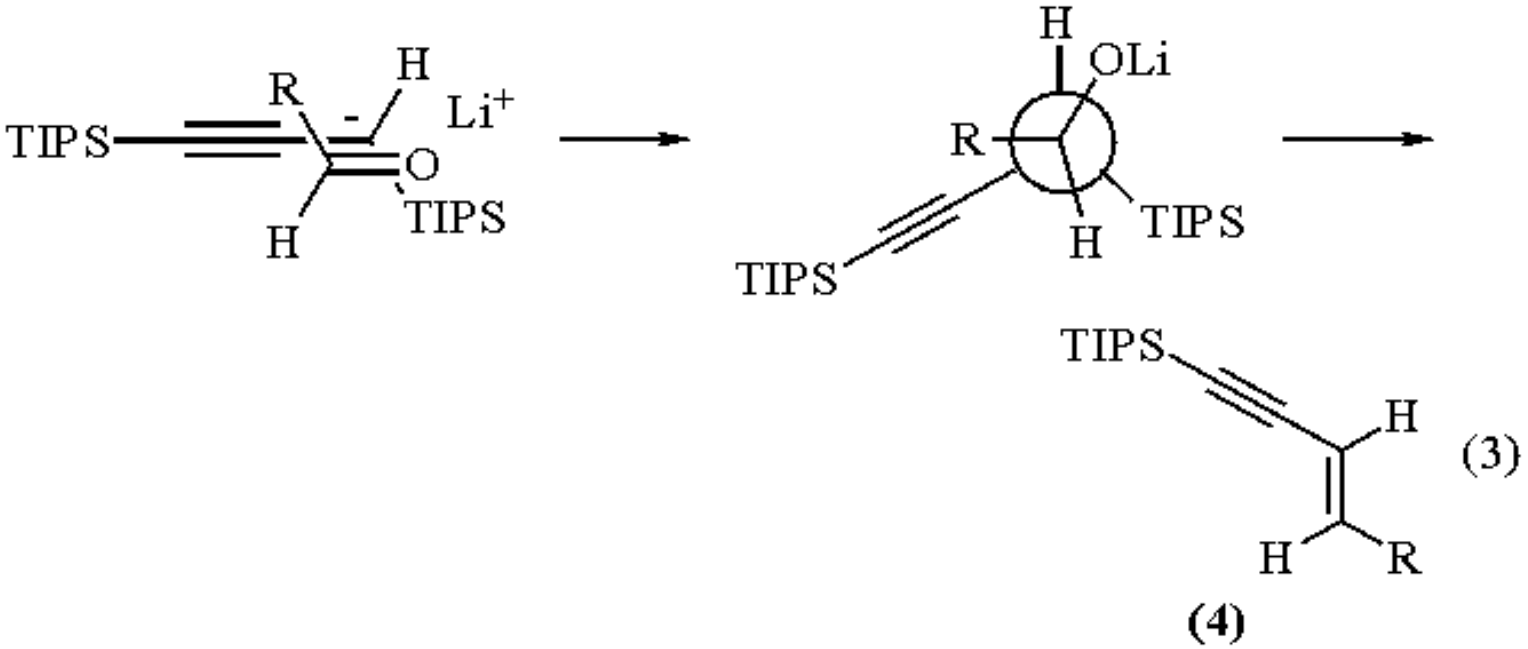

The stereochemical preferences of these reactions are less pronounced with aromatic aldehydes. For example, the reaction of (**1**/**2**) with benzaldehyde in THF gives a 2:1 mixture of *Z*:*E* enynes (-20 -> 0 °C, 1 h, 67%), whereas in the presence of 1 equiv HMPA mostly the (*E*)-enyne is obtained (1:9 selectivity, -78 °C, 10 s, 78%).

Enynes and Dienynes from Other Bis(silyl)propynes.

Corresponding Li reagents containing a less bulky silyl group at the propargylic carbon generally show lower selectivity for (*Z*)-enynes, e.g. the Li derivatives of 1,3-bis(trimethylsilyl)propyne, 1-trimethylsilyl-3-triethylsilyl-1-propyne, 1-trimethylsilyl-3-*t*-butyldimethylsilyl-1-propyne (TMS-C&tbond;C-CH_2-SiR_3 with R_3 = Me_3, Et_3, *t*-$BuMe_2$).[8] Selectivity could be improved by using a Mg or Ti counterion instead of Li.[8-10] Cinnamaldehyde, cyclohexanone, and *cis*- and *trans*-hydrindanones[11] likewise underwent the reaction.

1-Trimethylsilyl-3-triisopropylsilyl-1-propyne (TMS-C&tbond;C-CH_2-TIPS, **5**) was found to give essentially the same results (yield and stereoselectivity) as bis(TIPS)propyne in two cases of direct comparison (crotonaldehyde, cinnamaldehyde).[12] Scrambling of the silyl groups did not occur. Compound (**5**) is available from TMS-C&tbond;C-CH_2Br by reaction with ***Magnesium*** in the presence of 0.5% ***Mercury(II) Chloride*** followed by silylation with TIPS-OTf (76%). Silane (**5**) can also be prepared from propargyl bromide by reaction with (1) Mg/0.5% $HgCl_2$, (2) TIPS-OTf, (3) *n*-BuLi, (4) TMS-Cl (two-pot procedure, 63% overall).[12]

Using the lithio reagent obtained from (**5**) in THF, (*Z*)-dienynes were prepared in good yield and stereoselectivity from several α,β-unsaturated aldehydes (eq 4) (Table 1).[12,13] In the corresponding Wittig reactions, the yields and isomeric purity of enynes were far lower. Oxirane and aziridine groups are compatible with the reaction conditions (eq 5) (Table 2).[12]

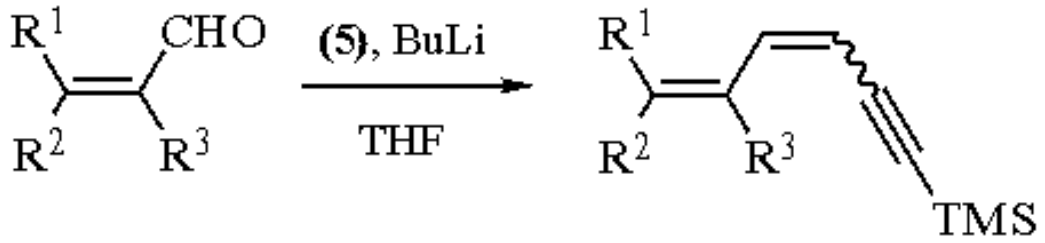

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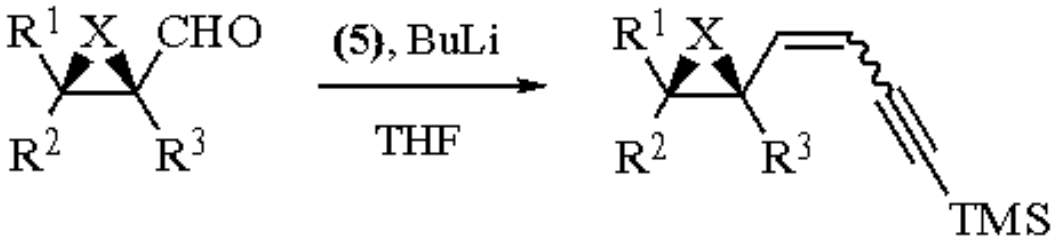

(5)

Table 1 TMS-Protected Dienynes from a,b-Unsaturated Aldehydes (eq 4)

R^1	R^2	R^3	Yield (%)	*Z*:*E*
H	Me	H	81[a]	4:1[a]
Me	Me	H	89	3.5:1
Me	H	Me	93	34:1
H	$(CH_2)_3$		80	13:1
H	$(CH_2)_3$		86[a]	21:1[a]
Ph	$(CH_2)_4$		74	>20:1
Ph	$(CH_2)_5$		85	37:1
Ph	$(CH_2)_6$		60	>20:1
Ph	$(CH_2)_{10}$		67	9:1
H	Ph	H	82	3.4:1
Ph	Ph	H	83	1.9:1
H	Ph	Me	89	24:1
H	Ph	Ph	91	98:1

[a] In the presence of 1 equiv $Ti(O\text{-}i\text{-}Pr)_4$.

Table 2 TMS-Protected Enynes from Oxirane (Aziridine) Carbaldehydes (eq 5).

X	R^1	R^2	R^3	Yield (%)	Z: E
O	H	Ph	H	60	1.5:1
O	Ph	H	Ph	63	1:1.5
O	H	Ph	Ph	75	>20:1
NCH_2Ph	Ph	H	H	73	>20:1

The preparation of (*Z*)-enynes by alternative methods (Wittig-Horner and others) is possible;[14-16] and is also possible for (*E*)-enynes (Wittig).[17-19]

Epoxide Opening.

The lithio propyne derivative (**1**/**2**) adds to epoxides in spite of its bulkiness. The TIPS group near the reaction center is useful for preventing secondary reactions in a polyepoxide substrate. Thus while the simple monoadduct (**6a**) from *cis*-benzene trioxide and 3-lithio-1-TIPS-1-propyne was formed as a minor product only (always accompanied by products (**7a**), (**8a**), (**9a**)), the monoadduct (**6b**) was isolated in 48% yield (two diastereomers) from the reaction with (**1**/**2**) along with 10% (**7b**); bisadducts (**8b**/**9b**) were not formed (eq 6).[20]

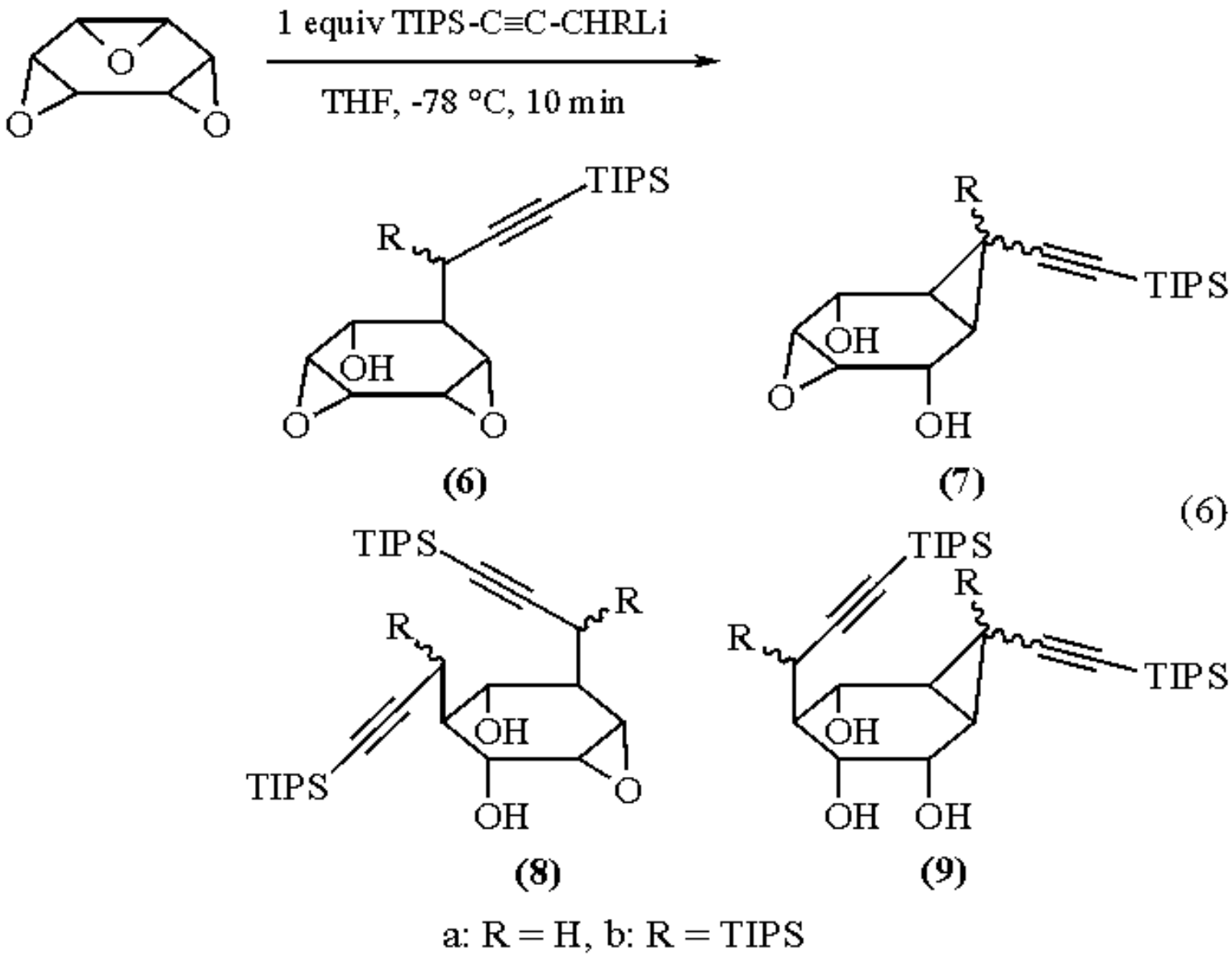

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20. Rücker, Ch. unpublished results.

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2,5-Bis(trimethylsilyloxy)furan[1]

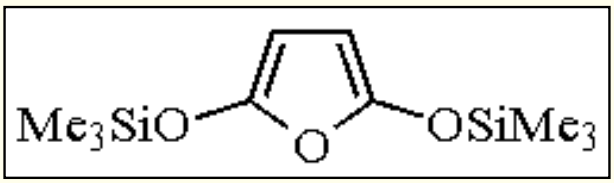

[77220-06-5] · $C_{10}H_{20}O_3Si_2$ · 2,5-Bis(trimethylsilyloxy)furan · (MW 244.44)

(diene for use in cycloadditions;[3] building block for quinones[3] and heterocycles[4-6])

Physical Data: bp 42-43 °C/0.01 mmHg.

Solubility: insol H_2O; sol aprotic organic solvents.

Preparative Methods: readily prepared by the reaction of ***Succinic Anhydride***, ***Triethylamine***, ***Zinc Chloride***, and ***Chlorotrimethylsilane*** in MeCN (eq 1). It can also be prepared in 66% yield using succinic anhydride, ***Trimethylsilyl Trifluoromethanesulfonate*** and triethylamine.[2]

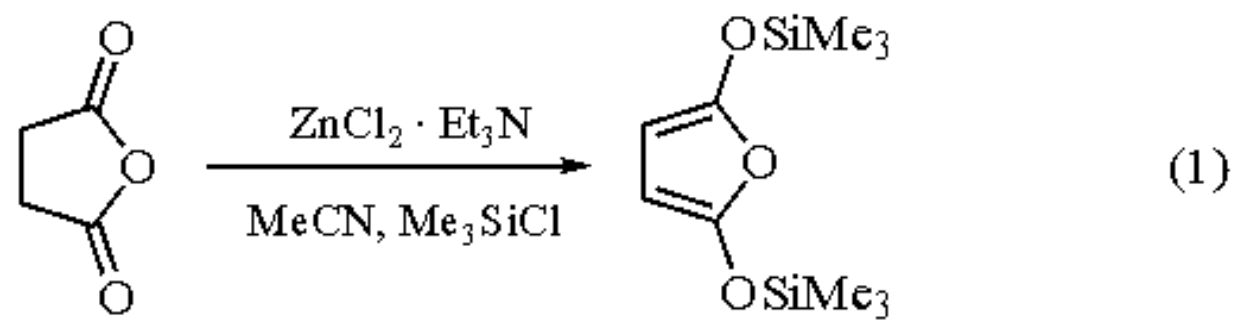

Handling, Storage, and Precautions: very unstable to air and moisture.

Cycloadditions.

The title reagent is very reactive in Diels-Alder reactions, affording adducts with ***Dimethyl Acetylenedicarboxylate*** and ***Ethyl Acrylate*** in good to excellent yields. The resulting adducts can be desilylated with ***Sodium Fluoride*** in wet acetonitrile (eq 2).[3]

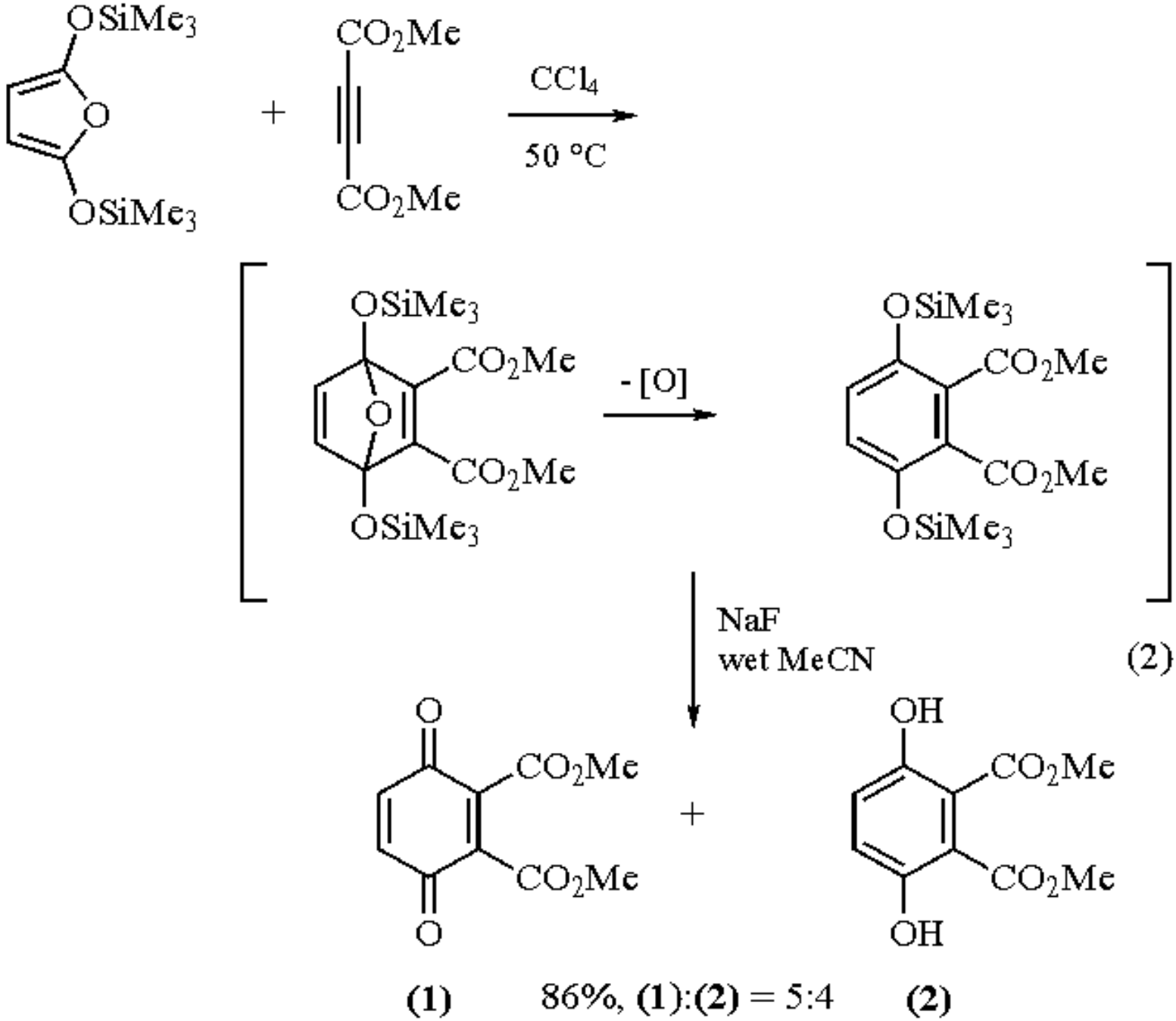

2,5-Bis(trimethylsilyloxy)furan also reacts with tetrachlorocyclopropene in carbon tetrachloride for 3 days to afford a bicyclic adduct in 33% yield (eq 3).[4]

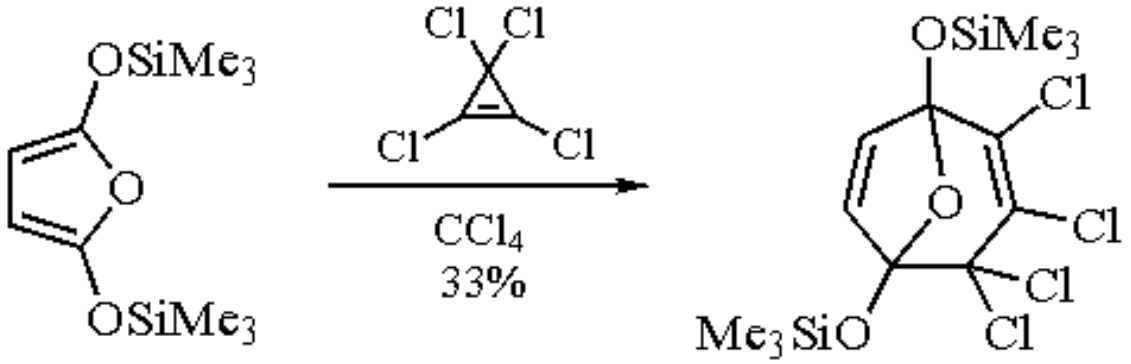

(3)

Nucleophilic Additions.

2,5-Bis(trimethylsilyloxy)furan reacts with carbonyl compounds in the presence of a Lewis acid to form an anhydride which upon workup affords a dilactone (eq 4). This one-step procedure constitutes a facile entry to the 3,7-dioxabicyclo[3.3.0]octane system.[5] This reaction is successful with both aldehydes and ketones.

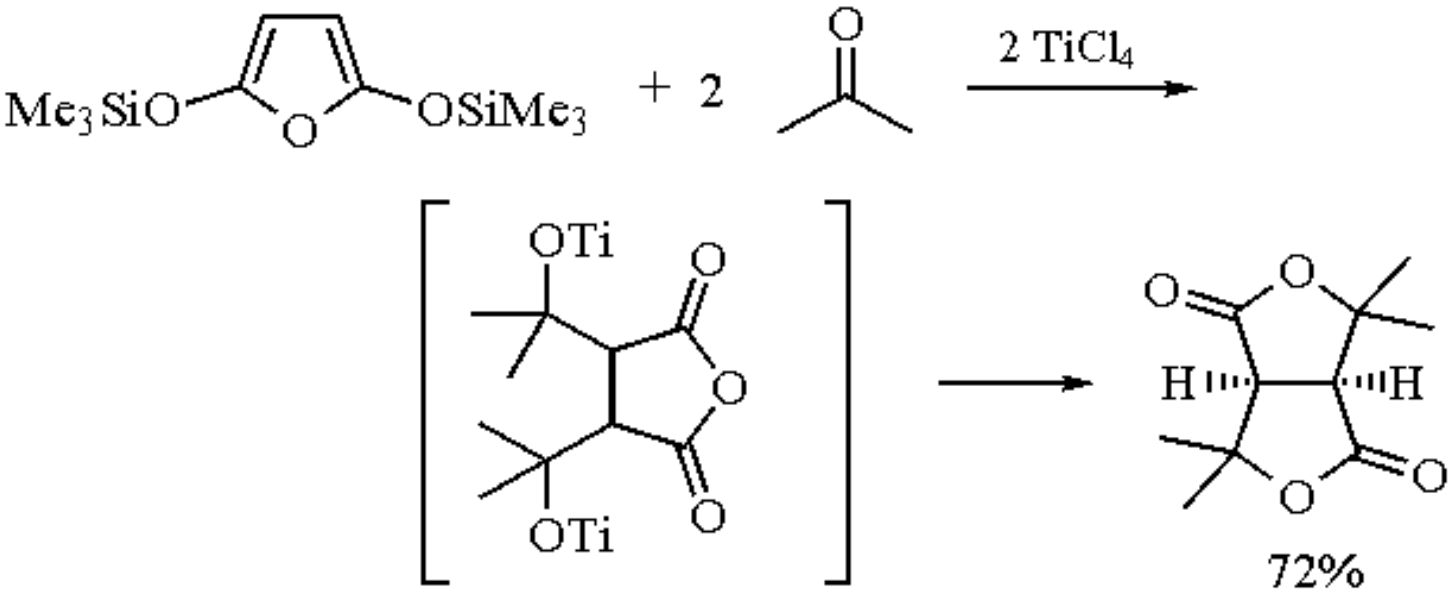

(4)

2,5-Bis(trimethylsilyloxy)furan reacts with methyl vinyl ketone to produce a novel diketo acid (eq 5). This reaction may be conducted either thermally or in the presence of a Lewis acid such as ***Titanium(IV) Chloride*** at -78 °C.[6]

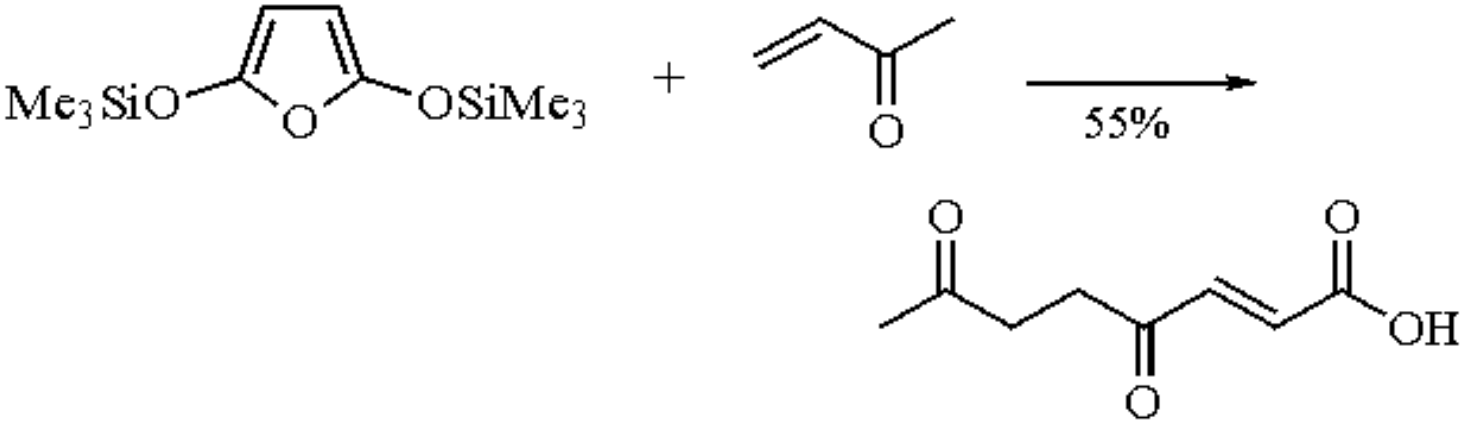

(5)

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1. Fieser, M. A. *FF*, *10*, 45.
2. Frick, U.; Simchen, G. *LA* **1987**, 839.
3. Brownbridge, P.; Chan, T.-K. *TL* **1980**, *21*, 3423.
4. Seitz, G.; Van Gemmern, R. *CZ* **1987**, *111*, 209.
5. Brownbridge, P.; Chan, T.-K. *TL* **1980**, *21*, 3427.
6. Brownbridge, P.; Chan, T.-K. *TL* **1980**, *21*, 3431.

N,O-Bis(trimethylsilyl)acetamide

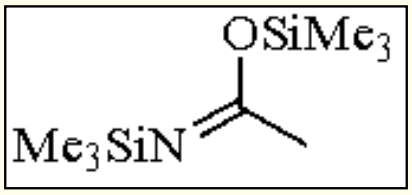

[10416-59-8] · $C_8H_{21}NOSi_2$ · *N,O*-Bis(trimethylsilyl)acetamide · (MW 203.43)

(powerful silylating agent; reacts with a wide range of functional groups)

Alternate Name: BSA.

Physical Data: bp 71-73 °C/35 mmHg.[1,2]

Solubility: very sol most organic solvents.

Form Supplied in: liquid; rapidly contaminated with trimethylsilylacetamide and acetamide if exposed to moist air. *Drying:* extreme moisture sensitivity; should be kept in a sealed container.

Preparative Method: made by the reaction of acetamide with a large excess of ***Chlorotrimethylsilane*** in the presence of ***Triethylamine***.[1,2]

Handling, Storage, and Precautions: no special handling and storage procedures; all work must be carried in an efficient fume hood.

Bis(trimethylsilyl)acetamide.

Bis(trimethylsilyl)acetamide (BSA) has been formulated as *N,N*-bis(trimethylsilyl)acetamide as well as the imidate form. The NMR spectra of a number of silylamide derivatives (^{13}C, ^{29}Si, ^{14}N, and ^{17}O) have been investigated. Whereas BSA is seen to exist in the imidate form, some analogs, for example bis(trimethylsilyl)formamide, exist in the *N,N*-bis(trimethylsilyl) form, and the product obtained by the interaction of ***1,2-Bis(chlorodimethylsilyl)ethane*** with BSA is also clearly in the alternative form.[3] Trimethylsilyl derivatives of hydroxamic acids are formed in reactions using ***Hexamethyldisilazane*** and are similar in structure to BSA.[4] This entry will concentrate on examples from the more recent literature.

Protection of Functional Groups.

Early reports of the use of BSA concentrated on the preparation of derivatives of a number of functional group types in

order to facilitate chromatographic analysis. The trimethylsilylation of amides, ureas, amino acids and dipeptides, carboxylic acids, enols and hindered phenols were reported under mild reaction conditions.[1,2] Substituted ureas are converted into their monosilylated derivatives because of the lone electron pair involvement and so ***N,N´-Bis(trimethylsilyl)urea*** is close in energy to BSA. By the same token, one of the trimethylsilyl residues in BSA is replaced more easily than the second. The conversion of *N*-haloamides into the *N*-haloimidic trimethylsilyl esters, for example *N*-chloroacetamide into *N*-chloroacetimidic trimethylsilyl ester, was probably the first reported use of BSA.[5] Part per billion traces in water of environmentally important phenols and carboxylic acids have been determined by concentration using macroreticular resins and subsequent derivatization using BSA before gas chromatography.[6] It has been claimed that trimethylsilylation of trichothecines prior to gas chromatography is best achieved by using bis(trimethylsilyl)trifluoroacetamide (BSTFA) rather than BSA.[7]

Protection of Hydroxy Groups.

The first example of the use of the trimethylsilyl group for the protection of a sterically hindered hydroxy group involved a 14-hydroxy steroid which was treated with bis(trimethylsilyl)acetamide in DMF at 78 °C.[8] Since that time a wide variety of alcohols have been protected using BSA. The product from the enantioselective hydroboration-oxidation of *N*-benzyloxycarbonyl-1,2,3,6-tetrahydropyridine was converted into its trimethylsilyl ether (TMS ether) in order to allow isolation by gas chromatography.[9] The osmylation of unsaturated ester components of insect pheromones, followed by a reductive workup and silylation with BSA, has been used to allow identification using GC-MS.[10] Bis(trimethylsilylation) using BSA has been shown to be the most convenient method for the protection of a range of biologically important dihydroarenediols prior to characterization using GC-MS.[11] High yields have been reported with other secondary alcohols using BSA,[12] including the example shown in eq 1.[13] The method has been used to effect the trimethylsilylation of an aldol product,[14] Ninhydrin reacts with allyltrimethylsilane and trimethylsilyl triflate in acetonitrile to give the expected 2,2-bis(trimethylsilyloxy)indan-1,3-dione. However, using BSA the major product incorporated an acetamido residue.[15] The replacement of an acetoxy group by an amido group (eq 2) presumably occurs via an oxonium species.[16]

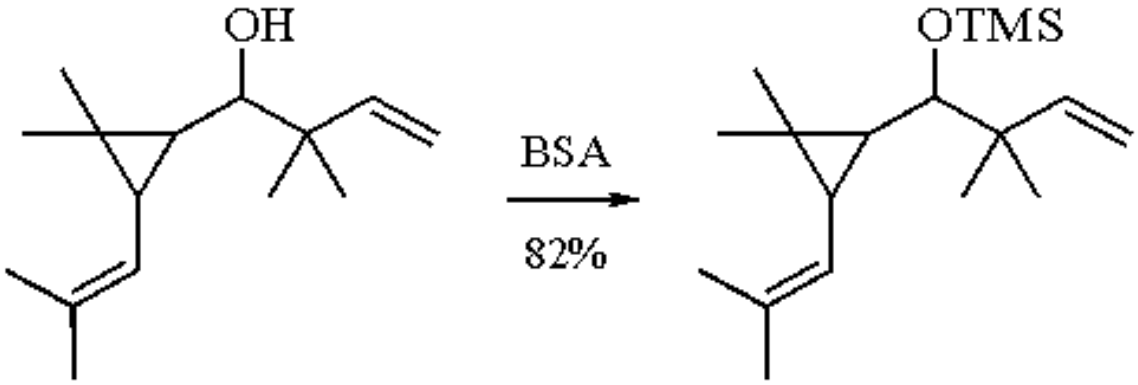

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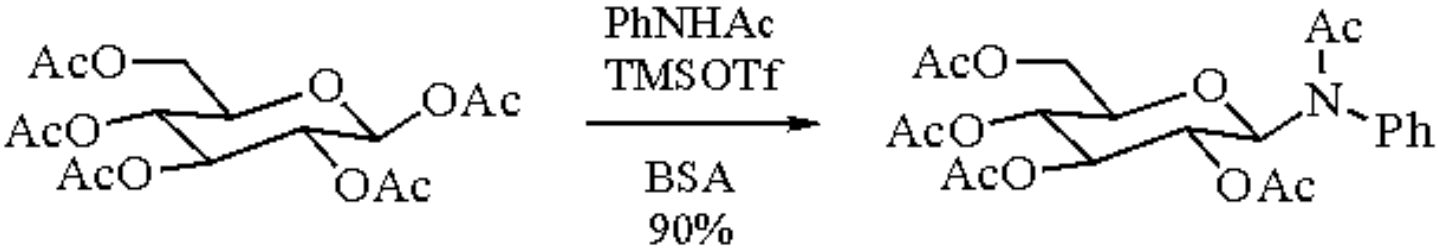

(2)

Bis(trimethylsilyl)acetamide has also been used to provide temporary protection of hydroxy and carboxy groups in a

number of coupling reactions involved in the preparation of cephalosporins and penicillins, as shown in eq 3.[17] The protection of nucleoside hydroxy groups prior to reduction using tributyltin hydride-AIBN has been reported.[18] The same method has also been used in connection with nucleoside coupling reactions.[19] Transglycosylation catalyzed by trimethylsilyl triflate has also been carried out on trimethylsilyl-protected nucleosides (eq 4), in which the prior protection was effected using BSA.[20] In the case of 6-oxopurineribonucleoside synthesis, the 7β-isomer is first formed and eventually affords the 9β-isomer, presumably by way of the 7,9-diribonucleoside.[21] It has been shown that BSA causes the debromination of some purine nucleosides in the presence of ***Potassium Fluoride*** and a crown ether.[22]

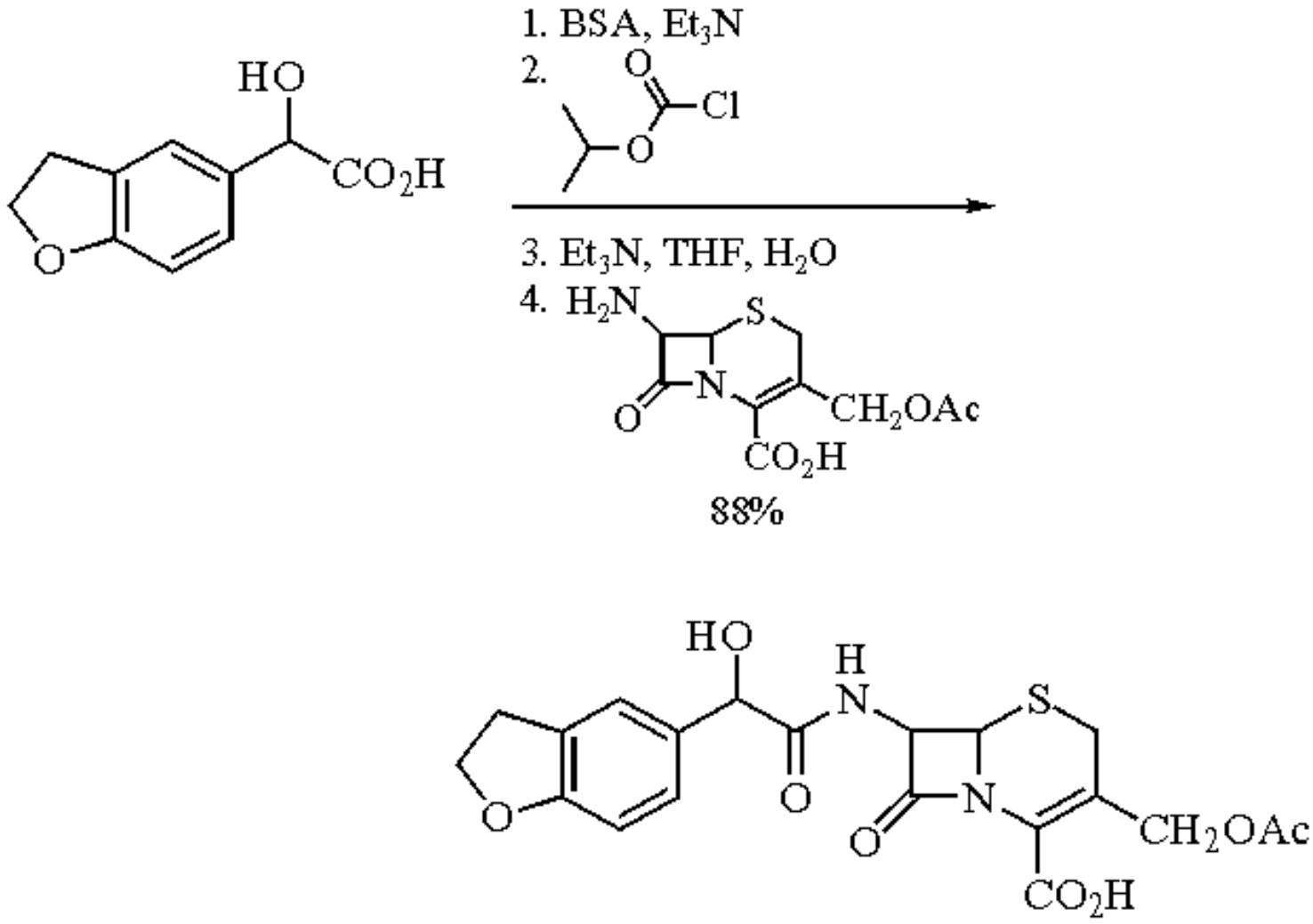

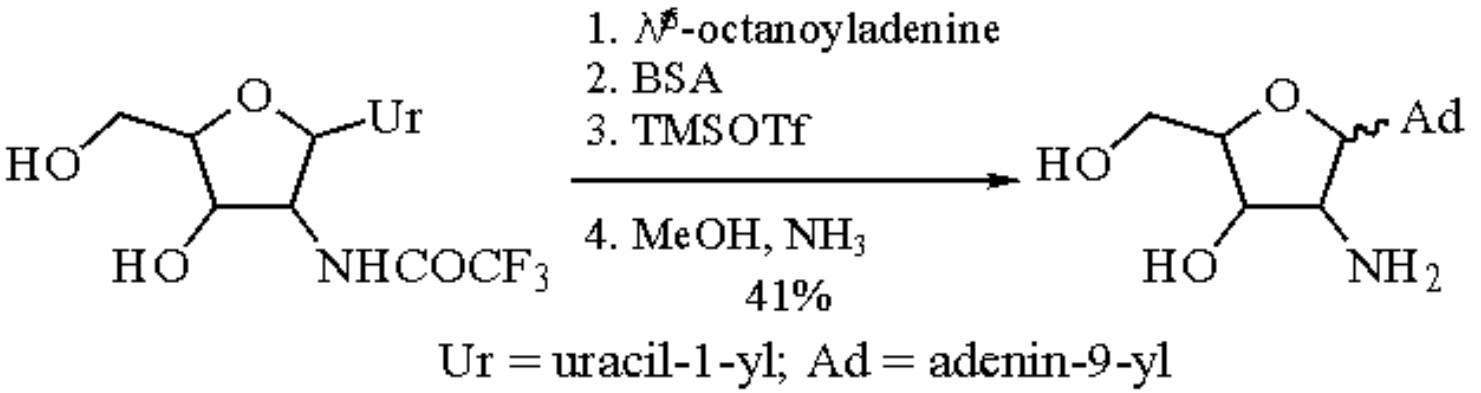

The silylation of tertiary alcohols in good yields has been reported, e.g. di-*t*-hydroxyadamantane.[23] The preparation of

2-methyl-2-trimethylsilyloxynonadecane was achieved in 84% yield using a combination of BSA, chlorotrimethylsilane, and ***N-(Trimethylsilyl)imidazole***.[24] 2-Methyl-2-trimethylsilyloxypentanone, a prototype for a series of compounds that are valuable intermediates used in a study of diastereoselective aldol reactions, can be prepared in good yield using BSA.[25] Even highly hindered silanols react with BSA as indicated in eq 5.[26] It is of interest to note that BSA has been used to reduce the influence of free hydroxy groups on surfaces. Difficult Diels-Alder reactions that require high temperatures and are carried out in sealed glass tubes may suffer from decomposition of the diene on the surface of the glass. Silylation with BSA is then worth investigating.[27] It has also been shown that the charcoal carrier for tungstic acid-***Tri-n-butylchlorostannane***, which is used in the catalyzed hydrogen peroxide epoxidation of alkenes, is improved by treatment with BSA. Decomposition of the hydrogen peroxide, catalyzed by surface hydroxy groups, is then less troublesome.[28]

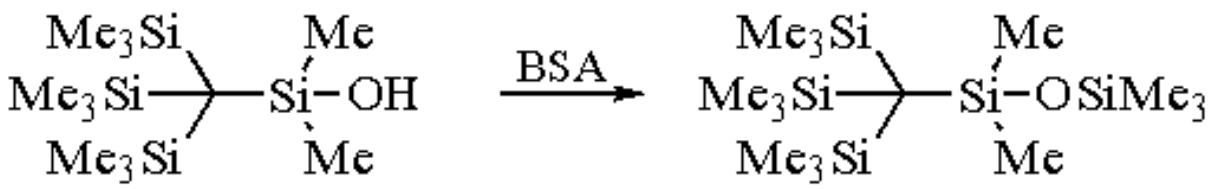

(5)

Formation of Trimethylsilyl Enol Ethers.

The silylation of enolizable aldehydes and ketones has been carried out using BSA in HMPA in the presence of very small amounts of metallic sodium. The method is highly regio- and stereoselective, giving the (*Z*)-isomer that results from kinetic control.[29] With more easily enolized compounds the reaction proceeds readily in the absence of other additives. In the case of the bis(trimethylsilylation) of oxindole (eq 6) the effect is evidently related to the gain in resonance energy on silylation at oxygen.[2] Similarly, the conversion of glutaconic anhydride into the silylated α-pyrone (eq 7) was achieved in very high yield using BSA.[30] The product is a very useful Diels-Alder diene. Other highly functionalized dienes have been prepared and used in Diels-Alder syntheses of highly functionalized naturally occurring anthraquinones. The dienes shown in eqs 8 and 9 were used in the syntheses of ceroalbolinic acid[31] and xantholaccaic acid,[32] respectively.

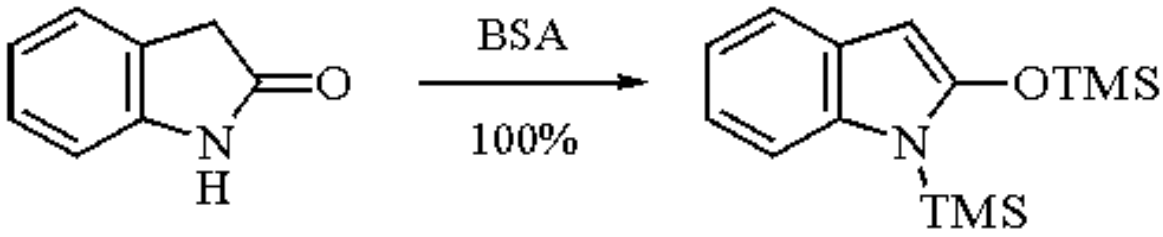

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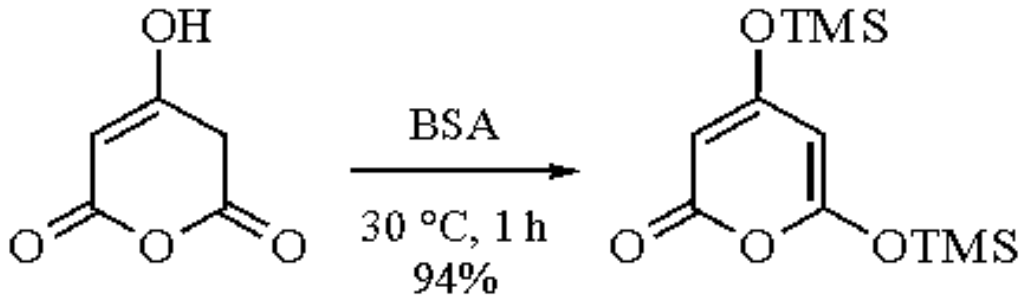

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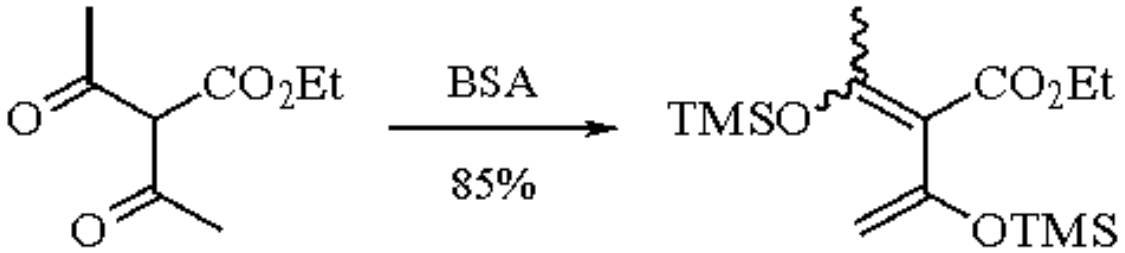

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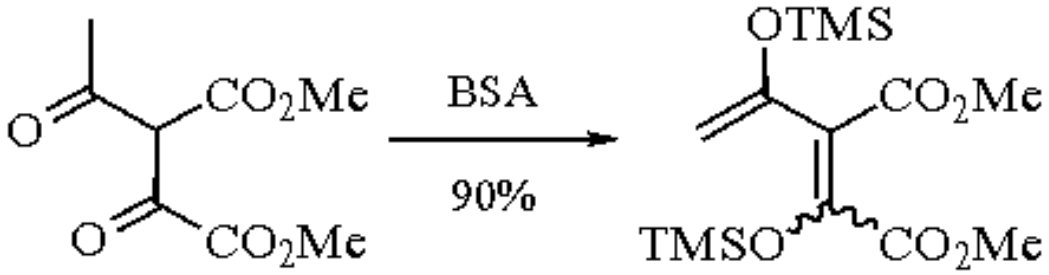

(9)

The protection of phenols was one of the first examples of the use of BSA, including the trimethylsilylation of 2,6-di-*t*-butylphenol.[2] 2,6-Di-*t*-butyl-4-vinylphenol has been protected with BSA and then polymerized by both cationic and radical initiators before liberating the free phenolic groups by cleavage with acid.[33] A number of calixarene trimethylsilyl ethers have been prepared from the phenols using BSA.[34] Calix[4]arene has been converted into a mixture of tris- and tetrakis(trimethylsilyl) ethers by heating the phenol with BSA in acetonitrile.[35]

Protection of Carboxy Groups.

As with hydroxy compounds, the conversion of carboxy groups into their trimethylsilyl derivatives is valuable in connection with GC-MS. The method has been used, for example, in assaying a perhydroindole ACE inhibitor.[36] Amino acid hydrohalides are silylated in almost quantitative yields by BSA in THF at reflux. Other methods require higher temperatures. The free amino acid can be isolated after treatment with water and another important feature is that no racemization was observed.[37] The use of BSA in peptide coupling reactions has been reported,[38] including examples where hydroxy amino acids are involved.[39] A coupling reaction involved in a total synthesis of the immunostimulating peptide FK156 also involved the formation of a peptide TMS ester.[40] The trimethylsilylation of (*E*)-3-bromoacrylic acid proceeds in good yield (eq 10) and has been used in conjunction with a protected alanyl anion in the synthesis of an unsaturated α-amino acid.[41] The bis(trimethylsilyl) ester of squaric acid, formed using BSA (eq 11), has been shown to be in dynamic equilibrium. The trimethylsilyl groups undergo rapid intermolecular migration, as established by crossover experiments.[42]

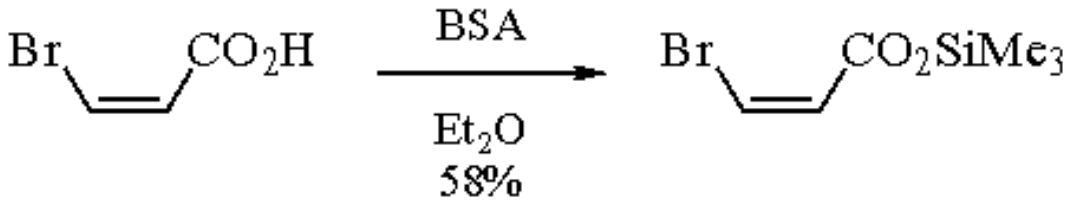

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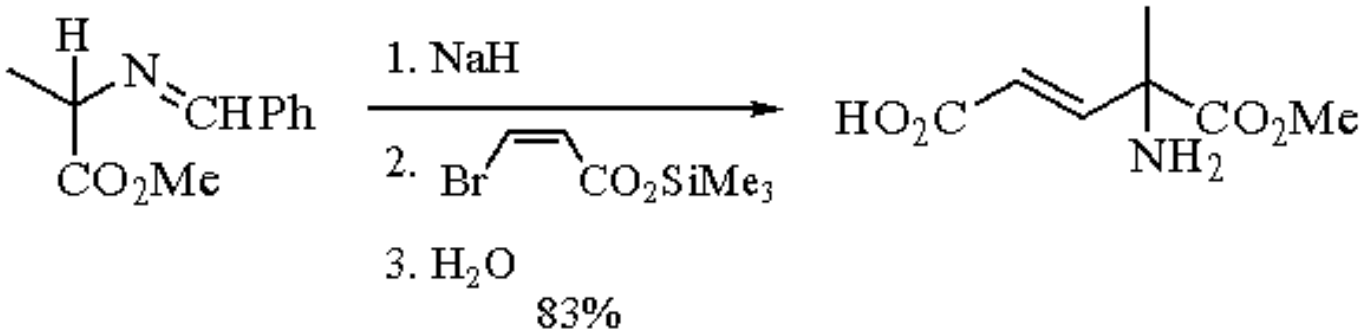

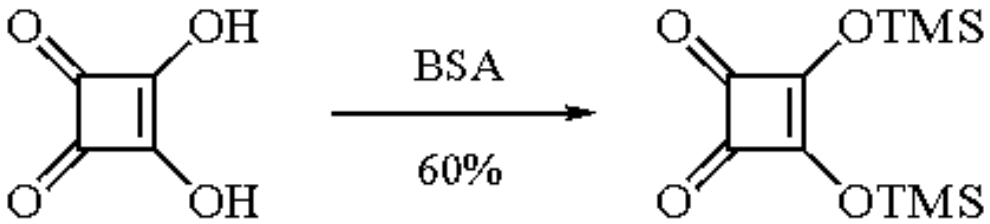

(11)

Reactions at Nitrogen.

The protection and activation of a number of nitrogen functional groups has been achieved using BSA, for example the silylation of aziridines.[43] Treatment of primary and secondary amines with BSA and then with a chloroformate gives good yields of carbamates.[44] Conversion of the guanine derivative into the bis(trimethylsilyl) derivative and the ***Trimethylsilyl Trifluoromethanesulfonate*** nucleoside coupling reaction (eq 12) was part of a synthesis of AzddMAP.[45] Similarly, the conversion of sulfoximines into their TMS derivatives, prior to deprotonation and reaction with a range of electrophiles, can be carried out in almost quantitative yields using BSA.[46] The preparation of the 1,3,4-oxadiazoline shown in eq 13 was achieved in 60-65% yield.[47]

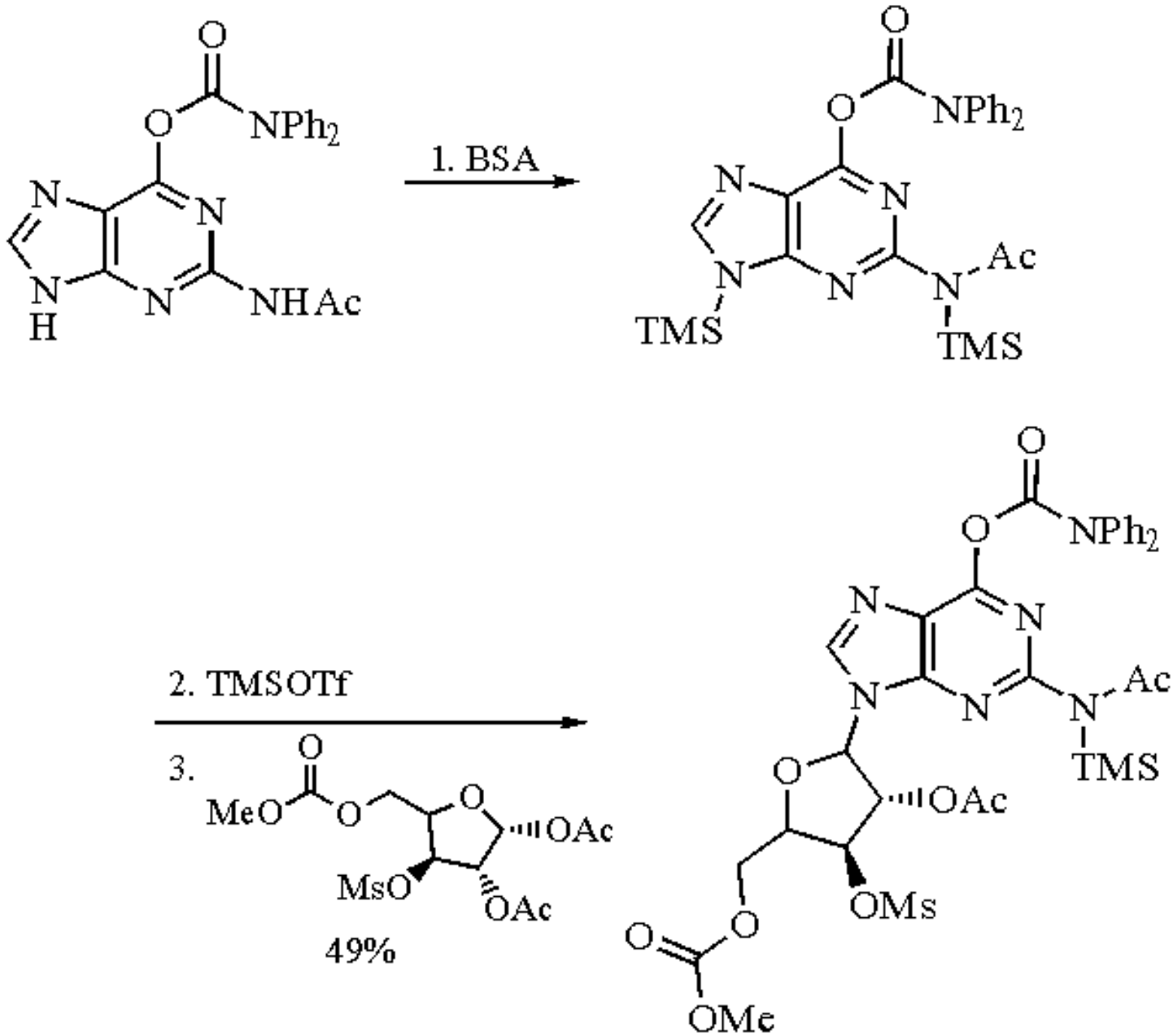

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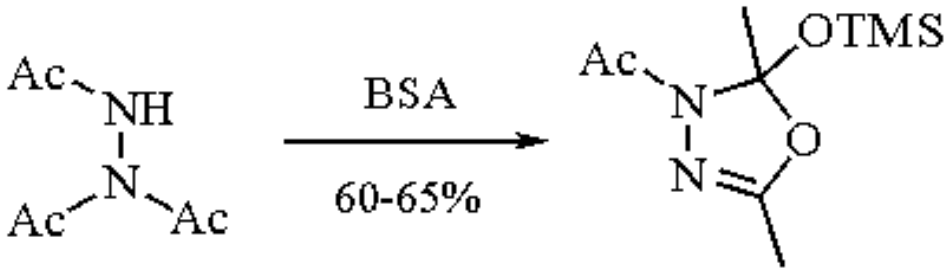

(13)

The increased volatility on silylation of pyrimido[4,5-*i*]imidazo[4,5-*g*]cinnoline has been investigated in connection with flash vacuum pyrolysis studies.[48] It has been reported that dihydropyrimidines and dihydro-*s*-triazines were dehydrogenated under vigorous trimethylsilylation conditions.[49] Apparently the reaction does not proceed in the absence of oxygen or in the presence of free radical inhibitors. Aromatic isocyanates react with BSA to give silylated azauracils as shown in eq 14, which are desilyated on treatment with ethanol.[50] We also note that BSA and other bis(trimethylsilyl)amides are converted into nitriles in high yields by treatment with ***Tetra-n-butylammonium***

Fluoride. Lewis acids, or ***Iron(II) Phthalocyanine***,[51] and a range of bis(trimethylsilyl)amides react with ***Phosgene*** to form acyl isocyanates.[52] Arylsulfonylacetonitriles undergo carbon-carbon coupling reactions when heated in BSA at 120-140 °C.[53] A range of silylnitronates have been prepared using BSA or the trifluoro analog (BSTFA). The products (eq 15) are useful intermediates for the synthesis of isoxazolidines.[54]

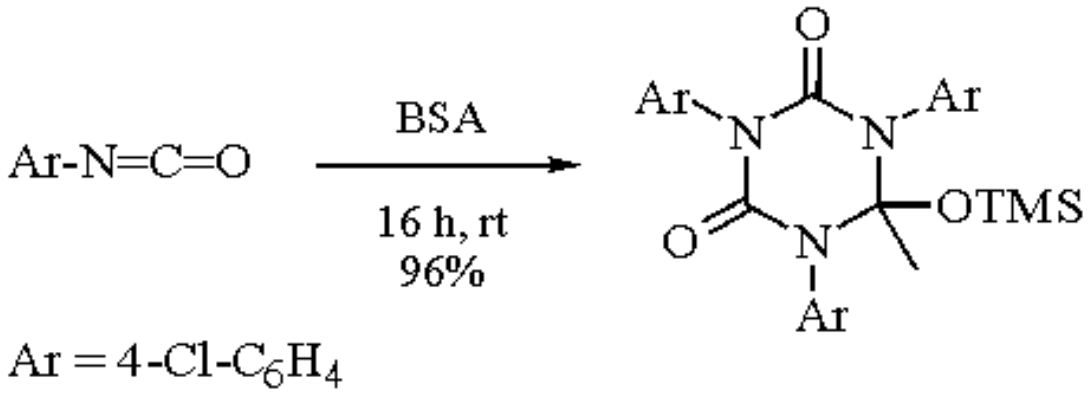

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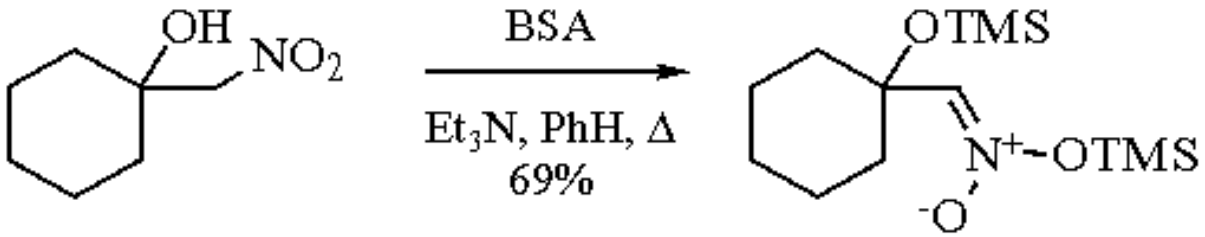

(15)

The Control of Protic Acids.

There are a number of examples where protic acids have been shown to have a deleterious effect on reactions and where partial or complete control is advantageous. The rearrangement of the benzylpenicillin sulfoxide to the cephalosporanic acid derivative (eq 16) gave the best yield using ***Hydrogen Bromide*** and ca. 30 mol % of BSA.[55] Similarly, the preparation of eight-membered oxygen heterocycles that are present in a number of marine natural products, has been achieved in moderate yields by Lewis acid promoted acetal-alkene cyclizations in the presence of BSA as shown in eq 17.[56] The same principle has been used to control Friedel-Crafts alkylation reactions involving, for example, methyl chloromethoxyacetate and *N*-methylindole.[57] In the absence of BSA a considerable amount of the indole derivative was converted into its dimer while the major product was methyl bis(1-methyl-3-indolyl)acetate. In the presence of BSA the formation of the dimer was suppressed and the initial product, methyl 1-methyl-3-indolylacetate, isolated in a 90% yield. Control in the highly diastereoselective alkylation of 1-methylindole using chiral pyrrole derivatives was achieved in a better yield when using BSA (eq 18).[58]

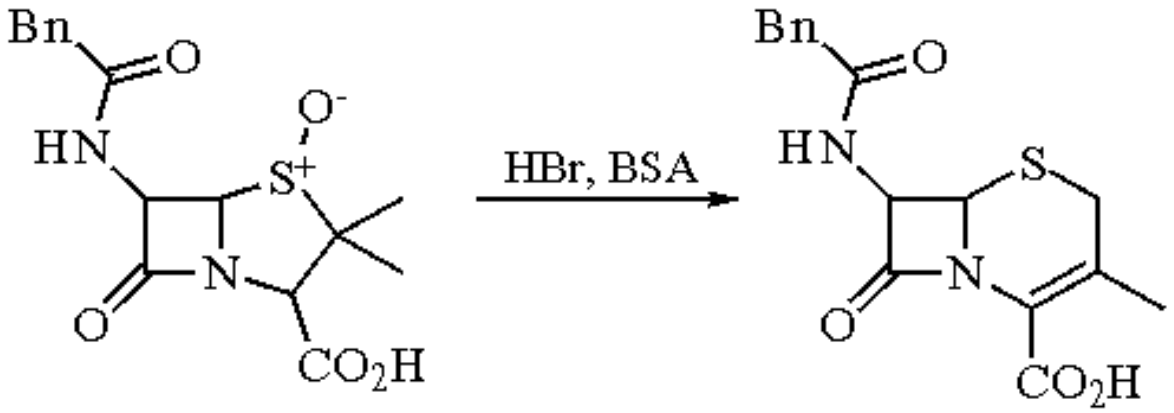

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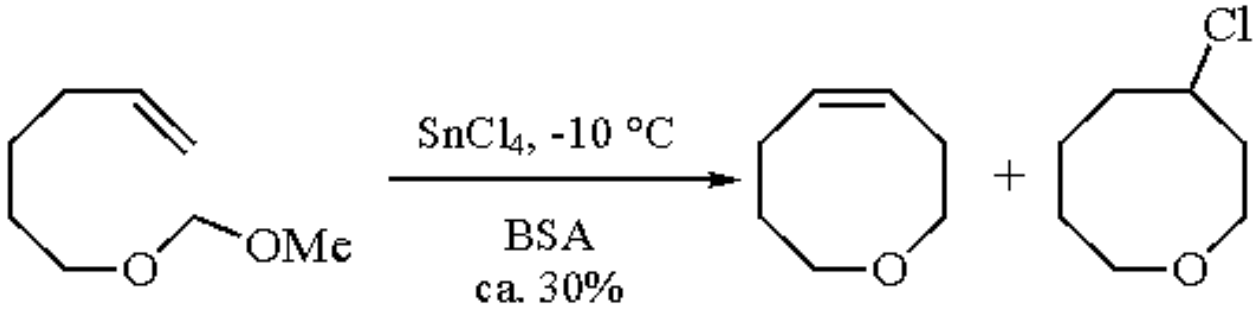

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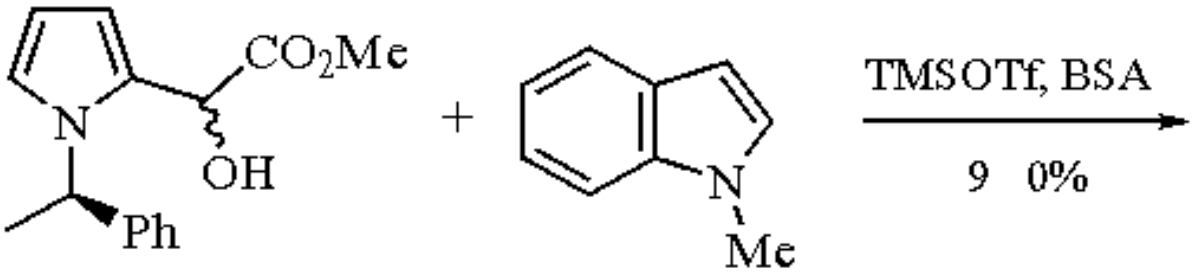

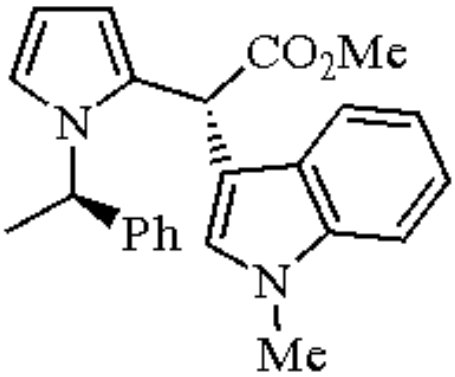

(18)

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Use has also been made of the oxophilicity of silicon, as compared to the azaphilicity of protons, in Mannich reactions of bis(aminol ethers) with heterocycles such as 2-methylfuran where a proton is liberated during the reaction.[59] The bis(methoxymethyl) derivative from *t*-butylamine gave an iminium salt when treated with hydrogen chloride in ether. In duplicate reactions using 2-methylfuran, one (eq 19) was treated with BSA while the other, in the absence of BSA, was worked up using Hünig's base and gave the expected secondary amine after a hydrolytic work up in 80% yield. Evidently in the first reaction the BSA reacted with the hydrogen chloride produced and gave chlorotrimethylsilane.

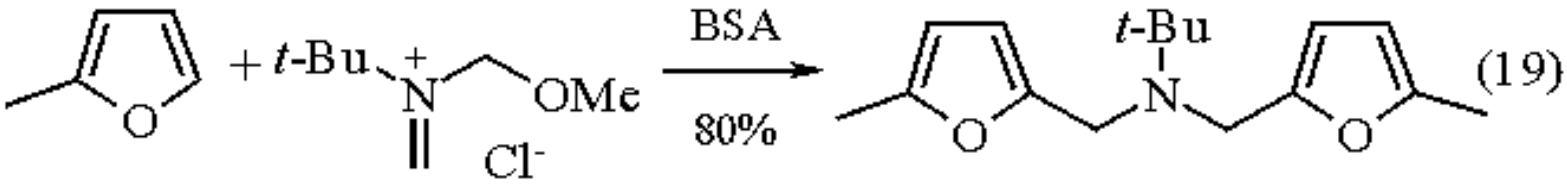

The reaction between triflic acid and *N*-trimethylsilyl-1,3-oxazolidin-2-one has been shown to afford trimethylsilyl triflate in a high yield, whereas the reaction of BSA with triflic acid gave only a 43% yield of trimethylsilyl triflate.[60] Despite that finding, in situ catalytic reactions involving trimethylsilyl triflate (eq 20)[58b] and trimethylsilyl fluorosulfonate (eq 21)[61] can be carried out in high yields when a catalytic amount of the acid is added to BSA.

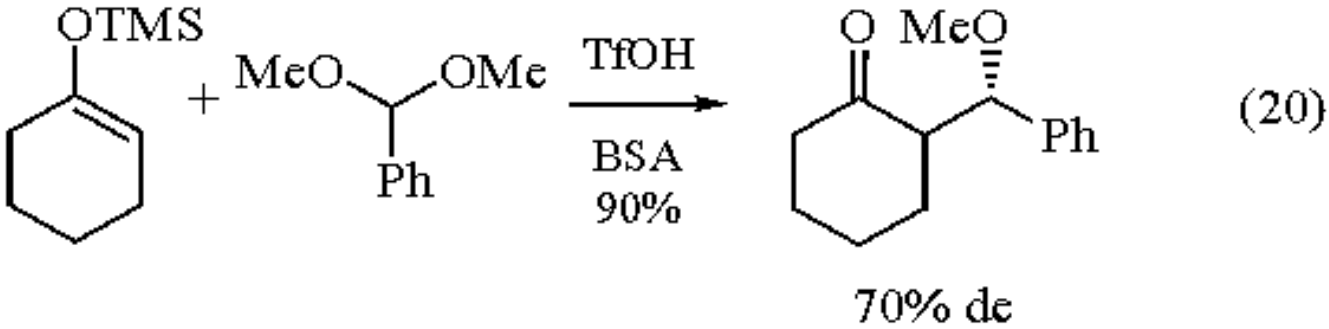

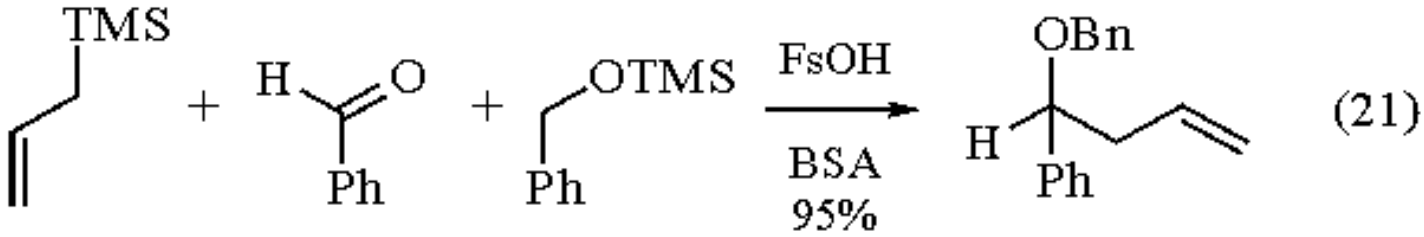

Reactions of the Anion from Bis(trimethylsilyl)acetamide.

The deprotonation of BSA using ***Lithium Diisopropylamide*** was used to generate the protected acetamide enolate ion for use in the synthesis of the dienone shown in eq 22.[62] It has been shown subsequently that the same product can be prepared by the reaction of the anion, generated from *n*-butyllithium and BSA, with 2,6-dibromo-1,4-benzoquinone.[63] The anion has also been used in reactions with a number of carbonyl compounds, including benzophenone.[64]

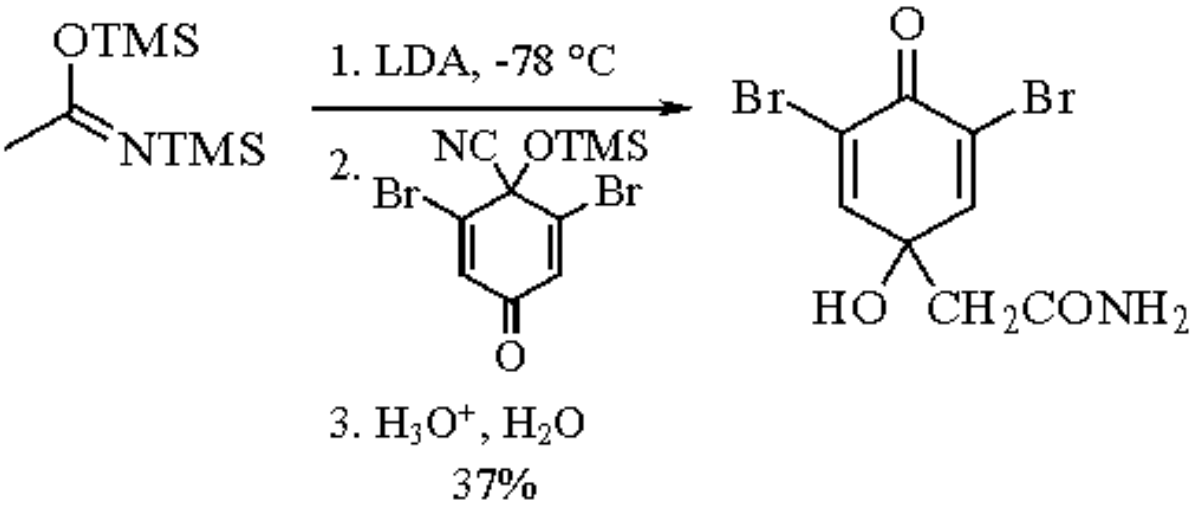

(22)

Reactions of Phosphorus Compounds.

A number of papers report the conversion of chlorophosphites, dichlorophosphites, and their thio analogs into trimethylsilyl derivatives.[65] The reaction between bromodifluorophosphine and BSA at -80 °C results in formation of an unstable product with a P-N bond together with bromotrimethylsilane.[66] Nucleoside phosphonates have been converted into the related bis(trimethylsilyl) phosphites by treatment with BSA. Subsequent reaction with an acyl chloride and triethylamine then rapidly affords the corresponding acyl phosphonate.[67] The Michael addition of phosphonous acids and esters by way of intermediate silyl alkyl phosphonites has been used in the preparation of phosphinic acids (eq 23).[68] The coupling of an activated acid with an acylphosphoranylidene in the presence of BSA (eq 24) has been used in the synthesis of the vicinal tricarbonyl portion of the immunosuppressant macrocyclic lactone FK-506.[69] The coupling in that case gave the required product in a 91% yield.

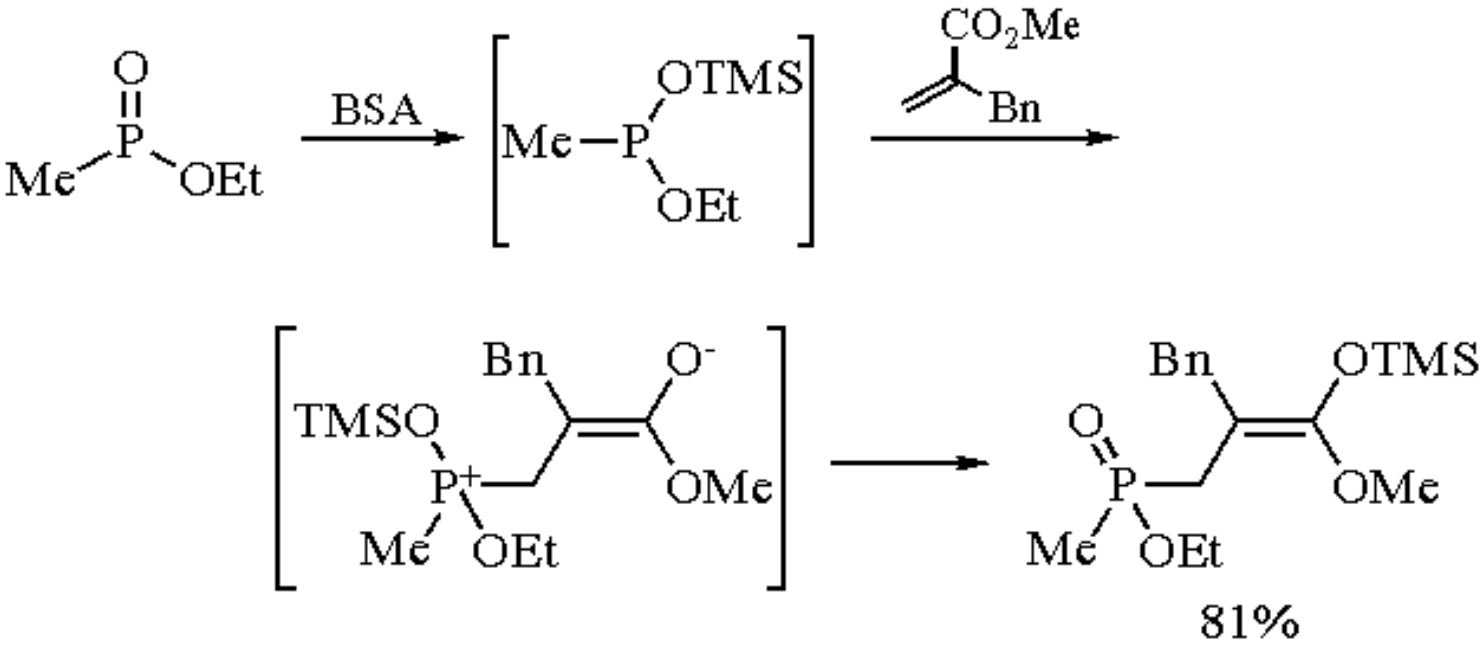

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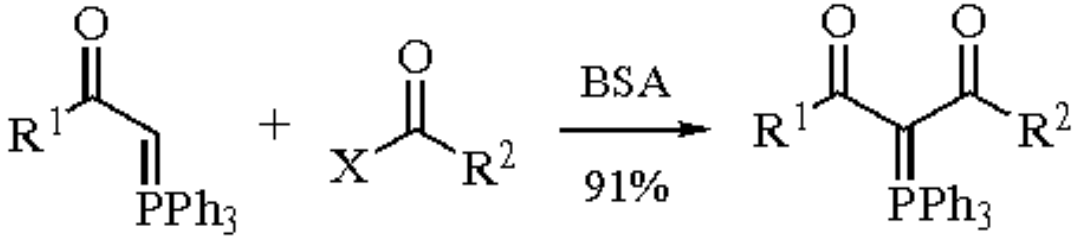

(24)

Metal Catalyzed Reactions of Allylic Esters.

Hexacarbonylmolybdenum catalyzed elimination of acetic acid in the presence of BSA is effective in a high yield route to conjugated dienes,[70] and BSA has been used as a base in an unexpected palladium catalyzed tandem elimination-cycloaddition reaction.[71] The alkylation of malonic esters with allylic acetates using hexacarbonyl molybdenum and BSA (eq 25) has been reported to give high yields.[72] β-Keto esters are also alkylated using palladium(0) catalysis. In reactions of 2-hydroxymethyl-2-propen-1-ol diacetate with methyl 4-methylcyclohexanone-2-carboxylate, the use of BSA gave the monoalkylated product whereas using DBU resulted in the formation of the bicycloannulation product.[73] The palladium catalyzed alkylation of sodium dimethyl malonate with a silylated allene acetate in the presence of BSA (eq 26) proceeds via the silylated ester.[74] The silylation step is necessary because of the sensitive nature of allenyl acetates. A stereoselective total synthesis of isolobophytolide used BSA to convert an allylic pivalate into the corresponding enol trimethylsilyl derivative and this was then used in the intramolecular allylation of a sulfonyl acetate anion using ***Tetrakis(triphenylphosphine)palladium(0)*** as catalyst.[75]

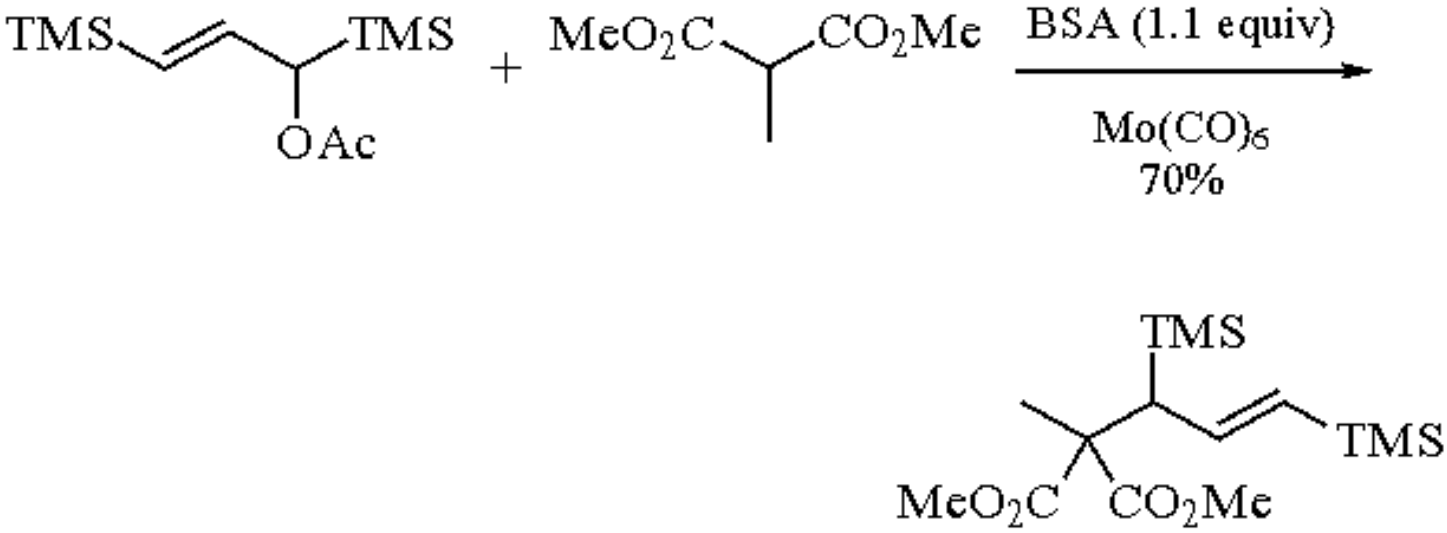

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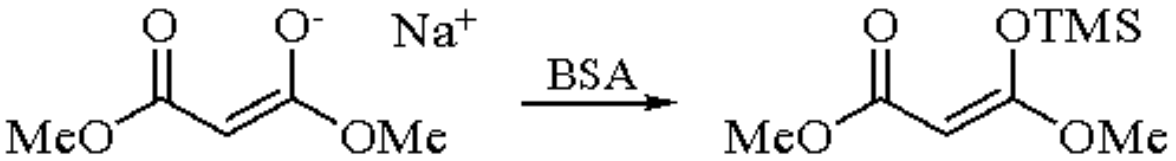

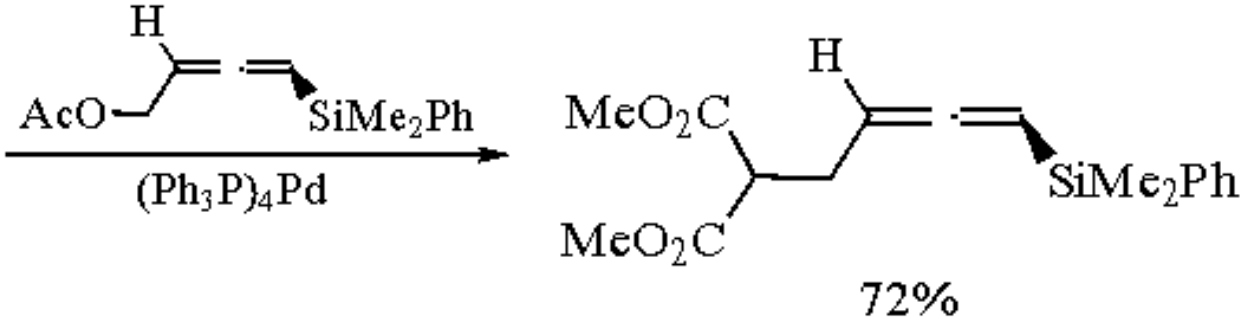

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Bis(trimethylsilyl)acetylene

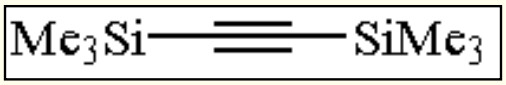

[14630-40-1] · $C_8H_{18}Si_2$ · Bis(trimethylsilyl)acetylene · (MW 170.40)

(nucleophile in Friedel-Crafts type acylations and alkylations; lithium trimethylsilylacetylide precursor; cycloaddition substrate)

Alternate Name: BTMSA.

Physical Data: mp 26 °C; bp 136-137 °C; *d* 0.752 g cm^{-3}.

Solubility: sol all commonly used organic solvents.

Form Supplied in: clear liquid; widely available.

Preparative Method: from acetylene by treatment with ***n-Butyllithium*** followed by ***Chlorotrimethylsilane***.[1]

Handling, Storage, and Precautions: the liquid is flammable and an irritant. Use in a fume hood.

Friedel-Crafts Alkylation/Acylation and Related Reactions.

Bis(trimethylsilyl)acetylene (BTMSA) can be added to a variety of Lewis acid-activated electrophiles. The most common variation which has been used in several total syntheses is the addition of BTMSA to acid chlorides in the presence of ***Aluminum Chloride*** to afford α,β-alkynic ketones in good yields (eq 1);[2,3] this complements the method by which monosubstituted alkynes are added to carboxylic acid anhydrides, esters and tertiary amides (see ***n-Butyllithium-Boron Trifluoride Etherate***). In addition to acid chlorides, BTMSA can be added to optically active acetals in the presence of ***Titanium(IV) Chloride*** to afford, after cleavage of the chiral template, α-hydroxyalkynes in excellent yield and high enantiopurity (eq 2).[4] BTMSA can also be added to the oxonium ion intermediate resulting from the treatment of tri-*O*-acetyl-D-glucal with ***Tin(IV) Chloride*** to give the α-alkynylated pyranose in excellent yield as a single stereoisomer (eq 3).[5] In a related example, it has been shown that BTMSA can be added to γ-lactols in the presence of ***Boron Trifluoride Etherate*** to afford highly substituted tetrahydrofuran-3-carboxylates in high stereoselectivity.[6]

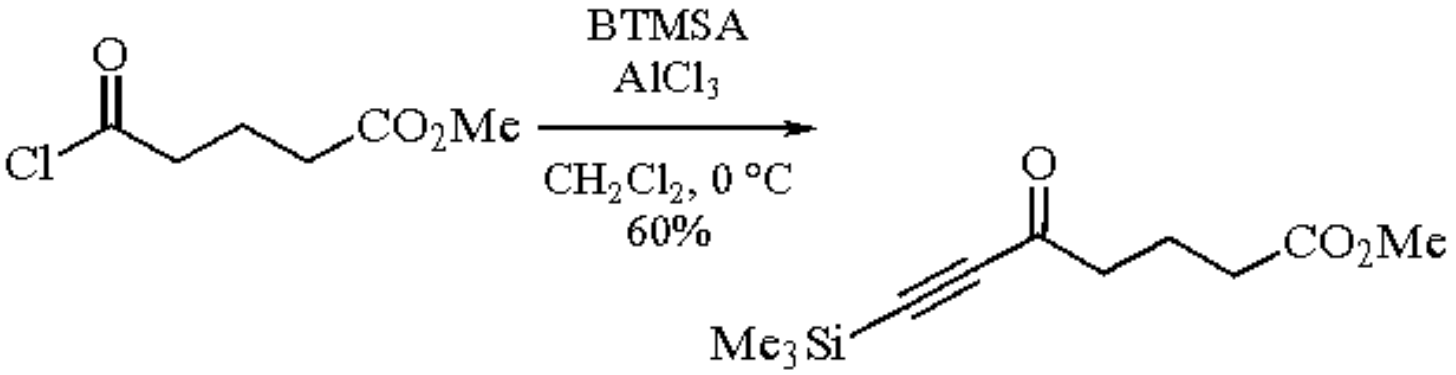

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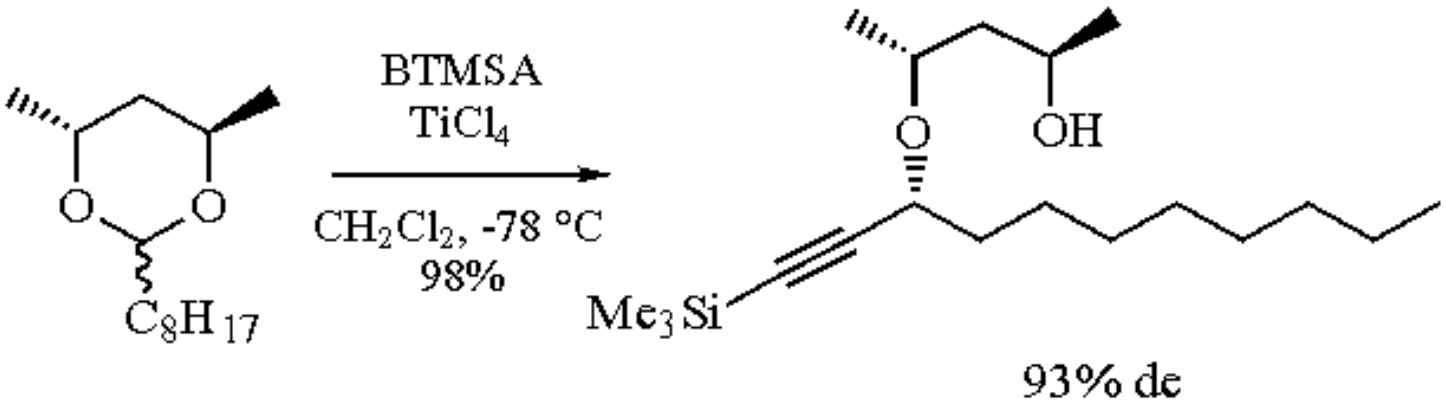

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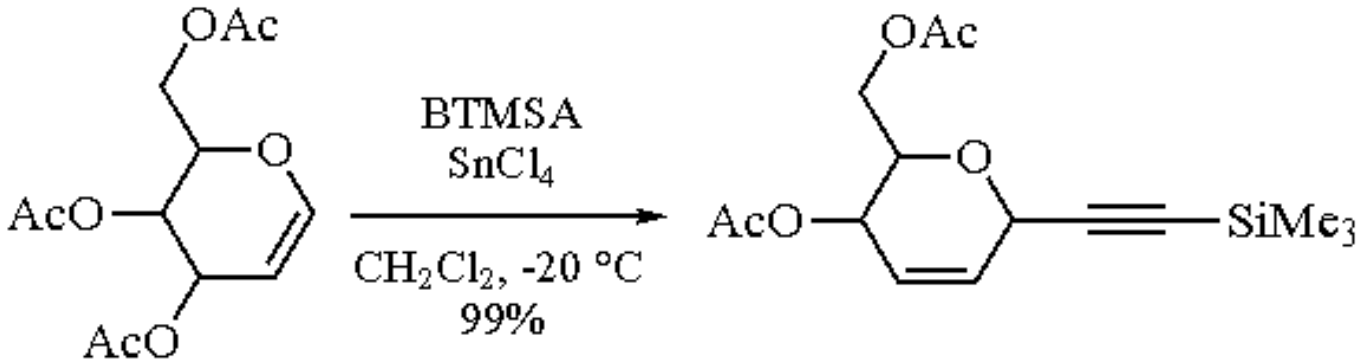

(3)

In addition, treatment of δ-methoxyproline derivatives[7] and γ-methoxy-γ-lactams[8] under the Lewis acid/BTMSA conditions gives δ-alkynic prolines and γ-alkynic γ-lactams, respectively. BTMSA will undergo a 1,4-addition to ethylenic acyl cyanides in the presence of $TiCl_4$ to give γ,δ-alkynic acyl cyanides in good yield (eq 4).[9] BTMSA will also add to tertiary[10] or activated halides in the presence of Lewis acids (eq 5).[11]

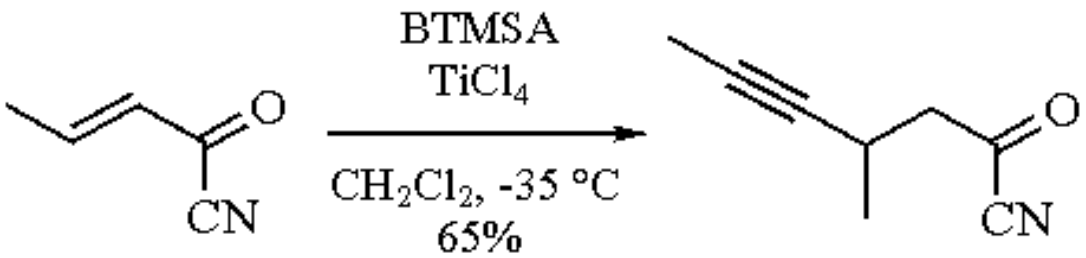

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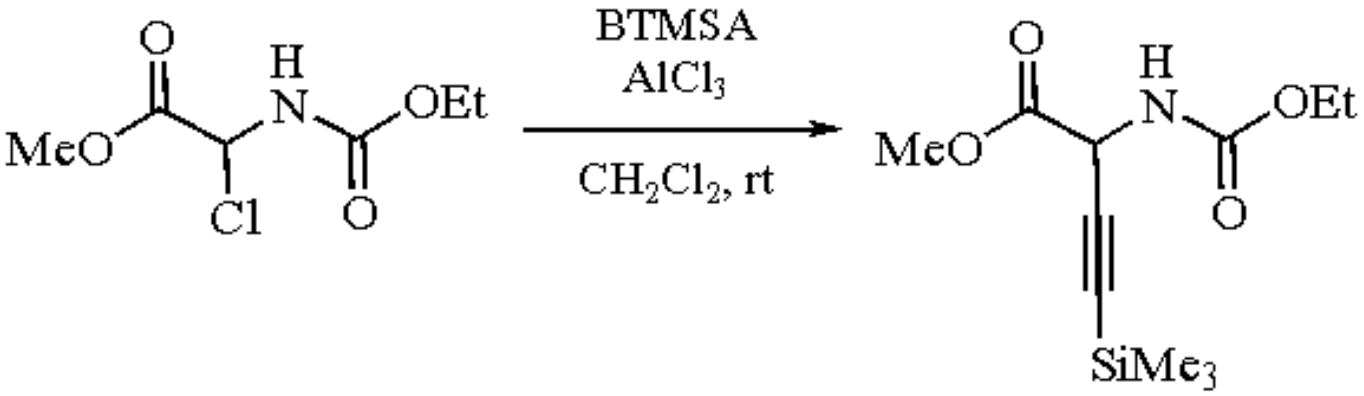

(5)

Concerning noncarbon electrophiles, addition of BTMSA to arylsulfonyl chlorides in the presence of aluminum chloride affords ethynyl sulfones[12] which have been used as Michael acceptors and Diels-Alder dienophiles.[13] It is presumed that the Lewis acid catalyzed processes summarized above proceed via a silicon-stabilized vinyl cation, which then loses the trimethylsilyl moiety to afford the alkynic products.

Trimethylsilylacetylide Alkylation Reactions.

While BTMSA adds to a number of electrophiles under Lewis acid-catalyzed conditions, this reagent can also be used as a trimethylsilylacetylide precursor. In this regard, it has been reported that treatment of BTMSA with ***Methyllithium***-LiBr complex in THF gives quantitative formation of lithium trimethylsilylacetylide (eq 6).[14] The utility of this reagent lies in its ability to provide access to a diverse group of protected, terminal alkynes. For example, this reagent, which is formed in situ, can be added to aldehydes to give secondary α-hydroxy alkynes,[14] ketones to afford tertiary α-hydroxy alkynes (eq 7),[15] epoxides to form β-hydroxy alkynes,[16] or alkyl halides to give monoalkylated alkynes.[17] Lithium trimethylsilylacetylide can be brominated with ***Bromine*** and coupled with copper acetylides to give 1,3-diynes[18] or iodinated with ***Iodine Monochloride***[19] and coupled with arylcopper reagents to afford aryl alkynes in good yields.[20] This lithium acetylide intermediate has also been transmetalated with ***Zinc Bromide*** and coupled with a vinyl iodide in the presence of Pd^0 to give a 1,3-enyne[21] (eq 8) or with ***Diethylaluminum Chloride*** and coupled with an enone in the presence of a nickel catalyst to afford a γ,δ-alkynic ketone (eq 9).[22]

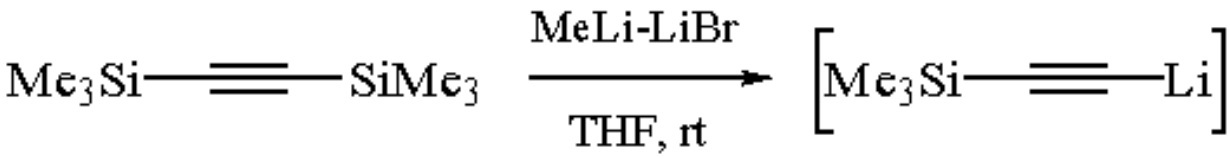

(6)

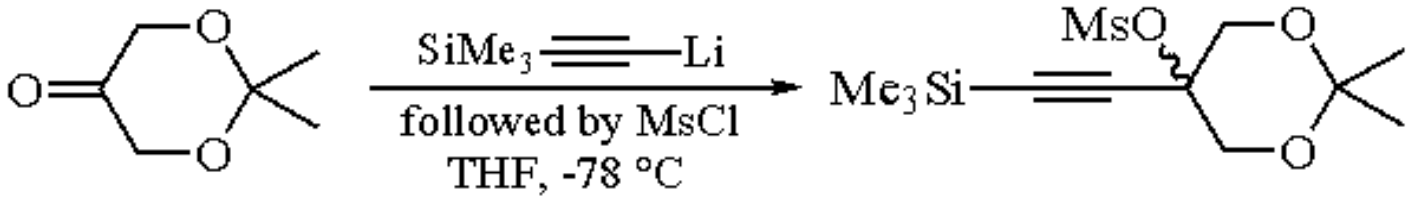

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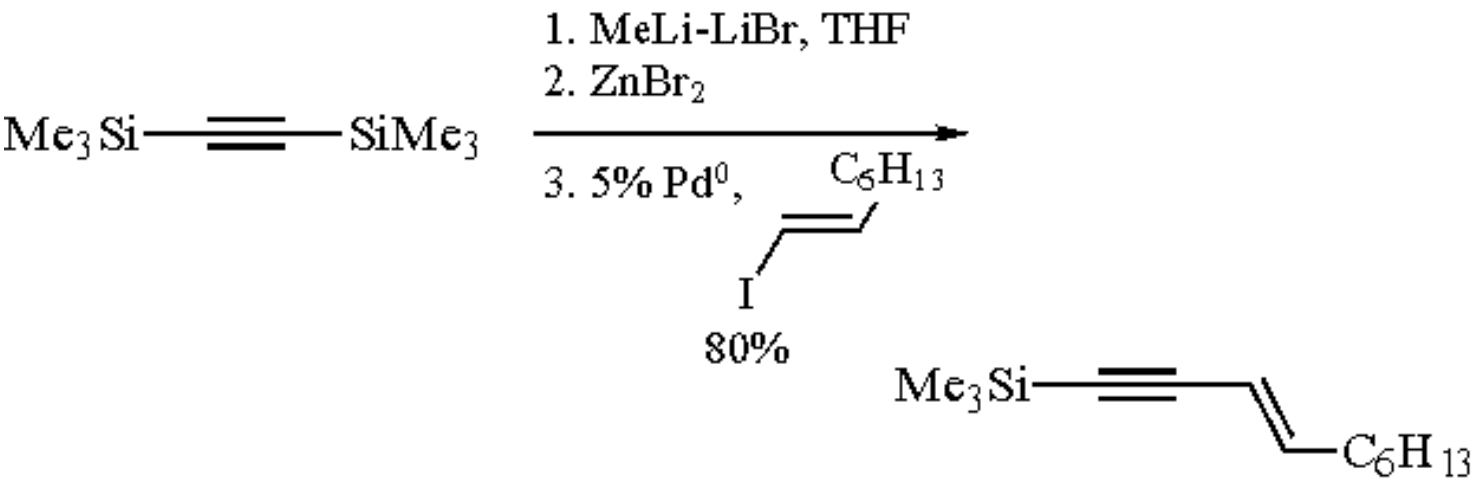

(8)

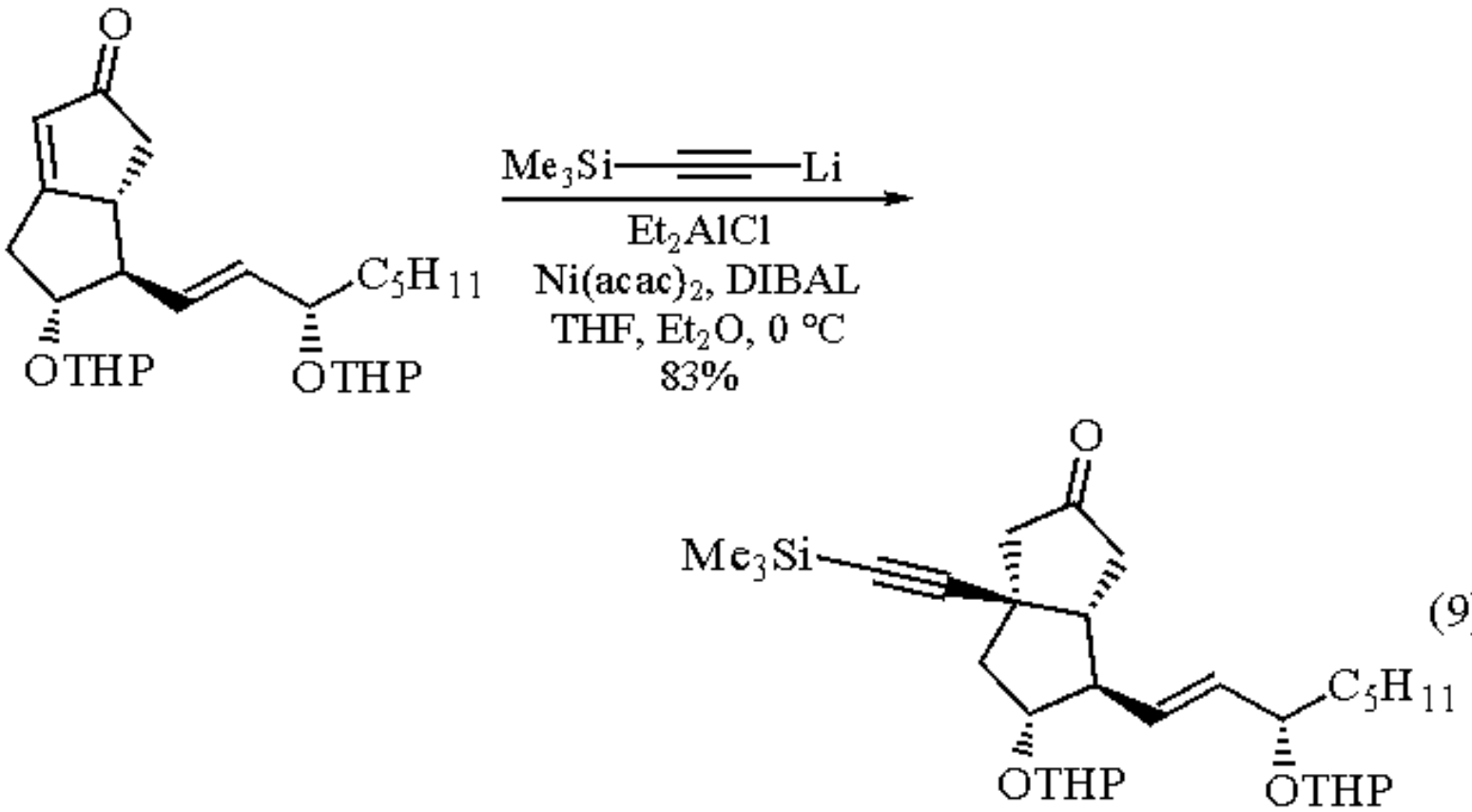

(9)

Cycloaddition Reactions.

BTMSA is a powerful substrate in a variety of cycloaddition reactions. The most common use of this reagent in that sense involves the transition metal-catalyzed [2 + 2 + 2] cycloaddition.[23] BTMSA can be added to 1,5-hexadiyne in the presence of a cobalt catalyst to afford the highly strained, versatile synthetic intermediate 4,5-bis(trimethylsilyl)benzocyclobutene (eq 10).[24] When this reaction is run on a diyne with a properly tethered vinyl group the initial adduct isomerizes to the corresponding *o*-xylylene and undergoes an intramolecular [4 + 2] cycloaddition to afford complex polycycles in high yields (eq 11);[25] this method was used in a concise total synthesis of (±)-estrone.[26] Varying the BTMSA acceptor in this reaction gives a number of polycyclic heterocycles including 2*H*-pyrans,[27] 2,3-dihydro-5(1*H*)-indolizinones,[28] anthraquinones,[29] tetrahydroisoquinolines (eq 12)[30] and 1,3-diazabiphenylenes (eq 13).[31]

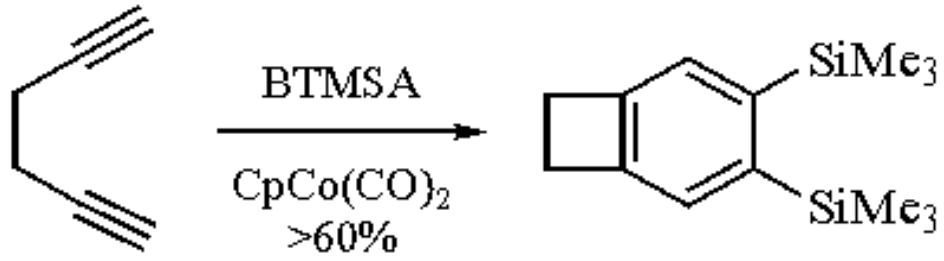
BTMSA
CpCo(CO)2
>60%
SiMe3
SiMe3

(10)

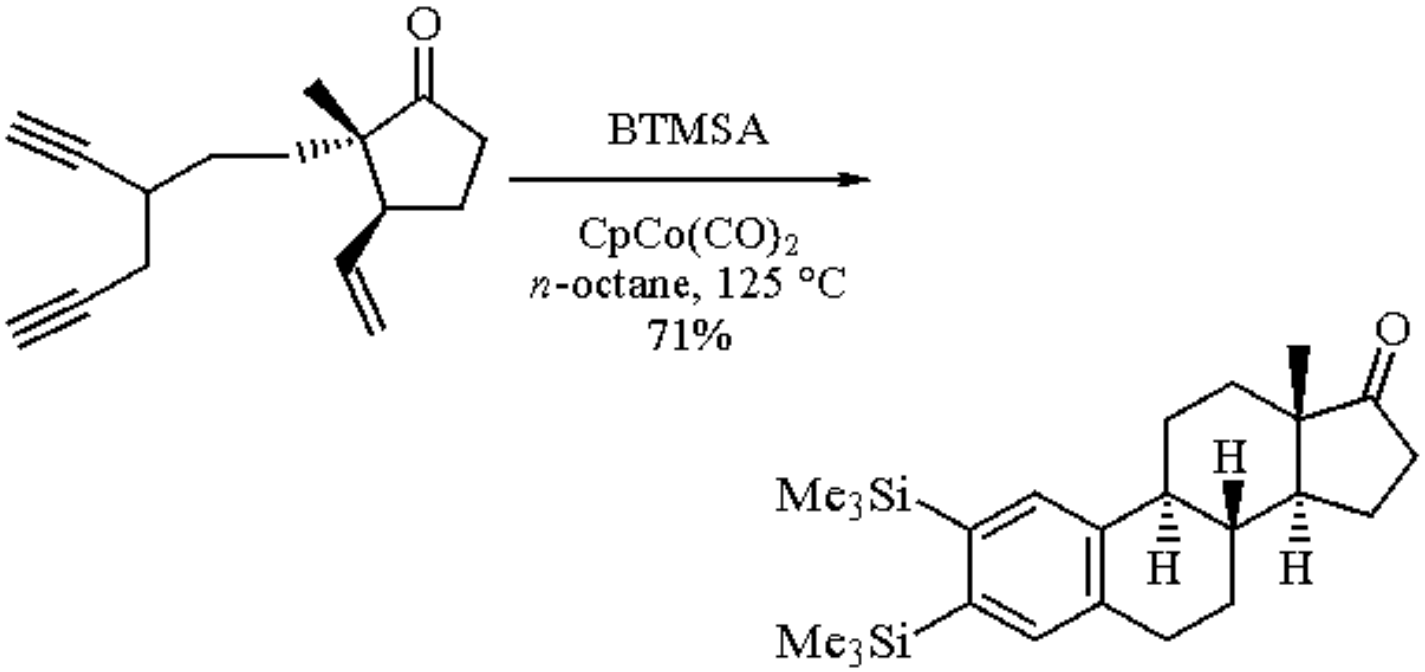
O
BTMSA
CpCo(CO)2
n-octane, 125 °C
71%
O
H
Me3Si
H
H
Me3Si

(11)

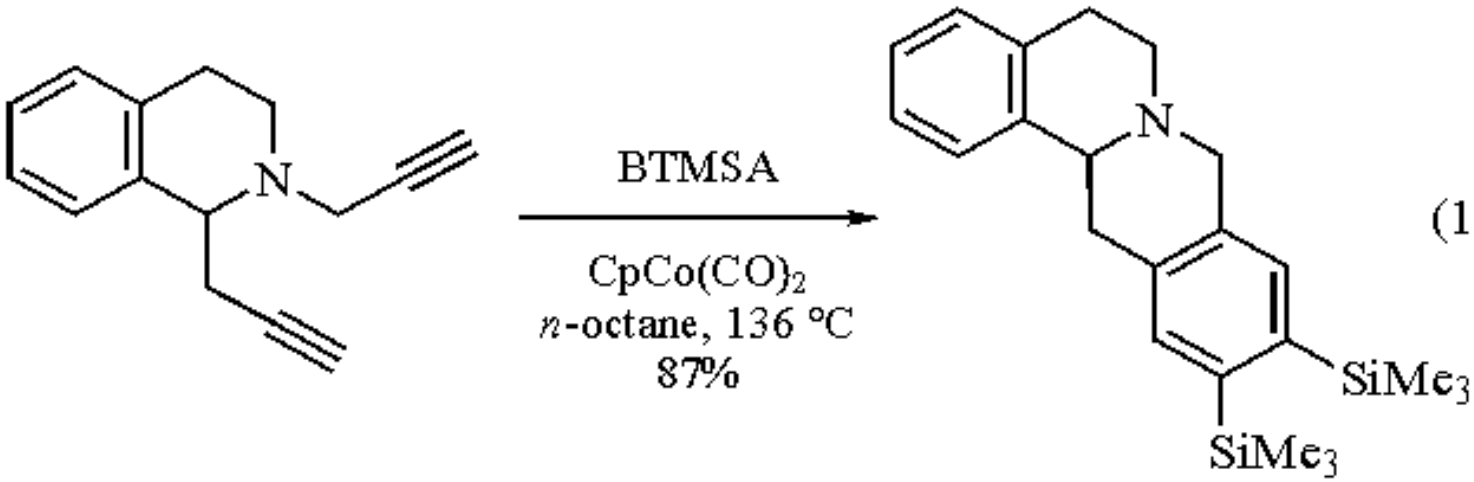
N
BTMSA
CpCo(CO)2
n-octane, 136 °C
87%
N
SiMe3
SiMe3

(12)

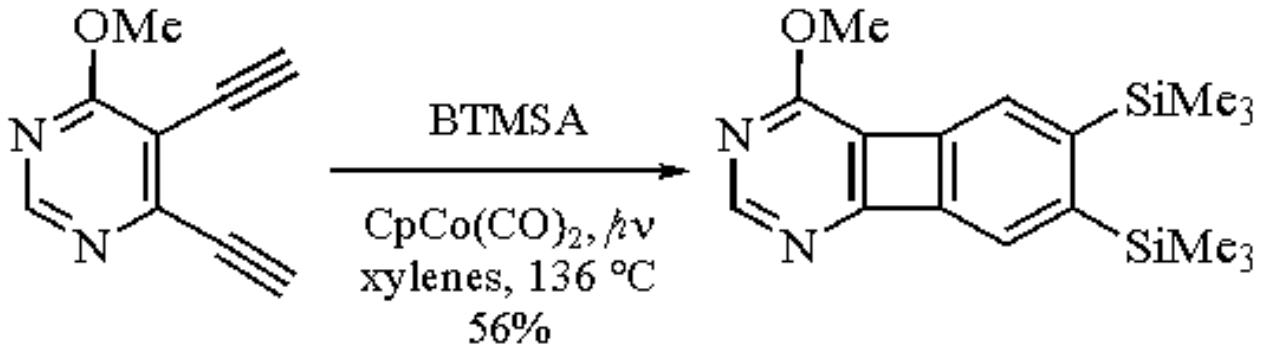

(13)

BTMSA can also be added to several dienes in Diels-Alder fashion. Pretreatment of hydrocarbon dienes such as 1,3-butadiene with catalytic $Et_2AlCl/TiCl_4$ followed by addition of BTMSA at 60 °C gives the corresponding bis(trimethylsilyl)cyclohexadienes in high yields.[32] BTMSA can be added to α-pyrone in decalin at 165 °C to give 1,2-bis(trimethylsilyl)benzene in good yield,[33] as well as to 6*H*-1,3-oxazin-6-ones in refluxing decalin to afford 3,4-bis(trimethylsilyl)pyridine in moderate yield.[34] In addition, BTMSA can be added to 4-phenyloxazole in the presence of catalytic triethylamine at 250 °C to give 3,4-bis(trimethylsilyl)furan in excellent yield.[35] BTMSA has also been used in other cycloadditions including cyclopropenation involving bis(methoxycarbonyl)carbene,[36] [2 + 2] cycloaddition with dichloroketene to give silylated cyclobutenedione,[37] 1,3-dipolar cycloaddition with pyridinium dicyanomethylides to afford silylated indolizines,[38] and with nitrile oxides to give isoxazoles.[39]

Miscellaneous Reactions.

In addition to BTMSA being used as an acetylide synthon, it can also be converted to the corresponding alkynyl(phenyl)iodonium tosylate[40] and treated with nucleophiles such as 1,3-dicarbonyl compounds.[41] 1-Nitro-2-(trimethylsilyl)acetylene has been prepared from BTMSA and undergoes a series of cycloadditions analogous to BTMSA itself.[42] In addition, BTMSA will undergo hydroboration with dialkylborane to afford 1-substituted 1,2-bis(trimethylsilyl)ethenes[43] or with ***Borane-Dimethyl Sulfide*** to give an acylsilane.[44] Finally, it was reported that BTMSA could be treated with cyclopropylcarbene-chromium complex to give silylated 3-methoxy-2-cyclopentenone in good yield.[45]

Related Reagents.

Trimethylsilylacetylene.

---

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(1*E*,3*E*)-1,4-Bis(trimethylsilyl)-1,3-butadiene

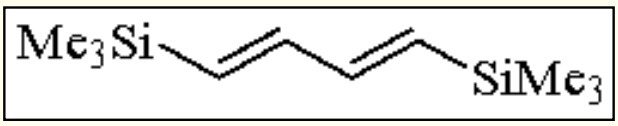

[22430-47-3] · $C_{10}H_{22}Si_2$ · (1*E*,3*E*)-1,4-Bis(trimethylsilyl)-1,3-butadiene · (MW 198.45)

(building block for the stereodefined construction of conjugated polyenyl chains[1-4])

Physical Data: bp 46-49 °C/15 mmHg; *n*20D 1.4679.

Analysis of Reagent Purity: GC/MS, IR, ^{1}H and ^{13}C NMR.

Preparative Methods: coupling of the Grignard reagent derived from (*E*)-2-(trimethylsilyl)-1-bromoethylene with the same bromo derivative leads to the silyldiene in 51% yield;[5] a higher yield (62%) is obtained by reaction of bis(trimethylsilyl)methyllithium with (*E*)-3-(trimethylsilyl)-2-propenal.[6] Other procedures involve the Pd^0-catalyzed demercuration of bis[(*E*)-(2-trimethylsilylvinyl)]mercury, prepared from (*E*)-2-(trimethylsilyl)-1-lithioethylene and $HgCl_2$ (77% yield),[7] or the reaction of (*E*)-1,4-bis(trimethylsilyl)-2-butene with *n*-BuLi and TMEDA and subsequent oxidation with $HgCl_2$ of the isolated bis-lithiated species, stabilized by complexation with TMEDA (57% yield).[8]

Handling, Storage, and Precautions: conveniently stored at -15 °C for several months, without appreciable isomerization.

Electrophilic Substitutions.

A highly selective substitution of a trimethylsilyl group is readily performed with acyl chlorides in the presence of ***Aluminum Chloride*** to obtain silylated ketones with high retention of configuration (>98%). Dicarbonyl compounds are prepared with a one-pot procedure, by simply adding the second acyl chloride after completion of the first step, without isolation of the monosubstitution product (eq 1).[1]

(1E,3E)-1,4-Bis(trimethylsilyl)-1,3-butadiene

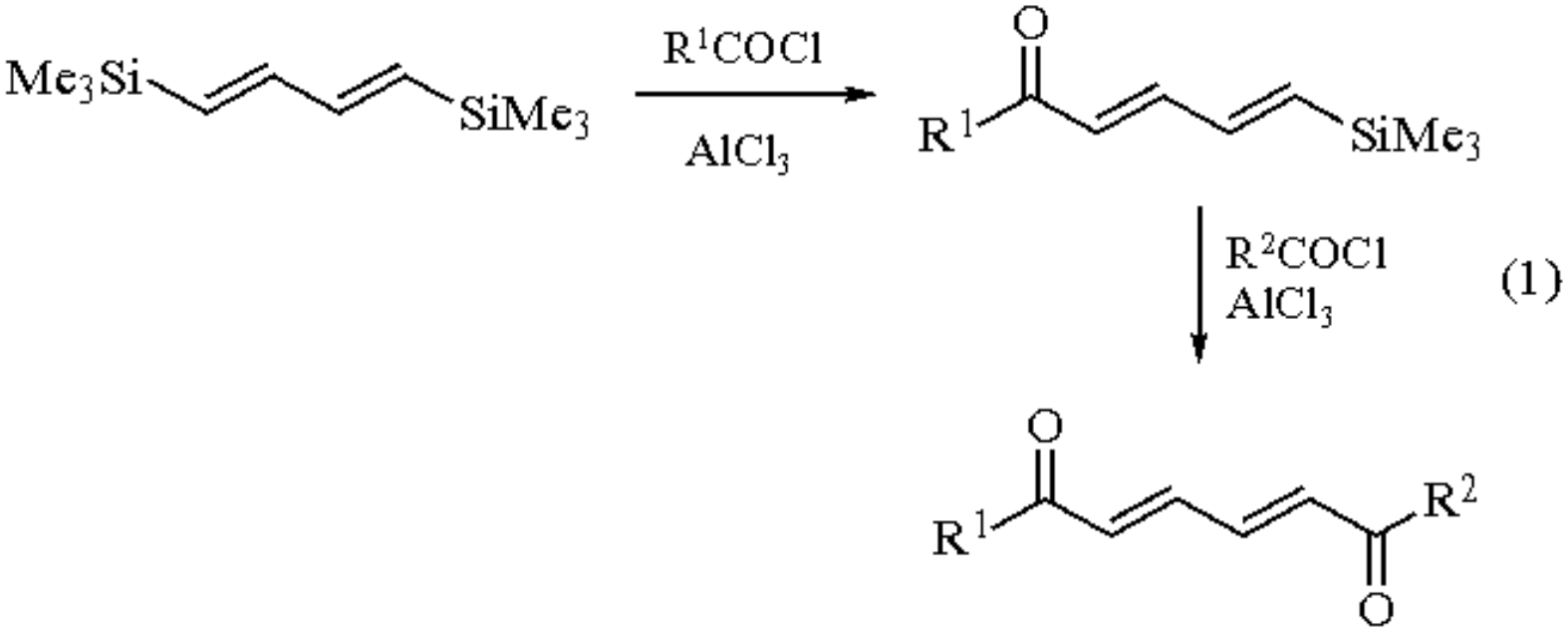

The versatility of this approach is illustrated by the synthesis of polyunsaturated fatty acids of special interest. Ostopanic acid, a cytotoxic fatty acid,[9] is directly obtained by acylation reactions with the appropriate acyl chlorides,[2] whereas β-parinaric acid methyl ester, an interesting fluorescent probe for biological membranes,[10] is prepared by a selective double acylation, followed by reduction and dehydration reactions (eq 2).[3]

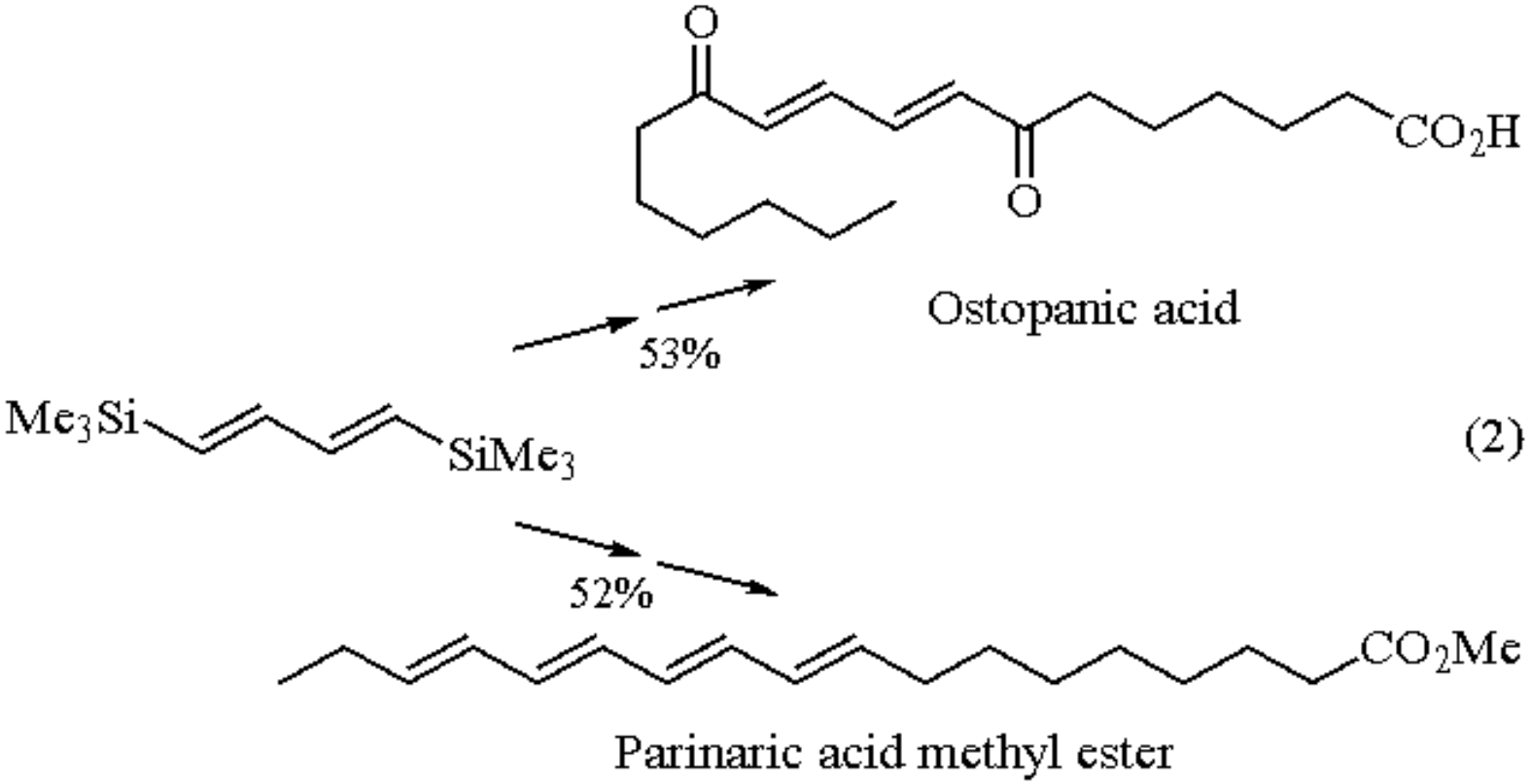

Moreover, unsaturated keto silanes and diketones obtained according to eq 1 can be easily reduced to saturated keto silanes or 1,6-dicarbonyl compounds;[11] unsaturated keto silanes can be transformed into enantiomerically enriched hydroxy derivatives by reduction and enzymatic kinetic resolution.[12] Monosilylated unsaturated sulfides, precursors of a variety of dienylsilanes,[13] can be also obtained by chemoselective electrophilic substitutions.[4]

Halogen Addition.

Bromine addition leads to a tetrabromo derivative which can be bromodesilylated to (1*Z*,3*Z*)-1,4-dibromobutadiene (eq 3).[14]

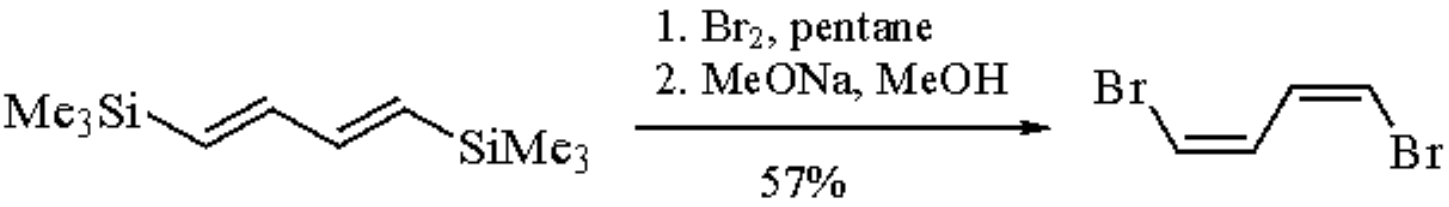

(3)

Cycloaddition Reactions.

Diels-Alder reactions with ***Maleic Anhydride*** (eq 4)[5,6] lead to cyclic allylsilanes, which can undergo further interesting elaborations.[6]

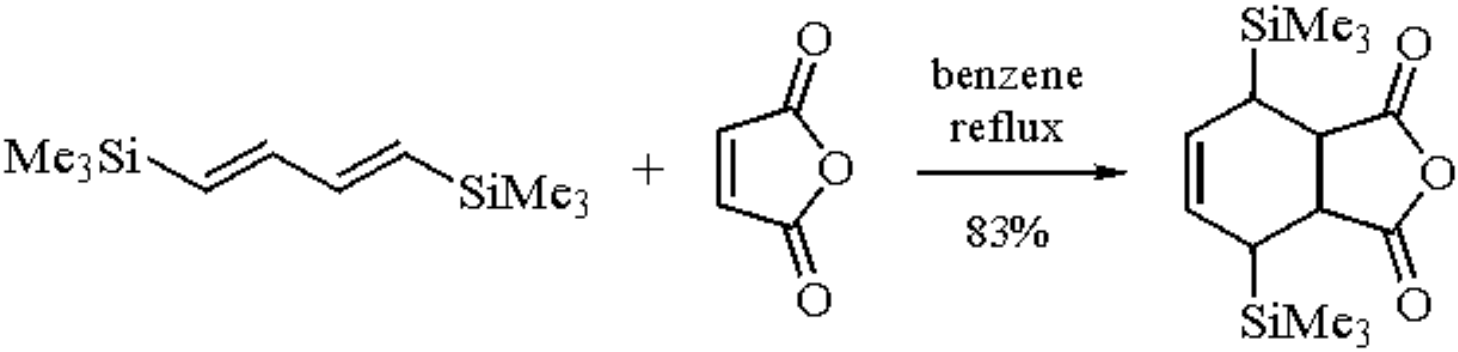

(4)

Related Reagents.

(1E,3E,5E)-1,6-Bis(trimethylsilyl)-1,3,5-hexatriene; ***2,3-Bis(trimethylstannyl)-1,3-butadiene***; ***(E)-1-Trimethylsilyl-1,3-butadiene***; ***2-Trimethylsilylmethyl-1,3-butadiene***.

---

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(1*E*,3*E*,5*E*)-1,6-Bis(trimethylsilyl)-1,3,5-hexatriene

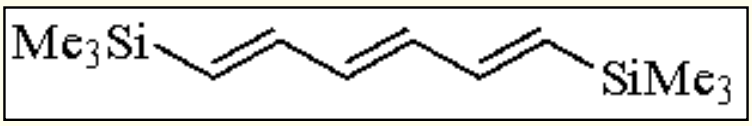

[133683-82-6] · $C_{12}H_{24}Si_2$ · (1*E*,3*E*,5*E*)-1,6-Bis(trimethylsilyl)-1,3,5-hexatriene · (MW 224.49)

(building block for the stereodefined construction of conjugated polyenyl chains[1-6])

Physical Data: bp 71-73 °C/0.75 mmHg.

Analysis of Reagent Purity: GC/MS, IR, ^{1}H and ^{13}C NMR.

Preparative Methods: conveniently prepared by means of the cross-coupling reactions of 2 equiv of the Grignard reagent derived from (*E*)-2-(trimethylsilyl)-1-bromoethylene with (*E*)-1,2-dichloroethylene (75% yield) or with (*E*)-2-phenylthio-1-chloroethylene (55% yield),[7] in the presence of $NiCl_2$(dppe) in THF at rt. [2-(Trimethylsilyl)-1-bromoethylene is commercially available in an (*E*)/(*Z*) 87/13 ratio. The mixture is distilled two or three times on a Fisher column MMS 202 at 50-52 °C/42 mmHg and fractions enriched in (*Z*)-isomer are collected. The (*E*)-isomer is recovered and purified by simple distillation (bp 54-55 °C/42 mmHg, stereoisomeric purity 98-99%)].

Handling, Storage, and Precautions: can be stored at -15 °C for several months, without isomerization.

Electrophilic Substitutions with Acyl Chlorides.

The reaction of the trienylsilane with equimolar amounts of acyl chloride and ***Aluminum Chloride*** at 0 °C in CH_2Cl_2 affords unsaturated keto silanes with high retention of configuration (>98%). Subsequent substitution of the second silyl group with another acyl chloride in the same reaction flask at rt leads to the diketone derivative (eq 1).[1]

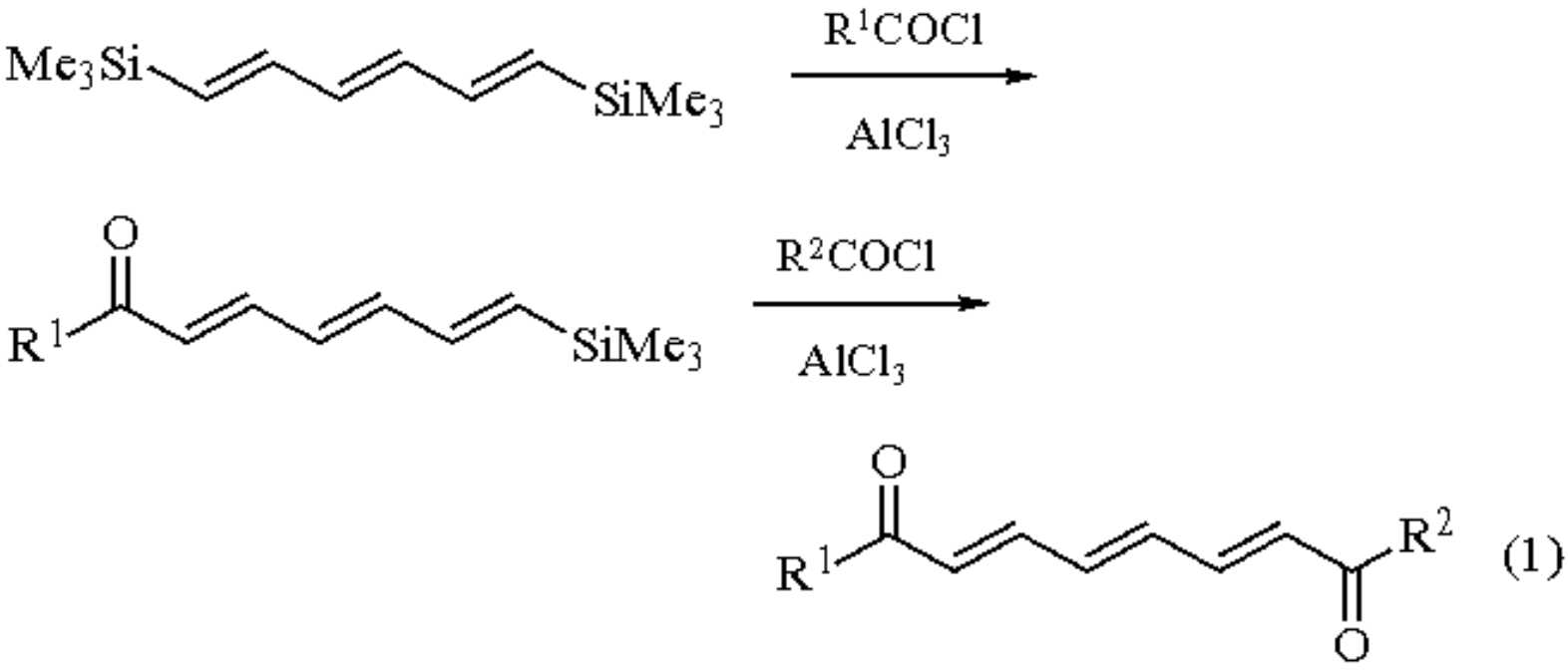

The highly efficient synthetic potential of the bis-silylated triene is illustrated by the synthesis of the (6*E*)-isomer of leukotriene B_3[2] and of SM-9064, a potential LTB_4 antagonist (eq 2).[3] The key step of the synthesis of both compounds is represented by the double acylation of the bis-silylated triene with the appropriate acyl chlorides [(6*E*)-LTB_3: nonanoyl chloride and methylglutaryl chloride; SM-9064: 3-(*p*-methoxyphenyl)propanoyl chloride and methylsuccinyl chloride]. Other steps require reduction with ***Sodium Borohydride*** of the diketo ester intermediates and, in the case of SM-9064, the amide formation reaction with ***Pyrrolidine*** in methanol.

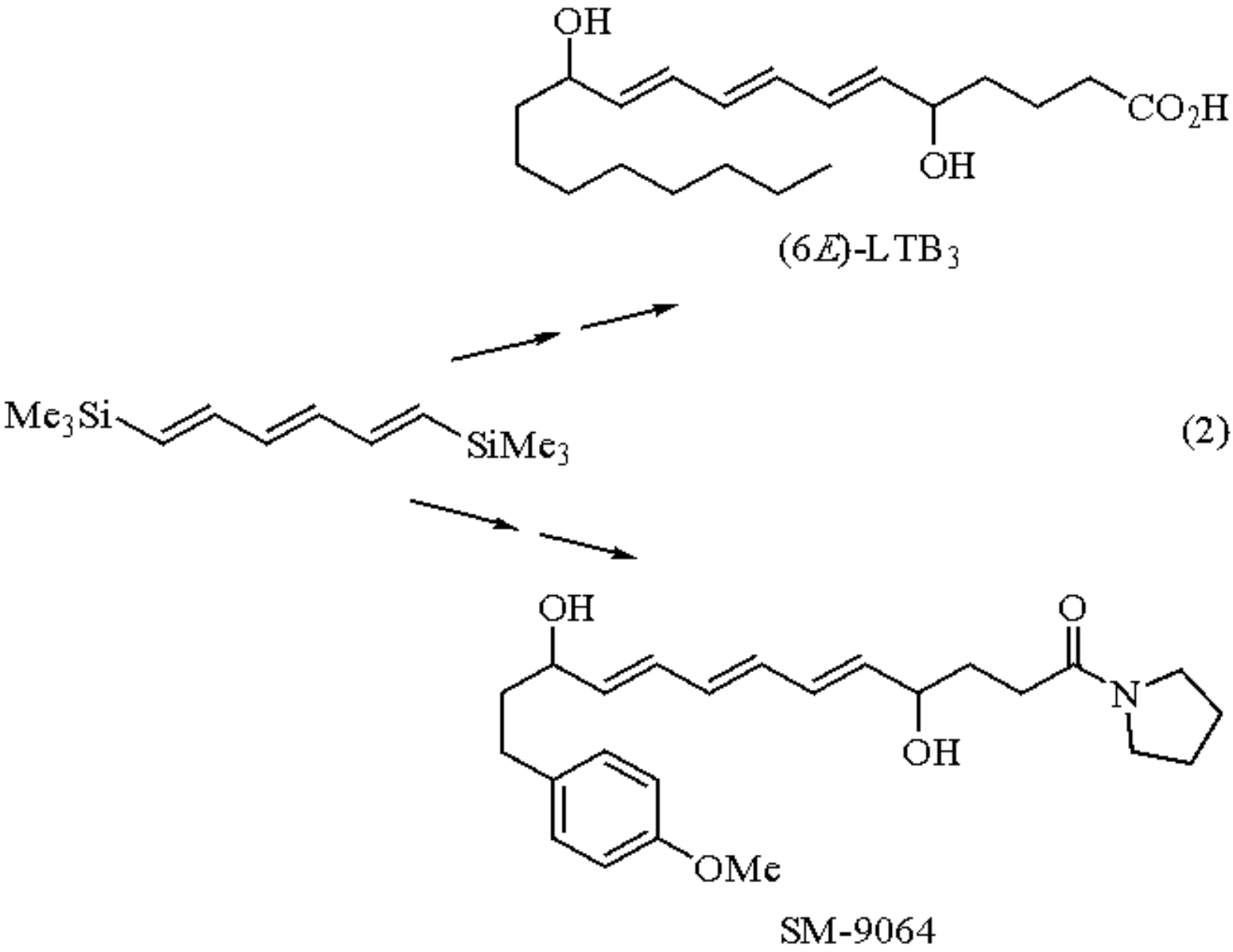

Unsaturated keto silanes and diketones prepared according to eq 1 can be further transformed into saturated keto silanes or 1,8-diketones by means of Pd-catalyzed selective hydrogenation reactions.[4]

Polyunsaturated secondary alcohols, obtained by reduction of keto silanes, can be kinetically resolved with a high (>97%) enantioselectivity by lipase-catalyzed transesterification with ***Vinyl Acetate***.[5] A representative example is reported in eq 3.

(1E,3E,5E)-1,6-Bis(trimethylsilyl)-1,3,5-hexatriene

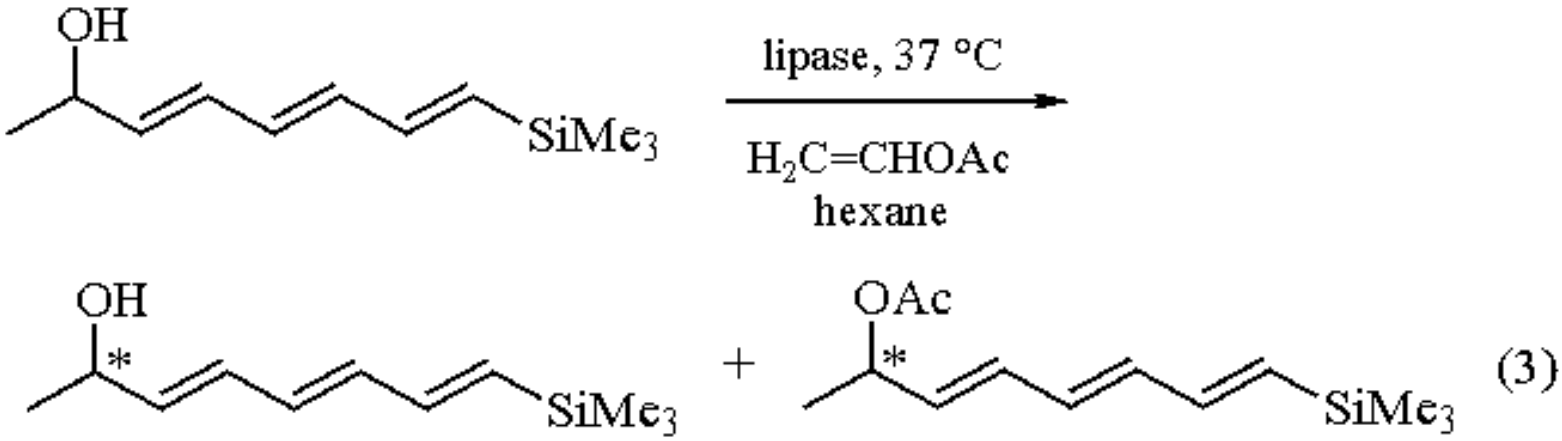

Electrophilic Substitutions with Sulfur Derivatives.

Reaction of the bis-silylated triene with ***Benzenesulfenyl Chloride*** in THF at rt leads to the trienyl sulfide with inversion of configuration at the terminal double bond (*Z*,*E*,*E*/*E*,*E*,*E* = 90/10).[6] The substitution reaction with the commercially available *S*-phenyl carbonochloridothioate leads to the corresponding monosilylated thioester with high retention of configuration. A straightforward decarbonylation reaction with Ni^0 in DMF[8] affords the corresponding sulfide (*E*,*E*,*E*/*Z*,*E*,*E* = 85/15) (eq 4).[6]

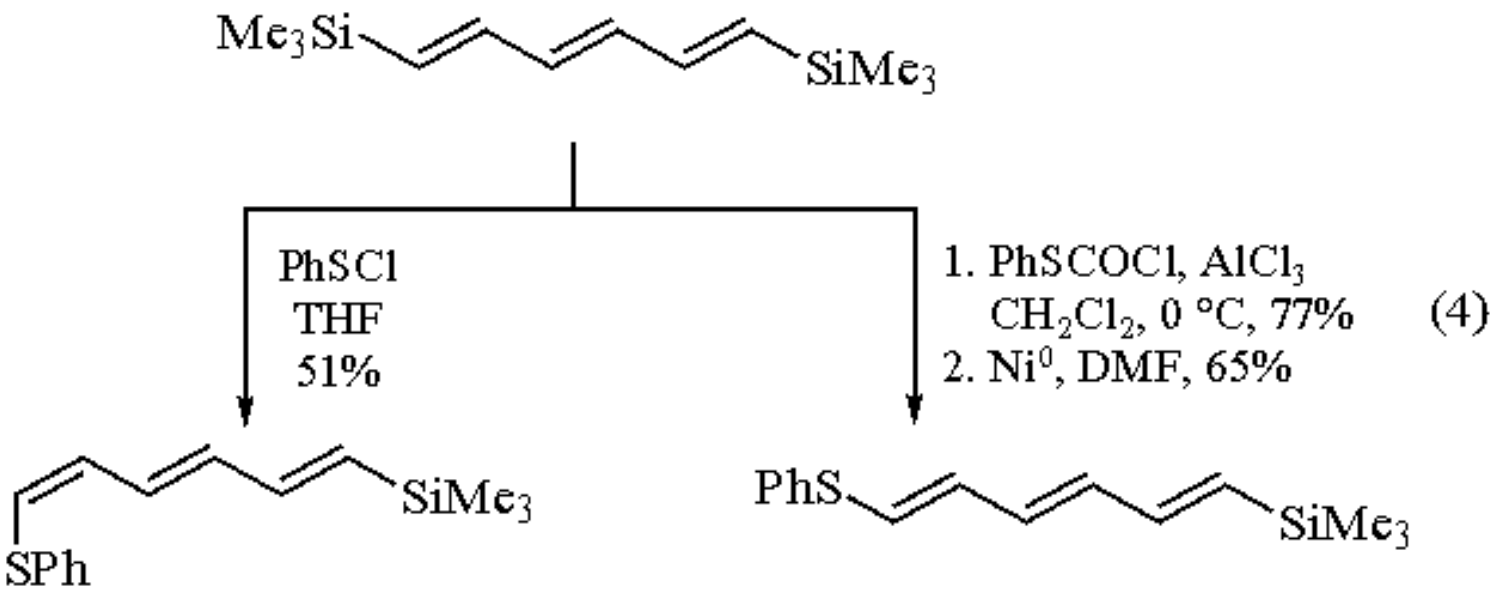

Related Reagents.

(1E,3E)-1,4-Bis(trimethylsilyl)-1,3-butadiene; ***(E)-1-Trimethylsilyl-1,3-butadiene***.

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1. Babudri, F.; Fiandanese, V.; Marchese, G.; Naso, F. *CC* **1991**, 237.
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3. Fiandanese, V.; Punzi, A. *SC* **1993**, *23*, 173.

4. Fiandanese, V.; Punzi, A.; Ravasio, N. *JOM* **1993**, *447*, 311.
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N,O-Bis(trimethylsilyl)hydroxylamine

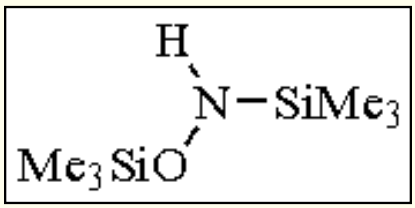

[22737-37-7] · $C_6H_{19}NOSi_2$ · *N,O*-Bis(trimethylsilyl)hydroxylamine · (MW 177.39)

(protected hydroxylamine synthon for the formation of isocyanates,[6] hydroxamic acids,[6] *N*-phosphinoylhydroxylamines,[12] and oximes[13])

Physical Data: bp 137-139 °C, 78-80 °C/100 mmHg; *d* 0.830 g cm^{-3}; flash point 28 °C.

Solubility: sol THF, ether, pentane, CH_2Cl_2.

Form Supplied in: liquid; widely available, but expensive.

Analysis of Reagent Purity: ^1H NMR (benzene-d_6) δ 0.16 (s, 9, $NSiMe_3$), 0.25 (s, 9, $OSiMe_3$), 4.6 (br s, 1, NH).[1-3]

Preparative Methods: can be prepared in 69% yield by treating dry ***Hydroxylamine*** with 2 equiv ***Chlorotrimethylsilane*** and 2 equiv ***Triethylamine***.[3] A safer preparation, which avoids the use of the explosive solid, hydroxylamine, uses the reaction of hydroxylamine hydrochloride with excess ***Hexamethyldisilazane*** (71-75% yield).[1,2] Alternatively, neutralization of hydroxylamine hydrochloride with ethylenediamine followed by addition of chlorotrimethylsilane can be used.[4]

Handling, Storage, and Precautions: flammable, corrosive liquid; hydrolyzed by moist air. Avoid inhalation and prevent contact with skin and eyes. The reagent should be stored under argon at 0-4 °C. Use in a fume hood.

Nucleophilic Reactions.

N,O-Bis(trimethylsilyl)hydroxylamine is a protected, lipophilic form of hydroxylamine. It reacts with a variety of electrophiles predominantly by attack on the nitrogen nucleophilic center. Reaction with acid chlorides (1 equiv) in the presence of triethylamine gives *N,O*-bis(trimethylsilyl)hydroxamic acids by *N*-acylation.[6] A related reagent, tris(trimethylsilyl)hydroxylamine, gives the same product in high yields, also by *N*-acylation.[5,6] Hydrolysis gives the free hydroxamic acids, whereas thermal fragmentation affords isocyanates (eq 1).[6]

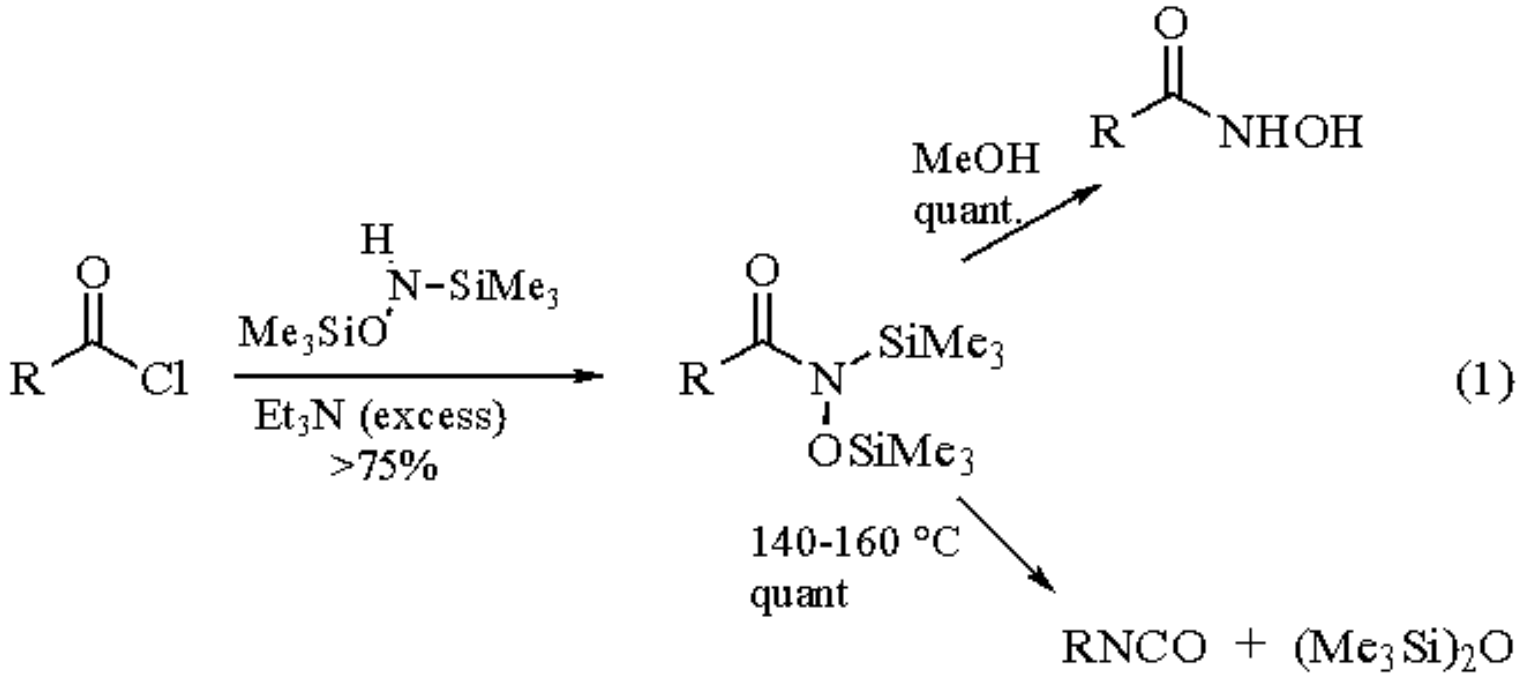

Excess ***Acetyl Chloride*** (and presumably other acyl chlorides) reacts with *N,O*-bis(trimethylsilyl)hydroxylamine to give *O*-acetyl acetohydroxamate in 88% yield after hydrolytic workup.[7] Isocyanates react exothermically with *N,O*-bis(trimethylsilyl)hydroxylamine to give *N,O*-bis(trimethylsilyl)-*N*-hydroxyureas in high yields.[8] Carboxylation of *N,O*-bis(trimethylsilyl)hydroxylamine with ***Carbon Dioxide*** in THF followed by silylation gives a tris(trimethylsilyl) derivative of *N*-hydroxycarbamic acid.[9] This intermediate rearranges in high yield to afford an *N*-trimethylsilyloxy isocyanate (eq 2).[10]

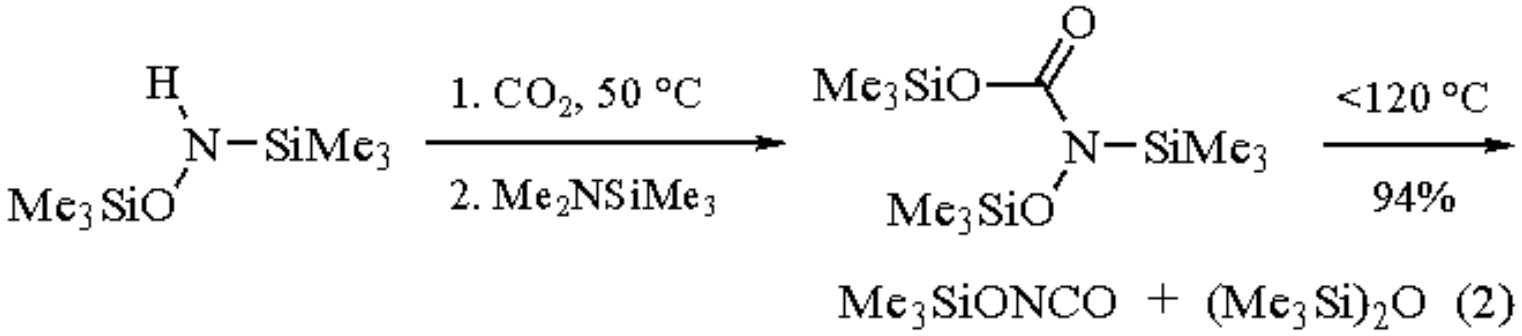

Reaction of *N,O*-bis(trimethylsilyl)hydroxylamine with ***Diketene*** affords the explosive *N,O*-bis(trimethylsilyl) derivative of acetoacetylhydroxamic acid. Deprotection and cyclization gives an isoxazole (eq 3) whose dianion serves as a useful β-keto amide synthon.[11]

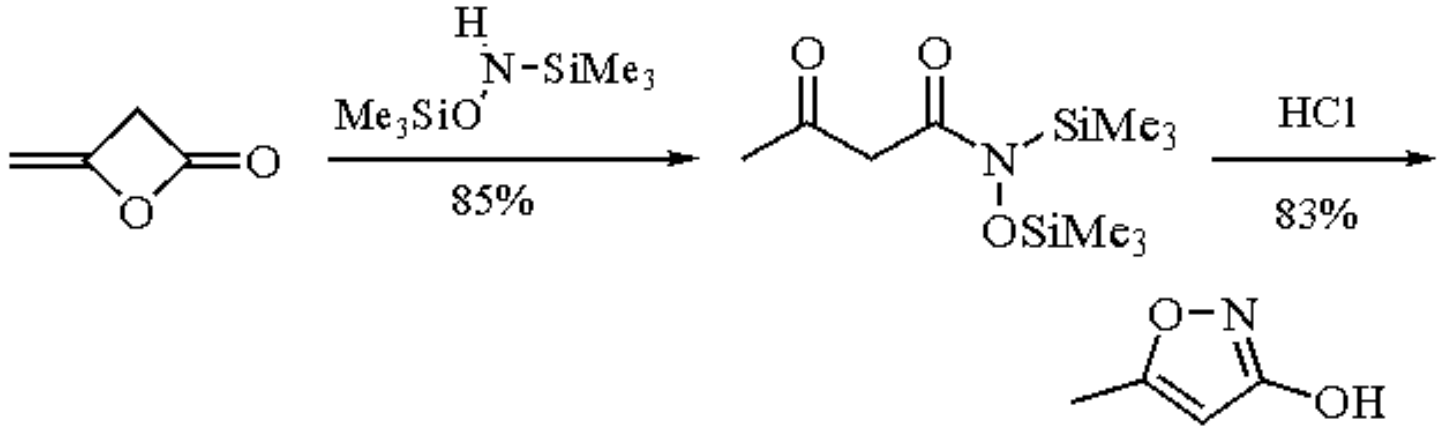

(3)

Phosphorus analogs of hydroxamic acids, prepared from phosphinic chlorides and *N*,*O*-bis(trimethylsilyl)hydroxylamine, tend to be unstable. The stable *O*-sulfonyl derivatives of the phosphinoylhydroxylamines undergo base-induced, Lossen-type rearrangement to phosphonamidates by aryl group migration from P to N (eq 4).[12]

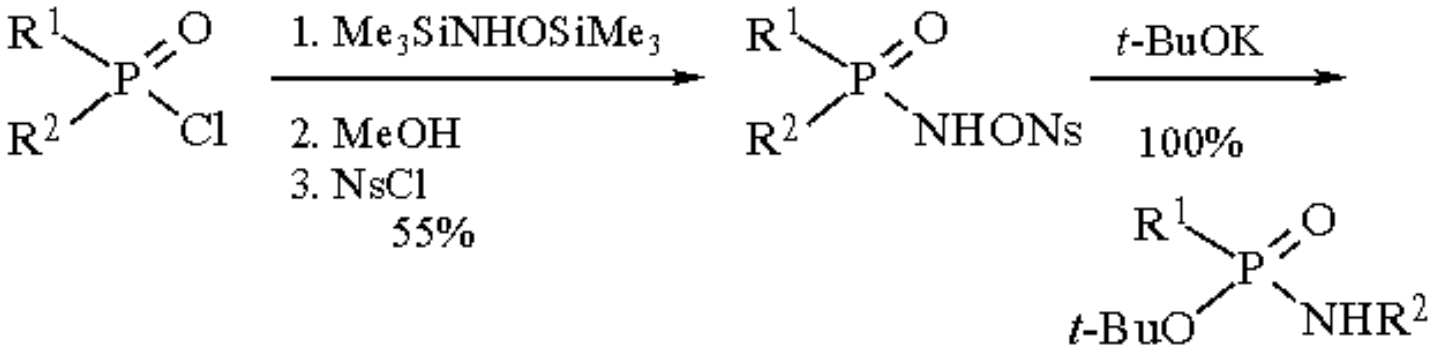

(4)

Deprotonation of *N*,*O*-bis(trimethylsilyl)hydroxylamine with ***n-Butyllithium*** or ***Potassium Hydride*** at low temperature yields the nitrogen centered anion *N*,*O*-bis(trimethylsilyl)hydroxylamide.[6,13] At higher temperatures the oxyanion *N*,*N*-bis(trimethylsilyl)hydroxylamide is formed by rearrangement.[1,14] Each reacts with acyl chlorides chemospecifically by *N*-acylation and *O*-acylation, respectively. The oxyanion also reacts with silyl halides,[1a] methyl iodide,[1] and sulfonyl chlorides[14] chemospecifically on oxygen. In a Peterson-type one-pot reaction, oximes and oxime derivatives can be prepared effectively from the N-anion of *N*,*O*-bis(trimethylsilyl)hydroxylamine and an aldehyde or ketone (eq 5).[13] Oximes of sterically hindered ketones can be formed in high yields by this procedure.

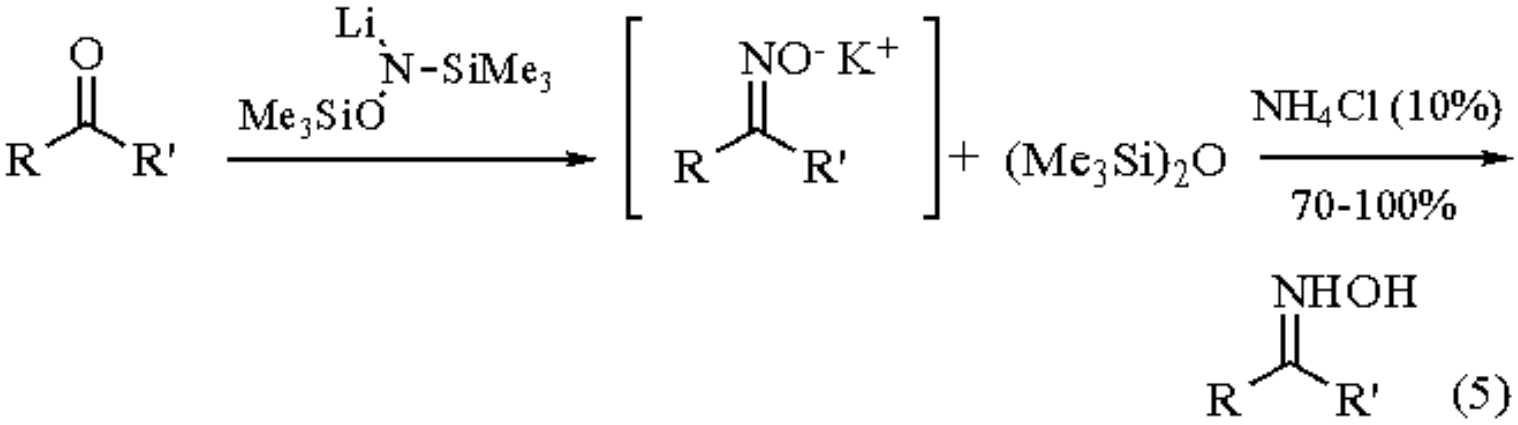

(5)

1. (a) West, R.; Boudjouk, P. *JACS* **1973**, *95*, 3987. (b) West, R.; Boudjouk, P.; Matuszko, A. *JACS* **1969**, *91*, 5184.
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Bis(trimethylsilyl) Malonate[1]

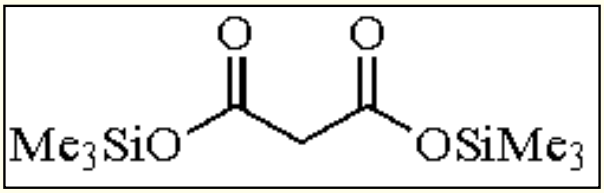

[18457-04-0] · $C_9H_{20}O_4Si_2$ · Bis(trimethylsilyl) Malonate · (MW 248.43)

(reagent useful in the synthesis of β-keto acids[2-4] and methyl ketones[3])

Physical Data: bp 63-66 °C/1 mmHg; *d* 0.974 g cm^{-3}.

Preparative Method: commercially available; alternatively, it can be easily prepared from malonic acid by a number of silylation procedures.[5]

Handling, Storage, and Precautions: flammable liquid, moisture sensitive.

Synthetic Applications.

In the homologation of activated carboxylic acid derivatives to β-keto acids, bis(trimethylsilyl) malonate has been shown to be a useful alternative to conventional methods.[4] However, despite the mild reaction conditions and generally high product yields, the reagent has seen limited use in organic synthesis.

The lithio derivative (**1**) adds smoothly to a variety of acid derivatives, including acid chlorides, mixed anhydrides, or HOBT esters, to provide β-keto acids following mild aqueous hydrolysis.[2] Thus benzoylacetic acid was obtained in 92% yield upon treatment of (**1**) with ***Benzoyl Chloride*** (eq 1).

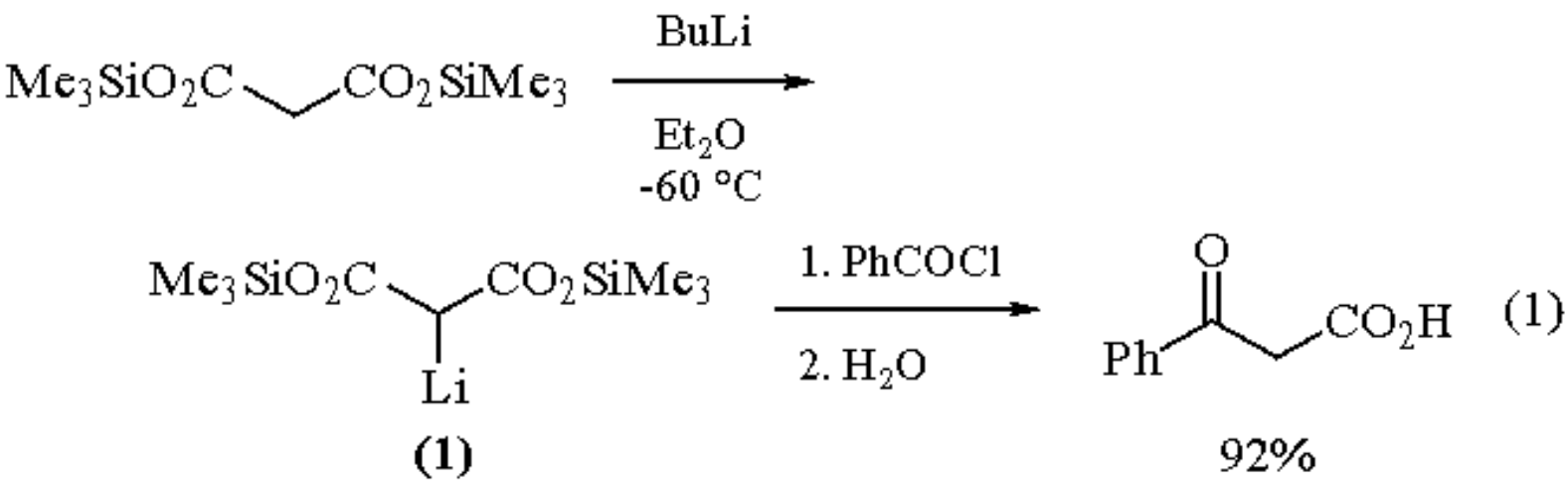

In the presence of lithium or magnesium salts, bis(trimethylsilyl) malonate can be acylated with acid chlorides under milder conditions.[3] Metal complexation enhances the acidity of malonates such that tertiary amines can be used as bases.[3b] The β-keto acids can be isolated after a mild aqueous workup, or the corresponding methyl ketone can be obtained directly using more vigorous conditions (eq 2).

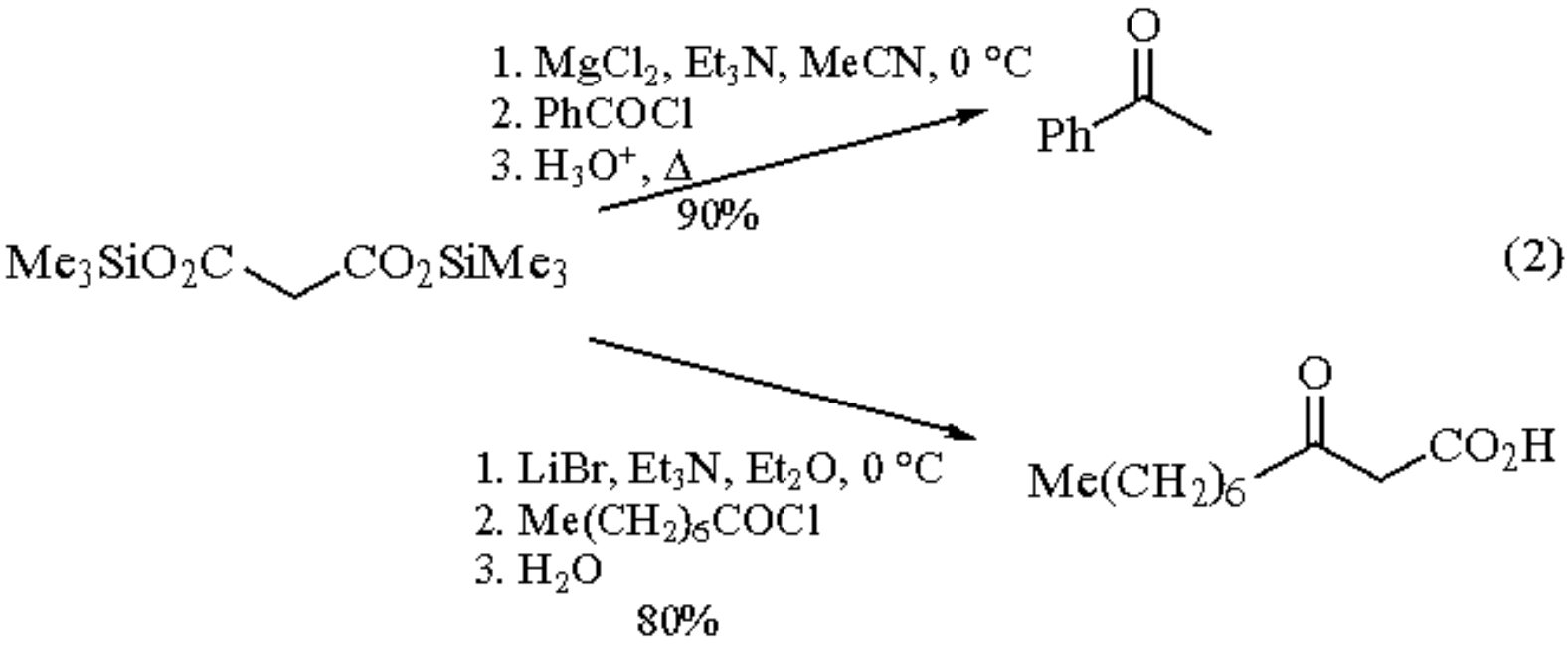

5-Acetyl-2-chloro-3-nitropyridine, an intermediate in the synthesis of analogs of the inotropic agent isomazole, was prepared from the corresponding acid chloride using this methodology (eq 3).[6]

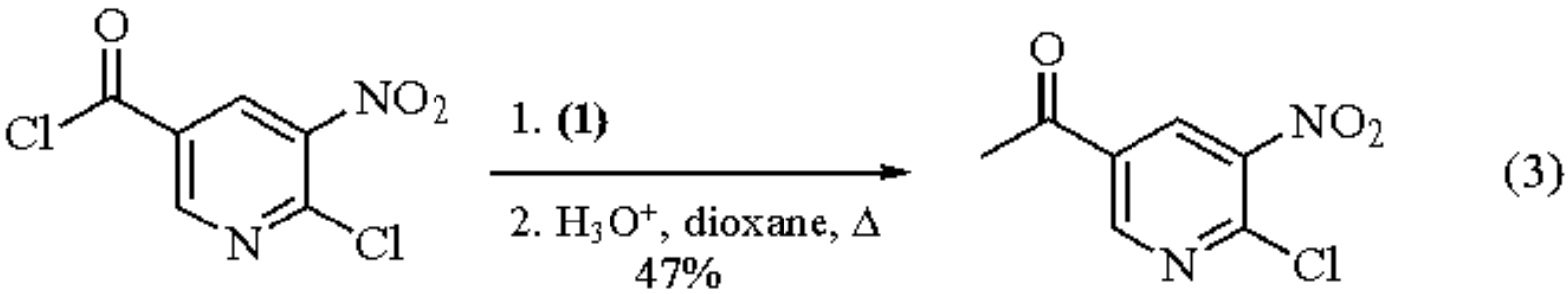

The α-substituted β-keto acid (**2**), an intermediate useful in the synthesis of chiral 2-methyl-3-hydroxybutyrolactones, was obtained via the reaction of the anion derived from methyl bis(trimethylsilyl) malonate (eq 4).[7]

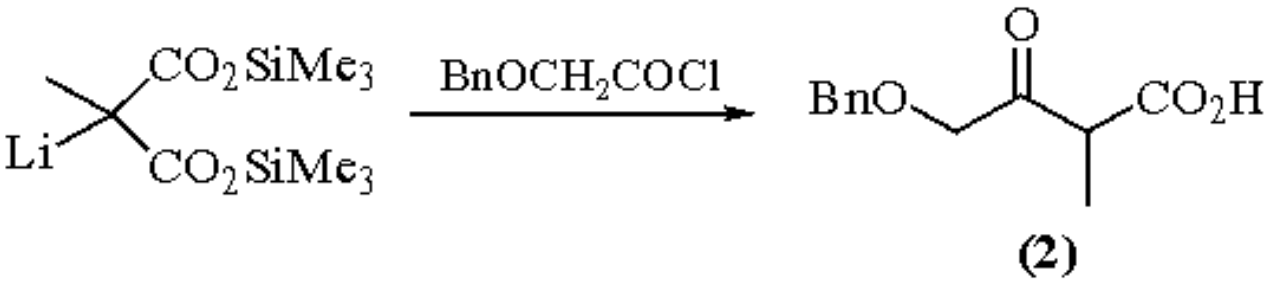

(4)

Related Reagents.

Diethyl Ethoxymagnesiomalonate; ***Diethyl Malonate***; ***Ethyl 3,3-Diethoxyacrylate***; ***Ethyl Malonate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Malonic Acid***; ***Methyl Cyanoformate***; ***Methyl Magnesium Carbonate***.

---

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Bis(trimethylsilyl)mercury[1]

$Hg(SiMe_3)_2$

[4656-04-6] · $C_6H_{18}HgSi_2$ · Bis(trimethylsilyl)mercury · (MW 346.97)

(precursor to trimethylsilyllithium;[2] debrominates 1,2- and 1,3-dibromides;[3] source of trimethylsilyl radical;[4] useful reagent for preparation of metal-silicon bonds[5])

Physical Data: mp 102-104 °C.

Solubility: sol diethyl ether, tetrahydrofuran, benzene, hexane, and carbon disulfide.

Form Supplied in: yellow crystals.

Preparative Methods: original procedure involves shaking ***Sodium Amalgam*** with ***Bromotrimethylsilane***.[6] The resulting bis(trimethylsilyl)mercury is readily purified by sublimation at 60 °C in vacuo. Several alternative procedures have been described.[7]

Handling, Storage, and Precautions: mercury and its organic derivatives are highly toxic and should be handled in an efficient fume hood. Bis(trimethylsilyl)mercury is air sensitive.

Treatment of bis(trimethylsilyl)mercury with ***Lithium*** metal in an ether or hydrocarbon solvent provides ***Trimethylsilyllithium*** (eq 1).[2] This method has proved particularly useful for the generation of this lithium reagent free from additives such as HMPA.[8]

$$Hg(SiMe_3)_2 + 2\,Li \longrightarrow 2\,Me_3SiLi + Hg \qquad (1)$$

Bis(trimethylsilyl)mercury can be utilized for the conversion of 1,2- and 1,3-dibromoalkanes into alkenes and cyclopropanes respectively (eqs 2 and 3).[3] 1,2-Diiodides react in a similar fashion. Adamantene has been generated and trapped in situ with dienes using this methodology.[9]

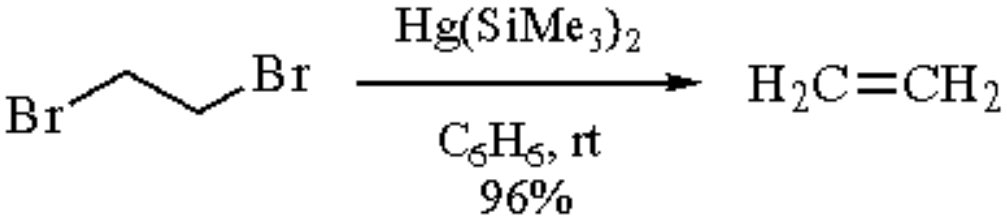

(2)

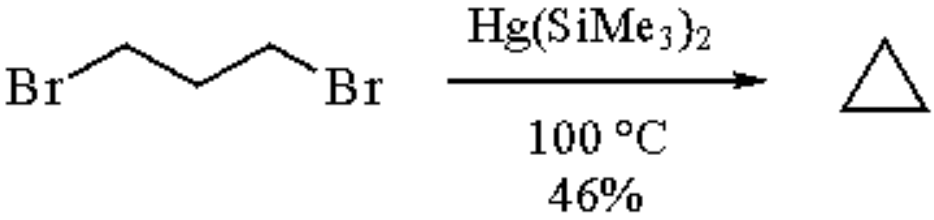

(3)

Photolysis of bis(trimethylsilyl)mercury with UV light leads to the formation of a trimethylsilyl radical.[4] Generation of this species in the presence of imines leads to the production of 1,2-diamines via an addition-dimerization process (eq 4).[10] Under similar conditions, polyfluorinated alkenes undergo an addition-elimination reaction, producing the corresponding vinyl silanes (eq 5).[11] The dealkylation of ethers such as anisole with bis(trimethylsilyl)mercury was originally speculated to involve the trimethylsilyl radical. However, more recent evidence suggests that this reaction proceeds predominantly via direct attack of the reagent on the ether linkage (eq 6).[12]

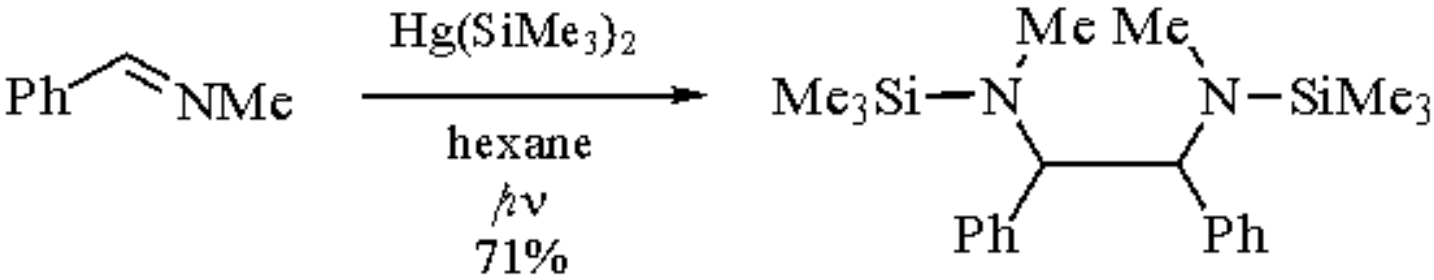

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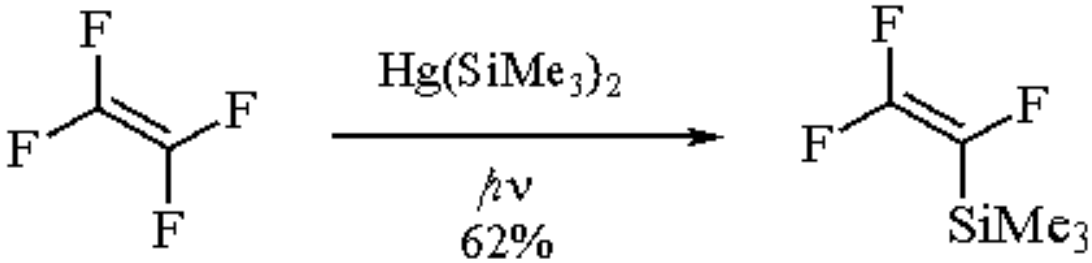

(5)

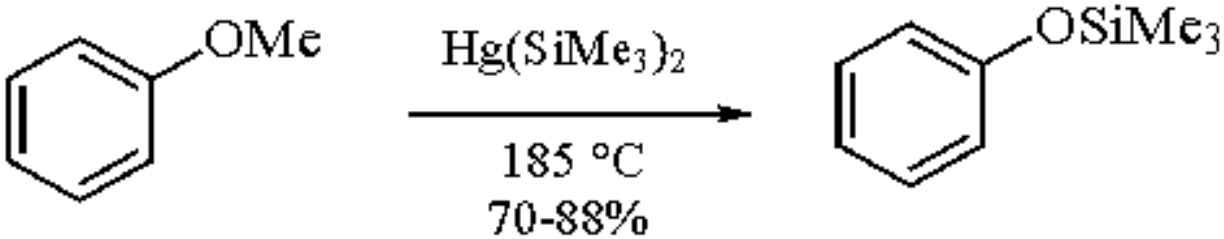

(6)

A number of organometallic complexes containing metal-silicon bonds have been prepared using

bis(trimethylsilyl)mercury as a source of the trimethylsilyl ligand.[5] Complexes derived from transition metal, lanthanide, and main group elements have all been synthesized using this chemistry.

---

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Bis(trimethylsilyl)methane[1]

$(Me_3Si)_2CH_2$

[2117-28-4] · $C_7H_{20}Si_2$ · Bis(trimethylsilyl)methane · (MW 160.41)

(precursor of $(Me_3Si)_2CHLi$ and Me_3SiCH_2Li, which are useful in Peterson alkenation reactions[3])

Physical Data: bp 132-133 °C; *d* 0.752 g cm^{-3}; *n*20D 1.41710.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; commercially available.

Analysis of Reagent Purity: ^1H NMR.

Purification: by distillation.

Handling, Storage, and Precautions: the reagent can be stored in a glass bottle.

Formation of Trimethylsilylmethyl Anion.

The carbon-silicon bond of bis(trimethylsilyl)methane can be cleaved by ***Sodium Methoxide*** in HMPA to form trimethylsilylmethylsodium, which subsequently reacts with ketones to form alkenes (eq 1).[2]

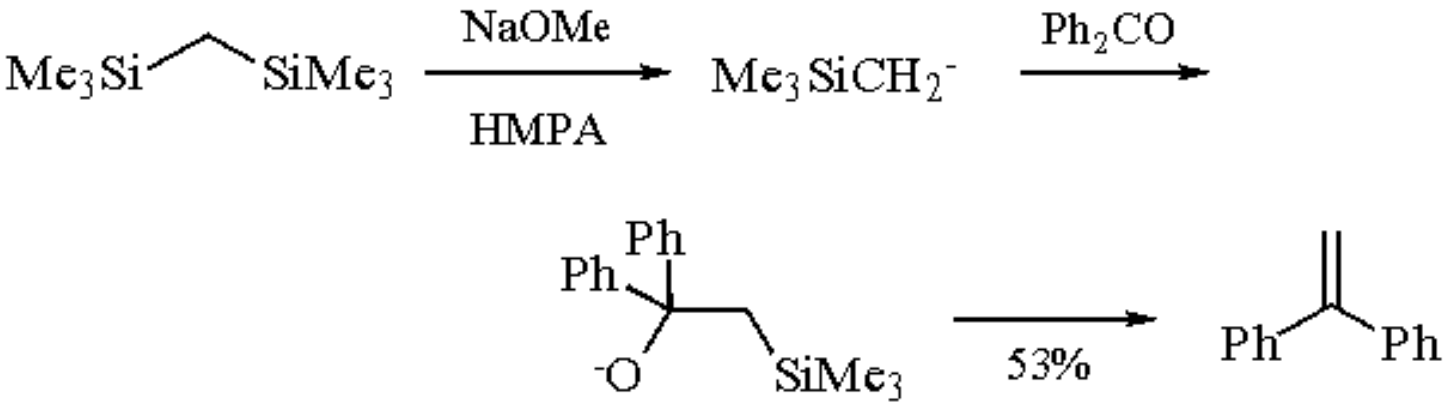

(1)

Similar reaction of bis(trimethylsilyl)phenylmethane (eq 2) gave triphenylethylene in 79% yield. Lithium methoxide

can be used instead of sodium methoxide.

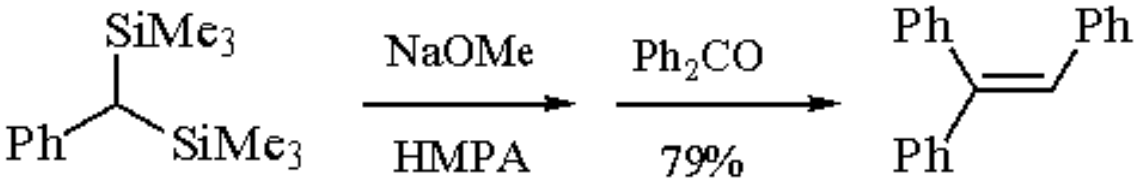

(2)

Formation of Bis(trimethylsilyl)methyllithium.

Bis(trimethylsilyl)methane can be metalated with ***Methyllithium***[3] or ***n-Butyllithium***[4] in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** to produce $(Me_3Si)_2CHLi$, which is a useful Peterson alkenation reagent (eq 3).

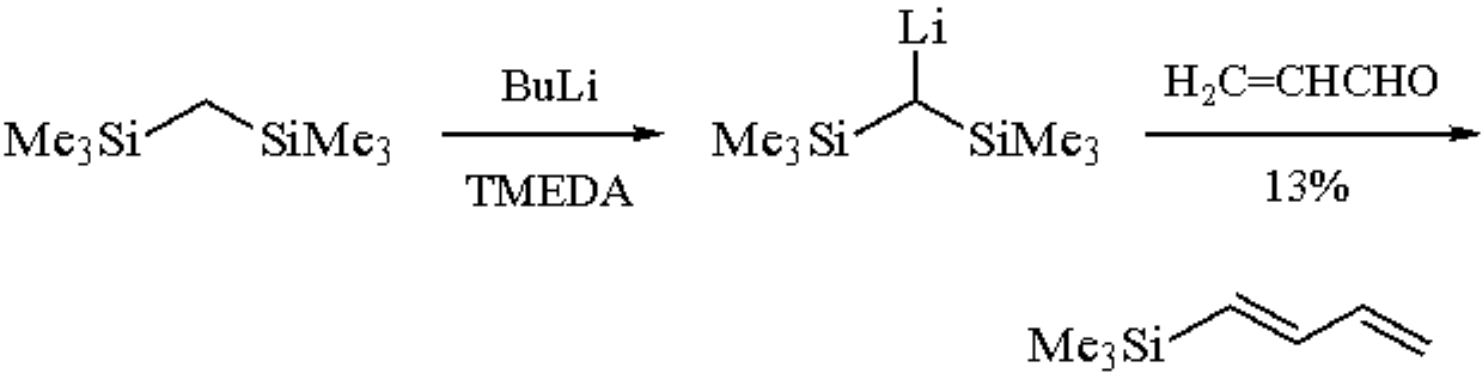

(3)

Related Reagents.

Tris(trimethylsilyl)methane.

---

1. (a) Fieser, M.; Fieser, L. F. *FF* **1975**, *5*, 617. (b) Fieser, M.; Fieser, L. F. *FF* **1979**, *7*, 396.
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4. Carter, M. J.; Fleming, I.; *FF* **1976**, 679.

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Bis(trimethylsilyl) Monoperoxysulfate

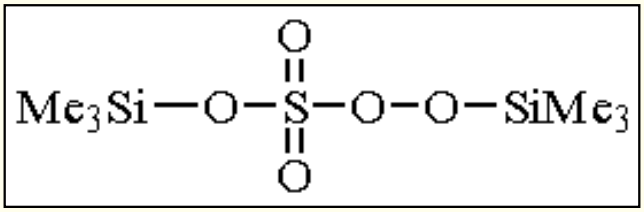

[23115-33-5] · $C_6H_{18}O_5SSi_2$ · Bis(trimethylsilyl) Monoperoxysulfate · (MW 258.44)

(strong oxidant; Baeyer-Villiger oxidant in nonprotic solvents;[1,2] oxidizes alkenes to ketones,[2] sulfides to sulfoxides,[2] and pyridine to its *N*-oxide[3])

Physical Data: colorless viscous liquid at -30 °C. ^{1}H NMR (CD_2Cl_2, 200 MHz, -30 °C) δ 0.38 (s);[2] (-50 °C) 0.28 (s) and 0.42 (s) due to nonequivalence of the Me_3Si groups.[4] ^{13}C NMR (CD_2Cl_2, 50 MHz, -30 °C) δ 0.53 (s).[2]

Solubility: sol CH_2Cl_2, CCl_4, and diethyl ether; sparingly sol petroleum ether.

Analysis of Reagent Purity: the oxidation of I^- to I_2 serves for the determination of the peroxide content (iodometric titration). Moreover, bis(trimethylsilyl) monoperoxysulfate is a sufficiently strong oxidizing agent to oxidize Cl^- or HCl gas to Cl_2 in CH_2Cl_2 solution at -20 °C.[3]

Preparative Method: the reagent is conveniently prepared[1,3] by adding dropwise a solution of ***Sulfur Trioxide*** (1 equiv or slightly less) in dry CH_2Cl_2 to a solution of ***Bis(trimethylsilyl) Peroxide***[6] in dry CH_2Cl_2 at -30 °C, followed by stirring further for 30 min at this temperature (eq 1). The yield is quantitative and the crude reagent can be used directly for oxidation reactions. Use of more than 1 equiv of SO_3 affords bis(trimethylsilyl) peroxydisulfate.[3]

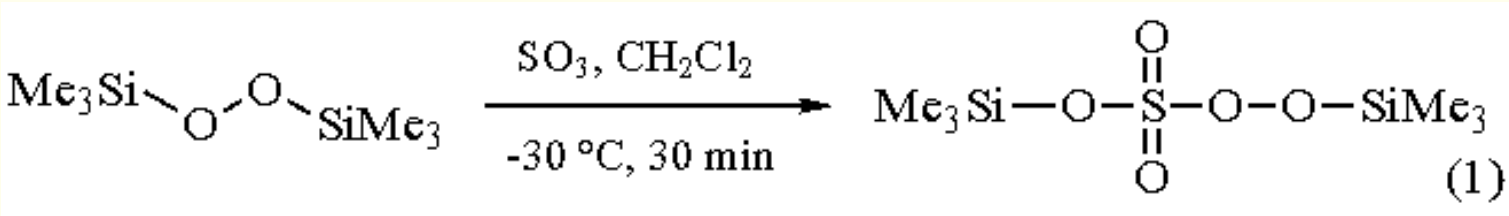

Handling, Storage, and Precautions: the reagent should be handled below -20 °C under anhydrous conditions and used immediately after preparation. It decomposes (explosion) on warming to rt, with the evolution of sulfur trioxide.[5] The reagent rearranges at rt in CH_2Cl_2 solution to the isomeric trimethylsilyl methoxydimethylsilyl sulfate within 1-2 d;[5] the rearrangement is slower at -30 °C and requires about 36 h for complete conversion.[2] The reagent undergoes hydrolysis in the presence of water to form hexamethyldisiloxane and peroxymonosulfuric acid.[3,5] A good fume hood, a safety shield, and all safety precautions required for peroxides are essential.

Baeyer-Villiger Oxidations.

Bis(trimethylsilyl) monoperoxysulfate is a convenient reagent for Baeyer-Villiger oxidations under mild conditions, in which high yields (88-98 %) of esters or lactones are obtained from the corresponding ketones (eq 2).[1,2] Usually 3-5 equiv of the reagent are required and the reaction is complete within a few hours (3-8 h). Its solubility in CH_2Cl_2 makes it a useful reagent for Baeyer-Villiger oxidations in nonprotic solvents, unlike ***Monoperoxysulfuric Acid*** (Caro's acid) or ***Potassium Monoperoxysulfate*** (Oxone). An important advantage of this reagent over monoperoxysulfuric acid is the fact that after oxygen transfer the byproduct, bis(trimethylsilyl) sulfate, is not acidic and therefore undesirable side products are usually minimized.

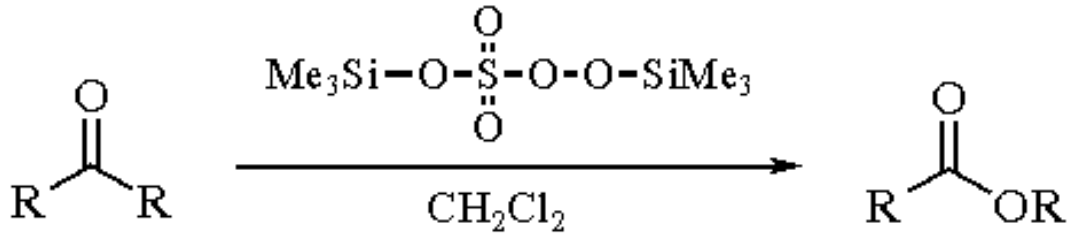

(2)

Bis(trimethylsilyl) monoperoxysulfate in CH_2Cl_2 oxidizes 4-heptanone, benzophenone, fluorenone, adamantanone, and tetracyclone to their corresponding Baeyer-Villiger rearrangement products in high yield.[1] Acetophenone gives mainly phenyl acetate, together with an appreciable amount (20 %) of methyl benzoate, despite the poor migratory aptitude of the methyl vs. phenyl group in Baeyer-Villiger oxidations.[2] Cyclohexanone affords ε-caprolactone in high yield, along with small amounts of γ-caprolactone.[2] Through the use of ^{18}O-labeled $Me_3SiOSO_2{}^{18}O{}^{18}OSiMe_3$ it was shown that this reaction proceeds via an intermediate dioxirane.[2]

The limitations of this reagent in Baeyer-Villiger oxidations are that α,β-unsaturated ketones react sluggishly and that double bonds are epoxidized.[1]

Alkene Oxidations.

Bis(trimethylsilyl) monoperoxysulfate in CH_2Cl_2 at low temperature oxidizes alkenes to ketones in high yield via the intermediacy of the corresponding epoxide (eqs 3 and 4). Addition of ketones to the reaction mixture remarkably increases the rate of this reaction.[2]

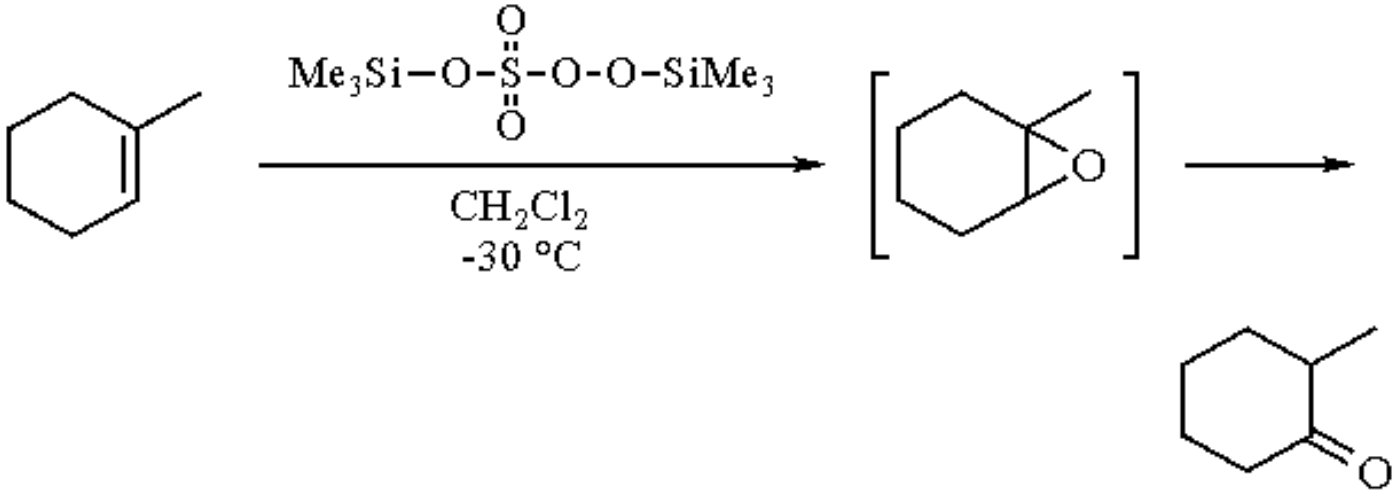

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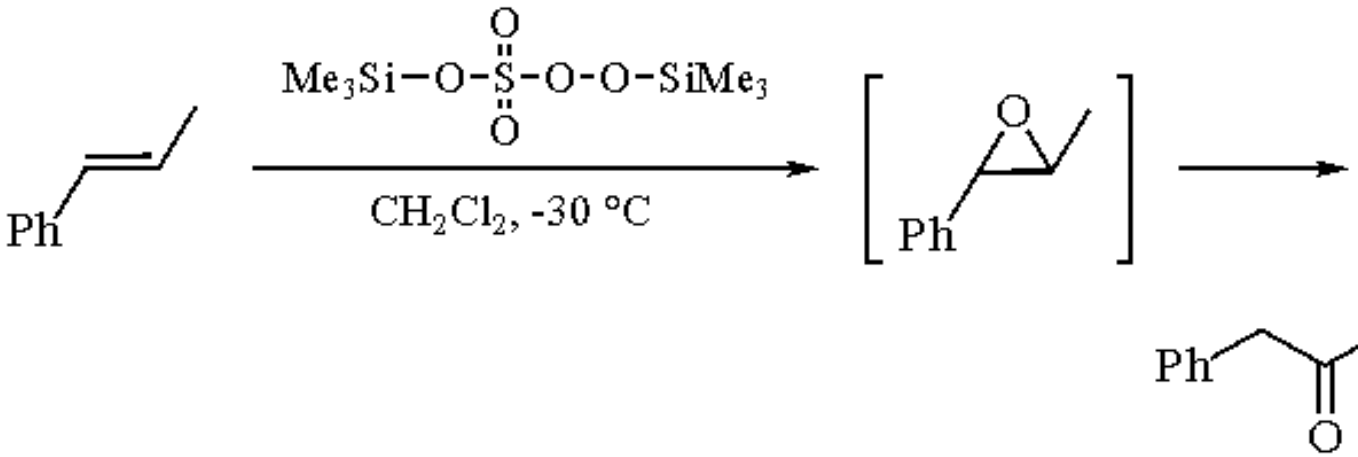

(4)

Heteroatom Oxidations.

Bis(trimethylsilyl) monoperoxysulfate reacts instantaneously with sulfides such as methyl *p*-tolyl sulfide to give the corresponding sulfoxide and bis(trimethylsilyl) sulfate (eq 5).[2] The reagent oxidizes pyridine to pyridine *N*-oxide at -30 °C in CH_2Cl_2 solution (eq 6).[3]

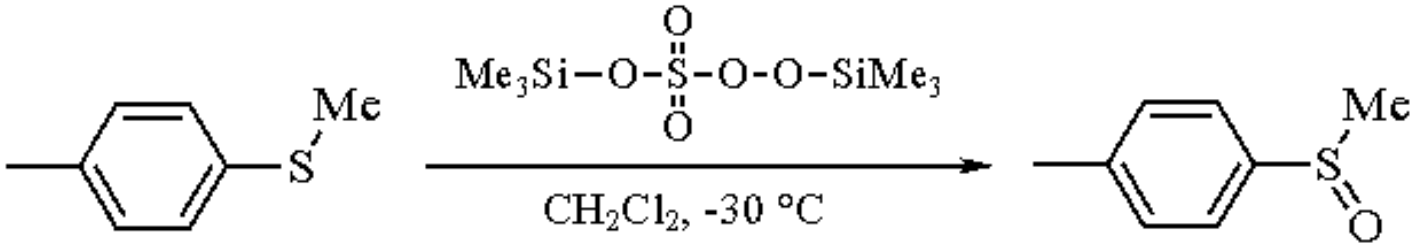

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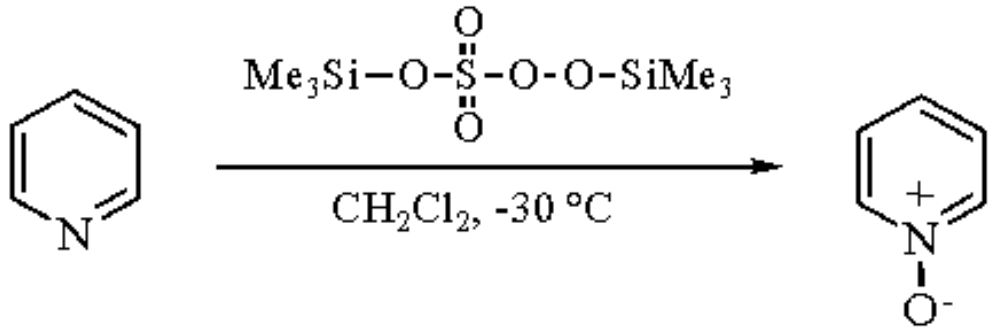

(6)

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1,2-Bis(trimethylsilyloxy)cyclobutene

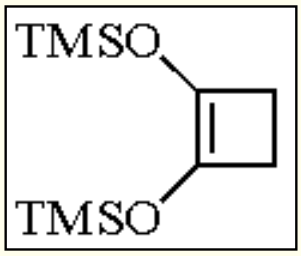

[17082-61-0] · $C_{10}H_{22}O_2Si_2$ · 1,2-Bis(trimethylsilyloxy)cyclobutene · (MW 230.45)

(a suitable reagent for annulation processes[1,2] and 4-keto ester synthesis[3])

Physical Data: bp 88-92 °C/13-14 mmHg; *d* 0.89 g cm^{-3}.

Solubility: sol hydrocarbons and ethers.

Form Supplied in: not commercially available.

Preparative Methods: prepared as a colorless liquid by acyloin condensation of ***Diethyl Succinate*** (dispersed Na in toluene or Et_2O, reflux) using ***Chlorotrimethylsilane*** as trapping agent.[4] An *Organic Synthesis* preparation is available.[4c]

Handling, Storage, and Precautions: use in a fume hood; the compound is stable for years if stored in a tightly screw-capped bottle. Prolonged exposure to moist air leads to decomposition.

Cyclopentane Annulation by Geminal Acylation.

1,2-Bis(trimethylsilyloxy)cyclobutene (**1**) reacts in an aldol-type reaction with aldehydes and acetals in the presence of ***Boron Trifluoride Etherate***. The adducts are easily converted into 2- or 2,2-substituted 1,3-cyclopentanediones in high yields via a pinacol rearrangement (eq 1). Acetals of cyclic ketones lead to spiro[4.*n*] ring systems.[1,5a] This two-step geminal acylation provides an efficient and general annulation procedure which can be carried out in a one-pot process. Cyclic acetals (dioxolanes, dioxanes), in the presence of a large excess of $BF_3.OEt_2$, provide a superior yield of the cyclopentanediones.[6] With ***Tetra-n-butylammonium Fluoride*** catalysis the reactions stop at the butanone stage.[7] Starting from thioacetals, the rearrangement can be carried out under mild, neutral conditions (***Mercury(II) Chloride***).[8]

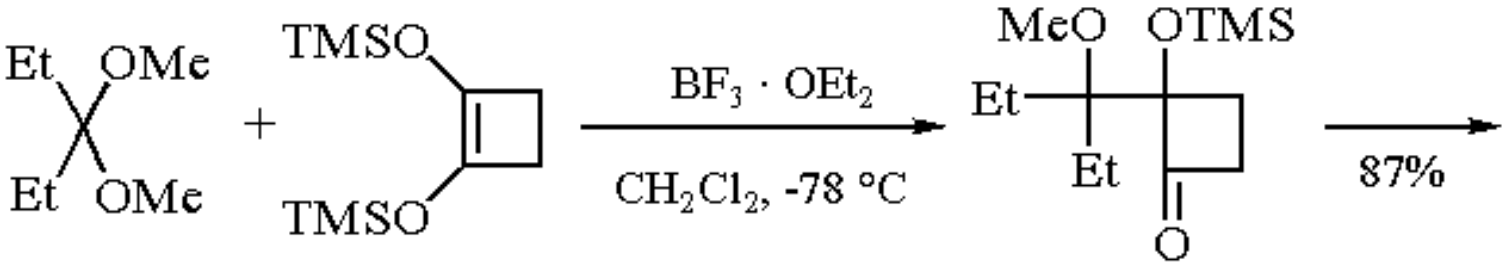

(1)

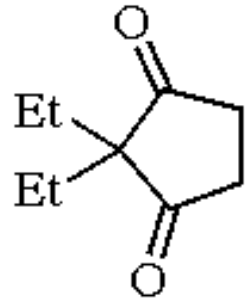

(1)

o-Alkynyl acetals react with (**1**) directly to give polycyclic unsaturated ketones (eq 2); a different pathway is observed for a terminal alkyne (eq 3).[9]

Differently functionalized cyclopentenones, β-hydroxy-cyclopentanone, or β-alkylidenecyclopentanones are obtained when the butanone is modified prior to the rearrangement.[1,5d] The spiroannulation is stereoselective because of equatorial preference of the aldol-type reactions and complete inversion during the pinacol rearrangement (eq 4).

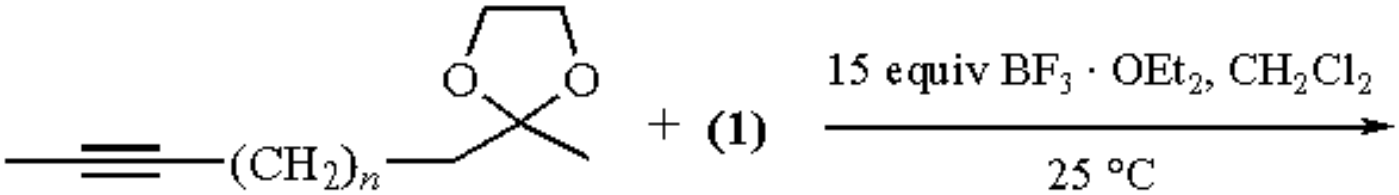

$n = 1$, 24 h, 58%; $n = 2$, 144 h, 87%

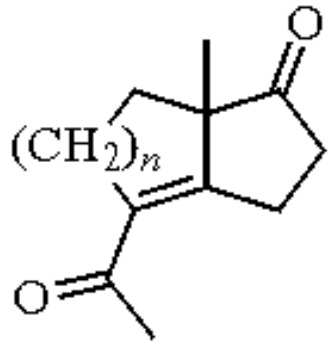

(2)

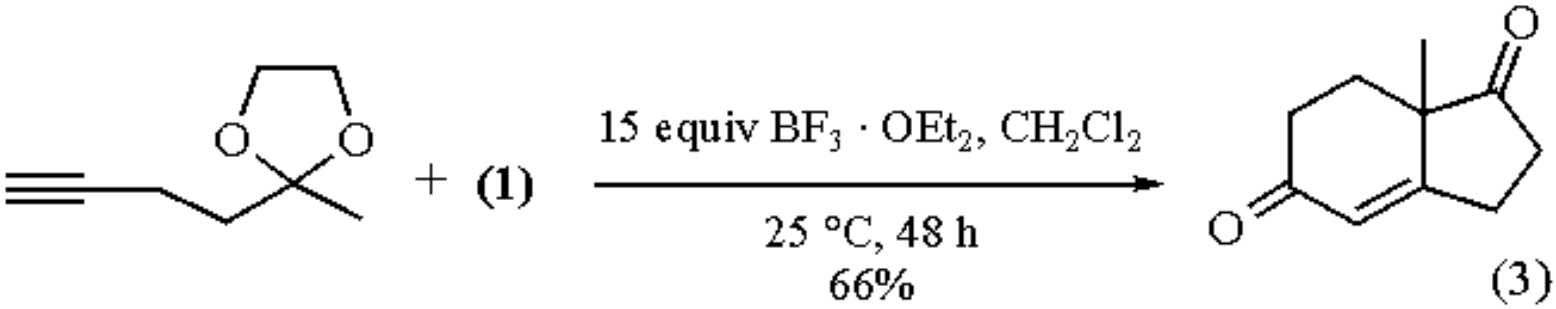

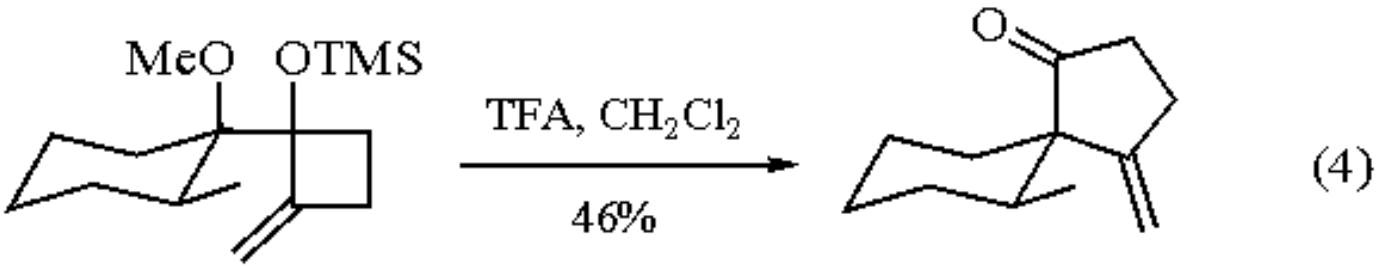

Reductive Succinoylation.

In the presence of ***Tin(IV) Chloride***, (**1**) and an acetal undergo two successive reactions, involving ring cleavage of the aldol adduct (eq 5).[3,5g] Reaction of the enol silyl ether with carbon or sulfur electrophiles leads to 5-substituted 4-keto esters.[1,3] Also 5-alkoxy-1,4-diketones can be obtained.[3,10]

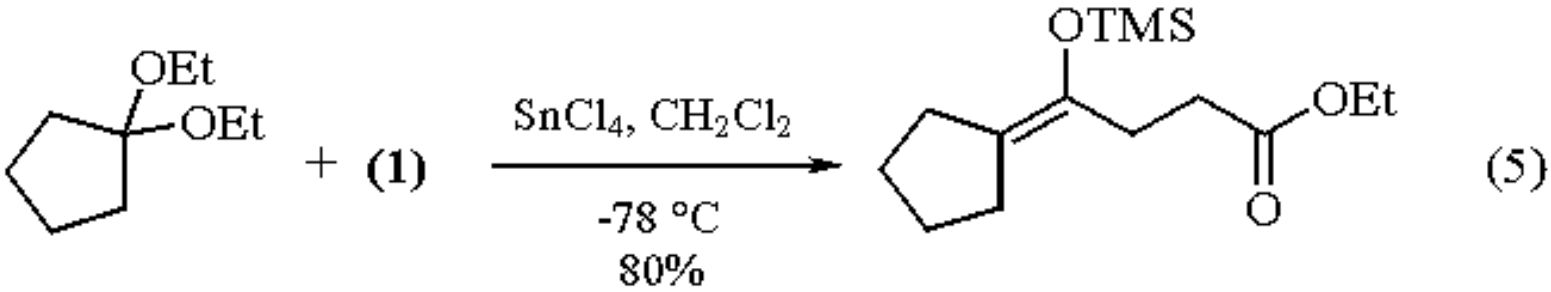

Cyclohexane Annulation.

Photochemical cycloaddition of (**1**) to 2-cyclopentenones and 2-cyclohexanones (except 2-alkyl-2-cyclohexenones) leads to tricyclo[4.3.0.0[2,6]]nonane-2-ones and tricyclo[4.4.0.0[2,7]]decane-2-ones, respectively.[2] With 5-alkyl-2-cyclohexenones the addition occurs *trans* to the 5-substituent (eq 6).[11] Subsequent to manipulation (reduction, organometallic, or Wittig reaction) of the keto function in the adduct, oxidative α-diol cleavage provides a facile entry into bicyclo[4.3.0]nona-2,5-diones and bicyclo[4.4.0]deca-2,5-diones.[2,11,12] The respective *cis*-hydrindanes and *cis*-decalanes, such as (**2**), are functionalized at three positions vicinal to the ring junction.

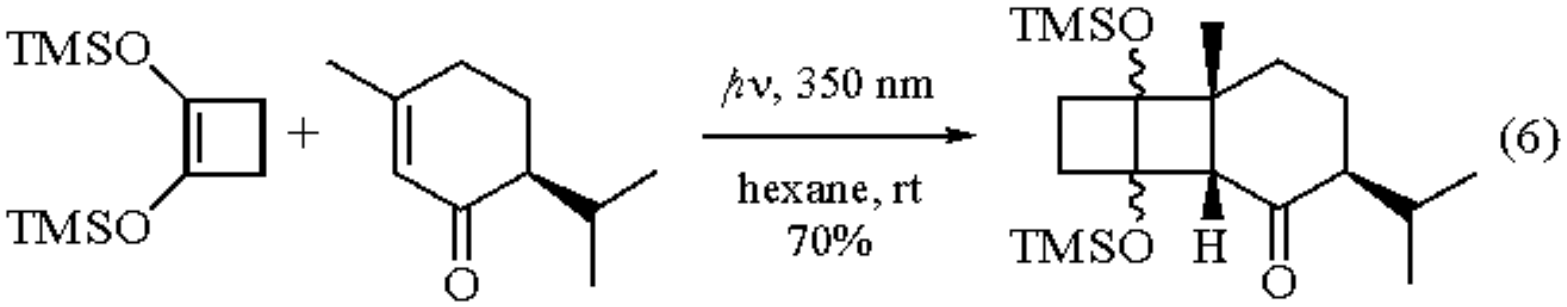

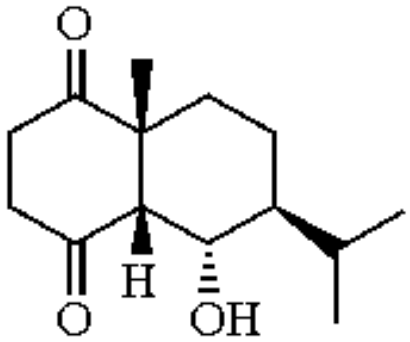

(2)

Cyclobutane Derivatives.

Reagent (**1**) can be transformed into 1,2-cyclobutanedione, *cis*-1,2-cyclobutanediol, 2-aminobutanone, and 2-*t*-alkyl-2-hydroxybutanone.[13] β-C-Glycosides are available upon ***Titanium(IV) Chloride***-mediated reaction of (**1**) with glycosyl acetates.[14]

2,3-Bis(trimethylsilyloxy)-1,3-butadiene.

This is obtained upon thermolysis (180 °C, 84%) of (**1**) and can be used in Diels-Alder reactions with alkynic esters.[15]

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2,3-Bis(trimethylsilyloxy)-1,3-cyclohexadiene

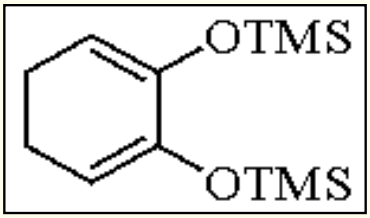

[59733-54-9] · $C_{12}H_{24}O_2Si_2$ · 2,3-Bis(trimethylsilyloxy)-1,3-cyclohexadiene · (MW 256.54)

(useful for Diels-Alder reactions giving highly functionalized [2.2.2] bicyclic systems)

Physical Data: bp 102-103 °C/12 mmHg.

Solubility: sol C_6H_6, Et_2O.

Preparative Method: by the sequential silylation of 1,2-cyclohexanedione with a weak base and ***Trimethylsilyl Trifluoromethanesulfonate***[1] or under strongly basic conditions.[2,3]

Handling, Storage, and Precautions: silyl enol ethers are susceptible to hydrolysis under basic and especially acidic conditions or in the presence of fluoride ion and other silyl specific nucleophiles (e.g. DMSO, DMF). Precautions should therefore be adopted to protect such enol ethers from moisture.

Silyl enol ethers are significantly more electron-rich than normal alkenes and this property dominates their reactivity.[4] They react with a wide variety of electrophiles, usually in the presence of a Lewis acid. It was also recognized, particularly by Danishefsky,[5] that these functional groups can serve as convenient surrogates for ketones in hetero-Diels-Alder reactions (eq 1).

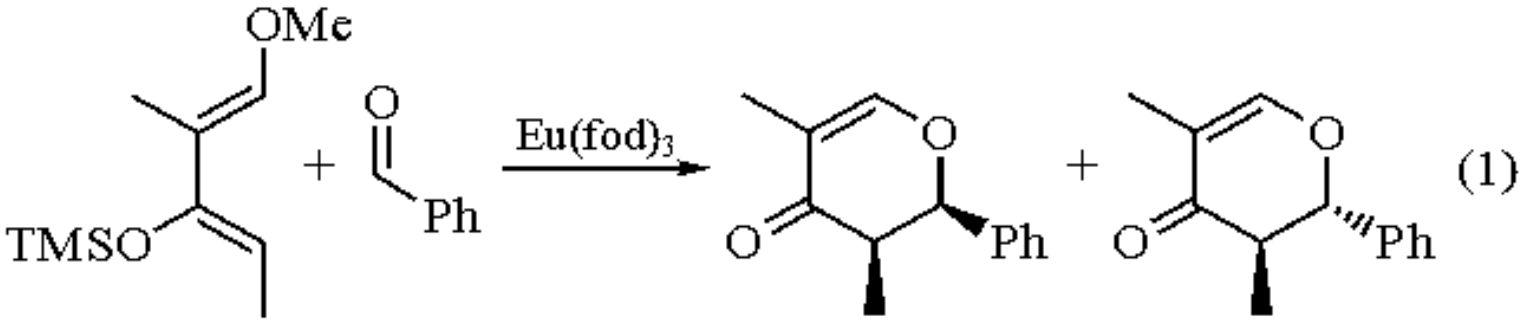

1,2-Diketones, somewhat more difficult materials to work with, can also be utilized in related reactions. The diketones,

by virtue of dipole repulsion, exist largely as the keto-enol form. Attempts to directly silylate cyclohexane-1,2-dione using LDA as the base were reported to be complicated by competing self-condensation.[2] Sequential silylation, however, led to the bis(silyloxy)diene.[2] Alternatively, with the bulky silicon base ***Sodium Hexamethyldisilazide***, self-condensation was less problematic (eq 2).[3] The bis(silyloxy)diene can also be directly prepared under less basic conditions from the dione using Me_3SiOTf/NEt_3 (eq 2).

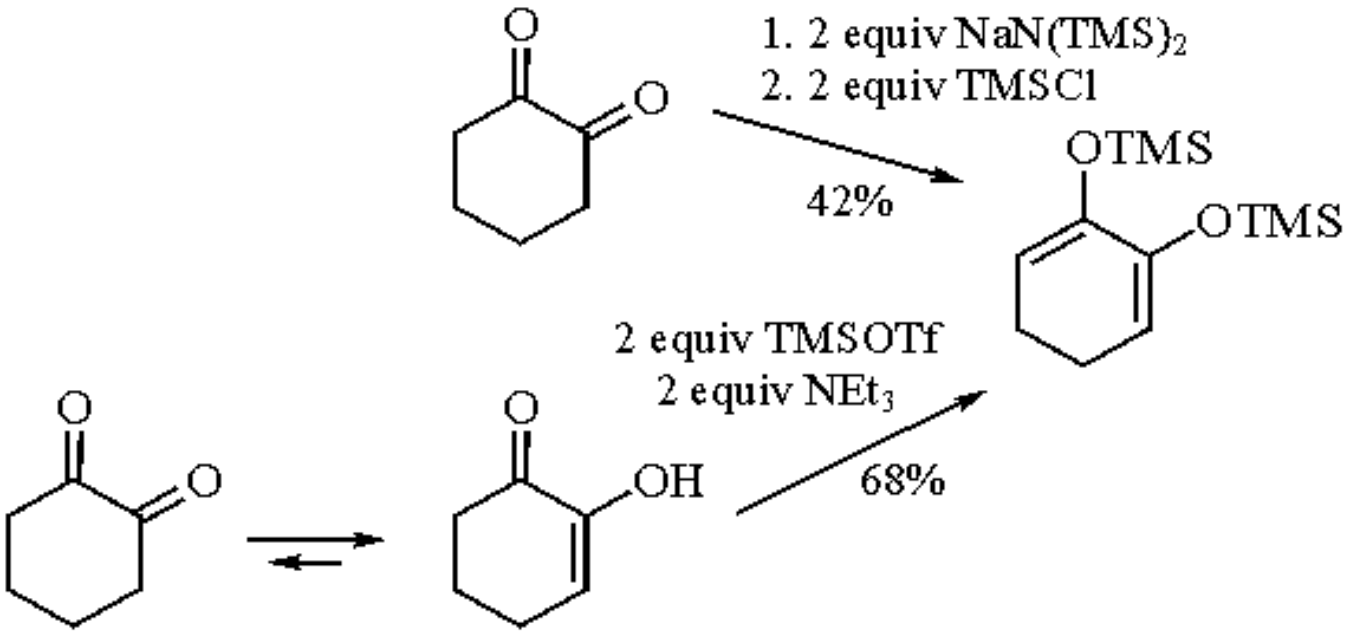

(2)

Reetz has shown that 2,3-bis(trimethylsilyloxy)-1,3-cyclohexadiene, an electron-rich diene, reacts readily in a Diels-Alder fashion with a variety of activated dienophiles (eq 3). In these reactions, *endo* addition was exclusively observed.[3]

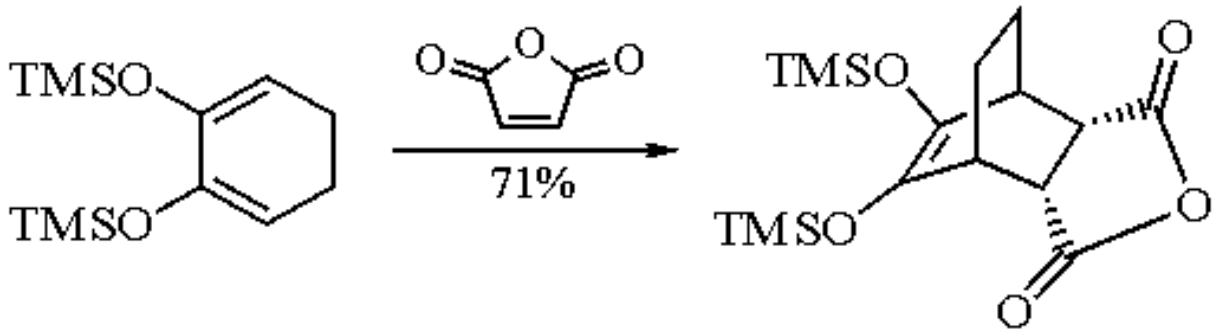

(3)

Related bis-2,3-silyloxy-1,3-dienes also undergo Diels-Alder reactions with various dienophiles, including heterodienophiles such as diazo compounds and imines (eqs 4 and 5).[6,7]

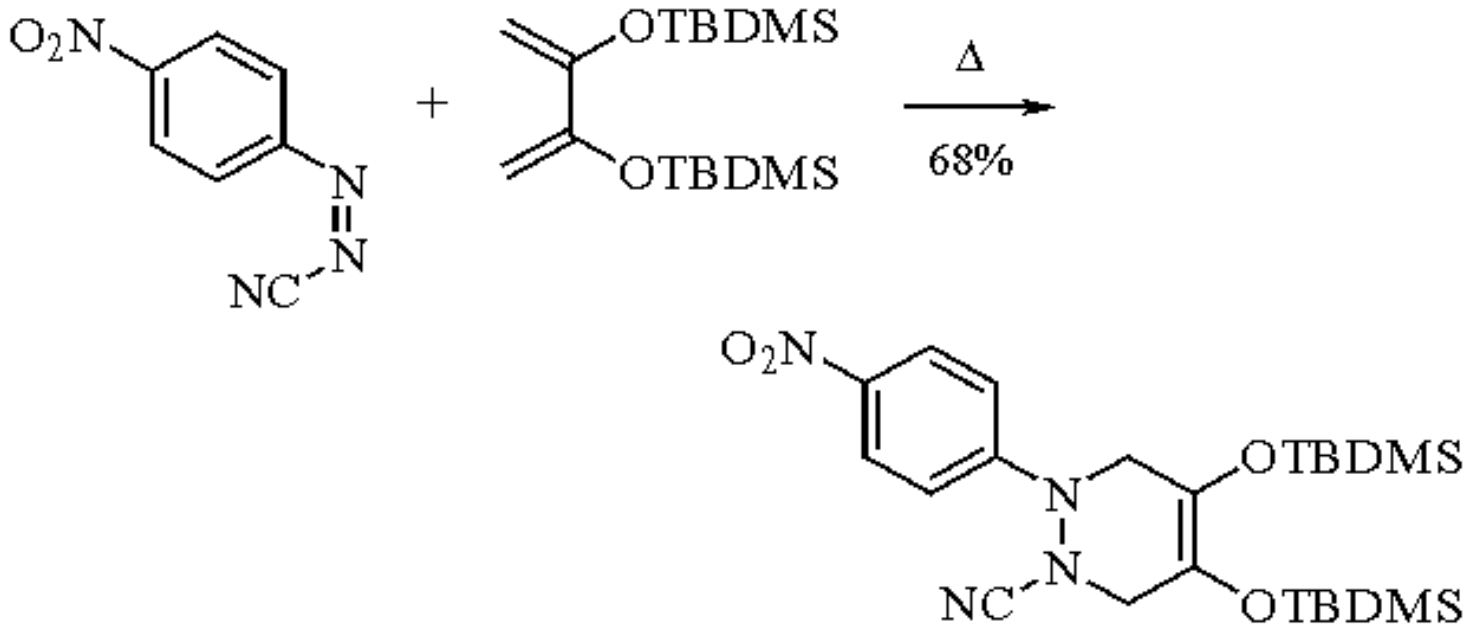

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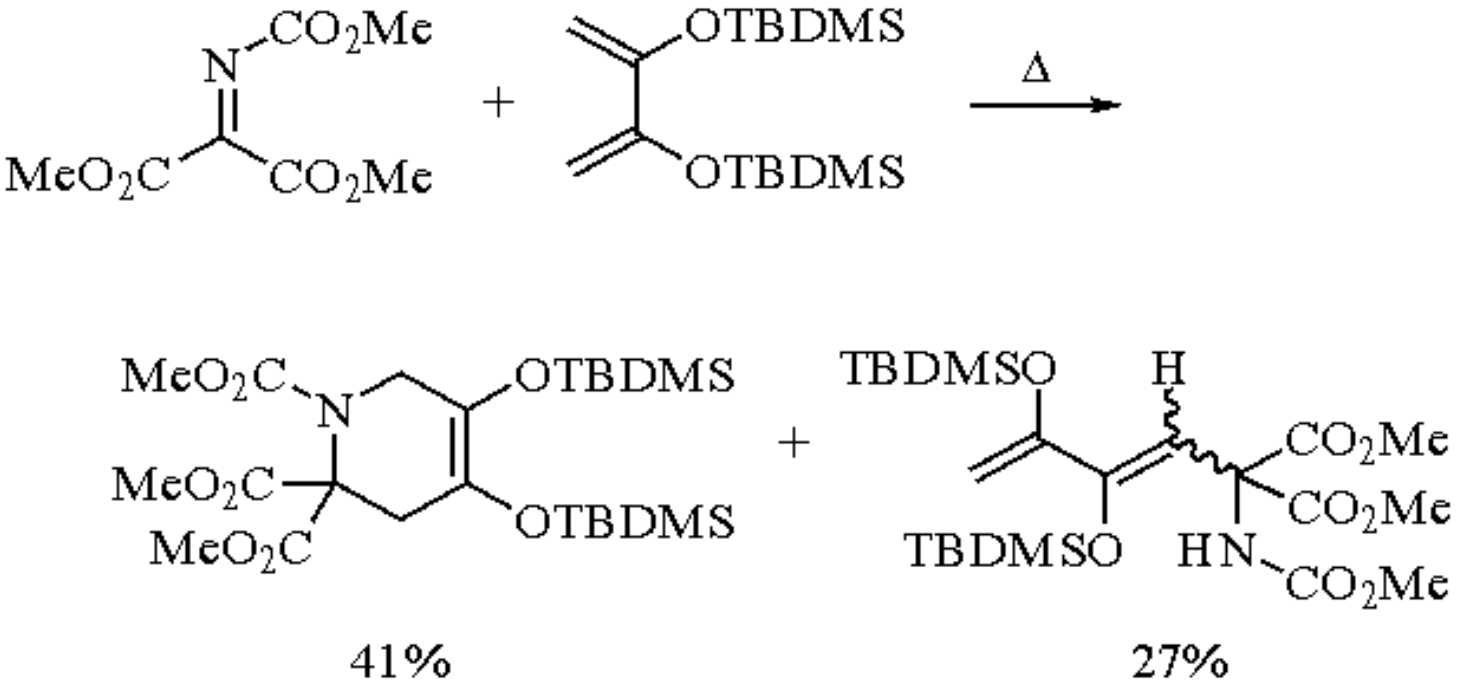

(5)

The products of these Diels-Alder reactions, bis(1,2-silyloxy)-1-alkenes, can undergo further synthetic elaboration. Although such reactions have not been described for the cyclohexane-1,2-dione derivatives, structurally related species may be desilylated to regenerate the 1,2-dione (eq 6).[3] The high electron density in the bis(1,2-silyloxy)-1-alkenes makes them suitable educts for inverse electron demand Diels-Alder reactions (eqs 7 and 8).[8,9] Finally, the silyl enol ether can undergo normal electrophilic addition to imines, leading to α-hydroxy carbonyl compounds (eq 9).[10]

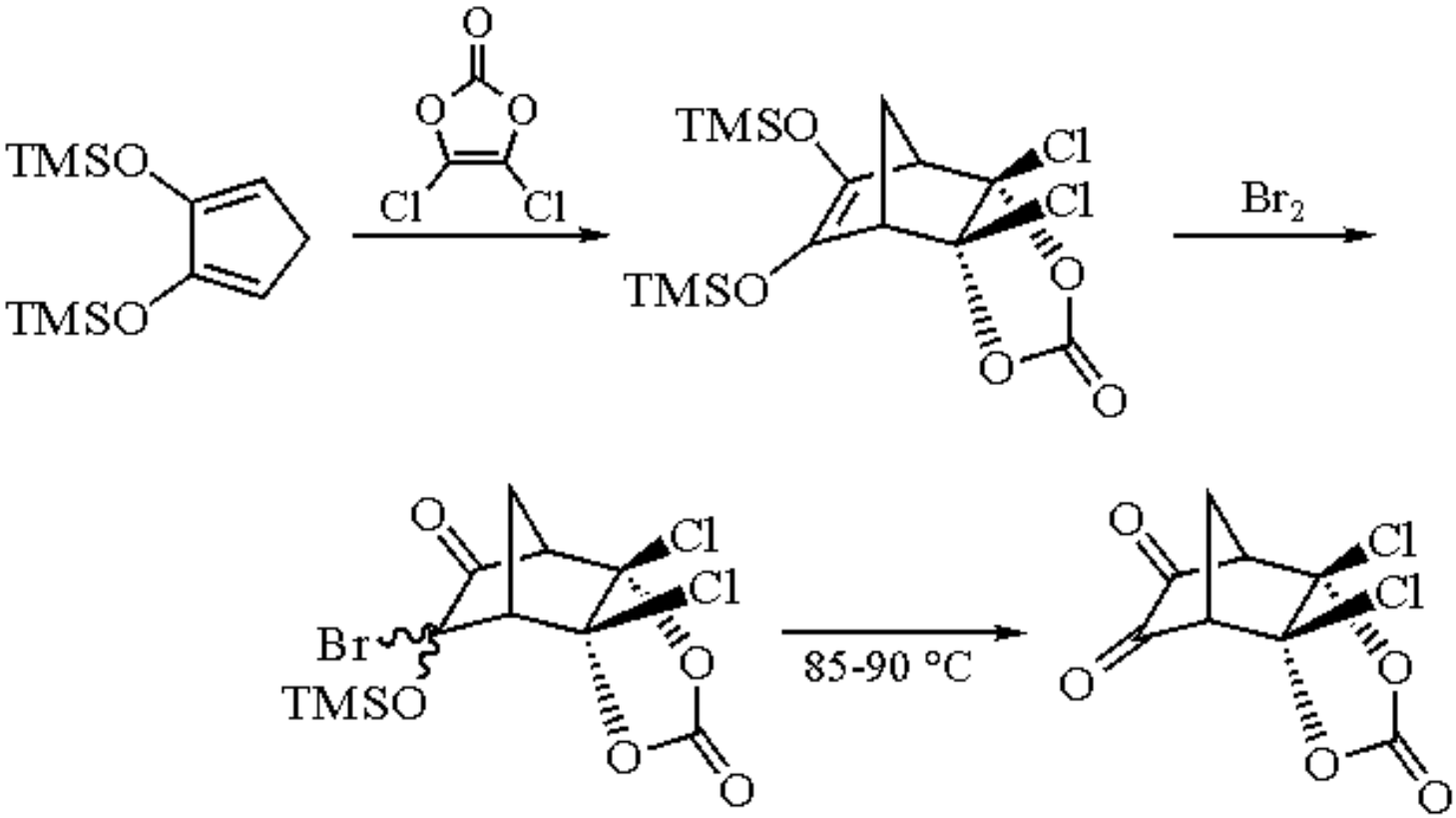
TMSO
TMSO
Cl
Cl
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Cl
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Br_2
Br
TMSO
85-90 °C

(6)

97%

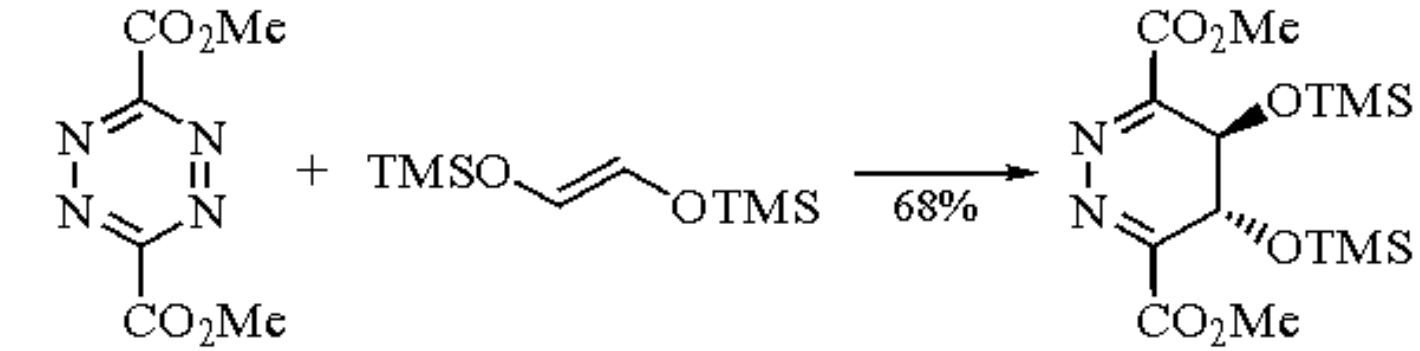
CO_2Me
CO_2Me
TMSO
OTMS
68%
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OTMS
CO_2Me
CO_2Me

(7)

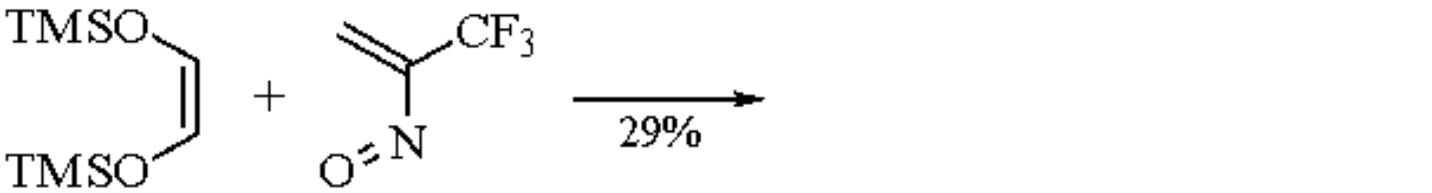
TMSO
TMSO
CF_3
N
29%

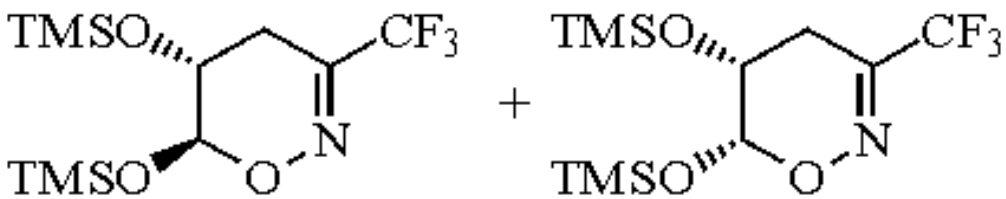
TMSO
TMSO
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(8)

33:67

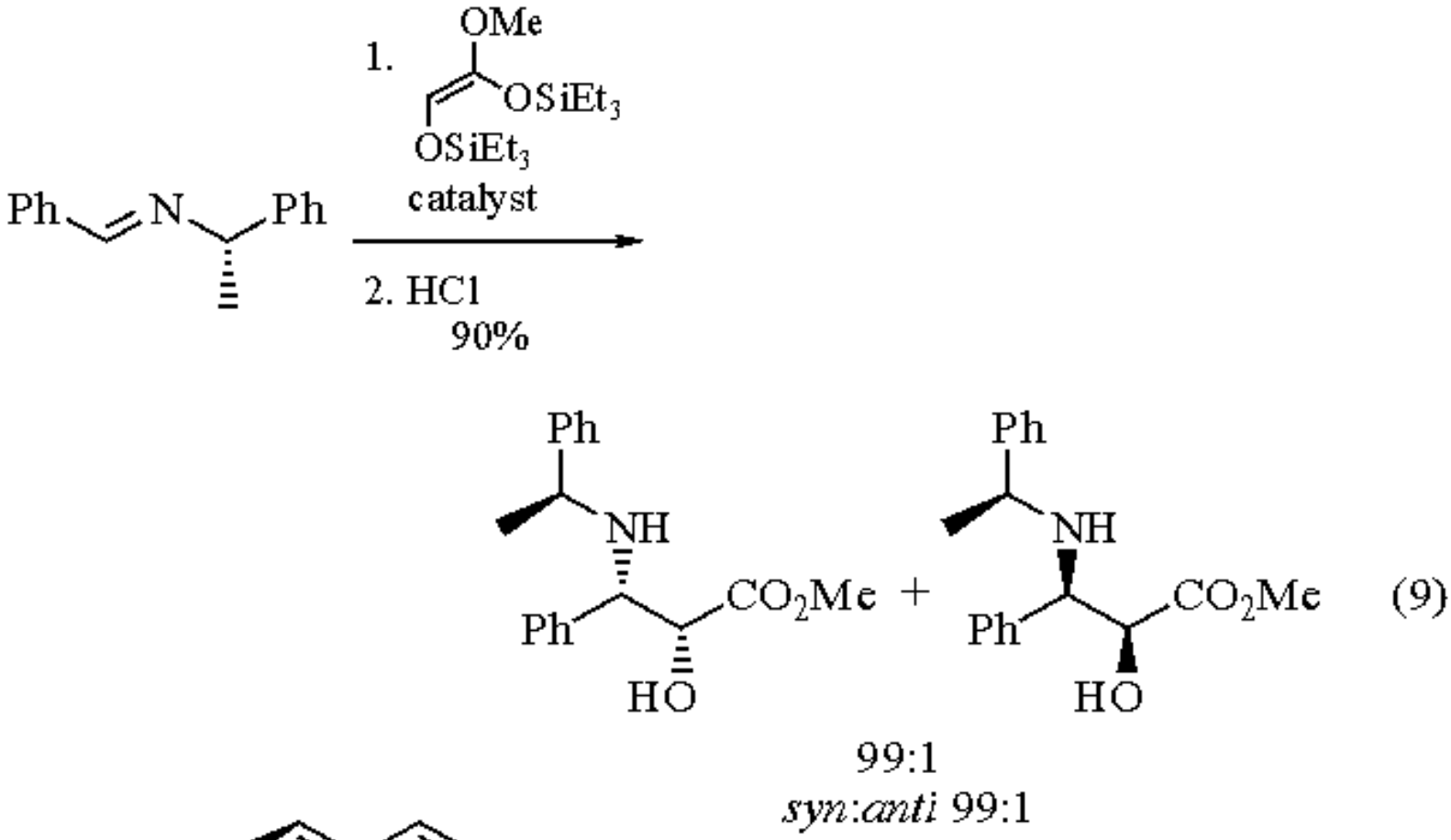

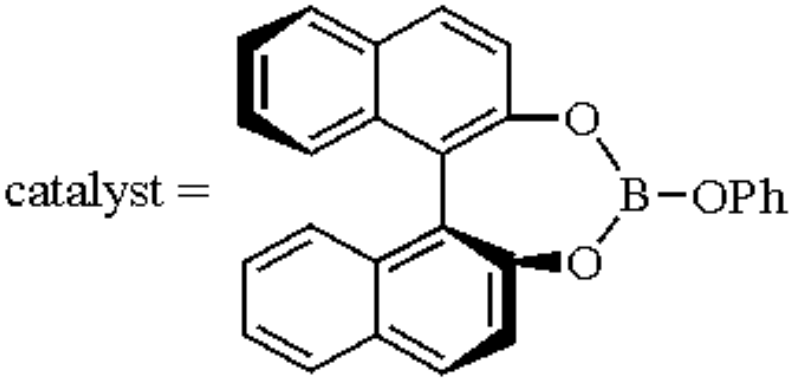

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Michael A. Brook

Bis(trimethylsilyl) Peroxide[1]

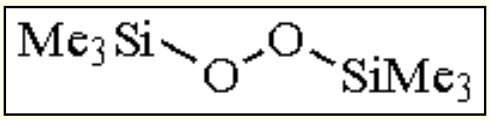

[5796-98-5] · $C_6H_{18}O_2Si_2$ · Bis(trimethylsilyl) Peroxide · (MW 178.38)

(a masked form of 100% hydrogen peroxide;[2] synthon of HO^+ for electrophilic hydroxylation;[3,4] source of Me_3SiO^+ for electrophilic oxidations;[4-6] a versatile oxidant for alcohols, ketones, phosphines, phosphites, and sulfides[1,2,7])

Physical Data: bp 41 °C/30 mmHg;[7] *n*20D 1.3970.[1b]

Solubility: highly sol aprotic organic solvents.

Form Supplied in: colorless oil; used as an anhydrous and protected form of hydrogen peroxide; 10% solution in hexane or in CH_2Cl_2.

Analysis of Reagent Purity: ^{1}H NMR (s) δ 0.18 ppm;[3] ^{29}Si NMR δ 27.2 ppm.[8]

Preparative Methods: obtained in 80-96% yields by reaction of ***Chlorotrimethylsilane*** with ***1,4-Diazabicyclo[2.2.2]octane***.$(H_2O_2)_2$,[3] ***Hexamethylenetetramine***.H_2O_2,[8] or ***Hydrogen Peroxide-Urea*** in CH_2Cl_2.[9]

Handling, Storage, and Precautions: thermally stable; can be handled in the pure state and distilled;[8] rearranges at 150-180 °C.[1c]

Electrophilic Oxidations.

Bis(trimethylsilyl) peroxide (**1**) functions as an electrophilic hydroxylating agent for aliphatic, aromatic, and heteroaromatic anions.[3] Reaction of their lithium or Grignard compounds with (**1**) often affords trimethylsiloxy intermediates, which undergo desilylation with HCl in methanol to give the corresponding alcohols in good yields. In the presence of a catalytic amount of ***Trifluoromethanesulfonic Acid***, (**1**) reacts with aromatic compounds to produce the corresponding phenols after acidic workup.[10] In these reactions the Me_3SiO^+ moiety is considered as a synthon of the hydroxyl cation (i.e. OH^+).

Lithium or Grignard enolates of vinyl compounds react with (**1**) to produce the corresponding α-hydroxy ketones

upon acidic workup.[4] Treatment of enolate anions derived from carboxylic acids and amides with (**1**) in THF at rt gives the corresponding α-hydroxy derivatives in 31-58% yields.[11] Furthermore, stereoselective synthesis of silyl enol ethers with retention of configuration is accomplished by oxidation of (*E*)- and (*Z*)-vinyllithiums, prepared from the corresponding bromides and *s*-BuLi, with (**1**) in THF at -78 °C.[6] Heterocyclic silyl enol ethers, such as 3-(trimethylsiloxy)furan and 3-(trimethylsiloxy)thiophene, can be obtained by reaction of (**1**) with 3-lithiofuran and 3-lithiothiophene, respectively.[5] In some reactions involving nucleophiles and (**1**), silylation may compete with siloxylation;[3] the outcome depends upon the counterion.[4]

Oxidative Desulfonylation and Selective Baeyer-Villiger Oxidation.

Aliphatic, alicyclic, and benzylic phenyl sulfones react with *n*-BuLi and then with (**1**) in situ to give aldehydes or ketones in 66-91% yields (eq 1).[12] On the other hand, reaction of ketones with (**1**) in the presence of a catalyst, such as ***Trimethylsilyl Trifluoromethanesulfonate***,[2] ***Tin(IV) Chloride***, or ***Boron Trifluoride Etherate***,[7] in CH_2Cl_2 gives esters in good to excellent yields (eq 2). This Baeyer-Villiger oxidation proceeds in a regio- and chemoselective manner: the competing epoxidation of a C-C double bond does not occur.

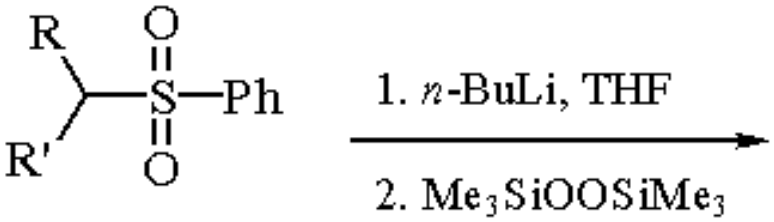

$$RR'C{=}O + Me_3SiOSiMe_3 + PhSO_2Li \quad (1)$$

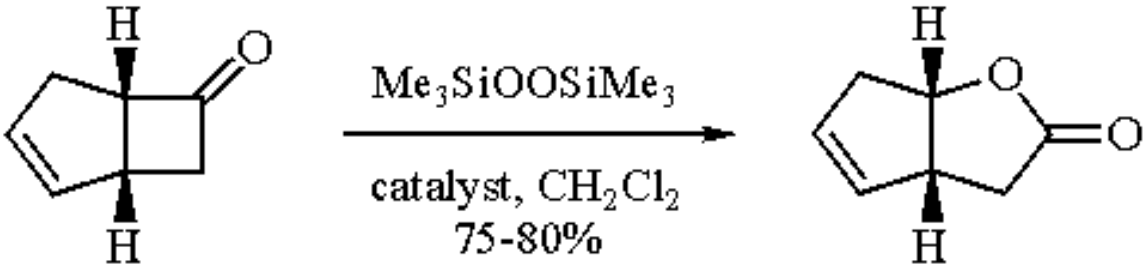

(2)

catalyst = $Me_3SiSO_3CF_3$, $SnCl_4$, $BF_3 \cdot OEt_2$

Oxidation of Alcohols, Sulfur, and Phosphorus Compounds as well as Si-Si and Si-H Bonds.

Bis(trimethylsilyl) peroxide acts as an effective oxidant for alcohols in the presence of ***Pyridinium Dichromate*** or $RuCl_2(PPh_3)_3$ complex as the catalyst in CH_2Cl_2.[13] By this method, primary allylic and benzylic alcohols can be selectively oxidized to α-enals in the presence of a secondary alcohol.

Sulfur Trioxide reacts with (**1**) in CH_2Cl_2 at -30 °C, affording ***Bis(trimethylsilyl) Monoperoxysulfate***, an oxidant useful for the Baeyer-Villiger oxidation.[14] In addition, sulfides can be converted to sulfoxides or sulfones by use of (**1**) in benzene at reflux.[1b,15,16] This peroxide can also oxidize phosphines and phosphites to the corresponding oxyphosphoryl derivatives with retention of configuration at the phosphorus center in high yields.[1b,17] Furthermore, it converts the P=S and P=Se functionalities to the P=O group with inversion of configuration at the phosphorus center.[17] The $CF_3SO_3SiMe_3$ or Nafion-$SiMe_3$ catalyzed oxidation of nucleoside phosphites to phosphates under nonaqueous conditions is applied to the solid-phase synthesis of oligonucleotides.[18,19]

Reactions between (**1**) and disilanes containing fluorine atoms or possessing ring strain proceed readily at ambient temperature to generate the corresponding disiloxanes.[20] Oxidation of hydrosilanes (R_3SiH) with (**1**) gives a mixture of R_3SiOH and $R_3SiOSiMe_3$. The ratio of R_3SiOH to $R_3SiOSiMe_3$ tends to decrease in the order $Et_3SiH > PhMe_2SiH > Me_3SiSiHMe_2$.

Isomerization of Allylic Alcohols and Formation of 1-Halo-1-alkynes.

Isomerization of primary and secondary allylic alcohols to tertiary isomers proceeds in CH_2Cl_2 at 25 °C in the presence of a catalyst that is prepared in situ by activation of ***Vanadyl Bis(acetylacetonate)*** or $MoO_2(acac)_2$ with (**1**) (eq 3).[21] On the other hand, terminal alkynes react with (**1**) in the presence of copper or zinc halides in THF at -15 °C to afford terminal 1-halo-1-alkynes in 40-85% yields.[22] By the same method, 1-cyano-1-alkynes are obtained in 65% yield by use of copper cyanide.

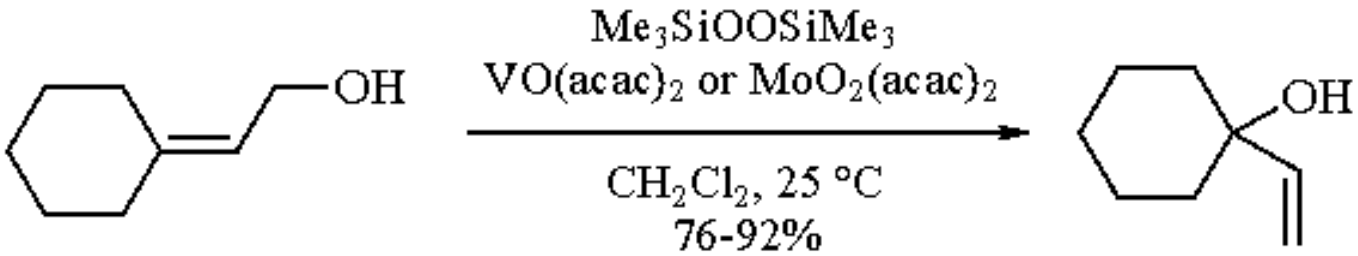

(3)

Related Reagents.

Bis(trimethylsilyl) Peroxide-Vanadyl Bis(acetylacetonate).

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Bis(trimethylsilyl) Peroxide-Vanadyl Bis(acetylacetonate)[1]

$Me_3SiO\text{-}OSiMe_3.V(O)(acac)_2$

[-] · $C_{16}H_{32}O_7Si_2V$ · Bis(trimethylsilyl) Peroxide-Vanadyl Bis(acetylacetonate) · (MW 443.54) $(TMSO)_2$

[5796-98-5] · $C_6H_{18}O_2Si_2$ · Bis(trimethylsilyl) Peroxide-Vanadyl Bis(acetylacetonate) · (MW 178.38) $VO(acac)_2$

[3153-26-2] · $C_{10}H_{14}O_5V$ · Bis(trimethylsilyl) Peroxide-Vanadyl Bis(acetylacetonate) · (MW 265.16)

(reagent for the transposition of allylic and allenic alcohols)

Physical Data: $Me_3SiOOSiMe_3$: bp 40-41 °C/28 mmHg;[2] $VO(acac)_2$: mp 255 °C (dec).

Solubility: sol dichloromethane.

Preparative Method: prepared in situ from bis(trimethylsilyl) peroxide (colorless liquid) and $VO(acac)_2$ (blue-green crystals).

Handling, Storage, and Precautions: bis(trimethylsilyl) peroxide is reported to be a reasonably stable, distillable liquid. Vanadyl acetylacetonate is air-sensitive and should be refrigerated under dry nitrogen or argon. See ***Bis(trimethylsilyl) Peroxide*** and ***Vanadyl Bis(acetylacetonate)***.

Isomerization of Primary and Secondary Allylic Alcohols.

The title reagent, prepared in situ by the addition of bis(trimethylsilyl) peroxide[2,3] to a dichloromethane solution of vanadyl bis(acetylacetonate) (3:1), is effective in catalyzing the allylic transposition of both cyclic and acyclic primary and secondary allylic alcohols to tertiary allylic alcohols in good yields (eqs 1-3). The conversion of primary allylic alcohols to secondary allylic alcohols is less effective (eq 4). The reaction is catalytic in vanadyl bis(acetylacetonate) (10 mol %), and produces only the (*E*)-alkenes in the secondary alcohols studied. It is noteworthy that this reagent shows no propensity to give epoxides from the allylic alcohols, in contrast to the Sharpless epoxidation reagent, ***t-Butyl Hydroperoxide***/$VO(acac)_2$.[4] $MoO_2(acac)_2$, with or without added $Me_3SiOOSiMe_3$, also catalyzes these allylic isomerizations but with inferior yields (e.g. 76% and 35%, respectively, for the transformation in eq 1).

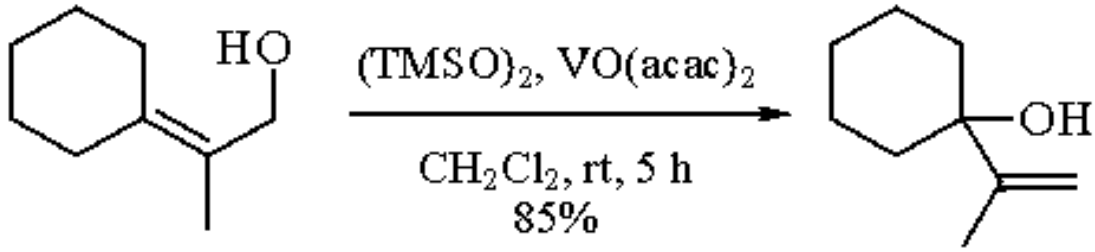

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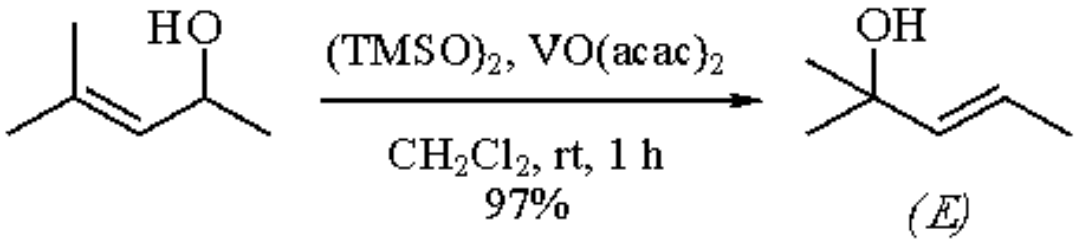

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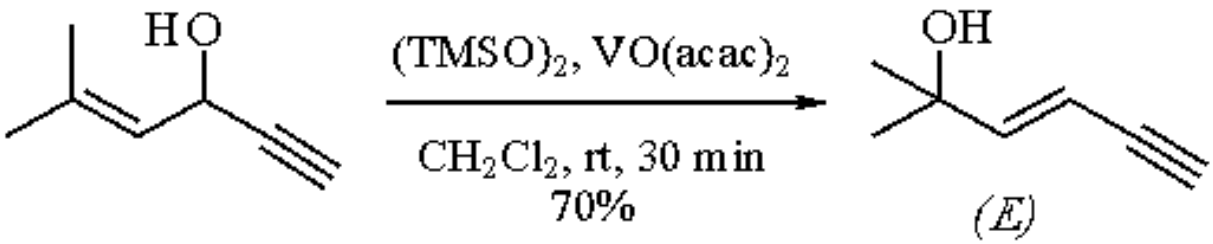

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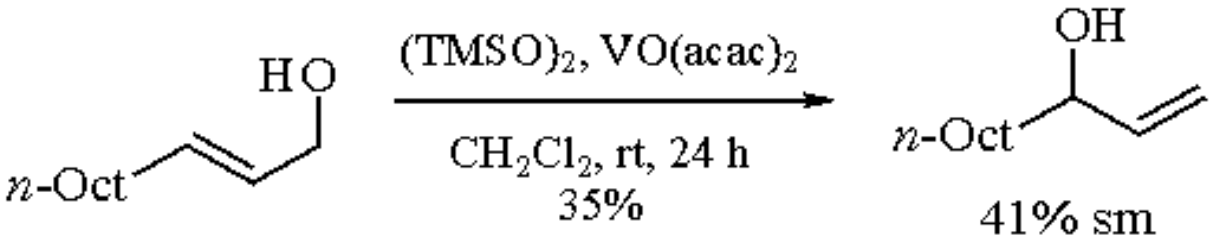

(4)

Allylic isomerization of geraniol (or nerol) gives linalool (eq 5) in 68-70% yield, with only trace formation of α-terpineol. This evidence suggests that the isomerization does not proceed via a free allylic cation. Further support for a primarily suprafacial vanadium-assisted allylic rearrangement is provided in eq 6, where (*S*)-(-)-3-methyl-2-cyclohexen-1-ol (40% ee) gives (*R*)-(+)-1-methyl-2-cyclohexen-1-ol (29% ee), with retention of hydroxy facial orientation.

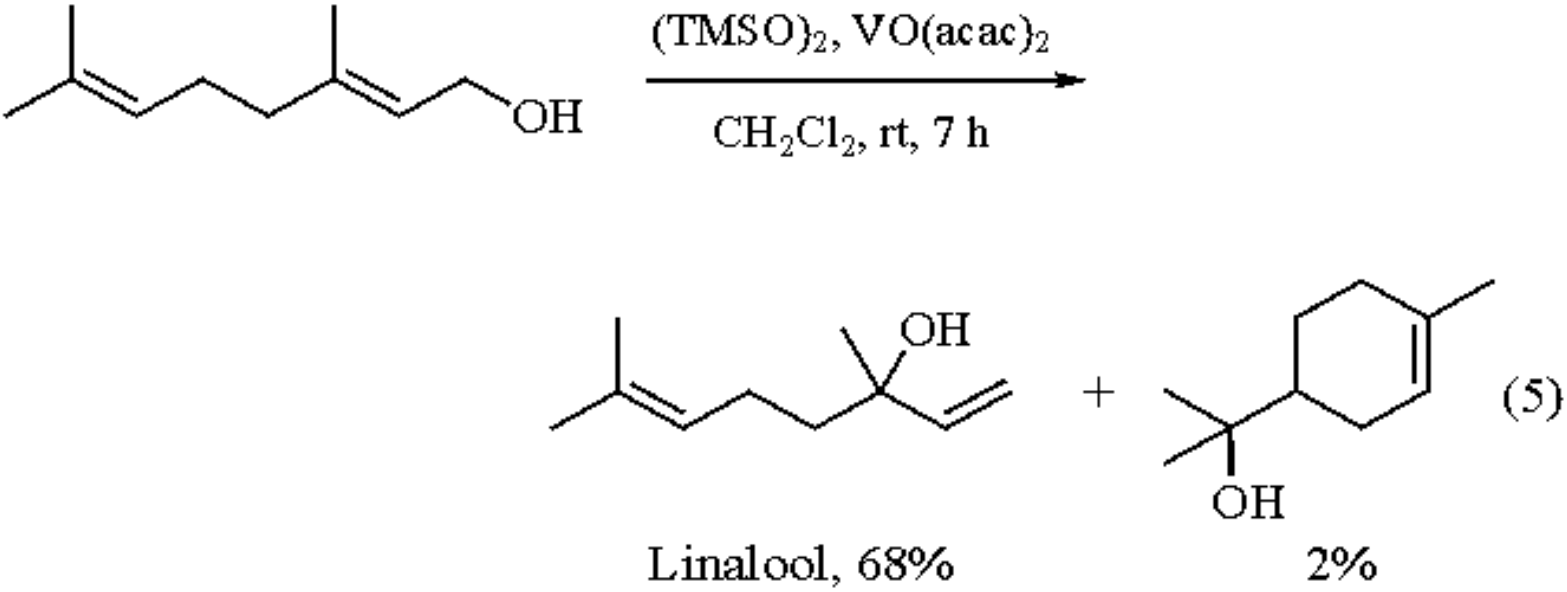

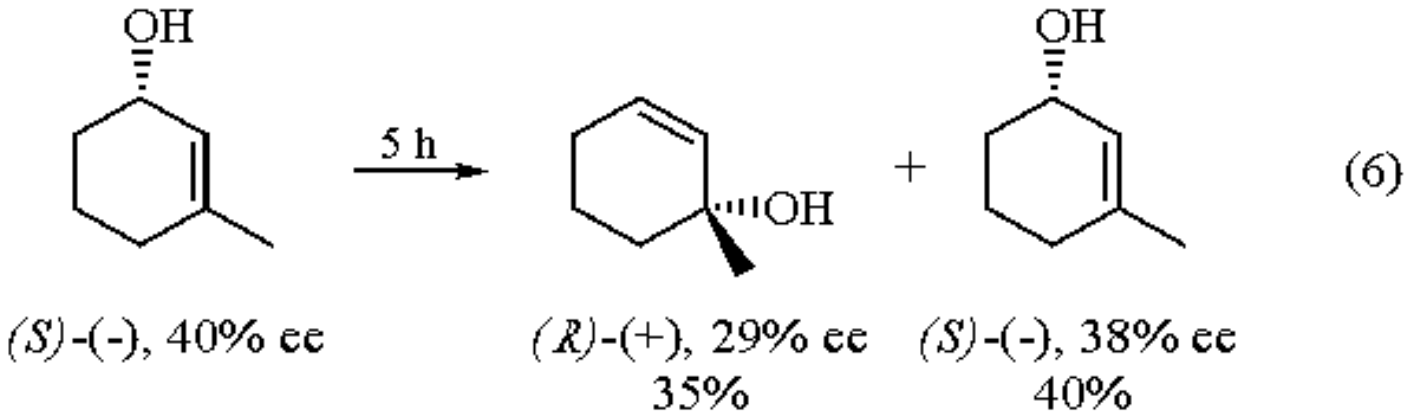

Isomerization of Secondary Allenic Alcohols.[2]

The $VO(acac)_2$-$Me_3SiOOSiMe_3$ catalytic system also effects allylic transposition in α-allenic alcohols. (*E*)-4-Phenyl-3-buten-2-one is produced in 81% yield from the addition of 10 mol % of the catalyst to a dichloromethane solution of 1-phenyl-2,3-butadien-1-ol (eq 7). However, in substrates where both allylic and allenic rearrangement is possible, the allylic transposition dominates (eq 8). In this particular case, the use of the catalyst $MoO_2(acac)_2$ at 5 mol % is more effective in promoting the isomerization to either of the two products, and without the use of the bis(trimethylsilyl) peroxide.[2] At 25 °C, $MoO_2(acac)_2$ gives 90% yield of the dienone (10 min), whereas at -78 °C, the allylic rearranged trienol product is formed in 94% yield (10 min).

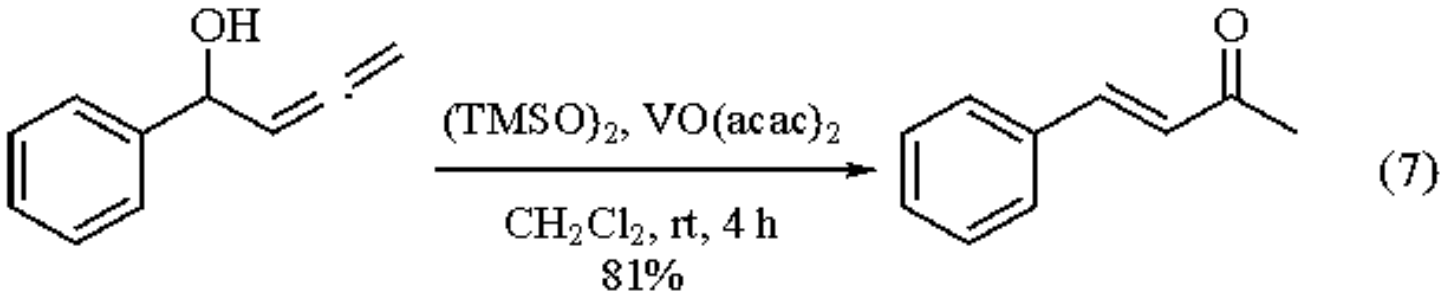

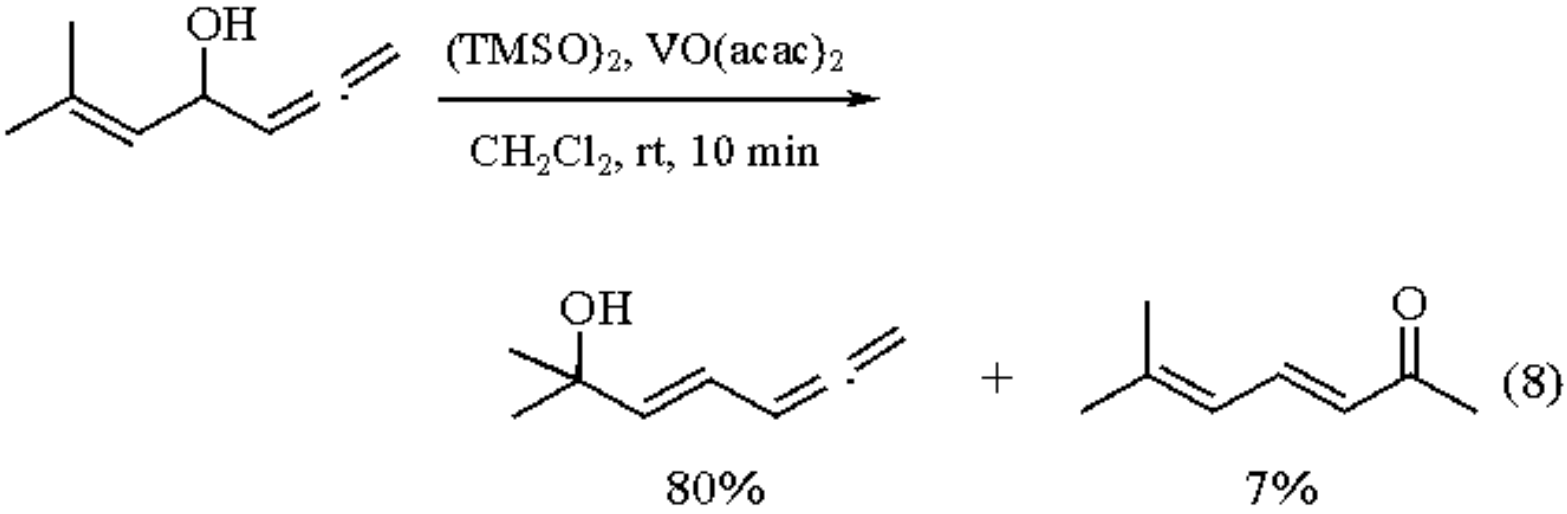

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Bis(trimethylsilyl) Selenide

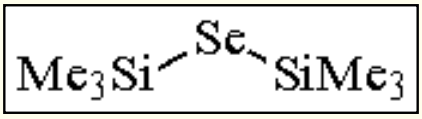

[4099-46-1] · $C_6H_{18}SeSi_2$ · Bis(trimethylsilyl) Selenide · (MW 225.34)

(synthesis of unsymmetrical selenides;[6] generation of selenoaldehydes;[7] reduction of sulfoxides, selenoxides, and telluroxides[4])

Physical Data: bp 45-46 °C/5.3 mmHg.

Solubility: sol Et_2O and THF.

Handling, Storage, and Precautions: is an air-sensitive, colorless oil. Because of the strong odor and the release of toxic hydrogen selenide on exposure to moisture, handling of bis(trimethylsilyl) selenide should be performed in a well-ventilated hood. It can be stored at -20 °C in an argon-flushed glass vessel for about a month; after this time, amorphous selenium (red color) is gradually deposited on the vessel.

Synthesis of Bis(trimethylsilyl) Selenide.

In the initial studies, bis(trimethylsilyl) selenide was synthesized by the following two methods: silylation of ***Sodium Selenide***[1] (or ***Lithium Selenide***[2]) with ***Chlorotrimethylsilane*** (eq 1) or reaction of bromobenzene, ***Magnesium***, and ***Selenium*** with chlorotrimethylsilane (eq 2).[3]

$$\mathrm{Se} \xrightarrow[\text{liq. } NH_3]{\text{Na (or Li)}} \underset{(\text{or } Li_2Se)}{Na_2Se} \xrightarrow[C_6H_6 \text{ (or } Et_2O)]{Me_3SiCl} \underset{83\%}{(Me_3Si)_2Se} \quad (1)$$

$$\mathrm{PhBr} + \mathrm{Mg} + \mathrm{Se} \xrightarrow{\mathrm{Et_2O}} \mathrm{Se(MgBr)_2} + \mathrm{Ph_2Se} \xrightarrow[\text{rt, 24 h}]{\mathrm{Me_3SiCl}} \underset{39\%}{(\mathrm{Me_3Si})_2\mathrm{Se}} \quad (2)$$

However, the former method requires the troublesome manipulation involved in preparing sodium selenide (or lithium selenide) in liquid ammonia[1b] and conducting the silylation in benzene (or diethyl ether). The latter method is inefficient and results in a low yield of the desired disilyl selenide. Thus a one-pot, high-yield procedure based on the ***Lithium Triethylborohydride*** reduction of elemental selenium has been developed, as depicted in eq 3.[4] In this method, both preparation of Li_2Se and silylation with Me_3SiCl are performed in THF. Technically important is the use of selenium shot; if selenium powder is utilized, the yield of Li_2Se decreases sharply. Moreover, addition of small amount of ***Boron Trifluoride Etherate*** (1.6 mol %) accelerates the silylation of Li_2Se.[5]

$$\mathrm{Se} \xrightarrow[\text{THF}]{\mathrm{LiBEt_3H}} \mathrm{Li_2Se} \xrightarrow[\text{THF}]{\mathrm{Me_3SiCl}} \underset{95\%}{(\mathrm{Me_3Si})_2\mathrm{Se}} \quad (3)$$

Recently it has been reported that the reaction of ***Lithium Diselenide*** (Li_2Se_2) with 2 equiv of chlorotrimethylsilane affords bis(trimethylsilyl) selenide in 73% yield with the concomitant formation of elemental selenium (eq 4).[5]

$$\mathrm{Se} \xrightarrow[\text{cat. PhC}\equiv\text{CPh}]{\text{Li, THF}} \mathrm{Li_2Se_2} \xrightarrow[\text{THF}]{\mathrm{Me_3SiCl}} \underset{73\%}{(\mathrm{Me_3Si})_2\mathrm{Se}} + \mathrm{Se} \quad (4)$$

Synthesis of Unsymmetrical Selenides.

Bis(trimethylsilyl) selenide reacts with equimolar amounts of ***n-Butyllithium*** to generate $Me_3SiSeLi$, alkylation of which then provides trimethylsilyl alkyl selenides. Similar treatment of Me_3SiSeR^1 with BuLi / R^2X successfully leads to unsymmetrical selenides in good yields (eq 5).[6] Use of acid chlorides in place of alkyl halides results in the formation of selenoesters.

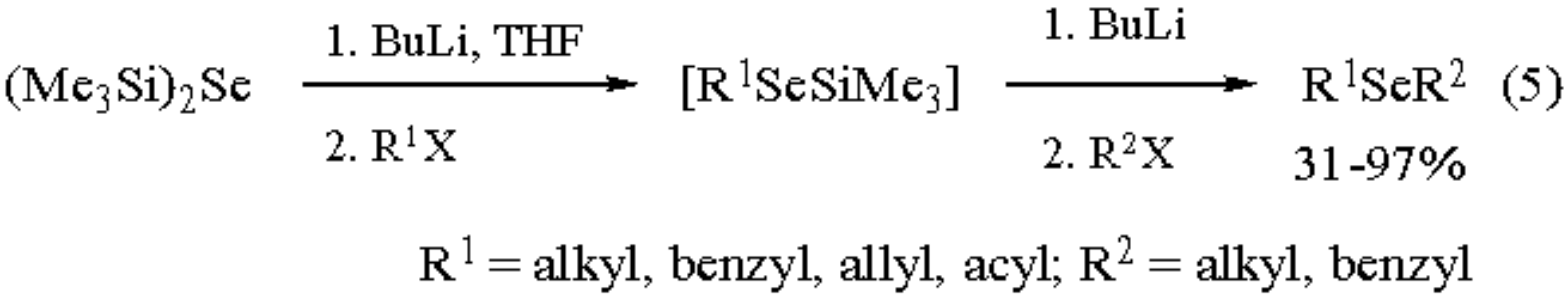

Generation and Diels-Alder Reaction of Selenoaldehydes.[7]

Direct conversion of aldehydes to selenoaldehydes has been achieved by treatment with bis(trimethylsilyl) selenide in the presence of a catalytic amount of butyllithium (eq 6).[7a]

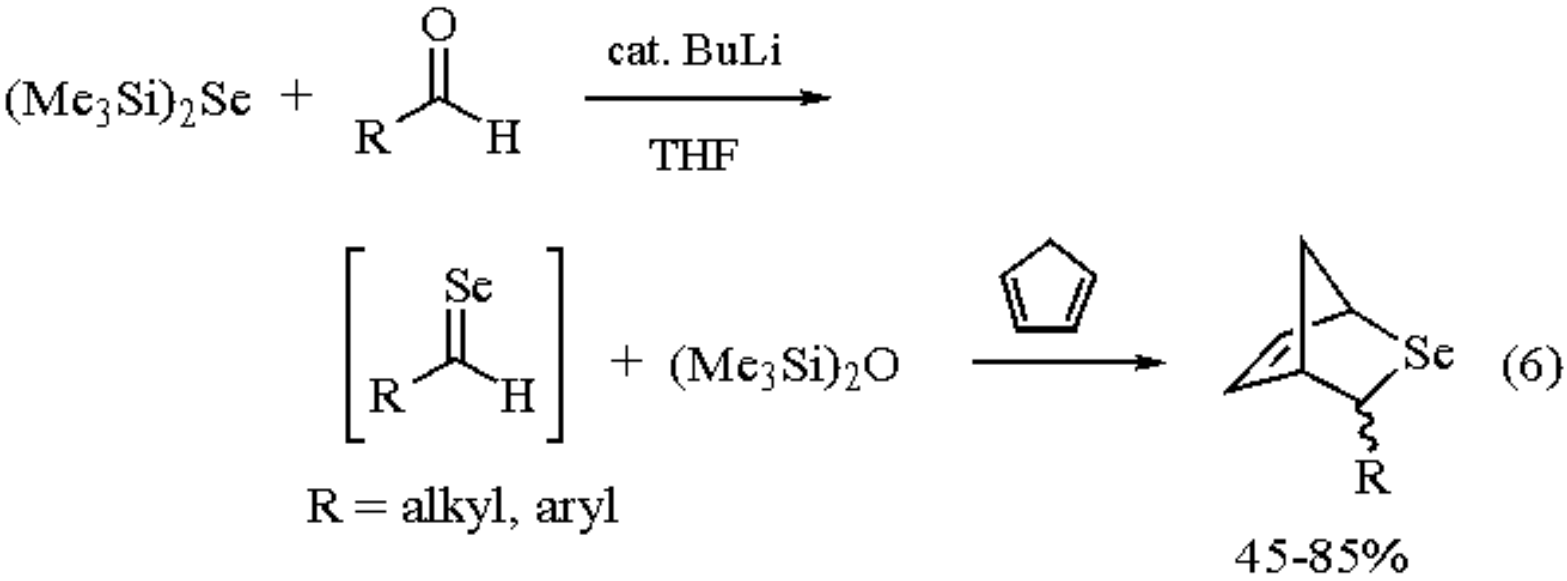

A mechanistic proposal includes addition of $Me_3SiSeLi$ to aldehydes, followed by elimination of Me_3SiOLi to generate selenoaldehydes, which undergo Diels-Alder reaction with dienes. Aldehydes bearing a conjugate diene unit provide intramolecular Diels-Alder adducts (eq 7).[7b]

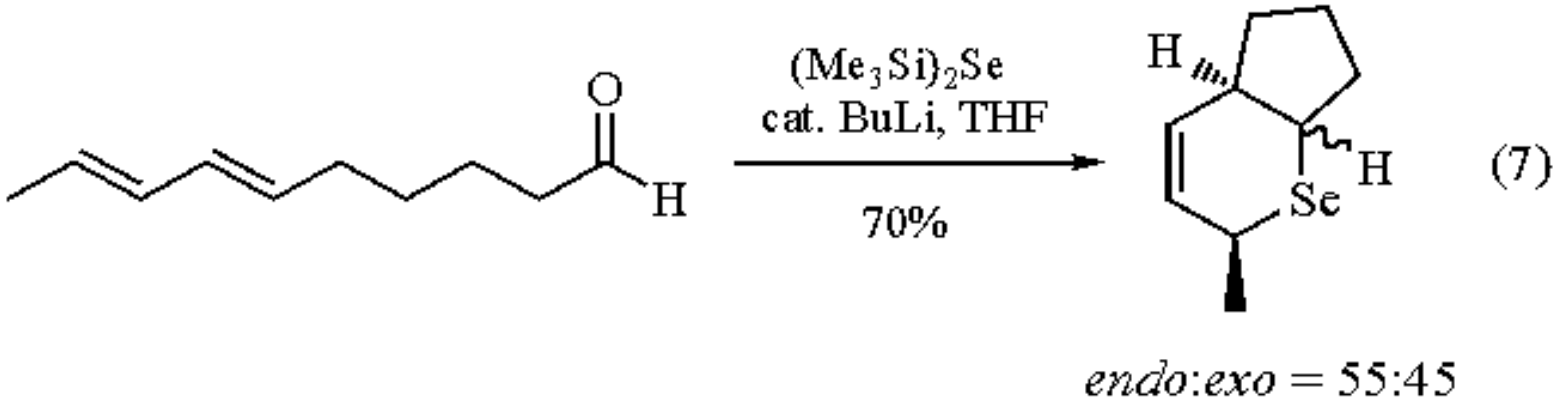

Reduction of Sulfoxides, Selenoxides, and Telluroxides.

Bis(trimethylsilyl) selenide is useful as a two-electron reducing agent for the reduction of sulfoxides, selenoxides, and telluroxides to corresponding sulfides, selenides, and tellurides, respectively (eq 8).[4]

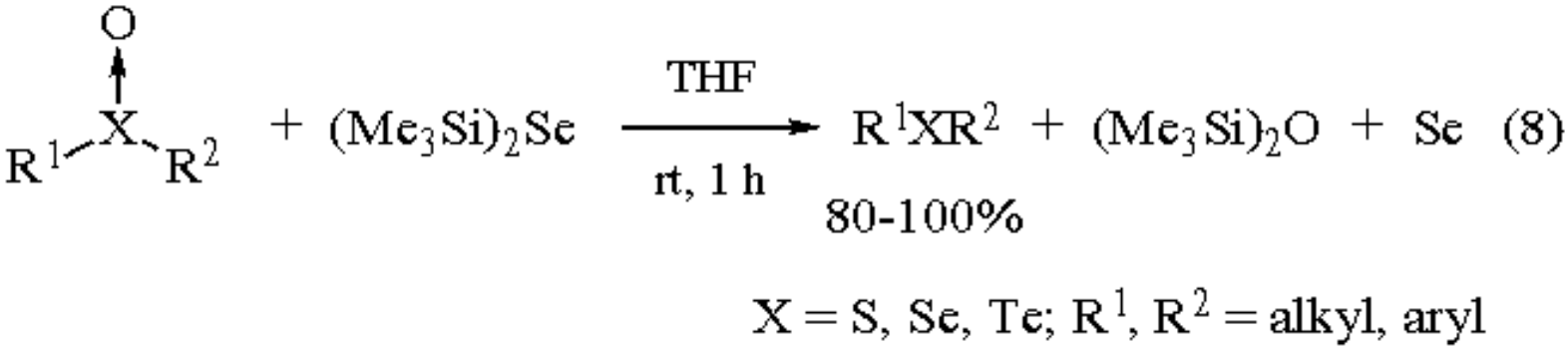

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Akiya Ogawa & Noboru Sonoda

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Bis(trimethylsilyl) Sulfide[1]

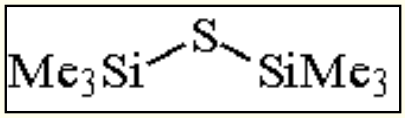

[3385-94-2] · $C_6H_{18}SSi_2$ · Bis(trimethylsilyl) Sulfide · (MW 178.44)

(reduction of S, Se, and Te oxides;[4] formation of thiocarbonyl derivatives under mild conditions;[7] formation of allylsilanes from ketones or allylic alcohols[13])

Alternate Name: TMS_2S.

Physical Data: bp 164 °C; *d* 0.846 g cm^{-3}.

Solubility: sol diethyl ether, THF, CH_2Cl_2, MeCN, and aromatic solvents.

Form Supplied in: colorless cloudy liquid, commercially available.

Handling, Storage, and Precautions: avoid strong oxidizing agents. The reagent is moisture sensitive, flammable, and decomposes to CO, CO_2, H_2S, and sulfur oxides. Stench, mucous membrane (lungs, eyes) and skin irritant. Store in cool dry place free of oxygen. Use in a fume hood.

Reducing Agent.

Bis(trimethylsilyl) sulfide (TMS_2S) is used to reduce aromatic nitro groups[2] to amines and the oxides of sulfur, selenium, and tellurium. Conditions for nitro group reduction (eq 1) are forcing; however, yields are good. Reactions of TMS_2S with primary aliphatic nitro groups[3] result in the formation of the thiohydroxamic acids (eq 2) which can be isolated or carried further to the nitrile. Secondary alkyl nitro derivatives provide oximes. Sulfoxides are reduced[4] to sulfides, selenoxides to selenides, and telluroxides to tellurides. Conditions are mild and work well on both the aliphatic and aromatic oxides.

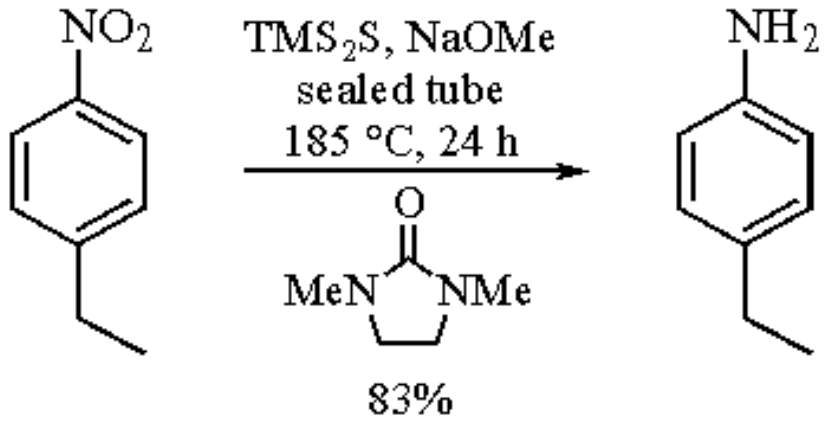

(1)

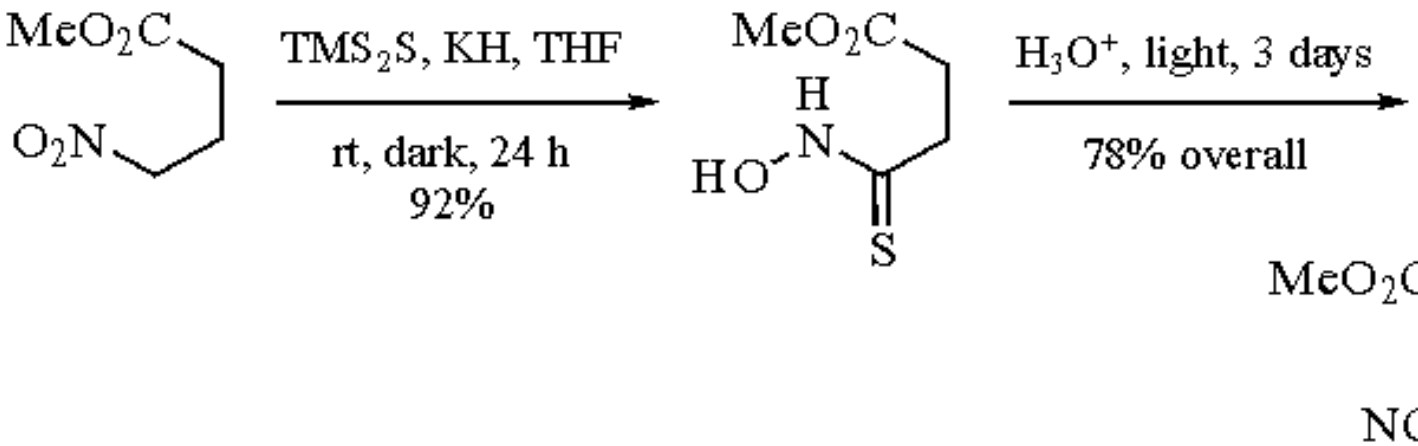

(2)

Sulfur Transfer Reagent.

Alkyl sulfides[5] can be formed from the corresponding alkyl halides using TMS_2S. Thioaldehydes,[6] thioketones (eq 3),[7] thioamides,[8] thioacid anhydrides,[9] thioacylsilanes,[10] divinyl sulfides (eq 4),[11] and thiranes (eq 5)[12] are also produced from TMS_2S and their respective carbonyl or alkenic compounds, in combination with the reagents shown.

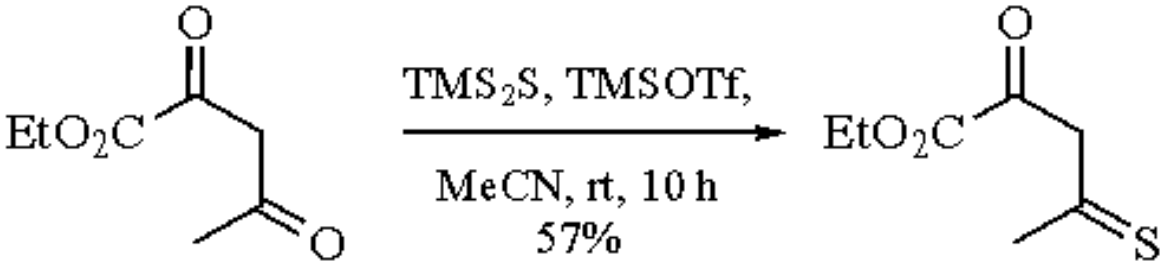

(3)

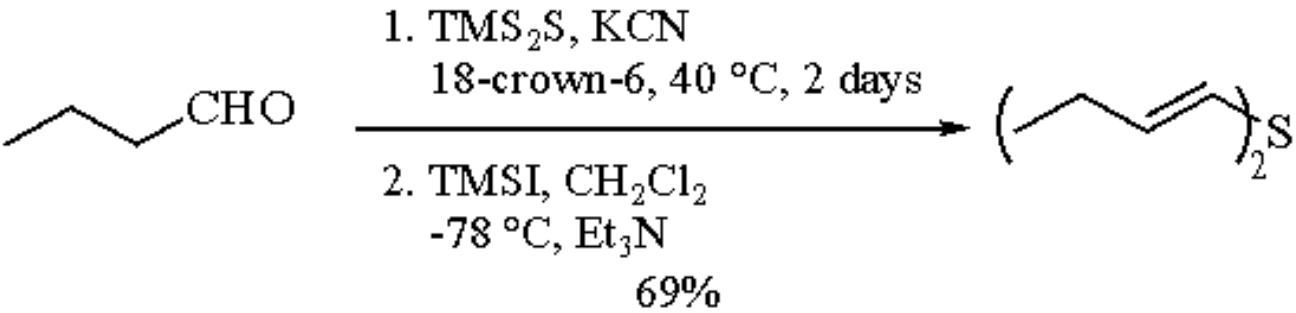

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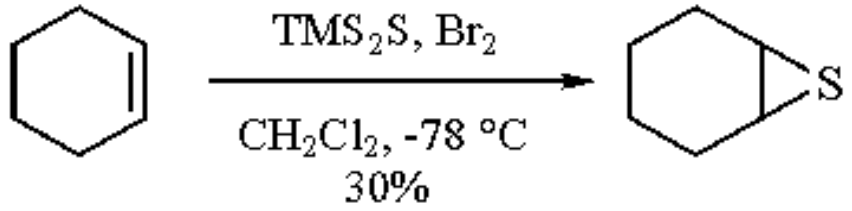

(5)

Silicon Transfer Reagent.

Bis(trimethylsilyl) sulfide can transform[1b] alcohols, acids, and amines into their silylated counterparts. Enol silanes[13] are also formed under the influence of this silyl transfer reagent.

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N,N´-Bis(trimethylsilyl)urea[1]

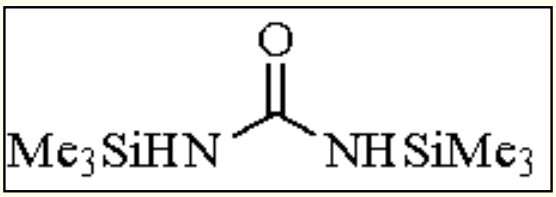

[18297-67-7] · $C_7H_{20}N_2OSi_2$ · *N,N´*-Bis(trimethylsilyl)urea · (MW 204.42)

(large-scale silylating reagent for alcohols and carboxylic acids;[1b] does not require acid or base catalysis and the urea byproduct is insoluble in CH_2Cl_2, which aids in the reaction workup)

Alternate Name: BSU.

Physical Data: mp 232 °C (dec).

Form Supplied in: white powder.

Handling, Storage, and Precautions: when using, wear protective clothing to prevent contact with eyes and skin. May cause irritation if inhaled, ingested, or comes in contact with skin. Toxicological properties have not been thoroughly investigated. Store in a cool dry place, under an inert atmosphere to prevent hydrolysis.

The use of a trimethylsilyl group as a protecting group in organic synthesis has become a widely used procedure, due to the fact that it may be easily removed under mild conditions.[1] The reagents which have been developed for its introduction are ***Chlorotrimethylsilane***,[2] ***Hexamethyldisiloxane***,[3,4] ketene methyl trialkylsilyl acetals,[5] ***Triethylsilyl Perchlorate***,[6] and allylsilanes.[7] However, problems exist with the above procedures, which include the necessity for acid[3,4,7] or base[2,6] catalysis, the silylating agent is not readily accessible,[5] or a gas is produced during the reaction which may cause problems when working on a large scale.[7]

As a silylating agent, *N,N´*-bis(trimethylsilyl)urea has primarily been used in industry for large-scale production of pharmaceuticals such as prostaglandins and semisynthetic penicillins and cephalosporins.[1b] Not until recently has this reagent been utilized in the laboratory as a silylating agent for smaller-scale organic transformations. Researchers have found that *N,N´*-bis(trimethylsilyl)urea can be generally used for the *O*-silylation of alcohols and carboxylic acids.[8]

The use of *N,N´*-bis(trimethylsilyl)urea as a silylating agent has many advantages over other reagents which perform the same purpose. The reaction conditions that are employed are very mild (0-40 °C, CH_2Cl_2). The urea byproduct formed is neutral and also precipitates out of solution, lending to easy reaction workups, and the reactions generally

proceed in excellent yields (>85%). The generality of this reagent is demonstrated in the following transformations of primary, secondary, and tertiary alcohols and carboxylic acids (eqs 1-4). This transformation is not limited to just alkanols, as aryl alcohols can also be transformed to their TMS ethers easily in high yields.

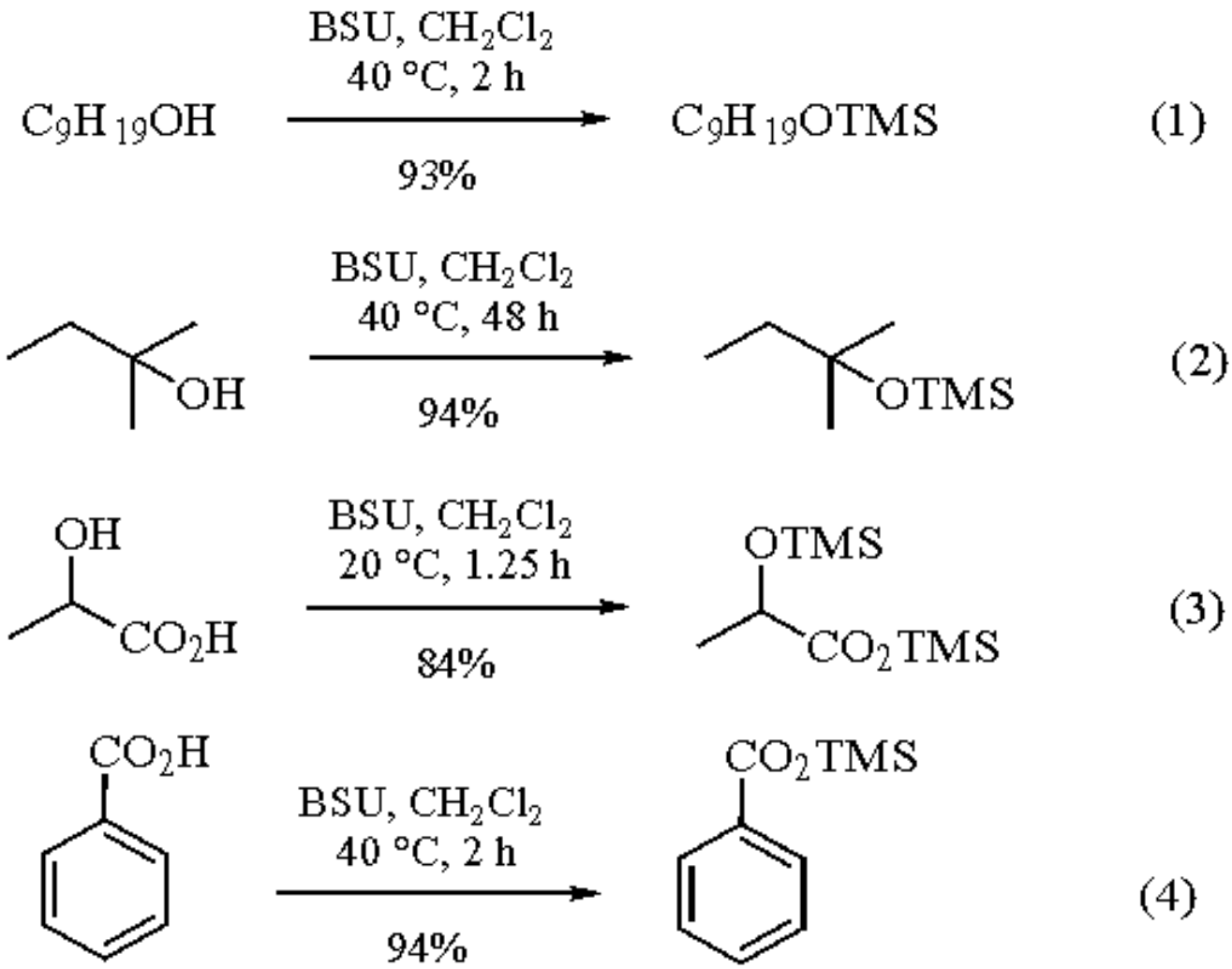

As a silylating agent *N,N´*-bis(trimethylsilyl)urea has been employed in the derivatization of carboxylic acids in peptide synthesis due to the solubility properties of the silylating agent and the urea byproduct.[9]

N,N´-Bis(trimethylsilyl)urea has also been employed in the silylation of primary amines, which are generated in situ and will readily add to arylethylene oxides to give β-hydroxyamines in good to excellent yields (eq 5).[10]

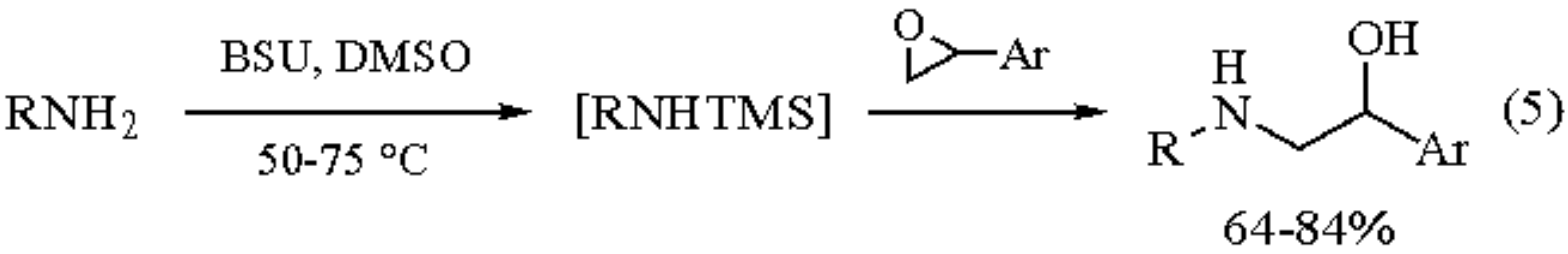

Related Reagents.

N,O-Bis(trimethylsilyl)acetamide; ***N-(Trimethylsilyl)imidazole***; ***Trimethylsilyl Nonaflate***; ***Trimethylsilyl Perchlorate***; ***Trimethylsilyl Trifluoromethanesulfonate***.

---

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Bis(trimethylstannyl) Benzopinacolate

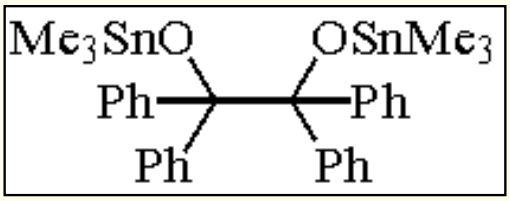

[39157-60-3] · $C_{32}H_{38}O_2Sn_2$ · Bis(trimethylstannyl) Benzopinacolate · (MW 692.03)

(reagent for radical mediated formation of C-C and Sn-X (X = C, O, N, etc.) bonds)

Alternate Name: TINPIN.

Physical Data: mp 122-124 °C.

Solubility: slightly sol petroleum ether; sol benzene, CH_2Cl_2.

Form Supplied in: not commercially available.

Preparative Method: prepared as a colorless solid by photolysis of a mixture of ***Hexamethyldistannane*** and benzophenone.[1]

Handling, Storage, and Precautions: avoid exposure of the reagent to light and heat; store protected from light in a refrigerator or freezer. Organotin compounds are highly toxic.

Preparation and Thermolysis.

Bis(trimethylstannyl) benzopinacolate (TINPIN) is prepared in the form of colorless crystals by photolysis of a mixture of benzophenone and $Me_3SnSnMe_3$ in benzene.[1] On thermolysis, TINPIN undergoes homolytic C-C cleavage, resulting in the formation of a (trimethylstannyloxy)diphenylmethyl radical, which can undergo further cleavage to give benzophenone and a trimethylstannyl radical (eq 1).

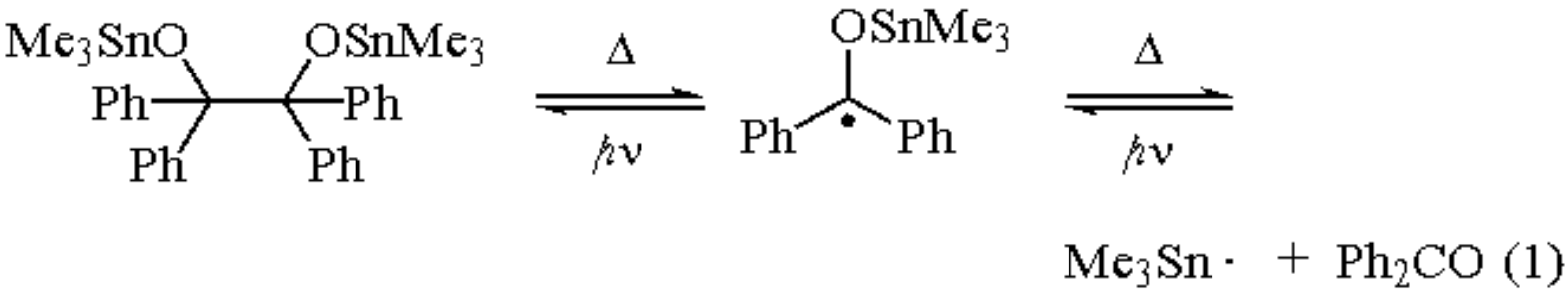

Radical C-C Bond Formation.

Under typical radical conditions, employing ***Tri-n-butylstannane*** and ***Azobisisobutyronitrile*** or $Me_3SnSnMe_3$, the intermolecular addition of alkyl radicals to *O*-benzylformaldoxime is inefficient. Hart and Seely overcame this problem by employing TINPIN in place of these conventional tin reagents (eq 2), a particularly interesting example being the synthesis of a *C*-glycosidic product starting with a glucosyl bromide (eq 3).[2]

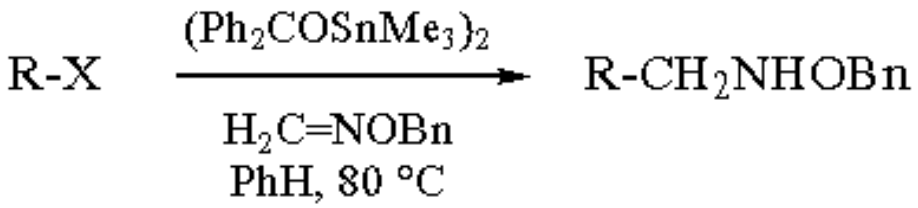

(2)

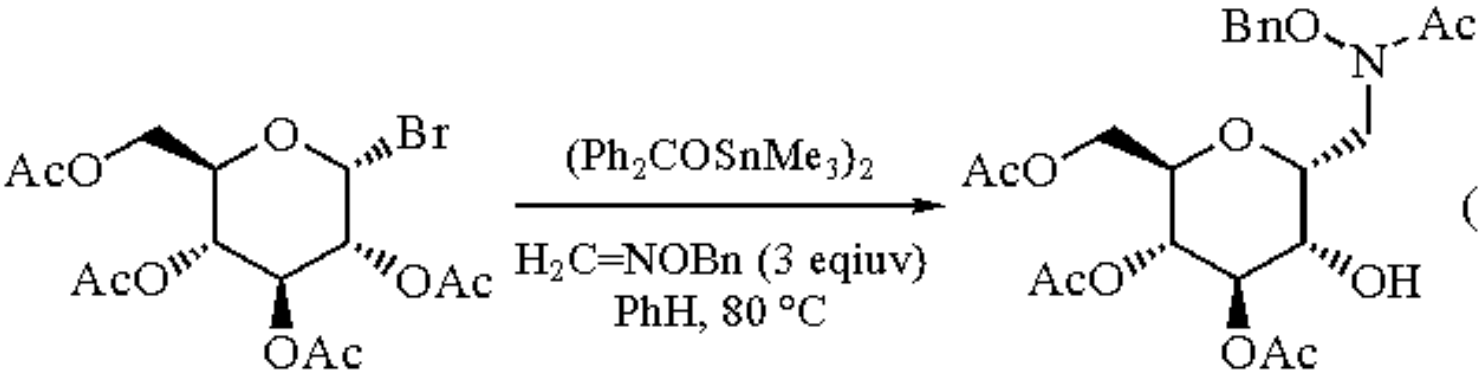

(3)

An interesting extension of this work, employing a functionalized oxime derivative, allowed the synthesis of a novel dinucleoside (eq 4).[3]

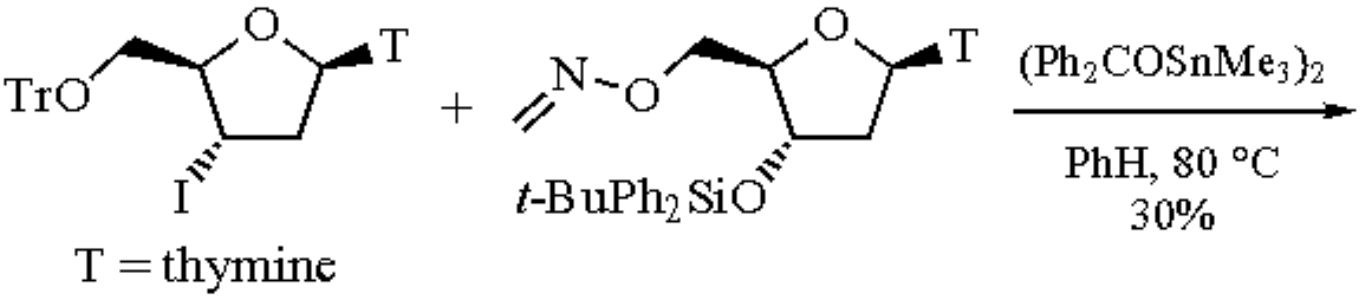

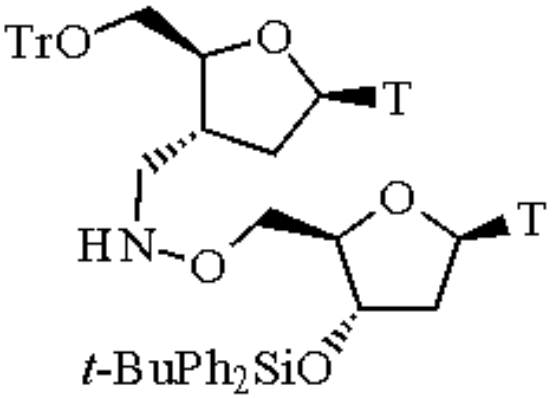

(4)

The report of Hart and Seely also mentions that TINPIN is a highly effective replacement for Bu_3SnH for the intermolecular radical addition of cyclohexyl iodide to ethyl acrylate (eq 5). The reaction is remarkable in that high yields of the desired adduct are obtained without the use of a large excess of acrylate radical acceptor. It is thought that this may be a radical nonchain process, involving trapping of the initial adduct radical by a (trimethylstannyloxy)diphenylmethyl radical, followed by a thermal retroaldol process to give the observed product (eq 6).[4]

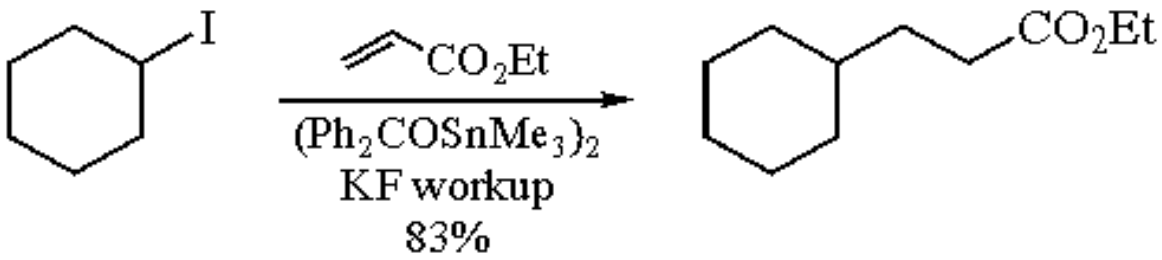

(5)

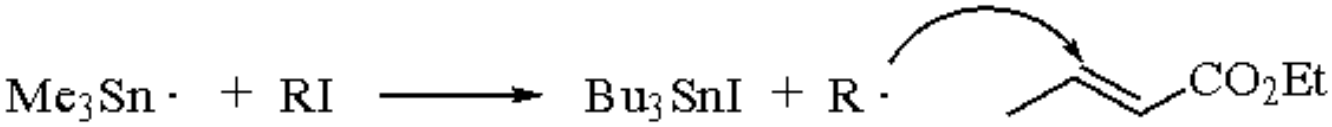

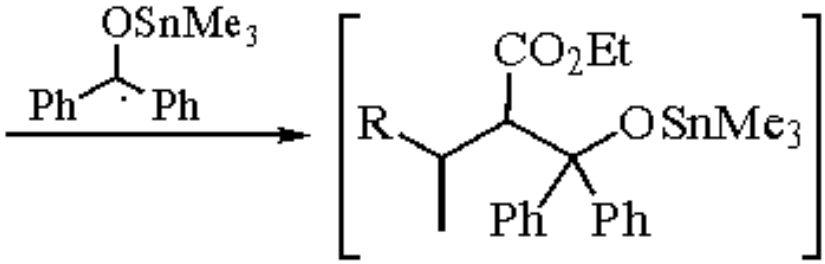

product (6)

The TINPIN reagent has also been employed in an intramolecular [3 + 2] radical-mediated addition reaction, enabling the synthesis of the cyclopenta[*b*]benzofuran ring system of the natural product rocaglamide (eq 7).[5] This stereoselective transformation involves initial attack of a trimethylstannyl radical on the thioamide group, followed by cyclopropane opening, double intramolecular radical cyclization, and final expulsion of the tin radical.

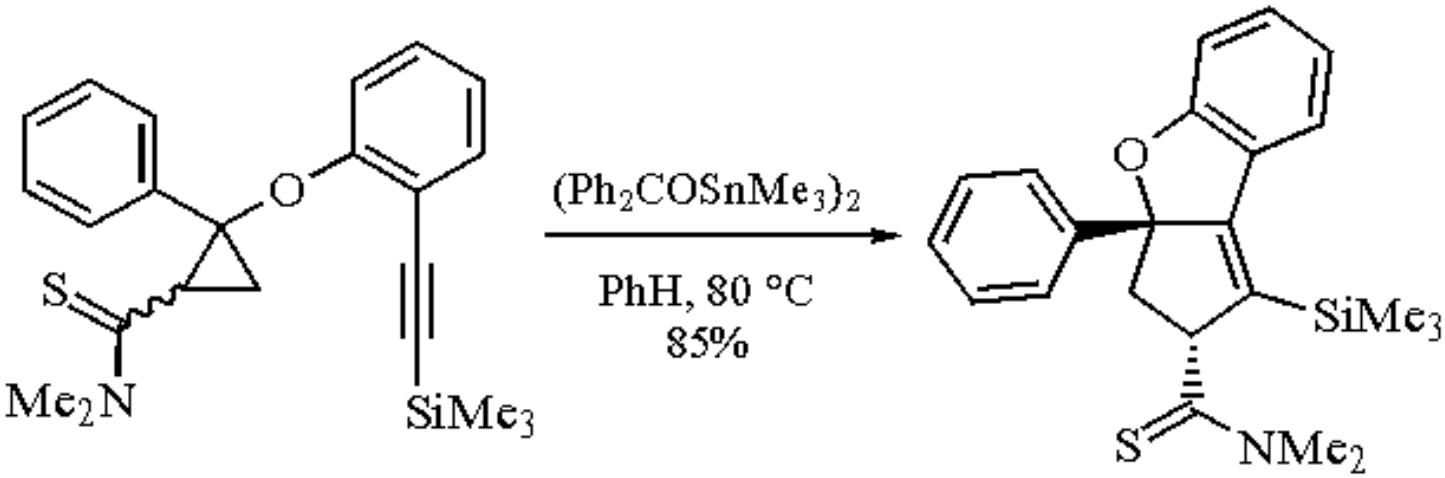

(7)

Formation of Tin-Heteroatom Bonds.

TINPIN is a highly effective reagent for the formation of stannylated derivatives from a range of heteroatom containing systems, including benzoquinone and NBS (eqs 8 and 9).[1,6]

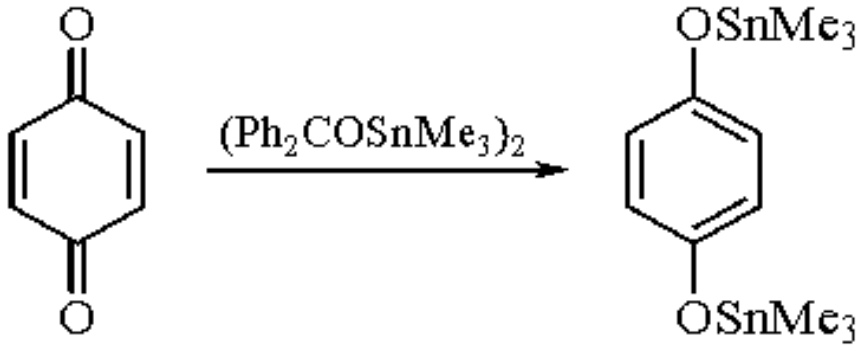

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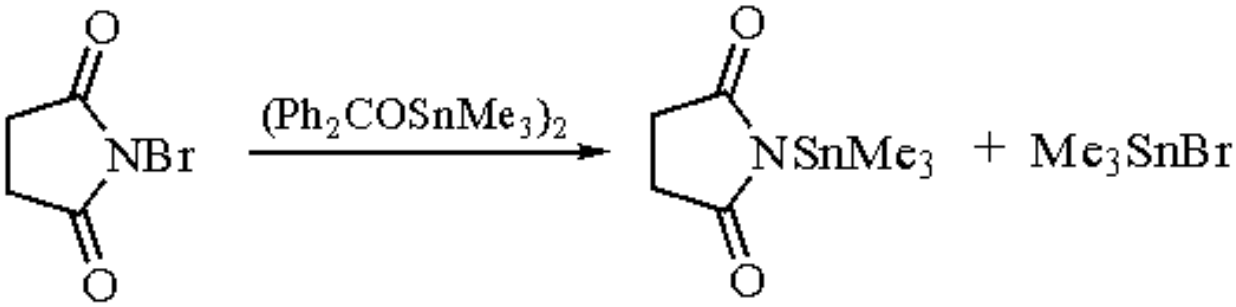

(9)

Examples of other systems which are effectively bis-stannylated include benzil and azobenzene.

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5. Feldman, K. S.; Burns, C. J. *JOC* **1991**, *56*, 4601.
6. Neumann, W. P.; Hillgärtner, H.; Baines, K. M.; Dicke, R.; Vorspohl, K.; Kobs, U.; Nussbeutel, U. *T* **1989**, *45*, 951.

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2,3-Bis(trimethylstannyl)-1,3-butadiene

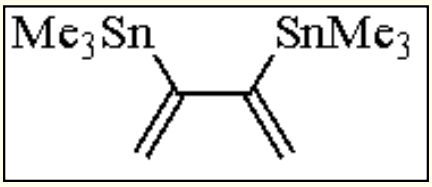

[19312-27-5] · $C_{10}H_{22}Sn_2$ · 2,3-Bis(trimethylstannyl)-1,3-butadiene · (MW 379.66)

(synthon for the 2,3-dianion of 1,3-butadiene)

Physical Data: low-melting solid, bp 65-66 °C/0.8 mmHg (distillation); stable indefinitely at -20 °C under nitrogen

Preparative Methods: [1] treatment of either 2,3-dichloro-1,3-butadiene or commercially available ***1,4-Dichloro-2-butyne*** with 2 equiv ***Trimethylstannyllithium*** in THF affords 1,4-bis(trimethylstannyl)-2-butyne as the kinetic product. This alkyne can be isomerized to 2,3-bis(trimethylstannyl)-1,3-butadiene by a catalytic amount of either ***Methyllithium*** or trimethylstannyllithium and 2 equiv of HMPA in THF (eq 1). Therefore either dihalide can serve as precursor to either stannane. A one-pot synthesis can be accomplished in 70% yield. It may be advantageous to prepare the trimethylstannyllithium reagent with lithium wire containing 1% sodium.[2]

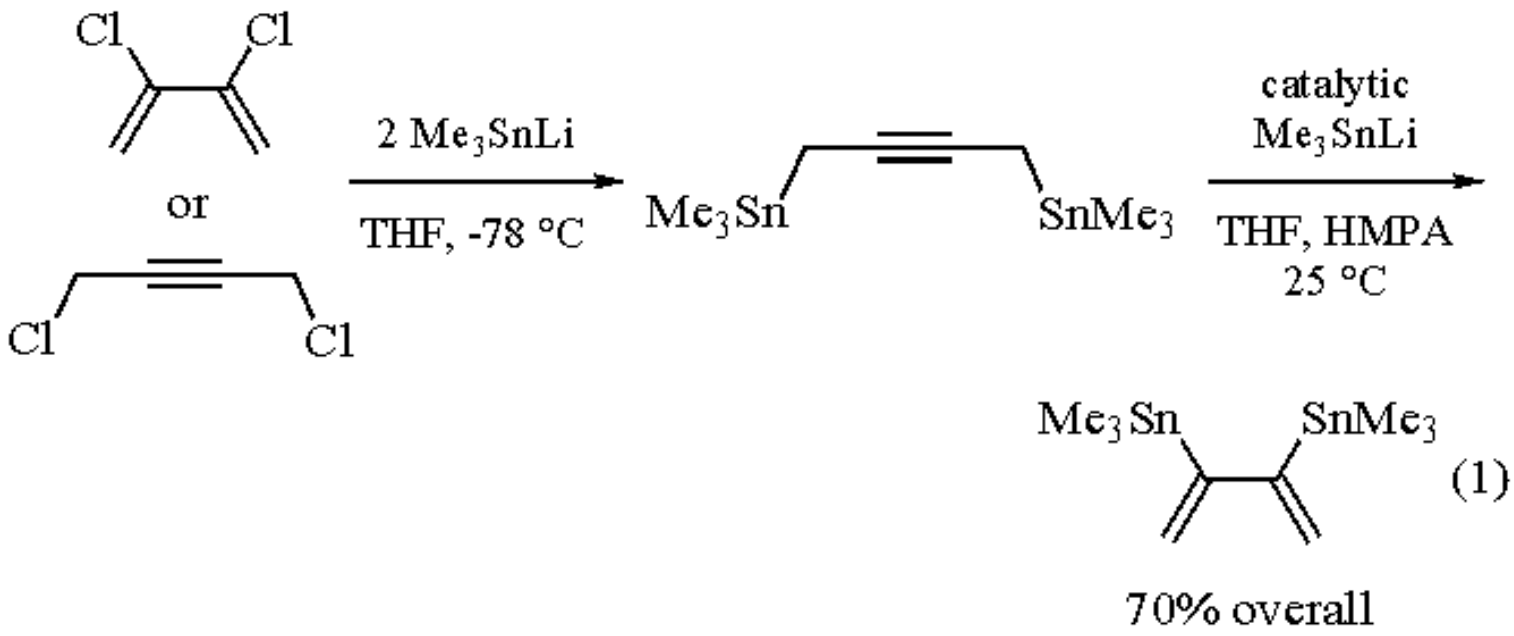

Handling, Storage, and Precautions: organotin compounds should be considered toxic and should be handled with appropriate care.

Lithium Reagents.

The divergence of kinetic and thermodynamic control among lithium reagents derived from Sn/Li transmetalation of 2,3-bis(trimethylstannyl)-1,3-butadiene can have profound synthetic implications (eqs 2 and 3). The monolithiated butadiene is less stable than the isomeric lithiated allene; their common dilithio species appears to be propargylic. Thus 2-lithio-3-(trimethylstannyl)-1,3-butadiene can furnish diene products, alkyne products, or mixtures depending on whether the lithium reagent is handled under strictly kinetic conditions or is allowed to equilibrate.

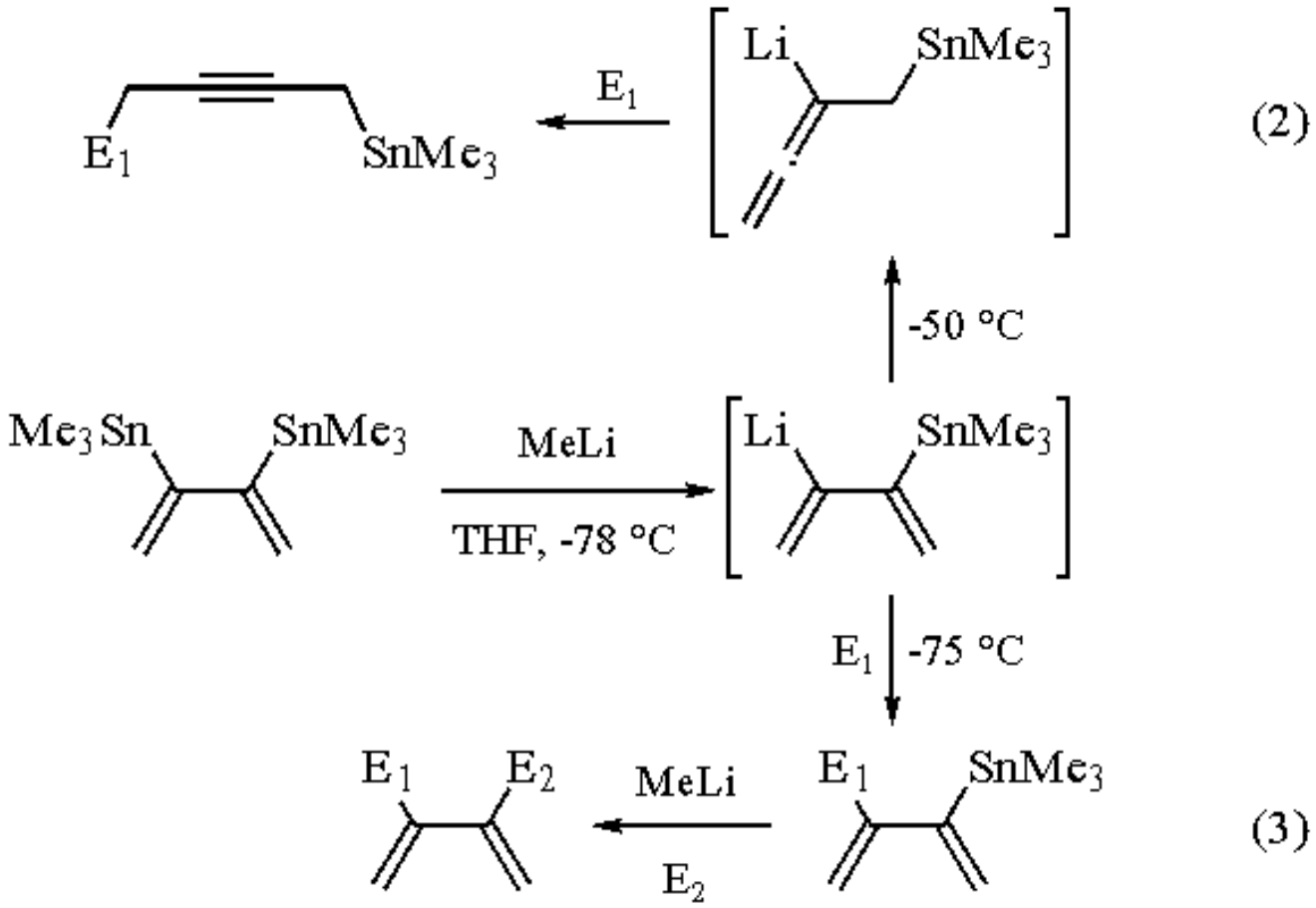

Monosubstitution Reactions.

A solution of 2-lithio-3-(trimethylstannyl)-1,3-butadiene is prepared at -78 °C in THF and then transferred by cannula (jacketed, -78 °C) to a solution of electrophile in THF, ether, or pentane at -78 °C. In this manner, silicon halides, positive halogen sources, sulfenylating reagents, primary alkyl halides, some secondary alkyl halides, elemental selenium, and carbon dioxide afford good yields of monosubstitution products.

When the 2-lithio-3(trimethylstannyl)-1,3-butadiene reacts with simple carbonyl electrophiles (eq 4; M = Li), diene products predominate with varying amounts of contamination by allenic substitution. If the lithiobutadiene is first transformed to the Grignard reagent by exchange with ***Magnesium Bromide*** (eq 4; M = MgBr), allenes are obtained.

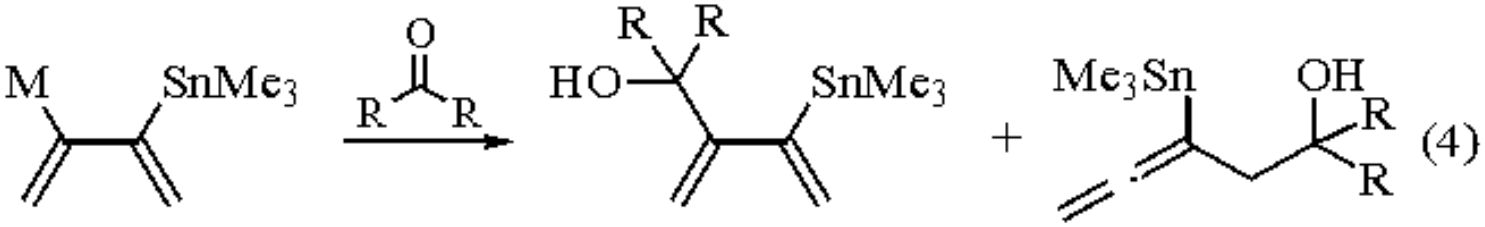

M = Li	R = Me	69%	18%
M = MgBr	R = Me		82%
M = Li	R = CH_2CH_2Ph	52%	
M = MgBr	R = CH_2CH_2Ph	14%	80%

The most effective organocopper species for conjugate addition reactions is derived from 2-lithio-3-(trimethylstannyl)-1,3-butadiene using ***Copper(I) Iodide-Tributylphosphine***. The reaction yield of 64% is based on chalcone (eq 5). No allenic products are formed, but the Gilman reagent requires 2 equiv lithiobutadiene.

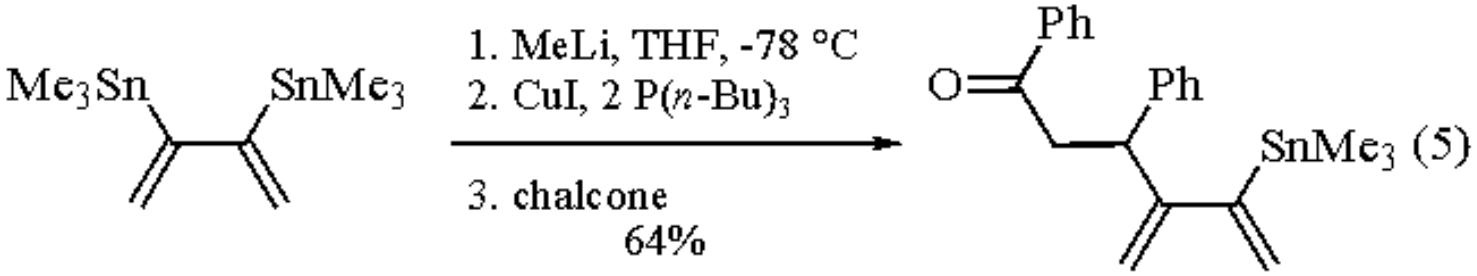

Disubstitution Reactions.

Since Sn/Li transmetalation of the stannylated butadienes is faster than the reaction of many electrophiles with methyllithium, some double derivatizations can be carried out in situ by simply adding 2-3 equiv of MeLi to a solution of 2,3-bis(trimethylstannyl)-1,3-butadiene and 2 equiv of electrophile in THF at -78 °C. Silicon halides, elemental selenium, and primary iodides are appropriate electrophiles for such reactions. Sequential disubstitution reactions may be carried out providing the first substituent is stable to methyllithium in THF.

Diels-Alder Reactivity.

Compared to the parent butadiene (k_{rel} = 1), 2,3-bis(trimethylstannyl)-1,3-butadiene is a poor Diels-Alder diene (k_{rel} = 0.05).

---

1. Reich, H. J.; Reich, I. L.; Yelm, K. E.; Holladay, J. E.; Gschneidner, D. *JACS* **1993**, *115*, 6625.
2. Reich, H. J.; Yelm, K. E.; Reich, I. L. *JOC* **1984**, *49*, 3438.

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Bis[trinitratocerium(IV)] Chromate[1]

$[Ce(NO_3)_3]_2CrO_4$

[93250-25-0] · $Ce_2CrN_6O_{22}$ · Bis[trinitratocerium(IV)] Chromate · (MW 768.26)

(mild oxidizing reagent capable of oxidizing several functional groups;[2,3] releases alcohols from allyl and propargyl silyl ethers[4] and carbonyl compounds from acetals[4])

Alternate Name: BTNCC.

Solubility: sol DMSO, DMF; moderately sol H_2O; sparingly sol EtOH, MeCN; insol PhH.

Form Supplied in: yellow-orange solid.

Preparative Method: to a solution of ***Potassium Dichromate*** (0.02 mol) in H_2O (100 mL), ***Cerium(IV) Ammonium Nitrate*** (0.02 mol) in H_2O (50 mL) is added, and the mixture diluted with H_2O (150 mL). The resulting precipitates are filtered, triturated with acetone, separated, and dried in air (70%).

Handling, Storage, and Precautions: stable at elevated temperatures (>200 °C) and to storage at rt for months. Chromate is a cancer suspect agent. Work with this reagent should be conducted in a fume hood.

Introduction.

Reactions with this reagent (BTNCC) proceed in dry benzene and residual oxidant can be separated by simple filtration. Drawbacks of other Ce^{IV} oxidations,[1,5] such as cleavage reactions, strong acidic conditions, and the necessity of employing polar solvents or cosolvents, are not encountered with this reagent.

Oxidations.

Hydroquinones, α-hydroxy ketones, and primary and secondary saturated and benzylic alcohols are converted to their quinones, α-diketones, and carbonyl compounds, respectively, in high yields (eqs 1-3).[2,4] Allyl, propargyl, and deactivated benzyl alcohols remain intact.

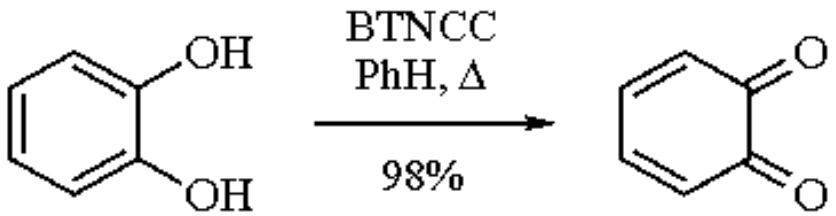

(1)

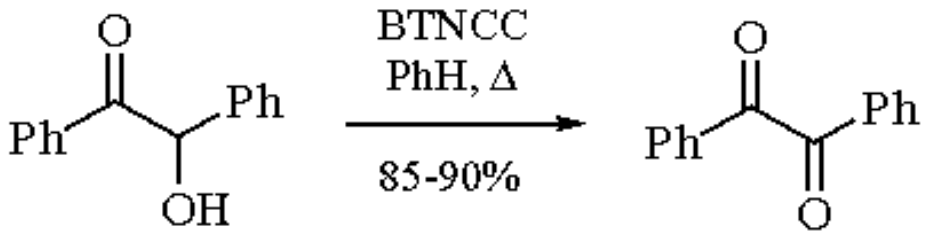

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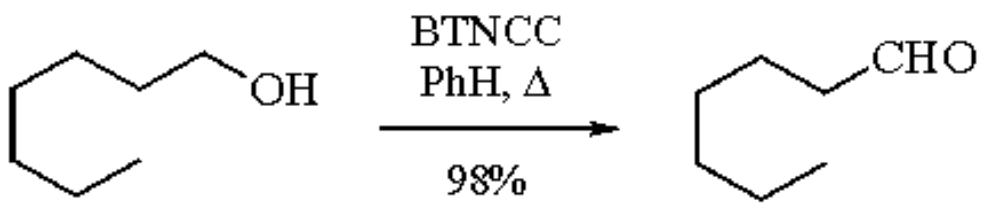

(3)

Benzyl silyl ethers are quantitatively converted to aldehydes (eq 4).[4]

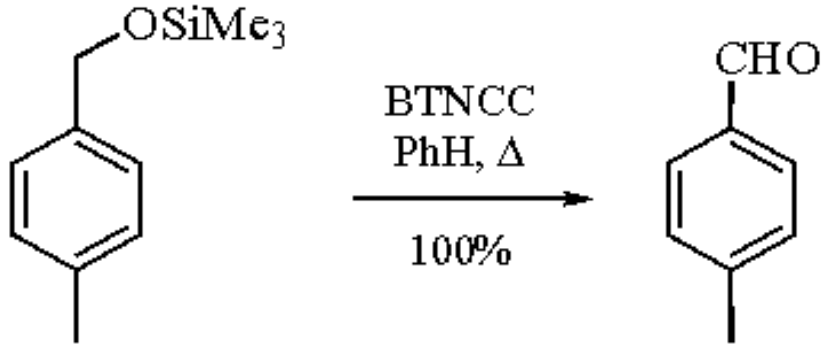

(4)

Smooth oxidation of thiols to disulfides (eq 5) in high yield[3] occurs with this mild reagent.

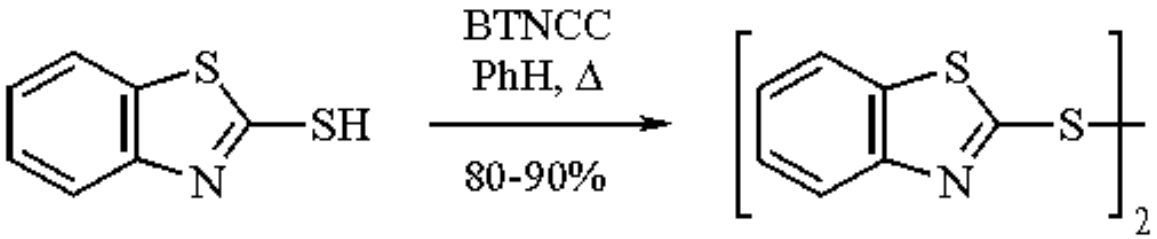

(5)

Deprotection Reactions.

This reagent releases alcohols from propargyl and allyl silyl ethers without further oxidation (eq 6).[4] Saturated silyl ethers remain intact.

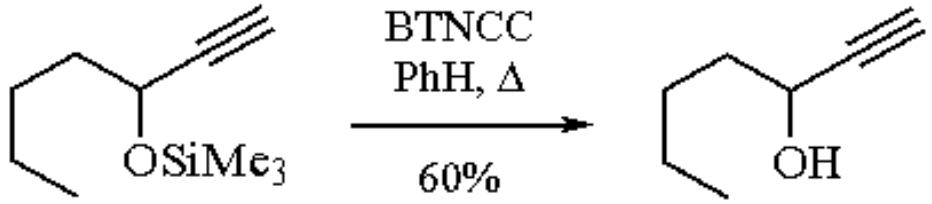

(6)

Deprotection of acetals proceeds well to produce carbonyl compounds (eq 7).

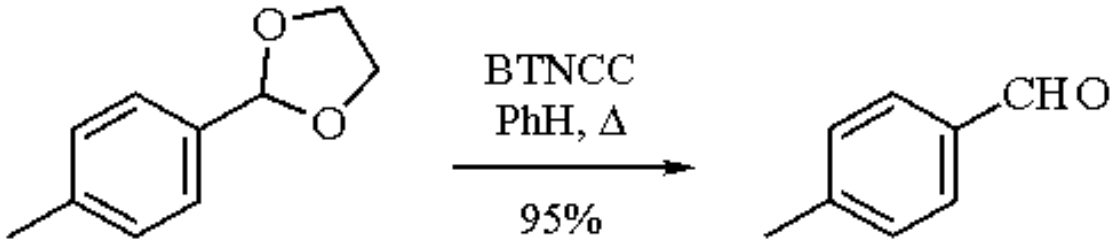

(7)

A brief comparison between this reagent, ***Cerium(IV) Ammonium Nitrate*** (CAN),[5,6] and ***Pyridinium Chlorochromate*** (PCC)[3,7] is shown in Table 1.

Table 1 Comparison of Cerium Reagents

Substrate	Product	BTNCC (%)	CAN (%)	PCC (%)
$PhCH_2OH$	PhCHO	85 95	94	80
PhCOCH(OH)Ph	PhCOCOPh	85 90	0	
FuCOCH(OH)Fu	FuCOCOFu	70 80	5	
$PhCH_2SH$	$(PhCH_2S)_2$	70 80	0	75
Ph_3P	Ph_3PO	0	100	
Hydroquinone	Benzoquinone	90	83.3	

1. (a) Ho, T. L. In *Organic Synthesis by Oxidations with Metal Compounds*; Mijs, W. J.; De Jonge, C. R. H. I., Eds.; Plenum: New York, 1986; Chapter 11. (b) Molander, G. A. *CRV* **1992**, *92*, 29.
2. Firouzabadi, H.; Iranpoor, N.; Parham, H.; Toofan, J. *SC* **1984**, *14*, 631.
3. Firouzabadi, H.; Iranpoor, N.; Parham, H.; Sardarian, A.; Toofan, J. *SC* **1984**, *14*, 717.
4. Firouzabadi, H.; Shiriny, F. Unpublished results.
5. Ho, T. L. *S* **1973**, 347.
6. Trahanovsky, W. S.; Young, L. B.; Brown, G. L. *JOC* **1967**, *32*, 3865.

Bis(triphenylphosphine)[1,2-bis(diphenylphosphino)ethane]palladium(0)

$(Ph_3P)_2Pd(Ph_2PCH_2CH_2PPh_2)$

[74790-18-4] · $C_{62}H_{54}P_4Pd$ · Bis(triphenylphosphine)[1,2-bis(diphenylphosphino)ethane]palladium(0) · (MW 1029.42)

(useful for trimethylenemethane cycloadditions;[1,2] sulfonylation or amination with epoxy nitro compounds;[3] allylic alkylation and amination of nitro compounds;[4,5] rearrangement of 2,3-epoxy ketones to β-diketones;[6,7] alkylation of enol stannanes;[8] opening of vinyloxetanes;[9] and macrocyclizations[10,11])

Solubility: sol THF, toluene, DMF, and MeCN.

Form Supplied in: generated in situ.

Preparative Method: in situ by the addition of slightly more than 1 equiv of ***1,2-Bis(diphenylphosphino)ethane*** (dppe) to 1 equiv of ***Tetrakis(triphenylphosphine)palladium(0)***.

Handling, Storage, and Precautions: as with most palladium(0) catalysts, this reagent should be used under an inert atmosphere and should not be allowed to sit for long periods of time in solution prior to use.

Trimethylenemethane Cycloadditions.

Trimethylenemethane (TMM) cycloaddition is an important tool in the synthesis of five-membered carbocycles.[1] The use of bis(triphenylphosphine)[1,2-bis(diphenylphosphino)ethane]palladium(0) (**1**; 3-9 mol %) with (2-acetoxymethylallyl)trimethylsilane (**2**) generates the TMM-Pd complex which, in turn, undergoes a [3 + 2] cycloaddition specifically with alkenes bearing an ester, lactone, nitrile, ketone, or sulfone moiety (eq 1). *Trans*-alkenes provide mainly the *trans* stereoisomer (95:5, *t:c*) while *cis*-alkenes isomerize to give a mixture of *cis* and *trans* products. The presence of 0.5-1 equiv of dppe in relation to palladium prolongs the lifetime of the catalyst and prevents the deposition of palladium black. An alternative catalytic system, which employs palladium(II), does not produce a significant difference in yields. However, the use of catalytic palladium(II) has two advantages: (1) the nature of the ligands of palladium(II) can easily be altered and (2) palladium(II) is not air-sensitive.

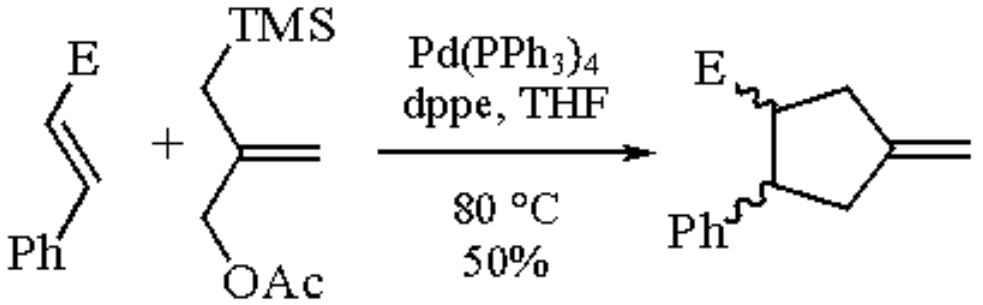

(1)

E = CO_2Me **(2)** *trans*:*cis* = 95:5

Trost extends his TMM methodology to include intramolecular [3 + 2] cycloadditions (eq 2).[2] With the use of catalyst (**1**), bicyclic compounds are effectively prepared in one step from acyclic substrates. Concomitant formation of five-membered rings yields only the *cis*-fused bicyclo[3.3.0]octanes (*n* = 1). Moderate yields are obtained for the formation of a six-membered ring (*n* = 2), and the ratio of *cis* to *trans* fused ring systems is 2:1. For the intramolecular reaction with TMM, ***Bis[1,2-bis(diphenylphosphino)ethane]palladium(0)*** is an efficient catalyst. The use of $(dppe)_2Pd$ and added dppe, or the use of ***Tetrakis(triphenylphosphine)palladium(0)*** with additional triphenylphosphine, produces the cyclized substrate in significantly lower yields. Catalytic ***Palladium(II) Acetate*** (5 mol %) with ***Triisopropyl Phosphite*** in the presence of ***N,O-Bis(trimethylsilyl)acetamide*** gives superior yields over catalyst (**1**) for the substrate in which *n* = 2, $R^1 = CO_2Me$ and $R^2 = SO_2Ph$.

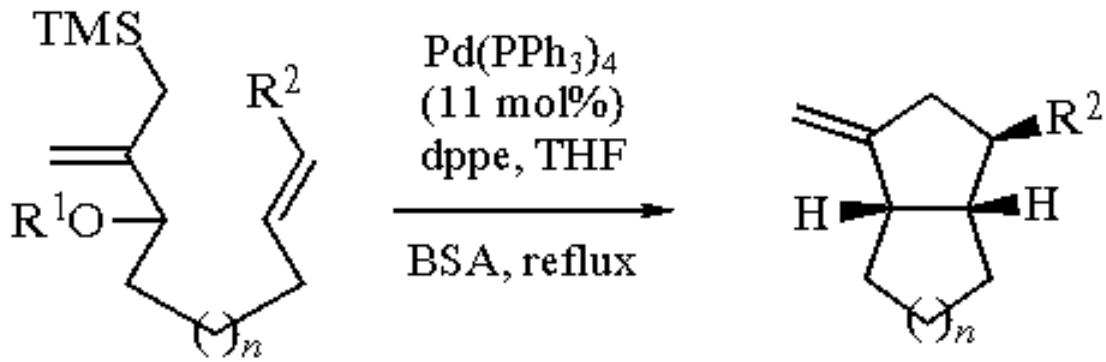

(2)

BSA = *N,O*-bis(trimethylsilyl)acetamide

$n = 1$, $R^1 = Ac$, $R^2 = CO_2Me$	51%
$n = 2$, $R^1 = Ac$, $R^2 = SO_2Ph$	43-70%, *cis*:*trans* = 2:1
$n = 2$, $R^1 = CO_2Me$, $R^2 = SO_2Ph$	73%, *cis*:*trans* = 1.5:1

Epoxide Opening with Nucleophilic Substitution.

In the presence of (**1**), which is generated in situ, β-alkyl-β,γ-epoxynitro compounds undergo epoxide opening, and subsequent displacement of the nitro group by various nucleophiles results (eq 3).[3] Nucleophiles that efficiently displace the nitro group are ***Sodium Benzenesulfinate*** and ***Piperidine***. Nucleophilic attack on the π-allyl intermediate is regiospecific for five-membered ring substrates, but only marginal regioselectivity is observed for the reaction of the six-membered ring substrates (eq 3). The absence of dppe results in a slight decrease in the yield of the desired product by 5-10%.

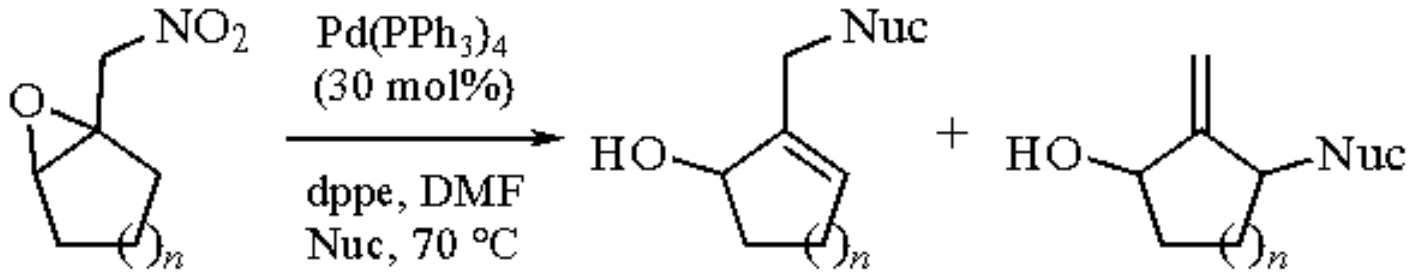

(3)

$n = 1$, Nuc = $PhSO_2^- Na^+$	60%	100:0
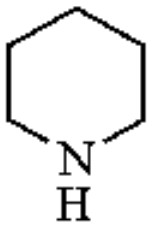	83%	100:0
$n = 2$, Nuc = $PhSO_2^- Na^+$	47%	55:45
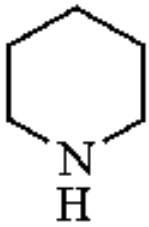	56%	64:36

Allylic Alkylation/Amination and Denitration of Nitro Compounds.

In a closely related study, complex (**1**) catalyzes substitutions of allylic nitro compounds with secondary amines and stabilized carbanions such as malonic and β-keto esters.[4] For cyclic allylic nitro compounds, the use of triphenylphosphine provides higher yields than when dppe is used as the co-ligand. Generally, five-membered ring substrates produce a single regioisomer in moderate yields, while the six-membered substrate gives a mixture of two regioisomers (eq 4). In the palladium-catalyzed allylic alkylation and amination of primary nitro compounds, mixtures of regioisomers and diastereomers are produced unless a sterically hindered alkene is used (eq 5). In this reaction, preferential bond formation occurs at the primary allylic carbon.

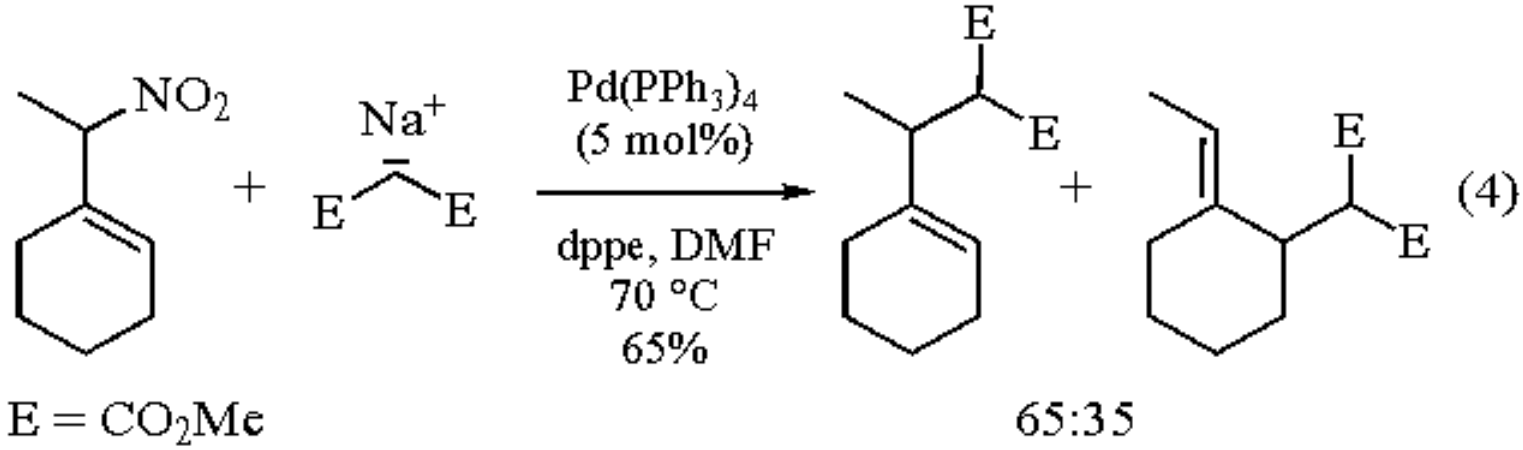

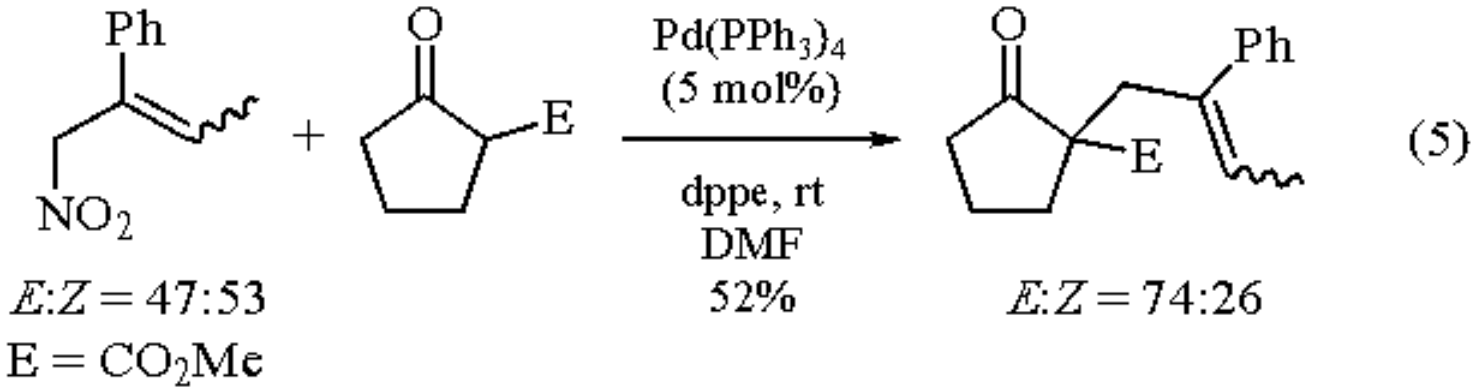

Compound (**1**) is also used for the catalysis of the denitroamination of α-nitroalkenes (eq 6).[4,5] Normally, α-nitroalkenes are excellent Michael acceptors. However, in the presence of (**1**) and a secondary amine, allylic amination occurs accompanied by denitration. In acyclic substrates the regiospecific nucleophilic attack occurs at the less hindered carbon, and β-hydride elimination yields only the (*E*) isomer. This same type of reaction proceeds with ***Sodium Benzenesulfinate*** as the nucleophile and ***Triethylamine*** as the base. Again, only the (*E*) isomer is produced as a result of nucleophilic attack at the least hindered site. The dppe ligand is thought to have two functions in the denitrosulfonylation. Dppe is believed not only to serve as an additional ligand for palladium, but also to function as a base in the isomerization of the α-nitroalkenes to the active allylic species.

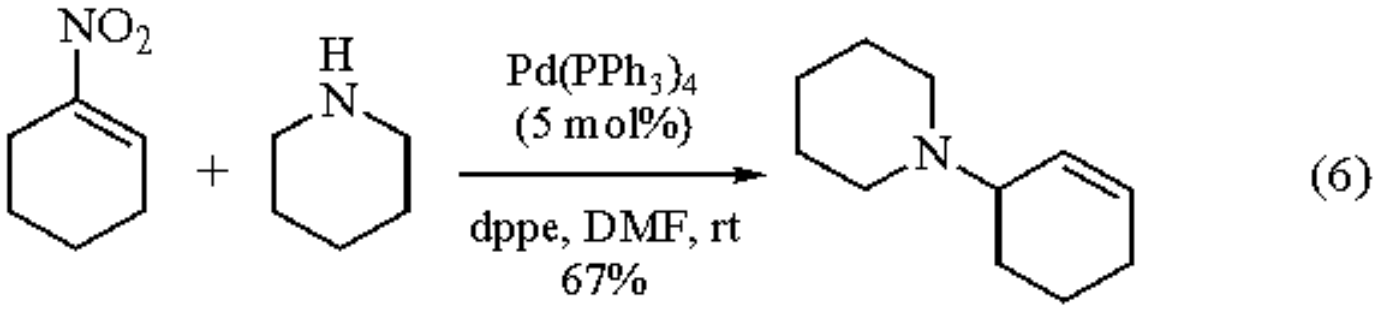

Rearrangements.

The rearrangement of 2,3-epoxy ketones to β-diketones is also facilitated by (**1**) (eq 7).[6] Treatment of 2,3-epoxy ketones with catalytic ***Tetrakis(triphenylphosphine)palladium(0)*** and dppe in equimolar amounts produces β-

diketones in moderate to excellent yields. This methodology presents a fairly mild procedure for the preparation of β-diketones under neutral and aprotic conditions as opposed to the strongly basic conditions of the Claisen condensation. The addition of dppe significantly improves the yields of β-diketone products, and the use of dppe is necessary to obtain a reasonable reaction rate and to avoid metal precipitation, which deactivates the catalyst. In a similar manner, diethyl (2,3-epoxy-4-oxoalkyl)phosphonates rearrange to give diethyl (2,4-dioxoalkyl)phosphonates promoted by the (dppe)Pd(PPh_3)$_2$ catalyst system (eq 8).[7]

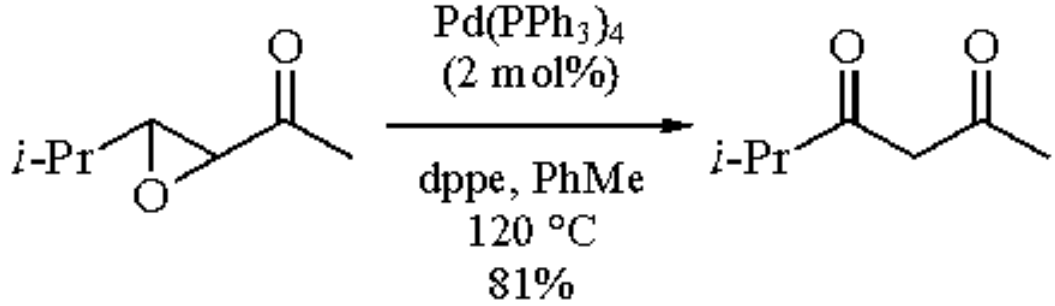

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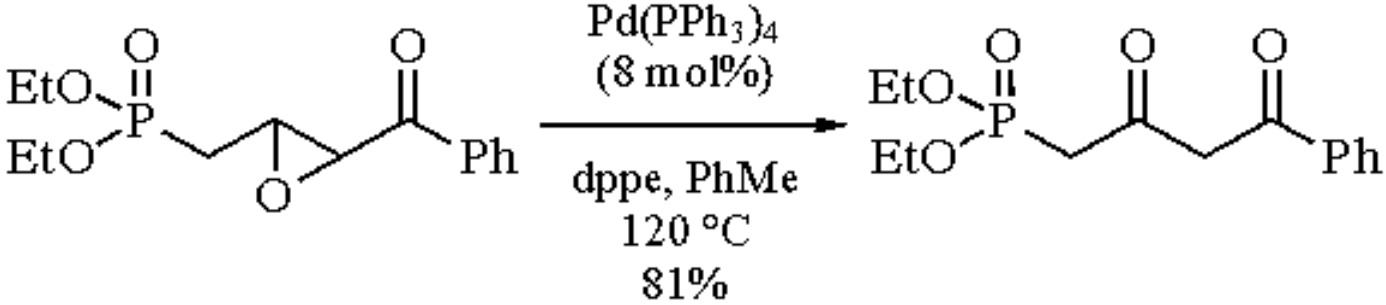

(8)

Alkylations.

Polyalkylation of enolates presents a problem for synthetic chemists. One procedure that promotes monoalkylation with high regioselectivity uses (**1**) to catalyze the coupling of enol stannanes with allyl acetates (eq 9).[8] Enol stannanes are alkylated with bifunctional silicon conjunctive reagents. Generally, the regioselectivity for alkylation with compound (**3**) favors alkylation α to the silicon. 3-Acetoxy-1-(trimethylsilyl)-1-propene can be used as an alternative to compound (**3**).

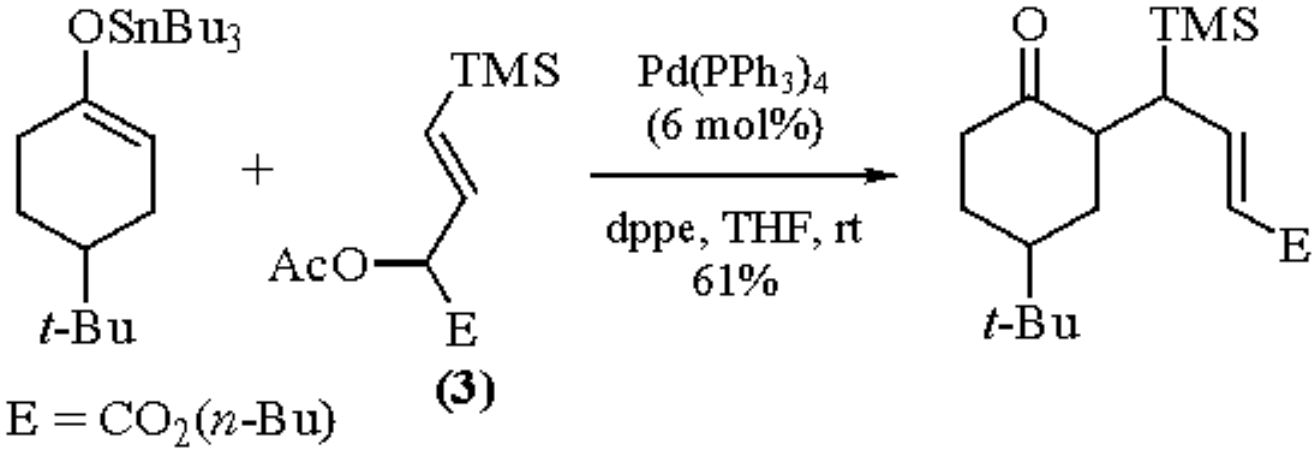

(9)

Oxetane Opening with Allylic Alkylation.

Vinyloxetanes are alkylated through nucleophilic opening of the oxetane to yield homoallylic alcohols (eq 10).[9] Although the formation of disubstituted alkenes can be accomplished simply with $Pd(PPh_3)_4$, synthesis of trisubstituted alkenes requires the use of compound (**1**). Various nucleophiles can take part in this general reaction, yet only stabilized enolates (β-diketones, malonates, and β-cyano esters) produce successful formation of trisubstituted alkenes.

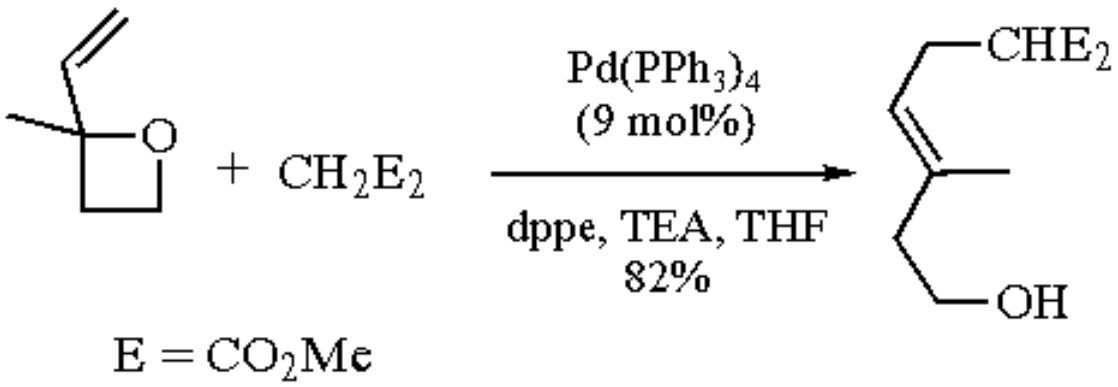

(10)

Macrocyclization.

Macrocyclization is accomplished by generating the π-allylpalladium species from the allylic pivalate with compound (**1**) (eq 11).[10] Intramolecular phenylsulfonylacetate attack of the π-allylpalladium species at the least hindered carbon generates the macrocyclic product used as an intermediate in the synthesis of isolobophytolide. A key step in the synthesis of antibiotic A26771B also employs this macrocyclization methodology (eq 12).[11] In this cyclization the intermediate π-allyl palladium species is generated from an acetate which is allylic to an enol ether. This methodology offers an alternative route to macrolactone formation. The conditions of this cyclization are tolerated by enol ethers, sulfones, esters, alkenes and hydroxy groups.

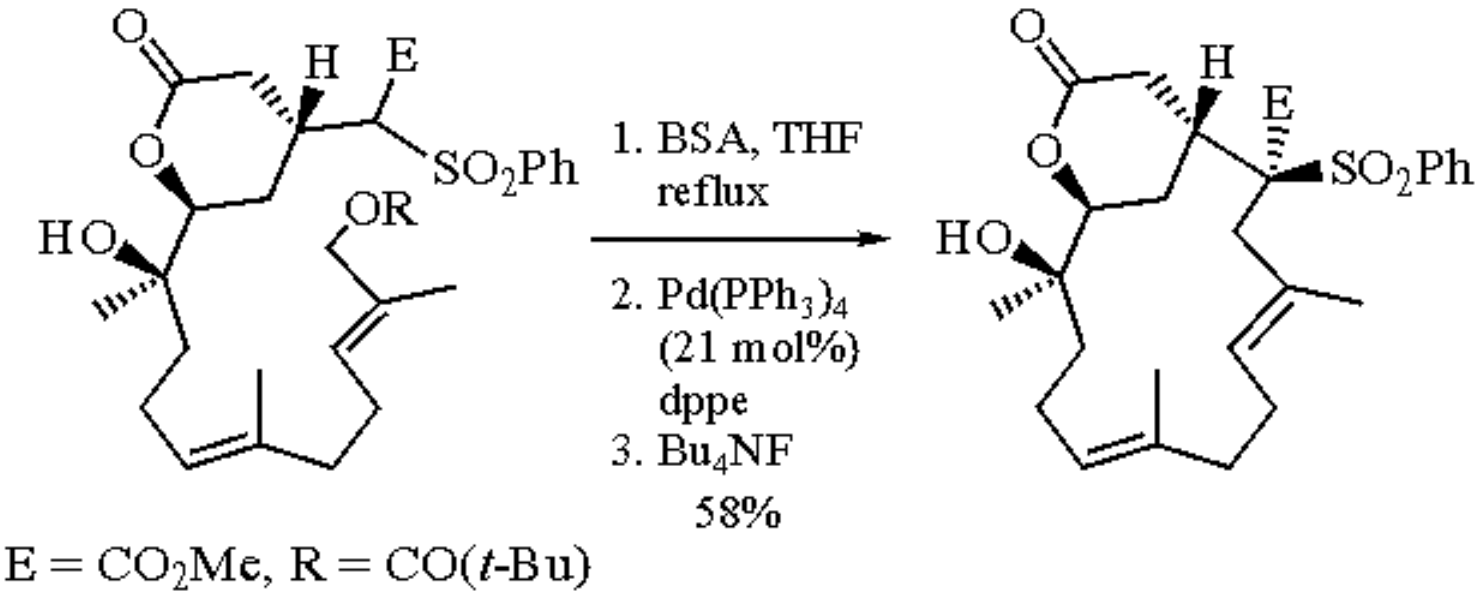

(11)

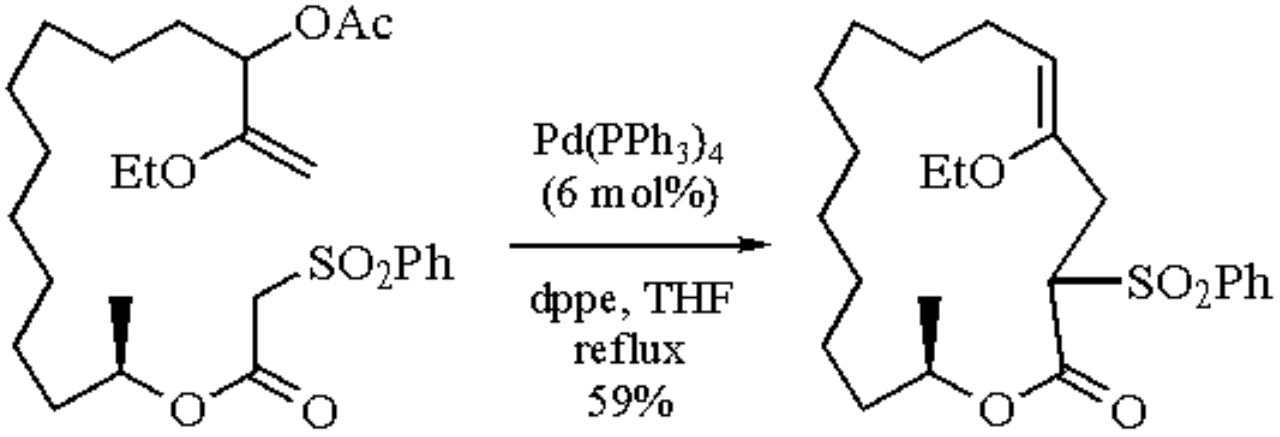

(12)

1. (a) Trost, B. M.; Chan, D. M. T. *JACS* **1979**, *101*, 6429. (b) Trost, B. M.; Chan, D. M. T. *JACS* **1983**, *105*, 2315.
2. Trost, B. M.; Grese, T. A.; Chan, D. M. T. *JACS* **1991**, *113*, 7350.
3. Tamura, R.; Kato, M.; Saegusa, K.; Oda, D.; Egawa, T.; Yamamoto, T. *JOC* **1987**, *52*, 1642.
4. Tamura, R.; Kai, Y.; Kakihana, M.; Hayashi, K.; Tsuji, M.; Nakamura, T.; Oda, D. *JOC* **1986**, *51*, 4375.
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Bis(triphenylphosphine)copper(I) Borohydride[1]

$(Ph_3P)_2CuBH_4$

[16903-61-0] · $C_{36}H_{34}BCuP_2$ · Bis(triphenylphosphine)copper(I) Borohydride · (MW 602.97)

(selectively reduces acid chlorides to aldehydes,[2,4] tosyl- and trisylhydrazones to alkanes,[5] aldehydes and ketones to alcohols,[6] and aromatic azides to anilines[7])

Alternate Name: (tetrahydroborato)bis(triphenylphosphine)copper.

Physical Data: mp 172-174 °C (dec) (from $CHCl_3$/ether);[2] 177 °C (dec) (from $CHCl_3$/ethanol);[3] recrystallizing from benzene/ethanol gives a stable 1:1 complex with benzene, mp 187 °C (dec),[3] as white needles.

Solubility: sol THF, $CHCl_3$, CH_2Cl_2, benzene; slightly sol acetone; insol ether, ethanol, and water.

Form Supplied in: commercially available as a white solid, or is easily prepared.

Preparative Method: by adding ***Copper(I) Chloride*** to a stirring solution of 2 equiv of ***Triphenylphosphine*** in chloroform. Once the copper chloride is dissolved the mixture is treated with a suspension of ***Sodium Borohydride*** (1 equiv) in ethanol for at least 15 min to ensure complete reaction. The solution is washed with water and dried over anhydrous magnesium sulfate. Diethyl ether is added to precipitate the reagent as fine white needles (90% yield).[2]

Purification: can be recrystallized from $CHCl_3$/ether or $CHCl_3$/ethanol mixtures.

Handling, Storage, and Precautions: stable to air and water. It should be handled in a well-ventilated hood; contact with the eyes and skin should be avoided.

Reductions of Acid Chlorides to Aldehydes.

Bis(triphenylphosphine)copper(I) borohydride selectively reduces many acid chlorides to aldehydes (eq 1) in good yields (Table 1).[2,4a] Acetone is the best solvent for these reductions, and addition of 2 equiv of triphenylphosphine to the reaction mixture increases yields. It is thought that 1 equiv binds to the bis(triphenylphosphine)copper(I) chloride byproduct and the second equiv traps the BH_3 given off in the reaction.[4a] Formation of an acylphosphonium salt as an intermediate in the reduction has also been postulated.[4c]

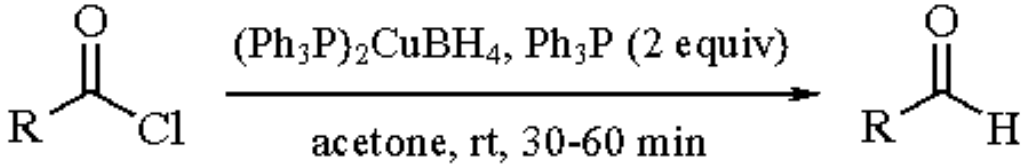

(1)

Table 1 Reduction of Acid Chlorides to Aldehydes with Bis(triphenylphosphine)copper(I) Borohydride (eq 1)

Acid chloride	Aldehyde	Yield (%)
Benzoyl	Benzaldehyde	78 83
Cinnamoyl	Cinnamaldehyde	77 78
4-Nitrobenzoyl	4-Nitrobenzaldehyde	57
Pivaloyl	Pivaldehyde	60
4-Chlorobenzoyl	4-Chlorobenzaldehyde	80
Decanoyl	Decanal	79
Cyclohexanecarbonyl	Cyclohexanecarbaldehyde	72
a-Acetoxypropionyl	a-Acetoxypropionaldehyde	23
Crotonyl	Crotonaldehyde	33

Reduction of *p*-Toluenesulfonylhydrazones (Tosylhydrazones) and 2,4,6-Triisopropylbenzenesulfonylhydrazones (Trisylhydrazones) to Alkanes.

The reduction of aldehydes and ketones to the corresponding alkanes can be achieved via the *p*-toluenesulfonylhydrazone derivative using the title reagent.[5] Tosylhydrazones of ketones (eq 2) are reduced consistently in good yield and tosylhydrazones of aldehydes are reduced in slightly lower yields (Table 2).[5a] The *p*-toluenesulfonylhydrazones derived from aromatic and α,β-unsaturated aldehydes and ketones cannot be reduced by this method. Sterically hindered hydrazones such as camphor tosylhydrazone are also reduced only with difficulty and in low yields.

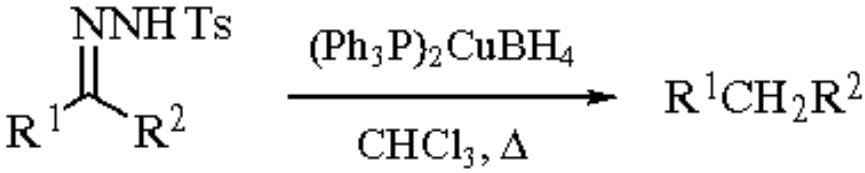

(2)

Table 2 The Reduction of Tosylhydrazones Using Bis(triphenylphosphine)copper(I) Borohydride (eq 2)

Tosylhydrazone of	Product	Yield (%)[a]
Cholestanone	Cholestane	70
Adamantanone	Adamantane	84
4-*t*-Butylcyclohexanone	4-*t*-Butylcyclohexane	74
Palmitaldehyde	Hexadecane	48
Nonanal	Nonane	56
4-Nitrobenzaldehyde	4-Nitrotoluene	0
Cinnamaldehyde	Allylbenzene	0
Camphor	Camphane	0

[a] Yield determined by GLC analysis.

A typical procedure involves mixing an equimolar ratio of the hydrazone and bis(triphenylphosphine)copper(I) borohydride in refluxing chloroform; benzene, toluene, and acetone may also be used. The reaction is usually complete in 2 h. Excess triphenylphosphine does not improve yields, as is the case for the reduction of acid chlorides to aldehydes. The reductions of 2,4,6-triisopropylbenzene (trisyl) hydrazones proceed in only moderate yields at rt. Increased temperature reduces the yields of trisylhydrazone reductions.

The reduction of a tosylhydrazone using this reagent has been performed in the synthesis of naturally occurring 12-tridecanolide (eq 3).[5b] The reduction of an aldehyde to the corresponding alkane via the tosylhydrazone, in the presence of other reducible and sensitive functional groups, has been demonstrated in the conversion of the 16-membered macrolide antibiotic tylosin to 20-dihydro-20-deoxytylosin (eq 4).[5c]

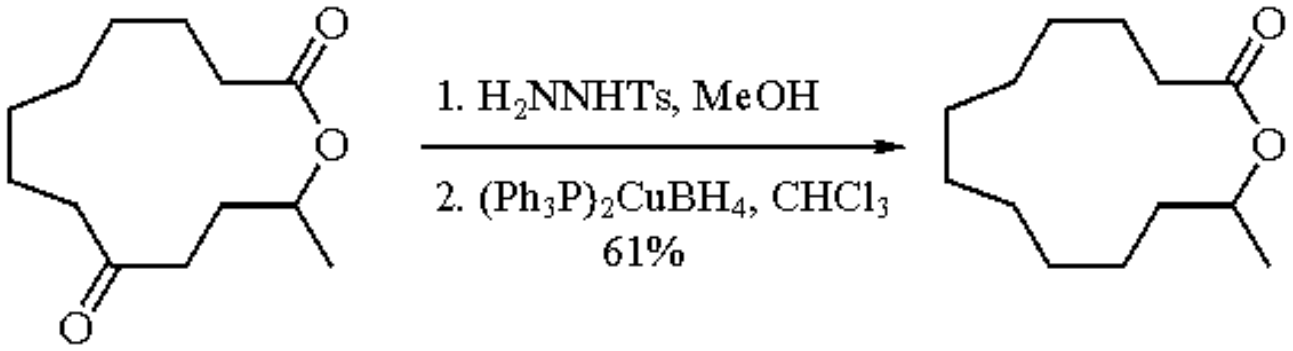

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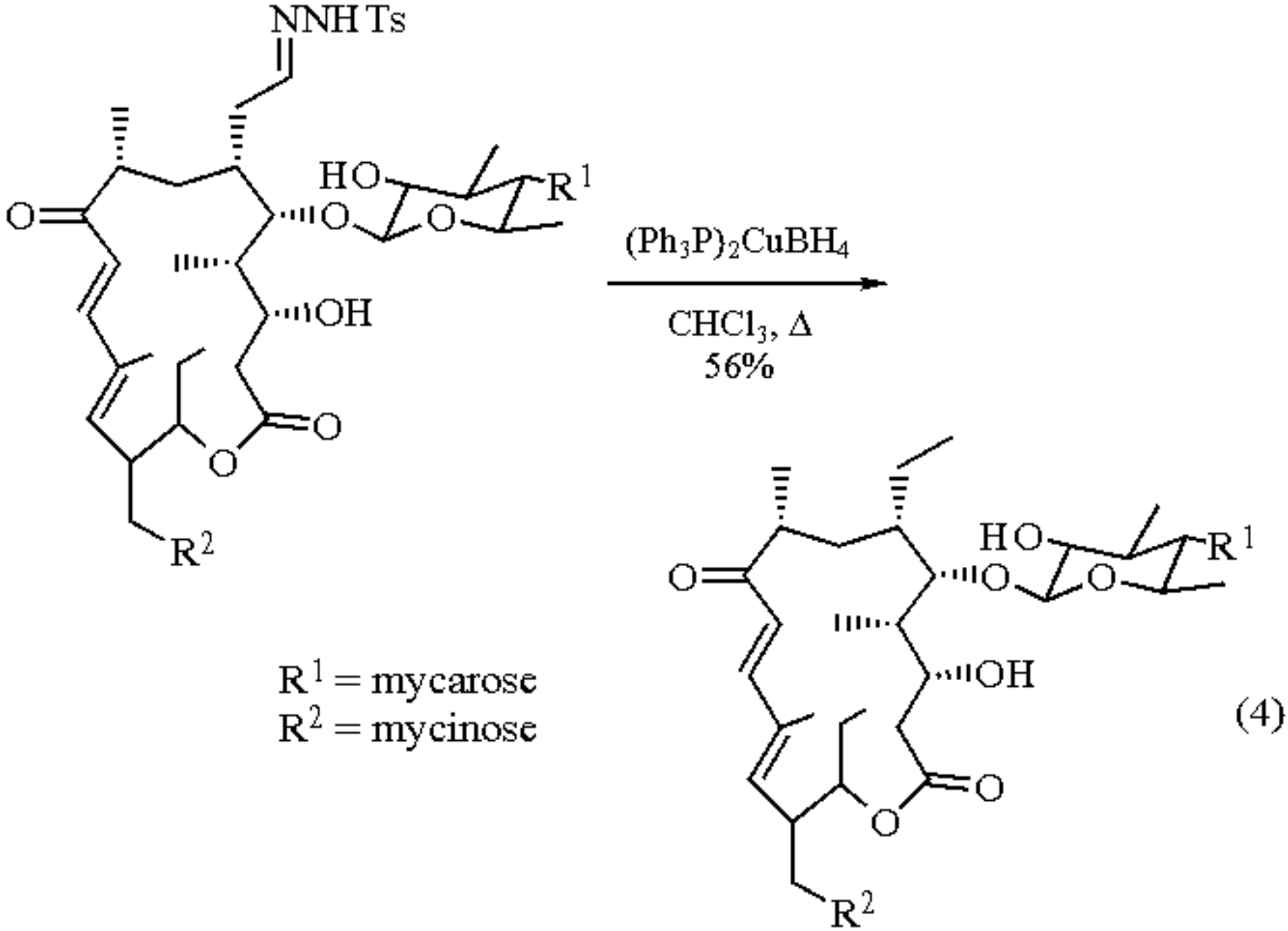

Reduction of Ketones and Aldehydes to Alcohols.

Strong acid-catalyzed reduction of aldehydes and ketones with the title reagent can be carried out with high chemo- and stereoselectivity.[6] While aldehydes were not reduced at room temperature in acetone under neutral conditions by using bis(triphenylphosphine)copper(I) borohydride, aromatic aldehydes such as 4-nitrobenzaldehyde containing strong electron-withdrawing groups were reduced quantitatively in chloroform or dichloromethane in the absence of a catalyst. In the presence of a strong acid catalyst, however, aldehydes and ketones are generally reduced (eq 5) in high yield to the corresponding alcohol (Table 3).[6]

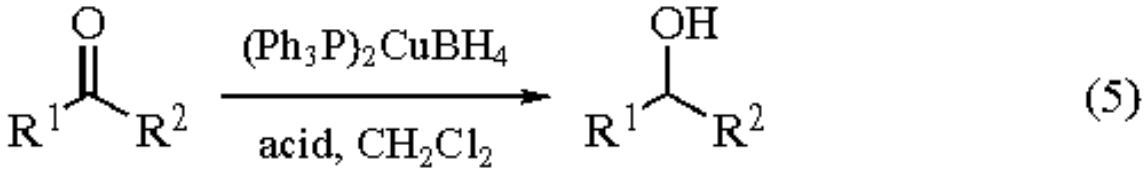

Table 3 Representative Acid-Catalyzed Reductions of Aldehydes and Ketones with Bis(triphenylphosphine)copper(I) Borohydride (eq 5)

Carbonyl compound	Acid	Equivalents of $(Ph_3P)_2CuBH_4$	Product	Yield (%)
4-*t*-Butylcyclohexanone	HCl (g)	1	4-*t*-Butylcyclohexanol	91 (94% *trans*)
	0.3 $AlCl_3$	1		92 (92% *trans*)
3,3,5-Trimethylcyclohexanone	$AlCl_3$	1.5	3,3,5-Trimethylcyclohexanol	86 (72% *trans*)
Camphor	HCl (g)	1	Isoborneol	0
	$2AlCl_3$	2		73 (98% *exo*)
Nonanal	HCl (g)	1	Nonanol	94
4-Nitrobenzaldehyde	none	1	4-Nitrobenzylalcohol	98
Cinnamaldehyde	HCl (g)	1	Cinnamyl alcohol	99
Cyclohexenone	HCl (g)	1		0

Typical conditions necessary to effect the reduction of aldehydes and ketones is to bubble gaseous hydrogen chloride through a dichloromethane solution of the carbonyl compound and 1 equiv of bis(triphenylphosphine)copper(I) borohydride at room temperature for 10 min. Sterically hindered ketones are not reduced under these conditions. A strong Lewis acid such as ***Aluminum Chloride***, however, will catalyze the high yield reduction of hindered ketones such as camphor and 3,3,5-trimethylcyclohexanone. The steric size of the reductant contributes to its good stereoselectivity in the reduction of ketones. α,β-Unsaturated aldehydes are easily reduced under these conditions to the primary allylic alcohol, but α,β-unsaturated ketones give complex mixtures of products.

Reduction of Aromatic Azides to Anilines.

Bis(triphenylphosphine)copper(I) borohydride can be used as an alternative reagent to ***1,3-Propanedithiol*** for the selective reduction of aromatic azides to aromatic amines.[7] One equiv of the reducing agent in chloroform at rt reduces aromatic azides in good yields (eq 6). Aromatic rings substituted with electron-withdrawing groups are reduced in 30 min, while aromatic rings substituted with electron-donating groups are reduced more slowly (Table 4).[7] The rates of these reductions increase in refluxing chloroform or in the presence of an acid catalyst. Aliphatic azides are not affected under the conditions necessary to reduce the more activated aromatic azides.

$$ArN_3 \xrightarrow[CHCl_3,\ rt]{(Ph_3P)_2CuBH_4} ArNH_2 \qquad (6)$$

Table 4 The Reduction of Aromatic Azides to Aromatic Amines with Bis(triphenylphosphine)copper(I) Borohydride (eq 6)

Azide/amine	Reaction time (h)	Yield (%)
4-Nitrophenyl	0.5	95
2-Nitrophenyl	0.5	83
4-Methyl-3-nitrophenyl	3	74
4-(Phenylazo)phenyl	14	69
4-Ethoxycarbonylphenyl	18	85

Related Reagents.

Lithium Tri-t-butoxyaluminum Hydride; ***Sodium Borohydride***.

---

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2. Fleet, G. W. J.; Harding, P. J. C. *TL* **1979**, 975.
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5. (a) Fleet, G. W. J.; Harding, P. J. C.; Whitcombe, M. J. *TL* **1980**, *21*, 4031. (b) Stach, H.; Hesse, M. *HCA* **1986**, *69*, 1614. (c) Ganguly, A. K.; Liu, Y.-T.; Sarre, O. *CC* **1983**, 1166.
6. Fleet, G. W. J.; Harding, P. J. C. *TL* **1981**, *22*, 675.
7. Clarke, S. J.; Fleet, G. W. J.; Irving, E. M. *JCR(S)* **1981**, 17.

David A. Barda

Bis(triphenylphosphine)copper(I) Cyanoborohydride

$(Ph_3P)_2CuBH_3CN$

[51321-47-2] · $C_{37}H_{33}BCuNP_2$ · Bis(triphenylphosphine)copper(I) Cyanoborohydride · (MW 627.98)

(selective, mild reducing reagent for the conversion of acid chlorides to aldehydes under neutral conditions, and reduction of aldehydes and ketones to alcohols in acidic media)

Alternate Name: μ-bis(cyanotrihydroborato)tetrakis(triphenylphosphine)dicopper(I).

Physical Data: white, nonhydroscopic solid, mp 176-177 °C; exists as a dimer.[1]

Solubility: sol acetone, $CHCl_3$, and THF; insol water, ethanol, and ether.

Preparative Method: from treating ***Copper(II) Sulfate*** or ***Copper(I) Chloride*** sequentially with excess ***Triphenylphosphine*** and ***Sodium Cyanoborohydride*** in ethanol.[2] The reagent is synthesized in an analogous manner to those described for the preparation of the corresponding BH_4 derivative, ***Bis(triphenylphosphine)copper(I) Borohydride***, substituting $NaBH_3CN$ for $NaBH_4$.[3]

Functional Group Reductions.

Under neutral conditions this reagent selectively reduces alkyl and aryl acid chlorides to aldehydes without further conversion to alcohols (Table 1).[2]

Table 1 Reduction of Acid Chlorides to Aldehydes in Acetone

Acid chloride	Aldehyde (% yield)
PhCOCl	84
p-ClC_6H_4COCl	92
p-$NO_2C_6H_4COCl$	48
$Me(CH_2)_8COCl$	82
PhCH=CHCOCl	61

In acidic (pH 3) media, aldehydes and ketones (except diaryl) are reduced to alcohols (Table 2). Reduction of 4-*t*-butylcyclohexanone under these conditions provides the *trans* isomer with 94:6 selectivity (eq 1).[2] The stereoselectivity of this reduction is among the highest observed for hydride reagents.[4]

Table 2 Reduction of Aldehydes and Ketones to Alcohols in Acidic THF (pH 3)

Carbonyl compound	Alcohol (% yield)
o-ClC_6H_4CHO	77
m-$NO_2C_6H_4CHO$	83
$Me(CH_2)_8CHO$	84
$MeCO(CH_2)_5Me$	74
PhCOMe	68
Ph_2CO	32

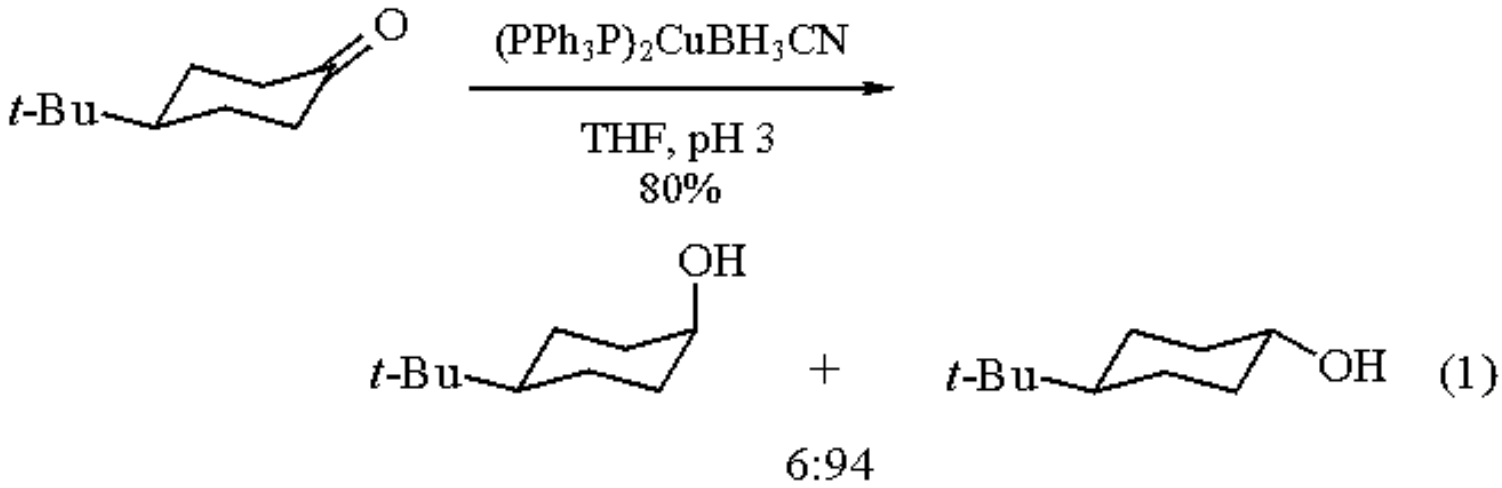

The ease and convenience of conducting reactions coupled with the excellent chemoselectivity possible under neutral conditions recommend this reagent for conversion of acid chlorides to aldehydes. No other functional groups are known to be reduced at ambient temperature.

Related Reagents.

Bis(triphenylphosphine)copper(I) Borohydride.

---

1. Melmed, K. N.; Li, T.; Mayerle, J. J.; Lippard, S. J. *JACS* **1974**, *96*, 69.
2. Hutchins, R. O.; Markowitz, M. *TL* **1980**, *21*, 813.
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4. (a) Review of stereochemistry of hydride reductions of ketones: Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53. (b) The same high selectivity for the *trans* isomer (*trans/cis* 94/6) is observed with $(Ph_3P)_2CuBH_4$ in acidic media: Fleet, G. W. J.; Harding, P. J. C. *TL* **1981**, *22*, 675.

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Bis(triphenylphosphine)nickel(0)[1]

$Ni(PPh_3)_2$

[33991-60-5] · $C_{36}H_{30}NiP_2$ · Bis(triphenylphosphine)nickel(0) · (MW 538.27)

(source of nickel(0) useful for the formation of carbonates from epoxides[2] and the coupling of alkenyl boranes with allylic epoxides[3])

Physical Data: mp 155-157 °C dec. (N_2).

Solubility: sol benzene, toluene, MeCN, THF.

Analysis of Reagent Purity: ^1H NMR: (C_6D_6) δ 7.67 (m), 7.13 (m); ^{31}P NMR: (C_6D_6) δ -22 ppm from $(MeO)_3PO$.

Preparative Methods: by the ***Sodium Amalgam*** reduction of ***Dibromobis(triphenylphosphine)nickel(II)***.[4] In the standard preparation, 22.3 g of $Ni(PPh_3)_2Br_2$ were added to a mixture of sodium amalgam (1.73 g Na, 0.075 g-atom in 300 mL Hg) and 500 mL acetonitrile. After removal of Hg and solvent, the precipitate was dissolved in benzene to remove the insoluble Hg occluded NaBr. Concentration of the dark brown benzene solution in vacuo gave 13-15 g of red-brown $Ni(PPh_3)_2$ (74-84%) which could be used without further purification. Optional recrystallization from benzene (or toluene)/hexane is possible but significant loss of the product occurs due to high solubility. Sodium amalgam reductions of similar systems have been problematic and ***n-Butyllithium*** was found to be a superior reducing agent.[5]

Handling, Storage, and Precautions: highly oxygen sensitive. Special inert-atmosphere techniques must be used.[6] Should be stored at 0 °C.

Reactions of Epoxides.

Bis(triphenylphosphine)nickel(0), $Ni(PPh_3)_2$, can react with epoxides by oxidative addition of Ni^0 into the strained C-O bond. Insertion of CO_2 into these organonickel complexes leads to alkenyl carbonates. Thus reaction of 1-chloro-2,3-epoxypropane (**1**) with $Ni(PPh_3)_2$ in the presence of CO_2 catalytically produced chloromethylene carbonate (**2**) in good yield (eq 1).[2]

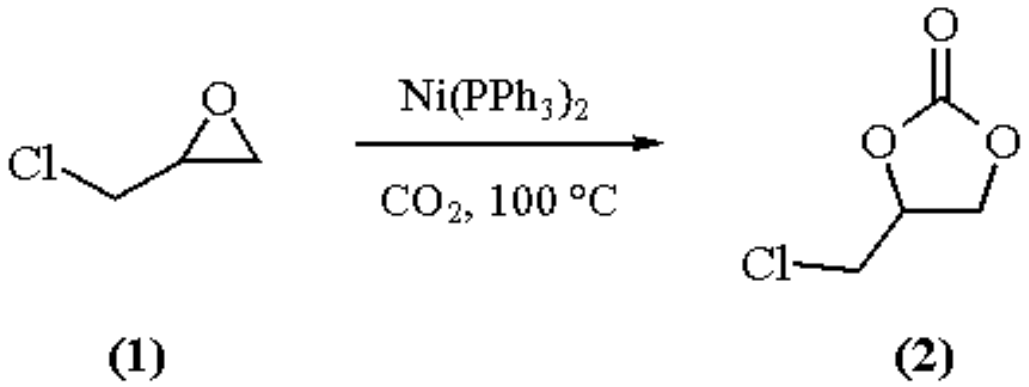

(1)

Alkenylboranes also react with these organonickel complexes to give alcohols in overall catalytic coupling reactions. When the hexenylborane (**3**) was reacted with 3,4-epoxy-1-butene (**4**) and the catalyst, a mixture of the two coupling products (**5**) and (**6**) was produced in 85% yield (eq 2).[3] The regioselectivity of the reaction was found to depend upon the nature of the catalyst used. When metal complexes such as ***Bis(dibenzylideneacetone)palladium(0)***, ***Tetrakis(triphenylphosphine)palladium(0)***, or $Ni(PPh_3)_n$ were used the predominant product was (**5**), whereas when ***Palladium(II) Chloride*** or ***Nickel(II) Acetylacetonate*** were used the formation of (**6**) was favored. Overall, the palladium complexes proved to be superior catalysts for this transformation. The best yield (92%) was obtained using $Pd(dba)_2$.

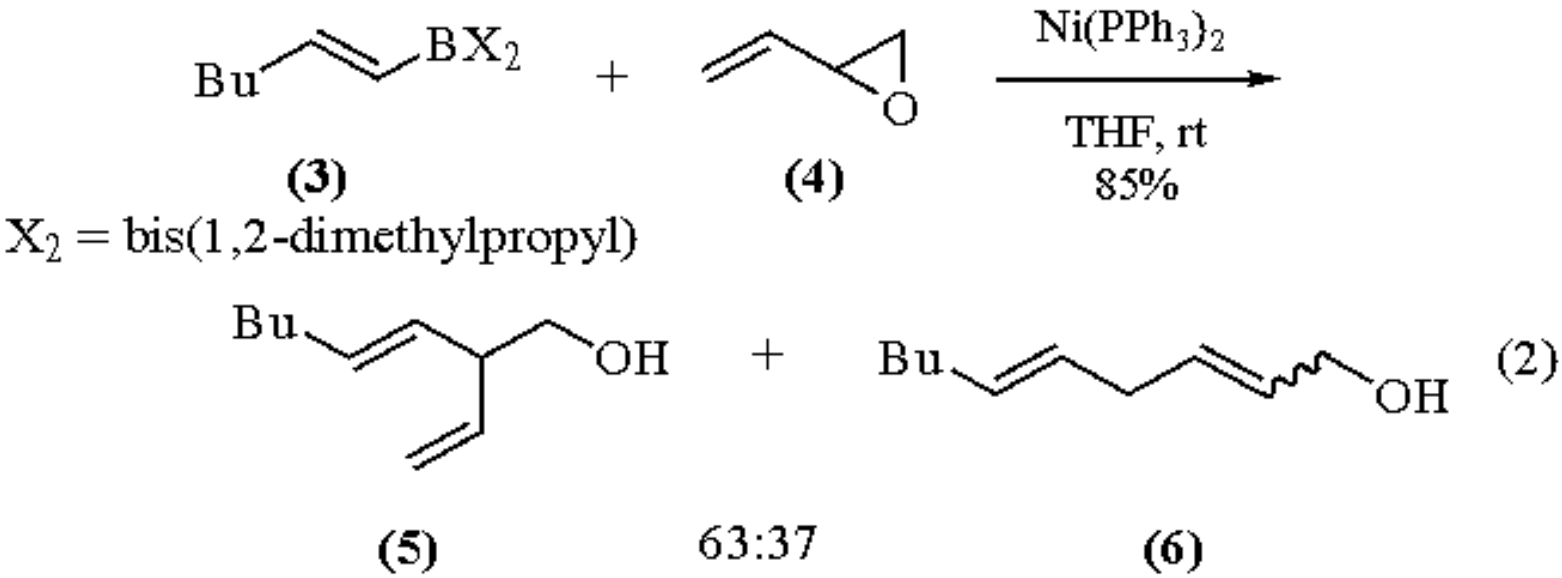

Other Uses.

Allene has been cyclooligomerized in the presence of a catalytic amount of $Ni(PPh_3)_2$ into a mixture of isomers with a cyclic pentamer being the major product.[4] The linear dimerization of ethylene and propene also takes place when this nickel complex along with ***Diethylaluminum Chloride*** is used as the catalytic system.[7]

Related Reagents.

Tetrakis(triphenylphosphine)nickel(0); ***Tris(triphenylphosphine)nickel(0)***.

1. Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*; Academic: New York, 1974; Vols. I and II.
2. De Pasquale, R. J. *JCS(C)* **1973**, 157.
3. Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *JOM* **1982**, *233*, C13.
4. De Pasquale, R. J. *JOM* **1971**, *32*, 381.
5. Millard, A. A.; Rathke, M. W. *JACS* **1977**, *99*, 4833.
6. Shriver, D. F. *The Manipulation of Air-Sensitive Compounds*; McGraw-Hill: New York, 1969.
7. (a) Furman, D. B.; Kudryashev, A. V.; Ivanov, A. O.; Pogorelov, A. G.; Yanchevskaya, T. V.; Bragin, O. V. *BAU* **1990**, 444. (b) Furman, D. B.; Ivanov, A. O.; Olenin, A. Y.; Vasil'kov, A. Y.; Munshieva, M. K.; Belyankin, A. Y.; Lisichkin, G. V.; Sergeev, V. A.; Bragin, O. V. *BAU* **1990**, 448.

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Bis(triphenylphosphine)palladium(II) Acetate

$Pd(PPh_3)_2(OAc)_2$

[14588-08-0] · $C_{40}H_{36}O_4P_2Pd$ · Bis(triphenylphosphine)palladium(II) Acetate · (MW 749.09)

(catalyst for various reactions, for example coupling reactions, dimerizations, cyclizations, carbonylations, and reductions)

Physical Data: lemon-yellow amorphous crystals; mp 136 °C (dec.).

Solubility: sol acetonitrile, benzene, dioxane, DMF, DMSO, THF; low sol petroleum ether.

Form Supplied in: commercially available solid.

Handling, Storage, and Precautions: store under argon at -18 °C; air and moisture sensitive; hygroscopic.

General Considerations.

This reagent has mainly been used in coupling reactions and cyclizations, but also for reductions, and carbonylations. Although commercially available, the catalyst is easily prepared by mixing ***Palladium(II) Acetate*** with an excess of ***Triphenylphosphine*** in benzene.[1] There is also evidence that mixing $Pd(OAc)_2$ with 2 equiv of PPh_3 generates a species with the same properties as $Pd(OAc)_2(PPh_3)_2$ (**1**). In most catalytic reactions, complex (**1**) generates Pd^0 in situ, which is the active catalyst.[2] Reagents able to do similar reactions as (**1**) are described in the following text.

Coupling and Dimerization Reactions.

Catalyst (**1**) has been used to couple and dimerize many types of substrates. For example, isoprene in the presence of (**1**), ***Formic Acid***, ***Triethylamine*** and an alcohol dimerizes to generate predominantly 1,6-diene (**2**) and 1,7-diene (**3**) (eq 1). The formic acid serves as a hydrogen donor. These two isomers were used to prepare the terpenes α,β-citronellol and linalool.[3] Under similar reaction conditions, alkynes react with iodobenzene to give alkenes.[4]

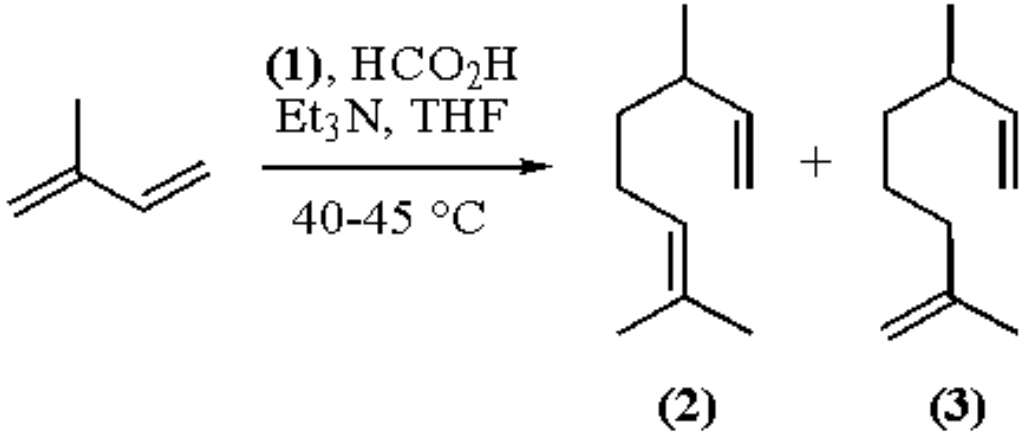

(1)

Although the most commonly used catalyst for Heck arylation and vinylation reactions[5] is $Pd(OAc)_2$, there are several examples where (**1**) has been used. For example, 2-bromopropene reacts with styrene (eq 2)[6a] or phenylacetylene (eq 3)[6b] to yield dienes or enynes, respectively.

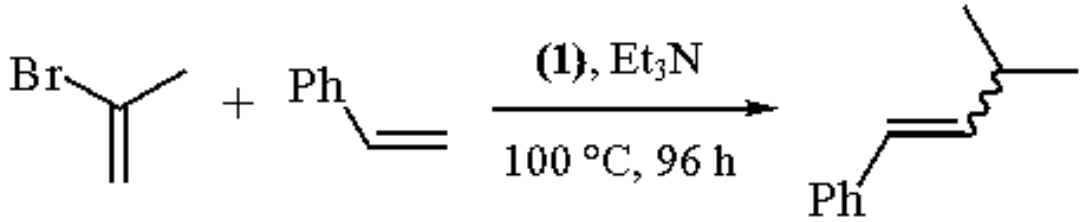

(2)

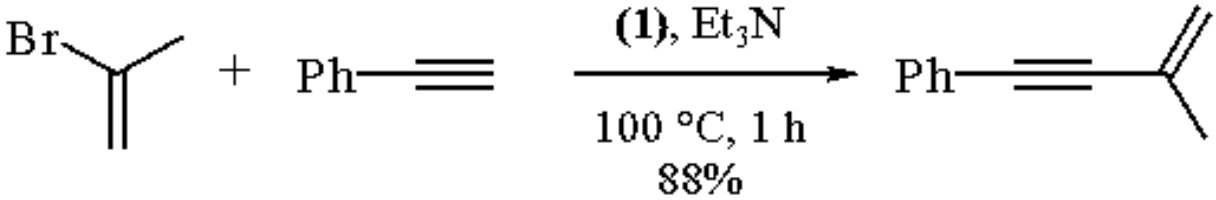

(3)

Reagent (**1**) catalyzes the coupling between fluorinated vinyl iodides and 1-alkynes to give excellent yields of fluorinated enynes.[7] The use of Dichlorobis(triphenyl-phosphine)palladium(II) (**4**) and ***Tetrakis(triphenylphosphine)palladium(0)*** as catalysts give similar results. Various substituted aryl bromides react with trimethylsilylacetylene in the presence of (**1**) to give terminal alkynes (eq 4).[8] In some cases, (**4**) has been used in place of (**1**). The corresponding aryl propargyl alcohols (which are easily converted to terminal alkenes) are made by ***Tetraethyl Pyrophosphate*** catalyzed cross-coupling of aryl halides with propargyl alcohol.[9]

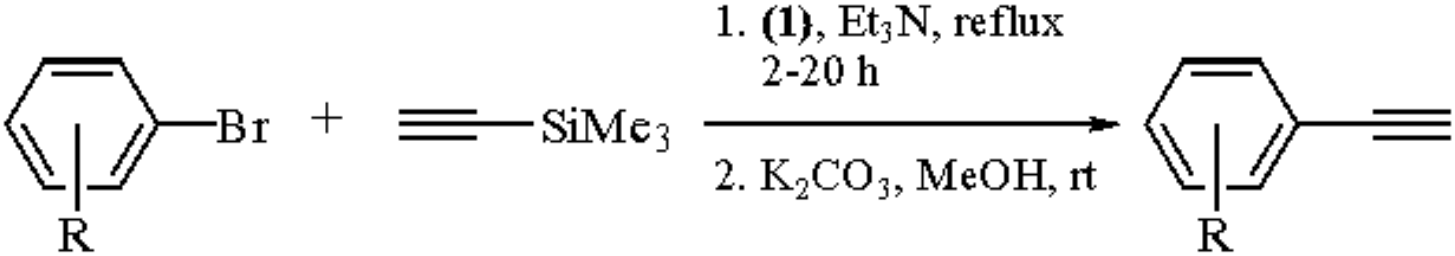

(4)

R = a variety of substituents

The coupling of aryl iodides with α,β-unsaturated ketones[10a,b] and aldehydes[10c] (eq 5) is catalyzed by (**1**). This reagent nicely catalyzes the coupling of vinyl and aryl triflates with various terminal alkynes in the presence of a base (eq 6).[11,12] Addition of *n*-Bu_4NCl increases the yield.

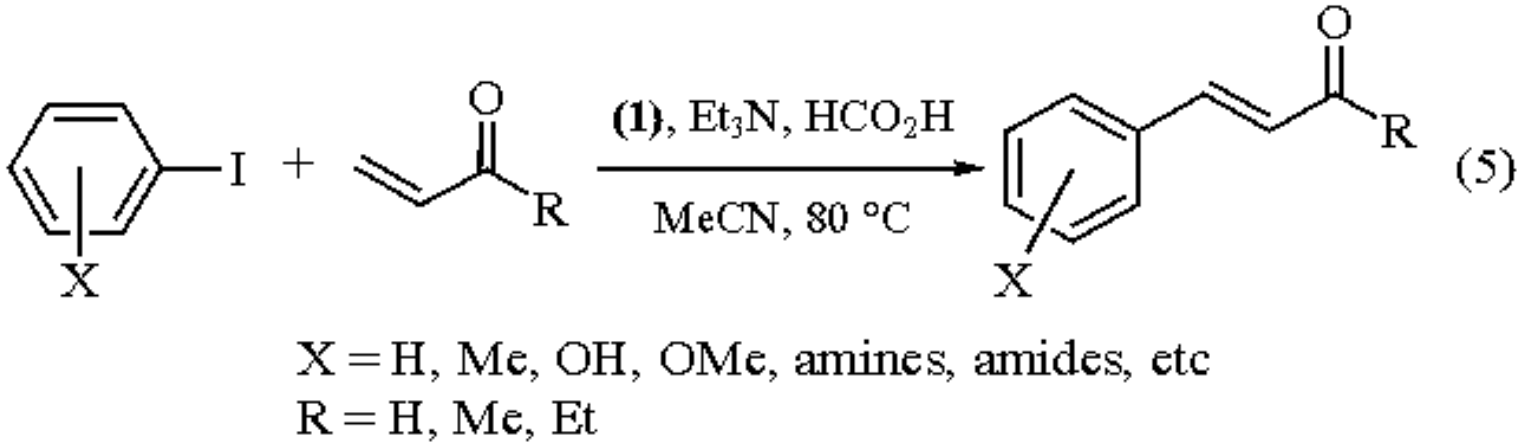

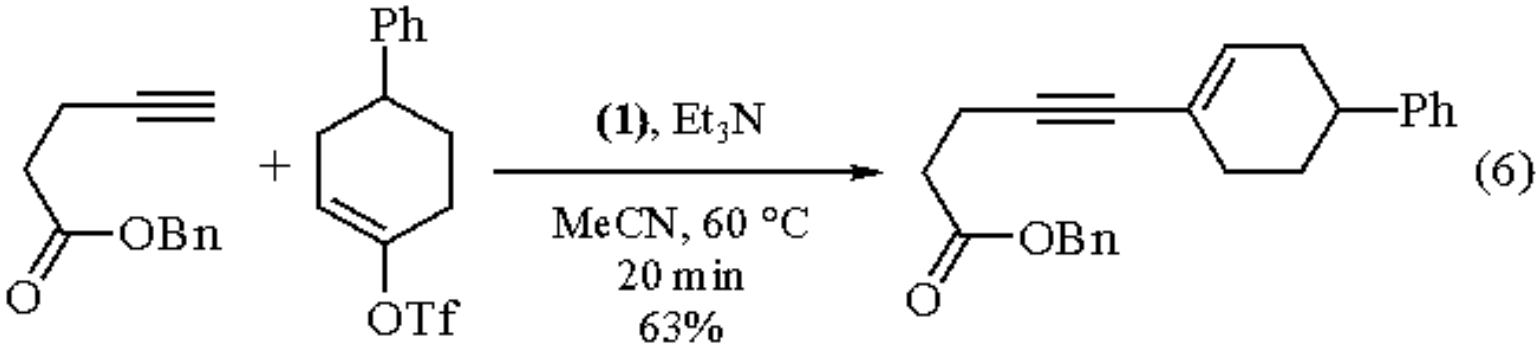

Cyclizations.

Complex (**1**) catalyzes the cyclization of 1,6-enynes to five-membered rings. Either 1,3- or 1,4-dienes are formed depending on the substituents (eqs 7 and 8).[13] When ***Diacetatobis(tri-o-tolylphosphine)palladium(II)*** is used the yield increases.

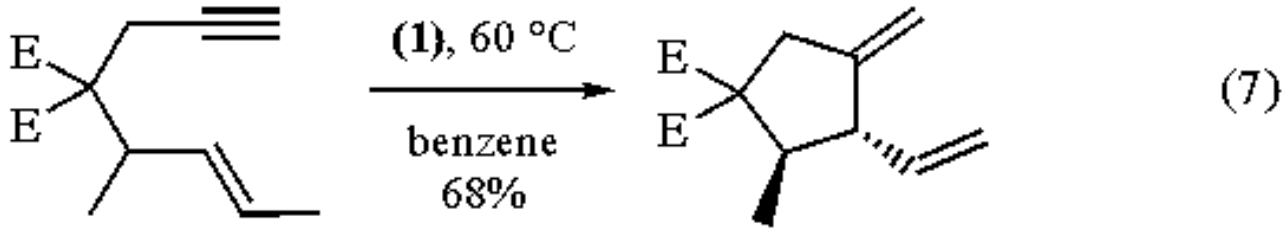

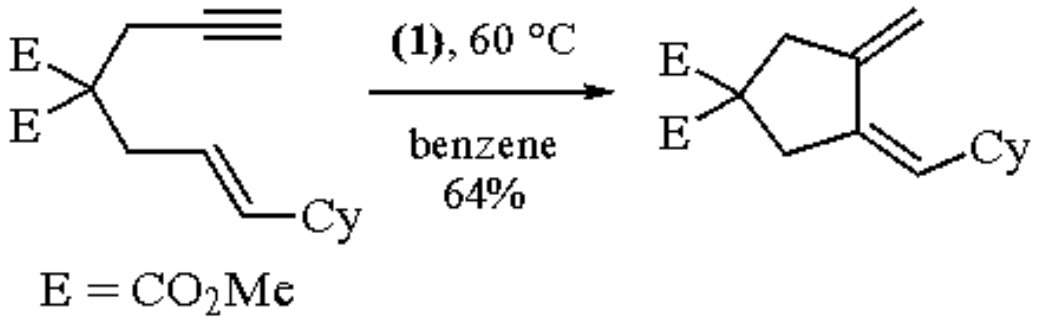

(8)

These cyclizations can be performed with full stereocontrol.[14] Functionalized butenolides are obtained with high stereo- and regioselectivity in a one-pot hydroarylation cyclization when α,β-alkynic esters are reacted in the presence of formic acid, ***Tri-n-butylamine***, and catalyst (**1**).[15]

Reductions.

Vinyl and aryl triflates are reduced in high yields with catalytic amounts of (**1**).[16] The reaction shown in eq 9 is used in a route to angelicin.[17]

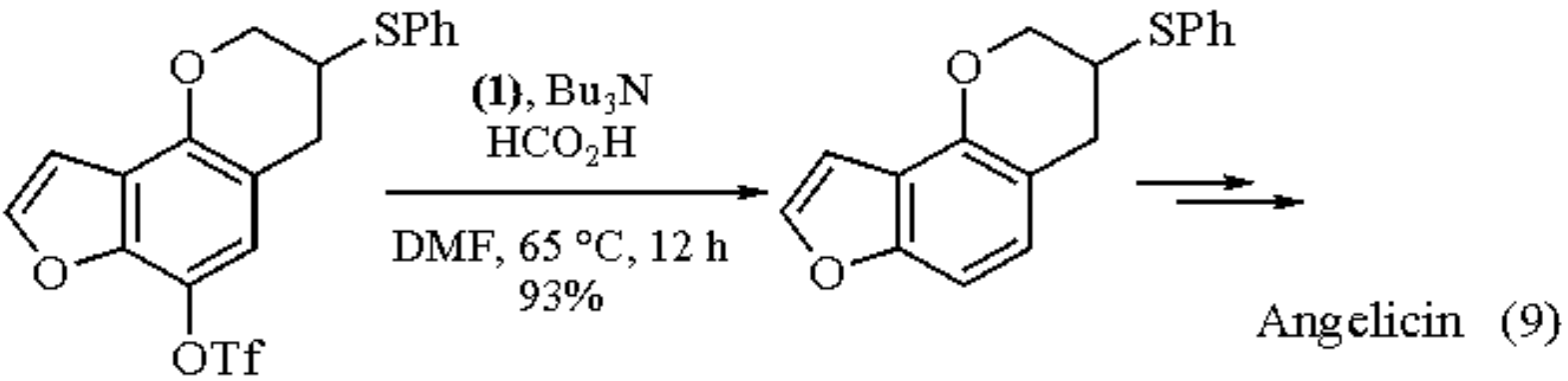

(9)

Carbonylations.

If ***Carbon Monoxide*** is present in place of formic acid, an insertion of a CO unit into the metal-carbon bond in the intermediate occurs to produce the corresponding acid. Vinyl alcohols and phenols, after conversion to triflates, undergo one-carbon homologation to the corresponding α,β-unsaturated and aromatic acids.[18] Vinyl triflates work best with the title catalyst, but with aryl triflates, better results are obtained with ***Palladium(II) Acetate*** and ***1,1´-Bis(diphenylphosphino)ferrocene*** (dppf) as an added ligand. Oxalic acid esters can be made from alcohols under 20-50 atm of CO employing (**1**) in stochiometric amounts (**4** gave no reaction).[19] The use of ***1,4-Benzoquinone*** as a reoxidant makes it possible to use (**1**) in catalytic amounts. For example, treatment of methanol with 1 mol % of (**1**) and carbon monoxide at a pressure of 1000 psi and 65 °C gives the methyl ester of oxalic acid in high yield.[20]

---

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(*R*)-3,3´-Bis(triphenylsilyl)binaphthomethylaluminum

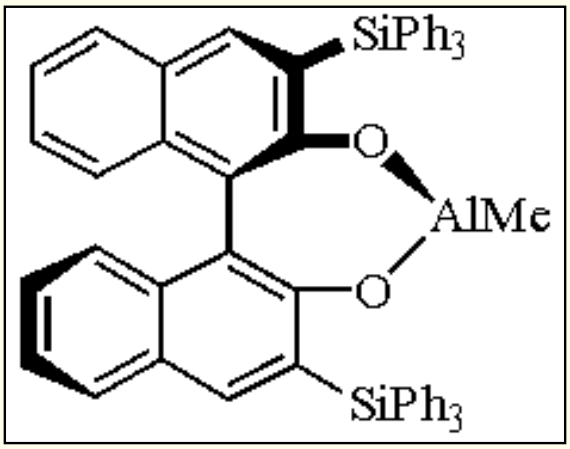

[118724-91-7] · $C_{57}H_{43}AlO_2Si_2$ · (*R*)-3,3´-Bis(triphenylsilyl)binaphthomethylaluminum · (MW 843.16)

(chiral Lewis acid for asymmetric hetero-Diels-Alder,[2,3] Diels-Alder,[6] and ene reactions,[7] Claisen rearrangement,[8,9] and polymerization[10])

Solubility: sol toluene and CH_2Cl_2; slightly sol hexane.

Form Supplied in: prepared and used in situ.

Preparative Methods: can be prepared by treatment of (*R*)-3,3´-bis(triphenylsilyl)binaphthol[1] in CH_2Cl_2 or toluene with a 1 M hexane solution of ***Trimethylaluminum*** room temperature for 1-2 h.[2] This reagent can be also generated in situ by discrimination of its racemates with optically active (-)-bromocamphor.[3]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Asymmetric Hetero-Diels-Alder Reaction.

This chiral organoaluminum reagent has been developed for effecting the hetero-Diels-Alder reaction of aldehydes and siloxydienes with high enantioselectivity.[2,4] Thus reaction of benzaldehyde with 1-methoxy-2-methyl-3-trimethylsiloxy-1,3-pentadiene under the influence of 10 mol % of the chiral aluminum reagent affords *cis*-dihydropyrone as a major product in 95% ee (eq 1). The enantioselectivity is highly dependent on the bulk of the triarylsilyl moiety of the aluminum reagent. Thus replacement of the triphenylsilyl group by the tris(3,5-xylyl)silyl

group enhances the enantio as well as *cis* selectivity, but replacement by trimethylsilyl groups lowers the enantioselectivity. This chiral aluminum reagent is generated in situ by discrimination of racemic organoaluminum reagents with (-)-bromocamphor by diastereoselective complexation, and utilized as a chiral Lewis acid for the asymmetric hetero-Diels-Alder reaction.[3]

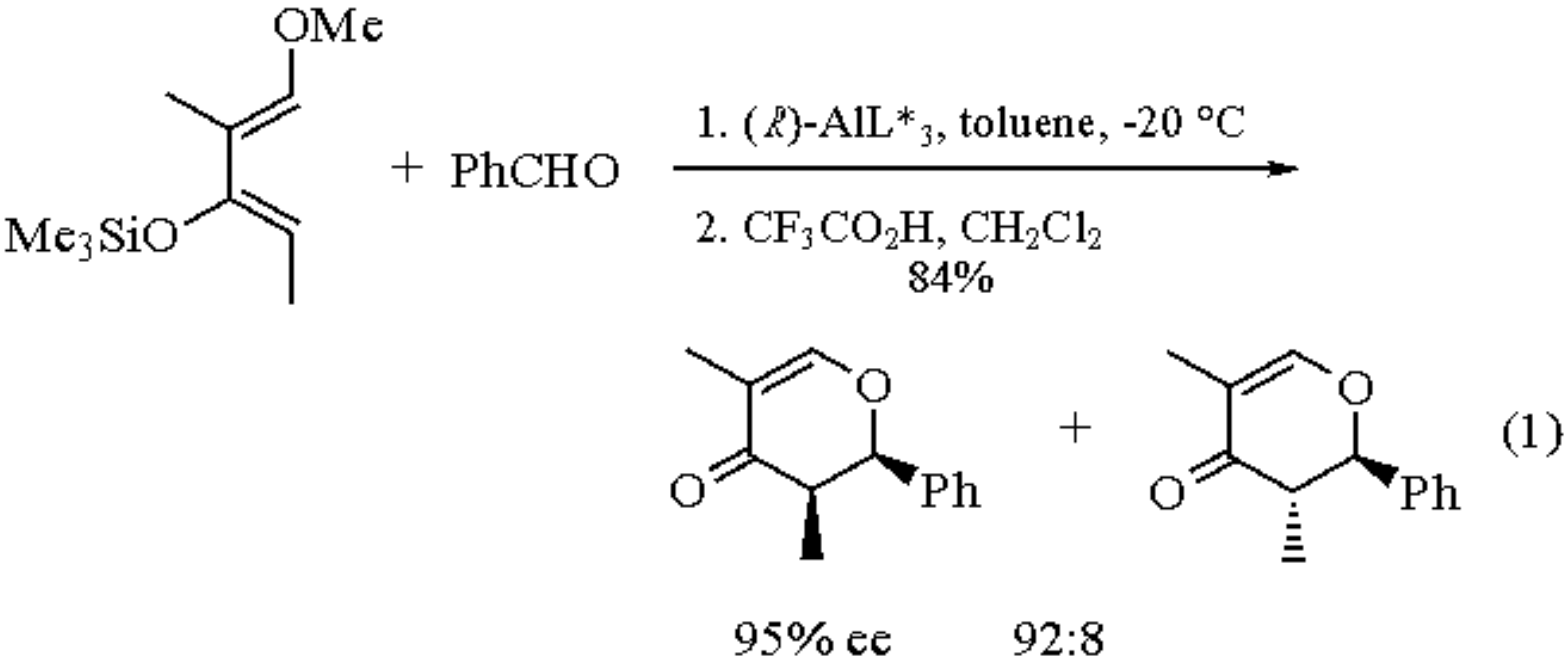

Asymmetric Diels-Alder Reaction.

Although the asymmetric Diels-Alder reaction of cyclopentadiene with methacrolein is quite disappointing (17-23% ee) with the chiral aluminum reagent,[5] the use of α,β-unsaturated esters as dienophiles gives good enantioselectivity (eq 2).[6]

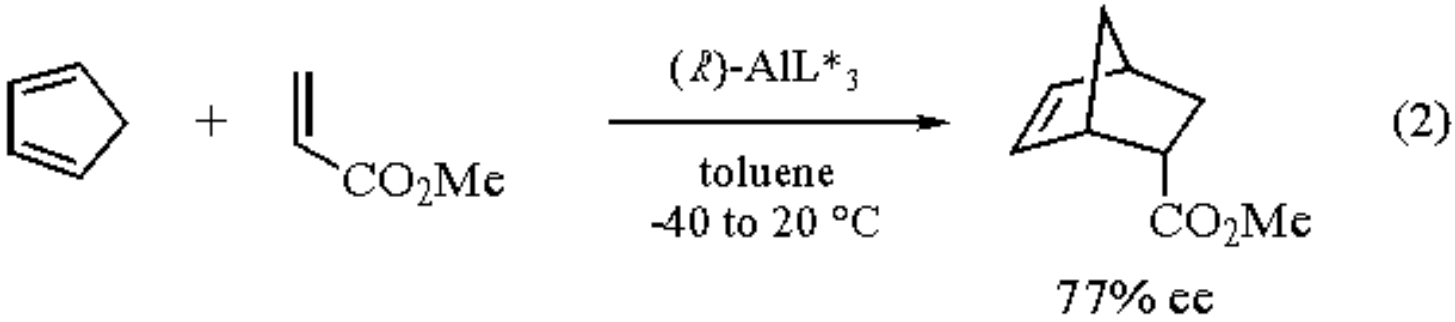

Asymmetric Ene Reaction.

The enantioselective activation of carbonyl groups with the chiral aluminum reagent also enabled the asymmetric ene reaction of electron-deficient aldehydes with various alkenes (eq 3).[7] In the presence of powdered 4 &AAring; molecular sieves, the chiral aluminum reagent can be utilized as a catalyst without loss of enantioselectivity.

(R)-3,3´-Bis(triphenylsilyl)binaphthomethylaluminum

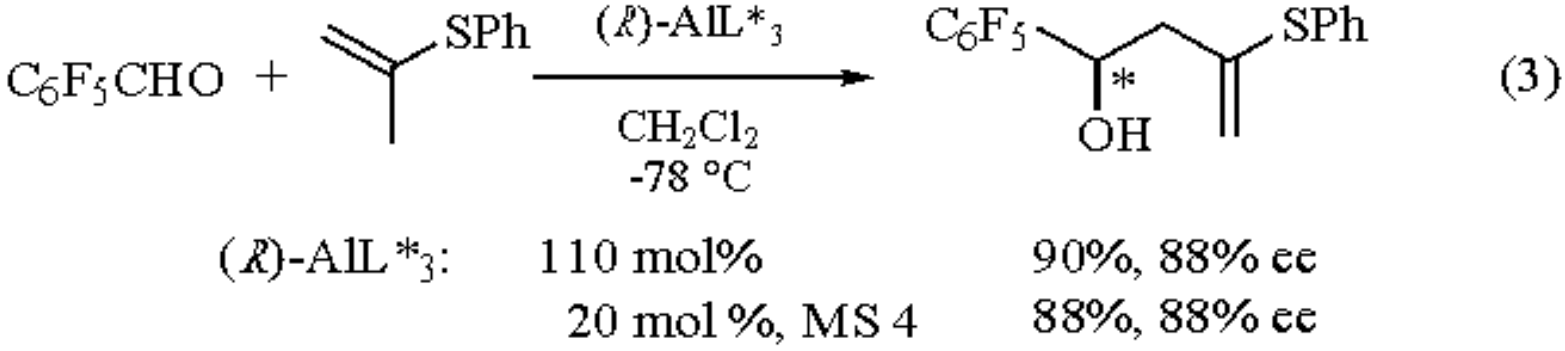

Asymmetric Claisen Rearrangement.

The enantioselective activation of an ether oxygen with the chiral organoaluminum reagent allows for the first example of the asymmetric Claisen rearrangement of allylic vinyl ethers.[8] This method provides a facile asymmetric synthesis of various acylsilanes and acylgermanes from allylic α-(trimethylsilyl)vinyl ethers and allylic α-(trimethylgermyl)vinyl ethers, respectively (eq 4). Among various trialkylsilyl substituents of the chiral aluminum reagent, use of the bulkier *t*-butyldiphenylsilyl group results in the highest enantioselectivity.

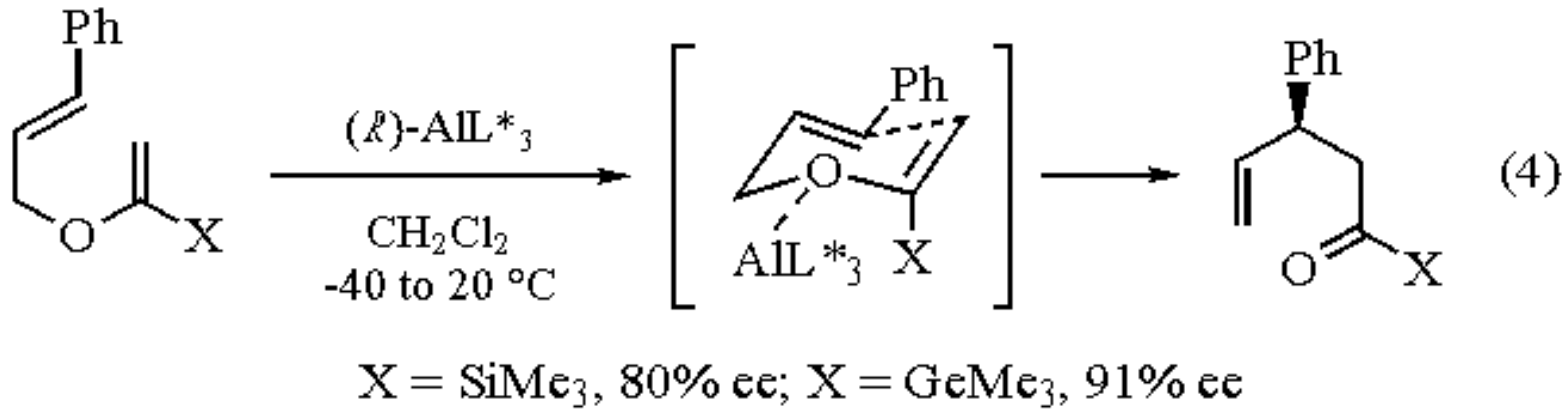

Notably, the asymmetric Claisen rearrangement of *cis*-allylic α-(trimethylsilyl)vinyl ethers with the chiral aluminum reagent produced optically active acylsilanes with the same absolute configuration as those from *trans*-allylic α-(trimethylsilyl)vinyl ethers (eq 5).[9]

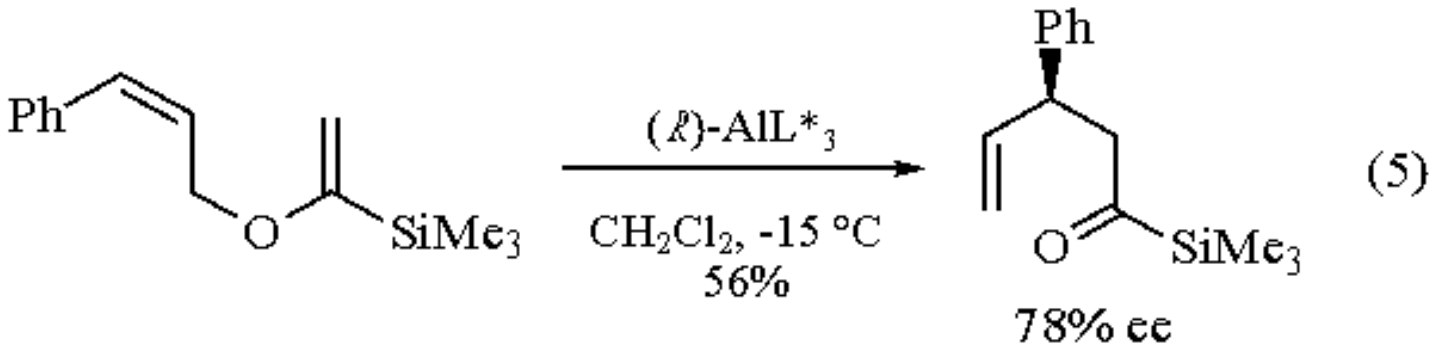

Asymmetric Polymerization.

(R)-3,3´-Bis(triphenylsilyl)binaphthomethylaluminum

The chiral organoaluminum catalyst is utilized for asymmetric polymerization of racemic α-methyl and β-methyl β-lactones.[10] Optically active polymers possessing negative optical rotation values are produced, suggesting that (*S*) enantiomers of racemic β-lactones are preferentially activated by the aluminum catalyst.

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9-Borabicyclo[3.3.1]nonane Dimer[1]

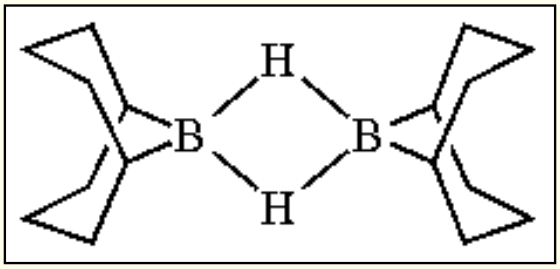

[70658-61-6] · $C_{16}H_{30}B_2$ · 9-Borabicyclo[3.3.1]nonane · (MW 244.03)

(highly selective, stable hydroborating agent;[1,3] anti-Markovnikov hydration of alkenes and alkynes;[1d] effective ligation for alkyl-, aryl-, allyl-, allenyl-, alkenyl- and alkynylboranes;[1a,4,5] forms stable dialkylboryl derivatives, borinate esters, and haloboranes;[1f] organoboranes from hydroboration and organometallic reagents;[1,5] precursor to boracycles;[1,11] can selectively reduce conjugated enones to allylic alcohols;[1a,30] organoborane derivatives for α-alkylation and arylation of α-halo ketones, nitriles, and esters;[1b] vinylation and alkynylation of carbonyl compounds;[1a,46] conjugate addition to enones;[1a,47] homologation; asymmetric reduction;[1,8] Diels-Alder reactions;[1a,18,50] enolboranes for crossed aldol condensations;[1a,20,52] Suzuki-Miyaura coupling[1a,54-57])

Alternate Name: 9-BBN-H.

Physical Data: mp 153-155 °C (sealed capillary); bp 195 °C/12 mmHg.[1,3]

Solubility: sparingly sol cyclohexane, dimethoxyethane, diglyme, dioxane (<0.1 M at 25 °C); sol THF, ether, hexane, benzene, toluene, CCl_4, $CHCl_3$, CH_2Cl_2, SMe_2 (ca. 0.2-0.6 M at 25 °C); reacts with alcohols, acetals, aldehydes, and ketones.[1,3]

Form Supplied in: colorless, stable crystalline solid; 0.5 M solution in THF or hexanes.

Analysis of Reagent Purity: the melting point of 9-BBN-H dimer is very sensitive to trace amounts of impurities. Recrystallization from dimethoxyethane is recommended for samples melting below 146 °C. The dimer exhibits a single ^{11}B NMR (C_6D_6) resonance at δ 28 ppm and ^{13}C NMR signals at 20.2 (br), 24.3 (t), and 33.6 (t) ppm.[1,3]

Handling, Storage, and Precautions: the crystalline 9-BBN-H dimer can be handled in the atmosphere for brief periods without significant decomposition. However, the reagent should be stored under an inert atmosphere, preferably below 0 °C. Under these conditions the reagent is indefinitely stable. In solution, 9-BBN is more susceptible both to hydrolysis and oxidation, and contact with the open atmosphere should be rigorously avoided. Many 9-BBN derivatives are pyrophoric and/or susceptible to hydrolysis so that individuals planning to use 9-BBN-H dimer should thoroughly familiarize themselves with the special techniques required for the safe handling of such reagents prior to their use.[1b] The reagent should be used in a

well-ventilated hood.

Organoboranes from 9-BBN-H.

First identified by Köster,[2] 9-BBN-H dimer is prepared from the cyclic hydroboration of 1,5-cyclooctadiene (eq 1).[3] As a dialkylborane, 9-BBN-H exhibits extraordinary steric- and electronic-based regioselectivities which distinguish these derivatives from the less useful polyhydridic reagents (Table 1).[4]

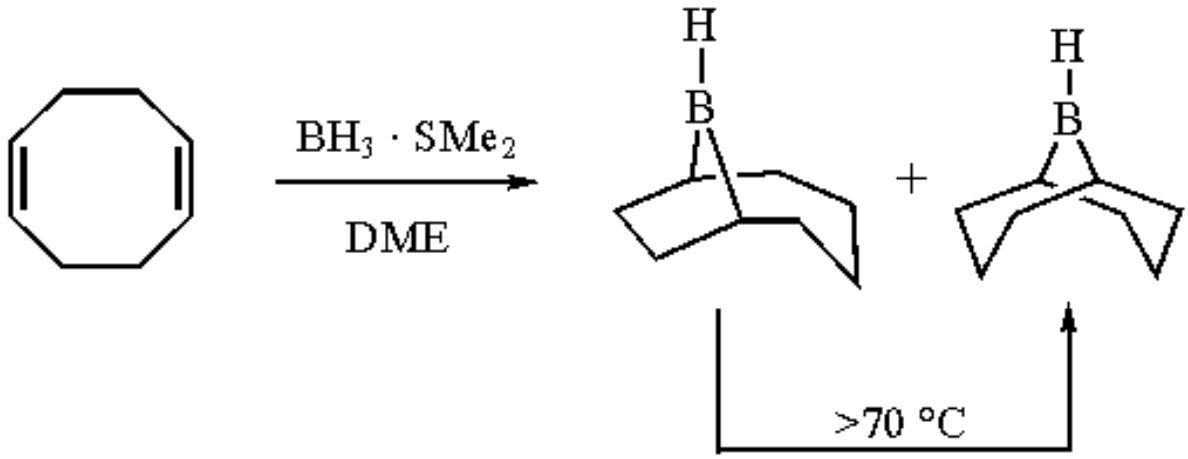

(1)

Table 1 Boron Atom Placement in the Hydroboration of Simple Alkenes

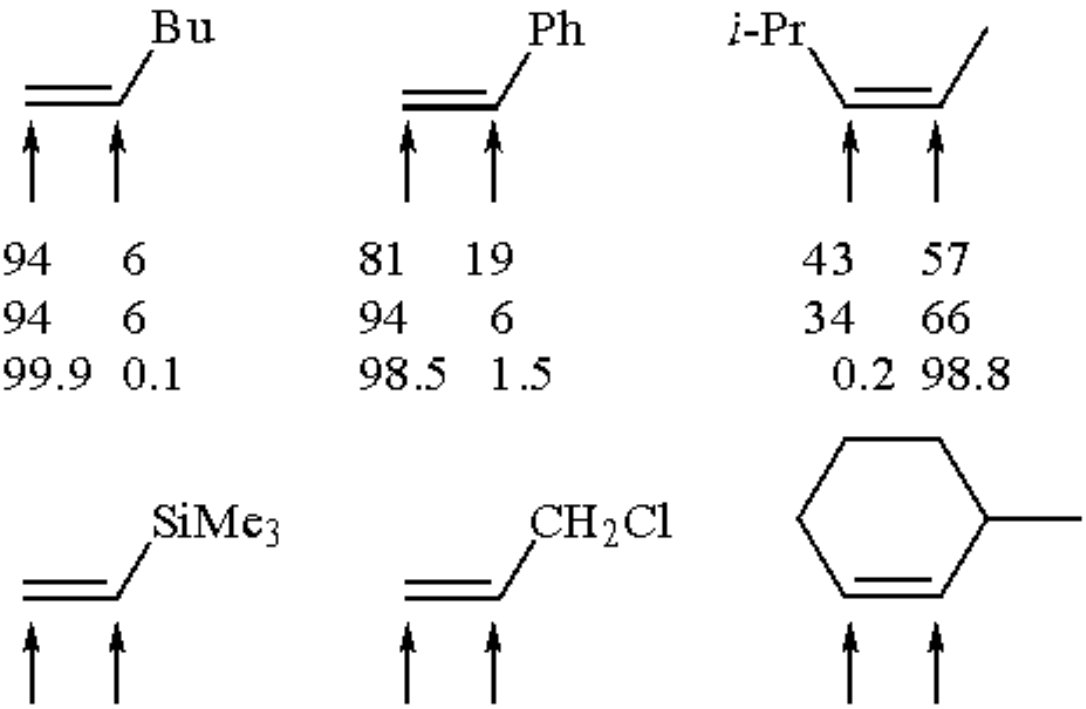

	Bu		Ph		i-Pr	
BH_3	94	6	81	19	43	57
t-$HxBH_2$	94	6	94	6	34	66
9-BBN-H	99.9	0.1	98.5	1.5	0.2	98.8

	$SiMe_3$		CH_2Cl			
BH_3	40	60	60	40	50	50
Sia_2BH	95	5	95	5	52	48
9-BBN-H	100	0	98.9	1.1	80	20

However, in contrast to other dialkylborane reagents (e.g. ***Disiamylborane*** or ***Dicyclohexylborane***) which must be freshly prepared immediately prior to their use, 9-BBN-H dimer is a stable crystalline reagent[1,3] which is commercially available in high purity. This feature of the reagent facilitates the control of reaction stoichiometry at a level unattainable with most borane reagents. The remarkable thermal stability of 9-BBN derivatives permits hydroborations to be conducted over a broad range of temperatures (from 0 °C to above 100 °C) either neat or in a variety of solvents.[4] The *B*-alkyl-9-BBN products can frequently be isolated by distillation without decomposition and fully characterized spectroscopically.[1,4,5] The integrity of the 9-BBN ring is retained even at elevated temperatures (200 °C), but positional isomerization in the *B*-alkyl portion can take place at ca. 160 °C.[6]

Like most other dialkylboranes, 9-BBN-H exists as a dimer, but hydroborates as a monomer (eq 2).[7] In general, the rates of hydroboration follow the order $R_2C{=}CH_2$ > $RHC{=}CH_2$ > *cis*-RHC=CHR > *trans*-RHC=CHR > $RHC{=}CR_2$ > $R_2C{=}CR_2$.[1,4] For relatively unsubstituted alkenes the dissociation of the 9-BBN-H dimer is rate-limiting ($T_{1/2}$ at 25 °C &AApprox; 20 min) so that the hydroborations of typical 1-alkenes are normally complete in less than 3 h at room temperature. Competitive rate studies have revealed that electron-donating groups enhance the rates within these groups, e.g. for *p*-$XC_6H_4CH{=}CH_2$, k_{rel} = 1 (X = CF_3), 5 (X = H), 70 (X = OMe).[4c]

$$[9\text{-BBN-H}]_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2\,[9\text{-BBN-H}] \qquad (2)$$

$$9\text{-BBN-H} \xrightarrow[k_2]{\text{alkene}} \text{R-9-BBN}$$

Hydroborations of more substituted alkenes such as α-pinene[8] or 2,3-dimethyl-2-butene[4b] with 9-BBN-H are slower (k_2 is rate-limiting) and require heating at reflux temperature in THF for 2 and 8 h, respectively, for complete reaction to occur. However, the enantioselective reducing agent[8a] Alpine-borane® (see ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane***) is formed quantitatively as a single enantiomer, the process taking place with complete Markovnikov regiochemistry, exclusively through *syn* addition from the least hindered face of the alkene (eq 3).

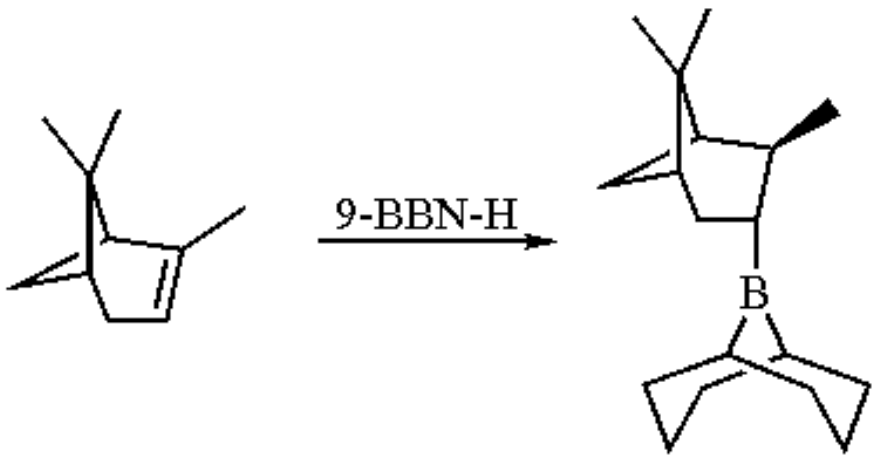

(3)

While the monohydroboration of symmetrical nonconjugated dienes with 9-BBN-H is thwarted by competing dihydroboration because these remote functionalities act as essentially independent entities, with nonequivalent sites the chemoselectivity of the reagent can be excellent (eq 4).[4] Also, whereas the monohydroboration of conjugated dienes is not always a useful process because of competitive dihydroboration, highly substituted dienes and 1,3-cyclohexadiene produce allylborane products efficiently. In contrast to the monohydroboration of allene itself, which gives a 1,3-diboryl adduct, 9-BBN-H is an effective reagent for the preparation of allylboranes from substituted allenes.[4g] For example, excellent selectivity has been observed for silylated allenes where hydroboration occurs *anti* to the silyl group on the allene and at the terminal position (eq 5).[9] It is also important to note that the diastereofacial selectivities of 9-BBN-H can be complementary to those obtained with Rh-catalyzed hydroborations (eq 6).[10]

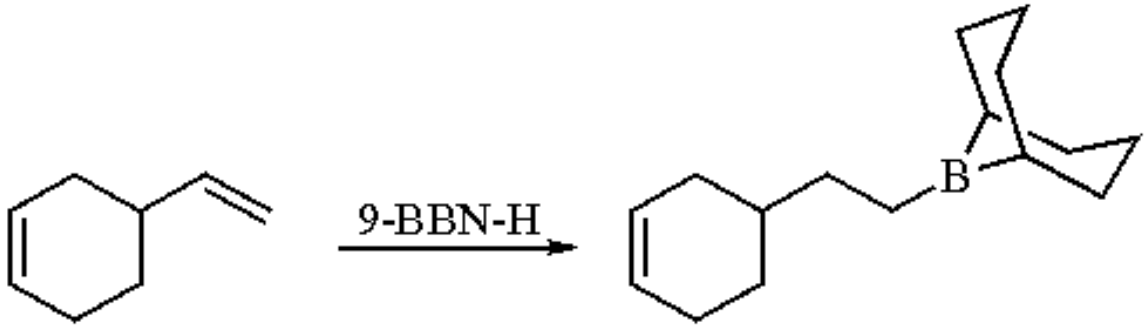

(4)

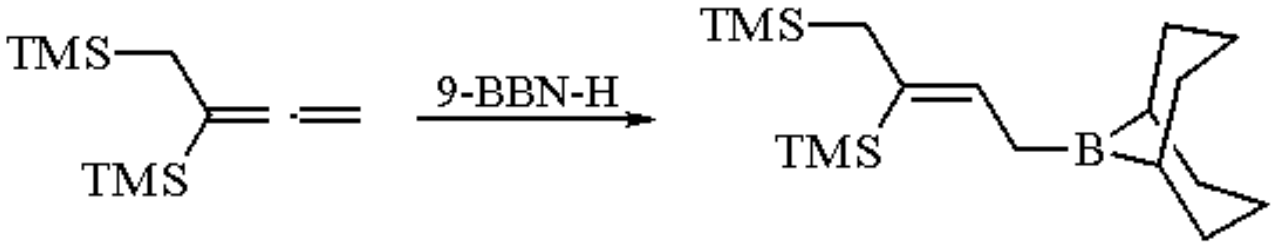

(5)

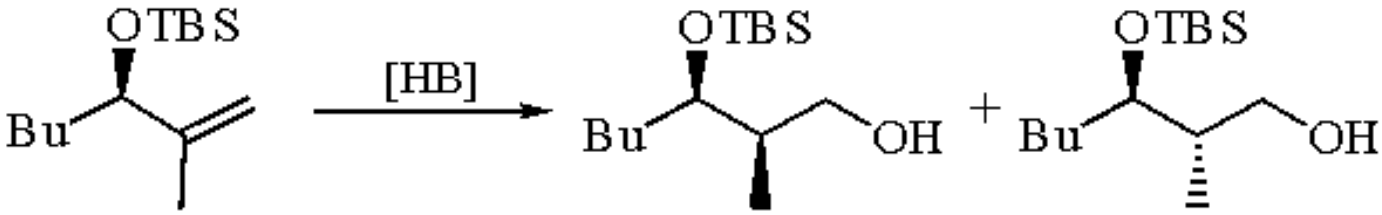

(6)

9-BBN-H	11:89
CatBH, $ClRh(PPh_3)_3$	96:4

Medium-ring boracycles are efficiently prepared by the dihydroboration of α,o-dienes with 9-BBN-H followed by exchange with borane.[11] In this process 9-BBN-H is particularly useful because it not only fixes the key 1,5-diboryl relationship, but also the 9-BBN ligands do not participate in the exchange process (eq 7).

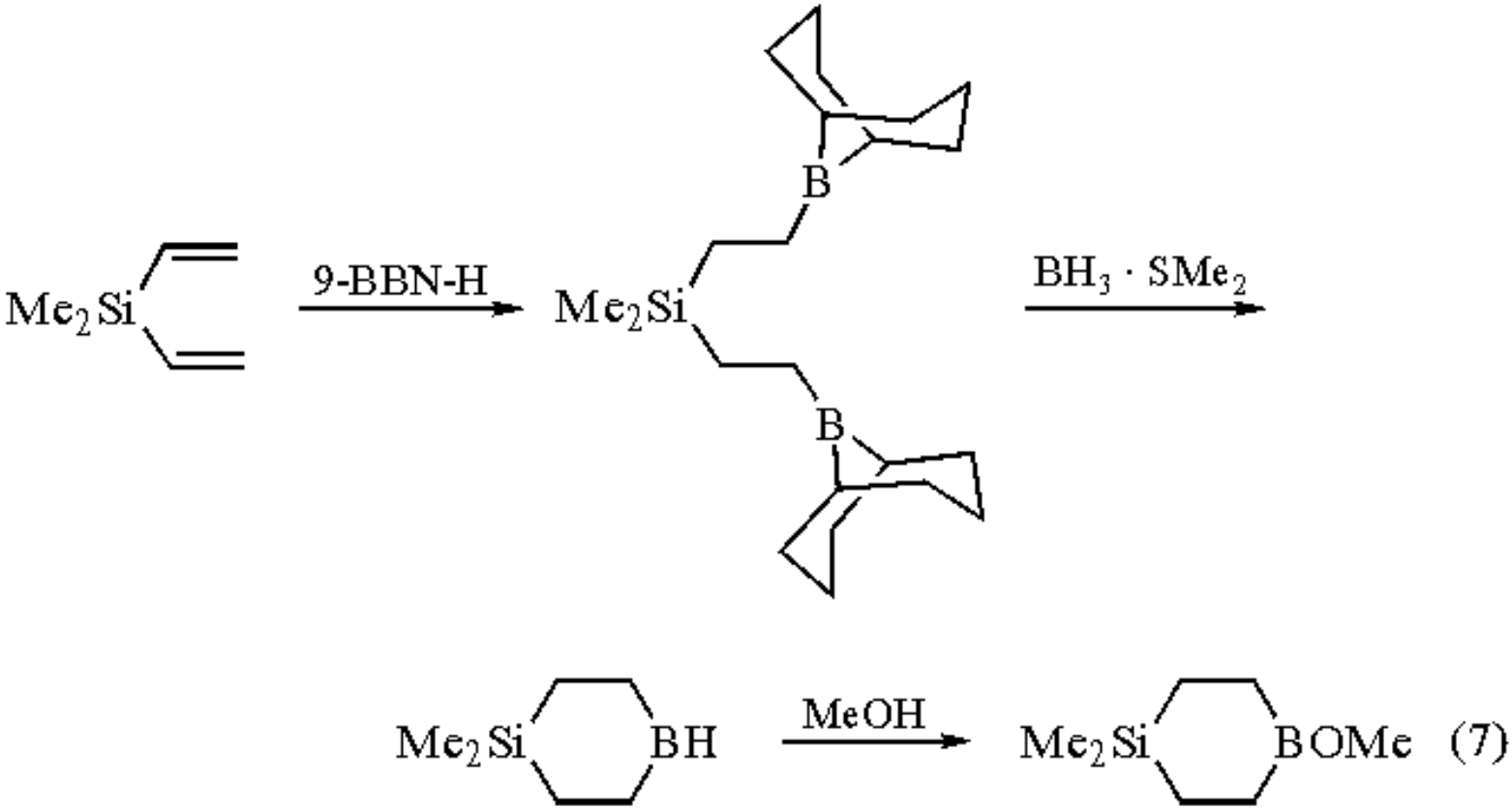

Unlike most dialkylboranes, 9-BBN-H hydroborates alkenes faster than its does the corresponding alkynes, a feature which leads to the competitive formation of 1,1-diboryl adducts in the hydroboration of 1-alkynes with 9-BBN-H employing a 1:1 stoichiometry (eq 8).[1,12,13] In some cases, the (*E*)-1-alkenyl-9-BBN derivative can be efficiently prepared by employing either a large excess of the alkyne[12,13] or through the use of 1-trimethylsilyl derivatives.[6] However, these vinylboranes are now perhaps best prepared through the dehydroborylation of their 1,1-diboryl adducts with aromatic aldehydes (eq 8).[12]

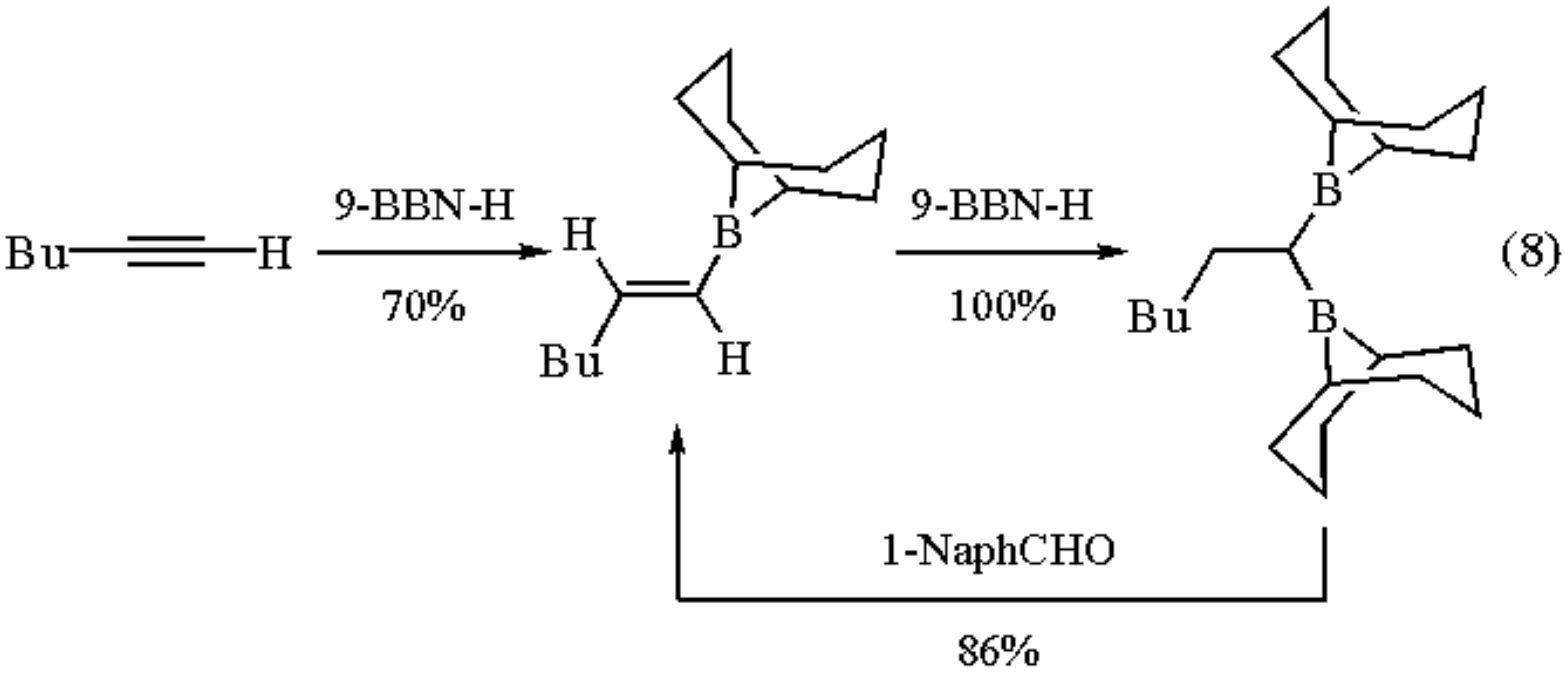

By contrast, 9-BBN-H effectively monohydroborates internal alkynes to produce the corresponding vinylboranes in >90% yields.[1,13] Compared to 1-alkynes, their 1-silyl counterparts also produce better yields of vinylboranes but, in contrast to normal internal alkynes, produce *vicinal* rather than *geminal* diboryl adducts with dihydroboration.[6,13,14] Larger silyl groups can effectively be used to redirect the boron to the internal position producing the silyl-Markovnikov vinylborane, exclusively, without competitive dihydroboration.[6] For 1-halo-1-alkynes, hydroboration with 9-BBN is slow, but the (*Z*)-1-halovinylboranes (eq 9) are produced cleanly and these are protonolyzed to provide *cis*-vinyl halides.[15] The isomeric (*Z*)-2-bromovinyl-9-BBN derivatives are available from the bromoboration of 1-alkynes with *B*-Br-9-BBN[16] (see ***9-Bromo-9-borabicyclo[3.3.1]nonane***). It is important to point out that the preference of 9-BBN-H to hydroborate alkenes in the presence of alkynes can have useful synthetic applications (eq 10).[17]

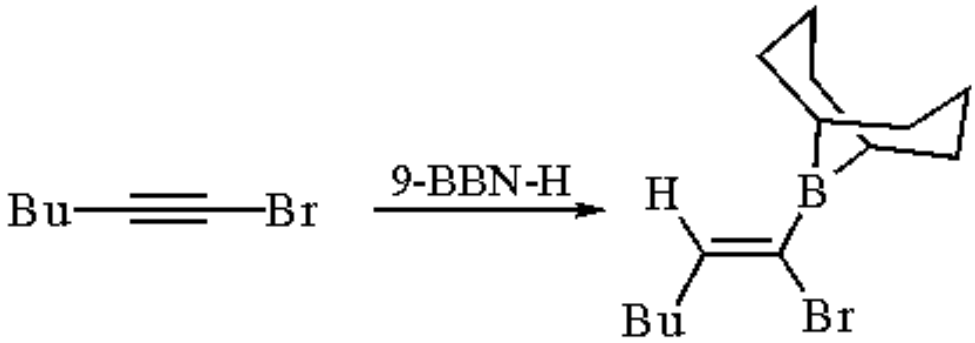

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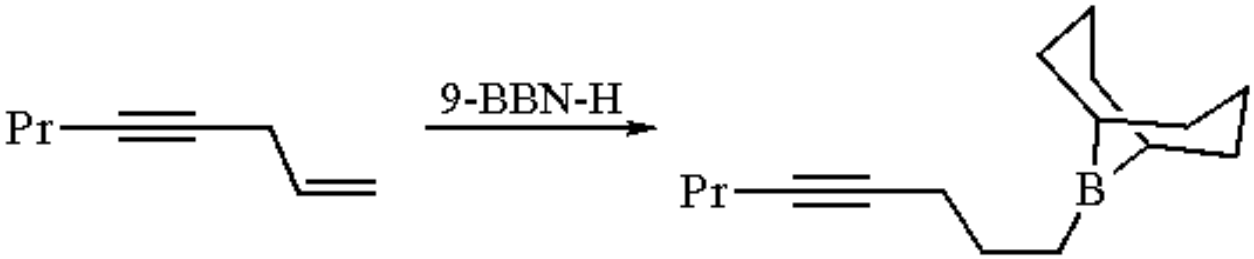

(10)

Organometallic reagents can provide very useful entries to many *B*-substituted 9-BBN derivatives. These are particularly important for organoboranes which cannot be prepared by hydroboration.[5] Both *B*-alkoxy and *B*-halo derivatives serve as useful precursors to *B*-alkyl, -allyl, -aryl, -vinyl or -alkynyl-9-BBN derivatives (eqs 11-16). *B*-Halo-9-BBN derivatives are effectively vinylated with organotin reagents.[18] However, *B*-MeO-9-BBN is superior to its *B*-halo counterparts for secondary and tertiary alkyllithium reagents where the latter undergo some reduction to 9-BBN-H through β-hydride transfer from the organolithium.

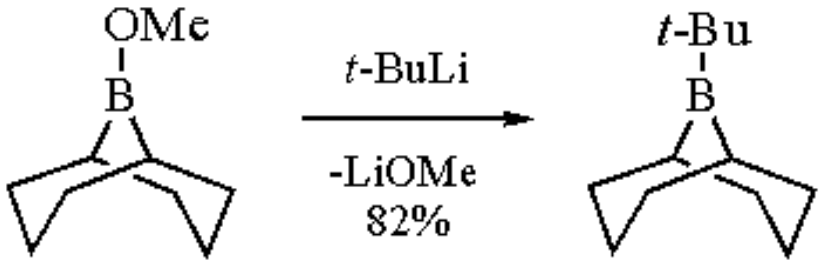

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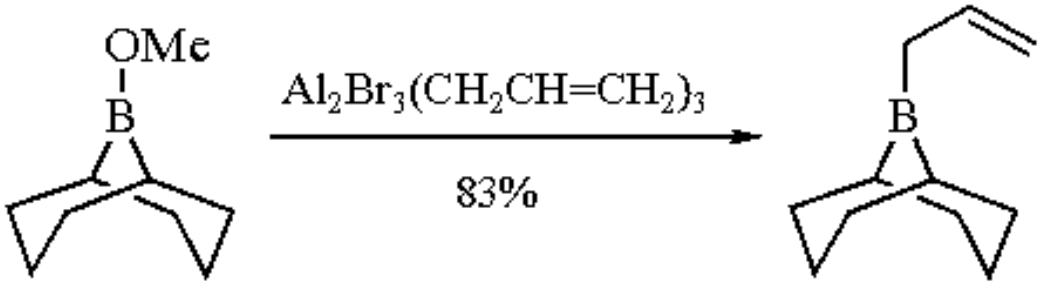

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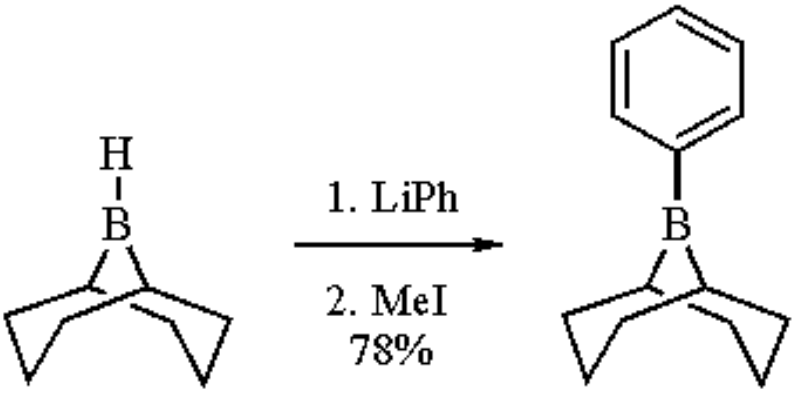

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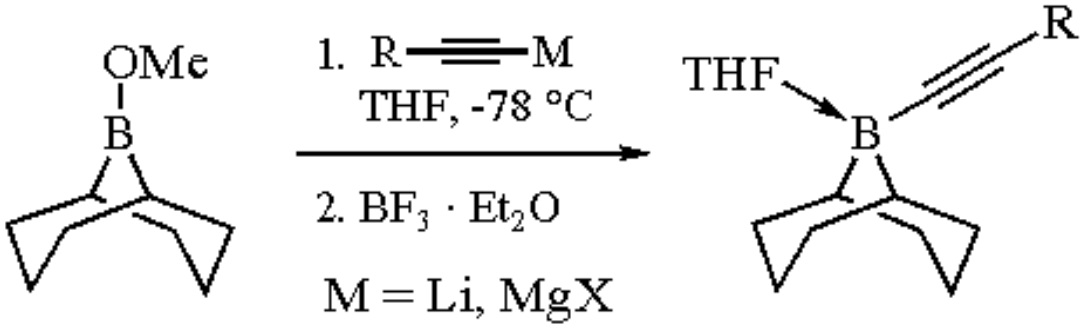

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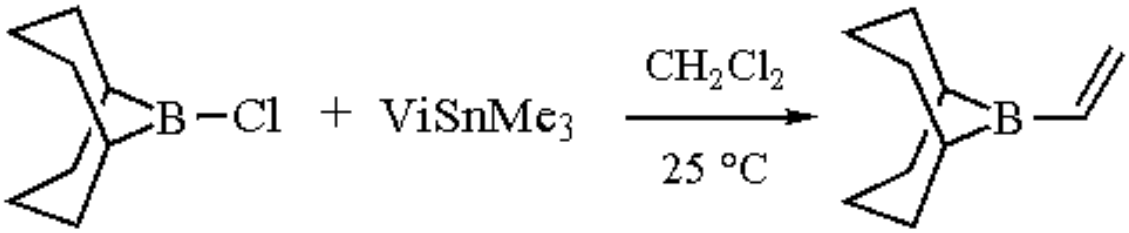

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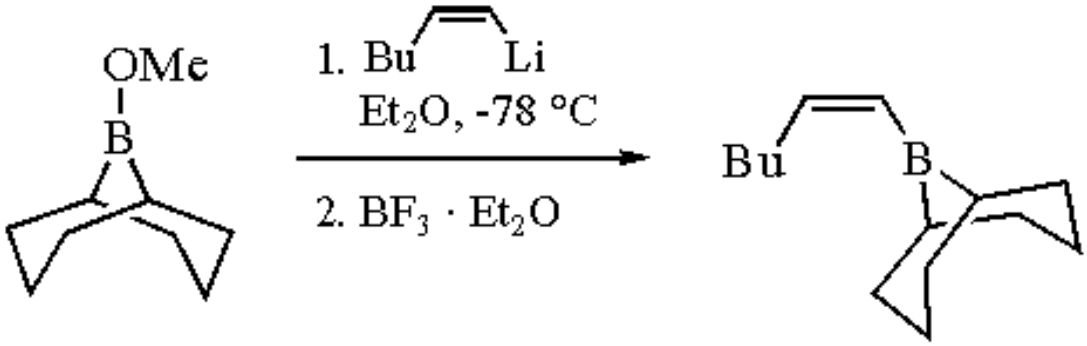

(16)

Hydroboration of the byproduct alkene gives isomeric *B*-alkyl-9-BBN products.[5b] Generally, hydrocarbon solvents are

preferable to ether or THF for this process because the greater stability of the intermediate methoxyborate complexes (i.e. Li[R(MeO)-9-BBN]) at -78 °C in these solvents prevents the product from being formed and competing with *B*-MeO-9-BBN for the alkyllithium reagent prior to its complete consumption.[5b] The complex is stable for alkenyl and alkynyl derivatives which require $BF_3.Et_2O$ to remove the methoxy moiety. The procedure has also been used for the preparation of *cis*-vinyl-9-BBN derivatives[19] since the normal route to such derivatives based upon the hydroboration of 1-haloalkynes, followed by hydride-induced rearrangement gives ring expansion products competitively with (*Z*)-1-halovinyl-9-BBNs.[20] Similar behavior has been observed for the reaction of α-methoxyvinyllithium with *B*-alkyl-9-BBNs (see ***1-Methoxyvinyllithium***).[21]

Derivatives of 9-BBN.

Like other boron hydrides, a variety of proton sources (ROH, RCO_2H, RSO_3H, HX (X = Cl, Br, OH, SH, $O_2P(OH)_2$, NHR)) as well as boron halides can be effectively employed to prepare useful derivatives from 9-BBN-H.[1d,5b,22] The synthetic value of *B*-MeO-9-BBN lies principally in the preparation of *B*-alkyl derivatives through organometallic reagents as described above. As a byproduct in other processes, it is also easily converted to 9-BBN-H with BMS (eq 17).[22]

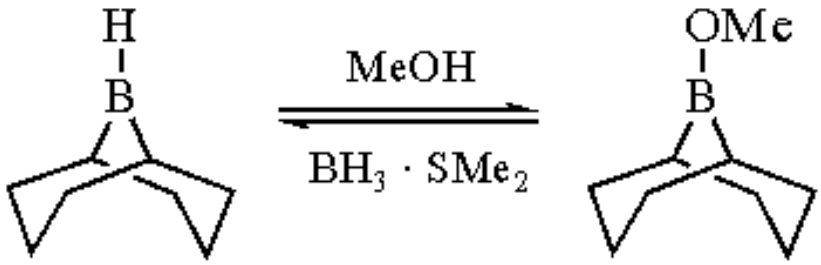

(17)

Efficient procedures have been developed for the preparation of *B*-Cl-9-BBN from 9-BBN-H (HCl in Et_2O)[5b] and *B*-Br-9-BBN (BBr_3 in CH_2Cl_2),[23] the latter being a useful reagent for ether cleavage, the bromoboration of 1-alkynes, and for conjugative additions to enones (see ***9-Bromo-9-borabicyclo[3.3.1]nonane***). 9-BBN triflate is highly useful in formation of enolboranes for stereoselective crossed aldol reactions[24] (see ***9-Borabicyclononyl Trifluoromethanesulfonate***). The *B*-acyloxy-9-BBN derivatives have been employed in conjuction with borohydrides for the reduction of carboxylic acids to aldehydes[25] (see ***Lithium 9-boratabicyclo[3.3.1]nonane***). Amine complexes of 9-BBN-H and borohydride derivatives are easily prepared from the addition of amines or metal hydrides to 9-BBN-H.[26] *B*-Alkyl-9-BBNs and their borohydrides are very selective reducing agents and, with chiral terpenoid or sugar appendages, can also effectively function as enantioselective reagents (eq 18)[8,27] (see ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane*** and ***Potassium 9-Siamyl-9-boratabicyclo[3.3.1]nonane***). 9,9-Dialkylborate derivatives of 9-BBN are also highly selective reducing agents[28] (see ***Lithium 9,9-Dibutyl-9-borabicyclo[3.3.1]nonanate***), transferring a bridgehead hydride with rearrangement to bicyclo[3.3.0]octylboranes. This process is best accomplished with ***Acetyl Chloride*** and provides a highly versatile entry to these organoboranes for subsequent conversions (eq 19).[29]

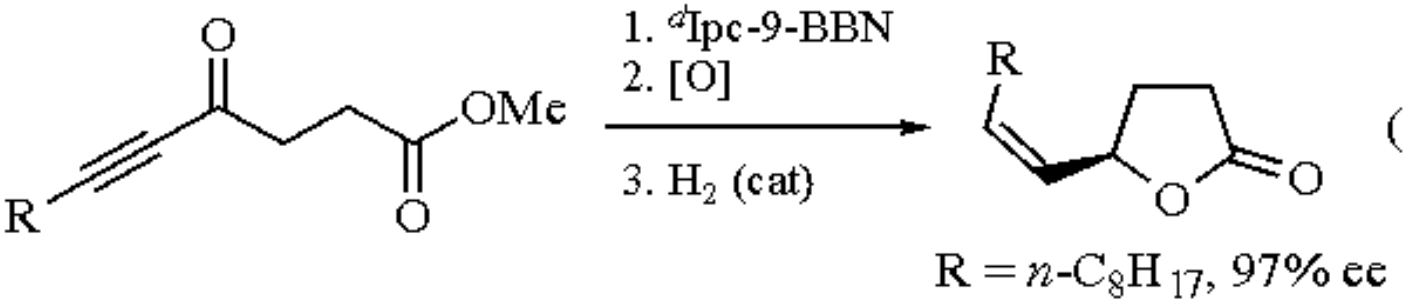

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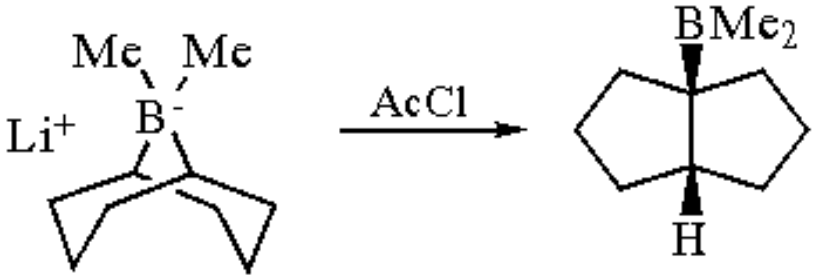

(19)

Functional Group Conversions with 9-BBN-H.

9-BBN-H selectively reduces acid chlorides, aldehydes, ketones, lactones, and sulfoxides at 25 °C.[1e] Alcohol rather than amine products are produced as the major products from tertiary amides, while primary derivatives are not reduced effectively. Reduction is slow with esters, carboxylic acids, nitriles, and epoxides, and does not occur with nitro compounds, nor with alkyl or aryl halides. At 65 °C, carboxylic acids and esters are cleanly reduced to alcohols, the former being significantly slower (18 vs. 4 h). Moreover, 9-BBN-H is a highly selective reducing agent for the reduction of enones to allylic alcohols (eq 20).[30]

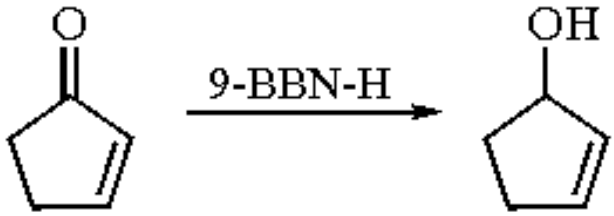

(20)

As noted earlier, *B*-substituted-9-BBN derivatives are available from a variety of sources and organoboranes serve as a versatile entry to other functionalities. Their oxidative conversion to alcohols with alkaline ***Hydrogen Peroxide*** or ***Sodium Perborate***[31] is quantitative and occurs with complete retention of configuration, making the process highly useful.[1] The 9-BBN moiety is oxidized to *cis*-1,5-cyclooctanediol (eq 21), a compound which can be removed from less polar products through extraction with water, selective crystallization, or by chromatography.[1] The monooxidation of 9-BBN derivatives with anhydrous ***Trimethylamine N-Oxide*** (TMANO) produces 9-oxa-10-borabicyclo[3.3.2]decanes (eq 22),[14] many of which are air-stable and undergo useful coupling reactions.

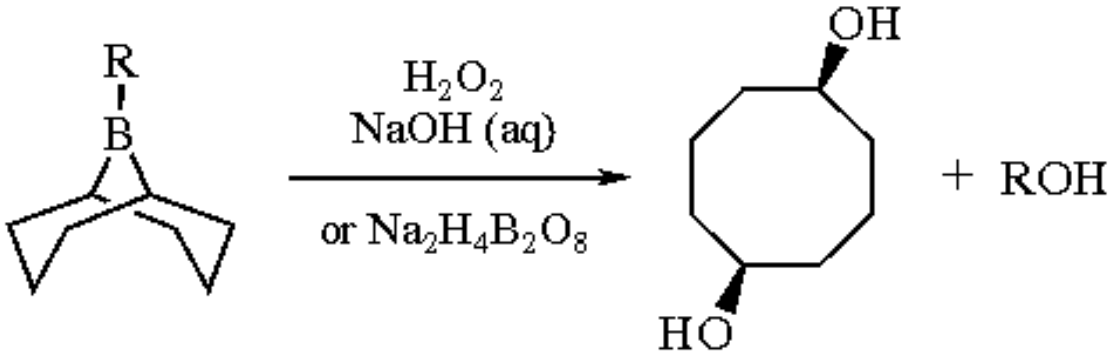

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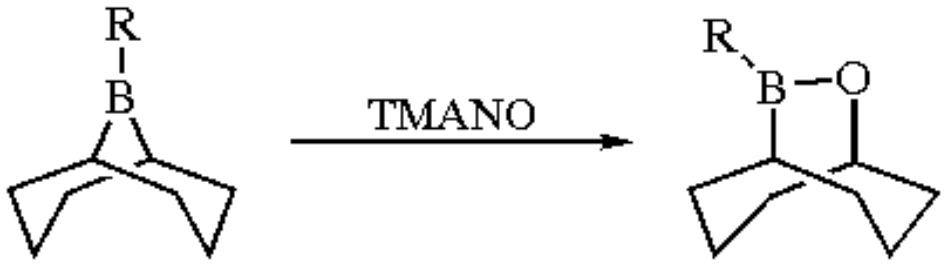

(22)

Anomalous oxidation products are observed from the oxidation of tetraalkylborate salts (i.e. Li(R_2-9-BBN)), which produces bicyclo[3.3.0]octan-l-ol as a co-product through a skeletal rearrangement which occurs during the oxidation process.[32] Moreover, the alkaline hydrogen peroxide oxidation of 1,1-di-9-BBN derivatives gives primary alcohols rather than aldehydes because of their solvolysis prior to oxidation.[6,13]

While the protonolysis of *B*-alkyl-9-BBNs, like other trialkylboranes, with carboxylic acids takes place only at temperatures above 100 °C, *B*-vinyl derivatives are readily cleaved by HOAc at 0 °C with complete retention of configuration.[1,13] This can be combined with other 9-BBN processes (e.g. thermal isomerization or dehydroborylation) to give remarkable overall conversions (eq 23).[6] The hydrolysis of allylic and alkynic 9-BBN derivatives is more facile, occurring even with water or alcohols.[5c,32]

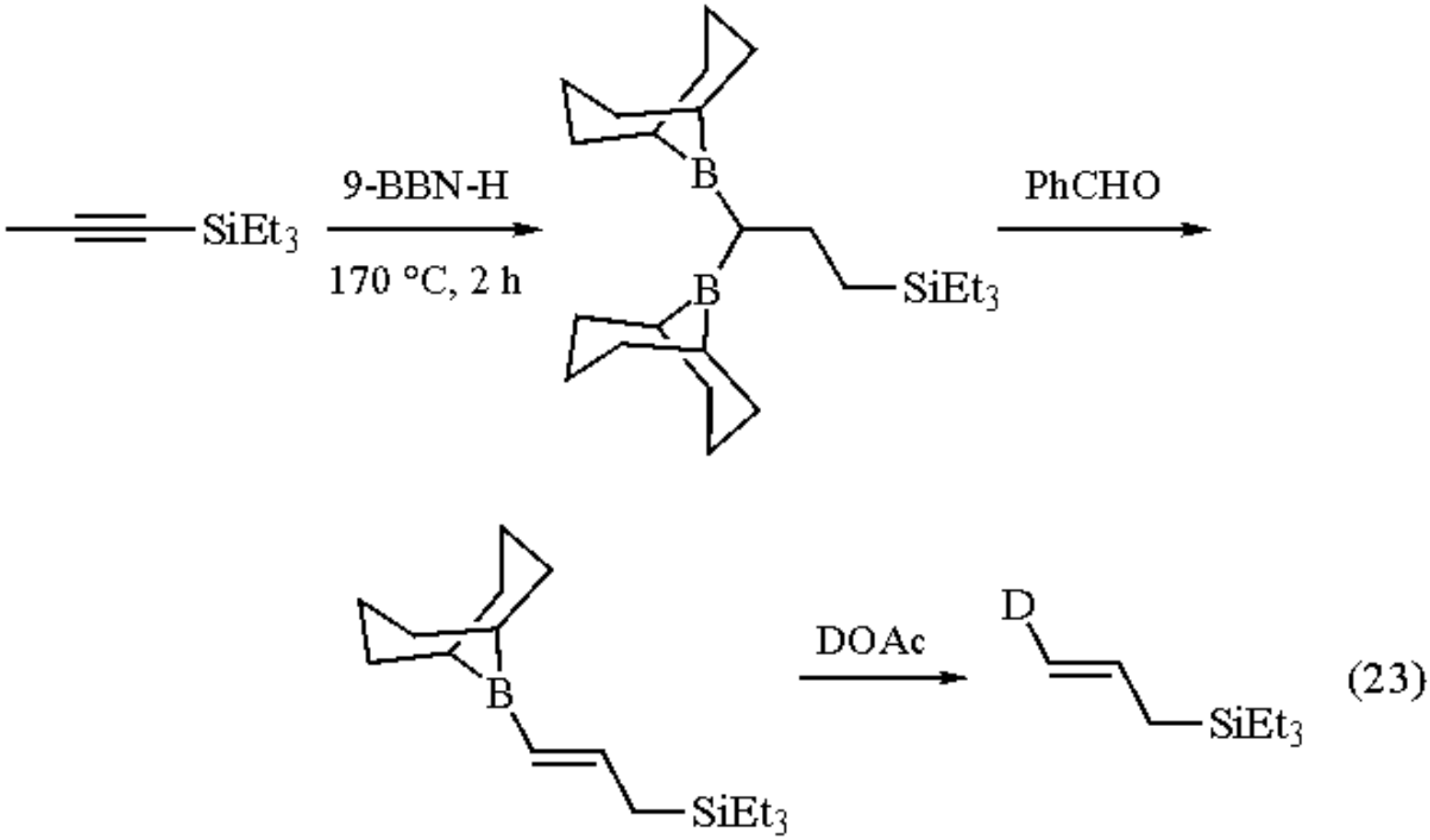

In the absence of light, molecular bromine readily cleaves *B*-(*s*-alkyl)-9-BBN derivatives through a hydrogen abstraction process, to give excellent yields of the corresponding alkyl bromides, the 9-BBN moiety being converted to 9-Br-9-BBN (eq 24).[33] However, bicyclo[3.3.0]octylborinic and -boronic acids are produced from *B*-Me- and *B*-MeO-9-BBN through this radical bromination under hydrolytic conditions where the facile 1,2-alkyl migration of a ring B-C bond occurs (eq 25).[1b,34] This latter compound serves as a convenient source of 9-oxabicyclo[3.3.1]nonane through base-induced iodination via an S_E2-type inversion.[35]

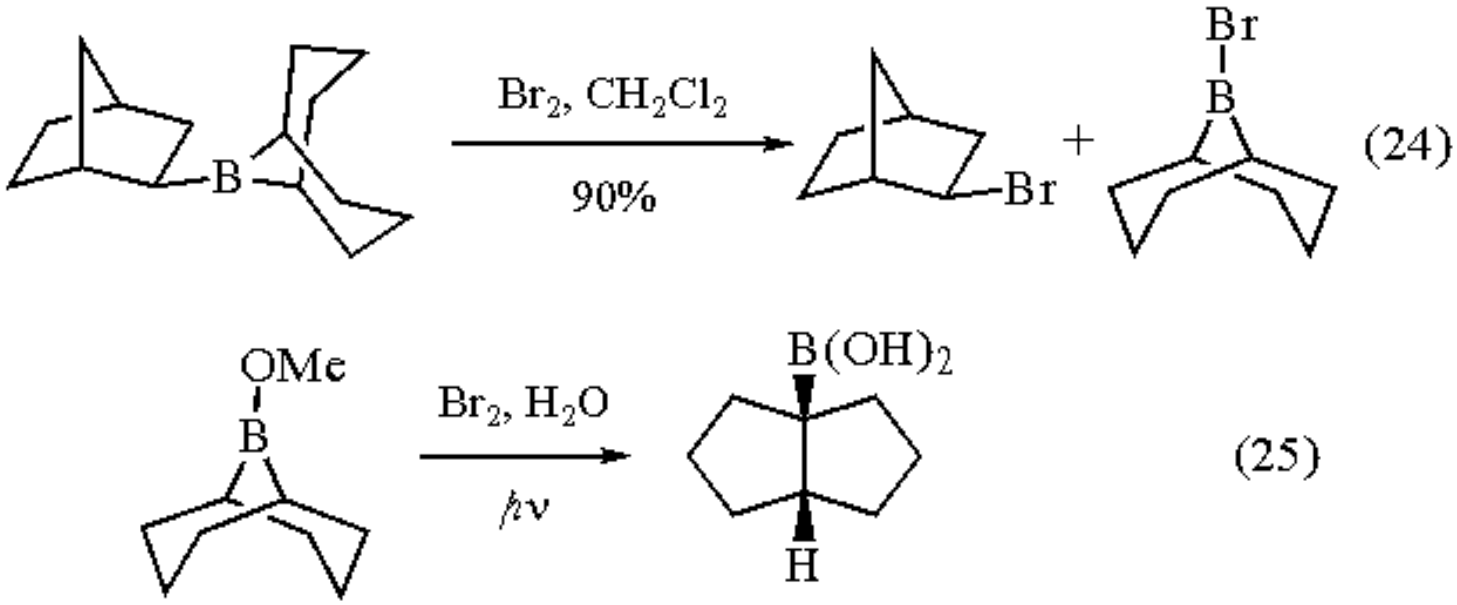

Mechanistically similar to the oxidation of 9-BBN derivatives with TMANO, the amination of *B*-alkyl-9-BBN proceeds through ring B-C migration rather than through *B*-alkyl migration (eq 26).[36] Similar behavior is observed for the thermal reaction of organic azides with these derivatives. Dichloroboryl derivatives have proved to be more versatile and general for the synthesis of amines, including optically active derivatives.[37]

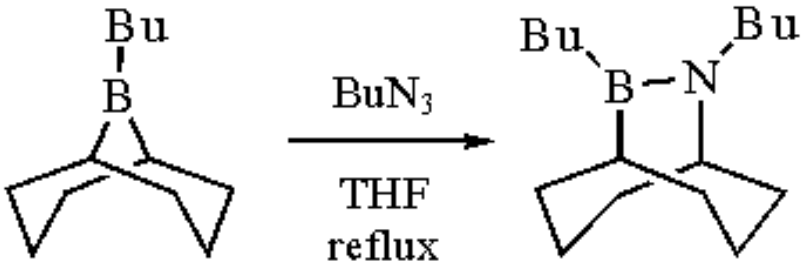

(26)

Carbon-Carbon Bond Formation via 9-BBN Derivatives.

Consistent with the versatility of organoboranes in synthetically useful chemical transformations, most conversions with 9-BBN derivatives are very efficient and occur with strict stereochemical control.[1] Of particular importance are those which involve the formation of new carbon-carbon bonds because valuable R groups can often be selectively transferred to the substrates without competition from the 9-BBN ring. For example, whereas only one of the alkyl, vinyl or aryl groups can be transferred from BR_3 to the anions derived from α-halo ketones, esters and nitriles, these reactions are ideally suited to *B*-R-9-BBN derivatives which transfer the *B*-R group selectively (eq 27).[1a,38] The vinylogous γ-alkylation of γ-bromo-α,β-unsaturated esters efficiently leads to γ-substituted-β,γ-unsaturated esters, the double bond transposition being commonly observed in the kinetic protonation of enolates with extended conjugation. Both sulfur ylides and α-bromo sulfones undergo related alkylations.[1a]

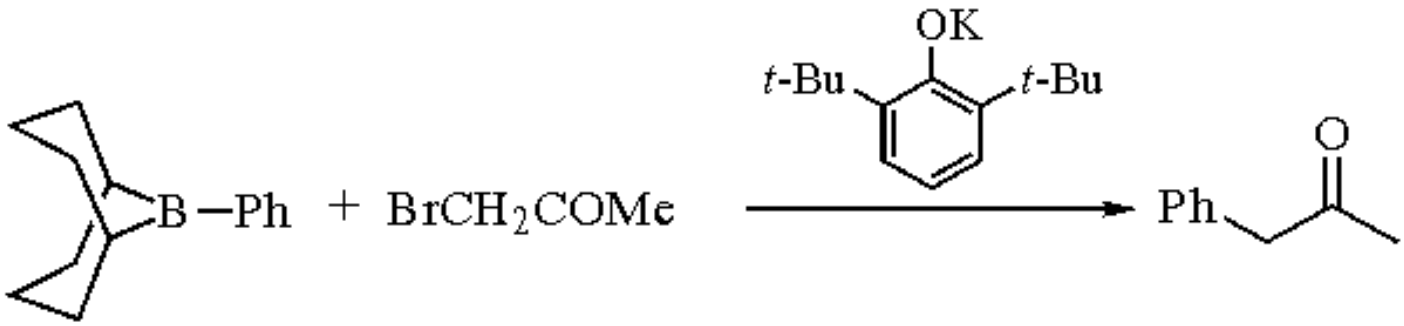

(27)

Base-induced eliminations of γ-haloalkyl-9-BBN derivatives give cycloalkanes (C_3 to C_6)[1b] with inversion of configuration at both carbon centers.[1,39] 1,1-Diboryl adducts from the dihydroboration of 1-alkynes with 9-BBN-H serve as useful precursors to *B*-cyclopropyl-9-BBN derivatives by a similar process (eq 28).

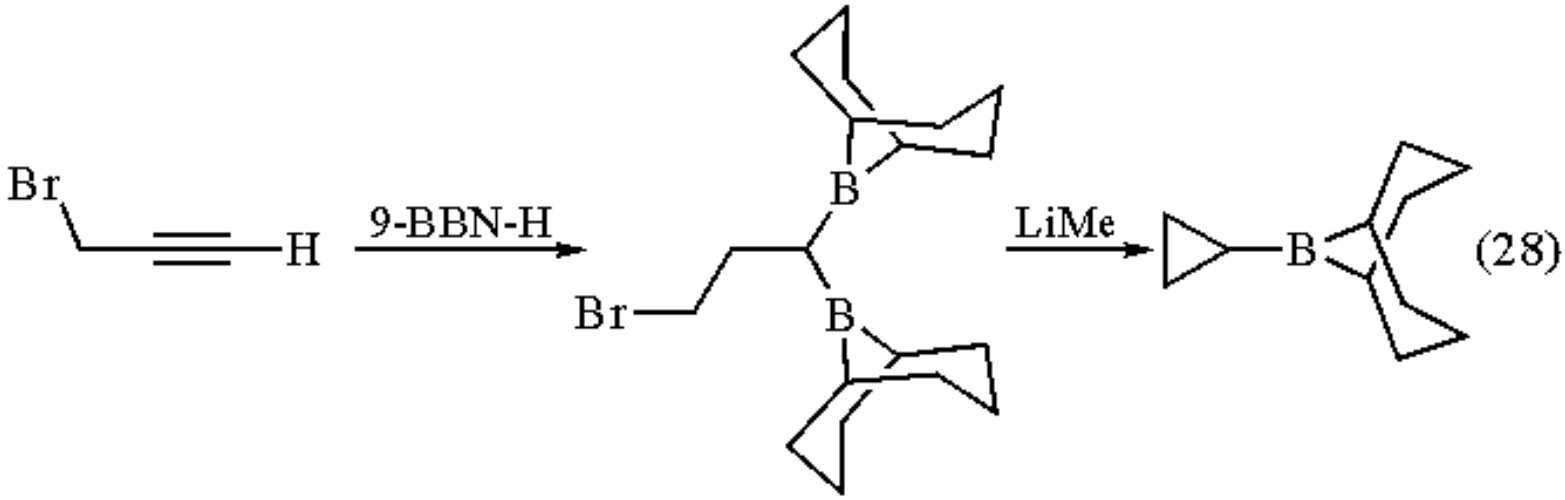

The carbonylation of *B*-alkyl-9-BBNs at 70 atm, 150 °C in the presence of ethylene glycol produces intermediate boronate esters which are oxidized with alkaline hydrogen peroxide to give high yields of the corresponding carbinols (Scheme 1).[40] In the presence of hydride-reducing agents (e.g. $LiHAl(OMe)_3$ or ***Potassium Triisopropoxyborohydride***), the carbonylation of *B*-R-9-BBN derivatives can be carried out at atmospheric pressures at 0 °C, producing an intermediate α-alkoxyalkylborane which can be further reduced with ***Lithium Aluminum Hydride***. This results in homologated organoboranes and, after oxidation, alcohols. Alternatively, the intermediate α-alkoxyalkylborane can be directly oxidized to produce aldehydes (Scheme 1).[1a,38c,41]

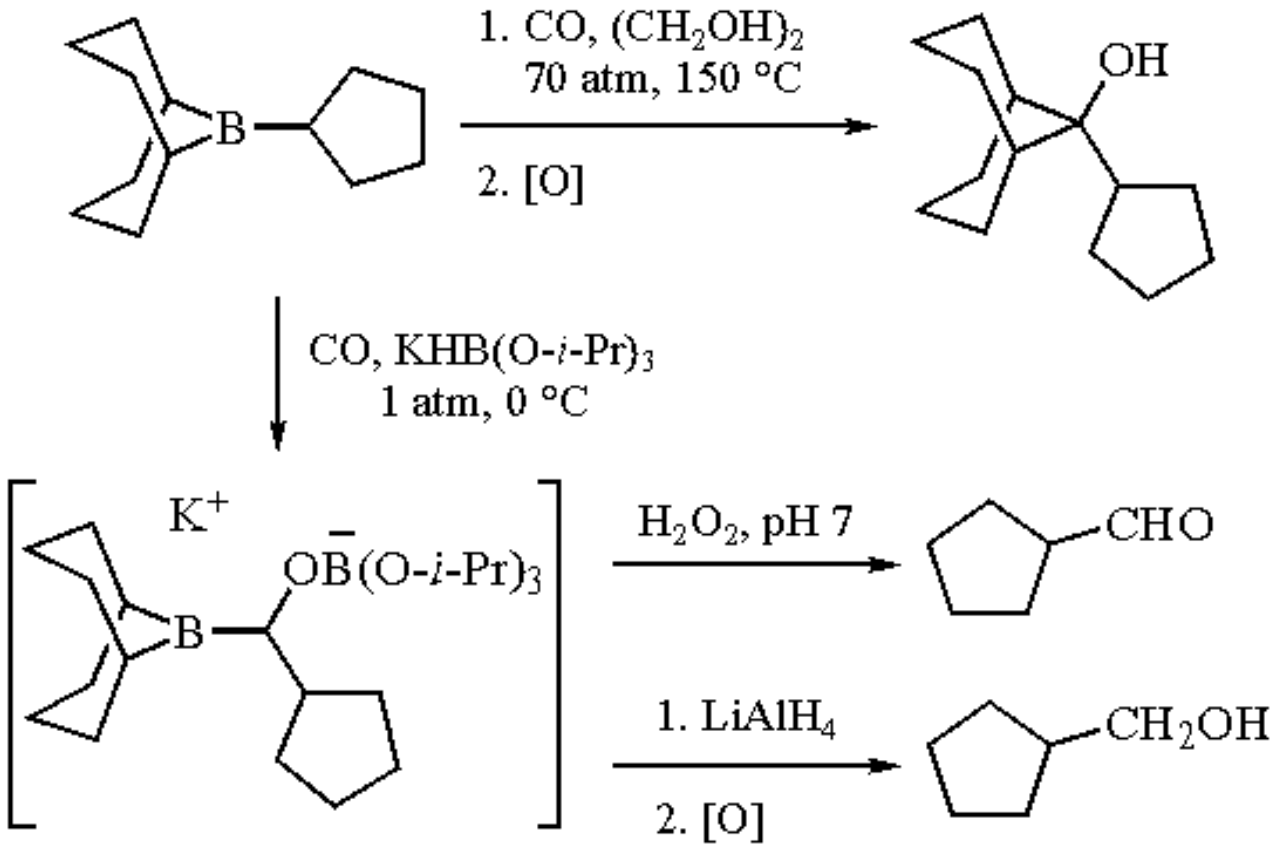

Scheme 1

As a useful alternative to carbonylation, the Brown dichloromethyl methyl ether (DCME) process has been effectively used for the synthesis of 9-alkylbicyclo[3.3.1]nonan-9-ols.[42] The ketone bicyclo[3.3.1]nonan-9-one (eq 29)[42b] has also

been prepared from a hindered *B*-aryloxy-9-BBN derivative, with simple *B*-alkoxy-9-BBN derivatives failing to undergo this process. However, most borinate esters are smoothly converted to ketones through this process, including germa- and silaborinanes (eq 30).[11e,f] In these cases, 9-BBN-H provides the essential 1,5-diboryl relationship which allows the formation of borinane by the exchange reaction described earlier.

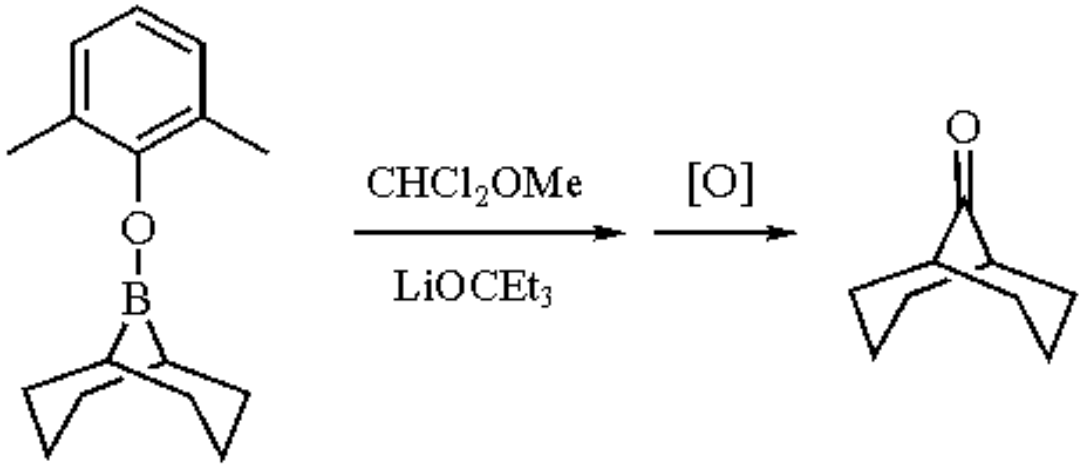

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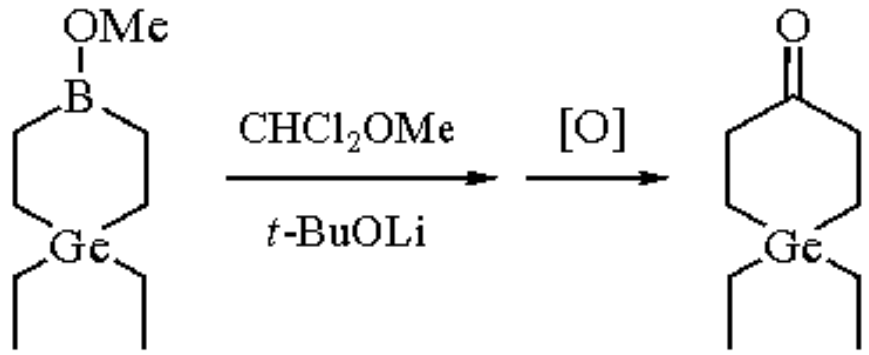

(30)

Allylboration with 9-BBN derivatives (see ***B-Allyl-9-borabicyclo[3.3.1]nonane***) is an efficient process, resulting in the smooth formation of homoallylic alcohols (eq 31).[43] Alkynylboranes also undergo 1,2-addition to both aldehydes and ketones.[44] As with other reactions producing *B*-alkoxy-9-BBN byproducts, the conversion of these to alcohols with ***Ethanolamine*** also results in the formation of an alkane-insoluble 9-BBN complex which is conveniently removed, thereby greatly simplifying the workup procedure.

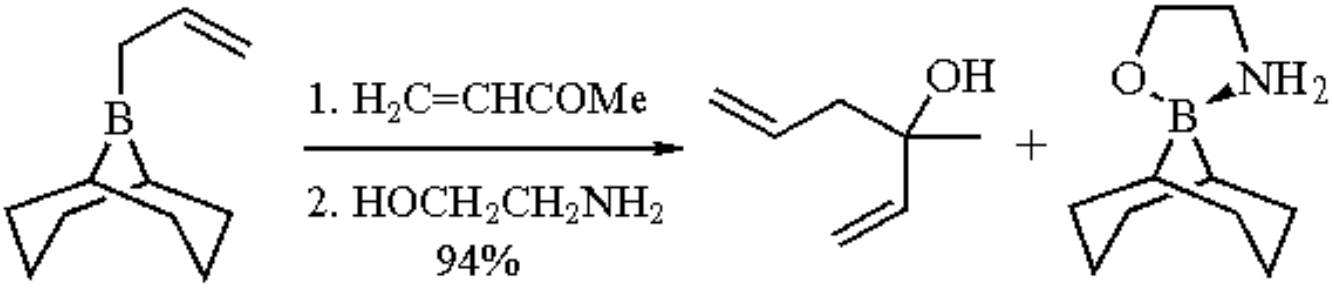

(31)

Vinyl derivatives of 9-BBN uniquely undergo Grignard-like 1,2-additions to aldehydes to produce stereodefined allylic alcohols (eq 32).[12,45] The thermal stability of the 9-BBN ring system, as well as its resistance to serve as a β-hydride source, facilitates this highly effective process. These vinylboranes are also the borane reagents of choice for the conjugate additions to enones which can adopt a *cisoid* conformation, providing a convenient entry to γ,δ-unsaturated

ketones from enones (eq 33).[46] Alkynylboranes undergo a related addition-elimination process with β-methoxyenones, giving enynones (eq 34).[47]

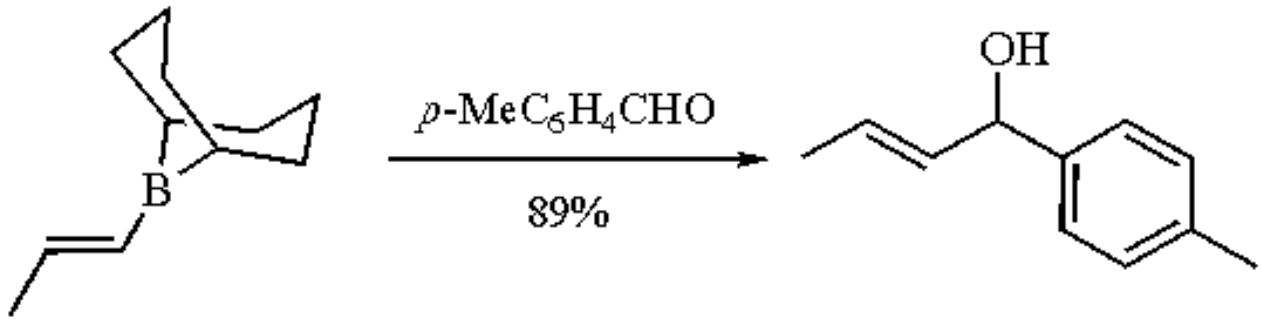

(32)

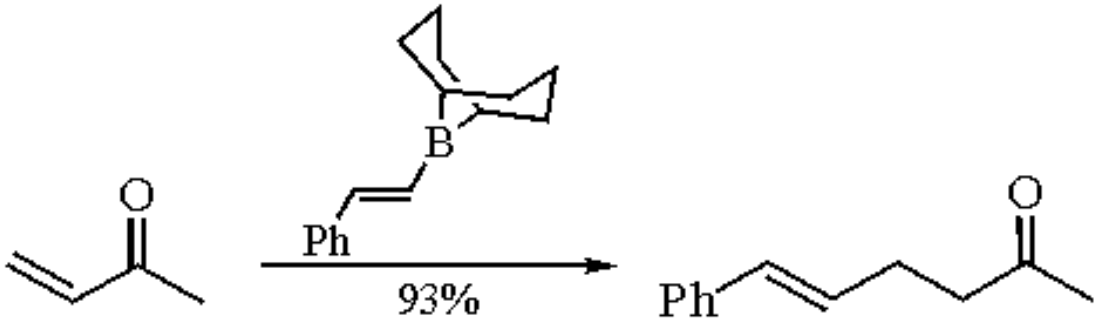

(33)

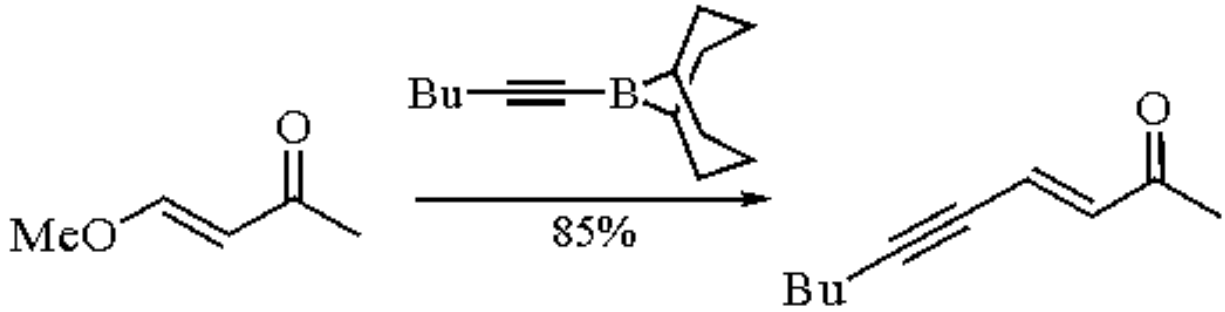

(34)

Vinyl(methoxy)-9-BBN ate complexes undergo an unusual homocoupling reaction when treated with ***Zinc Chloride*** (0.5 equiv) (eq 35).[48] Related intermediates, formed through the Cu^{I}-catalyzed addition of stannylborate complexes to 1-alkynes, can be coupled either through catalytic palladium or stoichiometric copper chemistry to produce stereodefined vinylstannanes (eq 36).[49]

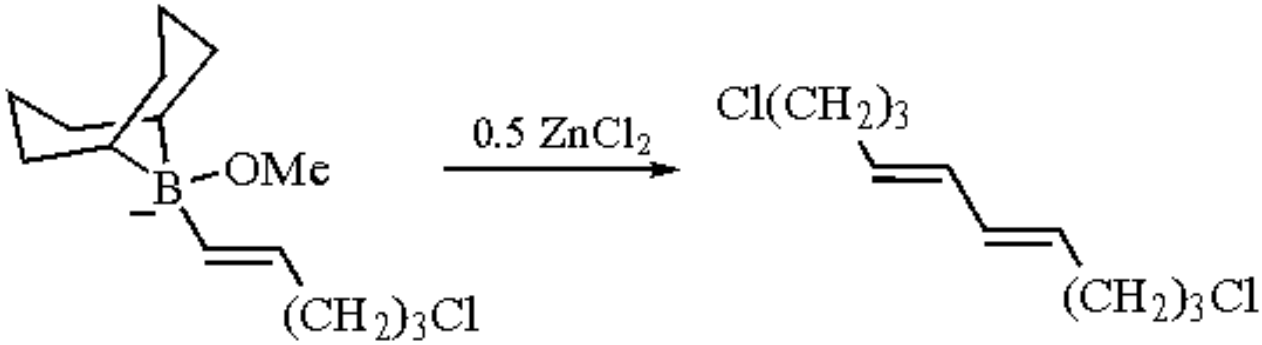

(35)

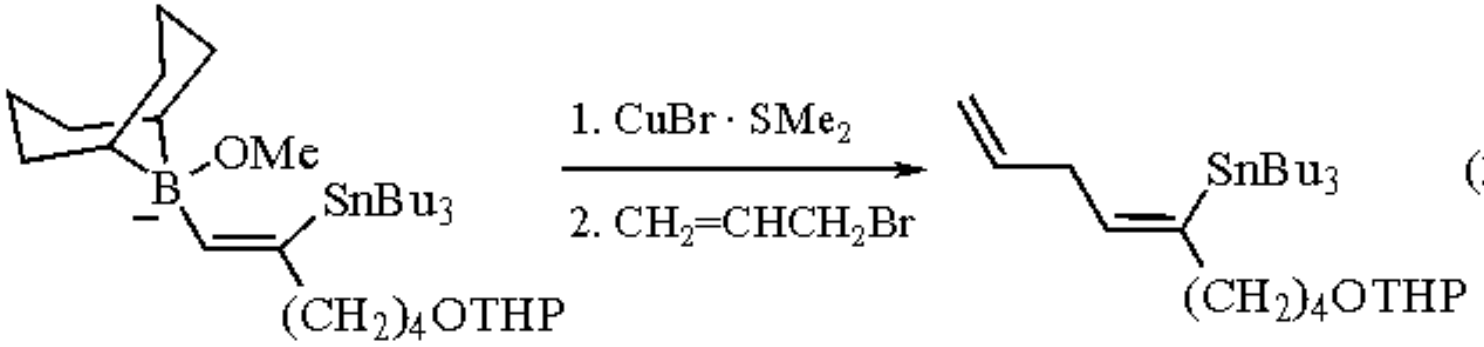

(36)

Both vinyl- and alkynyl-9-BBN derivatives are effective dienophiles in Diels-Alder cycloadditions, leading to boron-functionalized cyclohexenes in a selective manner (eqs 37 and 38).[18,50] Silylated allenylboranes add selectively as allylboranes to aldehydes, a reaction which has been effectively used to prepare the steroid nucleus through a Hudrlik elimination followed by a Bergman rearrangement (eq 39).[51]

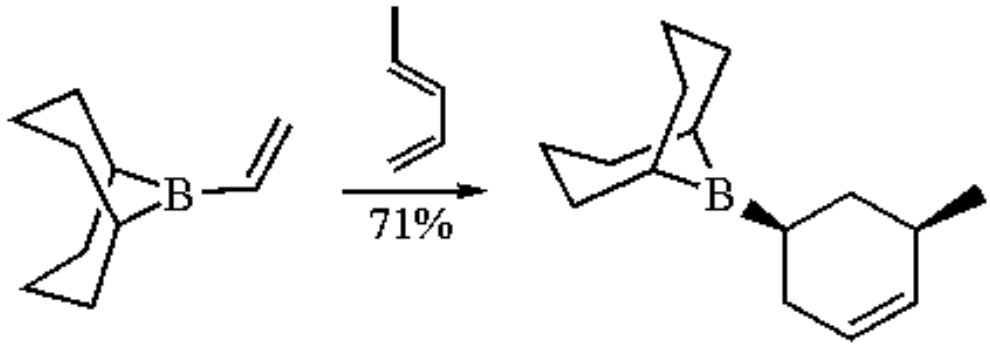

(37)

cis:*trans* = 92:8

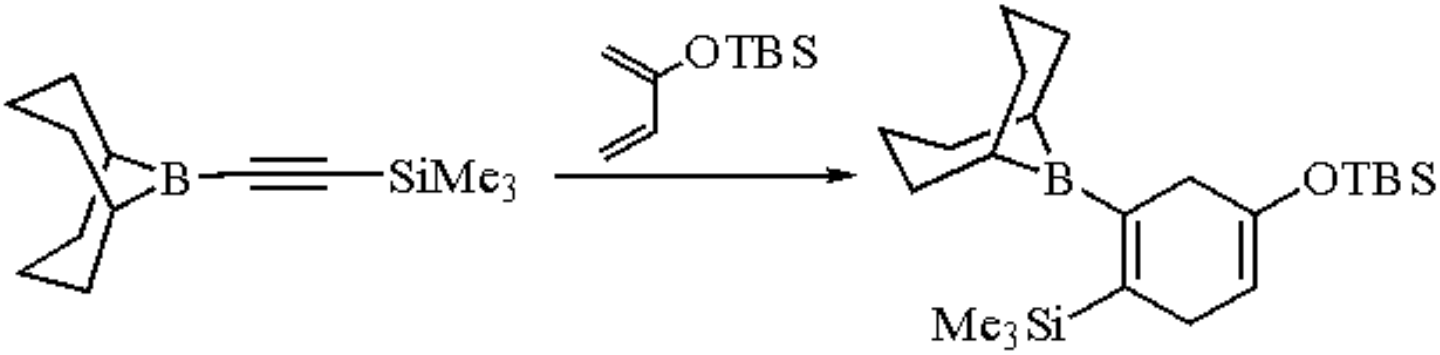

(38)

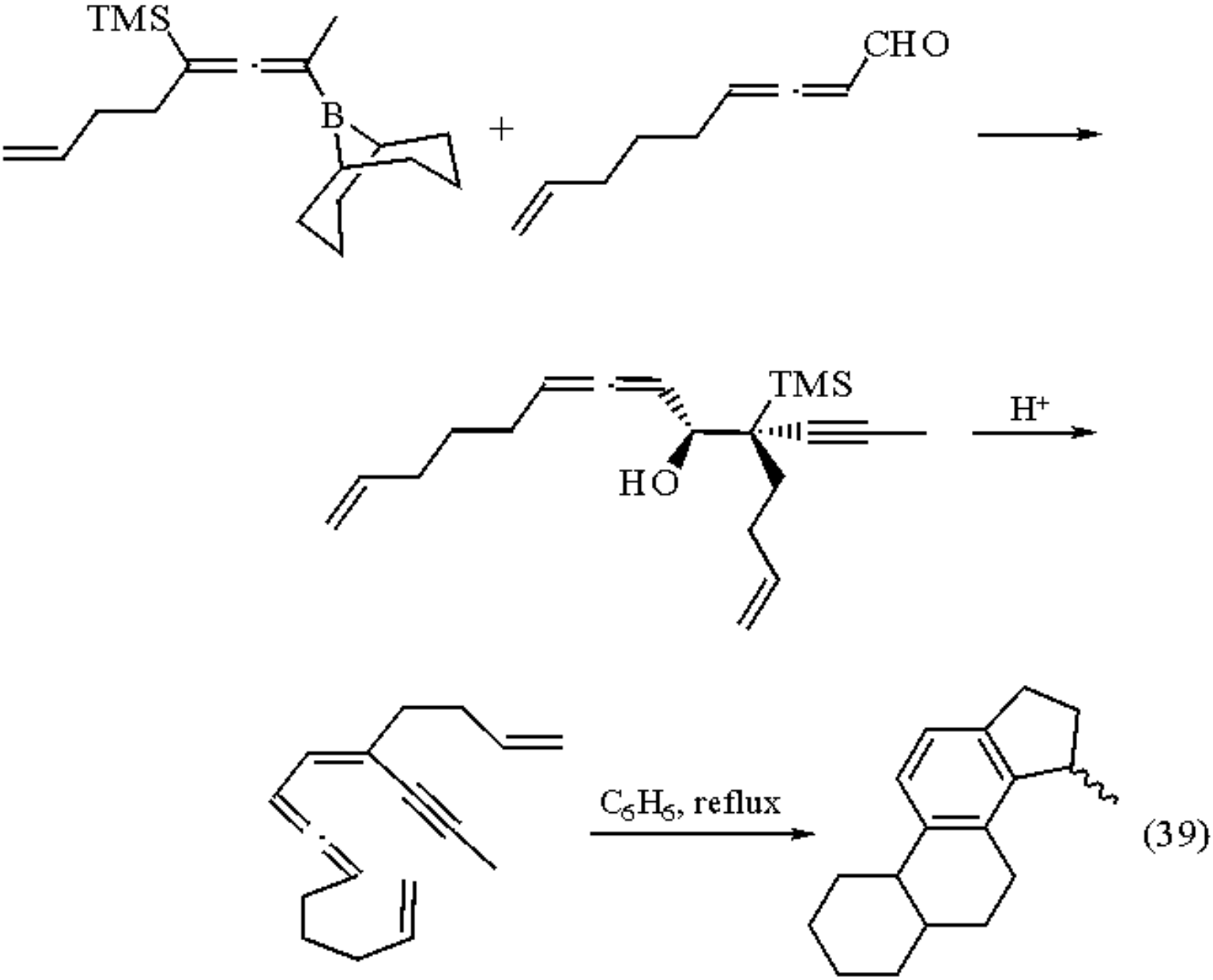

(39)

Stereodefined 9-BBN enolboranes which contain a directing chiral auxiliary undergo highly selective crossed aldol condensations as do other dialkylboryl systems (eq 40).[20,52] The conjugate addition of *B*-Br-9-BBN also produces enolboranes which condense with aldehydes to produce, after the elimination of the elements of *B*-HO-9-BBN, α-bromomethyl enones stereoselectively (eq 41).[53]

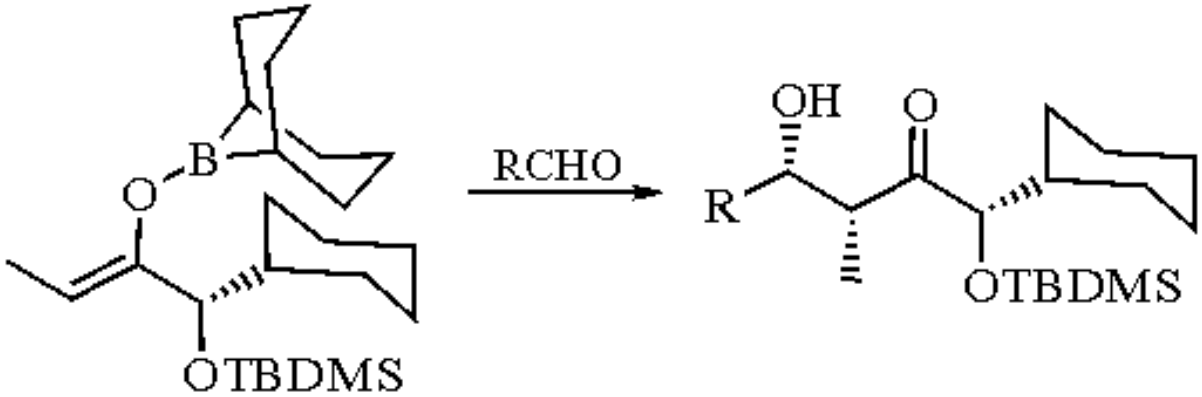

(40)

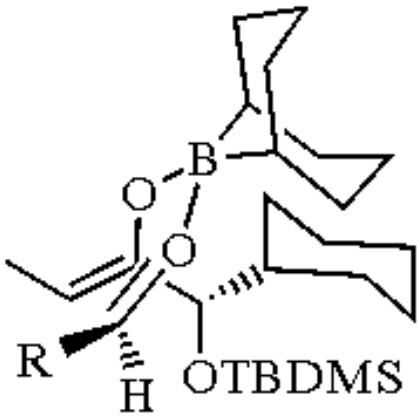

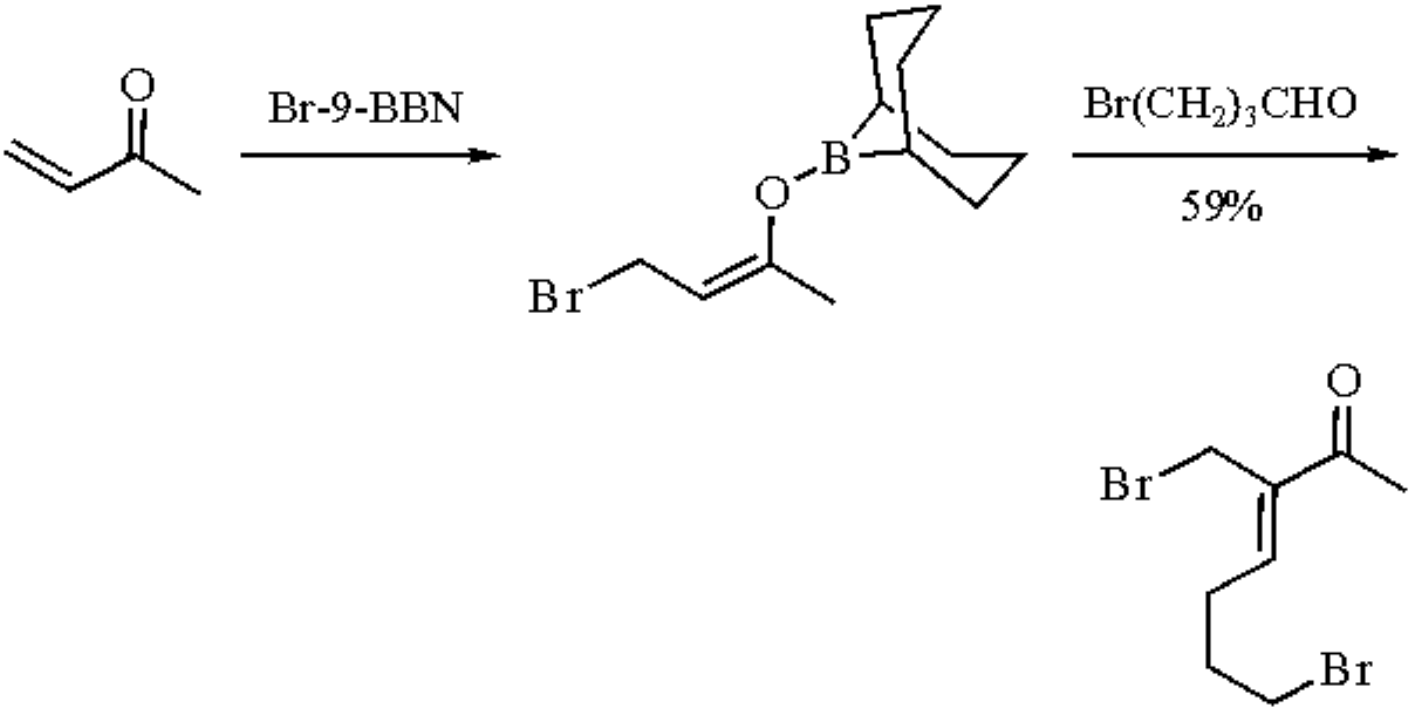

(41)

While catechol- and disiamylborane derivatives were originally employed in the Pd-catalyzed cross coupling of organoboranes to unsaturated organic halides under basic conditions (Suzuki-Miyaura coupling), 9-BBN has recently found an important place in this process. Initially, *B*-(primary alkyl)-9-BBNs, with added bases (NaOH, TlOH, NaOMe, or K_3PO_4), were found to undergo efficient coupling with iodobenzene using ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)*** as the catalyst.[54] However, while secondary alkylboranes may require

this catalyst, ***Tetrakis(triphenylphosphine)palladium(0)*** is perfectly satisfactory for the coupling of *n*- or *i*-alkyl-9-BBN derivatives to unsaturated bromides, iodides, or triflates under basic conditions (eqs 42-45).

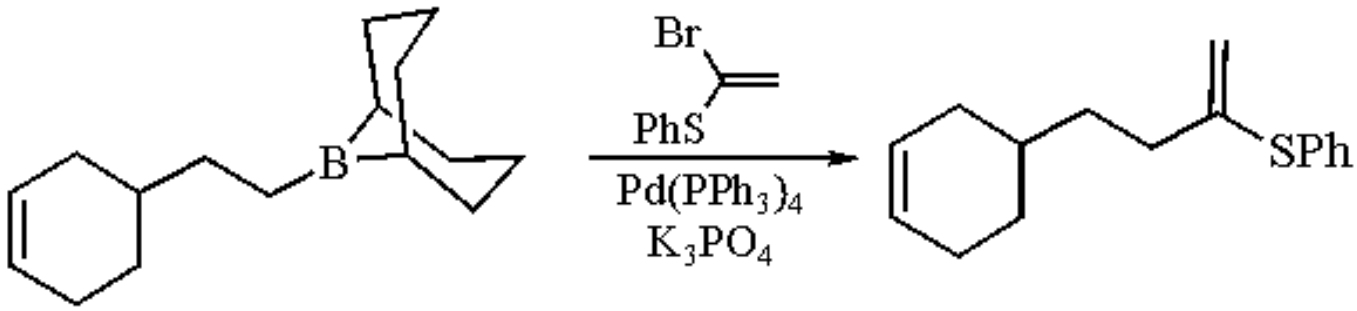

(42)

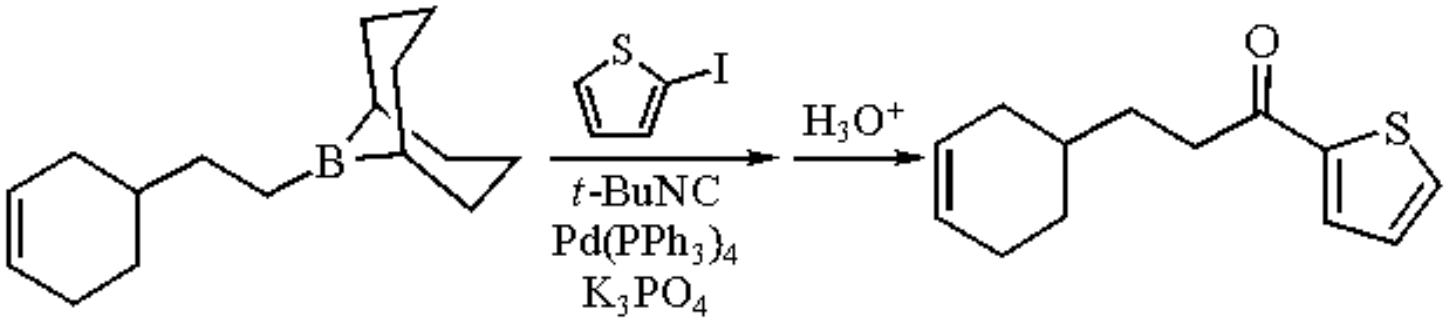

(43)

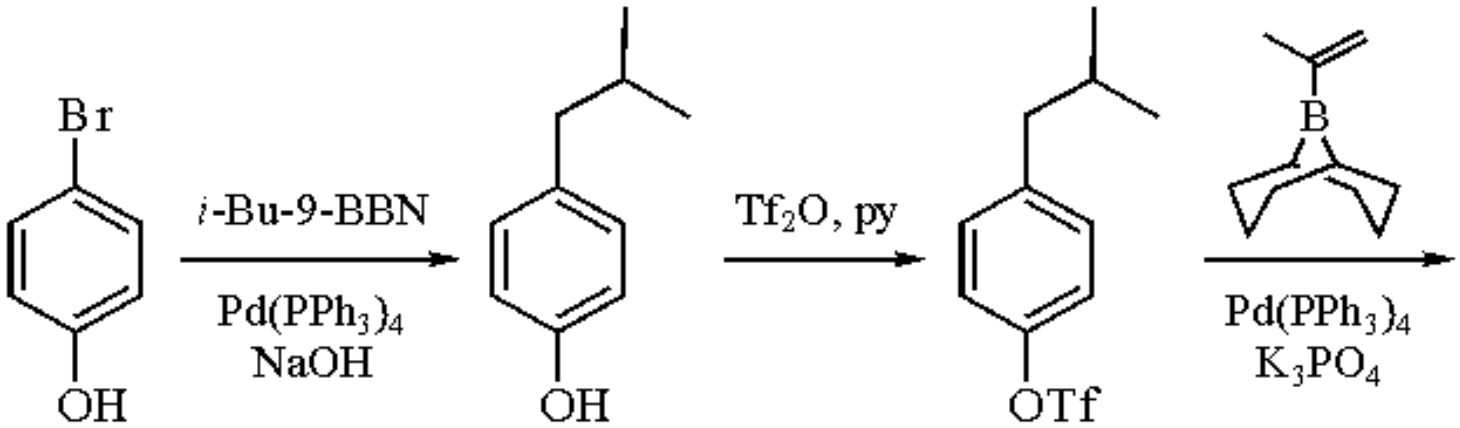

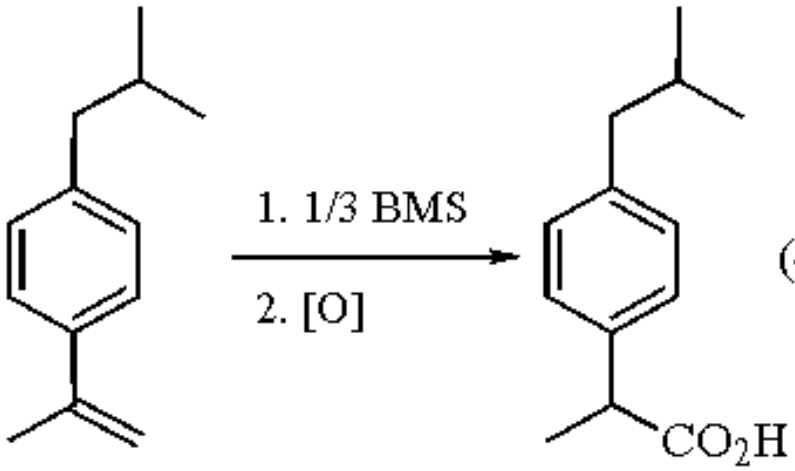

(44)

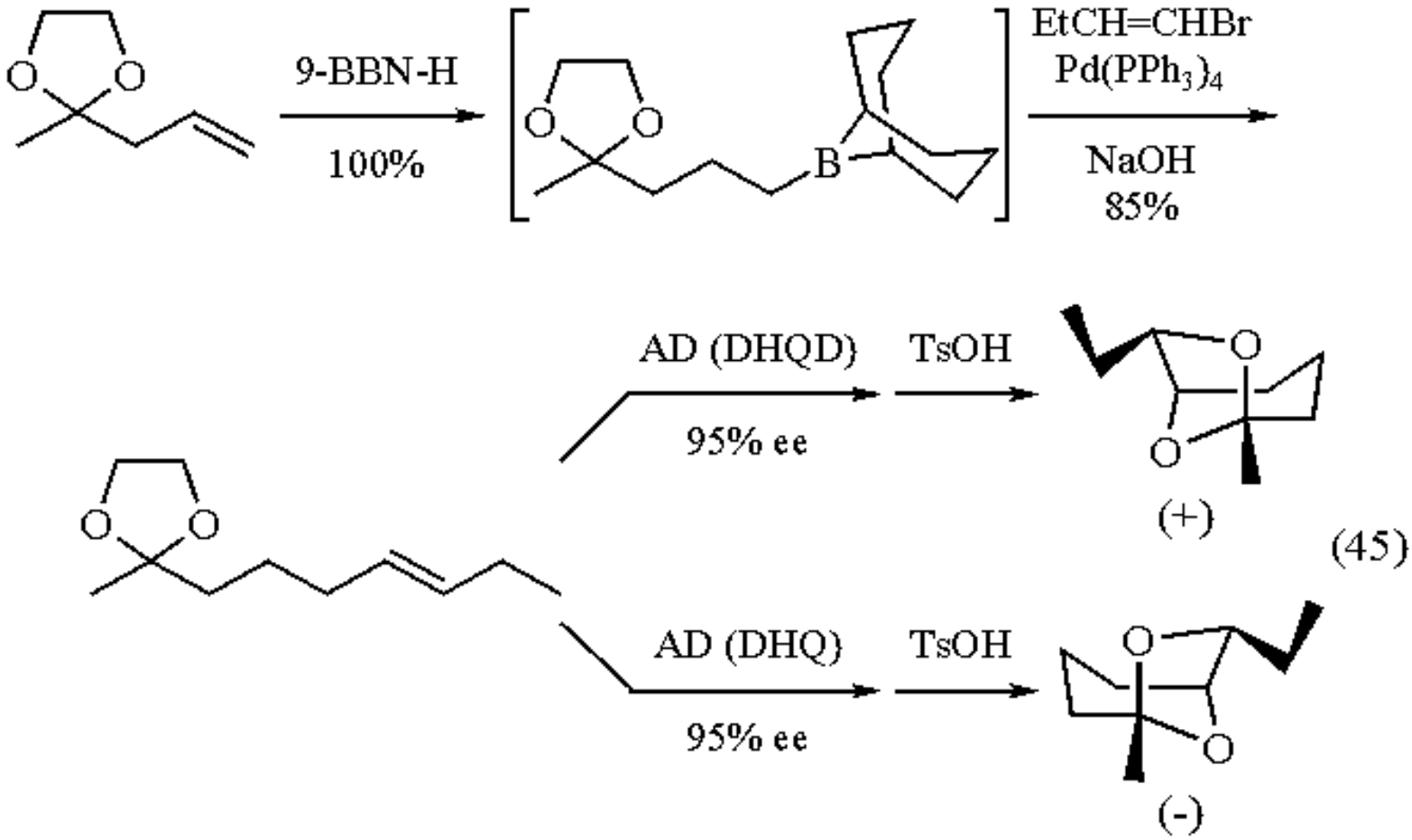

(45)

Several recent applications include the syntheses of pharmaceuticals, pheromones, and prostaglandins, with complete retention of configuration being observed with alkenyl substrates.[54b,55] Either carbon monoxide or ***t-Butyl Isocyanide*** can be used to prepare ketones through the sequential formation of two new carbon-carbon bonds with this reaction.[56] Moreover, vinyl-9-BBNs (eqs 46-48) are also smoothly cross-coupled with retention of configuration to these substrates and, with these now being readily available, their expanded use in this process should flourish.[12,57] It is important to mention that vinyl vs. primary alkyl group transfer is favored by oxygenated ligation on the borane.[52b,58]

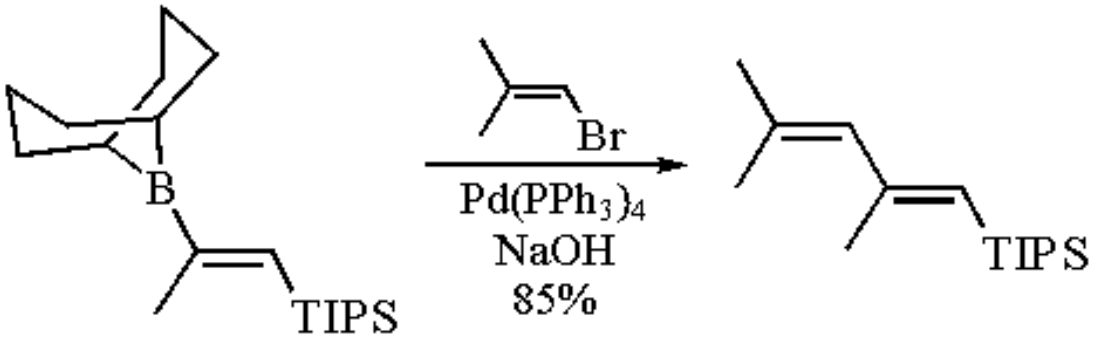

(46)

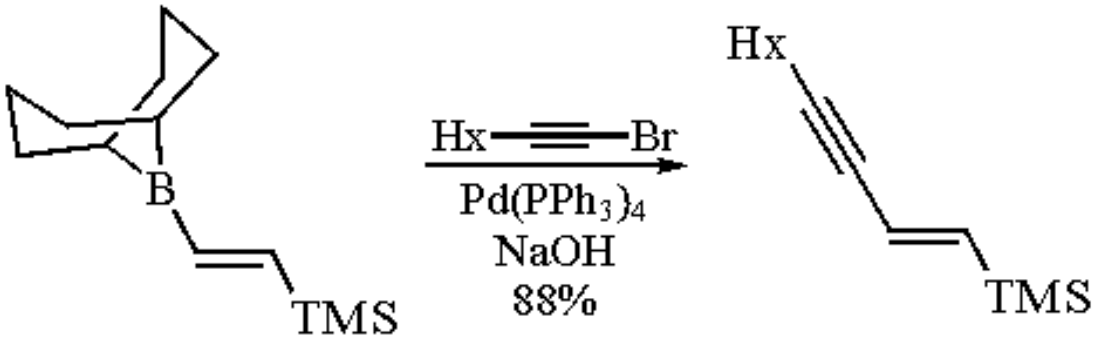

(47)

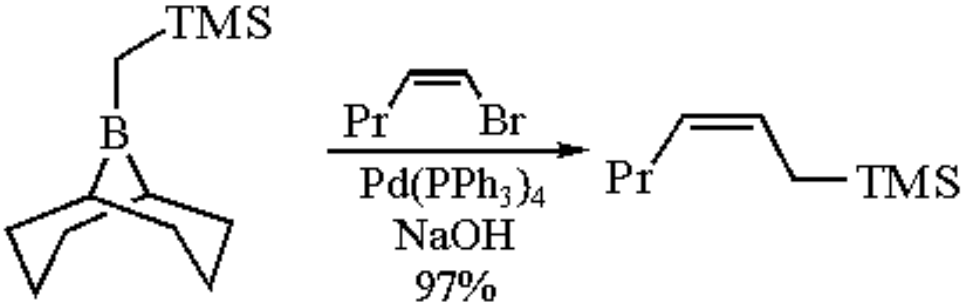

(48)

Related Reagents.

Borane-Dimethyl Sulfide; ***Borane-Tetrahydrofuran***.

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9-Borabicyclononyl Trifluoromethanesulfonate

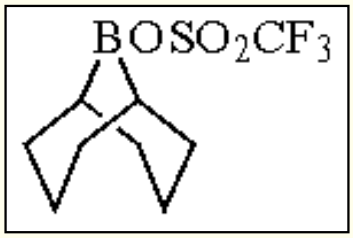

[62731-43-5] · $C_9H_{14}BF_3O_3S$ · 9-Borabicyclononyl Trifluoromethanesulfonate · (MW 270.08)

(Lewis acid for the preparation of vinyloxyboranes[1-4] and boryl azaenolates;[5-8] catalyst for coupling silyl enol ethers and acetals;[9] catalyst for isomerization of epoxides to allylic alcohols[10])

Alternate Name: 9-BBNOTf.

Physical Data: bp 81 °C/2.5 mmHg.

Solubility: sol common inert organic solvents such as Et_2O, CH_2Cl_2, and hexane.

Form Supplied in: 0.5 M solution in hexane.

Preparative Method: equimolar amounts of ***9-Borabicyclo[3.3.1]nonane*** and ***Trifluoromethanesulfonic Acid*** are mixed in hexane and stirred at 20 °C for 24 h after which time the product is isolated by vacuum distillation.[1]

Handling, Storage, and Precautions: use in a fume hood; the neat liquid as well as solutions are moisture and air sensitive; therefore the material should be stored and transferred under a dry inert atmosphere.

Vinyloxyborane Enolates.

9-Borabicyclononyl vinyloxyboranes are conveniently prepared from active methylene carbonyl-containing compounds utilizing 9-BBNOTf in combination with a sterically hindered amine base. Typically the base, either ***Diisopropylethylamine*** or ***2,6-Lutidine*** (2,6-lut), and 9-BBNOTf are premixed in Et_2O or CH_2Cl_2 at -78 °C and then the carbonyl component is added. Enolate generation is allowed to occur over the next 15-30 min at temperatures ranging from -78 °C to 0 °C, resulting in the formation of vinyloxyboranes which are suitable nucleophiles for reaction with aldehydes in a crossed aldol reaction. Other boryl triflate reagents have been shown to have similar or complementary utility in this process (see ***Di-n-butylboryl Trifluoromethanesulfonate*** (Bu_2BOTf) and ***Dicyclopentylboryl Trifluoromethanesulfonate*** ($(c\text{-}C_5H_9)_2BOTf$)).

With unsymmetrical methyl ketones, use of 9-BBNOTf and 2,6-lut results in the regioselective formation of the

vinyloxyborane at the more substituted carbon. However, if Bu_2BOTf and *i*-Pr_2NEt are used, the regioselectivity of vinyloxyborane formation is reversed (eq 1).[1]

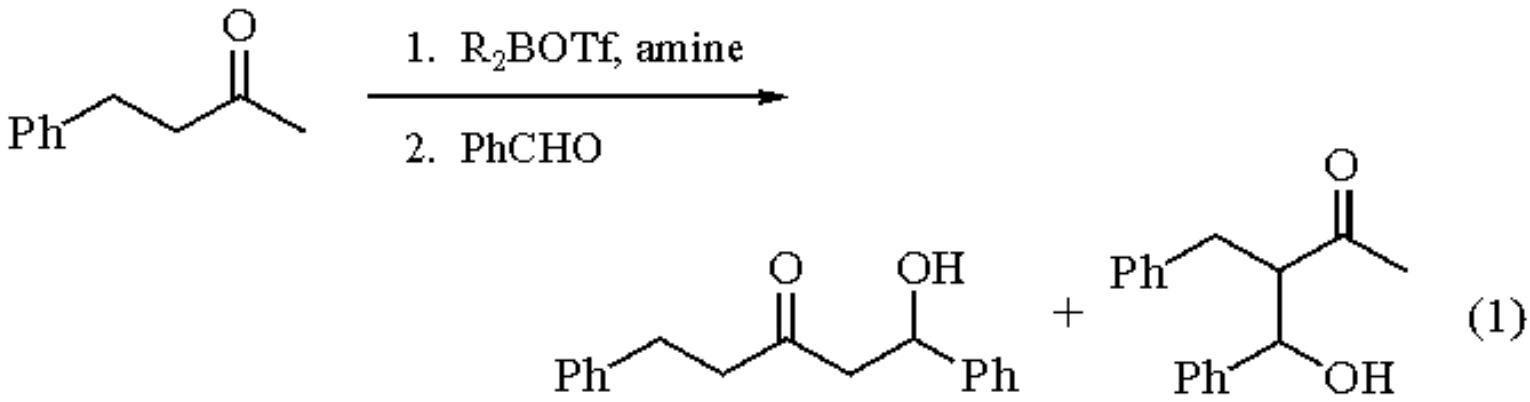

Bu_2BOTf, *i*-Pr_2NEt	100:0
9-BBNOTf, 2,6-lut	12:88

The relative stereochemistry of the two new chiral centers formed in the aldol product is a direct consequence of the vinyloxyborane enolate geometry with *Z*(O) enolates affording the 2,3-*syn* aldol products and the *E*(O) vinyloxyboranes leading to the 2,3-*anti* isomers. As a result, a number of studies have examined the effects of various boron reagents and amines on the geometry of the resulting enolate. For example, when the vinyloxyboranes of ethyl cyclohexyl ketone are generated with $(c\text{-}C_5H_9)_2BOTf$ or 9-BBNOTf in the presence of *i*-Pr_2NEt, and then treated with benzaldehyde, the ratio of crossed aldol products varies dramatically. As shown in eq 2, the enolate derived from $(c\text{-}C_5H_9)_2BOTf$ yields a preponderance of the 2,3-*anti* aldol product while that from 9-BBNOTf produces almost exclusively the 2,3-*syn* isomer.[11] When the ethyl ketone contains a sterically demanding *t*-butyl group, generation of the enolate with 9-BBNOTf and Et_3N produces predominately the *E*(O) vinyloxyborane. However, when the leaving group on the boron reagent is changed from triflate to iodide, the *Z*(O) vinyloxyborane predominates (eq 3).[2]

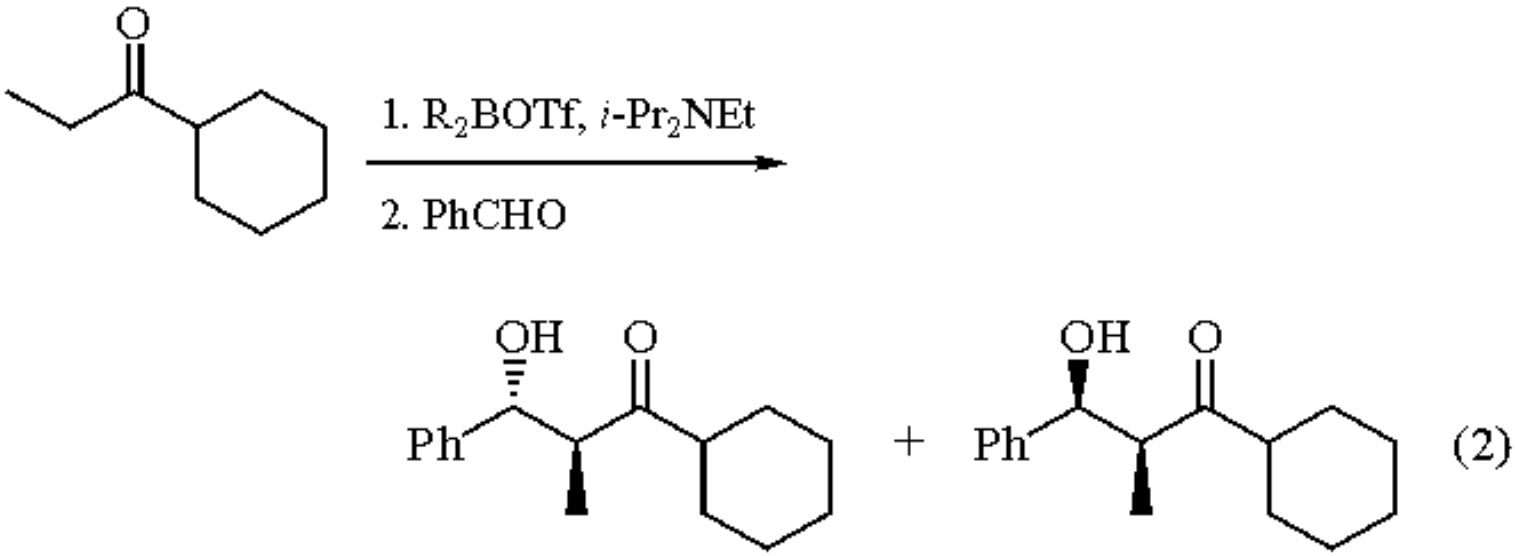

$R_2 = (c\text{-}C_5H_9)_2$	86:14	88%
9-BBN	<3:97	79%

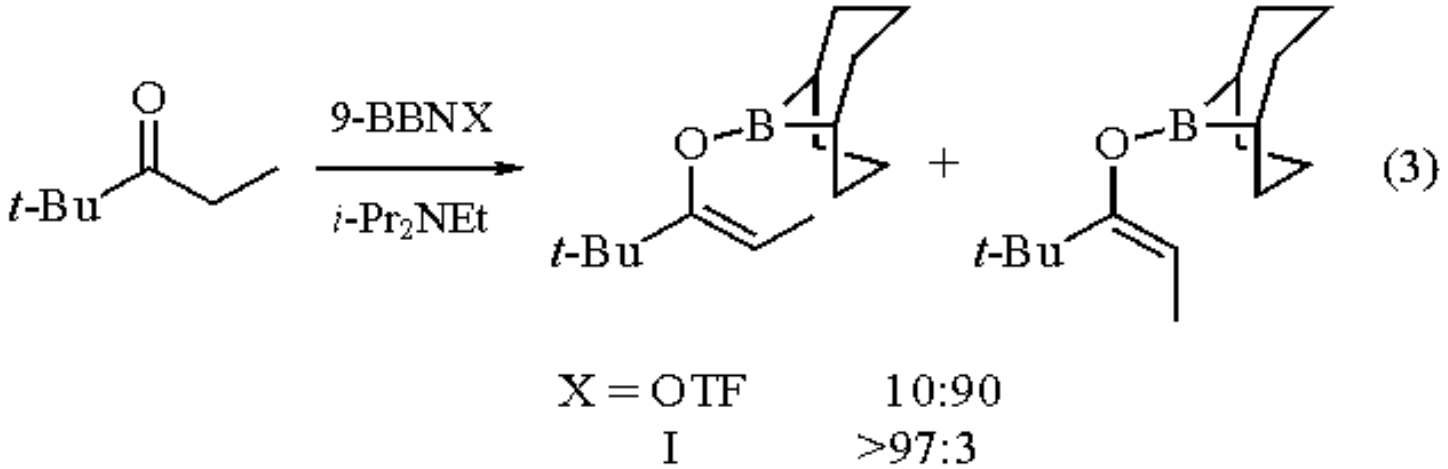

Several propionate synthons initially developed for the preparation of natural products containing polypropionate fragments have also been successfully utilized in combination with 9-BBNOTf to prepare vinyloxyboranes of *Z*(O) geometry. Generation of the enolate from *S*-phenyl propanethioate with 9-BBNOTf and *i*-Pr_2NEt followed by condensation with various model aldehydes gave predominately the 2,3-*syn* aldol products (eq 4).[3] These results are complementary to the cross aldol products obtained from *S*-*t*-butyl propanethioate. Treatment of the latter with $(c\text{-}C_5H_9)_2BOTf$, *i*-Pr_2NEt, and an aldehyde yields predominately the 2,3-*anti* aldol product (see ***Dicyclopentylboryl Trifluoromethanesulfonate***).

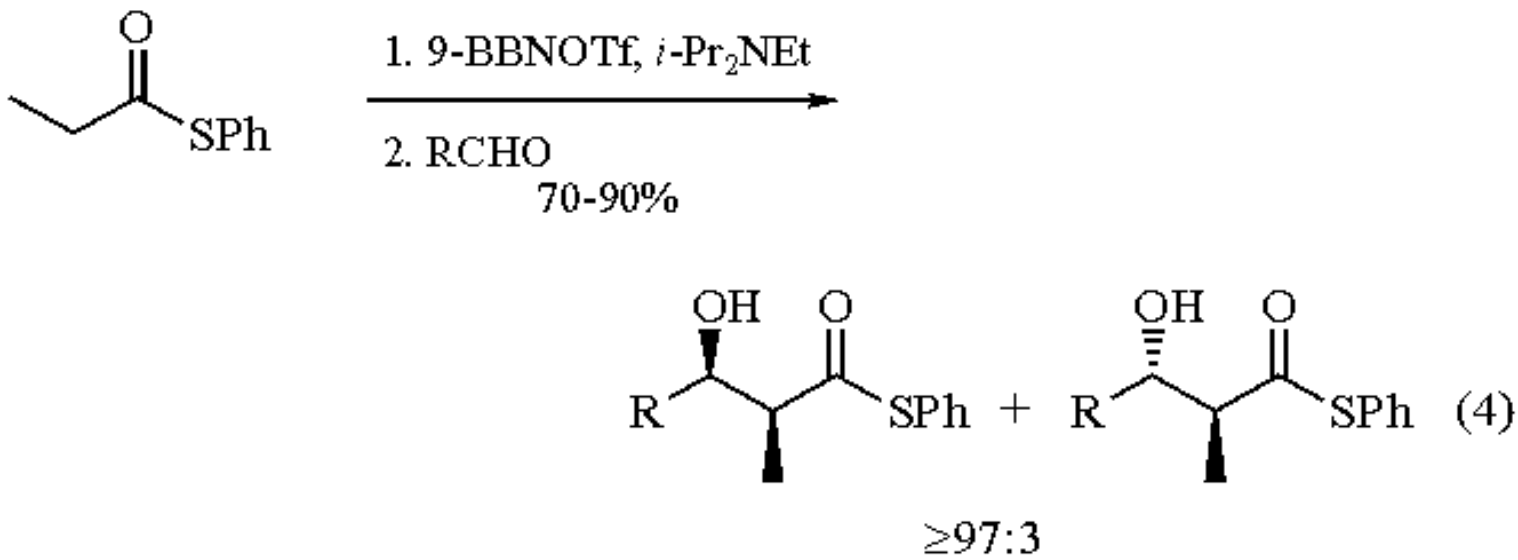

Further extension of this methodology has led to the development of chiral masked propionate equivalents in which the boryl triflate generates chiral vinyloxyboranes of defined enolate geometry. Upon reaction with an aldehyde the chiral enolate is able to exert an influence on the absolute stereochemistry of the two newly formed chiral centers in the crossed aldol product. The α-hydroxy ethyl ketones derived from the enantiomers of hexahydromandelic acid are examples of such reagents. For additional examples see ***Di-n-butylboryl Trifluoromethanesulfonate***. This reagent forms the *Z*(O) vinyloxyborane stereospecifically with 9-BBNOTf, Bu_2BOTf, and $(c\text{-}C_5H_9)_2BOTf$. Upon exposure to a sterically demanding aldehyde such as isobutyraldehyde, the reaction proceeds only with the enolates generated from 9-BBNOTf and Bu_2BOTf. Excellent stereoselection is achieved in both cases (eq 5). The fact that the reaction does not proceed with the bulky cyclopentyl ligands on the vinyloxyborane has been attributed to steric congestion in the transition state.[4]

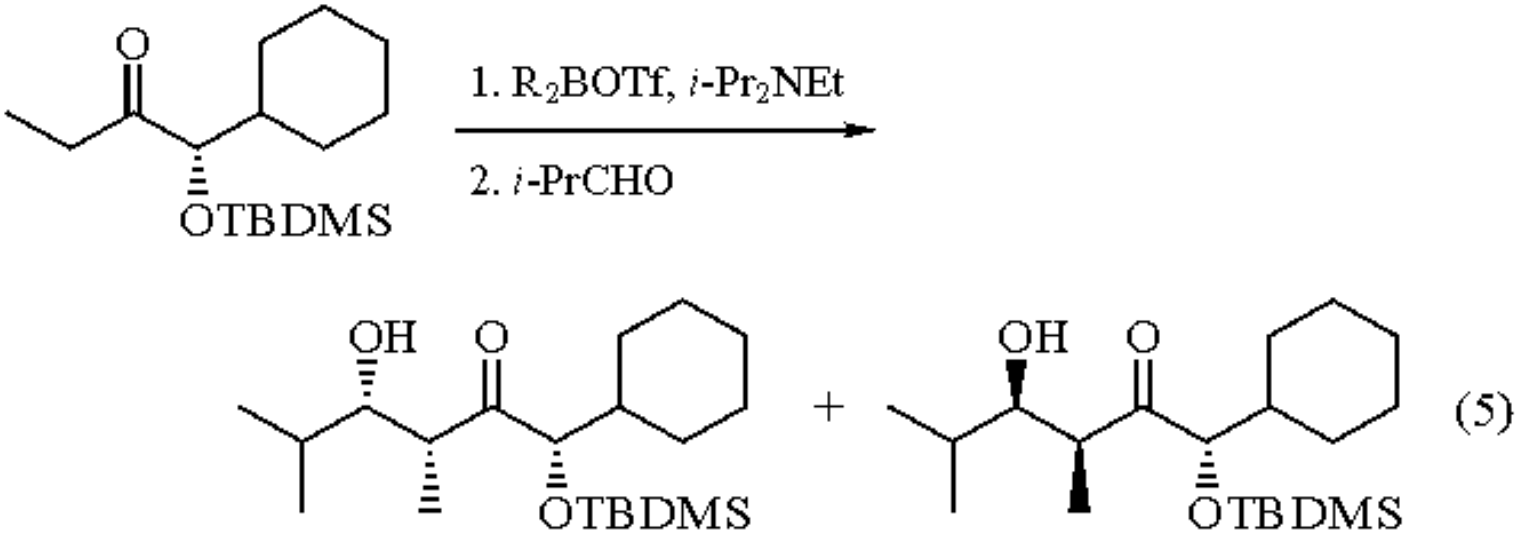

R_2 =	9-BBN	>100:1
	Bu_2	>100:1
	$(c\text{-}C_5H_9)_2$	no reaction

Boryl Azaenolates.

The azaenolate of a chiral 2-ethyloxazoline was prepared with 9-BBNOTf and *i*-Pr_2NEt (eq 6). Subsequent condensation with aldehydes afforded predominately the 2,3-*syn* aldol products. The stereoselectivity of this reaction was rather low, ranging from 40 to 60% de.[5]

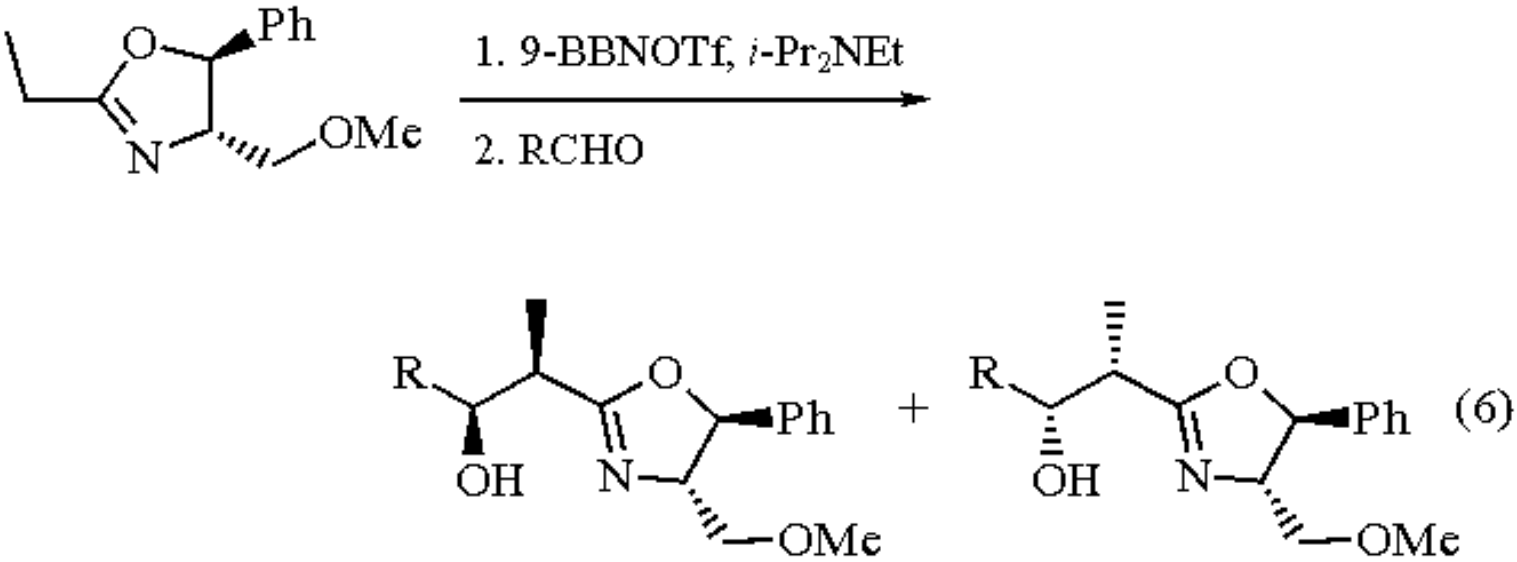

R =	Et	2.3:1	44%
	i-Pr	2.3:1	42%
	i-Bu	4.0:1	50%

A number of methyl substituted nitrogen-containing heteroaromatics have been examined as azaenolate precursors in reactions with benzaldehyde. The azaenolates were generated with 9-BBNOTf and *i*-Pr_2NEt in CH_2Cl_2 and, as shown in Table 1, many of the compounds are good substrates. 2-Methyl-4-phenyloxazole reacts selectively at the 2-position when the boron enolate is condensed with benzaldehyde. This contrasts to the lithium enolate in which condensation occurs exclusively at the 5-position (eq 7).[6] Similar results were observed with 2-methylthiazole, as shown in eq 8. Thus the regioselective functionalization of these methyl substituted five-membered heteroaromatics is achieved by judicious choice of the reaction conditions utilized for azaenolate generation.

Table 1 Aldol Reaction of Heteroaromatics with Benzaldehyde

Heteroaromatic	Yield (%)	Heteroaromatic	Yield (%)
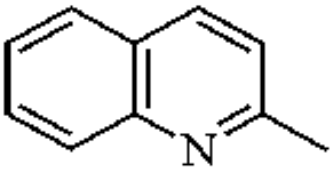	88	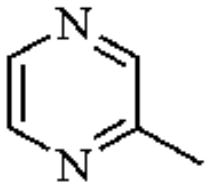	88
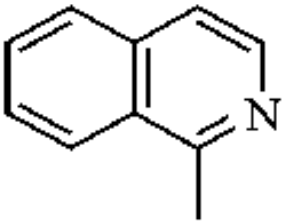	79	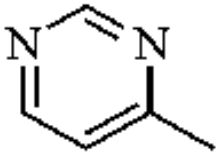	79
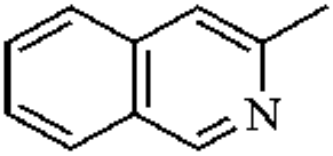	0	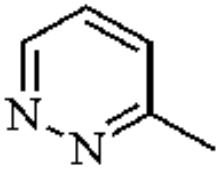	0

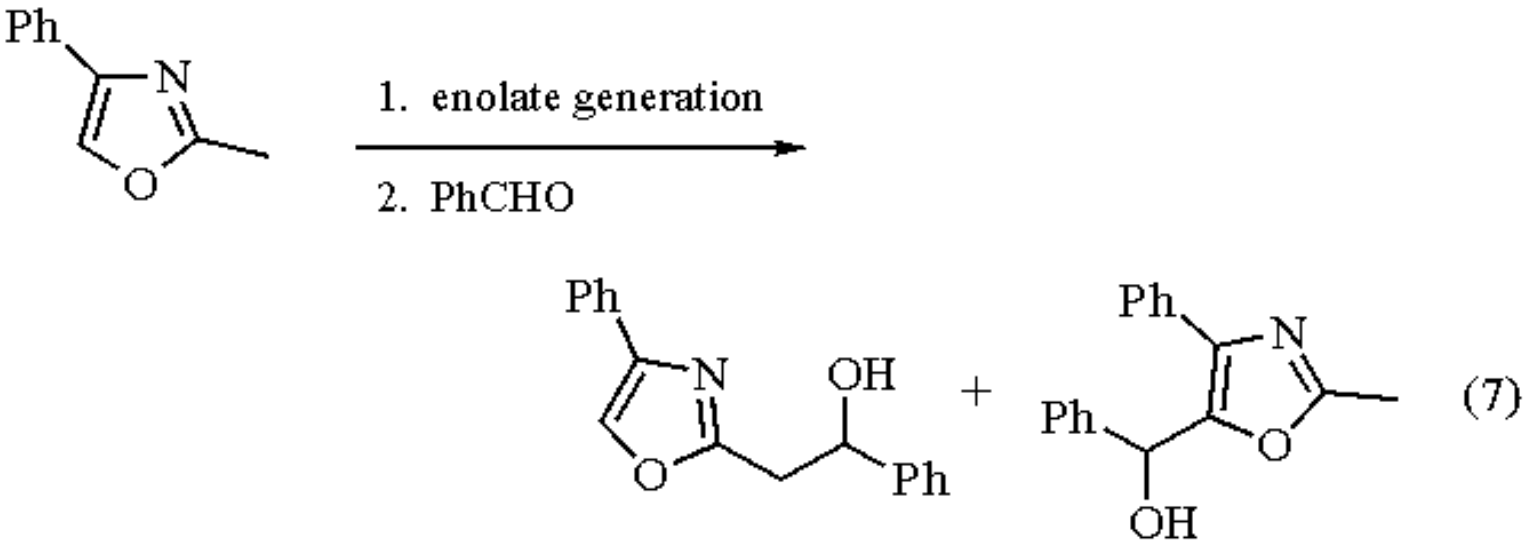

9-BBNOTf, *i*-Pr_2NEt	70%	0%
n-BuLi	0%	58%

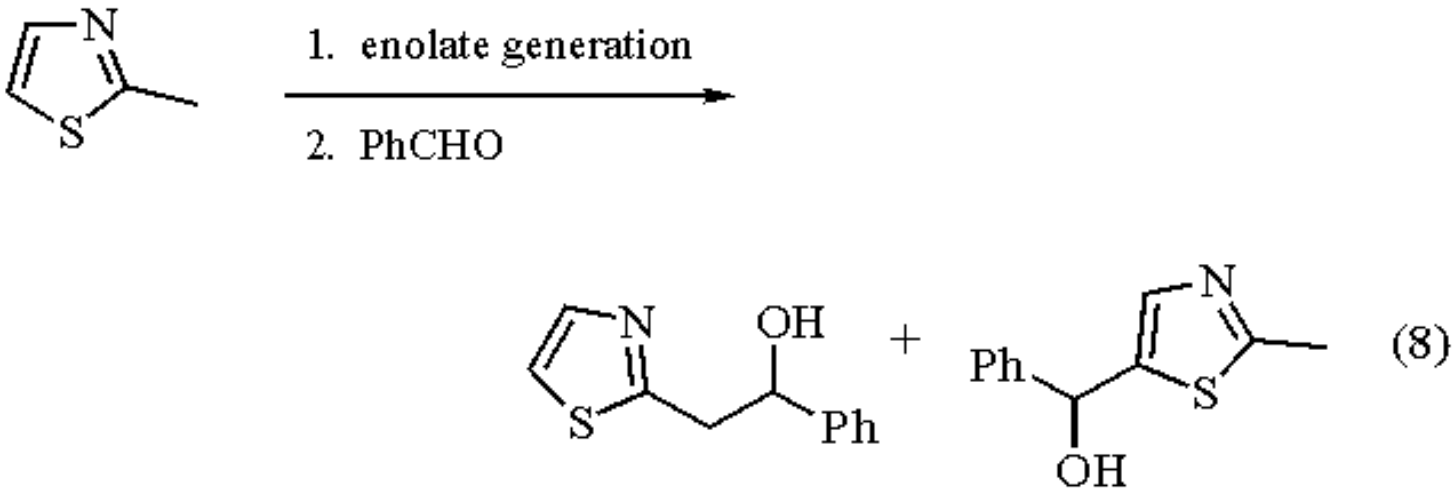

9-BBNOTf, *i*-Pr_2NEt	77%	0%
n-BuLi	18%	52%

Reaction of 2,4-lutidine with benzaldehyde gave aldol-like products arising from condensation at both the 2- and 4-positions. The regioselectivity of the reaction could be controlled by the choice of boryl triflate and amine utilized. 9-BBNOTf and *i*-Pr_2NEt produced an azaenolate which reacted with benzaldehyde exclusively at the 4-position while use of Bu_2BOTf and Et_3N generated an azaenolate which reacted solely at the 2-methyl group (eq 9).[7]

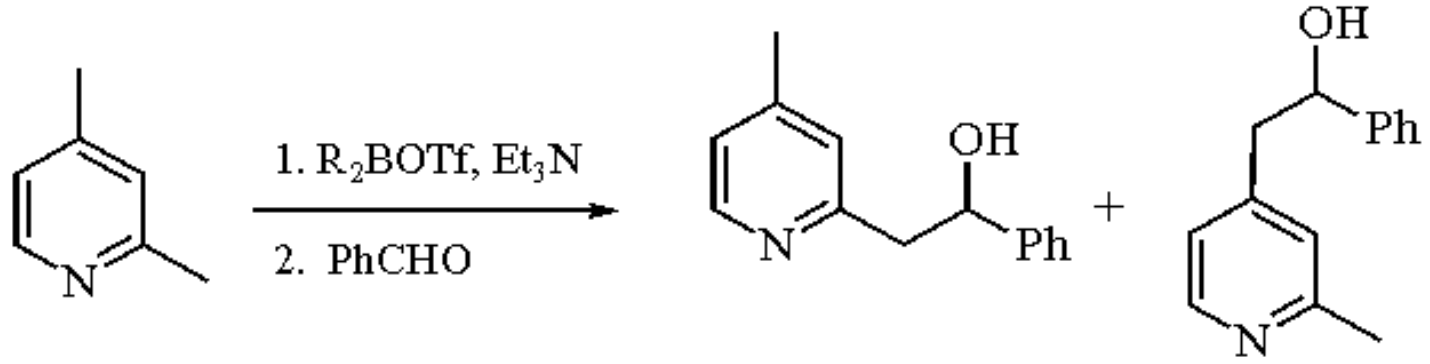

(9)

9-BBNOTf, *i*-Pr_2NEt	0:100	73%
Bu_2BOTf, Et_3N	100:0	68%

Nitrile derivatives also react with 9-BBNOTf and *i*-Pr_2NEt to produce an azaenolate which was condensed with various substituted benzaldehydes to yield β-hydroxy nitrile products.[8] The yields were low when aliphatic aldehydes were utilized as reactants, thus limiting the scope of this reaction.

Mukaiyama Reaction Catalyst.

β-Alkoxy ketones are produced when 9-BBNOTf is used to catalyze the coupling of enol silyl ethers with acetals (eq 10).[9]

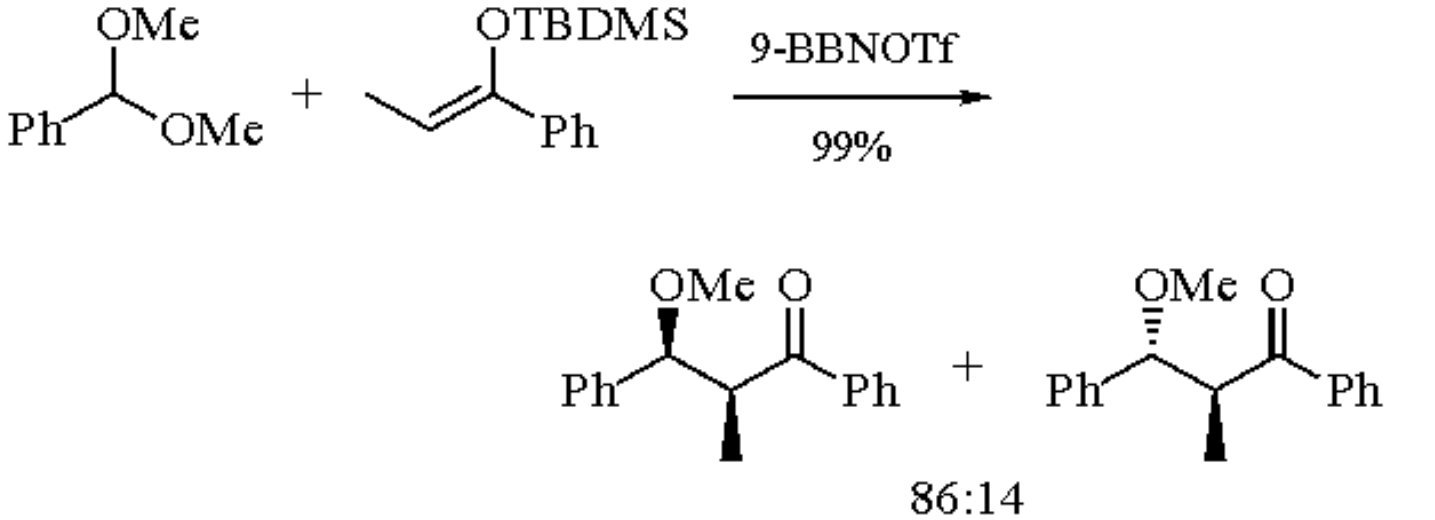

(10)

Allylic Alcohols from Epoxides.

Epoxides are isomerized to allylic alcohols in the presence of 9-BBNOTf and 2,6-lut. The reaction proceeds most efficiently when the substrate is treated with equimolar equivalents of the triflate and amine reagents. When the possibility of producing regioisomeric alkenes exists, as in the example shown in eq 11, both are observed.[10]

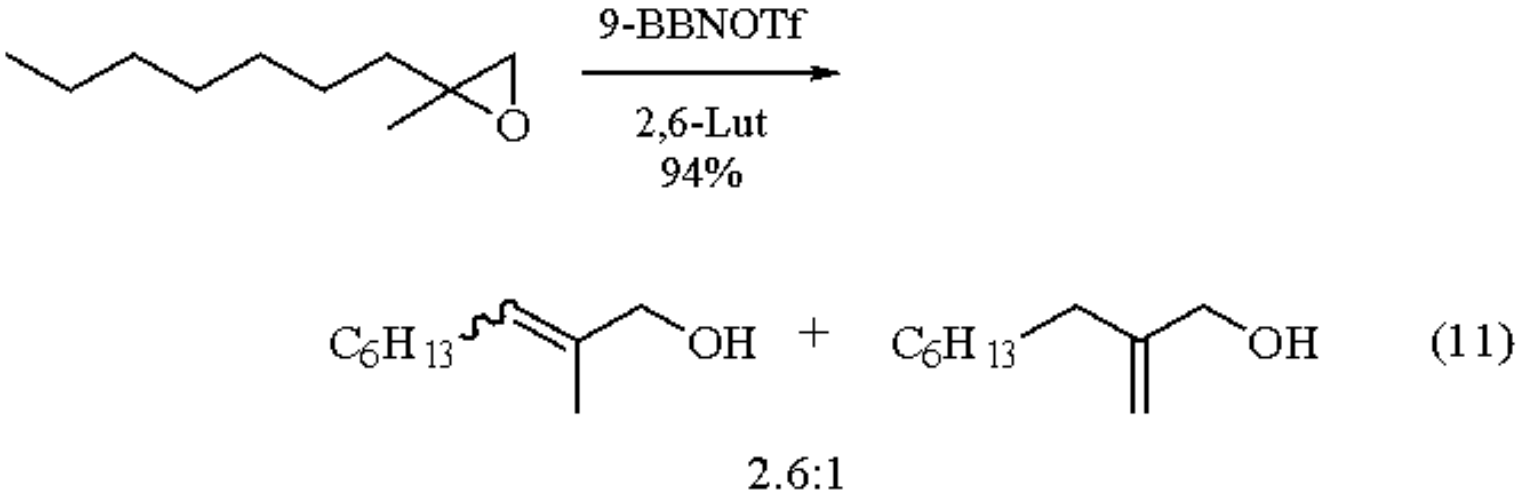

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Borane-Ammonia[1]

$NH_3.BH_3$

[13774-81-7] · BH_6N · Borane-Ammonia · (MW 30.86)

(strong chemo- and stereoselective, hydride-like reducing agent with greater hydrolytic stability than $NaBH_4$ in protic solvents (including water) and higher solubility in aprotic organic solvents; useful for the reduction of carbonyls and carbon-nitrogen double bonds)

Solubility: very sol methanol, THF, toluene, and dichloromethane; sol water and diethyl ether; insol hexane.[1]

Form Supplied in: waxy solid; commercially available as 90% technical grade.

Handling, Storage, and Precautions: explodes when heated; use in a fume hood. Borane-ammonia thermally decomposes to aminoborane with the evolution of hydrogen.[1] Heating the solid reagent presents an explosion hazard. $BH_3.NH_3$ is hygroscopic and undergoes slow degradation in the presence of moisture to ammonia and hydrogen gas. Bottles of ammonia borane should be stored in the cold, flushed with nitrogen, sealed to avoid contamination by atmospheric moisture and opened carefully due to potential pressure build-up. Because of its greater purity, indistinguishable reactivity and thermal and hydrolytic stability, the commercially available reagent borane-*t*-butylamine[1] should be substituted for borane-ammonia whenever possible.

Carbonyl Reductions.

Borane-ammonia is a non-ionic dative complex with reducing properties equivalent to ***Sodium Borohydride***. It is a mild reducing agent which is useful in a wide range of solvents (including water) at temperatures as low as -50 °C. Aliphatic and aromatic ketones, aldehydes, and enones are reduced, affording the corresponding alcohols in 65-97% isolated yields.[1] It is capable of transferring all three hydride equivalents and excess reagent can conveniently be hydrolyzed by quenching with dilute HCl. Because of its being intermediate in reactivity between the electrophilic reagent borane and the nucleophilic hydride reagents, $BH_3.HN_3$ exhibits unique stereo- and chemoselective reactivity.

Stereoselectivity.

In the reduction of 4-*t*-butylcyclohexanone, $BH_3.HN_3$ in methanol at -50 °C affords a high ratio (96:4) of axial hydride delivery.[2a] Stereoselective carbonyl reductions have been reported in the synthesis of lubimin,[3] and in the stereospecific reduction of a protected octulopyranosylonic acid.[4]

The reduction of (*S*)-γ-methytetronic acid in methanol/water (eq 1) gave a 25:75 ratio of the *cis*:*trans* hydroxy lactones (a ratio opposite to that observed with catalytic hydrogenation over rhodium).[5a] Six-member-ring analogs of tetronic acids were found to be reducible with $BH_3.NH_3$ but not with sodium borohydride or sodium cyanoborohydride.[5b]

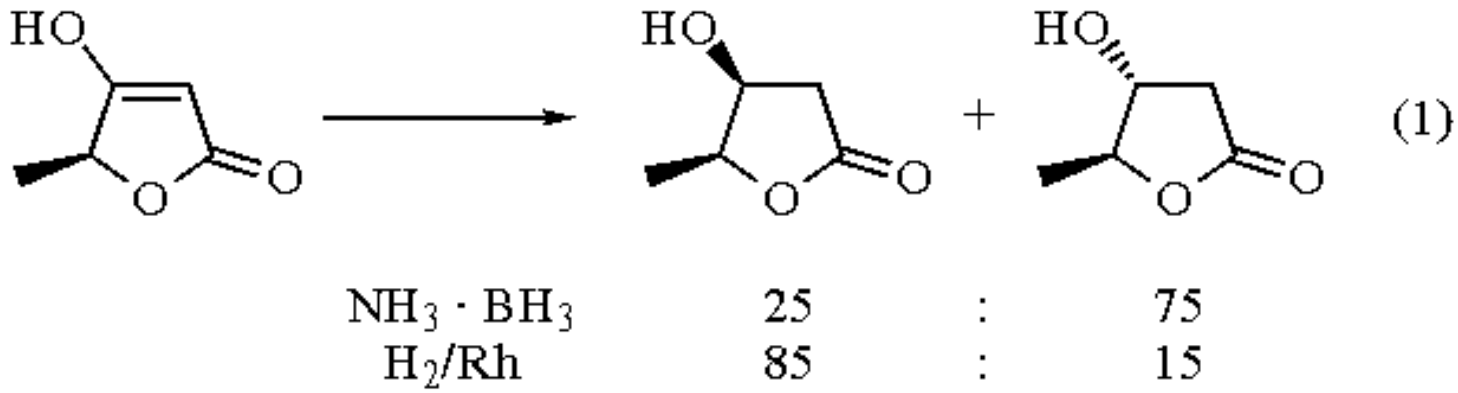

Diastereoselectivity has been observed in the reduction of an acyclic sterically hindered α-keto ester (eq 2).[6]

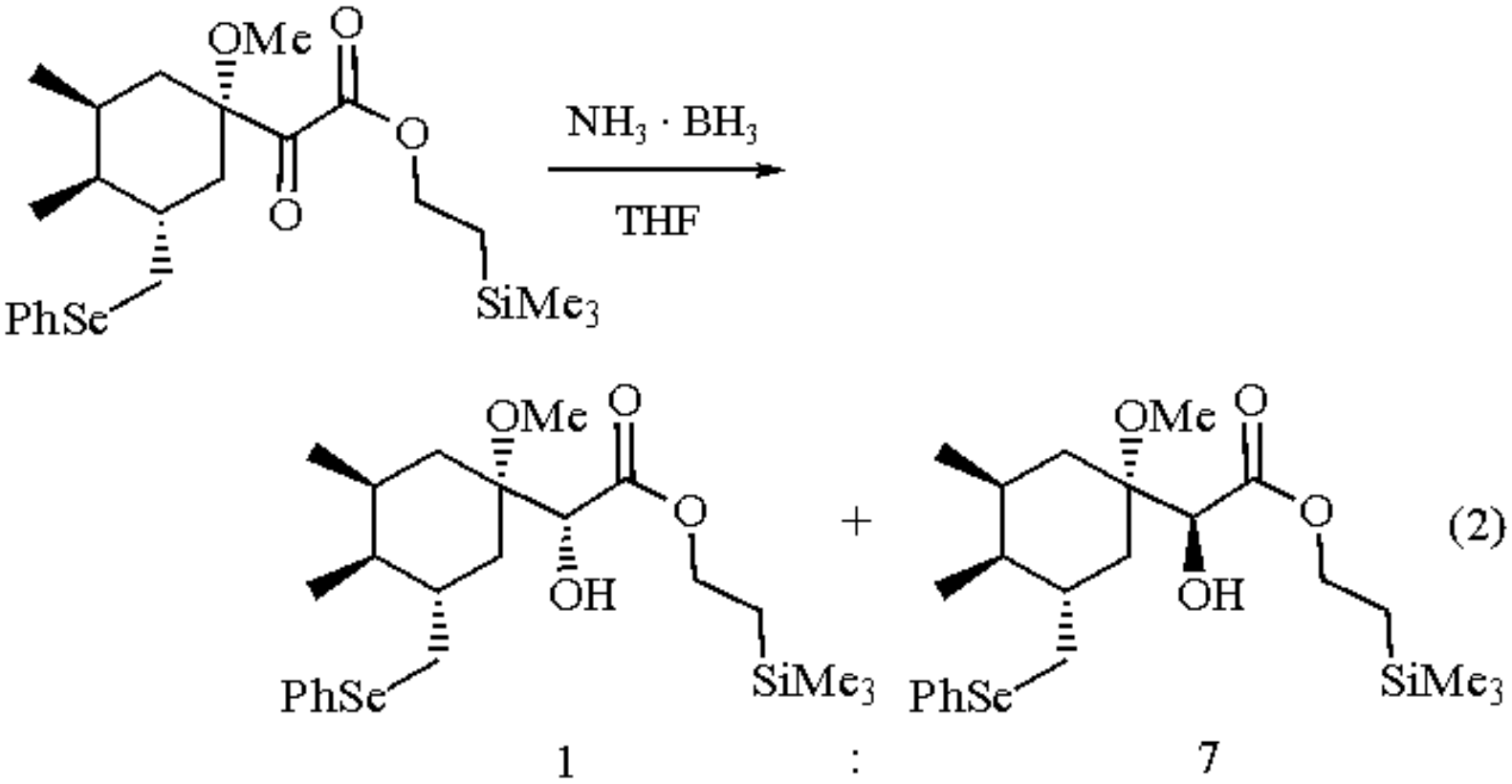

Reductions of aromatic ketones with $BH_3.NH_3$ complex and chiral ***18-Crown-6*** derivatives afford 63-80% yields of the corresponding alcohols with enantiomeric excesses of 28-67%.[7]

Chemoselectivity.

The reduction of a 1:1 molar mixture of benzaldehyde and acetophenone with 1 hydride equivalent affords a 98:2 ratio of benzyl alcohol to phenylethanol.[2b] The relative reduction rates decrease in the order aliphatic aldehyde > aromatic

aldehyde > hexanone > pentanone > arylketone > enone. Thus ketones may be reduced selectively in the presence of enones,[8,2b] and aliphatic aldehydes in the presence of ketone and/or lactone moieties.[9a,9b]

Reduction of Imines.

In the reduction of 4-substituted cyclohexyl imines, iminium salts, and enamines with $BH_3.NH_3$,[10] in contrast to the case with carbonyl reduction, equatorial attack of hydride is favored affording the corresponding reduced amines in 60-89% yield.

Related Reagents.

Sodium Borohydride; ***Sodium Cyanoborohydride***.

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Borane-Dimethyl Sulfide[1]

$BH_3.SMe_2$

[13292-87-0] · C_2H_9BS · Borane-Dimethyl Sulfide · (MW 75.96)

(hydroborating and reducing agent)

Alternate Name: BMS.

*Physical Data: d*204 = 0.801 g cm^{-3}.

Solubility: sol dichloromethane, benzene, toluene, xylene, hexane, diethyl ether, diglyme, DME, and ethyl acetate; insol but reacts slowly with water; reacts with alcohols, acetone.

Form Supplied in: neat complex, colorless liquid, ca. 10 M in BH_3; contains slight excess of dimethyl sulfide.

Analysis of Reagent Purity: active hydride is determined by hydrolysis of an aliquot in glycerol-water-methanol mixture and measuring the hydrogen evolved according to a standard procedure.[3a] ^{11}B NMR (CH_2Cl_2) δ -20.1 ppm (*q*, J_{B-H} = 104 Hz).[4]

Preparative Method: ***Diborane*** generated by the reaction of ***Sodium Borohydride*** with ***Boron Trifluoride Etherate*** in diglyme[3] is absorbed in ***Dimethyl Sulfide***.

Purification: commercial reagent can be purified and freed of excess dimethyl sulfide by vacuum transfer.[2]

Handling, Storage, and Precautions: use in a fume hood; flammable liquid with stench; reacts with atmospheric moisture forming a crust of boric acid. Store and handle under nitrogen or argon. Stable indefinitely when kept at 0 °C. Stable for prolonged periods at rt.

Introduction.

Borane-dimethyl sulfide (BMS) parallels ***Borane-Tetrahydrofuran*** in hydroboration and reduction reactions. Its advantages are stability, solubility in various solvents, and higher concentration.

Hydroboration.

Directive effects and stereoselectivity in the hydroboration of representative alkenes with BMS are shown in Figure 1.[5,6]

Oxidation of organoborane intermediates with a standard alkaline hydrogen peroxide in the presence of dimethyl sulfide requires a higher concentration of alkali to suppress slow concurrent oxidation of dimethyl sulfide. When its presence is not desirable, it can be removed by selective oxidation with sodium hypochlorite.[7] The oxidation of primary trialkylboranes with ***Pyridinium Chlorochromate*** in methylene chloride and with ***Chromium(VI) Oxide*** in acetic acid provides the corresponding aldehydes and acids, respectively. The method works best for α-alkyl-substituted alkenes undergoing hydroboration with high regioselectivity (eq 1).[8] BMS finds application for the synthesis of various hydroborating and reducing agents derived from hindered alkenes and other precursors.[9]

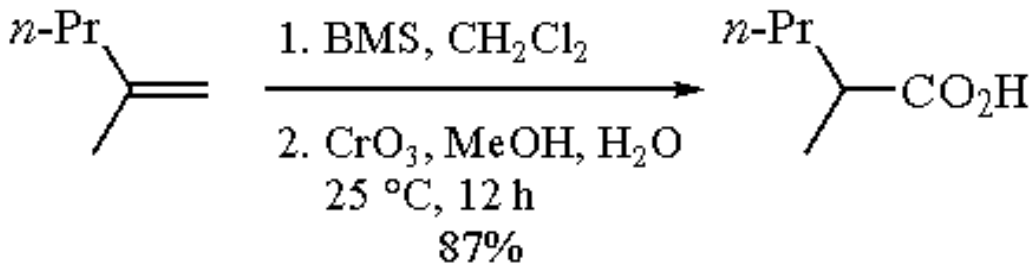

(1)

The reaction of internal alkynes with BMS (also with ***Borane-Tetrahydrofuran***) can be controlled to give the corresponding (*Z*)-alkenylborane. Photochemical isomerization of such alkenylboranes has been reported (eq 2).[10]

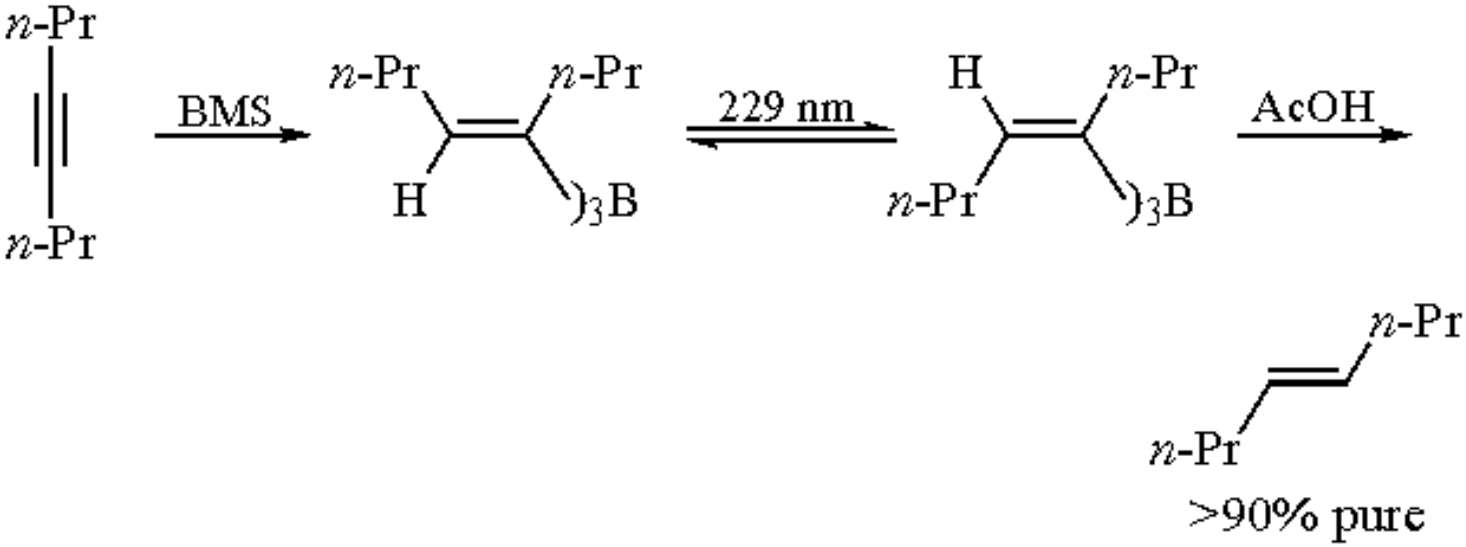

(2)

The hydroboration of cyclic dienes with BMS gives mixtures of products. Dihydroboration predominates for seven- and eight-membered ring dienes, whereas cyclopentadiene and 1,3-cyclohexadiene give mainly the homoallylic and allylic organoborane, respectively.[11] Acyclic α,o-dienes are transformed into bora heterocycles by cyclic hydroboration with ***9-Borabicyclo[3.3.1]nonane*** and BMS (eq 3).[9c,12]

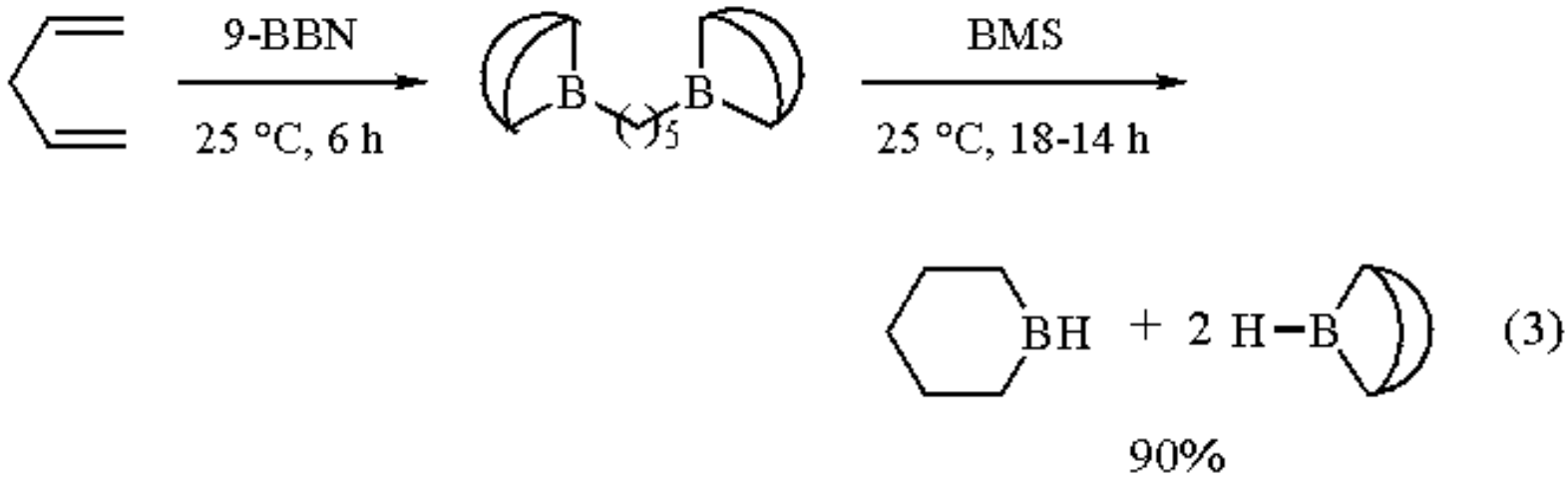

The hydroboration reaction tolerates many functional groups. A high level of acyclic diastereoselection is achieved in certain highly functionalized alkenes with BMS (eq 4)[13a] and also with borane-THF.[13b,c] Vinylic and allylic derivatives containing oxygen, sulfur, or nitrogen substituents react with high regioselectivity, placing boron at the β-position (Figure 2).[6,14] Although such organoboranes are prone to elimination reactions, pure products can often be obtained by a careful control of the reaction conditions.

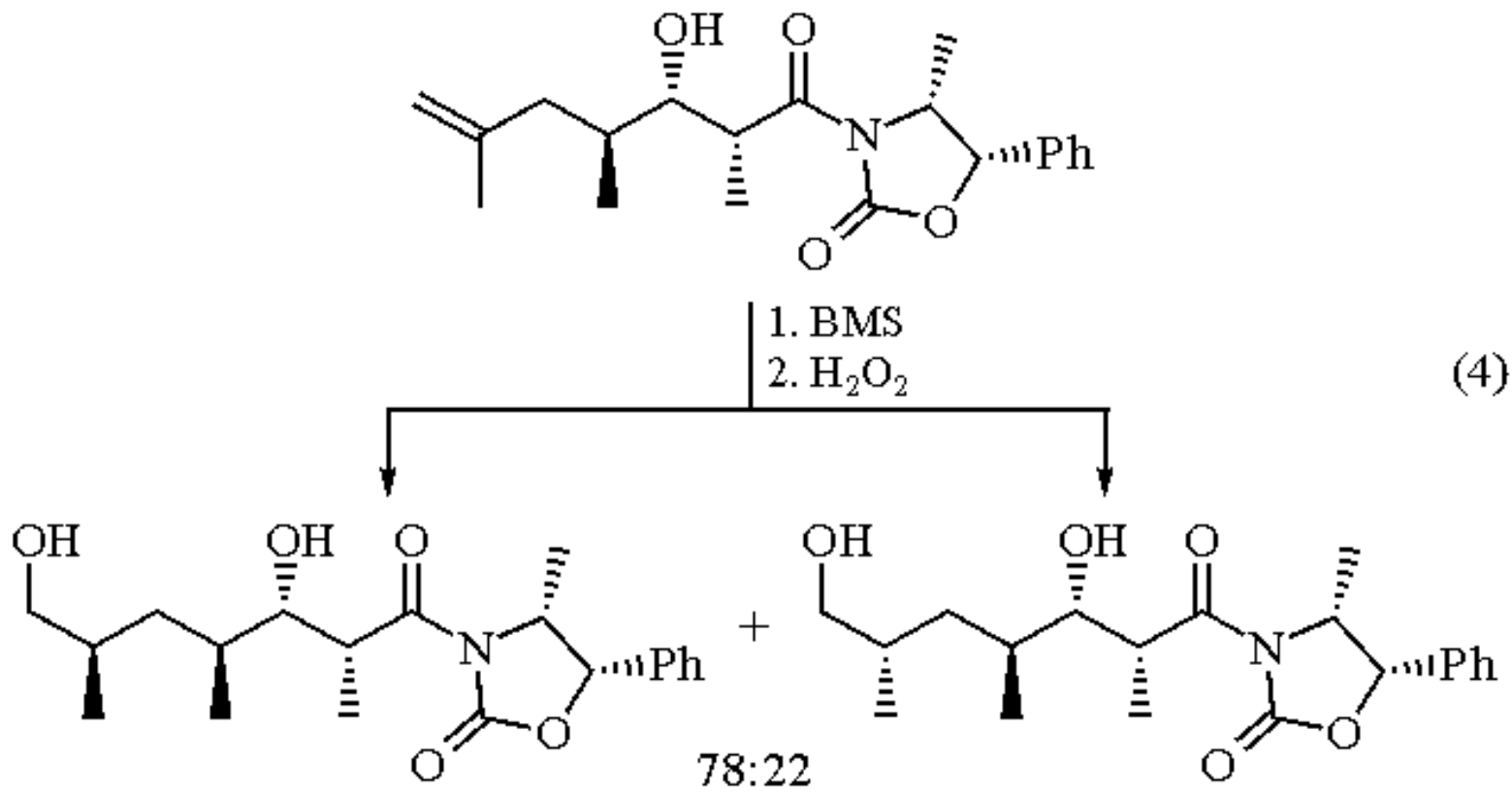

Generally, the hydroboration of allylic amines and sulfides proceeds only to the monoalkylborane stage due to intramolecular complexation.[15,16] The amino group can be protected by Boc, benzyloxycarbonyl, trimethylsilyl, or phosphoramido groups[14,17,18] (eq 5).[17] Allylic *N*-phosphoroamidates are readily transformed into γ-haloamines via hydroboration-halogenolysis.[18]

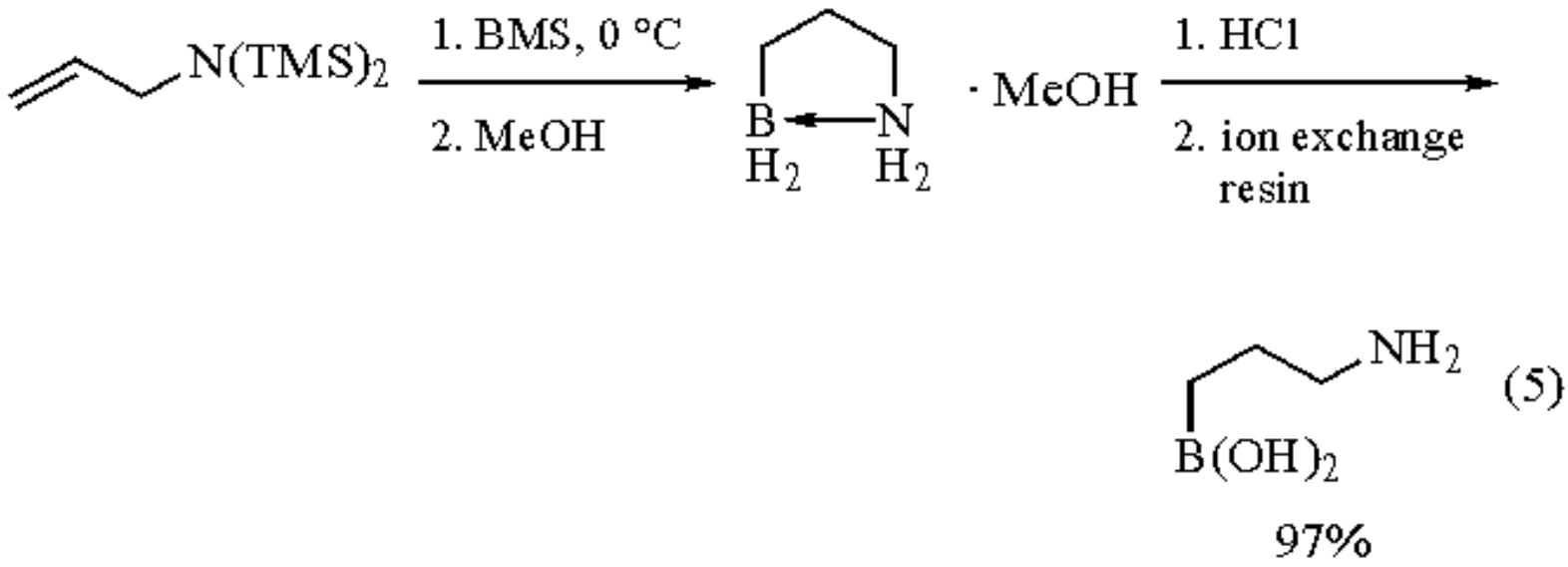

The hydroboration of β-monosubstituted enamines with BMS in THF affords [(2-dialkylamino)alkyl]boranes as the major product, which can be transformed into the corresponding boronates, boronic acids, amino alcohols, or alkenes, depending on the reaction conditions (eq 6).[16,19] Aldehydes and ketones can be stereoselectively transformed into (*E*)- or (*Z*)-alkenes by this method (eq 6).[19]

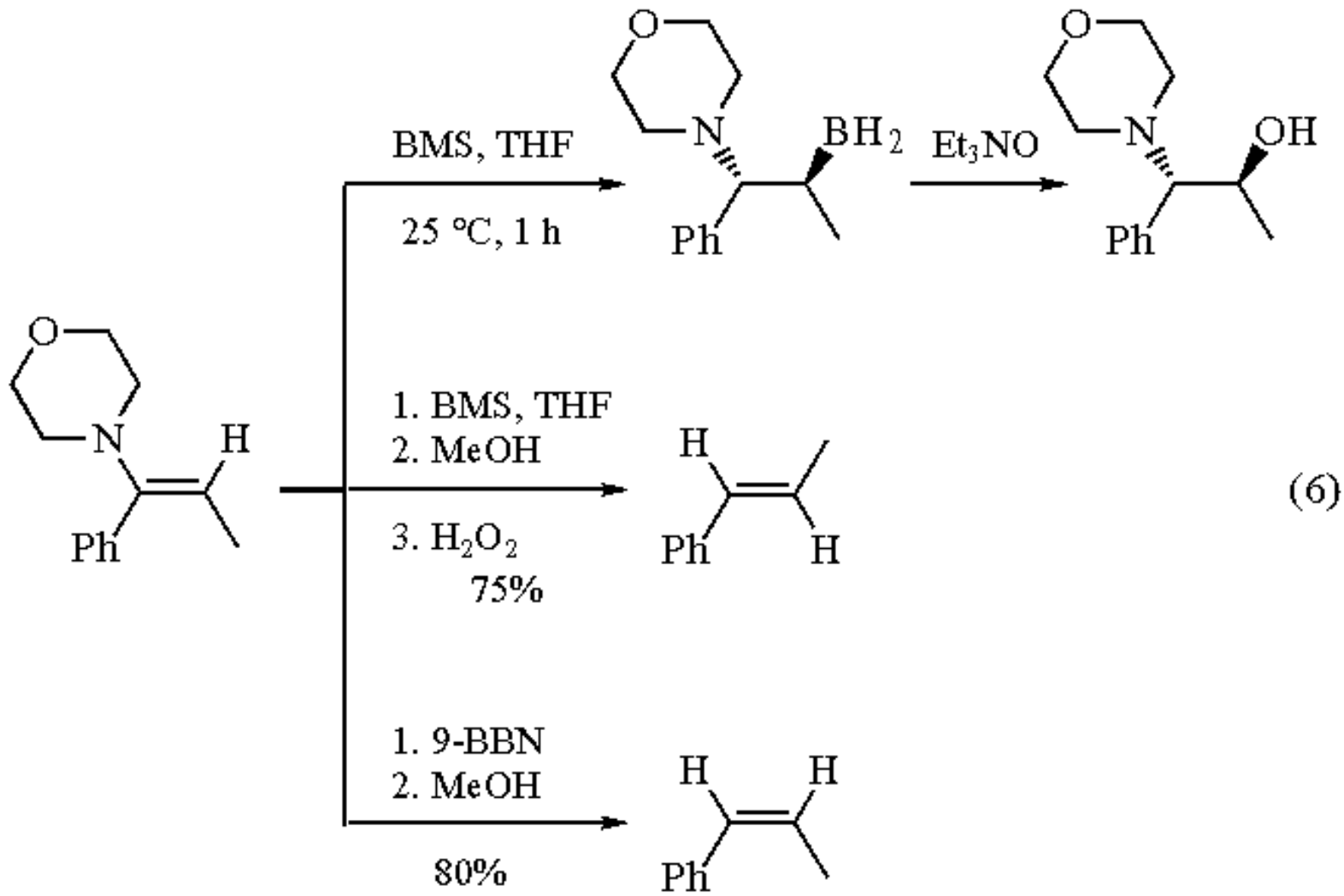

Directive effects in the addition of BMS to vinylic and allylic silicon derivatives are opposite to those observed for the oxygen and nitrogen derivatives (Figure 3).[20]

Several stereodefined organoboranes containing two different metals, boron and silicon, in a 1:3 relationship have been synthesized and transformed into 1,3-diols.[21] The hydroboration of alkynylsilanes provides a convenient access to acylsilanes (eq 7).[20b,22]

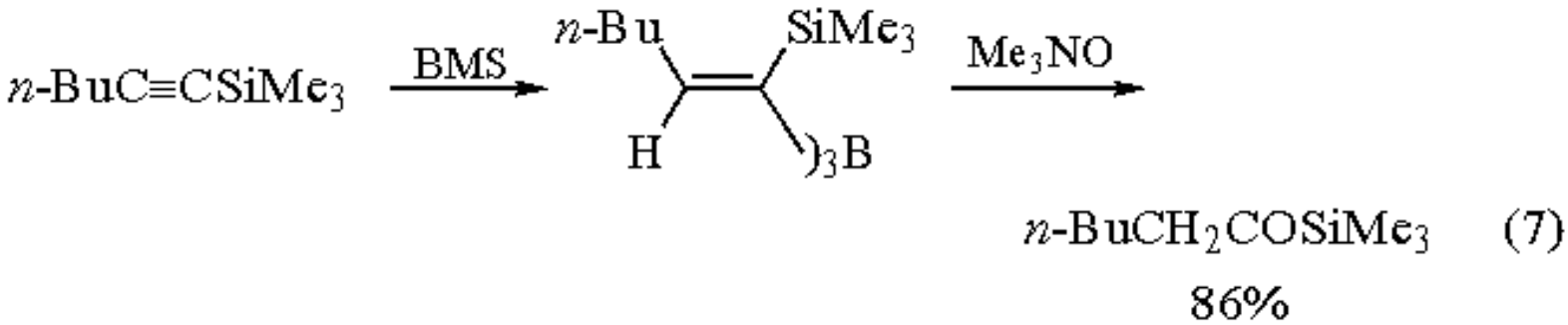

Following the analogy to cyclic hydroboration of dienes with 9-BBN/BMS, pharmacologically important 1-silacyclohexan-4-one has been synthesized via cyclic hydroboration of the divinylsilane derivative.[23,24]

Reduction of Functional Groups:[1,25,26] Carboxylic Acids and Derivatives.

Carboxylic acids,[16,27] thioacids,[28] and amino acids[29] are transformed into the corresponding alcohols, thiols, and amino alcohols. Aromatic acids are reduced in the presence of trimethoxyborane.[30] They may also undergo reduction to hydrocarbons.[31] Oxidation of the intermediate alkoxyboranes yields aldehydes.[27a] Since alkoxyboranes are readily prepared from alcohols,[32] the PCC oxidation of alkoxyboranes may be advantageous if water-sensitive groups are present (eq 8).[27a,32b]

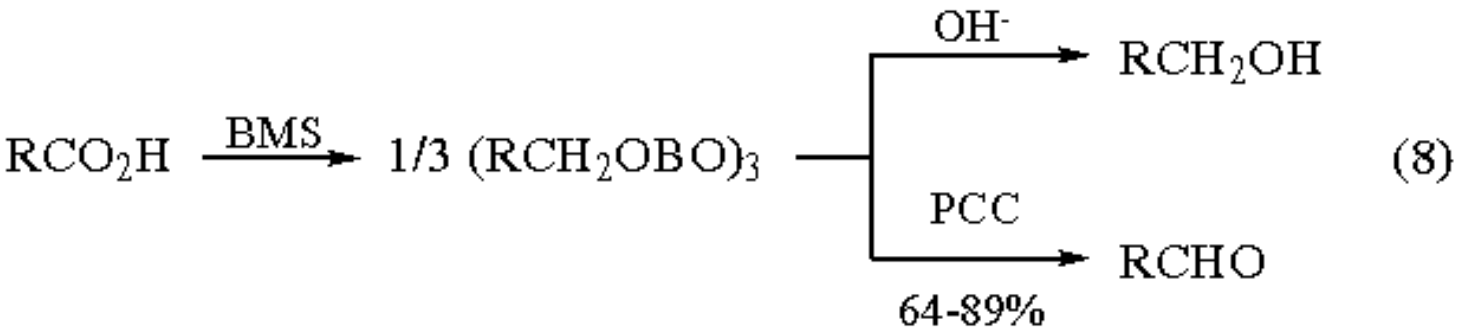

Carboxylic groups can be protected from BMS reduction as trialkylsilyl esters.[33] Aliphatic esters and lactones are rapidly reduced in refluxing THF. Aromatic esters react at a slower rate.[26] Site selective reductions of α-hydroxy esters in the presence of other ester groups have been achieved in both aliphatic and aromatic systems[34] (eq 9).[34a,b]

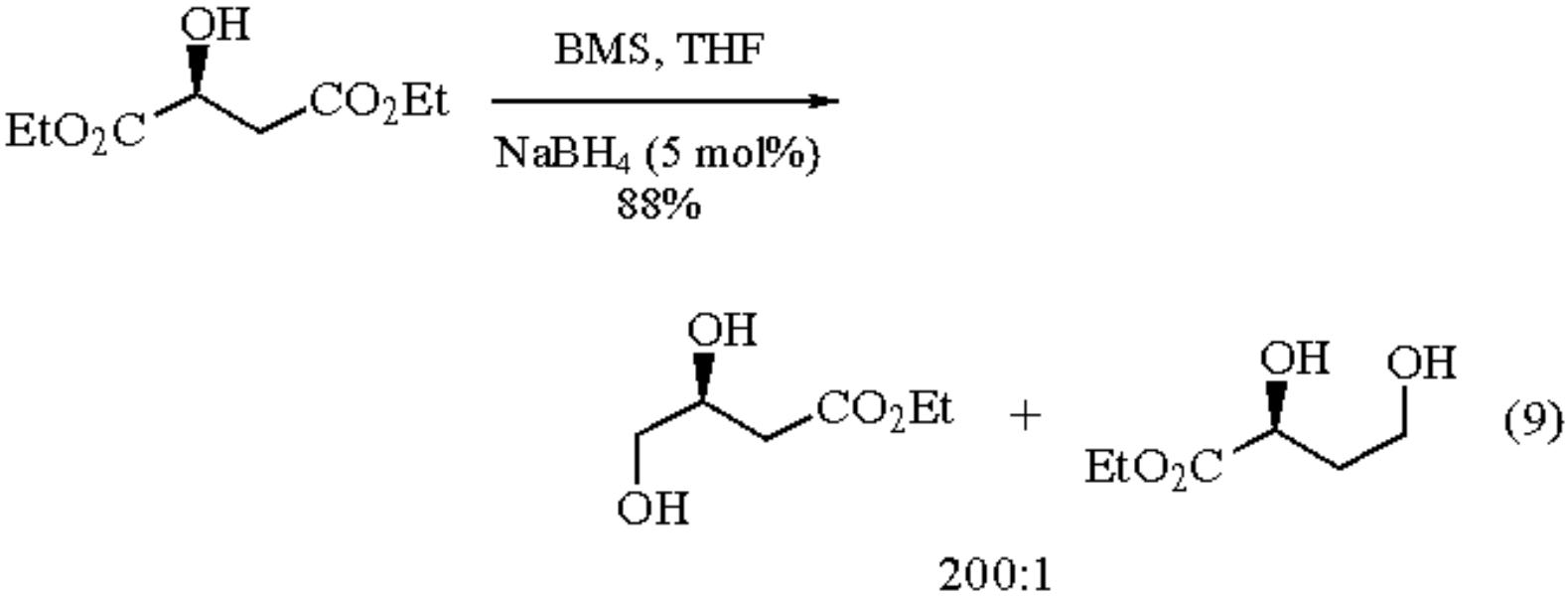

Amides and lactams are reduced to amines[35] (eq 10).[35b] α,o-Amido esters undergo reductive cyclization.[36] Formylation-reduction of primary amines provides convenient access to monomethylated amines.[37] For the isolation of amines, a decomplexing agent such as BF_3 is added, or the amine is isolated as a hydrochloride salt.[26] Alternatively, if a theoretical amount of BMS is used in refluxing toluene, neither distillation of dimethyl sulfide nor a decomplexing agent is necessary.[38] Both aliphatic and aromatic nitriles undergo fast reduction.[26]

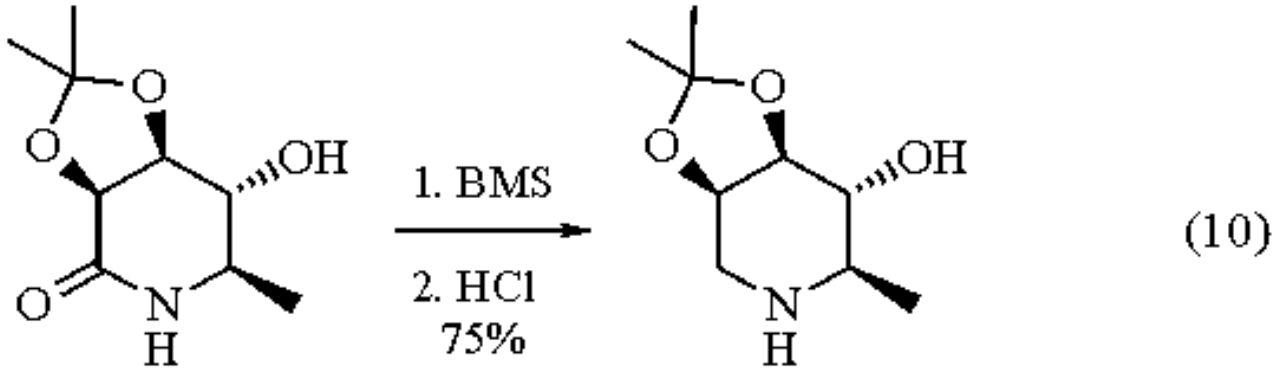

Ketones and Derivatives.

BMS is used as a source of borane in asymmetric reductions of prochiral ketones and derivatives catalyzed by oxazaborolidines (see ***Borane-Tetrahydrofuran***). It is also used for the synthesis of the catalysts.[39]

In stoichiometric ratios, BMS is a highly selective reducing agent for α-halo ketones and α-halo imines.[40] In the reduction of aldoximes and ketoximes, the reagent offers the advantage of a simpler isolation procedure as compared to reductions with borane-THF.[1b] Selective reduction of an aldehyde in the presence of a ketone and α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols has been demonstrated.[1a] Acetals are tolerated by the reagent and serve as protective groups for ketones in selective hydroborations and reductions. Efficient acetal opening is achieved upon activation with ***Trimethylsilyl Trifluoromethanesulfonate*** (eq 11).[41]

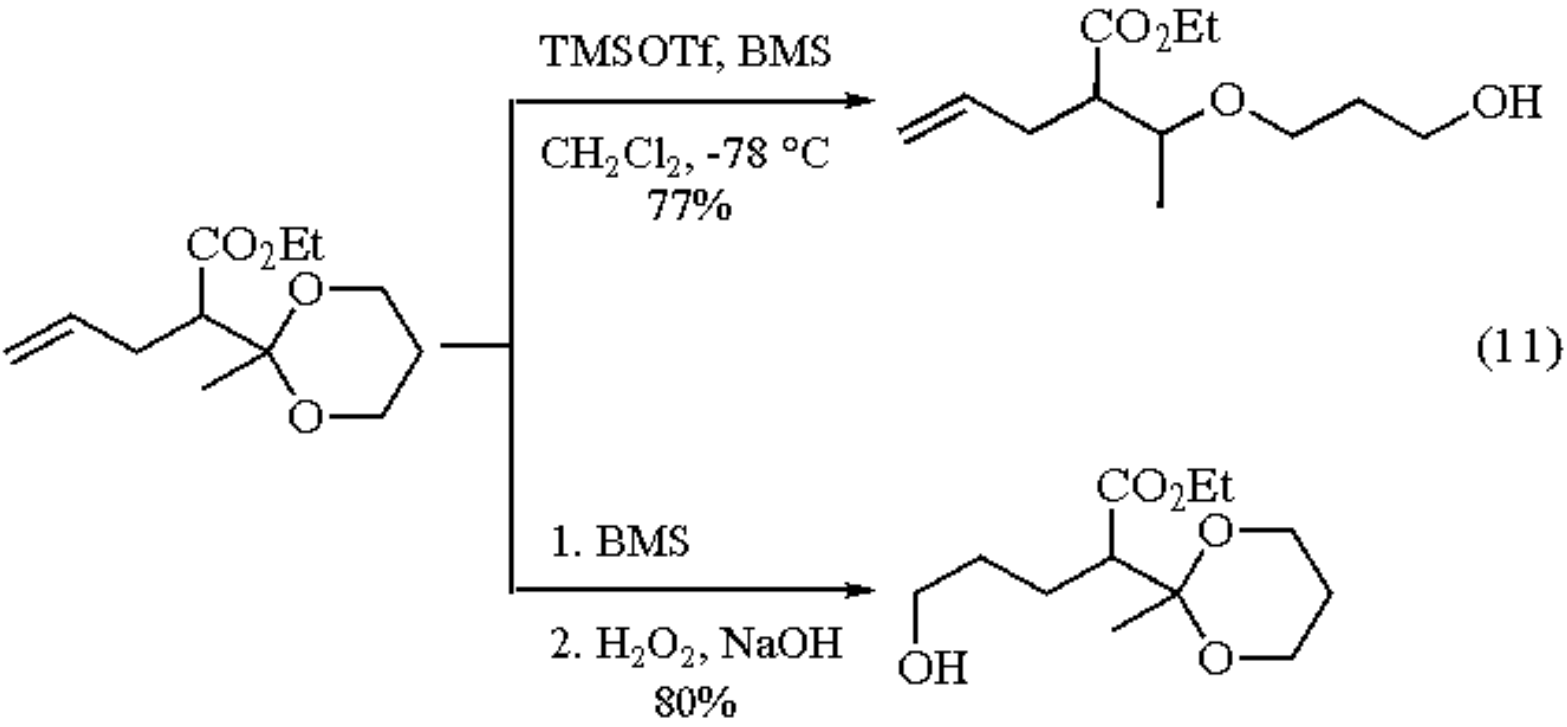

(11)

Cleavage of Single Bonds.

Simple ethers appear to be stable to BMS, for example THF is not cleaved when refluxed with BMS for long periods. However, methoxy groups attached to aromatic rings may undergo cleavage to phenols.[35c]

BMS is an efficient reagent for the direct reduction of ozonides to alcohols in methylene chloride solution.[42]

Other Applications.

BMS is used for the synthesis of various borane complexes, e.g. with amines,[43] phosphines,[44] azo compounds,[45] and oligonucleotides.[46] A novel staining method for transmission electron microscopy is based on the reduction (BMS)-oxidation of ester groups in polymeric materials.[47]

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Borane-Pyridine[1]

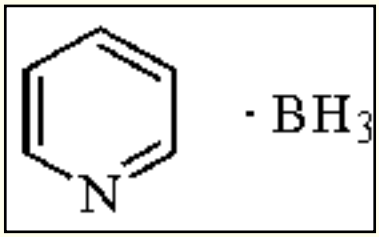

[110-51-0] · C_5H_8BN · Borane-Pyridine · (MW 92.93)

(mild reducing agent with greater hydrolytic stability than $NaBH_4$ in protic solvents and higher solubility in aprotic organic solvents; in solution with a weak organic acid or complexed with Lewis acids it is useful for reductive aminations, reduction of carbonyls, heterocycles, tosylhydrazones, and oximes; in strong acid it converts aldehydes to symmetrical ethers; weak hydroborating agent)

Physical Data: mp 10-11 °C; bp (dec).

Solubility: very sol methanol, THF, toluene, dichloromethane; sol water, diethyl ether; insol hexane.[1]

Form Supplied in: viscous liquid.

Handling, Storage, and Precautions: hydrolytically stable in neutral aqueous solution. Excess reagent may be decomposed with dilute HCl.[1] Use in a fume hood.

Reductive Amination.

Borane-pyridine in neutral or acidic solution is an inexpensive and less toxic alternative to ***Sodium Cyanoborohydride*** for the reductive amination of aldehydes and ketones.[2] Side products in reductive aminations of aldehydes, related to the presence of cyanide in cyanoborohydride, may be avoided using borane-pyridine in ethanol.[3] Borane-pyridine in acetic acid/toluene affords higher yields and product quality compared to ***Sodium Borohydride*** in the 3-aminofluoranthene tagging of aliphatic ketones and aldehydes.[4] Due to its solubility in aqueous solvent, borane-pyridine is the reagent of choice for the reductive methylation of proteins with formaldehyde[5] and is useful for the immobilization of proteins on

oxidized agarose beads in neutral aqueous media.[6]

Carbonyl Reductions.

Borane-pyridine is less reactive than borane complexes of primary and secondary amines and in aprotic solvents generally affords lower stereo- and chemoselectivity.[1,7a,7b] However, reduction rates are accelerated by weak organic acids. For example, the chemoselective reduction of the 2-oxo moiety of 2,5-diketogluconic acid in aqueous solution at 0 °C affords a 92:8 mixture of 2-ketogulonic to 2-ketogluconic acids in 79% yield.[7c] Polymers of 2- and 4-vinylpyridine-borane complexed with ***Boron Trifluoride Etherate***, or uncomplexed in acetic acid solution, exhibit enhanced reactivity and chemoselectivity in the reduction of aliphatic and aromatic ketones, enones, and aldehydes.[8,9]

Carbonyl Deoxygenation.

Borane-pyridine is effective for the reduction of tosylhydrazones of aryl carbonyl derivatives, affording the corresponding tosylhydrazines in 91-98% yields.[10a] This is a key feature in a procedure for the deoxygenation of aromatic ketone tosylhydrazones without the intermediate mercuration stage required for metal hydride reduction.[10b]

Other Functional Group Reductions.

Borane-pyridine in acetic acid reduces quinoline and indole at rt to 1,2,3,4-tetrahydroquinoline and indoline in 71 and 86% yields, respectively.[1] The indole rings of protein tryptophan residues are reduced under these conditions.[5] In ethanol/10% HCl solution, borane-pyridine converts aromatic and aliphatic oximes to hydroxylamines in the presence of ester, nitrile, nitro, amide and halide moieties.[11a] Its solubility in water facilitates the reduction of phosphorylacetaldehyde oximes to phosphorylhydroxylamines.[11b] Borane-pyridine in TFA reduces aliphatic and aromatic aldehydes to symmetric ethers in 55-87% yields. The reduction of aldehydes in alcohol produces unsymmetrical ethers. Aryl ketones are reduced directly to arenes, while dialkyl ketones are reduced to the corresponding alcohols.[12a,12b] Benzyl heptyl sulfide was obtained in 73% yield by the reduction of benzaldehyde with borane-pyridine/***Aluminum Chloride*** in the presence of 1-heptanethiol in dichloromethane.[12c]

Borane-pyridine has also been used as a weak hydroborating agent, for the reductive hydrogenolysis of aryl halide and the reduction of ozonides.[1]

---

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Borane-Tetrahydrofuran[1]

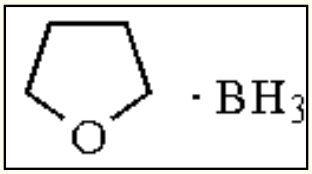

[14044-65-6] · $C_4H_{11}BO$ · Borane-Tetrahydrofuran · (MW 85.94)

(hydroborating and reducing agent)

Physical Data: d_4^{20} = 0.898 g cm^{-3} for 1 M solution in THF.

Solubility: sol THF; reacts violently with water.

Form Supplied in: solution in THF 1 M in BH_3, stabilized with 0.005 M sodium borohydride.

Analysis of Reagent Purity: ^{11}B NMR: δ -0.7 ppm (J_{B-H} = 103 Hz).[5] Active hydride is determined by hydrolysis of an aliquot in a mixture of glycerol and water (1:1) and measuring the hydrogen evolved according to a standard procedure.[6a] Boric acid formed by hydrolysis is determined by titration with standard sodium hydroxide in the presence of mannitol.

Preparative Methods: ***Diborane*** is conveniently generated by the reaction of ***Sodium Borohydride*** with ***Boron Trifluoride Etherate*** in diglyme and absorbed in THF.[2] The solution, ca. 2 M in BH_3, may contain traces of boron trifluoride, which poses problems only on rare occasions.[3] Diborane synthesis has been reviewed.[4]

Handling, Storage, and Precautions: use in a fume hood; air- and moisture-sensitive, flammable liquid; handle and store under nitrogen or argon. Commercial solutions are stable over prolonged periods when stored at 0 °C under nitrogen. Unstabilized solutions can be kept for several weeks under those conditions. However, in such solutions the BH_3 concentration may slowly decrease due to the cleavage of THF by borane.[6b]

Introduction.

The stoichiometry, directive effects, stereochemical and mechanistic aspects of the hydroboration of alkenes, dienes, alkynes, and functional derivatives are discussed in detail in monographs and reviews[1,7,8] (see also ***Borane-Dimethyl Sulfide***). Here, transformations of major synthetic importance involving organoboranes produced by hydroboration with borane-THF are outlined.

Hydroboration-Oxidation: Synthesis of Alcohols.

Oxidation of the intermediate organoborane with alkaline ***Hydrogen Peroxide***, the standard procedure, proceeds with complete retention of configuration to give alcohols in excellent yields (eq 1).[9]

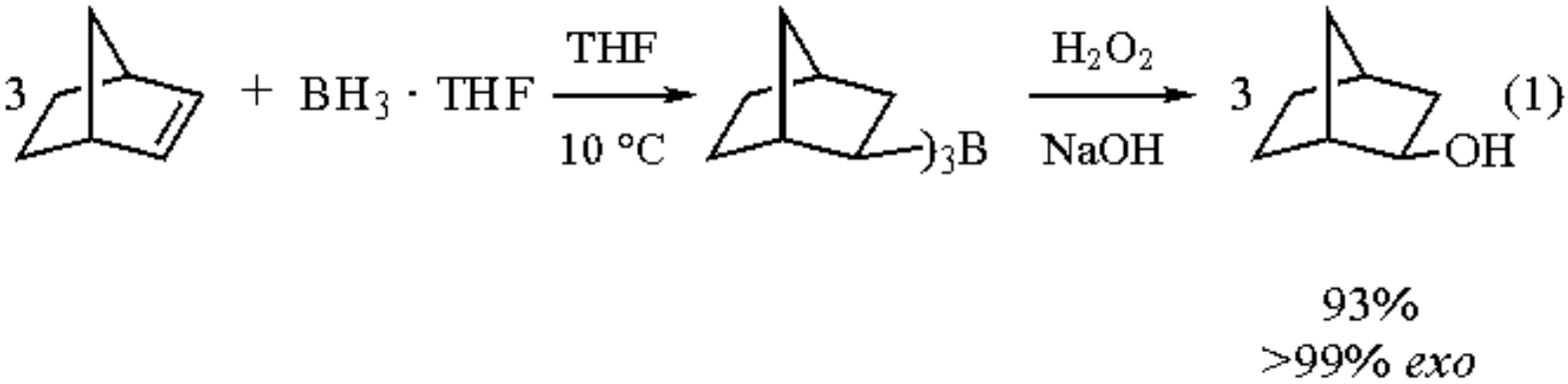

Many functional groups are tolerated.[10] Other oxidation procedures are known.[11] Generally, functional groups in isolated positions do not affect the hydroboration of double or triple bonds. However, proximate substituents may dramatically influence the regioselectivity of addition and stability of the organoborane product.[12-15]

Hydroboration-Elimination: Synthesis of Alkenes.

Enamines,[16] certain homoallylic alcohols,[17] and heterocyclic compounds[18] have been transformed into alkenes or dienes by elimination or fragmentation of the organoborane intermediate (eq 2).[17]

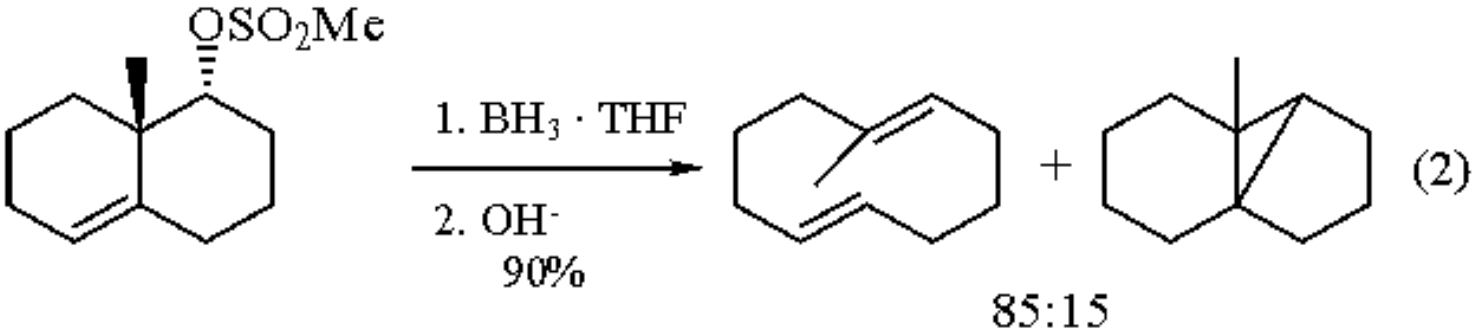

Synthesis of Hydroperoxides.

The low-temperature autoxidation of organoboranes in THF leads to the formation of diperoxyboranes, which provide the corresponding alkylhydroperoxides in excellent yields upon treatment with hydrogen peroxide. Two of the three alkyl groups on boron are utilized (eq 3).[19] The reaction involves a radical chain and the configurational integrity of the alkyl group is not retained.

$$R_3B + O_2 \xrightarrow[-78\ ^\circ C]{THF} (ROO)_2BR \xrightarrow{H_2O_2} 2\ ROOH + ROH \quad (3)$$

81-95%

Hydroboration-Protonolysis: Noncatalytic Stereospecific Hydrogenation.

Trialkylboranes undergo protonolysis by treatment with carboxylic acids.[20] The first alkyl group is readily cleaved. Complete removal of alkyl groups requires heating with acid. The protonolysis proceeds with retention of configuration (eq 4). Internal alkynes can be transformed into (*Z*)-alkenes (see also ***Borane-Dimethyl Sulfide***).

(4)

38%

Contrathermodynamic Isomerization of Alkenes.

Thermal isomerization of alkylboranes at 150-170 °C results in migration of the boron atom to the least hindered position.[21] In aliphatic systems, boron migrates along the carbon chain to the terminal position; however, it cannot pass quarternary centers. Treatment of the isomerized organoborane with a high boiling alkene brings about displacement,[22] and oxidation yields the primary alcohol (eq 5).[23]

$$Me(CH_2)_{13}CH{=}CH(CH_2)_{13}Me \xrightarrow[\text{diglyme, 160 °C, 12 h}]{\substack{1.\ BH_3 \cdot THF \\ 2.\ 2\ C_{14}H_{29}CH{=}CH_2}} \quad (5)$$

$$3.\ H_2O_2,\ NaOH$$

$$Me(CH_2)_{28}CH_2OH + s\text{-}C_{30}H_{61}H + C_{30}H_{60}$$

66% 13% 21%

Functional groups unreactive to borane, e.g. ethers, do not interfere; however, the direction of migration may be influenced by reactive groups, e.g. hydroxy.[24]

Amination: Synthesis of Primary and Secondary Amines.

Trialkylboranes are converted by hydroxylamine-*O*-sulfonic acid to primary amines. The reaction proceeds with complete retention of configuration (eq 6).[25a]

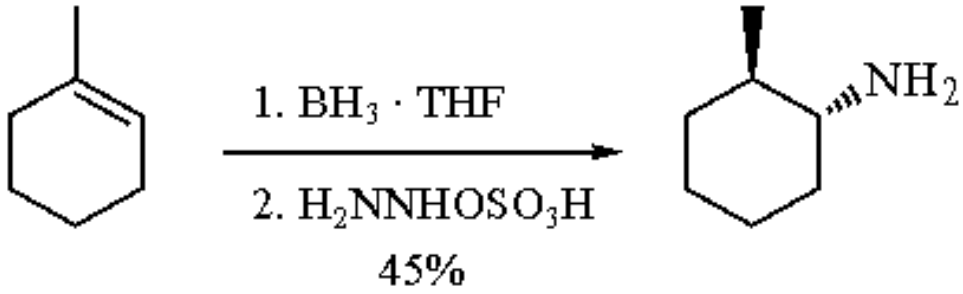

(6)

Other aminating reagents are also known.[26] Secondary amines can be prepared by the reaction of trialkylboranes with organic azides.[27] For better utilization of R groups in these reactions, $RBMe_2$ and $RBCl_2$ can be used, respectively.[25b,26]

Halogenolysis.

Alkylboranes are readily converted into the corresponding alkyl chlorides by radical reaction with ***Trichloramine***.[28a] The reaction is not stereospecific; however, with other reagents, e.g. dichloramine T, the stereochemical integrity of the alkyl group is retained.[28b] Brominolysis and iodinolysis of trialkylboranes proceed under mild conditions in the presence of a base.[29] The yields of primary alkyl bromides and iodides are excellent. Three alkyl groups are utilized in the brominolysis and two in the iodinolysis. Secondary alkyl groups react with predominant inversion of configuration (eq 7). In contrast, the dark bromination proceeds with complete retention of configuration (eq 7).[30]

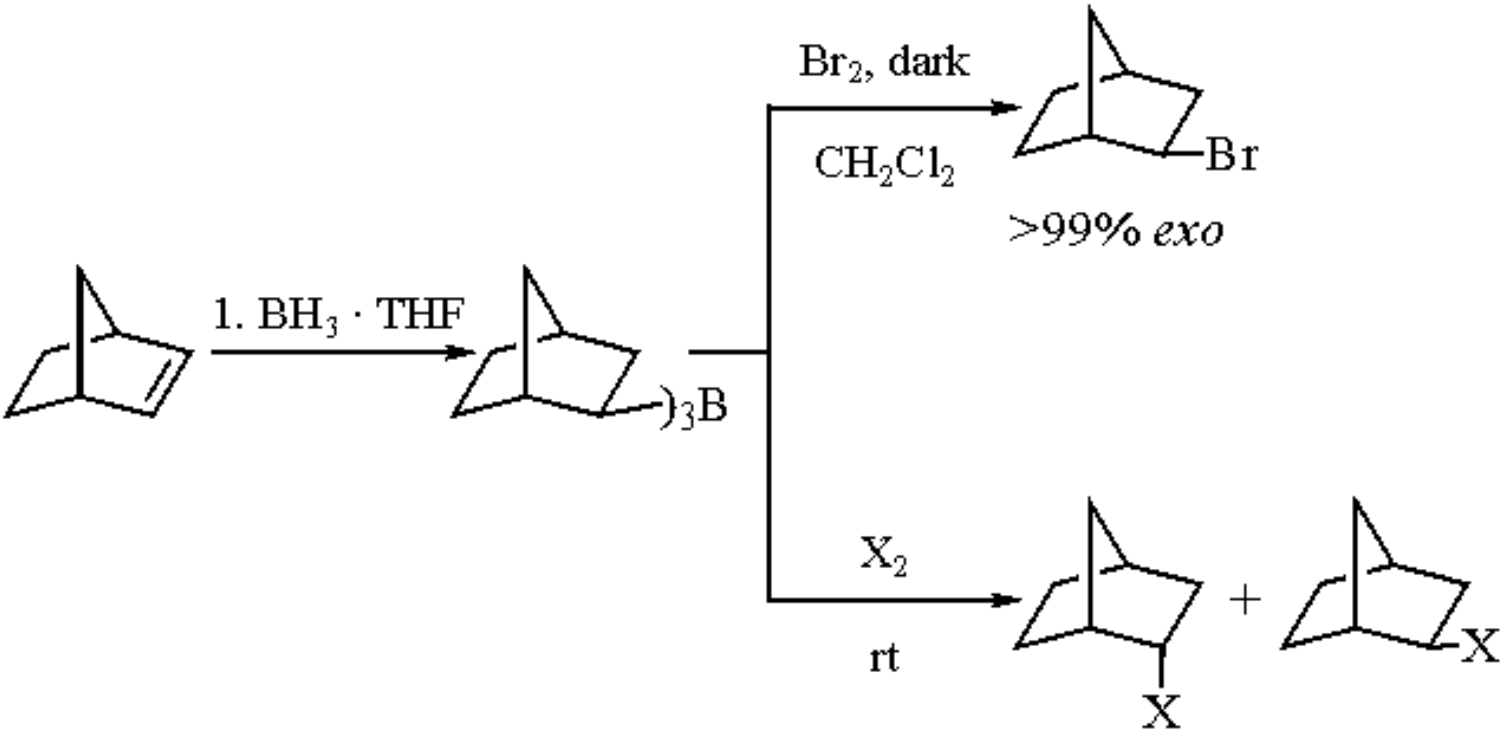

(7)

X = Br, base = NaOMe	75%	25%
X = I, base = MeOH	80%	20%

Mercuration.

Mercury(II) salts react with primary trialkylboranes to yield organomercurials (eq 8).[31] Mercuration of secondary alkylboranes is sluggish.

$$RCH{=}CH_2 \xrightarrow[\text{3. } H_2O,\ NaCl\ \ 91\text{-}97\%]{\text{1. } BH_3 \cdot THF\ \ \text{2. } Hg(OAc)_2} 3\ RCH_2CH_2HgCl \qquad (8)$$

Sulfuridation: Synthesis of Thioethers, Alkyl Thio- and Selenocyanates.

Trialkylboranes are cleaved by dialkyl and diaryl sulfides, producing mixed thioethers (eq 9).[32] The reaction is catalyzed by air. Alkyl thio- and selenocyanates are obtained by treatment of trialkylboranes with iron(III) thio- and selenocyanate, respectively.[33]

$$R_3B + MeSSMe \xrightarrow[74\text{-}94\%]{} RSMe + R_2BSMe \qquad (9)$$

Synthesis of Mono- and Dialkylboranes.[34]

Several valuable hydroborating and reducing agents,[34] e.g. ***Thexylborane***, ***Disiamylborane***, ***Dicyclohexylborane***, ***9-Borabicyclo[3.3.1]nonane*** (9-BBN, eq 10),[35] and borinane,[36] are synthesized by hydroboration of the corresponding alkenes or dienes with the reagent.

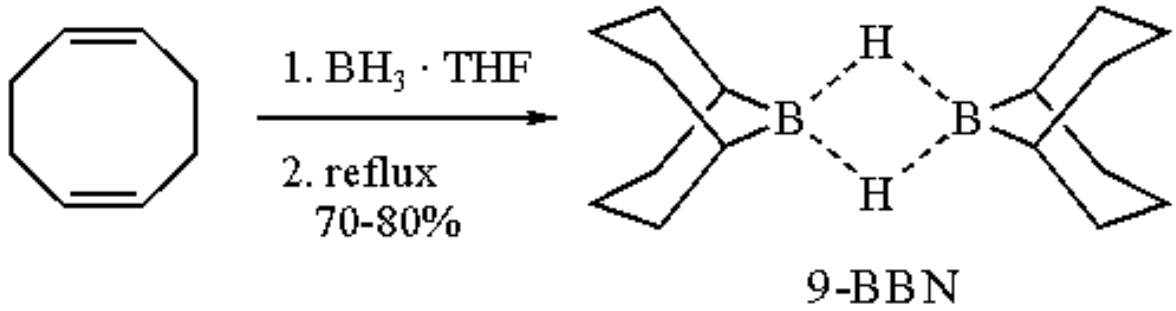

(10)

Single Carbon Homologation: Carbonylation, Cyanidation, Dichloromethyl Methyl Ether (DCME) Reaction; Synthesis of Alcohols, Aldehydes, and Ketones.

Trialkylboranes react with carbon monoxide at 100-125 °C in diglyme. The reaction proceeds stepwise and the migration of alkyl groups can be controlled to give products of one, two, or three group transfers (eq 11).[37] Cyanidation[38] and the DCME reaction[39a] lead to the same products under milder conditions. Highly hindered tertiary alcohols can be prepared. Annulation and spiroannulation of 1-allylcyclohexenes have been achieved.[39b] All reactions proceed with retention of configuration of alkyl groups. Functional groups, such as ether, ester, nitro, and chloro are tolerated. Unsymmetrically substituted ketones can be obtained by the reaction of trialkylboranes with acyl carbanion equivalents.[40]

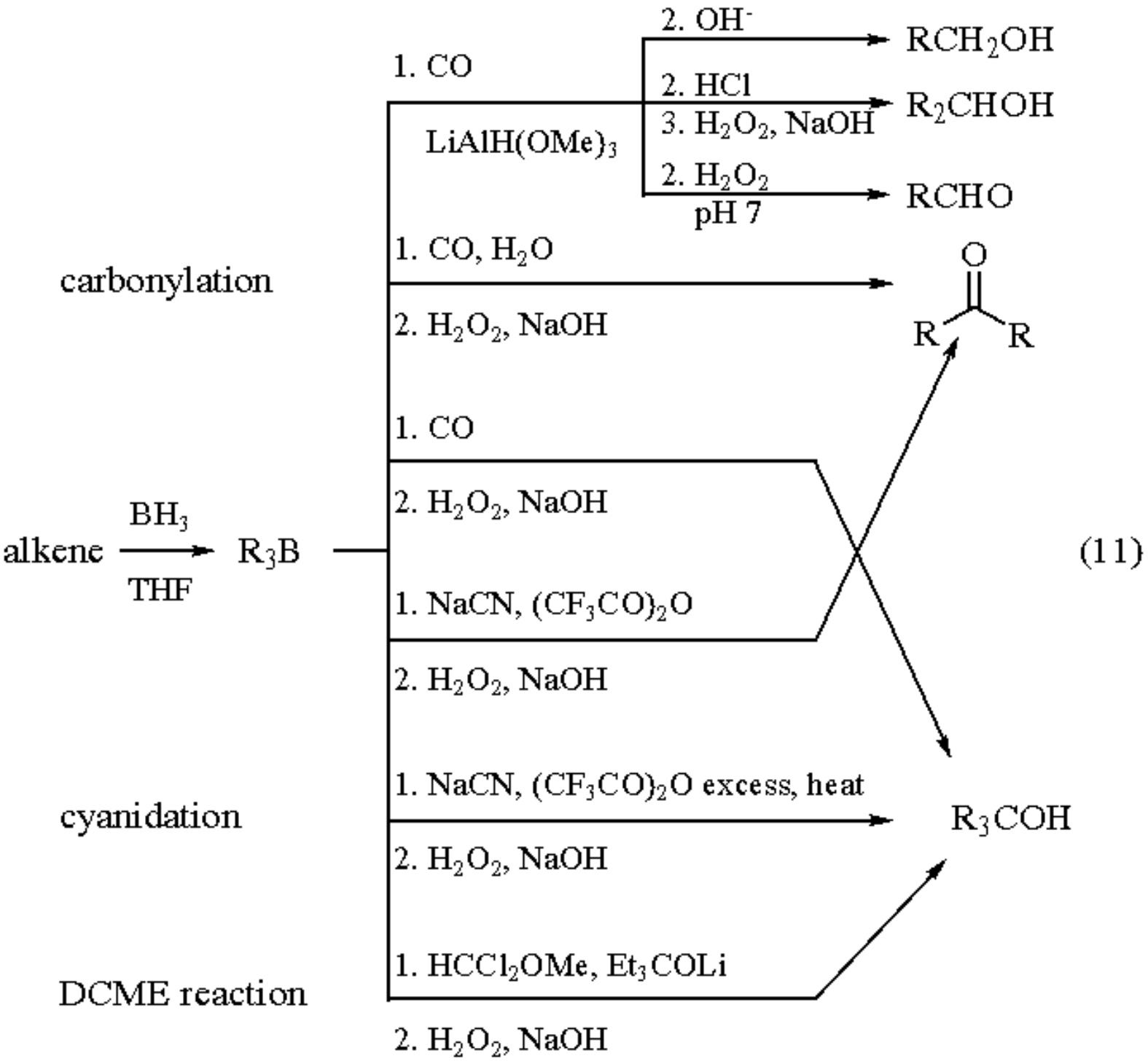

(11)

Coupling; Synthesis of Alkanes, Cycloalkanes and (*E*)-Alkenes.

Treatment of trialkylboranes with alkaline ***Silver(I) Nitrate*** solution results in coupling of the alkyl groups.[41] Yields for coupling of primary and secondary groups are in the range of 60-80% and 35-50%, respectively.

α-Alkylation of Esters, Ketones and Nitriles.

Trialkylboranes react with carbanions generated from α-halo esters, ketones, and nitriles, transferring the alkyl group from boron to carbon.[42] Two different groups can be introduced consecutively, starting with α,α-dihalonitriles.[42d] The anions are generated by hindered bases, e.g. *t*-butoxide, or better, 2,6-di-*t*-butylphenoxide for sensitive compounds (eq 12).

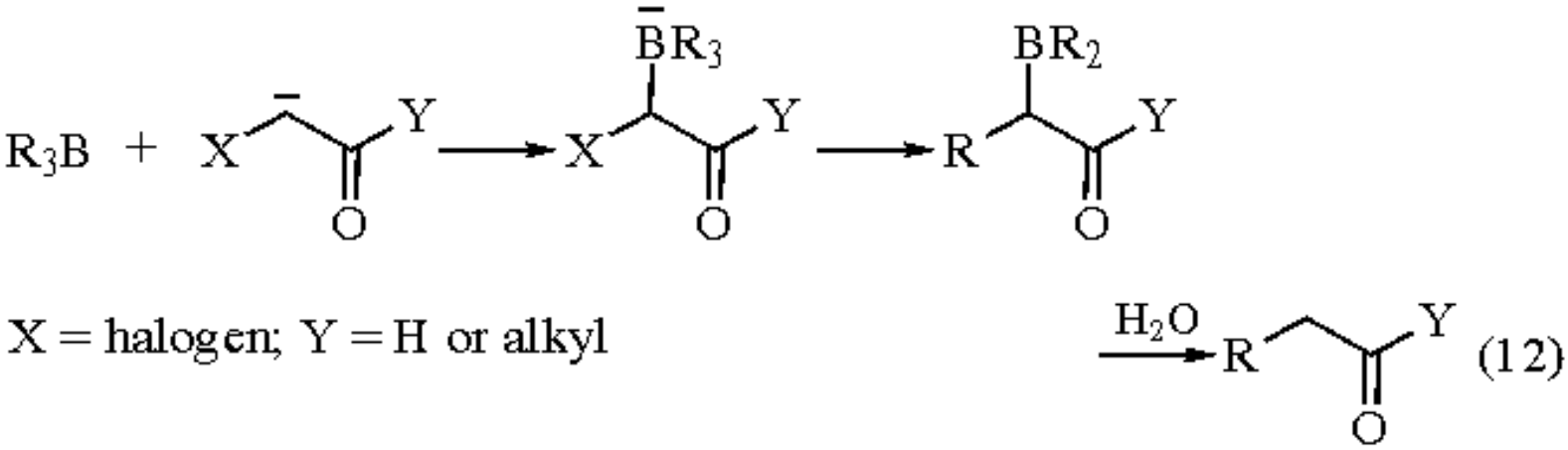

α-Diazocarbonyl compounds react with trialkylboranes directly in the absence of bases at -25 °C.[43] Mild conditions are advantageous when functionalities labile to bases are present (eq 13).[43a]

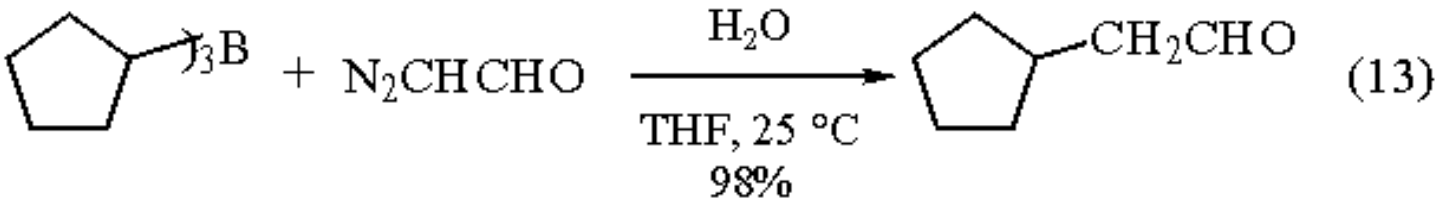

α-Bromination-Alkyl Group Transfer: Synthesis of Hindered Tertiary Alcohols.

The photochemical α-bromination of trialkylboranes with bromine proceeds readily. Weak bases such as water or THF are sufficient to induce the migration of alkyl groups from boron to the α-brominated carbon. All three alkyl groups may be utilized. It is possible to halt the reaction after the first group migration. Highly hindered tertiary alcohols can be prepared (eq 14).[44]

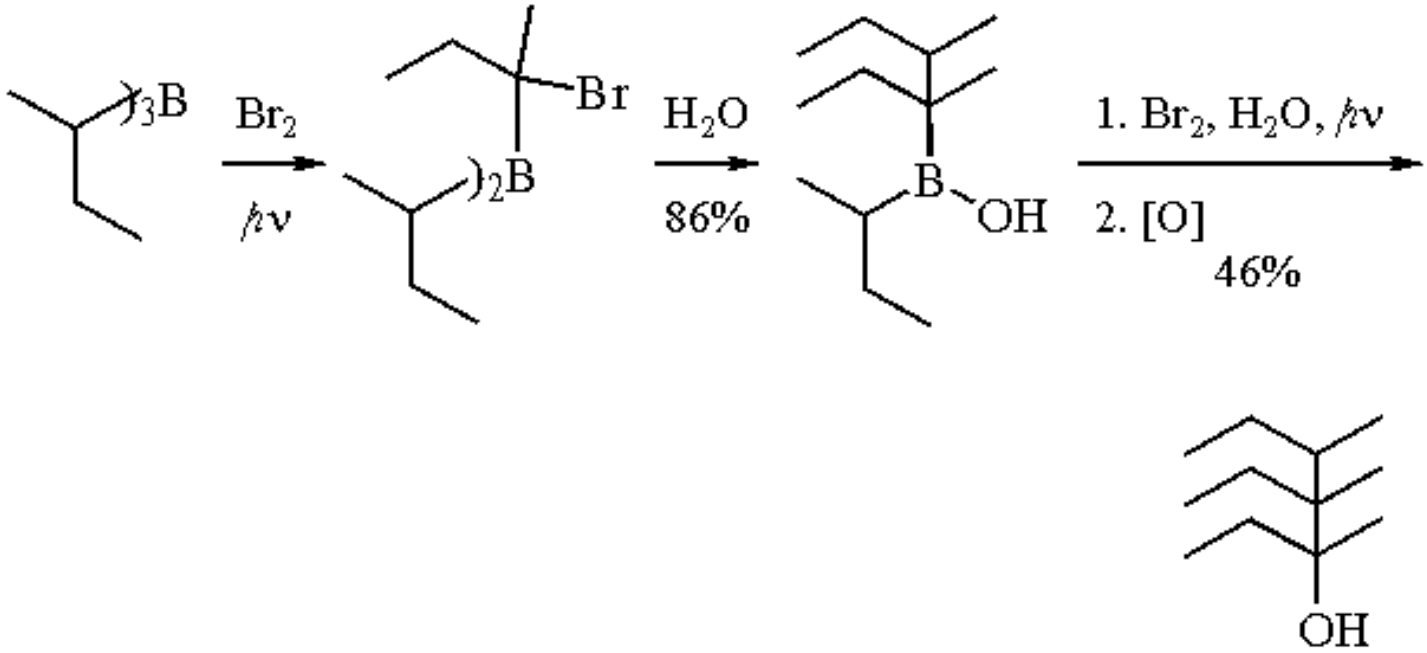

(14)

Addition to Carbonyl Compounds: Synthesis of Unsymmetrical Ketones.

Unlike Grignard and alkyllithium compounds, trialkylboranes are inert to carbonyl compounds. The air-catalyzed addition to formaldehyde is exceptional.[45] Alkyl borates are more reactive and can transfer primary alkyl groups to acyl halides. The reaction provides highly chemoselective boron-mediated synthesis of unsymmetrical ketones (eq 15).[46]

$$s\text{-}R^1{}_3B + R^2Li \longrightarrow s\text{-}R^1{}_3\bar{B}R^2\,Li^+ \xrightarrow{R^3COX} R^3COR^2 + s\text{-}R^1{}_3B + LiX \quad (15)$$

57-88%

β-Alkylation of Conjugated Carbonyl Compounds and Oxiranes.

Trialkylboranes undergo radical conjugate addition to various α,β-unsaturated carbonyl compounds, such as enals, enones, quinones, unsaturated nitriles, crotonaldimines, and ynones, and also to alkenyl- and alkynyloxiranes[47] (eq 16).[47b]

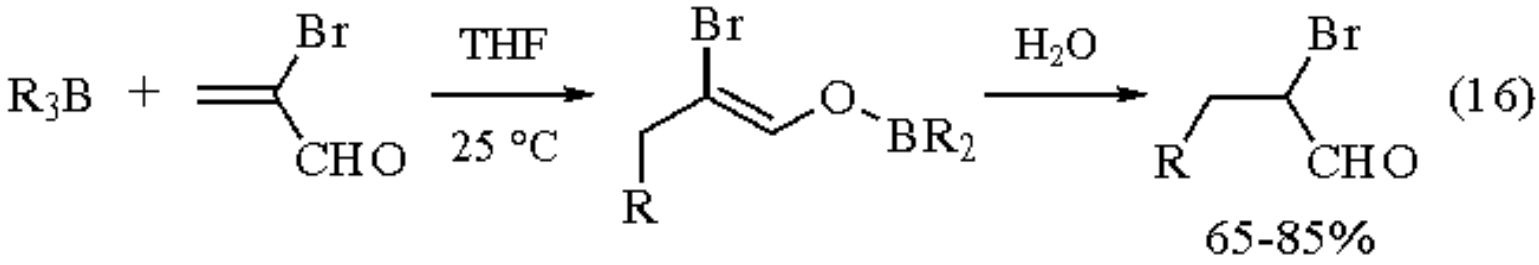

Functional Group Reductions.[48]

The reactivity order of representative functional groups toward borane-THF is[49a] carboxylic acids > aldehydes > ketones > alkenes >> nitriles > epoxides > esters > acid chlorides. Acid anhydrides, amides, lactones, acetals, oximes, oxime ethers, imines, and hydrazones are also reduced. Nitro compounds, organic halides, sulfones, sulfonic acids, disulfides, thiols, alcohols, phenols (hydrogen evolution), and amines are stable to borane-THF.[49]

Carboxylic Acids and Derivatives.

Borane-THF is the reagent of choice for the reduction of carboxylic acids to alcohols.[50-56] Selective reduction in the presence of esters, halogen derivatives, nitrileLane, C.s, amides, lactones, nitro compounds, amino, phenolic, and other groups is possible (eq 17).[51] Carboxylic acid salts are reduced with 2 equiv of BH_3.THF.[52]

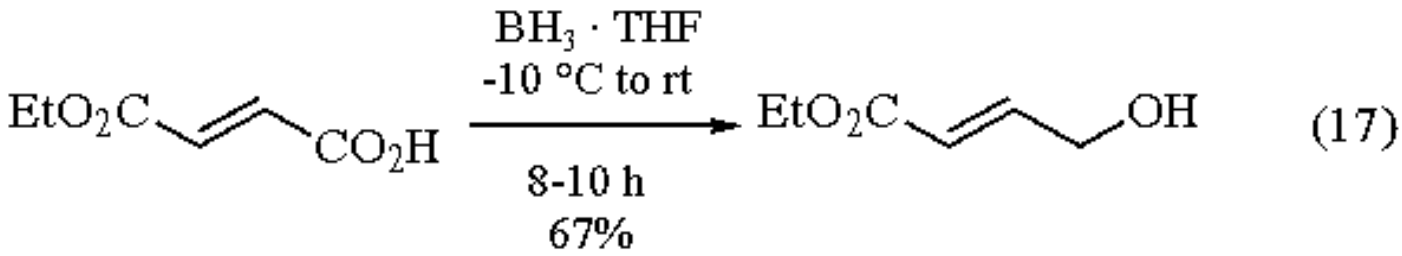

Aromatic acids containing electron-donating groups may undergo overreduction to hydrocarbons.[57] Other carboxylic groups can also be converted into the methyl group via the reduction of *N*-acyl-*N*´-tosylhydrazines.[58] Isotopically labeled chiral methyl groups have been obtained by a sequence of reactions involving BD_3.THF.[59]

Acid anhydrides are reduced to alcohols at a slower rate than carboxylic acids.[60] Aliphatic esters and lactones react slowly (6-12 h at 0 °C) to give alcohols or ethers.[49,61-65]

The reduction of amides to amines is another major synthetic application of the reagent. The reactivity order is tertiary > secondary >> primary. All types of amides and lactams are reduced rapidly and quantitatively by excess of borane in refluxing THF.[66-69]

A large-scale preparation of an intermediate in the synthesis of nitrobenzyl-DOTA, an efficient chelating agent for metal ions, used in biochemical studies, is shown in eq 18.[70]

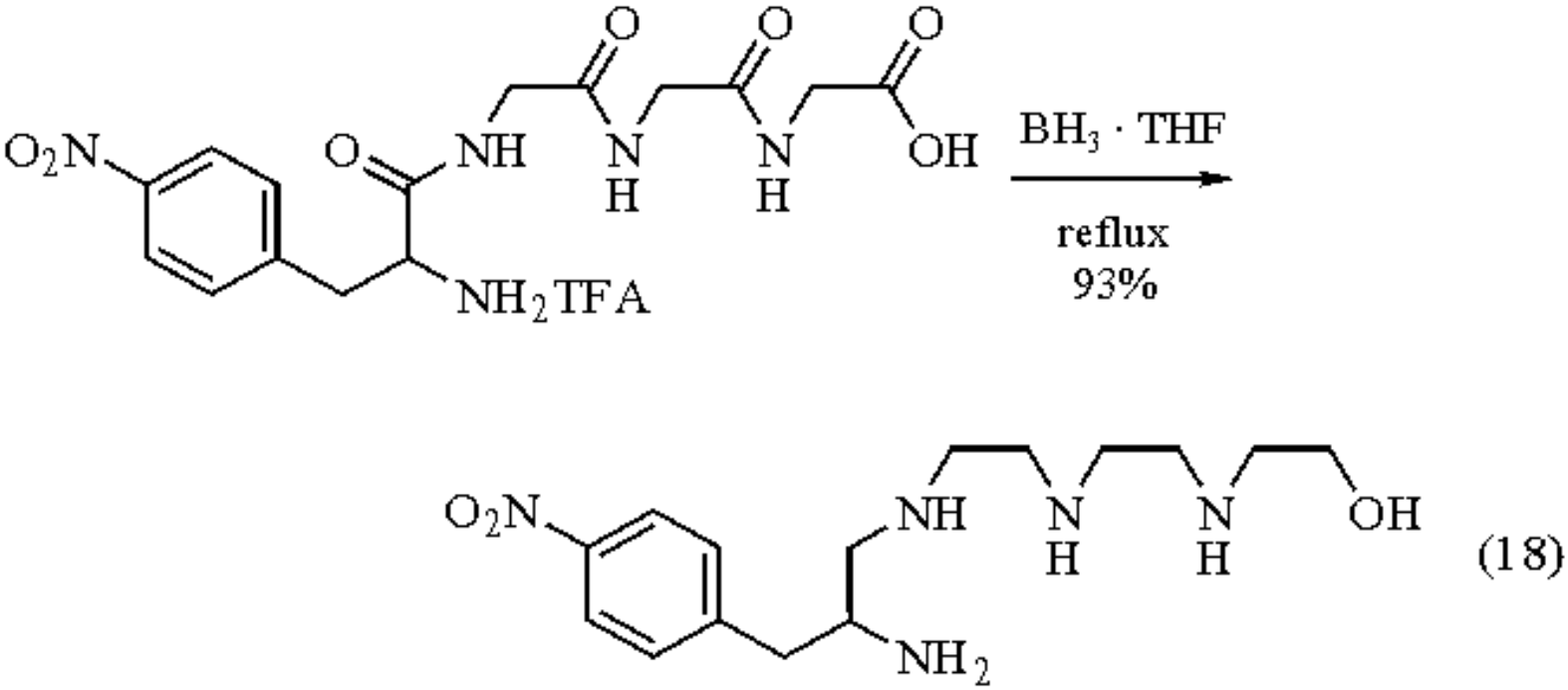

Nitriles are readily reduced with an excess of borane in refluxing THF to give the corresponding amines upon acid hydrolysis of the intermediate borazines.[66,71] Less reactive functional groups are tolerated. The initial intermediate *N*-borylimine can be alkylated to give carbinamines (eq 19).[72] Cyanohydrins are reduced to amino alcohols; however, α-aminonitriles undergo decyanation.[73]

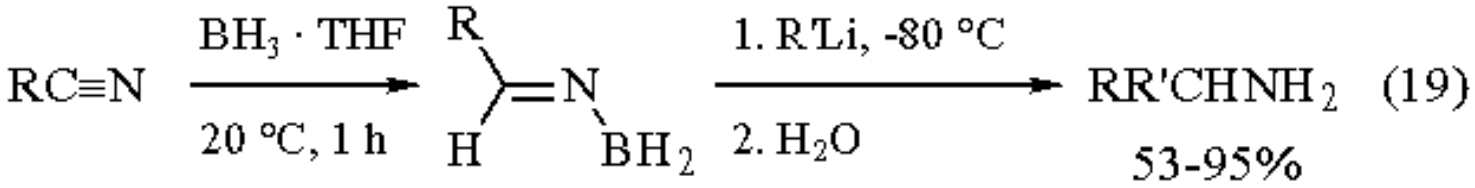

Ketones and Derivatives.

Although aldehydes and ketones are readily reduced by borane,[49] other reagents of higher selectivity are widely used for that purpose. In some cases, however, the use of borane may be advantageous, as demonstrated in the synthesis of ciramadol involving a stereoselective reduction of 2-(α-dimethylamino-*m*-hydroxybenzyl)cyclohexanone[74a] and in highly diastereoselective keto boronate reduction (eq 20).[74b]

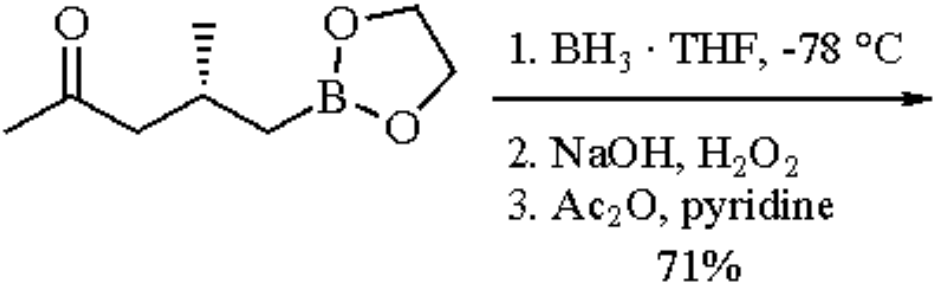

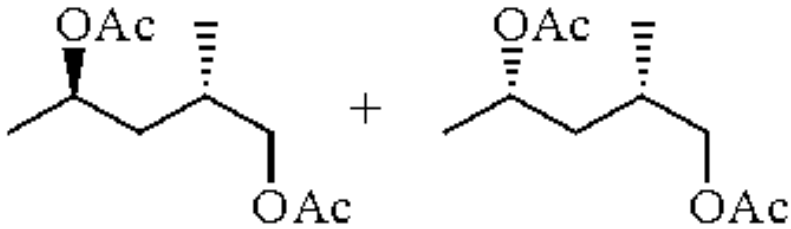

34:1 (20)

The asymmetric reductions of prochiral ketones are now dominated by catalytic reactions[75] and highly selective stoichiometric reagents.[76] Borane-THF reacts with chiral amino alcohols to give asymmetric reducing agents and serves as a source of BH_3 in enantioselective reductions of prochiral ketones catalyzed by oxazaboralidines and oxazaphospholidines (eq 21).[77] Catalysts of type 2 are best studied and new modifications are prepared.[75,78]

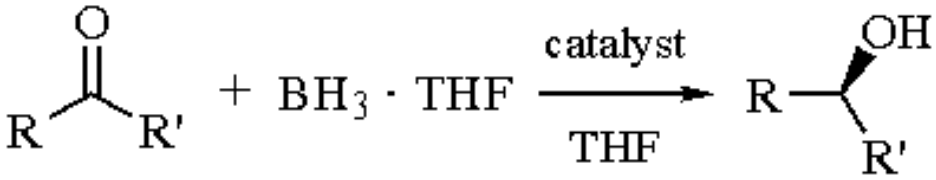

(21)

R,R' = Ph, Me cat. 1, 94% ee; cat. 2, 97% ee
R,R' = *i*-Pr, Me cat. 1, 60% ee; cat. 3, 92% ee

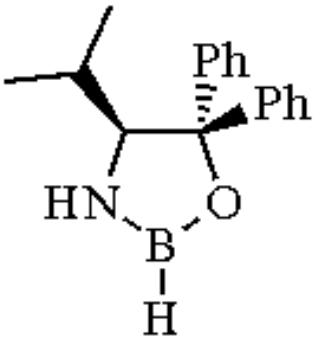

cat. 1

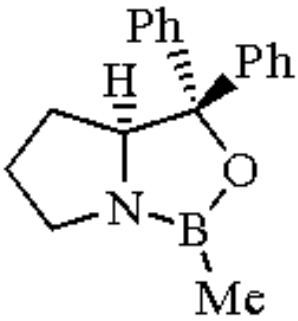

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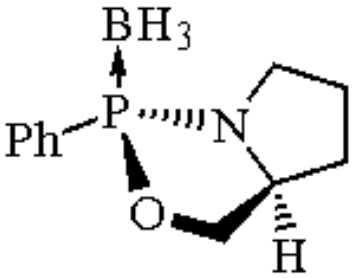

cat. 3

Oximes react with borane in refluxing THF to give the corresponding hydroxylamine derivatives (see also ***Borane-Dimethyl Sulfide***).[79] Oximes of aryltrifluoromethyl ketones are reduced at room temperature (not with BMS).[80] Oxime ethers and acetates react under mild conditions.[81] ***Aluminum Hydride*** (alane) is also a convenient reagent for these

reductions.[82] Reagents for asymmetric reduction of prochiral ketoxime *O*-alkyl ethers and imines are prepared from borane-THF and chiral amino alcohols.[75,77a,83]

Cleavage of Single Bonds.

Epoxides react slowly with borane-THF to yield mixtures of products.[84] In the presence of small amounts of sodium borohydride or boron trifluoride, the reaction is greatly accelerated and the epoxide ring is cleanly opened. Although anti-Markovnikov products predominate, the regioselectivity is high only in certain cases, e.g. styrene and indene epoxides give 2-phenylethanol and indan-2-ol, respectively.[84,85] In contrast, the reduction of *s*-cisoid α,β-unsaturated epoxides with borane-THF proceeds stereoselectively with the double bond shift to give allylic alcohols of (*Z*) configuration (eq 22).[86] Similarly, α,β-unsaturated aziridines are reduced to (*Z*) allylic amines.[87] Acetals and tetrahydropyranyl ethers undergo reductive cleavage[88] (eq 23).[88c]

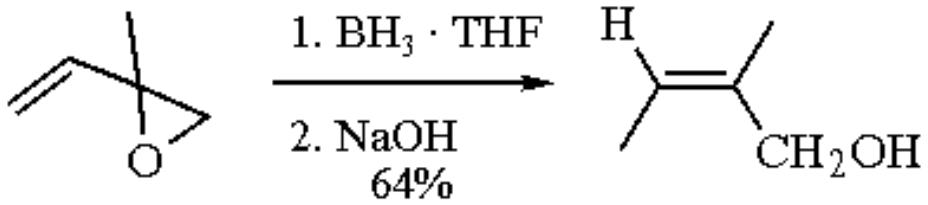

(22)

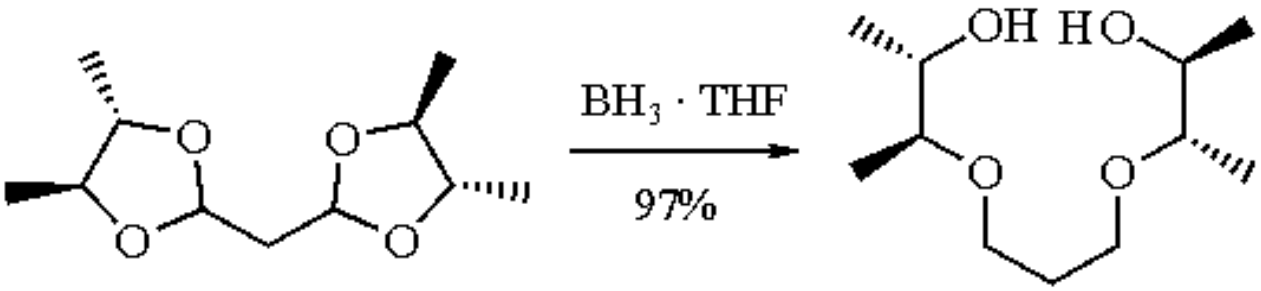

(23)

Imidazolidines and oxazolidines are also cleaved,[89] whereas thiazolidines appear to be stable to the reagent at rt.[90]

Nitro Compounds.

The nitro group itself is stable to the reagent; however, aci nitro salts and α,β-unsaturated nitro compounds are reduced to the corresponding hydroxylamines.[91,92]

Other Applications.

Borane-THF reacts with Grignard reagents, arylmercury, arylthalium, and allyl- and propargyllithium compounds to give organoboranes which can be oxidized to the corresponding alcohols, phenols, and 1,3-diols.[93] The reagent is used for blocking tertiary amine groups in Friedel-Crafts cyclizations and oxidative phenol coupling reactions in alkaloid syntheses.[94] It activates α,β-unsaturated acids in the reaction with 1,3-dienes[95] and is used in the synthesis of catalysts for asymmetric Diels-Alder and aldol reactions.[75] Trialkylboranes are useful intermediates in the synthesis of compounds labeled with various isotopes for medical applications.[96]

Related Reagents.

Borane-Ammonia; ***Borane-Dimethyl Sulfide***; ***Borane-Pyridine***; ***Diborane***.

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Boric Acid

H_3BO_3

[10043-35-3] · BH_3O_3 · Boric Acid · (MW 61.83)

(reacts with alcohols to form borate esters;[1] catalyzes dehydration,[2] hydrolysis,[3] decarboxylation,[4] and condensation reactions;[5] useful in carbohydrate chemistry[6])

Physical Data: mp 169 °C; *d* 1.435 g cm^{-3}. Heating boric acid above 100 °C gradually produces metaboric acid, HBO_2; at higher temperatures all water is lost and boron oxide, B_2O_3, results.

Solubility: sol cold water (1 g in 18 mL), boiling water (1 g in 4 mL), cold alcohol (1 g in 18 mL), boiling alcohol (1 g in 6 mL), glycerol (1 g in 6 mL), acetone (1 g in 15 mL).

Form Supplied in: white solid, widely available (see also ***Sodium Tetraborate***).

Purification: recrystallize three times from water (3 mL g^{-1}) with filtering. Dry over metaboric acid in a desiccator.

Handling, Storage, and Precautions: boric acid is hygroscopic. It is an irritant to eyes, skin, and mucous membranes, and should be handled with the appropriate precautions to eliminate contact with these areas. Death has resulted from ingestion of 5 to 20 g in adults. Use in a fume hood.

Borate Esters.

Trigonal borate esters are readily formed by condensing alcohols with boric acid; the reaction is driven by azeotropic removal of water. Borate esters are stable under a variety of anhydrous reaction conditions and can serve as a method of protecting alcohols.[1] The reactivity of carbonyl compounds can be enhanced by intramolecular coordination with an adjacent borate ester.[7] Borate esters are intermediates in boric acid-catalyzed dehydrations of primary, secondary, and tertiary alcohols.[2] Carbocation-derived rearrangements are a potential problem with this method.[8]

Imine Hydrolysis.

Imines can be hydrolyzed in quantitative yields by using boric acid in refluxing ethanol.[3] Imines that are susceptible to intra- and intermolecular attack in the presence of other catalysts have been successfully hydrolyzed using boric acid.[9] Conversion of isoxazolines into β-hydroxy ketones and β-hydroxy esters involves hydrogenolysis of the N-O bond and imine hydrolysis in a single step.[10] In the presence of boric acid, racemization is inhibited (eq 1).[10a]

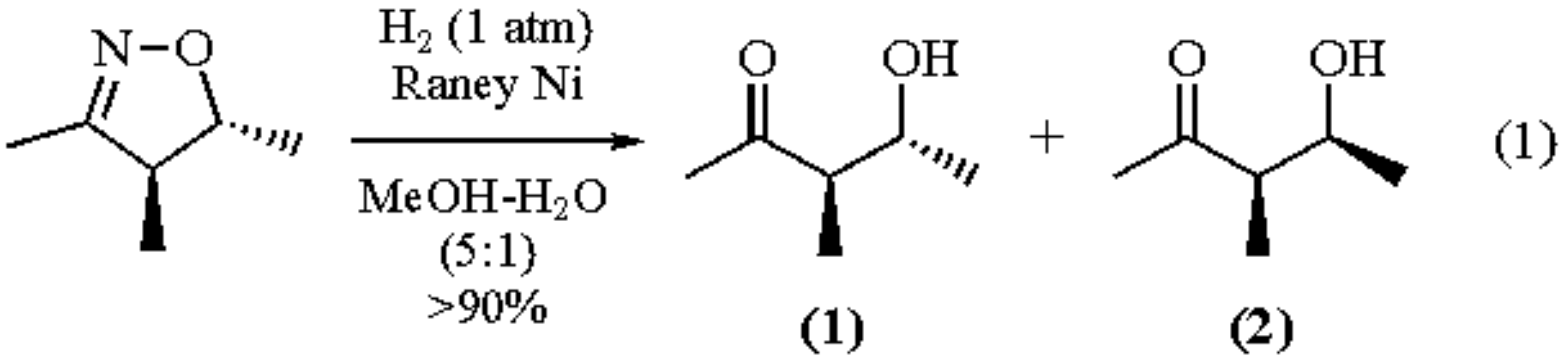

Additive (2-5 equiv)	(1)	:	(2)
acetate	91	:	9
phosphate	94	:	6
boric acid	100	:	0

Decarboxylation.

Boric acid has been used to catalyze the decarboxylation of β-keto esters and β-imino esters.[4,11] A convenient method for the production of γ-keto esters from diethyl α-acylsuccinates in high yield is shown in eq 2.[4] The conventional method of saponification, decarboxylation, and reesterification produced low yields.

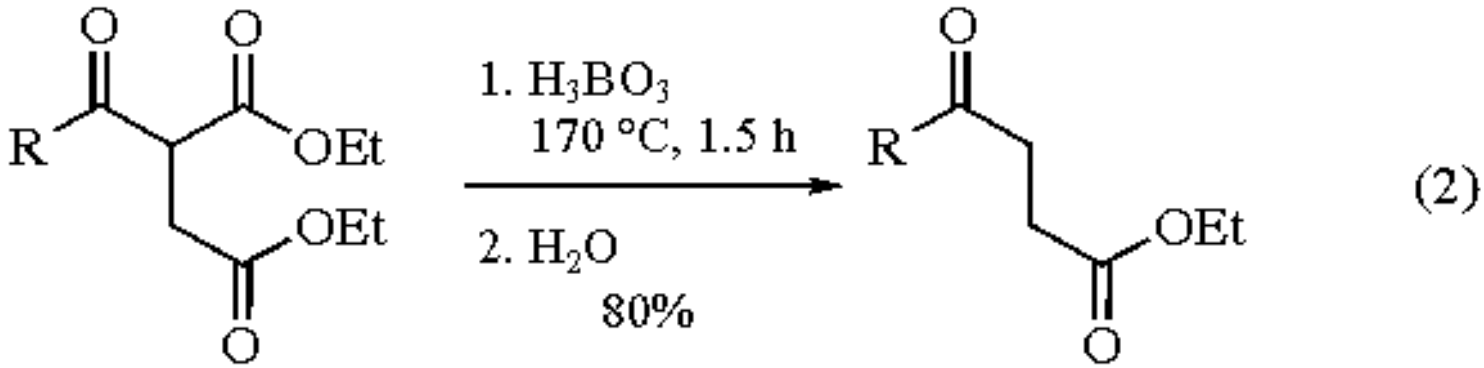

Condensation.

Boric acid catalyzes the self-condensation of aldehydes and ketones to produce α,β-unsaturated enones.[12] Yields were much higher than those reported with other acid or base catalysts. Under similar conditions, aldehydes which are not readily susceptible to aldol condensation, dismutate to form esters (Tischenko reaction).[13] A catalytic amount of boric acid/sulfuric acid mixture has been used to synthesize aryl esters (eq 3) in good yields.[5] The reaction was unsuccessful using mineral acids or boric acid alone.

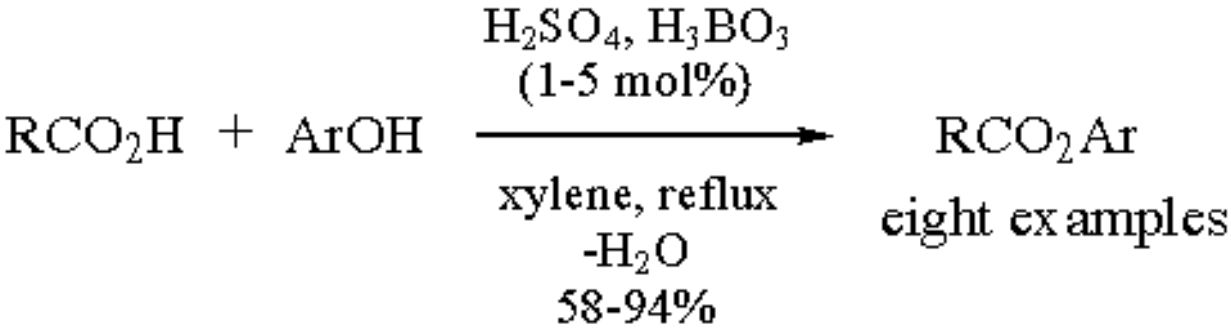

(3)

Indole can be condensed directly with various carboxylic acids in the presence of boric acid.[14] Traditional methods were found to be unsatisfactory due to low yields and the production of 3-acylated and 1,3-diacylated side products.

Carbohydrate Chemistry.

In alkaline solution, boric acid catalyzes the isomerization of aldoses into ketoses.[6] During the synthesis of mono- and diacylglycerides, the use of boric acid to remove acetal[15] and trityl[16] protecting groups minimizes undesired acyl group migrations.[17] The reductive acetylation of azidopyranosides to form *N*-acetylaminopyranosides is improved in the presence of boric acid.[18]

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Boron Tribromide[1]

BBr_3

[10294-33-4] · BBr_3 · Boron Tribromide · (MW 250.52)

(Lewis acid used for deprotection of OH and NH groups; cleaves ethers or esters to alkyl bromides; bromoborates allene and alkynes)

Physical Data: mp -45 °C; bp 91.7 °C; *d* 2.650 g cm^{-3}.

Form Supplied in: colorless, fuming liquid; a 1.0 M solution in dichloromethane and hexane; $BBr_3.Me_2S$ complex is available as either a white solid or a 1.0 M solution in dichloromethane.

Purification: by distillation.

Handling, Storage, and Precautions: BBr_3 is highly moisture sensitive and decomposes in air with evolution of HBr. Store under a dry inert atmosphere and transfer by syringe or through a Teflon tube. It reacts violently with protic solvents such as water and alcohols. Ether and THF are not appropriate solvents.

Removal of Protecting Groups.

BBr_3 is highly Lewis acidic. It coordinates to ethereal oxygens and promotes C-O bond cleavage to an alkyl bromide and an alkoxyborane that is hydrolyzed to an alcohol during workup (eq 1).[2]

$$R^1OR^2 \xrightarrow{BBr_3} R^1Br + Br_2BOR^2 \xrightarrow{H_2O} R^1Br + R^2OH \quad (1)$$

BBr_3 has been widely used to cleave ethers because the reaction proceeds completely under mild conditions. In a special case, BBr_3 has been used to cleave acetals that cannot be deprotected by usual acidic conditions.[3] Because alkyl aryl ethers are cleaved at the alkyl-oxygen bond to give ArOH and alkyl bromides, BBr_3 has been most generally used for the demethylation of methyl aryl ethers,[2,4] for example as the final step of zearalenone synthesis (eq 2).[5] Problems are sometimes encountered in attempts to deprotect more than one nonadjacent methoxy group on one aromatic ring, and when stable chelates are formed.[6] The presence of a carbonyl substituent facilitates the selective deprotection of polymethoxyaryl compounds (eq 3).[7]

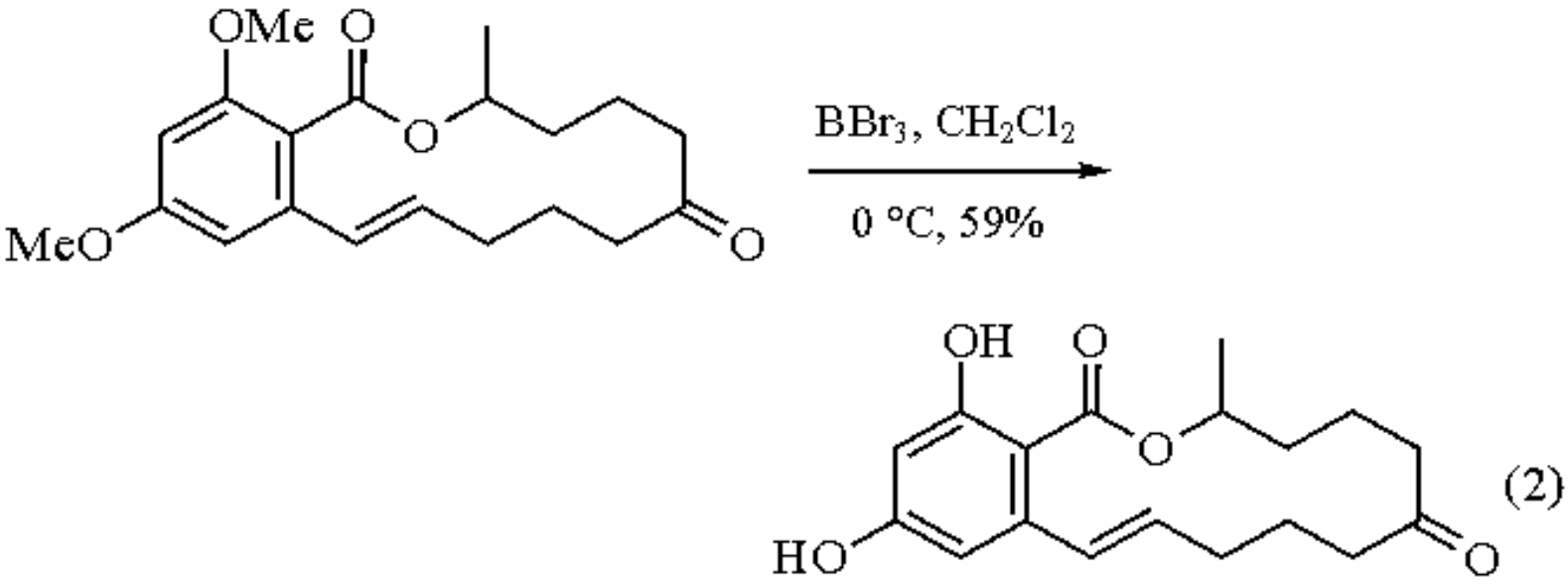

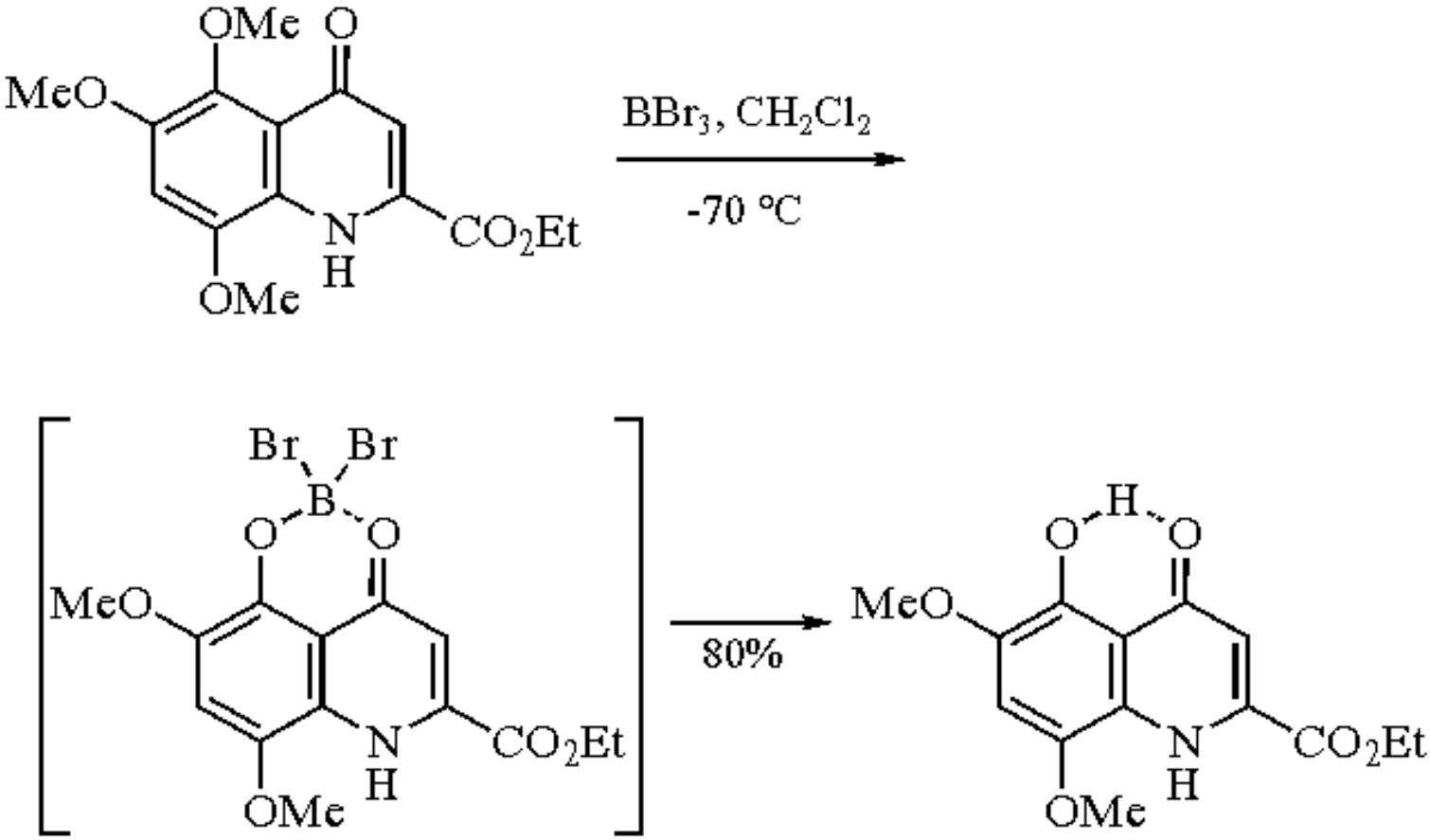

The cleavage of mixed dialkyl ethers occurs at the more substituted carbon-oxygen bond. Methyl ethers of secondary or tertiary alcohols give methanol and secondary or tertiary alkyl bromides selectively by the reaction with BBr_3,[8] although the addition of ***Sodium Iodide*** and ***15-Crown-5*** ether can change this selectivity (eq 4).[9] In contrast, methyl ethers of primary alcohols are generally cleaved at the Me-O bond, as demonstrated in Corey's prostaglandin synthesis (eq 5).[10]

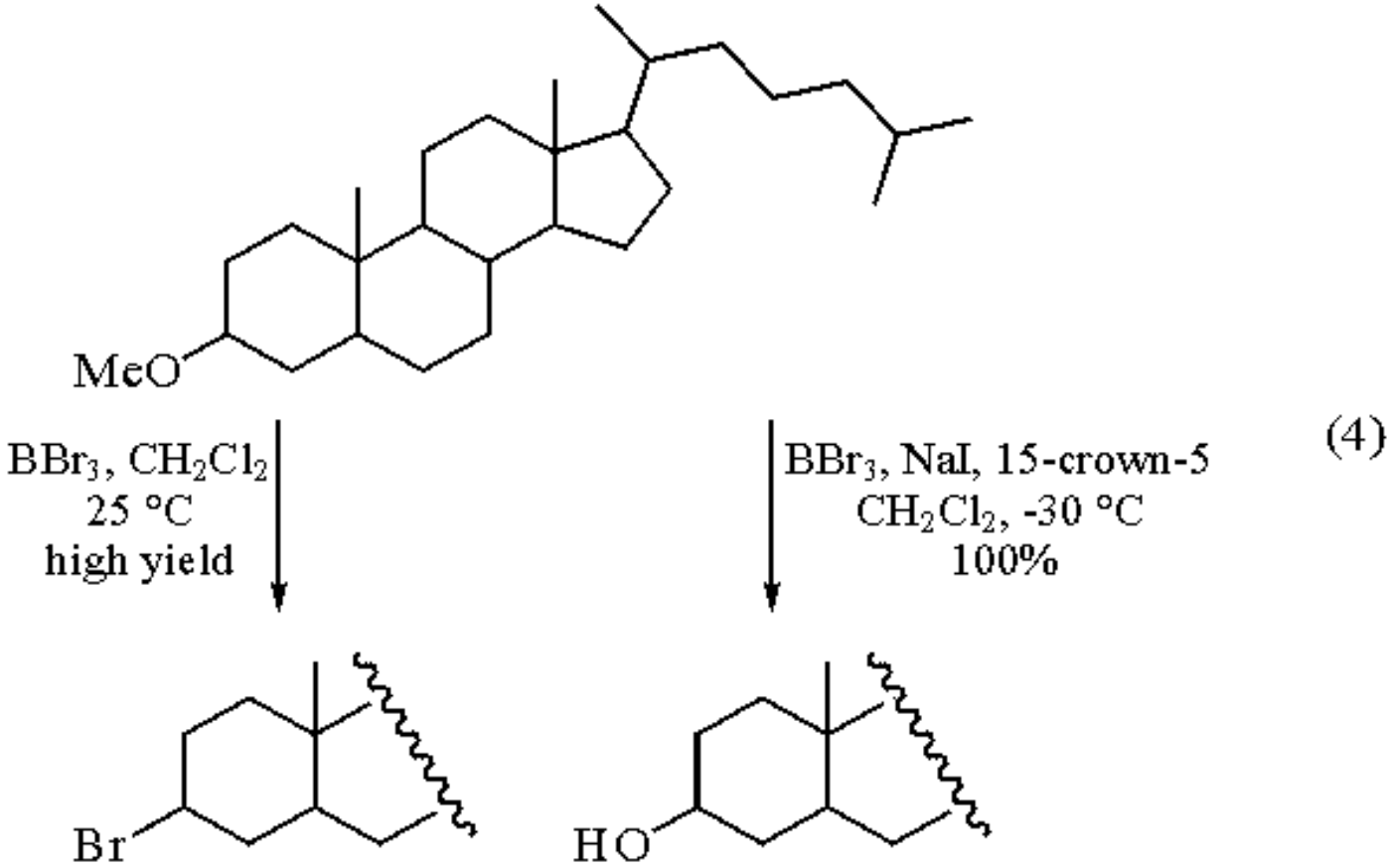

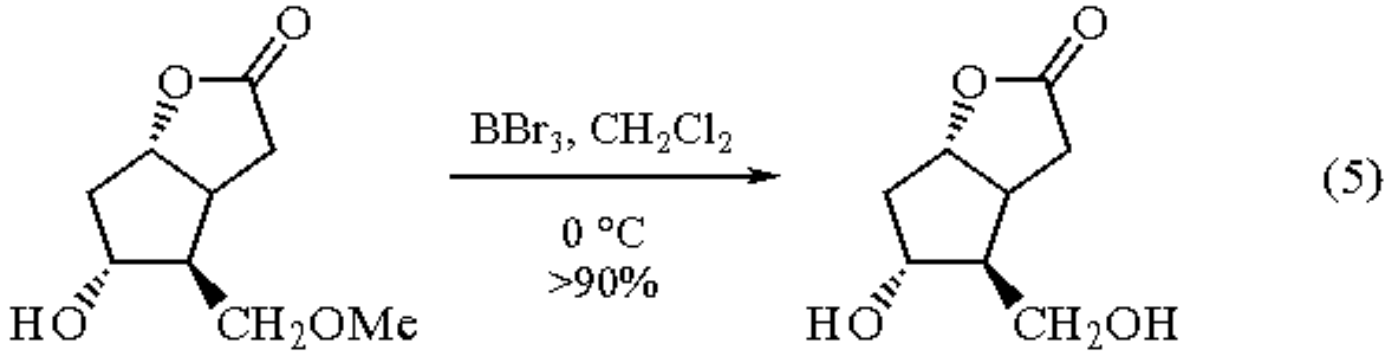

BBr_3 has been also used for the deprotection of carbohydrate derivatives[11] and polyoxygenated intermediates in the synthesis of deoxyvernolepin,[12] vernolepin,[13] and vernomenin.[13] Although one of the model compounds is deprotected cleanly (eq 6),[14] application of BBr_3 to more highly functionalized intermediates leads to cleavage of undesired C-O bonds competitively (eq 7).[12,13]

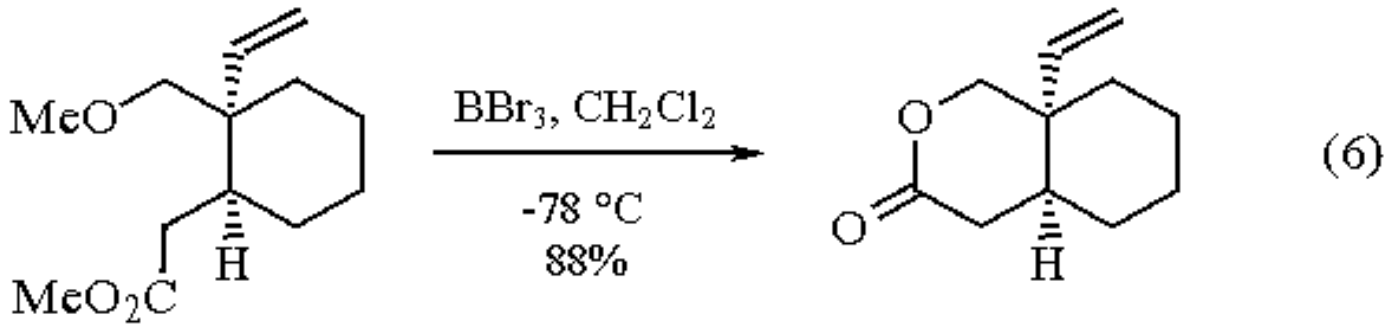

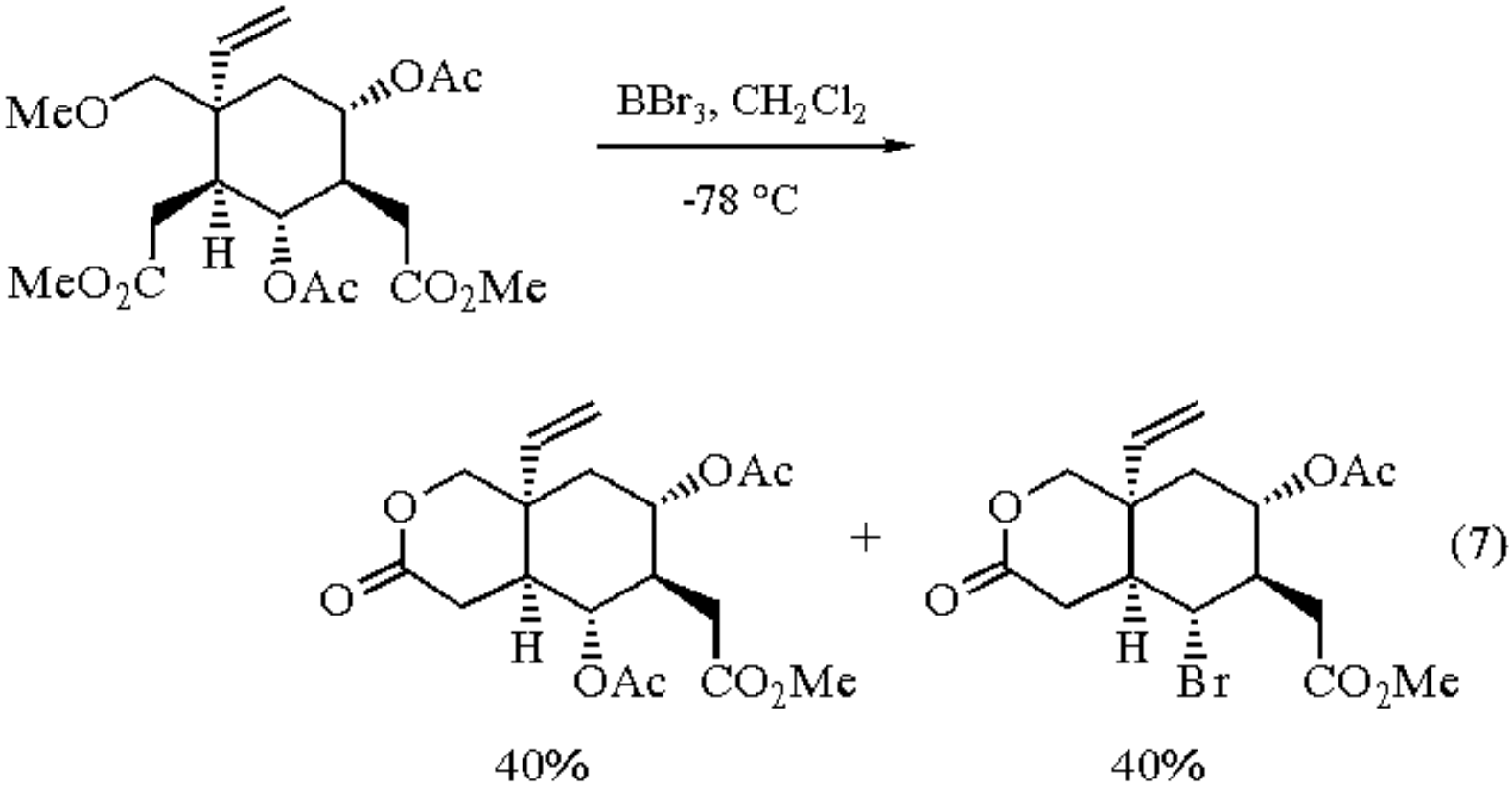

(7)

For the complete cleavage, 1 mol of BBr_3 is required for each ether group and other Lewis-basic functional groups. Sometimes it is difficult to find reaction conditions for the selective cleavage of the desired C-O bond. Recently, modified bromoboranes such as ***B-Bromocatecholborane***,[15] dialkylbromoboranes,[16] ***Bromobis(isopropylthio)borane***,[17] and ***9-Bromo-9-borabicyclo[3.3.1]nonane***,[18] have been introduced to cleave C-O bonds more selectively under milder conditions. $BBr_3.SMe_2$ is also effective for ether cleavage and has the advantage of being more stable than BBr_3. It can be stored for a long time and handled easily. However, a two- to fourfold excess of the reagent is necessary to complete the dealkylation of alkyl aryl ether.[19]

Amino acid protecting groups such as benzyloxycarbonyl and *t*-butoxycarbonyl groups are cleaved by BBr_3. However, the hydrolysis of the ester function also occurs under the same reaction conditions.[20] Debenzylation and debenzyloxymethylation of uracils proceed successfully in aromatic solvents, but demethylation is more sluggish and less facile (eq 8).[21]

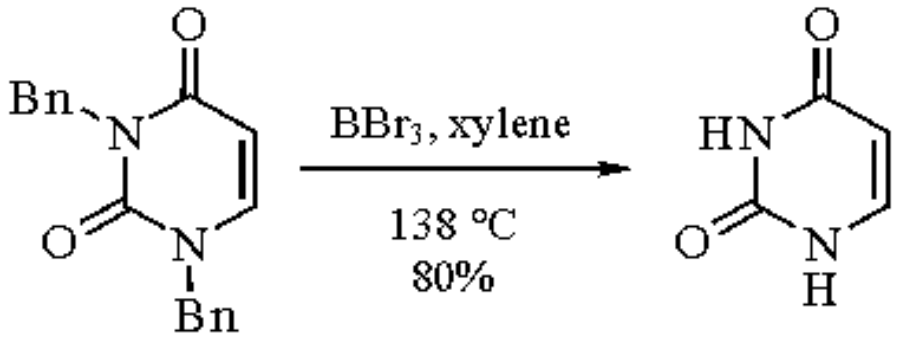

(8)

Substitution Reactions.

BBr_3 reacts with cyclic ethers to give tris(o-bromoalkoxy)boranes which provide o-bromoalkanols or o-bromoalkanals when treated with MeOH or ***Pyridinium Chlorochromate***, respectively (eq 9).[22] Unfortunately, unsymmetrically substituted ethers such as 2-methyltetrahydrofuran are cleaved nonregioselectively. Generally, ester groups survive under the reaction conditions for ether cleavage, but the ring opening of lactones occurs under mild conditions to give o-halocarboxylic acids in good yields (eq 10).[23]

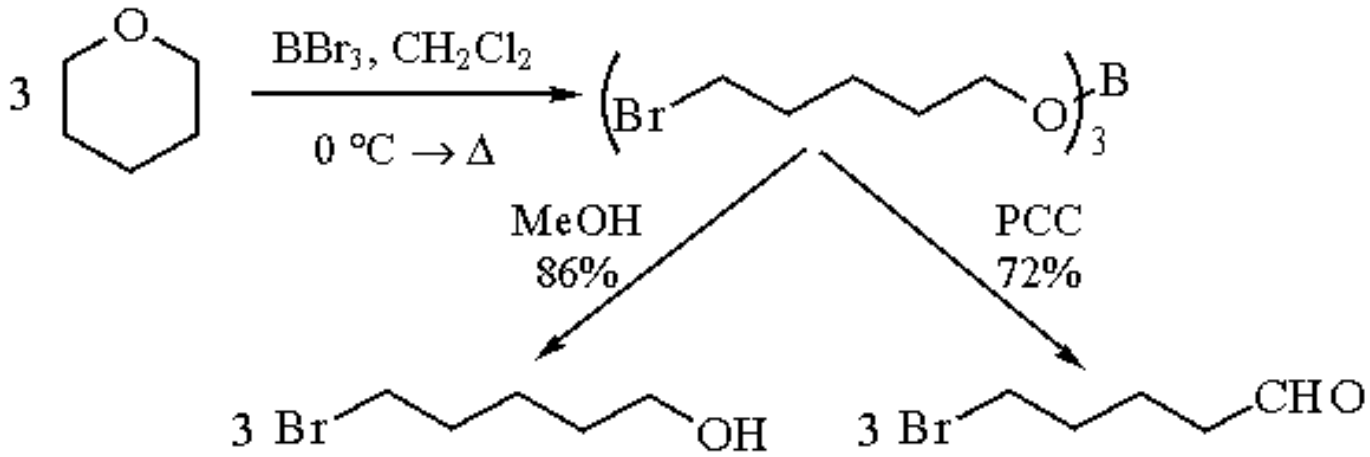

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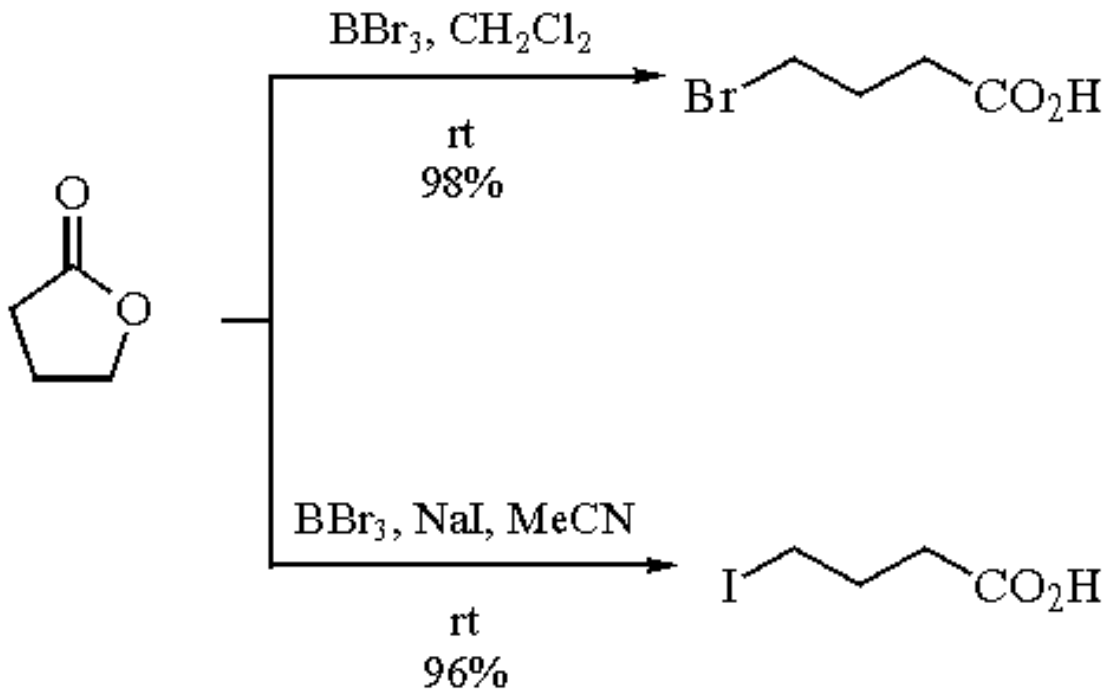

(10)

In the reaction with methoxybenzaldehyde, bromination of the carbonyl group takes place more rapidly than demethylation; therefore benzal bromide formation is generally observed in the reaction with aromatic aldehydes.[24] Cleavage of *t*-butyldimethylsilyl ethers or *t*-butyldiphenylsilyl ethers occurs at the C-O bond to give alkyl bromides.[25] Alcohols can be converted to alkyl bromides by this method.

In a special case, BBr_3 is used for the bromination of hydrocarbons. Adamantane is brominated by a mixture of ***Bromine***, BBr_3, and ***Aluminum Bromide*** to give 1,3-dibromoadamantane selectively.[26] Tetrachlorocyclopropene[27] and hexachlorocyclopentadiene[28] are substituted to the corresponding bromides by BBr_3 and, in the latter case, addition of $AlBr_3$ and Br_2 is effective to improve the result.[29]

Reduction of Sulfur Compounds.

Alkyl and aryl sulfoxides are reduced by BBr_3 to the corresponding sulfides in good yields.[30] Addition of ***Potassium Iodide*** and a catalytic amount of ***Tetra-n-butylammonium Iodide*** is necessary for the reduction of sulfonic acids and their derivatives.[31]

Transesterification of Esters or Conversion to Amides.

Transesterification reactions of carboxylic esters or conversion into the amides is promoted by a stoichiometric amount of BBr_3.[32]

Removal of Methyl Sulfide from Organoborane-Methyl Sulfide Complexes.

Methyl sulfide can be removed from $BrBR_2.SMe_2$ or $Br_2BR.SMe_2$, which are prepared by the hydroboration reaction of alkenes or alkynes with $BrBH_2.SMe_2$ or $Br_2BH.SMe_2$, by using BBr_3.[33] The resulting alkenyldibromoboranes are useful for the stereoselective synthesis of bromodienes (eq 11).[34]

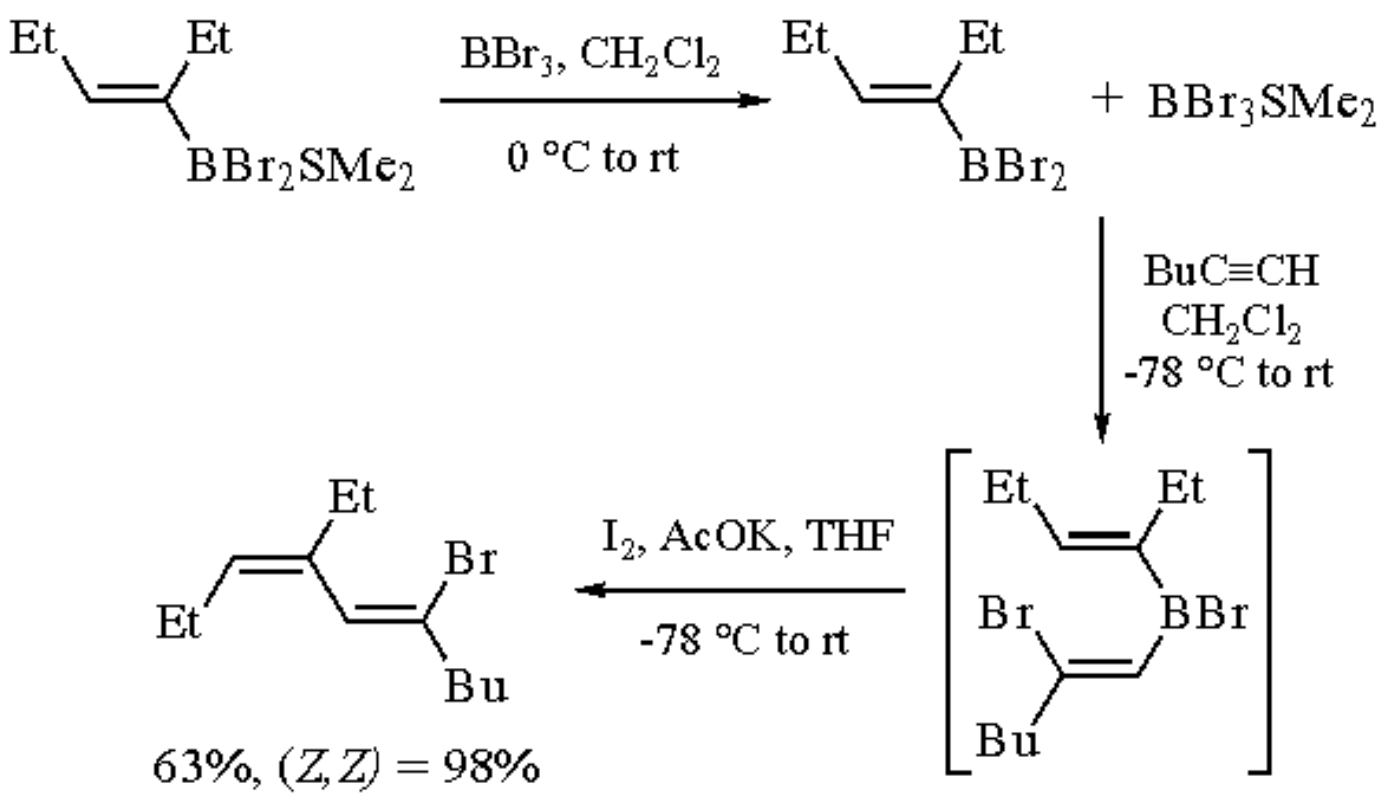

(11)

Bromoboration Reactions.

BBr_3 does not add to isolated double bonds, but reacts with allene spontaneously even at low temperature to give (2-

bromoallyl)dibromoborane,[35] which provides stable (2-bromoallyl)diphenoxyborane by the addition of anisole.[36] The diphenoxyborane derivative reacts with carbonyl compounds to give 2-bromohomoallylic alcohols in high yields (eq 12). Bromoboration of 1-alkynes provides (*Z*)-(2-bromo-1-alkenyl)dibromoboranes stereo- and regioselectively (eq 13),[37] which are applied for the synthesis of trisubstituted alkenes,[38] α,β-unsaturated esters,[39] and γ,δ-unsaturated ketones,[40] bromodienes,[41] 1,2-dihalo-1-alkenes,[42] 2-bromoalkanals,[43] and β-bromo-α,β-unsaturated amides.[44]

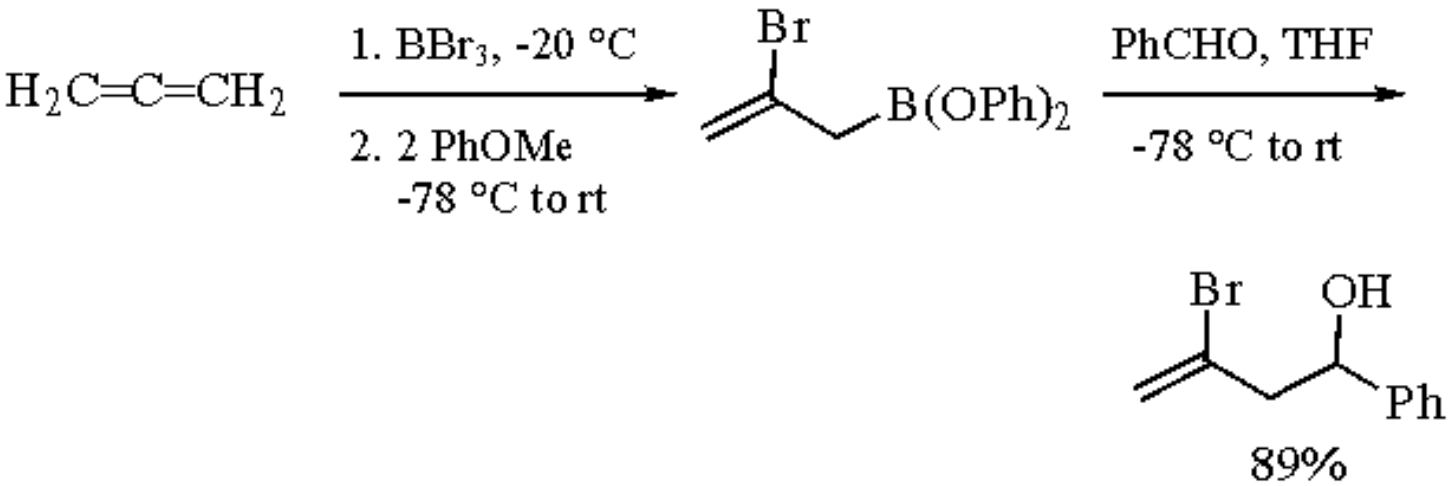

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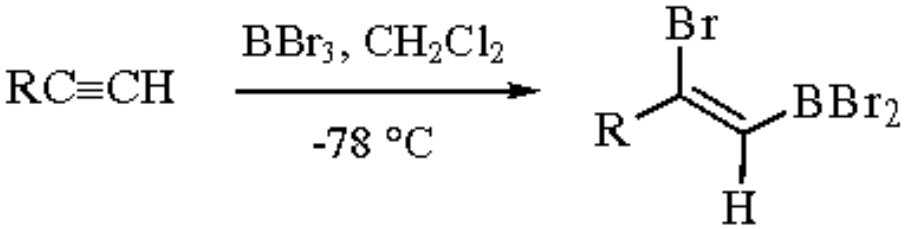

(13)

Chiral Bromoborane Reagents.

Complexes made from chiral 1-alkyl-2-(diphenylhydroxymethyl)pyrrolidines and BBr_3 are effective catalysts for asymmetric Diels-Alder reactions.[45] Bromoboranes prepared from chiral 1,2-diphenyl-1,2-bis(arenesulfonamido)ethanes[46,47] are used to prepare chiral allylic boranes,[47,48] allenylic borane,[49] propargylic boranes,[49] and enolates.[46,47,50] The *B*-bromodiazaborolidinene (**1**), prepared from 1,2-diphenyl-1,2-bis(*p*-toluenesulfonamido)ethane, is particularly effective in these applications. The reagents prepared from (**1**) are highly effective for the enantioselective synthesis of homoallylic alcohols (eq 14),[48] homopropargylic alcohols (eq 15),[49] propadienyl carbinols (eq 16),[49] and aldol condensation products (eq 17).[46]

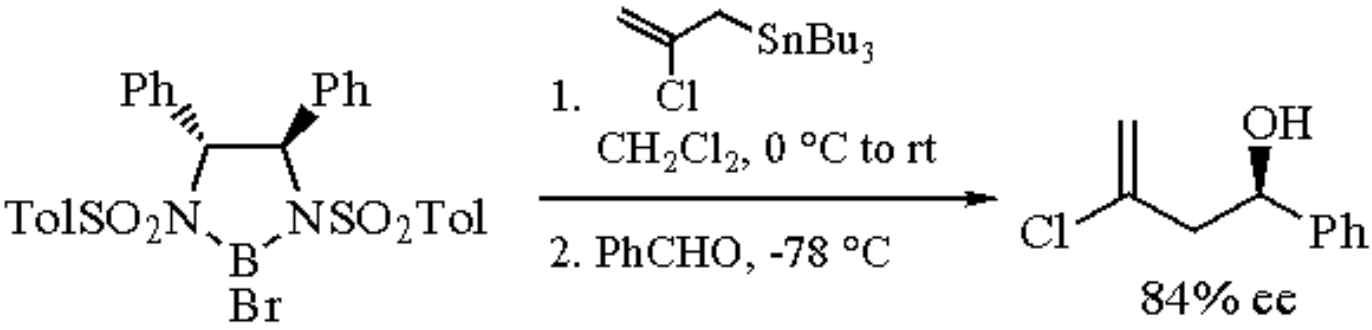

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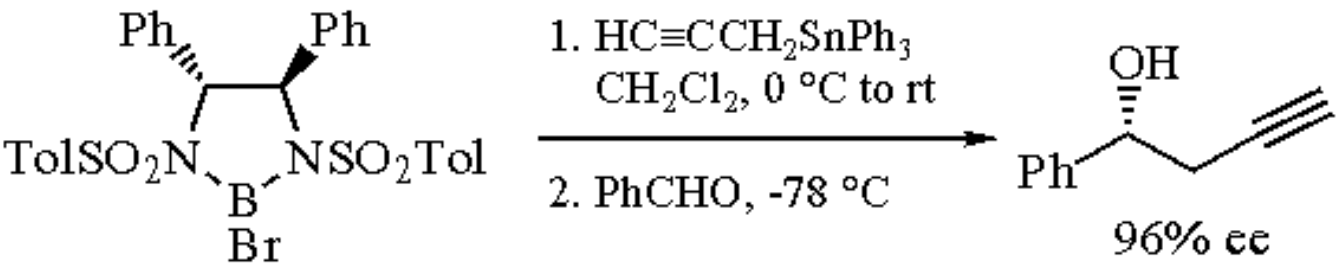

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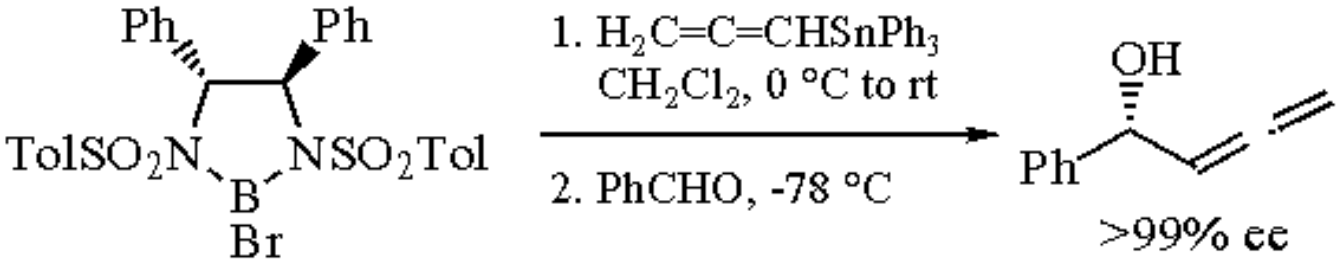

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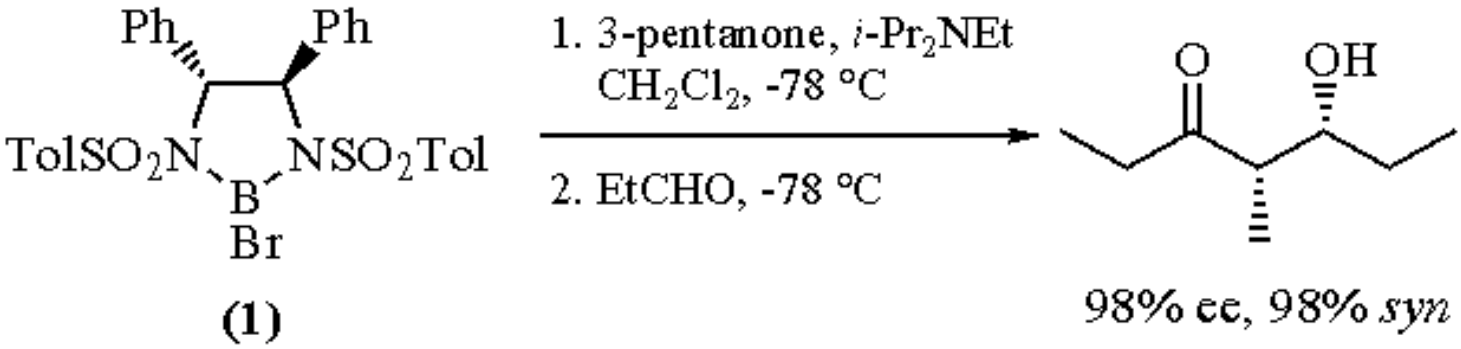

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Boron Trichloride[1]

BCl_3

[10294-34-5] · BCl_3 · Boron Trichloride · (MW 117.17)

(Lewis acid capable of selective cleavage of ether and acetal protecting groups; reagent for carbonyl condensations; precursor of organoboron reagents)

Physical Data: bp 12.5 °C; *d* 1.434 g cm^{-3} (0 °C).

Solubility: sol saturated and halogenated hydrocarbon and aromatic solvents; solubility in diethyl ether is approximately 1.5 M at 0 °C; stable for several weeks in ethyl ether at 0 °C, but dec by water or alcohols.

Form Supplied in: colorless gas or fuming liquid in an ampoule; $BCl_3.SMe_2$ complex (solid) and 1 M solutions in dichloromethane, hexane, heptane, and *p*-xylene are available.

Handling, Storage, and Precautions: a poison by inhalation and an irritant to skin, eyes, and mucous membranes. Reacts exothermically with water and moist air, forming toxic and corrosive fumes. Violent reaction occurs with aniline or phosphine. All operations should be carried out in a well-ventilated fume hood without exposure to the atmosphere. The gas can be collected and measured as a liquid by condensing in a cooled centrifuge tube and then transferred to the reaction system by distillation with a slow stream of nitrogen.

Cleavage of Ethers, Acetals, and Esters.

Like many other Lewis acids, BCl_3 has been extensively used as a reagent for the cleavage of a wide variety of ethers, acetals, and certain types of esters.[2] Ether cleavage procedures involve addition of BCl_3, either neat or as a solution in CH_2Cl_2, to the substrate at -80 °C. The vessel is then stoppered and allowed to warm to rt. Whereas the complexes of BCl_3 with dimethyl ether and diethyl ether are rather stable at rt, they decompose to form $ROBCl_2$ or $(RO)_2BCl$ with evolution of alkyl chloride upon heating to 56 °C.[1] Diaryl ethers are unreactive. Mixed dialkyl ethers are cleaved to give the alkyl chloride derived from C-O bond cleavage leading to the more stable carbenium ion. The transition state is predominantly S_N1 in character, as evidenced by partial racemization of chiral ethers[1,2] and the rearrangement of allyl phenyl ethers to *o*-allylphenols.[3] BCl_3 can be used for the deprotection of a variety of methoxybenzenes including hindered polymethoxybenzenes and *peri*-methoxynaphthalene.[1,2,4] When methoxy groups are *ortho* to a carbonyl group, the reaction is accelerated by the formation of a chelate between boron and the carbonyl oxygen atom (Scheme 1).[4a-c]

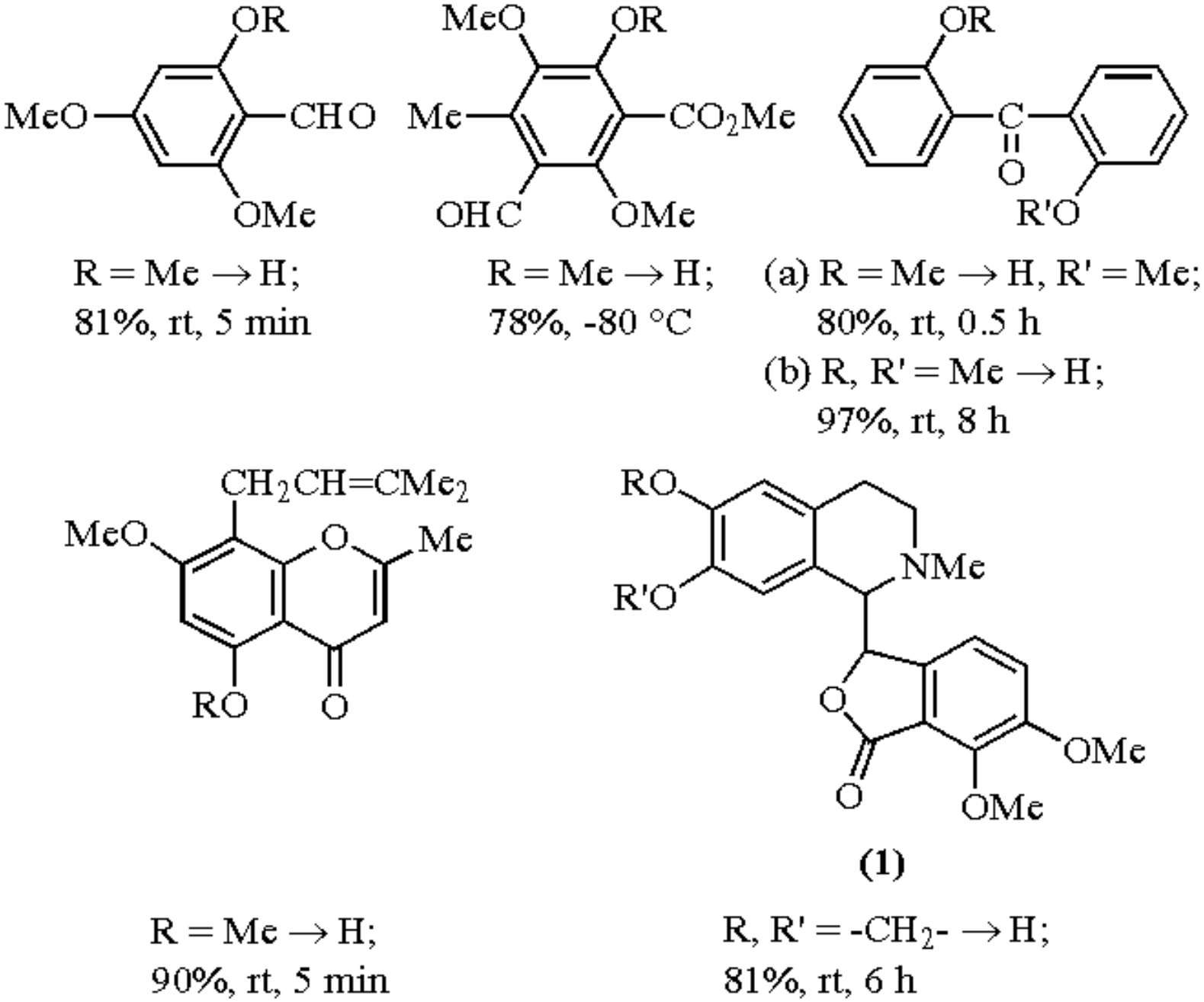

Scheme 1 Demethylation of aromatic ethers by BCl_3 in CH_2Cl_2

The reagent is less reactive than ***Boron Tribromide*** for ether cleavage; however, the type and extent of deetherification can be more easily controlled by the ratio of substrate to BCl_3 as well as the reaction temperature and time. The transformation of (-)-β-hydrastine (**1**) to (-)-cordrastine II is efficiently achieved by selective cleavage of the methylenedioxy group in preference to aromatic methoxy groups.[5] The demethylation of (-)-2-*O*-methyl-(-)-inositol in dichloromethane proceeds at -80 °C without cleavage of a tosyl ester group.[6] Methyl glycosides are converted into glycosyl chlorides at -78 °C without effecting benzyl and acetyl protecting groups.[7]

One of the difficulties with the use of BCl_3 arises from its tendency to fume profusely in air. The complex of BCl_3 with dimethyl sulfide is solid, stable in air, and handled easily. By using a two- to fourfold excess of the reagent in dichloroethane at 83 °C, aromatic methoxy and methylenedioxy groups can be cleaved in good yields.[8]

Another application of BCl_3 is for the cleavage of highly hindered esters under mild conditions. *O*-Methylpodocarpate (**2**) and methyl adamantane-1-carboxylate are cleaved at 0 °C.[9] The highly selective displacement of the acetoxy group in the presence of other potentially basic groups in 2-cephem ester (**3**) provides the corresponding allylic chloride. On the other hand, treatment of (**3**) with an excess of BCl_3 results in the cleavage of the acetoxy and *t*-butyl ester groups.[10]

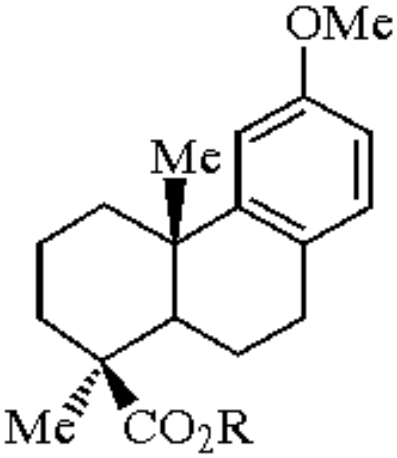

(2)

R = Me → H; 90%
BCl_3, CH_2Cl_2, 0 °C

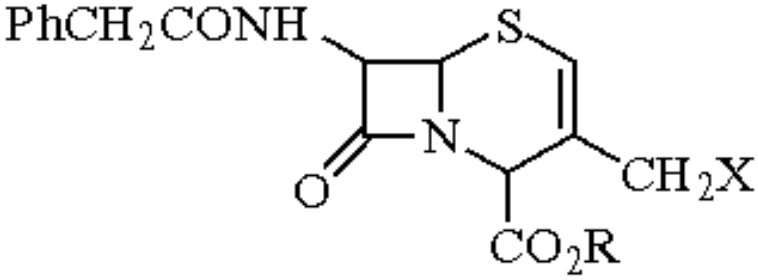

(3)

(1) R = *t*-Bu, X = OAc → Cl; 64%
BCl_3 (1 equiv), CH_2Cl_2, -5 °C
(2) R = *t*-Bu → H, X = OAc → OH; 68%
BCl_3 (3 equiv), CH_2Cl_2, rt

Tertiary phosphines are cleaved at the P-C bond to give diphenylphosphine oxides. Workup with ***Hydrogen Peroxide*** provides diphenylphosphinic acids (eq 1).[11]

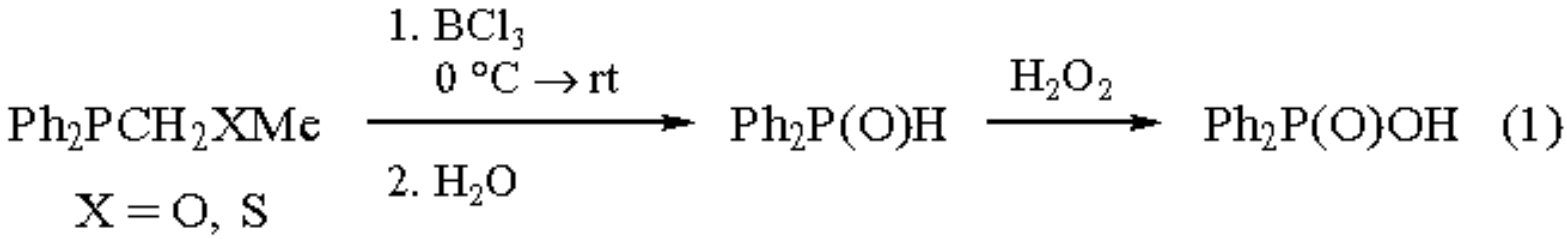

Condensation Reactions.

Boron trichloride converts ketones into (*Z*)-boron enolates at -95 °C in the presence of ***Diisopropylethylamine***. These enolates react with aldehydes with high *syn* diastereoselectivity (eq 2).[12] A similar condensation of imines with carbonyl compounds also provides crossed aldols in reasonable yields.[13] The reaction was extended to the asymmetric aldol condensation of acetophenone imine and benzaldehyde by using isobornylamine as a chiral auxiliary (48% ee).[14]

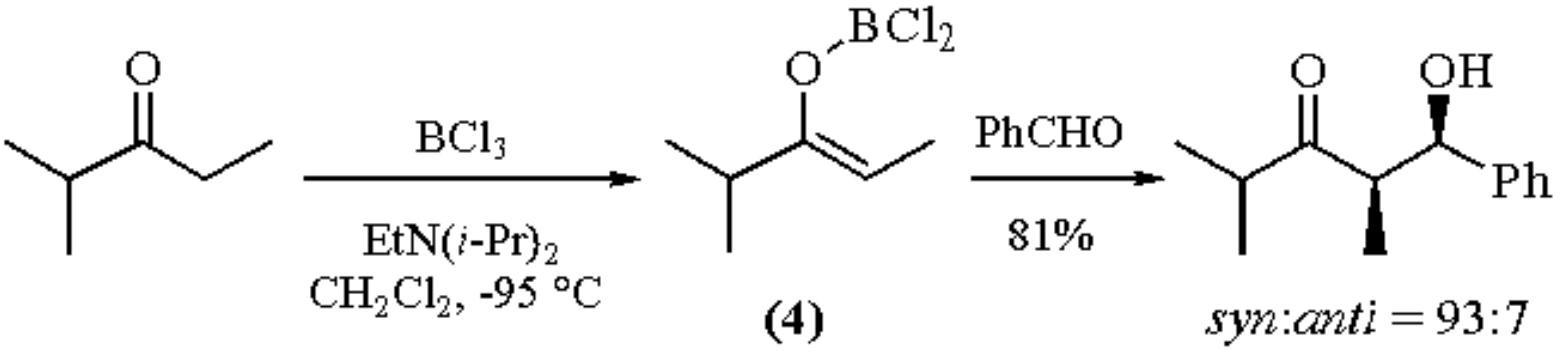

(2)

(*N*-Alkylanilino)dichloroboranes (**5**), prepared in situ from *N*-alkylanilines and boron trichloride, are versatile intermediates for the synthesis of *ortho*-functionalized aniline derivatives (eqs 3-5).[15] The regioselective *ortho* hydroxyalkylation can be achieved with aromatic aldehydes.[16]

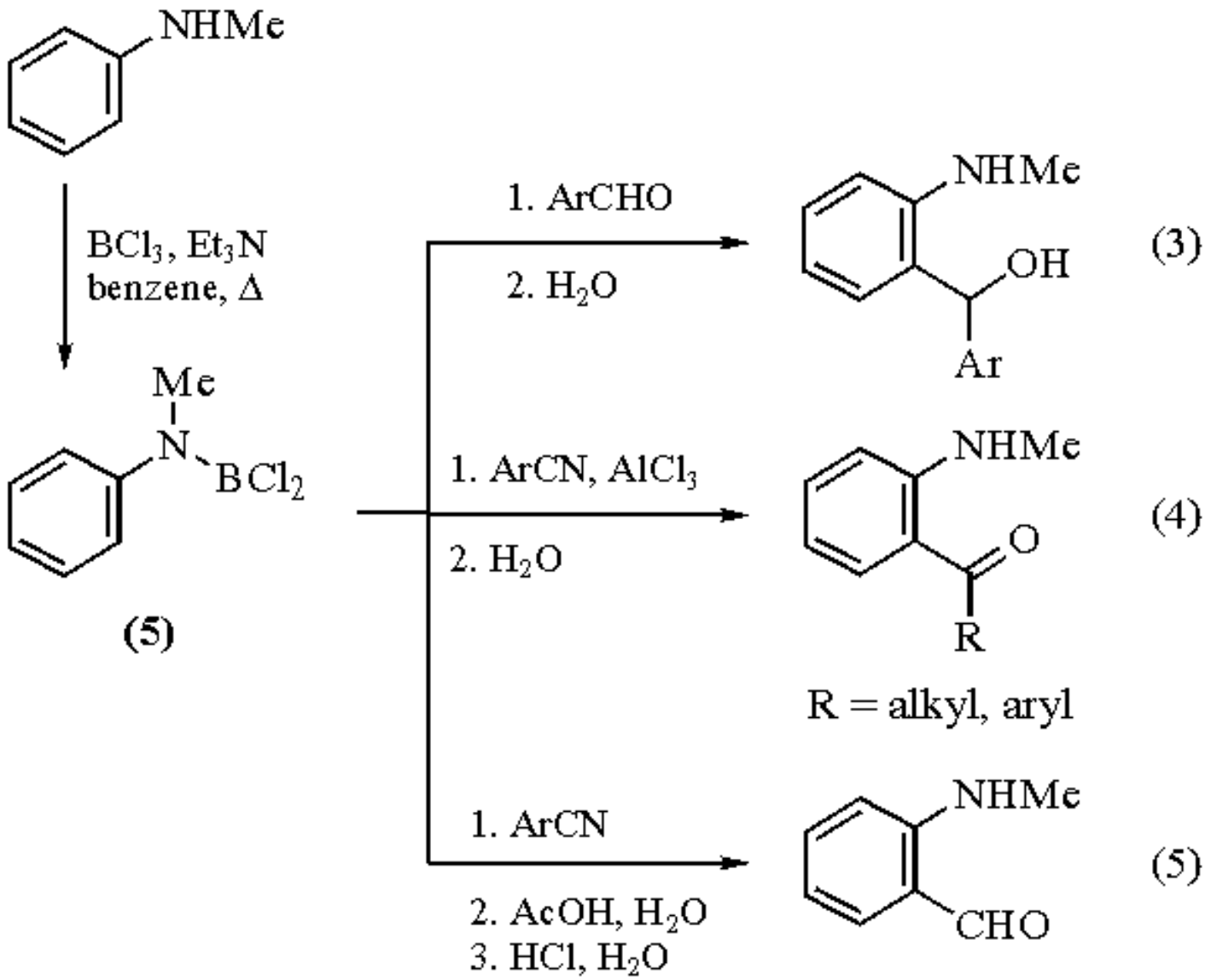

The reaction of (**5**) with alkyl and aryl nitriles and ***Aluminum Chloride*** catalyst provides *ortho*-acyl anilines.[16] When chloroacetonitrile is used, the products are ideal precursors for indole synthesis.[17] Use of isocyanides instead of

nitriles provides *ortho*-formyl *N*-alkylanilines.[18] Although these reactions with BCl_3 are restricted to *N*-alkylanilines, the use of ***Phenylboron Dichloride*** allows the *ortho*-hydroxybenzylation of primary anilines.[19]

Analogously, boron trichloride induces *ortho* selective acylation of phenols at rt with nitriles, isocyanates, or acyl chlorides (eq 6).[20] The efficiency and regioselectivity of these reactions are best with BCl_3 among the representative metal halides that have been examined. In both the aniline and phenol substitutions the boron atom acts as a template to bring the reactants together, leading to cyclic intermediates and exclusively products of *ortho* substitution. A similar *ortho* selective condensation of aromatic azides with BCl_3 provides fused heterocycles containing nitrogen.[21]

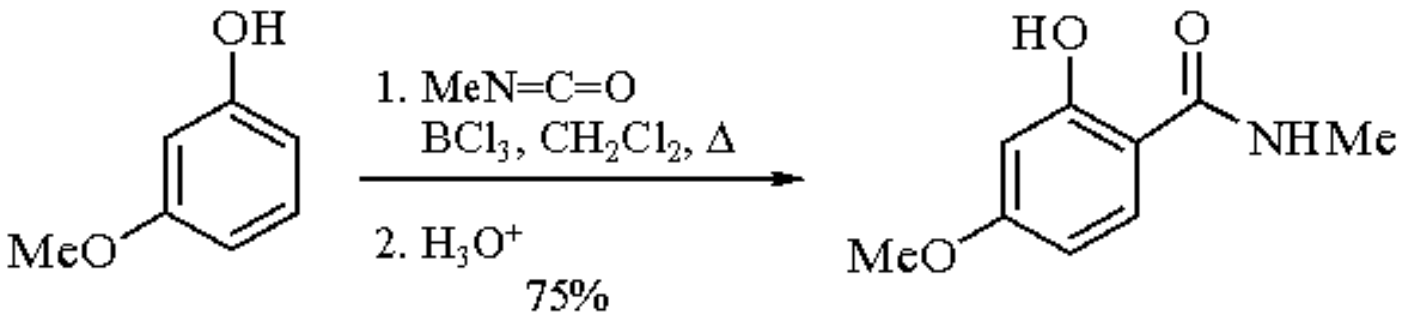

(6)

Aldehydes and ketones condense with ketene in the presence of 1 equiv of boron trichloride to give α,β-unsaturated acyl chlorides.[22] Aryl isocyanates are converted into allophanyl chlorides, which are precursors for industrially important 1,3-diazetidinediones (eq 7).[23]

(7)

Synthesis of Organoboron Reagents.

General method of synthesis of organoboranes consists of the transmetallation reaction of organometallic compounds with BX_3.[24] Boronic acid derivatives [$RB(OH)_2$] are most conveniently synthesized by the reaction of $B(OR)_3$ with RLi or RMgX reagents, but boron trihalides are more advantageous for transmetalation reactions with less nucleophilic organometallic reagents based on Pb,[25] Hg,[26] Sn,[27] and Zr[28] (eqs 8 and 9).

$$Ph_4Sn + 2\,BCl_3 \longrightarrow 2\,PhBCl_2 + Ph_2SnCl_2 \qquad (8)$$

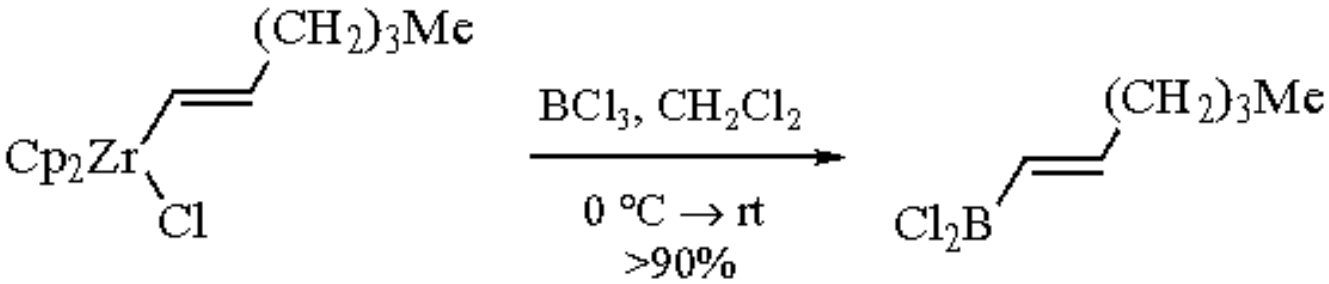

(9)

Redistribution or exchange reactions of R_3B with boron trihalides in the presence of catalytic amounts of hydride provides an efficient synthesis of RBX_2 and R_2BX.[29] Another convenient and general method for the preparation of organodichloroboranes involves treatment of alkyl, 1-alkenyl, and aryl boronates with BCl_3 in the presence of ***Iron(III) Chloride*** (3 mol %).[30] Organodichloroboranes are valuable synthetic reagents because of their high Lewis acidity, and their utility is well demonstrated in the syntheses of piperidine and pyrrolidine derivatives by the intramolecular alkylation of azides (eq 10)[31] or the synthesis of esters by the reaction with ***Ethyl Diazoacetate***.[32] The various organoborane derivatives, R_3B, R_2BCl, and $RBCl_2$, all react with organic azides and diazoacetates. However, especially facile reactions are achieved by using organodichloroboranes ($RBCl_2$).

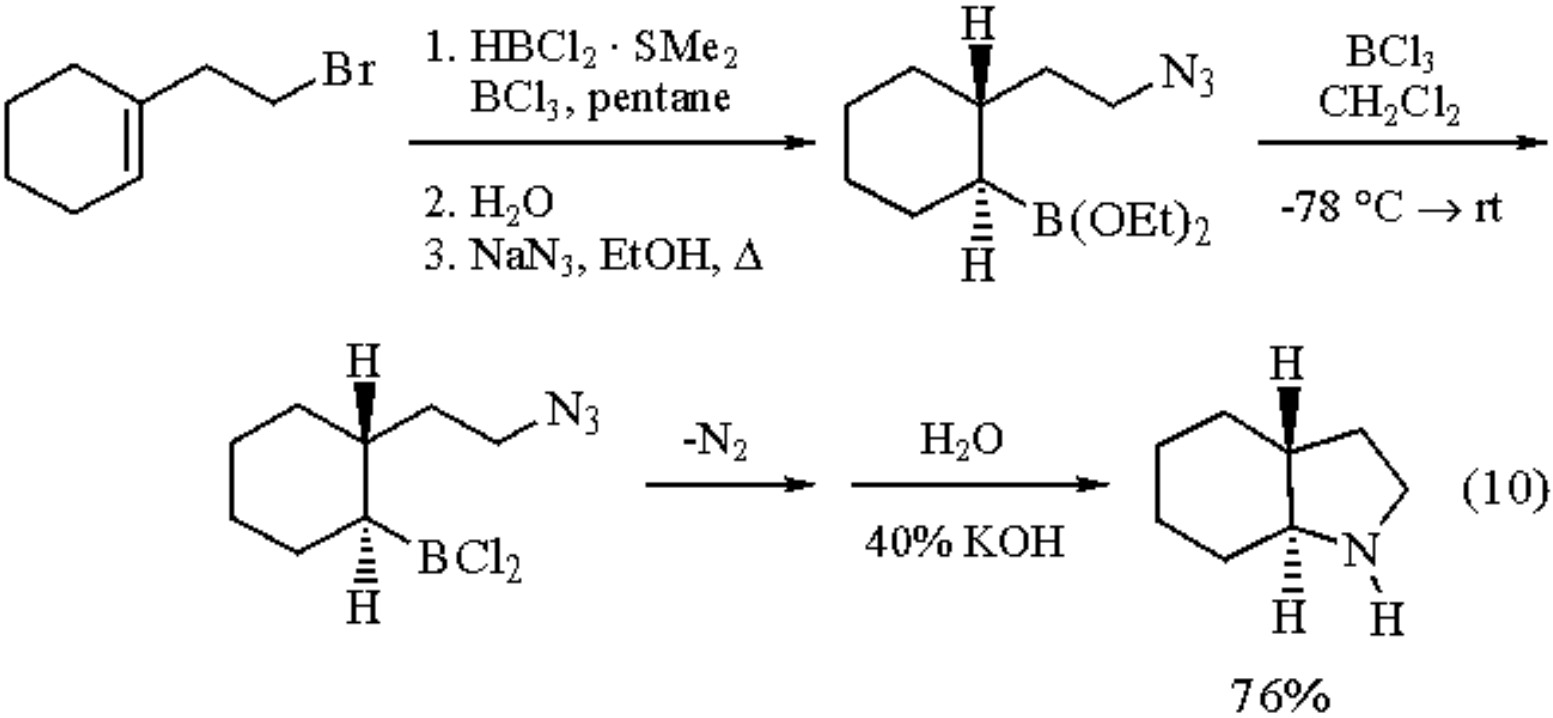

(10)

Dichloroborane and monochloroborane etherates or their methyl sulfide complexes have been prepared by the reaction of borane and boron trichloride.[33] However, hydroboration of alkenes with these borane reagents is usually very slow due to the slow dissociation of the complex. Dichloroborane prepared in pentane from boron trichloride and trimethylsilane shows unusually high reactivity with alkenes and alkynes; hydroboration is instantaneous at -78 °C (eq 11).[34]

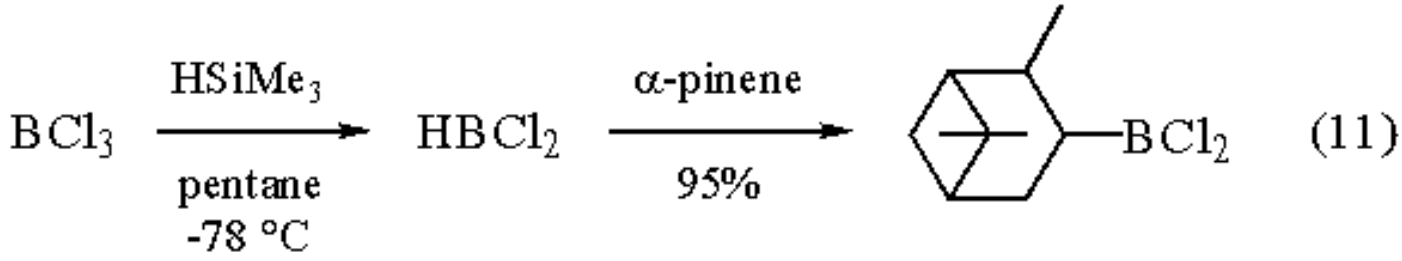

Direct boronation of benzene derivatives with BCl_3 in the presence of activated aluminum or $AlCl_3$ provides arylboronic acids after hydrolysis (eq 12).[35] Chloroboration of acetylene with boron trichloride produces dichloro(2-chloroethenyl)borane.[36] Similar reaction with phenylacetylene provides (*E*)-2-chloro-2-phenylethenylborane regio- and stereoselectively.[37]

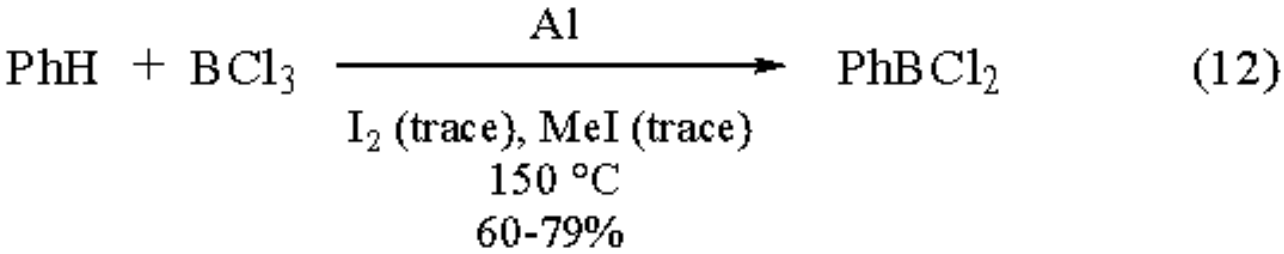

The syntheses of thioaldehydes, thioketones, thiolactones, and thiolactams from carbonyl compounds are readily achieved by in situ preparation of B_2S_3 from bis(tricyclohexyltin) sulfide and boron trichloride (eq 13).[38] The high sulfurating ability of this in situ prepared reagent can be attributed to its solubility in the reaction medium.

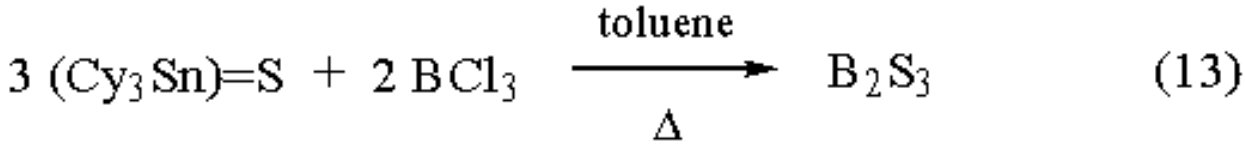

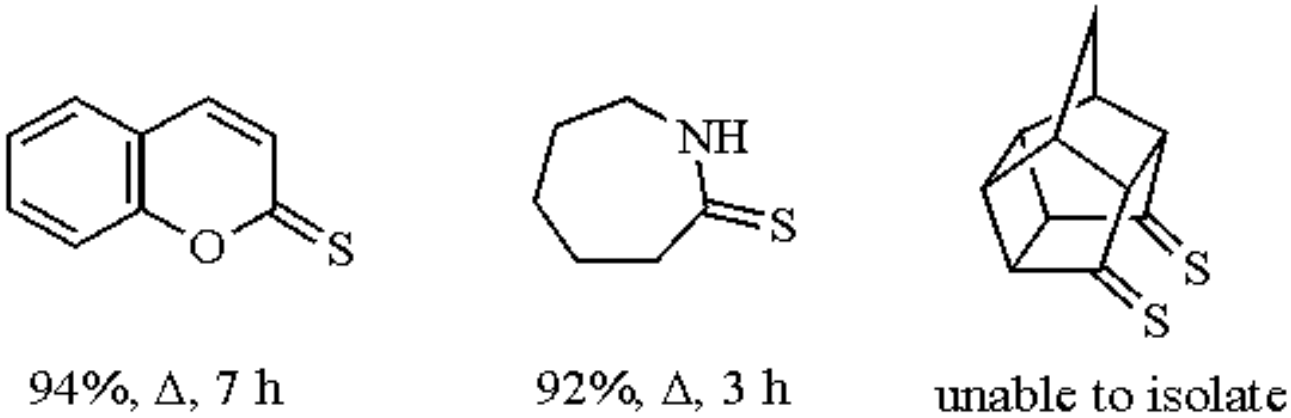

Related Reagents.

Bis(tricyclohexyltin) Sulfide-Boron Trichloride.

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Boron Trifluoride-Acetic Acid

$BF_3.(MeCO_2H)_2$

(BF_3)

[7637-07-2] · BF_3 · Boron Trifluoride-Acetic Acid · (MW 67.81) ($BF_3.MeCO_2H$)

[-] · $C_2H_4BF_3O_2$ · Boron Trifluoride-Acetic Acid · (MW 127.86) ($BF_3.(MeCO_2H)_2$)

[373-61-5] · $C_4H_8BF_3O_4$ · Boron Trifluoride-Acetic Acid · (MW 187.91) ($MeCO_2H$)

[64-19-7] · $C_2H_4O_2$ · Boron Trifluoride-Acetic Acid · (MW 60.05)

(mild Lewis acid)

Physical Data: solid monoacetic acid complex; liquid diacetic acid complex, *d* 1.353 g cm^{-3}.

Solubility: decomposes in water exothermically.

Form Supplied in: liquid diacetic acid complex 98%.

Preparative Methods: boron trifluoride monoacetic acid complex is made by passing ***Boron Trifluoride*** into anhydrous ***Acetic Acid*** in dichloroethane until a solid is produced; the liquid diacetic acid complex remains in solution. A solid with a composition of ca. 80 mol % absorption can be obtained by passing boron trifluoride into anhydrous acetic acid.[2]

Handling, Storage, and Precautions: extremely corrosive to the eyes and skin. If swallowed causes severe internal irritation and damage. Toxic irritating vapor. All work must be carried out in an efficient fume hood.

Desilylation Reactions.

These reactions are based on the well-known stabilization of a β-carbenium center by silicon. The conversion of allylsilanes into terminal alkenes using the boron trifluoride-diacetic acid complex has been studied in considerable detail. The reaction occurs by protonation, followed by nucleophile induced desilylation. The principle involved is shown in eq 1.[1] The stereochemical implications were considered in a detailed account, and in the deuteration-desilylation sequence shown in eq 2 the structure shown is the major product.[2] The method has been used as part of a total synthesis of carbocyclic cytochalasans, where the conversion of an endocyclic alkene into an exocyclic isomer was achieved in an 80% yield.[3] Protonation-desilylation of alkynes to give allenes in yields ranging from 70 to 97%

evidently can be rationalized as involving a β-vinyl cation. An example is shown in eq 3.[4]

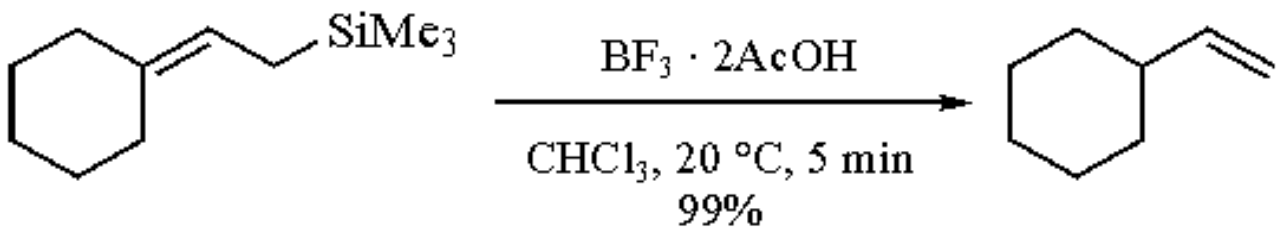

(1)

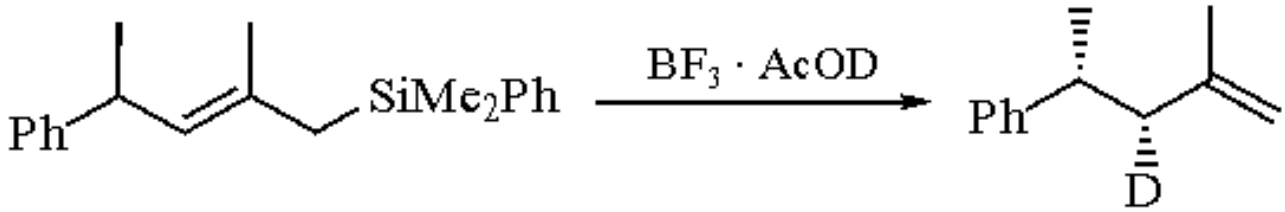

(2)

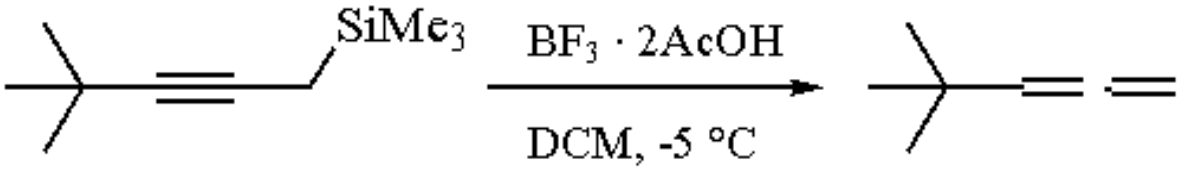

(3)

The formation of β-silicon-stabilized cations from γ-hydroxysilanes results from the normal pattern of pinacol rearrangements where hydride and phenyl migration is common. Desilylation then also affords an alkene.[5] Where the alkyl group is a ring residue, only hydride migration was observed, as shown in eq 4. Where a suitably positioned aryl residue can cyclize onto a second carbenium center, Friedel-Crafts cyclization takes place (eq 5). The full paper reports an additional number of interesting examples and also indicates that, while precedent might suggest that cyclopropane formation should be possible, none was observed.[6]

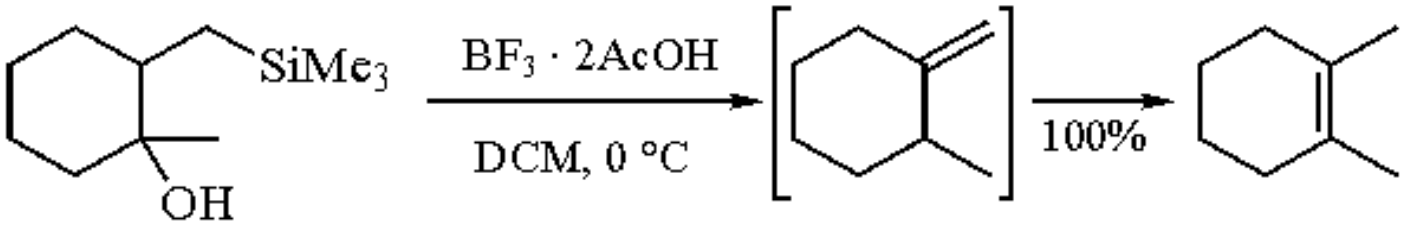

(4)

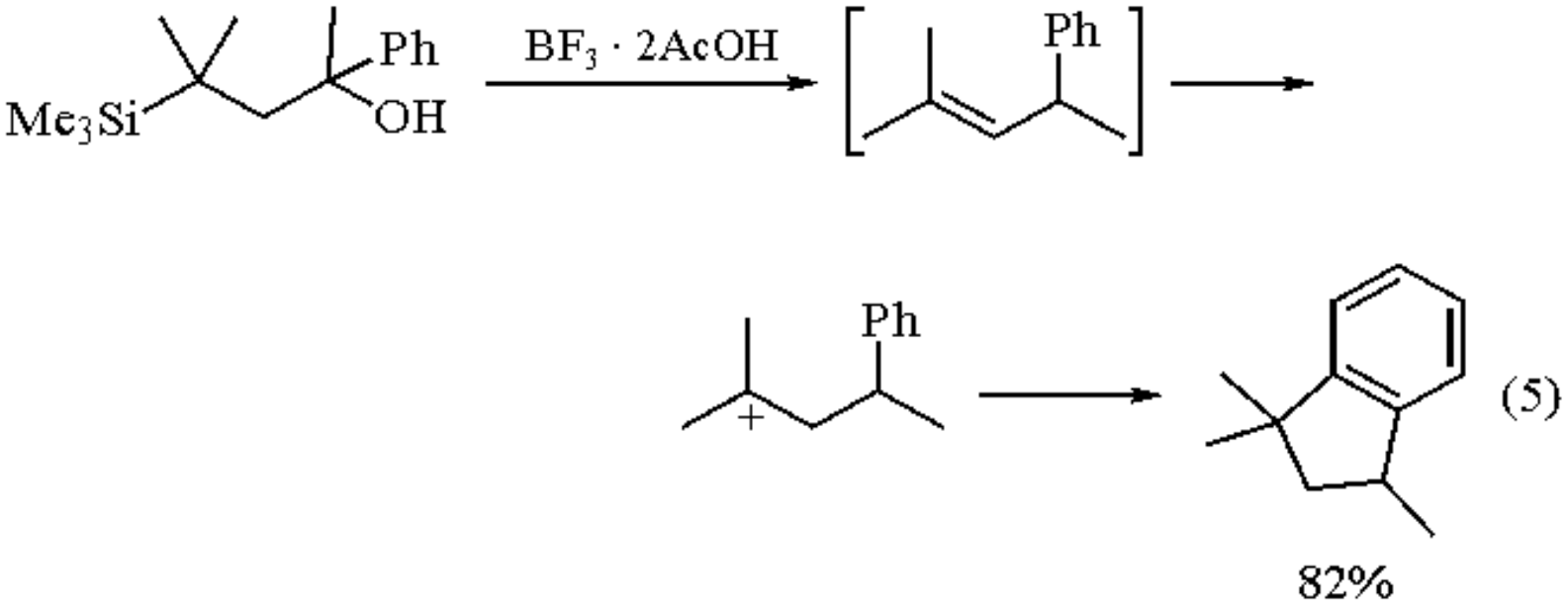

(5)

The phenyldimethylsilyl group can be converted in two steps into a hydroxy group and as such can be regarded as a masked hydroxy group. The first step involves the proto-desilylation of the phenyl group, which is then followed by a peracid-mediated rearrangement into a hydroxy group, with retention of configuration.[7] The sequence works well for primary, secondary, and tertiary silanes; the presence of ketone and ester functions does not cause a problem. Examples are shown in eqs 6-8.[7] The proto-desilylation-oxidation sequence has also been used in a formal synthesis of thienamycin.[8]

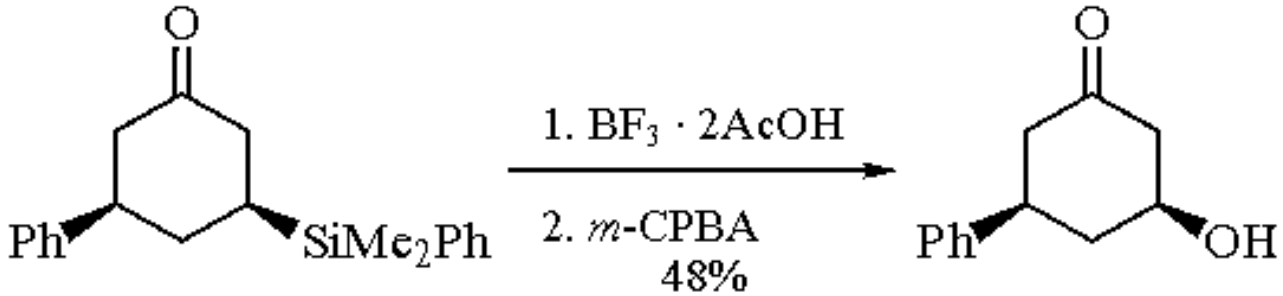

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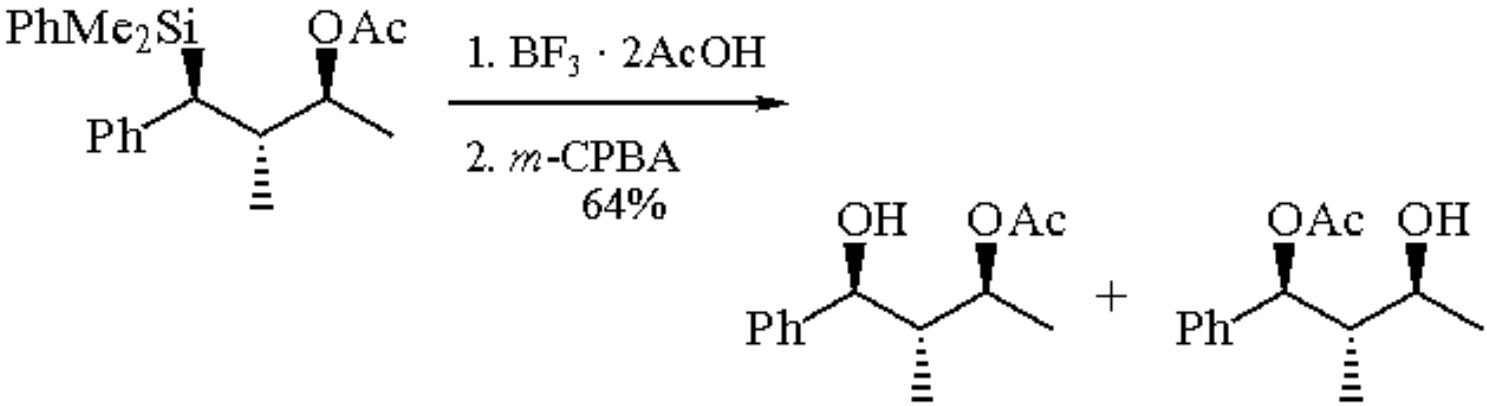

(7)

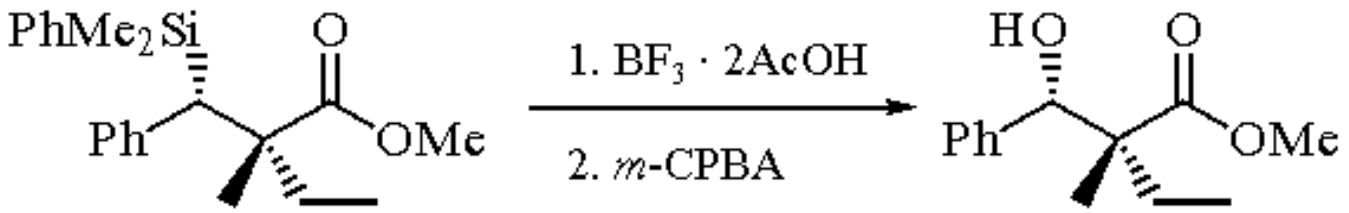

(8)

Destannylation Reactions.

The absence of cyclopropane formation in the silicon-based reactions reviewed above prompted an investigation of related tin chemistry. A large number of examples have been reported where cyclopropanes are formed in good yields and with remarkable stereoselectivity.[9] The yields are high even when the reacting centers are fully substituted (eq 9) and inversion of configuration occurs at both reacting centers. In the case of secondary benzyl alcohols the cyclopropanes are formed apparently with complete stereospecificity (eq 10).[9a]

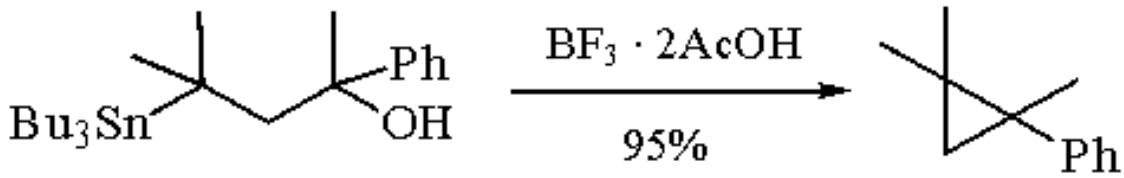

(9)

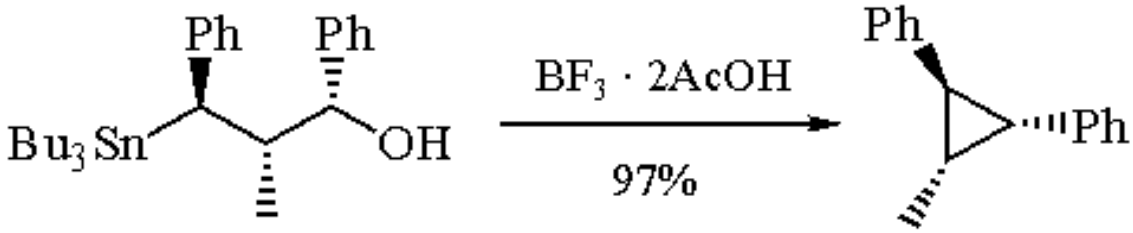

(10)

Miscellaneous Reactions.

Many of the other reactions using boron trifluoride/acetic acid complexes have been covered in the article on ***Boron Trifluoride-Acetic Anhydride***, which should be read in conjunction with this article. The hydrolysis of nitriles is an example,[10] but in the case of the hydrolysis to benzamide derivatives acylation α to the amide residue is not possible, and so as shown in eq 11, the addition of acetic anhydride would have been superfluous.[11] The Fries rearrangement is also discussed in connection with reactions of boron trifluoride and acetic anhydride, but in those cases the liberated phenolic group is acylated. Reaction also occurs using the boron trifluoride diacetic acid complex, as shown in eq 12.[12]

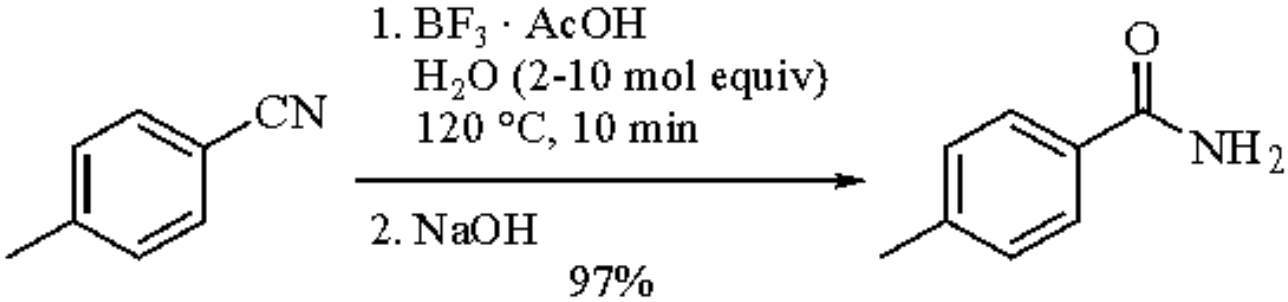

(11)

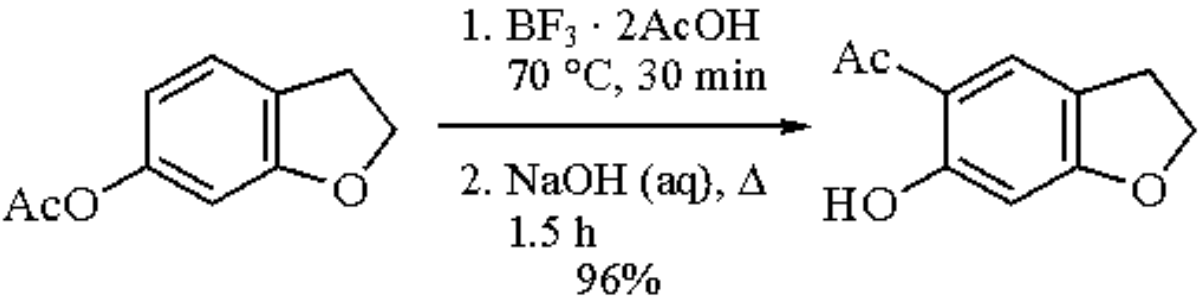

(12)

There are a large number of methods for the cleavage of ethers and esters that are based on boron trifluoride reagents and many of these are covered in other articles. An example that uses the boron trifluoride-acetic acid complex is concerned with protection of carboxy groups in peptides by means of the diphenylmethyl group.[13] The S-S bond in cystine is stable to the deprotection conditions.

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Boron Trifluoride-Dimethyl Sulfide[1]

$BF_3.SMe_2$

[353-43-5] · $C_2H_6BF_3S$ · Boron Trifluoride-Dimethyl Sulfide · (MW 129.93)

(reagent for the cleavage of benzyl ethers and carbamates)

Physical Data: solid at -78 °C, liquid at rt; P_{satn}(25 °C) 217 mmHg.[2a]

Solubility: sol most organic solvents such as pentane.

Form Supplied in: liquid complex sealed under nitrogen; commercially available.

Preparative Methods: made by the addition of equimolar amounts of the two components at -78 °C.[2a] Dissociation of the complex reported as 96.2% at 12 °C and 97.4% at 34 °C.[2a] Also formed when crystalline bromodimethylsulfonium tetrafluoroborate is aspirated at rt to give a colorless product without change in crystal form.[2b] The reagent system is normally assembled by adding a large excess of dimethyl sulfide to an excess of boron trifluoride etherate.[2c]

Handling, Storage, and Precautions: moisture-sensitive; use with carefully dried apparatus. All work must be carried out in an efficient fume hood.

Introduction.

A number of boron trifluoride-type reagents have been used for the cleavage of ethers and related compounds, and a review of the earlier work on ether cleavage exists.[3] Carbon-oxygen bond cleavage using boron trifluoride combined with a sulfide or a thiol is based on the principle that a hard acid will interact with the oxygen and that the sulfur, being a soft nucleophile, will attack carbon. Small variations in the balance between the electrophilic and nucleophilic components can result in important changes in reactivity. Although the boron trifluoride-dimethyl sulfide complex is commercially available, the majority of the work reported has used ***Boron Trifluoride Etherate*** in combination with ***Dimethyl Sulfide***.[2c] A number of related reagent systems are compared in this entry. It will be seen that, although boron trifluoride together with a thiol can cause ether cleavage, there are certain functionalities, notably the carbonyl group in aldehydes and ketones and the alkene residue in α,β-unsaturated esters, that are themselves reactive to the system. The reagent system ***Aluminum Chloride-Ethanethiol*** (or dialkyl sulfide) is much more reactive than the boron-based systems and is thereby less selective.[4] For example, aluminum chloride in the presence of ethanethiol demethylates methyl ethers and cleaves methylenedioxy derivatives,[4b] but it also dehalogenates *o*- and *p*-bromoanisole in addition to cleaving the ether.[4e] Ethyl 4-bromobenzoate gives the acid in 92.5% yield using aluminum chloride-

dimethyl sulfide.[4d] On the other hand, the system which uses aluminum chloride and ***Sodium Iodide*** in acetonitrile has been used to demethylate aliphatic methyl ethers selectively in the presence of phenolic methyl ethers.[5] The use of aluminum chloride in the presence of *N*,*N*-dimethylaniline has been recommended recently as a reagent for the cleavage of benzyl and allyl ethers.[6] The regioselective debenzylation of poly-*O*-benzylated monosaccharides has been achieved using ***Tin(IV) Chloride*** and ***Titanium(IV) Chloride***. Three appropriately located metal chelating groups are necessary for selective debenzylation to proceed.[7] Recent general reviews on the cleavage of ethers[8] and on the chemical deprotection of esters[9] have been published.

Dealkylation of Ethers.

The combination of an aliphatic thiol such as ethanethiol and boron trifluoride etherate has been used to remove benzyl groups. However, although that method works well it does suffer from an incompatibility with certain functional groups.[2c] The presence of an α,β-unsaturated ester in the same molecule can result in Michael addition as well as debenzylation (eq 1).[10] Boron trifluoride in the presence of dimethyl sulfide, being a milder reagent, does not cause this type of complication, as shown in eq 2.[11]

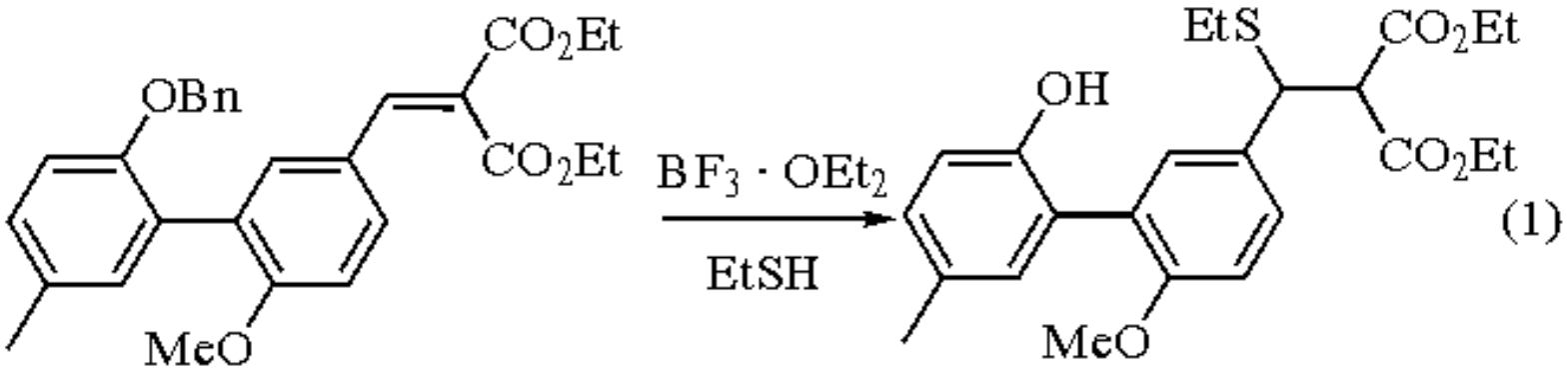

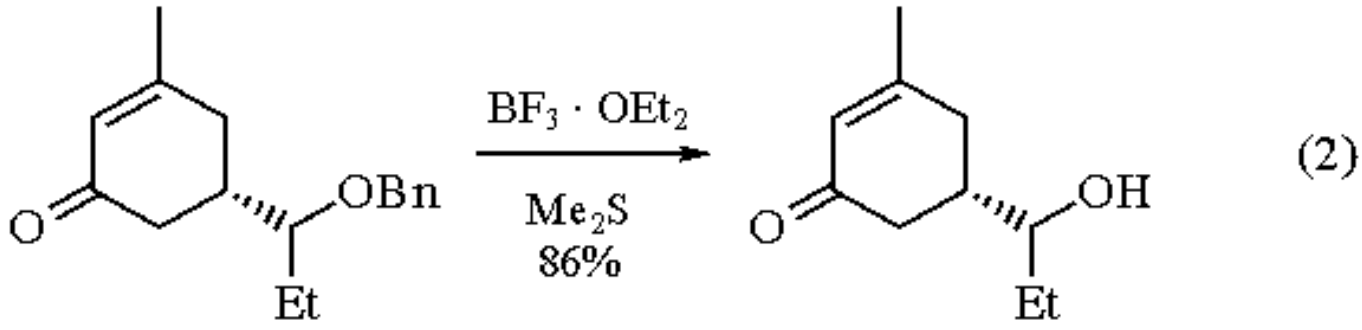

It is clear that boron trifluoride in the presence of a thiol will convert an aldehyde or ketone into the related thioacetal. For example, 4-benzyloxyacetophenone is converted into the ethyl thioacetal of 4-hydroxyacetophenone in 84% yield by $BF_3.OEt_2$-EtSH, whereas using $BF_3.OEt_2$-Me_2S gives 4-hydroxyacetophenone in 97% yield.[2c] The conversion of an acetal to a dithioacetal has also been reported using, for example 1,3-propanedithiol in the presence of BF_3; also known is the conversion of a dithiane into the related acyclic dithioacetal by using an excess of ***Methanethiol*** and BF_3.[12] It has also been found that the double bond in substituted styrenes is cleaved by boron trifluoride etherate-ethanethiol when an electron-withdrawing group is present at the β-position (eq 3).[13] It is of interest to note that, although the system using a thiol does not result in benzyl ester cleavage, the removal of an acetyl group from a highly functionalized pyrrole has been reported (eq 4).[14]

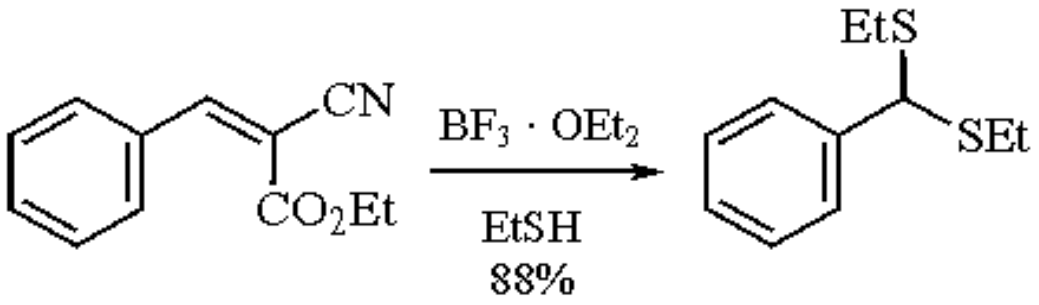

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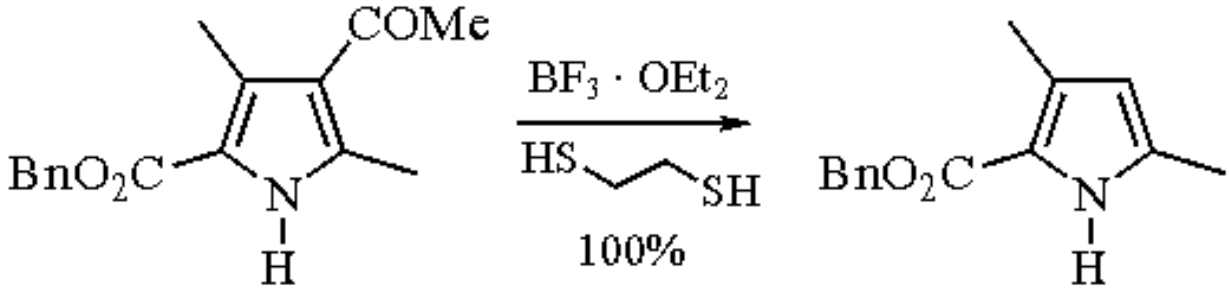

(4)

In a series of papers on the synthesis of benzopyrone derivatives, benzyl protection-deprotection of phenolic hydroxy groups has been a standard protocol.[15] It should be noted that in this series the yields of the debenzylated products are poor unless the boron difluoride complex is preformed. The example (eq 5) shown is part of a fulvic acid synthesis.[15c]

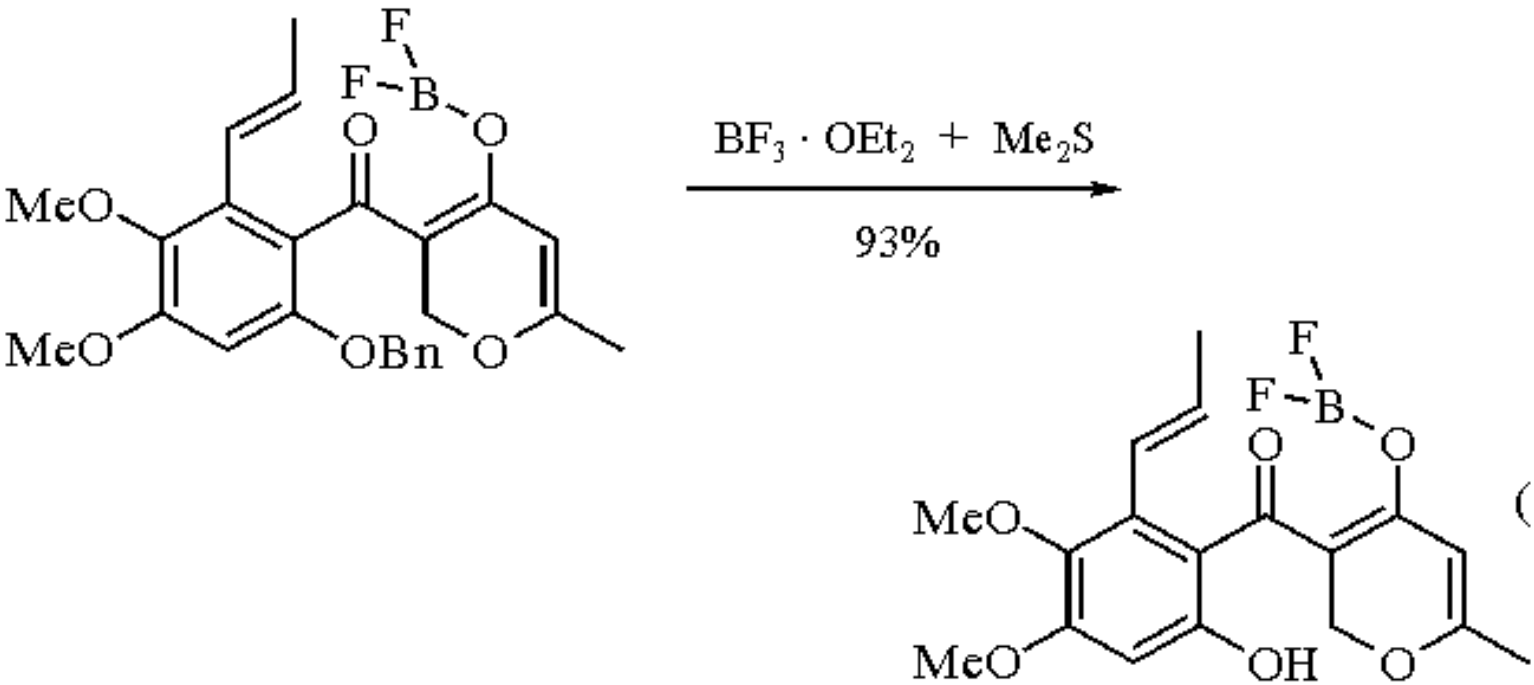

(5)

In the example shown in eq 6, the benzylic ether is part of a ring.[16] A number of other examples are recorded,[17] including cases where complex functionality and stereochemistry are unaffected by the procedure, as illustrated in eq 7.[18]

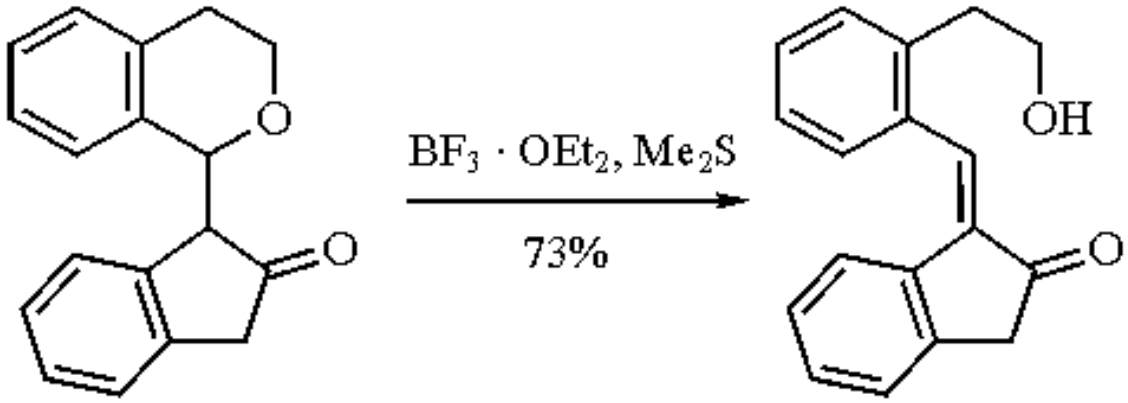

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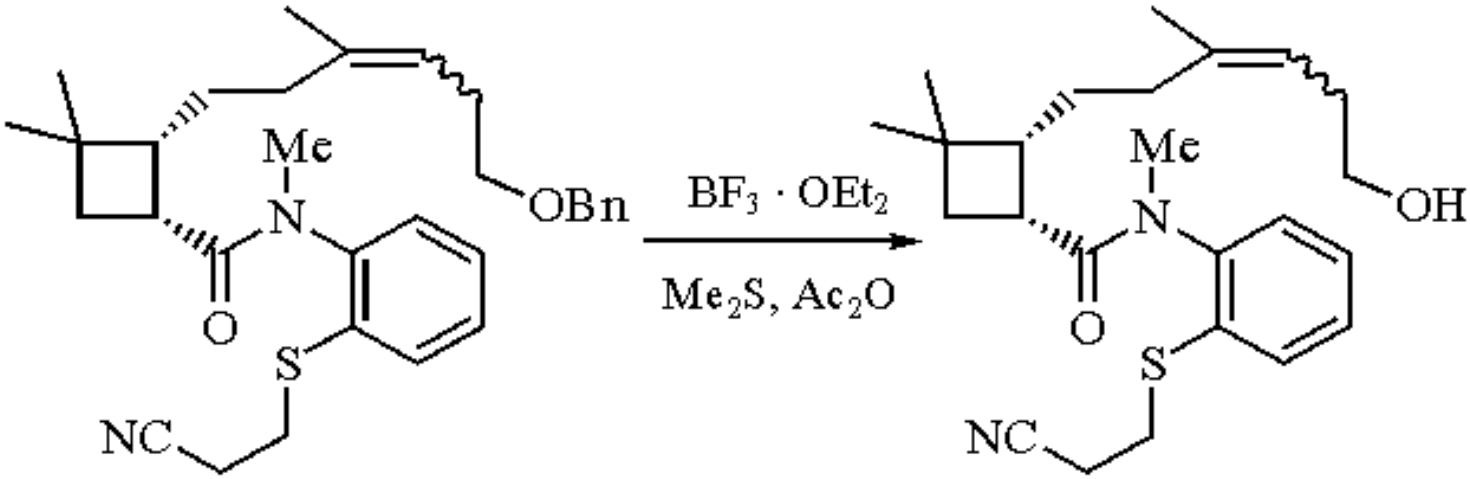

(7)

The method has also been used successfully to remove the methoxymethyl (MOM) group (eqs 8 and 9),[19,20] and should be compared once again with the use of boron trifluoride etherate-ethanedithiol (eq 10), which was used in a total synthesis of bruceantin.[21]

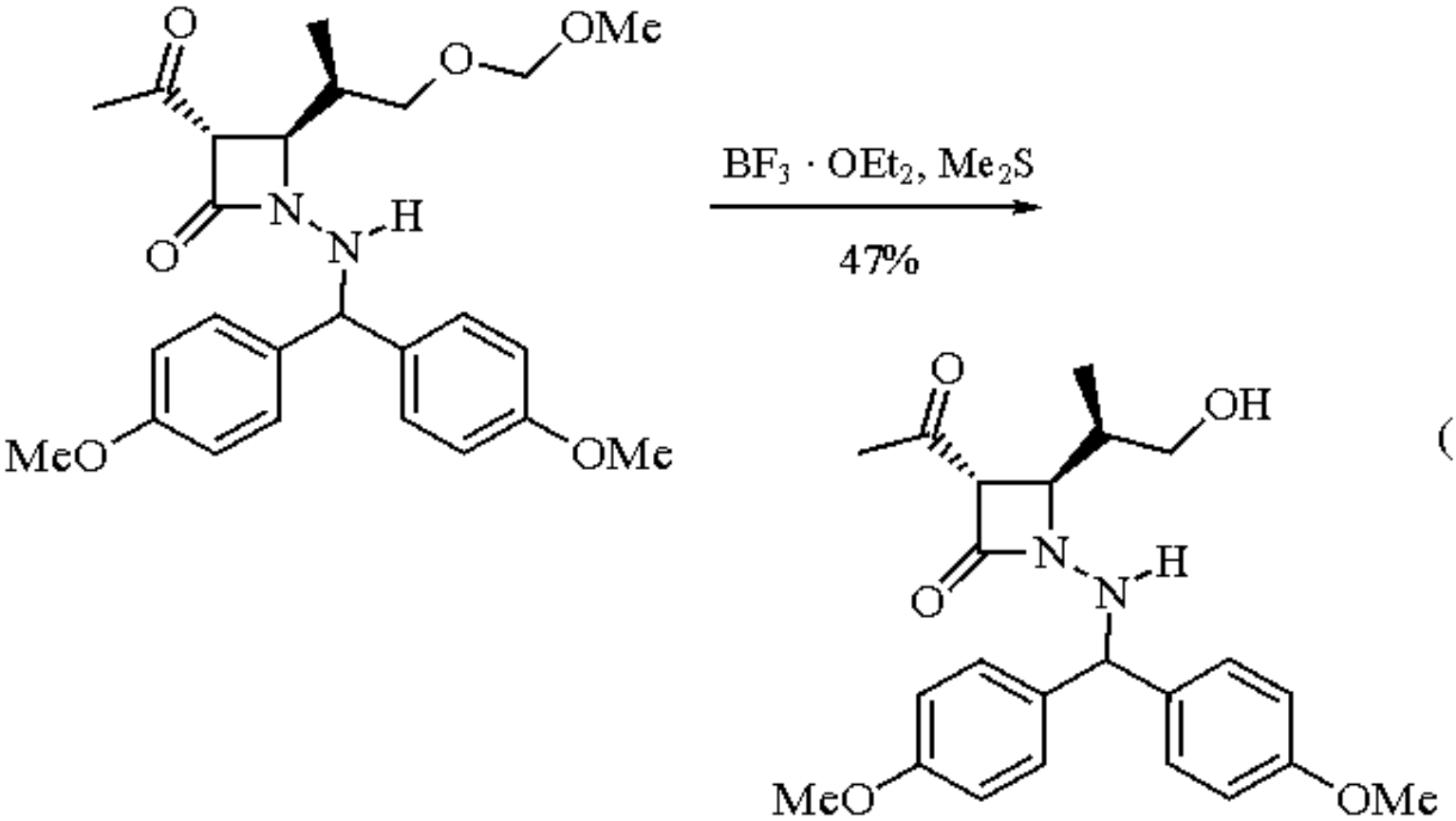
O
OMe
O
N
H
N
O
MeO
OMe
BF3 · OEt2, Me2S
47%
O
OH
N
H
N
O
MeO
OMe

(8)

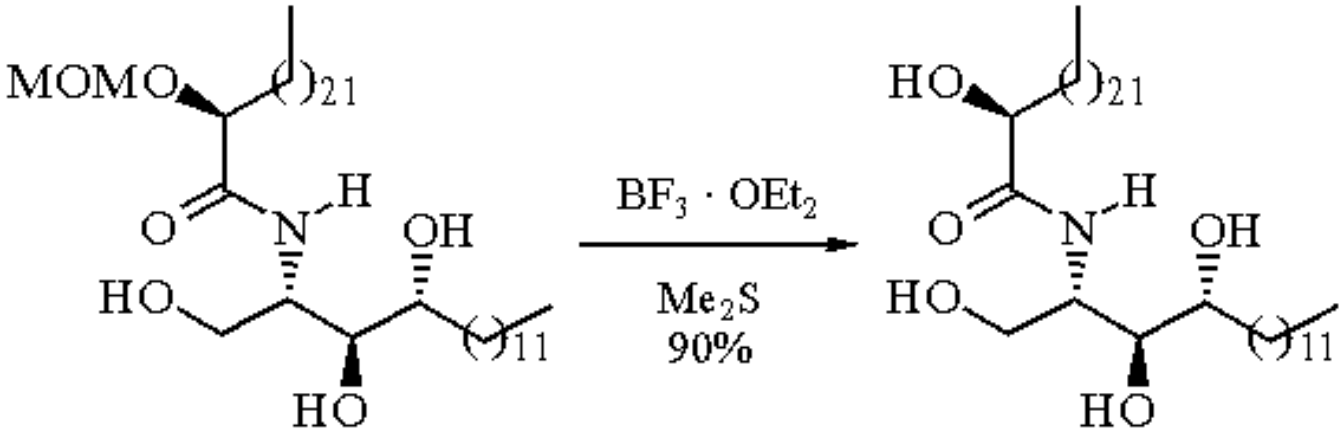
MOMO
21
O
N
H
OH
HO
11
HO
BF3 · OEt2
Me2S
90%
HO
21
O
N
H
OH
HO
11
HO

(9)

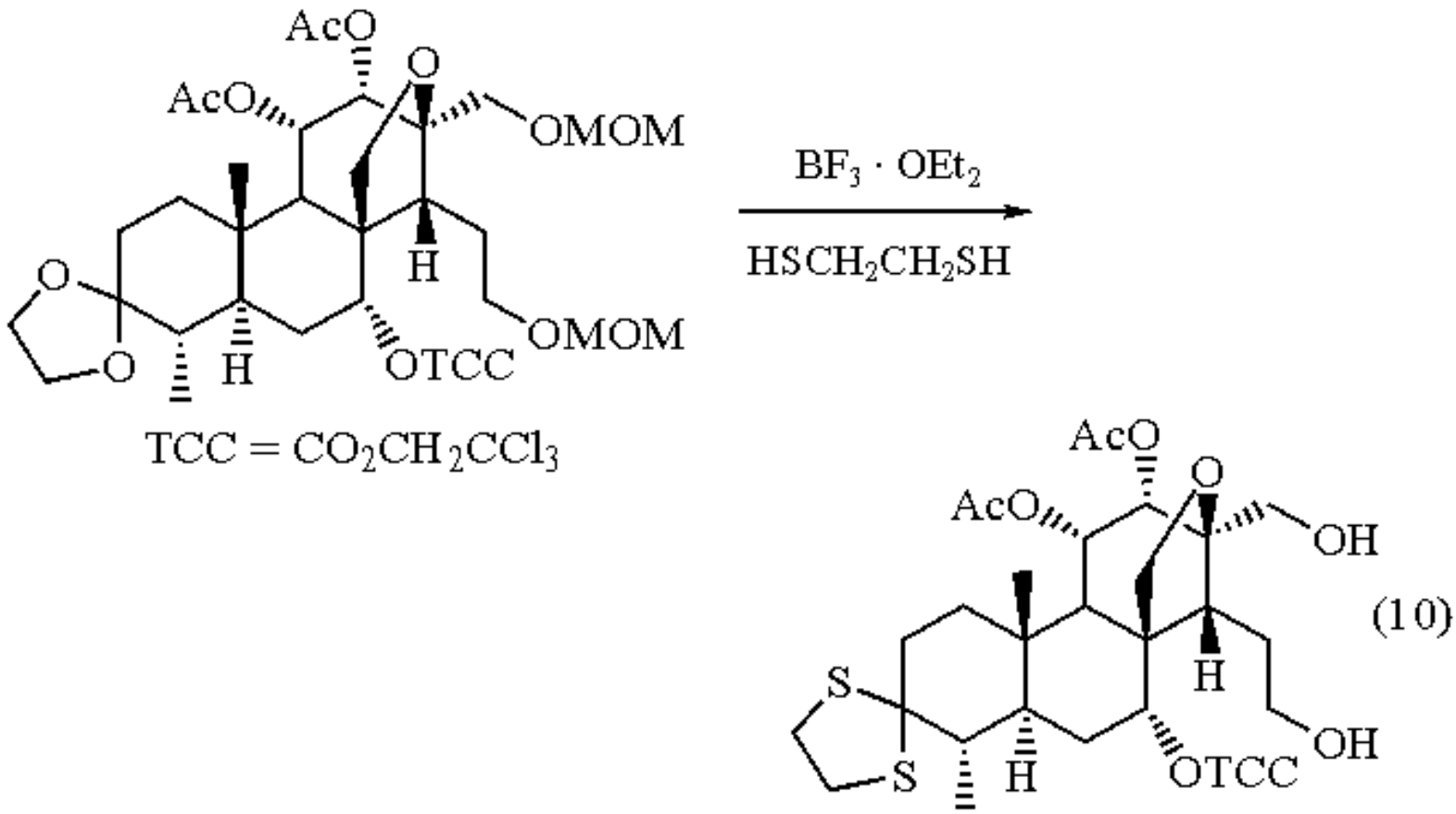

Cleavage of Benzyl Carbamates.

The removal of the benzyloxycarbonyl (Cbz) group from nitrogen can be achieved successfully using boron trifluoride etherate in the presence of either a thiol or dimethyl sulfide. The carbamates derived from secondary amines are cleaved more rapidly than those from primary amines using the ethanethiol method, even when using $BF_3.OEt_2$ as the solvent. The procedure allows reasonable selectivity, as shown in eq 11.[10]

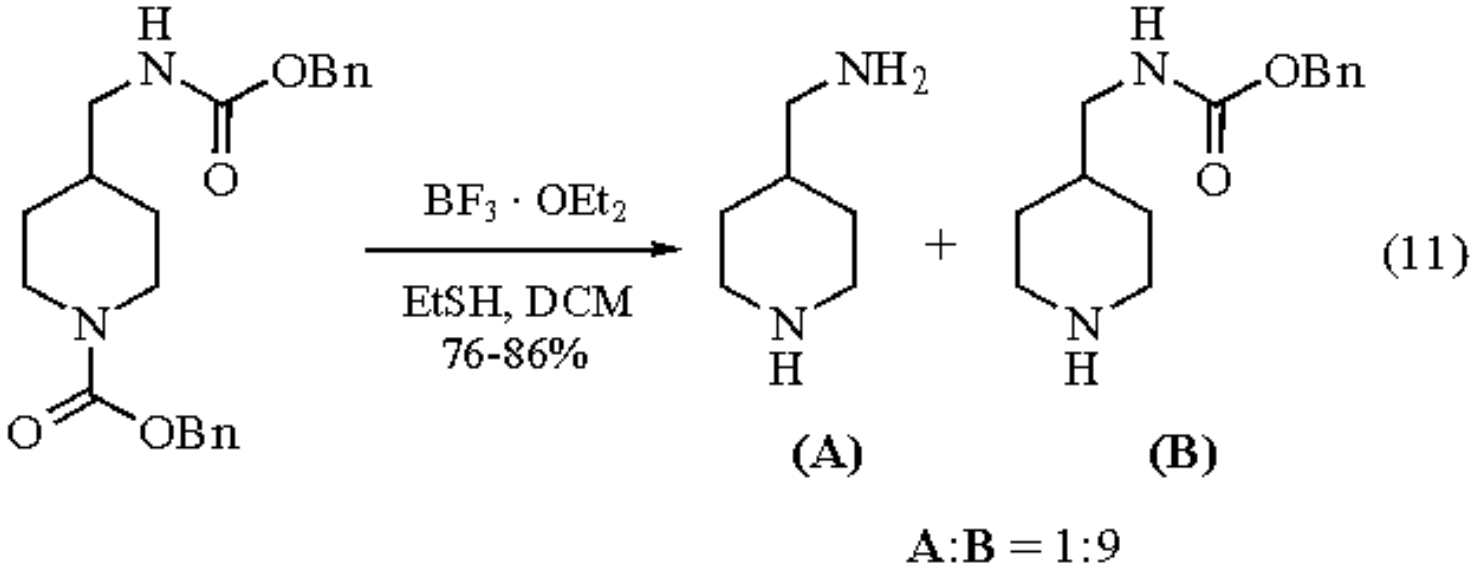

In another interesting example, the removal of the Cbz protecting group and concomitant intramolecular 1,4-addition of

the resulting amine to the spiroenone gave racemic dihydrooxocrinine in a single operation (eq 12).[22]

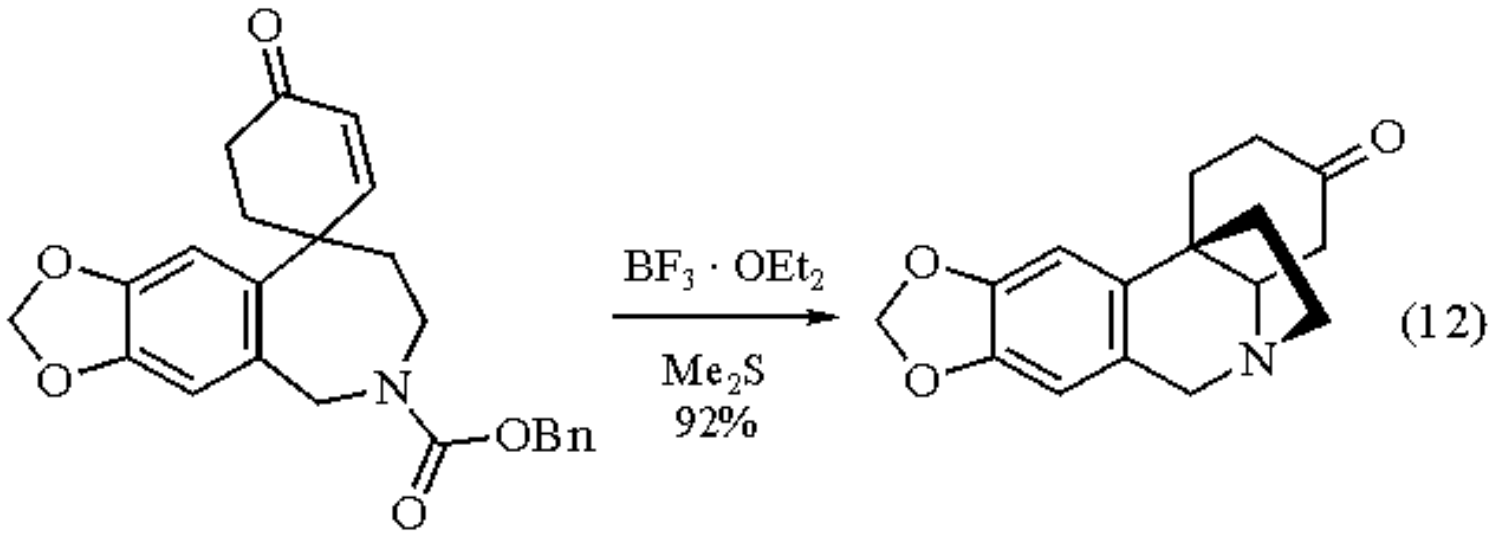

Related Reagents.

Boron Trifluoride-Acetic Acid; ***Boron Trifluoride-Acetic Anhydride***; ***Boron Trifluoride Etherate***; ***Boron Trifluoride***; ***Dimethyl Sulfide***; ***Tetrafluoroboric Acid***.

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Boron Trifluoride-Acetic Anhydride[1]

$BF_3.Ac_2O$

(BF_3)

[7637-07-2] · BF_3 · Boron Trifluoride-Acetic Anhydride · (MW 67.81) (Ac_2O)

[108-24-7] · $C_4H_6O_3$ · Boron Trifluoride-Acetic Anhydride · (MW 102.09)

(a mild Lewis acid catalyst, mainly used for the acylation of enolizable ketones and aromatic compounds)

Physical Data: see ***Acetic Anhydride*** and ***Boron Trifluoride***.

Solubility: BF_3 gas: very sol H_2O to form two hydrates; with a large excess of H_2O it slowly reacts to form fluoroboric acid; sol most organic solvents and forms well-defined complexes with ethers, alcohols, amines, and phosphines.

Form Supplied in: prepared in situ.

Preparative Methods: BF_3 gas: prepared by heating boron trioxide with calcium fluoride, ammonium fluoroborate, or potassium fluoroborate with conc sulfuric acid.[2]

Handling, Storage, and Precautions: all forms of BF_3 are extremely corrosive to eyes and skin. All work must be carried out in an efficient fume hood.

Acylation Reactions of Ketones.

A major use of the reagent system has been concerned with the conversion of enolizable ketones into 1,3-diketones. The reactions are carried out by treating a mixture of the carboxylic anhydride and ketone with a Lewis acid catalyst system based on ***Boron Trifluoride***.[2] The main catalyst systems used involve: (i) saturation of the reaction mixture with gaseous boron trifluoride, (ii) the use of either the solid (1:1) or liquid (1:2) complexes formed between boron trifluoride and acetic acid (see ***Boron Trifluoride-Acetic Acid***) to which sometimes is added a protic acid such as ***p-Toluenesulfonic Acid***, and (iii) the use of ***Boron Trifluoride Etherate***. Where different isomeric products are possible, the reactions carried out under different conditions sometimes lead to different products or product ratios. For example, in the reaction of 3-methylbutanone with acetic anhydride under different reaction conditions, the two possible products are formed in the proportions shown in eq 1.[3] Reaction conditions that use boron trifluoride diethyl etherate as the catalyst are less strong than the others and it is then not unusual for reaction not to occur at an α-carbon that carries two alkyl substituents.

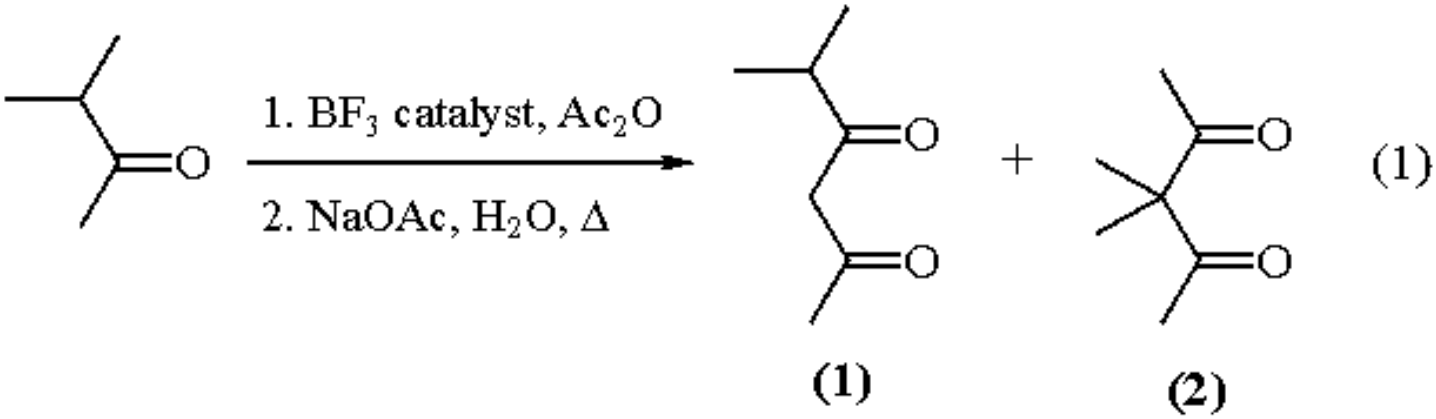

Reaction conditions	(1):(2)
BF_3 gas, rapid saturation, 0-10 °C	7.0:3.0
BF_3 gas, slow saturation, 0-10 °C	3.7:6.3
$BF_3 \cdot (AcOH)_2$, 25 °C	0.2:9.8
$BF_3 \cdot (AcOH)_2$, TsOH, 25 °C	0.0:10.0

The rapid saturation of the reaction mixture with boron trifluoride leads to the formation of the product derived from the kinetic enol, whereas in the presence of a protic acid the product formed from the thermodynamic enol may be the exclusive product. It is assumed that in the first case the nucleophile is the boron complex of the enol, while in the latter case an enol ester is involved (eq 2). In both sequences the final product is the boron difluoride complex (**3**) and in a number of examples such a complex has been isolated.[4] This explains why, in most of the reactions, 100 mol % of catalyst is required. The formation of the diketone (**2**) (eq 1) shows, however, that it is not a requirement that a complex of type (**3**) is formed. In many of the examples reported the boron difluoride complex was not observed because the hydrolytic sequences that were used gave the 1,3-diketone directly. Checked procedures have been published.[5] They include the preparation of pentane-2,4-dione in which the isolation of the product was facilitated by formation of the copper(II) complex.[5a] Reactions of cyclohexanone with a variety of anhydrides[6] include the reaction with 3-nitropropanoic anhydride[6b] and, in the case of homoveratric anhydride, reaction resulted in the formation of an octahydrophenanthrene derivative.[6c] Recent reports include the preparation of 1,3-diketones for use in an alkene synthesis involving the elimination of nitro and keto groups.[7] The acylation of benzyl methyl ketone[8] and pinacolone[9] proceed in good yield as expected. In the latter case the diketone was required in a tripyrrin-α-carboxylic acid synthesis.[10] The acetylation of aromatic ketones sometimes results, eventually, in the formation of heterocyclic derivatives. For example, the acetylation of acetophenone under forcing conditions can lead to the formation of 2,4-diphenyl-6-methylpyrylium fluoroborate,[11] and 4-(2-hydroxyphenyl)butane-2,4-dione was converted into 3-acetyl-2-methylchromone.[12]

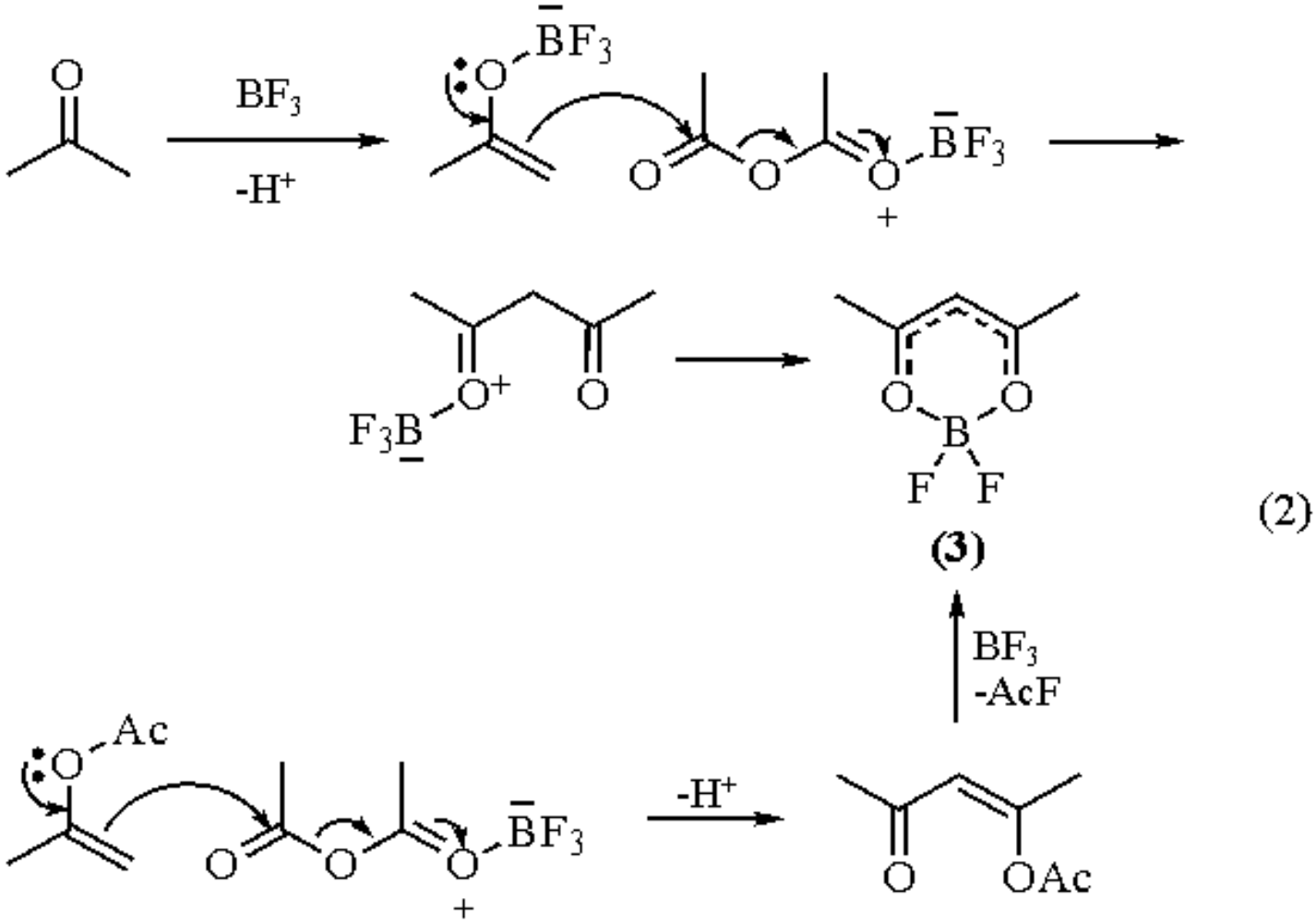

(2)

In accord with the suggested mechanisms, the expected enol acetate was isolated in low yield in an acetylation of butanone. On the other hand, it was not possible to form the enol acetate from acetophenone, and so it was concluded that a boron difluoride enol complex was involved.[2] The treatment of cyclohexanone with acetic anhydride and 14 mol % of boron trifluoride gave 1-acetoxycyclohexene in 22% yield, which was converted into 2-acetylcyclohexanone in 76% yield (eq 3).[2] Enol acetates have also been shown to afford boron difluoride complexes and acetyl fluoride on treatment with acetic anhydride and boron trifluoride.[13] Similarly, in a reaction of boron trifluoride with the enol benzoate derived from dibenzoylmethane, benzoyl fluoride was isolated along with the boron difluoride complex (eq 4).[13] Other enol acetates and enol benzoates have been converted into β-diketones by saturating the enol esters with boron trifluoride.[14] Boron difluoride complexes have also been isolated in reactions of chroman-4-one and its thia analog.[15]

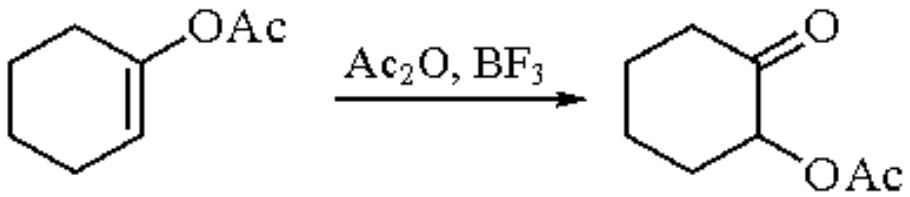

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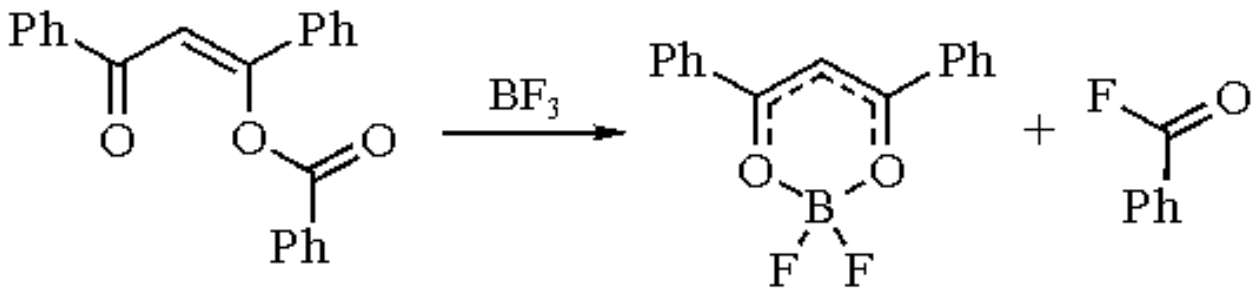

(4)

A further improvement to the experimental method was achieved by the rapid addition of the ketone-anhydride mixture to a solid boron trifluoride-acetic acid complex. In this way the acetylation of cyclohexanone was improved to afford an 86% yield of 2-acetylcyclohexanone.[16] The inverse addition method also gave an excellent yield of 2-butanoylcyclopentanone (eq 5).[16] The method has been used for the acylation of a wide range of cyclic ketones, including five- to eight-membered ring ketones,[17] including the example shown in eq 6.[17a] The acetylation of 3-methylcyclopentane-1,2,4-trione has also been reported.[18] The functionalization of 5,8-dimethoxy-1-tetralone (eq 7) was used as part of a daunomycinone aglycon synthesis.[19]

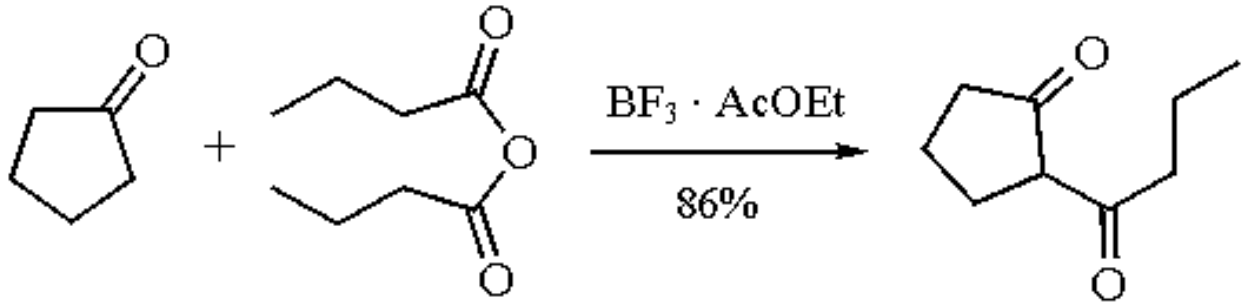

(5)

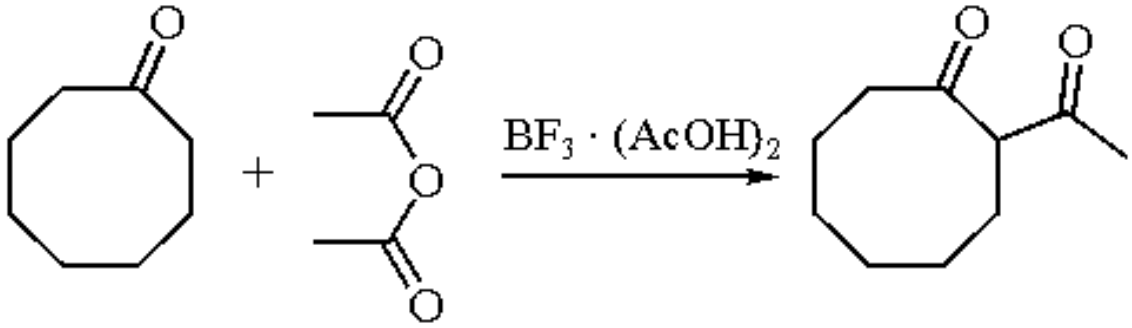

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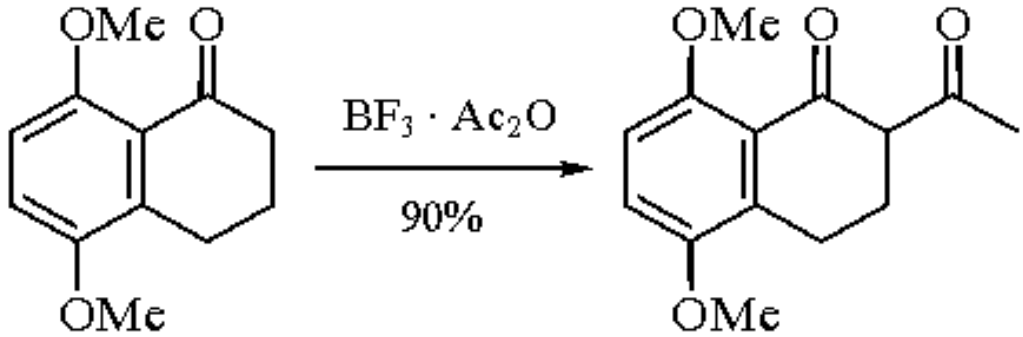

(7)

1,3-Diketones are important intermediates in the synthesis of substituted pyrroles and, as a result, improvements to the original procedures have been reported. Another recent improvement was established in the preparation of precursors required for octaalkylporphyrin synthesis. The classical work-up procedure involving steam distillation was replaced by

the hydrolysis of the boron fluoride complex with methanolic sodium hydroxide solution.[20] For example, boron trifluoride gas was bubbled through a mixture of pentan-2-one and propanoic anhydride and the complex was isolated in 89% yield; hydrolysis then gave the diketone in 80% yield (eq 8). The advantage of the acetylation procedure for the preparation of 3-methylpentane-2,4-dione from butanone, as compared with the alkylation of acetylacetone, has been noted as one of the steps in a study of the pentapyrrolic sapphyrins. The methylation of pentane-2,4-dione was found to lead to an impure product, whereas there were no detectable impurities in the acetylation of butanone.[21] A reaction of benzenesulfonylacetone with acetic anhydride and the boron trifluoride acetic acid 1:1 complex led to acetylation at the terminal methyl group in 85% yield.[22] The electron-withdrawing effect of the benzenesulfonyl group apparently does not favor enolization towards the methylene group. The self-condensation of anhydrides has been reported under mild conditions,[23] while under more forcing conditions diketones are formed.[24] Enolizable aldehydes are not *C*-acylated by an anhydride in the presence of a boron trifluoride reagent, but good yields of the *O*,*O*-diacylated products are obtained.[25]

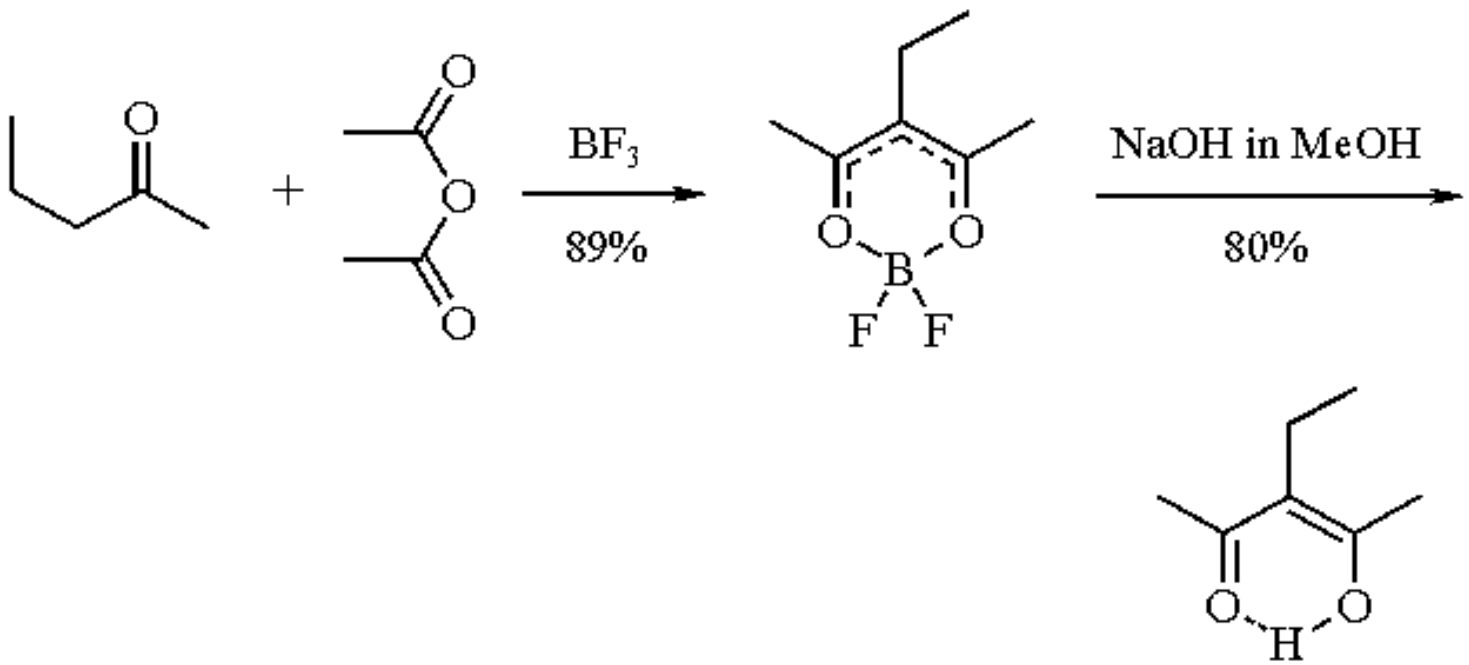

(8)

Reactions of steroidal ketone acetals, for example the ethylene acetals derived from cholestanone and androstan-17β-ol, give the related 2-acetyl enol ethers in good yield.[26] In rigid systems, such as those found in steroids, the direction of the kinetically favored enolization of a ketone depends on the stereochemistry of the ring junction. With 3-keto steroids the 2,3-enol is formed more rapidly with a *trans*-5,6-ring junction, whereas the formation of the 3,4-enol is favored when the ring junction is *cis*. This effect is exemplified in eqs 9 and 10.[27] Cholestenone is converted into a dienol acetate by acetic anhydride in the presence of boron trifluoride diethyl etherate; further reaction leads to the formation of a mixture of diastereomeric diketones.[27,28]

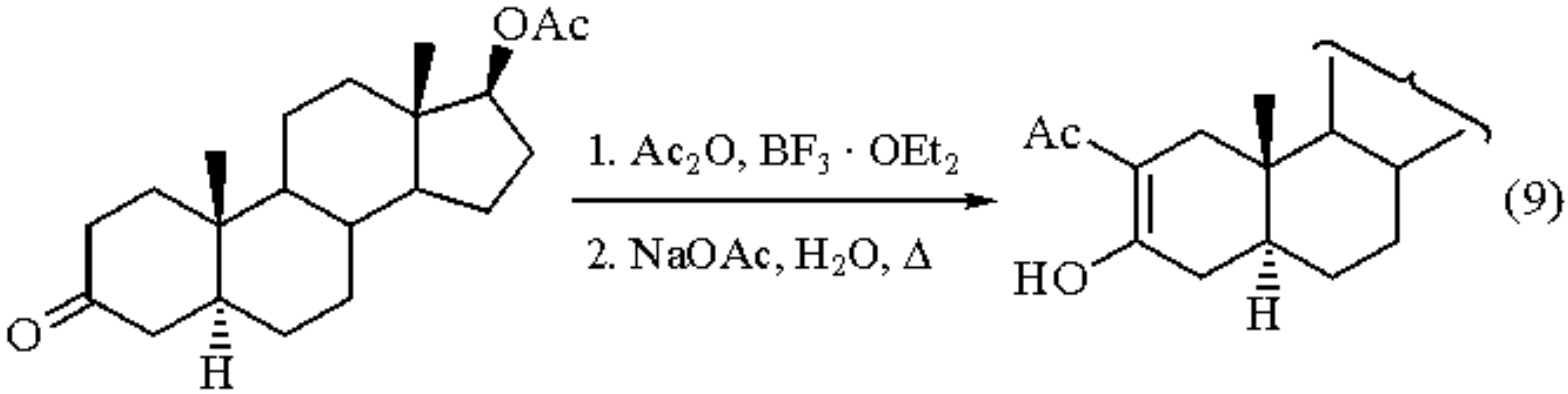

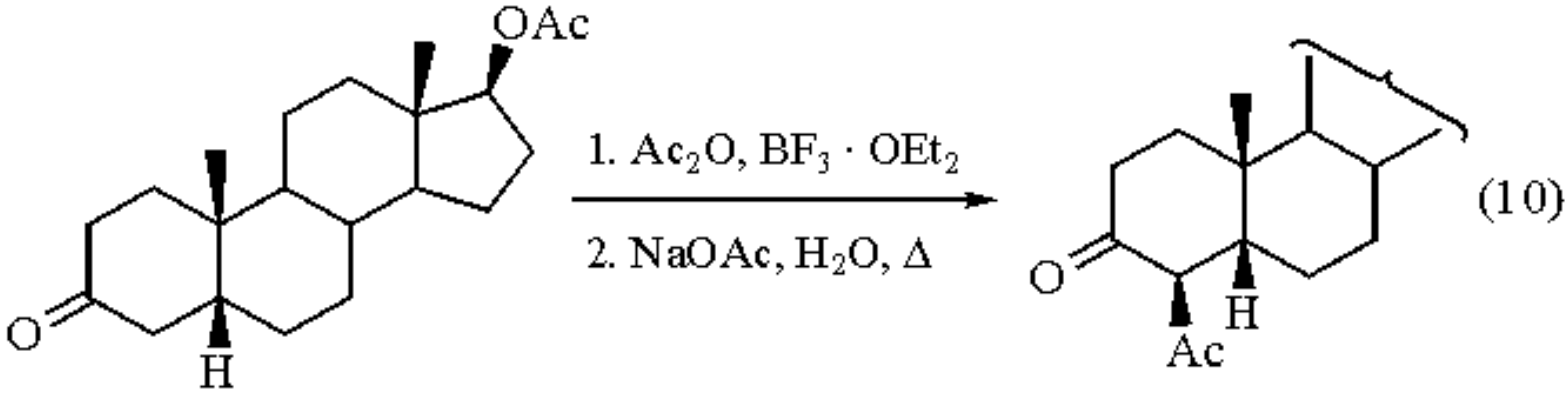

Acetylation of Nitriles and Amides.

The reaction between boron trifluoride and phenylacetonitrile in the presence of aqueous acetic acid had been shown to afford phenylacetamide in high yield.[29] This result led to an investigation of the reaction of phenylacetamide and phenylacetonitrile with acetic anhydride in the presence of the boron trifluoride-diacetic acid complex. Both reactions gave the same product after an aqueous workup as shown in eqs 11 and 12.[30] The suggested mechanism involves hydrolysis of phenylacetonitrile to phenylacetamide followed by *C*- and *N*-acylation. However, in view of the fact that *p*-tolunitrile and *p*-nitrobenzonitrile both afford the related benzamides on quenching the reaction mixtures with aqueous alkali, but not in the absence of an aqueous workup, it is suggested that the mechanisms probably involve an acylnitrilium species as shown in eq 13.

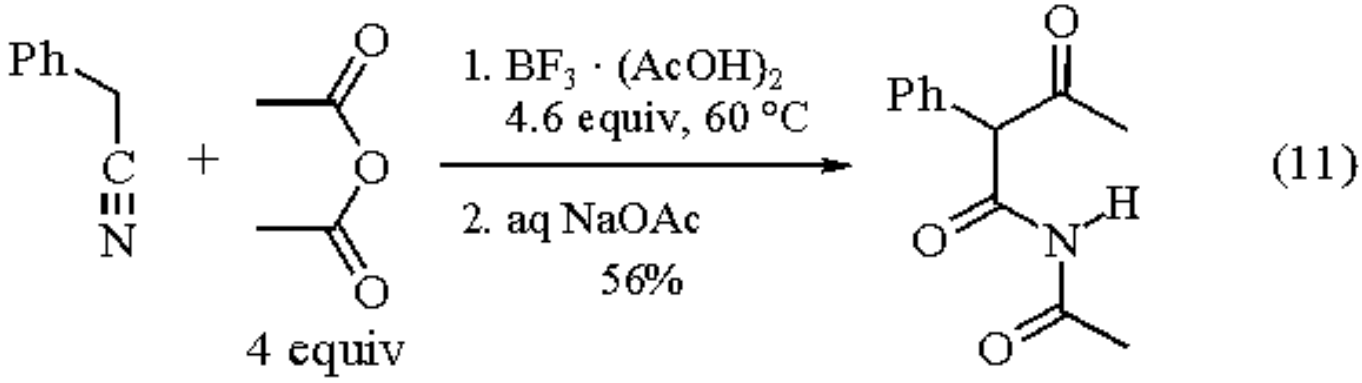

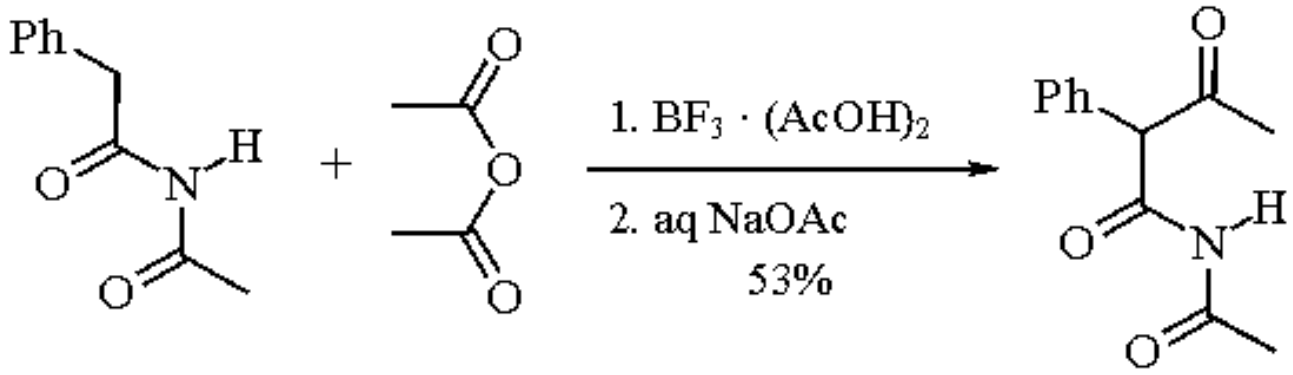

(12)

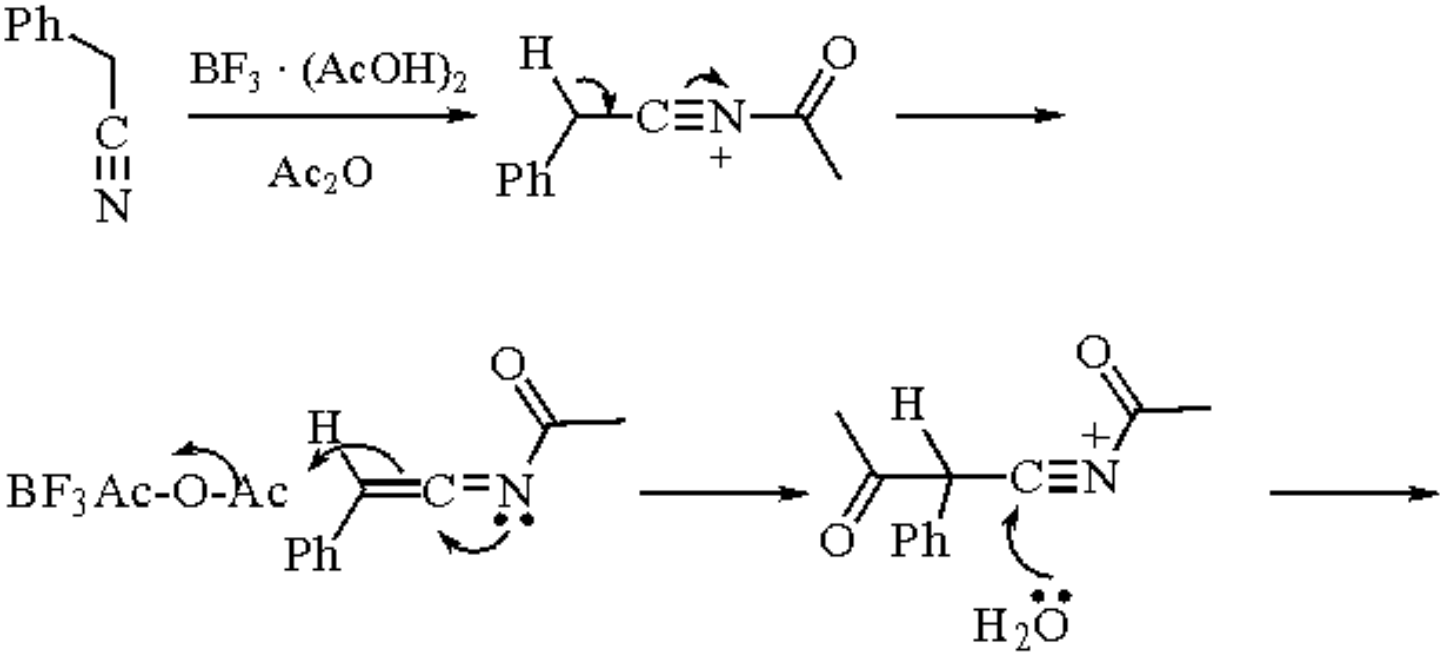

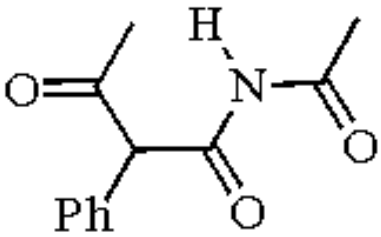

(13)

Friedel-Crafts Acylation Reactions.

Since a carboxylic anhydride and boron trifluoride constitute a mild Friedel-Crafts acylating system, it is not surprising that nucleophilic aromatic substrates such as toluene, mesitylene, and anisole have been acetoacetylated,[31a] as has fluorene[31b] and η^5-(acetylcyclopentadienyl)tricarbonylmanganese.[31c] The expected 1,3-diketones are formed when a sufficient excess of acetic anhydride is present in the reaction mixtures. The process is illustrated with anisole in eq 14.[31a] The acetylation of thiophene gives the so-called 2-triacetylthiophene,[32] but the product is in fact identical with the boron difluoride complex formed in the acetylation of 2-acetylthiophene.[33] Fries rearrangement reactions may be involved in some reactions of phenols; in the case of the acetylation of 4,8-dimethoxy-1-naphthol it was possible to isolate the initial *O*-acylated phenol in very high yield.[34] Reactions involving a wide variety of electron-rich heterocyclic compounds have been reported but, not surprisingly, low yields are sometimes obtained when electron-

withdrawing groups are present.[35] Normally the yields are good,[36] although it may be that destruction of labile heterocycles such as indole and pyrrole requires that great care is taken to avoid the presence of strong protic acids. Acetylation of 2-ethoxycarbonyl-5-hydroxybenzo[*b*]furan occurs in high yield at the 4-position.[37] The acylation of 1-benzenesulfonylpyrrole is of great interest because reaction occurs predominantly at the 2-position using boron trifluoride etherate as the Lewis acid (eq 15), while the regioselectivity is reversed using ***Aluminum Chloride***.[38]

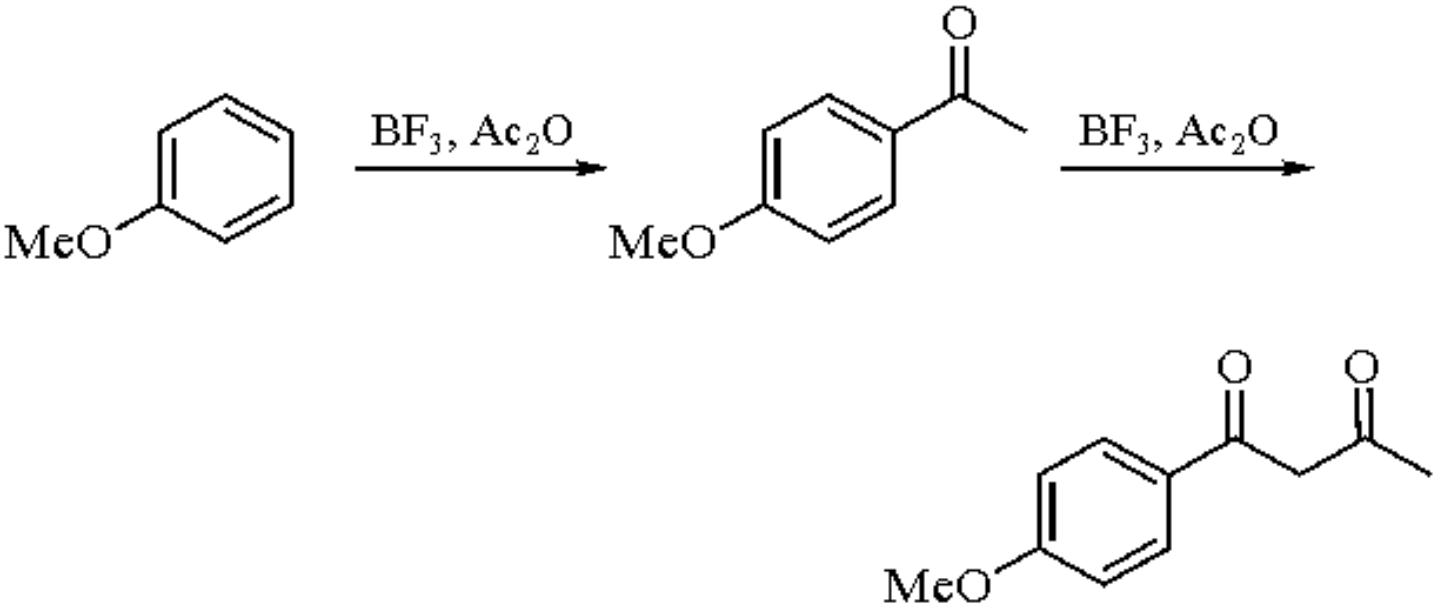

(14)

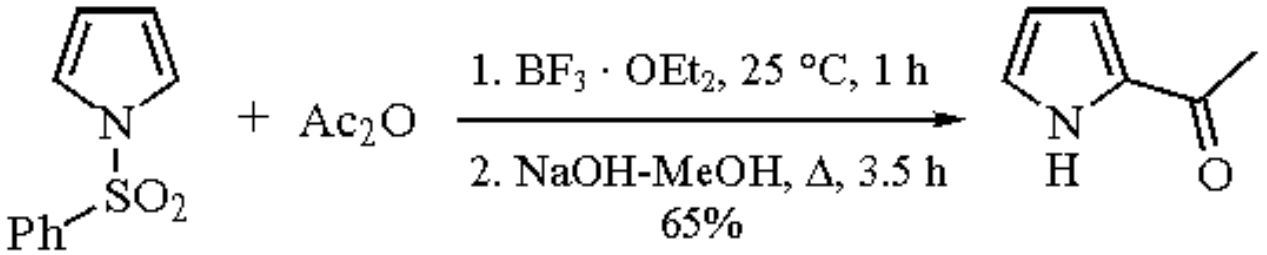

(15)

The acylation of a number of heterocyclic arylacetic acid derivatives has been used to great advantage in benzannulation reactions that proceed by way of α-pyrone derivatives.[39] The protocol is exemplified in eq 16[39e] and has also been used in a synthesis of the staurosporine aglycon.[39f]

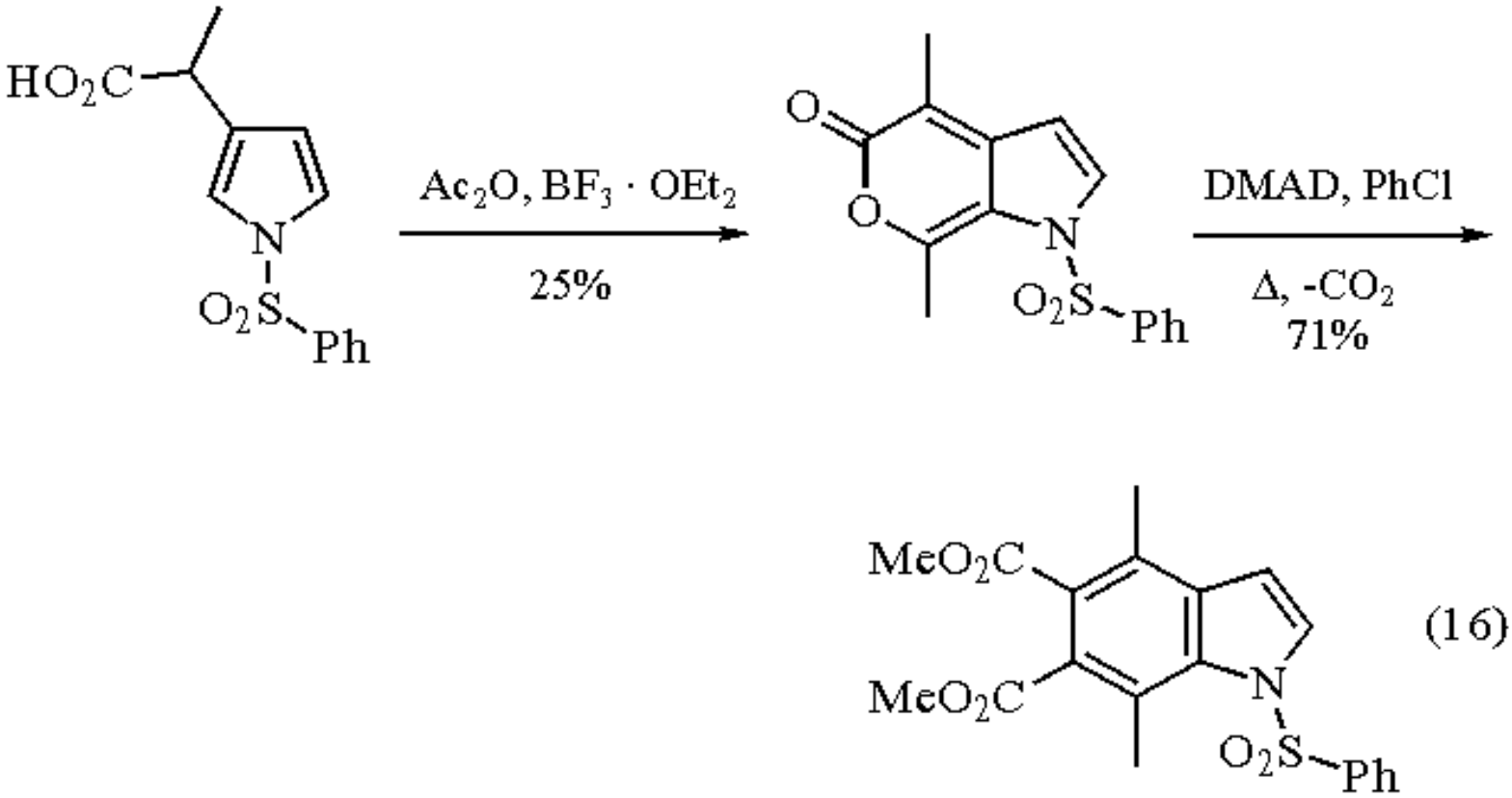

(16)

Alkylation and Acetoxylation Reactions.

The Pomeranz-Fritsch isoquinoline synthesis, where an acetal is cyclized to afford an isoquinoline after the loss of an alcohol, can be carried out using the boron trifluoride-diacetic acid complex in the presence of trifluoroacetic anhydride.[40] In many cases the conversion of quinones into acetoxyhydroquinone acetates is best achieved using boron trifluoride etherate together with acetic anhydride.[41a] Thus 1,4-naphthoquinone is converted into 1,2,4-triacetoxynaphthalene in 81% yield by this method,[41b] and although 2,5-dimethyl-1,4-benzoquinone reacts similarly, the related 2,6-dimethyl-1,4-benzoquinone apparently does not.[41c]

Cleavage and Rearrangement Reactions.

A large number of rearrangement reactions are initiated by boron trifluoride complexes in the presence of acetic anhydride, including the synthesis of functionalized and optically active pyrans from (+)-(*R*,*R*)-diethyl tartrate as indicated in eq 17.[42] The reaction of 1,4,5,5-tetramethylcyclopentene with paraformaldehyde and acetic anhydride in the presence of boron trifluoride etherate has been used in an approach to necrodane-type monoterpenes.[43] Other examples include the conversion of bicyclic into monocyclic[44] and tricyclic into bicyclic systems,[45] the acetolysis of glycosides resulting in the formation of the fully acetylated acyclic derivative,[46] the unusual migration of nitrogen in the dienone-phenol rearrangement of an *N*-methoxy-β-lactam,[47] and the cleavage of the tetrahydrofuran ring in compound (**4**) which gave the diacetate (**5**) (eq 18) with inversion of configuration at C-20.[48] Among other interesting reactions are the synthesis of adamantanone derivatives (eq 19)[49] and a one step synthesis of the twistane system (eq 20).[50]

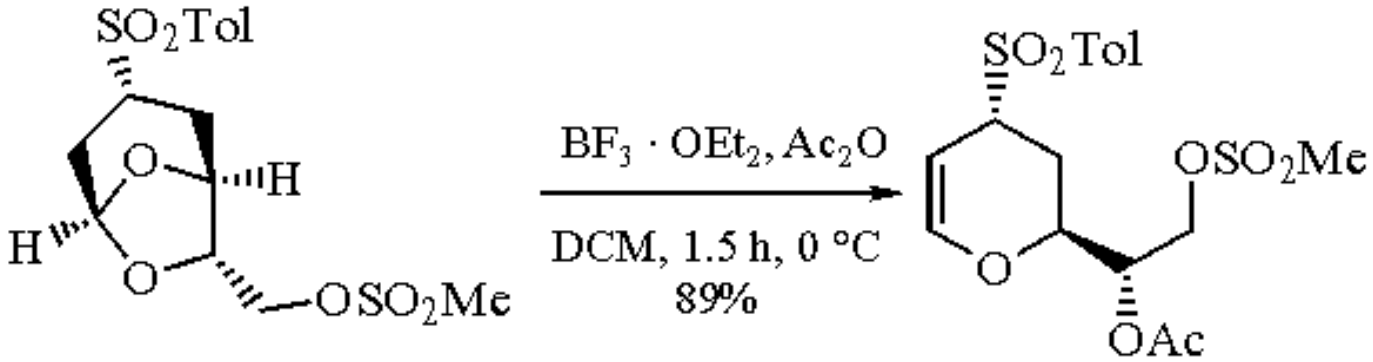

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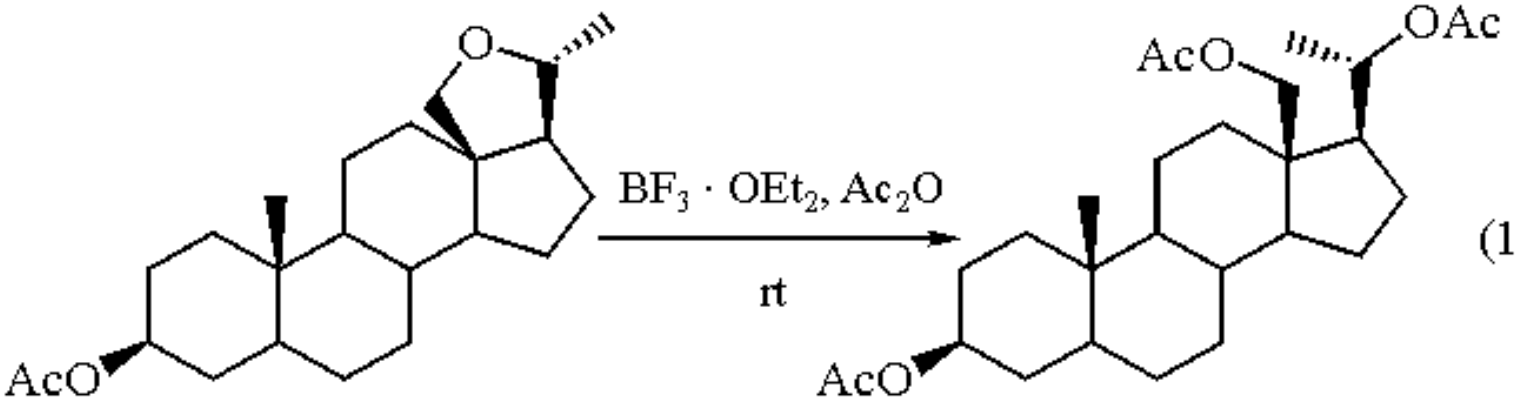

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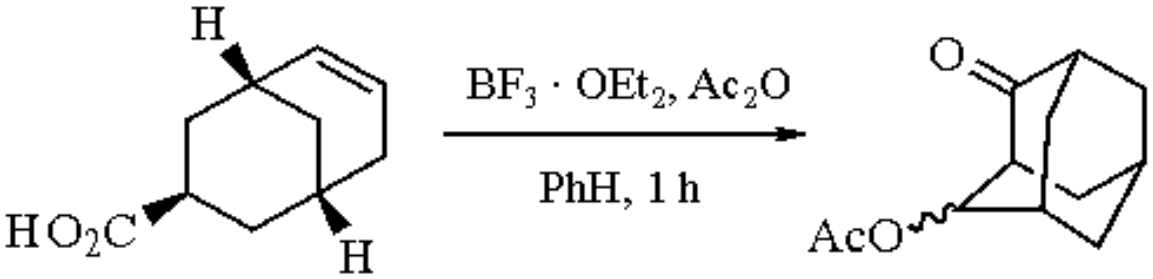

(19)

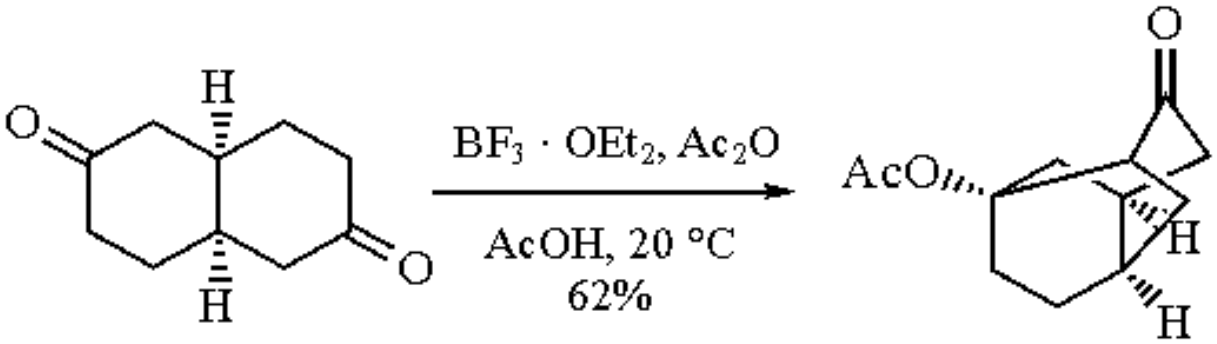

(20)

Protection and Deprotection Reactions.

There are a number of cases where the acetylation of hydroxy and amino groups is difficult to achieve and where the use of acetic anhydride in the presence of boron trifluoride etherate has been successful. Two representative examples are carbazole[51] and a hindered 17β-hydroxy steroid.[52] The demethylation-acetylation of methyl ethers has been carried

out using the same system but with the addition of ***Lithium Bromide***,[53] while a number of steroidal alcohols have been regenerated from their ethers in the absence of lithium bromide. Thus cholesterol methyl ether gave the corresponding acetate in 93% yield after 15 h at 0 °C, while the related 7β-methoxycholest-4-ene was more resistant to cleavage and gave the acetate after 50 h. The retention of configuration indicates homoallylic participation and, in accord with that suggestion, it was found that saturated steroidal methyl ethers gave mixtures of epimeric acetates and elimination products.[54] Acetic anhydride in the presence of catalytic boron trifluoride etherate in THF at low temperature has been reported more recently to give good chemoselectivity in the acetylation of the polyhydroxy tumor inhibitor oridonin. Among the wide range of additional examples, alcohols were shown to be acetylated in the presence of phenols.[55] The removal of the methoxymethyl group from indoles proved difficult. The involvement of the lone pair electrons in the aromatic system diminishes the hydrolytic lability of what would otherwise be an aminol ether; as a result, the reaction conditions that were found to be necessary restrict the substituent types that may be accommodated at other positions.[56] The deblocking of the anomeric position, protected as the 2-trimethylsilylethyl ether, has been achieved in high yields in examples drawn from mono-, di-, and trisaccharides.[57] The method is exemplified in eq 21. In the absence of acetic anhydride, the product with a free anomeric hydroxy group is obtained.

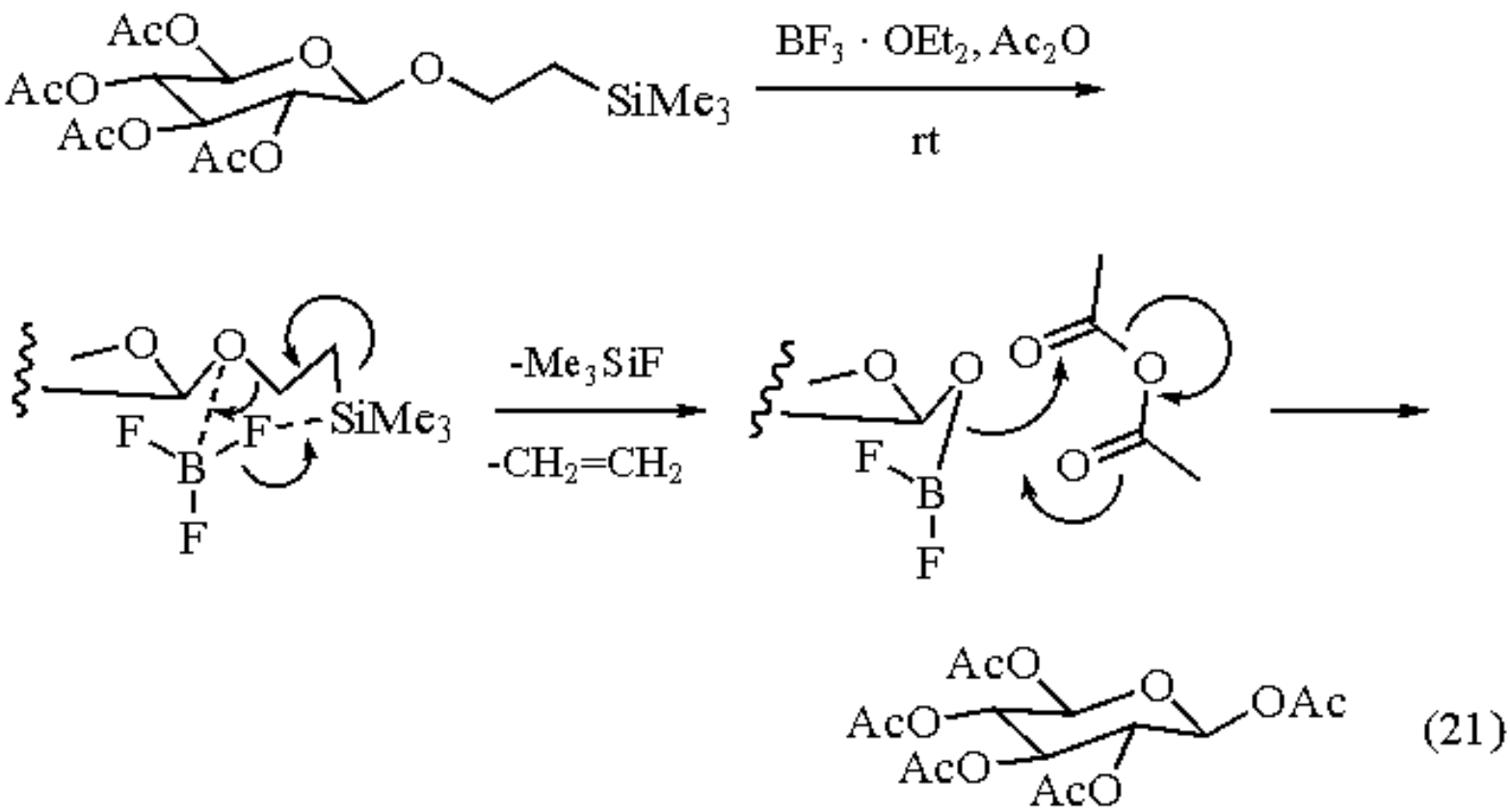

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Boron Trifluoride Etherate

$BF_3.OEt_2$

($BF_3.OEt_2$)

[109-63-7] · $C_4H_{10}BF_3O$ · Boron Trifluoride Etherate · (MW 141.94) (BF_3.MeOH)

[373-57-9] · CH_4BF_3O · Boron Trifluoride-Methanol · (MW 99.85)

($BF_3.OEt_2$: easy-to-handle and convenient source of BF_3; Lewis acid catalyst; promotes epoxide cleavage and rearrangement, control of stereoselectivity; BF_3.MeOH: esterification of aliphatic and aromatic acids; cleavage of trityl ethers)

Alternate Names: boron trifluoride diethyl etherate; boron trifluoride ethyl etherate; boron trifluoride ethyl ether complex; trifluoroboron diethyl etherate.

Physical Data: $BF_3.OEt_2$: bp 126 °C; *d* 1.15 g cm^{-3}; BF_3.MeOH: bp 59 °C/4 mmHg; *d* 1.203 g cm^{-3} for 50 wt % BF_3, 0.868 g cm^{-3} for 12 wt % BF_3.

Solubility: sol benzene, chloromethanes, dioxane, ether, methanol, THF, toluene.

Form Supplied in: $BF_3.OEt_2$: light yellow liquid, packaged under nitrogen or argon; BF_3.MeOH is available in solutions of 10-50% BF_3 in MeOH.

Preparative Methods: $BF_3.OEt_2$ is prepared by passing BF_3 through anhydrous ether;[1a] the BF_3.MeOH complex is formed from $BF_3.OET_2$ and methanol.

Purification: oxidation in air darkens commercial boron trifluoride etherate; therefore the reagent should be redistilled prior to use. An excess of the etherate in ether should be distilled in an all-glass apparatus with calcium hydroxide to remove volatile acids and to reduce bumping.[1b]

Handling, Storage, and Precautions: keep away from moisture and oxidants; avoid skin contact and work in a well-ventilated fume hood.

Addition Reactions.

$BF_3.OEt_2$ facilitates the addition of moderately basic nucleophiles like alkyl-, alkenyl-, and aryllithium, imines, Grignard reagents, and enolates to a variety of electrophiles.[2]

Organolithiums undergo addition reactions with 2-isoxazolines to afford *N*-unsubstituted isoxazolidines, and to the carbon-nitrogen double bond of oxime *O*-ethers to give *O*-alkylhydroxylamines.[3] Aliphatic esters react with lithium acetylides in the presence of $BF_3.OEt_2$ in THF at -78 °C to form alkynyl ketones in 40-80% yields.[4] Alkynylboranes, generated in situ from lithium acetylides and $BF_3.OEt_2$, were found to react with oxiranes[5] and oxetanes[6] under mild conditions to afford β-hydroxyalkynes and γ-alkoxyalkynes, respectively. (1-Alkenyl)dialkoxyboranes react stereoselectively with α,β-unsaturated ketones[7] and esters[8] in the presence of $BF_3.OEt_2$ to give γ,δ-unsaturated ketones and α-acyl-γ,δ-unsaturated esters, respectively.

The reaction of imines activated by $BF_3.OEt_2$ with 4-(phenylsulfonyl)butanoic acid dianion leads to 2-piperidones in high yields.[9] (Perfluoroalkyl)lithiums, generated in situ, add to imines in the presence of $BF_3.OEt_2$ to give perfluoroalkylated amines.[10] Enolate esters add to 3-thiazolines under mild conditions to form thiazolidines if these imines are first activated with $BF_3.OEt_2$.[11] The carbon-nitrogen double bond of imines can be alkylated with various organometallic reagents to produce amines.[12] A solution of benzalaniline in acetone treated with $BF_3.OEt_2$ results in the formation of β-phenyl-β-anilinoethyl methyl ketone.[13] Anilinobenzylphosphonates are synthesized in one pot using aniline, benzaldehyde, dialkyl phosphite, and $BF_3.OEt_2$;[14] the reagent accelerates imine generation and dialkyl phosphite addition. Similarly, $BF_3.OEt_2$ activates the nitrile group of cyanocuprates, thereby accelerating Michael reactions.[15]

The reagent activates iodobenzene for the allylation of aromatics, alcohols, and acids.[16] Allylstannanes are likewise activated for the allylation of *p*-benzoquinones, e.g. in the formation of coenzyme Q_n using polyprenylalkylstannane.[17]

Nucleophilic silanes undergo stereospecific addition to electrophilic glycols activated by Lewis acids. The glycosidation is highly stereoselective with respect to the glycosidic linkage in some cases using $BF_3.OEt_2$. Protected pyranosides undergo stereospecific *C*-glycosidation with C-1-oxygenated allylsilanes to form α-glycosides.[18,19] α-Methoxyglycine esters react with allylsilanes and silyl enol ethers in the presence of $BF_3.OEt_2$ to give racemic γ,δ-unsaturated α-amino acids and γ-oxo-α-amino acids, respectively.[20] β-Glucopyranosides are synthesized from an aglycon and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose.[21] Alcohols and silyl ethers also undergo stereoselective glycosylation with protected glycosyl fluorides to form β-glycosides.[22]

$BF_3.OEt_2$ reverses the usual *anti* selectivity observed in the reaction of crotyl organometallic compounds (based on Cu, Cd, Hg, Sn, Tl, Ti, Zr, and V, but not on Mg, Zn, or B) with aldehydes (eq 1a) and imines (eq 1b), so that homoallyl alcohols and homoallylamines are formed, respectively.[23-28] The products show mainly *syn* diastereoselectivity. $BF_3.OEt_2$ is the only Lewis acid which produces hydroxy- rather than halo-tetrahydropyrans from the reaction of allylstannanes with pyranosides.[29] The $BF_3.OEt_2$ mediated condensations of γ-oxygenated allylstannanes with aldehydes (eq 1c) and with activated imines (eq 1d) affords vicinal diol derivatives and 1,2-amino alcohols, respectively, with *syn* diastereoselectivity.[30,31] The activated imines are obtained from aromatic amines, aliphatic aldehydes, and α-ethoxycarbamates. The reaction of aldehydes with α-(alkoxy)-β-methylallylstannanes with aldehydes in the presence of $BF_3.OEt_2$ gives almost exclusively *syn*-(*E*)-isomers.[31]

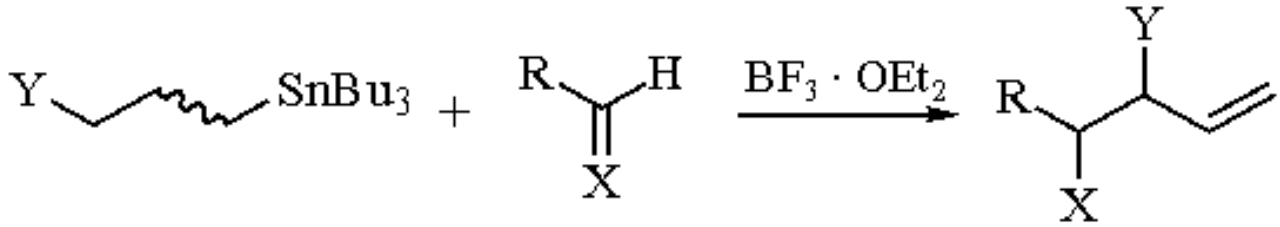

(1)

(a) X = O, Y = Me
(b) X = NR^2, Y = Me
(c) X = O, Y = OMe, OTBDMS
(d) X = NR^2, Y = OMe, OTBDMS or OCH_2OMe

(a) X = OH, Y = Me
(b) X = NHR^2, Y = Me
(c) X = OH, Y = OMe, OTBDMS
(d) X = NHR^2, Y = OH or derivative

The reaction of α-diketones with allyltrimethylstannane in the presence of $BF_3.OEt_2$ yields a mixture of homoallylic alcohols, with the less hindered carbonyl group being allylated predominantly.[32] The reaction between aldehydes and allylic silanes with an asymmetric ethereal functionality produces *syn*-homoallyl alcohols when ***Titanium(IV) Chloride*** is coordinated with the allylic silane and *anti* isomers with $BF_3.OEt_2$.[33]

Chiral oxetanes can be synthesized by the $BF_3.OEt_2$ catalyzed [2 + 2] cycloaddition reactions of 2,3-*O*-isopropylidenealdehyde-D-aldose derivatives with allylsilanes, vinyl ethers, or vinyl sulfides.[34] The regiospecificity and stereoselectivity is greater than in the photochemical reaction; *trans*-2-alkoxy- and *trans*-2-phenylthiooxetanes are the resulting products.

2-Alkylthioethyl acetates can be formed from vinyl acetates by the addition of thiols with $BF_3.OEt_2$ as the catalyst.[35] The yield is 79%, compared to 75% when $BF_3.OEt_2$ is used in conjunction with ***Mercury(II) Sulfate*** or ***Mercury(II) Oxide***.

α-Alkoxycarbonylallylsilanes react with acetals in the presence of $BF_3.OEt_2$ (eq 2).[36] The products can be converted into α-methylene-γ-butyrolactones by dealkylation with ***Iodotrimethylsilane***.

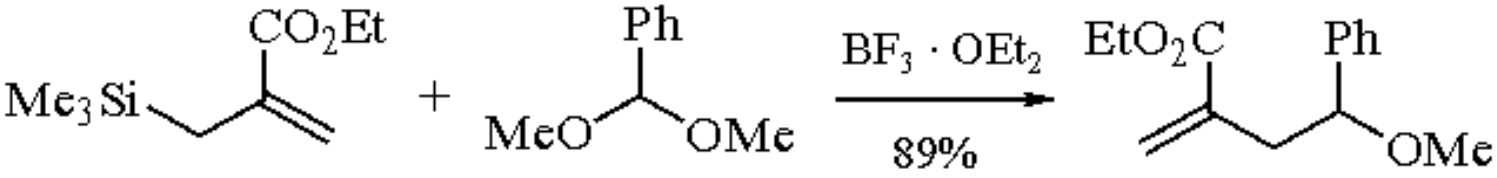

(2)

The cuprate 1,4-conjugate addition step in the synthesis of (+)-modhephene is difficult due to the neopentyl environment of C-4 in the enone, but it can occur in the presence of $BF_3.OEt_2$ (eq 3).[37]

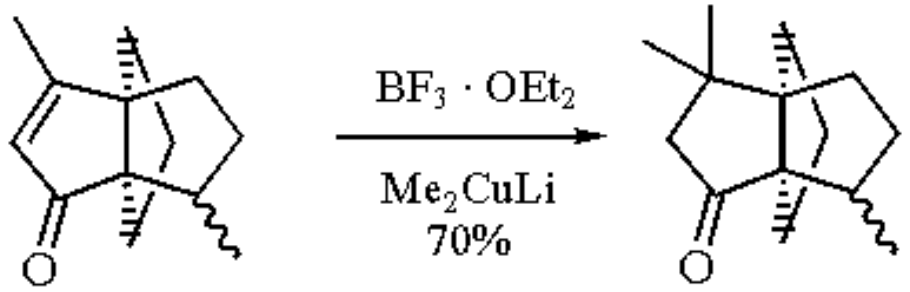

(3)

The reagent is used as a Lewis acid catalyst for the intramolecular addition of diazo ketones to alkenes.[38] The direct synthesis of bicyclo[3.2.1]octenones from the appropriate diazo ketones using $BF_3.OEt_2$ (eq 4) is superior to the copper-catalyzed thermal decomposition of the diazo ketone to a cyclopropyl ketone and subsequent acid-catalyzed cleavage.[38]

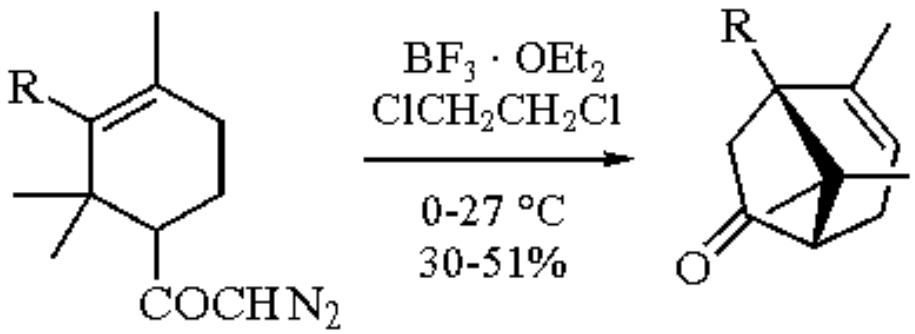

(4)

$BF_3.OEt_2$ reacts with fluorinated amines to form salts which are analogous to Vilsmeier reagents, Arnold reagents, or phosgene-immonium salts (eq 5).[39] These salts are used to acylate electron-rich aromatic compounds, introducing a fluorinated carbonyl group (eq 6).

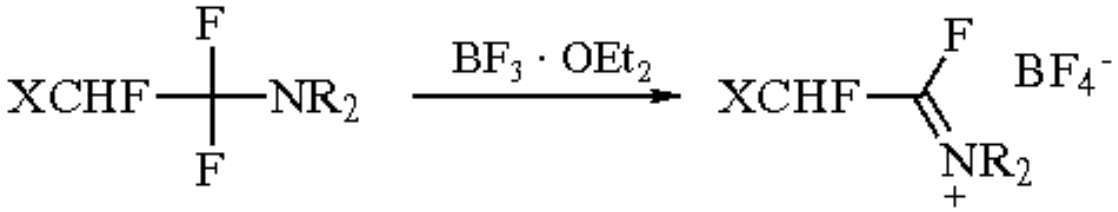

(5)

R = Et; X = Cl, F, CF_3 **(1)**

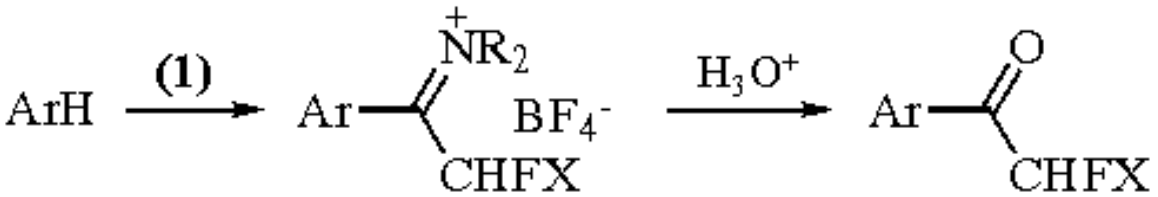

(6)

Xenon(II) Fluoride and methanol react to form ***Methyl Hypofluorite***, which reacts as a positive oxygen electrophile in the presence of BF_3 (etherate or methanol complex) to yield anti-Markovnikov fluoromethoxy products from alkenes.[40,41]

Aldol Reactions.

Although ***Titanium(IV) Chloride*** is a better Lewis acid in effecting aldol reactions of aldehydes, acetals, and silyl enol ethers, $BF_3.OEt_2$ is more effective for aldol reactions with anions generated from transition metal carbenes and with tetrasubstituted enol ethers such as (*Z*)- and (*E*)-3-methyl-2-(trimethylsilyloxy)-2-pentene.[42,43] One exception involves the preparation of substituted cyclopentanediones from acetals by the aldol condensation of protected four-membered acyloin derivatives with $BF_3.OEt_2$ rather than $TiCl_4$ (eq 7).[44] The latter catalyst causes some loss of the silyl protecting group. The pinacol rearrangement is driven by the release of ring strain in the four-membered ring and controlled by an acyl group adjacent to the diol moiety.

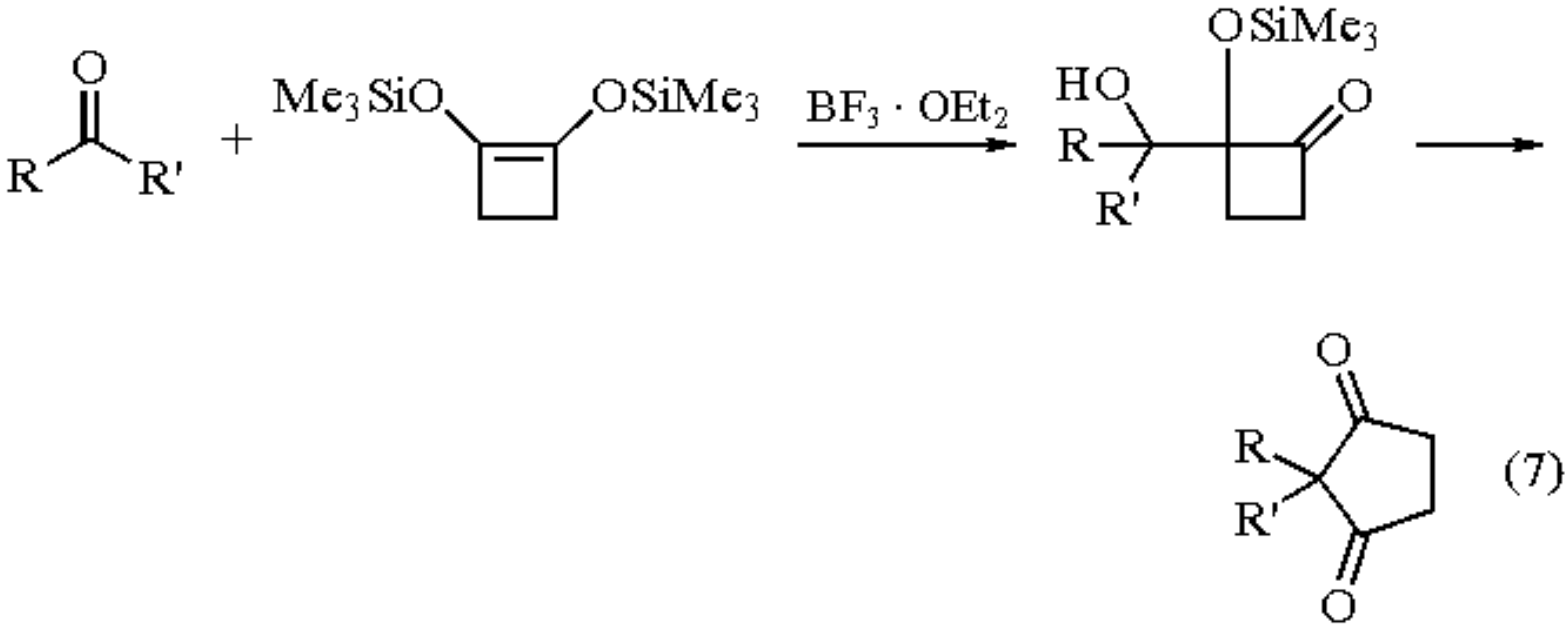

The reagent is the best promoter of the aldol reaction of 2-(trimethylsilyloxy)acrylate esters, prepared by the silylation of pyruvate esters, to afford γ-alkoxy-α-keto esters (eq 8).[45] These esters occur in a variety of important natural products.

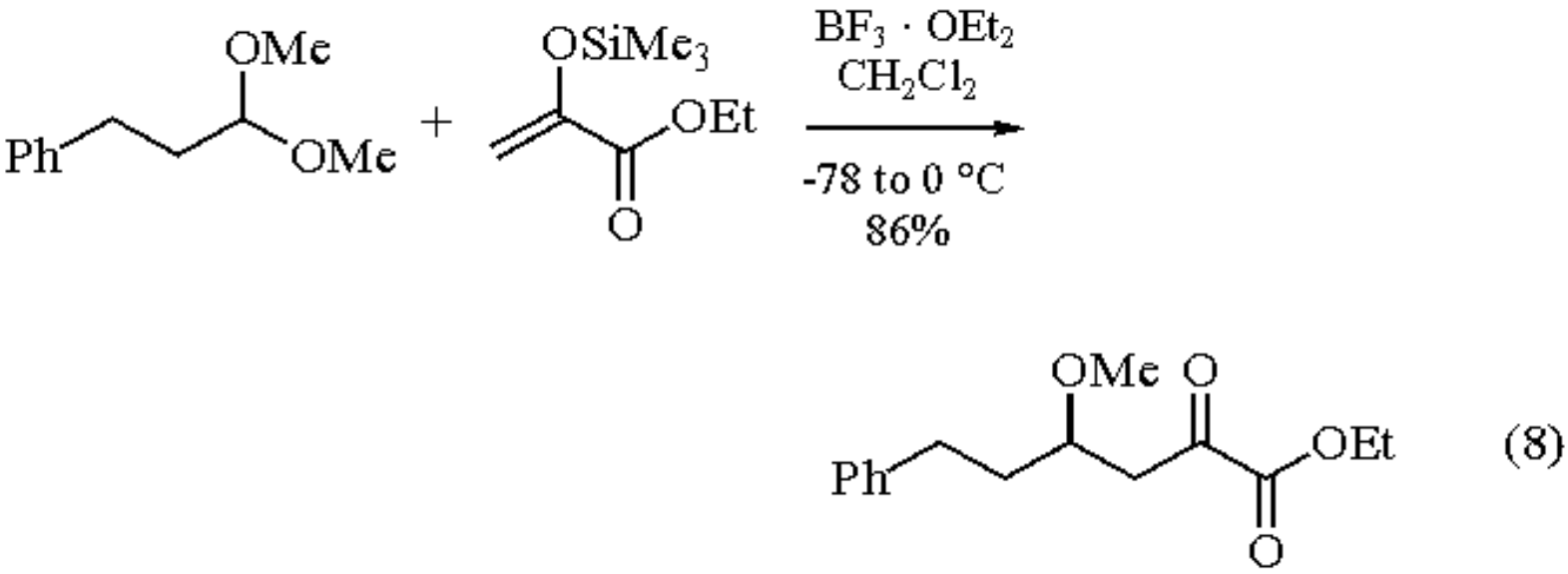

$BF_3.OEt_2$ can improve or reverse the aldehyde diastereofacial selectivity in the aldol reaction of silyl enol ethers with aldehydes, forming the *syn* adducts. For example, the reaction of the silyl enol ether of pinacolone with 2-

phenylpropanal using $BF_3.OEt_2$ gives enhanced levels of Felkin selectivity relative to the addition of the corresponding lithium enolate.[46,47] In the reaction of silyl enol ethers with 3-formyl-Δ^2-isoxazolines, $BF_3.OEt_2$ gives predominantly *anti* aldol adducts, whereas other Lewis acids give *syn* aldol adducts.[48] The reagent can give high diastereofacial selectivity in the addition of silyl enol ethers or silyl ketones to chiral aldehydes.[49] In the addition of a nonstereogenic silylketene acetal to chiral, racemic α-thioaldehydes, $BF_3.OEt_2$ leads exclusively to the *anti* product.[49]

1,5-Dicarbonyl compounds are formed from the reaction of silyl enol ethers with methyl vinyl ketones in the presence of $BF_3.OEt_2$ and an alcohol (eq 9).[50] α-Methoxy ketones are formed from α-diazo ketones with $BF_3.OEt_2$ and methanol, or directly from silyl enol ethers using iodobenzene/$BF_3.OEt_2$ in methanol.[51]

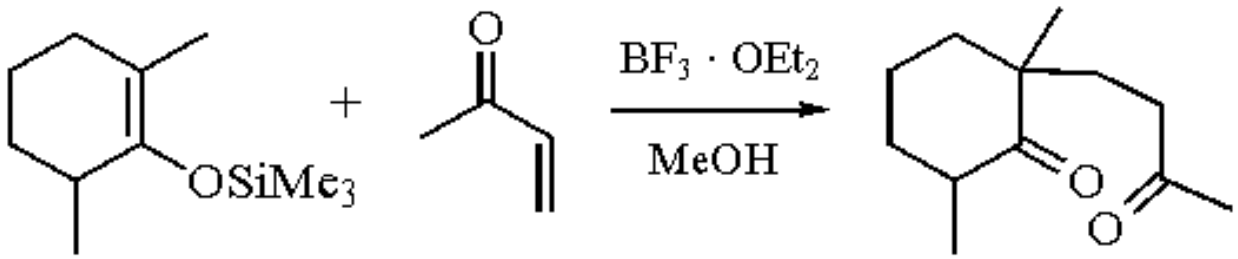

(9)

α-Mercurio ketones condense with aldehydes in the presence of $BF_3.OEt_2$ with predominant *erythro* selectivity (eq 10).[52] Enaminosilanes derived from acylic and cyclic ketones undergo *syn* selective aldol condensations in the presence of $BF_3.OEt_2$.[53]

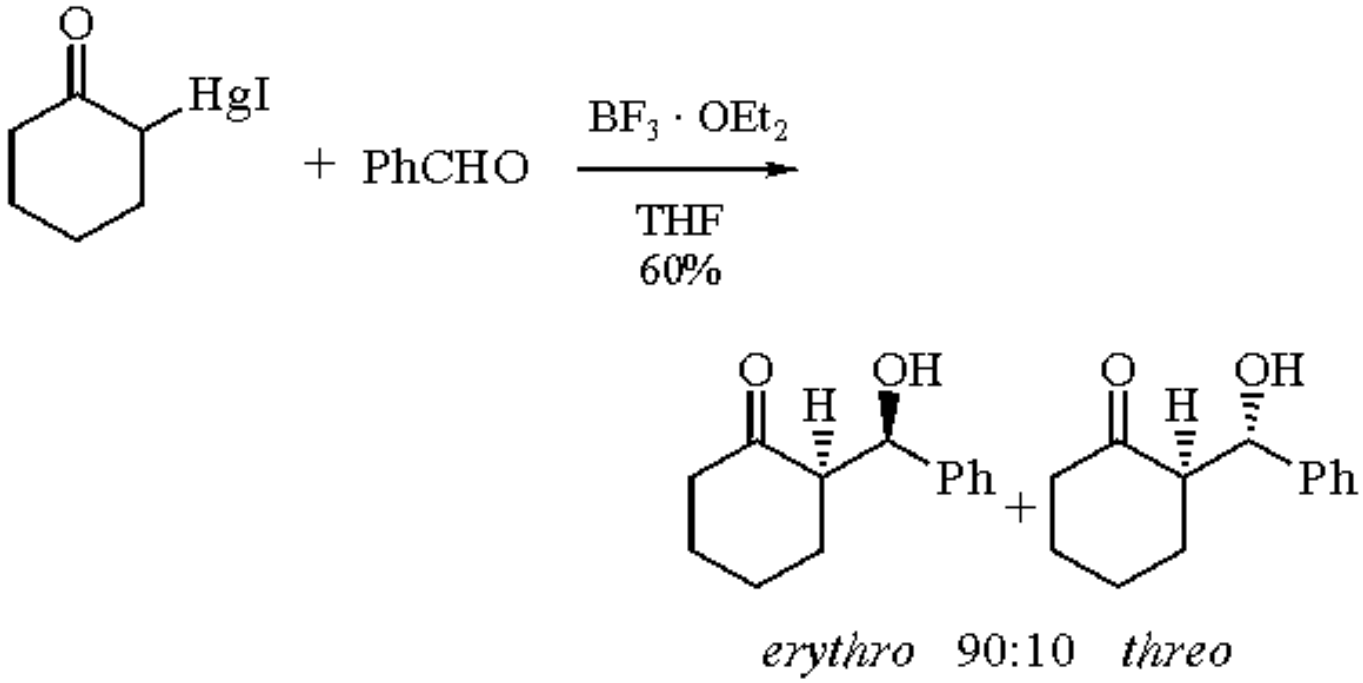

(10)

Cyclizations.

Arylamines can undergo photocyclization in the presence of $BF_3.OEt_2$ to give tricyclic products, e.g. 9-azaphenanthrene derivatives (eq 11).[54]

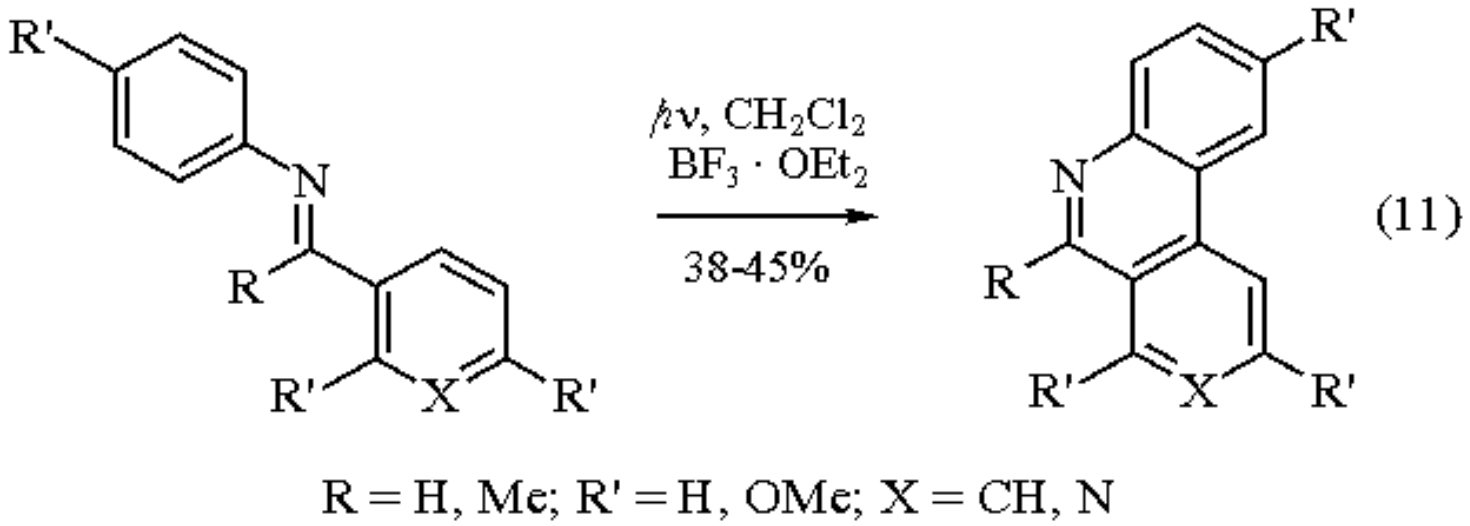

Substituted phenethyl isocyanates undergo cyclization to lactams when treated with $BF_3.OEt_2$.[55] Vinyl ether epoxides (eq 12),[56] vinyl aldehydes,[57] and epoxy β-keto esters[58] all undergo cyclization with $BF_3.OEt_2$.

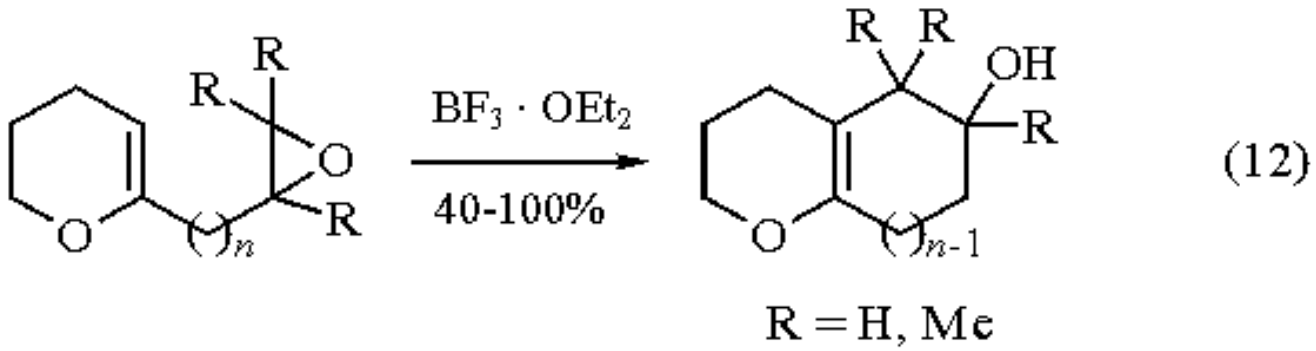

β-Silyl divinyl ketones (Nazarov reagents) in the presence of $BF_3.OEt_2$ cyclize to give cyclopentenones, generally with retention of the silyl group.[59] $BF_3.OEt_2$ is used for the key step in the synthesis of the sesquiterpene trichodiene, which has adjacent quaternary centers, by catalyzing the cyclization of the dienone to the tricyclic ketone (eq 13).[60] Trifluoroacetic acid and trifluoroacetic anhydride do not catalyze this cyclization.

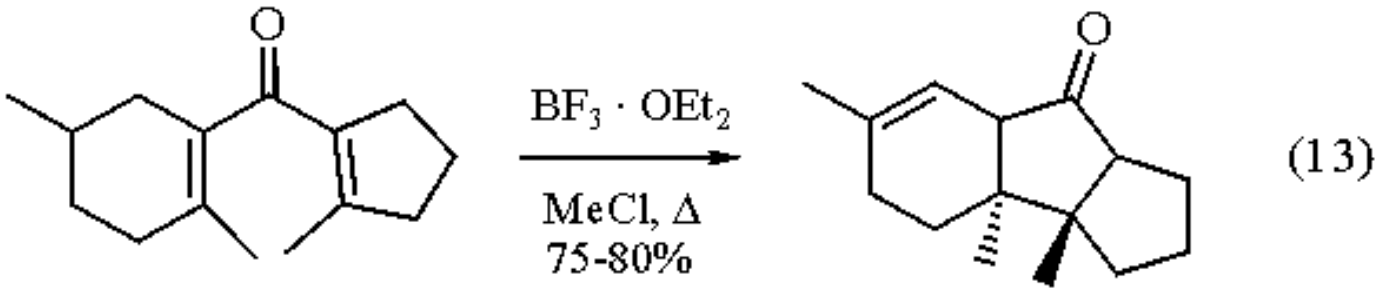

Costunolide, treated with $BF_3.OEt_2$, produces the cyclocostunolide (**2**) and a C-4 oxygenated sesquiterpene lactone (**3**), 4α-hydroxycyclocostunolide (eq 14).[61]

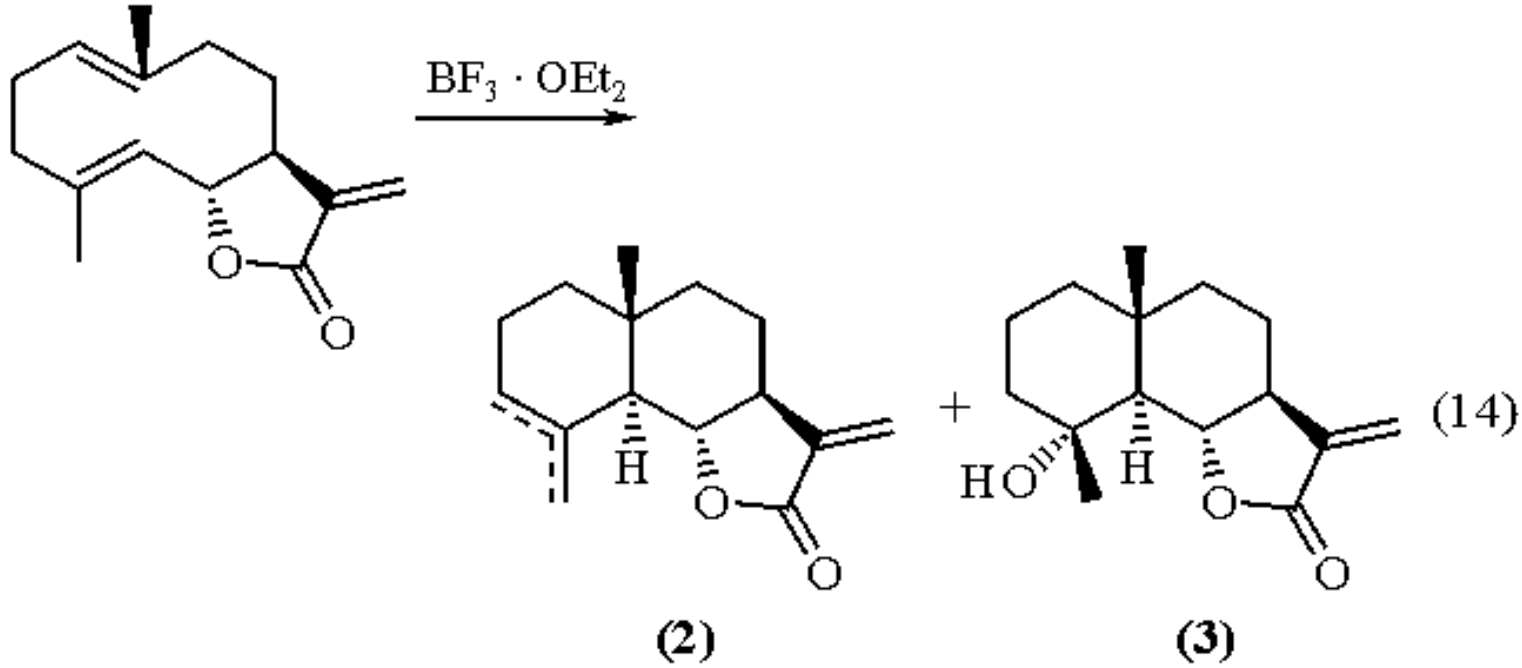

(14)

Other Condensation Reactions.

BF_3.MeOH and BF_3.OEt_2 with ethanol are widely used in the esterification of various kinds of aliphatic, aromatic, and carboxylic acids;[62] the reaction is mild, and no rearrangement of double bonds occurs. This esterification is used routinely for stable acids prior to GLC analysis. Heterocyclic carboxylic acids,[63] unsaturated organic acids,[64] biphenyl-4,4´-dicarboxylic acid,[65] 4-aminobenzoic acid,[63] and the very sensitive 1,4-dihydrobenzoic acid[65] are esterified directly.

The dianion of acetoacetate undergoes Claisen condensations with tetramethyldiamide derivatives of dicarboxylic acids to produce polyketides in the presence of BF_3.OEt_2 (eq 15).[66] Similarly, 3,5-dioxoalkanoates are synthesized from tertiary amides or esters with the acetoacetate dianion in the presence of BF_3.OEt_2 (eq 16).[66]

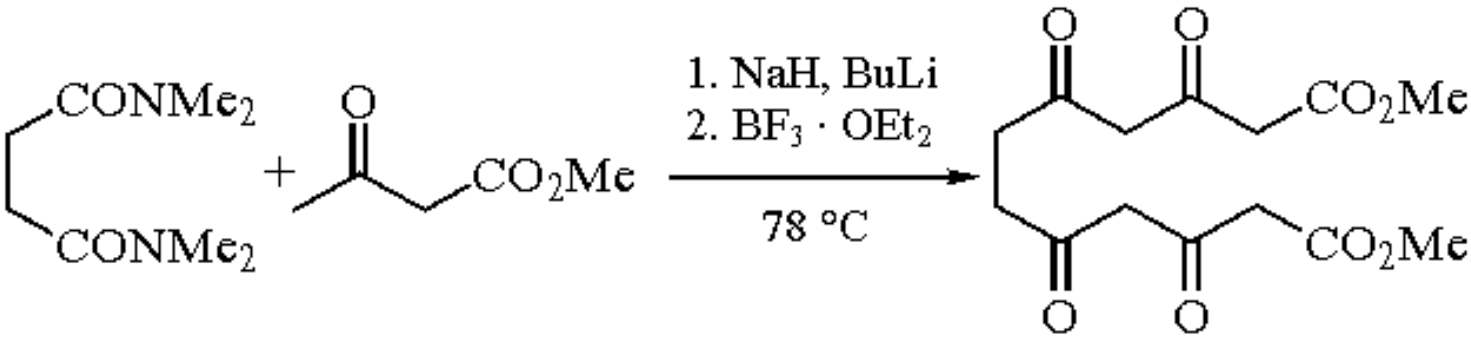

(15)

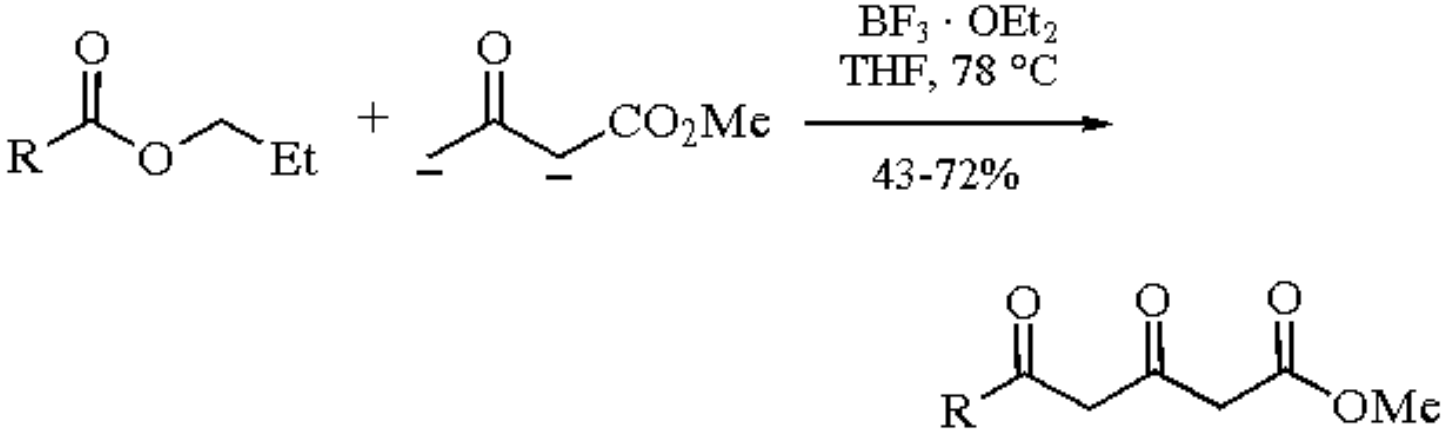

(16)

R = *n*-C_9H_{19}, $ClCH_2$, Ph

Aldehydes and siloxydienes undergo cyclocondensation with $BF_3.OEt_2$ to form pyrones (eq 17).[67] The stereoselectivity is influenced by the solvent.

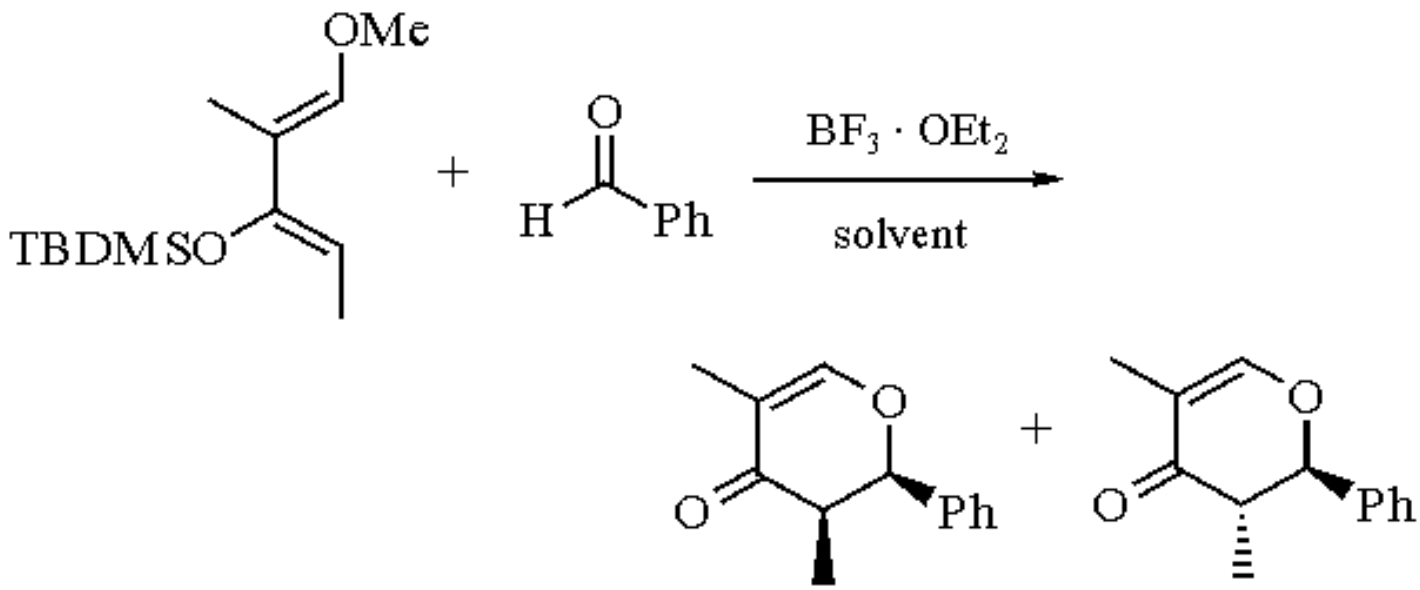

(17)

solvent:	CH_2Cl_2	1:2.3
	PhMe	7:1

$BF_3.OEt_2$ is effective in the direct amidation of carboxylic acids to form carboxamides (eq 18).[68] The reaction is accelerated by bases and by azeotropic removal of water.

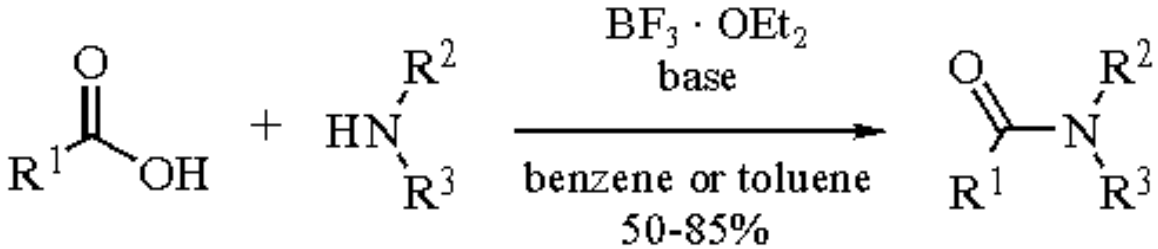

(18)

Carbamates of secondary alcohols can be prepared by a condensation reaction with the isocyanate and $BF_3.OEt_2$ or ***Aluminum Chloride***.[69] These catalysts are superior to basic catalysts such as pyridine and triethylamine. Some phenylsulfonylureas have been prepared from phenylsulfonamides and isocyanates using $BF_3.OEt_2$ as a catalyst; for example, 1-butyl-3-(*p*-tolylsulfonyl)urea is prepared from *p*-toluenesulfonamide and butyl isocyanate.[70] $BF_3.OEt_2$ is an excellent catalyst for the condensation of amines to form azomethines (eq 19).[71] The temperatures required are much lower than with ***Zinc Chloride***.

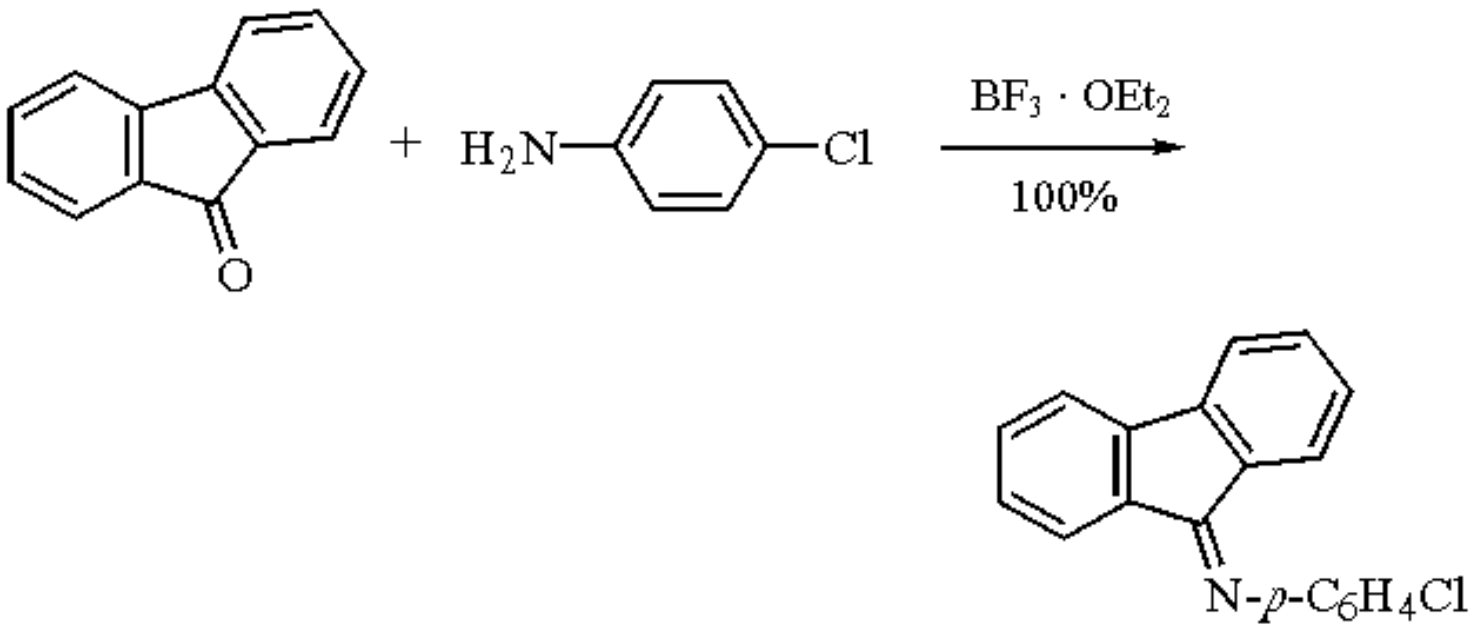

(19)

Acyltetrahydrofurans can be obtained by $BF_3.OEt_2$ catalyzed condensation of (*Z*)-4-hydroxy-1-alkenylcarbamates with aldehydes, with high diastereo- and enantioselectivity.[72] Pentasubstituted hydrofurans are obtained by the use of ketones.

Isobornyl ethers are obtained in high yields by the condensation of camphene with phenols at low temperatures using $BF_3.OEt_2$ as catalyst.[73] Thus camphene and 2,4-dimethylphenol react to give isobornyl 2,4-dimethylphenyl ether, which can undergo further rearrangement with $BF_3.OEt_2$ to give 2,4-dimethyl-6-isobornylphenol.[73]

The title reagent is also useful for the condensation of allylic alcohols with enols. A classic example is the reaction of phytol in dioxane with 2-methyl-1,4-naphthohydroquinone 1-monoacetate to form the dihydro monoacetate of vitamin K_1 (eq 20), which can be easily oxidized to the quinone.[74]

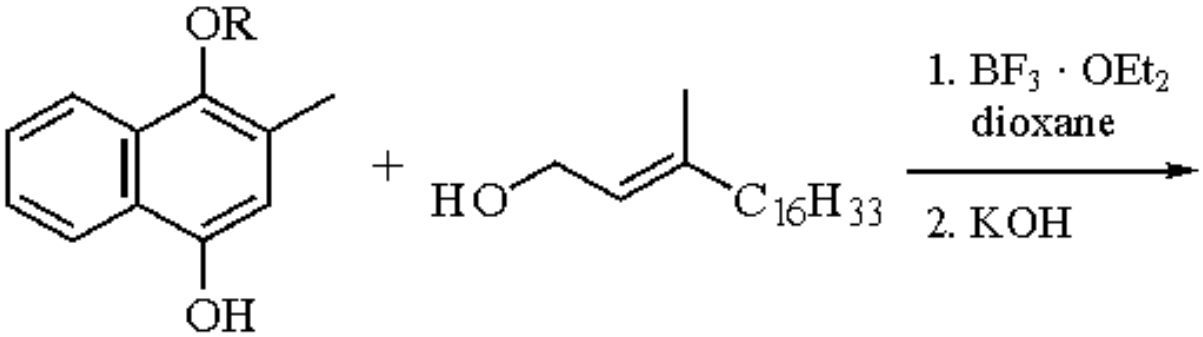

R = H or COMe

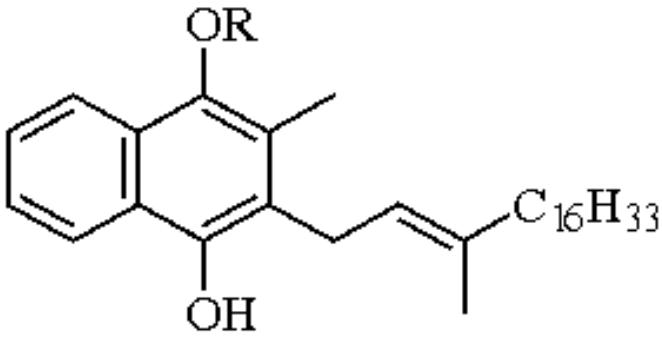

(20)

$BF_3.OEt_2$ promotes fast, mild, clean regioselective dehydration of tertiary alcohols to the thermodynamically most stable alkenes.[75] 11β-Hydroxysteroids are dehydrated by $BF_3.OEt_2$ to give $\Delta^{9(11)}$-enes (eq 21).[76,77]

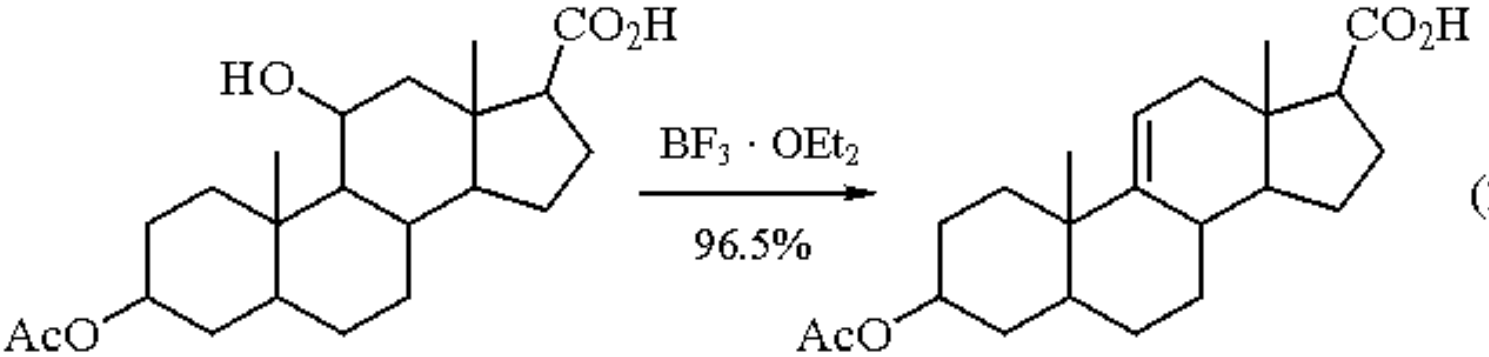

(21)

Epoxide Cleavage and Rearrangements.

The treatment of epoxides with $BF_3.OEt_2$ results in rearrangements to form aldehydes and ketones (eq 22).[78] The carbon α to the carbonyl group of an epoxy ketone migrates to give the dicarbonyl product.[79] The acyl migration in acyclic α,β-epoxy ketones proceeds through a highly concerted process, with inversion of configuration at the migration terminus.[80] With 5-substituted 2,3-epoxycyclohexanes the stereochemistry of the quaternary carbon center of the cyclopentanecarbaldehyde product is directed by the chirality of the 5-position.[81] Diketones are formed if the β-position of the α,β-epoxy ketone is unsubstituted. The 1,2-carbonyl migration of an α,β-epoxy ketone, 2-cycloheptylidenecyclopentanone oxide, occurs with $BF_3.OEt_2$ at 25 °C to form the cyclic spiro-1,3-diketone in 1 min (eq 23).[82]

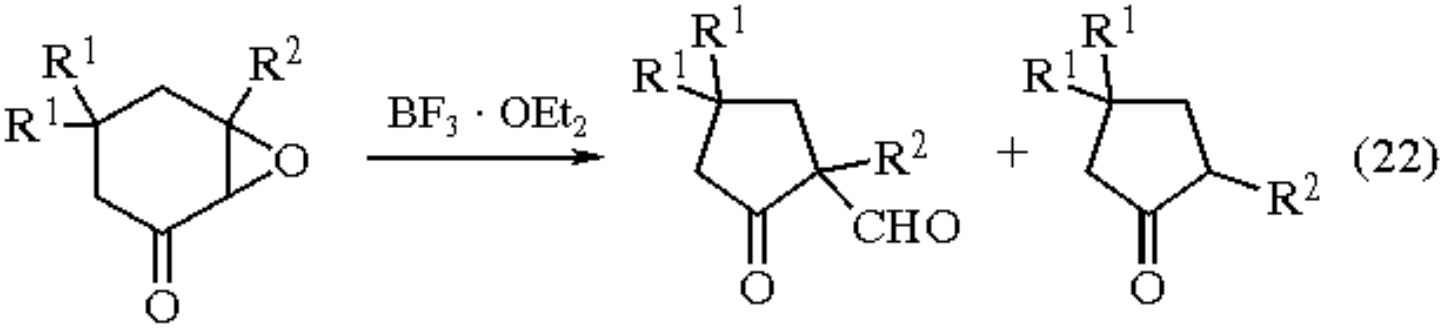

$R^1 = Me, H; R^2 = Me, Ph$

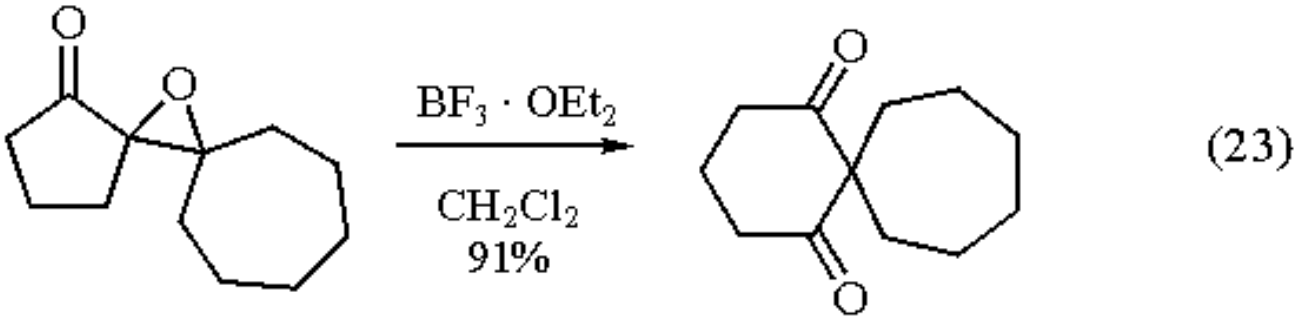

The migration of the carbonyl during epoxide cleavage is used to produce hydroxy lactones from epoxides of carboxylic acids (eq 24).[83] α-Acyl-2-indanones,[84] furans,[85] and Δ^2-oxazolines[86] (eq 25) can also be synthesized by the cleavage and rearrangement of epoxides with $BF_3.OEt_2$. The last reaction has been conducted with sulfuric acid and with tin chloride, but the yields were lower. γ,δ-Epoxy tin compounds react with $BF_3.OEt_2$ to give the corresponding cyclopropylcarbinyl alcohols (eq 26).[87]

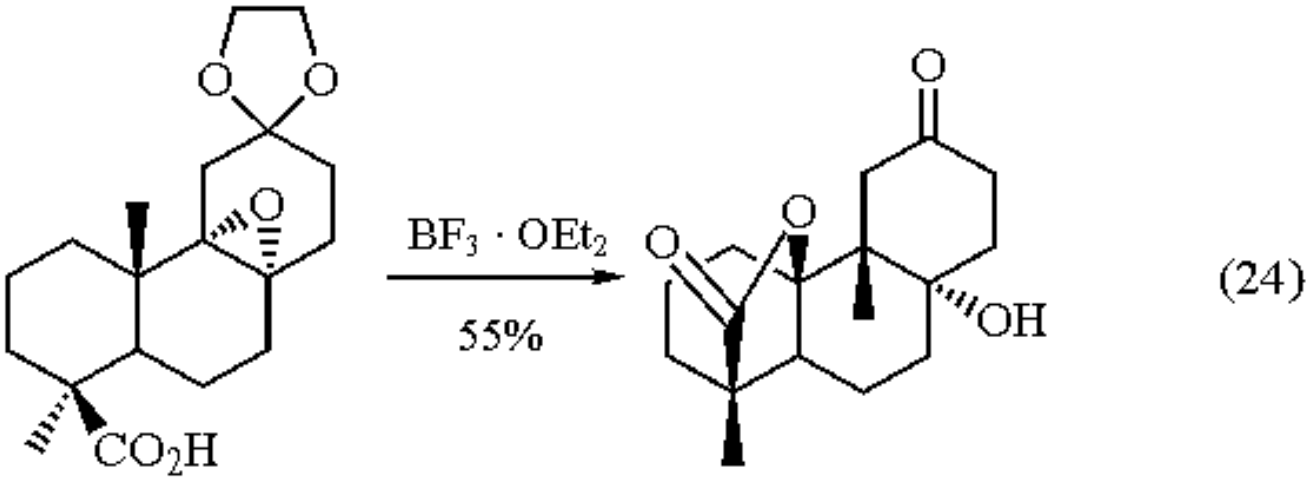

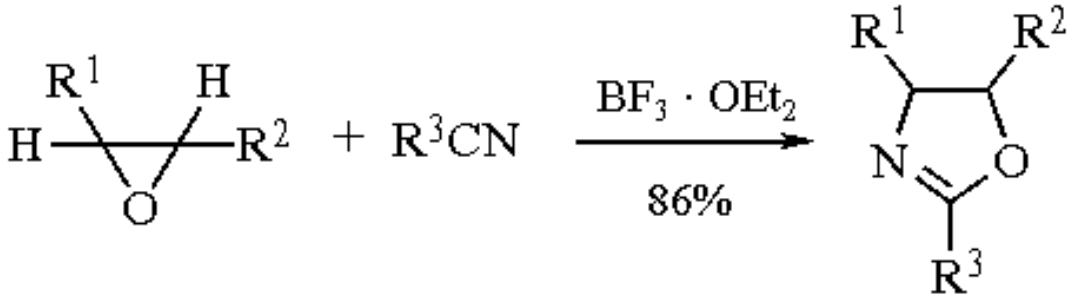

(25)

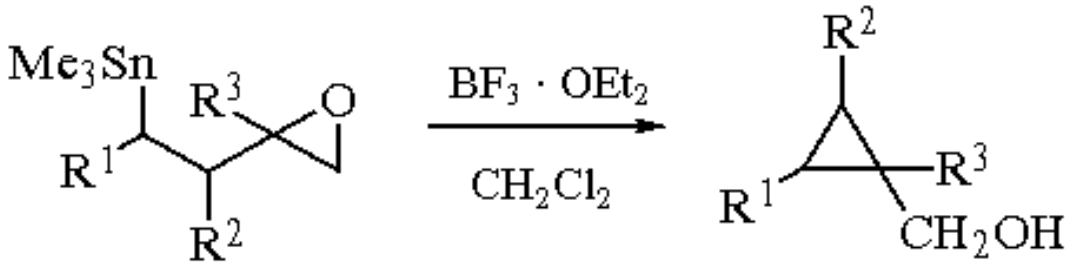

(26)

Remotely unsaturated epoxy acids undergo fission rearrangement when treated with $BF_3.OEt_2$. Hence, *cis* and *trans* ketocyclopropane esters are produced from the unsaturated epoxy ester methyl vernolate (eq 27).[88]

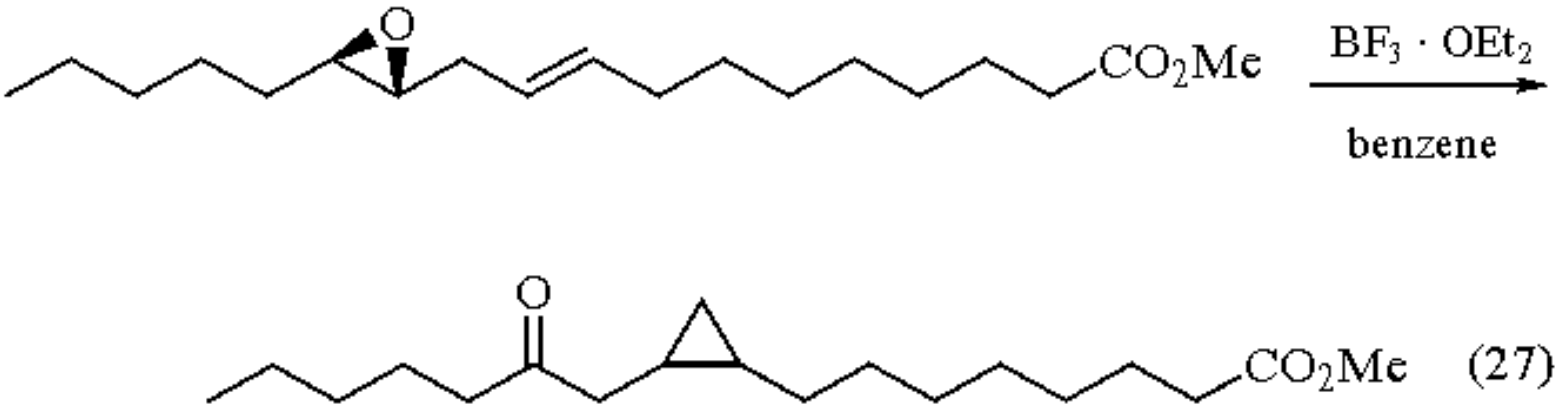

(27)

Epoxy sulfones undergo rearrangement with $BF_3.OEt_2$ to give the corresponding aldehydes.[89] α-Epoxy sulfoxides, like other negatively substituted epoxides, undergo rearrangement in which the sulfinyl group migrates and not the hydrogen, alkyl, or aryl groups (eq 28).[89]

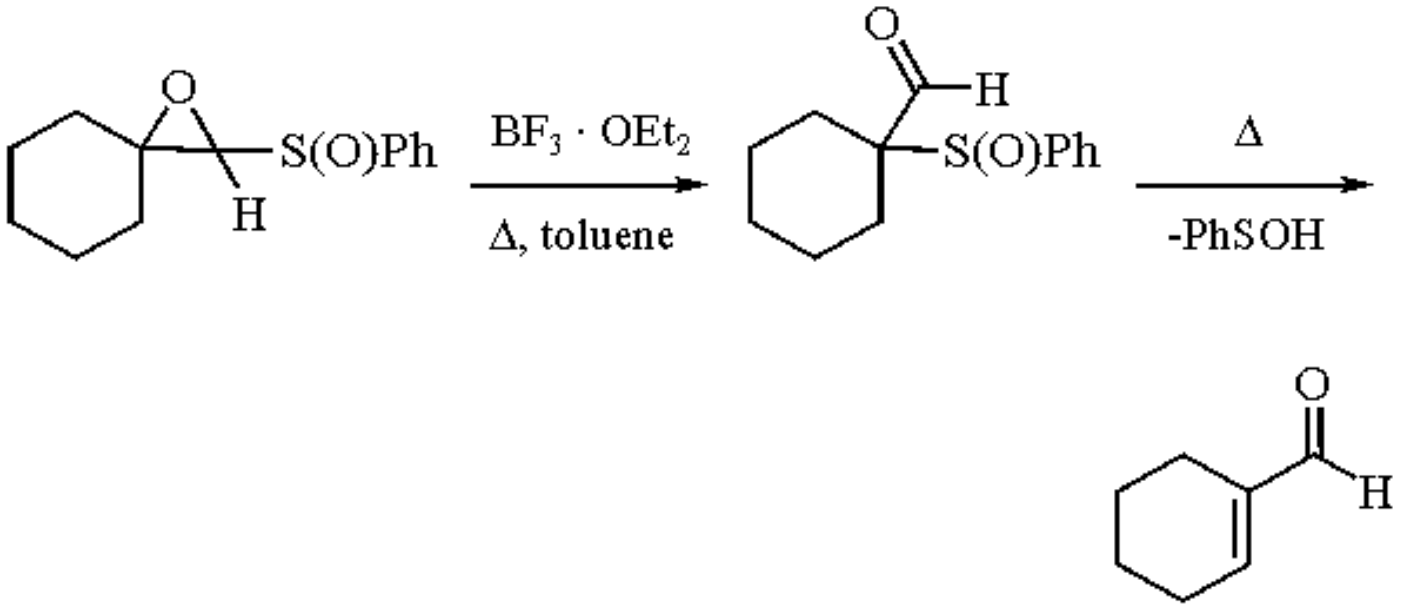

(28)

α,β-Epoxy alcohols undergo cleavage and rearrangement with $BF_3.OEt_2$ to form β-hydroxy ketones.[90] The rearrangement is stereospecific with respect to the epoxide and generally results in *anti* migration. The rearrangement of epoxy alcohols with β-substituents leads to α,α-disubstituted carbonyl compounds.[91]

The $BF_3.OEt_2$-induced opening of epoxides with alcohols is regioselective, but the regioselectivity varies with the nature of the substituents on the oxirane ring.[92] If the substituent provides charge stabilization (as with a phenyl ring), the internal position is attacked exclusively. On the other hand, terminal ethers are formed by the regioselective cleavage of the epoxide ring of glycidyl tosylate.[92]

A combination of cyanoborohydride and $BF_3.OEt_2$ is used for the regio- and stereoselective cleavage of most epoxides to the less substituted alcohols resulting from *anti* ring opening.[93] The reaction rate of organocopper and cuprate reagents with slightly reactive epoxides, e.g. cyclohexene oxide, is dramatically enhanced by $BF_3.OEt_2$.[94] The Lewis acid and nucleophile work in a concerted manner so that *anti* products are formed.

Azanaphthalene *N*-oxides undergo photochemical deoxygenation reactions in benzene containing $BF_3.OEt_2$, resulting in amines in 70-80% yield;[95] these amines are important in the synthesis of heterocyclic compounds. ***Azidotrimethylsilane*** reacts with *trans*-1,2-epoxyalkylsilanes in the presence of $BF_3.OEt_2$ to produce (*Z*)-1-alkenyl azides.[96] The *cis*-1,2-epoxyalkylsilanes undergo rapid polymerization in the presence of Lewis acids.

Other Rearrangements.

$BF_3.OEt_2$ is used for the regioselective rearrangement of polyprenyl aryl ethers to yield polyprenyl substituted phenols, e.g. coenzyme Q_n.[97] The reagent is used in the Fries rearrangement; for example, 5-acetyl-6-hydroxycoumaran is obtained in 96% yield from 6-acetoxycoumaran using this reagent (eq 29).[98]

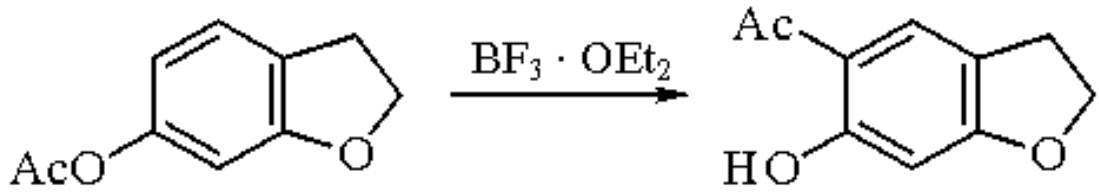

(29)

Formyl bicyclo[2.2.2]octane undergoes the retro-Claisen rearrangement to a vinyl ether in the presence of $BF_3.OEt_2$ at 0 °C (eq 30), rather than with HOAc at 110 °C.[99]

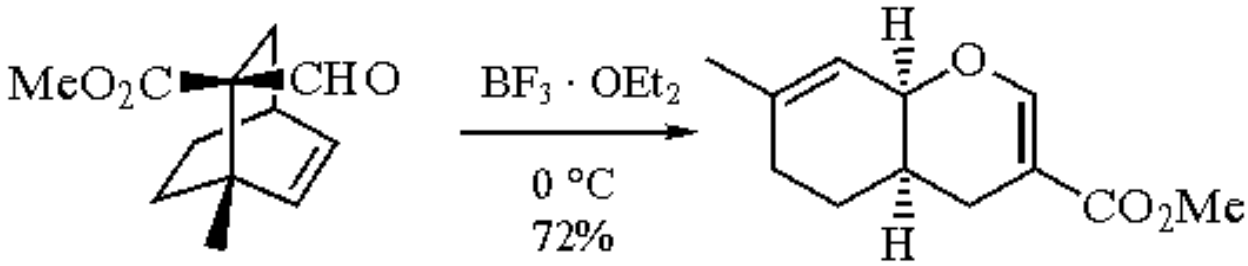

(30)

$BF_3.OEt_2$ is used for a stereospecific 1,3-alkyl migration to form *trans*-2-alkyltetrahydrofuran-3-carbaldehydes from 4,5-dihydrodioxepins (eq 31), which are obtained by the isomerization of 4,7-dihydro-1,3-dioxepins.[100] Similarly, α-alkyl-β-alkoxyaldehydes can be prepared from 1-alkenyl alkyl acetals by a 1,3-migration using $BF_3.OEt_2$ as catalyst.[101] *Syn* products are obtained from (*E*)-1-alkenyl alkyl acetals and *anti* products from the (*Z*)-acetals.

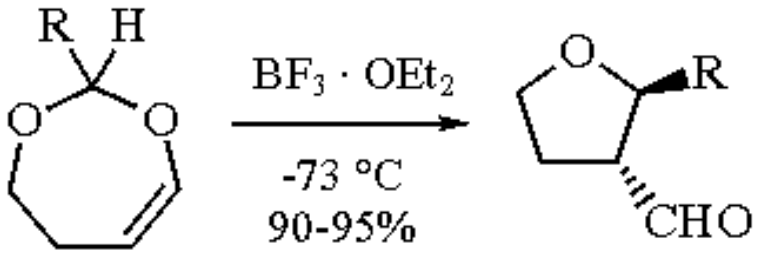

(31)

The methyl substituent, and not the cyano group, of 4-methyl-4-cyanocyclohexadienone migrates in the presence of $BF_3.OEt_2$ to give 3-methyl-4-cyanocyclohexadienone.[102] $BF_3.OEt_2$-promoted regioselective rearrangements of polyprenyl aryl ethers provide a convenient route for the preparation of polyprenyl-substituted hydroquinones (eq 32), which can be oxidized to polyprenylquinones.[103]

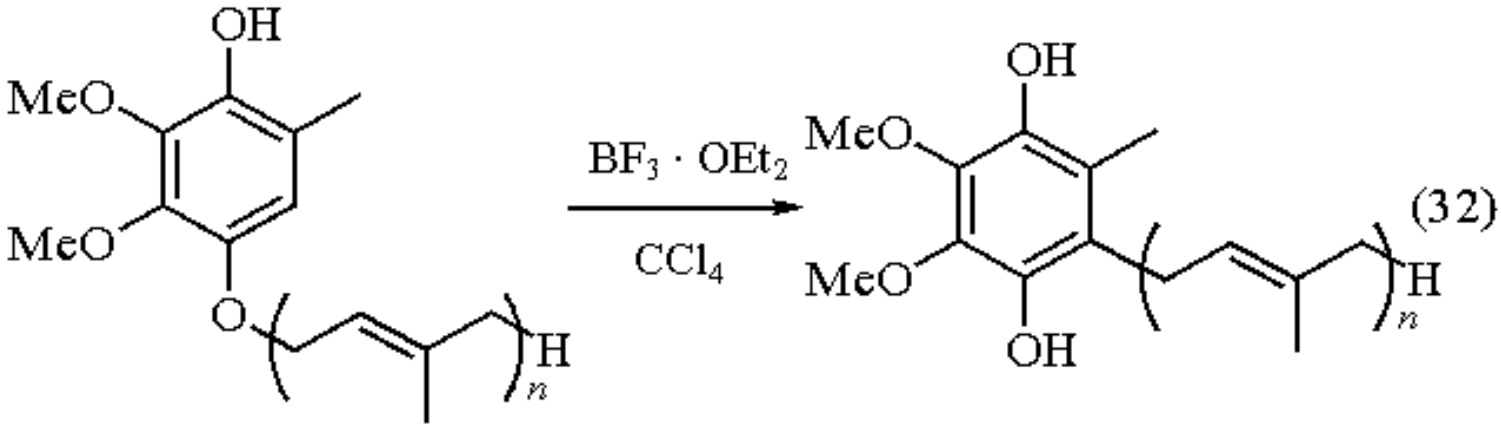

(32)

The (*E*)-(*Z*) photoisomerization of α,β-unsaturated esters,[104] cinnamic esters,[105] butenoic esters,[106] and dienoic esters[106] is catalyzed by $BF_3.OEt_2$ or ***Ethylaluminum Dichloride***. The latter two reactions also involve the photodeconjugation of α,β-unsaturated esters to β,γ-unsaturated esters. The BF_3.MeOH complex is used for the isomerization of 1- and 2-butenes to form equal quantities of *cis*- and *trans*-but-2-enes;[107] the $BF_3.OEt_2$-acetic acid complex is not as effective.

The complex formed with $BF_3.OEt_2$ and ***Epichlorohydrin*** in DMF acts as a catalyst for the Beckmann rearrangement of oximes.[108] Cyclohexanone, acetaldehyde, and *syn*-benzaldehyde oximes are converted into ε-caprolactam, a mixture of *N*-methylformamide and acetamide, and *N*-phenylacetamide, respectively.

The addition of $BF_3.OEt_2$ to an α-phosphorylated imine results in the 1,3-transfer of a diphenylphosphinoyl group, with resultant migration of the C-N=C triad.[109] This method is less destructive than the thermal rearrangement. The decomposition of dimethyldioxirane in acetone to methyl acetate is accelerated with $BF_3.OEt_2$, but acetol is also formed.[110] Propene oxide undergoes polymerization with $BF_3.OEt_2$ in most solvents, but isomerizes to propionaldehyde and acetone in dioxane.[111]

Hydrolysis.

$BF_3.OEt_2$ is used for stereospecific hydrolysis of methyl ethers, e.g. in the synthesis of (±)-aklavone.[112] The reagent is also used for the mild hydrolysis of dimethylhydrazones.[113] The precipitate formed by the addition of $BF_3.OEt_2$ to a dimethylhydrazone in ether is readily hydrolyzed by water to the ketone; the reaction is fast and does not affect enol acetate functionality.

Cleavage of Ethers.

In aprotic, anhydrous solvents, BF_3.MeOH is useful for the cleavage of trityl ethers at rt.[114] Under these conditions, *O*- and *N*-acyl groups, *O*-sulfonyl, *N*-alkoxycarbonyl, *O*-methyl, *O*-benzyl, and acetal groups are not cleaved.

$BF_3.OEt_2$ and iodide ion are extremely useful for the mild and regioselective cleavage of aliphatic ethers and for the removal of the acetal protecting group of carbonyl compounds.[115,116] Aromatic ethers are not cleaved, in contrast to other boron reagents. $BF_3.OEt_2$, in chloroform or dichloromethane, can be used for the removal of the *t*-butyldimethylsilyl (TBDMS) protecting group of hydroxyls, at 0-25 °C in 85-90% yield.[117] This is an alternative to ether cleavage with ***Tetra-n-butylammonium Fluoride*** or hydrolysis with aqueous ***Acetic Acid***.

In the presence of $BF_3.OEt_2$, dithio-substituted allylic anions react exclusively at the α-carbons of cyclic ethers, to give high yields of the corresponding alcohol products (eq 33).[118] The dithiane moiety is readily hydrolyzed with ***Mercury(II) Chloride*** to give the keto derivatives.

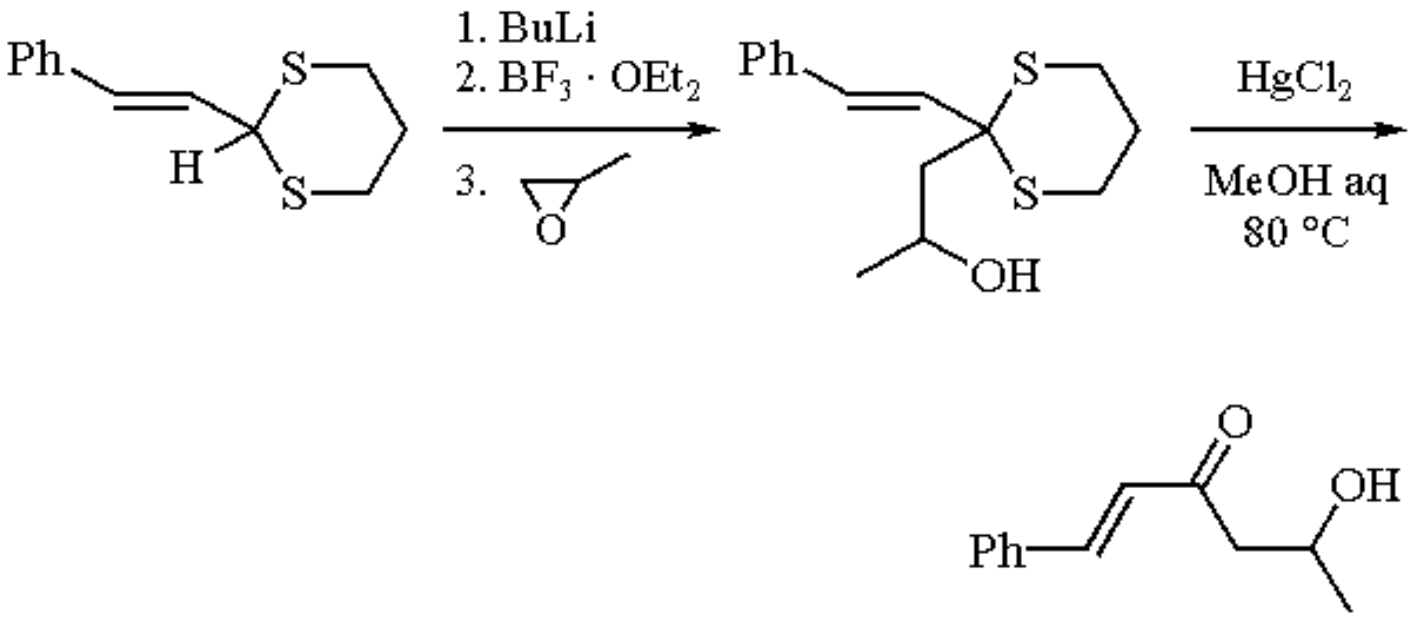

(33)

Inexpensive di-, tri-, and tetramethoxyanthraquinones can be selectively dealkylated to hydroxymethoxyanthraquinones by the formation of difluoroboron chelates with $BF_3.OEt_2$ in benzene and subsequent hydrolysis with methanol.[119] These unsymmetrically functionalized anthraquinone derivatives are useful intermediates for the synthesis of adriamycin, an antitumor agent. 2,4,6-Trimethoxytoluene reacts with cinnamic acid and $BF_3.OEt_2$, with selective demethylation, to form a boron heterocycle which can be hydrolyzed to the chalcone aurentiacin (eq 34).[120]

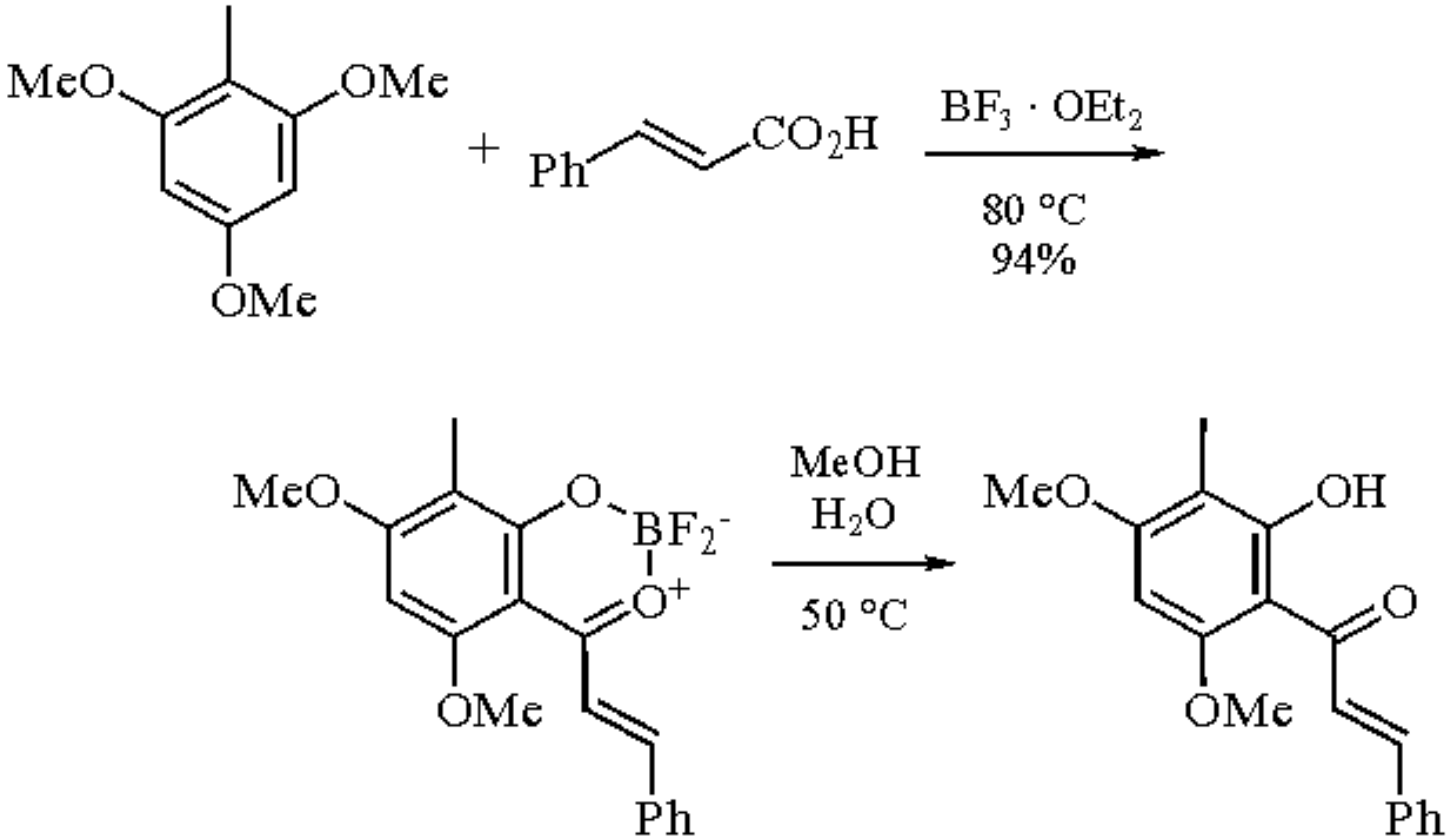

(34)

Reductions.

In contrast to hydrosilylation reactions catalyzed by metal chlorides, aldehydes and ketones are rapidly reduced at rt by ***Triethylsilane*** and $BF_3.OEt_2$, primarily to symmetrical ethers and borate esters, respectively.[121] Aryl ketones like acetophenone and benzophenone are converted to ethylbenzene and diphenylmethane, respectively. Friedel-Crafts acylation-silane reduction reactions can also occur in one step using these reagents; thus ***Benzoyl Chloride*** reacts with benzene, triethylsilane, and $BF_3.OEt_2$ to give diphenylmethane in 30% yield.[121]

$BF_3.OEt_2$ followed by ***Diisobutylaluminum Hydride*** is used for the 1,2-reduction of γ-amino-α,β-unsaturated esters to give unsaturated amino alcohols, which are chiral building blocks for α-amino acids.[122] α,β-Unsaturated nitroalkenes can be reduced to hydroxylamines by ***Sodium Borohydride*** and $BF_3.OEt_2$ in THF;[123,124] extended reaction times result in the reduction of the hydroxylamines to alkylamines. Diphenylamine-borane is prepared from sodium borohydride, $BF_3.OEt_2$, and diphenylamine in THF at 0 °C.[125] This solid is more stable in air than BF_3.THF and is almost as reactive in the reduction of aldehydes, ketones, carboxylic acids, esters, and anhydrides, as well as in the hydroboration of alkenes.

Bromination.

$BF_3.OEt_2$ can catalyze the bromination of steroids that cannot be brominated in the presence of HBr or sodium acetate. Hence, 11α-bromoketones are obtained in high yields from methyl 3α,7α-diacetoxy-12-ketocholanate.[126] Bromination (at the 6α-position) and dibromination (at the 6α- and 11α-positions) of methyl 3α-acetoxy-7,12-dioxocholanate can occur, depending on the concentration of bromine.[127]

A combination of $BF_3.OEt_2$ and a halide ion (tetraethylammonium bromide or iodide in dichloromethane or chloroform, or sodium bromide or iodide in acetonitrile) is useful for the conversion of allyl, benzyl, and tertiary alcohols to the corresponding halides.[128,129]

Diels-Alder Reactions.

$BF_3.OEt_2$ is used to catalyze and reverse the regiospecificity of some Diels-Alder reactions, e.g. with *peri*-hydroxylated naphthoquinones,[130] sulfur-containing compounds,[131] the reaction of 1-substituted *trans*-1,3-dienes with 2,6-dimethylbenzoquinones,[132] and the reaction of 6-methoxy-1-vinyl-3,4-dihydronaphthalene with *p*-quinones.[133] $BF_3.OEt_2$ has a drastic effect on the regioselectivity of the Diels-Alder reaction of quinoline- and isoquinoline-5,8-dione with piperylene, which produces substituted azaanthraquinones.[134] This Lewis acid is the most effective catalyst for the Diels-Alder reaction of furan with methyl acrylate, giving high *endo* selectivity in the 7-oxabicyclo[2.2.1]heptene product (eq 35).[135]

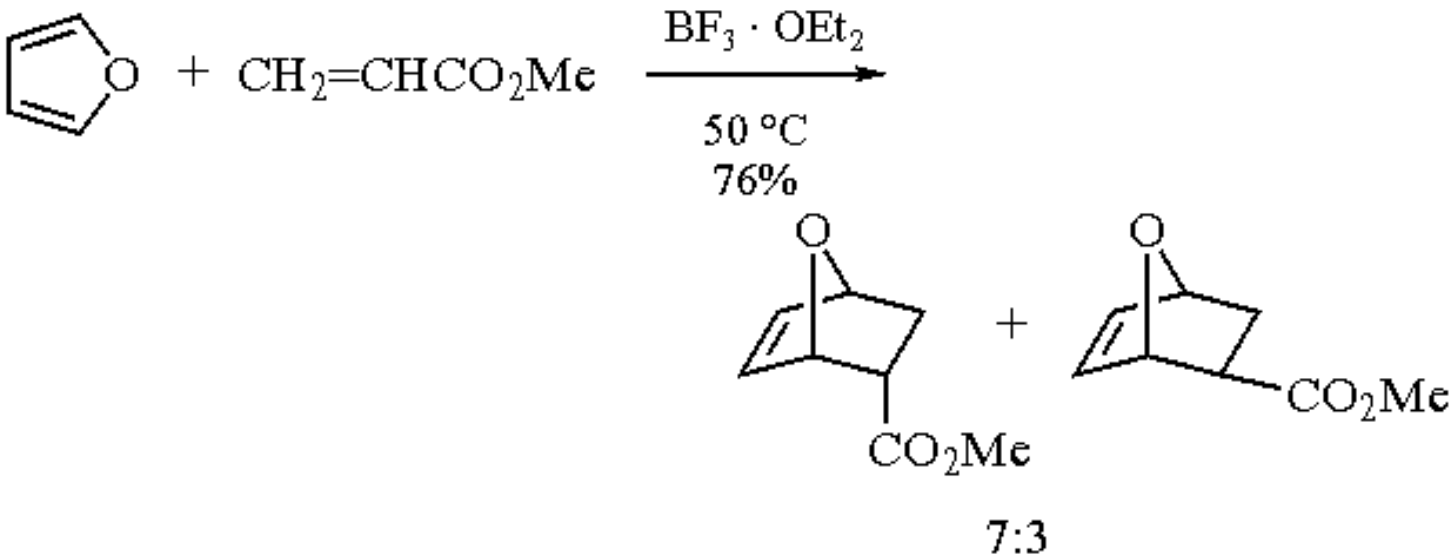

(35)

α-Vinylidenecycloalkanones, obtained by the reaction of ***Lithium Acetylide*** with epoxides and subsequent oxidation, undergo a Diels-Alder reaction at low temperature with $BF_3.OEt_2$ to form spirocyclic dienones (eq 36).[136]

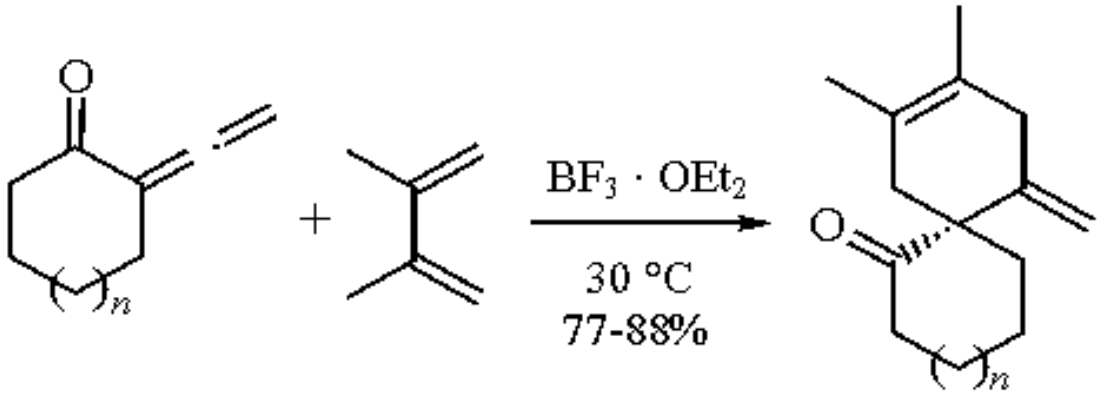

(36)

Other Reactions.

The 17-hydroxy group of steroids can be protected by forming the THP (*O*-tetrahydropyran-2-yl) derivative with 2,3-dihydropyran, using $BF_3.OEt_2$ as catalyst;[137] the yields are higher and the reaction times shorter than with *p*-toluenesulfonic acid monohydrate.

$BF_3.OEt_2$ catalyzes the decomposition of β,γ-unsaturated diazomethyl ketones to cyclopentenone derivatives (eq 37).[138,139] Similarly, γ,δ-unsaturated diazo ketones are decomposed to β,γ-unsaturated cyclohexenones, but in lower yields.[140]

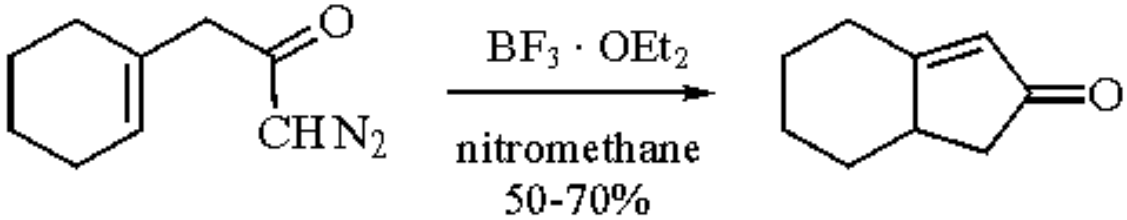

(37)

$BF_3.OEt_2$ is an effective reagent for debenzyloxycarbonylations of methionine-containing peptides.[141] Substituted 6*H*-1,3-thiazines can be prepared in high yields from $BF_3.OEt_2$-catalyzed reactions between α,β-unsaturated aldehydes, ketones, or acetals with thioamides, thioureas, and dithiocarbamates (eq 38).[142]

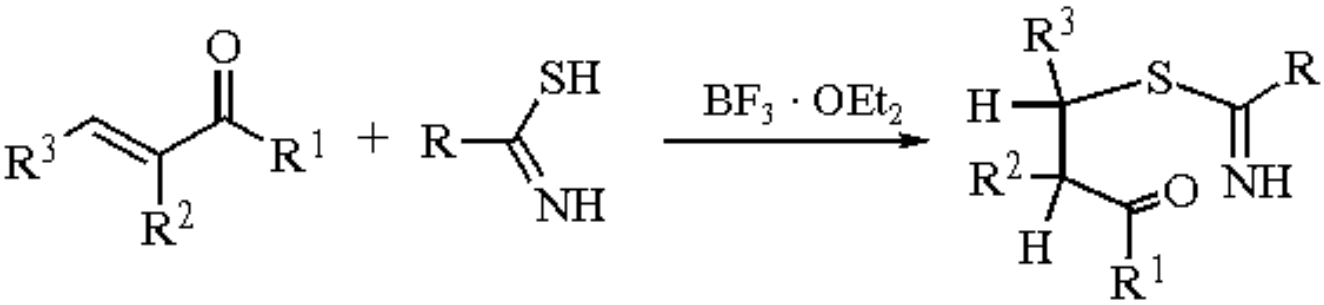

(38)

α-Alkoxy ketones can be prepared from α-diazo ketones and primary, secondary, and tertiary alcohols using $BF_3.OEt_2$ in ethanol.[143] Nitrogen is released from a solution of α-***Diazoacetophenone*** and $BF_3.OEt_2$ in ethanol to give α-ethoxyacetophenone.[143]

Anti-diols can be formed from β-hydroxy ketones using ***Tin(IV) Chloride*** or $BF_3.OEt_2$.[144] The hydroxy ketones are silylated, treated with the Lewis acid, and then desilylated with ***Hydrogen Fluoride***. *Syn*-diols are formed if ***Zinc Chloride*** is used as the catalyst.

$BF_3.OEt_2$ activates the formal substitution reaction of the hydroxyl group of γ- or δ-lactols with some organometallic reagents (M = Al, Zn, Sn), so that 2,5-disubstituted tetrahydrofurans or 2,6-disubstituted tetrahydropyrans are formed.[145]

A new method of nitrile synthesis from aldehydes has been discovered using *O*-(2-aminobenzoyl)hydroxylamine and $BF_3.OEt_2$, achieving 78-94% yields (eq 39).[146]

(39)

Carbonyl compounds react predominantly at the α site of dithiocinnamyllithium if $BF_3.OEt_2$ is present, as the hardness of the carbonyl compound is increased (eq 40).[147] The products can be hydrolyzed to α-hydroxyenones.

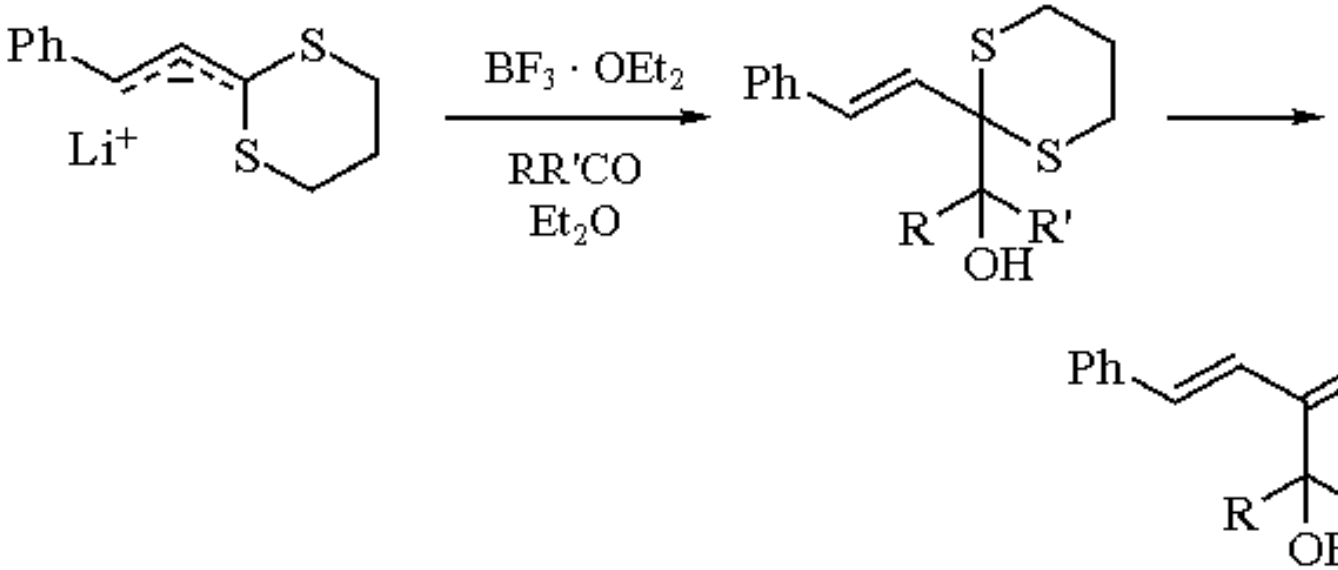

(40)

Optically active sulfinates can be synthesized from sulfinamides and alcohols using $BF_3.OEt_2$.[148] The reaction proceeds stereospecifically with inversion of sulfinyl configuration; the mild conditions ensure that the reaction will proceed even with alcohols with acid-labile functionality.

Related Reagents.

See entries for other Lewis acids, e.g. ***Zinc Chloride***, ***Aluminum Chloride***, ***Titanium(IV) Chloride***; also see entries for ***Boron Trifluoride*** (and combination reagents), and combination reagents employing boron trifluoride etherate, e.g. ***n-Butyllithium-Boron Trifluoride Etherate***, ***Cerium(III) Acetate-Boron Trifluoride Etherate***, ***Lithium Aluminum Hydride-Boron Trifluoride Etherate***, ***Methylcopper-Boron Trifluoride Etherate***

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Boron Trifluoride[1]

[7637-07-2] · BF_3 · Boron Trifluoride · (MW 67.81)

(strongly oxophilic Lewis acid)

Physical Data: gas, mp -127 °C; bp -100 °C/35 mmHg.[1,2]

Solubility: very sol water, and forms a mono- and dihydrate; it is only partially hydrolyzed to fluoroboric acid. Also sol most organic solvents such as pentane; forms complexes with compounds that contain heteroatoms with lone pair electrons.

Form Supplied in: gas in cylinders or lecture bottles; widely available.

Preparative Method: made by heating calcium fluoride with boron trioxide or from potassium fluoroborate with concentrated sulfuric acid. The product may be contaminated by silicon tetrafluoride unless the starting materials are free from silicon.[1b,2]

Purification: via distillation and aromatic addition compound formation.[40]

Handling, Storage, and Precautions: a monel metal valve or stainless steel regulator is recommended. Extremely moisture sensitive; should be used with carefully dried apparatus. Irritant, slowly hydrolyzes to give HF. All work must be carried out in an efficient fume hood.

Introduction.

Boron trifluoride acts as a Lewis acid but its major reactivity relates to the fact that the boron reagent is oxophilic, whereas ***Aluminum Chloride*** is mostly known for its reactions with halides.[3] Thus many of the reactions of boron trifluoride involve alcohols, ethers, carboxylic acids, and esters; the water which is frequently eliminated coordinates with the boron trifluoride. Esters are formed in the presence of boron trifluoride by the interaction of acids with alcohols,[4] acids with ethers,[5] and amides with alcohols and phenols.[6] Thus phenyl acetate is rapidly formed when phenol and acetamide are treated with boron trifluoride. Propene, in the presence of boron trifluoride, reacts with carboxylic acids to form isopropyl esters,[7] and with phenol to form the isopropyl ether.[8] When salicylic acid is treated with boron trifluoride and then propene the ester, isopropyl salicylate, is formed rapidly. With an excess of propene, isopropyl 2-hydroxy-3,5-diisopropylbenzoate is formed in an almost quantitative yield.[7] Ketones that are enolizable are converted into β-diketones in the presence of carboxylic anhydrides and boron trifluoride.[9] Similarly, phenyl alkyl

ethers afford alkyl phenols.[10,11] Benzidine and Beckmann rearrangements and the rearrangement of phenyl acetate to 4-hydroxyacetophenone have all been studied using boron trifluoride.[3] A number of the early investigations have been repeated.

Friedel-Crafts Alkylation Reactions.

Alcohols react with benzene[12] or naphthalene[13] to give alkylated products. The alkylation of benzene using cyclohexanol (eq 1) gives moderate yields, but no other alcohols give better results; for example, both 1-propanol and 2-propanol give mono- and 1,4-diisopropylbenzene in a combined yield of ca. 38%.[12a] The reactions of isobutanol with benzene in the presence of boron trifluoride, not unexpectedly, give *t*-butyl- and 1,4-di-*t*-butylbenzene.[12e] Similarly, naphthalene is alkylated in good yield using cyclohexanol (eq 2).[13]

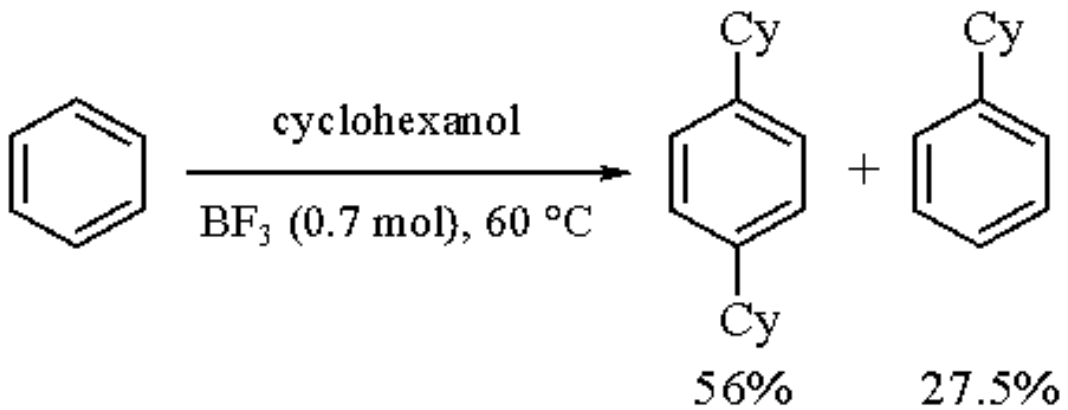

(1)

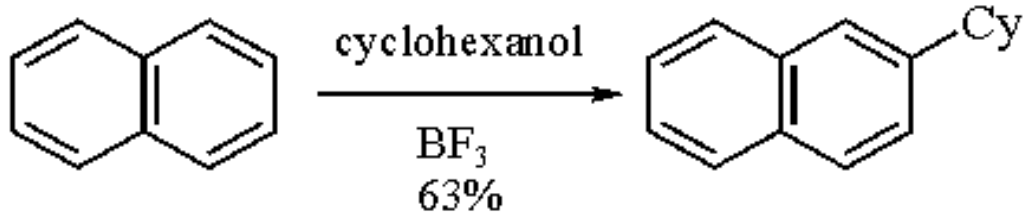

(2)

The alkylation of aromatic hydrocarbons using alkyl fluorides has also been investigated. Although the reactivity of boron trifluoride is lower than that of the other boron halides, the yields are usually better when using the fluoride. Methyl, ethyl, propyl, isopropyl, *t*-butyl, and cyclohexyl fluorides were shown to alkylate aromatic compounds in good yields. For example, benzene and cyclohexyl fluoride give the expected product in 85% yield.[12b] Normally, alkylation does not occur using alkyl halides other than the fluorides, and mixed halides afford products containing halogen. Although the reaction of cyclohexyl fluoride was successful, an attempted reaction using cyclohexyl bromide with toluene was unsuccessful.[12b] The preparation of cumene in high yield can be achieved using 2-fluoropropane in a reaction with benzene (eq 3); the lack of reactivity of other halogens is exemplified by the reaction of 1-chloro-3-fluoropropane, in which the product is 1-chloro-2-phenylpropane, and by eq 4, where the bromine is retained using 1-bromo-2-fluoroethane.[14]

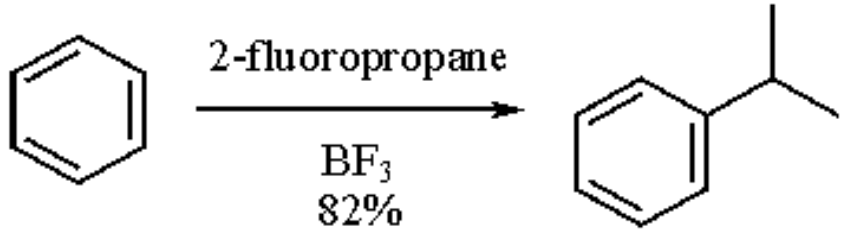

(3)

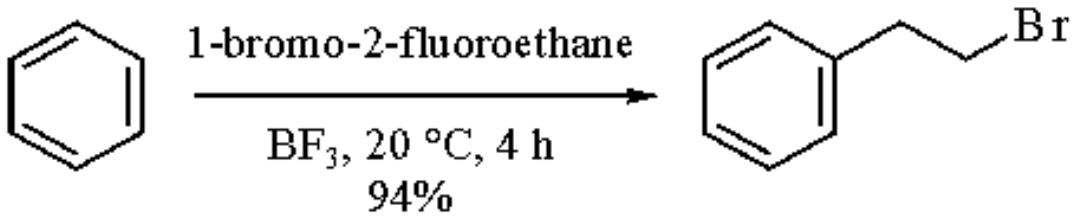

(4)

The use of alkenes as sources of the electrophiles involved in Friedel-Crafts alkylations has also been studied. In early examples the yields obtained were not as good as in alkylations using alcohols. For example, the yield of 2-cyclohexylnaphthalene is only 35% using cyclohexene.[13] On the other hand, the intramolecular alkylation of 1-(2-tolyl)-(*E*)-pent-3-ene gives 1,5-dimethyl-1,2,3,4-tetrahydronaphthalene in 95% yield, and the example shown in eq 5 was used in a synthesis of 1,3,6,8-tetramethyltriphenylene.[15] Related to this latter reaction, gaseous boron trifluoride has been shown to form a complex with nitromethane, which is particularly effective in catalyzing proton-initiated cascade cyclizations like the one shown in eq 6.[16]

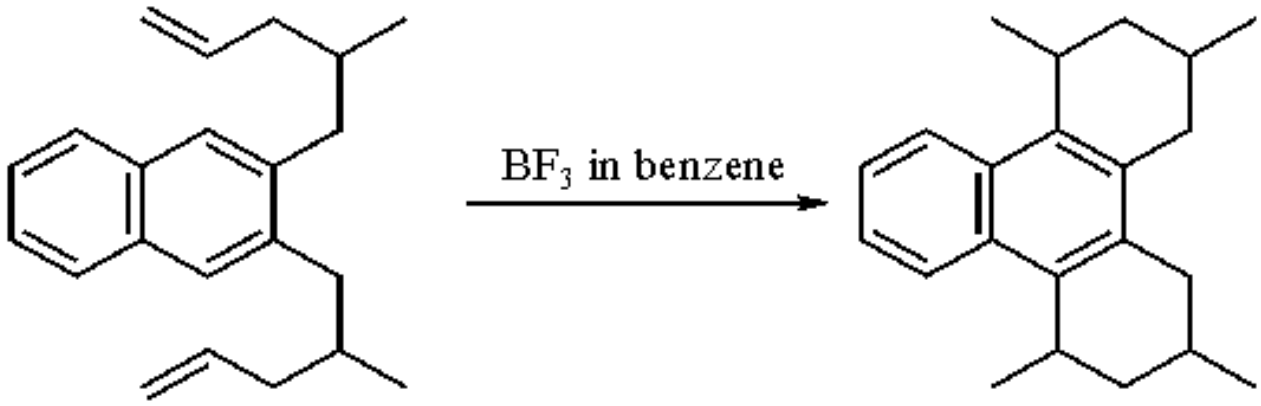

(5)

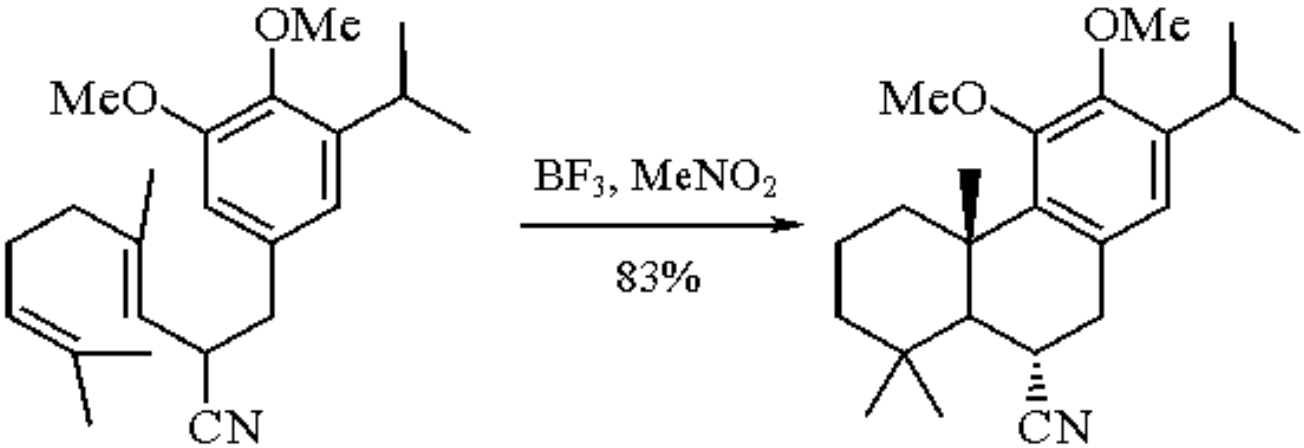

(6)

Diastereoselective alkylation reactions of furans have been studied using diacetoxypyrrolidinones as sources of an

acyliminium ion. Good yields and some diastereoselection were observed when using ***Zinc Bromide*** or ***Chlorotrimethylsilane*** as the Lewis acid but, unfortunately, no diastereoselection was observed using boron trifluoride.[17]

Friedel-Crafts Acylation Reactions.

The acylation of particularly electron-rich aromatic compounds can be achieved by a number of procedures; the number of options available that allow formylations to be carried out are fewer. The Vilsmeier protocols apply only to nucleophilic aromatic substrates, for example indoles and pyrroles. Formylation reactions using carbon monoxide, hydrogen chloride, and aluminum chloride function as if ***Formyl Chloride*** were produced. It is known, however, that formyl chloride is unstable at temperatures above -60 °C. On the other hand, ***Formyl Fluoride***, which may be prepared by the interaction of anhydrous hydrogen fluoride with the mixed anhydride of formic and acetic acids, and removed as it is formed (bp -29 °C), has been used in conjunction with boron trifluoride. Alkylbenzenes are formylated at low temperatures. In an alternative procedure, formyl fluoride and boron trifluoride are passed into a solution of the aromatic hydrocarbon in carbon disulfide.[18] Thus benzene gives benzaldehyde (56%), mesitylene gives mesitaldehyde (70%), and naphthalene gives a 1:5 mixture of α- and β-naphthaldehydes.

In other acylation reactions, acyl fluorides and boron trifluoride afford ketones with better regioselectivity than that observed with aluminum chloride as the Lewis acid. A reaction of isobutyryl fluoride with 2-methylnaphthalene gives an excellent yield of the product shown in eq 7.[19]

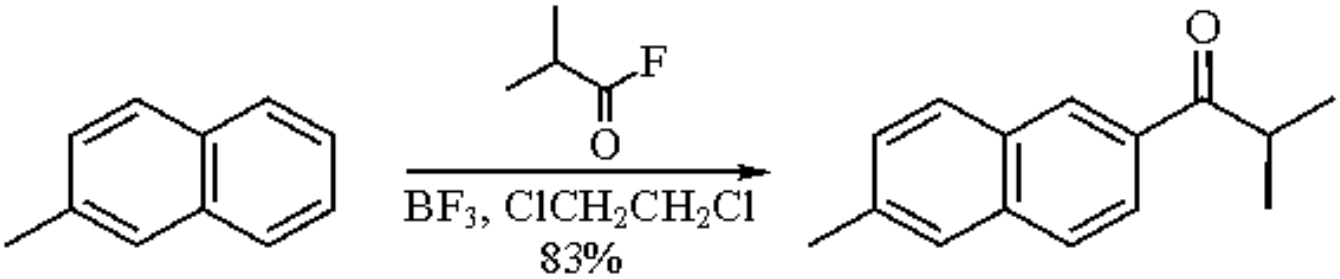

(7)

Boron trifluoride can, however, give rise to difficulties as a result of side-chain acylation, as exemplified in eq 8.[20] Carboxylic acids have been used in reactions of phenols[21] and aryl ethers together with boron trifluoride. Dealkylation of an ether residue *ortho* to the introduced acyl group is frequently encountered, as in the synthesis of baeckeol (eq 9).[22] Advantage of this effect was also taken in a synthesis of the naturally occurring phenol aurentiacin, as shown in eq 10.[23]

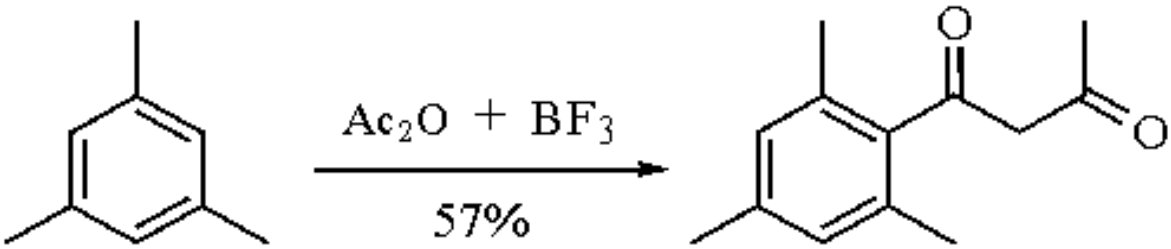

(8)

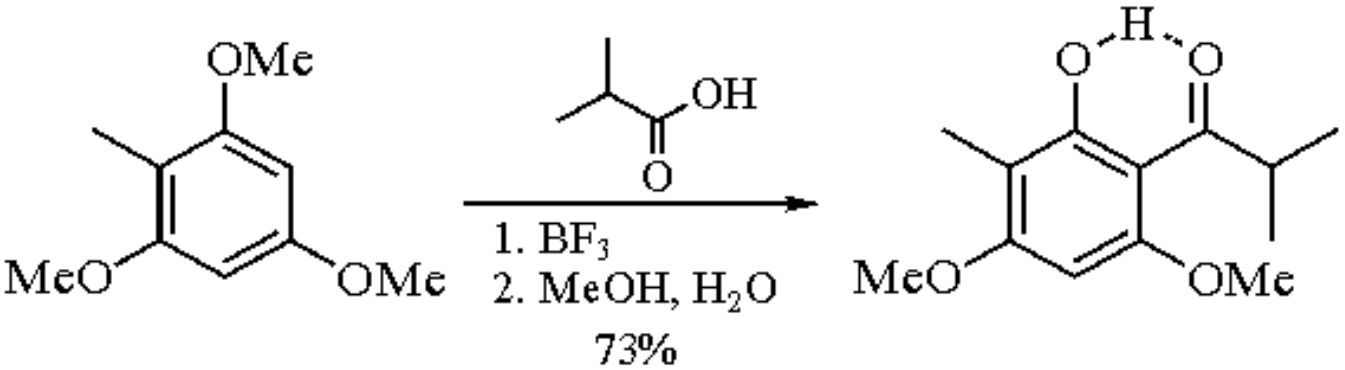

(9)

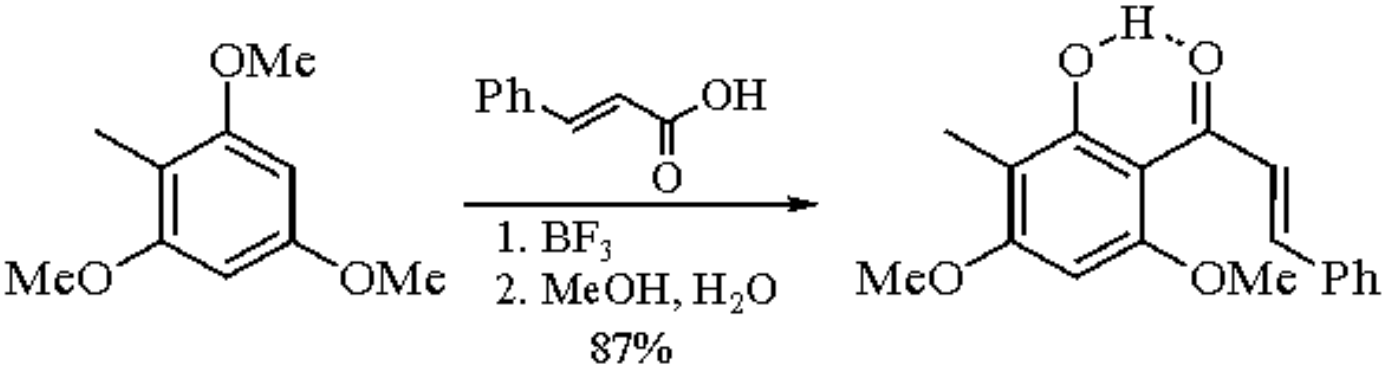

(10)

Carbonyl Group and Related Transformations.

The conversion of aldehydes and ketones into the related *gem*-difluoro compounds is effected by treatment with ***Molybdenum(VI) Fluoride*** at rt in the presence of catalytic amounts of boron trifluoride. The yields with ketones are significantly better than with aldehydes.[24] The acylation of enolizable carbonyl compounds was mentioned in the introduction.[9] A checked procedure for the acetylation of acetone, which affords pentane-2,4-dione in 80-85% yield, has been reported.[25] In general, it has been established that better yields of β-diketones are obtained if the intermediate boron difluoride complexes are isolated.[26] The boron difluoride complexes, isolated in yields of 75-92%, give the β-diketones in yields of 76-95%; the procedure is exemplified in eq 11. In another study, evidence was presented that implicated two mechanisms for the acetylation of ketones.[27] One route involves the formation of the enol acetate and the other involves the direct acetylation of the boron enolate. Thus the enol acetate derived from cyclohexanone is formed and isolated in 22% yield in a reaction in which cyclohexanone is allowed to interact with acetic anhydride in the presence of 14 mol % of boron trifluoride gas. The enol acetate was subsequently shown to afford 2-acetylcyclohexanone in 76% yield when treated with acetic anhydride and boron trifluoride. On the other hand, attempts to form the enol acetate from acetophenone were unsuccessful.

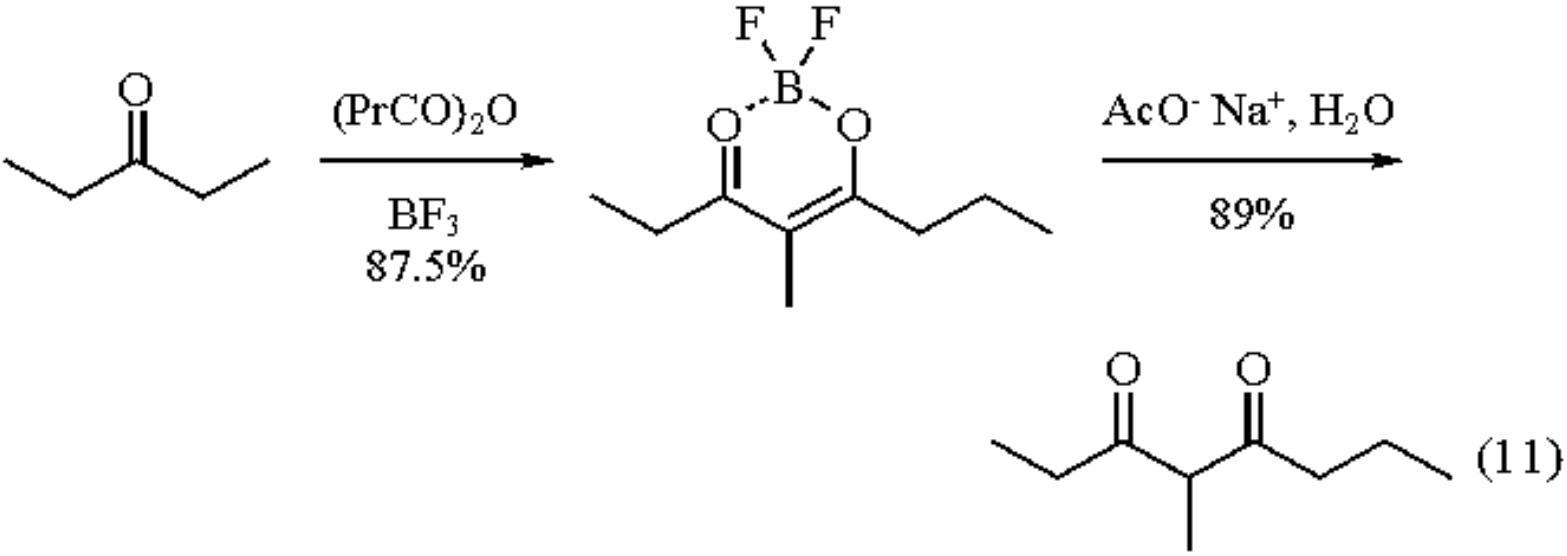

(11)

The alkylation of β-keto esters using an alcohol as the source of the electrophile can be effected by using boron trifluoride (eq 12).[28]

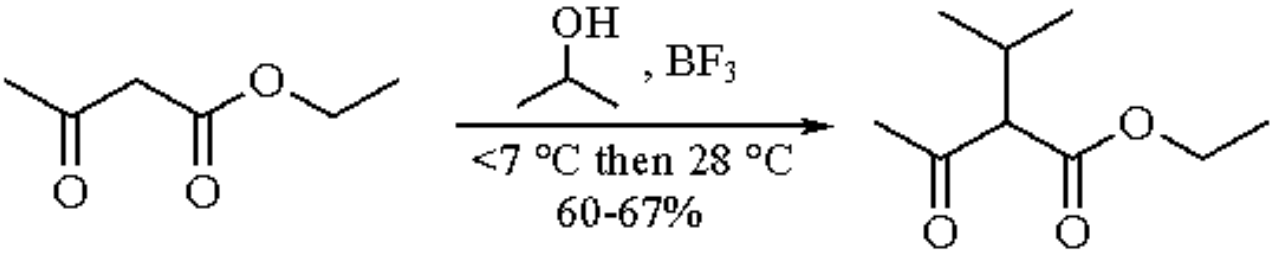

(12)

Beckmann rearrangements using boron trifluoride[3] have been investigated in more detail. For example, benzophenone oxime affords a 1:1 complex in 98% yield when boron trifluoride is passed into a solution of the oxime in light petroleum. The complex rearranges to *N*-phenylbenzamide in 83% yield when heated to 140-150 °C. The related benzophenone oxime *O*-methyl ether-boron trifluoride complex also gives *N*-phenylbenzamide at a lower temperature but in lower yield.[29] The isomerization of *syn*- to *anti*-arylaldoximes has also been reported via the boron trifluoride complexes.[30]

Cation-Assisted Rearrangement Reactions.

A number of interesting cyclization reactions leading to naturally occurring polycyclic ring systems have been investigated using boron trifluoride. The cedrane ring system is formed (eq 13) when the enol acetate is treated as shown; reaction of the ketone with ***Methyllithium*** then gives racemic cedrol.[31] In a detailed study of the reactions of an acetoxymenthadiene (eq 14), it was shown that racemic camphor can be obtained in 90% yield when a 0.1 % solution in wet dichloromethane is treated with boron trifluoride at room temperature for 10 min. Lower yields are obtained when higher concentrations of the diene are used, and boron trifluoride etherate fails to afford any of the required product as do other Lewis acids.[32] A Lewis acid-assisted fragmentation followed by a 1,2-methyl shift, driven by the enolate, is involved in the terpene rearrangement leading to the nootkatane skeleton shown in eq 15.[33] Rearrangement reactions of glycidic esters have been studied using boron trifluoride and are found to proceed in high yields.[34] For example, ethyl β-phenylglycidate gives ethyl phenylpyruvate, isolated in 80% yield as the 2,4-dinitrophenylhydrazone.

(13)

(14)

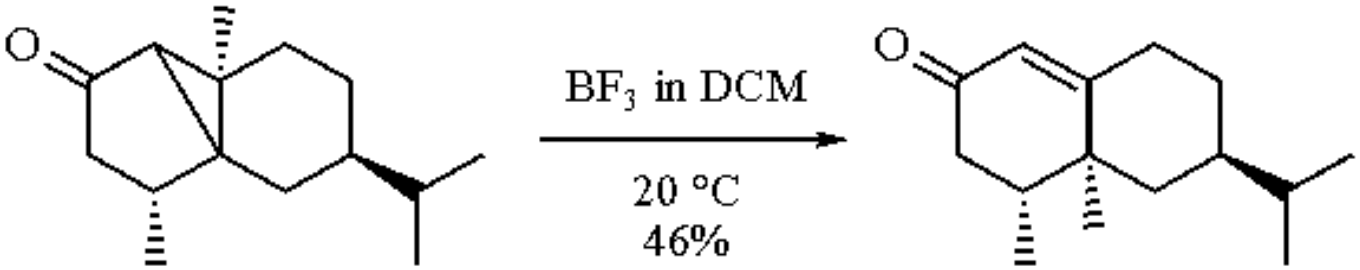

(15)

Diels-Alder Reactions.

Lewis acid-catalyzed Diels-Alder reactions are well known, and a number of examples have been studied using boron trifluoride. The regioselectivity of the reaction of unsymmetrical dienes with unsymmetrically substituted quinones can be directed in favor of either regioisomer depending on the catalyst used. This is exemplified in eq 16.[35] The regioselectivity has been explained on the basis that boron is capable of forming a tetracoordinate complex, whereas tin can complex via the more basic oxygen and the adjacent methoxy group. The analogous reaction using piperylene (penta-1,3-diene) shows, as expected, slightly improved regioselectivity. A study of diastereoselective Diels-Alder reactions using acrylate esters of 3,4-*O*-methylene-β-D-arabinoside has involved the use of a number of Lewis acids, including boron trifluoride.[36]

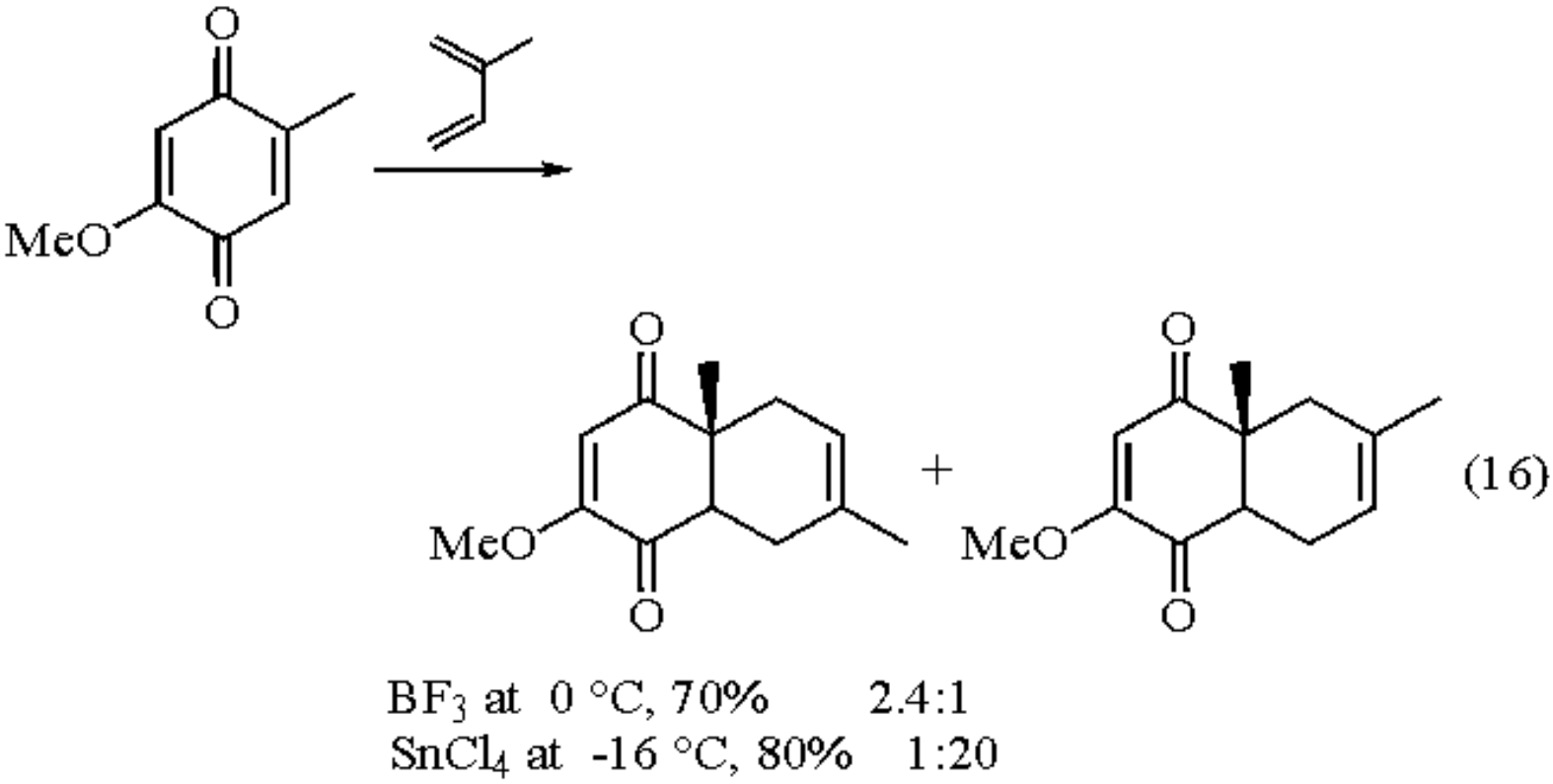

Miscellaneous Reactions.

The nitration of benzene derivatives using methyl nitrate in nitromethane in the presence of a Lewis acid leads to the formation of significant amounts of chlorinated products when using chlorine-containing Lewis acids. Side-chain nitration is also a problem sometimes. On the other hand, the nitrations of tetra- and pentamethylbenzenes proceed efficiently when boron trifluoride is used. Pentamethylbenzene affords the nitro derivative in an almost quantitative yield and durene gives mononitrodurene in 97% yield. When using a 3:1 excess of methyl nitrate and boron trifluoride, durene converts quantitatively into dinitrodurene.[37]

The reduction of alcohols using a trialkylsilane in the presence of a protic acid can be complicated by skeletal rearrangement and alkene formation as a result of carbenium ion formation. This problem is significantly reduced when using boron trifluoride as the acid (eq 17).[38] The preparation of peptide isosteres (eq 18) and related model compounds (eq 19) is achieved by the reductive elimination of γ-oxygenated-α,β-unsaturated carboxylates using boron trifluoride complexes of alkenylcopper reagents.[38]

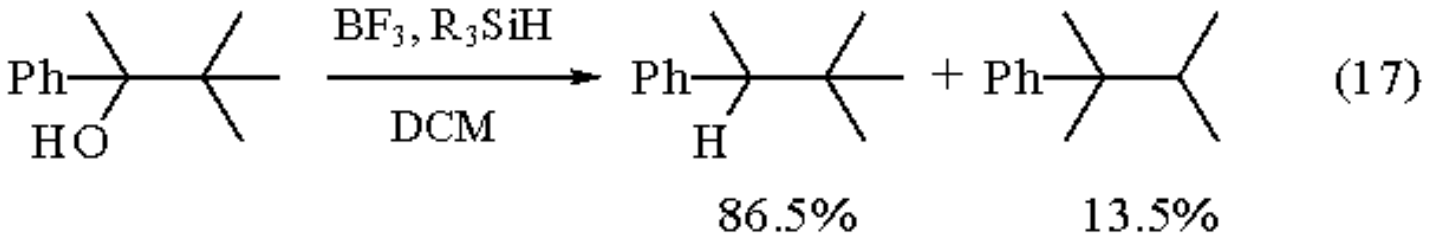

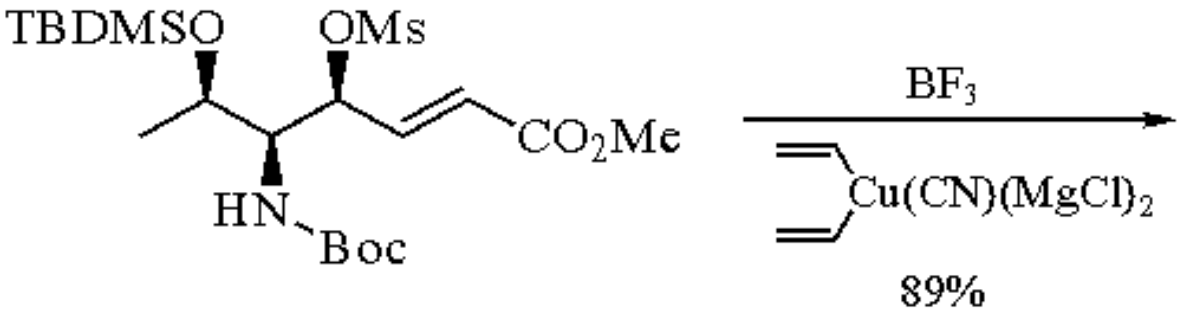

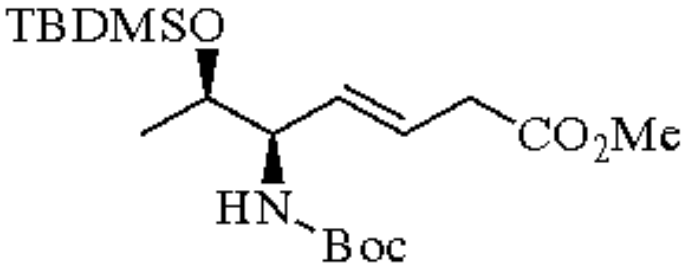

(18)

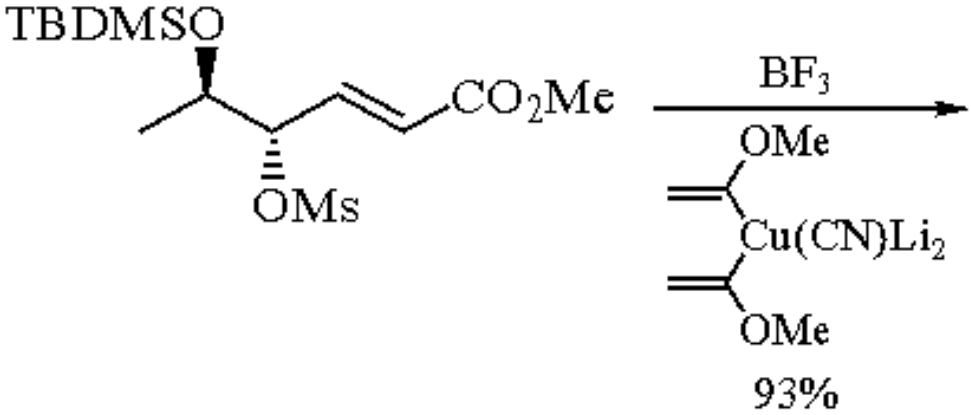

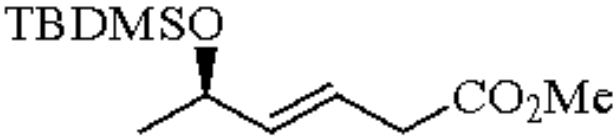

(19)

Finally, it is of interest to note that α-difluoroamino fluoroimines fragment to α-difluoroamino fluorides in dichloromethane in the presence of boron trifluoride (eq 20).[39]

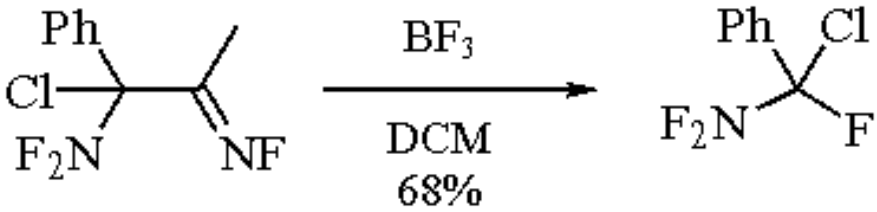

(20)

Related Reagents.

Boron Trifluoride-Acetic Acid; ***Boron Trifluoride-Dimethyl Sulfide***; ***Boron Trifluoride-Acetic Anhydride***; ***Boron***

Trifluoride Etherate; ***Hydrogen Peroxide-Boron Trifluoride***; ***Iodosylbenzene-Boron Trifluoride***; ***Lithium Dimethylcuprate-Boron Trifluoride***; ***Methylcopper-Boron Trifluoride Etherate***; ***Phenylcopper-Boron Trifluoride Etherate***; ***Tetrafluoroboric Acid***.

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Boron Triiodide[1]

BI_3

[13517-10-7] · BI_3 · Boron Triiodide · (MW 391.52)

(strong Lewis acid with labile, nucleophilic iodine atoms; cleaves ethers,[2] esters,[3] silanes,[4] halides,[5] and alcohols to alkyl iodides; reductively cleaves sulfonyl[6] and sulfinyl[7] groups to disulfides)

Physical Data: mp 50.5 °C; *d* 3.350 g cm^{-3}.

Solubility: sol hydrocarbons, CH_2Cl_2, $CHCl_3$, CCl_4, CS_2; reacts with oxygenated solvents.

Form Supplied in: volatile white solid (frequently has a pinkish color due to traces of I_2).

Preparative Methods: BI_3 of extremely high purity can be prepared in 25% yield by treating I_2 in heptane at 80 °C with KBH_4 (which has been recrystallized from H_2O).[8] Recrystallized $NaBH_4$ can also be used; if traces of chloride or bromide can be tolerated then $LiBH_4$ in hexane can be used.[9]

Purification: BI_3 has a vapor pressure similar to that of I_2 and can be purified by sublimation from Cu powder at 60 °C (in vacuo). Commercial material is usually contaminated with traces of other halides. While the presence of small amounts of BI_2Br and/or BI_2Cl does not usually interfere with most organic reactions, these impurities are not easily removed by sublimation or distillation.

Handling, Storage, and Precautions: use in a fume hood; reacts expositively with H_2O; traces of moisture result in the liberation of I_2 so the formation of any color indicates improper handling. BI_3 is also light sensitive; it photolyzes below 360 nm. It should be stored under an inert atmosphere in the dark.

Ether Cleavages.

All of the boron trihalides, except the fluorides, will cleave ethers with varying degrees of efficacy.[10] However, the nucleophilic character of iodine coupled with the strong Lewis acidity of boron makes boron triiodide the most potent of these reagents. It is a powerful reagent for the cleavage of C-O bonds in ethers, esters, and alcohols, resulting in the formation of alkyl iodides under mild conditions. Aryl alkyl ethers are cleaved to phenols (eq 1). Diaryl ethers are unreactive. BI_3 reacts at least an order of magnitude faster than ***Boron Tribromide*** in ether cleavages.[1] This is especially useful in the cleavage of the ethers of higher alkyl groups (eq 2).

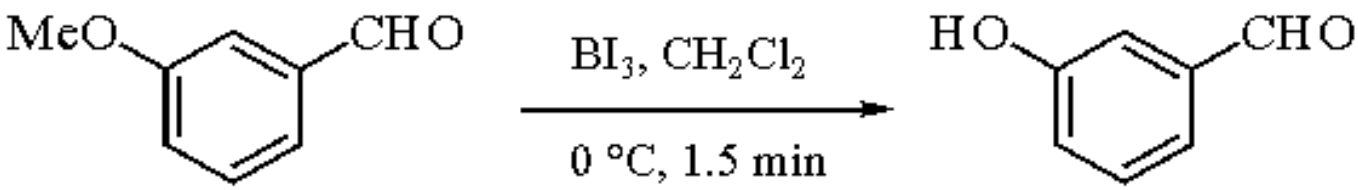

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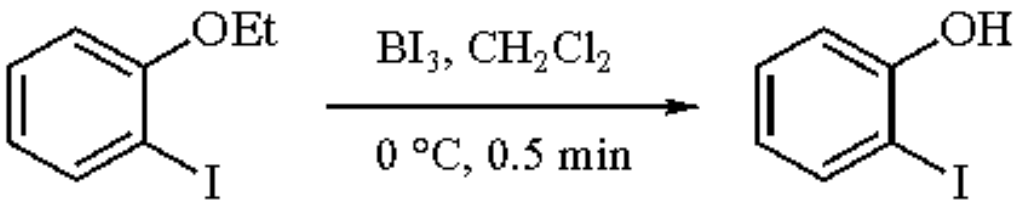

(2)

The initial products of ether cleavage are the alkyl halide and a borate ester, $(RO)_3B$. The borate esters are usually inert to further displacement but, because the iodide is more nucleophilic than the other halides, warming the borate esters (60-80 °C) in the presence of BI_3 will result in the complete conversion of all the alkyl residues to iodides (eq 3).[2]

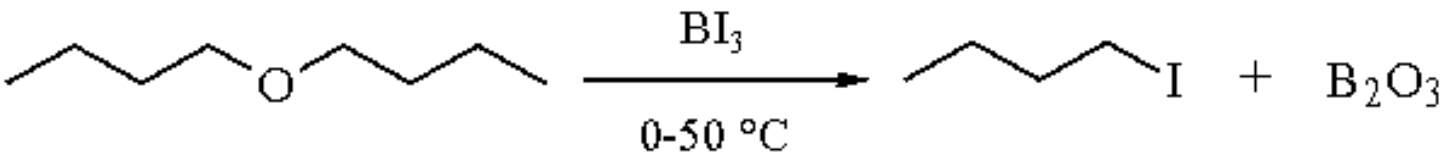

(3)

Other Cleavages.

Kabalka[3] and co-workers have shown that an attenuated form of BI_3, $BI_3.NEt_2Ph$, will cleave a variety of compounds containing C-O single bonds at elevated temperatures. Solutions of this reagent are prepared by reacting the commercially available amine-borane complex with I_2 in benzene at 80 °C for several hours. The reagent cleaves ethers,[11] esters,[3] and geminal diacetates.[11] Esters[3] are cleaved to an activated acyl intermediate RCOX which can be used to prepare acids, other esters, and amides (eq 4).

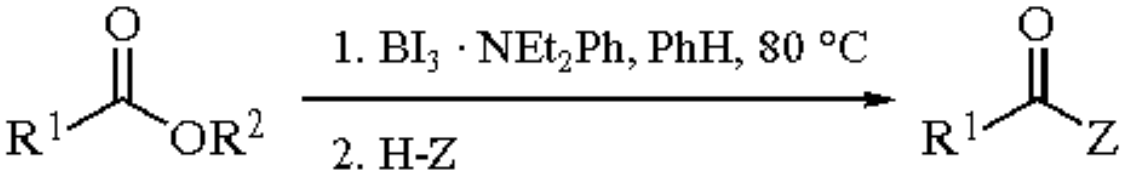

(4)

$R^1 = Ph,\ o\text{-}C_6H_4OH,\ o\text{-}C_6H_4Br,\ C_3H_7,\ \text{-}(CH_2)_2\text{-}CH{=}CH_2$

$R^2 = Me,\ Et,\ Bu,\ Bn$

$H\text{-}Z = H_2O,\ MeOH,\ EtOH,\ PhNH_2,\ PhCH_2NH_2$

Sulfinyl and sulfonyl compounds react with BI_3[6] and $BI_3.NEt_2Ph$[7] to afford disulfides (eq 5).

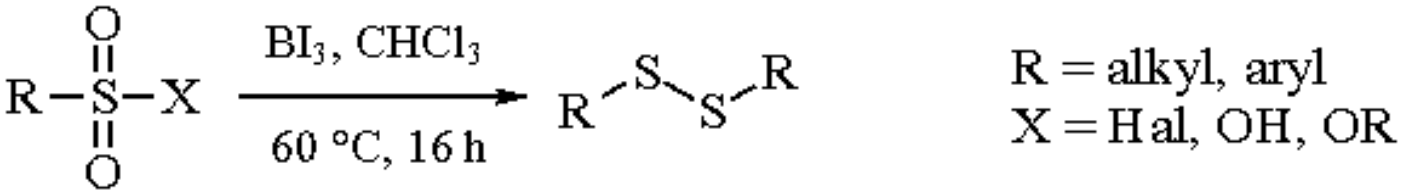

Sulfoxides are deoxygenated by $BI_3.NEt_2Ph$.[7] Sulfides are also cleaved by BI_3. Methionine reacts to yield a complex mixture of C-S bond cleavage products including homocysteic acid, homoserine, and homoserine lactone.[12]

Substitution Reactions.

As a powerful electrophile, BI_3 will effect aromatic and aliphatic substitution reactions on alkyl and aryl halides and silanes (eq 6).[4] Alkyl halides (R-Cl and R-Br) also undergo substitutions reactions in CH_2Cl_2 and CCl_4 solution, producing iodides without alkyl rearrangement. In CCl_4 the reaction is second order in alkyl halide.[5] At elevated temperatures the *ipso* substitution of aryl iodides occurs readily, resulting in borinic iodides eq 7).[13] The direct borylation of benzene is a photochemical process which most likely involves the formation of I&bdot; and I_2B&bdot; radicals (eq 8).[14]

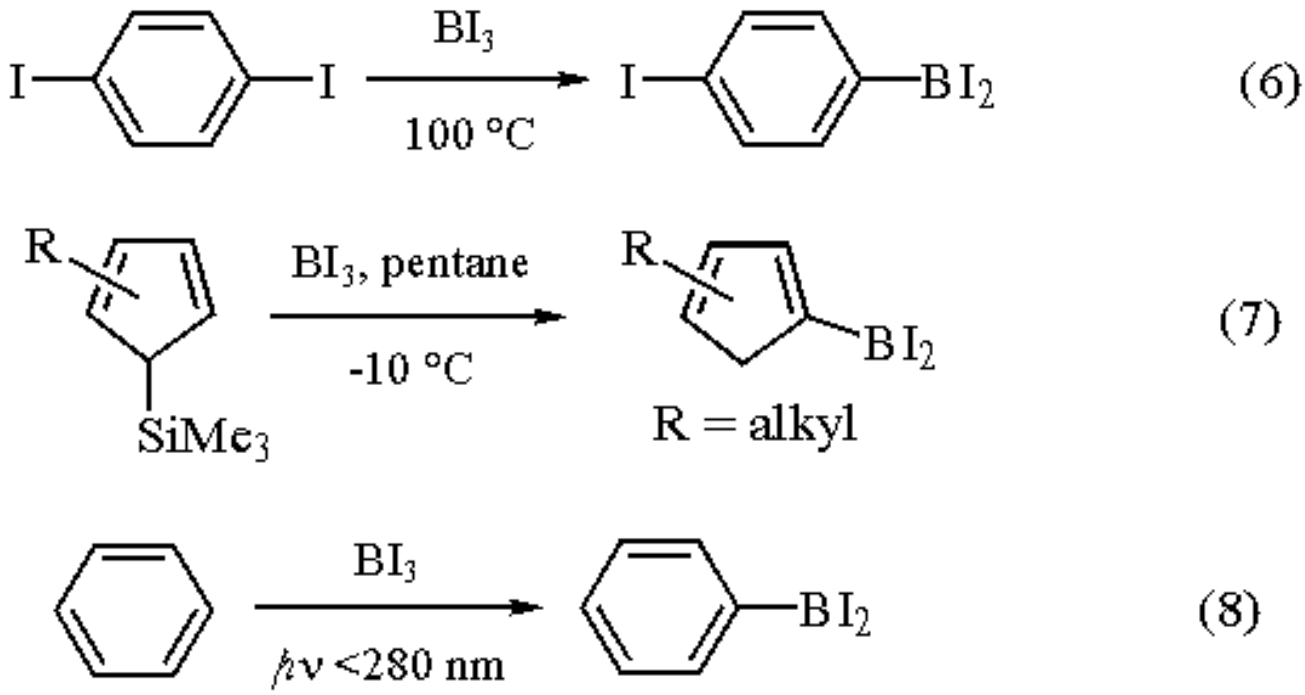

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Boron Tris(trifluoroacetate)[1]

$B(OCOCF_3)_3$

[350-70-9] · $C_6BF_9O_6$ · Boron Tris(trifluoroacetate) · (MW 349.86)

(mild Lewis acid)

Alternate Name: tris(trifluoroacetoxy)borane.

Physical Data: mp 88 °C (dec).

Solubility: decomposes in water exothermically; sol organic solvents.

Preparative Methods: obtained in quantitative yield by the interaction of BCl_3 or BBr_3 with trifluoroacetic acid.[2]

Handling, Storage, and Precautions: extremely corrosive to the eyes and skin. If swallowed causes severe internal irritation and damage. Toxic irritating vapor. All work must be carried out in an efficient fume hood.

Deprotection of the N-Terminus of Amino Acids and Peptides.

The major use of tris(trifluoroacetoxy)borane has been to remove protecting groups used during the synthesis of peptides and α-amino acids.[3] Although a number of boron-derived reagents, such as ***Boron Tribromide*** and ***Boron Triiodide***, are good reagents for the removal of the Z-group (benzyloxycarbonyl) from N-terminal residues in dichloromethane, the partial removal of ester groups has been reported. A further disadvantage is that dichloromethane is not a good solvent for long peptides. On the other hand, the hydroxy groups of serine or threonine and the thiol residue of cysteine are reported not to be attacked by the boron halides. The original communication indicated that a number of important functional groups were unaffected by tris(trifluoroacetoxy)borane.[3] The groups included methyl and ethyl esters, methyl ethers, and the amide bond. Benzyl esters were reported, however, to be deprotected. An example is shown in eq 1, in which it was pointed out that optical purity was maintained, but the presence of acid-sensitive groups precludes the use of this method.[4]

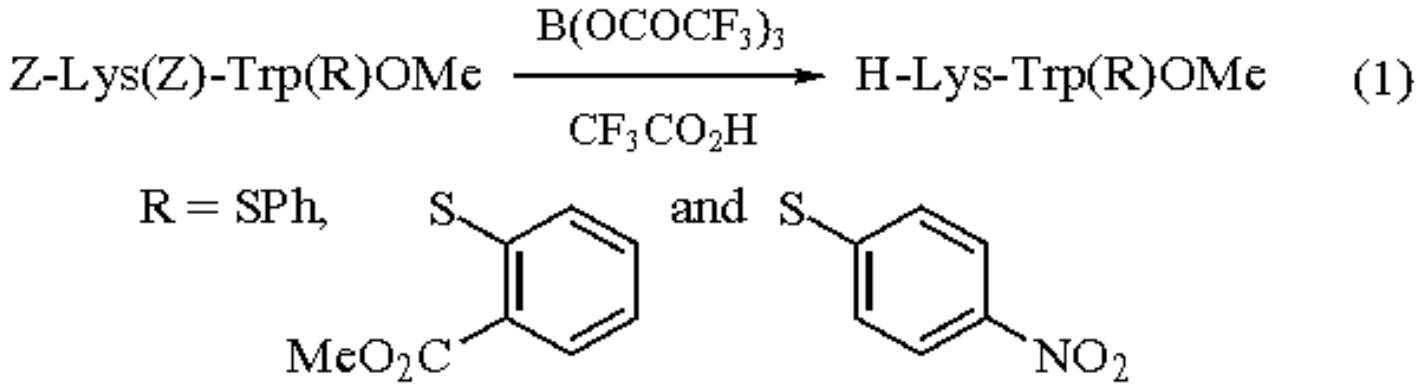

Since the first report, tris(trifluoroacetoxy)borane has been used in a number of peptide syntheses, for example the synthesis of the peptide fragment of the human myelin basic protein.[5] The method has been particularly useful in the final removal of protecting groups in those syntheses using the Merrifield technique.[6] The deprotection of side chains in peptides required in an investigation of human dihydrofolate reductase used the method successfully.[7] Protection with the Z-group and eventual deprotection has been used in structure elucidation, for example in the case of the peptide antibiotics herbicolin A and B.[8] In general, there have been few problems reported concerning the use of tris(trifluoroacetoxy)borane. However, although the deprotection shown in eq 2 was achieved very efficiently, the analog in which the unnatural tryptophan was present gave rise to a complex mixture.[9]

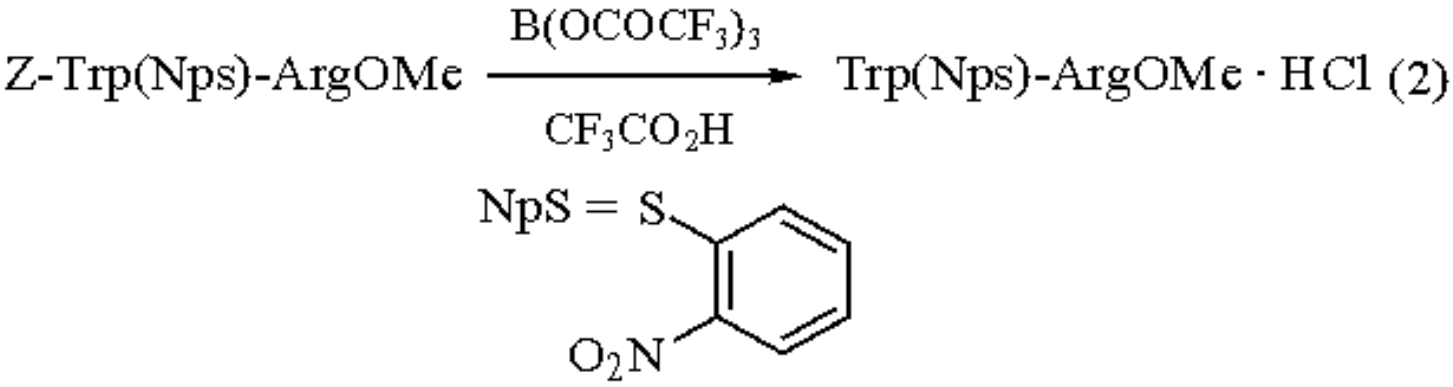

A synthesis of new inhibitors of enkephalin metabolism with improved protection from in vivo enzymic degradation has involved the modification of the C-terminal amino acid by the incorporation of a β-amino acid residue.[10] For the *N*-methyl derivative shown in eq 3, the *t*-butyl ester was removed using tris(trifluoroacetoxy)borane with simultaneous deprotection of the hydroxyamino group.

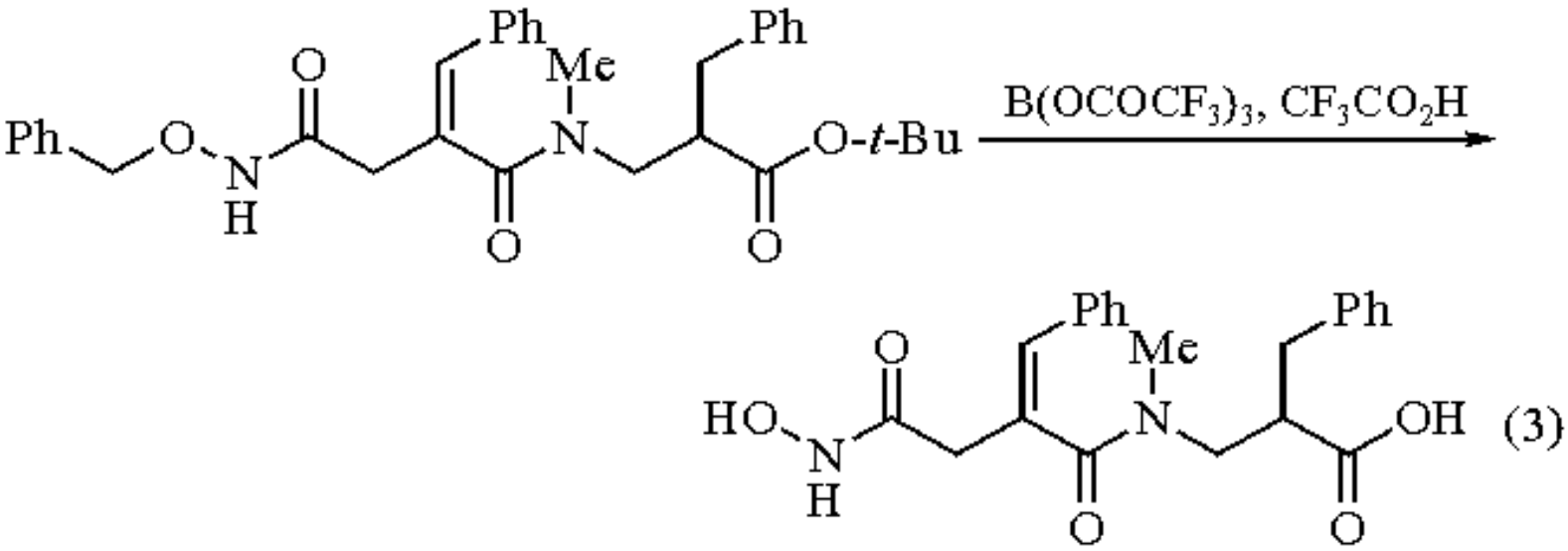

In the total synthesis of the antitumor antibiotic acivicin, an α-amino acid, the protective group removal was effected in 56% yield by using ***Boron Trichloride***.[11a] However, when tris(trifluoroacetoxy)borane was used to remove the Z-group and to cleave the oxazolidinone ring, the yield in the final step was improved to 89% (eq 4).[11b]

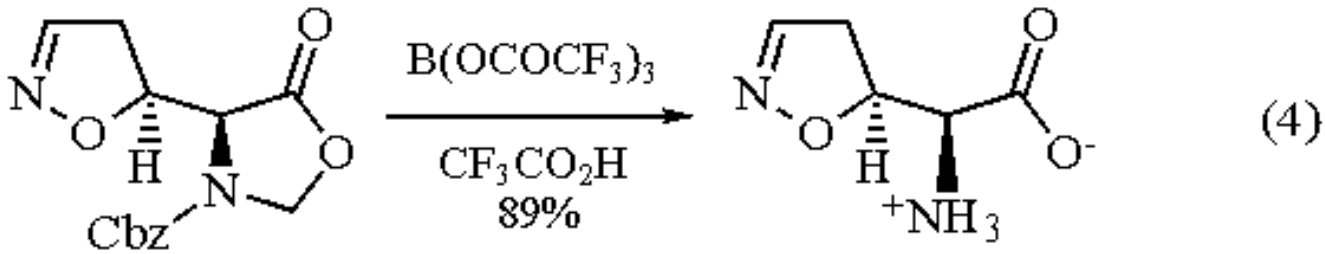

Friedel-Crafts Reactions.

The other use of tris(trifluoroacetoxy)borane has been in Friedel-Crafts reactions.[12] In principle the reagent can function as an acylating agent, but only in the case of a reaction using mesitylene (eq 5) did the reaction stop at that stage and afford 2,4,6-trimethyltrifluoroacetophenone (**1**). It is presumed that this effect is related to a steric problem. With benzene a low yield of 1,1,1-trifluoro-2,2,2-triphenylethane was obtained, but with a more nucleophilic aromatic compound such as anisole, a 90% yield of 1,1,1-trifluoro-2,2,2-tris(*p*-methoxyphenyl)ethane (**2**) was obtained (eq 6). With even more nucleophilic substrates, such as 1,3-dimethoxybenzene and phenol, the 1,1-diaryl-2,2,2-trifluoroethanol derivative was obtained. In the example shown, the product (**3**) was isolated in 82% yield (eq 6).

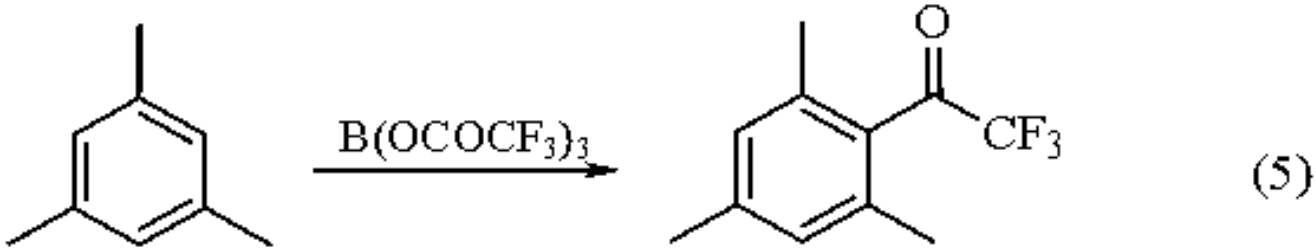

(1)

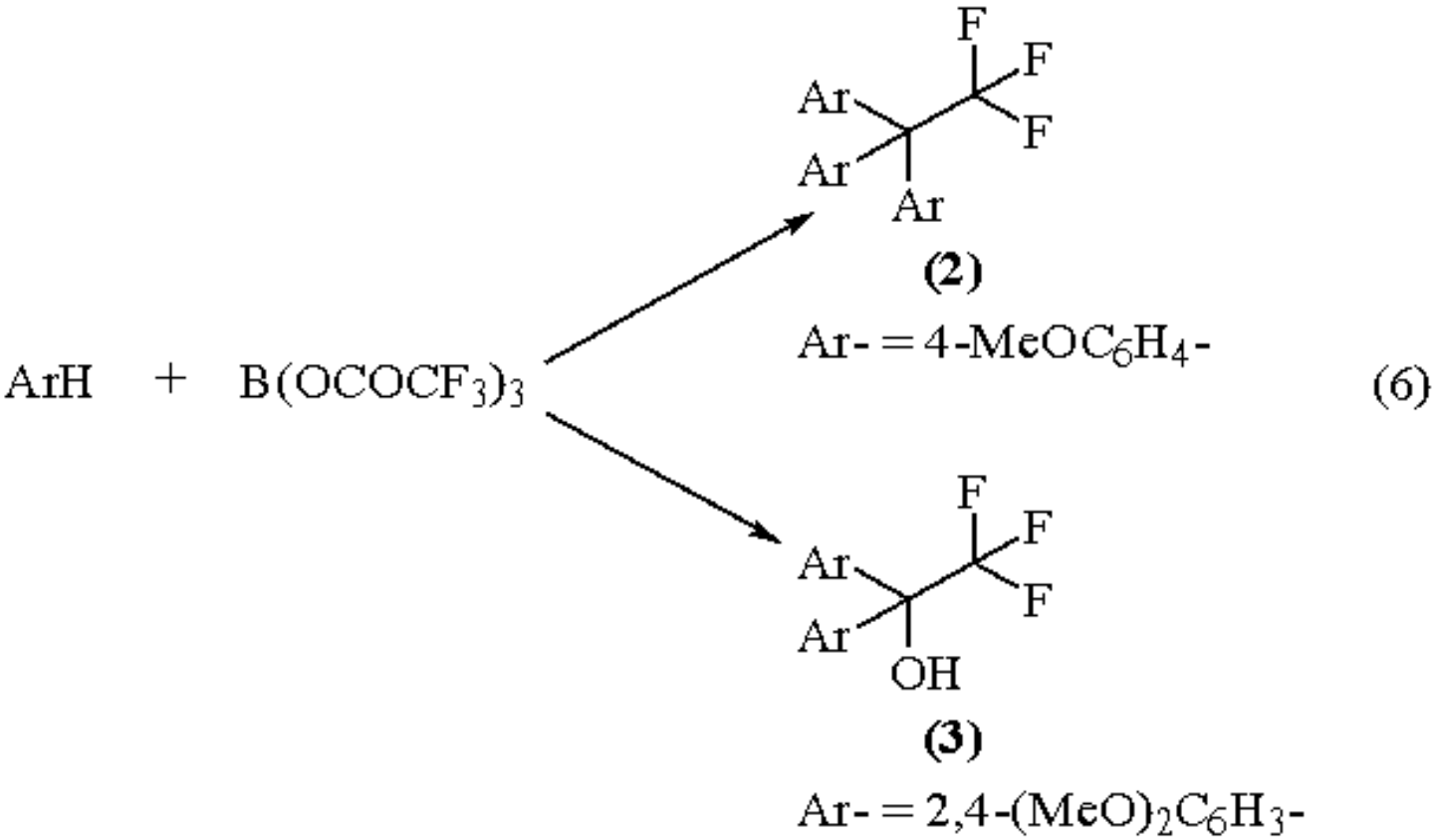

Related Reagents.

Boron Trifluoride-Acetic Anhydride.

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Boron Trisulfide

B_2S_3

[12007-33-9] · B_2S_3 · Boron Trisulfide · (MW 117.80)

(sulfuration agent of carbonyl to thiocarbonyl group;[1] sulfuration agent of phosphine oxide to phosphine sulfide;[8] dehydrogenating agent;[11] synthetic reagent for boroles[14])

Physical Data: monoclinic colorless crystals; mp 563 °C (dec); *d* 1.55 g cm^{-3}.

Solubility: sol ethanol, but decomposes.

Form Supplied in: white solid.

Handling, Storage, and Precautions: the dry solid is very flammable under air and immediately reacts with water to give boric acid and hydrogen sulfide.

Sulfuration Agent of Carbonyl to Thiocarbonyl Functional Group.

Boron trisulfide is used as a sulfuration agent in synthetic chemistry; it is especially efficient for the conversion of carbonyl to thiocarbonyl. 1,3,4,6-Tetrathiapentalene-2,5-dione is sulfurized with boron trisulfide in toluene under reflux to give a mixed carbonyl-thiocarbonyl compound. When a solid mixture of 1,3,4,6-tetrathiapentalene-2,5-dione and boron trisulfide is heated at 100 °C for long time, 1,3,4,6-tetrathia-2,5-dithione is formed as a yellow solid (eq 1).[1]

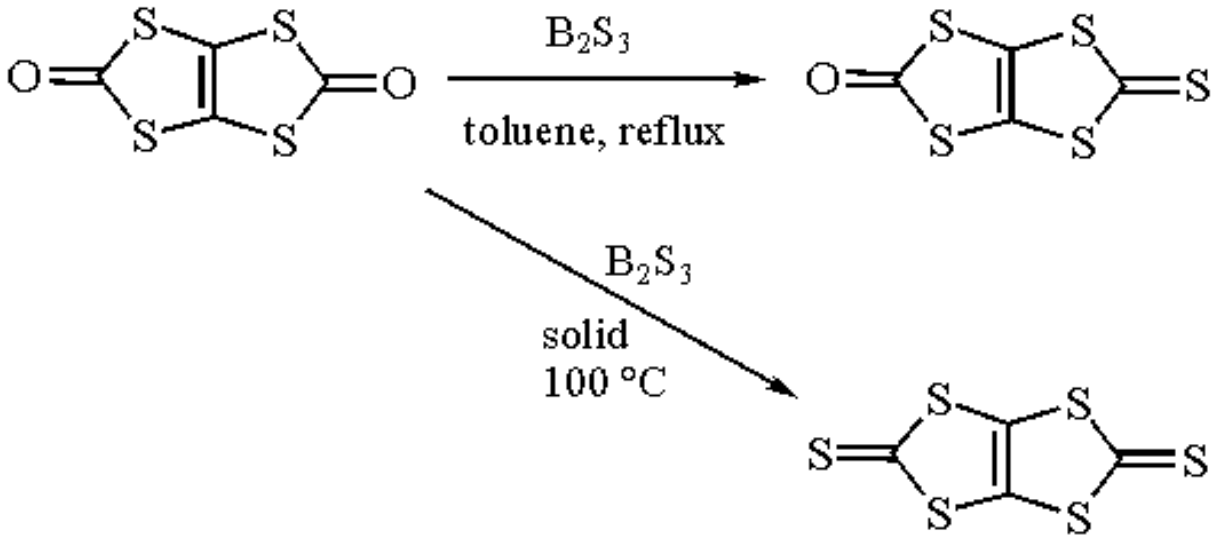

(1)

Boron trisulfide has advantages over ***Phosphorus(V) Sulfide*** for converting non-enolizable ketones such as 2-pyrones and 4-pyrones to the corresponding thiones (eq 2).[2] Boron trisulfide is very active and often effective at rt. 4-Selenapyranthione is formed from 4-selenapyranone by treating with boron trisulfide in chloroform (eq 3).[3]

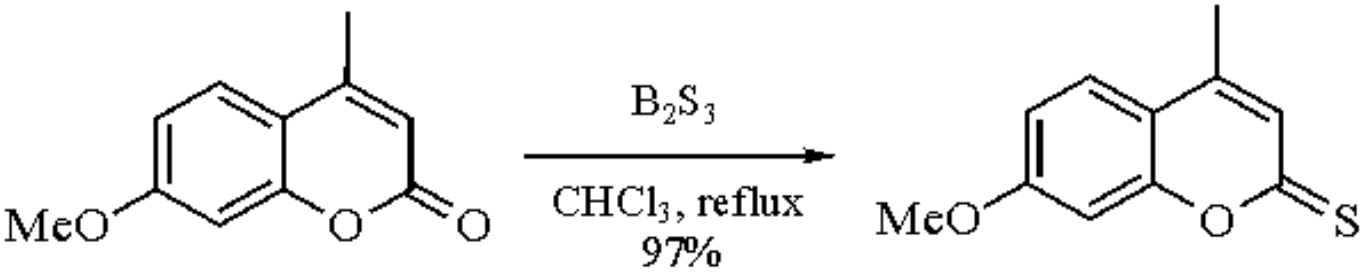

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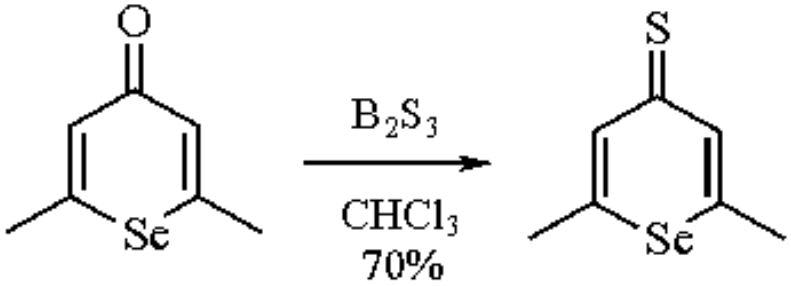

(3)

The reaction of boron trisulfide with aromatic aldehydes and aliphatic aldehydes gives a good yield of the corresponding thioaldehyde trimer via the monomer (eq 4).[4]

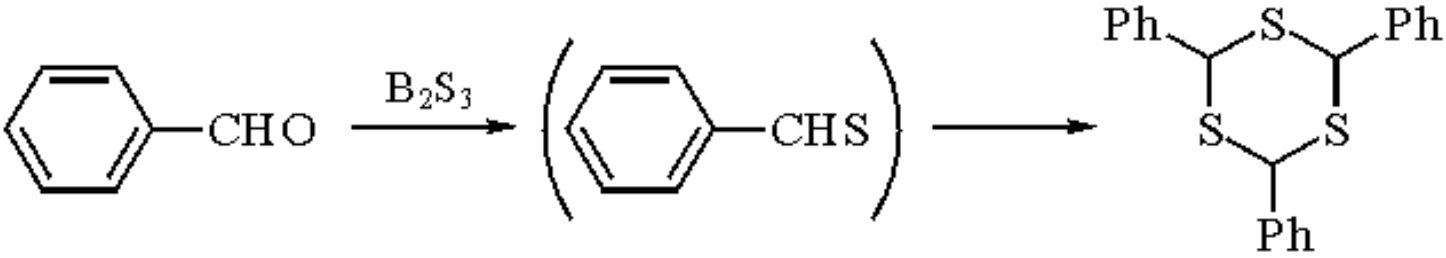

(4)

Steliou has reported that the treatment with ***Bis(tricyclohexyltin) Sulfide-Boron Trichloride*** converts carbonyls into the thiocarbonyl analogs in high yield. The intermediate formation of boron trisulfide has been postulated. This sulfurating method is efficient even with highly hindered ketones inert to direct sulfuration (eq 5).[5] The yields of the thiocarbonyl compounds obtained are shown in Table 1.

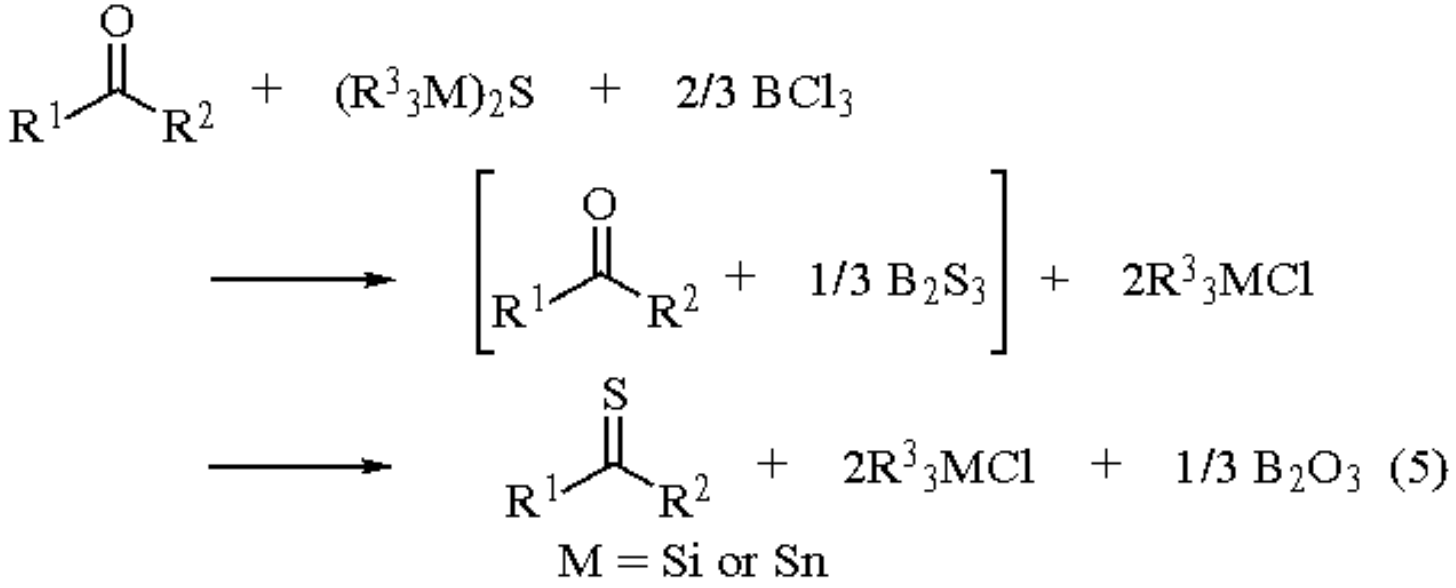

Table 1 Sulfuration of Various Carbonyl Compounds using Bis(tricyclohexyltin) Sulfide

Carbonyl compound	Yield (%)	Carbonyl compound	Yield (%)
Trimethylacetaldehyde	65	2-Adamantanone	72
Benzaldehyde	85	(±)-Camphor	95
p-Anisaldehyde	95	(-)-Fenchone	90
p-Nitobenzaldehyde	83	Coumarin	94
4,4¢Bis(dimethylamino) benzophenone	90	Pentacyclo[6.2.1.$0^{2,7}$.$0^{5,9}$]-undecane-3,6-dione	84
Di-*t*-butyl ketone	65	1,4-Diphenyl-3-methyl-2-azetidinone	90
e-Caprolactam	92		

Some orthoesters are also conveniently sulfurized with boron trisulfide to give the corresponding thioesters (eq 6).[6]

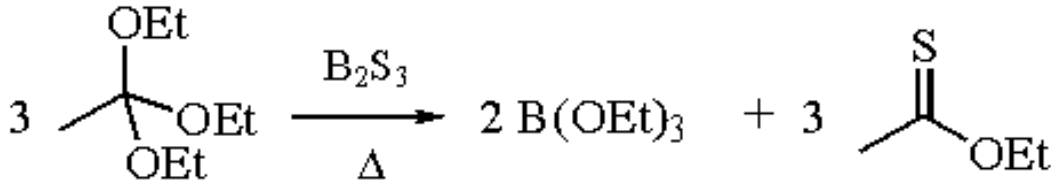

(6)

When methyl benzoate and boron trisulfide are refluxed under nitrogen for 28 h, the sulfurized cyclization product 2,3,4,5-tetraphenylthiophene is obtained (eq 7).[4,7] Boron trisulfide reacts with acyl complexes $(C_5H_5)Fe(CO)_2COR$ to give dithiocarboxylate complexes $(C_5H_5)Fe(CO)_2SCSR$ and $(C_5H_5)Fe(CO)SSCR$. Generally, the reactions with boron trisulfide are faster than those with phosphorus pentasulfide (eq 8).[8]

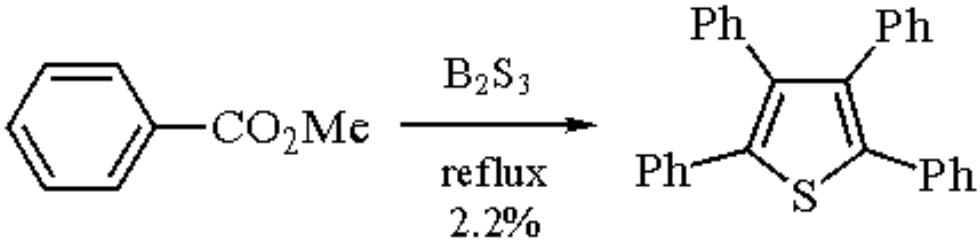

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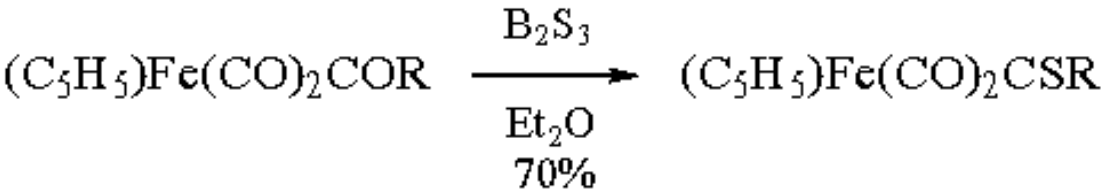

(8)

Sulfuration Agent for Other Compounds.

Boron trisulfide transforms tertiary phosphine oxides into the corresponding phosphine sulfides with net retention of configuration at phosphorus (eq 9).[9] Sulfoxides are reduced to give sulfides, presumably through an intermediate sulfothioxide (eq 10).[10]

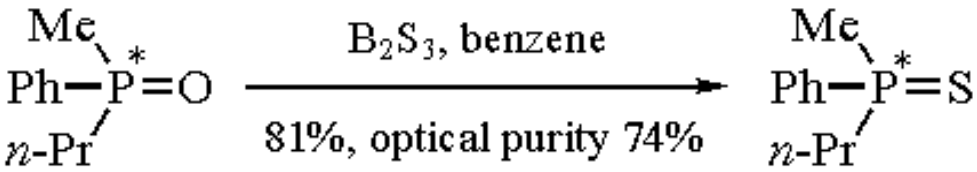

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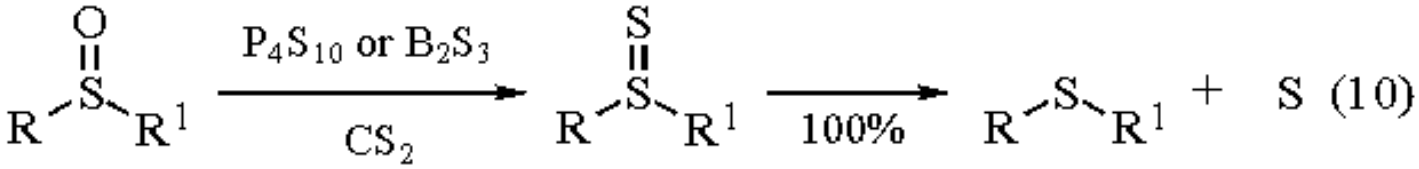

R	R¹	R	R¹
Me	Me	Ph	Pr
Me	Bn	Ph	Bn
Bn	Bn	Ph	Ph
Me	Ph	*p*-Tol	*p*-Tol

Dehydrogenating Agent.

Boron trisulfide behaves as a dehydrogenating agent with organic molecules containing labile hydrogens such as alcohols[11] and thiols[12] to give the corresponding orthoester and orthothioester. Moreover, several nitrogen bases, e.g. aniline and *N*,*N*-dimethylhydrazine, react with boron trisulfide under nitrogen in the dark to form tris(phenylamino)boron and tris(*N*,*N*-dimethylhydrazo)boron respectively (eq 11).[13] Catechol also reacts with boron trisulfide to give 2,2´-*o*-phenylenedioxybis(1,3,2-benzodioxaborole), while only the hydroxy function of salicylic acid reacts to give a quantitative yield of tris(*o*-carboxylphenoxy)borane. Phthalic acid, succinic acid, and maleic acid are not sulfinated by boron trisulfide (eq 12).[14]

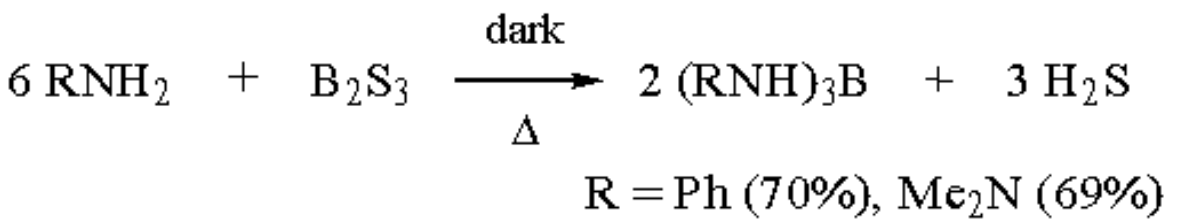

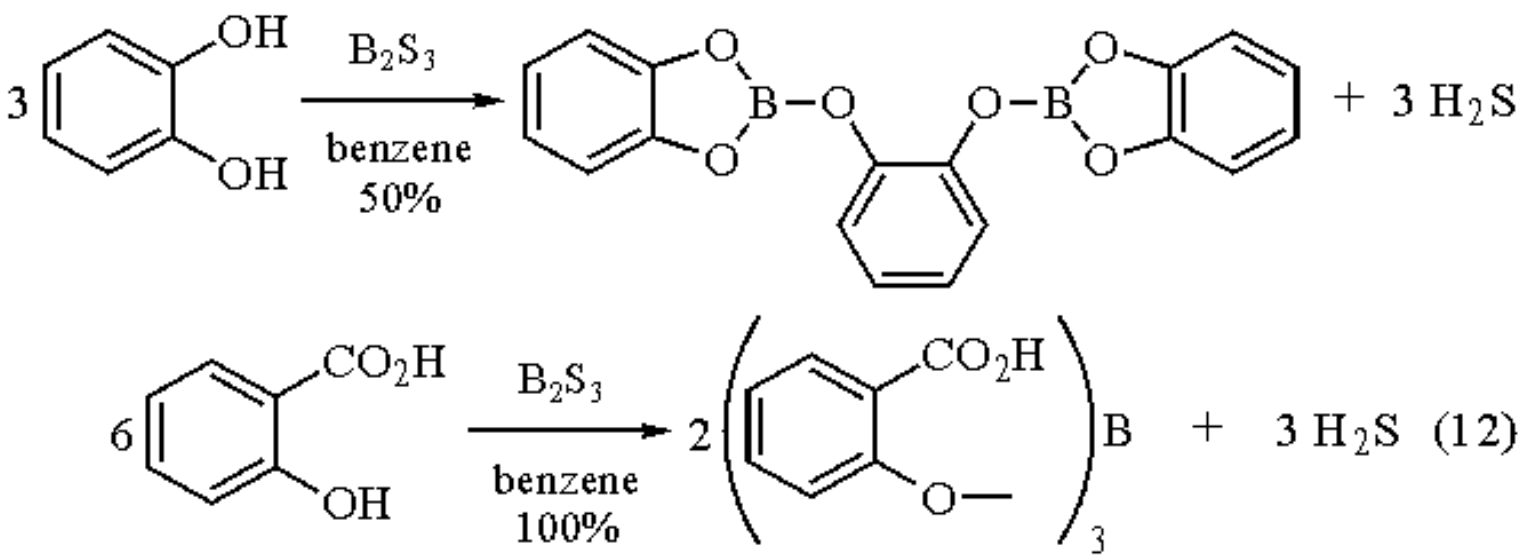

Related Reagents.

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide; ***Bis(tricyclohexyltin) Sulfide-Boron Trichloride***; ***Bis(trimethylsilyl) Sulfide***.

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Bromine[1]

[7726-95-6] · Br_2 · Bromine · (MW 159.81)

(powerful brominating and oxidizing agent; can initiate/participate in ring cleavage and rearrangement)

Physical Data: mp -7 °C; bp 59 °C; *d* 3.12 g cm^{-3}.

Solubility: sol H_2O, acetic acid, alcohol, ether, chloroform, carbon tetrachloride, carbon disulfide, hydrocarbon solvents (pentane, petroleum ether).

Form Supplied in: dark, red-brown, volatile liquid; also available as a 1 M solution in carbon tetrachloride.

Analysis of Reagent Purity: by iodometric titration.[79]

Purification: several methods have been described.[80]

Handling, Storage, and Precautions: bromine is an extremely corrosive and toxic reagent in both liquid and vapor form. As a liquid, it produces painful burns and blisters when spilled on the skin. Such burns should be flushed with water and neutralized with a 10% solution of sodium thiosulfate in water. Medical attention should be sought immediately. Protective clothing is therefore a must, including laboratory coat and apron, protective gloves, and a full-face respirator equipped with a NIOSH-approved organic vapor-acid gas canister. Bromine should be stored in a cool, dry area. It is incompatible with combustibles, liquid ammonia, alkali hydroxides, metals (including aluminum, mercury, magnesium, and titanium), and some types of rubber and plastic.[2] Use in a fume hood.

Halogenations.

Bromine is a very powerful brominating agent that has found utility in a variety of systems. While the bromination of alkanes is usually not a viable synthetic method,[3] alkylbenzenes can be brominated at the benzylic position under radical conditions (eq 1).[4] ***N-Bromosuccinimide*** (NBS) can also be used for this transformation.

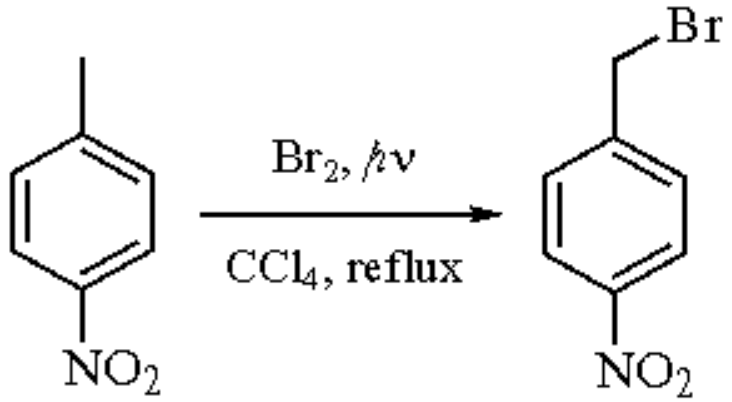

(1)

Electrophilic aromatic substitution occurs in the presence of Lewis acids to provide brominated aromatics.[5] Monobromination usually occurs due to the deactivating nature of the bromine. However, highly reactive aromatics, such as phenols, anilines, and polyalkylbenzenes, are frequently polybrominated, even in the absence of catalysts.

Bromine has been used in the bromination of heterocycles. However, the unique reactivity patterns of each heterocyclic ring system create a discussion beyond the scope of this review. The reader is directed to reviews on the subject.[1a,6]

The addition of bromine to alkenes[7] proceeds with formation of the cyclic bromonium ion (**1**), which can then be intercepted by an anionic species (Y^-), to give the product derived from *anti* addition (eq 2). In the case of bromine itself, this gives rise to *trans* vicinal dibromides (eq 2; Y = Br). Variations from ideality are not uncommon due to weakened, unsymmetrical bridging in the bromonium ion (eq 3),[8] transannular interactions (eq 4),[9] and substrates susceptible to rearrangements. Brominations in the presence of crown ethers[10] and zeolites[11] have been investigated to improve selectivity. Conjugated dienes give predominantly 1,4-addition, while alkynes are less susceptible to electrophilic attack.[12]

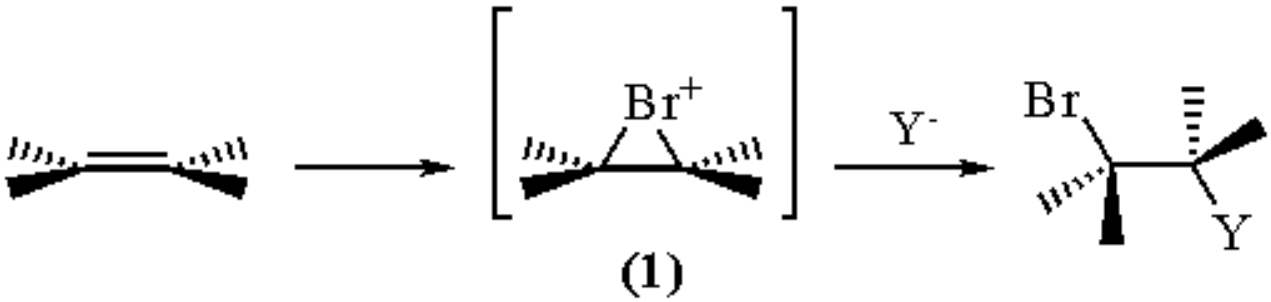

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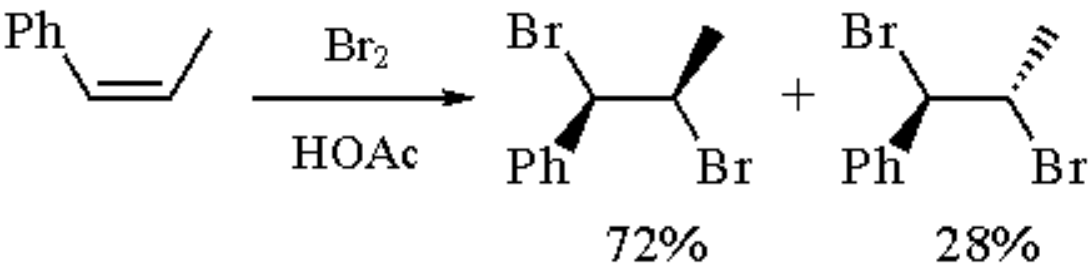

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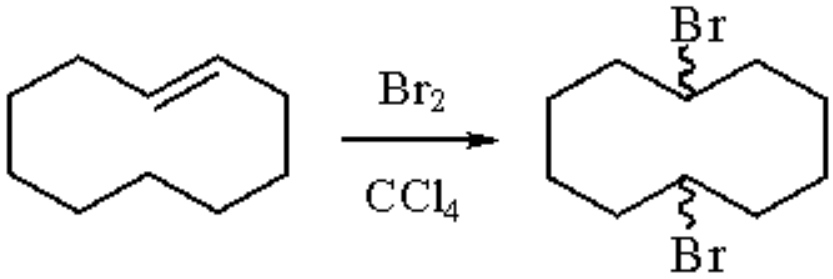

(4)

The addition of bromine to alkenes has been used as the first step in the oxidation of alkenes to 1,3-butadienes (eqs 5 and 6).[13,14] Alkenes can also be protected[15] or purified[16] by bromination and subsequent regeneration of the double bond.

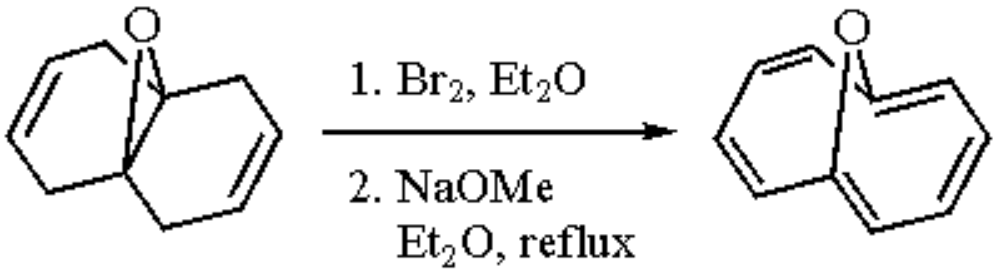

(5)

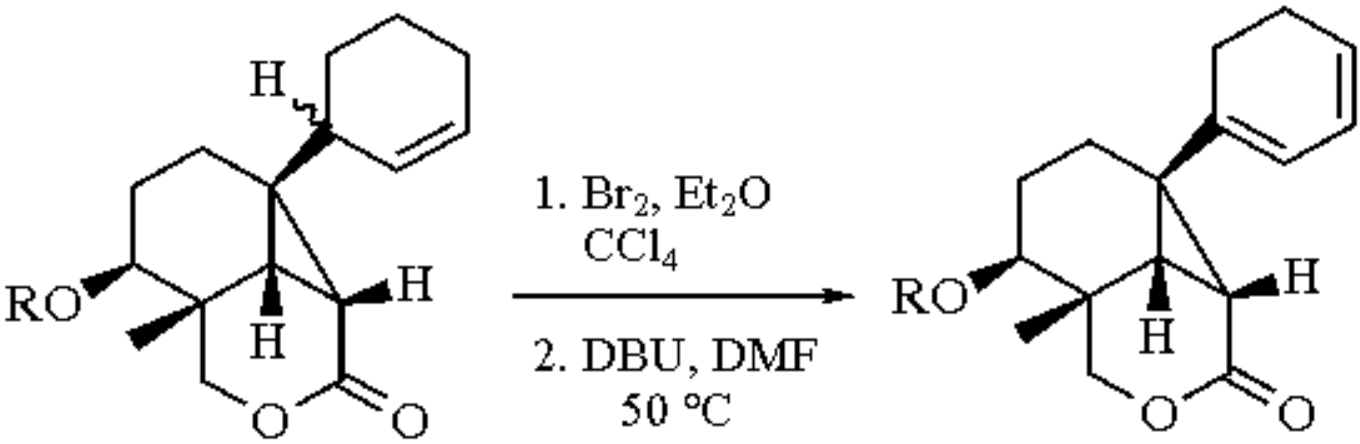

(6)

Alkenes bearing an electron-withdrawing group at one terminus are frequently converted to the α-bromo analogs via a bromination/dehydrobromination sequence (eqs 7 and 8).[17,18]

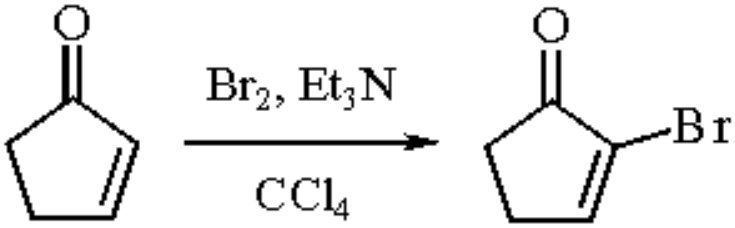

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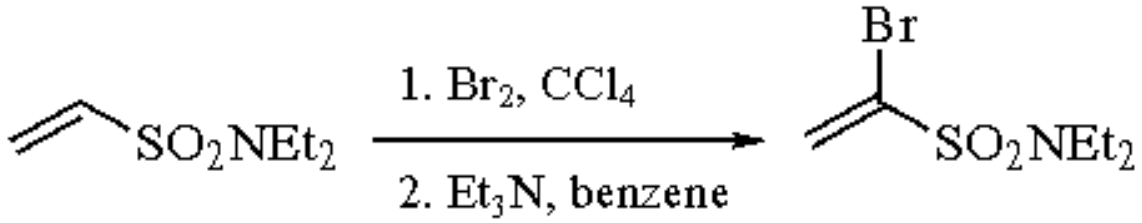

(8)

Cyclic bromonium ions (**1**) can be opened by a variety of other nucleophiles. Thus bromination of alkenes in aqueous systems can lead to bromohydrins. However, NBS has been shown to be superior to bromine for this transformation, presumably due to the minimization of competing bromide ion in the reaction mixture.[19] Alcohols react to give vicinal bromo ethers, in both inter- and intramolecular fashion (eq 9).[20]

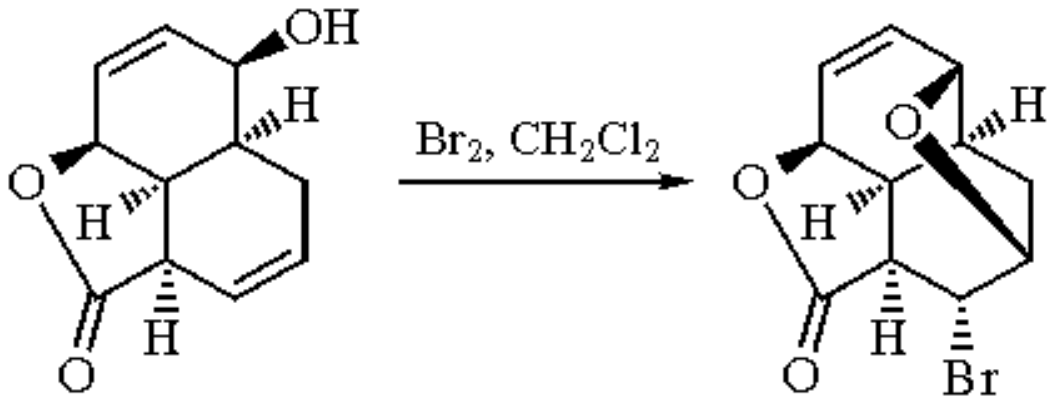

(9)

Bromolactonization of alkenic acids has been the subject of extensive investigation.[21] Cyclizations can be performed on the carboxylic acid salts as well as the free acids. Thallium(I) salts have proven to be especially efficacious.[21b,22] Treatment of the mercury(II) salts with bromine proceeds via a radical mechanism and provides the expected products in substrates where normal bromolactonization conditions lead to rearrangement (eq 10).[23] Other sources of electrophilic bromine can also give different products (eq 11).[21b]

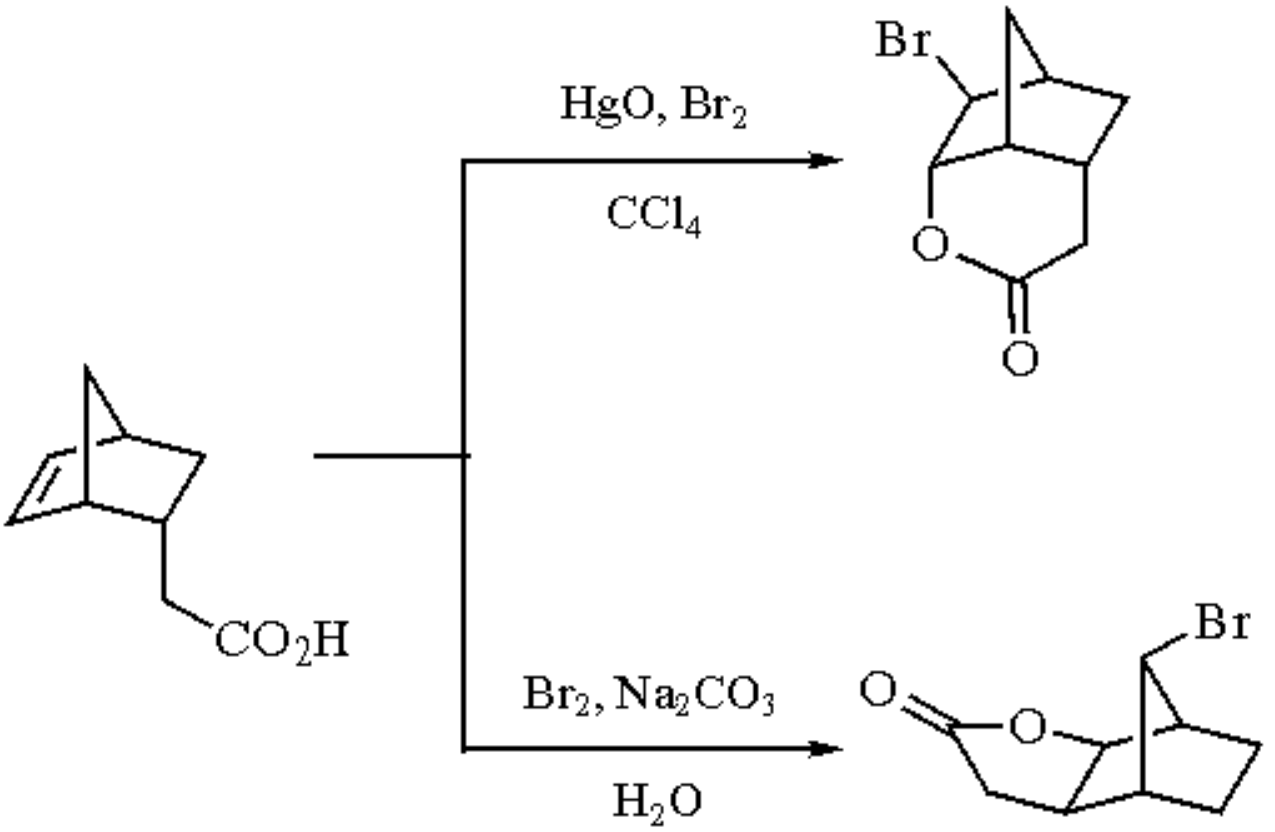

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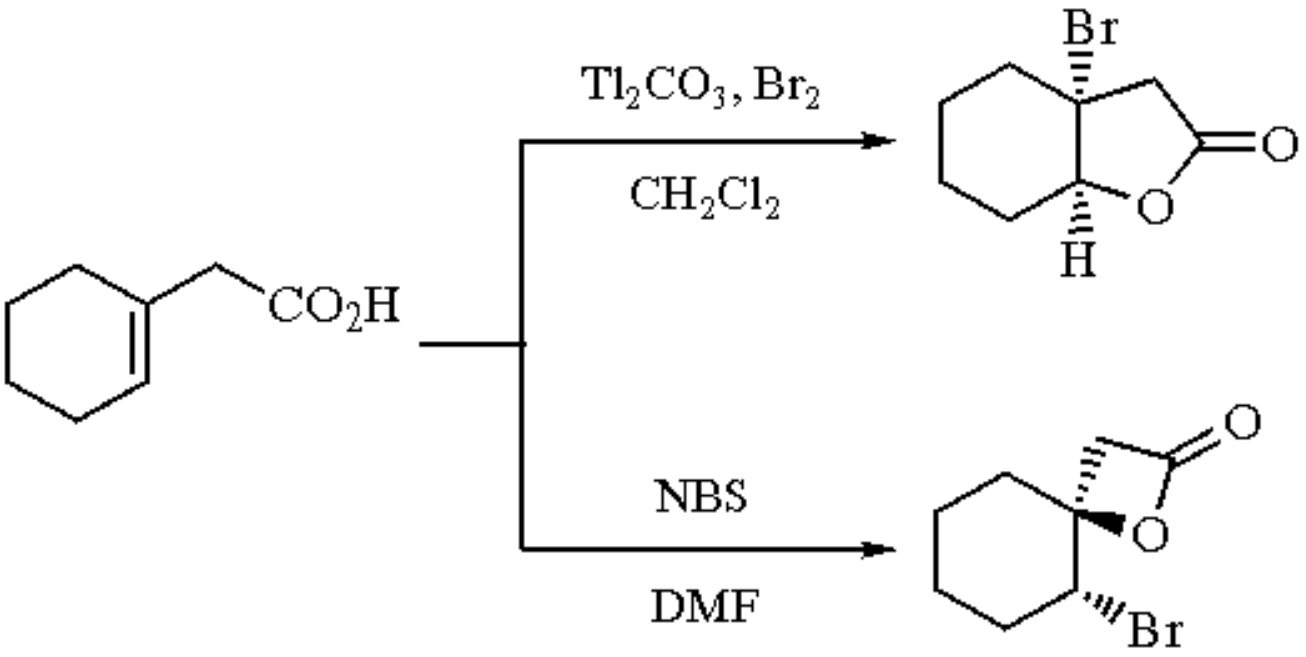

(11)

The enol lactonization of alkynic acids can be performed to give either the (*E*)- or (*Z*)-bromo enol isomers depending on reaction conditions (eq 12).[24]

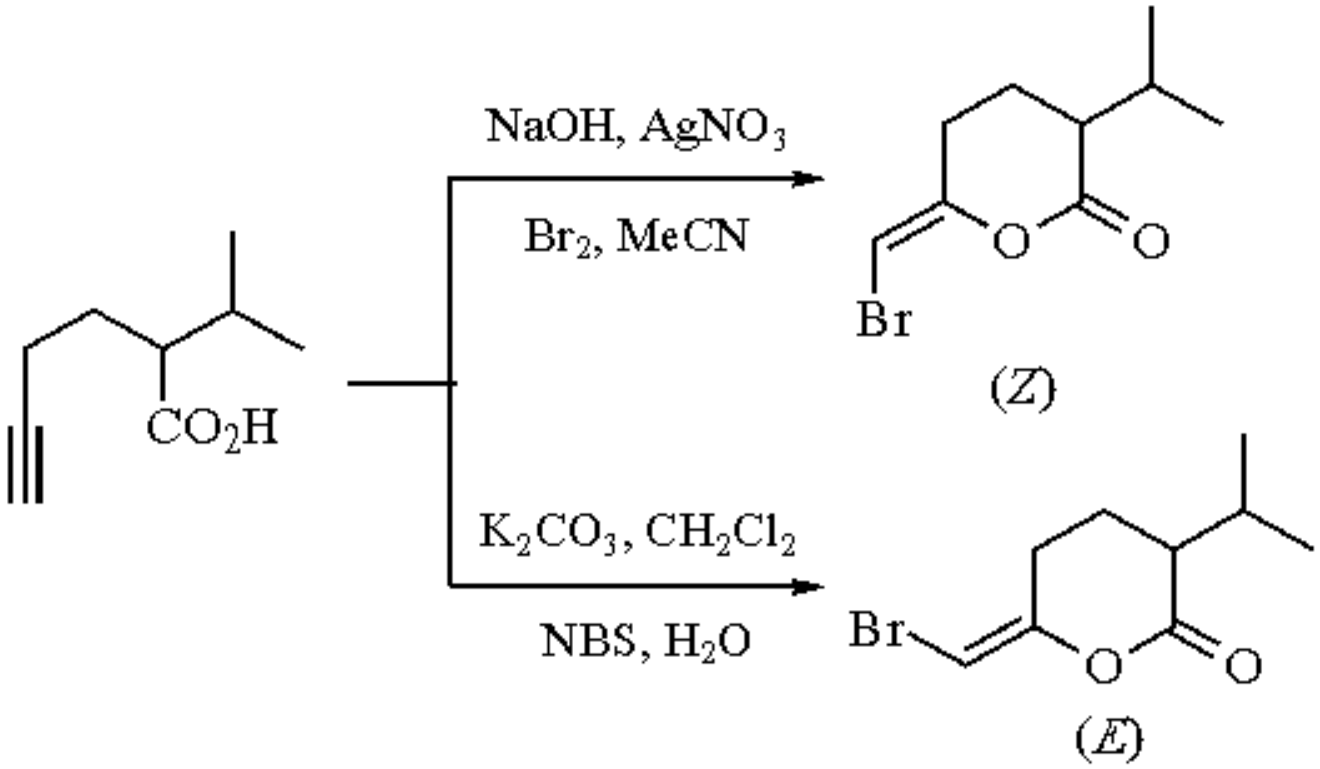

(12)

Alkenic amides cyclize under standard conditions to form lactones rather than lactams.[25] Bromolactamization can be achieved, however, by introduction of substituents on the amide nitrogen that serve to lower its pK_a (eqs 13 and 14).[26,27]

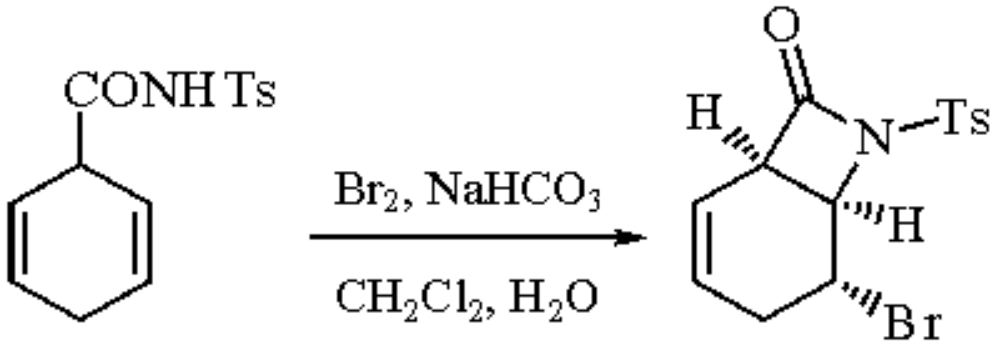

(13)

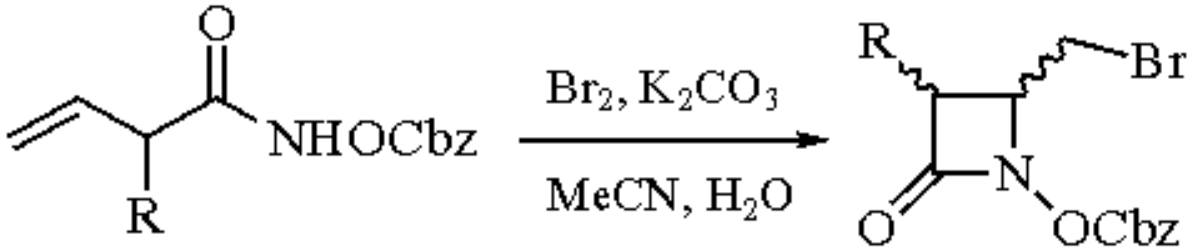

(14)

R = Me, *cis*:*trans* = 23:77
R = CbzNH, *cis*:*trans* = 70:30

Electron-rich alkenes, such as enol ethers[28] and enamines,[29] can be brominated to furnish the β-bromo compounds (eq 15).

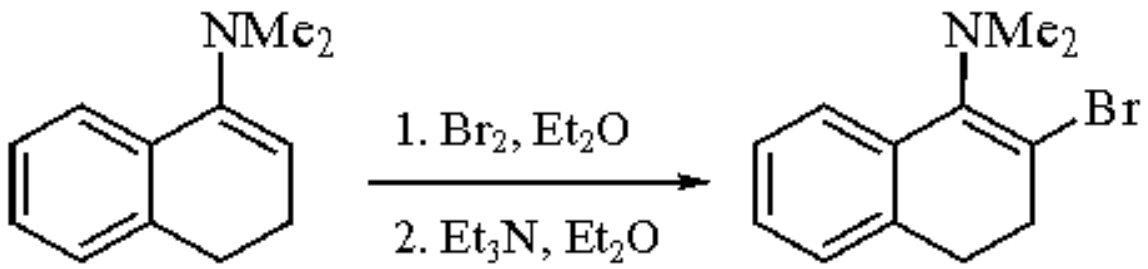

(15)

Bromine has been used for brominations α to carbonyl groups.[30] Carboxylic acids are brominated in the presence of phosphorus or phosphorus trihalides in the classical Hell-Volhard-Zelinski reaction (eq 16).[31] Variations on this include brominations in thionyl chloride[32] and in polyphosphoric acid.[33] The less reactive carboxylic esters are frequently converted to the acid halide, α-brominated, and subsequently re-esterified in one pot.[34,35]

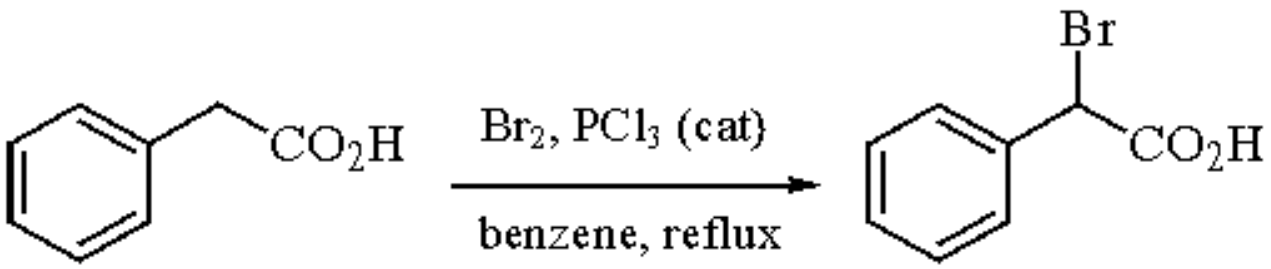

(16)

The bromination of ketones is believed to occur via acid-catalyzed enolization, followed by electrophilic attack on the enol form.[30] Unsymmetrical ketones can give rise to mixtures of bromo ketones due to mixtures of enols, and several approaches to overcome this shortcoming have been reported. Radical bromination in the presence of epoxides (as acid scavengers) allows for substitution at the more highly substituted position (eq 17).[36] Silyl enol ethers of aldehydes and ketones react with bromine (or NBS) to give the α-brominated carbonyl compounds (eq 18).[37] This, combined with the ability to regiospecifically prepare silyl enol ethers (kinetic vs. thermodynamic), makes for an extremely useful technique for the preparation of α-bromo carbonyl compounds.

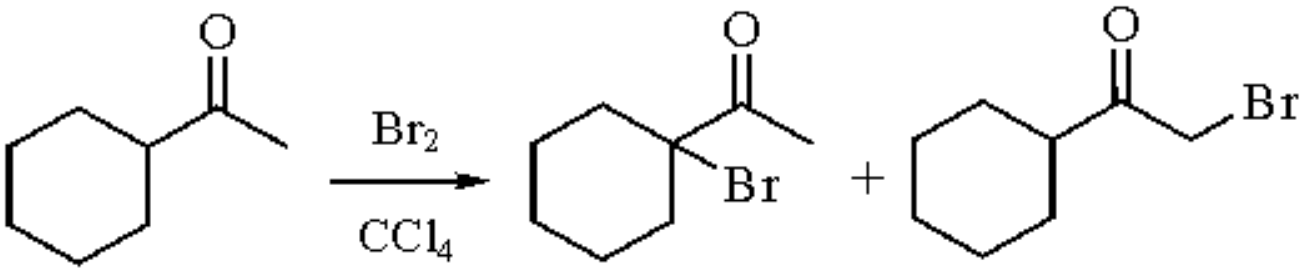

(17)

hν, epoxide	100: 0
dark, no epoxide	60:40

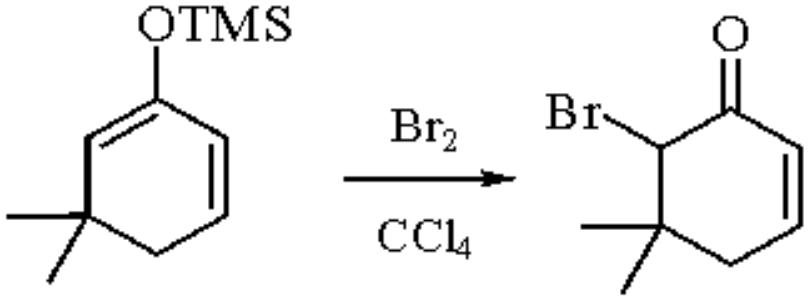

(18)

Sulfoxides are best α-brominated with a combination of bromine and NBS in pyridine.[38]

Bromine has been used in the halogenation of organometallic reagents. Organomagnesium,[39] organolithium,[40] and organoaluminum[41] reagents react to give the compounds in which the metal has been replaced by bromine. Organoboranes can react with bromine in several ways. Bromination in the presence of sodium methoxide gives the corresponding alkyl bromides.[42] Photobromination (in the absence of strong base) gives an initial α-bromo organoborane that can either give the corresponding alkyl bromide[43] or rearrange to a new organoborane.[44] Organoboranes can also be converted to alkyl bromides in aqueous media.[45] Alkenic bromides have been prepared from alkenylboronic esters with inversion of configuration (eq 19).[46]

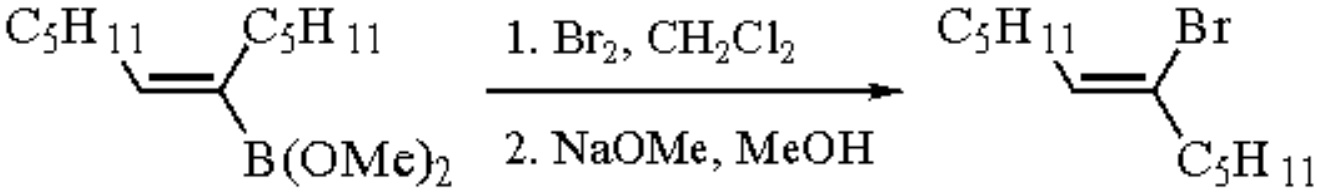

(19)

Enolates of ketones[47] and esters[48] can be brominated by treatment with bromine (eq 20), as can the anions of terminal alkynes.[49] The high reactivity of bromine, however, is sometimes a problem; milder sources of electrophilic bromine (such as ***1,2-Dibromoethane***) are occasionally used in its place.

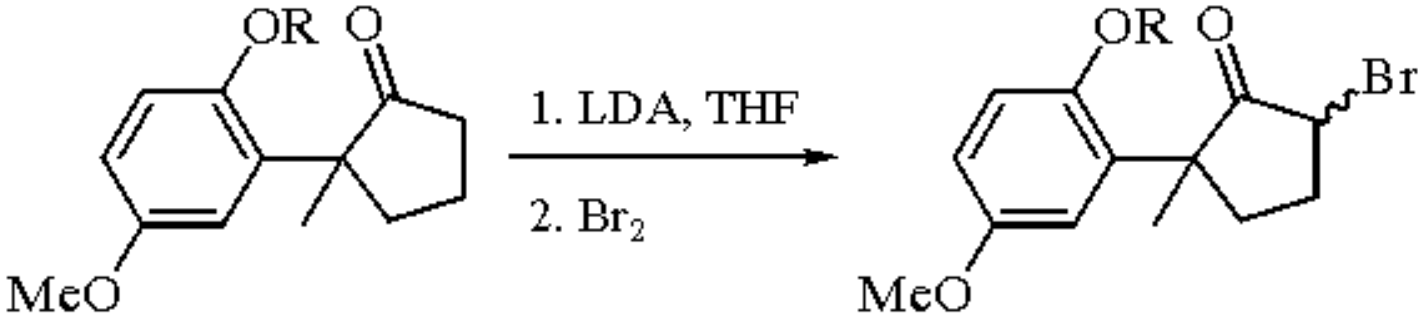

(20)

Oxidations.

Bromine reacts with secondary alcohols to give ketones. Since ketones are subject to bromination themselves (see above), the α-bromo ketones can sometimes be undesirable byproducts. However, in cases where there are no α-protons, this can provide an excellent method of oxidation (eq 21).[50]

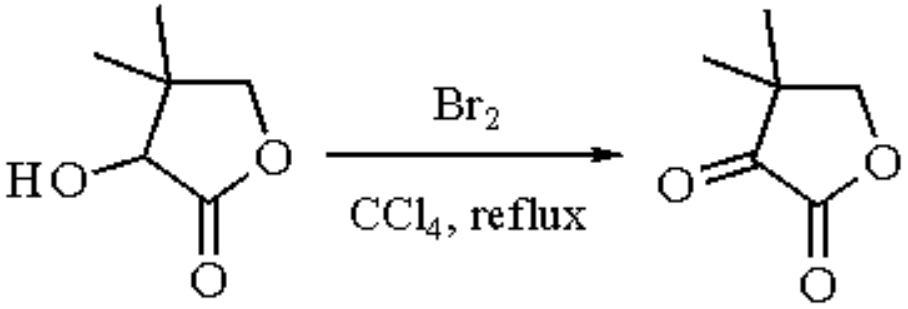

(21)

Primary alcohols are oxidized to either aldehydes or, more commonly, esters. An especially attractive corollary to this involves the oxidation of acetals to esters (eq 22).[51]

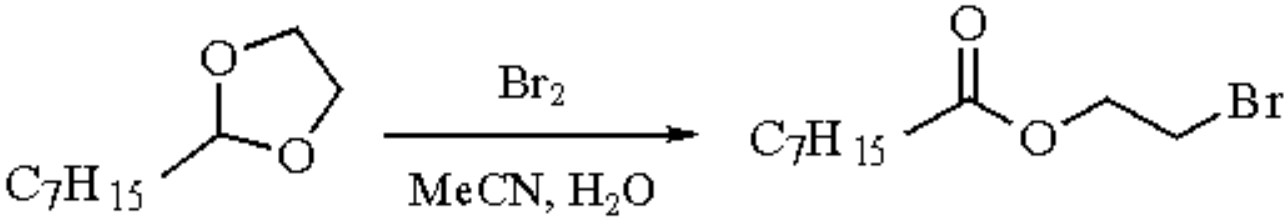

(22)

The addition of coreactants has provided a number of selective bromine-based oxidants. Both bromine/***Hexamethylphosphoric Triamide*** (HMPA)[52] and bromine/***Bis(tri-n-butyltin) Oxide*** (HBD)[53] have shown a preference for the oxidation of secondary vs. primary alcohols (eq 23), while bromine/nickel carboxylates[54] convert 1,4-diols to γ-butyrolactones by selective oxidation of the primary alcohols (eq 24).

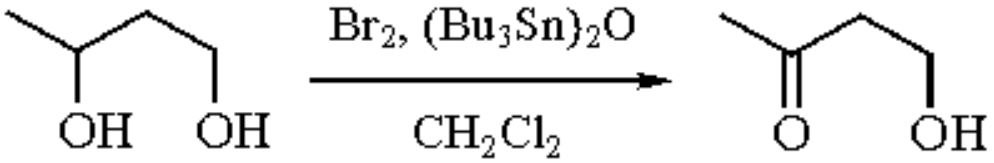

(23)

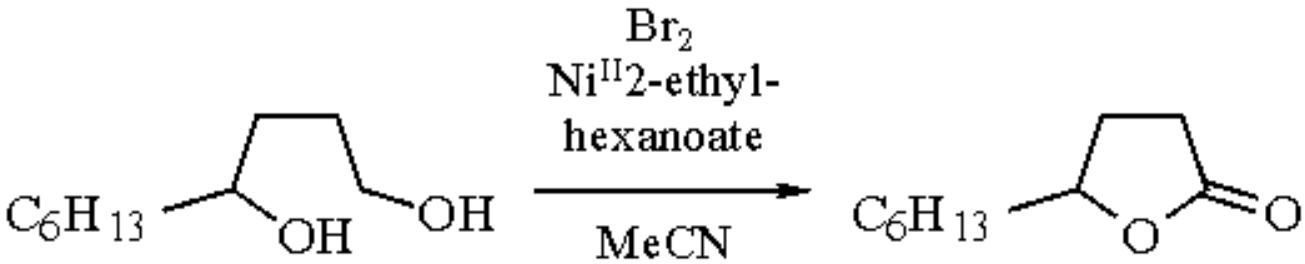

(24)

Tetrahydrofurans have been prepared from alcohols or diols by bromine/silver(I) salts (eq 25)[55] or bromine/DMSO,[56] respectively.

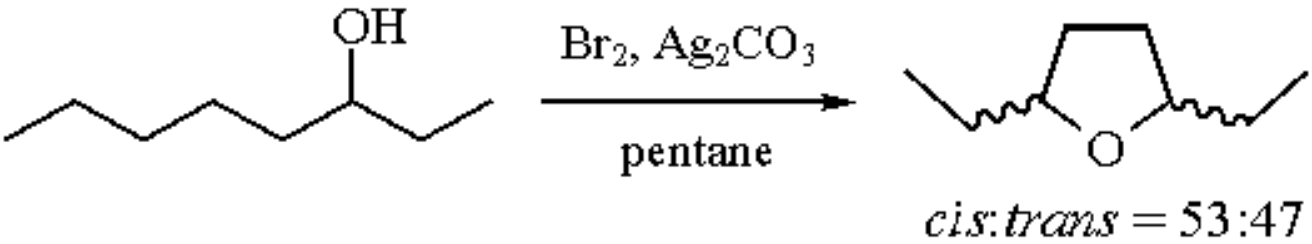

(25)

Bromine has demonstrated its superiority in the oxidation of enediol bis-trimethylsilyl ethers to α-diketones (eq 26).[57]

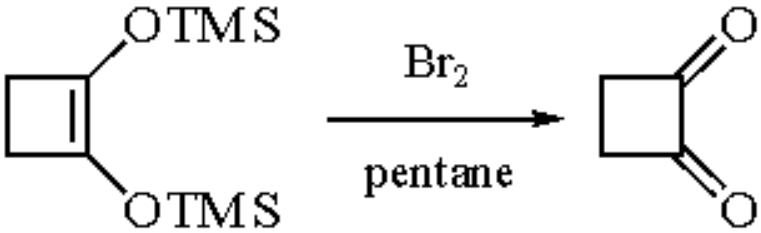

(26)

A number of other functional groups are oxidized by bromine; however, they do not appear to have gained widespread use. These include cyclohexenones,[58] ethers,[59] hydrazines,[60] oximes,[61] tertiary amines,[62] thiols,[63] sulfides,[64] and organoselenium reagents.[65]

Rearrangements.

Bromine reacts with a number of functional groups to effect bond cleavage or other skeletal rearrangements. In the classical Hofmann rearrangement,[66] treatment of primary amides with bromine in the presence of base gives isocyanates, carbamates, or amines, depending on the reaction conditions (eq 27).[67]

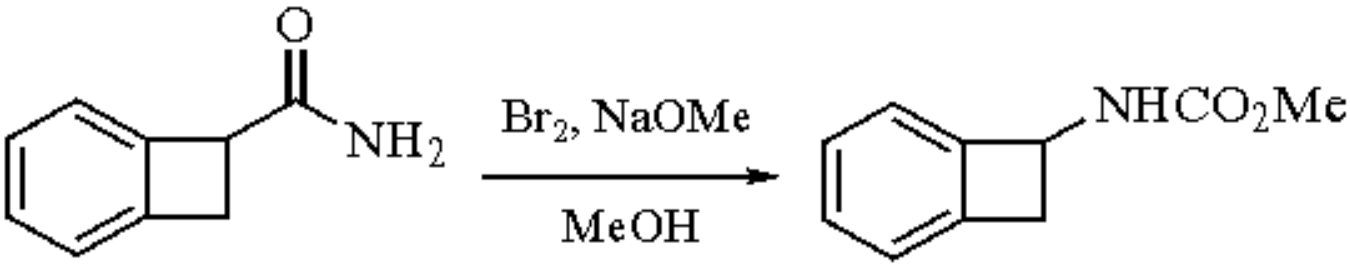

(27)

In the Hunsdiecker reaction,[68] treatment of silver salts of carboxylic acids with bromine furnishes the alkyl(aryl) bromides with one less carbon atom. Improvements that do not require the preparation of the dry silver salts include the use of mercury(II) salts (Cristol-Firth modification) (eq 28),[69] thallium(I) salts,[70] and photostimulation.[71]

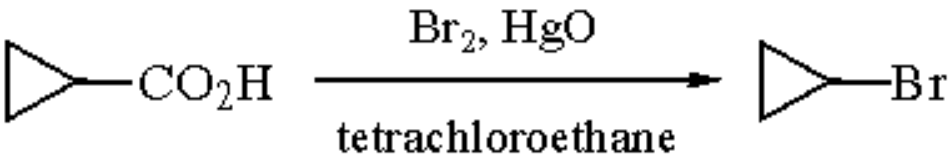

(28)

Three-membered rings are especially susceptible to reaction with bromine. Cyclopropanes are opened to give 1,3-dibromopropanes,[72] while cyclopropenylethanol derivatives rearrange in the presence of bromine to give 3-methylenetetrahydrofurans (eq 29).[73] Trimethylsilyl cyclopropyl ethers are opened to give β-bromo ketones (eq 30).[74] Epoxides can give either bromohydrins[75] or α-bromo ketones,[76] depending on the reaction conditions.

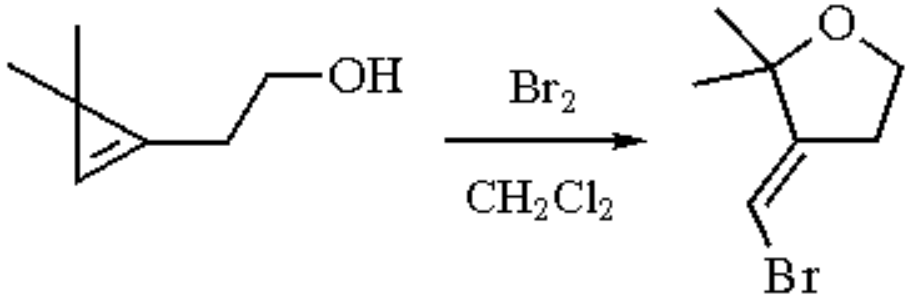

(29)

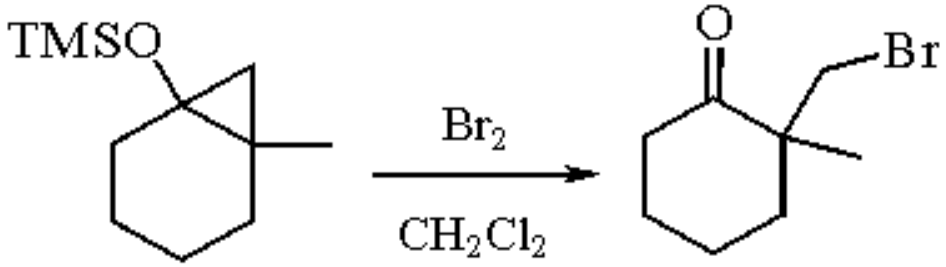

(30)

Mercury(II)-mediated cyclization of dienes allows access to bromine-containing natural products.[77] Thus, in the synthesis of aplysistatin, the key step was the cyclization of an acyclic precursor to the required bromoperhydro[1]benzoxepine ring system (eq 31).[78]

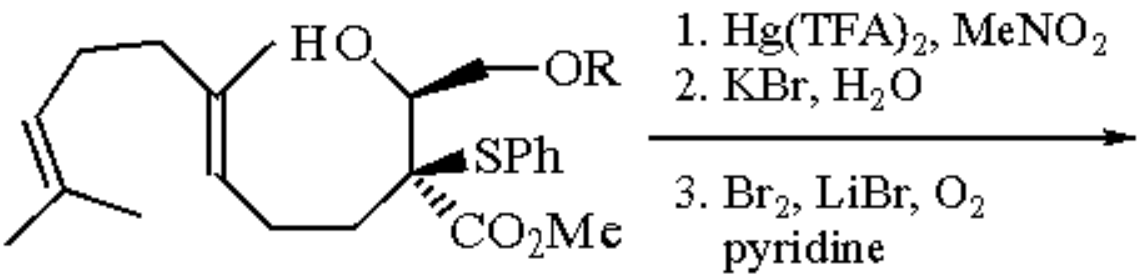

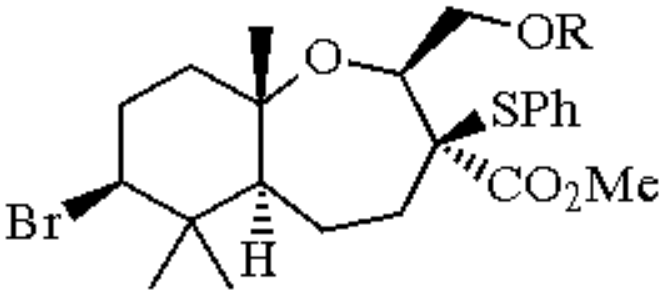

(31)

Related Reagents.

Bromine-t-Butylamine; ***Bromine Chloride***; ***Bromine-1,4-Diazabicyclo[2.2.2]octane***; ***Bromine-1,4-Dioxane***; ***Bromine-Silver(I) Oxide***; ***Bromine-Triphenyl Phosphite***; ***N-Bromosuccinimide***; ***N-Bromosuccinimide-Dimethylformamide***; ***N-Bromosuccinimide-Dimethyl Sulfide***; ***N-Bromosuccinimide-Sodium Azide***; ***Copper(II) Bromide***; ***Hydrobromic Acid***; ***Mercury(II) Oxide-Bromine***; ***Phosphorus(III) Bromide***; ***Pyridinium Hydrobromide Perbromide***; ***Sodium Bromide***; ***Thallium(III) Acetate-Bromine***.

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Bromine Azide[1]

BrN_3

[13973-87-0] · BrN_3 · Bromine Azide · (MW 121.92)

(used like ***Iodine Azide*** in additions to multiple bonds;[1-5] for introduction of the azide function;[1-5] in synthesis of aziridines,[3,6,7] vinyl azides,[4a] and azirines[7])

Alternate Name: azido bromide.

Physical Data: orange-red liquid, mp -45 °C;[1b] explosive when neat;[8] therefore should be prepared in situ in solution. Odor resembles that of the free halogen.

Solubility: sol most organic solvents.

Analysis of Reagent Purity: by titrimetric analysis.[1b]

Preparative Methods: BrN_3 is not available commercially, but can be prepared in situ from NaN_3, Br_2, and HCl, preferably in CH_2Cl_2 or ether.[2] It can also be prepared from NBS, HN_3, and *t*-BuOH in $CHCl_3$[3a] or from NBS and NaN_3 in DME-H_2O.[3b] Typical procedure for addition to alkenes:[2] to a well-stirred slurry of 32.5 g (0.5 mol) of NaN_3 in 100 mL of CH_2Cl_2 (or pentane) at 0 °C add 25 mL of 30% aq HCl, followed by 8.0 g (0.1 mol) of Br_2. After 30-60 min of further stirring, decant and dry the organic layer. Add 0.1 mol of alkene in $MeNO_2$ (ionic addition) or pentane (radical addition). Warm the mixture to 20 °C and stir for 8-24 h, then wash in turn with water and 5% aq sodium thiosulfate until colorless, and chromatograph (neutral alumina) or crystallize to afford the bromoazide adduct in 35-95% yield.

Handling, Storage, and Precautions: explosive liquid[1b] (see ***Iodine Azide***); use in a fume hood. After reaction with multiple bonds, the mixture should be washed with sodium bisulfite until colorless, to destroy excess BrN_3. Dilute solutions of BrN_3 in organic solvents can generally be handled safely.[1b] Keep away from strong reducing agents.

Additions to Alkenes.

Additions of BrN_3 to alkenes are much more influenced by solvent polarity than additions of IN_3 and lead to different regioisomeric adducts, depending upon the polarity of the solvent. Ionic additions, proceeding via a three-membered ring bromonium species, are achieved in polar solvents, such as $MeNO_2$-CH_2Cl_2, or in the presence of acid catalysts

and are usually stereospecific for aliphatic alkenes. Radical additions proceed by N_3 radical attack on the C=C double bond and are favored in nonpolar solvents such as pentane, in the presence of light or radical initiators, or when the reaction mixture is purged with N_2 to remove O_2, a radical inhibitor. Thus styrene reacts with BrN_3 in $MeNO_2$ to produce the regioisomer opposite to that formed in pentane solution (eq 1).[2]

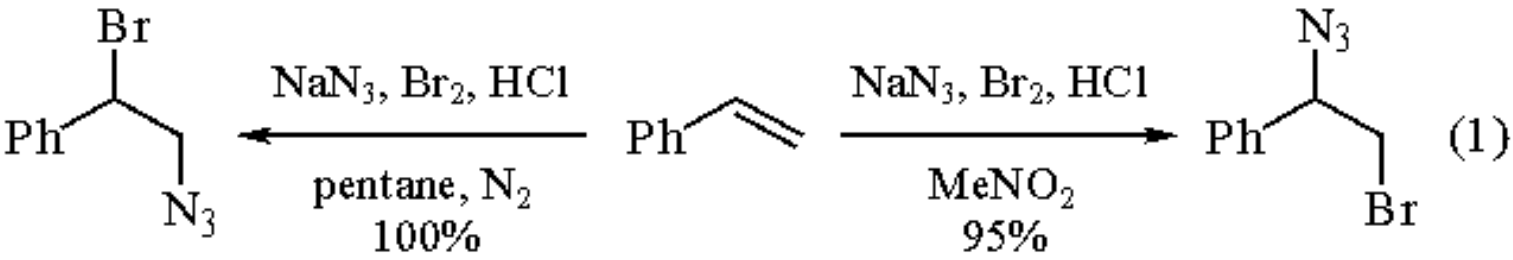

Such differences also exist for the behavior of IN_3 vs. BrN_3. Thus while IN_3 addition in MeCN to benzo[*b*]thiophene 1,1-dioxide leads to the *trans*-3-azido-2-iodo adduct, BrN_3 addition in CH_2Cl_2 affords the *trans*-2-azido-3-bromo product.[9]

In polar solvents the addition of BrN_3 to simple alkenes, such as *cis*- and *trans*-2-butene, proceeds stereospecifically *anti*.[2] Steroid 2-enes[2] and 5-enes[3a] afford the β-azido-α-bromo diaxial adducts via α-bromonium species, while radical addition to 2-cholestene gives a mixture of regioisomers (eq 2).

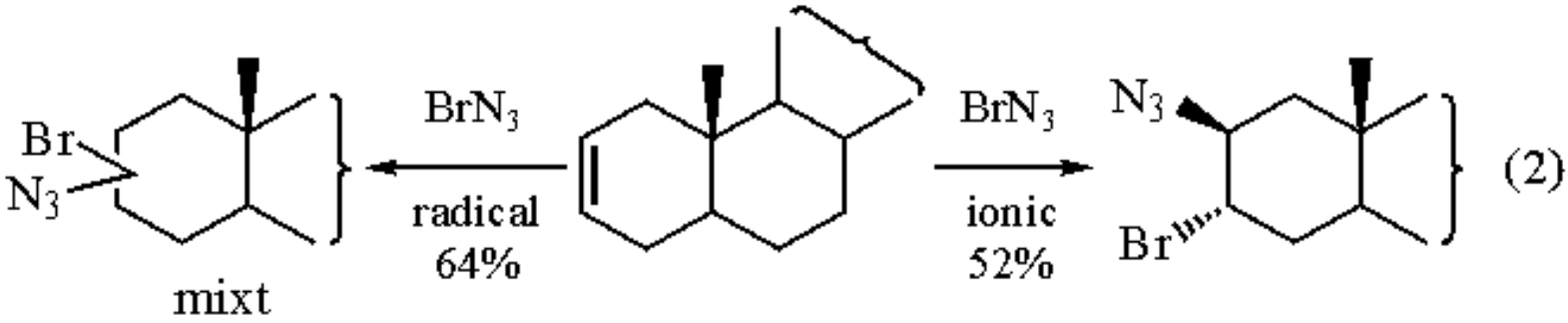

On the other hand, BrN_3 additions to steroid enones can lead to α-azido-β-bromo steroids or to *cis* adducts. Thus podocarp-6-enes give 7α-azido-6β-bromo adducts.[5b]

Enol ethers lead to formation of α-azido ethers as a mixture of stereoisomers.[2] However, reaction of sugar 2-enes with BrN_3 in the presence of ***Dibenzoyl Peroxide*** (radical reaction) led, after treatment with ***Mercury(II) Acetate***, to formation of 2-acetoxy-3-azido sugars.[10]

Aromatic or other substituents on a double bond, which can stabilize a positive charge well, can lead to a mixture of stereoisomers.[2b] In polar nucleophilic solvents (MeCN, DMF, HOAc, MeOH), reaction of BrN_3 with alkenes leads to solvent participation (eq 3).[11]

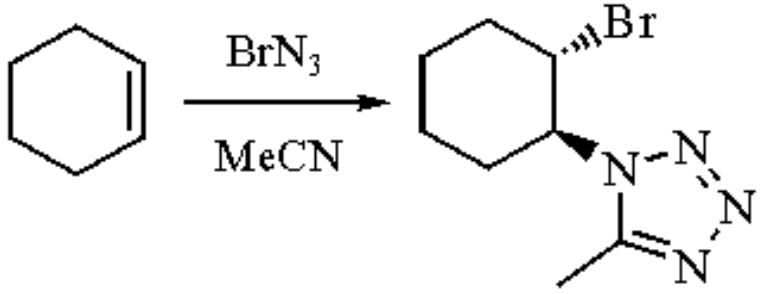

(3)

While ionic addition of BrN_3 to 3,3,3-triphenylpropene proceeds with phenyl migration, the radical addition to this alkene gives mainly the unrearranged product.[12]

Addition of BrN_3 to allenes at -65 °C leads, like IN_3, to a mixture of allylic azides, while addition at rt apparently proceeds via radicals to afford an unstable vicinal diazide.[13]

Synthesis of Aziridines.

BrN_3 addition to alkenes, followed by reduction with LAH or Ph_3P-H_2O, is a convenient method for the synthesis of aziridines (eq 4).[3,14]

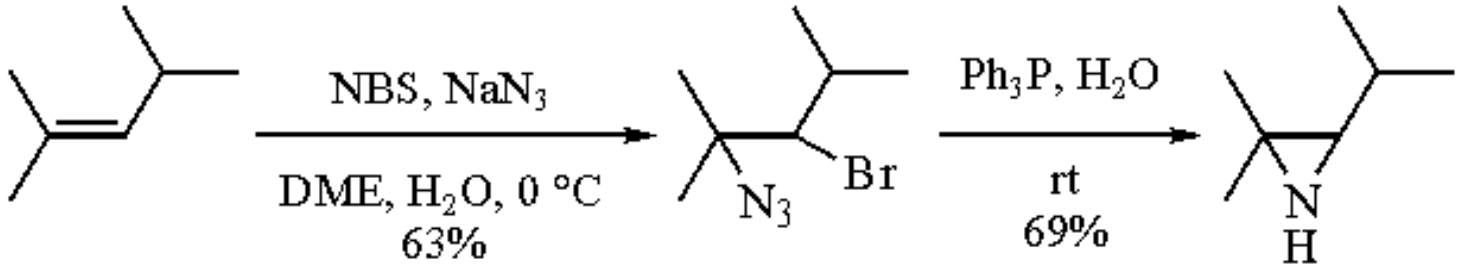

(4)

Synthesis of Vinyl Azides and Azirines.

Bases, like ***Potassium t-Butoxide***, cause stereospecific elimination of HBr from the adducts; the resulting vinyl azides[4a] provide useful routes for the synthesis of azirines or ketones, or for amination of aromatic compounds (see ***Iodine Azide***).

---

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Bromine-*t*-Butylamine

Br_2.*t*-$BuNH_2$

(Br_2)

[7726-95-6] · Br_2 · Bromine-*t*-Butylamine · (MW 159.81) (*t*-$BuNH_2$)

[75-64-9] · $C_4H_{11}N$ · Bromine-*t*-Butylamine · (MW 73.14)

(reagent for *ortho* bromination of phenols[1])

Alternate Name: bromine-2-methyl-2-propylamine.

Solubility: sol toluene.

Preparative Method: prepared in situ by addition of bromine to a solution of *t*-butylamine in toluene at -20 to -30 °C.

Handling, Storage, and Precautions: bromine-*t*-butylamine is prepared in situ, and is not generally stored. No particular hazards have been reported for this reagent combination (other than the corrosivity and toxicity hazards associated with bromine and *t*-butylamine), but the 1:1 complex between bromine and trimethylamine has been reported[2] to explode when heated in a sealed tube. This reagent should be handled in a fume hood.

Ortho Bromination of Phenols.

The combination of ***Bromine*** and ***t-Butylamine*** has been used for the selective *ortho* bromination of phenols.[1,3] Little or no *para* bromination is usually observed. The yields are generally good when 2,6-dibromination is desired (eq 1)[1] or when one of the *ortho* positions is blocked (eq 2).[4]

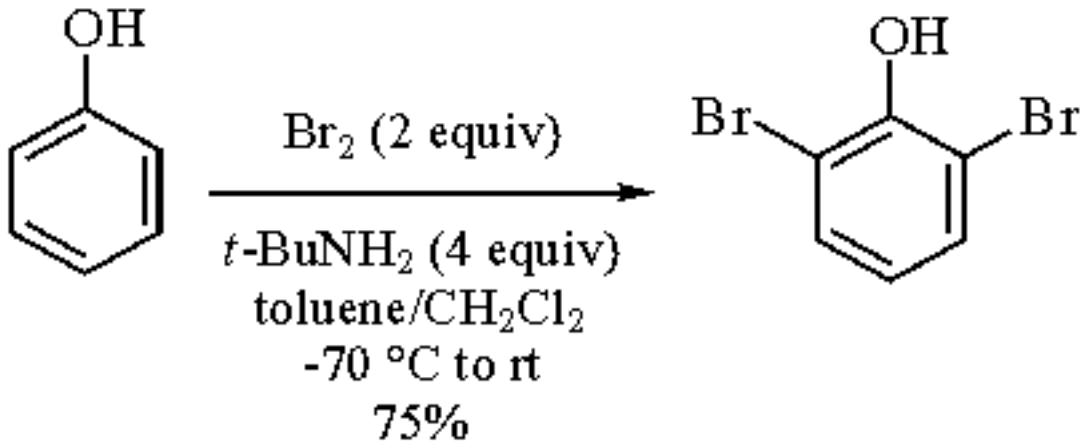

(1)

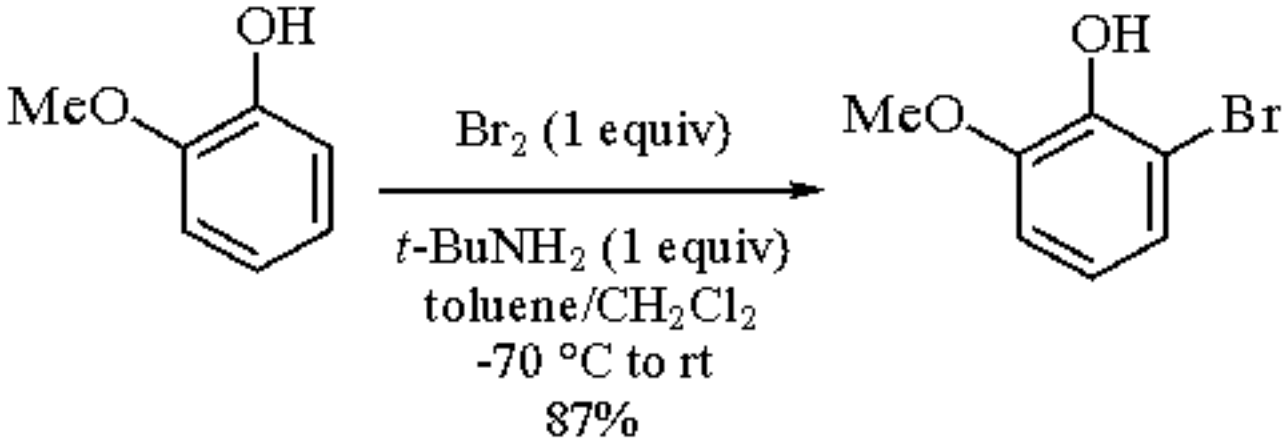

(2)

For substrates in which both *ortho* positions are open (eq 3),[1] or for highly activated substrates (eq 4),[5] it is sometimes difficult to obtain monobrominated products. In these cases less than 1 equiv of bromine has often been employed. Yields are then calculated on moles of bromine used.

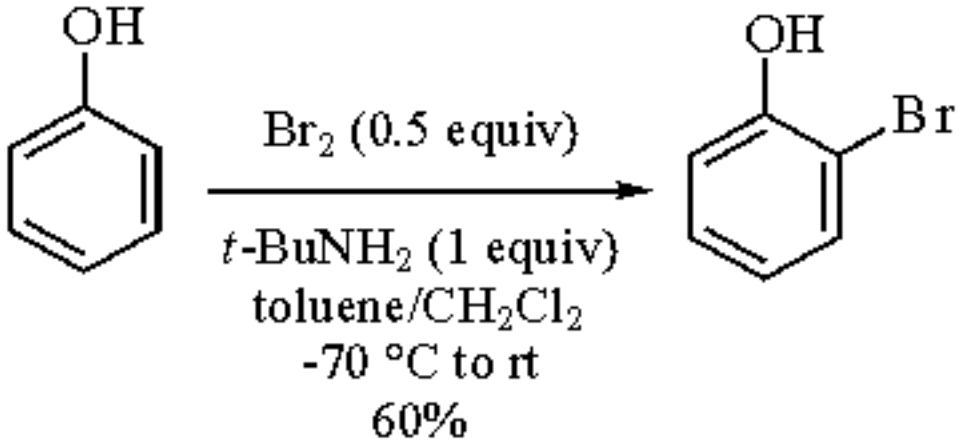

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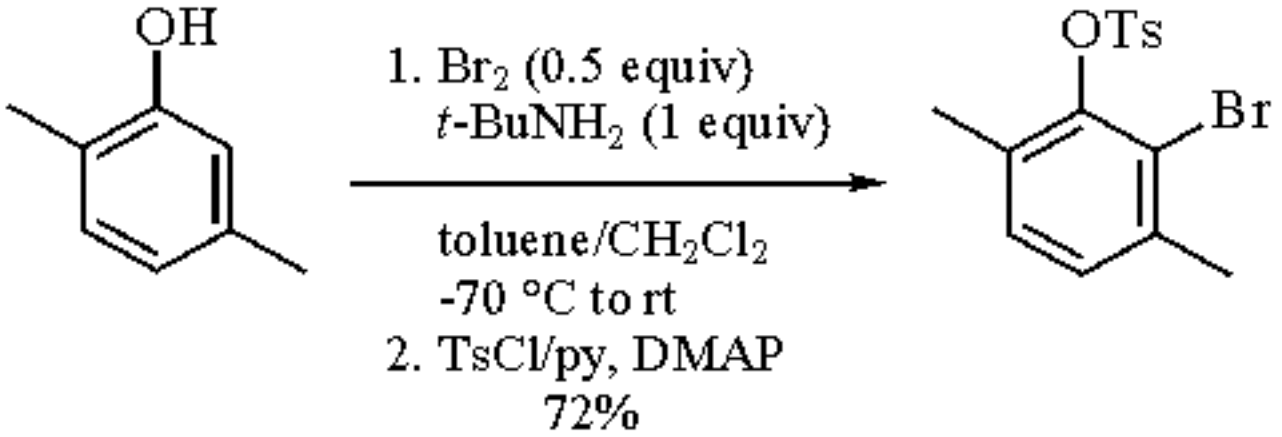

(4)

It has been speculated[1,6] that the source of selectivity with the Br_2.*t*-$BuNH_2$ reagent is due to the formation of a hypobromite intermediate which undergoes intramolecular bromine transfer.

An interesting use of the selective properties of this reagent is demonstrated in the chemoselective bromination of phenol (**1**) in the presence of a trisubstituted alkene to give bromide (**2**) in 85% yield. Compound (**2**) was used in a total synthesis of mycophenolic acid.[7]

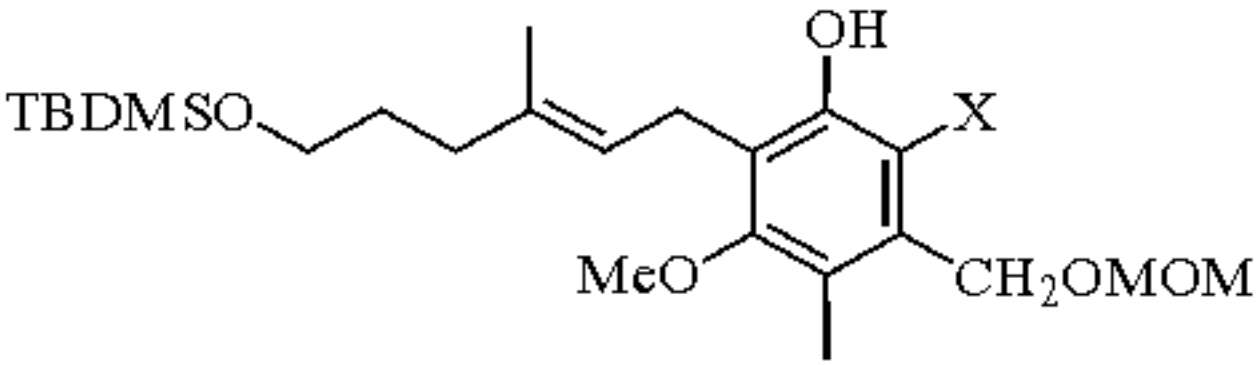

(1) X = H
(2) X = Br

For other reagents useful for the *ortho* bromination of phenols see ***2,4,4,6-Tetrabromo-2,5-cyclohexadienone***.

---

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Bromine Chloride

BrCl

[13863-41-7] · BrCl · Bromine Chloride · (MW 115.36)

(powerful brominating and/or bromochlorinating agent)

Physical Data: mp ca. -66 °C; bp ca. 5 °C.[1]

Solubility: sol H_2O, methylene chloride, chloroform, carbon tetrachloride, carbon disulfide, ether.

Form Supplied in: while bromine chloride (occasionally referred to incorrectly as chlorine bromide) is commercially available, it is more commonly prepared in the laboratory on demand.

Preparative Methods: these include the reaction of Br_2 and Cl_2 in solution;[2,3] reaction of HCl gas with either *N*-bromoacetamide (NBA)[4] or *N*-bromosuccinimide (NBS)[5] in halogenated solvents; reaction of NaBr with either Cl_2[6,7] or chloramine-T[7] in aqueous solution. Appropriate literature reference(s) should be consulted for particular applications.

Handling, Storage, and Precautions: as a source of positive halogen, all precautions associated with the use of halogens (see ***Bromine***, ***Chlorine***) should be observed. Protective clothing is a must, and in the case of gaseous BrCl (or preparations using corrosive gaseous reagents) the use of a respirator is advised. Use in a fume hood.

Bromination of Sulfones.

Bromine chloride has been used successfully in the photochemical bromination of sulfones. With 1 equiv of BrCl, tetrahydrothiophene 1,1-dioxide gave a 72% yield of the 2-bromo isomer, while diethyl sulfone gave a mixture due to α- and β-bromination.[2] Attempts to effect bromination using other conditions (***Bromine***, Br_2/Lewis acid, NaOBr, ***N-Bromosuccinimide***, dioxane dibromide) were unsuccessful. Thietane 1,1-dioxide (**1**) has been brominated in the 3-position (eq 1),[3,8] but the product was reported to be contaminated with some of the 3-chloro compound.[9]

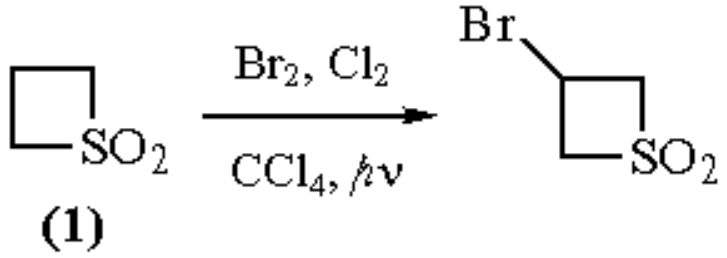

(1)

Bromination of Aromatic Rings.

Bromine chloride has been used as an alternative to Br_2 in the electrophilic bromination of aromatic rings.[6] In this case, chlorine was not incorporated onto the ring.

Addition to Alkenes.

The addition of BrCl to alkenes is governed by a combination of steric and stereoelectronic effects.[5,10,11] Thus while (**2**) reacts with BrCl to give a mixture of isomers (eq 2), the sterically more demanding (**3**) gives a single compound (eq 3).[5a] Steroids, with their highly rigid framework, also demonstrate excellent regio- and stereoselectivity (eqs 4 and 5).[4,5]

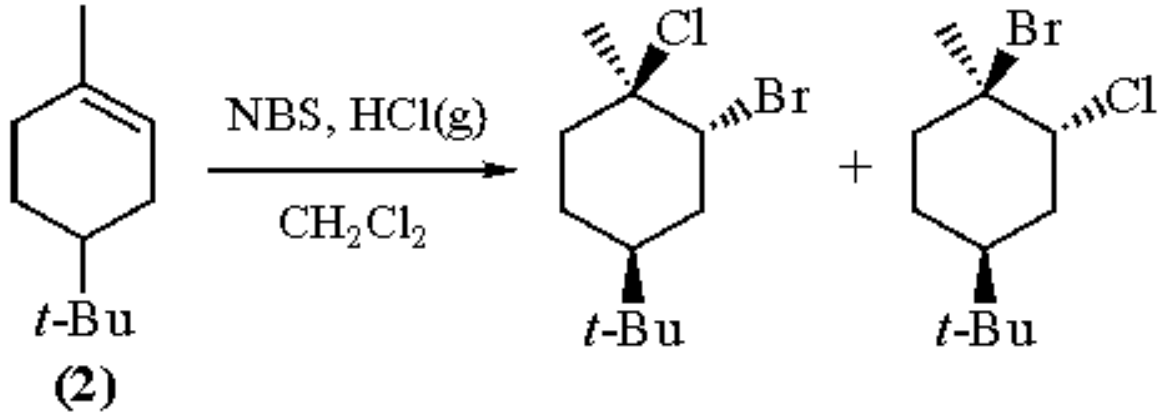

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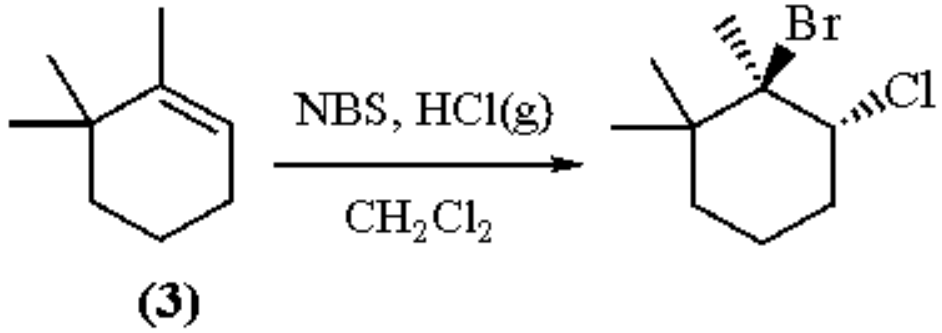

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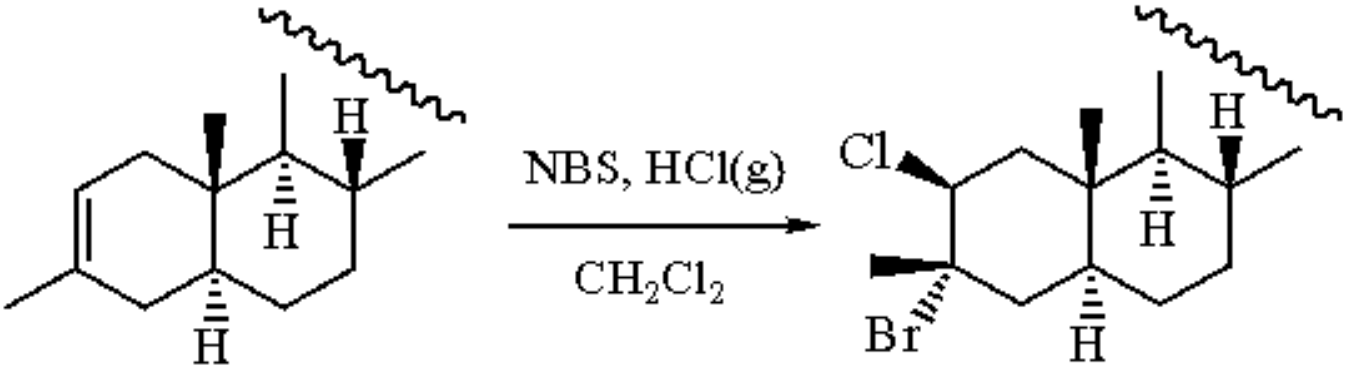

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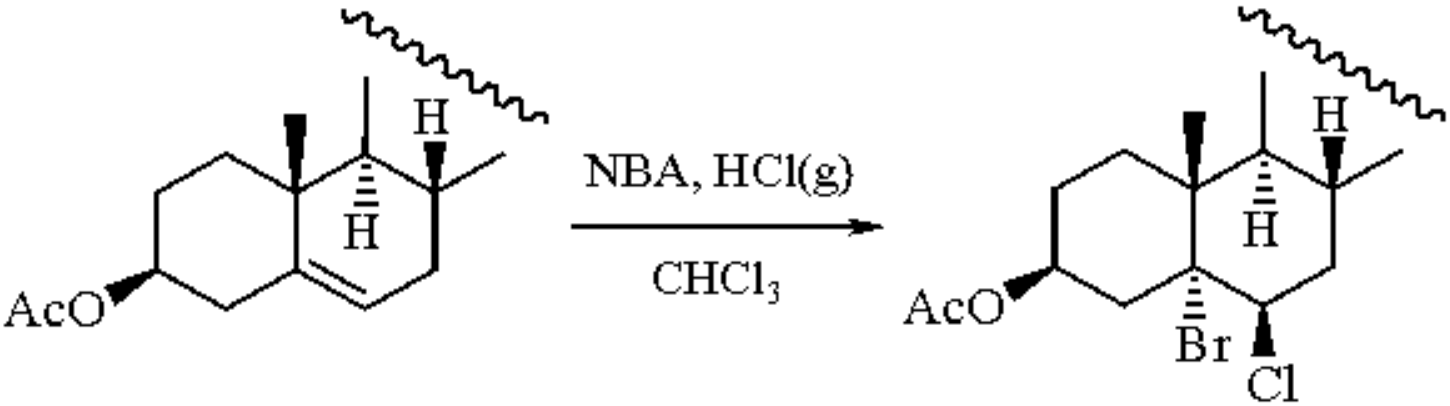

(5)

Bromination of Organoboranes Under Ionic Conditions.

When organoboranes are treated in the dark with BrCl (or Br_2) in the presence of H_2O, good yields of alkyl bromides are obtained.[7] This method works best for the synthesis of primary bromides from terminal alkenes (eq 6). In this sense it complements the radical bromination of organoboranes, which has been shown to prefer secondary alkyl groups.

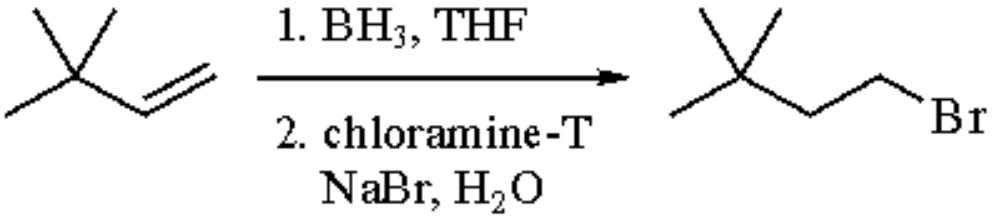

(6)

Related Reagents.

Bromine; ***N-Bromoacetamide***; ***N-Bromosuccinimide***; ***Chloramine-T***; ***Chlorine***; ***N-Chlorosuccinimide***; ***Sodium Bromide***.

---

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Bromine-1,4-Diazabicyclo[2.2.2]octane

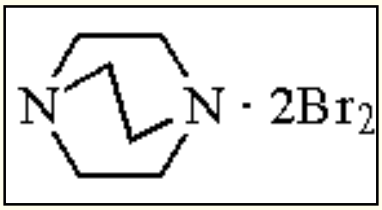

[5770-70-7] · $C_6H_{12}Br_4N_2$ · Bromine-1,4-Diazabicyclo[2.2.2]octane · (MW 431.79)

(mild oxidizing agent for oxidizing benzyl alcohols and secondary alcohols to benzaldehydes and ketones;[1] selectively oxidizes sulfides to sulfoxides;[2] oxidizes monothioacetals to aldehydes[3])

Alternate Name: DABCO.2Br_2; 1,4-diazabicyclo[2.2.2]octane, compound with Br_2.

Physical Data: mp 155-160 °C (dec).

Solubility: insol most organic solvents and water.

Form Supplied in: yellow amorphous solid (not commercially available).

Preparative Method: prepared by adding excess ***Bromine*** to solutions of ***1,4-Diazabicyclo[2.2.2]octane*** in benzene, carbon tetrachloride, or water[1-4] (95% yield obtained on 50 mmol scale).[4]

Handling, Storage, and Precautions: thermally stable in neutral or basic media; decomposes in acidic media. Nonhygroscopic and stable to air, water, and light. This reagent should be handled in a fume hood.

Introduction.

DABCO.2Br_2 is one of several complexes of halogens with amines, such as ***Chlorine-Pyridine***[5] and bromine/quinoline,[2] that are used as oxidants for organic molecules. This reagent is more convenient to use because it is readily prepared and is very stable to air, water, light, and basic media.[1-4] Acidic media decompose it. This stable complex allows for the more accurate measuring of active bromine, especially for small scale reactions. X-ray studies of DABCO.2Br_2 show that it exists as a novel complex of multiple

DABCO and bromine units.[6] Hudlický has reviewed this reagent and alternative oxidation reagents.[7]

Selective Oxidation of Alcohols.

DABCO.2Br_2 oxidizes benzyl alcohol and secondary aliphatic alcohols (eq 1) to benzaldehyde (97%) and ketones (36-71%) in acetonitrile or refluxing methylene chloride.[1] Primary alcohols are oxidized less readily (ca. 10%). Optimum yields are obtained after 3-6 h. Superior yields (62-100%), better selectivity, and shorter reaction times (2-60 min) are observed when bromine/HMPA is used as an oxidant.[8]

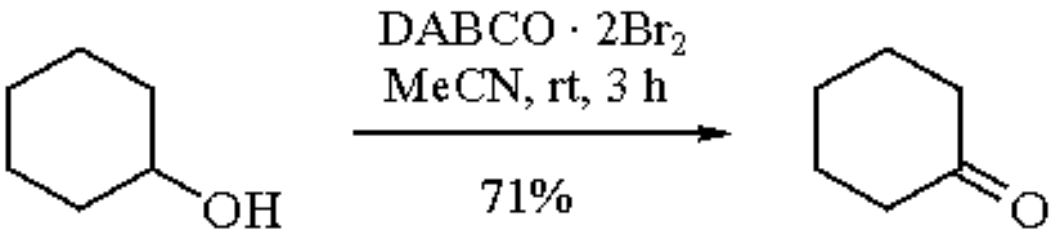

(1)

Oxidation of Sulfides to Sulfoxides.

DABCO.2Br_2 oxidizes sulfides to sulfoxides in 70% aqueous acetic acid without over-oxidation to sulfones.[2] Yields for substrates ranging from dibutyl sulfide to thianthrene (eq 2) varied between 70 and 95%. The reaction is fast enough to be used as a method to prepare ^{18}O-enriched sulfoxides from sulfides.[2] Sulfides can also be oxidized to sulfoxides with ***Dipyridine Chromium(VI) Oxide***, ***Manganese Dioxide***,[9] and ***Sodium Periodate***.[10]

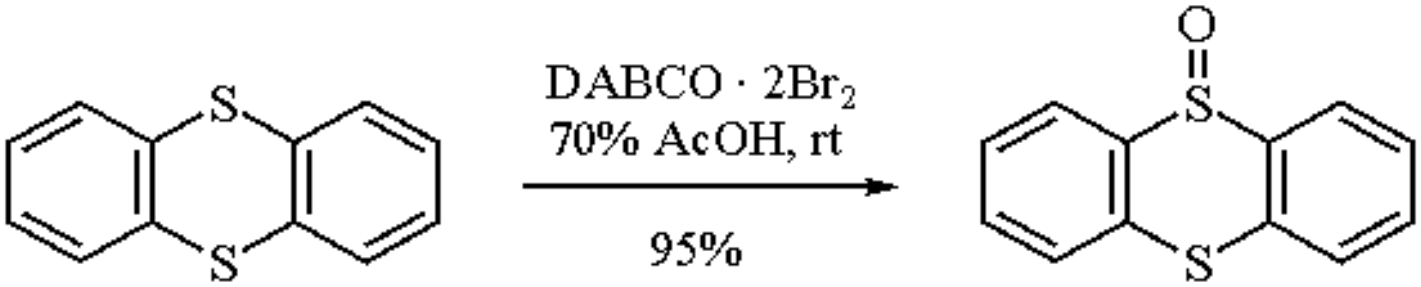

(2)

Other Applications.

DABCO.2Br_2 oxidizes monothioacetals to aldehydes (eq 3) in 40-83% yield.[3] No aldehydes were obtained when 3-chloroperoxybenzoic acid, sodium periodate, and selenium dioxide-hydrogen peroxide were used as oxidants.

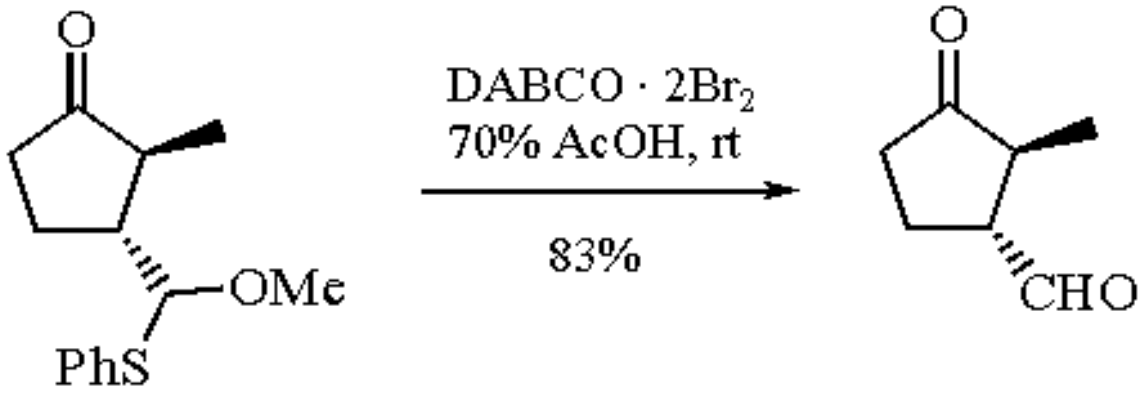

(3)

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M. P. Moon

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Bromine-1,4-Dioxane[1]

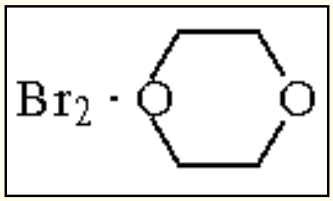

[15481-39-7] · $C_4H_8Br_2O_2$ · Bromine-1,4-Dioxane · (MW 247.91)

(reagent for bromination of phenols,[2] aromatic amines,[3] α-bromination of aldehydes[4] and ketones[5])

Alternate Name: dioxane dibromide.

Physical Data: mp 60 °C.

Solubility: sol 1,4-dioxane, THF, and ether.

Preparative Methods: a 1:1 complex between 1,4-dioxane and bromine has been prepared and isolated on a 2 mol scale by the addition of bromine to 1,4-dioxane.[6] The reagent has also been prepared in situ.[3,7]

Handling, Storage, and Precautions: the complex is reported to be volatile (much material was lost on drying).[6] It can be stored at 0 °C. This material should only be handled in a fume hood.

Aromatic Brominations.

Bromine and 1,4-dioxane form a stable 1:1 complex, which has been referred to in the literature as dioxane dibromide. This complex is a mild brominating agent which has been used for bromination of activated aromatic systems. Yanovskaya et al. have reported[2] the bromination of phenol to give *p*-bromophenol in 88% yield. Schlegel et al. were able to monobrominate 1,3-dimethoxybenzene in high yield (eq 1).[8] In this case, reaction with bromine was reported to give a mixture of products.

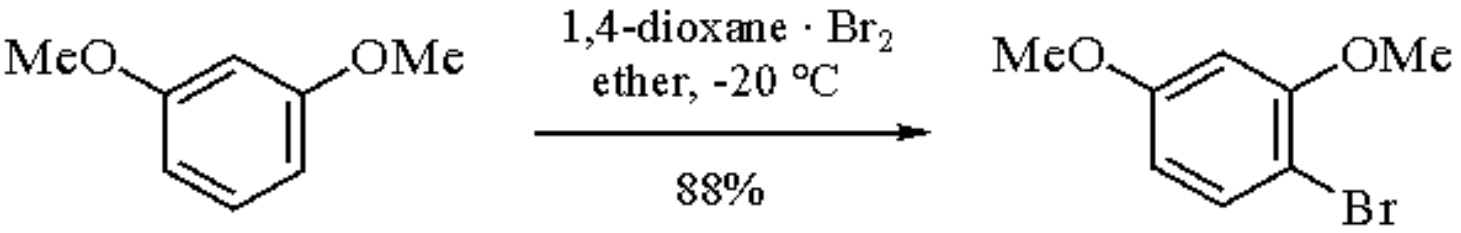

(1)

Aromatic amines can be monobrominated to give the *p*-bromo compounds in moderate to good yields (eq 2).[3] The yields are highest for tertiary amines.

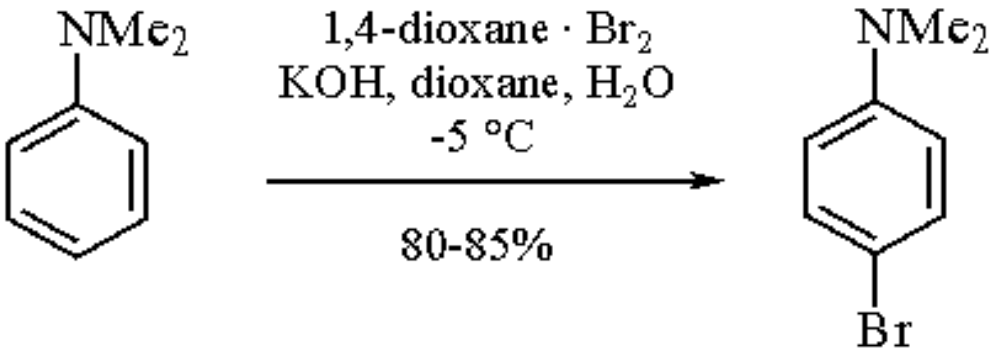

(2)

The bromination of 5-hydroxybenzimidazole is reported[9] to proceed at lower temperature and in higher yield with bromine-1,4-dioxane than with bromine alone (eq 3).

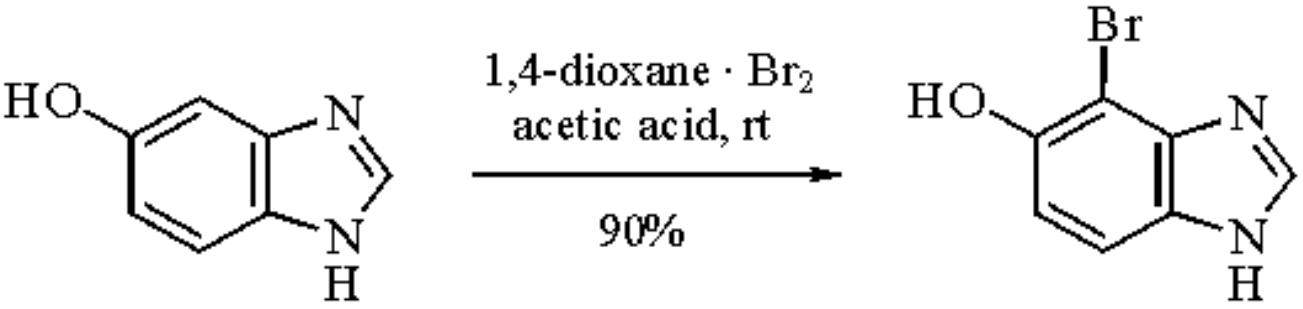

(3)

α-Bromination of Aldehydes and Ketones.

Bromine-1,4-dioxane is useful for the α-bromination of carbonyl compounds. Aldehydes have been brominated in moderate to good yields (eq 4).[4]

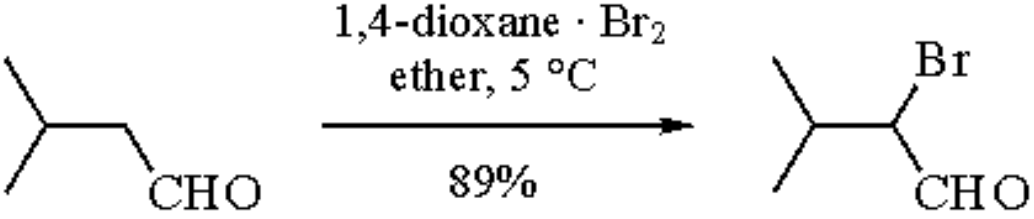

(4)

Hydroxy-substituted acetophenones can be brominated selectively on the alkyl side chain in good yields without

aromatic bromination using this reagent (eq 5).[5] A commonly used reagent for this transformation is ***Copper(II) Bromide***. Use of bromine-1,4-dioxane has the advantage that no heavy metal waste is generated.

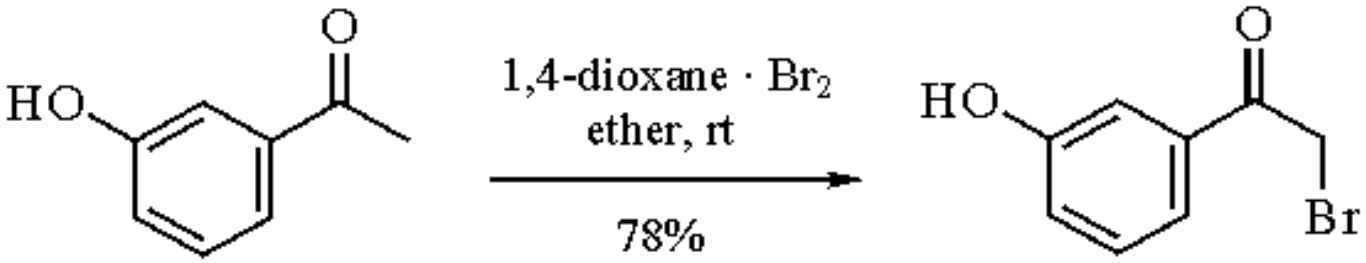

(5)

Other Applications.

Bromine-1,4-dioxane has also been used for the one-pot preparation of α-bromoacetals of aryl alkyl ketones,[7] for the conversion of thiocarbonyl compounds to their oxygen analogs,[10] for the hydrolysis of dithioacetals,[10] for the oxidation of thiols to disulfides,[10] and for the bromination of 1-trimethylsilylindene.[11]

Related Reagents.

Bromine; ***Bromine-t-Butylamine***; ***N-Bromosuccinimide***; ***Copper(II) Bromide***; ***Phenyltrimethylammonium Perbromide***; ***Pyridinium Hydrobromide Perbromide***; ***2,4,4,6-Tetrabromo-2,5-cyclohexadienone***.

---

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Bromine Monofluoride[1]

BrF

[13863-59-7] · BrF · Bromine Monofluoride · (MW 98.90)

(adds bromine and fluorine atoms across double and triple bonds;[2] brominates aromatic rings;[3] converts carbonyls, through their hydrazones[4] or dithiolanes,[5] to the CF_2 group; converts benzylic dithiocarboxylates and orthothioesters to $ArCF_3$[6])

Physical Data: mp -33 °C (dec to Br_2 and BrF_3); has not been isolated in pure form; orange-red crystals at low temperatures.[7,9]

Preparative Methods: unlike most organic reagents, the notation [BrF] has been designated to indicate a two-step reaction taking place when a mixture of two different agents, one a source of electrophilic bromine and the other of nucleophilic fluorine, is reacted with a substrate. The true molecule BrF can be prepared in situ by reaction between the corresponding elements[7] and by reacting bromine with BrF_3.[8] Many, but not all, reactions of [BrF] and BrF are quite similar.

Bromofluorination of Alkenes.

Adding the elements of bromine and fluorine across double bonds by using ***N-Bromosuccinimide*** (NBS), or similar N-Br derivatives, and anhydrous ***Hydrogen Fluoride*** is an established procedure employed extensively in steroid chemistry (eq 1).[10] The addition proceeds with relatively good regio- and stereospecificity (*anti* addition). Olah suggested replacing anhydrous HF, which is inconvenient for laboratory use, with the easier to handle HF.py[2a] (eq 2). Many variations on this procedure have since appeared. These include the following combinations: NBS-Et_3N/3HF,[11] NBS-AgF/CaF_2,[12] NBS-Bu_4NF,[13] NBS-NH_4HF_2/ultrasound,[14] and 1,3-dibromo-5,5-dimethylhydantoin (DBH)/SiF_4.[15]

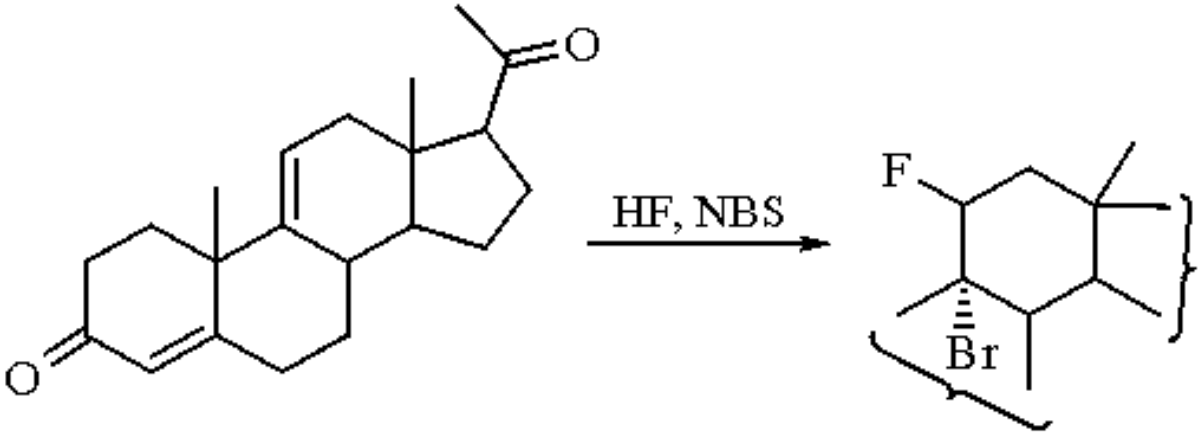

(1)

$$MeCH{=}CH_2 \xrightarrow{NBS,\ (HF)_x \cdot py} MeCHFCH_2Br$$

(2)

$$PhC{\equiv}CPh \xrightarrow{NBS,\ (HF)_x \cdot py} PhCBr{=}CFPh$$

The combination of agents which results in [BrF] is also used for converting carbonyls, through their hydrazones, into the CF_2 group (eq 3).[4] The same eventual results can also be achieved through the action of [BrF], made from NBS or DBH with HF.py, on various dithiolanes (eq 4).[5] A somewhat similar process is the reaction of [BrF] with methyl aryldithiocarboxylates, which can be directed to give either $ArCF_3$ or the thioethers $ArCF_2SMe$ (eq 5).[6a] Trifluoromethylarenes are also obtained when [BrF] is reacted with aryl orthothioesters (eq 6).[6b] An interesting variation is the reaction with arylxanthates, which forms aryltrifluoromethyl ethers (eq 7).[16]

$$Ph_2C{=}O \xrightarrow{H_2NNH_2} Ph_2C{=}NNH_2 \xrightarrow{NBS,\ (HF)_x \cdot py} Ph_2CF_2 \quad (3)$$

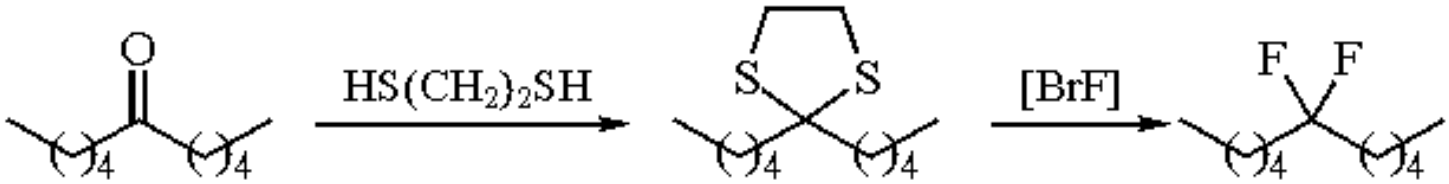

(4)

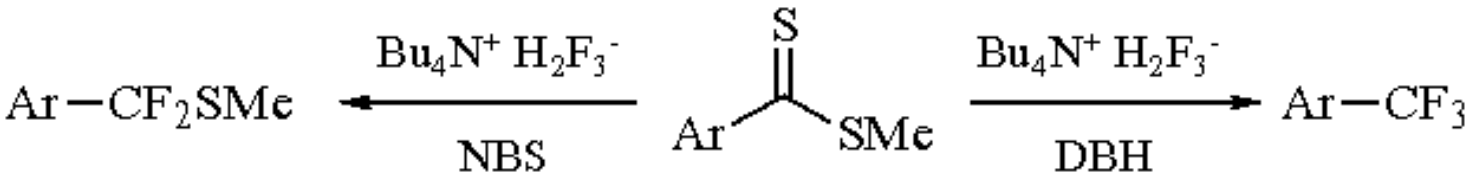

(5)

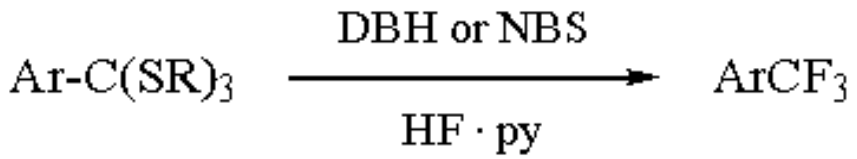

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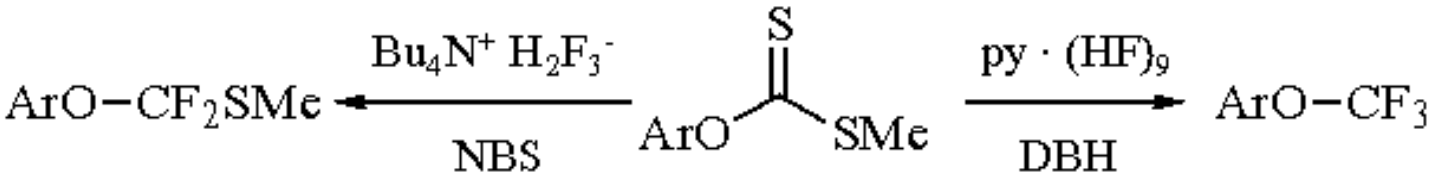

(7)

The molecular BrF, prepared in situ from the elements, adds across double bonds with similar results to [IF] (see ***Iodine Monofluoride***), but it also adds to very deactivated enones and ynones (eq 8).[2c] The strong electrophilicity of the bromine in molecular BrF is the driving force behind the very efficient bromination of practically any deactivated aromatic compounds without the need for any Friedel-Crafts catalyst (eq 9).[3]

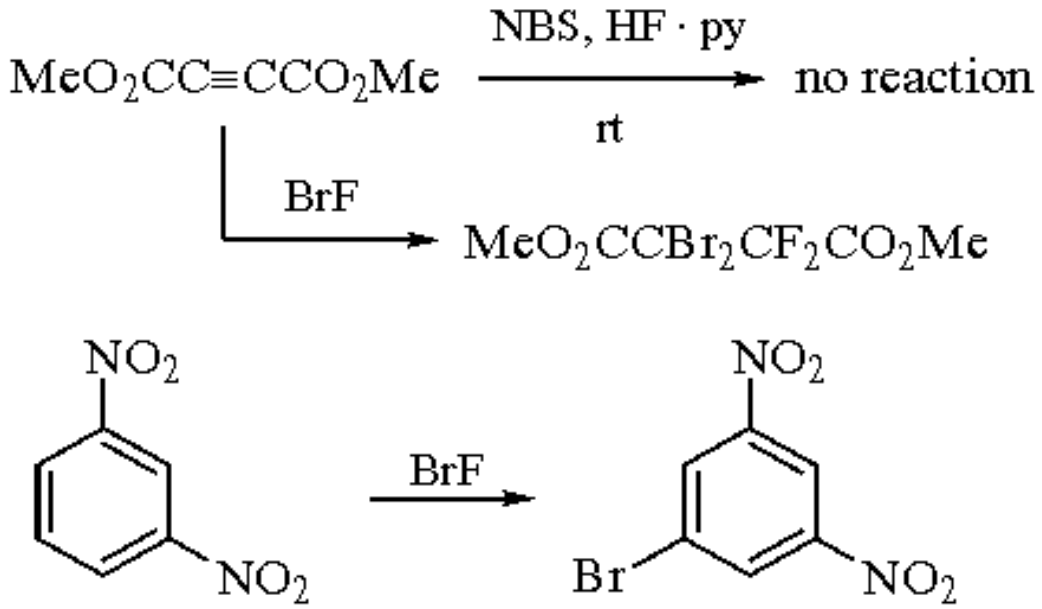

(8)

(9)

Related Reagents.

Bromine Trifluoride; ***N-Bromosuccinimide***; ***1,3-Dibromo-5,5-dimethylhydantoin***; ***Hydrogen Fluoride***.

---

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Bromine-Silver(I) Oxide

Br_2-Ag_2O

(Br_2)

[7726-95-6] · Br_2 · Bromine-Silver(I) Oxide · (MW 159.81) (Ag_2O)

[20667-12-3] · Ag_2O · Bromine-Silver(I) Oxide · (MW 231.74)

(oxidant; used to form tetrahydrofurans from alcohols via insertion into unactivated C-H bonds)

Physical Data: none available; reagent generated in situ.

Solubility: used as suspension in pentane, $CHCl_3$, CCl_4, or THF; marginally sol aqueous media.

Form Supplied in: generated in situ from ***Bromine*** and ***Silver(I) Oxide***.

Handling, Storage, and Precautions: reagent is generated in situ. Carrying out reaction in the dark is recommended by some authors, but is apparently unnecessary. Freshly prepared Ag_2O[6] (from Ag_2NO_3 and aq. NaOH followed by drying at 40-45 °C) is preferred to commercial samples.

Formation of Cyclic Ethers.

Remote functionalization of unactivated carbons using alcohol derivatives such as nitrites or hypohalites is well precedented.[1] A related process can be effected directly using the free alcohols in the presence of silver(I) oxide and bromine at room temperature. For example, 1,3,3-trimethylcyclohexanol underwent conversion to the bicyclic ether in 75% yield (eq 1).[2] The original report suggested that cyclization occurred via silver-assisted heterolytic cleavage of an intermediate hypobromite, with concomitant insertion of electrophilic oxygen into a δ C-H bond. A homolytic mechanism was considered less likely because the reaction proceeded readily in the dark and was unaffected by radical inhibitors. However, subsequent studies provided evidence for the intermediacy of alkoxyl radicals in the form of characteristic decomposition products,[3] racemization at the site of insertion,[4] and stereochemical dependence on hydrogen vs. deuterium abstraction.[5]

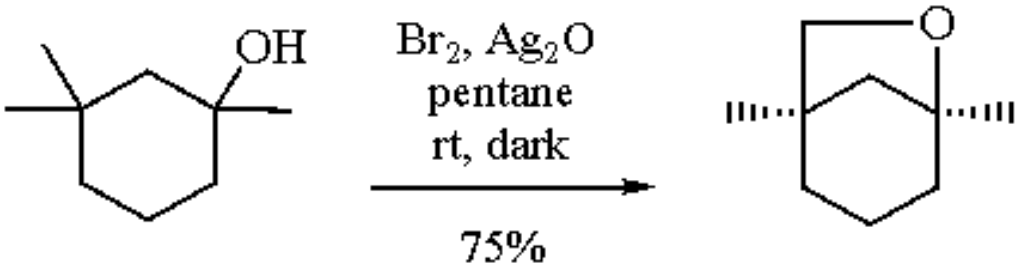

(1)

Primary and secondary alcohols led to mixtures of tetrahydrofurans and ketones or aldehydes (eq 2).[6] In some cases, yields were improved by carrying out the reaction in indirect daylight rather than in the dark. Cyclization of a benzylic alcohol to an *ortho* methyl group was found to be restricted to tertiary alcohols.[7] In an examination of the reaction of two secondary alcohols with bromine and other silver(I) salts, it was noted that the ratio of THF to ketone was sensitive to the acidity of the medium, with the addition of 1 equiv of trifluoro- or trichloroacetic acid leading to nearly complete selectivity for the ketone.[8] A more recent competition study has shown that the reaction is highly selective for methine carbons over methylenes or methyls (eq 3).[9]

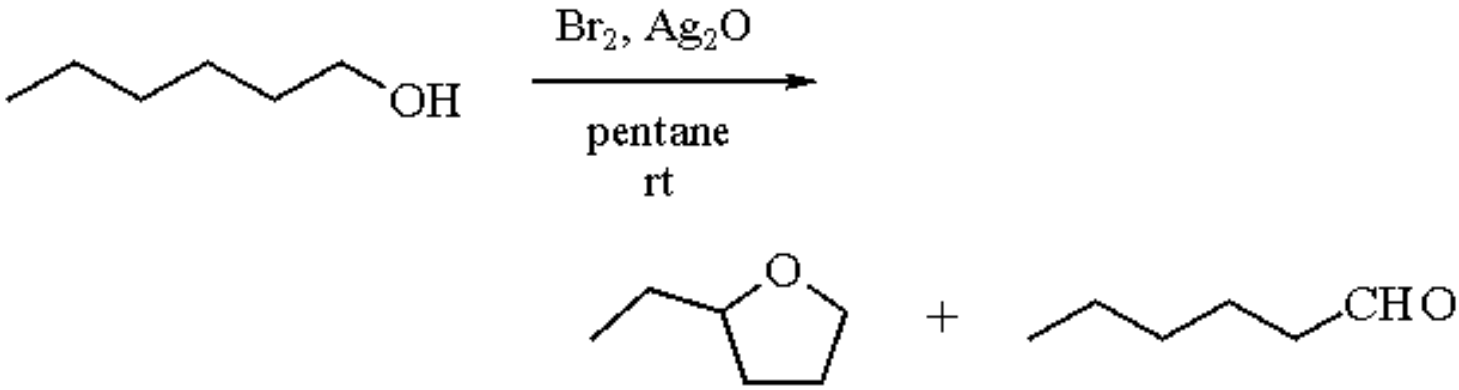

(2)

dark	61%	14%
daylight	71%	15%

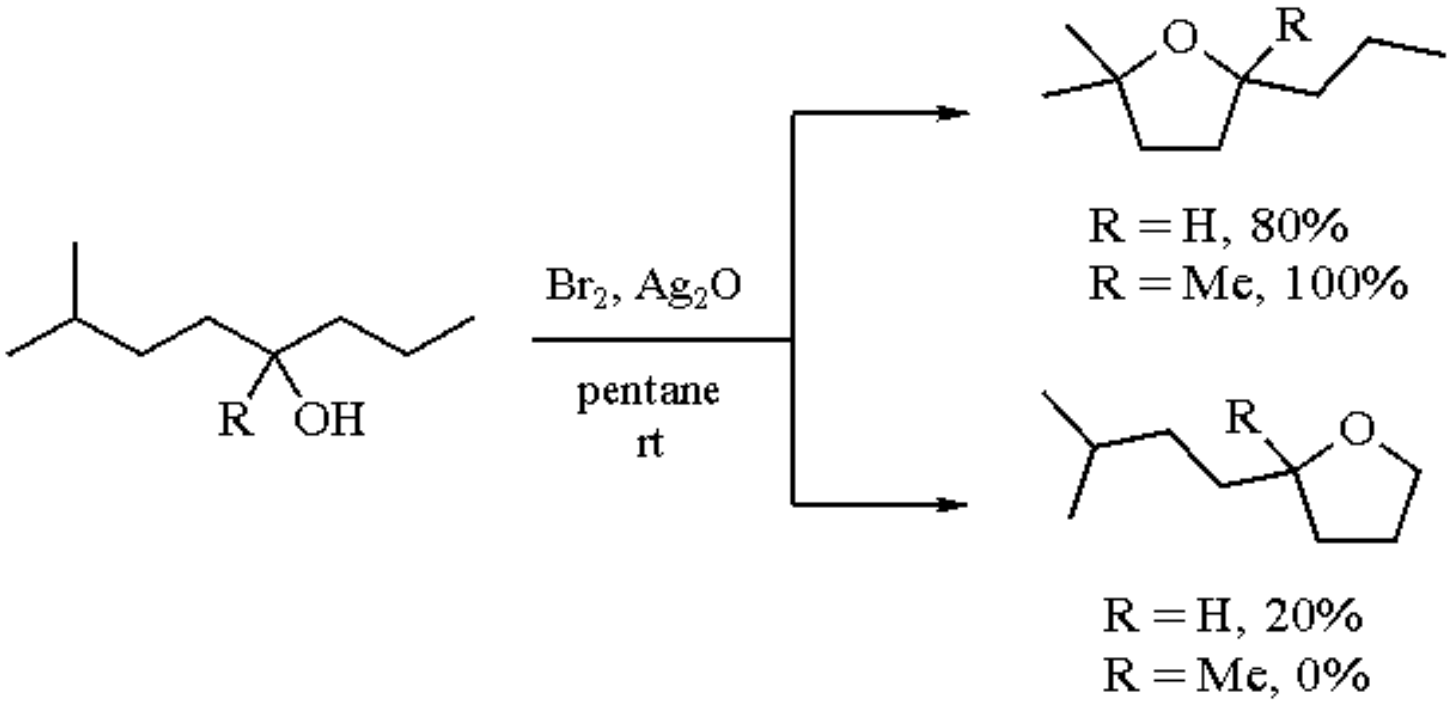

(3)

The observation of an induction period and a sigmoid curve for appearance of cyclic ether led to the suggestion of a possible autocatalytic mechanism.[10] In support of this, it was found that addition of 2 equiv of dimethyltetrahydrofuran eliminated the induction period and improved the yield of cyclization product. However, others have attributed this effect to the presence of peroxide impurities which could serve as initiators for a radical decomposition of the hypobromite intermediates.[11]

Overall, the fate of aliphatic alcohols in the presence of this reagent is analogous to that seen with ***Lead(IV) Acetate***, although the yields of cyclic ethers typically appear to be higher. The preponderance of evidence seems to favor a homolytic mechanism. The likely role of the silver salts is to facilitate the cyclization of the intermediate δ-bromo alcohols.[11,12]

---

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F. G. West & John A. Bender

Bromine Trifluoride[1]

BrF_3

[7787-71-5] · BrF_3 · Bromine Trifluoride · (MW 136.90)

(forms in situ bromine monofluoride,[2] oxidative fluorination on heteroatoms[3] and polyfluoroaromatics,[4] substituting aliphatic halogens[5] and tertiary hydrogens with fluorine,[6] brominating aromatic rings,[7] converting carbonyls through their azines and thioesters[8] to the CF_2 group)

Physical Data: mp 8.8 °C; bp 126 °C; d_{liq} 2.49 g cm^{-3}.

Form Supplied in: commercially supplied in cylinders as a volatile liquid, pale yellow when pure; orange-red crystals at low temperatures; dec at high temperature to Br_2 and BrF_5.[9]

Handling, Storage, and Precautions: use in a fume hood; BrF_3 can be stored in stainless steel or Teflon containers. It reacts violently with water and many oxygen-containing organic solvents.

Introduction.

The organic chemistry associated with BrF_3 is still in its infancy. The high reactivity of the reagent is one of the reasons that, until recently, its chemistry was not strongly developed. However, its commercial availability and the ease of preparation from the corresponding elements are changing this situation.

Bromofluorination of Alkenes.

When BrF_3 is mixed with bromine, the active species is ***Bromine Monofluoride***, which can be added to alkenes (eq 1)[2] or can brominate deactivated aromatic rings (eq 2).[7] Martin used BrF_3 to prepare compounds with hypervalent heteroatoms, many of them unattainable otherwise (eq 3).[3] A key step in Lemal's unique synthesis of perfluorocyclopentadiene also involved an oxidative fluorination (eq 4).[4] BrF_3 is capable of electrophilic fluorination and it can substitute halogens, as well as unactivated tertiary hydrogens whose bond with carbon is relatively electron rich (eqs 5 and 6).[5,6]

$$\underset{\substack{cis\\trans}}{CHCl{=}CHCl} \xrightarrow{BrF_3,\ Br_2} \underset{\substack{threo\\erythro}}{CHFCl\text{-}CHBrCl} \qquad (1)$$

$$PhNO_2 \xrightarrow{BrF_3,\ Br_2} m\text{-}BrC_6H_4NO_2 \qquad (2)$$

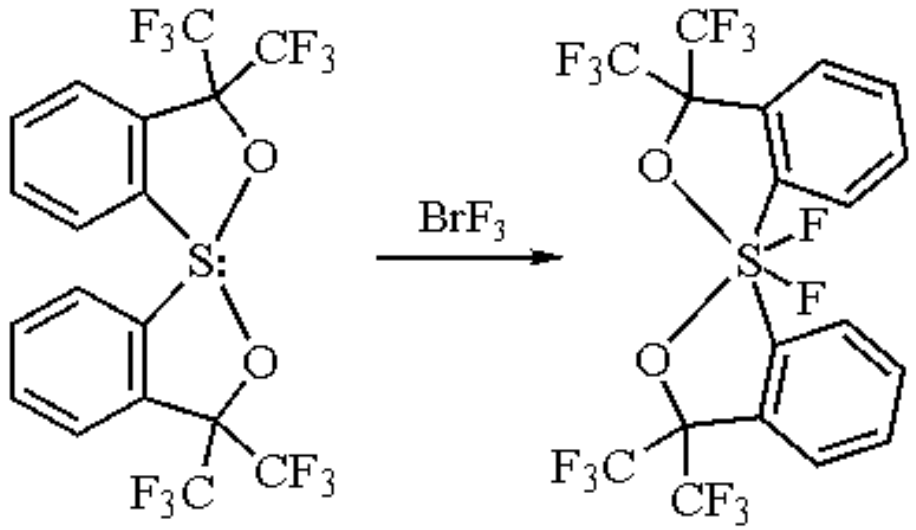

(3)

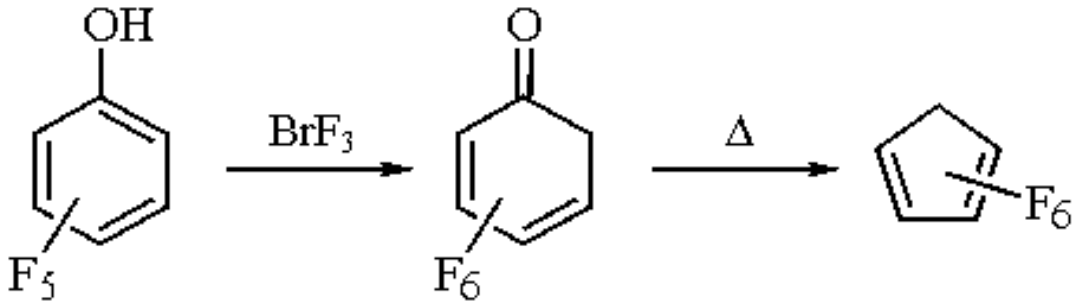

(4)

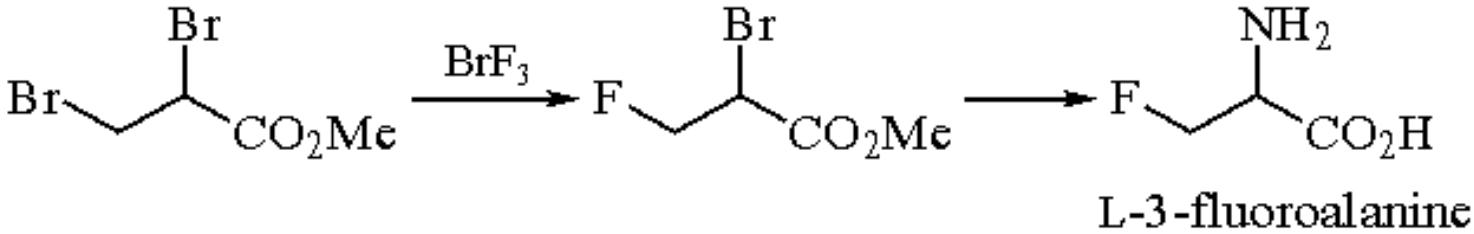

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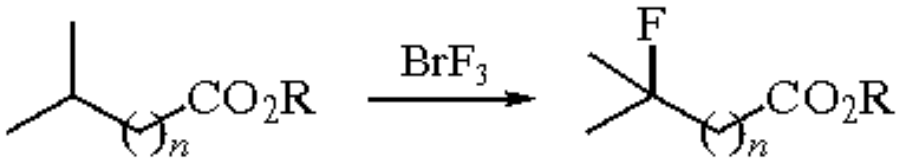

(6)

Recently, bromine trifluoride found promising use as a tool for converting carbonyls to the important CF_2 group. Aldehydes and ketones are converted through their easy-to-make azines (eq 7), while esters give the corresponding thioesters to form eventually α-fluoromethylene ethers (eq 8).[8]

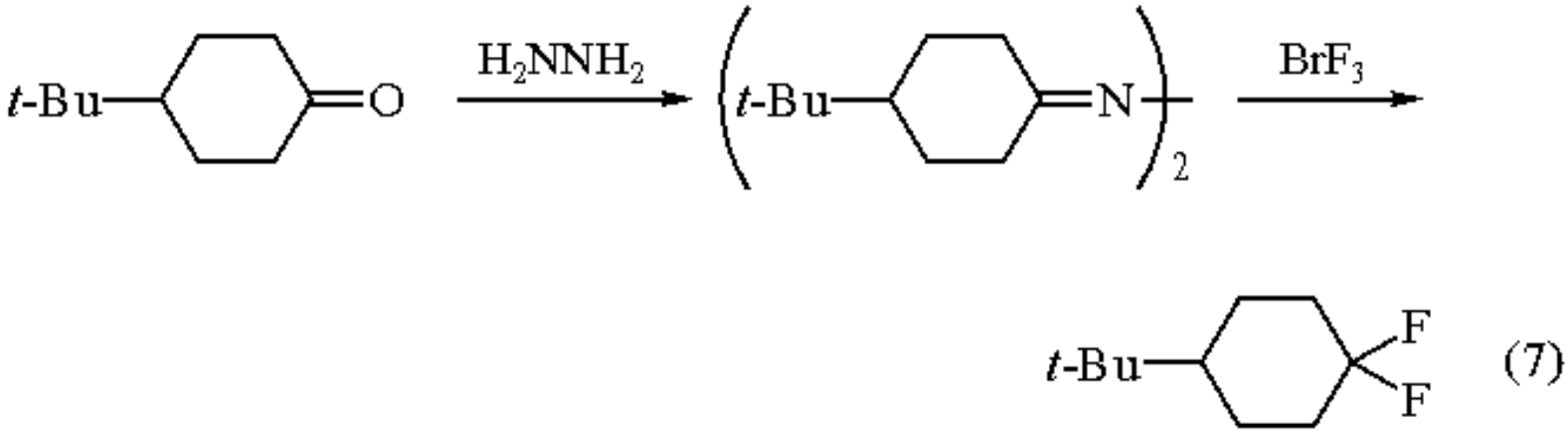

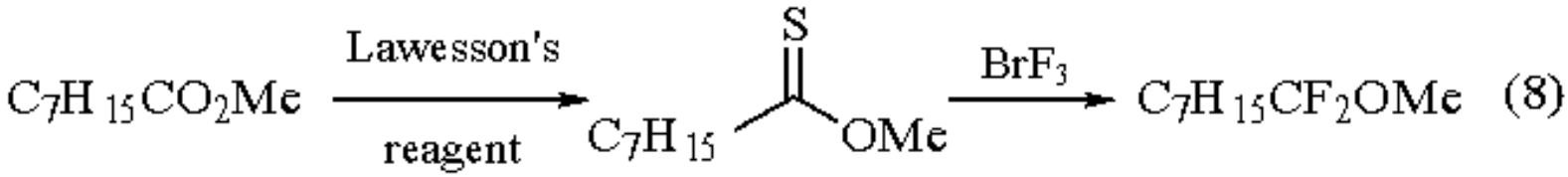

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2. Boguslavskaya, L. S.; Chuvatkin, N. N.; Kartashov, A. V.; Ternovskoi, L. A. *JOU* **1987**, *23*, 230.
3. (a) Michalak, R. S.; Wilson, S. R.; Martin, J. C. *JACS* **1984**, *106*, 7529; (b) Michalak, R. S.; Martin, J. C. *JACS* **1982**, *104*, 1683.
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8. (a) Rozen, S.; Mishani, E. *CC* **1993**, 1761. (b) Rozen, S.; Mishani, E.; Baz-Haim, A. *JOC* **1994**, *59*, 2918.
9. Stein, L. *JACS* **1959**, *81*, 1273.

Shlomo Rozen

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Bromine-Triphenyl Phosphite[1]

$Br_2.P(OPh)_3$

$Br_2.P(OPh)_3$

[76934-05-9] · $C_{18}H_{15}Br_2O_3P$ · Bromine-Triphenyl Phosphite · (MW 470.10) (Br_2)

[7726-95-6] · Br_2 · Bromine-Triphenyl Phosphite · (MW 159.81) ($P(OPh)_3$)

[101-02-0] · $C_{18}H_{15}O_3P$ · Bromine-Triphenyl Phosphite · (MW 310.29)

(reagent for the conversion of alcohols[3a,d] and phenols[5] to alkyl and aryl bromides, and aldehydes[6] to 1,1-dibromoalkanes)

Alternate Names: bromotriphenoxyphosphonium bromide;[2] triphenyl phosphite dibromide; dibromotriphenoxyphosphorane.

Physical Data: Br_2: mp -7.2 °C; bp 59.5 °C; *d*254 3.1023 g cm^{-3}. $(PhO)_3P$: mp ca. 25 °C; bp 360 °C; *d*204 1.1844 g cm^{-3}; *n*20D 1.590.

Solubility: Br_2: sol H_2O (0.214 M L^{-1}); very sol alcohol, ether, $CHCl_3$, CCl_4, CS_2. $(PhO)_3P$: insol H_2O; dec in hot H_2O; sol usual organic solvents.

Form Supplied in: not available in final form $Br_2P(OPh)_3$;[2] prepared in situ. The starting materials, Br_2 and $(PhO)_3P$, are both widely available; Br_2: dark red diatomic liquid; purity &egt;99.5%; $(PhO)_3P$: liquid which solidifies in the cold; purity &egt; 97%; typical impurities: $(PhO)_3PO$, PhOH.

Analysis of Reagent Purity: ^{31}P NMR δ: Br^- $Br+P(OPh)_3$ +4 ± 0.5; $(PhO)_3P$ +128 ± 1; $(PhO)_3P=O$ -18 ± 0.5.

Preparative Methods: the reagent is mainly prepared in situ[3a,b] or precipitated and washed just before use.[3c,e]

Handling, Storage, and Precautions: $Br_2P(OPh)_3$ is very hygroscopic and corrosive. Br_2 is a corrosive liquid with a suffocating odor which vaporizes rapidly at rt. $(PhO)_3P$ is harmful as a solid or liquid, is an irritant and is moisture sensitive; store in a cool dry place. This reagent should be handled in a fume hood.

Synthesis of Alkyl Bromides from Alcohols.

Alkyl bromides are prepared conveniently and in good yield from saturated alcohols,[3a] either by adding bromine to a mixture of the alcohol and triphenyl phosphite (eq 1) or by first preparing the triphenyl phosphite dibromide and then adding the alcohol (as in eq 3).

$$(PhO)_3P + ROH \xrightarrow[\text{0 °C then rt, 76-92\%}]{Br_2} RBr + OP(OPh)_3 + HBr \quad (1)$$

$$R = n\text{-Bu},\ t\text{-Bu},\ -(CH_2)_3-,\ MeCH(CO_2Et)-,\ PhCH_2CH_2-$$

In the preparation[3b] of optically active (-)-2-Bromo-3-methylbutane from (+)-3-methylbutan-2-ol (eq 2) without rearrangement, $(PhO)_3PBr_2$ proved to be less effective than ***Triphenylphosphine-Carbon Tetrabromide*** and particularly inferior compared to ***Triphenylphosphine Dibromide*** despite a better overall yield (eq 2).

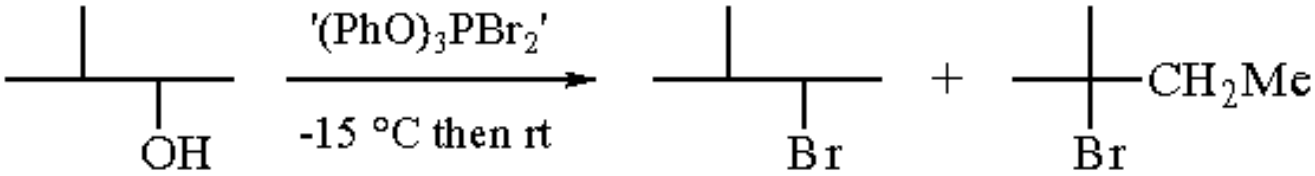

(2)

$(PhO)_3P, Br_2$	20%	55.6%
Ph_3P, CBr_4	39.3%	10%
Ph_3P, Br_2	42.3%	1.4%

Unsaturated alkenic,[3a,e] alkynic and allenic[3c,d] alcohols are converted into bromides by treating an equimolar mixture of each of them and pyridine with the previously generated $(PhO)_3PBr_2$ reagent (eq 3). This procedure avoids the addition of Br_2 and HBr to multiple bonds present in the substrate; Br_2 reacts first with the phosphite alone and pyridine acts as HBr scavenger. This method gives improved and more consistent yields (37-76%) and purer products than the conventional PBr_3 procedure.

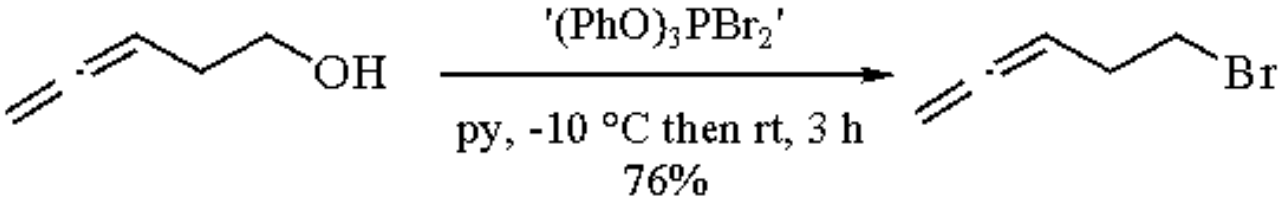

(3)

This reagent can also be used to convert hydroxy groups into bromides in carbohydrates[3f-h] and nucleosides.[3i] Carbon skeletal rearrangement is observed with hindered compounds such as the protected glucose (**1**) from which the 6-bromo derivative (**2**) is obtained instead of the expected 3-bromo derivative (eq 4). In all cases tested the migration of the hydroxy protecting group proceeds with retention of configuration.[3h] In spite of low yields, this reaction offers a new route to deoxy sugars after hydrogenolysis of the bromide intermediate.

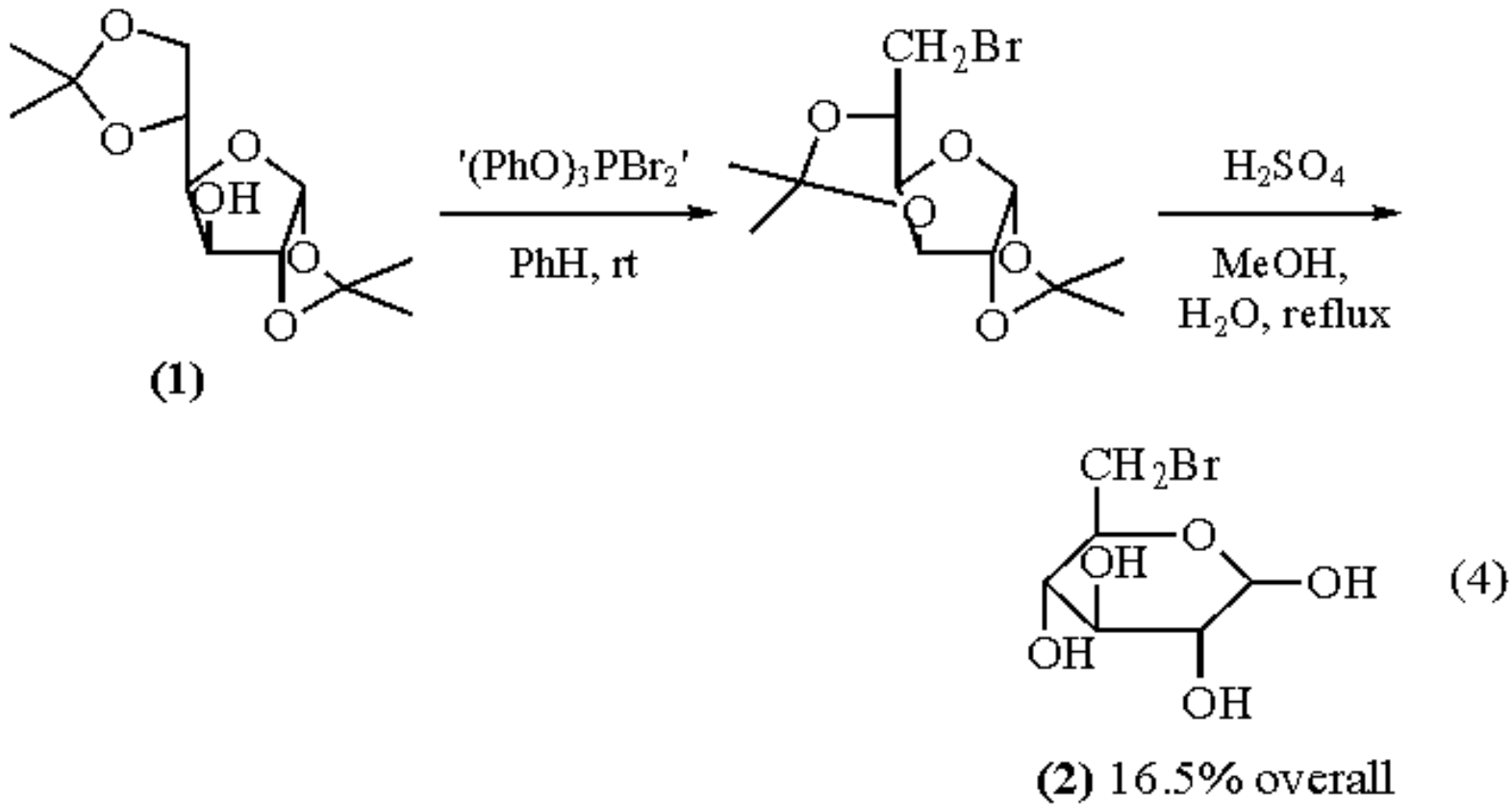

(4)

In the nucleoside field,[3i] a double activation has been performed, probably via the C-6-oxyphosphonium species, to give in one pot both a 5´-bromide and 6-phenylthioether (eq 5).

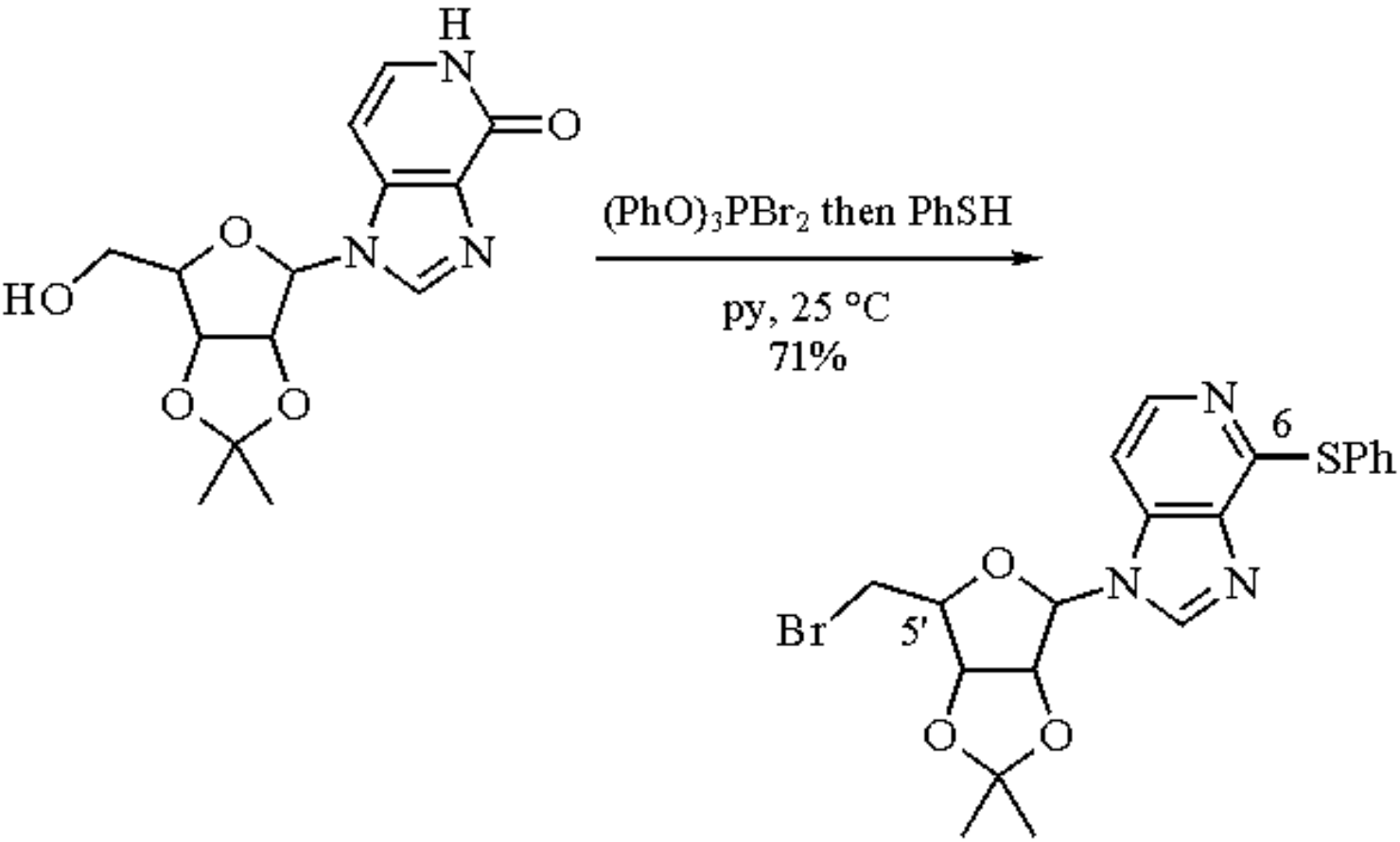

(5)

Ph_3PBr_2 effects also such conversions, but in some cases the removal of the $OPPh_3$ byproduct is problematic. This observation is quite general in the use of these reagents: the disadvantages of $(PhO)_3PBr_2$ are that phenol is produced as a byproduct and usually a mixture of phosphorus species is formed, but in many cases this reagent compares favorably with PPh_3-based reagents at the purification stage.

Synthesis of Aryl Bromides.[5]

Thermolysis of the tetraphenoxyphosphonium bromide obtained[4b] from $(PhO)_3P$ (2 parts) and Br_2 (eq 6) provides bromobenzene (eq 7). Other aryl bromides are also produced from $(PhO)_3$+POAr´ Br^- obtained by reacting Ar´OH with $(PhO)_3PBr_2$ (Ar´Br yields: Ar´ = 4-$NO_2C_6H_4$, 82%; 4-ClC_6H_4, 45%; 4-MeC_6H_4, 51%).

$$2\,(PhO)_3P \xrightarrow[\text{PhCl, 0 °C}]{Br_2} (PhO)_4PBr + (PhO)_2PBr \qquad (6)$$

$$(PhO)_4PBr \xrightarrow[\text{250 °C, 92\%}]{} PhBr + (PhO)_3PO \qquad (7)$$

Synthesis of 1,1-Dibromoalkanes.

Aliphatic and aromatic aldehydes[6] are converted into 1,1-dibromoalkyl derivatives using the $(PhO)_3PBr_2$ reagent with moderate to good yields (50-91%) (eq 8).

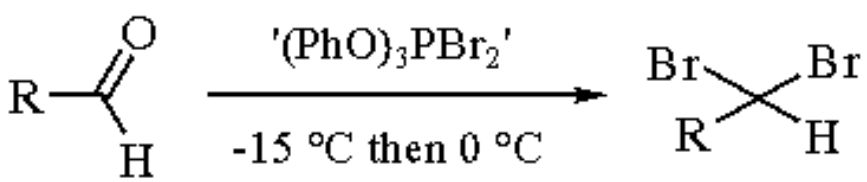

(8)

R = *n*-C_6H_{13}, 70%; MePrCH, 56%; Cy, 55%; *t*-Bu, 50%; $BnOCH_2$, 64%; Ph, 64%; 3-O_2N-4-Cl-C_6H_3, 91%; (*S*)-Me(OBn)CH, 62%

The use of this reagent is limited since substrates which are sensitive to Lewis acids, such as furfural, acrolein, and *O*-isopropylideneglyceraldehyde, undergo decomposition under these conditions; however, chiral (*S*)-2-benzyloxypropionaldehyde could be converted into the dibromo derivative without noticeable racemization.

---

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2. The reactive entity, the addition compound of the halogen and the phosphite, is in fact a mixture of several phosphorus species in equilibrium. The ratio of each component depends on the reaction conditions (solvent,

temperature, sense of the addition, etc.) as unequivocally shown by physical measurements:4 ^{31}P NMR4c,d clearly indicates the ionic tetracovalent nature of the phosphorus in $(PhO)_3$+PBr Br^- (δ ^{31}P = +4 ± 0.5 ppm).

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4. (a) Harris, G. S.; Payne, D. S. *JCS* **1956**, 3038. (b) Rydon, H. N.; Tonge, B. L. *JCS* **1956**, 3043. (c) Tseng, C. K. *JOC* **1979**, *44*, 2793. (d) Michalski, J.; Pakulski, M.; Skowrónska, A.; Gloede, J.; Gross, H. *JOC* **1980**, *45*, 3122.
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N-Bromoacetamide

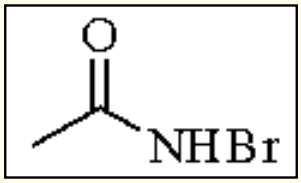

[79-15-2] · C_2H_4BrNO · *N*-Bromoacetamide · (MW 137.96)

(bromohydration and bromofluorination of alkenes; oxidation of alcohols)

Alternate Name: NBA.

Physical Data: mp 102-105 °C.

Solubility: sol $CHCl_3$, H_2O, acetone, THF; insol ether, hexane.

Form Supplied in: white needles; commercially available.

Preparative Method: *N*-bromoacetamide has been prepared by the reaction of acetamide with bromine and 50% aqueous potassium hydroxide at 0 °C.[1]

Purification: NBA can be recrystallized by dissolving in chloroform (10 mL g^{-1}), adding hexane (10 mL g^{-1}) and cooling to 0 °C. The purity of NBA may be determined by the standard bromide-thiosulfate titration method.[1]

Handling, Storage, and Precautions: *N*-bromoacetamide should be stored in the refrigerator, and protected from light and moisture to avoid decomposition. NBA is an irritating solid and precautions should be taken to avoid inhalation of the powder or contact with skin.

Bromohydration of Alkenes.

Although more expensive than ***N-Bromosuccinimide***, *N*-bromoacetamide is particularly effective for the electrophilic bromination of alkenes when a milder bromination reagent is needed, or when the ease of removal of the byproduct (acetamide) provides an advantage. The standard conditions for this reaction involve addition of NBA to a solution of the alkene in aqueous acetone, dioxane, or THF mixtures at 0 °C,[2] although for less reactive alkenes catalytic sulfuric acid has been added.[3] More recently, NBA has been chosen for the bromohydration of particularly reactive alkenes (eqs 1 and 2)[4,5] and for the synthesis of sensitive 1,2-anhydro sugars (glycal epoxides).[6] The reaction of alkenes with NBA in acetic acid has also been used for the preparation of bromoacetates.[7]

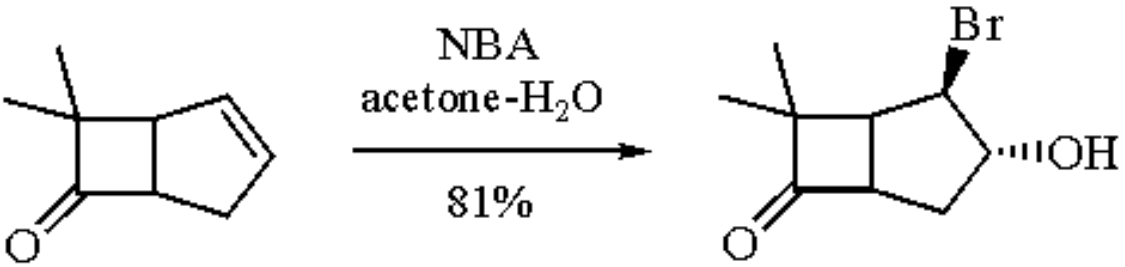

(1)

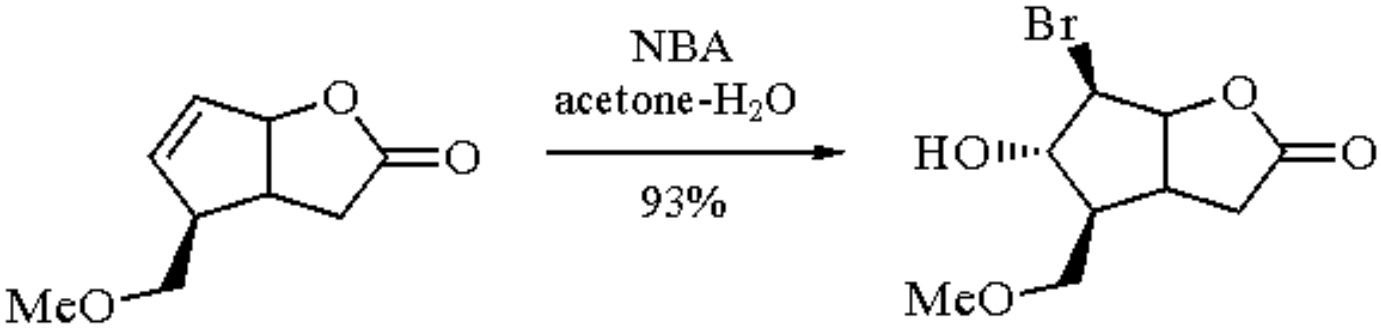

(2)

Bromofluorination of Alkenes.

Alkenes are converted to the corresponding 1,2-bromofluorides using NBA and anhydrous HF in ether.[8] This method has been especially useful for the synthesis of fluorinated steroids, fluorinated amino acids (eq 3), and other fluorine analogs of biologically important molecules.[9,10]

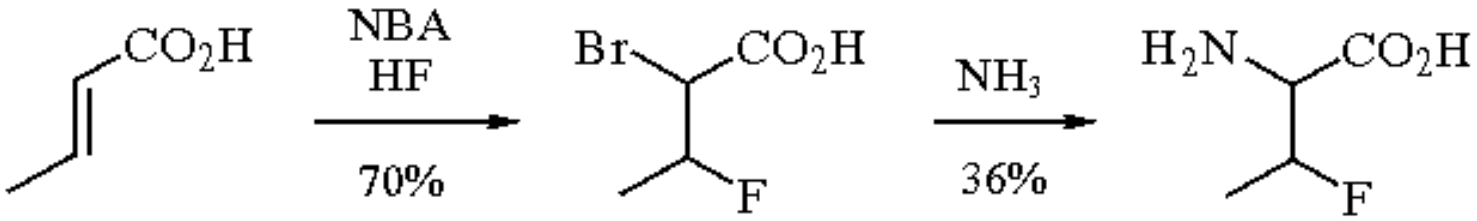

(3)

Oxidation of Alcohols.[11]

NBA has mild reactivity for the oxidation of alcohols in aqueous dioxane or THF at room temperature but is generally only of preparative value for the oxidation of secondary alcohols. Although the use of *N*-bromoacetamide and other *N*-bromoamides for the oxidation of alcohols has largely been displaced by chromium reagents and activated dimethyl sulfoxide reagents, the ease of handling and the unreactivity of the byproduct acetamide may favor the use of NBA in particular applications. In addition, secondary alcohols in different environments are oxidized at appreciably different rates by NBA and the selective oxidation of axial alcohols in the presence of equatorial alcohols has frequently been achieved in the steroid field.[12]

Related Reagents.

N-Bromoacetamide-Silver Acetate-Acetic Acid.

1. Oliveto, E. P.; Gerold, C. *OSC* **1963**, *4*, 104.
2. Reich, H.; Reichstein, T. *HVA* **1943**, *26*, 562.
3. (a) Winstein, S.; Buckles, R. E. *JACS* **1942**, *64*, 2780. (b) Fried, J.; Sabo, E. F. *JACS* **1953**, *75*, 2273.
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N-Bromoacetamide-Silver Acetate-Acetic Acid

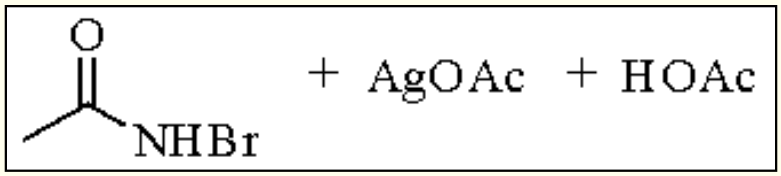

(MeCONHBr)

[79-15-2] · C_2H_4BrNO · *N*-Bromoacetamide-Silver Acetate-Acetic Acid · (MW 137.96) (AgOAc)

[563-63-3] · $C_2H_3AgO_2$ · *N*-Bromoacetamide-Silver Acetate-Acetic Acid · (MW 166.91) (HOAc)

[64-19-7] · $C_2H_4O_2$ · *N*-Bromoacetamide-Silver Acetate-Acetic Acid · (MW 60.05)

(*cis* dihydroxylation of alkenes)

For information on the individual components see ***N-Bromoacetamide***, ***Silver(I) Acetate*** and ***Acetic Acid***.

The mixture of *N*-bromoacetamide (NBA) with silver acetate serves as an extremely useful means of executing *cis* dihydroxylation of alkenes from the more hindered face, via the corresponding 1,2-diacetoxyalkane (eq 1).[1] In particular, the method offers an improvement over the previous reagents used to carry out most hindered dihydroxylations namely ***Iodine-Silver Acetate*** (the so-called Woodward hydroxylation[2]); under the latter conditions, the reaction represented in eq 1 produces a mixture of diastereoisomers. The use of NBA furnishes a single diol in all reactions of cyclohexenes except where methylcyclohexenes are employed; in the reaction of these substrates a product mixture very similar to that seen under Woodward conditions is obtained (Table 1), but yields of diol are improved.

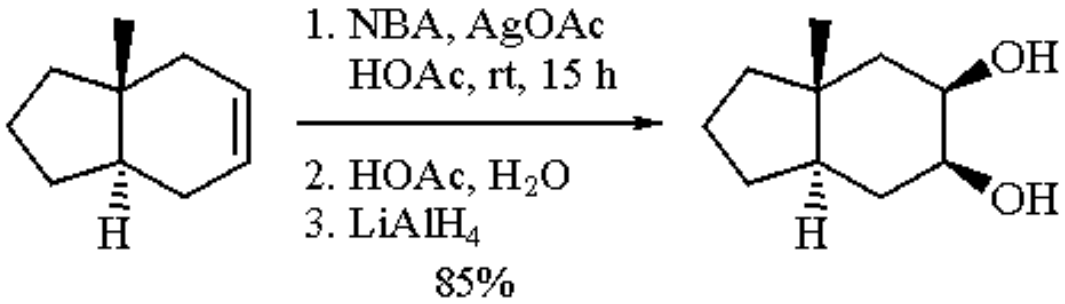

(1)

Table 1 Preparation of *cis*-1,2-Diols using NBA

Alkene	Diol	Yield (%)
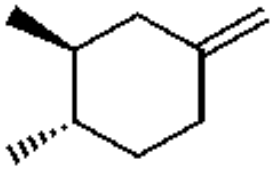	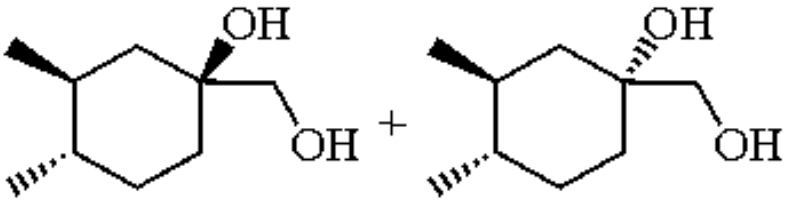 33:67	100 (65)[a]
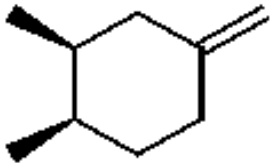	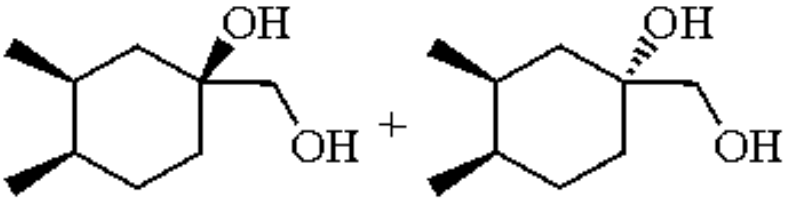 30:70	85 (65)[a]
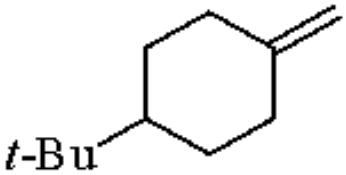	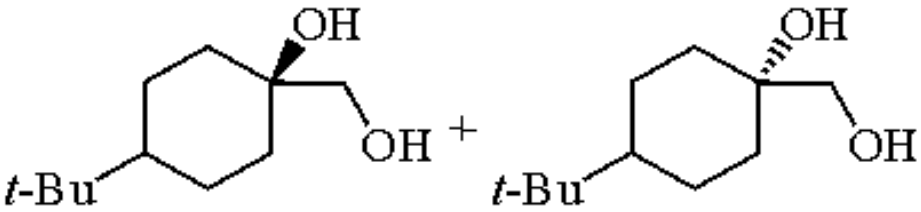 45:55	85 (60)[a]
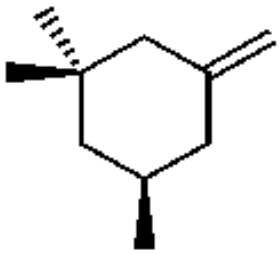	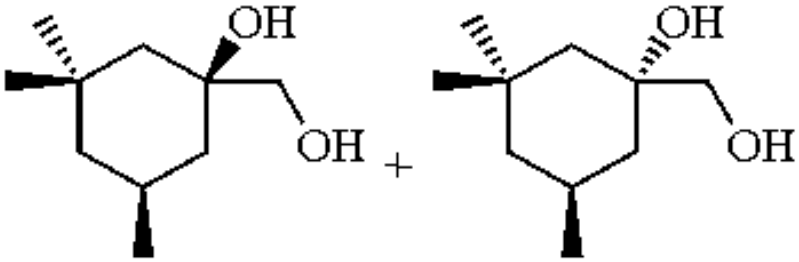 70:30	50 (0)[a]

[a] Yields obtained using I_2, AgOAc.

The NBA-AgOAc mixture is also effective in the hydroxylation of prochiral acyclic alkenes and has been thus employed in studies towards total synthesis of daunosamines (eq 2).[3,4] In these studies, reaction of (**1**) gave the desired L-*lyxo* stereoisomer in excess; use of Woodward conditions gave this isomer in minor amounts (4:1 *xylo*:*lyxo*) while ***Osmium Tetroxide*** gave only a slight preponderance of *lyxo* (1:2 *xylo*:*lyxo*).[3]

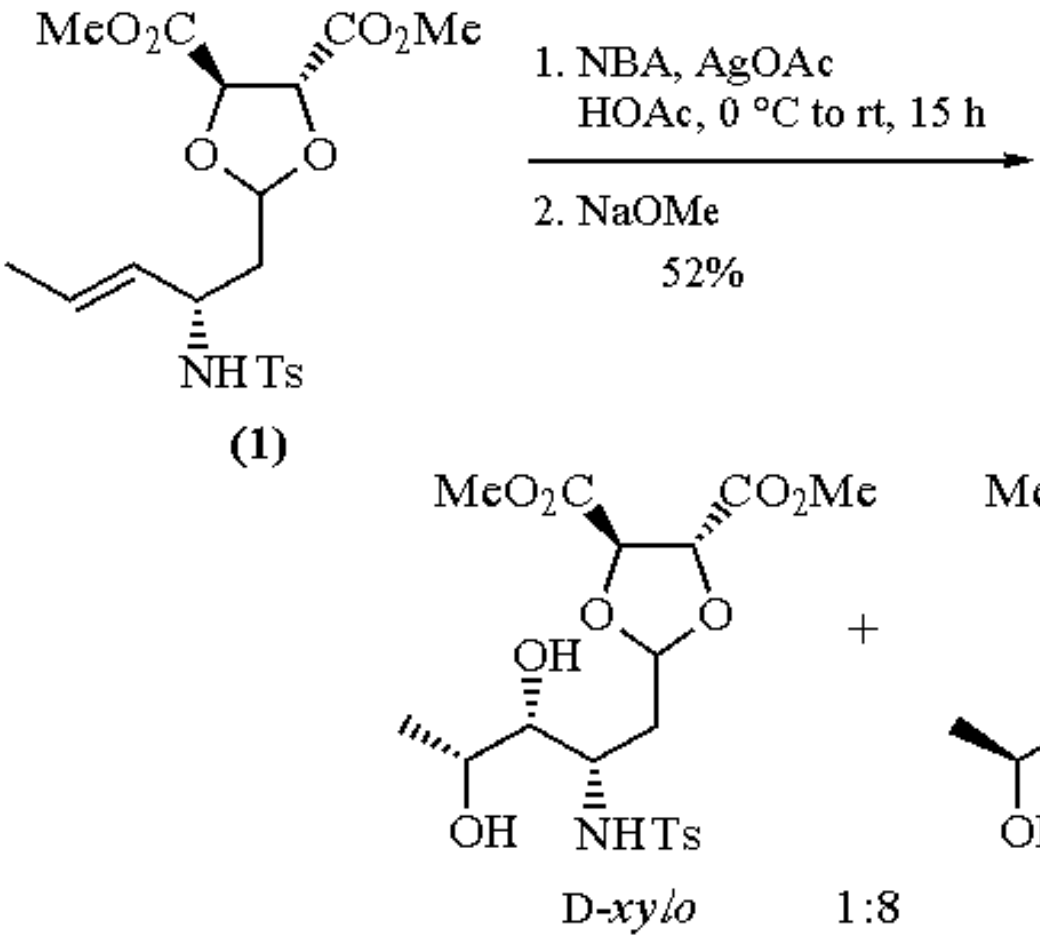

(2)

Contrary to one report, NBA-AgOAc is not claimed to effect bromoacetoxylation of alkenes.[5]

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1. Jasserand, D.; Girard, J. P.; Rossi, J. C. *TL* **1976**, 1581.
2. Woodward, R. B.; Brutcher, F. V. *JACS* **1958**, *80*, 209.
3. Dyong, I.; Wiemann, R. *CB* **1980**, *113*, 2666.
4. Dyong, I.; Friege, H.; zu Höne, T. *CB* **1982**, *115*, 256.
5. *FF* **1979**, *7*, 182.

Joseph Sweeney

University of Bristol, UK

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Bromoacetone[1]

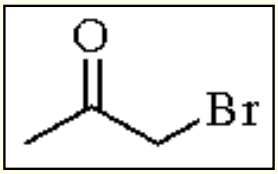

[598-31-2] · C_3H_5BrO · Bromoacetone · (MW 136.98)

(acetonylation; synthesis of heterocycles)

Alternate Name: 1-bromo-2-propanone.

Physical Data: bp 40-42 °C/13 mmHg;[2] 63.5-64 °C/50 mmHg;[3] 37-45 °C/12 mmHg;[4] 138-140 °C;[5] *n*15D 1.4697.

Solubility: sol most organic solvents; the use of nucleophilic solvents has to be avoided due to the high reactivity of the reagent for nucleophilic substitution.

Preparative Methods: bromoacetone is most conveniently prepared by bromination of ***Acetone*** with ***Bromine*** in aqueous acetic acid (eq 1)[2] or in aqueous medium in the presence of potassium chlorate (eq 2).[3] The yields are never excellent but these procedures are recommended due to the ease of operation and the inexpensive starting materials. However, it has been reported that acetone is brominated to give bromoacetone in almost quantitative yields by bromination with (*Z*)-5-nitro-2-furylvinylpyridinium tribromide[5] or 6-chloroperfluorohexanesulfonyl bromide.[6]

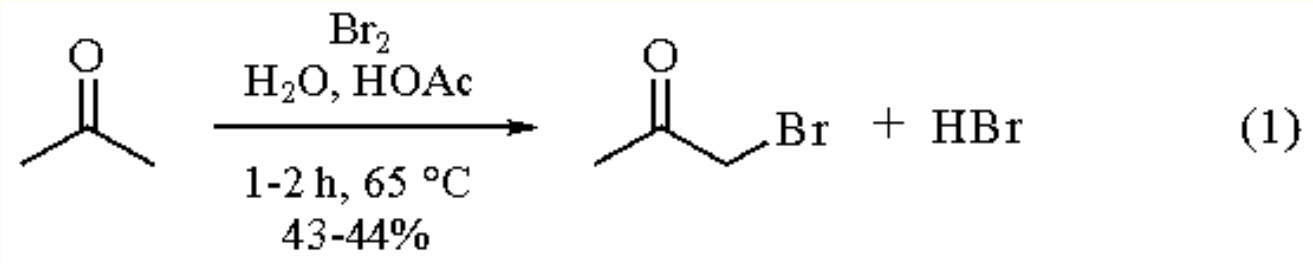

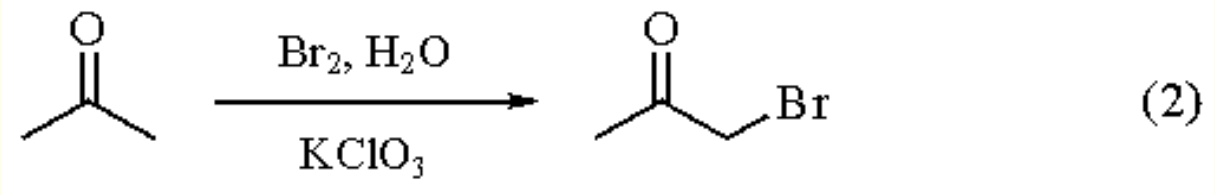

Handling, Storage, and Precautions: strong lachrymator; strong alkylating agent; toxic; strong vesicant; only use in a well-ventilated hood. The stability of bromoacetone is notably dependent upon its purity.[3] In the absence of any stabilizer the crude product appears to keep much better than the purified material, but the

situation is reversed when a trace of magnesium oxide is present. Complete decomposition occurs after several months on standing at rt in the dark. Pure bromoacetone can be kept over a trace of magnesium oxide as colorless liquid for years. Traces of water (0.01%) seem to stabilize this reagent.[3]

Introduction.

Like α-halo ketones in general, bromoacetone is an extremely versatile reagent or building block in organic chemistry.[1] A major application of bromoacetone is its use as an acetonylation reagent for a whole range of nucleophilic heteroatoms, e.g. oxygen, sulfur, nitrogen, phosphorus, and halides. Nucleophilic additions across the carbonyl group are also observed. In the former application, two major reactions are utilized in ring closure reactions with difunctional and polyfunctional substrates. To a lesser extent, aldol-type reactions of bromoacetone have been reported. Bromoacetone has been isolated from the red alga *Asparagopsis taxiformis*.[7]

Acetonylation of Oxygen Nucleophiles.

Reaction of bromoacetone with aqueous sodium hydroxide gives hydroxyacetone.[8] In this case the mechanism may occur by direct substitution or via rearrangement of the corresponding hydroxyepoxide. Phenolates easily substitute bromoacetone (eq 3).[9] When applied to functionalized phenols, e.g. pyrocatechol,[10] 5-bromosalicaldehyde (eq 4),[11] or 2-acetamidophenol (eq 5),[12] benzodioxanes,[10] 2-acetyl-5-bromobenzofuran,[11] or 4-acetyl-3-methyl-4*H*-1,4-benzoxazine[12] are produced, respectively. Also phenolic *p*-*t*-butylcalix[4]arenes are tetraacetonylated with bromoacetone.[13] Esterification of fatty acid chains by bromoacetone is quantitatively accomplished in the presence of quaternary ammonium salts (eq 6).[14]

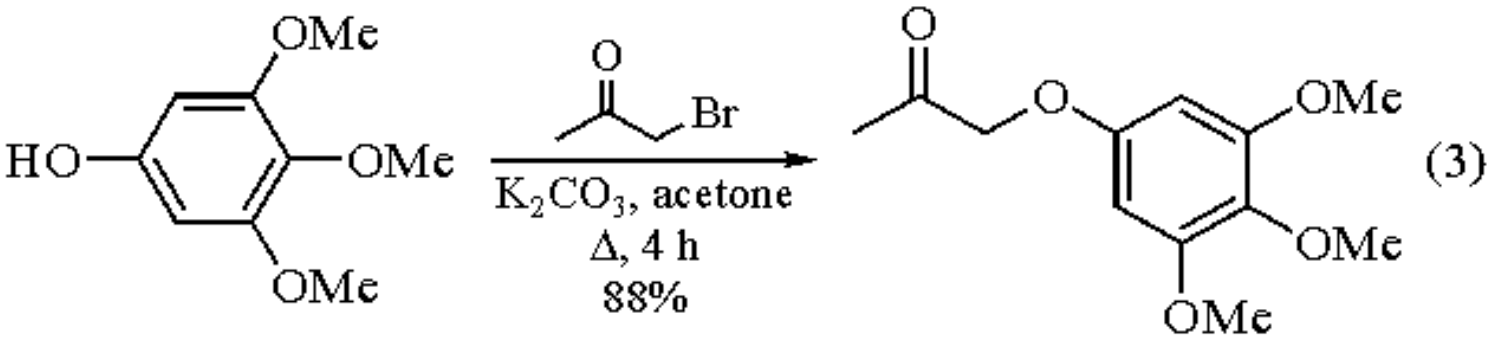

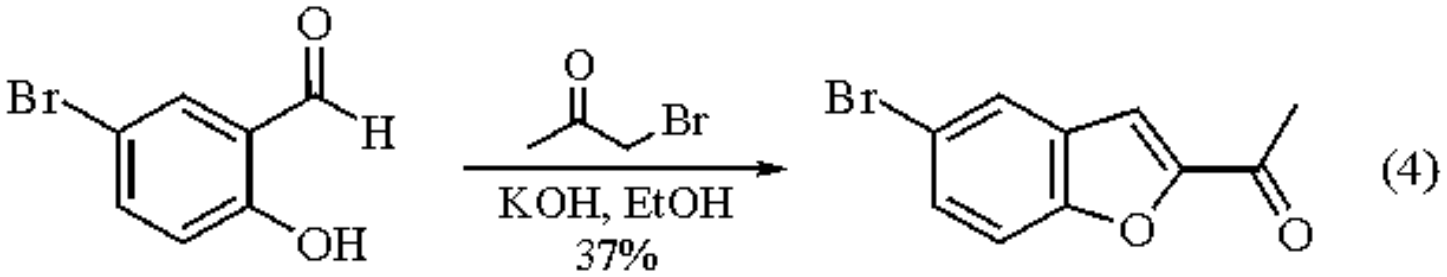

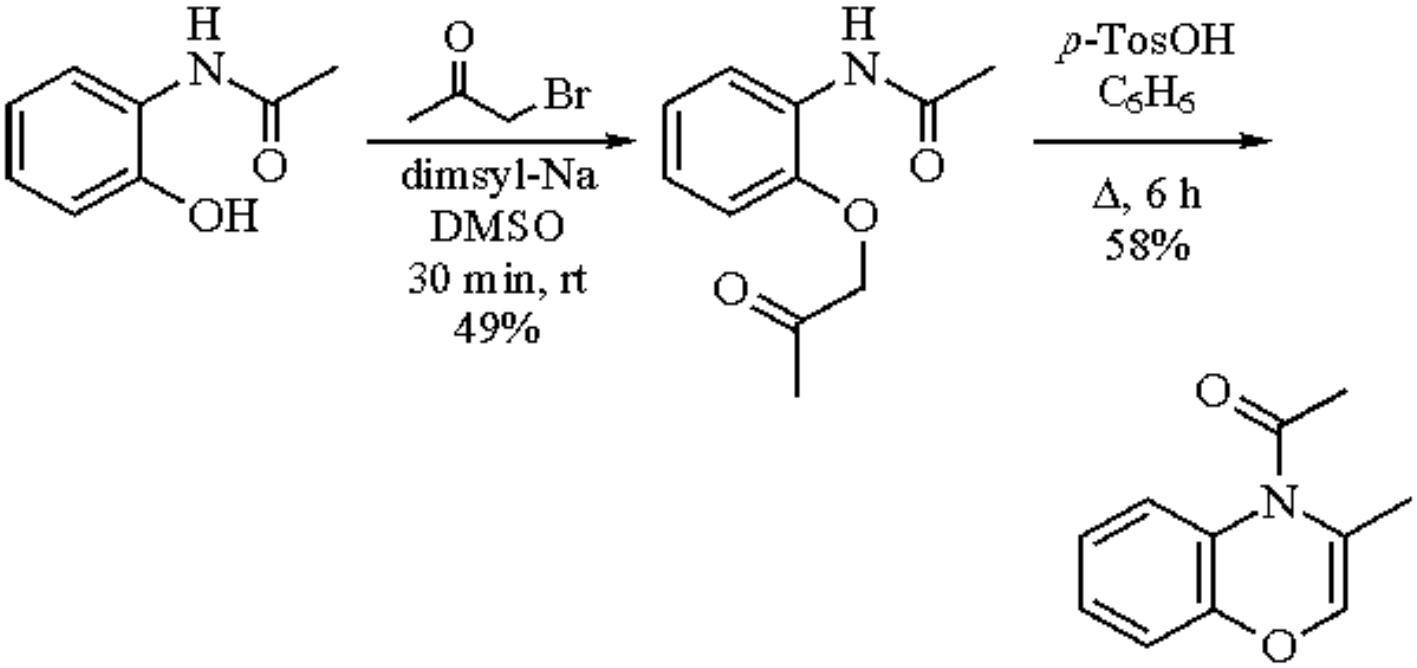

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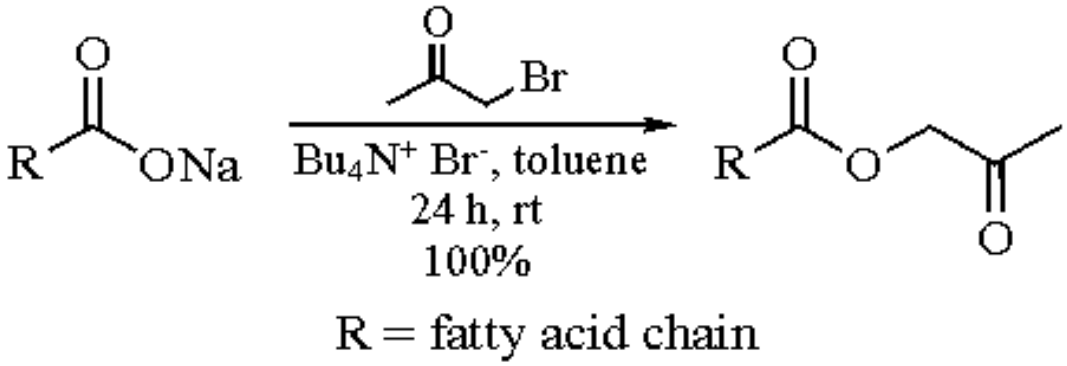

(6)

R = fatty acid chain

Acetonylation of Sulfur Nucleophiles.

Thiolates react smoothly with bromoacetone to afford α-sulfenylated acetones (eq 7).[15,16] However, lower alkyl thiolates give very low yields.[17] The substitution product with sodium thiolate undergoes cyclocondensation with ammonia in the presence of an aldehyde or ketone to yield 3-thiazolines.[18] Potassum thiocyanate[19] and thioacetic acid[20] undergo acetonylation by bromoacetone, the latter substitution product undergoing cyclization to 2,4-dimethylthiazole (eq 8).[20] This thiazole synthesis can also be accomplished in a one-step process.[20]

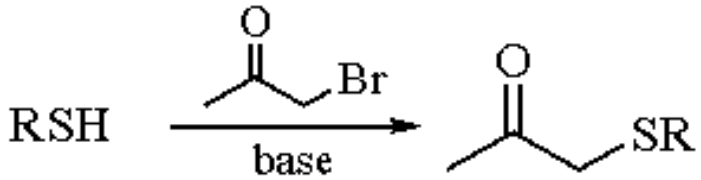

(7)

R = alkyl, 1-naphthyl

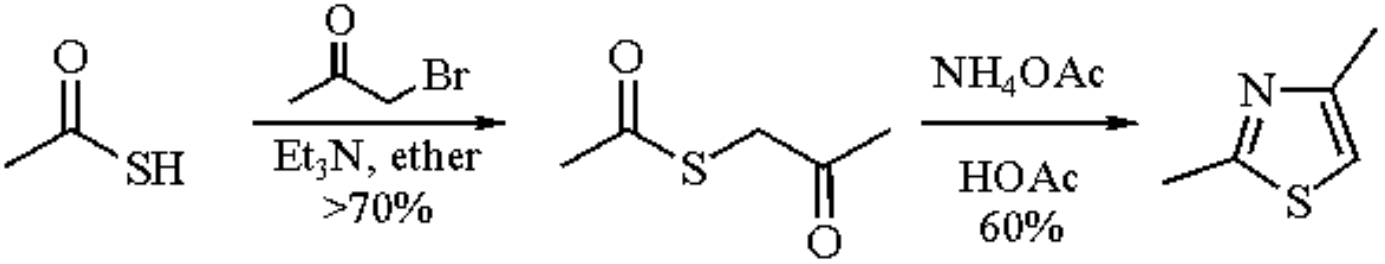

(8)

Thioamide-type compounds, e.g. pyrrolidine-2-thiones[21] and 2,4-dihydro-5-methyl-4-phenyl-3*H*-1,2,4-triazole-3-thione,[22] react with bromoacetone at sulfur. These acetonylated compounds are useful for desulfurization and further elaboration into (±)- hygrine (eq 9),[21] or can be cyclized into 1*H*-thiazolo[3,2-*b*]-*s*-triazolium salts.[22] Also thiourea reacts similarly with bromoacetone to give 2-amino-4-methylthiazole directly (eq 10).[8,23]

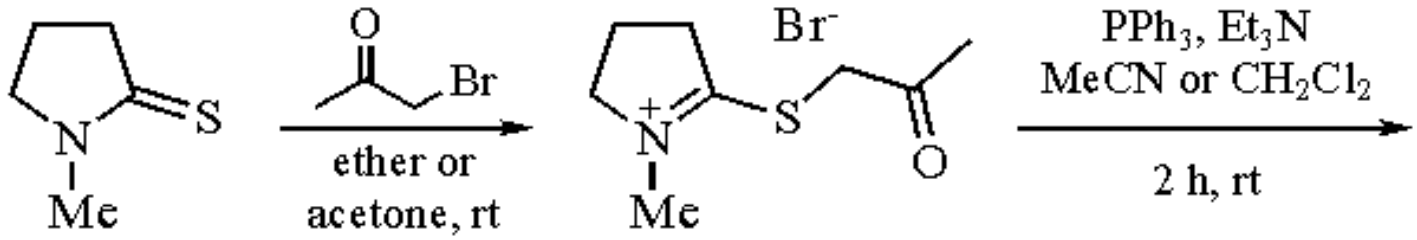

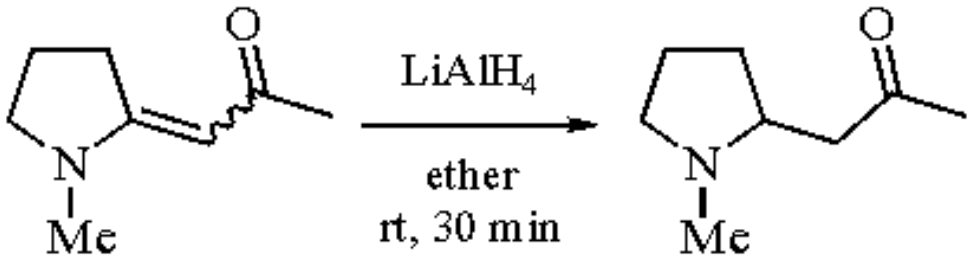

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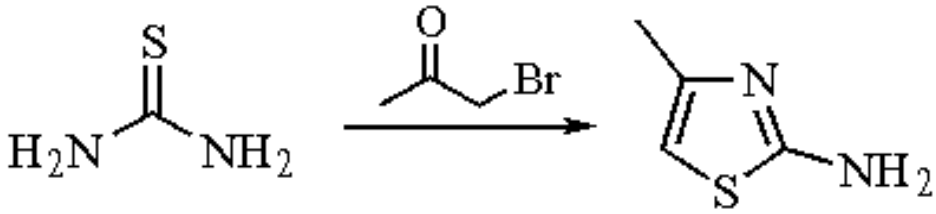

(10)

Acetonylation of Nitrogen Nucleophiles.

Primary amines are mono- or diacetonylated by bromoacetone (eq 11).[24,25] The diacetonylated compounds are useful substrates for the acid-catalyzed ring closure to tetrahydropyridin-3-ones (eq 11).[24,25] When mixed at rt for 4 days with excess primary amines, e.g. isopropylamine, bromoacetone is converted to the corresponding α-(*N*-alkylamino)imine, which undergoes cyclocondensation with ethyl acetoacetate to give pyrroles.[26] Secondary amines also give rise to nucleophilic substitution of the halogen in bromoacetone.[27-29] Heating of *N*-methyl formimidate with bromoacetone in toluene/1,2-dimethoxyethane gives access to the corresponding *N*-methylformamide (eq 12), which is a precursor for 1-(*N*-methylamino)-2-propanone.[30]

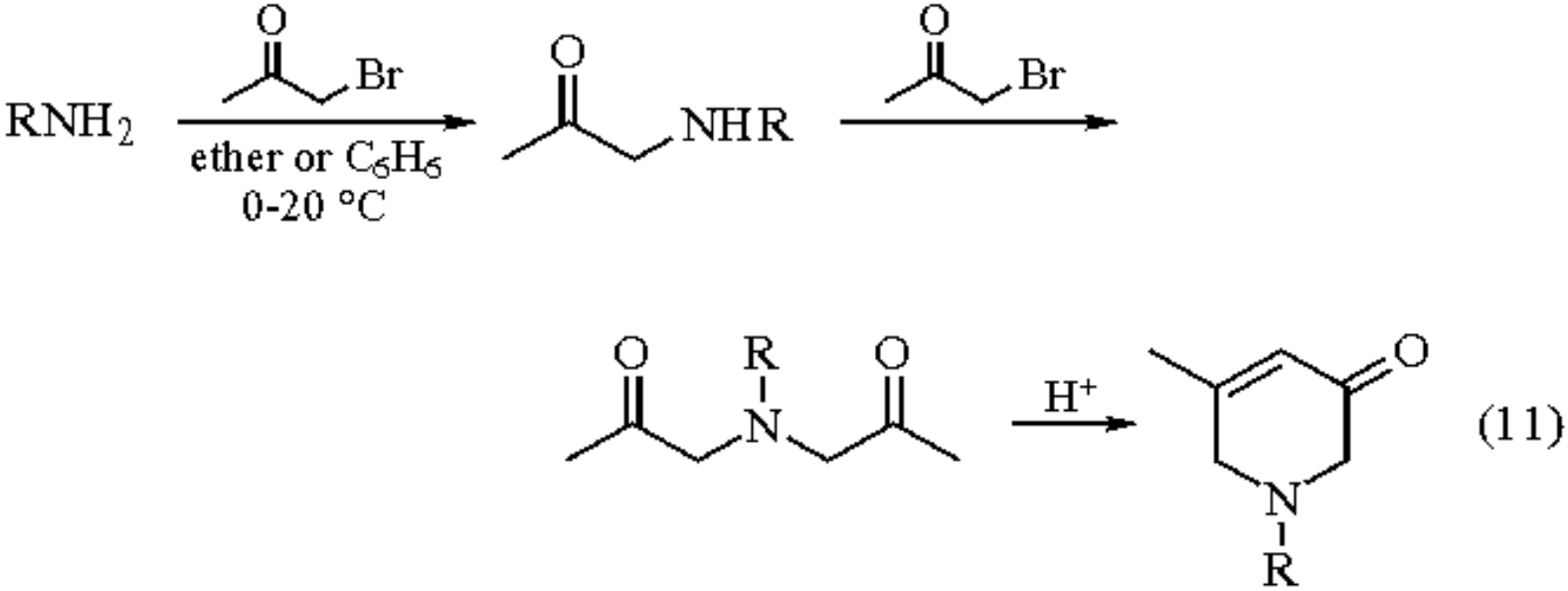

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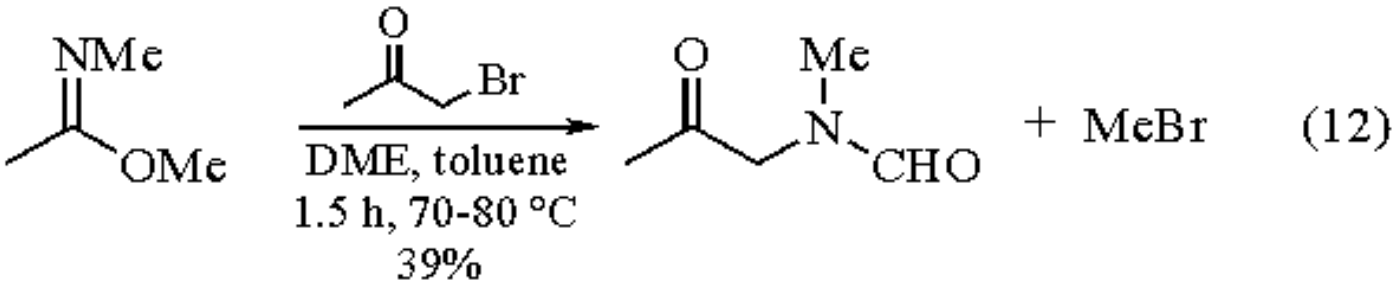

(12)

Imide-type compounds, e.g. thiazolidine-2,4-dione[31] and phthalimide,[32] are acetonylated by bromoacetone, while tosylamides[33] and 2-imidazolinones[34] are similarly alkylated at nitrogen. Quaternizations at nitrogen of pyridines (eq 13)[35,36] and other aza heterocycles, such as 2,4-dimethylthiazole (eq 14),[37] have been performed with bromoacetone. Some of these salts are useful for further cyclization into fused heterocycles, e.g. pyrrolothiazoles.[37]

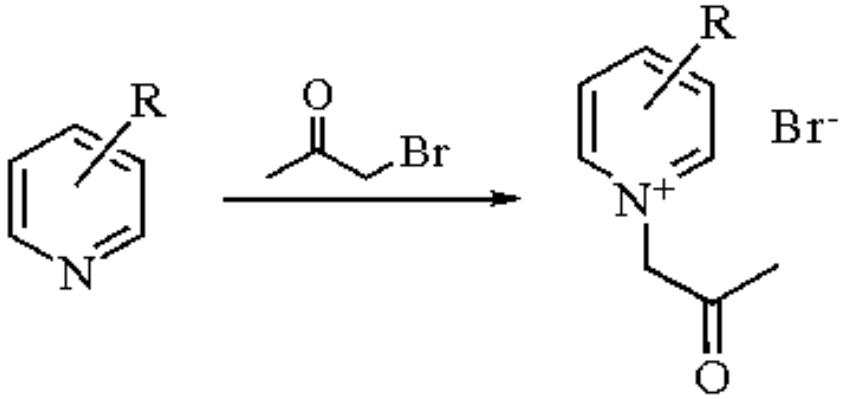

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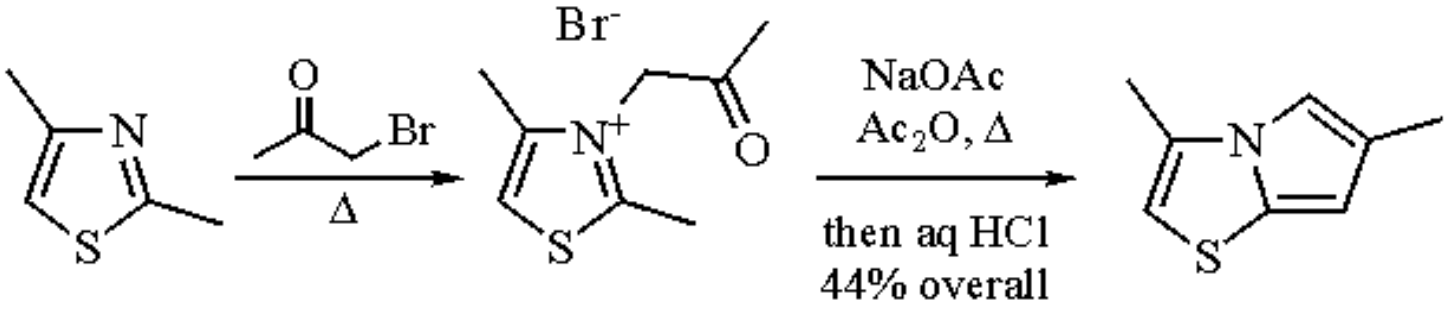

(14)

Acetonylation of Carbon Nucleophiles.

Active methylene functions of malonates (eq 15),[38] dicarboxylic esters (eq 16),[39] β-keto esters (eq 17),[40] β-diones,[41] and β-oxo sulfones (eq 18)[42] are alkylated by bromoacetone.

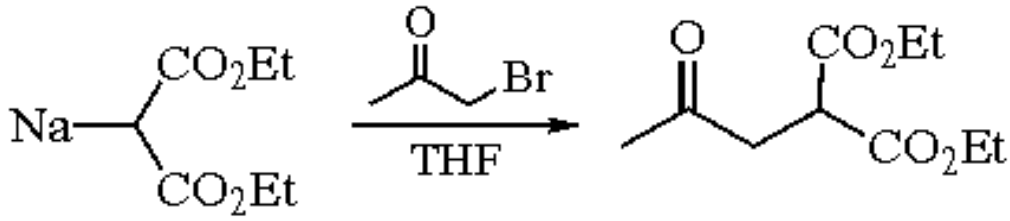

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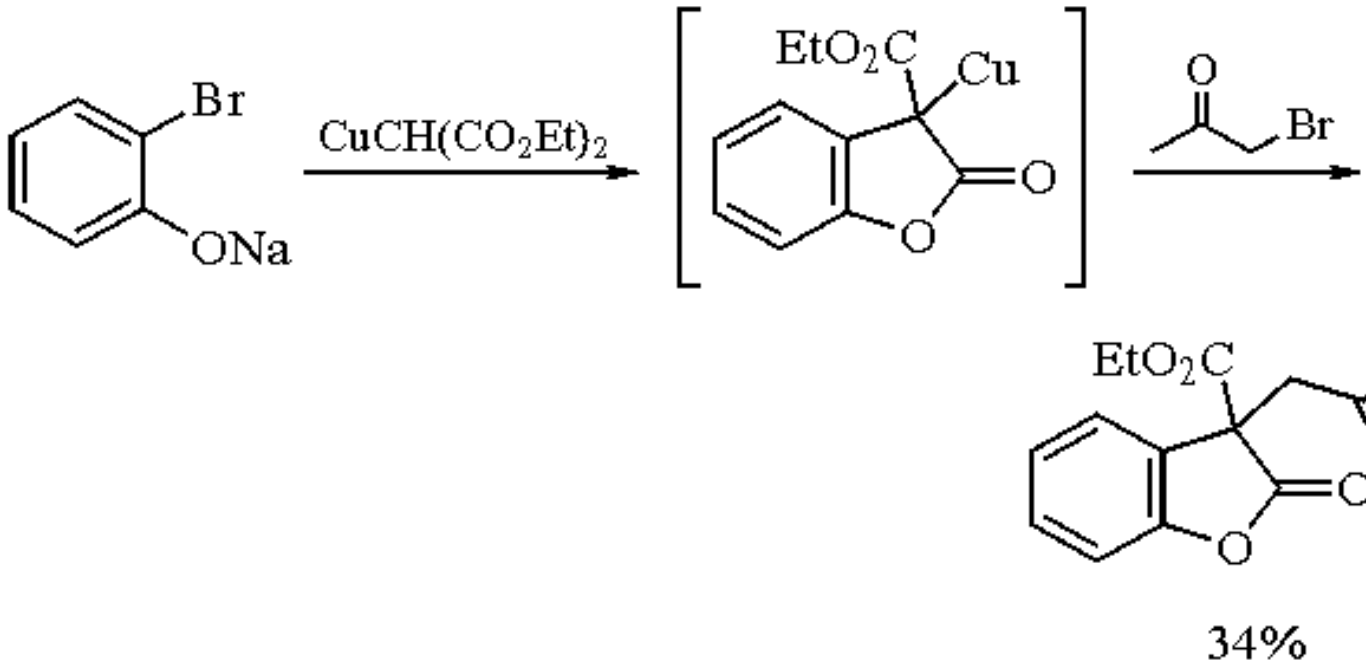

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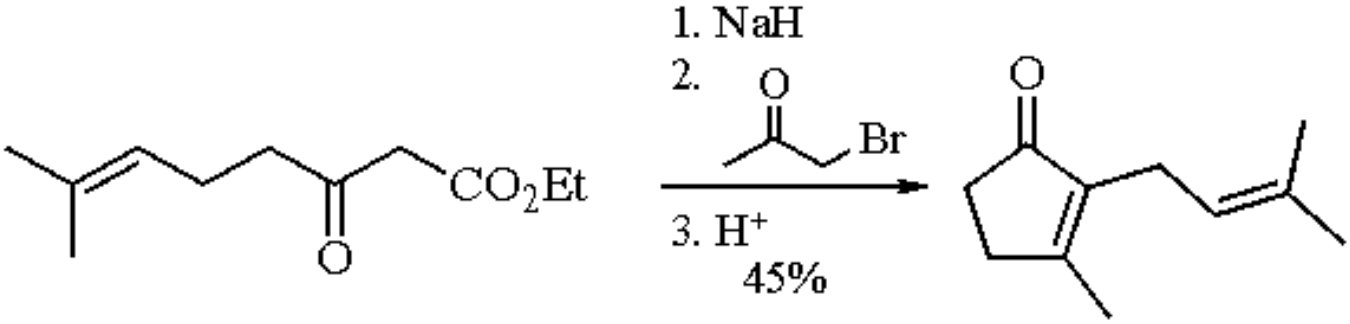

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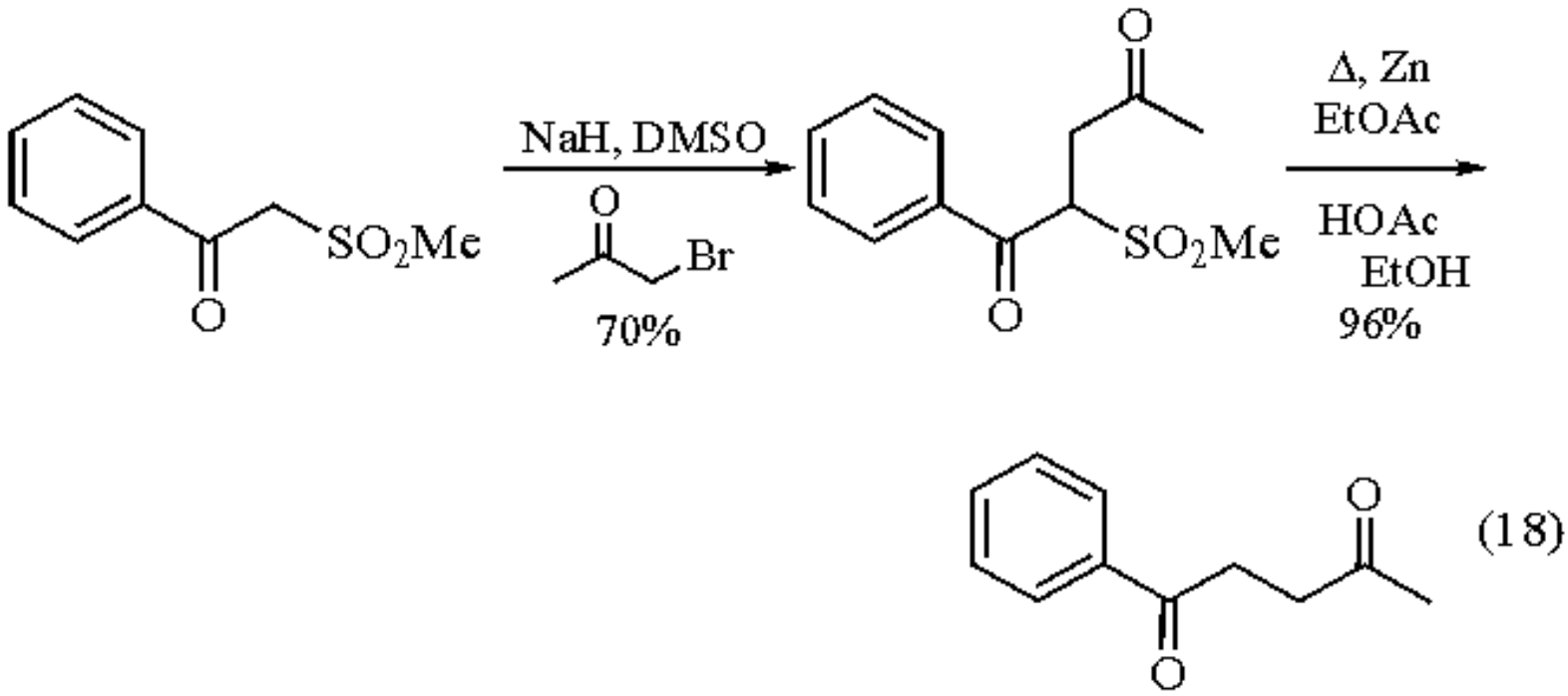

(18)

The methylcopper-catalyzed hydroalumination of 2-cyclohexenone with ***Diisobutylaluminum Hydride*** generates an aluminum enolate, which is trapped by bromoacetone to afford α-acetonylated cyclohexanone (eq 19).[43]

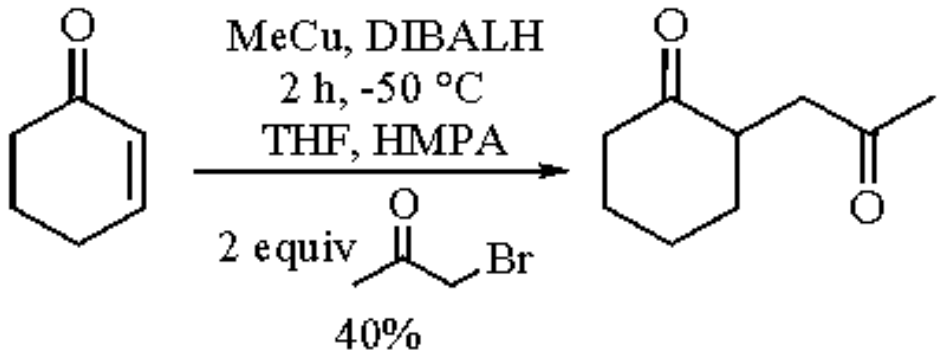

(19)

Enamines are useful nucleophiles towards bromoacetone, affording 1,4-dicarbonyl compounds (eq 20).[4,44,45] A convenient route to methyl ketones from bromoacetone consists of the reaction with boranes, e.g. tri-*n*-butylborane, in the presence of the potassium salt of 2,6-di-*t*-butylphenol (eq 21).[46]

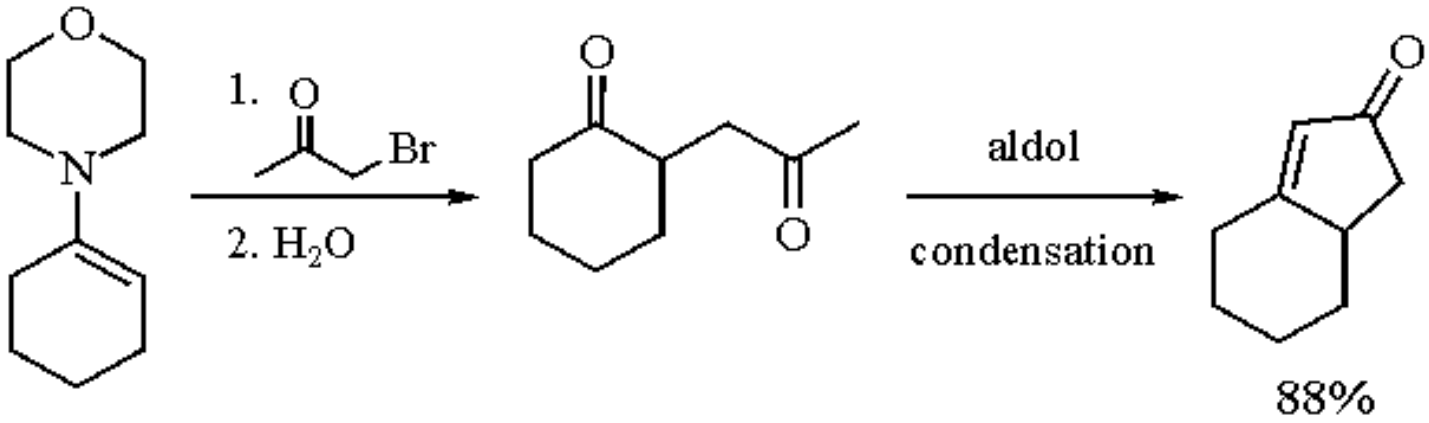

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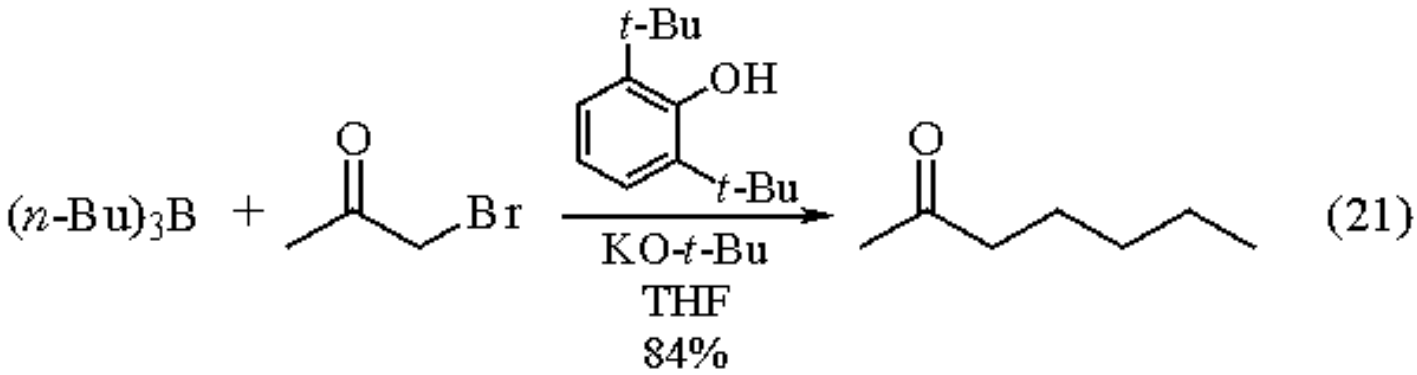

Reactions with Phosphorus Reagents.

The reaction of α-halo ketones and trialkyl phosphites is extremely complex and usually leads to vinyl phosphates and β-ketophosphonates according to Perkov and Arbuzov reaction mechanisms.[48] However, the reaction of bromoacetone with trimethyl phosphate in methanol is a suitable entry to dimethyl 1-methylvinyl phosphate (eq 22).[48,49] It has been reported that bromoacetone reacts with triethyl phosphite in ether at -70 °C in the presence of hydrogen chloride to give the adduct across the carbonyl group (eq 23).[50] Phosphines, e.g. 2-anisyldiphenylphosphine, give nucleophilic substitution, the resulting phosphonium salt being a precursor for phosphorus heterocycles (eq 24).[51]

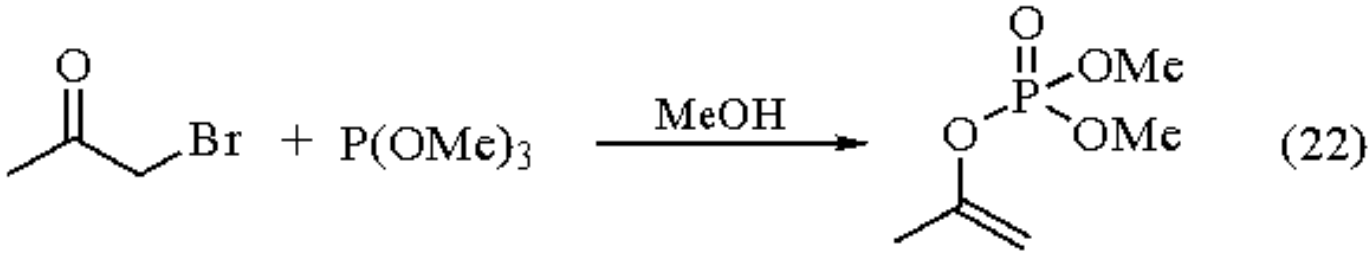

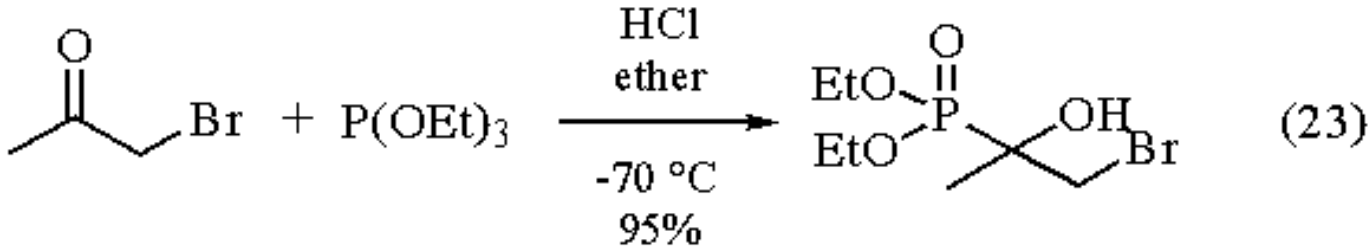

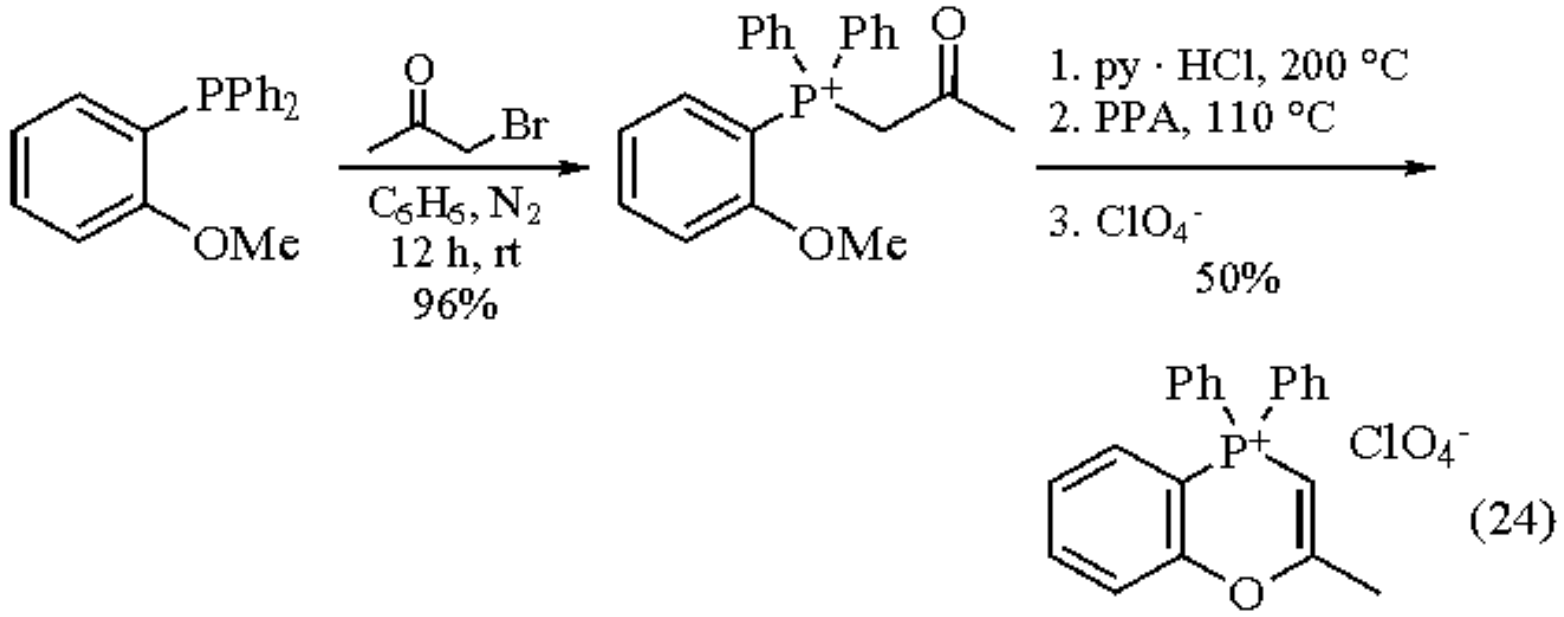

Addition Reactions across the Carbonyl Group.

Grignard reagents add to the carbonyl function of bromoacetone at low temperature.[52,53] These adducts can be used for further elaboration, such as in the synthesis of homologated tertiary alcohols (eq 25).[52] Acetalization of bromoacetone occurs smoothly under the usual conditions.[54] The dimethyl acetal of bromoacetone is converted into 3-bromo-2-methoxypropane, a suitable acetonylation reagent (eq 26).[54]

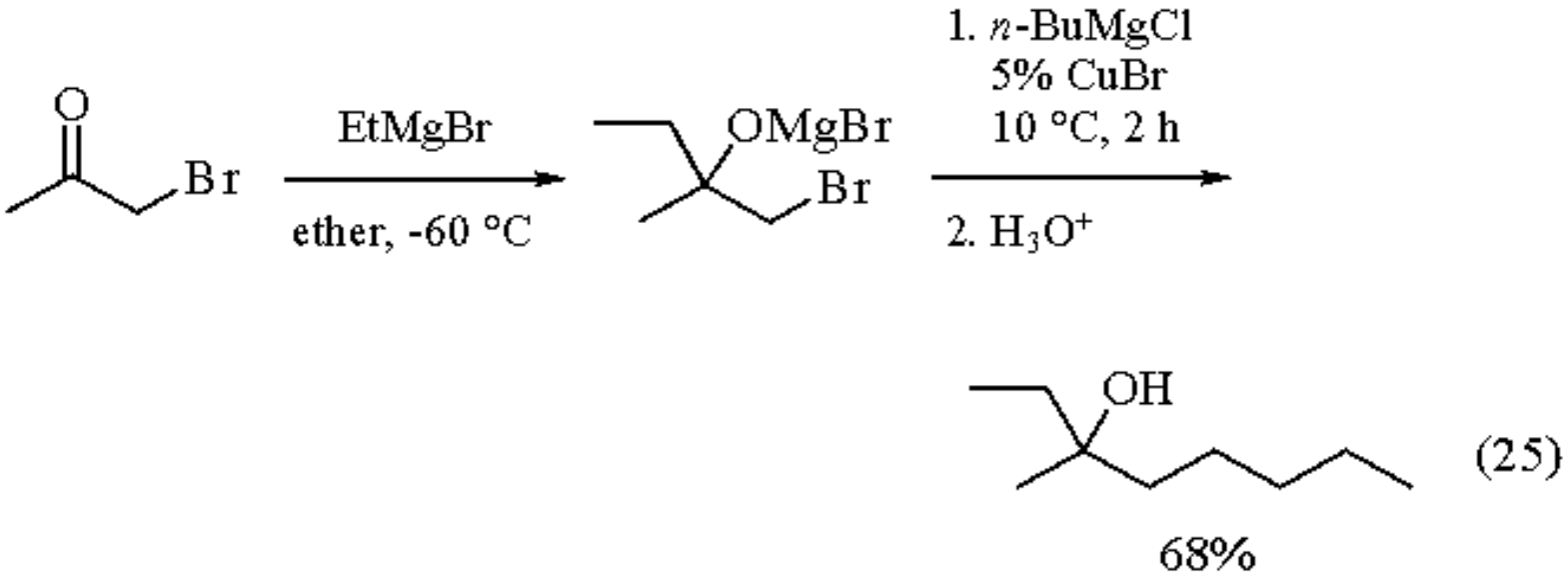

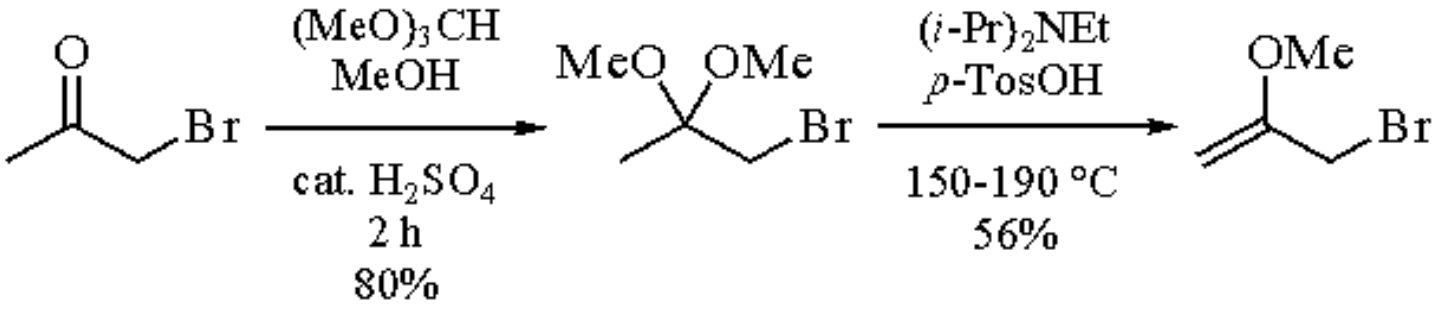

(26)

The oxime of bromoacetone is readily formed upon reaction with ***Hydroxylamine*** and is shown to be a suitable building block, after protection of the hydroxy function, for the synthesis of oxazaphospholines and 2-methylazirine (eq 27).[55] Bromoacetone condenses with ***p-Toluenesulfonylhydrazide*** to give the *syn-N*-tosylhydrazone exclusively,[56] while with ***Phenylhydrazine*** it gives rise to the *s-anti*-(*E,E*)-1,2-dihydrazone.[47]

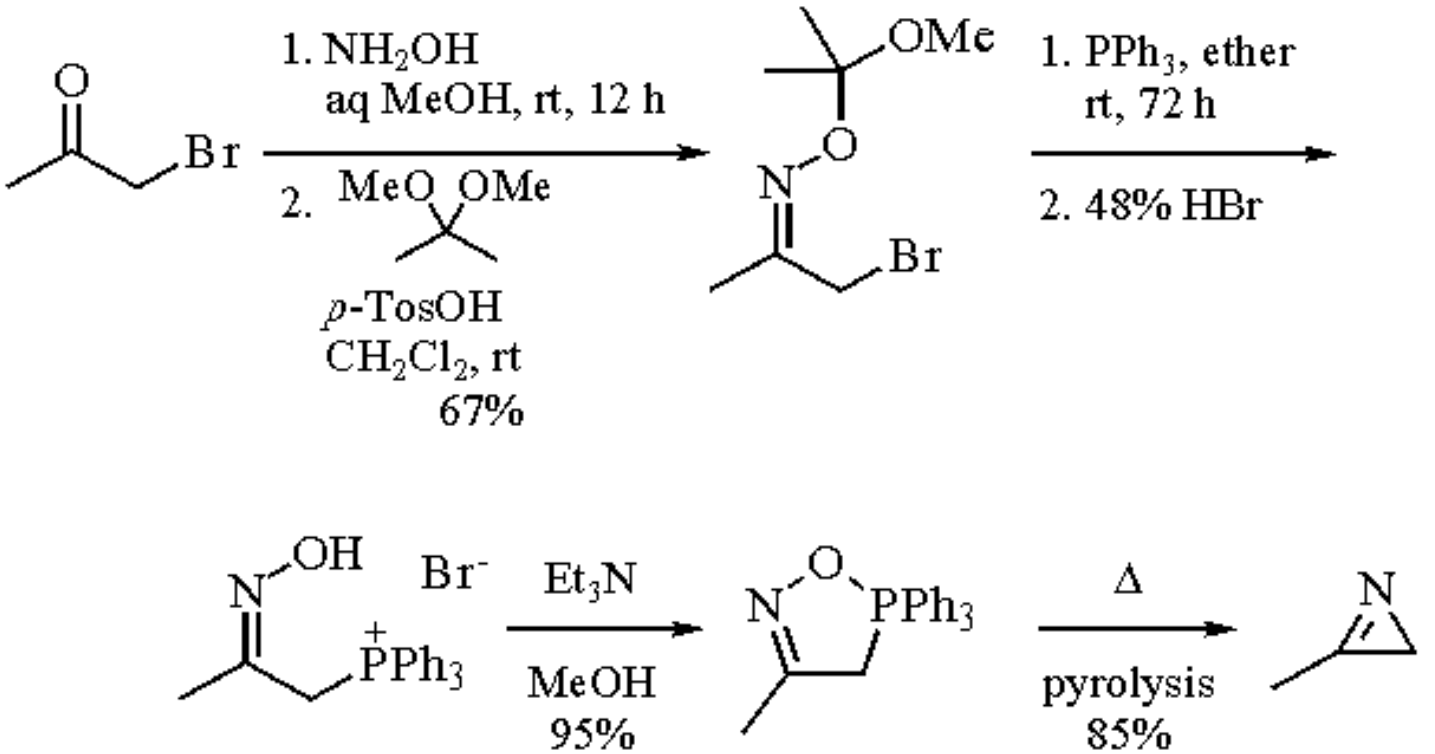

(27)

Aldol-Type Reactions.

The condensation of bromoacetone with aldehydes in the presence of ***Tin(II) Trifluoromethanesulfonate*** and a tertiary amine affords aldol-type adducts in which the bromo atom is retained in the final product (eq 28) allowing further elaboration, i.e. oxirane formation.[57,58]

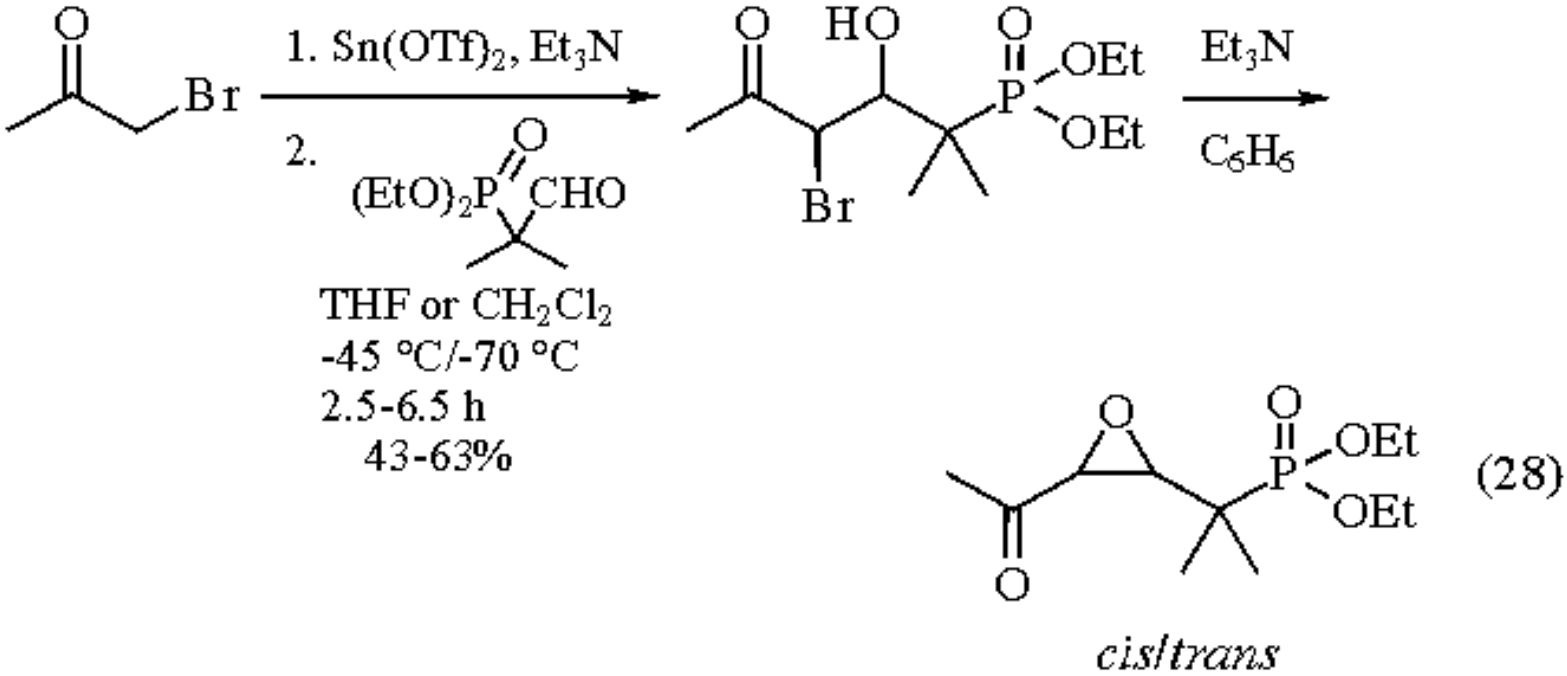

Aldol condensation with removal of the halogen is obtained under reducing conditions with ***Cerium(III) Chloride*** and ***Tin(II) Chloride*** (eq 29).[59]

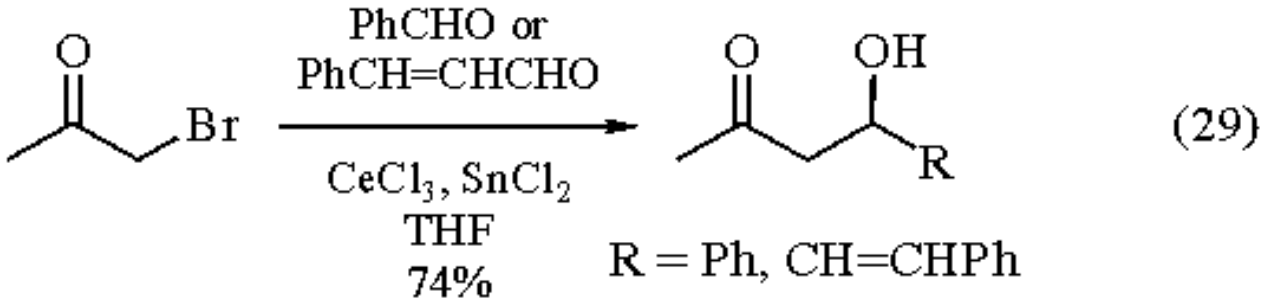

Synthesis of Heterocycles.

The condensation of bromoacetone with various multifunctional reagents leads to a whole range of heterocycles. In many cases the condensation proceeds by consecutive reactions, the order of which is not easily determined. Furans are obtained from bromoacetone by reaction with α-(tri-*n*-butyltin) ketones (eq 30)[59-61] and the sodio salt of ***Ethyl Acetoacetate*** (eq 31).[62] Furanones are obtained by condensation of bromoacetone with phosphonates under Wittig-Horner conditions,[63] while isocoumarins and benzofurans are accessible by reaction of bromoacetone with 3,5-dimethoxybenzoic acid[64] or 5-bromosalicaldehyde.[11] The reaction of bromoacetone with enamino thioketones leads to thiophenes (eq 32),[65] which are also accessible from the same bromo ketone and ketones in the presence of ***Sodium Sulfide***.[66] Dithiins result from the cyclocondensation of bromoacetone with ***1,2-Ethanedithiol***[67] and thiazolines are produced from bromoacetone, sodium sulfide, and ammonia.[18] Thiazoles are accessible from bromoacetone via Hantzsch condensation with thioureas (eq 33),[8,23,68] or by a one-pot synthesis with thioacids in the presence of ammonium acetate and acetic acid.[20] Thienoazepines are formed upon condensation of enaminothiones with bromoacetone.[69]

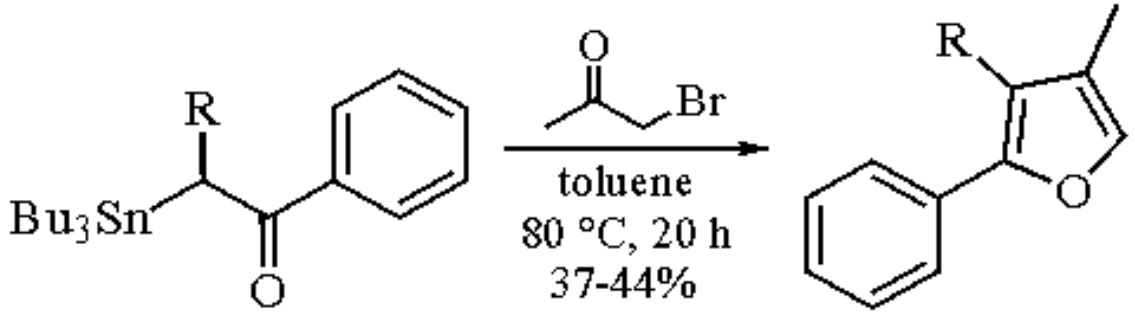

(30)

R = H, Me

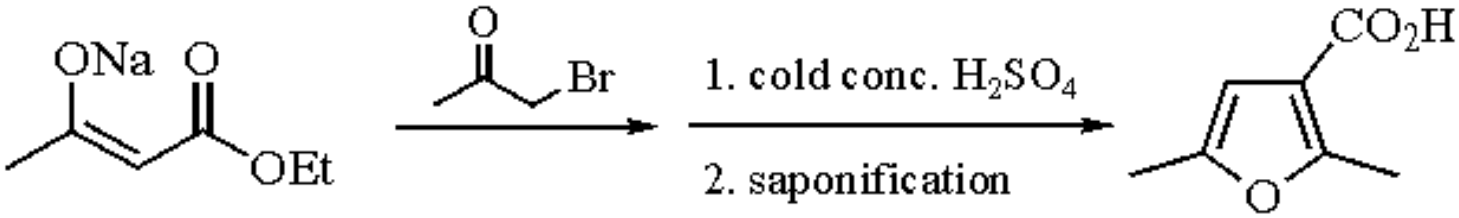

(31)

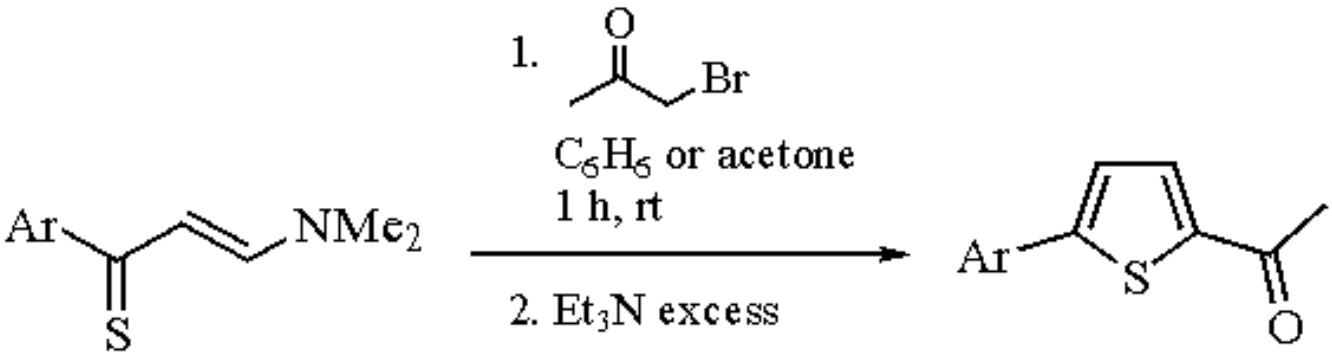

(32)

Ar = Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$

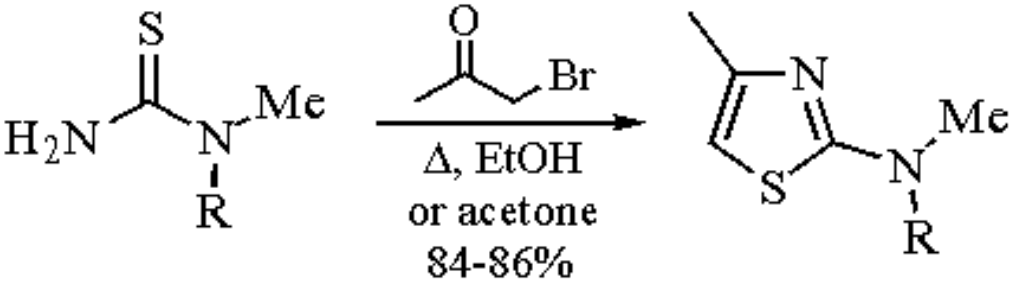

(33)

R = Me, Ph, Bn

Imidazoles result from a three-component reaction, consisting of bromoacetone, ammonia, and imidates under pressure (eq 34),[70] while functionalized imidazoles are formed upon reaction of bromoacetone with functionalized isothiourea derivatives.[71]

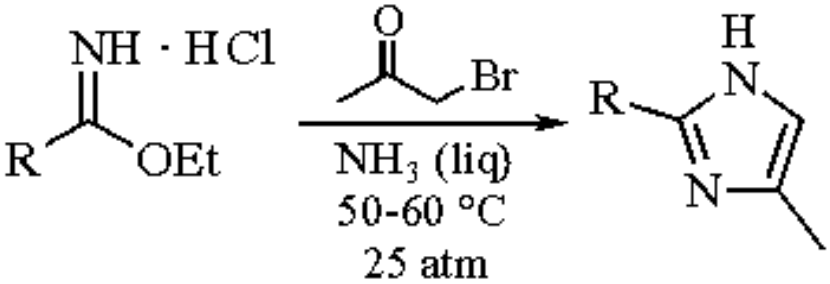

(34)

Pyrroles are accessible from the reaction of bromoacetone with *N*-vinyliminophosphoranes (eq 35)[72] or lithiated aldimines or ketimines.[73] In addition, the condensation of acetone dicarboxylic methyl ester with ***Ethanolamine*** and bromoacetone gives access to pyrroles.[74] Ethoxycarbonylacetamidine can be used as substrate for a pyrrole synthesis as well.[84]

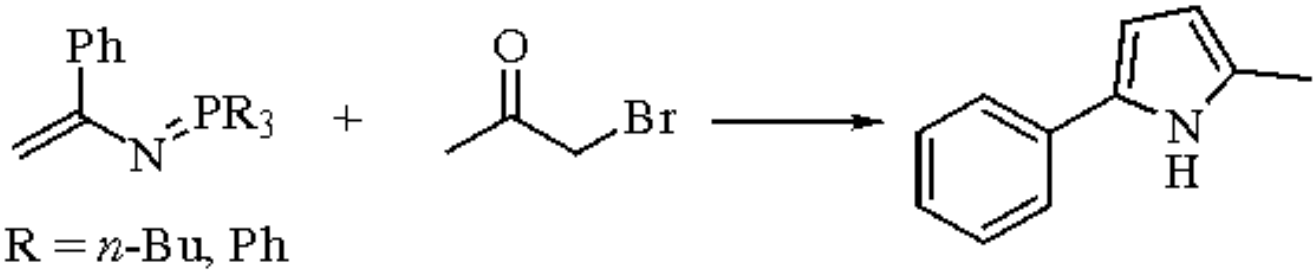

(35)

Bromoacetone is an especially useful building block for the construction of fused heterocycles. Cyclocondensation of heterocycles containing an amidino functionality with an exocyclic amino group, e.g. 3,9-dialkylguanines,[76] 3-methylguanine (eq 36),[77] 2-aminothiazole,[75] and 2-aminopyridines (eq 37),[83] readily condense with bromoacetone to give heterocycles with a fused imidazole ring. Pyrimidines also react with bromoacetone to give ring-fused heterocycles, e.g. 6-azaindolizines,[78,79] while 4-aminopyrimidines give rise to imidazo[1,2-*c*]pyrimidines.[80] 8-Aminoquinoline cyclocondenses with bromoacetone to produce fused heterocycles, which can be further elaborated to indolizinoquinoxalines.[81] Other examples leading to different fused heterocycles have been reported.[82,85]

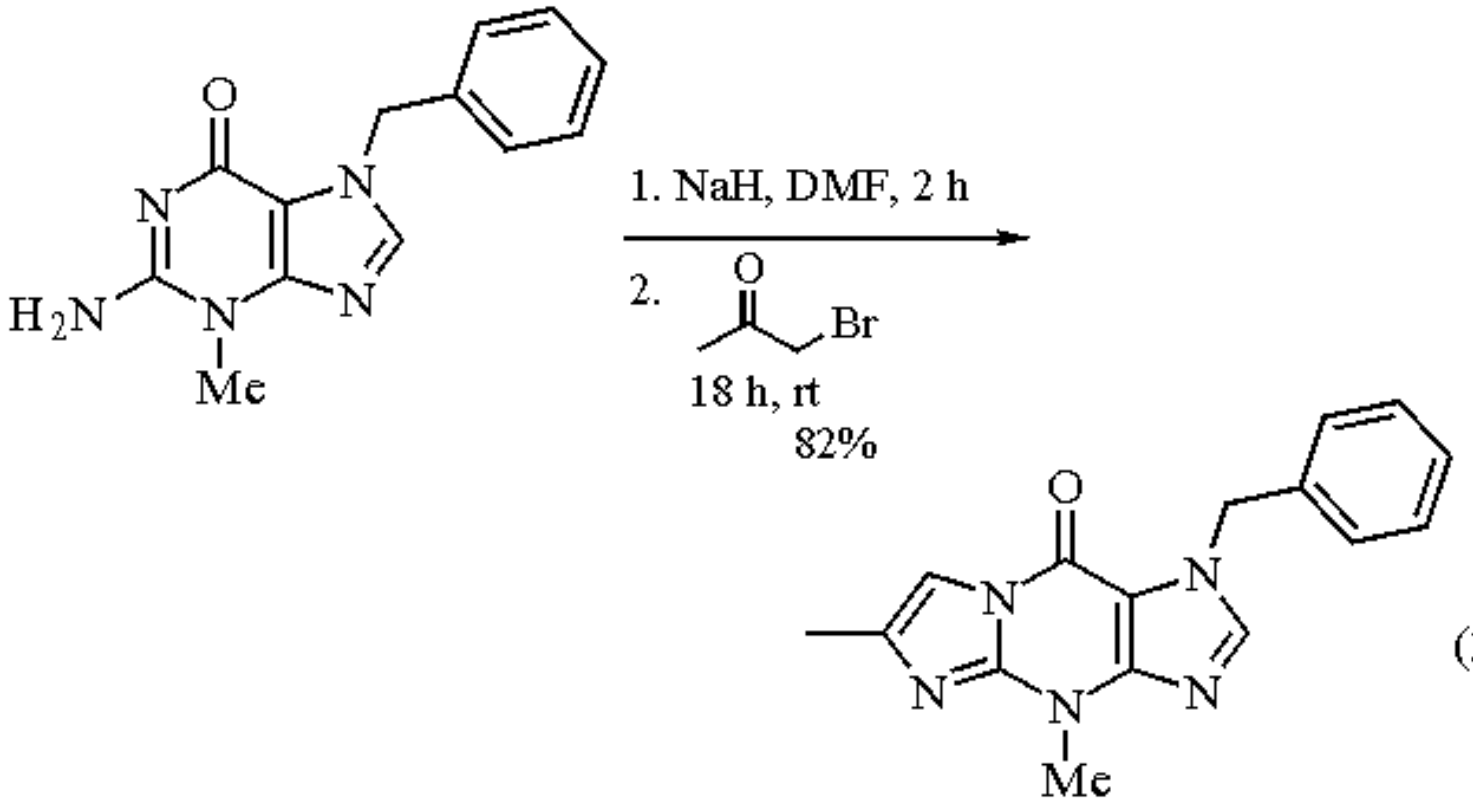

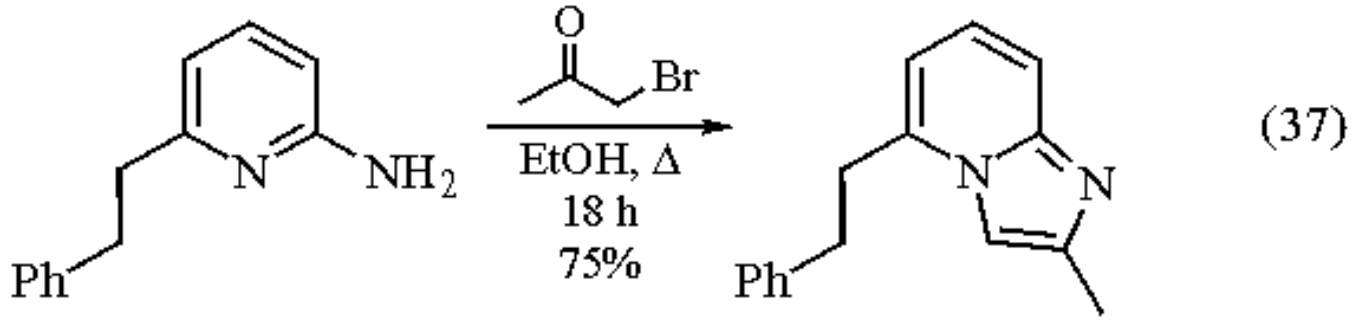

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Bromoacetyl Chloride

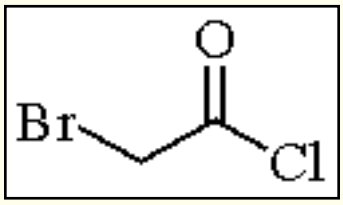

[22118-09-8] · C_2H_2BrClO · Bromoacetyl Chloride · (MW 157.39)

(bifunctional building block;[1-8] ketene precursor;[9-12] bromoacetylating agent[13,14])

Physical Data: bp 127-128 °C; *d* 1.908 g cm^{-3}.

Form Supplied in: colorless liquid, 98% pure or in lower grades [contaminated with $BrCH_2C(O)Br$ and $ClCH_2C(O)Cl$]; widely available.

Handling, Storage, and Precautions: readily hydrolyzed with formation of HCl; corrosive; lachrymator. This reagent should only be handled in a fume hood.

Bifunctional Building Block.

Bromoacetyl chloride has been used extensively as a bifunctional two-carbon building block.[1-8] Since both C-1 and C-2 are electrophilic, it can be used to link two nucleophilic units. Examples of intermolecular couplings[1-4] include sequences to prepare α-amino ketones,[1] α-heterosubstituted amides,[2] α-heterosubstituted esters (eq 1),[3] and Wittig-type reagents (eq 2).[4] Where both nucleophilic functionalities are on the same molecule, cyclic compounds result. Such intramolecular couplings[5-8] have been employed in syntheses of heterocycles such as morpholin-3-ones (eq 3),[5] aza-β-lactams,[6] and benzodiazepines.[7]

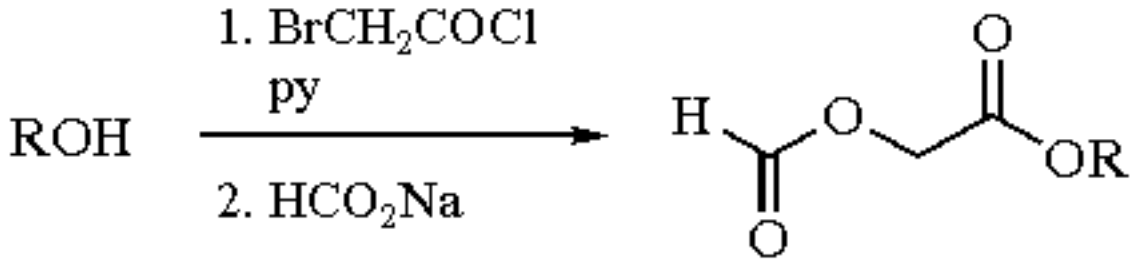

(1)

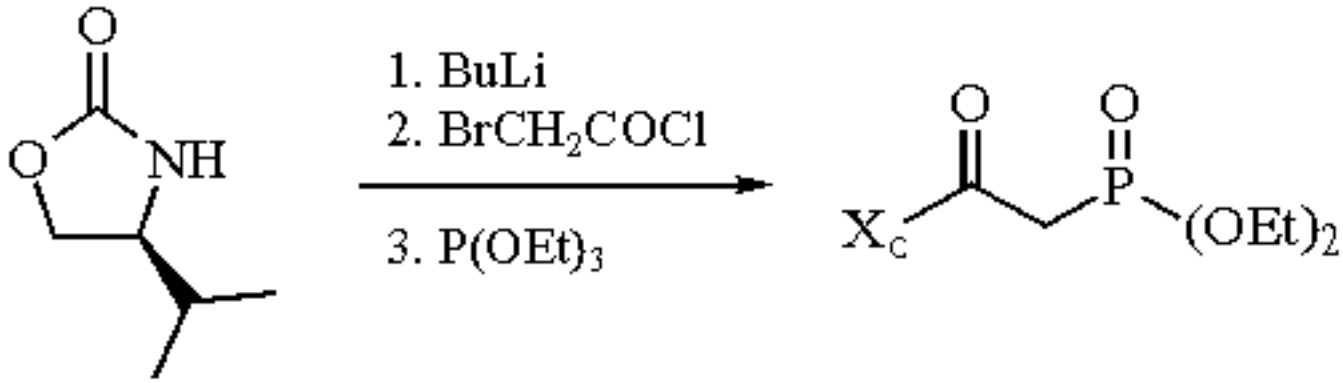

(2)

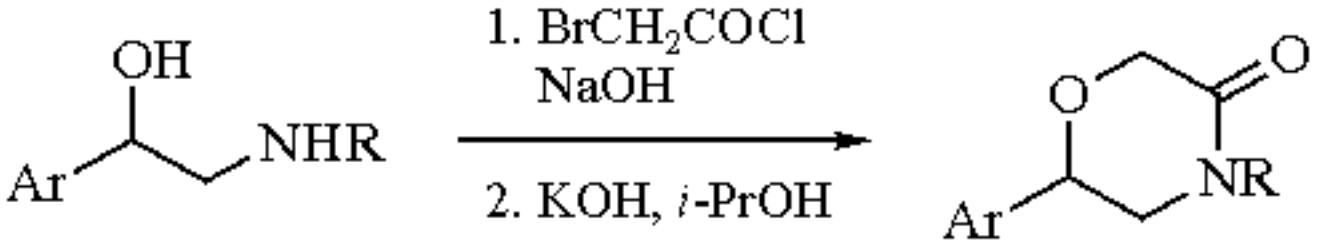

(3)

Ketene Precursor.

Treatment of bromoacetyl chloride with Et_3N in the presence of a suitable trapping agent (e.g. an imine) gives products derived from the expected intermediate ketene.[9-11] Such cycloaddition reactions with imines produce β-lactams (eq 4);[9] other heterocyclic compounds have also been prepared by this method.[11] Ketene itself may be prepared and distilled in solution by reaction of $BrCH_2C(O)Cl$ with pentacarbonylmanganate anion.[12]

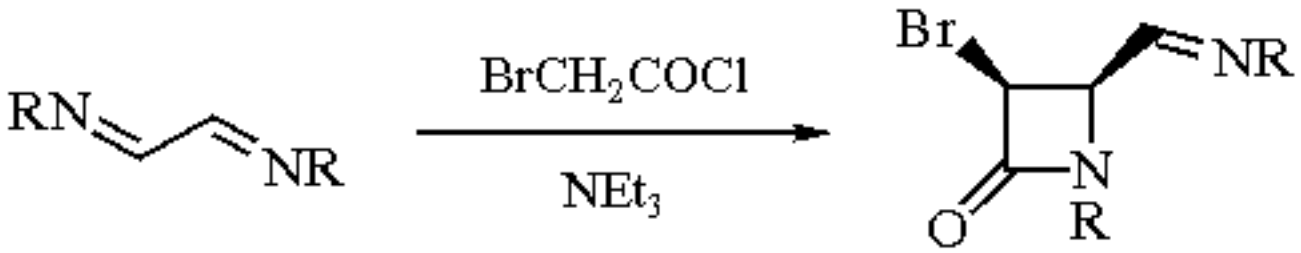

(4)

Bromoacetylating Agent.

Bromoacetyl chloride has been used as a reagent for the introduction of bromoacetyl groups.[13,14] There is some interest in preparing compounds bearing a bromoacetyl group (typically bromoacetamides) as possible pharmacological agents.[13] These compounds would be expected to be alkylating agents which could be anti-cancer drugs (by alkylation of DNA) or enzyme inhibitors (by alkylation of HO- or HS-containing residues in the active site.) The bromoacetyl group has also been used as a hydroxy-protecting group in carbohydrates.[14]

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Bromoacetylium Hexafluoroantimonate

$BrCH_2CO^+SbF_6^-$

[54854-60-3] · $C_2H_2BrF_6OSb$ · Bromoacetylium Hexafluoroantimonate · (MW 357.68)

(bromoacetylating agent)

Physical Data: mp 82 °C.

Preparative Method: prepared by treating $BrCH_2COF$ with antimony pentafluoride in Freon 113.[1a] Pure $BrCH_2CO^+SbF_6^-$ is obtained by washing the crude product with excess dry Freon 113.

Handling, Storage, and Precautions: corrosive and moisture sensitive. Store in a Teflon or a Nalgene bottle under anhydrous conditions. Use in a fume hood.

Bromoacetylium hexafluoroantimonate has been used to bromoacetylate aromatic compounds (eq 1). It reacts readily with benzene, toluene, *p*-xylene, and mesitylene to generate the corresponding bromoacylated products in high yields. In the case of toluene a 3.8:31.1:95.1 isomer distribution ratio is obtained for the *ortho*, *meta*, and *para* isomers.[1b]

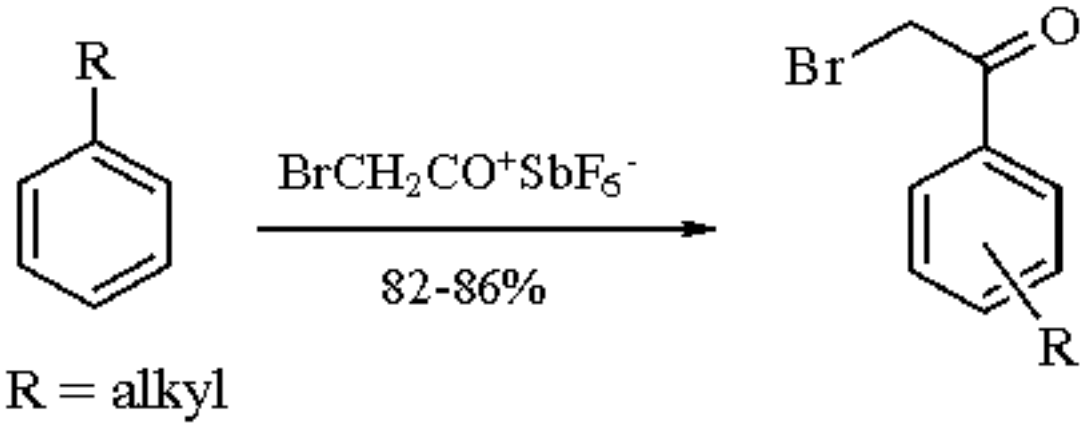

(1)

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Bromoallene[1]

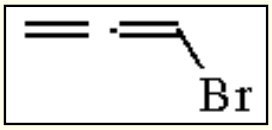

[10024-18-7] · C_3H_3Br · Bromoallene · (MW 118.96)

(useful reagent for synthesis of terminal alkynic compounds[2] and substituted allenes[3])

Physical Data: bp 73 °C; *d*204 1.5508 g cm^{-3}; *n*204 1.5212.

Solubility: sol most common organic solvents.

Form Supplied in: liquid; not available from common commercial suppliers.

Analysis of Reagent Purity: IR (cm^{-1}): 3080, 3005, 1961, 1740, 1432, 1078, 862, 681, 603, 519.[1] UV (nm (ε)): 269 (72), 192 (7780).[1] ^1H NMR (ppm): 5.95 (t, 1H, *J* = 6 Hz), 4.93 (d, 2H, *J* = 6 Hz).[4] ^{13}C NMR (ppm): 206.5, 86.8, 81.2.[4]

Preparative Methods: a tedious preparation[5] of bromoallene by isomerization of propargyl bromide in the presence of copper(I) bromide has been improved[6] and pure bromoallene can be obtained by removing the side product (propargyl bromide) with diethylamine (eq 1). Bromoallene has also been prepared by flash vacuum pyrolysis of bromocyclopropene[4] or by phase transfer catalysis using $CHBr(CH_2Br_2)$,[7] but in both cases reaction mixtures contained a significant amount of propargyl bromide.

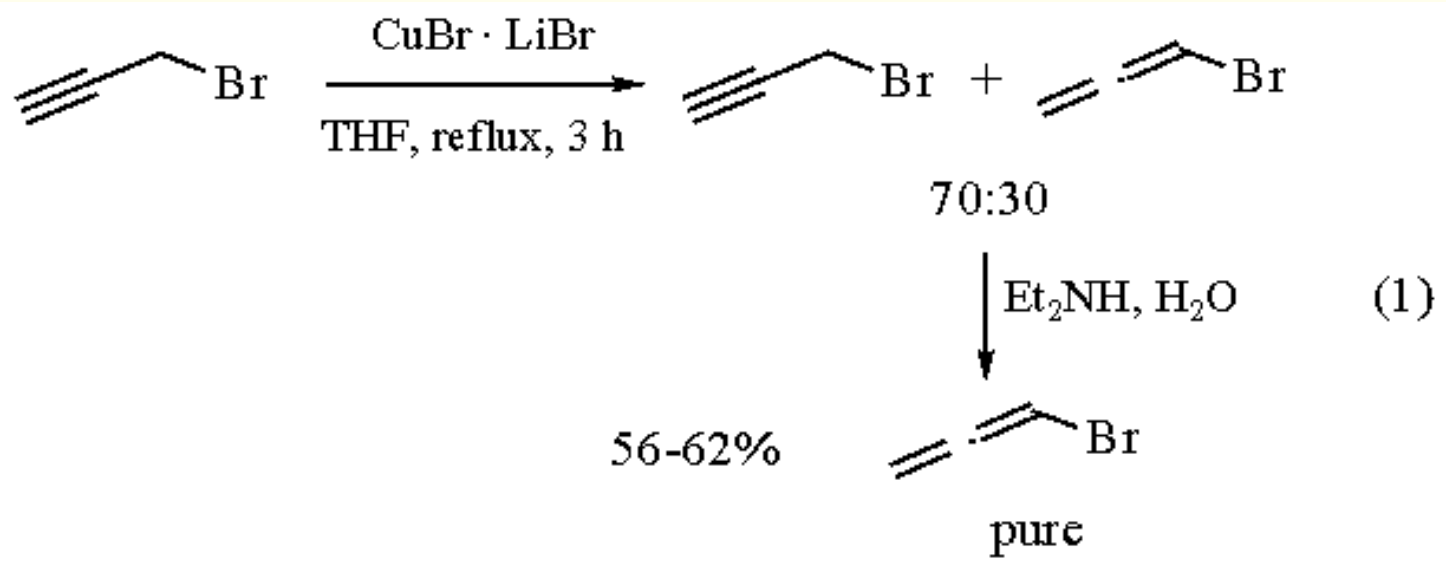

Bromoallene as an Electrophile.

The hydroalumination of 1-alkene followed by treatment with bromoallene in the presence of a catalytic amount of ***Copper(I) Chloride*** leads to terminal alkynic compounds (eq 2).[2]

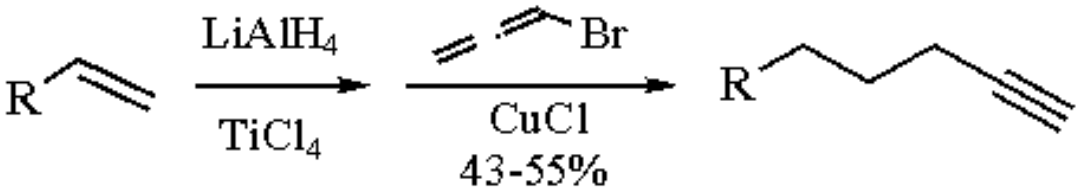

(2)

This bromide was also subject to nucleophilic substitution by the anion of ***Ethyl Acetoacetate*** in a basic medium, but it was found that propargyl bromide (see ***Propargyl Chloride***) gives identical results. A carbene mechanism was proposed (eq 3).[8]

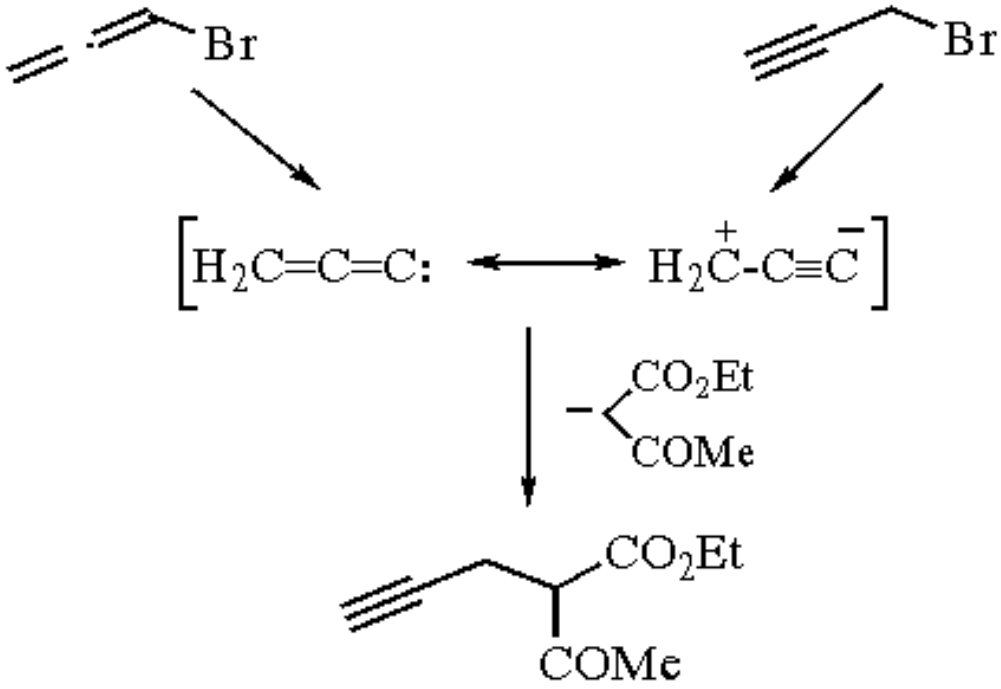

(3)

Formation of substituted allenes by reaction of bromoallene with 1-alkynylzinc chlorides and a Pd^0 catalyst is very useful. However, propargylic bromide or acetate can be used and seems more suitable for the preparation of unsymmetrical diallenes (e.g. R = *t*-BuCH=C=CH-) (eq 4).[3]

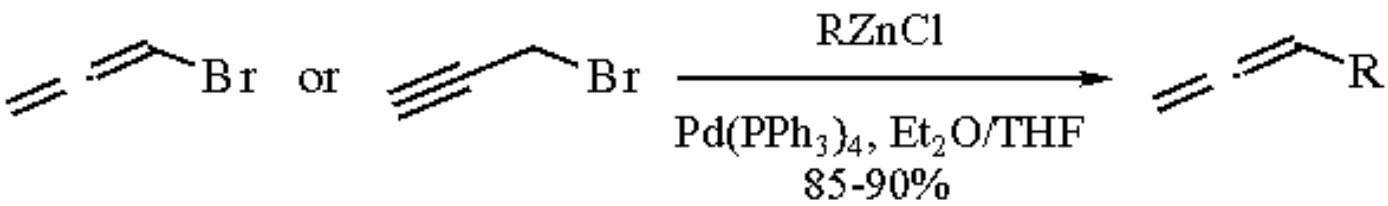

(4)

Bromoallene in Electrophilic Substitution via Metallic

Derivatives.

Allenylmagnesium Bromide.

Although this compound was earlier prepared from propargyl bromide, bromoallene may be used to synthesize allenylmagnesium bromide. It has been well established that propargyl or allenyl bromide deliver the same allenyl Grignard derivative (eq 5).[9]

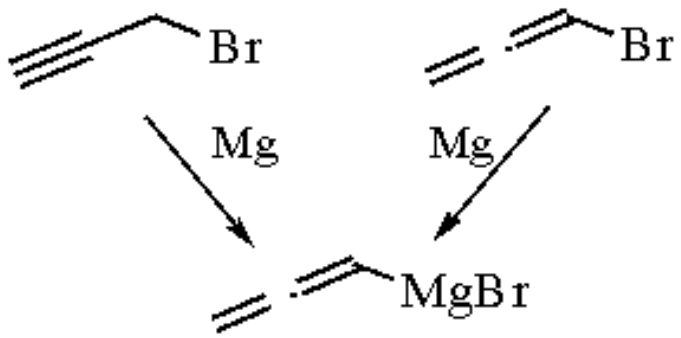

(5)

By a preferential attack at the 3-position (S_E2' type mechanism), this organometallic gives exclusively or mainly the alkynic compound when added to most electrophiles in ether (eq 6).[10] A reversal of reactivity may be encountered with polar aprotic solvents or with other organometallic compounds such as allenylzinc bromide (eq 7) or cadmium derivatives.[10]

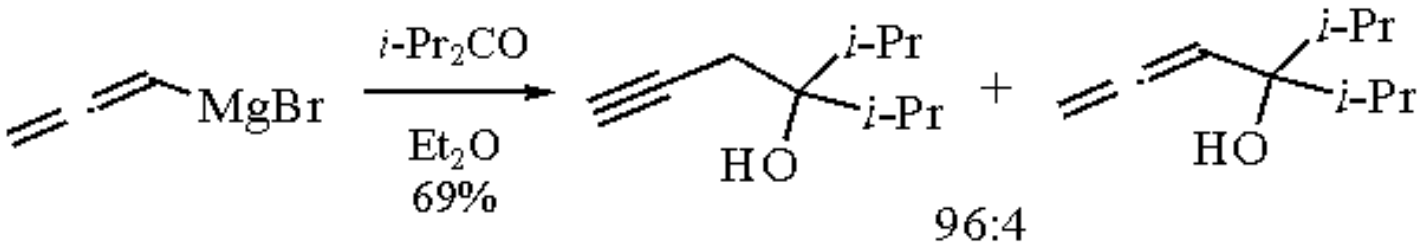

(6)

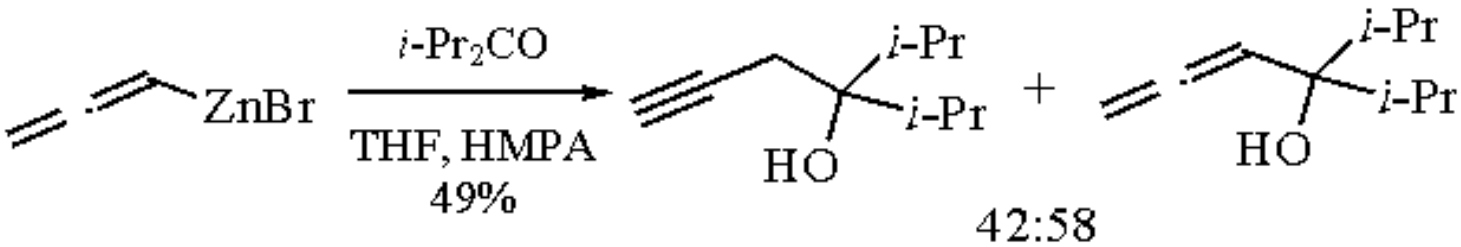

(7)

The addition of Cu^I salts leads to allene products (eq 8).[11]

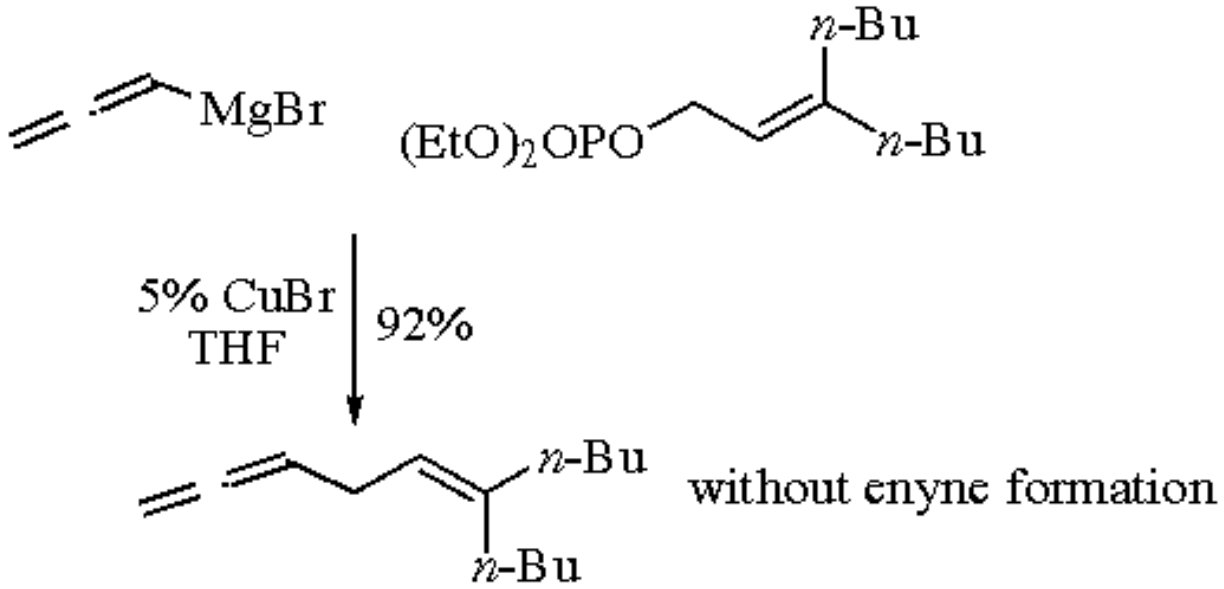

(8)

Cycloadditions.

Bromoallene gives a [4 + 2] cycloaddition by reacting with hexachlorocyclopentadiene, leading to the 5-bromomethylene adduct (eq 9).[12] A 1,3-dipolar cycloaddition with benzonitrile oxide[13] as well as photochemical cycloadditions of 9,10-phenanthraquinones[14] to bromoallene have also been investigated.

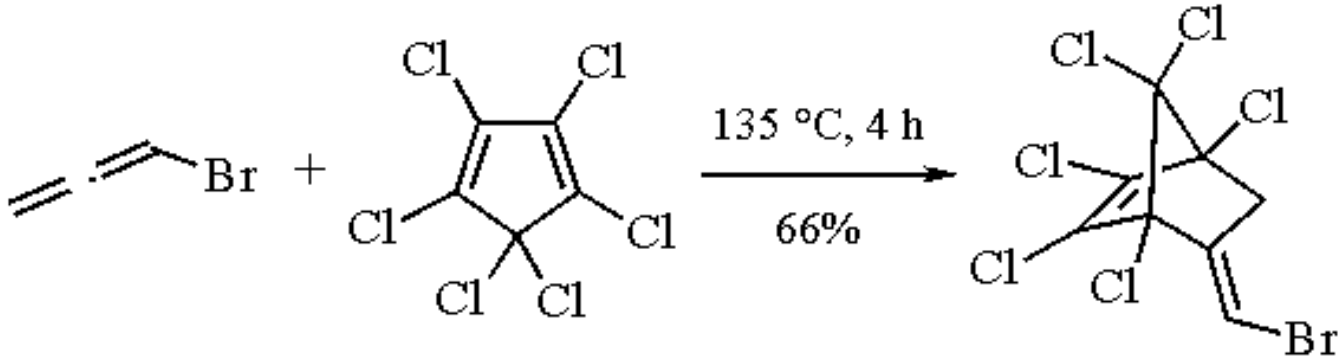

(9)

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4-Bromobenzenesulfonyl Azide

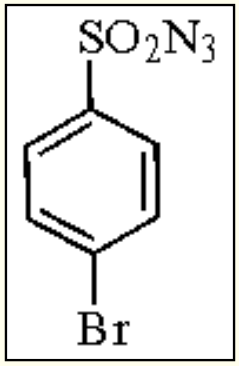

[6647-76-3] · $C_6H_4BrN_3O_2S$ · 4-Bromobenzenesulfonyl Azide · (MW 262.08)

(1,3-dipolar reagent that undergoes cycloaddition to vinyl and alkynyl ethers[1])

Physical Data: mp 54.5-56 °C.

Solubility: sol most organic solvents.

Preparative Method: by the reaction of ***4-Bromobenzenesulfonyl Chloride*** with excess ***Sodium Azide*** in a water-ethanol mixture.[2,3]

Purification: crystallization from ethanol.

Handling, Storage, and Precautions: should be used in solution. Azides are prone to violent detonation upon thermal, electrical, and mechanical shock.

Dipolar Cycloaddition.

The principal use of *p*-bromobenzenesulfonyl azide is in 1,3-dipolar cycloaddition reactions with functionally substituted alkenes. The reagent has been used at ambient temperature and pressure to convert simple trimethylsilyl[4] and methyl[5] enol ethers of cyclic ketones to ring-contracted *p*-bromobenzenesulfonimidates, and thence to the corresponding amides, esters, or acids (eqs 1 and 2).

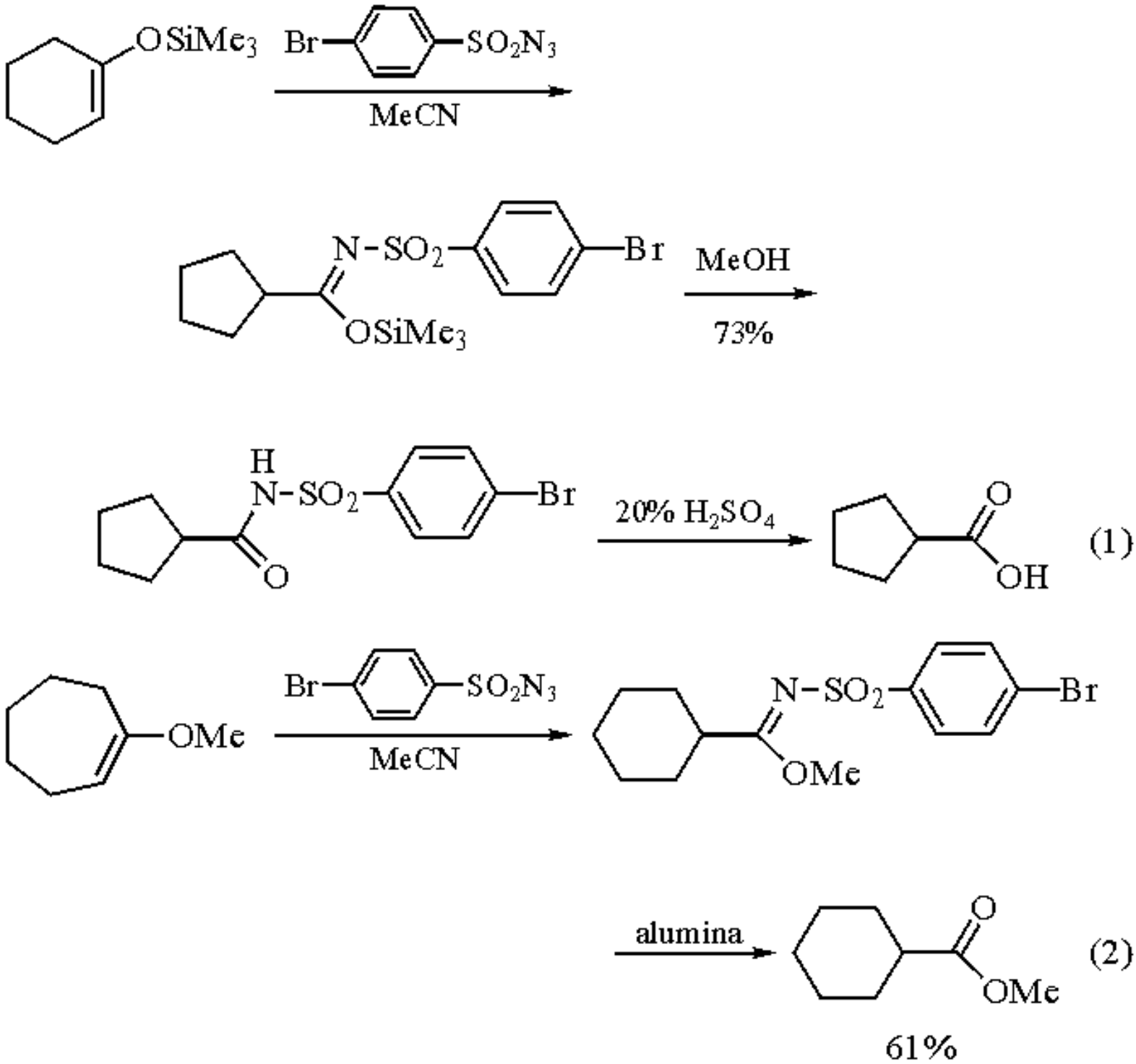

At high pressure (~15 kbar) the normally more sluggish *t*-butyldimethylsilyl enol ethers of cyclic ketones react in good yield to afford the ring contracted product (eq 3).[6,7]

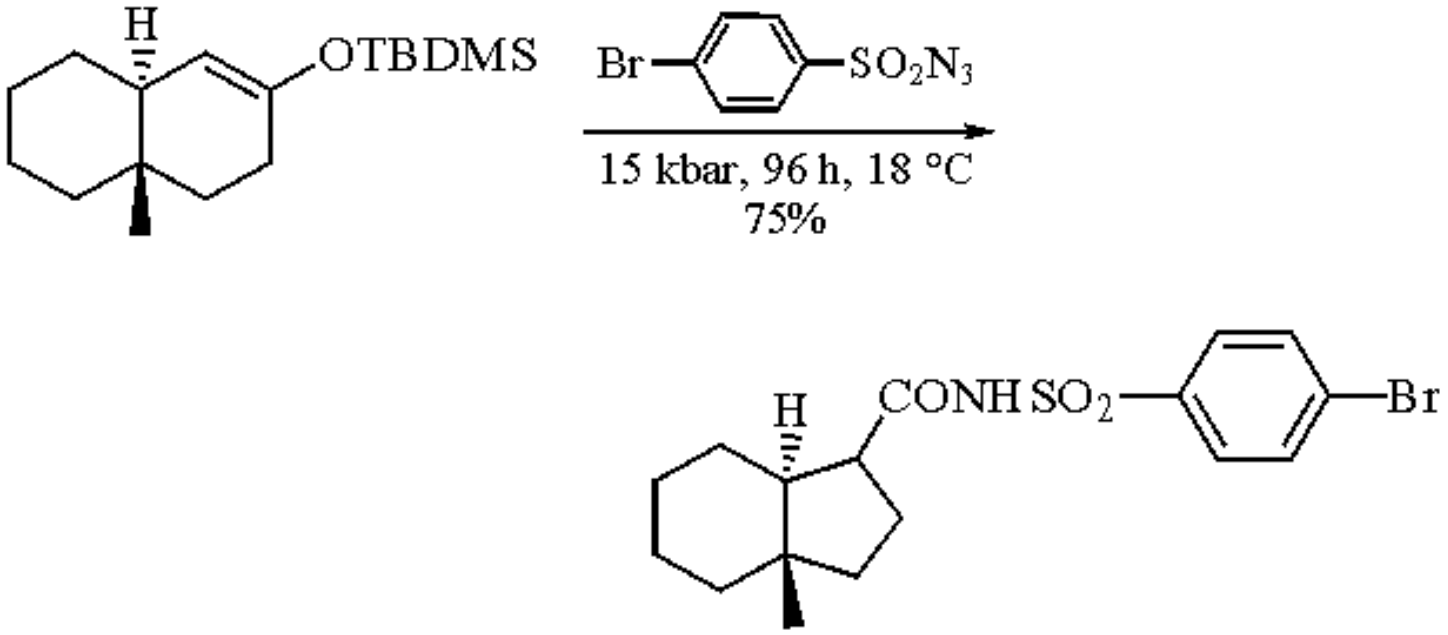

(3)

The chemo-, regio-, and stereoselectivity of the ring contraction process has been demonstrated with a variety of dienol ethers obtained by dissolving metal reduction of aromatic methyl ethers (eqs 4 and 5).[8]

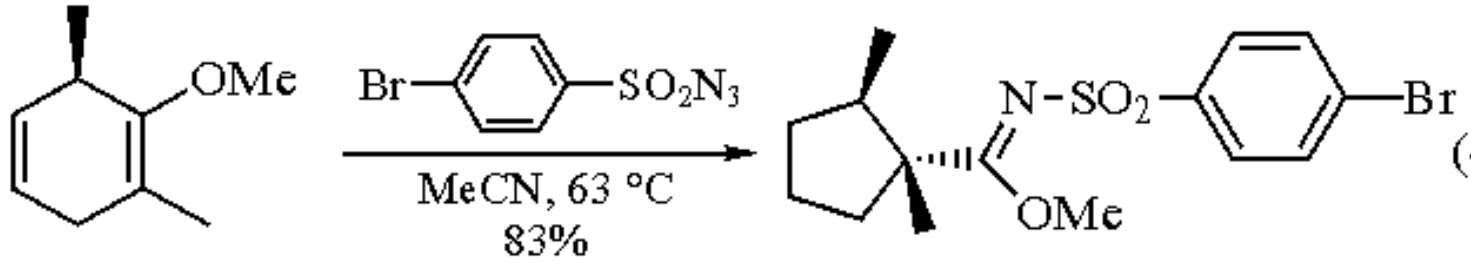

(4)

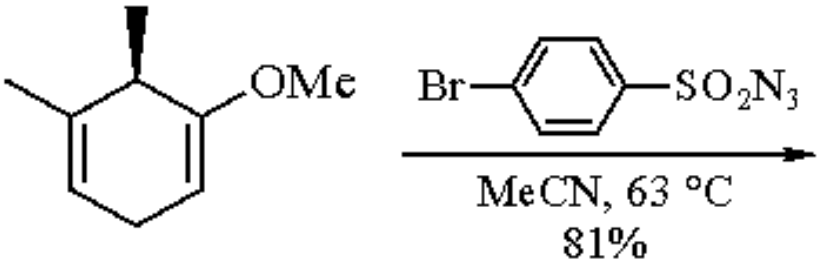

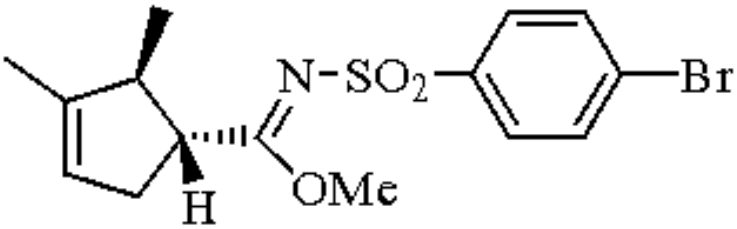

(5)

Methyl enol ethers which are unreactive under ambient conditions react in good yield to afford the corresponding *p*-bromobenzenesulfonimidates under the influence of low-wattage ultrasound (eqs 6 and 7).[9]

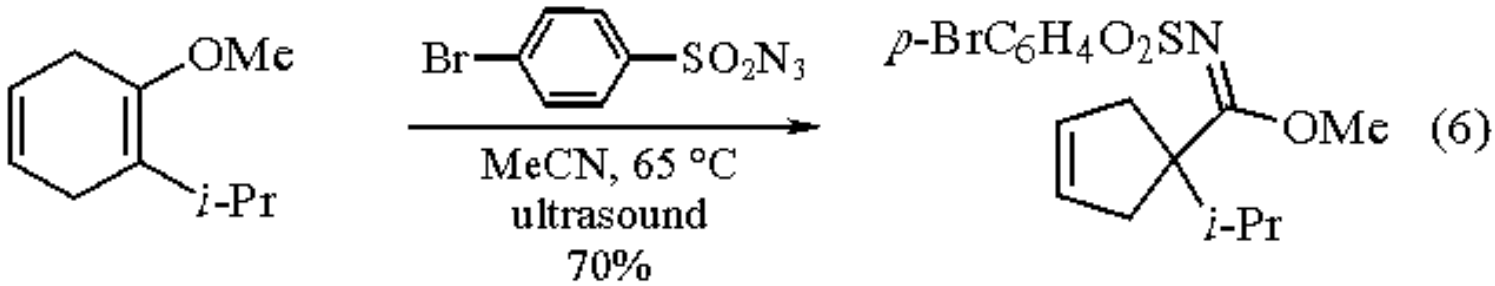

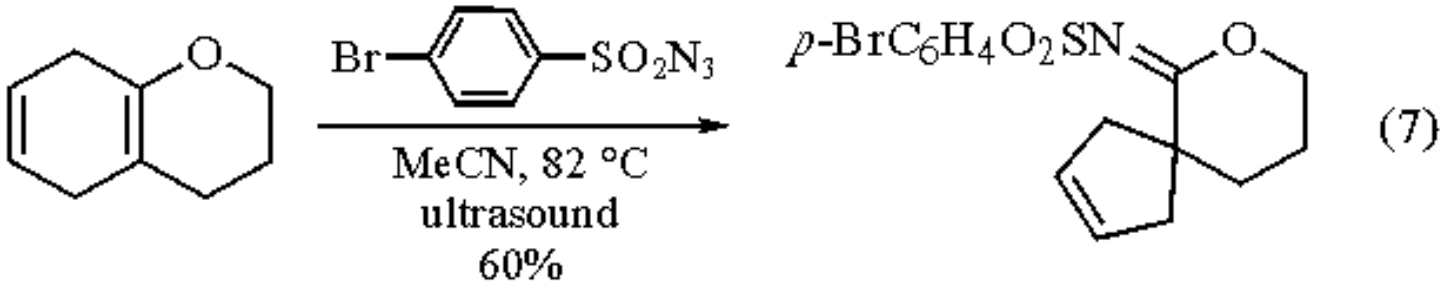

Cycloaddition of *p*-bromobenzenesulfonyl azide to alkynyl ethers affords equilibrium mixtures of triazole and diazocarboximidate. In the case of the ether in which both the carbon and the oxygen substituents of the alkynyl ether are methyl, only the triazole is found (eq 8).[10]

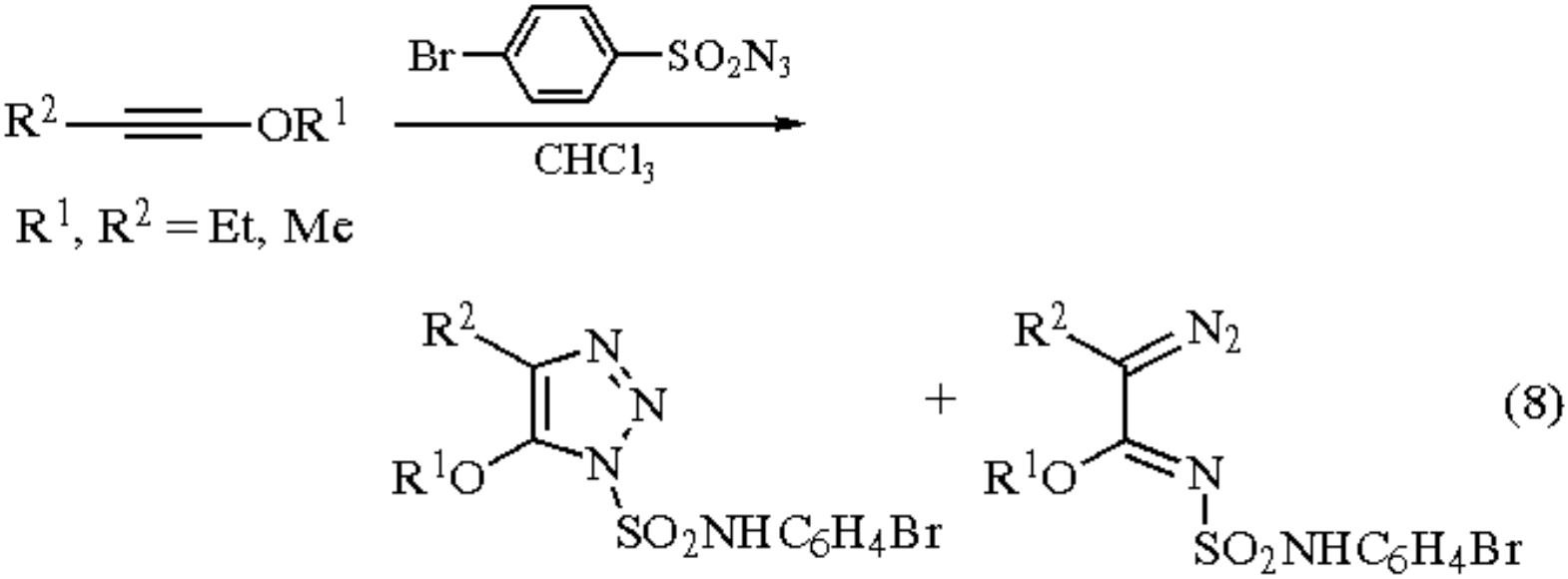

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4-Bromobenzenesulfonyl Chloride

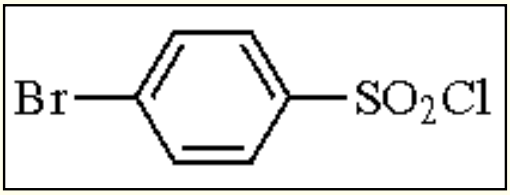

[98-58-8] · $C_6H_4BrClO_2S$ · 4-Bromobenzenesulfonyl Chloride · (MW 225.52)

(N-protection of amines; formation of sulfonamides, sulfonate esters, and carbodiimides)

Alternate Name: BsCl.

Physical Data: mp 73-75 °C.

Solubility: sol Et_2O, THF, petroleum ether and 1,4-dioxane.

Preparative Method: reaction of sodium *p*-bromobenzenesulfonate with ***Phosphorus(V) Chloride*** gives a 90% yield.[1]

Handling, Storage, and Precautions: harmful by skin absorption and ingestion and causes burns. The reagent is moisture sensitive and will react with nucleophilic solvents, e.g. alcohols, liberating HCl and therefore should be stored under an inert atmosphere.

Protection of Nitrogen, Formation of Sulfonamides.

p-Bromobenzenesulfonyl chloride (BsCl) has been widely used to N-protect amines (eqs 1 and 2)[2,3] (see also ***p-Toluenesulfonyl Chloride*** and ***Benzenesulfonyl Chloride***). Due to the relatively high molecular weight, *p*-bromobenzenesulfonyl derivatives have a higher melting point and may be more readily crystallizable than lower molecular weight derivatives.

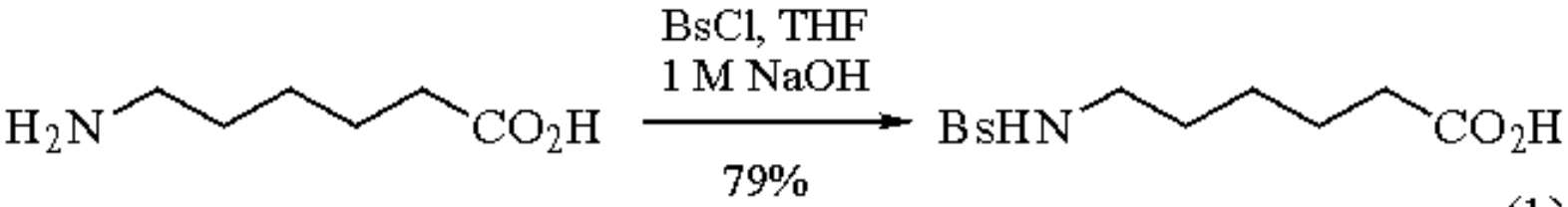

(1)

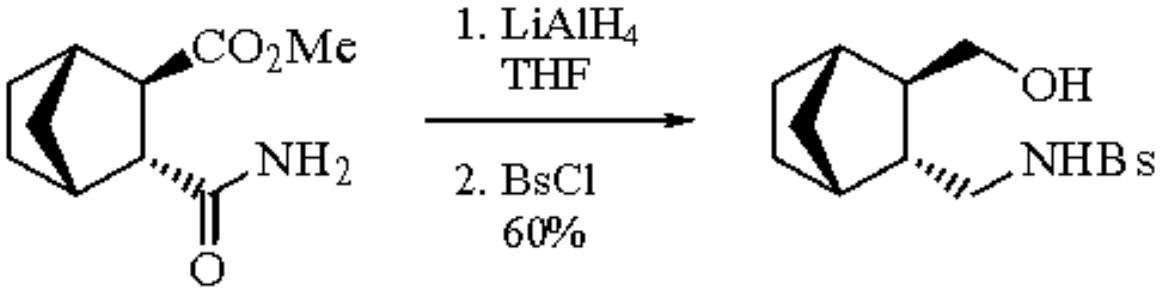

(2)

The electron-withdrawing nature of the *p*-bromobenzenesulfonyl group has been used, via the sulfonamide derivative of a pyridone, in inverse electron demand Diels-Alder reactions to great effect.[4]

Disulfonamides can be prepared from primary amines (eq 3), thereby converting the amine into a better leaving group.[5] The syntheses of sulfonamides derived from sulfamates have also been reported.[6]

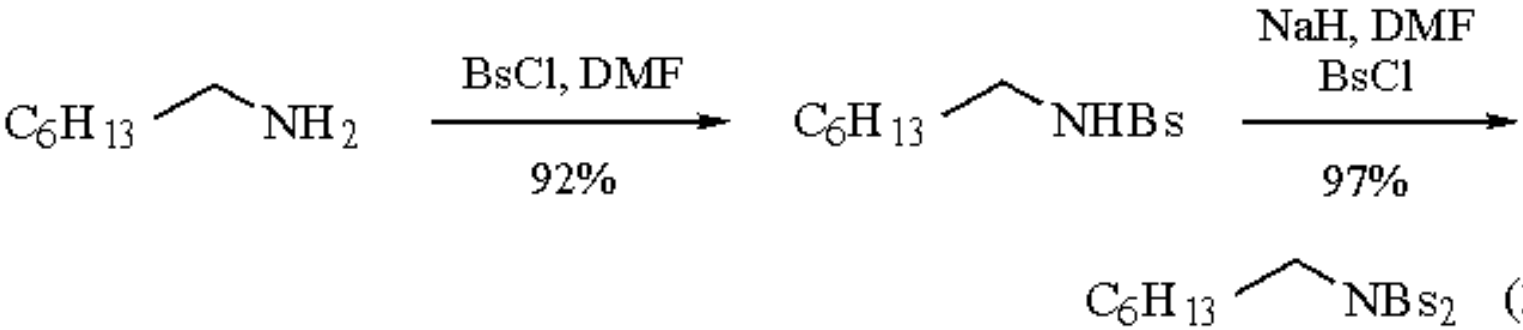

(3)

Formation of Sulfonate Esters.

The reaction of hydroxy groups with *p*-bromobenzenesulfonyl chloride gives *p*-bromobenzenesulfonates (brosylates) (eq 4).[7] The brosylate ester transforms the hydroxy functional group into a good leaving group and this has been exploited in synthesis. Inositol derivatives[8] have been prepared using brosylates in preference to the corresponding 4-methylbenzenesulfonates, the latter being a less effective leaving group in this particular case.

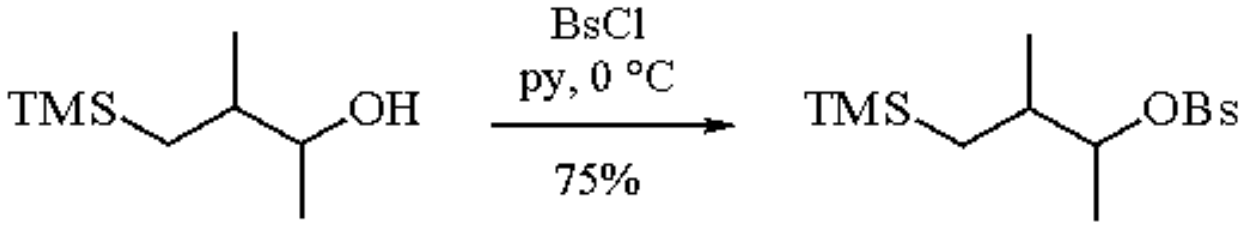

(4)

The reaction of β-hydroxy acids with *p*-bromobenzenesulfonyl chloride in the presence of a tertiary amine gives β-lactones (eq 5).[9,10] Brosylate esters of oximes have been manipulated in the Beckmann rearrangement of erythromycin derivatives[11] as an alternative to both 4-methylbenzenesulfonate esters and benzenesulfonate esters.

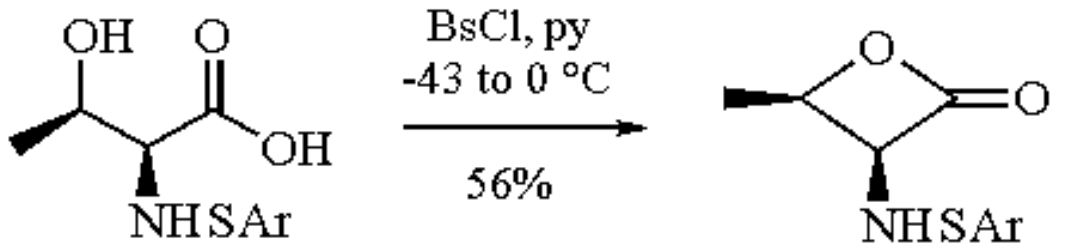

(5)

Formation of Carbodiimides.

p-Bromobenzenesulfonyl chloride reacts with ureas to form carbodiimides in good yield (eq 6).[12]

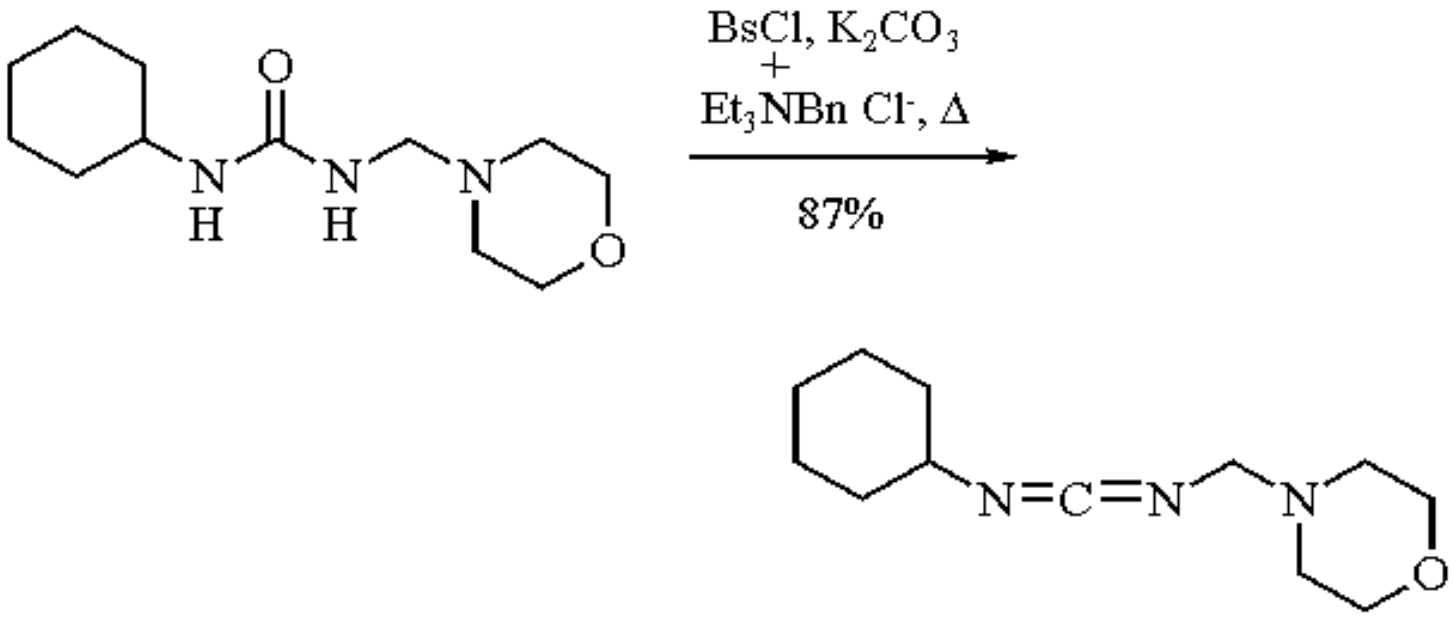

(6)

Reaction with Alkenes and Arenes.

p-Bromobenzenesulfonyl chloride will undergo desulfonylative coupling to alkenes and arenes using Pd^{II} catalysis (eq 7).[13]

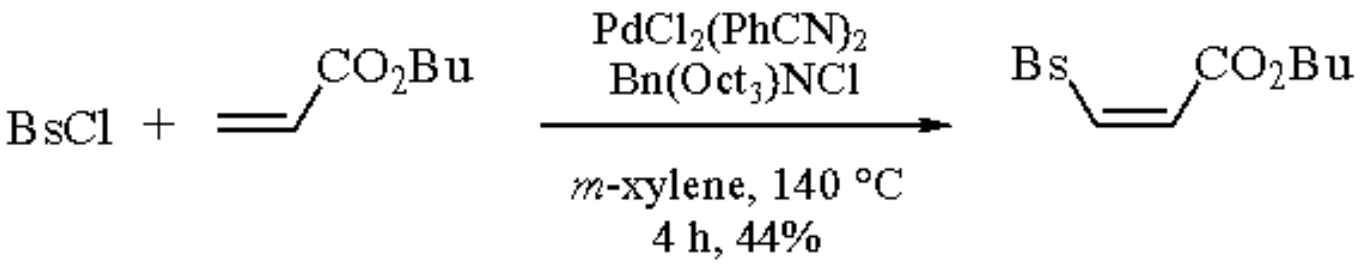

(7)

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4-Bromobenzyl Chloroformate

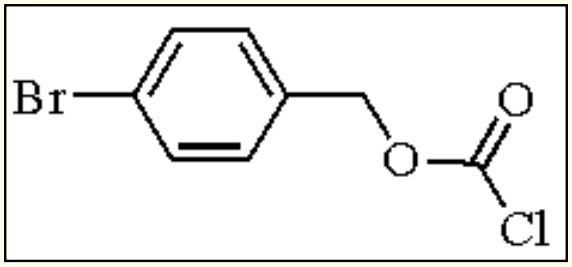

[5798-78-7] · $C_8H_6BrClO_2$ · 4-Bromobenzyl Chloroformate · (MW 249.49)

(N-protecting agent for α-amino acids)

Alternate Name: *p*-bromobenzyloxycarbonyl chloride.

Physical Data: mp 12 °C; *d* (20 °C) 1.5588 g cm^{-3}; *n*20D 1.6004.

Preparative Methods: not commercially available. It may be prepared[1] by the addition of a solution of 4-bromobenzyl alcohol in dioxane to a solution of excess ***Phosgene*** in toluene followed by stirring at rt for 24 h. Removal of the solvent by distillation in vacuo at 60 °C leaves a straw-colored oil. Three recrystallizations from hexane at -50 °C gives pure 4-bromobenzyl chloroformate in 78% yield as colorless needles. In a closely related alternate preparative procedure,[2] the crude oily product, obtained in 98% yield, was used in a preparative reaction without further purification.

Handling, Storage, and Precautions: although no details are available, the high toxicity and suspected carcinogenic properties of the closely related ***Benzyl Chloroformate*** suggest that 4-bromobenzyl chloroformate should be handled with caution.

N-Protection of α-Amino Acids.

Treatment of an α-amino acid[1] or an oligopeptide[3] with a dioxane solution of 4-bromobenzyl chloroformate and aq $NaHCO_3$ affords the *N*-(4-bromobenzyl) carbamate derivative in moderate to good yield (eq 1). Use of aq NaOH as the base gives similar results.[4] The resulting *N*-(4-bromobenzyloxycarbonyl)-α-amino acids have higher melting points than the corresponding *N*-benzyloxycarbonyl-α-amino acids[1,5] (see ***Benzyl Chloroformate***). Their highly crystalline nature allows for facile repeated recrystallization,[1,5] which makes them well-suited for use in the quantitation of α-amino acid racemization. The 4-bromobenzyl carbamate moiety is stable to the basic conditions (aq NaOH, ethanol) used to hydrolyze a methyl ester,[4] but is still readily cleaved by hydrogenolysis.[5]

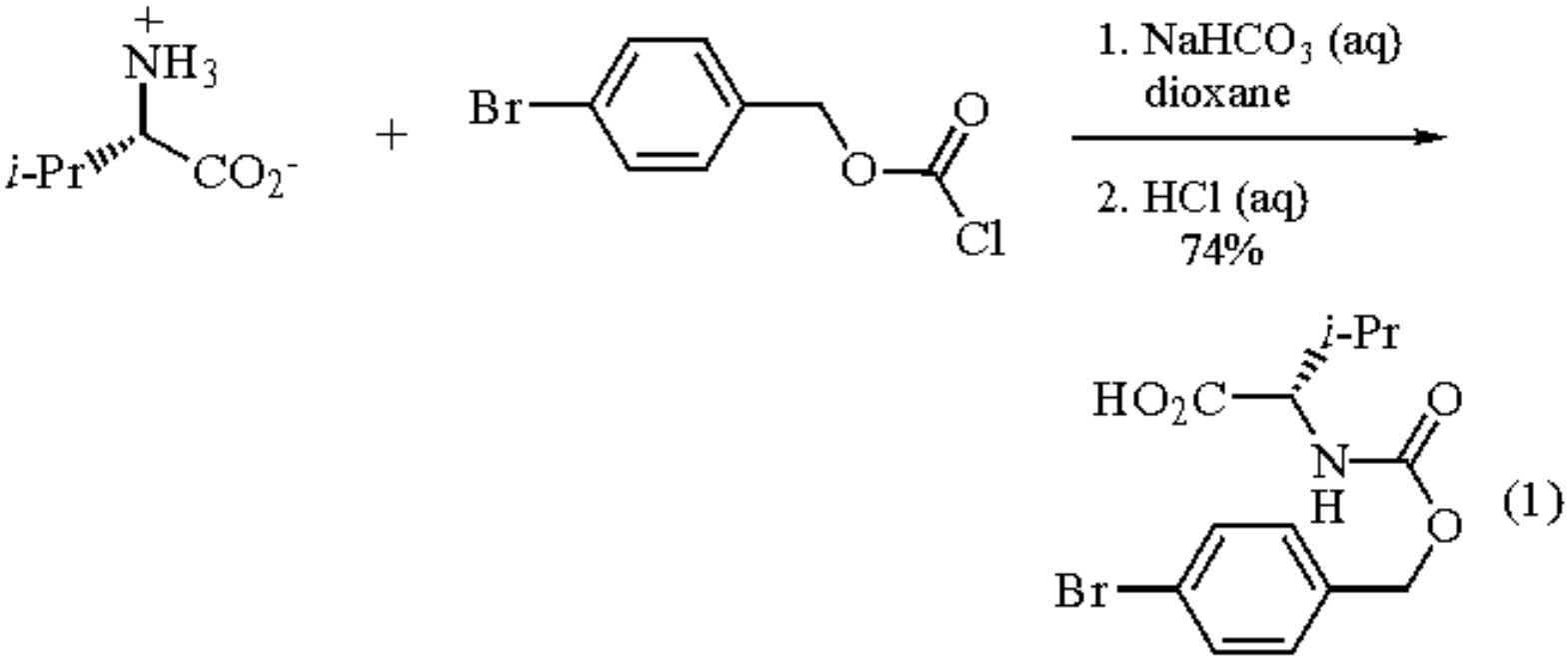

Protection of Carboxylic Acids.

Given the utility of benzyl chloroformate for the protection of carboxylic acids as their benzyl esters it is likely that the preparation of 4-bromobenzyl esters using 4-bromobenzyl chloroformate would be possible, although such chemistry has not yet been reported. Such a protection method would be useful, since it has been demonstrated that 4-bromobenzyl esters are 5-7 times more stable than the corresponding benzyl esters to acidic hydrolysis. For example, they are stable to 50% CF_3COOH used to cleave *N*-Boc-protected α-amino acids; they are cleaved quantitatively by exposure to HF (0 °C, 10 min).[6]

---

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2. Ovchinnikova, Y. I.; Fomin, V. A.; D'yachkov, A. I.; Etlis, V. S. *JGU* **1981**, *51*, 2031.
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Bromobis(isopropylthio)borane[1]

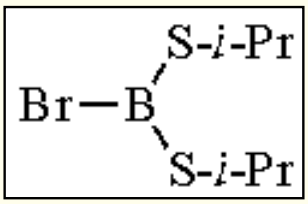

[89449-88-7] · $C_6H_{14}BBrS_2$ · Bromobis(isopropylthio)borane · (MW 241.01)

(mild Lewis acid capable of converting methoxyethoxymethyl (MEM) ethers into isopropylthiomethyl ethers;[1] deprotection of MEM ethers;[1] and cleavage of mono methoxymethyl (MOM) (or MEM) ethers of 1,2- and 1,3-diols[1])

Physical Data: bp 75-80 °C/2 mmHg; light-yellow oil.

Solubility: sol most organic solvents such as pentane, CH_2Cl_2, etc.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.64 (hept, 2H, *J* = 6.8 Hz, CH), 1.385 (d, 12H, *J* = 6.8 Hz, Me).

Preparative Method: [1] to a stirred mixture of 3.57 g (0.010 mol) of bis(isopropylthio)lead[2] in 20 mL of pentane under argon at 25 °C is added a solution of 0.95 mL (0.010 mol) of ***Boron Tribromide*** in 10 mL of pentane. After the mixture is stirred for 20 min, 10 mL of CH_2Cl_2 is added and the mixture is heated under reflux for 2.5 h. The reaction mixture is cooled to 25 °C and the white precipitate ($PbBr_2$) is removed by filtration under argon. The filtrate is distilled under argon to remove solvents and then distilled under reduced pressure: 2.13 g (90% yield) of a yellow oil; bp 75-80 °C/2 mmHg.

Handling, Storage, and Precautions: should be stored under argon at 0 °C. The compound has an unpleasant odor and reacts rapidly with water and other protic solvents.

Bromobis(isopropylthio)borane converts various MEM ethers into the corresponding isopropylthiomethyl ethers. Among several examples shown below, treatment of the MEM ether of cholesterol in CH_2Cl_2 at -95 °C with 3-5 equiv of (*i*-PrS)$_2$BBr for 5 min followed by the addition of ***4-Dimethylaminopyridine*** (DMAP) (2 equiv/equiv of boron reagent) and stirring the mixture at -95 °C for 15 min, then at -50 °C for 10 min, before quenching with aqueous potassium carbonate gives an 89% yield of the isopropylthiomethyl ether of cholesterol along with a 9% yield of cholesterol (eq 1).[1] Presumably, DMAP displaces isopropylthiolate anion from the boron complex, thereby providing a reactive S-nucleophile to attack the dioxymethylene carbon of the boron-coordinated MEM ether.

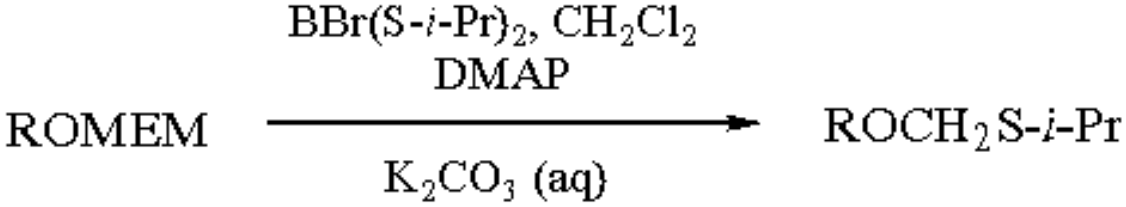

(1)

MEM = $-CH_2OCH_2CH_2OMe$

(1a) 84%

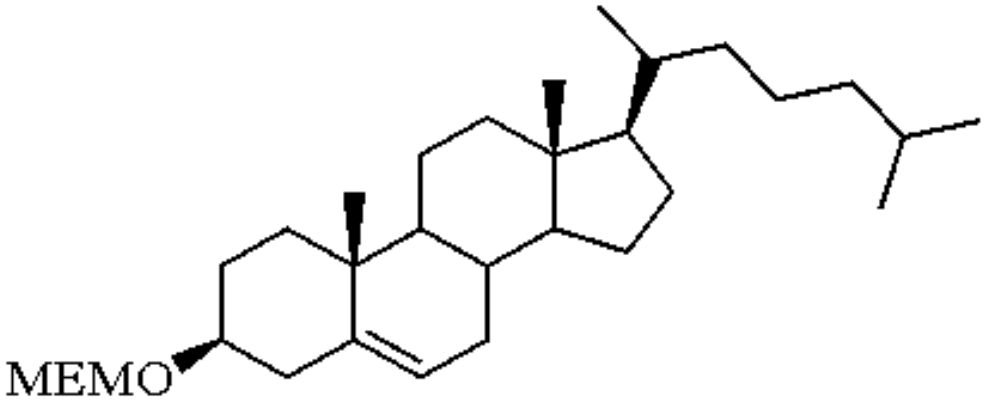

(1b) 89%

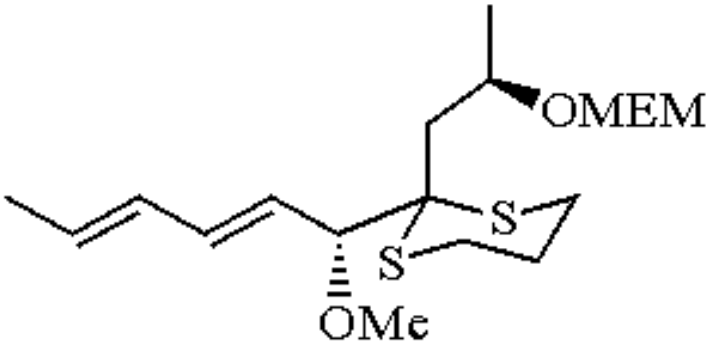

(1c) 90%

Under different conditions, $(i\text{-PrS})_2BBr$ cleaves MEM ethers into the corresponding alcohols. For example, in the absence of DMAP, reaction of MEM ether (**1c**) with 1.5 equiv of $(i\text{-PrS})_2BBr$ in CH_2Cl_2 at -95 °C for 5 min followed by treatment with aqueous sodium bicarbonate provides an 88% yield of the corresponding alcohol and only a 2% yield of the isopropylthiomethyl ether.

Bromobis(isopropylthio)borane also cleaves mono MOM (or MEM) ethers of 1,2- and 1,3-diols to the corresponding diols.[1] Treatment of glycol mono MOM ethers with 1.2 equiv of $(i\text{-PrS})_2BBr$ in CH_2Cl_2 at -78 °C followed by methanol at 23 °C for 1 h affords excellent yields of the corresponding diols (eqs 2-4). It should be noted that these glycol mono MOM ethers under conventional acid-catalyzed processes (using protic or Lewis acids) produce cyclic diol formals as the major product.

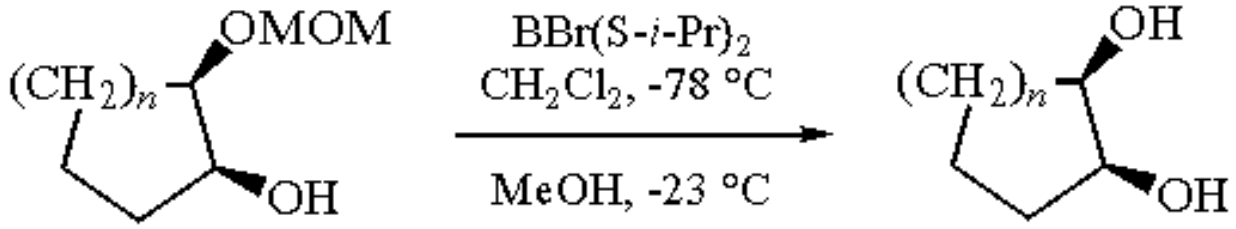

(2)

MOM = CH_2OMe

$n = 1$, 73%
$n = 2$, 96%
$n = 6$, 82%

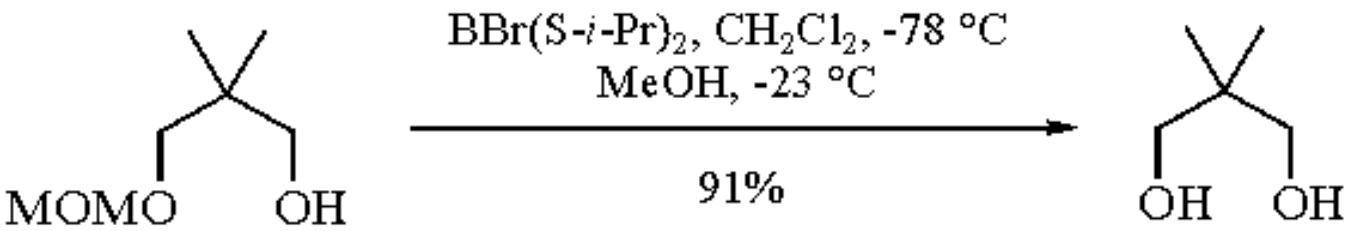

(3)

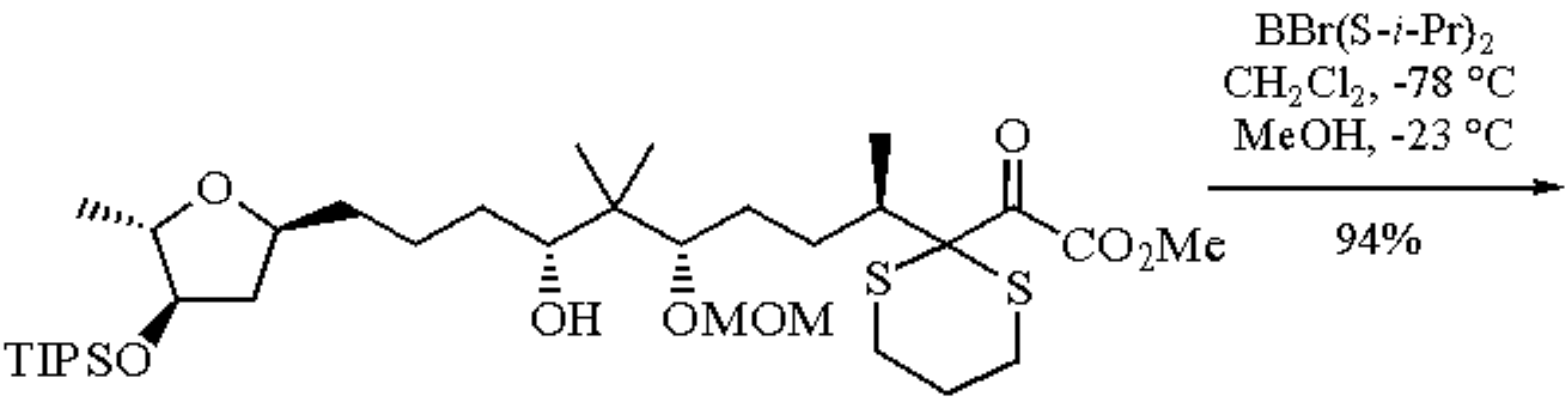

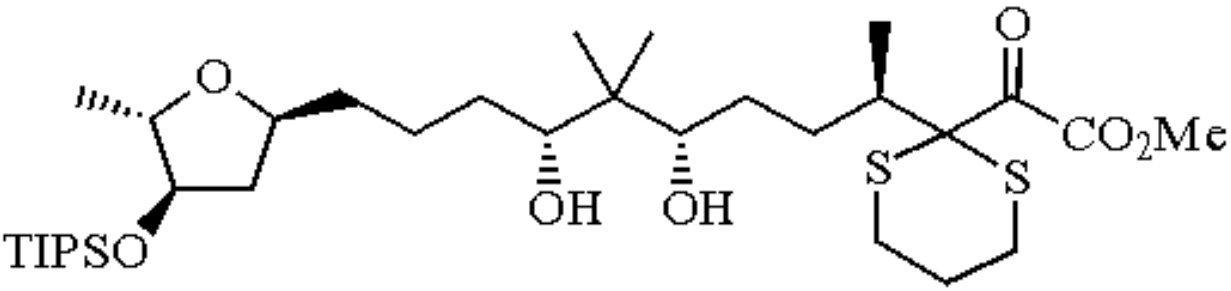

(4)

Deprotection of MEM ethers with other Lewis acidic boron reagents (such as 2-chloro-1,3,2-dithiaborolane[3] and ***Bromodimethylborane***[4]) to the corresponding alcohols has also been reported.

---

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9-Bromo-9-borabicyclo[3.3.1]nonane[1]

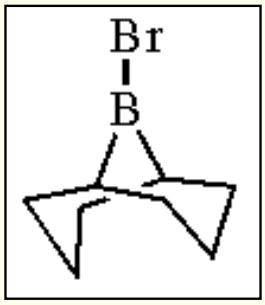

[22086-45-9] · $C_8H_{14}BBr$ · 9-Bromo-9-borabicyclo[3.3.1]nonane · (MW 200.91)

(selective reagent for the cleavage of ethers[2] and deoxygenation of sulfoxides;[3] adds regioselectively and stereoselectively to terminal alkynes;[4] undergoes conjugate addition to α,β-unsaturated ketones;[5] converts vinyltins to vinylboranes[10])

Alternate Name: Br-9-BBN.

Physical Data: colorless liquid; bp 54-59 °C/0.3-0.4 mmHg; mp -17 °C; *d* 1.315 g cm^{-3}.

Solubility: sol pentane, CH_2Cl_2; dec ethers, alcohols.

Form Supplied in: 1.0 M solution in CH_2Cl_2.

Analysis of Reagent Purity: the reagent exhibits a single resonance in its ^{11}B NMR (neat) spectrum at δ 83.9 (s) ppm.[2]

Handling, Storage, and Precautions: the reagent is pyrophoric and reacts violently with moisture and protic solvents. Individuals should thoroughly familiarize themselves with the special handling techniques required for such reagents prior to use.[1] Use in a well-ventilated fume hood.

Selective Cleavage of Ethers.

In methylene chloride solution, Br-9-BBN readily cleaves a variety of common ethers at 25 °C.[2] For dibutyl ether the reagent reacts smoothly to produce 1-bromobutane quantitatively in 24 h. This behavior contrasts to that of polyfunctional reagents such as ***Boron Tribromide*** whose rate is markedly slowed after two of its three bromides have been used. The bromine is selectively transferred to tertiary and secondary vs. primary groups, the process occurring with 73% inversion in the case of (*R*)-(-)-2-methoxyoctane (eq 1). Alkyl aryl ethers are also selectively cleaved, with no Claisen products from allyl phenyl ether as is observed with ***Boron Trichloride***. One of the methoxy groups in

hydroquinone dimethyl ether can be selectively cleaved with the reagent, whereas the methylenedioxy moiety must be completely removed with two equivalents of the reagent under more forcing conditions.

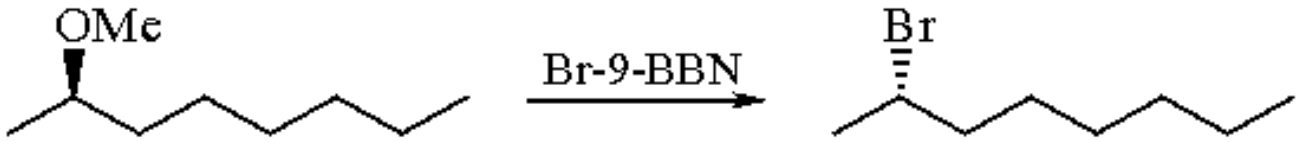

(1)

Deoxygenation of Sulfoxides.

Br-9-BBN rapidly and cleanly deoxygenates sulfoxides with no accompanying rearrangement in CH_2Cl_2 at or below 0 °C.[3] The reagent gives isolated yields which equal or exceed those from either ***Boron Tribromide*** or ***Bromodimethylborane***, all of which provide the corresponding sulfides in excellent yields even with polyfunctionalized substrates (eq 2).

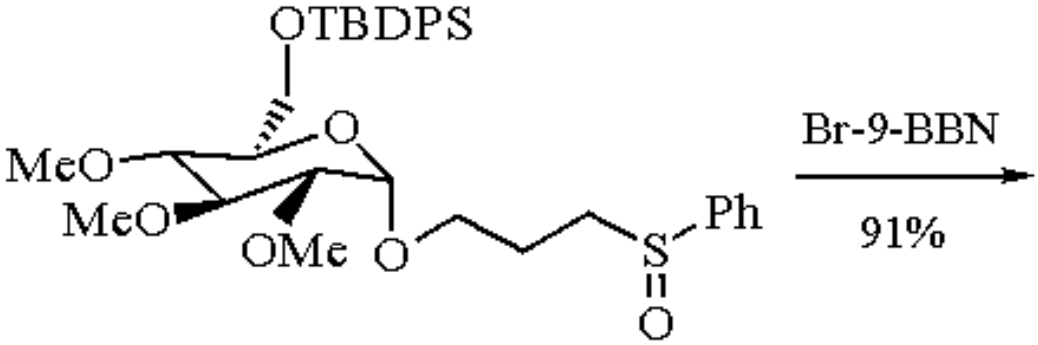

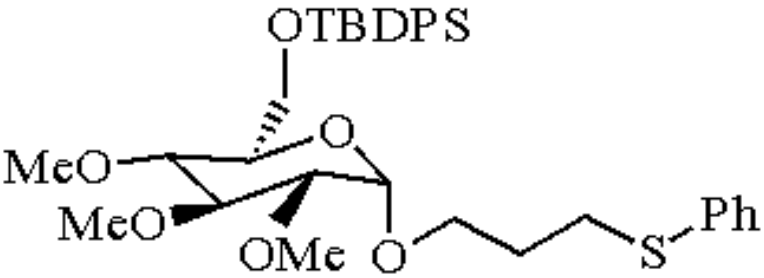

(2)

Addition to Terminal Alkynes.

The *syn* bromoboration of terminal acetylenes with Br-9-BBN provides a simple route to (*Z*)-2-bromovinylboranes (eq 3).[4] The addition is highly regioselective (98-99%) even for functionalized substrates such as propargyl bromide. Reaction occurs over ca. 3 h at 0 °C in CH_2Cl_2 and both ester and alkenic functionalities can be tolerated in the alkyne. The process has been effectively used in the asymmetric synthesis of (-)-ipsenol.[4b]

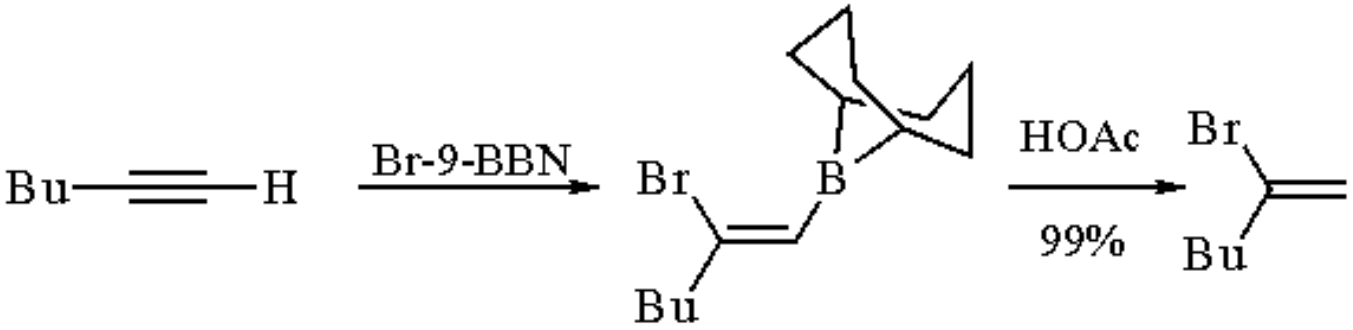

(3)

The (*Z*)-2-bromovinyl-9-BBN adducts undergo additional conversions which lead to stereoselective carbon-carbon bond formation. For example, the iodination of the alkynyl borate complexes derived from these vinylboranes produces the corresponding (*Z*)-brominated enynes in 53-72% yield for representative combinations (eq 4).[6] However, it must be mentioned that for certain applications (e.g. oxidation,[7] halogenation,[8] Pd-catalyzed cross coupling[9]) the use of the 1:1 adducts derived from the addition of BBr_3 to 1-alkynes is preferable to the corresponding 9-BBN derivatives.

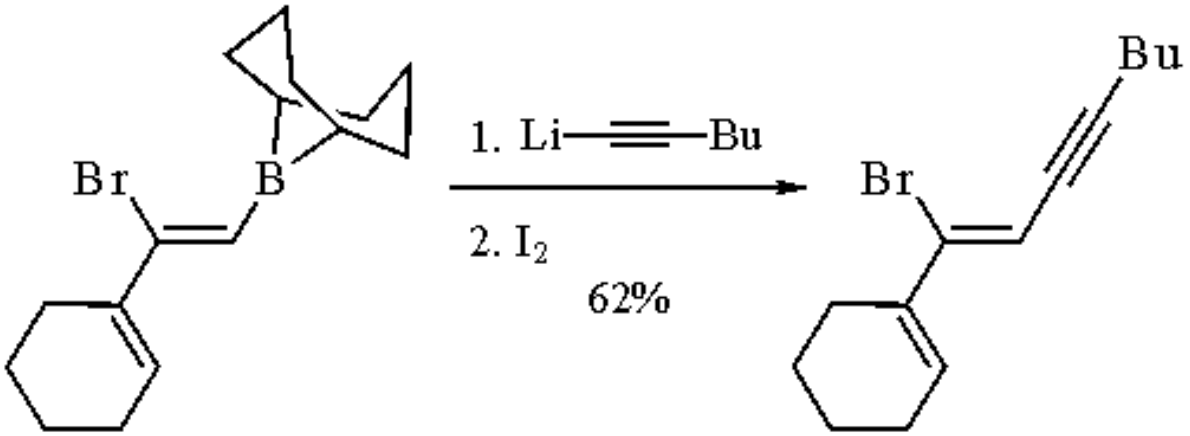

(4)

Conjugate Addition to α,β-Unsaturated Ketones and Aldol Reactions.

Br-9-BBN undergoes 1,4-addition to conjugated enones to produce γ-brominated (*Z*)-enolboranes which undergo stereoselective crossed aldol reactions with a variety of aldehydes.[5] Elimination occurs under the reaction conditions leading to α-bromomethylated enones in good overall yields (50-60%) in a one-pot sequence (eq 5). The stereochemistry and successful substrates suggest that the addition takes place through the *cisoid* form of the starting enone.

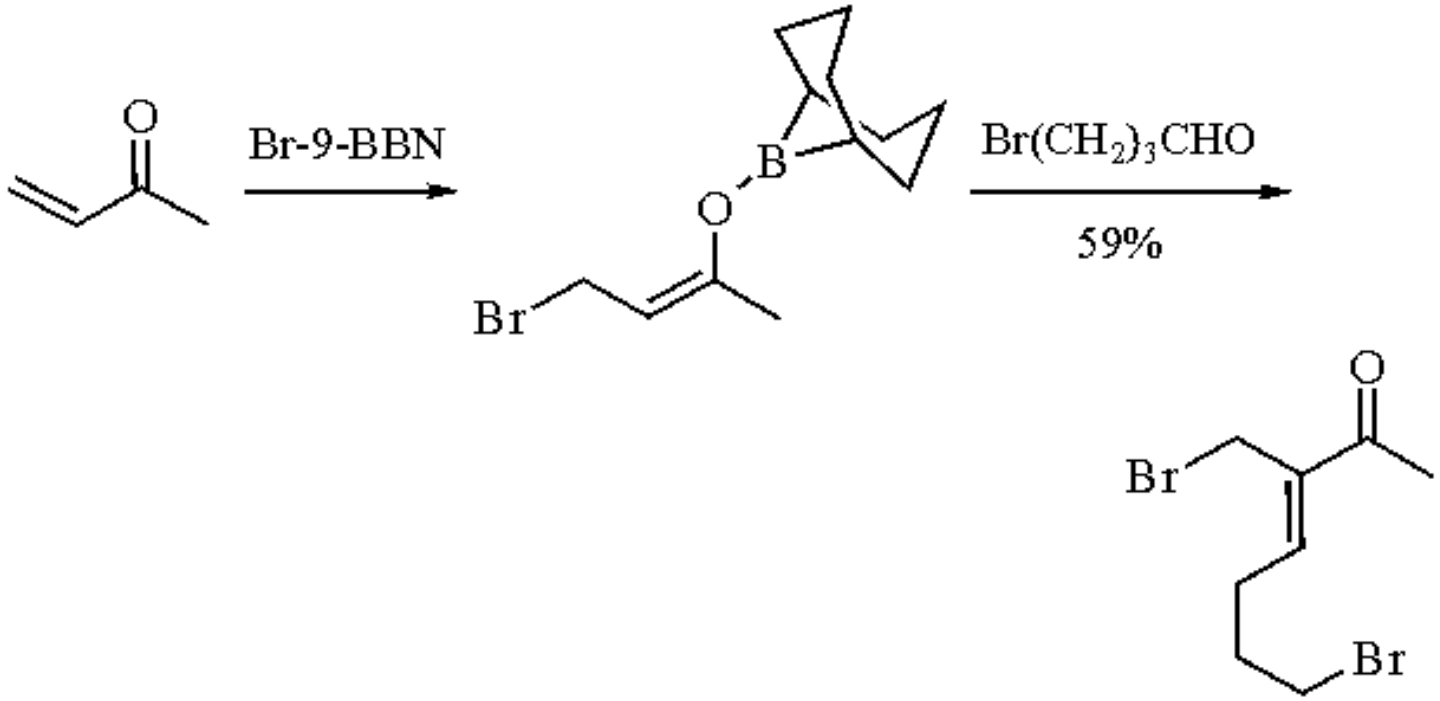

(5)

Vinylboranes from Vinylstannanes.

Like Cl-9-BBN, Br-9-BBN undergoes transmetalation with vinylstannanes to produce vinylboranes (eq 6), the *trans*-1,2-bis-9-BBN derivative being less stable than its BMe_2 or catecholboryl analog (see ***B-Bromocatecholborane***).[10]

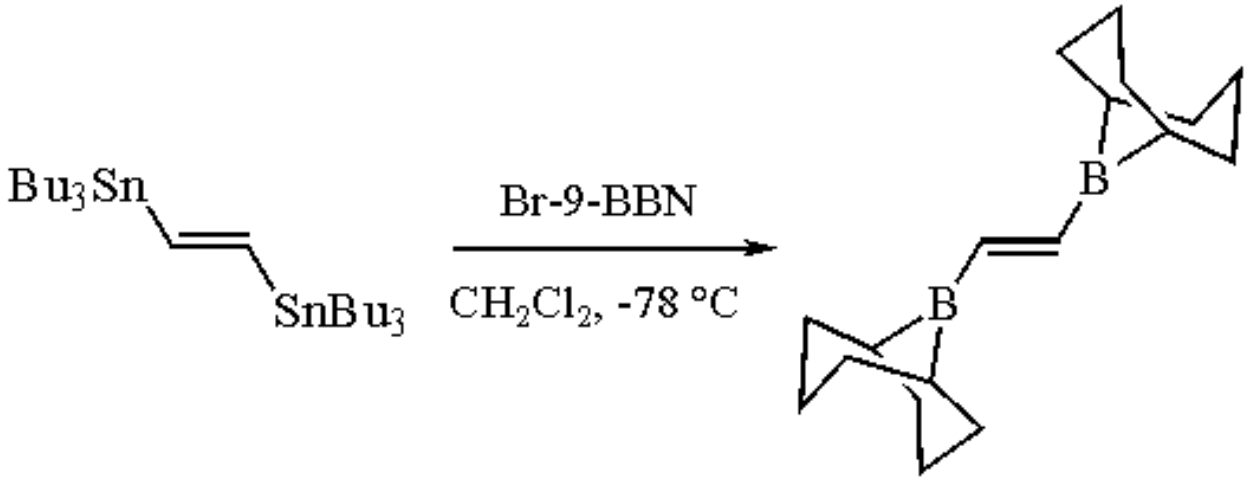

(6)

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10. Singleton, D. A.; Redman, A. M. *TL* **1994**, *35*, 509.

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Bromo(*t*-butyl)(methoxy)phenylsilane

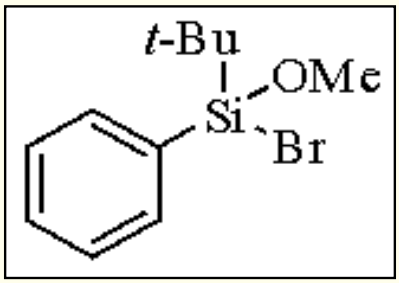

[94124-39-7] · $C_{11}H_{17}BrOSi$ · Bromo(*t*-butyl)(methoxy)phenylsilane · (MW 273.24)

(reagent for the protection of primary, secondary, and tertiary alcohols; reacts selectively with primary hydroxy groups in dichloromethane; *t*-butylmethoxyphenylsilyl ethers are highly reactive towards F^-, allowing for selective removal in the presence of other silyl protecting groups[1])

Alternate Name: bromo-(1,1-dimethylethyl)methoxyphenylsilane.

Physical Data: bp 97-102 °C/1 mmHg; *d* 1.201 g cm^{-3}; fp 106 °C.

Solubility: sol most organic solvents.

Form Supplied in: clear liquid.

Handling, Storage, and Precautions: corrosive, lachrymator; the reagent is light and moisture sensitive and should be handled under an inert atmosphere. Use in a fume hood.

Reactivity.

Bromo(*t*-butyl)(methoxy)phenylsilane reacts with primary, secondary, and tertiary alcohols in DMF, in the presence of ***Triethylamine***, to give the corresponding silyl ethers in good yield (eqs 1 and 2). Under the same conditions, enolizable ketones may be converted efficiently to silyl enol ethers (eq 3).

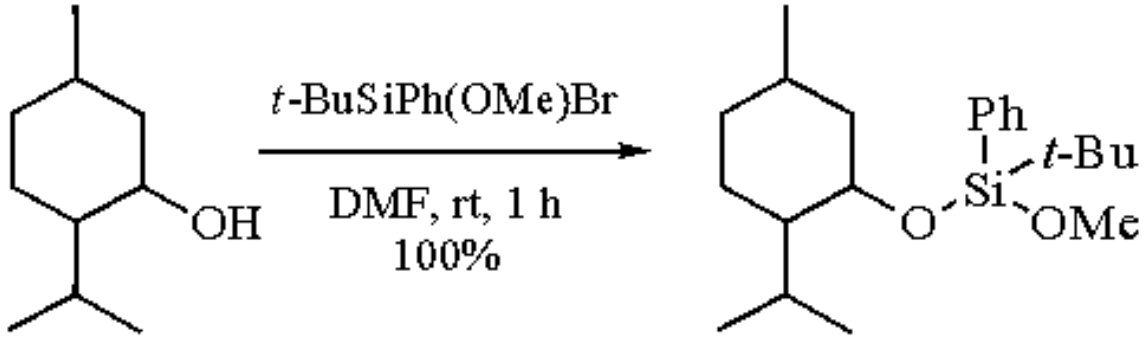

(1)

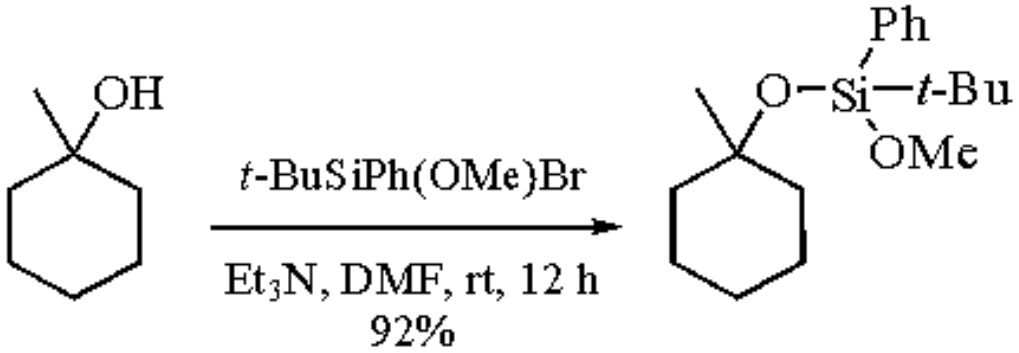

(2)

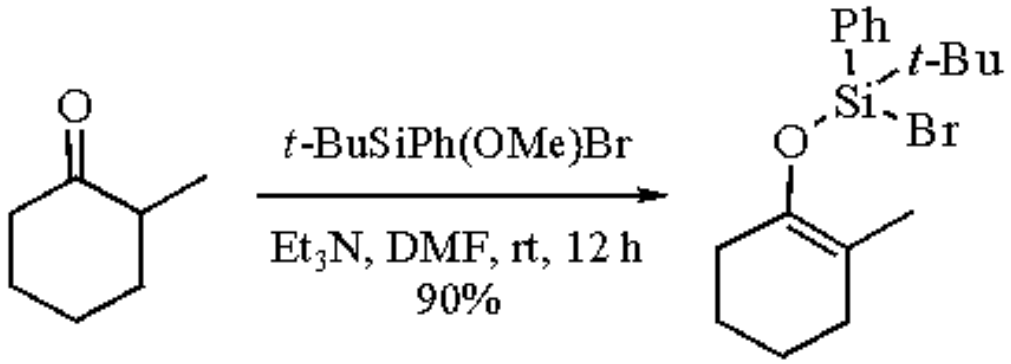

(3)

In the case of secondary alcohols, silylation can be achieved in dichloromethane in the presence of a small amount of DMF (0.02 equiv). This accelerating effect of DMF has been rationalized based on the involvement of a more reactive hexacoordinated silicon species. Chemoselective silylation of primary alcohols can be achieved when dichloromethane is used as the only solvent (eq 4).[1]

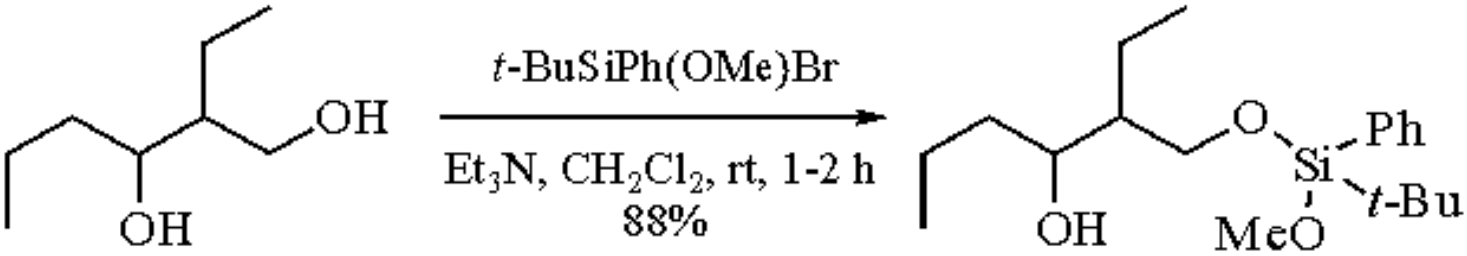

(4)

Stability.

One of the most striking and useful features of the *t*-butyl(methoxy)phenylsilyl ether group is its sensitivity to fluoride. Removal of this protecting group can be achieved using ***Tetra-n-butylammonium Fluoride*** (1M solution in THF) in

dry dichloroethane (10% v/v), in the presence of primary or secondary *t*-butyldimethylsilyl or *t*-butyldiphenylsilyl ethers (eqs 5 and 7).[1] Selective cleavage of a *t*-butyldimethylsilyl ether in the presence of a *t*-butyl(methoxy)phenylsilyl ether is possible under acidic conditions (eqs 6 and 8).

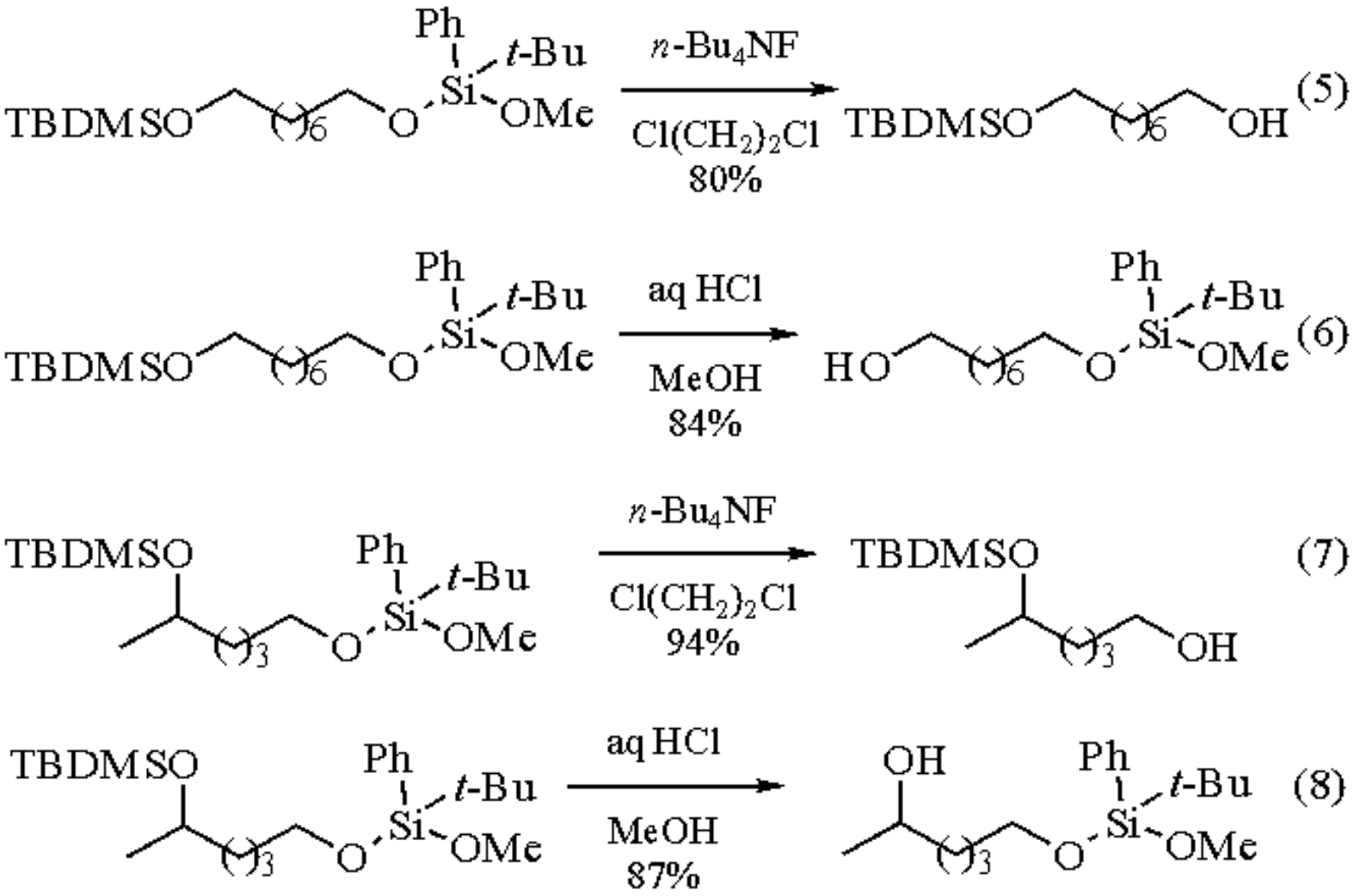

The *t*-butyl(methoxy)phenylsilyl protecting group is compatible with reactions such as PCC oxidation,[2] acylation, tosylation, $NaBH_4$ reduction, benzylation, and hydrogenolysis.

Note that the use of this reagent on chiral molecules will produce diastereoisomers; this may complicate interpretation of NMR spectra.

---

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Bio-Méga/Boehringer Ingelheim Research, Laval, Quebéc, Canada

3-Bromocamphor-8-sulfonic Acid[1]

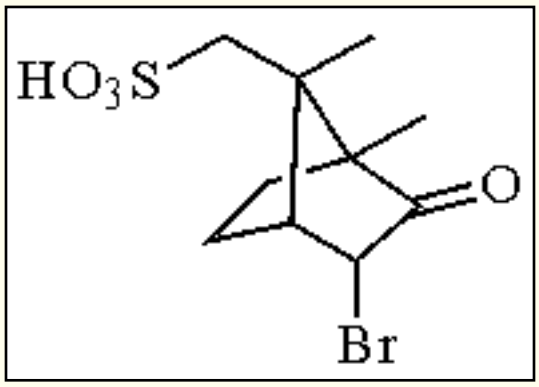

(1*S*)

[46472-20-2] · $C_{10}H_{15}BrO_4S$ · 3-Bromocamphor-8-sulfonic Acid · (MW 311.19) (1*R*)

[5344-58-1] (1*S*) (NH_4^+ salt)

[55870-50-3] · $C_{10}H_{18}BrNO_4S$ · Ammonium 3-Bromocamphor-8-sulfonate · (MW 328.22) (1*R*) (NH_4^+ salt)

[14575-84-9] (±) (NH_4^+ salt)

[122519-23-7]

(chemical resolutions;[1] starting material for the preparation of chiral reagents[2])

Alternate Names: α-bromocamphor-π-sulfonic acid; 3-bromocamphor-9-sulfonic acid.

Physical Data: free acid: mp 195-196 °C; (1*R*): $[\alpha]_D$ 88.3° (*c* 2.6, H_2O). NH_4^+ salt: mp 284 °C (dec); (1*R*): $[\alpha]_D$ 84.8° (*c* 4, H_2O)

Solubility: the ammonium salt is sol in water, slightly sol in EtOH, but essentially insol in acetone and Et_2O. The free acid is sol in EtOAc, MeCN, and 5% aq. NaOH.

Form Supplied in: both enantiomers are commercially available as ammonium salts.

Preparative Methods: by sulfonation of bromocamphor with ***Chlorosulfonic Acid*** in $CHCl_3$.[3] Alternatively, fuming ***Sulfuric Acid*** can be used as both the solvent and sulfonating agent.[4] Recently, an improved preparation with an easier isolation procedure was reported (34% yield).[5] The acid can be prepared by passing a solution of the NH_4^+ salt in H_2O through a Dowex resin (H^+) column.[6] Alternatively, it can be obtained by adding ***Acetyl Chloride*** to a suspension of the ammonium salt in a 2:1 mixture of $CHCl_3$ and absolute EtOH.[7] The corresponding sulfonyl chloride is readily prepared from the acid or the NH_4^+ salt upon treatment with ***Phosphorus(V) Chloride*** and ***Phosphorus Oxychloride***.[8,9]

Purification: crystallized from H_2O.

Handling, Storage, and Precautions: a 0.5 M solution of the free acid in dry MeCN is stable for at least 30 days at 5 °C in a closed vessel under N_2.[6]

Chemical Resolution of Compounds Containing Basic Groups.

3-Bromocamphor-8-sulfonic acid has been widely used as a resolving agent for compounds containing basic groups. A number of primary (**1**),[10] secondary (**2**),[11] and tertiary (**3**) amines[12] as well as oxazolines (**4**)[6] have been resolved by the formation of diastereomeric salts derived from 3-bromo-8-camphorsulfonic acid.

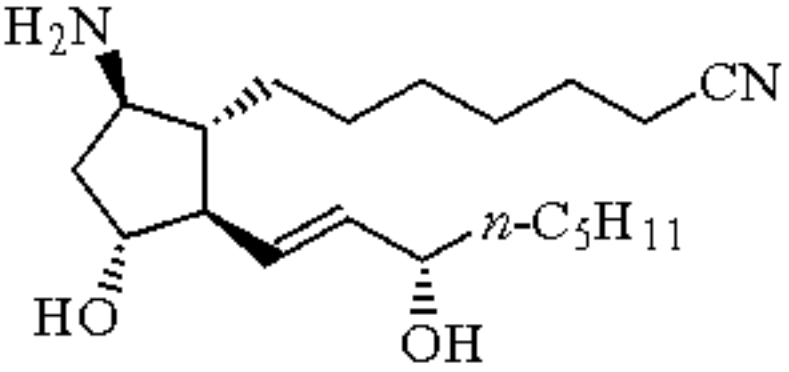

(1)

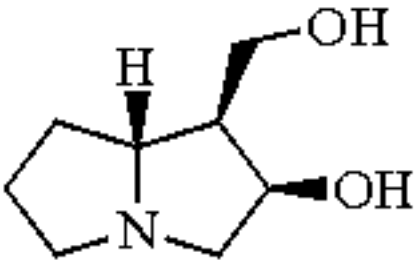

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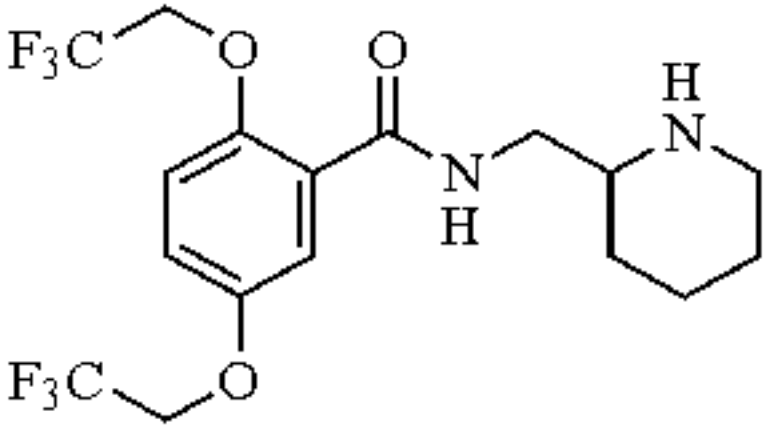

(2) Flecainide

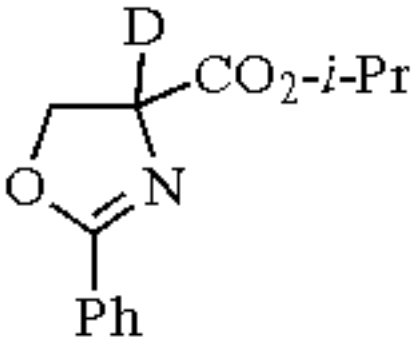

(4)

The optical resolution of racemic *p*-hydroxyphenylglycine with 3-bromocamphor-8-sulfonic acid has also been achieved.[13] This resolving agent has also been widely used in the preparation of optically pure chromium[14] and cobalt complexes.[15]

Preparation of Chiral Reagents.

3-Bromocamphor-8-sulfonic acid has been used as a starting material for the synthesis of chiral reagents.[16] Although the oxidation of sulfides to sulfoxides can be accomplished with the oxaziridine (**5**) or (**6**), other camphor-derived oxaziridines (**7** and **8**) are the reagents of choice to accomplish this transformation (eq 1).[2,9,17]

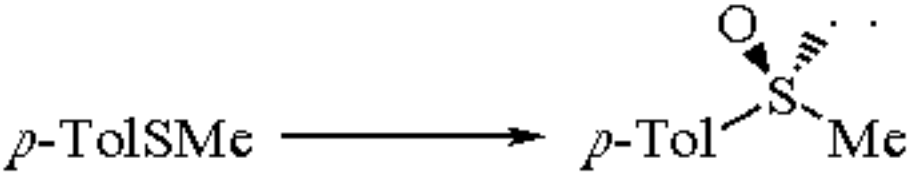

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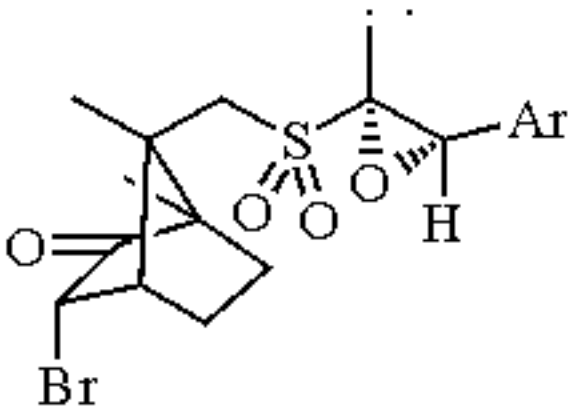

(5)
21% ee (*S*), 75-80% yield

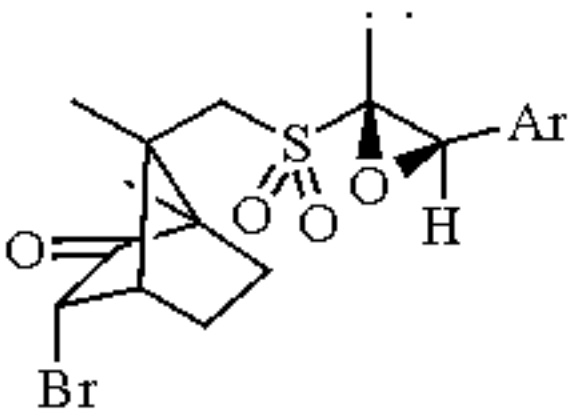

(6)
26% ee (*R*), 75-80% yield

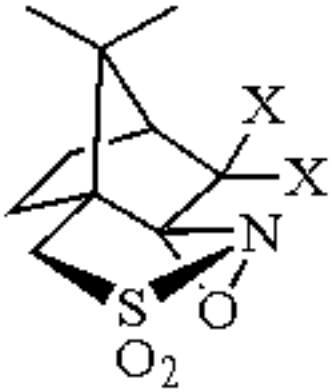

(7) X = H, 28% ee, (*S*), 80% yield
(8) X = Cl, 95% ee, (*S*), 95% yield

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B-Bromocatecholborane

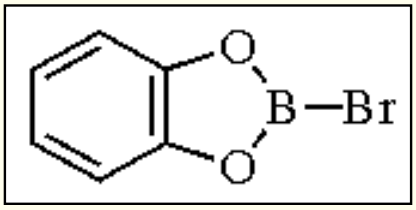

[51901-85-0] · $C_6H_4BBrO_2$ · *B*-Bromocatecholborane · (MW 198.81)

(mild Lewis acid capable of selective cleavage of ether, ester and carbamate protecting groups;[1,2] catalyst for Diels-Alder reactions[3,4])

Alternate Name: 2-bromo-1,3,2-benzodioxaborole.

Physical Data: mp 47 °C; bp 76 °C/9 mmHg; fp 41 °C.

Solubility: sol dichloromethane.

Form Supplied in: colorless solid which fumes in air.

Preparative Method: can be conveniently prepared by treating ***Catechol*** with ***Boron Tribromide***.[1,2,5] The reagent is isolated by distillation as a moisture-sensitive, low-melting solid.

Handling, Storage, and Precautions: flammable solid, moisture sensitive; may be conveniently stored and dispensed as a 0.2 M solution in dichloromethane. If properly protected from moisture, these solutions are stable for a period of months.[1] Use in a fume hood.

Cleavage of Ether, Ester, and Carbamate Protecting Groups.

B-Bromocatecholborane has been used to cleave a variety of ether, ester, and carbamate protecting groups.[1,2,6-9] The reactions typically proceed at rt in dichloromethane using 1-2 equiv of the reagent. ***Boron Trifluoride Etherate*** has been used as a coreagent.[2] After the cleavage of carbamate protecting groups the product amines should be freed of reactive bromide byproducts immediately upon workup in order to avoid problems of *N*-alkylation, especially when a reactive halide (e.g. benzyl bromide from cleavage of the Cbz protecting group) is involved.[1]

A series of competition experiments were performed in order to determine the relative reactivity of a number of common protecting groups towards *B*-bromocatecholborane. The results of these experiments suggest the following

tentative order of reactivity: MOM and MEM ethers > *t*-Boc > Cbz and *t*-Bu ethers > benzyl ethers > allyl ethers > *t*-Bu esters and secondary alkyl ethers > benzyl esters and primary alkyl ethers >> alkyl esters.[1] Selective cleavage of multifunctional substrates is possible when sufficient differences in reactivity exist; however, an excess of the reagent may be necessary when coordinating groups are present (eqs 1-4).[1,7]

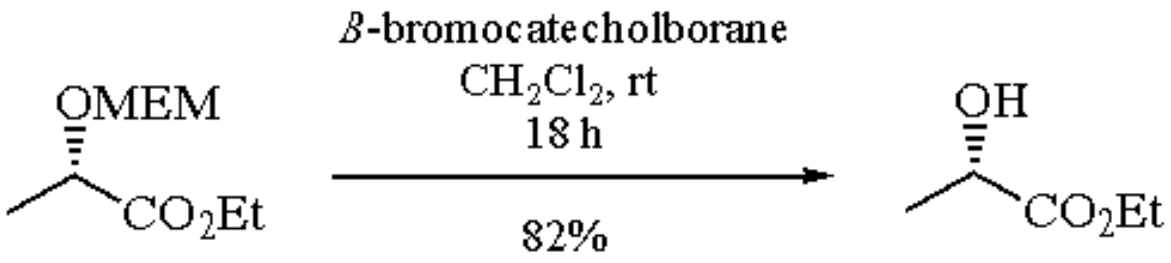

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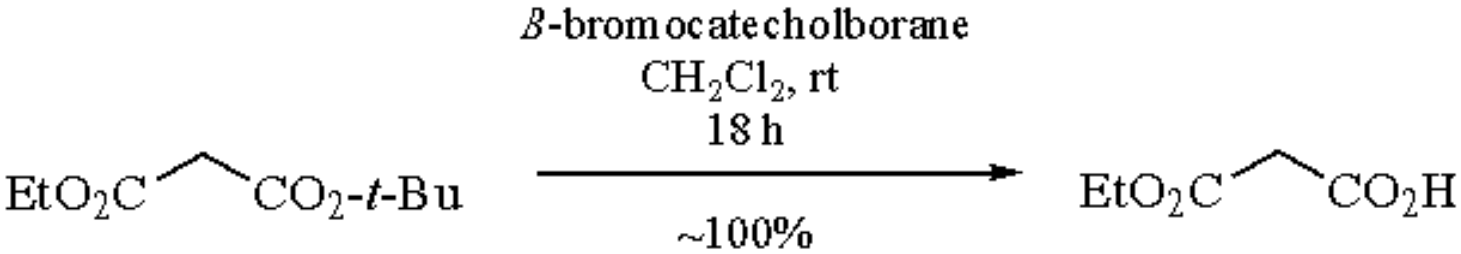

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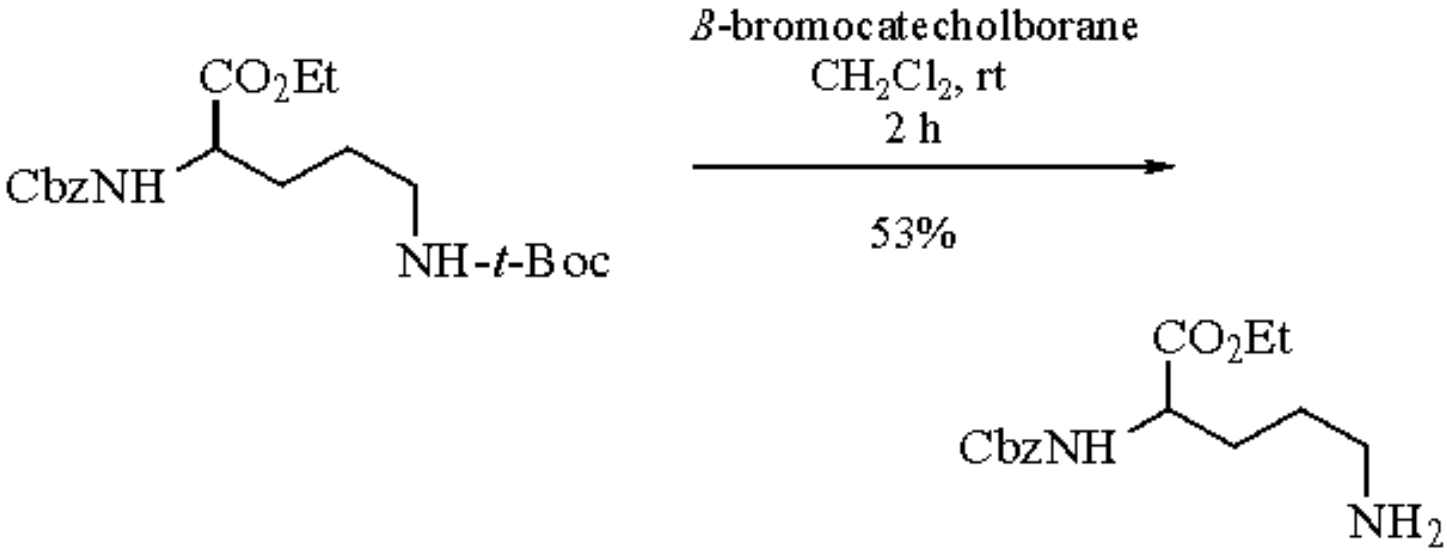

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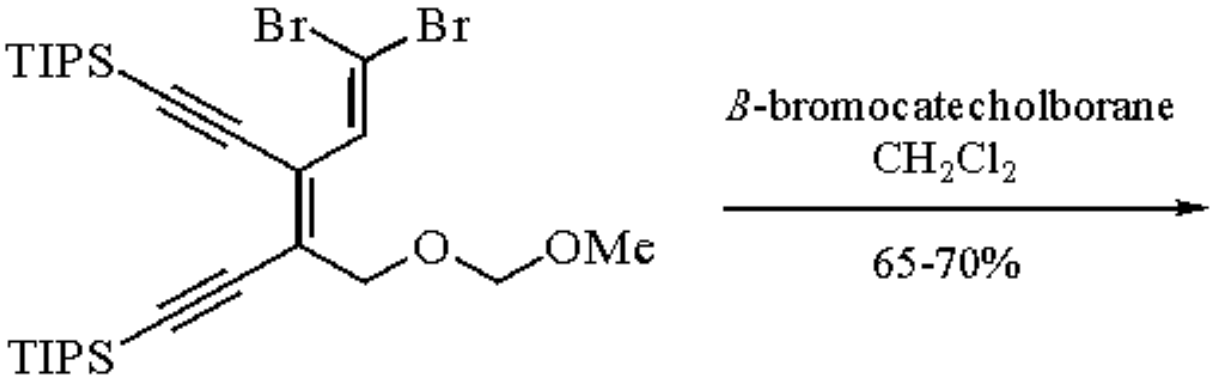

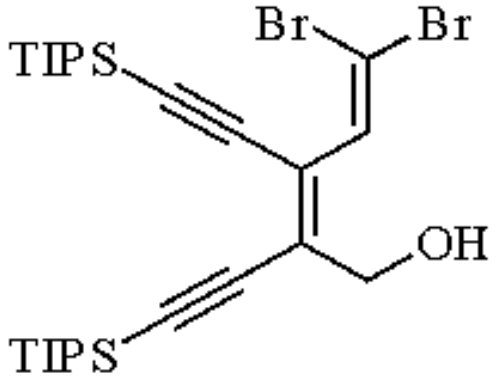

(4)

B-Chlorocatecholborane has been used for similar transformations.[1,9-11] This reagent is observed to be less reactive than the bromo analog and may be preferable when higher selectivity is required.[1]

Diels-Alder Reactions.

B-Bromocatecholborane also functions as a catalyst for the Diels-Alder reaction (eq 5).[3,4] It is a very effective catalyst with a wide variety of dienophiles including α,β-unsaturated aldehydes, ketones, esters, thioesters, and nitriles. Turnover was seen with all dienophiles tested with the exception of acrylonitrile.[3]

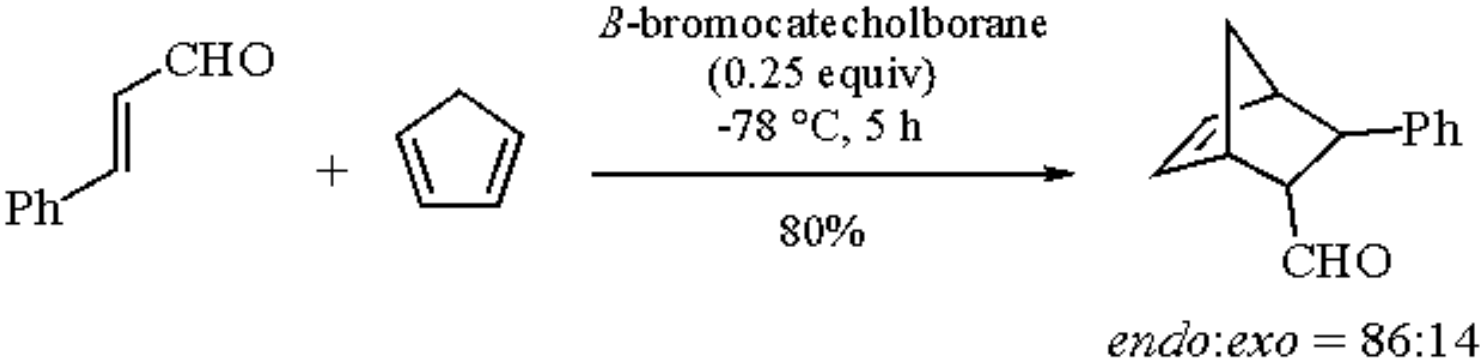

(5)

In a comparison of the Diels-Alder reaction of cyclopentadiene with a variety of α,β-unsaturated esters and thioesters catalyzed by ***Aluminum Chloride*** or *B*-bromocatecholborane, the latter reagent afforded higher levels of *endo* selectivity.[4]

Related Reagents.

Boron Tribromide; ***Bromodimethylborane***.

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Bromo(crotyl)(cyclopentadienyl)(nitrosyl)molybdenum

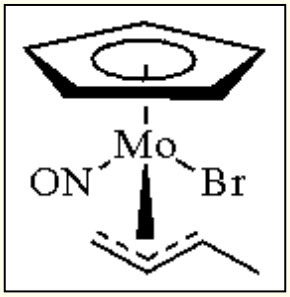

[133684-62-5] · $C_9H_{12}BrMoNO$ · Bromo(crotyl)(cyclopentadienyl)(nitrosyl)molybdenum · (MW 326.04)

(reagent for stereocontrolled synthesis of β-methyl homoallyl alcohols via crotyl addition to aldehydes)

Physical Data: mp ~150 °C (with dec).

Solubility: sol most polar organic solvents; very sol methylene chloride.

Form Supplied in: orange crystals; currently no commercial source.

Handling, Storage, and Precautions: indefinitely stable at rt under nitrogen or argon. The crystals can be handled in air for short periods with no significant decomposition.

Additions of crotyl organometallics to aldehydes provide a particularly effective route for the stereocontrolled synthesis of β-methyl homoallyl alcohols. CpMo(NO)(halide)(η^3-crotyl) reagents complement the crotylboron and crotyltitanium reagents, which are more reactive but can be more sensitive to decomposition by moisture (particularly the titanium complexes). As solids they have an indefinite shelf life and solutions are not particularly air-sensitive, although they are best handled under an inert atmosphere.

There are several methods of reagent preparation;[1-4] the most useful involves several straightforward steps via high yield reactions from the (*E*)- or (*Z*)-crotyl halide (eq 1).[4] (*Z*)-***Crotyl Chloride*** can be prepared readily from *cis*-2-butenol (commercially available or from hydrogenation of 2-butynol) by reaction with ***Triphenylphosphine*** and ***Hexachloroacetone***.[5]

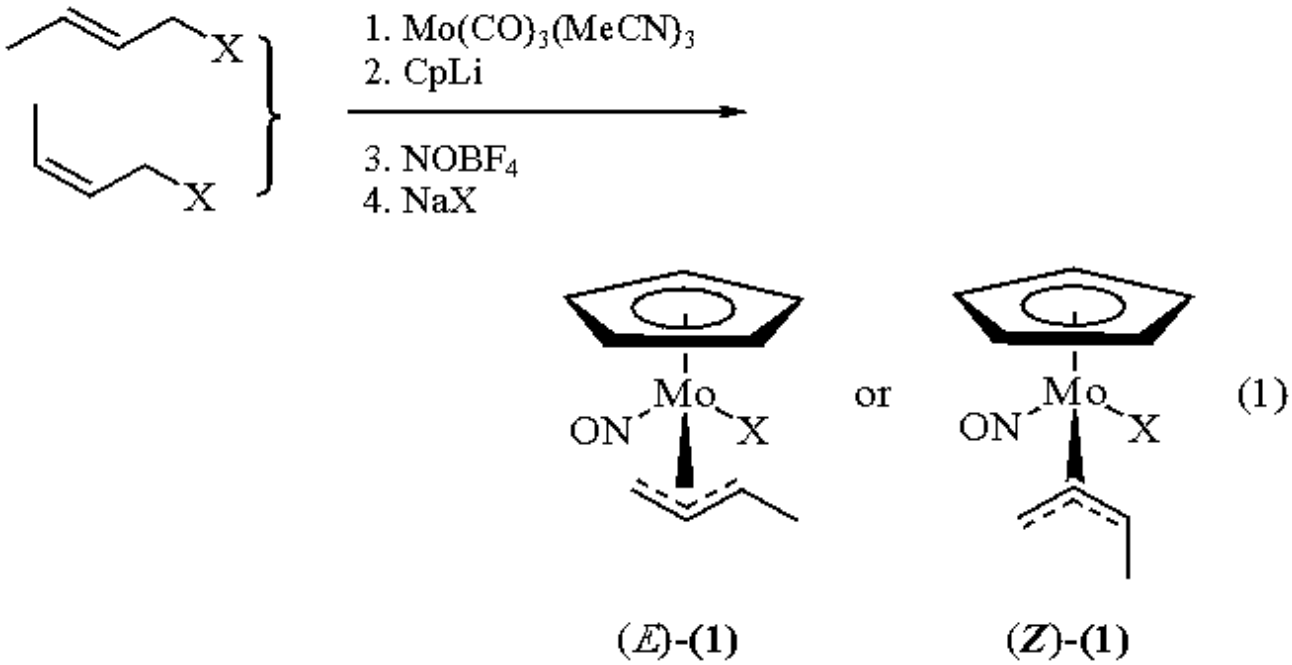

Since the (*E*)-crotyl complex is the stable form and the half-life for conversion of (*Z*) to (*E*) is ~0.4 days at rt in solution, the steps involving addition of crotyl halide and LiCp to the (*Z*)-crotyl complex are best carried out at 0 °C. An alternate efficient route to the (*Z*)-crotyl complex is via hydride reduction of $[CpMo(CO)(2\text{-butyne})_2]BF_4$ under an atmosphere of CO to yield the $CpMo(CO)_2$(crotyl) complex[6] followed by treatment with NO^+ and halide.[2] The various halides can be easily interconverted by treatment with excess NaX or LiX in acetone. Another preparation uses the commercially available $[CpMo(CO)_3]_2$ as the starting organomolybdenum reagent with *cis*- or *trans*-crotyl halides.[7] Liebeskind[8] has reported that use of diphenylphosphinates instead of halides may be useful for analogs of crotyl reagents.

When the (*Z*)-crotyl reagent is initially prepared it usually contains some (<15%) of the (*E*)-isomer. Since the (*Z*)-isomer is less soluble (particularly for the iodide and bromide), recrystallization (CH_2Cl_2/pentane at -15 °C) allows separation of 99% pure material. This step is often not necessary because the (*Z*)-isomer reacts much faster with aldehydes than the (*E*)-isomer; consequently, the de of the product is not affected to a great degree. This feature appears to be common to other crotyl reagents, since (*Z*)-crotyl boronates also react faster than their (*E*)-analogs.[9] One should note in this preparation that the addition of NO^+ yields exclusively the isomer with the NO group *trans* to the methyl group. This tends to weaken the Mo-C bond on the methyl-substituted terminus of the crotyl ligand. An η^1-crotyl is thus readily formed (*k* &AApprox; 0.5 s^{-1} at 25 °C). This allows interconversion of conformers of the reagent in solution. Characterization by NMR can be complicated by the presence of resonances for two conformers (*exo*:*endo* &AApprox; 2:1 for the (*Z*)-crotyl-iodide complex).

The reactivity of the CpMo(NO)(halide)(crotyl) complexes decreases in the order OTs > Cl > Br >> I. The iodide and bromide readily form large crystals from methylene chloride and are more easily handled than the chloride and tosylate. The greater reactivity of the bromide thus may make it the reagent of choice. The (*Z*)-crotyl complex yields the *syn*-homoallylic alcohol (eq 2), whereas the (*E*)-crotyl complex yields the *anti*-isomer (eq 3), as one might anticipate based on a chair-like transition state. With the racemic crotyl complexes, both of the enantiomers of (**2**) and (**3**) shown in eqs 2 and 3 are produced as well.

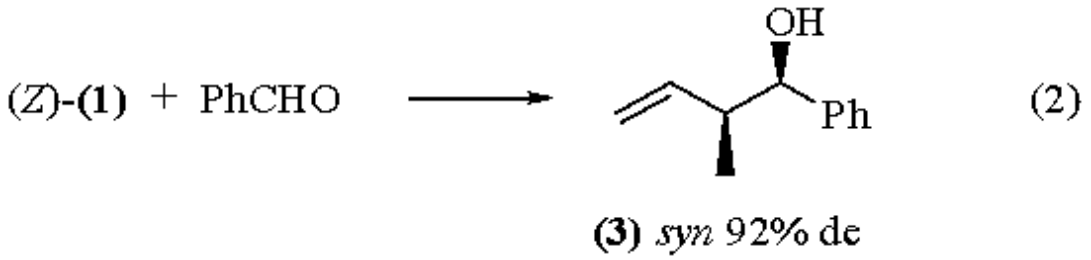

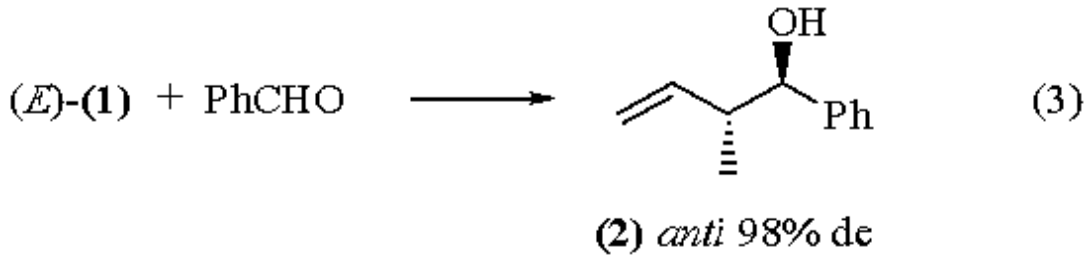

The reaction rates are slow by comparison with those of allyltitanium reagents, which are often used at low temperatures. The reactions are faster in methylene chloride than in chloroform. Since they are second-order reactions, the more concentrated the solutions, the higher the rate. The reactions are effective for alkyl, aryl, and α,β-unsaturated aldehydes, but not for ketones. Room temperature reactions typically require less than an hour for CpMo(NO)(Br)[(*Z*)-crotyl] and 12 hours for CpMo(NO)(Br)[(*E*)-crotyl]. The reaction rates with α-substituted aldehydes are slower and the more reactive tosylate may be required; nevertheless, the selectivity of the reaction with the bromide is high, but may take several days.

After attack of the crotyl on the bound aldehyde, a proton is required to remove the newly formed homoallylic alcoholate from molybdenum. In initial reports, methanol was added to the reaction mixture as a proton source. With slower reacting alcohols, problems can sometimes be encountered owing to hemiacetal or acetal formation. The water present in wet methylene chloride is sufficient to provide the needed proton for the alcohol and also generates a relative insoluble [CpMo(NO)X(OH)] dimer. The convenience of this reagent lies in the facility with which the reagent can be removed from the reaction mixture by filtration (or passage through a short silica gel column), which yields a solution of product and any remaining starting aldehyde. This approach also does not require carefully dried solvents.

Enantiomerically pure (neomenthylCp)Mo(NO)(Cl)[(*E*)-crotyl] complexes produce the *anti*-β-methyl homoallylic alcohols in high enantiomeric purity (>98% ee; 92% de).[1] Although it has been unsuccessful with the parent CpMo(NO)(X)(allyl) complex, the crotyl and 2-methallyl complexes can be resolved as the camphorsulfonate complexes and converted back to the halides.[10,11] These reactions also yield the *anti*-β-methyl homoallylic alcohols in high ee.

Variants of these reagents have been utilized by Liu et al. in stereoselective 1,3-diol (eq 4) and 1,3,5-triol syntheses.[7,12,13]

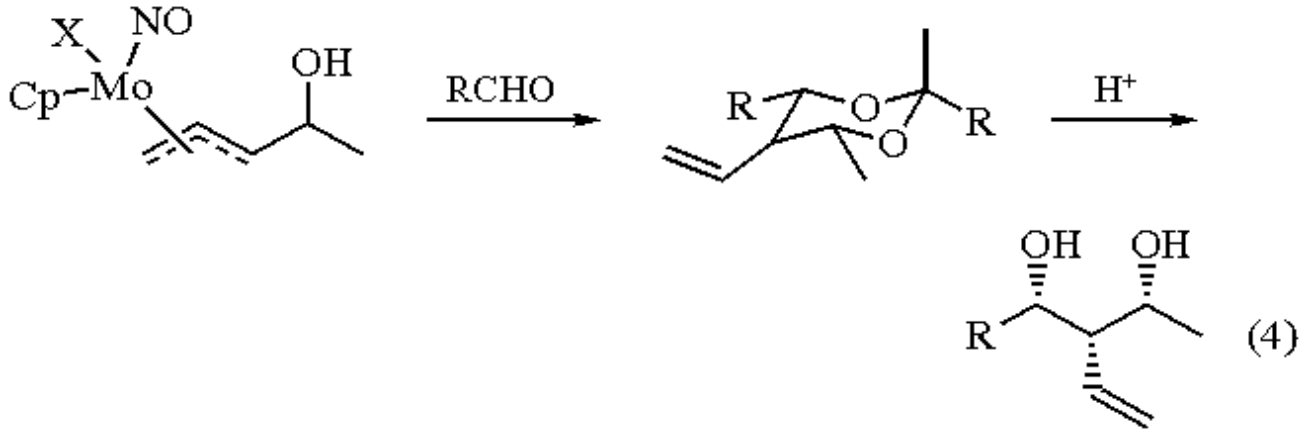

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2-Bromo-2-cyano-*N,N*-dimethylacetamide[1,2]

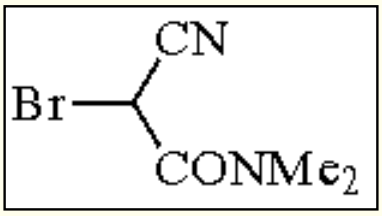

[15430-62-3] · $C_5H_7BrN_2O$ · 2-Bromo-2-cyano-*N,N*-dimethylacetamide · (MW 191.03)

(monobrominating agent selective for α-carbon of enolizable ketones[2])

Physical Data: mp 53-54 °C; bp 134-135 °C/0.3 mmHg.

Solubility: sol ethanol, benzene, chloroform, ethyl acetate, and THF; insol petroleum ether and hexane; slightly sol hot ether, isopropyl alcohol, and H_2O. It is stable at rt in neutral or acidic solution, but unstable in basic media.

Form Supplied in: colorless solid.

Preparative Method: via bromination of 2-cyano-*N,N*-dimethylacetamide with Br_2 in AcOH/Ac_2O at 8-10 °C.[3]

Handling, Storage, and Precautions: the reagent is fairly stable at rt. For long storage, keep at 0-10 °C, shielded from light. This reagent should be handled in a fume hood.

Regioselective Bromination.

This reagent is effective for the introduction of one bromine atom into ketones. Monobromination occurs regioselectively at the α-carbon of ketones on the side favorable to enolization. The reaction proceeds on refluxing the ketone substrate with an equimolar amount of the reagent, usually in benzene (eqs 1-8).[2] As the reaction most likely involves a radical mechanism,[2] nonpolar solvents are preferred. During the course of the reaction, the reagent is debrominated to 2-cyano-*N,N*-dimethylacetamide, which can be easily isolated and recycled to the original reagent through bromination.[2]

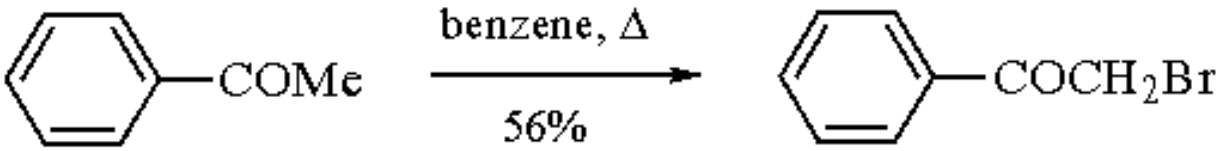
COMe
benzene, Δ
56%
COCH2Br

(1)

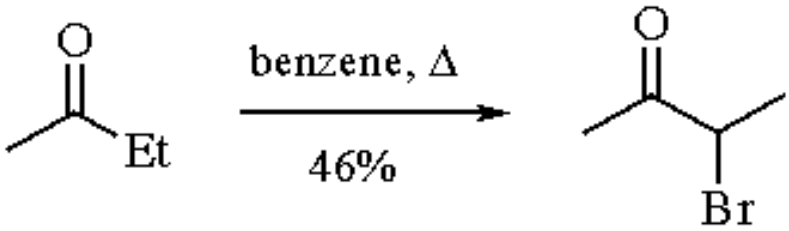
O
Et
benzene, Δ
46%
O
Br

(2)

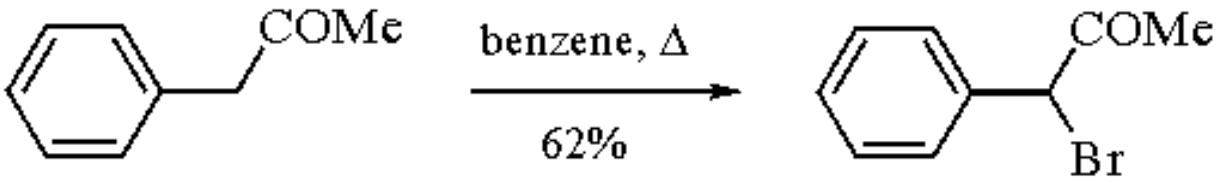
COMe
benzene, Δ
62%
COMe
Br

(3)

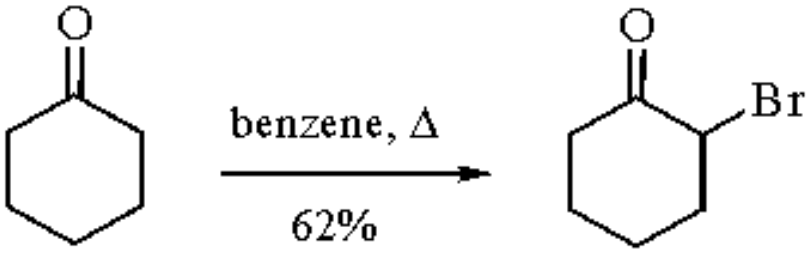
O
benzene, Δ
62%
O
Br

(4)

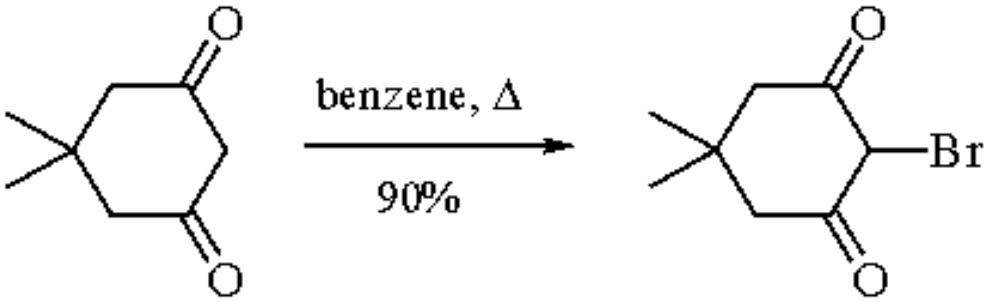
O
O
benzene, Δ
90%
O
Br
O

(5)

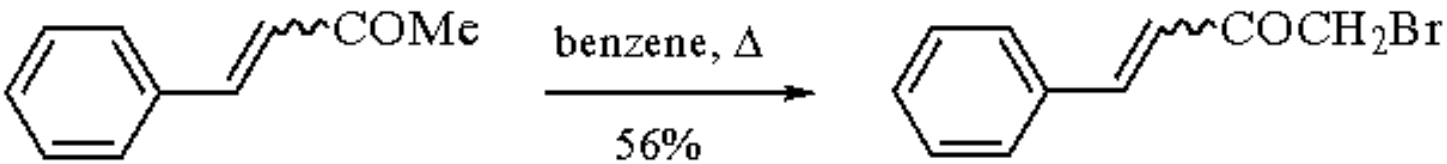
COMe
benzene, Δ
56%
COCH2Br

(6)

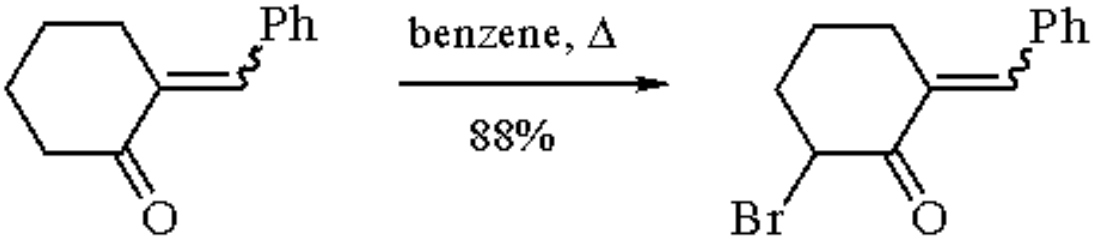
Ph
O
benzene, Δ
88%
Ph
Br
O

(7)

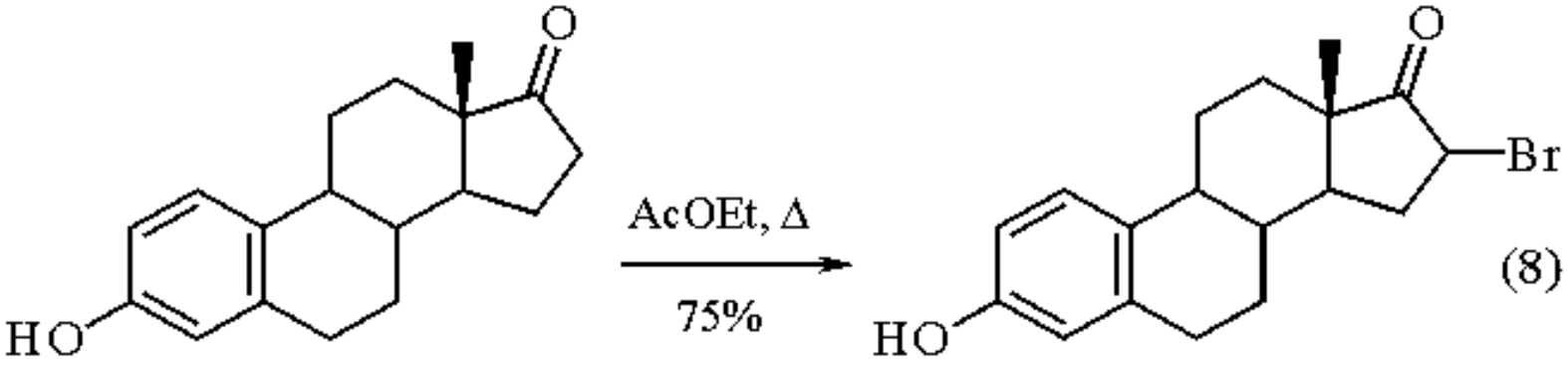

This highly selective reagent does not react with esters and does not add to carbon-carbon double bonds. Allylic bromination is not observed with this reagent. Bromomalononitrile shows reactivity similar to the reagent, but reacts with difficulty and in lower yield in some cases.[2] In the literature only a few examples of brominating reagents have appeared bearing bromine-carbon bonds, such as 2,2-dibromomalononitrile,[4] 2,2,2-tribromoacetophenone,[5] and ***5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione***.[6]

---

1. (a) Sekiya, M. *Yuki Gosei Kagaku Kyokaishi* **1977**, *35*, 297 (*CA* **1977**, *87*, 52 240). (b) Fieser, M.; Fieser, L. F. *FF* **1977**, *6*, 73.
2. Sekiya, M.; Ito, K.; Suzuki, K. *T* **1975**, *31*, 231.
3. Suzuki, J.; Suzuki, K.; Sekiya, M. *CPB* **1974**, *22*, 965.
4. Hata, T. *BCJ* **1964**, *37*, 547.
5. Kröhnke, F.; Ellegast, K. *CB* **1953**, *86*, 1556.
6. Bloch, R. *S* **1978**, 140.

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Minoru Sekiya

University of Shizuoka, Japan

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5-Bromo-1,3-cyclopentadiene

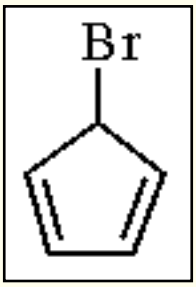

[41851-49-4] · C_5H_5Br · 5-Bromo-1,3-cyclopentadiene · (MW 145.00)

(Diels-Alder reaction;[1] 1,5-hydride shift;[2] bromocyclopentadienyl anion[3])

Physical Data: reactive intermediate typically stored in CCl_4 solution under nitrogen at -78 °C.

Form Supplied in: not commercially available.

Preparative Method: the compound may be prepared[1a] by addition of ***N-Bromosuccinimide*** to a solution of ***Thallium(I) Cyclopentadienide*** in dry CCl_4 at 0 °C.

Diels-Alder Reaction and 1,5-Hydride Shift.

Bromocyclopentadiene reacts with ***4-Phenyl-1,2,4-triazoline-3,5-dione*** (eq 1)[1a] and ***Dimethyl Acetylenedicarboxylate***[1b] to form the Diels-Alder adduct stereospecifically. The 5-iodo analog reacts similarly, while 5-chlorocyclopentadiene produces both chlorine epimers.[1]

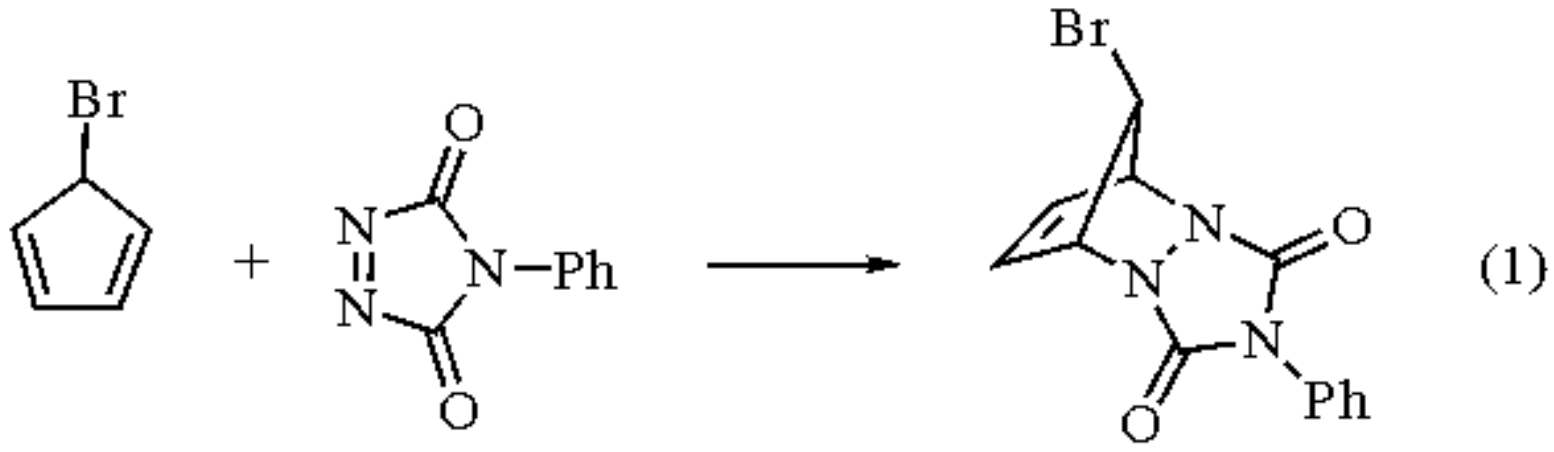

5-Halocyclopentadienes are much more prone to dimerization than ***Cyclopentadiene*** itself (dimerizing about 10^3 times faster).[1a] However, the cycloaddition of halocyclopentadienes with electrophilic dienes is slower than with cyclopentadiene.[1a]

The presence of halogen on the cyclopentadiene ring slows the rate of 1,5-hydride shift and, although iodine rapidly migrates around the ring, bromine does not.[2]

Bromocyclopentadiene Anions.

Both potassium[2] and thallium[3] bromocyclopentadienyl derivatives have been reported.

---

1. (a) Breslow, R.; Hoffman, J. M.; Perchonock, C. *TL* **1973**, 3723. (b) Franck-Neumann, M.; Sedrati, M. *TL* **1983**, *24*, 1391.
2. Breslow, R.; Canary, J. W. *JACS* **1991**, *113*, 3950.
3. Conway, B. G.; Rausch, M. D. *OM* **1985**, *4*, 688.

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Michigan Technological University, Houghton, MI, USA

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3-Bromo-1,1-dichloro-1-propene

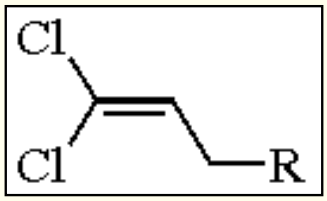

(R = Br)

[36469-73-5] · $C_3H_3BrCl_2$ · 3-Bromo-1,1-dichloro-1-propene · (MW 189.87) (R = CH_2OH)

[42134-33-8] · $C_4H_6Cl_2O$ · 4,4-Dichloro-3-buten-1-ol · (MW 141.00)

(chloroalkene annulating agent for synthesis of cycloalkane carboxylic acids,[1] halogenated vinyl epoxides,[2] halogen-substituted allylglycines,[3] and 1,1-dichloro terminal alkenes[4])

Physical Data: R = Br: bp 65-66.5 °C/17 mmHg; n_D^{20} 1.5363; d_{25} 1.7593 g L^{-1}. R = CH_2OH: bp 80-81.5 °C/10 mmHg.

Form Supplied in: R = Br: not available commercially; pale yellow liquid. R = CH_2OH: not available commercially; liquid.

Preparative Methods: R = Br: can be prepared by ***N-Bromosuccinimide***/***Dibenzoyl Peroxide*** bromination in CCl_4 of 1,1-dichloropropene with >60% yield.[1,2,5] Other methods of preparation are ***Hydrogen Bromide*** bromination of 1,1,3-trichloropropene (***Copper(I) Chloride***/***Copper(II) Chloride*** or ***Iron(III) Chloride*** catalyzed halogen exchange, 90% yield)[6] or 1,1-dichloropropen-3-ol (65% yield).[7] NMR, dipole moment, and IR studies of the reagent show that it exists in a *gauche* conformation in solution.[8] R = CH_2OH: can be prepared by the condensation of ***Chloral*** (hypnotic, sedative) and ***Malonic Acid***,[9] followed by acetylation (***Acetyl Chloride***/***Pyridine***), ***Zinc*** dechloroacetoxylation, and ***Lithium Aluminum Hydride*** reduction to produce 4,4-dichloro-3-buten-l-ol in 30% yield.[1]

Electrophilic Reactions.

These substituted alkenes are known for their utility in chloroalkene annulation reactions, which provide a useful synthesis of cycloalkanecarboxylic acids.[1,10] One example is the octalincarboxylic acid synthesis outlined in eq 1. A 1,1-dichloroalkene intermediate (**2**) is formed by alkylation of ***1-Pyrrolidino-1-cyclohexene*** (**1**) with 3-bromo-1,1-dichloro-1-propene. The ketone intermediate (**2**) is then converted to a mixture of isomeric octalincarboxylic acids (**3**) in two steps. First, ***Vinylmagnesium Bromide*** yields an allylic alcohol which then undergoes cyclization to (**3**) on treatment with ***Formic Acid*** at reflux. The *cis,cis*- and *cis,trans*-2-decalincarboxylic acids were obtained after

hydrogenation of (**3**) with Pt catalyst in acetic acid.

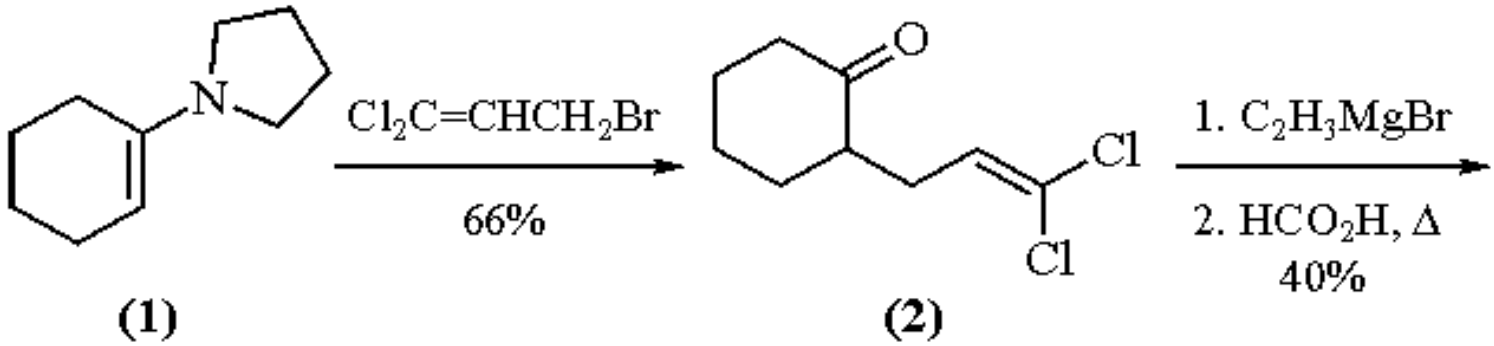

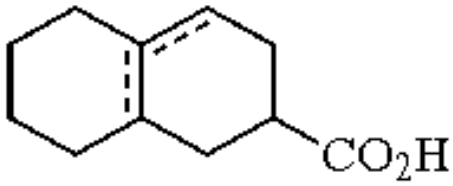

(1)

(3)

A related procedure employing 4,4-dichloro-3-buten-1-ol provides an efficient route to cyclopentanecarboxylic acid (**6**) (eq 2).[1,10] 4,4-Dichloro-3-buten-1-ol is first converted to the mesylate (**4**) (with ***Methanesulfonyl Chloride***), which in turn is used to alkylate deoxybenzoin to form ketone (**5**). Reduction of ketone (**5**) to the alcohol followed by formolysis (97% HCOOH, reflux overnight) results in cyclization to give *trans,trans*-2,3-diphenylcyclopentanecarboxylic acid (**6**).

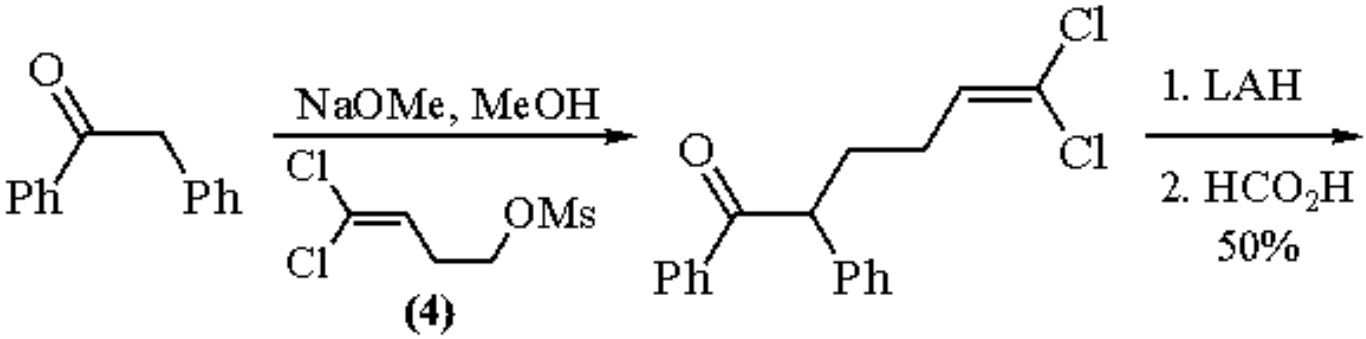

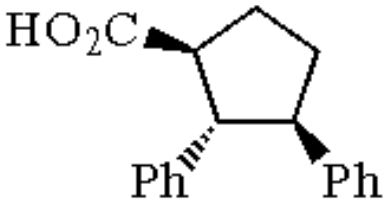

(2)

(6)

Advantages of this methodology are the inertness of the chloroalkene side chain toward a variety of reagents and the relatively mild formolysis conditions required for cyclization. Chloroalkene reagents may be homologated to allow for generation of rings with more than six members. The method is general and has been used with other related

haloalkene reagents.[11]

3-Bromo-1,1-dichloro-1-propene is also used to form halovinyl epoxides. A haloallylsulfonium salt (**8**) is prepared by reaction of tetrahydrothiophene (**7**) with 3-bromo-1,1-dichloro-1-propene in anhydrous acetone (eq 3).[2] Halogenated vinyl epoxides (**9**) are formed upon condensation of (**8**) with RCHO (R = MeCH=CH-, CH_2=C(Me)-, Ph). Other allylic chlorides and bromides have also been used in this reaction.[2]

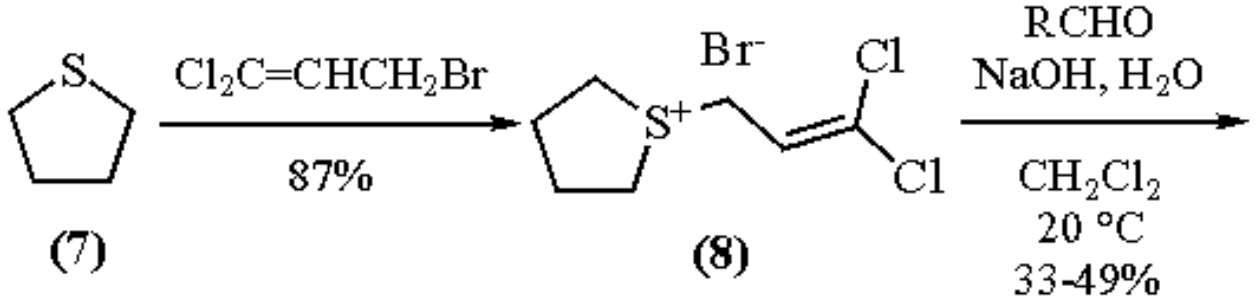

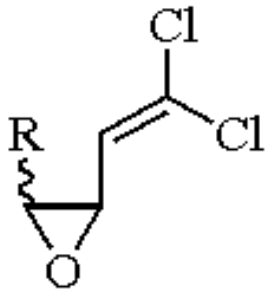

(3)

(**9**)

Halogenated allylic reagents have been used to synthesize substituted allylglycines.[3] Diethyl formamidomalonate (**10**) was alkylated with 3-bromo-1,1-dichloro-1-propene to form intermediate (**11**) (eq 4). The amino acid (**12**) is then obtained by hydrolysis with dilute HBr (reflux, 4 h).

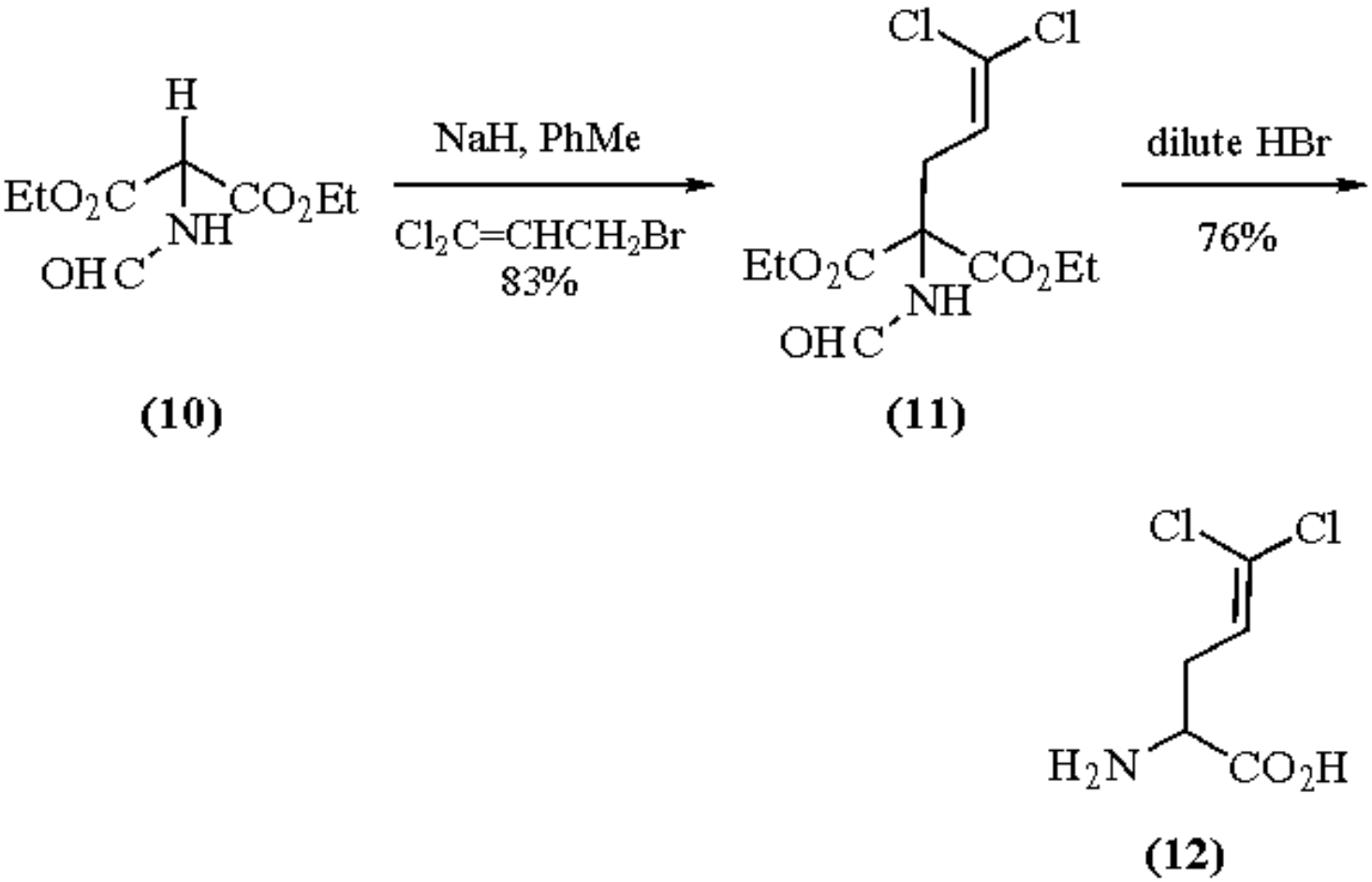

(4)

The 1,1-dichloropropen-3-yl ester of hexanoic acid has been found to be an antagonist of insect juvenile hormone.[4] This ester is prepared (93%) by reaction (K_2CO_3/55 °C/3 h/HMPA) of 3-bromo-1,1-dichloro-1-propene with hexanoic acid. Several patents have been filed for 1,1-dichloroalkene-substituted compounds which have antitumor, herbicide, or pesticide activity and are prepared using 3-bromo-1,1-dichloro-1-propene.

Nucleophilic Reactions.

It has been demonstrated that the 1,1-dichloroalkene moiety may also be introduced into organic molecules via conversion of the reagent to a nucleophile.[1,10] For example, 4,4-dichloro-3-buten-1-ylmagnesium bromide, obtained from bromide (**13**) ($Cl_2C{=}CH(CH_2)_2OH/PBr_3$), reacts with deoxybenzoin to yield alcohol (**14**) (eq 5). Formolysis of (**14**) in refluxing HCO_2H then provides the same cyclopentanecarboxylic acid (**6**) as was obtained in chemistry described earlier where $Cl_2C{=}CH(CH_2)_2OMs$ was employed as an electrophilic reagent (eq 2). The overall yields of the two reactions are similar and the same advantages of chloroalkene side-chain inertness and mild formolysis conditions apply. Other related chloroalkene reactions have been described in the literature.[11]

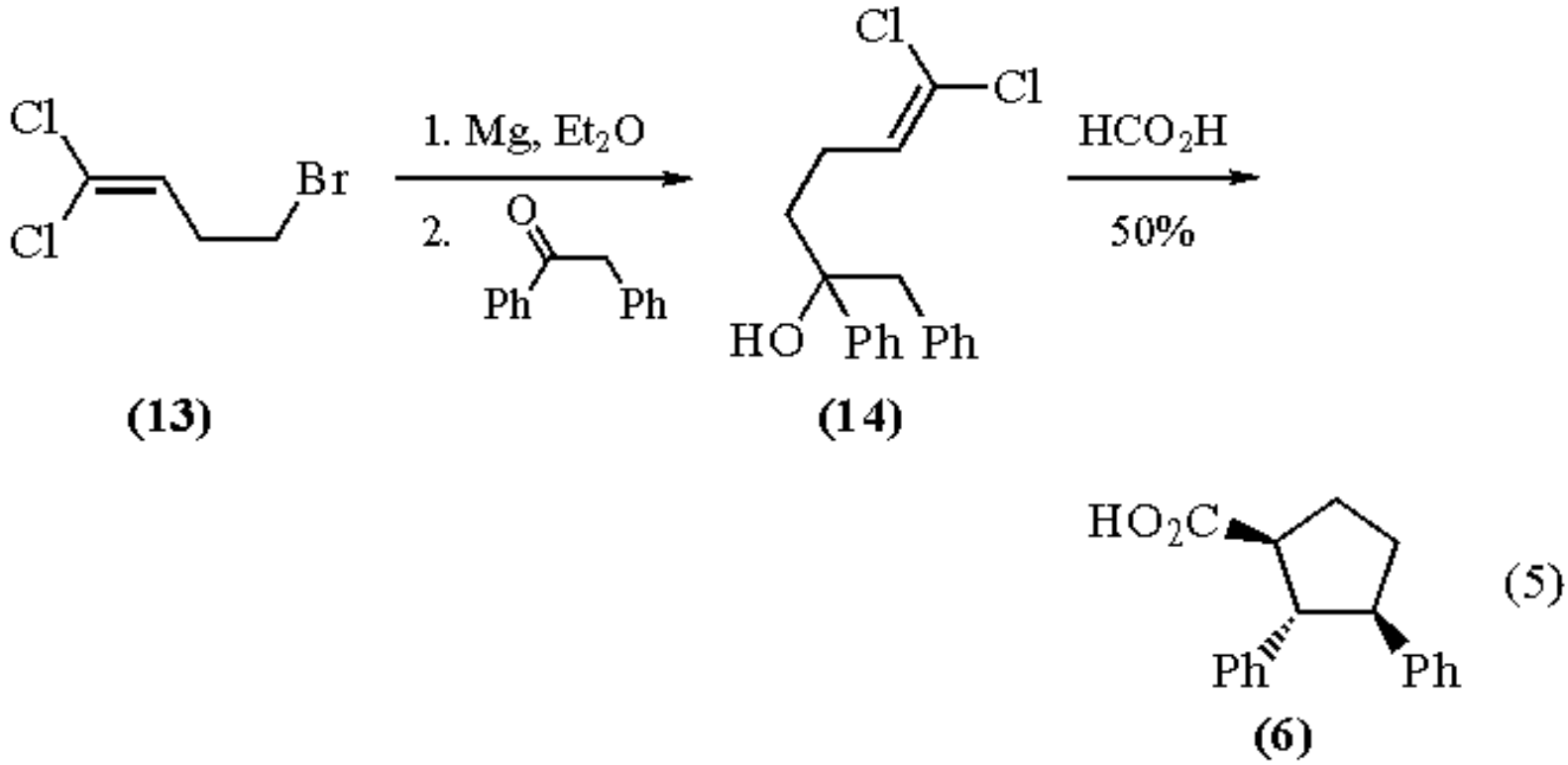

1. Lansbury, P. T.; Stewart, R. C. *TL* **1973**, 1569.
2. Beny, J. P.; Pommelet, J. C.; Chuche, J. *BSF(2)* **1981**, 369.
3. Shapir, J.; Dittmer, K. *JACS* **1960**, *82*, 1495.
4. Quistad, G. B.; Cerf, D. C.; Kramer, S. J.; Bergot, B. J.; Schooley, D. A. *J. Agric. Food Chem.* **1985**, *33*, 47.
5. Hatch, L. F.; Zimmerman, S. D. *JACS* **1957**, *79*, 3091.
6. (a) Kost, V. N.; Freidlina, R. Kh. *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1961**, 1252 (*CA* **1962**, *56*, 1328i). (b) Morlyan, N. M.; Muradyan, A. G.; Badanyan, Sh. O. *Arm. Khim. Zh.* **1975**, *28*, 633 (*CA* **1976**, *84*, 16 684w).
7. Turgarina, R. *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **1980**, *6*, 75 (*CA* **1981**, *94*, 208 285v).
8. Lere-Porte, J. P.; Chorro, C.; Petrissans, J. *CR(2)* **1982**, *295*, 1105.
9. Hurd, C. D.; Hayao, S. *JACS* **1954**, *76*, 5564.
10. Fieser, M.; Fieser, L. F. *FF* **1975**, *5*, 191.
11. (a) Bott, K.; Hulmann, H. *AG(E)* **1966**, *5*, 870. (b) Lansbury, P. T. *ACR* **1972**, *5*, 311. (c) Lansbury, P. T.; Wovkulich, P. M.; Gallagher, P. E. *TL* **1973**, 65. (d) Bott, K. *AG(E)* **1980**, *19*, 171. (e) Gesson, J.-P.; Jacquesy, J.-C.; Renoux, B. *T* **1989**, *45*, 5853. (f) Mayr, H.; Heilmann, W.; Bauml, E.; Vorbruggen, H. *CB* **1991**, *124*, 203. (g) Fraser, F. A.; Proctor, G. R.; Redpath, J. *JCS(P1)* **1992**, 445. (h) Zhu, L.; Shaughnessy, K. H.; Rieke, R. D. *SC* **1993**, *23*, 525.

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3-Bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole[1]

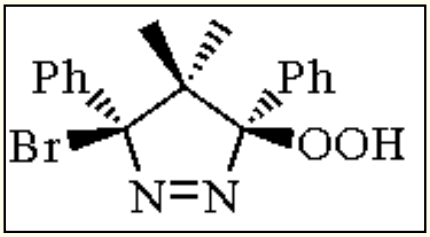

[76847-41-2] · $C_{17}H_{17}BrN_2O_2$ · 3-Bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole · (MW 361.24)

(oxygen-atom transfer reagent; heteroatom and alkene oxidation[2])

Physical Data: mp 77-80 °C (dec).

Solubility: sol $CHCl_3$, CH_2Cl_2, ether, acetone.

Analysis of Reagent Purity: [3] gravimetric analysis gives 96% of bromine theoretical yield. Analysis of gaseous products (thermolysis) shows an N_2 to O_2 ratio of 1:1. IR (KBr): stretching absorptions for OOH and N=N at 3250 and 1540 cm^{-1}, respectively. ^1H NMR ($CDCl_3$): -0.05 (s, 3H), 1.68 (s, 3H), 7.2-7.8 (m, 11H). ^{13}C NMR ($CDCl_3$): 19.9, 23.0, 25.8, 48.6, 102.4, 119.7, 125.7, 128.2, 128.3, 129.1, 132.1, 135.4, 138.9.

Preparative Method: [3] to a slurry of 2.0 g (8.0 mmol) of 4,4-dimethyl-3,5-diphenyl-4*H*-pyrazole in anhydrous ether at 0 °C is carefully added in small portions 6 g (159 mmol) of 90% ***Hydrogen Peroxide*** (caution: danger of explosion!). The solution is allowed to warm to rt and 1.17 g (4.1 mmol) of ***1,3-Dibromo-5,5-dimethylhydantoin*** is added as a powder, portionwise, over a 20-30 min period in the dark. The resulting solution is kept at -20 °C for 48 h, after which it is washed with cold 10% sodium bicarbonate and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure at 0 °C affords the crude product as a yellow oil; recrystallization from CH_2Cl_2/petroleum ether (below -20 °C) yields white crystals of the desired reagent in 75% yield.

Handling, Storage, and Precautions: should be stored at low temperature. Crystals have been kept at -30 °C for years with little or no detectable decomposition. Solutions of the hydroperoxide *must* contain small amounts of *cis*- or *trans*-3-hexene to prevent self-induced decomposition. Addition of 2 µL of the unreactive alkene per 1 mL of solvent stabilizes the reagent. All normal precautions used in the handling of peroxidic materials should be followed.

Heteroatom and Alkene Oxidation.[2]

3-Bromo-4,5-dihydro-5-hydroperoxy-4,4-dimethyl-3,5-diphenyl-3*H*-pyrazole (**1**) is one of the most reactive organic hydroperoxides known.[1] As an electrophilic oxygen-atom transfer reagent, its reactivity in heteroatom oxidation (eq 1)[2] is similar to that of flavin hydroperoxides and ca. two orders of magnitude faster than acyclic azo hydroperoxides.[4] Both *N*- and *S*-oxidation have been found to be first order in (**1**) and in substrate, respectively. No external proton source was required. The reactivity of (**1**) can be estimated[1] to be ca. 10^5 that of ***Hydrogen Peroxide*** and ***t-Butyl Hydroperoxide*** for *N*-oxidation. Heteroatom oxidation has been found[4b] to be an order of magnitude slower in acetone-d_6 than in $CDCl_3$.

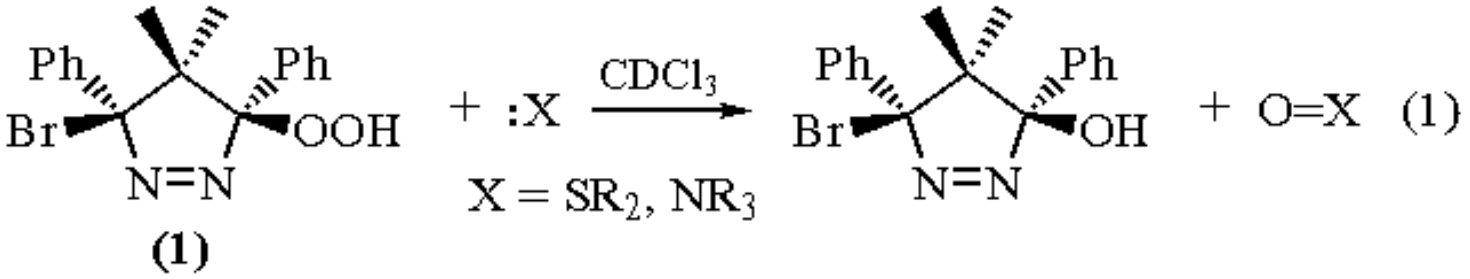

Azo hydroperoxide (**1**) has been found to be of sufficient reactivity to epoxidize alkenes (eq 2) in good yield under mild conditions.[2] The selectivity is essentially identical to that of peroxy acids. The reactivity of (**1**) is comparable to that of ***2-Hydroperoxyhexafluoro-2-propanol*** and roughly two orders of magnitude lower than that of ***Peracetic Acid***.[1] Representative product yields and second order rate constants for heteroatom and alkene oxidation are listed in Table 1.

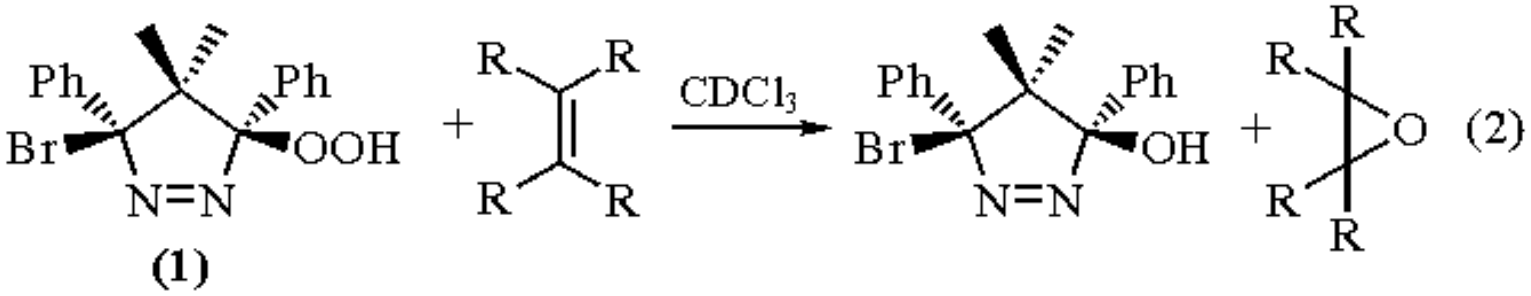

Table 1 Product Yields and Second Order Rate Constants for the Reaction of (**1**) with Sulfides, Amines, and Alkenes in $CDCl_3$ at 34 °C[2]

Substrate	*Oxide yield (%)*	k_2 ($M^{-1}s^{-1}$)	*Substrate*	*Oxide yield (%)*	k_2 ($M^{-1}s^{-1}$)
BnSMe	93	fast	2,3-Dimethyl-2-butene	94	0.0039
PhSMe	94	0.95	1,2-Dimethyl-cyclohexene	85	0.0021
BnSPh	90	0.80	2-Methyl-2-butene	79	0.00028
Ph_2S	92	0.010	1-Methylcyclohexene	72	0.00021
Et_3N	100	0.48	Cyclopentene	41	0.000032
$BnNMe_2$	97	0.16			
N-Methyl-morpholine	95	0.05			
$PhNMe_2$	90	0.0011			

Oxygen-atom transfer reagent (**1**) offers the following advantages: (a) high reactivity with normal selectivity; (b) mild reaction conditions with neutral products; and (c) long-term storage. Limitations for this reagent center on its synthesis. The procedure[3] must be followed in detail and the method has not been extended to additional compounds. Conc H_2O_2 is required in the preparation which greatly increases the difficulty in the preparation of labeled reagent. The newer generation[4b,5] of cyclic azo hydroperoxides are of equal reactivity but are prepared by the reaction of oxygen with 3,4-dihydro-2*H*-pyrazoles (eq 3). Thus these compounds can be prepared readily with ^{17}O or ^{18}O enriched oxygen for use as labeling reagents.[4a]

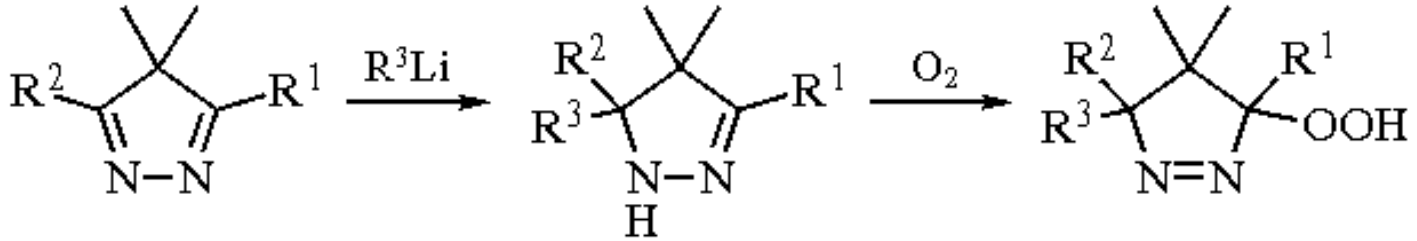

(3)

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Bromodimethylborane[1]

Me_2BBr

[5158-50-9] · $C_2H_6BBr_2$ · Bromodimethylborane · (MW 120.78)

(mild Lewis acid capable of selective cleavage of ethers[2,3] and acetals;[4,5] deoxygenation of sulfoxides[6])

Physical Data: mp -129 °C; bp 31-32 °C; *d* 1.238 g cm^{-3}; fp -37 °C.

Solubility: sol dichloromethane, 1,2-dichloroethane, hexane.

Form Supplied in: colorless liquid.

Preparative Method: can be conveniently prepared by treating ***Tetramethylstannane*** with ***Boron Tribromide***.[7]

Handling, Storage, and Precautions: flammable liquid, moisture sensitive; typically stored and dispensed as a 1.5-2 M solution in dichloromethane or dichloroethane. Solutions of this sort are stable for a period of months if stored at -15 °C and properly protected from moisture.

Cleavage of Ethers.

Bromodimethylborane (Me_2BBr) reacts with primary, secondary, and aryl methyl ethers,[2] in addition to trityl,[8] benzyl,[2,8] and 4-methoxybenzyl[9] ethers, to regenerate the parent alcohol in good to excellent yield (e.g. eq 1). The tertiary methyl ethers examined afforded the corresponding tertiary bromides.[2] The reaction is typically carried out in dichloromethane or 1,2-dichloroethane between 0 °C and rt, in the presence of 1.3-4 equiv of Me_2BBr. The reaction is usually complete in a matter of hours. ***Triethylamine*** (0.1-0.15 equiv per equiv of Me_2BBr) is often added as an acid scavenger. 4-Methoxybenzyl ethers are more reactive and are cleaved at -78 °C, whereas aryl methyl ethers require elevated temperatures to react. Other functional groups including acetates, benzoates, alcohols, ethyl esters, and *t*-butyldiphenylsilyl ethers are recovered unchanged under the standard reaction conditions.

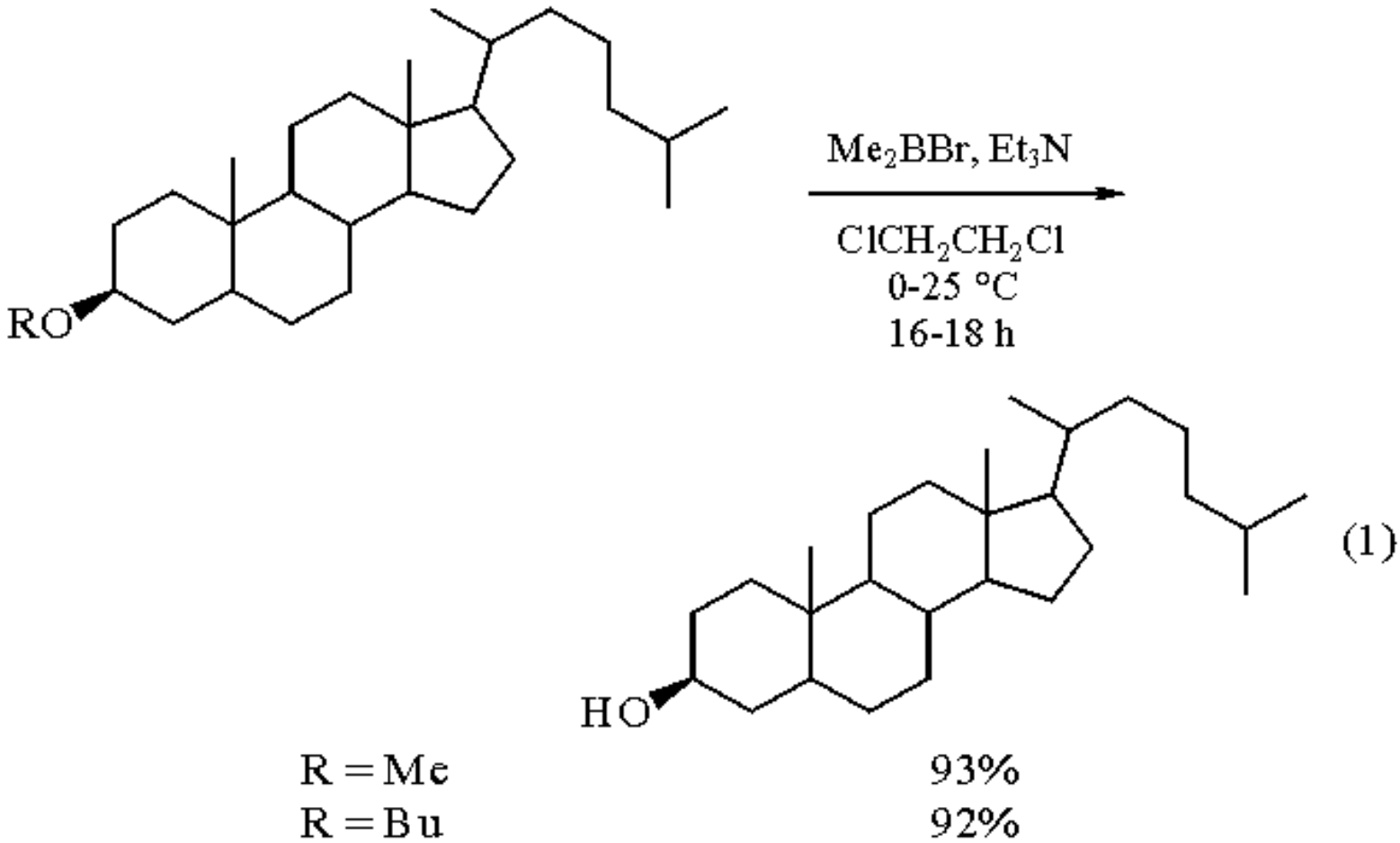

Bromodimethylborane is also effective for the cleavage of cyclic ethers.[2,3] Epoxides react at -78 °C while the analogous four- to seven-membered ring heterocycles react between 0 °C and rt. In contrast to other boron-containing Lewis acids, Me_2BBr reacts via a predominantly S_N2 mechanism. Tetrahydrofuran derivatives which are substituted at the 2-position give rise to primary bromides as the major or exclusive products. The nature of the substituent has a quantitative influence on the outcome of the reaction via steric effects and/or complexation to the reagent. It is of interest to note that tetrahydrofurans can be cleaved in the presence of acyclic ethers (eq 2).[3]

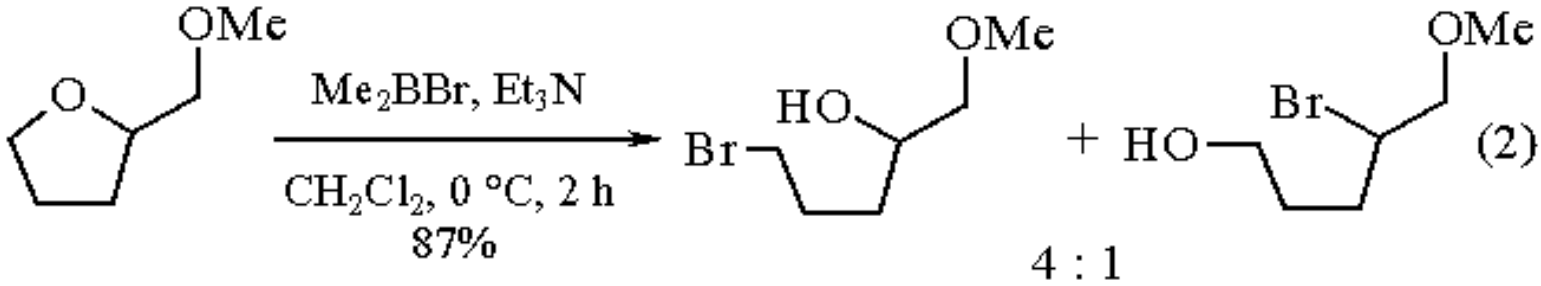

It is also of considerable interest to note that no β-elimination of the hydroxy group was observed in the ring-opening of 2-(ethoxycarbonylmethyl)tetrahydrofurans (eq 3),[3] whereas *C*-glycosides bearing more acidic protons on the aglycon react with Me_2BBr to generate acyclic alkenes (eq 4).[10]

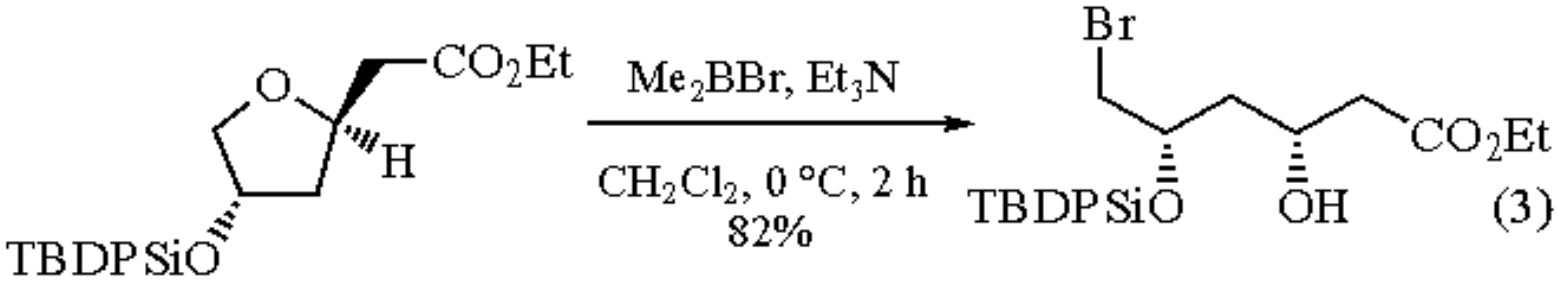

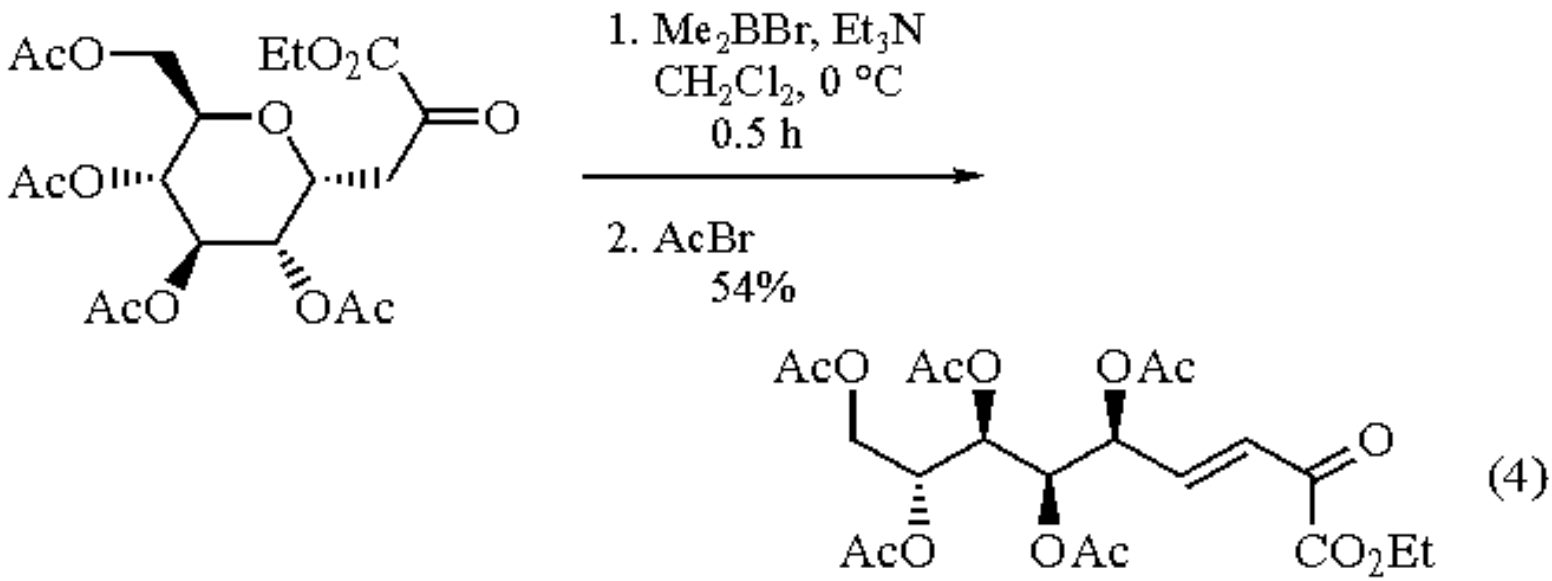

Bromodimethylborane has also been used in conjunction with ***Tetra-n-butylammonium Iodide*** to bring about the fragmentation of iodomethyl ether derivatives (eq 5).[11]

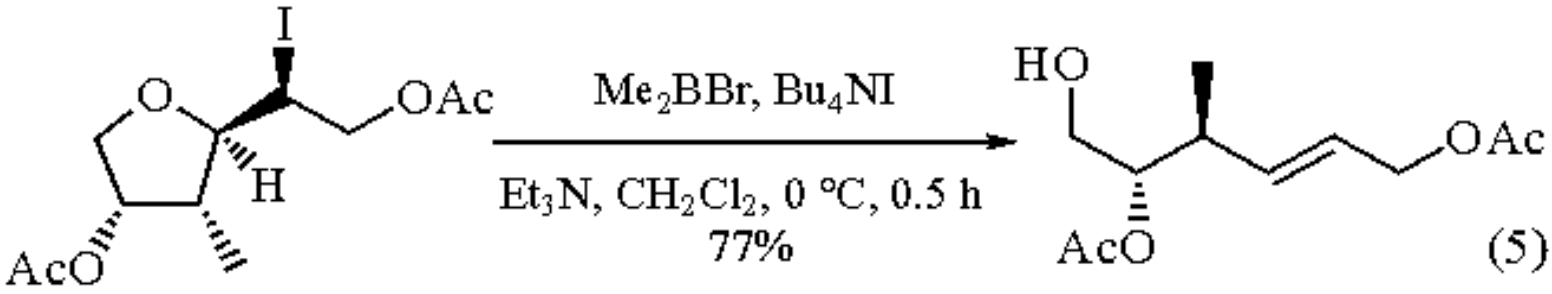

Cleavage of Acetals.[4,5]

Cyclic and acyclic acetals react with Me_2BBr at -78 °C to generate the parent aldehydes and ketones in excellent yield (e.g. eq 6). Primary, secondary, and tertiary (2-methoxyethoxy)methyl (MEM), methoxymethyl (MOM), and (methylthio)methyl (MTM) ethers also react at -78 °C to give, after aqueous workup, the corresponding alcohol. It is interesting to note that even tertiary MEM ethers cleanly regenerate the parent alcohol without formation of the corresponding bromide or elimination products (eq 7). Treatment of an acetonide with Me_2BBr gives the parent diol in high yield (eq 8).

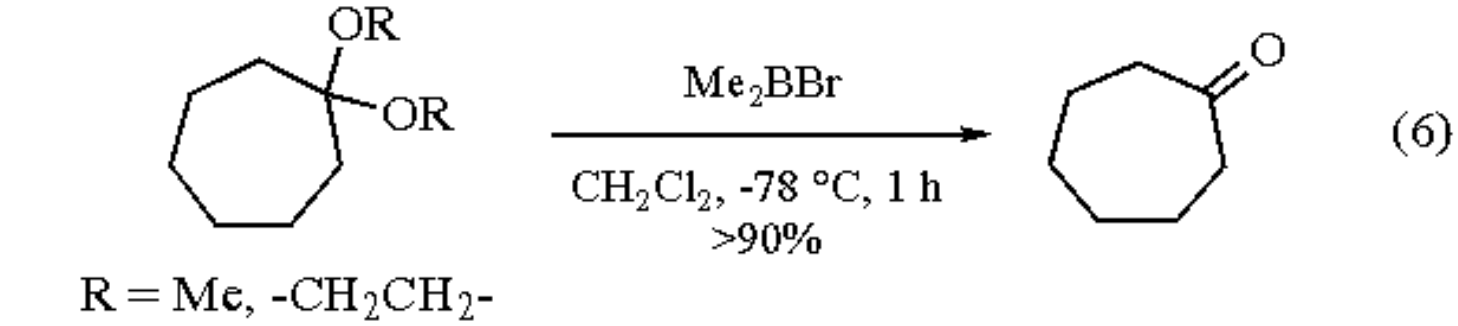

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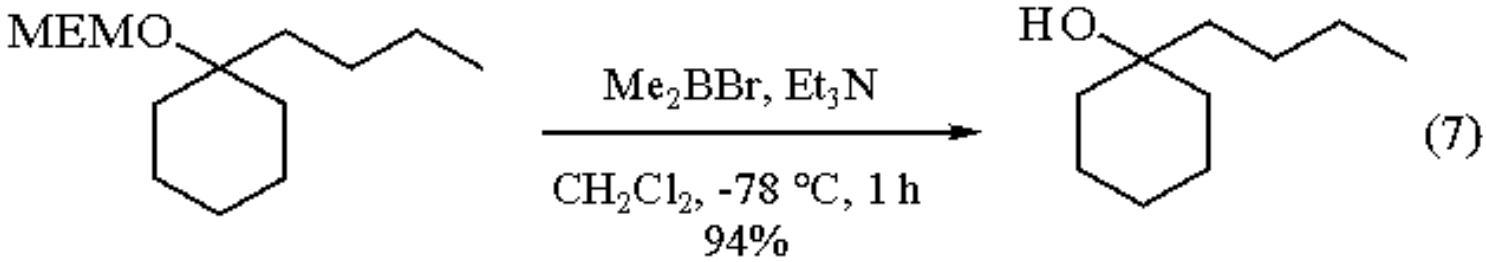

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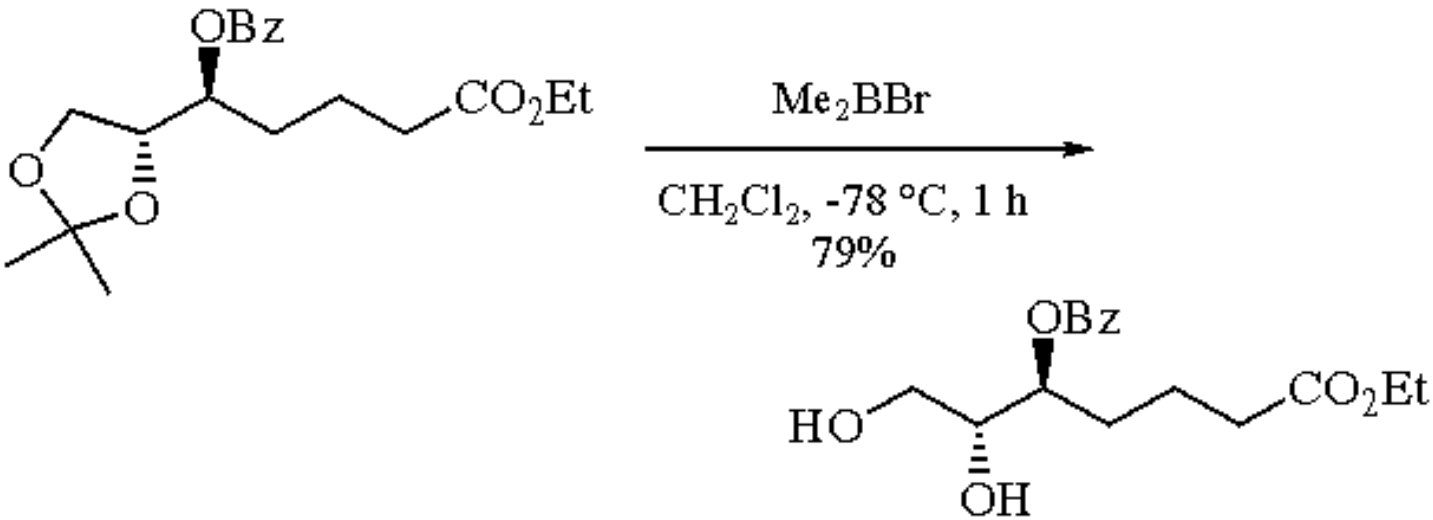

(8)

Tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) ethers are converted to the corresponding alcohols by Me_2BBr at rt (eq 9), although the acetals are cleaved at -78 °C (see below).

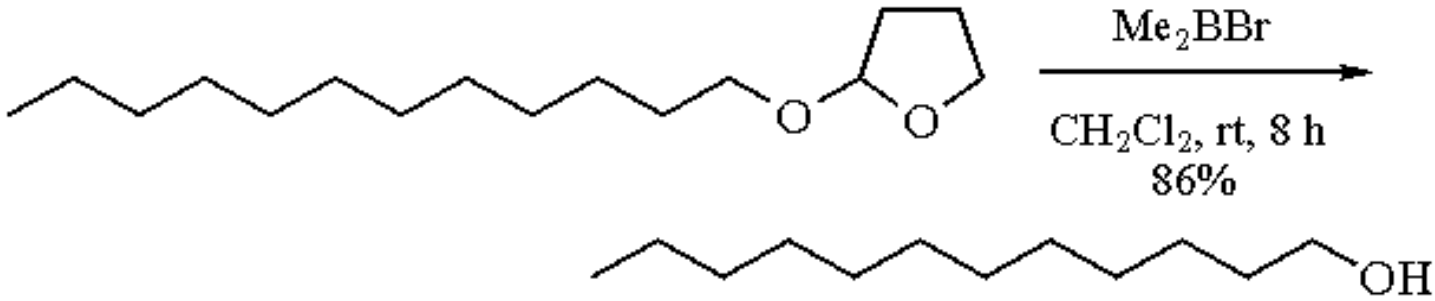

(9)

Bromodiphenylborane (Ph_2BBr) and ***9-Bromo-9-borabicyclo[3.3.1]nonane*** (Br-9-BBN) can often be used in place of Me_2BBr for the cleavage of acetals;[4,5] however, the purification of products from reactions employing Me_2BBr is facilitated by the volatility of Me_2B-containing byproducts, thus making Me_2BBr the reagent of choice in most instances.

Interconversion of Functional Groups.

The reaction of Me_2BBr with MEM and MOM ethers is believed to proceed via α-bromo ether intermediates. It is possible to trap these intermediates with nucleophiles such as thiols, alcohols, and cyanide. An example of the utility of this sequence is the conversion of a readily prepared MOM ether into an MTM ether (eq 10).[12]

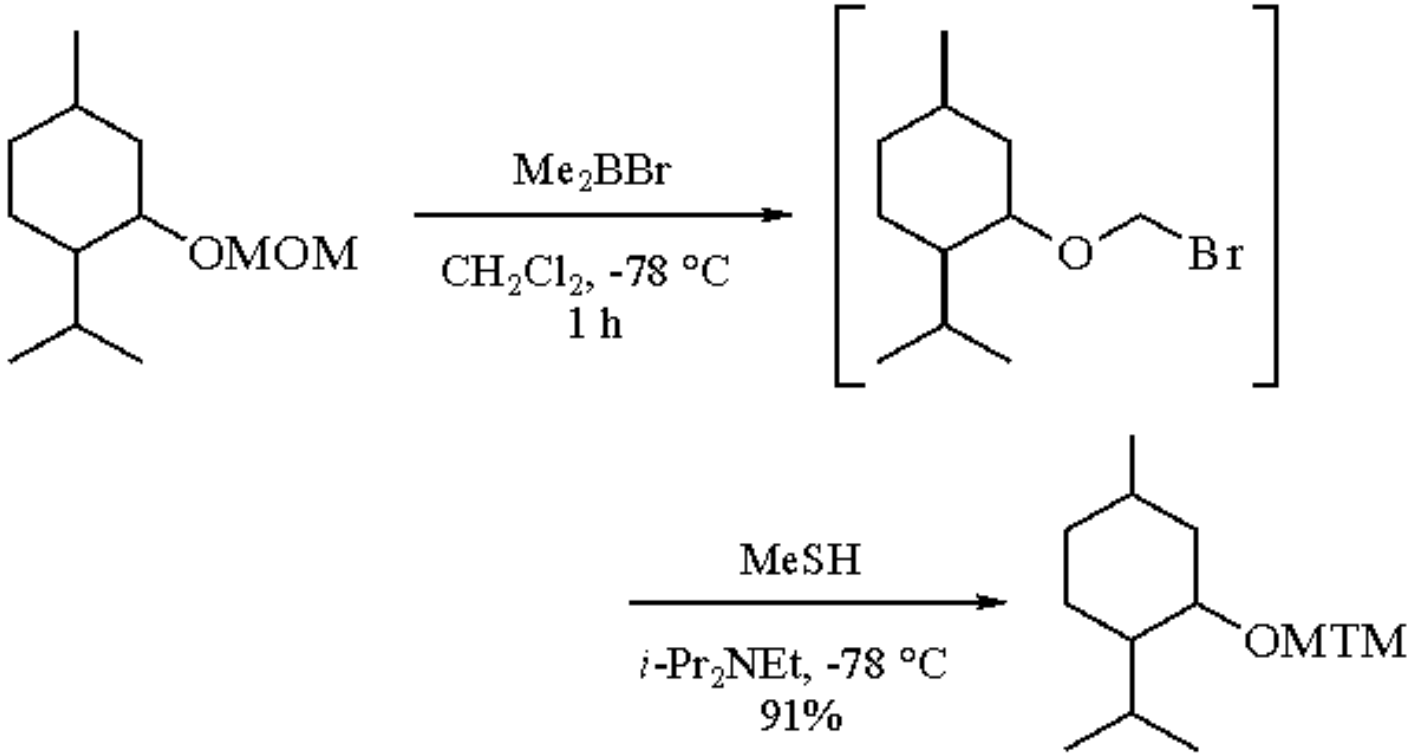

(10)

While THP and THF ethers are converted to the corresponding alcohols by Me_2BBr at rt, the acetal is cleaved at -78 °C.[13] The initial products of the reaction are acyclic α-bromo ethers. These can be trapped with a variety of nucleophiles to generate stable ring-opened products (eq 11).[13] This reaction has been extended to glycosides which, although less reactive, behave in a similar fashion.[14,15]

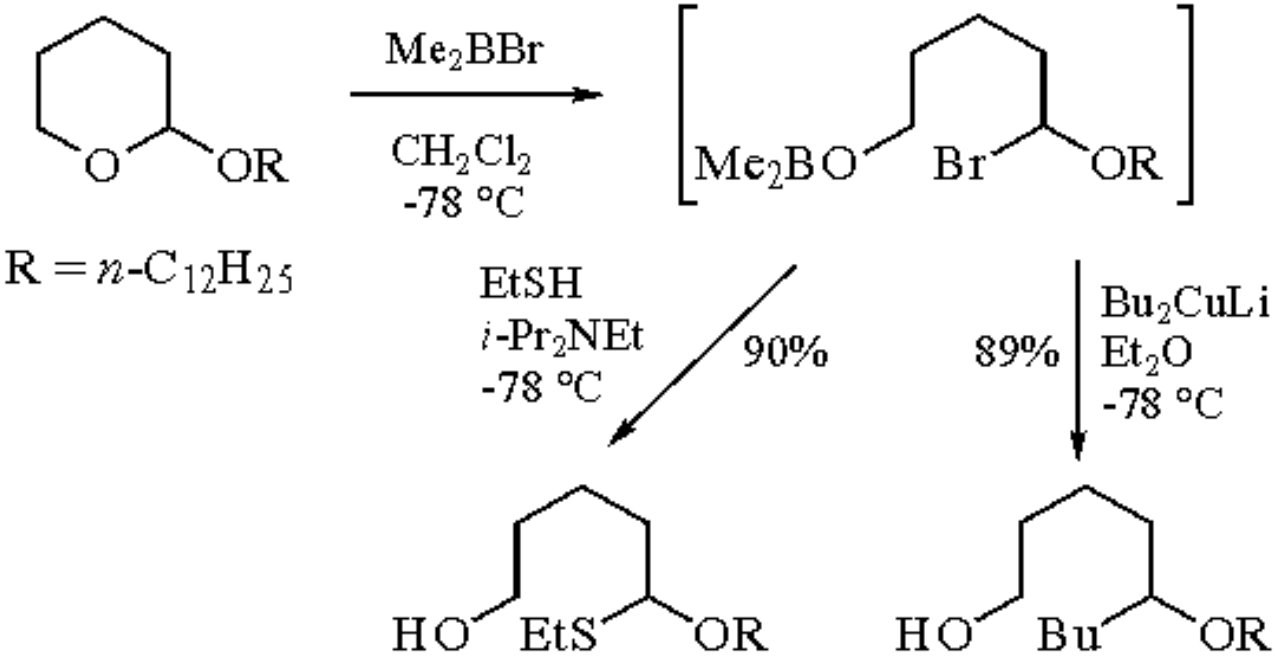

Benzylidene acetals are recovered unchanged when treated with Me_2BBr under conditions which are used to cleave other acetals.[16] It is, however, possible to cleave benzylidene acetals to generate hydroxy-*O*,*S*-acetals in excellent yield, by treatment with Me_2BBr at -78 °C followed by ***Thiophenol*** (eq 12).[16] Sterically encumbered bromoboranes optimize regioselective complexation of boron to the least hindered oxygen atom and are, therefore, the reagents of choice for this process (eq 12).[16] These experiments demonstrate that benzylidene acetals do indeed react with Me_2BBr at -78 °C, like other acetals.

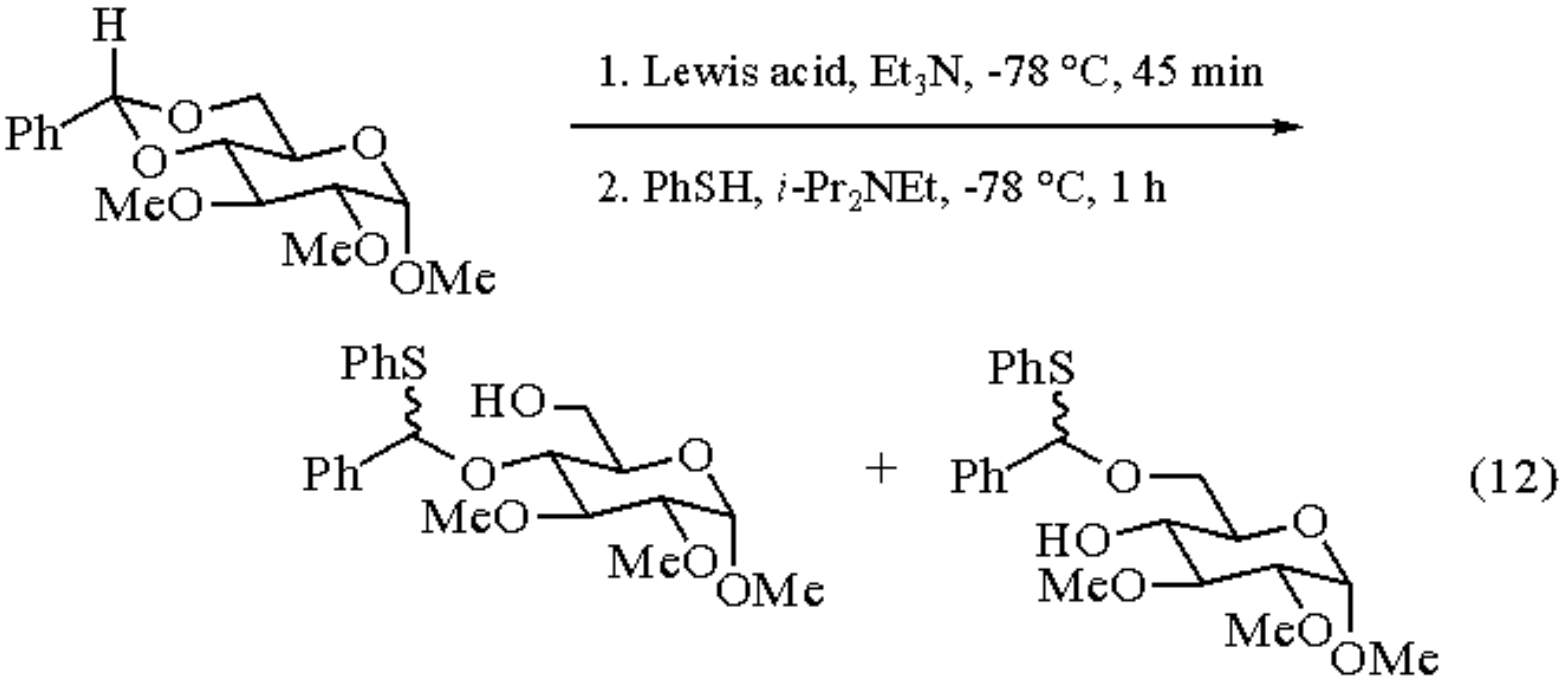

Me_2BBr	68%	17%
Ph_2BBr	96%	-
9-BrBBN	90%	-

Treatment of glycoside benzylidene acetals with a variety of disubstituted bromoboranes, followed by ***Borane-Tetrahydrofuran***, generates 4-*O*-benzyl-6-hydroxypyranosides in excellent yield (eq 13).[16]

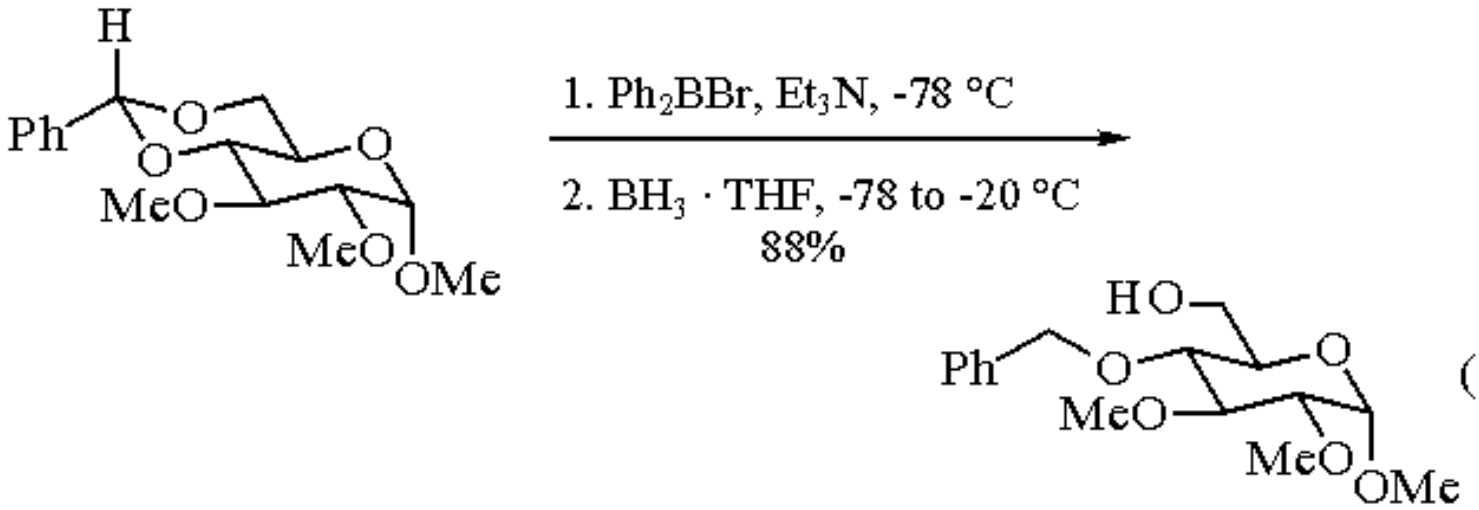

(13)

Acetals derived from ***Dimethyl L-Tartrate*** react with Me_2BBr to generate α-bromo ethers which react further with cuprate reagents to give optically active secondary alcohol derivatives (eq 14).[17] The alcohols may be liberated by treatment with ***Samarium(II) Iodide*** or by a straightforward sequence of reactions (mesylation and elimination to form an enol ether followed by exposure to methoxide in refluxing methanol). Selectivity is enhanced by the use of Ph_2BBr and by careful control of the reaction temperature at each step.

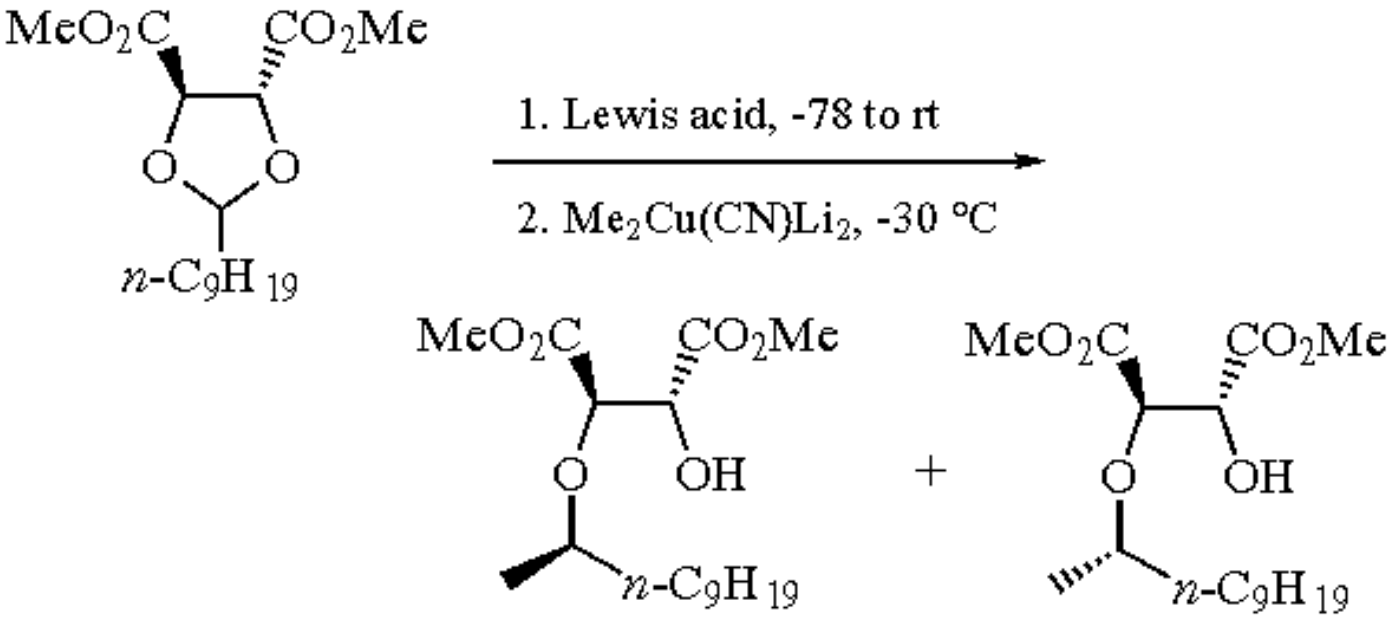

(14)

Me_2BBr, 80%	34:1
Ph_2BBr, 62%	82:1

Miscellaneous Reactions.

Bromodimethylborane can also be used to convert dialkyl, aryl alkyl, and diaryl sulfoxides to the corresponding

sulfides (eq 15).[6] Typically, the sulfoxides are treated with 2.5 equiv of Me_2BBr in dichloromethane at -23 °C for 30 min and at 0 °C for 10 min. Bromine is produced in the reaction and must be removed in order to avoid possible side reactions. This is accomplished by saturating the solution with propene prior to introducing the reagent or by adding cyclohexene. Phosphine oxides and sulfones failed to react under the conditions used to deoxygenate sulfoxides.

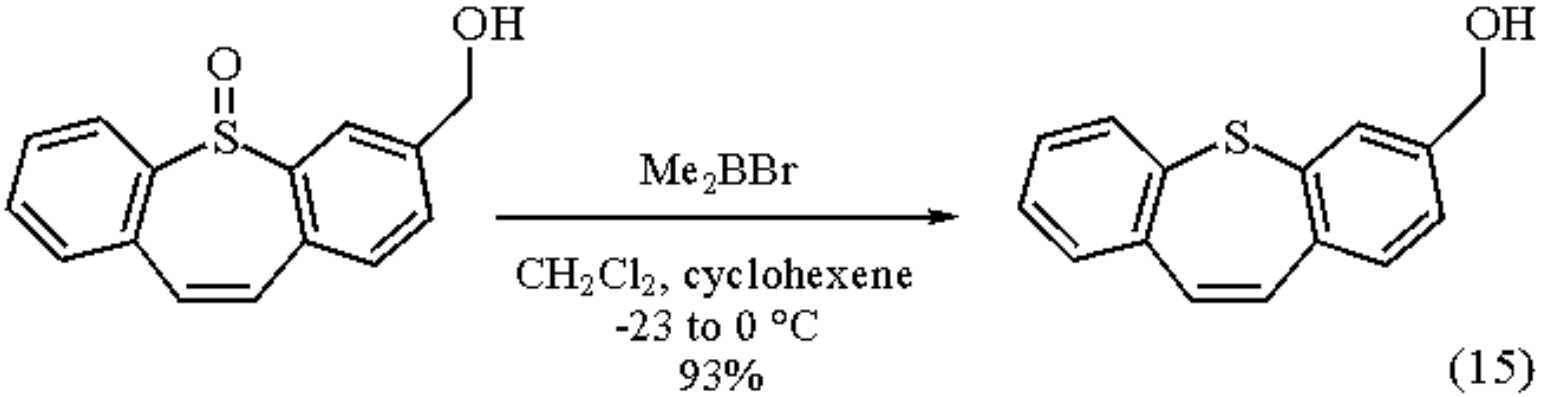

(15)

Bromodimethylborane has also been used as a catalyst for the Pictet-Spengler reaction (eq 16)[18] and to catalyze the 1,3-transposition of an allylic lactone.[19]

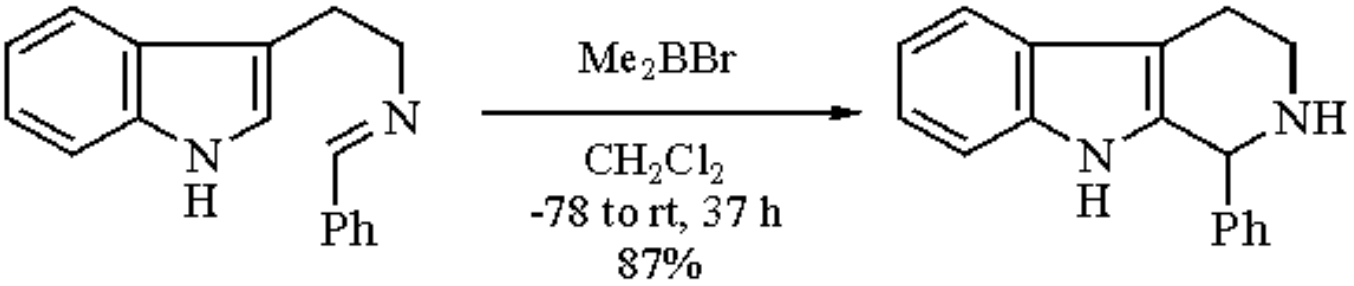

(16)

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3-Bromo-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one[1]

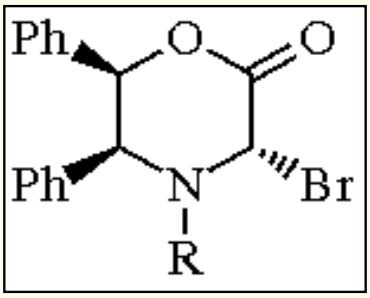

(R = *t*-Boc) (3*S*,5*S*,6*R*)

[112741-51-2] · $C_{21}H_{22}BrNO_4$ · 3-Bromo-4-*t*-butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one · (MW 432.31) (R = *t*-Boc) (3*R*,5*R*,6*S*)

[127420-01-3] (R = Cbz) (3*S*,5*S*,6*R*)

[111934-06-6] · $C_{24}H_{20}BrNO_4$ · 4-Benzyloxycarbonyl-3-bromo-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one · (MW 466.33) (R = Cbz) (3*R*,5*R*,6*S*)

[117527-28-3]

(electrophilic glycine equivalent useful for the preparation of α-substituted-α-amino acids in high enantiomeric excess[2])

Alternate Name: 3-bromo-5,6-diphenylmorpholin-2-one.

Physical Data: white solid, decomposes upon heating.

Solubility: sol THF, CH_2Cl_2.

Preparative Methods: *N*-*t*-Boc- and *N*-Cbz-3-bromo-5,6-diphenyl-2,3,5,6-tetrahydrooxazin-2-ones are not commercially available. They are prepared by addition of 1 equiv of ***N-Bromosuccinimide*** to a solution of the parent oxazinone (commercially available[3] as the individual enantiomers or as racemates) in CCl_4 at reflux. Upon cooling of the reaction mixture to 0 °C and filtering off the succinimide, the CCl_4 is removed under reduced pressure and the bromooxazinone is obtained in essentially quantitative yield as a white solid and is used without further purification.[2]

Handling, Storage, and Precautions: generally prepared immediately prior to use. Chromatography on silica gel results in decomposition.

General Reactivity.

The *N*-protected 3-bromo-5,6-diphenyl-2,3,5,6-tetrahydrooxazin-2-ones serve as chiral electrophilic glycine equivalents. They are prepared as discussed above to yield the *anti*-diastereomer exclusively (eq 1).[2] The bromide is subject to displacement by a variety of reagents under a range of conditions to afford the substituted oxazinone generally with the newly introduced substituent oriented *anti* to the C(5) and C(6) phenyl groups. Deprotection of the heterocyclic amino acid precursor is accomplished by scission of the benzylic carbon-heteroatom bonds via reductive or oxidative cleavage. The deprotection routes afford the amino acid zwitterion or *N*-*t*-Boc amino acid directly but also result in destruction of the chiral auxiliary. Hydrogenolysis of the bromooxazinone with deuterium[4c] or tritium[4a,b] using ***Palladium(II) Chloride*** as catalyst occurs with net retention of configuration to afford the chiral isotopically labeled glycine (eq 2). Ease of preparation and introduction of the isotope in the final step make this a valuable synthesis of chiral glycines.

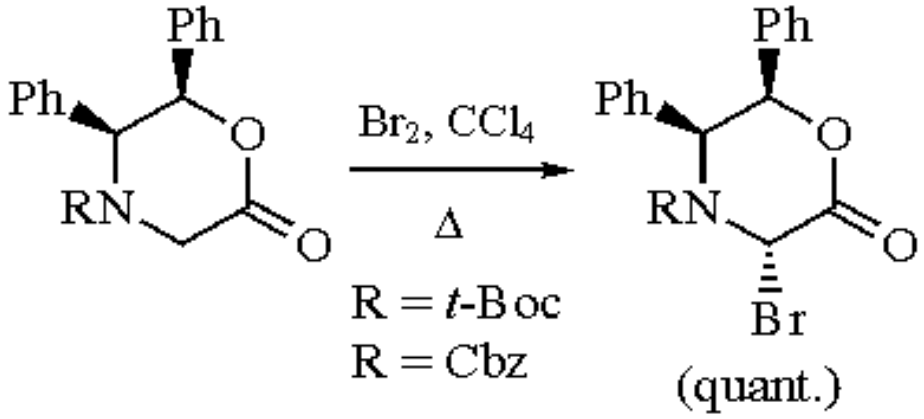

(1)

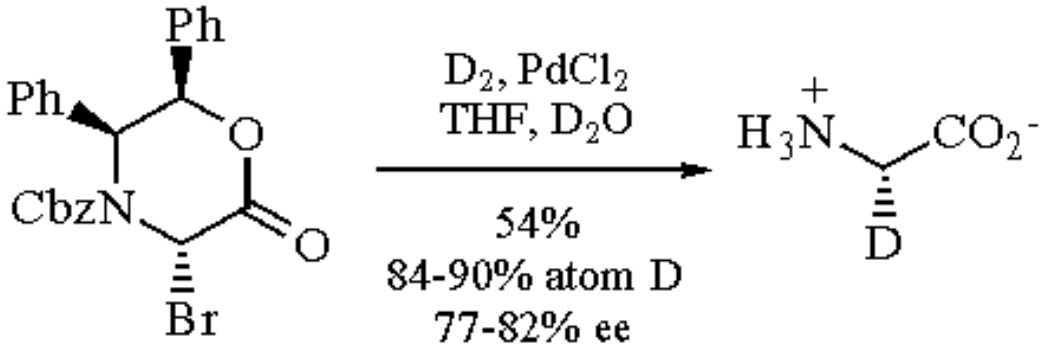

(2)

Coupling with Allylsilanes.

Allyltrimethylsilanes react with the bromooxazinone in the presence of ***Zinc Chloride*** in THF to afford the allylated heterocycles with high selectivity (eq 3).[2] The coupling is presumed to take place by an S_N1 mechanism in which the Lewis acid promotes expulsion of bromide resulting in iminium ion formation. The heterocyclic iminium ion then undergoes attack by the nucleophile on the least hindered face, giving the *anti* diastereomer. Hydrogenolysis of the Cbz protected oxazinone (20-50 psi) affords the amino acid zwitterion in good yield and high chemical purity (eq 4).

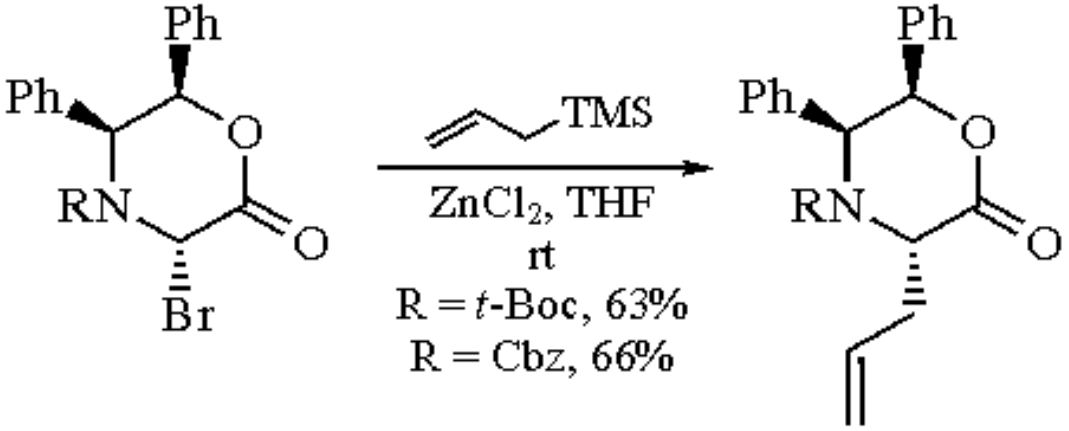

(3)

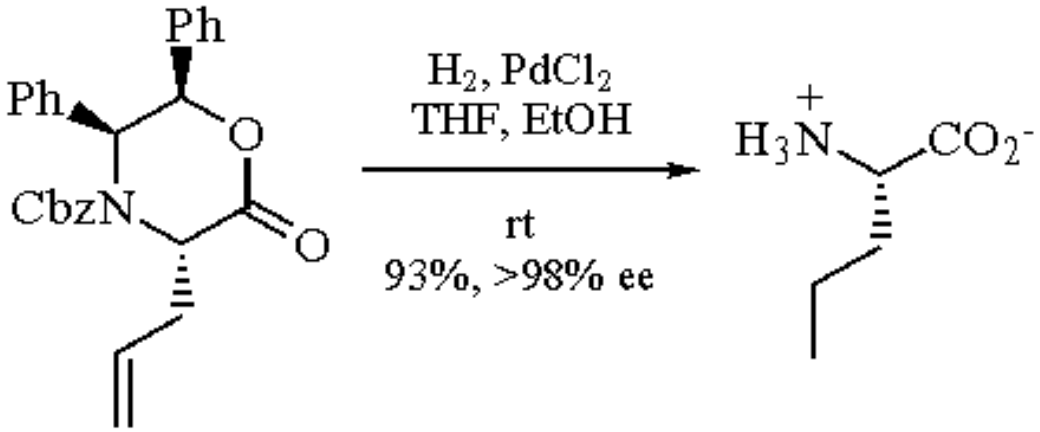

(4)

The amino acids can also be liberated by dissolving metal reduction.[2] Treatment of the oxazinone with ***Lithium*** or ***Sodium*** metal in liquid ammonia at -33 °C effects deprotection (eq 5). Ion exchange chromatography yields the zwitterionic amino acid free of inorganic salts. This procedure has the advantage of permitting the synthesis of amino acids possessing unsaturated side chains. When the dissolving metal reduction is carried out on the *t*-Boc protected oxazinone, the *N*-*t*-Boc amino acid is obtained directly (eq 6).

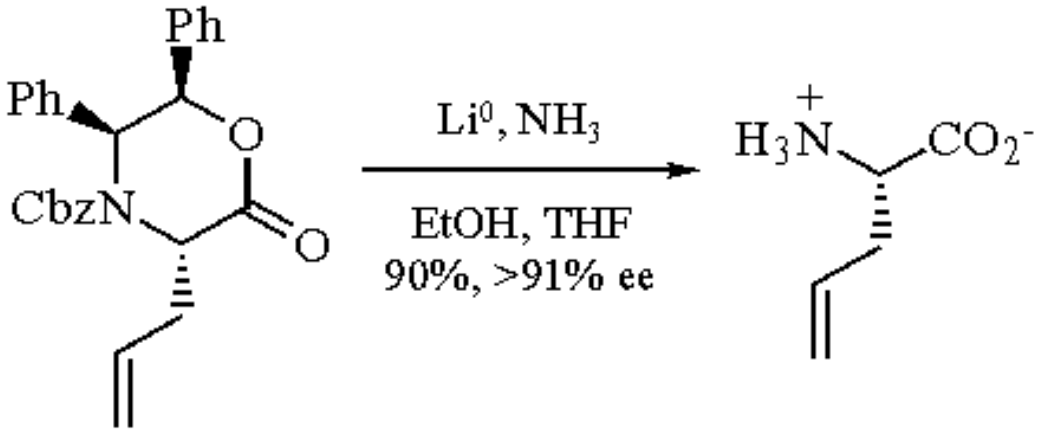

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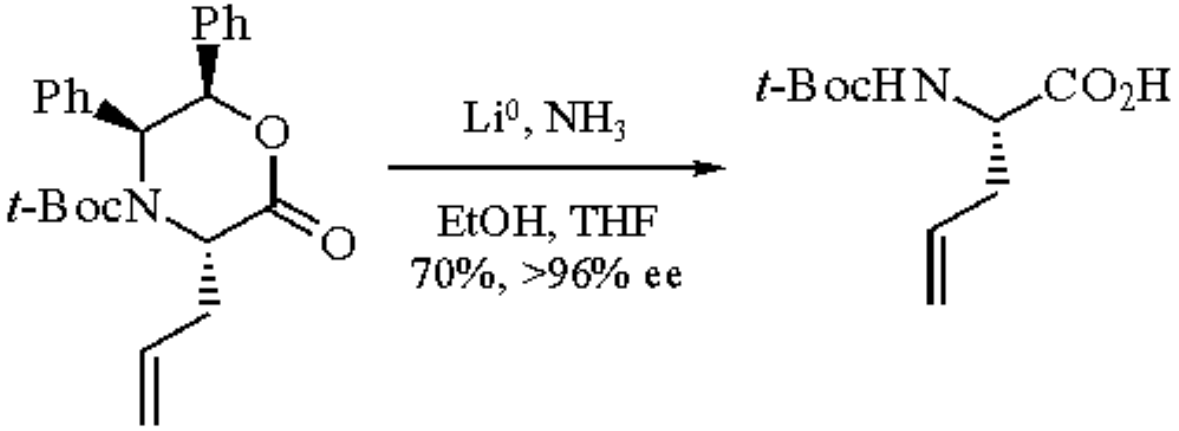

(6)

Coupling with Tin Acetylides.

Trialkyltin acetylides react with the bromooxazinone in the presence of $ZnCl_2$ to furnish the alkyne-substituted heterocycle (eq 7).[5] Hydrogenation of the Cbz-protected acetylide adducts yields the aliphatic amino acids in good yield and high enantiomeric excess (eq 8).[5b] Dissolving metal reduction affords the (*E*)-vinylglycines, though some racemization is observed. The use of sodium metal in the deprotection results in higher chemical yields (71-80%) and lower enantiomeric excess (56-68%) while the use of lithium metal gives better enantiomeric excess (65-98%) but much lower chemical yields (16-20%) (eq 9).[5a]

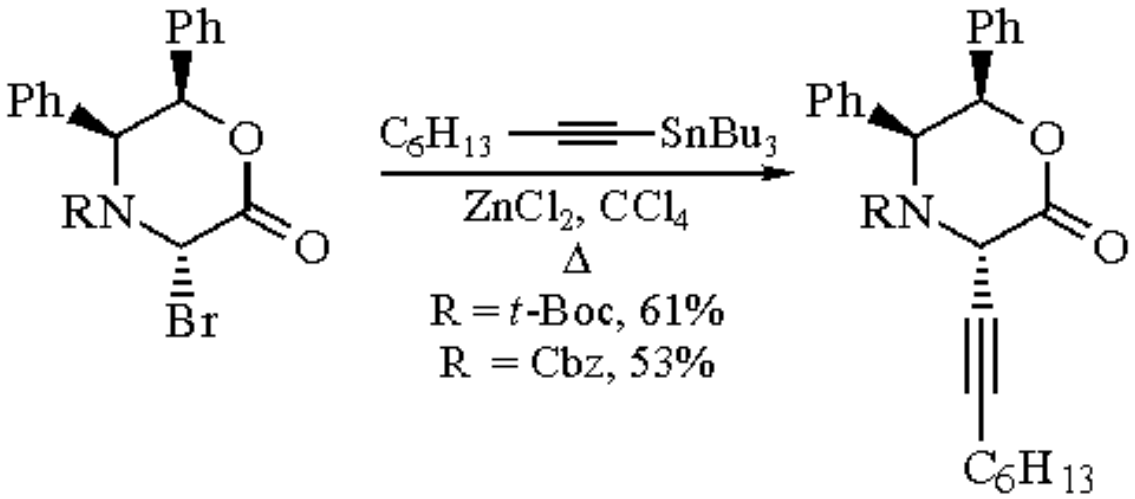

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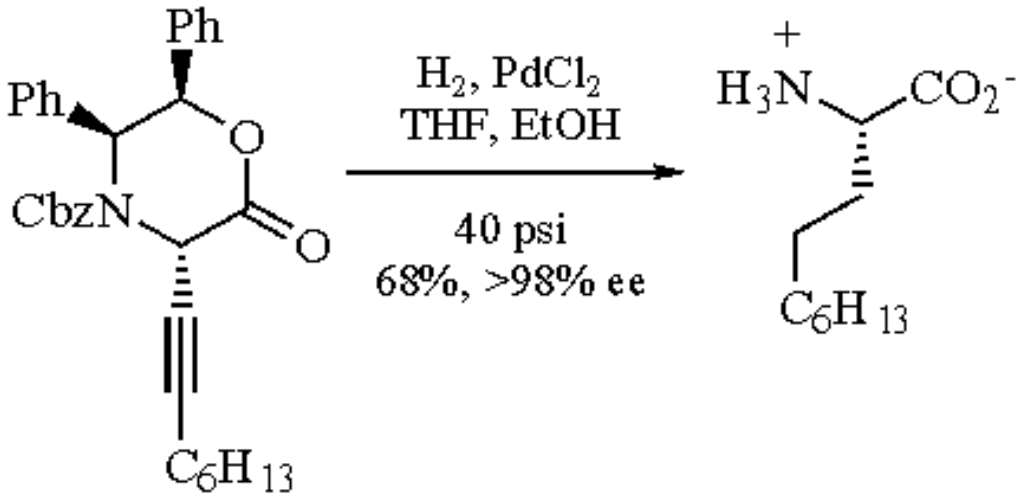

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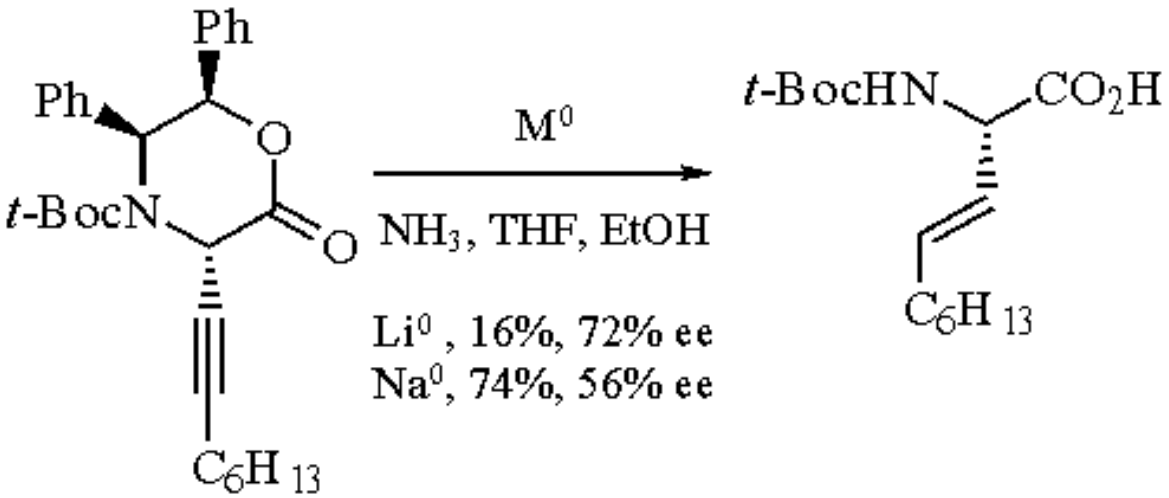

(9)

Coupling with Electron-Rich Arenes.

Electron-rich aromatics such as trimethoxybenzene, furan, and 2-methylfuran also couple the bromooxazinone in the presence of $ZnCl_2$ to afford the 3-aryloxazinones stereoselectively (eq 10).[2a,6] This process introduces a third benzylic carbon-heteroatom bond into the molecule and thereby precludes the reductive deprotections described. An alternative oxidative deprotection was developed.[6] Removal of the *t*-Boc protecting group followed by acid catalyzed opening of the heterocycle and subsequent oxidative cleavage with ***Sodium Periodate*** affords the arylglycines in moderate yield (eq 11).

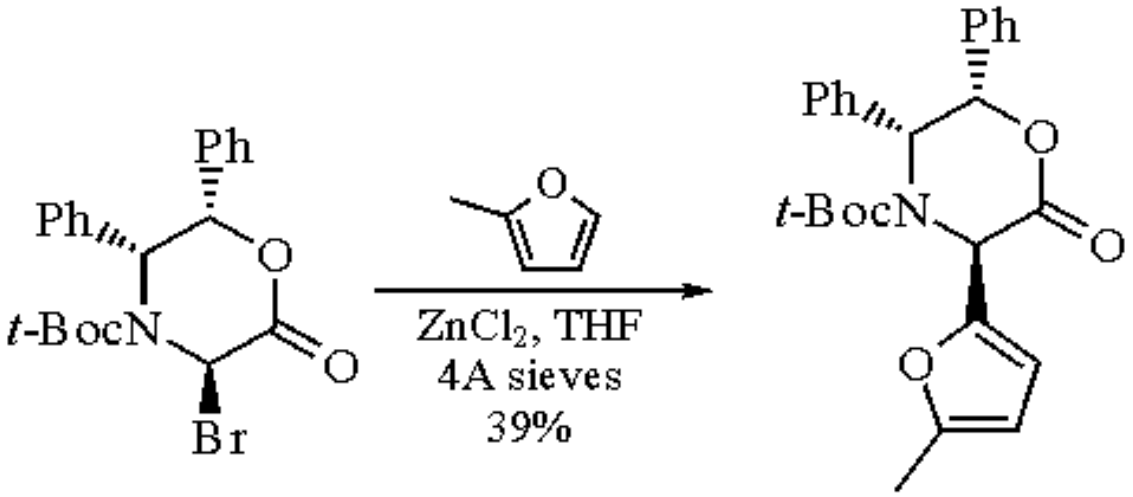

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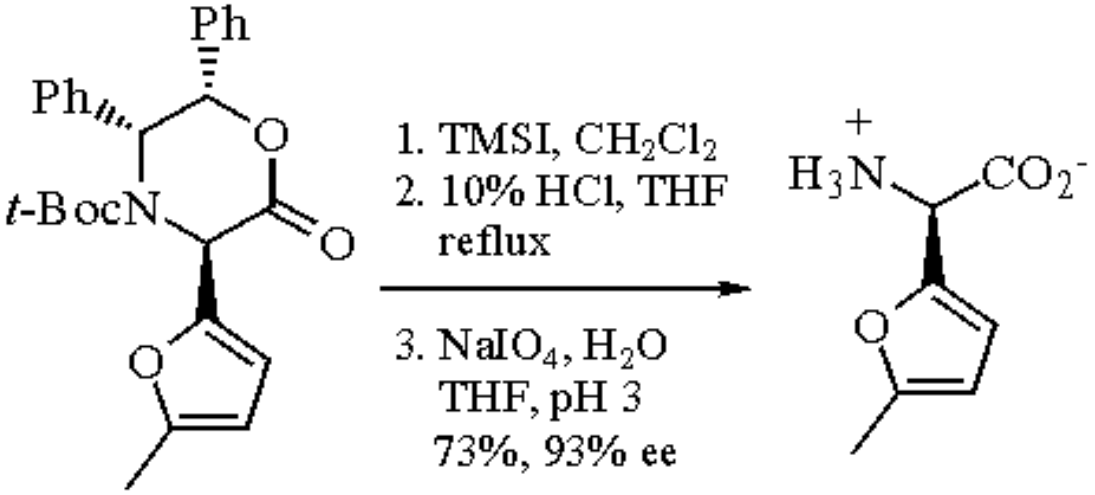

(11)

Coupling with Silyl Enol Ethers and Silyl Ketene Acetals.

Silyl enol ethers can couple to the bromooxazinone to give both the *syn* and *anti* diastereomers.[2,7] The reaction can proceed via the S_N1 mechanism discussed above or by a Lewis acid assisted S_N2 displacement of the bromide. The reaction conditions can be manipulated to favor the S_N1 (stronger Lewis acids, more polar solvents) or S_N2 path (weaker Lewis acids, less polar solvents) (eqs 12 and 13).[2a]

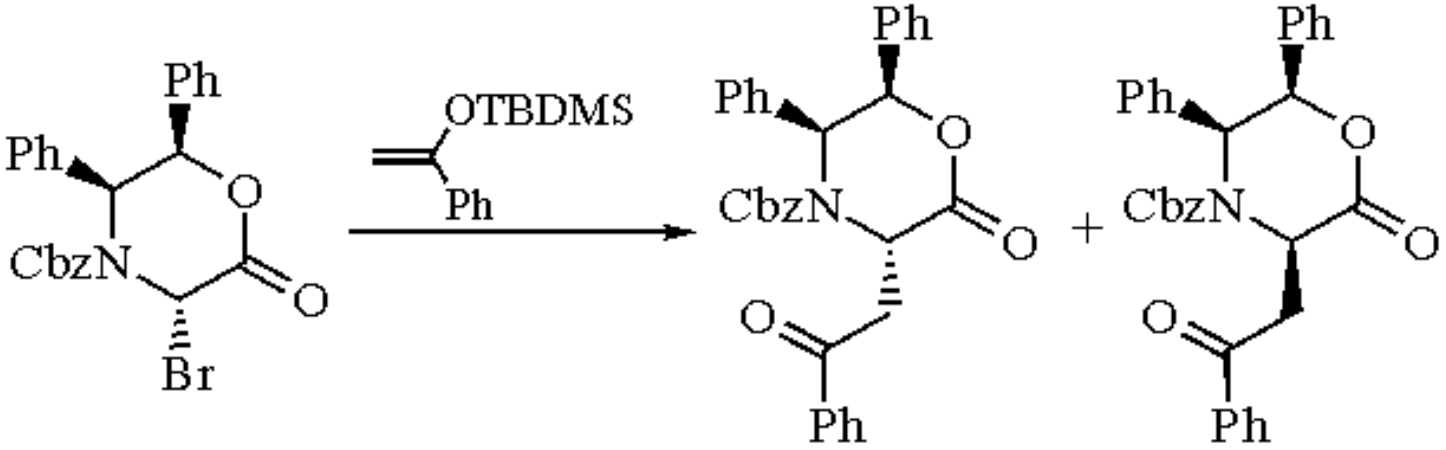

(12)

AgOTf, THF	24.5	1
$ZnCl_2$, MeCN	14.5	1
$ZnCl_2$, THF	7	1
$ZnCl_2$, CH_2Cl_2	1	34

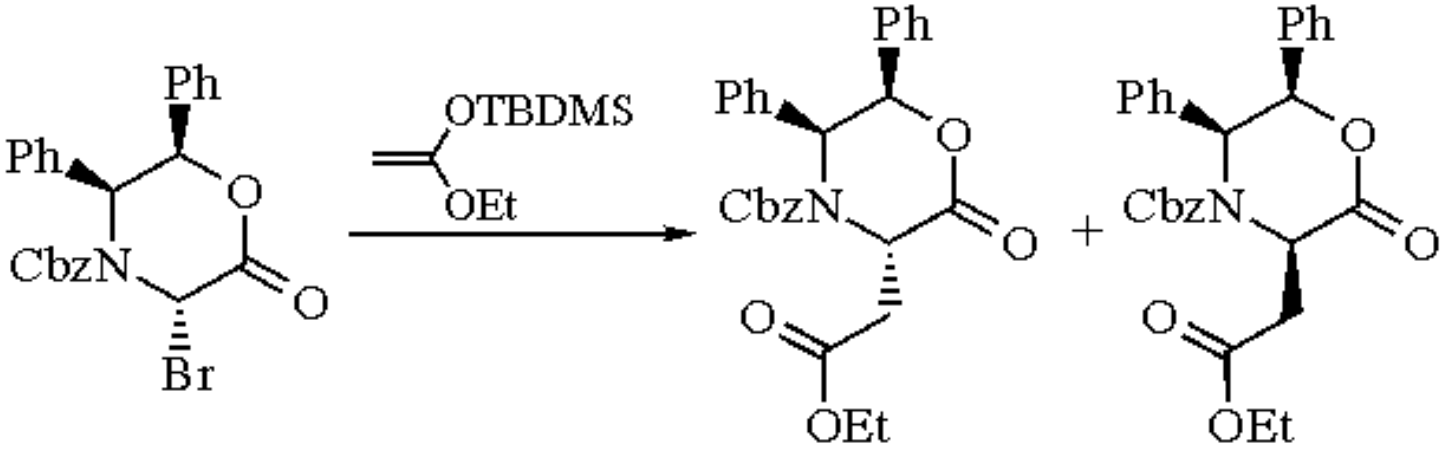

(13)

AgOTf, THF	1	2
$ZnCl_2$, THF	1	14-45
$ZnCl_2$, CH_2Cl_2	1	45

Coupling with Organozincs and Organocuprates.

Alkylzinc chlorides and alkyl- and arylcuprates couple with the bromooxazinones with a high degree of diastereoselection but in lower yields.[2,6] Reduction of the bromide to the parent oxazinone is a significant side reaction and is attributed to the reaction taking place via an electron-transfer, radical-radical coupling.[2a] Substituted phenyl and naphthyl glycines have been prepared by coupling of the bromide with the corresponding organocuprate and employing the oxidative deprotection described above (eqs 14 and 15).[6]

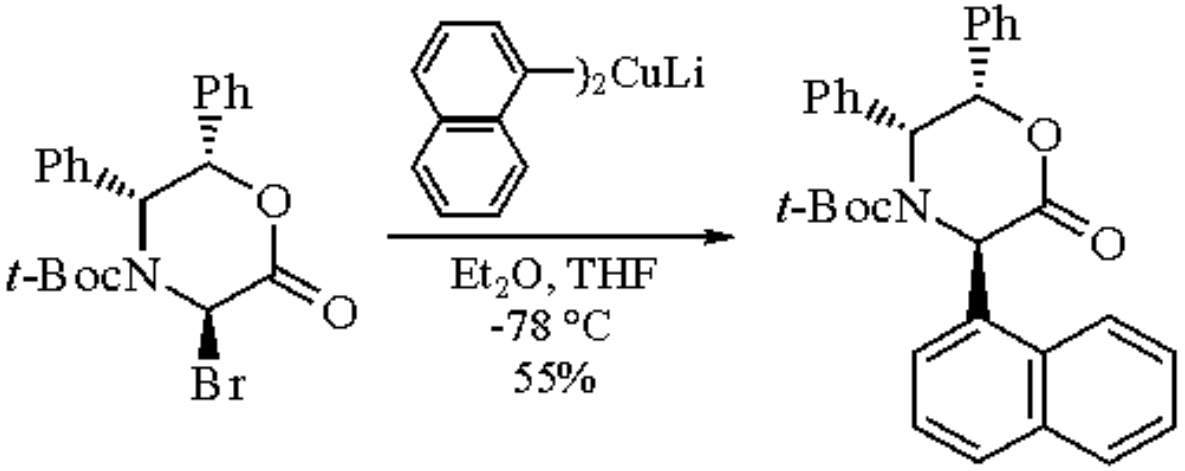

(14)

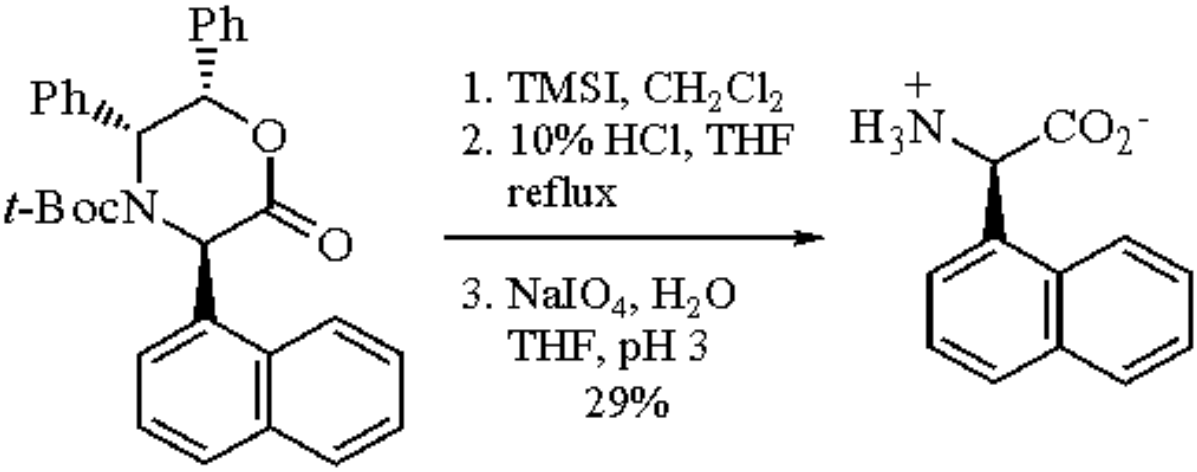

(15)

1-Aminocyclopropane-1-carboxylic Acids.

These amino acids are prepared by a multistep procedure involving treatment of the bromooxazinone with ***Trimethyl Phosphite*** to give the corresponding phosphonate at the 3-position. Ylide formation and condensation with an aldehyde produces the α,β-dehydrooxazinone adduct possessing the (*E*) configuration (eq 16). Cyclopropanation with either ***Diazomethane*** or ***Dimethylsulfoxonium Methylide*** occurs with little diastereoselectivity. In contrast, cyclopropanation with (diethylamino)phenylsulfoxonium methylide is highly selective (eq 17).[8] Unexpectedly, delivery of the methylene occurs on the face of the heterocycle *syn* to the phenyl rings. The reason for this selectivity has not yet been determined. Deprotection with Li^0/NH_3 yields the *N*-*t*-Boc-1-aminocyclopropane-1-carboxylic acids (eq 18).

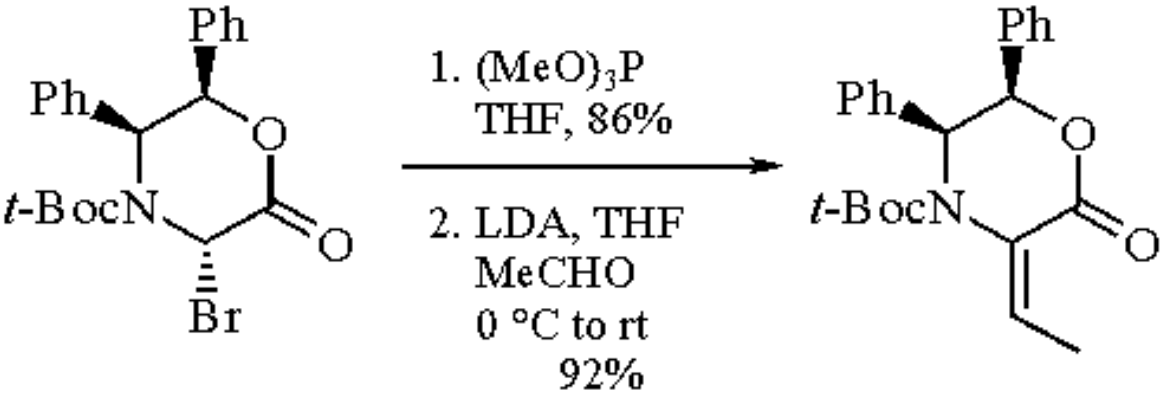

(16)

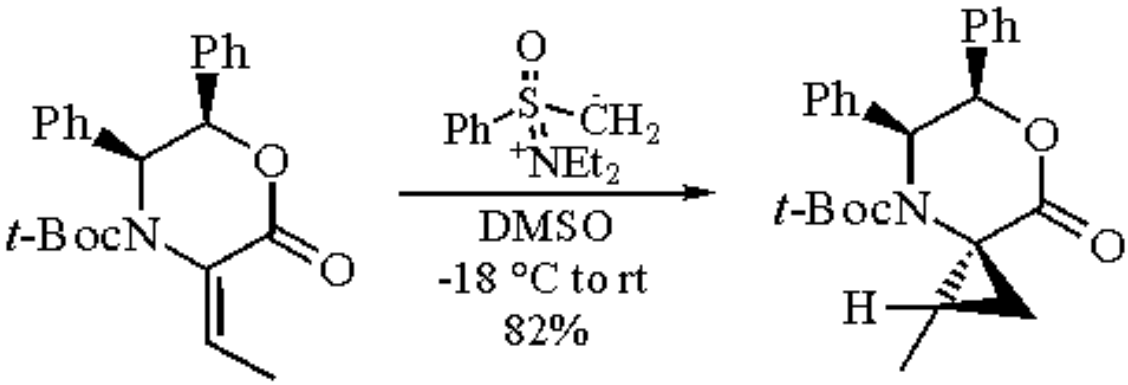

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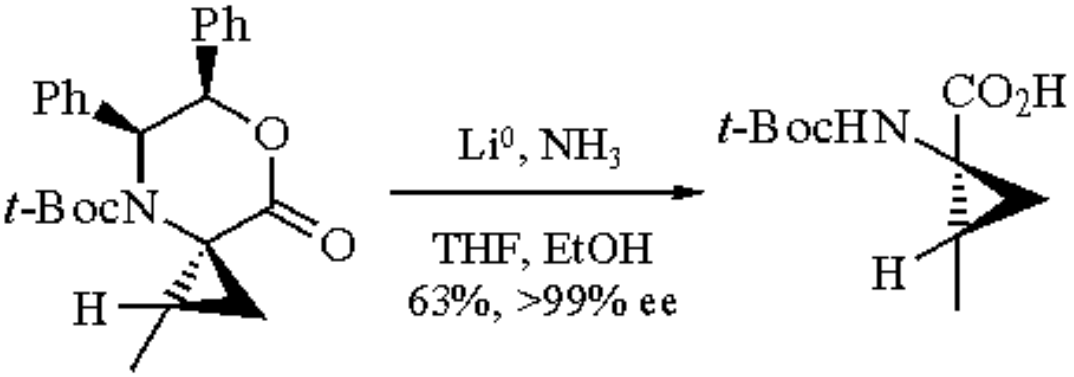

(18)

The α,β-dehydrooxazinone adducts can also undergo 1,3-dipolar cycloadditions as demonstrated in the synthesis of *S*-(-)-cucurbitine (eqs 19 and 20).[9]

For the complementary synthesis of α-substituted-α-amino acids via a chiral glycine enolate equivalent see ***4-t-Butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4H-oxazin-2-one***.

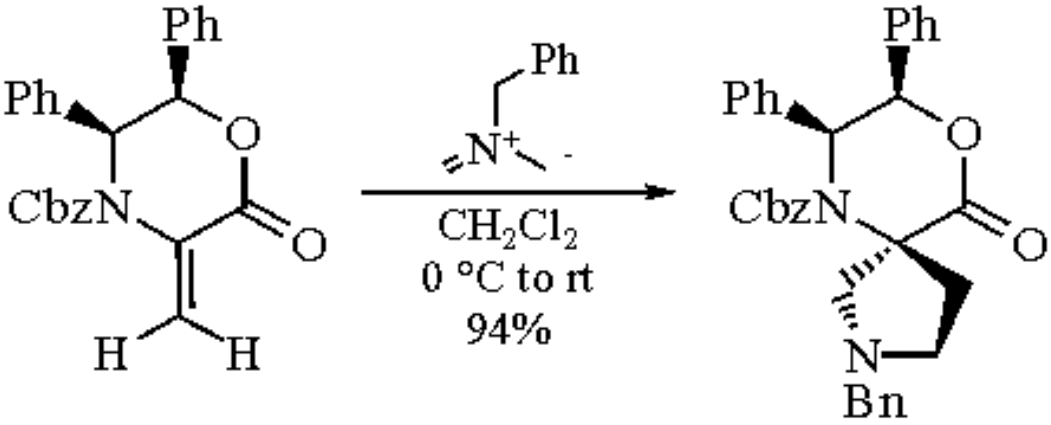

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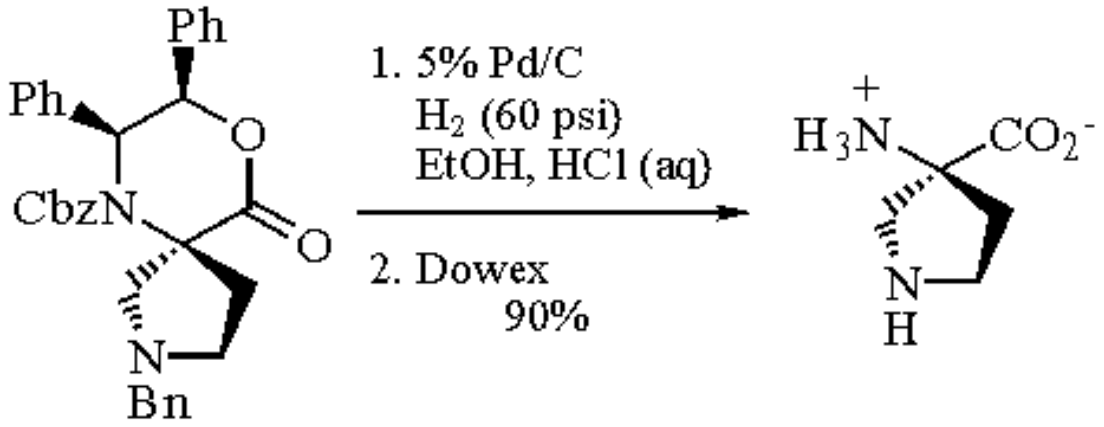

(20)

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1. (a) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (b) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: Oxford, 1989.
2. (a) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *JACS* **1988**, *110*, 1547. (b) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *JACS* **1986**, *108*, 1103.
3. Listed in the Aldrich Catalog as *t*-butyl 6-oxo-2,3-diphenyl-4-morpholinecarboxylate and benzyl 6-oxo-2,3-diphenyl-4-morpholinecarboxylate.
4. (a) Ramer, S. E.; Cheng, H.; Vederas, J. C. *PAC* **1989**, *61*, 489. (b) Ramer, S. E.; Cheng, H.; Palcic, M. M.; Vederas, J. C. *JACS* **1988**, *110*, 8526. (c) Williams, R. M.; Zhai, D.; Sinclair, P. J. *JOC* **1986**, *51*, 5021.
5. (a) Williams, R. M.; Zhai, W. *T* **1988**, *44*, 5425. (b) Zhai, D.; Zhai, W.; Williams, R. M. *JACS* **1988**, *110*, 2501.
6. (a) Williams, R. M.; Hendrix, J. A. *CRV* **1992**, *92*, 889. (b) Williams, R. M.; Hendrix, J. A. *JOC* **1990**, *55*, 3723.
7. Williams, R. M.; Sinclair, P. J.; Zhai, W. *JACS* **1988**, *110*, 482.
8. Williams, R. M.; Fegley, G. J. *JACS* **1991**, *113*, 8796.
9. Williams, R. M.; Fegley, G. J. *TL* **1992**, *33*, 6755.

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2-(2-Bromoethyl)-1,3-dioxane[1]

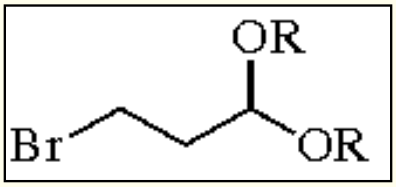

(**1**; R,R = $-(CH_2)_3-$)

[33884-43-4] · $C_6H_{11}BrO_2$ · 2-(2-Bromoethyl)-1,3-dioxane · (MW 195.06) (**2**; R,R = $-(CH_2)_2-$)

[18742-02-4] · $C_5H_9BrO_2$ · 2-(2-Bromoethyl)-1,3-dioxolane · (MW 181.03) (**3**; R,R = Me,Me)

[36255-44-4] · $C_5H_{11}BrO_2$ · 3-Bromopropionaldehyde Dimethyl Acetal · (MW 183.04)

(a group of bifunctional three-carbon reagents having the capacity to serve as electrophiles or as nucleophiles;[1] once the latent carbonyl is unmasked, annulation reactions of various types can be implemented; the application range of these reagents can be further enhanced by initial bromide displacement with nucleophiles possessing useful functionality)

Physical Data: (**1**) bp 67-70 °C/2.8 mmHg, *d* 1.431 g cm^{-3}; (**2**) bp 68-70 °C/8 mmHg, *d* 1.542 g cm^{-3}; (**3**) bp 58-60 °C/17 mmHg, *d* 1.341 g cm^{-3}.

Form Supplied in: all three acetals are colorless, commercially available liquids.

Preparative Methods: 3-bromopropionaldehyde acetals are prepared by bubbling anhydrous gaseous ***Hydrogen Bromide*** into a dichloromethane solution containing ***Acrolein*** and the alcohol or diol at or below rt.[2] More recently, the discovery has been made that ***Chlorotrimethylsilane*** can promote the conjugate addition of NaX (X = Br, I, SCN) to α,β-unsaturated acetals.[3]

Handling, Storage, and Precautions: these bromides are recognized to possess irritant properties and should therefore invariably be handled with gloved hands inside an efficient hood. It is also advisable that these reagents be refrigerated for long-term storage in order to minimize the potential for acid liberation.

As Electrophile in Alkylation Reactions.

These three-carbon bifunctional reagents have proven to be very serviceable electrophiles in a variety of settings. Doubly activated anions such as those derived from β-diketones,[4] β-keto esters (eq 1),[5] malonate esters,[6] and phosphono esters[7] are readily homologated by this means. This level of activation is hardly necessary as demonstrated

by the fact that anions derived from esters,[8] nitriles (eqs 2 and 3),[9] imines,[10] and isocyanides[11] behave comparably. Generally, the carbonyl group is subsequently unmasked and utilized in further chemical transformations. Where (**2**) and (**3**) are concerned, aqueous acid suffices to accomplish the hydrolysis. Dioxanes derived from (**1**) are much less reactive and often require prior conversion to the dimethyl acetal.[12] Sulfur-containing nucleophiles including α-sulfonyl,[13] thioallyl,[14] and 1,3-dithianyl anions[15] are also readily alkylated. In addition to (**4**) (eq 4), it has proven possible to prepare polyprenols stereoselectively,[14] to produce substituted 1,5-dienes, and to synthesize estrone in a modest number of steps.[15b]

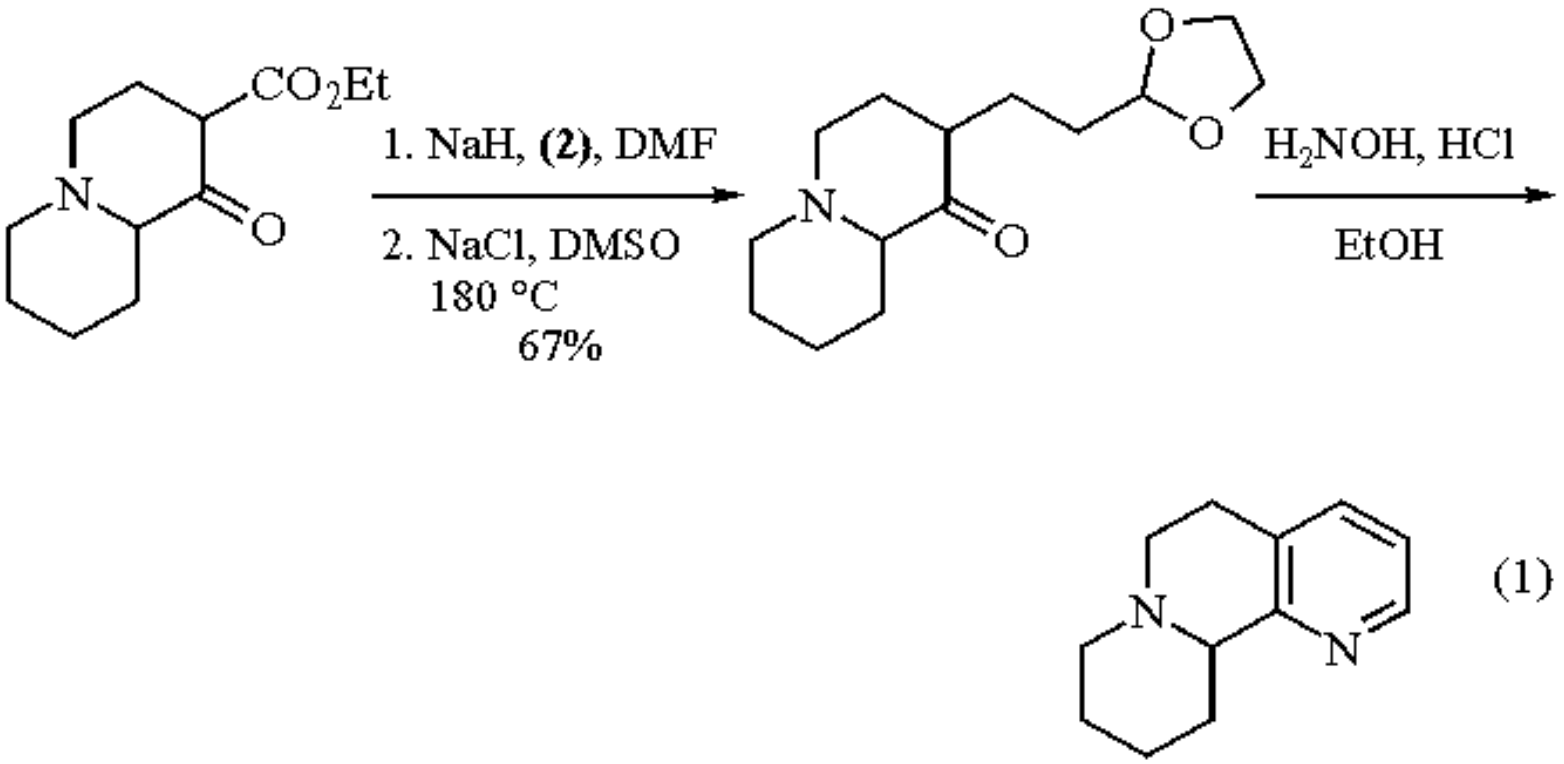

(1)

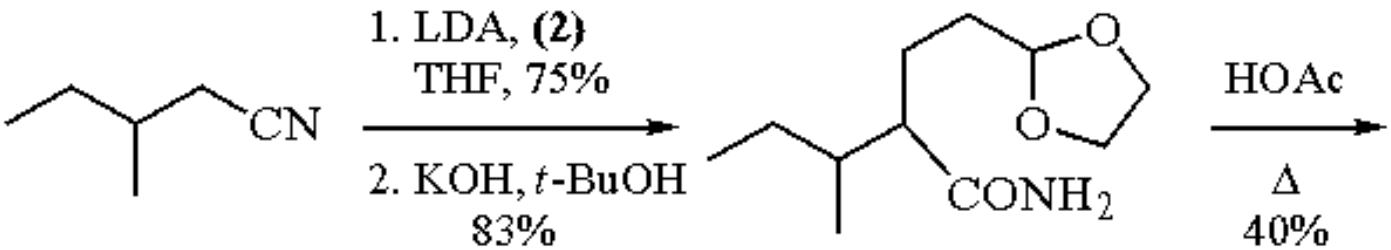

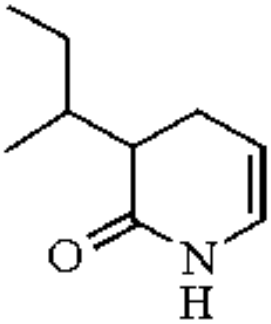

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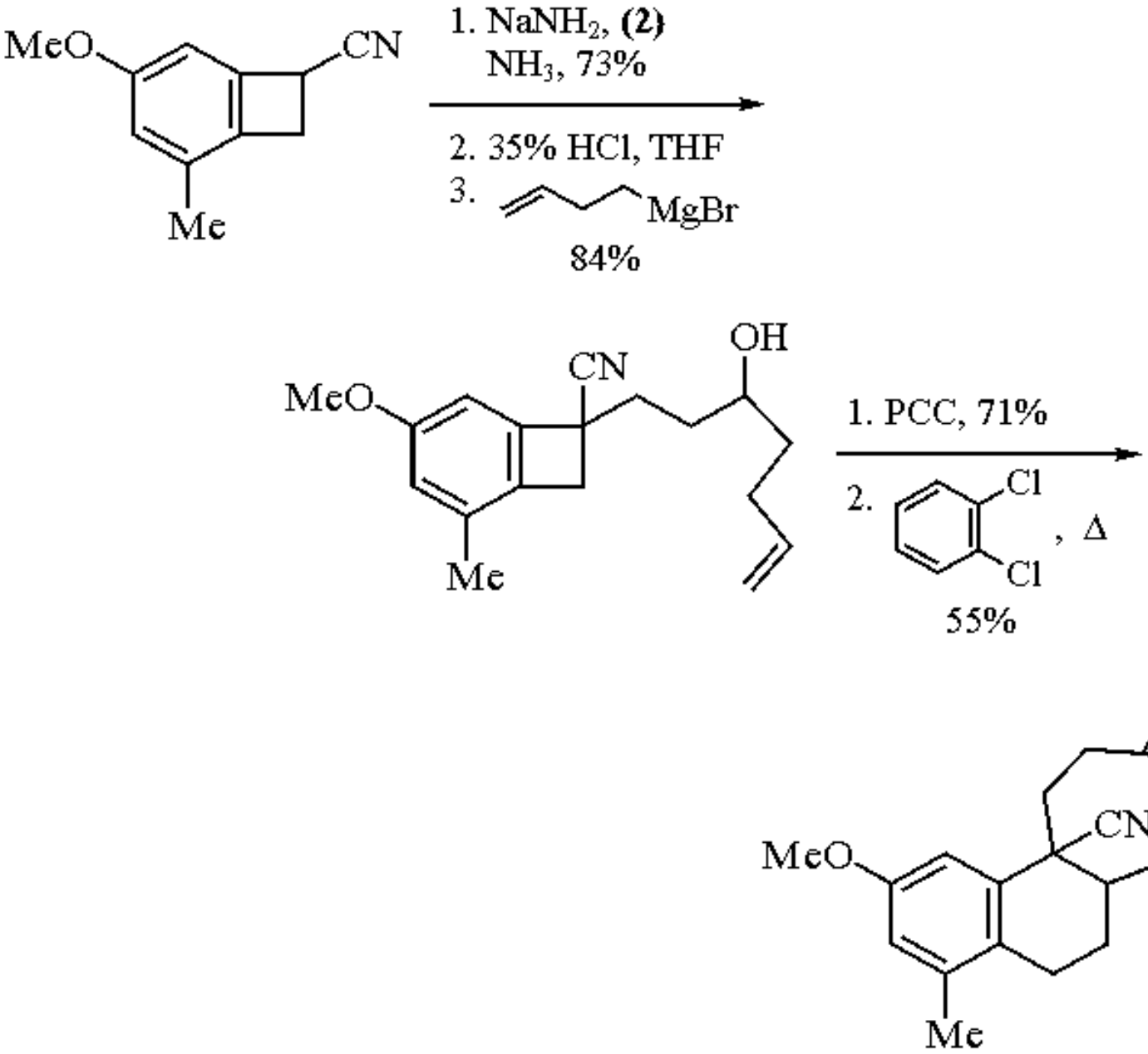
MeO
CN
Me
1. NaNH2, (2)
NH3, 73%
2. 35% HCl, THF
3.
MgBr
84%
OH
CN
MeO
Me
1. PCC, 71%
2.
Cl
Cl
, Δ
55%
O
CN
MeO
Me

(3)

2-(2-Bromoethyl)-1,3-dioxane

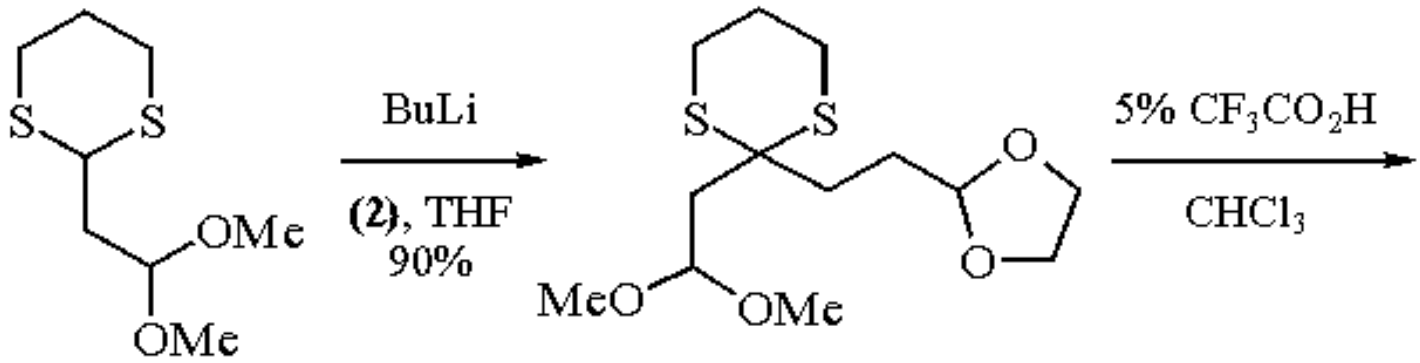

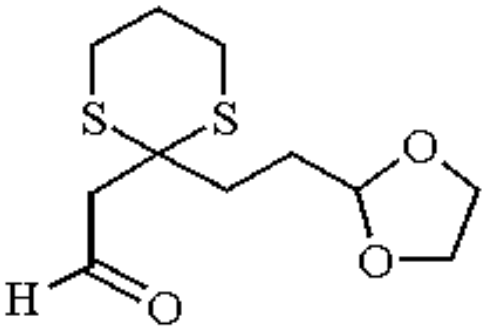

(4)

(4)

Birch reduction of benzoic acid followed by direct exposure to (**2**) produces (**5**).[16] Bromide displacement by sodium cyclopentadienide, in situ hydrolysis, condensation with $Ph_3P{=}CHCO_2Me$, and ultimately warming to 115 °C to effect intramolecular Diels-Alder cycloaddition delivers (**6**).[17] The means for fusing a pyran ring to an existing oxygenated ring to arrive at a polyether backbone such as (**7**) begins by condensation of (**2**) with a metalated vinyl ether (eq 5).[18]

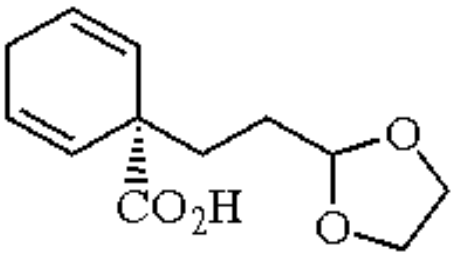

(5)
94%

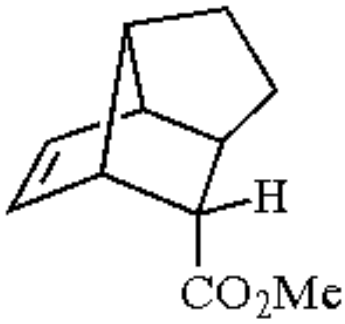

(6)
alkylation step, 79%

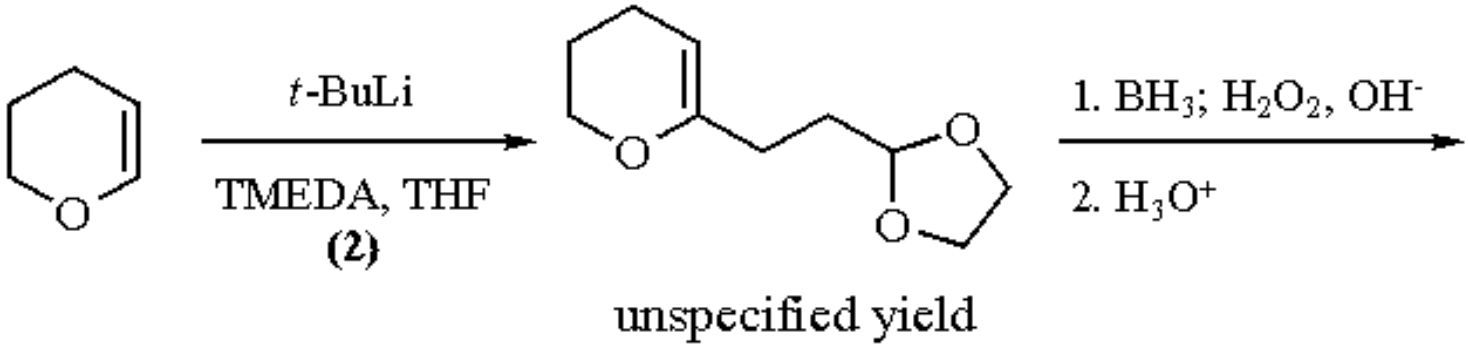

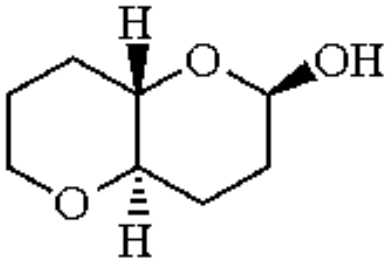

(7) (5)

Alkynyl anions have frequently been combined with (**1**)-(**3**).[19] For example, the directness with which (**8**) is constructed underscores the abbreviated route that produces both diastereomers of (**9**) (eq 6).[20] Similarly, the generation of enediyne (**10**) is central to the successful realization of an intramolecular [2 + 2 + 2] cycloaddition that gives rise to diene (**11**) (eq 7).[21] Allenyllithiums have proven equally effective (eq 8).[22]

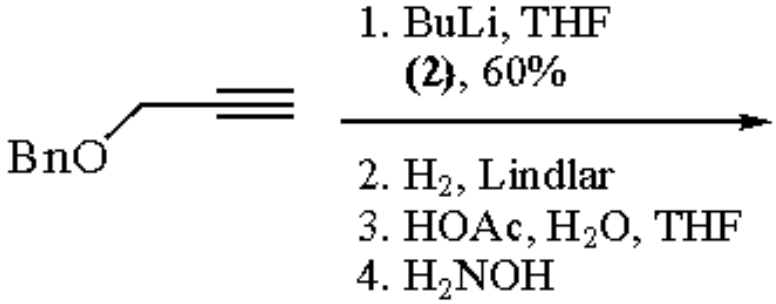
1. BuLi, THF
(2), 60%
BnO
2. H2, Lindlar
3. HOAc, H2O, THF
4. H2NOH

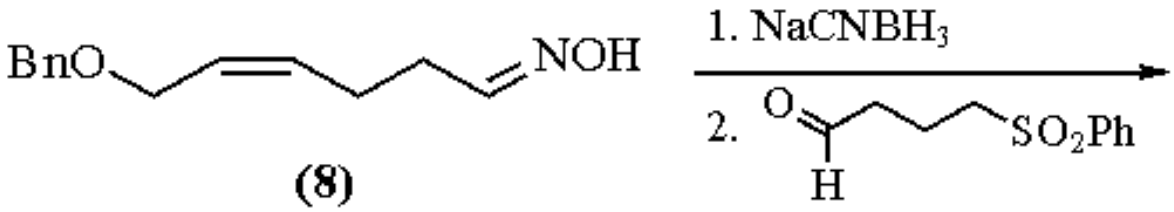
BnO
NOH
1. NaCNBH3
2.
O
H
SO2Ph

(8)

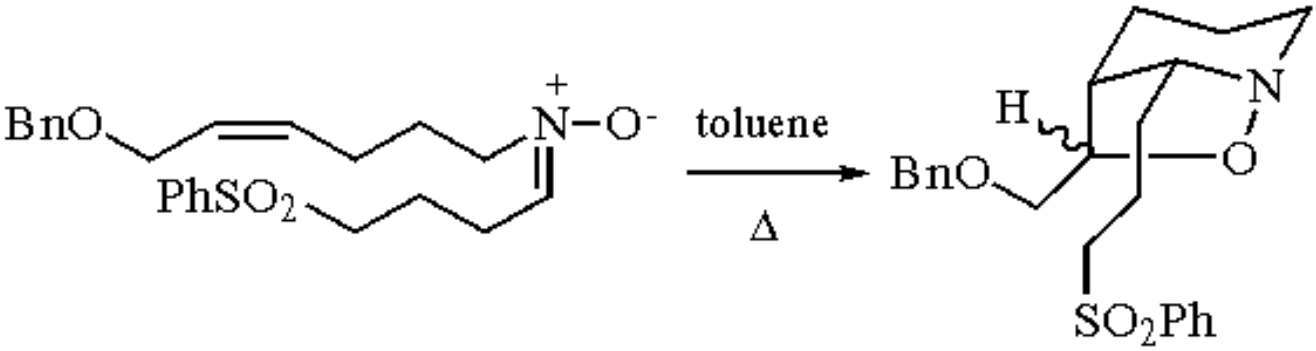
BnO
N
O
PhSO2
toluene
Δ
H
N
O
BnO
SO2Ph

(6)

(9)

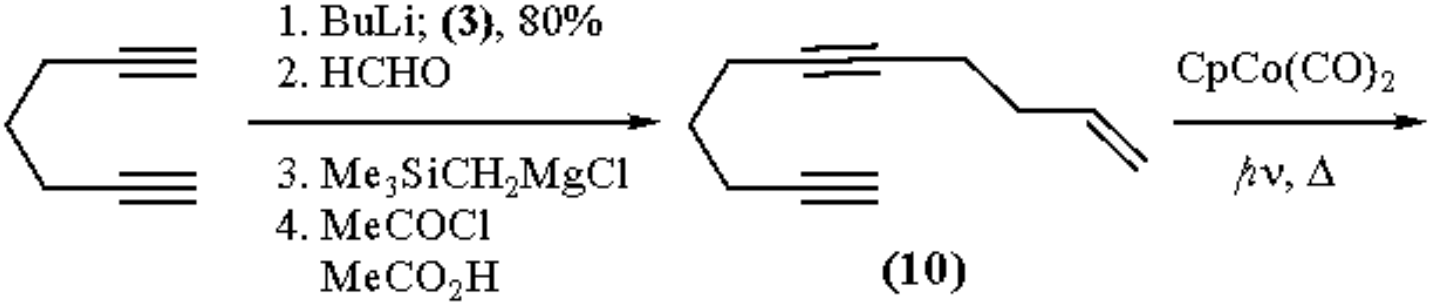
1. BuLi; (3), 80%
2. HCHO
3. Me3SiCH2MgCl
4. MeCOCl
MeCO2H
CpCo(CO)2
hν, Δ

(10)

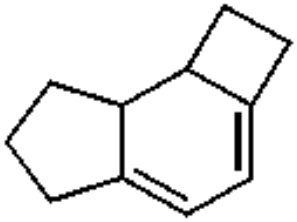

(7)

(11)

2-(2-Bromoethyl)-1,3-dioxane

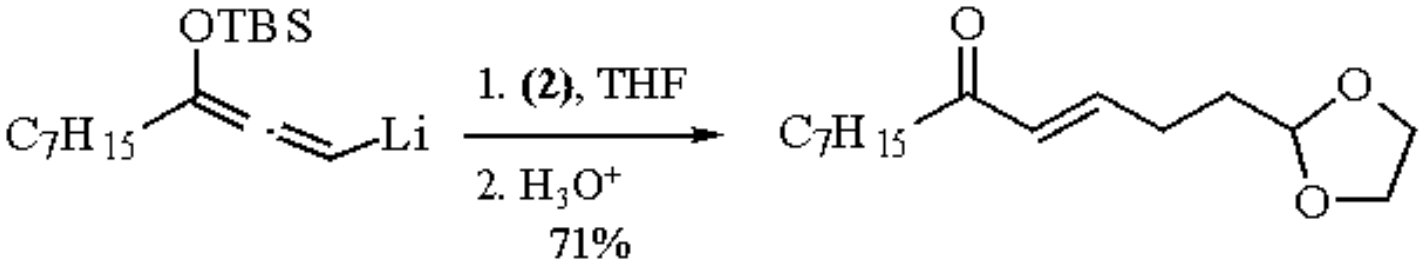

(8)

Since the lateral metalation of methyl-substituted aromatics can often be directly implemented, introduction of a functionalized sidechain is made possible by reaction of these anions with (**2**) and (**3**).[23] When dianions such as (**12**) and (**13**) are involved, chemoselectivity is manifested such that C-C bond formation is heavily favored kinetically (eqs 9 and 10).[24,25]

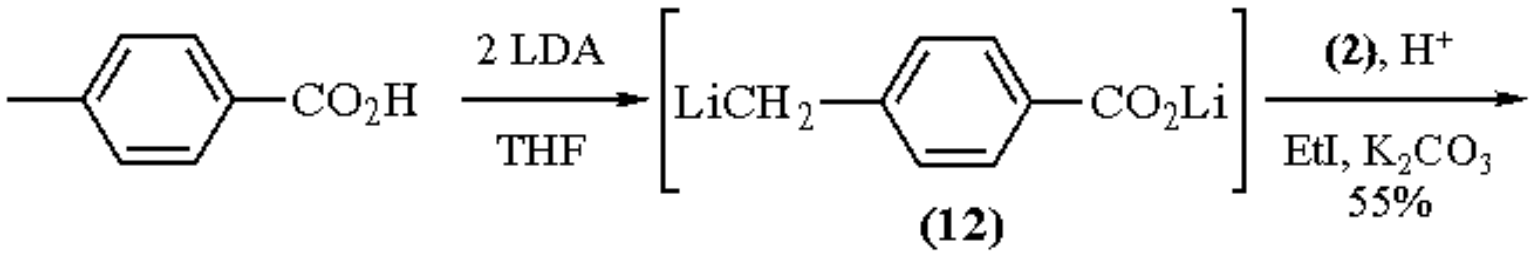

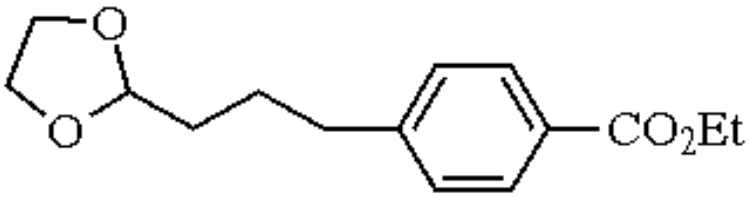

(9)

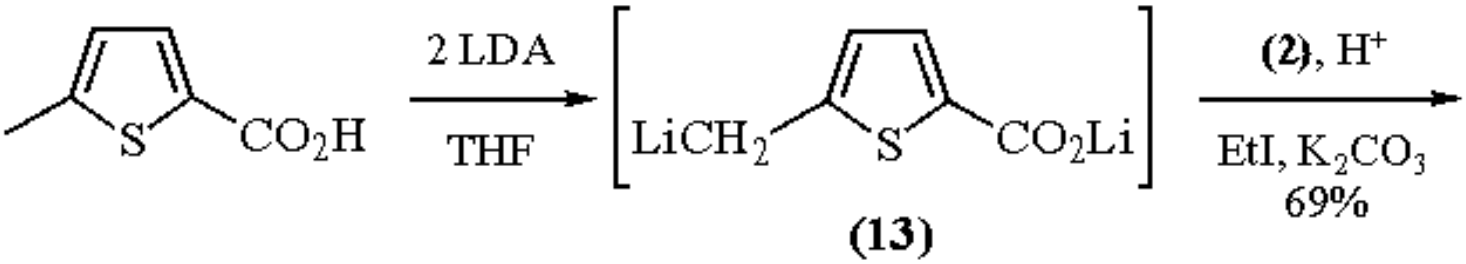

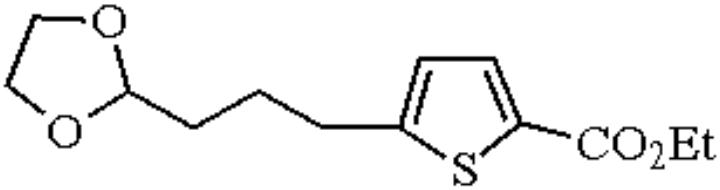

(10)

The (η^5-cyclohexadienylidene)$_2$[Cr(CO)$_3$]$_2$ dianion (**14**) reacts regioselectively with (**2**) to give intermediate (**15**); its further treatment, as shown in eq 11, leads ultimately to the doubly functionalized aromatic product (**16**).[26] The discovery has been made that the condensation of (**2**) with the anion of ethyl phenylsulfinylfluoroacetate leads to the α-

fluoro acrylate (**17**) (eq 12).[27]

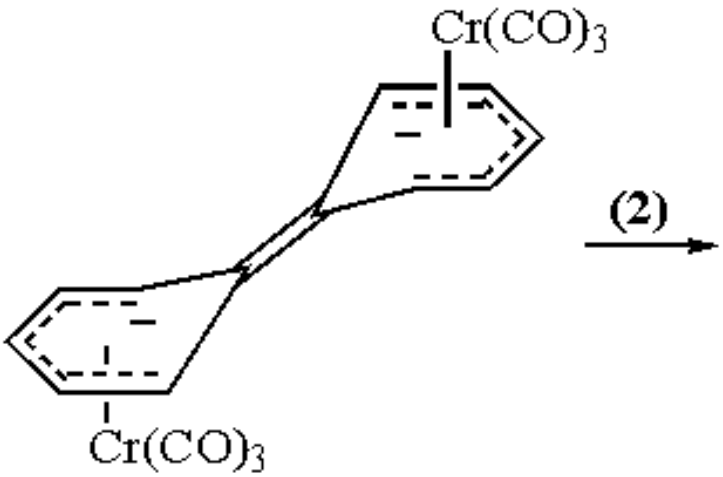

(14)

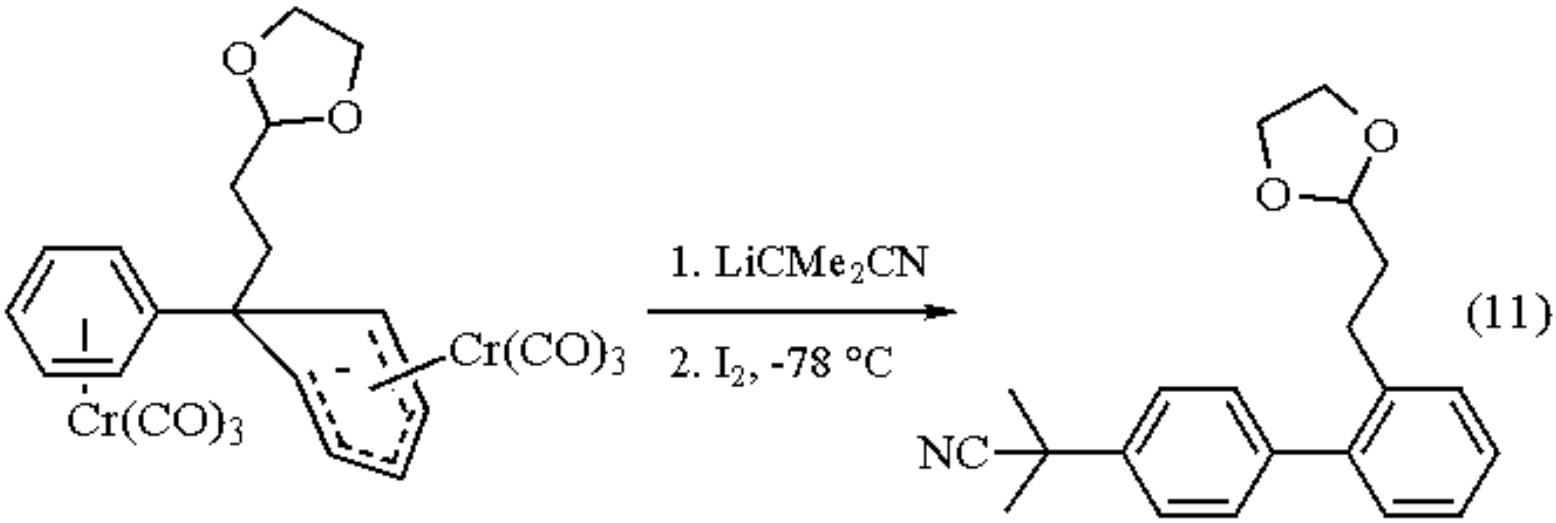

(11)

(15) **(16)** 49%

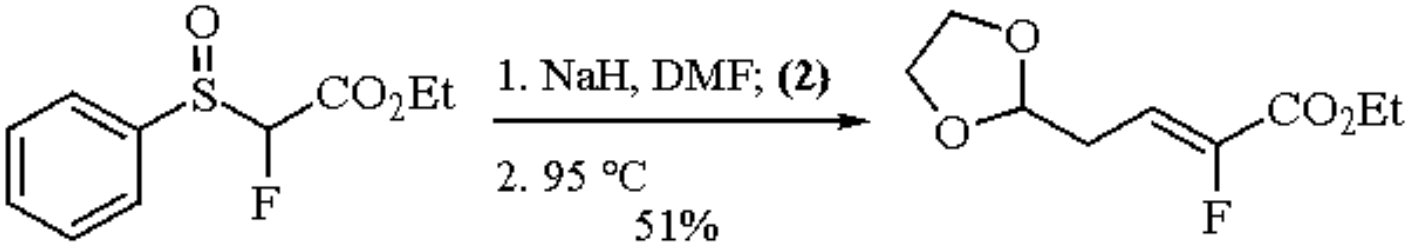

(12)

(17)

Alcohols and amines are also capable of condensing with these halo acetals. The conversion of a suitably protected hydroxyproline to (**18**) (eq 13)[28] and of the methylamino derivative to arecolone (**19**) are illustrative (eq 14).[29]

2-(2-Bromoethyl)-1,3-dioxane

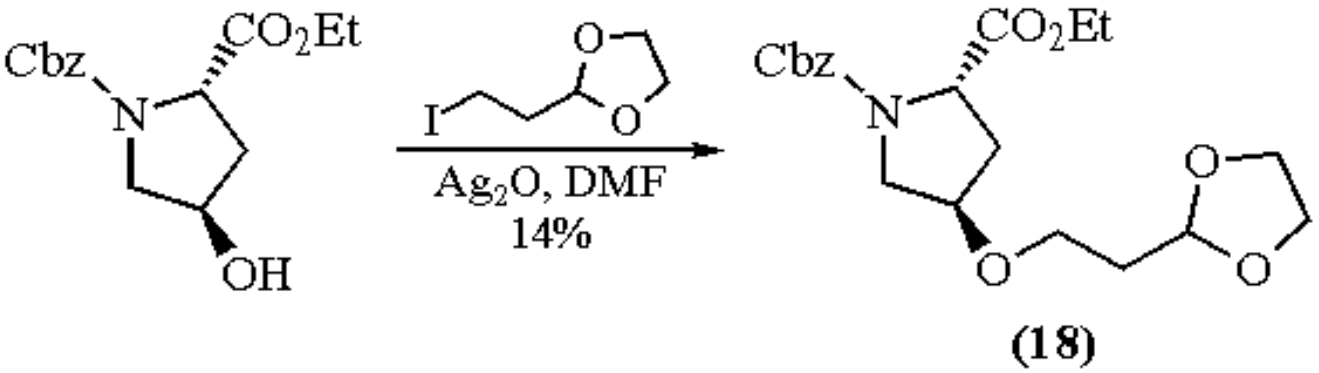

(13)

(18)

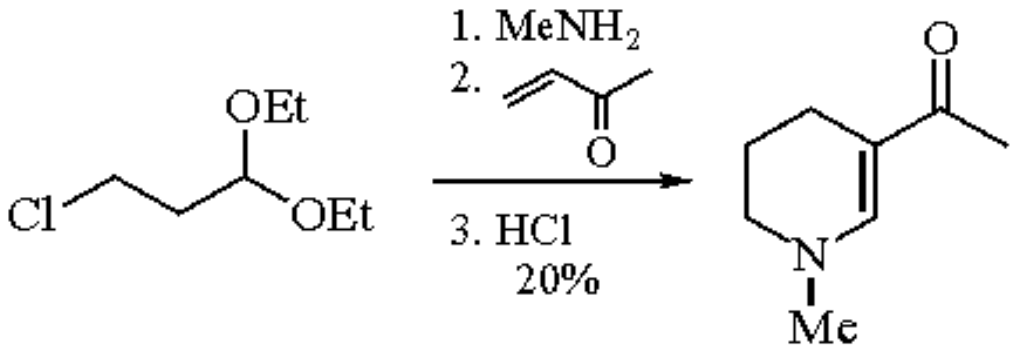

(14)

(19)

Use as Grignard Reagents.

The Grignard reagents derived from (**1**)-(**3**) exhibit a stability order that parallels their hydrolytic behavior. That derived from (**1**) is thermally stable,[12] while the dimethyl acetal (**3**-MgBr) is too labile to be useful.[30] Since the magnesium reagent derived from (**2**) decomposes at rt and above,[30,31] it must be generated and used below 25 °C. As expected, examples of simple additions of (**1**-MgBr) and (**2**-MgBr) to aldehydes[32] and ketones[33] abound. In the first instance, this process has evolved into a facile means for preparing 5-substituted butyrolactones.[34] The conversion of ketone (**20**) to norbisabolide (**21**) shows that ketones can be analogously processed (eq 15).[35] Clever use has been made of this condensation reaction in a total synthesis of clavukerin A,[36] where Grob fragmentation of adduct (**22**) was utilized to obtain the functionalized 3-cycloheptenone (**23**) (eq 16).

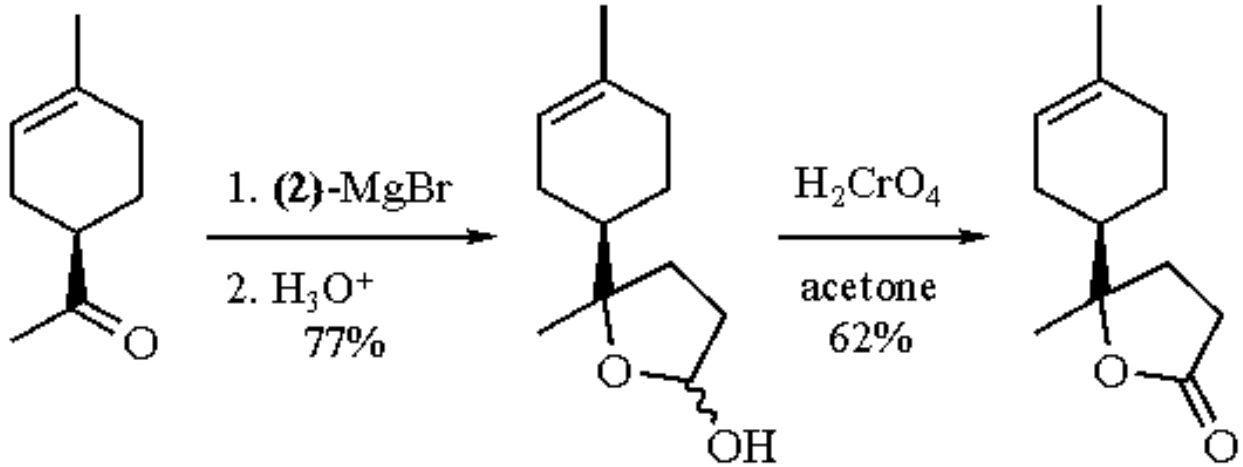

(15)

(20)

(21)

2-(2-Bromoethyl)-1,3-dioxane

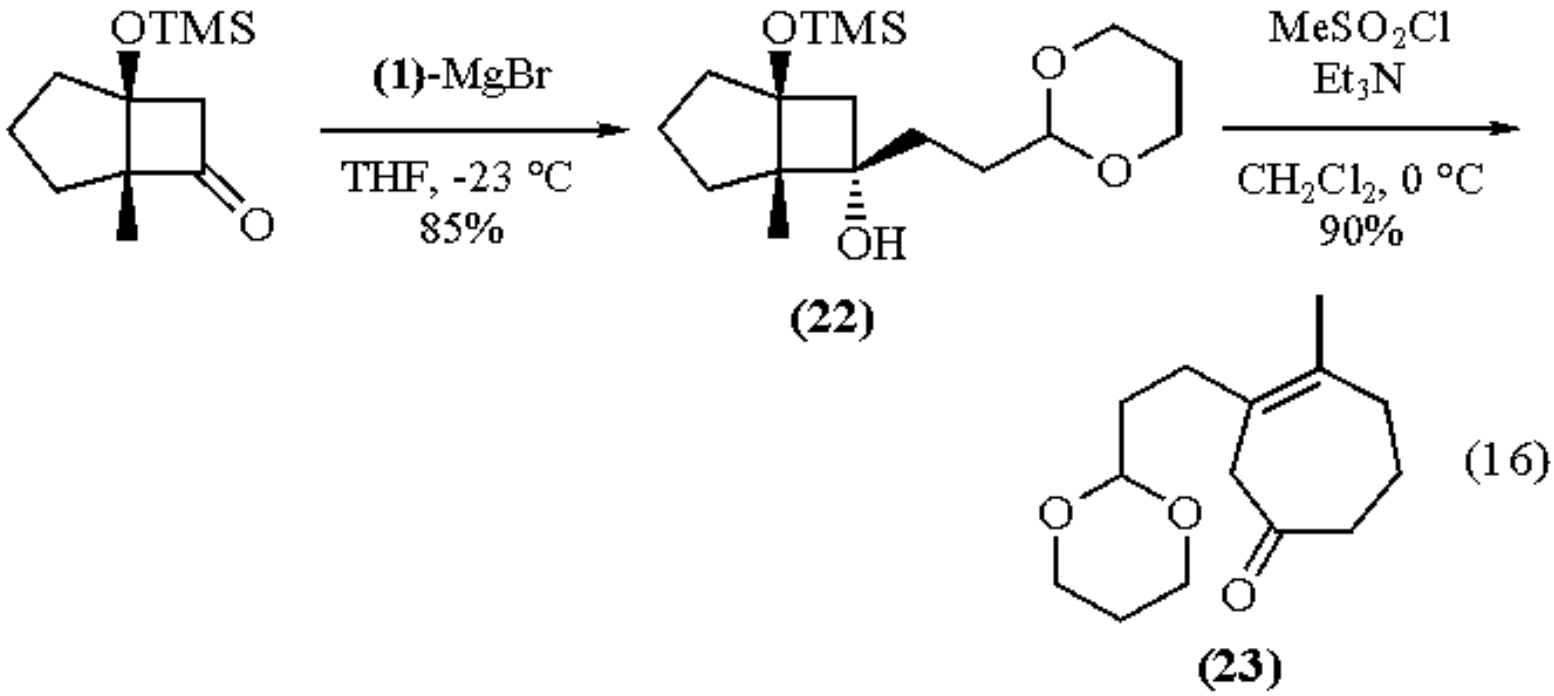

(16)

These Grignard reagents can be condensed directly with activated halides (eq 17).[37] Alternatively, related carbon-carbon bond formation can be realized by promoting the coupling with ***Dilithium Tetrachlorocuprate(II)*** (eq 18).[38]

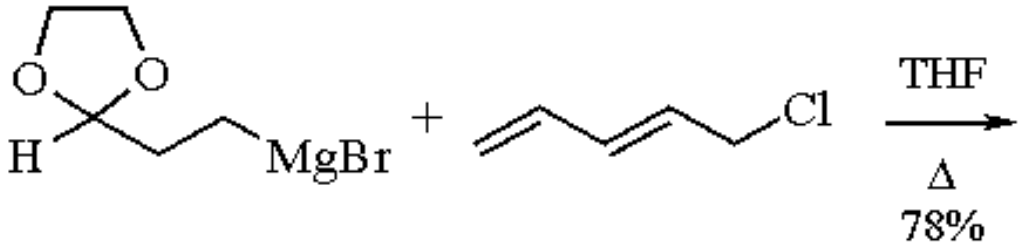

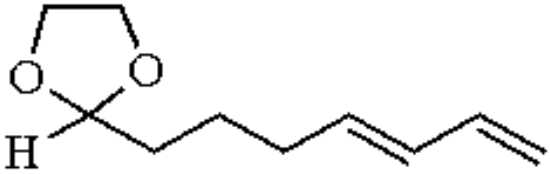

(17)

2-(2-Bromoethyl)-1,3-dioxane

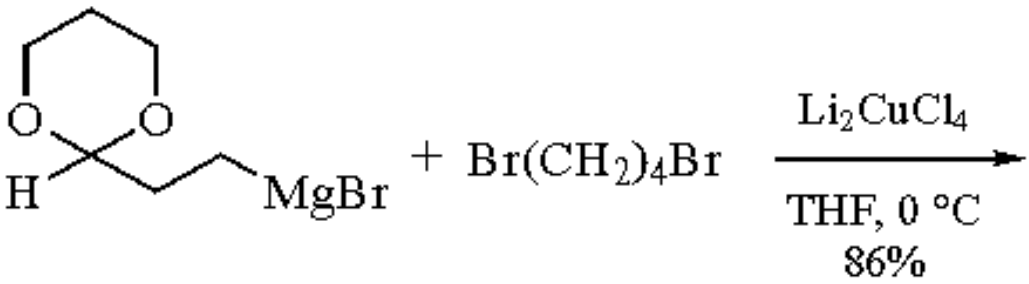

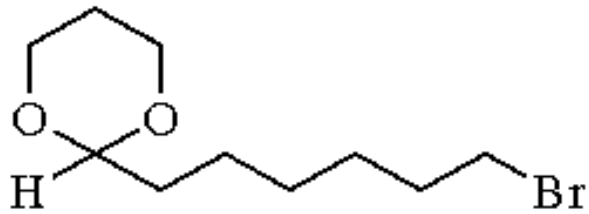

(18)

The presence of acetal oxygen atoms has been recognized to moderate the chemical reactivity of these Grignard reagents. As seen in eq 19, addition to cyclic enones at -78 °C affords principally the product of conjugate addition without the benefit of a Cu^{I} salt.[39] Additionally, these organometallics are widely known to react with acid chlorides to produce ketones without significant further conversion to tertiary alcohols.[12a,40] The substantial synthetic latitude provided by this process is reflected in eqs 20-22.[41-43]

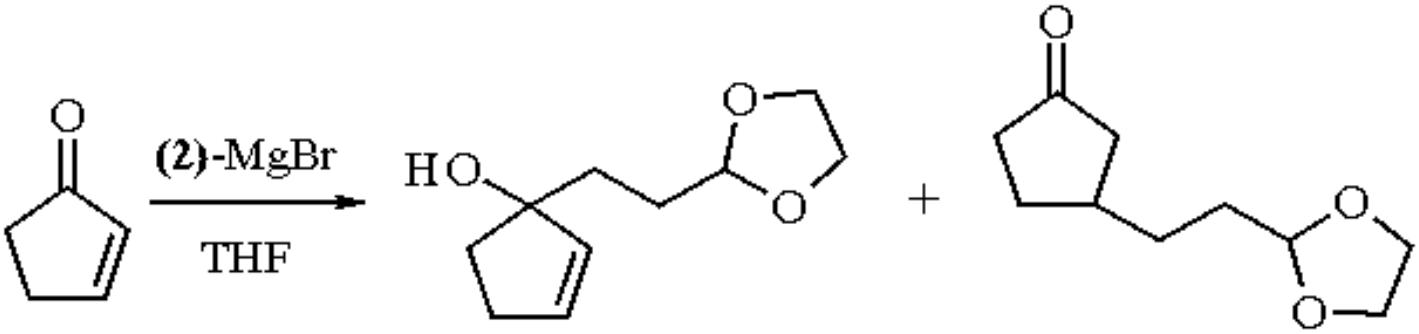

at 0 °C 1:1
at -78 °C 1:20 73%

(19)

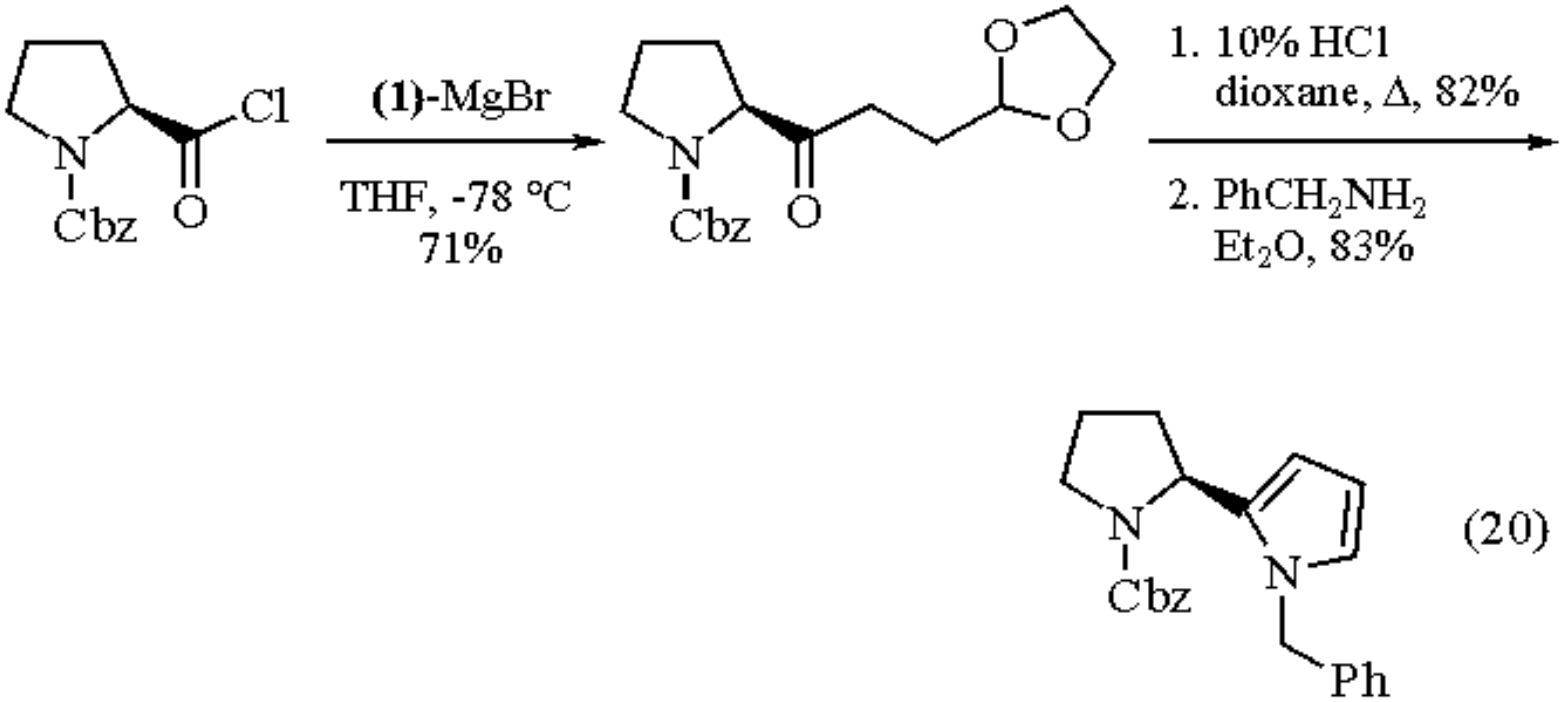
Cl
N
Cbz
O
(1)-MgBr
THF, -78 °C
71%
O
O
1. 10% HCl
dioxane, Δ, 82%
2. PhCH2NH2
Et2O, 83%
Ph

(20)

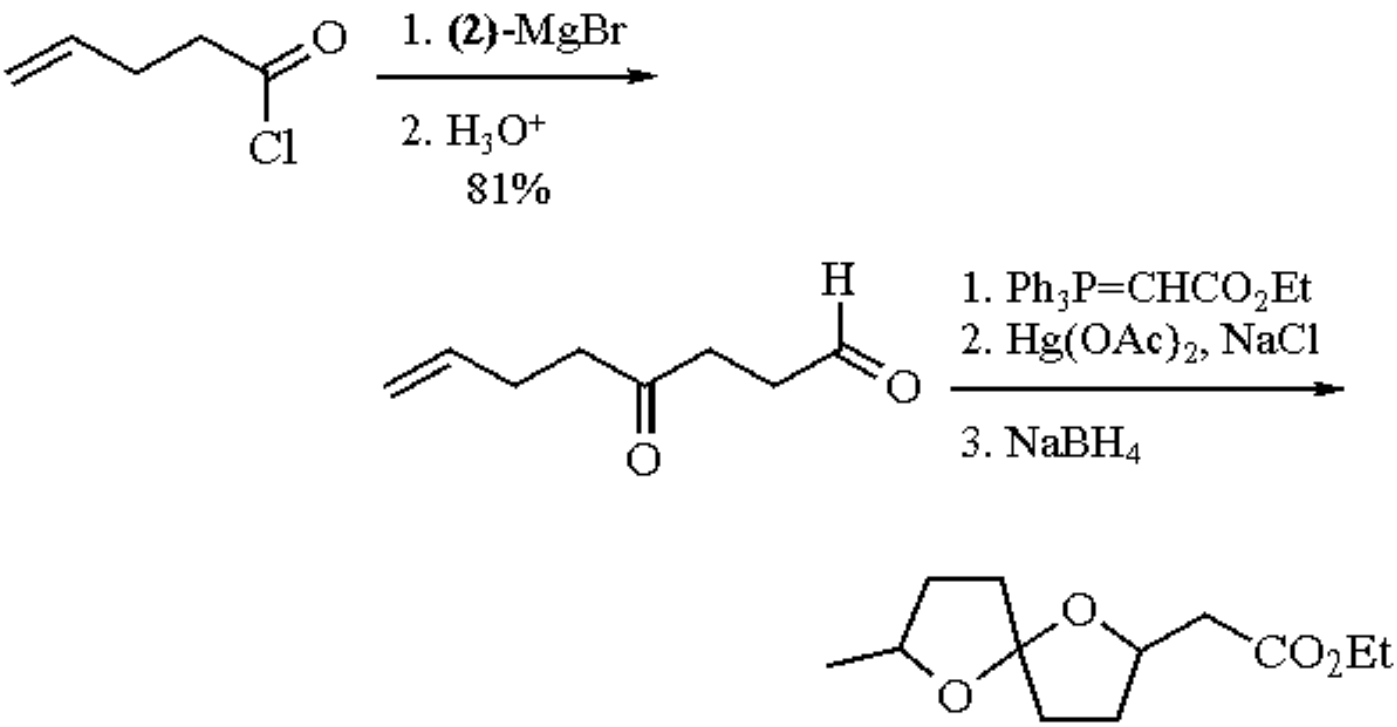
O
Cl
1. (2)-MgBr
2. H3O+
81%
H
1. Ph3P=CHCO2Et
2. Hg(OAc)2, NaCl
3. NaBH4
CO2Et

(21)

2-(2-Bromoethyl)-1,3-dioxane

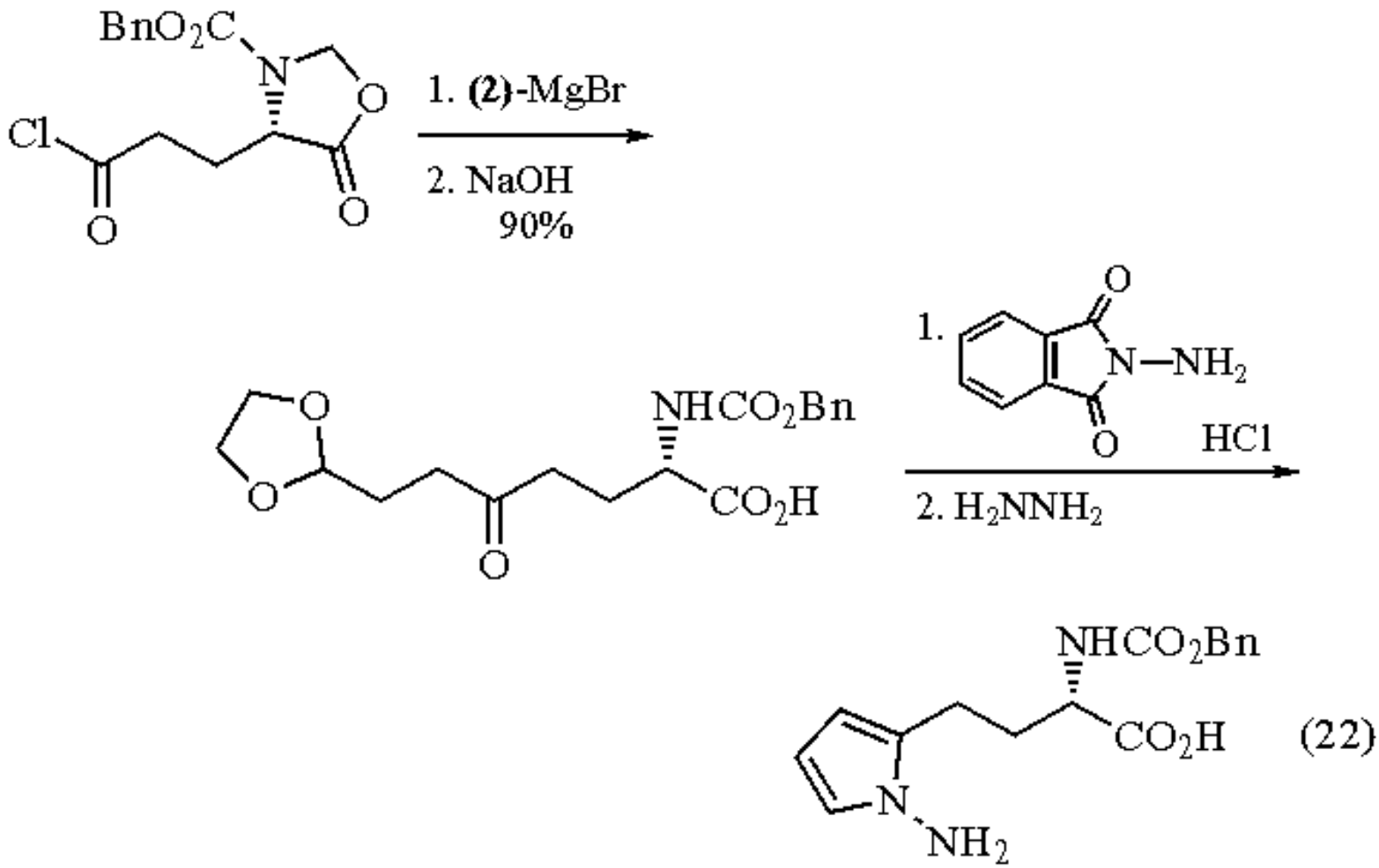

Other notable uses of (**2**-MgBr) can be found in syntheses of estafiatin (1,6-addition to tropone),[44] eupolauramine (displacement of an aryl oxazoline),[45] substituted eudistomins (capture by a nitrile group),[46] a tripeptide ACE inhibitor (addition to a thio ester),[47] the 1,7-dioxaspiro[5.5]undecane subunit of milbemycin β_3 (directed oxirane cleavage),[48] and the lipophilic sidechain of the cyclic hexadepsipeptide antibiotic L-156,602 (addition to an α-chloroboronate).[49]

Use as a Cuprate.

As noted above (eq 18), (**1**-MgBr) and (**2**-MgBr) give coupling reactions with halides and tosylates under conditions of copper catalysis.[38,50] Cuprate formation also results in successful condensation with allylic acetates (eq 23),[51,52] epoxides,[53] vinyl epoxides (eq 24),[54] and alkynes (eq 25).[55] Conjugate addition to α,β-unsaturated ketones can also be realized in this way,[56] this process often constituting the first step of an annulation sequence.

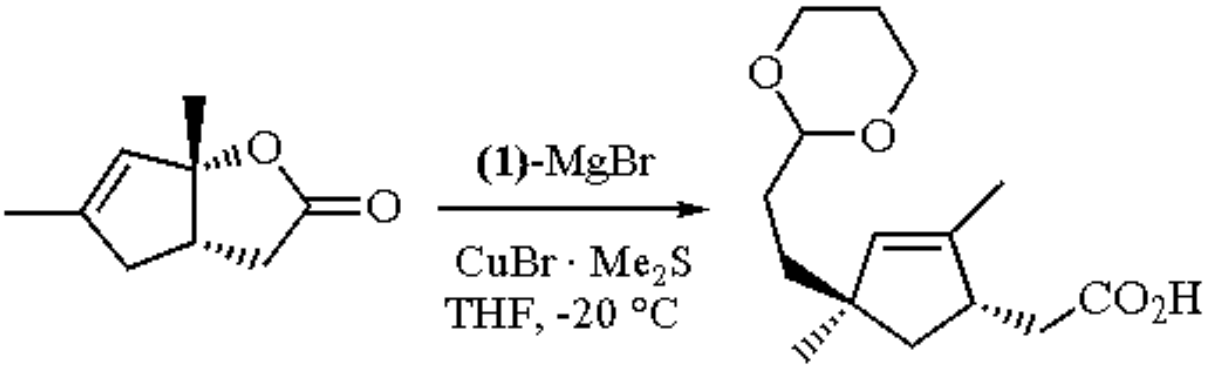

high yield

(23)

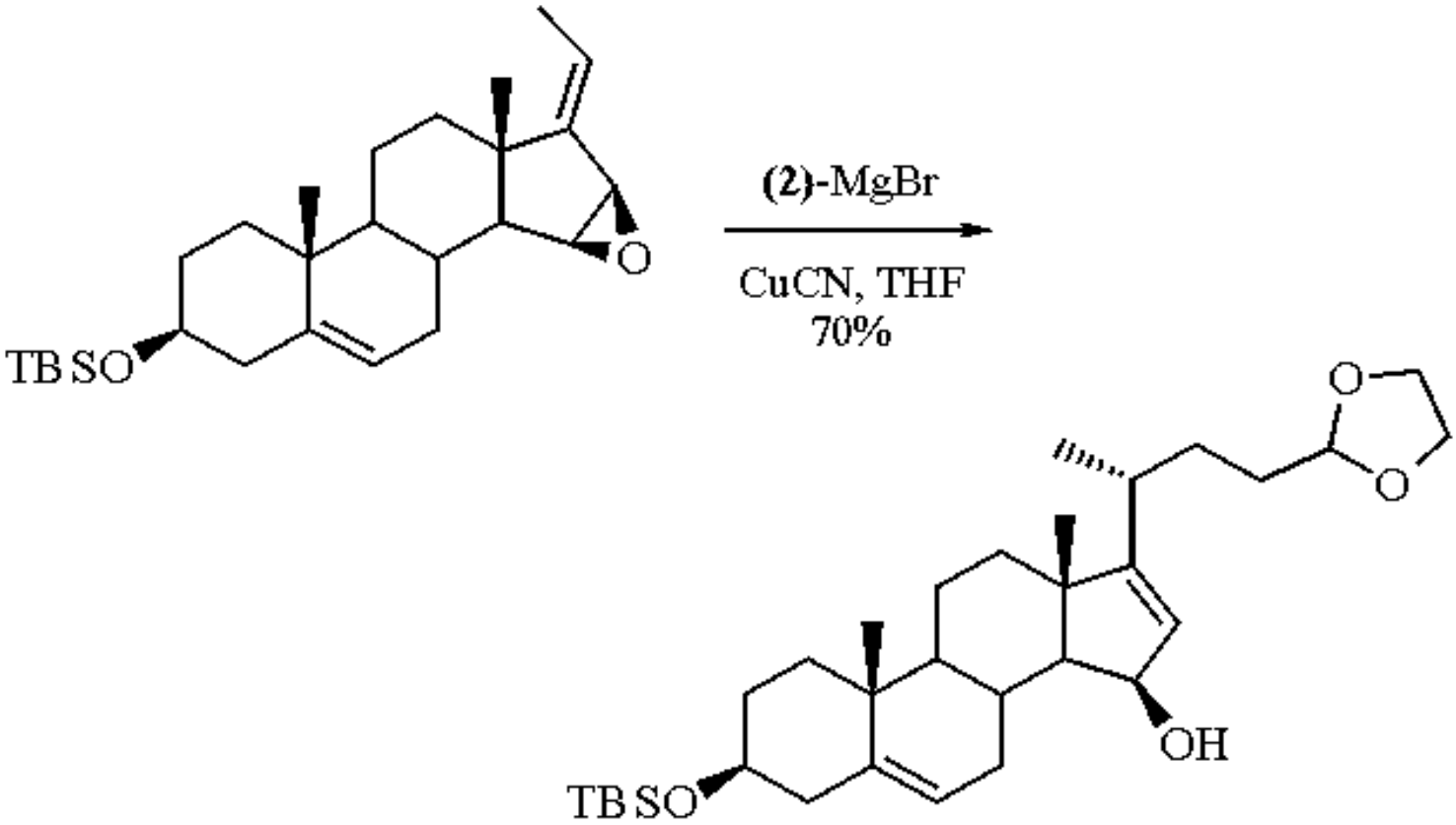

(24)

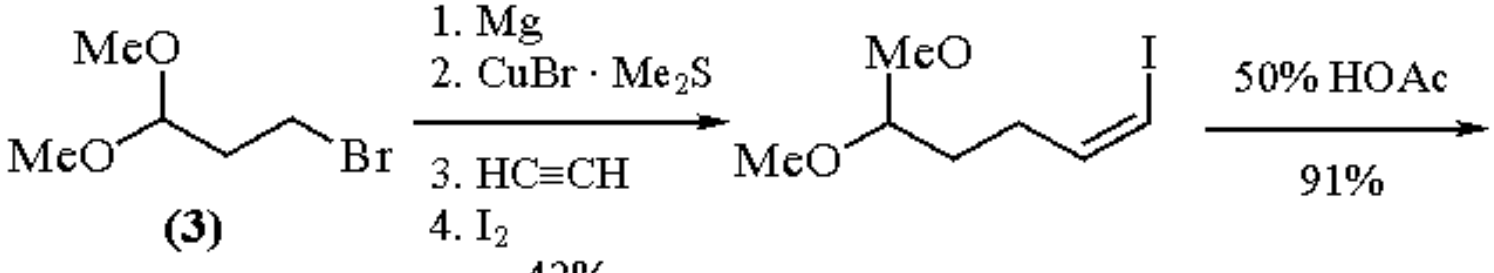

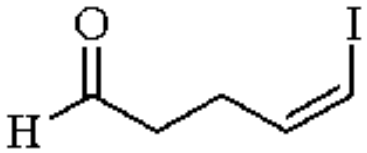

(25)

Annulation Reactions.

The keto acetals formed upon Cu^{I}-promoted 1,4-addition of acetal-containing Grignard reagents have found wide application in cyclopentene annulation.[57] When no α-substituent is present, the aldol condensation leads to a conjugated bicyclic enone (eq 26).[58] Dehydration is, of course, not spontaneous when an angular group is already in place; in such cases, dehydration must be implemented separately (eq 27).[59]

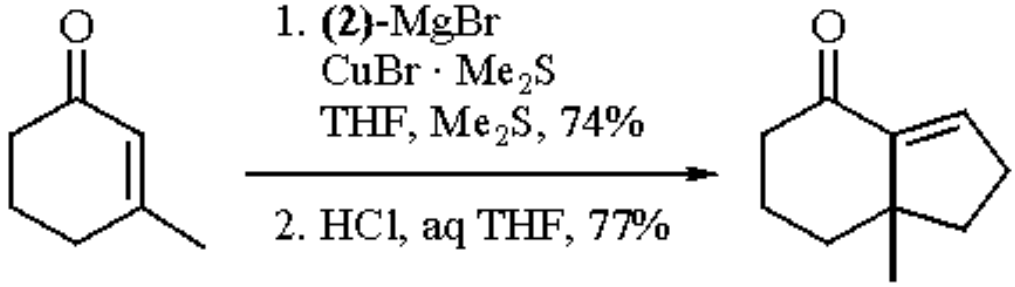

(26)

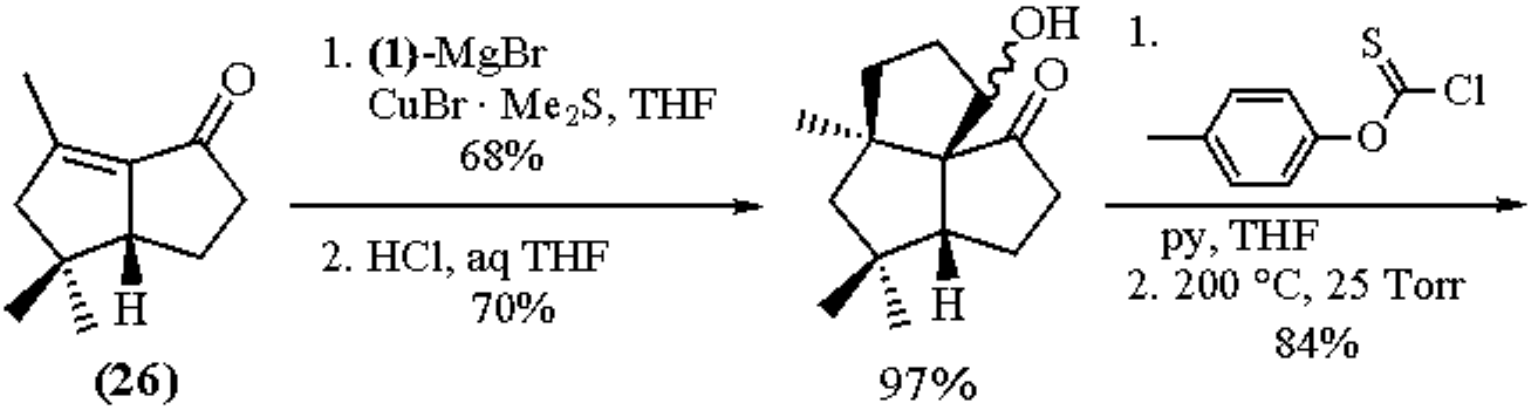

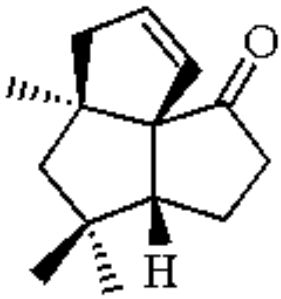

(27)

When the site of connectivity is external to an aromatic ring, cyclodehydration results in the elaboration of a six-membered ring.[60] Depending upon the method employed and the degree of substitution, the annulated ring may be singly unsaturated (eq 28)[61] or fully aromatic (eq 29).[62]

2-(2-Bromoethyl)-1,3-dioxane

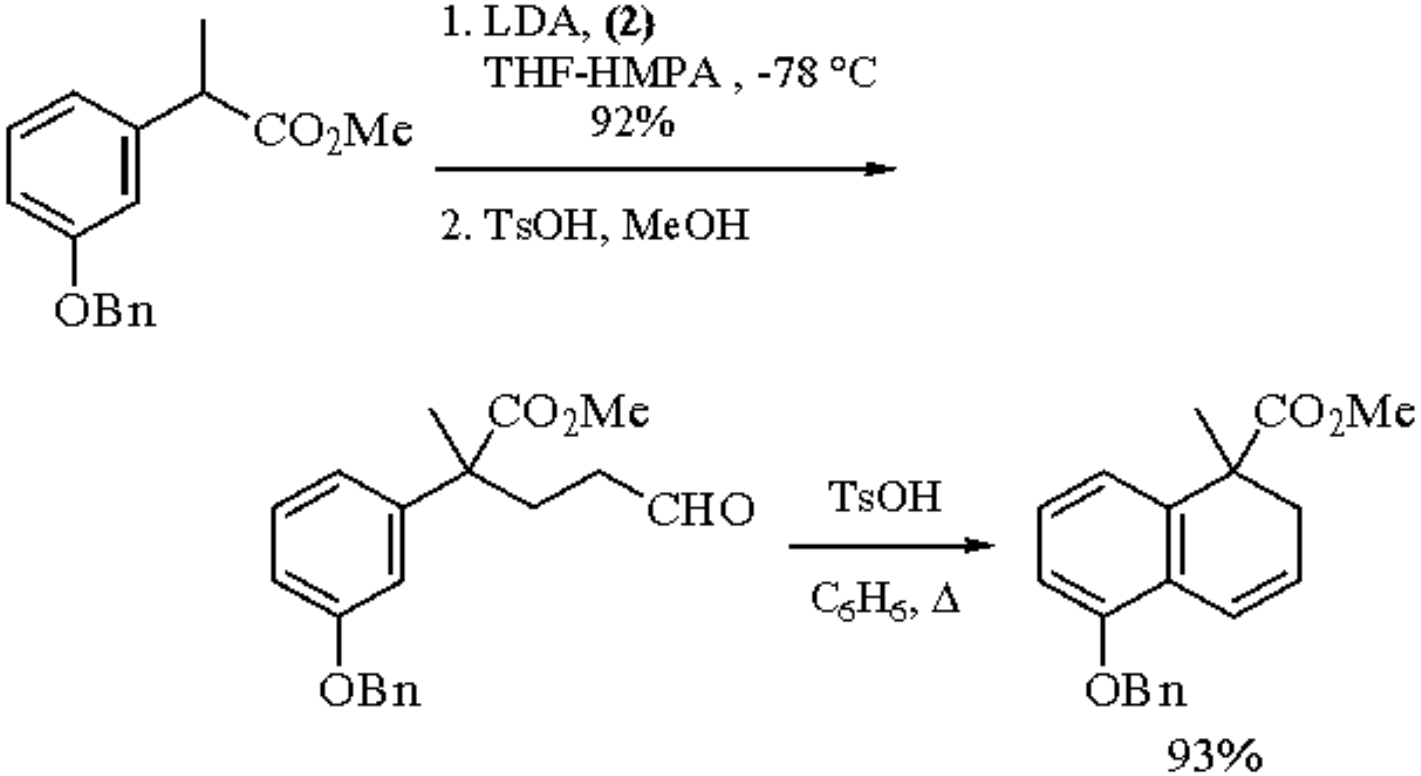

(28)

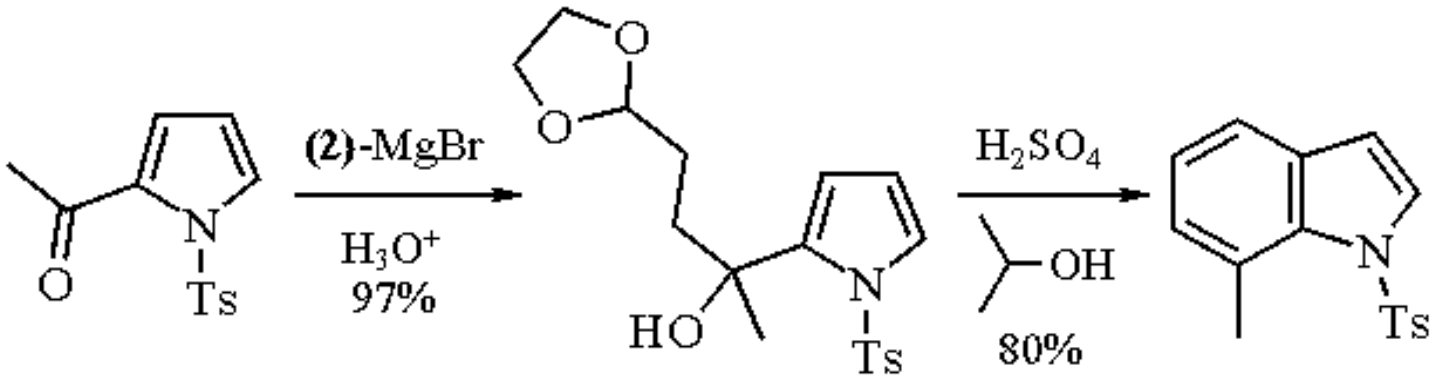

(29)

Pyridoannulations are also possible (eq 30).[63] Other nitrogen-containing rings have been elaborated either by radical means (eq 31)[64] or via the involvement of *N*-acyliminium ions (eq 32).[65] The potential for spirocyclic ring construction has been explored as well (eq 33).[66]

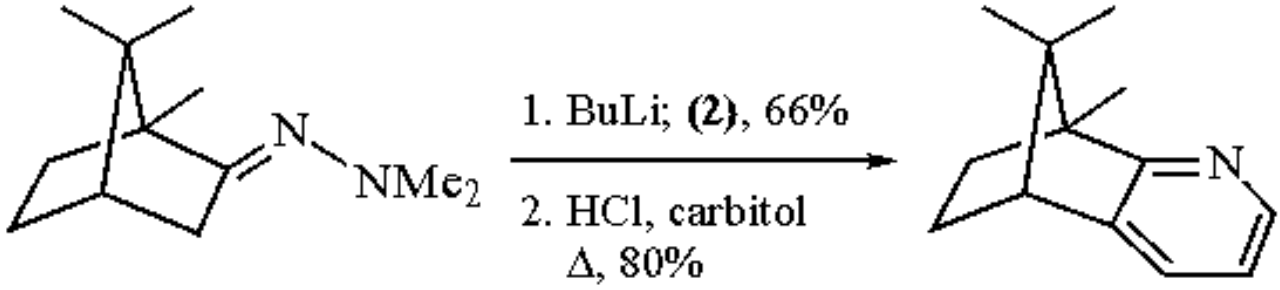

(30)

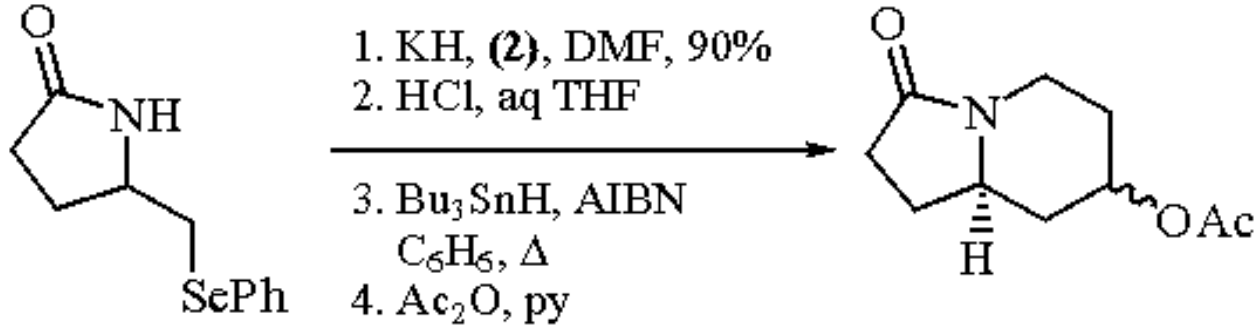
1. KH, (2), DMF, 90%
2. HCl, aq THF
3. Bu_3SnH, AIBN
C_6H_6, Δ
4. Ac_2O, py
NH
SePh
N
OAc
H

(31)

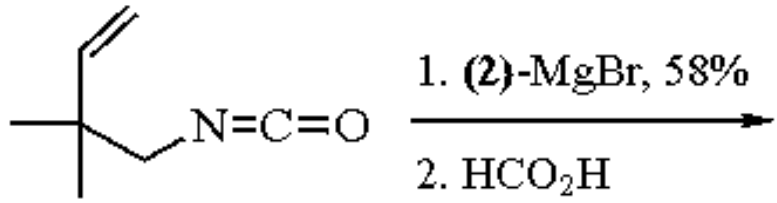
N=C=O
1. (2)-MgBr, 58%
2. HCO_2H

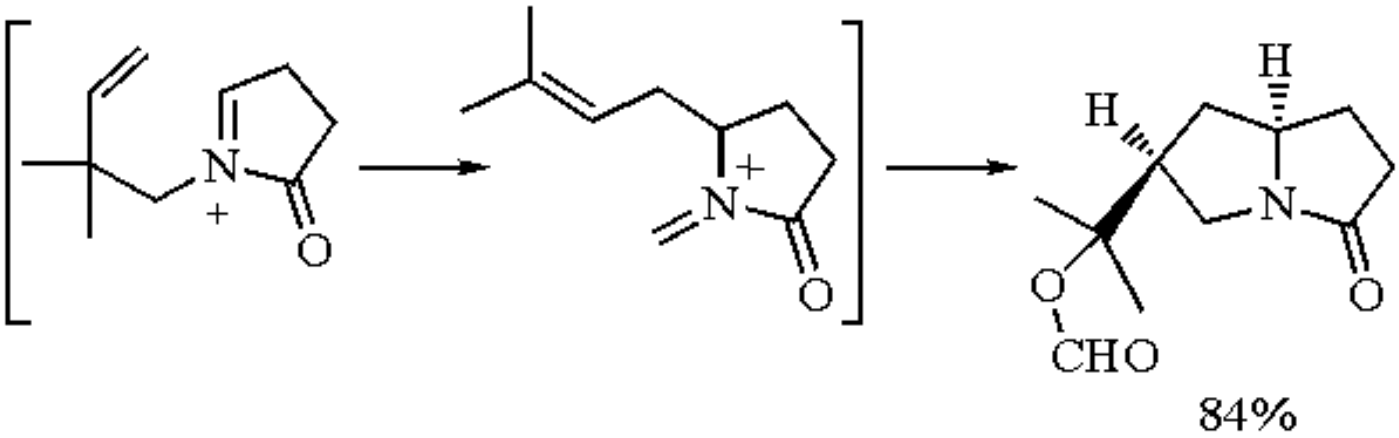
N
O
H
CHO
84%

(32)

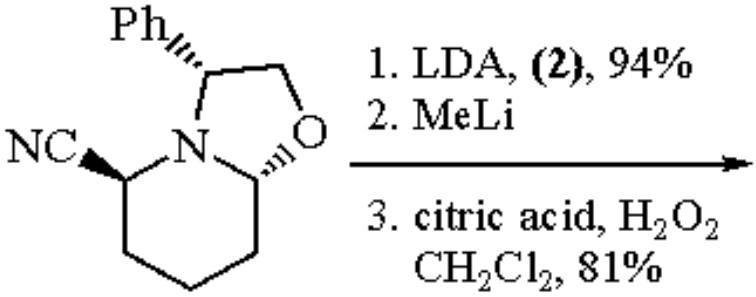
Ph
NC
N
O
1. LDA, (2), 94%
2. MeLi
3. citric acid, H_2O_2
CH_2Cl_2, 81%

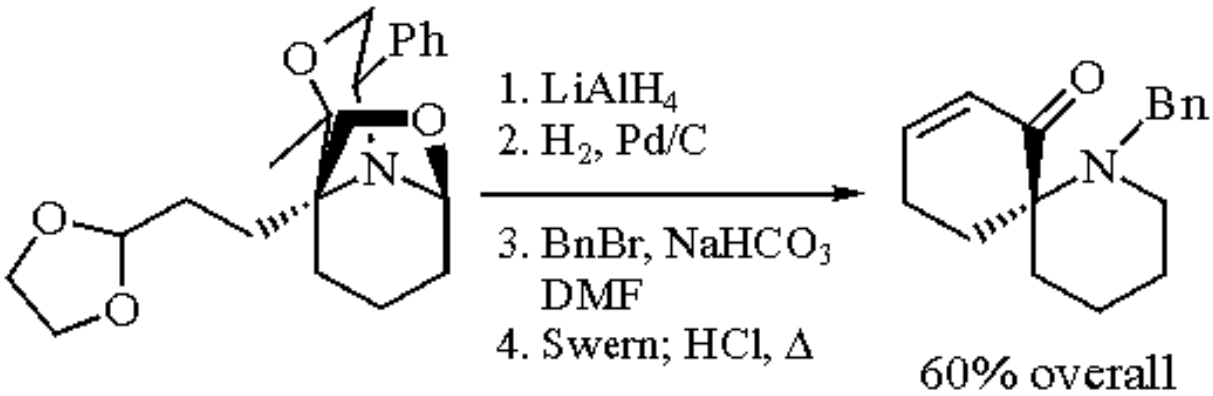
Ph
O
N
1. $LiAlH_4$
2. H_2, Pd/C
3. BnBr, $NaHCO_3$
DMF
4. Swern; HCl, Δ
Bn
60% overall

(33)

Allied Compounds.

The lithium derivative of (**1**) has been satisfactorily generated by exposure of the iodide to ***t-Butyllithium*** in *n*-pentane-ether (3:2) at -78 °C.[67] Bromo acetals (**1**)-(**3**) are quite amenable to functional group exchange in the manner represented by (**24a-h**).[68-73] Of these, (**24b**)[69] has held particular fascination as a consequence of its ability to serve as a reaction partner in [3 + 2] cycloadditions (eq 34).[69d] The dithianyl acetals of type (**25**) are notably serviceable as cyclohexane annulating agents (eq 35).[72b,74] Ynamine acetal (**26**) has found similar application (eq 36).[75]

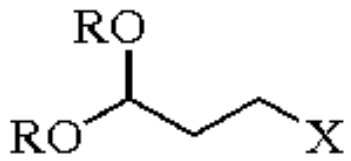

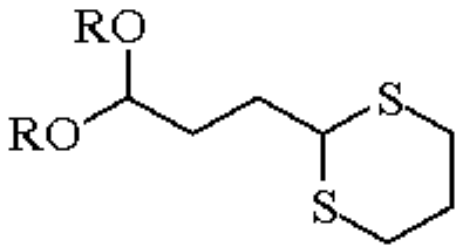

(24a) X = CO_2H **(24e)** X = CH_2NH_2
(24b) X = NO_2 **(24f)** X = $^+PPh_3Br^-$
(24c) X = NH_2 **(24g)** X = SO_2Ph
(24d) X = CN **(24h)** X = $SnMe_3$

(25)

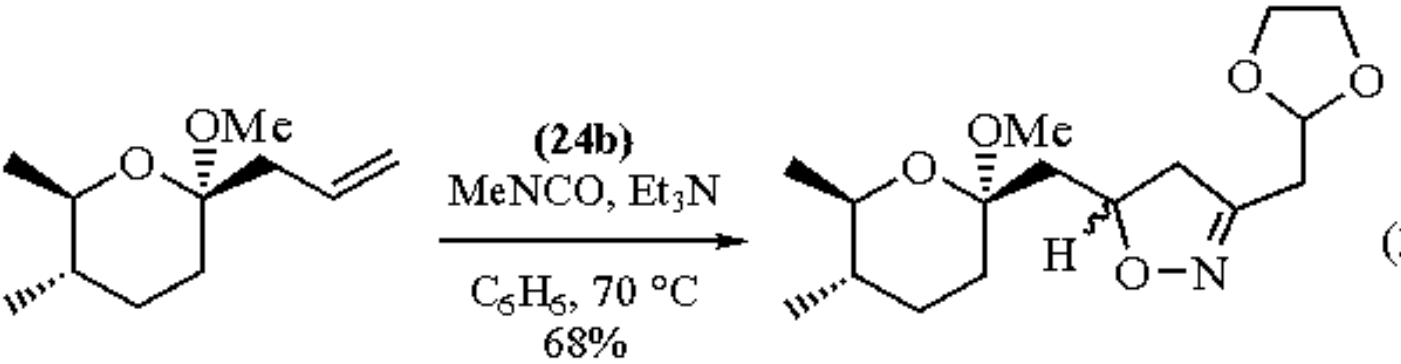

(34)

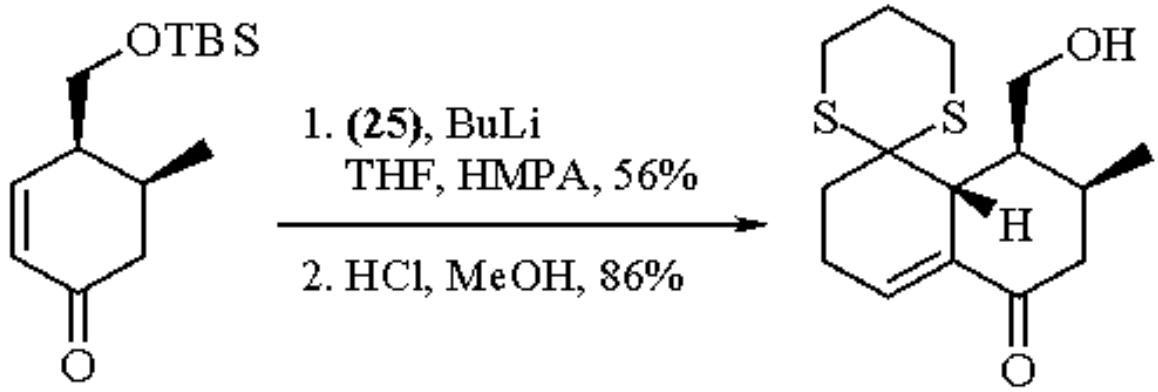

(35)

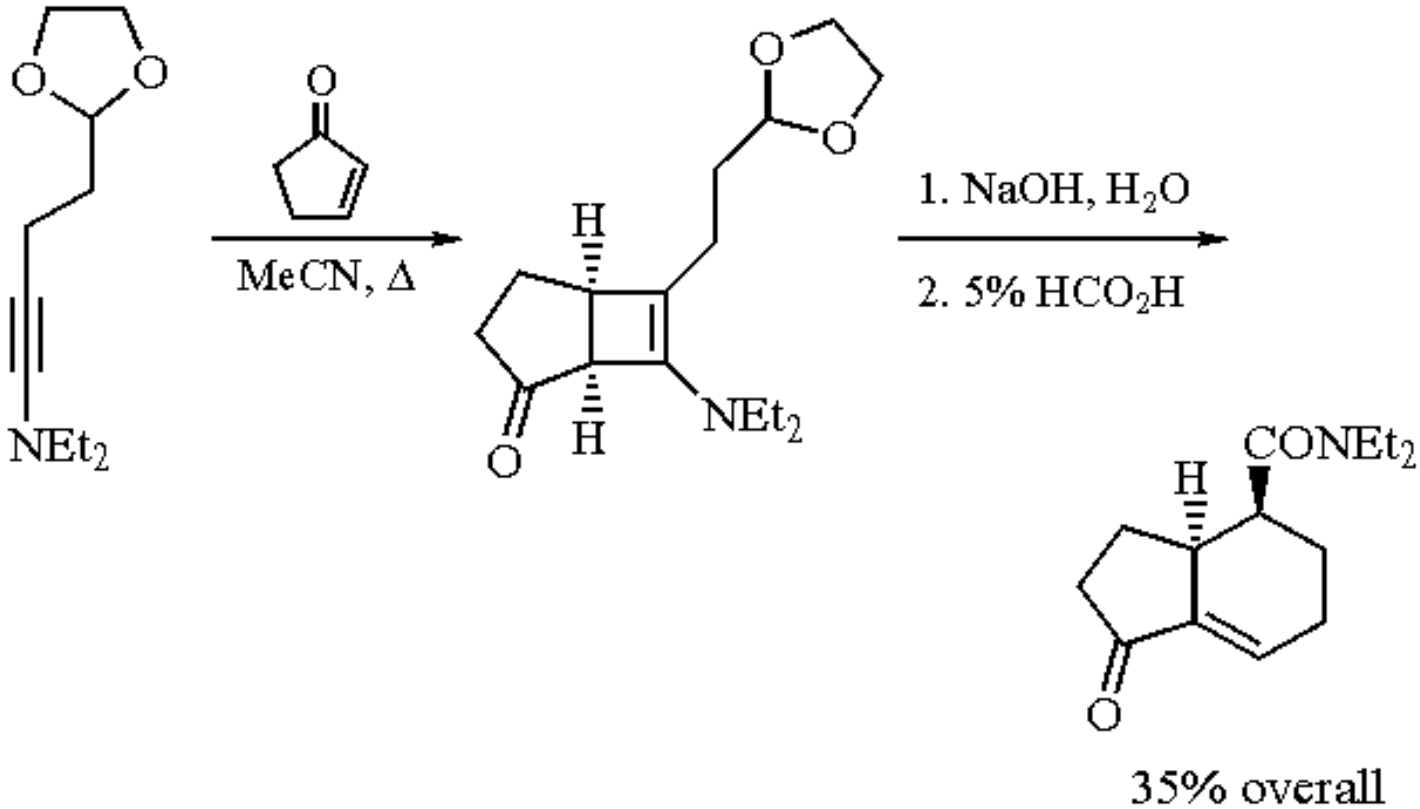

(36)

Related Reagents.

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane.

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1. Stowell, J. C. *CRV* **1984**, *84*, 409.
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2-(2-Bromoethyl)-2-methyl-1,3-dioxolane[1]

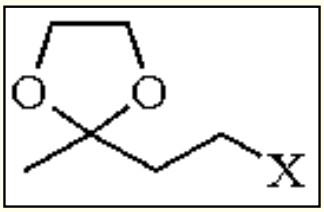

(**1**; X = Br)

[37865-96-6] · $C_6H_{11}BrO_2$ · 2-(2-Bromoethyl)-2-methyl-1,3-dioxolane · (MW 195.06) (**2**; X = I)

[53750-51-9] · $C_6H_{11}IO_2$ · 2-(2-Iodoethyl)-2-methyl-1,3-dioxolane · (MW 242.06) (**3**; X = Cl)

[57398-28-4] · $C_6H_{11}ClO_2$ · 2-(2-Chloroethyl)-2-methyl-1,3-dioxolane · (MW 150.60)

(methyl vinyl ketone equivalent; alkylating agents for attaching a 3-ketobutyl group to various nucleophiles; the derived organometallic reagents attach this group to electrophilic centers such as carbonyl groups; major use in the synthesis of monoprotected 1,4-, 1,5-, and 1,6-diketones and related 1,*n*-difunctional compounds)

Physical Data: X = Cl: bp 40-43 °C/1 mmHg; 73-74 °C/14 mmHg. X = Br: bp 42-46 °C/0.4 mmHg; 64-68 °C/9 mmHg; 84-88 °C/12 mmHg, 88-94 °C/27 mmHg. X = I: decomposes on distillation.

Preparative Methods: X = Br or I: addition of methyl vinyl ketone to a two-phase mixture of benzene and conc aq HX, followed by drying of the benzene phase, addition of ethylene glycol, and removal of water with a Dean-Stark trap.[1b,2] X = Cl: acetalization of 4-chloro-2-butanone with ethylene glycol;[3] the chloro ketone was made by acylation of ethylene[4] but, presumably, can also be made as above. Other preparations of these and related 4-halo-2-butanone acetals have been reported.[5]

Purification: X = Cl or Br: vacuum distillation from a trace of sodium bicarbonate; X = I: filter through a small plug of alumina; the acetal should not be distilled.

Handling, Storage, and Precautions: even purified samples contain some β-halo ketone which slowly loses HX, catalyzing further decomposition. Store at <=0 °C.

Electrophilic 3-Ketobutyl Reagent.

Attachment of a 3-ketoalkyl chain to the α-position of a preexisting ketone gives a 1,5-diketone which, upon treatment with base, undergoes aldol condensation to give a 2-cyclohexen-1-one.[6] In the case of relatively acidic ketones (such as β-dicarbonyl compounds), chain attachment can be effected by Michael addition of their enolates (generated with a

catalytic amount of base) to an alkyl vinyl ketone, generally in a protic solvent. With simple ketones, however, the high basicity of the enolate causes polymerization of the alkyl vinyl ketone. Furthermore, enolate equilibration often occurs, resulting in attachment of the chain to both the α- and α´-carbons. Compounds (**1**) and (**2**) have found some use in solving these problems in the case of α,β-unsaturated ketones (eq 1).[7]

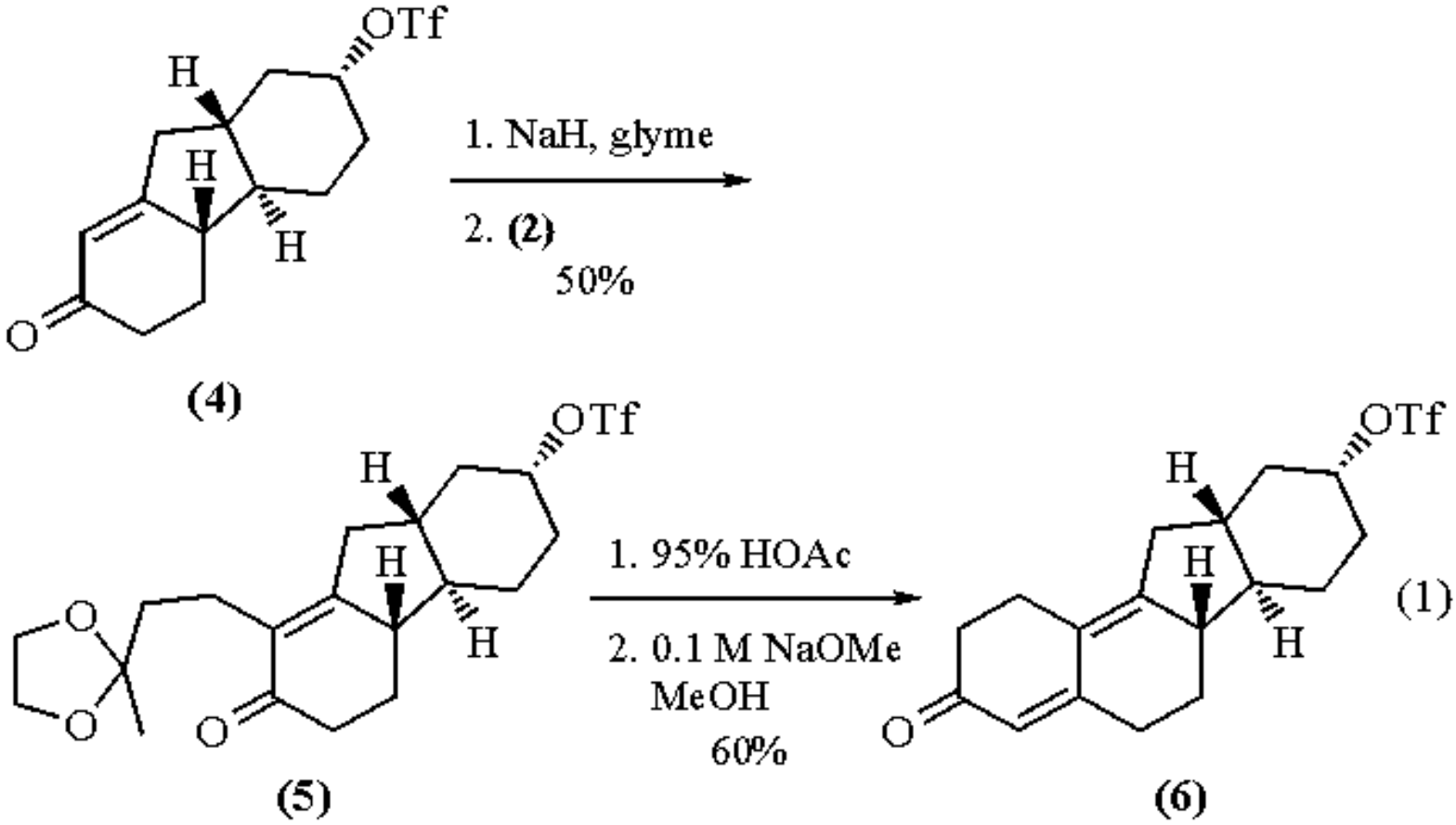

Reagents (**1**) and (**2**) have found little use in alkylation of unsymmetrical saturated ketones, presumably because they are insufficiently electrophilic to trap regiospecifically generated enolates. The high nucleophilicity of metallated enamines[8] and hydrazones,[9] along with the possibility for controlling the site of anion formation,[10] may extend the utility of β-haloacetals as annulating agents.[11] Reagents for bis-annulation have been prepared by alkylating acyclic carbonyl compounds with (**1**).[12] The variation in eq 2 exploits the synthetic equivalence of 2-alkylpyridines and 2-cyclohexen-1-ones.[13]

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane

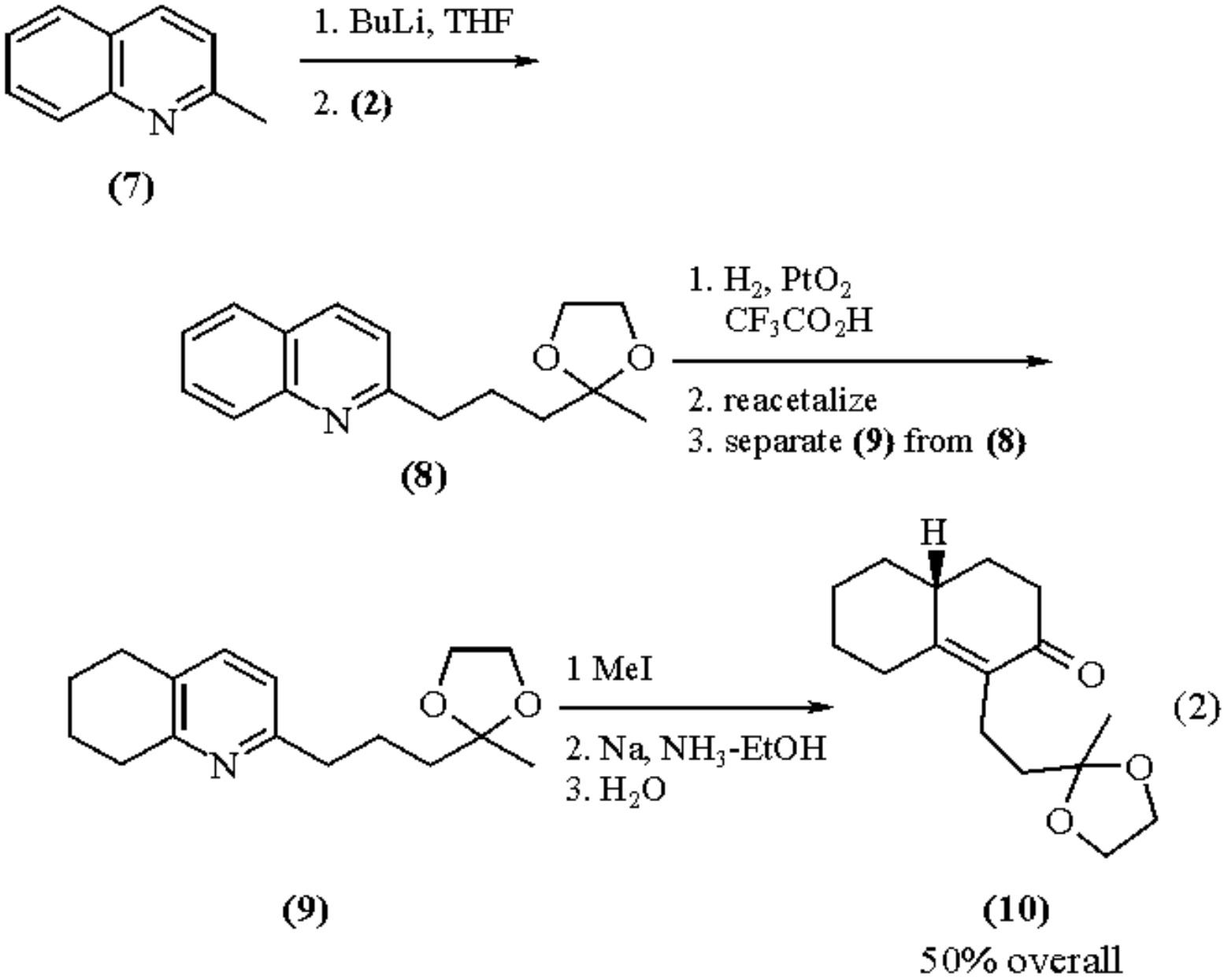

(2)

Alkylation of the anions of α-arylnitriles with (**1**) and (**2**), followed by ***Diisobutylaluminum Hydride*** reduction leads to 5,5-ethylenedioxy aldehydes which have been cyclized to (spiro) 4,4-disubstituted 2-cyclohexen-1-ones.[14] A related approach to spiro compounds involves alkylation of a lactone with (**2**).[15]

1,4-Diketones, useful as precursors of 2-cyclopenten-1-ones, furans, and other heterocycles, have been prepared by alkylation of terminal acetylides with (**1**) followed by regioselective hydration.[16] Alternatively, 1,4-diketones can be made by alkylation of α-tosyl isocyanide carbanions with (**1**) followed by hydrolysis;[17] both strategies have been used to make *cis*-jasmone. Presumably the pairing of (**1**) with other acyl anion equivalents[18] represents a general approach to differentially protected 1,4-diketones.

A variety of very basic carbanions have been alkylated with (**1**) and (**2**), including sulfoxide and sulfone anions,[19] dianions from β-dicarbonyl compounds[5d,i,12,20] and β-keto sulfoxides,[21] and carboxylic acid dianions.[22] Alkylation of allylic carbanions[23] with (**1**) or (**2**) has been used in syntheses of bridged dioxabicyclo[3.2.1]octanes[5d,i,23b,c] including (1*S*,5*R*)-frontalin (**14**) (eq 3).[23c]

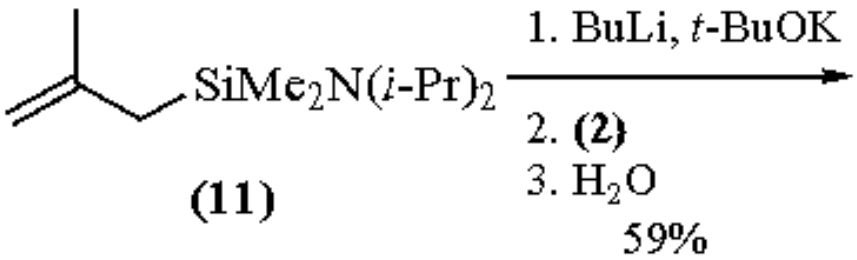

(11)

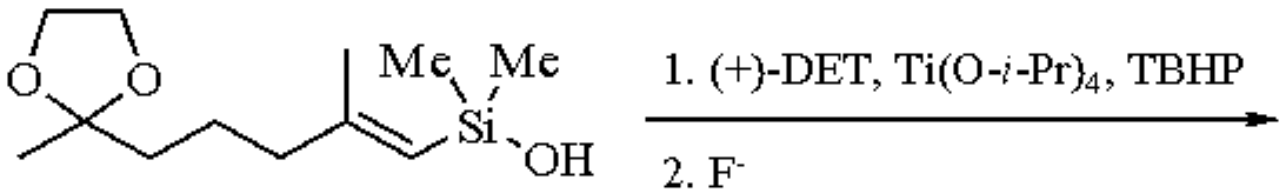

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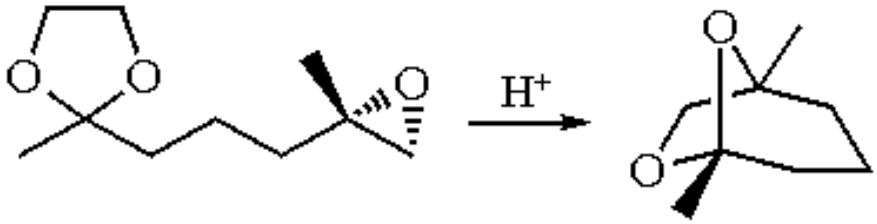

(3)

(13) (14) 85% ee

Nucleophilic 3-Ketobutyl Reagent.

Addition, at 25 °C, of a THF solution of (**1**) (containing ***1,2-Dibromoethane*** as an entraining agent) to excess ***Magnesium*** gives the Grignard reagent (**15**);[24a] ultrasonication is beneficial.[25] Reagent (**15**) reacts with electrophiles very slowly, presumably due to internal coordination of magnesium by the dioxolane ring. Its reaction with cyclohexanones or even aldehydes (used in syntheses of several natural products)[26] typically requires several hours at 25 °C. The lithium reagent from (**1**), made using ***t-Butyllithium*** in THF-Et_2O-pentane at -95 °C, is more reactive than (**15**), and gives 1,2-addition to a hindered α,β-unsaturated ketone within 1 h at 25 °C.[27] For use with cyclopentanones or aromatic ketones, (**15**) is prepared in benzene-THF (2:1); even in this solvent, complete consumption of 6-methoxy-1-tetralone required 4 h. An α-oxo group was then introduced, giving (**17**),[24a,24d] a precursor of (**18**), previously prepared[28] by Robinson annulation of the relatively inaccessible 6-methoxy-2-tetralone (eq 4). A more direct procedure was devised where the α-oxygen function is present before attachment of the ketobutyl group. Thus, for example, treatment of 2-benzoyloxycyclohexanone with (**15**) gave (**21**) directly,[24b] presumably via hydride shift[24c] in (**20**) (cf. the Serini reaction).[29] These reactions are examples of annulations in which a 3-ketobutyl unit is attached to a ketone at the carbonyl carbon, rather than next to it (eq 5).

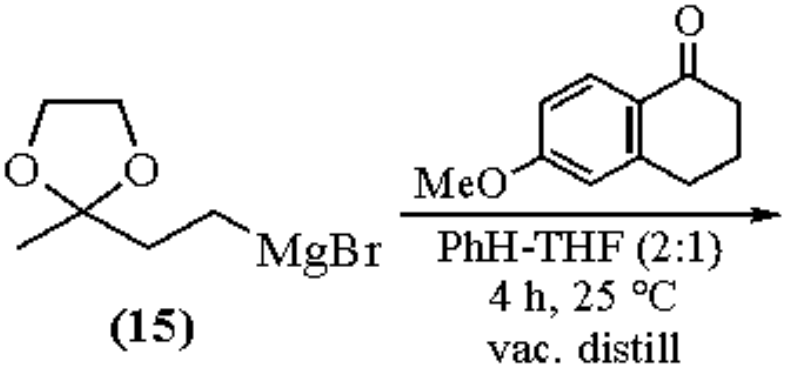

(15)

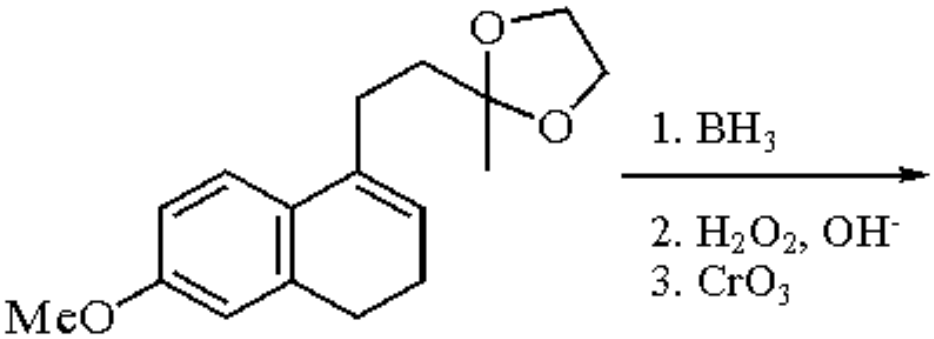

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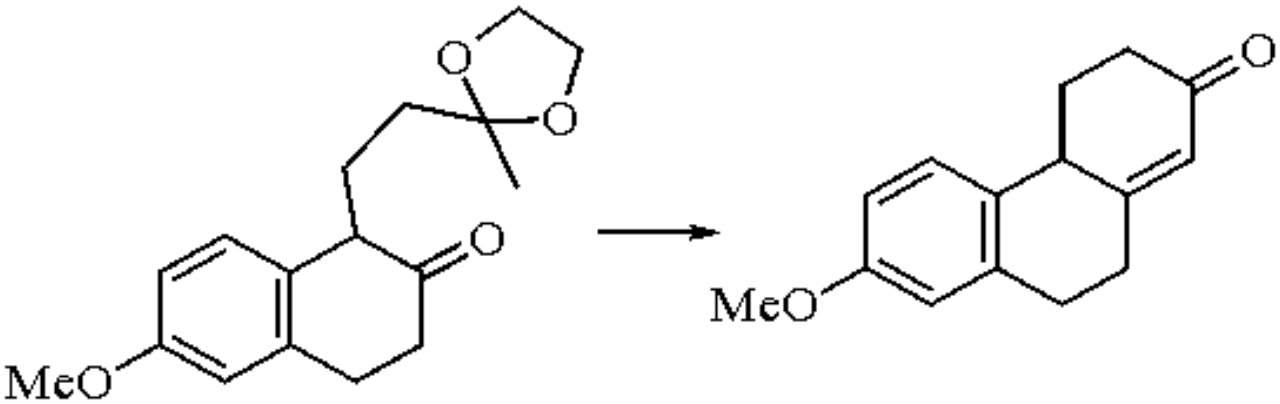

(4)

(17)

(18)
85% overall

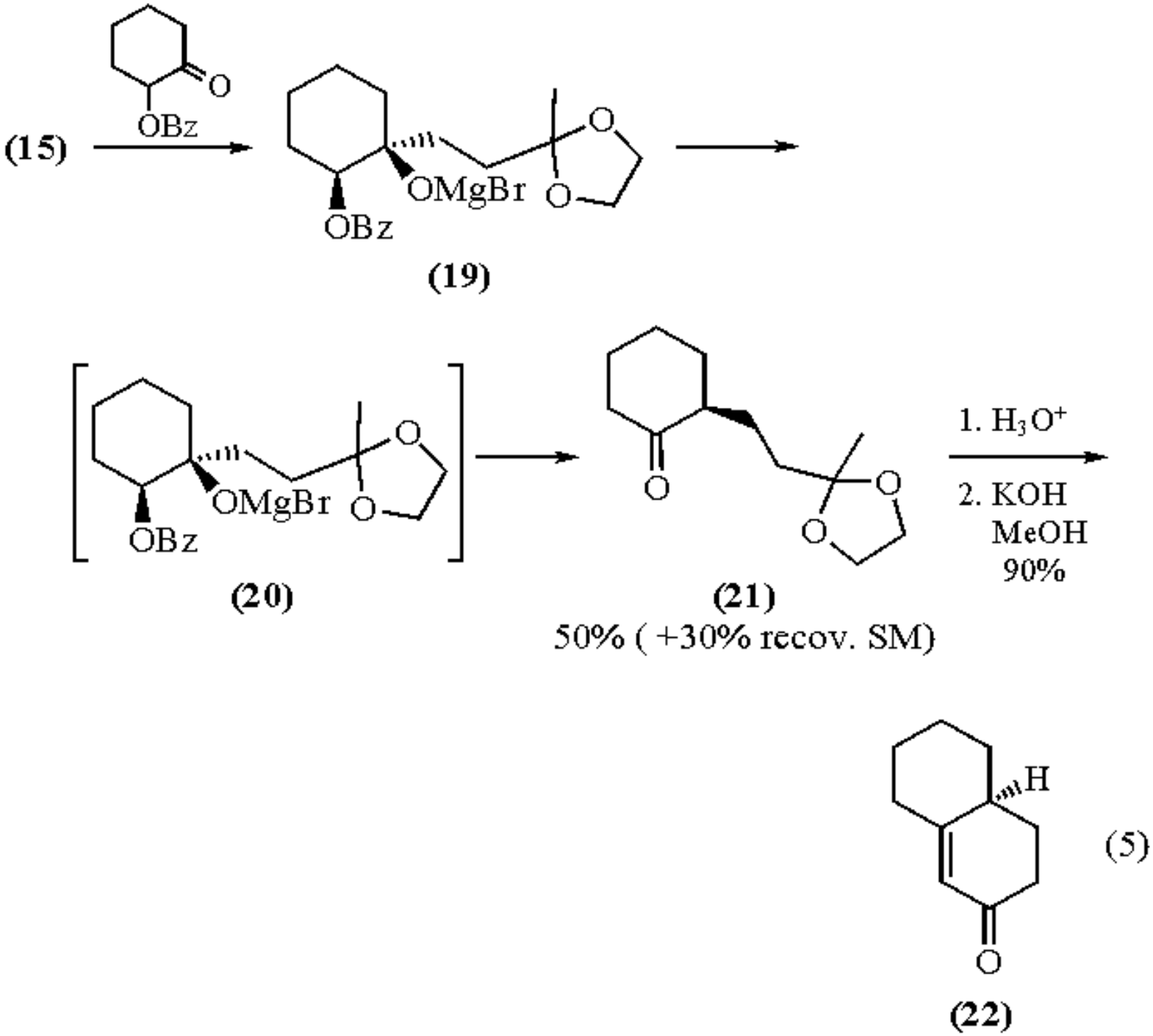

(5)

Several approaches to terpenes employ acid-catalyzed rearrangements in adducts between (**15**) and bicyclic alkoxyketones (eq 6).[25a,30]

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane

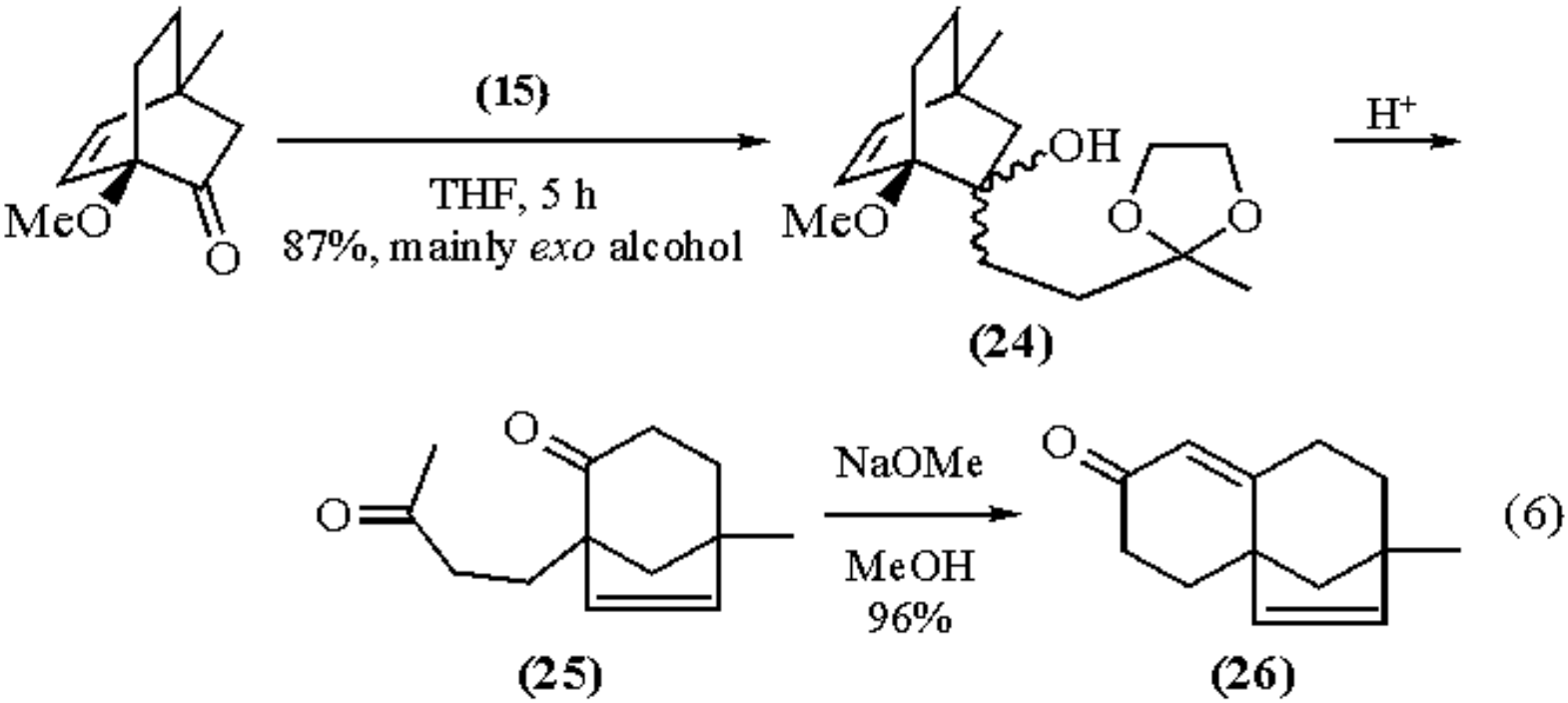

Ketones result from the reaction of (**15**) with acid chlorides at low temperatures;[24a] this idea is used in several syntheses of *cis*-jasmone (eq 7).[5e,31]

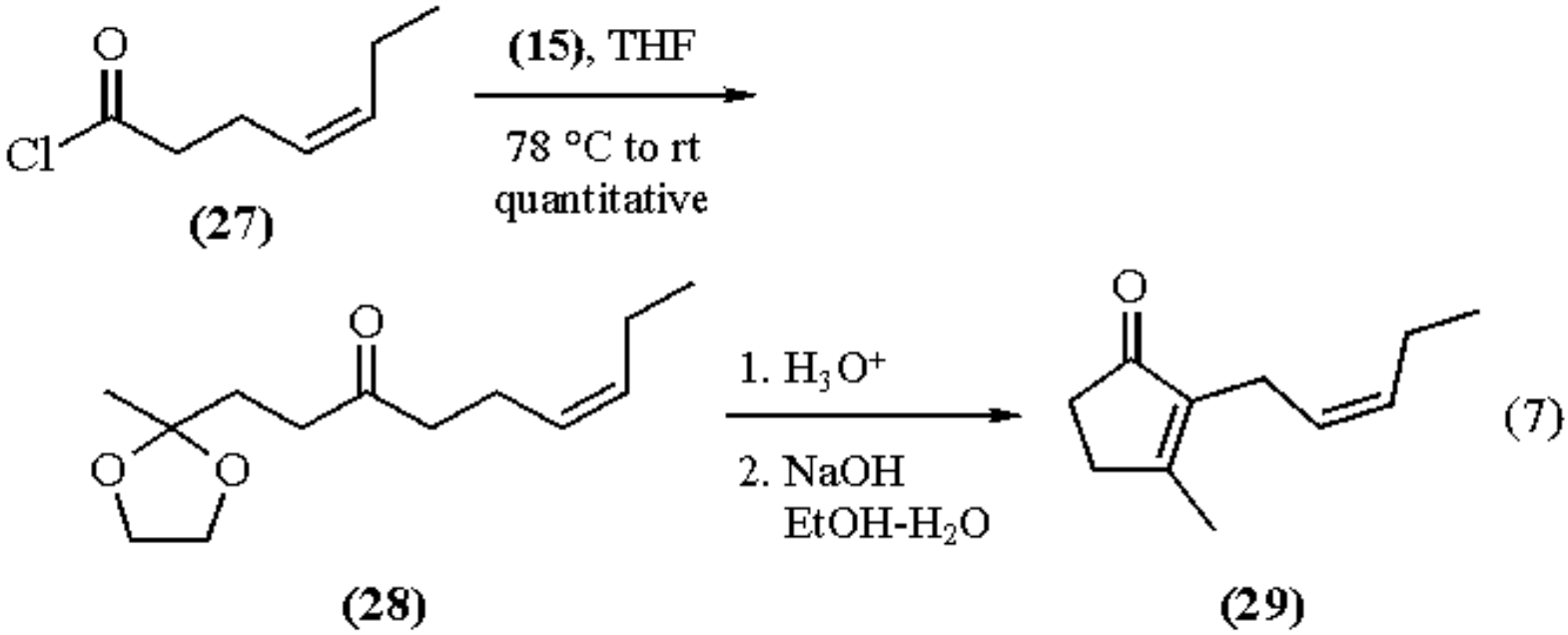

In the presence of copper(I) salts, (**15**) adds in conjugate fashion to α,β-unsaturated ketones[32a] and α,β-unsaturated lactones,[32b] leading to monoprotected 1,6-dicarbonyl compounds. This reaction has been used for annulation of a five-membered ring onto a preexisting ring (eq 8).[32a]

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane

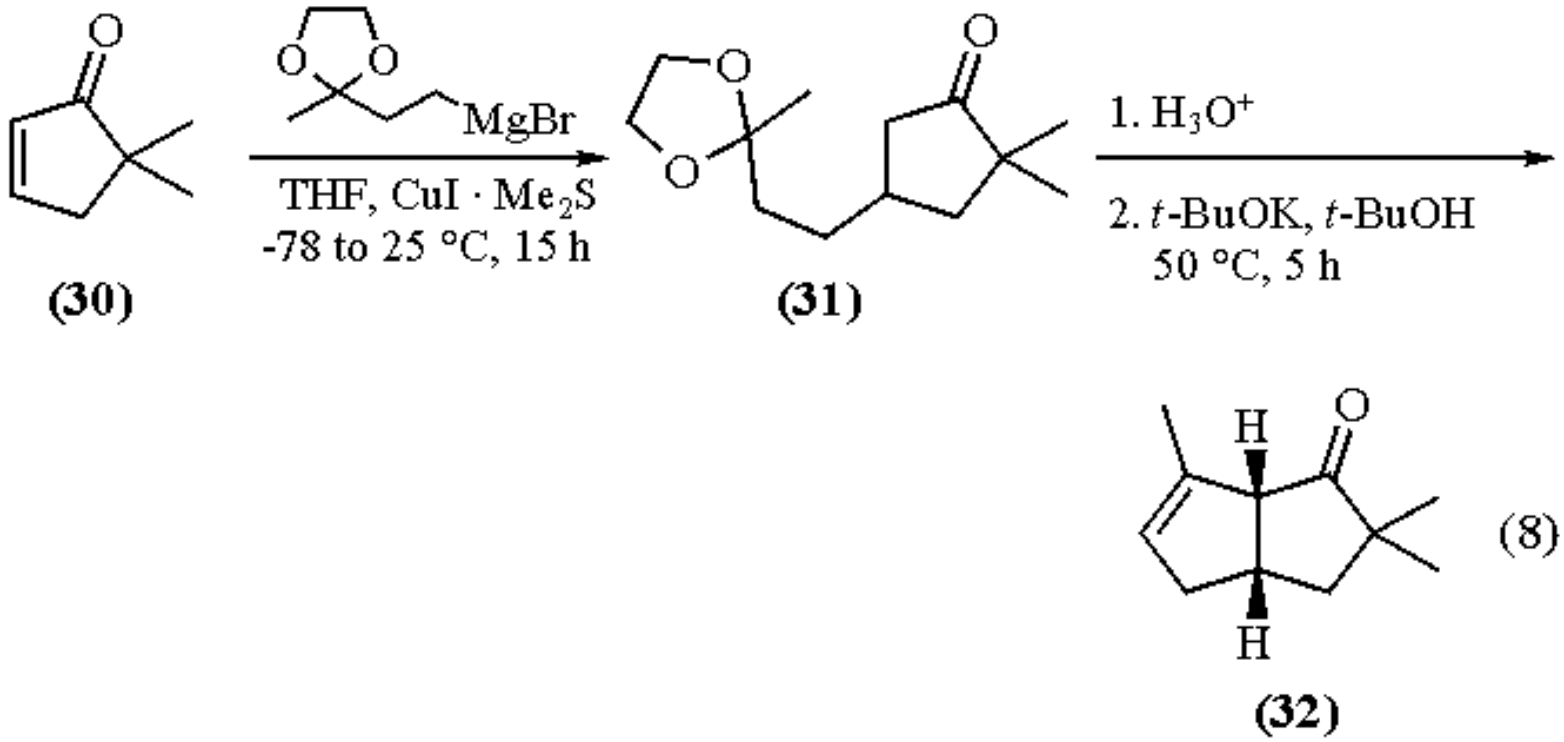

The Grignard reagent, in the presence of copper salts, has been used for nucleophilic substitution reactions with halides and sulfonate esters,[33] epoxides,[34] and β-lactones (alkyl-oxygen fission).[35]

Wittig reaction using the triphenylphosphonium salt from (**1**) (best prepared at 15 kbar pressure)[36] is employed in two syntheses of optically active brevicomins from carbohydrate-derived aldehydes.[37] The analogous diphenylphosphinyl carbanion also has synthetic utility for Wittig-Horner reactions.[38]

Related Reagents.

1-Bromo-2-iodo-2-butene; ***1,3-Dichloro-2-butene***; ***Methyl Vinyl Ketone***; ***3-Trimethylsilyl-3-buten-2-one***.

---

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9. The lithium salt of acetone dimethylhydrazone reacts with (**1**) or (**2**) to give 2,6-heptanedione 2-acetal 6-dimethylhydrazone in high yield: (a) Petersen, J. S.; Töteberg-Kanlan, S.; Rapoport, H. *JOC* **1984**, *49*, 2948. (b) Mitra, R. B.; Reddy, G. B. *S* **1989**, 694.
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2-Bromofluorobenzene[1]

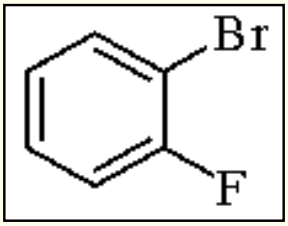

[1072-85-1] · C_6H_4BrF · 2-Bromofluorobenzene · (MW 175.00)

(starting material for coupling reactions; useful benzyne precursor)

Physical Data: bp 156-157 °C; bp 58-82 °C/50 mmHg; *d* 1.601 g cm^{-3}; *n*20D 1.5340.

Solubility: sol dichloromethane.

Form Supplied in: liquid; widely available.

Coupling Reactions.[1]

2-Bromofluorobenzene reacts with palladium in DMF containing ***Tri-n-butylamine*** to yield 2,2´-difluorobiphenyl (eq 1).[2]

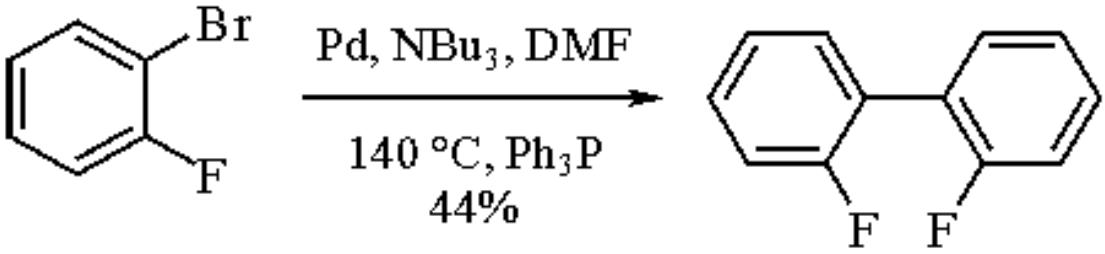

(1)

Ullmann-type Coupling.

2-Bromofluorobenzene can be coupled with amines using a copper catalyst (eq 2).[3]

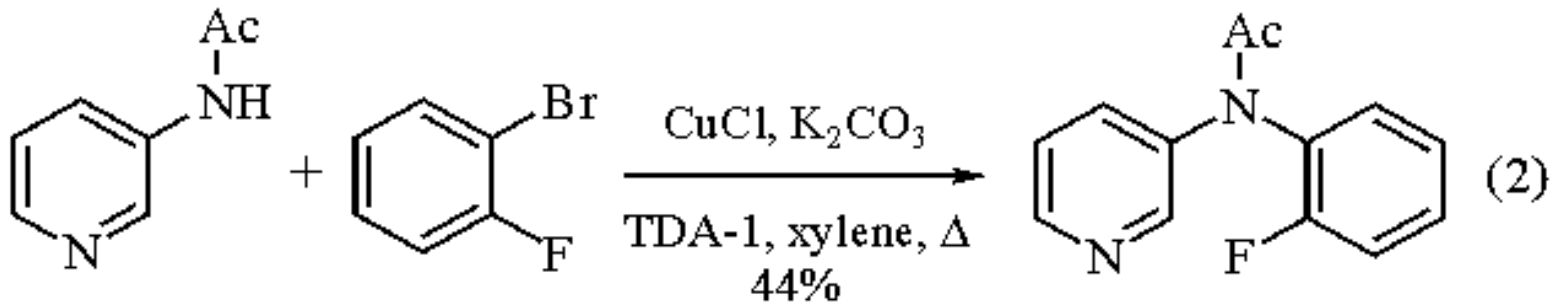

Generation of Benzyne.[4]

Benzyne can be generated by treatment of 2-bromofluorobenzene with lithium amalgam or ***Magnesium***(eq 3). This procedure for benzyne generation has been used for the synthesis of bridged polycyclic molecules such as triptycene (eq 4).[5]

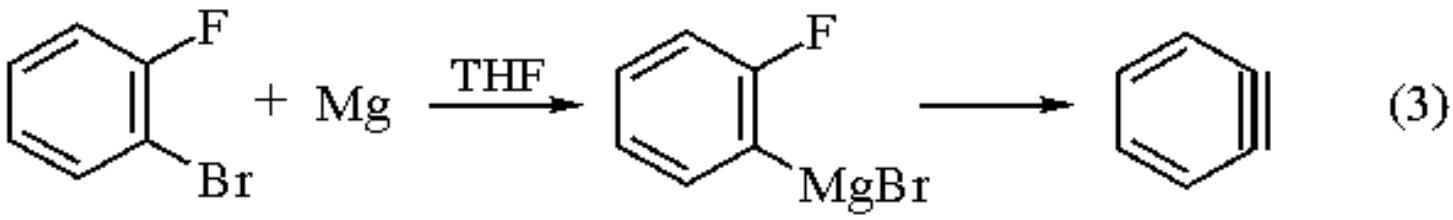

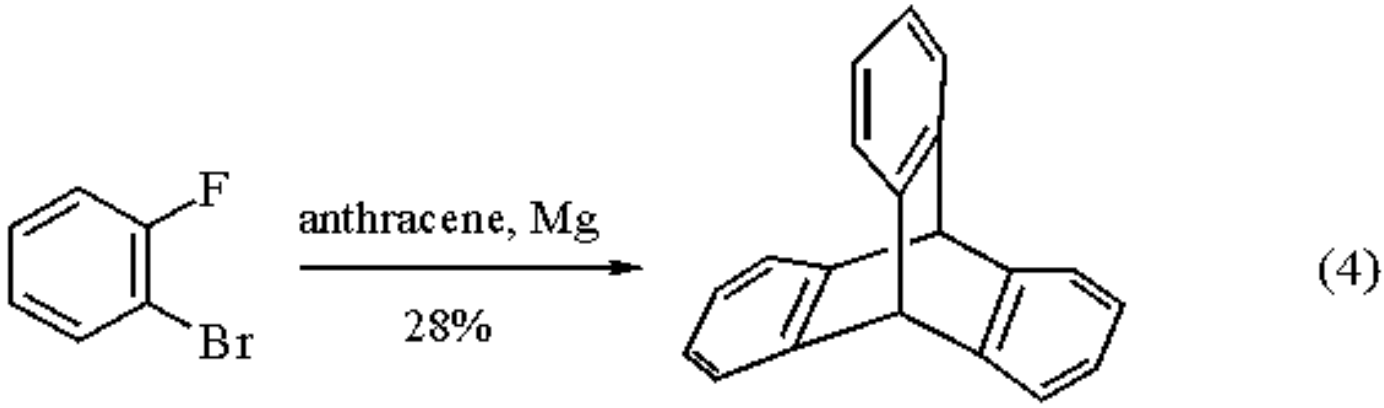

An alternative procedure for the generation of benzyne is based on the use of ***n-Butyllithium***. Under these conditions, benzyne reacts with pyrroles in a [4 + 2] cycloaddition (eq 5).[6]

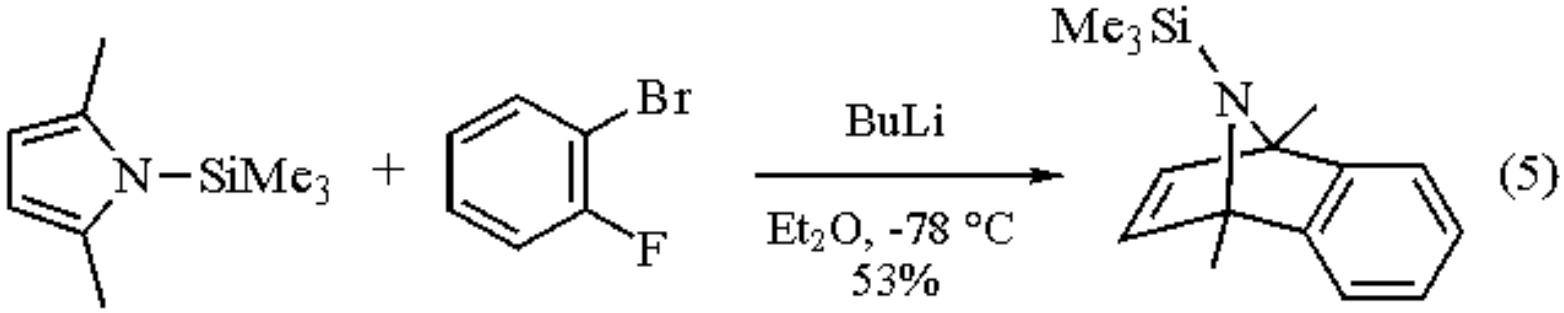

Very efficient cycloaddition occurs when benzyne is generated from 2-bromofluorobenzene and magnesium in the presence of a furan. This method has been applied to the synthesis of analogs of the antitumor agent ellipticine (eq 6).[7]

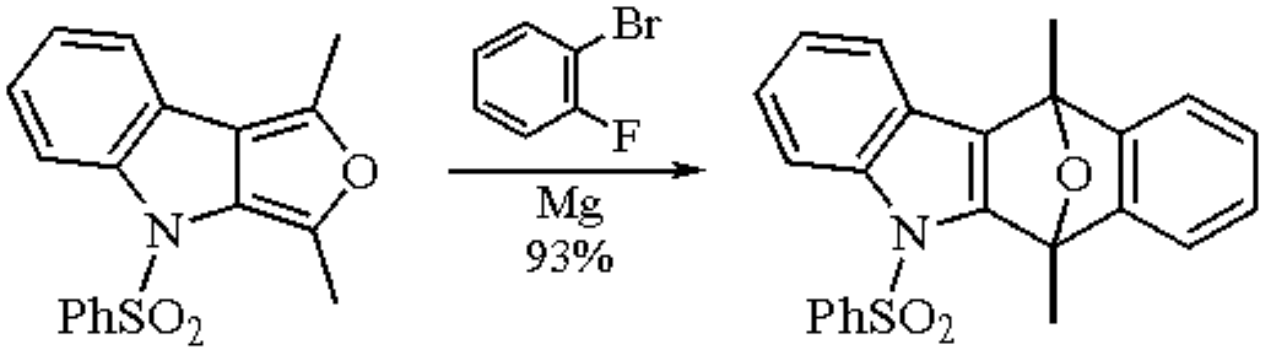

(6)

Benzyne generated by the same procedure has reacted with isoindoles to yield dibenzoazanorbornanes (eq 7).[8]

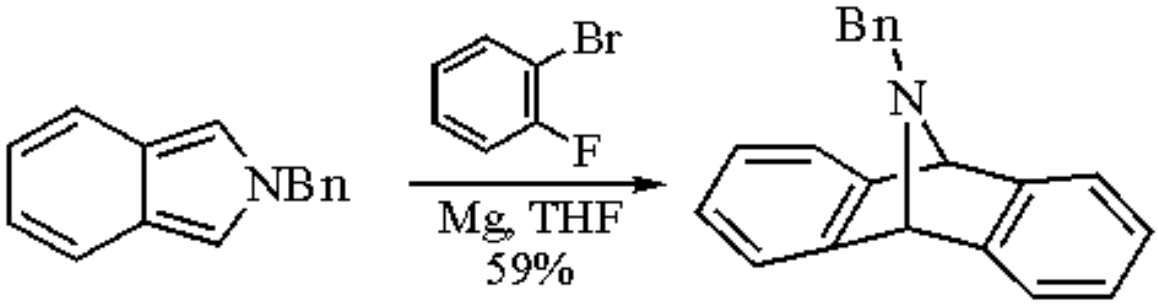

(7)

Germacyclopentadienes react with benzyne to afford dibenzogermanorbornanes (eq 8).[9] Silacyclopentadienes react with benzyne similarly (eq 9).[10]

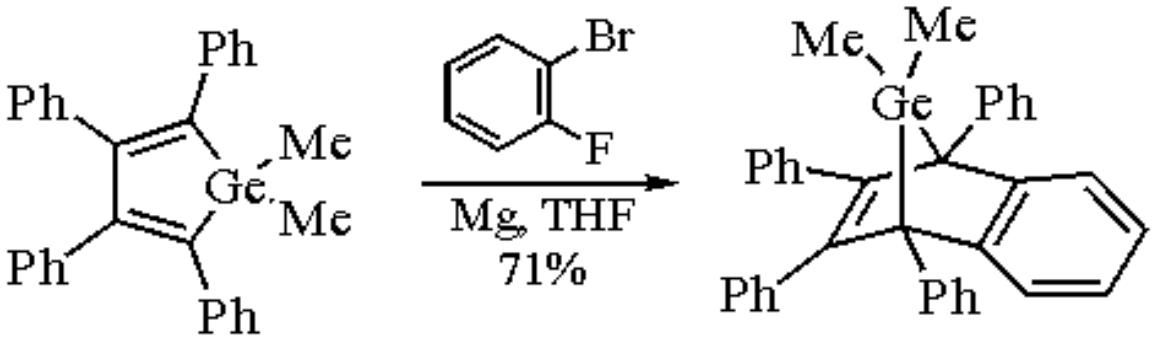

(8)

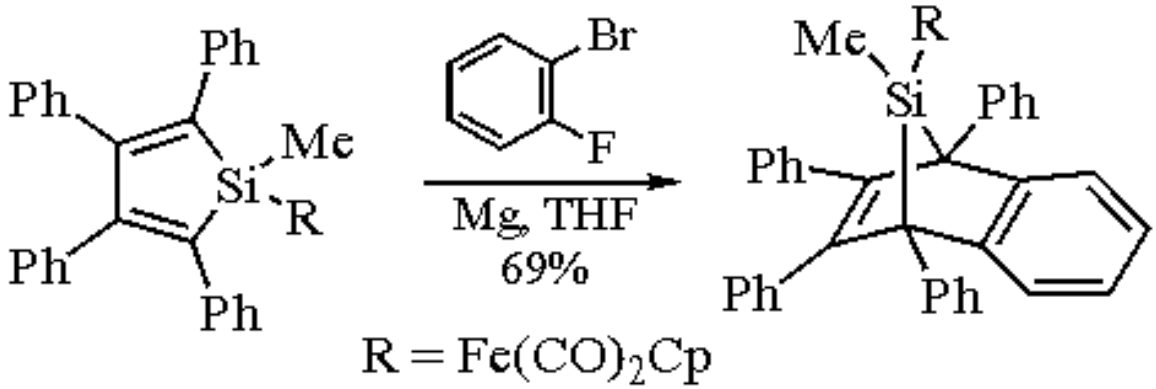

(9)

Related Reagents.

2-Bromoiodobenzene.

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Bromoform

$CHBr_3$

[75-25-2] · $CHBr_3$ · Bromoform · (MW 252.73)

(used in the synthesis of mono- and dibromocyclopropanes,[1] allenes[2] and cumulenes,[3] cyclopentadienes and fulvenes, α- and β-bromo-α,β-unsaturated carbonyl compounds, 1,1,3-tribromides, tribromomethyllithium carbonyl adducts, isocyanides,[4] α-hydroxy and α-aminoaryl acetic acids)

Alternate Name: tribromomethane.

Physical Data: mp 8.5 °C; bp 146-150 °C; *d* 2.827 g cm^{-3}.

Solubility: sol acetone, benzene, chloroform, ethanol, ether, petroleum ether.

Form Supplied in: commercially available with inhibitors present.

Analysis of Reagent Purity: technical (94%) and high purity (99+%).

Preparative Method: by reaction of acetone with sodium hypobromite.

Purification: wash with concentrated sulfuric acid and then water. The liquid is dried over $CaCl_2$ or K_2CO_3 then fractionally distilled.

Handling, Storage, and Precautions: store in closed containers away from light. Diphenylamine and ethanol are commonly used inhibitors. Do not breathe vapors as addiction may occur. Suspected cancer agent; lachrymator. Use in a fume hood.

Dibromocyclopropanes.[5]

Bromoform is a routinely used precursor to dibromocarbene which can be generated by many different methods (eq 1).[6] Dibromocarbene adds stereospecifically to alkenes[7] and its reactivity towards alkyl substituted alkenes is analogous to that of dichlorocarbene: tetrasubstituted > trisubstituted > unsymmetrical disubstituted > symmetrical disubstituted > monosubstituted alkenes.[8] Dibromocarbene has been prepared by treatment of bromoform with ***Potassium t-Butoxide***.[9] The yields of dibromocyclopropanes obtained using this method are typically no more than 70% for good cases and are usually lower. For example, reaction of cyclooctene with bromoform and potassium *t*-butoxide gave a 52-65% yield of dibromide (eq 2).[10] Dibromocarbene has also been generated by adsorbing a mixture of alkene and bromoform on basic

Alumina.[11] At elevated temperatures, ***Potassium Carbonate*** can generate dibromocarbene from bromoform in the presence of ***18-Crown-6***. Cycloheptatriene at 140 °C with these reagents gave 1-bromobenzocyclobutane in 18-45% yield (eq 3).[12]

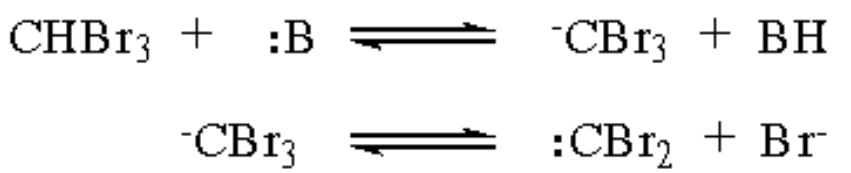

(1)

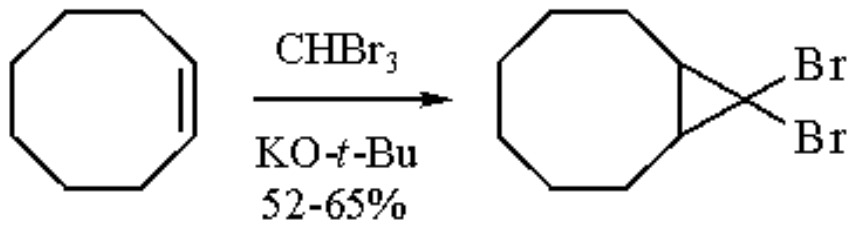

(2)

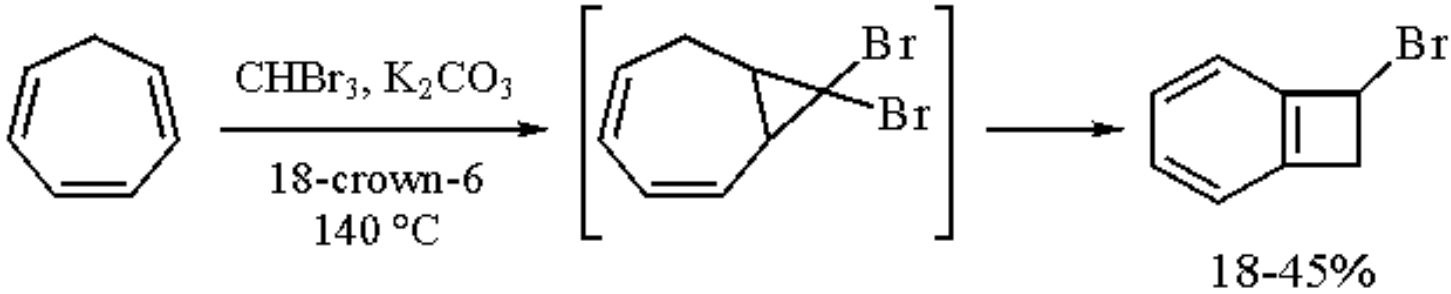

(3)

A significant improvement in the rate and yield of halocyclopropanes is realized if phase transfer catalysts[13] like triethylbenzylammonium chloride are used.[14] Yields for dibromocyclopropanes, however, while generally less than 50%, can be somewhat improved if a considerable excess of bromoform and 24-96 h reaction times are used.[15] Addition of a small amount of ethanol to the reaction mixture often results in 10-30% increase in the yield of dibromocyclopropanes. In a typical procedure, 50% aqueous NaOH is added over 10 min to a stirred mixture of bromoform, alkene, triethylbenzylammonium chloride (TEBA) and a small amount of ethanol at 40-45 °C. After 3 h at the same temperature the mixture is diluted with dichloromethane and poured into water. An extractive work-up and concentration of the organic phases provides the crude product which is typically purified by distillation. For this method a two- to three-fold molar excess of bromoform to alkene or the converse is ordinarily used.[16]

It has been observed that the nature of the phase transfer catalyst (PTC) can have a profound effect on the yield of product obtained.[17] For example, reaction of allylic bromides with bromoform can give either cyclopropanes or substitution products depending on the type of catalyst used (eq 4). When the phase transfer catalyst cetrimide [$(C_{16}H_{33})NMe_3Br$] is used, the cyclopropane product predominates. The product ratio is reversed when tetraphenylarsonium chloride (Ph_4AsCl) is used as the catalyst and the substitution pathway is preferred.[18] When α,β-unsaturated carbonyls are used, the choice of phase transfer catalyst also impacts the product distribution obtained between the cyclopropyl product and that of Michael addition.[19] For systems where only ring formation is expected, the reaction selectivities between different alkenes are not affected by alteration of the phase transfer catalyst.[20] The use of an optically active phase transfer catalyst has led to unprecedented but low levels of asymmetric induction.[21]

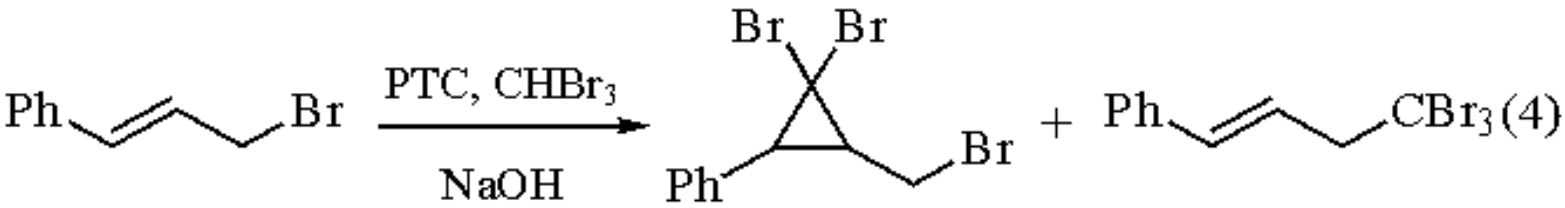

PTC	Product ratio cyclopropane:substitution
cetrimide	92:1
Ph_4AsCl	1:91

Dibromocarbene is also made via Seyferth's reagent.[22] The reagent, ***Phenyl(tribromomethyl)mercury***, is typically prepared from bromoform, a phenylmercury(II) halide, and potassium *t*-butoxide.[23] Another procedure for the synthesis of phenyl(tribromomethyl)mercury[24] using a phase transfer catalyst, ***Potassium Fluoride***, and ***Sodium Hydroxide*** has also been reported.[25] Using these types of methods, the carbene is released with elimination of phenylmercury(II) halide.[26] The ring expansion of 1-methylindenes into 3-bromo-1-methylnaphthalenes is accomplished in moderate yields (~55%) by reaction of the dibromocarbene released from this type of mercury reagent (eq 5). The same reaction using bromoform/potassium *t*-butoxide gave a 2-bromo-1-methylnaphthalene in only 14% yield.[27] An alternative to other straightforward syntheses of monobromocyclopropanes[28] from alkenes (eq 6) uses ***Diethylzinc-Bromoform-Oxygen***.[29]

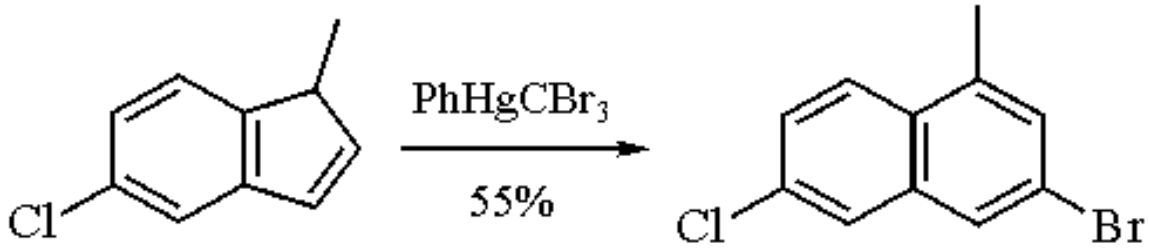

(5)

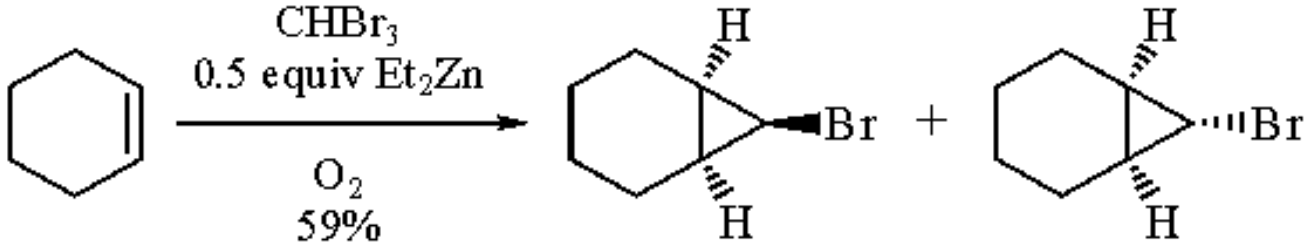

(6)

syn:*anti* = 62:38

Once having obtained the dibromocyclopropanes resulting from addition of dibromocarbene to different types of double bonds, chemists have been able to prepare a myriad of different structures (see also ***Chloroform*** and ***Iodoform***).

Allenes and Cumulenes.

Allenes have been prepared by reaction of dibromocyclopropanes with ***Magnesium***, but in low yield.[30] The use of

alkyllithiums leads to improved yields with ***Methyllithium*** being the reagent of choice.[31] 9,9-Dibromobicyclo[6.1.0]nonane is converted to 1,2-cyclononadiene with methyllithium (eq 7)[10,32,33] while the lower homolog, 8,8-dibromobicyclo[5.1.0]octane, leads to a complex mixture of products.[34] This is due, in large part, to intramolecular carbenoid insertions competing with allene formation. This property has been used to gain entry into the tricyclo[4.1.0.0^{2,7}]heptene ring system (eq 8).[35]

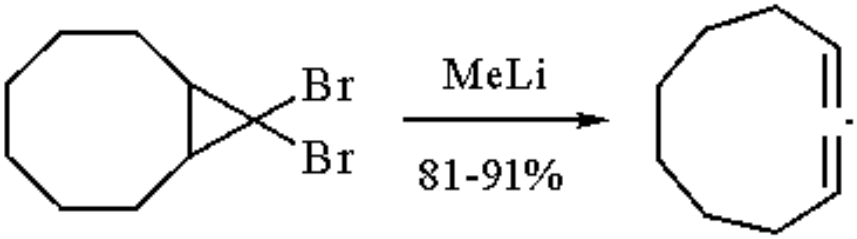

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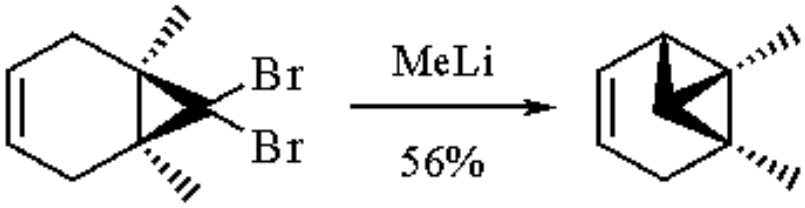

(8)

Reaction of dibromocarbene with allenes leads to cumulenes upon treatment of the intermediate dibromocyclopropane with methyllithium.[36,37] An example of the utility of this approach is shown in eq 9.[38,39]

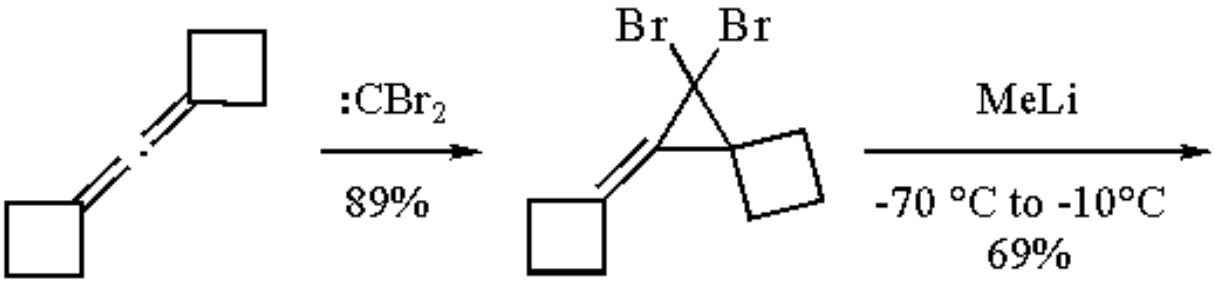

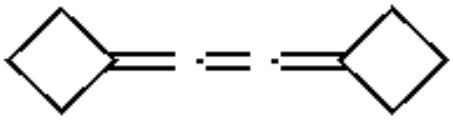

(9)

Cyclopentadienes and Fulvenes.

The Skattebøl rearrangement occurs when conjugated dienes are converted into 1,1-dibromo-2-vinylcyclopropanes and then treated with MeLi at -78 °C. The major products are typically cyclopentadienes with small amounts of vinylallenes (eq 10). The ratio of products vary with the substitution on the starting vinylcyclopropane.[40] An example of the Skattebøl rearrangement in the synthesis of an optically active cyclopentadiene is shown in eq 11.[41,42]

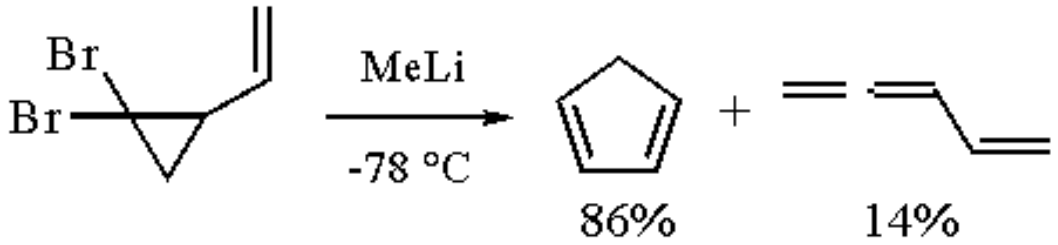

(10)

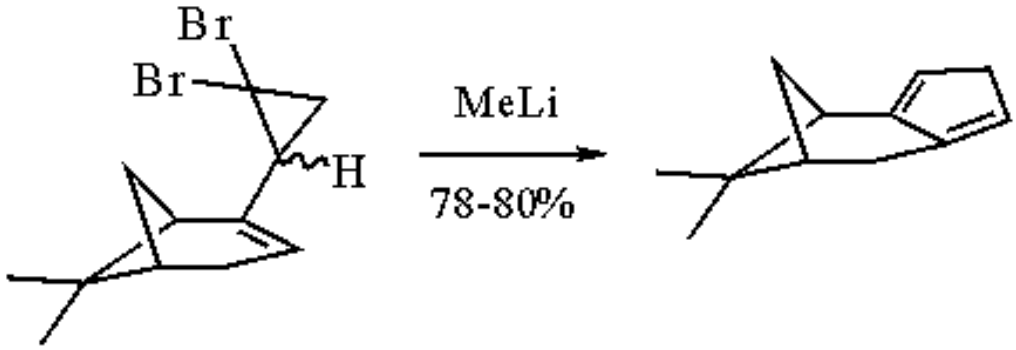

(11)

Similar treatment of 3,3,3´3´-tetramethyl-2,2,2´,2´-tetrabromobicyclopropyl with methyllithium yields a diallene as the major product (eq 12). When the dimethylbicyclopropyl analog is used, a fulvene is the major product with a diallene being a minor product (eq 13). This change in product distribution is believed to result from the difference in rates of allene formation versus that of rearrangement to a cyclopentylcarbene.[40,43]

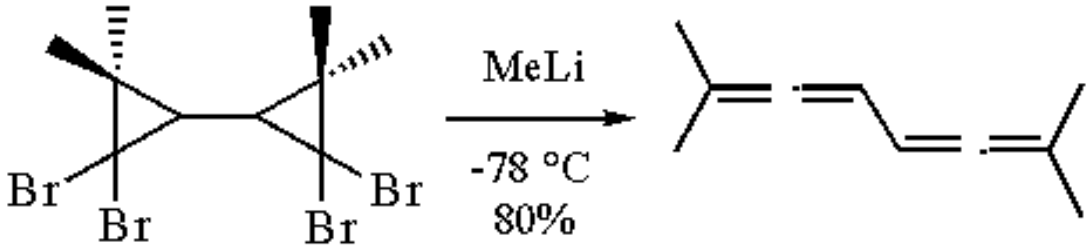

(12)

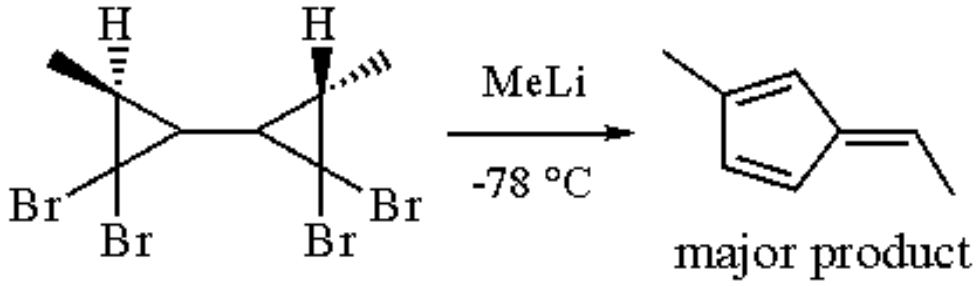

(13)

α-Bromo-α,β-Unsaturated Carbonyl Compounds.

Addition of dibromocarbene to a silyl enol ether has been shown to generate α-bromo-α,β-unsaturated carbonyl compounds after thermal or acid-catalyzed rearrangement of the intermediate dibromocyclopropane (eq 14).[44,45]

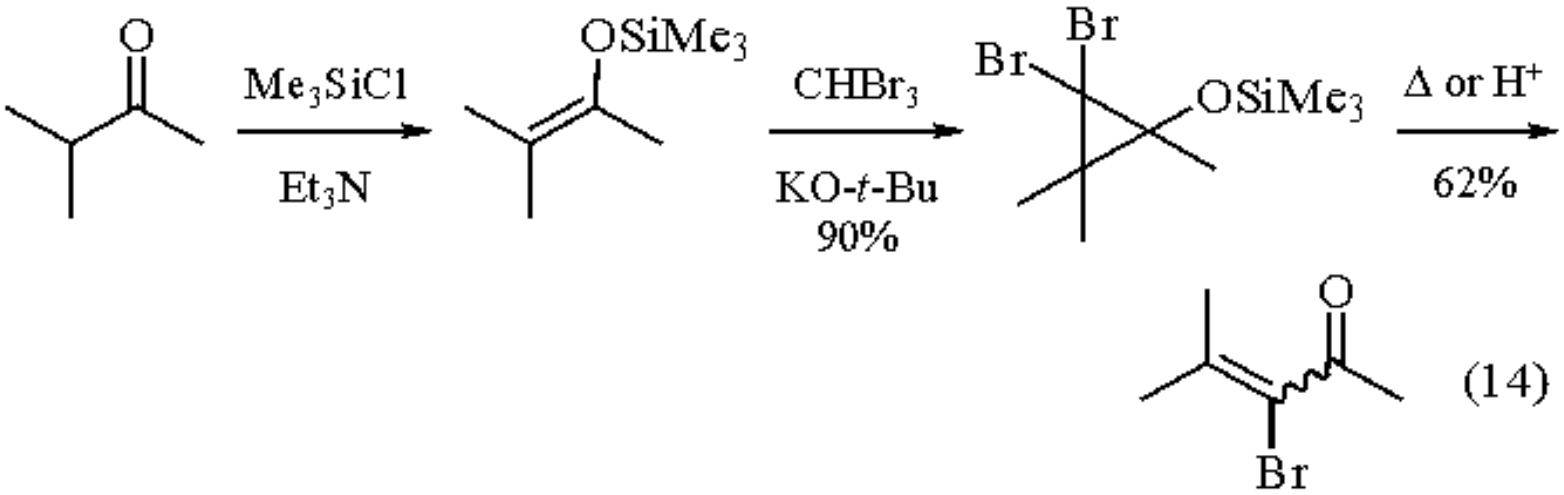

(14)

β-Bromo-α,β-Unsaturated Esters.

Reaction of unsubstituted ketene trialkylsilyl acetals with bromoform and a catalytic amount of ***Triethylborane*** affords 3-bromoacrylate (eq 15). The same conditions using a substituted ketene acetal provides a 2-dibromomethyl ester (eq 16).[46]

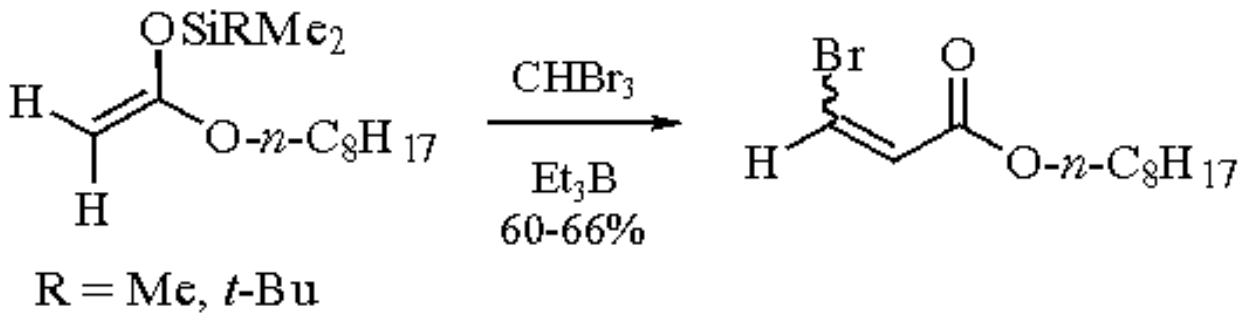

(15)

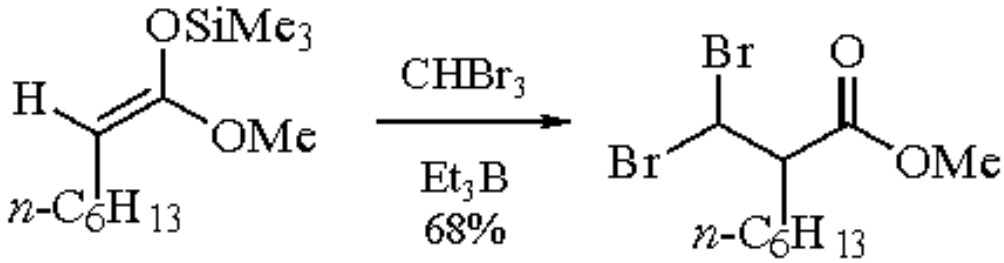

(16)

1,1,3-Tribromides.

Unlike chloroform, which adds under radical conditions across the double bond through the C-H bond,[47] bromoform typically reacts through one of the C-Br bonds (eq 17),[48] although mixtures of products are often obtained.[49]

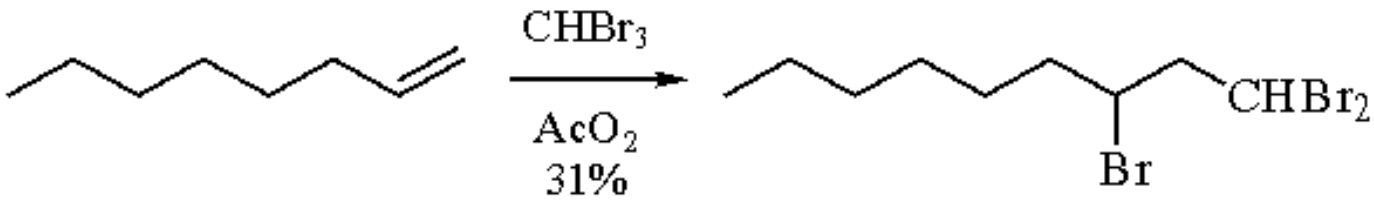

(17)

Tribromomethyllithium.

Bromoform is converted in situ into ***Tribromomethyllithium*** upon treatment with lithium dicyclohexylamide. The anion reacts with cyclohexanone to afford the corresponding tribromomethyl alcohol (eq 18).[50]

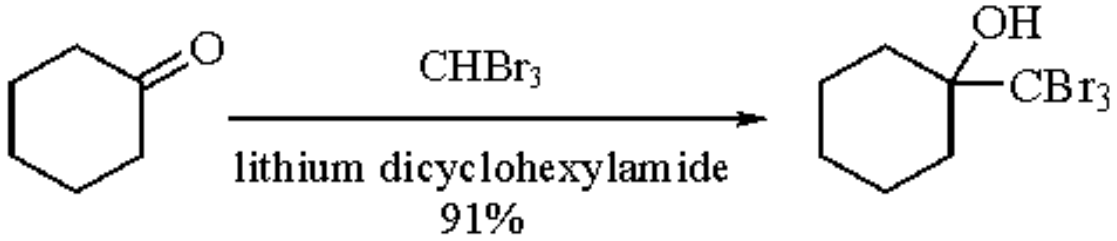

(18)

Isocyanides.

The use of phase transfer catalysis in the Hofmann isocyanide synthesis[51] is reported to result in improved yields.[52] Either chloroform or bromoform can be used. Bromoform is often used in the preparation of low-boiling isocyanides since the products can be easily removed from the reaction mixture (eq 19).

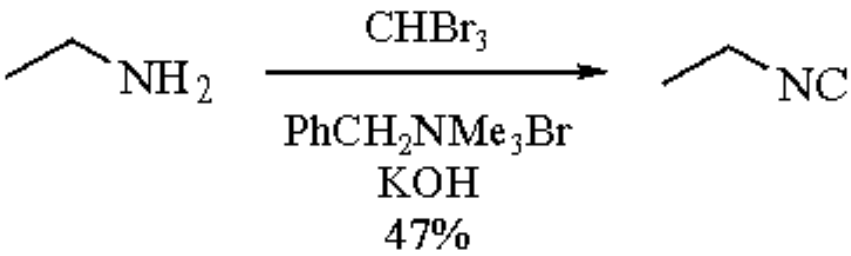

(19)

α-Hydroxyarylacetic and α-Aminoarylacetic Acids.

A one-pot synthesis of α-hydroxyarylacetic acids from bromoform, an aryl aldehyde, and ***Potassium Hydroxide*** occurs with ***Lithium Chloride*** as catalyst (eq 20).[53] By a similar process, α-aminoarylacetic acids can be made using bromoform, an aryl aldehyde, and ***Ammonia*** with potassium hydroxide and ***Lithium Amide*** as catalyst. This method reportedly gives higher yields than other single-pot procedures.[54]

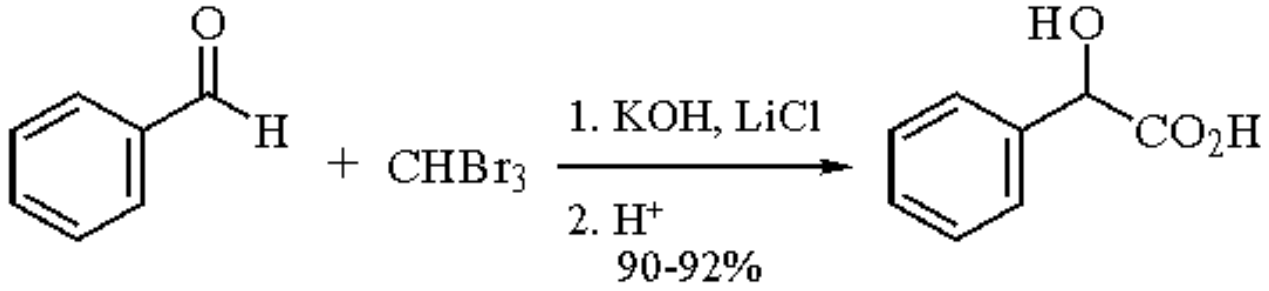

(20)

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2-Bromoiodobenzene

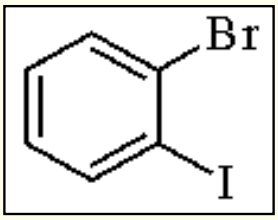

[583-55-1] · C_6H_4BrI · 2-Bromoiodobenzene · (MW 282.91)

(starting material for coupling reactions; useful benzyne precursor)

Physical Data: mp 9-10 °C; bp 257 °C/754 mmHg; 120-121 °C/15 mmHg; *d* 2.257 g cm^{-3}; *n*20D 1.6618.

Solubility: sol acetone.

Form Supplied in: liquid; widely available, sometimes stabilized with copper.

Coupling Reactions.

2-Bromoiodobenzene selectively couples with arenes,[1] alkenes,[1] and alkynes[2] to afford *ortho*-substituted bromobenzenes in which the bromine atom can be used for further synthetic manipulation.

Suzuki Coupling.[3]

2-Bromoiodobenzene has been coupled with phenylboronic acids to afford biaryls using ***Tetrakis(triphenylphosphine)palladium(0)*** as catalyst (eq 1).[4]

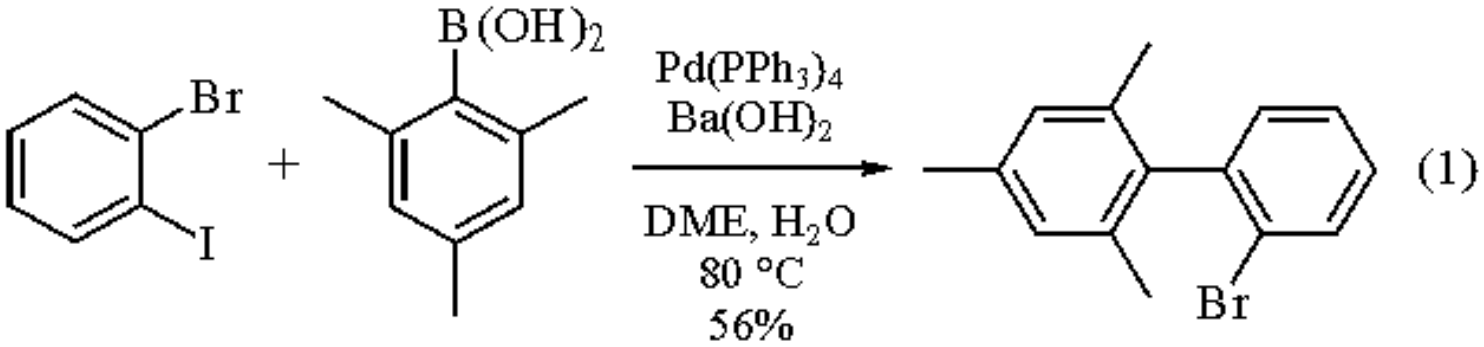

Castro Coupling.[5]

Coupling of 2-bromoiodobenzene with ***Phenylethynylcopper(I)*** yields a (phenylalkynyl)arene (eq 2).[6]

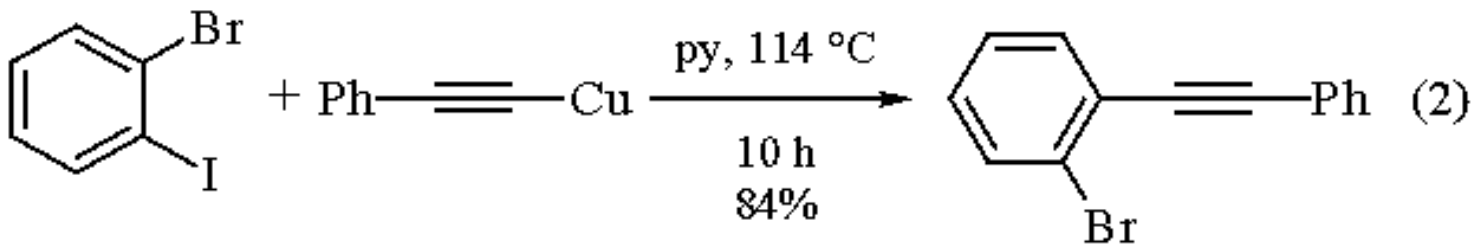

Heck Reaction.[7]

Palladium(II) Acetate-catalyzed coupling of 2-bromoiodobenzene with ***Acrylic Acid*** leads to 2-bromocinnamic acid (eq 3).[8]

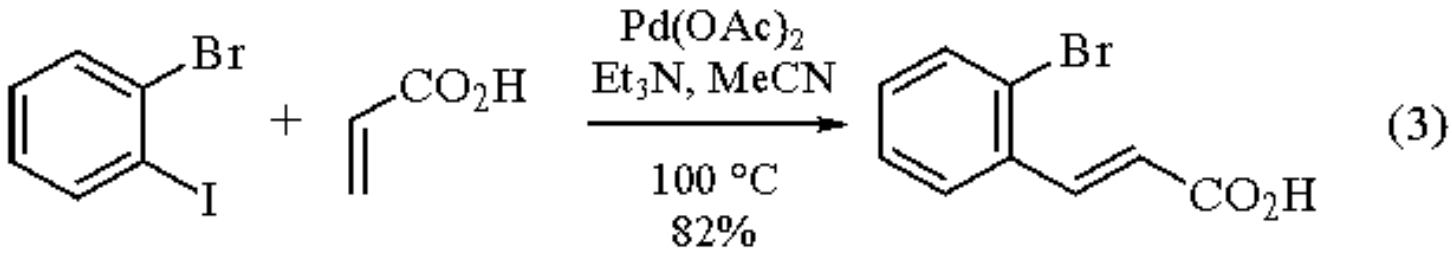

Coupling with vinylzinc derivatives has also been reported.[9]

Coupling with allylsilanes often presents problems as a result of a lack of regioselectivity. However, a regioselective palladium-catalyzed coupling with allyltrifluorosilanes has been achieved (eq 4).[10]

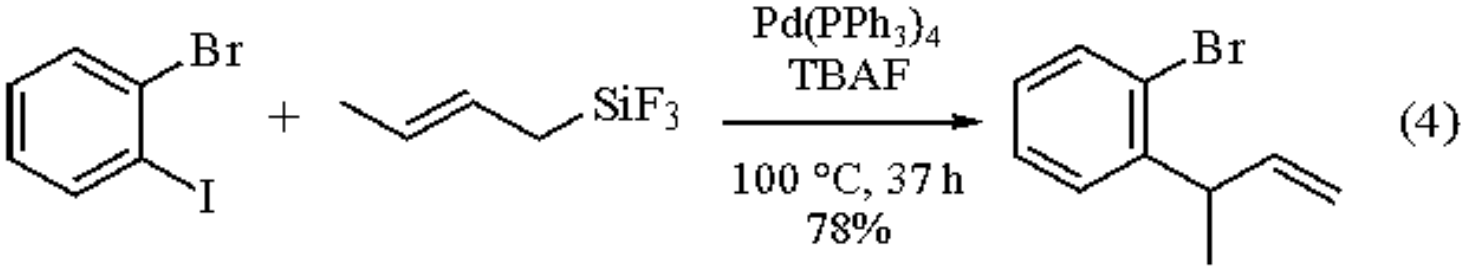

Eq 5 shows the synthetic potential of this reaction.[11] Coupling of 2-bromoiodobenzene with ***Trimethylsilylacetylene***, followed by lithium-bromine exchange with ***n-Butyllithium***, reaction with the monoacetal of *p*-quinone, desilylation, and treatment with base, afforded a spirovinyl ether.

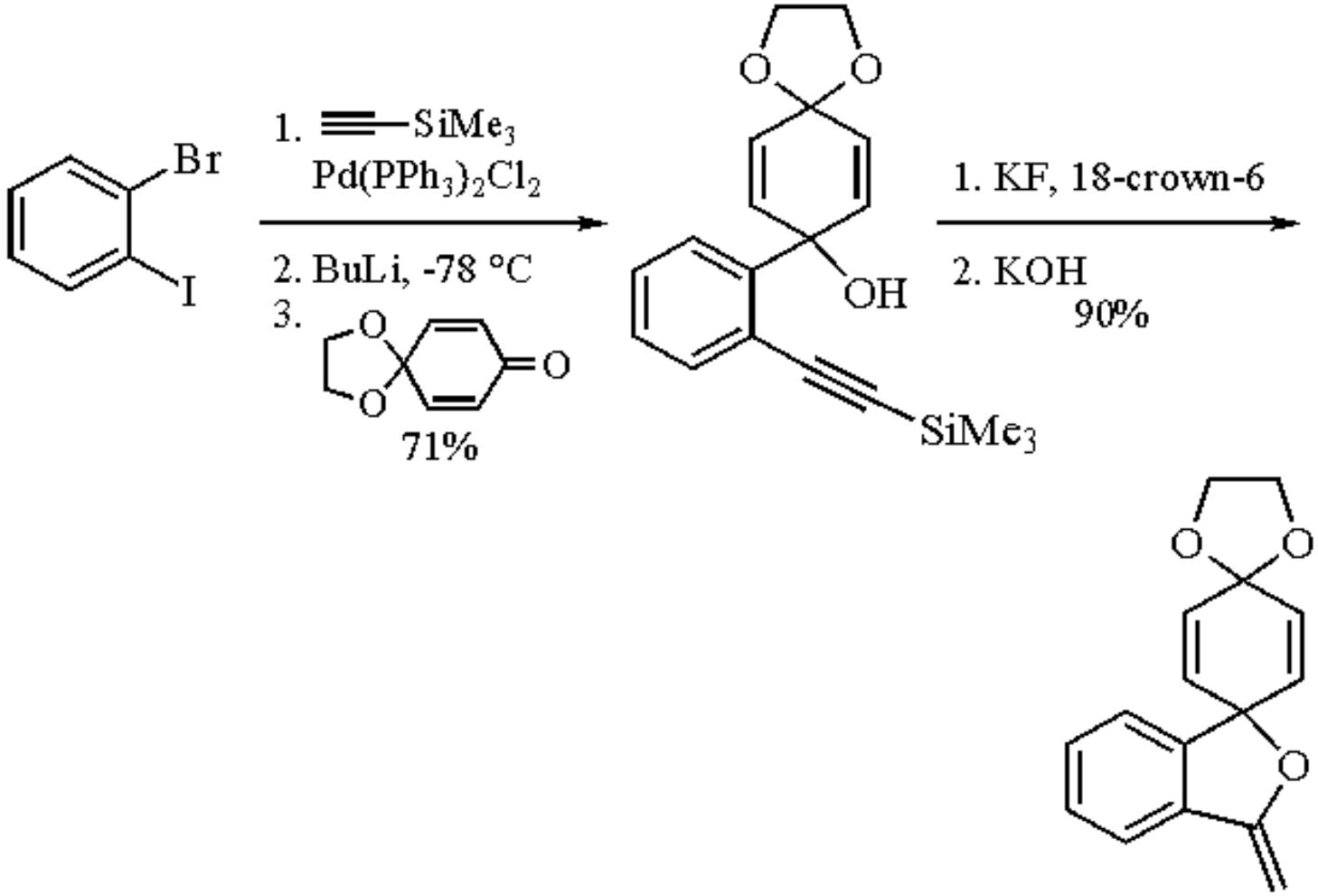

(5)

The different selectivities of the two halogens allows stepwise selective coupling. An application to the synthesis of angular phenylenes has recently been developed (eq 6).[12]

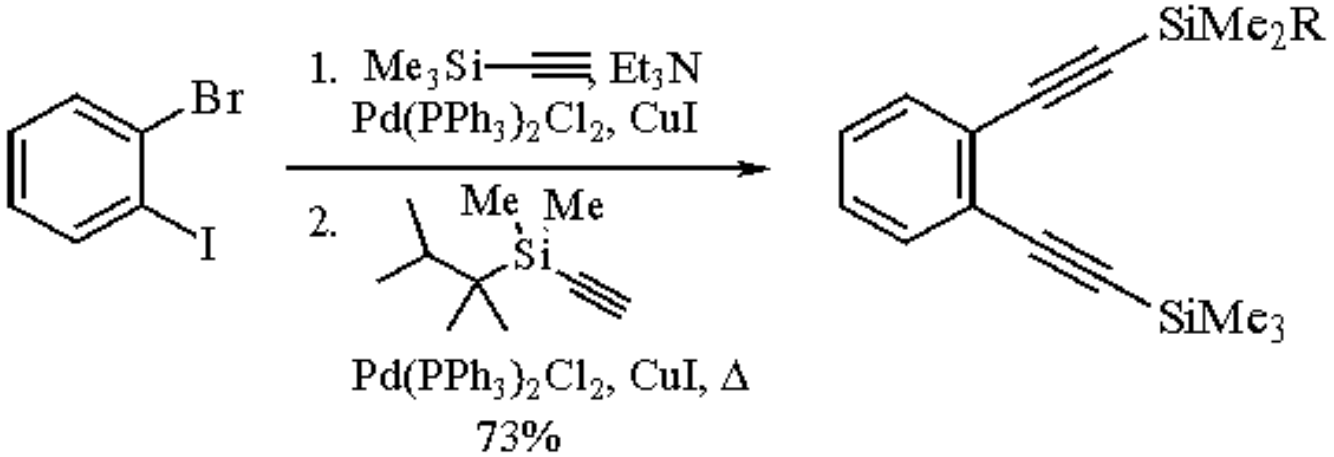

(6)

The same strategy has been used for the synthesis of a leukotriene analog (eq 7).[13]

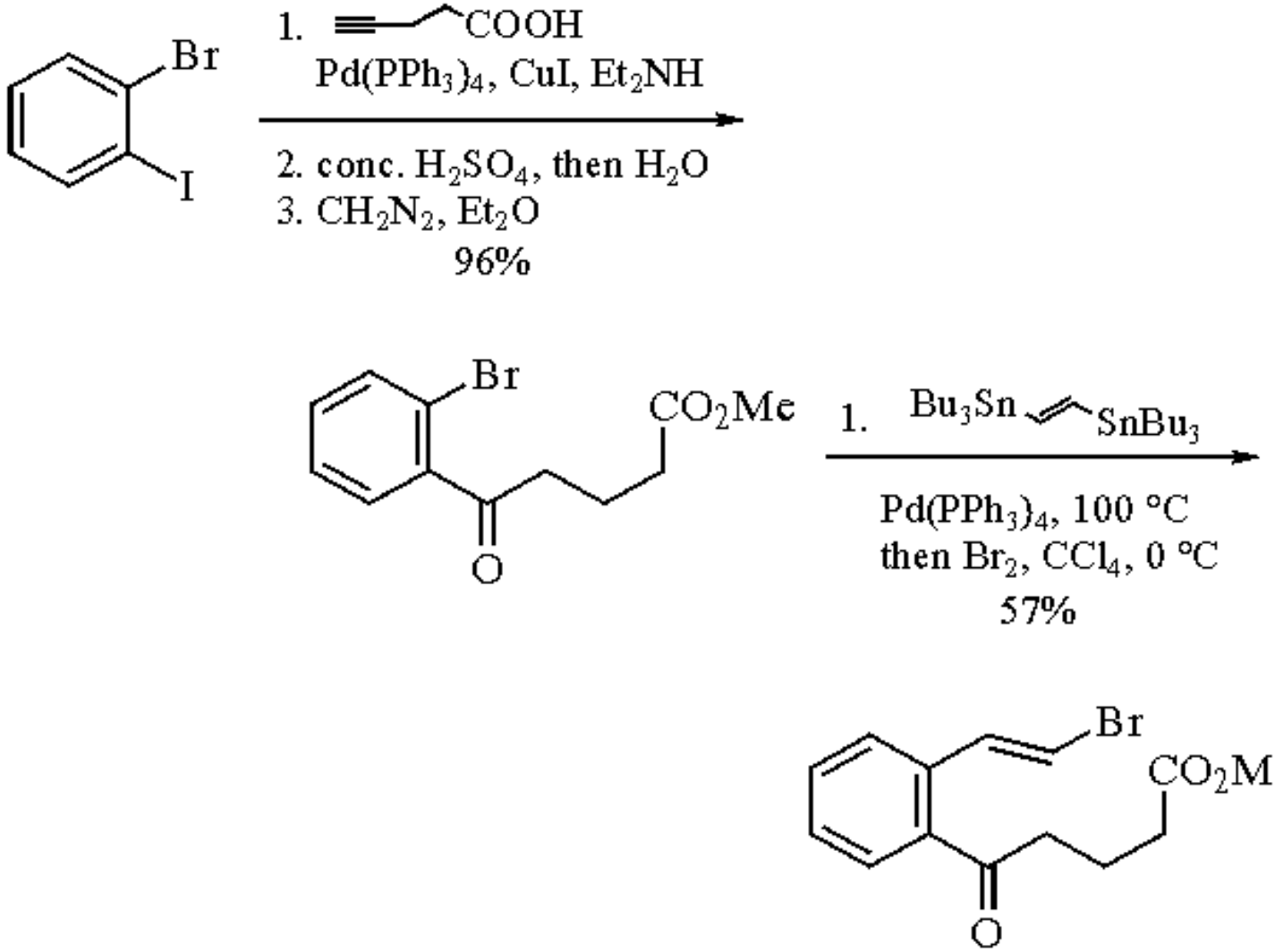

Generation of Benzyne.[14]

Treatment of 2-bromoiodobenzene with metallic ***Lithium*** in ether affords benzyne (eq 8),[15] which in the absence of a trapping agent trimerizes to triphenylene.[15]

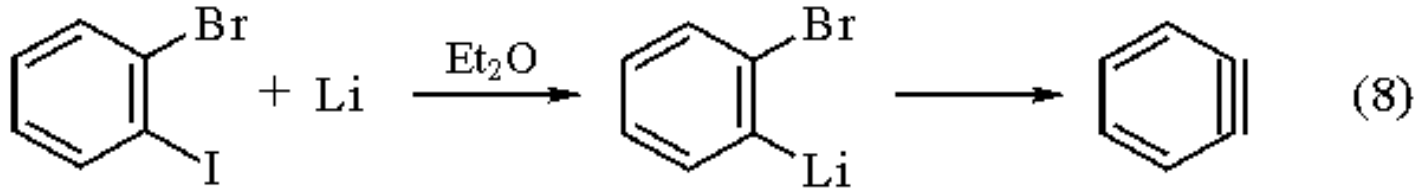

Benzyne can also be generated by treatment of 2-bromoiodobenzene with a Grignard reagent. Nucleophilic addition of a second equiv of the Grignard reagent to benzyne affords an arylmagnesium bromide which can be reacted with an allyl halide (eq 9).[16]

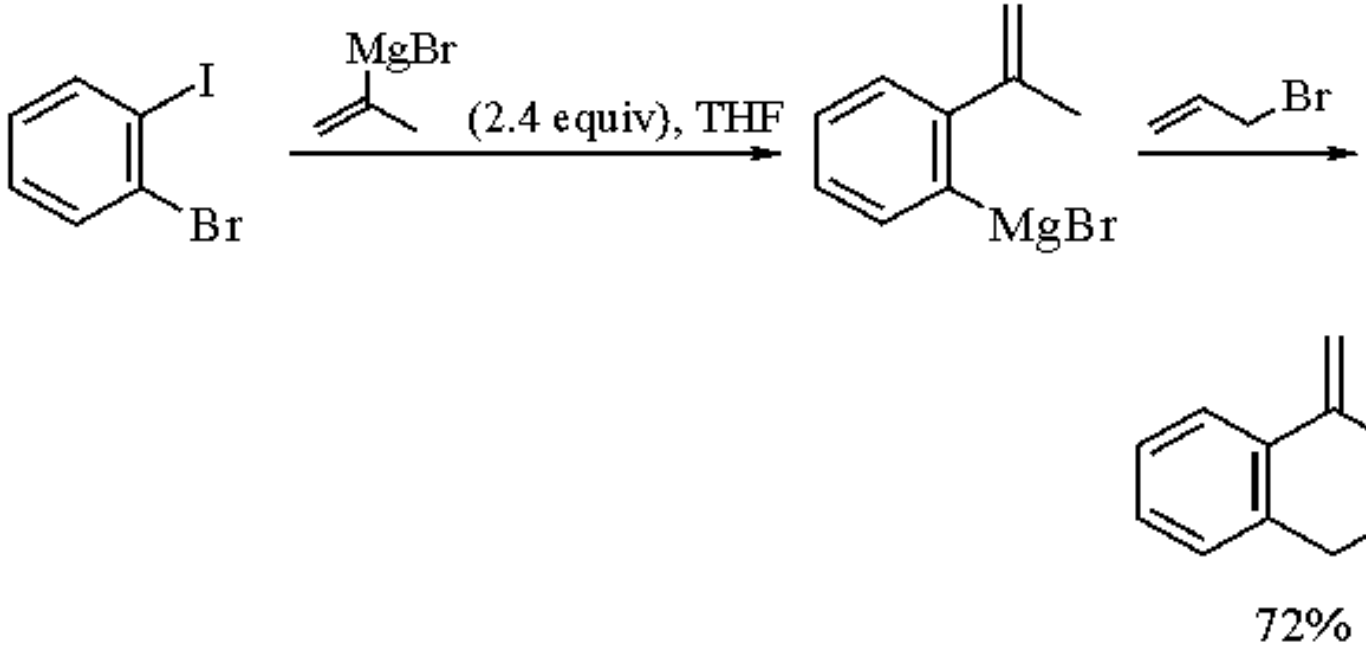

(9)

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1-Bromo-2-iodo-2-butene[1]

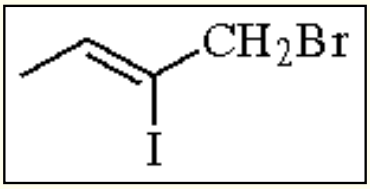

[147644-04-0] · C_4H_6BrI · 1-Bromo-2-iodo-2-butene · (MW 260.90)

(organopalladium Heck annulation)

Handling, Storage, and Precautions: as a low molecular weight allylic halide, this reagent can be expected to be lachrymatory; irritating to, and absorbed through, the skin and mucous membranes; especially hazardous via inhalation; suspect carcinogen. As an iodoalkene, it can be expected to be photochemically and/or thermally labile and susceptible to oxidation in air. Use in a fume hood.

Annulation.

In a new approach to *Strychnos* alkaloids, Rawal deployed 1-bromo-2-iodo-2-butene for construction of ring E via *N*-alkylation followed by Pd-catalyzed cyclization (intramolecular Heck reaction). Thus the reagent of (*Z*) configuration led to racemic dehydrotubifoline with correct exocyclic double bond stereochemistry (eq 1).[1] Prior model experiments demonstrated the stereospecific nature of the cyclization (eqs 2 and 3).[2] The requisite diastereomeric iodoalkenes were obtained by regio- and stereoselective addition of ***Tri-n-butylstannane*** to 2-butyn-1-ol, followed by iododestannylation (eqs 4 and 5).[2]

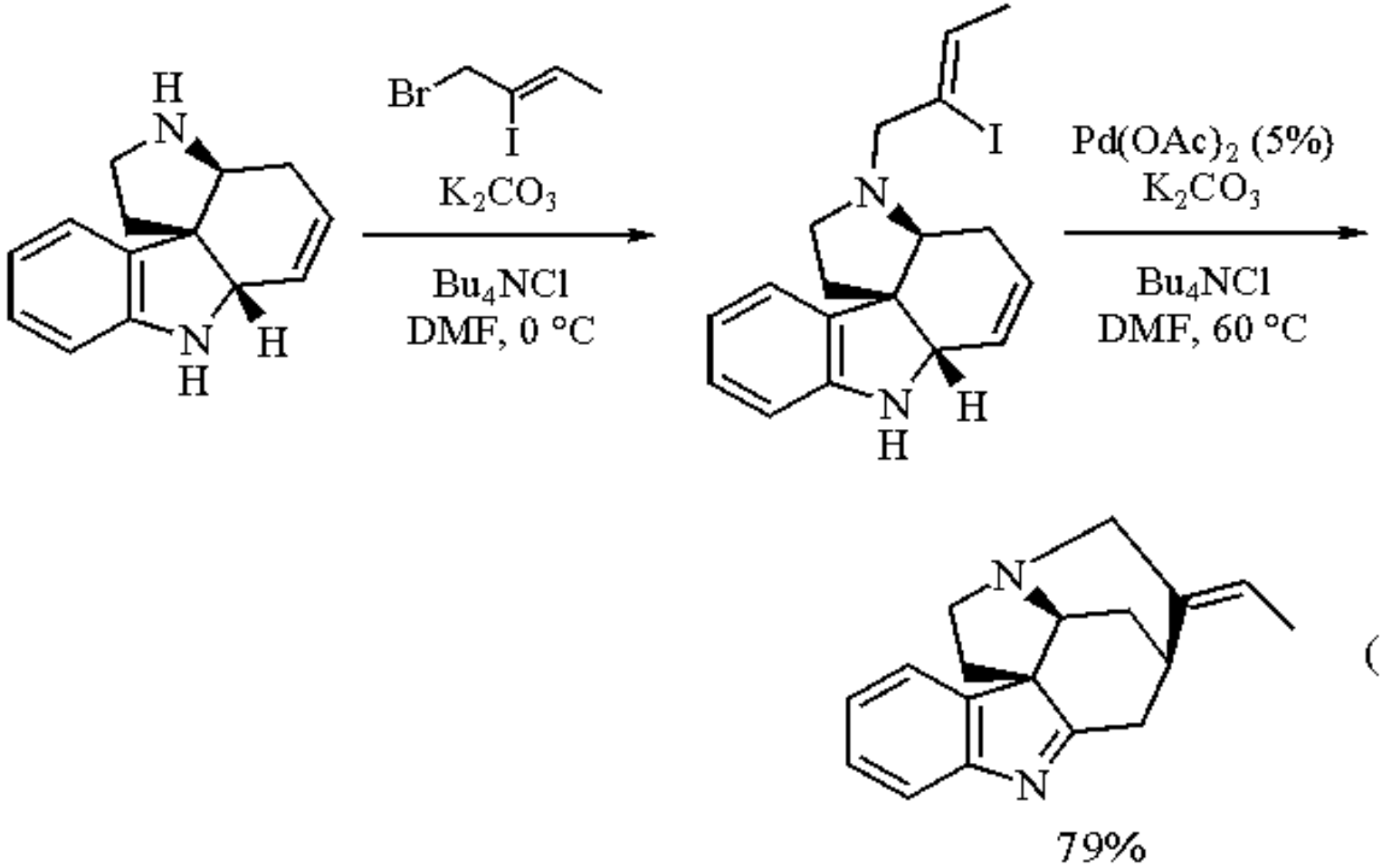
H
N
N
H
H
Br
I
K_2CO_3
Bu_4NCl
DMF, 0 °C
I
N
N
H
H
$Pd(OAc)_2$ (5%)
K_2CO_3
Bu_4NCl
DMF, 60 °C
N
N
79%

(1)

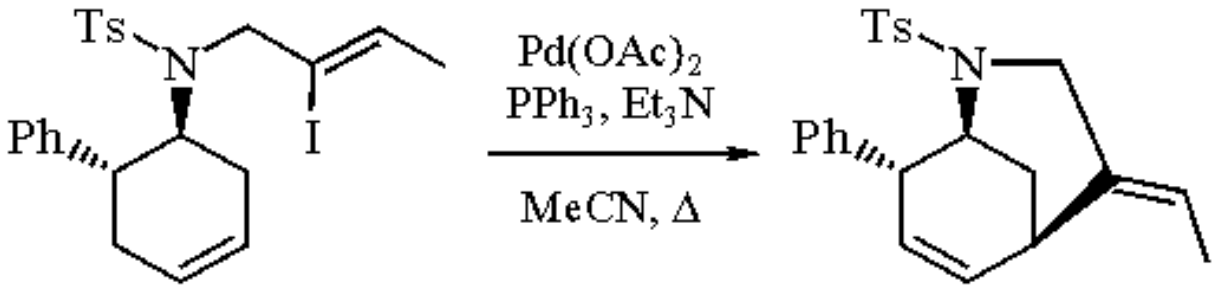
Ts
N
Ph
I
$Pd(OAc)_2$
PPh_3, Et_3N
MeCN, Δ
Ts
N
Ph

(2)

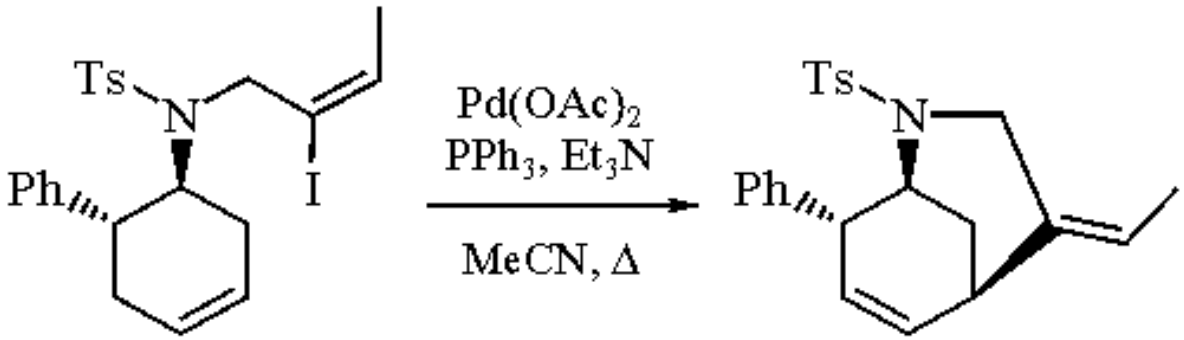
Ts
N
Ph
I
$Pd(OAc)_2$
PPh_3, Et_3N
MeCN, Δ
Ts
N
Ph

(3)

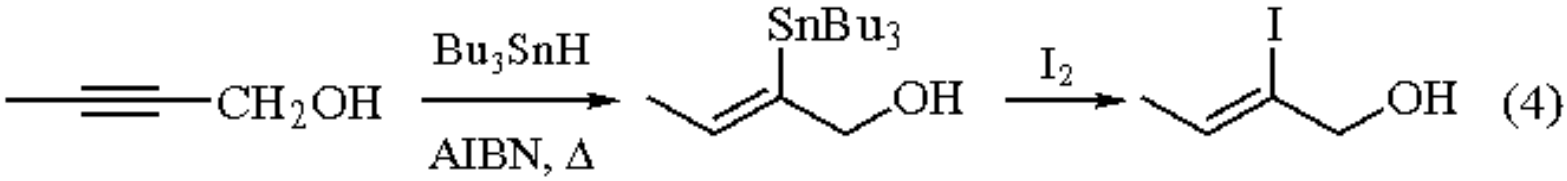

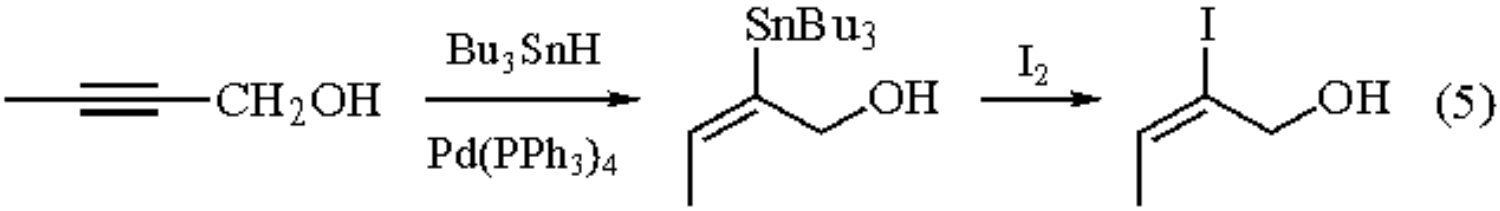

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(*Z*)-3-Bromo-1-iodopropene

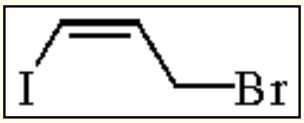

[133834-87-4] · C_3H_4BrI · (*Z*)-3-Bromo-1-iodopropene · (MW 246.87)

(bifunctional reagent employed in a cyclopentenone annulation method[1,2])

Physical Data: colorless liquid, distillation temperature (bulb-to-bulb) 25-45 °C/0.2 mmHg.

Solubility: insol H_2O; sol pentane, Et_2O, THF, CH_2Cl_2, $CHCl_3$.

Preparative Methods: (*Z*)-3-bromo-1-iodopropene (**3**) is readily prepared[1] by treatment of the corresponding alcohol (**2**) with ***Triphenylphosphine Dibromide*** in CH_2Cl_2 (eq 1).[3] Although a number of useful procedures for the synthesis of (**2**) have been reported,[4] probably the most convenient involves reduction of methyl (*Z*)-3-iodopropenoate (**1**)[5] with ***Diisobutylaluminum Hydride*** (eq 1).[1]

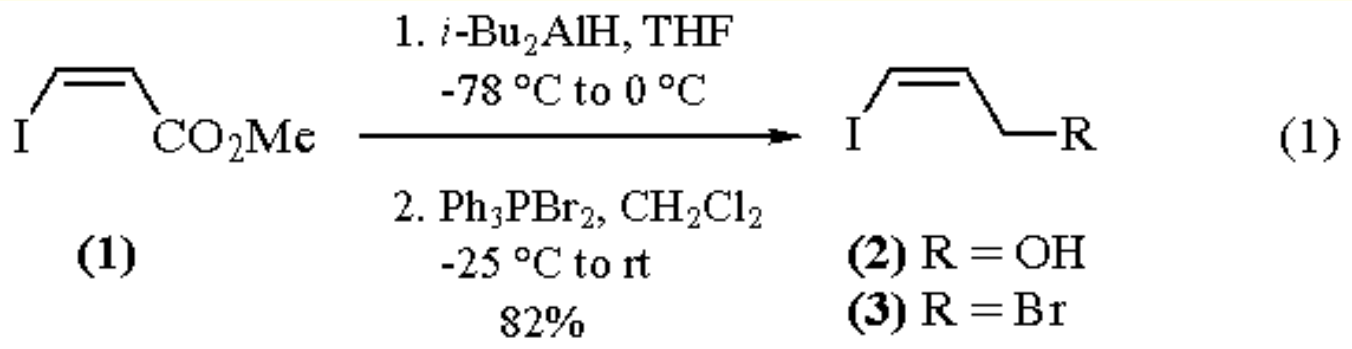

(1)

Handling, Storage, and Precautions: when stored in a freezer over copper wire under an inert atmosphere, this reagent is stable for months. It decomposes upon exposure to heat and/or light. A slight pink coloration does not affect its reactivity, but the reagent should be distilled from dried basic alumina and copper wire just prior to use. This substance is a lachrymator and should be prepared and handled only in a fume hood.

Cyclopentenone Annulations.

The use of reagent (**3**) in performing cyclopentenone annulations involves three steps: alkylation of a carbonyl compound with (**3**), ***n-Butyllithium***-mediated ring closure[6] of the resultant keto vinyl iodide to a tertiary allylic alcohol, and oxidative rearrangement of the latter species with a Cr^{VI} reagent to afford the 2-cyclopenten-1-one. The method is illustrated by the conversion of keto ester (**4**) into the bicyclic enone (**7**) (eq 2).[2] In those cases in which

direct alkylation of a ketone substrate is problematic, nitrogen-containing analogs (e.g. *N*,*N*-dimethylhydrazones)[7] may be employed effectively (eq 3).[2]

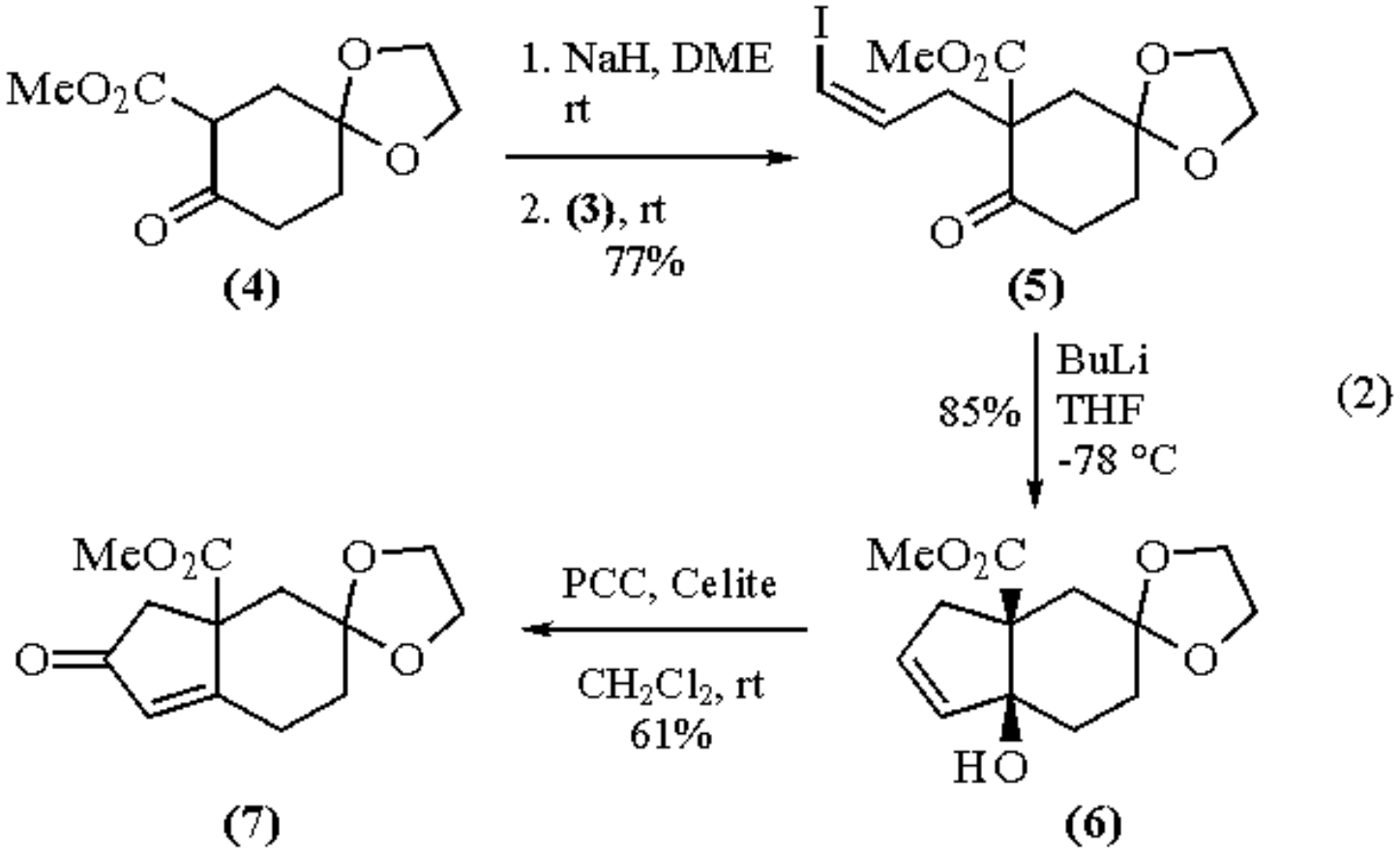

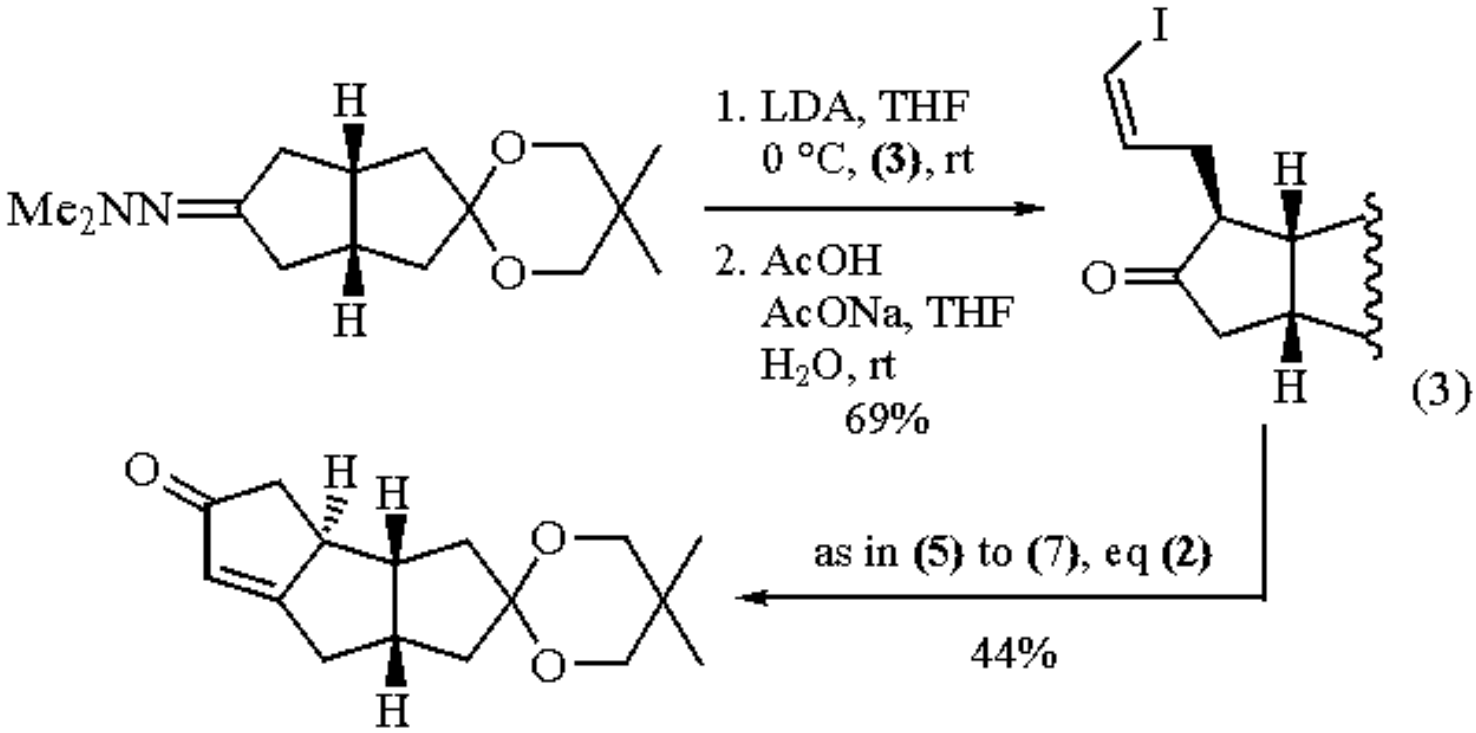

This annulation method played a key role in a recent total synthesis of the tetraquinane diterpenoid (±)-crinipellin B (**8**).[1] Attempts to effect conversion of the intermediate (**9**) into the enone (**10**) via the application of a number of known

cyclopentenone annulation methods[8] were unsuccessful.[1] However, alkylation of (**9**) with (**3**) and subsequent treatment of the resultant product with *n*-BuLi produced, efficiently, the allylic alcohol (**11**). Oxidation of (**11**) afforded the enone (**12**) as the major product (eq 4).[1] Interestingly, the latter reaction, in addition to effecting the expected transformation (enone formation), caused oxidative conversion of the (hindered) silyl ether group into the corresponding ketone function. The tetracyclic enone (**12**) served as a suitable intermediate for the total synthesis of (**8**).[1]

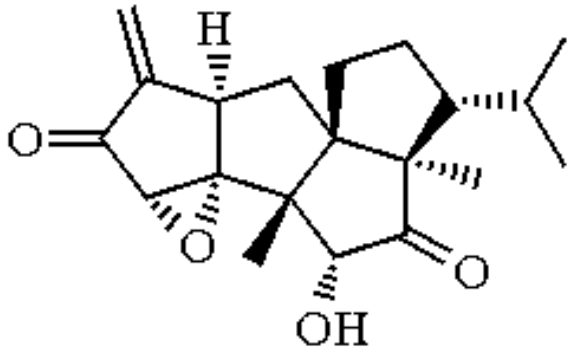

(8)

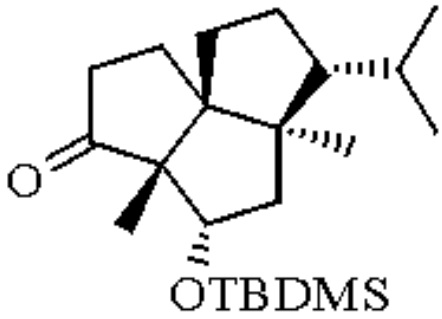

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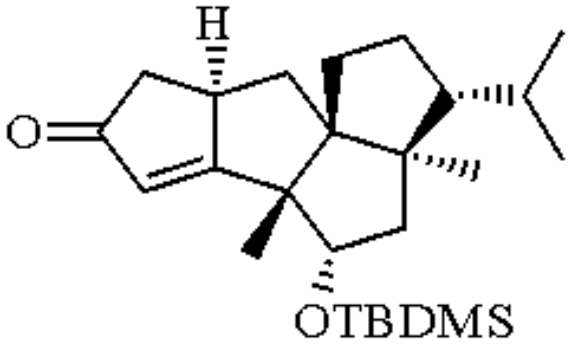

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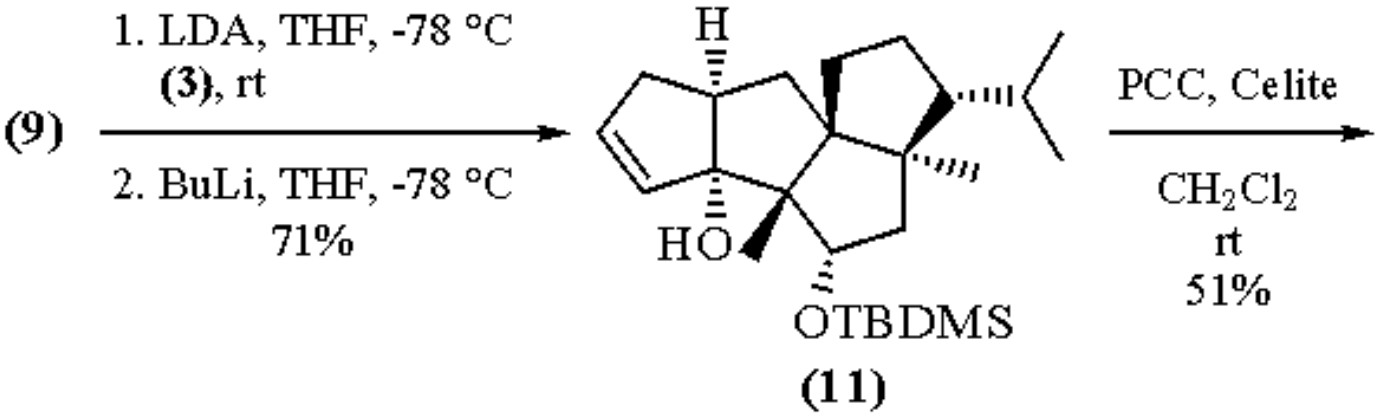

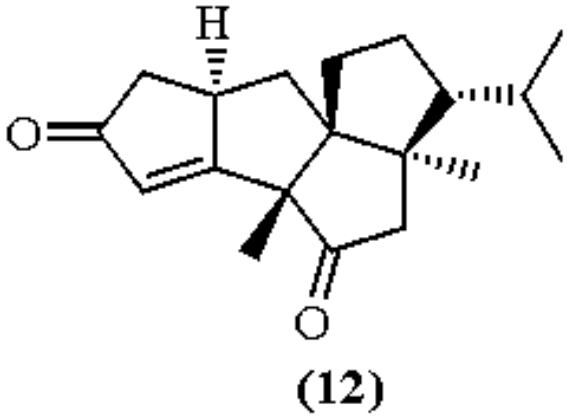

(4)

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1-Bromo-1-lithio-2-phenylcyclopropane

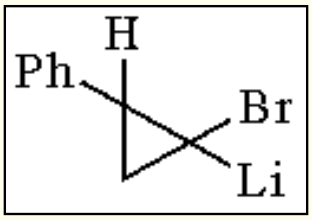

[107887-79-6] · C_9H_8BrLi · 1-Bromo-1-lithio-2-phenylcyclopropane · (MW 203.01)

(highly reactive organolithium compound, generated at low temperature in solutions of THF or diethyl ether; reacts with electrophiles at temperatures below -85 °C)

1-Bromo-1-lithio-2-phenylcyclopropane, which is generated in situ by treatment of 1,1-dibromo-2-phenylcyclopropane with ***Methyllithium***, undergoes spontaneous rearrangement to phenylallene under α-elimination of ***Lithium Bromide*** (eq 1).[1,2]

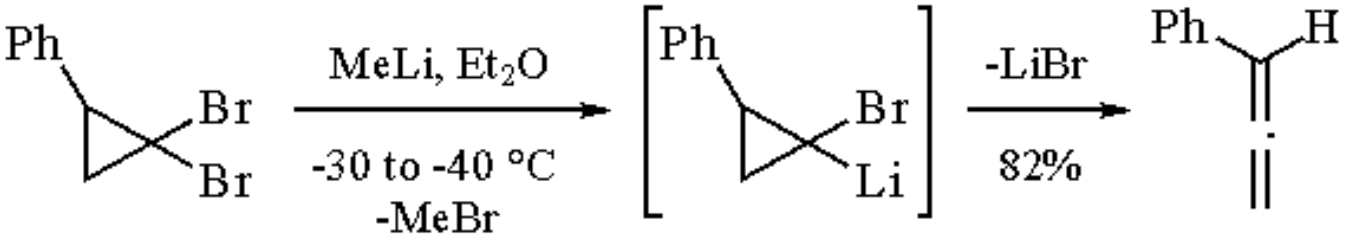

(1)

Solutions of 1-bromo-1-lithiocyclopropanes[3] can be generated in THF or diethyl ether or in mixtures of THF/diethyl ether and THF/diethyl ether/pentane at -110 to -85 °C. The bromine-lithium exchange of 1,1-dibromocyclopropanes turns out to be the most versatile method. Solutions of ^{13}C,^{6}Li-labeled 1-bromo-1-lithiocyclopropanes have been studied by NMR spectroscopy.[4] Solutions of such carbenoids react with a variety of electrophiles. When 1-bromo-1-lithiocyclopropanes are added to benzophenone the formation of cyclobutanones results via a spontaneous rearrangement of oxaspiropentanes (eq 2).[5]

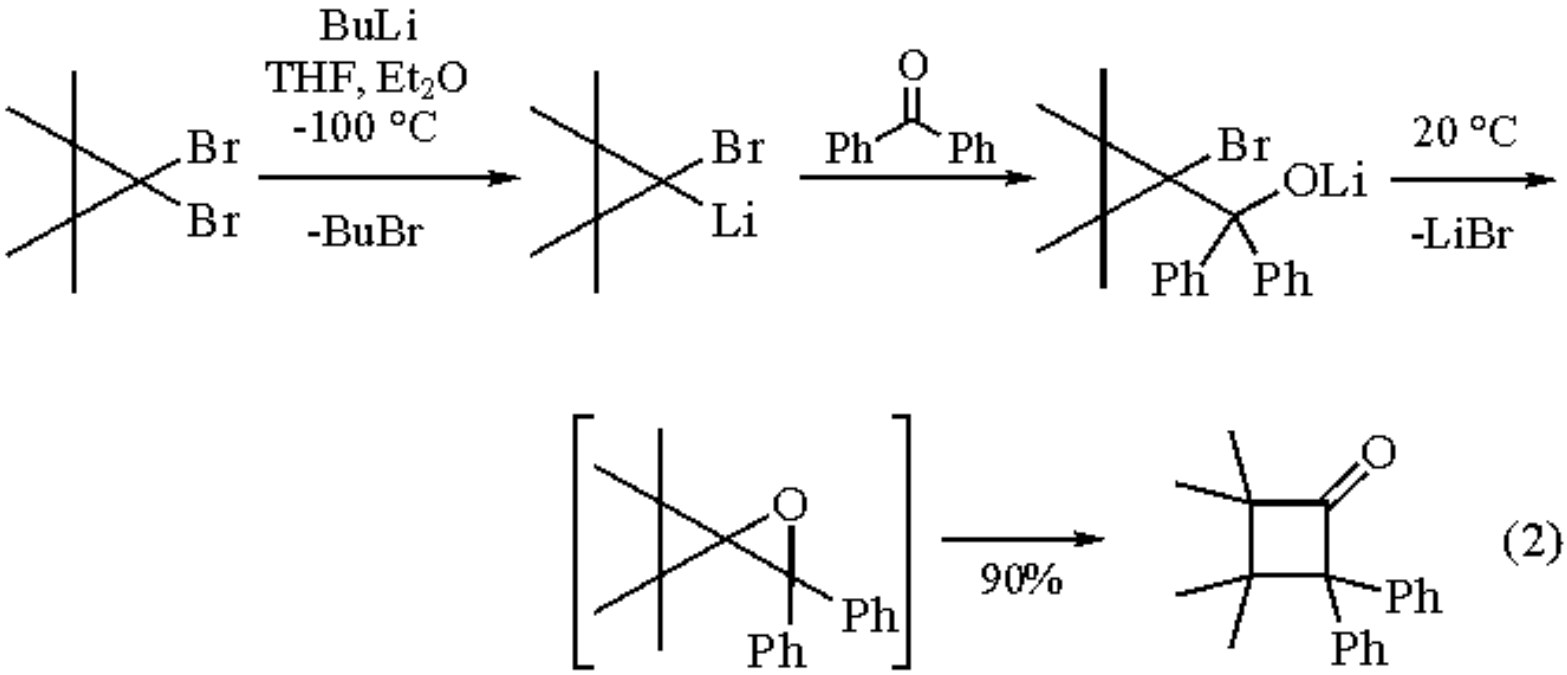

A stereoselective bromine-lithium exchange occurs upon treatment of 7,7-dibromonorcarane with ***n-Butyllithium*** to give *exo*-7-bromo-*endo*-7-lithiobicyclo[4.1.0]heptane (eq 3). A slight excess of dibromocyclopropane relative to butyllithium is required to achieve stereoselectivity. The *exo*-lithium stereoisomer, which is the favored product of a kinetically controlled lithiation, undergoes another bromine-lithium exchange reaction with dibromonorcarane to give ultimately the thermodynamically favored *endo*-lithium carbenoid (eq 4). The configuration of the latter reagent is proven by carboxylation (eq 3).[6]

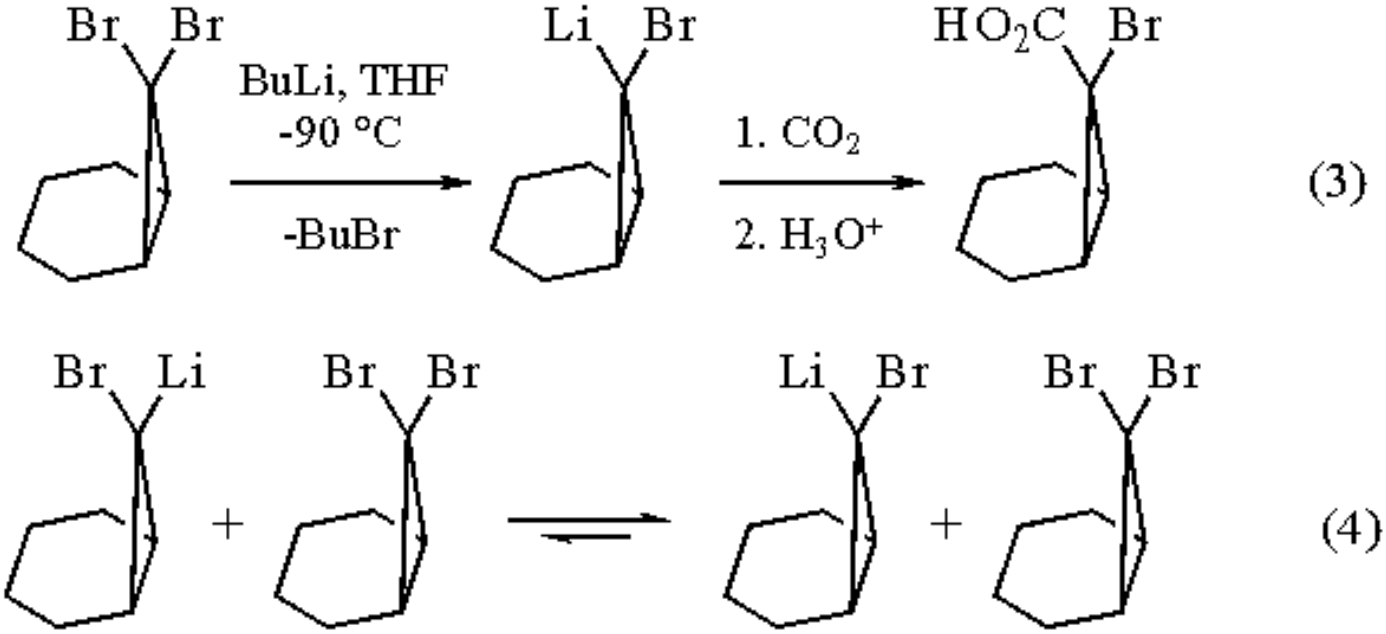

The following representative 1-bromo-1-lithiocyclopropanes have also been prepared by bromine-lithium exchange reactions:[12] 1-bromo-1-lithio-2-phenylcyclopropane (**1**),[6,7] 1-bromo-1-lithio-2,2-dimethylcyclopropane (**2**),[5] 13-bromo-13-lithiobicyclo[10.1.0]tridecane (**3**),[8] *endo*-7-bromo-*exo*-7-lithio-1-methoxybicyclo[4.1.0]heptane (**4**),[9] *exo*-9-bromo-*endo*-9-lithiobicyclo[6.1.0]nonane (**5**),[10] and *trans*-2-benzyloxymethyl-1-bromo-1-lithiocyclopropane (**6**).[7,11]

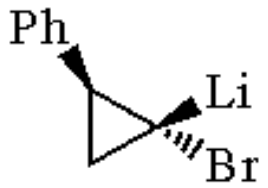

(1)

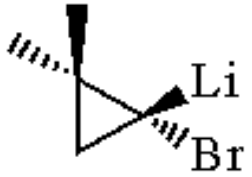

(2)

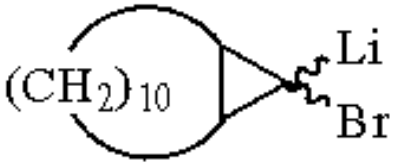

(3)

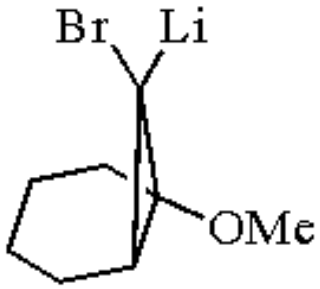

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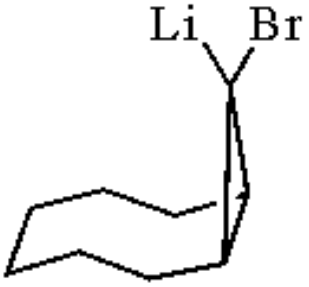

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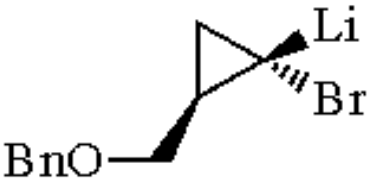

(6)

The treatment of *endo*-7-bromo-*exo*-7-(trimethylstannyl)bicyclo[4.1.0]heptane results in an exclusive tin-lithium exchange reaction to give *endo*-7-bromo-*exo*-7-lithionorcarane (eq 5).[13]

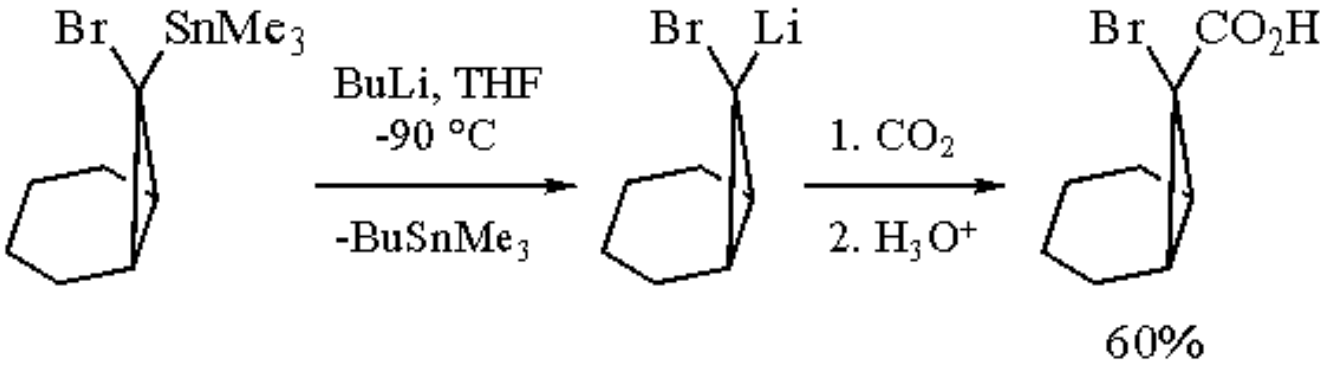

(5)

Related Reagents.

Cyclopropyllithium; ***Cyclopropylmagnesium Bromide***; ***1-Lithio-1-methoxycyclopropane***.

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Bromomagnesium Diethylamide

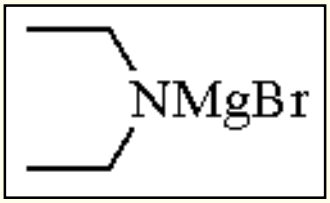

[5856-91-7] · $C_4H_{10}BrMgN$ · Bromomagnesium Diethylamide · (MW 176.34)

(aldol condensation; Claisen ester condensation)

Alternate Name: diethylaminomagnesium bromide.

Preparative Method: has been prepared from ***Ethylmagnesium Bromide*** and diethylamine in anhydrous ether by mixing at 0 °C, then stirring at rt followed by a 15 min reflux.[1,2]

Handling, Storage, and Precautions: use in a fume hood.

Although bromomagnesium diethylamide has been shown to be an effective base for the Claisen ester condensation of certain esters, its use is limited by its tendency to react with the ester group to form amides.[3,4] The related reagent ***Bromomagnesium Diisopropylamide*** does not suffer from this drawback and has been used more frequently.

Diethyl succinate has been successfully condensed with trifluoroacetophenones using bromomagnesium diethylamide (eq 1).[5,6]

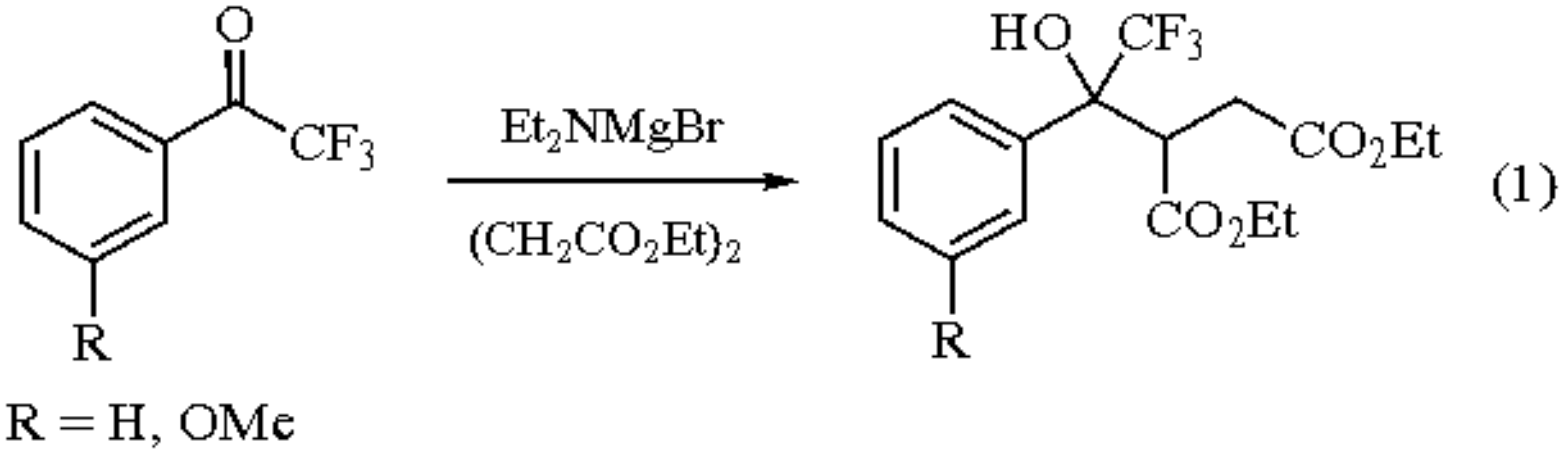

The condensation of (-)-menthyl acetate with alkyl phenyl ketones,[1,7] dialkyl ketones,[8] or aromatic aldehydes[8] gives optically active β-hydroxy esters which can be hydrolyzed to the optically active β-hydroxy acids (eq 2). Synthetic yields are 30-80% and optical yields are 16-60%. As the size of R increases, the optical yield decreases.[7]

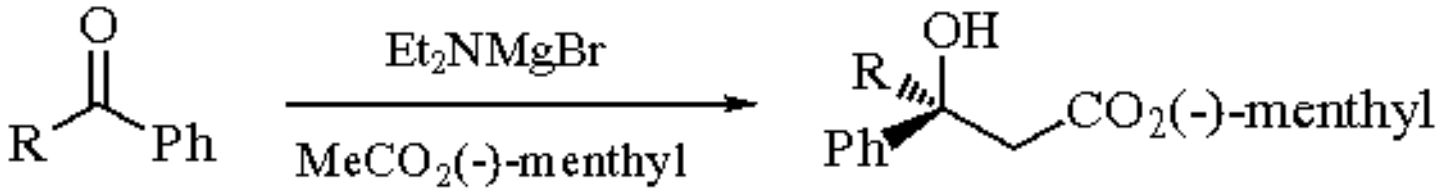

(2)

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Bromomagnesium Diisopropylamide

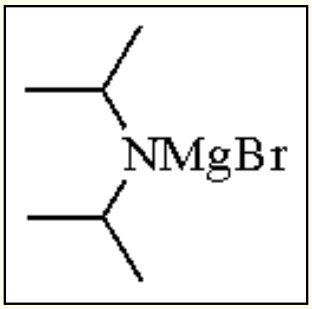

[50715-01-0] · $C_6H_{14}BrMgN$ · Bromomagnesium Diisopropylamide · (MW 204.39)

(thermodynamic enolate generation; aldol condensation; Claisen ester condensation)

Alternate Names: diisopropylaminomagnesium bromide; BMDA.

Preparative Methods: prepared from ***Diisopropylamine*** and ***Methylmagnesium Bromide*** or ***Ethylmagnesium Bromide*** using either THF or ether as the solvent. In THF a 1.5 M solution was prepared at 80 °C and stored at 50 °C (presumably to prevent precipitation).[1] A refluxing 0.5 M THF solution of BMDA was reported to be stable for several hours.[2] In ether, preparations have been reported at rt; however, BMDA is practically insoluble in ether and was used as a slurry.[3,4]

Handling, Storage, and Precautions: use in a fume hood.

Ester Condensations.

BMDA has been examined as a base for the Claisen ester condensation[3,5-7] and was found to be an excellent condensing agent for mixed condensations of methyl benzoate and methyl 2-furoate with aliphatic esters.[5] A small study of BMDA's use in the Dieckmann cyclization of diesters seemed to show no obvious advantage over other bases.[7] Intramolecular condensations using BMDA have been reported (eqs 1 and 2).[8,9] Thiolactones have been condensed with ***Diethyl Oxalate*** (eq 3).[10]

(1)

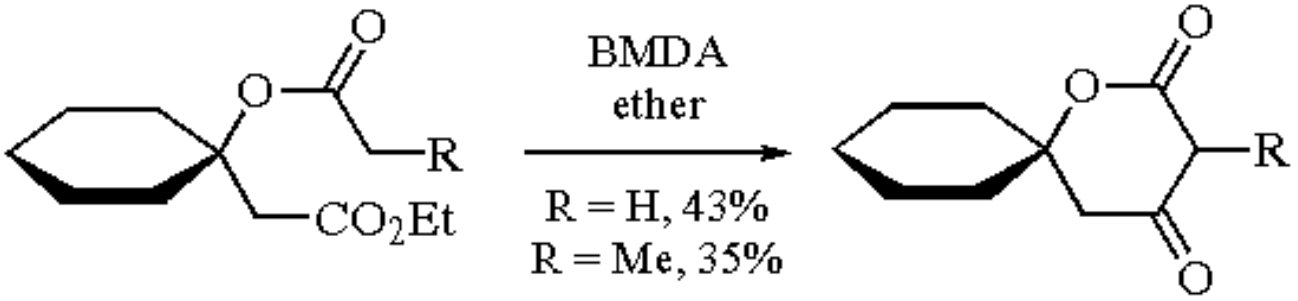

(2)

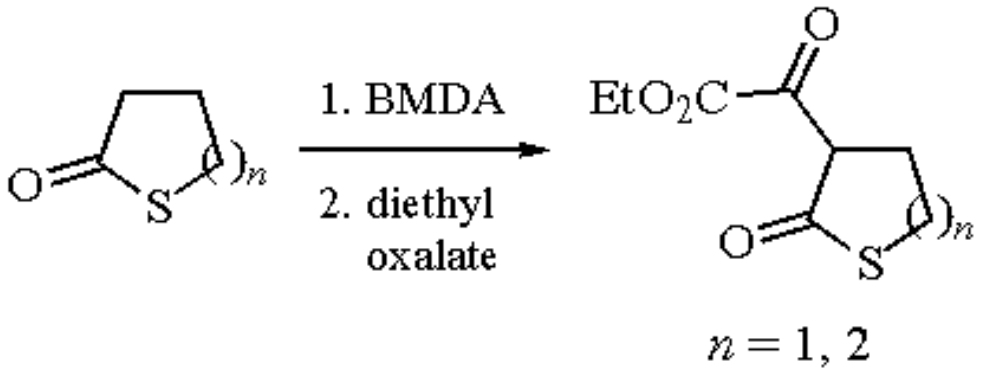

(3)

Nitrile Condensations.

The condensation of nitriles using BMDA has been investigated. Although acetonitrile gave very poor yields, reactions of propio-, valero-, and phenylacetonitriles proceeded in 65-80% yields (eq 4). The reactions were carried out in refluxing ether. When the reactions were carried out in refluxing *n*-butyl ether, they were more complex and cyclic trimers of the pyrimidine and pyridine classes were formed.[11]

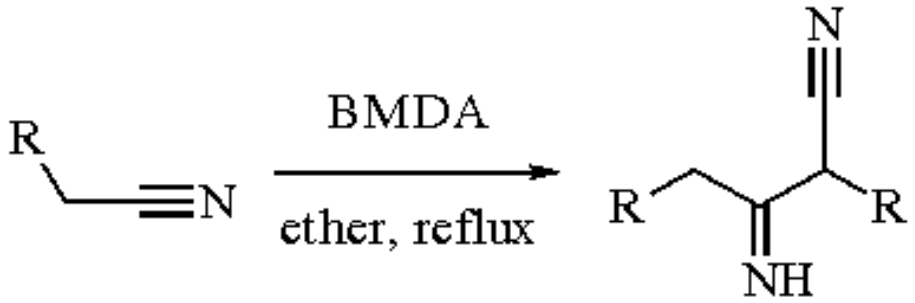

(4)

Aldol Condensations.

BMDA has found utility in a number of aldol condensations where other bases have failed. In Kishi's synthesis of monensin, BMDA was used to couple the left and right halves of the molecule (eq 5).[1]

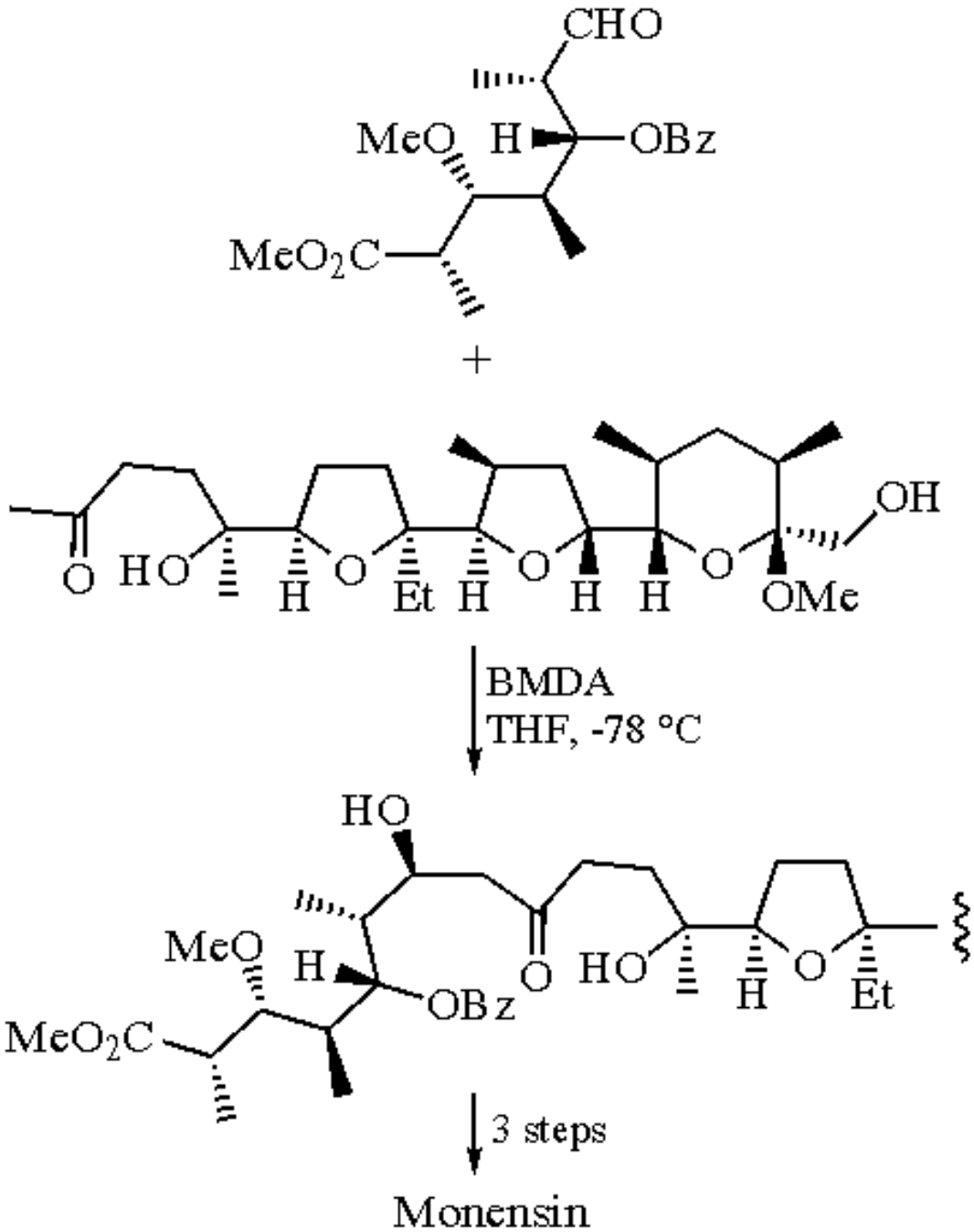

(5)

In a synthesis of the taxane ring system, Holton used BMDA to effect the intramolecular condensation to give (**2**) in 90% yield (eq 6).[12] Other reagents resulted in a retro Michael reaction.

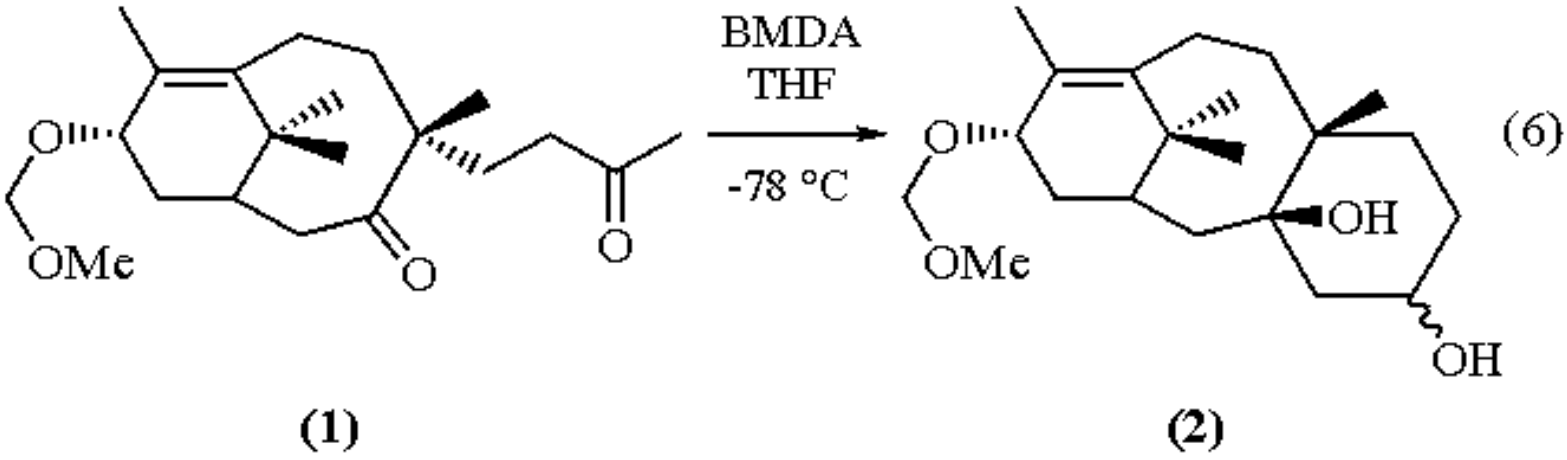

Annunziata et al. found magnesium bases such as BMDA superior in diastereoselectivity to lithium bases for the aldol condensation of the enantiomerically pure 3-*p*-tolylsulfinylmethyl-4,5-dihydroisoxazoles (eq 7).[13]

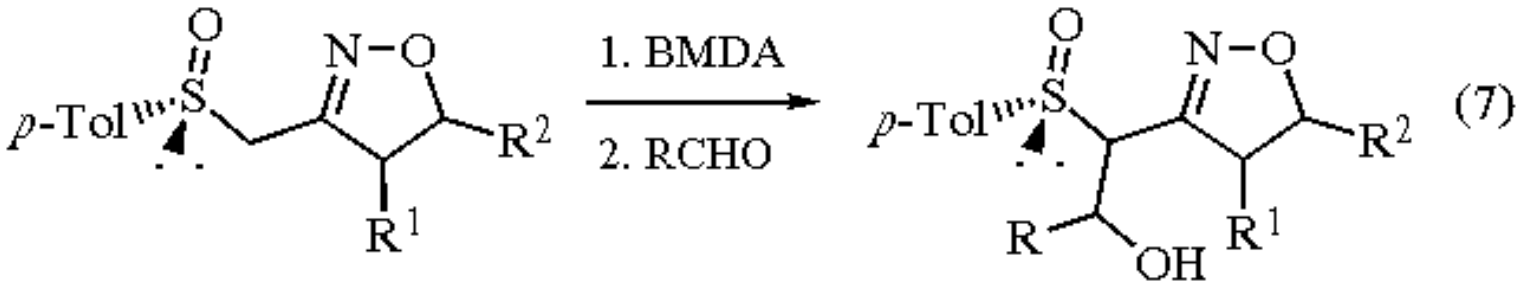

Similarly, Nokami et al. reported the condensation of another *p*-tolylsulfinyl compound with propargyl aldehyde (eq 8).[14]

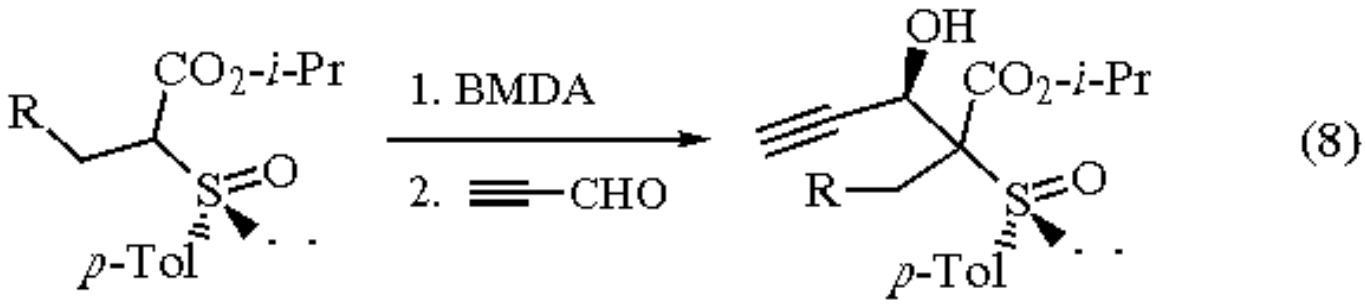

Enolate Generation.

Krafft and Holton reported the examination of a number of bases for the preparation of enolates. This examination showed that BMDA was the best base for the preparation of thermodynamic enolates. The enolate was trapped with ***Chlorotrimethylsilane*** and the product obtained in 85-95% yields with ratios of thermodynamic:kinetic product (**4:5**) of ca. 97:3 (eq 9).[4] ***Lithium Diisopropylamide*** gave a 1:99 ratio of (**4:5**). Other bases examined gave predominately (**4**); however, the ratios of (**4:5**) were inferior to BMDA. This procedure has been used in the synthesis of the taxane ring system,[12] intermediates for reserpine (trapped with ***t-Butyldimethylchlorosilane***),[15] dihydropallescensin D,[16] and other systems.[17] Thermodynamic enolates have also been trapped with ***N-Phenyltrifluoromethanesulfonimide*** to give vinyl triflates.[18,19] Scott and Stille observed that the use of excess BMDA with 2-methylcyclohexanone led to lower

ratios of thermodynamic:kinetic product when the enolate was trapped with either TMSCl or *N*-phenyltriflimide.[19]

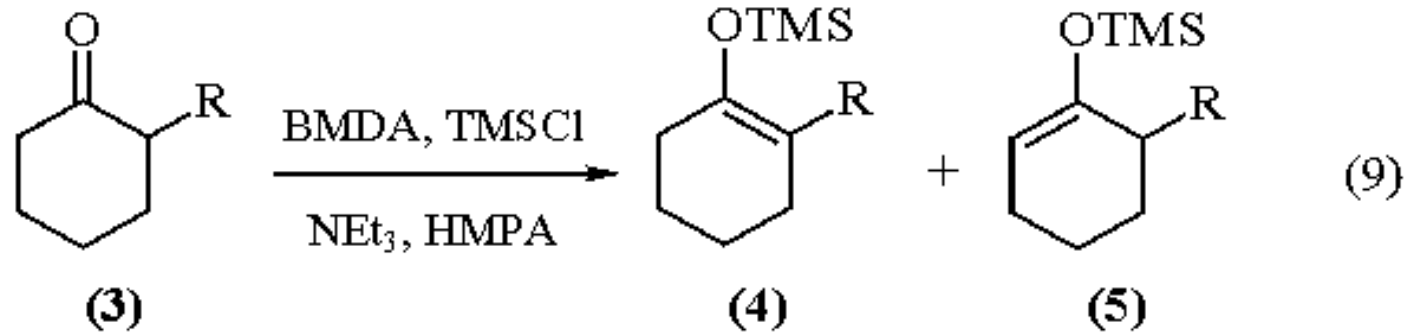

Carey and Helquist used BMDA to generate enolates in their synthesis of fused cyclopentanones (eq 10).[20]

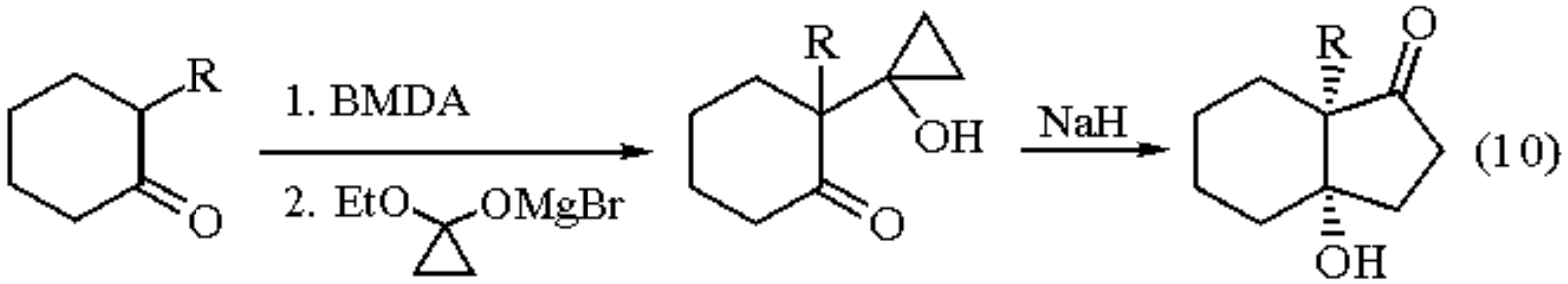

It should be noted that since BMDA can also promote aldol condensations, the use of BMDA to form enolates of ketones that are not relatively sterically hindered can lead to aldol products as the only reaction.[12,21]

Chiral Sulfoxides.

One synthetic route to optically active α-sulfinyl esters is the displacement of the *O*-menthyl group of an optically active sulfinate ester (eq 11).[22-24] When R = Me the ratio of diastereomers was 1:1 and when R = Et the ratio was 3:7. A similar reaction with cyclic ketones has been reported (eq 12).[21] When *n* = 1 the ratio of diastereomers was 3.0:1 and with *n* = 2 the ratio was 1.6:1.

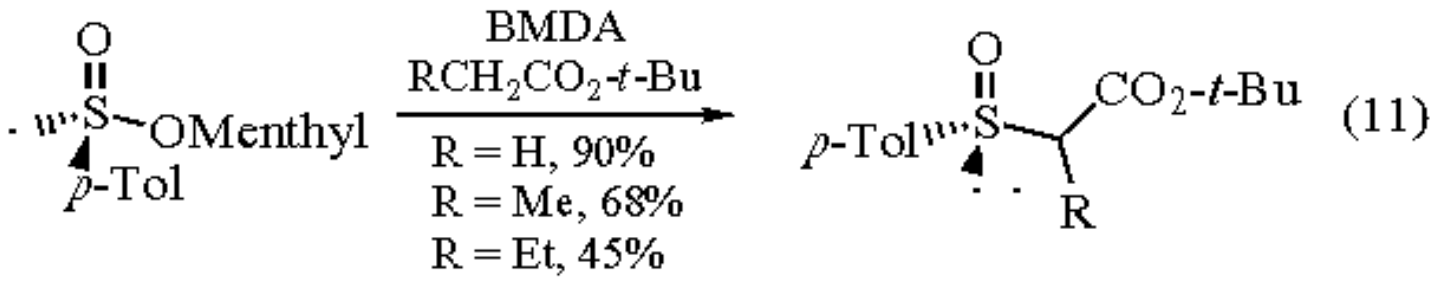

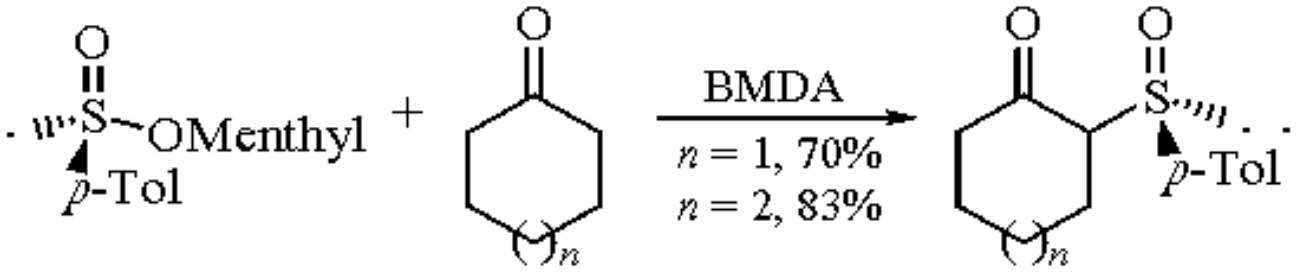

(12)

Other Reactions.

BMDA has proven useful for the functionalization of cubanes. Treatment of (**6**) with BMDA in refluxing THF gave the diester (**7**) as the product,[2] whereas at rt the monoester (**8**) is formed (eq 13).[2,25]

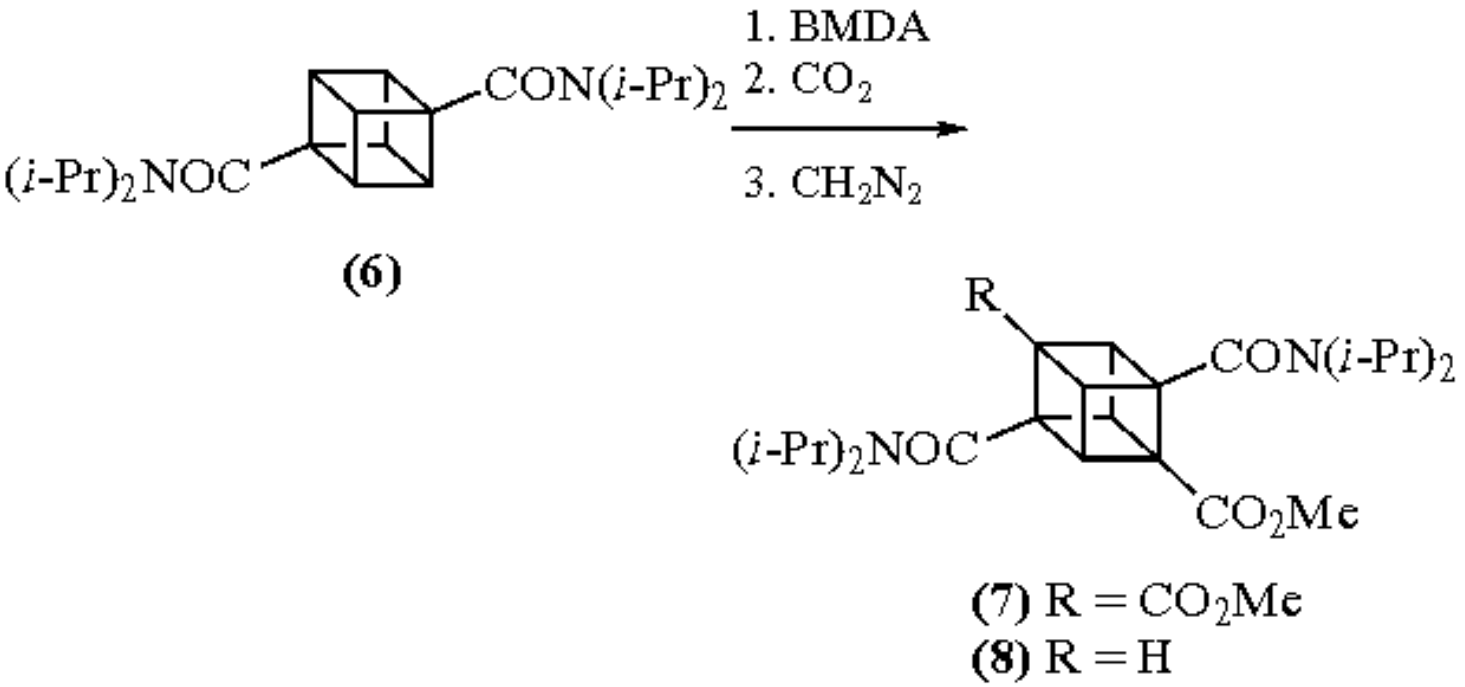

(13)

BMDA metalates (diphenylphosphinyl)ferrocene exclusively *ortho* to the diphenylphosphinyl group (eq 14).[26]

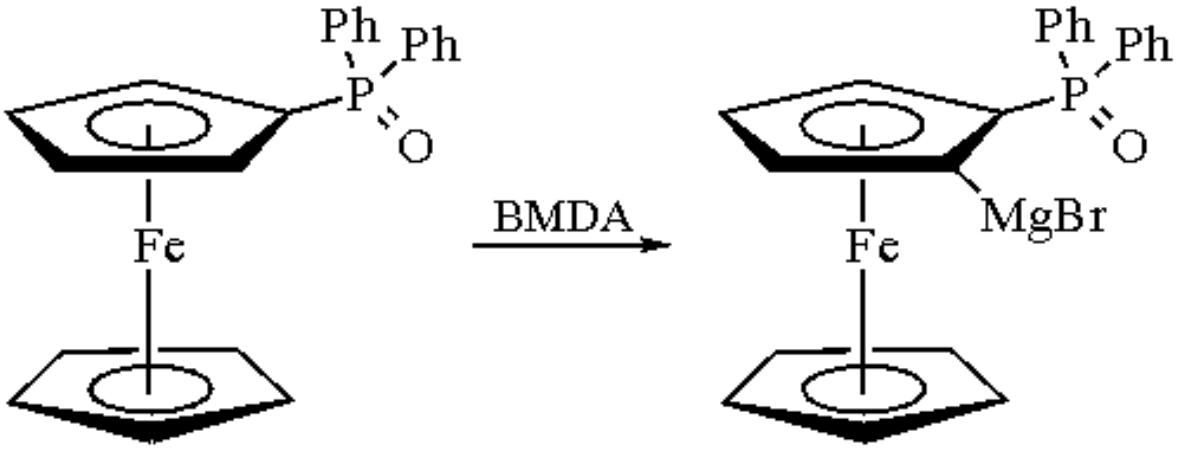

(14)

BMDA has been reported to be complementary to LDA in the acylation of 2-acyl-1,3-dithianes (**9**) (eq 15). When

R = aryl, LDA gave predominately *O*-acylation (**11**), whereas BMDA gave exclusive *C*-acylation (**10**). When R = Me, LDA gave 100% *O*-acylation and BMDA gave 78% *C*-acylation.[27]

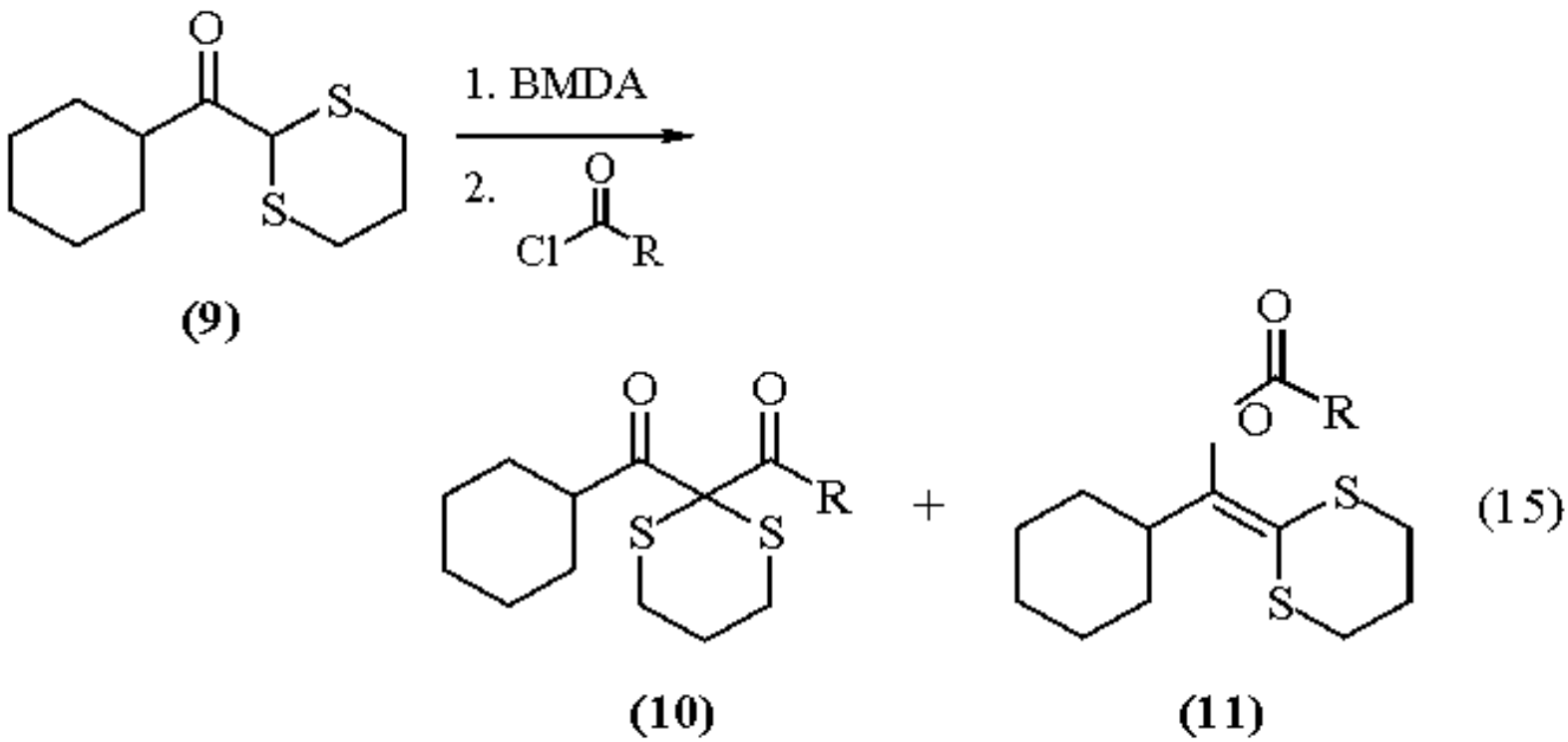

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Bromomagnesium Hexamethyldisilazide

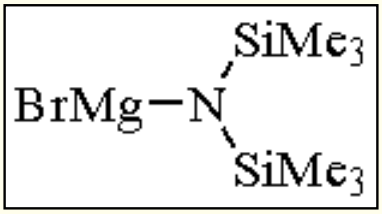

[50916-70-6] · $C_6H_{18}BrMgNSi_2$ · Bromomagnesium Hexamethyldisilazide · (MW 264.59)

(base for selective formation of magnesium enolates)

Physical Data: white solid from ether of composition $Mg_2Br_2[N(SiMe_3)_2]_2.2Et_2O$, mp 98 °C.

Solubility: sol benzene, cyclohexane, and toluene; very sol ether.

Preparative Method: ***Hexamethyldisilazane*** is added to ***Ethylmagnesium Bromide*** in ether. Cooling to -20 °C produces white crystals in good yield.[1]

Reaction with Carbonyl Compounds.

Although seldom used in comparison with ***Bromomagnesium Diisopropylamide***, bromomagnesium hexamethyldisilazide has the unique feature of high solubility in organic solvents.

Bromomagnesium hexamethyldisilazide and bromomagnesium diisopropylamide were the most effective of several magnesium bases examined for selective formation of the more substituted silyl enol ether from ketones (eq 1). Less-hindered ketones gave mainly aldol products.[2]

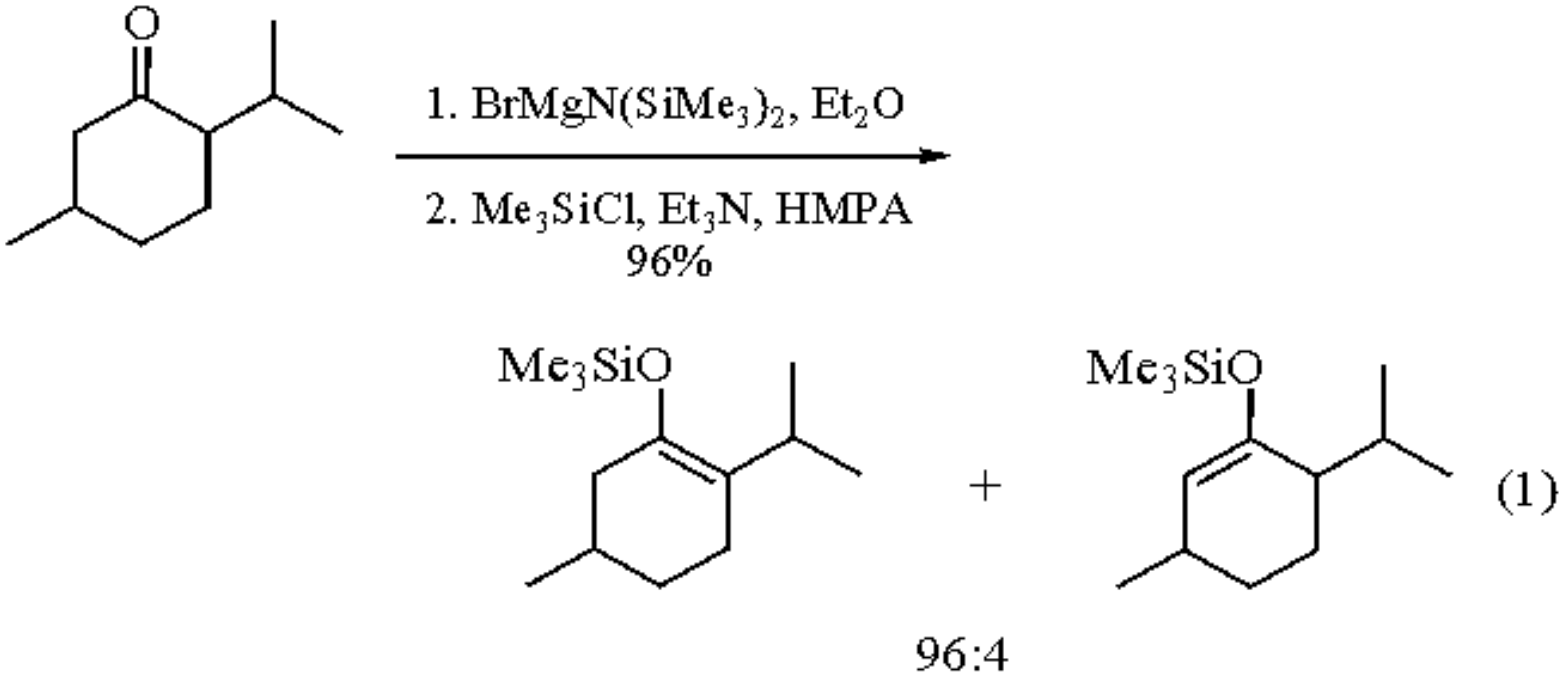

The reagent reacts with hindered esters to give isolable complexes, with no evidence for enolate formation (eq 2).[3]

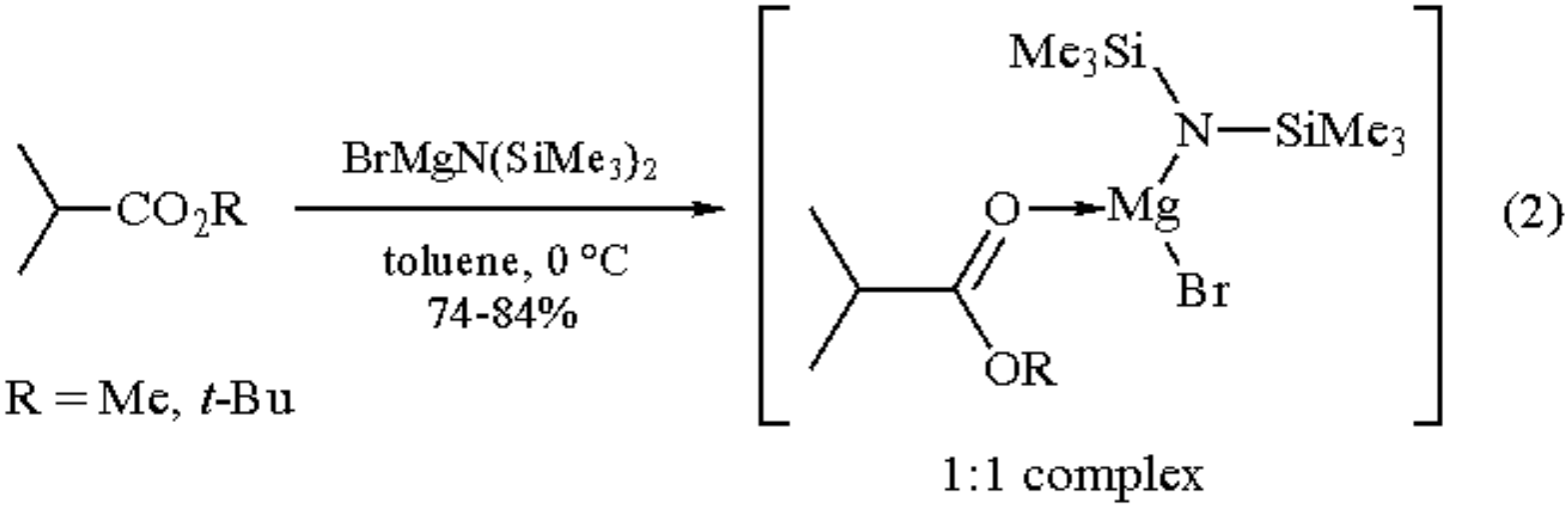

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Bromomethane[1]

CH_3Br

[74-83-9] · CH_3Br · Bromomethane · (MW 94.95)

(methylates C, N, O, P, S, Se, and Te nucleophiles; forms metal-Me systems which act as bases or which attack >C=O, -C&tbond;N)

Alternate Name: methyl bromide.

Physical Data: mp -93.66 °C; bp 3.56 °C; *d* 1.732 g cm^{-3} (0 °C).

Solubility: miscible with most organic solvents, sparingly with aqueous media.

Form Supplied in: colorless mobile liquid.

Purification: gas passed through conc. H_2SO_4 and dried with P_2O_5.

Handling, Storage, and Precautions: usually available in cylinders or as a solution in Et_2O or MTBE. Potent alkylating agent; high toxicity. Use in a fume hood.

Introduction.

CH_3Br is usually prepared by the bromination of methane[1a] or by the interaction of MeOH with ***Hydrogen Bromide***.[1b] Methyl bromide is the archetypal alkylating agent, either directly as a source of $Me^{\delta+}$ or through organometallic intermediates giving $Me^{\delta-}$. The alkyl group may also undergo substitution, usually selectively (e.g. bromination; 90% of the bromide is converted, giving a mixture of CH_2Br_2 and $CHBr_3$ (96:4, using $[Br_2]/[CH_3Br]$ = 10:1)).[1a]

Methylating Agent.

CH_3Br reacts readily with many nucleophiles including C-, O-, N-, and S-based systems; increased reactivity is often achieved through formation of the conjugate base (e.g. ROH -> RO^-). In this way, 2,3-dimethylcyclohexanone provides 2,2,3-trimethylcyclohexanone (eq 1).[2]

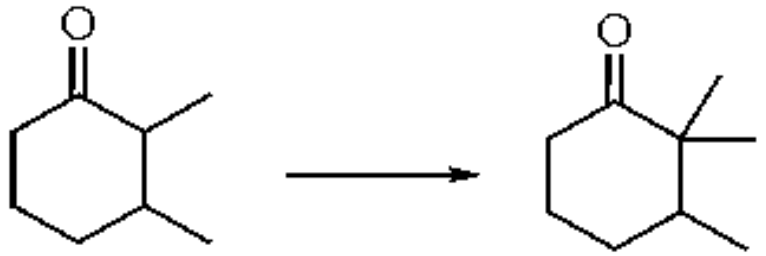

(1)

Ru-coordinated dibenzotetrathiacyclodecane dianion is methylated at the position α to sulfur,[3] and bridged annulene dianions (e.g. **1**) are correspondingly attacked.[4] Unsubstituted or monosubstituted malonic esters are methylated in the absence of solvent, forming the carbanion by adding NaOEt and distilling out the EtOH.[5]

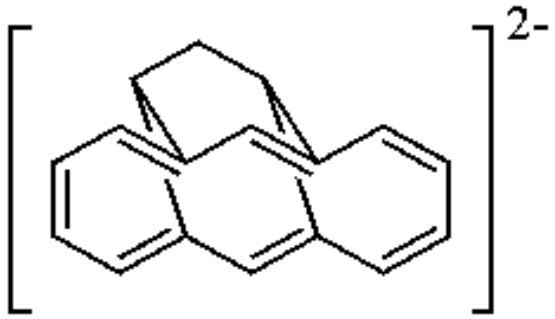

(1)

Other carbanions which may be methylated include the perfluoro-2-methylpentyl carbanion[6] and lithiated phenanthrene-9-carbamate, which provides the 10-Me analog.[7] Superacids (***Tetrafluoroboric Acid***, ***Boron Trifluoride***, or ***Trifluoromethanesulfonic Acid***) allow the carbonylation of MeCl or MeBr, giving a mixture of AcOH and AcOMe; this process is cheaper than those involving Rh catalysis.[8]

Asymmetric induction is achieved in the methylation of enones of α-aryl-substituted ketones, esters, and lactones by using chiral phase-transfer catalysts derived from cinchonine, cinchonidine, or their dihydro analogs.[9] Similarly, $CpFe(CO)(PPh_3)(COCH_2R)$ is deprotonated (***n-Butyllithium***) to form exclusively the (*E*)-enolate; alkylation of this substitutes the α-position of the acyl ligand. The greatest stereoselectivity of attack is shown by more bulky electrophiles.[10] A study of the methylation of lithiated silacyclopentenes reflects many uses of MeBr as a small electrophile which shows little influence by steric factors. Thus the allylic carbanion formed when silacyclopentene (**2**) (Ar = *p*-*t*-BuC_6H_4; R = R´ = H) reacts with ***t-Butyllithium*** is deuterated (D_2O) or methylated (MeBr) at the α-position (eq 2) (R = D or Me), whereas ***Triisopropylsilyl Chloride*** attacks at the γ-position to give the rearranged product (**3**) (R = H, R´ = *i*-Pr_3Si).[11]

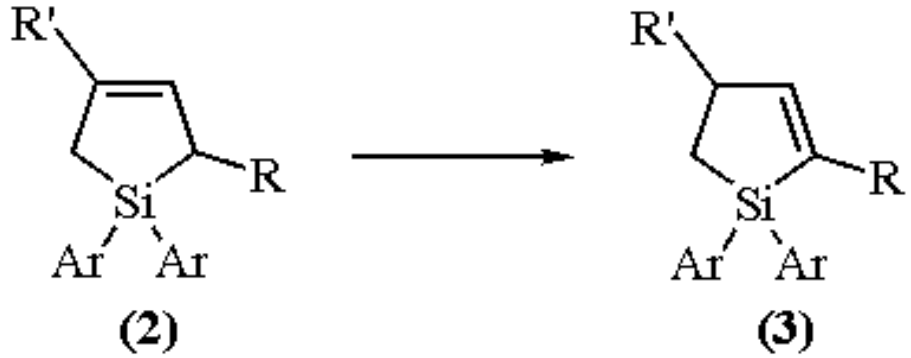

(2)

The methylation of aminobenzothiazoles (MeBr-DMF) on nitrogen exemplifies the use of aprotic solvents to encourage alkylation; it is accompanied by formylation at C-2 in these substrates.[12] $[Mo(N_2)_2(Et_2PCH_2CH_2PEt_2)_2]$ reacts with MeBr to provide the *N*,*N*-dimethylhydrazine derivative $[Mo(NNMe_2)_2(Et_2PCH_2CH_2PEt_2)_2]Br$.[13]

Organometallic Reagents.

The Grignard reagent ***Methylmagnesium Bromide*** is formed readily and quantitatively in Et_2O. The reaction with carbon-11 CO_2 is the first step in a synthesis of $Me^{11}CH_2I$ via labelled EtOH in a convenient one-pot process (eq 3).[14]

$$MeBr + Mg \longrightarrow MeMgBr \longrightarrow Me^{11}CO_2H \longrightarrow Me^{11}CH_2OH \longrightarrow Me^{11}CH_2I \quad (3)$$

Similar reactions with carbonyl compounds[15a] are widely used to incorporate methyl groups, while the corresponding processes often occur with great diastereoselectivity.[15b] The ring opening of epoxides proceeds in good yield with no loss of chirality both in systems such as (**4**) (Z = SO, SO_2, CO_2R) with RMgBr + CuI in Et_2O-THF at -60 °C which provide $EtCH(OH)CH_2Z$ (eq 4)[16] and in the reaction between either (*R*)- or (*S*)-glycidol with (RMgBr + $2LiCl/CuCl_2$) in THF at -5 °C when, for example, (*S*)-glycidol gives (*S*)-butane-1,2-diol in 70% yield and with 97% ee (eq 5).[17]

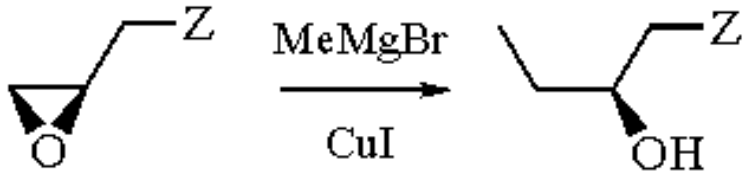

(4)

(4)

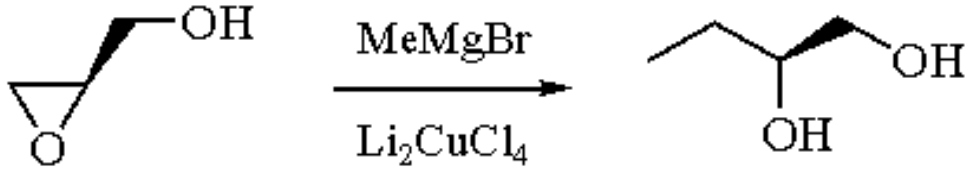

(5)

Related Reagents.

Chloromethane; ***Iodomethane***.

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Bromomethanesulfonyl Bromide

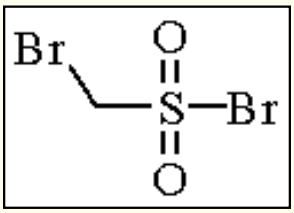

[54730-18-6] · $CH_2Br_2O_2S$ · Bromomethanesulfonyl Bromide · (MW 237.89)

(converts alkenes into 1,3-dienes[1-7] including 1-vinyl-1-cycloalkenes,[1,3] 3-methylene-1-cycloalkenes,[1,3] 2-alkyl-1,3-butadienes;[1,6] also converts silyl enol ethers into α-methylene ketones[1,5] and alkynes into enynes[1])

Physical Data: bp 68 °C/0.55 mmHg;[2] *n*20D 1.5706.[1]

Solubility: sol CH_2Cl_2, Et_2O; insol H_2O.

Analysis of Reagent Purity: ^{1}H NMR (60 MHz) δ 5.05 (s, 2H).

Preparative Methods: to a stirred suspension of *sym*-trithiane (0.73 mol) in water was added Br_2 (7.1 mol) dropwise to maintain a reaction temperature of 35-40 °C. Cooling by ice bath may be required. After the addition of Br_2 is complete, the reaction is stirred for an additional 15 min. The product is extracted into CH_2Cl_2, washed with 5% sodium bisulfite solution, and dried. Concentration and distillation yields bromomethanesulfonyl bromide in 42-48% yield as a pale yellow liquid.[1,2]

Handling, Storage, and Precautions: reactive sulfonylating agent: avoid contact with skin and mucous membranes. Stable at 25 °C for at least 2 weeks. Decomposes forming CH_2Br_2 and SO_2. Use in a fume hood.

Addition to Alkenes.

Light-initiated bromosulfonylation of alkenes occurs readily at -20 °C via a radical chain reaction and is generally more efficient than the thermal reaction (see also ***Benzenesulfonyl Bromide***). Regioselective addition of sulfonyl bromides with mono-, 1,1-disubstituted, and 1,1,2-trisubstituted alkenes occurs to give the more substituted alkyl bromide.[1,3] Chemoselective addition to alkenes is observed with nonconjugated dienes: monoalkyl > 1,1-dialkyl > 1,1,2-trialkyl. Subsequent treatment of the adducts with base yields α,β-unsaturated sulfones (eq 1). Stereoselectivity with terminal alkenes is observed, favoring the (*E*) configuration.[1,3]

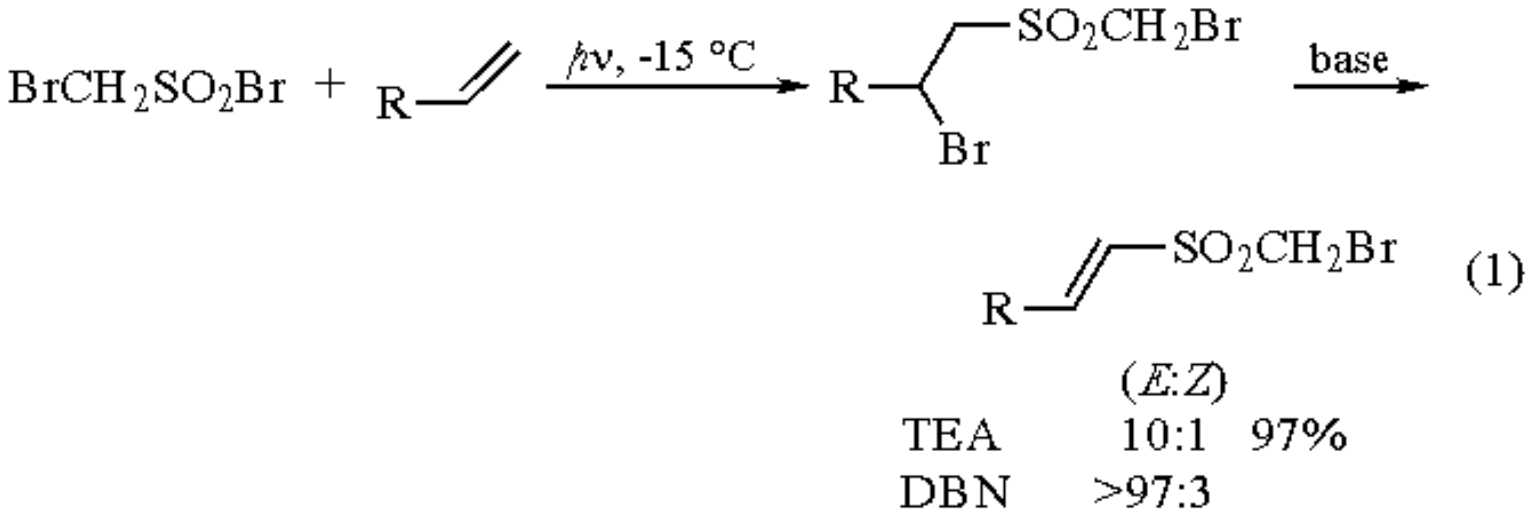

α,β-Unsaturated bromomethyl sulfones are converted into 1,3-dienes upon further treatment with base via a vinylogous Ramberg-Bäcklund reaction.[1-7] Employing this procedure, a variety of 1,3-diene products have been prepared (Table 1).

Table 1 Diene and Enyne Synthesis using Bromomethylsulfonyl Bromide

Alkene	1,3-Diene (*E*:*Z*)	Yield (%)
n-$C_6H_{13}CH{=}CH_2$	n-$C_5H_{11}CH{=}CHCH{=}CH_2$ (2:1)	61
n-$C_5H_{11}CMe{=}CH_2$	n-$C_5H_{11}C({=}CH_2)CH{=}CH_2$	72
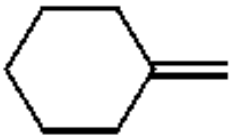	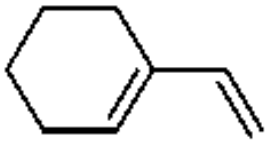	53
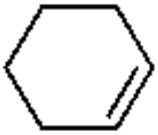	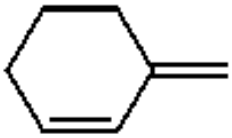	41
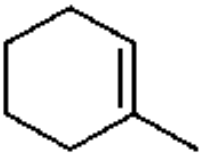	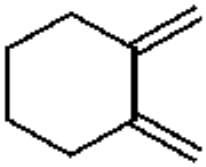	65
$PhCH_2CH{=}CH_2$	$PhCH{=}CHCH{=}CH_2$ (1:8)	85
$Me_3SiCH_2CH{=}CH_2$	$Me_3SiCH{=}CHCH{=}CH_2$ (1:10)	41
$C_5H_{11}C{\equiv}CH$	$C_4H_9C{\equiv}CCH{=}CH_2$	29
$B(OR)_2$	$B(OR)_2$	

81

The γ-deprotonation of α,β-unsaturated sulfones may occur *syn* or *anti* to the sulfonyl group, which would give a mixture of dienes from unsymmetrical precursors. The regioselectivity observed appears to be controlled by steric factors (***Potassium t-Butoxide*** deprotonates at the less hindered position) and by coordination of the alkali cations to the sulfonyl group (***Lithium t-Butoxide*** favors deprotonation *syn* to the sulfonyl group even when sterically hindered).

By this procedure, allylsilanes[1,4] and 2-propenyl boronates[7] are transformed into 1-trialkylsilyl-1,3-butadiene and electron-deficient 1,3-butadienyl-2-boronic esters, respectively (Table 1). However, reaction of allylstannanes with bromomethylsulfonyl bromide does not give the adduct but yields only allyl bromomethyl sulfone and stannyl bromides.[1,4]

Trimethylsilyl enol ethers are transformed into α-keto bromomethyl sulfones by bromomethylsulfonyl bromide in good yield. Subsequent treatment with ***1,5-Diazabicyclo[4.3.0]non-5-ene*** yields a mixture of α-methylene ketones and 1,3-oxathiole 3,3-dioxide heterocycles, depending on the solvent and reaction conditions.[1,5] Good yields of α-methylenecycloheptanone can be obtained (eq 2).

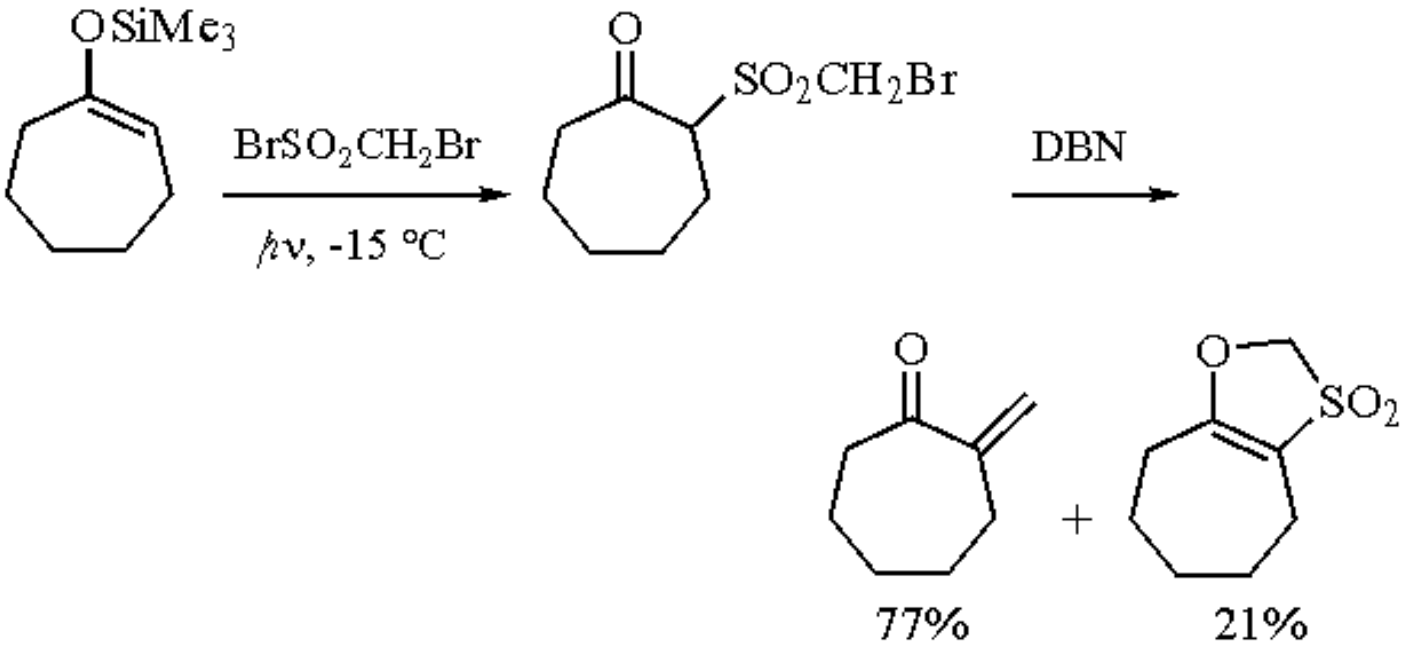

(2)

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1-Bromomethoxy-4-chlorobutane

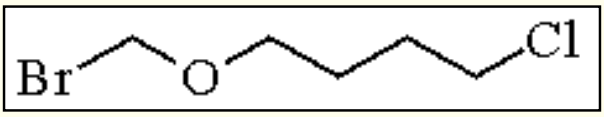

[53970-36-8] · $C_5H_{10}BrClO$ · 1-Bromomethoxy-4-chlorobutane · (MW 201.49)

(bromomethylating agent)

Physical Data: bp 94 °C/5 mmHg.

Preparative Method: can be prepared by treating 4-chloro-1-butanol with ***Paraformaldehyde*** and dry ***Hydrogen Bromide***.[1] Subsequent aqueous workup, separation, and distillation provides the desired product in 49% yield.

Handling, Storage, and Precautions: is much less volatile and therefore more convenient and safer compared to traditional halomethylating agents such as ***Chloromethyl Methyl Ether***, but it is still a potential carcinogenic compound. Thus, caution should be exercised while handling this compound. Use in a fume hood.

1-Bromomethoxy-4-chlorobutane is primarily used as a bromomethylating agent.[1] It is a safer halomethylating reagent compared to the traditionally used agents such as chloromethyl methyl ether, which is highly volatile. 1-Bromomethoxy-4-chlorobutane reacts readily with arenes under ***Zinc Chloride*** or ***Titanium(IV) Chloride*** catalysis to produce bromomethylated arenes in good yields with THF as the byproduct, the formation of which facilitates the reaction (eq 1).

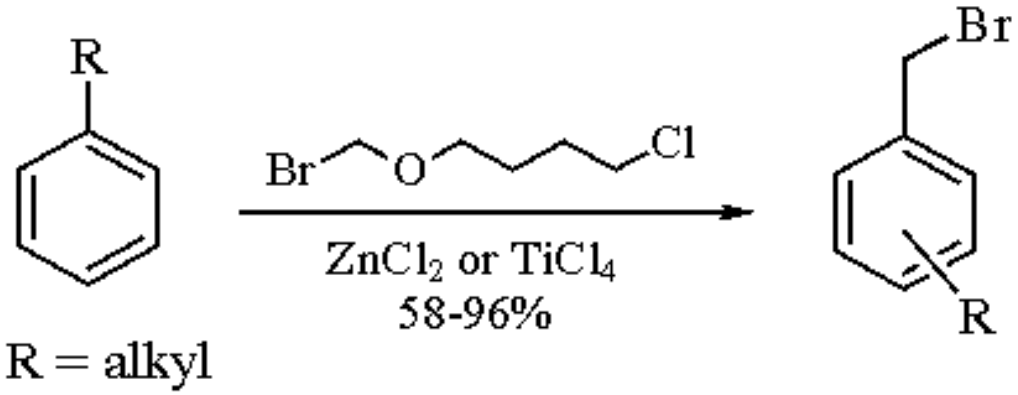

(1)

1-Bromomethoxy-4-chlorobutane can also serve as a precursor to the δ-chlorobutyl carboxonium ion, which can be further utilized for the alkylation of tetrahydrofuran and tetrahydrothiophene (eq 2).[2]

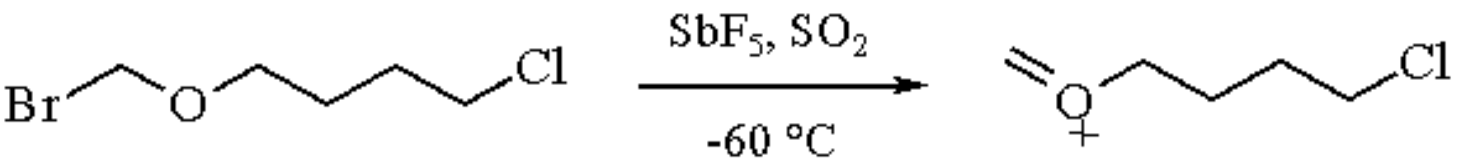

(2)

Related Reagents.

Bromomethyl Methyl Ether; ***Chloromethyl Methyl Ether***.

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1-Bromo-3-methyl-2-butene

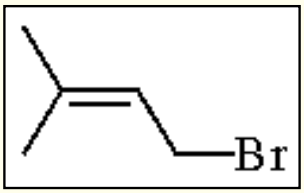

[870-63-3] · C_5H_9Br · 1-Bromo-3-methyl-2-butene · (MW 149.03)

(alkylating (prenylating) agent)

Alternate Names: prenyl bromide; isoprene hydrobromide.

Physical Data: bp 59-60 °C/60 mmHg; *d* 1.293 g cm^{-3}; fp 32 °C.

Form Supplied in: colorless liquid stabilized with silver wool.

Preparative Method: is readily prepared by treatment of ***Isoprene*** with ***Hydrogen Bromide*** (eq 1).[1-3]

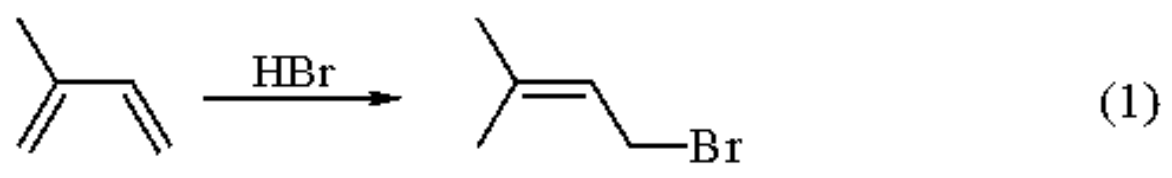

Handling, Storage, and Precautions: flammable liquid; corrosive; use in a fume hood.

Alkylating Agent.

Enantiomerically pure (2*S*)-1-phenylsulfonylalkan-2-ols are available from the ketones by asymmetric reduction with ***Baker's Yeast***. Alkylation of the dianion from these sulfonyl alcohols with 1-bromo-3-methyl-2-butene provides the (*S*,*S*)-alcohol in 66% yield (eq 2). Phenylseleno cyclization followed by oxidation-elimination afforded enantiomerically pure 2,5-disubstituted tetrahydrofurans.[4]

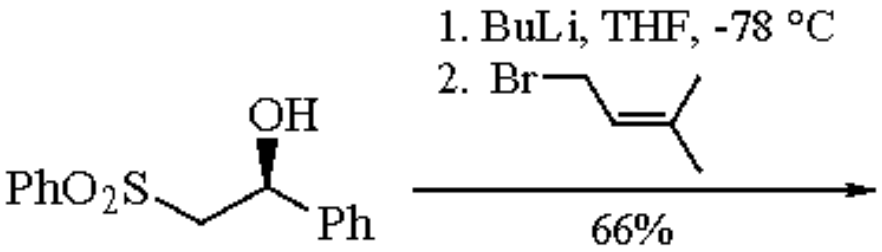

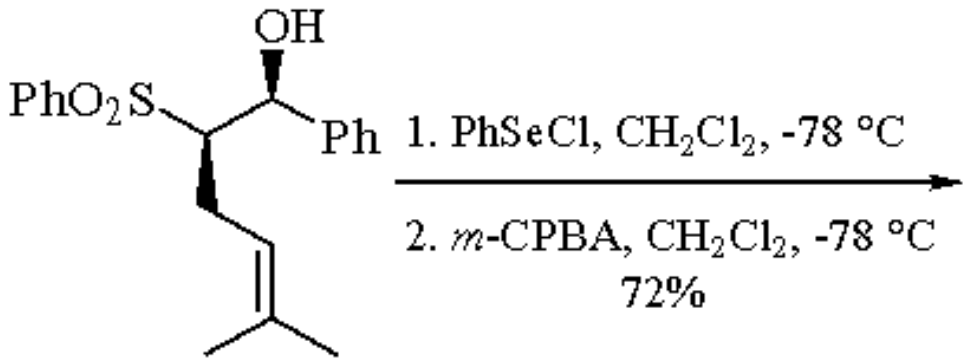

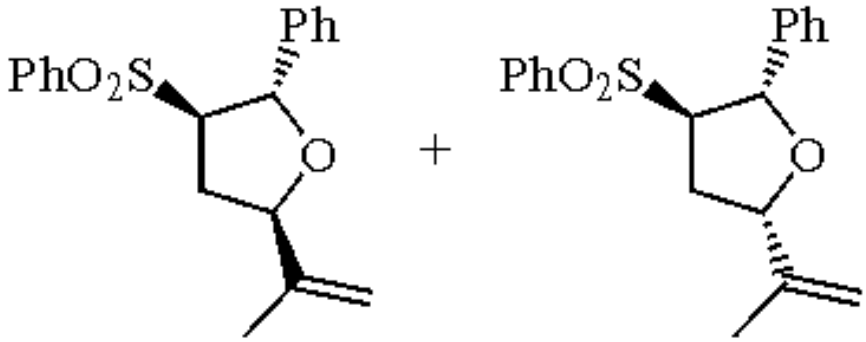

(2)

64:36

The anion derived from a trimethylsilyl (TMS)-capped alkynic Schiff base can be alkylated quite readily with 1-bromo-3-methyl-2-butene (eq 3). The imine can then be converted to an *N*-acetyl group, followed by introduction of the second nitrogen atom via the Ritter reaction. After deprotection, the *gem*-dimethyl diamino product was obtained.[5]

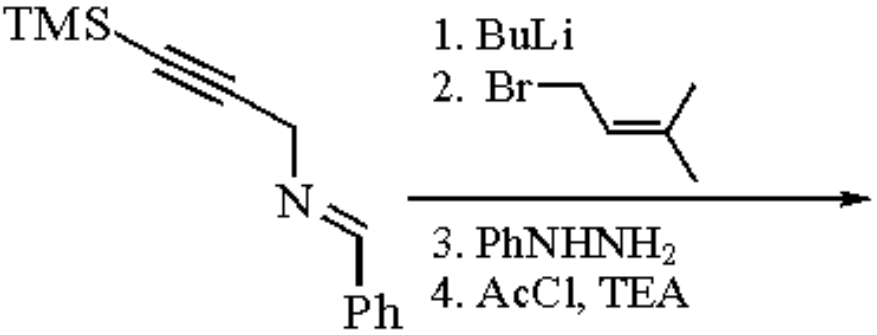

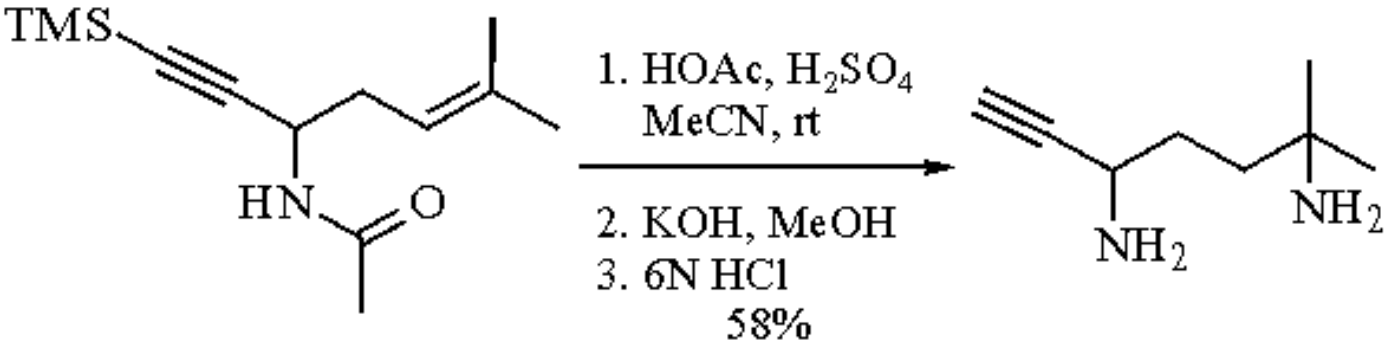

(3)

Intramolecular cyclization of allylic propiolates derived from *O*-alkylation of a carboxylic acid with various allylic halides has been used to study stannyl radical additions. The products resulting from radical addition to the propiolate lead to moderate yields of α-methylene-γ-butyrolactones after treatment of the vinyl α-tributylstannyl intermediate with HCl or HI in ether or benzene for several hours (eq 4).[6] A competing pathway with the radical cyclization is simple addition of tin hydride across the propiolate.

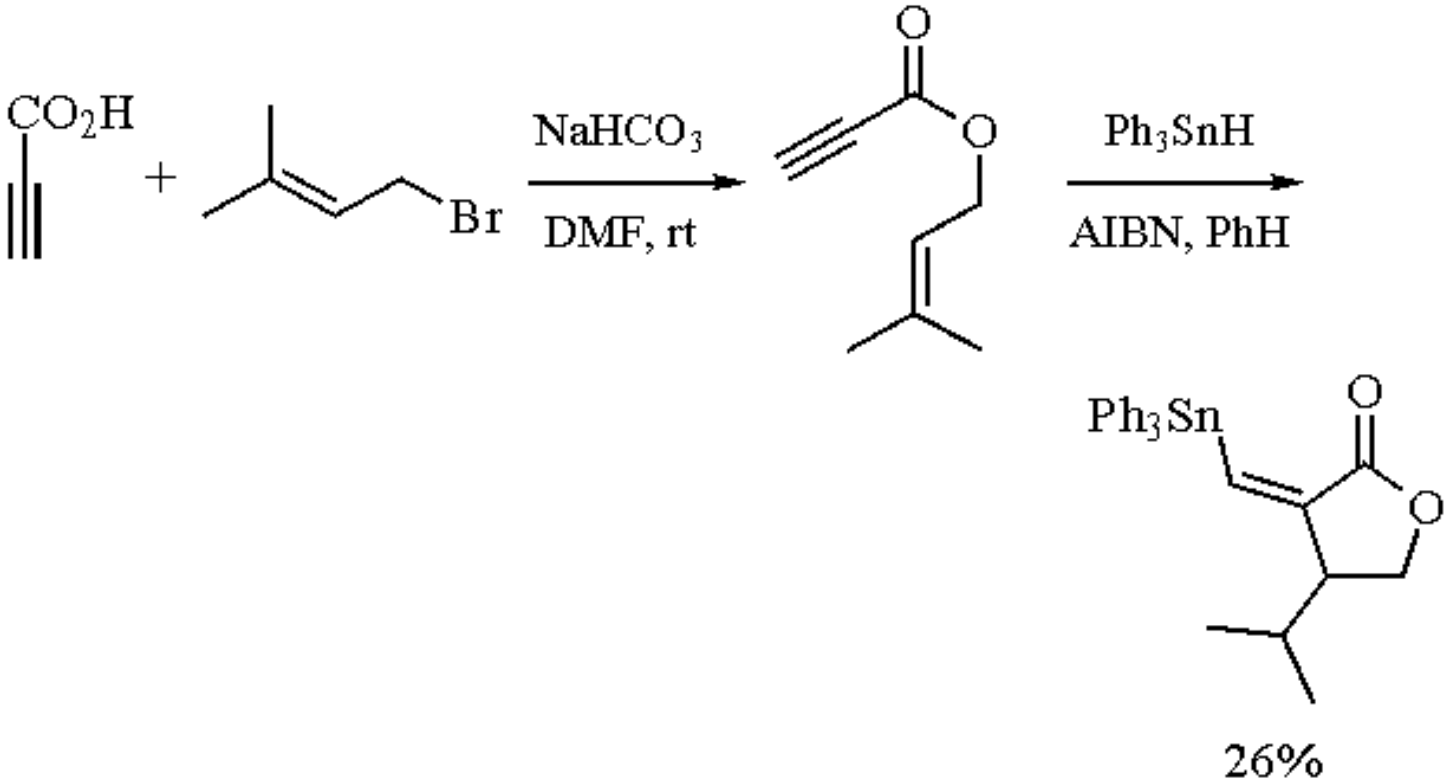

(4)

Treatment of the pyrido[2,3-*d*]pyrimidine nucleus with 1-bromo-3-methyl-2-butene in DMF afforded the N-8 alkylated

system in good yield (eq 5).[7-12]

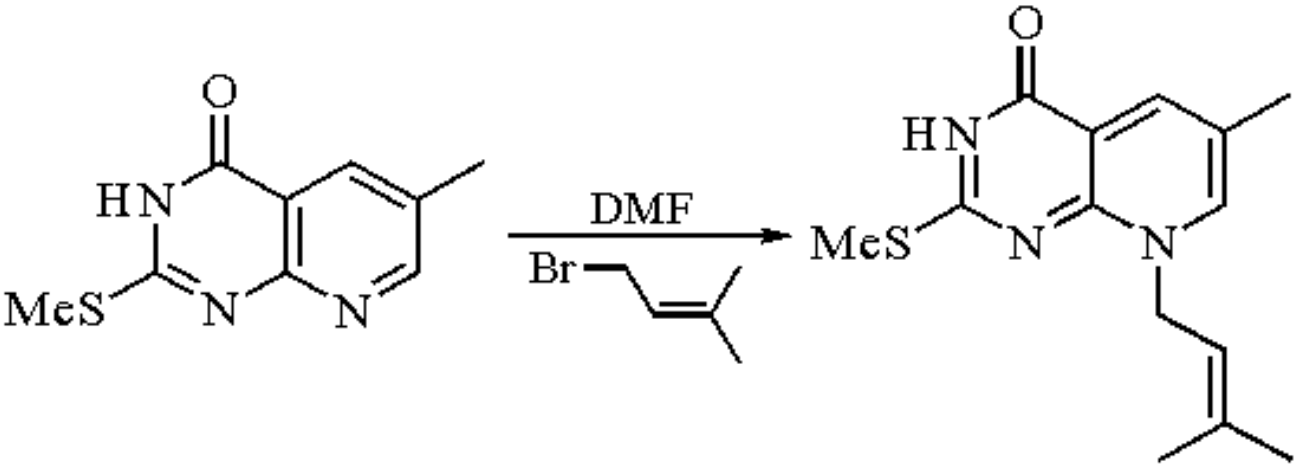

(5)

Derived Grignard Reagents.

3-Bromo-1-(phenylsulfonyl)-1-propene (a mixture of *cis*/*trans* isomers, 1:4), which is available from ***Allyl Phenyl Sulfone***, reacts with prenylmagnesium bromide to give *trans*-2-substituted cyclopropyl sulfones (eq 6). It is interesting that the Grignard reagent from 1-bromo-3-methyl-2-butene yields only the *trans*-2-(α,α-dimethylallyl)cyclopropyl phenyl sulfone. Alkyl Grignard reagents failed to yield the cyclopropyl sulfones. This represents an interesting cyclopropane synthesis via addition of unsaturated organometallics to alkenyl sulfones.[13]

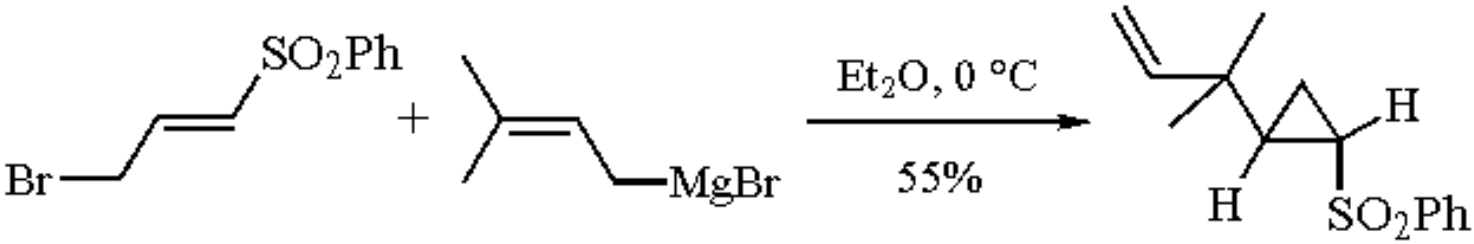

(6)

Nickel Coupling.

Treatment of 1-bromo-3-methyl-2-butene with excess ***Tetracarbonylnickel*** in benzene yields μ-3-methylbut-2-enylnickel bromide (eq 7). This π-allylnickel intermediate undergoes cross-coupling with aryl bromides in polar solvents such as DMF in quite good yield. This methodology was used in the synthesis of various vitamin K analogs,[14] as well as in the synthesis of (+)-epicamphorenone and (+)-epi-β-santalene.[15]

1-Bromo-3-methyl-2-butene

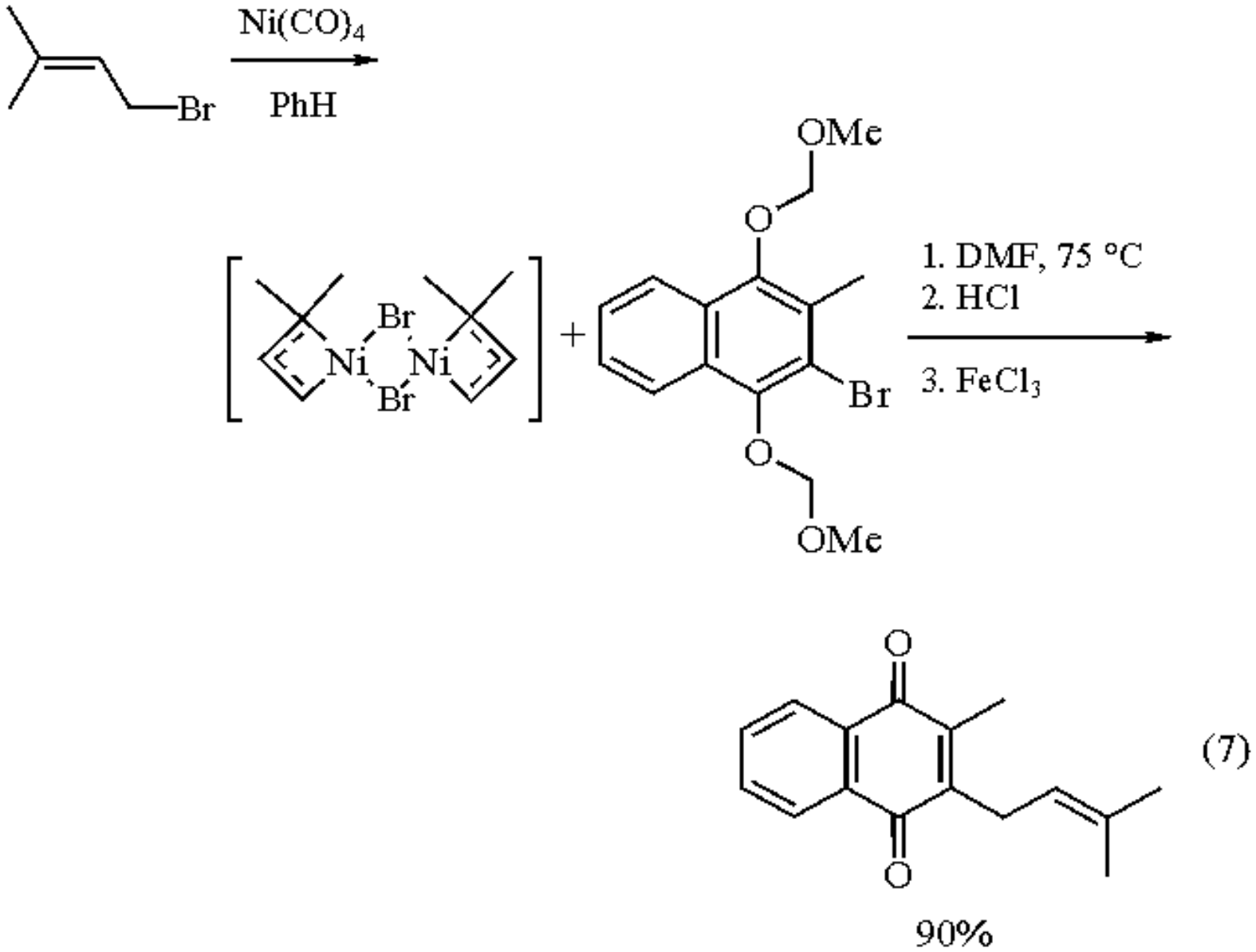

Derived Copper Reagents.

Allyltriphenylstannane compounds have been used to make allyl lithium reagents which are useful for the synthesis of difficult-to-prepare cuprates. Reaction of the cuprate derived from 1-bromo-3-methyl-2-butene with an unstable 3-furan tosylate afforded perillene in modest yield (eq 8).[16,17]

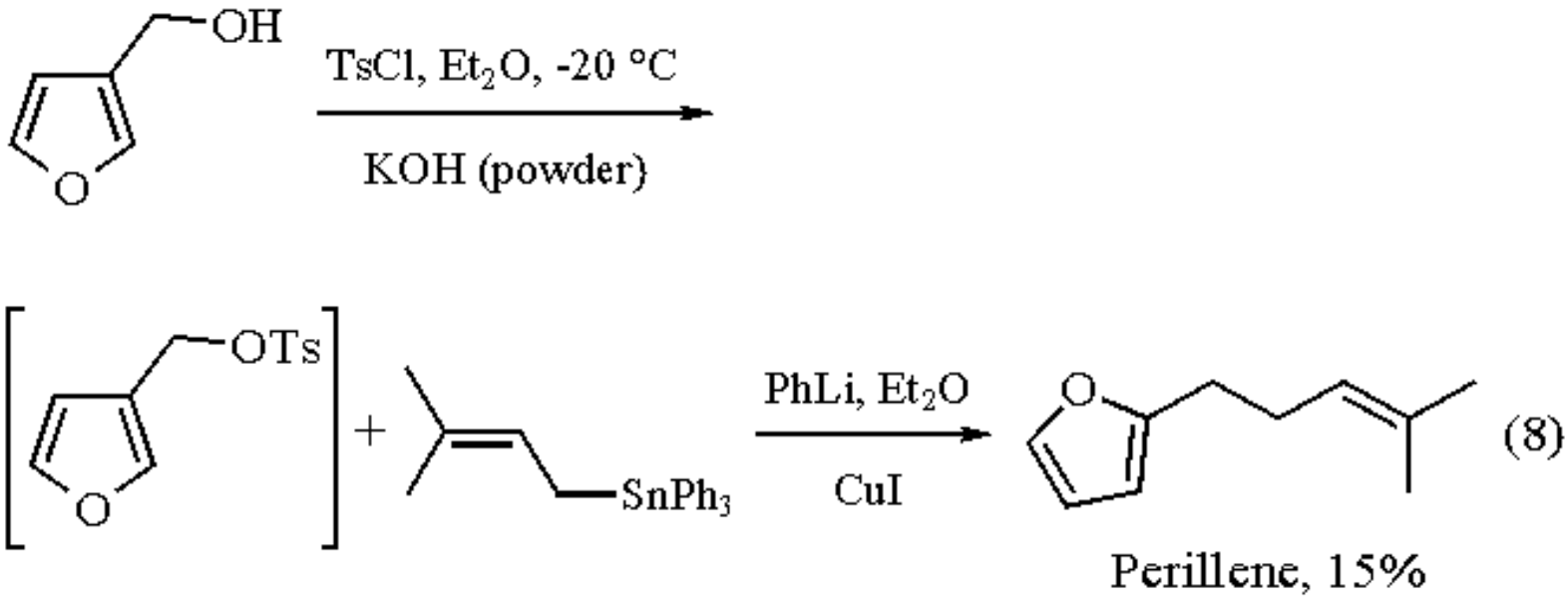

Derived Phosphorus Reagents.

Alkylation of diphenylmethylphosphine oxide with 1-bromo-3-methyl-2-butene provided an unsaturated phosphine, which upon further deprotonation afforded an anion which added to a cyclohexenyl methyl ketone to yield a mixture of *erythro* (53%) and *threo* (4%) products (eq 9). Elimination of $Ph_2PO_2^-$ from the *erythro* intermediate afforded (*Z*)-α-bisabolene.[18] A related synthesis of disubstituted alkenes relies on a hydride reduction to establish the correct stereochemistry prior to the elimination step.[19]

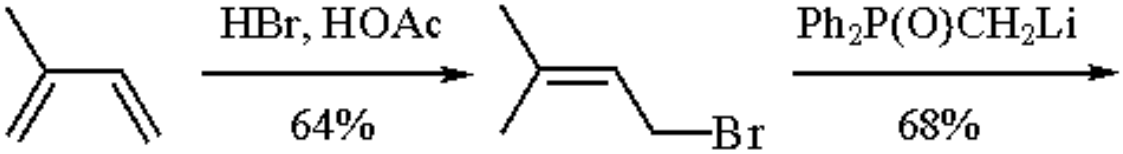

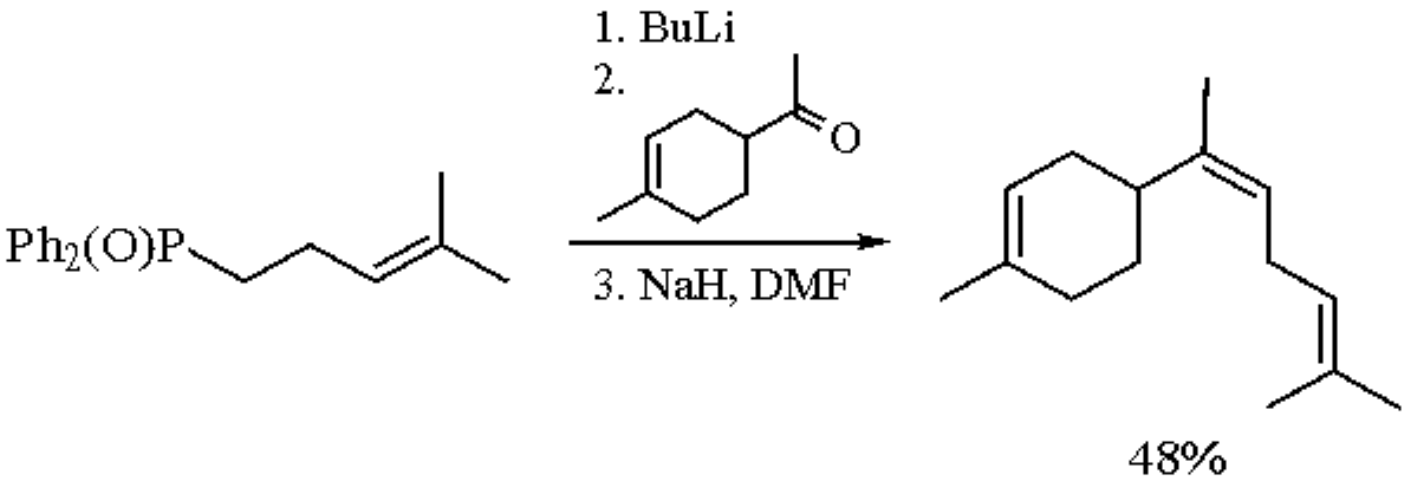

(9)

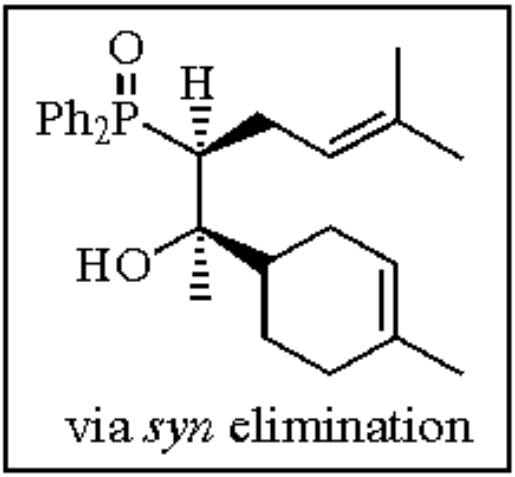

Addition of the Wittig reagent derived from ***Triphenylphosphine*** and 1-bromo-3-methyl-2-butene (γ,γ-dimethylallyltriphenylphosphonium bromide) to 2,3-indolinedione (eq 10) afforded an (*E*)/(*Z*) mixture of indolinones which are the major components from the rhizomes of *Cimicifuga dahurica* Maxim.[20]

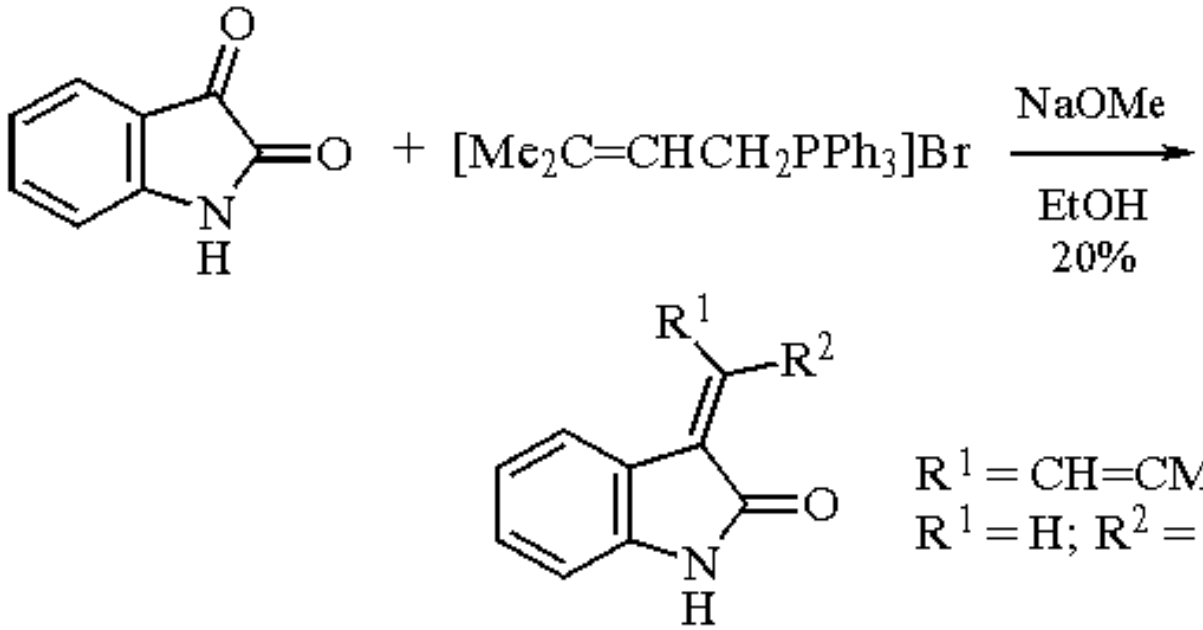

$R^1 = CH{=}CMe_2;\ R^2 = H$
$R^1 = H;\ R^2 = CH{=}CMe_2$ (10)

Sigmatropic Rearrangements.

Adducts derived from the alkylation of phenols with 1-bromo-3-methyl-2-butene have been used as substrates for thermal rearrangements leading to natural products, as well as being used in mechanistic studies (eq 11). Depending on the reaction temperature, several reaction pathways are possible, leading to both normal and abnormal Claisen rearrangement products. Interestingly, in the case cited the abnormal rearrangement product leads to the natural product anisoxide.[21]

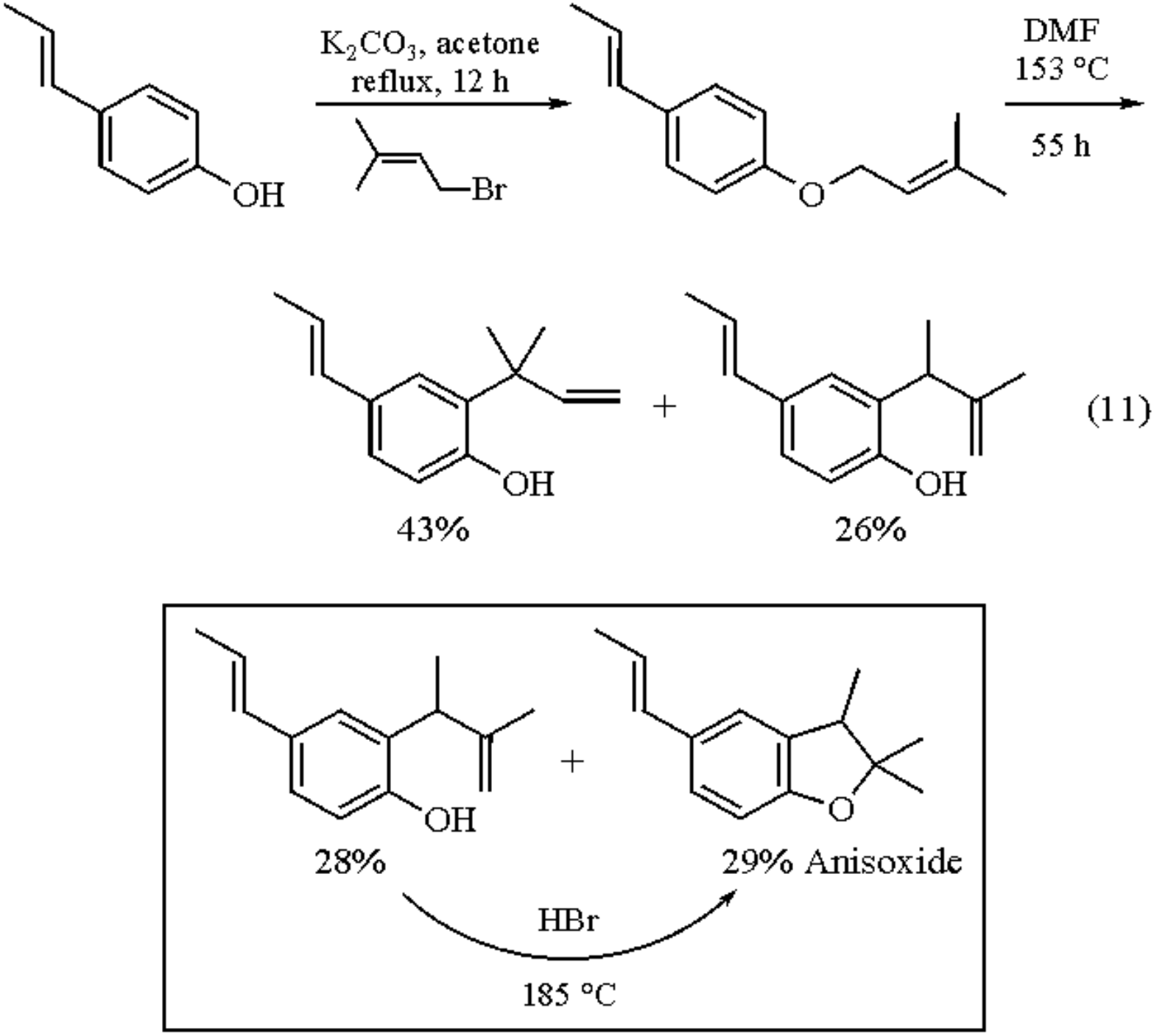

Base-catalyzed rearrangements of quaternary ammonium salts, derived from the reaction of tertiary amines with allylic halides (such as 1-bromo-3-methyl-2-butene), generally proceed via a [3,2]-sigmatropic rearrangement in aprotic solvents (eq 12). There is, however, often a competing 1,2-Stevens rearrangement. Treatment of diallylammonium cations with base in protic solvent led to a series of events (double bond isomerization, [3,3]-sigmatropic rearrangement, hydrolysis) ultimately yielding an aldehyde in excellent yield.[22]

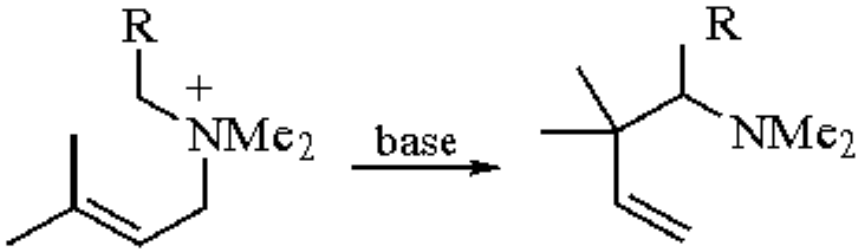

R = CH_2=CH-, Me_2C=CH-, Ph—≡

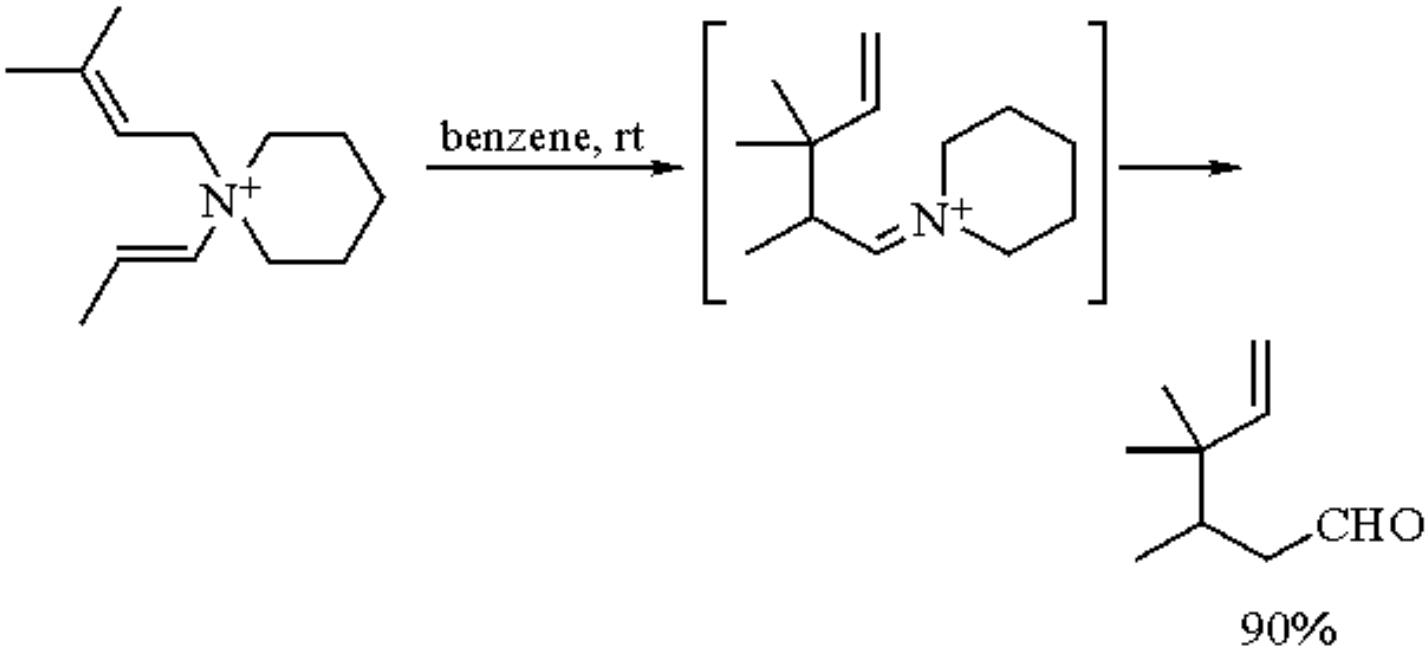

(12)

α-Allokainic and α-kainic acids are neurophysiologically interesting constituents of algae. *N*-Alkylation of the bis(ethoxycarbonyl) (*Z*)-enoate with ^{13}C-labeled 1-bromo-3-methyl-2-butene provided mechanistic evidence for a concerted ene reaction (eq 13). The desired *N*-alkylation could not be achieved using the corresponding tosylate or chloride.[23]

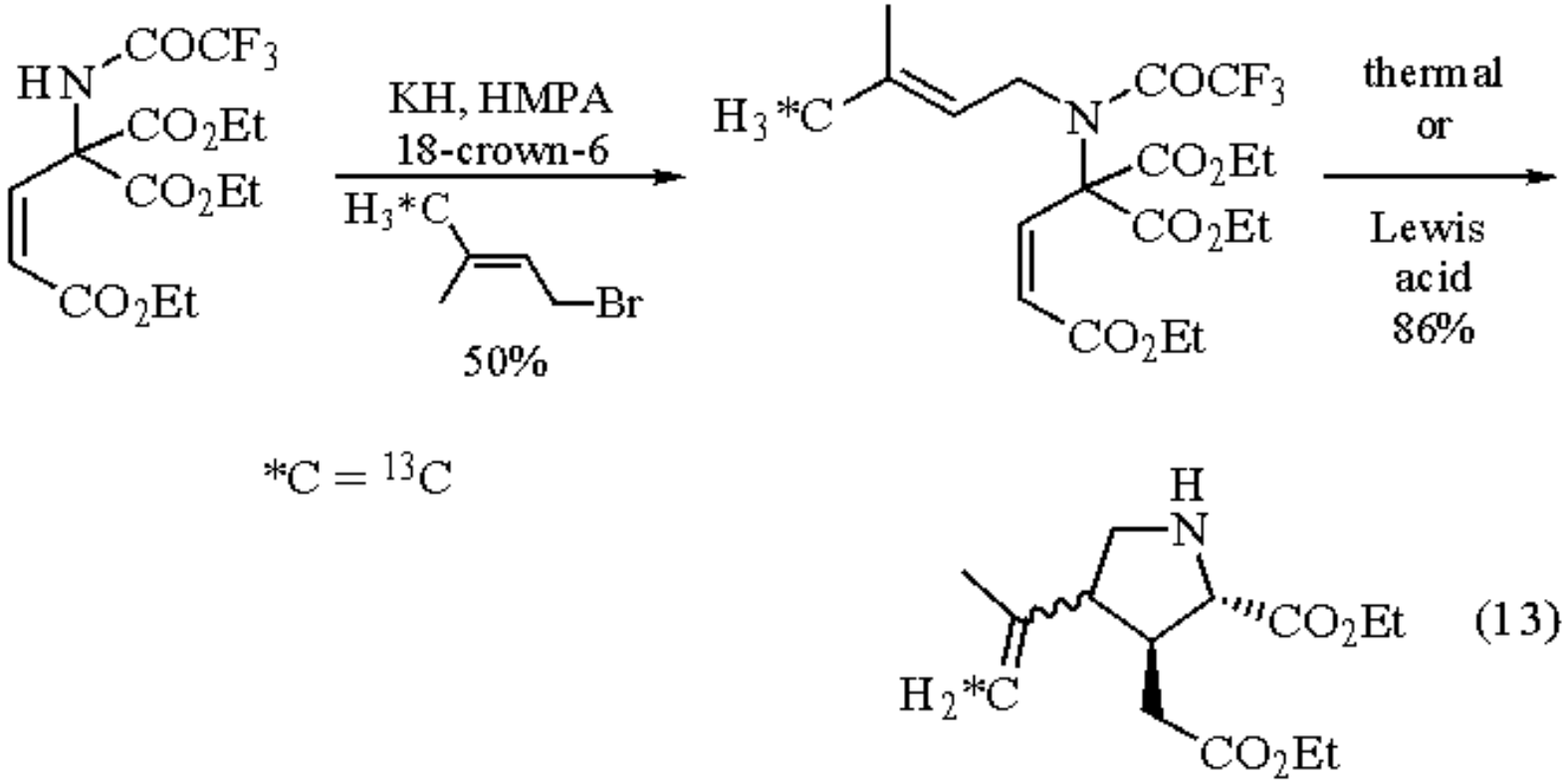

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Ronald B. Gammill

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(Bromomethyl)chlorodimethylsilane[1]

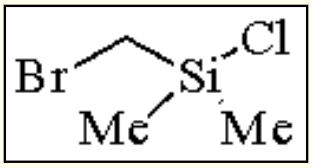

[16532-02-8] · $C_3H_8BrClSi$ · (Bromomethyl)chlorodimethylsilane · (MW 187.54)

(allylic,[2] propargylic,[3] and homoallylic[4] bromomethylsilyl ethers are used for regio- and stereoselective introduction of hydroxymethyl[2-4] or methyl[2c,d] groups through radical cyclization; derivatizing agent for electron capture GC[5])

Physical Data: bp 133-135 °C; bp 130 °C/740 mmHg; *d*204 1.386; *n*20D 1.466.

Solubility: sol most organic solvents including benzene, THF, methylene chloride, chloroform, and pyridine.

Form Supplied in: commercially available colorless liquid with 98% (GC) purity.

Analysis of Reagent Purity: GC analysis appears best; the following spectroscopic information may also be used: FTIR (vapor phase at 225 °C): 2978 (w), 1392 (w), 1264 (m), 822 (s) cm^{-1};[6] ^1H NMR ($CDCl_3$) δ 0.58 (s, 6H), 2.65 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 0.27, 16.47.

Handling, Storage, and Precautions: moisture-sensitive; toxicological properties have not been thoroughly investigated; symptoms of exposure may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea, and vomiting.[7] Use in a fume hood.

Use as a Source of α-Silyl Radicals.

Treatment of hydroxy groups with $(BrCH_2)Me_2SiCl$ in the presence of ***Triethylamine*** often with a catalytic amount of ***4-Dimethylaminopyridine*** provides the (bromomethyl)dimethylsilyl ether derivatives in high yield. α-Silyl radicals generated from (bromomethyl)dimethylsilyl derivatives of cyclic allylic alcohols undergo highly regio- and stereoselective 5-*exo* radical cyclization reactions to provide the corresponding siloxanes (eq 1).[2,8] These five-membered siloxanes can be efficiently oxidized to 1,3-diols[2a-d,8] by the use of Tamao's conditions[9] or cleaved to β-methyl alcohols with ***Potassium t-Butoxide-Dimethyl Sulfoxide*** (eq 1).[2c,d] Radicals generated from the (bromomethyl)dimethylsilyl ethers of acyclic alcohols also exhibit similar regioselectivity during radical cyclization.[2a] Formation of *trans*-3,4-disubstituted 1-sila-2-oxacyclopentanes is generally favored (eq 2).[2a] However, propensity toward increased 6-*endo* cyclization, as is observed in the cyclization of 2-sila-5-hexen-1-yl radicals,[10] can be clearly manifested in certain α-silyl radicals (eq 3).[2a,11] This 6-*endo* mode of cyclization is observed for α-silyl radicals with

appropriate structural bias (eq 4).[12] Detailed studies on the factors that affect these two competing modes of cyclization of allylic α-silyl radicals have resulted in the development of new methodology for the introduction of an angular hydroxymethyl group (eq 5).[13,14]

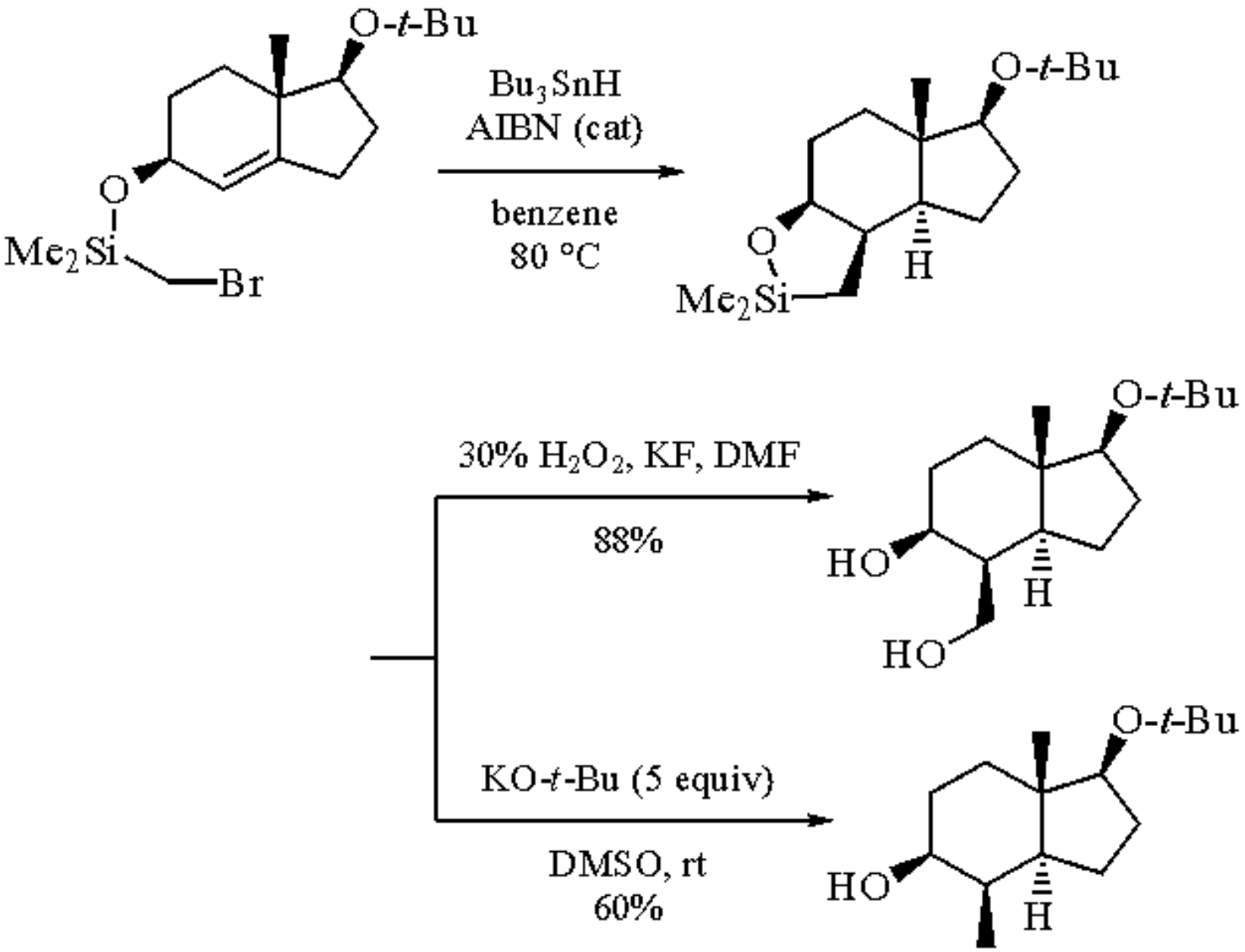

(1)

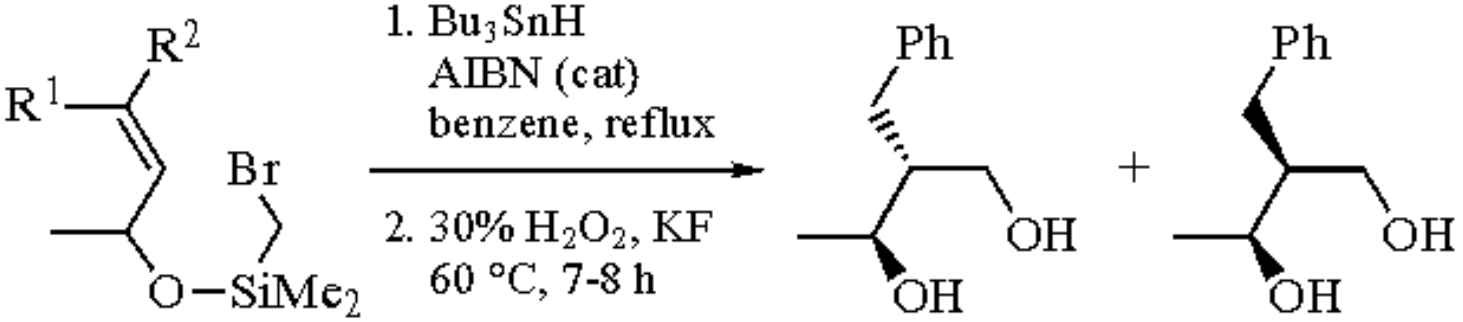

(2)

$R^1 = H, R^2 = Ph$ 84:16 (85%)
$R^1 = Ph, R^2 = H$ 100:0 (94%)

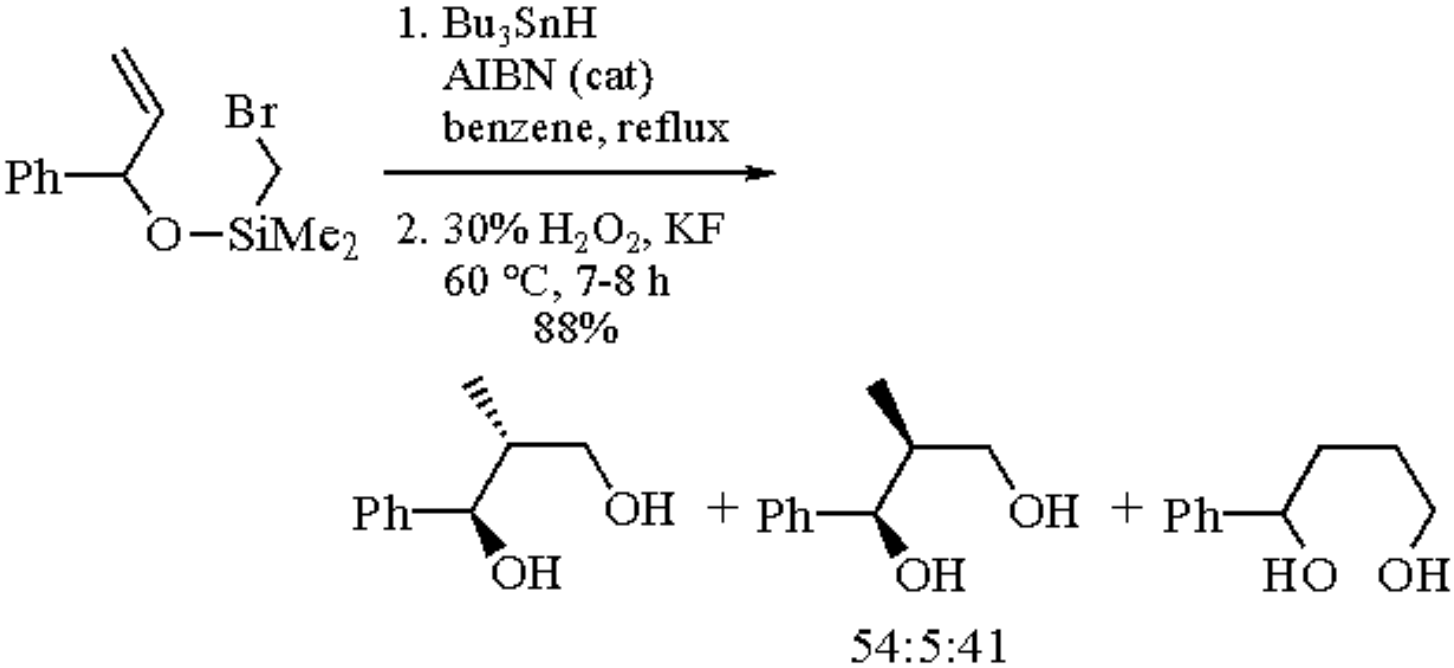
1. Bu3SnH
AIBN (cat)
benzene, reflux
2. 30% H2O2, KF
60 °C, 7-8 h
88%
Ph
Br
O–SiMe2
OH
54:5:41

(3)

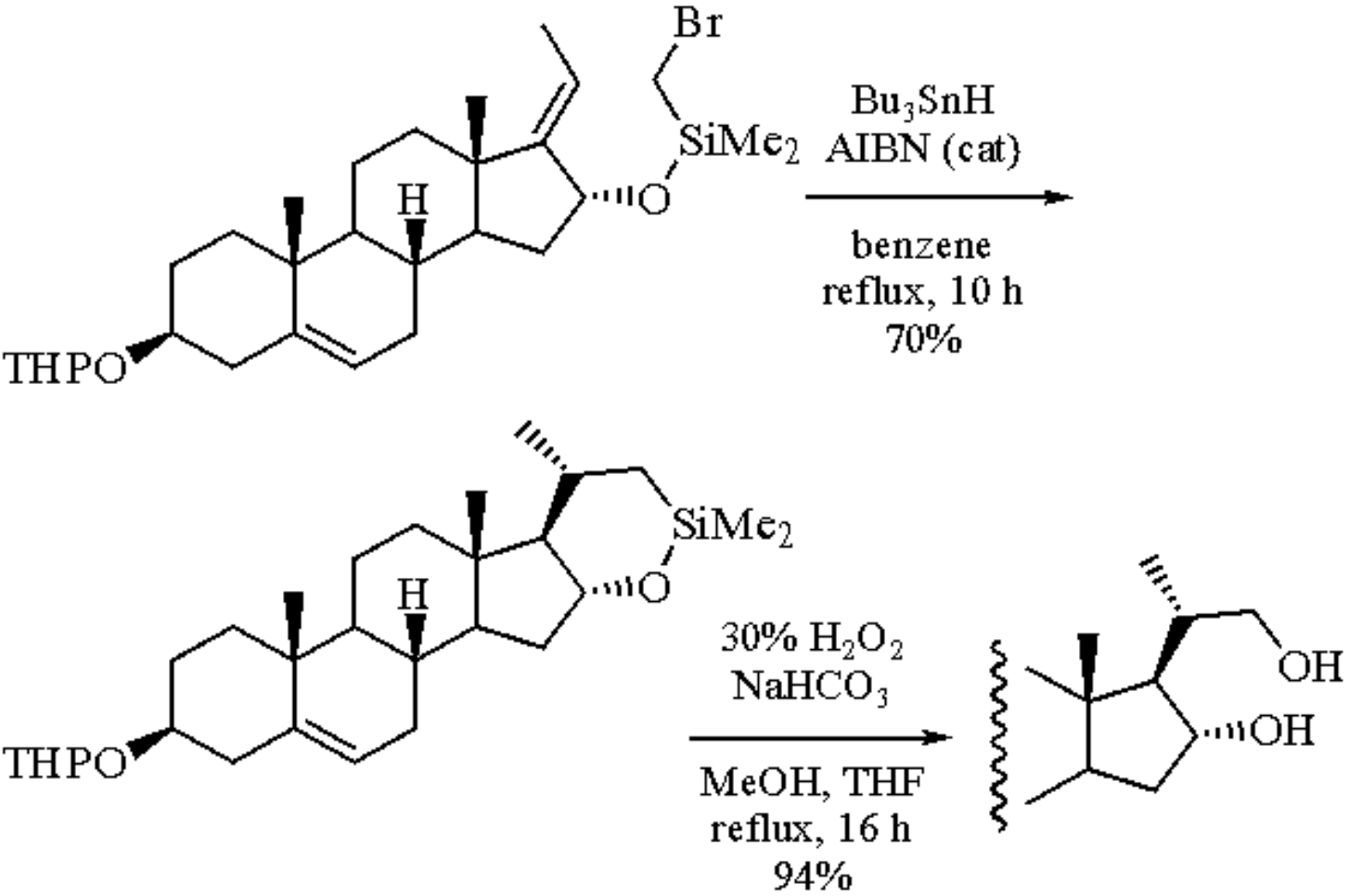
Br
SiMe2
H
O
THPO
Bu3SnH
AIBN (cat)
benzene
reflux, 10 h
70%
30% H2O2
NaHCO3
MeOH, THF
reflux, 16 h
94%
OH

(4)

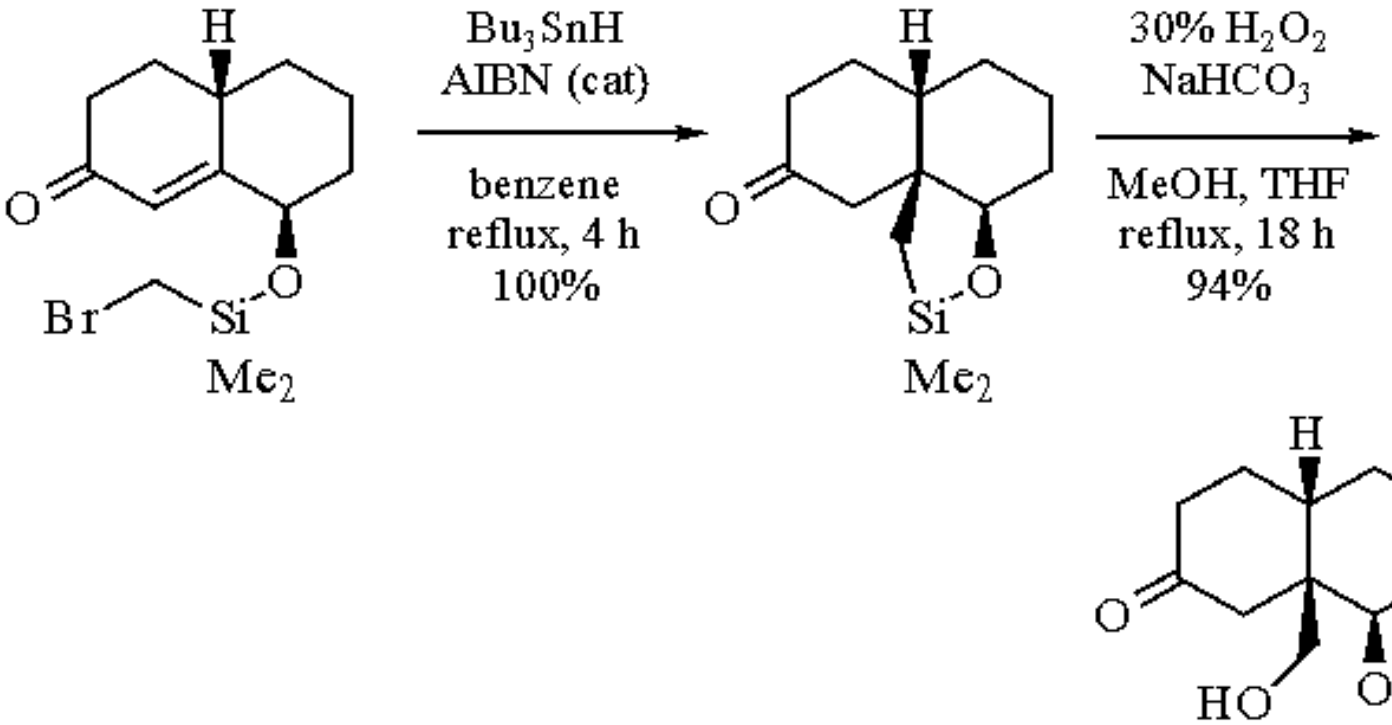

(5)

(Bromomethyl)dimethylsilyl propargylic ethers undergo highly regio-, stereo-, and chemoselective radical cyclization.[3,15] The α-silyl radicals cyclize in a 5-*exo* fashion to provide siloxanes with an exocyclic alkene having *trans* stereochemistry between the newly formed C-C and C-H bonds (eq 6).[15] This stereochemical preference is reversed when a substituent at the distal sp carbon is a TMS or phenyl group. When there are competing sites for addition between alkenic and alkynic carbons by the 5-*exo*-mode of cyclization, these α-silyl radicals preferentially attack an sp (5-*exo*-dig) over sp^2 carbon (5-*exo*-trig).[15]

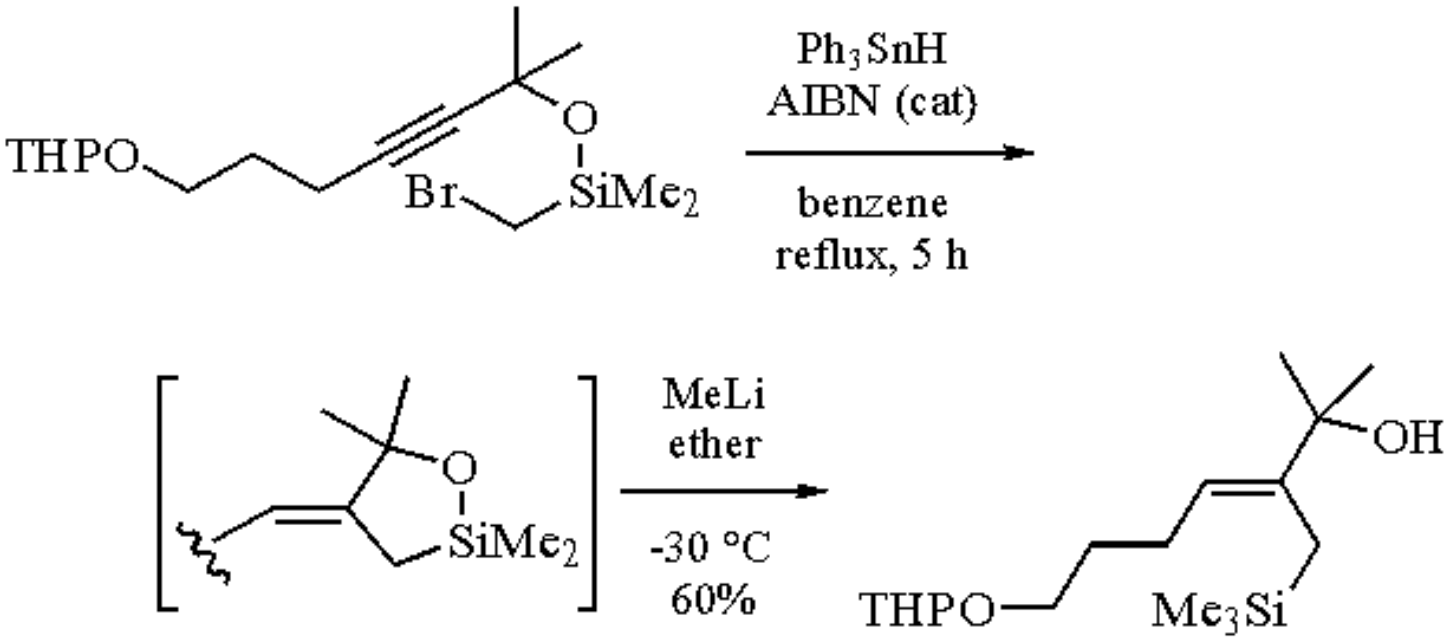

(6)

The mode of cyclization of α-silyl radicals generated from homoallylic (bromomethyl)dimethylsilyl ethers is highly dependent upon the substitution pattern on the distal alkenic carbon.[4] Thus while those with unsubstituted distal alkene carbons provide seven-membered siloxanes (7-*endo*) (eq 7),[4] those having substituted carbons undergo a 6-*exo*-mode of radical cyclization in a highly regio- and stereoselective manner (eq 8).[4] These six-membered siloxanes provide,

upon Tamao oxidation,[9] branched chain 1,4-diols (eq 8).[4]

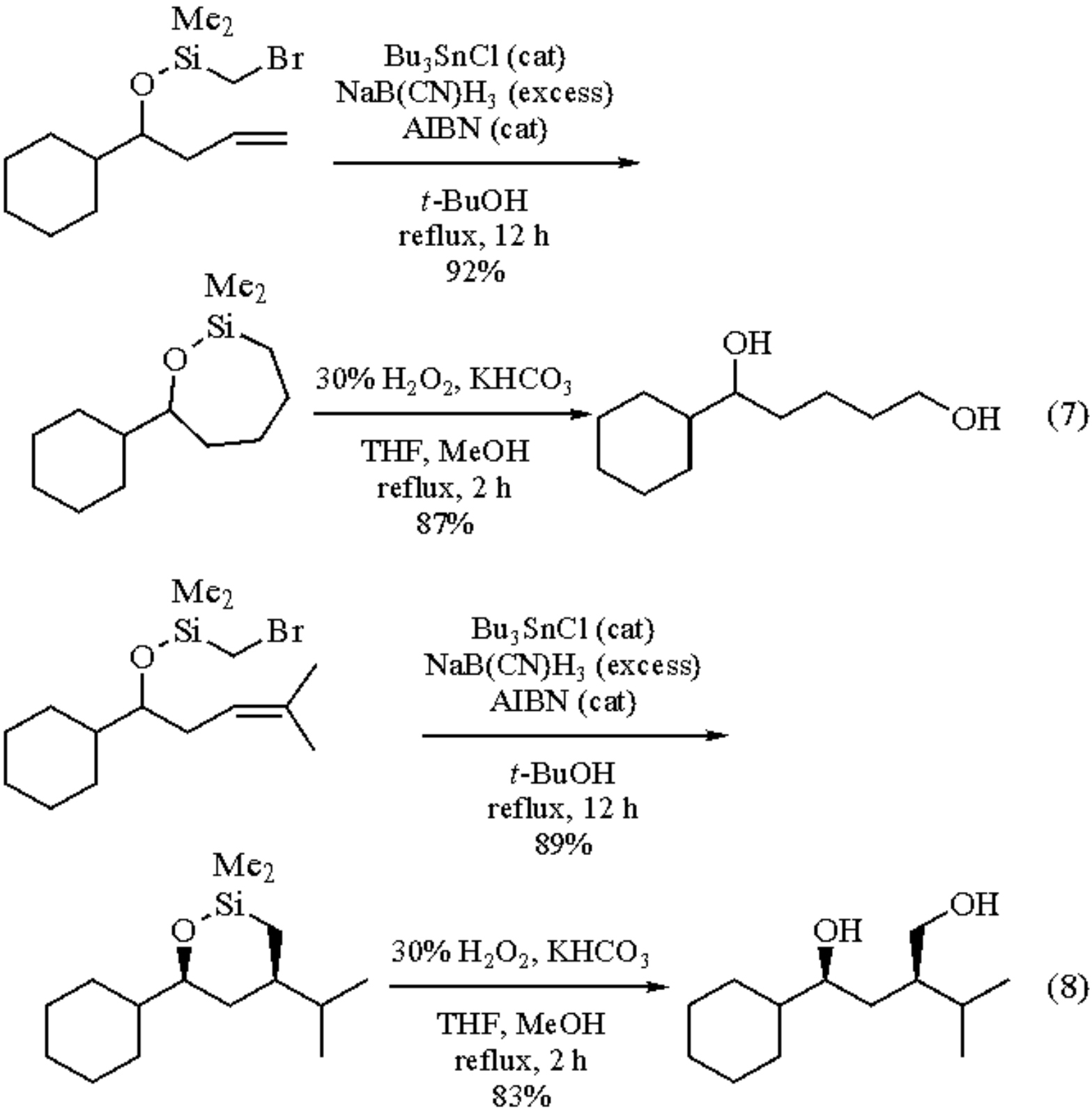

Generation of Chloro(lithiomethyl)dimethylsilane.

Treatment of (bromomethyl)chlorodimethylsilane in THF/ether with 1 equiv of ***n-Butyllithium*** in hexanes at -120 °C produces chloro(lithiomethyl)dimethylsilane. This lithiated derivative spontaneously eliminates LiCl to give an

intermediate silaethylene species, which undergoes dimerization to afford 1,1,3,3-tetramethyl-1,3-disilacyclobutane (45%), together with a small amount of 1,1,3,3,5,5-hexamethyl-1,3,5-trisilacyclohexane (15%) (eq 9).[16]

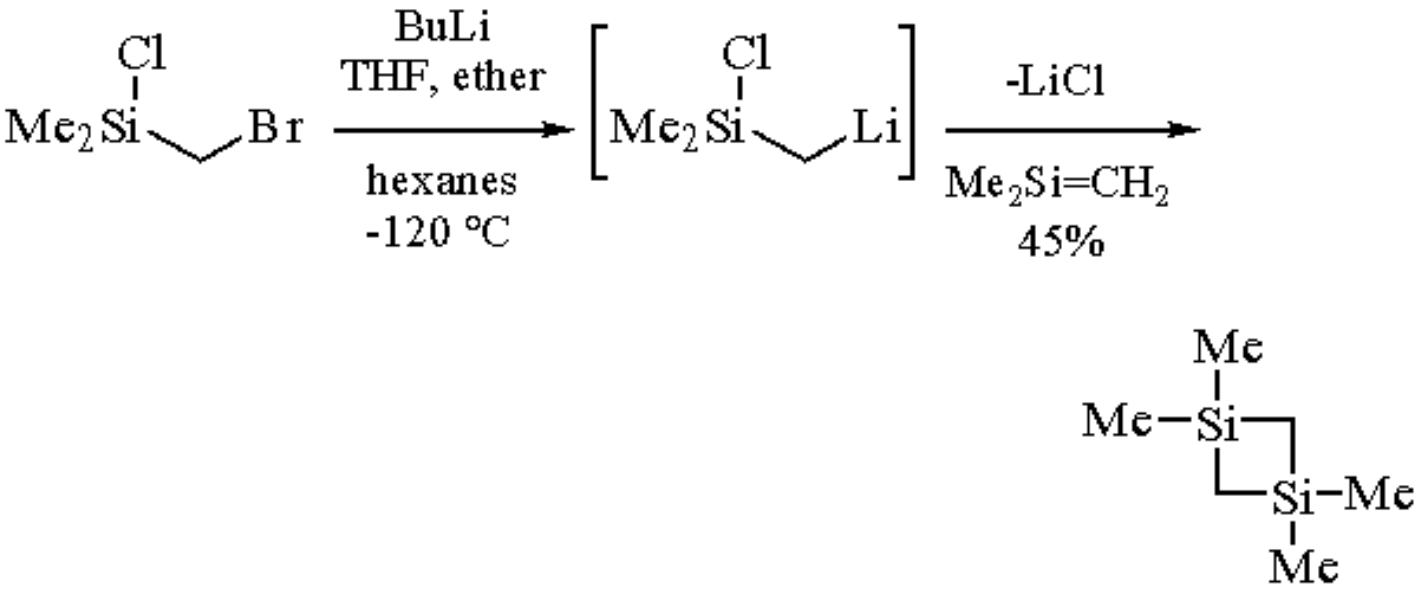

(9)

Silazole Synthesis.

(Bromomethyl)dimethylsilyl derivatives obtainable from 2-mercaptoimidazoles and -benzimidazoles undergo cyclodehydrohalogenation, in the presence of a slight excess of a proton sponge (***1,8-Bis(dimethylamino)naphthalene***), providing silazoles (eq 10).[17]

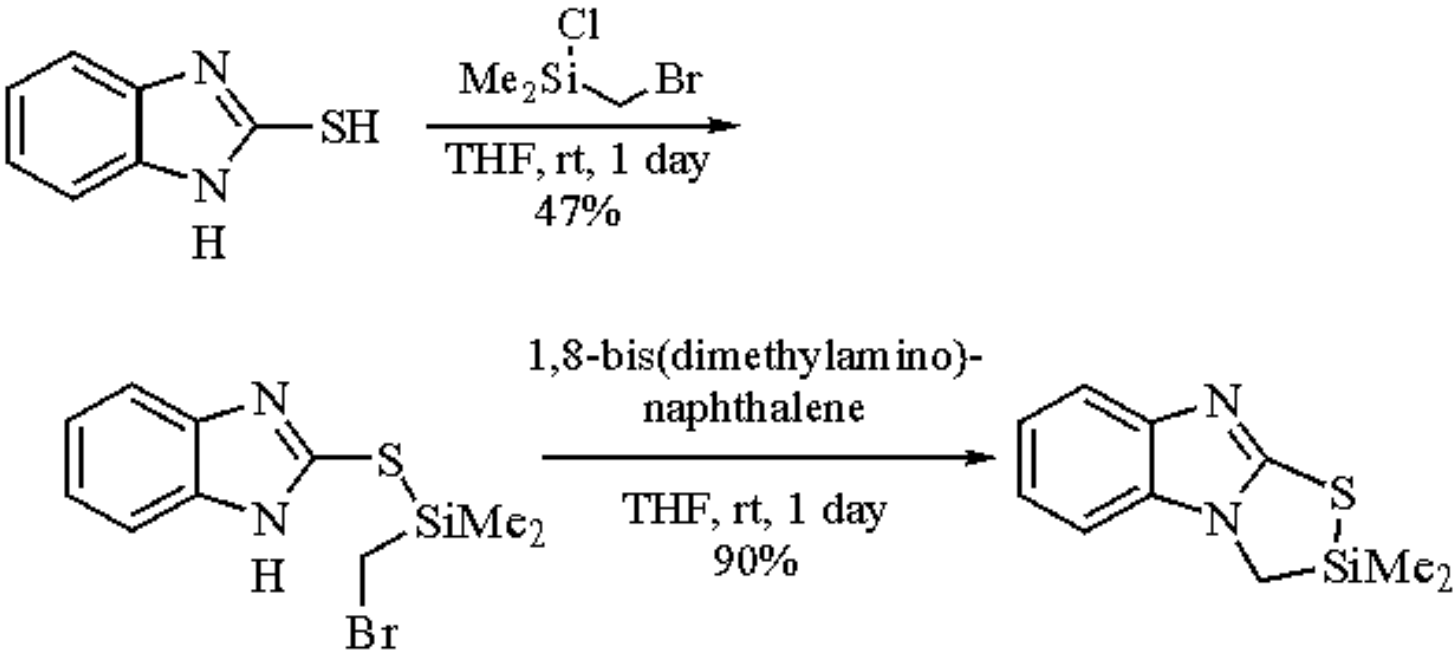

(10)

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Bromomethylenetriphenylphosphorane[1]

$Ph_3P{=}CHBr$

[39598-55-5] · $C_{19}H_{16}BrP$ · Bromomethylenetriphenylphosphorane · (MW 355.21)

(Wittig reagent for the formation of 1-bromoalkenes from aldehydes and ketones; terminal alkynes are formed by elimination of HBr)

Solubility: sol THF and ether; reacts with water and other acidic protons.

Preparative Method: by using strong base to deprotonate the salt bromomethyltriphenylphosphonium bromide, which is available commercially or synthetically.[2]

Handling, Storage, and Precautions: the ylide is generally prepared in situ and used immediately, but can be stored under nitrogen for short periods. The ylide will decompose upon exposure to air or water.

Preparation of the Ylide and Stereoselectivity.

The Wittig reaction of bromomethylenetriphenylphosphorane forms 1-bromoalkenes from carbonyl compounds with complete regioselectivity. Unlike most phosphorus ylides, treatment of the starting phosphonium salt with butyllithium does not give the desired bromo-substituted ylide, but forms $Ph_3P{=}CH_2$ via halogen-metal exchange.[2,3] The use of PhLi and lithium piperidide are also not recommended.[2,4] Bromomethylenetriphenylphosphorane has been cleanly prepared from the dry bromomethyl phosphonium salt using either ***Potassium t-Butoxide*** in THF[5] or ***Potassium Hexamethyldisilazide*** in toluene.[6] With these bases the Wittig reaction with aldehydes and ketones proceeds in good yield and often, in the case of aldehydes, with high (*Z*) selectivity. Table 1 gives results for the ylide prepared using *t*-BuOK at low temperature (eq 1),[5] and shows that (*Z*)-bromoalkenes were prepared with good selectivity. When 2 equiv of base were used in these reactions, terminal alkynes were formed as the final product.[5]

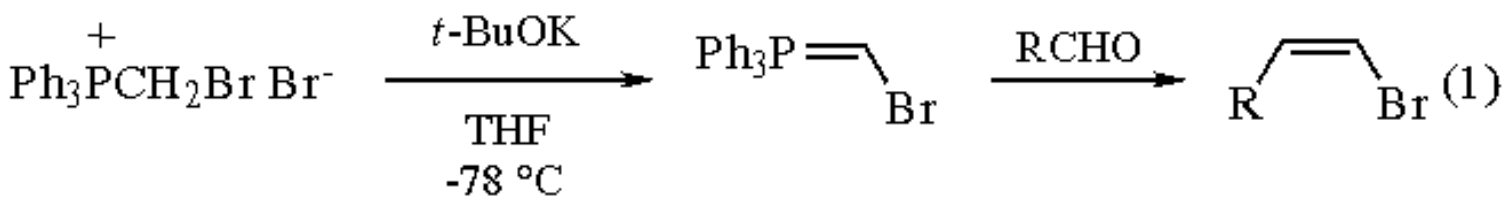

Table 1 Wittig Reaction of Bromomethylenetriphenylphosphorane with Aldehydes

Aldehyde	Yield (%)	(*E*:*Z*) Ratio
PhCHO	71	83:17
a-NaphthylCHO	81	86:14
$PhCH_2CH_2CHO$	47	86:14
PhCH=CHCHO	72	77:23

High selectivity was also reported in the reaction of the bromo-substituted ylide (prepared from KHMDS in toluene) with an α-keto amino acid derivative (eq 2), which gave a 95:5 (*Z*:*E*) ratio of bromoalkenes in 80% yield.[6]

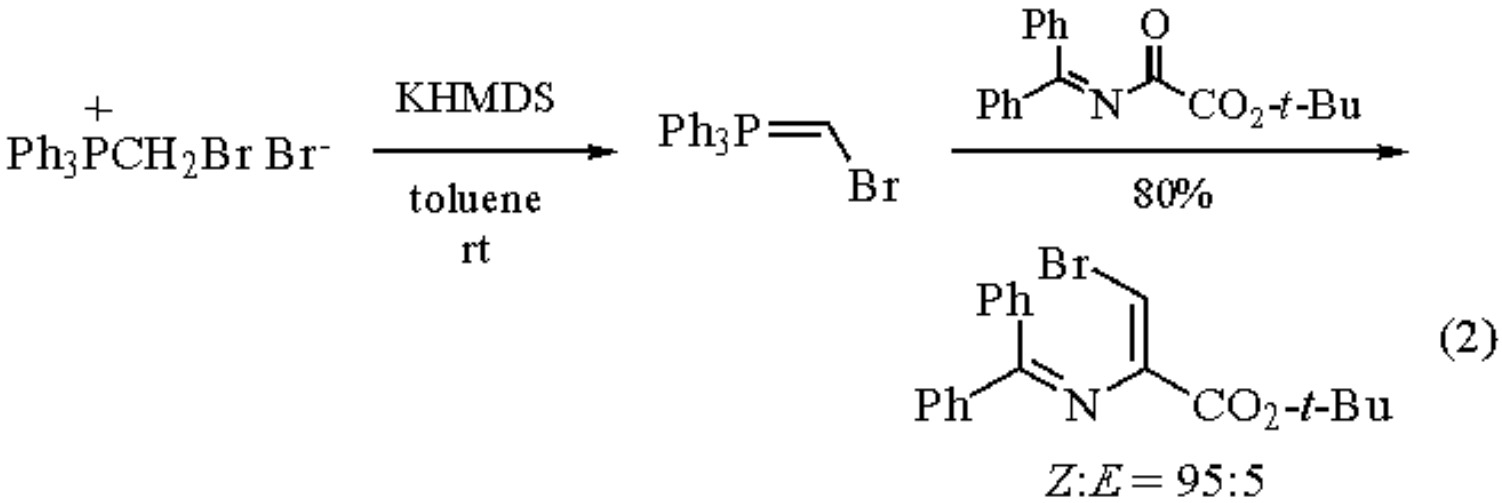

(2)

Synthetic Uses.

The bromoalkene products of the Wittig reaction have most often been used for the preparation of alkynes or in palladium-catalyzed coupling reactions. HBr elimination with an excess of strong base (***Lithium Diisopropylamide*** or *t*-BuOK) gives terminal alkynes in good yield. The overall transformation (RCHO to RC&tbond;CH) has been used in the synthesis of leukotriene B_4 (eq 3),[7] derivatives of vitamin D_3,[8] and methynolide intermediates.[9] Palladium(0) coupling of 1-bromoalkenes with alkynes has also been reported, such as in the synthesis of antitumor agent CI-920[10] and carotenoids.[11]

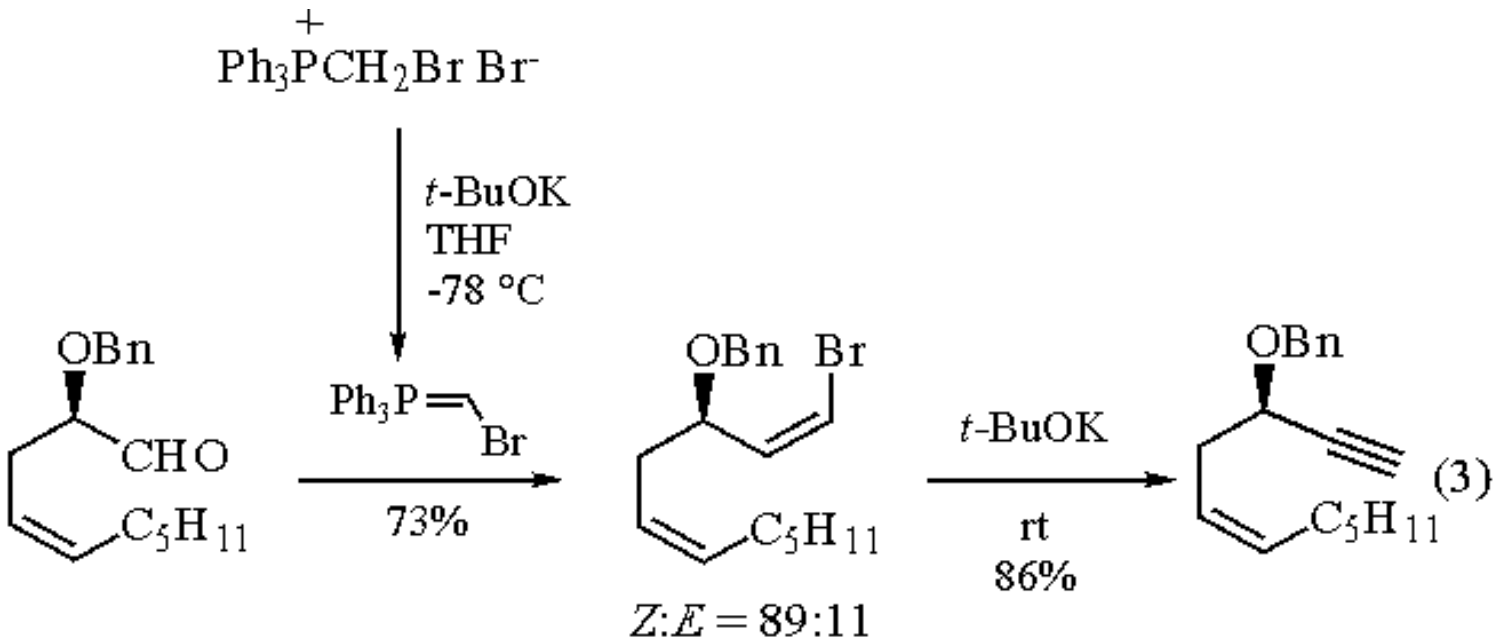

A useful alternative to the Wittig reaction for vinyl halide synthesis is the reaction of ***Bromoform*** with $CrBr_3/LiAlH_4$ in the presence of an aldehyde.[12] The organochromium intermediate formed in situ reacts with aliphatic and aromatic aldehydes to give bromoalkenes with good (*E*) selectivity in 55-70% yield. This transformation, however, requires 6 equiv of the expensive chromium reagent. For preparation of vinyl bromides from ketones, addition of lithiated methylene bromide to the carbonyl group followed by reduction with ***Zinc-Acetic Acid*** gives 1-bromoalkenes in good yield.[13]

---

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Bromomethyllithium[1]

$BrCH_2Li$

[92533-92-1] · CH_2BrLi · Bromomethyllithium · (MW 100.87)

(converts aldehydes or ketones to oxiranes;[1] $B(OR)_3$ to $BrCH_2B(OR)_2$;[1] $R^1B(OR^2)_2$ to $R^1CH_2B(OR^2)_2$[1])

Physical Data: stable at -110 °C in the presence of LiBr; unstable at higher temperatures; unstable even at -130 °C in the absence of LiBr.[4,5]

Preparative Methods: preferably by addition of MeLi/LiBr or *n*-BuLi solution dropwise to a vigorously stirred solution of CH_2Br_2 and the substrate in THF cooled with a dry ice-acetone bath.[1]

Handling, Storage, and Precautions: see ***n-Butyllithium*** and ***Dibromomethane***. The reagent must be generated under an inert atmosphere of nitrogen or argon.

Oxirane Formation.

Aldehydes and ketones are efficiently converted to oxiranes by $BrCH_2Li$ generated by addition of BuLi to CH_2Br_2 in the presence of the carbonyl compound in THF cooled with a -78 °C bath (internal temperature below -65 °C), followed by standing at rt for 15 h (eq 1).[1]

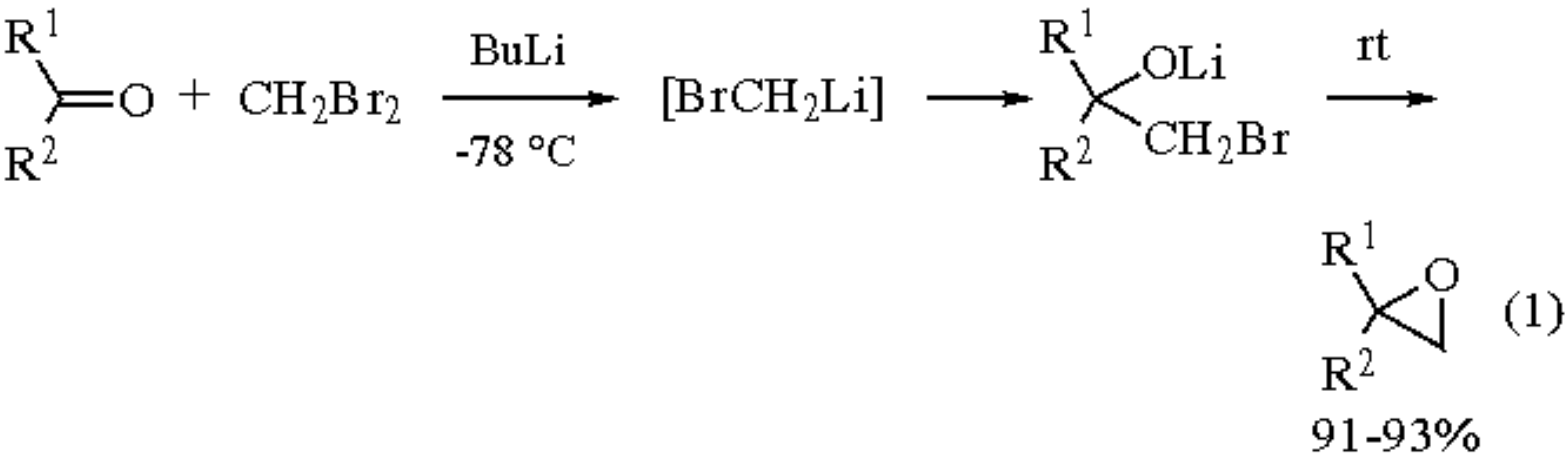

With $BrCH_2Li$ the yields were uniformly high in all four examples illustrated (eqs 2-5). The first three transformations had been carried out previously with ***Chloromethyllithium***, with reported yields of 91-99%[2] and replicated yields of 88-

93%.[1] However, with the last example, ethyl levulinate, $ClCH_2Li$ yielded only 40% oxirane and $BrCH_2Li$ yielded 93%. Thus $BrCH_2Li$ appears to be the more selective reagent, at least with regard to interfering ester functionality.

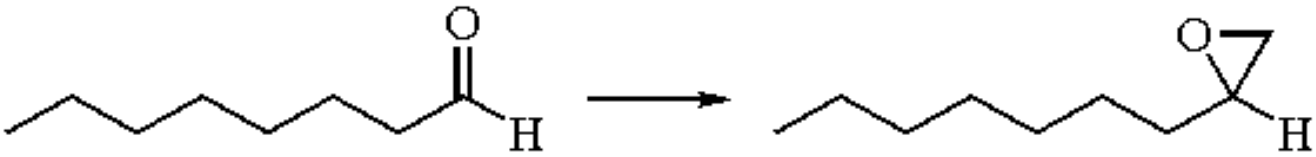

(2)

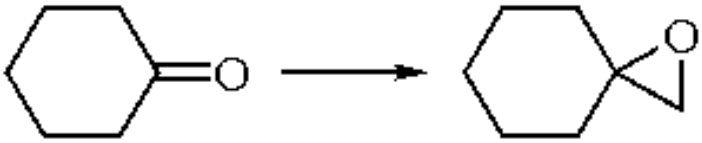

(3)

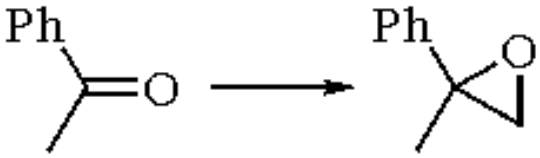

(4)

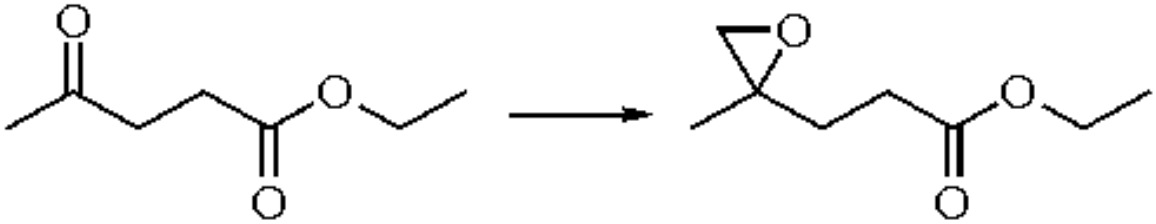

(5)

The first reported generation of $BrCH_2Li$ from CH_2Br_2 and BuLi in the presence of a ketone yielded only 20% of the corresponding oxirane.[3] Present knowledge implies that there was an error in experimental procedure, possibly mere failure to allow enough time for oxirane ring closure. The use of Li dispersion with CH_2Br_2 yielded 35-52% of oxiranes in eight examples, 95% in one,[3] and is clearly not a practical method.

It is also possible to preform the $BrCH_2Li$ in the presence of LiBr in THF-Et_2O-pentane at -115 °C.[4] The reagent is unstable in the absence of LiBr or above -110 °C.[4,5] Although the preformed reagent gives satisfactory yields of oxiranes, this method is obsolete for any known practical purpose.

Boronic Esters.

Dropwise addition of BuLi to a mixture of CH_2Br_2 and ***Triisopropyl Borate*** in THF stirred below -65 °C (-78 °C bath) results in the formation of an addition compound of $BrCH_2Li$ with the borate, which is converted by anhydrous acid to diisopropyl (bromomethyl)boronate (eq 6).[1] This preparation is easily scaled up to 2-mol batches.

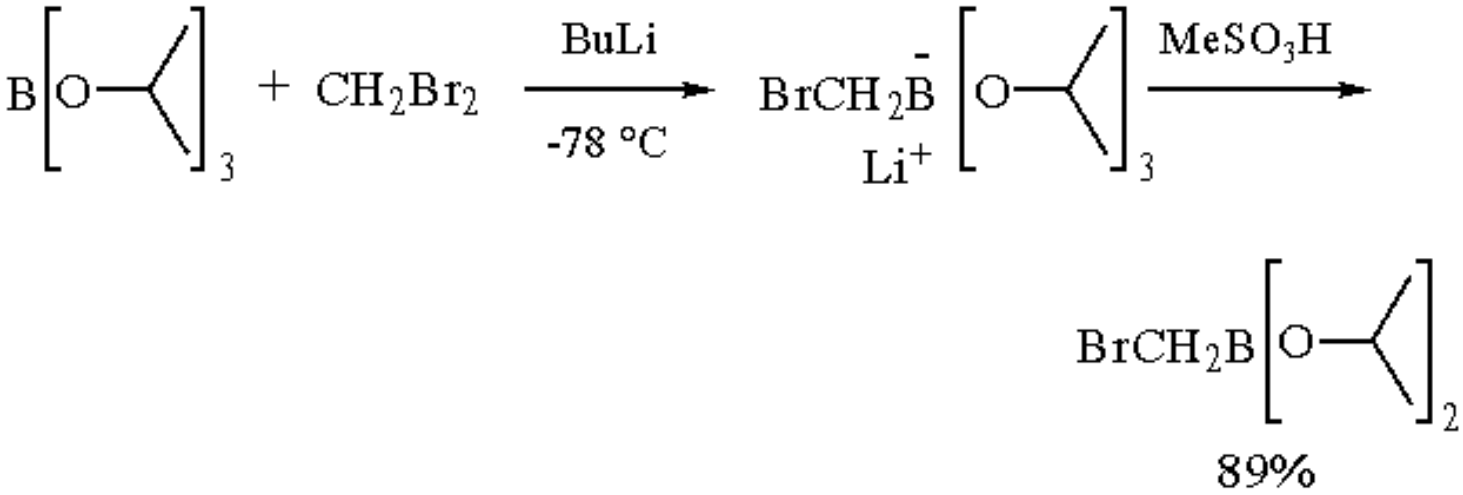

(6)

With simple boronic esters, $BrCH_2Li$ adds to the boron atom to form a borate complex, which on warming to rt rearranges to form the homologous boronic ester (eqs 7 and 8).[1] Unexpectedly, the presence of oxygen functionality has a severely adverse effect on boronic ester homologation with $BrCH_2Li$ (eq 9).[1] This result contrasts with the previous finding with $ClCH_2Li$, which accomplished the conversion of eq 9 in 90% yield.[2]

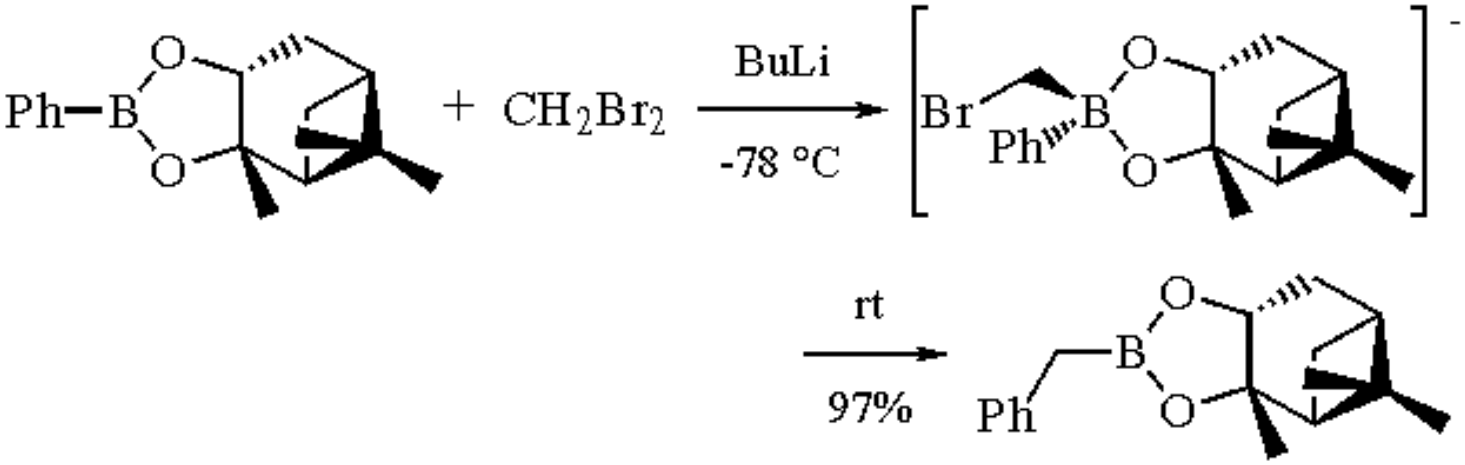

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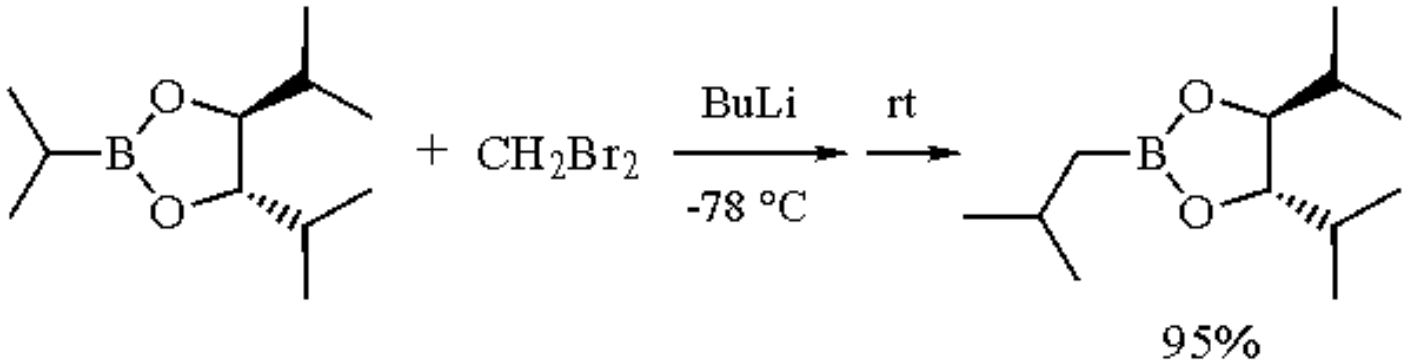

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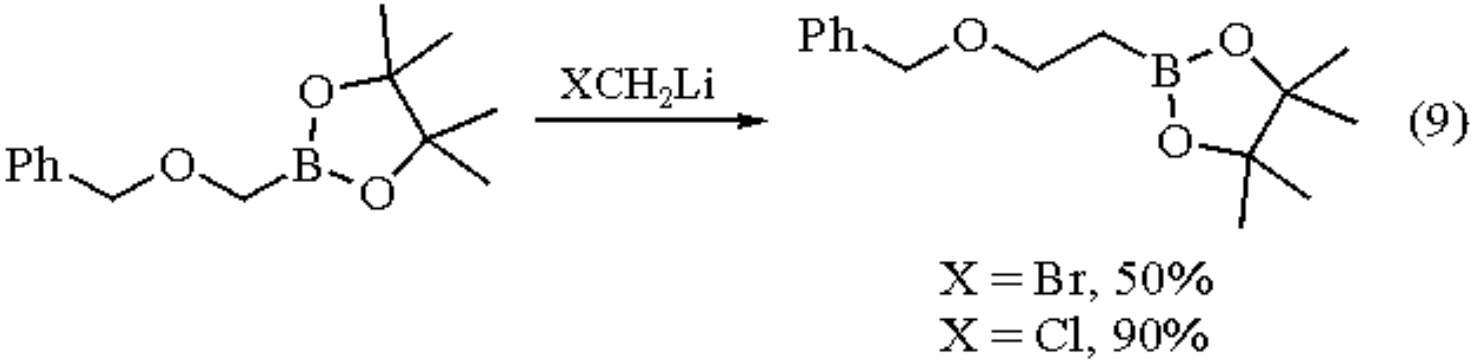

Homologs of Bromomethyllithium.

Although the first attempt to use BuLi to generate $BrCH_2Li$ from CH_2Br_2 in the presence of a ketone gave an anomalous poor result,[3] similar treatment of $MeCHBr_2$, Me_2CBr_2, $PhCHBr_2$, or $EtOCHBr_2$ readily yielded the corresponding oxiranes.[6] Typical examples are illustrated (eqs 10 and 11). It should be noted that where both the carbonyl compound and the halide are unsymmetrical, diastereomeric mixtures result.

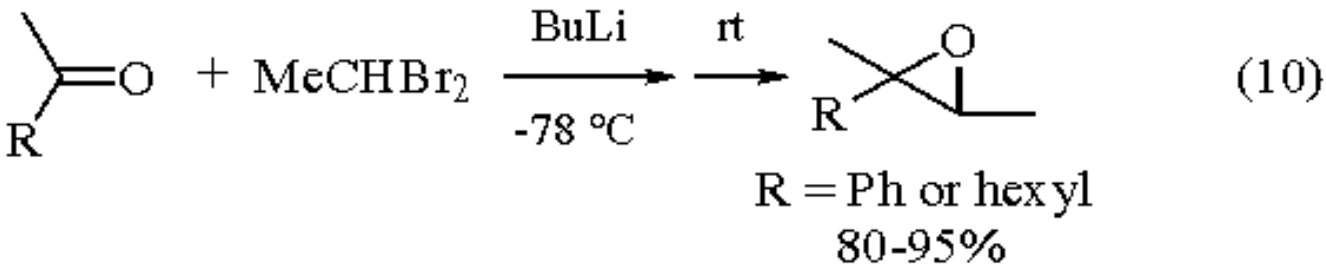

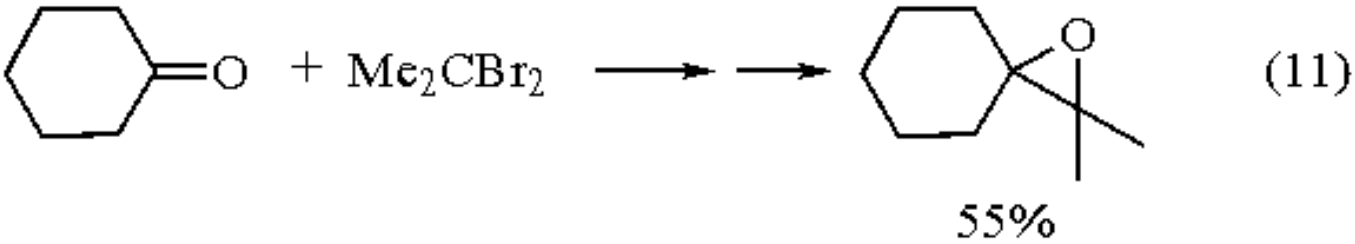

Several examples of RCHBrLi have also been preformed at -115 °C and reacted with carbonyl compounds to form oxiranes or bromohydrins.[4,7]

Related Reagents.

Chloromethyllithium; ***Dibromomethyllithium***; ***Dichloromethyllithium***; ***Dimethylsulfonium Methylide***; ***Tribromomethyllithium***; ***Trichloromethyllithium***.

---

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Bromomethyl Methyl Ether

$MeOCH_2Br$

[13057-17-5] · C_2H_5BrO · Bromomethyl Methyl Ether · (MW 124.96)

(alkylating agent; formaldehyde equivalent;[1-8] alcohol protecting group[9-14])

Alternate Name: BMME.

Physical Data: bp 87 °C; *d* 1.531 g cm^{-3}.

Form Supplied in: colorless to light yellow liquid.

Handling, Storage, and Precautions: lachrymator, possible carcinogen, handle with care. Extremely destructive to tissue of mucous membranes, eyes, and skin. Wear respirator, chemical-resistant gloves, and safety goggles.

Alkylating Agent.

Bromomethyl methyl ether (BMME) has been used in the preparation of α-methylene ketones[1] and lactones.[2] Reaction of a silyl enol ether with 1.5 equiv of BMME in the presence of 5 mol% of ***Tin(II) Bromide*** leads to good yields of α-methylene ketones after treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) (eq 1). The reaction is thought to proceed via an intermediate stannane complex which is attacked by bromide ion to give an α-bromomethyl ketone. The reaction can be carried out in a one-pot operation, and proceeds in modest to good yields.

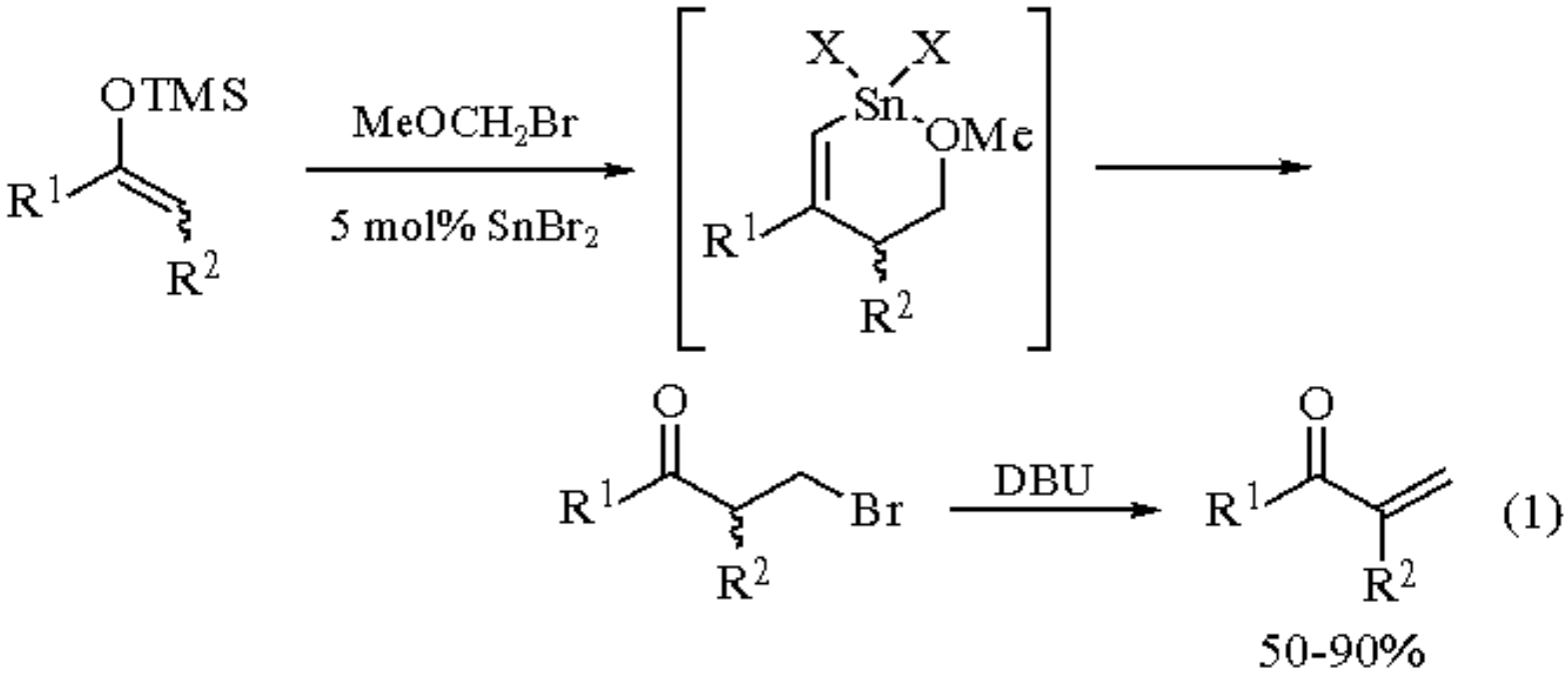

In the course of their synthesis of the pseudoguaianolide aromaticin, Lansbury et al. used BMME as a latent formaldehyde equivalent. Alkylation of the functionalized lactone (eq 2) with BMME (***Lithium Diisopropylamide***, HMPA) was followed by hydrolysis to a hydroxy acid and in situ elimination of the methoxy group. Careful quenching of the reaction was necessary to avoid methanol addition to the newly formed α-methylene lactone.

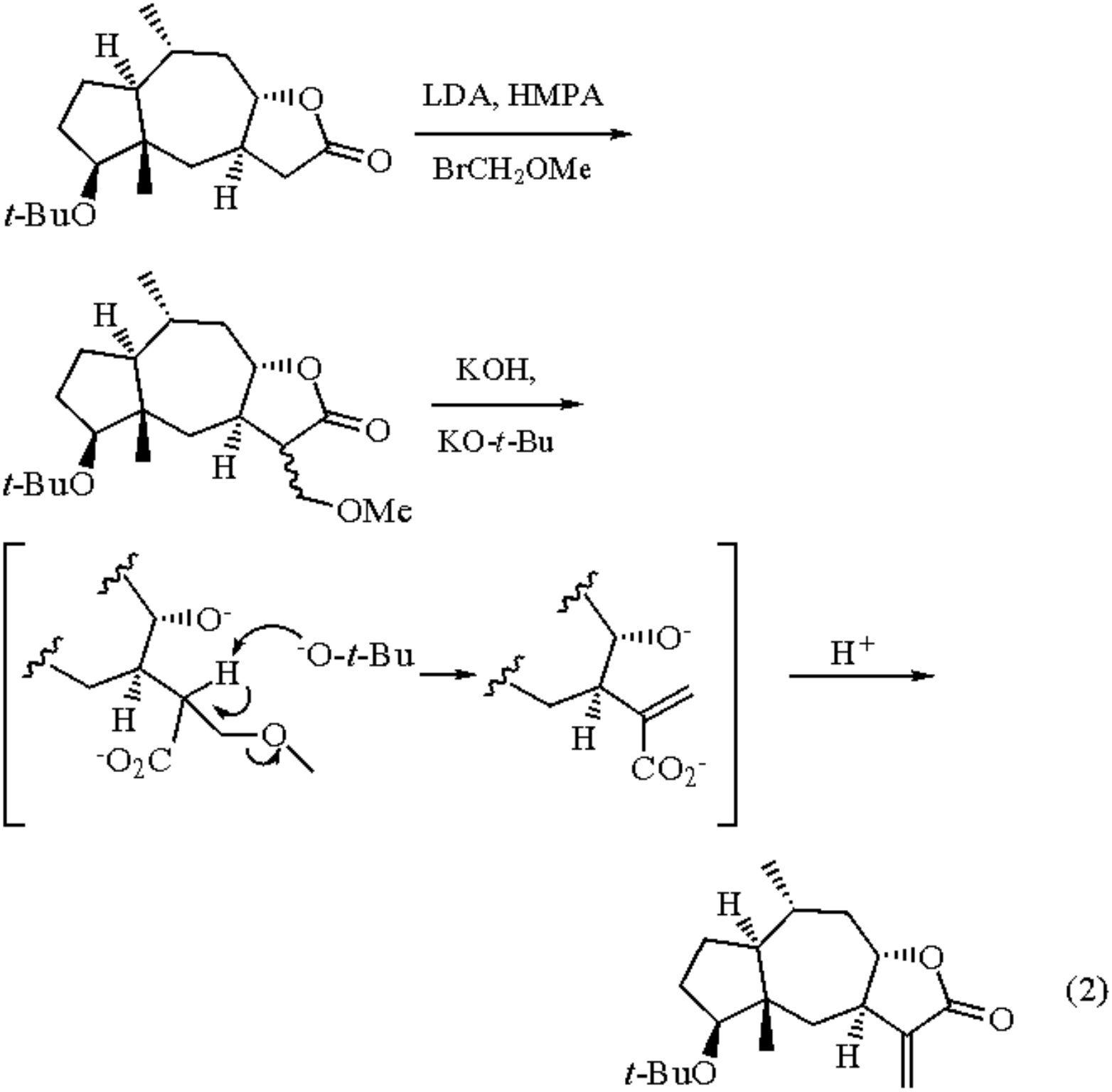

(2)

Williams[3] utilized bromomethyl methyl ether in an enantioselective synthesis of 2,6-diamino-6-(hydroxymethyl)pimelic acid (eq 3). The chiral oxazinone was first alkylated with iodobutene followed by subsequent alkylation with bromomethyl methyl ether. The bis-alkyl adduct was then converted to the desired product after a number of steps.

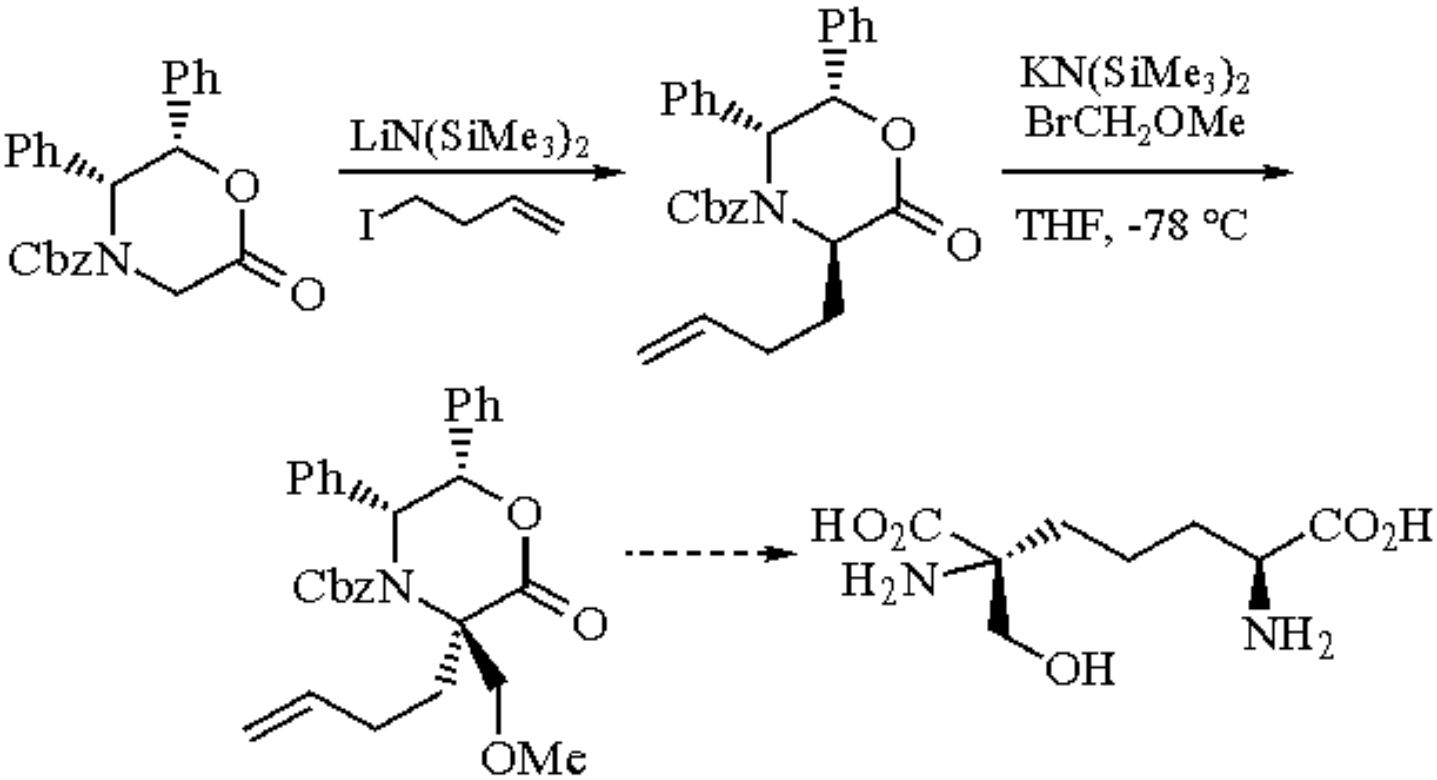

(3)

Schank[4] studied the alkylation of sulfinate anions (eq 4) with bromomethyl methyl ether. Alkylation occurs predominantly on the sulfinyl oxygen to give an unstable compound along with minor amounts of *S*-alkylated product. The unstable compound rearranges upon heating to give the product.

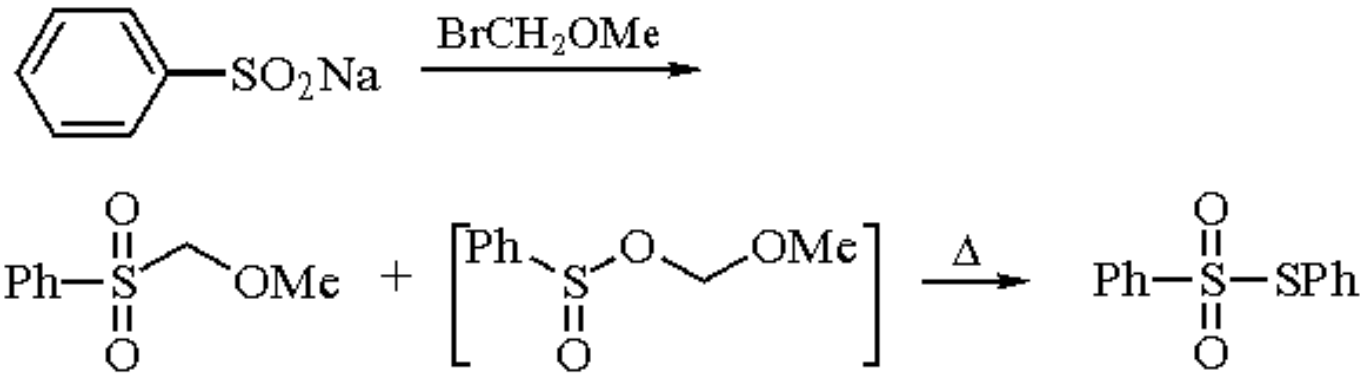

(4)

Alcohol Protecting Group.

Eqs 5-7 illustrate the use of bromomethyl methyl ether for forming the methoxymethyl ether (MOM) protecting group.[9-14] Typically the alcohol is reacted with BMME in the presence of ***Diisopropylethylamine*** (DIEA) as an acid scavenger.

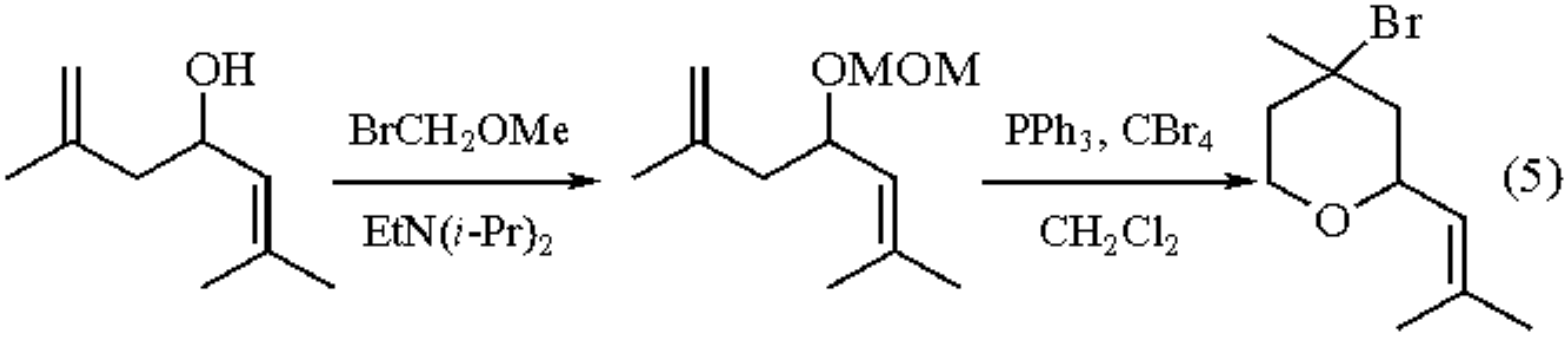

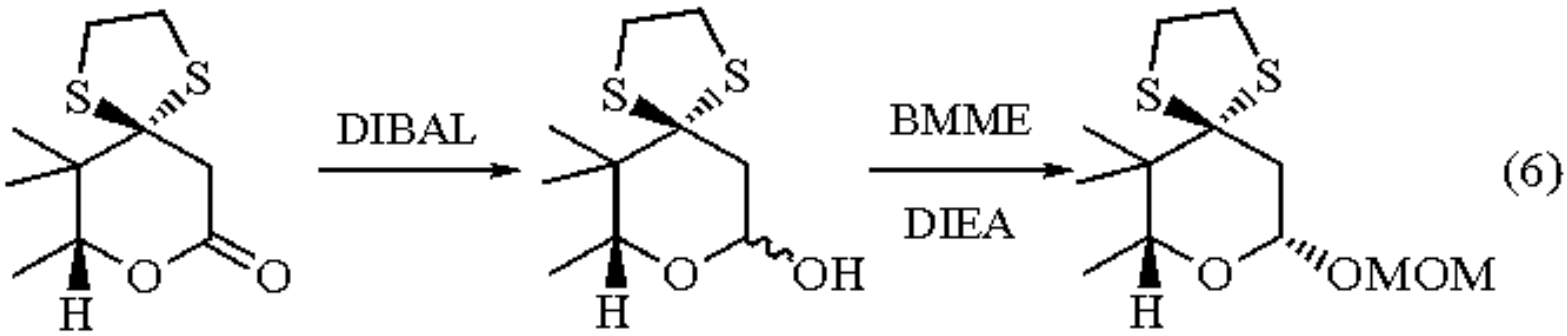

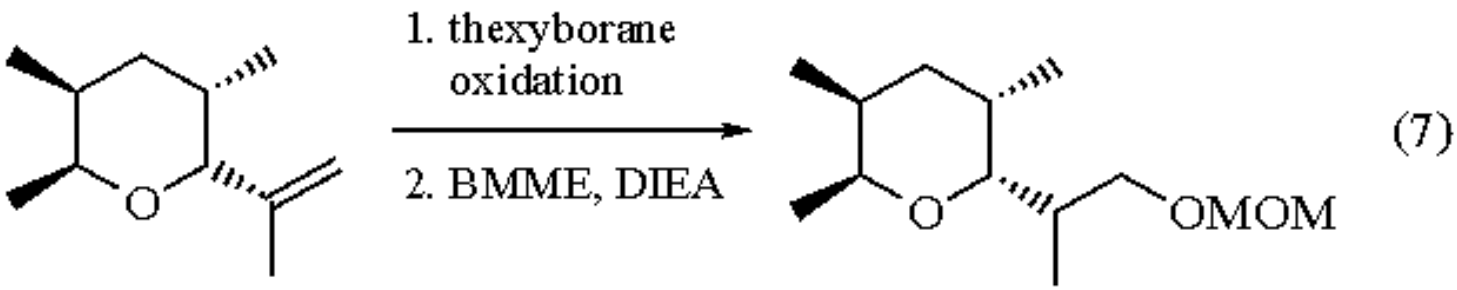

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2-Bromo-2-methylpropionyl Bromide[1]

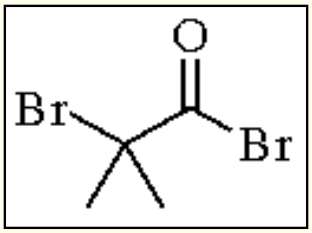

[20769-85-1] · $C_4H_6Br_2O$ · 2-Bromo-2-methylpropionyl Bromide · (MW 229.90)

(useful reagent for the preparation of ketenes,[1,2] amides,[3,4] alkynic ketones,[5] and macrocyclic amides[6,7])

Physical Data: bp 162-164 °C; *d* 1.860 g cm^{-3}.

Solubility: sol polar aprotic and nonpolar solvents; reacts with protic solvents.

Form Supplied in: colorless liquid, widely available.

Handling, Storage, and Precautions: should be handled in a dry atmosphere. Hydrogen bromide is evolved upon exposure to water and protic solvents. A well-ventilated fume hood should be used when handling this compound. Adequate skin and eye protection should also be worn.

Preparation of Ketenes.

Treatment of 2-bromo-2-methylpropionyl bromide with ***Zinc*** turnings in ethyl acetate affords dimethylketene in 46-54% yield (eq 1).[1] The dimethylketene is obtained as a 9-10% solution in ethyl acetate by distillation of the reaction mixture at 300 mmHg. Treatment of 2-bromo-2-methylpropionyl bromide with propargyl alcohol affords the propargyl ester, which is converted to the ketene acid upon treatment with zinc dust in benzene (eq 2).[2] The transformation of the propargyl ester to the ketene acid occurs by formation of the zinc enolate, followed by a [3,3]-sigmatropic rearrangement.[2a]

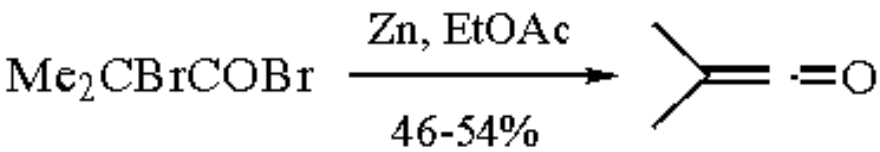

(1)

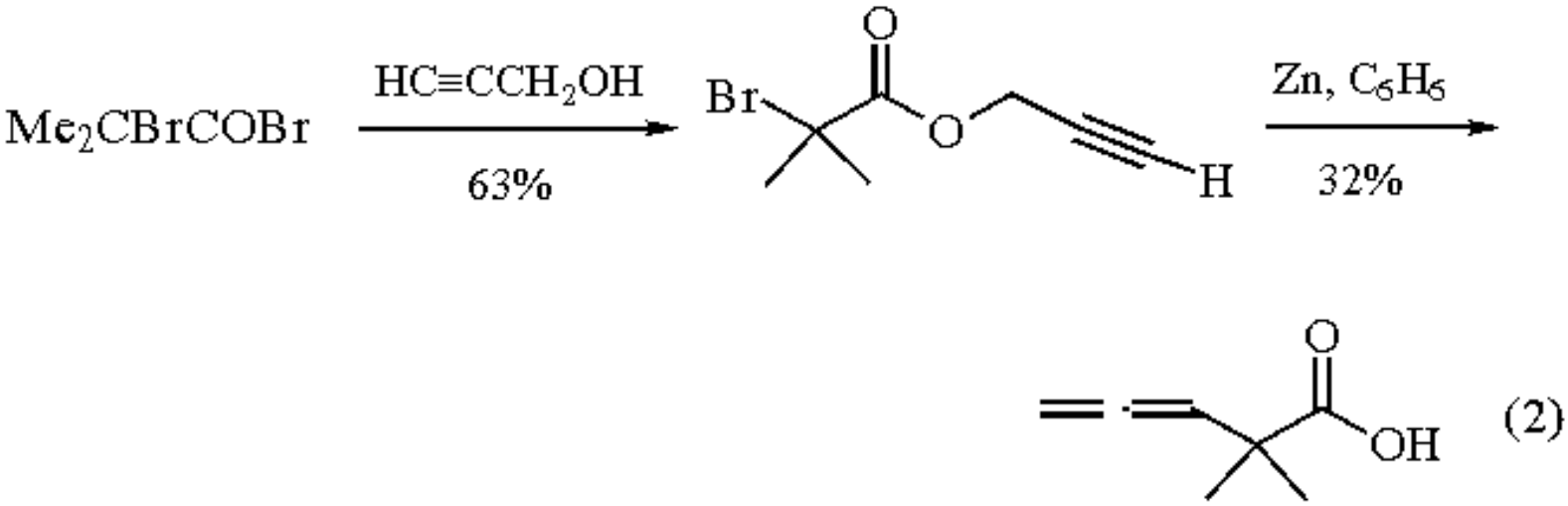

(2)

Preparation of Amides.

A variety of aromatic and aliphatic amines react with 2-bromo-2-methylpropionyl bromide to afford the corresponding amides.[3] These amides have then been used in a variety of subsequent reactions that take advantage of the bromocarbon functionality. For example, treatment of 6-amino-1,3-dihydro-2*H*-indol-2-one with 2-bromo-2-methylpropionyl bromide afforded the intermediate acyl derivative, which was cyclized to 5,7-dihydro-3,3-dimethylbenzo[1,2-*b*:5,4-*b*´]dipyrrole-2,6-(1*H*,3*H*)-dione upon treatment with ***Aluminum Chloride*** (eq 3).[4]

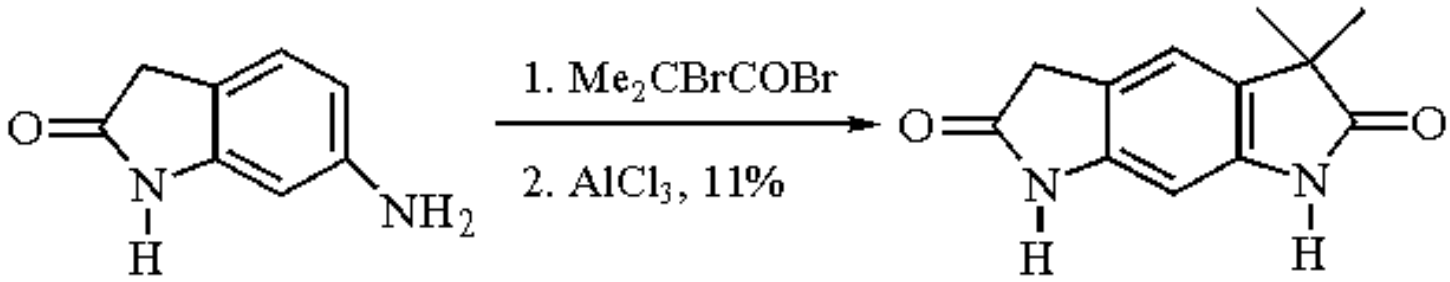

(3)

Preparation of Alkynic Ketones.

Treatment of phenyl(trimethylsilyl)acetylene with 2-bromo-2-methylpropionyl bromide in the presence of aluminum chloride afforded 4-bromo-4-methyl-1-phenylpent-1-yn-3-one (eq 4).[5] This alkynic ketone could also be made from phenylacetylene and 2-bromo-2-methylpropionyl bromide using dichlorobis(triphenylphosphine)palladium(II)-***Copper(I) Iodide*** as catalyst. This alkynic ketone served as a key precursor to the natural product bullatenone.

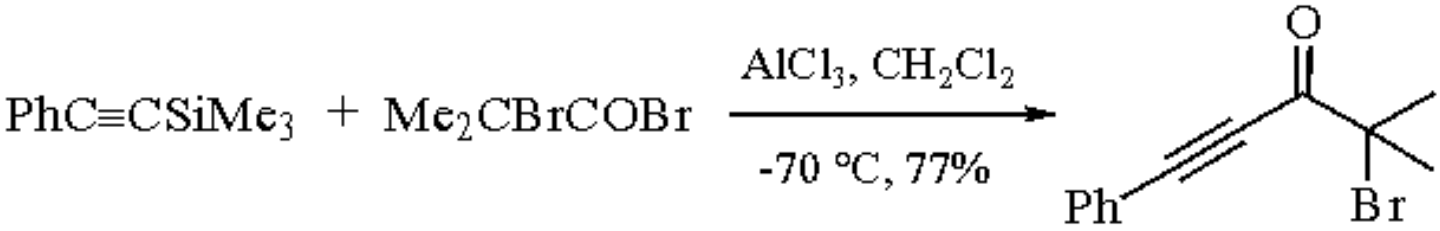

(4)

Preparation of Macrocyclic Amides.

Treatment of ethylenediamine with 2-bromo-2-methylpropionyl bromide in chloroform in the presence of ***Pyridine*** afforded *N,N´*-ethylenebis(2-bromoisobutyramide) (eq 5), which served as a precursor to macrocyclic nitrogen-sulfur compounds.[6] These macrocycles were then used as ligands for transition metals. Several other macrocyclic nitrogen ligands have been prepared using 2-bromo-2-methylpropionyl bromide.[7]

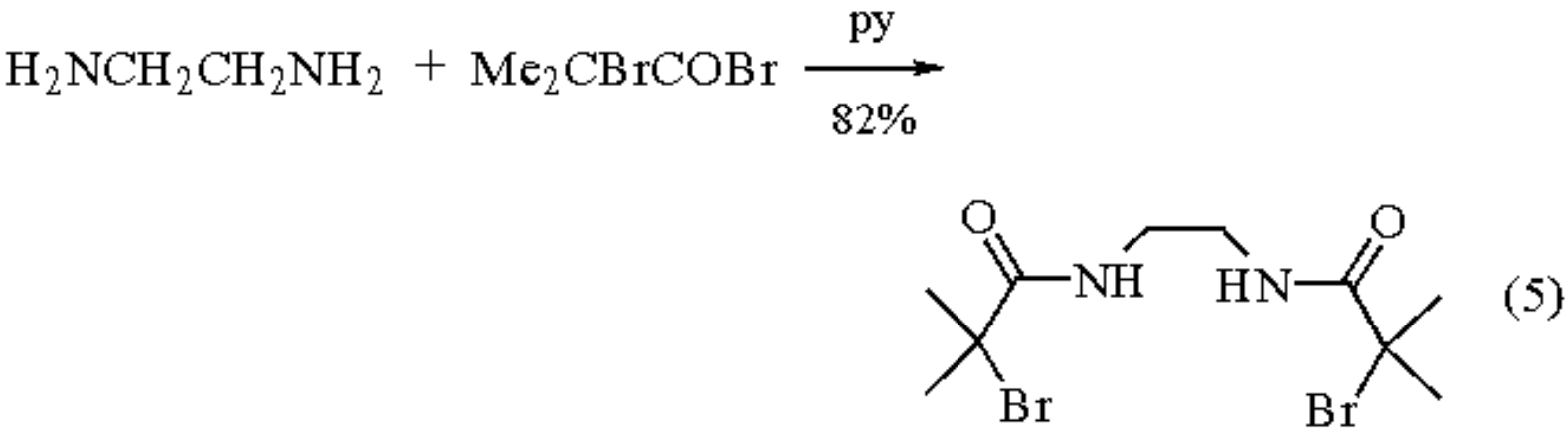

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2-Bromo-1-methylpyridinium Iodide[1]

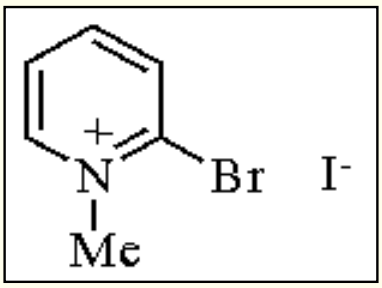

[52693-56-8] · C_6H_7BrIN · 2-Bromo-1-methylpyridinium Iodide · (MW 299.94)

(dehydrative coupling and activation of alcohols)

Preparative Methods: the title reagent (**1a**) as well as the chloro analog (**1b**) can be prepared by adding 1.2 equiv of MeI to an acetone solution of 2-bromo- or 2-chloropyridine at 0 °C. After stirring for 3 days at rt the precipitated pyridinium salt is filtered off and washed with dry ether. Further drying under vacuum results in 80-90% yield of the pyridinium salt as a colorless solid which may be used without further purification.[2b,c]

General.

The reagent (**1a**) is a member of the widely used 2-halo-*N*-alkylpyridinium salts pioneered by Mukaiyama in the mid-1970s. Two general uses have arisen: dehydrative coupling and conversion of alcohols to leaving groups followed by subsequent nucleophilic displacement. Several variants of (**1**) exhibit analogous reactivity and this discussion will include some of these alternative reagents. The uses of 2-halo-*N*-alkylpyridinium salts up to 1979 have been reviewed.[1]

Dehydrative Coupling.

The C-2 bromide of (**1a**) (as well as the corresponding chloride of **1b**) is easily displaced by carboxylates in the presence of an amine base to generate 2-acyloxypyridinium salts (**2**) which, in turn, can acylate a variety of nucleophiles to provide esters,[2] amides,[3] thiolesters[4] (eq 1), and 3-acylthiazolidine-2-thiones.[5] The reactions generally proceed well in a variety of solvents, including diethyl ether, dichloromethane, acetonitrile, pyridine, and toluene. As bases, ***Triethylamine***, ***Tri-n-butylamine***, and ***2,6-Lutidine*** give good results. It was found that less basic pyrimidinone derivatives such as (**7**) and (**8**) allow the reaction to be carried out under essentially neutral conditions.[6]

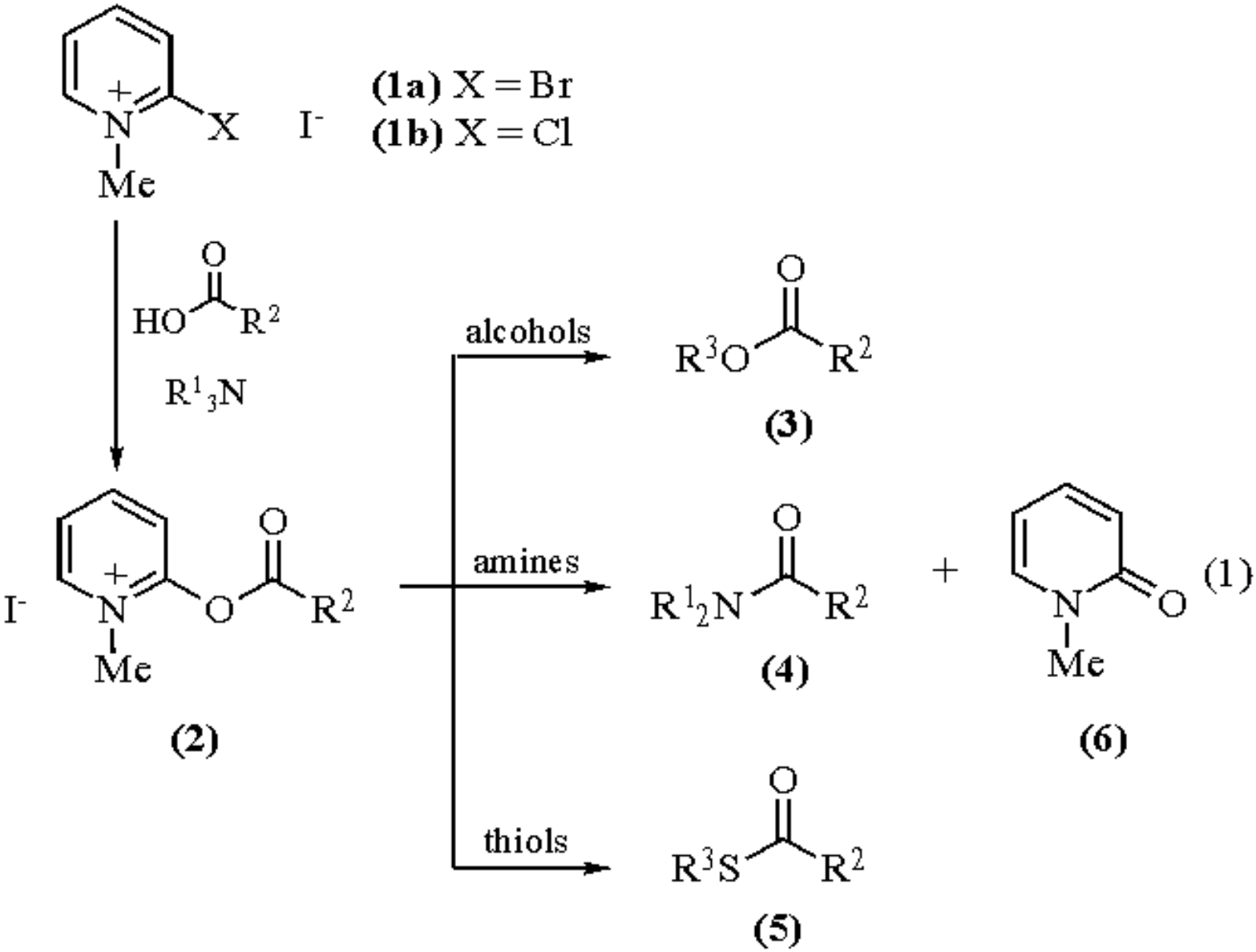

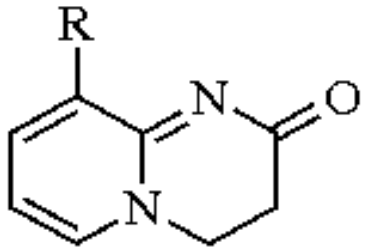

(7) R = H
(8) R = Me

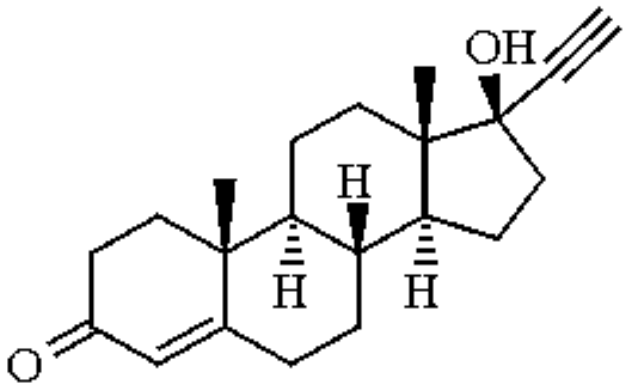

(9)

Ring closure via intramolecular acylation to produce lactones[7] (including macrocyclizations[8]) and β-lactams[9] have also been demonstrated with (**1b**). These dehydrative processes have two outstanding characteristics: a number of

functional groups can tolerate the mild reaction conditions, and even hindered nucleophiles may be acylated. For example, pivalic acid (**10**) may be converted to its *t*-butyl ester (**12**) in 54% yield (eq 2). However, the steroidal alcohol (**9**) was acylated in only 10-15% yield using 2-bromo-1-ethylpyridinium iodide after 5 days at 100 °C.[10] The mildness of the conditions was demonstrated in the macrolactamization which produced (**13**) in 81% yield using (**1b**) with Et_3N in CH_2Cl_2 at 20 °C.[11]

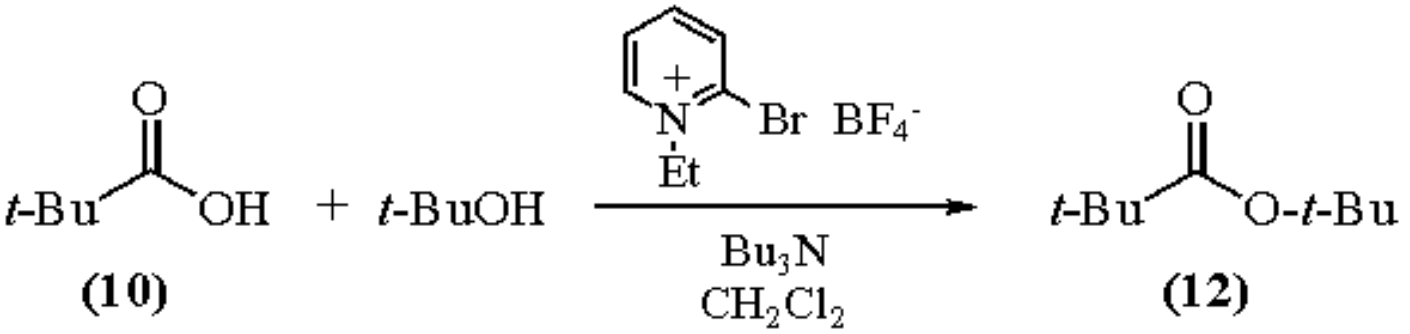

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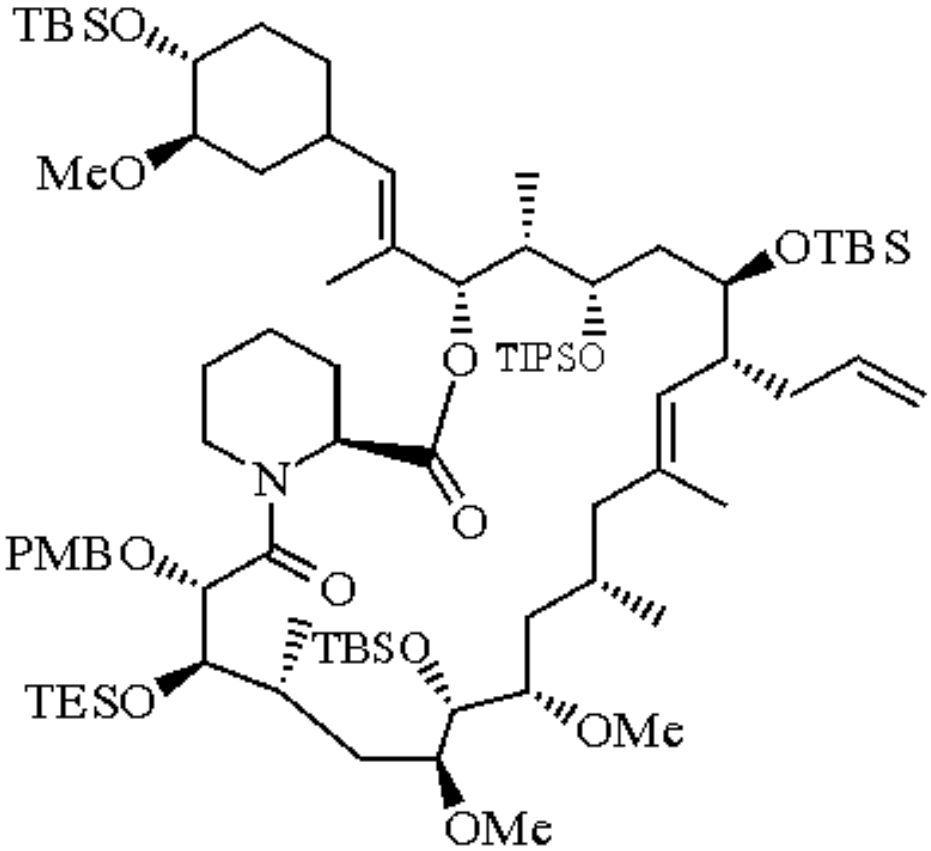

(13)

Activation of Alcohols.

This aspect of the Mukaiyama reagents has not been studied as intensely as dehydrative coupling. In many respects the activation of alcohols by 2-halo-1-methylpyridinium salts mirrors that of the ***Triphenylphosphine-Diethyl Azodicarboxylate*** (Mitsunobu reagent). That is, alcohols are converted to good leaving groups and can then undergo invertive substitution with nucleophiles (eq 3). Thus activated, both primary and secondary alcohols have been

displaced with Grignard reagents,[12] trichloroacetic acid/Et_3N[13] (to eventually induce the equivalent of the Mitsunobu process), iodide (-> R-I) and chloride ion (-> R-Cl),[14] sulfides (-> R-SR),[15] sodium *N*,*N*-dimethyldithiocarbamate (-> R-SH),[16] and azide ion (-> R-NH_2).[17] With secondary alcohols, complete inversion normally occurs. The 2-chlorobenzoxazolium salt (**17**) plays the same role as (**14**) in several of the processes.

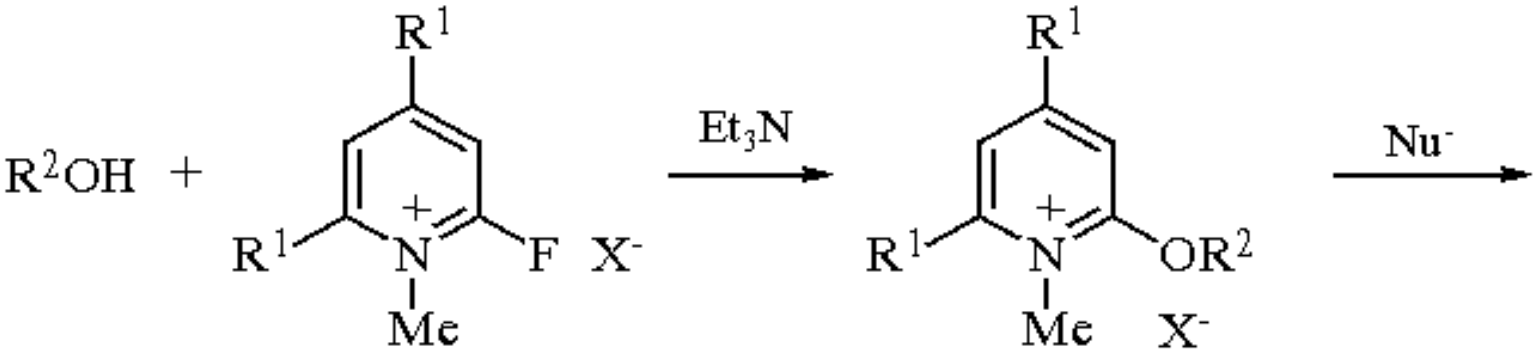

(14) **(15)**

$R^1 = H$ or Me; $X = OTs$ or BF_4

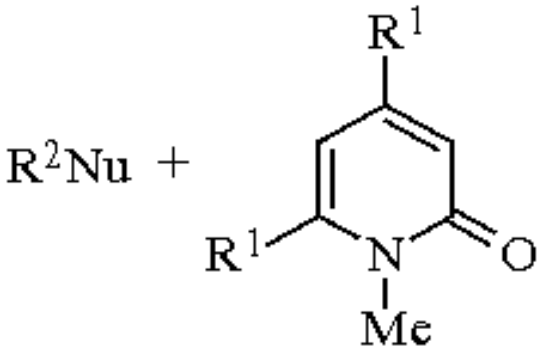

(3)

(16)

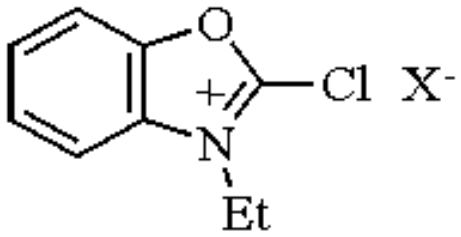

(17)

Other Uses.

These reagents also promote the following: reductive elimination of β-hydroxy sulfides to give alkenes,[18] preparation of nucleosides,[19] phosphorylation,[20] carbocation formation as a prelude to cationic cyclizations,[21] Beckmann and pinacol rearrangements,[22] preparation of isothiocyanates,[23] carbodiimides,[24] and isocyanates from amines,[25] and dehydration of amides to give nitrile and isocyanides.[26] None of these latter processes have been utilized beyond their original descriptions.

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23. Shibanuma, T.; Shiono, M.; Mukaiyama, T. *CL* **1977**, 573.
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Bromonium Di-*sym*-collidine Perchlorate[1]

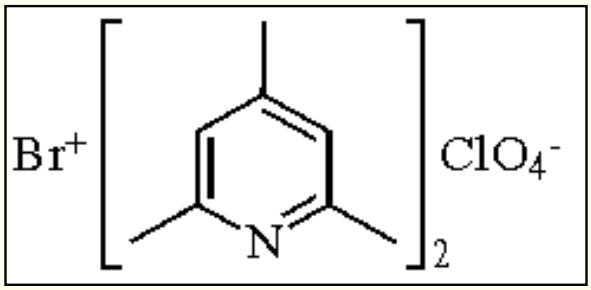

[4836-12-8] · $C_{16}H_{22}BrClN_2O_4$ · Bromonium Di-*sym*-collidine Perchlorate · (MW 421.72)

(reactive electrophilic brominating agent; activates alkenes towards nucleophilic reagents;[2] reagent for bromocyclization,[3,4] useful in the preparation of *cis*-α-alkylamino alcohols)

Alternate Names: bromonium dicollidine perchlorate; bis(collidine)bromonium perchlorate.

Physical Data: mp 230 °C.

Solubility: sol chloroform; insol ether.

Form Supplied in: fine colorless crystalline powder.

Preparative Method: it is important in the preparation of this reagent to be sure that conditions are anhydrous, otherwise bromine tends to be reliberated. Silver di-*sym*-collidine perchlorate is prepared by adding *sym*-collidine (20 mL) to a solution of silver nitrate (9 g) and sodium perchlorate (11 g) in 100 mL of water, while stirring vigorously, to give a curdy white precipitate. After washing repeatedly with water, the product is washed with ethanol and ether and finally dried under vacuum over P_2O_5. The yield is quantitative. Silver di-*sym*-collidine perchlorate (13.47 g, 30 mmol) is suspended in 150 mL of chloroform and 1 mL of *sym*-collidine. Bromine (1.65 mL, 30 mmol) is added. Silver bromide rapidly precipitates and is filtered through Celite. The clear pale-yellow filtrate gives a fine, white crystalline precipitate on the addition of ether. The crystals are dried under high vacuum.

Handling, Storage, and Precautions: perchlorates are potentially powerful explosives. This compound detonates on strong heating and so due precautions[1] must be taken. The compound is stored under anhydrous conditions. This reagent should be handled in a fume hood.

Preparation of Glycosides and Nonreducing Disaccharides.[1]

Reaction of D-glucal triacetate (**2**) with equimolar amounts of methanol and bromonium di-*sym*-collidine complex (**1**) dissolved in chloroform gives virtually quantitative yields of acetylated methyl 2-deoxy-2-bromoglycosides. Unlike pyridine or 2-methylpyridine, the steric hindrance to *N*-glycoside formation provided by the methyl groups at the 2- and 6-positions of *sym*-collidine is required for successful *O*-glycoside synthesis. If 2,3,4,6-tetra-*O*-acetyl-β-D-glucose (**3**) is used as the alcohol, the 2-deoxy-2-bromo disaccharide heptaacetate (**4**) is formed (eq 1). Deacetylation with ***Triethylamine*** in aqueous methanol followed by hydrogenolysis with ***Palladium on Carbon*** as the catalyst affords β-D-glucopyranosyl-2-deoxy-α-D-*arabino*-hexopyranoside (2-deoxyneotrehalose), isolated as the crystalline heptaacetate (**5**).

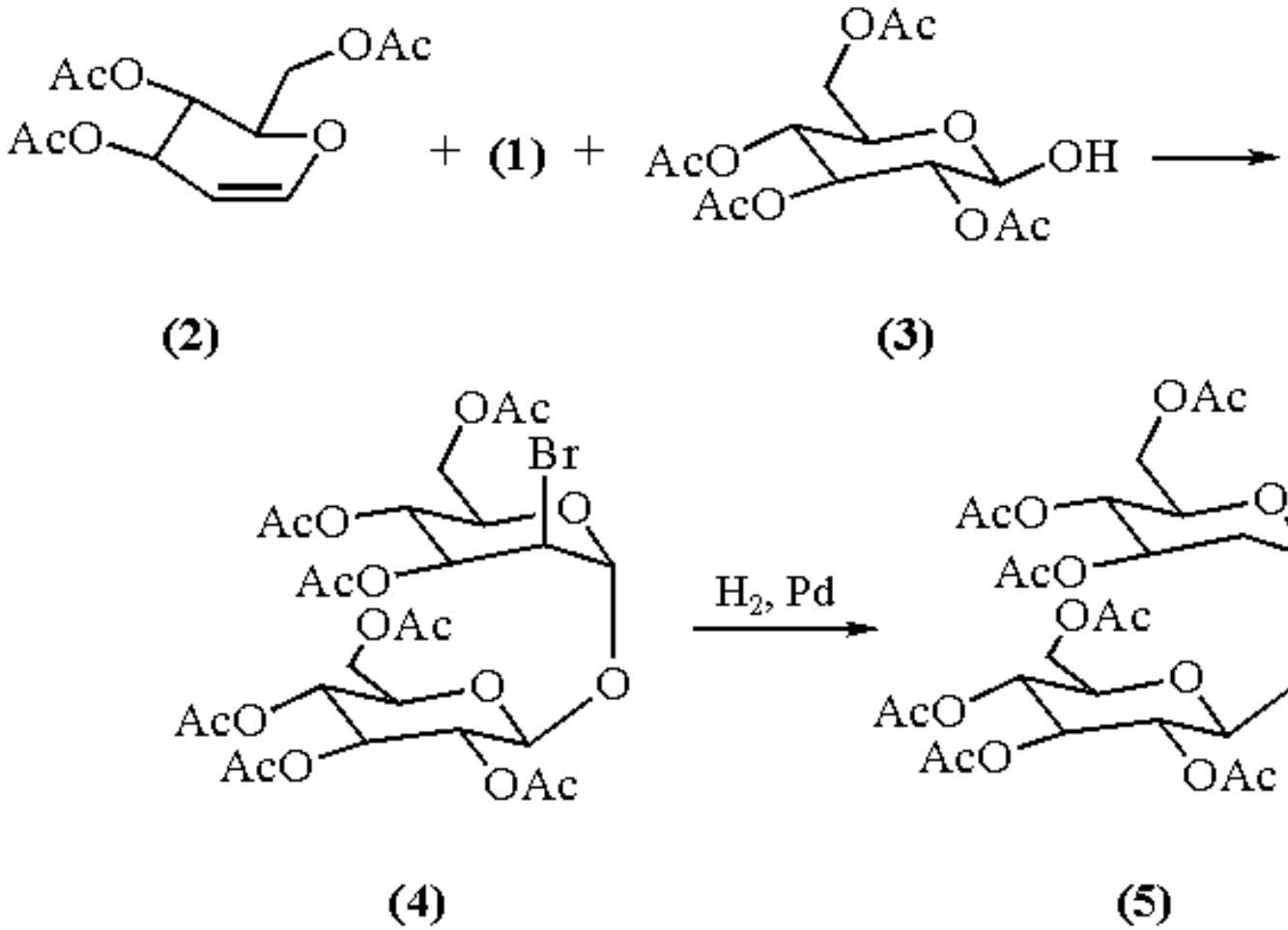

(1)

Bromocyclization[3] of Unsaturated Thiocarbamidates.

This reagent can effect the stereo- and regiospecific functionalization of alkenes to furnish *cis*-1,2-methylamino alcohols in protected form. For example, unsaturated thiocarbamates, prepared as shown in eq 2, on treatment with bromonium dicollidine perchlorate cyclize to bromocarbamates. This cyclization has been successfully applied to several cyclic and acyclic unsaturated alcohols using methyl, benzyl, and *t*-butyl isothiocyanates. In all cases the condensation step (**6** to **7**) is essentially quantitative. The product (**8**) can be converted into *cis*-α-alkylamino alcohols by reduction of the bromine with ***Tri-n-butylstannane*** followed by alkaline hydrolysis. When R is a *t*-butyl group it can be removed in high yield by treatment with ***Trifluoroacetic Acid*** at 25 °C. The value of these transformations for the synthesis of aminocyclitols is illustrated by the conversion of bromocarbamate (**9**) to (±)-sporamine (**10**) in three steps (TFA; *n*-Bu_3SnH; aqueous NaOH, 25 °C) in better than 90% overall yield (eq 3). Sporamine is the aminocyclitol portion of the broad-spectrum antibiotic sporacin A.

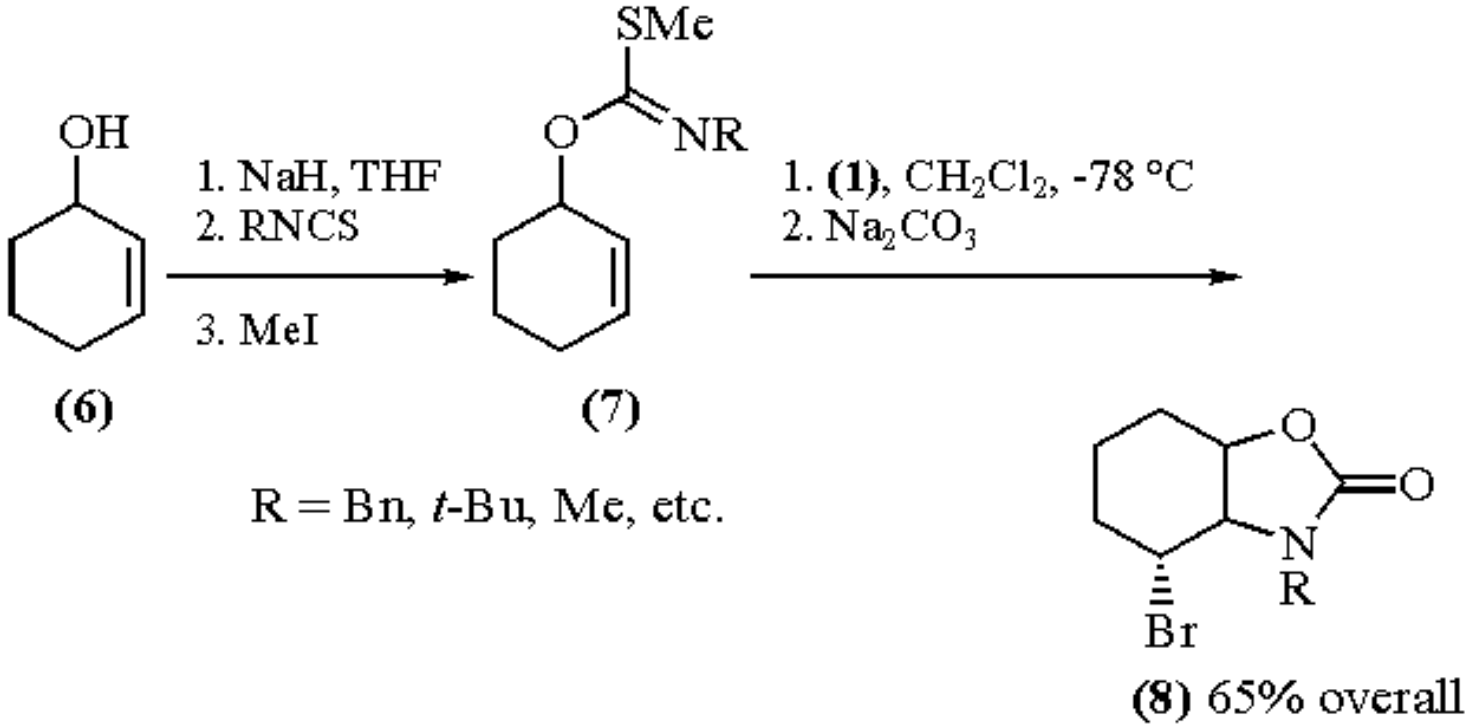

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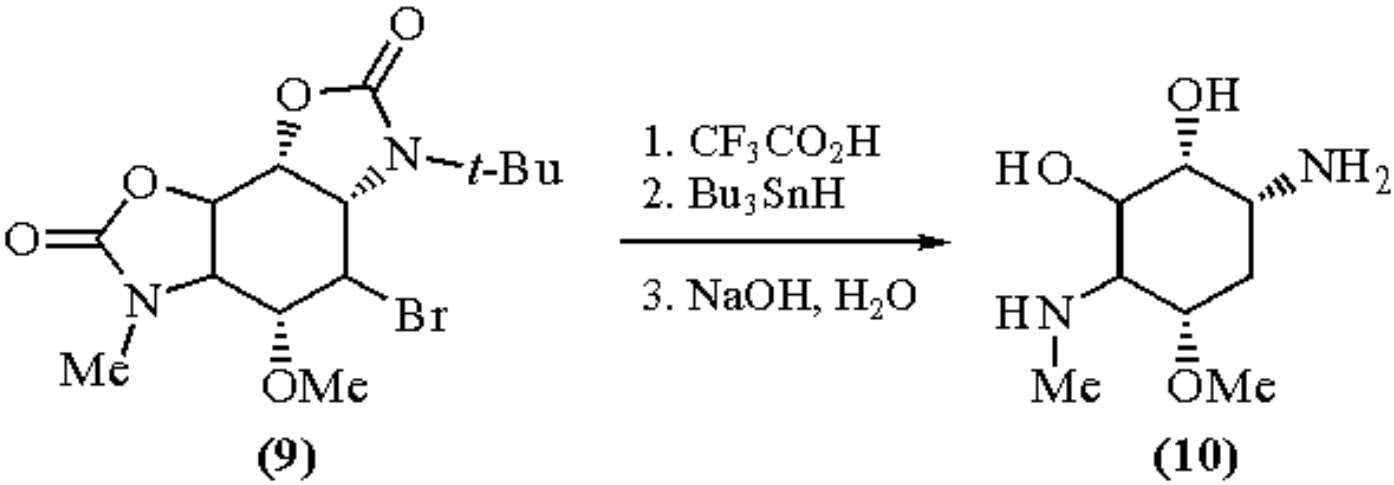

(3)

Bromolactamization.

Esoaminuroic acid (**11**), an amino sugar, is present in esomycin A, which is an antifungal antibiotic isolated from *Streptomyces*. The key step in its synthesis is the transannular bromolactamization of an unsaturated amide (eq 4).[4]

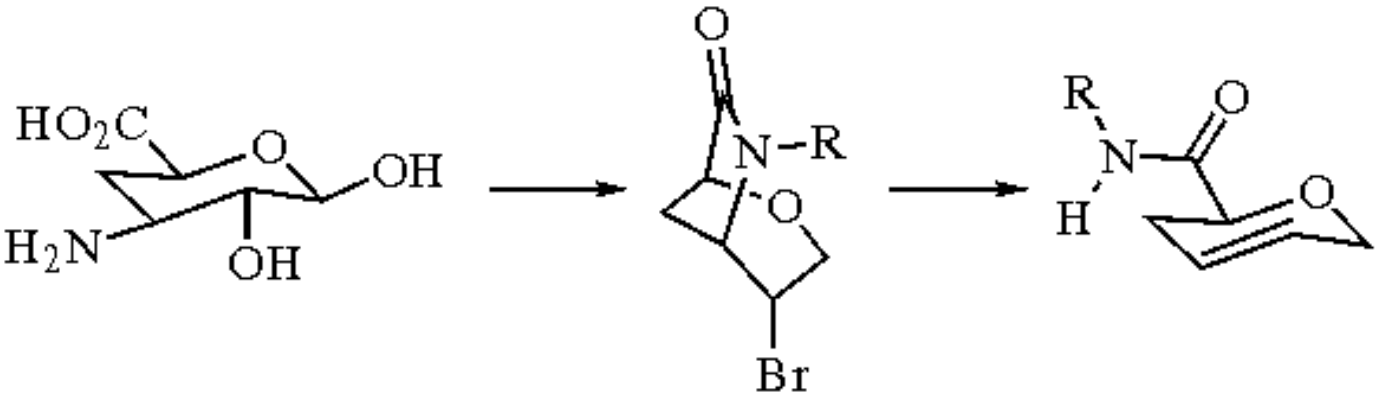

(4)

N-(*R*)-*p*-Methoxyphenethylamides were subjected to the bromolactamization sequence involving the use of ***Trimethylsilyl Trifluoromethanesulfonate*** as the amide silylating agent, and bromonium dicollidine perchlorate as electrophile. The desired [3.2.1] lactams were the only cyclization products, with yields exceeding 75% (eq 5). No [2.2.2] lactams were formed in detectable quantities. It may be noted that the *N,O*-bis(*t*-butyldimethylsilyl) derivative gave more [2.2.2] product, particularly at higher temperature.[5]

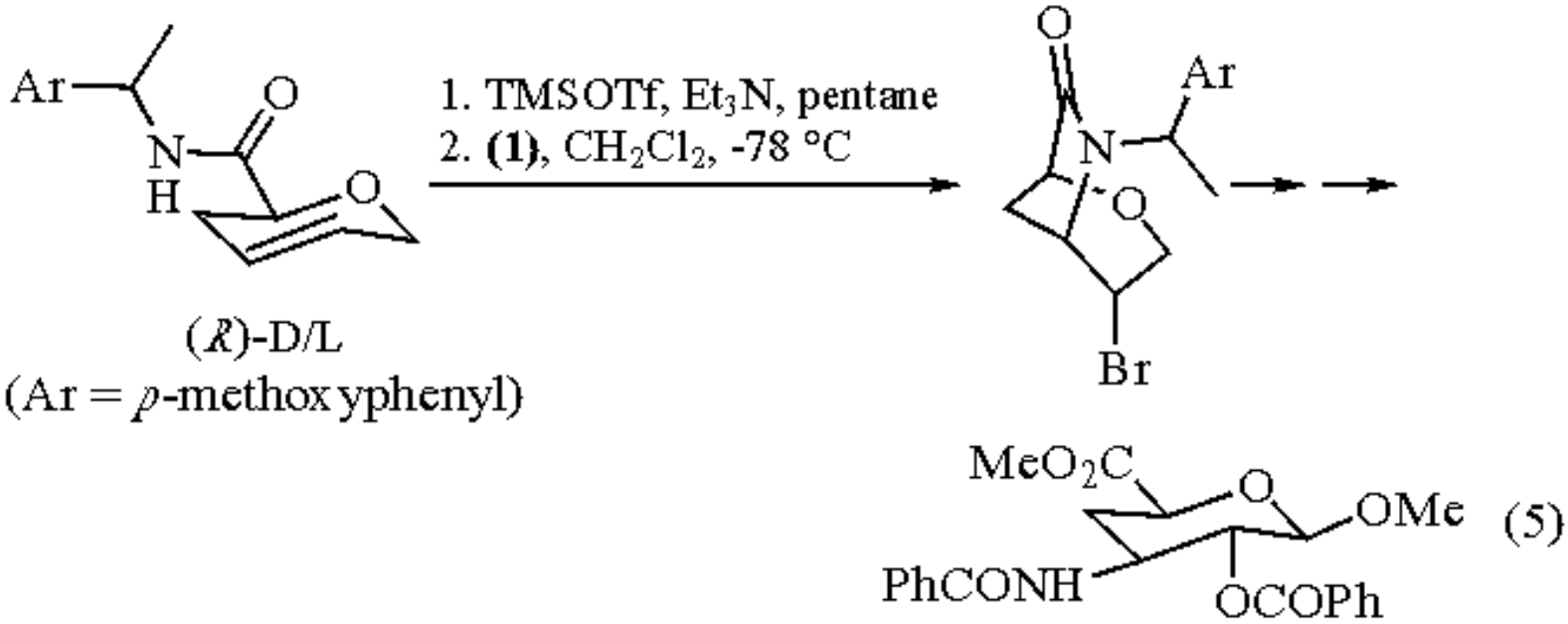

(5)

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5. (a) Takaoka, K.; Kuwayama, T.; Aoki, A. *Jpn. Pat.* 615 332, 1971. (b) Sakata, K.; Sakurai, A.; Tamura, S. *ABC* **1973**, *37*, 697.

Tapan Ray

Sigma Radiochemical Co., St. Louis, MO, USA

(*E*)-1-Bromo-2-phenylthioethylene[1]

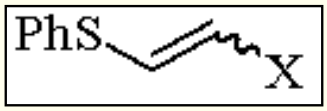

(*E*)-(**1**; X = Br)

[17101-82-5] · C_8H_7BrS · (*E*)-1-Bromo-2-phenylthioethylene · (MW 215.11) (*Z*)-(**2**; X = Br)

[17101-71-2] (*E*)-(**3**; X = Cl)

[26620-11-1] · C_8H_7ClS · (*E*)-1-Chloro-2-phenylthioethylene · (MW 170.66)

(building blocks for stereospecific synthesis of alkenes and dienes)

Alternate Name: 2-bromovinyl phenyl sulfide.

Physical Data: (**1**) bp 44.5-45 °C/0.04 mmHg; (**2**) bp 59-60 °C/0.04 mmHg; (**3**) bp 119-120 °C/15 mmHg.

Analysis of Reagent Purity: GC/MS, IR, and ^{1}H NMR.

Preparative Methods: (i) 3-phenylthioacrylic acid is first formed by thiophenol addition to propiolic acid, and is then subjected to a one-pot bromine addition and subsequent decarboxylative dehalogenation. This gives a ca. 1:4 mixture of (**1**) and (**2**) (overall yield 69%);[2] (ii) by a PTC reaction between thiophenol and 1,2-dibromoethylene (only isomer (**2**), yield 48%);[3] and (iii) by addition of sulfenyl chloride to acetylene (only compound (**3**), yield 73%).[4]

Purification: by distillation; the isomeric mixture of (**1**) and (**2**) is separated into its components by careful distillation,[5] or by flash chromatography (silica gel; petroleum ether eluent).

Handling, Storage, and Precautions: if refrigerated (-10 to 0 °C) they can be stored for several weeks without isomerization. Avoid inhaling; use in a fume hood.

Synthesis of Stereodefined Alkenes.

Reagents (**1**), (**2**), and (**3**) can be subjected to two, sequential, cross-coupling reactions with Grignard reagents in the presence of a Ni^{II} or Pd^{II} catalyst, with the substitution of the halogen and phenylthio group (eqs 1 and 2) yielding stereodefined alkenes.[1,5,6]

(E)-1-Bromo-2-phenylthioethylene

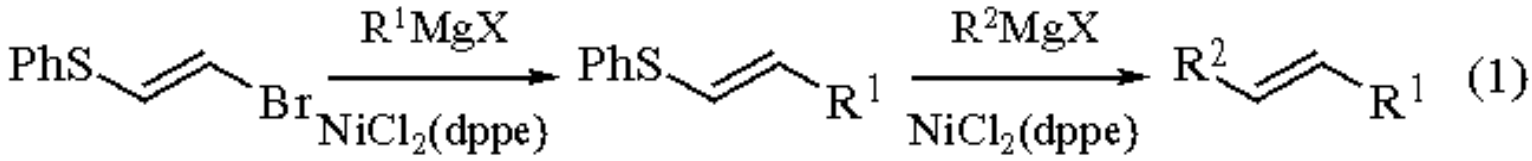

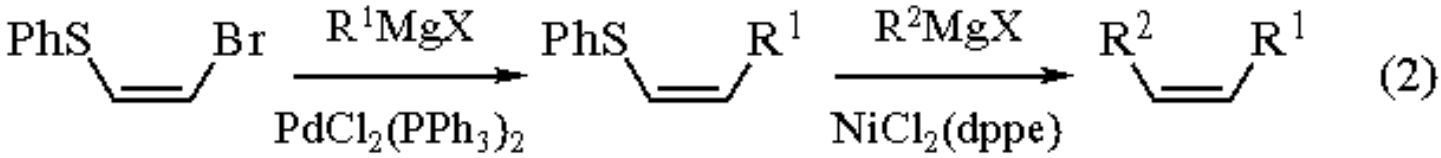

The substitution of the phenylthio group is much slower than the replacement of the halogen, and can be performed only using longer reaction times and an excess of Grignard reagent. In order to prepare nonsymmetrical alkenes, it is necessary to use a different Grignard reagent after completion of the first step.[6] Often, it is unnecessary to isolate the vinyl sulfide intermediate and the procedure can be performed successfully in one pot. Moreover, the isomeric purity of the final product is higher than 99% in the case of the (*E*) isomers, and slightly lower for the (*Z*) isomers (95-98%). In the second step of the procedure (e.g. the substitution of the phenylthio group), Ni catalysts cannot be replaced by Pd catalysts.

An application of the described method is the synthesis of many monoalkenic insect sex pheromones in high isomeric purity (>98%), and in isolated overall yields in the range 65-75% for the (*Z*) isomers and 80-90% for the (*E*) isomers.[5] The procedure can also be applied to the synthesis of pheromones with an alkenyl acetate structure (eqs 3 and 4), using Grignard reagents derived from 1-halo-o-tetrahydropyranyloxyalkanes in the first step, and acetylating the tetrahydropyranyl-protected alkenols after the second cross-coupling step.[5]

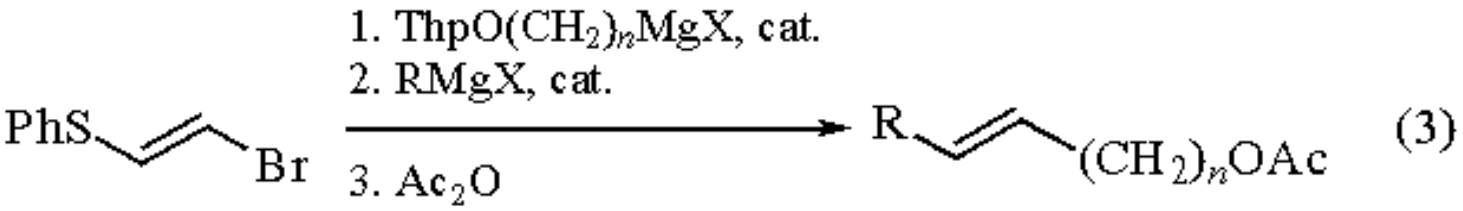

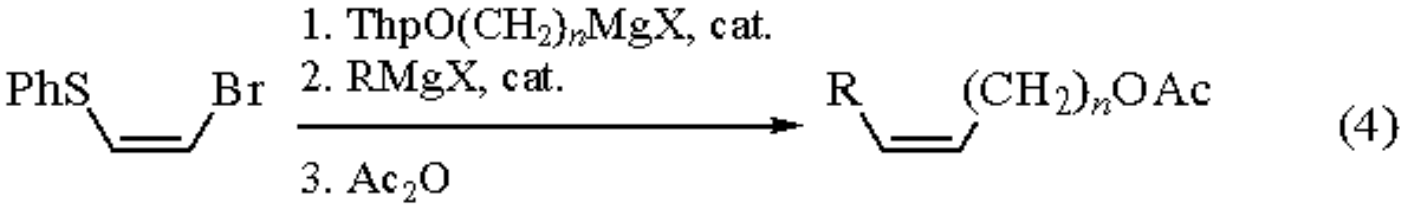

Synthesis of Stereodefined Alkenyl Sulfides.

The substitution of the halogen atom occurs at a rate much greater than the phenylthio group; thus alkenyl sulfides can be conveniently obtained (eqs 5-7).[3,5,6]

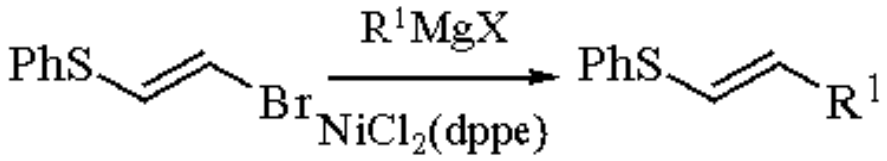

(5)

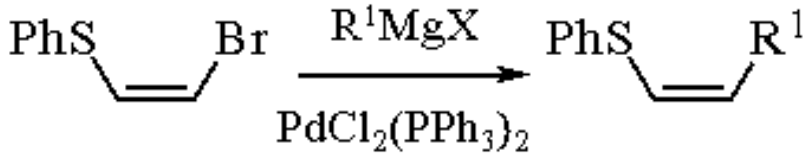

(6)

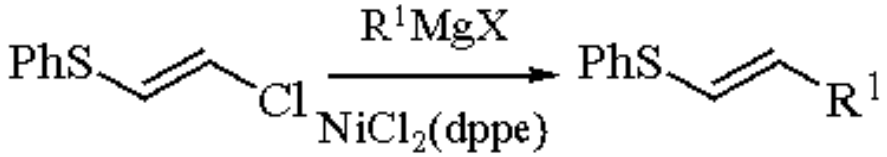

(7)

It is worth noting that the use of a Pd catalyst in the reaction leading to (*Z*) isomers gives better stereochemical results. The phenylthio group of alkenyl sulfides is easily converted to a carbonyl group.[7]

Alkenyl sulfides can be also obtained in an enantioselective manner (51-57% ee) by a cross-coupling reaction of (**1**) or (**2**) with a secondary Grignard reagent in the presence of chiral Ni^{II} or Pd^{II} catalysts, at 0 °C or at rt, in THF or ether (eq 8).[3] The best results are obtained with the complex of the chiral phosphine PPFA (PPFA = ***(R)-N,N-Dimethyl-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethylamine***).

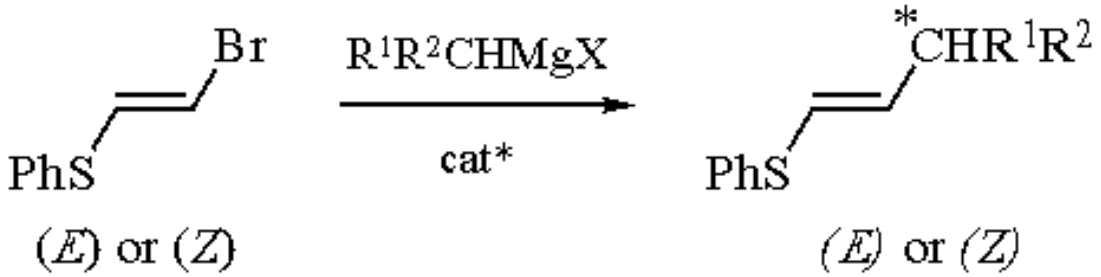

(8)

Occasionally, when secondary organomagnesium reagents are used, isomerization of the secondary alkyl/primary alkyl group is observed. Iron(III) complexes, for example ***Tris(dibenzoylmethide)iron(III)*** and $Fe(DPM)_3$ (DPM = dipivaloylmethide), completely suppress this isomerization process.[8]

The cross-coupling process leading to (*Z*)-alkenyl sulfides can also be performed with other organometallic compounds, e.g. by combining (**2**) with 9-alkyl-9-BBN in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** (as catalyst) and a base,[9a] or with (dialkoxyboryl)methylzinc reagents in the presence of the same catalyst.[9b]

Reagent (*E*)-(**3**) can be transformed into vinyl selenides by action of MeSeLi or PhSeNa (eq 9), with retention of configuration.[10]

(E)-1-Bromo-2-phenylthioethylene

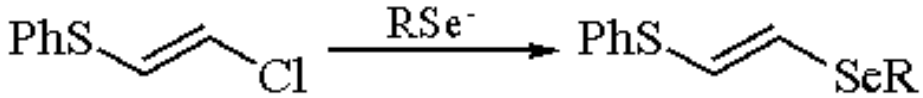

(9)

R = methyl, phenyl

Synthesis of Stereodefined Dienes.

1,3-Dienes.

1-Trimethylsilyl-1,3-dienes.

(1*E*,3*E*)- and (1*E*,3*Z*)-1-trimethylsilyl-1,3-dienes can be obtained by the appropriate cross-coupling reaction between (**1**) or (**2**) and (*E*)-2-trimethylsilylvinylmagnesium bromide (eqs 10 and 11) in the presence of $NiCl_2$(dppe).[11]

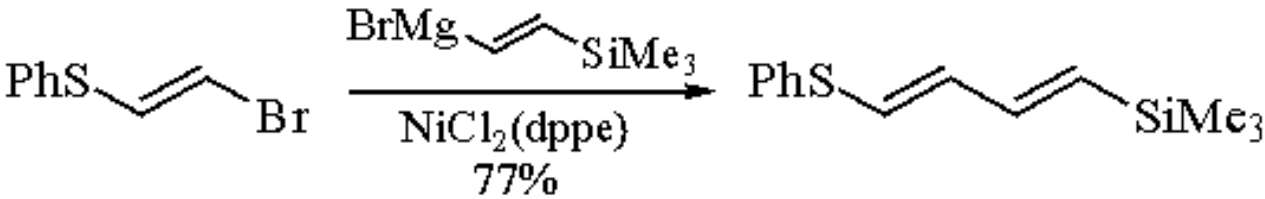

(10)

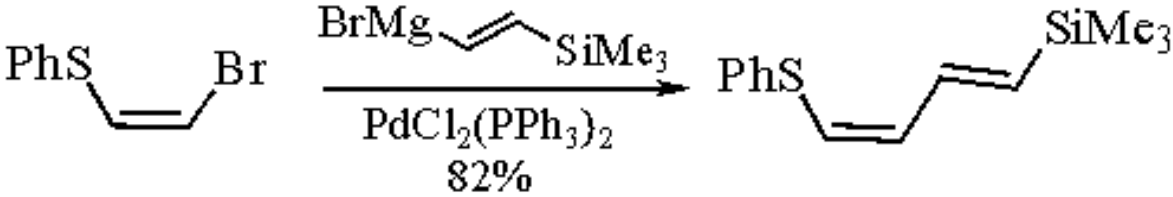

(11)

These compounds can be employed in the synthesis of more complex targets, since both the phenylthio and the trimethylsilyl groups can be substituted in different ways (e.g. the trimethylsilyl group can be replaced by acyl groups using acyl chlorides in the presence of $AlCl_3$).[1]

1-Phenylthio-1,3-dienes.

Reagents (**1**) and (**2**) react with 1-alkenyl-1,3,2-benzodioxaborole in the presence of $Pd(PPh_3)_4$ and a base to yield 1-phenylthio-1,3-alkadienes or -1,3,5-alkatrienes (eqs 12 and 13).[12] These intermediates are easily converted into important natural products, e.g. *cis*(C_{10})-allofarnesene, by the substitution of the arylthio group with a Grignard reagent in the presence of Ni^{II} complexes.

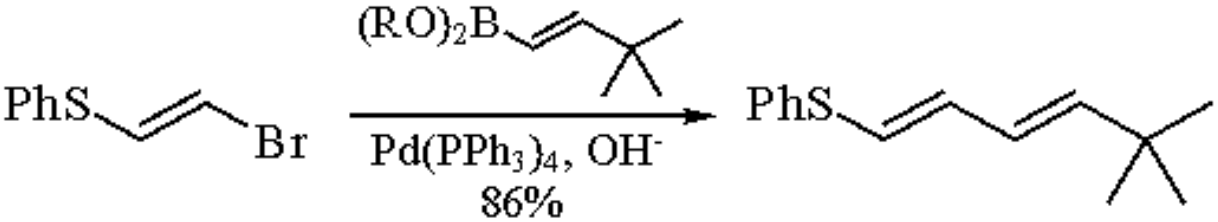

(12)

(E)-1-Bromo-2-phenylthioethylene

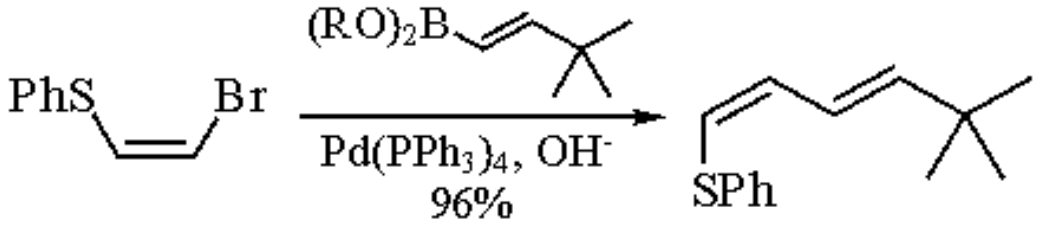

(13)

(*E*,*Z*)- and (*Z*,*E*)-Dienes.

Reagent (**2**) can give ***Phenylthioacetylene***,[2] to which (*Z*)-dialkenylcuprates are added (eq 14).[13]

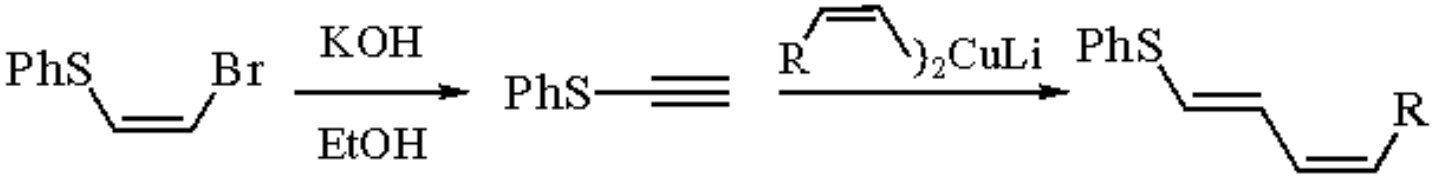

(14)

The arylthio group of the resulting (*E*,*Z*)- and (*Z*,*E*)-1-phenylthio-1,3-dienes can be substituted by a Grignard reagent in the presence of $NiCl_2$(dppe) to yield the corresponding dienes (eq 15). A variety of pheromones having a conjugated diene structure can be prepared using this approach.[13]

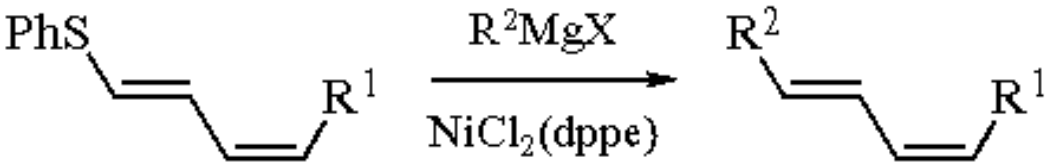

(15)

1,4-Dienes.

Phenylthiopentadiene.

Reagent (**2**) is converted (eq 16) by a cross-coupling reaction with ***Allylmagnesium Bromide*** in the presence of $NiCl_2$(dppe) to a 1-phenylthio-1,4-diene.[14] This compound can be easily metalated with ***n-Butyllithium*** to give phenylthiopentadienyllithium, which can be reacted with various C-electrophiles, or can be first transmetalated and then reacted with C-electrophiles. The stereo- and regiochemistry of the process can be properly tuned.

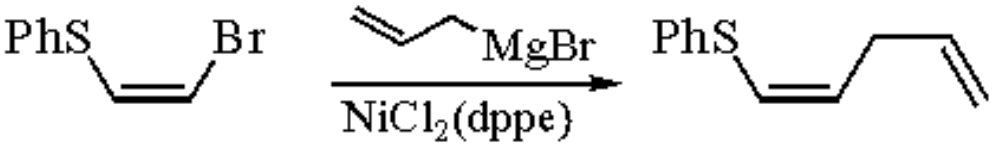

(16)

Synthesis of Sulfoxides.

Vinyl Sulfoxides.

Reagents (**1**), (**2**), and (**3**) can be oxidized by ***m-Chloroperbenzoic Acid*** to the corresponding sulfoxides, which react in two different ways (eq 17), according to the organometallic reagent employed.[15]

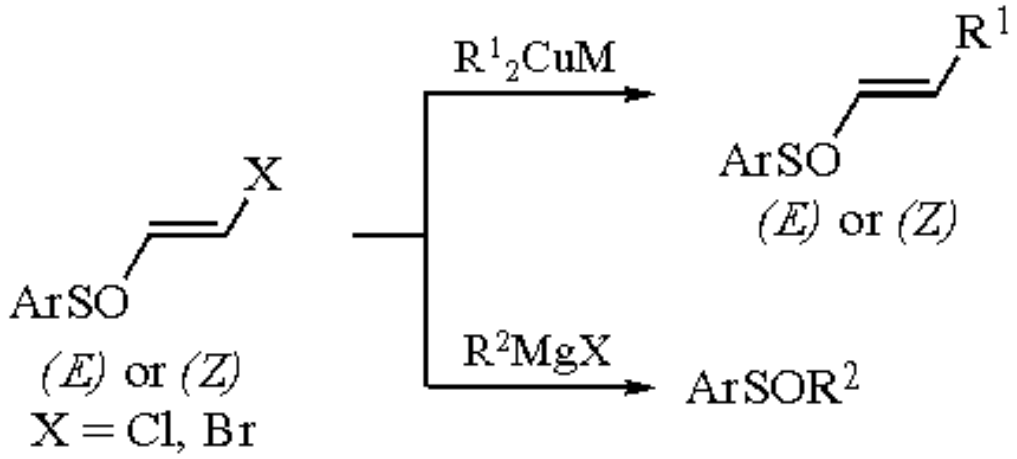

(17)

Organocuprates give the cross-coupling process with substitution of the halogen group. Grignard reagents attack the sulfur atom with substitution of the whole halovinyl moiety. Starting with optically active halovinyl aryl sulfoxides, alkyl aryl or diaryl sulfoxides can be obtained in a highly enantioselective manner.[16]

Vinylstannanes.

Reagent (**3**) can generate vinylstannanes after *m*-CPBA oxidation to sulfoxides, and subsequent treatment with ***Hexamethyldistannane*** (eq 18) in the presence of $Pd_2(dba)_3/PPh_3$.[17]

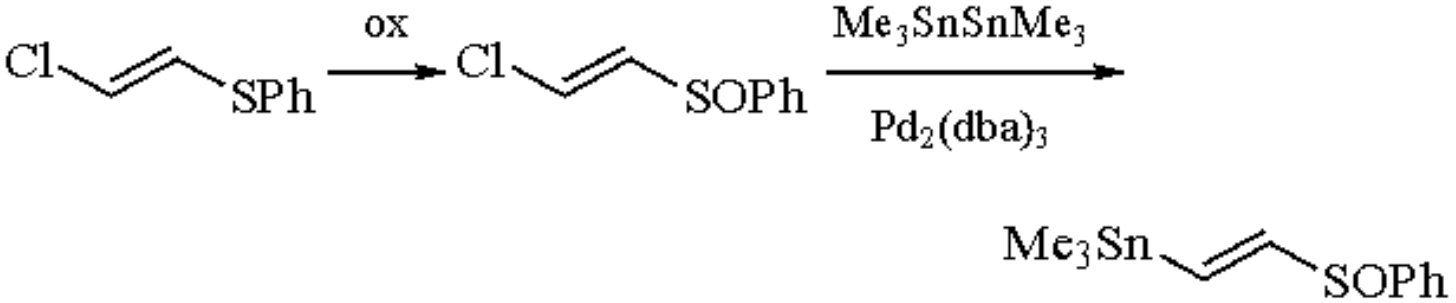

(18)

Recently, reagent (**3**) has been transformed into 1-bromo-1-phenylthio-1,3-butadiene, thus leading to a general approach to conjugated (*E*,*E*)-dienes, through sequential coupling reactions.[18]

Related Reagents.

Phenylthioacetylene.

---

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6. Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. *CC* **1982**, 647.
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14. Florio, S.; Ronzini, L.; Sgarra, R. *TL* **1991**, *32*, 1114; **1990**, *31*, 2327.
15. Cardellicchio, C.; Fiandanese, V.; Naso, F. *JOC* **1992**, *57*, 1718.
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18. Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *TL* **1994**, *35*, 8847.

Francesco Naso, Vito Fiandanese & Cosimo Cardellicchio

CNR, Centre MISO, University of Bari, Italy

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3-Bromo-1,2-propanediol[1]

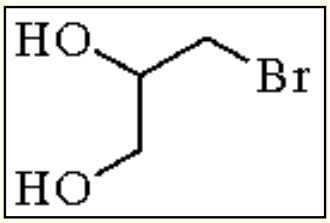

[4704-77-2] · $C_3H_7BrO_2$ · 3-Bromo-1,2-propanediol · (MW 154.99)

(carbonyl protecting group which can be cleaved under neutral conditions[2])

Physical Data: bp 92-94 °C/1.5 mmHg; *d* 1.769 g cm^{-3}.

Form Supplied in: widely available as 95% or 98% pure; viscous colorless liquid.

Preparative Method: prepared according to the procedure of Winstein and Goodman.[4] Epibromohydrin (**1**) is treated with a catalytic amount of *p*-toluenesulfonic acid in H_2O at refluxing temperature for 7 h (eq 1). Distillation of the final product gives a 65% yield of the desired diol (**2**).

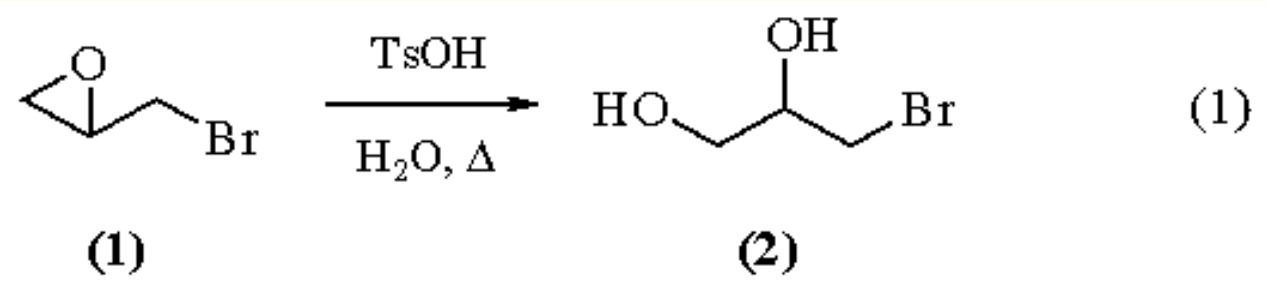

Handling, Storage, and Precautions: harmful liquid and fumes (CO, CO_2, HBr); incompatible with strong oxidizing agents; corrosive; irritant; use in fume hood only; refrigerate.[3]

Synthetic Utility.

The transformation of aldehydes and ketones to cyclic acetals is a commonly used method for the protection of the carbonyl functional group. The cleavage of these acetal protecting groups is usually accomplished with acidic media, rendering acid incompatible functional groups unsuitable for schemes employing such deprotection steps. The development of 3-bromo-1,2-propanediol as a protecting group for carbonyls stemmed from the need for a protecting group which could be removed under neutral conditions in high yields. 4-*t*-Butylcyclohexanone (**3**) in the presence of bromoglycol (**2**) and catalytic ***p-Toluenesulfonic Acid*** in refluxing benzene gives 98% of acetal (**4**) (eq 2).

Deprotection of the bromomethylethylene acetal (**4**) is accomplished by treating it with ***Zinc*** dust in refluxing methanol for 12 h to afford 89% of 4-*t*-butylcyclohexanone (**3**) (eq 2).[2]

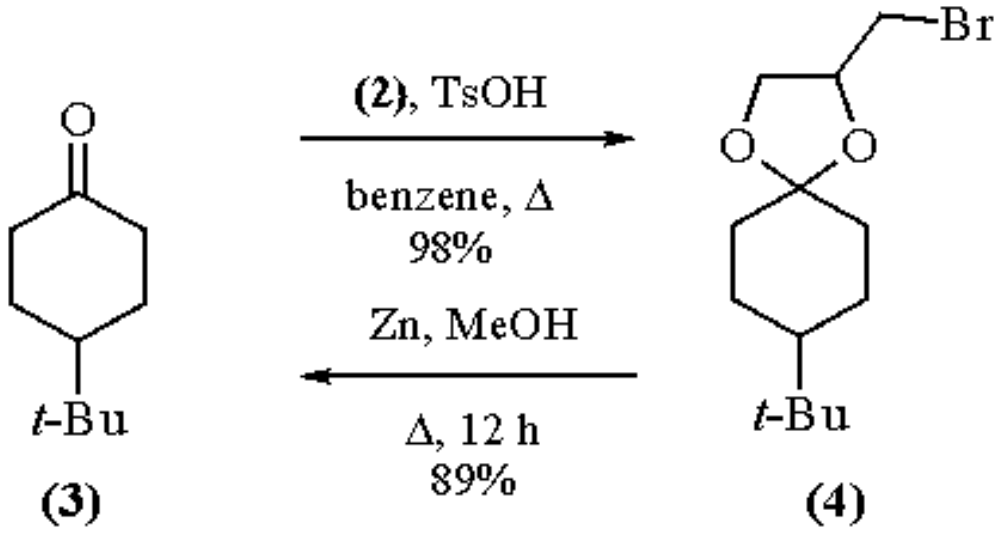

(2)

Under acidic conditions, α,β-saturated ketones can be selectively protected in the presence of their α,β-unsaturated counterparts. For example, exposure of enedione (**5**) to 3-bromo-1,2-propanediol and *p*-toluenesulfonic acid in refluxing benzene gives a mixture of isomeric acetals (**6a** and **6b**) and the monoprotected compound (**7**). Treatment of this mixture with *p*-toluenesulfonic acid and acetone gives pure (**7**) in 74% overall yield (eq 3).[5]

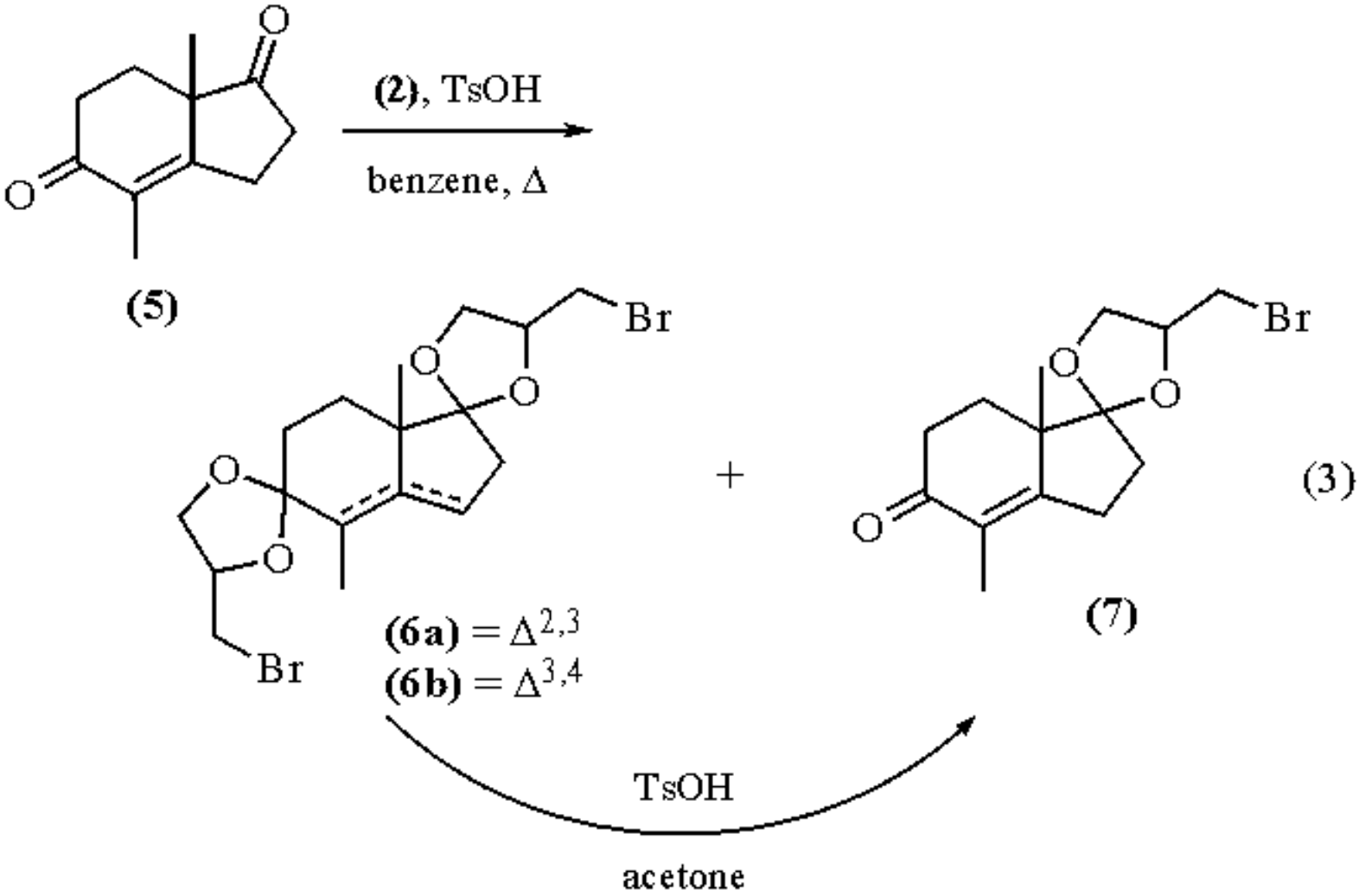

Formation of this acetal has also been used to shift the double bond of an α,β-unsaturated enone. For example, treatment of enone (**8**) with 3-bromo-1,2-propanediol under standard conditions gives a mixture of acetals (**9** and **10**) (eq 4). The mixture of isomers can be deprotected without separation with zinc in refluxing methanol for 18 h. Enone (**11**) is isolated in 37% yield after chromatographic separation of the alkenic isomers.[6]

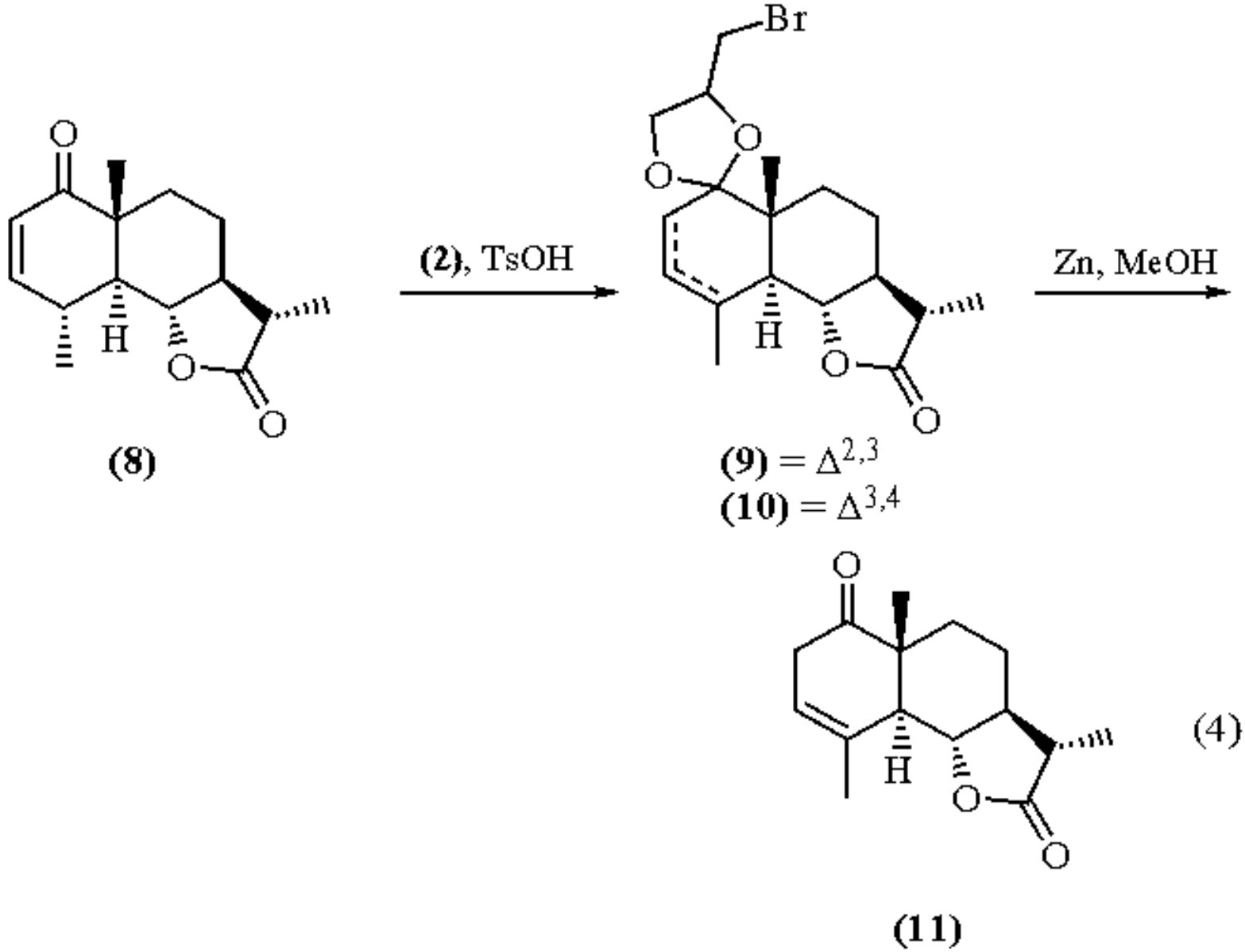

Stability of the Acetal.

The bromomethylethylene acetal moiety is stable to a variety of reagents that react with carbonyl groups. For example, treatment of acetal (**4**) with ***m-Chloroperbenzoic Acid***, ***Ammonia***, ***Sodium Borohydride***, ***Methyllithium***, or ***Chromium(VI) Oxide*** gives a quantitative recovery of the starting material.[2] On the other hand, while there are many hydroxy, amino, and carbonyl protecting groups that are stable to the reductive conditions employed to remove this protecting group,[2,7] the β-halo ethers (**12** and **13**) are incompatible with such conditions.

(12) **(13)**

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Dartmouth College, Hanover, NH, USA

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3-Bromo-2-propen-1-ol

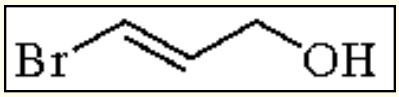

[37675-33-5] · C_3H_5BrO · 3-Bromo-2-propen-1-ol · (MW 136.98)

(used in palladium-catalyzed cross-coupling reactions with alkynes)

Physical Data: bp 94-97 °C/55 mmHg. *cis* isomer: bp 81 °C/25 mmHg; d^{25} 1.6623. *trans* isomer: bp 87 °C/25 mmHg; d^{25} 1.6567.

Analysis of Reagent Purity: satisfactory microanalytical data reported.[1]

Preparative Methods: by alkaline hydrolysis of 1,3-dibromopropene,[1,2] by hydrobromination of methyl propiolate followed by reduction,[3] or by sequential hydrostannylation and bromination of propyn-3-ol.[4]

3-Bromo-2-propen-1-ol has been widely used in palladium-catalyzed cross-coupling reactions of hydroxylated alkynes. Synthetic routes to leukotriene B_4,[5] leukotriene E_4 metabolites,[4] lipoxin A_1,[6] coriolic acid, and dimorphecolic acid[7] have utilized such reactions as pivotal steps (eqs 1-4, respectively). Intermediates for the preparation of other arachadonic acid metabolites have also been prepared by this method (eq 5).[8]

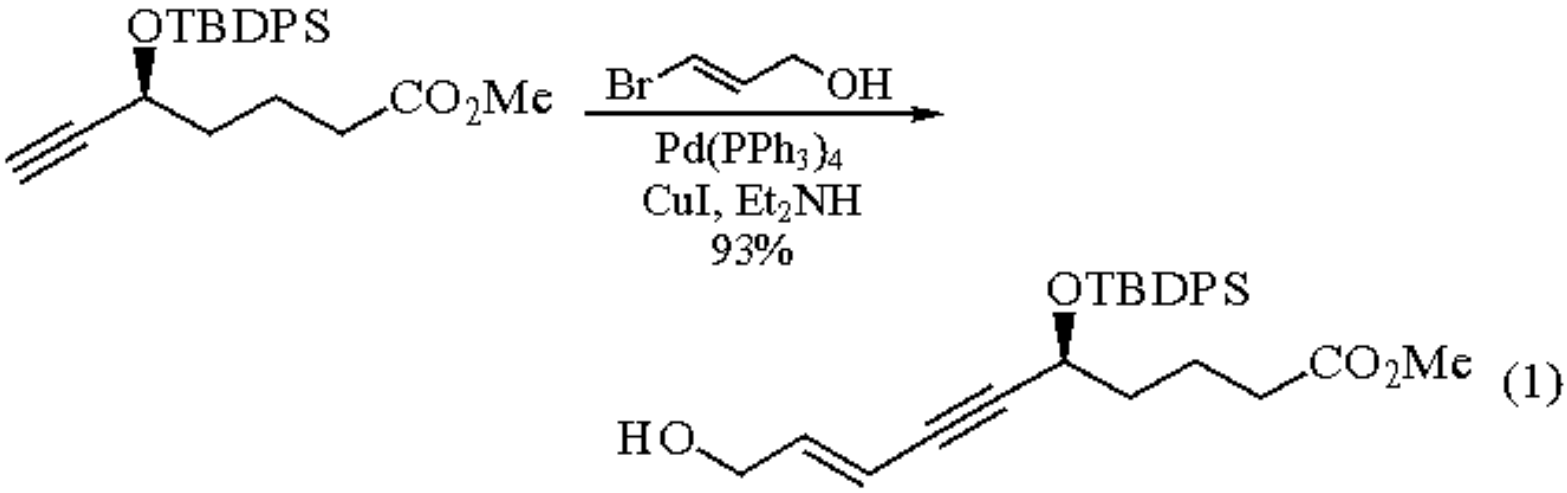

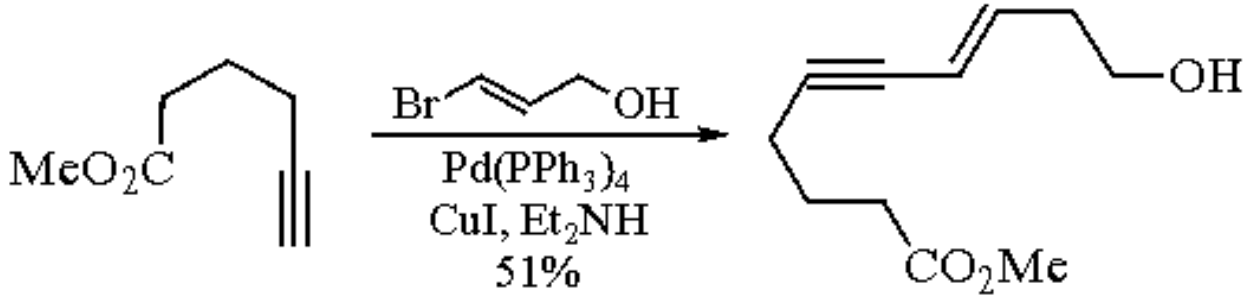
MeO2C
Br
OH
Pd(PPh3)4
CuI, Et2NH
51%
OH
CO2Me

(2)

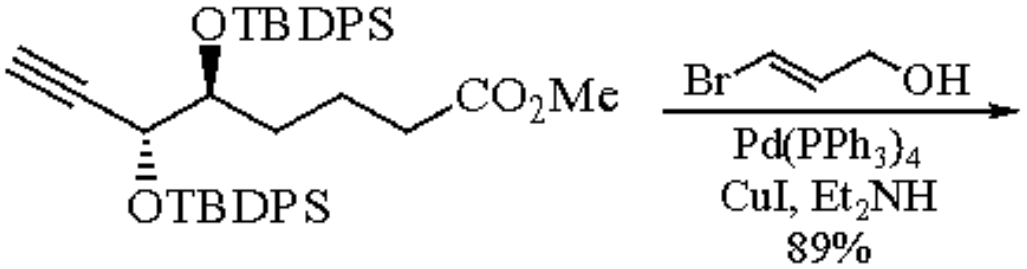
OTBDPS
CO2Me
OTBDPS
Br
OH
Pd(PPh3)4
CuI, Et2NH
89%

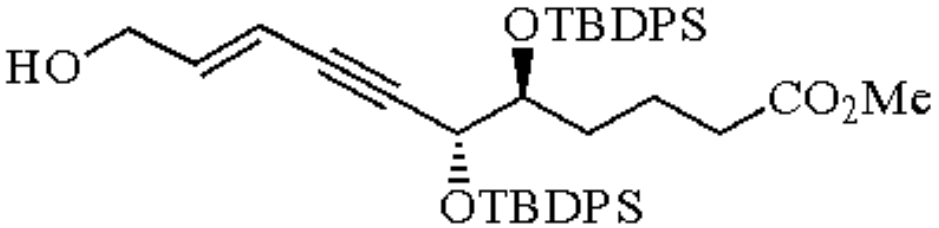
HO
OTBDPS
CO2Me
OTBDPS

(3)

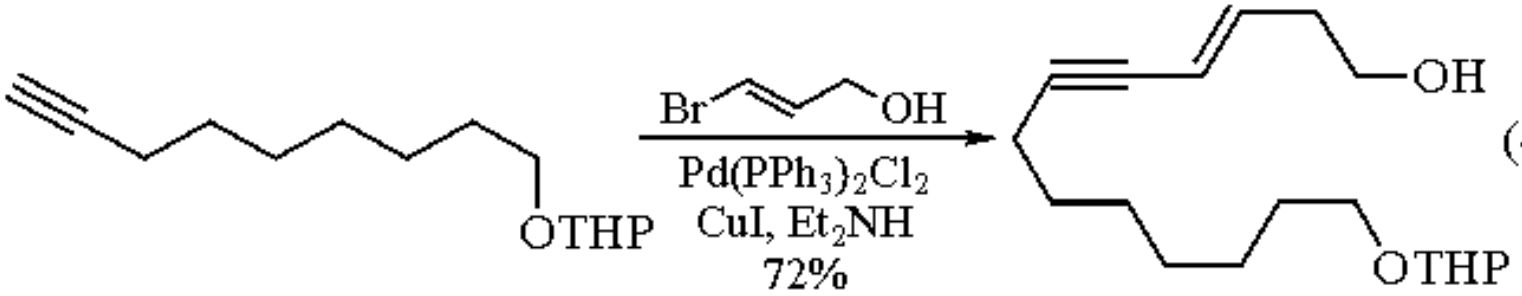
OTHP
Br
OH
Pd(PPh3)2Cl2
CuI, Et2NH
72%
OH
OTHP

(4)

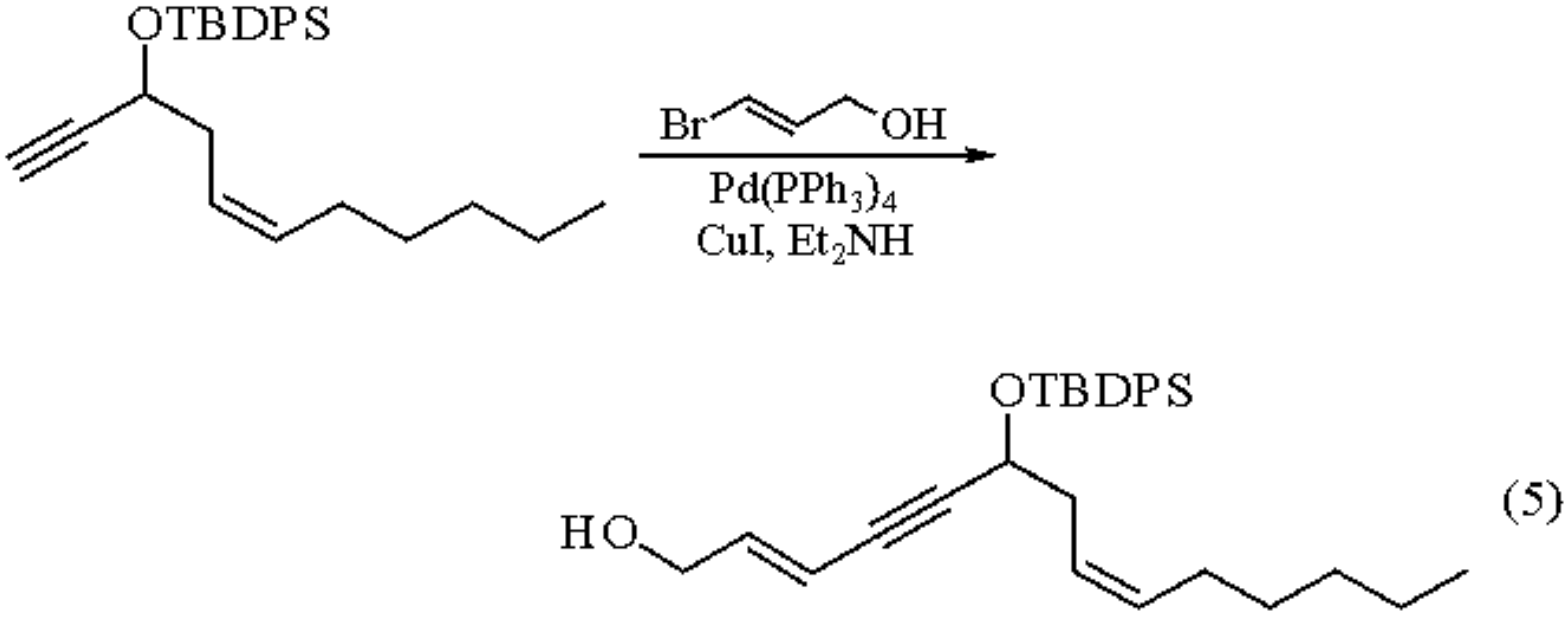

Trienals derived from linolenic acid may be prepared using the process (eq 6).[9]

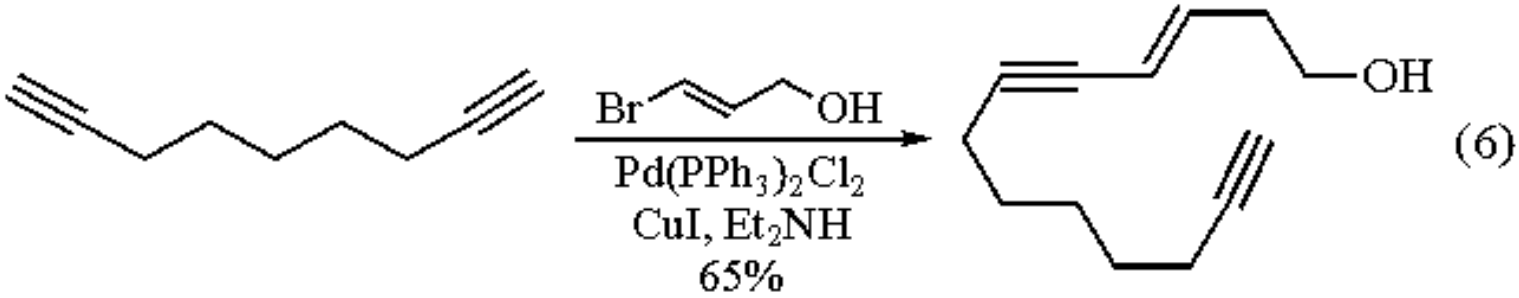

Oxidation of bromopropenal gives the highly unstable 3-bromopropenal that may be converted in situ to the corresponding dimethyl acetal (eq 7), which has been examined as a substrate for Heck reactions with alkenes.[4]

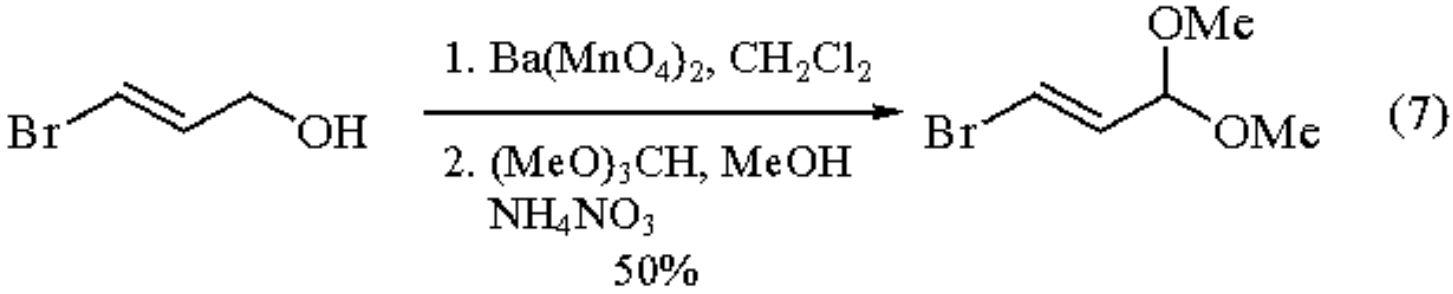

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3-Bromopropionyl Isocyanate

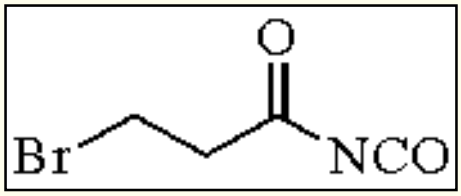

[18926-24-4] · $C_4H_4BrNO_2$ · 3-Bromopropionyl Isocyanate · (MW 177.99)

(derivatizing agent for alcohols,[1] phenols,[2] and arylamines;[3] brominating agent potentially present in *N*-bromosuccinimide brominations;[4] bifunctional cyclization reagent[5])

Alternate Name: 3-bromopropanoyl isocyanate.

Physical Data: volatile liquid.

Solubility: sol chlorinated, aromatic, and ethereal solvents; reacts violently with H_2O, and with basic and protic solvents.

Form Supplied in: prepared from ***N-Bromosuccinimide*** as needed.[6]

Handling, Storage, and Precautions: lachrymator; corrosive; use only in a fume hood; wear protective gloves and preferably a NIOSH-approved respirator. All transfers and reactions should be carried out under anhydrous conditions. Store in a cool dry place, taking care to avoid contamination with protic, basic, or organometallic materials, as these may induce polymerization. Toxicity data for isocyanates are available.[7]

Derivatization of Alcohols, Phenols, and Amines.

Like other isocyanates, 3-bromopropionyl isocyanate reacts rapidly with N- or O-nucleophiles to give urea and carbamate derivatives, respectively (eq 1).[8] Crystalline materials are obtained from primary and unhindered secondary alcohols, while tertiary alcohols give alkenes via elimination.[1] Phenols react extremely well, except those containing multiple nitro groups.[2] Anilines afford ureas, unless hindered or containing more than one amino group.[3] Aliphatic amines usually cause elimination of HBr from the isocyanate, thus yielding *N*-acryloylurea impurities.[3] Note that the presence of the Br atom in these derivatives simplifies crystal structure determination by heavy atom methods.

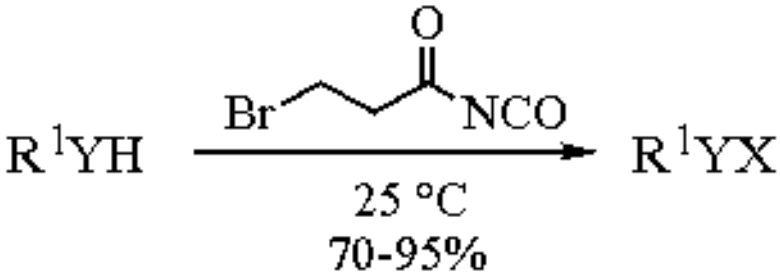

(1)

R^1 = primary or secondary alkyl, aryl; YH = OH, NH_2, NHR^2

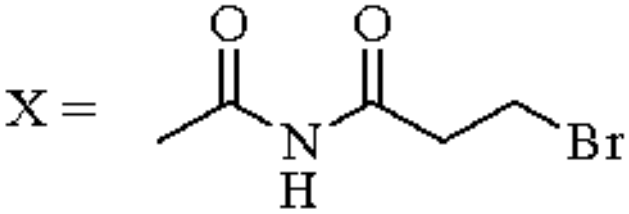

Isomeric Brominating Agent Present in *N*-Bromosuccinimide Reactions.

Much recent interest in elucidating the exact nature of the radical chain carriers in *N*-bromosuccinimide reactions (π-versus σ-centered radicals)[9] and their respective chemoselectivities has led in turn to a greater understanding of the radical chemistry of 3-bromopropionyl isocyanate. Indeed, radical scavengers form adducts with 3-bromopropionyl isocyanate in several solvents.[4,10] The current status of the debate holds that the rate of intramolecular cyclization of 3-bromopropionyl isocyanate (3.7×10^6 at 328 K) is more consistent with a σ-centered radical (eq 2).[11]

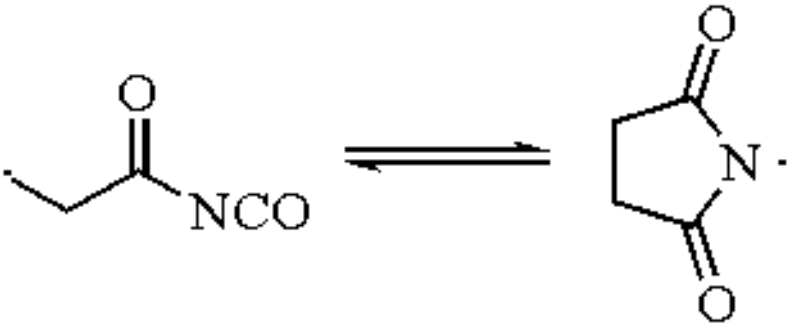

(2)

Bifunctional Cyclization Reagent.

This molecule contains two reactive centers (isocyanate and bromide) of appreciably different reactivity. Thus far, this relationship has been exploited in the preparation of dihydrouracil antibacterial agents (eq 3).[5] It must also be noted that the bromine substituent may be eliminated to give an acryloyl moiety,[3] which may

give additional modes of reactivity.

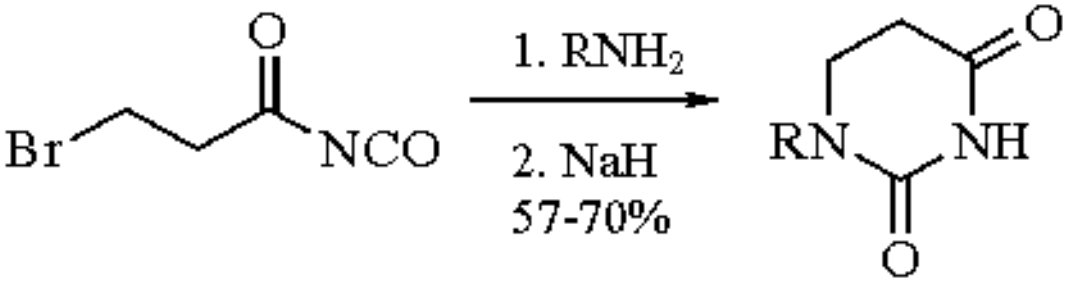

(3)

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2-(3-Bromopropyl)-2-methyl-1,3-dioxolane

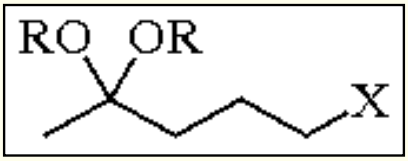

(**1**; X = Br, R,R = $-CH_2CH_2-$)

[24400-75-7] · $C_7H_{13}BrO_2$ · 2-(3-Bromopropyl)-2-methyl-1,3-dioxolane · (MW 209.08) (**2**; X = Cl, R,R = $-CH_2CH_2-$)

[5978-08-5] · $C_7H_{13}ClO_2$ · 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane · (MW 164.63) (**3**; X = I, R,R = $-CH_2CH_2-$)

[3695-28-1] · $C_7H_{13}IO_2$ · 2-(3-Iodopropyl)-2-methyl-1,3-dioxolane · (MW 256.08) (**4**; X = I, R,R = Me,Me)

[88794-75-6] · $C_7H_{15}IO_2$ · 5-Iodo-2-pentanone Dimethyl Acetal · (MW 258.10)

(alkylating agents for attaching a 4-ketopentyl group to various nucleophiles; the derived organometallic reagents attach this group to electrophilic centers such as carbonyl groups; the major use has been for synthesis of monoprotected 1,5- and 1,6-diketones and related 1,*n* difunctional compounds)

Alternate Name: 5-bromo-2-pentanone ethylene acetal.

Physical Data: bp (**1**), 94-97 °C/10 mmHg; (**2**), 79-81 °C/8 mmHg; (**3**), 70-72 °C/2 mmHg; (**4**) 100 °C/11 mmHg.

Preparative Methods: acetalization of the 5-halo-2-pentanone (made by opening 2-acetylbutyrolactone with HX).[1] 5-Chloro-2-pentanone is commercially available, and has been converted to 5-iodo-2-pentanone by treatment with sodium iodide/acetone.[1g,2] Alternatively, (**2**) is treated with sodium bromide/ethyl bromide to give (**1**);[3a] (**1**) or (**2**) may be treated with sodium iodide to give (**3**).[3b-d]

Purification: vacuum distillation from a trace of sodium bicarbonate.

Handling, Storage, and Precautions: store at <=0 °C; use in a fume hood.

Electrophilic 4-Ketopentyl Reagent.

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane

Alkylation of ketone enolates with (**1**) gives 1,6-diketone monoacetals.[4] Similarly, enolate equivalents, namely the anions of acetone dimethylhydrazone[5a] and acetylmethylenetriphenylphosphorane,[5b] have been alkylated with (**1**) to give, after partial hydrolysis, 7,7-ethylenedioxy-2-octanone. These substances can be cyclized to acetylcyclopentenes (eq 1).[4a]

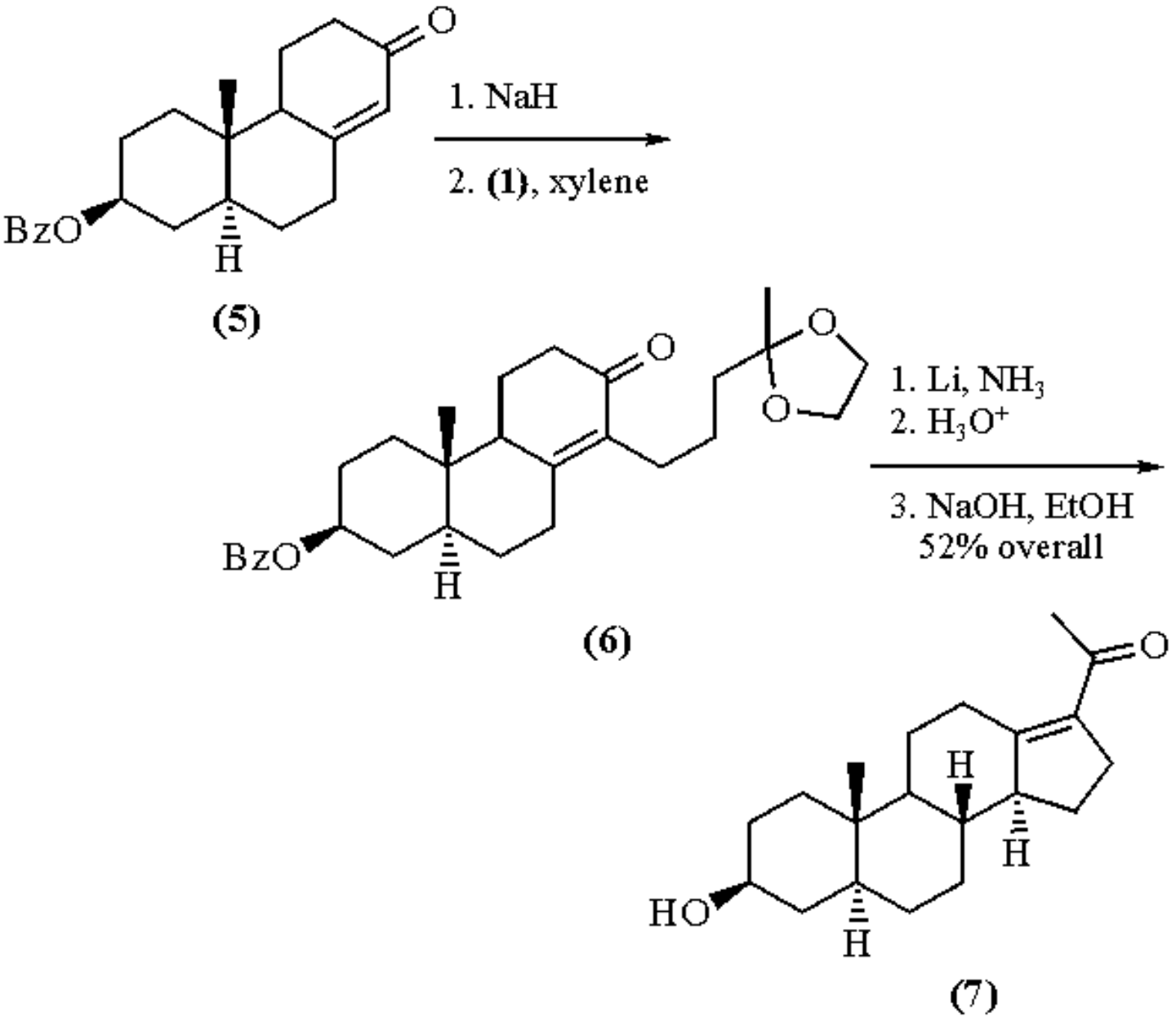

(1)

Alkylation of (**8**) followed by acetalization/deacetalization leads to the tricyclic alkaloid intermediate (**11**) (eq 2).[6]

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane

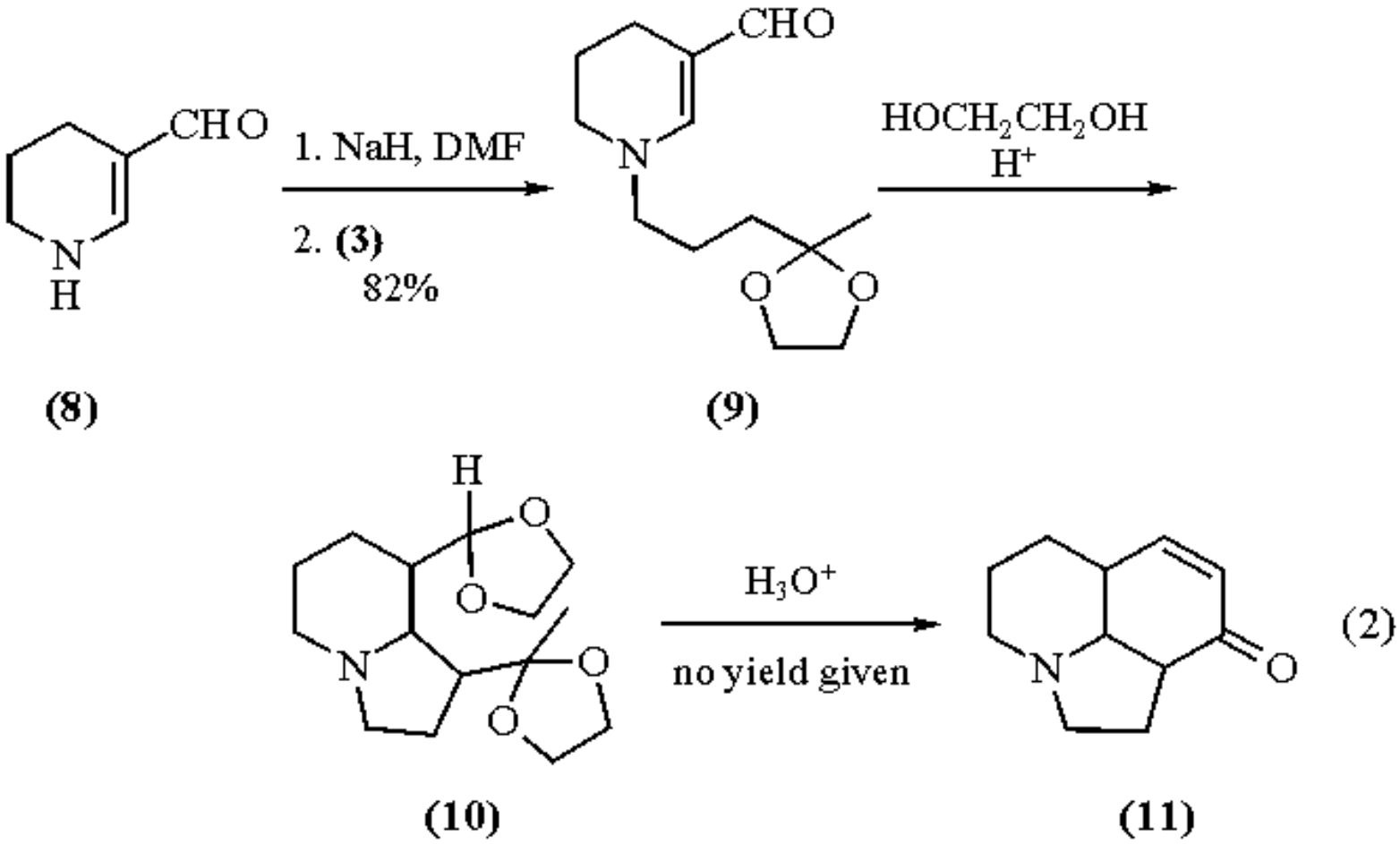

Alkylation of nitriles[7] and α-aminonitriles[8] with 5-halo-2-pentanone acetals is well established. A nonstereoselective synthesis of (-)-pumiliotoxin-C (**15**) starts with the alkylation of (**12**) (eq 3).[8c]

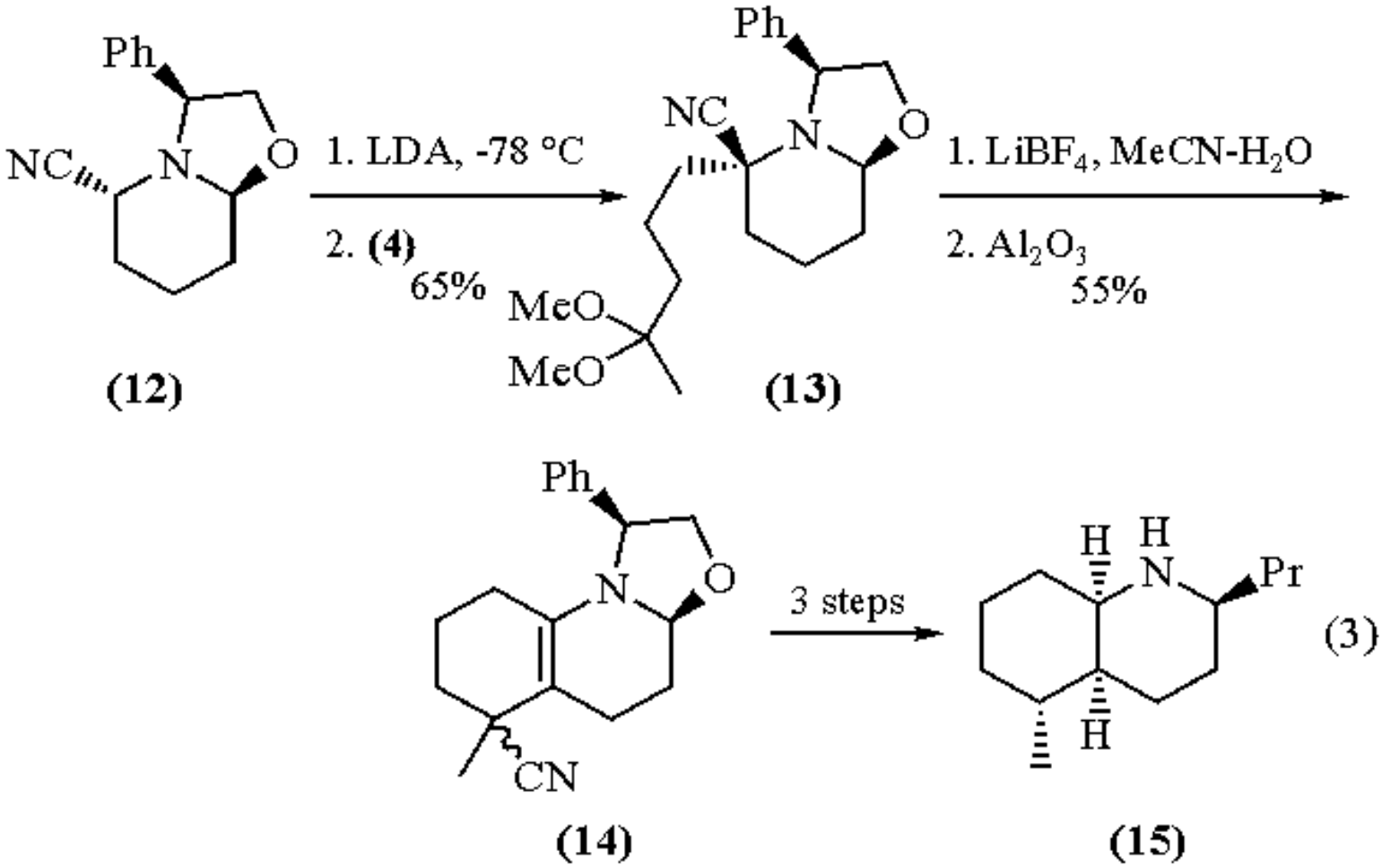

o-Halo-2-alkanone acetals have been used in the synthesis of *n,m*-dihydroxy-2-alkanones which, upon internal acetalization, give various bridged dioxabicyclic insect pheromones (see ***2-(2-Bromoethyl)-2-methyl-1,3-dioxolane***). Stereoselective alkylation of lactone (**16**)[9] (derived from L-lactic acid) with (**4**) is the basis of an enantioselective synthesis of (-)-frontalin (**18**) (eq 4).[1g] A different approach to (**18**) involves Sharpless epoxidation of (**21**) derived from alkylation of malonic ester with (**1**) (eq 5).[10a] Several examples of alkylation of monoanions of 1,3-dicarbonyl and 2-cyanocarbonyl compounds with 5-halo-2-pentanone acetals are known.[10]

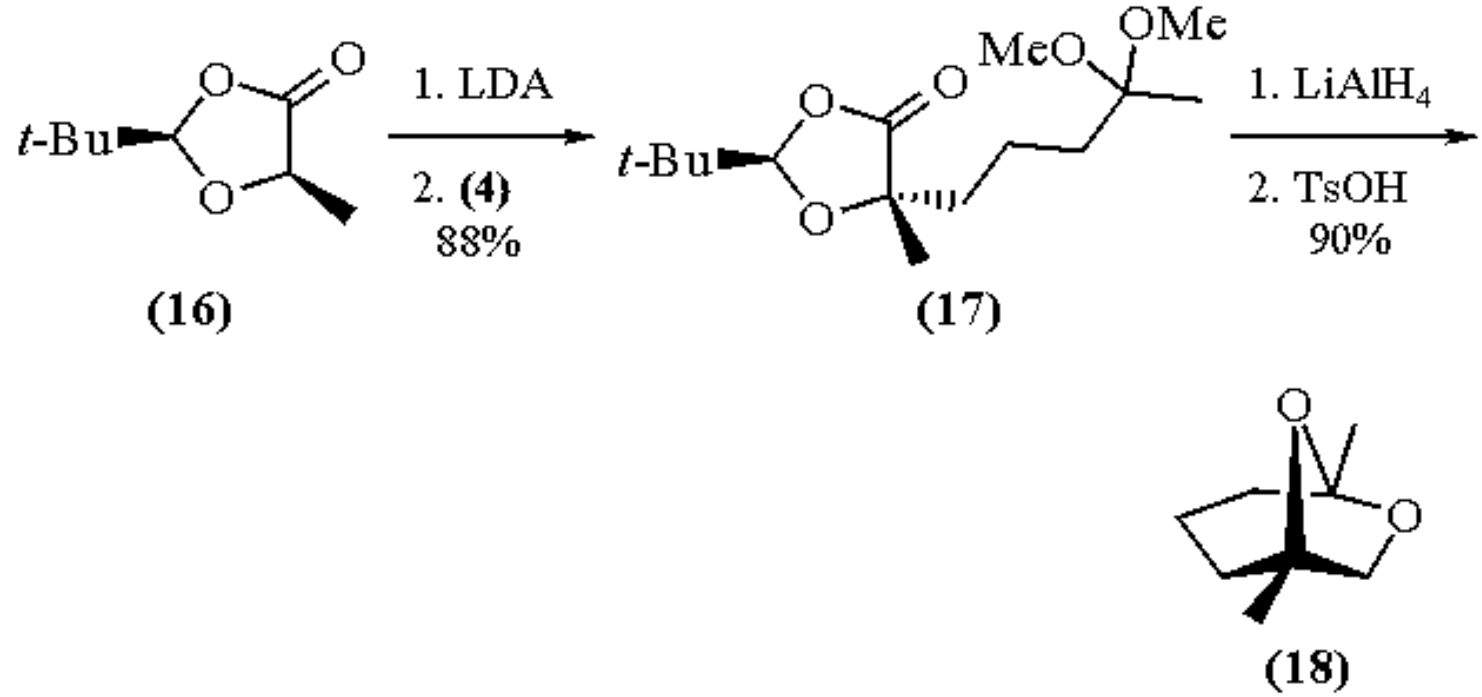

(4)

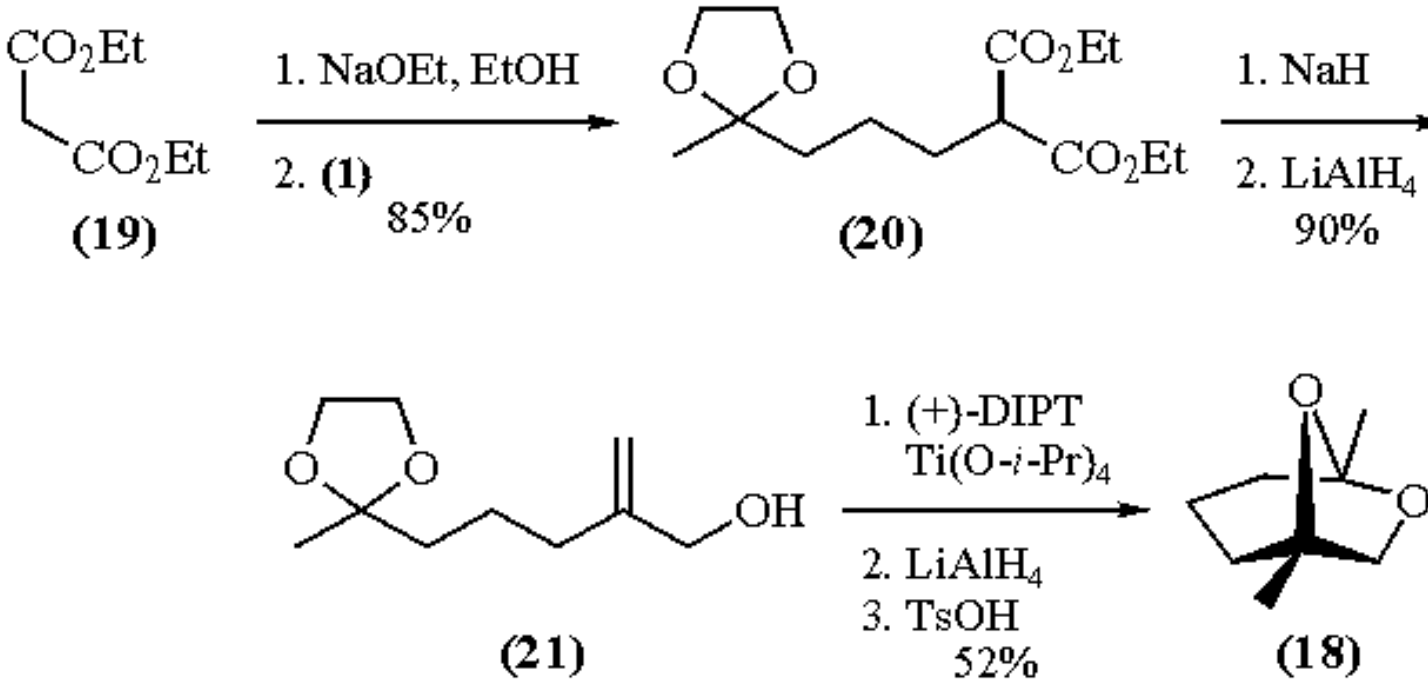

(5)

A short synthesis of (+)-*endo*-brevicomin (**25**) involves alkylation of the dianion of (**22**) (readily available from ***Baker's Yeast*** reduction of 2-propionyl-1,3-dithiane), followed by chemoselective monohydrolysis of (**23**) and stereoselective reduction (eq 6).[11a] Other 1,3-dithianes have been alkylated with 5-halo-2-pentanone acetals in connection with syntheses of insect substances[11b,c] and the macrocyclic lactone zearalenone.[11d] A synthesis of (*E*)-9-keto-2-decenoic acid (queen substance) relies on alkylation of a 1,3-disulfone with (**3**).[12]

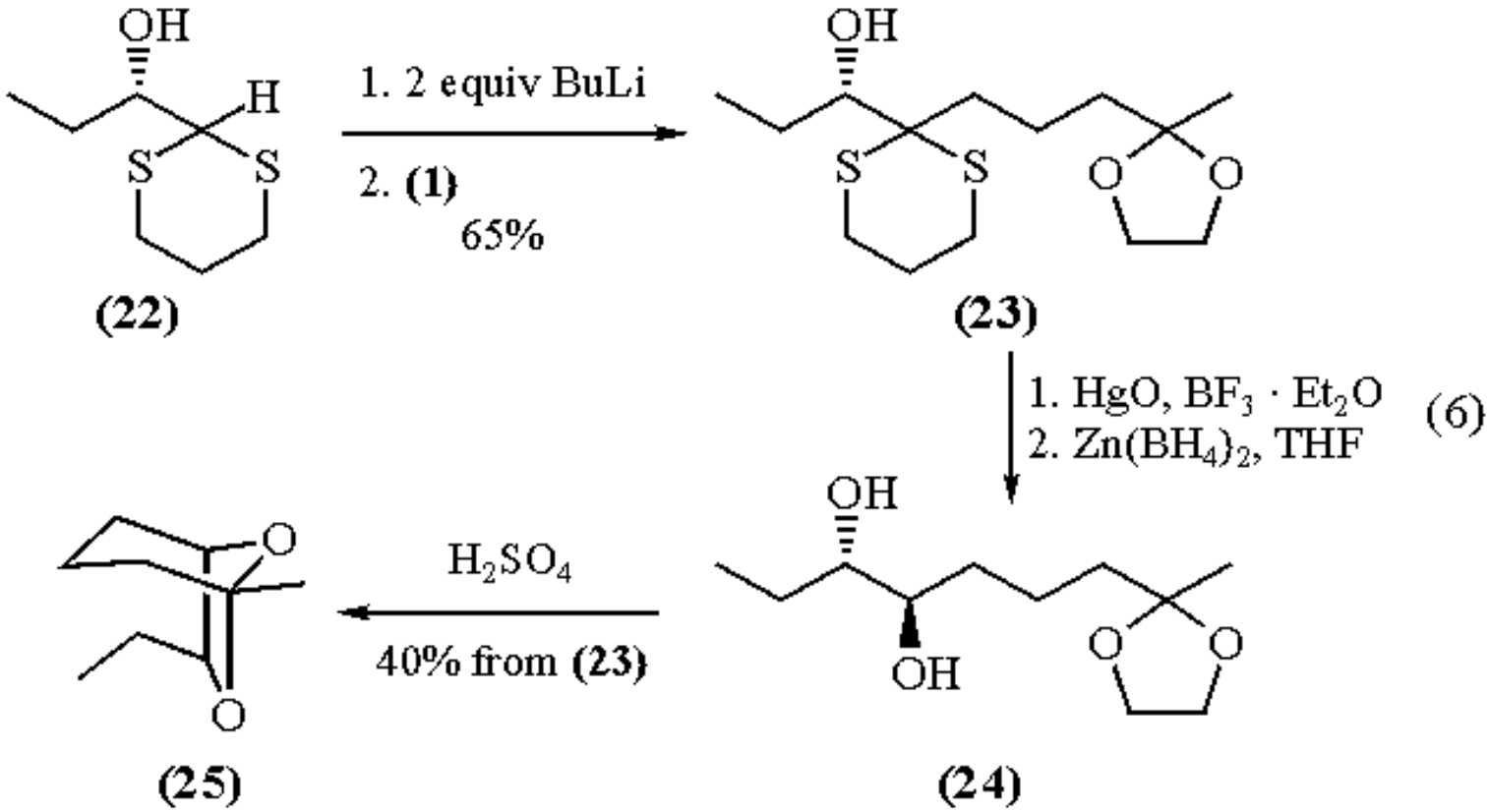

5-Halo-2-pentanone acetals have been used to alkylate lithium and sodium acetylides,[1b,c,13] allenyllithiums,[14] alkenyllithiums[15] and -cuprates,[16] allylic lithiums,[17] 3-furyllithiums,[18] and an allylic phosphonate anion.[19] Several of these applications lead to dioxabicyclic insect pheromones.[13a,b,16b,17b,19]

Nucleophilic 4-Ketopentyl Reagent.

Feugeas and Normant noted in 1963 that the Grignard reagents (**26a**) and (**26b**) (from (**1**) and (**2**), respectively) could be prepared in THF but not in diethyl ether (where dioxolane ring cleavage occured).[20] Despite this caveat, at least three other groups have prepared (**26a**) in diethyl ether[21] and, to further complicate the picture, a fourth group has claimed that, even in THF, the preparation of (**26b**) is capricious.[22] It is likely that the key to success in both solvents is temperature control[23] and the use of freshly distilled (**1**) or (**2**);[21a] the use of Rieke ***Magnesium***[24] has been recommended,[25] as has also the use of ***1,2-Dibromoethane*** as an entraining agent.[26a] In two reports,[1b,22] reaction of (**26b**) with aldehydes produces, in addition to the expected secondary alcohol, large amounts of ketone, presumably via Oppenauer-like intramolecular hydride transfer. Reaction of (**26**) with ketones frequently gives low yields of tertiary alcohols;[27] in one case this has been traced to production of large amounts of secondary alcohol,[27c] presumably via β-hydride transfer. Despite these problems, reaction of (**26**) with aldehydes and ketones has often been used successfully in natural products synthesis;[21,27a,b,28] for example, in the synthesis of monomorine I(**29**) (eq 7).[28a]

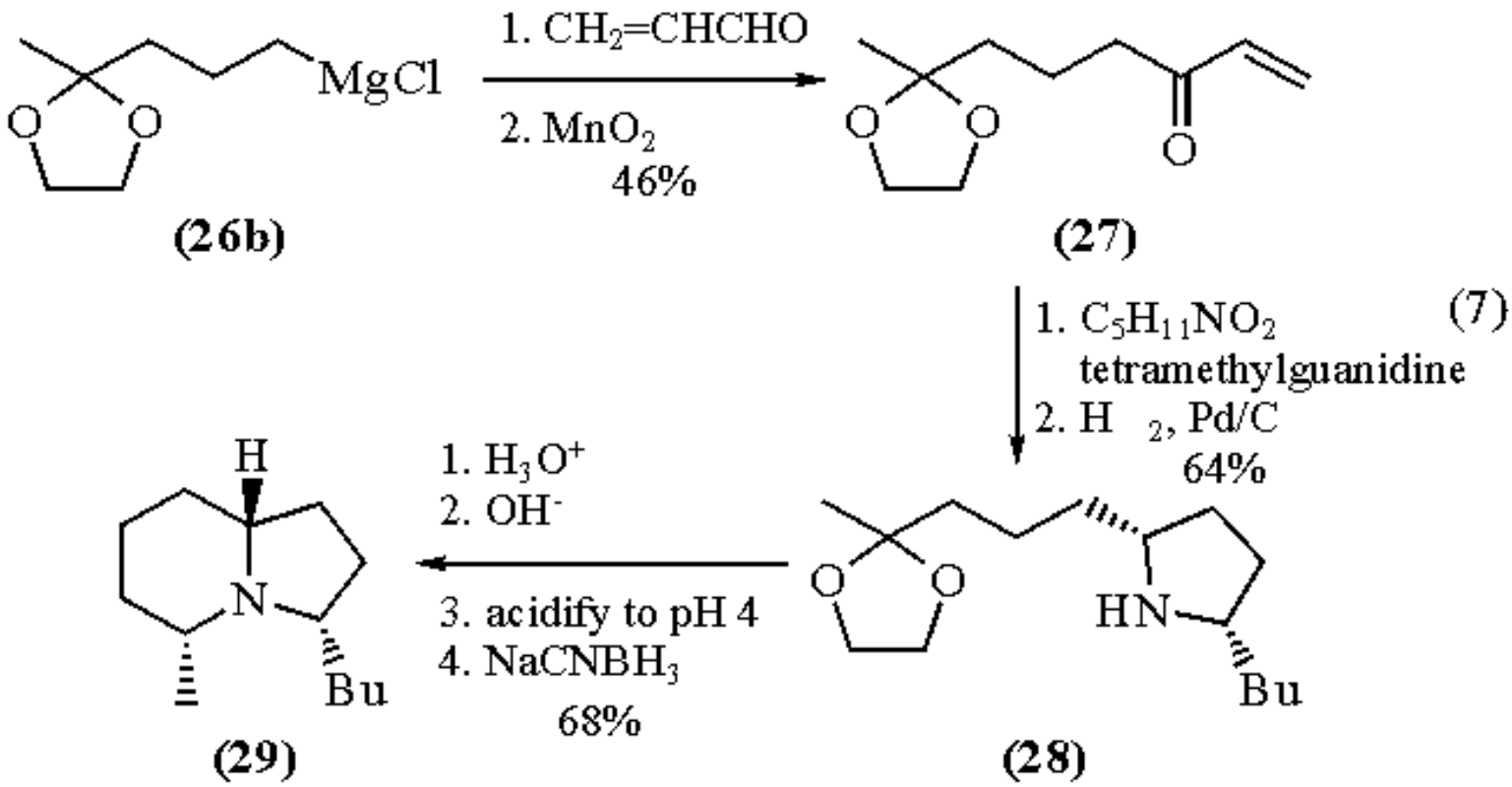

The corresponding lithium reagent (**30**) has been prepared by reaction of (**1**) in diethyl ether with ***Lithium*** containing 1-2% sodium,[29] or with lithium-arene radical anions.[30] Reagent (**30**) reacts more rapidly than (**26**) with aldehydes and ketones, and reacts selectively with a variety of electrophiles.[30a] Townsend and co-workers used both (**26a**)[25a] and (**30**)[29a] with equally good results in syntheses of averrufin (**33**) (eq 8).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane

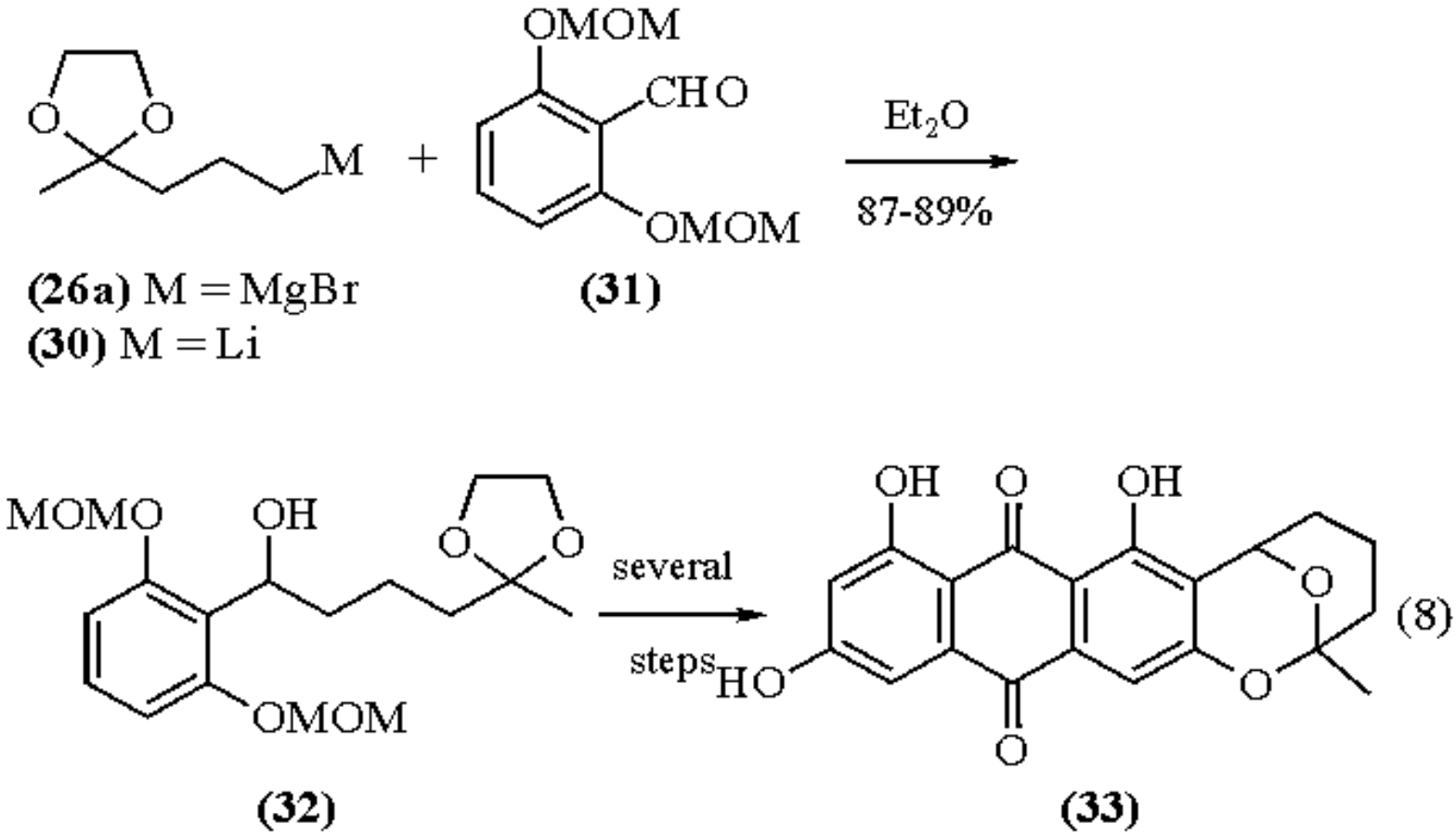

The relatively low reactivity of (**26**) allows the reaction with acid chlorides[31a] and anhydrides[31b,c] to be stopped after monoaddition, enabling preparation of 1,5-diketone monoacetals. Reagent (**26a**) has been paired successfully with enol lactones[21c,31c,32] in the Fujimoto-Belleau reaction (eq 9).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane

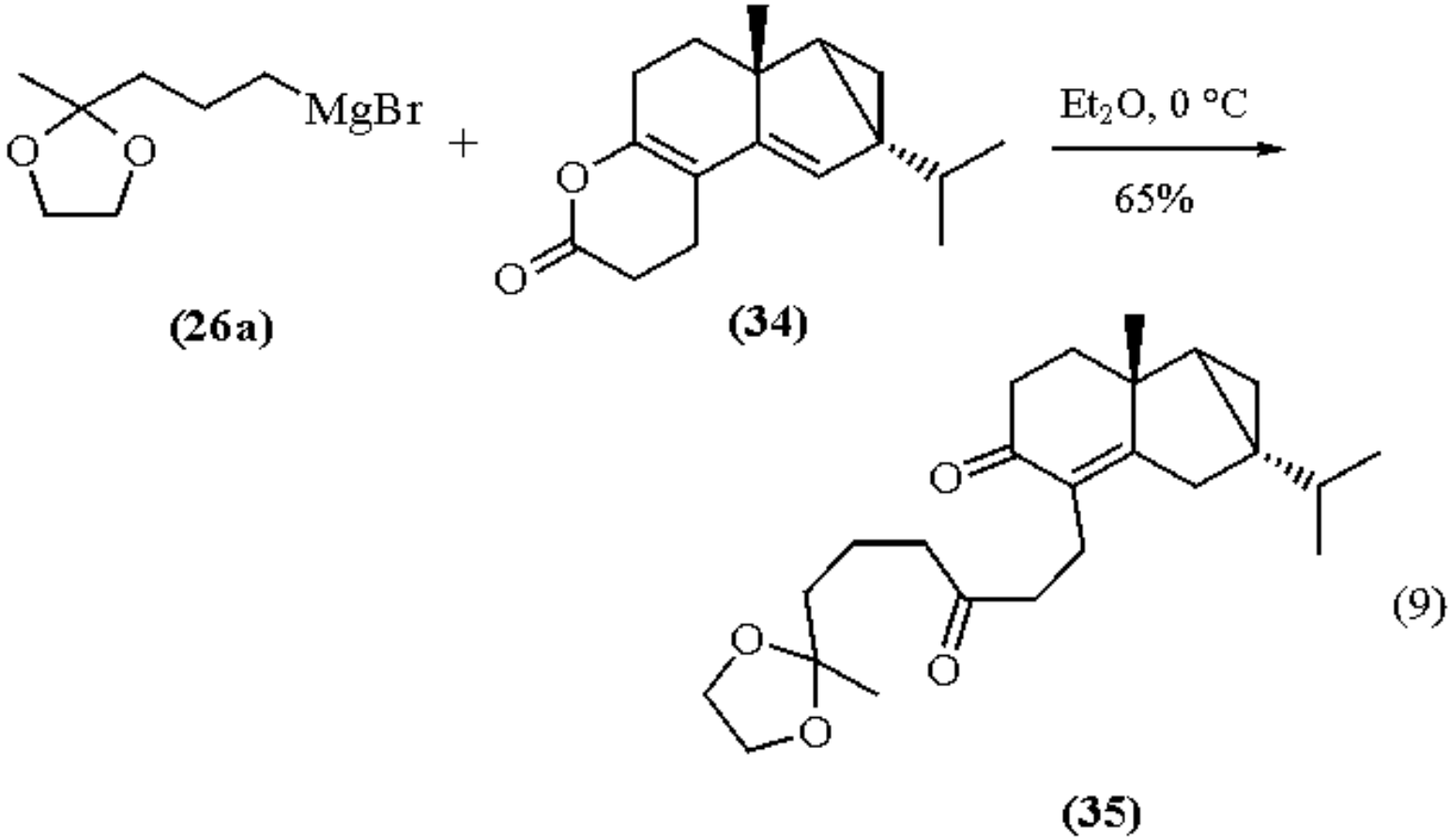

Simple esters, such as ethyl formate, consume 2 mol of the Grignard reagent (producing secondary alcohols),[33] but monoaddition to oxalate esters can be effected at -40 °C, leading to α-keto esters; this latter process has been used in syntheses of anatoxin A.[25b,c] Reactions of (**26a**) and (**26b**) with hemi-aminals and immonium salts,[34a] carbon disulfide,[34b] triphenyltin chloride,[34c] and trimethyl borate[34d] have been reported.

The Grignard reagent (**26a**) in the presence of copper salts has been used for nucleophilic substitution reactions with saturated alkyl halides and sulfonate esters,[26] and with allyl[35] and propargyl[36] halides and sulfonates (1,3-substitution). The triphenylphosphonium ylide derived from (**1**)-(**3**) has been treated with carbonyl compounds to make alkenes.[2,3b,37] For example, deprotonation of (**36**) with ***Sodium Amide*** in benzene, filtration (to produce a salt-free ylide), and reaction with acetaldehyde gives, in 35% overall yield, (**39c**) (contaminated by 5% of (**39t**), an intermediate in the synthesis of cinerolone.[37a] The Horner-Wittig variant, employing the diphenylphosphine oxide (**37**), has the advantage that either *cis*- or *trans*-alkenes may be prepared (eq 10). Very high levels of isomer purity may be achieved since the intermediate *erythro*/*threo* hydroxy compounds are crystalline and easily separated by chromatography.[1a]

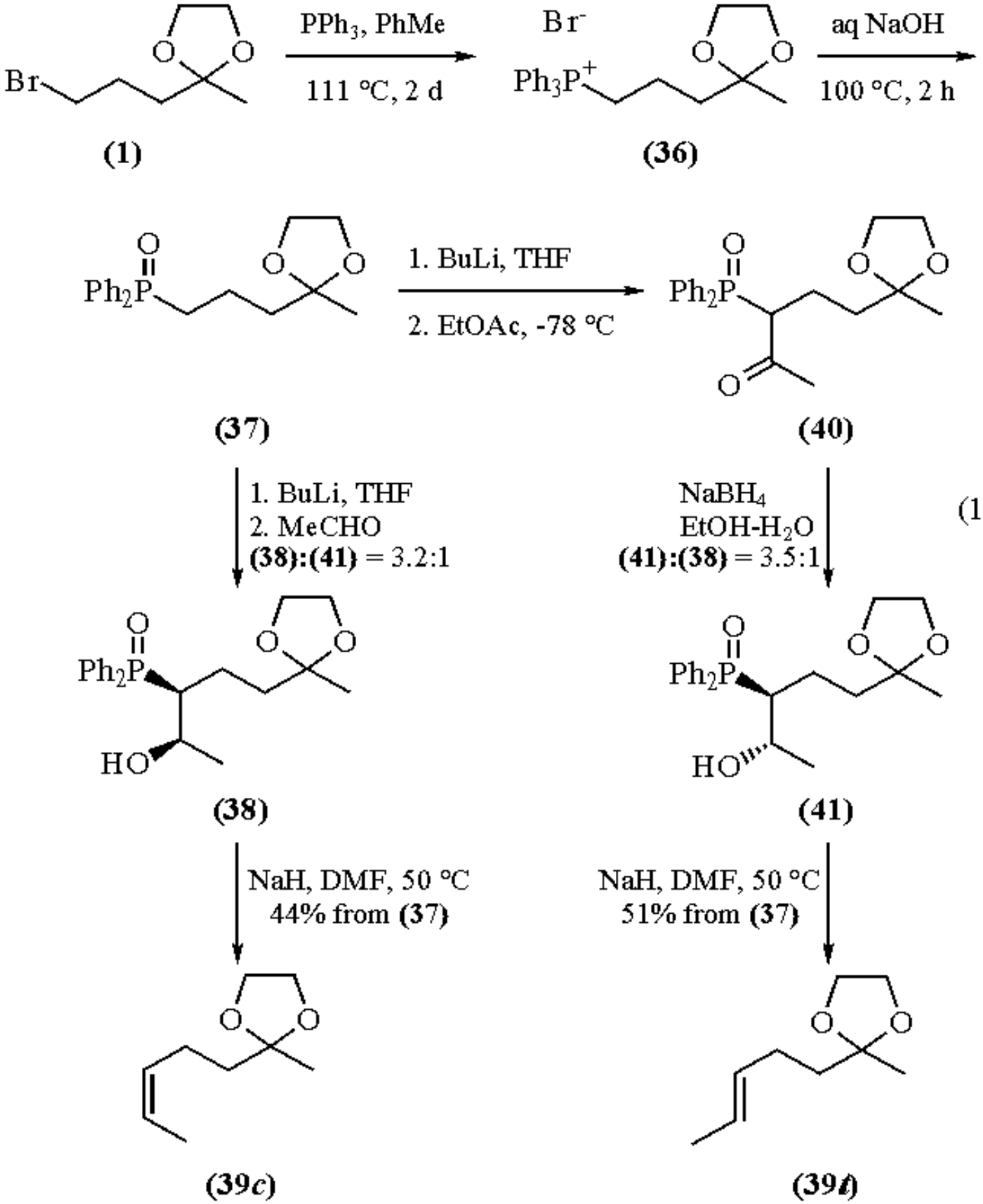
PPh3, PhMe
111 °C, 2 d
aq NaOH
100 °C, 2 h
(1)
(36)
1. BuLi, THF
2. EtOAc, -78 °C
(37)
(40)
1. BuLi, THF
2. MeCHO
(38):(41) = 3.2:1
NaBH4
EtOH-H2O
(41):(38) = 3.5:1
(38)
(41)
NaH, DMF, 50 °C
44% from (37)
NaH, DMF, 50 °C
51% from (37)
(39c)
(39t)

(10)

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N-Bromosuccinimide[1]

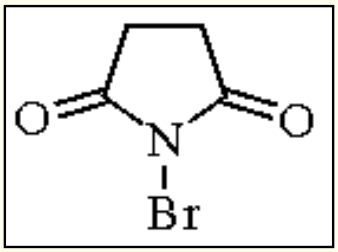

[128-08-5] · $C_4H_4BrNO_2$ · *N*-Bromosuccinimide · (MW 177.99)

(radical bromination of allylic and benzylic positions; electrophilic bromination of ketones, aromatic and heterocyclic compounds; bromohydration, bromoetherification, and bromolactonization of alkenes)

Alternate Names: NBS; 1-bromo-2,5-pyrrolidinedione.

Physical Data: mp 173-175 °C (dec); *d* 2.098 g cm^{-3}.

Solubility: sol acetone, THF, DMF, DMSO, MeCN; slightly sol H_2O, AcOH; insol ether, hexane, CCl_4 (at 25 °C).

Form Supplied in: white powder or crystals having a faint odor of bromine when pure; widely available.

Purification: in many applications the use of unrecrystallized material has led to erratic results. Material stored for extended periods often contains significant amounts of molecular bromine and is easily purified by recrystallization from H_2O (AcOH has also been used). In an efficient fume hood (caution: bromine evolution), an impure sample of NBS (200 g) is dissolved as quickly as possible in 2.5 L of preheated water at 90-95 °C. As filtration is usually unnecessary, the solution is then chilled well in an ice bath to effect crystallization. After most of the aqueous portion has been decanted, the white crystals are collected by filtration through a bed of ice and washed well with water. The crystals are dried on the filter and then in vacuo. The purity of NBS may be determined by the standard iodide-thiosulfate titration method.

Handling, Storage, and Precautions: should be stored in a refrigerator and protected from moisture to avoid decomposition. One of the advantages of using NBS is that it is easier and safer to handle than bromine; however, the solid is an irritant and bromine may be released during some operations. Therefore, precautions should be taken to avoid inhalation of the powder and contact with skin. All operations with this reagent are best conducted in an efficient fume hood. In addition, since reactions involving NBS are generally quite exothermic, large-scale operations (>0.1 mol) should be approached with particular caution.

Introduction.

N-Bromosuccinimide is a convenient source of bromine for both radical substitution and electrophilic addition reactions. For radical substitution reactions, NBS has several advantages over the use of molecular ***Bromine***, while ***1,3-Dibromo-5,5-dimethylhydantoin*** is another reagent of use. ***N-Chlorosuccinimide*** and ***N-Iodosuccinimide*** generally do not facilitate analogous substitution reactions. For electrophilic substitutions, ***Bromine***, ***N-Bromoacetamide***, ***Bromonium Di-sym-collidine Perchlorate***, ***1,3-Dibromoisocyanuric Acid***, and ***2,4,4,6-Tetrabromo-2,5-cyclohexadienone*** also have applicability and the analogous halogenation reactions are generally possible using NCS, NIS, and I_2. Possible impurities generated during NBS brominations include conjugates of succinimide and, if basic conditions are employed, β-alanine (formed by the Hofmann reaction) and its derivatives may be isolated.

Allylic Bromination of Alkenes.[2]

Standard conditions for allylic bromination involve refluxing of a solution of the alkene and recrystallized NBS in anhydrous CCl_4 using ***Dibenzoyl Peroxide***, irradiation with visible light (ordinary 100 W light bulb or sunlamp[3]), or both to effect initiation. Both NBS and the co-product succinimide are insoluble in CCl_4 and succinimide collects at the surface of the reaction mixture as the reaction proceeds.[4] High levels of regioselectivity operate during the hydrogen-abstraction step of the chain mechanism, such that allylic methylene groups are attacked much more rapidly than allylic methyl groups.[5] However, a thermodynamic mixture of allylic bromides is generally isolated since both the allylic radical and the allylic bromide are subject to isomerization under the reaction conditions.[6] High levels of functional group selectivity are characteristic of this reaction, for example alkenic esters may be converted to allylic bromides prior to intramolecular cyclization (eq 1).[7] Brominations of α,β-unsaturated esters (eq 2)[8] and lactones (eq 3) are also successful.[9]

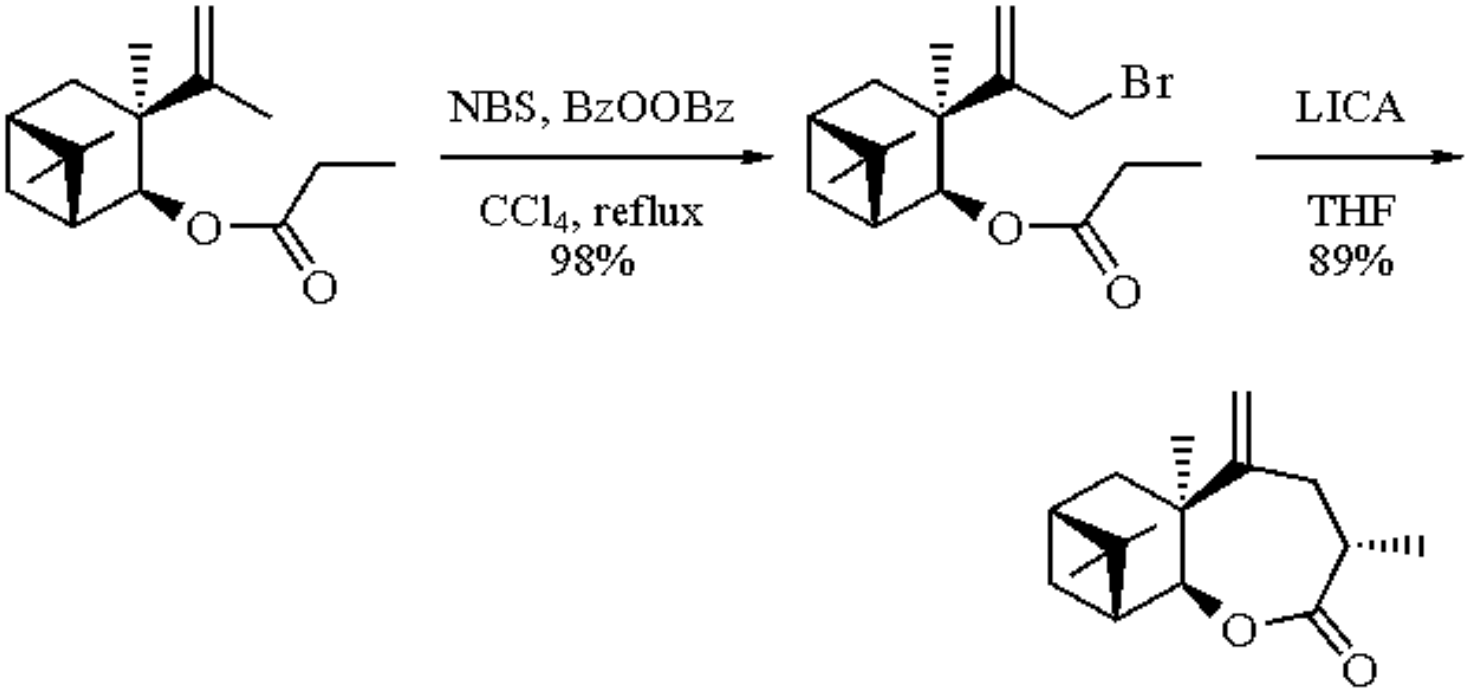

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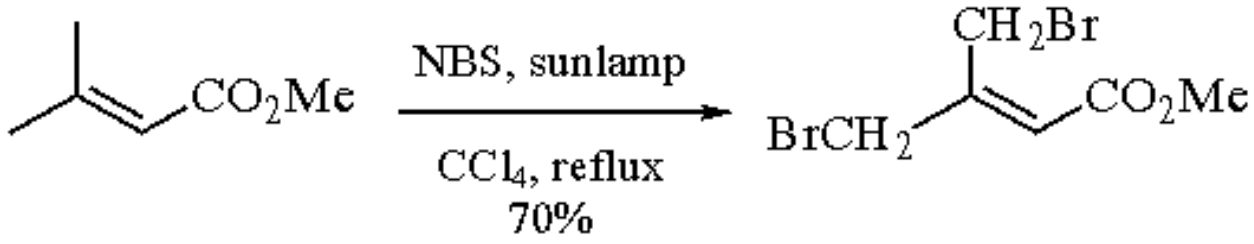

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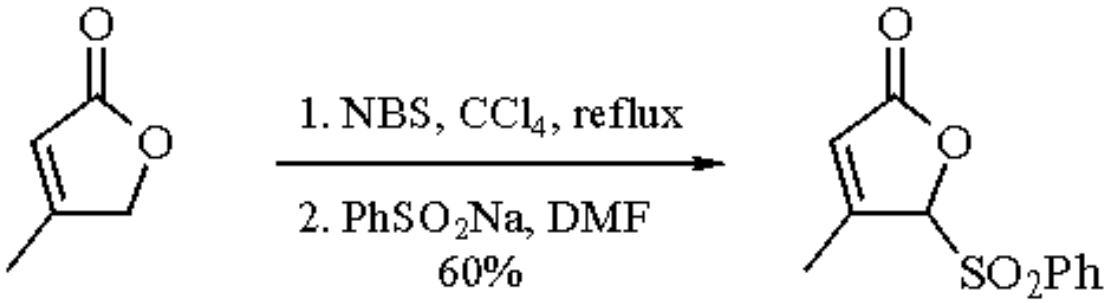

(3)

Benzylic Bromination of Aromatic Compounds.

Using the conditions described above, NBS also effects the bromination of benzylic positions.[10] Bromine is also regularly used for benzylic bromination (eq 4);[11] however, many functional groups are sensitive to the generation of HBr during the reaction, including carbonyl groups which suffer competing acid-catalyzed bromination. These considerations render NBS as the reagent of choice for bromination of polyfunctional aromatic compounds. Selectivity can be anticipated with polyfunctional molecules based on the predicted stabilities of the radical intermediates (eq 5).[12] Accordingly, the use of NBS allows the bromination of alkyl groups attached to sensitive heterocyclic compounds (eq 6).[13] Complications which may arise from this method include *gem*-dibromination (eq 7)[14] of methyl substituents as well as in situ elimination of the product benzylic bromide (see also ***1,3-Dibromo-5,5-dimethylhydantoin***).

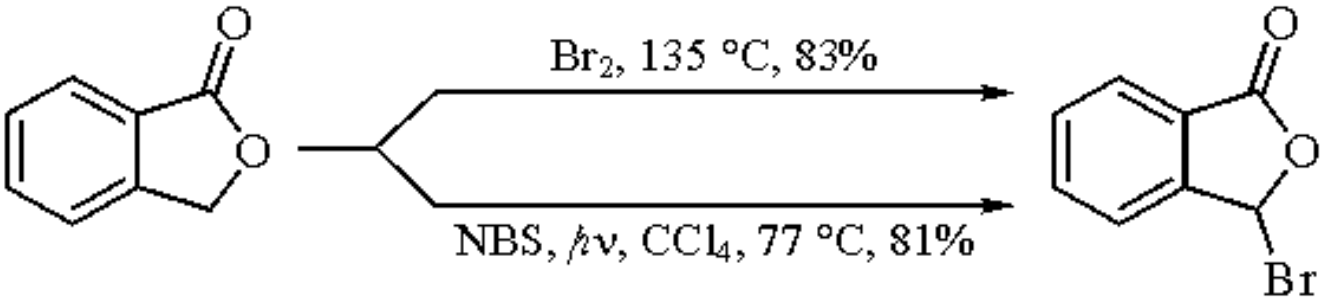

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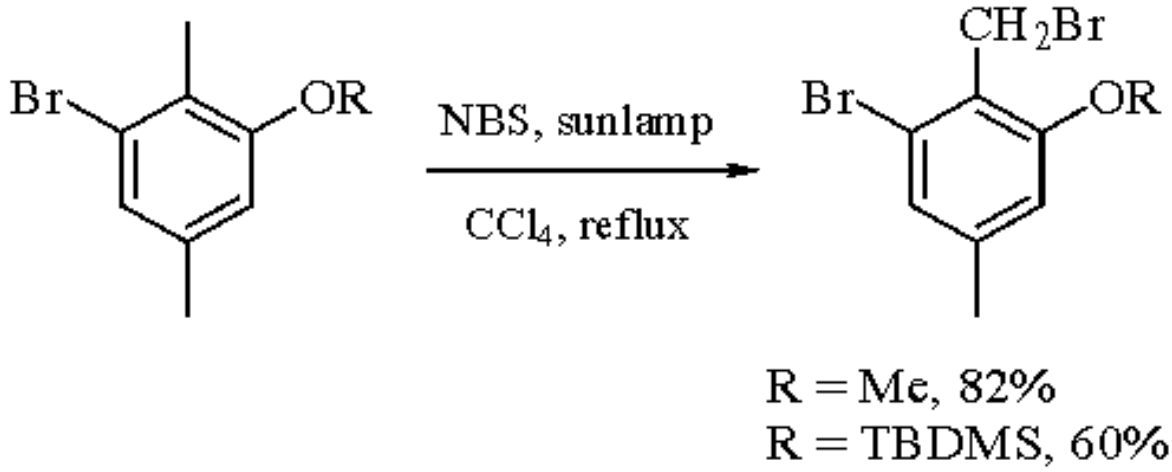

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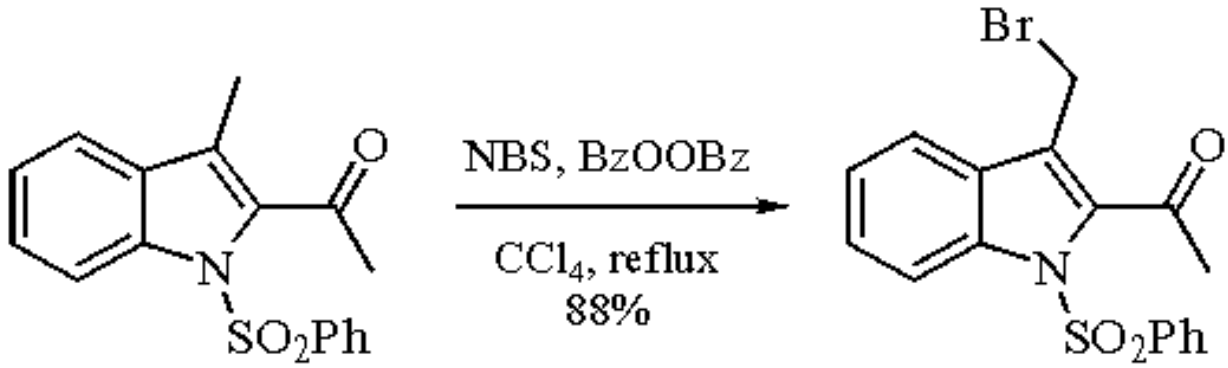

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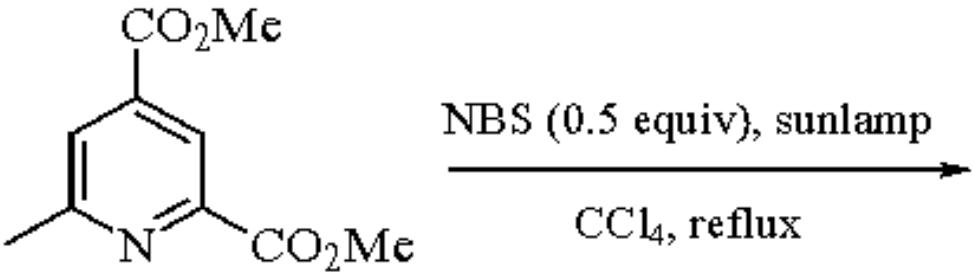

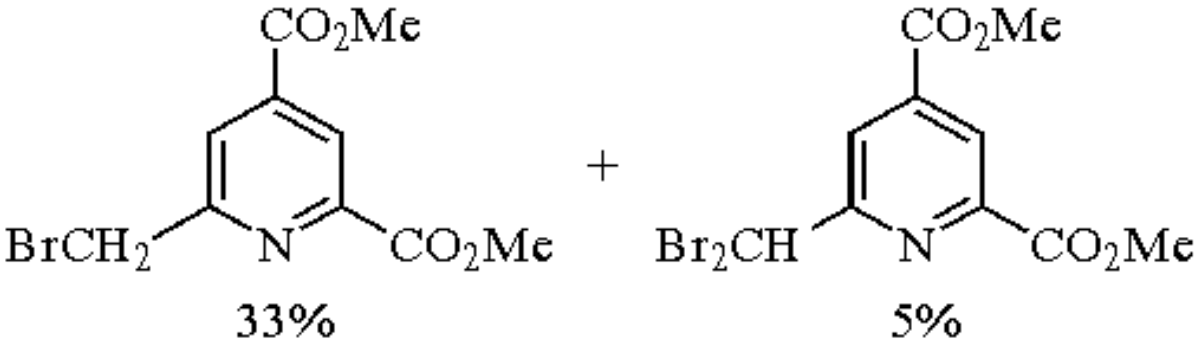

(7)

The regioselective cleavage of benzylidene acetals using NBS has been used widely in the synthesis of natural products from carbohydrates (eq 8)[15] and other chiral materials (eq 9).[16] It is rather important that the reaction be conducted in anhydrous CCl_4 (passage through activated alumina is sufficient), since in the presence of water the hydroxy benzoate is formed.[17] Barium carbonate is generally added to maintain anhydrous and acid-free conditions, and the addition of $Cl_2CHCHCl_2$ often improves solubility of the substrate. Selectivity is usually very high in cases in which a primary bromide can be produced, but may also be obtained in systems such as shown in eq 10.[18] As alkoxy substituents serve

to further stabilize the adjacent radicals, these reactions proceed with high selectivity in the presence of other functional groups. Other applications in the carbohydrate field include the cleavage of benzyl ethers and benzyl glycosides (to the corresponding glycosyl bromides) and the bromination of pyranoses in the 5-position.[19]

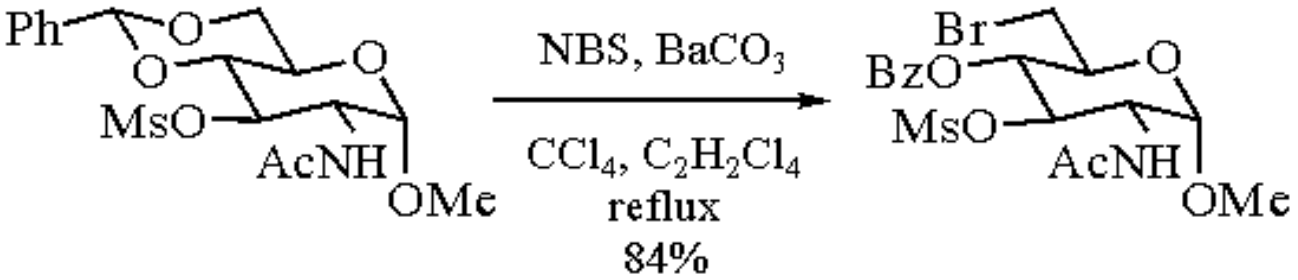

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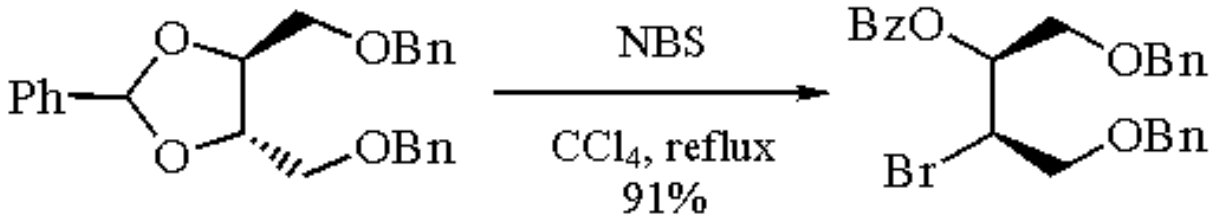

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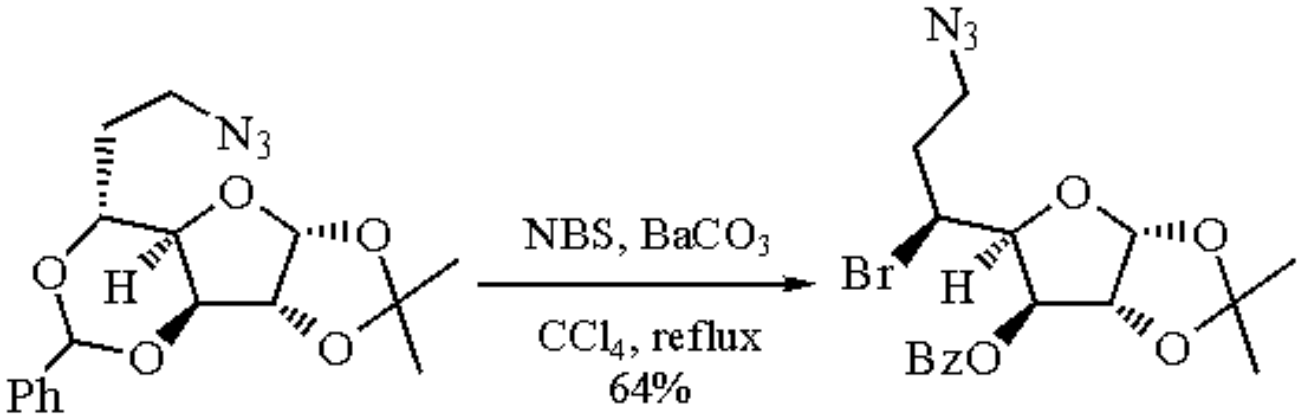

(10)

Unsaturation and Aromatization Reactions.[20]

Unsaturated aldehydes, esters, and lactones can be accessed via strategies involving radical bromination and subsequent elimination. The allylic bromination of unsaturated lactones may be followed by elimination with base to obtain dienoic and trienoic lactones (eqs 11 and 12).[21] Conversion of an aldehyde to the enol acetate allows the radical bromination at the C_β position to proceed smoothly and, upon ester hydrolysis, the α,β-unsaturated aldehyde is obtained (eq 13).[22]

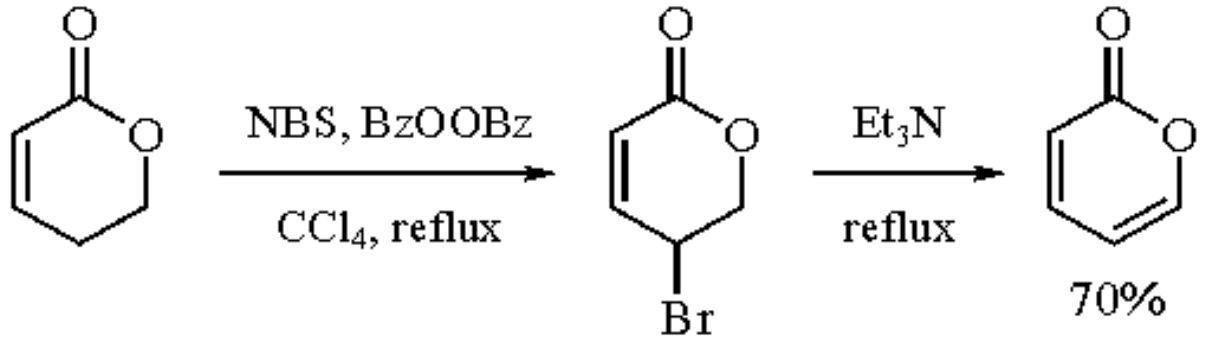

(11)

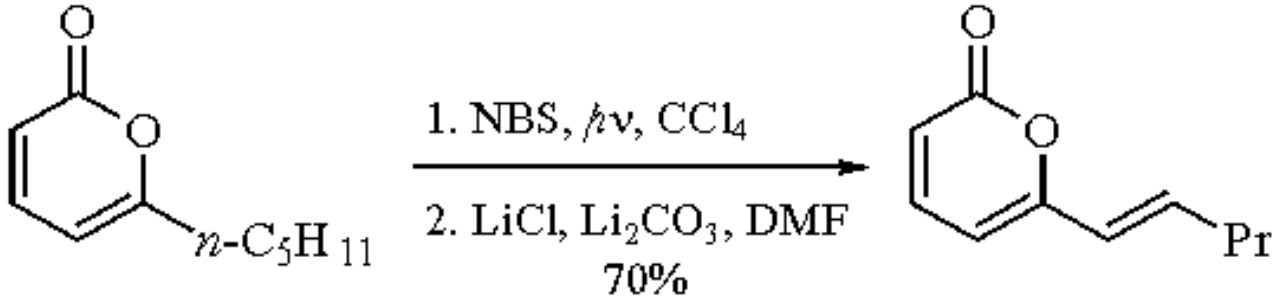

(12)

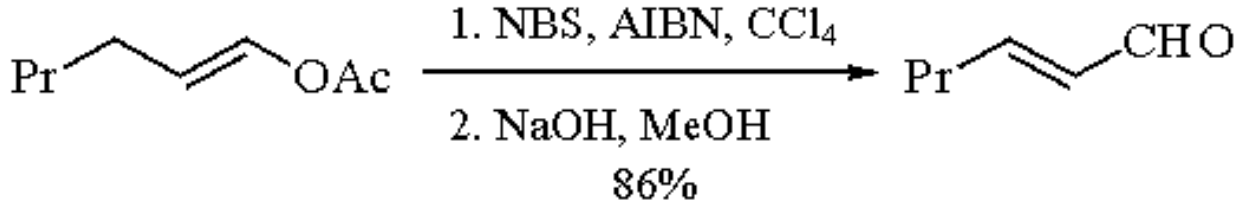

(13)

The direct bromination of β-alkoxylactones at the β position initially generates the α,β-unsaturated lactones (eq 14); however, the required radical abstraction is not so facile and further bromination of the α,β-unsaturated lactone proceeds competitively to afford the mono- and dibrominated products.[23] NBS is also used for the oxidative aromatization of polycyclic compounds, including steroids and anthraquinone precursors (eq 15).[24]

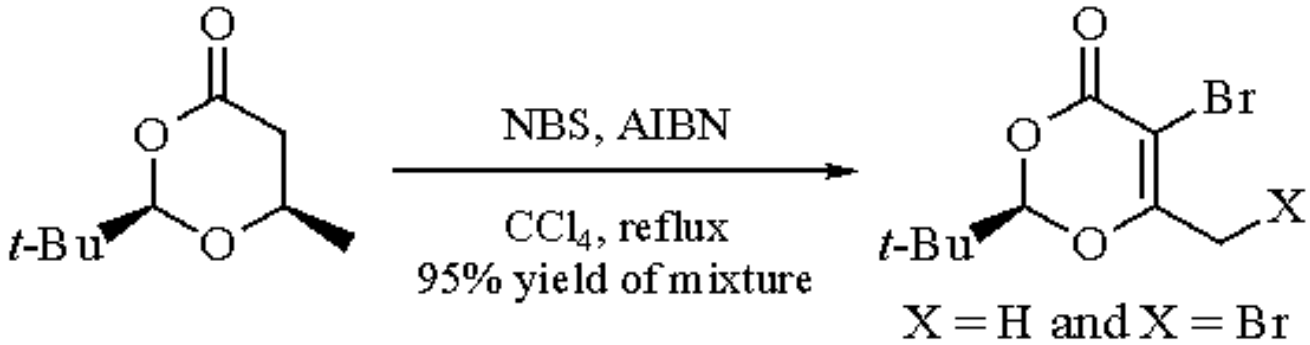

(14)

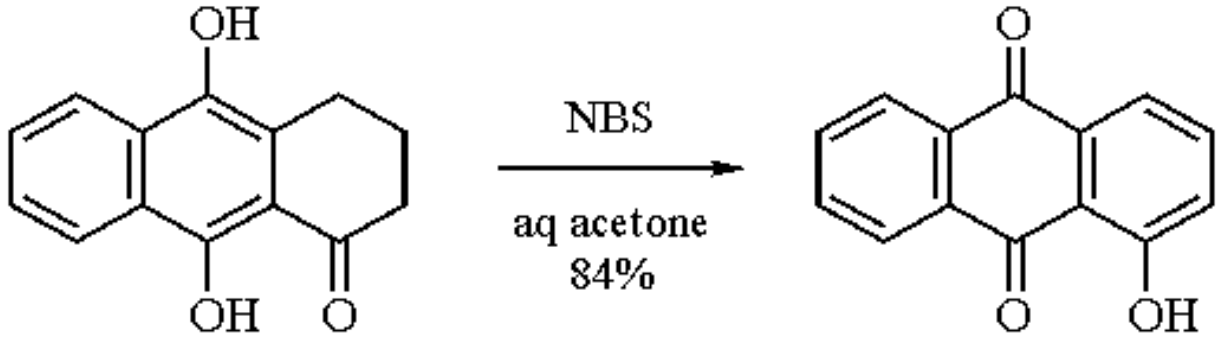

(15)

α-Bromination of Carbonyl Derivatives.

Although simple carbonyl derivatives are not attacked in the α-position under radical bromination conditions, substitution by electron-donating groups stabilizes the radical intermediates by the capto-dative effect[25] and thus facilitates the substitution reaction which has been applied to a number of useful synthetic strategies. Protected glycine derivatives are easily brominated by NBS and benzoyl peroxide in $CHCl_3$ or CCl_4 at reflux to afford the corresponding α-bromoglycine derivatives.[26] These compounds are stable precursors of *N*-acyliminoacetates, which may be alkylated by silyl enol ethers in the presence of Lewis acids, organometallic reagents, and other nucleophiles to afford novel α-amino acids (eq 16).[27] Diketopiperazines and related heterocycles are also substituted in good yields (eq 17).[28] Furthermore, in contrast to aldehydes which undergo abstraction of the aldehydic hydrogen (see below), *O*-trimethylsilylaldoximes are readily brominated at the α-position under radical bromination conditions and can be converted to substituted nitrile oxides (*O*-trimethylsilylketoximes react similarly).[29]

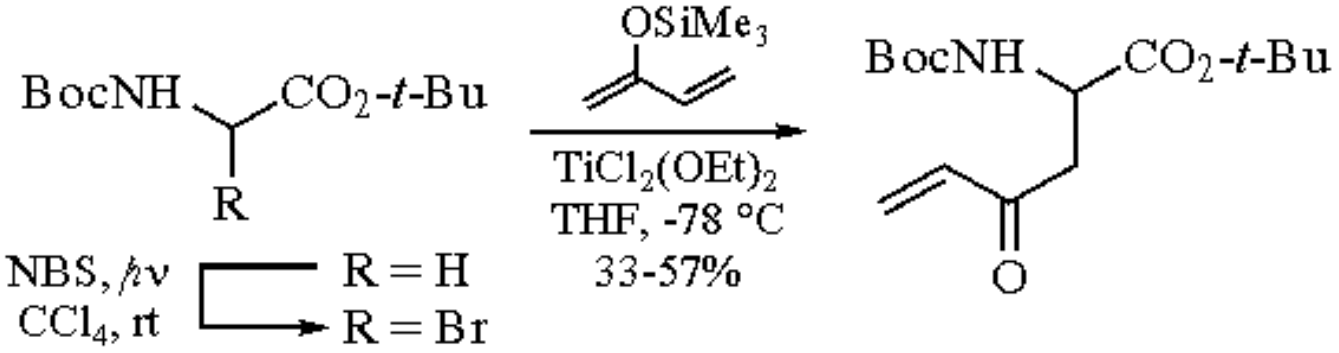

(16)

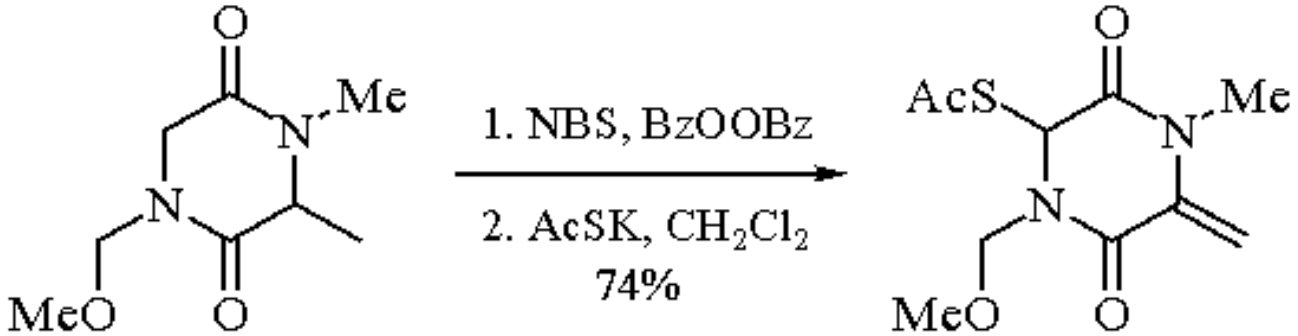

(17)

The use of NBS in the presence of catalytic ***Hydrogen Bromide*** has proven to be more convenient than Br_2 for the conversion of acid chlorides to α-bromo acid chlorides.[30] The reaction of the corresponding enolates, enol ethers, or enol acetates with NBS (and other halogenating agents) offers considerable advantages over direct acid-catalyzed

halogenation of ketones and esters.[31] Although both reagents may afford the α-brominated products in high yields, NBS is more compatible than is bromine with sensitive functional groups and has been used in the asymmetric synthesis of α-amino acids.[32] The bromination of cyanoacetic acid proceeds rapidly with NBS to afford dibromoacetonitrile[33] and, similarly, β-keto esters, β-diketones, and β-sulfonyl ketones may be reacted with NBS in the presence of base to afford the products of bromination and in situ deacylation (see ***N-Chlorosuccinimide***).[34] (5*E*)-Bromovinyluridine derivatives are readily prepared by bromodecarboxylation of the corresponding α,β-unsaturated acids with NBS (eq 18).[35]

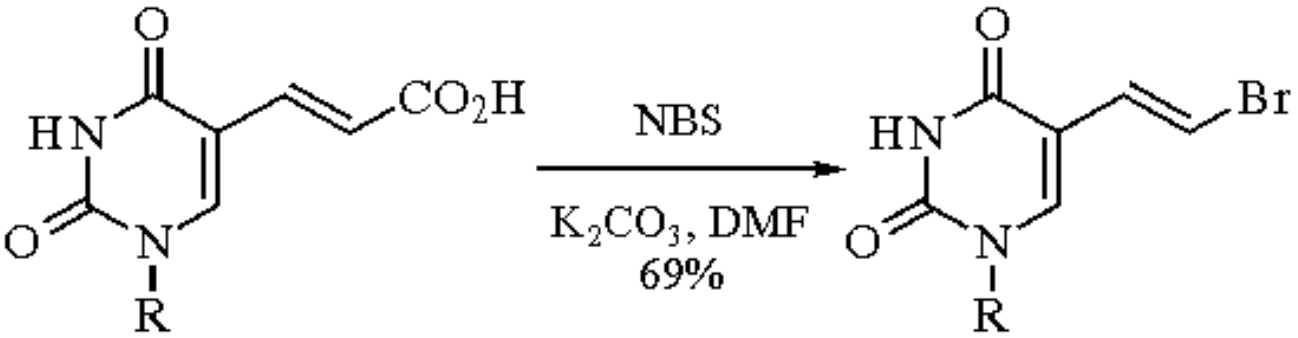

(18)

Reaction with Vinylic and Alkynic Derivatives.

NBS is a suitable source of bromine for the conversion of vinylcopper and other organometallic derivatives to the corresponding vinyl bromides.[36] Vinylsilanes, prepared from the corresponding 1-trimethylsilylalkyne by reduction with ***Diisobutylaluminum Hydride***, can be isomerized from the (*Z*) to the (*E*) geometry by irradiation with NBS and ***Pyridine***, thus making (*E*)-vinylsilanes readily available stereoselectively in three steps from the corresponding alkyne (eq 19).[37] Allylsilane can be brominated by NBS under radical conditions, whereas more reactive allylsilanes are bromodesilated by NBS in CH_2Cl_2 at -78 °C.[38] 1-Bromoalkynes can be prepared under mild conditions by reaction with NBS in acetone in the presence of catalytic ***Silver(I) Nitrate***.[39]

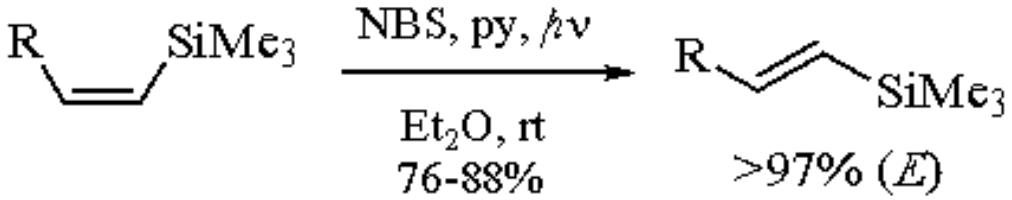

(19)

Bromination of Aromatic Compounds.

Phenols, anilines, and other electron-rich aromatic compounds can be monobrominated using NBS in DMF with higher yields and higher levels of *para* selectivity than with Br_2.[40] *N*-Trimethylsilylanilines and aromatic ethers are also selectively brominated by NBS in $CHCl_3$ or CCl_4.[41] *N*-Substituted pyrroles are brominated with NBS in THF to afford 2-bromopyrroles (1 equiv) or 2,5-dibromopyrroles (2 equiv) with high selectivity, whereas bromination with Br_2 affords the thermodynamically more stable 3-bromopyrroles.[42] The use of NBS in DMF also achieves the controlled bromination of imidazole and nitroimidazole.[43] Thiophenes are also selectively brominated in the 2-position using NBS in acetic acid-chloroform.[44]

Bromohydration, Bromolactonization, and Other Additions to C=C.[45]

The preferred conditions for the bromohydration of alkenes involves the portionwise addition of solid or predissolved NBS (recrystallized) to a solution of the alkene in 50-75% aqueous DME, THF, or *t*-butanol at 0 °C. The formation of dibromide and α-bromo ketone byproducts can be minimized by using recrystallized NBS. High selectivity for Markovnikov addition and *anti* stereochemistry results from attack of the bromonium ion intermediate by water. Aqueous DMSO can also be used as the solvent; however, since DMSO is readily oxidized under the reaction conditions, significant amounts of the dibromide byproduct may be produced.[46,47] In the bromohydration of polyalkenic compounds, high selectivity is regularly achieved for attack of the most electron-rich double bond (eq 20).[48] With farnesol acetate, squalene, and other polyisoprenes, choice of the optimum proportion of water is used to effect the selective bromohydration at the terminal double bond (eq 21),[49] and the two-step sequence shown is often the method of choice for the preparation of the corresponding epoxides.[50]

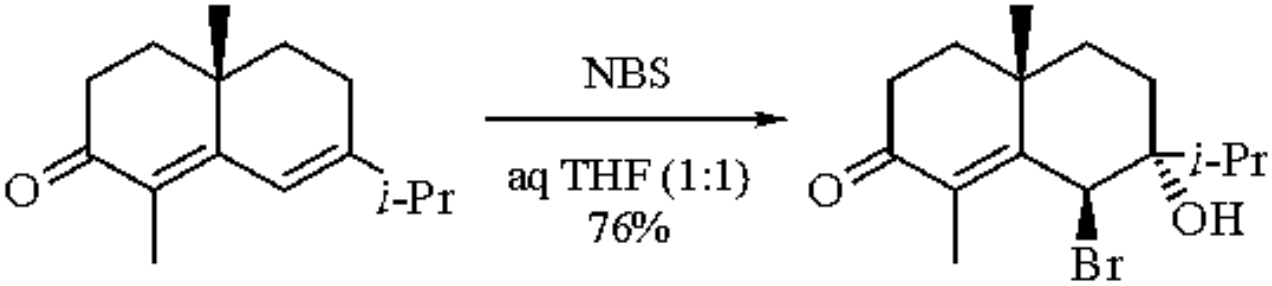

(20)

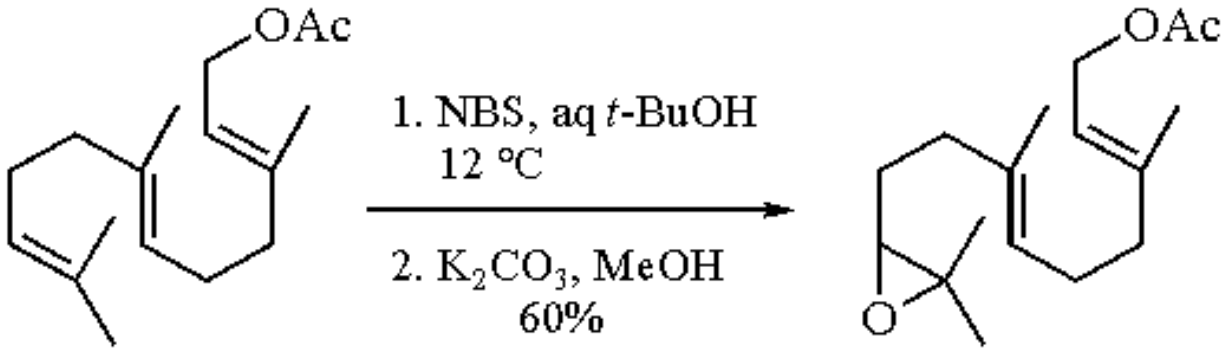

(21)

Bromoetherification of alkenes can be achieved using NBS in the desired alcohol as the solvent. The reaction of 1,3-dichloropropene with NBS in methanol yields an α-bromo dimethyl acetal in the first step in a convenient synthesis of cyclopropenone.[51] Using propargyl alcohol the reaction depicted in eq 22 has been extended to an annulation method for the synthesis of α-methylene-γ-butyrolactones.[52] Intramolecular bromoetherification and bromoamination reactions are generally very facile (eq 23).[53] In natural products synthesis, bromoetherification has been used for the synthesis of cyclic ethers (by subsequent debromination, see ***Tri-n-butylstannane***) and for the protection of alkene appendages as cyclic bromoethers (regenerated by reaction with zinc).[54]

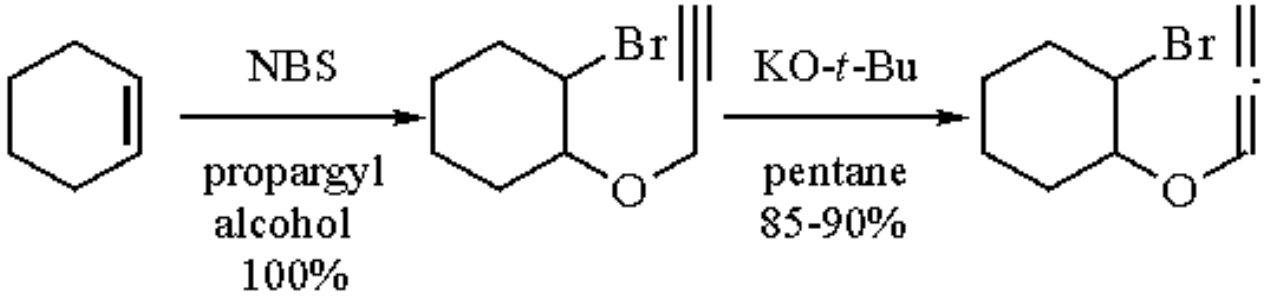

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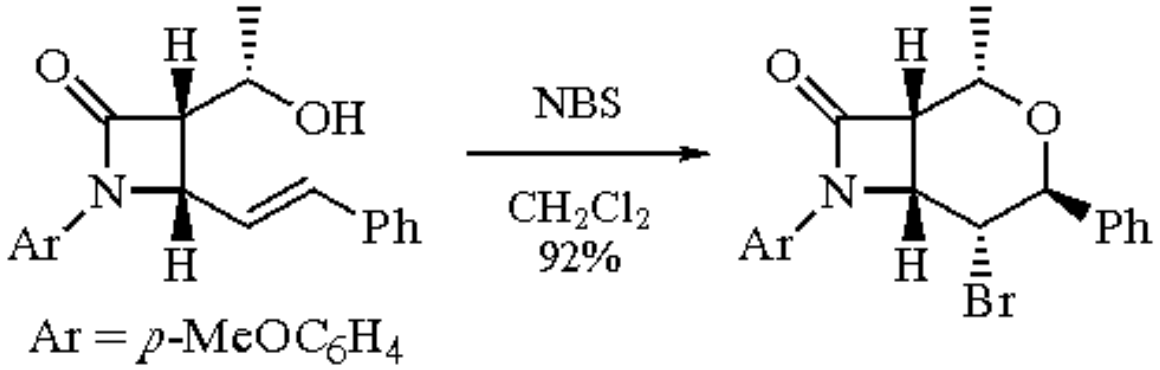

(23)

NBS is also an effective reagent for bromolactonization of unsaturated acids and acid derivatives with the same high stereo- and Markovnikov selectivity (see also ***Iodine***). Dienes, such as the cycloheptadiene derivative shown, may react exclusively via *syn*-1,4-addition (eq 24).[55] Alkynic acids are converted to the (*E*)-bromo enol lactones by NBS in a biphasic medium, whereas the combination of bromine and silver nitrate afford the (*Z*)-bromo enol lactones (eq 25).[56] α,β-Unsaturated acylprolines react with NBS in anhydrous DMF to afford the corresponding bromolactones having diastereomeric excesses up to 93%, which can be converted to chiral α-hydroxy acids by debromination followed by acidic hydrolysis (eq 26).[57] In contrast to alkenic amides, which generally react with NBS to afford bromolactones (via the cyclic iminoether derivatives), alkenic sulfonamides readily undergo cyclization on nitrogen when reacted with NBS to afford the bromosulfonamides in high yields.[58] *N*-Methoxyamides have also proven effective for bromolactamization, leading to diketopiperazines (eq 27)[59] (see also ***Bromonium Di-sym-collidine Perchlorate***).

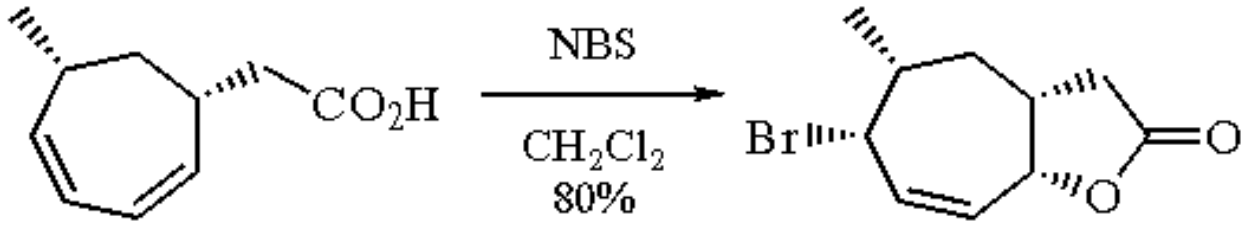

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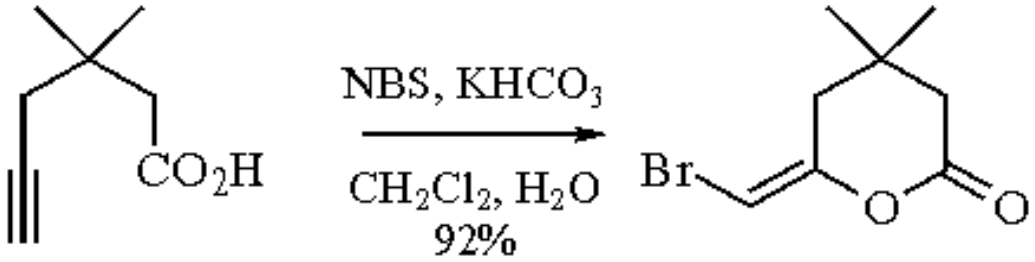

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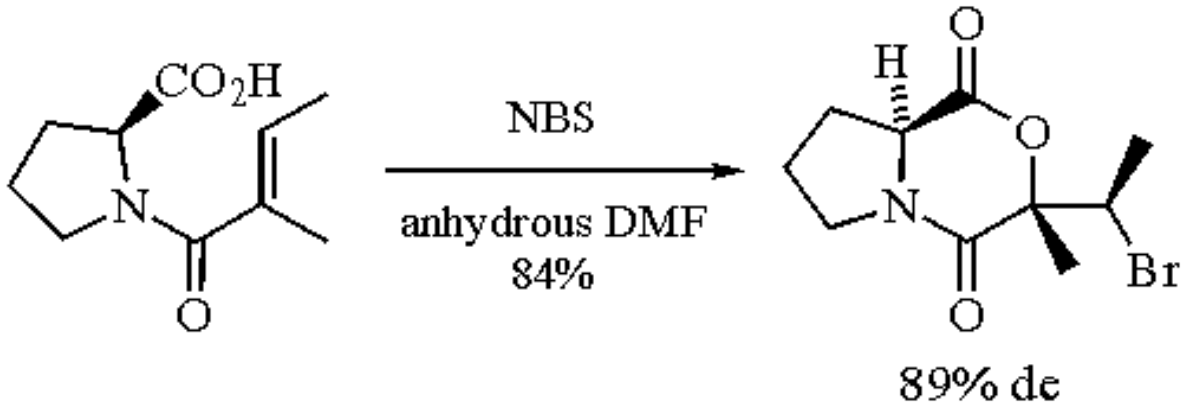

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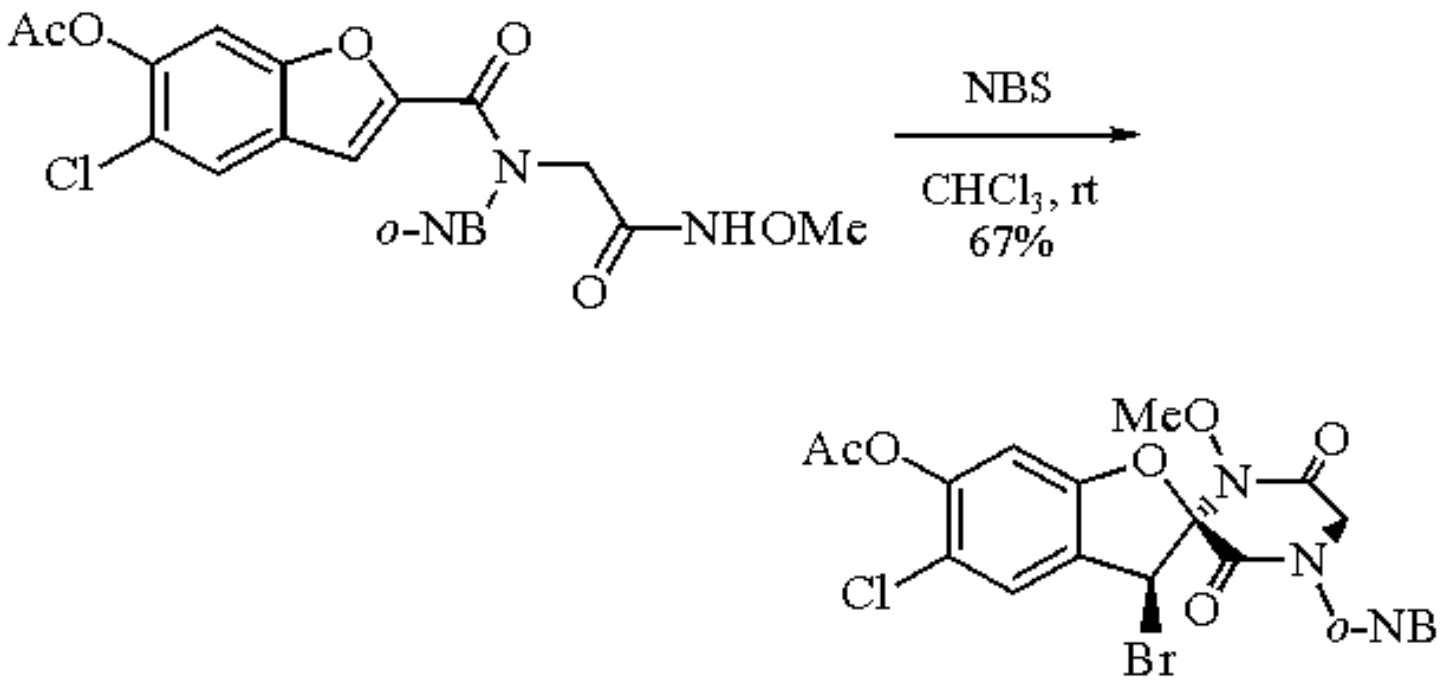

(27)

Addition of NBS to an alkene in the presence of aqueous ***Sodium Azide*** affords fair yields of the corresponding β-bromoazides, which can be converted by ***Lithium Aluminum Hydride*** reduction to aziridines.[60] Intermolecular reactions of alkenes with NBS and weaker nucleophiles can be achieved if conducted under anhydrous conditions to avoid the facile bromohydration reaction. In this manner, bromofluorination of alkenes has been extensively studied using ***Pyridinium Poly(hydrogen fluoride)***, triethylammonium dihydrogentrifluoride or tetrabutylammonium hydrogendifluoride as the fluoride ion source.[61]

Oxidation and Bromination of Other Functional Groups.

Conjugate bases of other functional groups can be α-brominated with NBS. Nitronate anions of aliphatic nitro compounds react with NBS to afford the *gem*-bromonitro compounds in high yield.[62] The α-bromination of sulfoxides can be performed in the presence of pyridine and proceeds more satisfactorily using NBS in the presence of catalytic Br_2 than with either reagent alone.[63] NBS also reacts with sulfides to afford sulfoxides when methanol is used as a solvent, or to form α-bromo sulfides in anhydrous solvents.[64] NBS is a favored reagent for the deprotection of dithianes and dithioacetals to regenerate carbonyl groups (eq 28)[65] (see also ***N-Chlorosuccinimide*** and ***1,3-Diiodo-5,5-dimethylhydantoin***).

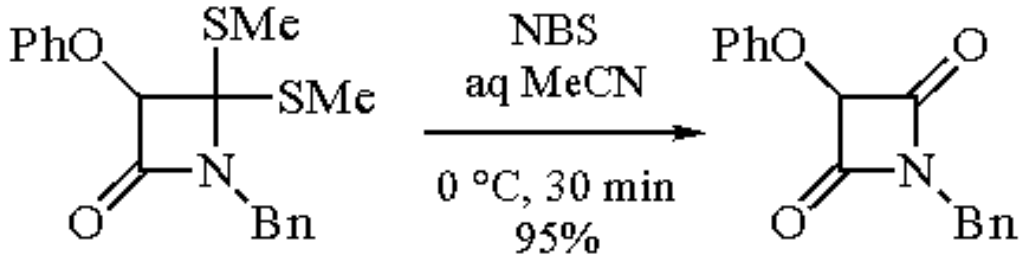

(28)

In polar media, NBS effectively oxidizes primary and secondary alcohols to carbonyl compounds via hypobromite or alkoxysuccinimide intermediates. Although this transformation is more commonly effected by the use of chromium reagents or activated ***Dimethyl Sulfoxide***, the most notable application of NBS and related reagents lies in its selectivity for the oxidation of axial vs. equatorial hydroxy groups in steroid systems (see ***N-Bromoacetamide***).[66] Often, a single secondary alcohol may be converted to the ketone in the presence of many other alcohol groups.

Under radical conditions, aldehydes are readily oxidized by NBS to acid bromides.[67] The oxidation of aldoximes to nitrile oxides using NBS and ***Triethylamine*** in DMF is superior to the use of aqueous hypochlorite.[68] Tosylhydrazones are cleaved by reaction with NBS in methanol,[69] and hydrazines and hydrazides are oxidized to azo compounds.[70]

Related Reagents.

N-Bromosuccinimide-Dimethylformamide; ***N-Bromosuccinimide-Dimethyl Sulfide***; ***N-Bromosuccinimide-Hydrogen Fluoride***; ***N-Bromosuccinimide-Sodium Azide***; ***Triphenylphosphine-N-Bromosuccinimide***.

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N-Bromosuccinimide-Dimethylformamide

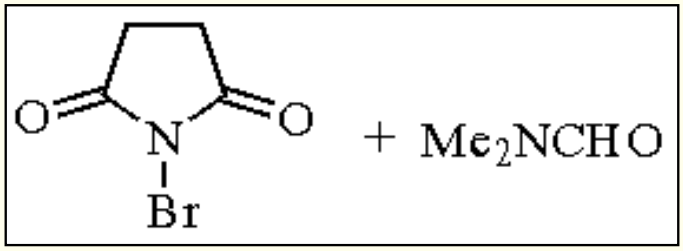

(NBS)

[128-08-5] · $C_4H_4BrNO_2$ · *N*-Bromosuccinimide-Dimethylformamide · (MW 177.99) (DMF)

[68-12-2] · C_3H_7NO · *N*-Bromosuccinimide-Dimethylformamide · (MW 73.09)

(mild selective bromination reagent[1] for reactive electron-rich aromatic hydrocarbons, heterocycles, phenols, and anilines)

Alternate Name: NBS-DMF.

Physical Data: see individual entries for ***N-Bromosuccinimide*** and ***N,N-Dimethylformamide***.

Handling, Storage, and Precautions: NBS (recrystallized from water and dried under vacuum) should be freshly dissolved in DMF (dried over molecular sieves) immediately before use. Note: use of old NBS and undried DMF may reduce yields in some cases.

Aromatic Hydrocarbons.

The main advantage of NBS-DMF is that monobromination usually occurs cleanly with 1 equiv of reagent at rt in high yields (80-98%). At least three alkyl groups must be present on a benzene ring, or two on a naphthalene ring; however, unsubstituted anthracene,[1] biphenylene,[2] and pyrene[1] are sufficiently reactive (eqs 1-3).

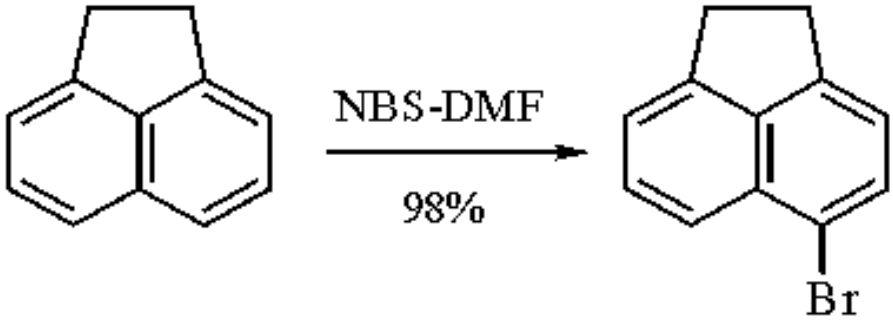

(1)

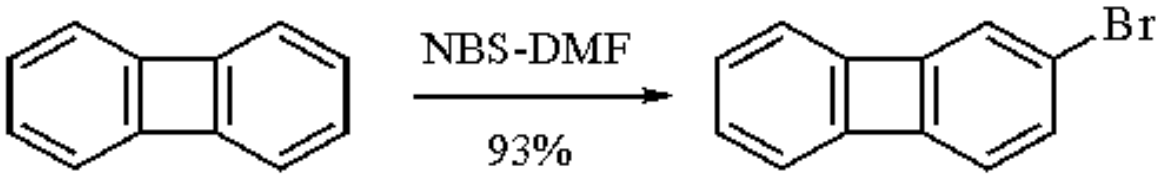

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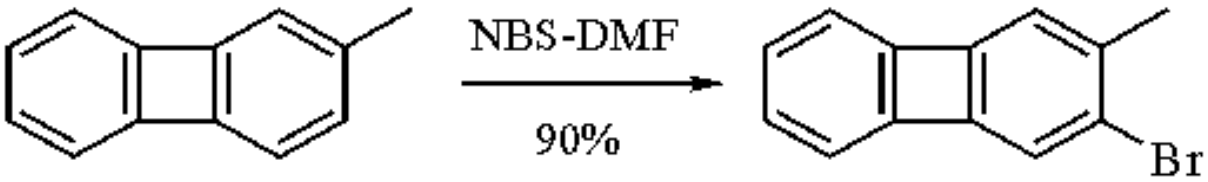

(3)

Phenols and Anisoles.

Selective monobromination of a phenol[1,3] is achieved, particularly if the DMF is dry (eqs 4 and 5). However, in some cases, dibromination also occurs (eq 6).[4] A difference in regiochemistry was observed[5] between the phenols (eq 7) and anisoles (eq 8). Anisoles, even with several methoxy groups, can also be selectively monobrominated;[6-9] an example is given in eq 9.

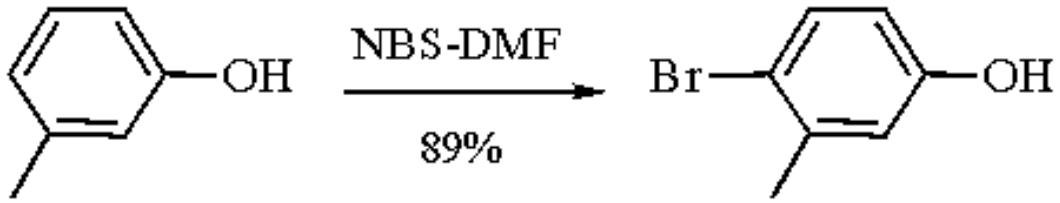

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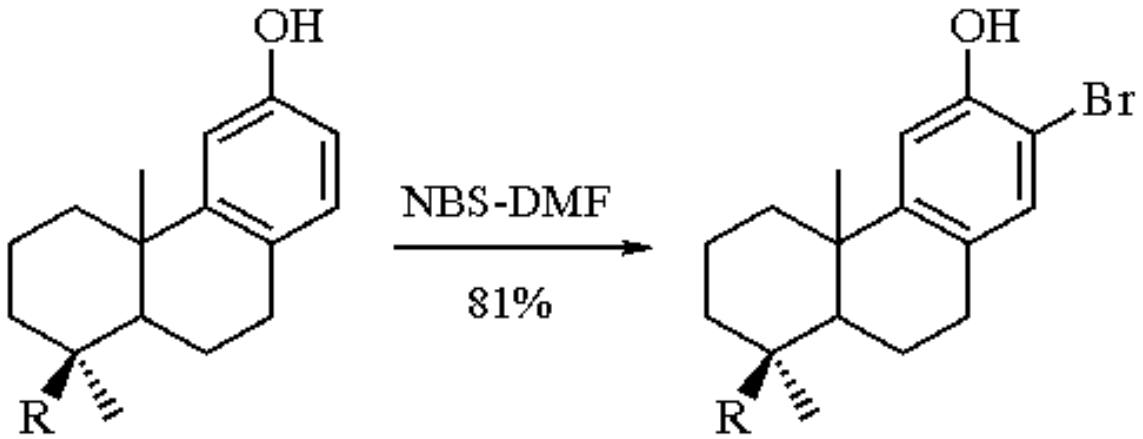

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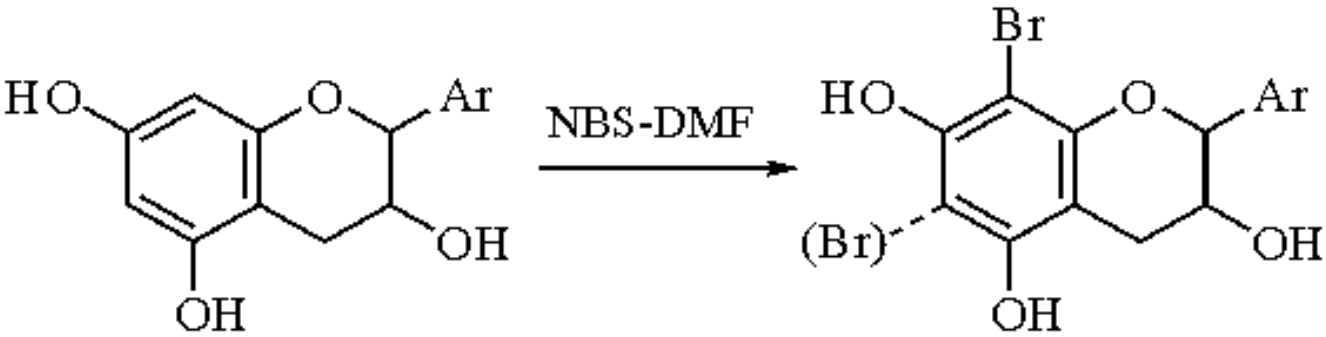

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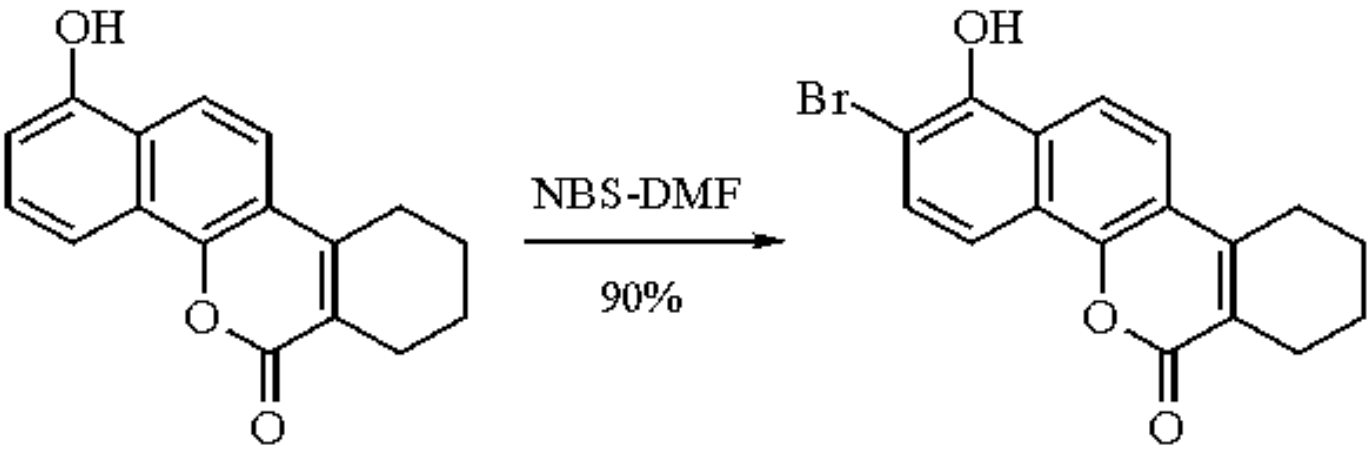

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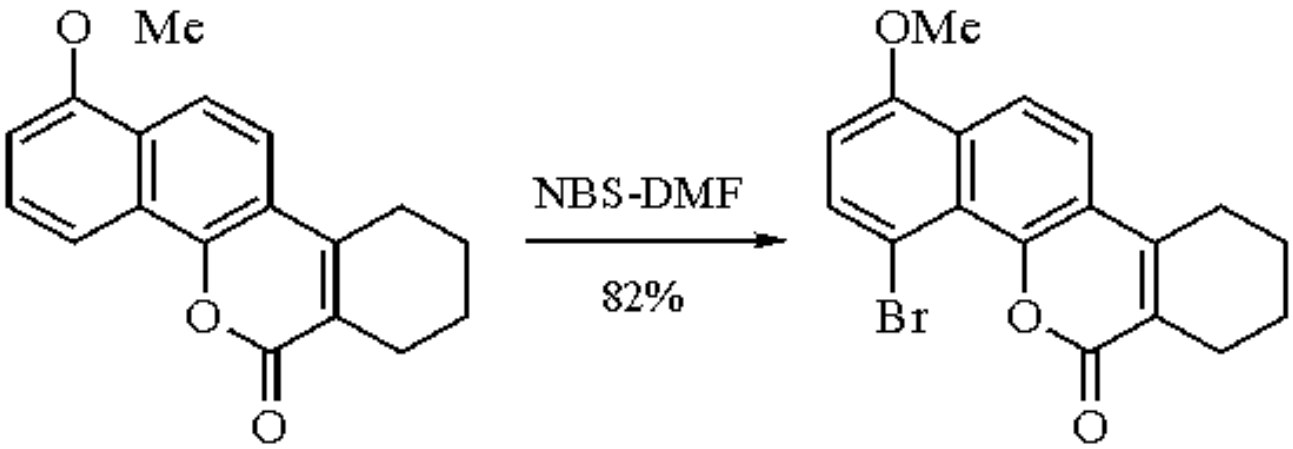

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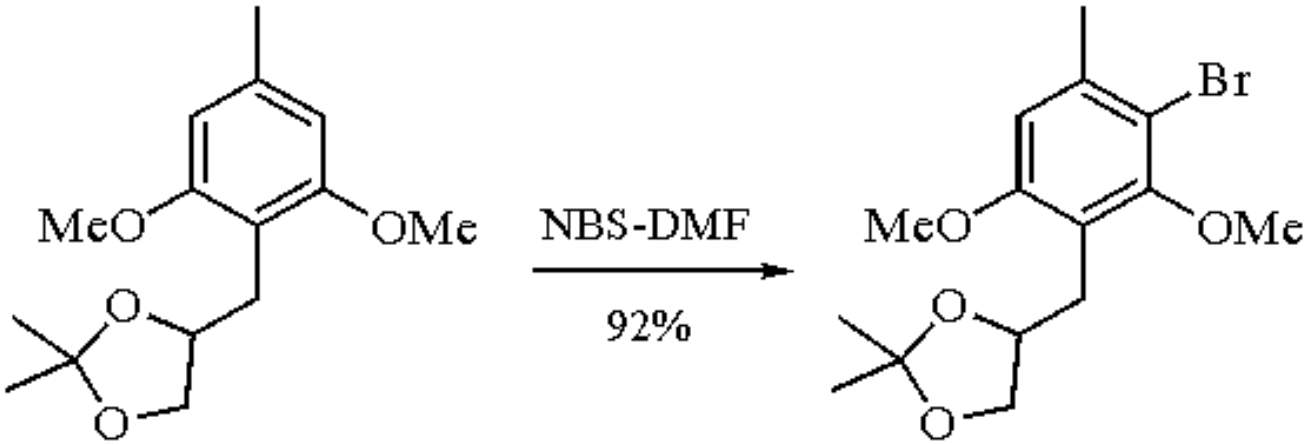

(9)

Anilines.

These are normally rather difficult to selectively brominate without oxidation; however, several examples[1,10-13] have now been reported with NBS-DMF (for example eq 10).

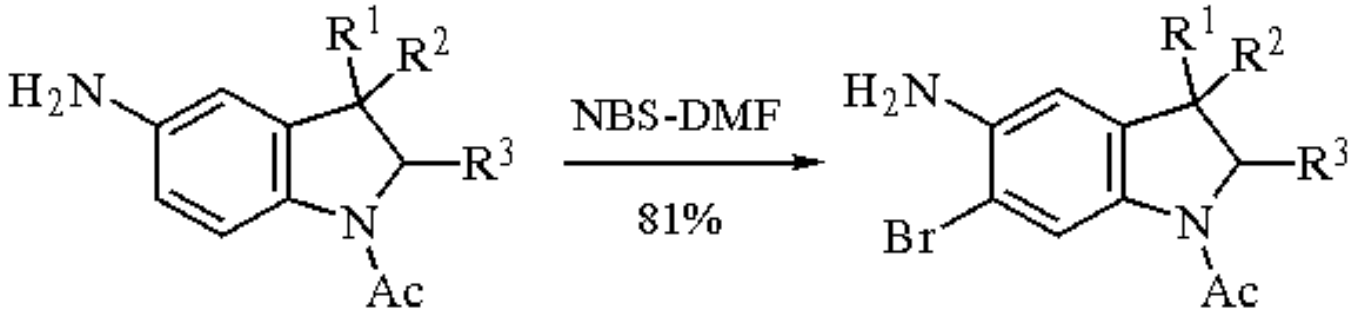

(10)

Five-Membered Ring Heterocycles.

Furans,[14] imidazoles,[15] and thiophenes[16] have now been brominated with NBS-DMF. In the thiophene shown in eq 11, 1.1 equiv of NBS gives the monobromide in 56% yield, while 2.4 equiv gives the dibromide in 70% yield.

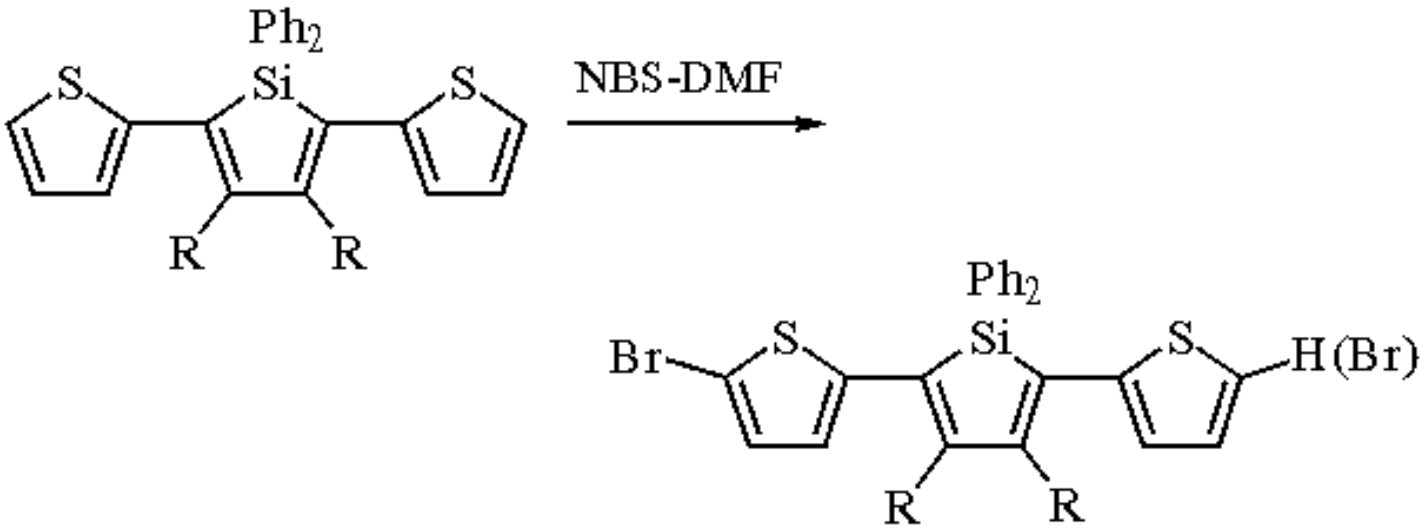

(11)

Oxidation.

Hydroquinone is oxidized by NBS-DMF to *p*-benzoquinone.[1] It has been recently found[17] that dimethyldihydropyrene also forms the quinone when >2 equiv of NBS in *wet* DMF are used (eq 12).

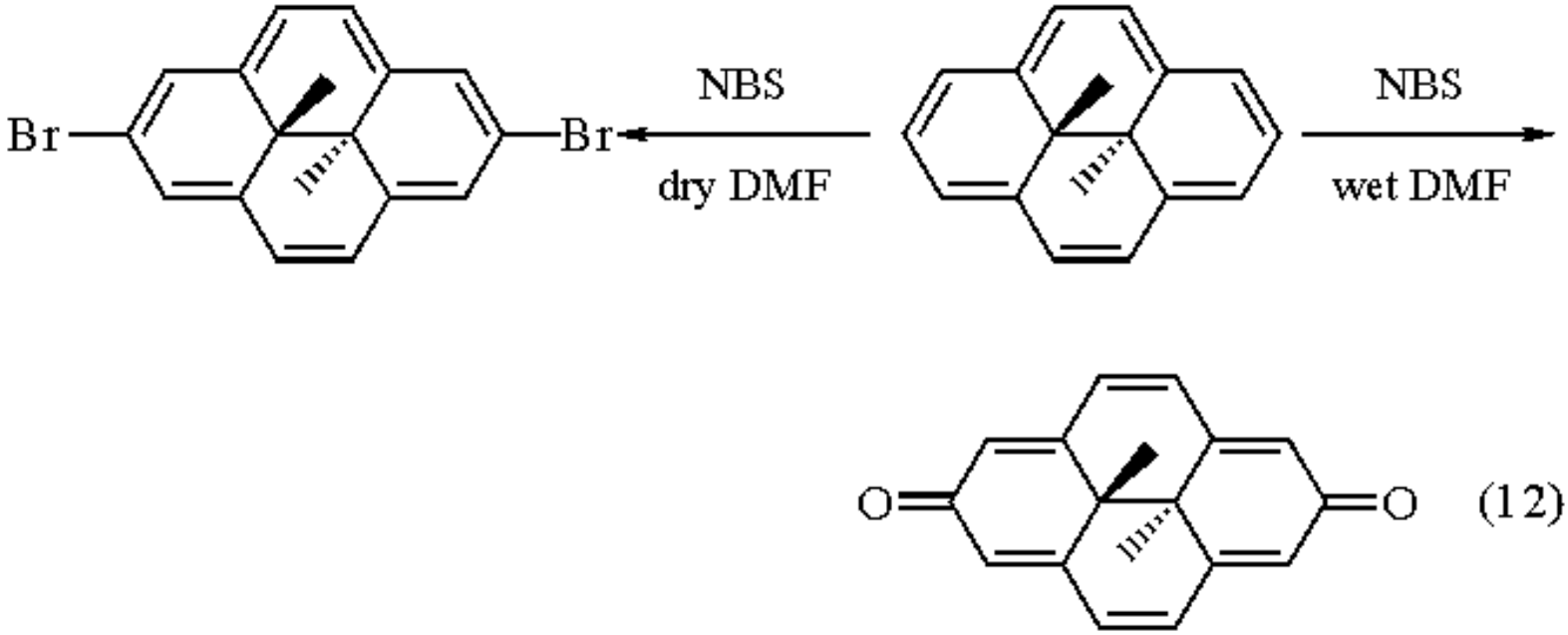

Side Products.

In general the above reactions are fairly clean, and the main side product is usually the dibromide. The mildness, selectivity, ease of use, and ready availability of both NBS and DMF makes the use of this reagent a convenient option over alternatives such as the more reactive ***Thallium(III) Acetate-Bromine***,[18] or ***Copper(II) Bromide***,[19] or bromine itself (which is often not selective).

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Reginald H. Mitchell

N-Bromosuccinimide-Dimethyl Sulfide[1]

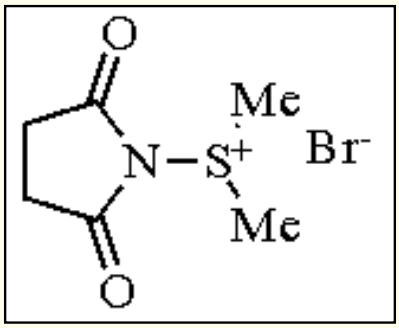

(NBS)

[128-08-5] · $C_4H_4BrNO_2$ · *N*-Bromosuccinimide-Dimethyl Sulfide · (MW 177.99) (DMS)

[75-18-3] · C_2H_6S · *N*-Bromosuccinimide-Dimethyl Sulfide · (MW 62.13)

(converts allylic and benzylic alcohols to bromides under neutral conditions;[1] slowly converts primary alcohols to bromides;[1] oxidizes primary and secondary alcohols to aldehydes or ketones[2])

Alternate Name: NBS-DMS.

Physical Data: reagent is formed in situ. See entries for ***N-Bromosuccinimide*** and ***Dimethyl Sulfide***.

Solubility: sol methylene chloride, carbon tetrachloride, toluene.

Preparative Method: freshly prepared by dissolving *N*-bromosuccinimide (5.4 g, 30 mmol) in methylene chloride (100 mL) at 0 °C under argon and slowly adding excess dimethyl sulfide (2.23 g, 36 mmol). Stir the resultant yellow slurry for 1 h at 0 °C before use.[3] Oxidation and bromide replacement reactions are typically carried out between -25 and 0 °C in methylene chloride.

Handling, Storage, and Precautions: use protective clothing; use in a fume hood.

Conversion of Alcohols to Bromides.

The principal use for NBS-DMS is to convert allylic and benzylic alcohols to allylic and benzylic bromides (see ***N-Chlorosuccinimide-Dimethyl Sulfide*** (NCS-DMS)). Eqs 1-3[1,3,4] illustrate typical replacements of the hydroxy group of a primary allylic alcohol without rearrangement. This reaction is a much milder way of introducing bromide than the standard ***Phosphorus(III) Bromide*** reaction, which is incompatible with acid-sensitive functionalities because it generates HBr. In some cases, secondary allylic alcohols (eqs 4 and 5) tend to undergo an S_N2' displacement of the

allylic alcohol and rearrange to the primary allylic bromides. In these examples[5,6] bearing a sulfoxide or sulfone, the rearrangements proceed with high (*E*) selectivity.

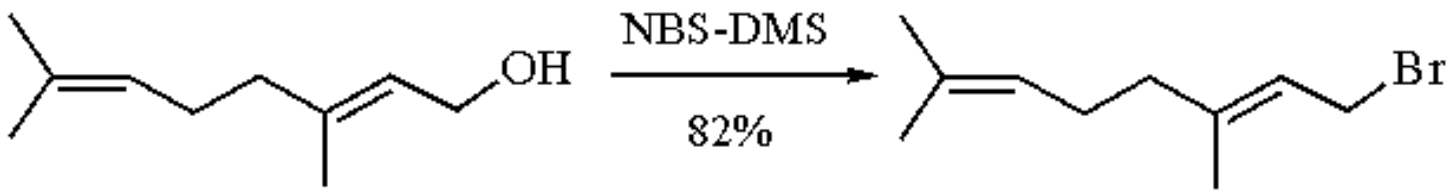

(1)

(2)

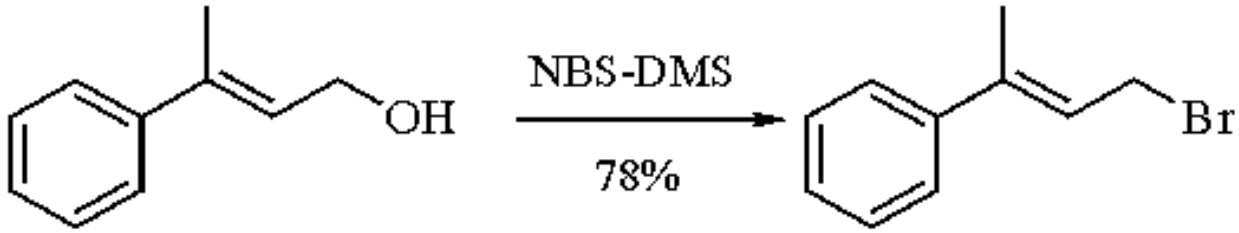

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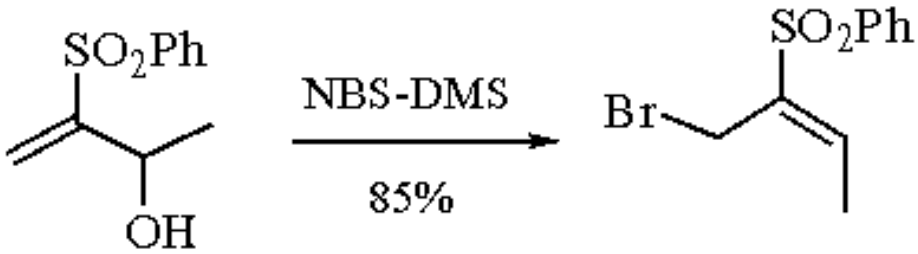

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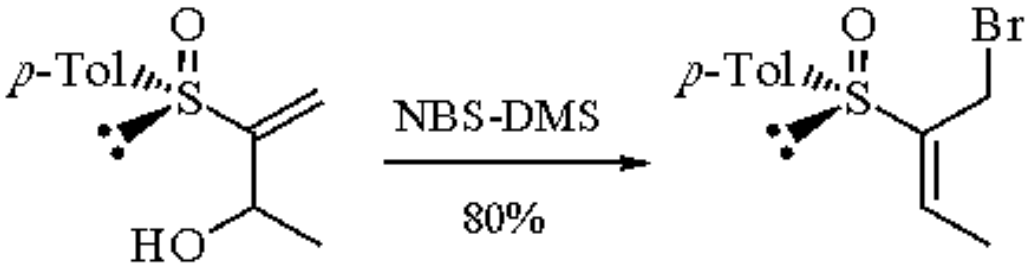

(5)

NBS-DMS is also a mild and practical reagent for synthesizing benzylic bromides from benzylic alcohols. As in the case of allylic alcohols, it is superior to PBr_3 when sensitive functionality is involved because no HBr is produced. Reactions of NBS-DMS proceed rapidly in high yield and high purity (eq 6).[7]

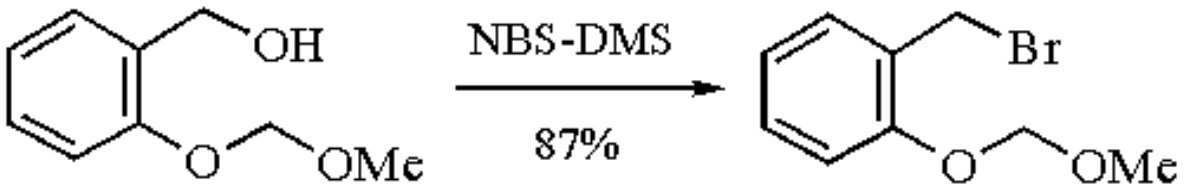

(6)

NBS-DMS is also capable of converting alkyl alcohols to bromides in reasonable yields. Eq 7 shows an example of this type of conversion that occurs at 20 °C in 36 h[1] (see also ***Carbon Tetrabromide*** and ***Triphenylphosphine Dibromide***).

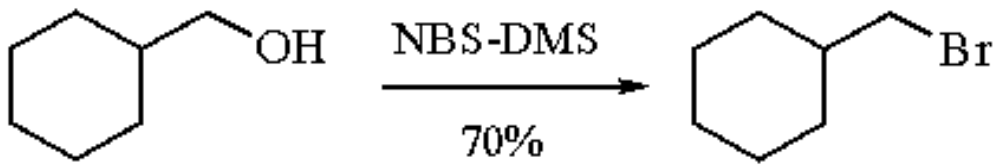

(7)

Oxidation of Primary and Secondary Alcohols.

Oxidations using NBS-DMS are part of a larger family of sulfonium ion-type oxidations (see also ***Dimethyl Sulfoxide-Oxalyl Chloride*** and ***Dimethyl Sulfide-Chlorine***), and are carried out in a similar manner to the NCS-DMS oxidation.[8] The reactions take place in 2 h at temperatures between 0 °C and -78 °C. The sulfoxonium ion intermediate is decomposed with ***Triethylamine*** to generate the carbonyl compound (eqs 8 and 9), as with NCS-DMS. This reagent is not useful for oxidizing allylic or benzylic alcohols because of the bromide replacement reaction described above.[2]

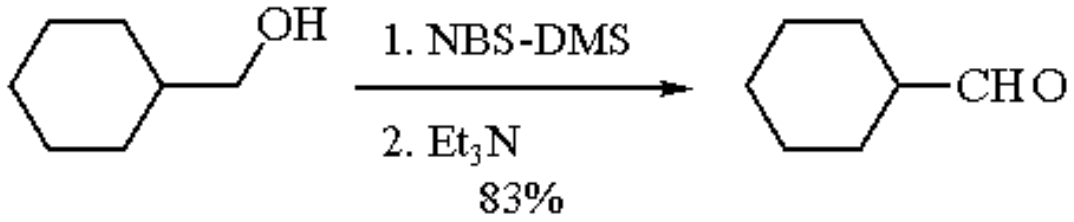

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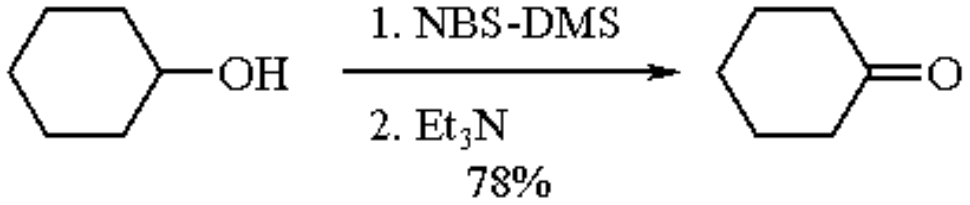

(9)

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N-Bromosuccinimide-Hydrogen Fluoride

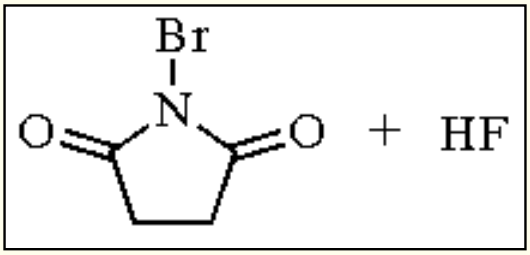

(NBS)

[128-08-5] · $C_4H_4BrNO_2$ · *N*-Bromosuccinimide-Hydrogen Fluoride · (MW 177.99) (HF)

[7664-39-3] · FH · *N*-Bromosuccinimide-Hydrogen Fluoride · (MW 20.01)

(reagent for the bromofluorination of alkenes and fluorination of dithioesters)

Alternate Name: NBS-HF.

Physical Data: NBS: mp 173-175 °C; *d* 2.098 g cm^{-3}. HF: mp -83.1 °C; bp 19.54 °C; *d* 0.991 g cm^{-3}.

Solubility: NBS: sol water, acetone, alcohol, acetic acid, ethyl acetate. HF: sol water, alcohol, benzene, pyridine; slightly sol ether.

Form Supplied in: NBS: off-white to yellow crystalline material; widely available. HF: widely available as aqueous solutions, or anhydrous solutions in pyridine (70% HF, 30% pyridine).

Handling, Storage, and Precautions: NBS: eye protection and rubber gloves should be worn when handling this material. This reagent should only be handled in a fume hood. Absorbed through the skin; high concentrations are destructive to mucous membranes and the tissues of upper respiratory systems. HF: eye protection and rubber gloves should be worn when handling this material. This reagent should only be handled in a fume hood. Corrosive, highly irritating, and poisonous. Should not be stored in glass containers; will etch glass. Causes severe burns, which may not be immediately apparent. Extremely destructive to mucous membranes and tissues of the upper respiratory system. Pyridine solutions are moisture sensitive.

Fluorination and Bromofluorination of Alkenes.

N-Bromosuccinimide used in conjunction with poly(hydrogen fluoride)/tertiary amine reagents bromofluorinates alkenes[1] and polymeric alkenes (eq 1).[2] In ether, using HF/pyridine, the products exhibit typical Markovnikov

regioselectivity, with the bromide adding to the least substituted end of the alkene.[3] Bromofluorination also occurs with NBS and liquid ***Hydrogen Fluoride***, but these conditions are more harsh and are more difficult to carry out due to the need for low temperature and high pressure.[4] The reaction is stereoselective, giving *anti* addition products (eq 2).[3,5a] This reaction can be done with HF supported on crosslinked poly(styrene-*co*-4-vinylpyridine) or poly-4-vinylpyridinium, and exhibits the same regio- and stereoselectivity as that with HF supported on pyridine.[5] If ***Silver(I) Fluoride*** is added to the reaction after completion, *vic*-difluorides can be formed by exchange of the bromofluoroalkane to the difluoride.[1] If any water is present, the vicinal halohydrin can also be formed.[6]

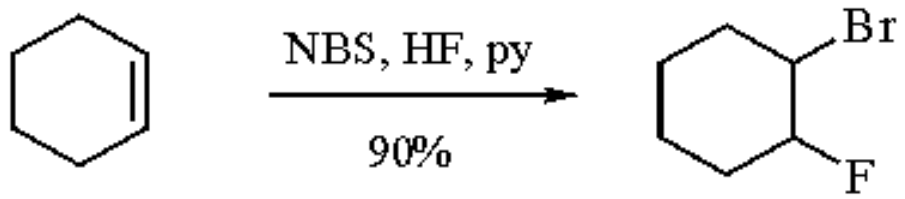

(1)

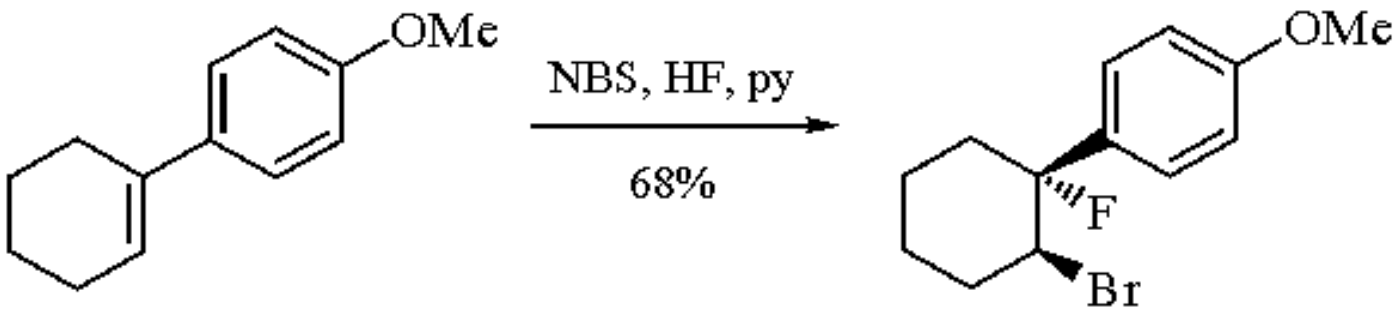

(2)

In the reaction of NBS-HF/pyridine, several factors influence the stereoselectivity.[3,7] Normal *anti* selectivity results from the NBS-HF complex reacting with one face of the alkene, thus preventing fluoride ion from adding in a *syn* fashion. If the concentration of HF is increased, the complexing effects are lessened, and fluoride can add to the carbocation from either face.[7] The reaction of 1-phenyl-4-*t*-butylcyclohexene demonstrates the selectivity, reacting to give two *anti* products, resulting from complexation on either face of the alkene (eq 3).[3c] In addition to concentration, the diastereoselectivity for bromofluorination of alkenes is dependent on solvent effects[7] and alkene geometry.[4,8]

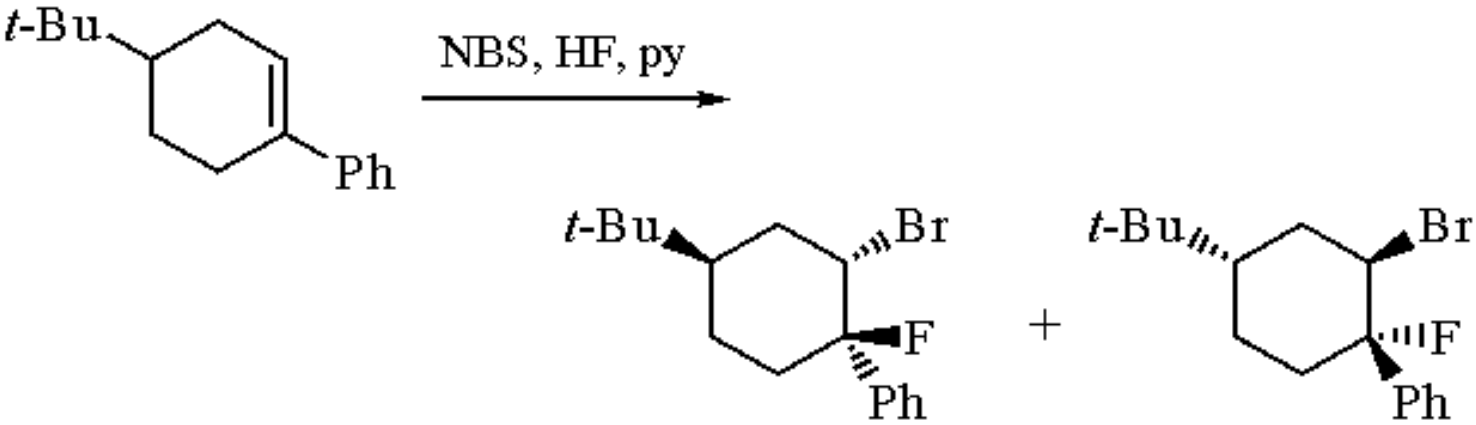

(3)

For large cyclic alkenic compounds containing an oxirane group, bromofluorination fails to give the expected α-bromo-β-fluoro compound, due to competing complexation with the oxirane ring. Instead, a mixture of bicyclic ethers substituted with bromine and fluorine is produced (eq 4).[9]

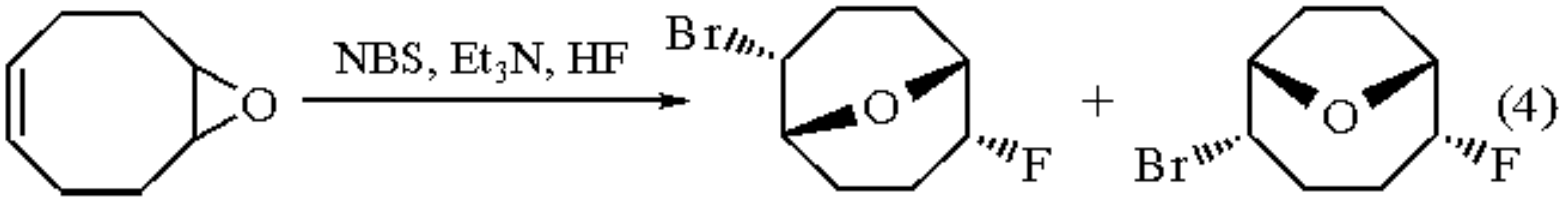

NBS-HF/pyridine or poly-4-vinylpyridinium reacts with diazoalkanes and diazo ketones to give the α,α-bromofluoroalkanes and ketones (eq 5).[10] Hydrazones of aldehydes and ketones also react under these conditions, giving the *gem*-difluoro compounds, with the fluoride substituents replacing the hydrazone, in effect allowing the transformation of carbonyls to *gem*-difluoro compounds (eq 6).[11]

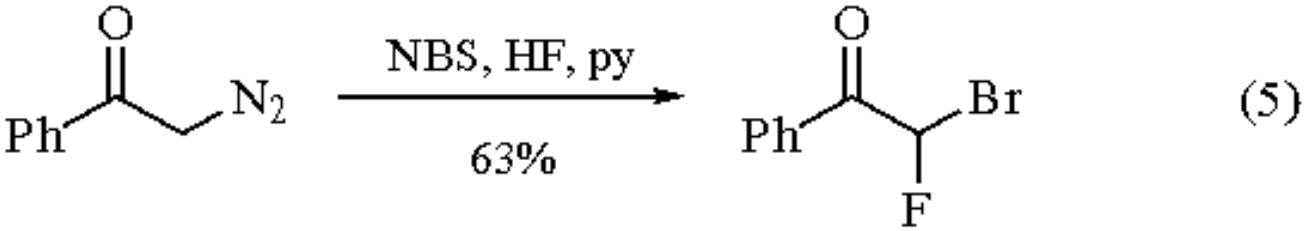

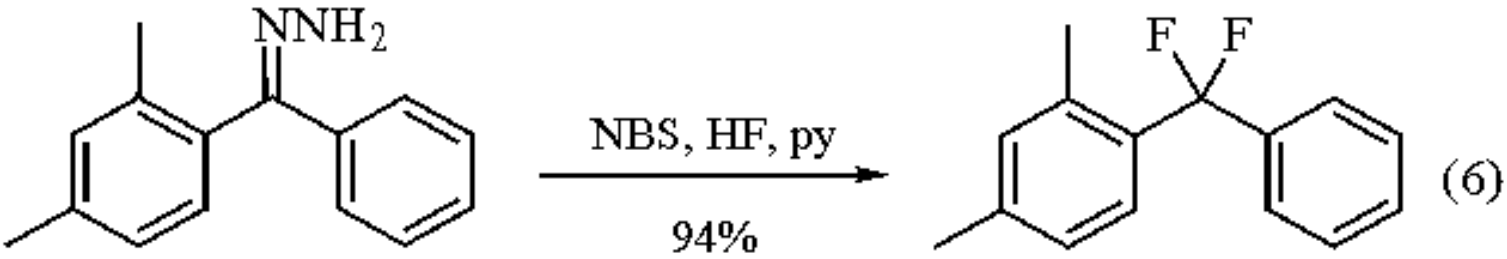

NBS-HF/pyridine has also been used for the fluorination of dithioesters of aromatic acids, which react to give trifluoromethyl substituted aromatic compounds (eq 7).[12] This reaction can also be carried out on sulfides where one of the substituents is $ArCF_2$, to give trifluoromethylaryl compounds.

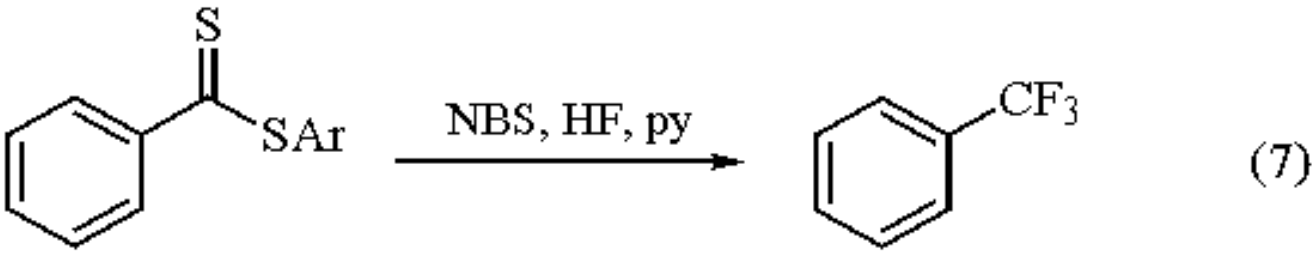

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N-Bromosuccinimide-Sodium Azide

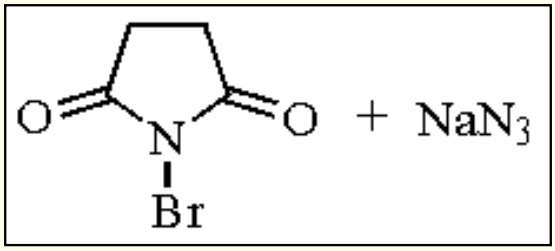

(NBS)

[128-08-5] · $C_4H_4BrNO_2$ · *N*-Bromosuccinimide-Sodium Azide · (MW 177.99) (NaN_3)

[26628-22-8] · N_3Na · *N*-Bromosuccinimide-Sodium Azide · (MW 65.01)

(source of BrN_3 in conversion of alkenes to β-bromoalkyl azides and, upon reduction, to aziridines)

Physical Data: for physical data see ***N-Bromosuccinimide*** and ***Sodium Azide***.

Introduction.

Sodium azide-*N*-bromosuccinimide can transfer an azido group and a Br atom to C=C double bonds. Reduction of the resulting β-bromoalkyl azides with ***Lithium Aluminum Hydride*** produces aziridines. This combination has been used as an in situ source of bromine azide BrN_3 and is a good substitute for the classical method of Hassner,[1,2] which requires the synthesis of potentially explosive[3] BrN_3 in acetonitrile or pentane.

Scope and Limitations.

The reaction is usually carried out at temperatures around -5 °C, by adding NBS in small portions to a mixture (4/1 or 3/1) of organic solvent (DME, THF, or DMF) and water in which is dissolved an excess of NaN_3 and the suspended alkene. It has been successfully carried out up to a molar scale.[4] It is still unclear if BrN_3 is effectively formed or if the azido anion reacts with the intermediate bromonium ion resulting from the interaction of the alkene with NBS. 1,1-Disubstituted,[5] 1,2-disubstituted,[6] trisubstituted,[6,7] and tetrasubstituted[4,8] alkenes (eqs 1-5) as well as indenes (eq 6)[9,10] and allylic alcohols (eq 7)[10] are transformed in reasonably good yields (40-60%) to the corresponding β-bromoalkyl azides.

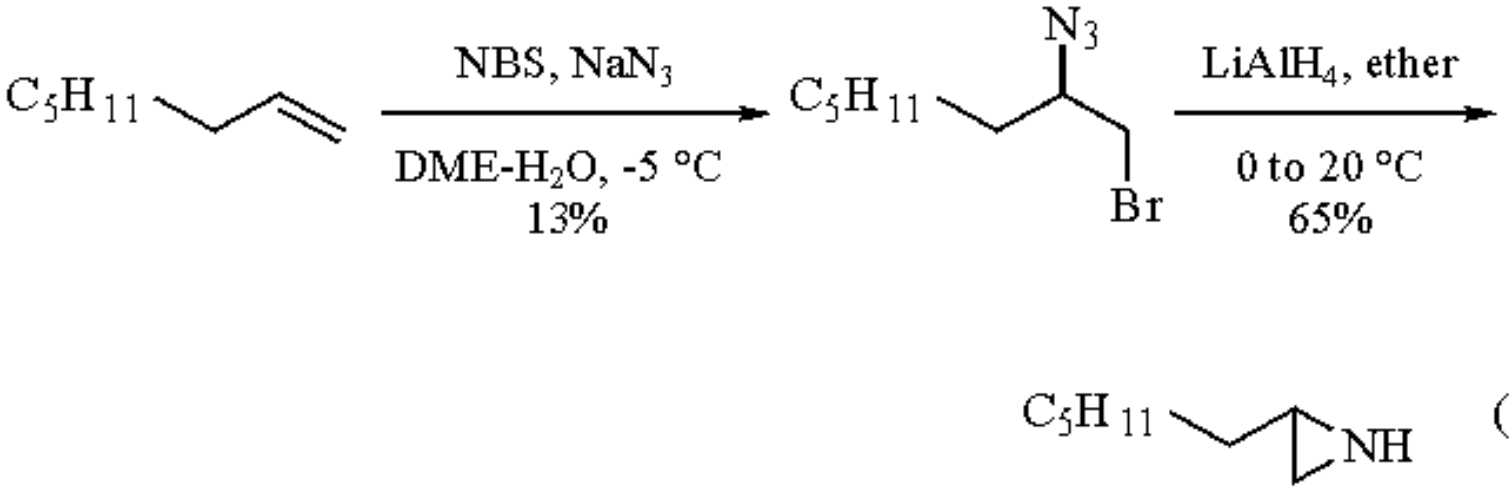

(1)

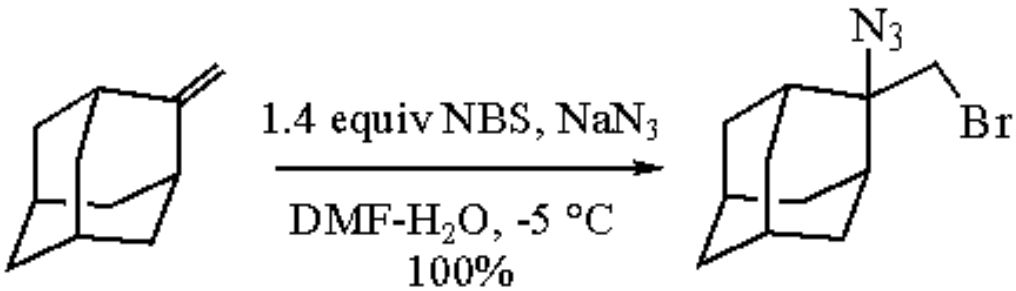

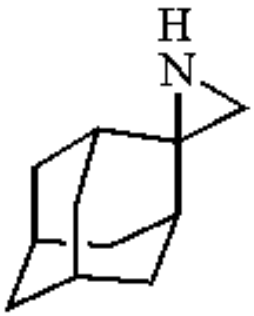

(2)

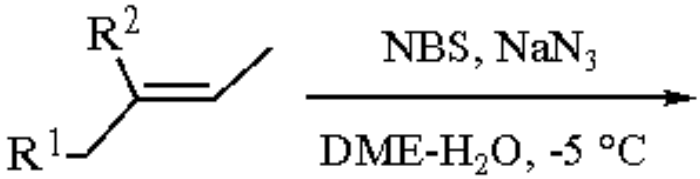

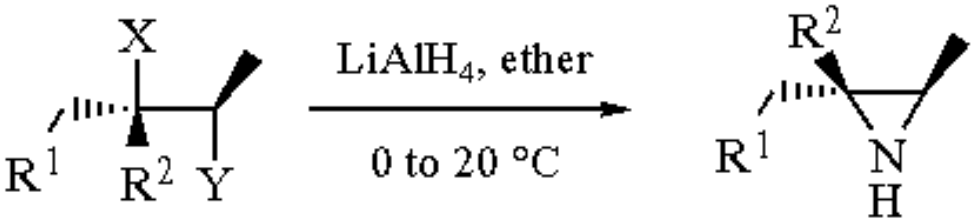

(3)

$R^1 = Bu$, $R^2 = H$; $(X = Br, Y = N_3) + (X = N_3, Y = Br)$; 65%; 42% overall
$R^1, R^2 = Me$; $X = N_3$, $Y = Br$; 36% overall

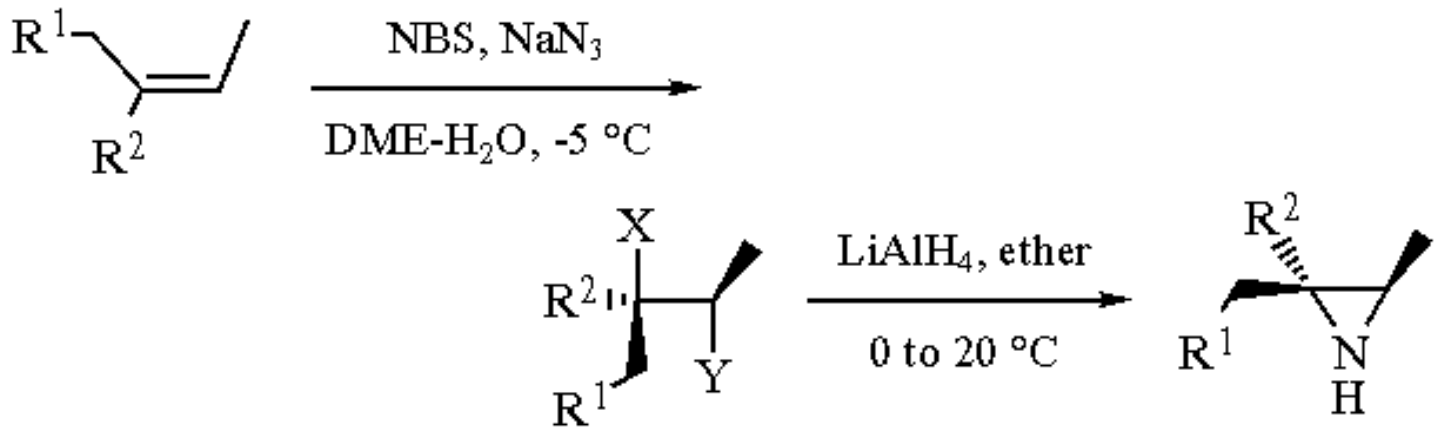

(4)

$R^1 = H$, $R^2 = Bu$; $(X = Br, Y = N_3) + (X = N_3, Y = Br)$; 42% overall
R^1, $R^2 = Me$; $X = N_3$, $Y = Br$; 36% overall

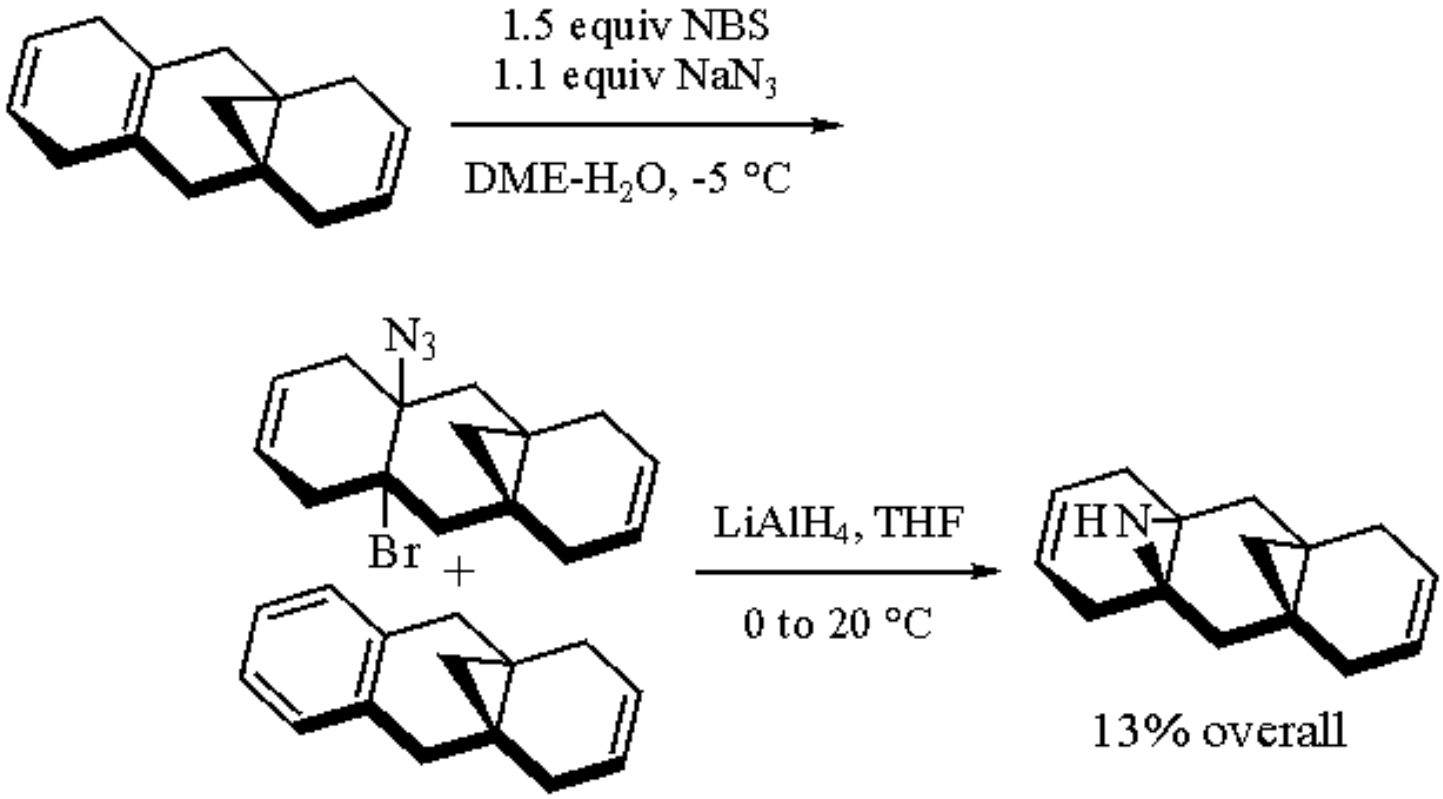

(5)

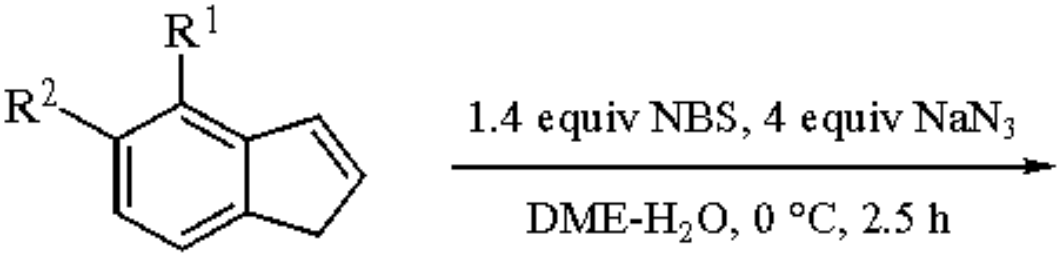

$R^1, R^2 = H$	
$R^1 = H, R^2 = MeO$	DME-H_2O, 0 °C, 5 h
$R^1 = MeO, R^2 = H$	DME-H_2O, 0 °C, 2.5 h

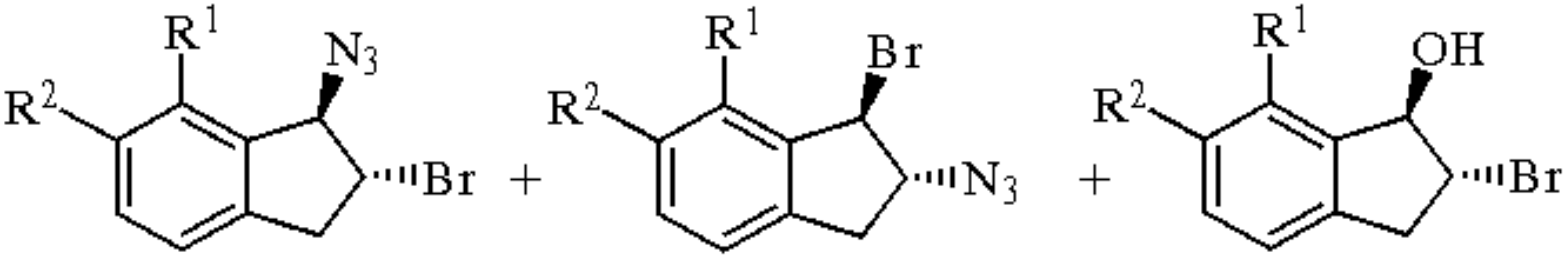

85%	-	-
40%	-	-
51%	15%	30%

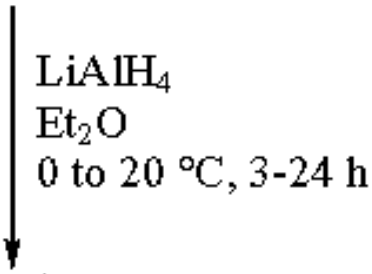

(6)

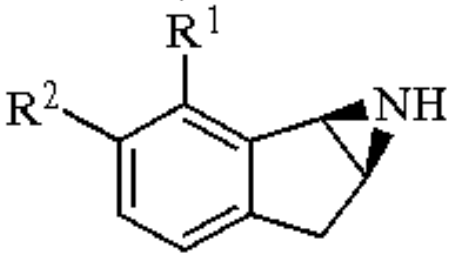

$R^1, R^2 = H$	61%
$R^1 = H, R^2 = MeO$	75%
$R^1 = MeO, R^2 = H$	unstable

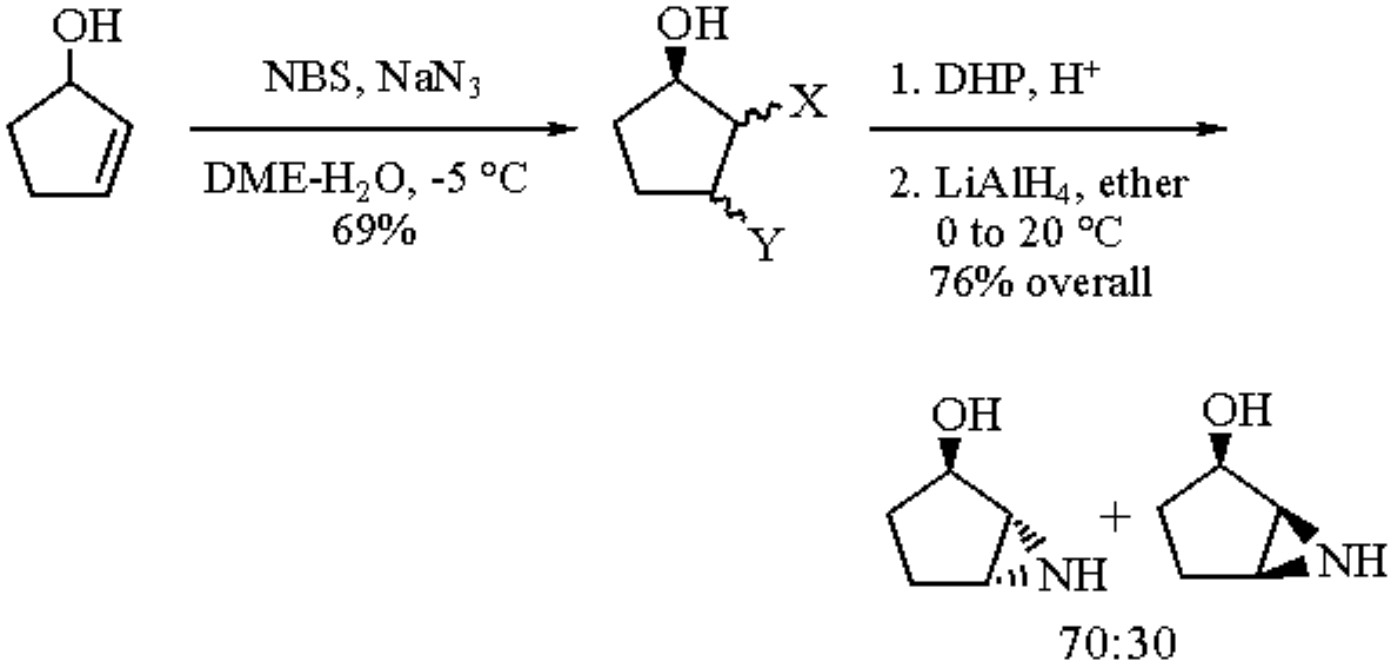

(7)

The reaction is difficult with less reactive C=C double bonds. For example, monosubstituted alkenes give poor yields of 1-bromoalkyl azides and bromohydrins are formed.[6] This results from the reaction with HOBr, formed along with N_2 by the decomposition of BrN_3 in water. The same process is also observed with 7-methoxyindene (eq 6).[9] Phenanthrene does not react[11] and is recovered in high yield under these conditions. Again, decomposition of BrN_3 by water is responsible for this failure, since preformed bromine azide in CH_2Cl_2 adds to the 9,10-C=C double bond (eq 8).[11] In some cases, e.g. 9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indoles (eq 9)[12] and 1,4,5,8,9,10-hexahydro-4a,9a-methanoanthracene and related derivatives (eq 5),[4,8] aromatization totally or partially competes with the formation of the β-bromoalkyl azide. In some other cases, loss of HBr occurs during the purification of the crude mixture (eq 8)[11] or even during the reaction (eq 10).[13] In such cases the vinyl azides first generated are able to react further with BrN_3 to produce β-bromo-α,α-bis(alkylazido)alkanes (eq 10).[13]

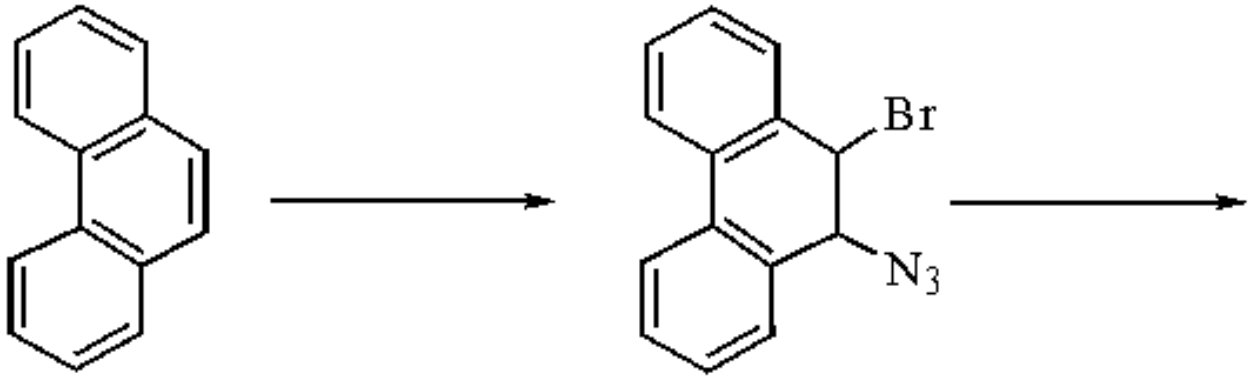

a) 1.4 equiv NBS, NaN_3 DME-H_2O, -5 °C — 0%

b) BrN_3, CH_2Cl_2, -10 °C, 3 h — 50%

a) SiO_2, Merck 7733, 20 °C

b) $LiAlH_4$, THF, -15 °C, 0.5 h

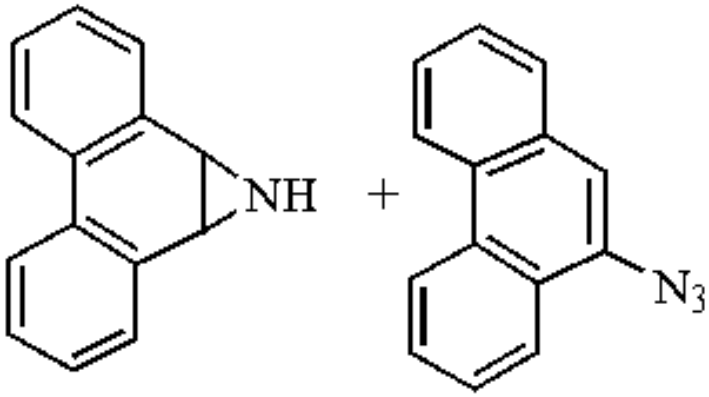

(8)

-	70%
60%	4%

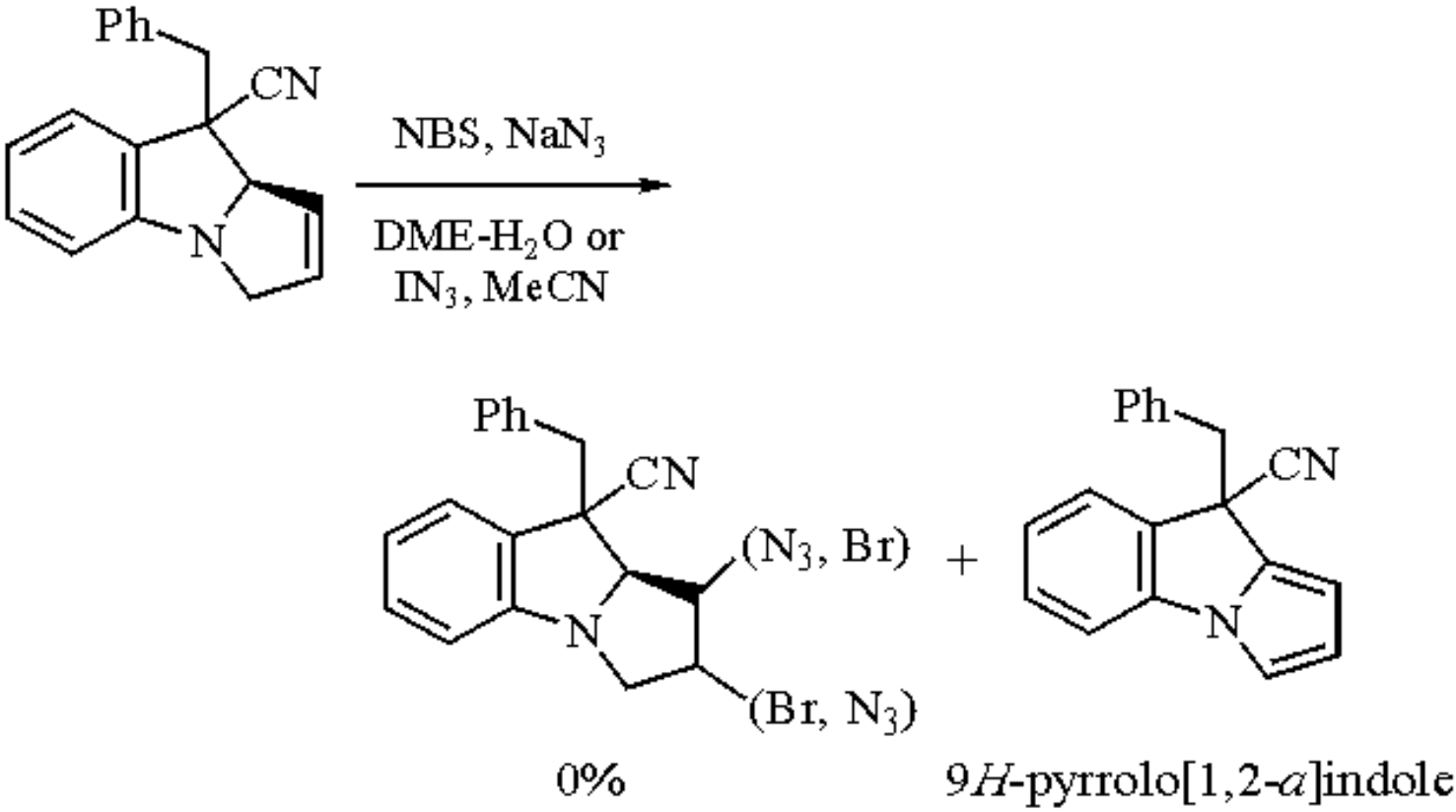

(9)

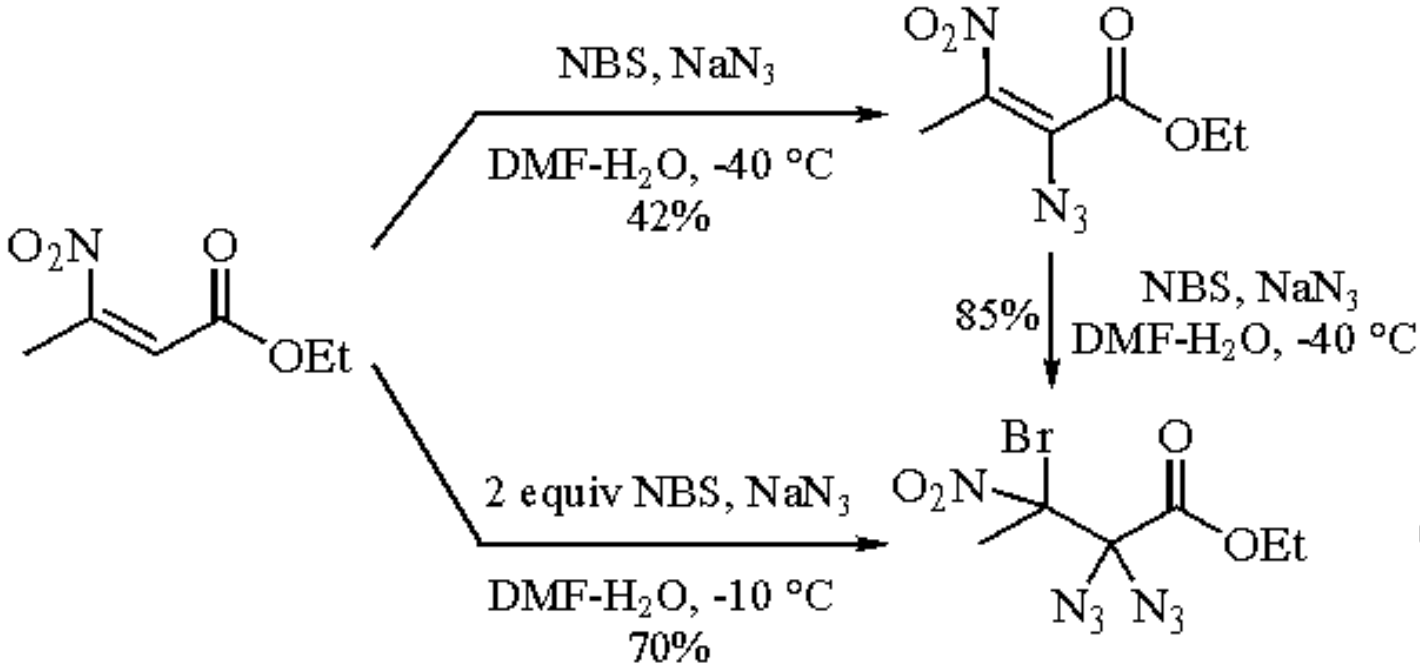

(10)

Regioselectivity (rs).

The addition is highly regiospecific with terminal[5,6] and trisubstituted[6] alkenes and produces the β-bromoalkyl azide in which the bromine atom is attached to the least substituted carbon atom (rs >95%; eqs 1-5). This is remarkable, since preformed BrN_3 reacts in a nonregioselective manner with terminal alkenes in acetonitrile and leads to an 8/2 mixture of β-bromoalkyl azides, in which the product bearing the bromine atom at the least substituted carbon prevails (Markovnikov rules).[6] The higher electronegativity of Br compared to that of I and probably to that of N_3 explains why,

under similar conditions, BrN_3 possesses a much higher propensity than its iodo analog to react in a radical process.[2] The high polarity of the medium in the NaN_3-NBS reaction favors the ionic process.[6] This reagent adds regioselectively to indenes (eq 6)[9,10] and nonregioselectively to dialkyl substituted C=C double bonds bearing two different alkyl substituents (eqs 3 and 4)[6] and to 2-cyclopenten-1-ol (eq 7).[14]

Stereoselectivity (ss).

The addition of the Br atom and N_3 moiety is *anti* stereospecific (ss >98%) with tri- and tetrasubstituted alkenes (eqs 3 and 4) and, therefore, the whole process NaN_3-NBS, $LiAlH_4$ allows the highly stereoselective synthesis of aziridines which possess the same stereochemistry as their parent alkenes. This occurs[6] with a much higher stereoselectivity than observed in the conventional BrN_3, $LiAlH_4$ method,[2] due to the absence of radical reactions, and therefore more closely resembles the reaction IN_3, $LiAlH_4$.[2]

Asymmetric induction is very poor with 2-cyclopenten-1-ol (eq 7)[14] but very high with 1,4,5,8,9,10-hexahydro-4a,9a-methanoanthracene (eq 5).[8] In the latter case the ionic addition to the tetrasubstituted double bond is sterically controlled by the cyclopropane ring and, after reductive cyclization, affords a compound in which both three-membered rings are on the same face of the tricyclic derivative.[14]

Chemoselectivity.

NaN_3-NBS proved to be more reactive toward tetra- than disubstituted double bonds (eq 5).[4,8] It also reacts chemoselectively on the terminal nonfunctionalized C=C double bond of geranyl and farnesyl acetates as well as of squalene,[7] which possess two, three, and six identically trisubstituted C=C double bonds, respectively (eqs 11 and 12). Presumably, the polyene is coiled in the highly polar medium used (DME-H_2O) and presents its terminal double bond to the attack of the extensively solvated bromonium ion.[7] A similar explanation was previously given to rationalize the high chemoselective addition of BrOH towards the same polyalkenes.[15] Interestingly, the conventional BrN_3 method[7] as applied to geranyl and farnesyl acetates not only produces the corresponding β-bromoalkyl azides in very low yields but also shows very little terminal preference. Poor chemoselectivity is also observed if squalene is reacted with IN_3 under conventional conditions.[16]

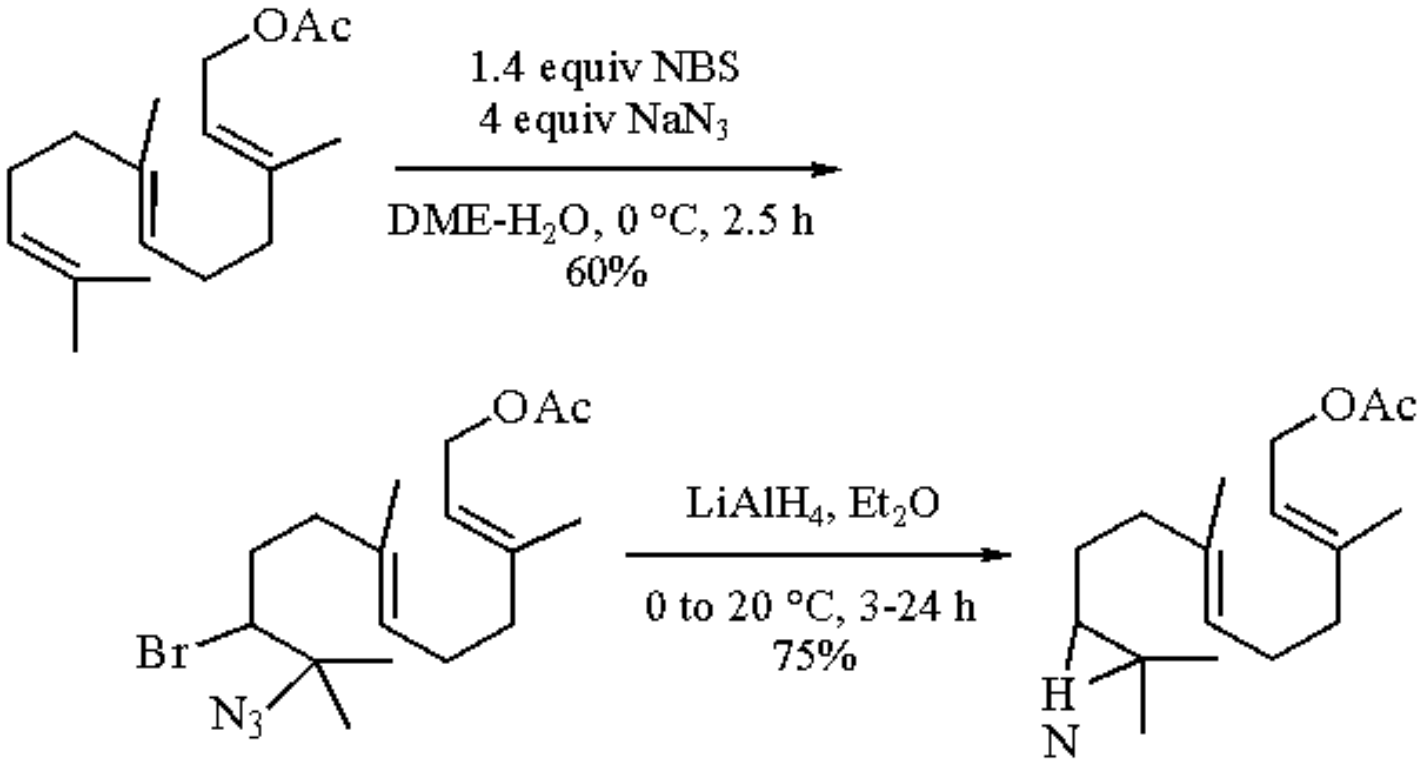
OAc
1.4 equiv NBS
4 equiv NaN3
DME-H2O, 0 °C, 2.5 h
60%
OAc
Br
N3
LiAlH4, Et2O
0 to 20 °C, 3-24 h
75%
OAc
H
N

(11)

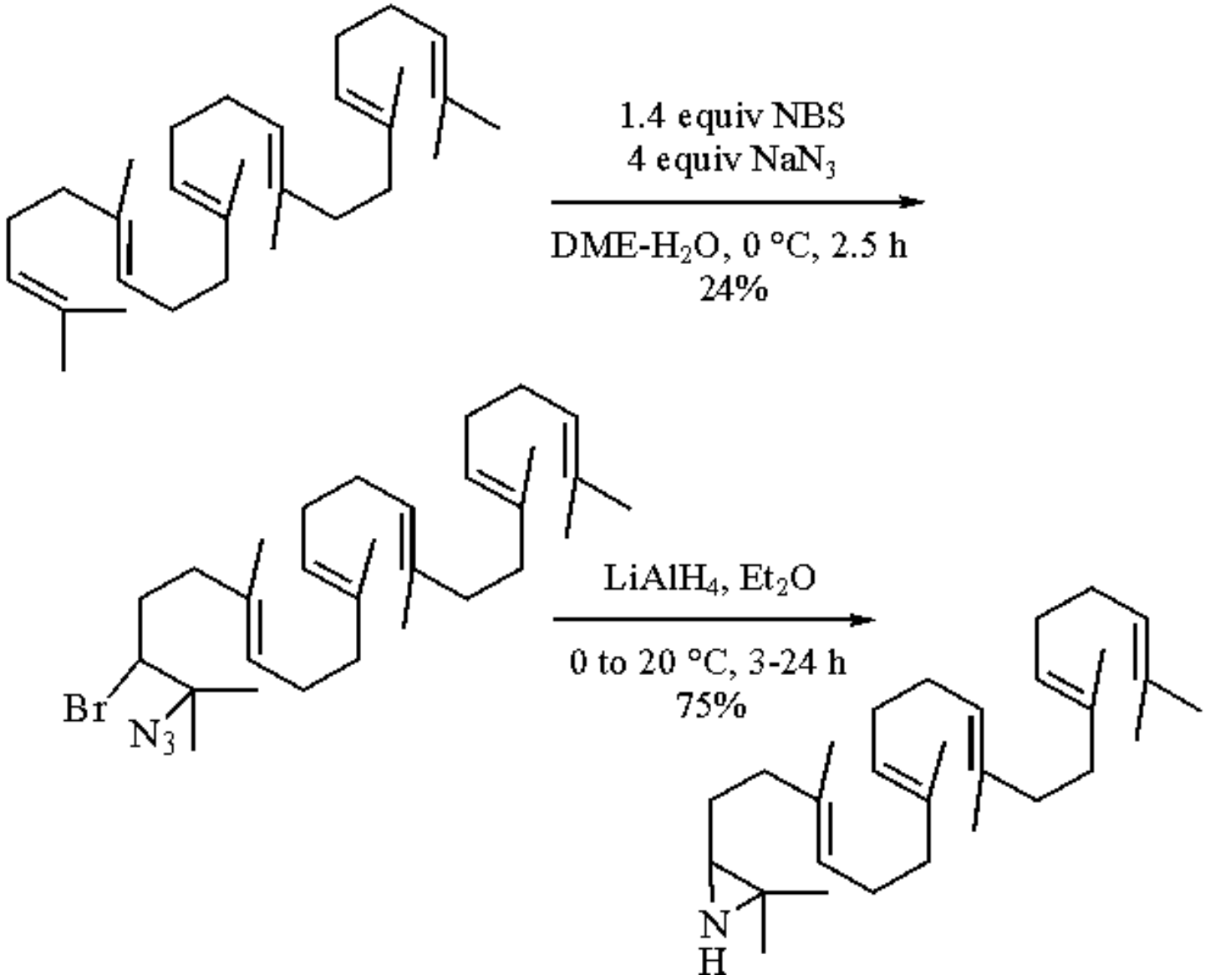
1.4 equiv NBS
4 equiv NaN3
DME-H2O, 0 °C, 2.5 h
24%
Br
N3
LiAlH4, Et2O
0 to 20 °C, 3-24 h
75%
N
H

(12)

The NaN_3-NBS, $LiAlH_4$ method proved, for aziridine synthesis from alkenes, to be superior to the alternative method of epoxide ring opening by azide ion followed by reaction of the corresponding tosylate with $LiAlH_4$.[17]

Related Reagents.

Bromine Azide; ***N-Bromosuccinimide***; ***Iodine Azide***; ***Sodium Azide***.

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trans-Bromotetracarbonyl(ethylidyne)tungsten

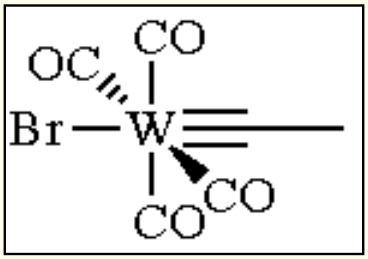

[50726-31-3] · $C_6H_3BrO_4W$ · *trans*-Bromotetracarbonyl(ethylidyne)tungsten · (MW 402.84)

(couples with alkynes[1])

Alternate Name: trans-bromotetracarbonyl(methylmethylidyne)tungsten.

Physical Data: solid at 25 °C; mp dec; yellow crystals.

Solubility: sol pentane, THF, Et_2O.

Form Supplied in: not commercially available.

Preparative Methods: prepared from the reaction of pentacarbonyl(1-methoxyethylidene)tungsten and ***Boron Tribromide***[2] or tetramethylammonium acetyl(pentacarbonyl)tungstate and ***Oxalyl Bromide***.[3]

Purification: after synthesis, *trans*-bromotetracarbonyl(ethylidyne)tungsten is purified by chromatography on silica gel at -30 °C using 1:1 pentane-dichloromethane as an eluent, followed by recrystallization from pentane at -78 °C. Purification by extensive washing with pentane at low temperature is apparently sufficient for use in alkyne coupling reactions.[1]

Handling, Storage, and Precautions: unstable above 35 °C; decomposes in air.

Reactions with Alkenes and Alkynes.

Coupling of diynes and *trans*-bromotetracarbonyl(ethylidyne)tungsten leads to ring-fused phenol derivatives in moderate yield (eq 1).[1] The reaction is most efficient for the construction of indanols, and less so for preparation of tetrahydronaphthols and benzocyclobutanols. A similar reaction pathway is observed for the analogous carbene complex;[4] involvement of carbene complexes in these processes has not been ruled out. Cyclization of enynes is less

efficient, leading to pentadienyltungsten complexes having the sickle geometry (eq 2).[5] Enynes having methylene group tethers did not display the reactivity depicted in eq 2. Additional reactions of *trans*-bromotetracarbonyl(ethylidyne)tungsten with unsaturated hydrocarbons include alkyne polymerization and ring opening metathesis polymerization (ROMP) of cycloalkenes.[6]

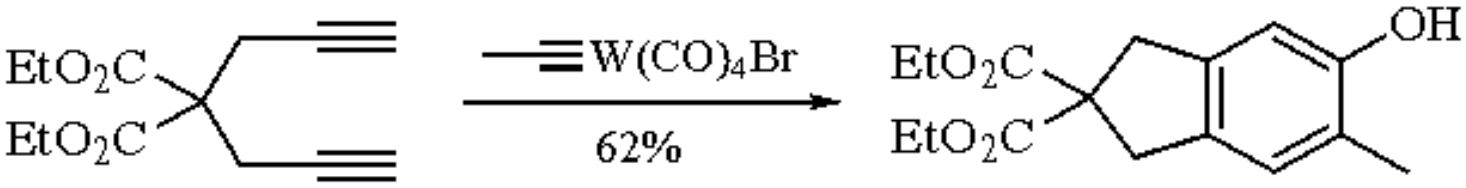

(1)

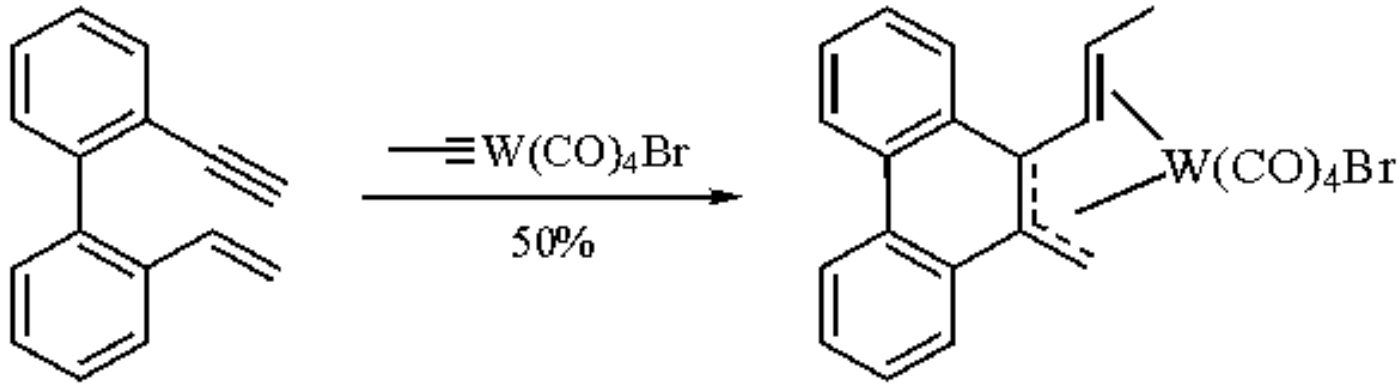

(2)

Ligand Exchange.

A limited number of synthetic transformations have been reported employing *trans*-bromotetracarbonyl(ethylidyne)tungsten; however, substitution of the CO ligands for phosphine ligands provides a more stable carbyne complex (eq 3). These ligand-modified complexes have been the focus of considerable investigation.[7]

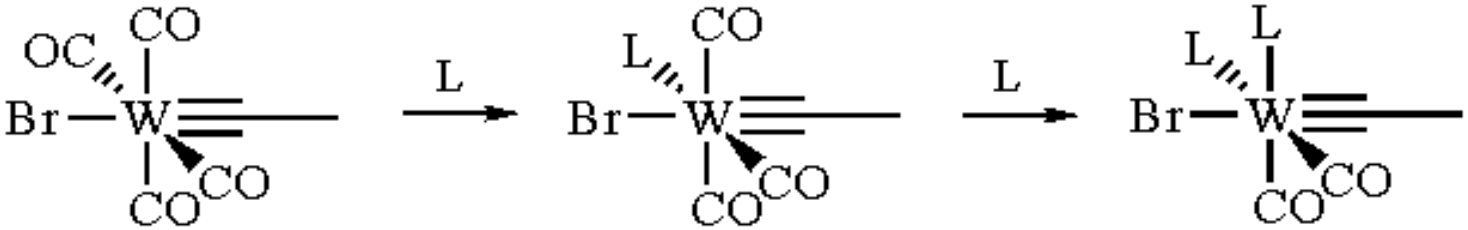

(3)

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1-Bromo-1,2,2,2-tetrafluoroethyl(phenyl)mercury[1]

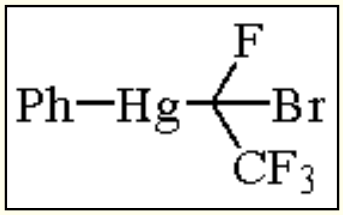

[42201-75-2] · $C_8H_5BrF_4Hg$ · 1-Bromo-1,2,2,2-tetrafluoroethyl(phenyl)mercury · (MW 457.62)

(excellent source of tetrafluoroethylidene, **:**$CFCF_3$; cyclopropanates alkenes; inserts into Si-H bonds; reacts with C=S bonds)

Physical Data: mp 121-122 °C.

Solubility: sol THF, benzene, dichloromethane.

Analysis of Reagent Purity: spectroscopic data: IR, NMR (^{1}H and ^{19}F).[2]

Preparative Method: prepared in 65% yield by reaction of PhHgCl with CF_3CHFBr in dry THF in the presence of MeONa-MeOH.[2,3]

Purification: recrystallization from hexane (colorless prisms).

Handling, Storage, and Precautions: flame-dried glassware and an atmosphere of dry nitrogen are used for the reactions. Organomercury(II) compounds should be carefully handled and skin contact and inhalation should be particularly avoided. All reactions must be conducted in a well-ventilated hood.

Cyclopropanation of Alkenes.

The reagent was introduced[3] as an attractive alternative source of divalent **:**$CFCF_3$ to circumvent problems of volatility and toxicity[4] associated with $Hg(CFBrCF_3)_2$[5] and $Hg(CFClCF_3)_2$.[6] In this context, $PhHgCFBrCF_3$ has proven to be a valuable and synthetically useful reagent for transferring tetrafluoroethylidene to alkenes. Its reaction with several representative alkenes has been studied; for instance, cyclopropanation of cyclooctene occurs with almost quantitative yield (isomer ratio based on ^{19}F NMR data) (eq 1).

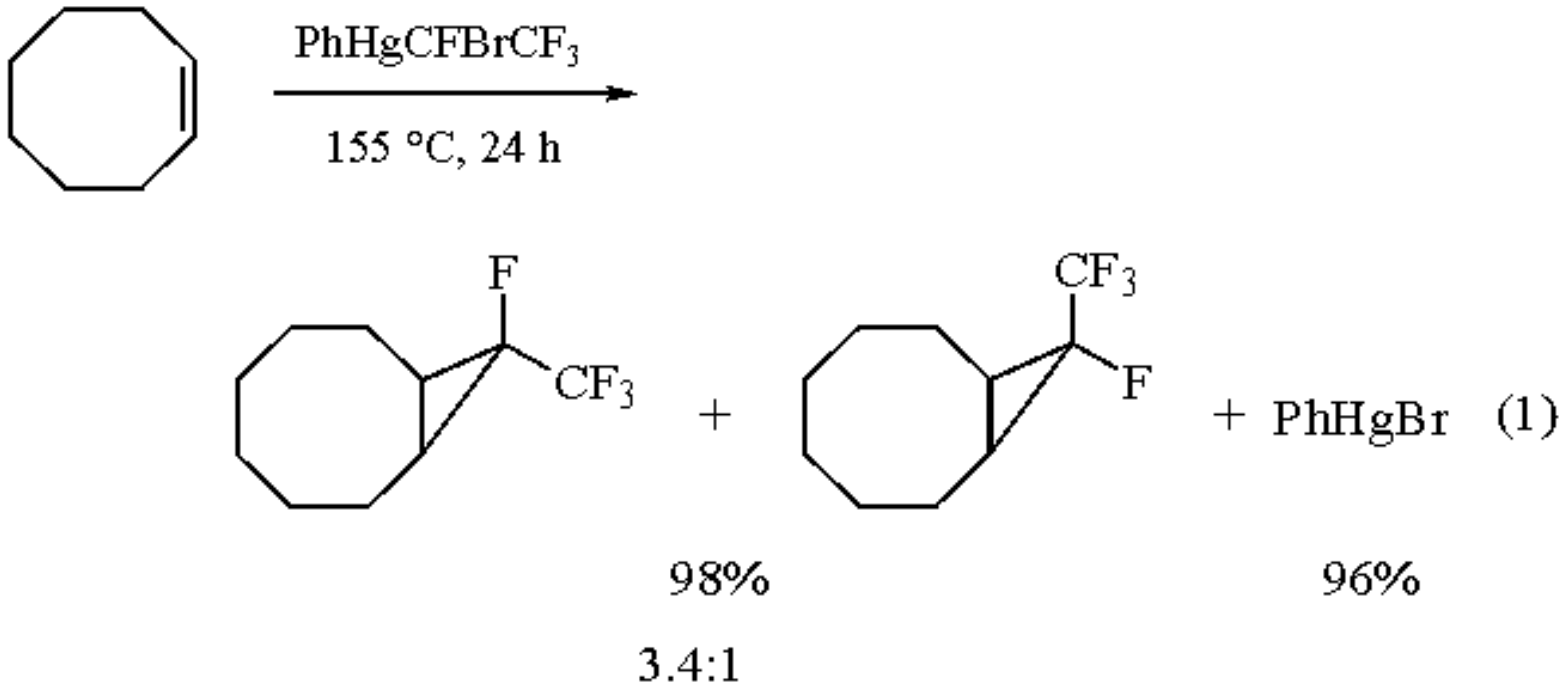

As anticipated, thermal treatment of $PhHgCFBrCF_3$ transfers the **:**$CFCF_3$ species and eliminates PhHgBr with no evidence of competitive PhHgF formation being observed.[7,8] Another interesting feature is that the yield of cyclopropane formation and mercury elimination correlates well and, thus, side reactions do not take place.[9] Reactions were carried out in sealed tubes and similar results are obtained for acyclic mono- and disubstituted alkenes. Allylsilane is also a good partner for $PhHgCFBrCF_3$, affording the corresponding cyclopropane in 93% yield; however, in the case of vinylsilane the yield is quite low (16%) and does not correlate well with the amount of PhHgBr recovered from the reaction mixture (60%). Finally, $PhHgCFBrCF_3$ is superior to $PhHgCFClCF_3$ as a source of **:**$CFCF_3$; the latter requires longer reaction times (typically 5 days at 140 °C).[10]

Insertion into Si-H Bond.

Thermal reaction of Et_3SiH with $PhHgCFBrCF_3$ furnishes $Et_3SiCHFCF_3$ in 53% yield after 24 h at 155 °C in a sealed tube,[2] the result of insertion of divalent carbon into the Si-H bond.[1]

Reaction with Thiobenzophenone.

The C=S bond of thiobenzophenone reacts with the organomercury reagent at 155 °C for 40 h in a sealed tube, affording $Ph_2C{=}CFCF_3$ and sulfur (eq 2).[2] The expected thiirane ring is not isolated, although it is presumably formed; instead it probably undergoes, under the reaction conditions, sulfur extrusion to the observed alkene, as depicted (eq 2).

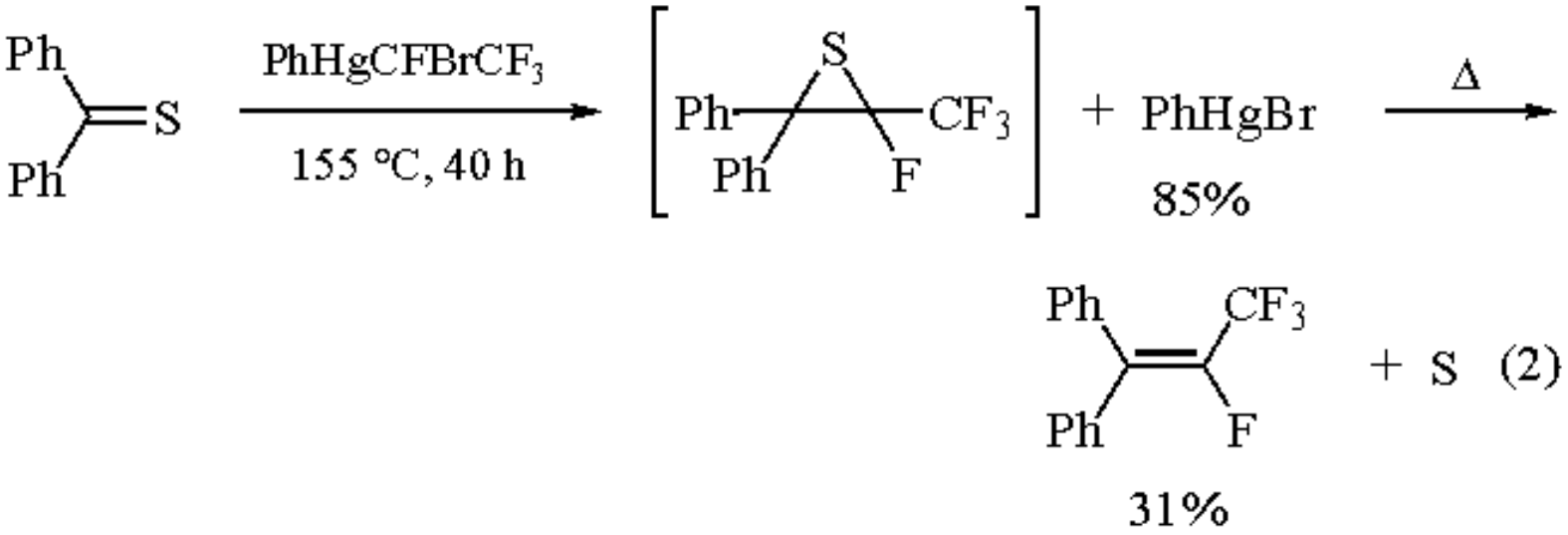

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1-Bromo-3-tetrahydropyranyloxy-1-propyne

Br-C&tbond;C-CH_2OR

(**1**; R = -$CH(CH_2)_4O$)

[14420-47-4] · $C_8H_{11}BrO_2$ · 1-Bromo-3-tetrahydropyranyloxy-1-propyne · (MW 219.08) (**2**; R = $SiMe_3$)

[56958-33-9] · $C_6H_{11}BrOSi$ · 1-Bromo-3-trimethylsilyloxy-1-propyne · (MW 207.14)

(alkoxymethylalkynylating agent; propargyl alcohol cation equivalent)

Physical Data: (**1**) bp 69 °C/0.8 mmHg; (**2**) bp 34-36 °C/2 mmHg.

Solubility: sol any common organic solvent.

Preparative Methods: by protection of 3-bromo-2-propynol: (**1**) with ***3,4-Dihydro-2H-pyran*** and a catalytic amount of 10 N HCl,[1] scale 0.5 mol, yield 60%; (**2**) by treatment with ***Sodium Hydride*** and ***Chlorotrimethylsilane***,[2] scale 0.5 mol, yield 70%. 3-Bromo-2-propynol is prepared from ***Propargyl Alcohol*** and ***Bromine*** in basic medium,[3] scale 0.5 mol, in quantitative yield. Conversely, 1-tetrahydropyranyloxy-2-propyne can be brominated with ***N-Bromosuccinimide*** and ***Silver(I) Nitrate*** in acetone[4] (scale 3 mmol, yield 59%).

Handling, Storage, and Precautions: use in a fume hood; store in the absence of moisture, preferably over K_2CO_3, at 0 °C in the dark.

Electrophilic Propargylation with (1).

A limited number of nucleophiles have been reacted with this reagent to date; an example is sodium diethyl phosphite, which leads to phosphonates (eq 1).

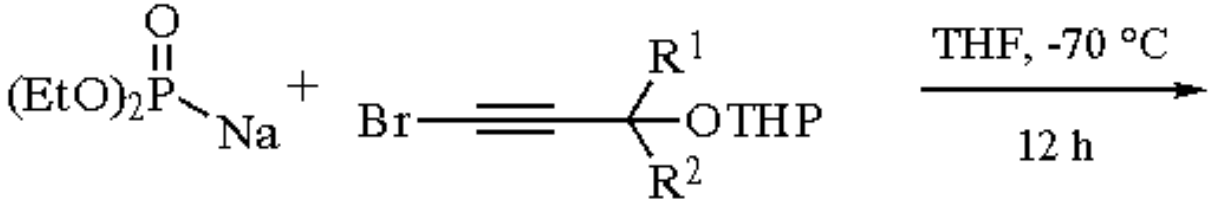

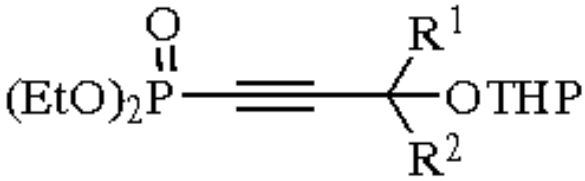

(1)

Vinylcopper reagents lead to enynols (eq 2) provided that 1.2-2 equiv of TMEDA are added[4] to prevent the formation of diene and diyne.

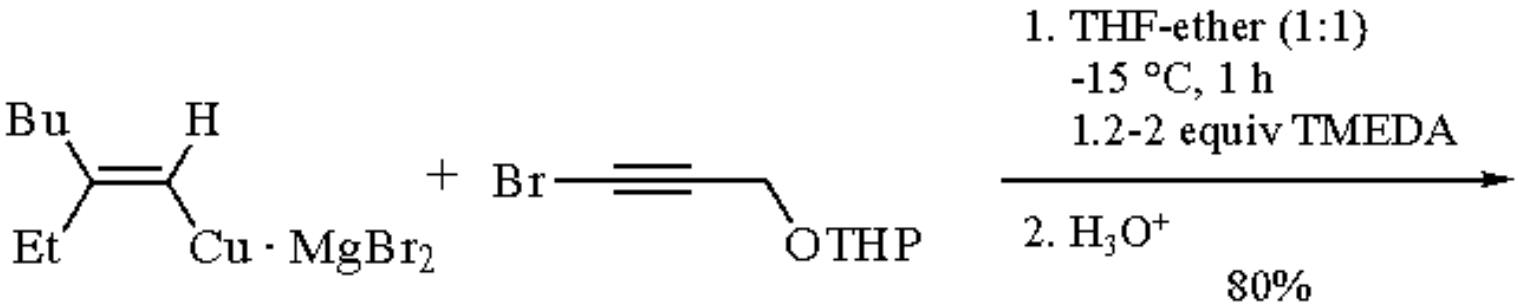

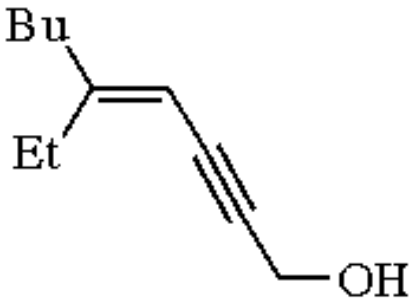

(2)

Vinyl zincacyanocuprates derived from tin also react (eqs 3 and 4).[5] The starting copper reagents are made in situ via stannyl cupration. A Cadiot-Chodkiewicz coupling, with a terminal alkyne, leads to the corresponding diynol.[6]

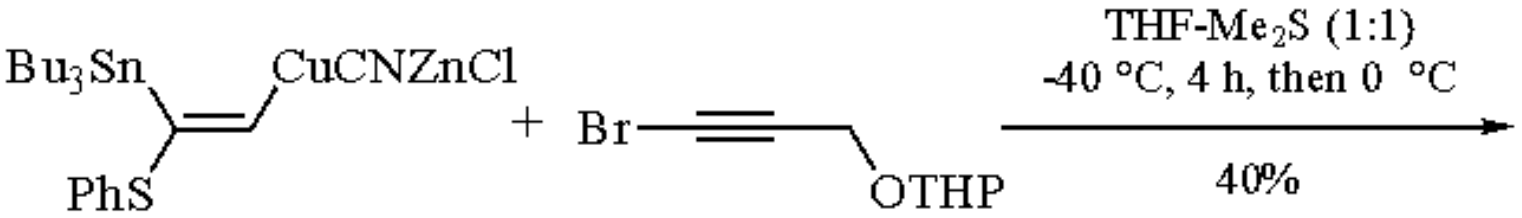

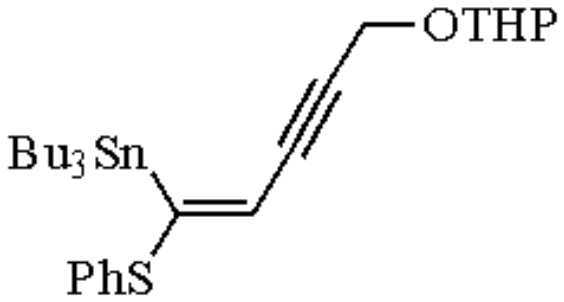

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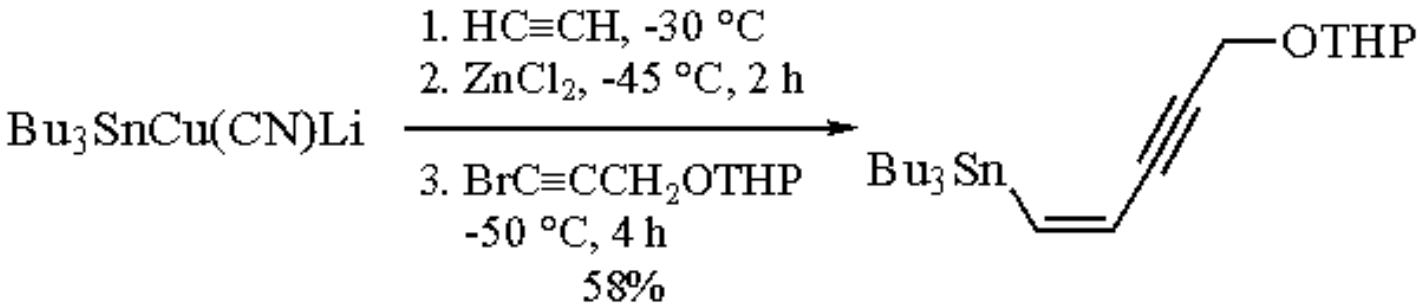

(4)

Electrophilic Propargylation with (2).

Vinylcopper reagents react similarly (eq 5) and are used to prepare (*Z*,*E*)-dienols of high purity (after LAH reduction). The reaction described in eq 2 with this reagent affords the same alcohol (82% yield). Also, the use of (**2**) in eq 4 leads to the corresponding silylated enynol in 65% yield.

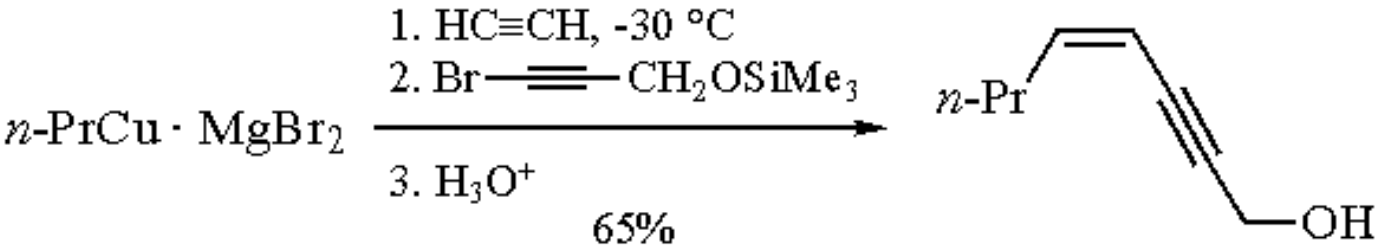

(5)

Higher Homolog.

The compound Br-C&tbond;C-$(CH_2)_2OSiMe_3$ is prepared analogously from the bromo alcohol.[4] Vinyl cuprates derived from acetylene react better if they are first converted to the vinylcopper species with CuI (eq 6).[7]

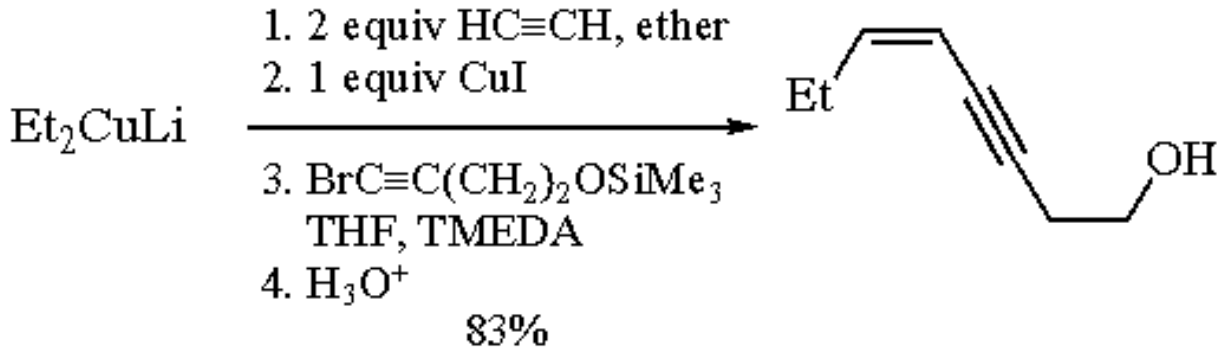

(6)

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Bromo(*o*-tolyl)bis(triethylphosphine)nickel(II)

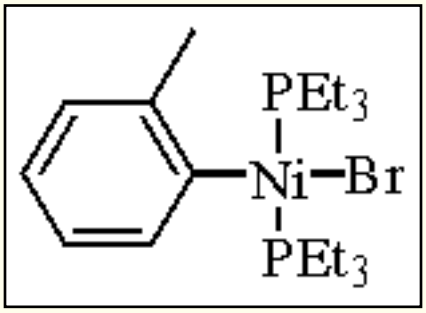

[26521-33-5] · $C_{19}H_{37}BrNiP_2$ · Bromo(*o*-tolyl)bis(triethylphosphine)nickel(II) · (MW 466.06)

(Ullmann[1] and cross-coupling[2] reactions; halogen exchange of aryl and vinyl halides;[1,3] oligomerization reactions[4])

Physical Data: mp 102-103 °C.

Solubility: sol benzene, diethyl ether, THF, DMF, ethanol, DMSO, acetone, cyclohexane, cumene, nitromethane, dichloromethane.

Form Supplied in: brown, air stable, crystalline solid.

Preparative Method: prepared in 67% yield by treating a benzene solution of dibromobis(triethylphosphine)nickel(II) with an ethereal solution of *o*-tolylmagnesium bromide.[2,5]

Purification: recrystallization from ethanol.

Handling, Storage, and Precautions: although no special precautions are reported, this complex is likely to be toxic, as with many nickel reagents.[6]

Biaryl Syntheses and Cross-Coupling Reactions.

As part of a study examining the syntheses of biaryls under nickel catalysis,[1] the title reagent (**1**) and other nickel(II) complexes were found to react with aryl halides to give biaryls via a radical chain process and were thus proposed as intermediates in nickel(0)-catalyzed Ullmann coupling reactions. The reactions of (**1**) are most efficiently conducted in a sealed, evacuated tube at 70 °C with a nonpolar organic solvent such as benzene or toluene. In a similar study (**1**) was found, upon treatment with ***Methyllithium*** and heating in hexanes, di-*n*-butyl ether, or 1,2-dimethoxyethane, to provide *o*-xylene, suggesting that nickel(II) species are intermediates in the cross coupling of Grignard reagents and aryl halides with nickel(0) reagents.[2]

Halogen Exchange with Aryl and Vinylic Halides.

A number of nickel complexes have been found to catalyze the substitution of aryl halides with nucleophiles such as amines, phosphines, and cyanide.[7] Reagent (**1**) is well suited for the exchange of aryl and vinyl halides with more electronegative halides (eqs 1-4). These reactions are most frequently carried out in refluxing benzene or THF in the presence of an appropriate ammonium halide salt.[1,3] In cases where *cis*- or *trans*-vinyl halides are used (eqs 3 and 4), no detectable isomerization is observed.

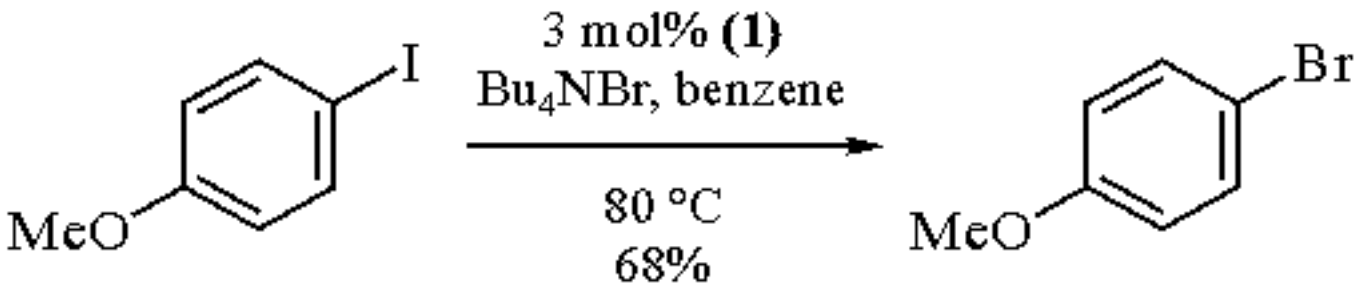

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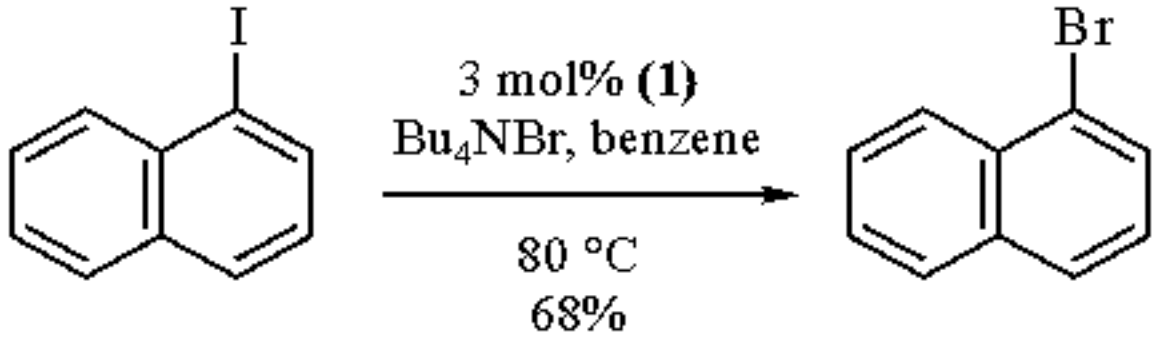

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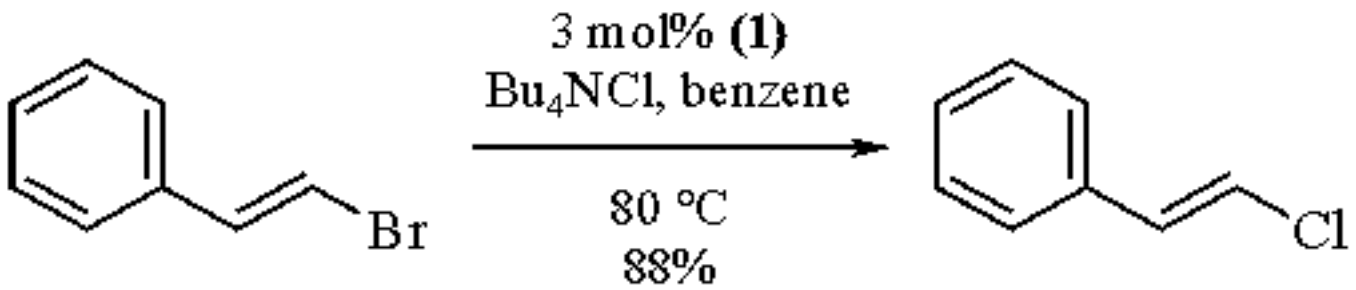

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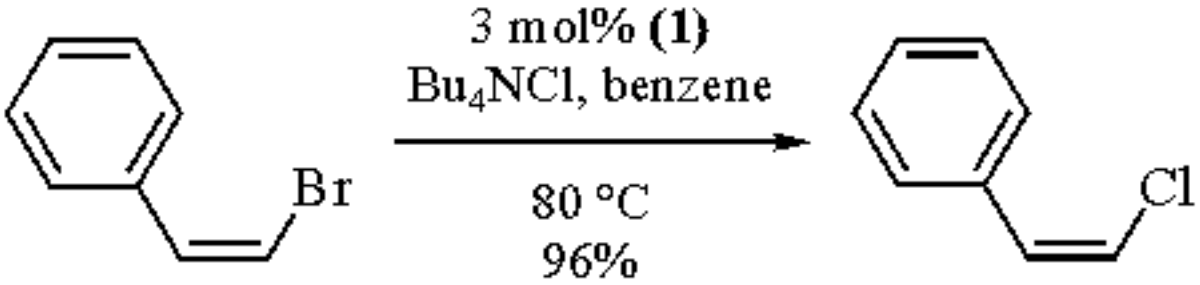

(4)

Oligomerization Reactions.

The cyclodimerization of butadiene to provide 2-methylenevinylcyclopentane (eq 5) is carried out quite efficiently with (**1**) and other nickel catalysts.[4] This process is best carried out at an elevated temperature in benzene in the presence of (**1**) and methanol. The use of protic reagents other than methanol leads to a diminished yield of 2-methylenevinylcyclopentane and the formation of other cyclodimerized products.

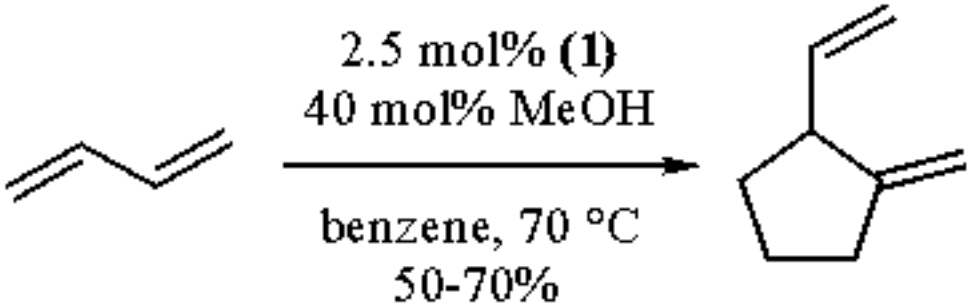

(5)

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5-Bromo-2,2,5-trimethyl-1,3-dioxane-4,6-dione

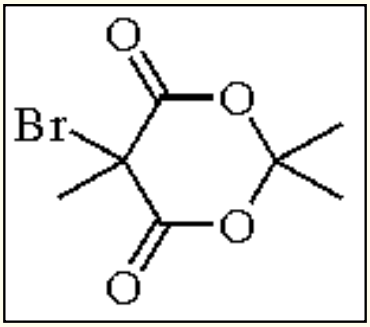

[34817-42-0] · $C_7H_9BrO_4$ · 5-Bromo-2,2,5-trimethyl-1,3-dioxane-4,6-dione · (MW 237.05)

(brominating agent;[1-4] transfer alkylating agent;[1] used to synthesize 1,2-diketones[5])

Physical Data: colorless crystalline solid, mp 86 °C.

Solubility: commonly used in THF solution.

Preparative Methods: by treating a chloroform solution of 2,2,5-trimethyl-1,3-dioxane-4,6-dione[6] with ***Bromine*** and anhydrous ***Sodium Fluoride***.

Purification: recrystallization from 2-propanol.

Handling, Storage, and Precautions: good laboratory practice should be sufficient when handling this reagent. The reagent is a relatively stable brominating agent and no special measures are required for its storage.

Bromination.

Addition of the anion of 3,3-dimethylthietane 1,1-dioxide (**1**) to a THF solution of the title reagent (**2**) afforded the bromo sulfone in good yield (eq 1).[2] Alternative reagents such as ***Bromine***, ***N-Bromosuccinimide***, and ***1-Chlorobenzotriazole*** did not effect the required transformation. Similarly, deprotonation of keto ester (**3**) and treatment with (**2**) afforded α-bromo ketone (**4**) stereoselectively. The addition of norbornene improved the efficiency of the reaction (eq 2).[3] Treatment of azlactone (**5**) with (**2**) in the presence of ***Potassium Carbonate*** afforded the corresponding unsaturated azlactone via bromination and concomitant dehydrobromination. Reagents such as bromine, ***Sulfuryl Chloride***, NBS, ***2-Pyrrolidone Hydrotribromide***, ***1,3-Dibromo-5,5-dimethylhydantoin***, and 1-chlorobenzotriazole were, however, more effective for this transformation (eq 3).[4]

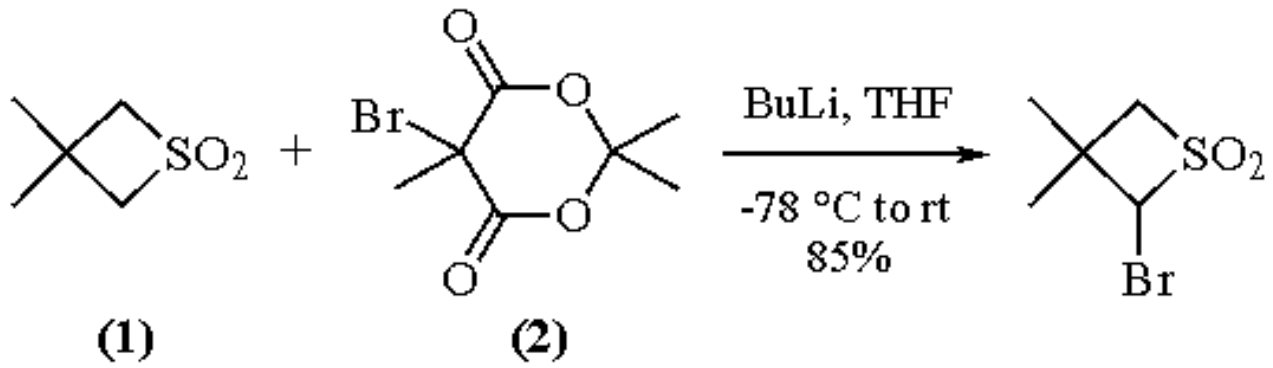

(1)

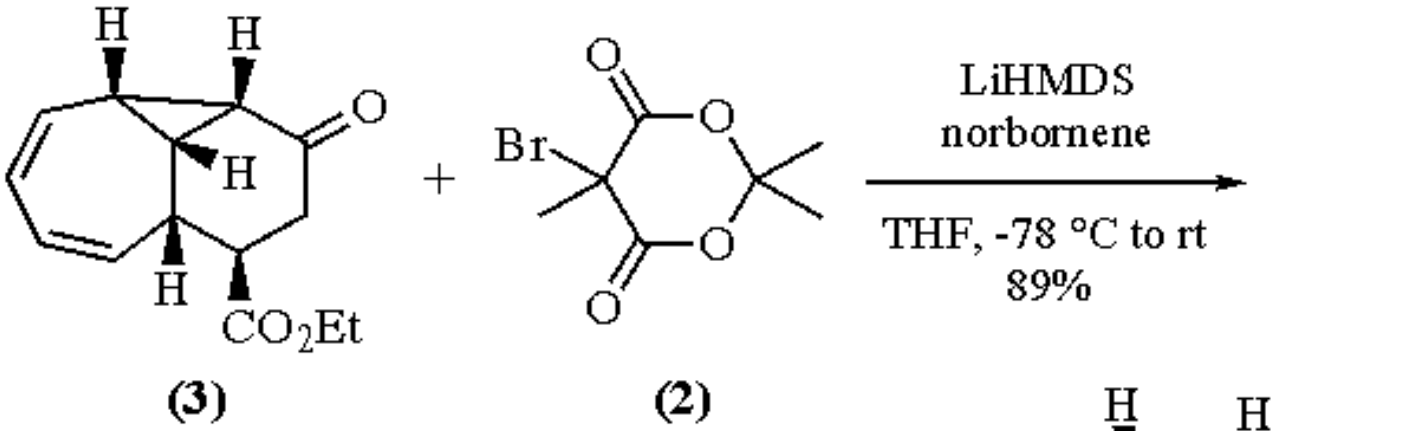

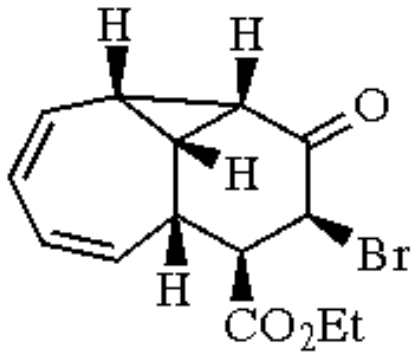

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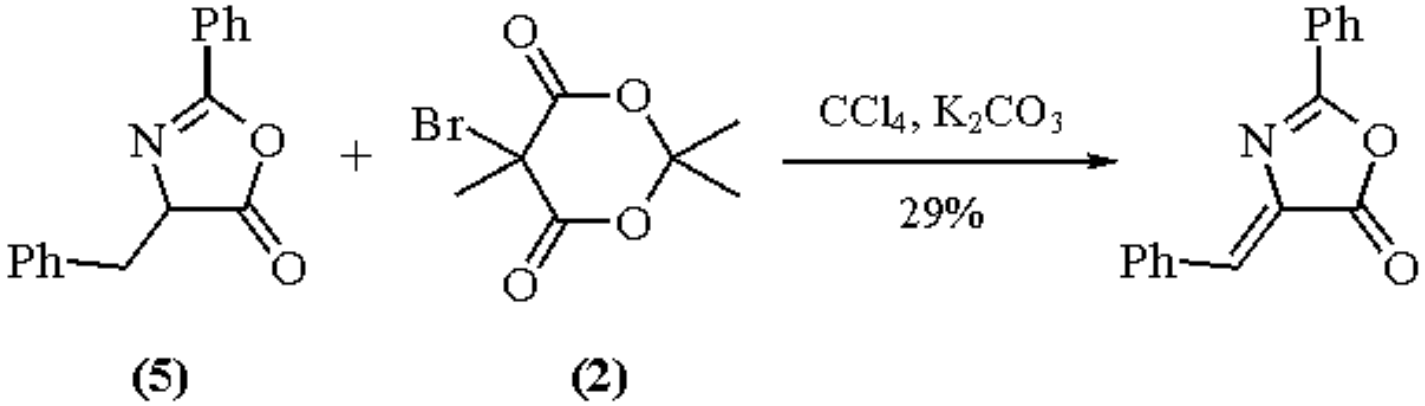

(3)

Transfer Alkylation.

Deprotonation of methyl 3-(methoxycarbonyl)-3,5-heptadienoate (**6**) with LDA in THF solution and treatment with (**2**)

resulted in α-bromination and precipitation of the corresponding lithium salt of (**2**). Subsequent introduction of HMPA effected dissolution of this salt and resulted in S_N2'' alkylation. The product of this reaction can be smoothly hydrolyzed and subsequently decarboxylated (eq 4).[1,2]

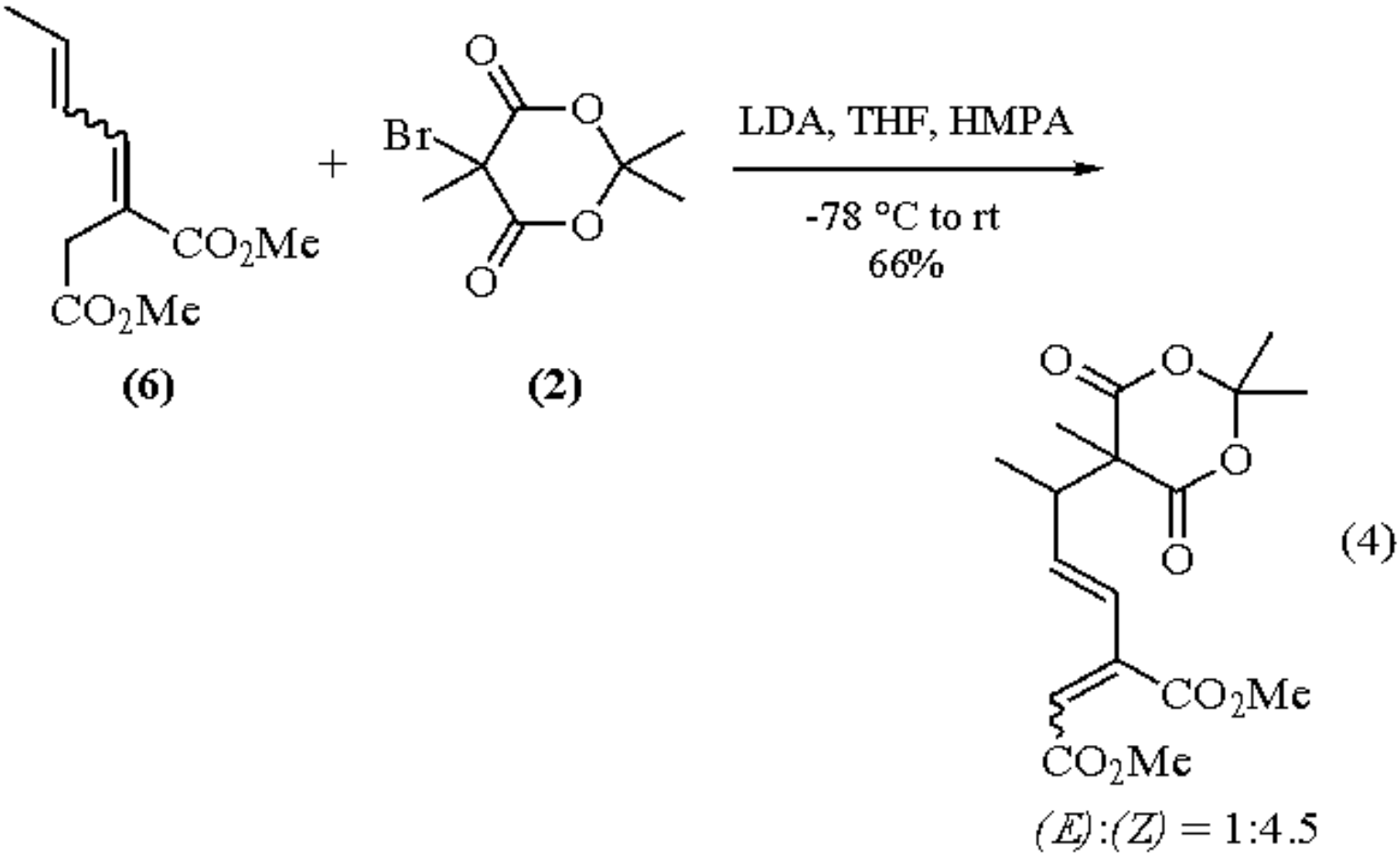

Diketone Synthesis.

Treatment of (**2**) with potassium acetate and subsequent pyrolysis has afforded butane-2,3-dione (eq 5).[5]

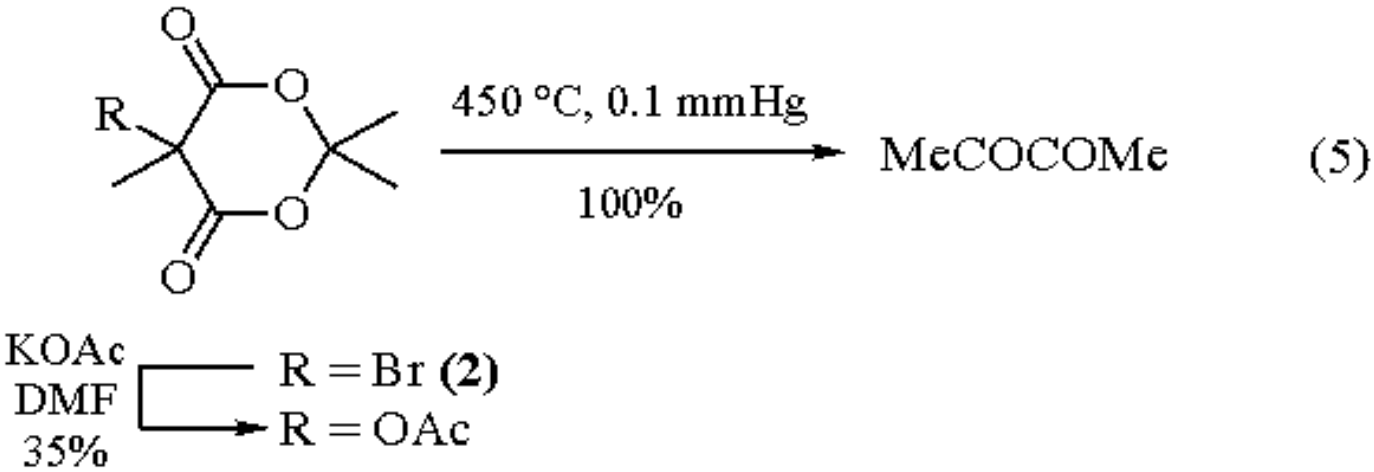

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Bromotrimethylsilane[1]

Me_3SiBr

[2857-97-8] · C_3H_9BrSi · Bromotrimethylsilane · (MW 153.09)

(mild and selective reagent for cleavage of lactones, epoxides, acetals, phosphonate esters and certain ethers; effective reagent for formation of silyl enol ethers; can function as brominating agent)

Alternate Name: TMS-Br.

Physical Data: bp 79 °C; *d* 1.188 g cm^{-3}; *n*20D 1.4240; fp 32 °C.

Solubility: sol CCl_4, $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, MeCN, toluene, hexanes; reactive with THF (ethers), alcohols, and somewhat reactive with EtOAc (esters).

Form Supplied in: colorless liquid, packaged in ampules.

Analysis of Reagent Purity: well characterized by ^1H, ^{13}C, and ^{29}Si NMR spectroscopy.

Preparative Methods: although many methods are reported,[1] only a few are provided here: ***Chlorotrimethylsilane*** undergoes halogen exchange with either ***Magnesium Bromide***[2] in Et_2O or ***Sodium Bromide***[3] in MeCN, which allows in situ reagent formation (eq 1); alternatively, ***Hexamethyldisilane*** reacts with ***Bromine*** in benzene solution or neat, to afford only TMS-Br with no byproducts (eq 2).[4] TMS-Br may also be generated by reaction of hexamethyldisiloxane and ***Aluminum Bromide*** (eq 3).[5] However, it should be noted that the reactivity of in situ generated reagent appears to depend upon the method of preparation.

$$Me_3SiCl \xrightarrow[\text{or NaBr, MeCN}]{MgBr_2,\ Et_2O} Me_3SiBr + LiBr \text{ or } NaBr \qquad (1)$$

$$Me_3Si\text{-}SiMe_3 + Br_2 \longrightarrow Me_3SiBr \qquad (2)$$

$$Me_3SiOSiMe_3 + AlBr_3 \longrightarrow Me_3SiBr \qquad (3)$$

Purification: by distillation.

Handling, Storage, and Precautions: extremely sensitive to light, air, and moisture; fumes in air due to hydrolysis (HBr), and becomes discolored upon prolonged storage (free Br_2).

Ester Cleavage.[6]

Although esters are readily cleaved with ***Iodotrimethylsilane***, reaction of esters with TMS-Br under similar conditions gives somewhat lower yields of silyl esters or acids upon hydrolysis (eq 4). Lactones, however, react with TMS-Br at 100 °C to afford o-bromocarboxylic acids after hydrolysis of the silyl ester (eq 5).[7]

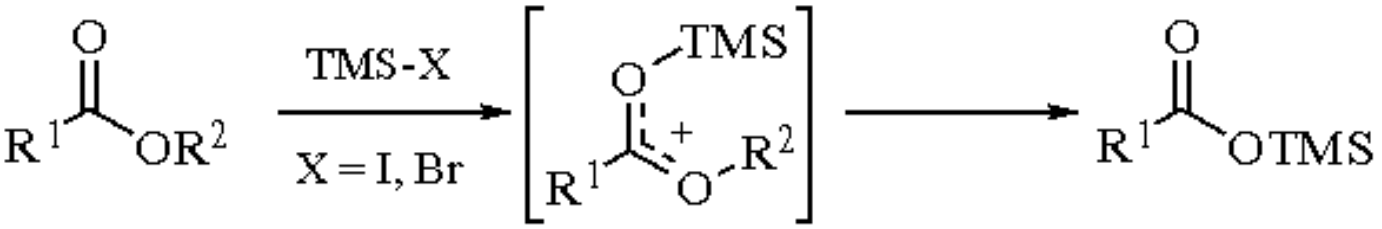

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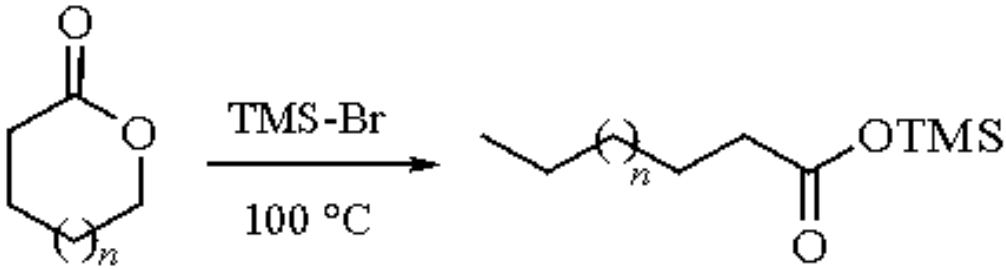

(5)

Ether Cleavage.

THF[8] reacts with TMS-Br, thereby rendering ethereal solvents incompatible with the reagent. Smooth removal of the methoxymethyl (MOM) protecting group can be accomplished with TMS-Br at 0 °C (eq 6).[9] Whereas acetals, THP and silyl ethers are slowly cleaved with TMS-Br, the reagent generated in situ effects selective MOM ether cleavage in the presence of an acetonide.[10] The majority of published ether cleavages have been accomplished with TMS-I, although limited data show that the more vigorous conditions necessary for ethyl ether cleavage also result in bromide formation.[8]

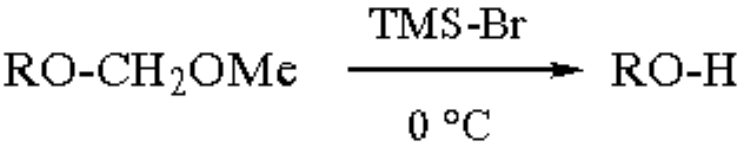

(6)

Cleavage of Epoxides.

Epoxide opening with TMS-Br occurs to provide the primary alkyl bromide at -60 °C (eq 7).[8]

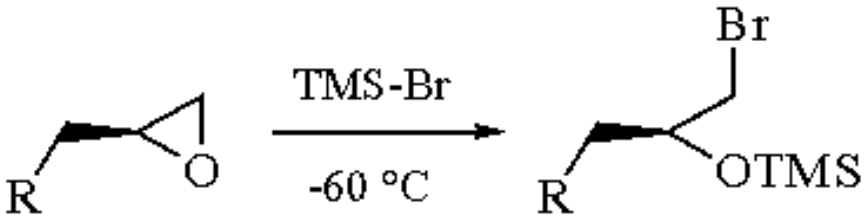

(7)

Cleavage of Acetals.

Acetals can be cleaved by analogy to ethers, providing the parent carbonyl species.[3c,6b] Glycosyl bromides have been prepared from the corresponding acetate by reaction with TMS-Br in $CHCl_3$ at rt (eq 8).[11] In conjunction with $CoBr_2$ and ***Tetra-n-butylammonium Bromide***, TMS-Br converts the glucopyranose to the α-D-glucoside in the presence of an alcohol (eq 9).[12]

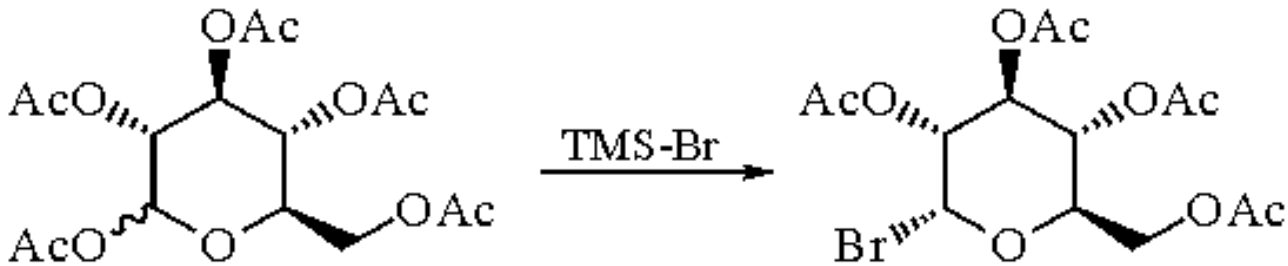

(8)

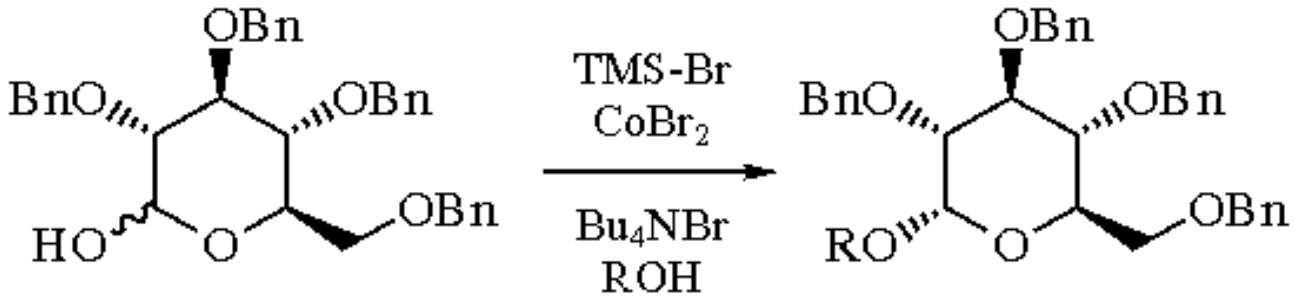

(9)

An interesting solvent effect was noted in the cleavage of the acetonide moiety in some nucleoside derivatives (eq 10).[13] In CH_2Cl_2, TMS-Br converted the acetonide to the anhydrouridine within 1.5 h, but in MeCN the bromide is formed after 10 min.

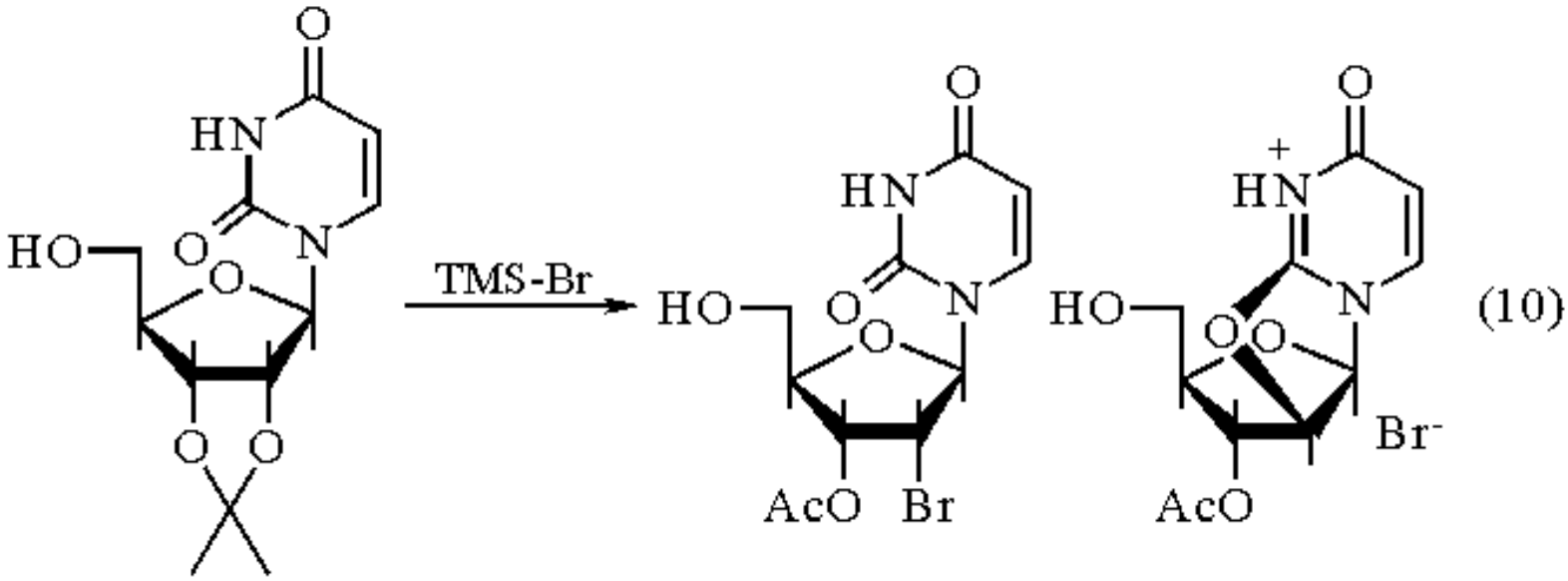

Formation of Enol Ethers.[14]

Bromotrimethylsilane with ***Triethylamine*** in DMF is an effective medium for production of thermodynamic (*Z*) silyl enol ethers (eq 11).

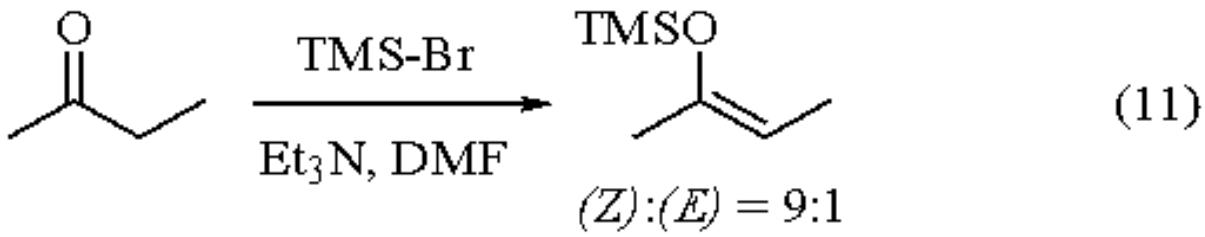

Formation of Alkyl Bromides.[6b]

Alcohols react with excess TMS-Br (1.5-4 equiv) at 25-50 °C to form the alkyl bromide and hexamethyldisiloxane (eq 12). Benzylic and tertiary alcohols react faster than secondary alcohols.

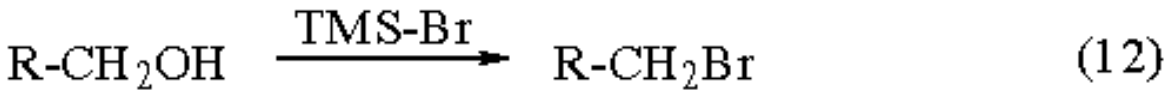

Reaction with Acid Chlorides.[15]

Acid bromides may be prepared from acid chlorides by reaction with TMS-Br (eq 13).

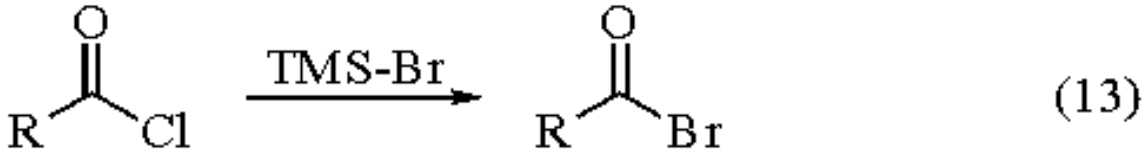

Cleavage of Phosphonate Esters.[16]

Compared to the reactivity of TMS-I with phosphonate and phosphate esters, TMS-Br is more selective and will cleave phosphonate esters even in the presence of carboxylic esters and carbamates. Benzyl ester protecting groups on aryl phosphates are selectively removed with TMS-Br.[17] The reaction of phosphonate esters with TMS-Br proceeds through a mechanism similar to ester cleavage, providing a silyl ester which is subsequently hydrolyzed with MeOH or H_2O (eq 14).

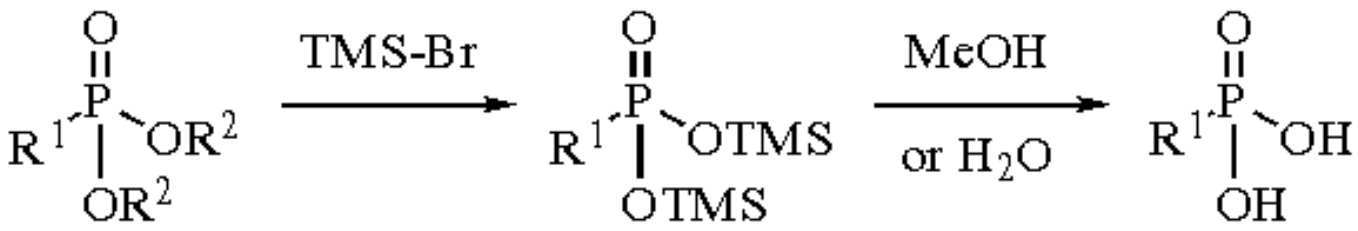

(14)

Reaction with Amines.

Amines react with TMS-Br to form isolable adducts, which react readily with ketones to form enamines under mild conditions (eq 15).[18]

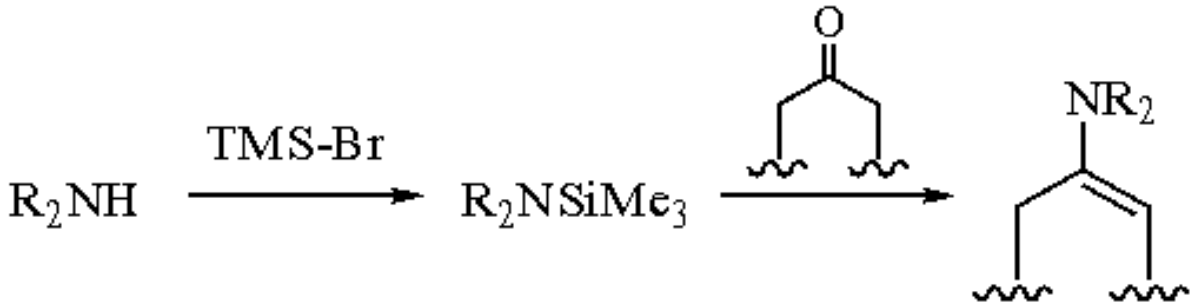

(15)

Conjugate Addition.

α,β-Unsaturated ketones undergo conjugate addition with TMS-Br. Treatment of the intermediate with ***p-Toluenesulfonic Acid*** and ethylene glycol provides β-bromoethyldioxolanes (eq 16).[19]

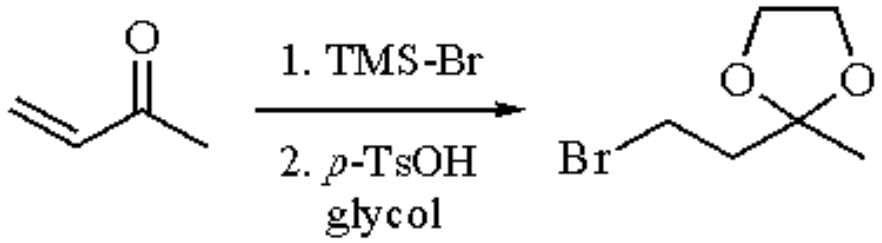

(16)

Bromolactonization.

o-Unsaturated carboxylic acids react with TMS-Br in the presence of a tertiary amine in DMSO yielding bromolactones, resulting from *cis* addition across the double bond (eq 17).[20]

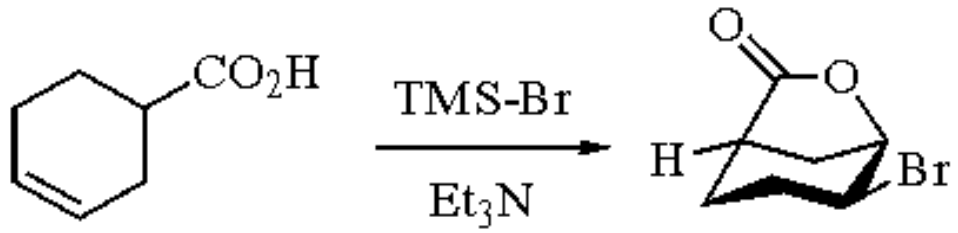

(17)

Ylide Formation.

Methylenetriphenylphosphorane reacts with TMS-Br to provide the corresponding ylide (eq 18).[21]

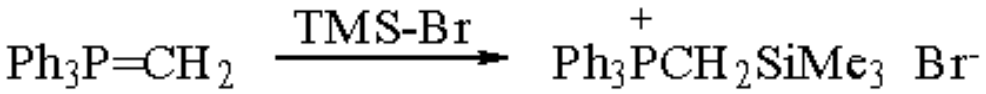

(18)

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(*Z*)-2-Bromo-1-(trimethylsilyloxy)ethylene

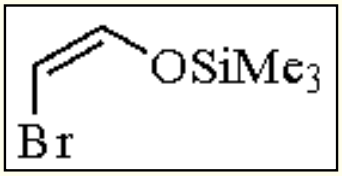

[64556-66-7] · $C_5H_{11}BrOSi$ · (*Z*)-2-Bromo-1-(trimethylsilyloxy)ethylene · (MW 195.13)

(reagent used as a precursor of (*Z*)-(trimethylsilyloxy)vinyllithium, α-bromo aldehydes, and α-disilylketene)

Physical Data: bp 48-49 °C/15 mmHg.[1]

Solubility: sol Et_2O, THF and most organic solvents; fairly sol cold water.

Analysis of Reagent Purity: ^1H NMR (C_6D_6) (*Z*) isomer: 6.37 (d; *J* = 3.8); 5.02 (d; *J* = 3.8); 0.05 (s). (*E*) isomer: 6.61 (d; *J* = 11.4); 5.52 (d; *J* = 11.4); -0.06 (s).

Preparative Methods: addition of ***Bromine*** to trimethylsilyl vinyl ether in CH_2Cl_2 or Et_2O at -60 °C, followed by dehydrobromination with ***Triethylamine*** (50%)[1] or by reaction of trimethylsilyl 2,2-dibromoethyl ether with two equiv of ***n-Butyllithium*** in Et_2O from -70 °C to rt (86%)[2] (*Z*/*E*:95/5).[3]

Purification: vacuum distillation.

Handling, Storage, and Precautions: must be stored at -20 °C in the absence of moisture (flushing with dry Ar or N_2). It turns pale yellow on storage. It is instantaneously hydrolyzed by dilute acidic aqueous solutions.

(*Z*)-2-Bromo-1-(trimethylsilyloxy)ethylene (**1**) is used essentially as a precursor of ***(Z)-2-(Trimethylsilyloxy)vinyllithium*** (eq 1).[3]

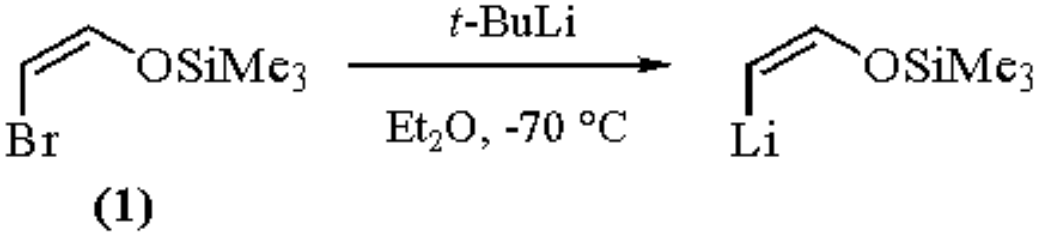

(1)

(Z)-2-Bromo-1-(trimethylsilyloxy)ethylene

Reagent (**1**) has been condensed with allylic alcohols in the presence of a catalytic quantity of a Lewis acid (such as ***Boron Trifluoride Etherate***) to achieve a new synthesis of α,β-unsaturated aldehydes (eq 2).[4] This reaction is analogous to the widely used Müller-Cunradi-Pieroh reaction[5] except that the oxidation state of the cationic species is one unit lower and that of the nucleophilic species is one unit higher. Thus condensation with β-ionol leads to an α-bromo aldehyde which was transformed into β-ionylideneacetaldehyde by dehydrobromination, using ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.[4]

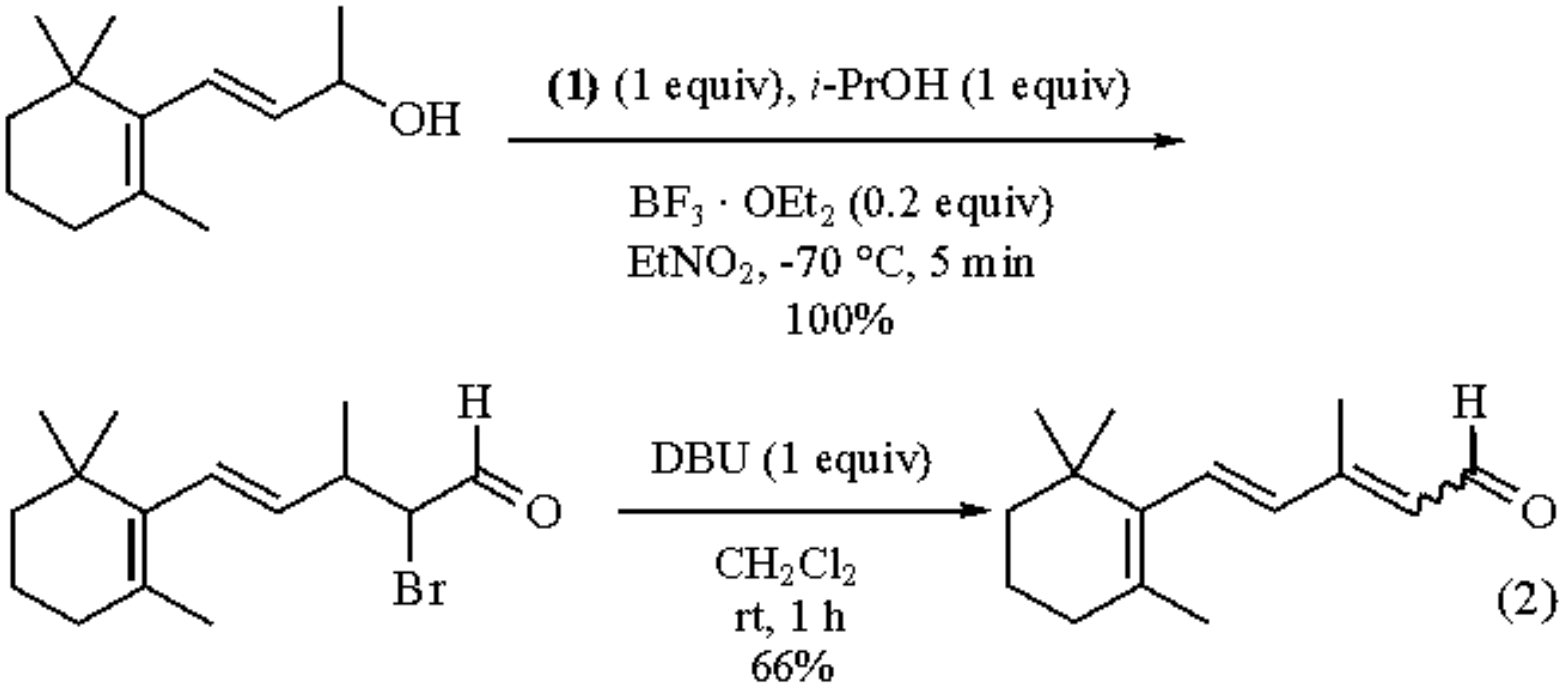

(2)

The reaction of (**1**) with ***Lithium Diisopropylamide*** followed by treatment with ***Chlorodimethylsilane*** was reported to give the disilylketene (**2**) in a modest yield,[6] instead of the expected alkynic ether (**3**) (eq 3).[2] The hydridosilylketene (**2**) is transformed by flash vacuum thermolysis (FVT) to trimethylsilylacetylene by expulsion of dimethylsilanone.[6]

(Z)-2-Bromo-1-(trimethylsilyloxy)ethylene

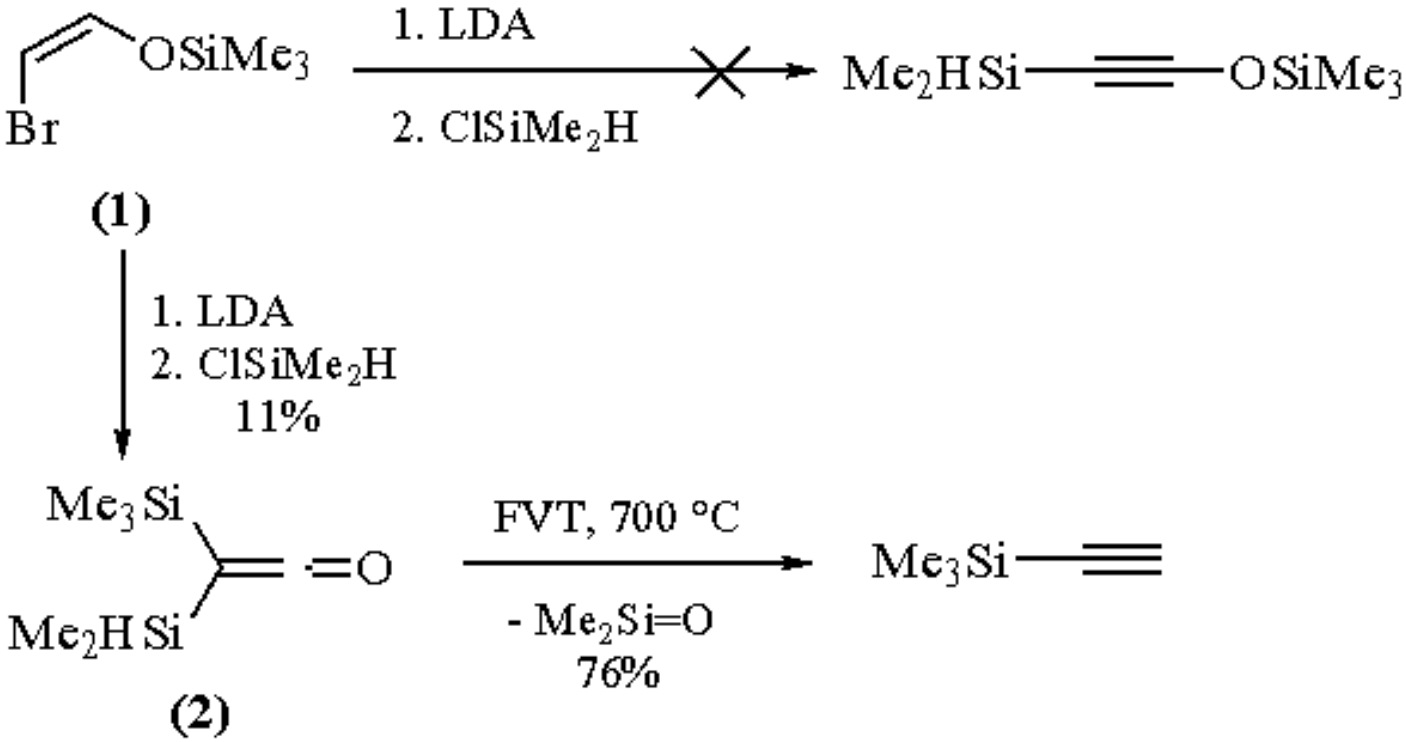

(3)

It is noteworthy that compounds homologous with (**1**) couple with Grignard reagents in the presence of nickel-phosphine complexes to produce alkylated and arylated enol ethers (eq 4).[7]

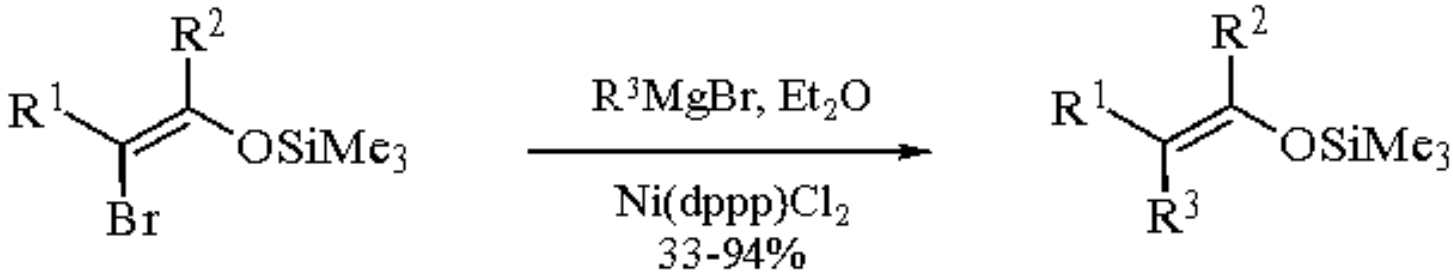

(4)

$R^1, R^2 = H$, alkyl, aryl; $R^3 =$ alkyl, aryl

---

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4. (a) Ancel, J. E.; Bienaymé, H.; Duhamel, L.; Duhamel, P.; Fr. Patent **1991**, 14 699; Eur. Patent **1991**, 544 588 (*CA* **1993**, *119*, 271 443v). (b) Duhamel, L.; Duhamel, P.; Ancel, J. E. *TL* **1994**, *35*, 1209.
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7. Tamao, K.; Zembayashi, M.; Kumada, M. *CL* **1976**, 1239.

Lucette Duhamel

2-Bromo-3-trimethylsilyl-1-propene

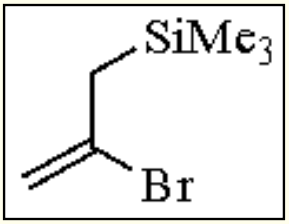

[81790-10-5] · $C_6H_{13}BrSi$ · 2-Bromo-3-trimethylsilyl-1-propene · (MW 193.16)

(synthon for CH_2=-CCH_2TMS[1-3] and CH_2=CBr-CH_2;[2] for synthesis of 1-trimethylsilylmethyl-substituted 1,3-butadienes[4])

Alternate Name: 2-bromoallyltrimethylsilane.

Physical Data: bp 46-50 °C/20 mmHg,[3] 64-65 °C/38-39 mmHg.[1]

Solubility: sol alcohol, acetone, ether, THF, pentane; insol water.

Preparative Methods: (1) reaction of ***2,3-Dibromopropene*** with lithium (trimethylsilyl)cuprate in HMPA at 0 °C (63-90%);[3,5] (2) reaction of 2,3-dibromopropene with ***Trichlorosilane*** in the presence of ***Triethylamine*** and ***Copper(I) Chloride***, followed by treatment with ***Methylmagnesium Bromide*** (63-71%).[1,3,6]

Handling, Storage, and Precautions: no special requirements, except refrigeration in a brown bottle is recommended for long-term storage.

Synthon for CH_2=-CCH_2TMS.

The 1-trimethylsilylmethylvinyl anion CH_2=C(M)CH_2TMS (**2**) (M = Li, Mg, Cu, etc.), readily prepared from 2-bromo-3-trimethylsilyl-1-propene (**1**) under typical conditions, allows the introduction of the synthetically useful 1-trimethylsilylmethylvinyl group to a wide variety of substrates. Ring opening of 1-butene oxide with the Grignard reagent (**2**) (M = MgBr) in the presence of ***Copper(I) Iodide*** gives only one regioisomer. Subsequent desilylative oxidation of this allyl alcohol to α-methylene-γ-lactones provides further utility of (**1**) as a 1-hydroxymethylvinyl anion equivalent, i.e. CH_2=-CCH_2OH (eq 1).[1] Alternatively, the alcohol from *trans*-2,3-epoxybutane provides a route to the unstable six-membered β,γ-unsaturated lactone (eq 2).[7] The copper-catalyzed 1,4-addition to the typically unreactive mesityl oxide proceeds smoothly. The versatility of the allylsilane moiety is again illustrated in the ***Ethylaluminum Dichloride***-induced cyclization of the adduct to a tertiary cyclopentanol in high yield (eq 3).[2]

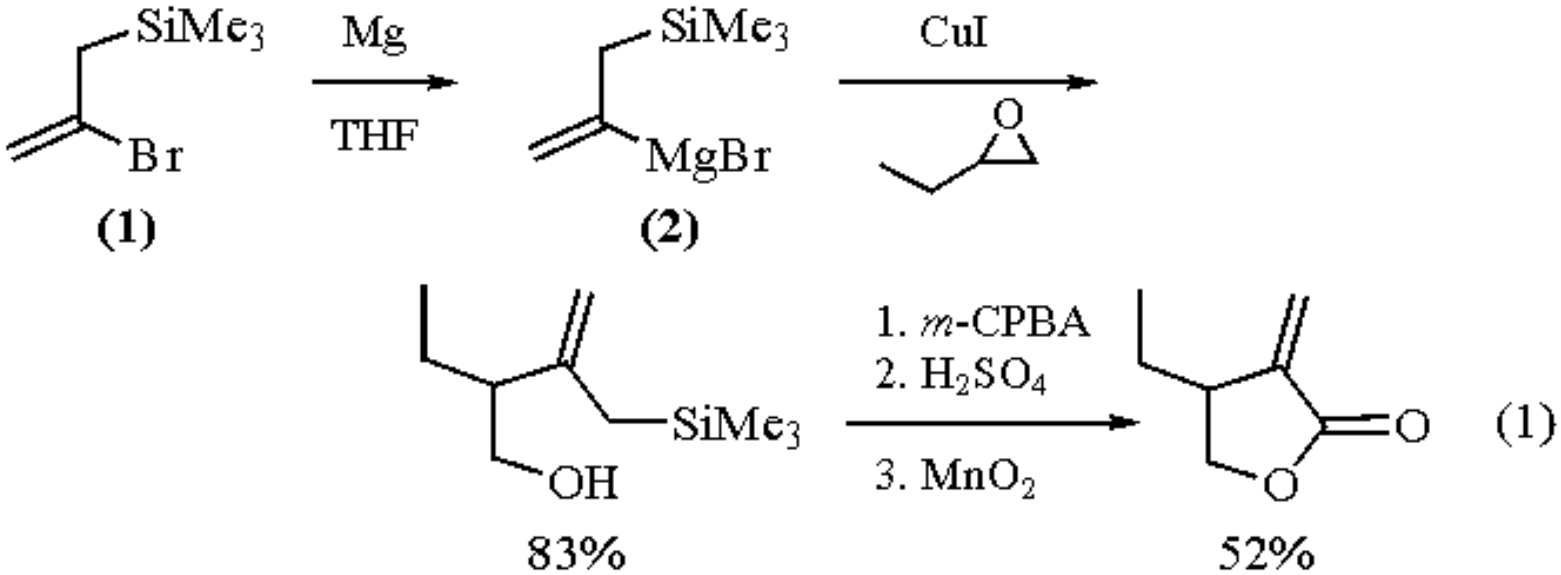

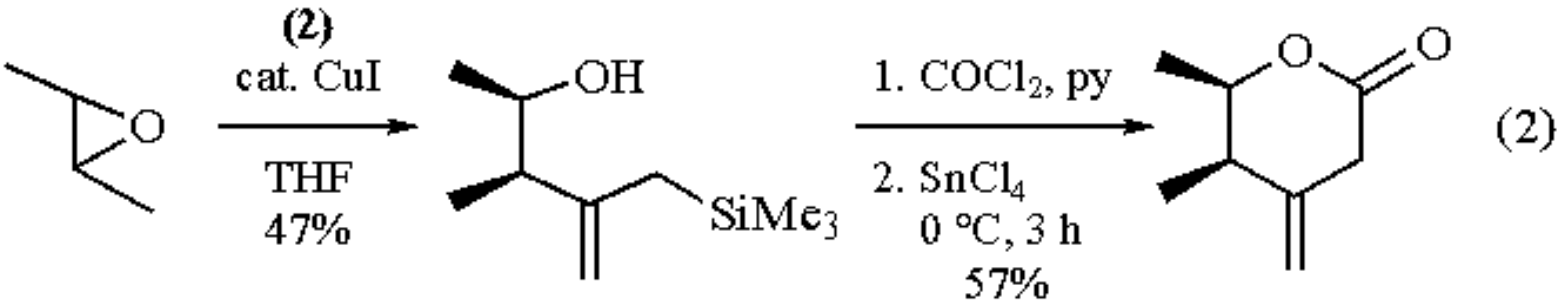

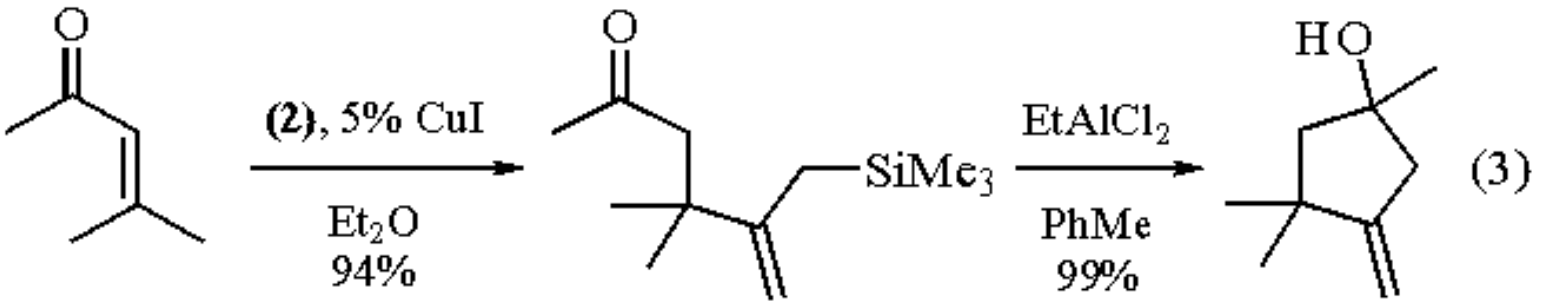

Addition of (**2**) to α,o-substituted aldehydes and ketones is an efficient entry to inter- and intramolecular [3 + 2] cycloaddition approaches to methylenecyclopentanes.[8] For example, chemoselective addition of the Grignard reagent (**2**) to the aldehyde (**3**), followed by acetylation and treatment with a palladium(0) catalyst, gives a bicyclo[3.3.0]octane (eq 4).[3] Similarly, the ketosulfone (**5**), which derives from the lithium reagent (**2**) (M = Li) and the ketodithiane (**4**), cyclizes to the perhydroindanone system (eq 5).[9] This methodology has also been extended to the synthesis of methylenetetrahydrofurans, e.g. in the formation of the phyllanthocin ring system (eq 6).[10] Lewis acid-mediated cycloadditions, both inter- and intramolecular, have also been developed.[11,12] An intermolecular case which generates the zizaene skeleton is depicted in eq 7.[11]

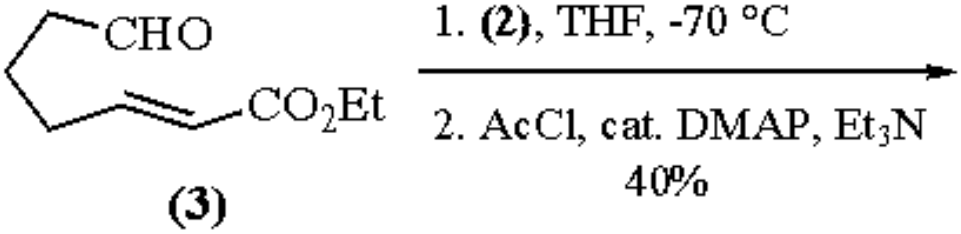
CHO
CO2Et
1. (2), THF, -70 °C
2. AcCl, cat. DMAP, Et3N
40%

(3)

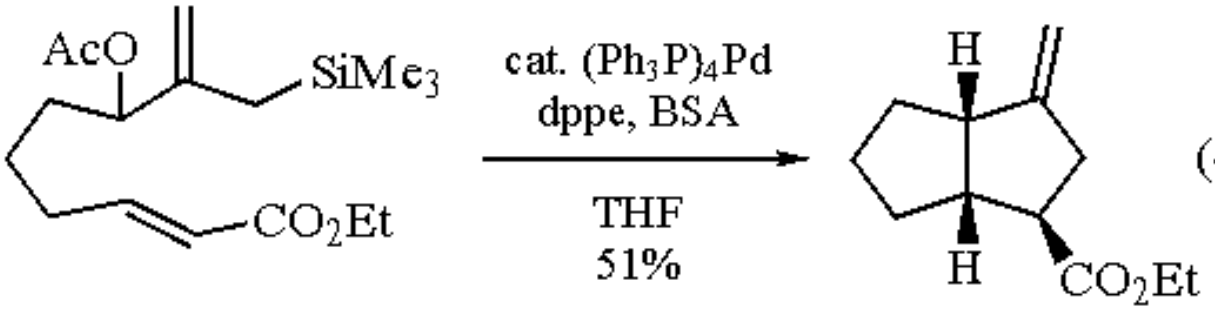
AcO
SiMe3
CO2Et
cat. (Ph3P)4Pd
dppe, BSA
THF
51%
H
H
CO2Et

(4)

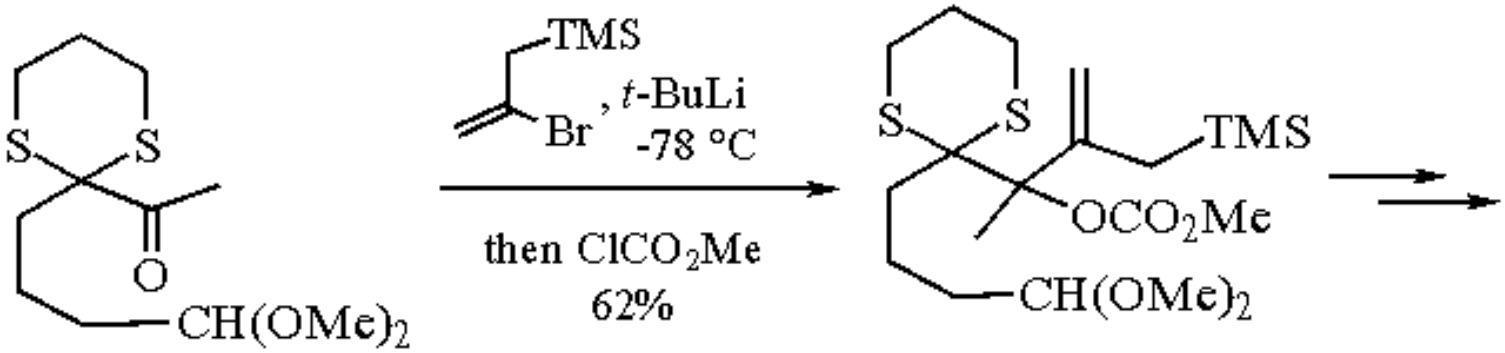
S
S
O
CH(OMe)2
TMS
Br
, t-BuLi
-78 °C
then ClCO2Me
62%
S
S
TMS
OCO2Me
CH(OMe)2

(4)

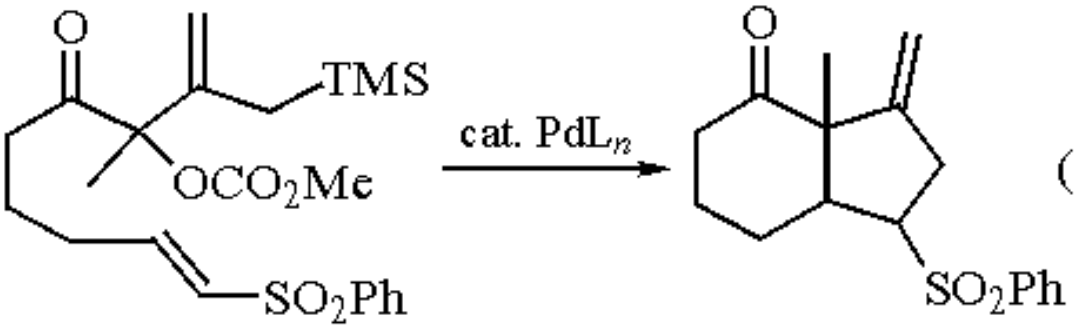
O
TMS
OCO2Me
SO2Ph
cat. PdLn
O
SO2Ph

(5)

(5)

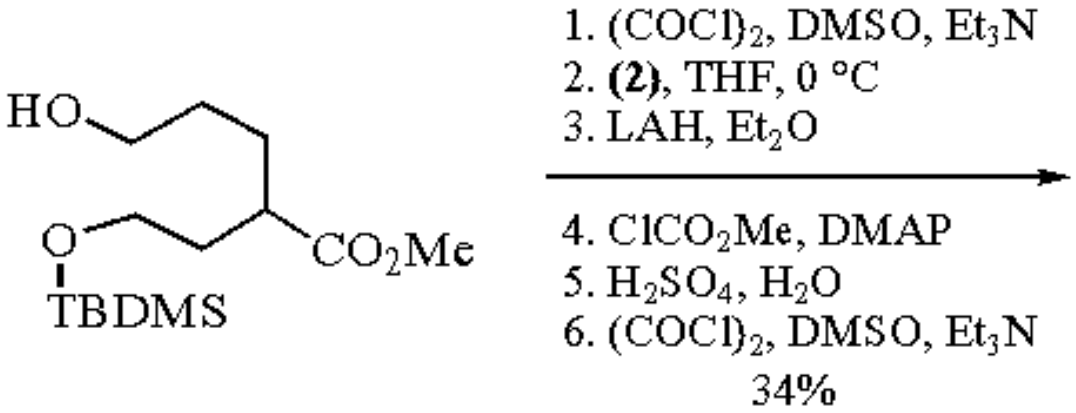

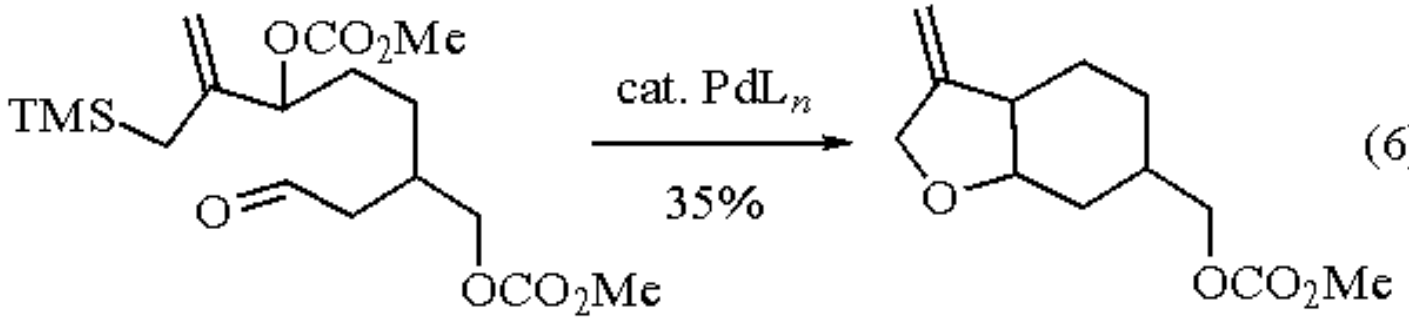

(6)

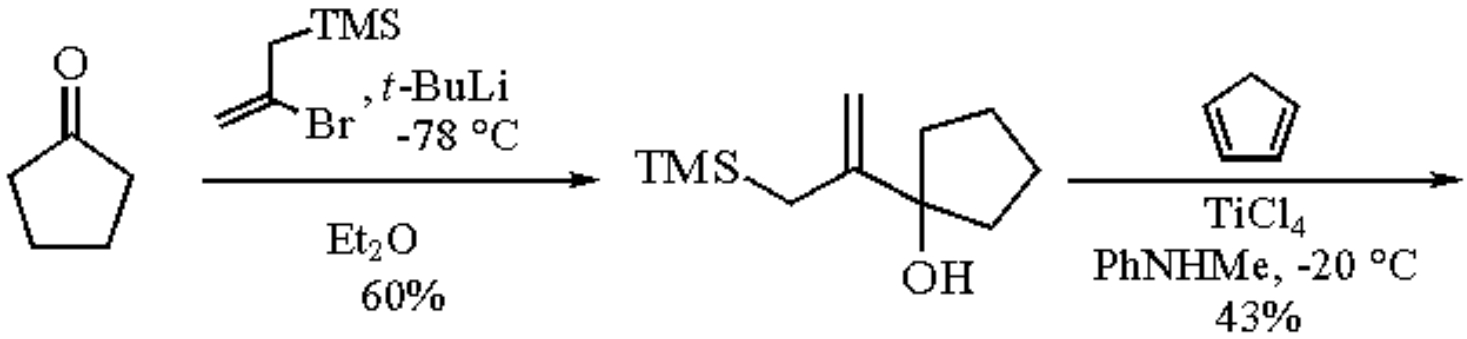

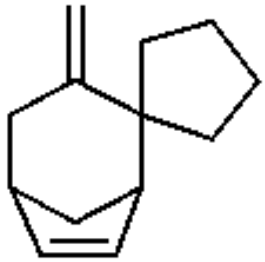

(7)

The tin analog of (**2**) (M = Me_3Sn) undergoes smooth coupling with various aryl bromides and acyl chlorides to produce 2-substituted allylsilanes (eq 8).[13] Interestingly, the organozinc reagent (**2**) (M = ZnCl) has been shown to equilibrate to the allyl isomer (**6**) and react as such with electrophiles to produce vinylsilanes.[14a] However, it is possible in some cases to control the product distribution with the choice of catalyst (eq 9).[14b]

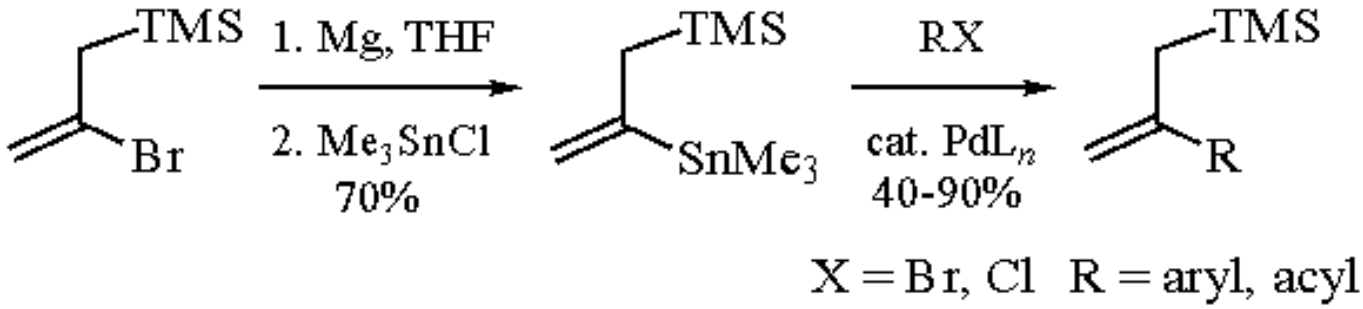

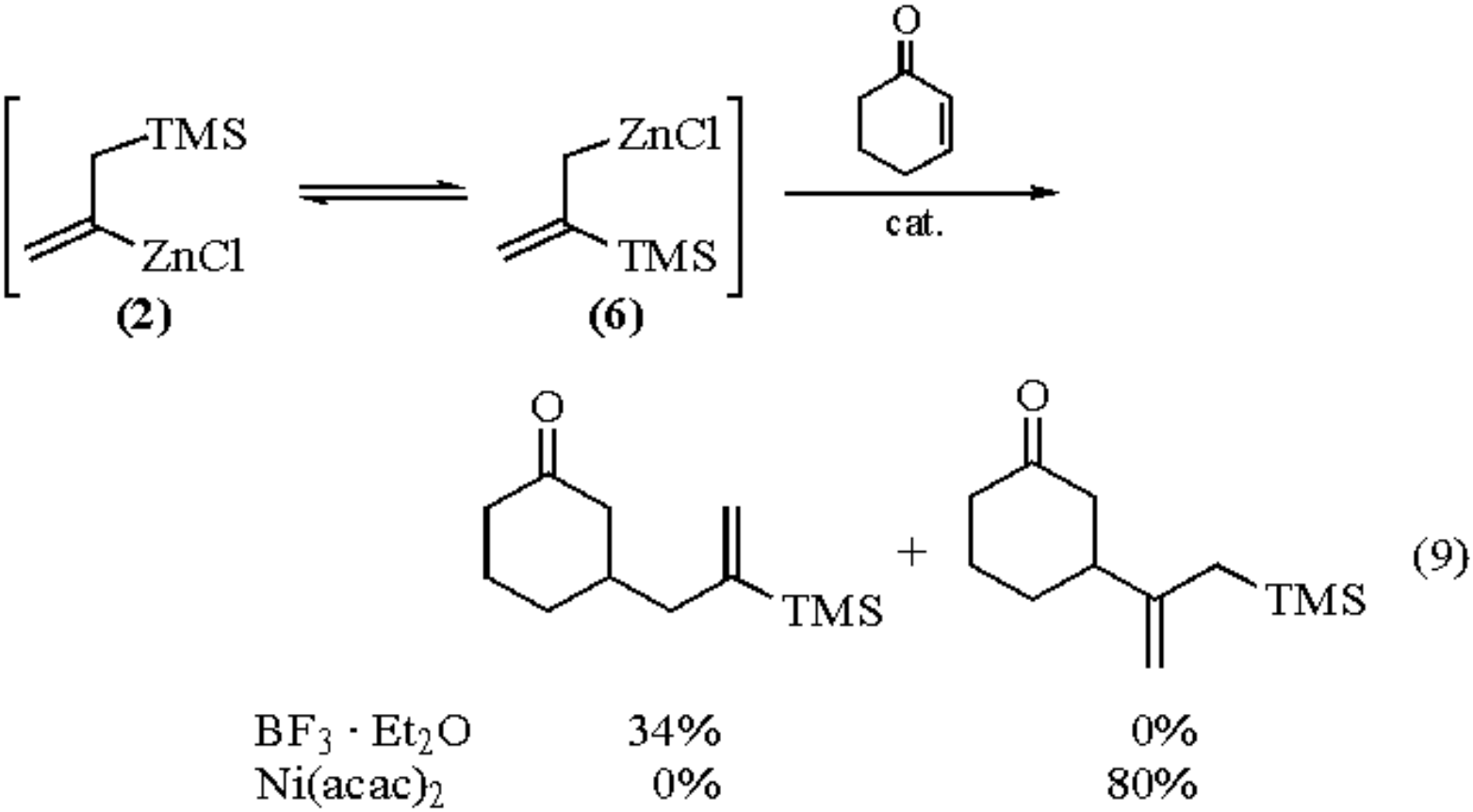

Synthon for CH_2=CBr-CH_2.

Lewis acid-mediated addition of the silyl bromide (**1**) to electrophiles provides a convenient way to introduce the CH_2=$CBrCH_2$ moiety. In the case of carbonyl substrates, aldehydes react well while aliphatic ketones require higher concentration and aromatic ketones fail to participate. High stereoselectivity is achieved in many cases, e.g. in the addition to aldehyde (**7**). The subsequent conversion of the adduct by carbonylation to a α-methylene-γ-butyrolactone illustrates the synthetic versatility of the vinyl bromide unit (eq 10).[2] Conjugate addition to enones has also been demonstrated.[2,15] In the case of 1-acetylcyclopentene, intramolecular Barbier reaction of the *cis* isomer of the adduct gives an excellent yield of the cyclopentanol (eq 11).[2] Thus by combining the nucleophilic properties of the allylsilane with the ability to effect transmetalation of the vinyl bromide unit, the silyl bromide can serve also as a synthon for CH_2=-C--CH_2. Furthermore, the vinyl bromide moiety can be a source of a vinyl radical. The synthesis of a propellane ring skeleton is made possible using this strategy (eq 12).[16]

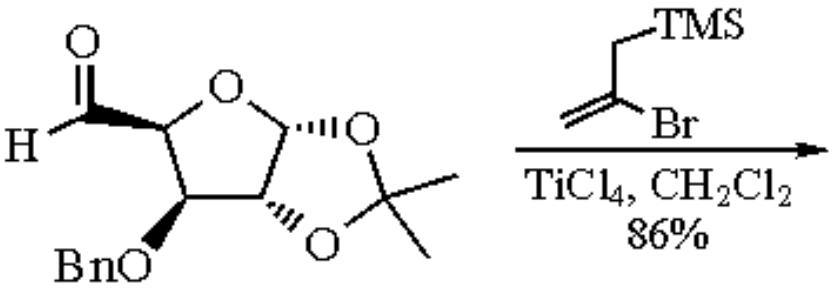

(7)

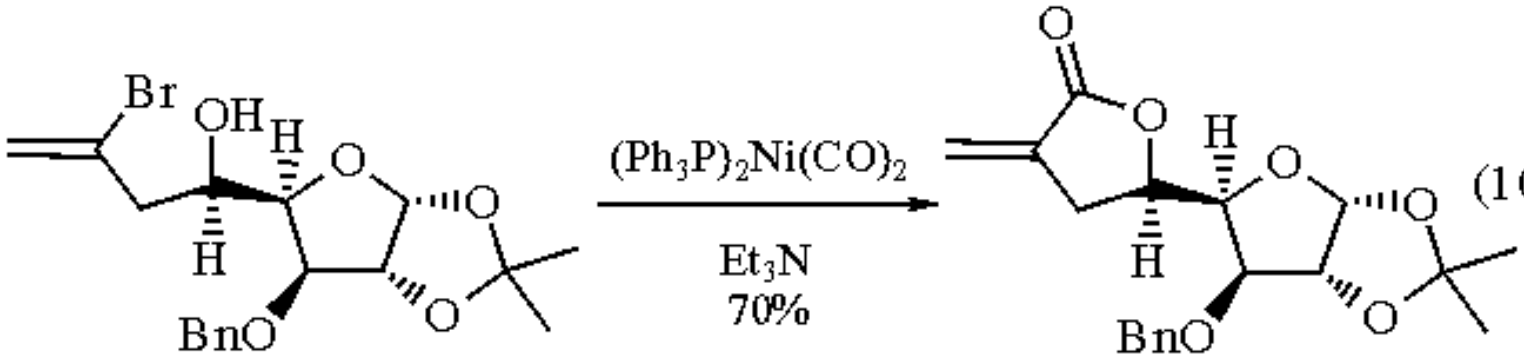

(10)

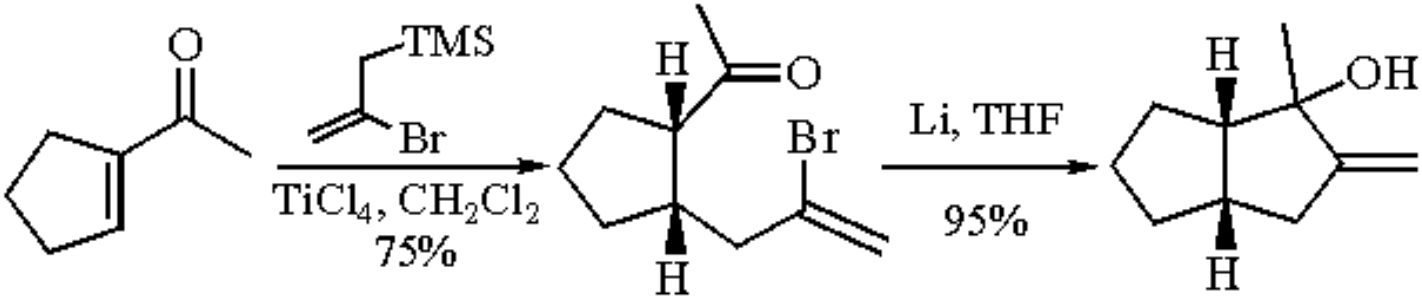

(11)

+ *trans* isomer

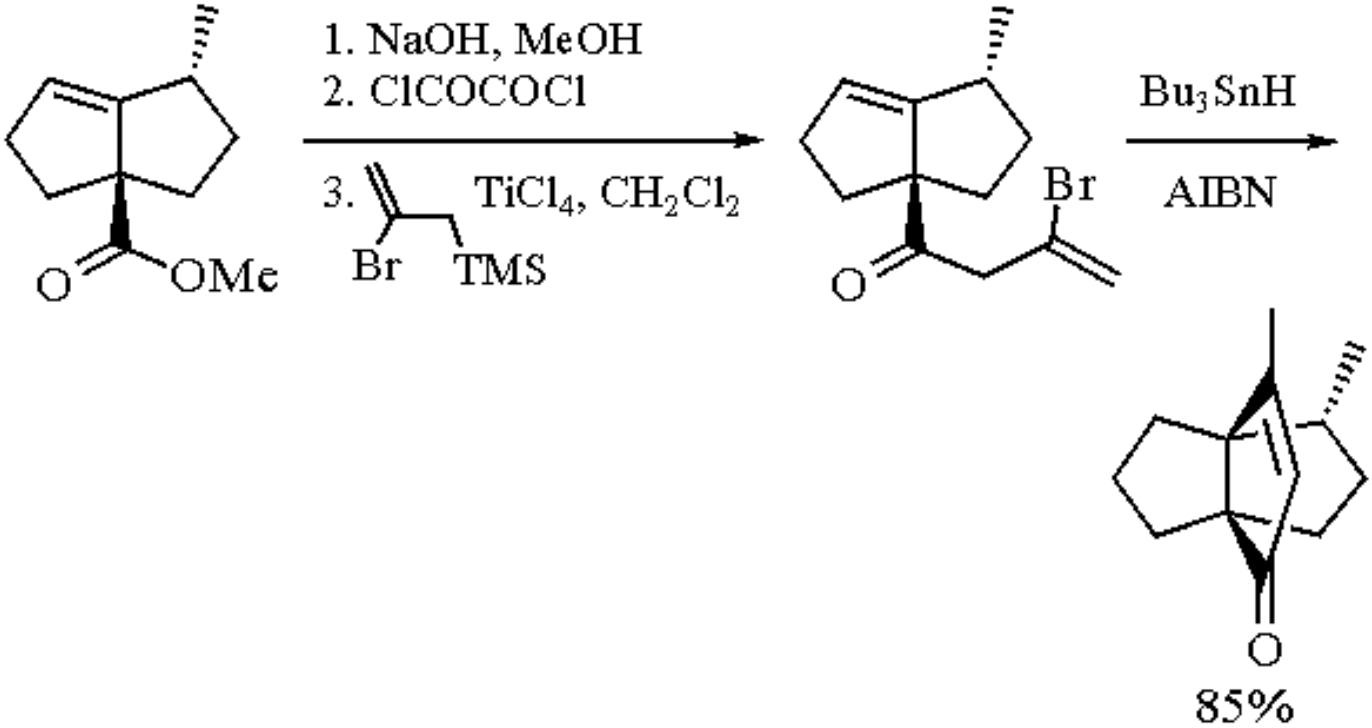

(12)

85%

Under Lewis acidic conditions, the silyl bromide (**1**) and α,α´-dimethoxylated amides undergo a [3 + 3] type annulation which is useful for the construction of the piperidine skeleton (eq 13).[17] The silyl bromide (**1**) is also an excellent reagent for the stereoselective introduction of a functionalized allyl group at the anomeric center of the glucosides (eq 14).[6,18]

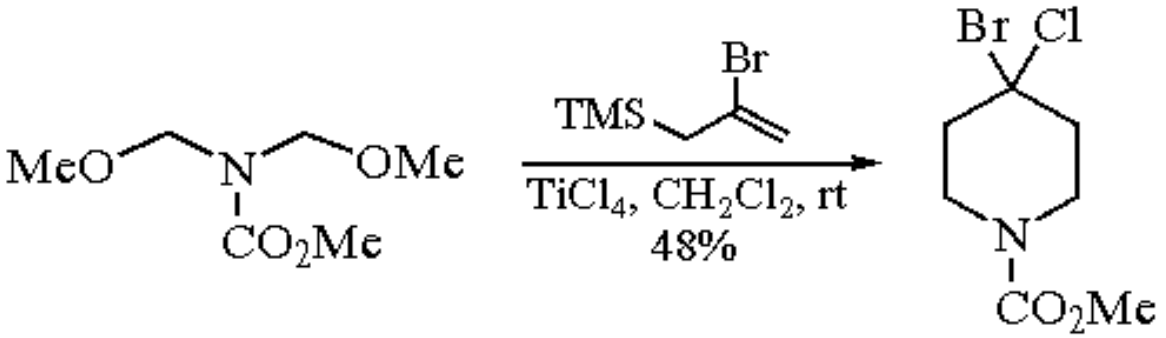

(13)

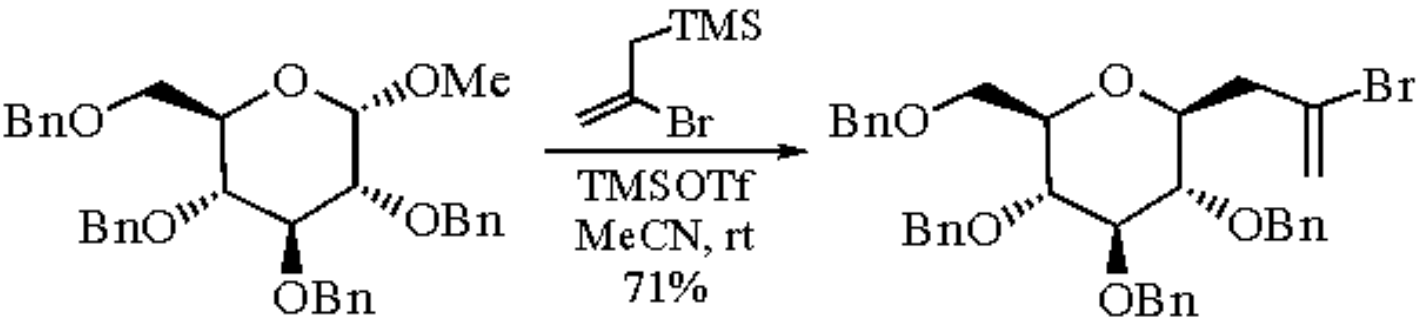

(14)

Coupling Reactions to Dienes and Enynes.

The silyl bromide (**1**) participates readily in copper or transition metal-mediated coupling reactions to produce 1,3-butadienes, which are very useful synthetic intermediates. For example, 2,3-bis[(trimethylsilyl)methyl]-1,3-butadiene (**8**), derived from the oxidative dimerization of cuprate (**2**) (M = Cu) is useful for rapid construction of multicyclic systems via tandem Diels-Alder reactions, as depicted in eq 15.[19] The diene 2-dimethylaminomethyl-3-trimethylsilylmethyl-1,3-butadiene (**9**) functions similarly in the synthesis of a [6,7] ring system (eq 16).[20]

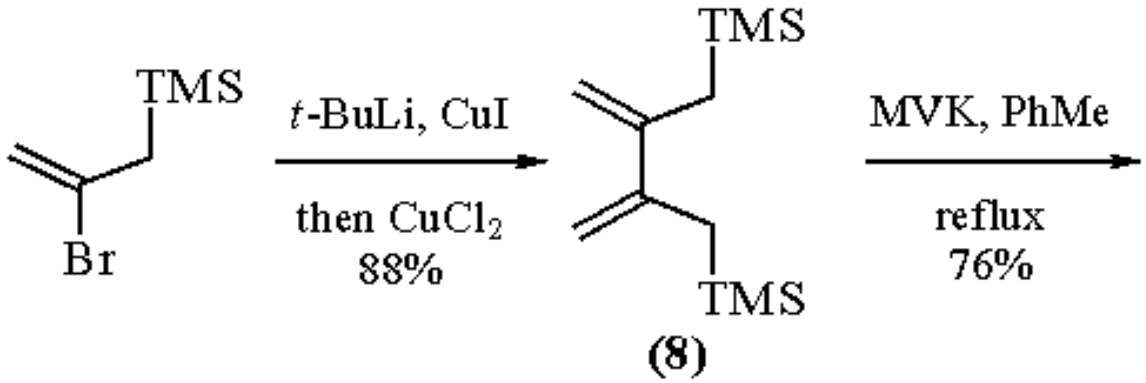

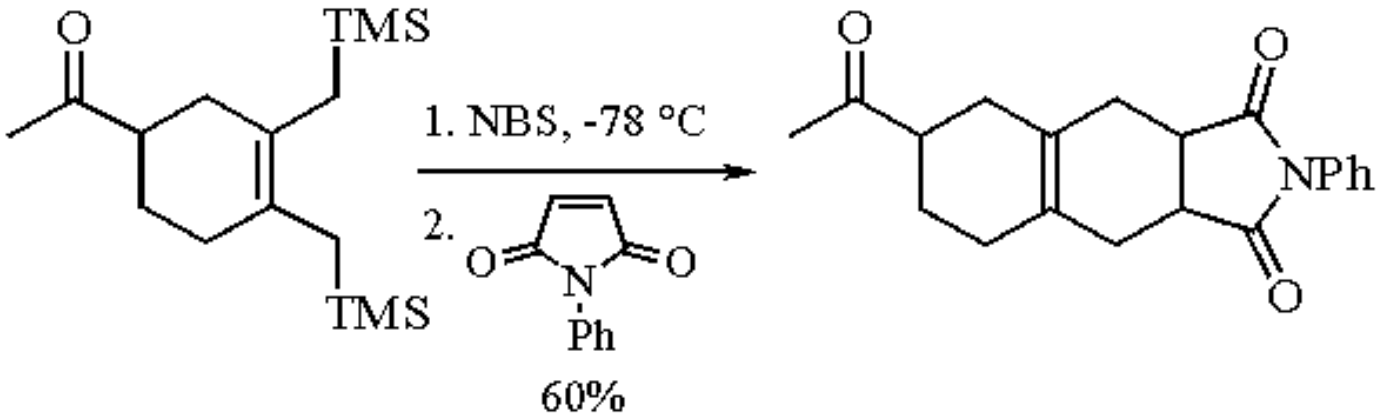

(15)

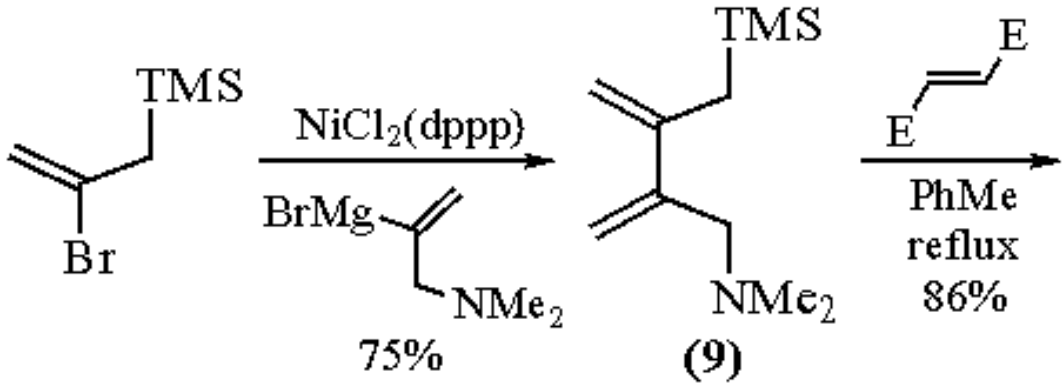

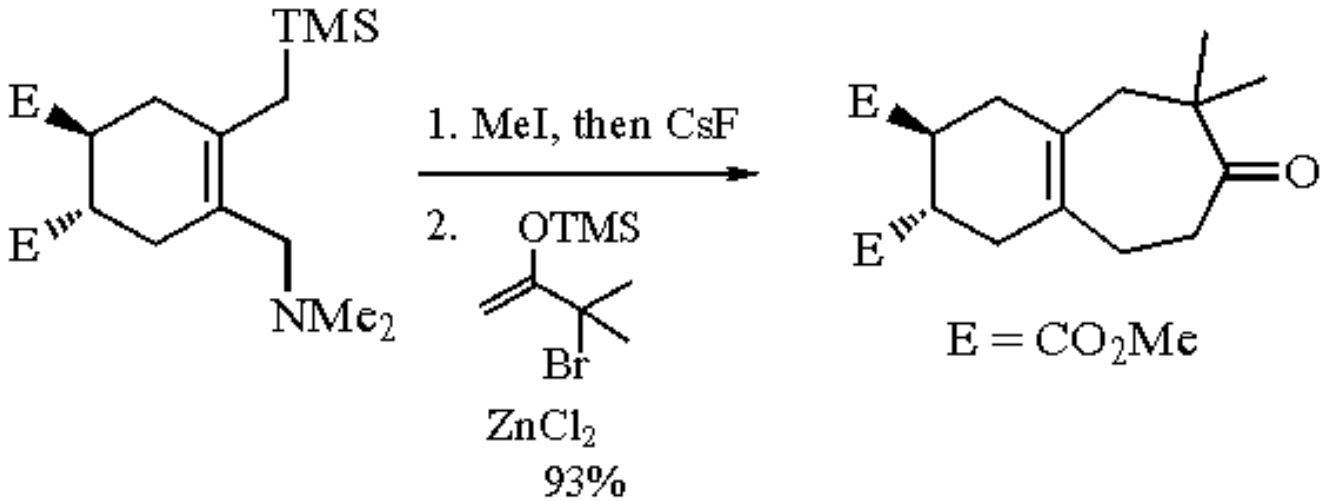

(16)

Nickel-catalyzed cross coupling of Grignard reagent (**2**) (M = MgBr) with other vinyl bromides provides an easy access to isoprenylsilanes that display high reactivity and regioselectivity toward various dienophiles, as illustrated in the

synthesis of a dihydropyran (eq 17).[4] Carbopalladation of allene with the silyl bromide (**1**) in the presence of a nucleophile also produces dienes. In one case the allylsilane unit is used to generate a cyclohexyl ring (eq 18).[21]

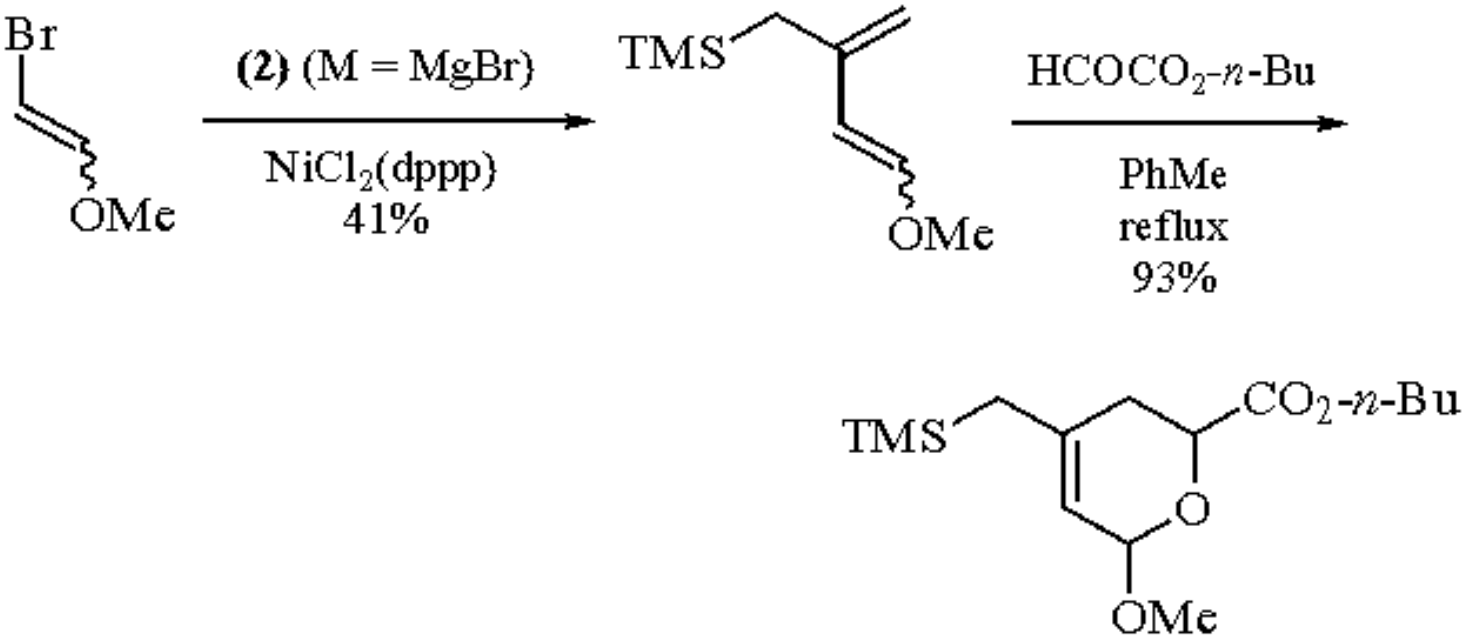

(17)

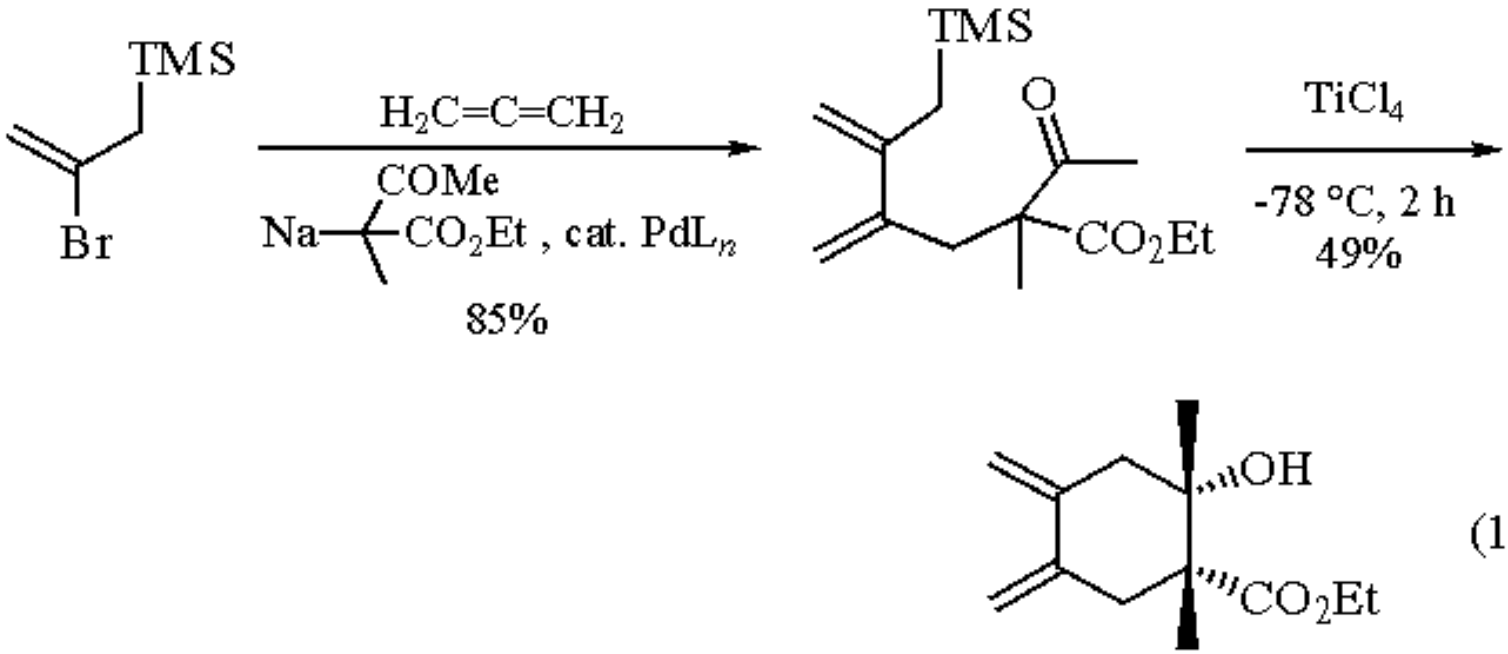

(18)

Palladium-catalyzed coupling of the silyl bromide to the terminal alkyne (**10**) gives the propargylic allylsilane (**11**), which is a key intermediate in the synthesis of a 10-membered cyclodiynol analog (**12**) of the antitumor agent neocarzinostatin (eq 19).[22]

2-Bromo-3-trimethylsilyl-1-propene

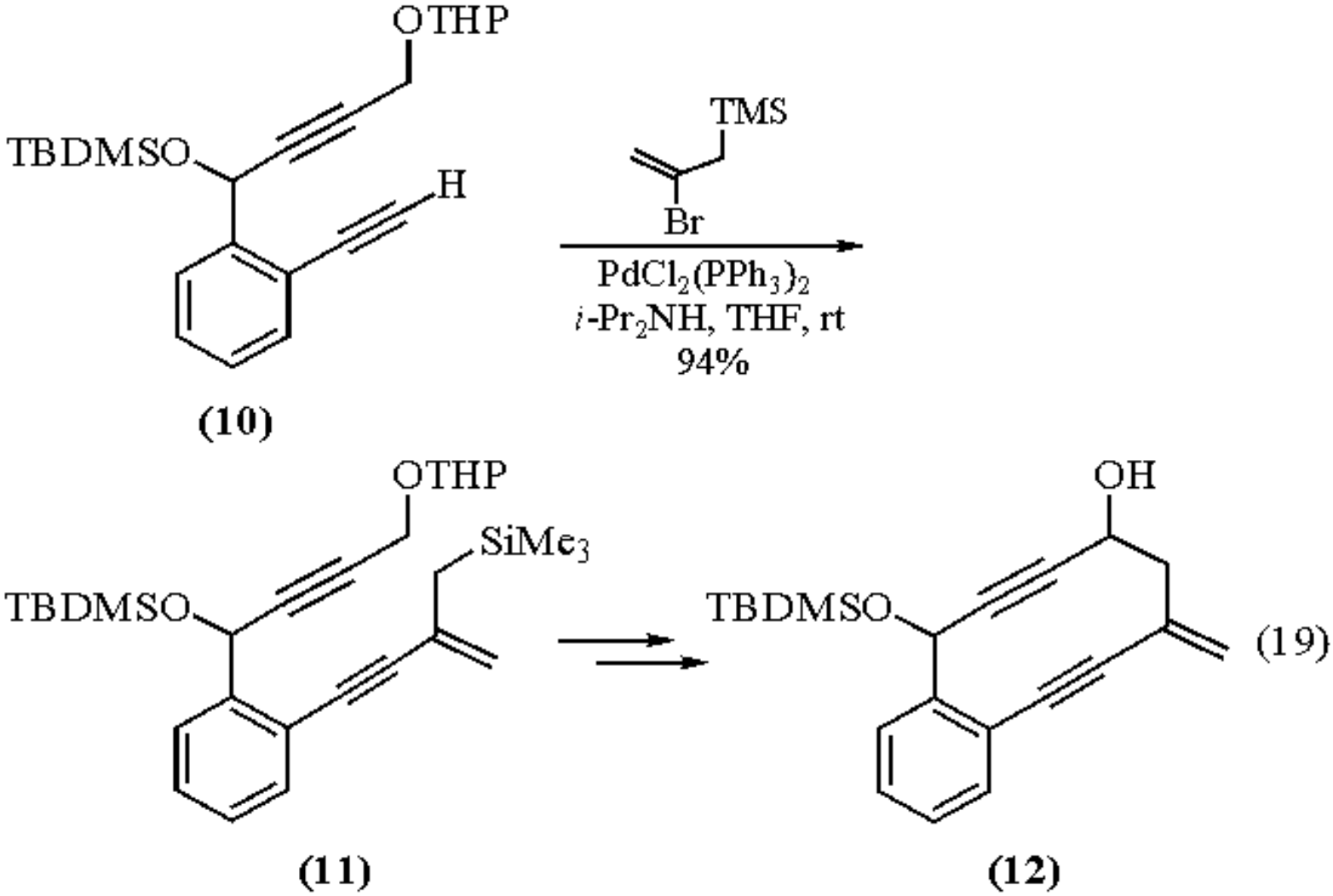

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19. Trost, B. M.; Shimizu, M. *JACS* **1982**, *104*, 4299.
20. Hosomi, A.; Otaka, K.; Sakurai, H. *TL* **1986**, *27*, 2881.
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Dominic M. T. Chan

DuPont Agricultural Products, Newark, DE, USA

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3-Bromo-1-trimethylsilyl-1-propene

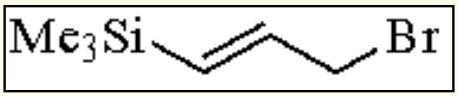

[84673-88-1] · $C_6H_{13}BrSi$ · 3-Bromo-1-trimethylsilyl-1-propene · (MW 193.16)

(preparation of functionalized vinylsilanes[1])

Physical Data: bp 88-90 °C/63 mmHg.

Solubility: insol H_2O; sol most common organic solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: GLC, NMR.

Preparative Methods: bromination (***Phosphorus(III) Bromide***, 0 °C;[2,3] ***N-Bromosuccinimide-Dimethyl Sulfide***[4]) of 3-(trimethylsilyl)allyl alcohol, which in turn can be prepared by ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** reduction of 3-trimethylsilylpropargyl alcohol.[5] Allylic bromination of ***Allyltrimethylsilane*** gives a mixture of the title compound and its regioisomers, which is also useful for some applications.[6]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: stable in air, and should be kept in a tightly capped bottle.

Use as an Electrophile.

The allylic bromide and congeners serve as excellent alkylating agents of enolate anions, providing a useful synthetic route to a variety of substituted vinylsilanes. The lithium enolate of 2-methylcyclohexanone reacts with the trimethylsilyl allylic iodide in excellent yield, and subsequent oxidation of the vinylsilane group smoothly gives a 1,5-diketone (eq 1).[1]

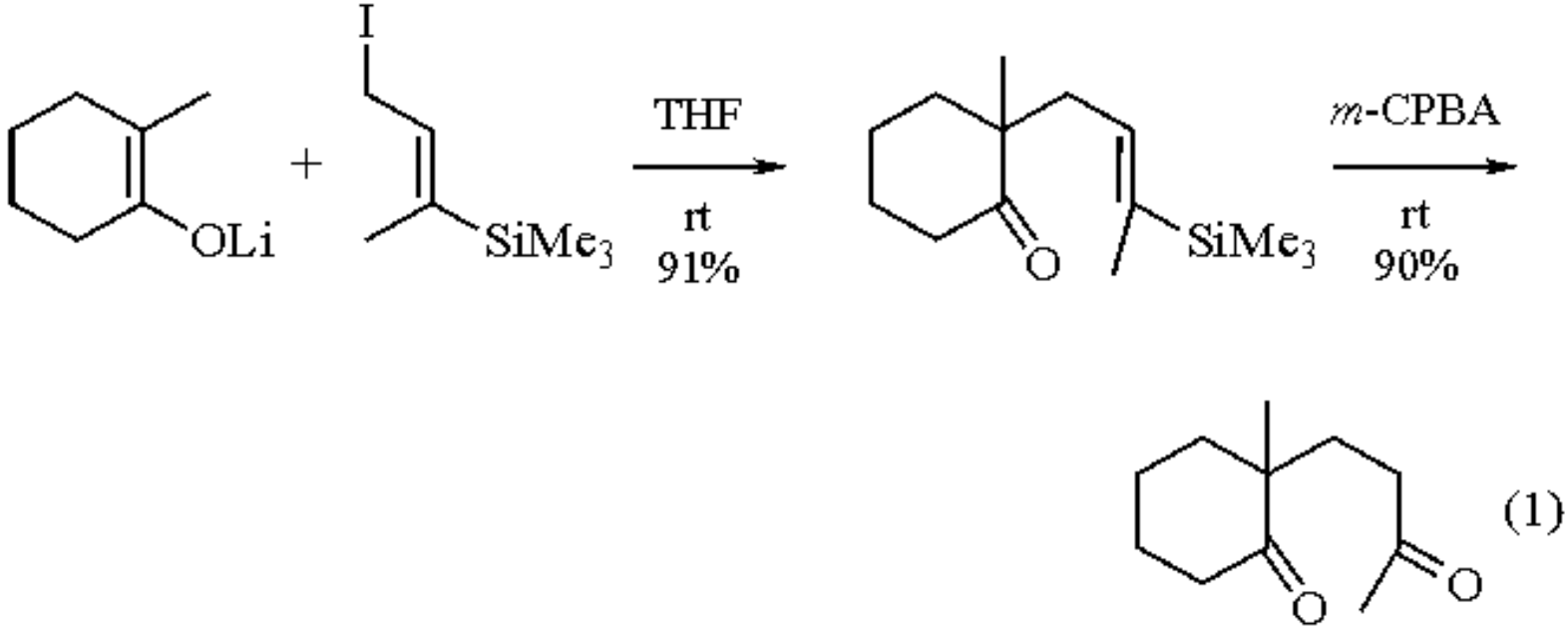

(1)

The S_N2 regioselectivity of the nucleophilic displacement of the bromide group is due to the steric bulk of the silyl group, and is general not only for lithium enolates but for other enolates,[7] lithioenamines, cuprates, and enamines (eq 2).[8]

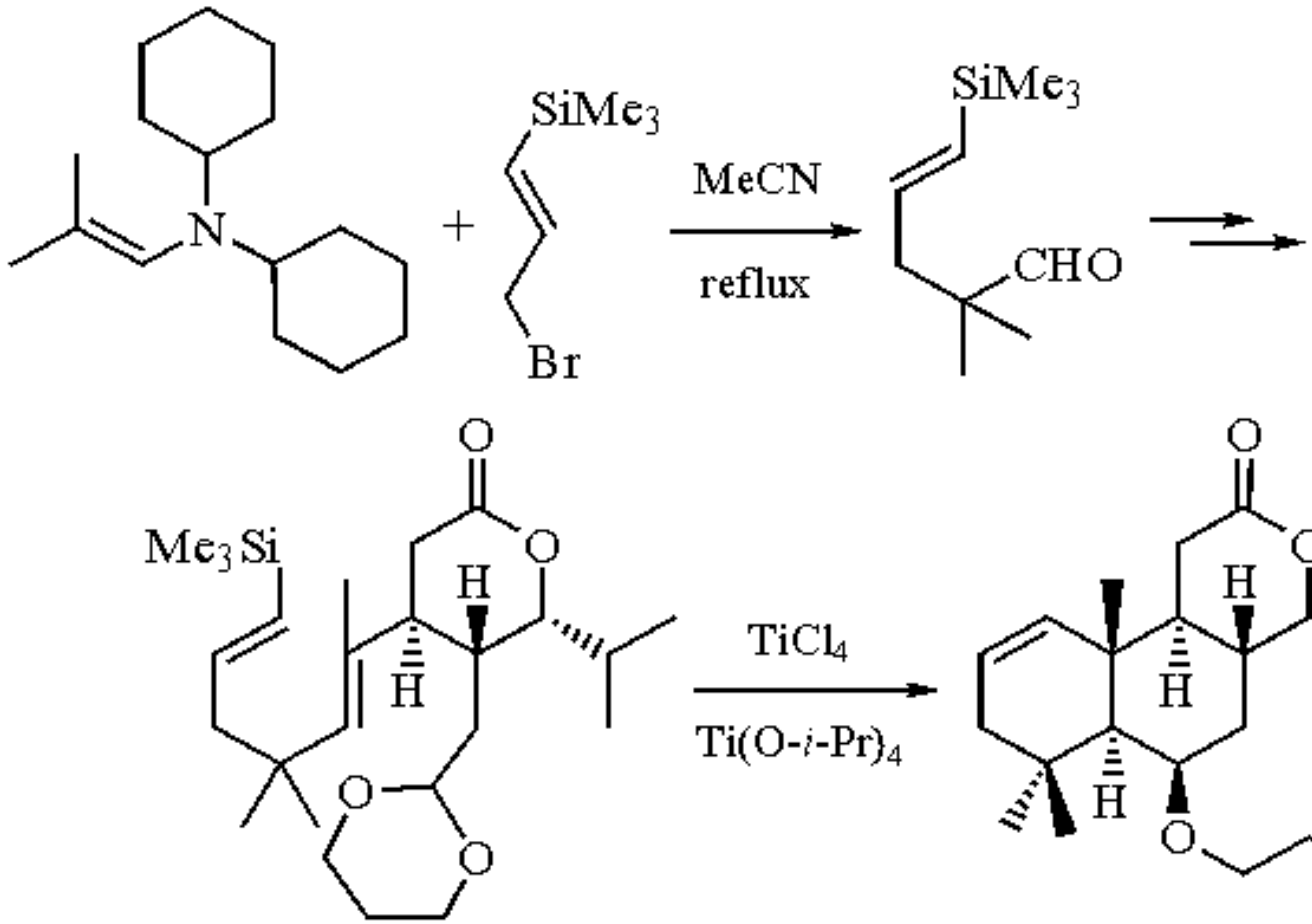

(2)

The vinylsilanes thus obtained have been used as substrates of polyene cyclization (eq 2),[4,9] and intramolecular acylation (eq 3);[2] the vinylsilane moiety was found to be more electrophilic than the simple allyl group.

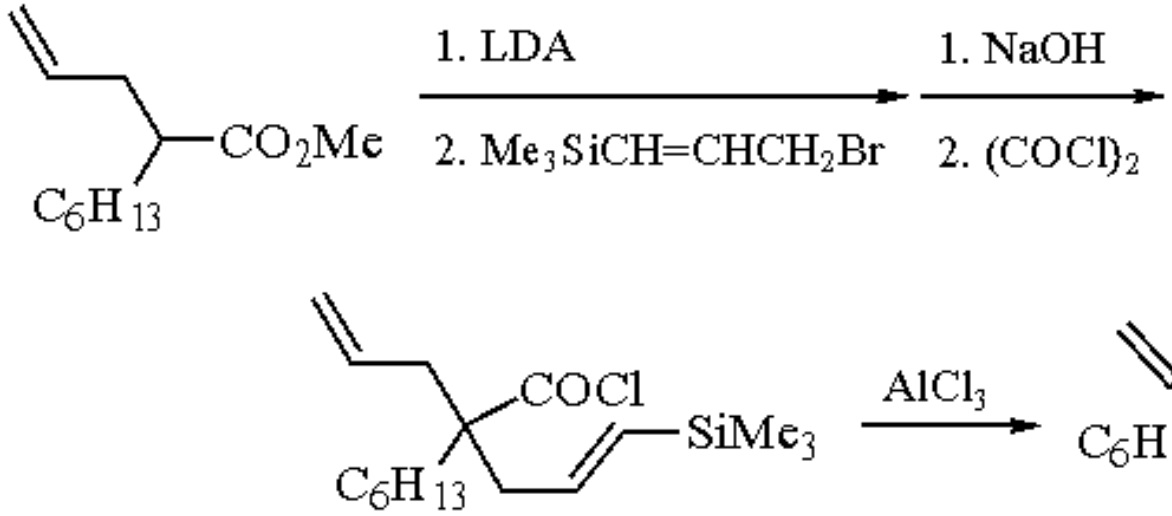

(3)

Use as a Nucleophile.

Reduction of the bromide with a low-valent metal generates a nucleophilic allylating reagent, which undergoes highly S_E2'-selective allylation reactions. Thus the reaction of a regioisomeric mixture of the bromide with ***Chromium(II) Chloride*** in the presence of an aldehyde proceeds via a trimethylsilyl allylic chromium reagent with excellent regio- and stereoselectivity to give a β-hydroxysilane (eq 4).[6] Similarly, allylic lead and zinc reagents prepared in situ undergo regio- and chemoselective addition to carbonyl compounds[10] or imines.[11]

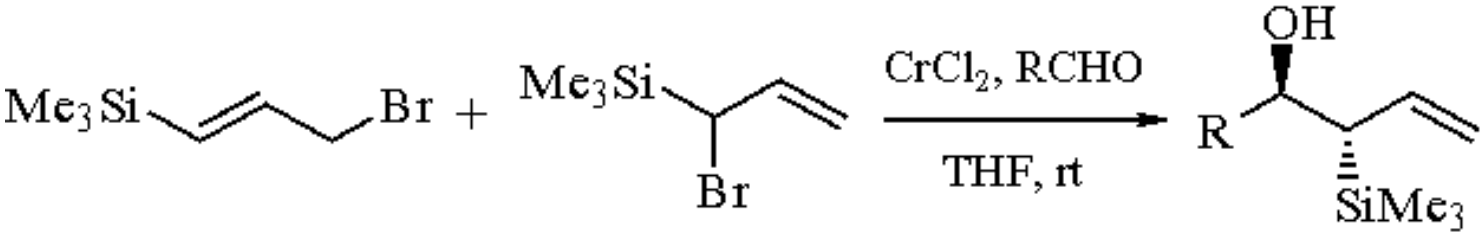

(4)

The reaction of the silyl allylic bromide with ***Triphenylphosphine*** readily provides an allylic phosphonium salt, which upon treatment with ***n-Butyllithium*** and an appropriate carbonyl compound (e.g. acetone, cyclohexanone, fluorenone) gives 1-trimethylsilylbutadiene derivatives (eq 5).[3]

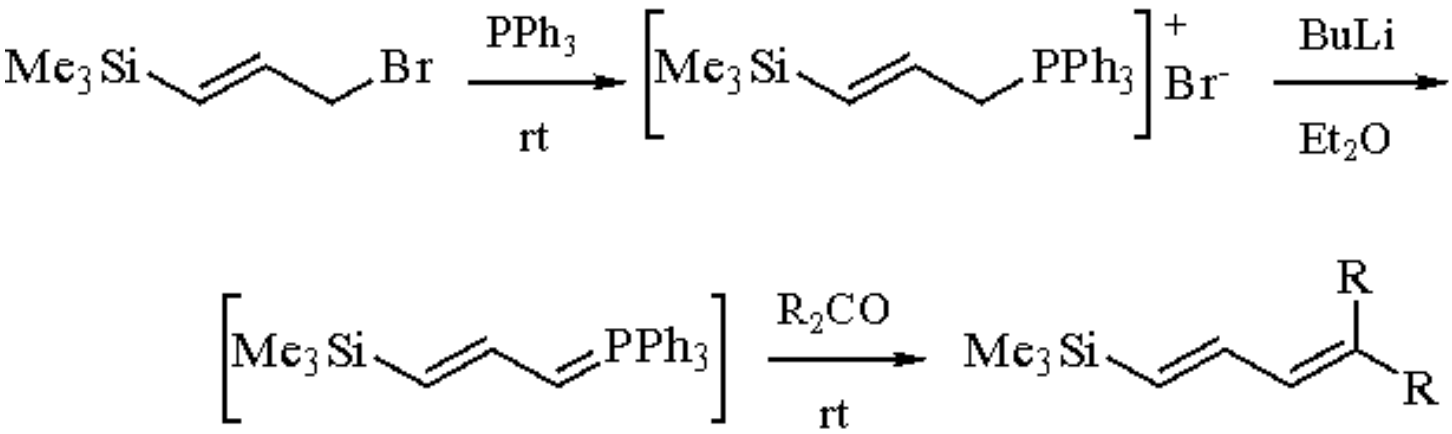

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(*E*)-(2-Bromovinyl)diisopropoxyborane[1]

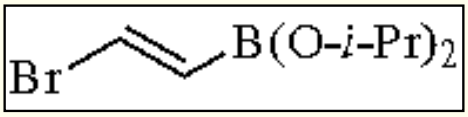

[119441-89-3] · $C_8H_{16}BBrO_2$ · (*E*)-(2-Bromovinyl)diisopropoxyborane · (MW 234.93)

((*E*)-vinylation reagent, useful for synthesis of (*E*)-alkenes, α,β-unsaturated ketones, and α,β-unsaturated esters)

Physical Data: bp 73 °C/12 mmHg.

Solubility: sol ether, THF, CH_2Cl_2, and $CHCl_3$.

Form Supplied in: colorless liquid; not available commercially.

Analysis of Reagent Purity: purity is analyzed by ^{1}H NMR ($CDCl_3$): δ 1.17 (d, *J* = 6 Hz, 12H), 4.22-4.56 (m, 2H), 6.37 (d, *J* = 15 Hz, 1H), 7.06 (d, *J* = 15 Hz, 1H).

Preparative Methods: by the bromoboration of acetylene with tribromoborane,[2] followed by the addition of isopropanol to the resulting 2-(bromovinyl)dibromoborane (eq 1).[3,4] The reagent is isolated by distillation under nitrogen. Large quantities may be prepared and stored in a refrigerator.

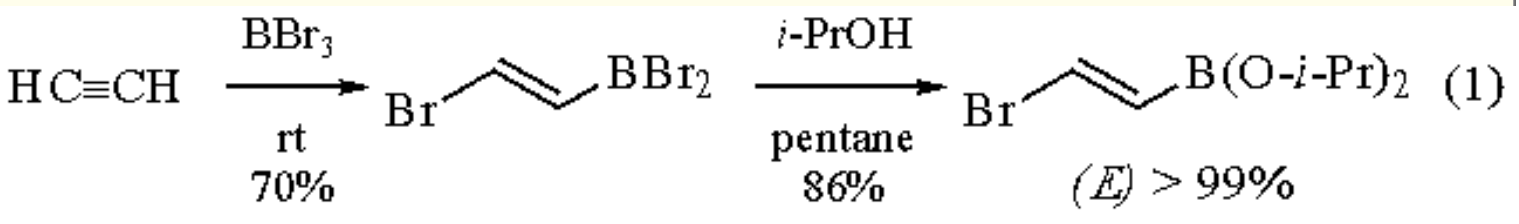

Handling, Storage, and Precautions: moisture sensitive; can be handled in air for a short time but is gradually hydrolyzed to the boronic acid by moisture. It should be stored in a refrigerator under a dry inert gas and transferred by syringe. After prolonged storage it should be distilled under a dry inert gas before use. Sensitive to both base and acid; base treatment causes rapid decomposition by β-elimination.

Synthesis of (*E*)-Alkenes via Palladium-Catalyzed Stepwise Cross-Coupling Reactions.

Cross-coupling reactions of alkenylboranes with organic halides are known to proceed in the presence of a palladium

catalyst and an appropriate base.[5] In the absence of base, (*E*)-(2-bromovinyl)diisopropoxyborane reacts with organozinc compounds as a simple organic halide to give (*E*)-(1-alkenyl)diisopropoxyboranes. Subsequent addition of base and an organic halide promotes the coupling reaction between the alkenylborane and the organic halide to provide (*E*)-alkenes stereoselectively (eq 2).[4] Though the isolation of the alkenylborane intermediate is possible, the reaction can be carried out without isolation of any intermediates. Alkynyl, alkenyl, alkyl, and aryl groups can be introduced on to both sides of the double bond. This method is an alternative to the cross-coupling reaction of alkenylboranes prepared by the hydroboration of alkynes, and is preferable especially when an alkyne is difficult to synthesize or has functional groups that are sensitive to hydroboration reactions.

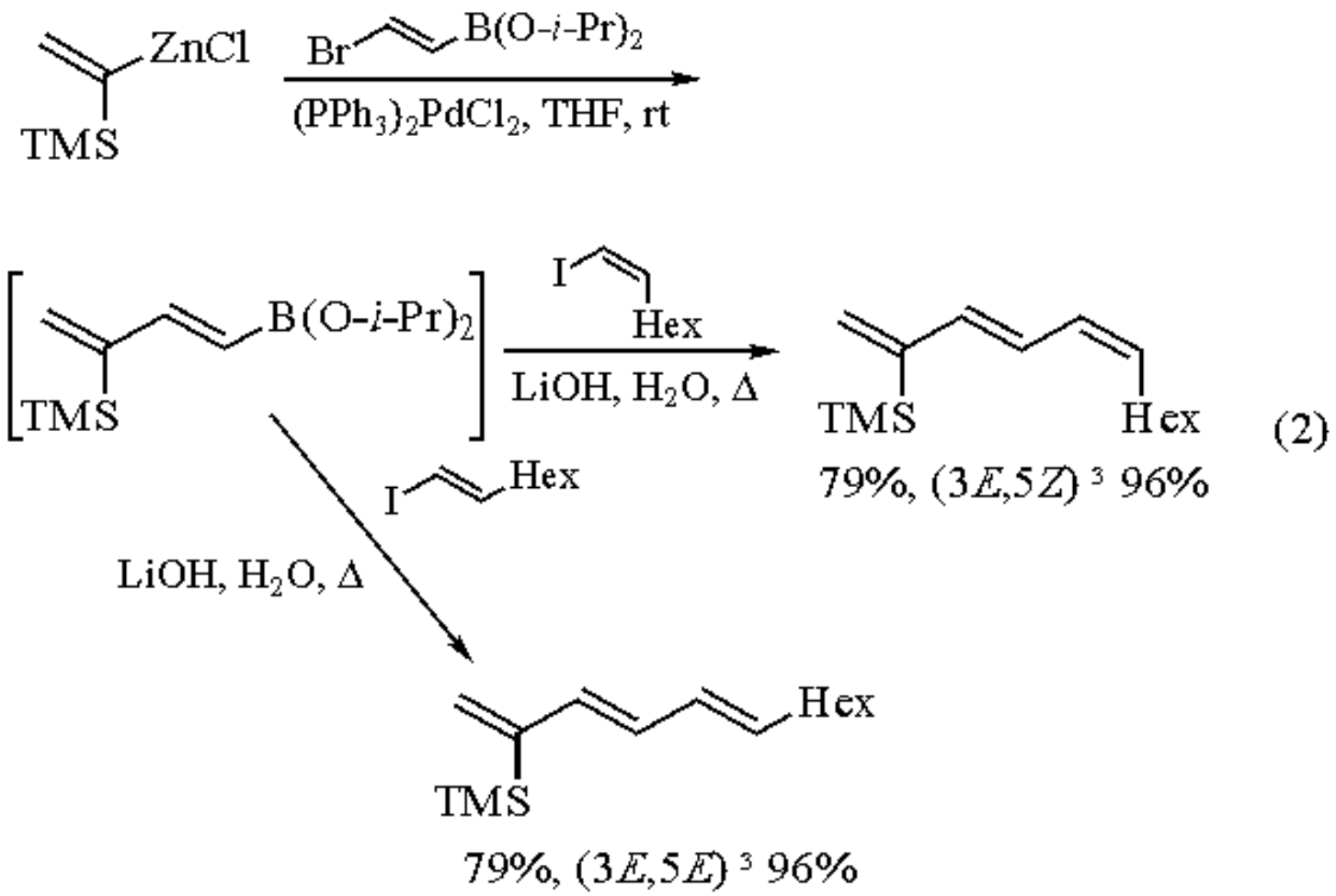

α,β-Unsaturated Ketones.

This methodology is effective for the synthesis of α,β-unsaturated ketones using α-alkoxyalkenylzinc chlorides in the first cross-coupling step.[6] The reaction proceeds under mild conditions, and is applicable for the synthesis of polyenones such as pseudoionone (eq 3).

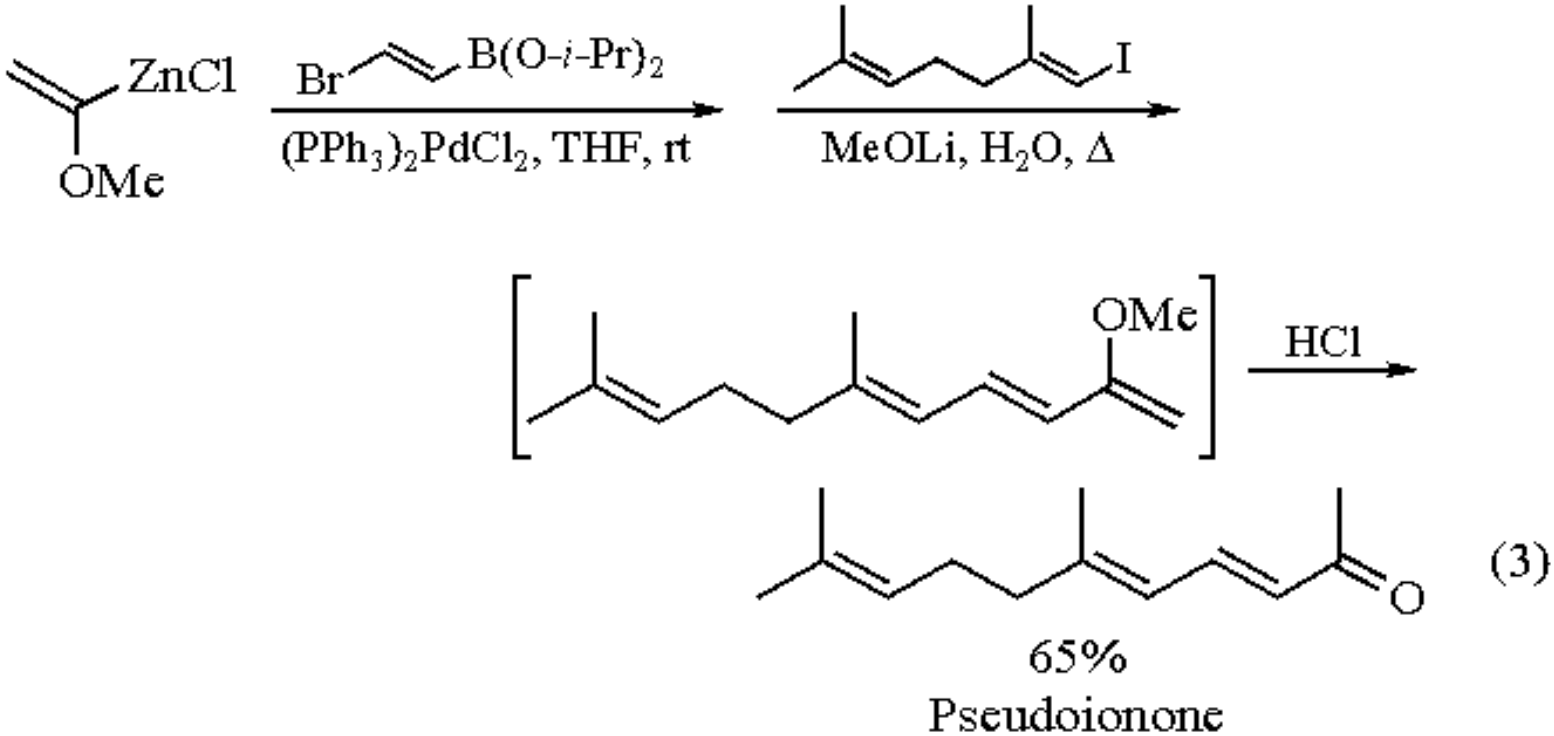

This reaction has been applied to the synthesis of prostaglandin B_1(PGB_1).[7] Stepwise cross-coupling of (1-methoxy-1-pentenyl)zinc chloride with (*E*)-(2-bromovinyl)-diisopropoxyborane followed by 3-bromo-2-[6-(methoxycarbonyl)hexyl]-2-cyclopenten-1-one (**1**) provides 15-dehydro-PGB_1 directly in a one-pot operation (eq 4).

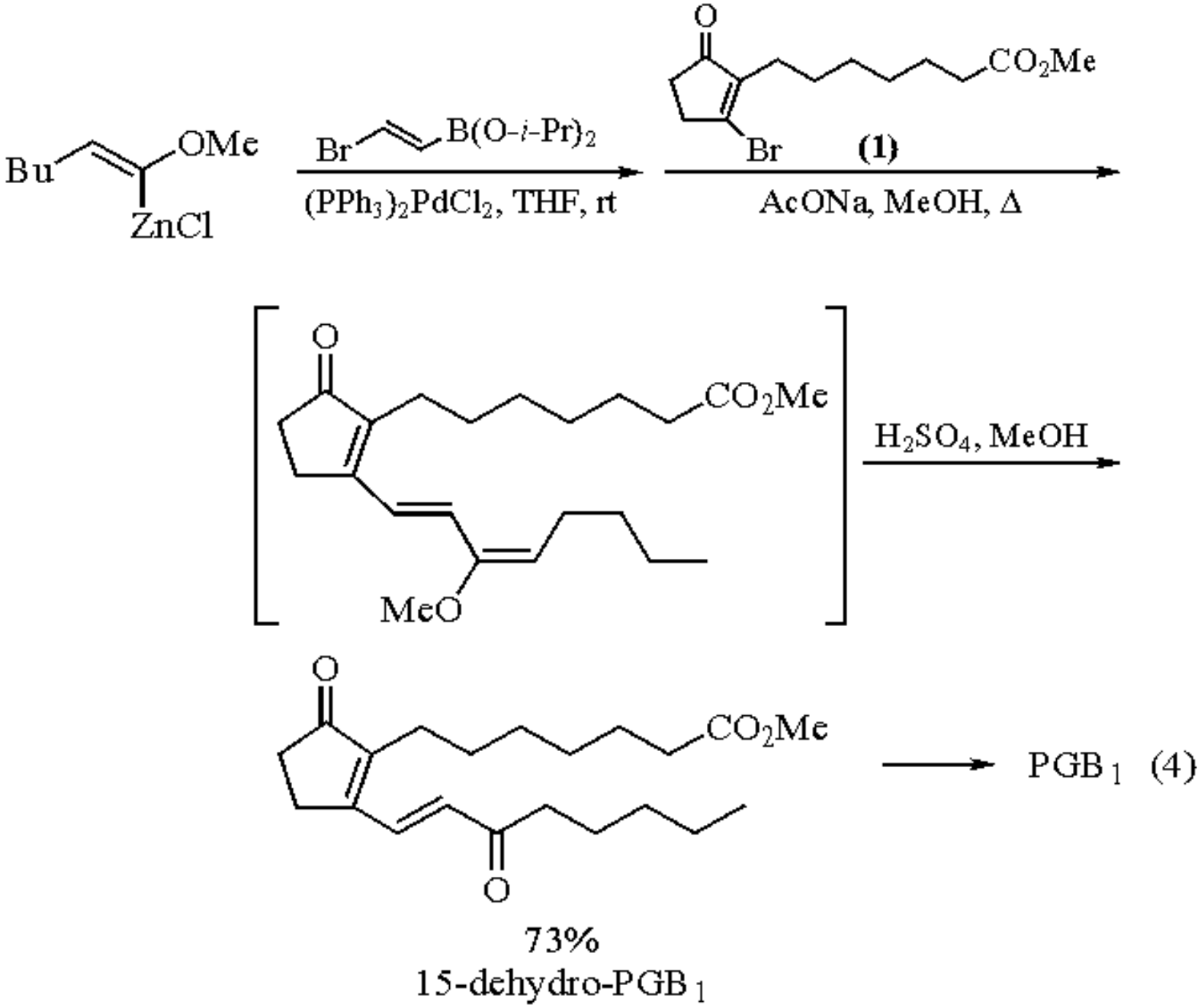

α,β-Unsaturated Esters.

A sequence involving cross-coupling and alkoxycarbonylation reactions of (*E*)-2-(bromovinyl)diisopropoxyborane gives α,β-unsaturated esters.[8] Isolation of alkenylborane intermediates is not necessary, but removal of the solid generated in the first step is required. The second step is carried out under a carbon monoxide atmosphere after the addition of the other reagents (eq 5).

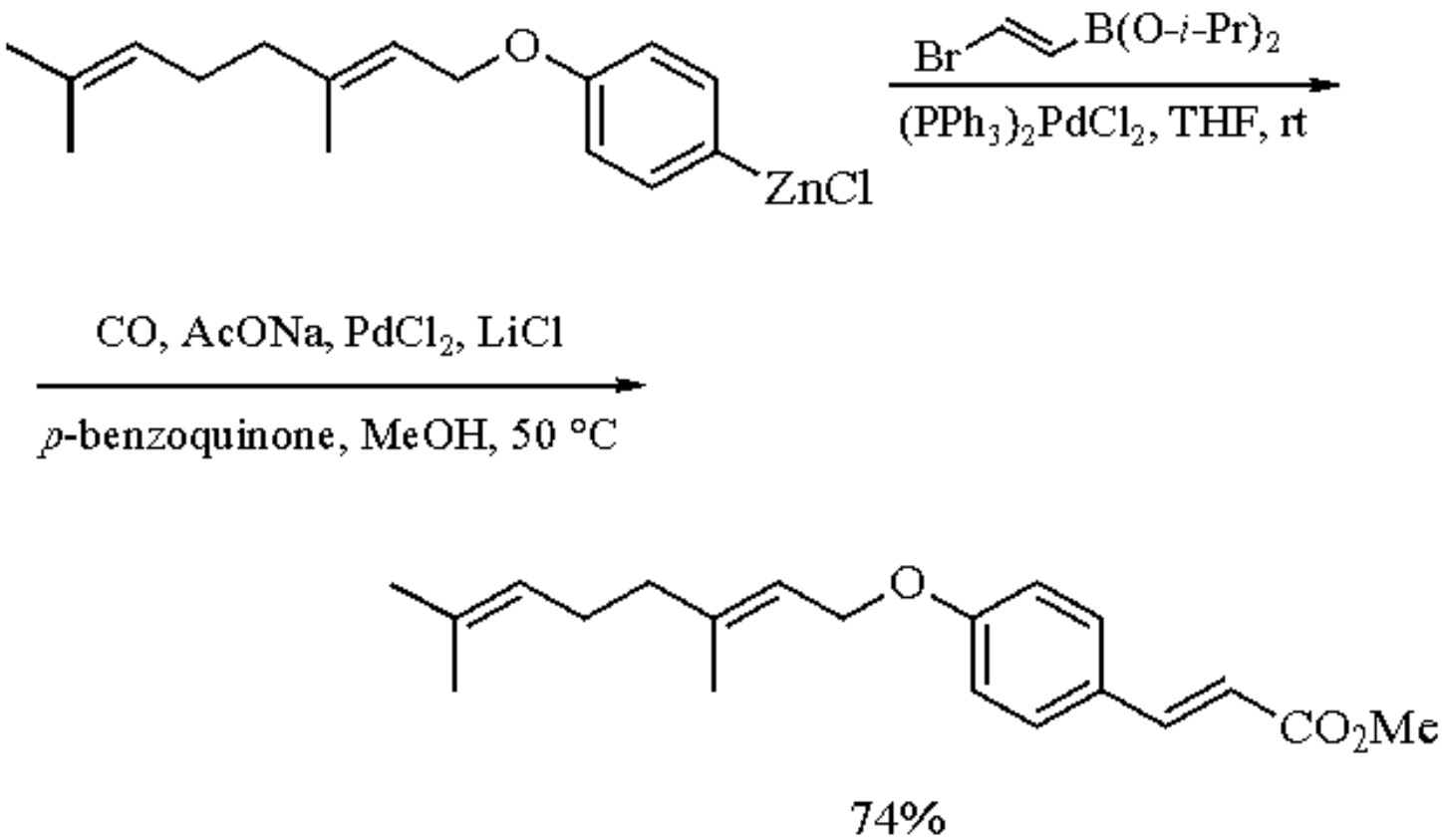

(5)

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α-Bromovinyl Methyl Sulfone

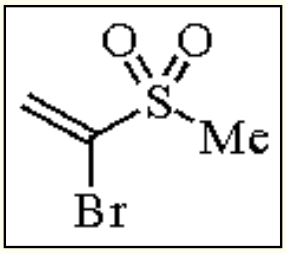

[35495-31-9] · $C_3H_5BrO_2S$ · α-Bromovinyl Methyl Sulfone · (MW 185.05)

(dienophile equivalent to allene in cycloaddition reactions via Ramberg-Bäcklund reaction of the adducts;[1] gives aziridines with primary amines in DMSO[2])

Physical Data: bp 63-64 °C/0.4 mmHg.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Preparative Method: prepared by bromination-dehydrobromination of methyl vinyl sulfone in 80% yield.[1]

The reaction of α-bromovinyl methyl sulfone with cyclopentadiene affords a mixture of the expected cycloadducts which, upon treatment with ***Sodium Methoxide*** in DMSO, give 5-methylene-2-norbornene via the Ramberg-Bäcklund rearrangement in over 90% yield. Using 2N ***Sodium Hydroxide*** as the base, the adducts give, besides the expected 5-methylene-2-norbornene, 37-59% yield of the rearranged adduct (eq 1).[1] The latter product arises from a radical rearrangement.

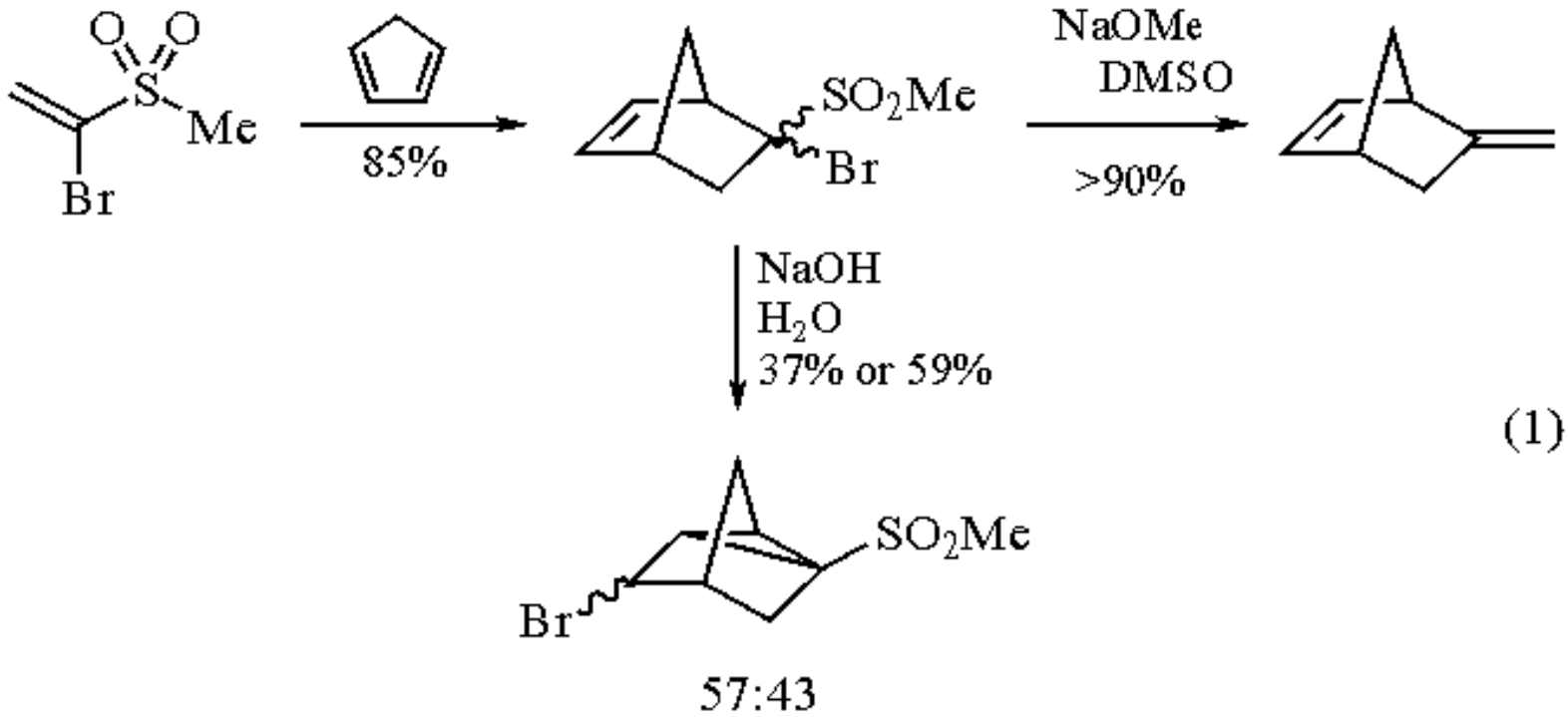

(1)

The action of ***Dimethyl Sulfoxide*** and a primary amine on α-bromovinyl methyl sulfone gives aziridines (eq 2).[2]

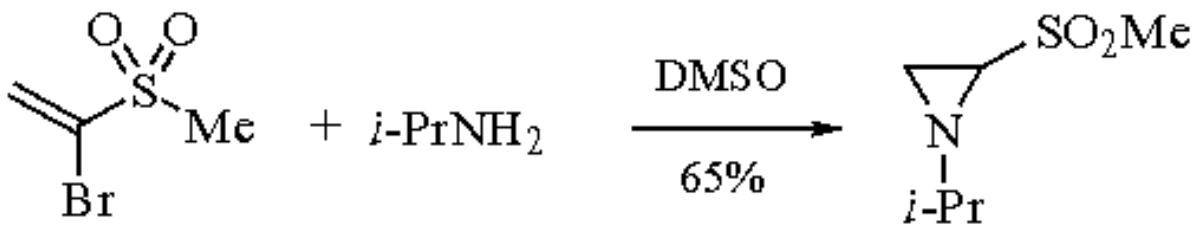

(2)

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(1-Bromovinyl)trimethylsilane[1]

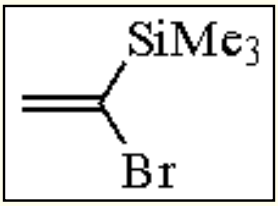

[13683-41-5] · $C_5H_{11}BrSi$ · (1-Bromovinyl)trimethylsilane · (MW 179.13)

(undergoes lithium-halogen exchange in the presence of alkyllithium;[2] used as a dienophile in [4 + 2] cycloaddition reactions;[3] used in palladium-catalyzed reactions;[4] substrate for cyclopropanation[5])

Alternate Names: 1-(trimethylsilyl)vinyl bromide; 1-bromo-1-(trimethylsilyl)ethylene.

Physical Data: bp 124 °C/745 mmHg; *d* 1.156 g cm^{-3}.

Solubility: completely miscible with THF and Et_2O.

Form Supplied in: clear liquid.

Analysis of Reagent Purity: ^1H and ^{13}C NMR can be used.

Preparative Methods: prepared, in good yield, from the reaction of ***Vinyltrimethylsilane*** with ***Bromine*** at low temperature followed by dehydrohalogenation in the presence of an amine base.[1] Alternative syntheses and reagents, i.e. (1-bromovinyl)triphenylsilane and (1-bromovinyl)triethylsilane, are also known.[2a]

Handling, Storage, and Precautions: store in a dry area.

Vinyltrimethylsilane Metal.[2]

1-Trimethylsilylvinyl metal species are mostly used as acyl anion equivalents and as hindered vinyl anion substitutes. ***1-(Trimethylsilyl)vinyllithium*** is easily accessible from (1-bromovinyl)trimethylsilane by treatment with ***n-Butyllithium*** at -78 °C in ether (eq 1).[2a] Other solvents and alkyllithiums can also be used for the metal-halogen exchange.[2b] The use of (1-chlorovinyl)trimethylsilane or the direct reaction of (1-bromovinyl)trimethylsilane with lithium metal are not proper methods for generating the lithium species.[2c]

(1-Bromovinyl)trimethylsilane

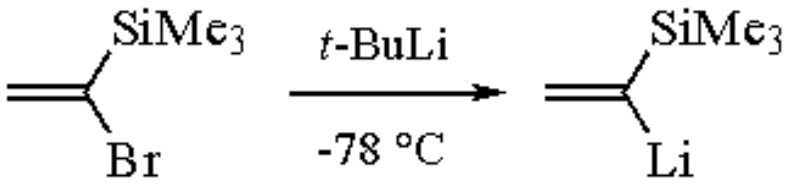

(1)

The corresponding Grignard reagent is made by reaction of ***Magnesium*** with (1-bromovinyl)trimethylsilane in THF (eq 2).[2d] It has the same general uses as the lithium analog (***1-(Trimethylsilyl)vinyllithium***). Furthermore, it has been shown to react with allylic acetates, in the presence of palladium catalysts, to give the corresponding dienes in moderate to low enantiomeric excess when the catalyst was chiral (eq 3).[6] Generally, Grignard reagents will add to the carbonyl of the acetate group in preference to allylic substitution. The authors described 1-(trimethylsilyl)vinylmagnesium bromide as a soft stabilized anion to explain this peculiar reactivity.

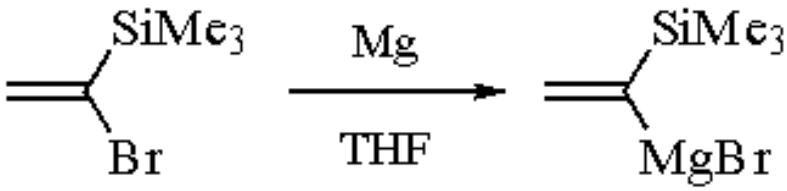

(2)

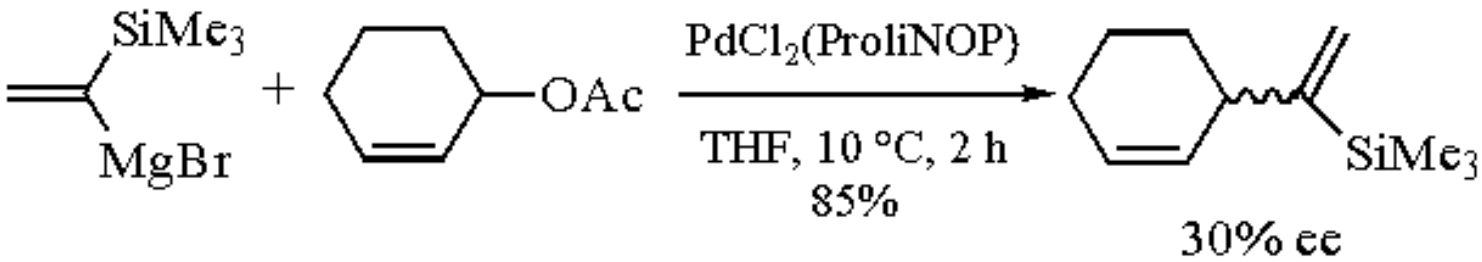

(3)

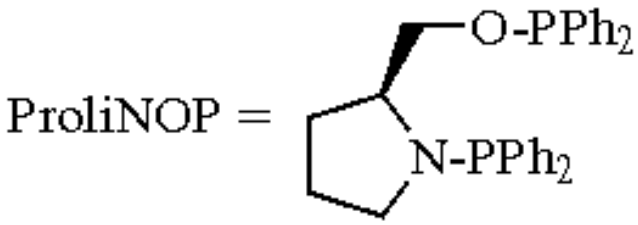

This Grignard reagent has also been reacted with ***Carbon Dioxide***[2f] and the cuprate of this Grignard reagent adds to alkynyl compounds and provides a practical synthesis of 1,3-butadienes (eq 4).[2g]

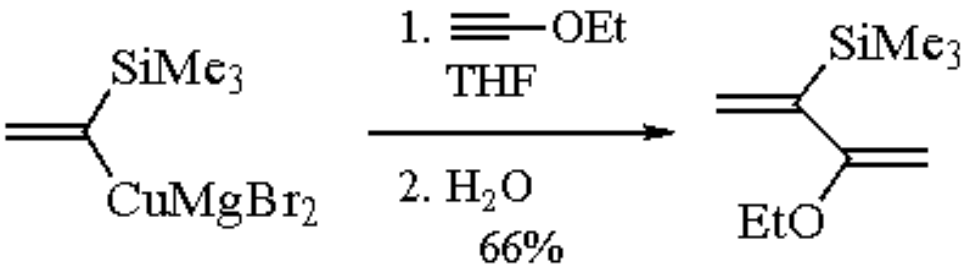

(4)

[4 + 2] Cycloaddition Reactions.[3]

A number of substituted vinyltrimethylsilanes react with dienes and nitrile oxides in Diels-Alder[6] and 1,3-dipolar cycloadditions.[3] The trimethylsilyl group has a deactivating effect. This reaction with ***Benzonitrile Oxide*** gives 3-phenyl-5-trimethylsilylisoxazole (eq 5).

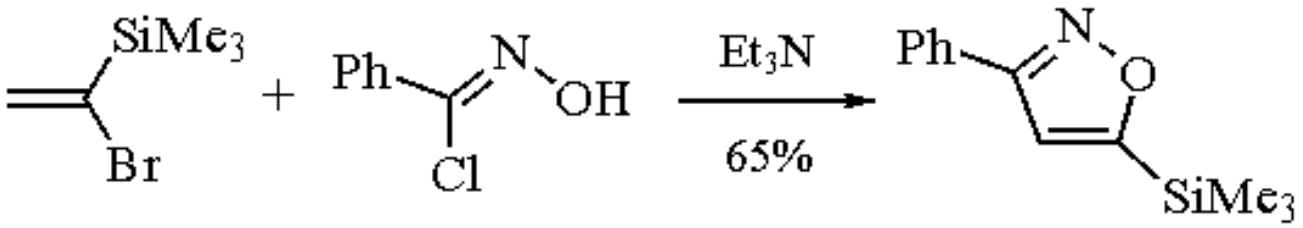

(5)

Palladium-Catalyzed Reactions.[4]

Numerous nucleophiles react with (1-bromovinyl)trimethylsilane in the presence of palladium complexes. The bromine has been substituted by phenylthio,[4a] vinyl,[4b] and aryl[4c] groups. This approach gives reasonable yields of the desired products. However, the substitution reactions sometimes lack regiospecificity. For example, a mixture of regioisomers was obtained in eq 6. Two mechanisms have been proposed for the formation of the β-substituted product. One involves an elimination step to give ***Trimethylsilylacetylene*** as an intermediate, which then undergoes catalyzed additions with the nucleophile at either the α- or β-positions.[4a] The other mechanism involves the formation of a pentacoordinated palladium intermediate, leading to the formation of isomeric products.[4c]

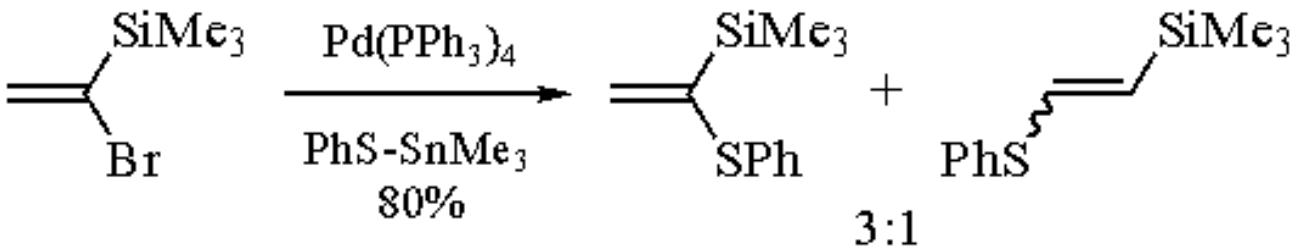

(6)

Substrate for Cyclopropanation.[5]

Dichlorocarbene adds to vinyltrimethylsilane, and the adduct is a source of 1-chlorocyclopropene, a reactive dienophile for Diels-Alder reactions.[5b] Dichlorocarbene also reacts with (1-bromovinyl)trimethylsilane[5a] to form (1-bromo-2-dichlorocyclopropyl)trimethylsilane. β-Elimination in the presence of ***Tetra-n-butylammonium Fluoride*** gives 1-bromo-2-chlorocyclopropene, another reactive dienophile (eq 7).

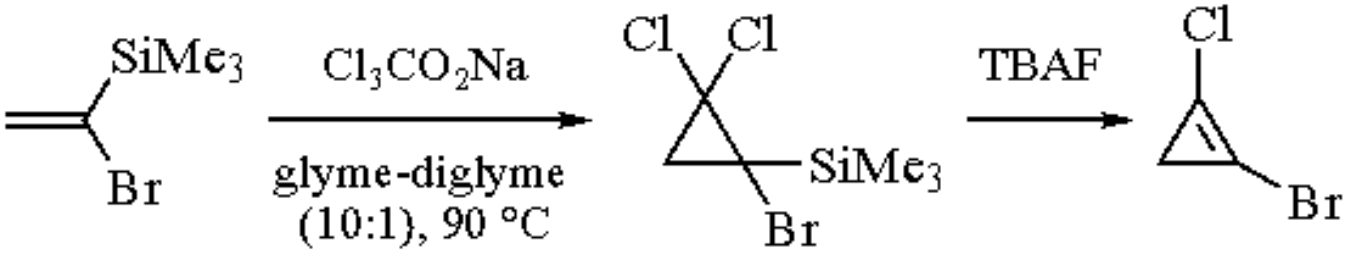

(7)

Related Reagents.

(2-Bromovinyl)trimethylsilane; ***1-(Trimethylsilyl)vinyllithium***; ***(E)-2-(Trimethylsilyl)vinyllithium***; ***Vinylmagnesium Bromide***.

---

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(2-Bromovinyl)trimethylsilane

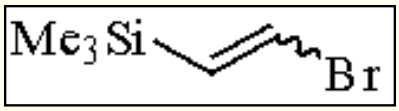

[13682-94-5] · $C_5H_{11}BrSi$ · (2-Bromovinyl)trimethylsilane · (MW 179.13) (*E*)

[41309-43-7] (*Z*)

[70737-20-1]

(for introduction of the β-(trimethylsilyl)vinyl moiety; the resulting alkenylsilanes undergo useful electrophilic substitutions of the TMS group[1])

Alternate Name: 1-bromo-2-trimethylsilylethylene.

Physical Data: (*E*)-isomer: bp 54-55 °C/56 mmHg; *d* 1.16 g cm^{-3}. (*Z*)-isomer: bp 50-52 °C/56 mmHg.

Form Supplied in: (*E*)-isomer, typically containing ca. 10% (*Z*)-isomer.

Analysis of Reagent Purity: ^{1}H NMR (CH=CH) of (*E*)-isomer: δ 6.48 (s); (*Z*)-isomer: δ 6.35, 6.50, 6.86, 7.01 (AB pattern, *J* = 9 Hz).

Preparative Methods: (*E*)-isomer: by the sequence of eq 1,[2] or more directly from the readily available ***Vinyltrimethylsilane***[3] (eq 2).[4] (*Z*)-isomer: by bromination-debromosilylation of 1,2-bis(trimethylsilyl)ethylene (eq 3).[5]

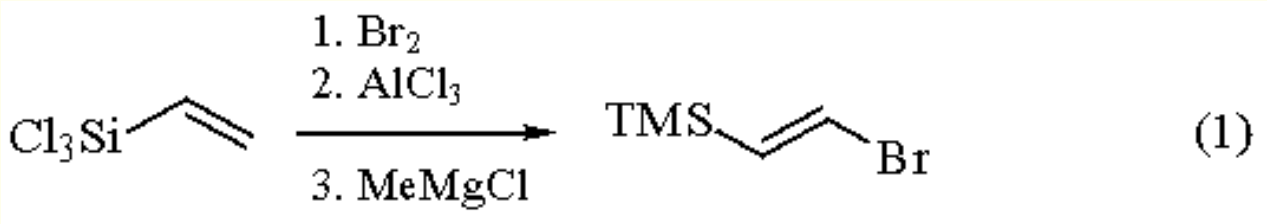

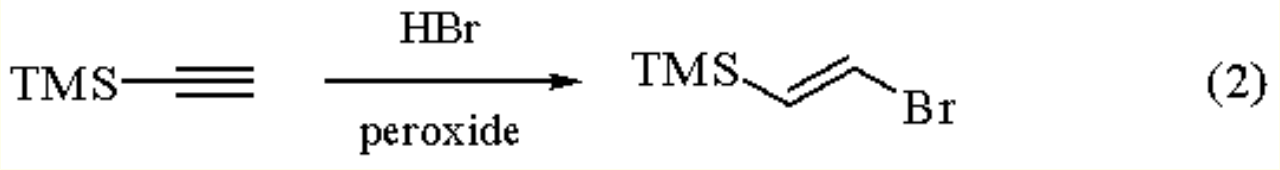

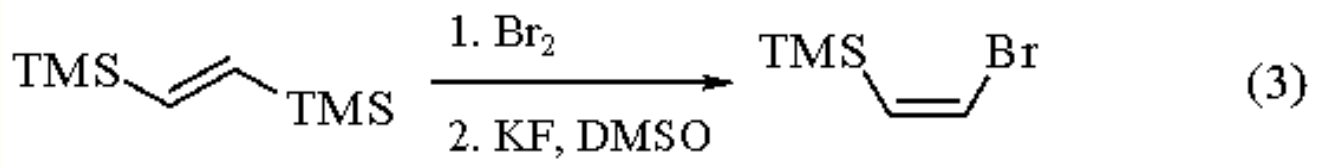

Purification: An 87:13 (*E*):(*Z*) mixture was enriched to 98-99% (*E*) by fractionation.[6]

Handling, Storage, and Precautions: use in a fume hood.

Introduction.

Methods for the introduction of the β-(trimethylsilyl)vinyl moiety into organic frameworks using (2-bromovinyl)trimethylsilane (**1**) may be grouped into two broad categories: those which employ (**1**) as an electrophilic component, or organometallic derivatives of (**1**) as nucleophilic reaction components.

As Nucleophilic Component.

The first such reagent[7] prepared from (**1**) was (*E*)-β-(trimethylsilyl)vinylmagnesium bromide (**2**) (eq 4).[2] This undergoes expected reactions with a number of electrophiles (eqs 5-8)[2,8,9] as well as coupling with (**1**) (eq 9).[10]

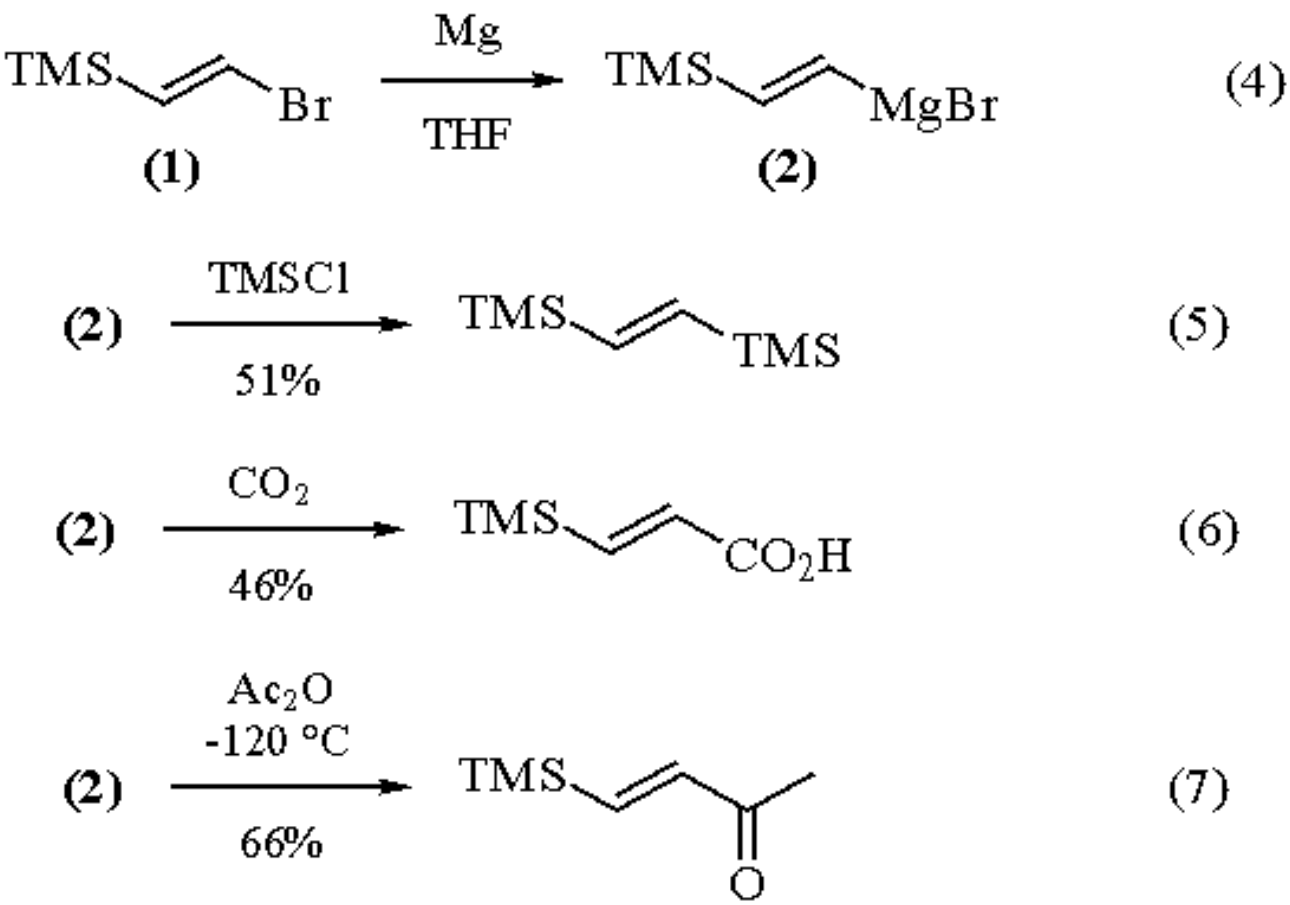

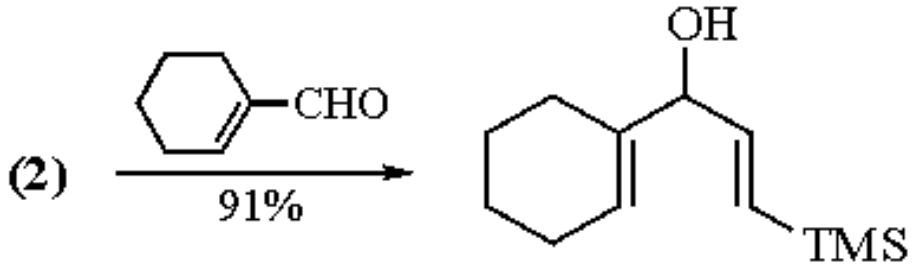

(8)

(9)

In addition, coupling of the Grignard (**2**) with both alkenyl and alkyl halides has been promoted by metal ion catalysis (eqs 10-12).[5,11] Under copper(I) catalysis, (**2**) reacts with conjugated enones in a 1,4-fashion (eq 13),[11,12] and the diorganocuprate derived from (**2**) behaves in a similar fashion (eq 14).[13]

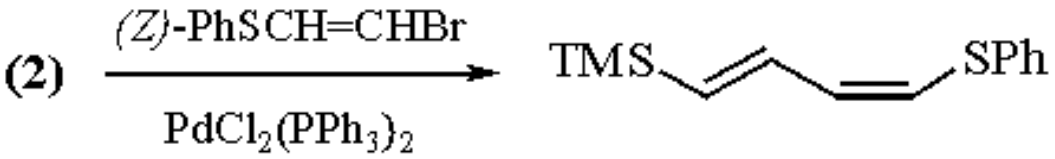

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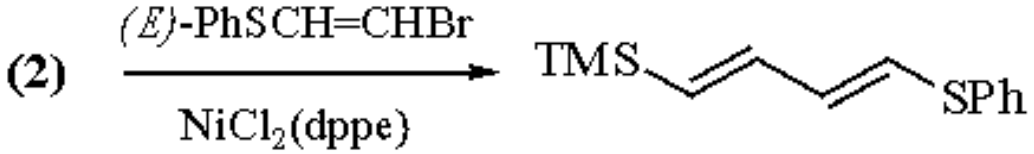

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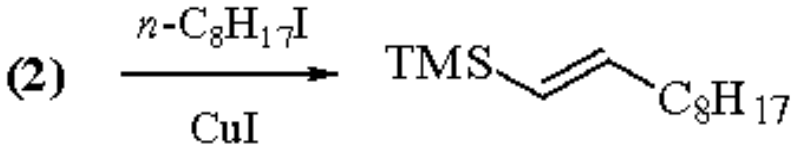

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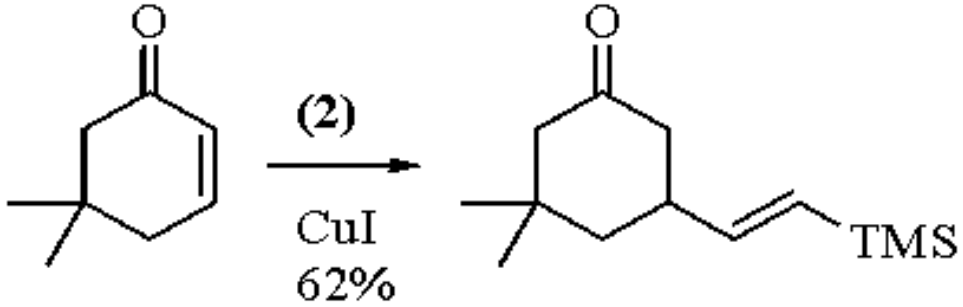

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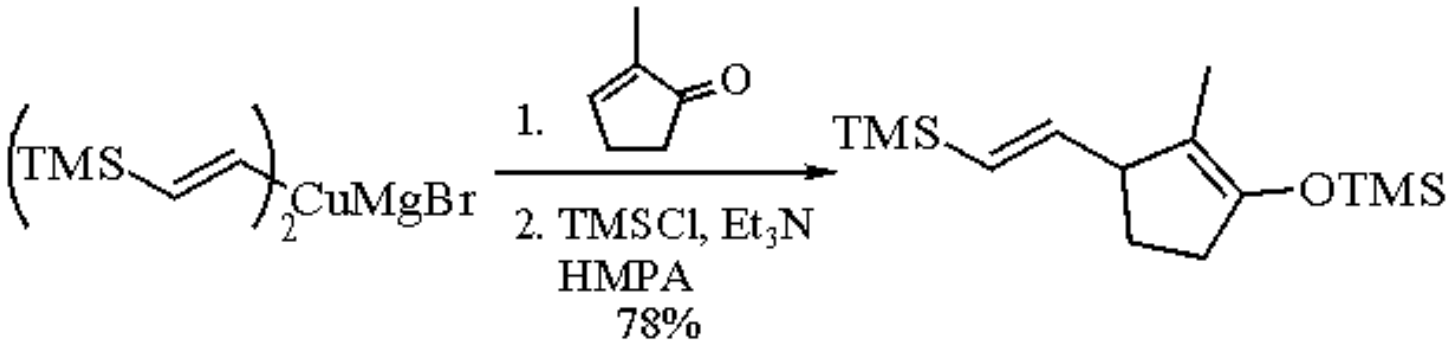

(14)

As Electrophilic Component.

Although an example of coupling between (**1**) and a lithium diorganocuprate is known (eq 15),[14] most substitution reactions of this nature employ palladium catalysis. In this way, organomagnesium (eq 16),[11] as well as organozinc (eqs 17 and 18),[15,16] alkynyltin (eq 19),[15b] and alkenylaluminum compounds (eq 20)[15] have been effectively used as coupling agents. Although the commonly available 9:1 (*E*)/(*Z*) mixture of (**1**) was utilized in these couplings, the alkenylsilane products were obtained in high stereoisomeric (*E*) purity.[15] The cross-coupling of an alkenylzinc reagent with (**1**) was used for a direct synthesis of a dihydrobenzisoquinoline (eq 21).[17]

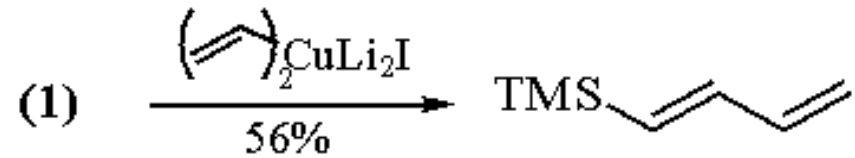

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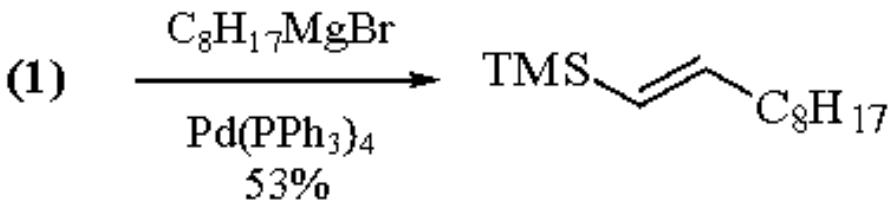

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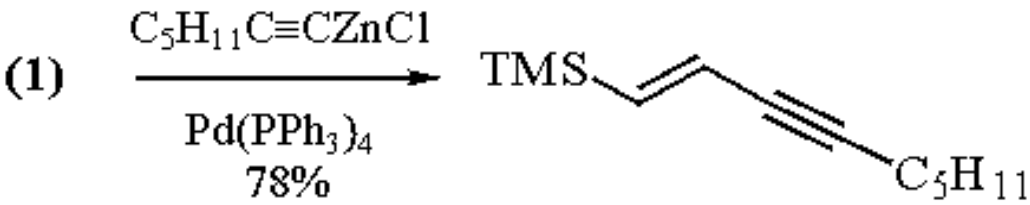

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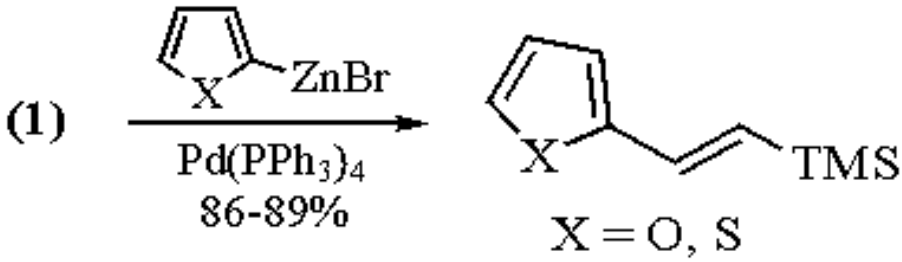

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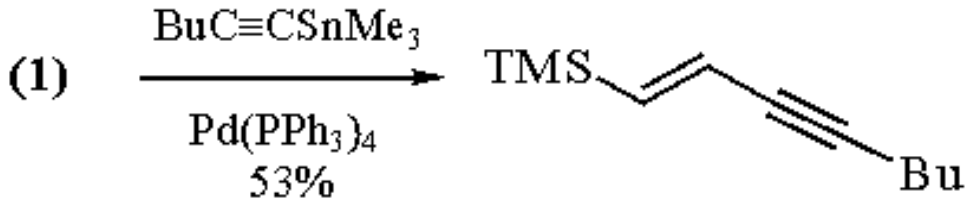

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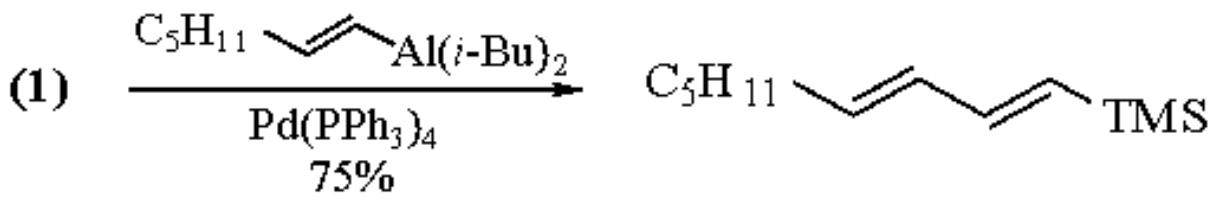

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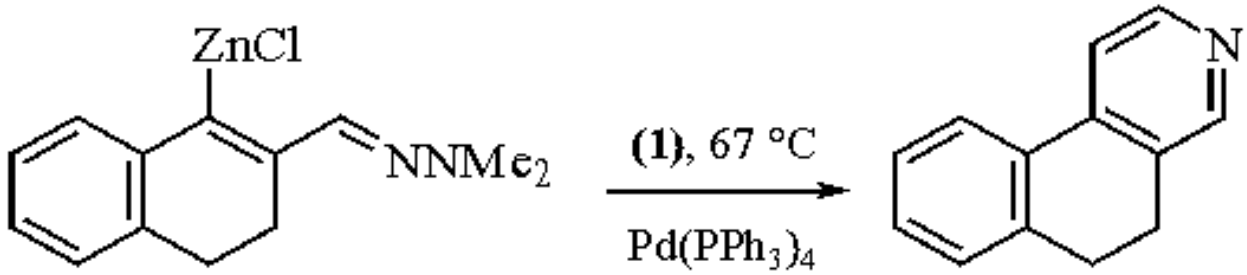

(21)

Couplings of more highly ionic organometallic coreactants with (**1**) have also proven amenable to palladium catalysis. These procedures are often tolerant of accompanying electrophilic functionalities (eqs 22 and 23).[18,19] Palladium catalysis has also been utilized for the formation of (*E*)-β-(trimethylsilyl)vinyl sulfides from (**1**) (eq 24).[20] A stereoisomeric purity of >99% was observed for the product. Although (**1**) has generally been found to be much more reactive than its (*Z*)-isomer (**3**) is cross-coupling reactions,[15,20] the latter has been efficiently employed in the stereospecific transformation of eq 25.[21]

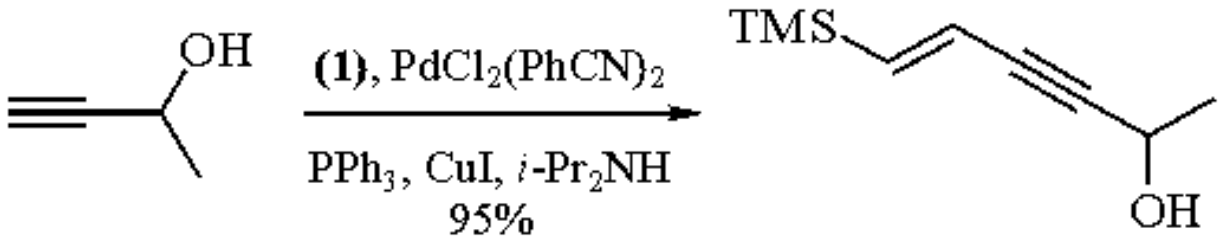

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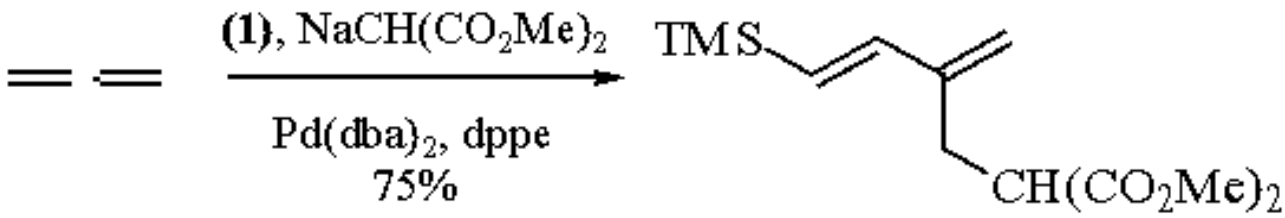

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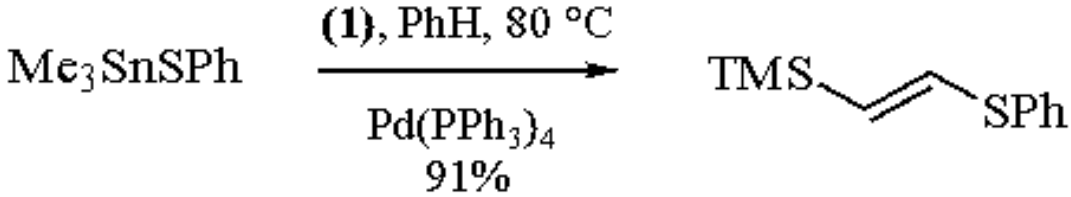

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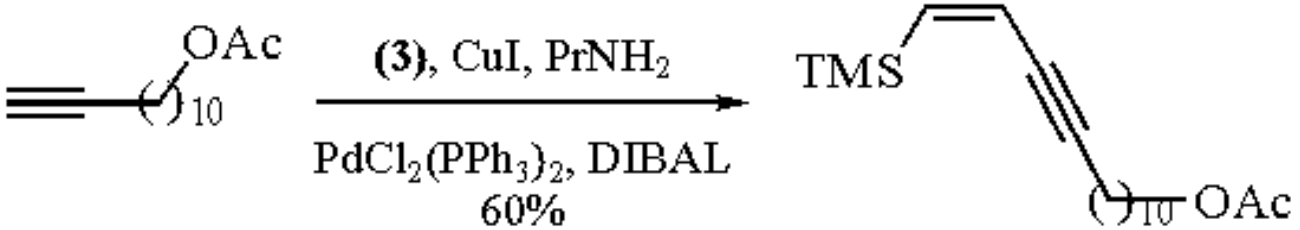

(25)

In behavior separate from those described above, (**3**) undergoes electrophilic substitution of the TMS group characteristic of alkenylsilanes[1] when treated with acyl chloride-***Aluminum Chloride*** mixtures (eq 26).[5]

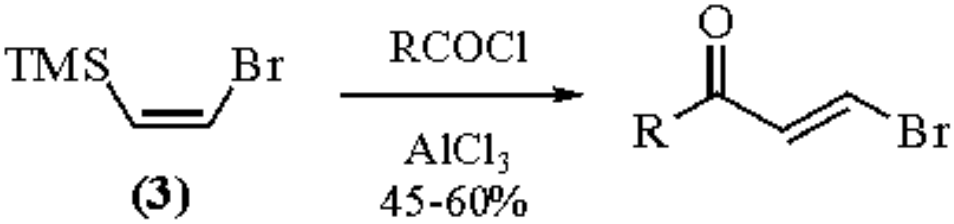

(26)

Related Reagents.

(E)-1-Lithio-2-tributylstannylethylene; ***(E)-2-(Trimethylsilyl)vinyllithium***.

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15. (a) Andreini, B. P.; Carpita, A.; Rossi, R. *TL* **1988**, *29*, 2239. (b) Andreini, B. P.; Carpita, A.; Rossi, R.; Scamuzzi, B. *T* **1989**, *45*, 5621.
16. Ennis, D. S.; Gilchrist, T. L. *T* **1990**, *46*, 2623.
17. Gilchrist, T. L.; Healy, M. A. M. *TL* **1990**, *31*, 5807.
18. Clark, D. L.; Chou, W. N.; White, J. B. *JOC* **1990**, *55*, 3975.
19. Cazes, B.; Colovray, V.; Gore, J. *TL* **1988**, *29*, 627.

20. Carpita, A.; Rossi, R.; Scamuzzi, B. *TL* **1989**, *30*, 2699.
21. Arsequell, G.; Camps, F.; Fabrias, G.; Guerrero, A. *TL* **1990**, *31*, 2739.

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Brucine[1]

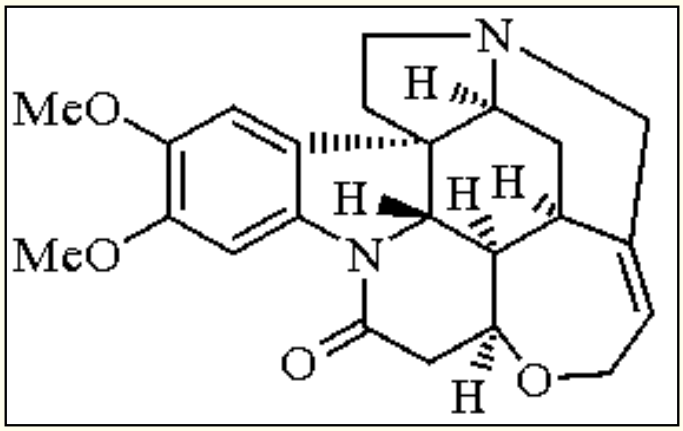

[357-57-3] · $C_{23}H_{26}N_2O_4$ · Brucine · (MW 394.47)

(reagent for the resolution of acids, alcohols, and other neutral compounds[1])

Physical Data: colorless needles (acetone/water) mp 178 °C; $[\alpha]_D$ -79.3° (*c* 1.3, EtOH).

Solubility: very sol methanol, ethanol, and chloroform; mod sol ethyl acetate or benzene.

Form Supplied in: colorless needles or plates. The free base, which is available from multiple commercial sources, is usually hydrated. Dihydrated and tetrahydrated forms have been characterized. Anhydrous brucine can be obtained by heating at 100-120 °C in vacuo for 24 h. The hydrated forms can be used for most applications.

Purification: the commercial reagent is often used without further purification. However, the reagent can be purified by recrystallization from ethanol/water (1:1).[2] Recovered reagent[3] should be purified before reuse.

Handling, Storage, and Precautions: EXTREMELY POISONOUS. Oral LD_{50} in rats is 1 mg kg^{-1}. Handle in well-ventilated hood only.

Introduction.

The alkaloid brucine has been a key resolving agent for over a century, in spite of its highly toxic nature. The group of chiral bases represented primarily by brucine, its homolog strychnine, and the cinchona alkaloids quinine, quinidine, cinchonidine, and cinchonine, has been extremely useful for the resolution of all types of acids.[1] No empirical rules have emerged from all of this work to help in predicting the optimal resolving agent for a given type of acid. Acid resolution is still primarily an empirical process that requires the evaluation of several diastereomeric salts. An inherent limitation to the use of alkaloids as resolving agents for acids is the availability of only one antipode, which sometimes

allows the practical isolation of only one of the acid enantiomers in a pure form. Nevertheless, there are reports of resolutions with brucine that are so efficient that the less crystalline enantiomer can be isolated directly from the mother liquors (see below for examples). In other cases, pairs of pseudoenantiomeric cinchona alkaloids (i.e. quinine and quinidine, cinchonine and cinchonidine), or brucine and another alkaloid, display opposite selectivities for the enantiomers of a racemic acid (see below).[1a]

Resolution of Acids.

The number of acids resolved with brucine is too large to attempt to list even a small portion of them in this synopsis. An excellent tabulation of all published resolutions with brucine up to 1972 is available.[1a] Only a few representative examples will be described here (eqs 1-4).[4-9] In all these cases, the resolved acids were obtained in high yield and with almost absolute enantiomeric purity. The solvents most frequently used for brucine resolutions are acetone and alcohol solvents. However, water, hexane, and others have also been used as cosolvents.

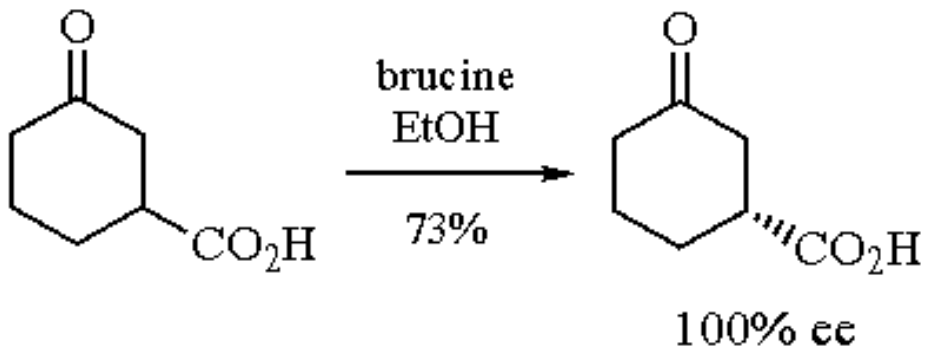

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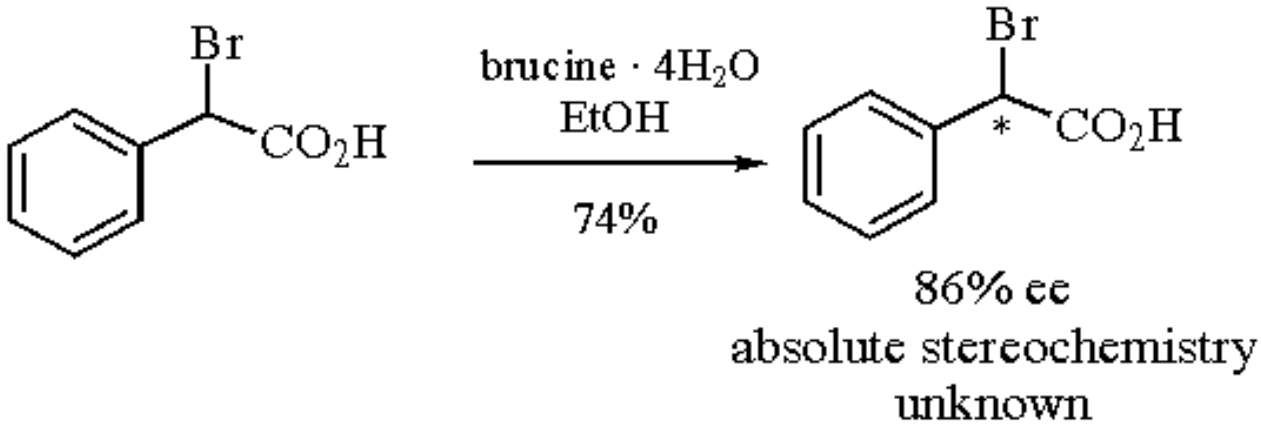

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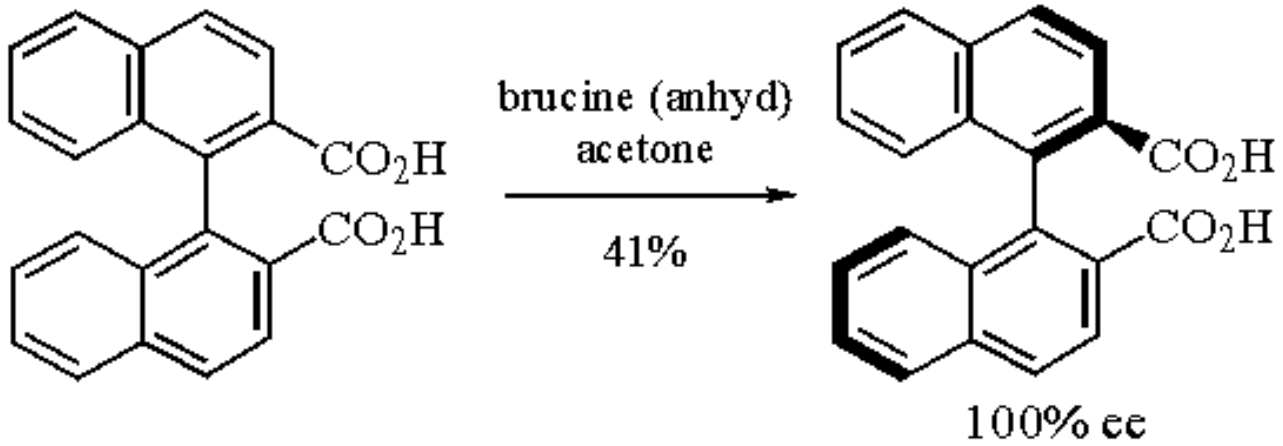

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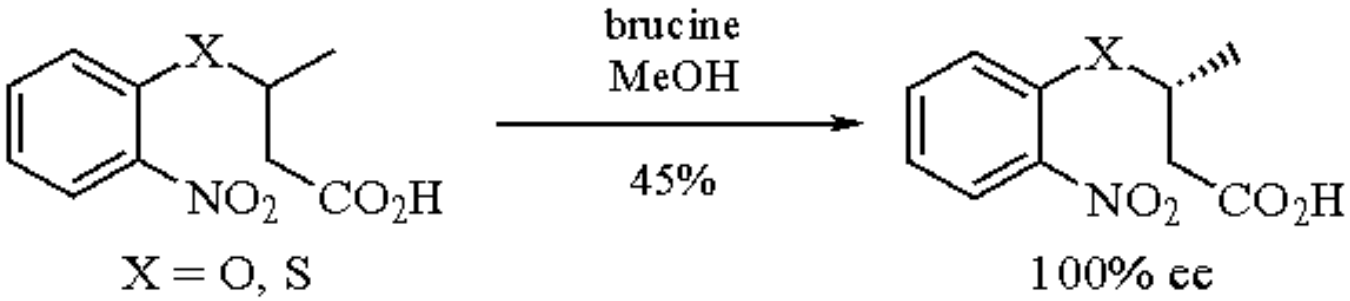

(4)

Additional types of carboxylic acids that have been successfully resolved with brucine are represented by structures (**1**)-(**5**).[10-14]

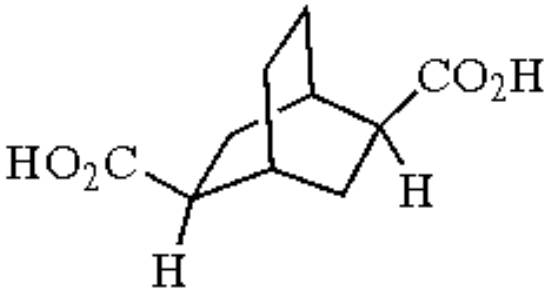

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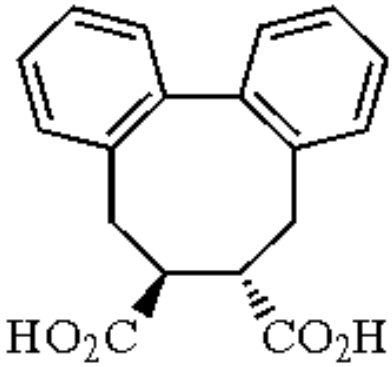

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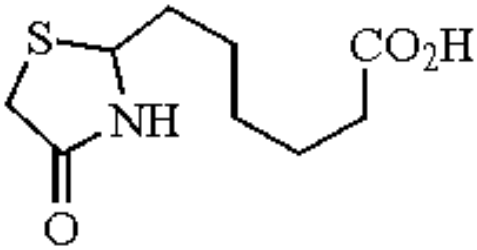

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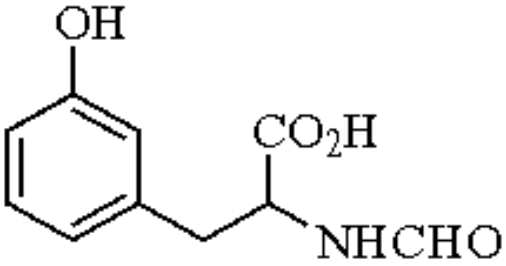

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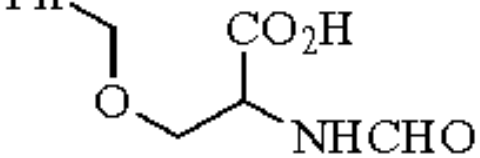

(5)

As mentioned above, one of the limitations of using naturally occurring resolving agents is that only one enantiomer of the compound being resolved may be readily accessible by resolution. However, many examples have been described where brucine and some other alkaloid favor crystallization with opposite enantiomers of a given acid. For example, resolution of acid (**6**) with brucine yields the (+)-enantiomer, while cinchonidine provides material that is enriched in the (-)-enantiomer of the acid.[15] Similarly, diacid (**7**) is resolved into its (-)-enantiomer by brucine and into its (+)-enantiomer by strychnine.[16] The (+)-enantiomer of acid (**8**) can be obtained with brucine, while the (-)-enantiomer crystallizes with cinchonidine.[17] Additional examples of the same phenomenon can be found in the literature.[1a]

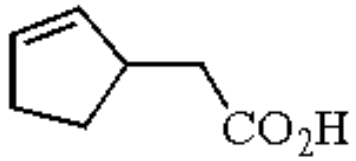

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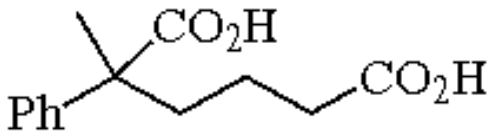

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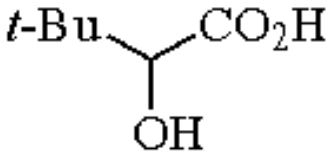

(8)

Resolution of Alcohols.

Although not a well exploited use of brucine, a variety of secondary benzylic alcohols have been resolved by complexation and crystallization with brucine (eq 5).[18] About a dozen alcohols were obtained in close to enantiomeric purity by this procedure.[18] Also resolved by crystallization of their brucine inclusion complexes were a series of tertiary propargylic alcohols (eq 6).[19] In this case, the enantiomer that does not crystallize with brucine can be obtained in almost complete optical purity from the mother liquors.

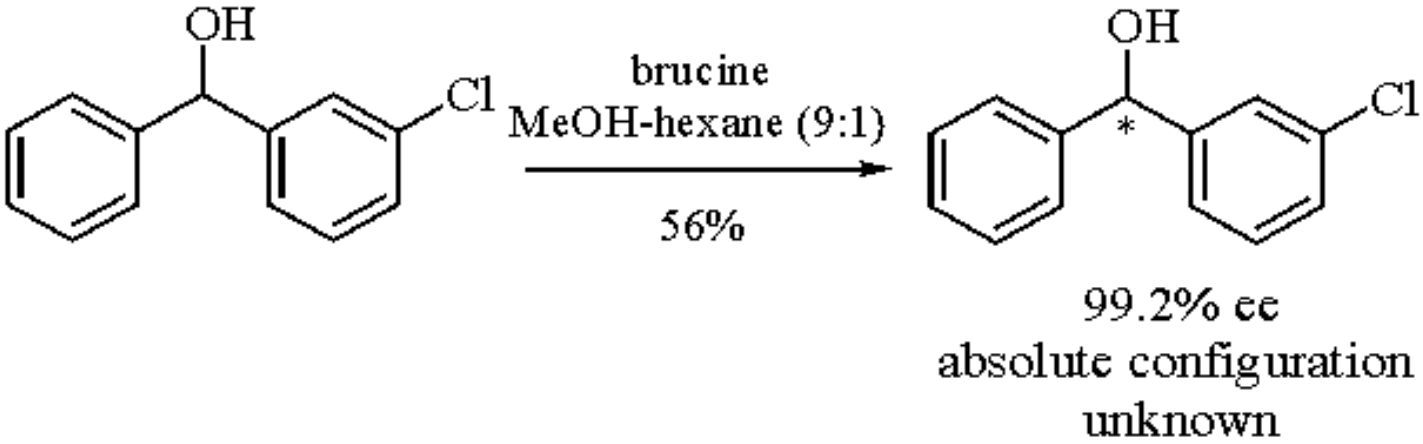

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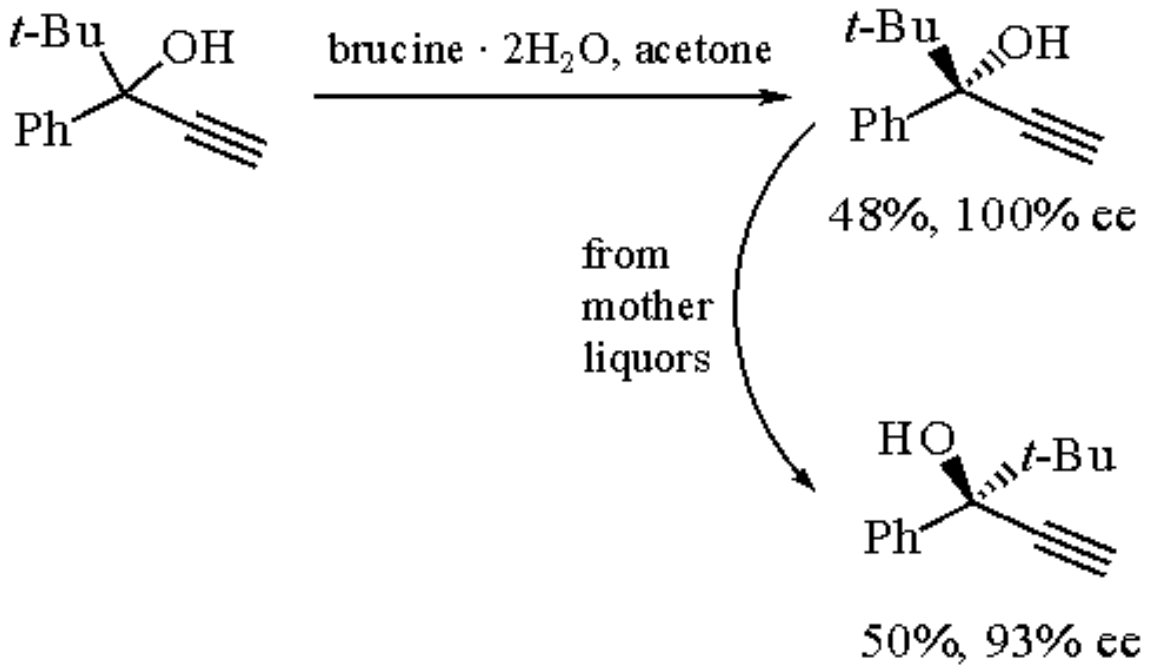

(6)

A more traditional and general approach to the resolution of alcohols is the formation of the corresponding hemiphthalate or hemisuccinate esters, followed by resolution of these acidic derivatives with brucine or some other chiral base (eqs 7-9).[20-23] The resolved alcohols are liberated by alkaline hydrolysis of the esters. High enantiomeric purity is frequently achieved by this procedure, which has been applied successfully to primary, secondary, and tertiary alcohols.

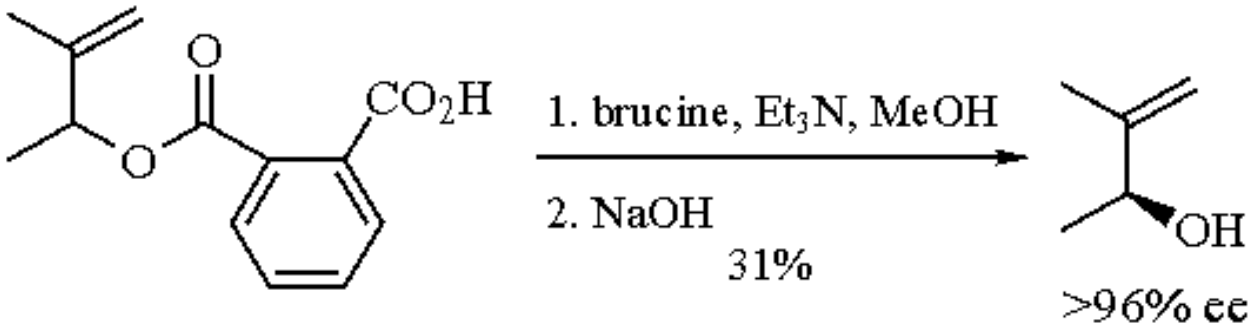

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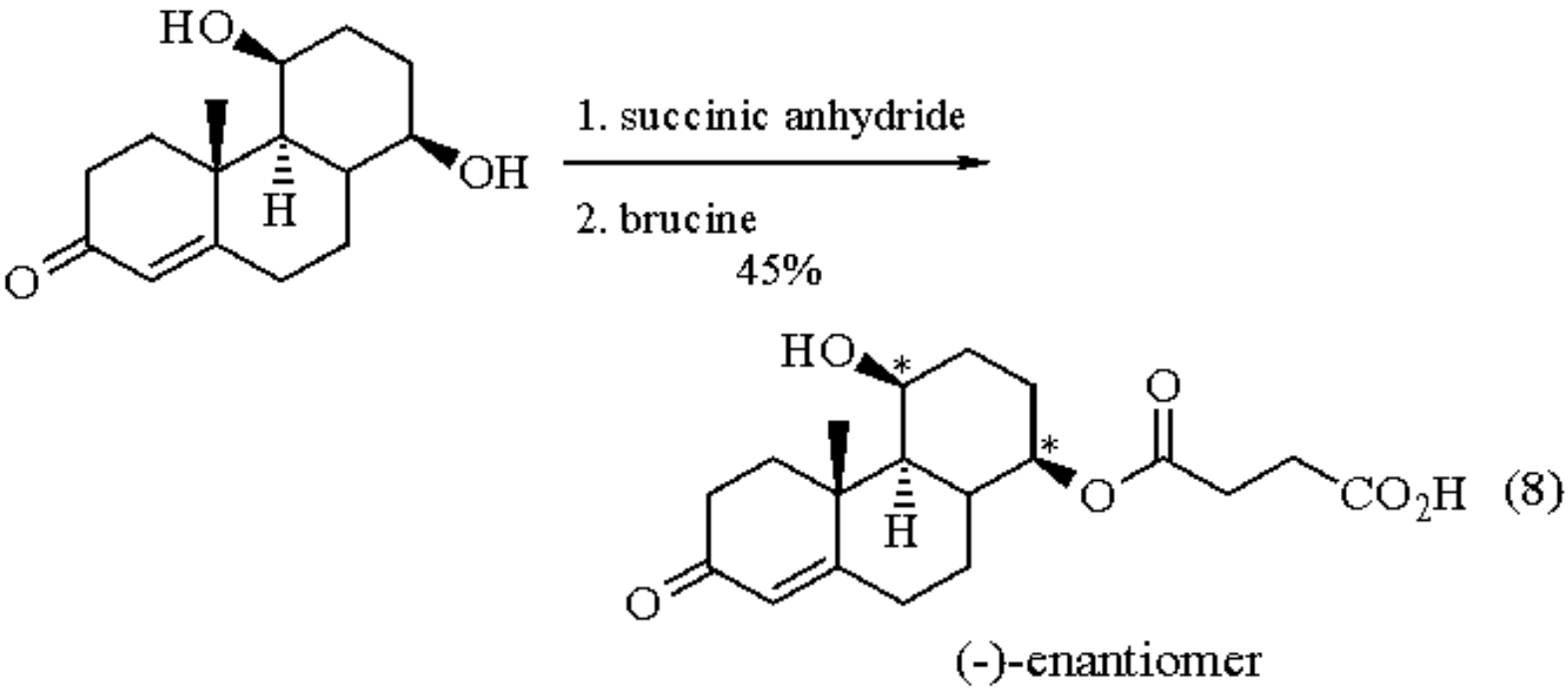

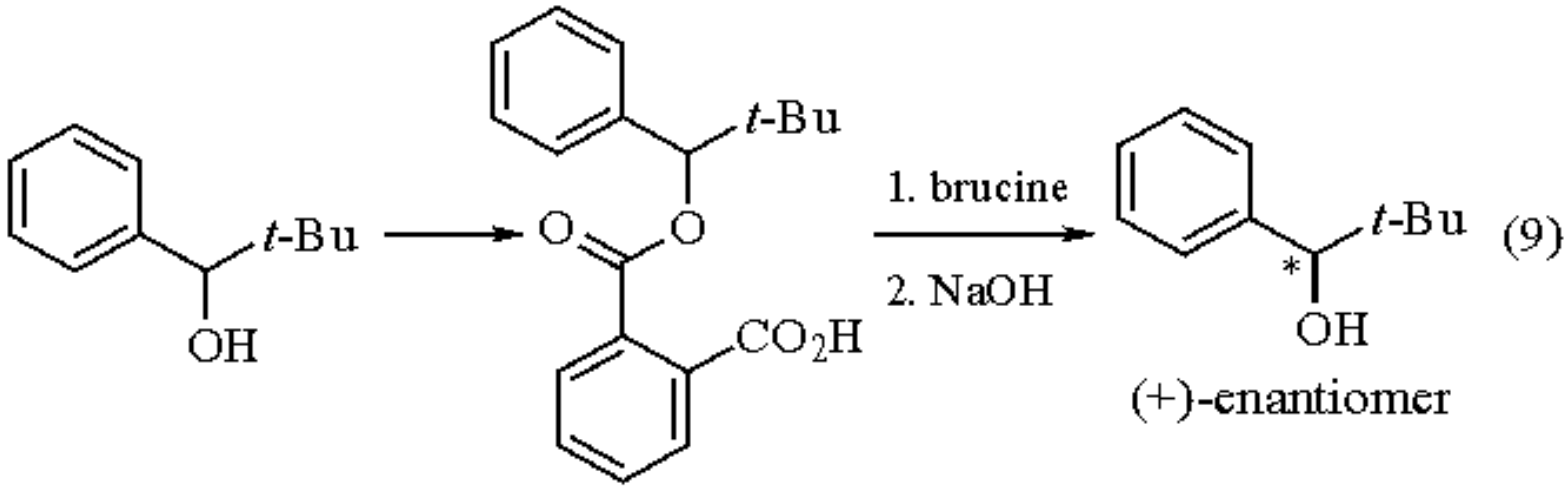

Resolution of Ketones.

Brucine has not been used very extensively for the resolution of neutral compounds. However, in some cases, ketones or ketone derivatives may form diastereomeric inclusion complexes with brucine, providing an opportunity for their resolution. For example, the cyanohydrin of a bicyclic ketone has been resolved by this procedure (eq 10).[24] Following resolution of the cyanohydrin, the ketone was regenerated and determined to be of 94% ee.

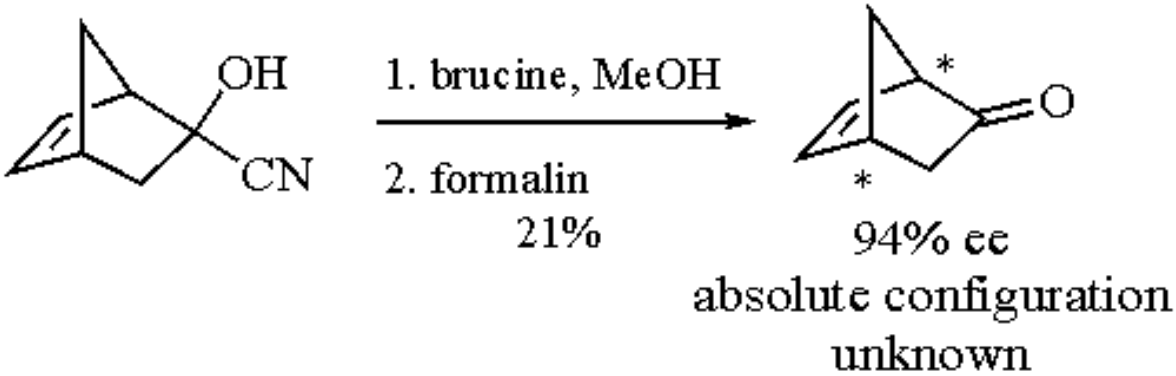

(10)

Resolution of Sulfoxides.

Although it can be considered as the resolution of an unique type of carboxylic acid, some racemic sulfoxides containing carboxylic acids have been resolved via diastereomeric crystalline complexes with brucine (eq 11).[25]

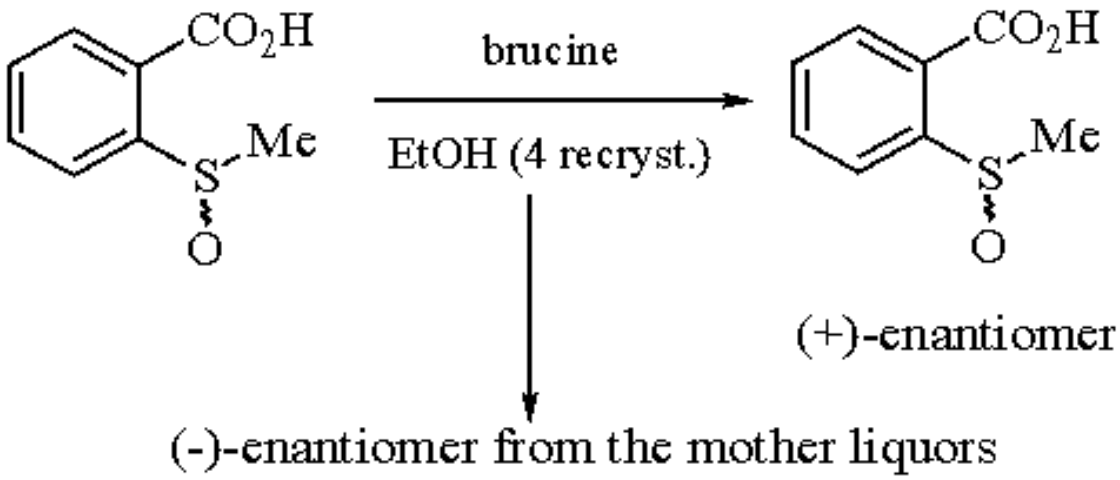

(11)

Chiral Catalysis.

Brucine has been utilized as chiral catalyst in a variety of reactions. For example, its incorporation into a polymer support provides a chiral catalyst for performing enantioselective benzoin condensations.[26] It has also been used as a chiral catalyst in the asymmetric synthesis of (*R*)-malic acid via the corresponding β-lactone, which results from the asymmetric cycloaddition of chloral and ketene (eq 12).[27] Though brucine yields malic acid with 68% ee, quinidine was found to be a more selective catalyst (98% ee).

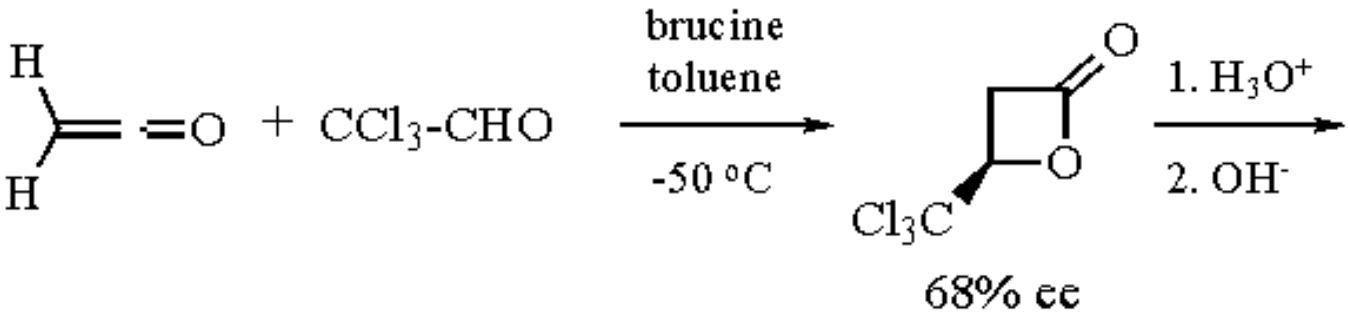

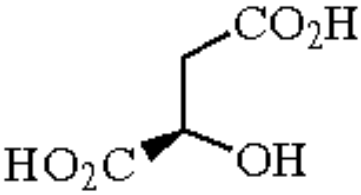

(12)

(*R*)-malic acid

Brucine has been used as an enantioselective catalyst in the kinetic resolution of alcohols. For example, an azirinylmethanol was reacted with 0.5 equiv of ***Acetic Anhydride*** in the presence of 25 mol % brucine. The resulting acetate was found to possess 24% ee (eq 13).[28]

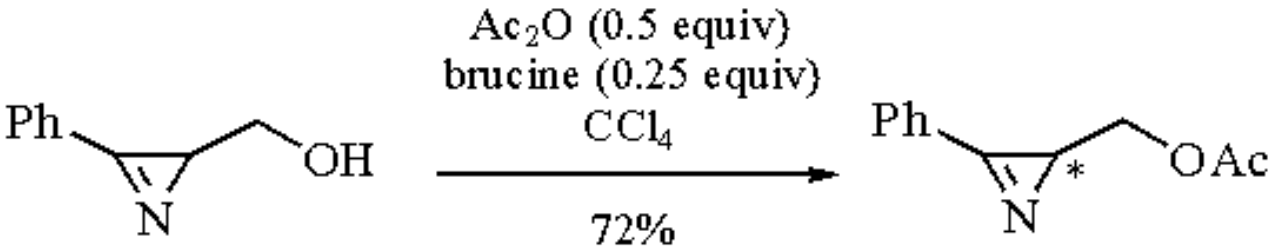

(13)

24% ee
absolute stereochemistry
unknown

Brucine has been used to produce enantiomerically enriched compounds by selective reaction with or destruction of one of the enantiomers. The optical purity of the resulting compound is usually modest, although some exceptions have been described. For example, dibromo compound (**9**) was obtained (enriched in the (-)-enantiomer) by selective destruction of the (+)-enantiomer with brucine in chloroform.[29] The resolution of (±)-2,3-dibromobutane may have also been a case of enantioselective destruction,[30] although more recent reports suggest that it is more likely a case of enantioselective entrapment in the brucine crystals (eq 14).[31]

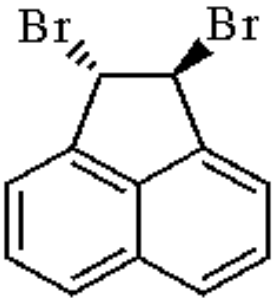

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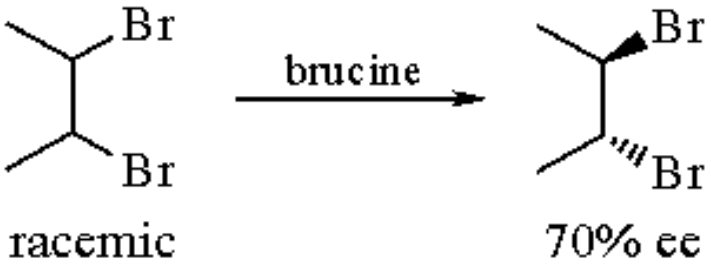

(14)

Miscellaneous.

Brucine greatly accelerates the decarboxylation of certain β-oxo carboxylic acids at rt (eq 15),[32] as well as the decarbalkoxylation of β-oxo esters.[33] In some cases the products of these reactions possess some (modest) enantiomeric excess.[34]

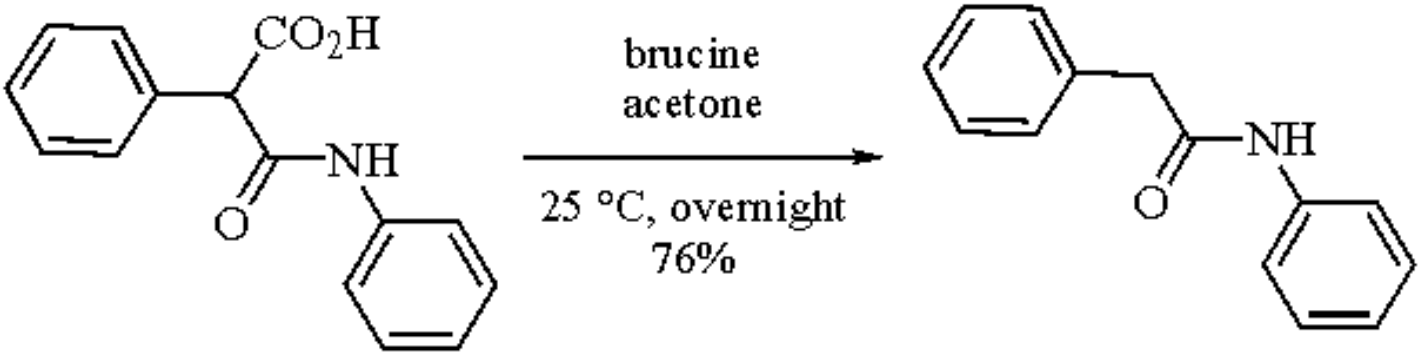

(15)

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1,3-Butadiene

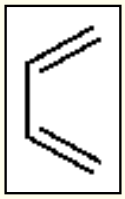

[106-99-0] · C_4H_6 · 1,3-Butadiene · (MW 54.09)

(co-monomer in synthetic elastomers and polymers, polybutadiene rubber, chloroprene, and nylon intermediate;[1] 4π partner in Diels-Alder reactions[2])

Alternate Names: butadiene; α,γ-butadiene; bivinyl; divinyl; vinylethylene; biethylene.

Physical Data: bp -4.5 °C/760 mmHg; mp -109 °C; fp <-7 °C; ρ-64 0.650.

Solubility: sol common organic solvents.

Form Supplied in: widely available in compressed liquid phase. Supplied in several grades ranging from 99.0-99.8% purity. Sizes available range incrementally from lecture bottles (100 g) to large gas cylinders (61 kg).

Preparative Methods: butadiene sulfone (2,5-dihydrothiophene 1,1-dioxide), a crystalline, nonhygroscopic, commercially available solid, can be used to generate 1,3-butadiene in situ: heating the sulfone at 100-130 °C induces loss of SO_2.[3b,3c]

Handling, Storage, and Precautions: extremely flammable liquid and gas. Avoid polymerization initiators. Relatively nontoxic. Suspected chronic carcinogen. Acutely irritating to respiratory tract. 1,3-Butadiene (**1**) is used in the laboratory by condensing the gas directly into a reaction vessel, or by forming a saturated solution of the gas in the reaction solvent. For reactions run below rt (e.g. Lewis acid-catalyzed reactions), normal reaction flasks can be used. For higher temperature reactions, sealed tubes are required to prevent escape of (**1**). A particularly convenient, reusable apparatus is available from Ace Glass, Inc., and consists of a heavy-walled glass tube sealed on one end and threaded on the other. The threaded end can be sealed with a heavy Teflon plug fitted with an O-ring.

Reactivity.

1,3-Butadiene (**1**) participates as the 4π partner in $[_{\pi}4_s + _{\pi}2_2]$ cycloaddition reactions with a variety of dienophiles. The majority of these cycloadditions are normal Diels-Alder reactions ($HOMO_{diene}$-$LUMO_{dienophile}$ controlled).[2,3a] Theoretical predictions on the mechanism of Diels-Alder reactions of butadiene have pointed towards a synchronous concerted mechanism.[4] 1,3-Butadiene (**1**) is typically less reactive than substituted butadienes, except when steric

factors prevent the diene from attaining the reactive *s-cis* conformation. For example ***Tetracyanoethylene*** reacts more slowly with (**1**) than with (*E*)-1-methyl-1,3-butadiene (103×), 2-phenyl-1,3-butadiene (191×), or (*E*)-1-methoxy-1,3-butadiene (50 934×).

Lewis Acid-Catalyzed Cycloadditions.

Friedel-Crafts type catalysts are reported to facilitate the cycloaddition reactions of (**1**) with α,β-unsaturated carbonyl compounds.[5] With methyl vinyl ketone (eq 1), cycloaddition was effected in the presence of less than 1 molar equivalent of ***Aluminum Chloride***, ***Tin(IV) Chloride***, ***Boron Trifluoride***, ***Iron(III) Chloride***, or ***Titanium(IV) Chloride*** for 1 h at 25 °C. For comparison, the uncatalyzed reaction required 8-10 h at 140 °C in a sealed tube (75%). ***Acrolein***, ***Methyl Vinyl Ketone***, and ***Acrylic Acid*** all underwent effective catalyzed Diels-Alder reactions with (**1**) in good yields. The principal limitation of this reaction is polymerization of the 1,3-diene. For example, 2,3-dimethylbutadiene and cyclopentadiene underwent polymerization and dimerization, respectively, under these conditions.

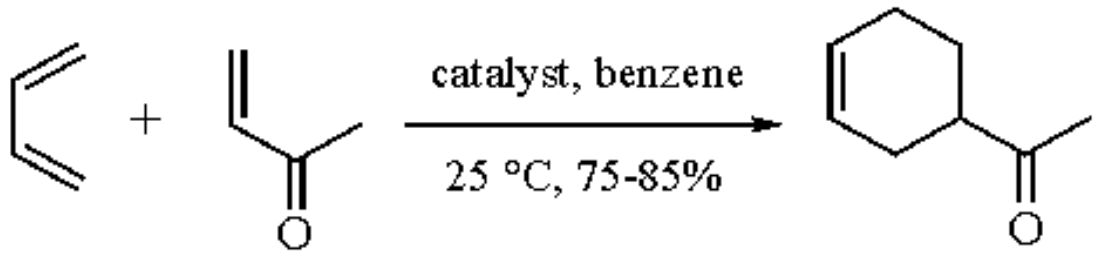

(1)

In the cycloaddition of (**1**) with 2,5-cyclohexadienones in an approach to *cis*-clerodanes, the facial selectivity depended on the length of the carboxylate side-chain (eq 2).[6] When the carboxylate was a significant distance from the ring (*n* = 2), cycloaddition occurred *syn* to the less bulky methyl group to afford the *anti* cycloadduct. Facial selectivity eroded with *n* = 1, and was reversed when the carboxylate was directly attached to the ring, to afford exclusively the *syn* diastereomer.

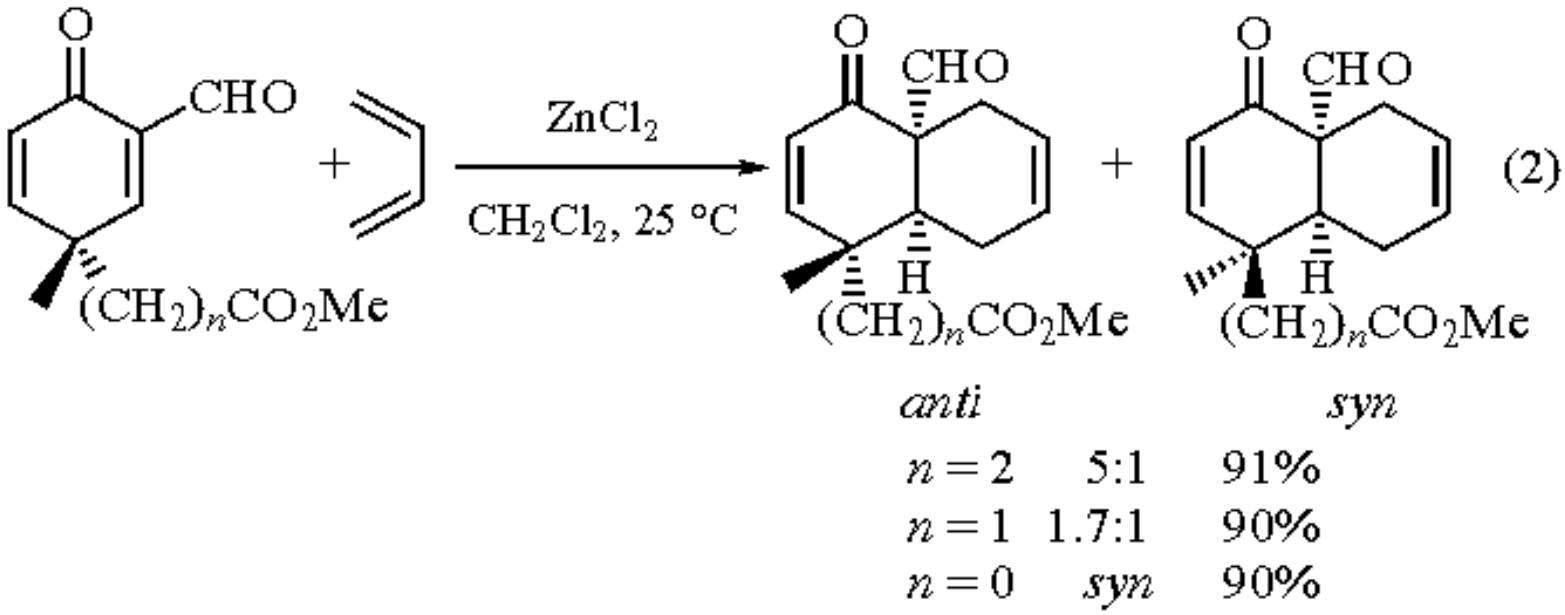

(2)

Lewis acids have also been used to catalyze the cycloaddition of (**1**) with alkynes (eq 3).[7] A mixture of $TiCl_4$ and ***Diethylaluminum Chloride*** promoted the [4 + 2] cycloaddition of phenyl(trimethylsilyl)acetylene and (**1**) to afford the

dihydrobenzene adduct in 84% yield, which could be aromatized thermally to afford the *ortho*-disubstituted benzene in 92% yield. Cycloaddition of cycloalkenones with butadiene in the presence of $AlCl_3$ affords the expected *cis*-fused systems for *n* = 2, 3, 4 (eq 4).[8] Partial or total isomerization of the *cis* adduct to the more stable *trans* isomer was observed with R = H.

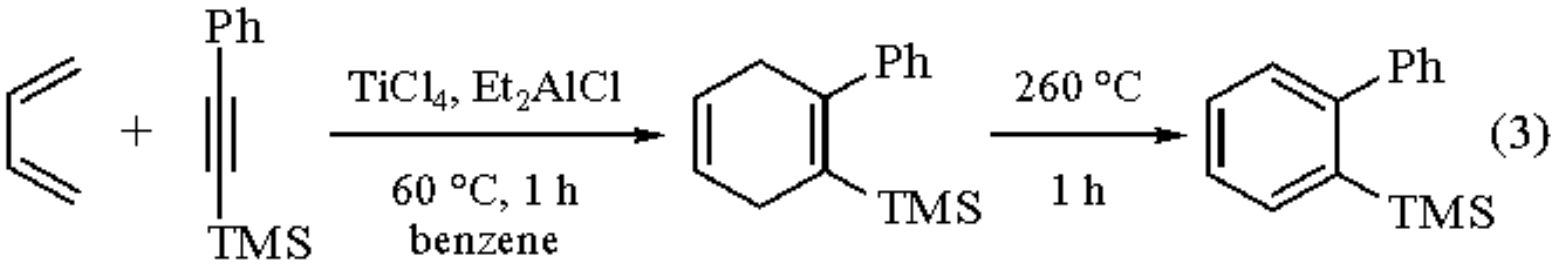

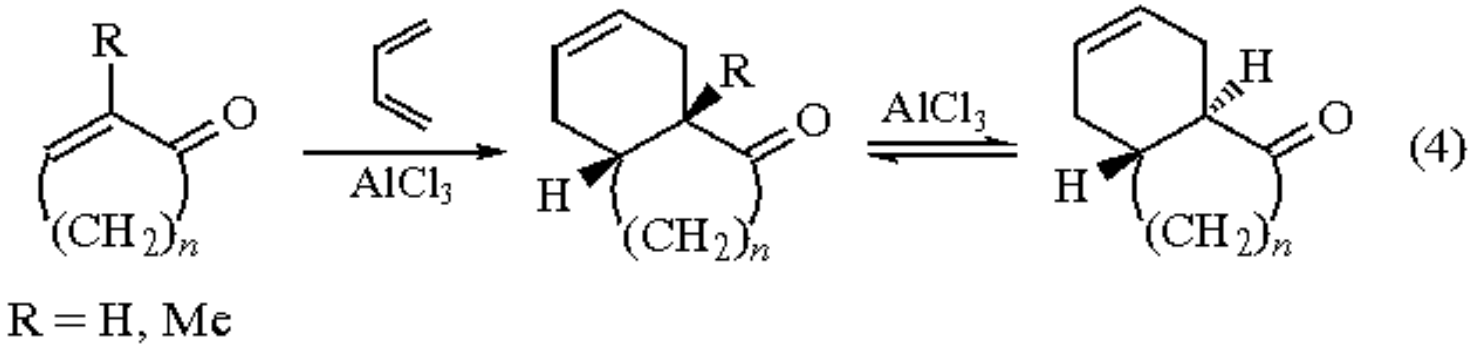

A highly regioselective and moderately stereoselective cycloaddition of (**1**) with the γ,δ-double bond of a dienone was effected by $AlCl_3$ catalysis in 37% yield (eq 5).[9] The cycloadduct formally arising from approach of butadiene *syn* to the enone ring predominated initially, and was shown to isomerize to the more stable *anti* product under the reaction conditions. Contrasteric facial selectivity was observed in the Lewis acid-catalyzed cycloaddition of (**1**) with γ-alkoxycycloalkenones (eq 6).[10] When *n* = 1, cycloaddition at rt in the presence of catalytic $AlCl_3$ afforded predominately the *syn* cycloadduct (76%; 13:1 *syn/anti*). Under similar reaction conditions with *n* = 2, the *syn* cycloadduct was also the major product (10:1 *syn/anti*). The divergence of these results with those obtained with γ-alkylcycloalkenones was discussed, and a tentative theoretical model was proposed to account for the *syn* selectivity.

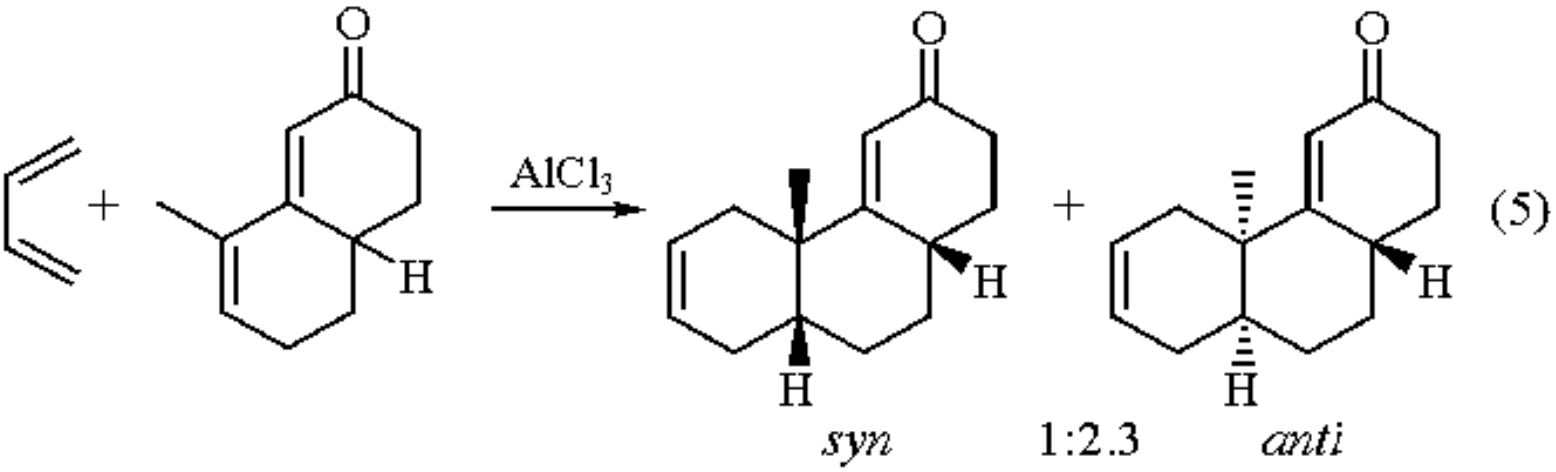

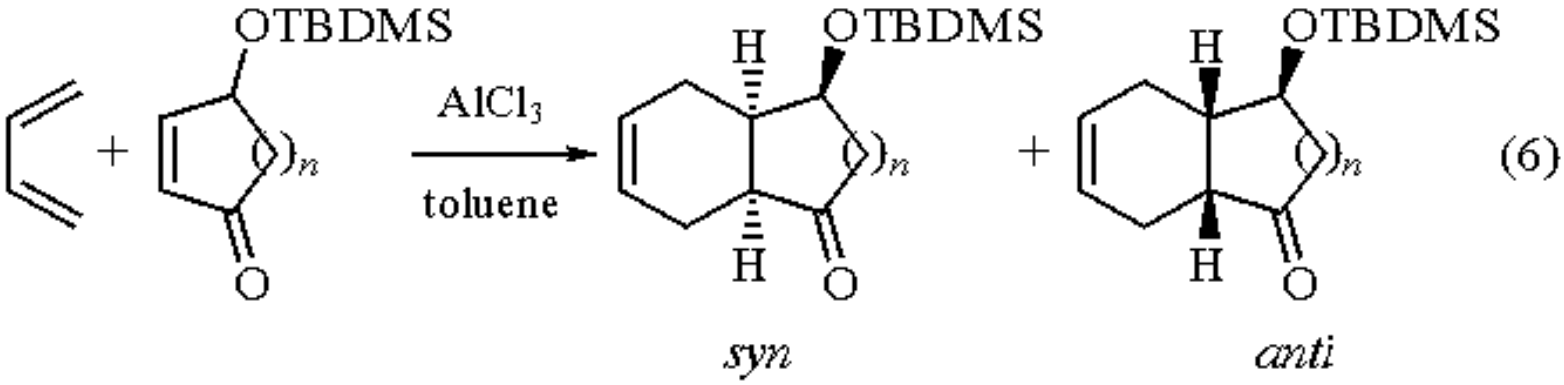

Montmorillonite K10 exchanged with Fe^{III} has been reported to catalyze the Diels-Alder reaction of butadiene with acrolein (eq 7).[11] Cycloaddition occurs at rt in high yield in the presence of 1.8 g catalyst per 15 mmol cycloaddition partners. Other dienes reacted with equal facility with acrolein under these conditions.

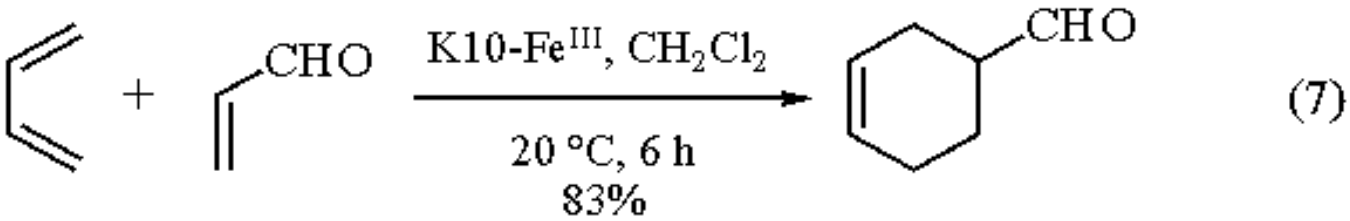

Asymmetric Diels-Alder Reactions.

Cycloaddition of (**1**) with a methacrylate dienophile using a camphor lactam imide in the presence of Lewis acid affords the cyclohexenecarboxylate cycloadduct in 61% yield with 85:15 π-facial selectivity.[12] Presumably the steric bulky of the coordinated metal forces the methacrylate to adopt an *s-trans* conformation as shown (eq 8), and cycloaddition occurs from the less crowded bottom face of the complex. A pyrrolidin-2-one auxiliary containing the bulky 5-(trityloxymethyl) group was effective at asymmetric induction in the Lewis acid-catalyzed cycloaddition of (**1**) with a fumarate dienophile (eq 9).[13] The cyclohexenedicarboxylate was obtained in 52% yield and 96% de. Other dienophiles and Lewis acids were examined and found to be equally effective, giving high *endo* selectivity (&egt;97:3) and excellent diastereoselectivity (&egt;94% de).

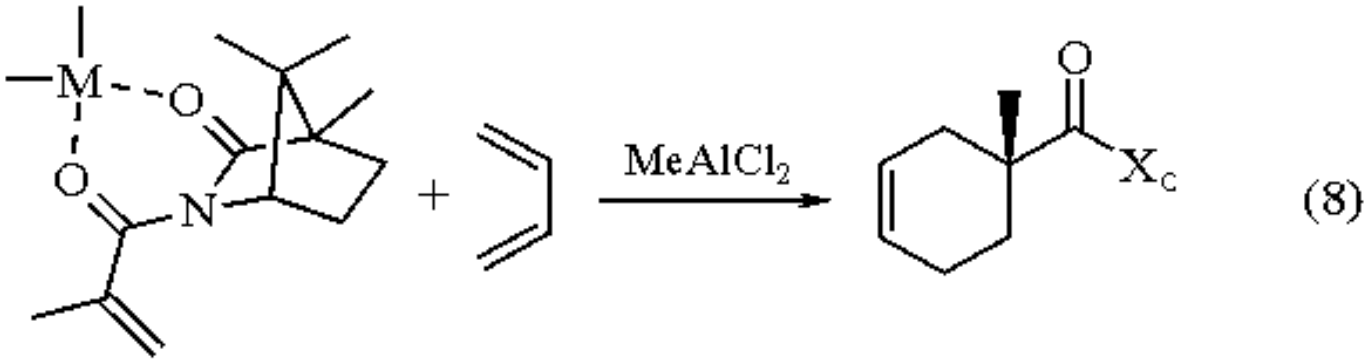

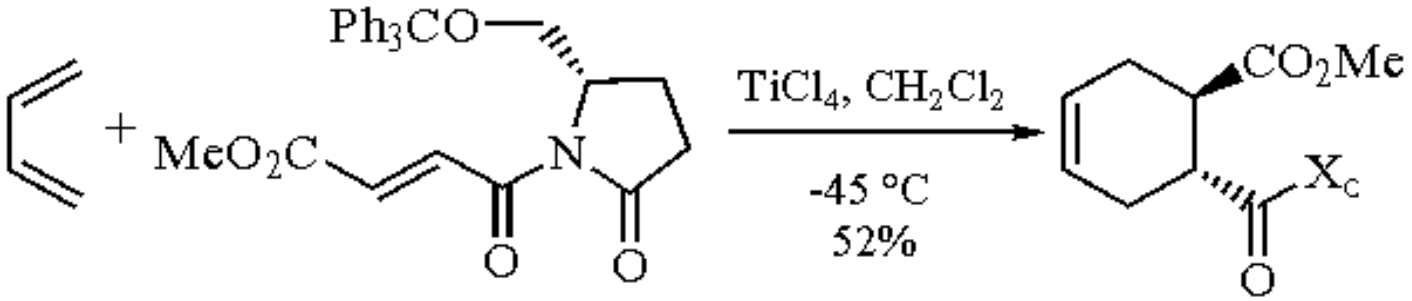

(9)

Carbohydrate-based chiral auxiliaries have proven effective in cycloadditions with (**1**).[14] The auxiliary derived from 3-*O*-acryloyldihydro-D-glucal (eq 10; R = pivaloyl) afforded the (*S*)-cyclohexenecarboxylate (8:92 *R/S*), whereas the pseudoenantiomeric system, 3-*O*-acryloyldihydro-L-rhamnal (eq 11; R = pivaloyl), afforded the (*R*)-cycloadduct (95:5 *R/S*). Complexation of the titanium catalyst to each of the ester carbonyl oxygens was postulated to rigidify the acryloyl group, locking it in the conformation depicted. In both cases, cycloaddition presumably occurs to the less hindered face of the acrylate away from the bulky 4-*O*-pivaloyl group.

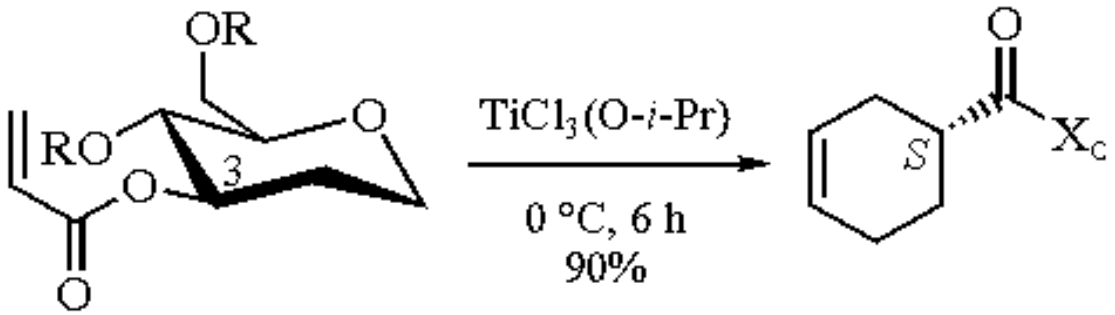

(10)

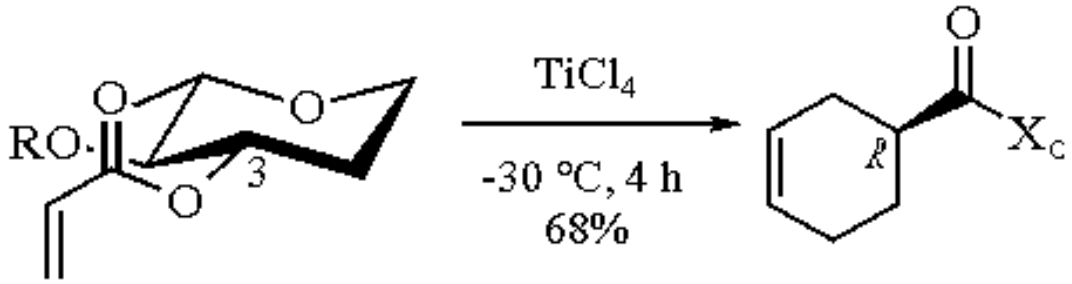

(11)

Chiral titanium-based catalysts have been used in asymmetric Diels-Alder reactions of (**1**). A mixture of $TiCl_4$ and ***Titanium Tetraisopropoxide*** was used with a tartrate-derived auxiliary in the cycloaddition of (**1**) with a quinone (eq 12) to afford the expected bicyclic system in 88% yield and 63% ee.[15] Other dienes underwent stereoselective cycloadditions with better asymmetric induction. A similar catalyst system was used in the cycloaddition of (**1**) with fumarate[16] and acrylate[17] derivatives. The catalyst was prepared by alkoxy exchange with the tartrate-derived auxiliary and ***Dichlorotitanium Diisopropoxide***, and was treated with the cycloaddition partners at rt for 24 h to afford the cyclohexenecarboxylate in 81% yield and in 93% optical purity (eq 13). Other dienes underwent asymmetric cycloaddition with equal success. A model was proposed for the catalyst-dienophile complex.

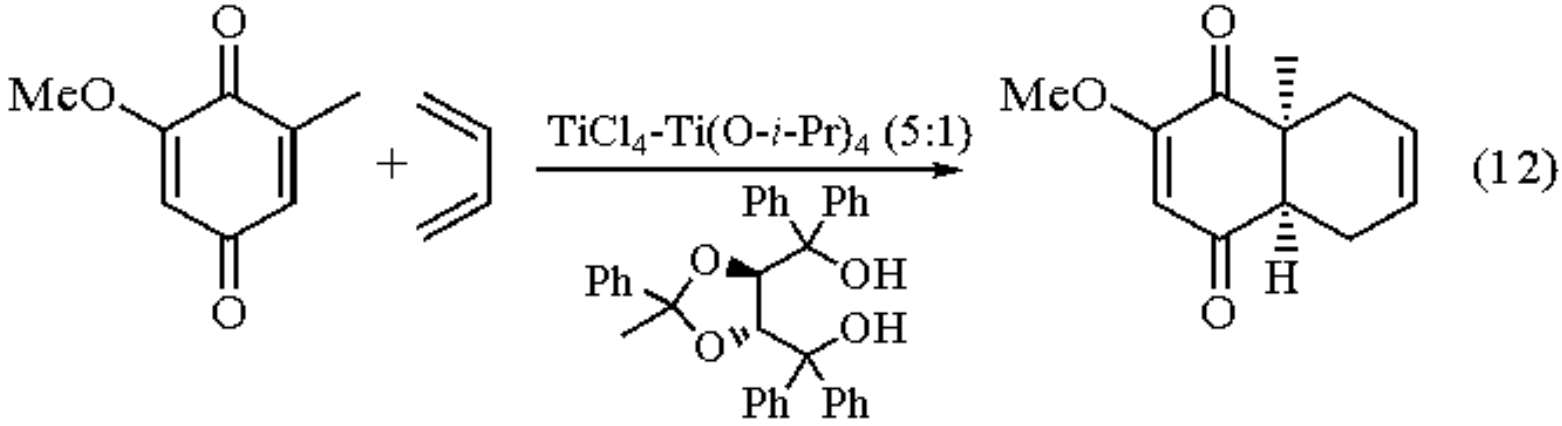

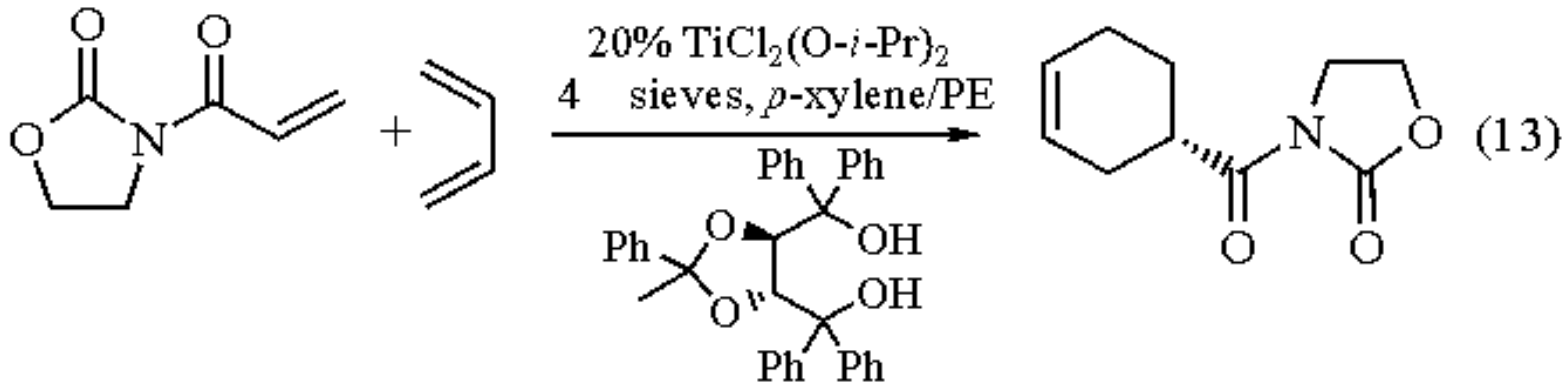

The C_2-symmetric hydrobenzoin complexed with $TiCl_4$ promoted the cycloaddition of (**1**) with ***Dimethyl Fumarate*** to afford the cyclohexenedicarboxylate in 78% yield with a modest 60% ee (eq 14).[18] Carboxylic ester dienophiles have typically participated ineffectively in asymmetric Diels-Alder reactions.

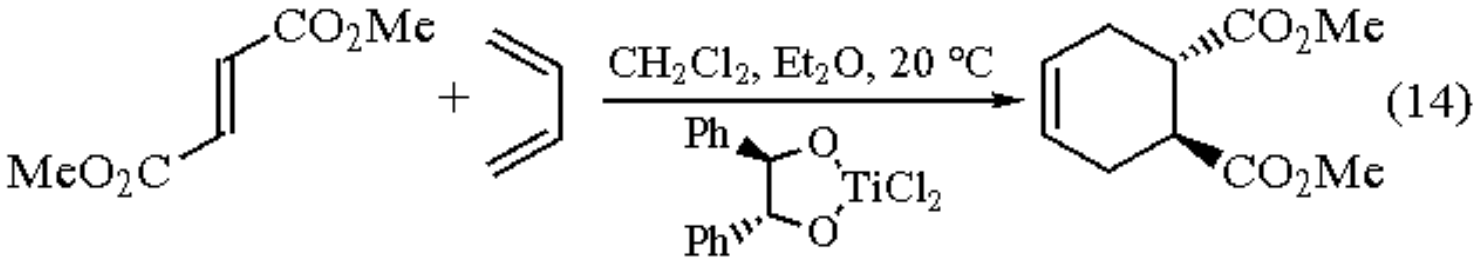

Applications in Synthesis.

Butadiene is a widely used reagent in organic synthesis. It is primarily used as the 4π participant in the Diels-Alder construction of carbocyclic and heterocyclic six-membered rings,[2] although numerous other uses have been recorded.

Butadiene cycloaddition was a key step in the synthesis of constrained phenanthrenamine derivatives that are active as noncompetitive NMDA antagonists.[19] Reaction of dihydronaphthalenecarboxylic acid with (**1**) in toluene at 110 °C in the presence of polymerization inhibitor afforded the tricyclic adduct in 60% yield (eq 15). Hydrogenation of the resulting double bond afforded the hydrophenanthrenecarboxylic acid, which was converted to a variety of tetracyclic structures where the carboxylate was converted to an amine by modified Curtius rearrangement.

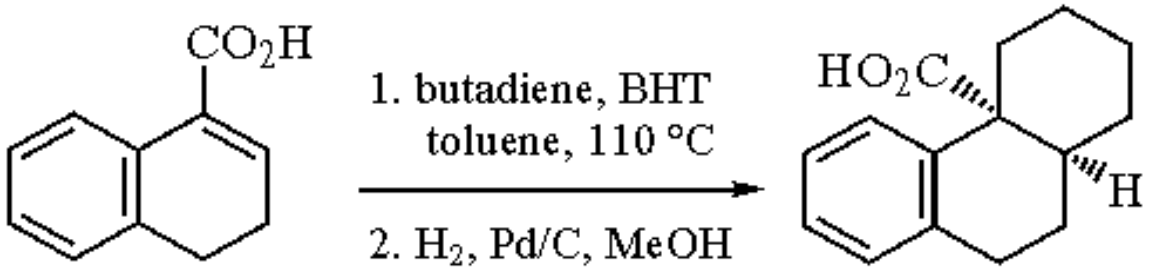

(15)

Three reports have described the use of butadiene in the asymmetric construction of the C-28-C-34 fragment of the immunosuppressant FK-506.[20-22] In the first report (eq 16), the acrylate ester of (*S*)-(+)-pantolactone was reacted with (**1**) in the presence of $TiCl_4$ to afford the cyclohexenecarboxylate in excellent yield and in 91% de.[20] In the second report, the same Diels-Alder reaction was performed with a chiral sultam auxiliary under $EtAlCl_2$ catalysis to give the cyclohexenecarboxylate in 86% yield in 93% ee (eq 17).[21] In the third report, an acryloyl-(*S*)-2-hydroxysuccinimide underwent cycloaddition with (**1**) under catalysis by $TiCl_4$ to afford the cyclohexenecarboxylate in 85% yield in 98% ee (eq 18).[22] The double bond of all three cycloadducts was subsequently converted to the *anti*-diol of FK-506. A cycloaddition reaction identical to that shown in eq 16 was used as a key step in the asymmetric synthesis of the cyclohexane ring of (+)-phyllanthocin.[23] In this instance the cycloaddition proceeded in 70% yield and in 97% ee.

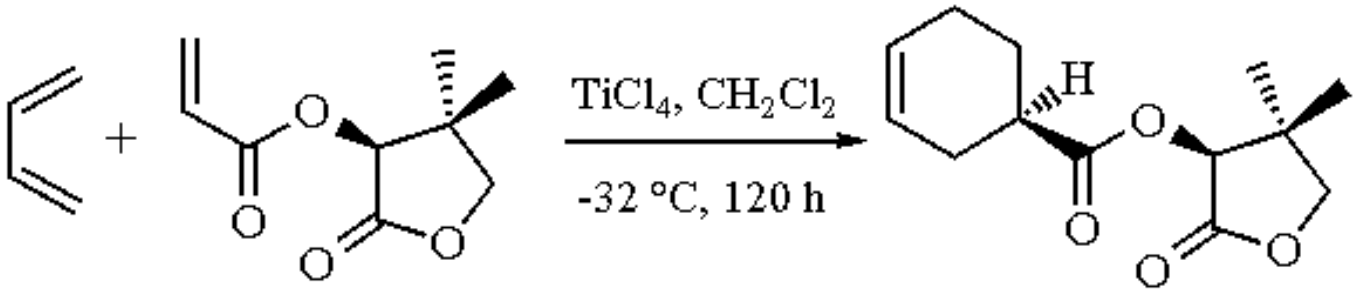

(16)

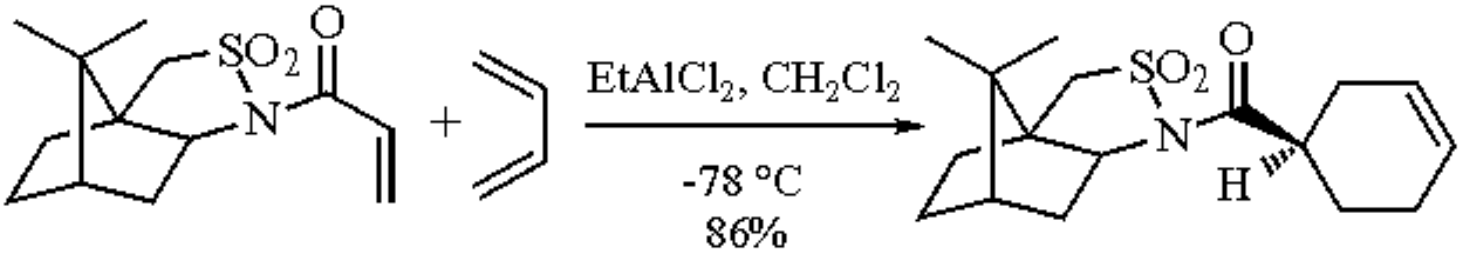

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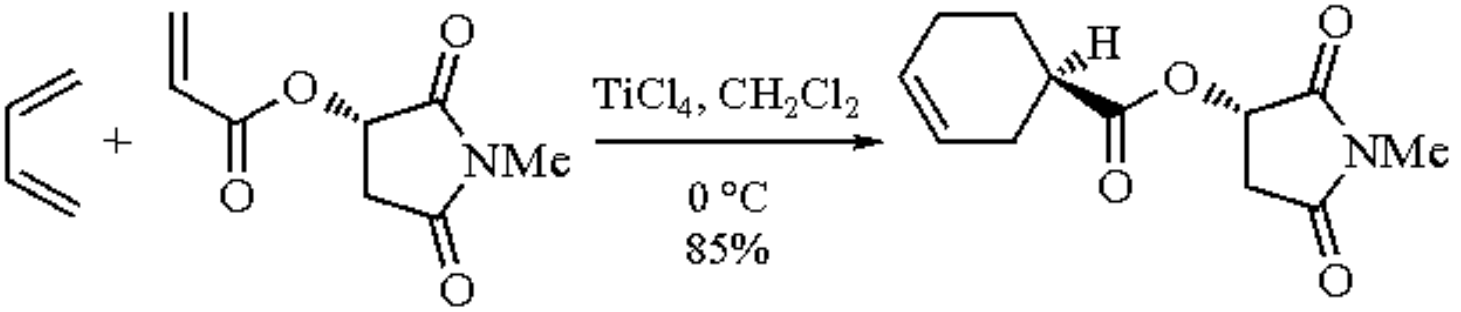

(18)

A β-pinene-derived dienophile was used as the 2π cycloaddition partner with (**1**) in an approach to the morphine skeleton (eq 19).[24] Thermal cycloaddition occurred stereoselectively from the face opposite the substituted bridge to afford the adduct in 82% yield. Cycloaddition was also effected in lower yield under Lewis acid-catalyzed conditions

($Cu(BF_4)_2$, CH_2Cl_2, 25 °C, 12 h, 34%). Further elaboration of the cycloadduct afforded the *cis*-Δ^6-1-octalone acetal possessing the required absolute configuration at three contiguous stereogenic centers for conversion to morphine-related compounds. In a synthetic approach to analogs of the potassium channel activator aprikalim, butadiene was used in a hetero Diels-Alder reaction for the construction of a thiopyran ring (eq 20).[25] Thus reaction of the thiocarbonyl group of an α-thioketo ester (generated in situ) with (**1**) afforded the desired thiopyran in 65% yield.

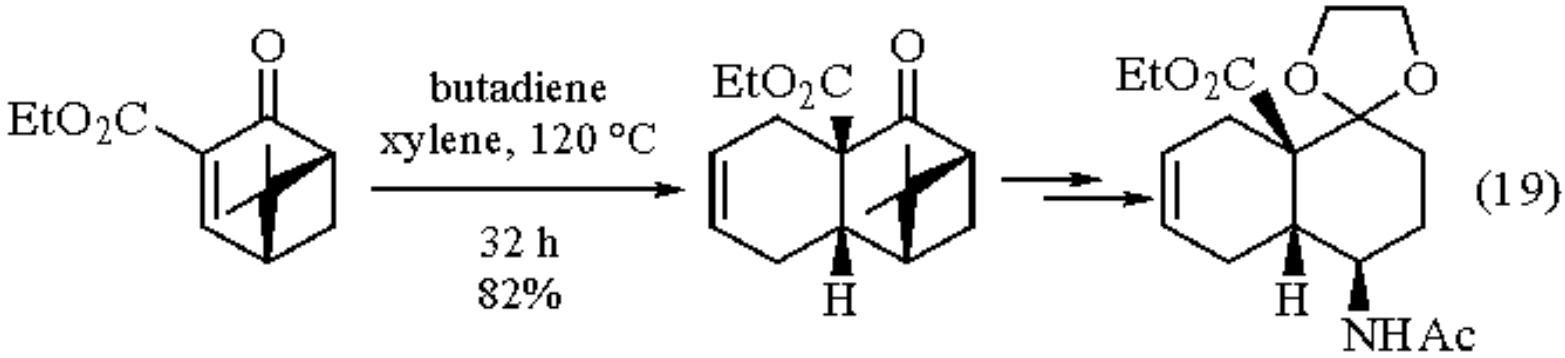

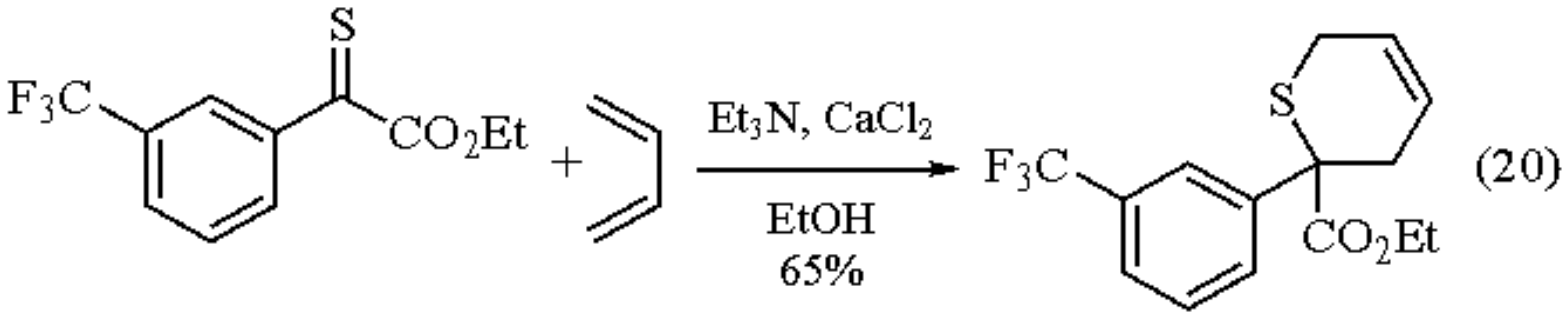

An asymmetric Diels-Alder reaction of (**1**) with a phenylalaninol-derived auxiliary was used to construct the B-ring of (+)-compactin and (+)-mevinolin (eq 21).[26] Cycloaddition of the (*E*)-crotonic acid derivative with butadiene in the presence of catalytic Et_2AlCl afforded the desired cycloadduct in 56% yield and greater than 95% de. The auxiliary was removed and the desired *cis*-isomer of the 2-methyl-4-cyclohexenecarboxylate was obtained by base-promoted epimerization of the *trans*-isomer (65:35 *cis/trans* equilibrium mixture). Use of the corresponding (*Z*)-crotonoyl auxiliary was not examined as the (*Z*) configuration of the alkene is not preserved under the reaction conditions.[27]

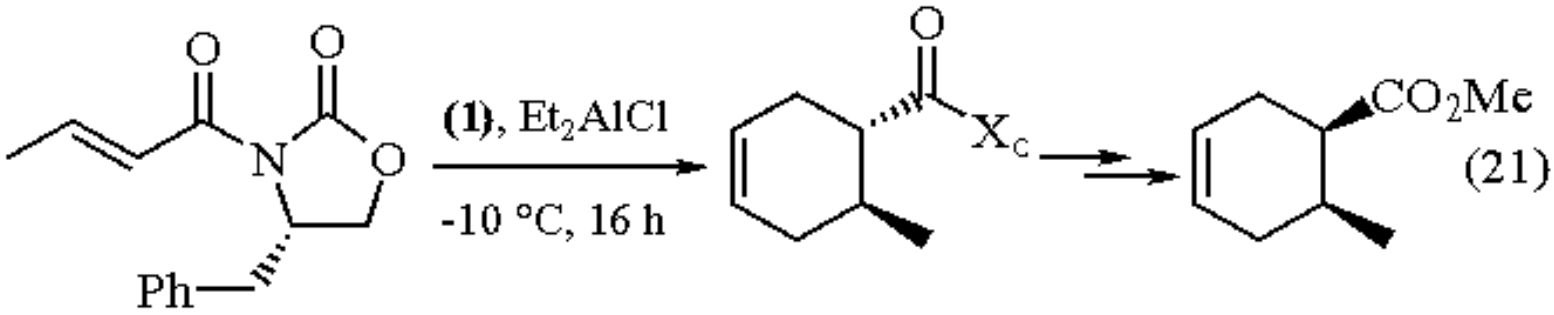

A rapid and stereospecific construction of the 2-azabicyclo[3.3.1]nonane ring system characteristic of *Strychnos* alkaloids was initiated with a Diels-Alder reaction of β-nitrostyrene and (**1**) (eq 22).[28] After reduction of the nitro group and *N*-acylation, the desired aminocyclohexene was obtained in 63% overall yield. Subsequent elaboration to the 2-azabicyclo[3.3.1]nonane system involved a high-yielding stereoselective Heck reaction. Butadiene sulfone was used for in situ generation of (**1**) in an approach to cephalotaxine analogs. In a key step, a β-nitrostyrene dienophile was treated

with butadiene sulfone at 135 °C to afford the butadiene cycloadduct in 74% yield (eq 23).[29]

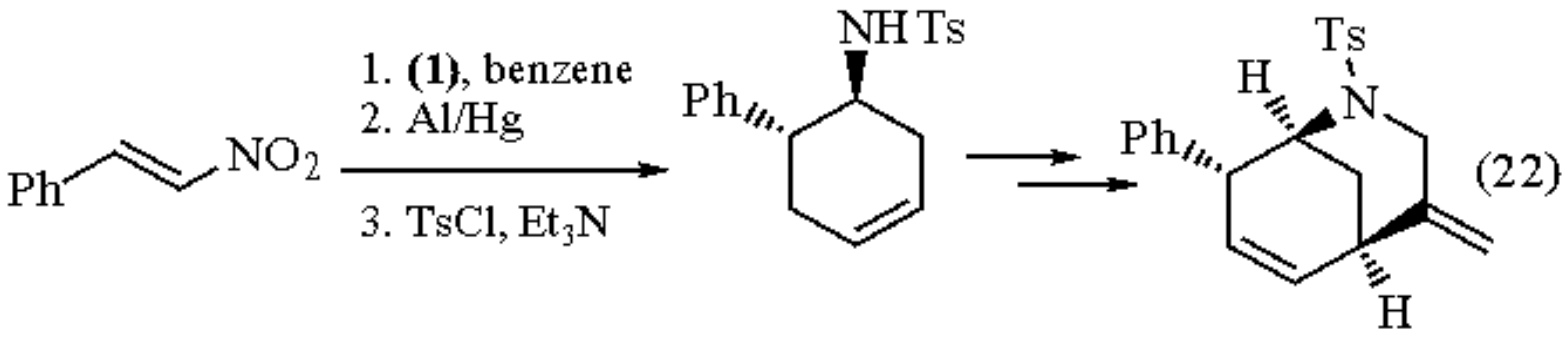

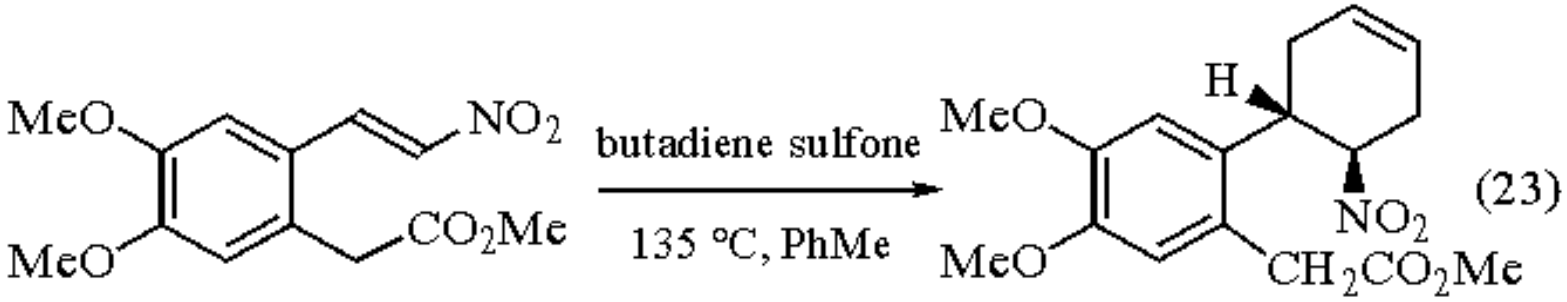

Miscellaneous Reactions.

The novel dienophile 2-trimethylsilylvinyl-9-BBN was shown to undergo facile Diels-Alder reaction with butadiene to afford the 2-trimethylsilylcyclohexenol in 85% yield after oxidation of the intermediate trialkylborane (eq 24).[30] The cycloadduct was shown to be a precursor to 5-trimethylsilyl-1,3-cyclohexadiene and -1,4-cyclohexadiene, thus making the dienophile an acetylene equivalent.

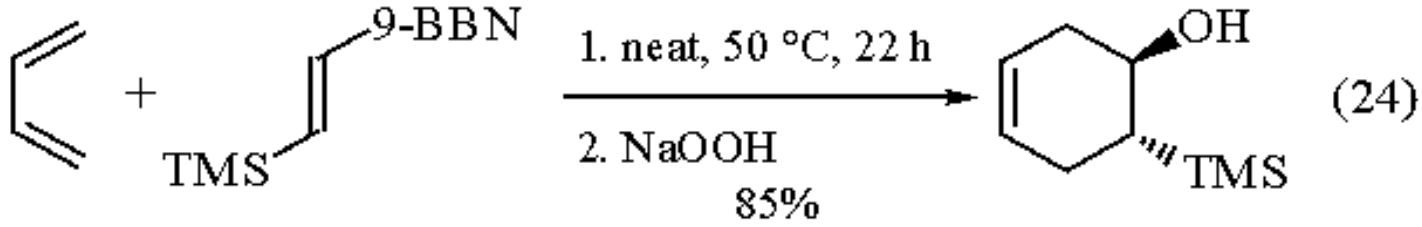

Catalytic osmylation was used to convert 1,3-butadiene to a polyol with good control of relative stereochemistry (eq 25).[31] Under standard osmylation conditions, (**1**) was converted to the 2,3-*anti*-tetraol in 80% yield in a 5:1 *anti/syn* ratio. The stereoselectivity of this reaction is consistent with previous findings on the osmylation of allylic alcohols and ethers.

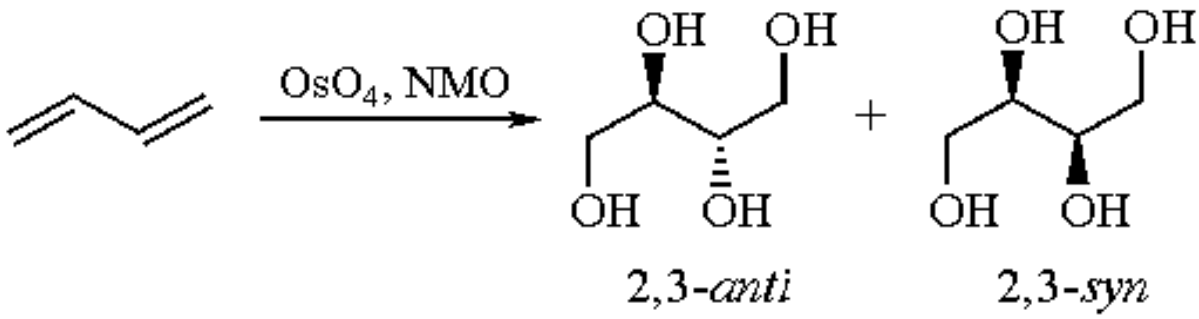

(25)

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1,3-Butadiene Monoxide

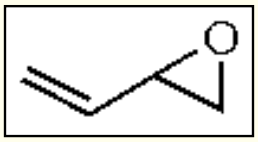

[930-22-3] · C_4H_6O · 1,3-Butadiene Monoxide · (MW 70.09)

(ambident electrophile)

Alternate Names: 3,4-epoxy-1-butene; butadiene epoxide; vinyl epoxide; vinyloxirane.

Physical Data: bp 70 °C; *d* 0.9006 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear liquid.

Preparative Method: few attempts have been reported to epoxidize conjugated dienes. Recently, a manganese catalyst was employed in a method developed to epoxidize butadiene selectively in one step (eq 1).[1]

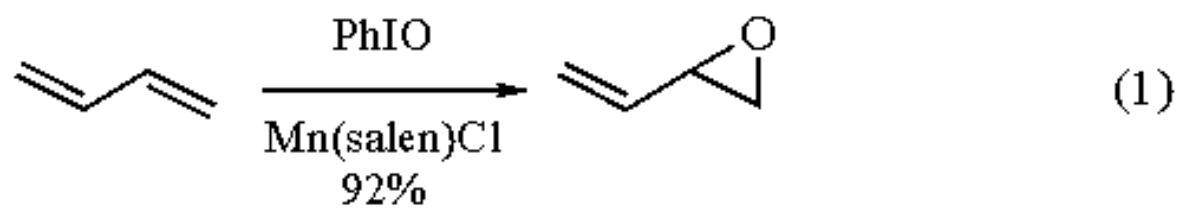

Handling, Storage, and Precautions: the flammable liquid, flash point -50 °C, is a possible carcinogen and should be used in a fume hood.

Nucleophilic Opening at C(1).

Butadiene monoxide is a versatile four-carbon synthon in organic synthesis.[2] With the careful choice of reagents one can selectively react nucleophiles at three sites on the carbon backbone. α-Selenobenzyllithiums react at the C(1) position and the resulting intermediates have been transformed into cyclopropanes (eq 2).[3] Aminolead reagents displayed even greater selectivity for attack at the C(1) position (eq 3).[4]

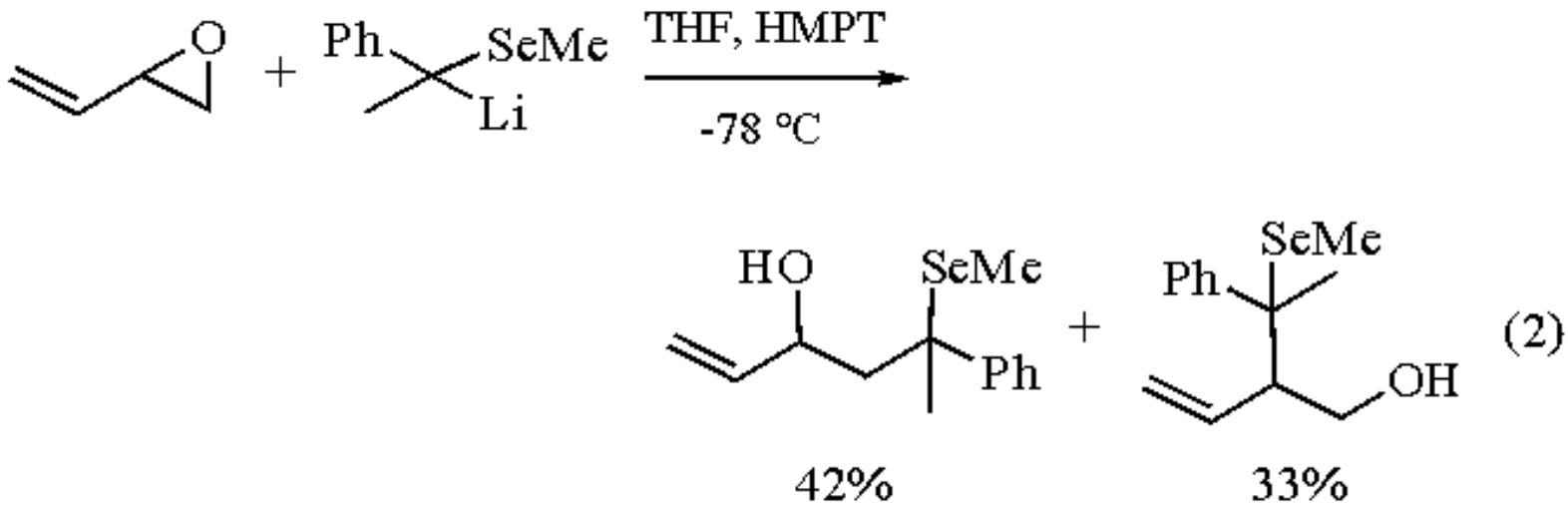

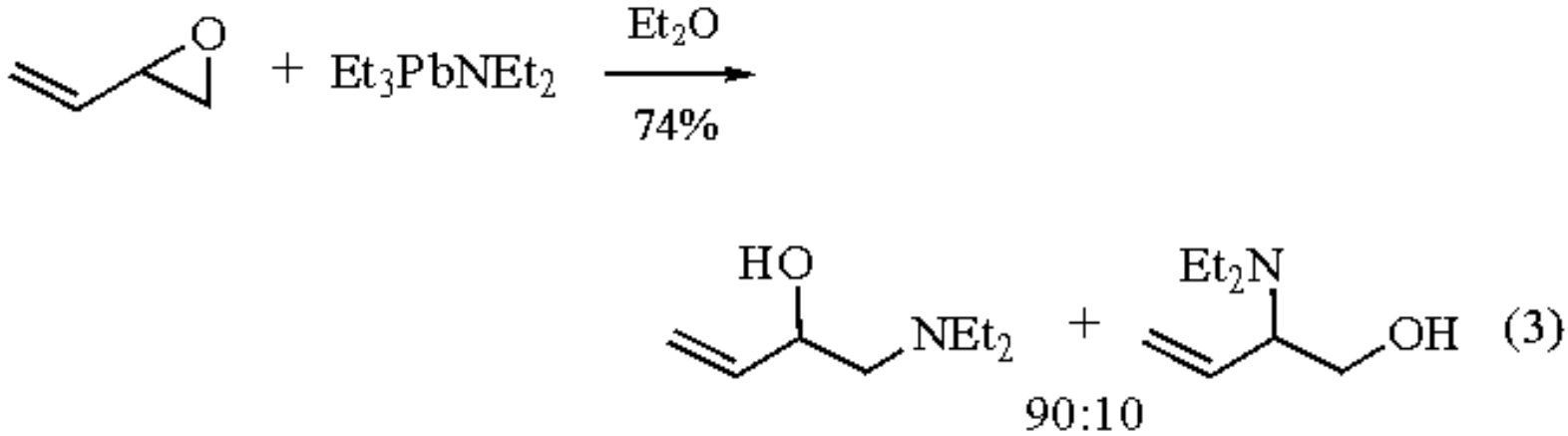

Nucleophilic Opening at C(2).

In Et_2O, allylcerium reagents were found to be more regioselective in additions to the 2-position of butadiene monoxide than allyllithium reagents (eq 4).[5] In THF the yields and product ratios were comparable. ***Vinylmagnesium Bromide*** also adds selectively at the 2-position provided 2-3 equiv of the Grignard reagent are employed (eq 5).[6]

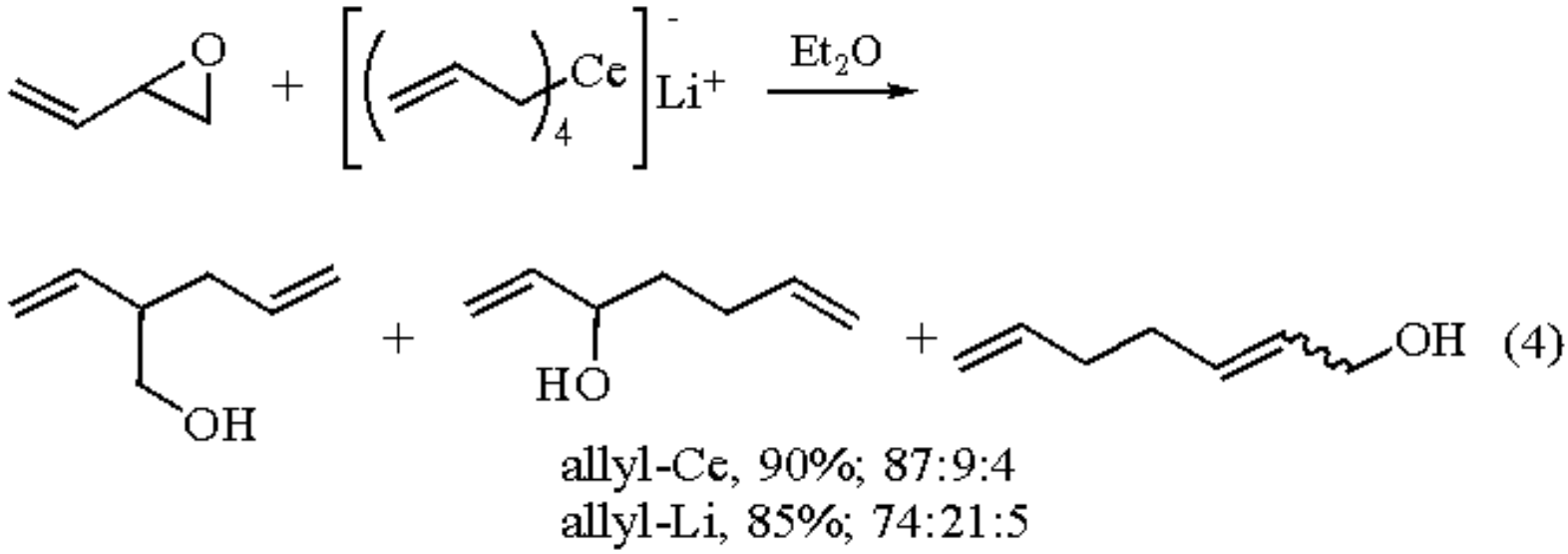

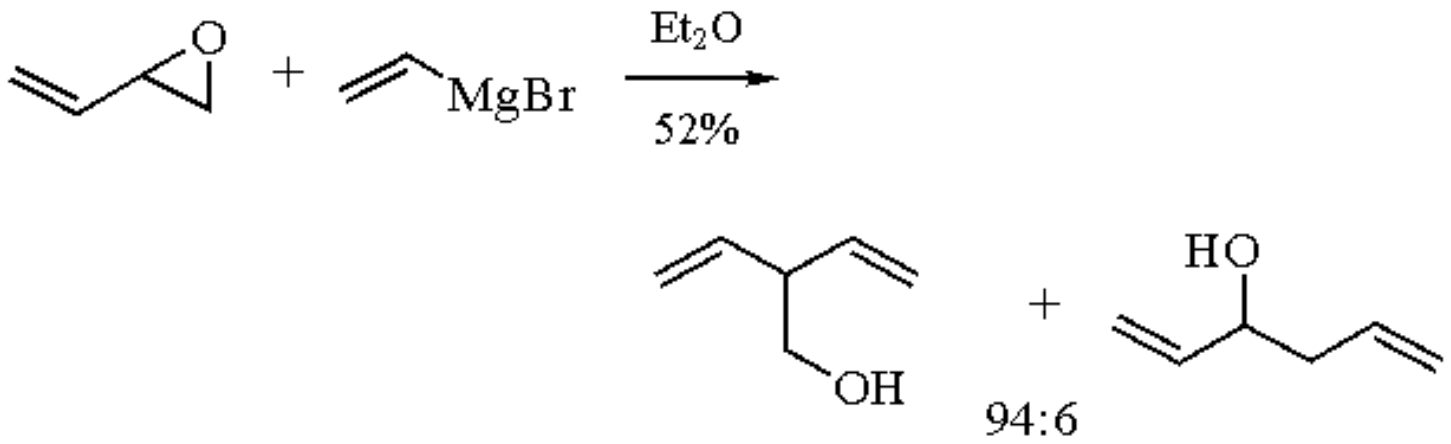

(5)

Nucleophilic Opening at C(4).

The S_N2' reaction of organocopper reagents with vinyloxiranes has recently been reviewed.[7] A number of S_N2' reactions with butadiene monoxide have been facilitated by a palladium catalyst.[8] A recent example is found in the synthesis of a linear diene alcohol that was further converted into a cyclopropane-containing eicosanoid of marine origin (eq 6).[9] Under standard metalation conditions enol carbamates are readily lithiated, and these acyl anion equivalents also react selectively at the C(4) position without a catalyst (eq 7).[10]

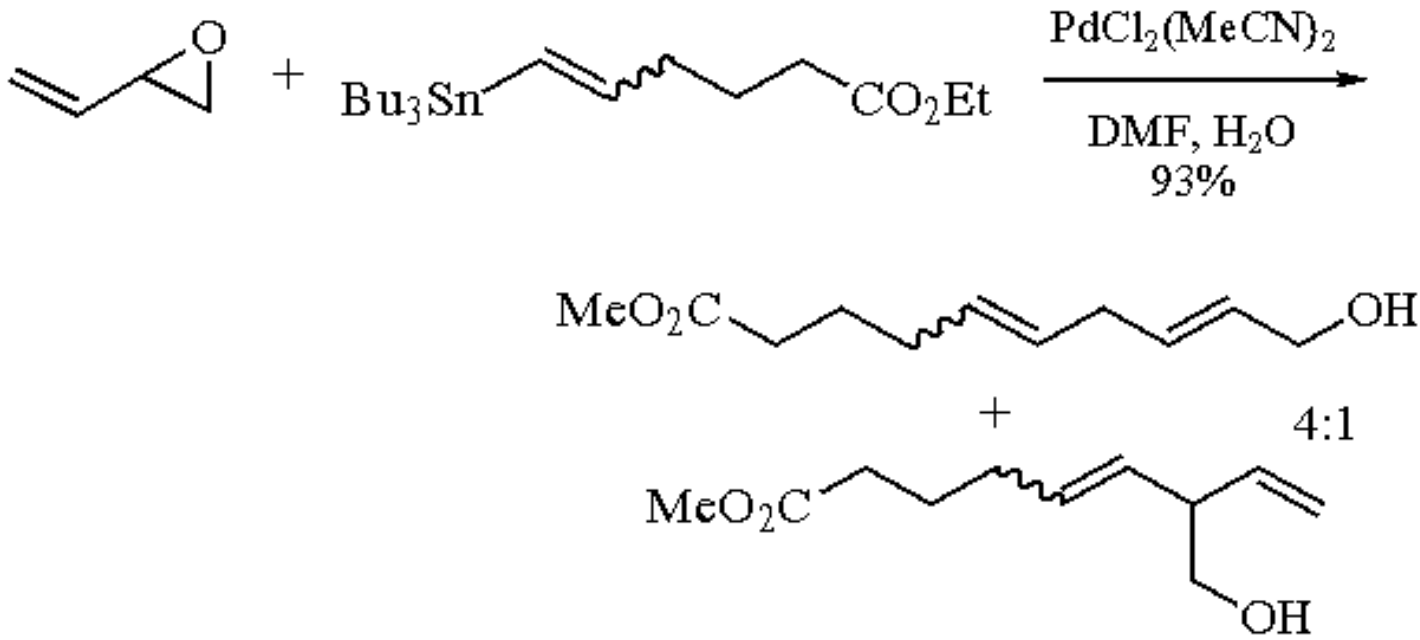

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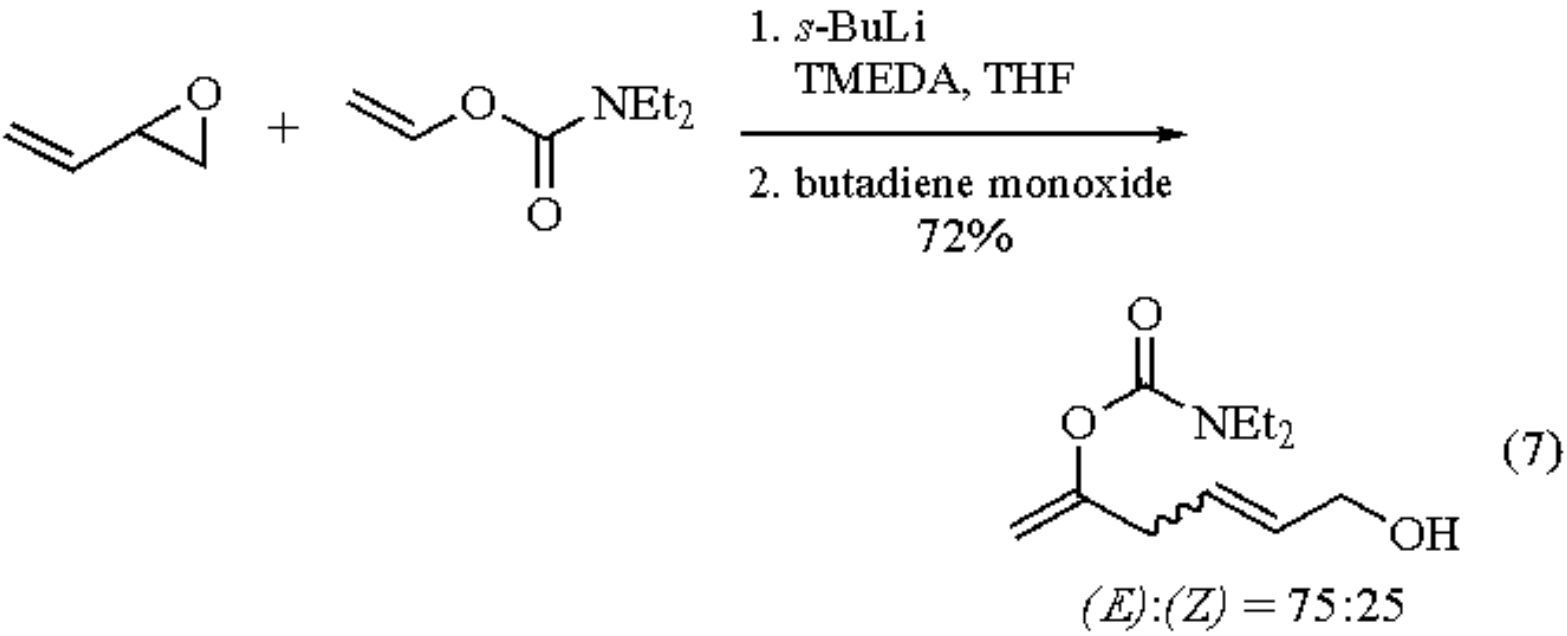

Functionalization at C(2).

The proton at the 2-position of butadiene monoxide can be selectively deprotonated with ***t-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine*** and silylated with ***Chlorotrimethylsilane***.[11] A similar and perhaps more useful reaction involves the reductive metalation of epoxides by various metals.[12] Employing ***Chromium(II) Chloride***, the 2-position of butadiene monoxide can be functionalized with reasonable selectivity (eq 8).[12a]

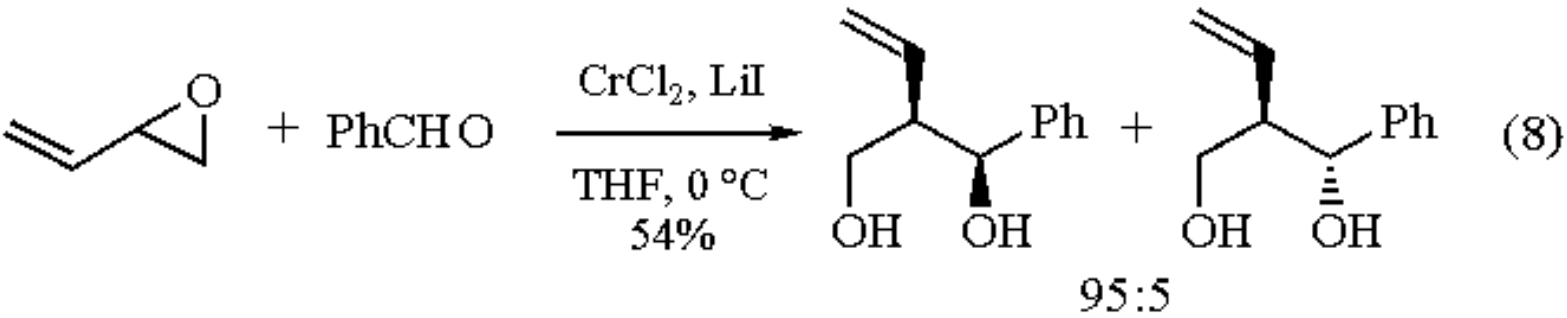

Related Reagents.

Ethylene Oxide; ***Isoprene Epoxide***; ***Propylene Oxide***.

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10. Sengupta, S.; Snieckus, V. J. *JOC* **1990**, *55*, 5680.
11. Eisch, J. J.; Galle, J. E. *JOC* **1990**, *55*, 4835.
12. (a) Fujimura, O.; Takai, K.; Utimoto, K. *JOC* **1990**, *55*, 1705. (b) Cohen, T.; Jeong, I-H.; Mudryk, B.; Bhupathy, M.; Awad, M. M. A. *JOC* **1990**, *55*, 1528.

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2,3-Butadienenitrile

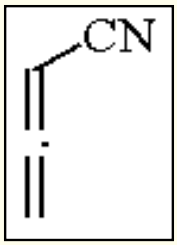

[1001-56-5] · C_4H_3N · 2,3-Butadienenitrile · (MW 65.07)

(reactive in transformations involving nucleophilic conjugate addition,[1] radical addition,[2] and dipolar addition, especially with nitrones[3])

Alternate Names: allenecarbonitrile; cyanoallene; cyanopropadiene.

Physical Data: bp 50-51.5 °C/50 mmHg.

Solubility: sol EtOH, THF, toluene, chloroform, benzene.

Analysis of Reagent Purity: IR 1970, 2230 cm^{-1}.

Preparative Methods: this reagent is not commercially available, but at least two preparative methods have been reported. One proceeds through a Wittig reaction between cyanomethylidenetriphenylphosphorane and ketene.[4] However, the procedure to be recommended involves the formation of 3-butynenitrile and its isomerization in situ to 2,3-butadienenitrile (eq 1).[5] The indicated product mixture can be produced on a scale near 100 g, and its fractional distillation affords pure 2,3-butadienenitrile.

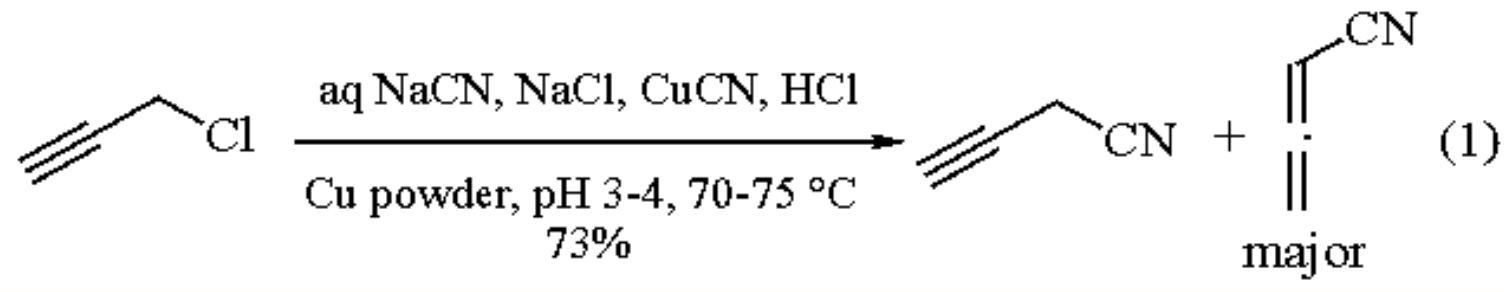

Purification: vacuum distillation.

Handling, Storage, and Precautions: this reagent has been reported[6] to cause severe allergic reactions in some individuals. Handling with double, heavy-duty rubber gloves is recommended. This reagent should only be handled in a fume hood.

Procedures Involving Nucleophilic Conjugate Addition to 2,3-Butadienenitrile.

Transformations in which this reagent behaves as a conjugate addition electrophile are well known. For example, eq 2[1] shows an unsaturated amino acid synthesis based on this concept.

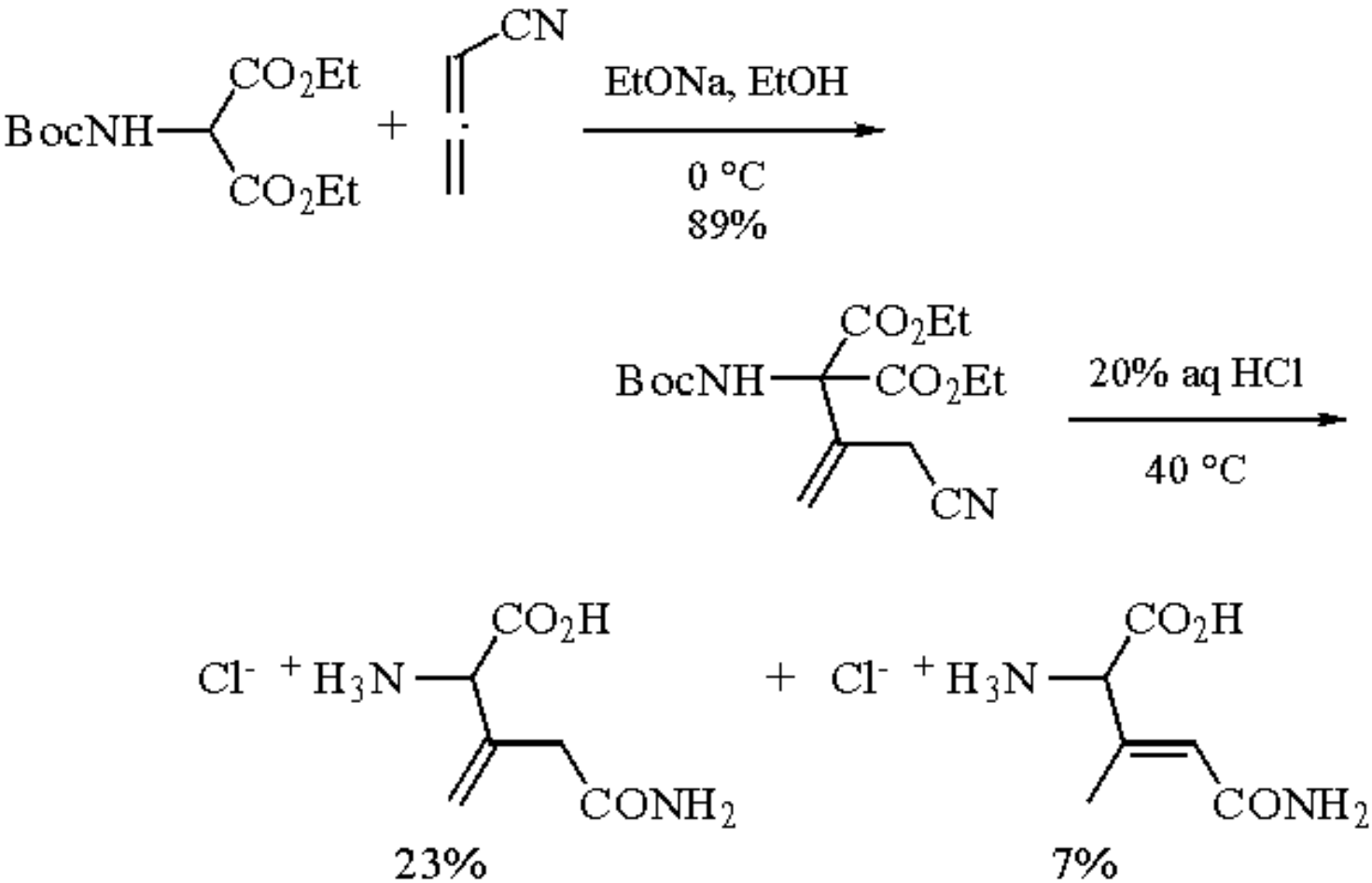

(2)

A similar process underlies the [2 + 2] cycloaddition between 2,3-butadienenitrile and cyclohexanone morpholine enamine (eq 3).[7]

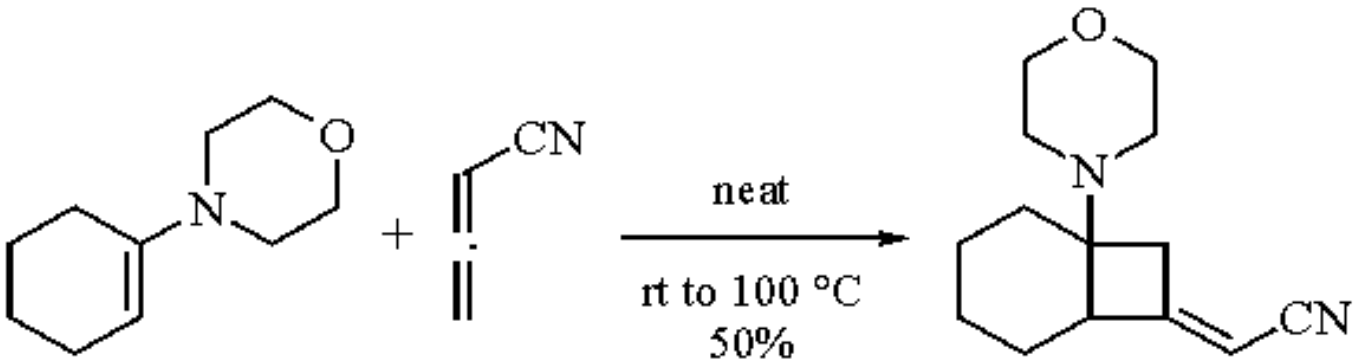

(3)

A more sophisticated exploitation of this chemistry is incorporated in the procedure[8] for alkylation *ortho* to aromatic

amino nitrogen (eq 4). This protocol delivers an intermediate cyano ketone through nucleophilic addition of the hydroxamate anion to 2,3-butadienenitrile and subsequent [3,3]-sigmatropic rearrangement and tautomerization. ***Formic Acid*** treatment of the cyano ketone then produces the 2-substituted indole. Likewise, a mechanistically related sequence carried out on a substrate incapable of tautomerization and rearomatization delivers carbocyclic products (eq 5).[9]

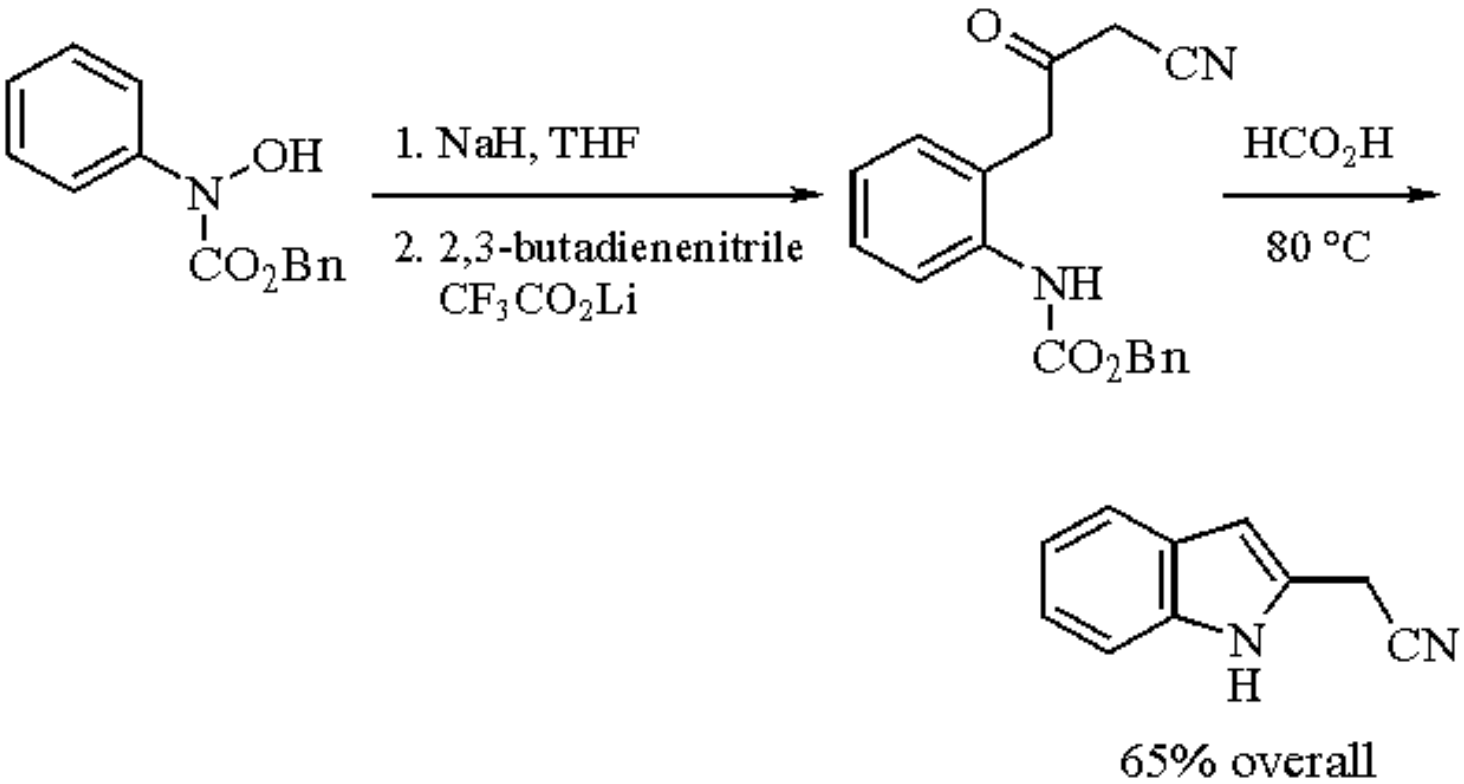

(4)

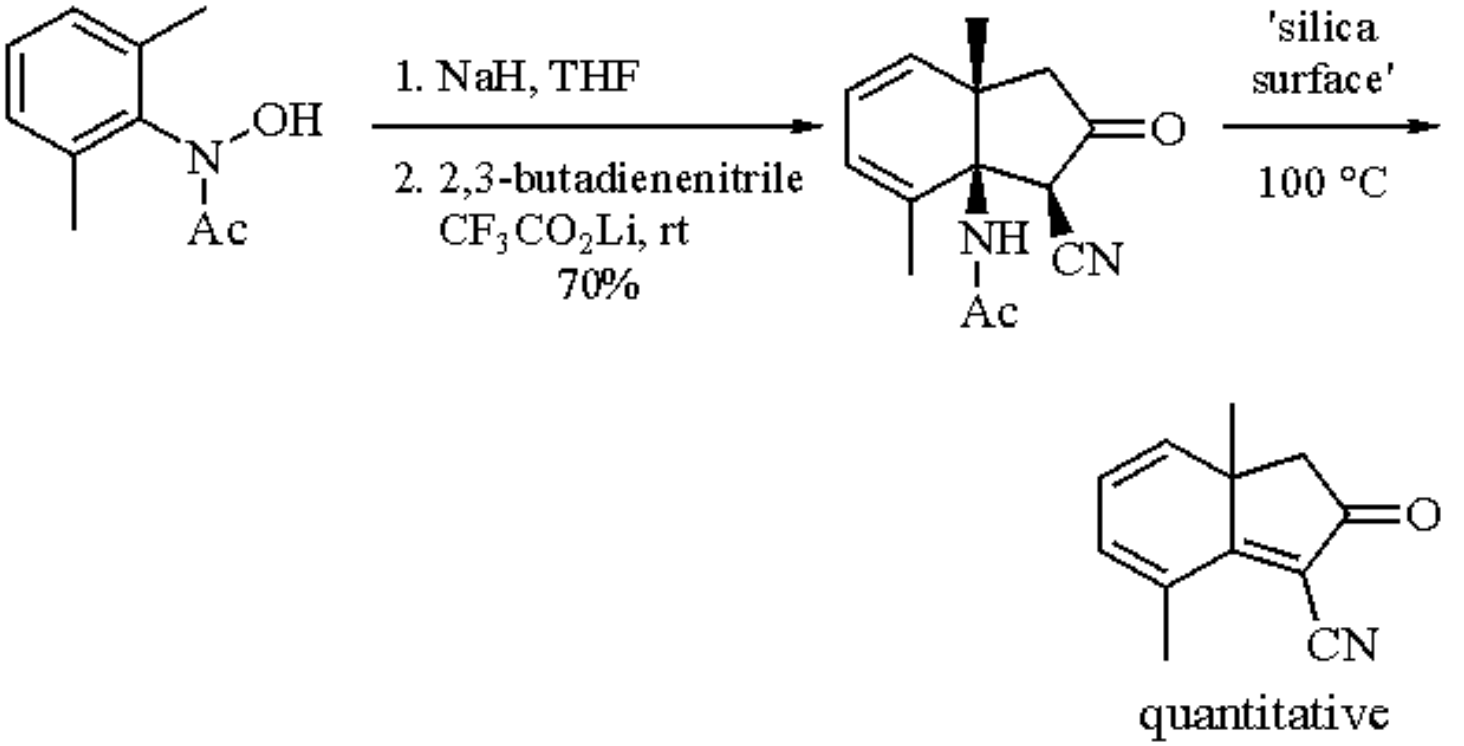

(5)

2,3-Butadienenitrile can also function in a formal sense as the nucleophilic component in the conjugate addition to

Methyl Vinyl Ketone depicted in eq 6.[10] However, this transformation also occurs by way of conjugate addition of methoxide to this reagent, followed by reaction of the derived allylic nitrile anion with methyl vinyl ketone and base-induced ejection of methoxide to deliver the observed product.

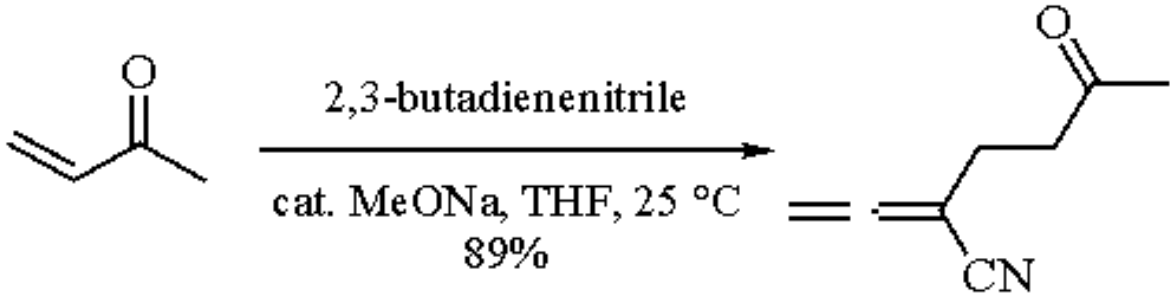

(6)

Transformations Involving Radical Addition to 2,3-Butadienenitrile.

Several transformations in which radicals add to 2,3-butadienenitrile have been reported. For example, 1-adamantyl engages the central carbon in the reagent to provide a modest yield of the corresponding 2-substituted 2-butenenitrile (eq 7).[2] Related reactions are shown in eqs 8[11] and eq 9.[6]

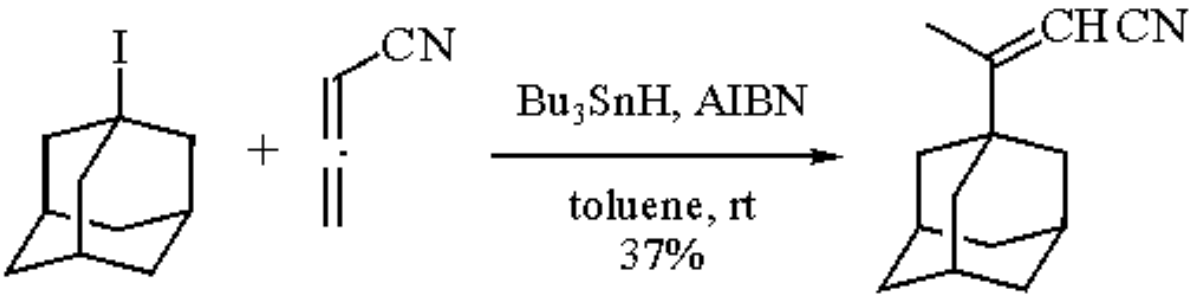

(7)

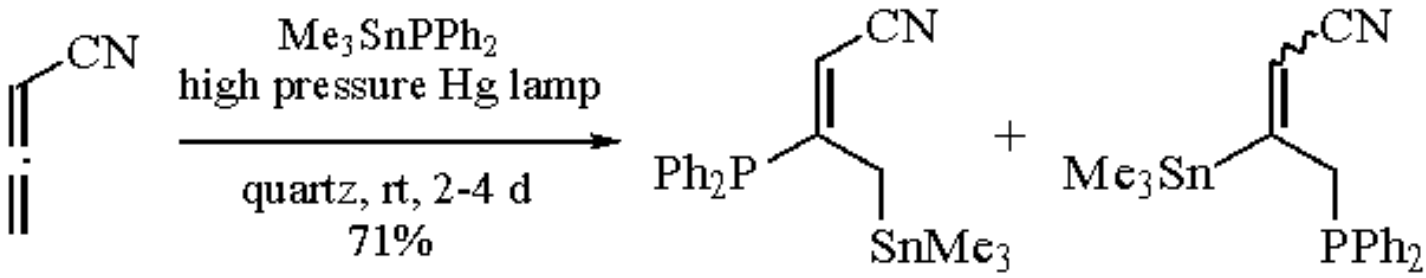

99:1

(8)

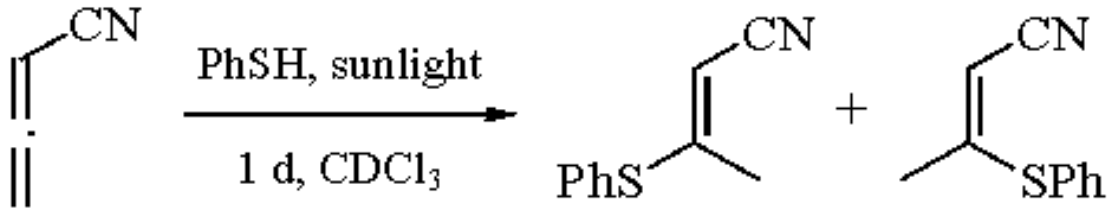

61:39

(9)

Dipolar Additions of Nitrones to 2,3-Butadienenitrile.

Eq 3 formally constitutes a cycloadditive process involving this reagent. However, among cycloadditions involving 2,3-butadienenitrile, dipolar additions of nitrones are the most commonly encountered (eqs 10 and 11).[3] When the nitrone carries a sterically demanding group on the nitrogen, *cis* stereoselectivity is eroded (eq 11).

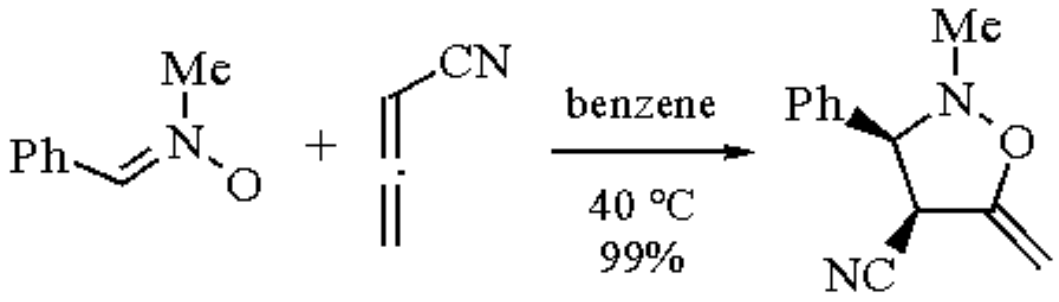

(10)

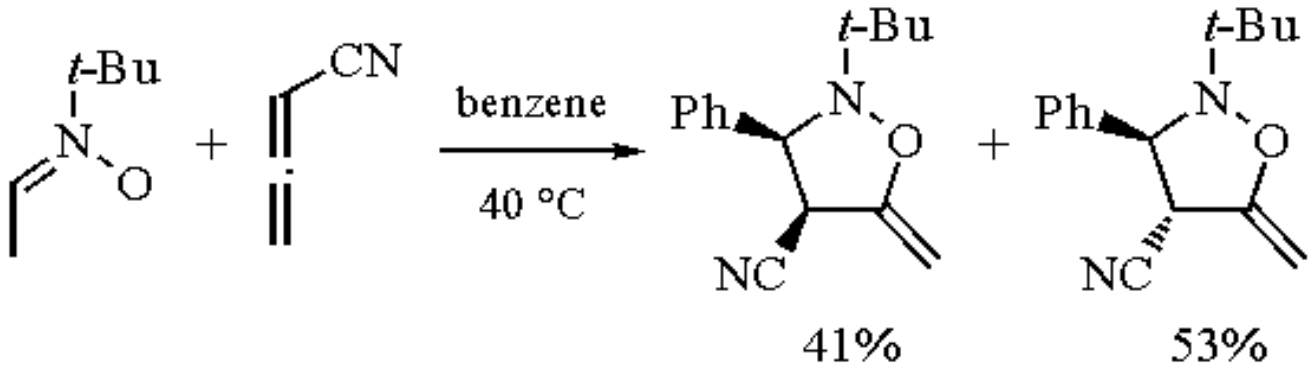

(11)

A transformation reminiscent of eq 4 is illustrated in eq 12.[12] Formation of the nitrone occurs in situ, and initiates a sequence involving dipolar addition, [3,3]-sigmatropic rearrangement, and further transformation into the 2-vinylindole indicated through a one-pot procedure.

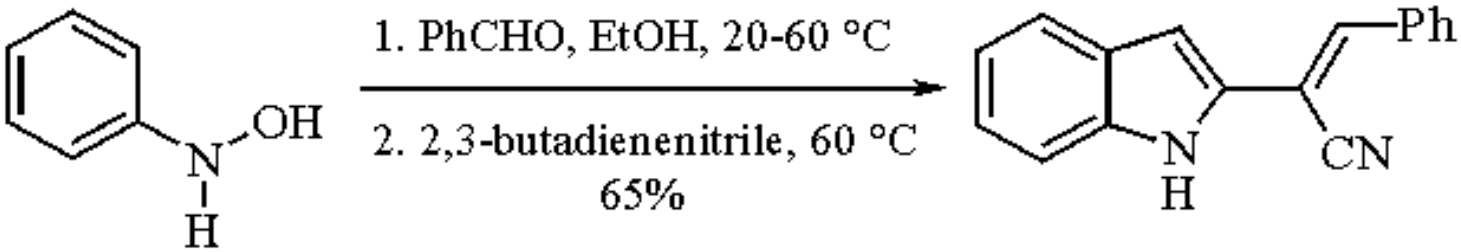

(12)

Related Reagents.

Allene; ***Propynenitrile***.

---

1. Paik, Y. H.; Dowd, P. *JOC* **1986**, *51*, 2910.
2. Ohno, M.; Ishizaki, K.; Eguchi, S. *JOC* **1988**, *53*, 1285.
3. Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *JOC* **1987**, *52*, 3909.

4. Hamlet, Z.; Barker, W. D. *S* **1970**, 543.
5. Kurtz, P.; Gold, H.; Disselnkötter, H. *LA* **1959**, *624*, 1.
6. Pasto, D. J.; L'Hermine, G. *JOC* **1990**, *55*, 685.
7. (a) Baldwin, J. E.; Fleming, R. H.; Simmons, D. M. *JOC* **1972**, *37*, 3963. (b) For an experimental procedure but an incorrect assignment of the product structure, see: Reid, W.; Käppeler, W. *LA* **1965**, *687*, 183.
8. Blechert, S. *HCA* **1985**, *68*, 1835.
9. Bosum, A.; Blechert, S. *AG(E)* **1988**, *27*, 558.
10. Padwa, A.; Yeske, P. E. *JOC* **1991**, *56*, 6386.
11. Mitchell, T. N.; Belt, H.-J. *JOM* **1990**, *386*, 167.
12. Wilkens, J.; Kühling, A.; Blechert, S. *T* **1987**, *43*, 3237.

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1,3-Butadienyl-2-lithium

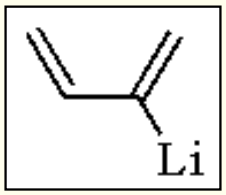

[84531-04-4] · C_4H_5Li · 1,3-Butadienyl-2-lithium · (MW 60.02)

(reagent for carbon-carbon bond forming reactions with carbonyls[1,2] and α,β-alkenyl esters[3,4])

Preparative Methods: 1,3-butadienyl-2-lithium is synthesized by transmetalation of 1,2-butadienyl-2-tributyltin (eq 1)[1] or by the Shapiro reaction of 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$SO$_2$NHN=CMeCH=CH$_2$ with ***Methyllithium*** (eq 2).[2] 3-Methyl-1,3-butadienyl-2-lithium has been prepared by lithium-bromine exchange.[5].

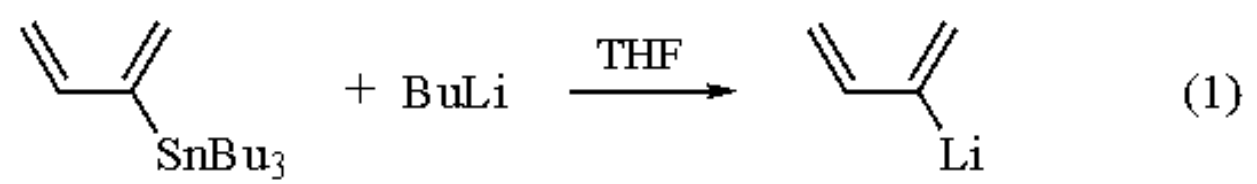

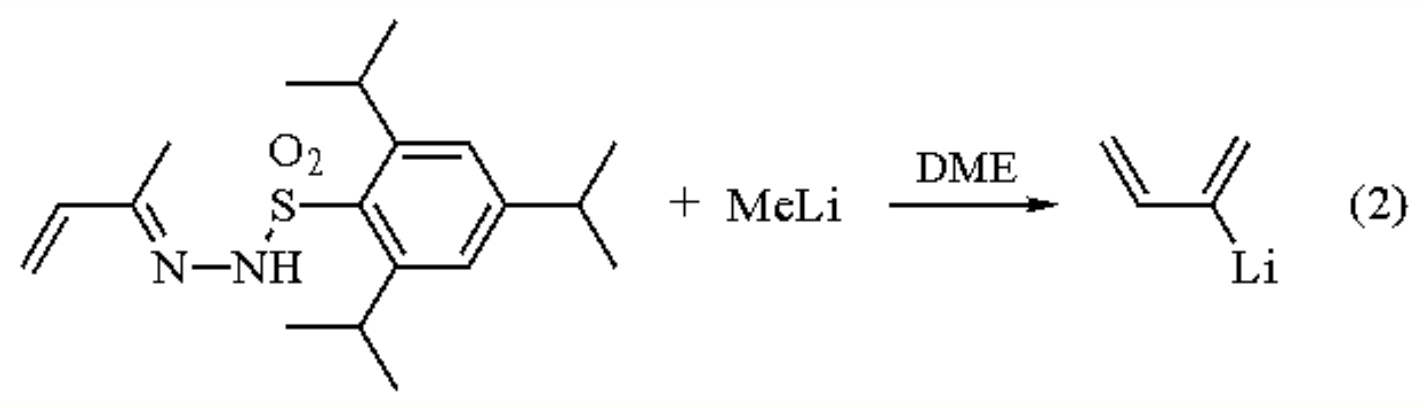

Analysis of Reagent Purity: 1,3-butadienyl-2-lithium is synthesized and used direclty without further isolation or purification.

Handling, Storage, and Precautions: use in a fume hood.

Reaction with Aldehydes and Ketones.

1,3-Butadienyl-2-lithium reacts with aldehydes and ketones. Dienyl carbinols are generally obtained as major products, along with small amounts of allenyl carbinols (eq 3). Compared with ***1,3-Butadienyl-2-magnesium Chloride***, a stronger

preference for dienyl products is observed (Table 1).[1]

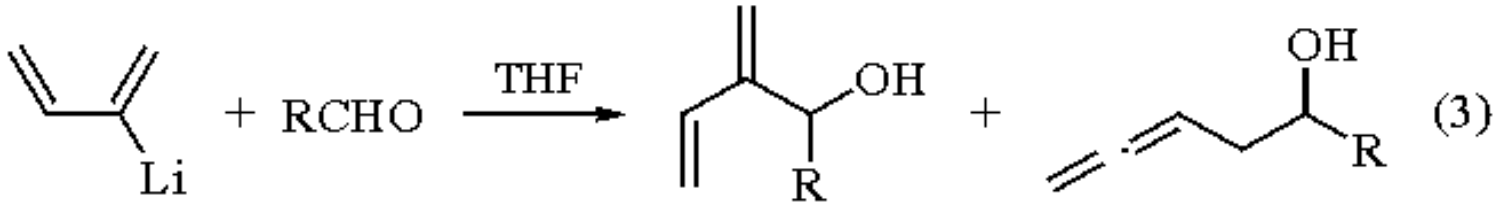

Table 1 Reaction of 1,3-Butadienyl-2-lithium with Carbonyl Compounds

Carbonyl compound	Yield and selectivity (%) (diene/allene)	Selectivity by 1,3-butadienyl-2-magnesium chloride (diene/allene)
PhCHO	80 (91:9)	39:61
$Me(CH_2)_5CHO$	61 (100:0)	
PhCH=CHCHO	76 (19:1)	7:9
PhCOMe	70 (9:1)	19:81
PhCOPh	73 (1:1)	0:100

1,3-Butadienyl-2-lithium undergoes Michael addition to α,β-alkenyl esters. The reaction with methyl 2-(trimethylsilyl)propenoate affords the corresponding lithium enolate, which upon alkylation yields a series of α-silyl esters (eq 4).[3]

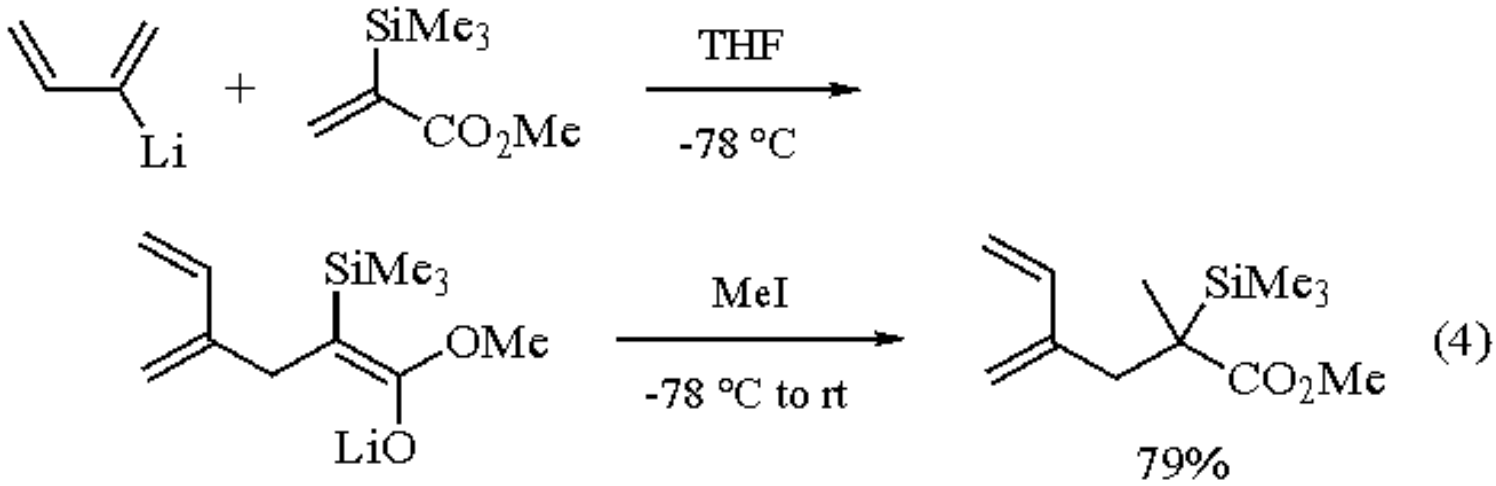

Treatment of the Michael adduct with an aldehyde followed by Peterson alkenation furnishes the dienyl α,β-alkenyl ester (eq 5).[4] Stereoselectivities of the products vary with the substrate (*E*/*Z* = ca. 3:1 to *Z* only).[4]

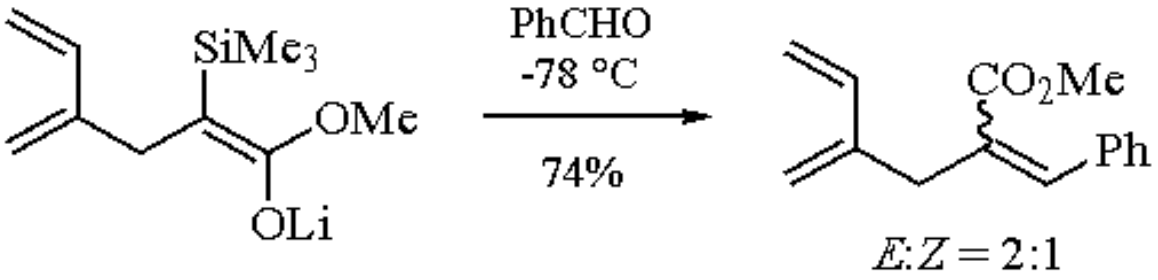

(5)

Substituted 2-lithiobutadienes which have been prepared include 3-methyl-,[5] 3-trimethylstannyl-,[6] 3-trimethylsilyl-,[6] 3-hexyl-,[6] and 4-methoxy-1,3-butadienes.[7]

Related Reagents.

1,3-Butadienyl-1-lithium; ***1,3-Butadienyl-1-magnesium Chloride***; ***1,3-Butadienyl-2-magnesium Chloride***.

---

1. Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *BCJ* **1985**, *58*, 1942.
2. (a) Brown, P. A.; Jenkins, P. R. *TL* **1982**, *23*, 3733. (b) *JCS(P1)* **1986**, 1129.
3. Tanaka, J.; Kanemasa, S.; Ninomiya, Y.; Tsuge, O. *BCJ* **1990**, *63*, 476.
4. (a) Tsuge, O.; Kanemasa, S.; Ninomiya, Y. *CL* **1984**, 1993. (b) Tanaka, J.; Kanemasa, S.; Ninomiya, Y.; Tsug, O. *BCJ* **1990**, *63*, 466.
5. Shea, K. J.; Sakata, S. T. *TL* **1992**, *33*, 4261.
6. Reich, H. J.; Reich, I. L.; Yelm, K. E.; Holladay, J. E.; Gschneidner, D. *JACS* **1993**, *115*, 6625.
7. Schreiber, S. L.; Kiessling, L. L. *JACS* **1988**, *110*, 631.

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1,3-Butadienyl-1-lithium

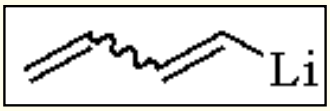

[4843-71-4] · C_4H_5Li · 1,3-Butadienyl-1-lithium · (MW 60.02) (*E*)

[91892-10-3]

(reagent for single-step introduction of the 1,3-butadienyl group)

Solubility: sol THF and ether.

Preparative Method: (*E*)-1,3-butadienyl-1-lithium was generated from (*E*)-butadienyltributylstannane and BuLi in hexane at -78 °C for 15 min.[1] Concentration of the reagent solution can be determined by titration.[2]

Handling, Storage, and Precautions: the reagent is moisture- and air-sensitive. All solvents must be dried before use.

1,3-Butadienyl-1-lithium Reagents.

A common approach for the preparation of the 1,3-butadienyl-1-lithium reagents is transmetalation of butadienyltrialkylstannanes with ***Methyllithium***[3] or ***n-Butyllithium***.[1,3-7] Rapid transmetalation proceeds with complete retention of diene configuration (eq 1). The butadienylstannanes are commonly prepared by hydrostannylation of alkynes,[3-5] or addition of (phenylthio)(trimethylstannyl)cuprate to alkynes.[3]

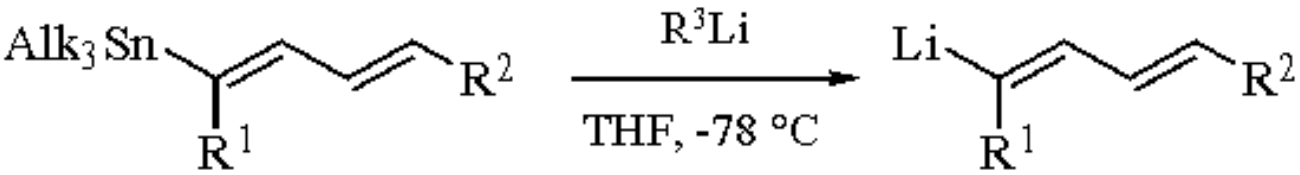

(1)

$R^1 = R^2 = H$; $R^1 = Me$, $R^2 = H$; $R^1 = H$, $R^2 = OEt$; $R^3 = Me$, Bu

A convenient method for the preparation of 4-alkoxy-[8a] and 4-silyloxy-1,3-butadienyl-1-lithium[8] derivatives is bromine-lithium exchange with ***t-Butyllithium*** (eq 2).

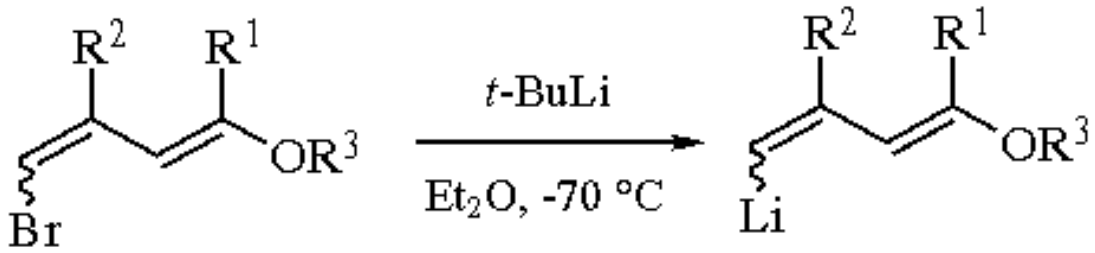

(2)

$R^1 = H, Me; R^2 = H, Me; R^3 = Et, SiMe_3$

Metal-halogen exchange between equimolar quantities of (*E*,*E*)-1-bromo-1-(trimethylsilyl)penta-1,3-diene and ***s-Butyllithium*** (THF-cyclohexane, -78 °C, 30 min) affords lithiated species (eq 3).[9]

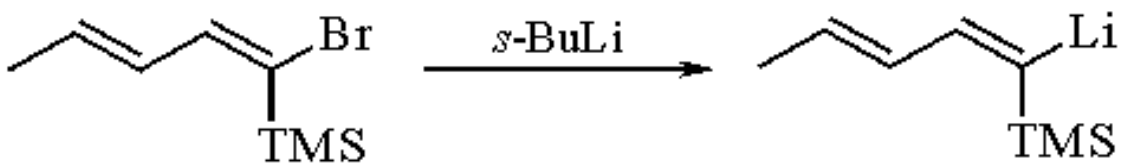

(3)

Exchange of one bromine atom in unstable 1,4-dibromobutadiene occurs with *s*-BuLi (1 equiv) or *t*-BuLi (2 equiv) (eq 4), whereas the use of *n*-BuLi favors polymer formation.[10] Both bromine atoms are exchanged with an excess of *t*-BuLi (4 equiv).

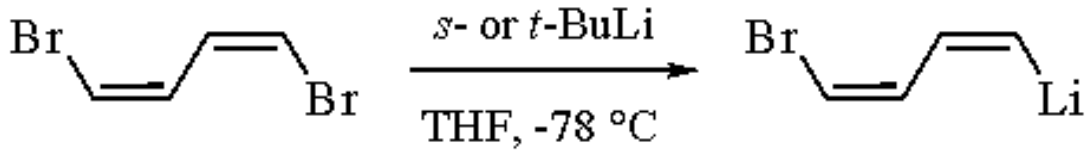

(4)

1,3-Dienyl ethers are readily lithiated at C-1 using *t*-BuLi (R = Me),[11a] *s*-BuLi (R = MOM),[11b] or *n*-BuLi and ***Potassium t-Butoxide*** in THF (R = Me, Ph; diene:*t*-BuOK:*n*-BuLi ratio is 1:1.04:1.10).[11c] The butadienyl-1-potassium formed first is subsequently transmetalated. The metalation of ethers and (*E*)-dienylic sulfides occurs with retention of configuration (eqs 5 and 6), while in the case of (*Z*)-dienylic sulfides the structure of the products depends on both reaction conditions and the *S*-alkyl substituent: higher temperatures and more bulky thioalkyl groups promote inversion of configuration (eq 7).[11c]

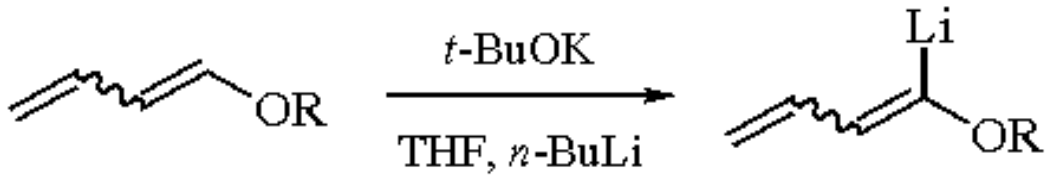

(5)

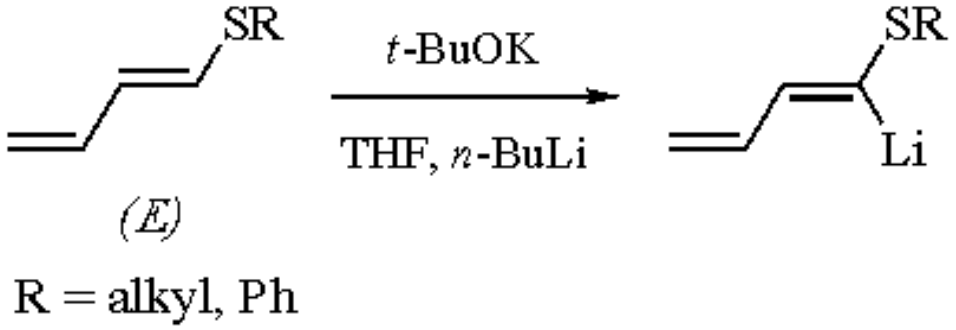

(6)

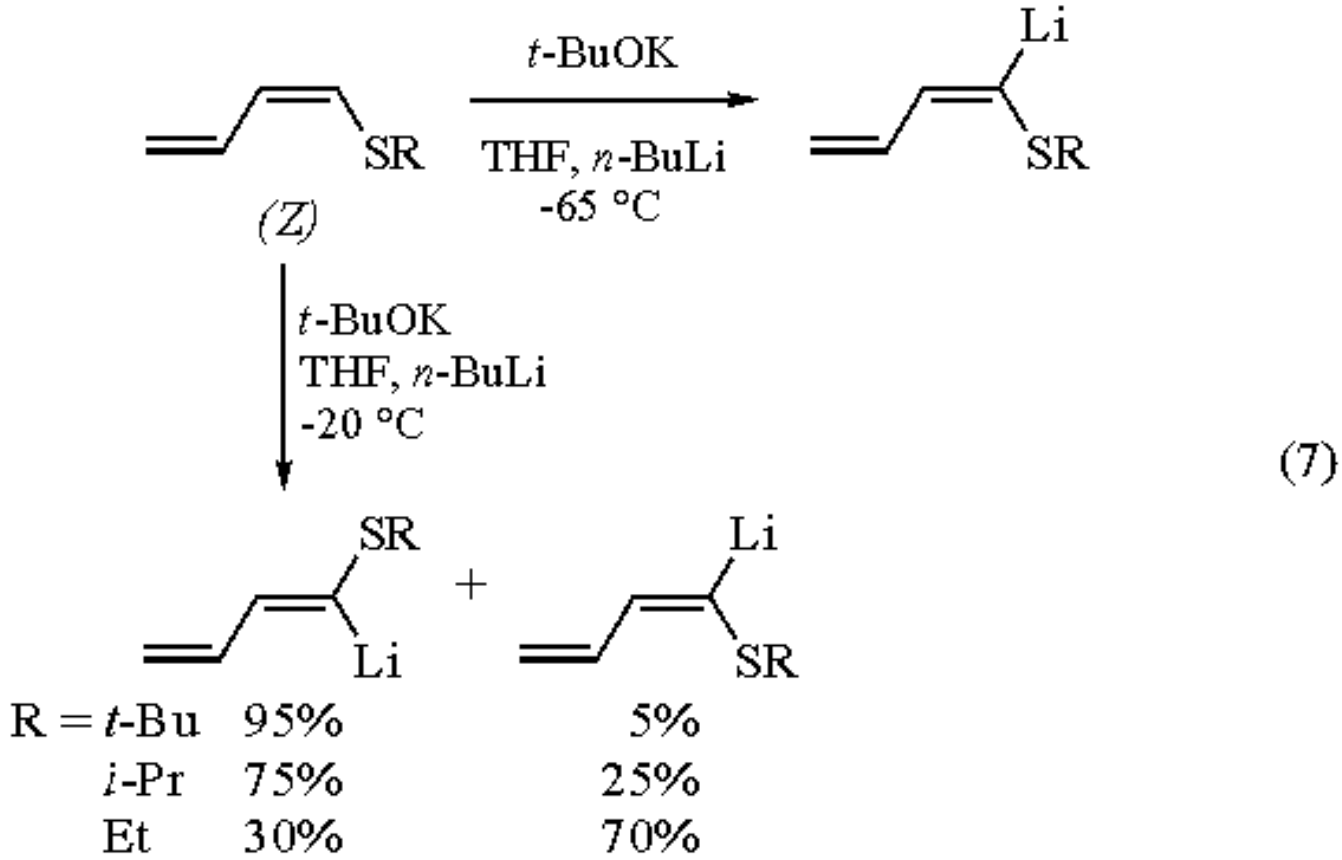

(7)

Higher temperatures also promote side reactions (1,4-addition of BuLi) and tar production. Treatment of butadienyl monosulfides with alkyllithium (*n*-, *s*- or *t*-Bu) reagents in THF in the absence of *t*-BuOK gives insignificant metalation even in the presence of TMEDA (***N,N,N´,N´-Tetramethylethylenediamine***). The main reaction is 1,4-addition of R^2Li to the conjugated diene (eq 8). On the other hand, 1,4-bis(methylthio)buta-1,3-dienes are monolithiated with *n*-BuLi in THF-TMEDA mixtures at low temperature.[12] When (1*Z*,3*E*)-bis-sulfides are used, lithium is introduced exclusively at the (*E*) double bond (eq 9).

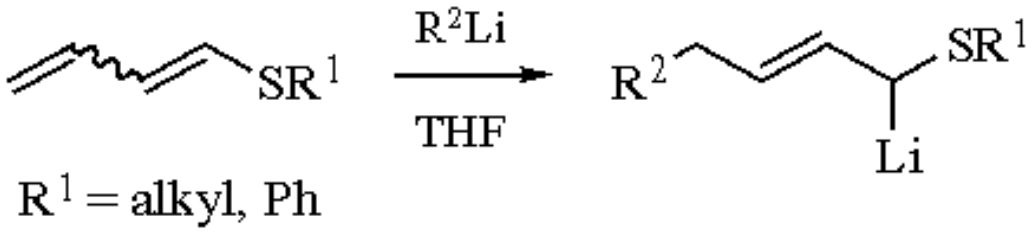

(8)

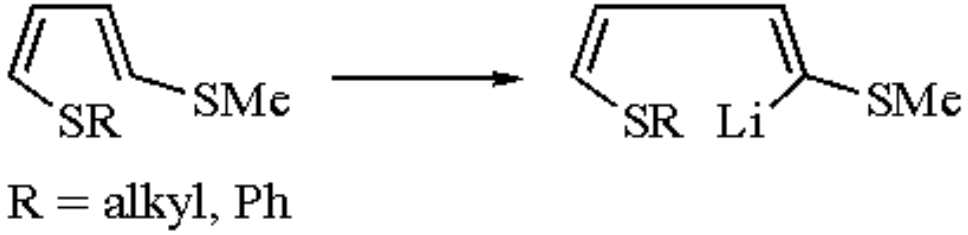

(9)

Reactions of 1,3-Butadienyl-1-lithium Reagents.

The 1,3-butadienyl-1-lithium reagents (4-lithio-1,3-pentadiene,[3,13] 1-alkoxy-,[11] and 1-alkylthio-1,3-butadienyl-1-lithium[11c]) react smoothly with a variety of electrophiles (halides, methyl thiocyanate, aldehydes, and ketones) and produce the corresponding substituted dienes (eqs 10 and 11).

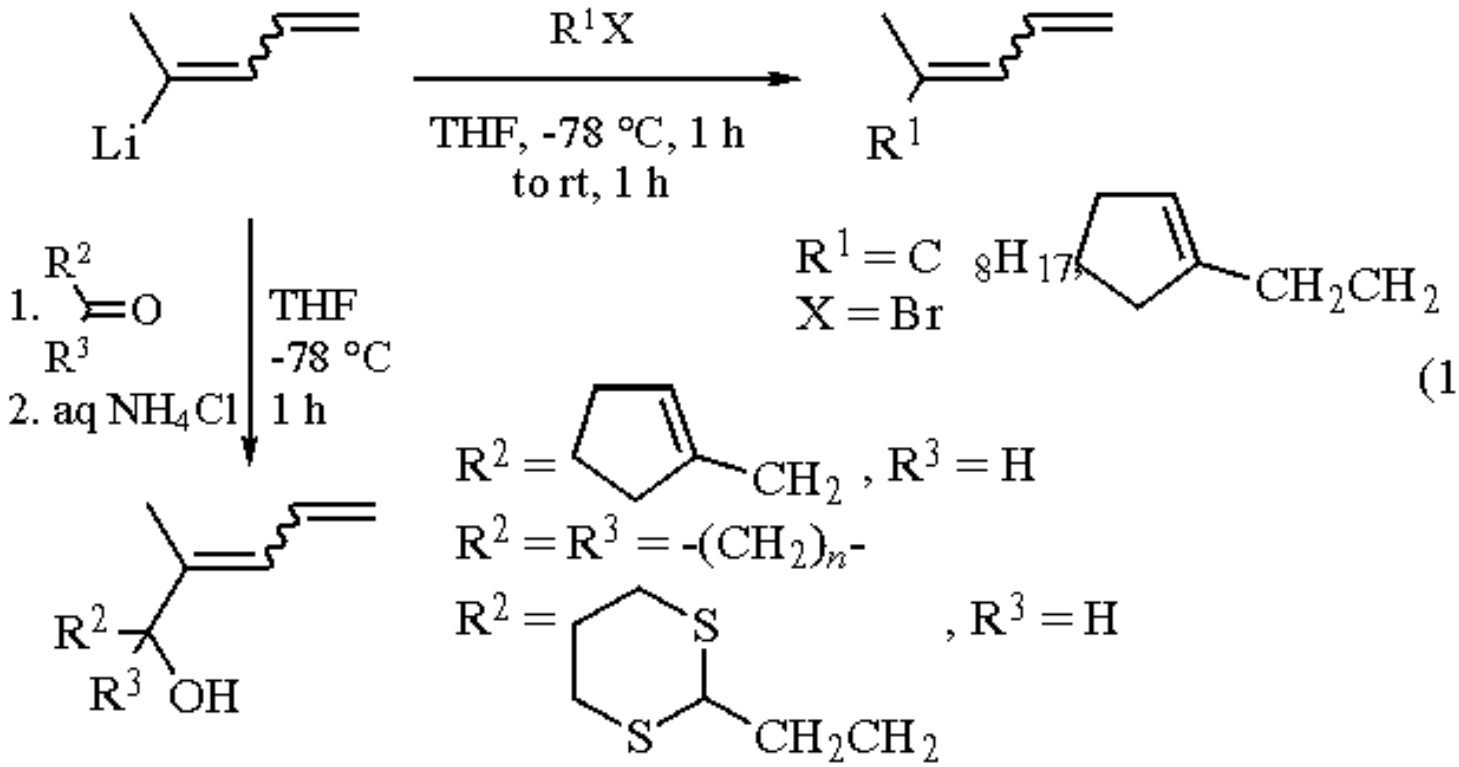

(10)

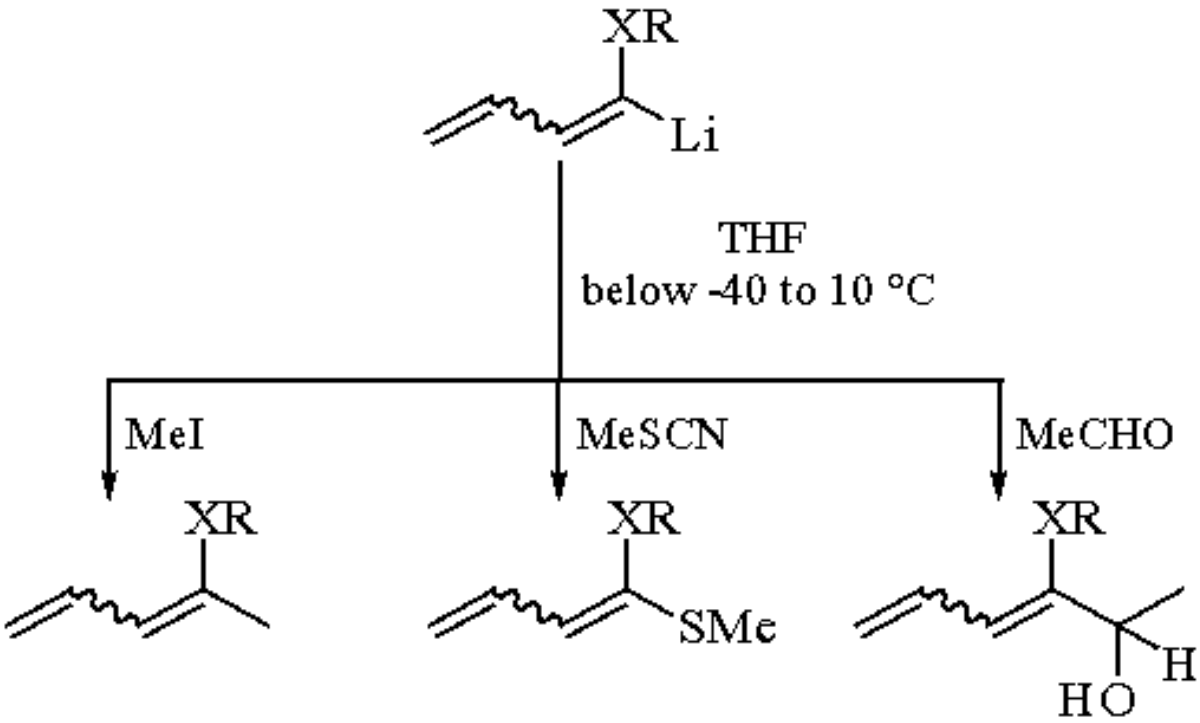

(11)

RX = OMe, SMe, *t*-BuS, PhO

Electrophilic substitution at the lithiated carbon proceeds with retention of configuration. Yields of the substituted dienes are as high as 90% for methylation and 60-75% for alkylation with higher alkyl halides and carbonyl compounds.

Lithiobutadienyl alkyl and silyl ethers are suitable intermediates in the synthesis of polyethylenic aldehydes and ketones (eq 12). These are important building blocks in natural product synthesis (polyene and macrolide antibiotics and terpenes). Starting from (*E*)-lithiated ethers and aldehydes or ketones, exclusively (*E*)-isomers are obtained.[7,8] An exception is benzophenone, which gives some loss of stereochemistry.[8b] Yields of the dienols (dieno ketones) are 70-90%.

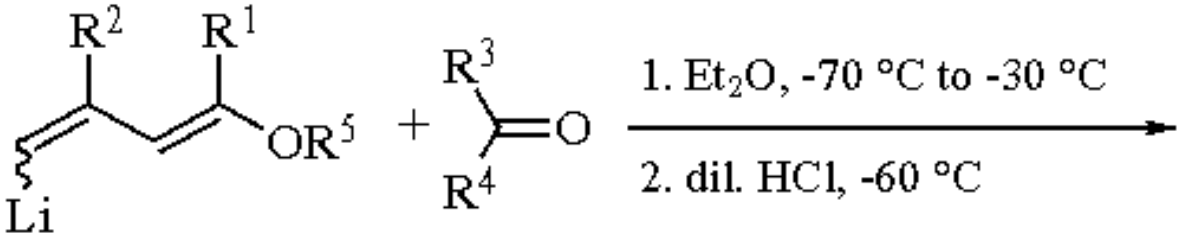

$R^1 = R^2 = H$; $R^5 = SiMe_3$, Et
$R^1 = Me$, $R^2 = H$; $R^1 = H$, $R^2 = Me$

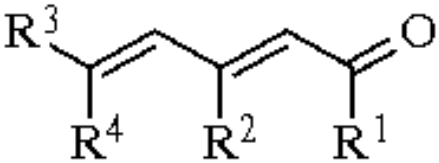

(12)

The condensation of lithiated dienol ethers with conjugated carbonyl compounds and the hydrolysis of the intermediate adduct leads in one pot to polyconjugated ketones. Use of the lithiated dienol ether is recommended over that of the lithiodioxolane (eq 13).[8a]

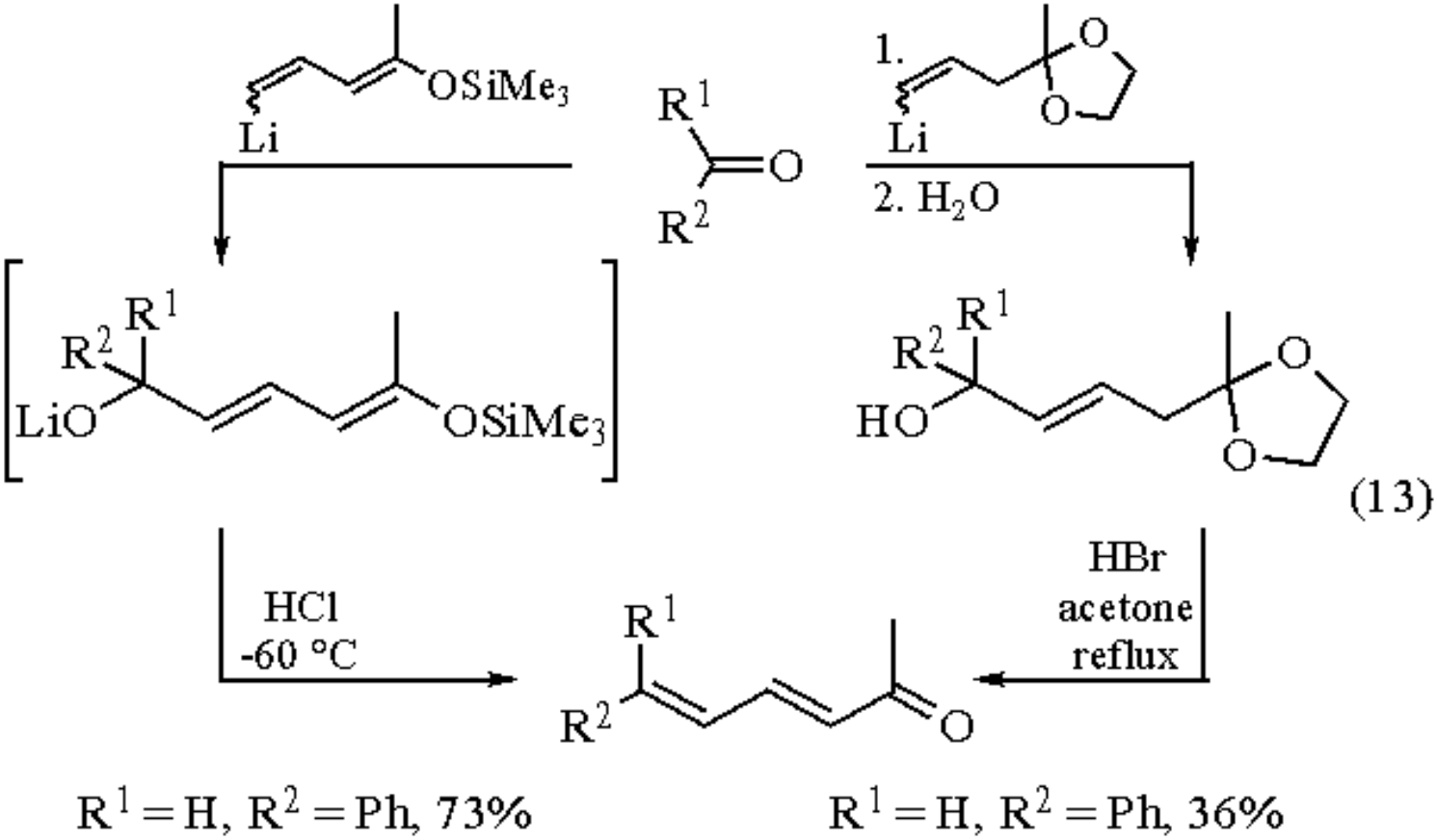

Reaction of 1,3-butadienyl-1-lithium with chloro ketones is used for the sequential introduction of two neighboring 1,3-butadienyl groups on a cyclohexane ring (eq 14).[4,6] The silylated product undergoes thermal [5,5]-sigmatropic rearrangement to form a macrocyclic enol ether, giving cyclotetradecatrienone after hydrolysis.[1]

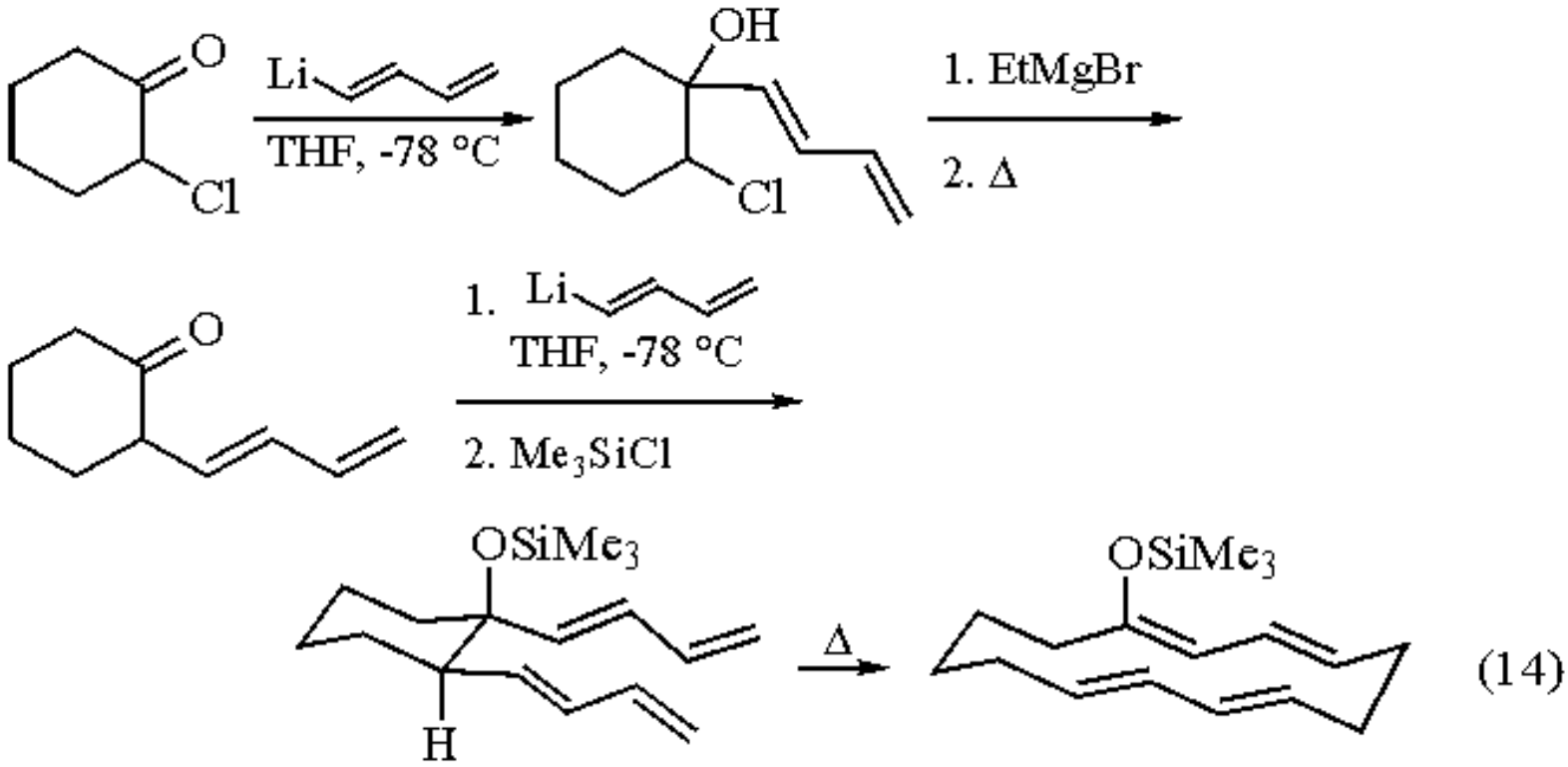

A mixed cuprate derived from a lithiodiene and *n*-PrC&tbond;CCu in ether-$(Me_2N)_3P$ reacted with an unsaturated ketone to yield the 1,4-addition product (eq 15).[5]

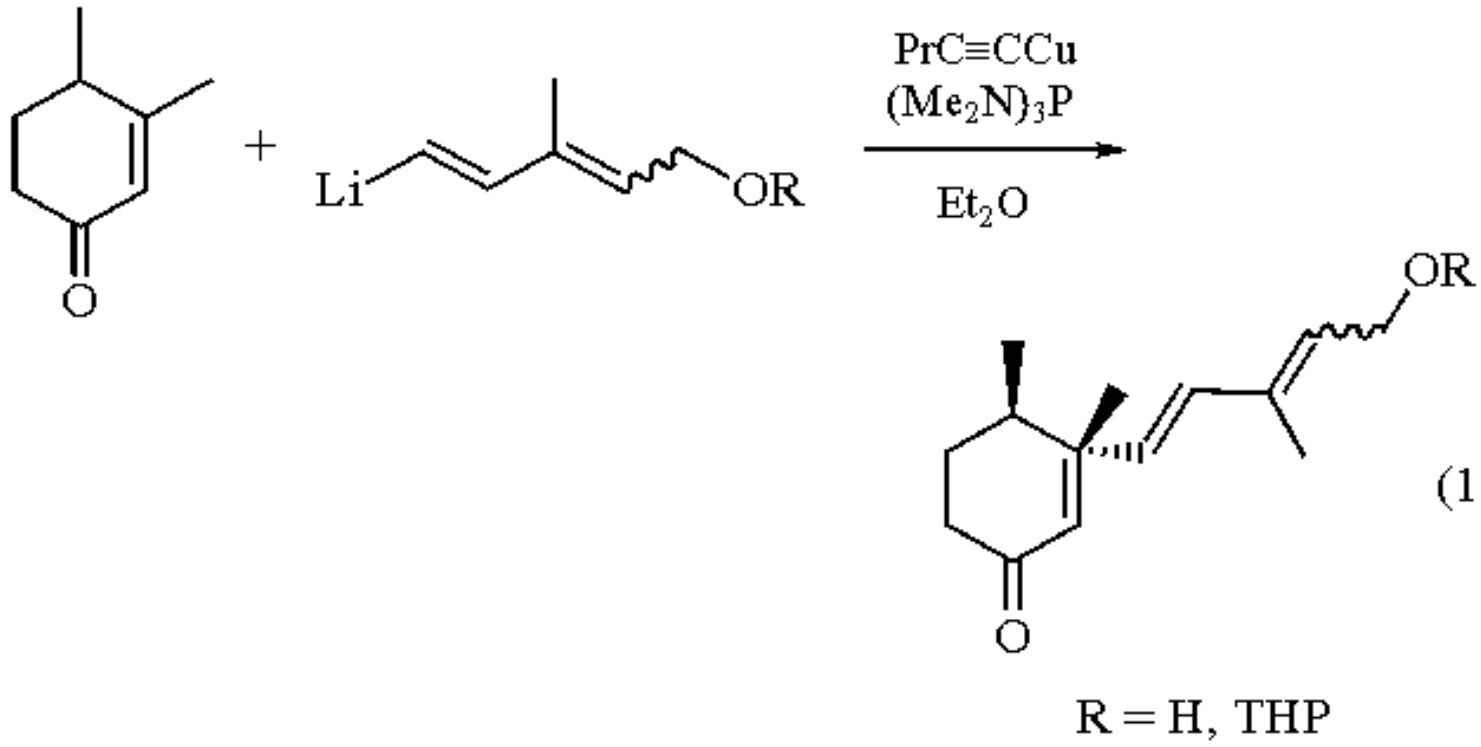

(15)

Lithiated 1,3-butadienyl 1,4-disulfides can be alkylated or cyclized to form thiophenes, depending on reaction conditions (eq 16).[12]

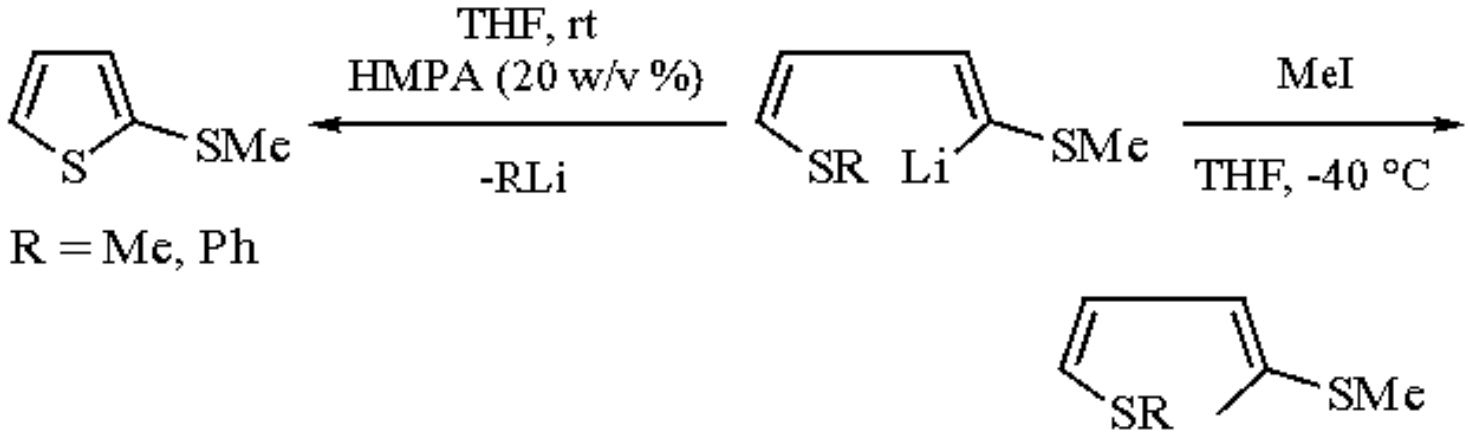

(16)

1,3-Butadienyllithium derivatives are suitable intermediates for transmetalation reactions (eqs 17 and 18). The 1-trimethylsilyl-1,3-pentadienyl-1-lithium is transmetalated to the corresponding magnesium derivative by interaction with freshly prepared ***Magnesium Bromide*** (obtained from the reaction of Mg with $BrCH_2CH_2Br$ in 3:1 ether-benzene solvent).[9] The reaction of cyclopentadienyldicarbonyliron iodide with 4-bromobutadienyl-1-lithium proceeds with the retention of configuration.[10]

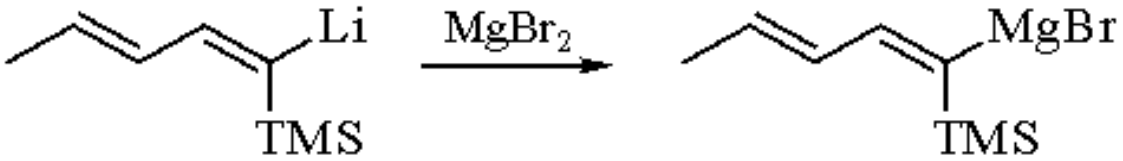

(17)

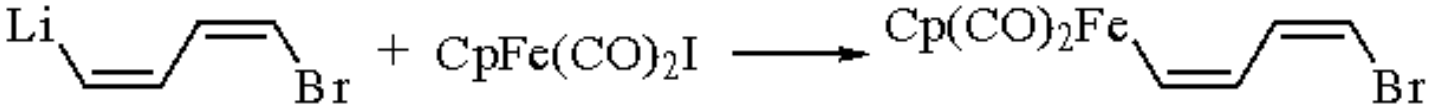

(18)

Related Reagents.

1,3-Butadienyl-2-lithium; ***1,3-Butadienyl-2-magnesium Chloride***; ***1,3-Butadienyl-1-magnesium Chloride***.

---

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11. (a) Soderquist, J. A.; Hassner, A. *JACS* **1980**, *102*, 1577. (b) McDougal, P. G.; Rico, J. G. *JOC* **1987**, *52*, 4817. (c) Everhardus, R. H.; Gräfing, R.; Brandsma, L. *RTC* **1978**, *97*, 69.
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Viesturs Lūsis

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1,3-Butadienyl-2-magnesium Chloride

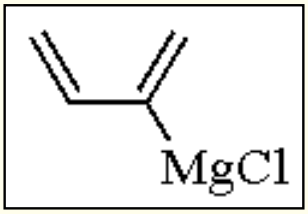

[32657-89-9] · C_4H_5ClMg · 1,3-Butadienyl-2-magnesium Chloride · (MW 112.84)

(reagent for a variety of carbon-carbon bond forming reactions with carbonyls, epoxides, and alkyl and aryl halides; precursor of organotin and organosilicon compounds via transmetalation reactions)

Analysis of Reagent Purity: the IR spectrum of a THF solution of 1,3-butadienyl-2-magnesium chloride showed a strong absorption of a conjugated diene at 1600 cm^{-1}. A butadienyl, rather than allenyl, structure is also indicated by the ^1H NMR spectrum.[1] The concentration of 1,3-butadienyl-2-magnesium chloride is determined by titration with 1 M HCl.

Preparative Method: 1,3-butadienyl-2-magnesium chloride is synthesized by Grignard reaction of 4-chloro-1,2-butadiene with ***Magnesium*** in ether (eq 1)[1] or 2-chloro-1,3-butadiene (chloroprene) with magnesium in the presence of ***1,2-Dibromoethane*** and a catalytic amount of ***Zinc Chloride*** in THF (eq 2).[2] The experimental procedure is as follows: to a flask equipped with a mechanical stirrer under nitrogen were charged magnesium turnings, well activated by scratching (0.15 mol), 0.5 mL of 1,2-dibromoethane, and 5 mL of THF. On cooling, $ZnCl_2$ (3 mol%) was added. To this mixture was added a small amount of freshly distilled chloroprene (ca. 1 g), and the solution was stirred vigorously with heating until initiation occurred. Several drops of dibromoethane may be added to assist initiation. After initiation occurred, chloroprene (100 mmol) in THF (100 mL) was added dropwise at a rate to maintain gentle reflux. An additional 3 h of reflux ensured complete reaction. 1,3-Butadienyl-2-magnesium chloride is generally used directly for further reactions as the solution.

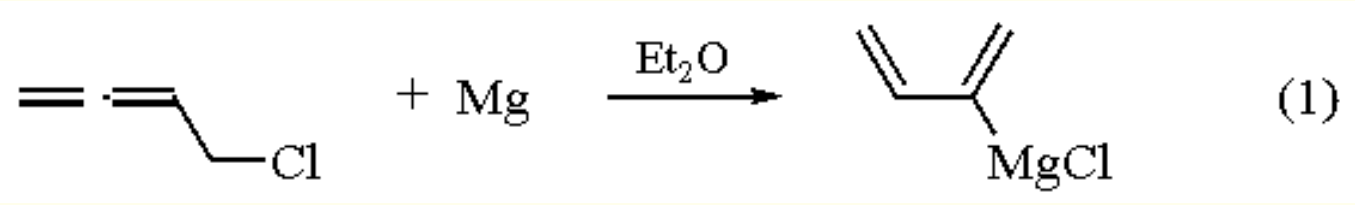

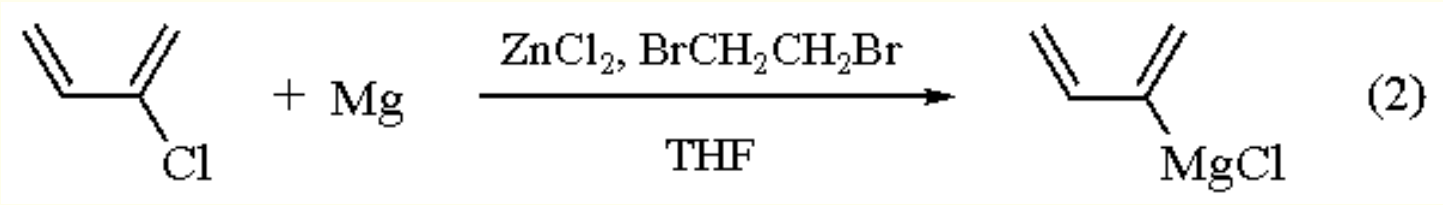

Carbon-Carbon Bond Forming Reactions.

1,3-Butadienyl-2-magnesium chloride is suitable for a variety of carbon-carbon bond forming reactions with carbonyl compounds,[3] epoxides, and alkyl and aryl halides.[4] The reaction generally gives a mixture of regioisomers. The selectivity depends significantly upon the substrate, solvent (as well as co-solvent) and additive. When the dienyl Grignard reagent is treated with acetaldehyde, the reaction affords an 84:16 mixture of 1,3-dienyl alcohol and allenyl alcohol (eq 3).

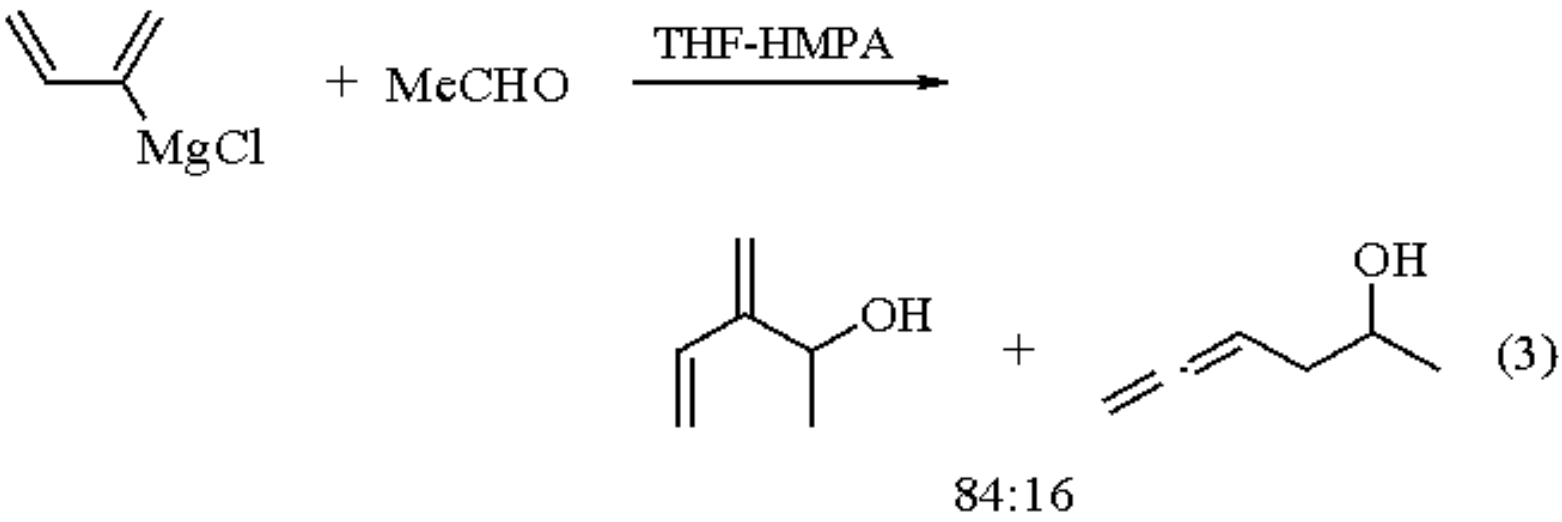

1,3-Butadienyl-2-magnesium chloride also induces the ring opening of epoxides and Michael reactions (eq 4). 1,3-Butadienyl-2-magnesium chloride reacts with alkyl halides to yield the corresponding alkylated products, which are available for intra- and intermolecular Diels-Alder reactions. The cross-coupling reaction with alkyl and aryl halides proceeds in the presence of catalytic ***Dilithium Tetrachlorocuprate(II)*** or Pd^0, as shown in eq 5.

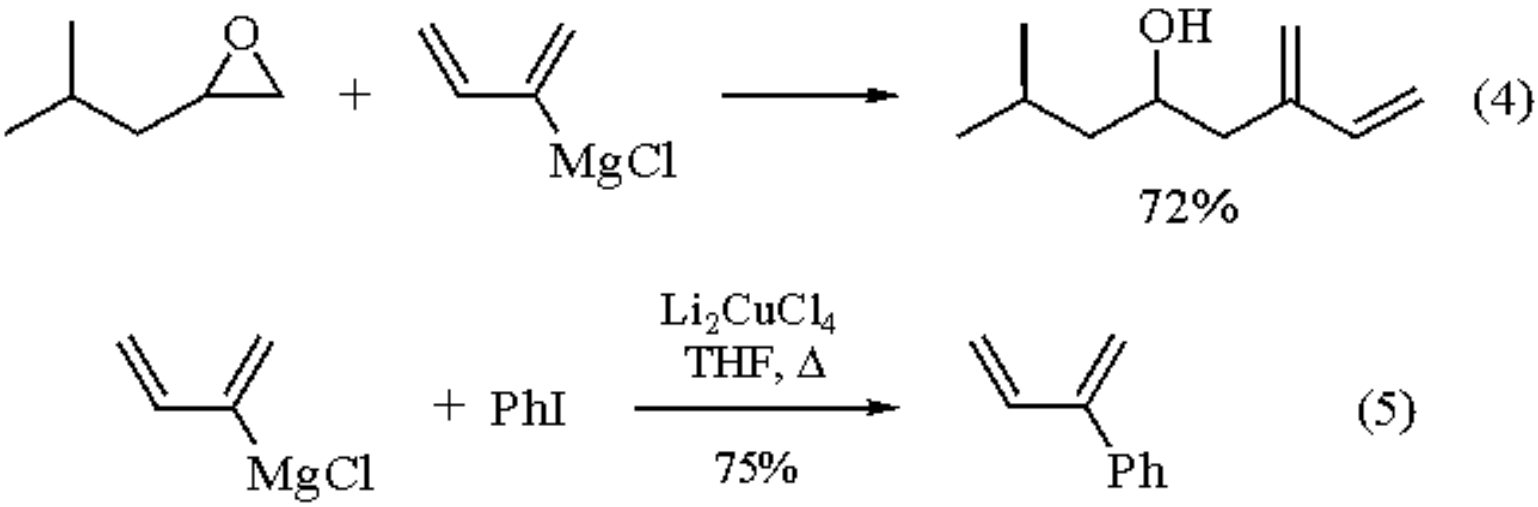

Transmetalation.

Treatment of 1,3-butadienyl-2-magnesium chloride with ***Dichlorodimethylsilane*** gives, via transmetalation, the corresponding 2-silylated butadiene, which is an intermediate for the preparation of a monomer of side-chain liquid

crystalline polymers.[5] The reaction of 1,3-butadienyl-2-magnesium chloride with ***Tri-n-butylchlorostannane*** affords a 1,3-butadienyl-2-stannyl compound and with ***Benzeneselenenyl Chloride*** gives 2-phenylseleno-1,3-butadiene (eq 6).[6,7] The former is a useful precursor for ***1,3-Butadienyl-2-lithium***.[6]

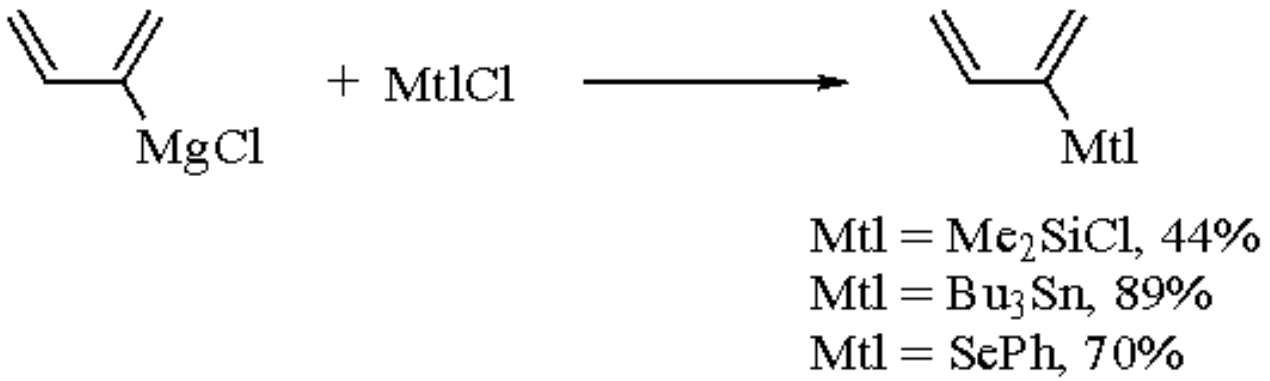

Related Reagents.

1,3-Butadienyl-2-lithium; ***1,3-Butadienyl-1-lithium***; ***1,3-Butadienyl-1-magnesium Chloride***.

---

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1,3-Butadienyl-1-magnesium Chloride

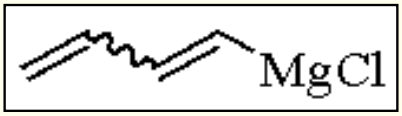

[114073-55-1] · C_4H_5ClMg · 1,3-Butadienyl-1-magnesium Chloride · (MW 112.84) (*E*)

[112564-81-5] (*Z*)

[112564-82-6]

(reagent for single-step introduction of the terminal 1,3-butadienyl group to various organic skeletons)

Solubility: sol THF, dioxane, DMF, 1,2-diethoxyethane, diethylene glycol dimethyl or diethyl ether, as well as in combinations of these solvents with aliphatic (*n*-hexane, *n*-octane) or aromatic (benzene, xylene) hydrocarbons.[1]

Preparative Method: [2,3] a mixture of ***Magnesium*** (24 g, 1.0 mol) and zinc chloride (6.8 g, 0.05 mol) was dried at 130 °C for 2 h under vacuum. Dried THF (30 mL) and ***1,2-Dibromoethane*** (2.0 mL) were added and the mixture was stirred vigorously under an argon atmosphere. After the exothermic reaction had subsided, the reaction mixture was diluted by additional THF (350 mL), and then a solution of 1-chloro-1,3-butadiene (44 g, 0.5 mol) and 1,2-dibromoethane (4 mL) in THF (70 mL) was added dropwise over 1 h and the mixture was heated under reflux for 2 h. The concentration of the reagent solution is determined[4] by titration using 1,10-phenanthroline as indicator. The average yield of 1,3-butadienyl-1-magnesium chloride was about 70%.

Handling, Storage, and Precautions: the reagent is moisture sensitive. Solvents must be carefully dried before use, and the preparation and reactions should be carried out under nitrogen or argon atmosphere.

Addition to Carbonyl Compounds.

Treatment of ketones or aldehydes with 1,3-butadienyl-1-magnesium chloride after hydrolytic work-up gave excellent yields of alcohols containing the 1,3-butadienyl group: 80-98% for aldehydes and aliphatic and alicyclic ketones, and approximately 70% for aromatic ketones and enones (eq 1).[1-3] In these reactions the initial stereochemical (*E*)/(*Z*) ratio, of the 1,3-butadienyl group of the Grignard reagent was found to be retained in the reaction products.

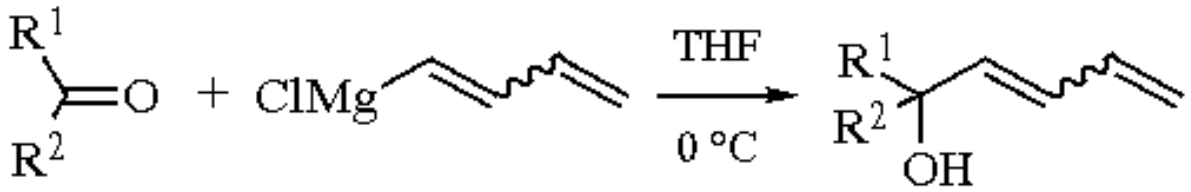

(1)

$R^1 = H$; $R^2 = n$-Hept, i-Pr, MeCH=CH-
$R^1 = Me$; $R^2 = Et$, Ph, Me
$R^1, R^2 = -(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_3-CH=CH-$

Butadienylmagnesium chloride usually reacts at the carbonyl group of conjugated ketones, whereas in the presence of ***Copper(I) Iodide*** (addition of 50 mol % CuI forms the butadienylmagnesium Cu^I complex), 1,4-addition is observed (eq 2).

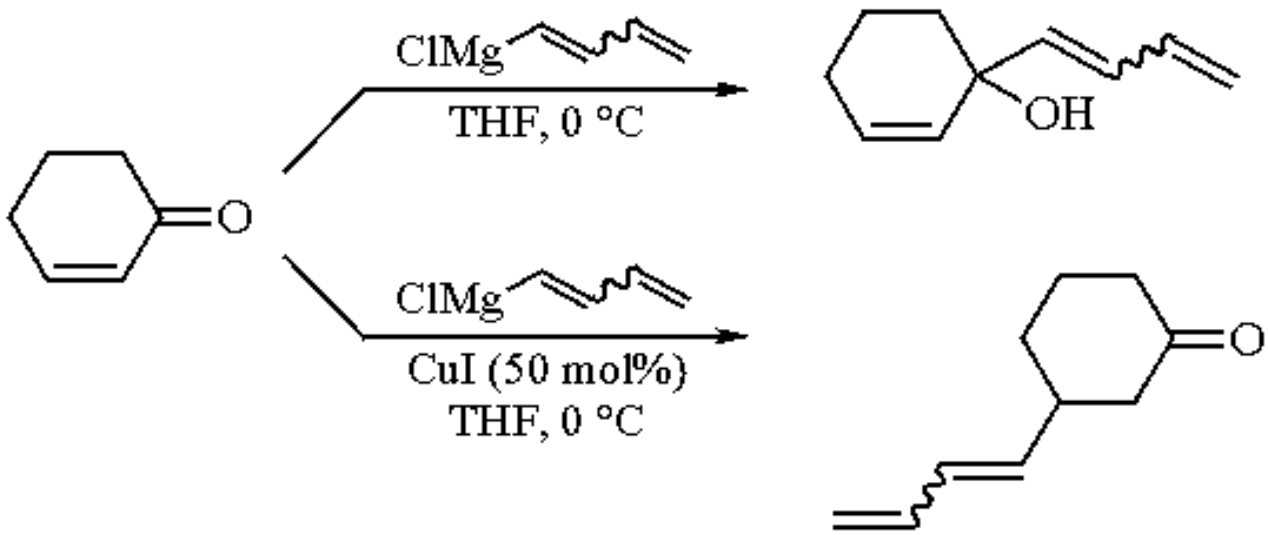

(2)

Grignard analogs of higher 1,3-dienes (penta-, hepta-, octa-)[1] or their silylated derivatives (e.g. (*E*,*E*)-1 bromo-1-(trimethylsilyl)penta-1,3-diene)[5] react with carbonyl compounds in a similar manner (eq 3).

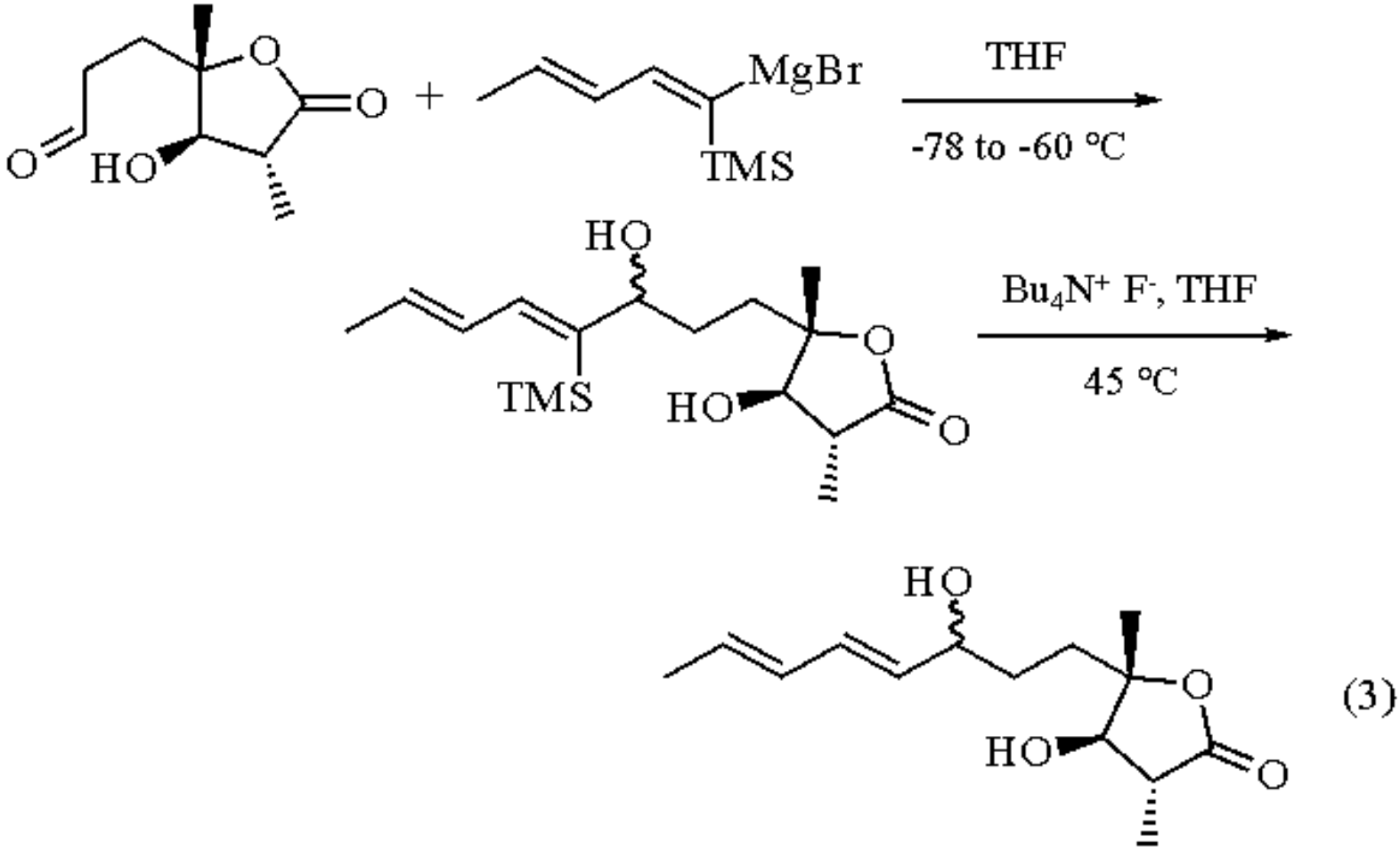

For the introduction of the butadienyl moiety, Grignard reagents are preferred to the lithium derivatives due to the lower basicity of the former. The silylated pentadienyl Grignard reagent in eq 3 was superior to both the precursor lithium reagent and pentadienyllithium itself.[5]

Coupling with Alkyl Halides.

The coupling of 1,3-butadienyl-1-magnesium chloride with alkyl bromides or iodides is catalyzed by CuI and proceeds under mild conditions (eq 4).[3] The stereochemistry of the dienyl moiety is retained in the reaction product. The coupling reaction with 5-bromo-2-methyl-1-penten-3-yne was accompanied by allene formation (eq 5).[6]

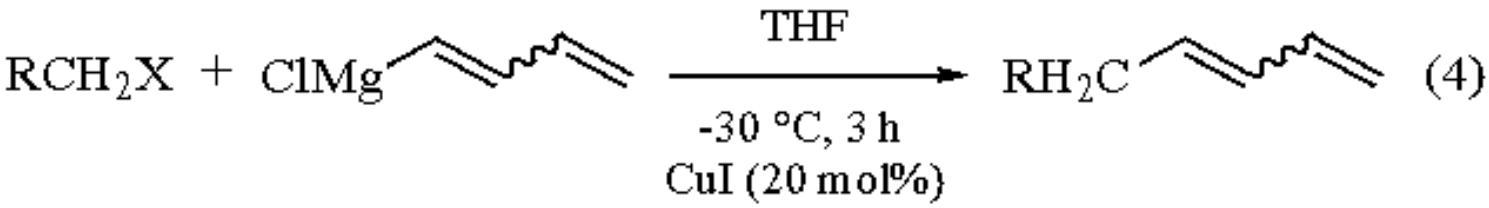

X = Br, I
R = Me(CH$_2$)$_4$, R^{1}O(CH$_2$)$_7$, Ph; R^1 = THP, Et

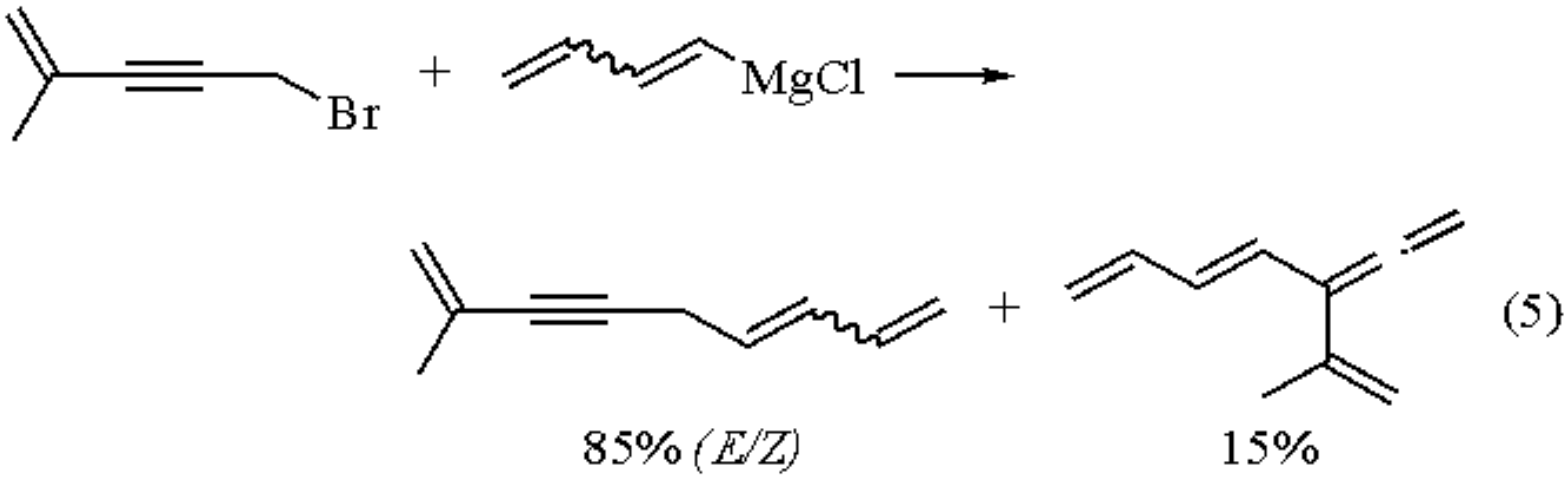

The configuration of the introduced butadienyl group corresponds to the configuration of the starting chlorobutadiene (for purification and isomerization of (*Z*)- and (*E*)-1-chlorobuta-1,3-dienes, see Onishchenko[7]). A mixture of (*Z*)- and (*E*)-isomers of the butadienyl derivatives obtained after reaction of butadienylmagnesium chloride with ketones and aldehydes could be transformed by the action of alkyllithium reagents, ***Dimethylphenylsilyllithium***, ***Trimethylstannyllithium***, or ***Lithium Diethylamide***, into the pure (*E*)-diene with simultaneous lengthening of the chain (eq 6).[2]

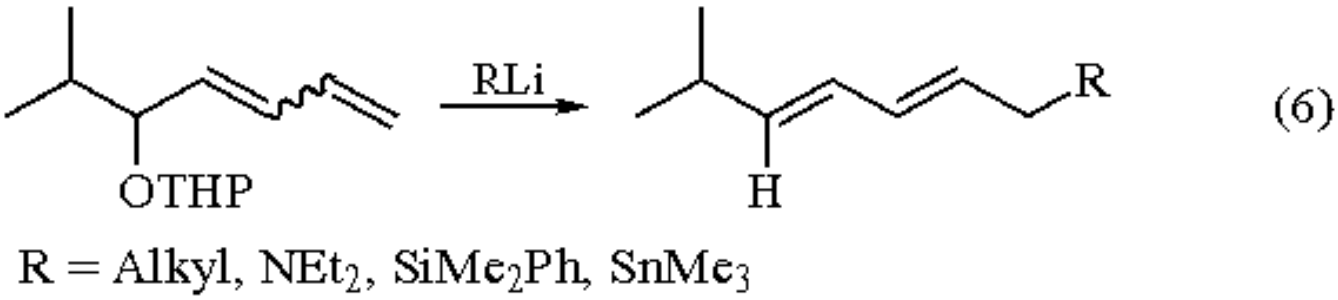

4-Substituted-(*Z*,*Z*)-butadienyl cuprates can be prepared by addition of cuprates to alkynes. These form 1,4-disubstituted (*Z*,*Z*)-butadienes with typical electrophiles (alkyl halides, enones, CO_2) (eq 7).[8]

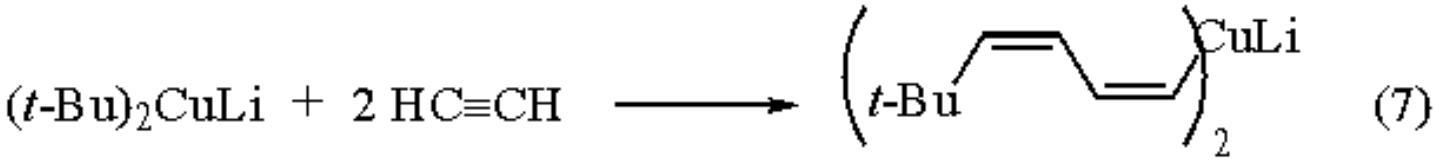

Related Reagents.

1,3-Butadienyl-2-lithium; ***1,3-Butadienyl-1-lithium***; ***1,3-Butadienyl-2-magnesium Chloride***.

---

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Viesturs Lūsis

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Butadiyne

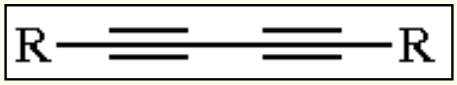

(R = H)

[460-12-2] · C_4H_2 · Butadiyne · (MW 50.06) (R = $SiMe_3$)

[4526-07-2] · $C_{10}H_{18}Si_2$ · 1,4-Bis(trimethylsilyl)buta-1,3-diyne · (MW 194.42)

(butadiyne is an intermediate for synthesis of substituted 1,3-diynes.[1-3] The silylated derivative is used for Friedel-Crafts acylation,[5-7] for the synthesis of heterocycles,[8-11] and for the preparation of (*Z*)-methyl-1,4-bis(trimethylsilyl)-1-buten-3-yne derivatives;[12] hydrosilation gives access to vinylsilane derivatives;[13] trimethylsilylbuta-1,3-diynyllithium may be acylated or alkylated[14-17] and used in the synthesis of (*Z*)- or (*E*)-enyne derivatives[15,18,19])

Physical Data: R = H: mp -36 to -35 °C; bp 10 °C. R = $SiMe_3$: mp 107-108 °C.

Solubility: R = H or $SiMe_3$: sol most organic solvents.

Preparative Methods: R = H: from dehydrochlorination of 1,4-dichloro-2-butyne with sodium or potassium hydroxide.[4] R = $SiMe_3$: by dimerization of trimethylsilylacetylene under copper catalysis and in the presence of TMEDA.[5]

Handling, Storage, and Precautions: R = H: irritant, extremely flammable, and potentially explosive. Readily polymerizes above 0 °C. THF solutions can be stored for at least 3 d at -20 °C; storage of large quantities should be avoided. R = $SiMe_3$: stable white solid.

Alkylation and Acylation Reactions of Butadiyne.

Formation of the mono- or bis-sodium anion of butadiyne can be achieved directly from ***1,4-Dichloro-2-butyne*** with 3 or 4 equiv of sodamide.[1,2] This avoids isolation of the highly unstable parent compound. Alkylation or acylation in situ with alkyl halides or carbonyl compounds is then possible (eq 1). The mono- or bis-lithium anion can also be produced in situ by deprotonation and elimination of (*Z*)-1-methoxybut-1-en-3-yne with either 2 or 3 equiv of ***n-Butyllithium*** (eq 2).[3]

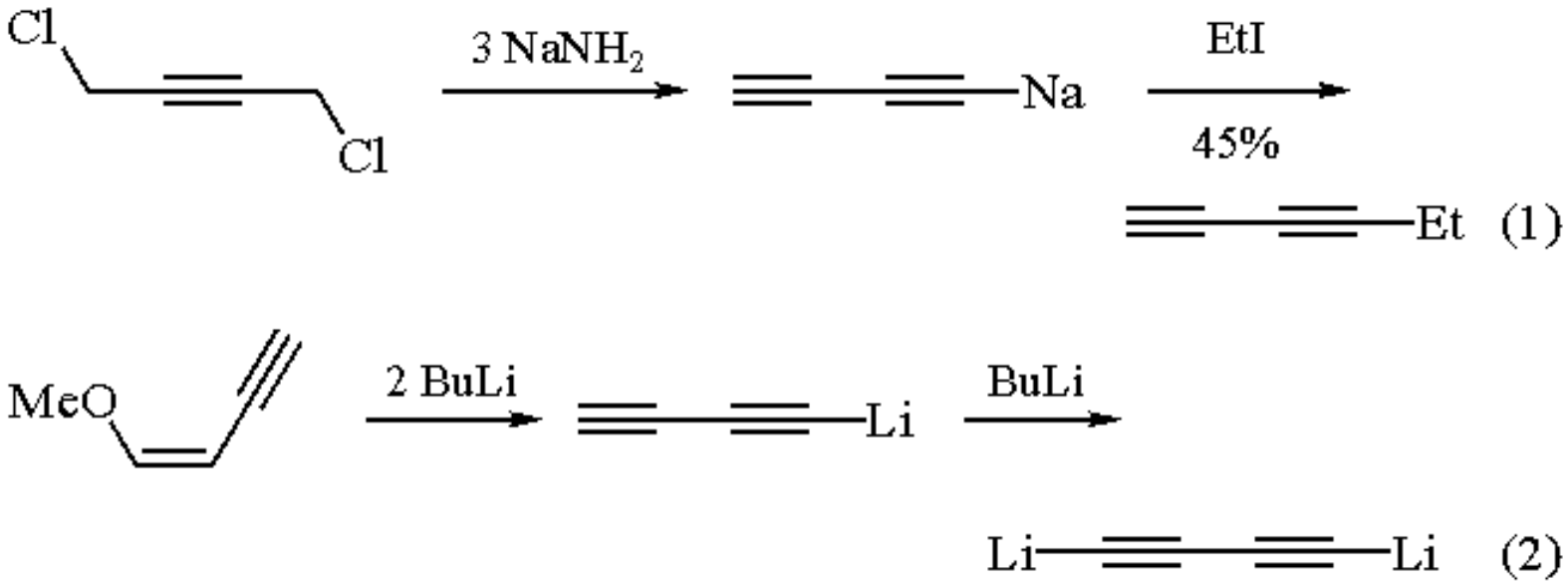

Conjugated Diynones.

1,4-Bis(trimethylsilyl)buta-1,3-diyne has been used in Friedel-Crafts acylation reactions under Lewis acid catalysis (eq 3).[5-7]

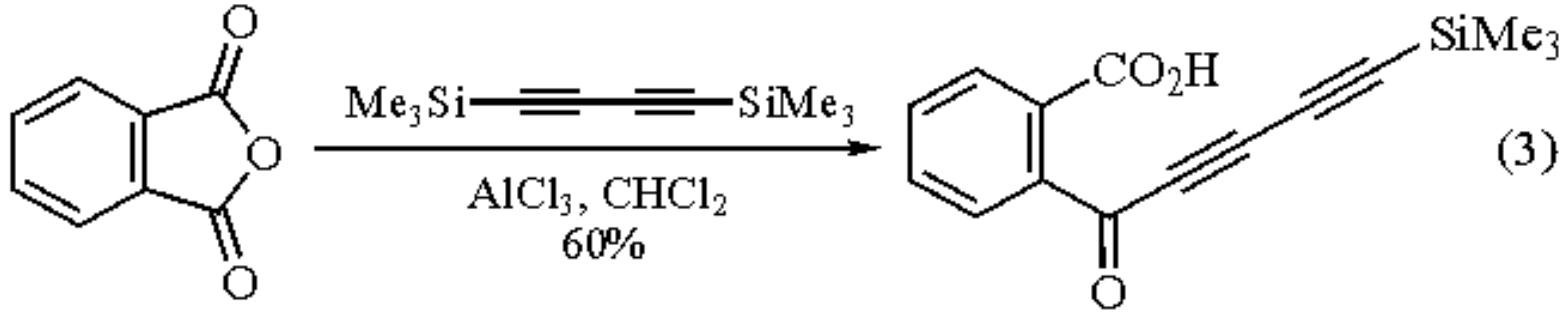

Diels-Alder Reactions.

1,4-Bis(trimethylsilyl)buta-1,3-diyne has been used with varying degrees of success as a dienophile in Diels-Alder cycloadditions (eq 4).[8-10]

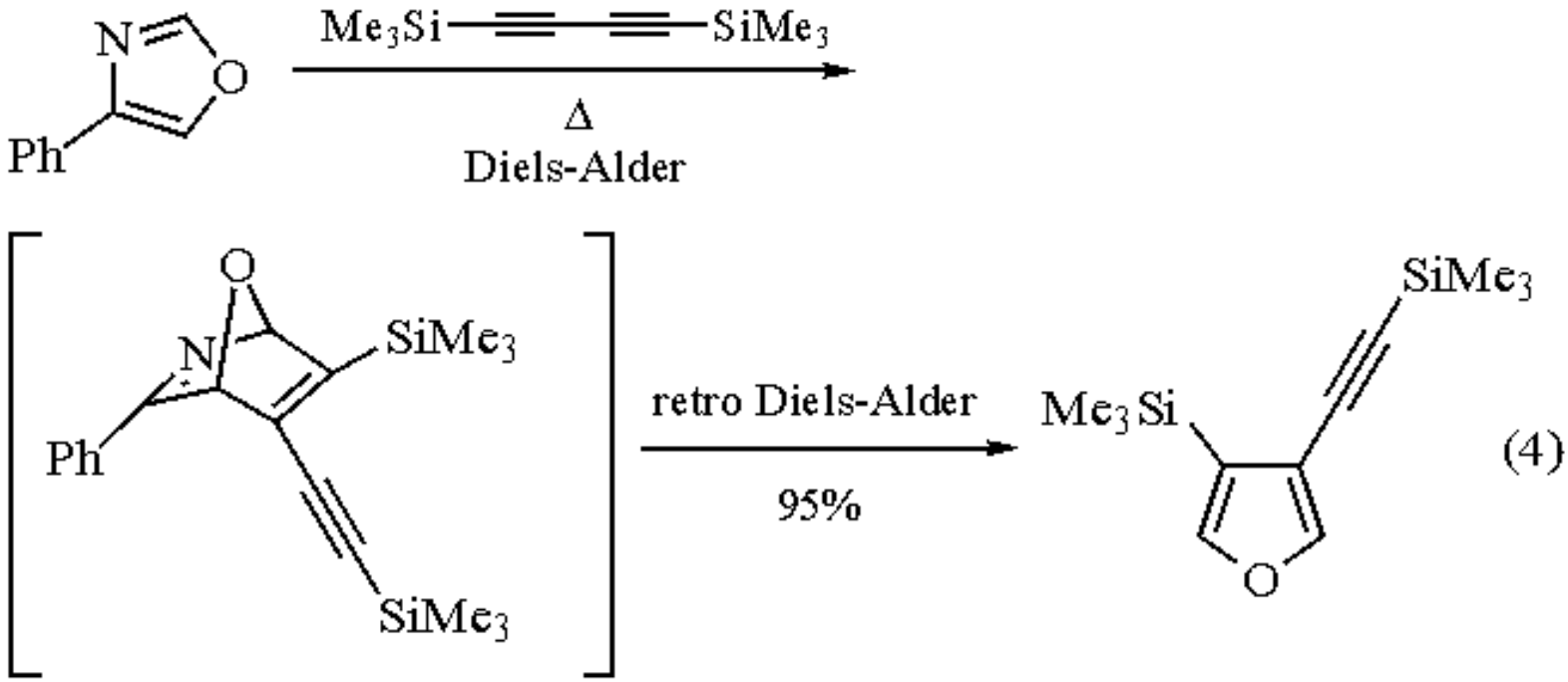

Synthesis of Pyrazoles and Isoxazoles.

1,4-Bis(trimethylsilyl)buta-1,3-diyne has been used for the synthesis of pyrazoles and isoxazoles;[11] for example, reaction with ***Hydrazine*** gives the indicated pyrazole (eq 5).

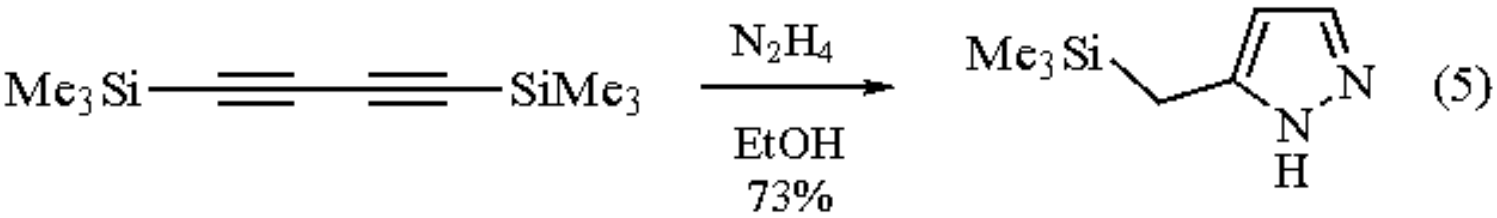

(*Z*)-Methyl-1,4-bis(trimethylsilyl)-1-buten-3-yne Derivatives.

Zirconium catalyzed carbometalation of 1,4-bis(trimethylsilyl)buta-1,3-diyne with ***Trimethylaluminum*** followed by addition of electrophiles gives access to the title derivatives (eq 6).[12]

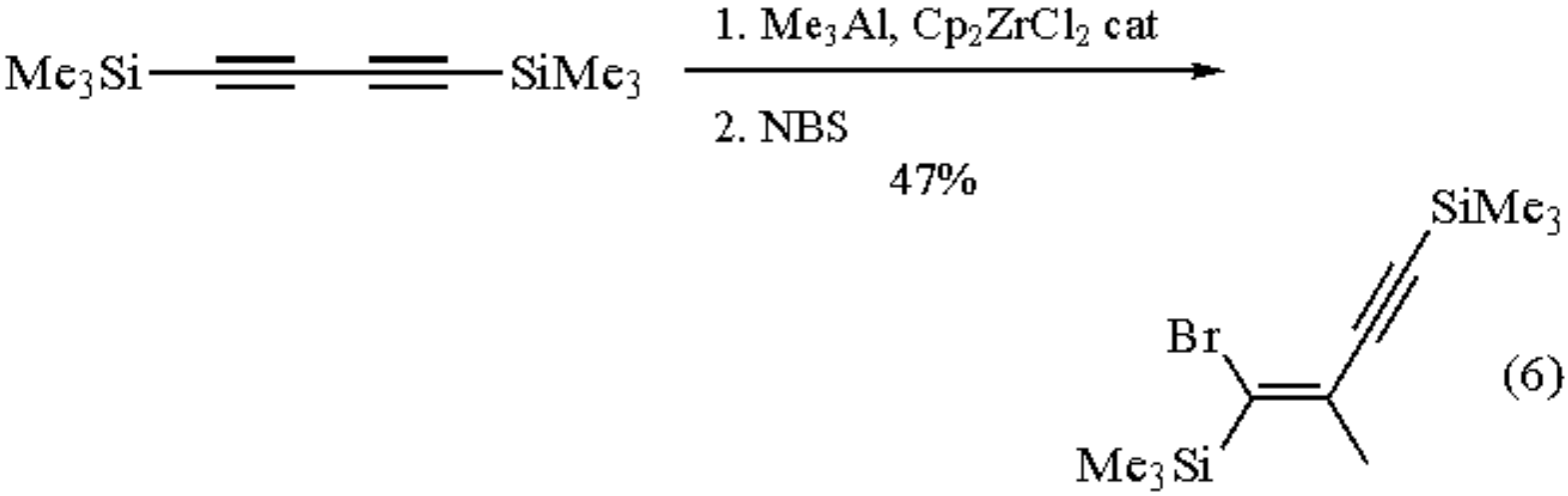

(6)

Vinylsilanes.

Hydrosilation of 1,4-bis(trimethylsilyl)buta-1,3-diyne gives access to a range of vinylsilane derivatives.[13]

Trimethylsilylbuta-1,3-diynyllithium.

Treatment of 1,4-bis(trimethylsilyl)buta-1,3-diyne with ***Methyllithium-Lithium Bromide*** selectively produces trimethylsilylbuta-1,3-diynyllithium (eq 7).[14] This reagent combines with various electrophiles to produce substituted 1,3-diynes (e.g eq 8).[15-17] The same anion can be synthesized from (*Z*)-4-trimethylsilyl-1-methoxybut-1-en-3-yne by deprotonation and elimination with 2 equiv of *n*-BuLi (eq 2).[3]

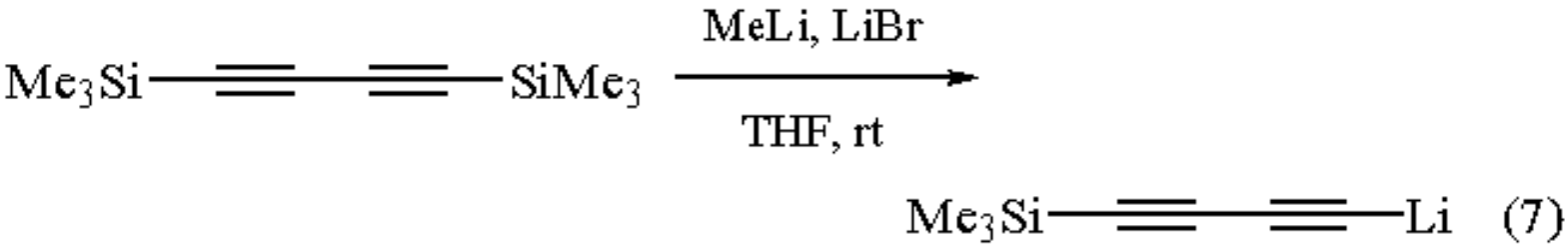

(7)

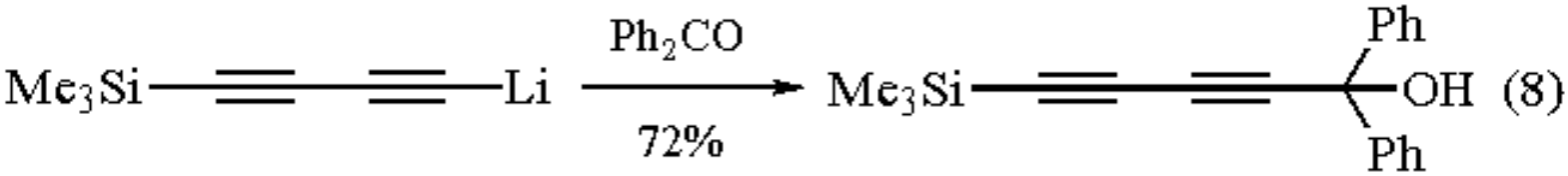

(8)

Hydrogenation.

Hydrogenation of siladiynes selectively reduces the triple bond which is furthest from the silicon protecting group, yielding silyl protected *cis*-enynes.[16,18] Formation of the corresponding *trans*-enyne derivatives is possible by hydroalumination.[7,17,19]

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2,3-Butanediol[1]

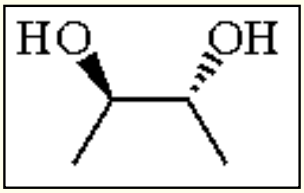

[513-85-9] · $C_4H_{10}O_2$ · 2,3-Butanediol · (MW 90.12) (2*R*,3*R*)

[24347-58-8] (2*S*,3*S*)

[19132-06-0]

(resolution of enantiomers;[2] determination of enantiomeric purity by ^{13}C NMR;[3] asymmetric aldol reactions;[4] asymmetric cleavage of chiral acetals;[5] asymmetric β-elimination of chiral alkynic acetals;[6] asymmetric allylations;[7] cyclization of chiral dienic acetals;[8] enantioselective epoxidation;[9] diastereoselective cyclopropanation;[10] boronic ester homologation[11])

Physical Data: bp 179-182 °C; *d* 0.99 g cm^{-3}.

Solubility: sol H_2O, alcohol, ether, acetone.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: avoid breathing vapor. Avoid contact with eyes, skin, and clothing. Hygroscopic. Air sensitive. Store under nitrogen in a cool dry place.

Resolution of Enantiomers.

The availability of optically pure tartrate-derived diols has led to their widespread use in asymmetric synthesis. Mixtures of diastereomeric acetals prepared from (2*R*,3*R*)-(-)-2,3-butanediol are usually easily separated. Resolution of DL-camphor[12] was one of its earliest uses, but many nonracemic mixtures have been separated more recently.[2,13-15] Acetals prepared from this reagent also give distinct ^{13}C NMR spectra which can be interpreted to determine the enantiomeric purity of the starting ketones.[3,16-23]

Enantiomeric Monoacetalization of Diones.[24]

The acid-catalyzed monoacetalization of diones with (2*R*,3*R*)-(-)-2,3-butanediol forms a separable mixture of

diastereomeric acetals. Retro-Claisen fragmentation of the β-keto acetals with TsOH in benzene under reflux, followed by transesterification with methanol, provides a route to optically active 2,3-disubstituted cycloalkanones (eq 1).[24b]

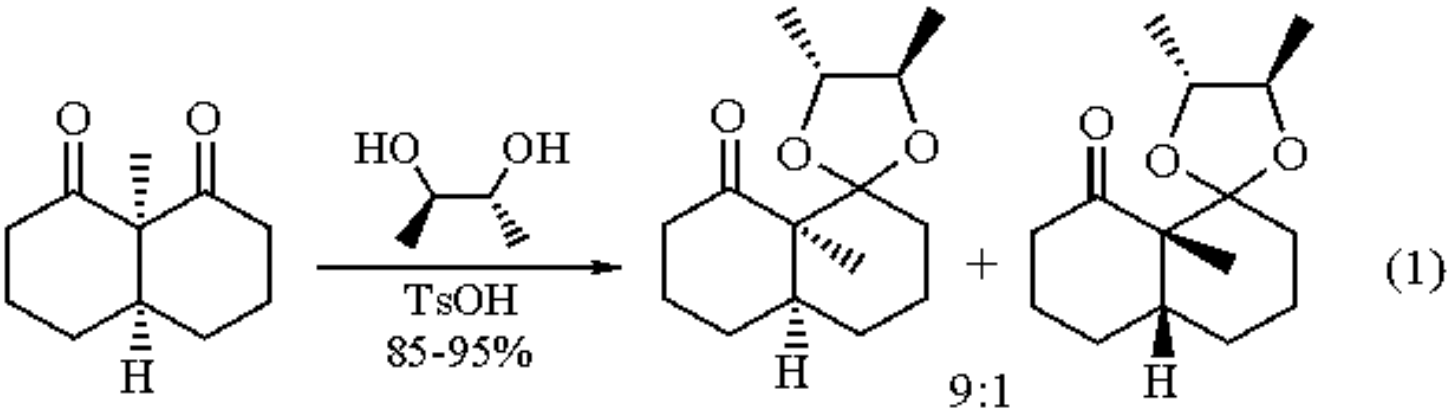

Asymmetric Aldol Reactions.[4]

Acetals prepared from (2*R*,3*R*)-(-)-2,3-butanediol react cleanly with α-silyl carbonyl compounds in the presence of ***Tin(IV) Chloride*** to give the crossed aldol products with high ee (eq 2).[4b] The product can be converted into an optically active β-hydroxy ketone by Swern or ***Pyridinium Chlorochromate*** oxidation, Baeyer-Villager oxidation, and methanolysis in an overall yield of 70%. The asymmetric aldol reaction is also catalyzed by ***Boron Trifluoride***.

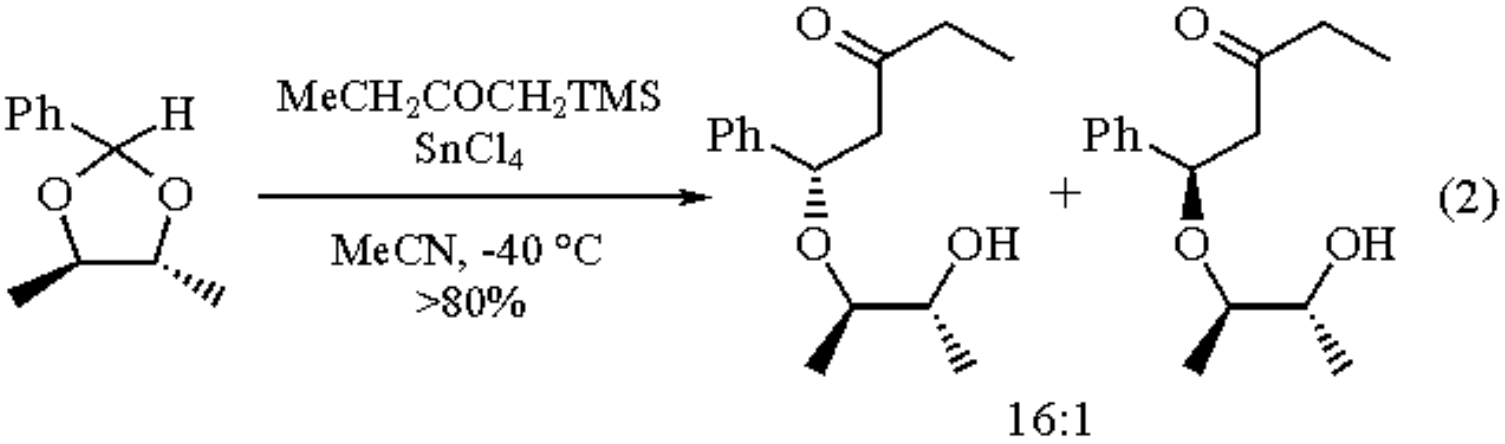

Diastereoselective Nucleophilic Addition.

(2*R*,3*R*)-(-)-2,3-Butanediol α-keto acetals react with Grignard reagents[25] with poor stereoselectivity, but reduction of β-keto acetals with ***Lithium Aluminum Hydride*** occurs with good de (eq 3).[26]

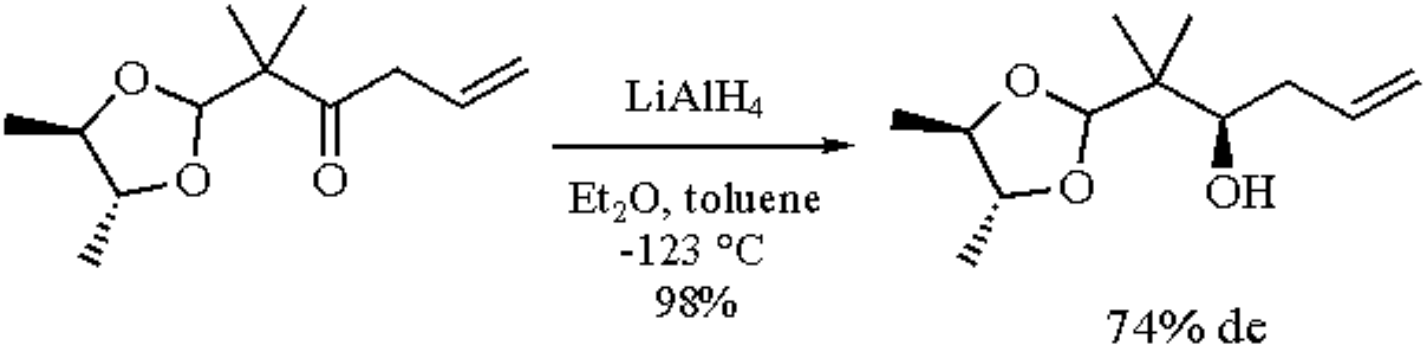

(3)

Asymmetric cleavage of chiral acetals by R_2CuLi/BF_3 gives the corresponding ring-opened products with high de (eq 4).[5] The diastereoselectivity of this ring opening is due to an unfavorable 1,3-diaxial interaction. A similar interaction in the β-elimination reaction of chiral alkynic acetals with Grignard reagents gives alkoxyallenes with very high de (eq 5).[6]

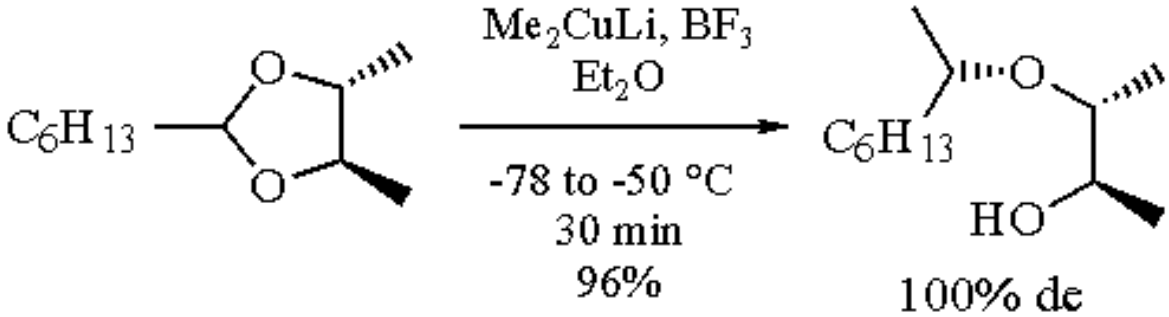

(4)

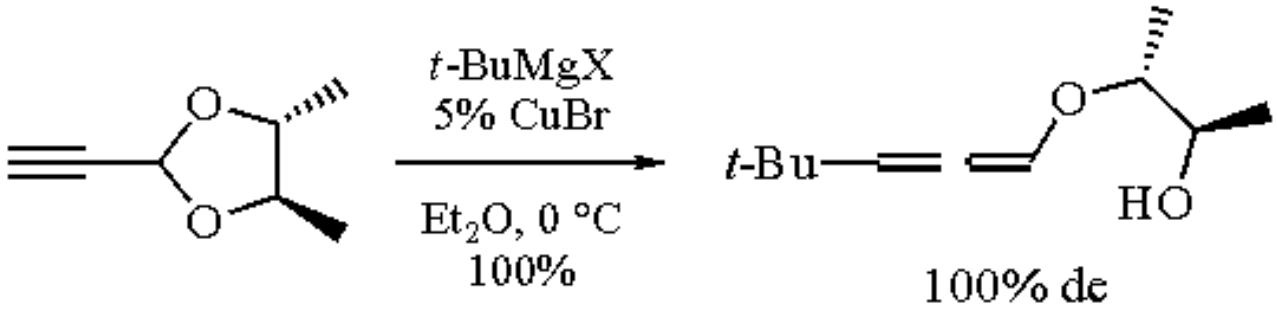

(5)

Asymmetric allylations of protected cyclopentenonecarbaldehydes proceed with high de. Subsequent anionic oxy-Cope rearrangement provides a convenient route to the prostaglandins (eq 6).[7]

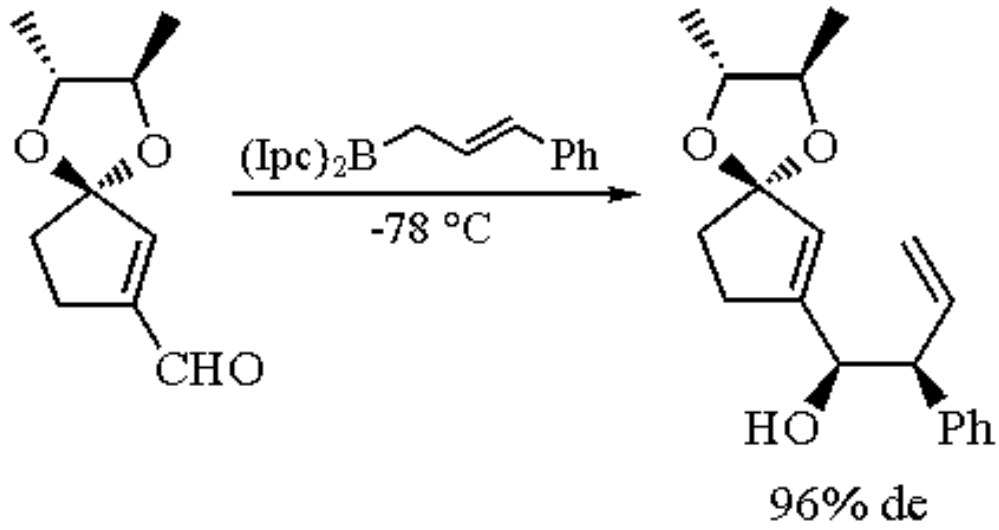

(6)

Asymmetric Diels-Alder Reaction.[27,28]

The chiral aluminum diolates prepared from ***Ethylaluminum Dichloride*** and 2,3-butanediol catalyze the Diels-Alder reaction of methacrolein and cyclopentadiene in good yield, but the ee is very low. The catalyst prepared from (*S*)-1,1-diphenyl-1,2-dihydroxypropane gives superior results, with 74% ee.[27]

Intramolecular Cyclization.

The $SnCl_4$-catalyzed cyclization of dienic acetals derived from (2*R*,3*R*)-(-)-2,3-butanediol occurs with a high degree of asymmetric induction (eq 7).[8]

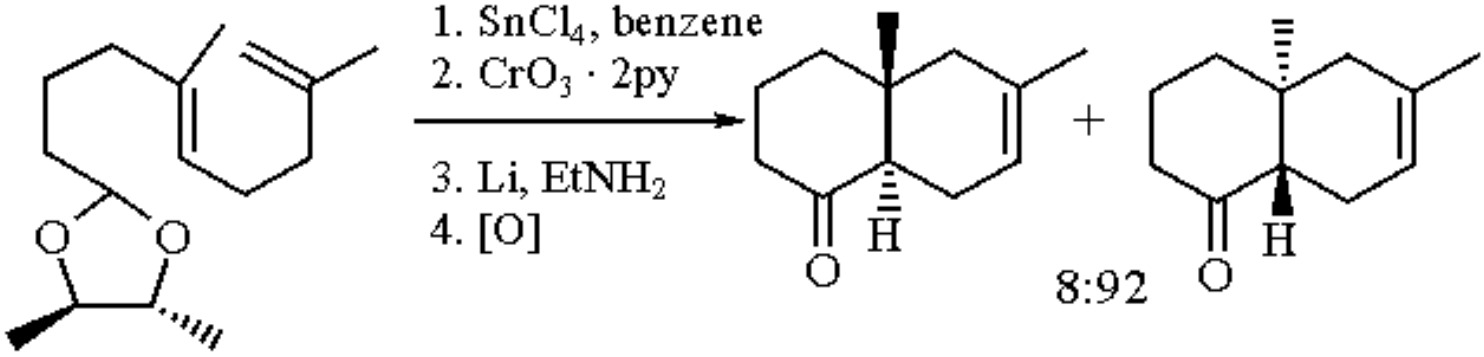

(7)

Enantioselective Epoxidation.

Asymmetric epoxidation of aliphatic alkenes with molybdenum(VI) (oxo-diperoxo) reagents in the presence of either (2*S*,3*S*)- or (2*R*,3*R*)-2,3-butanediol in nitromethane gives high ee, probably because of an efficient kinetic resolution of the oxiranes formed (eq 8).[9] This method makes possible asymmetric syntheses of epoxides not available by other routes (e.g. Sharpless epoxidation).

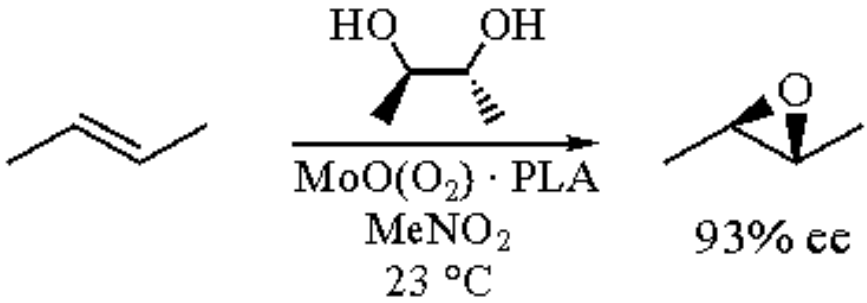

(8)

Diastereoselective Cyclopropanation.[10]

Diastereoselective Simmons-Smith cyclopropanation of 2-cyclohexen-1-one acetals of 2,3-butanediol occurs with good de (eq 9).[10a]

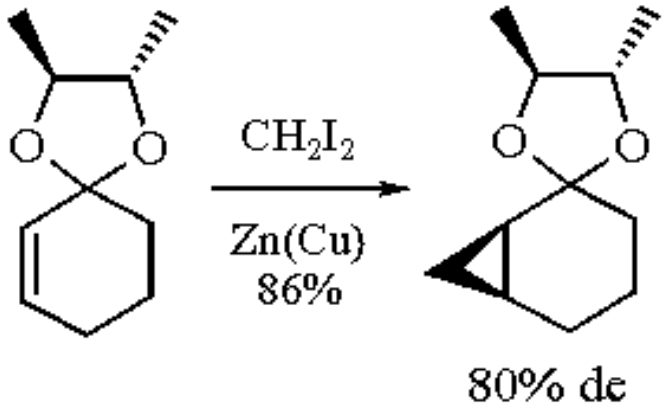

(9)

Boronic Ester Homologation.[11,29]

Dichloromethaneboronic esters of (2*R*,3*R*)-2,3-butanediol react with alkyllithium reagents to give a borate complex which rearranges diastereoselectively in the presence of ***Zinc Chloride*** with the introduction of a chiral center adjacent to boron (eq 10).[11a]

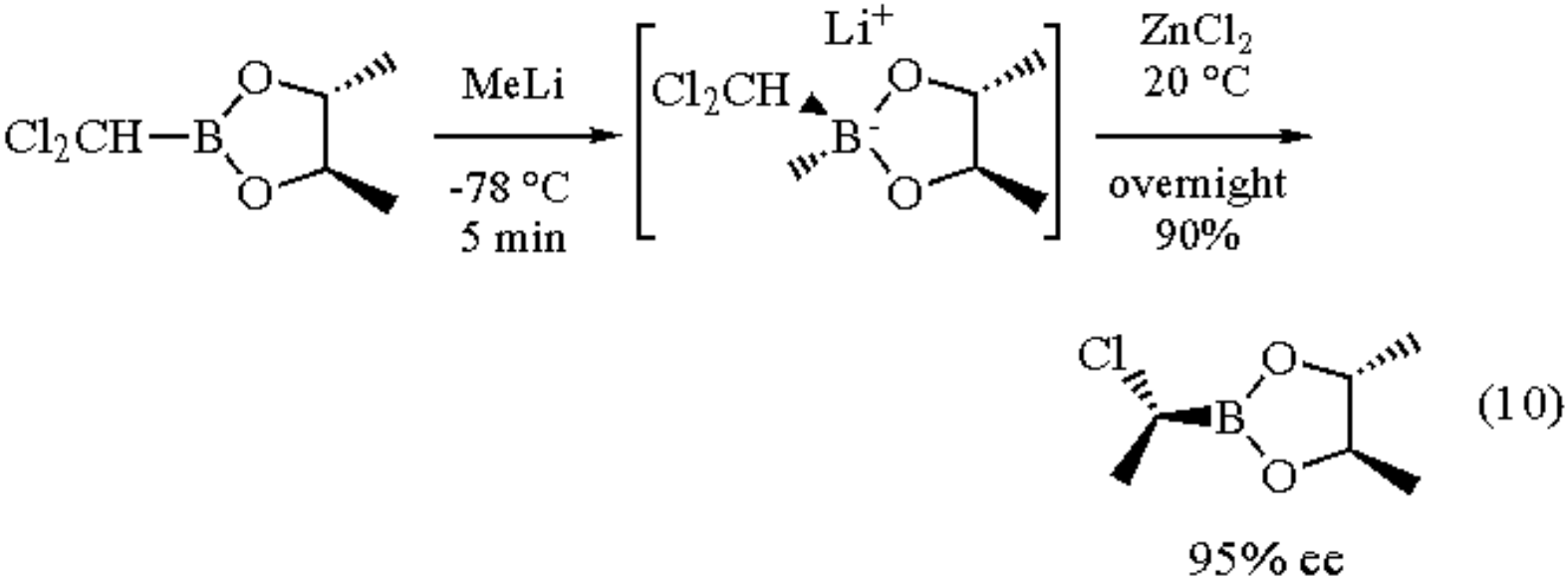

(10)

Substitution Reactions.

Both (2*R*,3*R*)- and (2*S*,3*S*)-2,3-butanediol have been used as starting materials for the preparation of optically pure compounds, such as (2*R*,3*R*)-***2,3-Bis(diphenylphosphino)butane***,[30] (2*S*,3*R*)-3-bromo-2-butanol,[31] and (*R*)-acetoin.[32]

---

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2,3-Butanedione

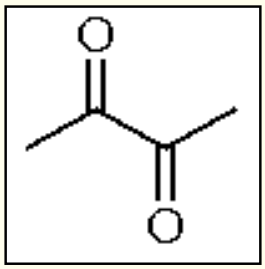

[431-03-8] · $C_4H_6O_2$ · 2,3-Butanedione · (MW 86.09)

(cyclocondensations; reacts with Wittig reagents; condensations)

Alternate Name: biacetyl.

Physical Data: mp 2.4 °C; bp 88 °C/760 mmHg; *d* 0.981 g cm^{-3}; fp <21 °C.

Solubility: sol water (25 g/100 mL); miscible with alcohol and ether.

Form Supplied in: yellowish green liquid; quinone odor.

Purification: dried over anhydrous $CaSO_4$, $CaCl_2$, or $MgSO_4$, then vacuum distilled under nitrogen. The middle fraction is taken and stored at dry ice temperature in the dark (to prevent polymerization).

Handling, Storage, and Precautions: highly flammable, moderately toxic.

Cyclocondensations.

2,3-Butanedione (**1**) reacts with 1,3-dimethylurea in refluxing benzene containing 10% ***Trifluoroacetic Acid*** to form a bis adduct, 4,4´-methylenebis(1,3,5-trimethyl-4-imidazolin-2-one), whose structure has been confirmed by X-ray analysis (eq 1).[1]

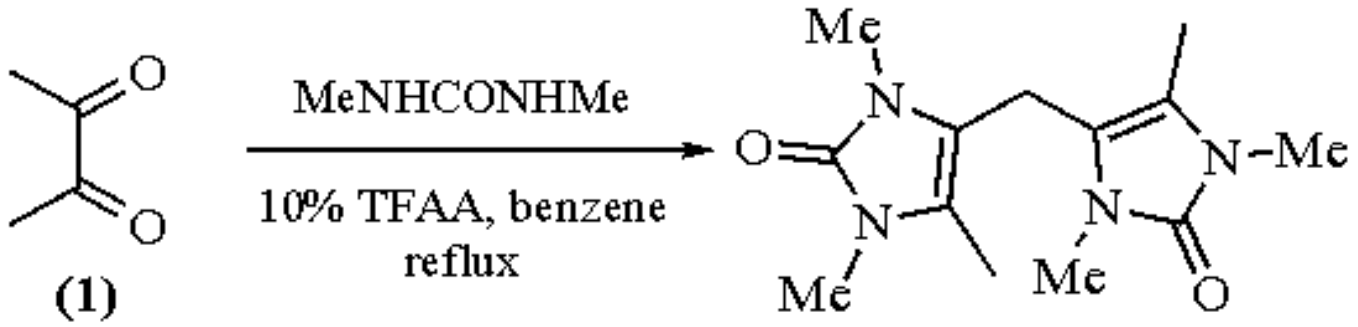

Reaction of (**1**) with malononitrile catalyzed by ***Sodium Ethoxide*** furnishes the 1,5-dimethyl-3,7-dioxo-2,8-diaza-*cis*-bicyclo[3.3.0]octane-4,6-dicarbonitrile (eq 2).[2] On the other hand, ***Piperidine***-catalyzed condensation of (**1**) with 2-cyanacetamide forms 4,5-dimethyl-5-hydroxy-2-oxo-3-pyrrolinecarbonitrile (eq 3).[3]

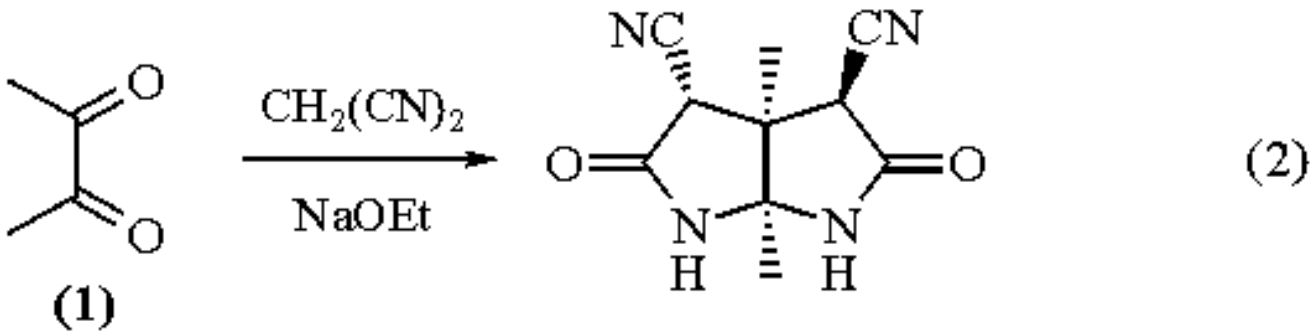

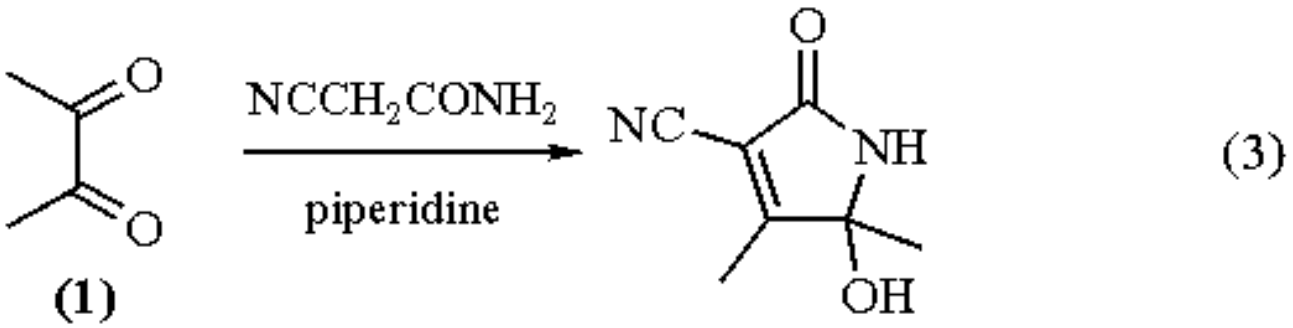

Condensation of (**1**) with 4,5-diamino-2-thioxo-6-oxotetrahydropyrimidine,[4] 3,4-diamino-2-(methylthio)-5-cyanothiophene,[5] and amidrazone,[6] individually, affords 6,7-dimethyl-4-oxo-2-thioxotetrahydropteridine, 2-(methylthio)thieno[3,4-*b*]pyrazine, and triazine derivatives, respectively (eqs 4-6).

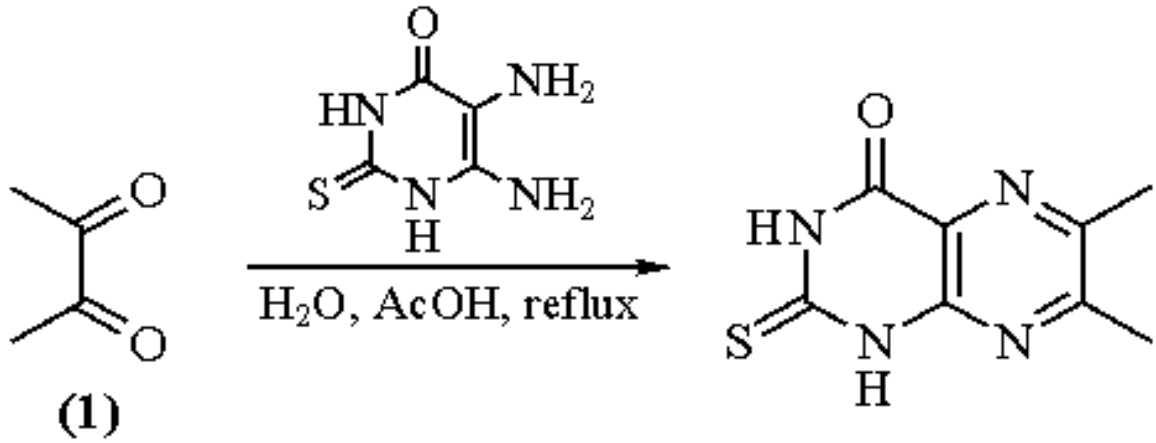

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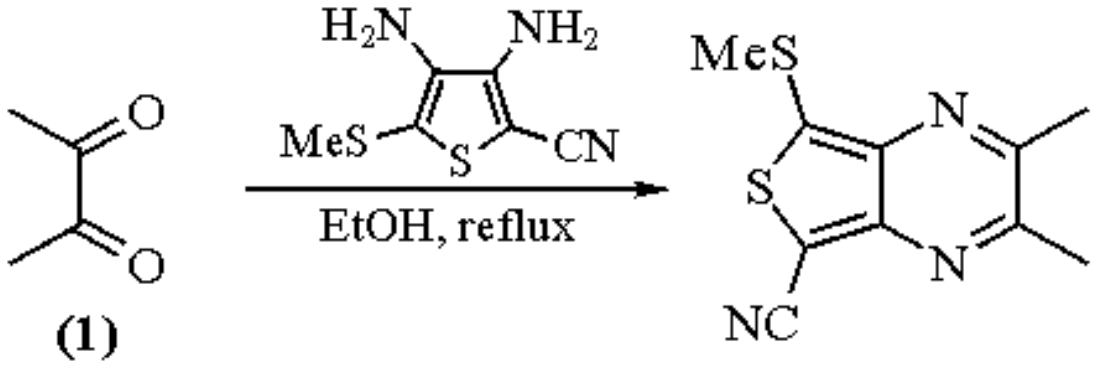

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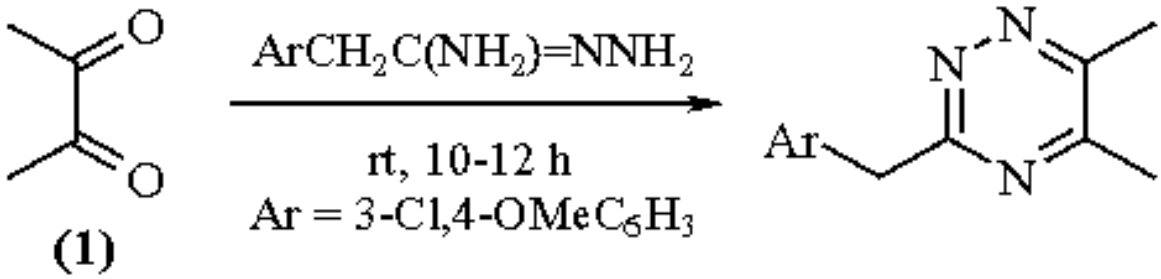

(6)

Condensation of (**1**) with an aldehyde (RCHO) in liquid ***Ammonia*** at 50-60 °C/20-25 atm furnishes the 4,5-dimethylimidazole (eq 7),[7] whereas condensation with ***Hydroxylamine*** or its HCl salt in EtOH forms the corresponding 4,5-dimethyl-1-hydroxyimidazole oxide (eq 8).[8]

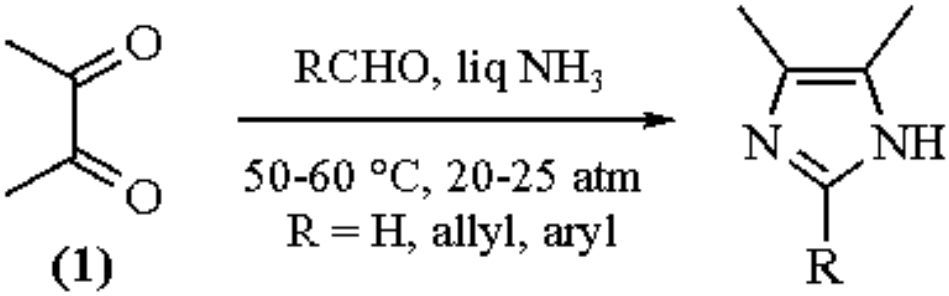

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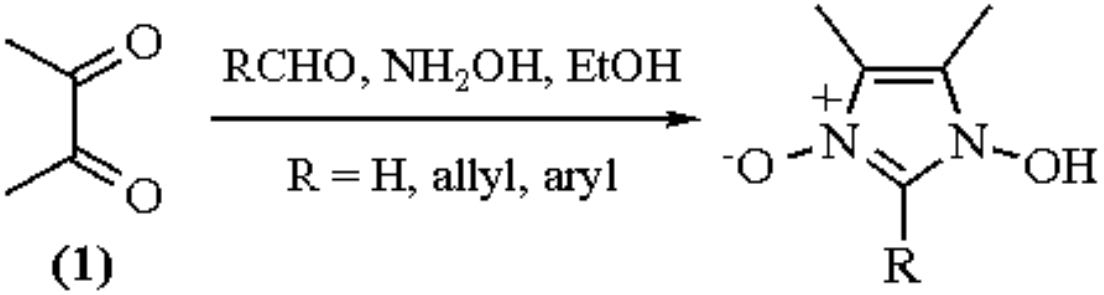

(8)

Biacetyl (**1**) with dihydrazino thiophosphites in a 1:1 ratio forms thiophosphatetraazacycloheptadienes (eq 9),[9] whereas stirring with tris(trimethylsilyl) phosphite in benzene at rt furnishes the 3-trimethylsiloxy-2-butene-2-[bis(trimethylsilyl)] phosphate (eq 10).[10]

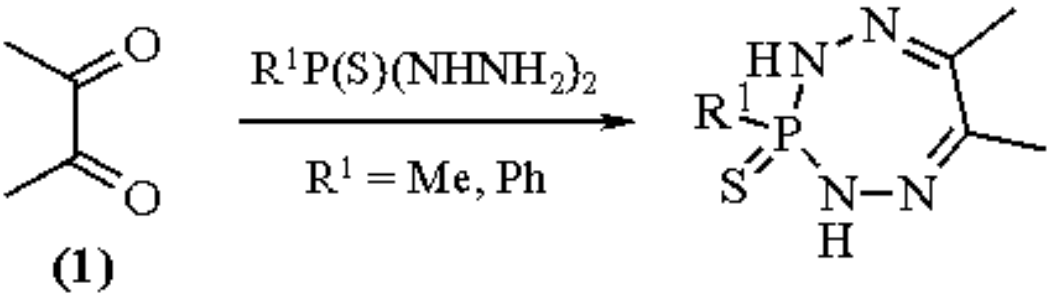

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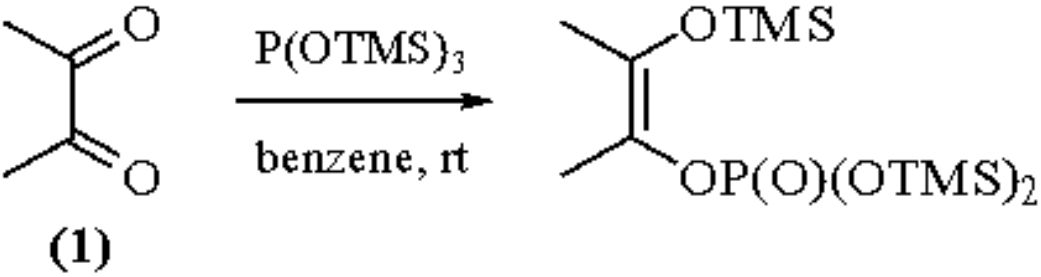

(10)

Reaction with Wittig Reagents.

2,3-Butanedione (**1**) undergoes the Wittig reaction with propylenetriphenylphosphorane to furnish a mixture of *cis*- and *trans*-3-methyl-3-hexen-2-ones in a 45:55 ratio (eq 11),[11] whereas stirring (**1**) with excess ***Cyanomethylenetriphenylphosphorane*** provides the bis Wittig adduct (*E*,*E*)-3,4-dimethylmuconononitrile (eq 12).[12]

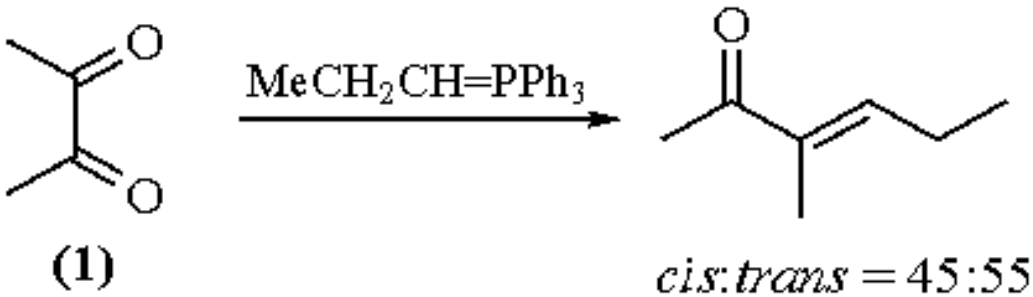

(11)

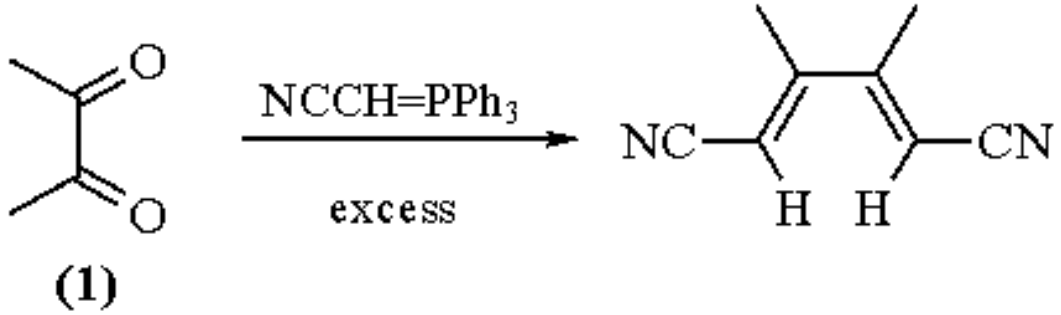

(12)

Reaction of (**1**) with ***Diazomethane*** in ether containing excess methanol or 1 mol of ***Boron Trifluoride*** provides 2-methyl-1-epoxybutan-3-one (eq 13),[13] and with ***Diphenyldiazomethane*** furnishes 2-methyl-1,1-diphenyl-1,2-epoxybutan-3-one (eq 14).[14]

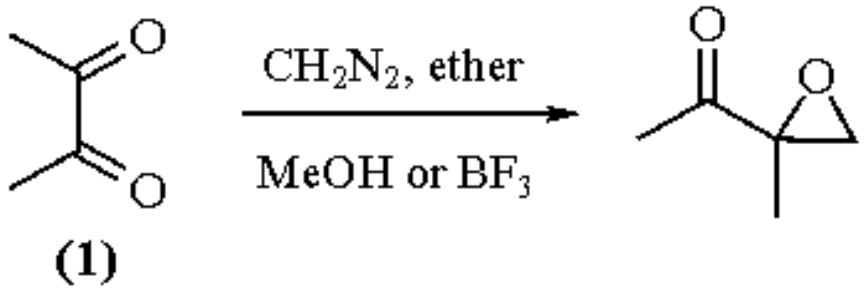

(13)

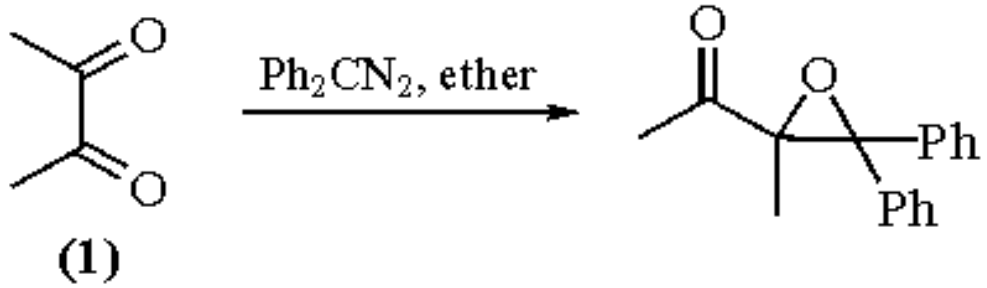

(14)

Reaction of (**1**) with *p*-cresol furnishes the benzofuro[3,2-*b*]benzofuran (eq 15).[15]

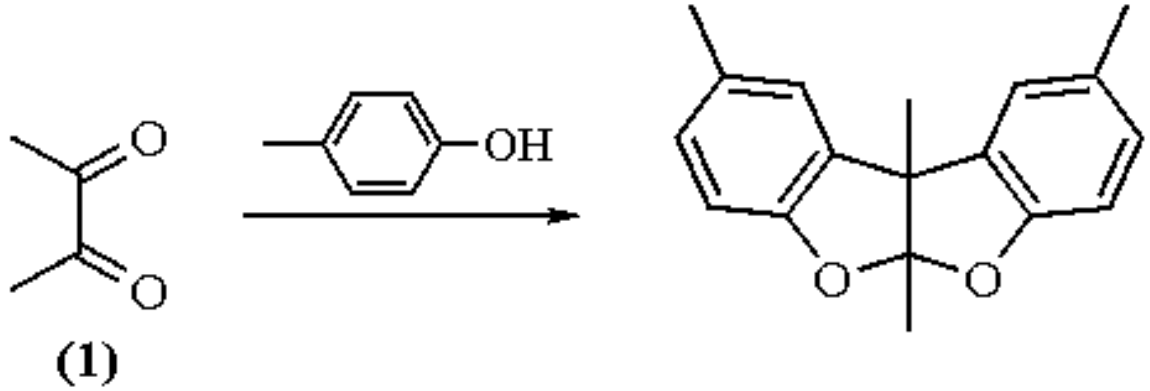

(15)

Condensation with Dimethyl 1,3-Acetonedicarboxylate.

The dione (**1**) undergoes the Weiss-Cook process with ***Dimethyl 1,3-Acetonedicarboxylate*** to form tetramethyl 1,5-dimethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (eq 16) in excellent yield.[16]

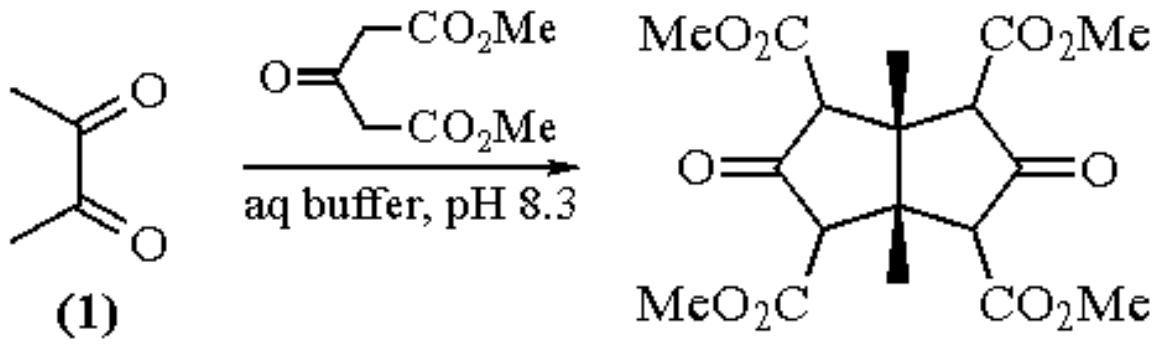

(16)

Acid-catalyzed reaction of (**1**) with *cis*-1,2-cyclohexanediol forms normal mono- and diacetals, whereas stirring with *trans*-cyclohexanediol provides a different bisacetal, represented in eq 17.[17]

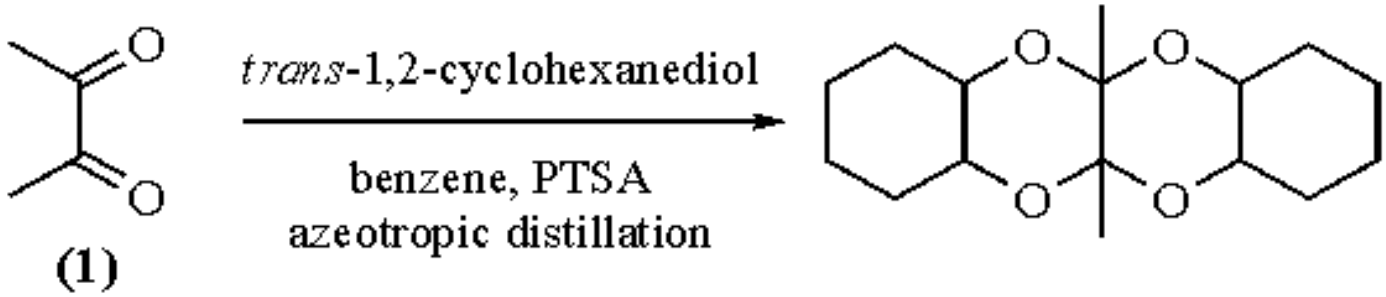

(17)

Reaction of (**1**) with 2 equiv of allylzinc, prepared from ***Allyl Bromide***, followed by acidic hydrolysis gives the γ-ethylenic α-hydroxy ketone (eq 18).[18]

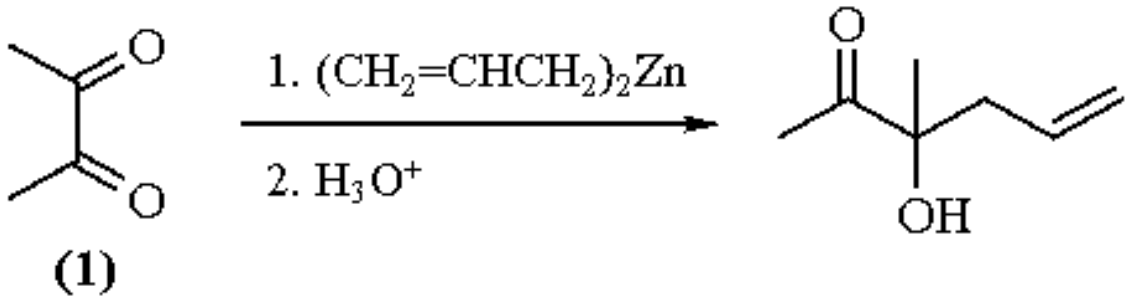

(18)

Thermal-mediated reaction of (**1**) with 1,1-diethoxyethene gives 2,2-diethoxy-4-acetyl-4-methyloxetane (eq 19);[19] furthermore, (**1**) reacts with acetoxyphenylketene (generated in situ by reacting 2-acetoxyphenacyl chloride with ***Triethylamine*** in the cold) to give the β-lactone, which rearranges to a tricyclic orthoester lactone at temperatures above 130 °C (eq 20).[20]

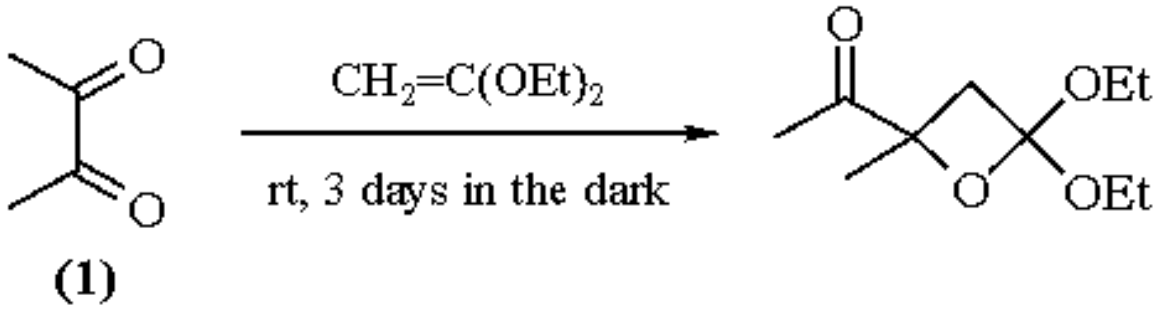

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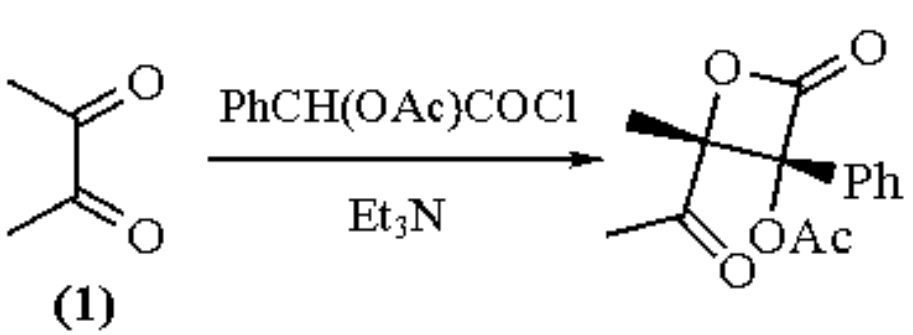

(20)

Biacetyl (**1**) condenses with malonic acid in the presence of ***Titanium(IV) Chloride*** in pyridine-THF to furnish the α-carboxy-β,γ-dimethyl-γ-hydroxy-$\Delta^{\alpha,\beta}$-butenolide (eq 21),[21] a very useful precursor for the synthesis of eudesmane and certain elemane sesquiterpenes.

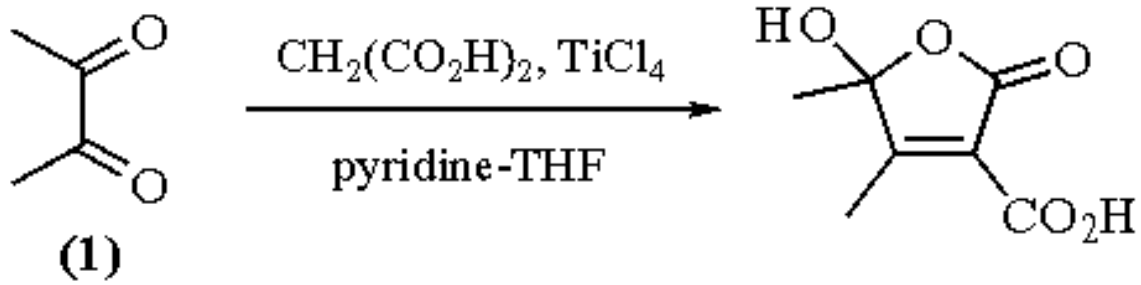

(21)

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University of Wisconsin-Milwaukee, WI, USA

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2-Butanone Ethylene Acetal

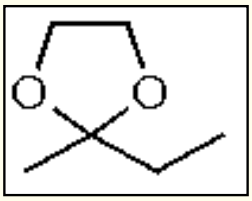

[126-39-6] · $C_6H_{12}O_2$ · 2-Butanone Ethylene Acetal · (MW 116.16)

(reagent for production of cyclic acetals by acid-catalyzed transacetalization[1])

Alternate Names: 2-methyl-2-ethyldioxolane; MED.

Physical Data: bp 116-117 °C; *d* 0.929 g cm^{-3}.

Solubility: miscible with organic solvents.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: the reagent is a flammable liquid; it is an irritant.

Transacetalizations.

The reagent (MED) has been employed for the syntheses of cyclic acetals from ketones as an alternative to ethylene glycol.[1] In the initial report of the reagent, superior selectivity in acetal formation over that observed with ***Ethylene Glycol*** was noted.[1] MED also has been reported to be superior to the analogous transacetalization reagent prepared from acetone (2,2-dimethyl-1,3-dioxolane).[1] The transacetalization reactions appear to be more subject to steric effects than to electronic effects.

Several general methods initially reported[1] have been used extensively. In a typical application, MED is employed in large excess, often as the solvent, although cosolvents such as benzene and CH_2Cl_2 have been employed. In some cases, acetalization reactions have been conducted with excess MED and a small amount of ethylene glycol. In cases where monoacetalization of a di- or polyketone is desired, a stoichiometric amount of MED may be employed, but monoacetalizations of diketones are usually conducted with excess MED. Reactions are generally run at reflux for several hours with ***p-Toluenesulfonic Acid*** (TsOH) as the catalyst. Hindered ketones have been acetalized employing MED as solvent at reflux for several days,[1] but some transacetalization reactions have been conducted over extended periods at rt.

The selectivity of transacetalizations with MED has been studied. Simple saturated ketones are acetalized more readily

than α,β-unsaturated ketones.[1] Thus the Wieland-Mischer ketone reacts with MED to give the monoacetal shown in eq 1 in 95% yield with 2% of the diacetal;[2] when the reaction was conducted with ethylene glycol, the monoacetal was produced in 78% yield, the diacetal was formed in 10% yield, and 12% of unreacted diketone remained. The enhanced reactivity of MED with simple ketones over that observed with α,β-unsaturated ketones can be used in a chemical separation scheme; for example, reaction of a 1:1 mixture of the saturated and unsaturated ketones shown in eq 2 with 0.5 equiv of MED in benzene at reflux with TsOH catalysis resulted in the acetal of the saturated ketone and unreacted unsaturated ketone as the only products observed.[3]

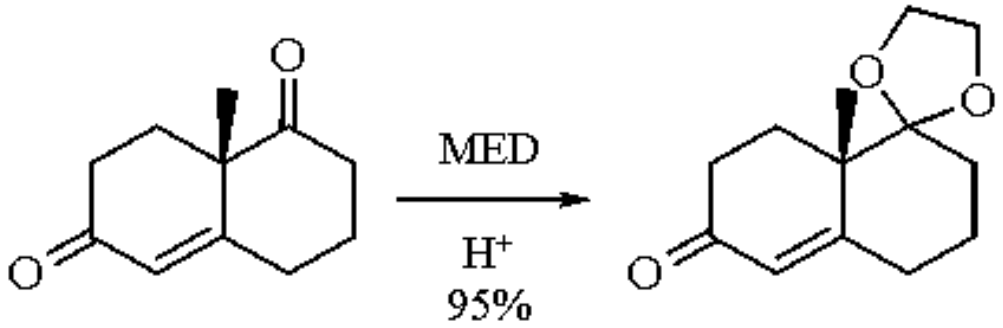

(1)

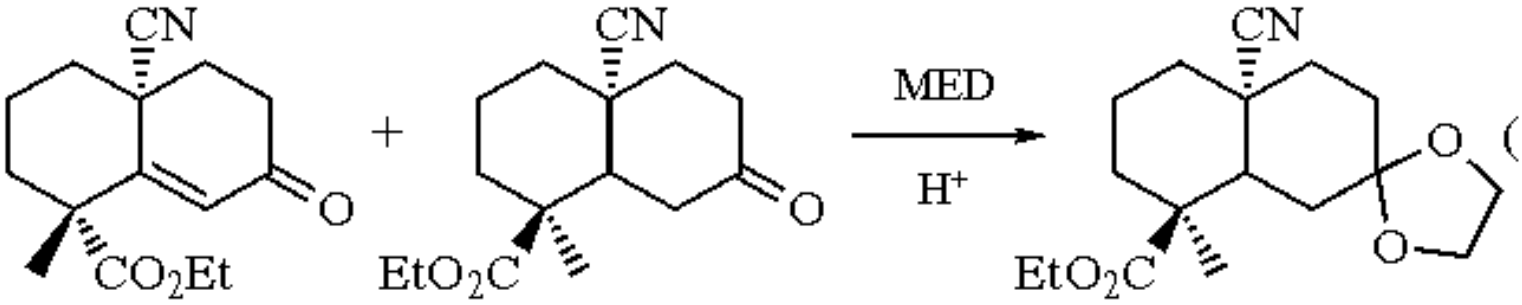

(2)

Steric and ring strain effects can overwhelm electronic effects in transacetalizations with MED. Thus a mixture of monoacetals was produced from the diketone shown in eq 3,[4] and transacetalization of Δ^4-androstene-3,17-dione with MED gave the monoacetal shown in eq 4.[1] The double bond migrations shown in these reactions are common for transacetalizations of α,β-unsaturated ketones with MED as they also are in ethylene glycol acetalizations. The product composition reflects the stability of the double bonds; for example, an equilibrium mixture of acetals was obtained from 2-cyclohexenone (eq 5).[5] An advantage of MED transacetalization of α,β-unsaturated ketones over direct ethylene glycol acetalization is seen in the 2-cyclohexenone reaction; when the acetalization was conducted with ethylene glycol, the mixture of unsaturated acetals was obtained with the ether product as a minor impurity.[5]

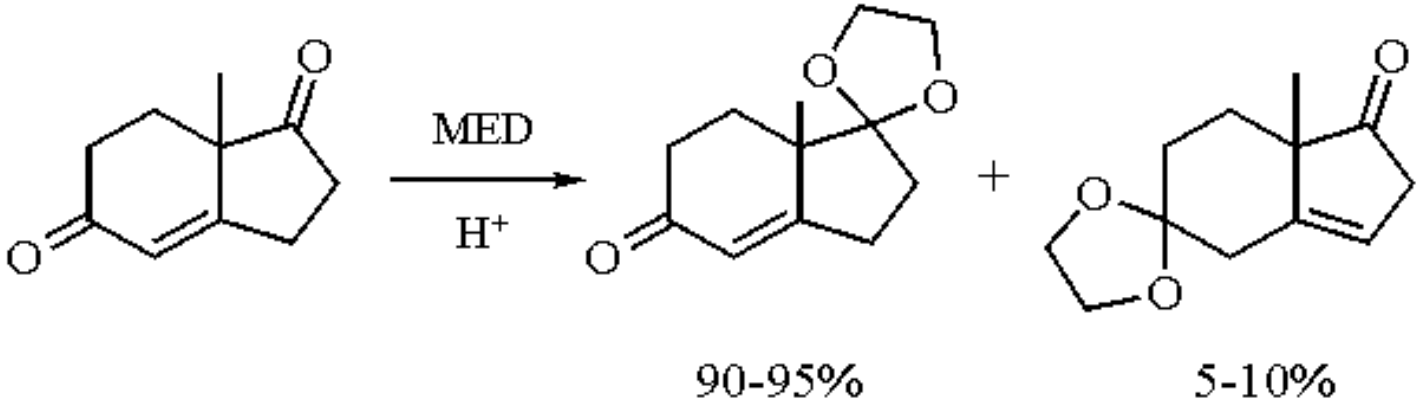

(3)

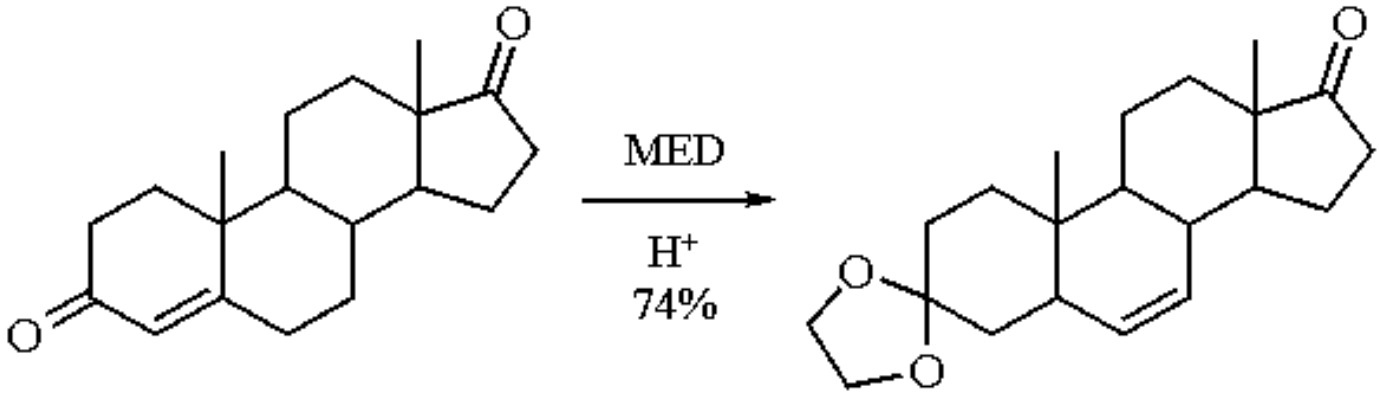

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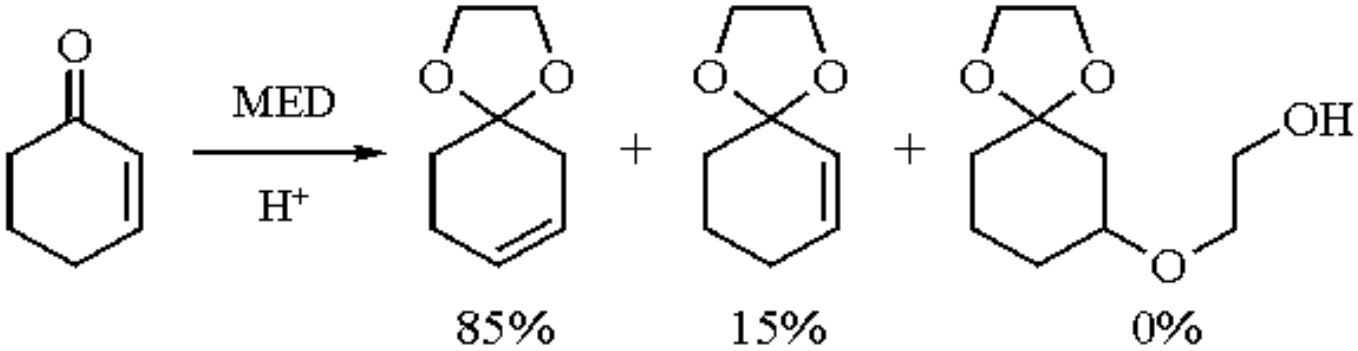

(5)

Monoacetalization of a 1,3-dione proceeds in good yields, as shown in eq 6.[6] In this reaction an eightfold excess of MED was used in CH_2Cl_2 solvent with ***10-Camphorsulfonic Acid*** as the catalyst.

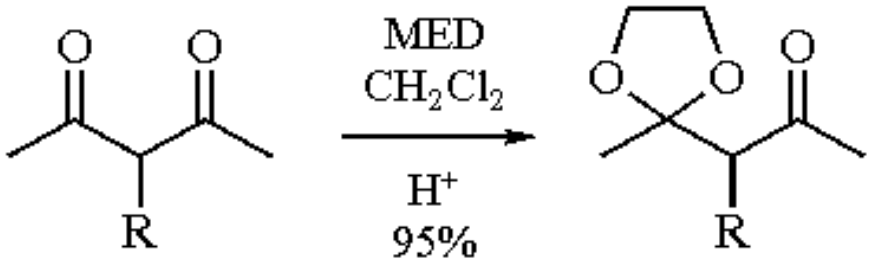

(6)

The transacetalization reactions with MED appear to provide kinetic products as demonstrated in the transacetalization of Δ^4-androstene-3,16,17-trione (eq 7).[7] Reaction in the presence of excess MED with TsOH catalysis at reflux for 5 min gave monoacetal (**1**) in 66% yield. Slow distillation of the reaction mixture over 30 min gave (**1**),(**2**), and (**3**) in 7%, 30%, and 13% yields, respectively. Heating the reaction mixture at reflux for 5 h gave triacetal (**3**) in 43% yield.

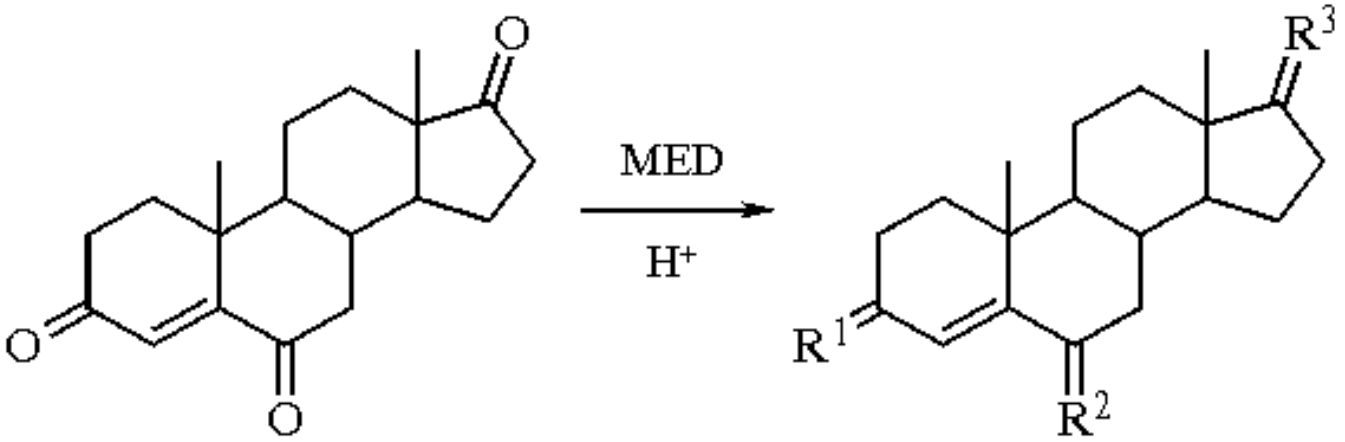

(7)

a) $R^1 = -OCH_2CH_2O-$, $R^2 = R^3 = O$
b) $R^1 = R^2 = -OCH_2CH_2O-$, $R^3 = O$
c) $R^1 = R^2 = R^3 = -OCH_2CH_2O-$

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α,β-Butenolide[1]

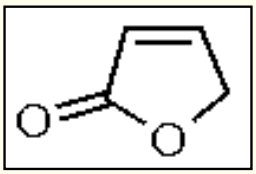

[497-23-4] · $C_4H_4O_2$ · α,β-Butenolide · (MW 84.07)

(can be transformed into derivatives of 2-furanol including esters[2] and silyl ethers;[3] provides 3-(1´-hydroxyalkyl)-2(5*H*)-furanones by regioselective aldolization;[4] undergoes highly regio- and stereoselective reactions with sulfinylallyl anions;[5] serves as keystone for the convergent assembly of lignans[6] and prostaglandin analogs[7] through tandem vicinal difunctionalization[8])

Alternate Names: γ-crotonolactone; 2(5*H*)-furanone; but-2-en-4-olide.

Physical Data: bp 86-87 °C/12 mmHg; mp 5 °C; *d* 1.185 g cm^{-3}. A pK_a value of 18.8 has been determined for its equilibrium acidity in DMSO (pK_{HA}), but this may not be correct.[9]

Solubility: sol most organic solvents, e.g. CCl_4, CH_2Cl_2, Et_2O, toluene, THF, MeOH, and MeCN.

Form Supplied in: colorless or pale yellow liquid, commercially available; expensive.

Preparative Methods: obtainable by oxidation of furfural[10] or by dehydrobromination of α-bromo-γ-butyrolactone[10a,11] at very low cost.

Handling, Storage, and Precautions: avoid contact with skin or eyes; do not inhale or ingest; vapor is irritating to the eyes and upper respiratory track. It should be stored at 4 °C or below. Use in a fume hood.

Tautomerism.

In the free state, isomerization of α,β-butenolide (**1**) to β,γ-butenolide (**2**) or 2-furanol (**3**) does not occur to any detectable amount (eq 1). According to MO calculations the order of decreasing stability is (**1**) > (**2**) > (**3**).[12] In practice, (**3**) may not even exist. On the other hand, (**2**) is easily prepared in multigram quantities although it isomerizes to (**1**) at a rate of 3% per month on standing at rt.[10a]

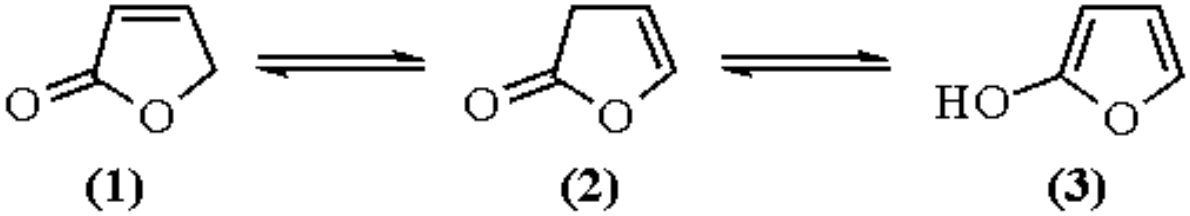

(1)

Derivatives of 2-Furanol.

Acid chlorides lacking α-hydrogens and alkyl chloroformates are converted into esters and carbonates by using ***Triethylamine*** as a base (eq 2).[2] Similarly, noncarbon electrophiles such as ***Phosphorus Oxychloride***[10b] and silylating agents[3] readily afford the corresponding furanol derivatives. 2-Trialkylsilyloxyfurans thus obtained (eq 3)[13] can be subsequently transformed into a variety of 5-substituted 2(5*H*)-furanones (see ***2-Trimethylsilyloxyfuran***).

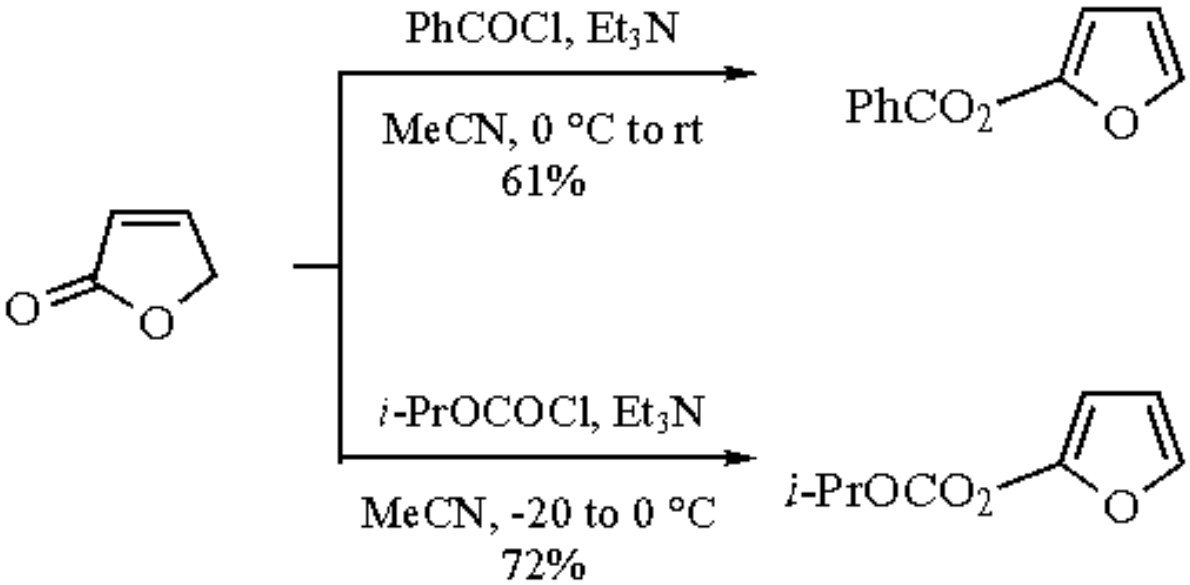

(2)

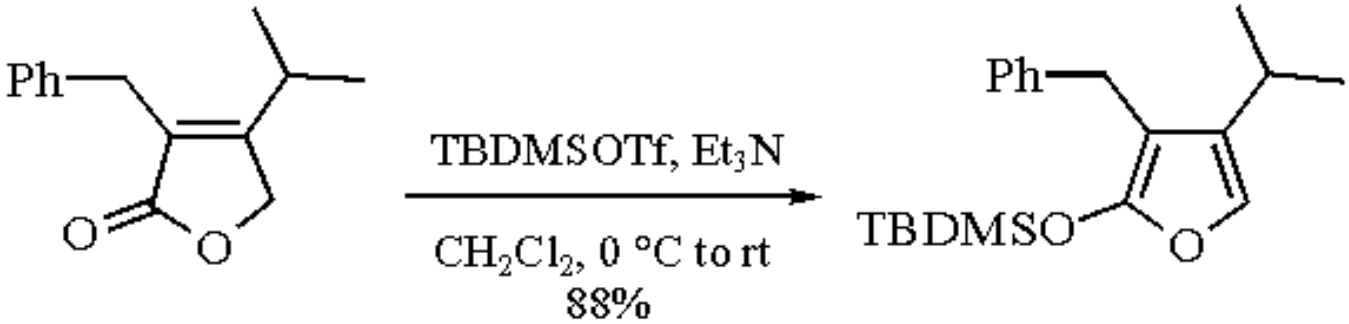

(3)

Reactions of 2-Furanolates with Carbon Electrophiles.

The alkylation of α,β-butenolide by conversion to lithium 2-furanolate (***Lithium Diisopropylamide***/THF, -78 °C) and subsequent in situ reaction with prenyl bromide in the presence of HMPA, leads to a mixture of mono- and bis-α-alkylated lactones in low yield.[14] Under similar conditions, aldol condensation with aldehydes is only modestly regioselective, giving α- and γ-adducts in a 3:1 ratio.[15] In contrast, high regioselectivity and yields of 3-(1´-

hydroxyalkyl)-2(5*H*)-furanones are obtained with dialkylboron 2-furanolates (eq 4).[4] The α regioselectivity is explained by the intervention of a boron-containing six-membered chelate. This method has served as key step in the synthesis of the marine antimicrobial bromobeckerelide.[16]

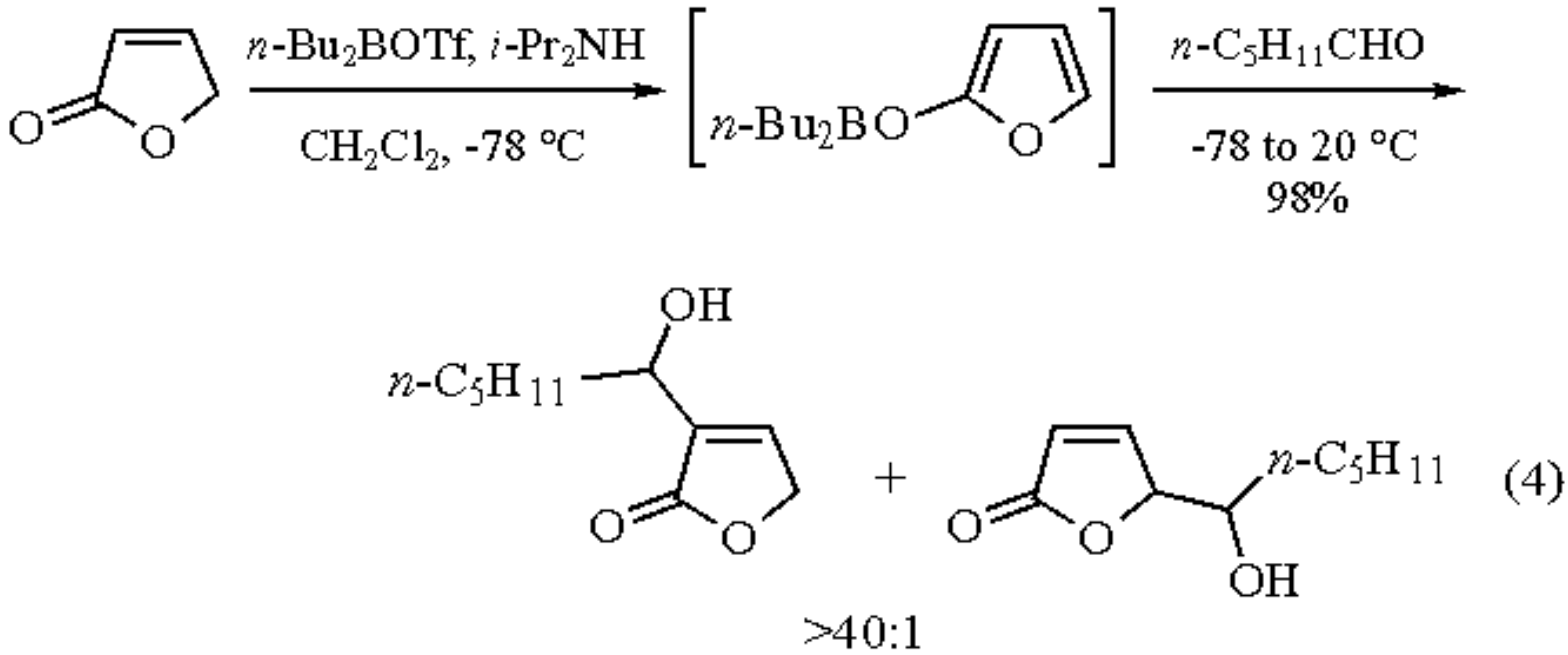

(4)

In certain cases γ regioselectivity is also attainable. Thus base-induced condensation of α,β-butenolide with 5-aryl-2-furaldehydes affords 4-ylidenebutenolides (eq 5).[17] Likewise, alkali metal 2-furanolates undergo γ-selective conjugate addition to enones (eq 6).[18]

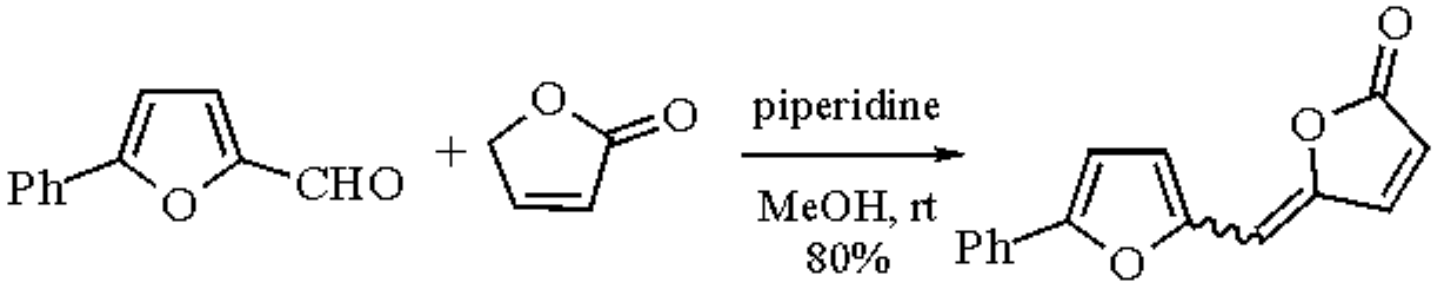

(5)

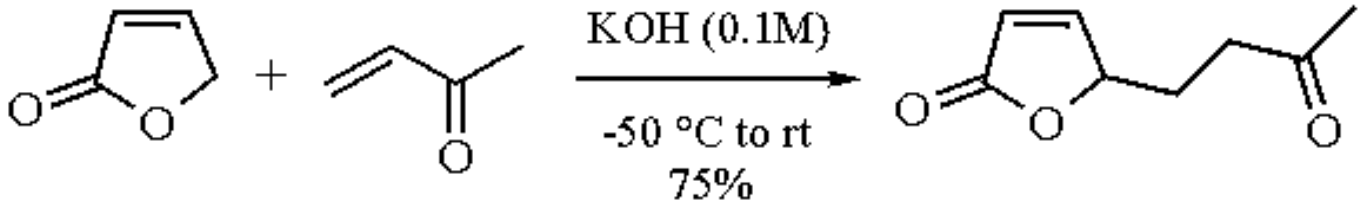

(6)

Bromination.

5-Bromo-2(5*H*)-furanones can be conveniently prepared from the corresponding α,β-butenolides by radical bromination (eq 7).[19] They are useful for the synthesis of alfatoxins[20] and other bioactive substances.[21] For an alternative viable method for preparing 5-bromo-2(5*H*)-furanones, see ***2-Trimethylsilyloxyfuran***.

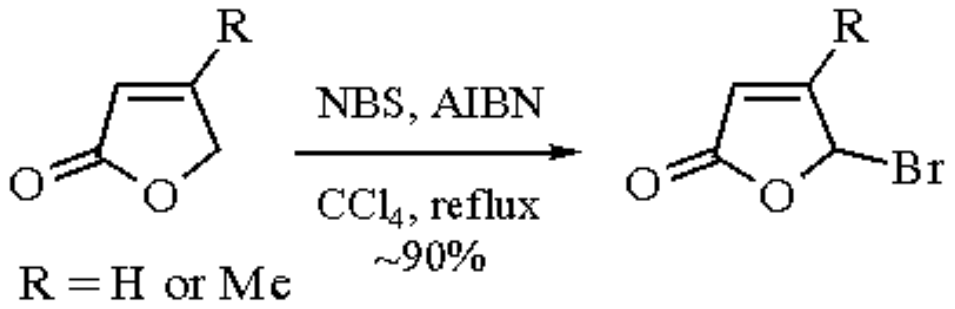

(7)

Michael Acceptor.

A variety of carbon and noncarbon nucleophiles undergo conjugate addition to α,β-butenolides.[22] These include organocopper reagents,[23] stabilized carbanions,[24] amines,[25] and thiols[22,26] among others.[27] Ambident allylic anions derived from γ-substituted allyl sulfoxides add to butenolide in a highly regio- and diastereoselective manner (eq 8).[5a] The relative configuration at the allylic carbon in the product is determined by the geometry of the starting sulfoxide. A *trans*-decalyl-like transition state accounts for both the regio- and stereochemical features of this process.[5a] This chemistry has been applied to the synthesis of enantiomerically enriched β-alkyl-γ-butyrolactones (eq 9).[5b]

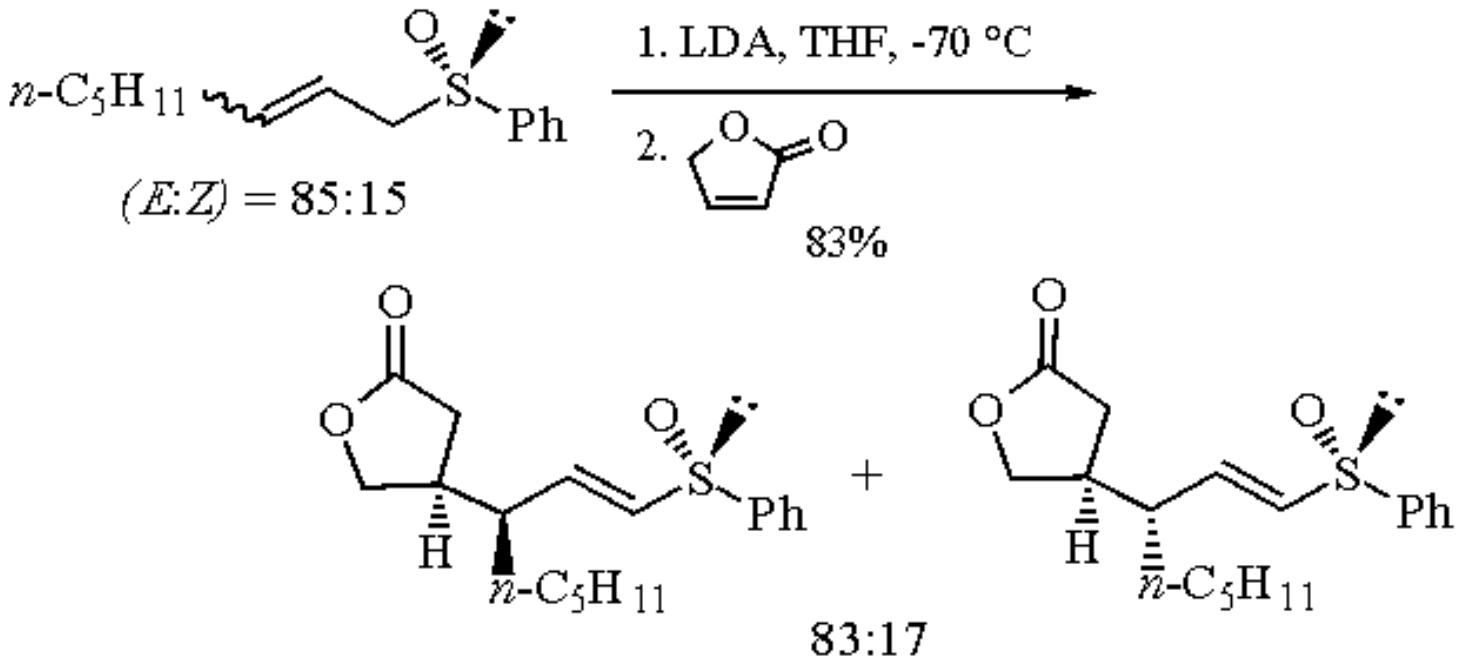

(8)

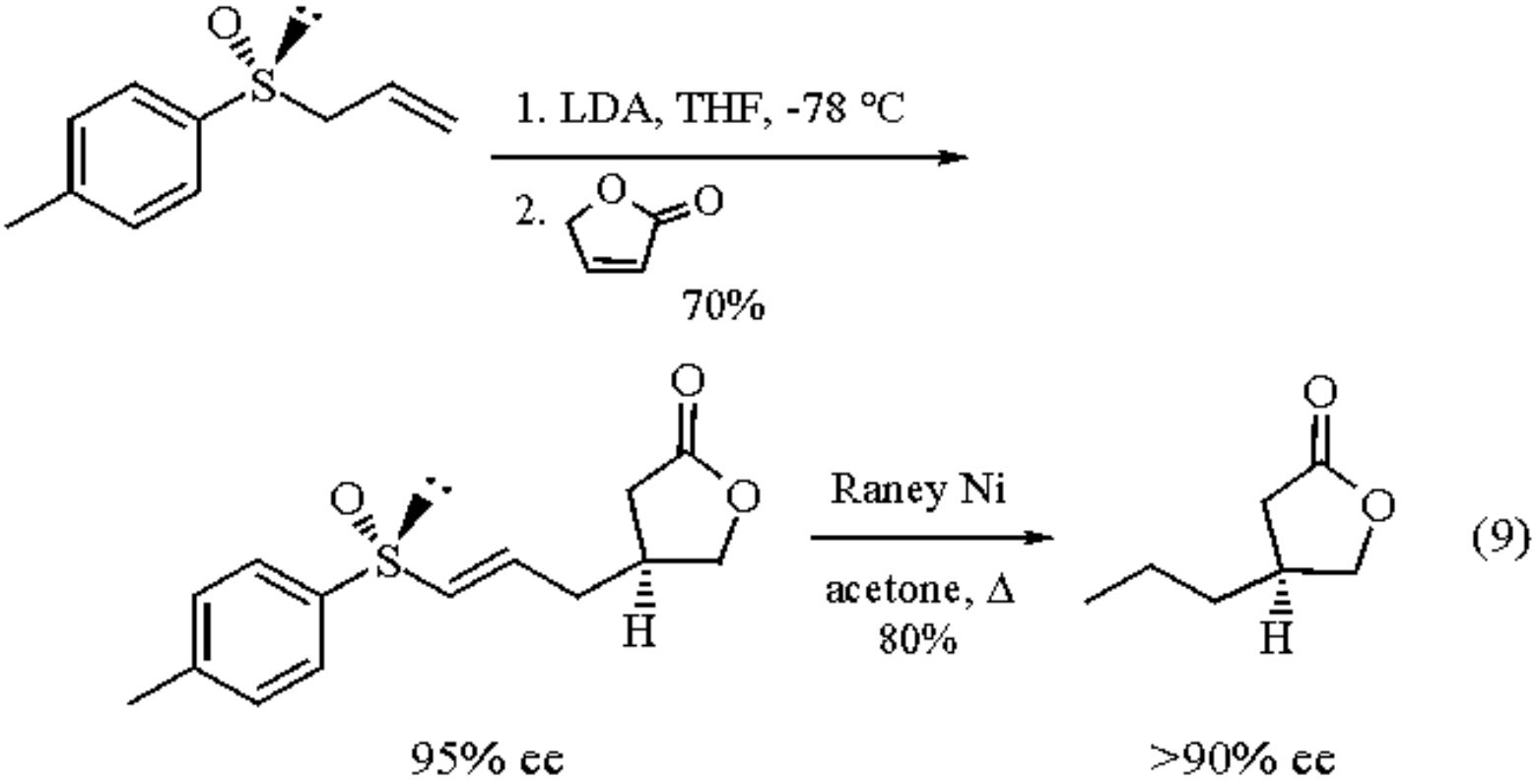

(9)

Tandem Vicinal Difunctionalization.

An initial conjugate addition of a nucleophile, and subsequent capture of the resulting enolate with a suitable electrophile, enables rapid introduction of two vicinal substituents.[6,8] The intermolecular process leads invariably to *trans*-α,β-disubstituted lactones (eqs 10 and 11).[6a,28] Moreover, when aldehydes are used as electrophiles, aldolization can be effected in a highly *syn* stereoselective fashion by using ***Zinc Bromide*** as additive (eq 11).[28] The intramolecular version of this process, known as type II Michael-initiated ring closure (MIRC), provides *cis*-fused lactones (eq 12).[29]

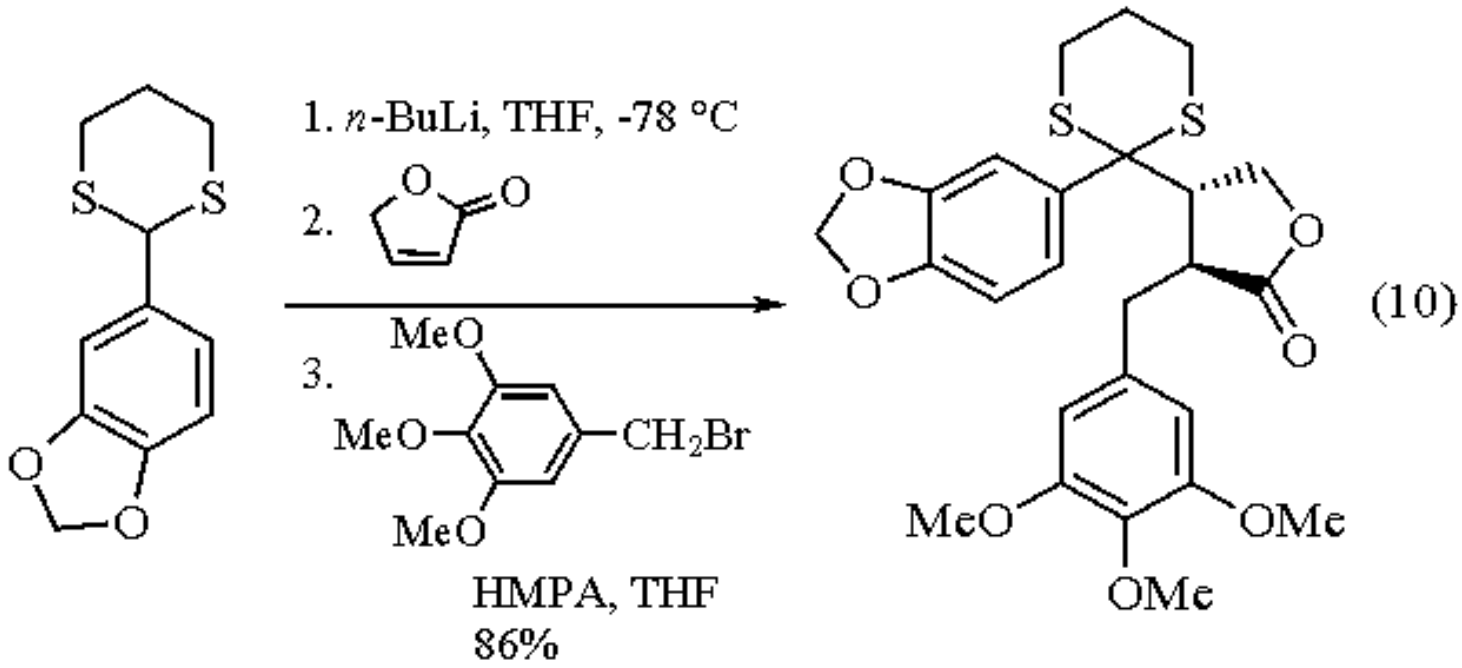

(10)

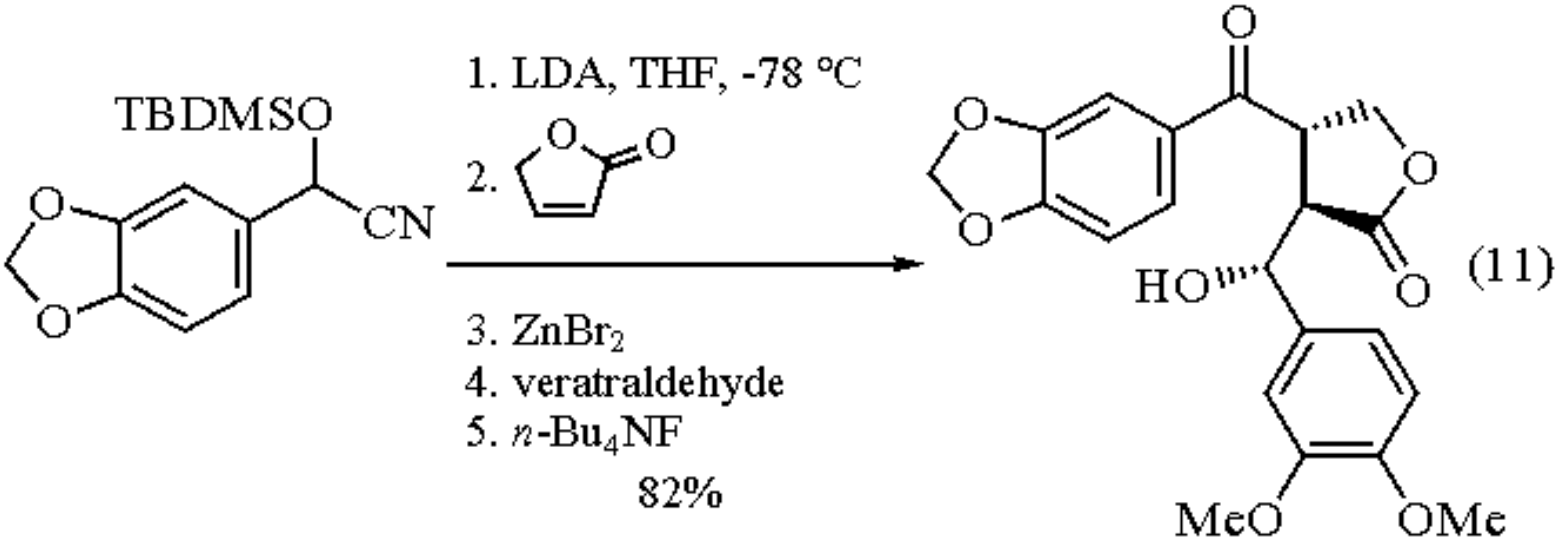

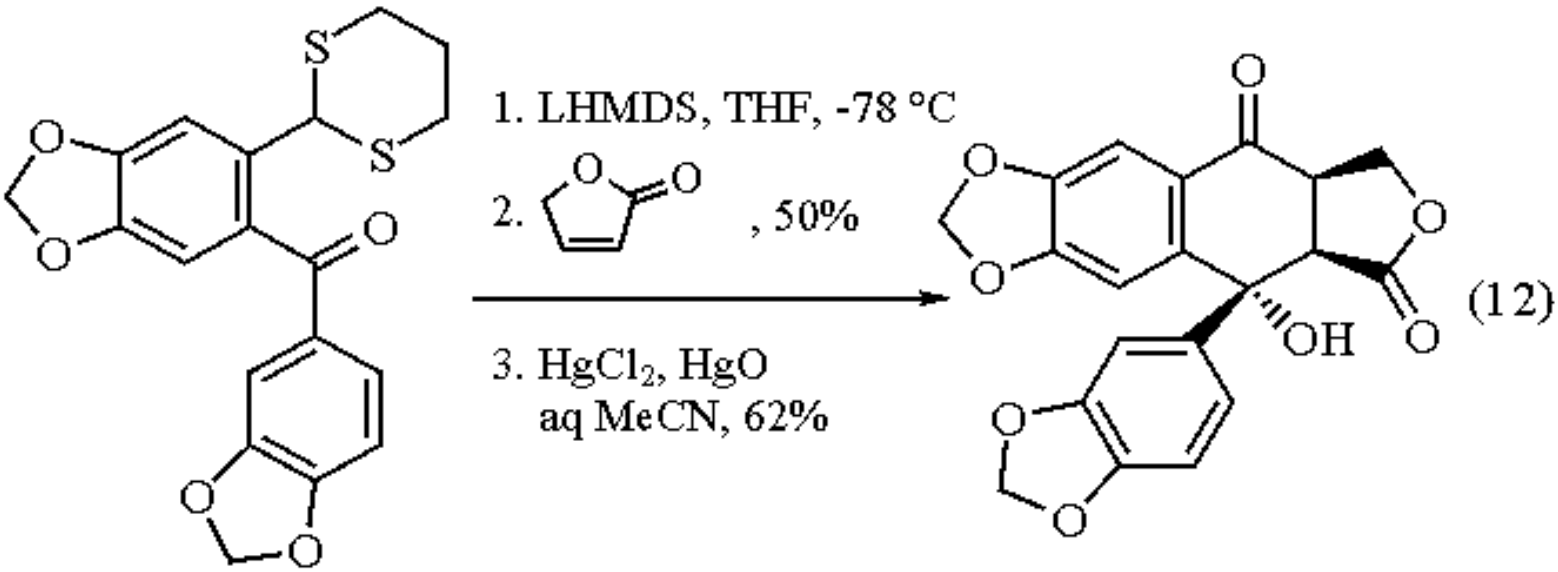

Not surprisingly, this methodology has been widely exploited for convergent access to various types of lignans[6,28-30] and prostaglandin analogs.[7] Applications to the synthesis of enantiomerically pure lignans have also been reported.[22,31]

Cycloaddition Reactions.

Although α,β-butenolide and its substituted analogs undergo various concerted reactions, such as Diels-Alder[32] and [2 + 2] cycloadditions,[33] relatively few synthetic applications are known.[34] A noteworthy example is the 1,3-dipolar addition to diazomethane.[23a,b] This process leads to pyrazolinolactones which on thermolysis afford the corresponding 4-methyl-2(5*H*)-furanones in good yields (eq 13).[23b,35] Thus replacement of the β hydrogen by a methyl group can be achieved in just two steps. Other substituents can be installed in this manner by selecting the appropriate diazoalkane, diazo ester or diazo ketone.[13,35]

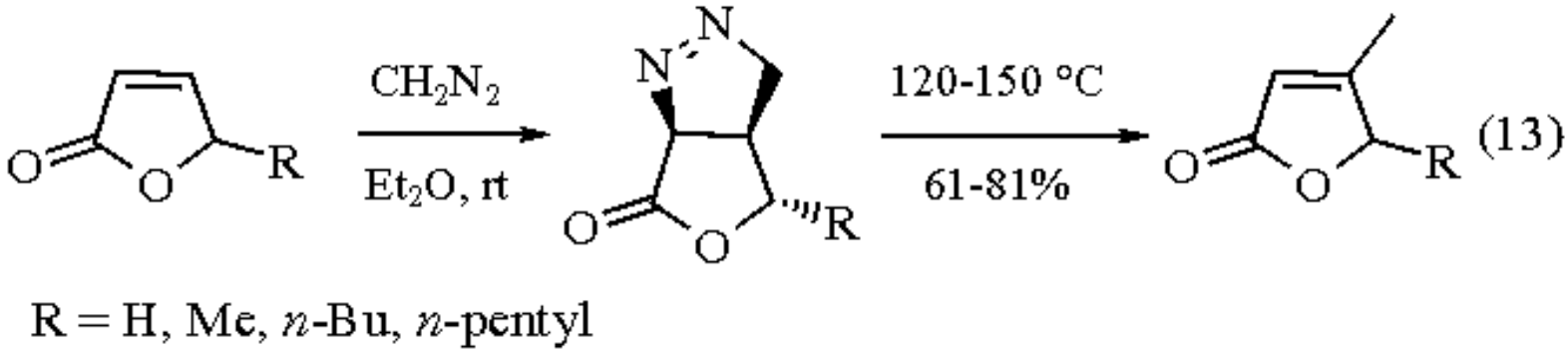

Related Reagents.

γ-Butyrolactone; ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***; ***(R)-Pantolactone***; ***β-Propiolactone***; ***2-Trimethylsilyloxyfuran***; ***β-Vinyl-α,β-butenolide***.

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3-Butenyl-1-magnesium Bromide

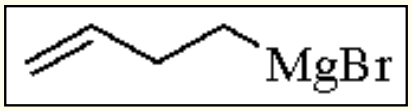

[7103-09-5] · C_4H_7BrMg · 3-Butenyl-1-magnesium Bromide · (MW 159.31)

(nucleophilic Grignard reagent used as a synthetic equivalent of the 3-butenyl anion)

Solubility: normally prepared in THF and used in situ.

Handling, Storage, and Precautions: Grignard reagent sensitive to moisture. Normally prepared and used immediately.

Nucleophilic Additions.

This reagent, like the analogous organolithium reagent, is employed in synthetic chemistry as a synthetic equivalent of the 3-butenyl anion and also as a synthon for the 3-oxopropyl anion. The reagent is normally used in ether solvents, typically diethyl ether or THF, and is readily prepared under standard conditions for Grignard reagent formation by dropwise addition to ***Magnesium*** turnings, with external cooling following reaction initiation. Four principal types of addition reaction are seen: addition to carbonyl groups and their various derivatives, conjugate addition to α,β-unsaturated ketones, displacements of halides and other leaving groups from alkyl or even aryl substrates, and addition to epoxides with ring cleavage. Metal-metal exchange is also observed.

Addition to prochiral carbonyl groups of aldehydes and ketones is common, as in the representative examples shown in eqs 1-4,[1-4] and often takes place with high stereoselectivity. Interestingly, addition to ***γ-Butyrolactone*** takes place successfully to give the hemiacetal (eq 5).[5] In contrast, simple esters have been shown to undergo double addition leading to carbinols; this property has been utilized in a clever synthesis of functionalized dienes by use of α-silyl-β,γ-unsaturated esters as substrates; an in situ Peterson elimination then takes place upon alkoxide formation to give the conjugated dienes (eq 6).[6] *N,O*-Dimethylhydroxamates have been used to limit nucleophilic addition to 1 equiv of reagent, giving the ketonic product.[7]

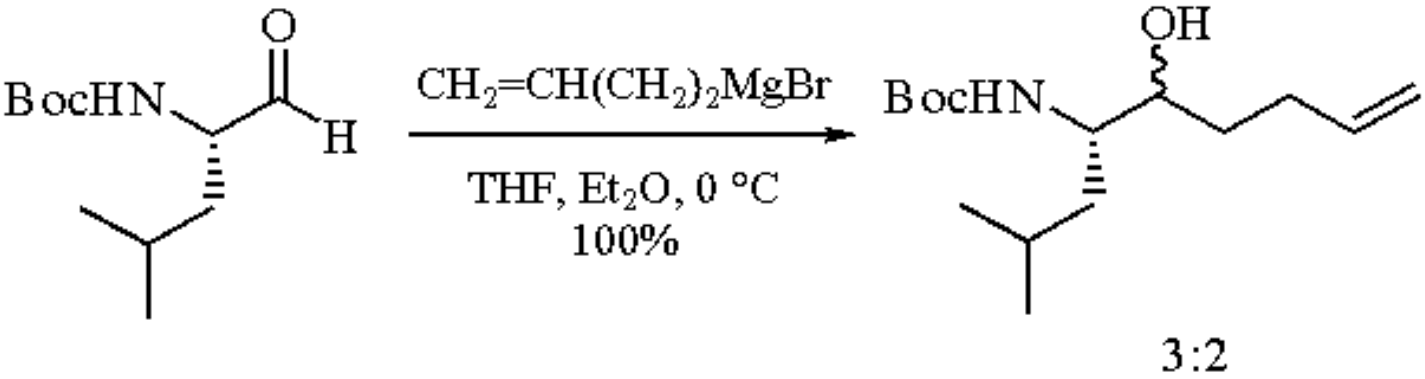
BocHN
O
H
CH2=CH(CH2)2MgBr
THF, Et2O, 0 °C
100%
OH
BocHN
3:2

(1)

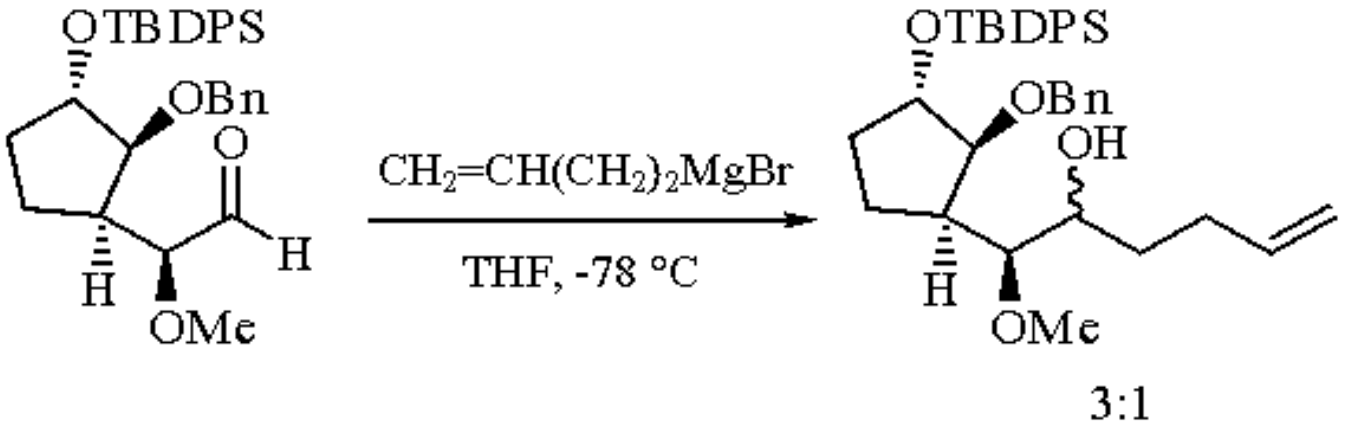
OTBDPS
OBn
O
H
H
OMe
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THF, -78 °C
OTBDPS
OBn
OH
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OMe
3:1

(2)

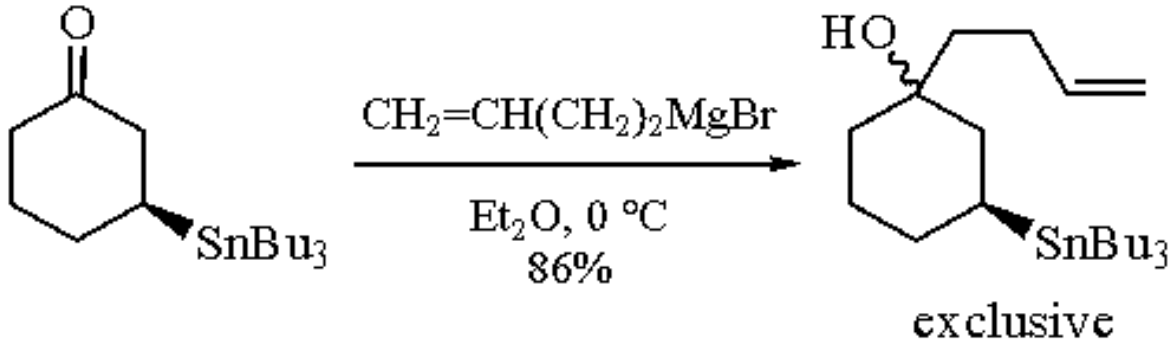
O
SnBu3
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Et2O, 0 °C
86%
HO
SnBu3
exclusive

(3)

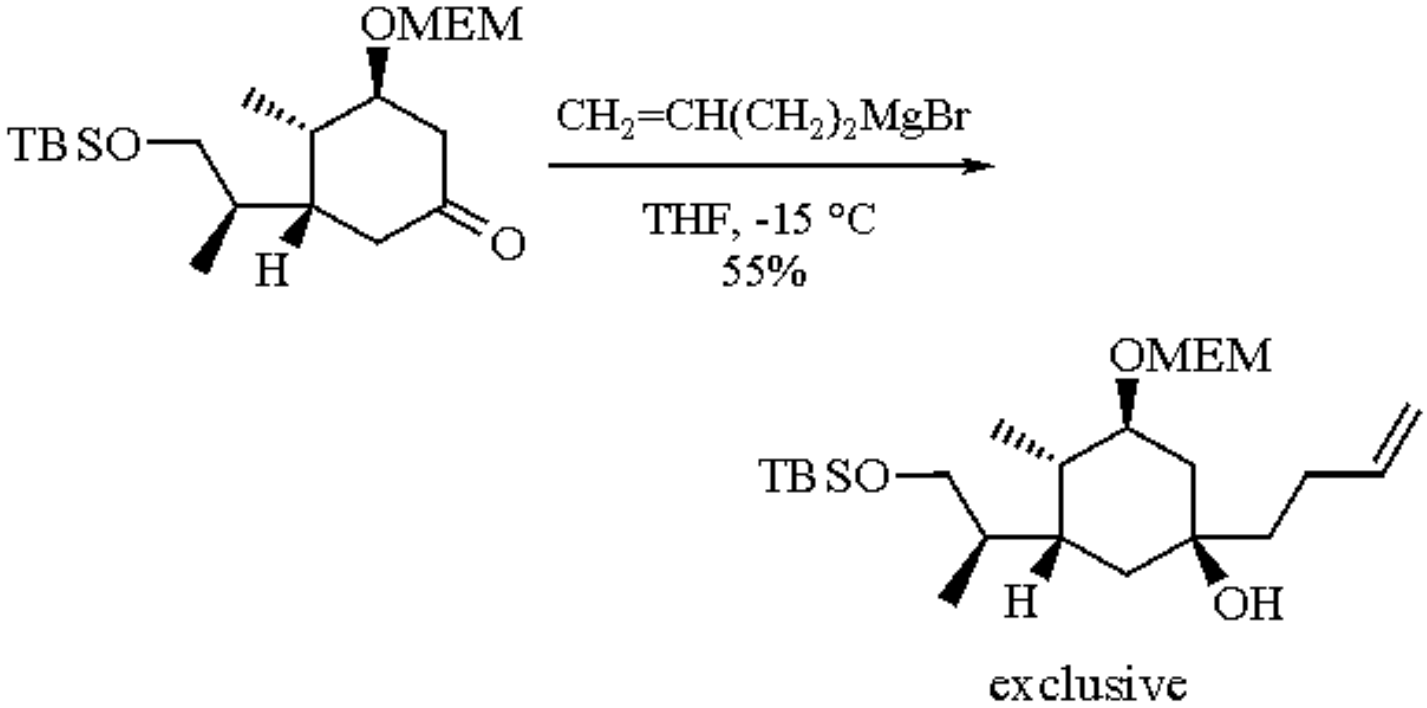

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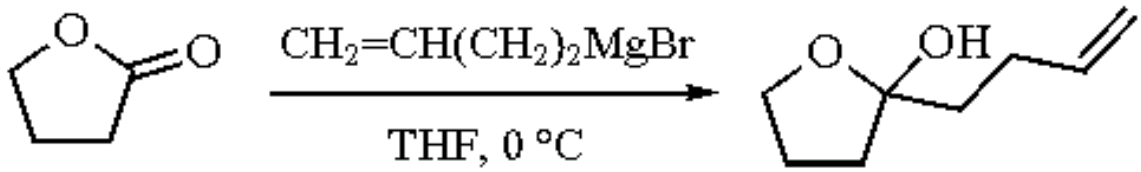

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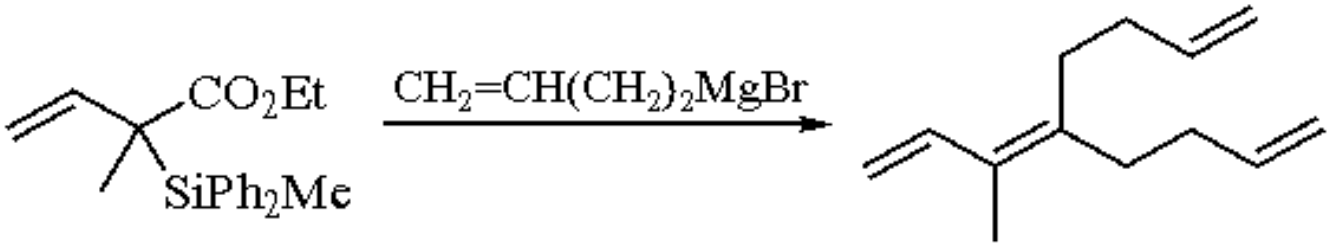

(6)

Imines are also successful substrates for the copper-catalyzed addition of 3-butenylmagnesium bromide in the presence of Lewis acids (eq 7). The δ,ε-unsaturated amine products may be cyclized by intramolecular aminoselenation to produce pyrrolidine derivatives.[8]

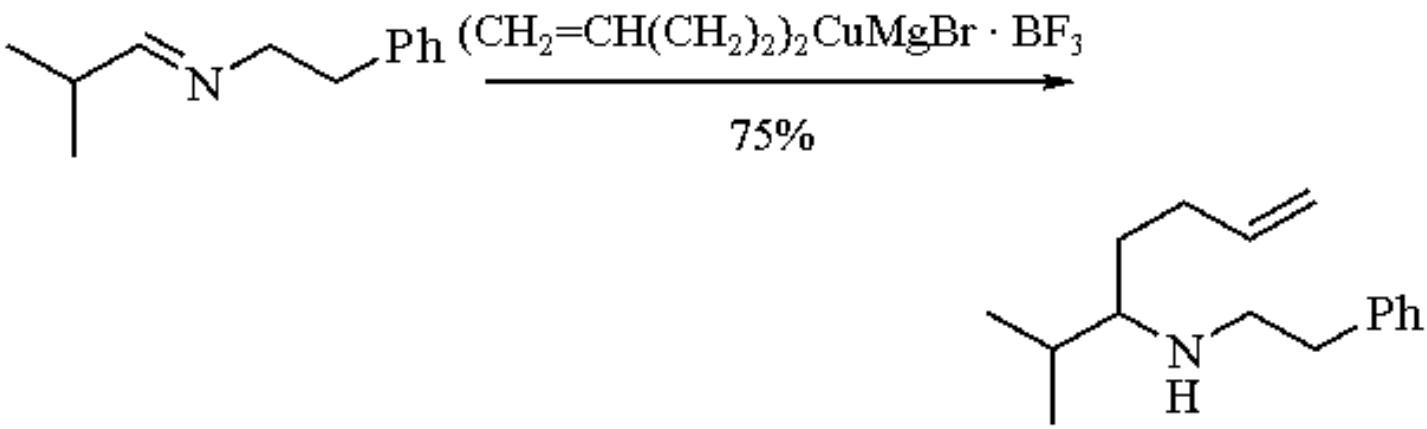

(7)

Copper-catalyzed conjugate addition is an equally general and successful procedure, and was employed by Ley in his synthesis of ajugarin I in a highly stereoselective reaction (eq 8).[9] In this case it was essential to add the enone, in ethereal solution, dropwise to a solution of the organometallic. Corresponding reactions with similar oxoacetals are much less stereoselective.[10] Other representative examples are given in eqs 9-11.[11-14]

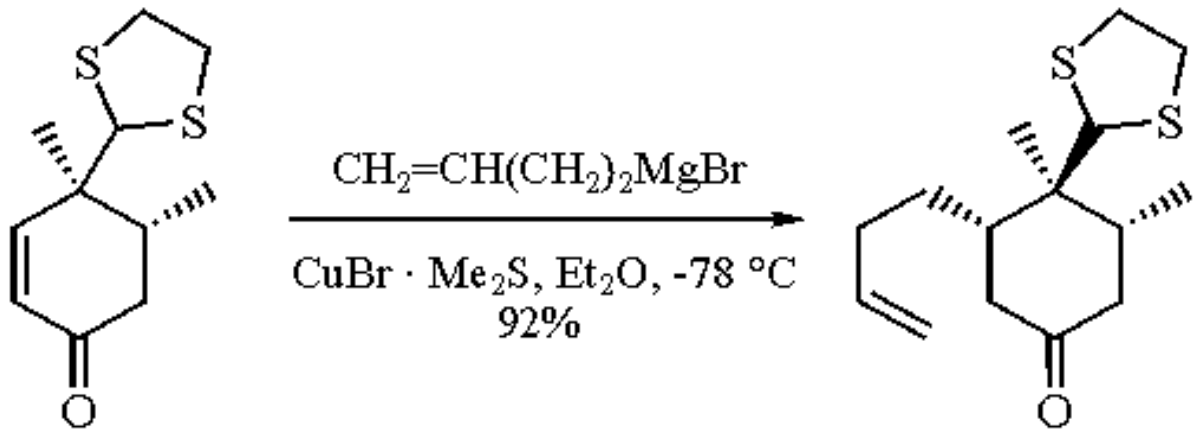

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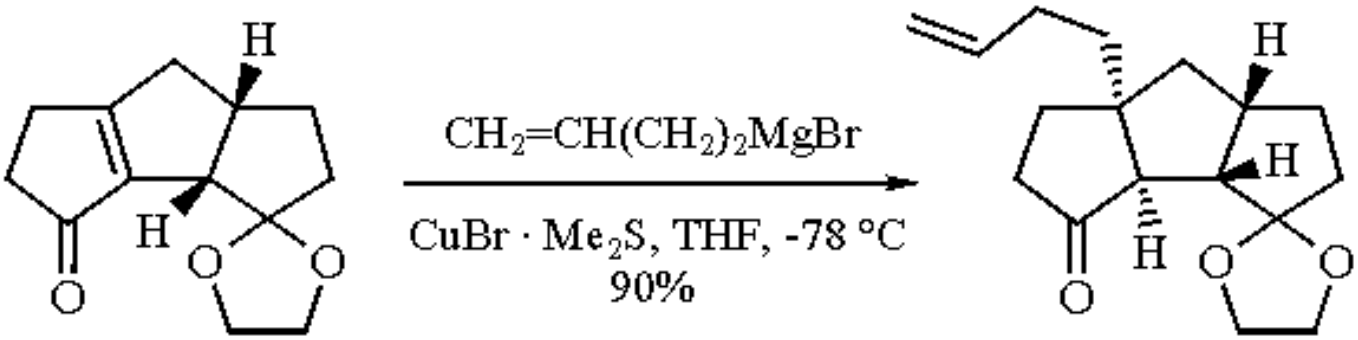

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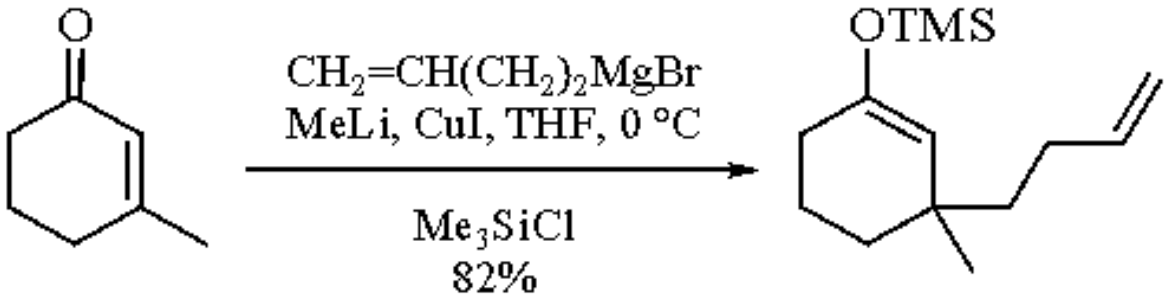

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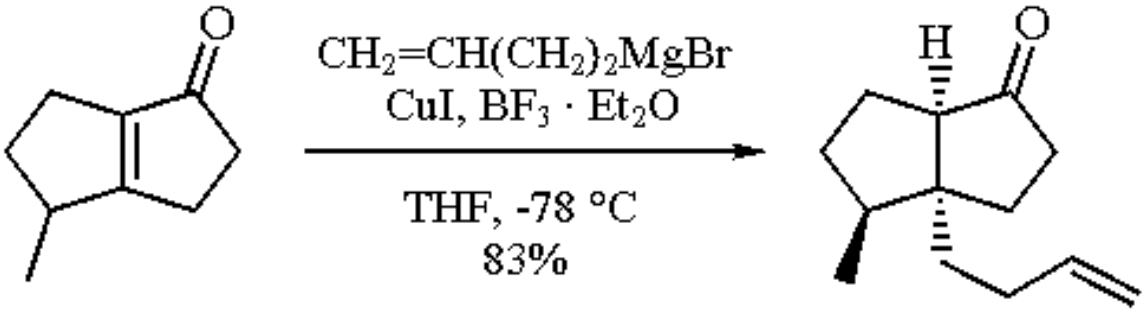

(11)

There are relatively few examples of nucleophilic substitution reactions involving this reagent. Whiting has reported

the efficient displacement of a secondary pivaloyloxy group (eq 12),[15] and an interesting displacement of chloride from an α-chlorinated glycine derivative is shown in eq 13.[16] The reagent has also been used at -20 °C for selective aromatic nucleophilic substitution of one cyanide group from tetrafluoroterephthalonitrile in 60% yield.[17]

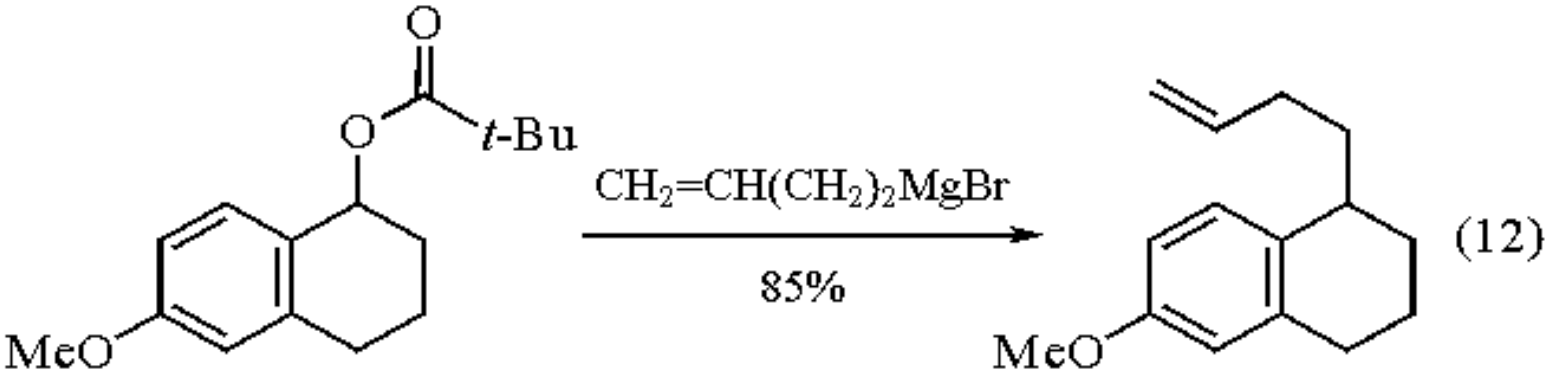

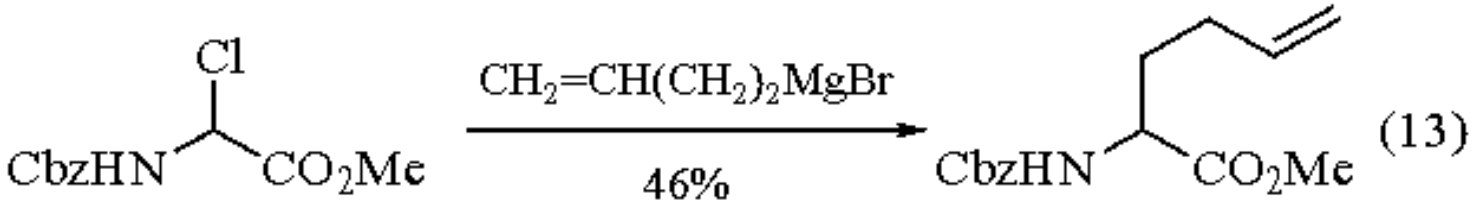

The corresponding addition to epoxides can be very efficient. For example, addition to (*R*)-(-)-1-nonene oxide in the presence of ***Copper(I) Bromide*** occurs at -10 °C to give the enantiomerically pure secondary alcohol in 90% yield (eq 14),[18] and the THP ether of glycidol undergoes addition under similar conditions, again in 90% yield (eq 15).[19]

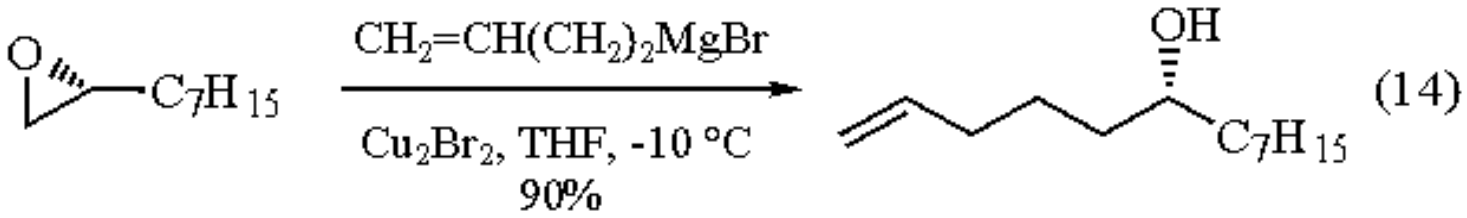

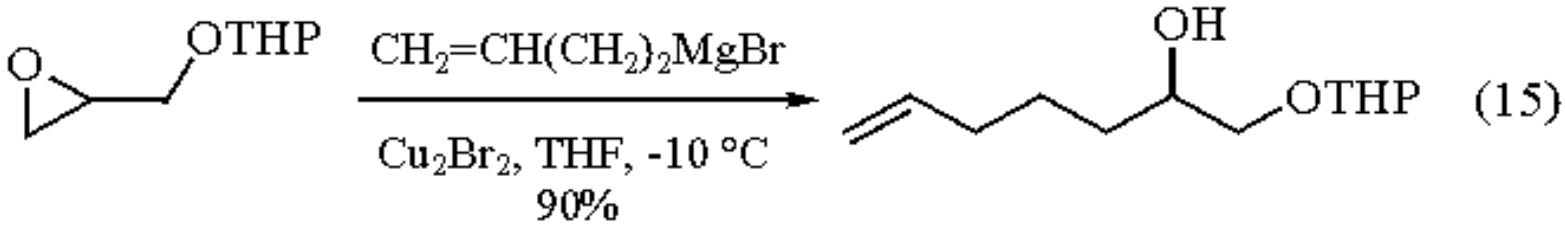

3-Butenyl-1-magnesium bromide has also been used to generate the corresponding organozinc species by metal exchange using ***Zinc Chloride***. The organozinc species was used in enantioselective addition to aldehydes catalyzed by a spirotitanate derived from (*R*,*R*)-tartaric acid.[20]

Although 3-butenylmagnesium bromide is known to be in equilibrium with small amounts of cyclopropylmethylmagnesium bromide,[21] cyclopropyl products are not observed.

Related Reagents.

***2-(2-Bromoethyl)-1,3-dioxane*; *3-(1-Ethoxyethoxy)propylmagnesium Bromide*.**

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2-(2-Butenylthio)benzothiazole

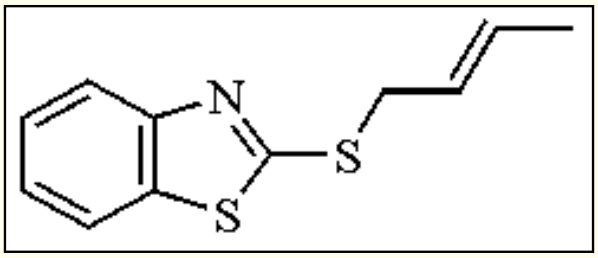

[89805-98-1] · $C_{11}H_{11}NS_2$ · 2-(2-Butenylthio)benzothiazole · (MW 221.37)

(allylic electrophile which allows efficient control of the chemo-,[1] regio-, and stereoselectivity[2,3] in the C-C coupling process by reaction with organocopper reagents)

Solubility: sol all solvents except water.

Form Supplied in: white oils or solids; not commercially available.

Preparative Methods: 2-allyloxybenzothiazoles are prepared by reaction of potassium allyloxides with 2-chlorobenzothiazole in dry ether at rt.[2] 2-Allylthiobenzothiazoles are prepared by reaction of allylic alcohols with 2,2´-dithiobis(benzothiazole) and triphenylphosphine or with benzothiazole-2-thiol, diethyl azodicarboxylate, and triphenylphosphine in dry toluene at rt.[3]

Handling, Storage, and Precautions: store at 5 °C. Safety and handling data not available.

2-Allylthiobenzothiazoles.

The reaction of these substrates with organocopper reagents, prepared by reaction of Grignard reagents with ***Copper(I) Bromide***, leads to C-C coupling products (eq 1).

2-(2-Butenylthio)benzothiazole

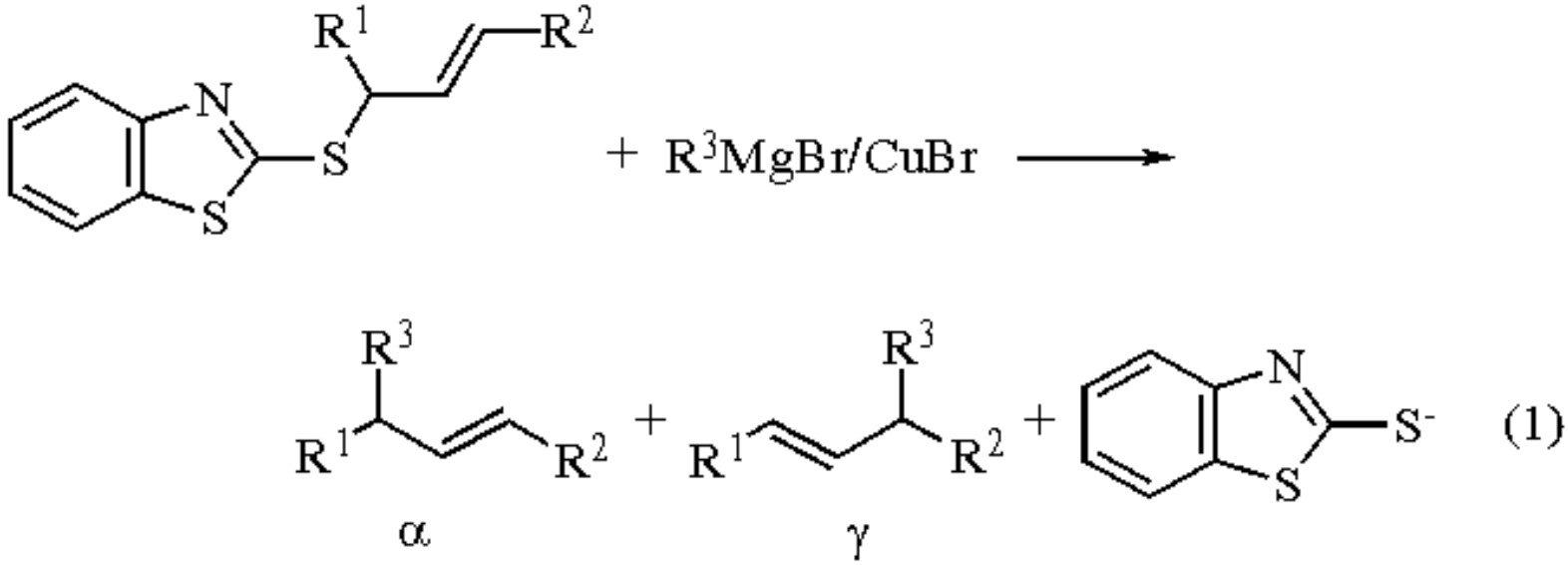

Efficient regiocontrol of this process (α- or γ-substitution) depends on the nature of the organometallic reagent. High ratios of RMgX:CuX, which favor the formation of organocuprates, give only α-substituted products, whereas lower ratios, which favor the formation of organocopper reagents RCu, afford exclusively γ-substituted products (eq 2).[3] γ-Substitution occurs independently of the steric hindrance of the R^2 group in the allylic sulfide (eq 3).

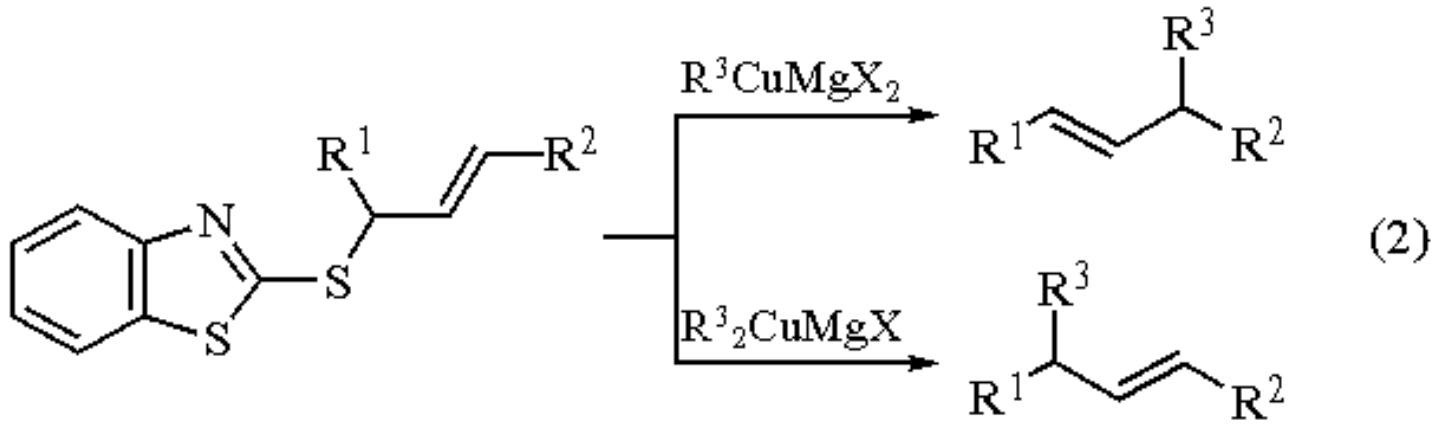

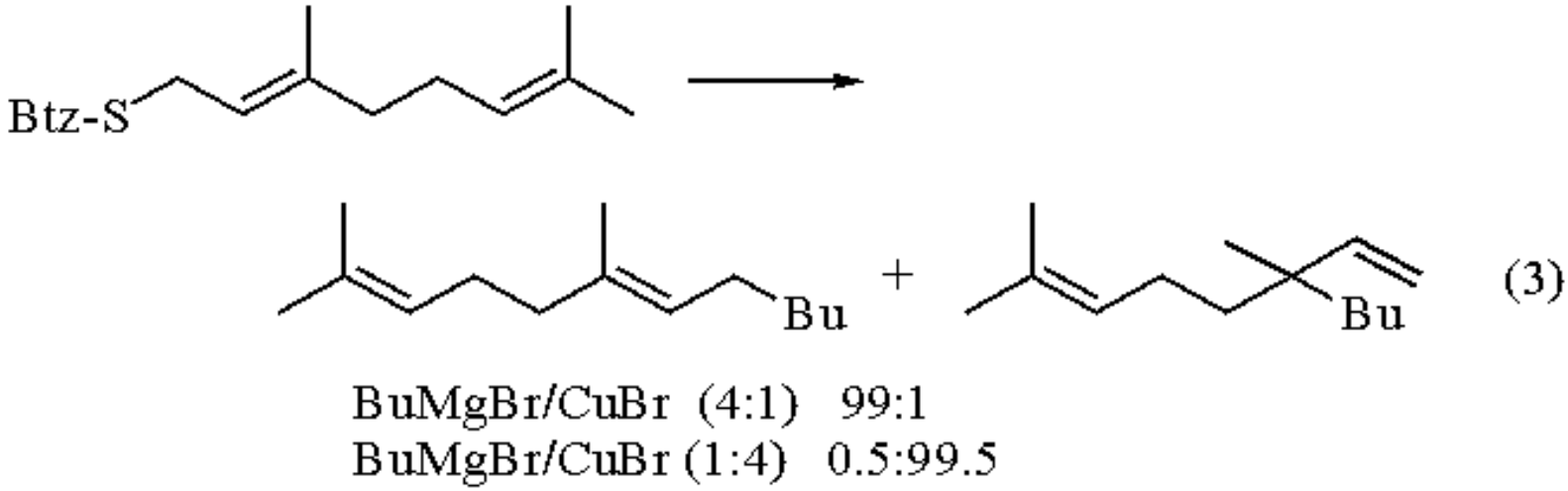

These features have been applied to a simple synthesis of California red scale pheromone[4] starting from the

benzothiazole sulfide/benzyl ether of (*S*)-(-)-citronellol (eq 4).

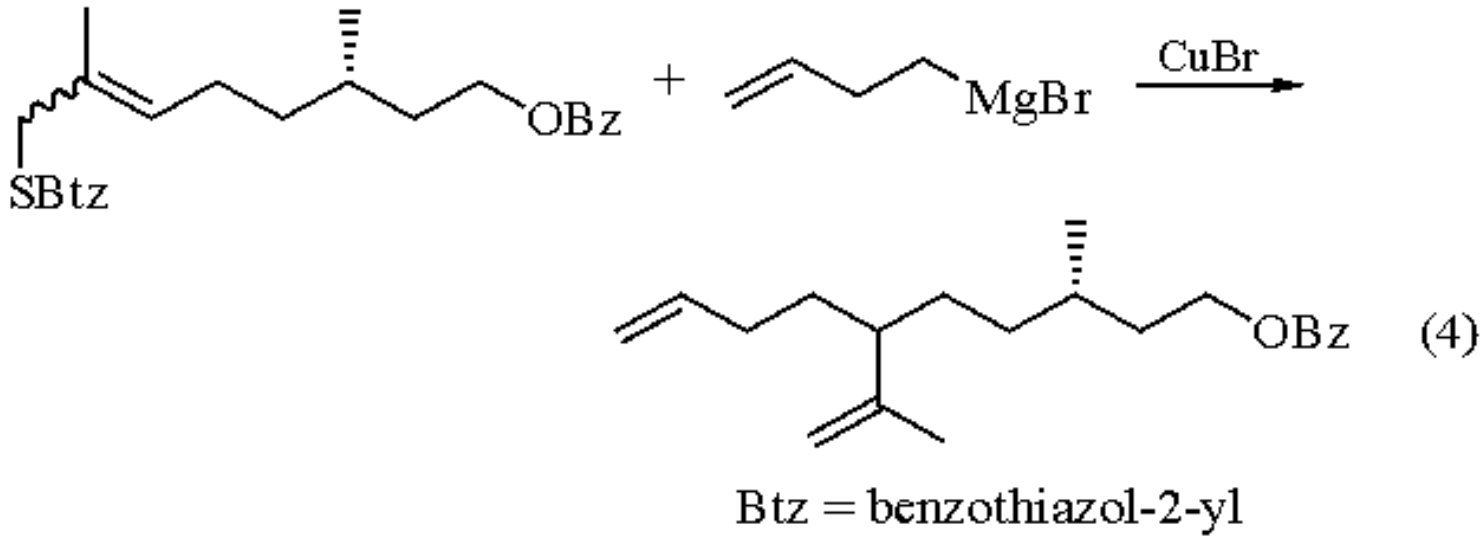

Stereodivergent pathways relative to other allylic systems (e.g. allylic acetates)[5] have been found[6] in the reactions of cyclic allylic sulfides or ethers of benzothiazole with organocopper reagents. In this case the S_N2' process occurs with *syn* stereochemistry (eq 5) and is due to the anchimeric coordination of the organometallic reagent with the heterocyclic moiety. This has been utilized for regio- and stereocontrolled access to branched-chain sugars.

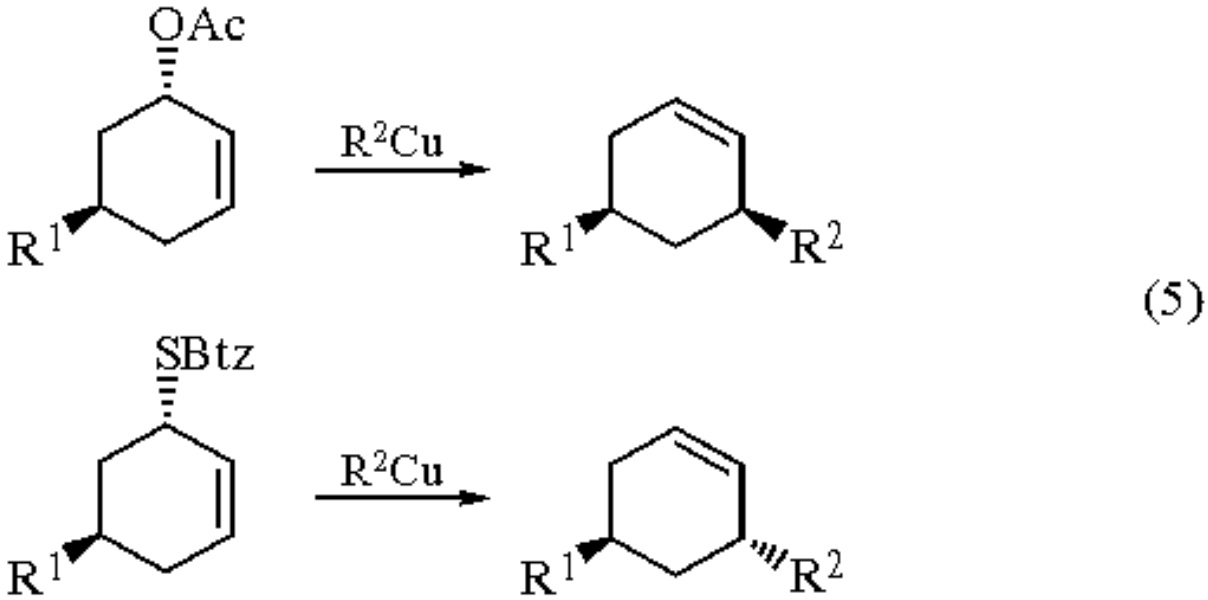

The importance of coordination in dictating the stereo- and regioselectivity is further demonstrated[7] by the reactions of α,β-enoates γ-substituted by a *S*-benzothiazolyl group with organocopper reagents to give, in a anti-Michael fashion, α-alkylated-β,γ-enoates (eq 6).

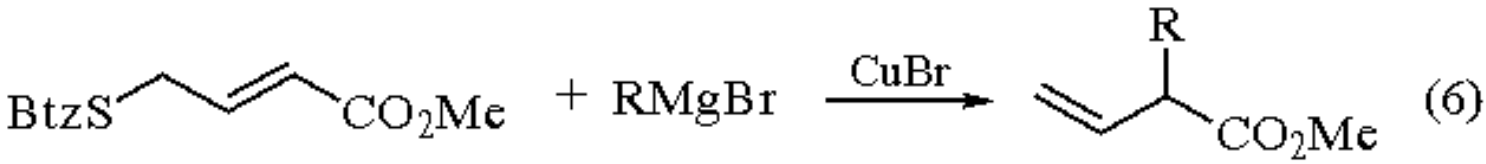

2-(2-Butenylthio)benzothiazole

The control of chemo-, regio-, and stereochemistry in the reactions of allylic electrophiles with two different leaving groups with organocopper reagents is difficult to achieve since many chemo-, regio-, and stereochemical reactions occur together with the desired one.[8] These difficulties can be overcome by using the benzothiazolyl group as one of the leaving groups which is selectively replaced. This has been used for a synthesis of homoallylic pivalates (eq 7).[1]

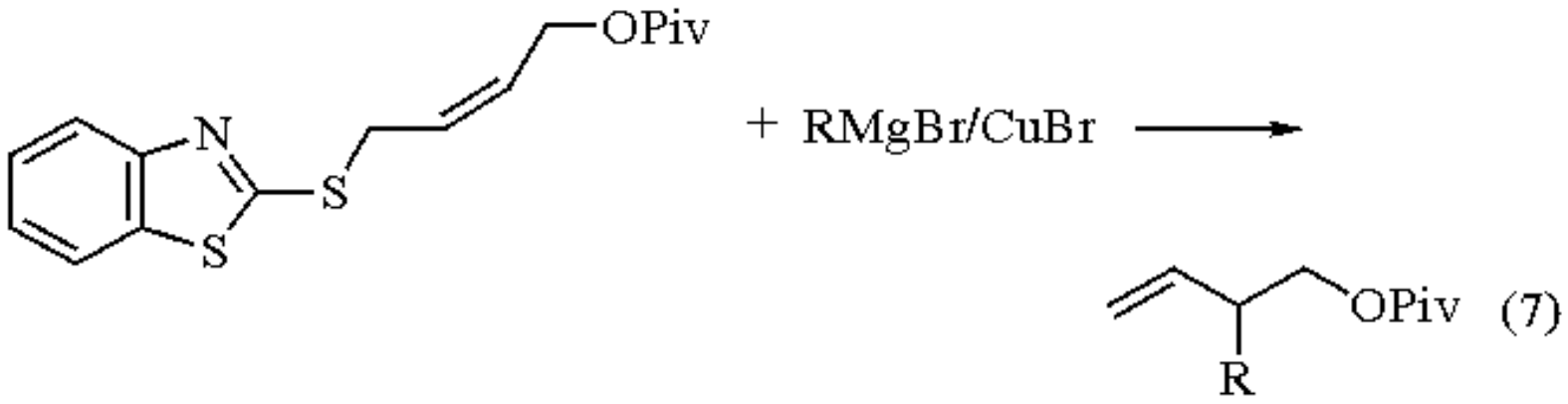

2-Allyloxybenzothiazoles.

Coupling of these reagents with allylic Grignard reagents in the presence of CuBr allows regioselective synthesis of 1,5-dienes, thus overcoming the difficulties found for different allylic electrophiles.[9] The C-C coupling occurs exclusively in a head-to-tail fashion. Contrary to this the same electrophiles, when complexed with CuBr before the addition of the allylic Grignard reagent, give only 1,5-dienes derived from head-to-head coupling process (eq 8).[10]

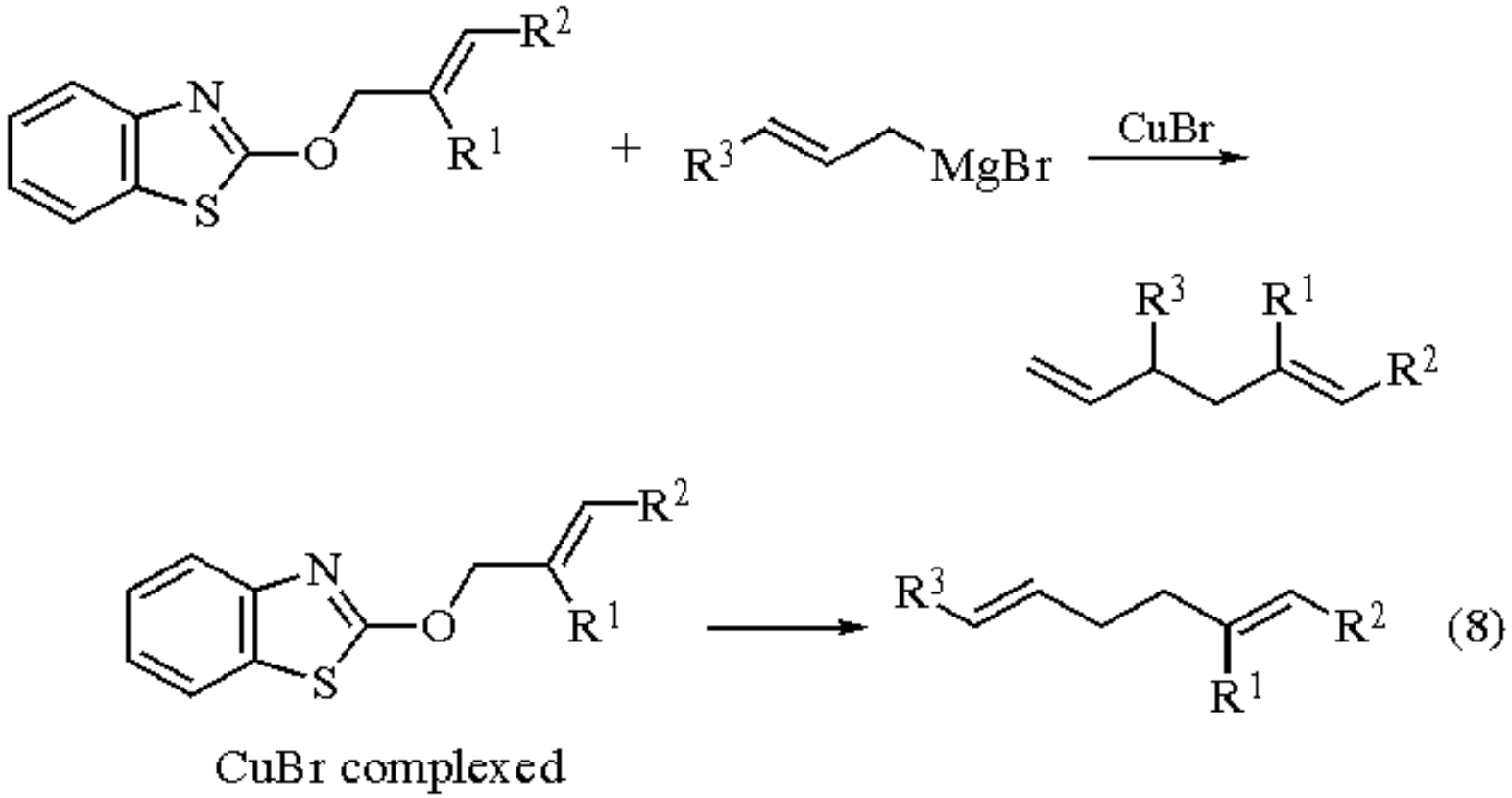

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t-Butoxyacetylene

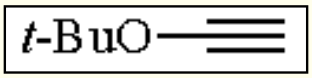

[89489-28-1] · $C_6H_{10}O$ · *t*-Butoxyacetylene · (MW 98.16)

(thermal and Cu^I-catalyzed dimerization;[1] synthesis of silylketenes;[2] synthesis of macrocyclic lactones via ketene intermediates[3])

Physical Data: bp ca. 23 °C/22 mmHg.

Solubility: sol organic solvents.

Form Supplied in: pale yellow liquid.

Analysis of Reagent Purity: ^{1}H NMR, ^{13}C NMR, IR, and gas chromatography.

Preparative Methods: bromination of ethyl vinyl ether and displacement by *t*-butanol provides a mixed acetal (eq 1); substitution of ethoxy by chloride and dehydrochlorination then gives rise to β-bromovinyl ether (eq 2), which upon dehydrobromination with base generates *t*-butoxyacetylene (eq 3).[4] The overall yield from ethyl vinyl ether is 34%. This substance has also been prepared by bromination of *t*-butoxy vinyl ether followed by stepwise elimination of HBr.[5] The preparation of *t*-butoxyacetylene from an appropriate 1-chloro-1-fluoroalkene has also been reported.[6]

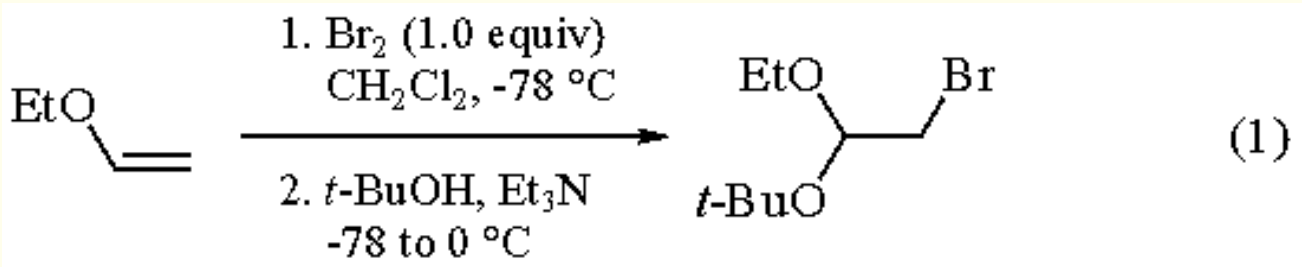

(1)

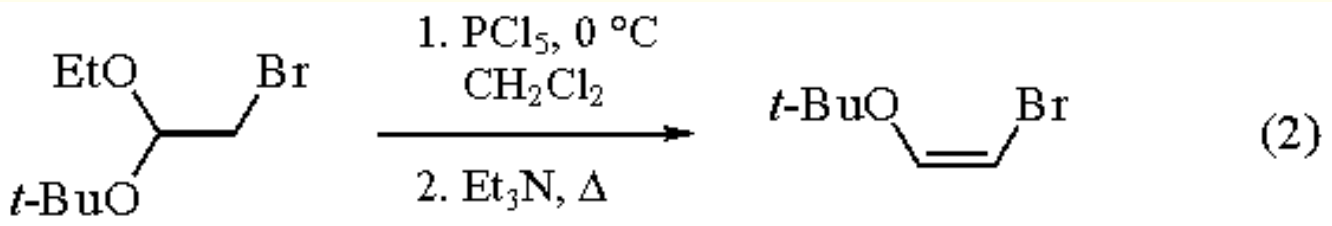

(2)

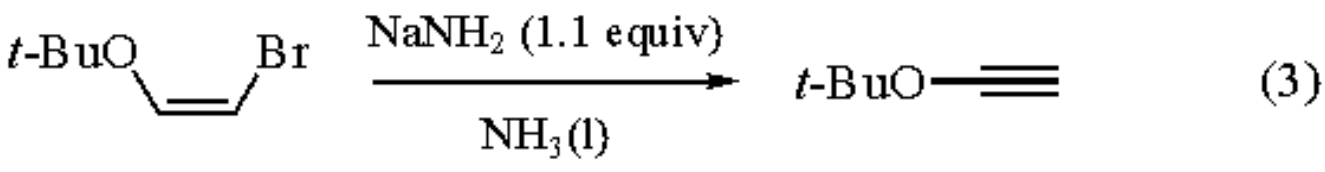

Purification: distillation at 23 °C/0.5 mmHg, collecting material at -78 °C, followed by redistillation at 23 °C/22 mmHg, collecting at 0 °C.

Handling, Storage, and Precautions: *t*-butoxyacetylene should be used as distilled for best results (clear liquid). It turns pale yellow upon storage at -10 °C (freezer) and is stable for a few months under these conditions.

Dimerization.

The Cu^I-catalyzed oxidative dimerization of *t*-butoxyacetylene under modified Hay conditions has been found to proceed smoothly (eq 4).[1a] The resulting 1,4-di-*t*-butoxy-1,3-butadiyne is interesting with respect to its polymerization properties. The controlled polymerization of *t*-butoxyacetylene via tungstacarbene compounds has been reported.[7] Thermal dimerization of *t*-butoxyacetylene under mild conditions, so that the generated low concentration of the parent ketene prevents its oligomerization, provides 3-*t*-butoxycyclobutenone in good yield (eq 5) which in turn can be hydrolyzed to 1,3-cyclobutanedione.[1b]

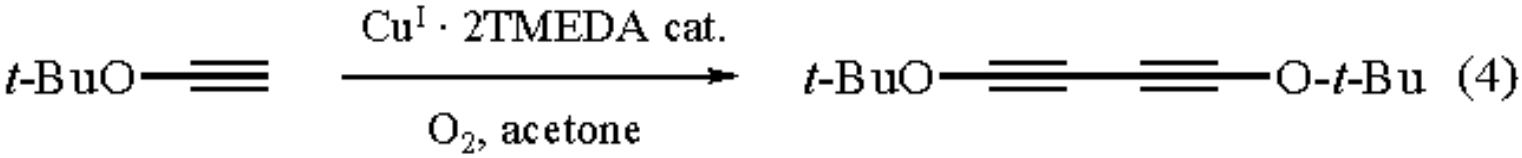

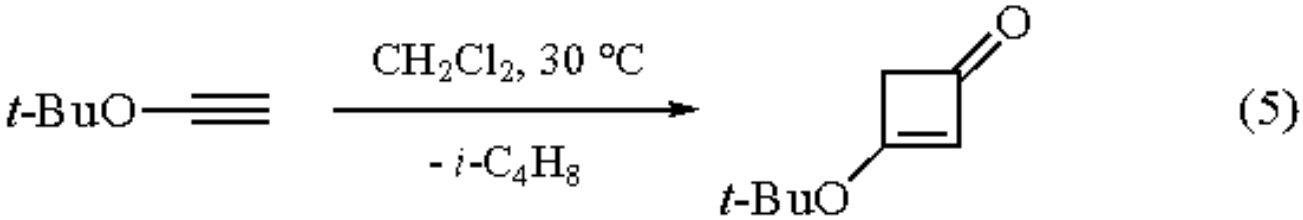

Synthesis of Silylketenes.

The *C*-silylation of *t*-butoxyacetylene has been achieved by deprotonation and subsequent silylation (eq 6).[2] Thermally induced elimination of isobutylene from these derivatives via a retro-ene type rearrangement delivers silylketenes at much lower temperature than from the corresponding ethoxyacetylene compounds (eq 7).[8] In the case of 1-*t*-butoxy-2-(trimethylsilyl)acetylene, thermolysis at 50-55 °C in the presence of diphenylamine provided *N*,*N*-diphenyl(trimethylsilyl)acetamide in high yield (eq 8).[2] The *C*-alkylation of *t*-butoxyacetylene can be carried out in a similar manner.[3a,4]

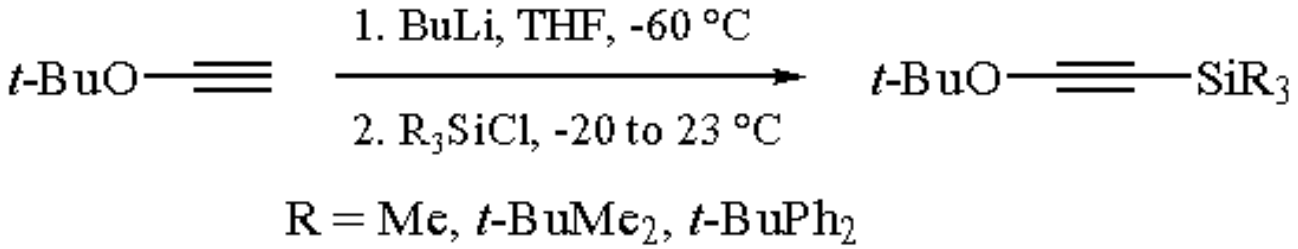

(6)

R = Me, *t*-BuMe$_2$, *t*-BuPh$_2$

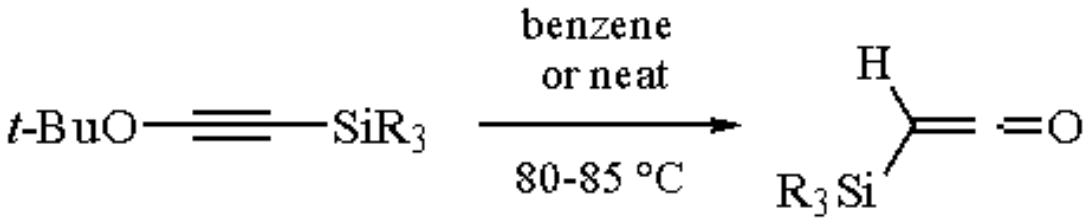

(7)

R = *t*-BuMe$_2$, *t*-BuPh$_2$

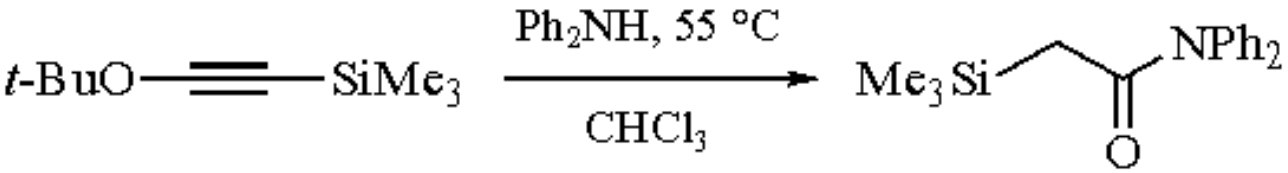

(8)

Macrocyclic Lactones.

Addition of substituted *t*-butoxyacetylene derivatives to refluxing MeCN and ***Triethylamine*** under high-dilution conditions produces macrocyclic lactones in 57% yield via a ketene intermediate (e.g. eq 9).[3a] Similar lactonizations are shown in eqs 10 and 11. As indicated, the cross-coupling of *t*-butoxyacetylene with conjugated enynes (eq 10) is more efficient than that with simple alkynes (eq 11).[3b]

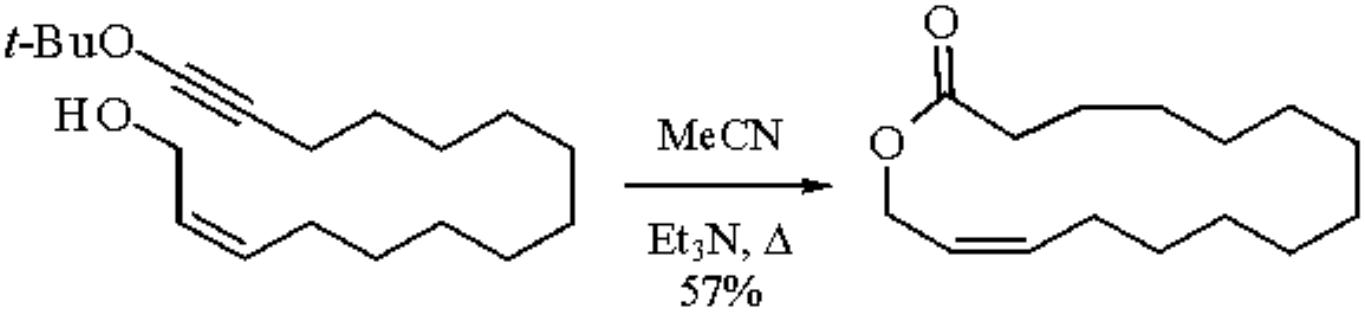

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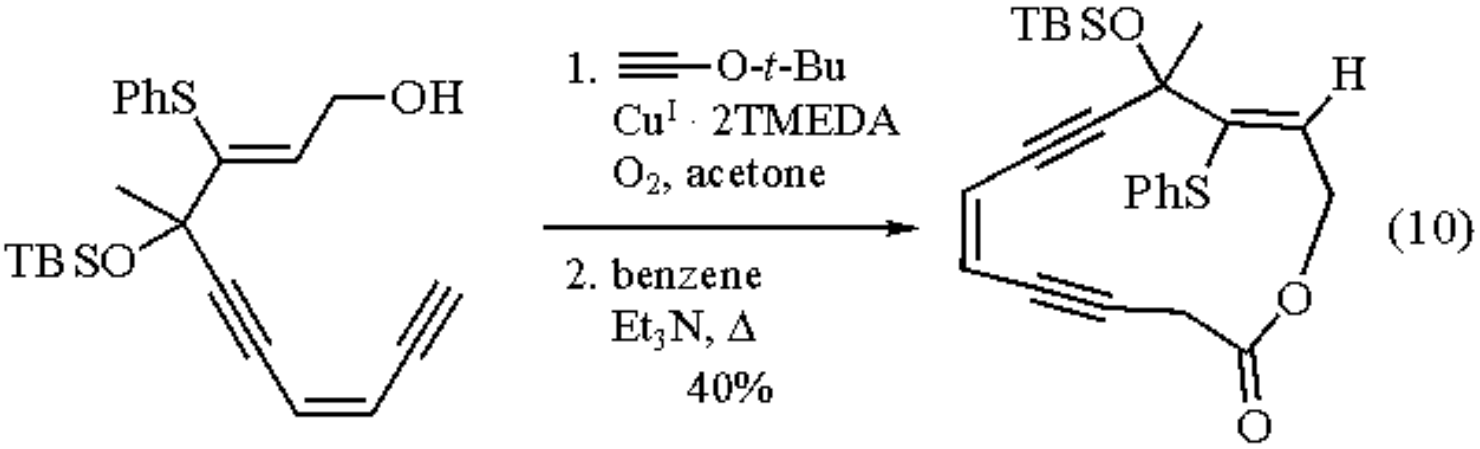

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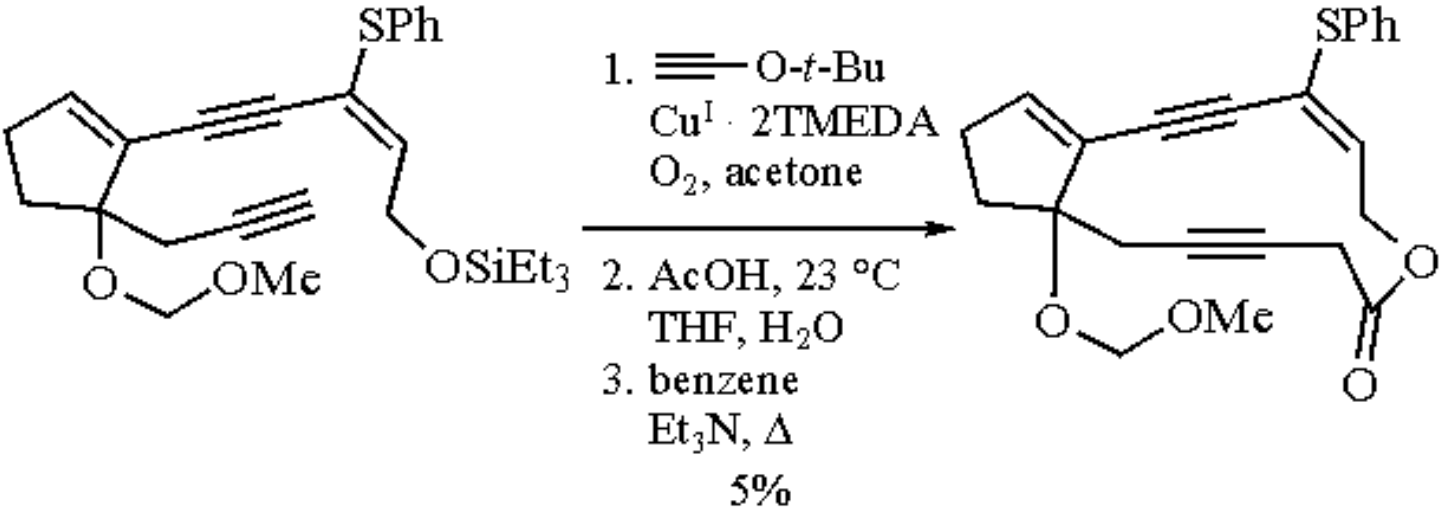

(11)

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5. (a) Van Daalen, J. J.; Kraak, A.; Arens, J. F. *RTC* **1961**, *80*, 810. (b) Potman, R. P.; Janssen, N. J. M. L.; Scheeren, J. W.; Nivard, R. J. F. *JOC* **1984**, *49*, 3628.
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8. (a) Brandsma, L.; Bos, H. J. T.; Arens, J. F. *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Dekker: New York, 1969; pp 808-810. (b) Moyano, A.; Pericàs, M. A.; Serratosa, F.; Valentí, E. *JOC* **1987**, *52*, 5532. (c) Ruden, R. A. *JOC* **1974**, *39*, 3607.

Plato A. Magriotis

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t-Butoxybis(dimethylamino)methane[1]

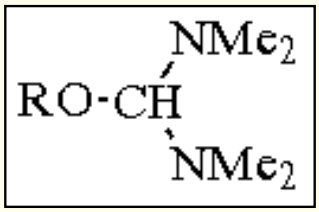

(**1**; R = *t*-Bu) (*t*-BAE)

[5815-08-7] · $C_9H_{22}N_2O$ · *t*-Butoxybis(dimethylamino)methane · (MW 174.33) (**2**; R = Me) (MAE)

[1186-70-5] · $C_6H_{16}N_2O$ · Methoxybis(dimethylamino)methane · (MW 132.24)

(aminal esters reactive as aminomethylenating reagents (formylating reagents) for CH_2- and NH_2-acidic compounds. The *t*-butyl analog is somewhat more reactive than the methyl derivative; bis(dimethylamino)carbene can be generated from both compounds)

Alternate Name: Bredereck's reagent.

Physical Data: (**1**) bp 50-52 °C/12 mmHg; *n*20D = 1.4250. (**2**) bp 128 °C/760 mmHg; 32-33 °C/25 mmHg; *n*20D = 1.4158.

Solubility: miscible with nonpolar aprotic waterfree solvents (benzene, toluene, cyclohexane, diethyl ether, etc.); react with protic solvents like water (hydrolysis to DMF) or alcohols (alcoholysis affords DMF acetals). Even common solvents like acetonitrile or acetone which are weakly CH-acidic react with the aminal esters on heating.

Form Supplied in: colorless to weak yellow, strong amine-smelling liquids.

Analysis of Reagent Purity: the best method is ^{1}H NMR spectroscopic examination of a neat sample.

Handling, Storage, and Precautions: both compounds should be handled in a fume hood, with strict exclusion of atmospheric moisture. They should be stored in tightly sealed containers in a refrigerator under an atmosphere of dry nitrogen or argon.

Introduction.

Alkoxybis(dimethylamino)methanes can be obtained in good yields from *N*,*N*,*N*´,*N*´-tetraalkylformamidinium salts and alcohol-free alkoxides.[2] The reactions have to be conducted in inert, strictly anhydrous solvents like cyclohexane,

hexane, ether, or THF, in which unfortunately both reagents are insoluble. As a consequence it is necessary to use relatively large amounts of the solvent and long reaction times (eq 1). In the patent literature it is claimed that by the use of a mixture of DMF and mesitylene as solvent, the yields can be improved to about 95%.[3]

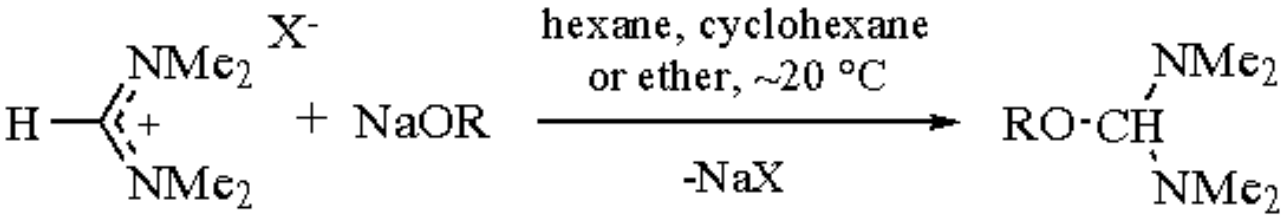

(1)

X	R	Solvent	Reaction time (h)	Yield (%)
$MeSO_4$	Me	Ether	1-2	62
$MeSO_4$	*t*-Bu	Cyclohexane	1-2	70
Cl	*t*-Bu	Ether	24	75

In another method,[4] bis(dimethylamino)acetonitrile is used as the starting compound. Alcohol-free alkoxides suspended in absolute ether substitute the cyano group to give the corresponding aminal ester (eq 2). In contrast to the aforementioned method, less solvent and shorter reaction times are needed because the nitrile is soluble in ether and the product yields are normally 5-20% higher.

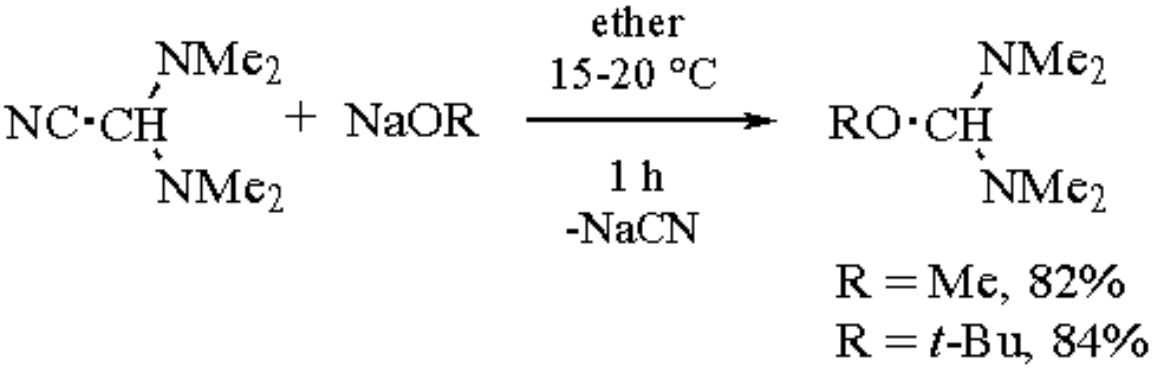

(2)

The purity and stability of the product are determined by the quality of the metal alkoxide. Traces of alcohol catalyze the disproportionation of the aminal ester to the corresponding DMF acetal and tris(dimethylamino)methane (eq 3),[5] which may complicate spectroscopic investigations. For preparative purposes the disproportionation reaction can be disregarded; at higher temperatures the orthoamides interconvert very rapidly to the aminal ester, and usually the condensation reactions of aminal esters are not affected by the equilibrium.

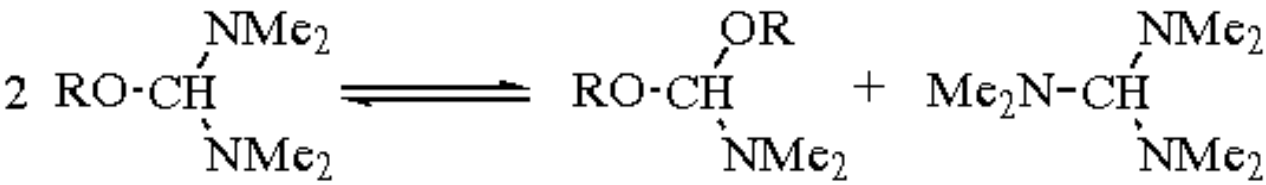

(3)

Reactions.

The reactivity of aminal esters is very similar to that of ***Tris(dimethylamino)methane***. In the first step of the reaction the compounds dissociate, forming strong basic alkoxide anions which set up an equilibrium with the XH_2-acidic compounds (eq 4). The HX^- anions thus formed combine with the formamidinium ions. β-Elimination of dimethylamine from the adduct is the final step of the condensation reaction.

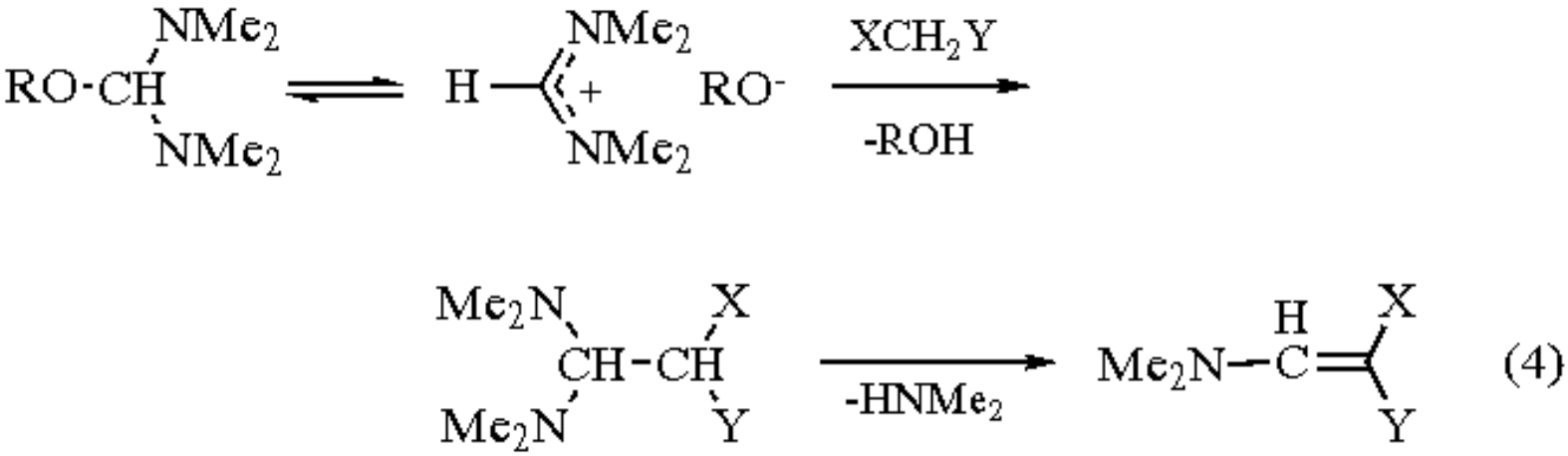

Because of their high reactivity with XH_2-acidic compounds, aminal esters have found widespread application as formylating reagents; especially with CH_2-acidic ketones such as simple dialkyl ketones,[6-9] aryl alkyl ketones,[6,10-16] heteroaryl alkyl ketones,[17-19] 1-alkenyl alkyl ketones,[20] α-dialkylamino ketones,[21] α-glycosyl alkyl ketones,[22] cycloalkanones,[10,11,16,20,23 -28] 4-piperidinones,[29] and steroidal ketones.[30,31] If an additional acidic functional group is present (e.g. an NH_2 group), this may also be aminomethylenated by the reagent,[10] in some cases accompanied by ring closure.[32] The resulting difunctional compounds formed have been transformed into various types of product. Eqs 5-11 give an overview of these applications.[6-27,32]

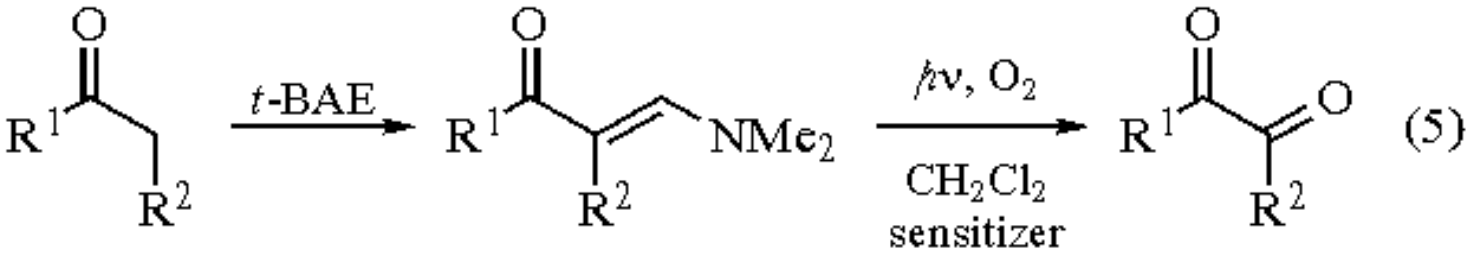

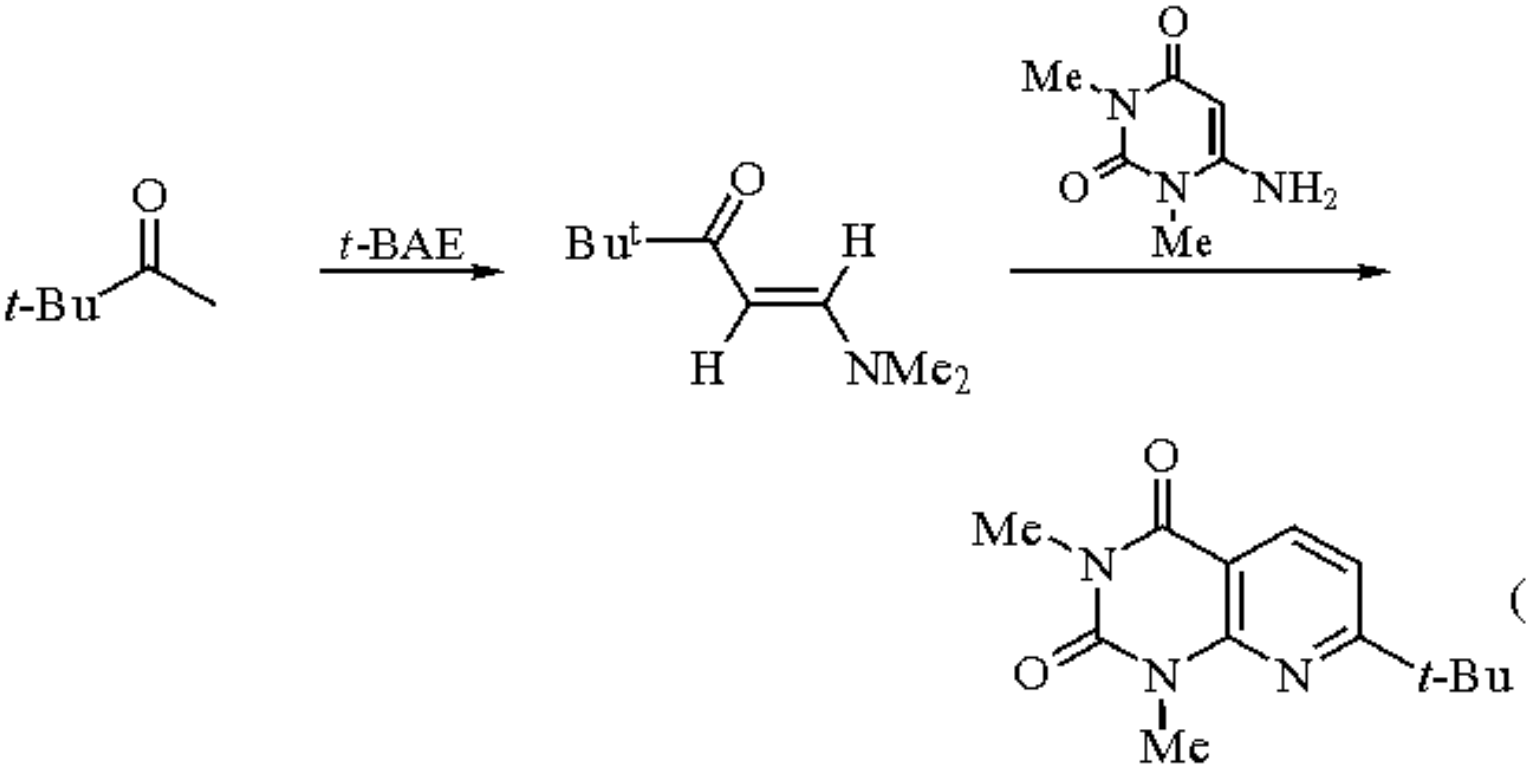
t-BAE
Bu^t
H
H
NMe2
Me
N
O
O
N
NH2
Me
t-Bu

(6)

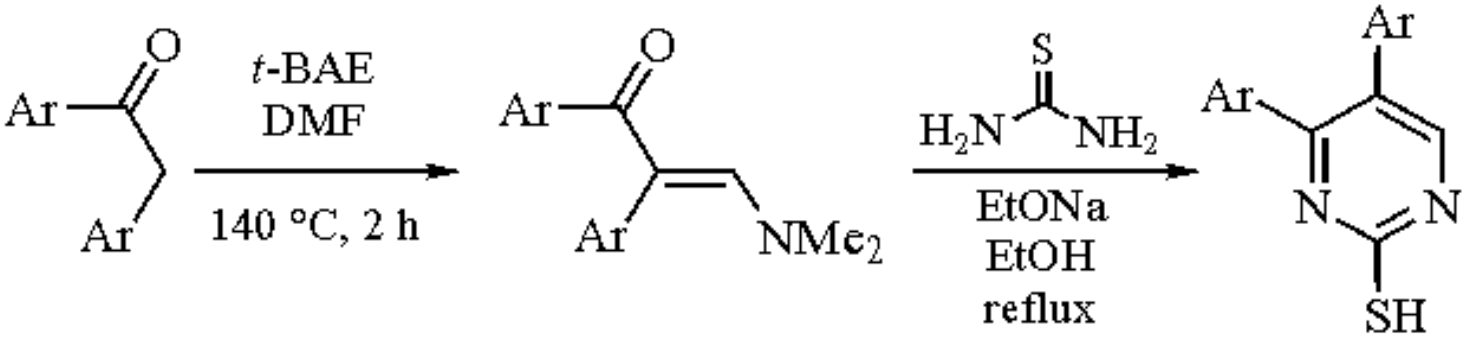
Ar
Ar
t-BAE
DMF
140 °C, 2 h
NMe2
S
H2N
NH2
EtONa
EtOH
reflux
SH

(7)

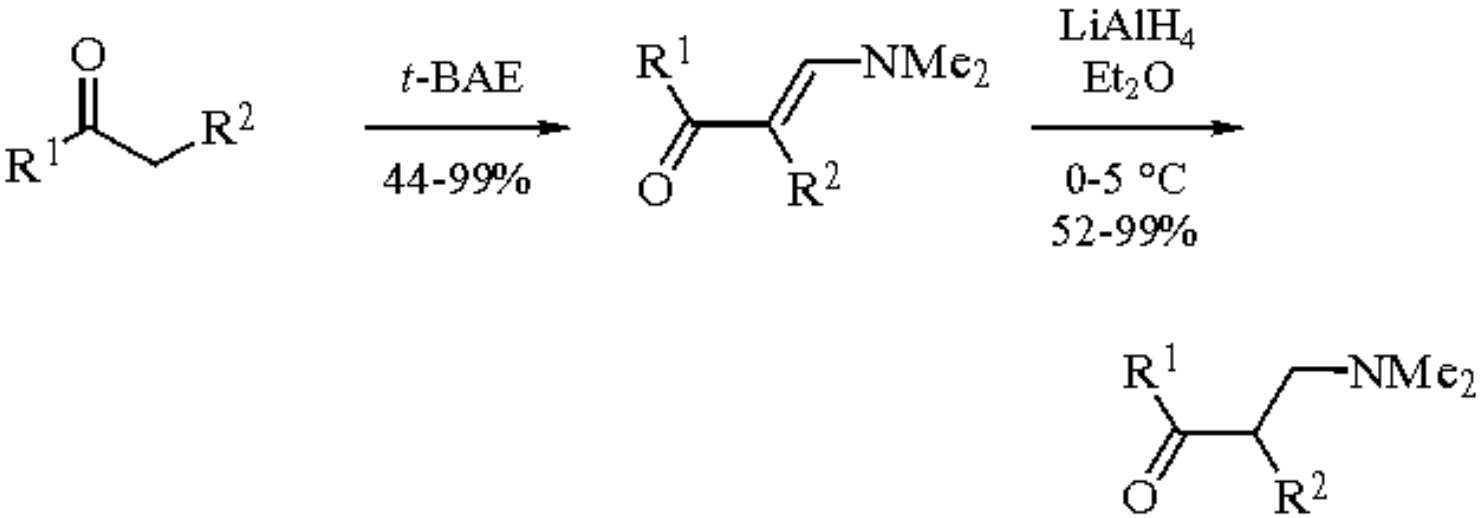
R1
R2
t-BAE
44-99%
NMe2
LiAlH4
Et2O
0-5 °C
52-99%

(8)

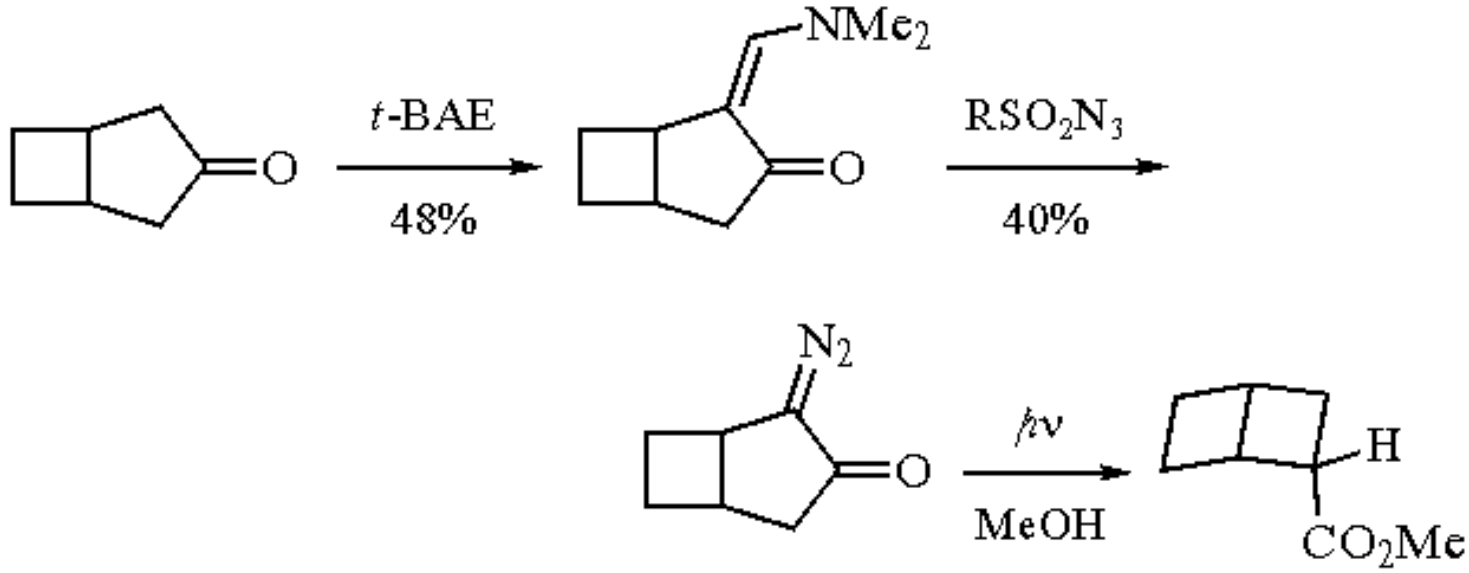
NMe2
t-BAE
48%
RSO2N3
40%
N2
hν
MeOH
H
CO2Me

(9)

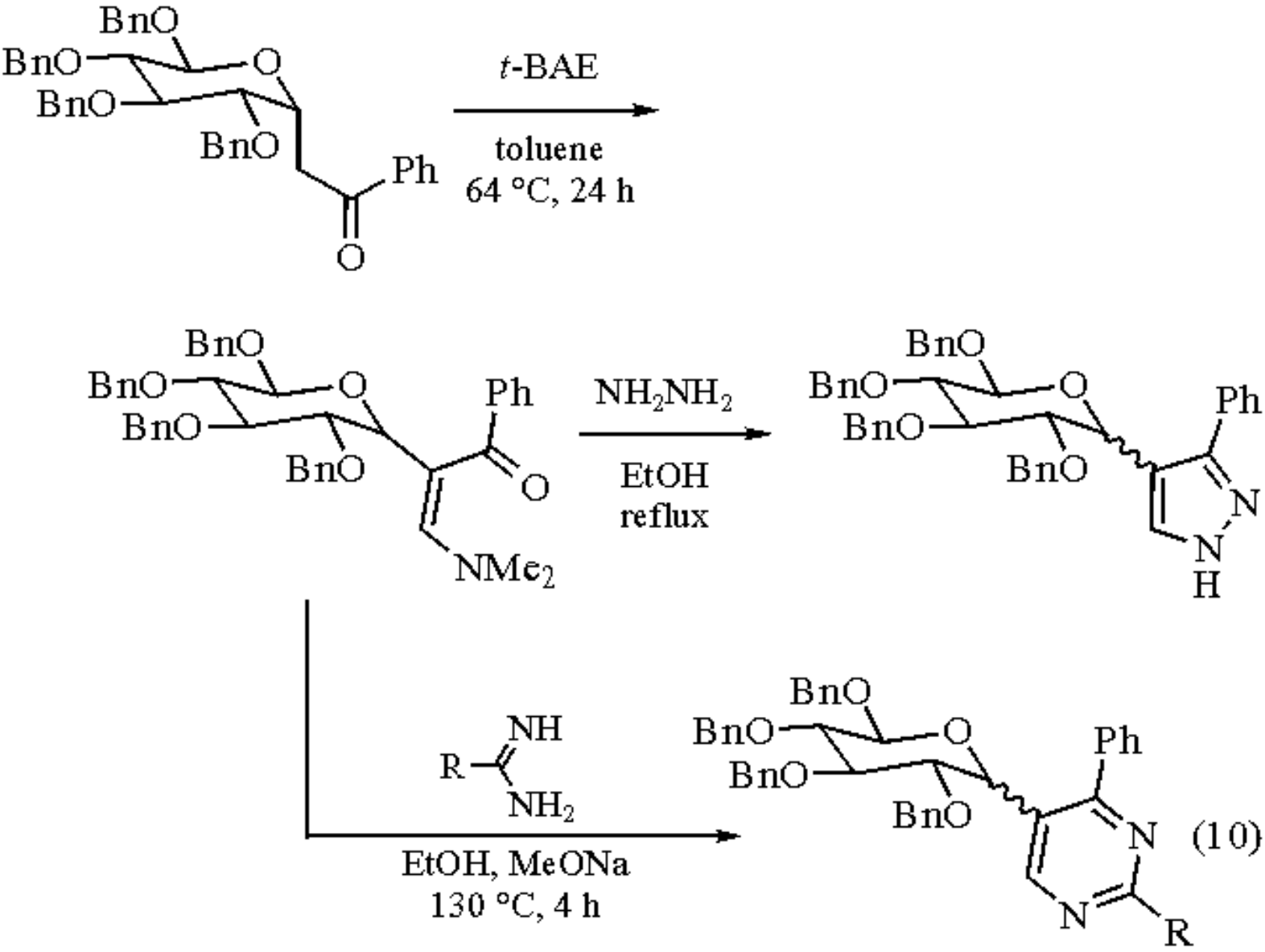
BnO
BnO
BnO
BnO
O
Ph
O
t-BAE
toluene
64 °C, 24 h
NMe2
NH2NH2
EtOH
reflux
N
N
H
NH
R
NH2
EtOH, MeONa
130 °C, 4 h
R

(10)

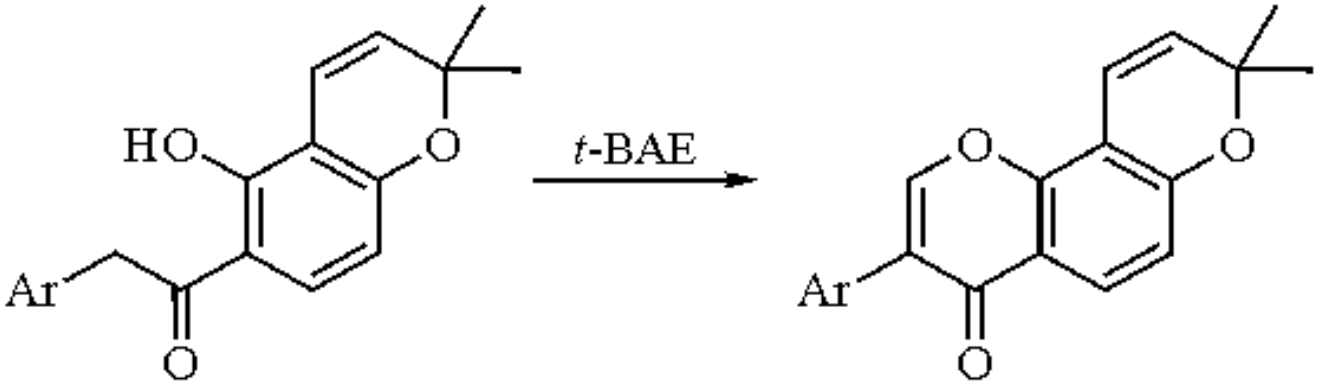

(11)

This type of condensation reaction of aminal esters may proceed with even weaker CH-acidic compounds (eq 12), such as esters[33-35] which have in the α-position, amino,[21,36-39] alkoxy[21,40] and heteroaryloxy,[39] thio,[21,39] phosphonyl,[41] and silyl groups.[41] Aminomethylenation reactions have also been reported for the following functionalities or compound classes: lactones,[33,42-51] α,β-unsaturated esters[38,52] and lactones,[53] thioesters,[33] imidates,[41] isocyanides[41] and nitriles,[6,21,41] amides[33] and lactams,[27,33,54-58] cyclic imides,[55,59] thioamides[33] and thiolactams,[33,60] amidines,[41] amidinium[41] and phosphonium salts,[61,62] phosphonates,[41,62] ketone hydrazones,[63,64] cyclopentadienes,[60-67] xanthene,[68] toluenes,[68-73] nitroarenes,[74] 2-methyl-1-pyrroline *N*-oxides,[75] 2-alkyl-5-nitroimidazole,[17] 4-methylpyridine,[68,73,76,77] methylpyrimidines,[68,77-79] 3-methylpyridazine,[78,80] 2-methylpyrazine,[78] 2-pyridones,[81] 1,3,4-thiadiazoles,[82] 1,4-dihydro-4-oxo-1,8-naphthyridine,[83] pyrimidine acids[84] and esters,[85] 3-arylidenebenzothiazines[86] and 3-methyl-1,2,4-triazines.[87]

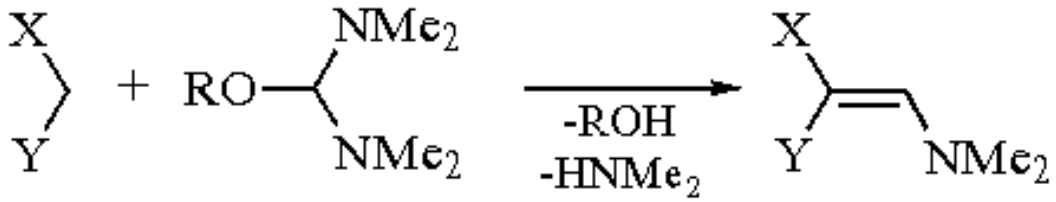

(12)

X = H, alkyl
Y = CO_2R, COSR, CS_2R, C(NR)OR, NC, CN, $CONR_2$, $CSNR_2$
$C(NR)NR_2$, $C(NMe_2)_2^+$, PPh_3^+, $PO(OR)_2$, C(NNHR')Ar
aryl, heteroaryl

The condensation products thus available can be transformed into various types of compounds. Eqs 13-17 give some examples.[34,35,43,46,70,73,79,81]

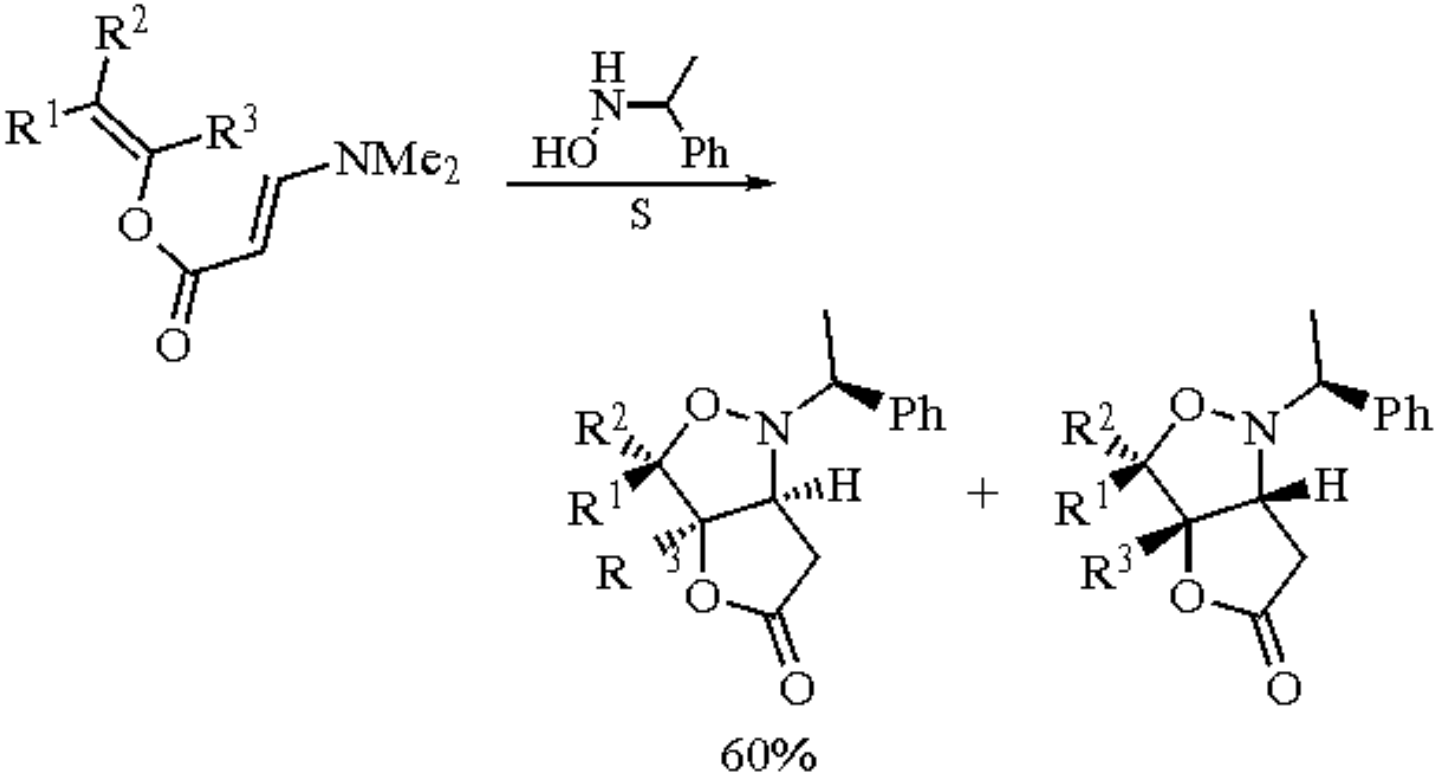
R2
R1
R3
NMe2
O
O
H
N
HO
Ph
S
O
N
Ph
R2
R1
H
R3
O
O
60%
+
O
N
Ph
R2
R1
H
R3
O
O

(13)

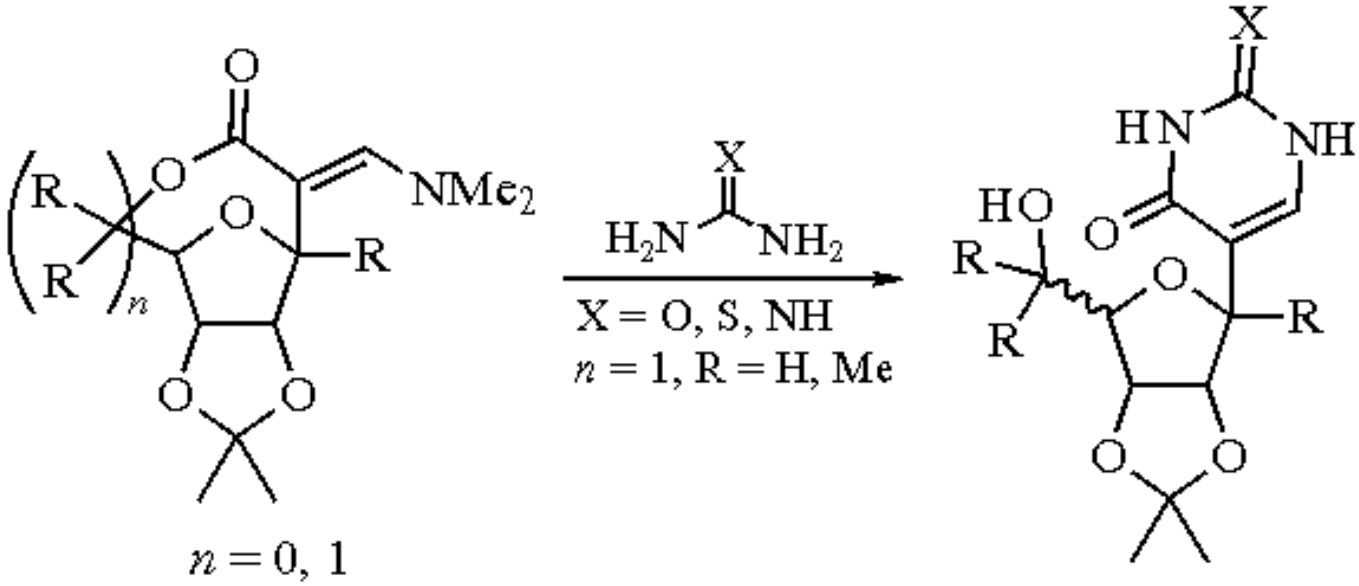
O
R
R
n
O
O
NMe2
R
O
O
n = 0, 1
X
H2N
NH2
X = O, S, NH
n = 1, R = H, Me
X
HN
NH
HO
O
R
R
O
R
O
O

(14)

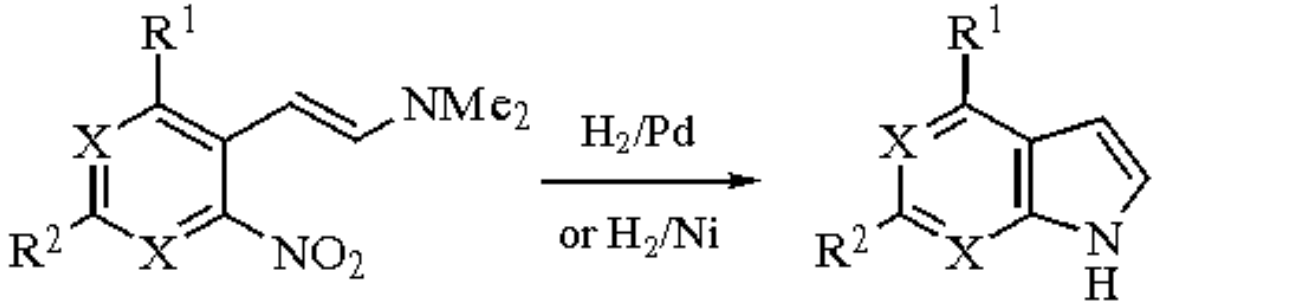

(15)

X = CH, R^2 = H, 52-84%
X = N, R^1 = R^2 = OMe, 27%

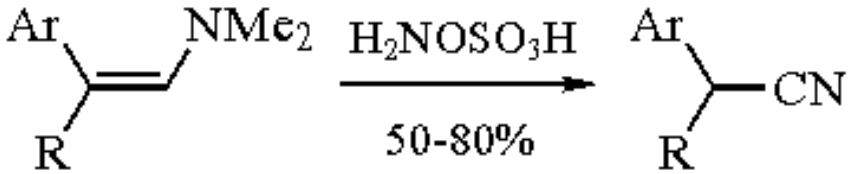

(16)

Ar = 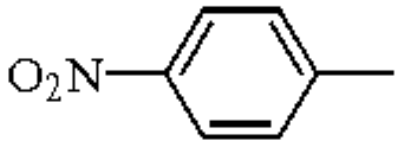

, 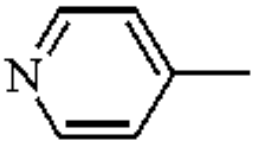

; R = H, Me, CO_2Et

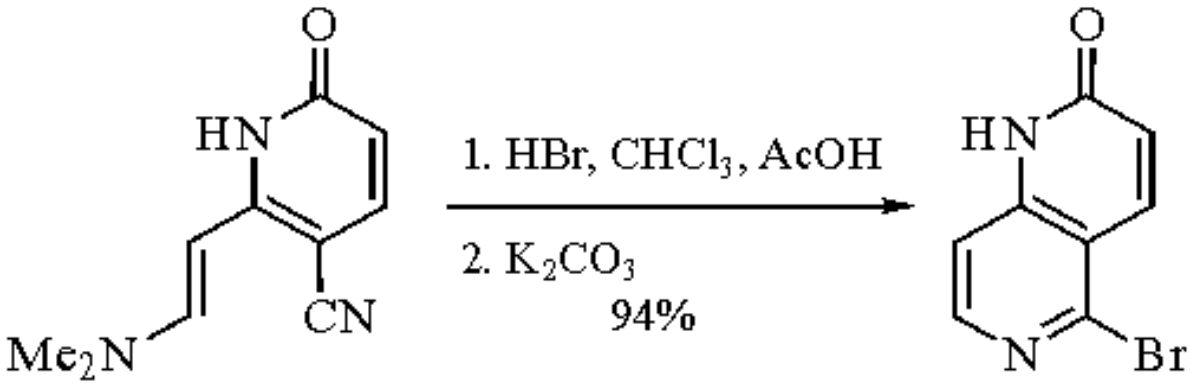

(17)

Compounds containing two acidic CH_2 groups can be formylated once or twice; examples of this type of reaction have been demonstrated with dinitriles,[59,88] 1,2-bis(phenylsulfonyl)ethane,[21] 2,2-dimethyl-1,3-cyclopentanedione,[59] 5,10-dihydroindeno[2,1-*a*]indene,[67] ethyl 4-oxoglutarate,[59] diethyl succinate,[59] diethyl adipate,[59] diethyl tetrathioadipate,[59] *N*-alkylsuccinimides,[59] and *N*-alkylglutarimides.[59] NH_2-Acidic compounds react with aminal esters analogously to CH_2-acidic compounds, i.e. the nitrogen atom is aminomethylenated. A few amides have been converted to the corresponding acylamidines (eq 18).[33,89] This condensation reaction is of less importance, because the same results can be achieved with the more accessible DMF acetals.

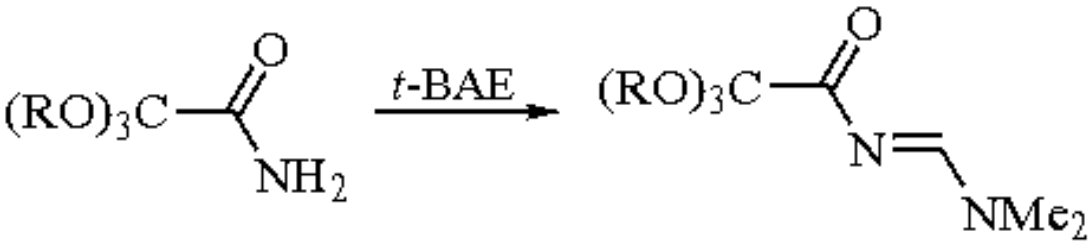

(18)

Since the primary condensation products from amides still contain an acidic methylene group, further formylation can occur (eq 19).[33] Similar results were obtained in the formylation of diethyl aminomethylphosphonate (eq 20).[90]

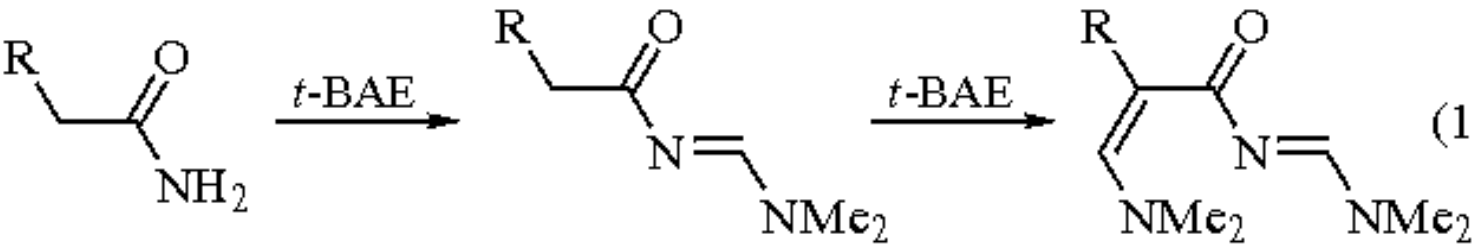

(19)

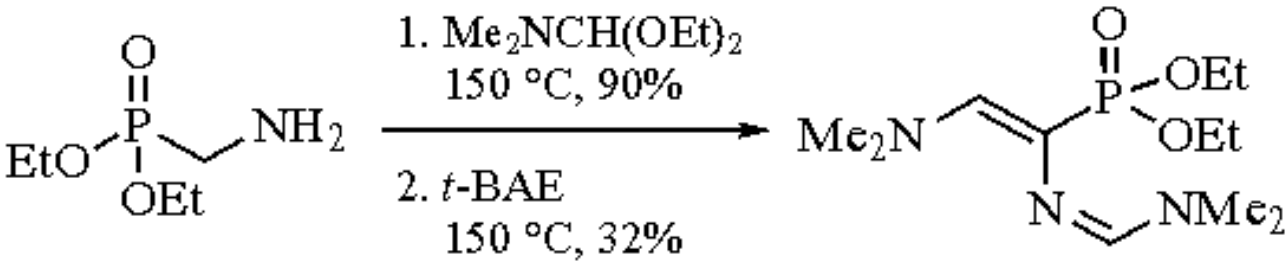

(20)

If two acidic functions of the type XH_2 and XH are present in suitable positions, the condensation reaction can be used for ring closure (eq 21).[91] In some cases the desired condensation reaction is accompanied by transformations of other functional groups present in the molecule (eqs 22 and 23).[77,92]

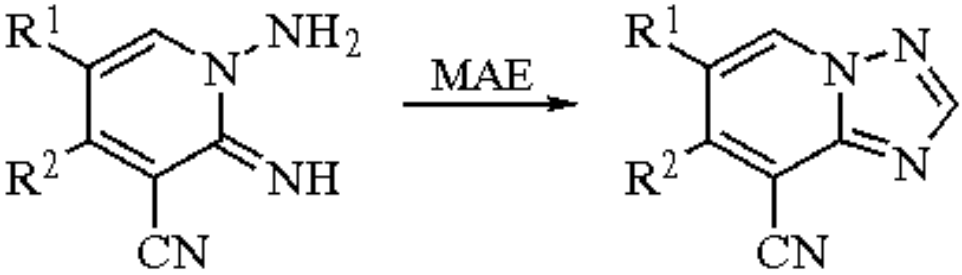

(21)

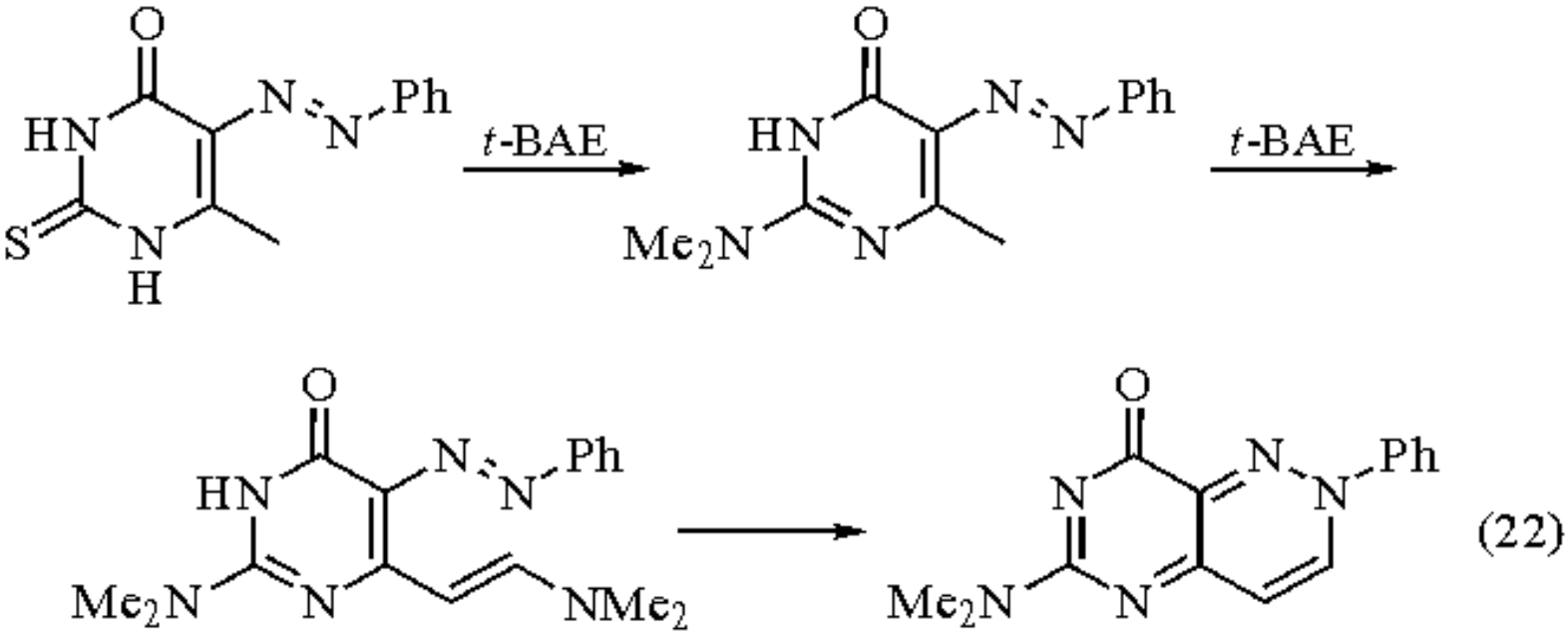

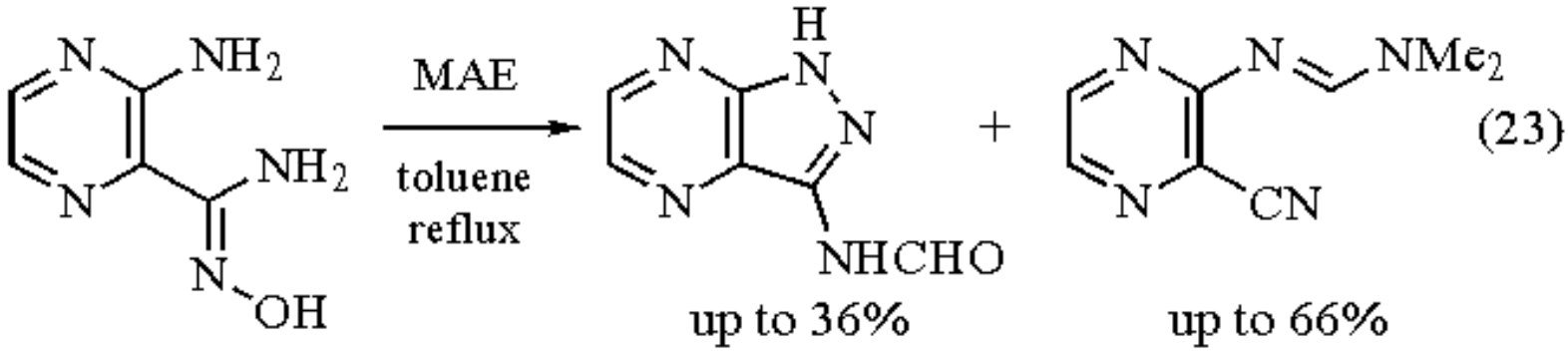

Weakly acidic heteronucleophiles substitute for the alkoxy group in aminal esters. Thus hydrocyanic acid,[83] terminal alkynes,[93] and thiols[94] afford cyano, alkynyl, and alkylthio aminals (eq 24). With secondary amines the substitution of the alkoxy group is accompanied by a transamination to give tris(dialkylamino)methanes (eq 25).[95] The alcoholysis of aminal esters proceeds very similarly, giving rise to the formation of DMF acetals,[4,84] whereas phenols are formylated in the 4-position. *N*-Monosubstituted formamides are converted by *t*-BAE to *N*,*N*′,*N*′-trisubstituted formamidines (eq 26).[38,43]

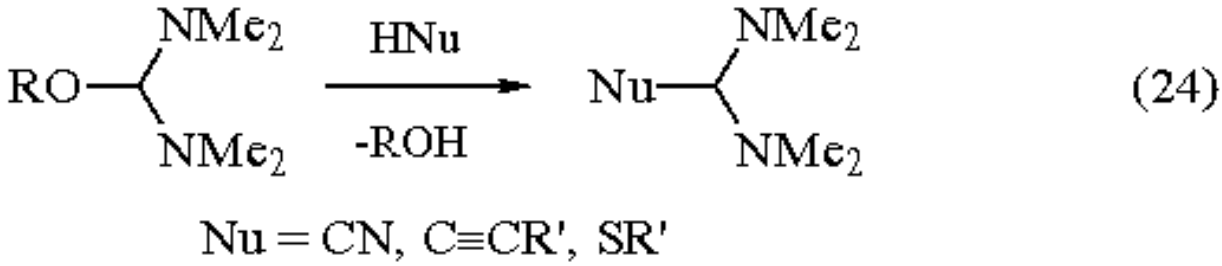

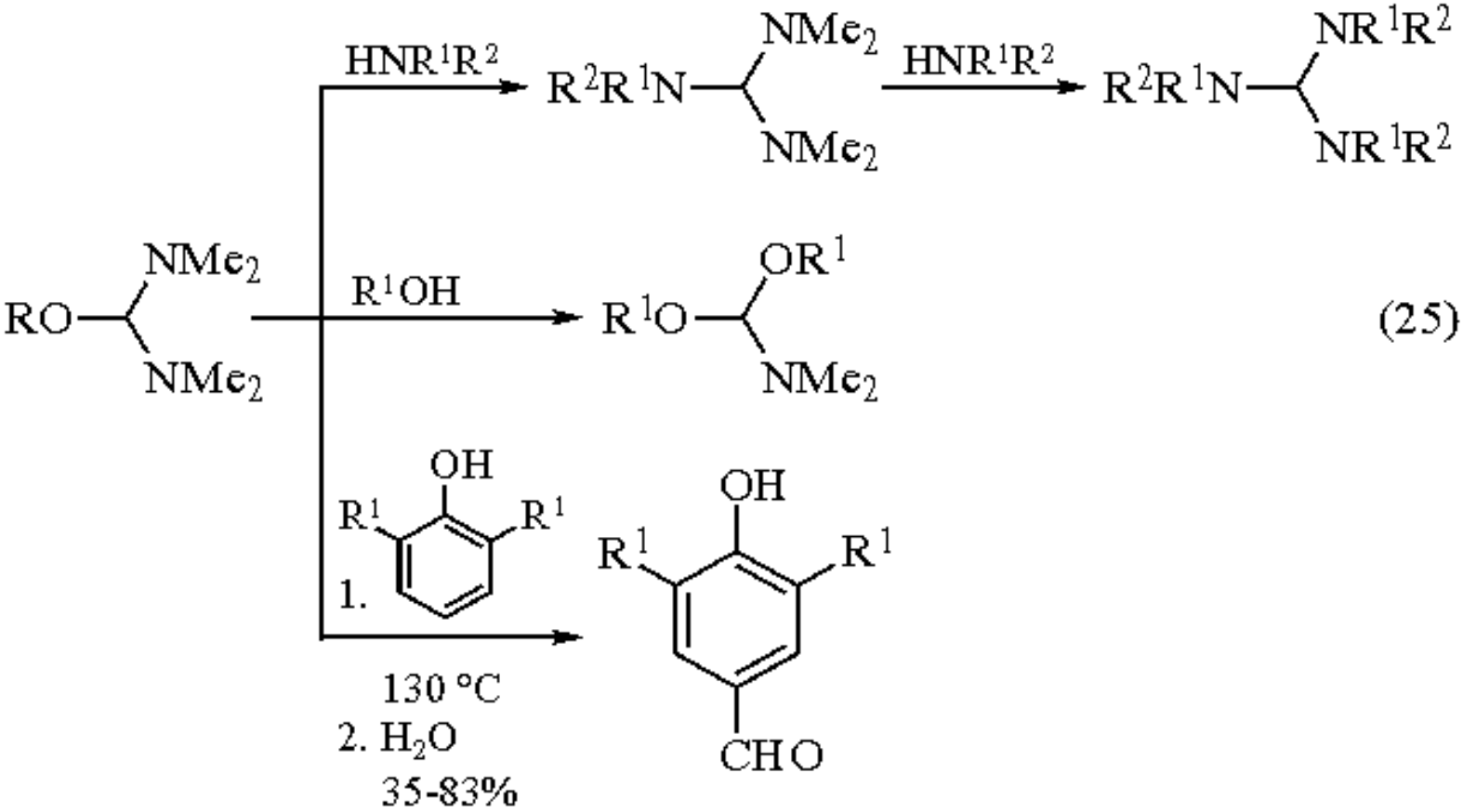

(25)

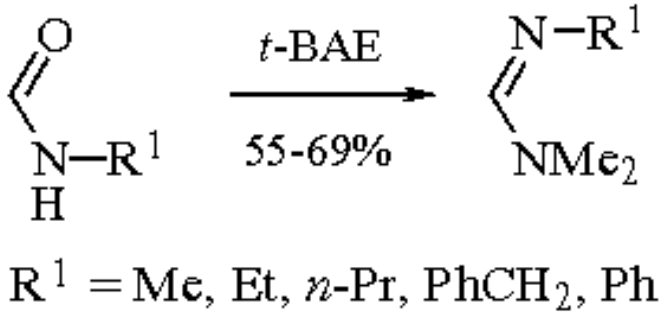

(26)

With stronger CH-, NH-, or OH-acidic compounds such as phenols bearing electron-attracting groups,[1c] imides of dicarboxylic acids,[59] tertiary CH-acidic acids,[93] and extremely strong CH_2-acidic compounds,[96] as well as mineral acids, the aminal esters act as a base to give formamidinium salts (eq 27).

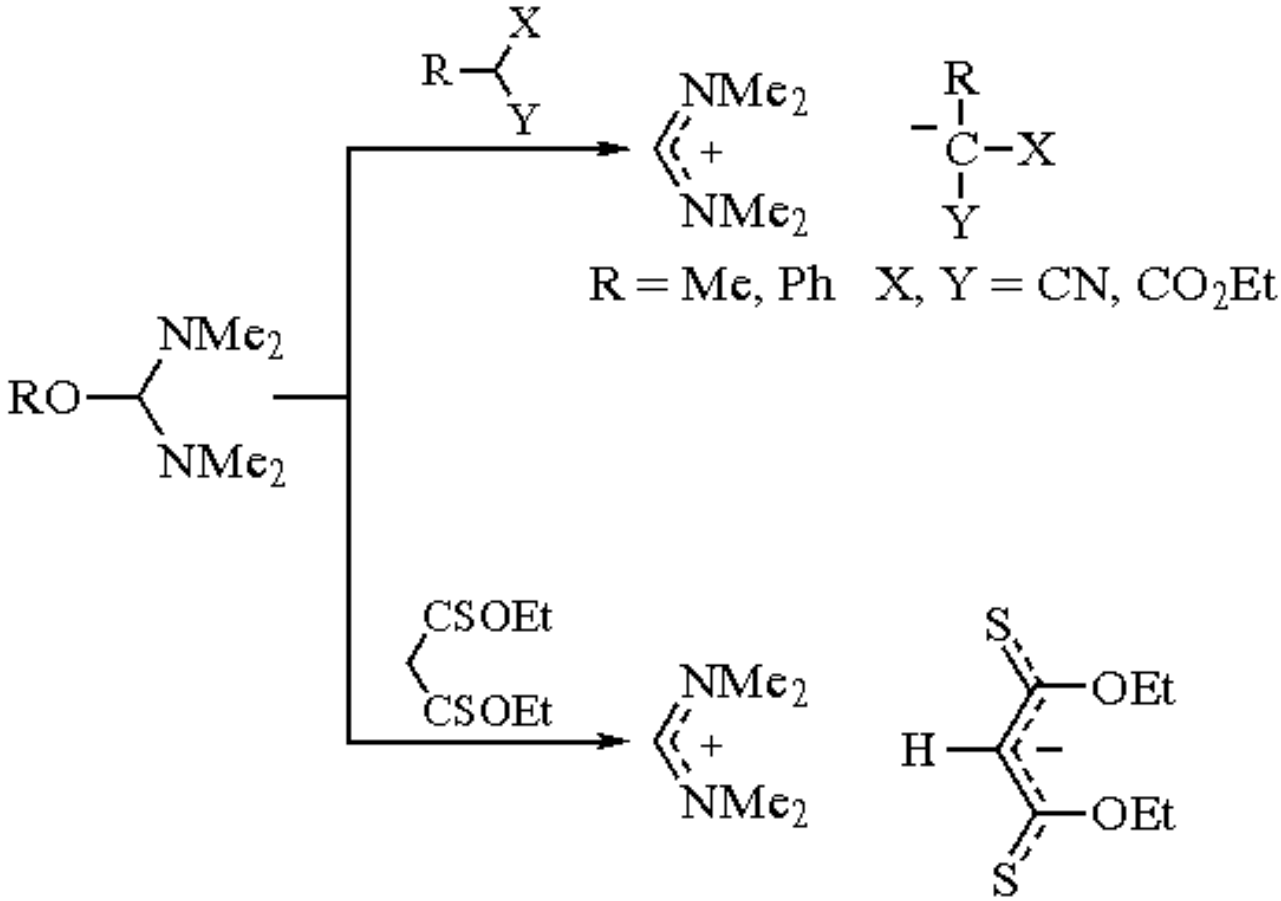

(27)

The strong basicity of *t*-BAE is exploited in the synthesis of methylenedioxybenzenes from catechols and dichloromethane.[97] Electrophilic reagents such as acyl cyanides,[98] acyl azides,[99] CS_2,[1c] isothiocyanates,[100] and *N*-chloroamides[101] undergo a variety of unusual reactions with aminal esters. Although the mechanisms of these interesting reactions have been investigated thoroughly, they are - with a few exceptions - of less importance in the preparative sense because the resulting products are often obtainable with better yields from DMF acetals. Eq 28 gives three examples.

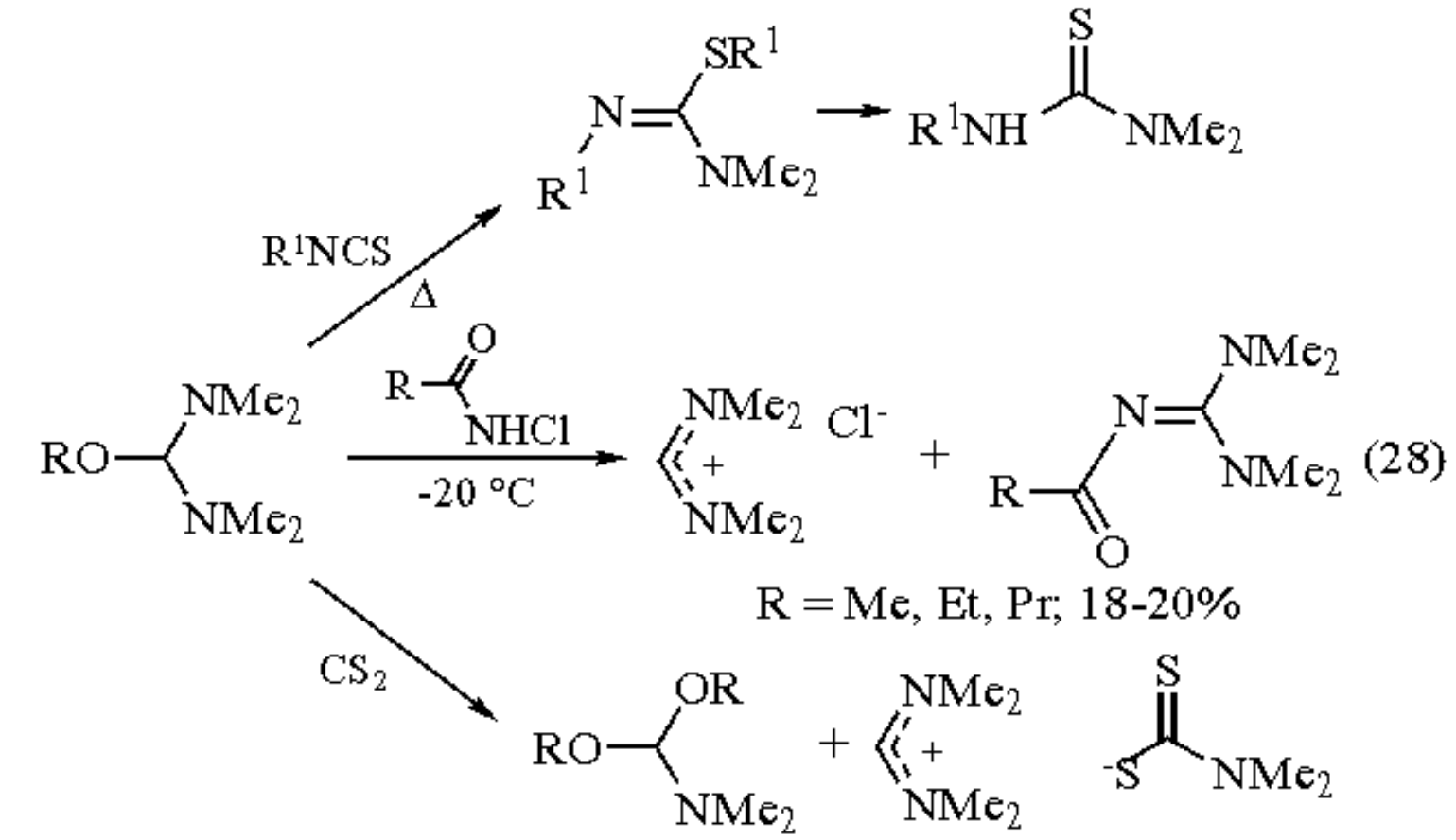

The reaction of *t*-BAE with Schiff bases of aromatic aldehydes, heteroaromatic aldehydes, and benzalazines at temperatures of about 160 °C represents a valuable synthesis of 1,1,2-triaminoethylenes and 1,1-diaminoethylenes (eq 29).[102] The reaction of *t*-BAE with aromatic aldehydes affords mixtures which are not easy to separate (eq 30).[103] 1,2-Diaminoethylene derivatives were isolated from reactions with *p*-tolyl- and anisaldehyde.[104]

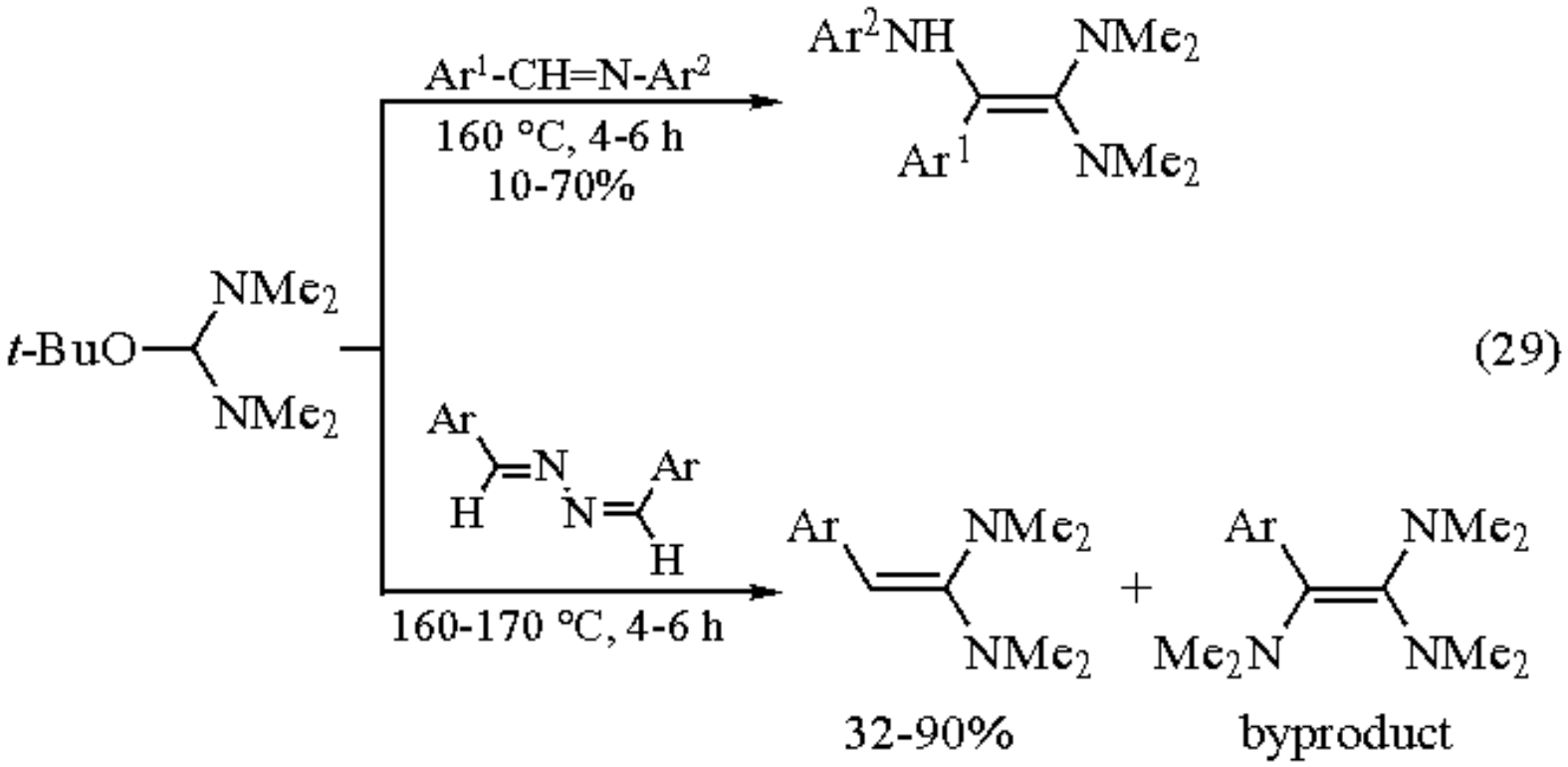

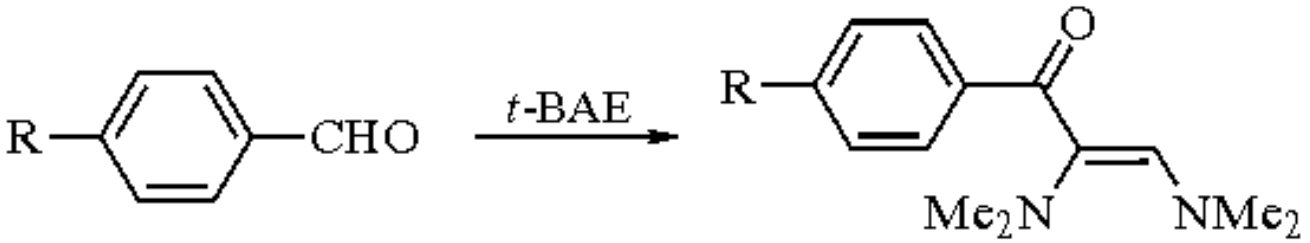

(30)

Heating selenium and *t*-BAE produces *N,N,N´,N´*-tetramethylselenourea.[105] Oxidation of MAE with peroxides affords *N,N,N´,N´*-tetramethylurea,[106,107] whereas with dibutyldiborane *N,N,N´,N´*-tetramethylformaldehydaminal is formed.[108] Formamidinium (dimethylcarbamoyltetracarbonyl)ferrate is obtained from ***Pentacarbonyliron*** and aminal esters (eq 31).[108]

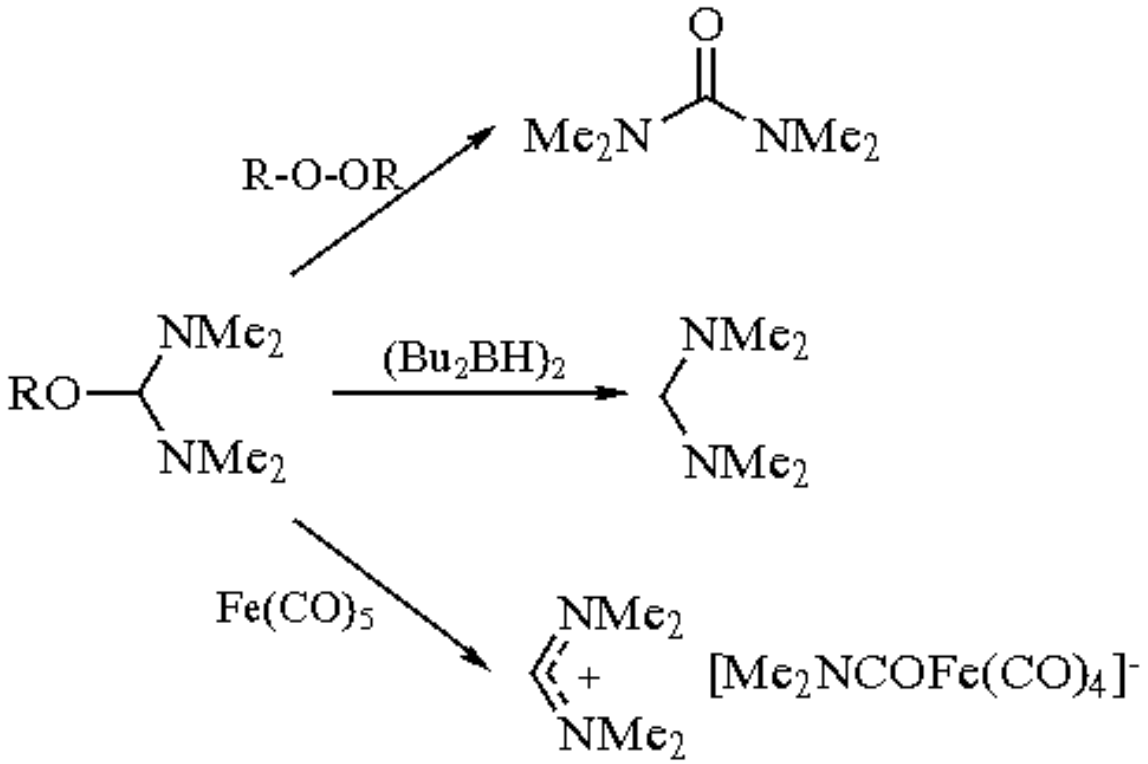

(31)

Related Reagents.

N,N-Dimethylformamide; ***N,N-Dimethylformamide Diethyl Acetal***; ***Tris(dimethylamino)methane***; ***Tris(formylamino)methane***; ***Dimethylchloromethyleneammonium Chloride***.

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4-*t*-Butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one[1]

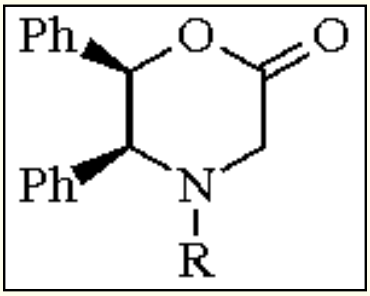

(5*R*,6*S*)-(R = *t*-Boc)

[112741-50-1] · $C_{21}H_{23}NO_4$ · 4-*t*-Butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one · (MW 353.45) (5*S*,6*R*)-(R = *t*-Boc)

[112741-49-8] (5*R*,6*S*)-(R = Cbz)

[105228-46-4] · $C_{24}H_{21}NO_4$ · 4-Benzyloxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-one · (MW 387.46) (5*S*,6*R*)-(R = Cbz)

[100516-54-9]

(chiral glycine enolate equivalent useful for the preparation of α-substituted α-amino acids and α,α-disubstituted α-amino acids in high enantiomeric excess[2,3])

Alternate Name: t-butyl 6-oxo-2,3-diphenyl-4-morpholinecarboxylate.

Physical Data: R = *t*-Boc: mp 206 °C. R = Cbz: mp 205 °C.

Solubility: sol THF, CH_2Cl_2.

Form Supplied in: commercially available as the individual enantiomers or as racemates.

Preparative Method: via a three-step procedure from *erythro*-2-amino-1,2-diphenylethanol.[4]

Handling, Storage, and Precautions: no special handling required.

α-Substituted α-Amino Acids.

The *N*-protected 5,6-diphenyl-2,3,5,6-tetrahydrooxazin-2-ones serve as chiral nucleophilic glycine equivalents by deprotonation at C-3 to give the corresponding enolates.[2,3] The enolates are formed using ***Lithium Hexamethyldisilazide*** or ***Sodium Hexamethyldisilazide*** in THF at low temperature.[2] Alkylation is best achieved by addition of the base to a solution of the oxazinone and electrophile in THF-HMPA (10:1) at -78 °C (eq 1)[2a] or by formation of the sodium enolate in the presence of ***15-Crown-5*** at -78 °C and subsequent addition of the electrophile (eq 2).[3] Alkylation takes place with very high stereoselectivity to afford the C-3 modified oxazinone with the new substituent oriented *anti* to the C-5 and C-6 phenyl groups.[2]

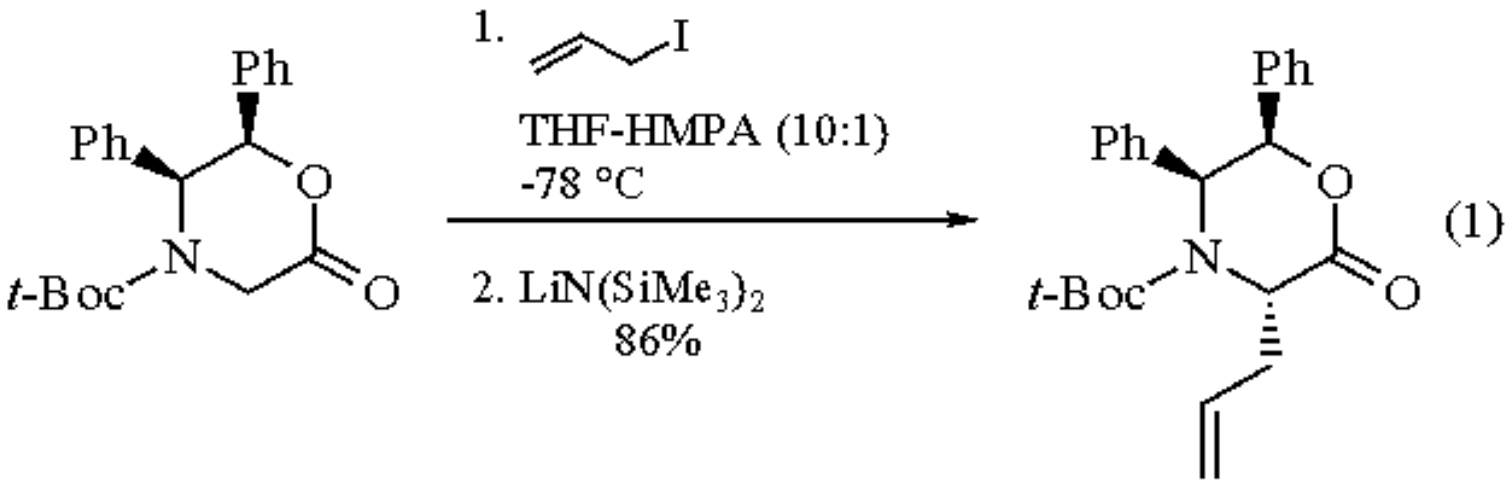

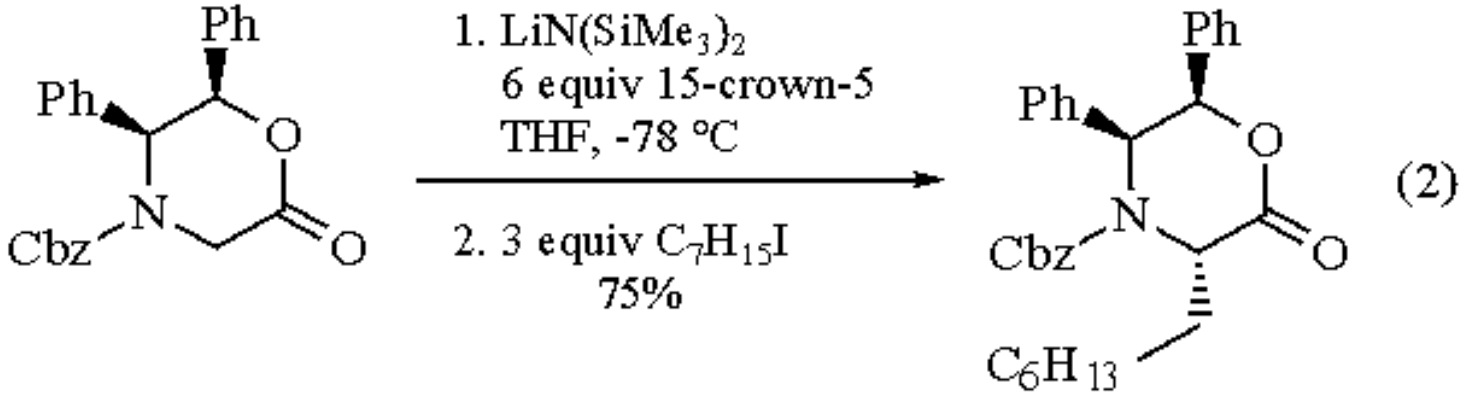

The amino acid is released by scission of the benzylic carbon-heteroatom bonds, generally via a reductive process.[2-5] Hydrogenolysis and dissolving metal reduction of the Cbz-protected oxazinone gives the amino acid zwitterion directly (eq 3). The *t*-Boc protected oxazinone undergoes dissolving metal reduction to give the *t*-Boc amino acid (eq 4). Alternatively, the *t*-Boc group can be removed from the oxazinone by treatment with ***Iodotrimethylsilane*** or ***Trifluoroacetic Acid*** and the resulting compound can then be hydrogenated to afford the amino acid zwitterion. Amino acids possessing alkyl, allyl, (ethoxycarbonyl)methyl, hydroxyalkyl, o-aminoalkyl, and methyl-β-D-ribofuranose functionality have been prepared via this enolate chemistry.[2,3,6,7]

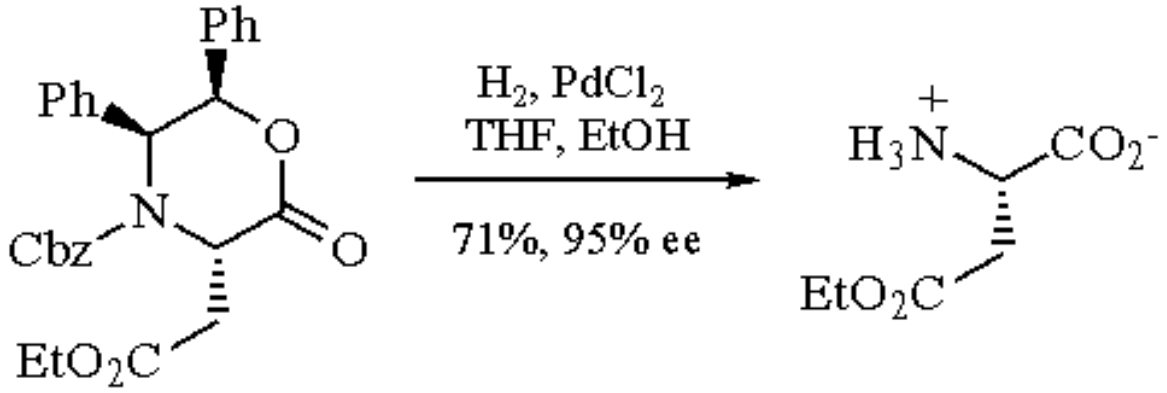

(3)

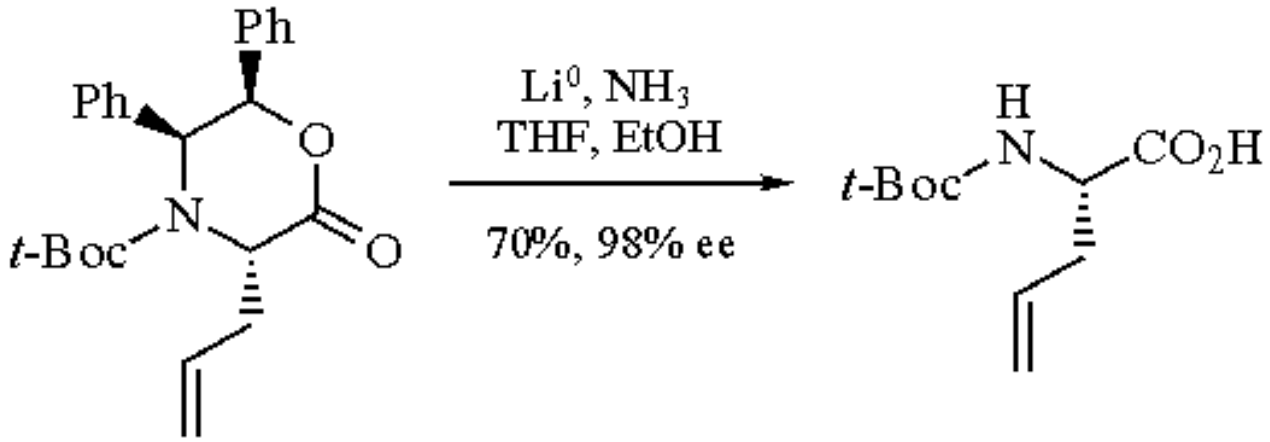

(4)

α,α-Disubstituted α-Amino Acids.

The 3-alkyloxazinones also undergo enolization and subsequent alkylation to afford, upon deprotection, α,α-dialkyl α-amino acids.[2a,3,8,9a] Again, the newly introduced alkyl group is oriented *anti* to the phenyl groups of the oxazinone. Alkylation by addition of the base to a solution of the oxazinone and electrophile works only with allylic and benzylic halides and can require as much as 2-5 equiv of ***Potassium Hexamethyldisilazide*** (eq 5).[2a,8] Alternatively, formation of the sodium enolate in the presence of 15-crown-5 followed by addition of the electrophile permits coupling of the enolate even to simple alkyl halides (eq 6).[3,9a] The disubstituted amino acids are liberated as described above (eq 7).

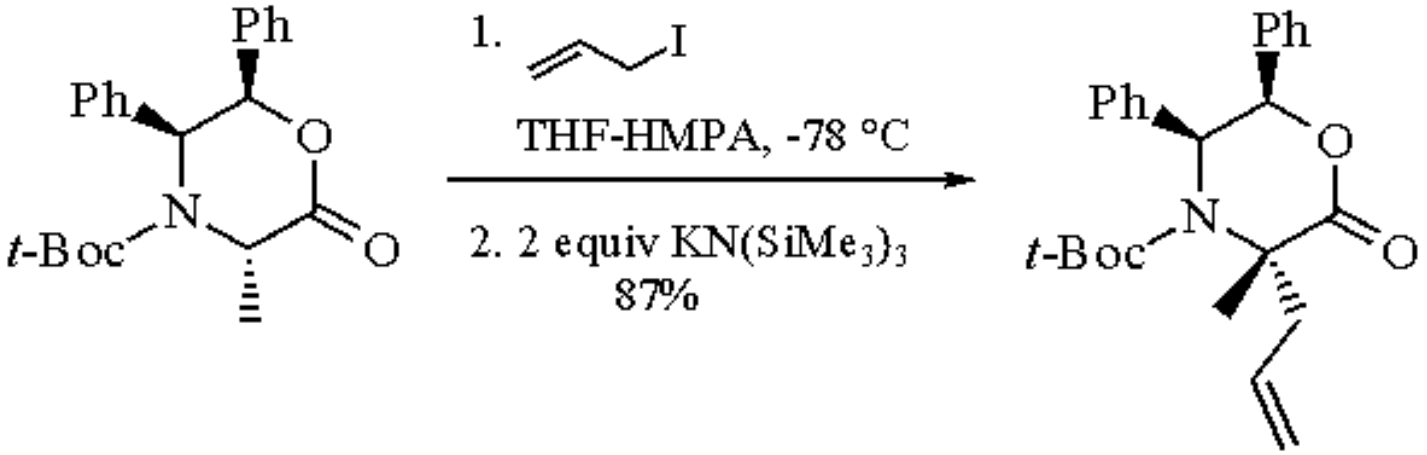

(5)

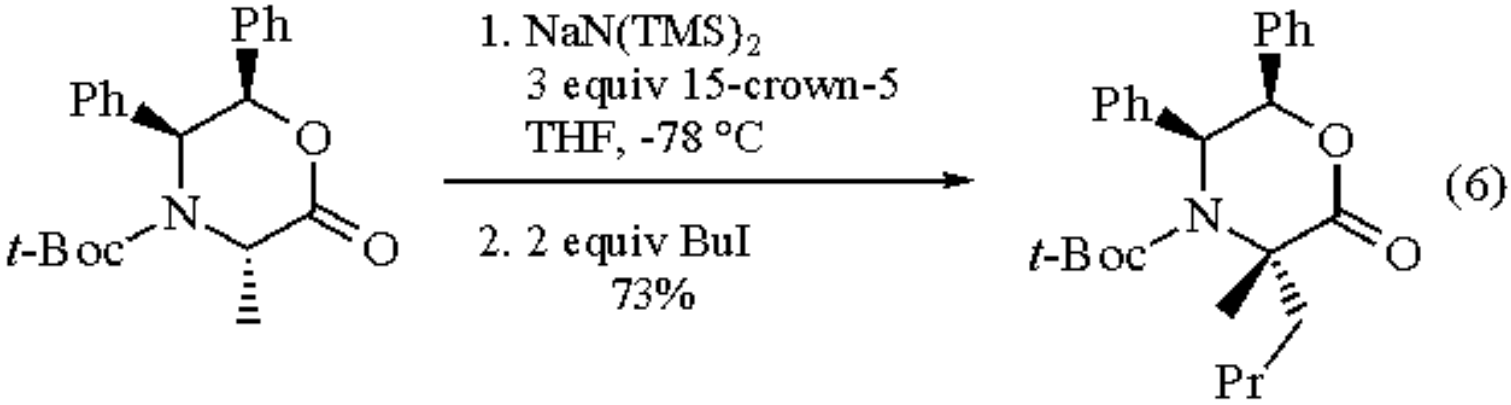

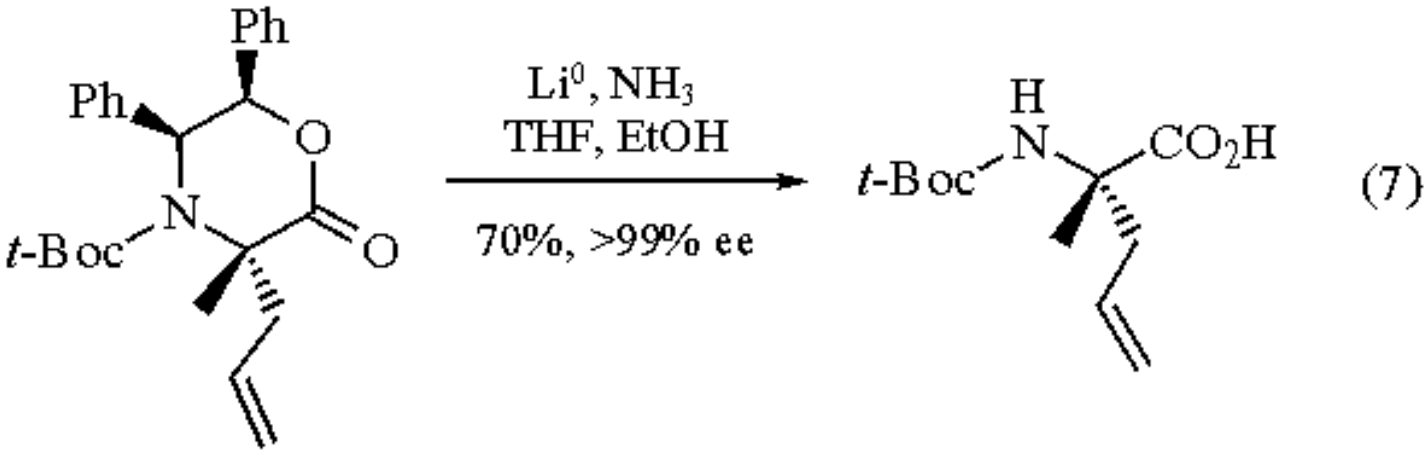

Boron Enolates.

The oxazinones can be converted to their corresponding boron enolates by treatment with ***Di-n-butylboryl Trifluoromethanesulfonate*** and ***Triethylamine*** in CH_2Cl_2.[9] The boron enolates react with aldehydes at -78 °C to give β-(hydroxy)alkyl-substituted oxazinones. Condensation of the boron enolate with acetaldehyde followed by recrystallization of the major product and then deprotection affords allothreonine (eqs 8 and 9).[9c] This approach has been used in the asymmetric synthesis of diaminopimelic acid and derivatives thereof.[9a,b]

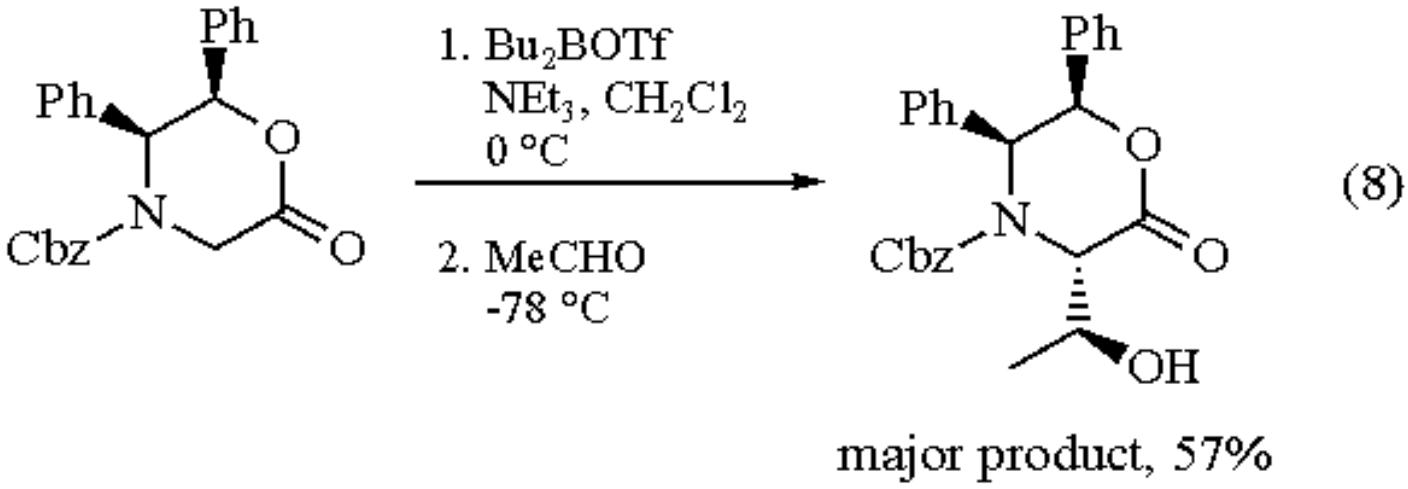

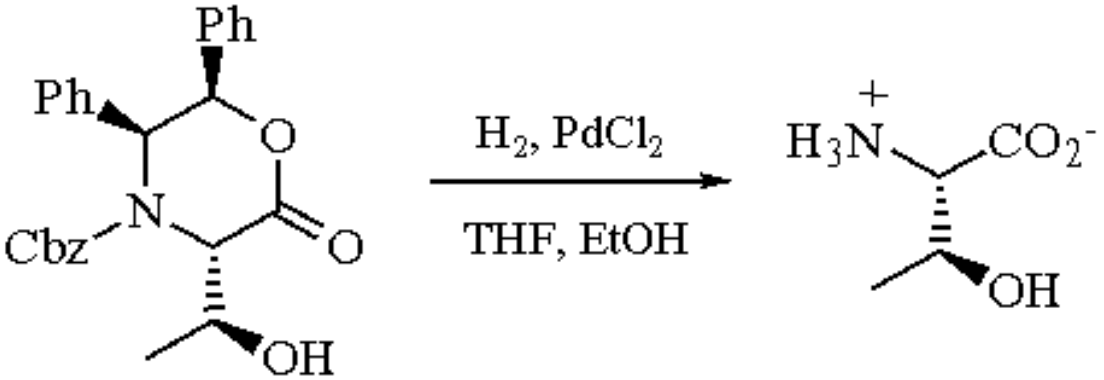

(9)

[3 + 2] Dipolar Cycloadditions.

Highly substituted proline derivatives can be prepared by removal of the *t*-Boc protecting group from the oxazinone followed by condensation of the heterocycle with an aldehyde in the presence of ***p-Toluenesulfonic Acid*** in benzene. Under these conditions, Schiff base formation and ylide generation occur. Subsequent [3 + 2] cycloaddition with a dipolarophile affords the bicyclic heterocycle, which is then deprotected to yield the desired proline derivative (eqs 10 and 11).[10]

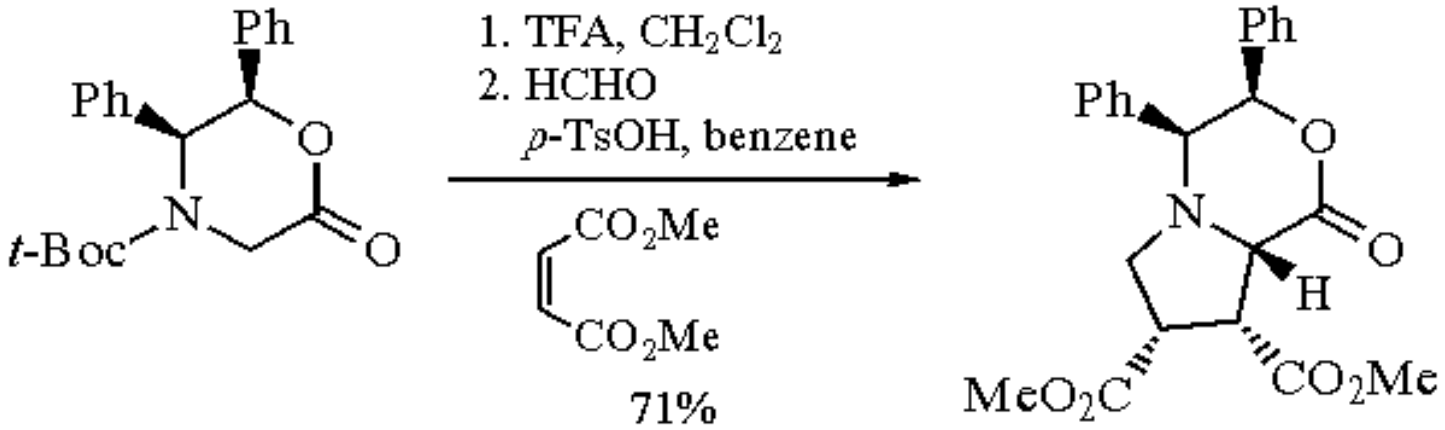

(10)

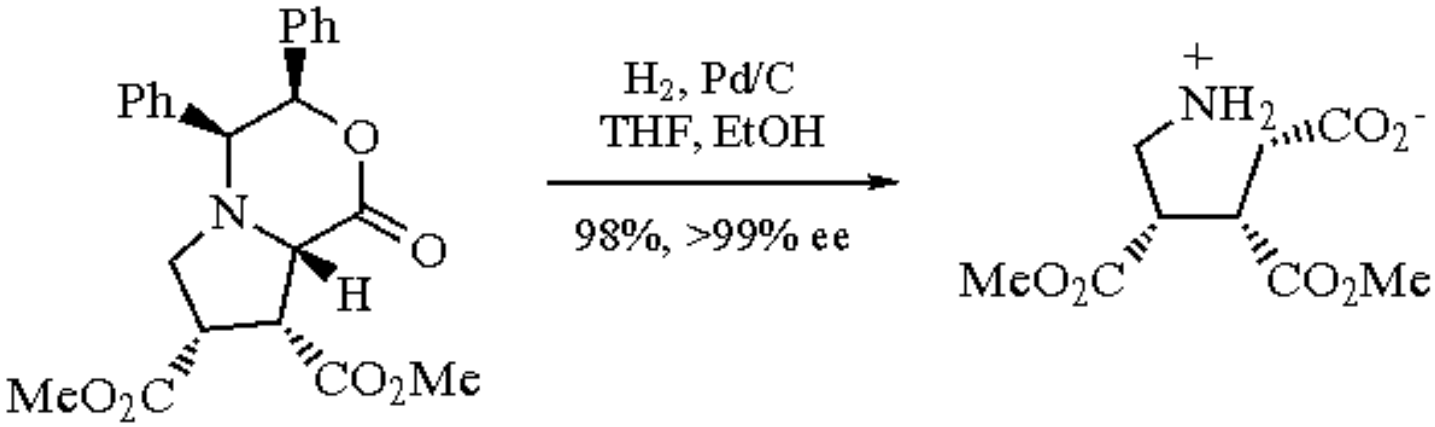

(11)

Related Reagent.

For the complementary synthesis of α-substituted α-amino acids via a chiral electrophilic glycine equivalent, see ***3-***

Bromo-5,6-diphenyl-2,3,5,6-tetrahydro-4H-oxazin-2-one.

---

1. (a) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (b) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon: Oxford, 1989.
2. (a) Williams, R. M.; Im, M.-N. *JACS* **1991**, *113*, 9276. (c) Williams, R. M.; Im, M.-N. *TL* **1988**, *29*, 6075.
3. Baldwin, J. E.; Lee, V.; Schofield, C. J. *SL* **1992**, 249.
4. (a) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *JACS* **1988**, *110*, 1547. (b) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *JACS* **1986**, *108*, 1103.
5. For an oxidative deprotection see: Williams, R. M.; Hendrix, J. A. *JOC* **1990**, *55*, 3723.
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7. Dudycz, L. W. *Nucleosides Nucleotides* **1991**, *10*, 329.
8. Baldwin, J. E.; Lee, V.; Schofield, C. J. *H* **1992**, *34*, 903.
9. (a) Williams, R. M.; Yuan, C. *JOC* **1992**, *57*, 6519. (b) Williams, R. M.; Im, M.-N.; Cao, J. *JACS* **1991**, *113*, 6976. (c) Reno, D. S.; Lotz, B. T.; Miller, M. J. *TL* **1990**, *31*, 827.
10. Williams, R. M.; Zhai, W.; Aldous, D. J.; Aldous, S. C. *JOC* **1992**, *57*, 6527.

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1-(*t*-Butoxycarbonyl)imidazole

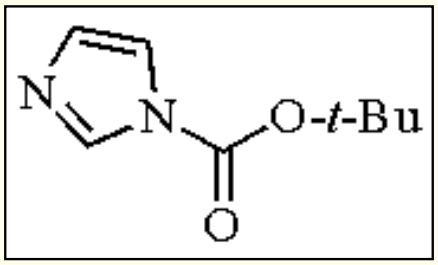

[49761-82-2] · $C_8H_{12}N_2O_2$ · 1-(*t*-Butoxycarbonyl)imidazole · (MW 168.20)

(a reagent for the introduction of the *t*-butoxycarbonyl group at nucleophilic sites[1])

Physical Data: mp 44.5-47 °C; bp 64 °C/1 mmHg.

Solubility: sol CH_2Cl_2, $CHCl_3$, THF, hexane, acetone, and DMF, among others.

Form Supplied in: not commercially available.

Preparative Method: 1-(*t*-butoxycarbonyl)imidazole (**1**) can be prepared from the reaction of imidazole and 1,2,2,2-tetrachloroethyl-*t*-butyl carbonate[1a] or the reaction of *t*-butanol and *N,N´*-carbonyldiimidazole[1b] in high yield. The reagent has been reported to be stable at rt.[2]

Handling, Storage, and Precautions: anhydrous conditions are recommended.

t-Butoxycarbonylation.

The amine functions of various amino acids have been protected with the *t*-butoxycarbonyl (Boc) group by (**1**) (eq 1).[1b,3] Polar anhydrous organic solvents have been used in general, although traces of moisture can be tolerated.

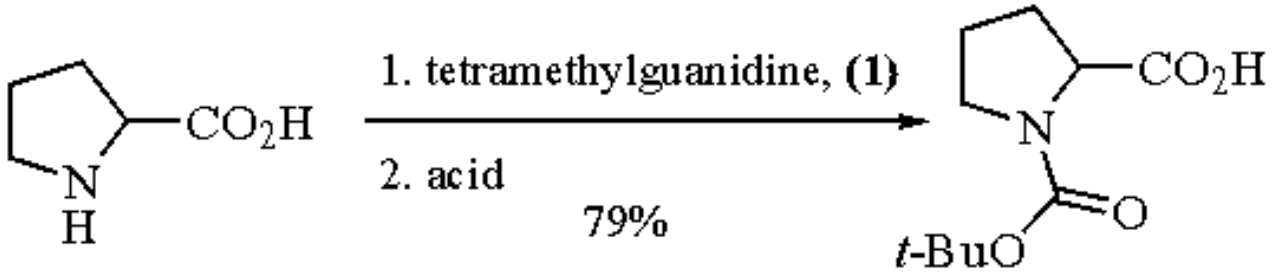

(1)

Alkylation of (**1**), or its silver perchlorate complex, produces water-soluble imidazolium salts with enhanced

electrophilic character (eq 2).[4] The perchlorate and tetrafluoroborate salts of this type are remarkably stable and they have been used to protect amino acids in aqueous media (eq 3).[4]

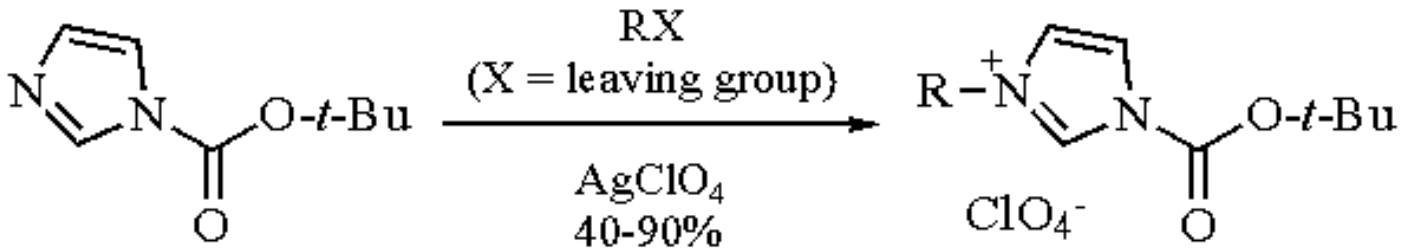

(2)

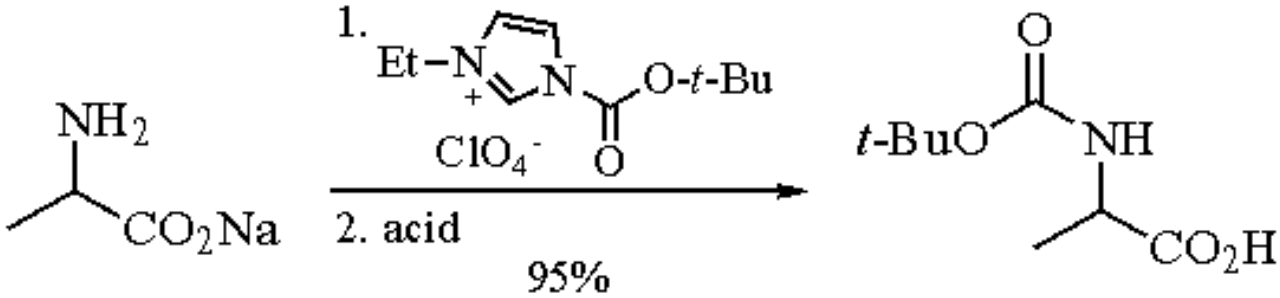

(3)

Selective protection of a single amine in alkyl diamines by (**1**) is reported (eq 4).[5] Furthermore, the reaction of ***Hydrazine*** with (**1**) affords *t*-butoxycarbonylhydrazide, which is a useful reagent in peptide chemistry.[1b]

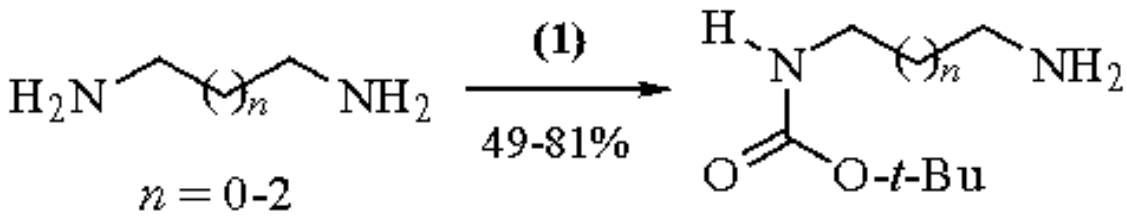

(4)

Incorporation of the Boc group at the aromatic nitrogen of the pyridine ring system (eq 5)[6] and at a carbon nucleophile (eq 6)[7] by (**1**) has also been reported.

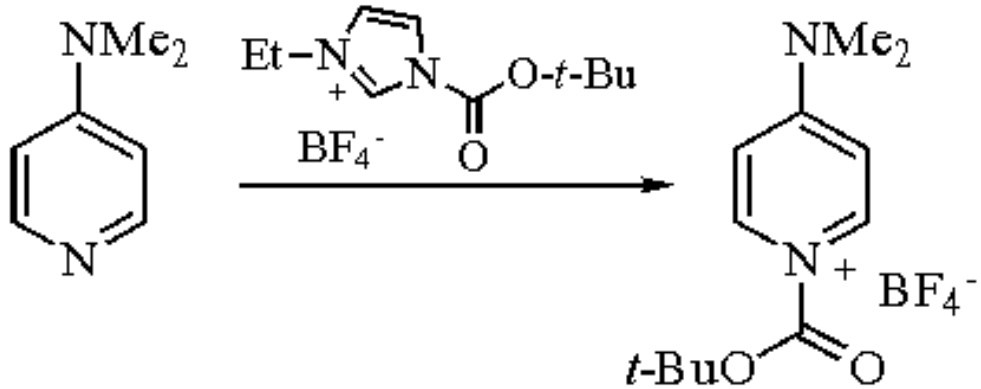

(5)

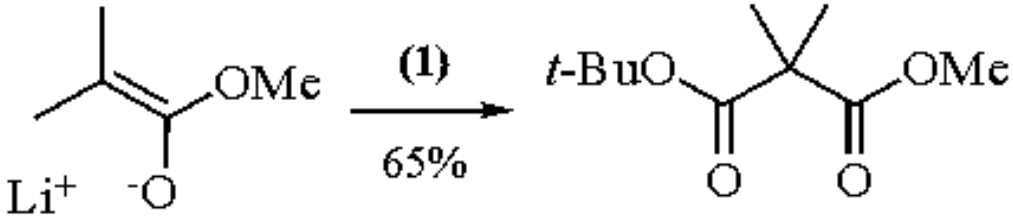

(6)

Formation of *O*-Alkylperoxycarbonic Acids.

Epoxidation of alkenes in a biphasic system could be performed by in situ generation of *O*-alkylperoxycarbonic acids (eq 7).[2] The reaction is typically carried out by the addition of 35% ***Hydrogen Peroxide*** to a solution of (**1**) and the alkene substrate in an organic solvent. The epoxide of cholesteryl acetate was prepared quantitatively in a 3:1 ratio of α- to β-epoxide by this method.

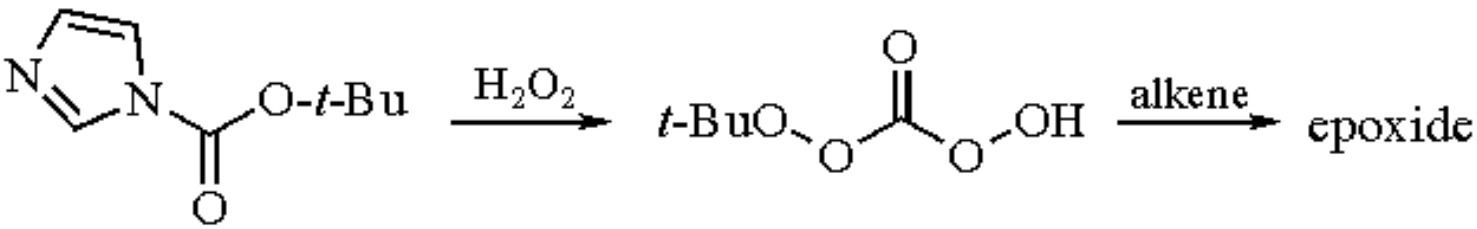

(7)

Related Reagents.

1-t-Butoxycarbonyl-1,2,4-triazole.

---

1. (a) Barcelo, G.; Senet, J. P.; Sennyey, G. *JOC* **1985**, *50*, 3951. (b) Klee, W.; Brenner, M. *HCA* **1961**, 2151.
2. Tsunokawa, Y.; Iwasaki, S.; Okuba, S. *TL* **1982**, *23*, 2113.
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7. Bourgeois, M. J.; Montaudon, E.; Campagnole, M.; Maillard, B. *BSB* **1982**, *91*, 871.

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N-t-Butoxycarbonyl-*N*-methylaminomethyllithium[1]

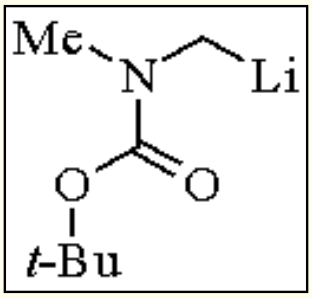

[-] · $C_7H_{14}LiNO_2$ · *N-t*-Butoxycarbonyl-*N*-methylaminomethyllithium · (MW 151.13)

(α-amino carbanion nucleophile for displacement and addition reactions[1])

Alternate Name: N-Boc-α-lithiodimethylamine.

Preparative Methods: can be prepared by stirring *N*-Boc-dimethylamine with ***s-Butyllithium*** at -50 °C in THF for 2 h. The organolithium reagent reacts with electrophiles to provide substitution products in good yields. *N*-Boc-dimethylamine can be prepared from the reaction of ***Potassium t-Butoxide*** and ***Dimethylcarbamoyl Chloride*** in THF.

α-Amino Organolithium Reagents.

α-Amino organolithium reagents useful for the elaboration of amines via α-amino carbanion synthetic equivalents can be prepared from *N*-Boc secondary amines which bear a methyl or methylene group. The general application of this methodology for amine elaboration is shown in eq (1). Lithio derivatives of *N*-benzyloxycarbonyl (Cbz) and *N*-methoxycarbonyl amines can also be generated by tin-lithium exchange reactions.[2] The generation and use of other *N*-substituted organometallic reagents has been reviewed.[3]

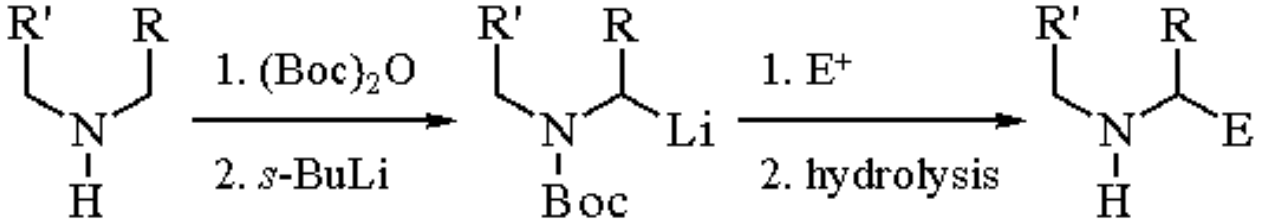

(1)

Conversion to the α-lithioamine synthetic equivalents is achieved by reaction with ***s-Butyllithium*** or *s*-BuLi/***N,N,N´,N´-Tetramethylethylenediamine*** in diethyl ether or THF at low temperatures.[1] Addition of electrophiles provides the α-

substituted *N*-Boc amines in good yields. The *N*-Boc groups can be cleaved under acidic or basic conditions to provide the elaborated secondary amines. It is important that the solvent and reagents be anhydrous and the *s*-BuLi be of good quality. A specific case for the key steps of lithiation and substitution for *t*-butoxycarbonyl-*N*-methylaminomethyllithium is shown in eq (2). Selectivity for the less substituted position is usually observed as shown in eq (3).

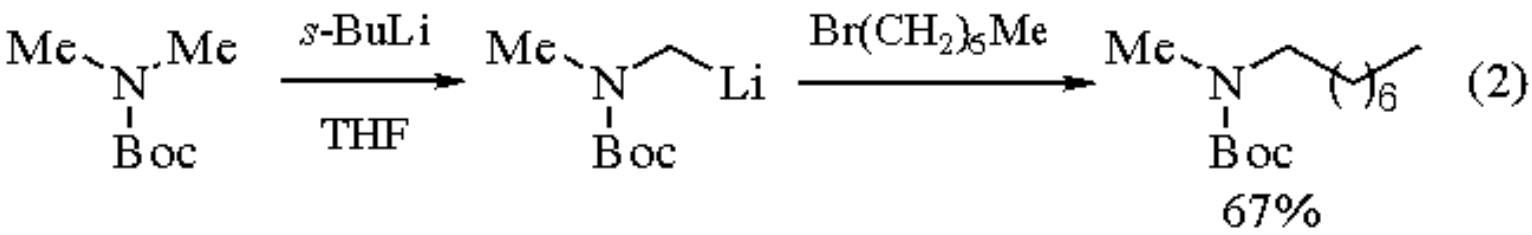

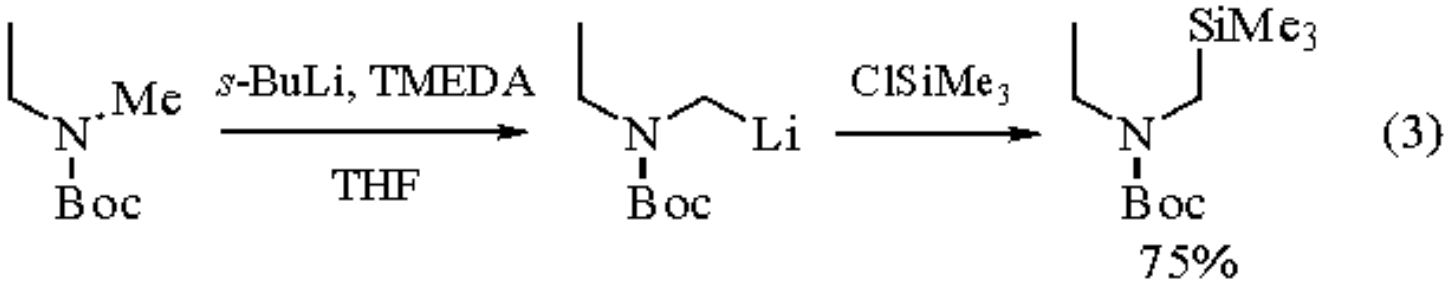

Extensions of this methodology to heterocyclic amines have been achieved with control of stereochemistry. Lithiation of *N*-Boc-piperidine followed by electrophilic substitutions provide 2-substituted *N*-Boc-piperidines. When the electrophile is an aldehyde, the *syn* and *anti* isomers are obtained in ca. 1:1 ratio. Lithiation and substitution of 4-substituted *N*-Boc-piperidines gives diequatorial *cis*-2,4-disubstituted *N*-Boc-piperidines.[4] Lithiation and substitution of 2-substituted *N*-Boc-piperidines provides *trans*-2,6-disubstituted piperidines. The stereochemical outcome is consistent with equatorial lithiation and substitution with retention of configuration of the carbon-lithium bond (eq 4). The 2-substituted *N*-Boc-piperidine undergoes lithiation to generate a 2-axial substituent because of allylic ($A^{1,3}$) strain. This methodology has been used to prepare a 2,6-*trans*-disubstituted piperidine alkaloid, solenopsin A, from *N*-Boc-piperidine.[4] By taking advantage of the equilibration of a *trans*-2,6-disubstituted piperidine to the more stable *cis* isomer, a derivative of a *cis*-2,6-disubstituted piperidine alkaloid, the author also prepared *cis*-dihydropinidine.[5] Similar lithiation-substitution sequences have been reported with *N*-Boc-pyrrolidine and *N*-Boc-perhydroazepine.[5]

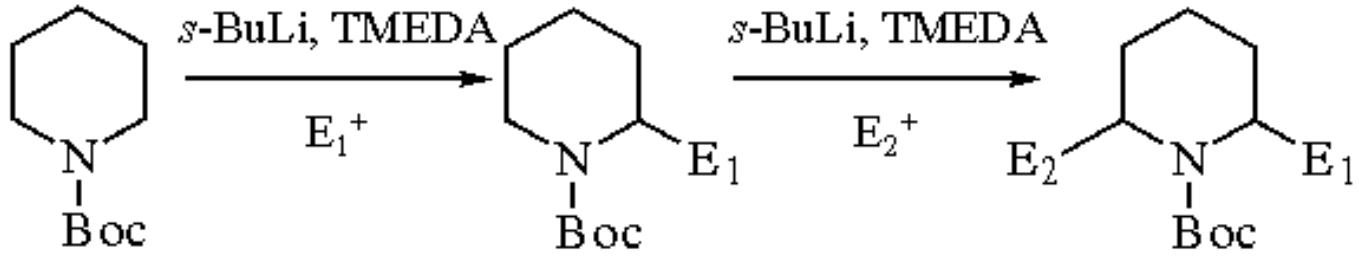

E_1 = Me, 89%; $SiMe_3$, 94%; PhCHOH, 76%; CHO, 65%; CyCHOH, 46%

E_2 = PhCHOH, 96%; CHO, 87% (4)

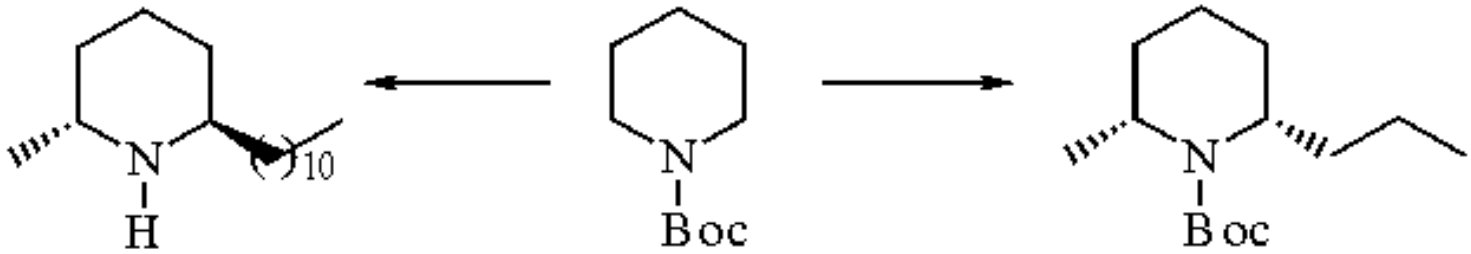

Solenopsin *N*-Boc-dihydropinidine

With a leaving group adjacent to the site of lithiation, elimination can occur followed by a second lithiation; for 3-methoxy-*N*-Boc-piperidine with 2 equiv of *s*-BuLi, *N*-Boc-2-substituted Δ^2-piperidines are obtained (eq 5).[5]

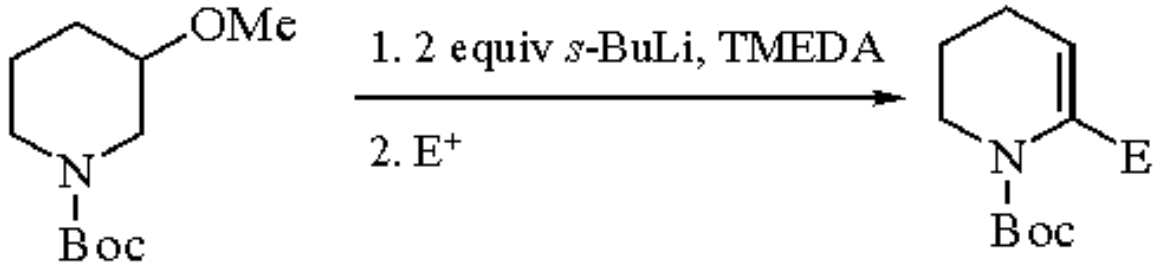

(5)

E = $SnBu_3$, 92%
CHO, 75%
$SiMe_3$, 92%

High enantioselectivities are observed in the lithiation-substitution sequence when *s*-BuLi/***(-)-Sparteine*** is used as the lithiating base for *N*-Boc-pyrrolidine (eq 6).[6] The sequence proceeds by an asymmetric deprotonation to provide an enantioenriched organolithium intermediate which maintains configuration and reacts with electrophiles stereoselectively to give highly enantioenriched products.[6] Repetition of this sequence for a second substitution with enantioenriched reactant gives a substantial amplification of enantioenrichment of (*S*,*S*)-2,5-dimethyl-*N*-Boc-pyrrolidine (eq 7).[7]

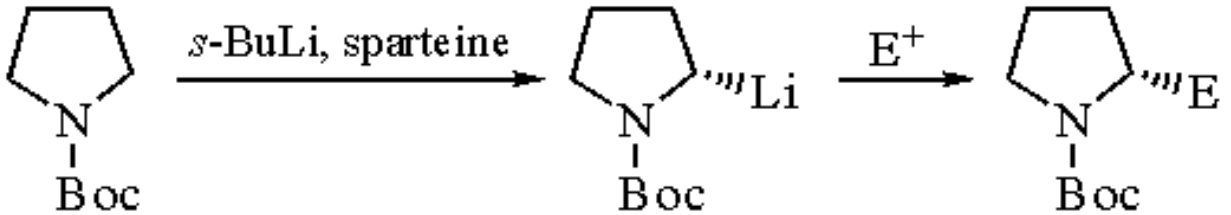

(6)

E = $SiMe_3$, 87%, 96% ee
Ph_2COH, 75%, 90% ee
CO_2Et, 55%, 88% ee
Me, 88%, 95% ee

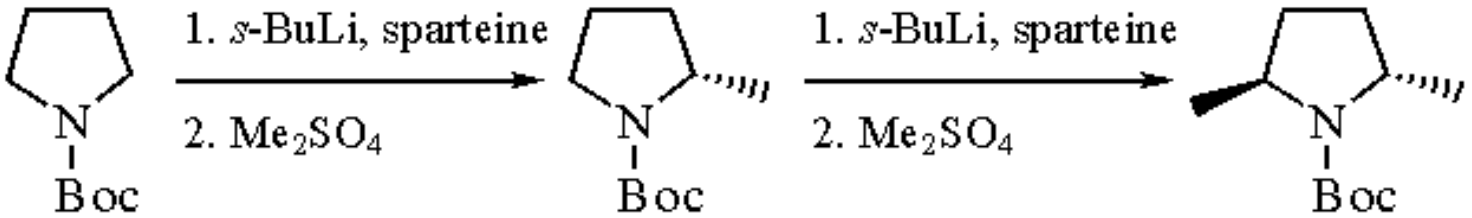

(7)

95% ee >99% ee

Related Reagents.

Diphenyl(methoxymethyl)phosphine; ***s-Butyllithium***; ***Dimethylaminomethyllithium***; ***N-Nitrosodimethylamine***; ***N,N,N´,N´-Tetramethylethylenediamine***.

---

1. Beak, P.; Lee, W. K. *TL* **1989**, *30*, 1197.
2. (a) Pearson, W. H.; Lindbeck, A. C. *JOC* **1989**, *54*, 5651. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *JACS* **1993**, *115*, 2622.
3. For summaries of related methodology, see (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *CRV* **1984**, *84*, 471. (b) Gawley, R. E.; Rein, K. *COS*, **1991**, *1*, 65, 459. (c) Hart, D. J. In *Alkaloids; Chemical and Biological Perspectives*, Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, p 227. (d) Hishsmith, T. K.; Meyers, A. I. In *Advances in Heterocyclic Natural Products Synthesis*; Pearson, W. H., Ed.; JAI: Greenwich, CT, 1990; Vol. 1, p 94.
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7. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *JACS* **1994**, *116*, 3231.

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1-*N*-(*t*-Butoxycarbonyl)-1*H*-benzotriazole 3-*N*-Oxide

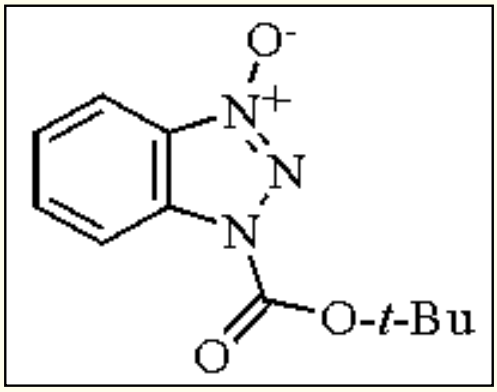

[111615-82-8] · $C_{11}H_{13}N_3O_3$ · 1-*N*-(*t*-Butoxycarbonyl)-1*H*-benzotriazole 3-*N*-Oxide · (MW 235.27)

(a reagent for protection of amines with the *t*-butoxycarbonyl group[1])

Physical Data: mp 105 °C.

Solubility: sol DMF, CH_2Cl_2, and dioxane, among others.

Form Supplied in: the reagent is a white solid; however, it is not commercially available.

Handling, Storage, and Precautions: anhydrous conditions are not necessary for reactions, and the reagent can be stored at rt.

Introduction.

The subject of this review was believed initially to be 1-*N*-(*t*-butoxycarbonyloxy)benzotriazole. However, a single-crystal X-ray analysis established the structure unequivocally as 1-*N*-(*t*-butoxycarbonyl)-1*H*-benzotriazole 3-*N*-oxide (**1**). It is likely that initially the carbonate, i.e. 1-*N*-(*t*-butoxycarbonyloxy)benzotriazole, is formed, and it then rearranges to the more stable carbamate (**1**). Two syntheses for (**1**), which actually had been originally targeted for 1-*N*-(*t*-butoxycarbonyloxy)benzotriazole, are reported. In the first synthesis, ***1-Hydroxybenzotriazole*** is converted to its chloroformate, which in turn is allowed to react with *t*-butanol to give 1-*N*-(*t*-butoxycarbonyloxy)benzotriazole (eq 1).[1] In the second synthesis, 1-hydroxybenzotriazole is deprotonated by ***Triethylamine***, and subsequent mixing with ***Di-t-butyl Dicarbonate*** affords the carbonate which rearranges to (**1**) (eq 2).[2]

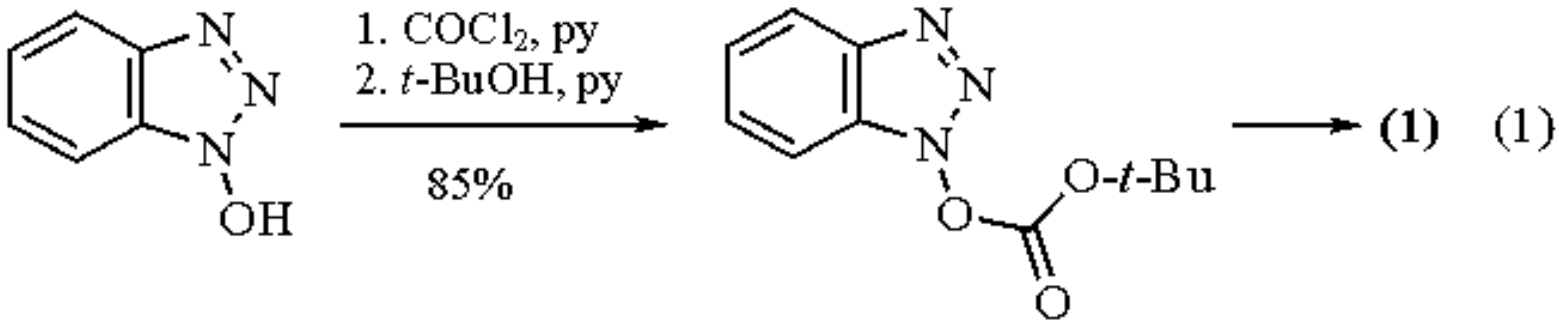

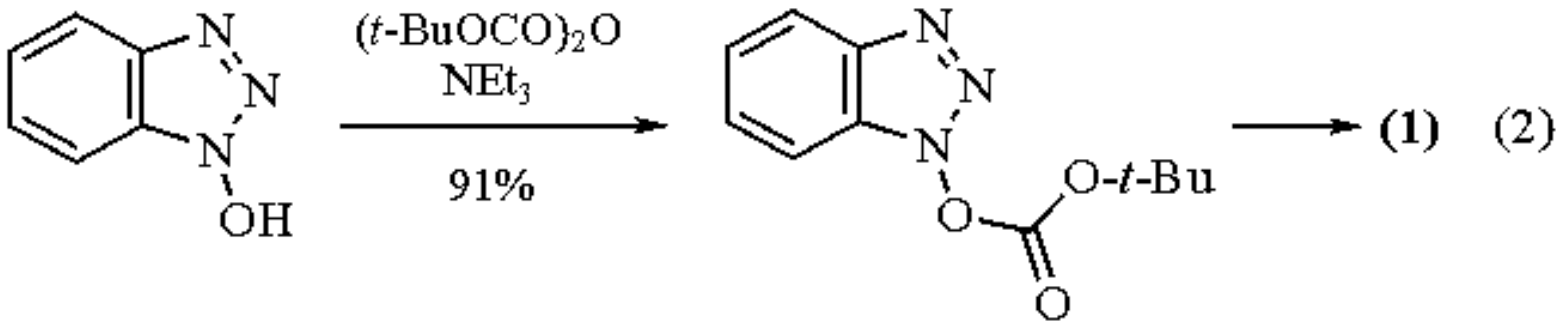

t-Butoxycarbonylation.

Reagent (**1**) is exceptionally effective in N-protection of amino acids. For example, when 1 equiv of the reagent was added to a solution of L-proline and triethylamine in aqueous dioxane, an essentially quantitative conversion to the corresponding N-Boc amino acid took place in under 1 min.[1] The reaction in aqueous DMF proceeds somewhat more sluggishly; however, the reaction reaches completion within 30 min. The speed of these reactions is in sharp contrast to the more commonly used reagents for *N*-*t*-butoxycarbonylation, such as ***Di-t-butyl Dicarbonate***, ***2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile*** (Boc-ON), 1,2,2,2-tetrachloroethyl *t*-butyl carbonate, or ***t-Butyl Azidoformate***, which usually require from a few hours to overnight reaction duration. The isolated yields for the products of the reactions of several typical amino acids with (**1**) have been reported in the range of 80-99% (eq 3).

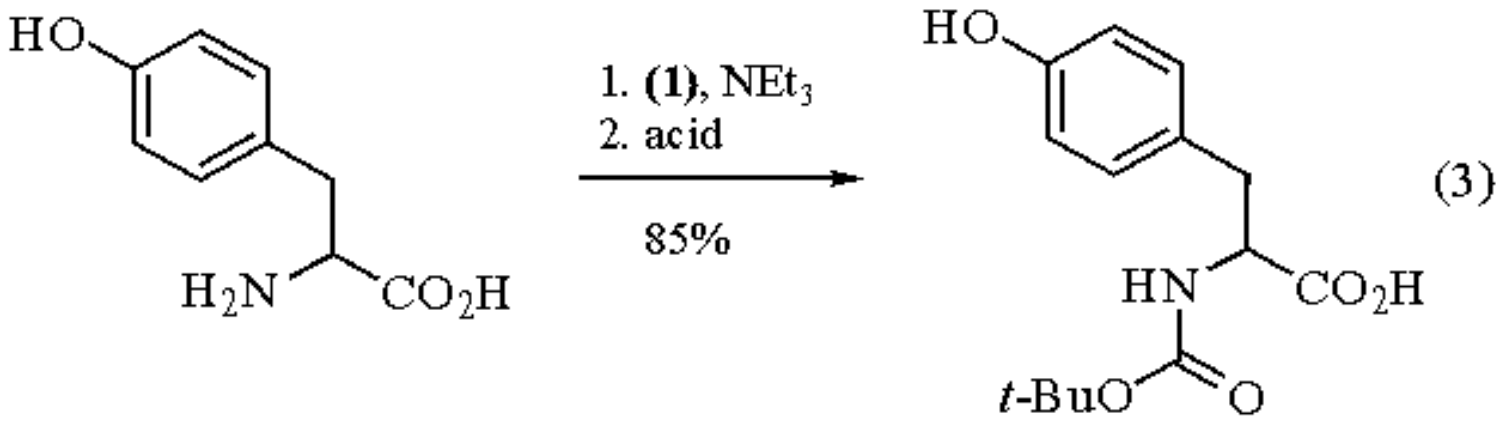

The reaction of (**1**) with simple amines, such as ***Piperidine*** or benzylamine, or even less reactive amines, such as aniline (eq 4) or ***Imidazole***, have been reported.[1] In contrast to the reactions with amino acids, simpler amines appear to require somewhat longer reaction times.

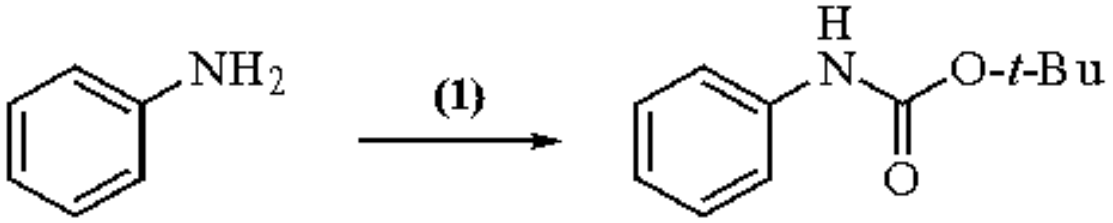

(4)

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1. Kim, S.; Chang, H. *CC* **1983**, 1357. Kim, S.; Chang, H. *Bull. Korean Chem. Soc.* **1986**, *7*, 70.
2. Singh, J.; Fox, R.; Wong, M.; Kissick, T.; Moniot, J.; Gougoutas, J.; Malley, M.; Kocy, O. *JOC* **1988**, *53*, 205.

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2-(*t*-Butoxycarbonyloxyimino)-2-phenylacetonitrile

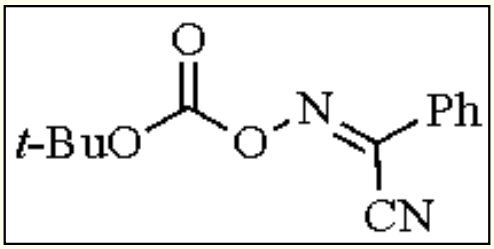

[58632-95-4] · $C_{13}H_{14}N_2O_3$ · 2-(*t*-Butoxycarbonyloxyimino)-2-phenylacetonitrile · (MW 246.27)

(reagent for protection of amino acids as *t*-butyl carbamates[1-3] and for protection of alcohols as *t*-butyl carbonates[4])

Alternate Name: Boc-ON.

Physical Data: mp 87-89 °C.

Solubility: very sol ethyl acetate, ether, benzene, chloroform, dioxane and acetone; sol methanol, 2-propanol, and *t*-butanol; insol petroleum ether and water.

Form Supplied in: solid.

Handling, Storage, and Precautions: contact with the reagent may cause irritation. The toxicological properties of the reagent have not been thoroughly investigated. The reagent should be stored in a brown bottle at -20 °C to prolong shelf life. After several weeks at rt the reagent undergoes gradual decomposition with evolution of CO_2.

Amine Protection.

The reagent, informally referred to as Boc-ON, has been widely employed for the protection of amines as their *t*-butoxycarbonyl (Boc) derivatives. The original description of Boc-ON reports its utility for the N-protection of α-amino acids (eq 1),[1] and this use is still the major application.[5]

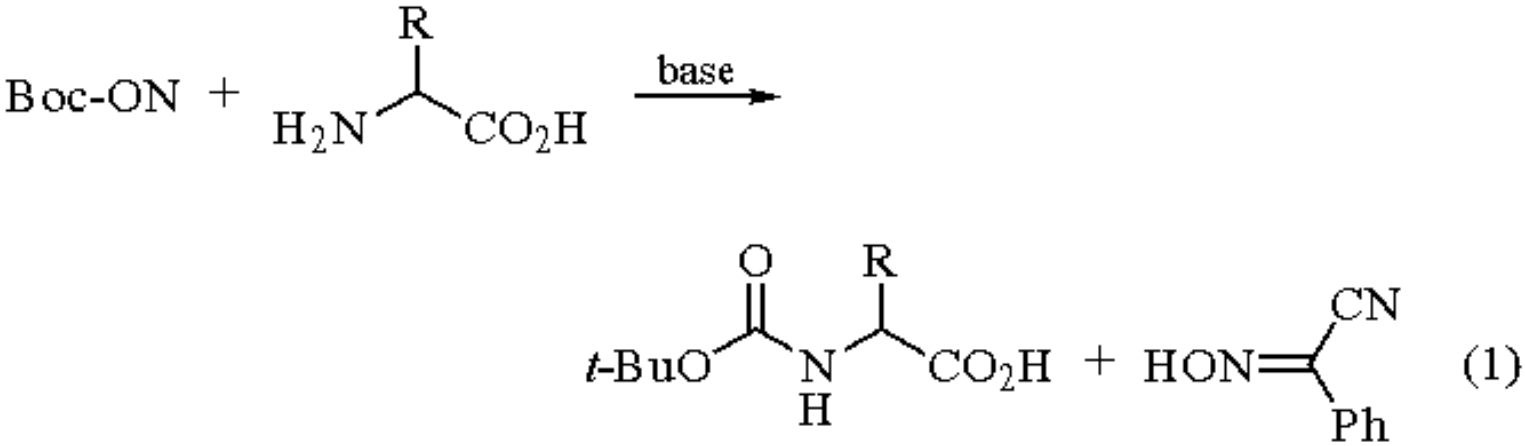

The reaction is generally carried out using 1.1 equiv of Boc-ON and 1.5 equiv of ***Triethylamine*** in either 50% aqueous dioxane or 50% aqueous acetone. Boc derivatives are obtained in high yields after 4-5 h at 20 °C or 1 h at 45 °C. The oxime byproduct (eq 1) can be easily and completely removed from the reaction mixture by extraction with ether, ethyl acetate, or benzene. To secure high purity and high yield, distillation of the dioxane or acetone prior to extraction of the oxime byproduct is recommended, though direct extraction may be feasible in most cases. Yields for various amino acids range from good to virtually quantitative (Table 1).

Table 1 Examples of Boc-Amino Acids Prepared with Boc-ON[2]

Boc-amino acid	Reaction time (h)	Oxime extraction solvent	Yield (%)
Ala-OH	4	Ether	80
Asn-OH	20	EtOAc	86
$Glu(OH)_2$	3	EtOAc	78
Gly-OH	2	EtOAc	87
Leu-OH·$0.5H_2O$	3	Ether	99
Met-OH·DCHA[a]	3	EtOAc	82
Phe-OH·DCHA[a]	5	Ether	98
Pro-OH	1.5	Benzene	88
Trp-OH	3	EtOAc	99

[a] DCHA = dicyclohexylamine.

Boc-ON offers a distinct advantage over *t*-Boc azide which can require reaction temperatures of 50-60 °C.[6] In addition, *t*-Boc azide is thermally unstable and decomposes with apparent detonation at temperatures above 80 °C. Boc-ON is comparable to ***Di-t-butyl Dicarbonate*** in terms of reaction times, yields, convenience, availability, and work-up

procedure.[7]

Boc-ON has also been employed for the protection of secondary amines (eqs 2 and 3).[8,9]

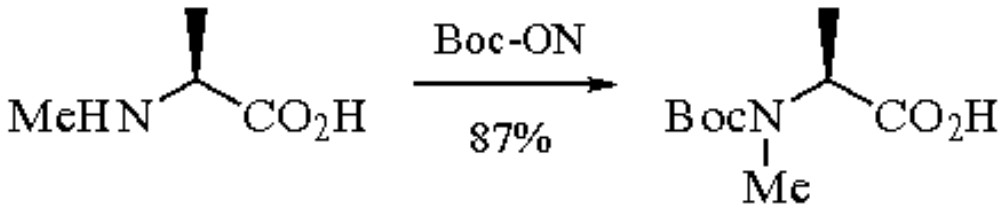

(2)

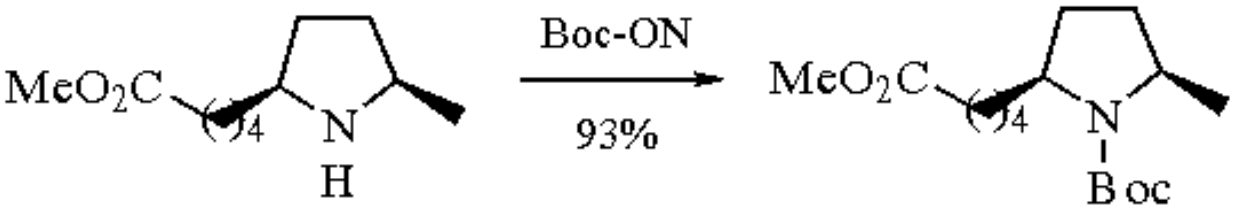

(3)

The reagent will selectively protect the amino group in the presence of alcohols and phenols as well as carboxylic acids. Examples include the Boc protection of a kanamycin A derivative (eq 4)[10] and of the glycopeptide antibiotic A41030A (eq 5).[11]

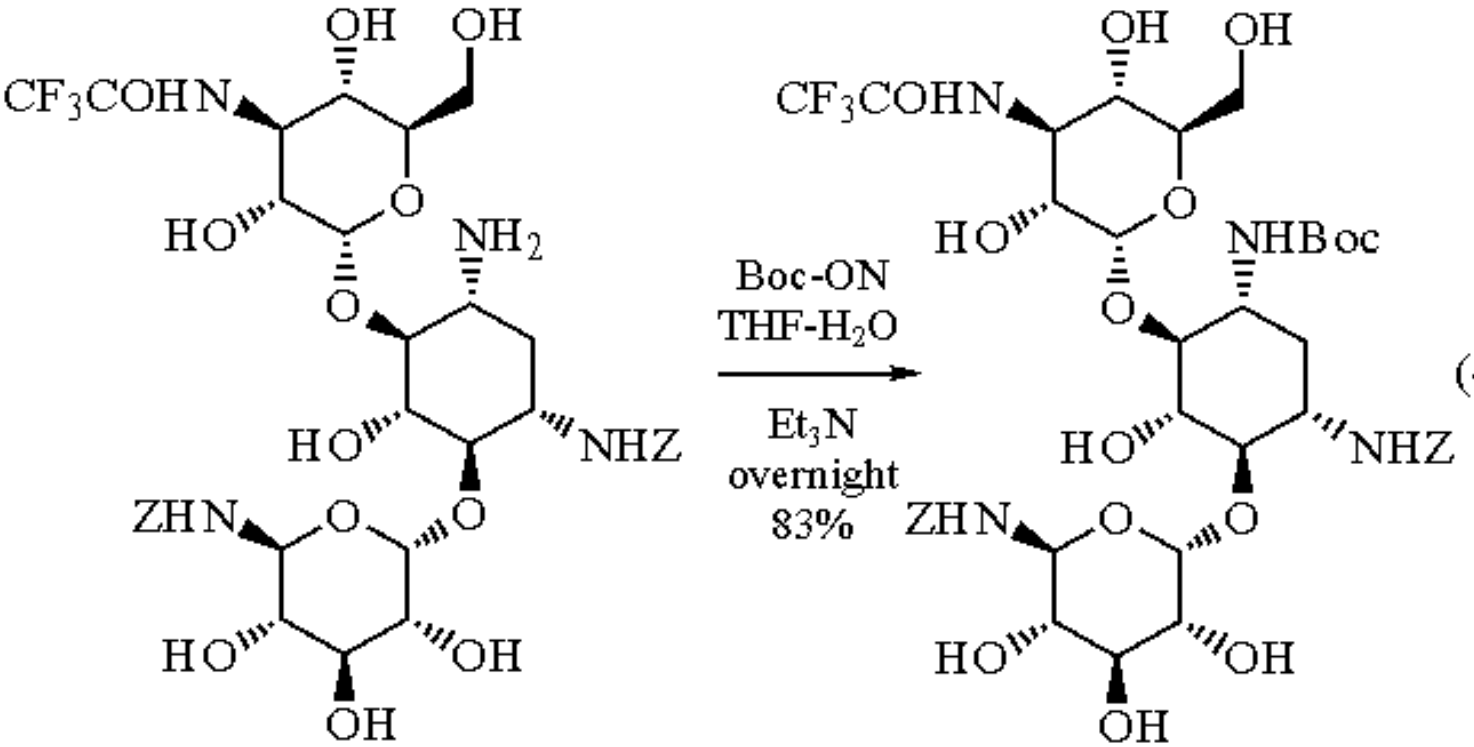

(4)

2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile

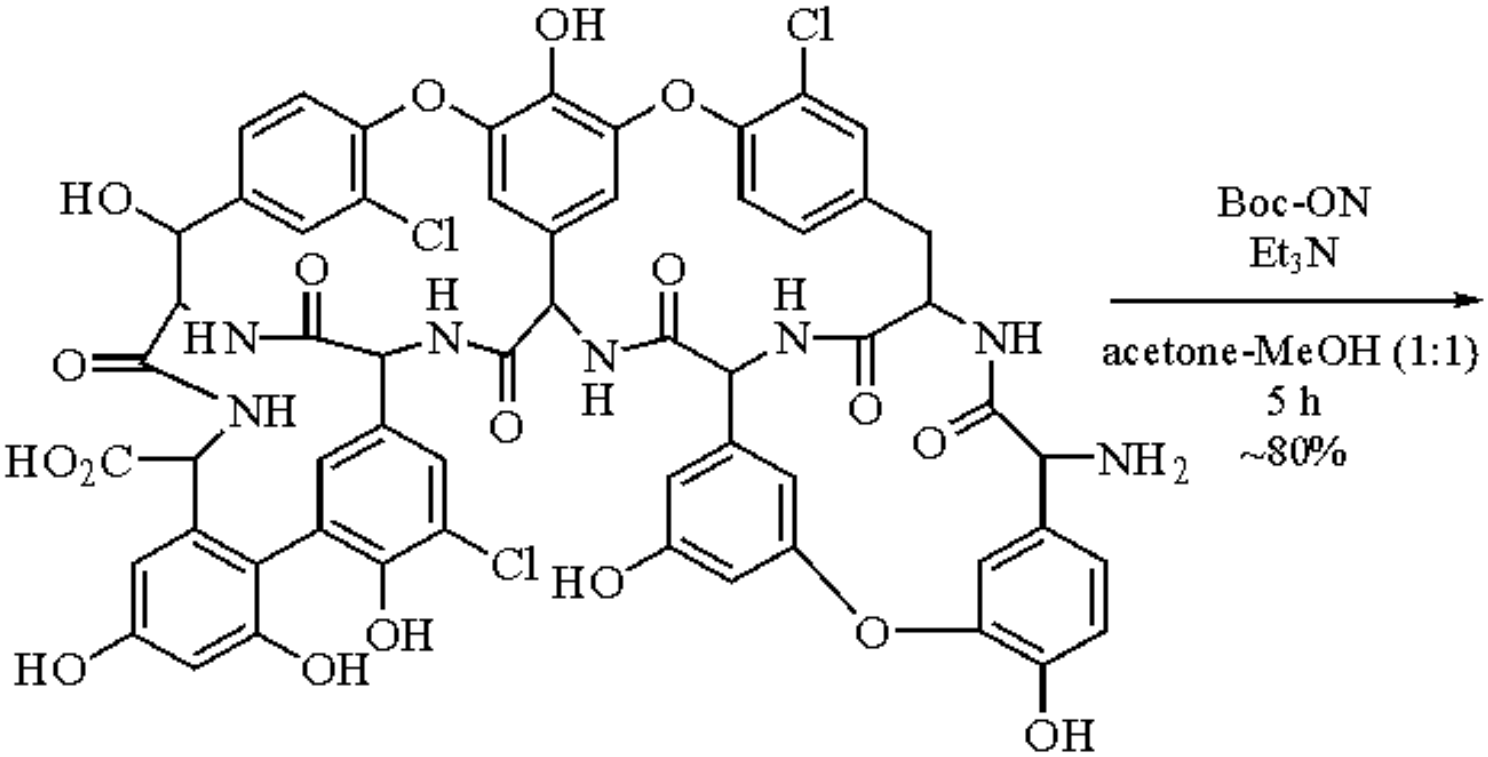

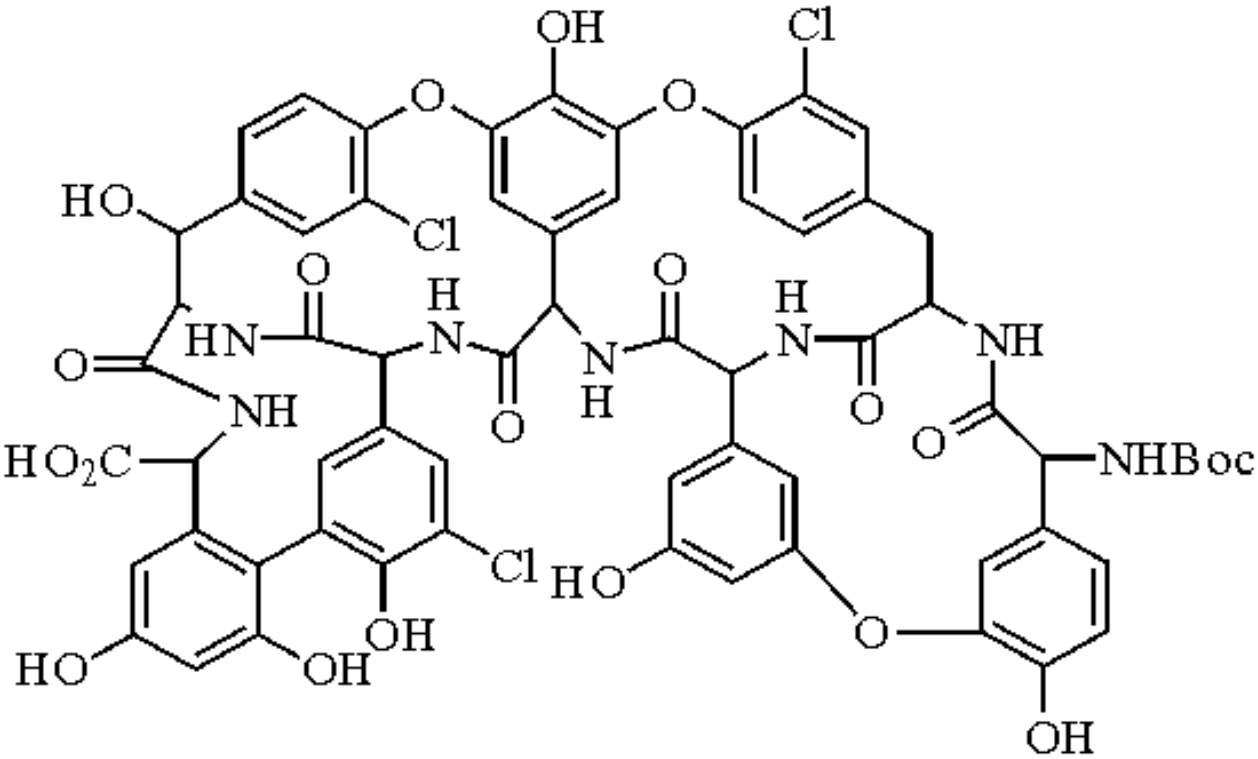

(5)

In the case of diamino acids, such as ornithine or lysine, Boc-ON has been used to effect selective protection of N^W at pH 11 (eqs 6 and 7).[12,13]

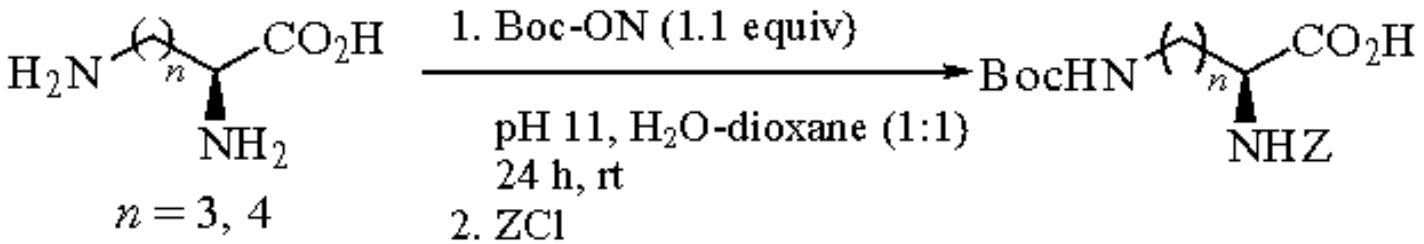

(6)

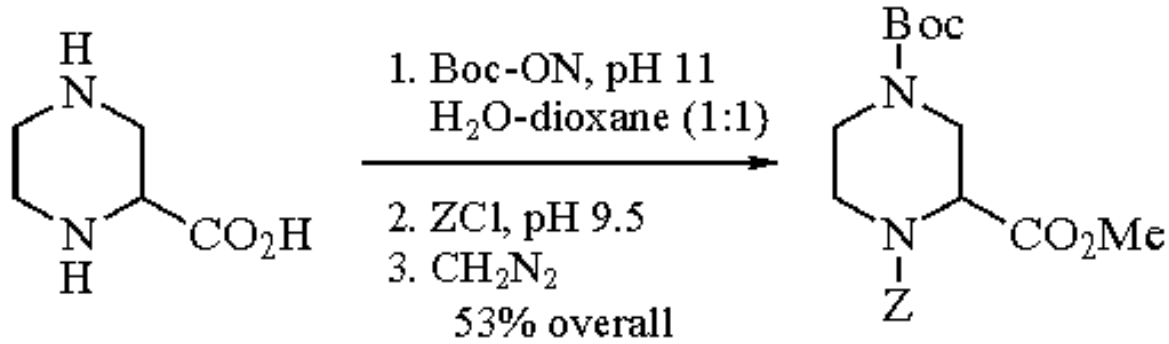

(7)

This selective protection has also been accomplished with copper-chelated diamino acids (eq 8).[14]

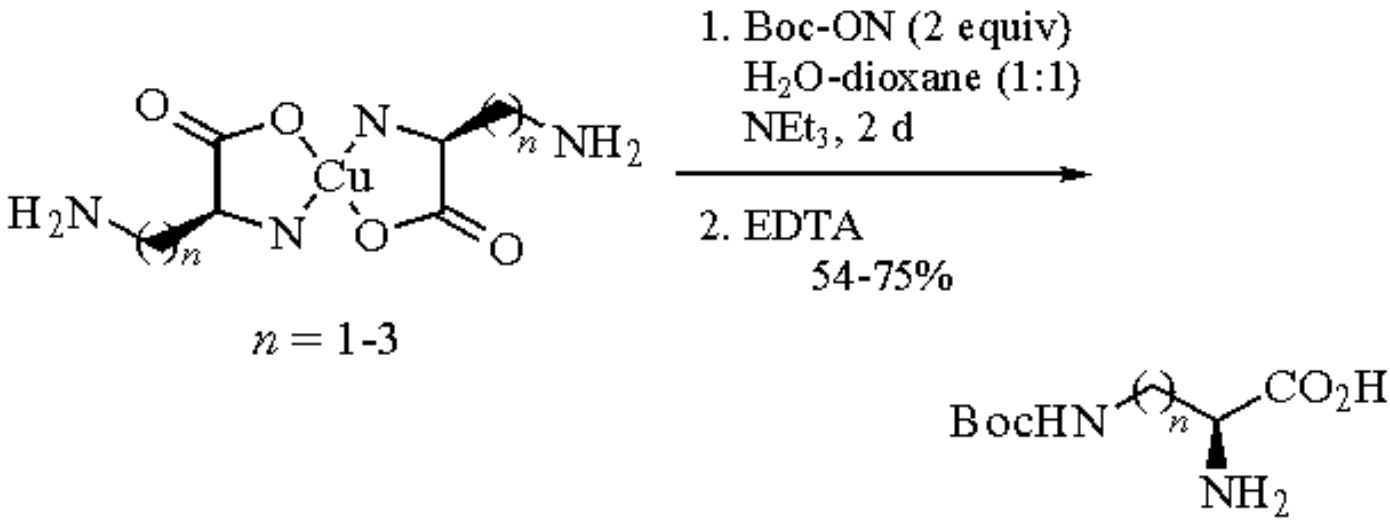

(8)

Alcohol Protection.

Boc-ON has also been employed to protect alcohols as their *t*-butyl carbonates.[4,15,16] For this application the alcohol must first be deprotonated to its alkoxide conjugate base (eqs 9 and 10).

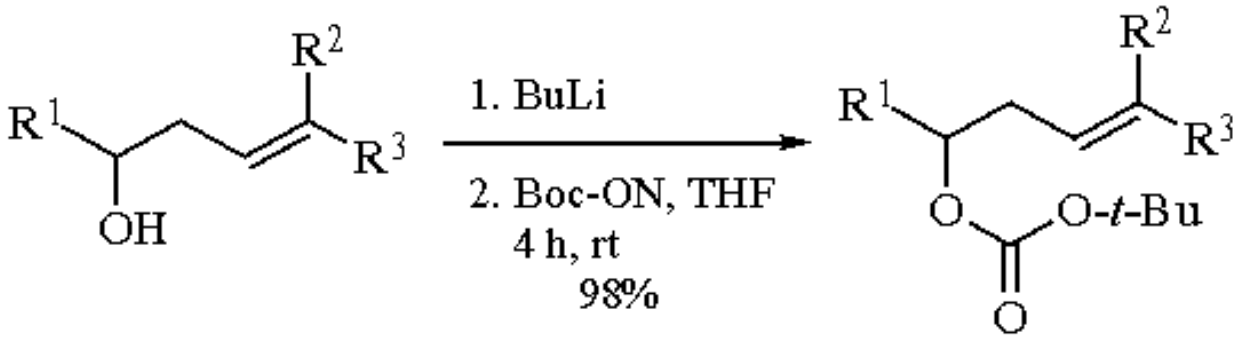

(9)

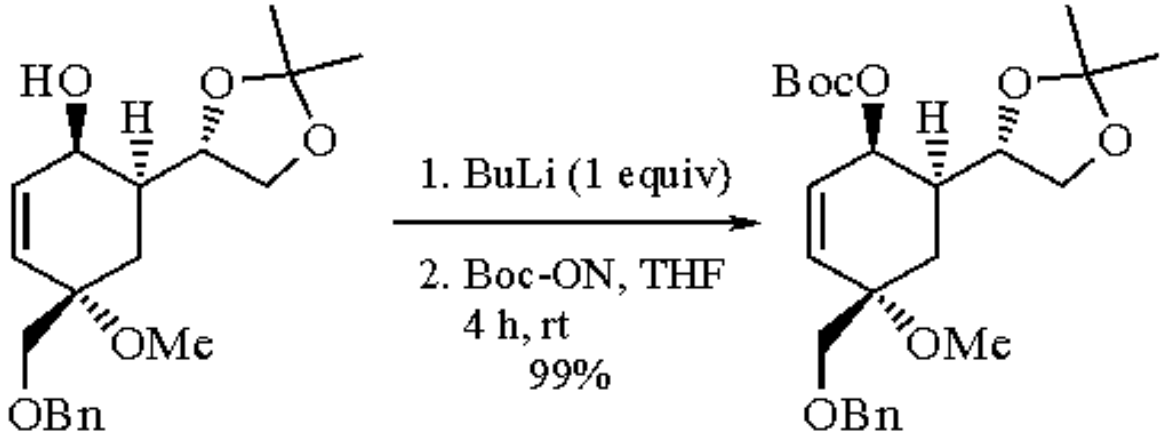

(10)

Related Reagents.

N-(t-Butoxycarbonyloxy)phthalimide; ***N-(t-Butoxycarbonyloxy)succinimide***; ***t-Butyl Azidoformate***; ***Di-t-butyl Dicarbonate***.

---

1. Itoh, M.; Hagiwara, D.; Kamiya, T. *TL* **1975**, *49*, 4393.
2. Itoh, M.; Hagiwara, D.; Kamiya, T. *BCJ* **1977**, *50*, 718.
3. Itoh, M.; Hagiwara, D.; Kamiya, T. *OS* **1980**, *59*, 95.
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6. *OS* **1977**, *57*, 122.
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16. Martin, S. F.; Zinke, P. W. *JOC* **1991**, *56*, 6600.

Michael S. Wolfe

N-(*t*-Butoxycarbonyloxy)phthalimide

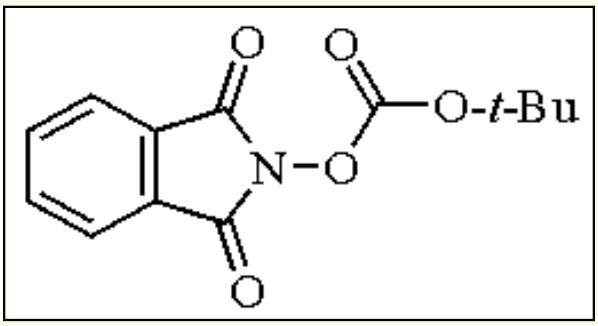

[15263-20-4] · $C_{13}H_{13}NO_5$ · N-(*t*-Butoxycarbonyloxy)phthalimide · (MW 263.25)

(reagent for protection of amino acids as *t*-butyl carbamates[1])

Physical Data: mp 118 °C (dec).

Solubility: sol *t*-butanol and THF; insol water.

Form Supplied in: solid.

Handling, Storage, and Precautions: contact with the reagent may cause irritation. The toxicological properties of the reagent have not been thoroughly investigated.

Amine Protection.

N-(*t*-Butoxycarbonyloxy)phthalimide (**1**) has been utilized for the protection of amines as their *t*-butoxycarbonyl (Boc) derivatives, particularly for the N-protection of α-amino acids (eq 1).[1]

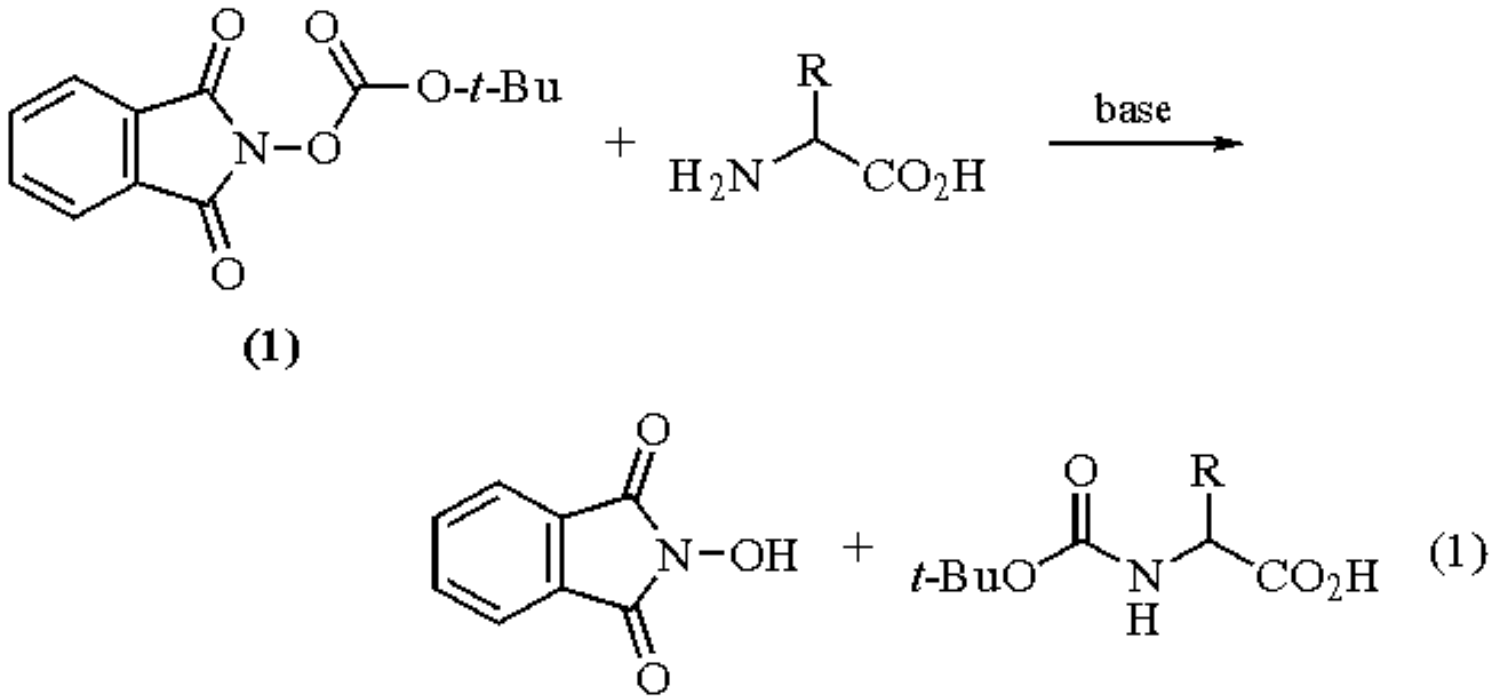

Equimolar amounts of (**1**), a base (NaOH or Na_2CO_3), and the amino acid in *t*-butanol-water (2:1) are heated to 90 °C for 2 h. Upon cooling, the byproduct sodium hydroxyphthalimide precipitates. The filtrate is then acidified to pH 3 with citric acid and extracted with chloroform. The extract is washed with water to obtain the Boc derivatives in moderate to good yield (Table 1). A related reagent where the phthalimide moiety is replaced by a succinimide can give comparable or superior yields (Table 1).[1,2] The 9-fluorenylmethyloxycarbonyl (Fmoc) succinimide has also been prepared and can give good yields of Fmoc-protected amino acids.[3]

Table 1 Examples of Boc-Amino Acids Prepared with *N*-(*t*-Butoxycarbonyloxy)phthalimide or *N*-(*t*-Butoxycarbonyloxy)-succininide[1]

Boc-amino acid	Reagent	Yield (%)
Ala-OH	Phthalimide-NOBoc	76
Ala-OH	Succinimide-NOBoc	75
Asn-OH	Phthalimide-NOBoc	81
[*S*-Bn]-Cys-OH	Succinimide-NOBoc	80
Gly-OH	Phthalimide-NOBoc	73
Gly-OH	Succinimide-NOBoc	78
Leu-OH	Succinimide-NOBoc	74
Pro-OH	Phthalimide-NOBoc	65
Pro-OH	Succinimide-NOBoc	87

These reagents offer some advantage over *t*-Boc azide, which is thermally unstable and decomposes with apparent detonation at temperatures above 80 °C. However, ***2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile***[4,5] and ***Di-t-butyl Dicarbonate***[6] are generally the reagents of choice because the reactions are complete at ambient temperature within 2-4 h and because the yields are usually higher.

The reagent will selectively protect the amino group in the presence of alcohols, and may show selectivity for less hindered amines. The antibiotic sisomicin (eq 2) reacted with (**1**) to give a clean product by TLC. However, after silica gel chromatography the sole product isolated was obtained in only 26% yield, with the remainder of the starting material recovered. The authors suggest that while the reaction was remarkably selective and went to apparent completion, the product was unstable to silica gel.[7]

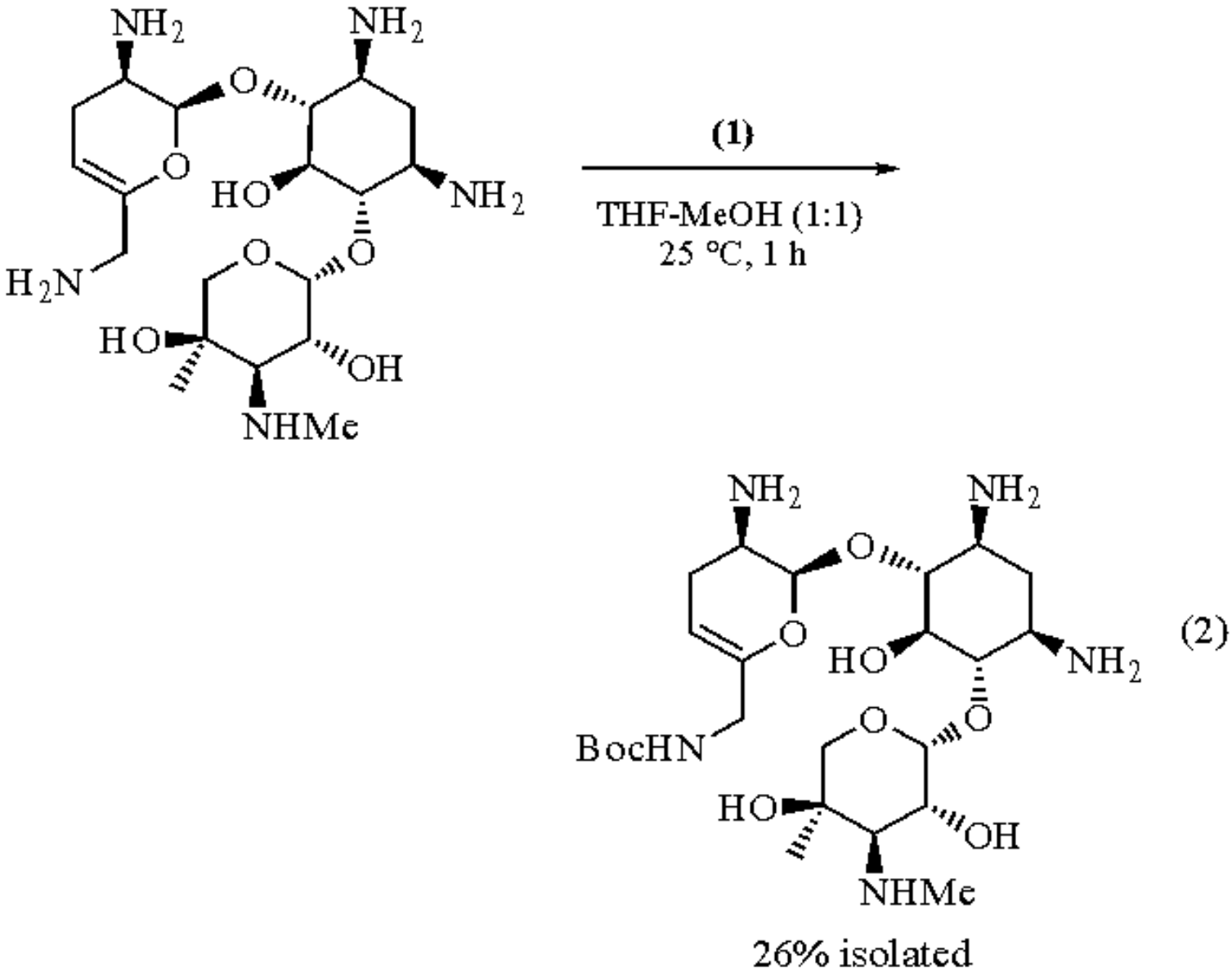

Related Reagents.

2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile; ***N-(t-Butoxycarbonyloxy)succinimide***; ***Di-t-butyl Dicarbonate***; ***9-Fluorenylmethyl Chloroformate***.

---

1. Gross, H.; Bilk, L. *LA* **1969**, *725*, 212 (*CA* **1961**, *71*, 91 846k).
2. Frankel, M.; Ladkany, D.; Gilon, C.; Wolman, Y. *TL* **1966**, 4765.
3. Paquet, A. *CJC* **1982**, *60*, 976.
4. Itoh, M.; Hagiwara, D.; Kamiya, T. *TL* **1975**, 4393.
5. Itoh, M.; Hagiwara, D.; Kamiya, T. *BCJ* **1977**, *50*, 718.
6. Persio, G.; Piani, S.; De Castiglione, R. *Int. J. Peptide Protein Res.* **1983**, *21*, 227.
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Michael S. Wolfe

N-(*t*-Butoxycarbonyloxy)succinimide

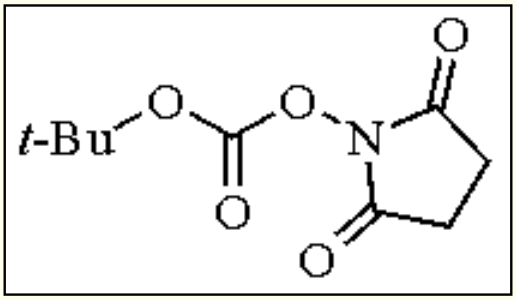

[13139-12-3] · $C_9H_{13}NO_5$ · *N*-(*t*-Butoxycarbonyloxy)succinimide · (MW 215.21)

(reagent for the protection of amino groups, including amino acids[2])

Alternate Name: Boc-OSu.

Physical Data: mp 98-100 °C.[1]

Solubility: sol ether, ethyl acetate, acetone; insol water, petroleum ether.

Form Supplied in: white solid, widely available.

Handling, Storage, and Precautions: stable under normal storage conditions. No known toxicity.

Protection of Amino Compounds.

N-(*t*-Butoxycarbonyloxy)succinimide (Boc-OSu) has been developed to supplement the unstable ***t-Butyl Chloroformate*** for the protection of amino compounds and especially of amino acids. The reagent is a stable compound easily prepared from *t*-butanol and *N*-oxysuccinimide chloroformate[1] and has been used for the protection of various compounds including amino acids, peptides,[2] proteins,[3,4] and amino saccharides.[5] *N*-Oxysuccinimide carbonates have been shown to give very pure N-protected amino acids with a particularly low content of dipeptide byproduct.[6] It is also noteworthy that both the Boc and the OSu groups can be introduced into amino acids almost simultaneously in a one-pot synthesis of Boc-protected *N*-oxysuccinimide active esters of amino acids (eq 1).[7]

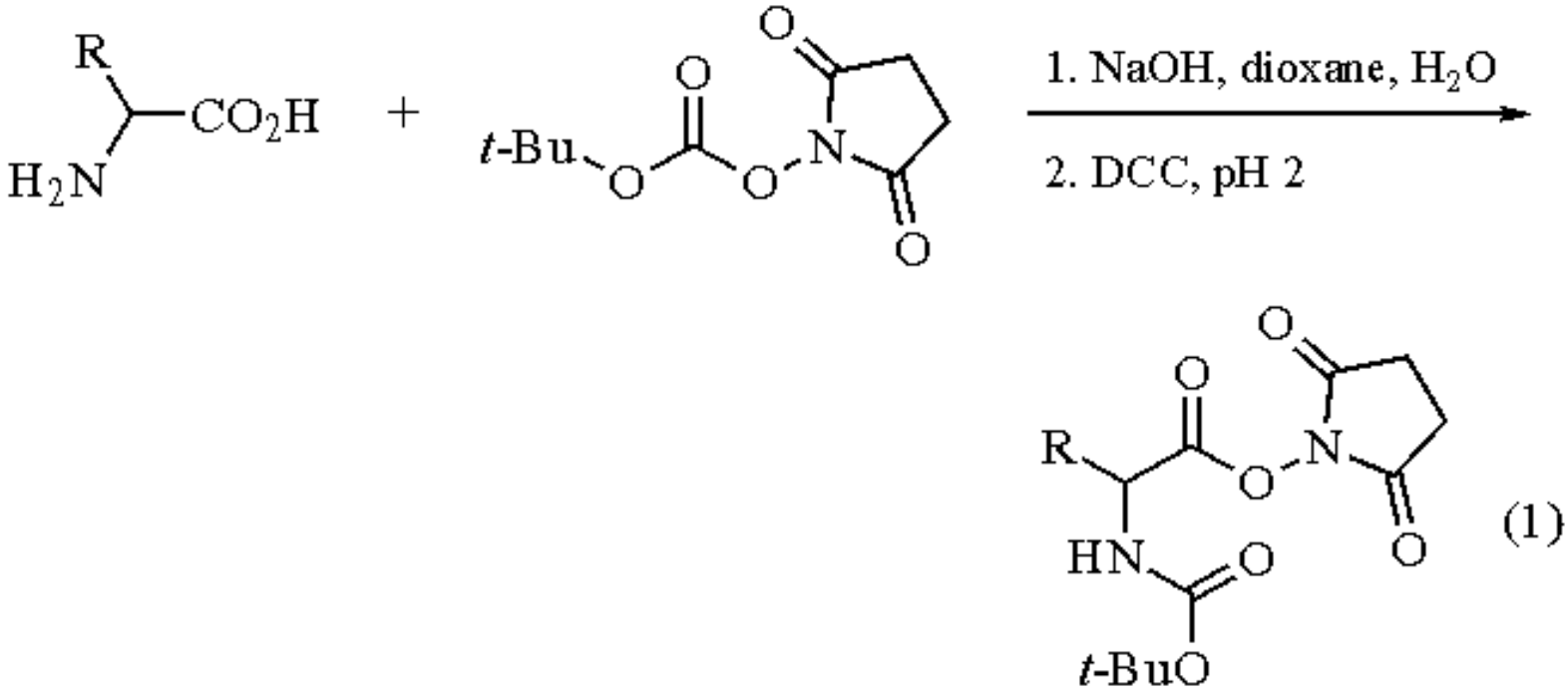

Attempts to protect α-hydrazino acids regioselectively led to almost no discrimination between N-α and N-β protection, compared to the very good regioselectivity observed with benzyloxycarbonyloxysuccinimide (eq 2).[8]

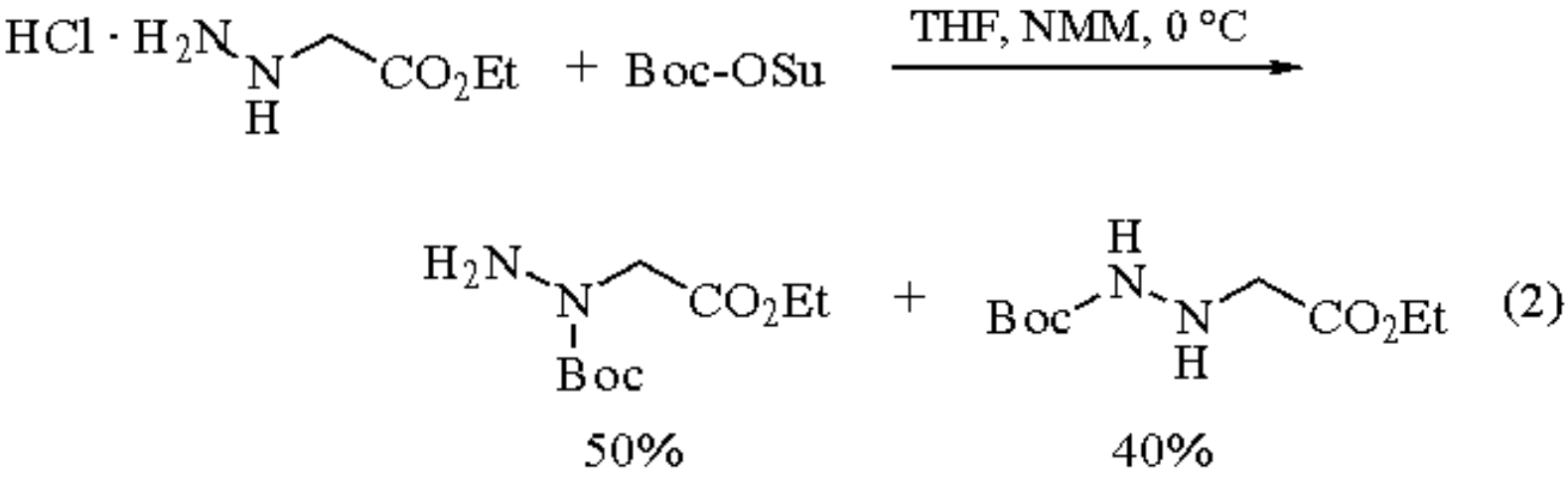

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1. Gross, H.; Bilk, L. *LA* **1969**, *725*, 212.
2. Hojo, H.; Aimoto, S. *BCJ* **1992**, *65*, 3055.
3. Losse, G.; Naumann, W.; Raddatz, H. *ZC* **1983**, *23*, 22.
4. Grau, U. E. Ger. Patent 3 326 472 (*CA* **1985**, *103*, 88 221).
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7. Frankel, M.; Ladkany, D.; Gilon, C.; Wolman, Y. *TL* **1966**, 4765.
8. Lecoq, A.; Marraud, A.; Aubry, A. *TL* **1991**, *32*, 2765.

G. Sennyey

N-(*t*-Butoxycarbonyl)pyrrole

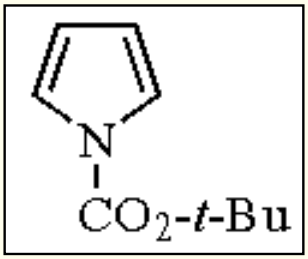

[5176-27-2] · $C_9H_{13}NO_2$ · *N*-(*t*-Butoxycarbonyl)pyrrole · (MW 167.21)

(used as a synthetic equivalent of pyrrole; the *t*-butoxycarbonyl group can be cleaved under acidic or basic conditions[1])

Physical Data: bp 98-99 °C/19 mmHg.

Solubility: freely sol common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Method: see Reese and Dhanak.[1]

Purification: distillation under reduced pressure.

N-(*t*-Butoxycarbonyl)pyrrole is prepared by the deprotonation of pyrrole with ***Sodium Hydride*** followed by acylation with phenyl *t*-butyl carbonate.[1] Other preparative methods include the acylation of pyrrole with ***Di-t-butyl Dicarbonate*** in the presence of ***Triethylamine*** and catalytic ***4-Dimethylaminopyridine***,[2] and treatment of the potassium salt of pyrrole with ***t-Butyl Azidoformate***.[3]

N-(*t*-Butoxycarbonyl)pyrrole serves as a convenient synthetic equivalent of pyrrole. Many of the synthetically important transformations of pyrrole, substituted pyrroles, and indoles involve strongly basic conditions and it is often necessary to protect the nitrogen. The *t*-butoxycarbonyl group can be attached and removed under mild conditions and is also stable to a variety of conditions used for functionalization of the pyrrole ring. Thus 2-lithio-*N*-(*t*-butoxycarbonyl)pyrrole can be generated quantitatively with ***Lithium 2,2,6,6-Tetramethylpiperidide*** and trapped with ***Chlorotrimethylsilane*** or other electrophiles. The protecting group can be subsequently removed using a solution of ***Sodium Methoxide*** in methanol (eq 1).[4] Under these conditions, (1-hydroxy)alkylpyrroles (derived from the addition of the 2-lithiopyrrole to aldehydes) are converted to (1-methoxy)alkylpyrroles. The *t*-butoxycarbonyl group can also be cleaved under acidic conditions using ***Trifluoroacetic Acid*** in CH_2Cl_2.[1,2]

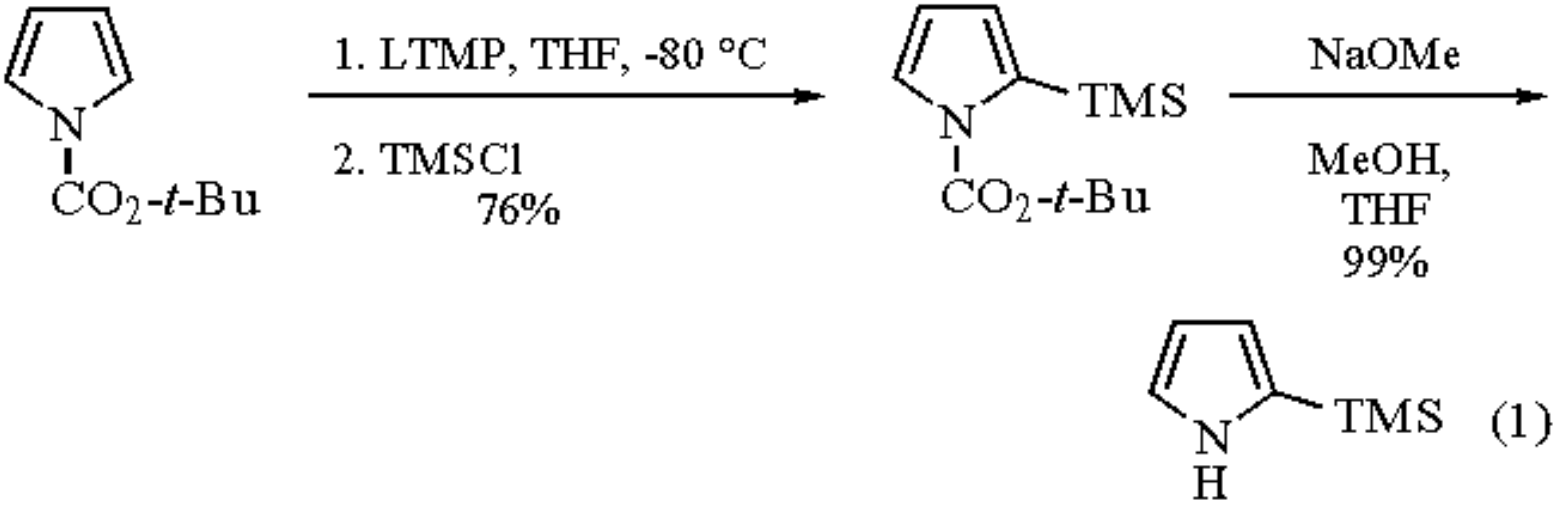

N-(*t*-Butoxycarbonyl)pyrrole also undergoes Diels-Alder reactions with acetylene, benzyne, and their derivatives. Thus reaction of *N*-(*t*-butoxycarbonyl)pyrrole with benzyne generated from bromofluorobenzene and magnesium gave the adduct in 41% yield (eq 2).[3]

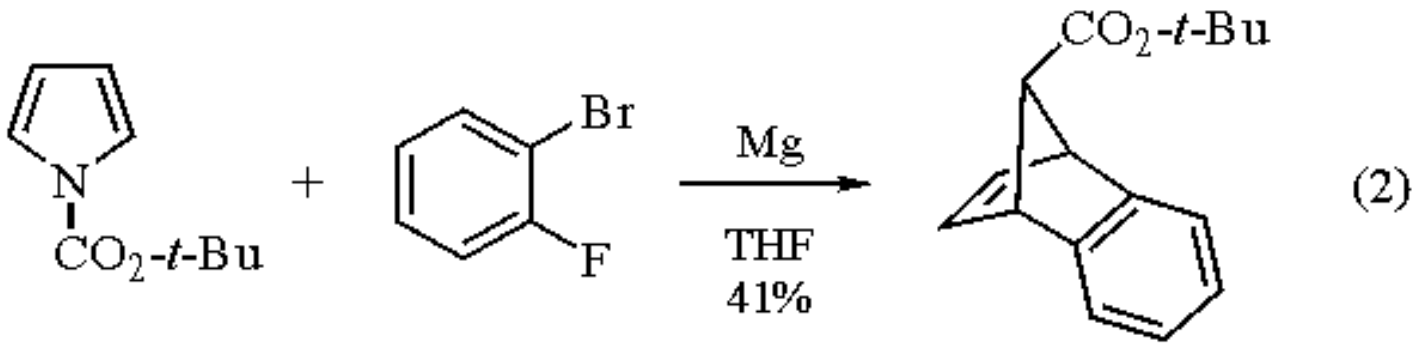

Other alternatives to *N*-(*t*-butoxycarbonyl)pyrrole that can be used for some of the reactions described above include various *N*-trialkylsilylpyrroles[1,5] and methoxycarbonylpyrrole.[6]

---

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2. Grehn, L.; Ragnarsson, U. *AG(E)* **1984**, *23*, 296.
3. Carpino, L. A.; Barr, D. E. *JOC* **1966**, *31*, 764.
4. Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *JOC* **1981**, *46*, 157.
5. Anderson, P. S.; Christy, M. E.; Engelhardt, E. L.; Lundell, G. F.; Ponticello, G. S. *JHC* **1977**, *14*, 213.
6. Swenton, J. S.; Oberdier, J.; Rosso, P. D. *JOC* **1974**, *39*, 1038.

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The University of Michigan, Ann Arbor, MI, USA

N-(*t*-Butoxycarbonyl)-*p*-toluenesulfonamide

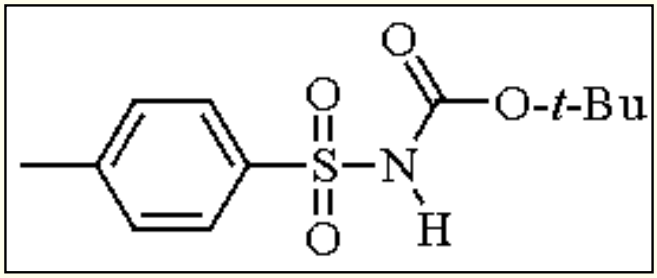

[18303-04-3] · $C_{12}H_{17}NO_4S$ · *N*-(*t*-Butoxycarbonyl)-*p*-toluenesulfonamide · (MW 271.33)

(useful component in Mitsunobu reactions for the direct preparation of protected amines from alcohols)

Physical Data: mp 121-123 °C.

Solubility: sol most common organic solvents.

Form Supplied in: white solid; commercially available.

Preparative Method: the title compound (**1**) is readily prepared in high yield by addition of *t*-butanol to tosyl isocyanate.[1]

Handling, Storage, and Precautions: the reagent can be stored for extended periods of time in an amber bottle at rt.

Mitsunobu Reactions.

Under standard Mitsunobu conditions, primary (eq 1),[1] secondary (eq 2),[1] and allylic *N*-Boc sulfonamides (eq 3)[4] have been prepared in good yields. The reagent has a pK_a of 8.5 in DMSO,[2] making it a suitably acidic component in the Mitsunobu[3] reaction.

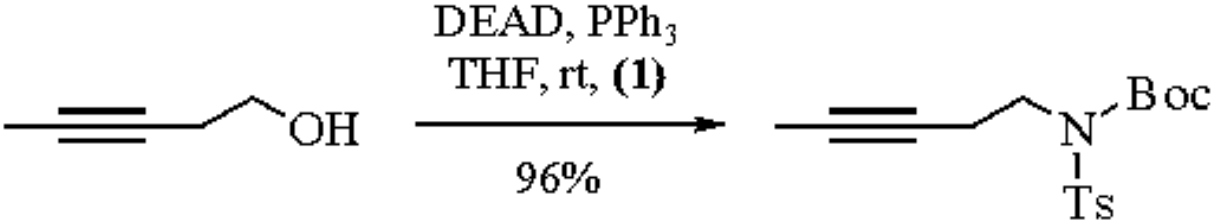

(1)

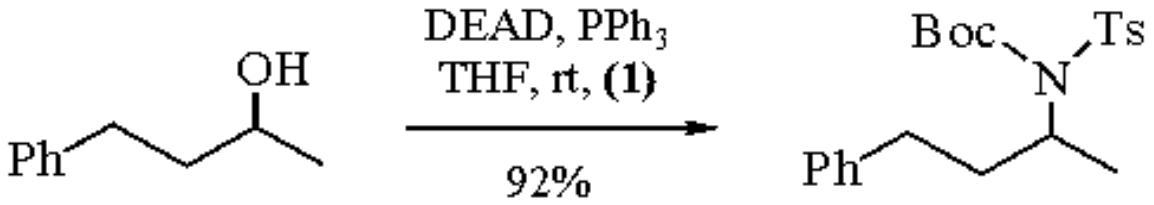

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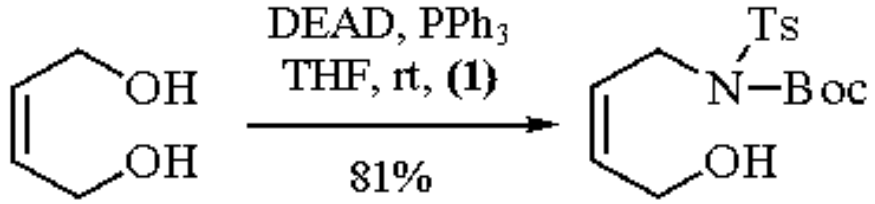

(3)

It is possible to selectively remove either of the nitrogen protecting groups of these *N*-Boc sulfonamides.[1] For example, treatment of (**2**) with ***Trifluoroacetic Acid***, or thermolysis in ***Dimethyl Sulfoxide*** affords sulfonamide (**3**) (eq 4). Alternatively, ***Sodium Naphthalenide*** serves to deprotect (**2**) to give the *N*-Boc compound (**4**).

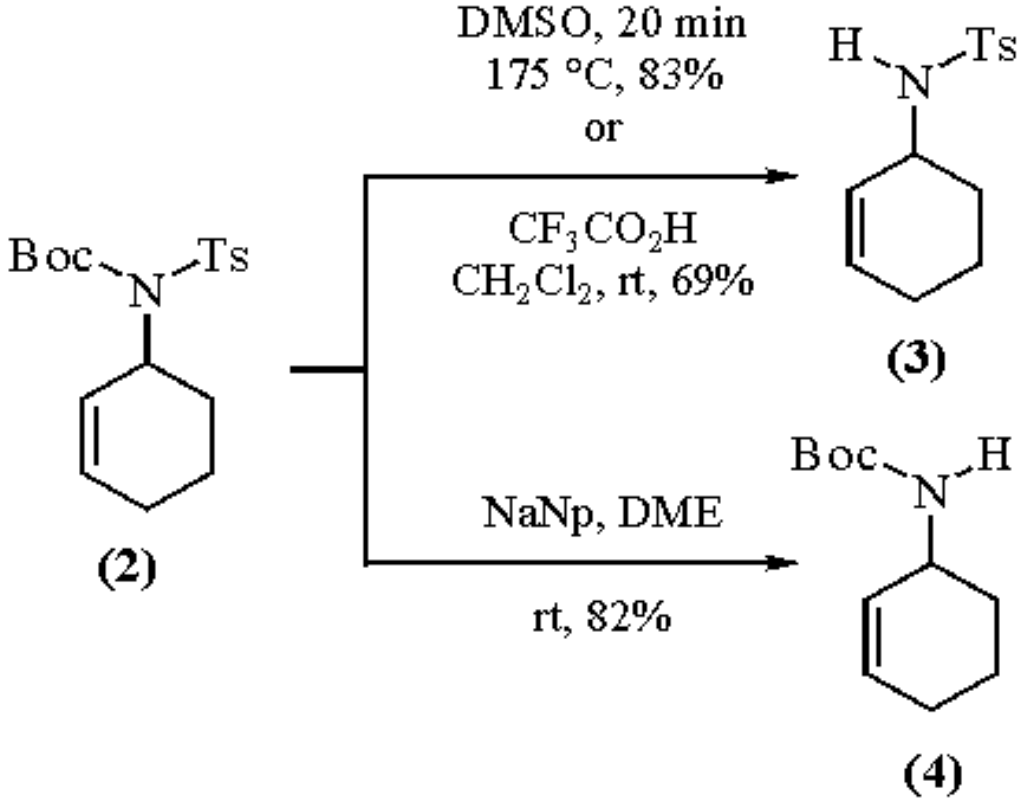

(4)

Compound (**1**) has been effectively used for the formation of the *N*,*N*-diprotected ethyl (*R*)-alaninate (**6**) from the corresponding (*S*)-alcohol (**5**) with clean inversion of stereochemistry (eq 5).[5]

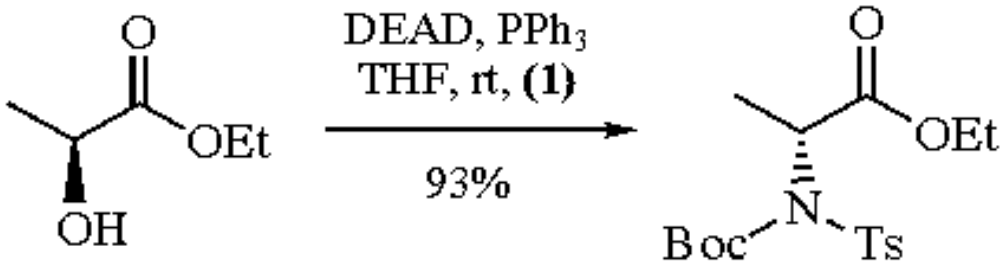

(5) (6) (5)

N-Boc sulfonamide (**1**) has also proved useful in the synthesis of the thromboxane A_2 antagonist (**10**).[6] The Mitsunobu reaction with (**1**) was carried out on scalemic ester alcohol (**7**) to provide the desired *N*-Boc sulfonamide (**8**) along with diene (**9**) (eq 6).

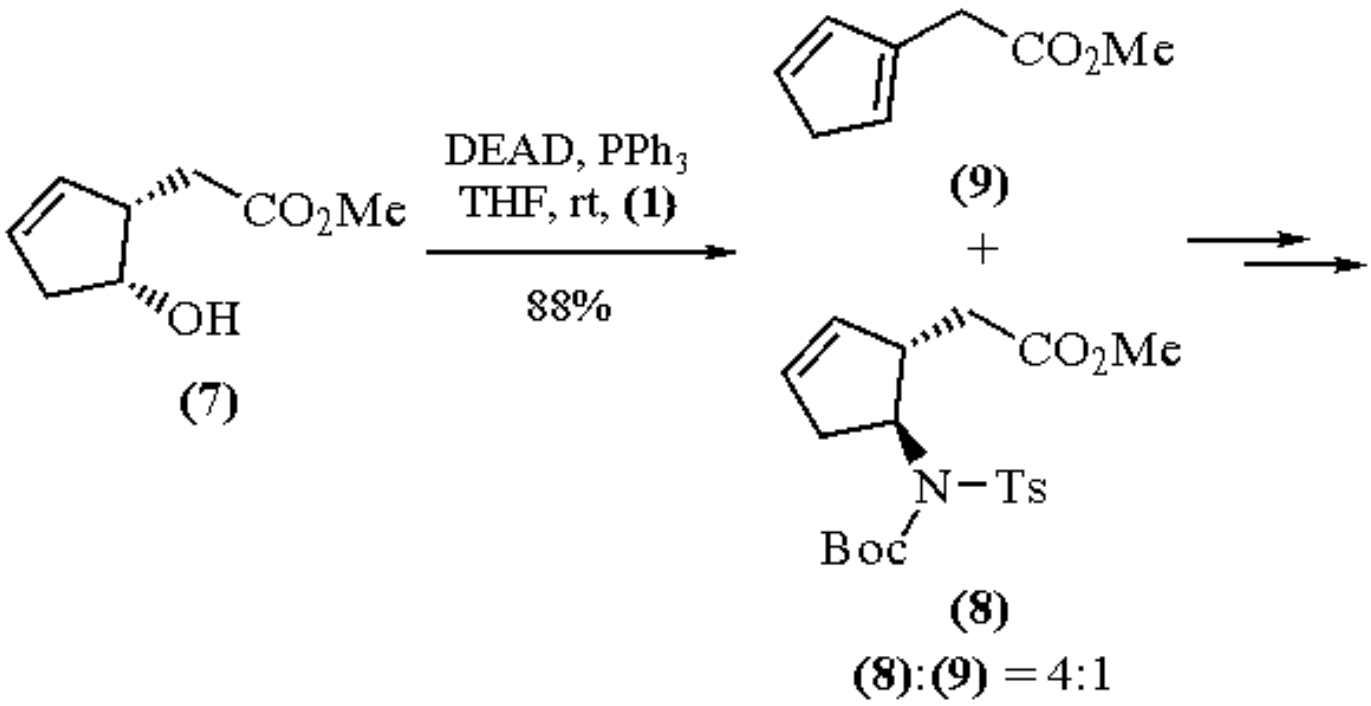

(7) (9) (8)

(8):(9) = 4:1

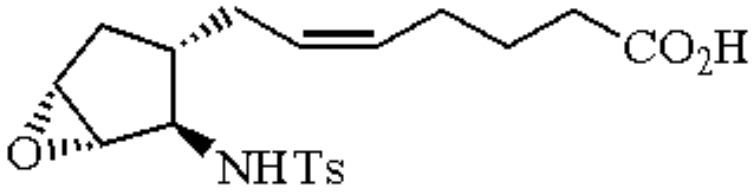

(10) (6)

A related compound, *t*-butyl ((2-(trimethylsilyl)ethyl)sulfonyl)carbamate (**12**), prepared from methanesulfonamide (**11**) in two steps (eq 7), has also been shown to be an effective component in the Mitsunobu reaction (eq 8) (see also β-***Trimethylsilylethanesulfonyl Chloride***).[7]

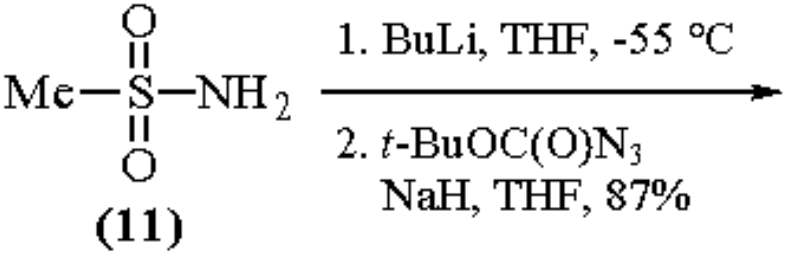

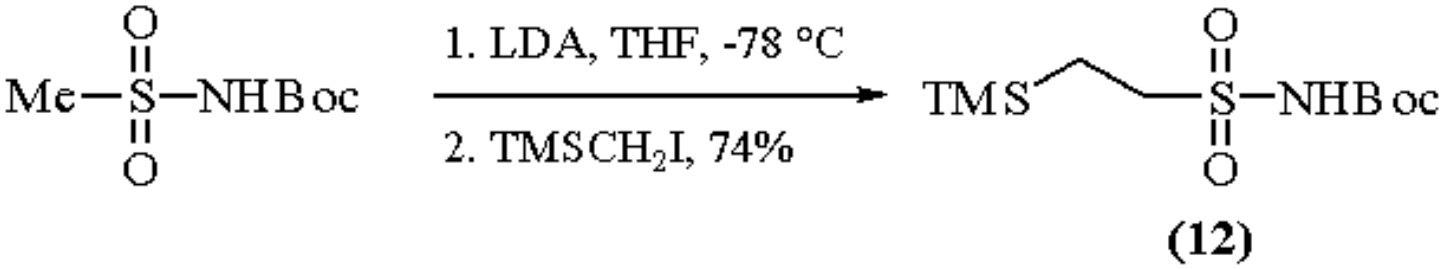

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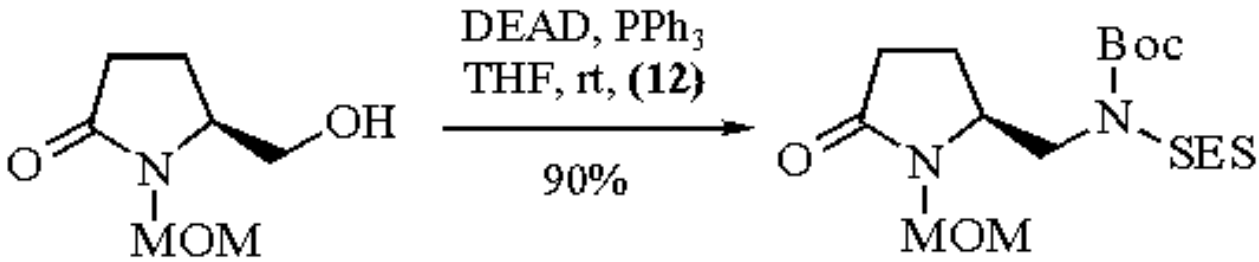

(8)

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1-*t*-Butoxycarbonyl-1,2,4-triazole

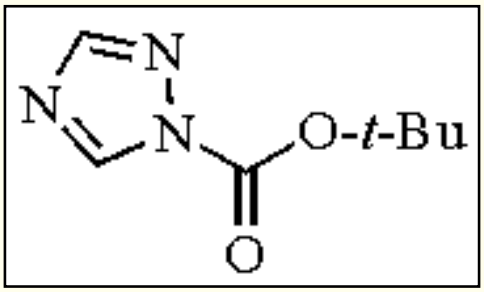

[41864-24-8] · $C_7H_{11}N_3O_2$ · 1-*t*-Butoxycarbonyl-1,2,4-triazole · (MW 169.18)

(a reagent for protection of amines with the *t*-butoxycarbonyl group[1])

Physical Data: mp 40 °C.

Solubility: sol DMF and DMSO.

Form Supplied in: the reagent is commercially available and is supplied as a solid.

Preparative Method: 1-*t*-butoxycarbonyl-1,2,4-triazole (**1**) is available commercially, but it can readily be prepared from the reaction of *t*-butoxycarbonyl azide with 1-trimethylsilyl-1,2,4-triazole or reaction of *t*-butanol with *N,N´*-carbonyl-di-1,2,4-triazole in high yield.[1]

Handling, Storage, and Precautions: anhydrous conditions are recommended for reactions, and the reagent is best stored at 0-4 °C.

t-Butoxycarbonylation.

(**1**) is exceedingly reactive towards amines. Simple amines react with (**1**) to give the corresponding carbamates in high yields. However, the reaction has been reported to proceed somewhat more slowly with carboxylate salts of amino acids. Nonetheless, yields for the protection of amino acids under these conditions are in the range of 80-92%.[1]

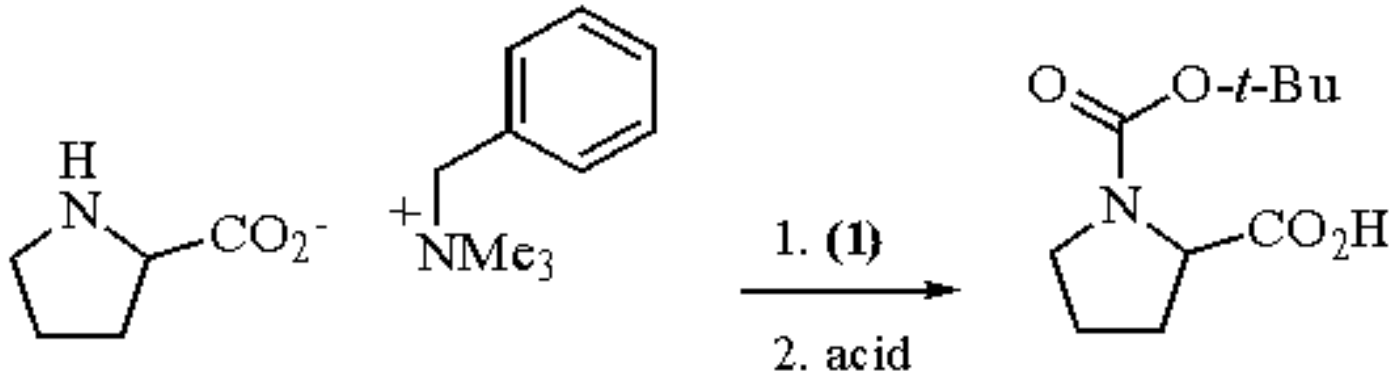

(1)

Related Reagents.

2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile; ***N-(t-Butoxycarbonyloxy)phthalimide***; ***N-(t-Butoxycarbonyloxy)succinimide***; ***t-Butyl Azidoformate***; ***t-Butyl Chloroformate***; ***Di-t-butyl Dicarbonate***.

---

1. Bram, G. *TL* **1973**, 469.

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t-Butoxychlorodiphenylsilane

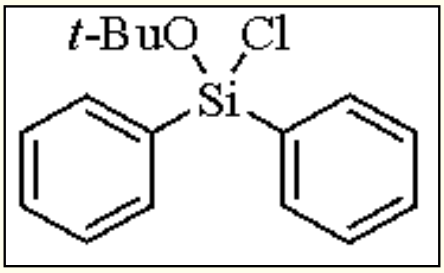

[17922-24-6] · $C_{16}H_{19}ClOSi$ · *t*-Butoxychlorodiphenylsilane · (MW 290.86)

(reagent for the protection of primary, secondary, and tertiary alcohols; reacts selectively with primary hydroxy groups in dichloromethane; *t*-butoxydiphenylsilyl ethers are highly reactive towards F^-, allowing for selective removal[1])

Alternate Name: *t*-butoxydiphenylsilyl chloride.

Physical Data: bp 130-145 °C/0.5 mmHg; *d* 1.075 g cm^{-3}; fp 56 °C.

Solubility: sol most organic solvents.

Form Supplied in: pale yellow oil; stabilized with calcium carbonate.

Handling, Storage, and Precautions: corrosive; the reagent is moisture sensitive and should be handled under an inert atmosphere.

Reactivity.

t-Butoxychlorodiphenylsilane reacts with primary, secondary, and tertiary alcohols in DMF, in the presence of ***Triethylamine***, to give the corresponding silyl ethers in good yield (eq 1).[1] Secondary alcohols can also be silylated in dichloromethane; however, small amounts of ***4-Dimethylaminopyridine*** (0.1 equiv) or ***N,N-Dimethylformamide*** (0.1 equiv) are required to catalyze the reaction (eq 2). Selective silylation of primary alcohols can be achieved using dichloromethane alone (eq 3).

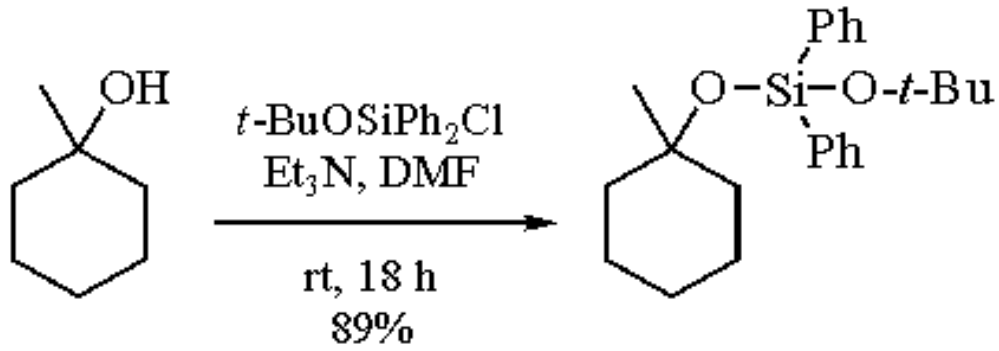

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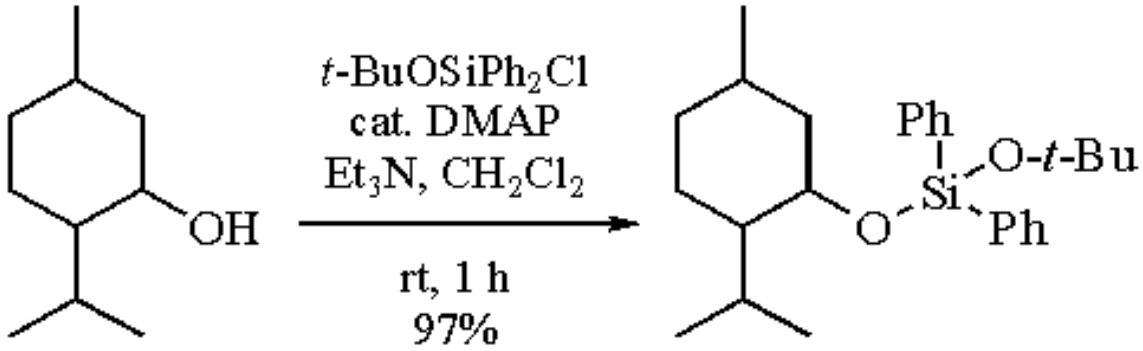

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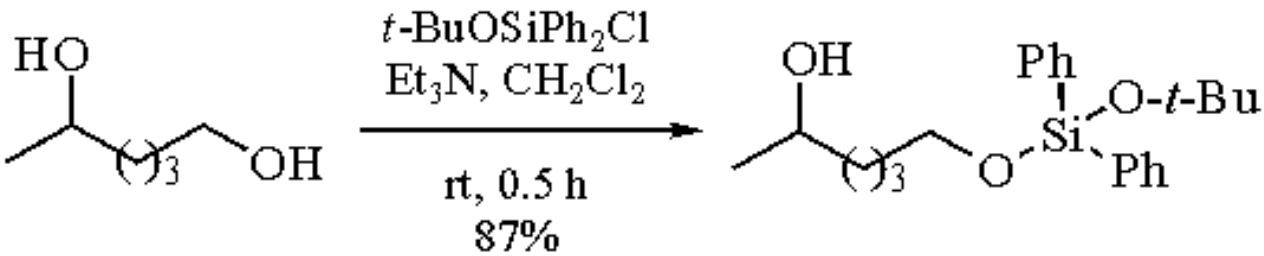

(3)

Stability.

One of the most interesting attributes of the *t*-butoxydiphenylsilyl protecting group is its sensitivity to fluoride. A primary *t*-butoxydiphenylsilyl ether can be cleaved selectively in the presence of a primary or secondary *t*-butyldimethylsilyl ether, using 2 equiv of ***Tetra-n-butylammonium Fluoride*** (1 M solution in THF) in dry dichloromethane (eqs 4, 6, 7).[1,2] Alternatively, selective cleavage of the *t*-butyldimethylsilyl ethers can be achieved using acidic conditions (eq 5).[1]

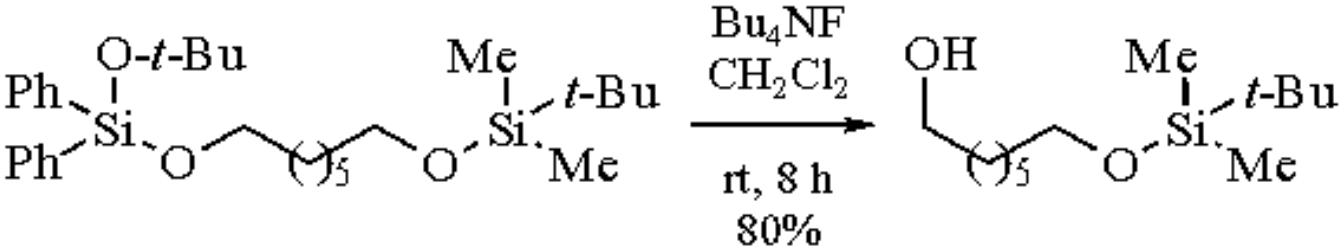

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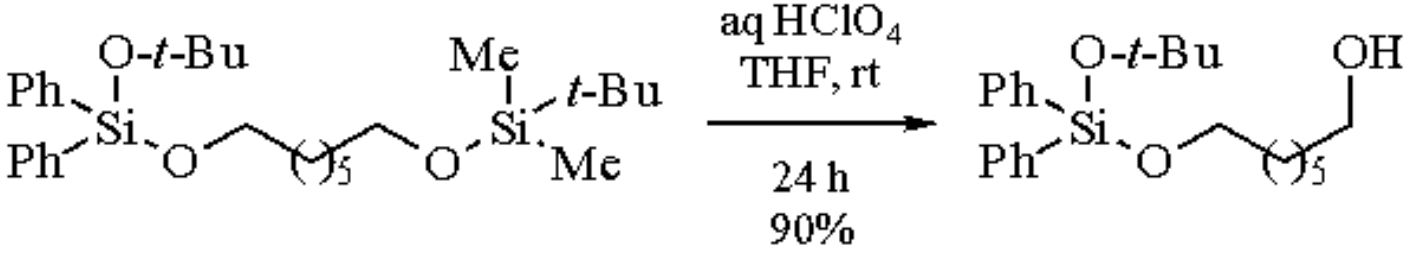

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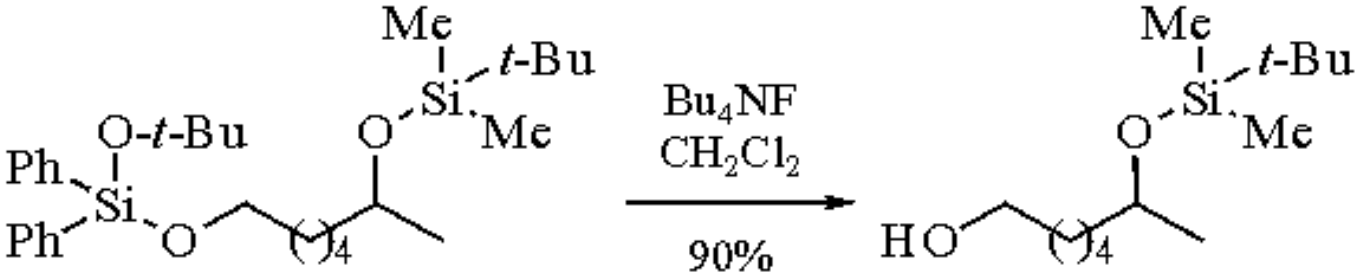

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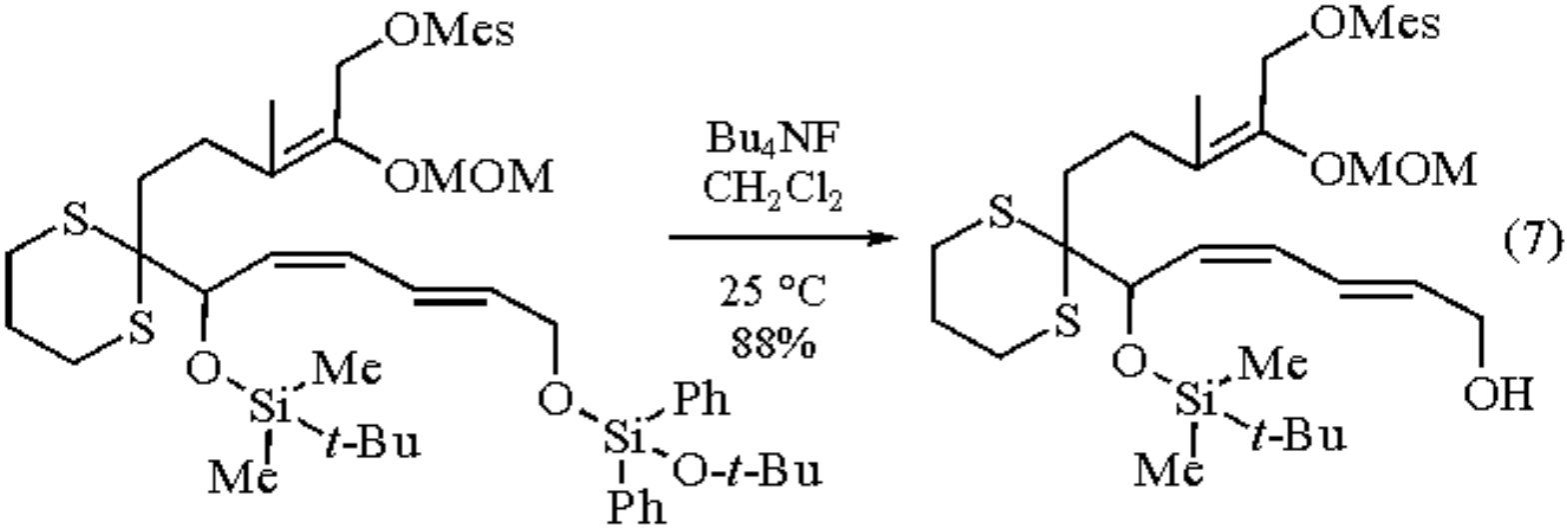

(7)

Selective cleavage of a secondary *t*-butoxydiphenylsilyl ether in the presence of a primary *t*-butyldimethylsilyl ether could not be achieved (eq 8). This problem can be circumvented by the use of the diphenylisopropoxysilyl protecting group (eqs 9 and 10).[1,3]

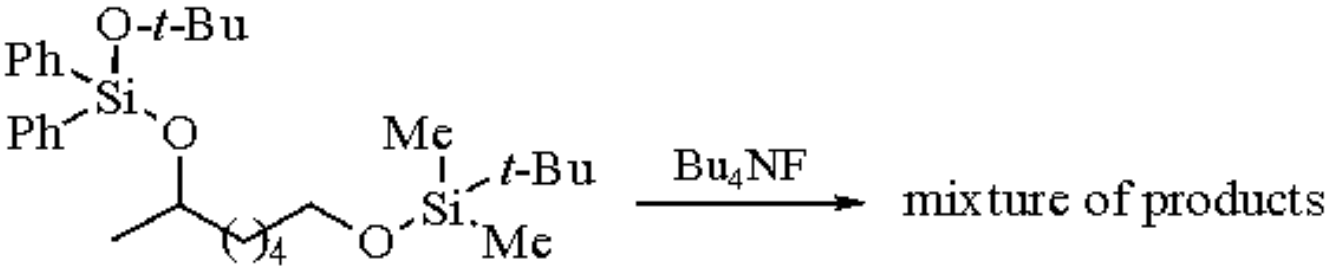

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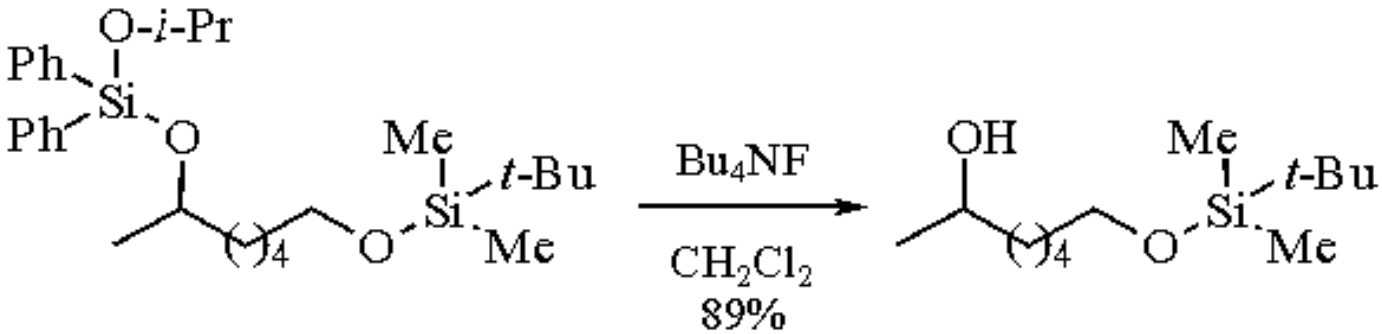

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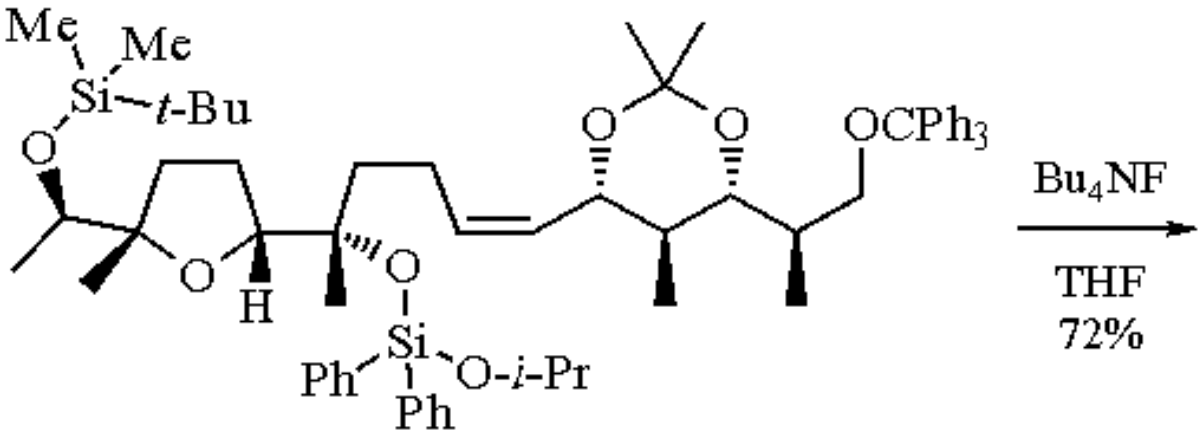

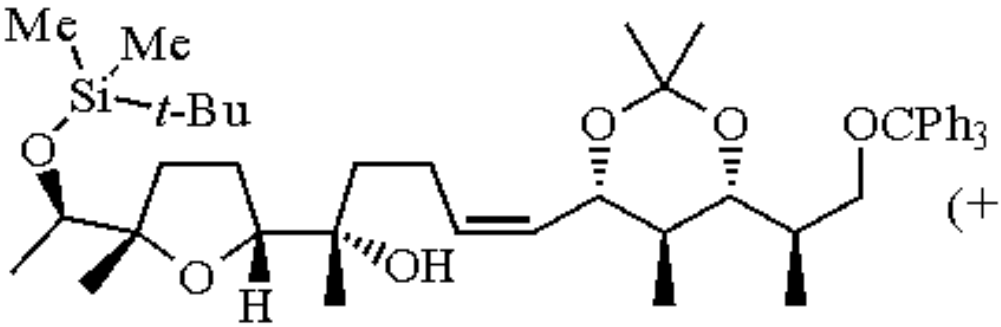

(+ 14% diol) (10)

The *t*-butoxydiphenylsilyl protecting group is compatible with reactions such as ***Pyridinium Chlorochromate*** oxidation,[4] acylation, and reduction. Highly reactive nucleophiles such as ***n-Butyllithium*** should, however, be avoided.

---

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t-Butoxymagnesium Bromide

t-BuOMgBr

[19065-60-2] · C_4H_9BrMgO · *t*-Butoxymagnesium Bromide · (MW 177.32)

(associated alkoxide base)

Preparative Method: the reagent is prepared in situ by reacting anhydrous *t*-BuOH with 1.0 equiv EtMgBr in Et_2O or THF.[1,2] The crystalline solid, which has a dimeric structure, is obtained by the reaction of MeMgBr with acetone in Et_2O.[3]

Handling, Storage, and Precautions: use the same precautions that are recommended for ***Potassium t-Butoxide***, i.e. avoid contact of solutions with eyes, skin, and clothing. Conduct all reactions under an inert atmosphere.

Oxidation of Alcohols.

Bromomagnesium alkoxides of a variety of alcohols including saturated primary alcohols (eq 1) react with ***N-Chlorosuccinimide*** in the presence of *t*-BuOMgBr to give the corresponding carbonyl compounds in good yields.[2] A very low yield of the aldehyde is produced when the unsaturated alcohol, 7-phenyl-4-hepten-1-ol, is reacted similarly (eq 2). Although the substitution of ***m-Chloroperbenzoic Acid*** or ***Diacetatobis(tri-o-tolylphosphine)palladium(II)*** for NCS leads to a significant improvement in the yield of the unsaturated aldehyde, best results are obtained if ***1,1´-(Azodicarbonyl)dipiperidine*** is used as the oxidizing agent (eq 2).[2] This method gives high yields of oxidation products when applied to a variety of other alcohols as well. The combination of *t*-BuOMgBr and 1,1´-(azodicarbonyl)dipiperidine is capable of oxidizing keto alcohols to diketones without prior formation of the halomagnesium alkoxide of the substrate (eq 3).[2]

$$Me(CH_2)_6CH_2OMgBr + NCS \xrightarrow[\text{THF, rt}]{t\text{-BuOMgBr}} Me(CH_2)_6CHO \quad (1)$$

80%

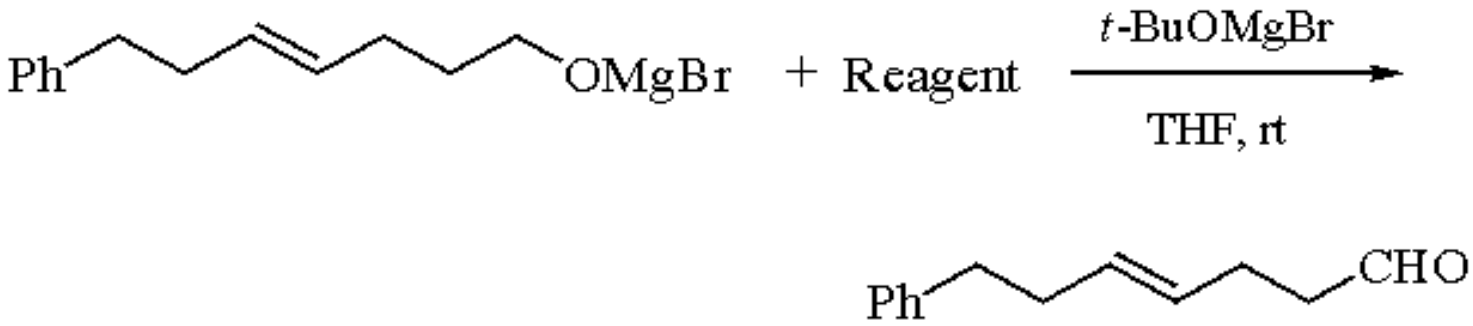

(2)

NCS	34%
m-CPBA	74%
$PhI(OAc)_2$	76%

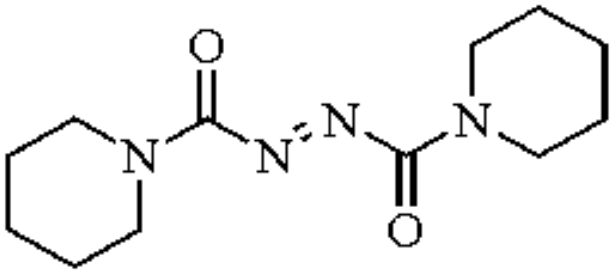

89%

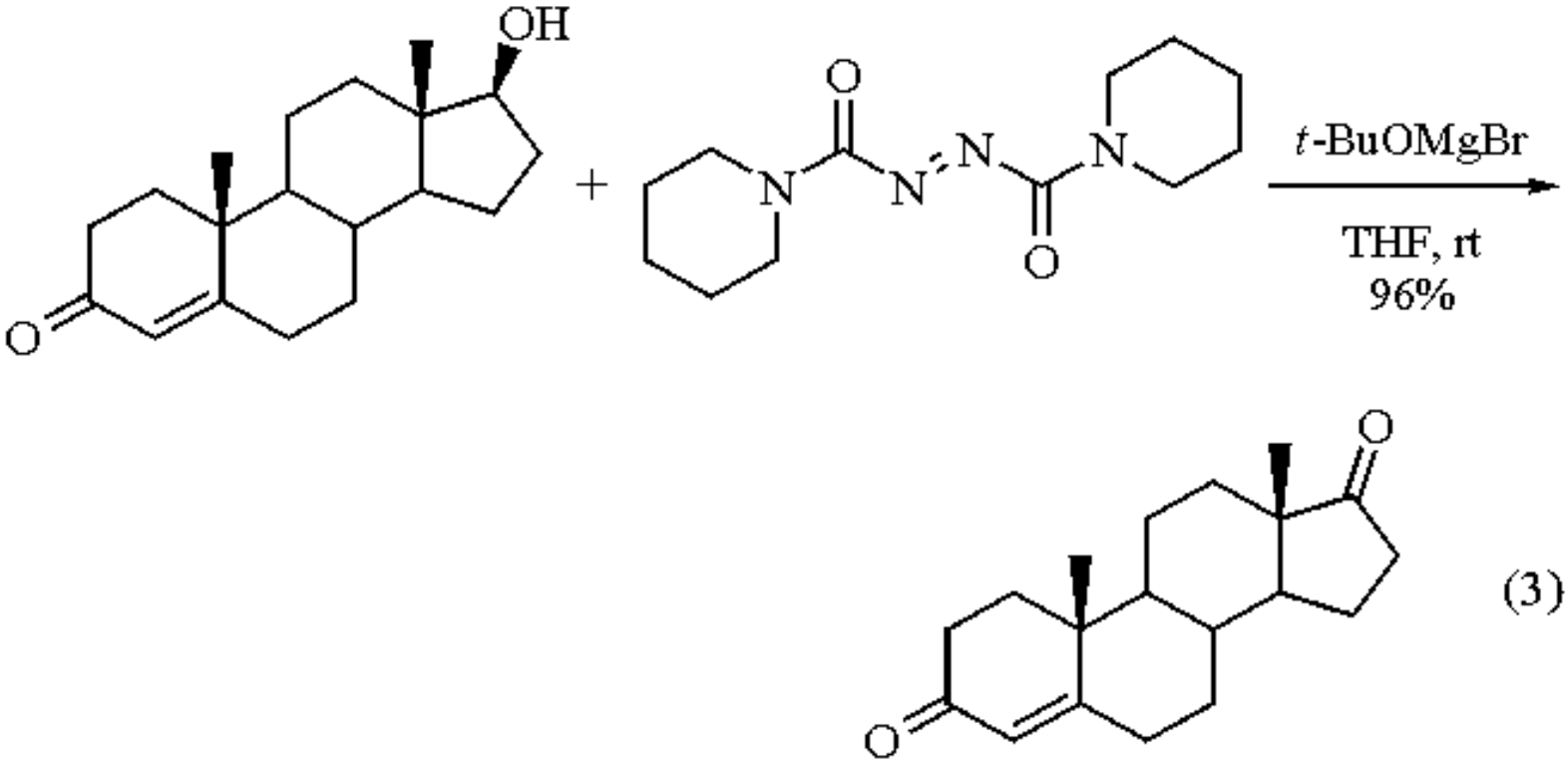

(3)

Rearrangement Reactions.

Cis- and *trans*-2,4-diphenylthietane dioxides rearrange to the corresponding *cis*- and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxides (eqs 4 and 5, respectively) upon reaction with *t*-BuOMgBr.[1] These reactions are

stereospecific with respect to the phenyl groups, but stereoselective with respect to the oxygen atoms on sulfur. When EtMgBr is used as the base, both of these sulfones undergo stereoselective rearrangement to the *trans*-1,2-diphenylcyclopropanesulfinate anion. The influence of *t*-BuOMgBr on the course of these reactions is attributed to its unique dimeric structure.[4]

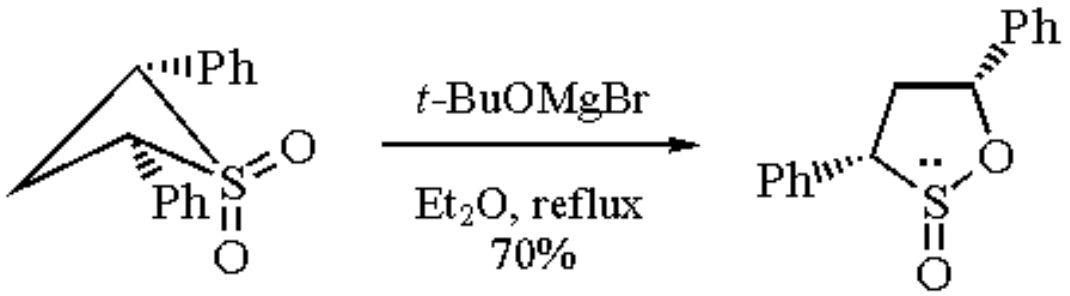

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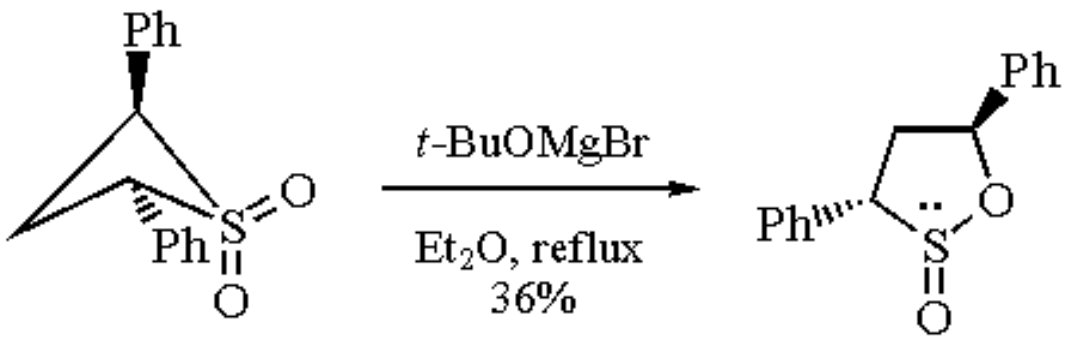

(5)

The protected aldopyranose 2,3,4,6-tetra-*O*-benzyl-D-glycopyranose is readily converted into the protected ketopyranose 1,3,4,5-tetra-*O*-benzyl-L-sorbopyranose by an internal hydride transfer process in the presence of 5.0 equiv of *t*-BuOMgBr in CH_2Cl_2 (eq 6).[5] This rearrangement proceeds poorly in THF and not at all in PhH or MeCN. Bromomagnesium alkoxides of other alcohols, e.g. *i*-PrOH, 2,4,6-trimethylphenol, and 4-chlorophenol, in CH_2Cl_2 were also reasonably effective for the reaction.[5]

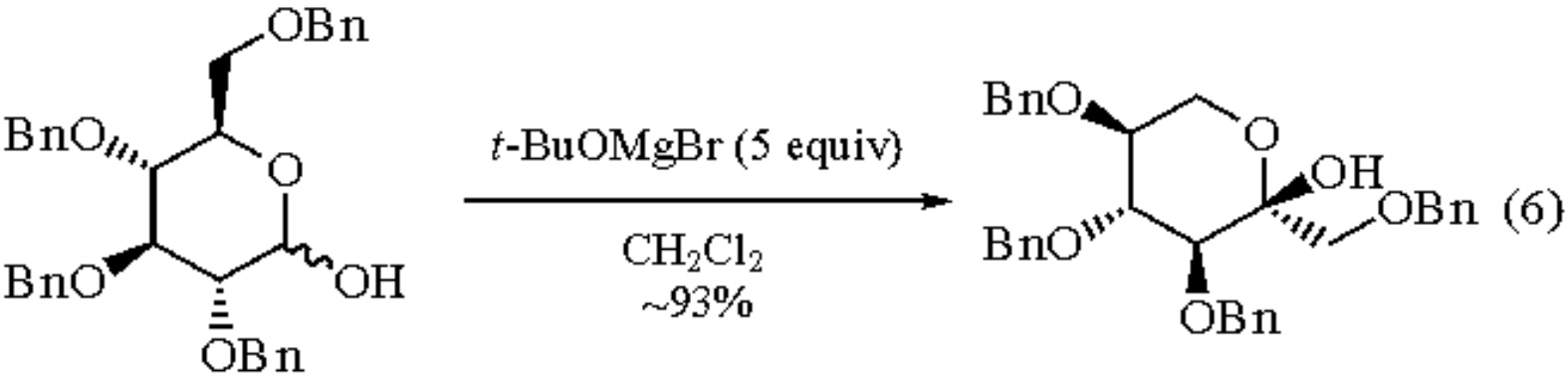

(6)

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t-Butoxymethyllithium[1]

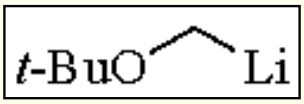

[87996-22-3] · $C_5H_{11}LiO$ · *t*-Butoxymethyllithium · (MW 94.08)

(hydroxymethyl anion equivalent[2])

Solubility: sol THF.

Preparative Methods: generated in situ by a tin-lithium exchange reaction between butyllithium and an α-stannyl ether[3] or by metalation of *t*-butyl methyl ether with an *s*-butyllithium/potassium *t*-butoxide reagent.[2]

Handling, Storage, and Precautions: stable at low temperature (-10 °C or less) in solution.

Reagent Preparation.

A general method for the preparation of *t*-butoxymethyllithium and closely related reagents, such as methoxymethyllithium [*14704-15-5*], ethoxymethyllithium [*104681-85-8*], and benzyloxymethyllithium [*71316-95-5*], involves the use of a tin-lithium exchange reaction. Several of these reagents have been made by treatment of α-chloro ethers with a complex of ***Tin(II) Chloride*** and ***Lithium Bromide*** in THF to generate α-trihalostannyl ethers. These ethers undergo tin-lithium exchange with ***n-Butyllithium*** to give the desired reagents (eq 1).[3a] This transmetalation will also proceed smoothly with butyllithium and alkoxymethyltributyltin (eq 2). In this case, the tributyltin compound is formed from benzyl alcohol/NaOH/tributylstannylmethyl iodide,[3b] benzyloxymethyl Grignard/***Tri-n-butylchlorostannane***,[3b] ***Chloromethyl Methyl Ether***/tributylstannyl Grignard,[3c] or diethoxymethyltributyltin/***Acetyl Chloride***/***Tri-n-butylstannane***.[3c]

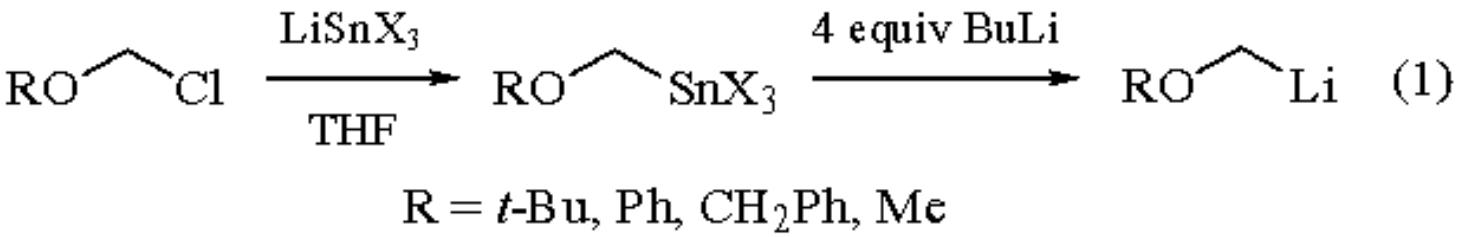

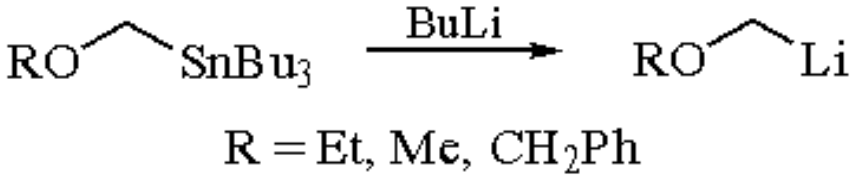

(2)

The transmetalation strategy has also been used to form alkoxymethyllithium reagents from alkoxymethyl telluride by lithium-tellurium exchange.[4] This reaction proceeds in solvents of low polarity, such as toluene and hexane, in which tin-lithium exchange is sluggish.

For *t*-butoxymethyllithium, a more practical preparation for large-scale work is the direct metalation of *t*-butyl methyl ether (TBME) with ***s-Butyllithium*** and ***Potassium t-Butoxide*** (eq 3).[2] The metalation is done in neat TBME to form *t*-butoxymethylpotassium, which is converted to the desired reagent by addition of a solution of LiBr in THF. *t*-Butoxymethyl- and methoxymethylpotassium have also been prepared by metalation of the corresponding ethers with butylpotassium.[5]

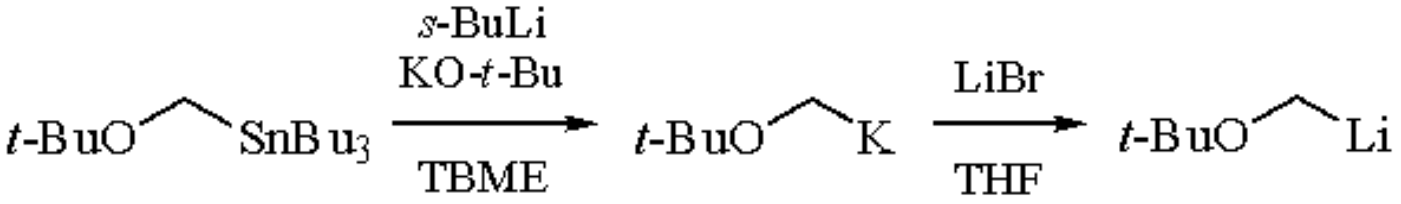

(3)

A third option for generating methoxymethyllithium involves treatment of ***Chloromethyl Methyl Ether*** with ***Lithium*** metal (eq 4).[6] This reaction proceeds smoothly in dimethoxymethane, but does not work in ether or THF.

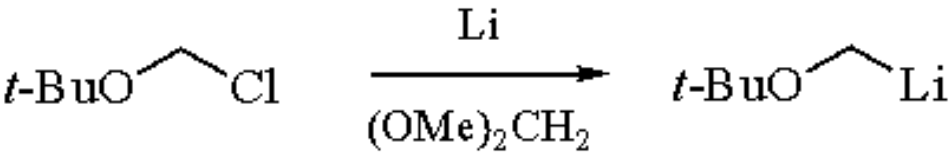

(4)

1,2-Addition to Carbonyls.

One of the most common uses of alkoxymethyllithium reagents is addition to ketones and aldehydes to generate monoalkylated 1,2-diols in good yields (eq 5).[2,3c,7] Subsequent reaction with ***Acetic Anhydride/Iron(III) Chloride*** cleaves the *t*-butyl group and forms a diacetate, which can be hydrolyzed to a diol.[2] A variety of carbonyl compounds can participate in the 1,2-addition reaction, including α,β-unsaturated ketones[8-10] and aldehydes,[11] amides,[12] and lactones.[13]

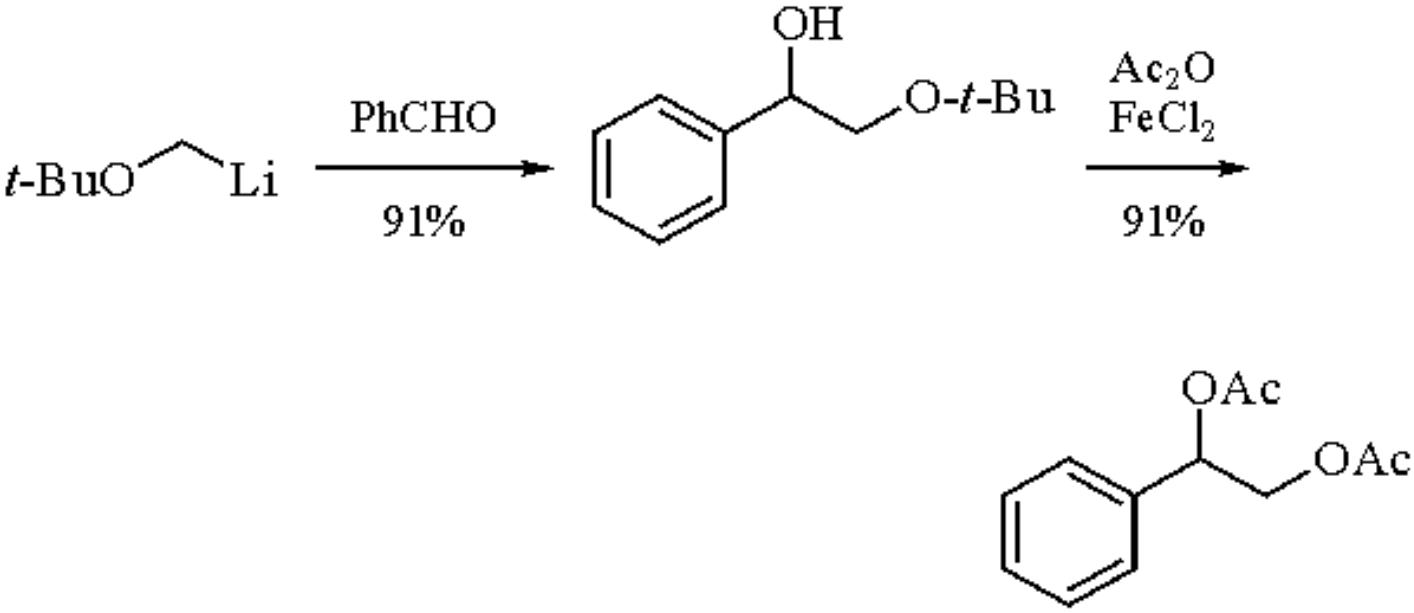

(5)

1,4-Addition to Carbonyls.

When converted to an organocopper reagent by reaction with 1 equiv of copper(I) bromide *N* dimethyl sulfide, *t*-butoxymethyllithium can be used for conjugate addition of *t*-butoxymethyl to α,β-unsaturated carbonyls (eq 6).[2,14] In addition, the copper reagent can be used in enantioselective conjugate additions.[15] A complexed copper reagent formed from a chiral ligand derived from (-)-ephedrine, ***Copper(I) Iodide***, and *t*-butoxymethyllithium reacts efficiently with 2-cyclohexenone to give (*R*)-3-(*t*-butoxymethyl)cyclohexanone (75% yield, 89% ee).

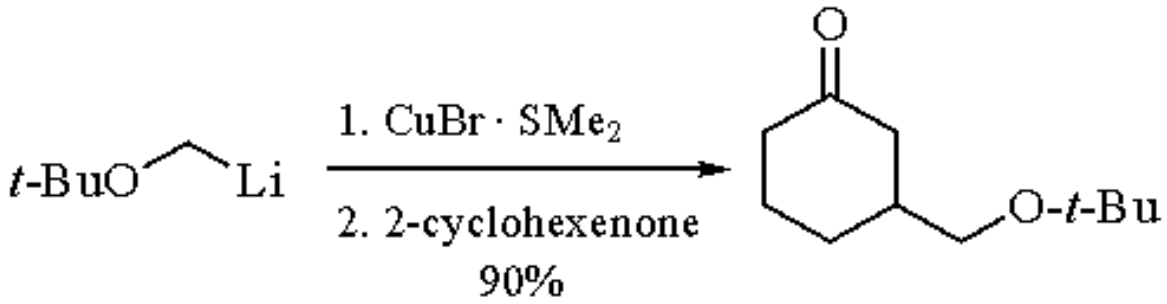

(6)

Other Reactions.

t-Butoxymethyllithium can be used to convert acid chlorides to *t*-butoxymethyl ketones in one step (eq 7).[2] Addition of 1 equiv of ***Copper(I) t-Butoxide*** to the lithium reagent generates an organocopper derivative which reacts cleanly with acid chlorides.

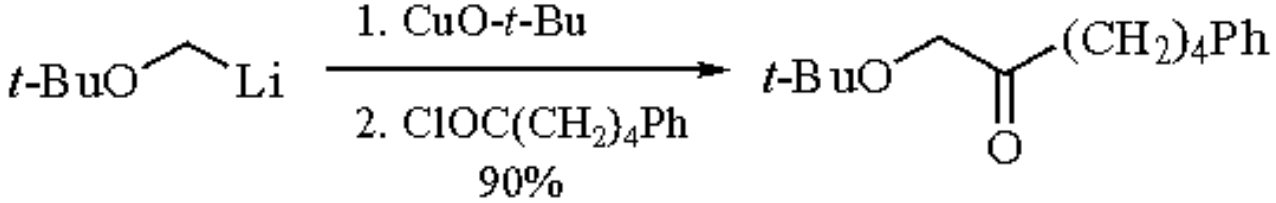

(7)

The alkoxymethyllithium reagents also provide a convenient route to alkyl α-stannyl and α-silyl ethers. Alkoxymethyllithium reacts with either ***Chlorotrimethylsilane*** or trialkyltin chloride to yield trimethylsilylmethyl methyl ether[6b] or *t*-butyl α-stannyl ether,[2] respectively (eq 8). In addition, *t*-butoxymethyllithium can be alkylated efficiently with ***Benzyl Bromide*** to give $Ph(CH_2)_2O$-*t*-Bu in 84% yield.[2]

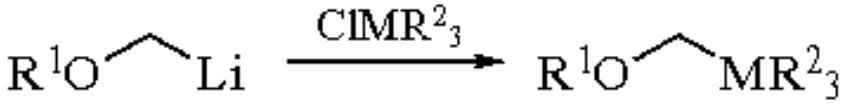

(8)

$R^1 = Me, M = Si, R^2 = Me, 81\%$
$R^1 = t\text{-}Bu, M = Sn, R^2 = Me, 94\%$
$R^1 = t\text{-}Bu, M = Sn, R^2 = Bu, 94\%$

Related Reagents.

A number of similar hydroxymethyl anion equivalents have been developed, including (methoxymethoxy)methyllithium,[16] (ethoxyethoxy)methyllithium,[17] and (benzyloxymethoxy)methyllithium.[18] These reagents are usually formed by protection of trialkylstannylmethanol, followed by a tin-lithium exchange reaction. Seebach has generated $LiOCH_2Li$ by treating tributylstannylmethanol with 2 equiv of butyllithium.[19] Others have used alkoxymethylmagnesium halides,[6a,20] metalated esters,[21] and metalated amides[22] as hydroxymethyl anion equivalents.

Dialkoxymethyllithium reagents have been used as one-carbon nucleophiles to generate a variety of functionalized acetals.[23] These reagents are prepared by reductive lithiation of phenylthio-substituted precursors or transmetalation of tri-*n*-butylstannyl compounds.

See also ***1-(Benzyloxymethoxy)propyllithium***, ***(Diisopropoxymethylsilyl)methylmagnesium Chloride***, ***1-Lithio-1-methoxycyclopropane***, ***1-Methoxyallyllithium***, and ***Tri-n-butyl[(methoxymethoxy)methyl]stannane***.

---

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t-Butylamine

***t*-BuNH$_2$**

[75-64-9] · $C_4H_{11}N$ · *t*-Butylamine · (MW 73.14)

(reagent for preparation of hindered imines and amides;[1] reagent for selective cleavage of methyl phosphate esters; solvent for metal reductions and couplings; solvent for selective bromination of phenols; hindered base; equivalent of ammonia)

Physical Data: bp 45 °C, *d* 0.698 g cm^{-3}.

Solubility: broadly sol organic solvents.

Form Supplied in: mobile liquid; widely available.

Purification: distillation from sodium hydroxide.

Handling, Storage, and Precautions: as a volatile amine, handling should always be done in a fume hood. Store in tightly capped bottles at rt in ventilated cabinets.

Hindered Imines.

Numerous procedures are available for the preparation of *N*-*t*-butyl imines utilizing various dehydrating methods. Aldehydes condense readily without solvent or catalyst, or with sieves as dehydrating agent.[1,3,5,6] Ketones require a catalyst such as ***Titanium(IV) Chloride***,[4] ***Potassium Carbonate***,[3a] or dry EtOH.[2] The steric hindrance provided by the *t*-butyl group typically discourages reaction at the imine carbon as in the monoalkylation of ketones and aldehydes through their magnesio-imines (eq 1),[3] and the cyclization of α-chloro ketimines to cyclopropanes (eq 2).[4] The *t*-butyl group has also been an excellent substituent for the preparation of stable oxaziridines from imines (eq 3).[5] The differences in the rate of reaction typically seen between aldehydes and ketones have been used to prepare *t*-butyl imines of the former selectively.[6] Numerous examples also exist of the use of *t*-butyl amides for the purpose of discouraging reaction at the amide carbonyl group.[7]

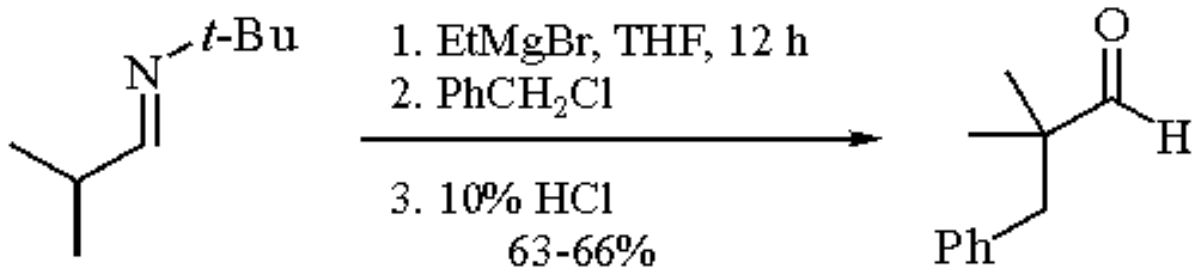

(1)

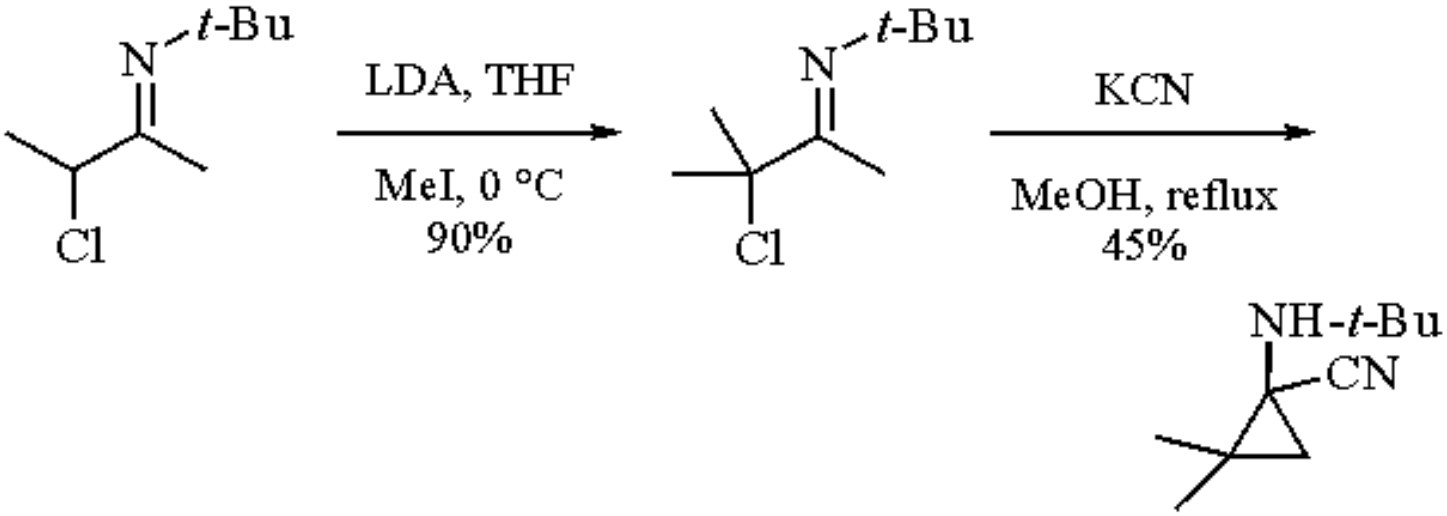

(2)

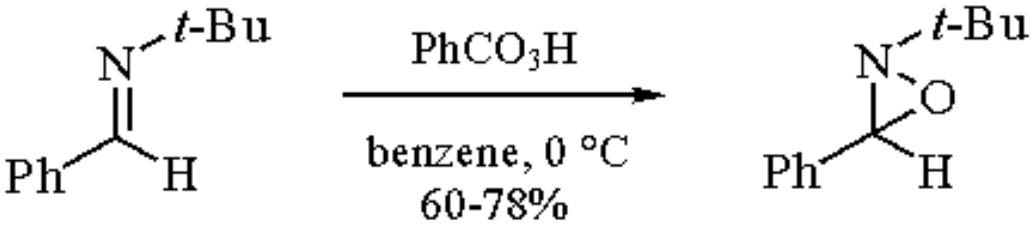

(3)

Phosphate Ester Cleavage.

This reagent has found a unique advantage in the selective S_N2 cleavage of *methyl* esters of phosphoric acid in the presence of *ethyl* esters allowing nucleotide chemists unusual flexibility (eq 4).[8a] Selective cleavage of a β-cyanoethyl phosphate ester has also been effected through hindered base elimination in pyridine.[8b]

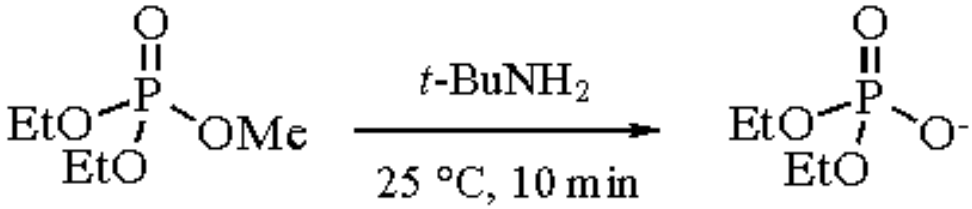

(4)

Solvent for Metal-Catalyzed Couplings and Reductions.

Substitution of *t*-butylamine for ethylamine or ammonia in dissolving metal reductions is often advantageous.[9] Useful advantage has been made in Cu catalyzed couplings of acetylenes and naphthols.[10]

Hindered Base in Eliminations.

Several examples are available of the use of the hindered amine function in eliminations.[8c,11]

Selective *o*-Bromination of Phenols.

This amine has been used to successfully act as acid scavenger in the bromination of phenols, producing only *ortho* products. Effective removal of HBr by precipitation of the amine salt as it is formed is crucial to the regioselectivity.[12] See ***Bromine-t-Butylamine***.

Ammonia Equivalent.

The facile acid removal of the *t*-butyl group in *t*-butyl esters has been extended in some cases to amides and amines.[4,13] The typical acidic reagents for this transformation are harsher, limiting the utility. While sulfonamides are more typical as ammonia carriers, acid cleavage does allow selective production of the sulfonamide from an *N*-*t*-butyl benzenesulfonamide.[13]

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2-(*t*-Butylamino)-3-methyl-2-butenenitrile

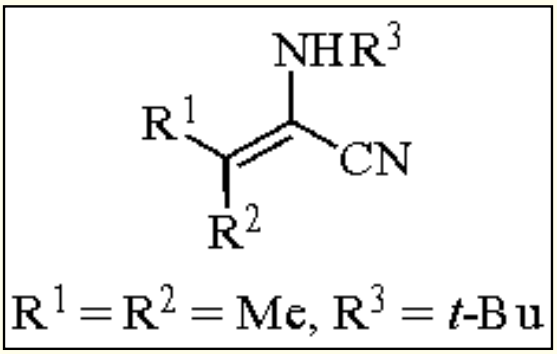

(**1**; $R^1 = R^2 = R^3 = Me$)

[66875-75-0] · $C_6H_{10}N_2$ · 2-(Methylamino)-3-methyl-2-butenenitrile · (MW 110.16) (**2**; $R^1 = R^2 = Me$, $R^3 = Et$)

[73404-99-6] · $C_7H_{12}N_2$ · 2-(Ethylamino)-3-methyl-2-butenenitrile · (MW 124.19) (**3**; $R^1 = R^2 = Me$, $R^3 = i$-Pr)

[63364-15-8] · $C_8H_{14}N_2$ · 2-(Isopropylamino)-3-methyl-2-butenenitrile · (MW 138.21) (**4**; $R^1 = R^2 = Me$, $R^3 = t$-Bu)

[63364-14-7] · $C_9H_{16}N_2$ · 2-(*t*-Butylamino)-3-methyl-2-butenenitrile · (MW 152.24) (**5**; $R^1 = R^2 = Me$, $R^3 = Cy$)

[63364-25-0] · $C_{11}H_{18}N_2$ · 2-(Cyclohexylamino)-3-methyl-2-butenenitrile · (MW 178.27) (**6**; $R^1 = Me$, $R^2 = Et$, $R^3 = i$-Pr)

[66102-53-2] · $C_9H_{16}N_2$ · 2-(Isopropylamino)-3-methyl-2-pentenenitrile · (MW 152.24) (**7**; $R^1 = Me$, $R^2 = Et$, $R^3 = t$-Bu)

[66102-54-3] · $C_{10}H_{18}N_2$ · 2-(*t*-Butylamino)-3-methyl-2-pentenenitrile · (MW 166.27) (**8**; $R^1 = R^2 = Et$, $R^3 = i$-Pr)

[66102-55-4] · $C_{10}H_{18}N_2$ · 2-(Isopropylamino)-3-ethyl-2-pentenenitrile · (MW 166.27) (**9**; $R^1 = R^2 = Et$, $R^3 = t$-Bu)

[63364-26-1] · $C_{11}H_{20}N_2$ · 2-(*t*-Butylamino)-3-ethyl-2-pentenenitrile · (MW 180.30) (**10**; $R^1 = R^2 = Et$, $R^3 = Cy$)

[63364-27-2] · $C_{13}H_{22}N_2$ · 2-(Cyclohexylamino)-3-ethyl-2-pentenenitrile · (MW 206.33) (**11**; R^1,R^2 = -$(CH_2)_5$-, R^3 = *i*-Pr)

[73171-65-0] · $C_{11}H_{18}N_2$ · Cyclohexylidene(isopropylamino)acetonitrile · (MW 178.27) (**12**; R^1,R^2 = -$(CH_2)_5$-, R^3 = *t*-Bu)

[63364-28-3] · $C_{12}H_{20}N_2$ · *t*-Butylamino(cyclohexylidene)acetonitrile · (MW 192.30) (**13**; R^1,R^2 = -$(CH_2)_5$-, R^3 = Cy)

[63364-29-4] · $C_{14}H_{22}N_2$ · Cyclohexylamino(cyclohexylidene)acetonitrile · (MW 218.34)

(geminal donor-acceptor-substituted alkenes;[1] for synthesis of trialkylketenimines and -amidines,[2,3] α-functionalized imidoyl cyanides,[4] carboxylic amides,[5] and 1-aza-2-cyano-1,3-dienes[6])

Alternate Names: N-t-butyl-β,β-dimethyl-α-cyanoenamine; 2-(*t*-butylamino)-3-methylcrotononitrile.

Physical Data: bp (**1**) 97-98 °C/21 mmHg; (**2**) 89-94 °C/15 mmHg; (**3**) 95-96 °C/12 mmHg; (**4**) 112-117 °C/14 mmHg; (**5**) 135-146 °C/12 mmHg; (**6**) 94-101 °C/11 mmHg; (**8**) 98-100 °C/11 mmHg; (**9**) 110-114 °C/12 mmHg; (**10**) 146-157 °C/12 mmHg; (**11**) 83 °C/0.017 mmHg; (**13**) 115-125 °C/0.05 mmHg; mp (**3**) 30 °C; (**11**) 44 °C.

Solubility: sol most organic solvents; compatible with all solvents.

Form Supplied in: commercially available (R^1 = R^2 = Me, R^3 = *i*-Pr, *t*-Bu) as colorless liquid or low-melting solid.

Analysis of Reagent Purity: ^{1}H NMR (GC cannot be used as these reagents are subject to tautomerize into stable imidoyl cyanides).

Preparative Methods: highly reproducible synthesis from cyanation of α-chloro aldimines with potassium cyanide in methanol under reflux (eq 1).[6] This reaction is amenable to large-scale preparation (1-2 mol) and synthesis of several higher homologs.[6,7] DMSO, DMF, or water can be used as well in these cyanation reactions.[4]

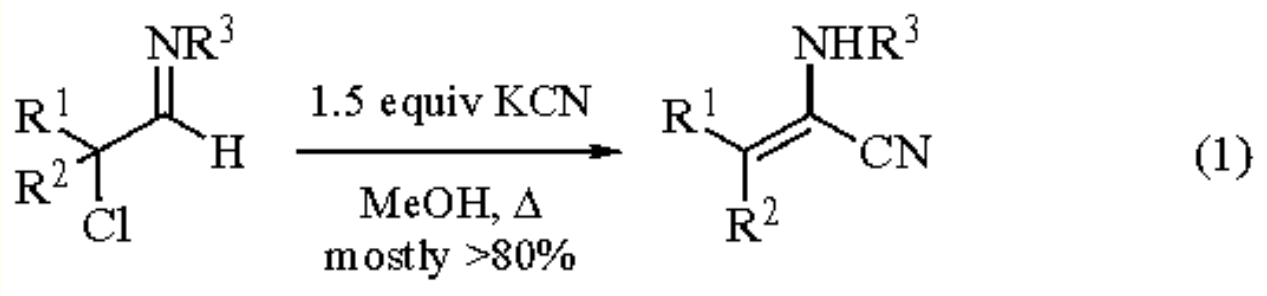

Handling, Storage, and Precautions: these reagents are stable for a long period at -20 °C. Stable at rt for several weeks. As the reagents might act as a cyanide source, use in a well-ventilated fume hood is recommended.

Introduction.

α-Cyano enamines are a class of geminal donor-acceptor-substituted alkenes.[1] Upon heating, e.g. distillation in vacuo or gas chromatographic analysis, α-cyano enamines tautomerize partially into imidoyl cyanides (eq 2).[6] Both α-cyano enamines and imidoyl cyanides are stable isolable species.

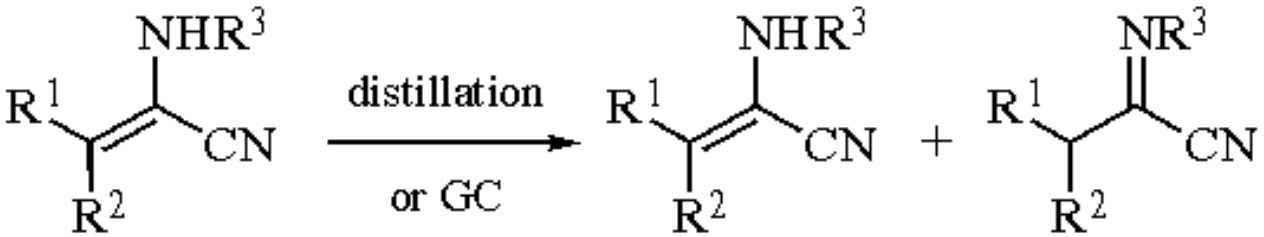

(2)

Synthesis of Trialkylketenimines and Amidines.

Numerous syntheses of ketenimines, having at least one aryl substituent on carbon or nitrogen, have been reported hitherto. The rare and labile trialkylketenimines are easily accessible from α-cyano enamines by reaction with methylmagnesium iodide or ***Methyllithium*** in diethyl ether (eq 3).[2,3] Trialkylketenimines may be isolated or treated in situ with primary amines to afford amidines (eq 4).[2]

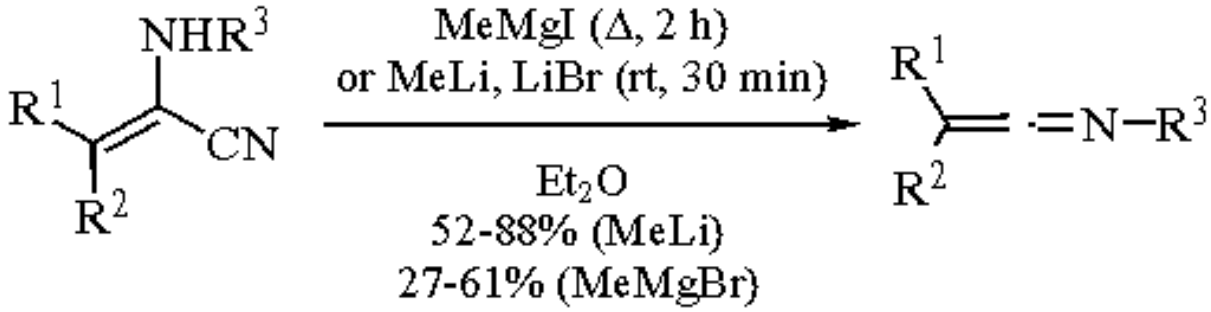

(3)

$R^1 = Me, Et; R^2 = Me, Et; R^3 = i\text{-}Pr, t\text{-}Bu, Cy$

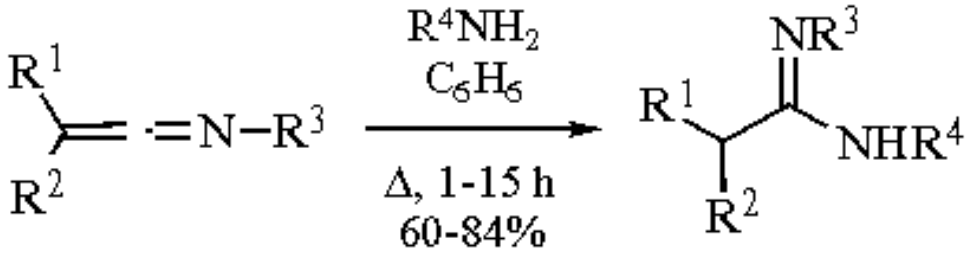

(4)

$R^4 = Ph, i\text{-}Pr, 4\text{-}MeC_6H_4, 4\text{-}MeOC_6H_4$

Functional Group Transformation of Aldehydes into

Carboxylic Amides.

Heating of α-cyano enamines with dry hydrogen chloride in an anhydrous alcohol, e.g. methanol, ethanol, or *n*-butanol, produces carboxylic amides and the corresponding alkyl chlorides (eqs 5 and 6).[5] The intermediate enammonium chlorides are accessible by reaction of α-cyano enamines with dry ***Hydrogen Chloride*** in benzene (eq 5).[8] As α-cyano enamines are easily accessible from aldehydes, this conversion corresponds to the transformation of an aldehyde into a carboxylic amide.[9]

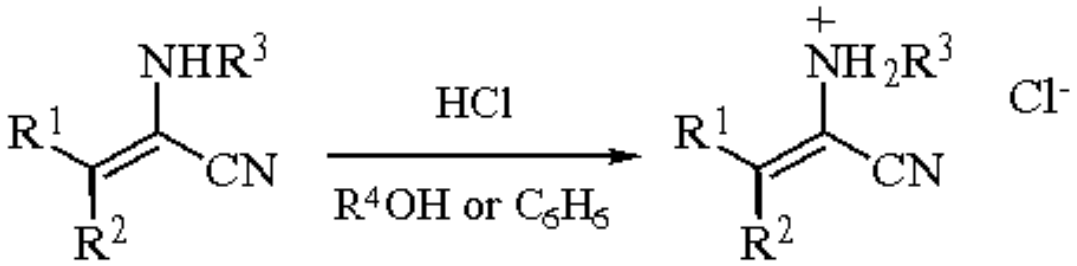

(5)

R^4 = Me, Et, *n*-Bu

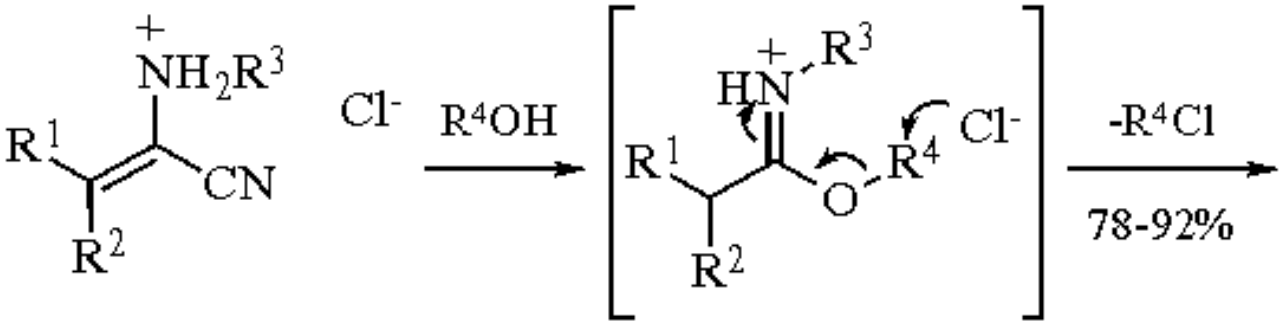

R^4 = Me, Et, *n*-Bu

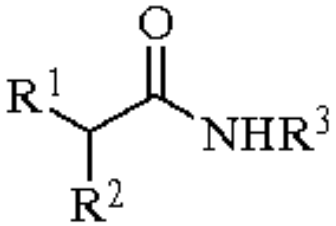

(6)

Synthesis of Functionalized Imidoyl Cyanides.

α-Cyano enamines react instantaneously in CCl_4 at rt with ***N-Bromosuccinimide*** and ***N-Chlorosuccinimide*** to give access to stable α-chloro- and α-bromoimidoyl cyanides (with practically no limitations in the substitution pattern of higher analogs) (eq 7).[4] The α-halo substituent of these trifunctional compounds is easily displaced by nucleophiles, such as thiolates, to give α-sulfenylated imidoyl cyanides (eq 8).[10] On the other hand, α-bromoimidoyl cyanides are readily converted into 1-aza-2-cyano-1,3-dienes by treatment with ***Sodium Methoxide*** in methanol under reflux (eq 9).[10]

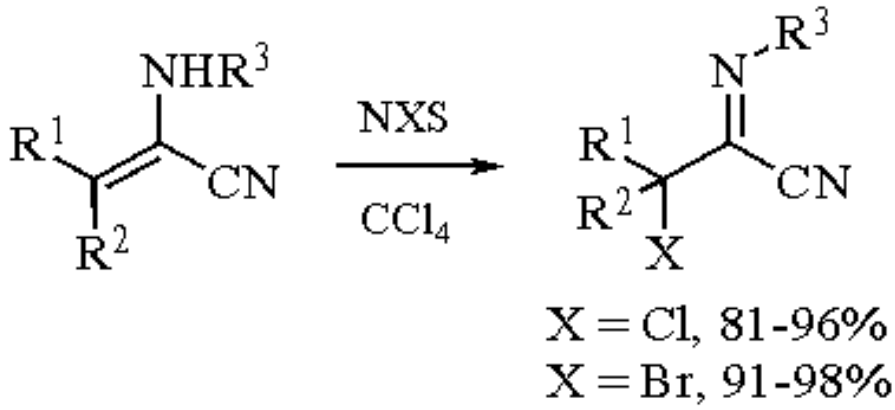

(7)

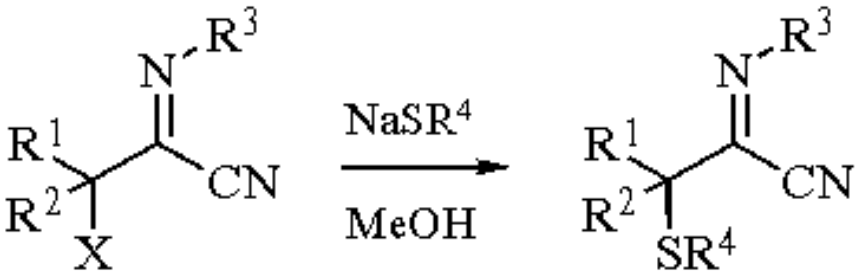

(8)

R^4 = Et, *i*-Pr, *t*-Bu, *s*-Bu, Ph, Bn, *i*-Bu, *n*-Bu

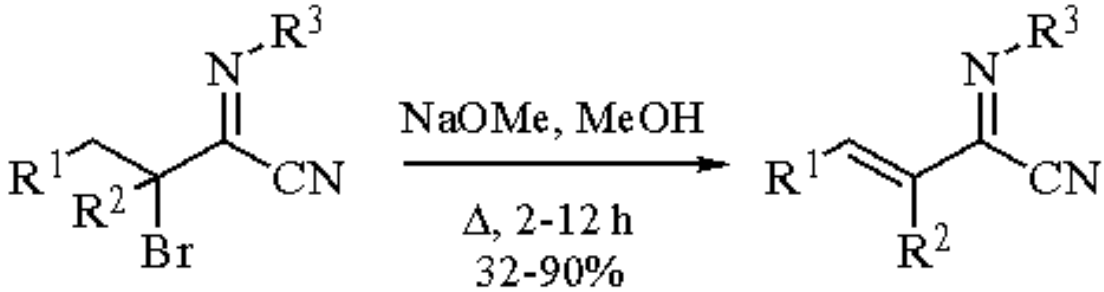

(9)

R^1 = H, alkyl; R^2 = alkyl

Synthesis of Nontautomerizable α-Cyano Enamines.

N-Alkylation of tautomerizable α-cyano enamines is readily accomplished with a variety of alkylating agents, including alkyl fluorosulfonates, dialkyl sulfates, or ***Triethyloxonium Tetrafluoroborate*** (eq 10).[11]

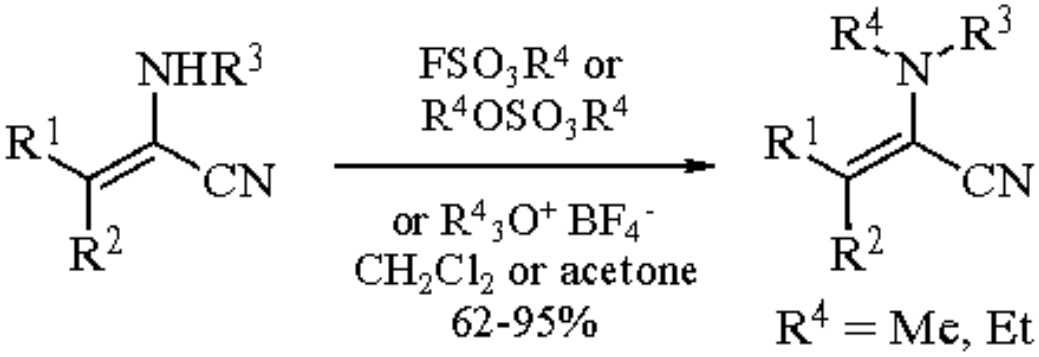

(10)

Similar α-cyano enamines may also be obtained by reaction of α-chloro enamines with ***Potassium Cyanide*** (eq 11).[12] Addition of organolithium reagents to the cyano group followed by acidic hydrolysis provides α-diketones.[12]

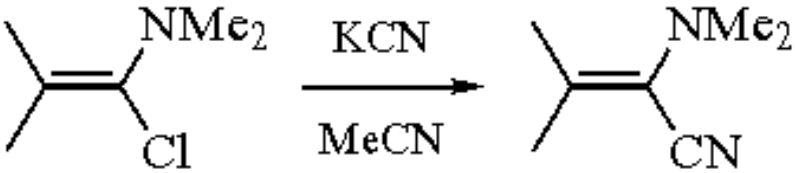

(11)

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2. De Kimpe, N.; Verhé, R.; De Buyck, L.; Chys, J.; Schamp, N. *JOC* **1978**, *43*, 2670.
3. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *OPP* **1982**, *14*, 213.
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Norbert De Kimpe

University of Gent, Belgium

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t-Butyl Azidoformate

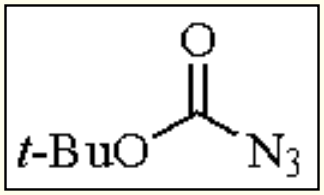

[1070-19-5] · $C_5H_9N_3O_2$ · *t*-Butyl Azidoformate · (MW 143.15)

(electron-deficient azide; can undergo cycloadditions with alkenes to yield triazolines;[1] used for the introduction of a *t*-Boc group on alcohols and amines)

Physical Data: bp 57-61 °C/40 mmHg; n^{24} 1.4224-1.4230.

Solubility: freely sol common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: see Insalaco and Tarbell.[10]

Handling, Storage, and Precautions: as with all azides of low molecular weight, *t*-butyl azidoformate is sensitive to both heat and shock. It is usually purified by distillation under reduced pressure and detonation under these conditions has been reported.[2] All operations involving this reagent should be carried out with great caution in a fume hood and behind a safety shield. The vapors of this reagent are toxic and inhalation is known to cause giddiness, nausea, and severe headache. It is recommended that the reagent be used immediately after preparation. The original literature should be thoroughly consulted before preparation and use of this reagent.

Introduction.

t-Butyl azidoformate is prepared by the reaction of *t*-butylcarbonic diethylphosphoric anhydride and potassium azide.[10] Other preparations involve the reaction of *t*-butyl carbazate with nitrous acid,[3] and the reaction of ***t-Butyl Chloroformate*** with tetramethylguanidinium azide.[4] *t*-Butyl azidoformate has been used in three broad classes of reactions: for the generation and reactions of the corresponding nitrenes, for the cycloaddition of the azide moiety to alkenes and other unsaturated groups, and for the *t*-butyloxycarbonylation of a wide variety of functional groups.

t-Butoxycarbonylnitrenes.

The nitrenes can be generated from *t*-butyl azidoformate both by thermolysis and photolysis. The synthetic utility of these nitrenes is limited because they often react by a variety of pathways to give a mixture of products. One of the few useful reactions involves heating *t*-butyl azidoformate in DMSO to give the corresponding sulfoximides via the nitrene (eq 1).[5]

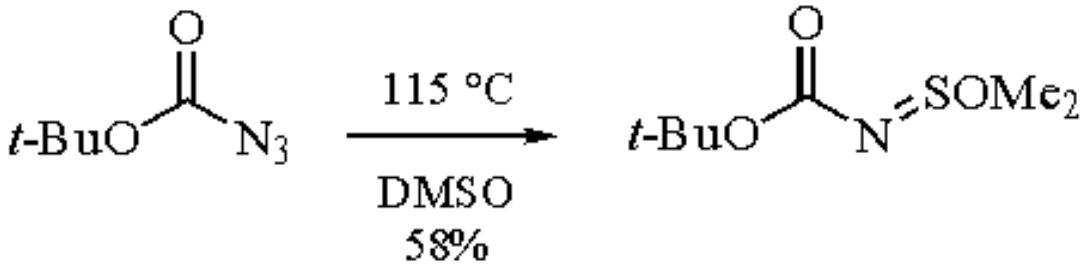

(1)

Cycloaddition Reactions.

t-Butyl azidoformate has been used only sparingly in cycloadditions to alkenes. Azidoformates usually begin to decompose above 60 °C and only cycloadditions that proceed readily below this temperature are synthetically useful. This requirement has limited the cycloaddition partners to strained and/or electron-rich alkenes. The Δ^2-triazolines formed may be isolated or subjected to irradiation directly to give the aziridines. Cycloadditions to strained alkenes often proceed in high yields but with poor regioselectivity. However, if aziridines are the desired products, the poor regioselectivity in the cycloaddition is not a drawback since both regioisomeric triazolines lead to the same aziridine. Heating the substituted 7-oxabicyclo[2.2.1]hept-2-ene with *t*-butyl azidoformate in the dark followed by irradiation of the crude mixture of regioisomeric triazolines gives the aziridine in 63% yield (eq 2).[6]

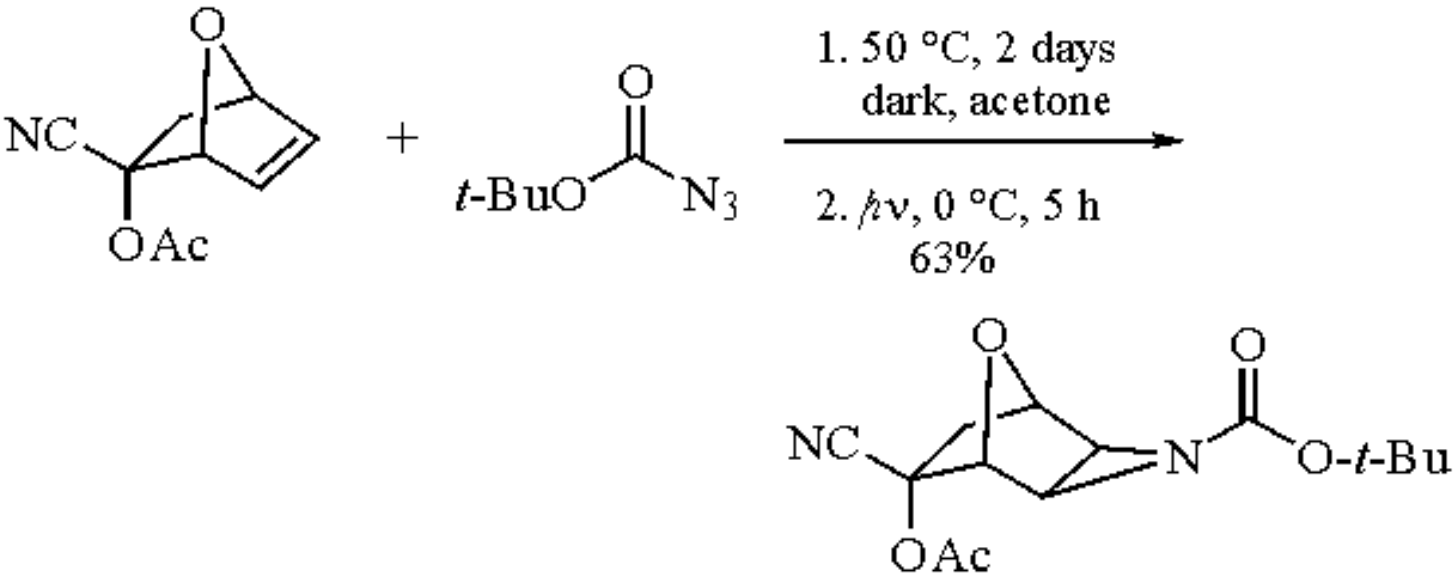

(2)

t-Butoxycarbonylation.

t-Butyl azidoformate has been used for the *t*-butoxycarbonylation of a variety of functional groups such as alcohols, phenols, and amines.[7] Eq 3 illustrates the use of this reagent for the *t*-butoxycarbonylation of an amine.[7a] The mild conditions of the reaction coupled with the importance of the *t*-Boc functionality as a protecting group has made the reagent popular and it has found widespread use in peptide chemistry.[8] The *t*-butoxycarbonylation of pyrroles and

indoles has also been accomplished using this reagent.[9] However, in recent years, other commercially available compounds have replaced *t*-butyl azidoformate as the reagent of choice for such reactions in view of the potentially explosive properties of the latter.

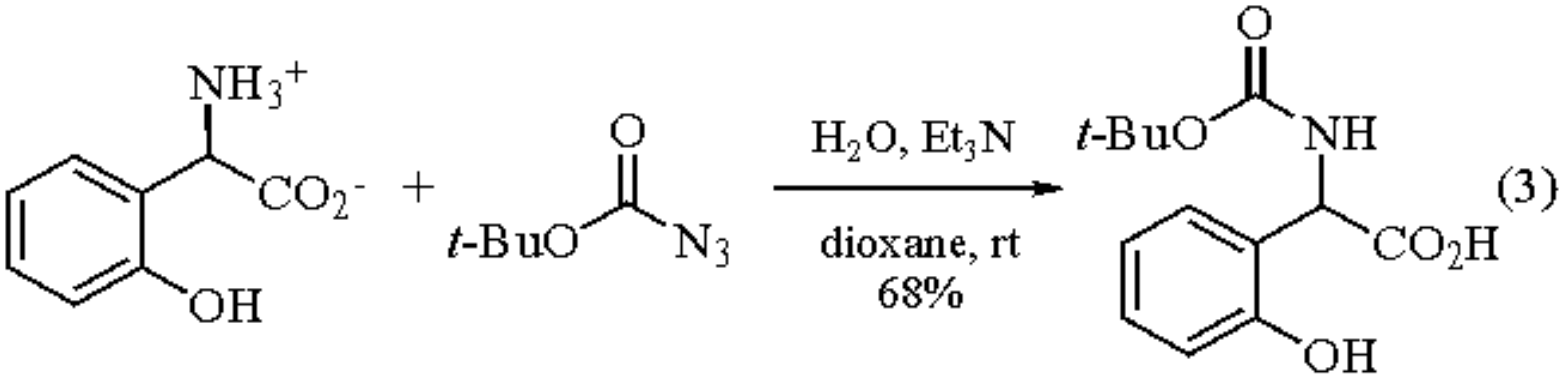

Related Reagents.

1-(t-Butoxycarbonyl)imidazole; ***1-N-(t-Butoxycarbonyl)-1H-benzotriazole 3-N-Oxide***; ***2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile***; ***N-(t-Butoxycarbonyloxy)phthalimide***; ***1-t-Butoxycarbonyl-1,2,4-triazole***; ***Di-t-butyl Dicarbonate***.

---

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t-Butyl 4-Benzoylperbenzoate

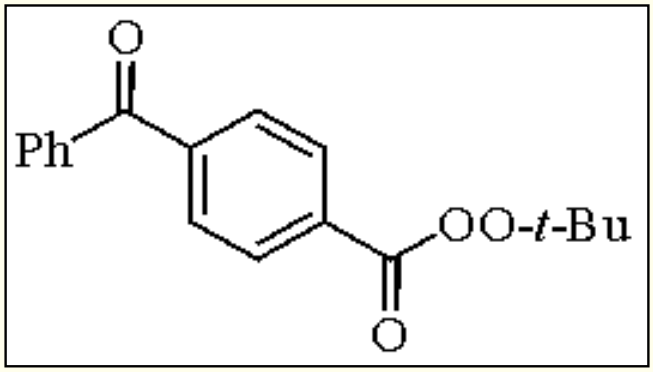

[71616-77-8] · $C_{18}H_{18}O_4$ · *t*-Butyl 4-Benzoylperbenzoate · (MW 298.34)

(reagent for low-temperature initiation of radical reactions)

Physical Data: mp 62-64 °C.

Solubility: sol benzene, methanol, cyclohexane.

Form Supplied in: not commercially available.

Preparative Method: prepared from the corresponding carboxylic acid chloride by treatment with ***t-Butyl Hydroperoxide***.[1]

Handling, Storage, and Precautions: avoid exposure of the reagent to light and heat; store protected from light in a refrigerator or freezer.

In the search for efficient photoinitiators for polymerization processes and radical C-C bond forming reactions a range of novel peresters were prepared, including *t*-butyl 4-benzoylperbenzoate (**1**).[1] On photolysis this compound undergoes efficient homolysis of the peroxide linkage, producing a carboxyl radical and a *t*-butoxy radical (eq 1). The latter is able to initiate further radical chemistry by hydrogen atom abstraction from a suitable donor. The advantages of using this system are that radical chemistry can be initiated at relatively low temperatures (contrasting with the thermal conditions often employed, such as ***Azobisisobutyronitrile*** in benzene at reflux) and the irradiation is carried out at relatively long wavelength (360 nm) which should not cause unwanted excitation in most other reactants.

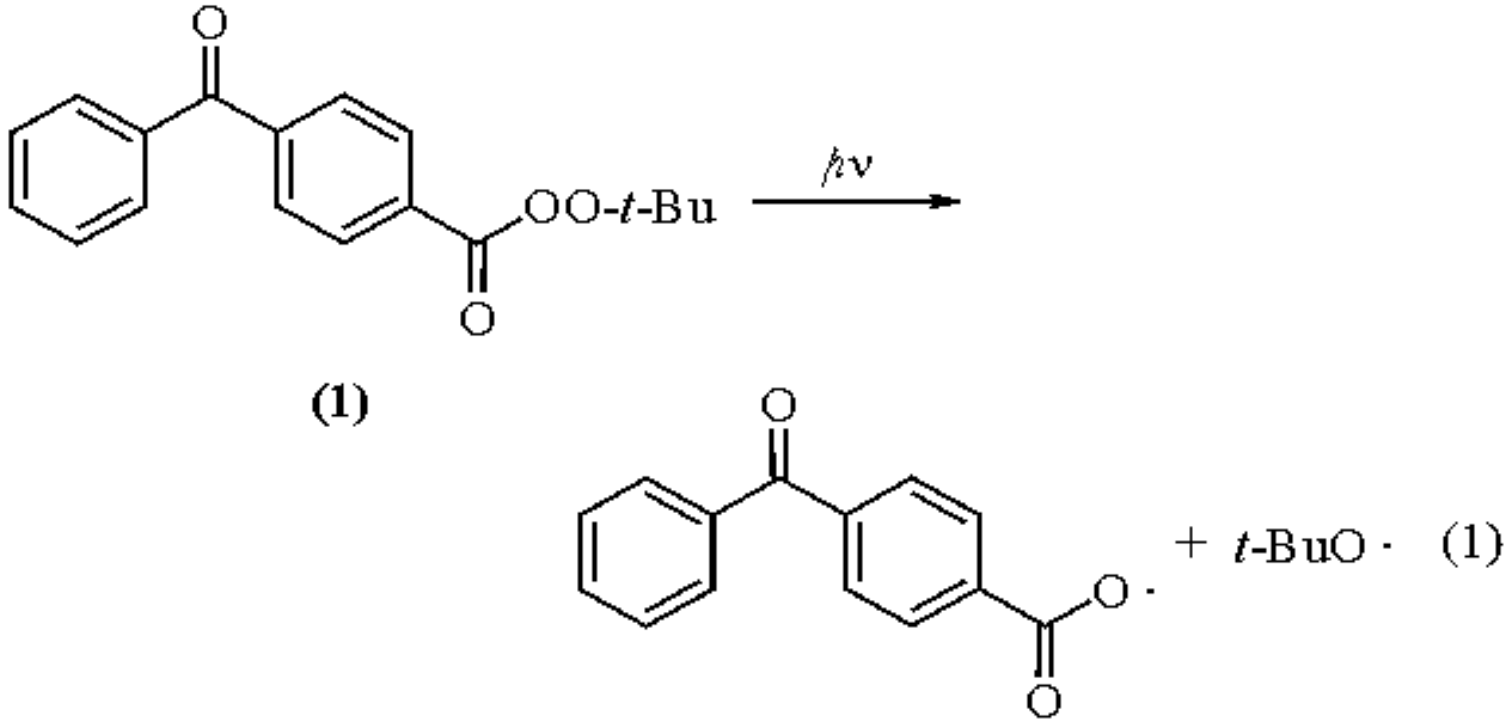

The use of this initiator has been examined in some Kharasch-type additions of acyl radicals to alkene acceptors (eqs 2 and 3).[2]

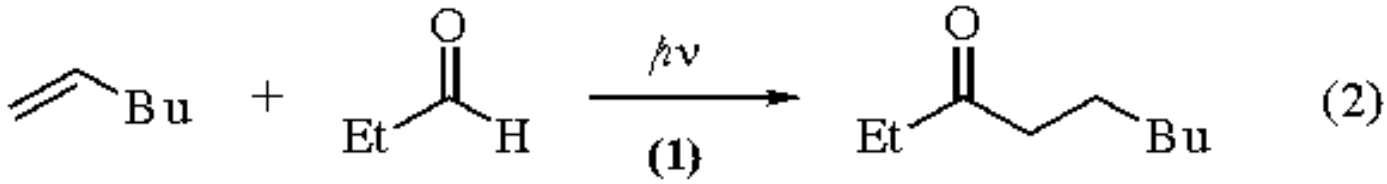

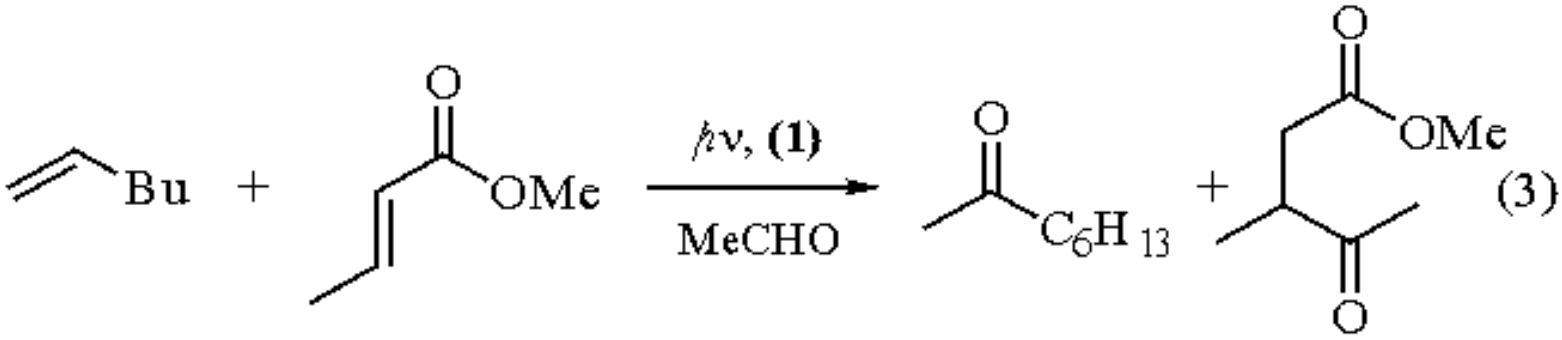

4 °C	1:10.4
rt	1:6.3
78 °C	1:2.1

In competition reactions, involving addition to either 1-hexene or methyl crotonate, addition to methyl crotonate is preferred with the highest selectivity being observed when the reaction was conducted at 4 °C. This selectivity was then utilized to effect a cyclization reaction (eq 4).

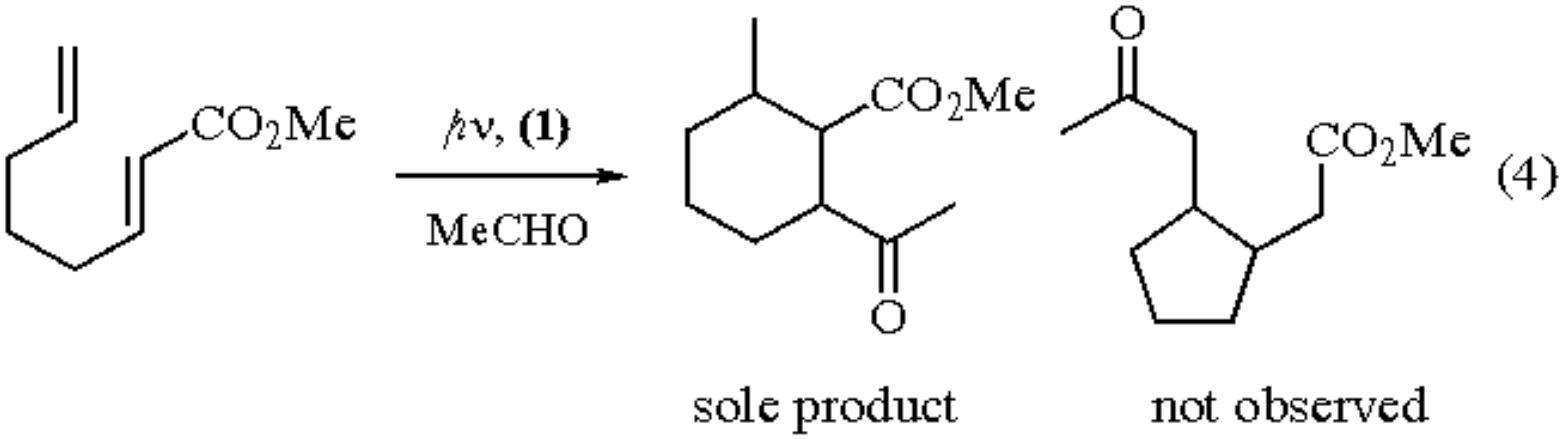

Of the two possible pathways, only that resulting in the six-membered ring product is observed, due to the high regioselectivity in the initial acyl radical addition. Alternative methods of initiation of the reaction, using ***Dibenzoyl Peroxide*** or photolysis in the presence of benzophenone, were tried for comparison, but gave markedly lower yields of product.

---

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t-Butyl 2-*t*-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate

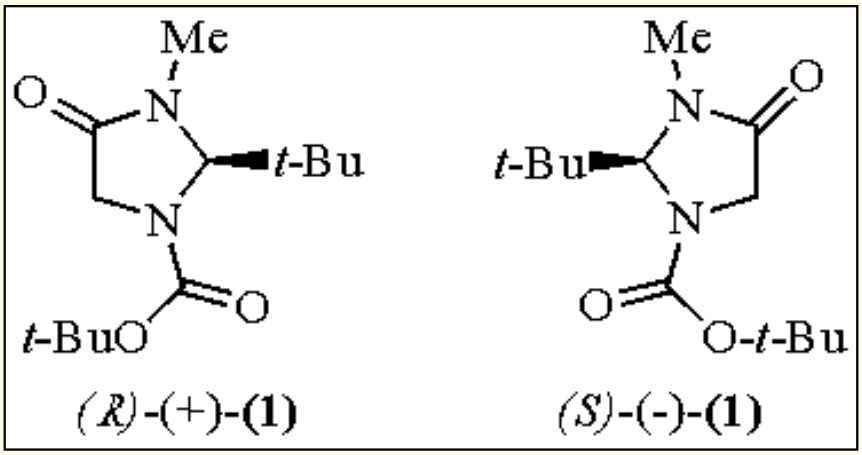

(*R*)-(+)-(**1**)

[119838-44-7] · $C_{13}H_{24}N_2O_3$ · *t*-Butyl 2-*t*-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate · (MW 256.34)
(*S*)-(-)-(**1**)

[119838-38-9]

(chiral glycine derivatives[1] for the synthesis of amino acids)

Alternate Names: N-t-butoxycarbonyl-2-*t*-butyl-3-methylimidazolidin-4-one; Boc-BMI.

Physical Data: mp 68-70 °C; [α]rtD = 14.6° (*c* = 1.18, $CHCl_3$).

Solubility: sol all common organic solvents.

Form Supplied in: colorless crystalline solid.

Preparative Method: the commercial glycine *N*-methylamide hydrochloride is converted to the racemic imidazolidinone (**2**) by imine formation with ***Pivalaldehyde*** and cyclization under acidic conditions (eq 1).[1,2] The mandelate salt of like configuration is less soluble and is used for highly efficient resolution; subsequent treatment with Boc anhydride (***Di-t-butyl Dicarbonate***) gives the enantiomeric Boc-BMI (**1**) (eq 2).

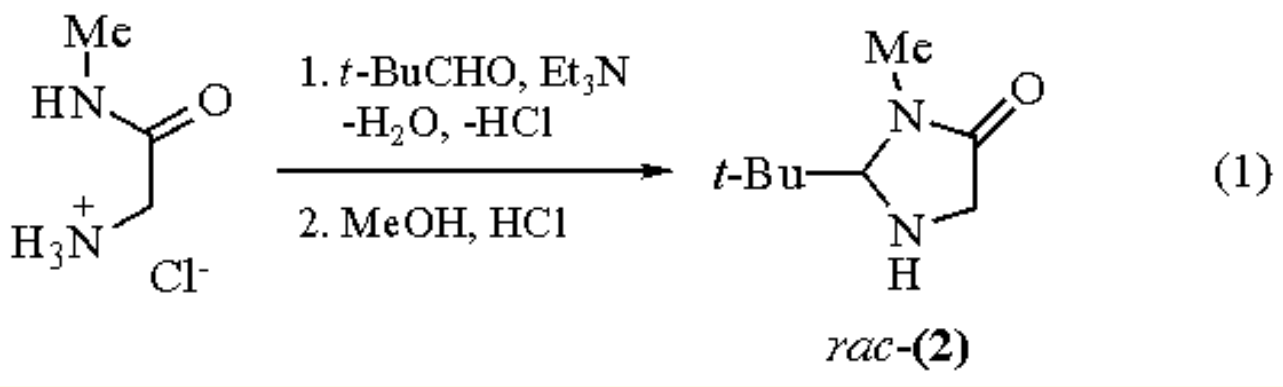

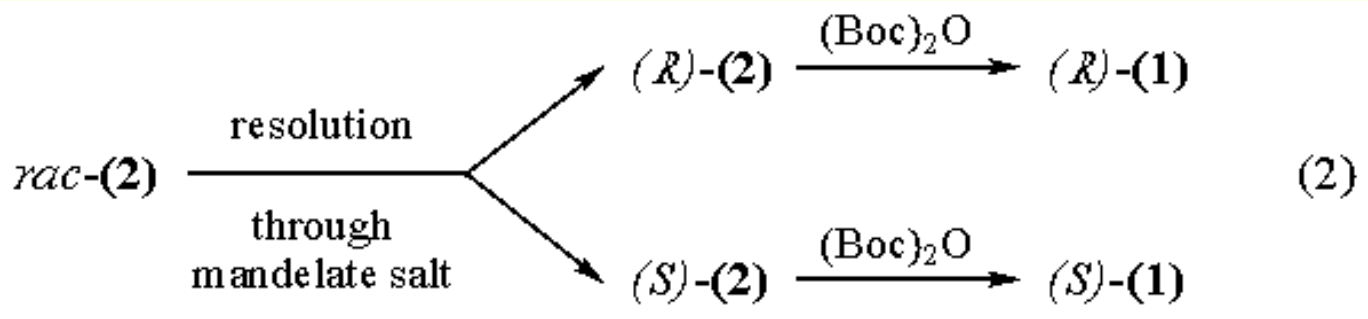

Handling, Storage, and Precautions: stable in a bottle at rt for years.

Reactions of Boc-BMI with Electrophiles.

The enolate of Boc-BMI is generated with ***Lithium Diisopropylamide*** in THF at -75 °C; the resulting solutions of this highly nucleophilic reagent are stable up to 0 °C. All reactions occur from the face of the enolate *trans* to the *t*-Bu group at C(2). Alkylations[1,3-6] even with secondary alkyl halides are so efficient, to give (**3**), that one-pot double alkylations, which yield (**4**), are possible; the sequence in which two different alkyl halides are employed determines the absolute configuration of the α-branched α-amino acids eventually obtained.

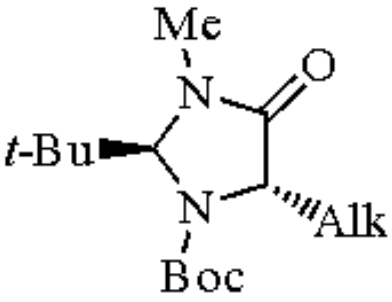

(3)

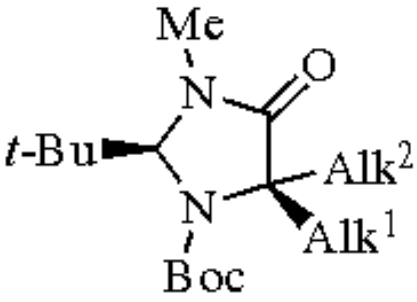

(4)

The method has been used to prepare isotopically labelled amino acids.[3,7] While Boc-BMI enolate adds to aldehydes with only moderate diastereoselectivity, reduction of the acylation products (**5**) gives allothreonine derivatives (**6**).[8] Michael additions to α,β-unsaturated esters,[9] ketones,[10] and nitro compounds[1] lead to products of type (**7**) and (**8**) (for a general discussion see Suzuki and Seebach[9]).

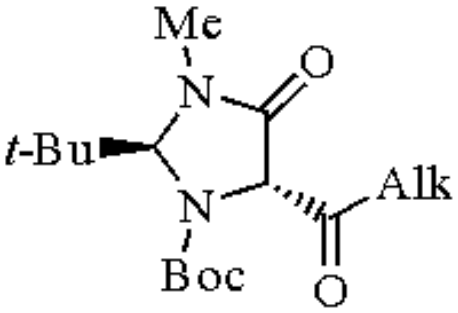

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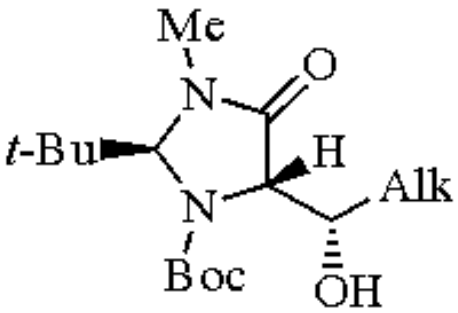

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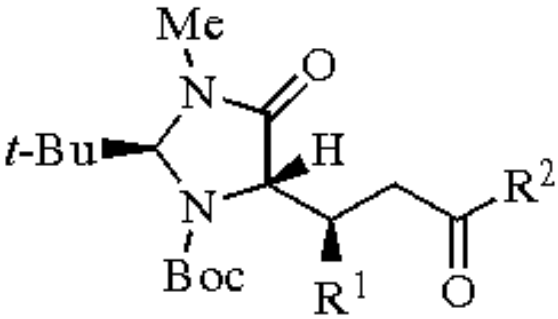

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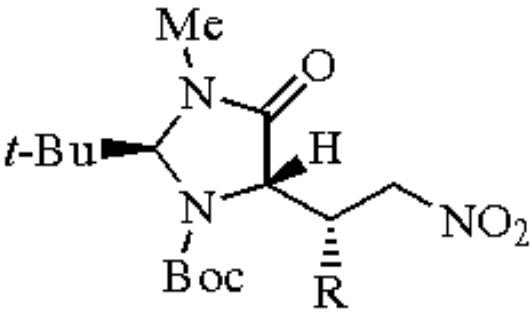

(8)

Preparation of and Michael Addition to 5-Alkylidene Boc-BMI.

Radical bromination to give (**9**) (eq 3),[11] Arbuzov reaction, and alkenation lead to (*E*)-5-alkylidene-Boc-BMI, to which cuprates add highly diastereoselectively with formation of the imidazolidinones (**10**) containing two new stereogenic centers (eq 4).[12]

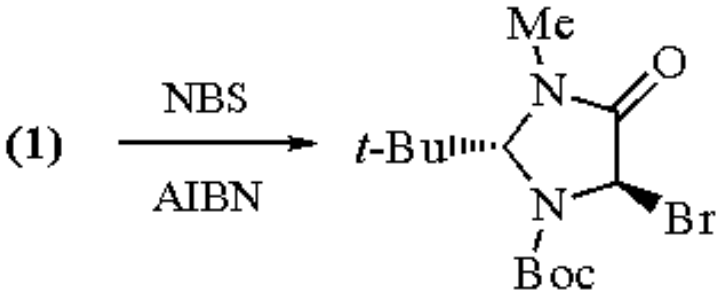

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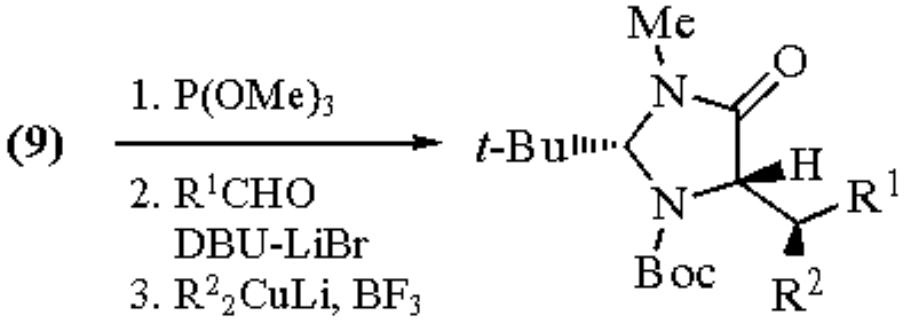

(10) (4)

Hydrolysis to Nonproteinogenic Amino Acids.

Numerous amino acids, including α-branched ones, have been prepared from Boc-BMI. Only a few examples can be alluded to here: (**11**) from (*S*)-(**1**), EtI, and $Br(CH_2)_4Cl$;[3] (**12**) from (*S*)-(**1**), 3-methylbutanoyl chloride, and ***Lithium Triethylborohydride***;[8] (**13**) from (*R*)-(**1**), butanal, and dibutylcuprate;[12] (**14**) from (*S*)-(**1**) and 4-phenylbut-2-enoate.[9]

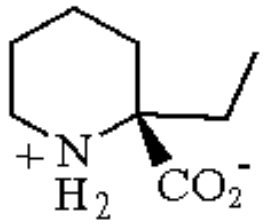

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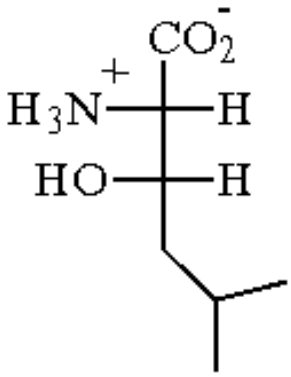

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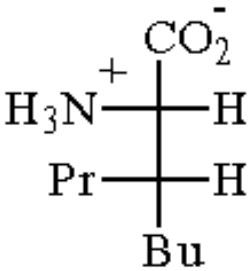

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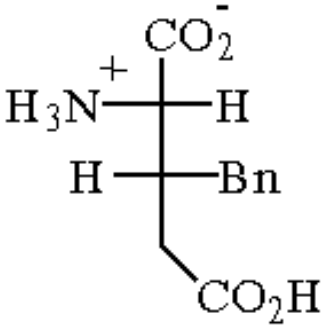

(14)

The method is applicable to the synthesis of amino acids with extremely bulky substituents in the α-position.[4b]

Chiral Imidazolidinones with Other Substitution Patterns.

The intermediate imidazolidinone (**2**) can also be *N*-acylated by ***Benzoyl Chloride*** or ***Benzyl Chloroformate***, and other

substituents on the acetal center and/or on the N(3) nitrogen can be present, depending upon the aldehyde used for the imine formation and upon the glycine amide employed at the beginning of the synthesis. Chiral substituents, such as the 1-phenylethyl group may be placed on N(3), and the imidazolidinone may be derived from a dipeptide. Some examples are collected for (**15**), with references, in Table 1.[1,5,13-17] These different derivatives have advantages of their own, depending on the particular synthetic application. An access to Boc-BMI by kinetic resolution has recently been described.[18]

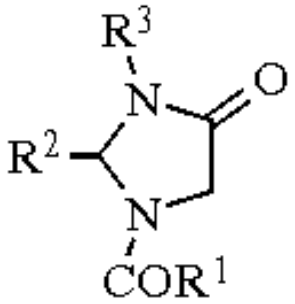

(15)

Table 1 Chiral Imidazolidinones (**15**) with Different Substitution Patterns

R^1	R^2	R^3
t-BuO[5]	*i*-Pr	Me
t-BuO[1]	*t*-Bu	Bn
BnO[1]	*t*-Bu	Me
BnO[1]	*t*-Bu	Bn
BnO[13]	*t*-Bu	CH_2CO_2R
BnO[13]	*t*-Bu	(*S*)-$CHMeCO_2Me$
BnO[14]	H	(*S*)-CHMePh
Ph[15,16]	*t*-Bu	Me
Ph[1]	*t*-Bu	Bn
Ph[17]	*t*-Bu	(*S*)- or (*R*)-CHMePh

Other Synthetic Building Blocks from Boc-BMI.

Deoxygenation of Boc-BMI leads to the imidazolidine (**16**) which can be lithiated on the methylene group next to N(1), and thus converted to compounds (**17**); from the corresponding ester ($R^E = CO_2Me$), 2,3-diaminopropionic acid derivatives (**18**) and (**19**) are available.[19]

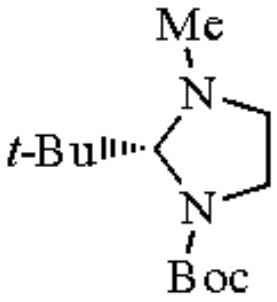

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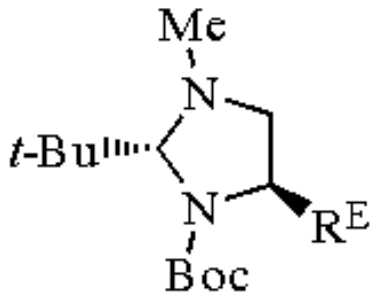

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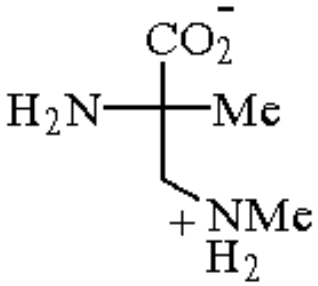

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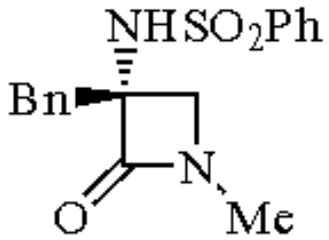

(19)

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***; ***N-Benzyloxycarbonyl-L-serine β-Lactone***; ***N-t-Butoxycarbonyl-N-methylaminomethyllithium***; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***N,N-Diethylaminoacetonitrile***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Ethyl Isocyanoacetate***; ***Methyl α-Phenylglycinate***.

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t-Butyl Chloride-Aluminum Chloride[1]

t-BuCl.AlCl$_3$

(t-BuCl)

[507-20-0] · C_4H_9Cl · *t*-Butyl Chloride-Aluminum Chloride · (MW 92.57) ($AlCl_3$)

[7446-70-0] · $AlCl_3$ · *t*-Butyl Chloride-Aluminum Chloride · (MW 133.34)

(*t*-butylating agent;[1] hydrocarbon isomerization promoter;[1] sludge $AlCl_3$ catalyst[3])

Physical Data: *t*-BuCl: bp 51-52 °C; $AlCl_3$: sublimes at 178 °C.

Solubility: both *t*-BuCl and $AlCl_3$ sol organic solvents such as CH_2Cl_2 and $CHCl_3$ as well as CS_2.

Form Supplied in: *t*-BuCl: liquid; $AlCl_3$: solid. Both are commercially available.

Preparative Method: prepared by mixing equimolar amounts of *t*-BuCl and $AlCl_3$ at -78 °C.[2] This compound is a white or pale yellow needle-like crystal, which is stable and can be stored indefinitely at -78 °C. However, it decomposes at about -30 °C to yield a reddish liquid and HCl. In most reactions involving the use of *t*-BuCl.$AlCl_3$, both *t*-BuCl and $AlCl_3$ are generally added to the reaction solution independently without premixing. The ratio between *t*-BuCl and $AlCl_3$ may also vary, depending on the requirement of the specific reaction.

Handling, Storage, and Precautions: *t*-butyl chloride-aluminum chloride is corrosive and moisture sensitive. Thus it should be handled in an anhydrous atmosphere.

Introduction.

t-Butyl chloride-***Aluminum Chloride*** (1:1 molar ratio) is prepared at -78 °C, but is not stable at -30 °C and decomposes into a reddish liquid,[2] which belongs to a family of catalysts called aluminum chloride sludges.[3] The sludges are valuable catalysts for commercial-scale alkylation reactions since the liquid state of the catalysts ensures continuous flow operations.[3] Sludge catalysts have also found application in hydrocarbon isomerization.[3,27] Reagents derived from *t*-BuCl.$AlCl_3$ are not limited to the 1:1 molar ratio of the components. In many reactions, varying ratios of *t*-BuCl and $AlCl_3$ may be used, depending on the need of the specific reaction, and the addition of *t*-BuCl and $AlCl_3$ is generally performed without premixing the two components.

t-Butylation.

t-Butyl chloride-aluminum chloride is primarily used as a *t*-butylating agent in organic synthesis.[1] Efforts have been made to determine the structure and nature of this reagent. ^{1}H NMR analysis showed that the crystalline compound, isolated from the reaction of 1:1 molar equivalent of *t*-BuCl and $AlCl_3$ at -78 °C, is only a donor-acceptor complex since the complex did not contain any free *t*-butyl cation. However, *t*-BuCl was completely ionized to $Me_3C^+Al_2Cl_7^-$ in anhydrous HCl with excess $AlCl_3$ (eq 1).[4]

$$t\text{-BuCl} \xrightarrow[\text{HCl}]{\text{excess } AlCl_3} Me_3C^+\ Al_2Cl_7^- \qquad (1)$$

Friedel-Crafts alkylation with *t*-BuCl.$AlCl_3$ as a *t*-butylating agent has been well studied.[1] Early interest in this reaction was directed toward the mechanism of ionization.[1,5] The practical importance of the *t*-butylation in the perfume industry for the preparation of xylene musk also provided further impetus for examination.[1a] Recently, this reaction has been employed in organic synthesis to protect certain positions of arenes.[6] The *t*-butyl group introduced can be readily removed later.[7] Two important features have been established regarding the use of *t*-BuCl.$AlCl_3$ as an alkylating agent in aromatic substitution.[1a] It is difficult to achieve *ortho* substitution of substituted aromatic compounds, with the exception of fluorine substituted compounds. This is due to the steric bulk of the *t*-butyl group. Further, due to the strong Lewis acidic character of $AlCl_3$, *t*-butylation of aromatic compounds using *t*-BuCl.$AlCl_3$ is always accompanied by isomerization and disproportionation. These side reactions can be suppressed by employing solvents such as $MeNO_2$ and varying the reaction conditions.

Various arenes have been alkylated by *t*-BuCl.$AlCl_3$ (eq 2). The reaction occurs readily with benzene, monosubstituted benzene (alkyl and halo), *o*-xylene, and *m*-xylene as substrates.[1,8] However, abnormal reactions were encountered when arenes such as *p*-xylene and *p*-chlorotoluene are used as substrates, which only have *ortho* positions available for the intended *t*-butylation.[9] For example, the principal products from the reaction of *p*-xylene with *t*-BuCl.$AlCl_3$ are isobutane, toluene, *m*- and *p*-*t*-butyltoluenes, 3,5-di-*t*-butyltoluene, 2-(*p*-methylbenzyl)-*p*-xylene, and di-*p*-xylylmethane (eq 3).[9a,9b] With an excess of *t*-BuCl, 1,3,5-tri-*t*-butylbenzene can be prepared from di-*t*-butylbenzene in good yield (eq 4).[10] The *t*-BuCl.$AlCl_3$ system is able to alkylate phenols, but the best results with these substrates were obtained by use of alkenes and alcohols as alkylating agents.[1a] *t*-Butylation of naphthalene and its derivatives is also successfully achieved with *t*-BuCl.$AlCl_3$.[11] In the case of naphthalene, only the thermodynamic product, 2-*t*-butylnaphthalene, is observed (eq 5).[1a] When acenaphthene is used in the alkylation, both mono- and disubstitution products are obtained (eq 6).[12]

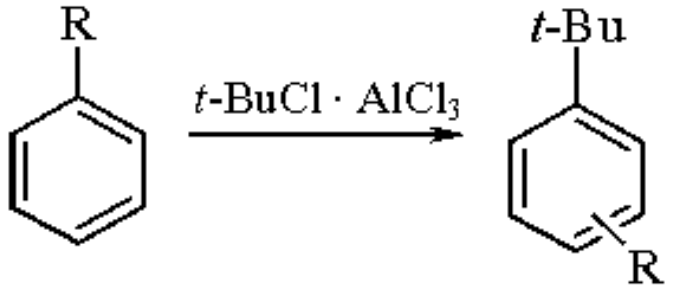

(2)

R = alkyl, halo

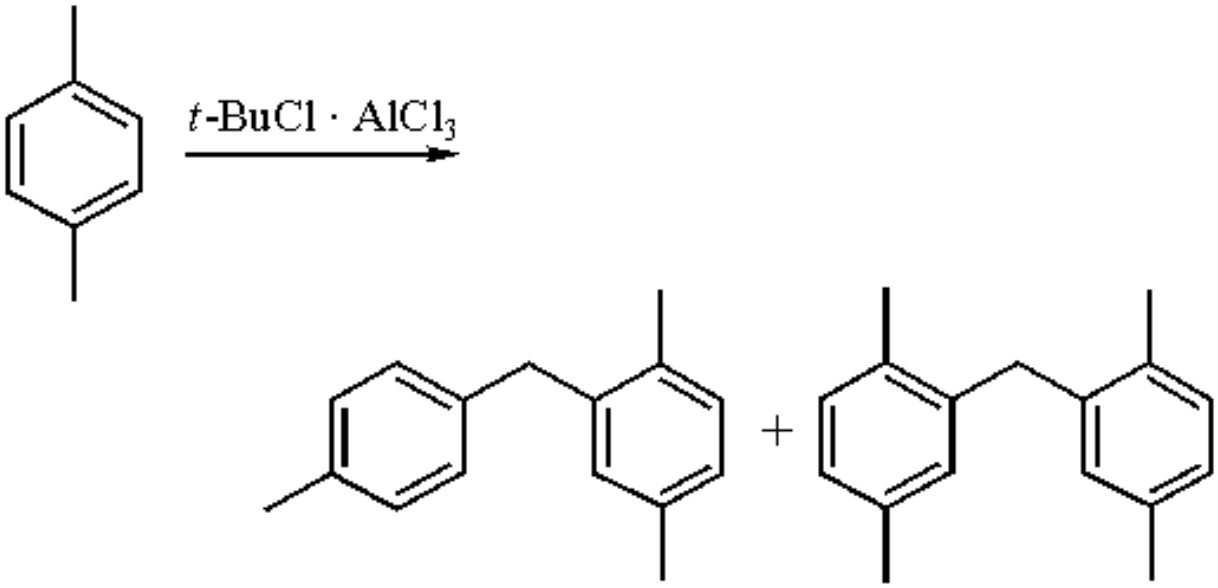

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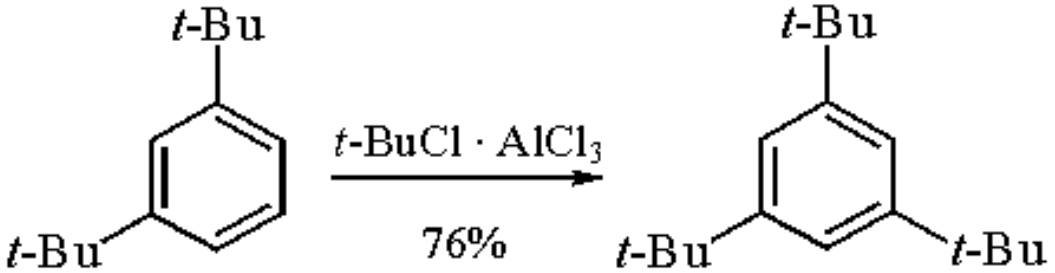

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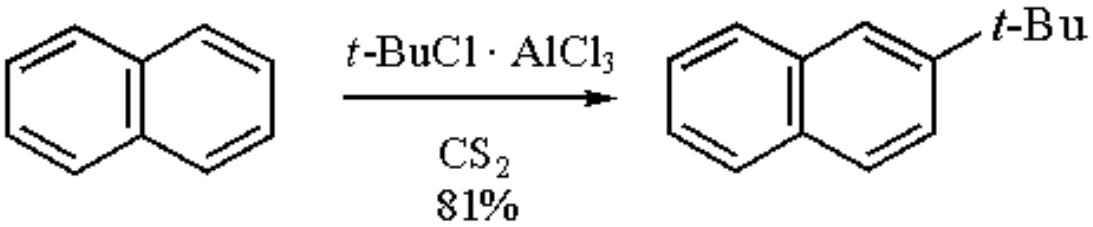

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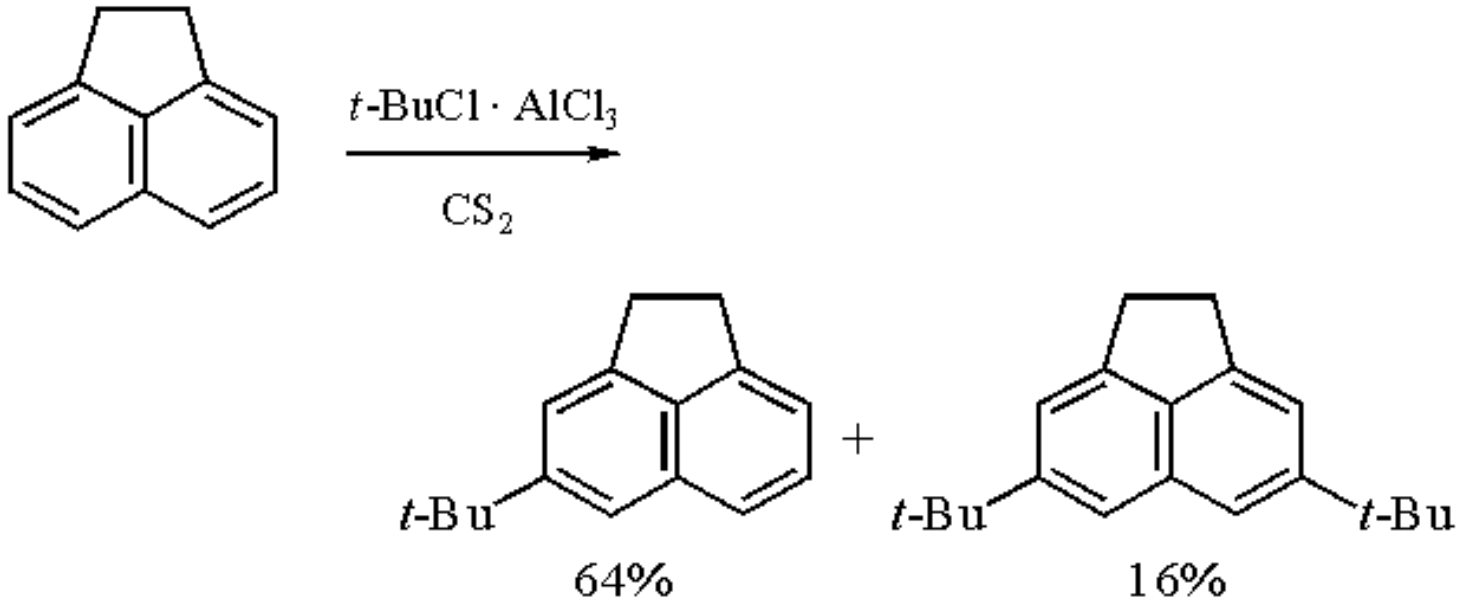

(6)

t-Butyl chloride-aluminum chloride has also been used for the *t*-butylation of alkenic substrates. Its reaction with alkenes was widely studied due to its obvious industrial importance.[13,14] Although oligomerization of alkenes can occur,[13e] it is possible to obtain β-*t*-butylalkyl chlorides as the major addition products of the reaction (eq 7).[14a-d] Elimination of HCl in situ led to the formation of *t*-butylated alkenes.[13a,14] Silyl enol ethers react with *t*-BuCl.$AlCl_3$ to yield α-*t*-butyl ketones or aldehydes (eq 8).[15] However, the best Lewis acid for this type of reaction is ***Titanium(IV) Chloride***. Compounds which contain very acidic C-H bonds, such as malononitrile, can be similarly *t*-butylated, presumably through enolization.[16]

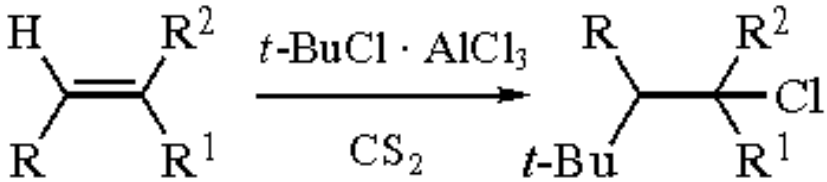

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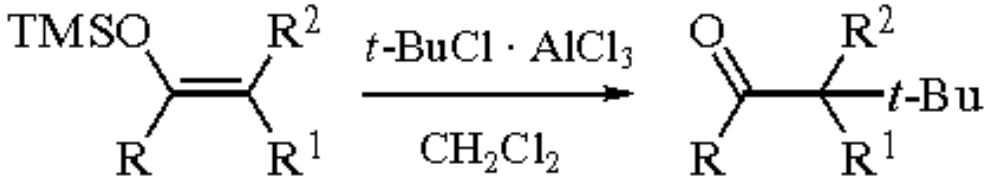

(8)

Silylalkynes react with *t*-BuCl.$AlCl_3$ to form *t*-butylated alkynes (eq 9).[17]

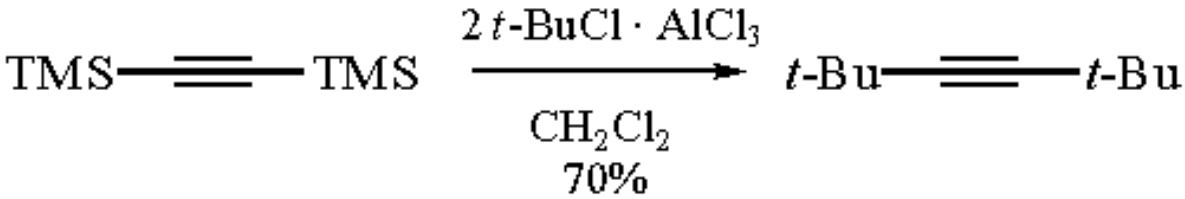

(9)

t-Butyl chloride-aluminum chloride has been used to *t*-butylate PCl_3.[18] When PCl_3 is treated with *t*-BuCl.$AlCl_3$, *t*-butylphosphonyl dichloride is obtained upon hydrolysis (eq 10) (Clay reaction). This reaction is also applicable to a

number of organophosphorus compounds such as dichlorophenylphosphine (eq 11) and chlorodiphenylphosphine.[19] Reaction with diphosphorus pentasulfide leads to the formation of *t*-butylphosphinothioic acids after hydrolysis.[20]

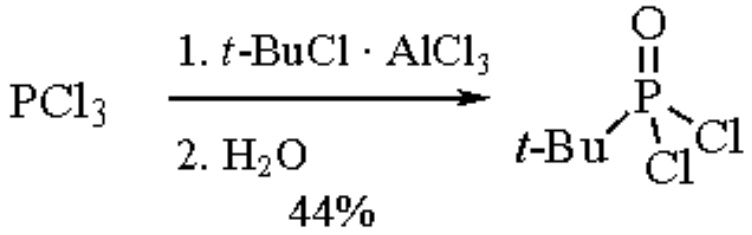

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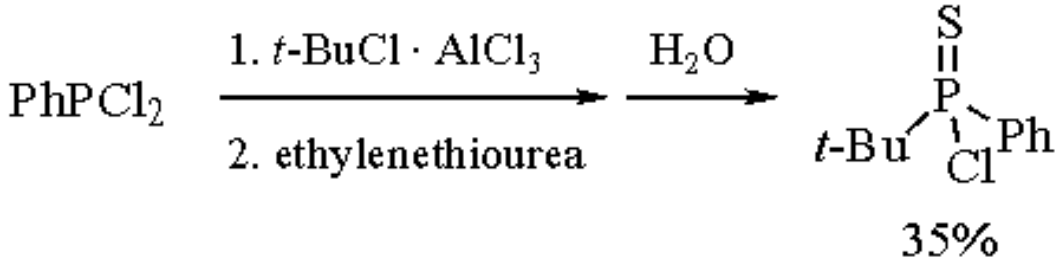

(11)

Reaction between *t*-BuCl.$AlCl_3$ and chloroamines was also investigated.[21] When trichloroamine is used, 90% *t*-butylamine is obtained, along with 8% of 2,2-dimethylaziridine as a minor product (eq 12). However, the use of monochloroamine decreased the yield of *t*-butylamine to a range of only 7-20%.

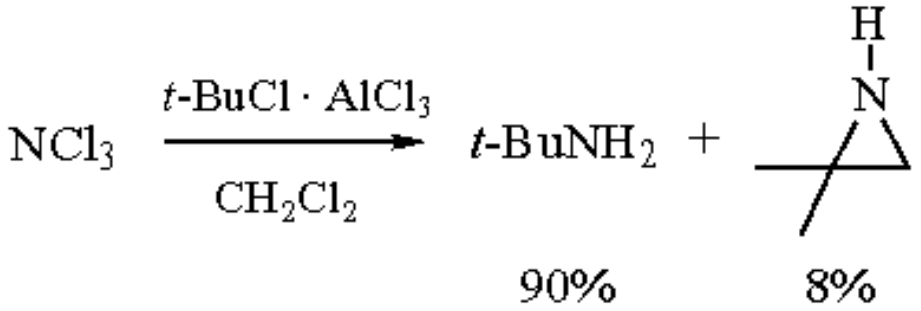

(12)

Hydride Abstraction and Isomerization.

When *t*-BuCl.$AlCl_3$ reacts with crowded arenes such as *p*-xylene, abnormal reactions occur.[9] This results from initial hydride abstraction by *t*-BuCl.$AlCl_3$ from the benzylic positions. Similar reactions are observed with *p*-chlorotoluene and other crowded aromatics. When the *t*-butylation is conducted in the presence of an isoalkane, not only *t*-butylated products but also the alkylarenes derived from the isoalkane are observed (eq 13).[22] This phenomenon can also be explained by hydride abstraction by *t*-BuCl.$AlCl_3$ from the alkanes. This hydride abstraction has been elegantly utilized in the preparation of polyalkyltetralins (intermediates in the manufacture of musk aroma compounds, eq 14).[23] The polyalkyltetralins are prepared by combining *p*-cymene with alkenes under the catalysis of *t*-BuCl.$AlCl_3$. The reaction goes through initial hydride abstraction by *t*-BuCl.$AlCl_3$ from the *p*-cymene to generate the cumyl cation, which is subsequently alkylated by an alkene. A concurrent cyclization yields the final product.[23] 1,1,4,4,5,5,8,8-octamethyl-1,2,3,4,5,6,7,8-octahydroanthracene can be prepared by combining 1,3,5-tri-*t*-butylbenzene with *t*-BuCl.$AlCl_3$ (eq 15).[24]

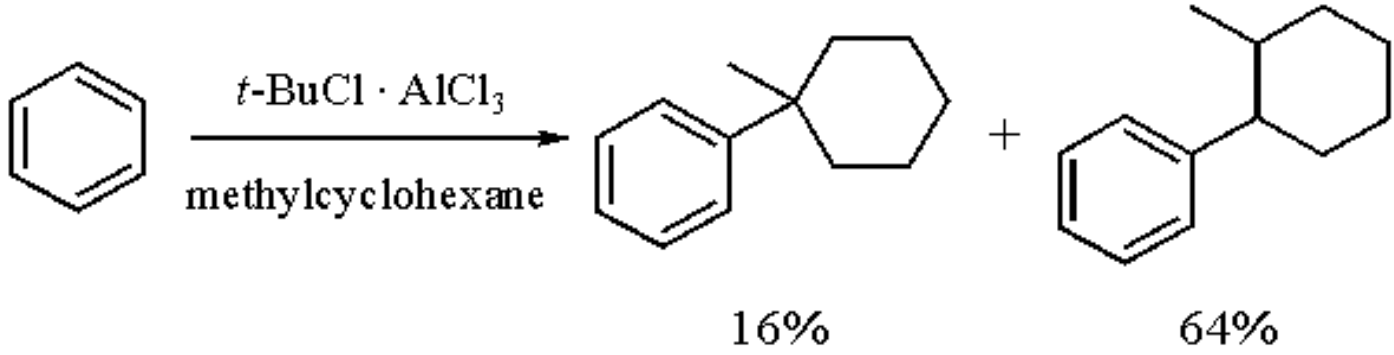

(13)

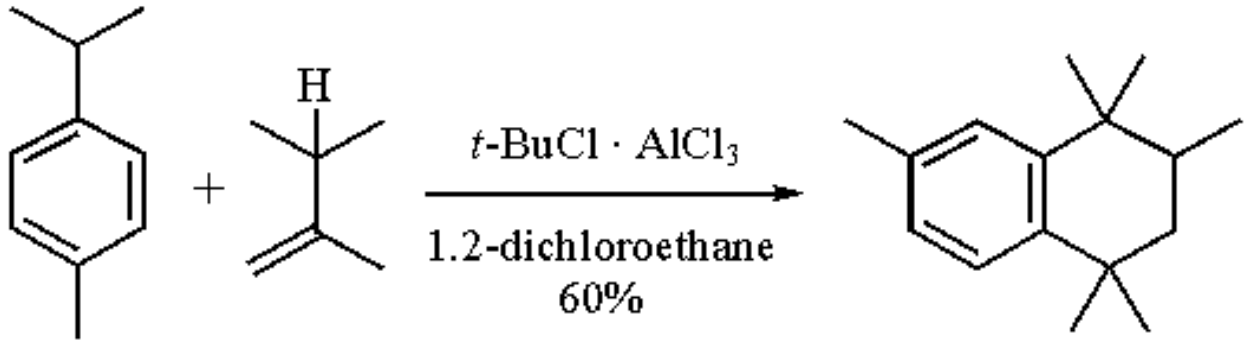

(14)

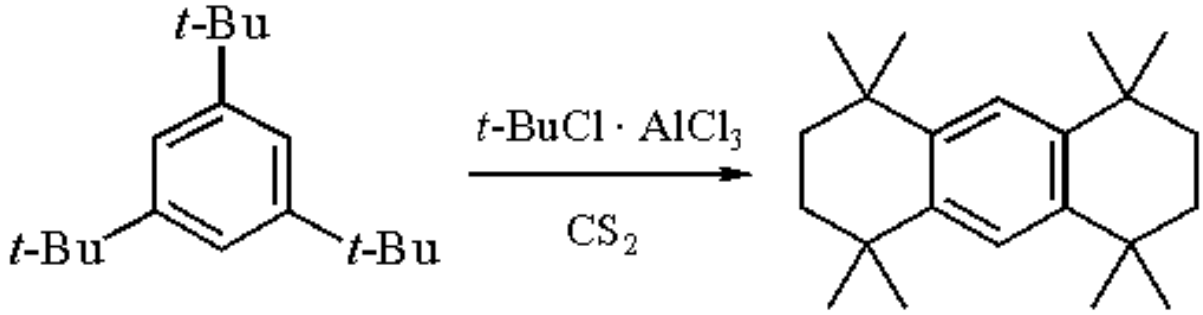

(15)

t-Butyl chloride-aluminum chloride is exploited in the preparation of diamondoid compounds.[25] It was found that *t*-BuCl facilitates the isomerization of trimethylenenorbornane to adamantane by $AlCl_3$ (eq 16). The same reagent is also employed in the isomerization of heptacyclo[8.4.0.0^{2,12}.0^{3,8}.0^{4,6}.0^{5,9}.0^{11,13}]tetradecane (binor-S).[26] Compared to the *t*-BuBr.$AlBr_3$ system, *t*-BuCl.$AlCl_3$ is less well documented in the literature for this type of isomerization.[27]

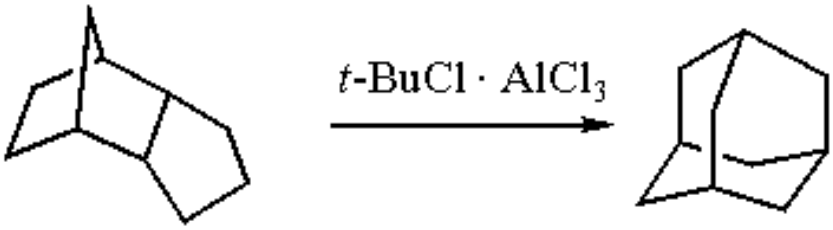

(16)

t-Butyl chloride-aluminum chloride is also found to facilitate the methylation of methylcyclohexane with tetramethylsilane (eq 17).[28] Only 5% 1,1-dimethylcyclohexane is obtained when methylcyclohexane was treated with $Me_4Si.AlCl_3$. In contrast, 85% 1,1-dimethylcyclohexane was obtained when *t*-BuCl was added to the reaction system.

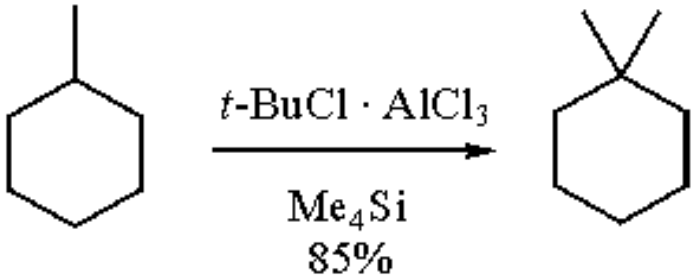

(17)

Other Reactions.

t-Butyl chloride-aluminum chloride is a good chlorinating agent for isoalkanes. It has been successfully used to selectively chlorinate 2,3-dimethylbutane (eq 18) and methylcyclohexane at the tertiary positions in excellent yields.[29] Dehydrochlorination of 2-chloro-2,3-dimethylbutane led to formation of 2,3-dimethylbutenes. When 1-chloro-1-methylcyclohexane was subjected to the same treatment, both 1-methylcyclohexene and methylenecyclohexane were obtained. The two reactions, along with recycling of HCl and isobutene, led to an industrial process for the manufacture of tertiary monoalkenes.[29]

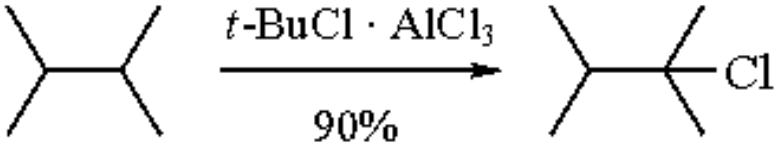

(18)

t-Butyl chloride interacts with $AlCl_3$ to eliminate HCl to form isobutene, which can be polyacetylated by ***Acetyl Chloride***.[30] Upon treatment of the reaction mixture with aqueous ***Ammonia***, 2,4,6-trimethylpyridine, 4-acetonyl-2,6-dimethylpyridine, and 1,3,6,8-tetramethyl-2,7-naphthyridine were obtained in total 92% yield with a ratio of 36:40:24, respectively. If liquid ammonia is used, the yield of the reaction remained the same, but the proportion of 1,3,6,8-tetramethyl-2,7-naphthyridine increased to 63%, while only traces of 4-acetonyl-2,6-dimethylpyridine could be detected. The amount of 2,4,6-trimethylpyridine obtained was essentially the same (eq 19).

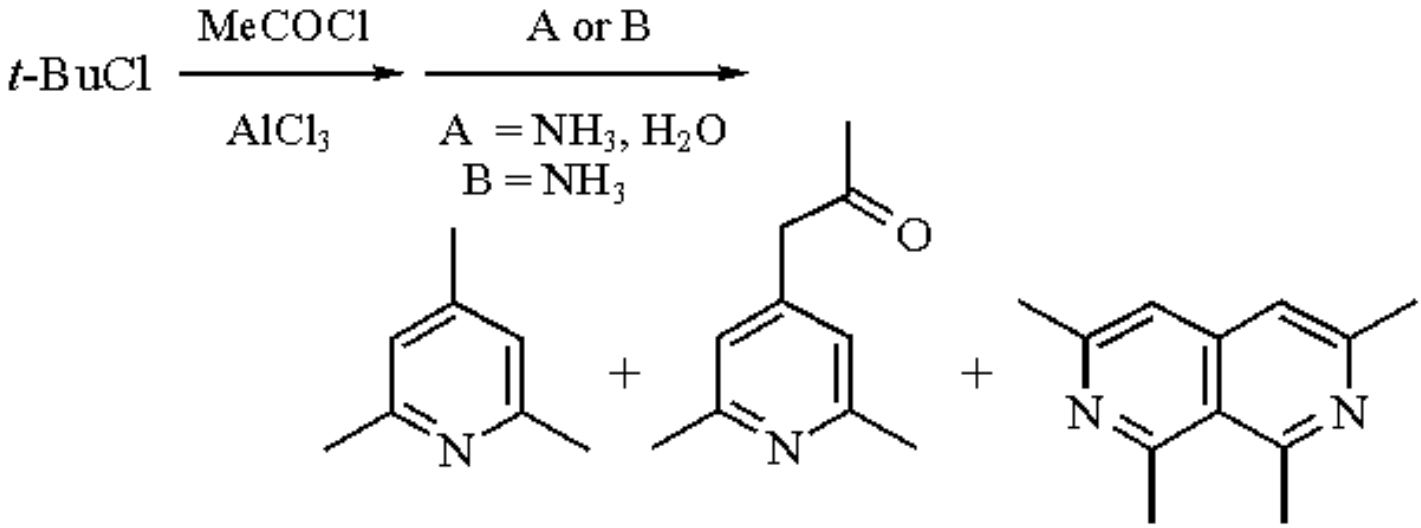

(19)

A: total yield 92%	36%	40%	24%
B: total yield 91%	37%	traces	63%

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University of Southern California, Los Angeles, CA, USA

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t-Butyl Chloroacetate

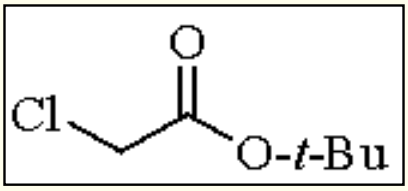

[107-59-5] · $C_6H_{11}ClO_2$ · *t*-Butyl Chloroacetate · (MW 150.60)

(reagent used in glycidic ester condensations[1] and as a two-carbon alkylating agent[2])

Physical Data: bp 48-49 °C/11 mmHg.

Form Supplied in: colorless liquid; widely available.

Preparative Method: prepared by treatment of chloroacetyl chloride with *t*-butyl alcohol.[3]

Handling, Storage, and Precautions: is a lachrymator and should be used in a well-ventilated fume hood.

t-Butyl chloroacetate has been used extensively in the formation of glycidic esters via the Darzens reaction[4] since the reagent minimizes metal enolate self-condensation.[1,5] Darzens reaction of *t*-butyl chloroacetate (**1**) and chiral η^6-$Cr(CO)_3$ complexed aromatic aldehydes (**2**) leads to a mixture of *cis* and *trans* glycidic esters of high optical purity (eq 1).[6] A related chloroacetate has been used in an asymmetric Darzens glycidic ester condensation for the synthesis of the calcium channel blocker diltiazem.[7] α-Halo ketones undergo a novel Darzens-type reaction in the presence of *N*-tri-*n*-butylstannylcarbamates.[8] Condensation of enolates of *t*-butyl chloroacetate with chiral imines leads to 3-haloazetidinones or aziridines, depending on the metal enolate.[9] The triisopropoxytitanium enolate of (**1**) gives (3*R*,4*R*)-chloroazetidinone (**4**) (eq 2), while lithium (eq 3) and zinc enolates (eq 4) give only (2*R*,3*S*) (**5**) and (2*S*,3*R*) (**6**) aziridines, respectively.

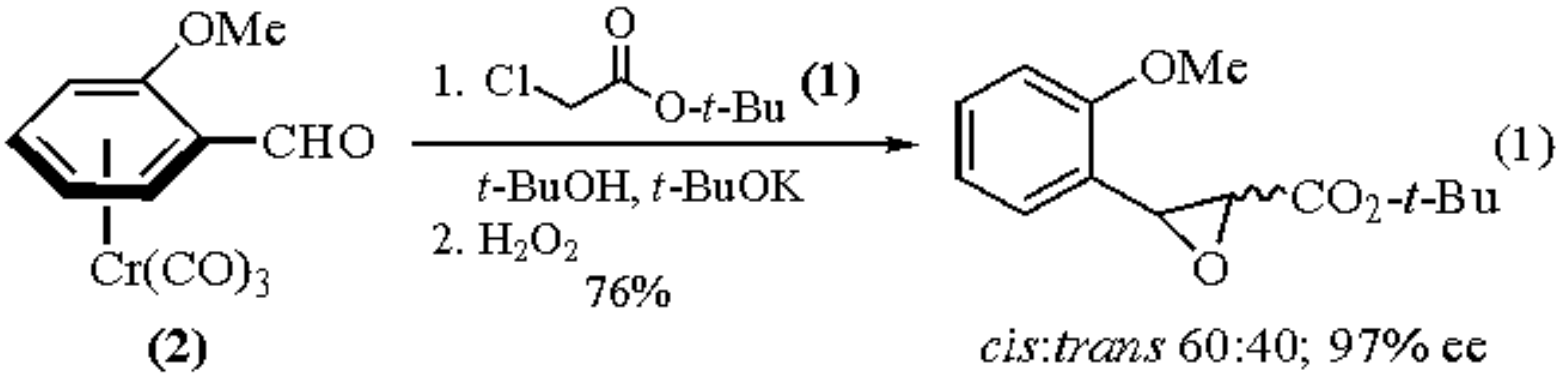

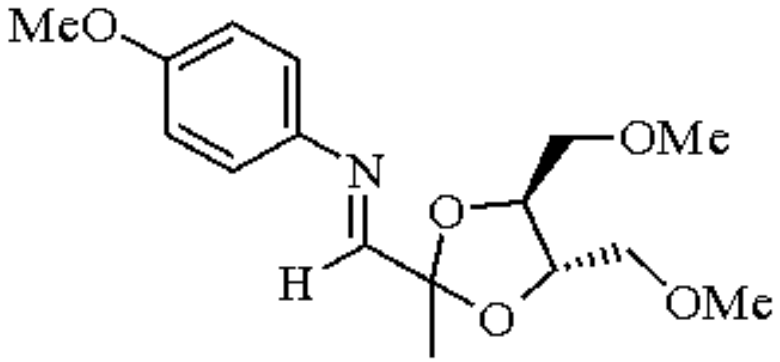
MeO
N
H
O
O
OMe
OMe

(3)

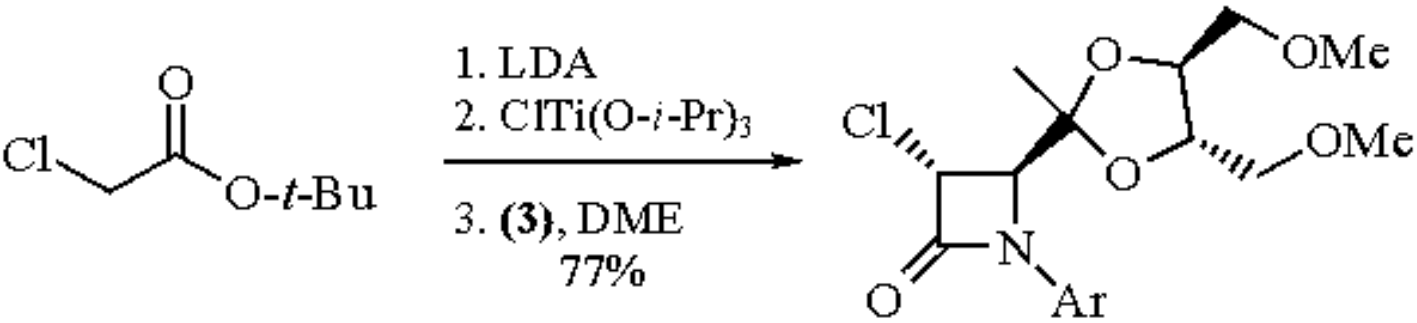
Cl
O
O-t-Bu
1. LDA
2. ClTi(O-i-Pr)3
3. (3), DME
77%
Cl
O
O
OMe
OMe
N
O
Ar

(2)

(1) **(4)**

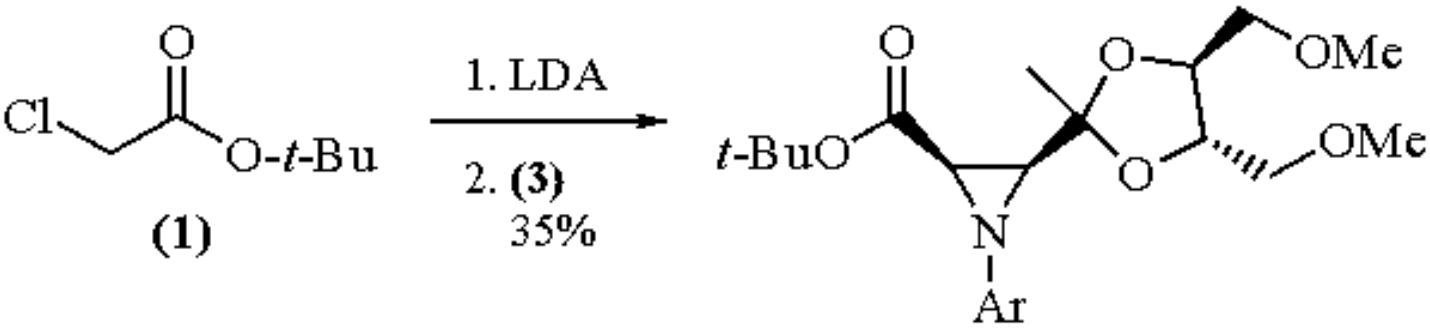
Cl
O
O-t-Bu
1. LDA
2. (3)
35%
t-BuO
O
O
O
OMe
OMe
N
Ar

(3)

(1) **(5)**

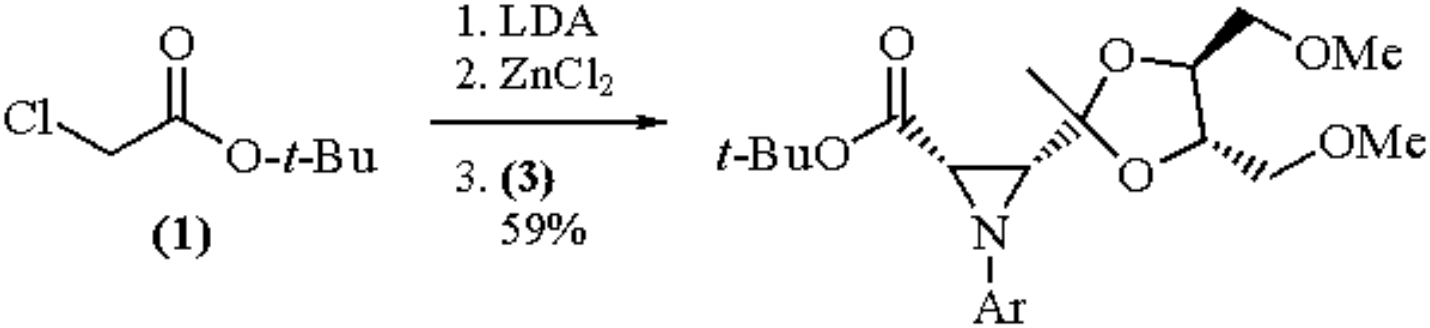
Cl
O
O-t-Bu
1. LDA
2. ZnCl2
3. (3)
59%
t-BuO
O
O
O
OMe
OMe
N
Ar

(4)

(1) **(6)**

t-Butyl chloroacetate is the reagent of choice for the vicarious nucleophilic substitution of hydrogen in nitroarenes.[10] This reaction has been applied to the formal total synthesis of eupolauramine (eq 5).[11]

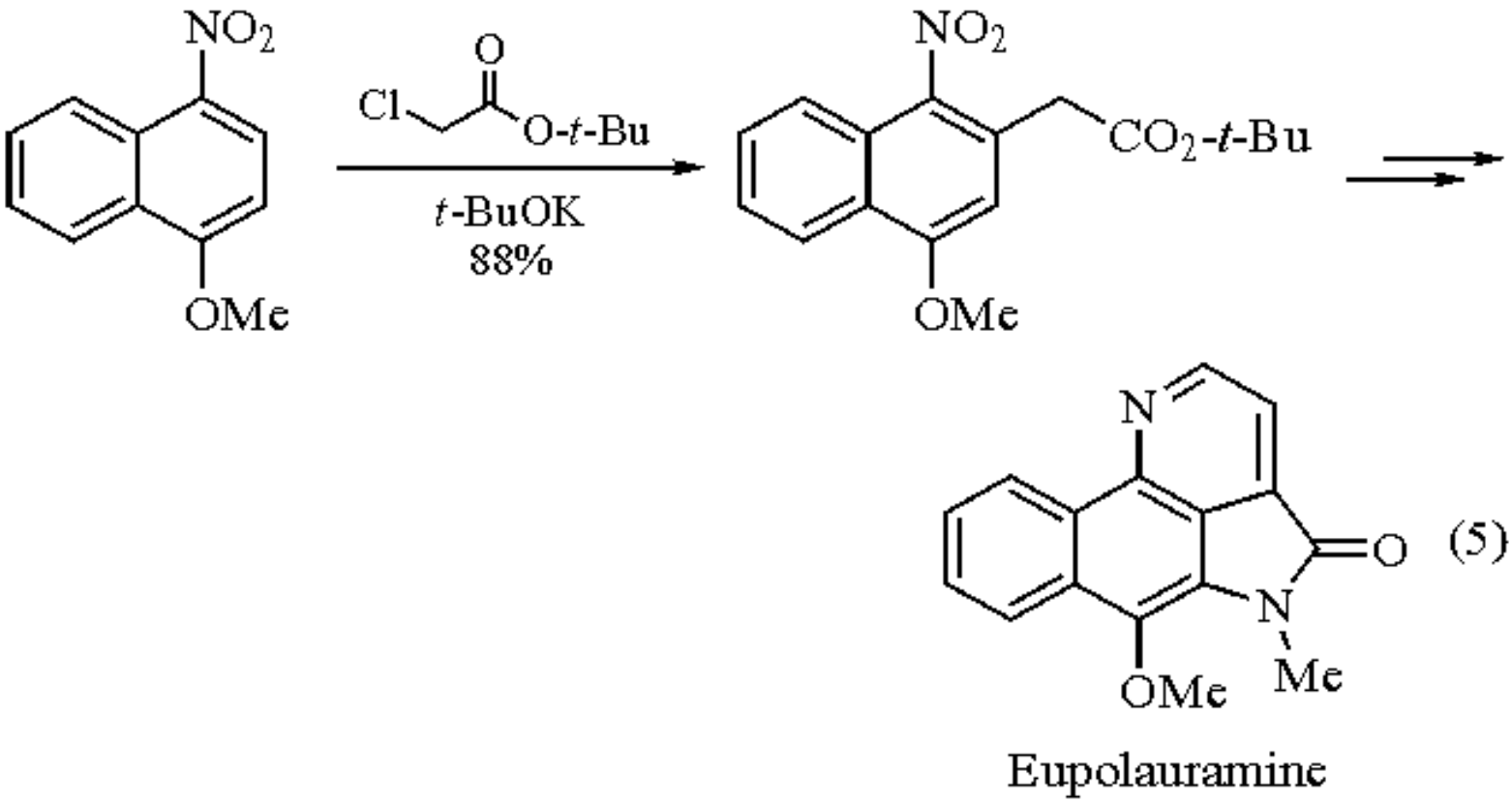

Although less reactive than the corresponding bromide, *t*-butyl chloroacetate has been used as a two-carbon alkylating agent. For example, *N*-formylglycine is formed by the reaction of (**1**) and sodium diformylamide.[2] The synthesis of dialkyl alkoxycarbonylmethanephosphonates,[12] rhenium enolate complexes,[13] and *t*-butyl (triphenylphosphoranylidine)acetate[14] also rely upon the electrophilic nature of (**1**).

The limitations of *t*-butyl chloroacetate as an electrophile is illustrated in the synthesis of (-)-8-azaestrone by Meyers (eq 6).[15] Reaction of the lithium anion of (**7**) with (**1**) gives a 2:1 ratio of (**8**) to (**9**). The undesired lactam (**9**) is formed by nucleophilic attack of (**10**) on the chlorine atom of (**1**), presumably due to the steric bulk of the alkylating agent (eq 7).

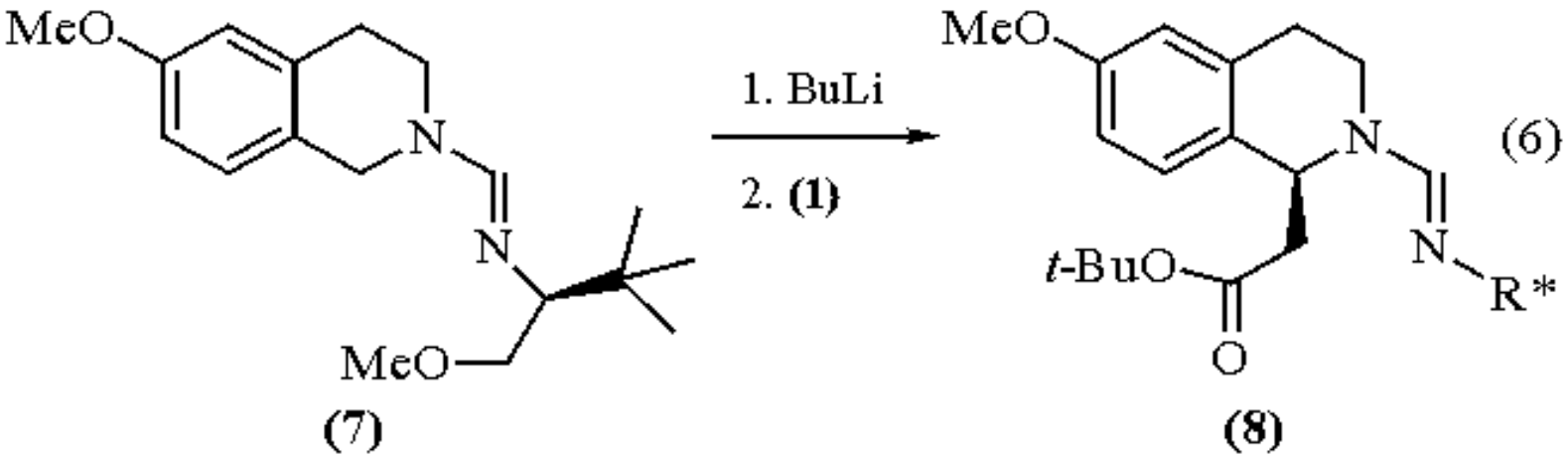

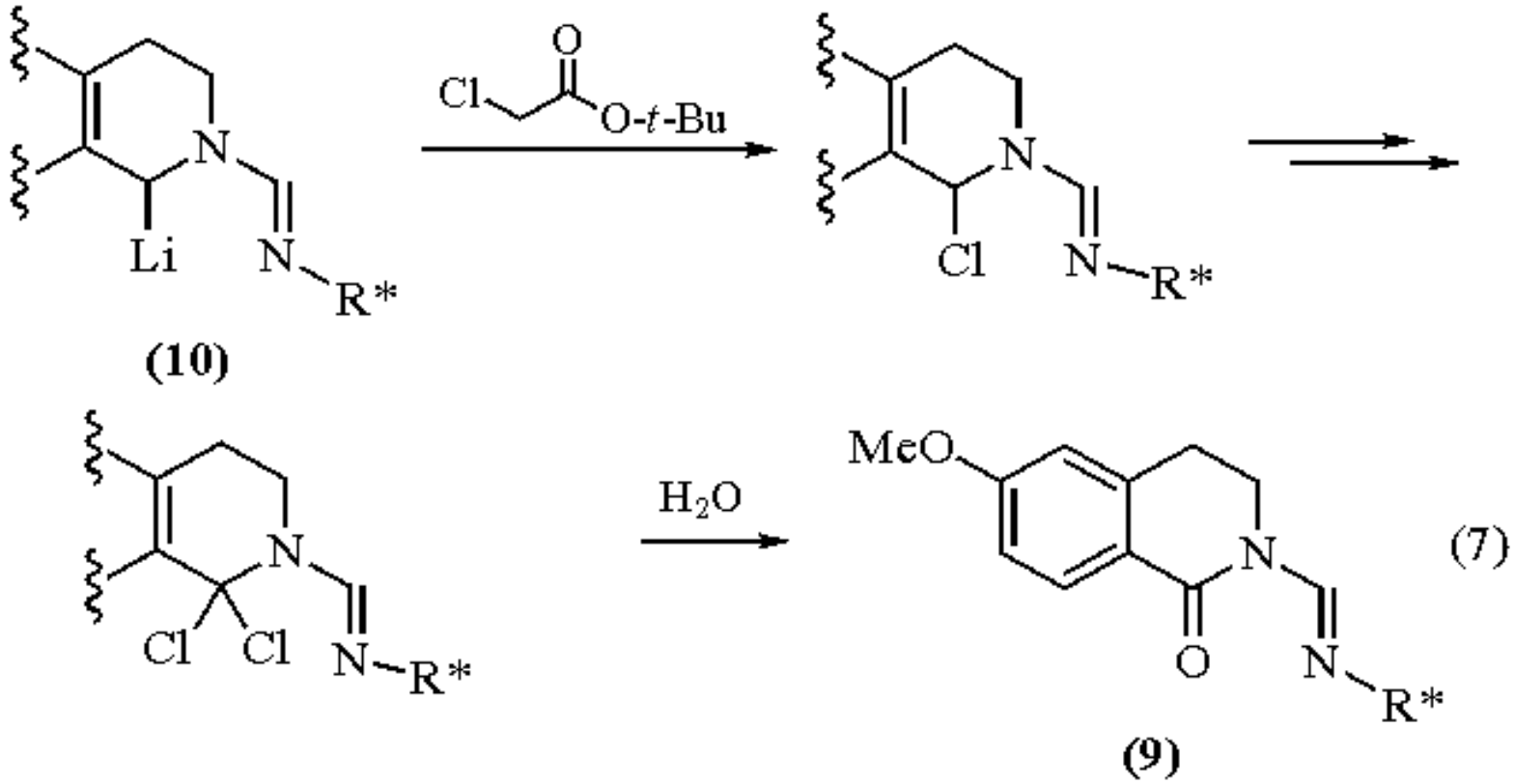

Related Reagents.

Methyl Bromoacetate; ***Methyl Chloroacetate***.

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t-Butyl Chloroformate

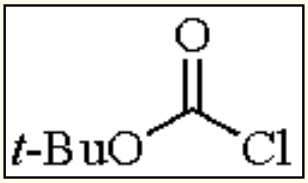

[24608-52-4] · $C_5H_9ClO_2$ · *t*-Butyl Chloroformate · (MW 136.58)

(reagent for the protection of amino groups, including amino acids[2])

Alternate Name: Boc-Cl.

Physical Data: bp 3-4 °C/0.9-1.7 mmHg.[1]

Solubility: sol ether, toluene, and most organic aprotic solvents.

Form Supplied in: not commercially available; should be prepared from *t*-butanol[2] or potassium *t*-butoxide[1,3] and phosgene shortly before use.

Handling, Storage, and Precautions: unstable at rt. *t*-Butyl chloroformate should be kept as a solution in anhydrous solvent at low temperature (deep freezer) and for a period of time not exceeding a few days. Decomposition leads to high pressure in the storage vessel. May contain some residual phosgene. Reacts with DMSO or DMF.

Protection of Amino Groups.

t-Butyl chloroformate (Boc-Cl), first prepared by Choppin and Rogers in 1948,[1] has been used, despite the reagent's instability, for the *t*-butyloxycarbonyl (Boc) protection of amino compounds and especially of amino acids. Boc protection has gained considerable importance because of the resistance of the protecting group to strong base hydrolysis and catalytic hydrogenation, as well as the ease of deprotection under mildly acidic conditions. Boc protection has become a fundamental tool of modern peptide synthesis and particularly of the Merrifield strategy for solid-phase peptide synthesis. Most amino acids have been protected with Boc-Cl using slightly modified Schotten-Baumann conditions (eq 1).[2]

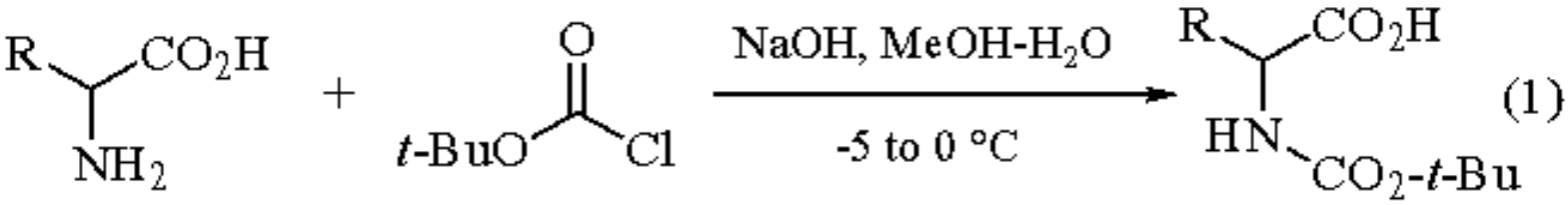

Reaction of pyridine compounds with Boc-Cl and ***Sodium Borohydride*** in methanol at -65 °C afforded the corresponding *N*-*t*-butyloxycarbonyldihydropyridine derivatives in good yield (eq 2).[4]

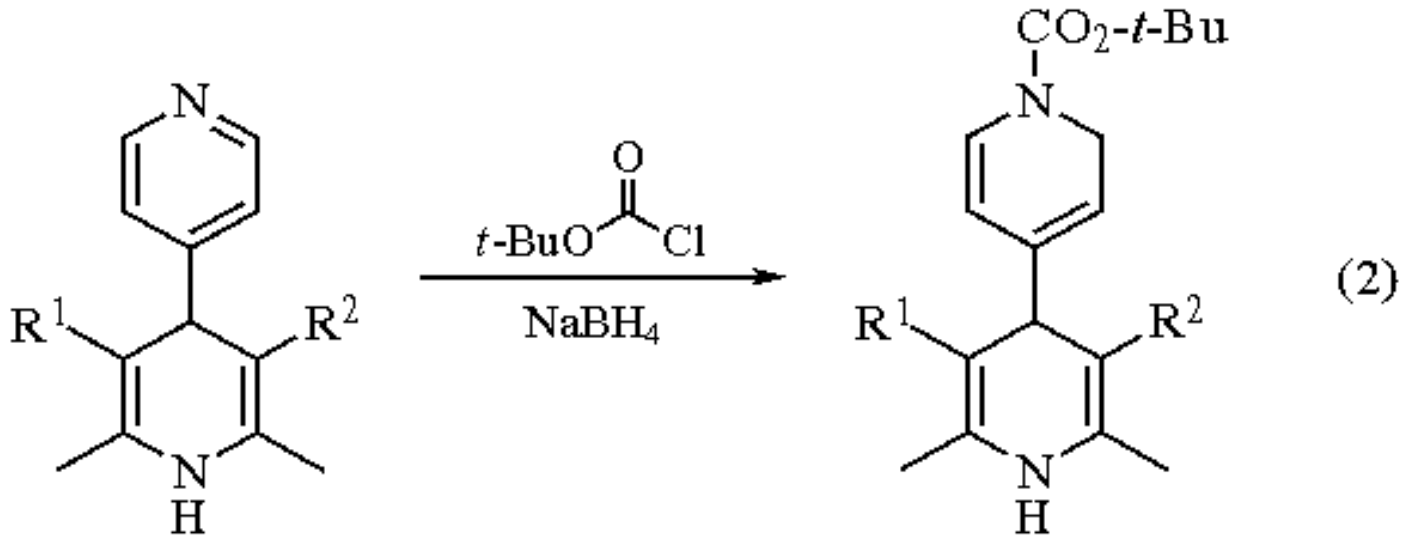

The main drawback of the reagent remains its very low stability and the difficulties encountered in its preparation. Various preparative procedures are currently available in the literature.[5] It is also necessary to determine the reagent concentration in solution accurately, which can be done by reacting an aliquot with a selected amino compound before use. These liabilities notwithstanding, *t*-butyl chloroformate can be a cheap and valuable reagent for Boc protection and in some cases it is the best reagent available. This is, for instance, the case in the synthesis of Boc-protected *N*-carboxy anhydrides, which are used as building blocks in peptide synthesis (eq 3).[6] ***Di-t-butyl Dicarbonate*** required much longer reaction times in this case. These Boc-UNCAs (urethane-protected *N*-carboxy anhydrides) are, in fact, best prepared from the reaction of Boc-Cl with Leuchs anhydride in the presence of *N*-methylmorpholine or any nonnucleophilic organic base.

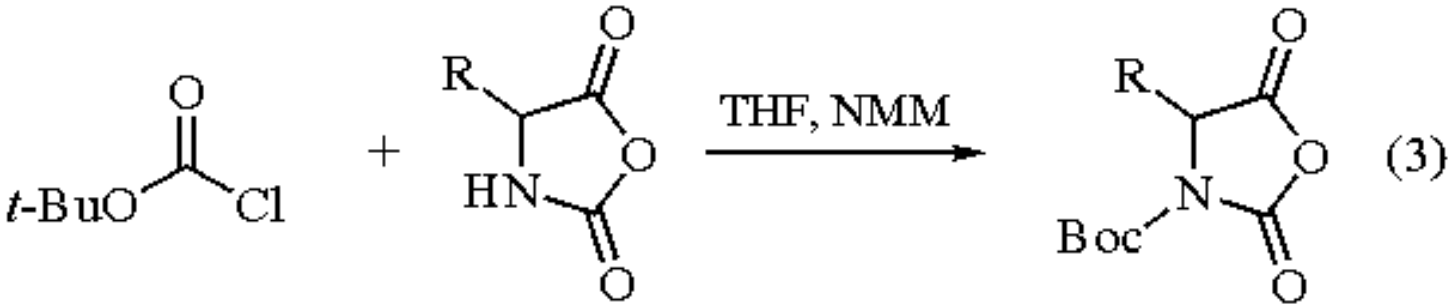

Preparation of Other Reagents for Boc Protection.

Because of its low stability, *t*-butyl chloroformate has mainly been used as a source of various other reagents that are

easier to handle under ordinary conditions. ***t-Butyl Azidoformate***, the most widely employed reagent before the discovery of ***Di-t-butyl Dicarbonate***, is conveniently obtained from Boc-Cl through the formation of *t*-butyl carbazate (eq 4).[7]

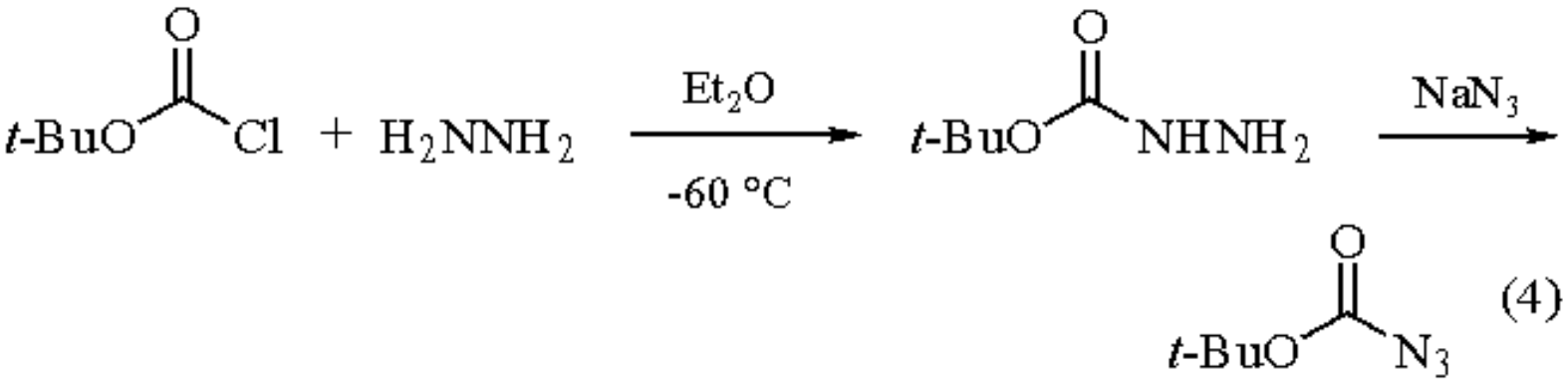

t-Butyl azidoformate is also obtained more directly from Boc-Cl and hydrazoic acid (eq 5).[8]

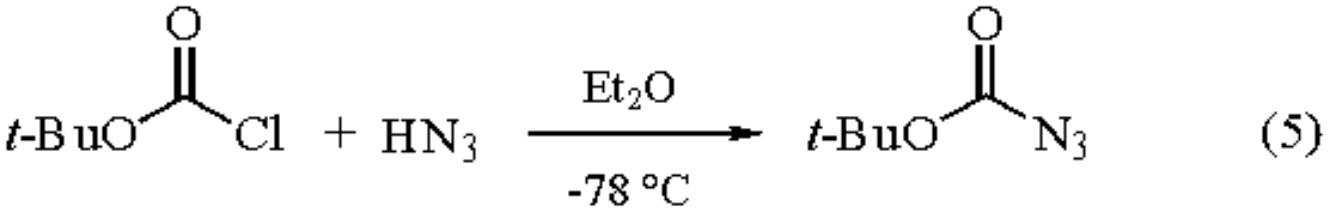

Various active carbonates, which are primarily used for the preparation of stable reagents for the introduction of the Boc protection, have been prepared from Boc-Cl.[9]

Exchange reactions utilizing hydrogen fluoride[10] and various salts such as sodium[11] and silver fluoride do not lead to the more stable *t*-butyl fluoroformate, which has to be prepared instead from carbonyl chlorofluoride or fluorophosgene.[12]

t-Butyl Carbonates and Carbamates.

Because Boc-Cl is potentially the cheapest reagent for the synthesis of *t*-butyl carbonates, e.g. (**1**) and (**2**), or carbamates, it has been claimed in numerous patents and may have growing utility in industrial processes, such as for the production of carbonates as components in thermal recording materials.[13]

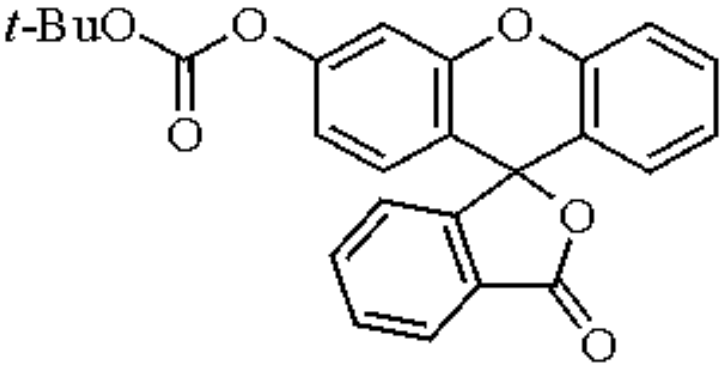

(1)

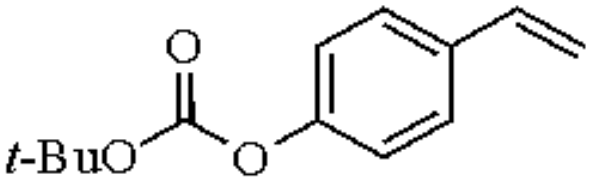

(2)

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13. Jpn. Patent 04 213 368 (*CA* **1993**, *118*, 14 048).

G. Sennyey

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s-Butyl Chloroformate

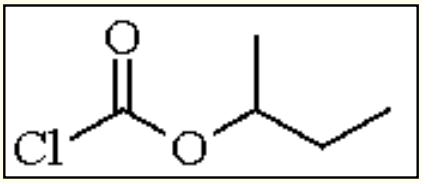

[17462-58-7] · $C_5H_9ClO_2$ · *s*-Butyl Chloroformate · (MW 136.58)

(reagent for preparation of mixed anhydrides for peptide synthesis[1,2])

Physical Data: bp 115-117 °C; *n*24D 1.4037.

Preparative Method: prepared (50% yield) by reaction of *s*-butanol with 1.5 equiv of phosgene.[1]

Purification: purified by distillation.

Handling, Storage, and Precautions: no information available.

Mixed Anhydrides for Peptide Synthesis.

s-Butyl chloroformate (**1**) reacts with *N*-protected amino acids to give the mixed anhydride (**2**); treatment with an amino acid ester (or an alkaline aqueous solution of an unprotected amino acid) results in amide bond formation, affording (**3**) (eq 1).[1,2] The method is rapid and clean; since the only byproducts of the reaction are CO_2 and *s*-butanol, the products are obtained in a high state of purity, and sometimes crystallize directly from the reaction mixture. Other simple alkyl chloroformates may of course be used in place of (**1**), but Vaughan and Osato noted that (**1**) and *i*-butyl chloroformate provided highest yields, with a slight advantage for the former.[1]

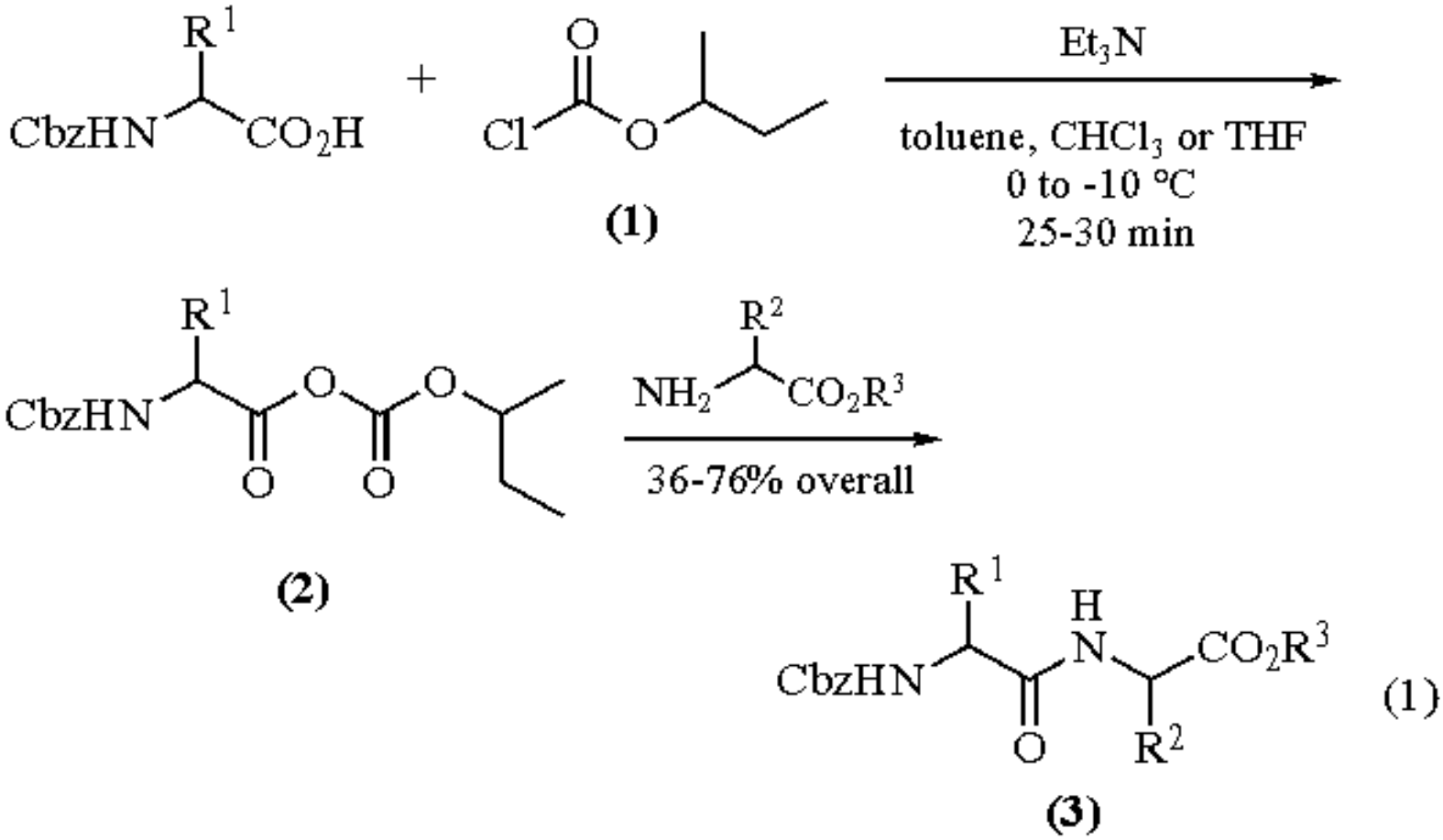

While racemization is generally not observed in the synthesis of dipeptides, careful choice of conditions is necessary for the preparation of higher peptides. The use of THF as solvent in the anhydride formation step is recommended, along with shorter reaction times (5-10 min at -5 °C) if racemization is likely to be a problem.[3]

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University of Bath, UK

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t-Butyl Chloromethyl Ether

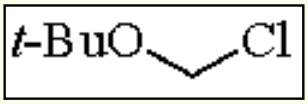

[40556-01-2] · $C_5H_{11}ClO$ · *t*-Butyl Chloromethyl Ether · (MW 122.59)

(reagent for introducing an acid-labile alcohol- or an imidazole-protecting group[1])

Physical Data: decomposes upon attempted isolation.

Solubility: sol CH_2Cl_2, $CHCl_3$, CCl_4.

Form Supplied in: generated immediately prior to use.

Analysis of Reagent Purity: ^{1}H NMR (CCl_4, δ 5.6[1] or 5.4[2] (2H, s), 1.2 (9H, s)).

Preparative Methods: chlorination of *t*-butyl methyl ether using NCS,[1] treatment of *t*-butyl methylthiomethyl ether with sulfuryl chloride,[2] or cleavage of *t*-butyl methoxymethyl ether with BCl_3.[4]

Handling, Storage, and Precautions: solutions in CH_2Cl_2 appear to remain unchanged upon standing at rt for several days.[2] Concentration apparently leads to decomposition. The structurally similar ***Chloromethyl Methyl Ether*** is a putative carcinogen.

Protection of Alcohols.

This reagent was introduced in 1978 as a reagent for protecting alcohols as *t*-butoxymethyl ethers.[1] An acetal protecting group analogous to the more common methoxymethyl (MOM) group, the *t*-butoxymethyl moiety can be removed under significantly milder conditions (see below). The initial report described its preparation via treatment of methyl *t*-butyl ether (MTBE) with ***N-Chlorosuccinimide*** in CCl_4 under sunlamp irradiation. Removal of succinimide by filtration gave a crude CCl_4 solution of *t*-butyl chloromethyl ether which was stable under nitrogen at rt. A subsequent report highlighted the importance of excluding both oxygen and acid during the chlorination, recommending carrying out the reaction under dry nitrogen and advocating the addition of *N*,*N*-diisopropyl-3-pentylamine as a proton scavenger.[3] An interesting study detailing a general entry into a variety of chloromethyl ethers described the conversion of *t*-butyl methoxymethyl ether into *t*-butyl chloromethyl ether using ***Boron Trichloride*** (eq 1).[4] A related procedure has been reported, entailing preparation of *t*-butyl methylthiomethyl ether and its nearly quantitative conversion to the desired reagent by treatment with ***Sulfuryl Chloride*** in CH_2Cl_2 (eq 2).[2]

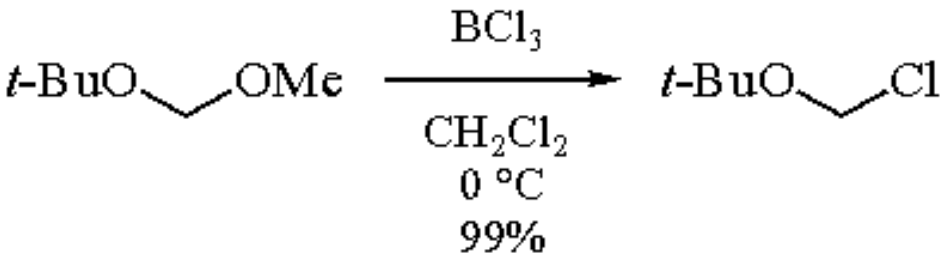

(1)

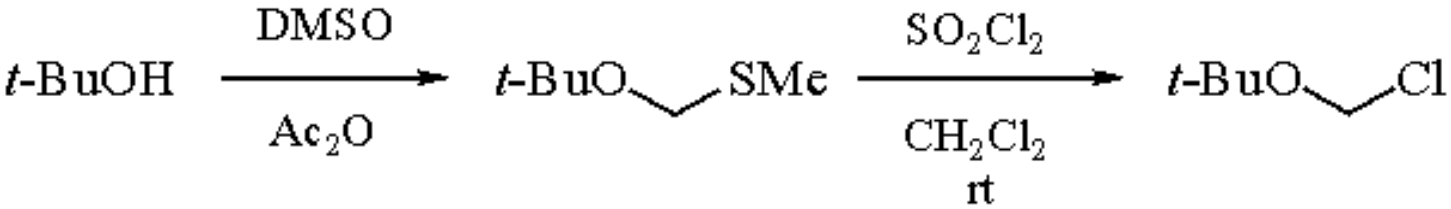

(2)

Protection of alcohols proceeds by addition of the crude solution of *t*-butyl chloromethyl ether to a THF solution of the alcohol and 4 equiv ***Triethylamine*** at -20 °C (eq 3), followed by warming to rt.[1] The product *t*-butoxymethyl ethers can be chromatographed on alumina. Deprotection is effected by treatment with aqueous ***Trifluoroacetic Acid*** in THF at rt, conditions which do not lead to deprotection of methoxymethyl ethers (eq 4). The imidazole N-H of histidine derivatives can also be protected using *t*-butyl chloromethyl ether.[3] This group is stable to nucleophilic or basic reagents and catalytic hydrogenolysis, conditions which might be encountered during peptide synthesis, but can be removed with trifluoroacetic acid or with anhydrous ***Hydrogen Chloride*** or ***Hydrogen Bromide*** in acetic acid.

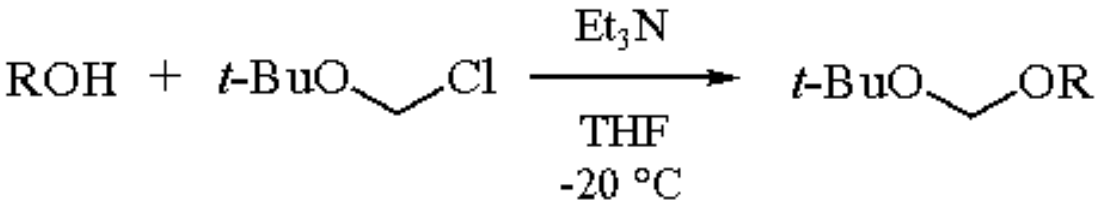

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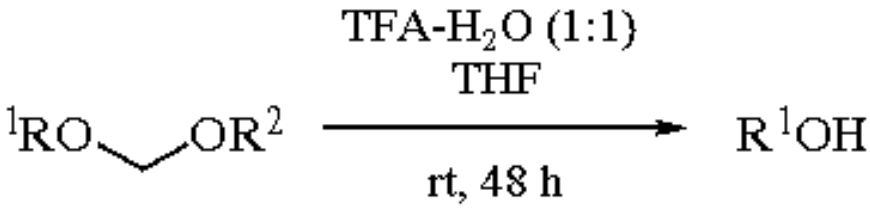

(4)

$R^2 = t\text{-Bu}$, 85-90%; $R^2 = \text{Me}$, 0%

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t-Butyl 2-Chloro-2-trimethylsilylacetate

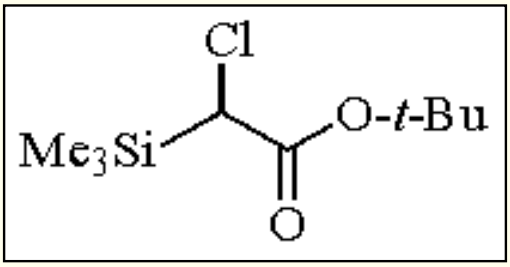

[66406-43-7] · $C_9H_{19}ClO_2Si$ · *t*-Butyl 2-Chloro-2-trimethylsilylacetate · (MW 222.79)

(alkenation of enolizable ketones leading to functionalized, tetrasubstituted alkenes (α,β-unsaturated esters) via a Peterson alkenation)

Physical Data: bp 55 °C/1.4 mmHg.

Solubility: sol THF.

Preparative Method: prepared from ***t-Butyl Chloroacetate*** by sequential reaction with ***Lithium Diisopropylamide*** and ***Chlorotrimethylsilane*** followed by aqueous workup and distillation.[1]

Handling, Storage, and Precautions: as this material is an activated alkyl halide, it must be considered a potential alkylating agent and lachrymator and handled with care and suitable protective clothing (e.g. gloves) in a fume hood.

The classical method for alkenation of an aldehyde utilizes Wittig reagents (phosphorus ylides) or related species such as the Wadsworth-Emmons reagent. These reagents do not generally give useful yields in the alkenation of ketones because of problems of steric hindrance between the ketone and the phosphorus reagent and because of competing enolization of the ketone. α-Silyl carbanions are generally less basic and less subject to steric encumbrance than the corresponding phosphorus ylides.[2] Therefore the Peterson alkenation[2] of ketones by α-silyl carbanions frequently provides superior results to the phosphorus reagents such as in the alkenation of cyclopentanone (eq 1).[3]

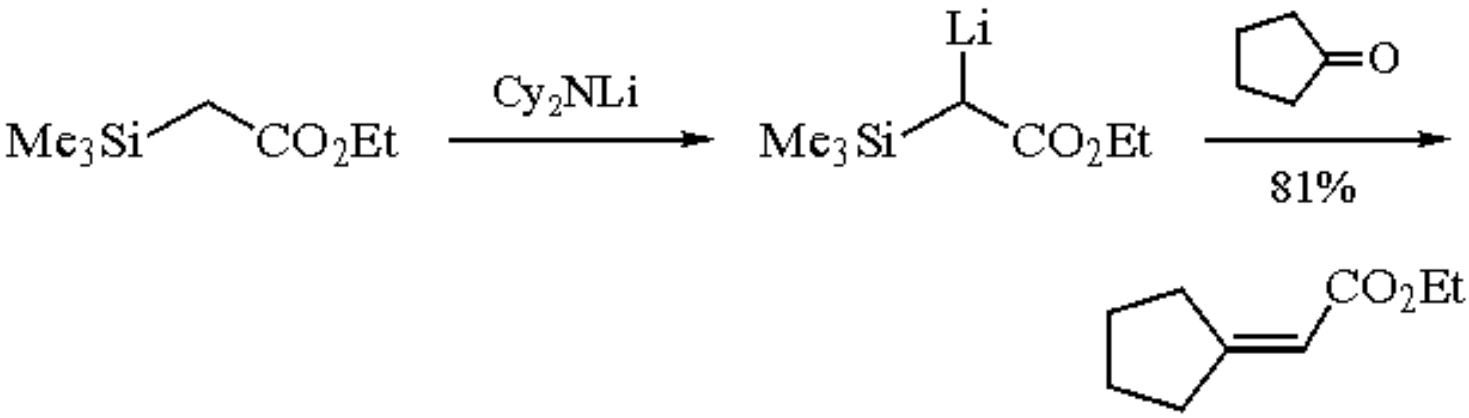

(1)

If the α-silyl carbanion is also functionalized with a leaving group such as chloride, condensation with carbonyl compounds can lead to epoxysilanes (eq 2).[4]

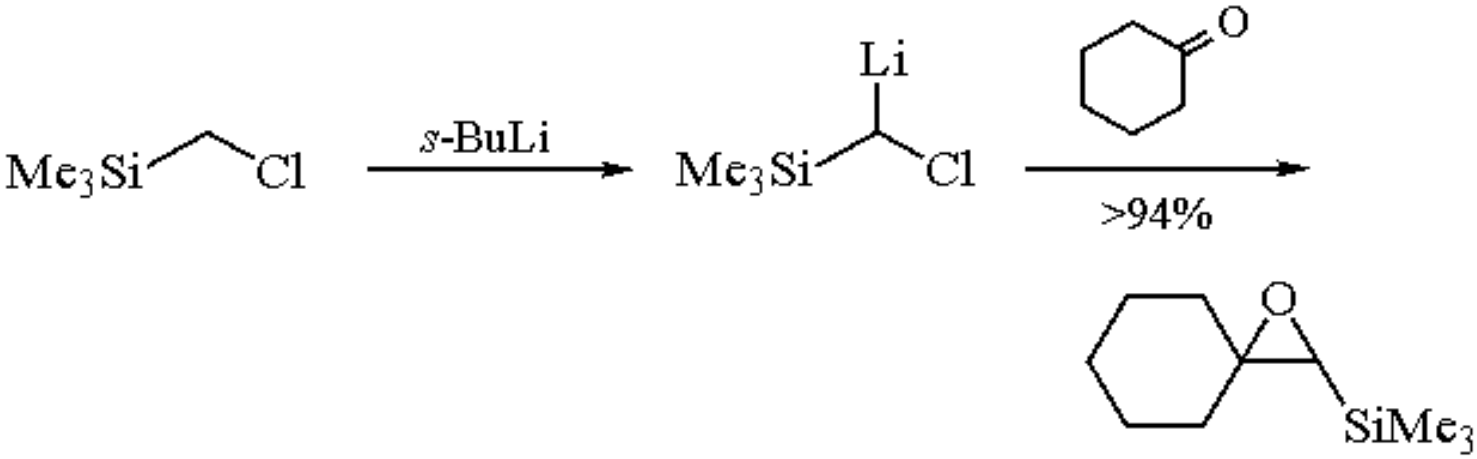

(2)

If the carbanion is further substituted with a *t*-butoxycarbonyl group, the epoxysilane reaction pathway is suppressed and Peterson alkenation is the normal reaction course. Thus the reaction of *t*-butyl 2-chloro-2-lithio-2-trimethylsilylacetate, derived from *t*-butyl 2-chloro-2-trimethylsilylacetate by reaction with LDA, with aldehydes (eq 3) and ketones (eq 4) leads to tri- and tetrasubstituted functionalized alkenes, α-chloro-α,β-unsaturated esters.[1]

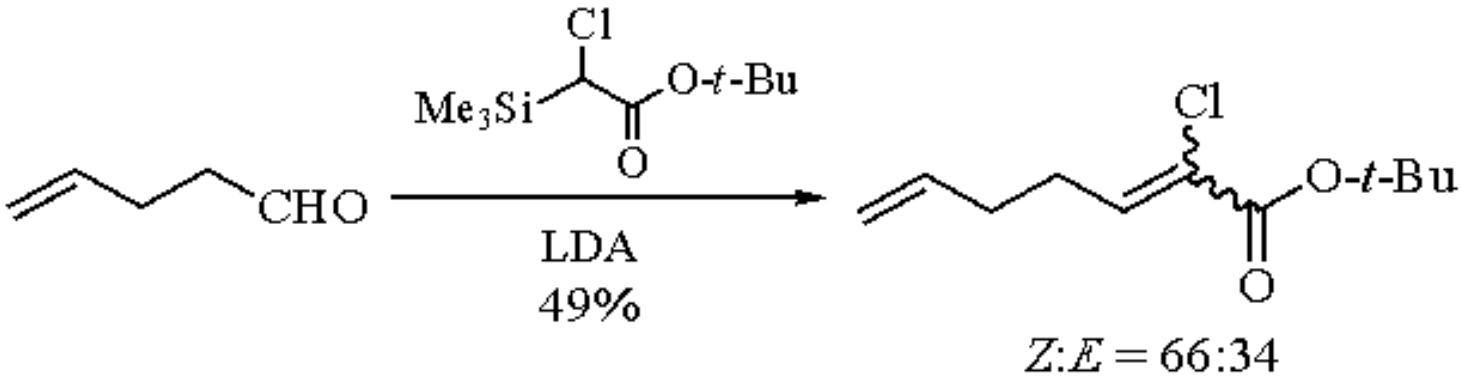

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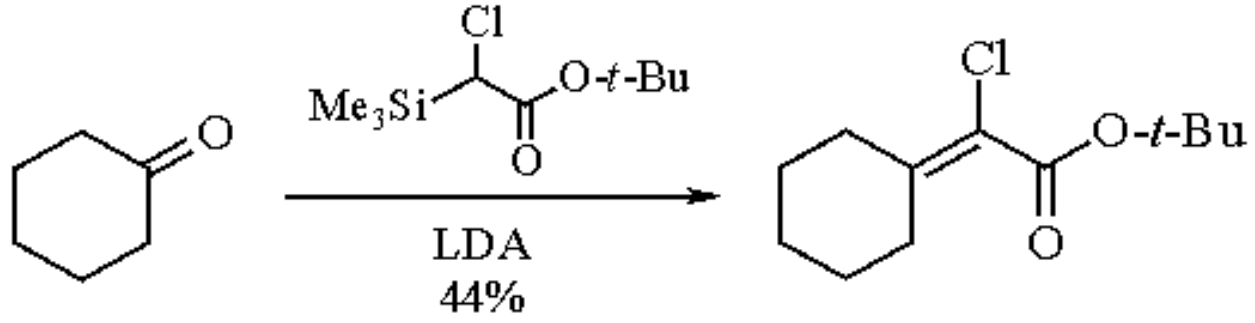

(4)

In the case of unsymmetrical ketones, moderate (eq 5) to good (eq 6) degrees of stereoselection are observed in the alkenation process, although yields are typically low.

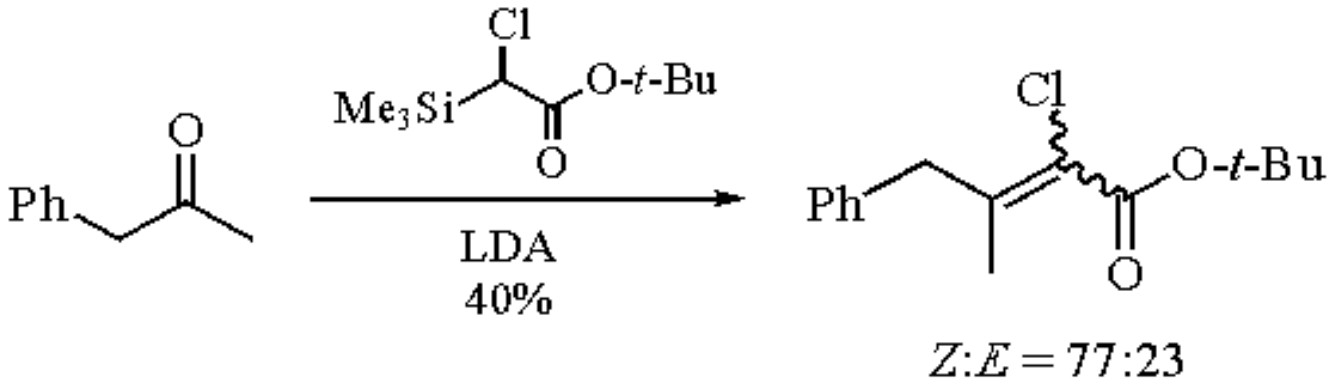

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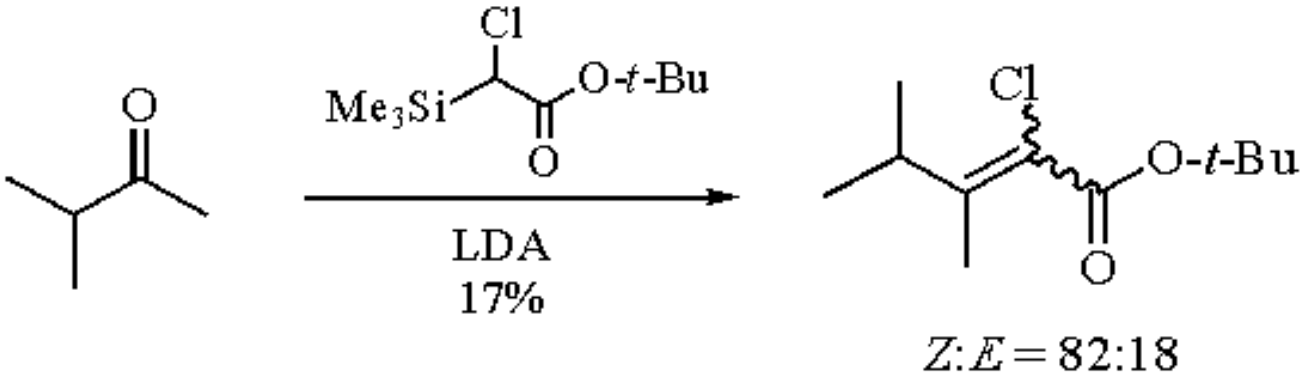

(6)

Chloro *t*-butoxycarbonylalkenes are of use as functional intermediates in, for example, the total synthesis of prostaglandins.[5] More general is the interest in these products as herbicides,[6] insecticides,[7] and antibiotics.[8] In the latter case, the Peterson alkenation was utilized to prepare C(2)-substituted monic acid esters (eq 7).

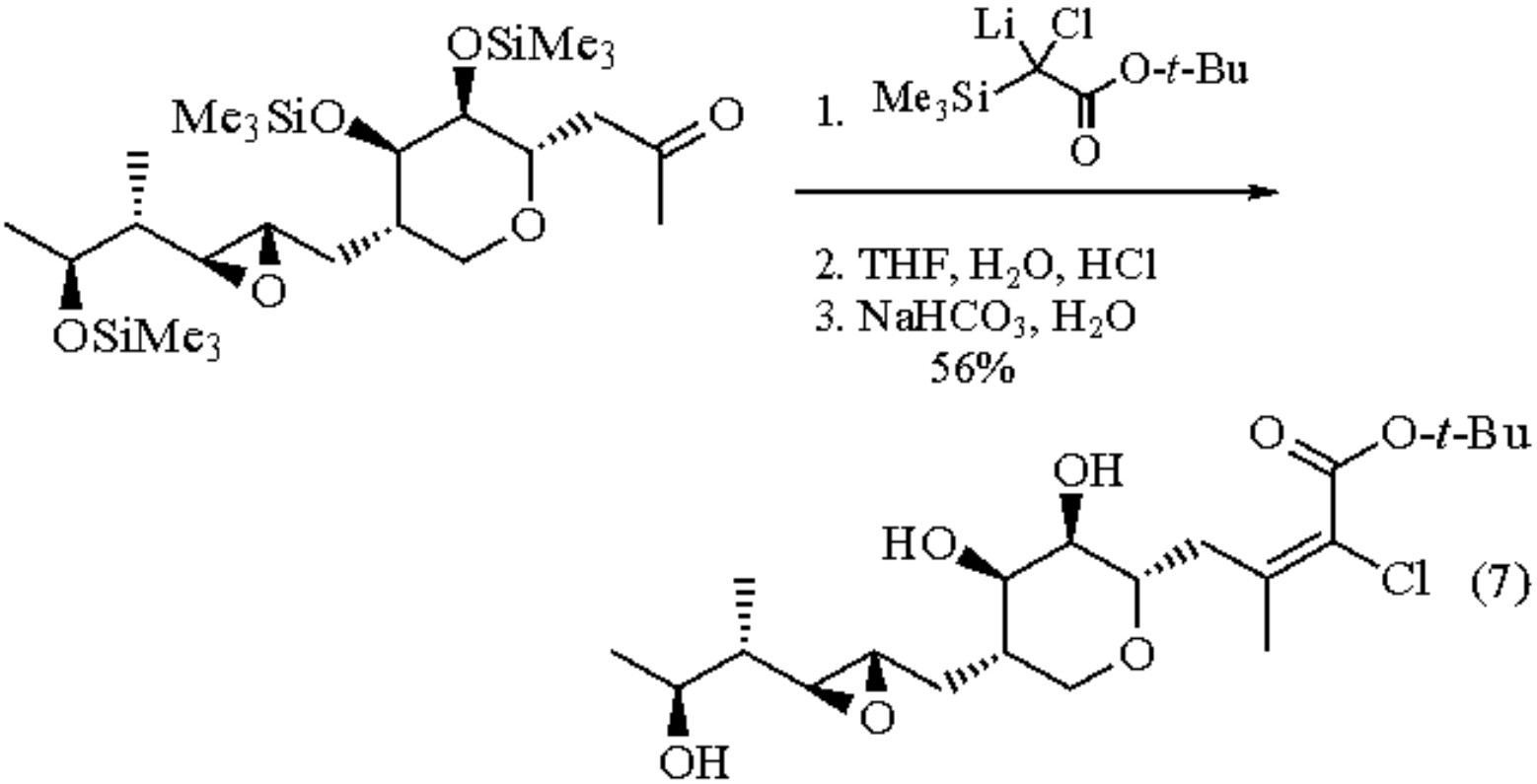

(7)

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t-Butyldimethylchlorosilane

t-BuMe$_2$SiCl

[18162-48-6] · $C_6H_{15}ClSi$ · *t*-Butyldimethylchlorosilane · (MW 150.72)

(widely used reagent for the protection of alcohols, amines, carboxylic acids, ketones, amides, thiols, and phenols;[1] useful for regioselective silyl enol ether formation[2] and stereoselective silyl ketene acetal formation[3])

Alternate Names: *t*-butyldimethylsilyl chloride; TBDMSCl; TBSCl.

Physical Data: mp 86-89 °C; bp 125 °C.

Solubility: very sol nearly all common organic solvents such as THF, methylene chloride, and DMF.

Form Supplied in: moist white crystals, commonly available.

Handling, Storage, and Precautions: hygroscopic, store under N_2; harmful if inhaled, swallowed, or absorbed through skin; should be used and weighed out in a fume hood.

Protecting Group.

The reactions of TBDMSCl closely parallel those of ***Chlorotrimethylsilane*** (TMSCl). However, TBDMS ethers are about 10^4 more stable toward hydrolysis than the corresponding TMS ethers.[1,4] The hydrolytic stability of the TBDMS group has made it very valuable for the isolation of many silicon-containing molecules. Since its introduction in 1972, the TBDMS protecting group has undoubtedly become the most widely used silicon protecting group in organic chemistry.[1] Alcohols are most commonly protected as their TBDMS ethers by treatment of the alcohol in DMF (2 mL g^{-1}) at rt with 2.5 equiv of ***Imidazole*** (Im) and 1.2 equiv of TBDMSCl. Alcohol protection in the presence of ***4-Dimethylaminopyridine*** (DMAP) allows a greater range of solvents to be used (protection of alcohols in solvents other than DMF using TBDMSCl alone are sluggish) and distinguishes a kinetic preference for protection of primary alcohols in the presence of secondary alcohols.[5] Table 1 outlines conditions for the selective protection of primary and secondary alcohols using TBDMSCl and DMAP as catalyst.

Table 1 Use of DMAP to Catalyze the Protection of Diols With TBDMSCl

Amine(s)	Solvent	GC ratio of A:B:C
DMAP (0.04 equiv), Et_3N (1.1 equiv)	CH_2Cl_2	95:0:5
Im (2.2 equiv)	DMF	59:11:30
Im (0.04 equiv), Et_3N (1.1 equiv)	DMF	No reaction
DMAP (0.04 equiv), Et_3N (1.1 equiv)	DMF	0:0:96

Alcohol:

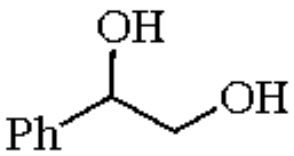

Products:

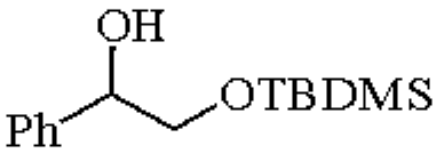

A

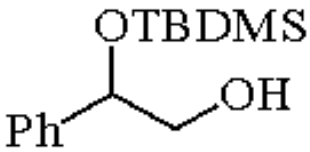

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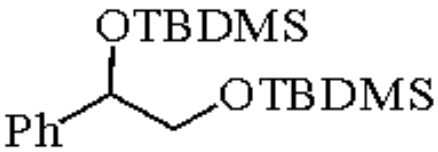

C

Table 2[6] compares the rate of hydrolysis of several bulky silicon ethers with acid, base, and fluoride; TBDMS ethers are less resistant to hydrolysis than the corresponding TIPS (triisopropylsilyl) and TBDPS (*t*-butyldiphenylsilyl) ethers.

Table 2 Comparison of TBDMS, TIPS, and TBDPS rates of hydrolysis by F^-, H^+, and OH^- ($t_{1/2}$).

$ROSiR'_3$	R = *n*-Bu[a]		R = Cy[a,b]		
	H^+	OH^-	H^+	OH^-	F^-
TBDMS	<1 min	1 h	<4 min	26 h	76 min
TIPS	18 min	14 h	100 min	44 h	137 min
TBDPS	244 min	<4 h	360 min	14 h	

[a] H^+ refers to 1% HCl in 95% EtOH at 22 °C; OH^- refers to 5% NaOH in 95% EtOH at 90 °C. [b] F^- refers to 2 equiv of *n*-Bu_4NF in THF at 22 °C.

The TBDMS group is also suitable for the protection of amines, including heterocycles, carboxylic acids, and phenols. Other more reactive reagents are also available for introduction of the TBDMS group including ***t-Butyldimethylsilyl Trifluoromethanesulfonate***, MTBSA, and TBDMS-imidazole.[1,7]

Anion Trap.

TBDMSCl is useful as an anion trapping reagent. For example, TBDMSCl was found to be an efficient trap of the lithio α-phenylthiocyclopropane anion.[8] When dichlorothiophene was treated with 2 equiv of ***n-Butyllithium*** followed by 2 equiv of TBDMSCl the di-TBDMS-thiophene was isolated.[9] The lithium anions of primary (eq 1) and secondary (eq 2) nitriles were trapped with TBDMSCl to give *C,N*-disilyl- and *N*-silylketenimines in excellent yields.[10]

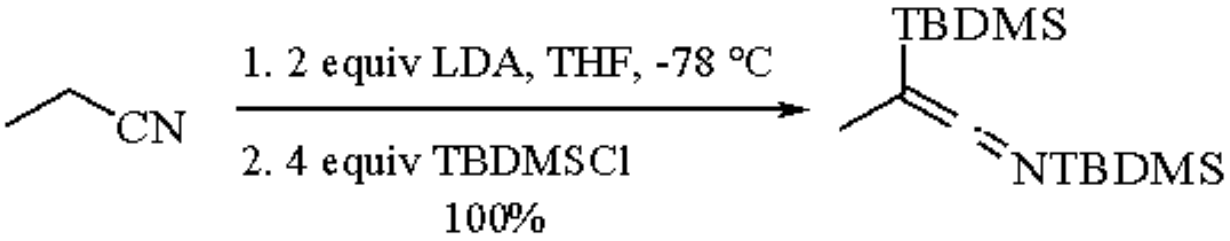

(1)

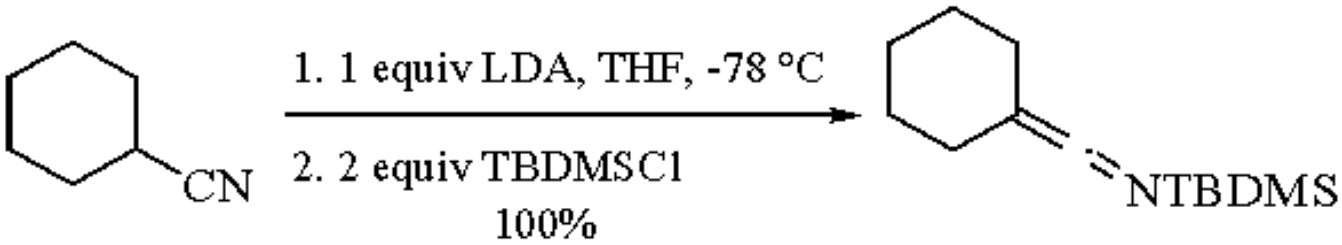

(2)

Silyl stannanes have been prepared by trapping tin anions with TBDMSCl or other silyl chlorides. Alkynes treated with with silyl stannanes and catalytic ***Tetrakis(triphenylphosphine)palladium(0)*** give *cis*-silyl stannylalkenes in good yields.[11]

Silyl Ketene Acetals.

The lithium enolates of esters may be trapped with TBDMSCl to prepare the corresponding ketene silyl acetals.[3] The resulting TBDMS ketene acetals are more stable than the corresponding TMS ketene acetals and have a greater preference for *O*- vs. *C*-silylation products. When TMSCl was used to trap the enolate of methyl acetate, a 65:35 ratio of *O*- to *C*-silated products was obtained. In addition, *O*-(TMS) silyl ketene acetals are thermally and hydrolytically unstable. However, similar treatment of lithium enolates with TBDMSCl provided the corresponding *O*-(TBDMS) silyl ketene acetals exclusively (eq 3). The *O*-TBDMS ketene acetals generally survive extraction from cold aqueous acid. ***Lithium Diisopropylamide*** was found to be satisfactory for the preparation of the ester enolates. The lower reactivity of TBDMSCl requires that the enol silation be performed at 0 °C with added HMPA.[12]

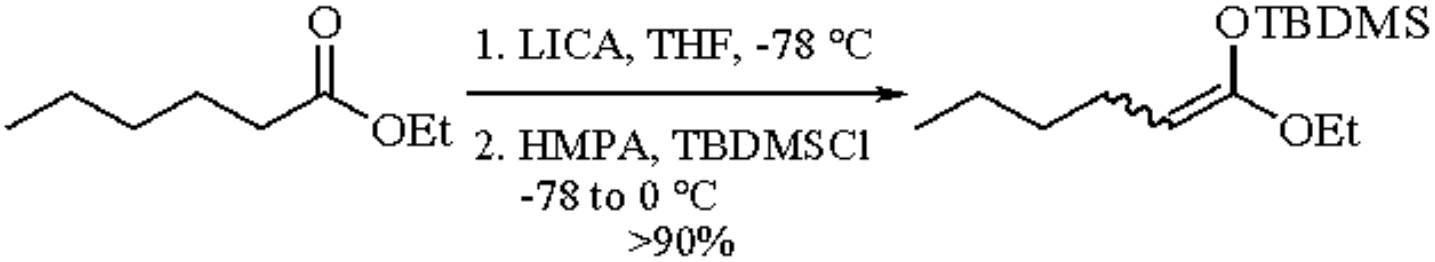

(3)

A detailed study of the formation of (*E*)- and (*Z*)-silyl ketene acetals was recently published.[3d] It was found that the formation of silyl enolates does not correspond to simple kinetic vs. thermodynamic formation of the enolates. Formation of the ester enolates occurred under kinetic control and a kinetic resolution accounted for selective formation of (*E*)- and (*Z*)-silyl ketene acetals. Table 3 summarizes some of these results.

Table 3 Effects of Reaction Conditions on (*Z*):(*E*) Ratio of TBDMS Silyl Ketene Acetal Formation of Ethyl Propionate

Ester:base ratio	Base	Solvent	Additive	(*Z*):(*E*) Silyl ketene acetal ratio	Yield (%)
1:1	LDA	THF	-	6:94	90
1.05:1	LDA	THF	45% DMPU	≥98:2	80
1.2:1	LDA	THF	23% HMPA	93:7	65
1:1	LDA	THF	23% HMPA	85:15	80
1:1	LHMDS	THF	23% HMPA	>91:9	85
1.1:1	LHMDS	THF	23% HMPA	>95:5	60

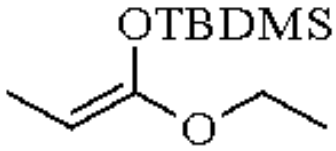

(*Z*)

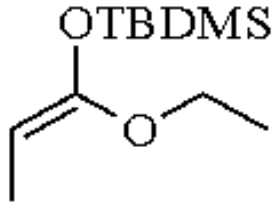

(*E*)

Claisen Rearrangement.

The first silyl ketene acetal Claisen rearrangement was introduced in 1972 using TMS ketene acetals. Since then, the silyl Claisen rearrangement using TBDMS ketene acetals has found widespread use in organic synthesis.[13,14] One advantage of the silyl ketene acetal Claisen rearrangement is that the ketene acetal geometry may be predictably controlled (see above). Two components of the reaction contribute to stereocontrol: the geometry of the silyl ketene acetal and the contribution of boat vs. chair transition state. A useful variant of the Claisen rearrangement involves the use of an enantiomerically pure α-silyl secondary alcohol prepared by Brook rearrangement of a TBDMS-protected primary alcohol. In this reaction the stereochemistry at the silicon-bearing center is transferred to the Claisen product.[15] The (*E*)-enolate was prepared by treatment of the ester with ***Lithium Hexamethyldisilazide*** (eq 4); the (*Z*)-enolate was prepared by treatment of the ester wit h LDA (eq 5).[15b] As expected, the (*Z*)- and (*E*)-silyl ketene acetals gave the corresponding *syn* and *anti* Claisen products in good selectivity. The vinylsilane was hydrolyzed to the alkene using 50% HBF_4 in acetonitrile at 55 °C.

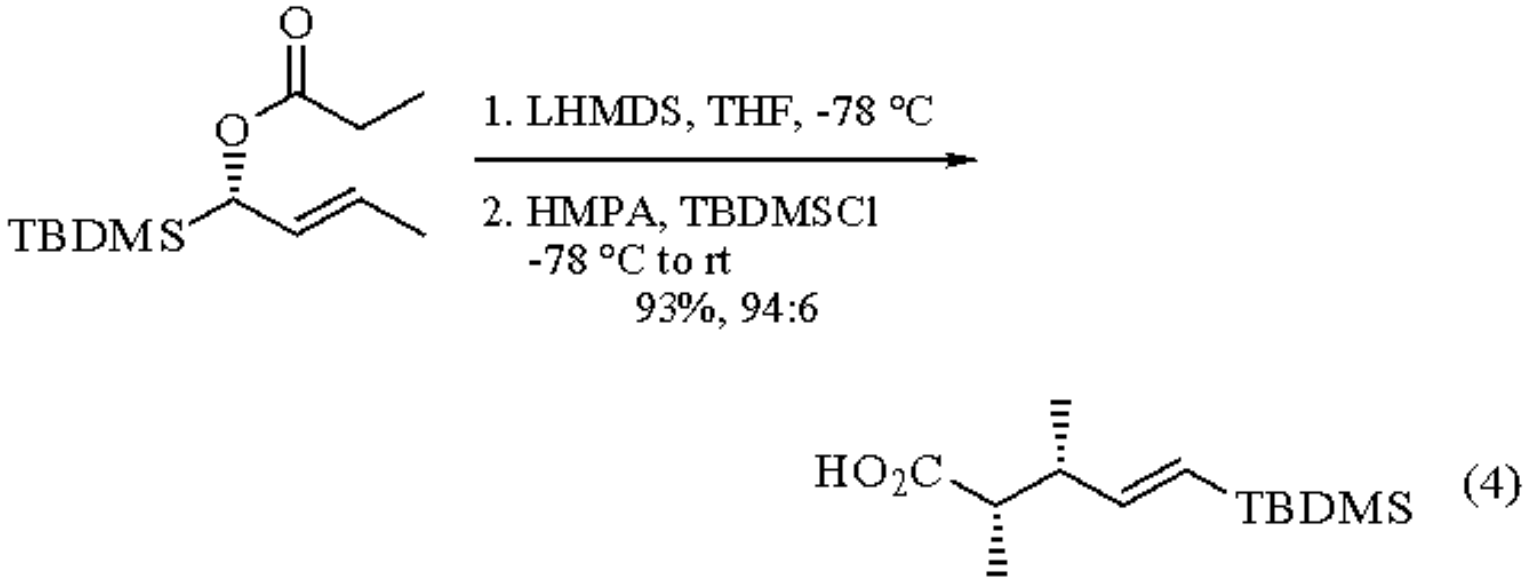

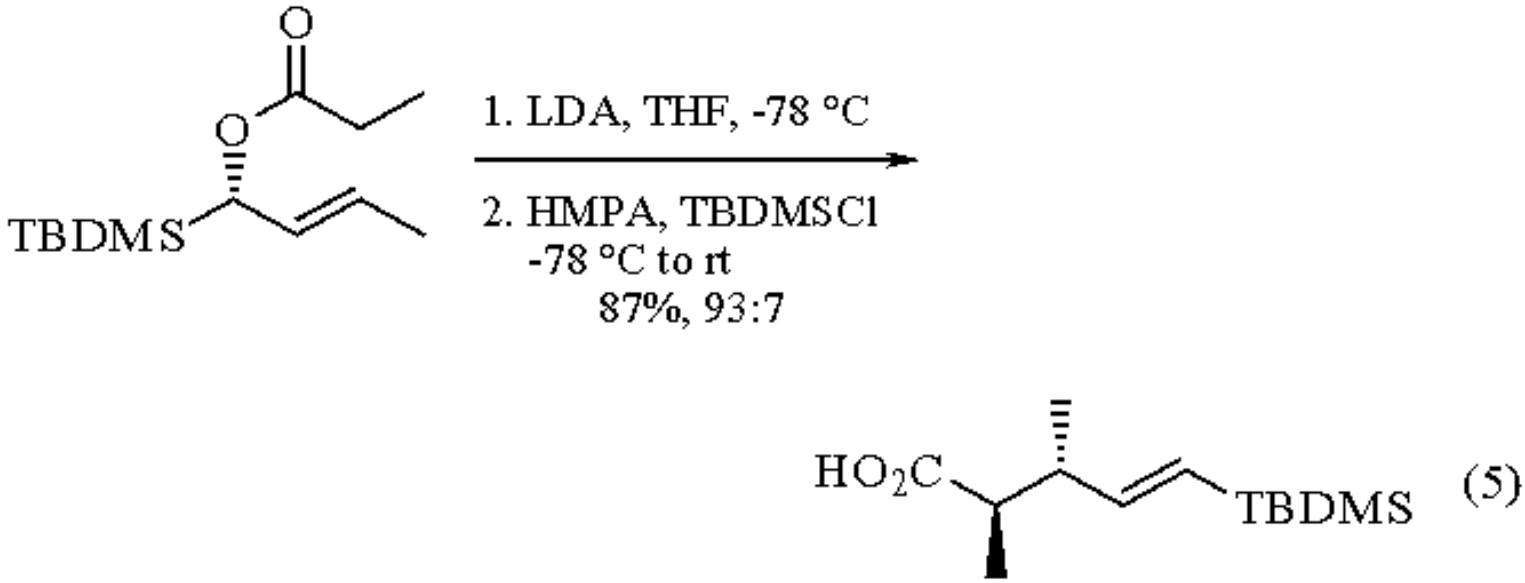

The silyl ketene acetals of methyl α-(allyloxy)acetates were found to undergo [3,3]-sigmatropic rearrangement, whereas the corresponding lithium enolates undergo [2,3]-sigmatropic rearrangement.[16] An interesting ring contraction based on the TBDMS silyl ketene acetal Claisen rearrangement has also been reported.[17]

TBDMS Enol Ethers.[18]

Enolates trapped with TBDMSCl to prepare the corresponding enol ethers are more stable than the corresponding TMS enol ethers.[19] The potassium enolate of 2-methylcyclohexanone, prepared by addition of ***Potassium Hydride*** to a solution of the ketone and TBDMSCl in THF at -78 °C followed by warming to rt, gave the thermodynamic enol ether in a 56:44 ratio. In the presence of HMPA, the ratio improves to 98:2 (eq 6). This method works especially well with ketones with a propensity for self-condensation.[20]

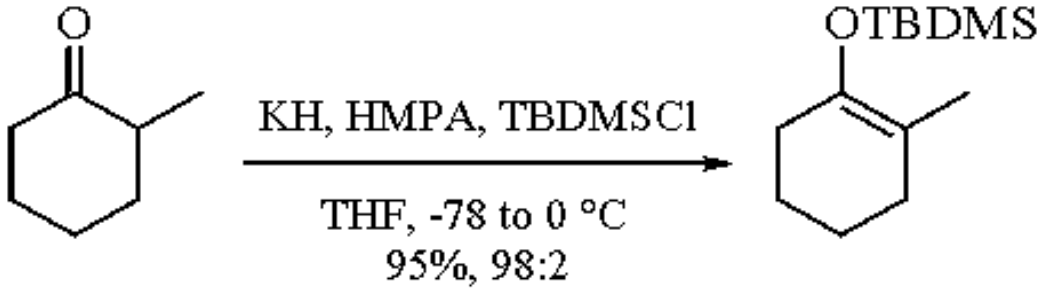

(6)

Potassium enolates derived from acylfulvalenes were trapped with TBDMSCl but not TMSCl or diphenylmethylsilyl chloride.[21] Interestingly, TBDMSCl was found to be compatible with CpK anion at -78 °C. TBDMS enol ethers have also been used as β-acyl anion equivalents.[22] The TBDMS-silyl enol ethers of diketones (eq 7) and β-keto esters (eq 8) may be prepared by mixing them with TBDMSCl in THF with imidazole.[23] Alcohols may be protected under acidic conditions as their TBDMS ethers by treatment with β-silyl enol ethers in polar sovents.

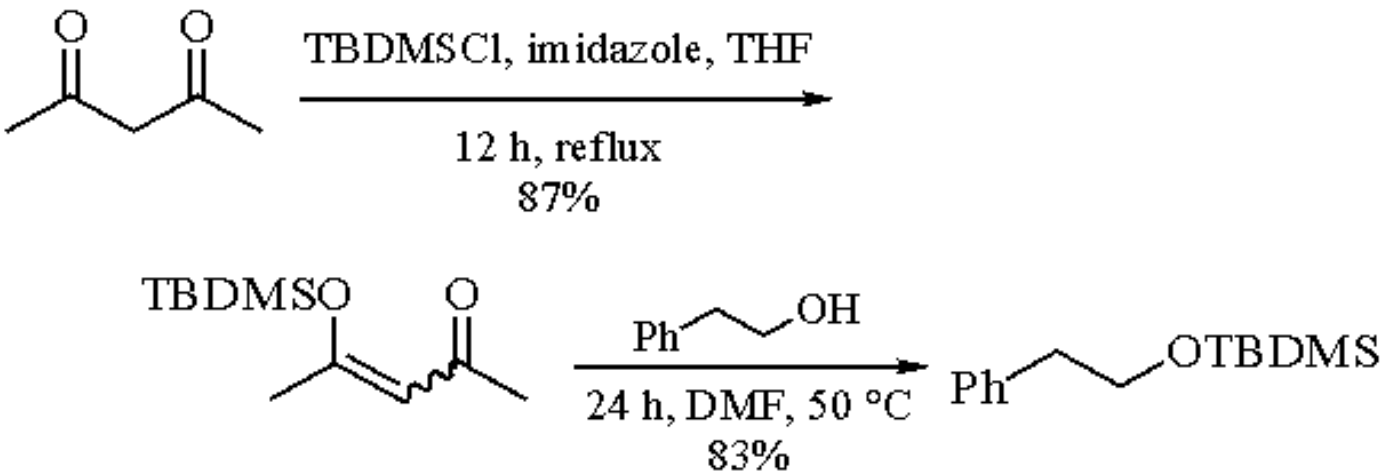

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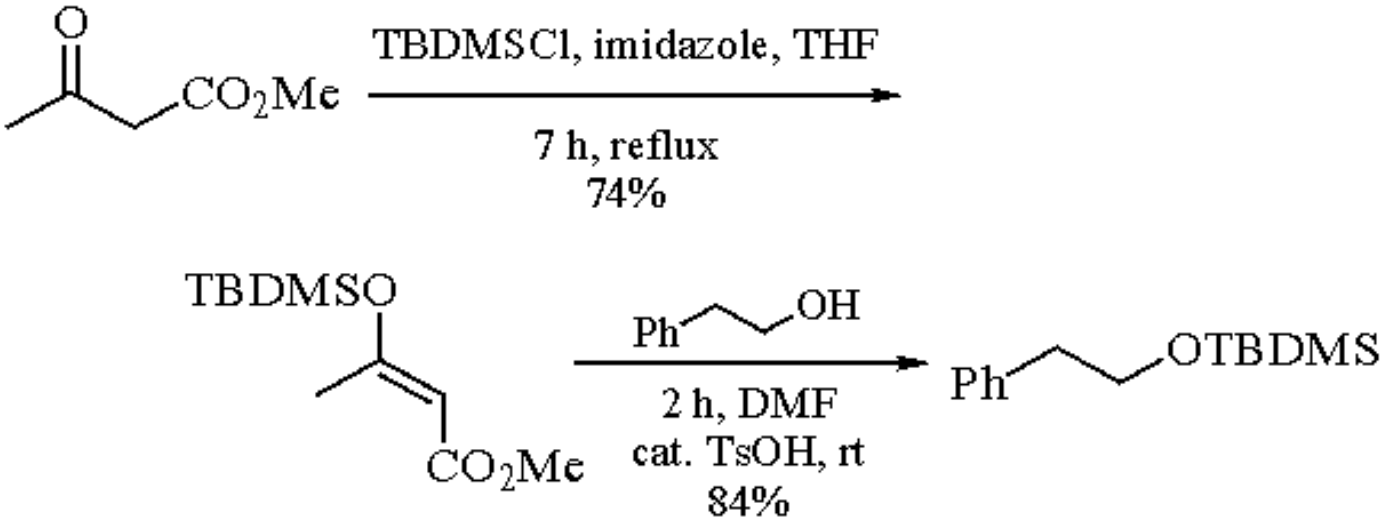

(8)

Aldol Reaction.

The catalyst system TBDMSCl/$InCl_3$ selectively activates aldehydes over acetals for aldol reactions with TBDMS enol ethers.[24] Acetals and aldehydes are activated towards aldol reactions using TMSCl/$InCl_3$ or Et_3SiCl/$InCl_3$ as catalysts (eq 9).

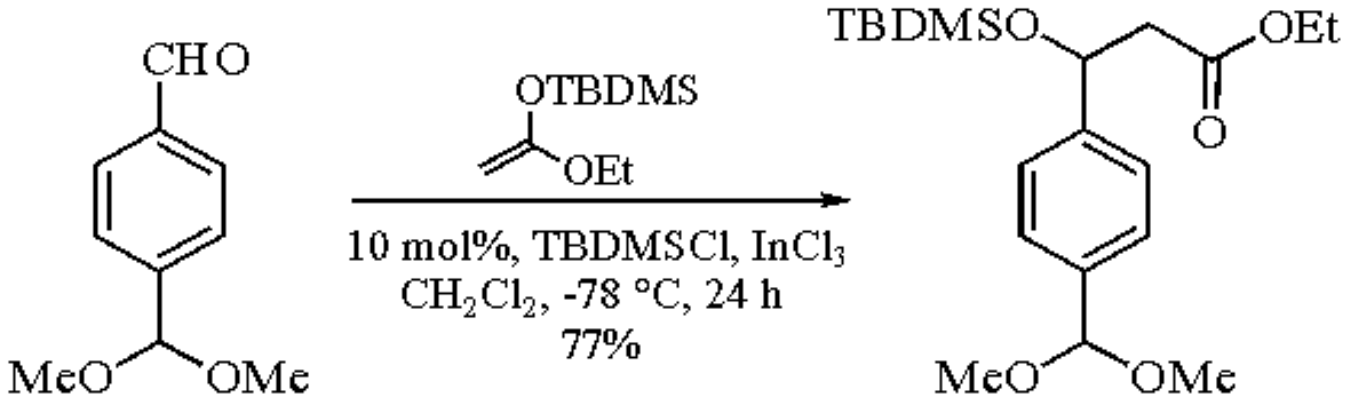

(9)

TBDMSCl as Cl⁻ Source.

TBDMSCl was used as a source of chloride ion in the Lewis acid-assisted opening of an epoxide.[25] The epoxide was treated with TBDMSCl and ***Triethylamine*** followed by ***Titanium Tetraisopropoxide*** and additional TBDMSCl to give the *trans* chloride as the major product in 67% yield (eq 10).

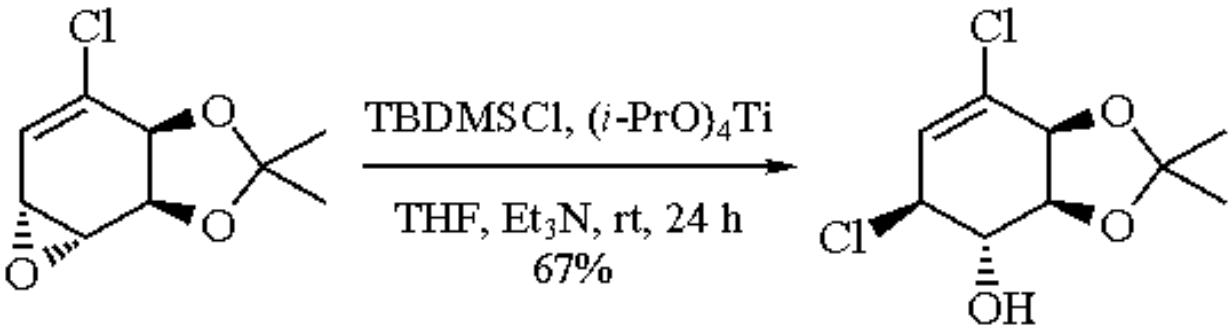

(10)

TBDMSCl-Assisted Reactions.

Nitro aldol (Henry) reactions have been reported to be promoted by TBDMSCl.[26] To a THF solution of ***Tetra-n-butylammonium Fluoride*** is added sequentially equimolar amounts of the nitro compound, aldehyde, and Et_3N, followed by an excess of TBDMSCl (eq 11). Substitution of TMSCl for TBDMSCl reduces the yield of nitro aldol product. The authors speculate that TBDMSCl is responsible for activation of the aldehyde while *n*-Bu_4NF activates the nitro compound. In a related method, primary and secondary nitro alkanes were treated with LDA in THF followed by addition of TBDMSCl to give the corresponding silyl nitronates. The silyl nitronates reacted with a variety of aliphatic and aromatic aldehydes which gave vicinal nitro TBDMS aldol products.[27]

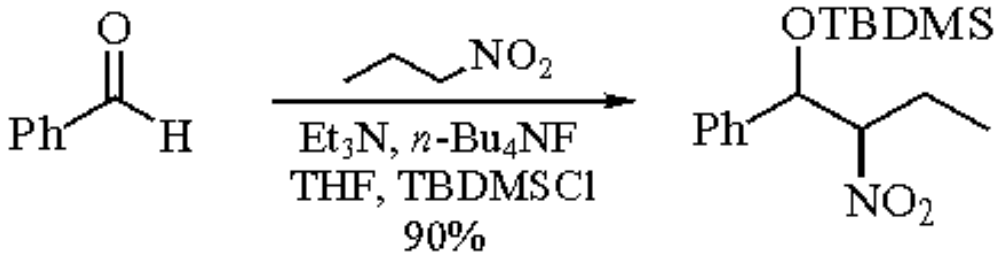

(11)

Reaction with Nucleophiles.

TBDMSCl is the reagent of choice for the preparation of other TBDMS-containing reagents. For example, ***t-Butyldimethylsilyl Cyanide*** may be prepared by the reaction of TBDMSCl and ***Potassium Cyanide*** in acetonitrile containing a catalytic amount of ***Zinc Iodide***.[28] TBDMSCN has also been prepared by treatment of TBDMSCl with KCN and ***18-Crown-6*** in CH_2Cl_2 at reflux and by treatment of TBDMSCl with ***Lithium Cyanide*** prepared in situ.[29] ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** is prepared by treatment of TBDMSCl with ***Trifluoromethanesulfonic Acid*** at 60 °C.[30] Other nucleophiles, such as thiolates, also react with TBDMSCl.[31] ***t-Butyldimethylsilyl Iodide*** was prepared by treatment of TBDMSCl with ***Sodium Iodide*** in acetonitrile.[32] In contrast to THF cleavage reactions using TMSI, the more stable TBDMS-protected primary alcohol may be isolated from the reaction in eq 12.

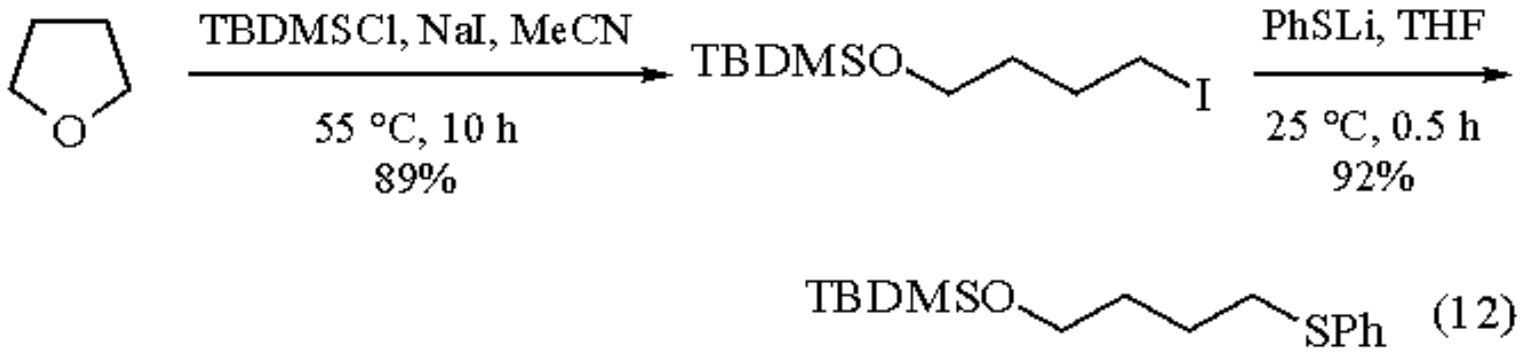

(12)

Mannich Reaction.

The Mannich reaction of *N*-methyl-1,3-oxazolidine with 2-methylfuran was shown to proceed smoothly in the presence of TBDMSCl and catalytic ***1,2,4-Triazole*** in 61% yield. Interestingly, this reaction failed with TBDMSOTf due to the destruction of 2-methylfuran. The reaction proceeds with decreased yield (31%) in the absence of triazole. These reaction conditions allowed for the isolation of the TBDMS-protected alcohol (eq 13).[33]

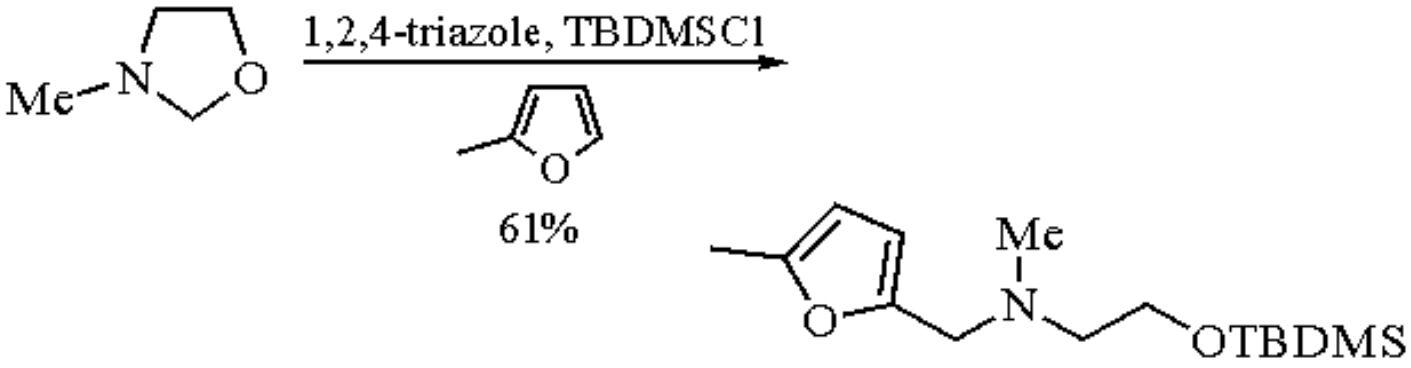

(13)

Acid Chlorides.

TBDMS esters, when treated with DMF and ***Oxalyl Chloride*** in methylene chloride at 0 °C, give the corresponding acid chlorides in excellent yields under neutral conditions (eq 14).[34] Similarly, *N*-carboxyamino acid anhydrides were prepared via the intermediacy of an acid chloride prepared from a TBDMS ester (eq 15).[35]

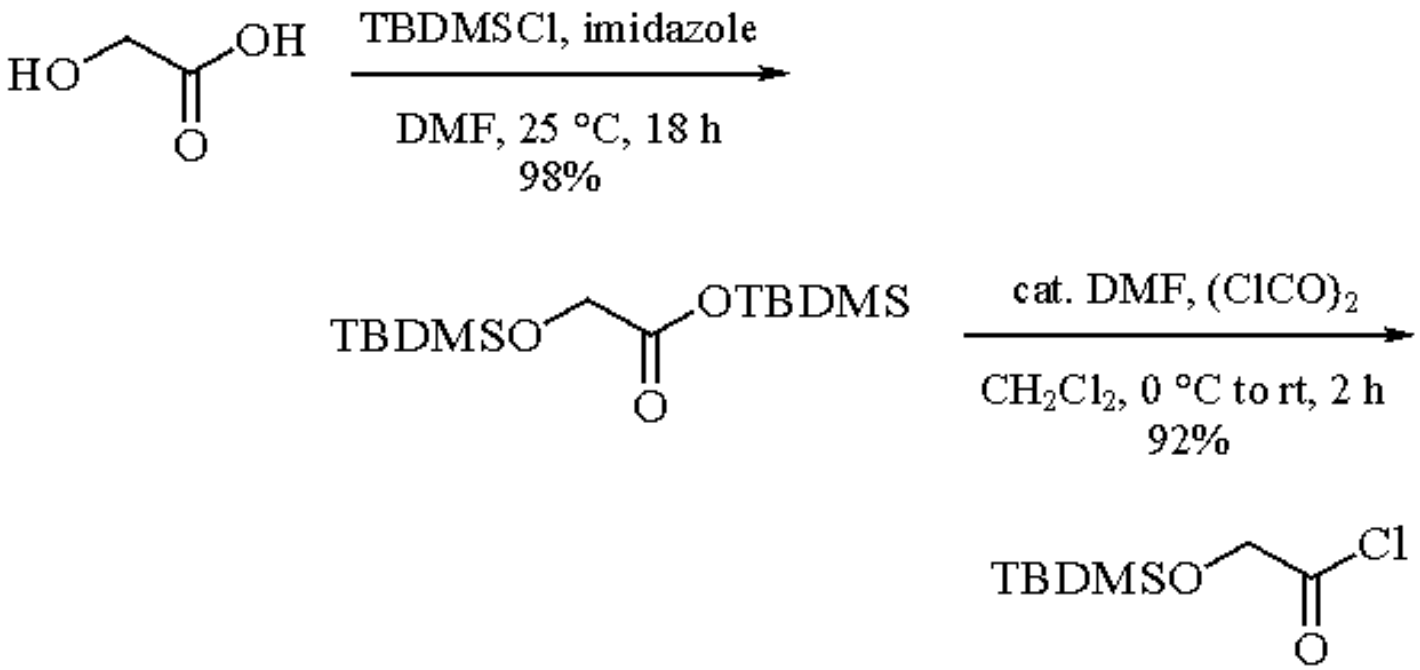

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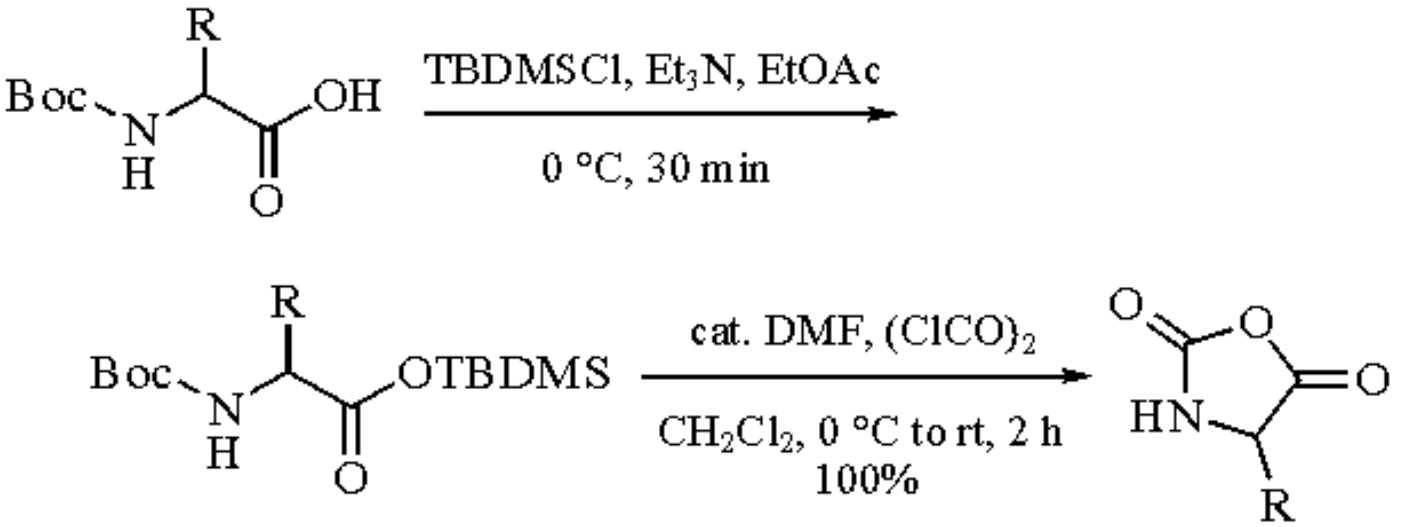

(15)

Conjugate Additions.

When a mixture of TBDMSCl and a β-aryl enone (2:1) was added to $Bu_2CuCNLi_2$ at -78 °C, the TBDMS group added 1,4 to the enone to give β-silyl carbonyl compounds (eq 16).[36] *N*-TBDMS silyliminocuprates also add to α,β-unsaturated carbonyl compounds.[37]

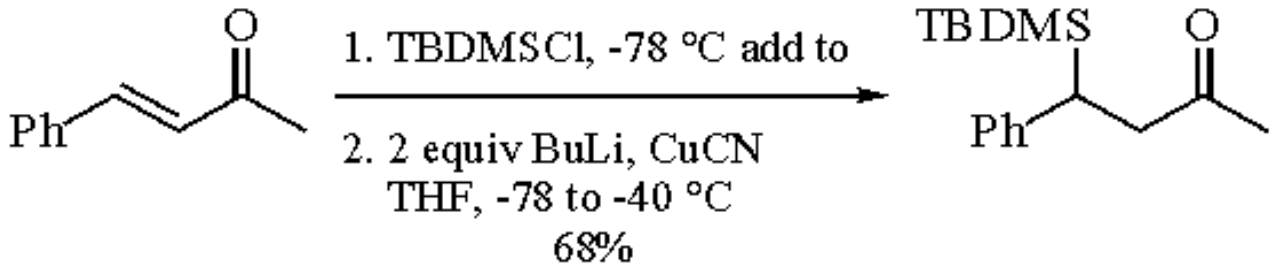

(16)

α-Silyl Aldehydes.

Initial attempts to isolate TMS α-silyl aldehydes were unsuccessful due to the lability of the TMS group. However, the α-silyl aldehyde was prepared from the cyclohexyl imine of acetaldehyde by treatment with LDA followed by TBDMSCl (eq 17). Typical of TBDMSCl trapping reactions of imines and hydrazones, *C*-silylation was observed. The imine was hydrolyzed with HOAc in CH_2Cl_2 which gave the α-silyl aldehyde. These compounds, after treatment with organometallic reagents such as ***Ethylmagnesium Bromide*** or ***Ethyllithium***, may be eliminated in a Peterson-like manner to give either *cis* or *trans* alkenes (eq 18).[38]

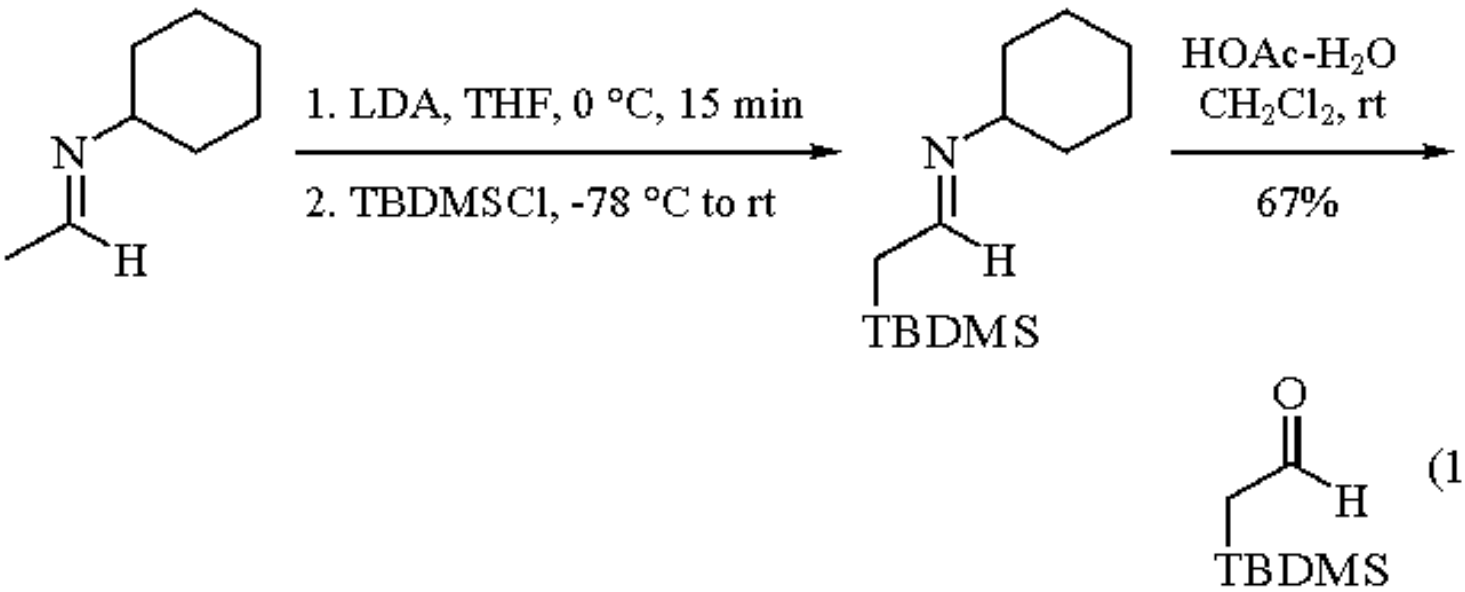

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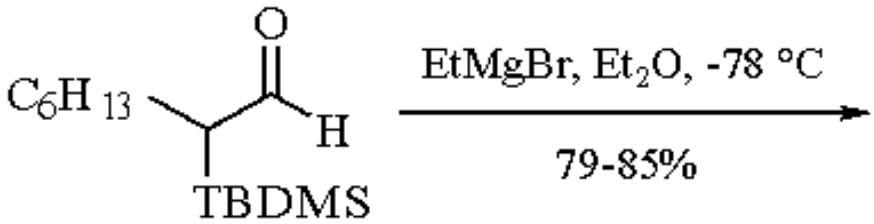

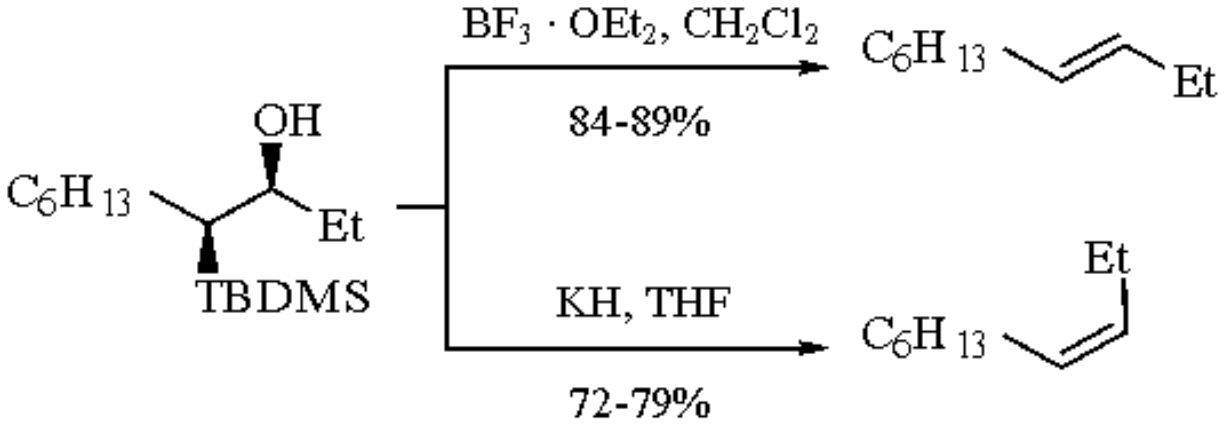

(18)

α-Silyl Ketones.

When SAMP or RAMP hydrazones were treated with LDA followed by TBDMSCl, the corresponding α-silyl hydrazones were isolated. Ozonolysis of the hydrazone gave the enantiomerically enriched α-silyl ketones (eq 19).[39] Yields for the overall process are 52-79% for the preparation of α-silyl ketones and 22-42% for the preparation of α-silyl aldehydes. TBDMSOTf may also be used for quench of the SAMP/RAMP hydrazone enolate.

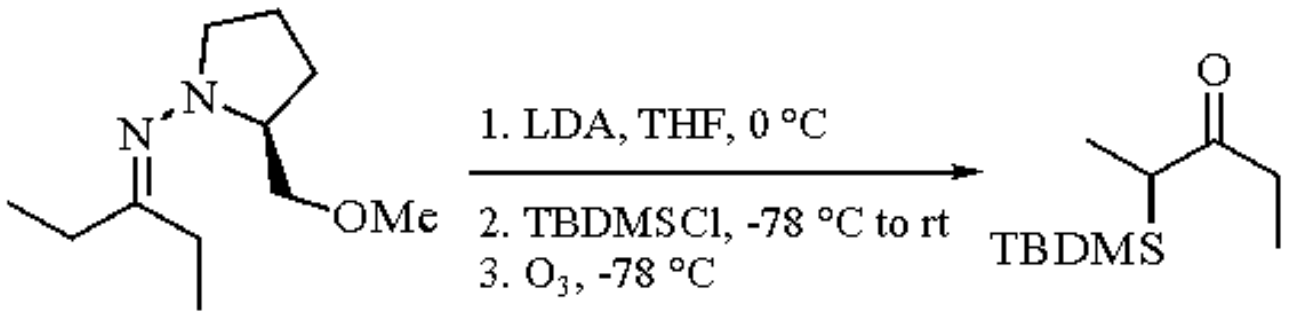

(19)

Acyl Silanes.

Although acyl trimethylsilanes are known, they are usually unstable and lead to poor diastereoselectivity in aldol reactions.[40] TBDMS acyl silanes, however, were prepared in 50% yield from 1-methoxy-1-lithiopropene in the presence of TMEDA at rt (eq 20). The lithium enolates of TBDMS acyl silanes were treated with aldehydes to give the corresponding aldol products in reasonable yields.

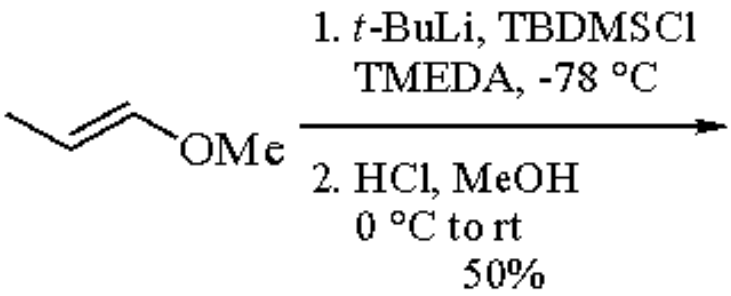

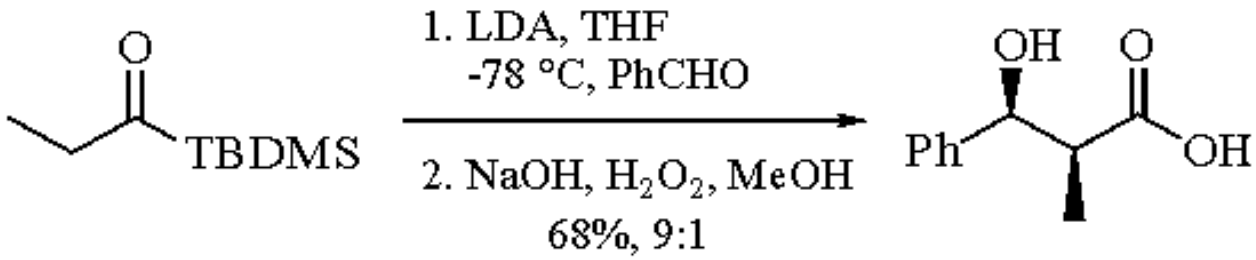

(20)

TBDMS acyl enones were prepared by treatment of an ethoxyethyl (EE)-protected alkoxyallene with *n*-BuLi at -85 °C followed by treatment of resulting anion with TBDMSCl (eq 21). Acid hydrolysis of the OEE group led to the TBDMS acyl enones in good yield.[41]

t-Butyldimethylchlorosilane

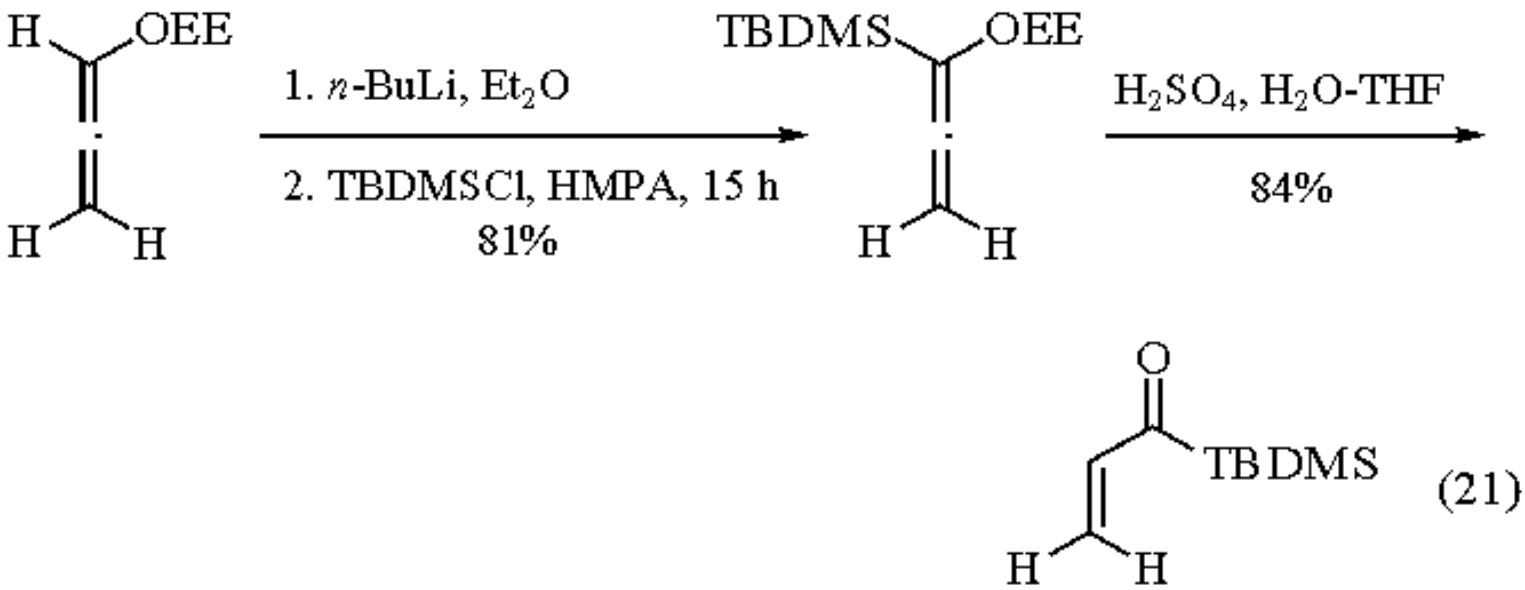

(21)

Modified Amine Base.

The regioselectivity of ketone deprotonation was improved by the use of lithium *t*-butyldimethylsilylamide as base.[42] The base was prepared by deprotonation of isopropylamine with *n*-BuLi in THF (eq 22). The resulting anion was quenched with TBDMSCl to give the amine in 70% yield after distillation. Deprotonation of various ketones using this amide base was found to be equally or more selective than LDA. For example, the TBDMS-modified base gave a 62:38 ratio of kinetic to thermodynamic enolate, whereas LDA gave a 34:66 ratio with phenyl acetone.

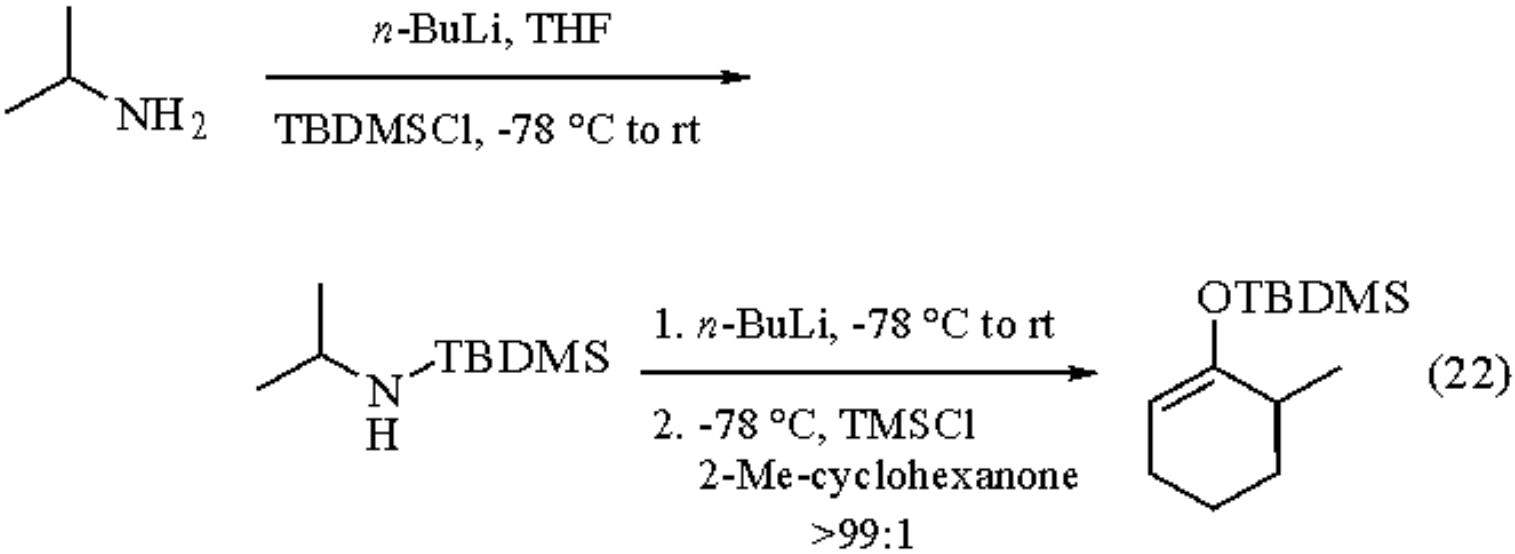

(22)

N-Formylation.

When secondary amines were treated with TBDMSCl, DMAP, and Et_3N in DMF the corresponding *N*-formyl derivatives were formed (eq 23).[43] It was found that the reaction proceeds through a Vilsmeier type reagent formed by the reaction of TBDMSCl and DMF. It is possible that other TBDMS alkylation reactions, such as protection of alcohols in DMF, may proceed through a similar DMF-derived Vilsmeier reagent.

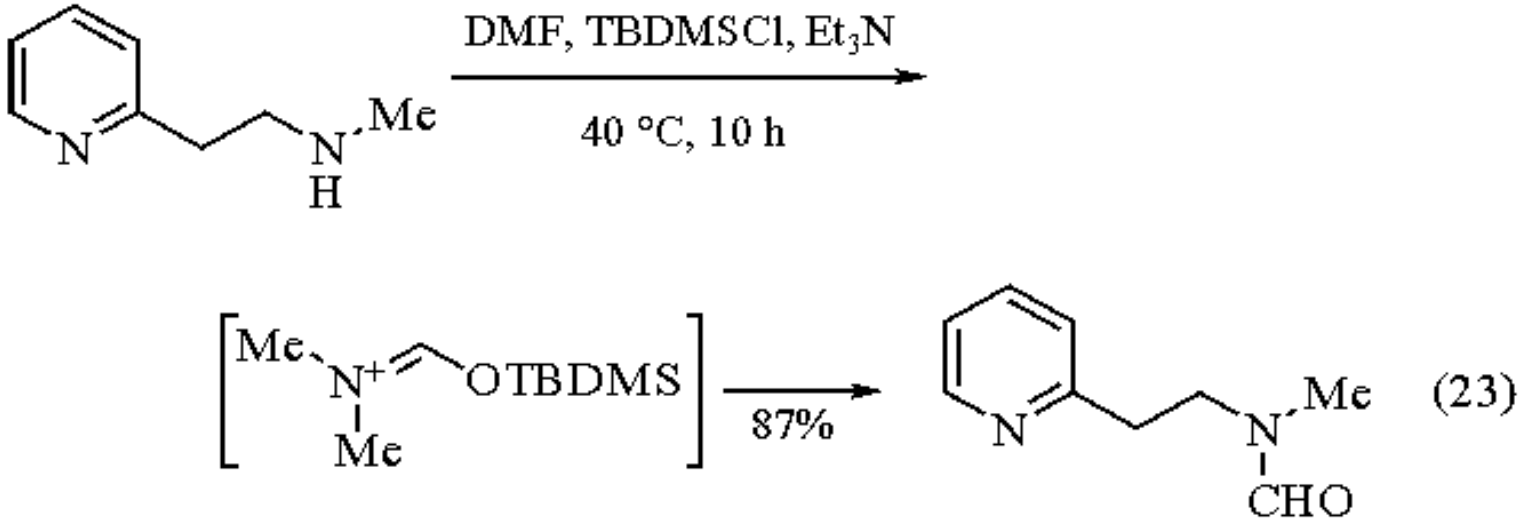

N-Silyl Imines.

When aldehydes were treated first with tris(trimethylstannyl)amine followed by TBDMSCl, the corresponding *N*-TBDMS imines were isolated in good yields.[44] These silyl imines reacted with ester enolates to give β-lactams (eq 24).

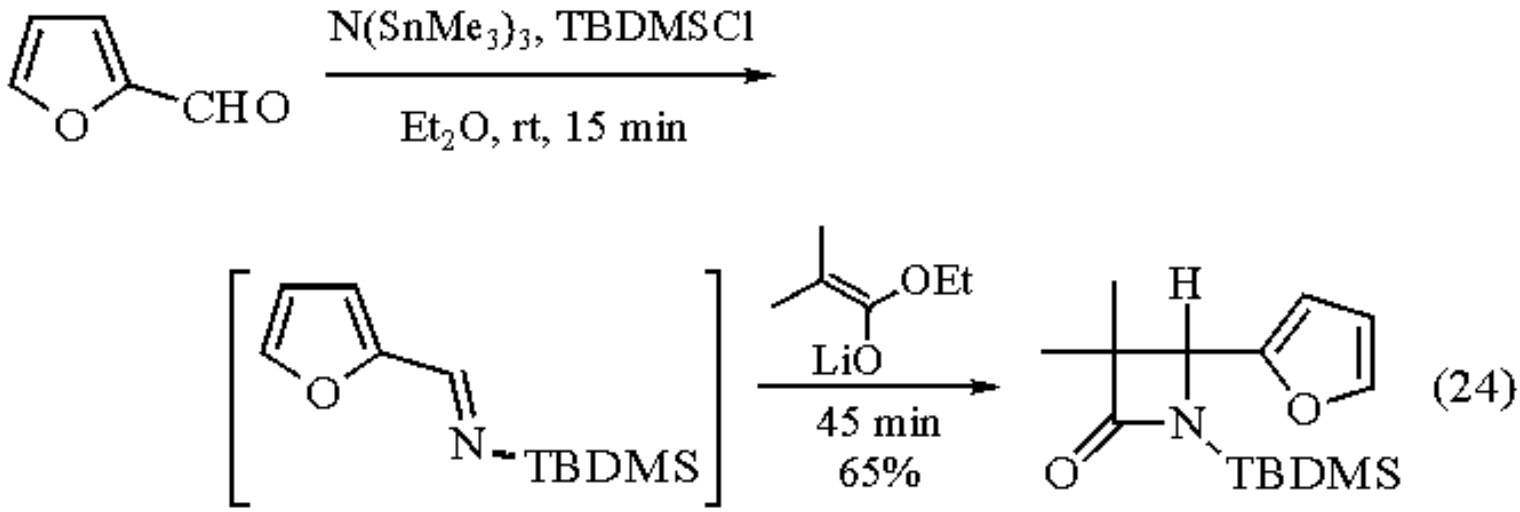

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N´-t-Butyl-*N,N*-dimethylformamidine[1]

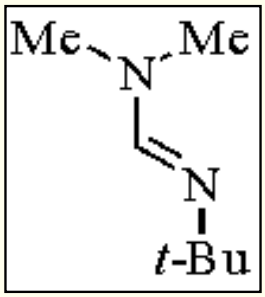

[3717-82-6] · $C_7H_{16}N_2$ · *N´-t*-Butyl-*N,N*-dimethylformamidine · (MW 128.22)

(lithiation of the title reagent generates an aminomethyl carbanion equivalent which reacts with electrophiles to give, after hydrolysis, homologated *N*-methylamines; exchange with a secondary amine allows for its subsequent lithiation and alkylation)

Physical Data: bp 133-134 °C.

Preparative Method: condensation of ***t-Butylamine*** with either *N,N*-dimethylformimidate salts or with dimethylformamide dimethyl acetal cleanly affords *N´-t*-butyl-*N,N*-dimethylformamidine (eq 1).[1,2a,b]

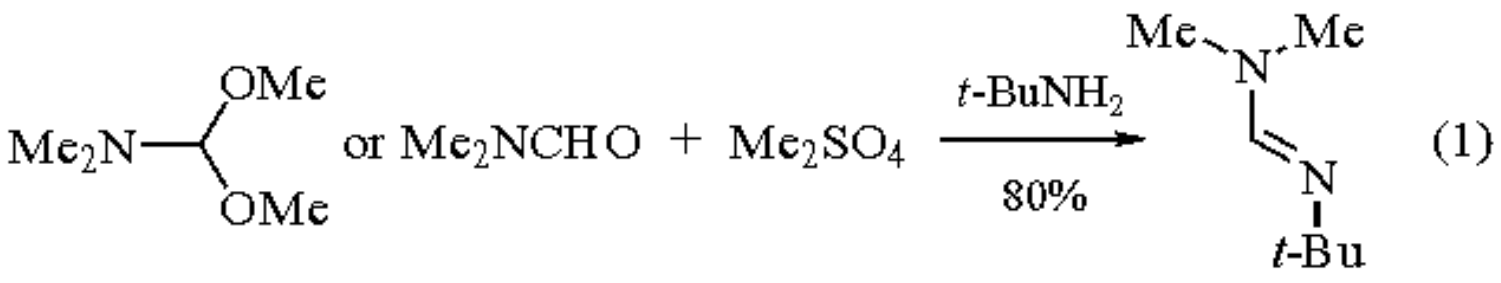

Handling, Storage, and Precautions: store under an inert atmosphere.

Synthetic Utility.

Deprotonation of *N´-t*-butyl-*N,N*-dimethylformamidine produces a dipole-stabilized carbanion.[1,2c] Treatment of this species with electrophiles followed by hydrolysis of the formamidine affords the corresponding α-substituted amine (eq 2).[2a,d]

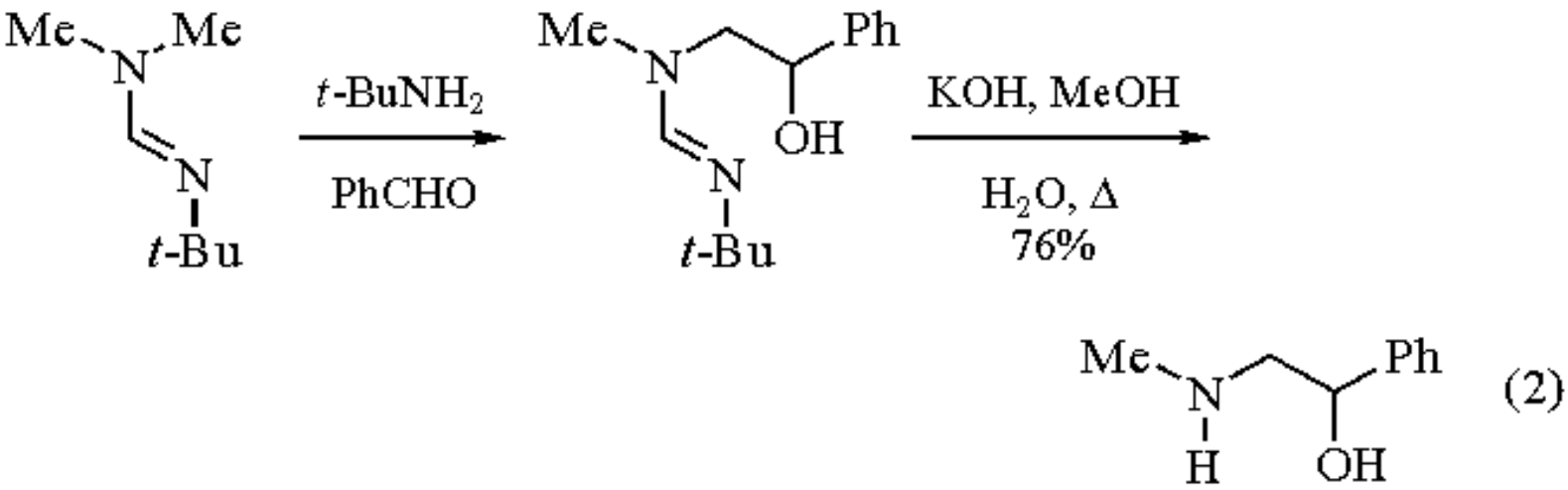

The related *N´-n*-butyl- and *N´*-cyclohexylformamidines (**1**) and (**2**) are also effective in the above procedure.[2a,3]

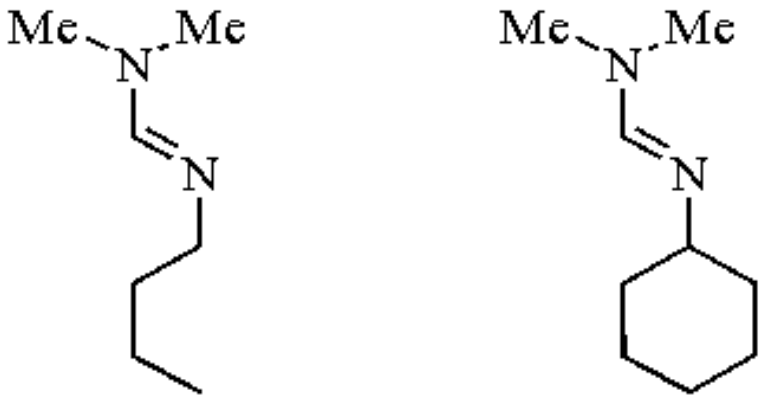

(1) **(2)**

When the title formamidine (or the *n*-butyl or cyclohexyl analog) is heated in the presence of a secondary amine, dimethylamine is displaced producing a new formamidine derivative of the secondary amine. Deprotonation and alkylation followed by formamidine hydrolysis allows entry into a host of 1-substituted amines.[1] For example, a variety of 1-substituted tetrahydroisoquinolines (eq 3) can be prepared by this method.

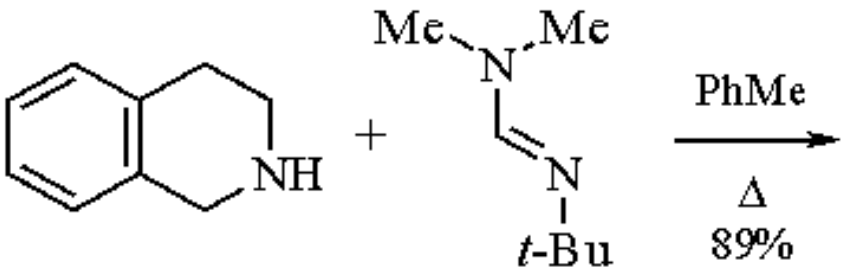

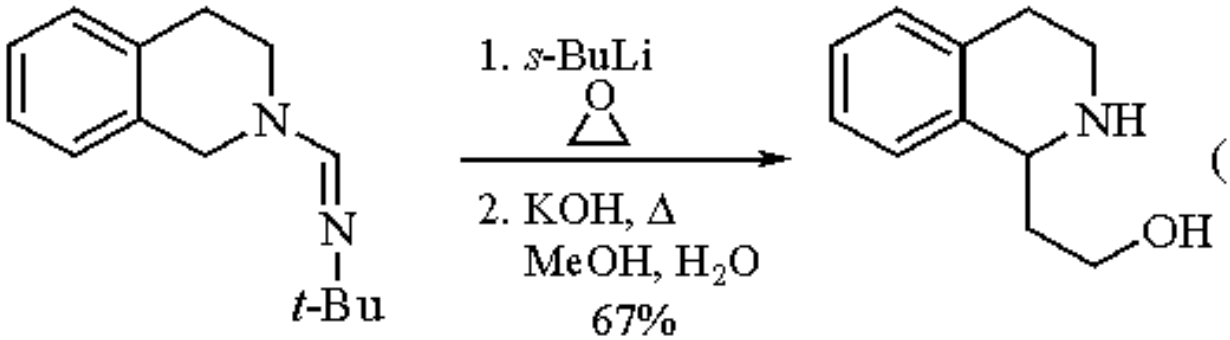

(3)

In addition to the exchange method with the title reagent, the *t*-butylformamidines of secondary amines can be prepared by aminolysis of *O*-ethyl formimidate salts (eq 4).[4]

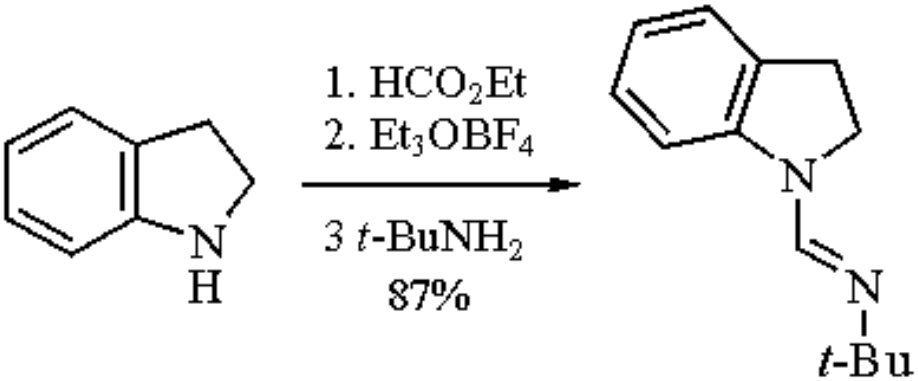

(4)

This route has been used to alkylate indolines (eq 5),[4a] tetrahydroquinolines,[4a] dihydroisoindoles,[4b] and *N*-methylanilines.[4a]

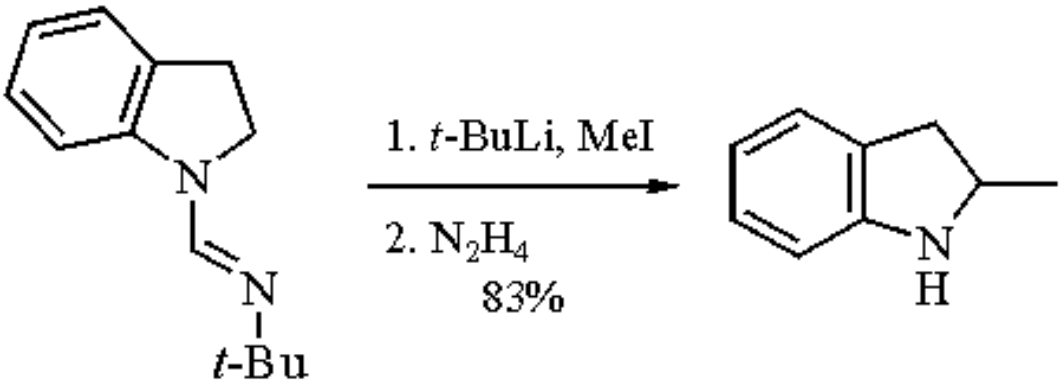

(5)

Exchange of the title reagent with tetrahydro-β-carbolines followed by lithiation and alkylation gives access to a variety of indole alkaloids.[5] Piperidines,[2b,6,7] pyrrolidines,[2b,7] perhydroazepines (eq 6)[2b] and *cis*- and *trans*-decahydroquinolines,[8] as well as others,[7f] can also be alkylated via their formamidine derivatives.

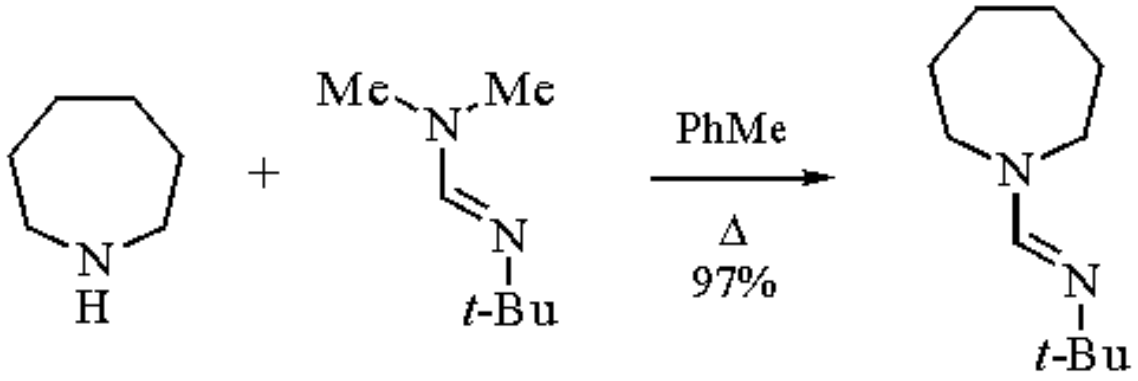

(6)

α-Arylpyrrolidines and -piperidines can be accessed by bridging dialkylations of *N*-benzyl-*N*-methylamines with 1,3- or 1,4-dihalides.[9] Other amine heterocycles, such as thiazolidine and 1,3-thiazine, may be alkylated at the carbon between the nitrogen and sulfur.[2b]

Unsaturated cyclic formamidines can be prepared by the sequence of formamidine exchange, metalation, selenation, and selenoxide elimination (eq 7).[10]

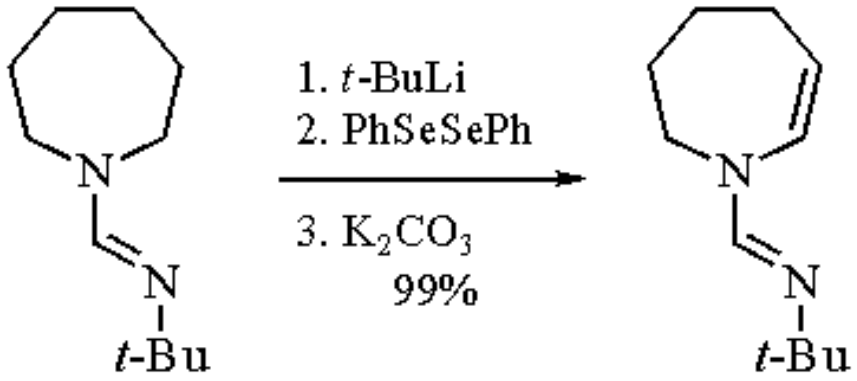

(7)

These unsaturated formamidines can be alkylated by the formamidine methodology. Metalation causes deprotonation of the alkenic proton adjacent to the ring nitrogen (eq 8).[10]

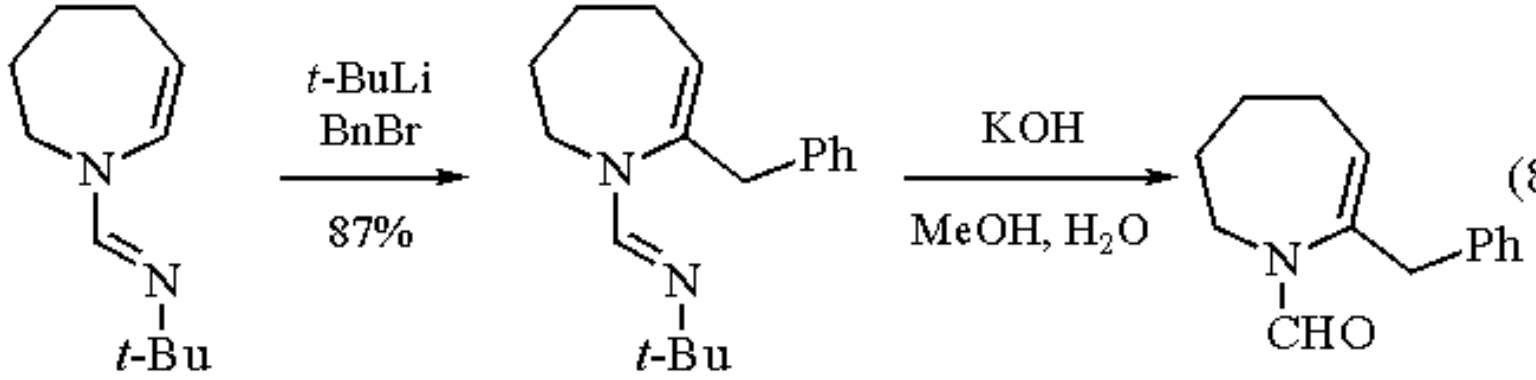

(8)

Nucleophilic additions adjacent to nitrogen have also been effected by using α´-methoxyformamidines. In this case the methoxyformamidines were not prepared from the title reagent and the formamidine is serving as a protecting and stabilizing group for the α-amino ether (eq 9).[11]

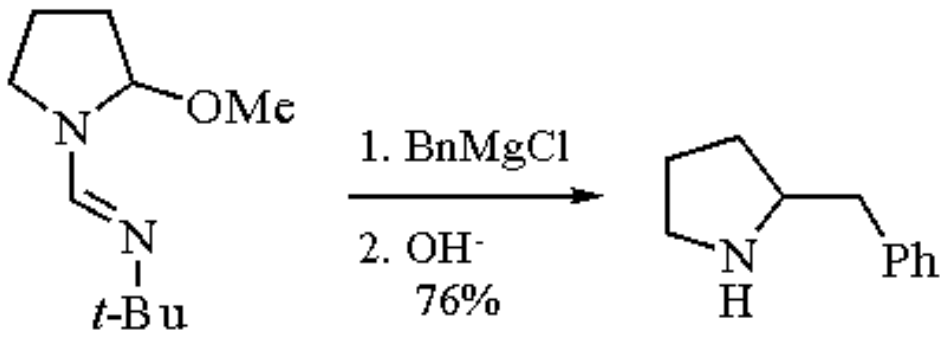

(9)

Various achiral formamidines that contain a chelating group have also been successfully utilized.[12] Thus by incorporation of a methoxy group on the formamidine, spiroisoquinolines (eq 10)[12a] and fused annulated isoquinolines can be prepared efficiently using the above methodology.

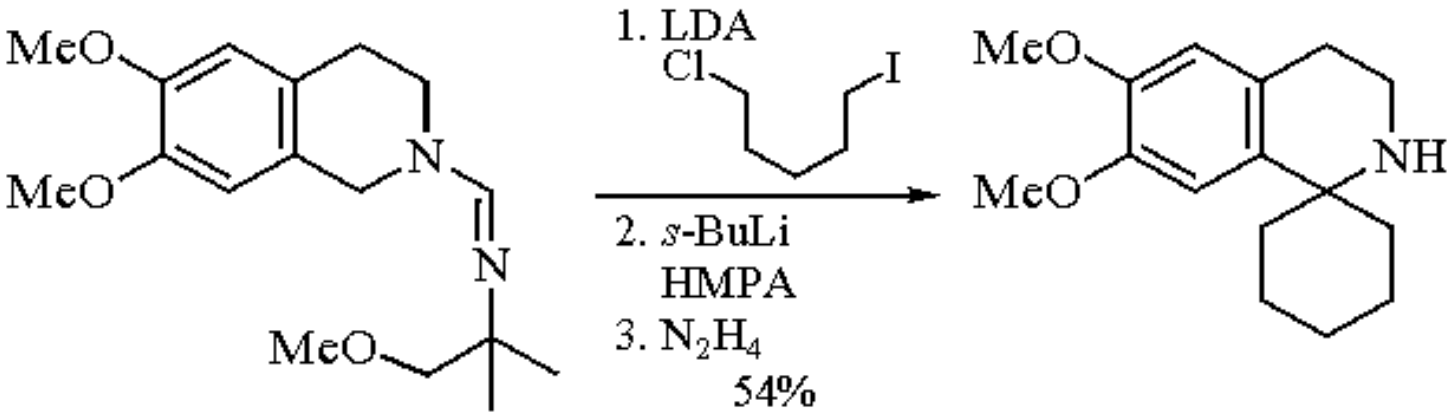

(10)

Conversion of the title reagent to ***N´-t-Butyl-N-methyl-N-trimethylsilylmethylformamidine*** (eq 11) allows for the one-carbon homologation of carbonyl compounds to nitriles, amines, aldehydes, and ketones.[13]

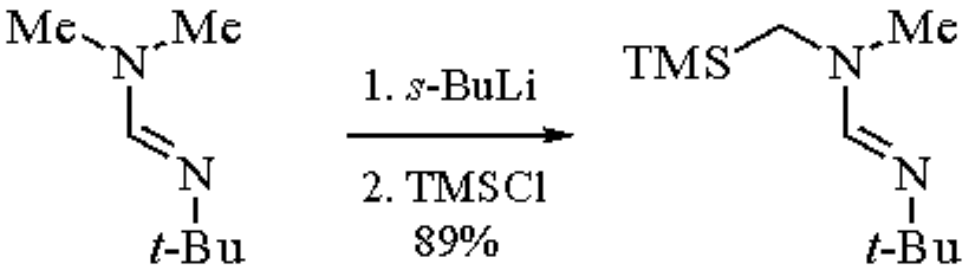

(11)

Formamidines form higher order cyanocuprates which add in a 1,4 fashion to Michael acceptors.[14] Incorporation of a chiral auxiliary in the formamidine results in high levels of asymmetric induction (see the chiral enantiopure ***(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine***).[1,15]

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t-Butyldimethylsilyl Cyanide

***t*-BuMe$_2$SiCN**

[56522-24-8] · $C_7H_{15}NSi$ · *t*-Butyldimethylsilyl Cyanide · (MW 141.29)

(preparation of stable silylated cyanohydrins;[1] silylating agent;[2] synthesis of isocyanides via oxirane ring opening[3])

Alternate Names: t-butylcyanodimethylsilane; TBDMSCN.

Physical Data: bp 163-167 °C/760 mmHg; mp 76-78 °C.

Solubility: sol organic solvents (methylene chloride, THF, chloroform); reacts rapidly with water and protic solvents.

Preparative Methods: conveniently prepared by refluxing ***t-Butyldimethylchlorosilane*** (1 equiv), ***Potassium Cyanide*** (1.3 equiv) and ***18-Crown-6*** (0.31 equiv) in dry methylene chloride under nitrogen.[4] The reagent can also be prepared by the reaction of ***Silver(I) Cyanide*** with *t*-butyldimethylchlorosilane,[2] or stirring at 60 °C for 4 h a mixture of sodium cyanide, Amberlite XAD-4 resin, and *t*-butyldimethylchlorosilane in acetonitrile.[5]

Handling, Storage, and Precautions: must be protected from moisture and handled in a well-ventilated fume hood. Exposure to water releases highly toxic HCN gas.

Cyanosilylation.

The Lewis acid-catalyzed reaction of *t*-butyldimethylsilyl cyanide (TBDMSCN) with aldehydes and ketones affords the corresponding silylated cyanohydrins in good yield (eq 1).[1,6,7] These have a greater stability than the silylated cyanohydrins obtained by using ***Cyanotrimethylsilane***. The addition of TBDMSCN to sterically hindered ketones proceeds smoothly in the presence of a catalytic amount of ***Zinc Iodide*** or potassium cyanide/18-crown-6 (eqs 2-4).[8] A chelation-controlled stereoselective synthesis of silylated cyanohydrins has also been reported (eq 5).[9]

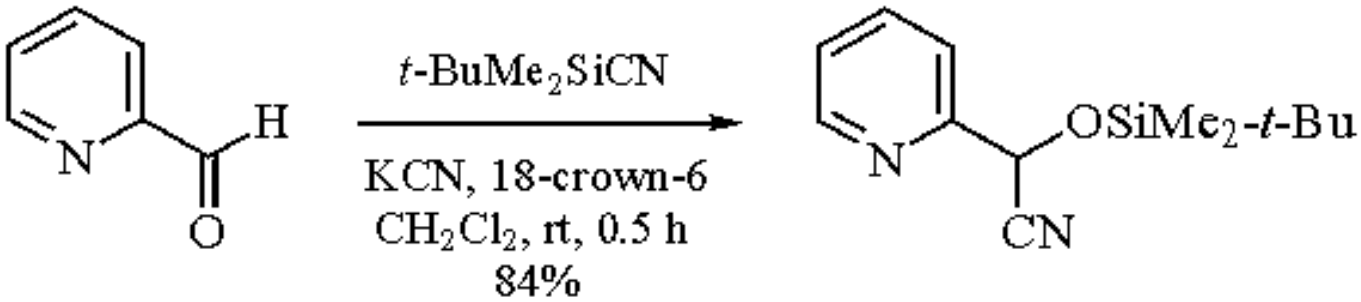

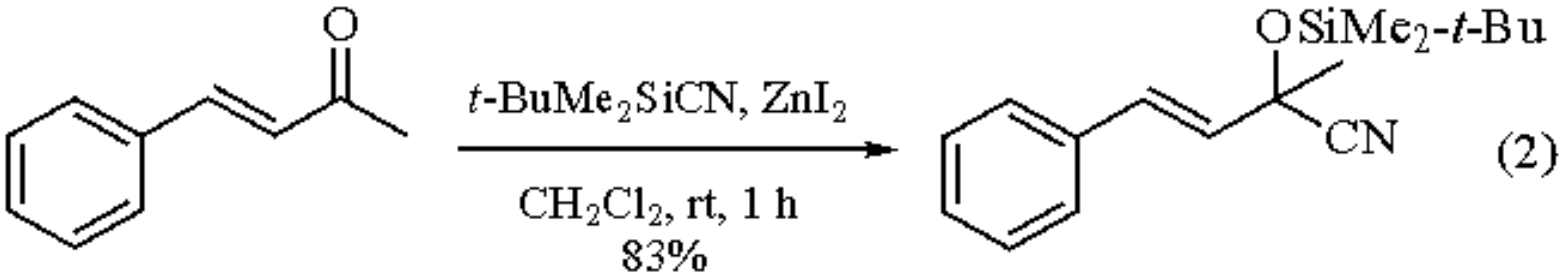

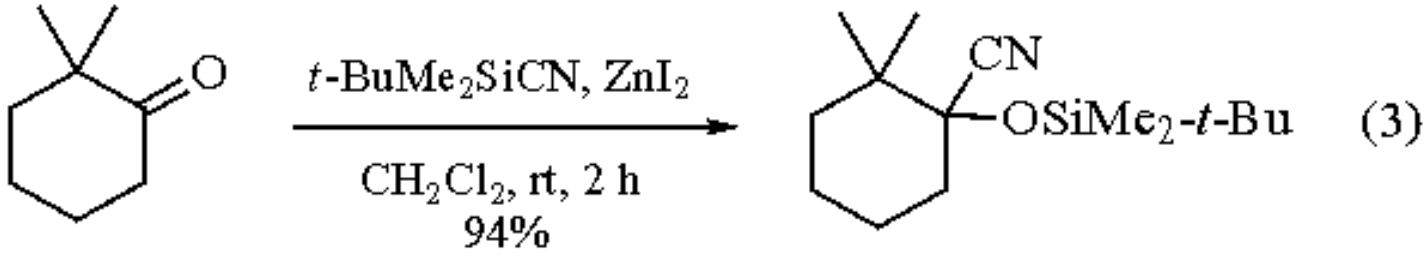

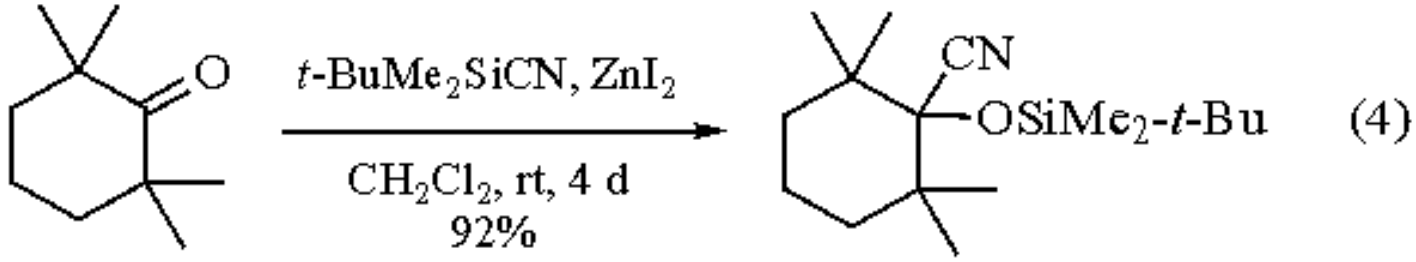

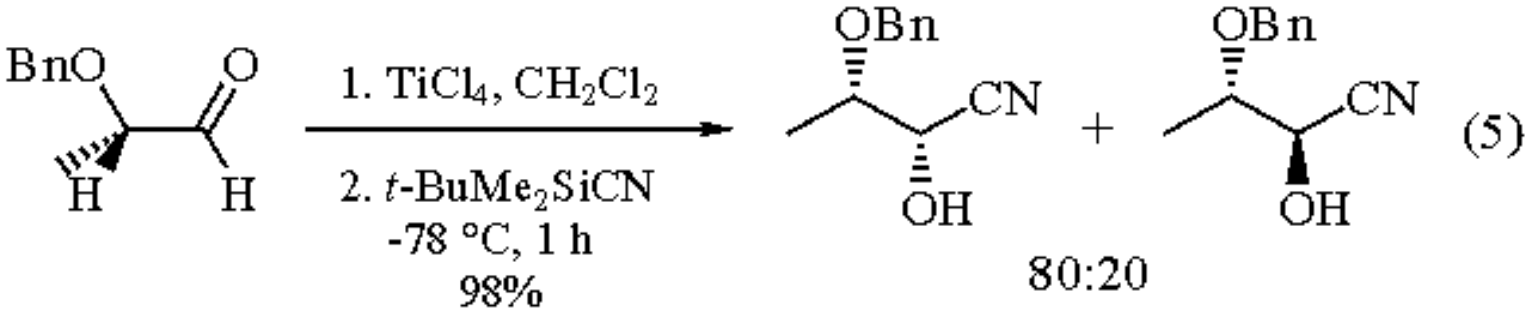

Silylation.

TBDMSCN silylates alcohols, phenols, and carboxylic acids efficiently and in high yield.[2]

Oxirane Ring Opening.

Oxiranes undergo ring opening when refluxed with TBDMSCN/zinc iodide in methylene chloride, yielding isocyanides (eq 6).[3] The rate of the oxirane ring opening is slower than the corresponding reactions with trimethylsilyl cyanide/zinc iodide.[10]

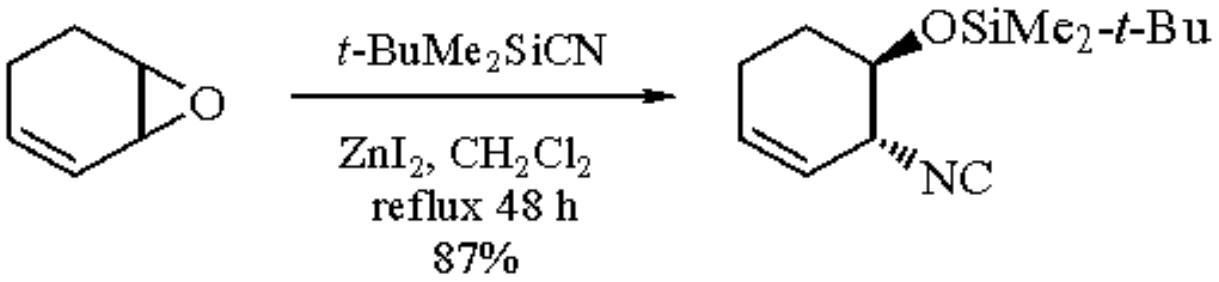

(6)

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1. LaMattina, J. L.; Mularski, C. J. *JOC* **1986**, *51*, 413.
2. Mai, K.; Patil, G. *JOC* **1986**, *51*, 3545.
3. Gassman, P. G.; Haberman, L. M. *JOC* **1986**, *51*, 5010.
4. Hwu, J. R.; Lazar, J. G.; Corless, P. F. *S* **1984**, 1020.
5. Sukata, K. *BCJ* **1987**, *60*, 2257.
6. Baker, C. B.; Putt, S. R.; Showalter, H. D. H. *JHC* **1983**, *20*, 629.
7. Corey, E. J.; Crouse, D. N.; Anderson, J. E. *JOC* **1975**, *40*, 2140.
8. Golinski, M.; Brock, C. P.; Watt, D. S. *JOC* **1993**, *58*, 159.
9. Reetz, M. T.; Kesseler, K.; Jung, A. *AG(E)* **1985**, *24*, 989.
10. Gassman, P. G.; Guggenheim, T. L. *JACS* **1982**, *104*, 5849.

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t-Butyldimethylsilyl Ethylnitronate

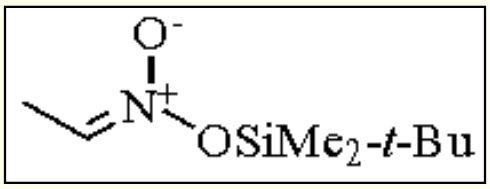

[77242-15-0] · $C_8H_{19}NO_2Si$ · *t*-Butyldimethylsilyl Ethylnitronate · (MW 189.33)

(reagent for diastereoselective nitro-aldol condensations;[1] dipole in thioaldehyde [2 + 3] cycloadditions;[2] oxygen source for thioketone to ketone conversion;[3] oxidative coupling with silyl enol ethers[4])

Physical Data: bp 30 °C/0.05 mmHg.[1b]

Solubility: sol THF.

Form Supplied in: colorless oil. *Drying:* similar trimethylsilyl derivatives are water sensitive.[5]

Preparative Method: must be synthesized from ***Nitroethane***.[5]

Handling, Storage, and Precautions: this reagent is presumed to be moisture sensitive; the hydrolysis product is nitroethane. All nitro compounds should be treated with caution. Use in a fume hood.

Nitro-Aldol Condensation.

Nitro-aldol condensations of *t*-butyldimethylsilyl ethylnitronate (**1**) with aldehydes give the *erythro* isomer almost exclusively (eq 1).[1] The silylnitronate must be distilled, the ***Tetra-n-butylammonium Fluoride*** (TBAF) must be freshly dried over molecular sieves, and the reaction time must not be too long or else the diastereoselectivity may be compromised.[1b] The nitroaldol (**2**) may also be obtained by deprotonation/reprotonation of a mixture of (**2**) and its diastereomer, but -100 °C is required to achieve high diastereoselectivity in this reaction. For the nitro-aldol reaction the *t*-butyldimethylsilyl nitronates are less labile and more selective than the trimethylsilyl derivatives.

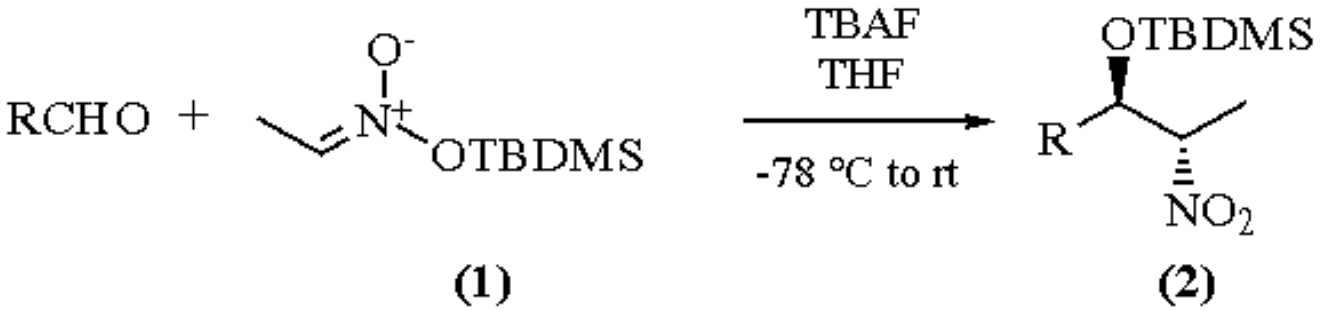

(1)

1,3-Dipole in [3 + 2] Cycloadditions.

t-Butyldimethylsilyl ethylnitronate has been used as a highly reactive dipole to trap thiopivaldehyde (**4**) (R = *t*-Bu)[2a,b] and other reactive thioaldehydes (**4**) (eq 2),[2c] which are generated by photolysis of phenacyl sulfides (**3**), to give heterocycles (**5**) (Table 1). Use of this reagent to titrate thioaldehyde solutions has also been demonstrated.[2d]

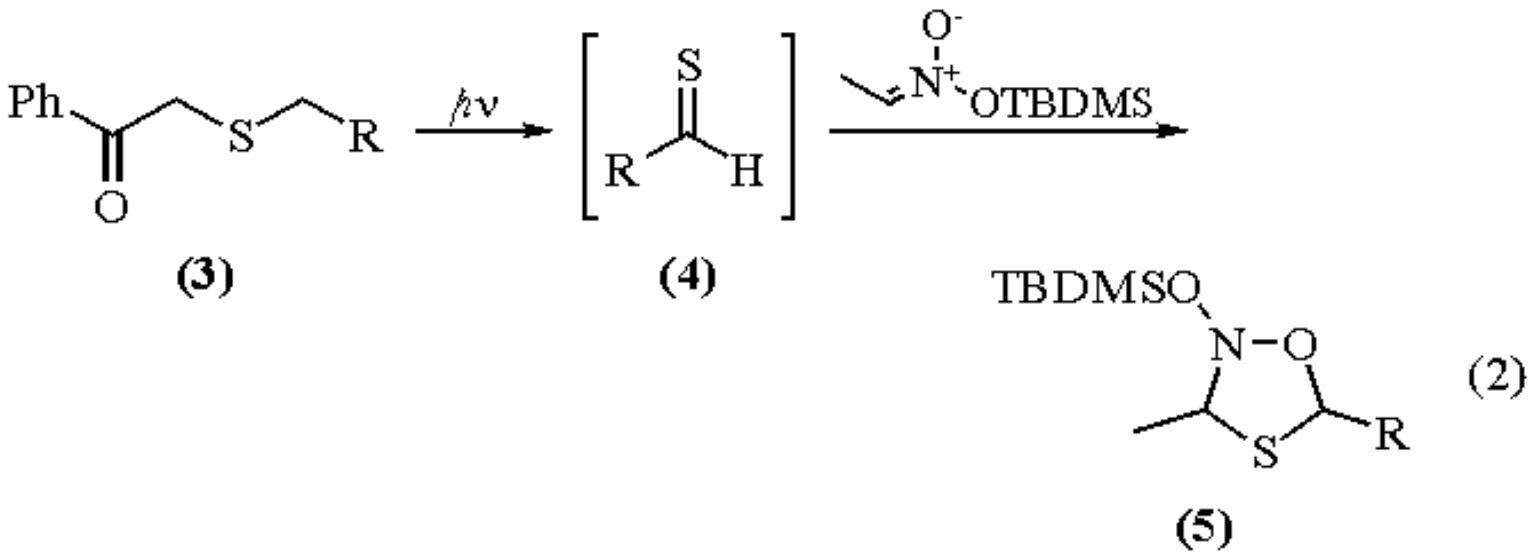

Table 1 Ethylnitronate plus Thioaldehyde [3 + 2] Cycloadditions (eq 2)

R	Yield of (**5**) (%)	Diastereomeric mixture
t-Bu	93	No
H	73	No
$CH{=}CH_2$	92	Yes
CH_2CH_2Ph	91	Yes

Other more complex phenacyl sulfides have been photolytically cleaved to thioaldehydes and trapped with (**1**),[2e] culminating with its use as a dipole in the total synthesis of (±)-methynolide (eq 3).[3] A thiocarbonyl to carbonyl conversion is the end result of the transformation using this reagent.

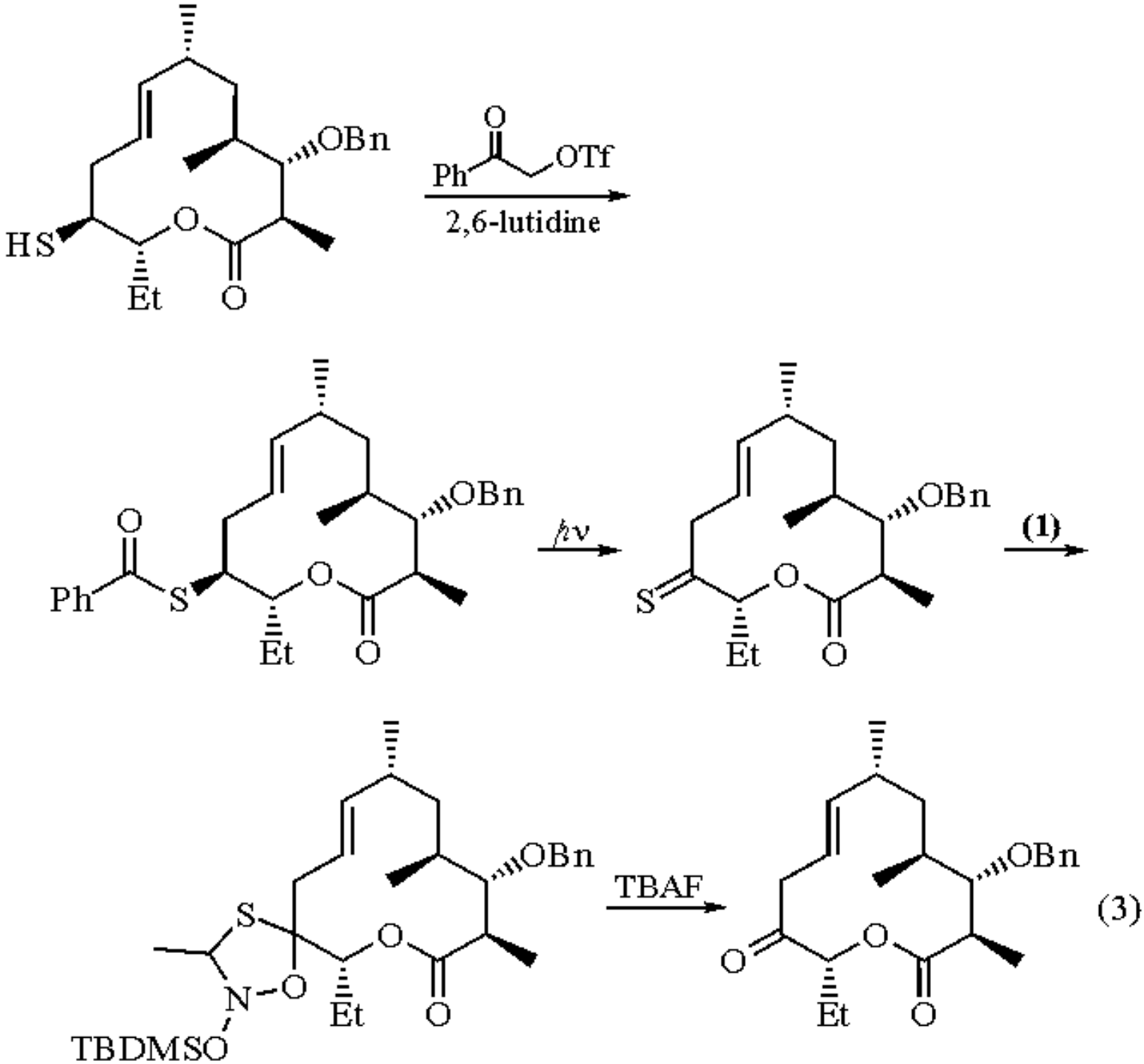

Oxidative Coupling.

Oxidative coupling of *t*-butyldimethylsilyl ethylnitronate with a silyl enol ether in DMF using manganese(III) pyridinecarboxylate [$Mn(pic)_3$] as the reducing agent gives an enone after elimination of nitrous acid (eq 4).[4]

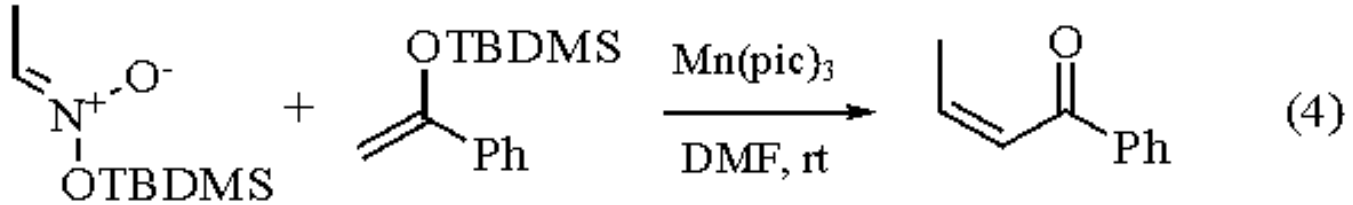

Related Reagents.

Nitromethane.

---

1. (a) Seebach, D.; Beck, A. K.; Lehr, F.; Weller, T.; Colvin, E. *AG(E)* **1981**, *20*, 397. (b) Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *HCA* **1982**, *65*, 1101.
2. (a) Vedejs, E.; Perry, D. A. *JACS* **1983**, *105*, 1683. (b) Vedejs, E.; Wilde, R. G. *JOC* **1986**, *51*, 117. (c) Vedejs, E.; Perry, D. A.; Houk, K. N.; Rondan, N. G. *JACS* **1983**, *105*, 6999. (d) Vedejs, E.; Perry, D. A.; Wilde, R. G. *JACS* **1986**, *108*, 2985. (e) Vedejs, E.; Perry, D. A. *JOC* **1984**, *49*, 573.
3. Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *JACS* **1989**, *111*, 8430.
4. Narasaka, K.; Iwakura, K.; Okauchi, T. *CL* **1991**, 423.
5. Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Kai, Y.; Dunitz, J. D. *HCA* **1980**, *63*, 697.

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t-Butyldimethylsilyl Hydroperoxide-Mercury(II) Trifluoroacetate

t-$BuMe_2SiOOH + Hg(CF_3CO_2)_2$

(t-$BuMe_2SiOOH$)

[78957-19-4] · $C_6H_{16}O_2Si$ · *t*-Butyldimethylsilyl Hydroperoxide-Mercury(II) Trifluoroacetate · (MW 148.28) ($Hg(CF_3CO_2)_2$)

[13257-51-7] · $C_4F_6HgO_4$ · *t*-Butyldimethylsilyl Hydroperoxide-Mercury(II) Trifluoroacetate · (MW 426.62)

(peroxymercuration of alkenes[1])

Physical Data: $(CF_3CO_2)_2Hg$: mp 171-173 °C; t-$BuMe_2SiOOH$: mp -8 °C, bp 20-35 °C.

Solubility: $(CF_3CO_2)_2Hg$: sol THF, DME, dioxane; insol hexane; t-$BuMe_2SiOOH$: sol most common organic solvents.

Form Supplied in: $(CF_3CO_2)_2Hg$: white, hygroscopic crystals; t-$BuMe_2SiOOH$: colorless liquid. Widely available.

Handling, Storage, and Precautions: acute poison. $(CF_3CO_2)_2Hg$ is easily absorbed through the skin and is corrosive. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light. *t*-Butyldimethylsilyl hydroperoxide is a strong oxidant, and reacts readily with traces of metals.

The title hydroperoxide, in combination with $(CF_3CO_2)_2Hg$, effects peroxymercuration of alkenes. The corresponding intermediate is then reduced with ***Sodium Borohydride*** to furnish an epoxide (eq 1).[1] In contrast to the OH-directed epoxidation of allylic alcohols, this method appears to provide an avenue to the epoxy alcohols of opposite relative configuration (2-cyclopenten-1-ol and 2-cyclohexen-1-ol have been employed to demonstrate this stereoselectivity).[1]

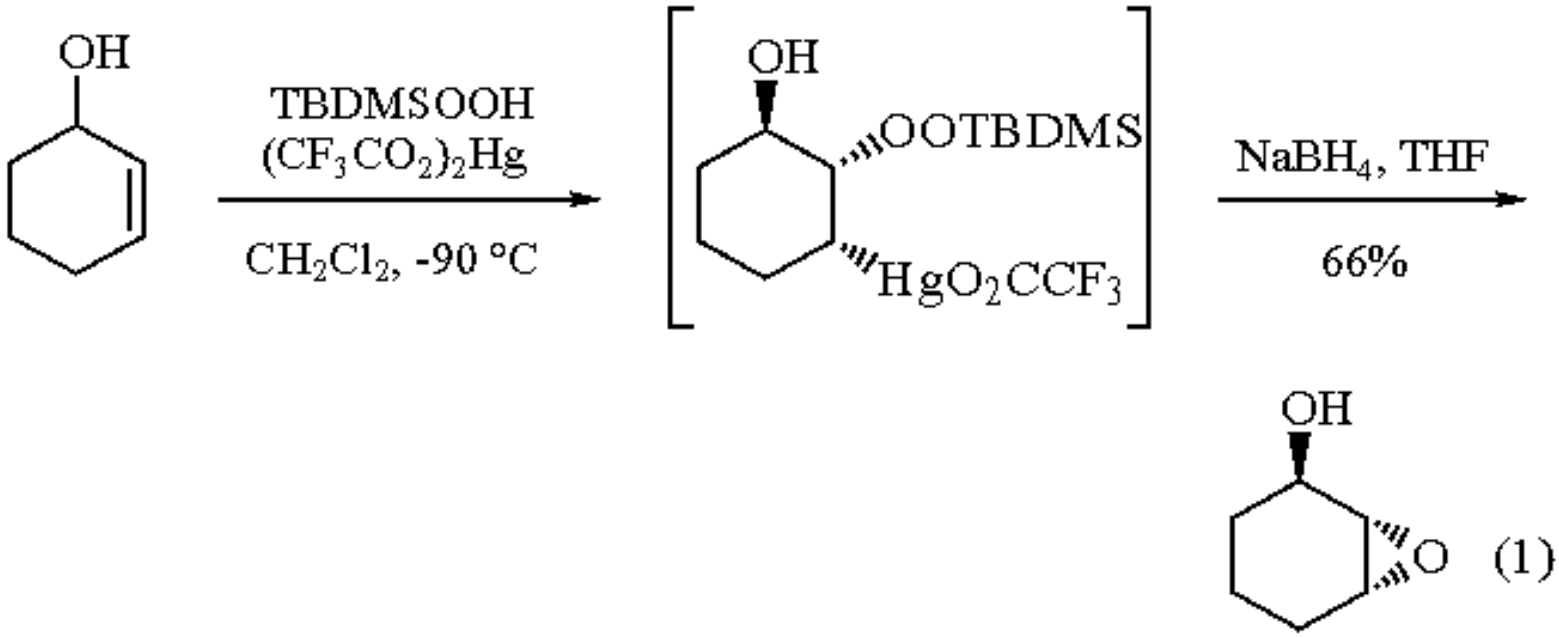

Similarly, a mixture of *t*-$BuMe_2SiOOH$ and $(AcO)_2Hg$ has been reported to promote ring opening of cyclopropanes, giving the corresponding mercurated peroxides.[2]

Related Reagents.

Mercury(II) Acetate; ***Mercury(II) Trifluoroacetate***.

---

1. Corey, E. J.; Schmidt, G.; Shimoji, K. *TL* **1983**, *24*, 3169.
2. Bloodworth, A. J.; Chan, K. H.; Cooksey, C. J.; Hargreaves, N. *JCS(P1)* **1991**, 1923.

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O-(*t*-Butyldimethylsilyl)hydroxylamine

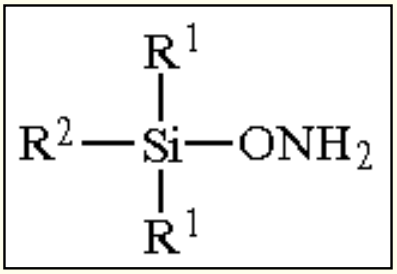

(**1**; R^1 = Me, R^2 = *t*-Bu)

[41879-39-4] · $C_6H_{17}NOSi$ · *O*-(*t*-Butyldimethylsilyl)hydroxylamine · (MW 147.29) (**2**; R^1 = R^2 = Me)

[22737-36-6] · $C_3H_{11}NOSi$ · *O*-(Trimethylsilyl)hydroxylamine · (MW 105.21) (**3**; R^1 = Ph, R^2 = *t*-Bu)

[103587-51-5] · $C_{16}H_{21}NOSi$ · *O*-(*t*-Butyldiphenylsilyl)hydroxylamine · (MW 271.43)

(preparation of *O*-silyloximes;[1] generation of nitrosoalkenes;[1,2] generation of azadienes[3])

Physical Data: (**1**) mp 62-65 °C; bp 87-90 °C/40 mmHg. (**2**) bp 98-100 °C; *d* 0.860 g cm^{-3}. (**3**) mp 74-75 °C; bp 175 °C/0.6 mmHg.

Solubility: freely sol hexane, chloroform, and most organic solvents; insol water.

Form Supplied in: colorless solid or liquid; commercially available.

Preparative Methods: the reagents are most conveniently prepared by treatment of ***Hydroxylamine*** hydrochloride with ethylenediamine in dichloromethane, followed by the appropriate chlorosilane.[4] A two-step procedure using ammonia in place of ethylenediamine has also been reported.[1]

Purification: reagents are purified via distillation and/or recrystallization (>97% GC).

Handling, Storage, and Precautions: *O*-silylhydroxylamines should be protected from moisture and handled in a fume hood.

Preparation of *O*-Silyloximes and Oximes.

O-Silylhydroxylamines are used to prepare *O*-silyloximes via treatment of carbonyl compounds with these reagents in

$CHCl_3$ in the presence of 4 Å molecular sieves.[1] Treatment of *O*-silyloximes with fluoride ion yields the desilylated oximes, thus allowing the oximation of acid- or base-sensitive ketones and aldehydes.

A series of 3-alkyl-2-chlorocyclohexanone silyloximes (methyl, ethyl, *i*-propyl) have been prepared and their conformations extensively examined.[5] By analysis of the vicinal interproton coupling, these compounds were shown to exist predominantly in the diaxial chair conformation (**5**) while the precursor ketones prefer the diequatorial conformation (**4**). This observation was corroborated by an X-ray crystal structure of *trans*-3-methyl-2-chlorocyclohexanone *t*-butyldiphenylsilyloxime, which showed that the chair with diaxial substituents is indeed preferred in the solid state. A strong hyperconjugative stabilization of the axial conformation, termed the vinylogous anomeric effect, was proposed to be the origin of this preference.

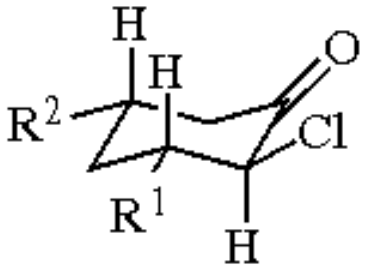

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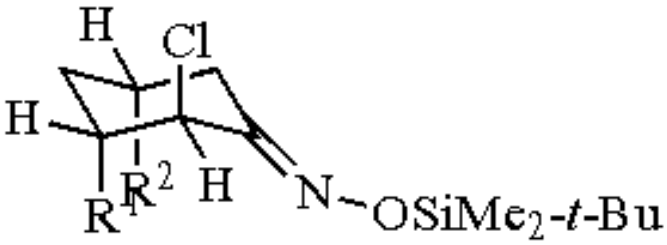

(5)

Generation of Nitrosoalkenes.

Treatment of silyloximes of α-halocarbonyl compounds with fluoride ion generates nitrosoalkenes without extraneous nucleophilic species present.[1] Nitrosoalkenes generated from (**6**) have been used in intramolecular [4 + 2] cycloadditions (eq 1).[2] Electron-rich alkenes are required for concerted cycloadditions as this is an inverse electron-demand cycloaddition. The choice of fluoride source is critical for success in that the highest yields are obtained when the nitrosoalkene is slowly generated via use of sparingly soluble metal fluorides such as ***Cesium Fluoride*** or ***Potassium Fluoride***.

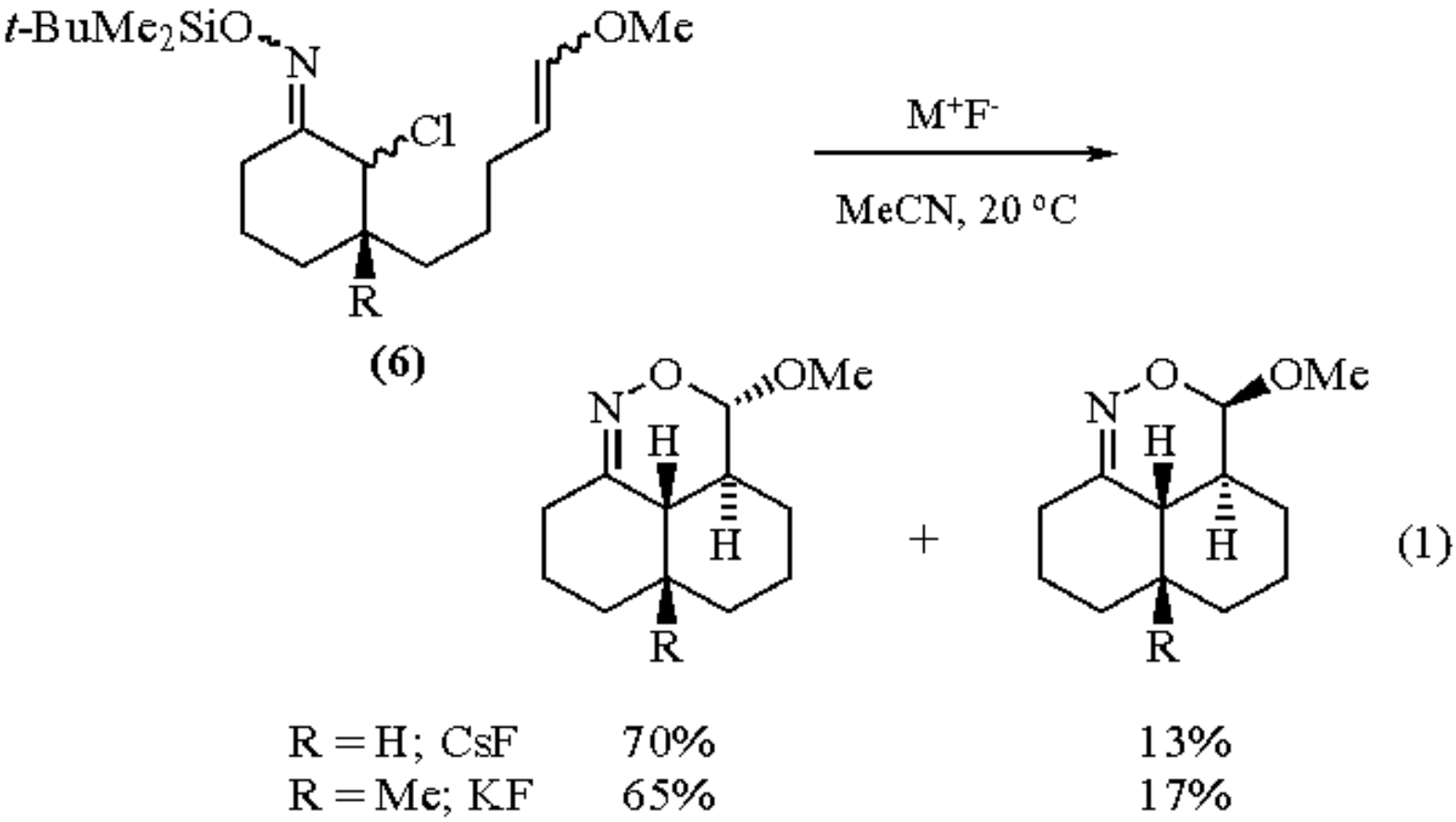

Generation of 1-Azadienes.

O-Silyloximes have also been used to generate 1-azadienes for [4 + 2] cycloadditions.[3] Thus an *O*-silyloxime of an α,β-unsaturated aldehyde can be treated with an acid chloride or chloroformate in the presence of ***Chlorotrimethylsilane*** and ***Aluminum Chloride*** to give an α-cyanohydroxamic acid derivative, which upon mild thermolysis forms an azadiene (eq 2). These azadienes undergo efficient intermolecular [4 + 2] cycloadditions or, with an tethered alkene, intramolecular cycloadditions.

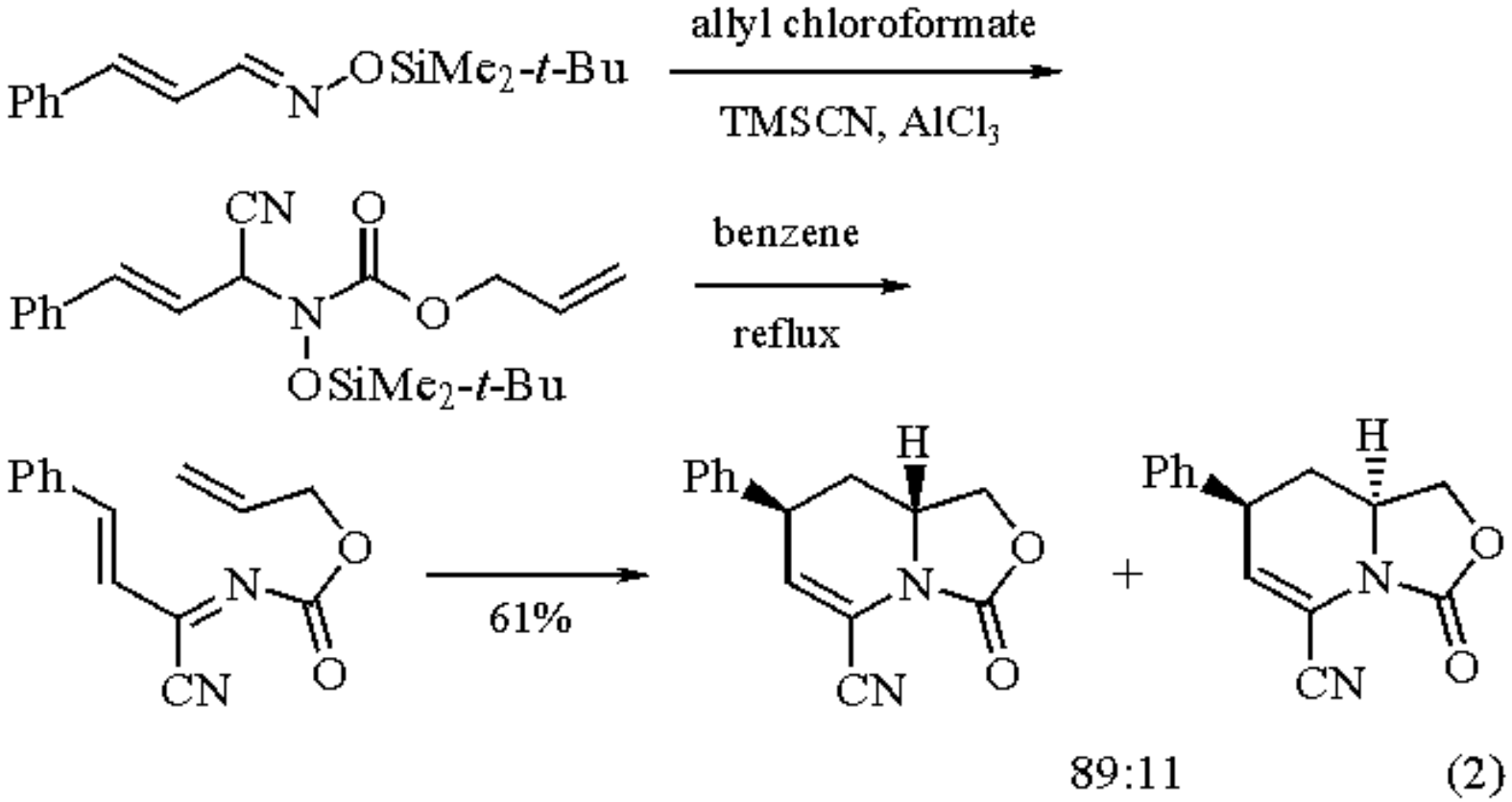

Reactions at the Hydroxylamine Nitrogen.

These reagents have been used as *O*-protected forms of hydroxylamine for synthetic transformations involving the unprotected nitrogen. Thus *O*-silylhydroxylamines have been used to prepare *N*-hydroxy-β-lactams[6] and substituted dihydro-3-hydroxy-1,2,3-benzotriazines,[7] as well as *N*-alkylated hydroxylamines for use as leukotriene biosynthesis inhibitors.[8]

Related Reagents.

O-Benzylhydroxylamine Hydrochloride; ***N,O-Bis(trimethylsilyl)hydroxylamine***; ***Hydroxylamine***; ***O-(Mesitylsulfonyl)hydroxylamine***.

---

1. Denmark, S. E.; Dappen, M. S. *JOC* **1984**, *49*, 798.
2. Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *JOC* **1984**, *49*, 4741.
3. Teng, M.; Fowler, F. W. *JOC* **1990**, *55*, 5646.
4. Bottaro, J. C.; Bedford, C. D.; Dodge, A. *SC* **1985**, *15*, 1333.
5. Denmark, S. E.; Dappen, M. S.; Sear, N. S.; Jacobs, R. T. *JACS* **1990**, *112*, 3466.
6. Zercher, C. K.; Miller, M. J. *TL* **1989**, *50*, 7009.
7. Jakobsen, M. H.; Buchardt, O.; Holm. A.; Meldal, M. *S* **1990**, 1008.
8. Stewart, A. O.; Martin, J. G. *JOC* **1989**, *54*, 1221.

Michael S. Dappen

t-Butyldimethylsilyl Iodide

***t*-BuMe$_2$SiI**

[72726-45-5] · $C_6H_{15}ISi$ · *t*-Butyldimethylsilyl Iodide · (MW 242.17)

(reagent capable of converting oxiranes into hydrolytically stable allylic silyl ethers, which can then be converted into their corresponding allylic alcohols without rearrangement[1-3])

Alternate Name: TBDMSI.

Physical Data: mp 53-60 °C dec.[2]

Solubility: sol most organic solvents.

Handling, Storage, and Precautions: should be used as prepared.

t-Butyldimethylsilyl iodide (TBDMSI) is typically generated in situ by the treatment of (phenylseleno)-*t*-butyldimethylsilane with 0.5 equiv of ***Iodine*** in acetonitrile.[1,2] It is then used as prepared owing to the instability of the pure form.[1]

A wide variety of hydrolytically stable allylic silyl ethers can be easily prepared from oxiranes using this reagent. Oxiranes react with TBDMSI in acetonitrile at 0 °C to form silylated halohydrins. These were then isolated and reacted with ***1,5-Diazabicyclo[4.3.0]non-5-ene*** (DBN) in refluxing THF to afford the desired allylic silyl ethers.[1,2] The net change in this sequence is the conversion of oxiranes into allylic alcohols (eqs 1-4).

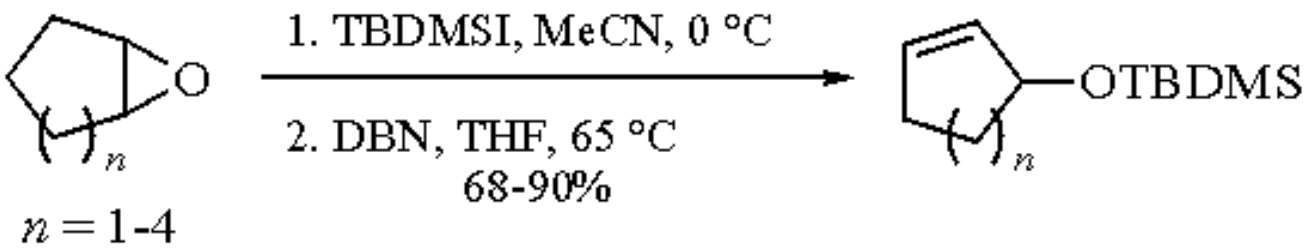

(1)

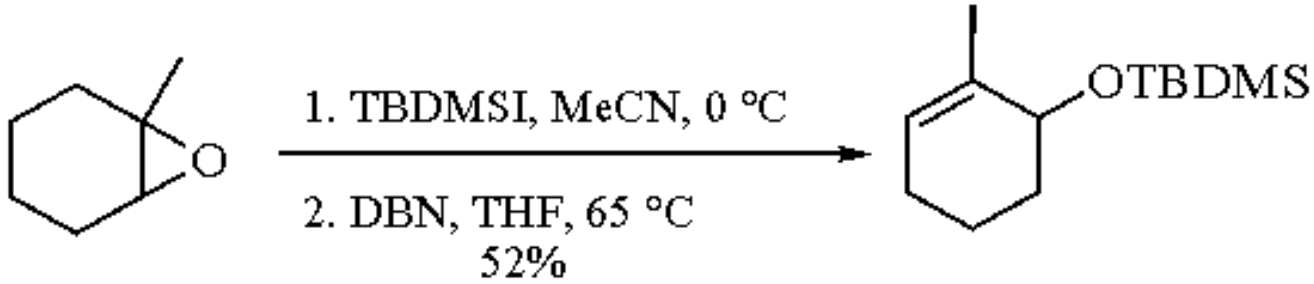

(2)

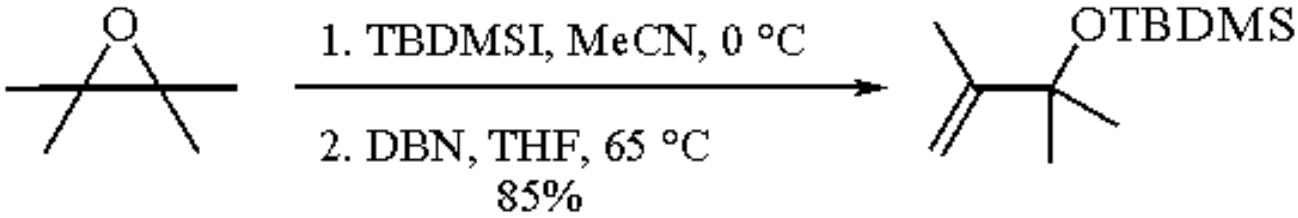

(3)

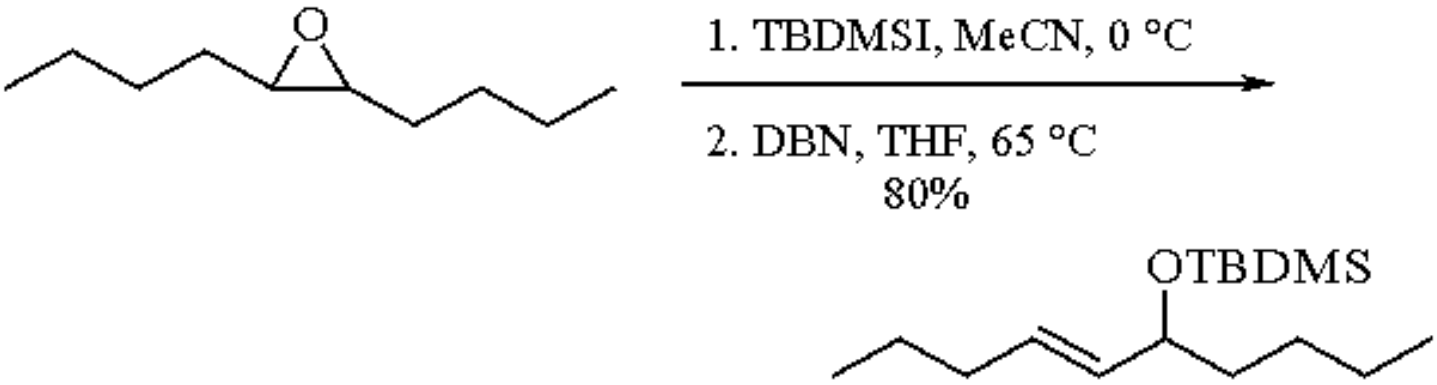

(4)

The protecting group can be removed by treatment of the allylic silyl ethers with ***Tetra-n-butylammonium Fluoride*** in moist DMSO or THF. Desilylation may also be accomplished by the use of ***Potassium Fluoride*** in the presence of a catalytic amount of ***18-Crown-6***.[1,2]

Related Reagents.

Iodotrimethylsilane.

---

1. Detty, M. R. *JOC* **1980**, *45*, 924.
2. Detty, M. R.; Seidler, M. D. *JOC* **1981**, *46*, 1283.
3. Detty, M. R.; Seidler, M. D. *TL* **1982**, *25*, 2543.

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N-(*t*-Butyldimethylsilyl)-*N*-methyltrifluoroacetamide[1]

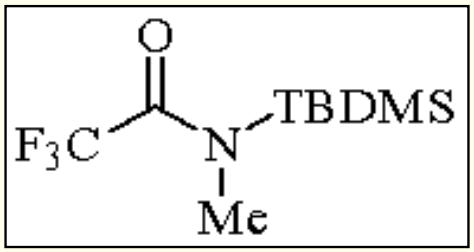

[77377-52-7] · $C_9H_{18}F_3NOSi$ · *N*-(*t*-Butyldimethylsilyl)-*N*-methyltrifluoroacetamide · (MW 241.33)

(excellent *t*-butyldimethylsilylating reagent for alcohols, amines, carboxylates, thiols, and inorganic oxyanions;[1,2] is often used to protect hydroxy and amino groups;[1] derivatizing reagents for GC-MS analysis[3])

Alternate Name: BSMTFA.

Physical Data: bp 168-170 °C; *d* 1.12 g cm^{-3}.[1]

Solubility: sol most aprotic organic solvents.[1]

Form Supplied in: colorless liquid;[1] neat or with 1% *t*-butyldimethylsilyl chloride commercially available.[4,5]

Preparative Method: obtained in 91% yield by reaction of *N*-methyl-2,2,2-trifluoroacetamide (1.0 equiv) in benzene and acetonitrile (1:1 v/v) with NaH (1.0 equiv) and then with *t*-$BuMe_2SiCl$ (1.2 equiv) at 4 °C.[1]

Handling, Storage, and Precautions: moisture-sensitive; is easily transferable with a gas-tight syringe.[1]

t-Butyldimethylsilylation of Functional Groups.[1]

In the presence of 1% of ***t-Butyldimethylchlorosilane*** as the catalyst, *N*-(*t*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide (BSMTFA) functions as an extremely reactive *t*-butyldimethylsilylating reagent for alcohols, amines, carboxylic acids, and thiols. Silylation is generally completed within 5 min at 25 °C in acetonitrile.[1] This amide is more reactive than *N*-(*t*-butyldimethylsilyl)-*N*-methylacetamide.

In the protection of a hydroxy group, the resultant *t*-butyldimethylsilyl (TBDMS) ethers are stable under the conditions for acetate saponification and hydrogenation.[1] These silyl ethers also remain intact towards the Jones reagent and

Wittig reagents. The TBDMS ethers are approx. 10^4 times more stable against hydrolysis than the corresponding trimethylsilyl (TMS) ethers.[6] Selective removal of the TBDMS group can be accomplished by use of dilute acetic acid or ***Tetra-n-butylammonium Fluoride*** in THF at 25 °C.

Silylation of ketones by use of BSMTFA occurs in ***Triethylamine*** and DMF at 40-60 °C to give the corresponding silyl enol ethers in good to excellent yields (eq 1).[7,8] In addition, silyl ether formation takes place in ***N-Hydroxysuccinimide*** (88% yield) and *N*-hydroxypyrrole (99% yield) by use of BSMTFA in THF.[9]

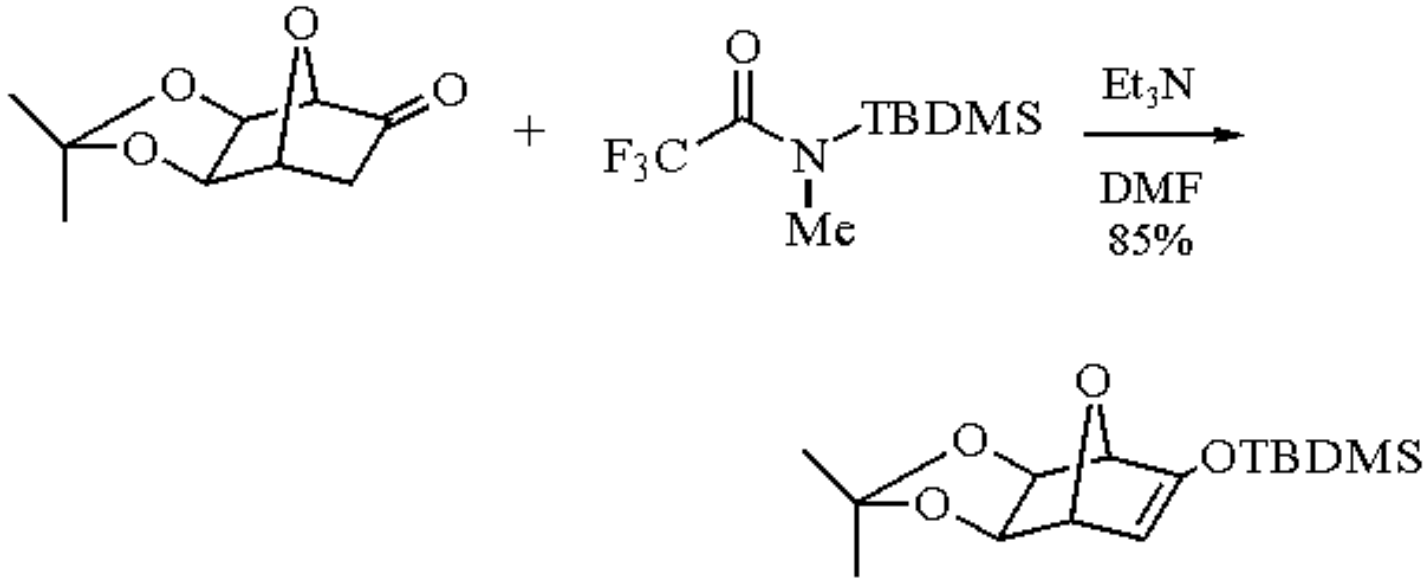

(1)

TBDMS amines are approx. 100 times more stable than the labile TMS ethers towards solvolysis.[1] Reaction of dibenzyl aspartate with BSMTFA in acetonitrile and then with *t*-BuMgCl in ether affords an *N*-silylated β-lactam in 75% yield (eq 2).[10] On the other hand, *N*-silylation of the sulfoximine PhMeS(=O)=NH proceeds in 92% yield with BSMTFA at 90 °C.[11] The oxime and amide functionalities can also be silylated with BSMTFA (eq 3).[12,13]

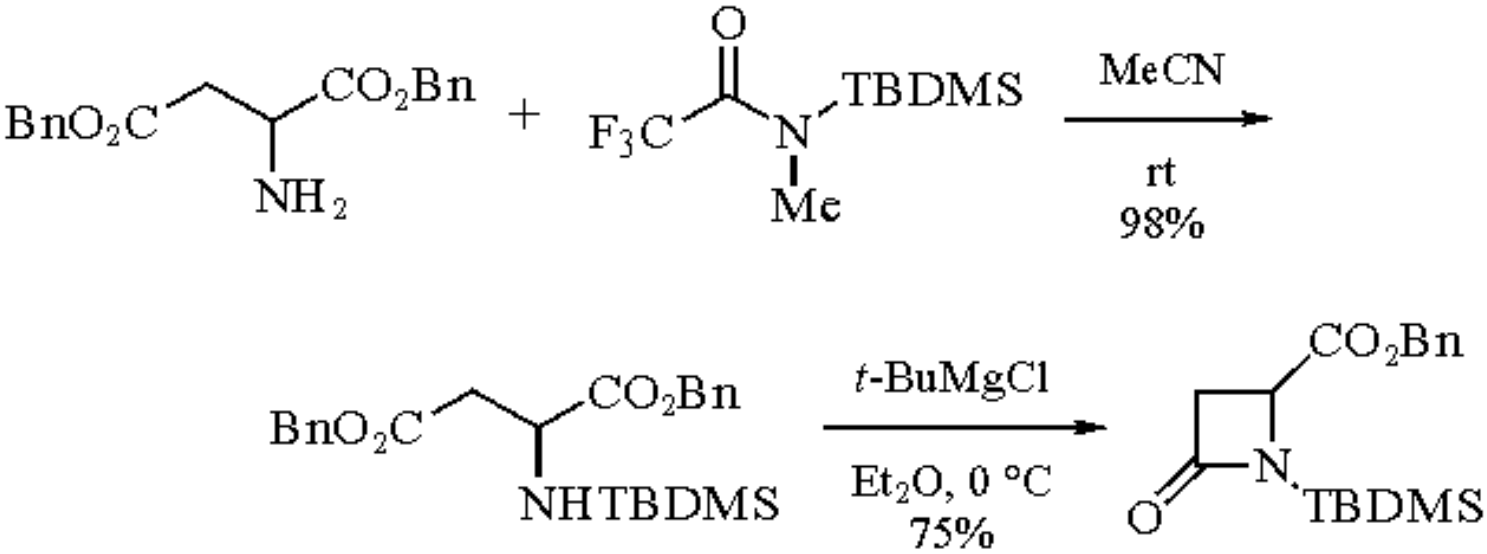

(2)

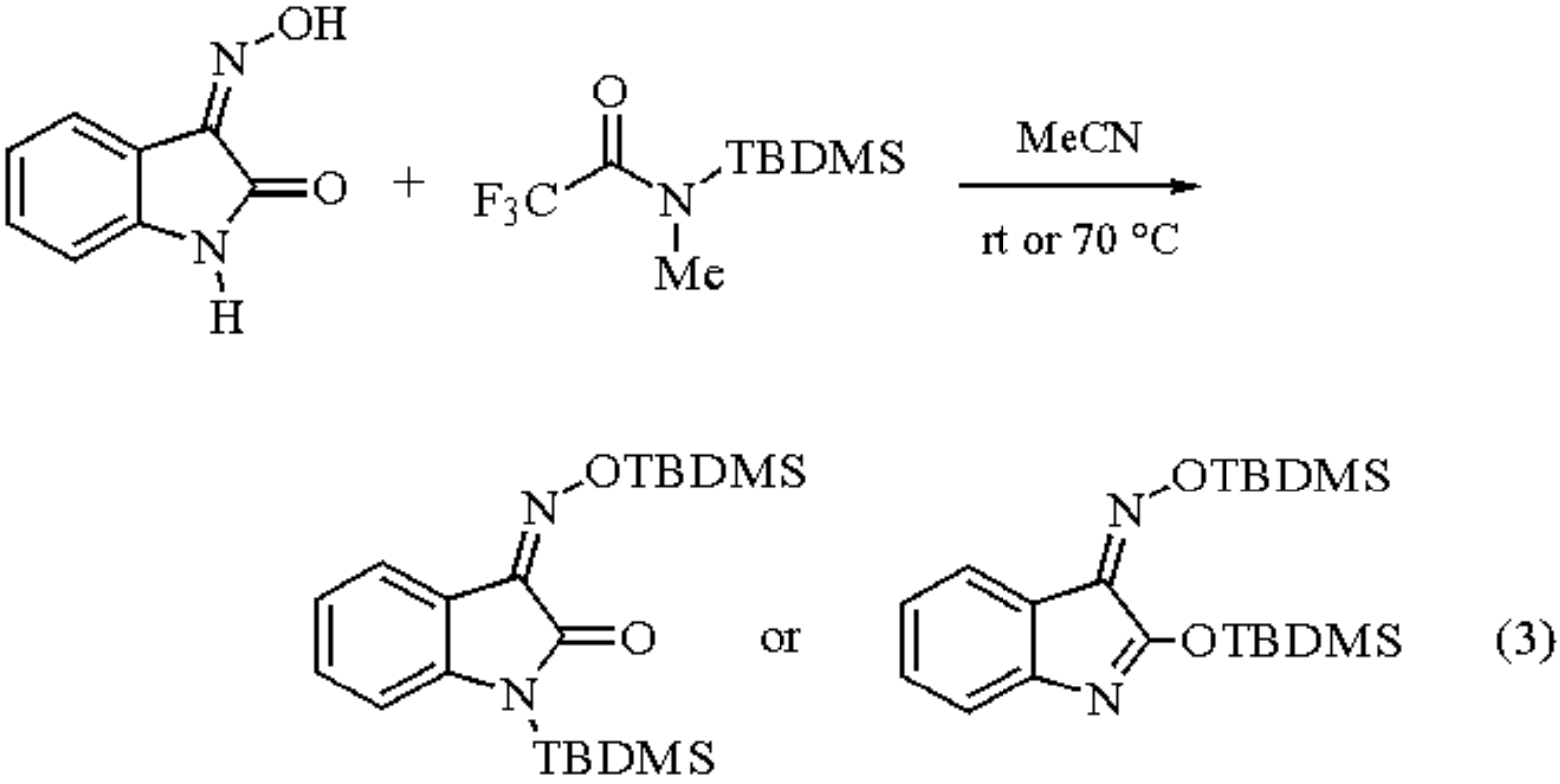

Selective Silylation.

The bulkiness of the TBDMS group enables BSMTFA to possess greater selectivity than the corresponding TMS-containing agents in silylation. In general, *t*-butyldimethylsilylation of secondary amines, which are sterically more congested, proceeds more slowly than that of alcohols, carboxylates, thiols, and primary amines.[1,4] Reaction of alkyldiamines with BSMTFA gives disilylated derivatives, in which each of the two primary amino groups is monosilylated. Trisilylation occurs after a prolonged reaction time.[5] Selective monosilylation of a dihydroxy aromatic compound can be accomplished in 92% yield by use of 1.5 equiv of BSMTFA in a mixture of DMF and THF (eq 4).[14]

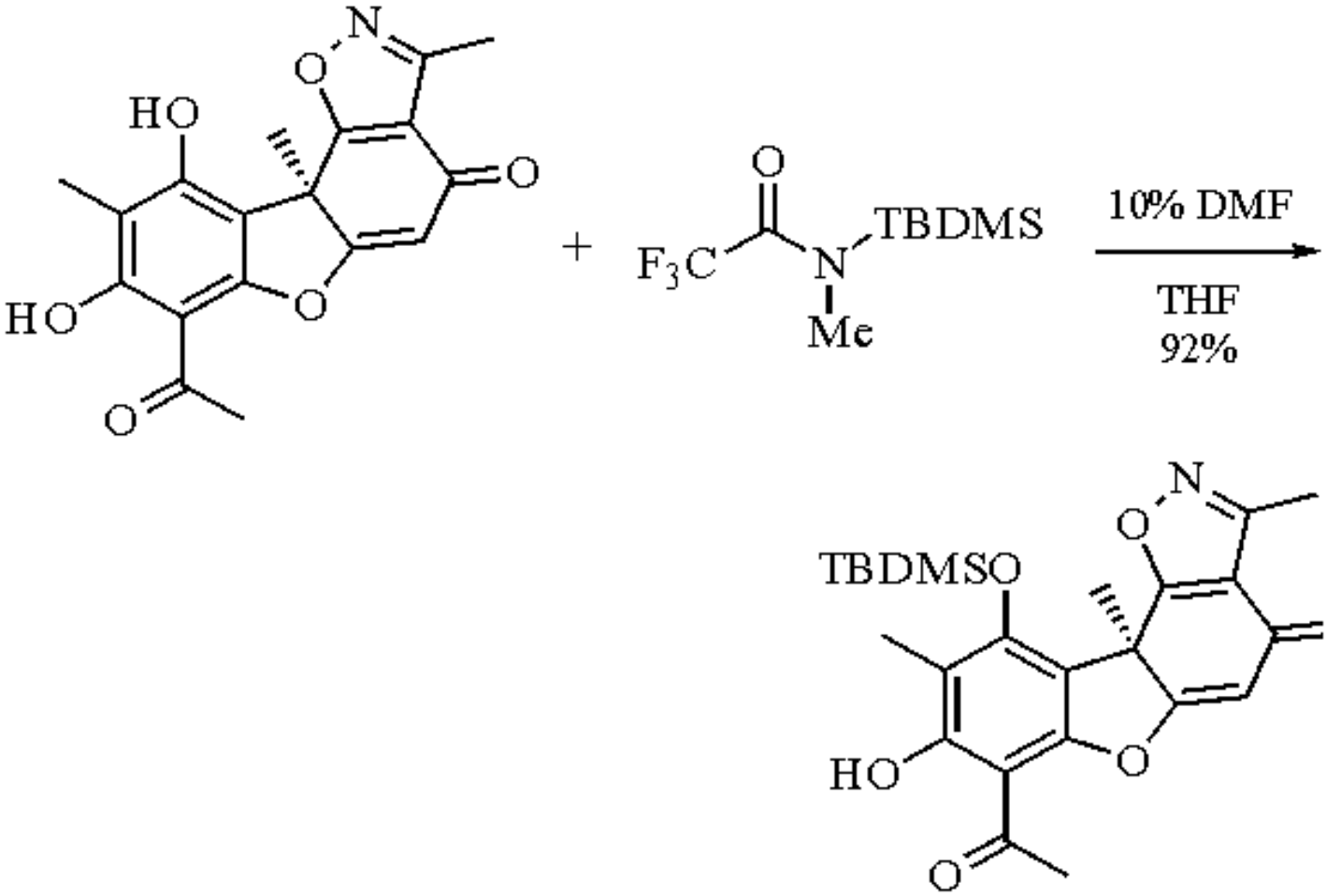

(4)

Derivatizing Reagent for GC-MS Analyses.

For organic compounds containing active protons (e.g. alcohols, amines, carboxylates, and thiols), silylation is often used to improve resolution and peak symmetry, or to decrease adsorption on the column for GC-MS analysis.[3,15-17] Use of BSMTFA as the derivatizing reagent produces a mass spectrum with a prominent peak at *M* - 57 *m*/*z*, which represents loss of a *t*-butyl group from the molecular ion of the silylated species. In comparison, the trimethylsilylated amino acids are often unstable, easily hydrolyzed, and produce varying GC results.[17]

Silylation of Inorganic Oxyanions.[2,18]

The TBDMS derivatives of some inorganic oxyanions can be prepared by reaction of the corresponding free acids or the ammonium salts with BSMTFA in DMF. Those oxyanions include arsenate, arsenite, borate, carbonate, molybdenate, phosphate, phosphite, pyrophosphate, selenate, selenite, sulfate, sulfite, and vanadate. The *t*-butyldimethylsilylated inorganic oxyanions are relatively stable in comparison with the corresponding TMS derivatives, which show significant degradation on GC. Moreover, those *t*-butyldimethylsilylated oxyanions display single, sharp, and symmetrical chromatographic peaks without tailing on GC and produce easily interpretable mass spectra dominated by a characteristic *M* - 57 ion peak.

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t-Butyldimethylsilyl Perchlorate

t-BuMe$_2$Si-OClO$_3$

[67124-66-7] · $C_6H_{15}ClO_4Si$ · *t*-Butyldimethylsilyl Perchlorate · (MW 214.72)

(silylating reagent)

Form Supplied in: clear liquid.

Preparative Methods: prepared in a one-step trityl salt-silyl hydride exchange reaction between *t*-butyldimethylsilane and ***Triphenylmethyl Perchlorate*** (eq 1).[1]

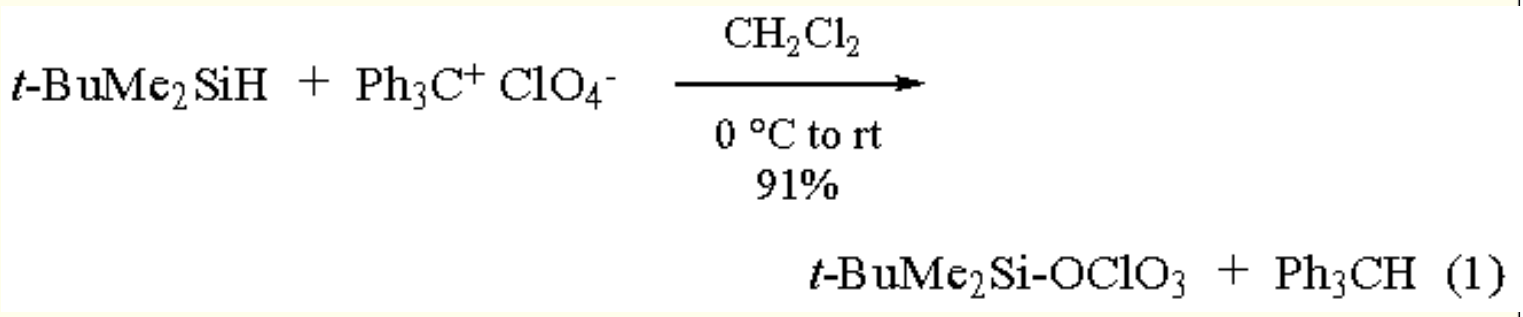

Purification: distillation under reduced pressure.[1]

Handling, Storage, and Precautions: potentially explosive; moisture sensitive; safety shield recommended.

The hindered *t*-butyldimethylsilyl (TBDMS) group has synthetic utility as a very stable alcohol-protecting group. The advantage of TBDMS perchlorate over the corresponding chloride in the protection of secondary and tertiary alcohols is reflected in the relative rates of silylation (Table 1).[1]

Table 1 Reaction Rates

Alcohol	*t*-BuMe$_2$SiOClO$_3$; py-MeCN	*t*-BuMe$_2$SiCl; imidazole-DMF
t-BuOH	$t_{1/2}$ ~30 s; 100% in 5 min	30% in 3 days
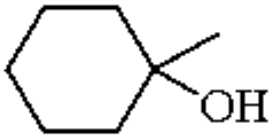	$t_{1/2}$ ~3 min; 100% in 20 min	10% in 3 days

Although stable, removal of the protecting group with 1% HCl in 95% EtOH at rt is quantitative after 15 min.[1]

---

1. Barton, T. J.; Tully, C. R. *JOC* **1978**, *43*, 3649.

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t-Butyldimethylsilyl Trifluoromethanesulfonate[1]

t-BuMe$_2$SiOSO$_2$CF$_3$

[69739-34-0] · $C_7H_{15}F_3O_3SSi$ · *t*-Butyldimethylsilyl Trifluoromethanesulfonate · (MW 264.33)

(highly reactive silylating agent and Lewis acid capable of converting primary, secondary, and tertiary alcohols[1b] to the corresponding TBDMS ethers, and converting ketones[2] and lactones[2a,3] into their enol silyl ethers; promoting conjugate addition of alkynylzinc compounds[4] and triphenylphosphine[5] to α,β-enones; activation of chromones in [4 + 2] cycloaddition reactions;[6] rearrangement of allylic tributylstannyl silyl ethers;[7] activation of pyridine rings toward Grignard reagents[8] and transalkylation of tertiary amine *N*-oxides;[9] and transformation of *N*-*t*-butoxycarbonyl groups into *N*-alkoxycarbonyl groups[10])

Alternate Name: TBDMS triflate.

Physical Data: bp 60 °C/7 mmHg; colorless oil, *d* 1.151 g cm^{-3}.

Solubility: sol most organic solvents such as pentane, CH_2Cl_2, etc.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H, *t*-Bu), 0.45 (s, 6H, Me).

Form Supplied in: liquid; widely available.

Preparative Method: [1b] to 24 g (0.16 mol) of ***t-Butyldimethylchlorosilane*** at 23 °C under argon is added 14 mL (0.16 mol) of ***Trifluoromethanesulfonic Acid*** dropwise. The solution is heated at 60 °C for 10 h, at which time no further hydrogen chloride evolves (removed through a bubbler). The resulting product is distilled under reduced pressure: 34 g (80% yield) of TBDMS triflate; bp 60 °C/7 mmHg.

Handling, Storage, and Precautions: the material should be stored under argon at 0 °C. The compound has an unpleasant odor and reacts rapidly with water and other protic solvents.

Silylation of Alcohols.[1]

Primary, secondary, and tertiary alcohols are silylated by reaction with TBDMS triflate in excellent yields. For instance, treatment of *t*-butanol with 1.5 equiv of TBDMS triflate and 2 equiv of ***2,6-Lutidine*** in CH_2Cl_2 at 25 °C for 10 min gives a 90% yield of (*t*-butoxy)-*t*-butyldimethylsilane.[1b] The following alcohols are similarly silylated in

excellent yields (70-90%): 2-phenyl-2-propanol, *endo*-norborneol, *cis*-2,2,4,4-tetramethylcyclobutane-1,3-diol, and 9-*O*-methylmaytansinol (converted to the 3-TBDMS derivative) (eq 1).[1b]

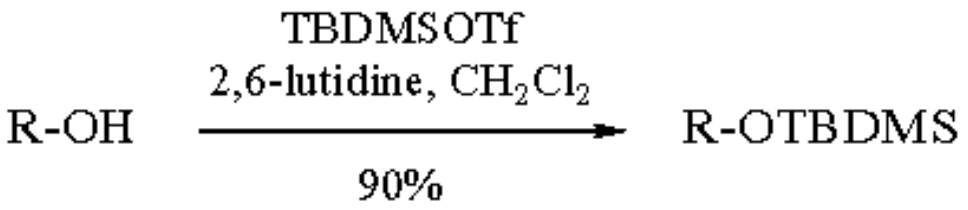

(1)

Formation of Enol Silyl Ethers.[2,3]

Various sterically hindered ketones have been converted into enol silyl ethers by treatment with 1-2 equiv of TBDMS triflate and 1.5 equiv of ***Triethylamine*** in CH_2Cl_2 or 1,2-dichloroethane at rt. A representative example is depicted in eq 2.[2a]

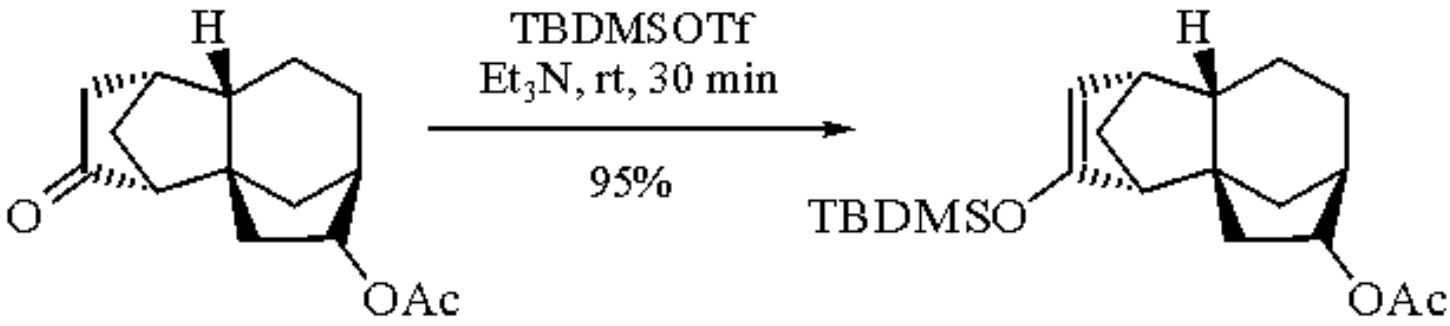

(2)

Reactions of chiral β-keto sulfoxides with 1.1 equiv of ***Lithium Diisopropylamide*** in THF at -78 °C followed by 1.2 equiv of TBDMS triflate at -78 °C produce the corresponding (*Z*)-enol silyl ethers (eq 3).[2b]

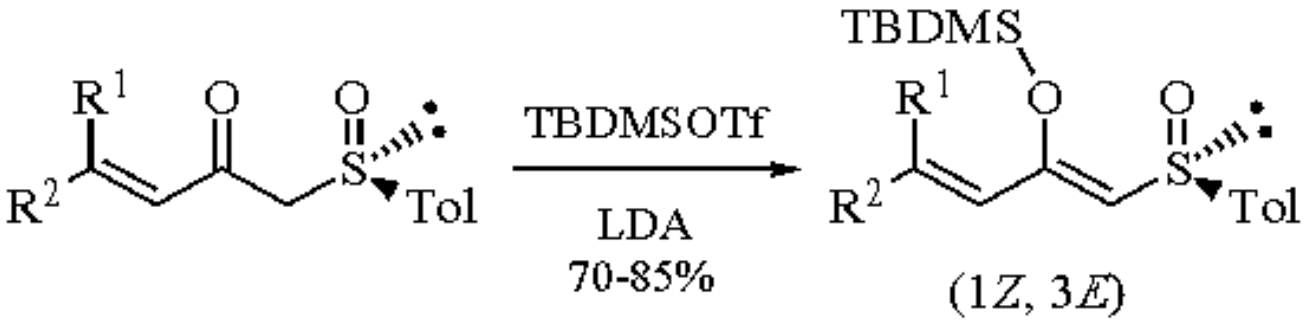

(3)

$R^1 = H, R^2 = Me; R^1 = R^2 = Me; R^1 = H, R^2 = Ph$

Lactones have also been transformed into silyl ketene acetals upon treatment with TBDMS triflate and triethylamine in CH_2Cl_2 (eqs 4 and 5).[2a,3] In the case of 8a-vinyl-2-oxooctahydro-2*H*-1,4-benzoxazine, the resulting silyl ketene acetal undergoes Claisen rearrangement to provide the octahydroquinoline (eq 6).[3]

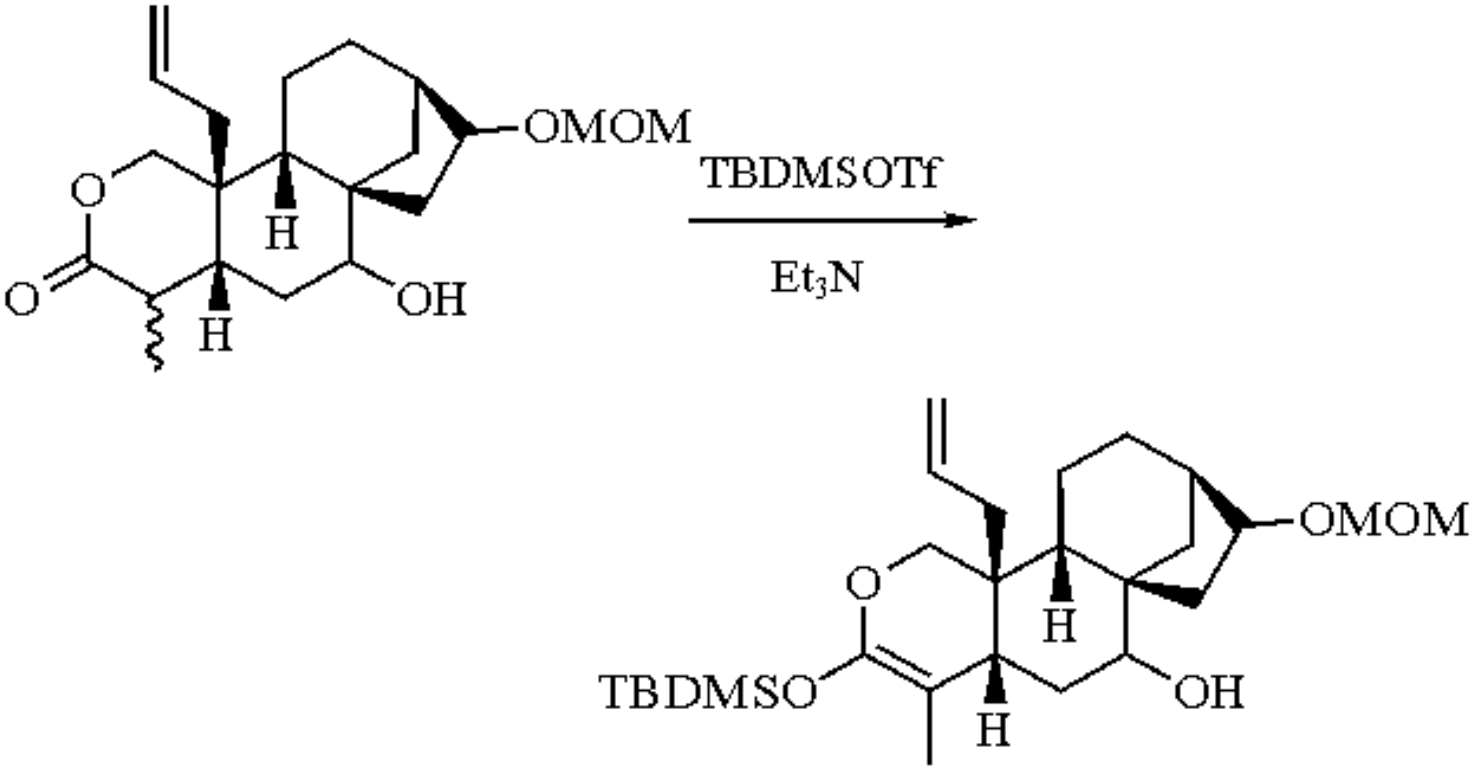

(4)

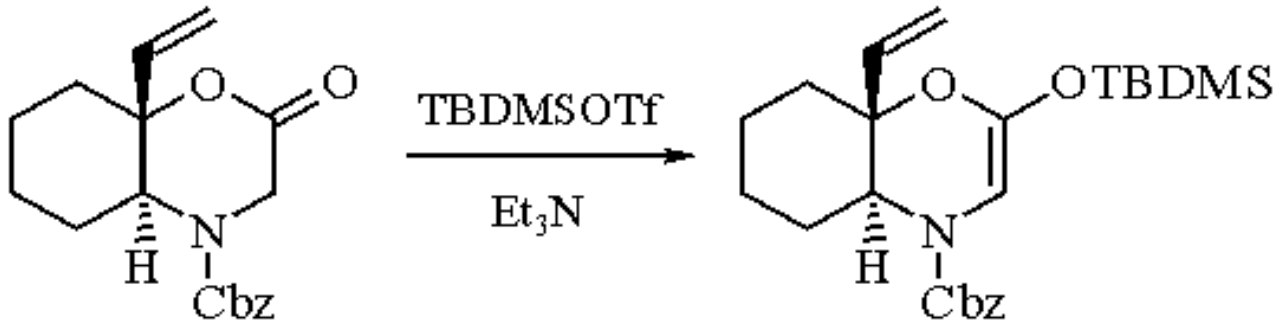

(5)

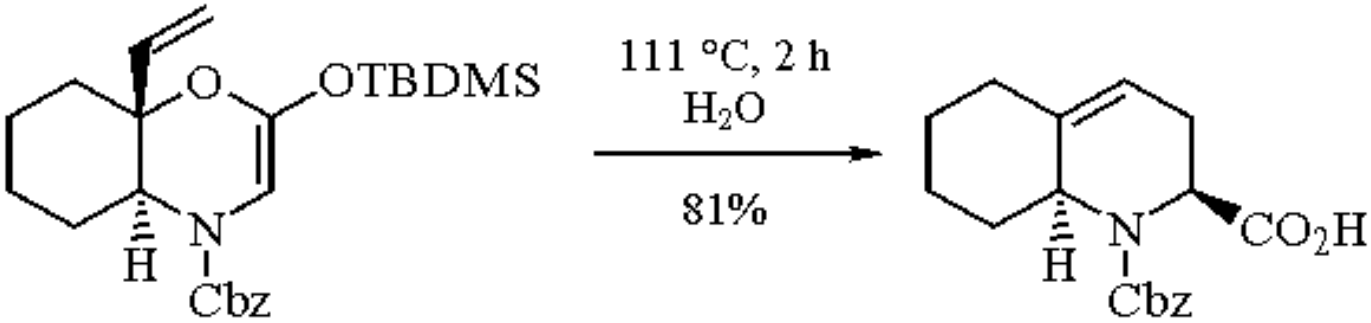

(6)

Conjugate Addition of Alkynylzinc Bromides.[4]

Alkynylzinc bromides undergo conjugate addition with α,β-unsaturated ketones in the presence of TBDMS triflate in ether-THF at -40 °C to give the corresponding 1,4-adducts (54-96% yields). A representative example is illustrated in eq 7.[4] Other trialkylsilyl triflates such as ***Triisopropylsilyl Trifluoromethanesulfonate*** or ***Trimethylsilyl Trifluoromethanesulfonate*** can effectively replace TBDMS triflate.

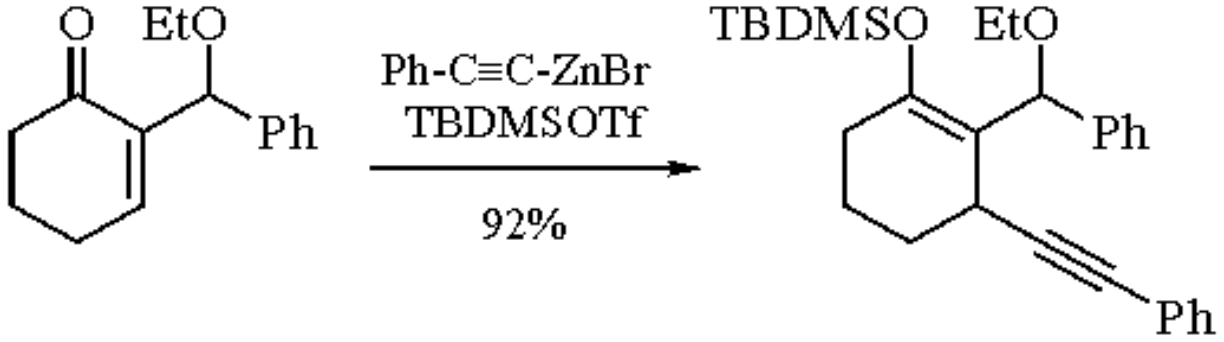

(7)

Phosphoniosilylation.[5]

Cyclic enones treated with TBDMS triflate and ***Triphenylphosphine*** in THF at rt provide the corresponding 1-(3-*t*-butyldimethylsilyloxy-2-cycloalkenyl)triphenylphosphonium triflates (eq 8) which, upon lithiation with ***n-Butyllithium*** followed by Wittig reaction with aldehydes, afford various conjuated dienes.[5]

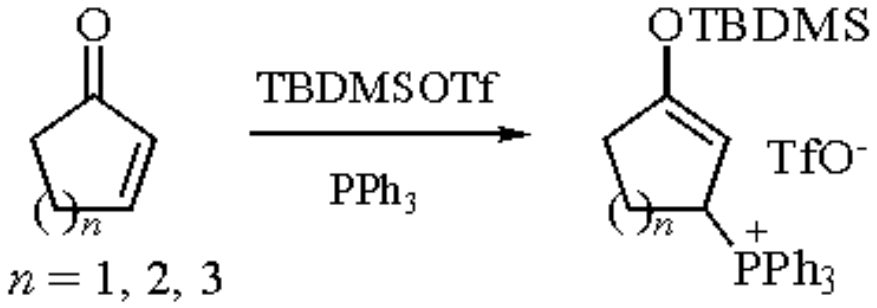

(8)

Silylation of Chromones.[6]

The preparation of 4-*t*-butyldimethylsilyloxy-1-benzopyrylium triflate is carried out by heating chromone and TBDMS triflate at 80 °C for 1 h (without solvent) under nitrogen (eq 9).[6b] The silylated chromones undergo addition reaction with enol silyl ethers and 2,6-lutidine,[6b] and [4 + 2]-type cycloaddition reactions with α,β-unsaturated ketones in the presence of TBDMS triflate and 2,6-lutidine. An example of the cycloaddition reaction is shown in eq 10.[6a]

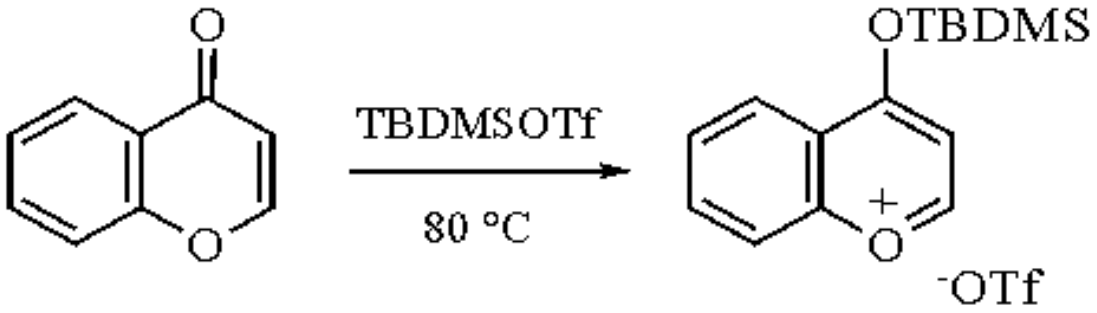

(9)

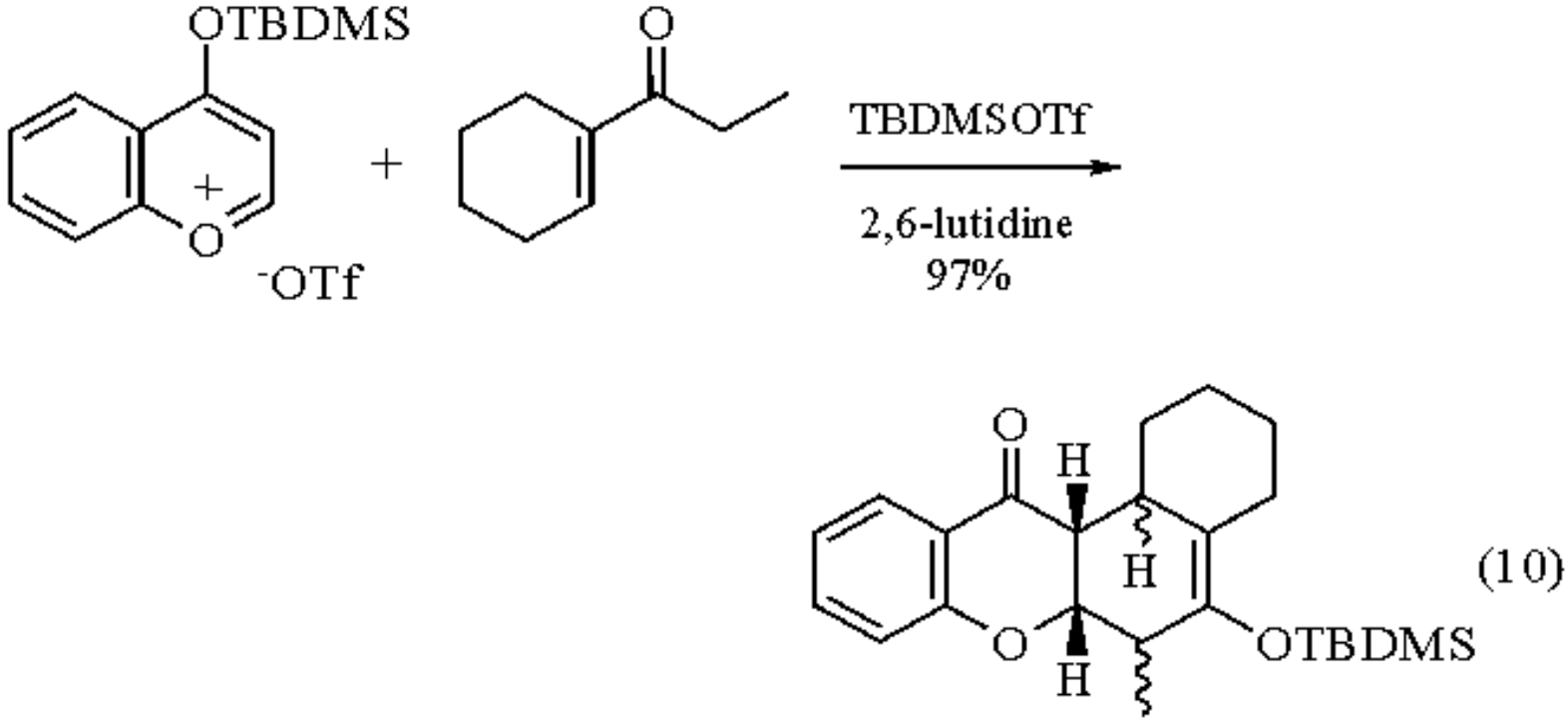

Rearrangement of Allylic Tributylstannyl Silyl Ethers.[7]

α-Silyloxy allylic stannanes are isomerized with TBDMS triflate to (*Z*)-γ-silyloxy allylic stannanes (eq 11).[7] The resulting allylic stannanes undergo addition reactions with aldehydes in the presence of ***Boron Trifluoride Etherate*** to provide the 3-(*t*-butyldimethylsilyloxy)-4-hydroxyalkenes.[7a]

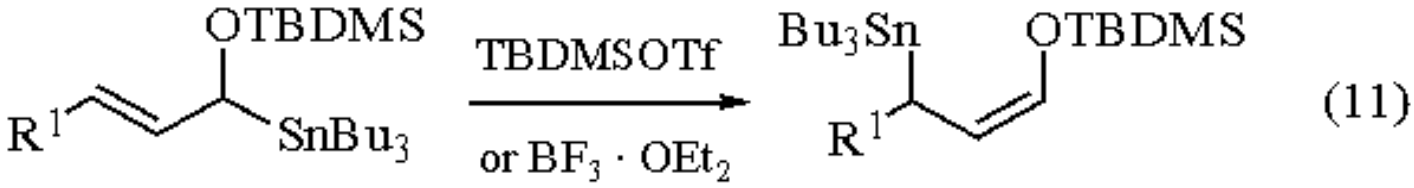

Activation of Pyridine.[8]

N-(*t*-Butyldimethylsilyl)pyridinium triflate, prepared from pyridine and TBDMS triflate in CH_2Cl_2 at rt, undergoes addition reactions with alkyl and aryl Grignard reagents to give 4-substituted pyridines after oxidation with oxygen (eq 12).[8] Only about 1% of the 2-substituted pyridines were formed in the cases studied.

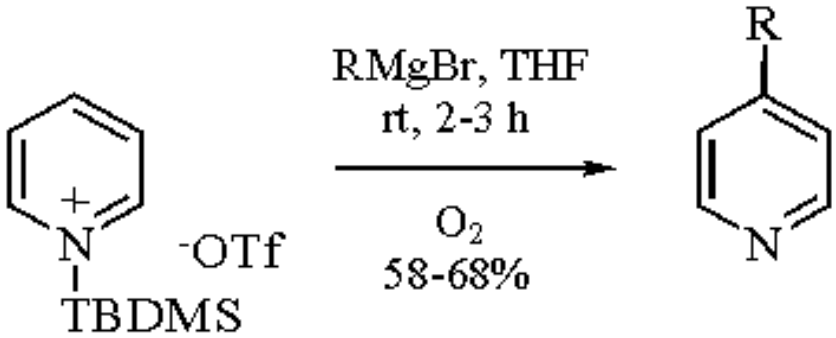

(12)

Transalkylation of Tertiary Amine *N*-Oxides.[9]

N-(*t*-Butyldimethylsilyloxy)-*N*-methylpiperidinium triflate is quantitatively formed from the reaction of *N*-methylpiperidine *N*-oxide (eq 13).[9b] The resulting amine salts derived from various trialkylamine *N*-oxides undergo transalkylation by treatment with ***Methyllithium*** in THF at 0 °C followed by alkyl halides and ***Tetra-n-butylammonium Fluoride*** in a sealed tube at 110 °C for 10 h, to afford trisubstituted amines (eq 14).[9a]

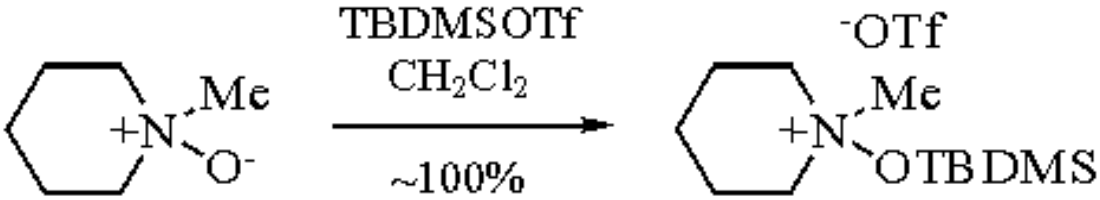

(13)

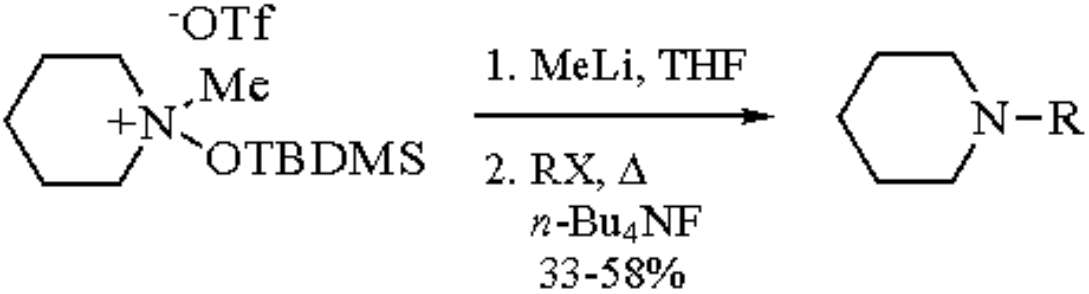

(14)

Interconversion of *N*-Boc Group into *N*-Alkoxycarbonyl Group.[10]

Treatment of *t*-butyl alkylcarbamates with 1.5 equiv of TBDMS triflate and 2 equiv of 2,6-lutidine in CH_2Cl_2 at rt for about 15 min furnishes the corresponding TBDMS carbamates (eq 15).[10] Desilylation of these silyl carbamates with aqueous fluoride ion gives excellent yields of the corresponding primary amines. The silyl carbamates are also converted into other *N*-alkoxycarbonyl derivatives by treatment with TBAF and alkyl halides in THF at 0 °C (82-88% yields).[10]

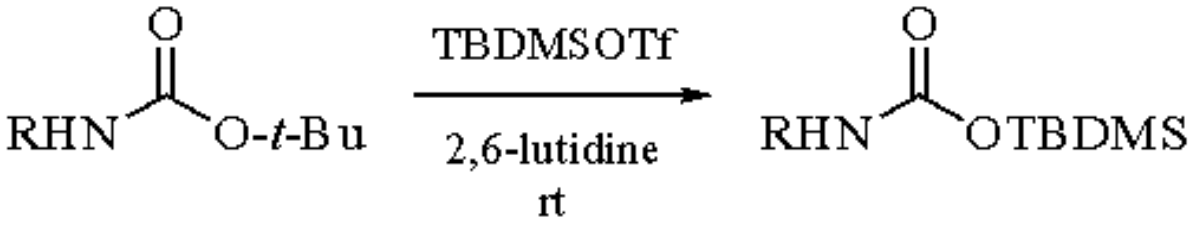

(15)

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10. Sakaitani, M.; Ohfune, Y. *TL* **1985**, *26*, 5543.

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t-Butyldiphenylchlorosilane[1]

t-$BuPh_2SiCl$

[58479-61-1] · $C_{16}H_{19}ClSi$ · *t*-Butyldiphenylchlorosilane · (MW 274.86)

(reagent for the temporary protection of hydroxy groups as their *t*-butyldiphenylsilyl ethers; selectivity can be obtained for primary vs. secondary hydroxy groups; other protection (carbonyl, amine, etc.) is also possible;[2] deprotection is conveniently effected with fluoride ion, strong acid, or base; the TBDPS ether group is compatible with a large number of organic functional group transformations,[1-3] in nucleoside chemistry,[1] as well as in numerous examples in which polyfunctional molecules are chemically manipulated[4])

Alternate Name: TBDPS-Cl.

Physical Data: colorless liquid, bp 93-95 °C/0.015 mmHg; n_D^{20} 1.5680; *d* 1.057 g cm^{-3}.

Solubility: miscible in most organic solvents.

Form Supplied in: colorless liquid 98%.

Preparative Method: a dry 1 L, three-necked round bottomed flask is equipped with a magnetic stirring bar, a 500 mL equalizing dropping funnel fitted with a rubber septum, a reflux condenser, and nitrogen inlet tube. The flask is flushed with nitrogen, then charged with 127 g (0.5 mol) of diphenyldichlorosilane in 300 mL of redistilled pentane. A solution of ***t-Butyllithium*** in pentane (500 mL, 0.55 mol), is transferred under nitrogen pressure to the dropping funnel using a stainless steel, double-tip transfer needle. This solution is slowly added to the contents of the flask and when the addition is complete, the mixture is refluxed 30 h under nitrogen with stirring. The suspension is allowed to cool to rt, the precipitated lithium chloride is rapidly filtered through a pad of Celite, and the latter is washed with 200 mL of pentane. The solvent is removed by evaporation, and the colorless residue is distilled through a short (10 cm), Vigreux column, to give 125-132 g of the colorless title compound.

Handling, Storage, and Precautions: the reagent is stable when protected from moisture and protic solvents. A standard M solution of the reagent can be prepared in anhyd DMF and kept at 0 °C under argon in an amber bottle. Use in a fume hood.

Preparation of *t*-Butyldiphenylsilyl Ethers and Related Transformations.

A standard protocol[1] involves the addition of the reagent (1.1 equiv) to a solution of the alcohol (1 equiv) and ***Imidazole*** (2 equiv) in DMF at 0 °C or at room temperature. When silylation is complete, the solution is diluted with water and ether or dichloromethane and the organic layer is processed in the usual way. In some instances the addition of ***4-Dimethylaminopyridine*** (DMAP) can enhance the reaction rate.[5,6] Selective protection of the primary hydroxy group in carbohydrate derivatives has been achieved using this reagent and ***Poly(4-vinylpyridine)*** in CH_2Cl_2 or THF in the presence of ***Hexamethylphosphoric Triamide***.[7] Enol *t*-butyldiphenylsilyl ethers are easily formed by trapping of enolates with the chloride.[8] Amines can be selectively converted into the corresponding primary *t*-butyldiphenylsilylamines essentially under the same conditions.[9] *t*-Butyldiphenylsilyl cyanohydrins are prepared in the presence of ***Potassium Cyanide***, ***Zinc Iodide***, and a carbonyl compound.[10]

Selectivity and Compatibility of *O*- and *N*-*t*-Butyldiphenyl Silyl Derivatives.

The *O*-*t*-butyldiphenylsilyl ether protective group offers some unique advantages and synthetically useful features compared to other existing counterparts.[1,2] Silylation of a primary hydroxy group takes place in preference to a secondary, giving products that are often crystalline, and detectable on TLC plates under UV light, because of the presence of a strong chromophore. The TBDPS group is compatible with a variety of conditions[1] used in synthetic transformations such as hydrogenolysis ($Pd(OH)_2$, C/H_2, etc.), *O*-alkylation (NaH, DMF, halide), de-*O*-acylation (NaOMe, NH_4OH, K_2CO_3/MeOH), mild chemical reduction with hydride reagents, carbon-carbon bond formation with organometallic reagents, transition metal-mediated reactions, Wittig reactions, etc. These reactions were tested during the total synthesis of thromboxane B_2[11] for which the TBDPS group was originally designed. Subsequently, numerous related organic transformations have been carried out in the presence of TBDPS ethers in the context of natural product synthesis[3,4] and functional group manipulations.[2] It is distinctly more acid stable than the *O*-trityl, *O*-THP, and *O*-TBDMS groups, and is virtually unaffected under conditions that cause complete cleavage of these groups (50% HCO_2H, 2-6 h; 50% aq TFA, 15 min; HBr/AcOH, 0 °C, few min; 80% aq acetic acid, few h).[1] It is also compatible with conditions used for the acid-catalyzed formation and hydrolysis of acetal groups and in the presence of some Lewis acids (e.g. TMSBr,[12] $BCl_3.SMe_2$,[13] Me_2AlCl,[8] etc.). The mono-TBDPS derivative of a primary amine[9] is stable to base, as well as to alkylating and acylating reagents. Thus a secondary amine can be acylated in the presence of a primary *t*-butyldiphenylsilylamino group.

Deprotection.[1,2]

The *O*-TBDPS group can be cleaved under the following conditions: ***Tetra-n-butylammonium Fluoride*** in THF at rt; variations of F^--catalyzed reactions (e.g. F^-/AcOH; HF/pyridine;[14] HF/MeCN,[15] etc.); aqueous acids and bases[1] (1 N HCl, 5 N NaOH, aq methanolic NaOH or KOH); ion exchange resins;[7] ***Potassium Superoxide***, ***Dimethyl Sulfoxide***, ***18-Crown-6***.[16] Selective cleavage of a TBDPS ether in the presence of a TBDMS ether in carbohydrate derivatives involves treatment with ***Sodium Hydride***/HMPA at 0 °C.[17] Although the *O*-TBDPS group is stable to most hydride reagents, ***Lithium Aluminum Hydride*** reduction of an amide group has resulted in the cleavage[18] of an adjacent *O*-TBDPS ether, possibly via internal assistance. TBDPS-amines are cleaved by 80% AcOH or by HF/pyridine.[9]

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N-t-Butylformamide

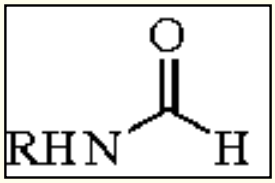

(R = *t*-Bu)

[2425-74-3] · $C_5H_{11}NO$ · *N-t*-Butylformamide · (MW 101.15) (R = H)

[75-12-7] · CH_3NO · Formamide · (MW 45.04)

(amidation of alkenes; amidation of heterocycles; synthesis of secondary amines)

Physical Data: N-t-butylformamide: mp 16 °C; bp 202 °C; *d* 0.903 g cm^{-3}. Formanide: mp 2 °C; bp 111 °C/20 mmHg; *d* 1.133 g cm^{-3}.

Solubility: N-t-butylformamide is miscible with most common organic solvents and with water.

Form Supplied in: commercially available in 98% purity.

Preparative Method: N-t-butylformamide is prepared from ***t-Butylamine*** and ethyl formate.[1]

Purification: by distillation.

Hydroamidation of Alkenes.

t-Butylformamide adds across the double bond of alkenes in a Markovnikov fashion using ***1,1-Di-t-butyl Peroxide*** as the radical initiator (eq 1).[2] Dimerization of *t*-butylformamide occurs under these conditions in the absence of an alkene. The related reagent formamide undergoes similar reactions with alkenes (eq 2) and these reactions have been initiated both photochemically and by peroxides.[3-5]

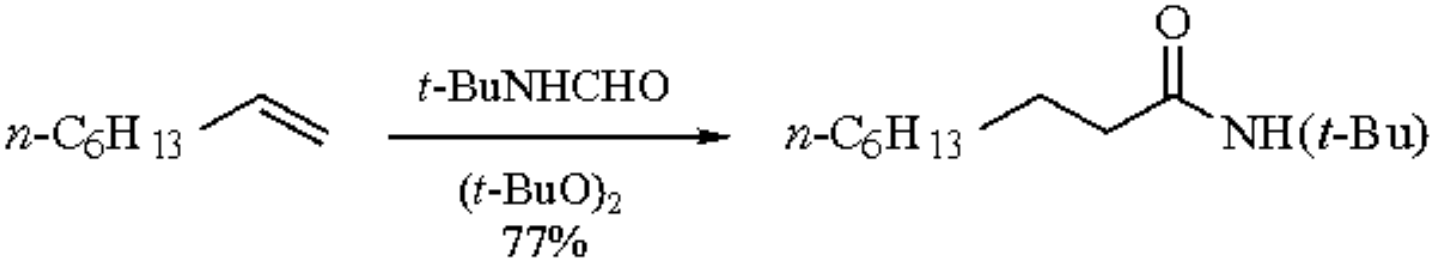

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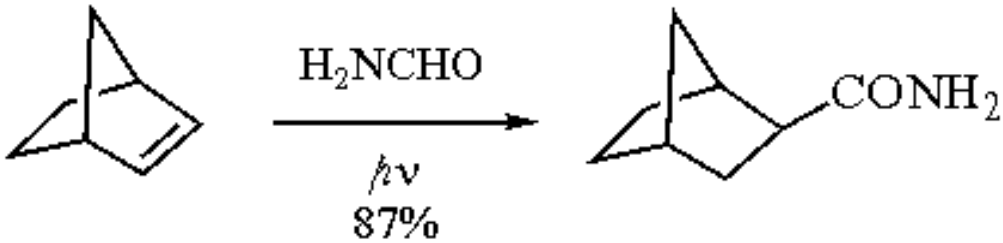

(2)

Amidation of Pyridines.

Pyridines undergo amidation when combined with *t*-butylformamide and ***t-Butyl Hydroperoxide*** and Fe^{II} but the reactions show little regioselectivity and the yields are poor. Higher yields and good regiochemical control are obtained with formamide (eq 3).[6]

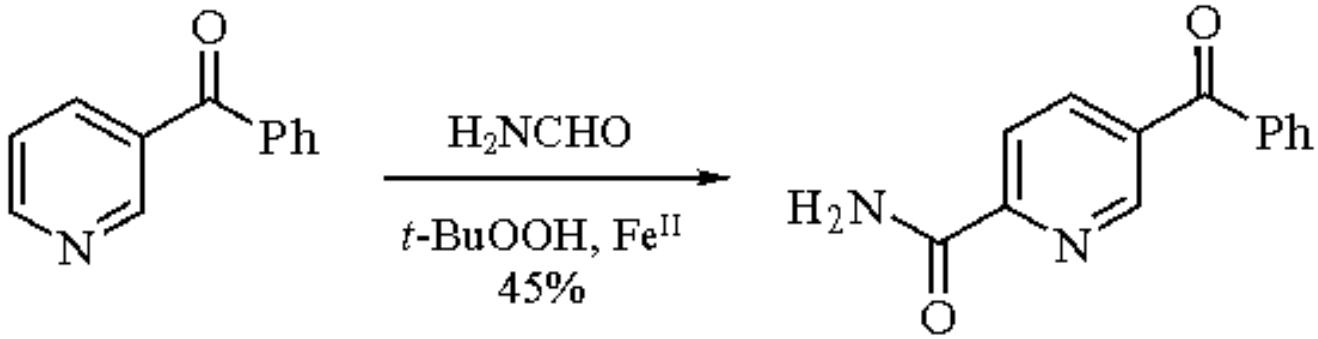

(3)

Numerous heteroaromatic bases, mostly substituted quinolines and pyridines, have been amidated with formamide under radical conditions (eq 4).[7] The radicals for these amidations have been generated from formamide by a variety of means, usually from ***Hydrogen Peroxide-Iron(II) Sulfate***, but also from decomposition of ***Hydroxylamine-O-sulfonic Acid***,[8] or from ***Iodosylbenzene*** and ***Sodium Azide***.[9] These amidations and related reactions with nitrogen heterocycles have been reviewed.[10] Amidations under these conditions provide a useful method for acylating pyridines, quinolines, and related compounds that cannot ordinarily be acylated under conventional Friedel-Crafts conditions.

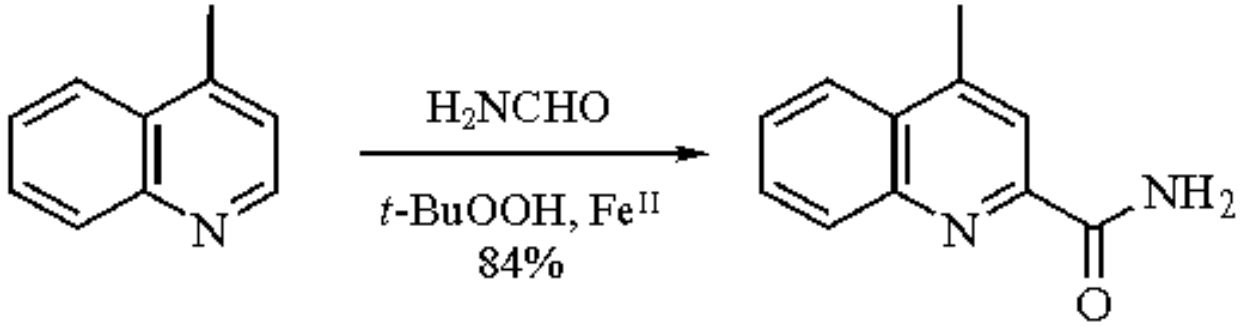

(4)

Synthesis of Secondary Amines.

t-Butylformamide is alkylated under phase transfer conditions to yield *N*,*N*-dialkylformamides in good yield. Hydrolysis provides secondary amines. This reaction provides an alternative to the Ritter reaction and works with a variety of tertiary amines (eq 5).[11]

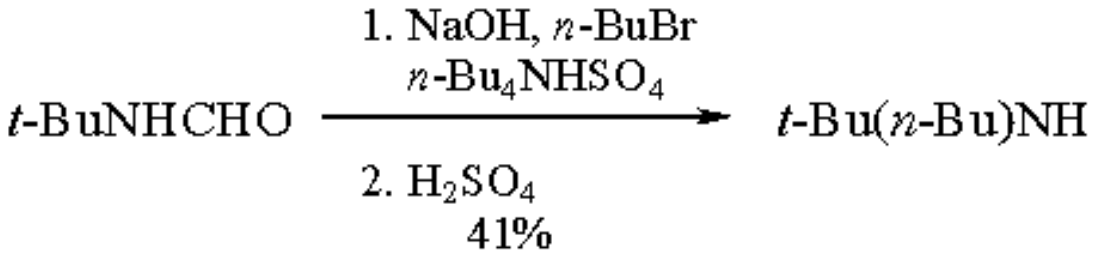

(5)

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t-Butyl Hydroperoxide[1-3]

***t*-Bu-O-OH**

[75-91-2] · $C_4H_{10}O_2$ · *t*-Butyl Hydroperoxide · (MW 90.12)

(oxidizing agent used for the oxidation of alcohols and alkenes to allylic oxygenated compounds and epoxides[1,2])

Alternate Name: TBHP.

Physical Data: the following data are for a 90% aqueous solution: flash point 35 °C; *d* 0.901 g cm^{-3}; *n*20D 1.3960. The density of a 70% aqueous solution is 0.937 g cm^{-3}.

Solubility: sol alcohol, ether, chloroform; slightly sol H_2O, DMSO.

Form Supplied in: clear colorless liquid; widely available as 70-90% aqueous solutions, and anhydrous in hydrocarbon solvents. Aqueous solutions may be dried by a phase separation procedure, followed by azeotropic distillation to remove the last vestiges of water if necessary.[1]

Handling, Storage, and Precautions: eye protection and rubber gloves should be worn when handling this material; avoid skin contact; this reagent should be handled only in a fume hood. Eye and skin irritant; immediately flush with water if contact is made with the eyes. Flammable liquid; oxidizer; sensitive to shocks and sparks. May react explosively with reducing agents. Store in an explosion-proof container, and keep away from reducing materials and strong acids and bases. Avoid using high strength solutions; do not distill. The use of molecular sieves for drying is not recommended.

General Considerations.

The title reagent is used in oxidations of various substrates to give epoxides, ketones, aldehydes, carboxylic acid esters, and nitro or azoxy compounds. The reagent and its metal complexes have been extensively reviewed.[1-3] This article describes representative applications to problems in organic synthesis.

Oxidations of Alkenes.

Hydroxylation.

Under basic conditions (tetraethylammonium hydroxide, Et_4NOH), in the presence of catalytic amounts of ***Osmium Tetroxide***, TBHP vicinally hydroxylates alkenes (eq 1).[4] This method is preferable over the use of osmium tetroxide stoichiometrically due to the expense and toxicity of the latter (see also ***Osmium Tetroxide-t-Butyl Hydroperoxide***). This method is also preferable to the use of osmium tetroxide catalytically with ***Hydrogen Peroxide***[5] or metal chlorates,[6] both of which give lower yields for tri- and tetrasubstituted alkenes, and can lead to over-oxidation. Et_4NOH can be replaced with Et_4NOAc, which allows this reaction to be carried out on alkenes containing base-sensitive functional groups, and often gives better yields than the use of Et_4NOH (eq 2).[7]

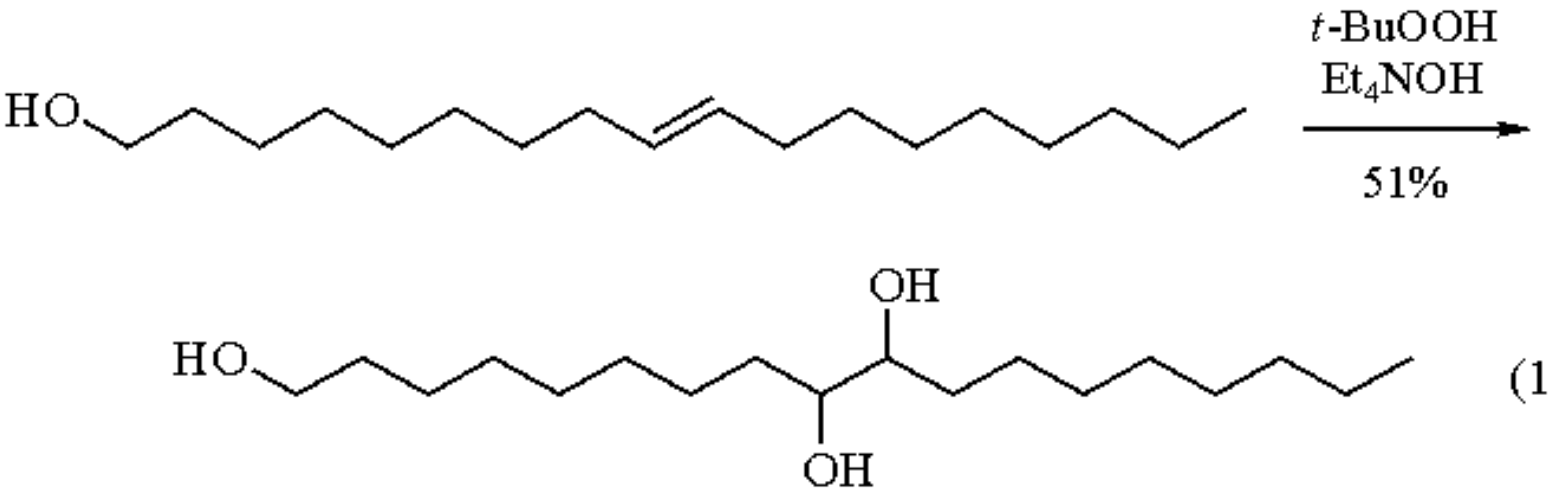

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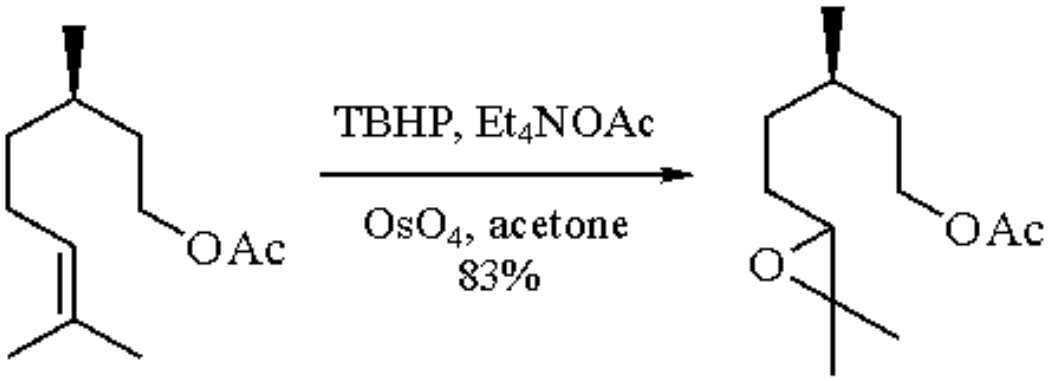

(2)

Chlorohydroxylation of nonfunctionalized alkenes can be accomplished (eq 3) through the reaction of TBHP with ***Titanium(IV) Chloride***.[8] Chlorohydroxylation can also be done asymmetrically to the alkenes of allylic alcohols using TBHP with ***Dichlorotitanium Diisopropoxide*** and an asymmetric tartrate catalyst, and the stereochemistry can be controlled by the ratio of titanium to tartrate (eq 4) varying (see below).

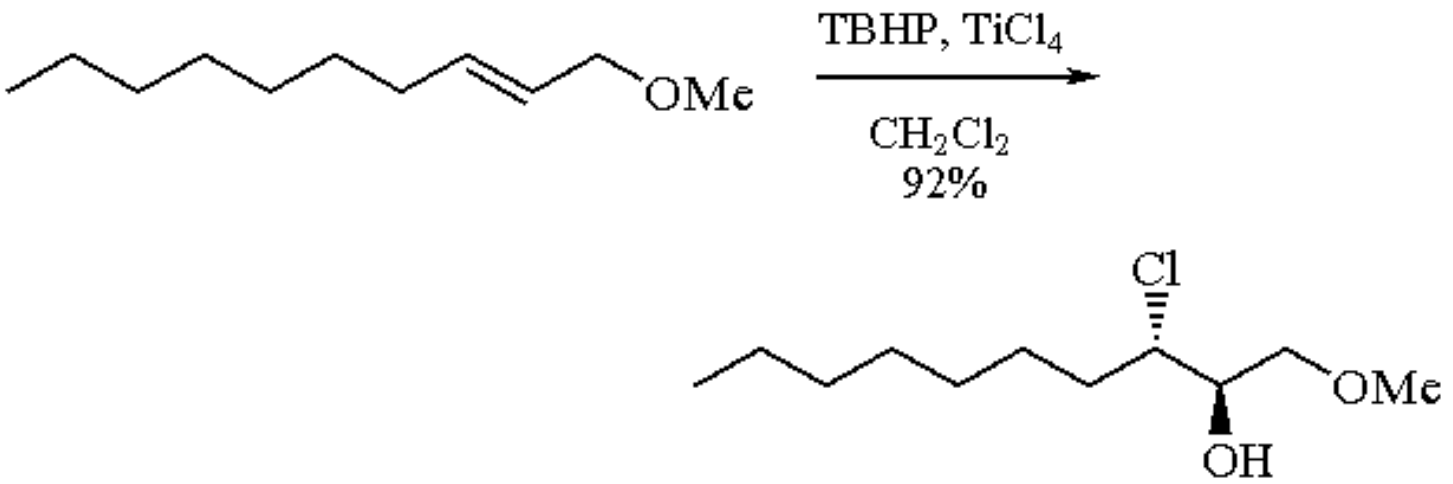

(3)

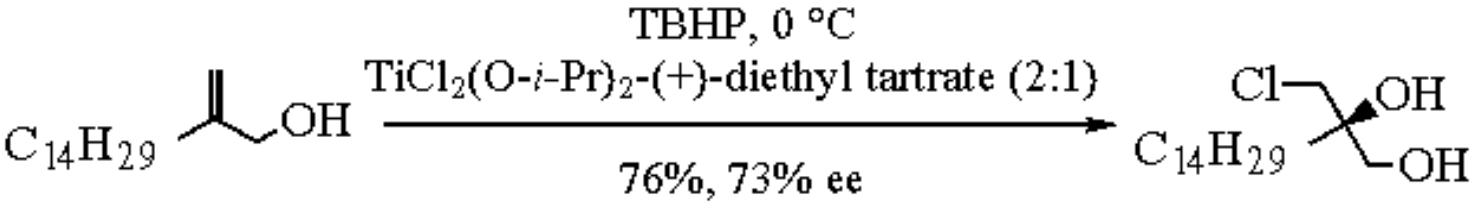

(4)

Oxidation of Allylic, Benzylic, and Propargylic Carbons.[1,2]

Alkenes with an allylic hydrogen can be selectively oxidized to the allylic alcohol by TBHP in the presence of ***Selenium(IV) Oxide*** (eq 5).[9] This is preferable to the oxidation using stoichiometric SeO_2 by itself, which leads to reduced forms of selenium and can make isolation and purification of the product difficult. Less substituted alkenes require 0.5 equivalents of SeO_2 while for more substituted alkenes it may be present in catalytic amounts. The regioselectivity of this reaction favors the more substituted site being oxidized. The addition of small amounts of carboxylic acids also aids this reaction with certain alkenes (eq 5). See also ***Selenium(IV) Oxide-t-Butyl Hydroperoxide***.

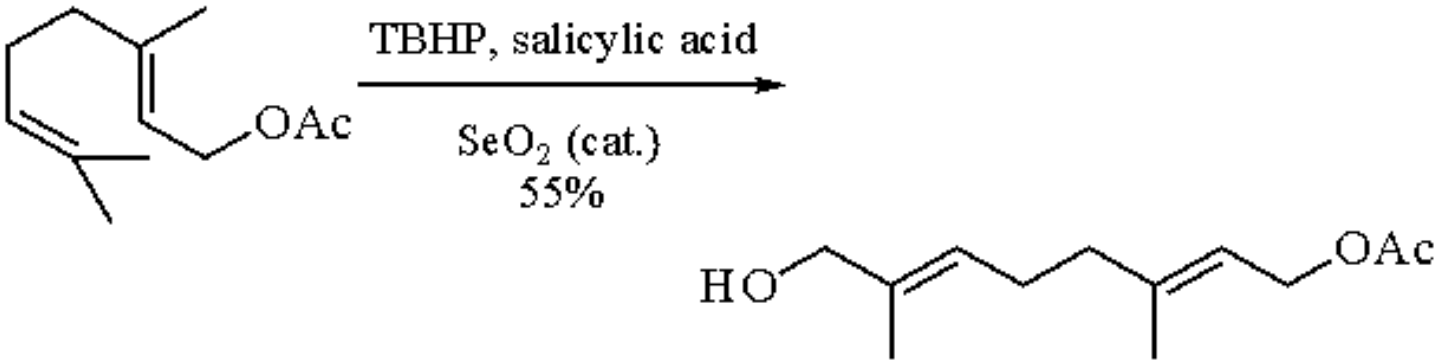

(5)

Alkenes can also be oxidized to give rearranged allylic alcohols using TBHP with phenylselenenic acid and ***Diphenyl Diselenide*** (eq 6).[10] The reaction proceeds through a β-hydroxyl phenylselenide adduct of the alkene, which then eliminates the selenide to give the allylic alcohol and a phenylselenenic acid byproduct. This method is preferable to the use of phenylselenenic acid with hydrogen peroxide, since the latter can lead to epoxidation of the alkene of the product to give the epoxy alcohol. This method also does not oxidatively remove the selenium from the phenylselenenic acid byproduct, as the H_2O_2 method does, allowing the phenylselenenic acid to be recovered and

easily reduced back to diphenyl diselenide.

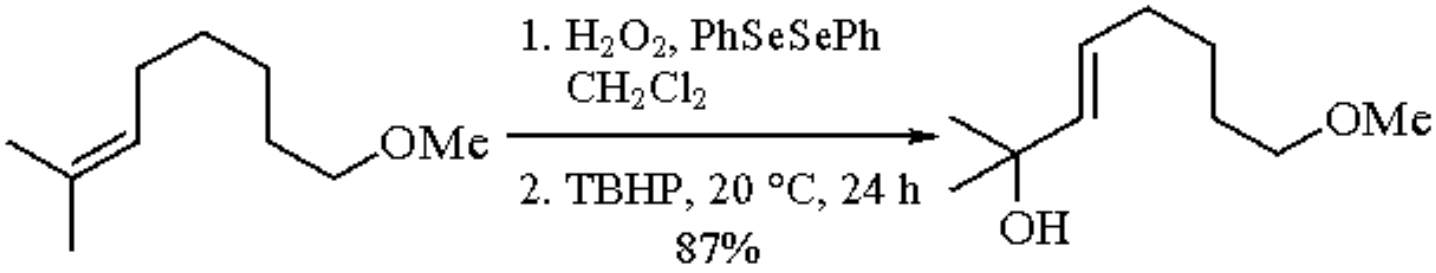

(6)

Oxidations of allylic carbons to carbonyls to give enones may be effected by the reaction of the alkene with TBHP catalyzed by ***Hexacarbonylchromium*** (eq 7).[11] These reaction conditions are milder than other chromium reagents used for the same purpose, and are selective towards allylic carbons. This system has also been used for the oxidation of benzylic carbons to carbonyls, with much better yields than ***Chromic Acid*** oxidations.[12] Other chromium(VI) catalysts can also be used along with TBHP to oxidize allylic and benzylic carbons to the corresponding carbonyl.[13]

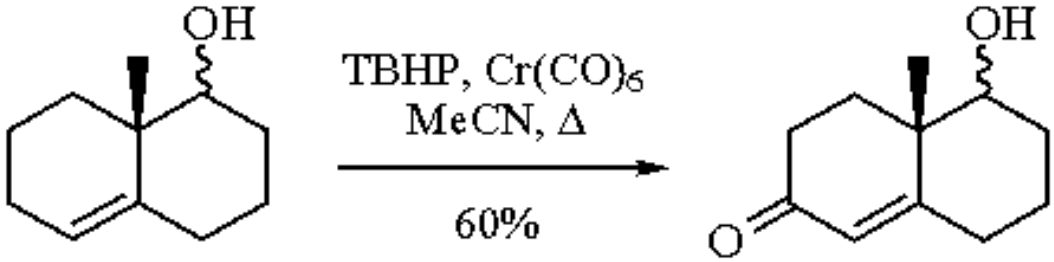

(7)

Propargylic carbons can also be oxidized, using TBHP and SeO_2 (eq 8).[14] Unlike allylic systems, propargylic systems show a great tendency towards oxygenation on both sides of the triple bond, and are generally more reactive towards α oxygenation. A mixture of the propargylic alcohol, ketone, diol, and ketol will generally result from this reaction. If there are two sites possible for oxygenation, methine and methylene groups have about the same reactivity towards these conditions, while methyl groups show a lesser preference for oxidation. In symmetrical alkynes the diol is prevalent, and in some cases where the alkyne is in conjugation with other π systems the ketone is an important product, whereas in most other cases the ketone and ketol are minor products. If the alkyne has one methine and one methylene substituent, the enynone can be an important product.

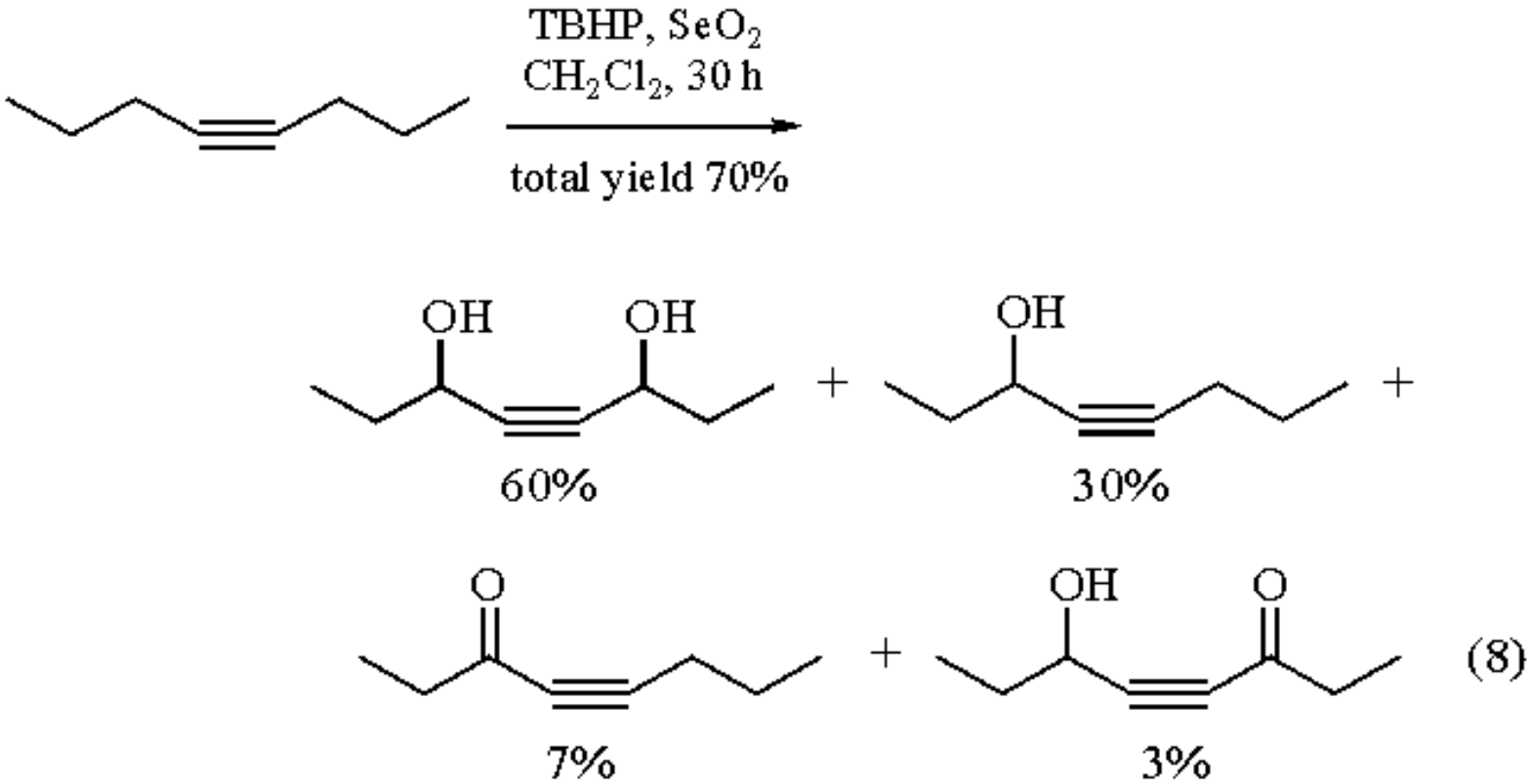

If a chromium(VI) catalyst is used in the presence of TBHP, propargylic carbons will be oxidized to the alkynic ketone (eq 9).[15] The more highly substituted alkyl substituent on the alkyne is preferentially oxidized, and symmetrical alkynes give the monoketone accompanied by the diketone.

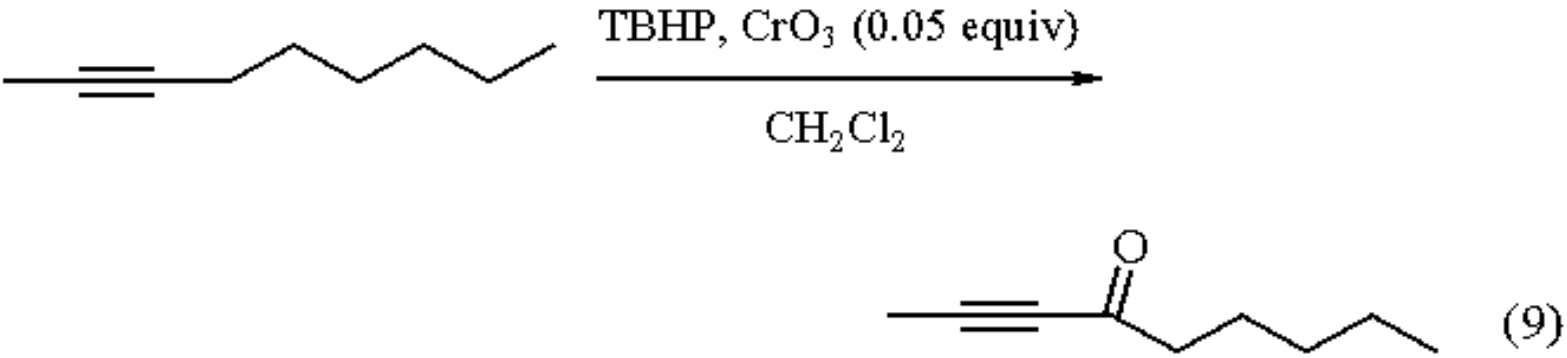

Oxidation of π-allylpalladium complexes can also occur with TBHP using a molybdenum(IV) catalyst to give the allylic alcohol (eq 10).[16] Hydroxyl attack will occur axially, *syn* to the complexed palladium. This conversion can also be carried out with peroxy acids or singlet oxygen, but these methods are not as selective.

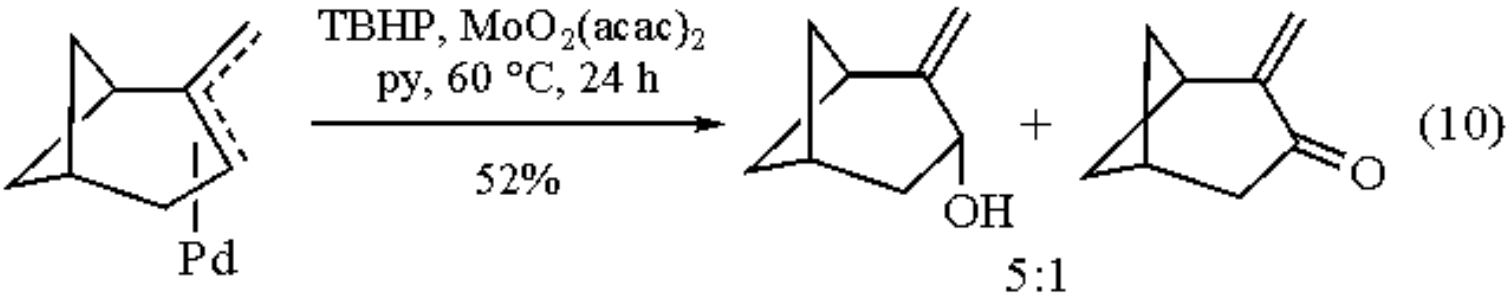

Epoxidation.[1,2,17]

TBHP is widely used as an epoxidizing agent, both synthetically and industrially.[18] TBHP has been used to effect regiospecific, stereospecific, and asymmetric epoxidations. In general, the rates of epoxidations using TBHP are slowed by polar solvents, and increased with higher alkyl substitution of the alkene. TBHP is considered superior to hydrogen peroxide for epoxidations, because it is soluble in hydrocarbon solvents, while hydrogen peroxide can readily transform the epoxide to the *vic*-glycol.

Epoxidations of simple alkenes can be carried out using TBHP with a vanadium or molybdenum catalyst (eq 11).[19]

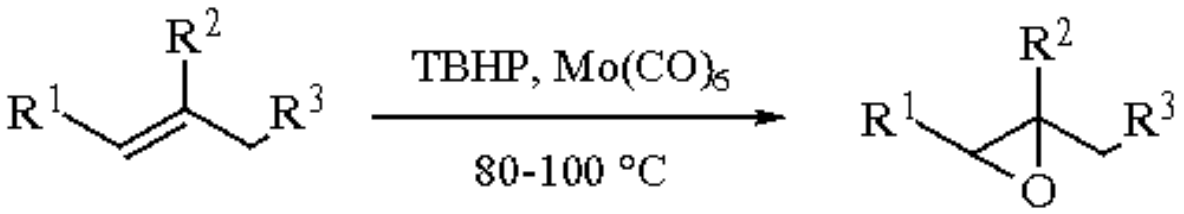

(11)

Epoxidations of alkenes in compounds containing other functional groups can also be accomplished using TBHP with a molybdenum catalyst (eq 12).[19,20] For nonconjugated dienes, more highly substituted alkenes can be selectively epoxidized over less substituted alkenes. Conjugated dienes are less susceptible to epoxidation than isolated alkenes, but the regioselectivity for the different double bonds of a conjugated system follows the same pattern as that for isolated alkenes (eq 13).

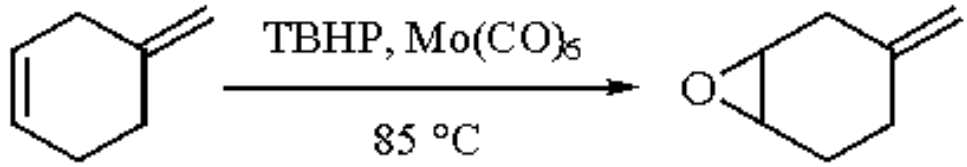

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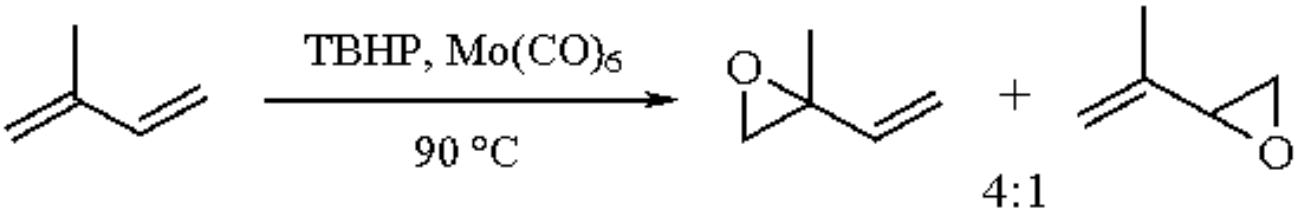

(13)

Epoxidations of compounds with functional groups in the allylic position can also be effected using TBHP and a molybdenum or vanadium catalyst, but the yields are not as high as those for isolated double bonds, and longer reaction times are required.[21] TBHP epoxidizes the alkenes of allylic and homoallylic alcohols stereoselectively with either molybdenum or vanadium catalysts (eqs 14 and 15).[21] With acyclic systems, vanadium-catalyzed epoxidations give predominantly the *erythro* product, and molybdenum-catalyzed epoxidations give predominantly the *threo* product.[22]

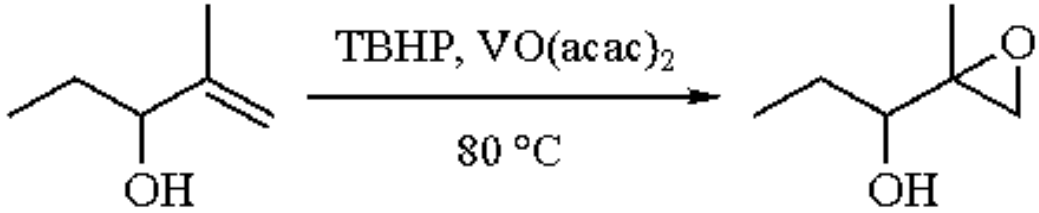

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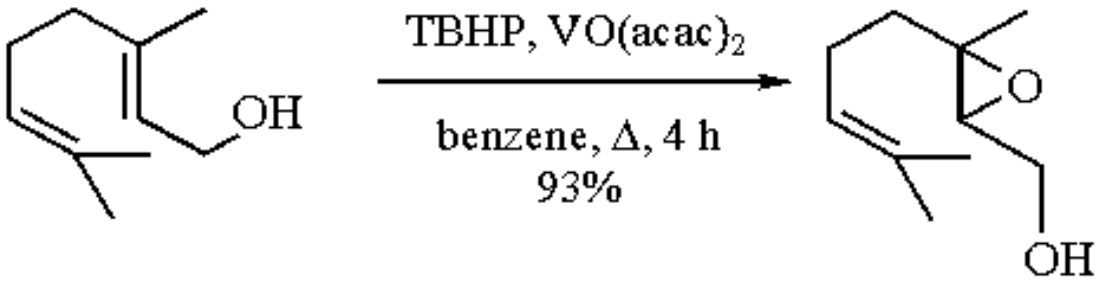

(15)

98% isomeric purity

For cyclic systems, vanadium- and molybdenum-catalyzed reactions give predominantly the *cis* product (eq 16).[23] There are several factors that can affect the selectivity of this reaction for cyclic allylic alcohols. With increasing ring size, the selectivity decreases slightly for vanadium-catalyzed reactions, and more dramatically for molybdenum-catalyzed reactions. The selectivity was also observed to be better for cyclic allylic alcohols where the hydroxyl is in a quasi-axial position.

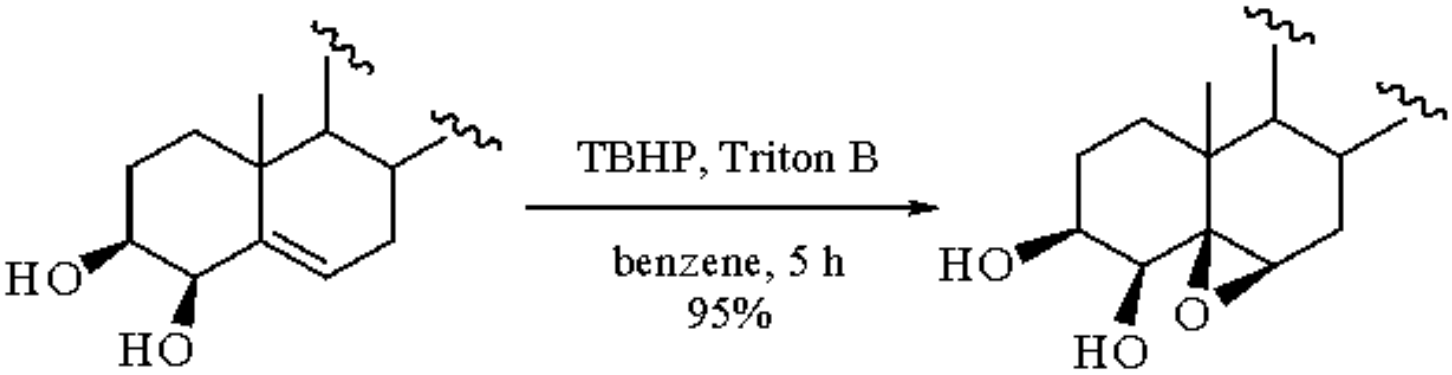

(16)

>95% isomeric purity

The epoxidation of α,β-unsaturated ketone and aldehyde compounds is accomplished by TBHP in the presence of catalytic amounts of Triton-B (***Benzyltrimethylammonium Hydroxide***) (eq 17).[24] This method has also been used for the synthesis of mono- and diepoxy-1,4-benzoquinones (eq 18).[25]

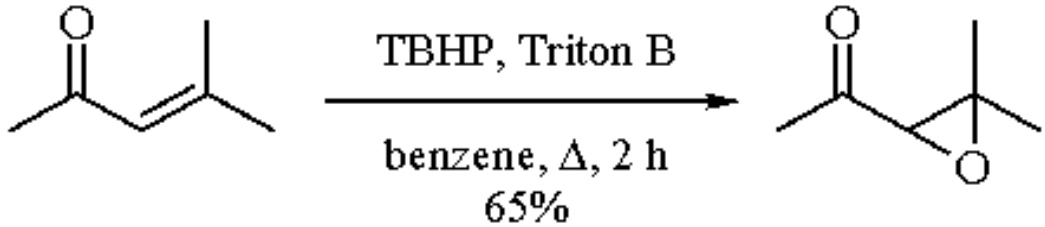

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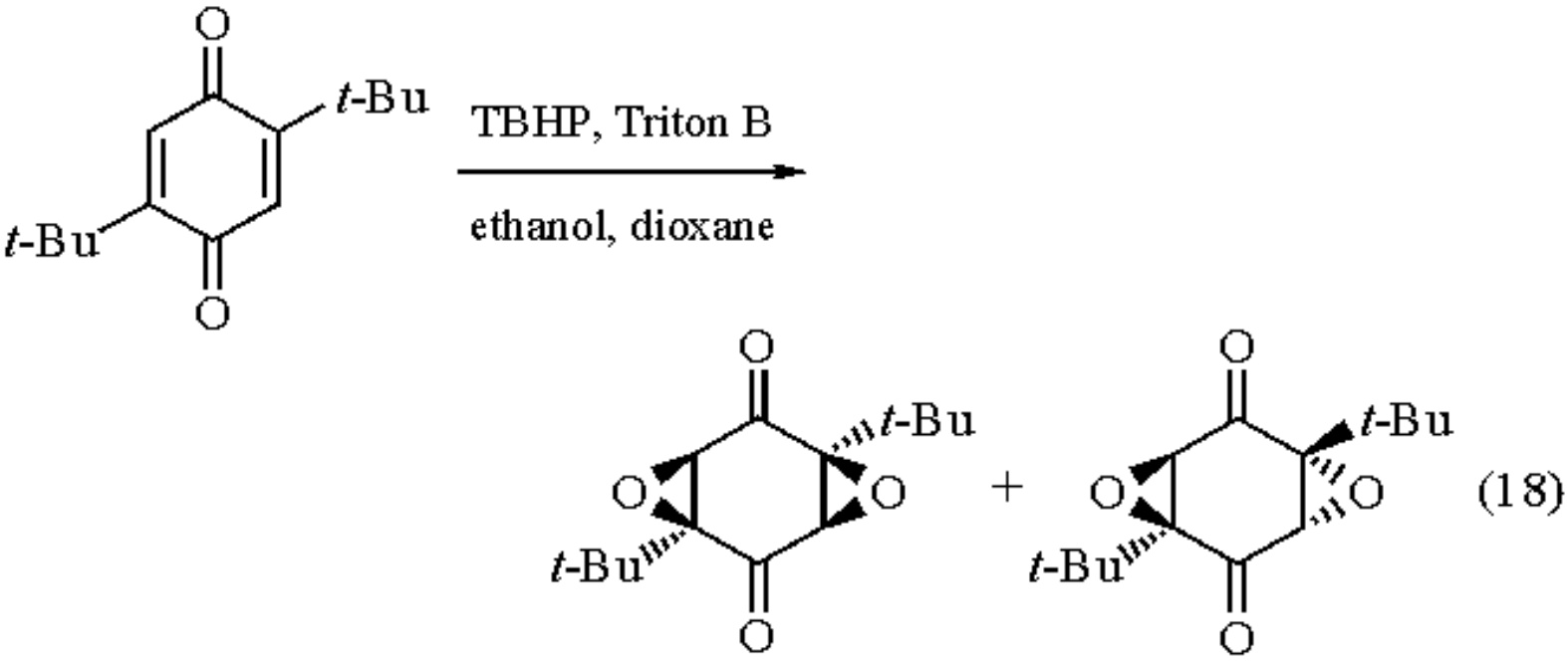

Cyclic allylic alcohols conjugated to a second alkene react with TBHP catalyzed by vanadium to give not the epoxy but a bicyclic ether and new allylic alcohols, with the oxygen bridging the original allylic alcohol to the terminus of the conjugated diene (eq 19).[26]

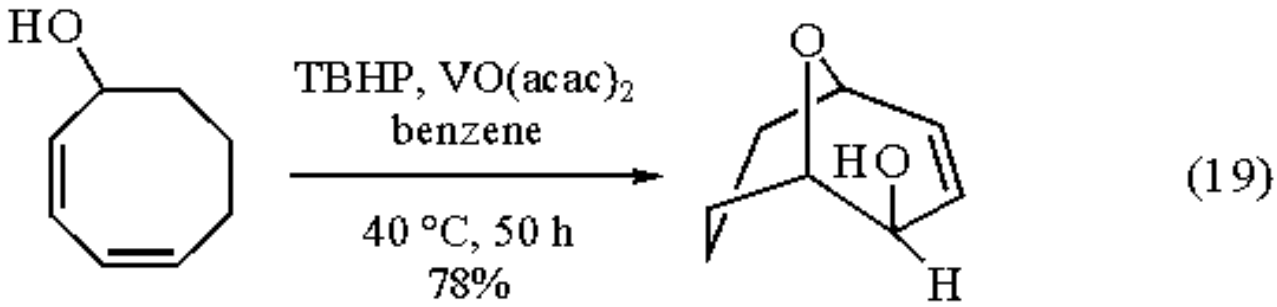

Stereoselective epoxidation of unactivated alkenes can be effected by remote chiral auxiliaries in the presence of molybdenum or vanadium catalysts. The configuration of the remote alcohol determines which face of the alkene is epoxidized (eq 20).[27]

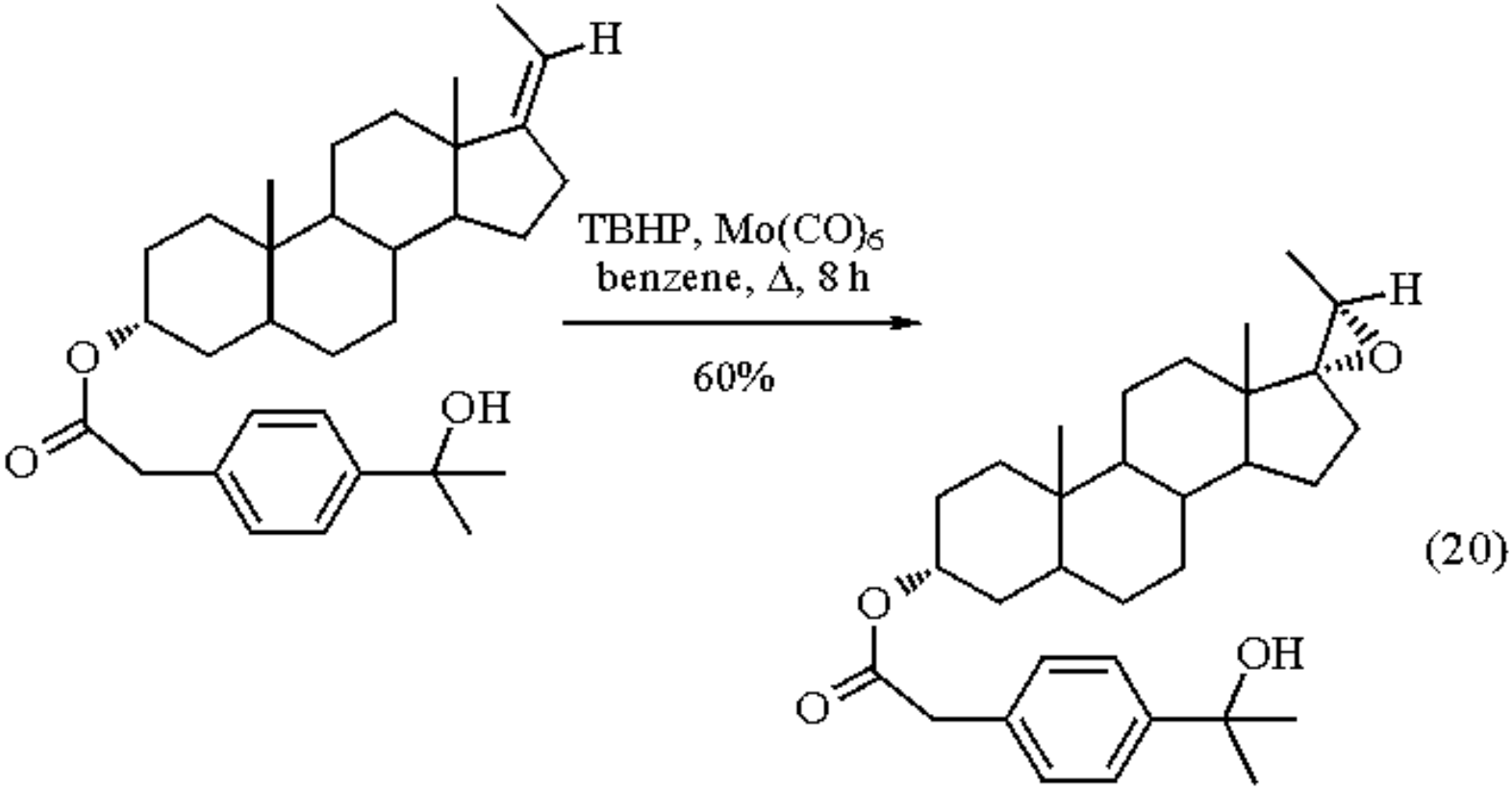

Allylic alcohols can be asymmetrically epoxidized with TBHP and stoichiometric quantities of a titanium-diethyl tartrate complex, generated in situ.[28] Either enantiomer can be formed by using either (+)- or (-)-diethyl tartrate, or by varying the ratio of titanium catalyst to (+)-diethyl tartrate (eq 21), because the nature of the titanium catalyst changes as the molar ratio of titanium to tartrate changes. This latter method is generally preferred due to the ready availability and relatively low cost of (+)-diethyl tartrate. In the presence of 3Å or 4Å molecular sieves, the titanium/tartrate complex may be used in catalytic quantities, but with somewhat lower product enantiomeric purities.[29] These methods can also be used for the stereospecific epoxidation of homoallylic alcohols, but in lower degrees of enantiomeric purity, because the hydroxyl group is further away from the reacting center, lessening its directing effec ts.[30]

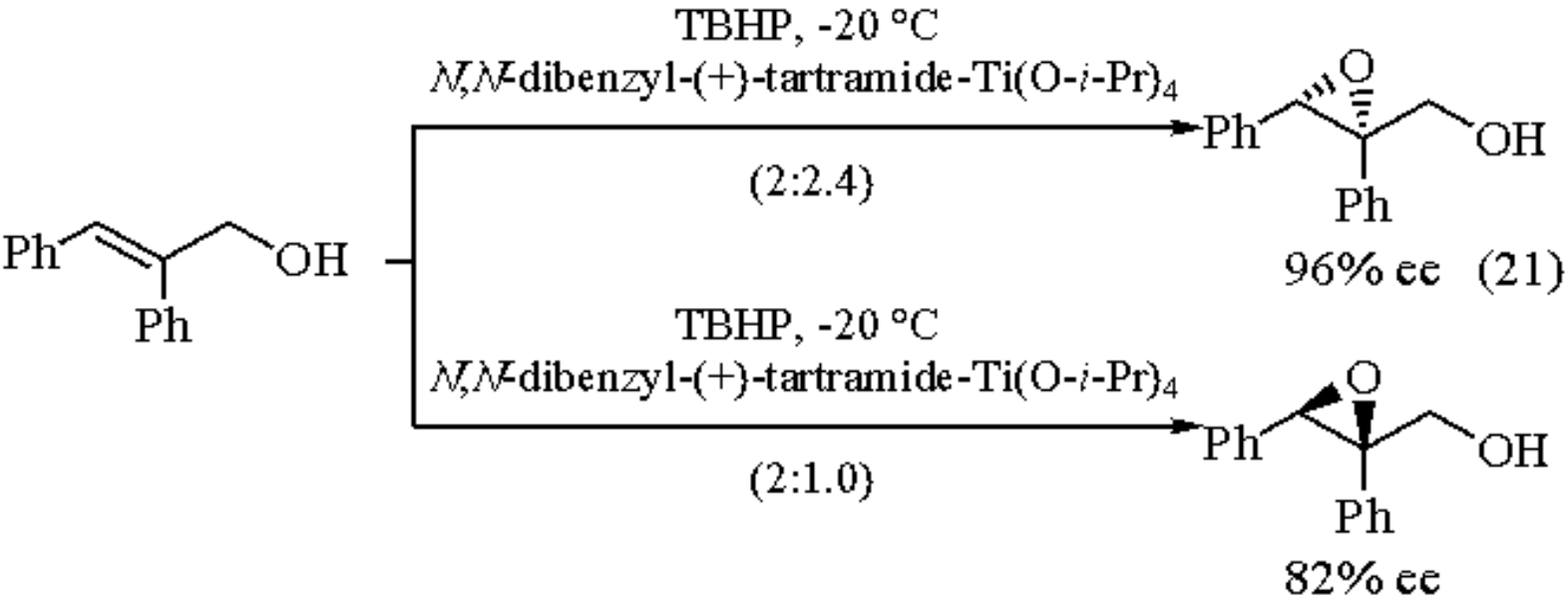

The use of TBHP and a titanium/tartrate complex in either stoichiometric or catalytic quantities is known as the

Sharpless asymmetric epoxidation.[1] This method gives better stereo- and enantioselectivity than epoxidations using peroxy acids. Asymmetric epoxidations can be carried out using other transition metal catalysts and chiral ligands, but the enantioselectivities are not as high.[31] The Sharpless asymmetric epoxidation can also be used for the kinetic resolution of allylic alcohols.[32]

Asymmetric epoxidations of simple alkenes can be accomplished by Sharpless epoxidation of alkenylsilanols.[33] The alkenylsilanols are prepared from lithium alkenes, and after the Sharpless epoxidation the silyl group is removed by fluoride ion to give the simple epoxide (eq 22). Asymmetric epoxidations can also be done on alkenes without other functional groups using optically active diols as the solvent, but the ee values are generally very low.[34]

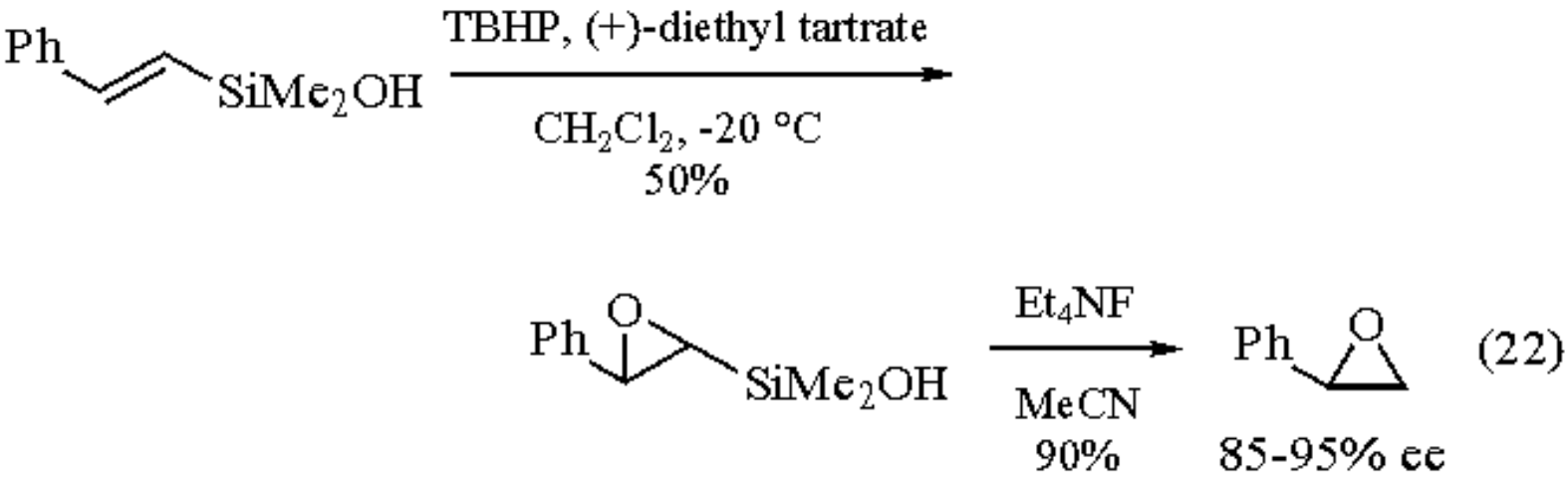

Epoxidation of vinyl allenes by TBHP and ***Vanadyl Bis(acetylacetonate)*** catalyst leads to the formation of cyclopentenones (eq 23).[35] The intermediate in this reaction is an epoxide of the allene. The stereochemistry of the double bond can be retained. The stereoselectivity is kinetic in nature, and can be lost due to epimerization of the kinetic product if the reaction is continued for long periods of time.

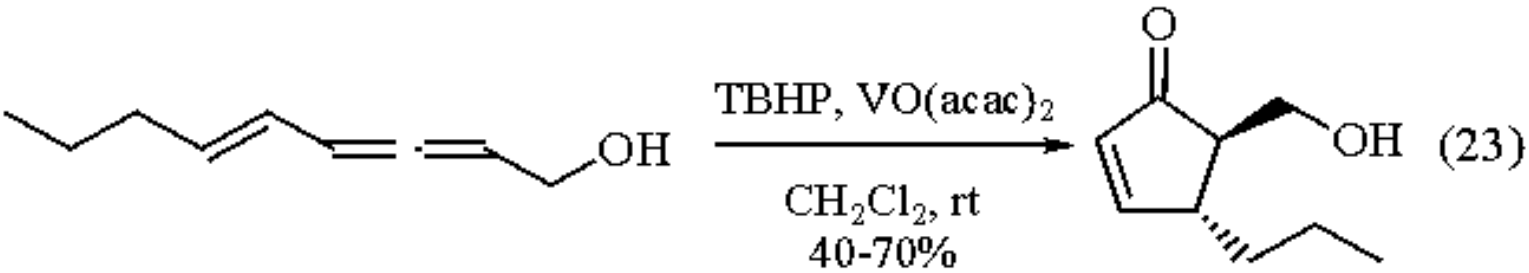

Other Reactions with Alkenes.

Double bonds of silyl enol ethers can be oxidatively cleaved to the corresponding ketones or carboxylic acids using TBHP with $MoO_2(acac)_2$ as a catalyst (eq 24).[36] The ease with which enols can be generated regiospecifically makes this a very powerful method in organic synthesis. This reaction selectively cleaves the double bond of silyl enol ethers in the presence of other double bonds within the molecule.

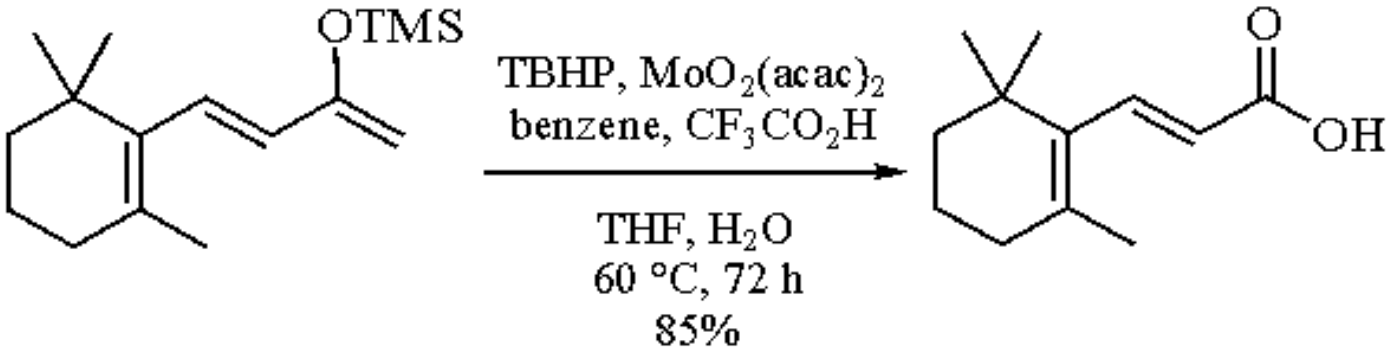

(24)

The alkenes of allylic alcohols can also be cleaved under these conditions (eq 25).[37] In addition to cleaving the double bond of the allylic alcohol, the single bond between the alkene carbon and the allylic carbon bearing the hydroxyl group is also cleaved under these conditions. Vicinal diols are also cleaved to give the corresponding ketones or carboxylic acids (eq 26).[38]

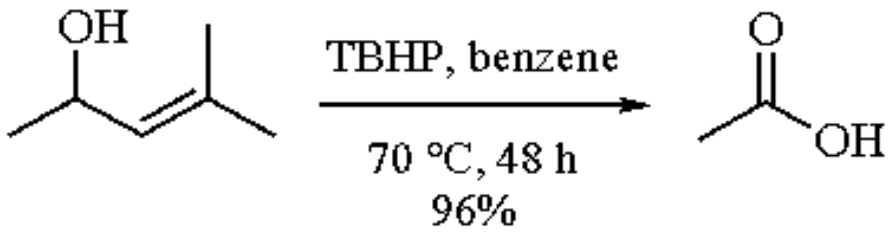

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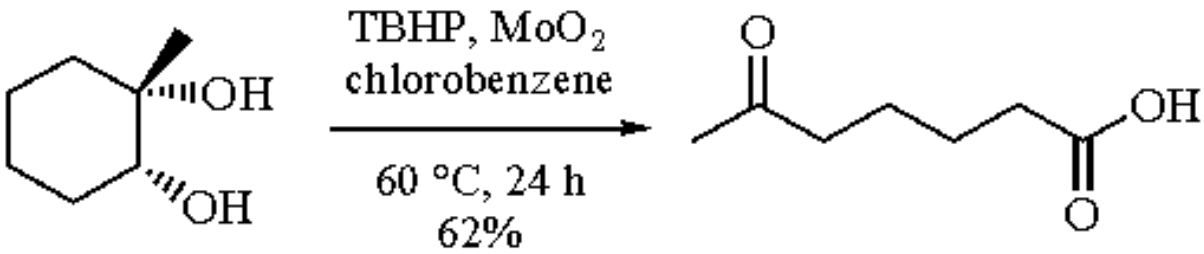

(26)

Oxidation of α,β-unsaturated esters and ketones with palladium-catalyzed TBHP gives β-keto esters or 1,3-diketones (eq 27).[39] Hydrogen peroxide can also be used as the oxidant for this reaction.

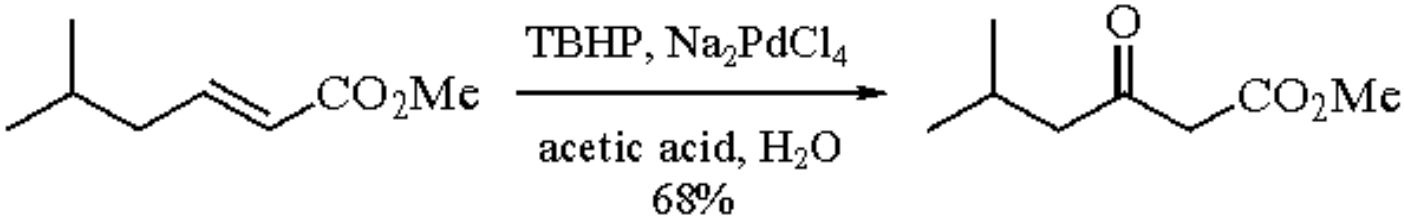

(27)

Under basic conditions, TBHP can add in Michael fashion to a double bond that has an electron withdrawing group attached (eq 28).[40]

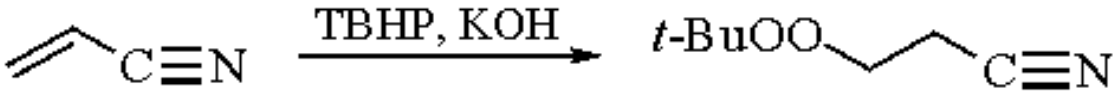

(28)

Reactions with Other Functional Groups.

Oxidation of Alcohols.[1,2]

In the presence of catalytic amounts of diphenyl diselenide, TBHP oxidizes benzylic and allylic alcohols to the corresponding ketones (eq 29).[41] Saturated alcohols can be oxidized to the corresponding carbonyl compounds as well if bis(2,4,6-trimethylphenyl) diselenide is used as the catalyst and a small amount of a secondary or tertiary amine is present. These conditions do not affect other double bonds present in the substrate. This system can also be used for the oxidation of α-hydroxy selenides and thiols, selectively oxidizing the hydroxy function to the carbonyl.

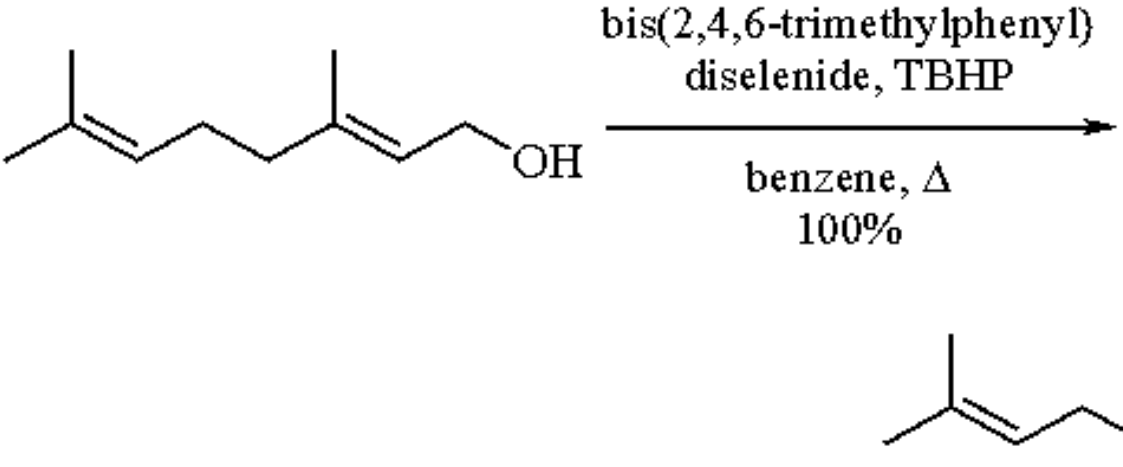

(29)

Saturated alcohol oxidation can also be achieved without oxidizing alkenes by the reaction of the alcohol with TBHP and benzyltrimethylammonium tetrabromooxomolybdate (BTMA-Mo) as a catalyst, and secondary alcohols will be oxidized preferentially over primary ones under these conditions (eq 30).[42] If the reaction time is lengthened, primary alcohols will be converted to the appropriate acid derivative depending upon the conditions used. Using $VO(acac)_2$ as the catalyst will oxidize secondary alcohols over primary ones selectively as well.[43]

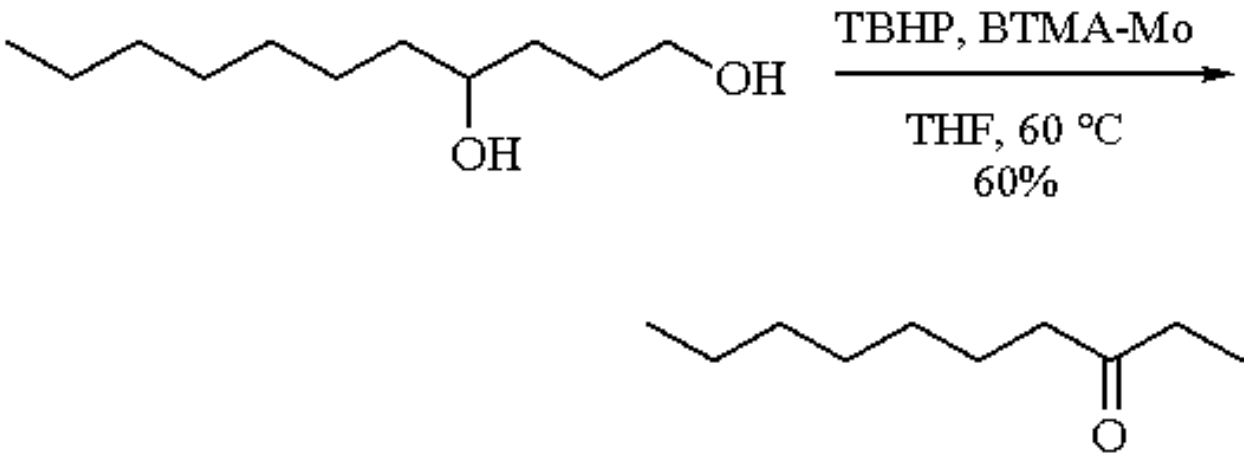

(30)

Oxidation of alcohols can also be done using TBHP and a chromium(VI) catalyst (eq 31).[44] This system works best for allylic, benzylic, and propargylic alcohols, and will selectively oxidize these in the presence of other alcohols.

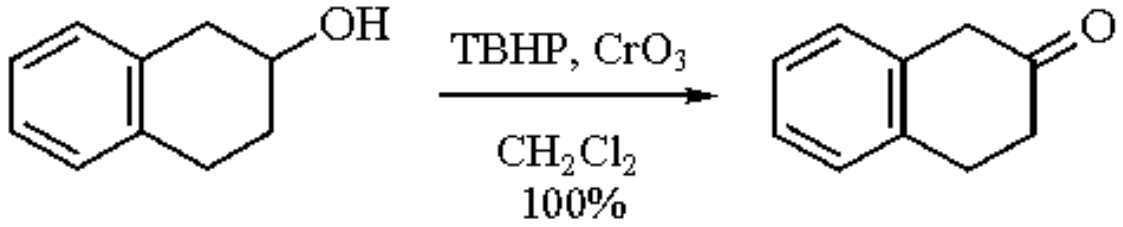

(31)

Oxidation of Sulfur-Containing Compounds.[2]

Sulfides can be oxidized with TBHP to give sulfoxides.[45] If vanadium, molybdenum, or titanium catalysts are used, the addition of one equiv of TBHP will furnish the sulfoxide, while the use of excess TBHP will oxidize the sulfide to the sulfone (eqs 32 and 33). In the absence of metal catalysts the oxidation cannot be carried beyond the sulfoxide.[46] If only one equivalent of TBHP is used, sulfides will be preferentially oxidized over any alkenes present; however, excess TBHP will also oxidize alkenes. The oxidation of thiols with TBHP and Mo^{VI} or V^{V} catalysts produces sulfonic acids (eq 34).[47]

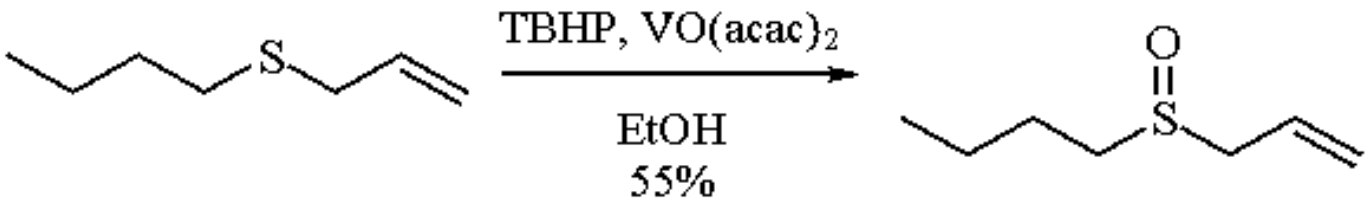

(32)

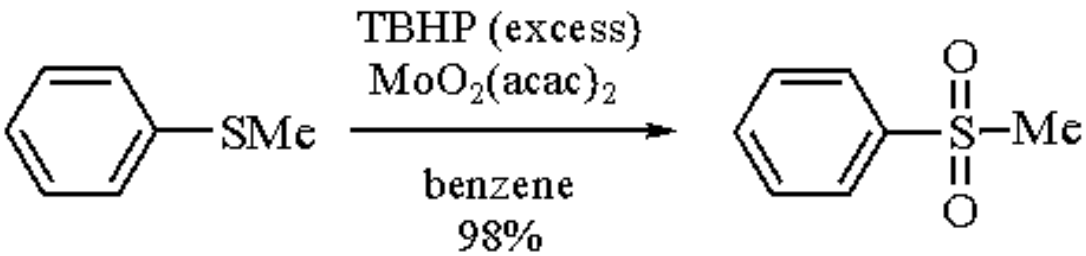

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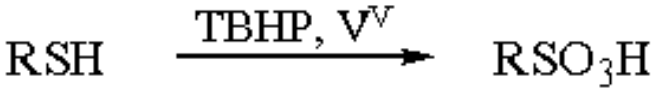

(34)

Using Sharpless asymmetric epoxidation conditions (see above), modified by the addition of one mol equiv of water, unsymmetrical sulfides could be asymmetrically oxidized to sulfoxides (eq 35).[48] Asymmetric oxidations of sulfides to sulfoxides have also been carried out using optically active diols with TBHP and a molybdenum catalyst, but the enantioselectivities were very low (~10%).[49]

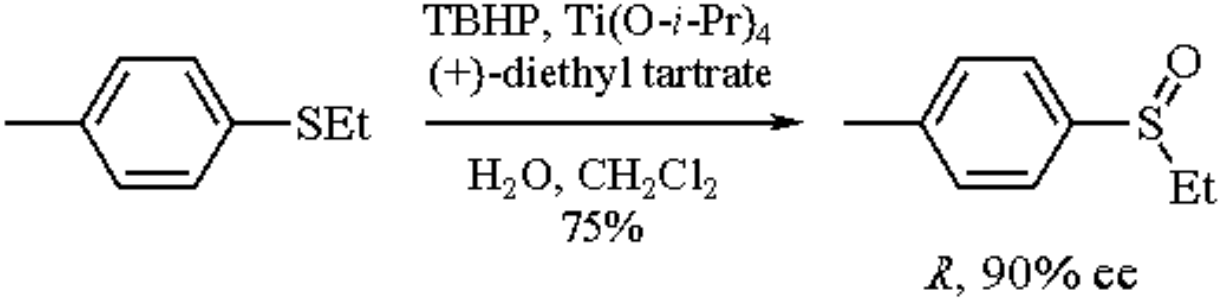

(35)

Oxidation of Phosphines.

Alkyl phosphines can be oxidized to the appropriate phosphine oxides by TBHP (eq 36).[50]

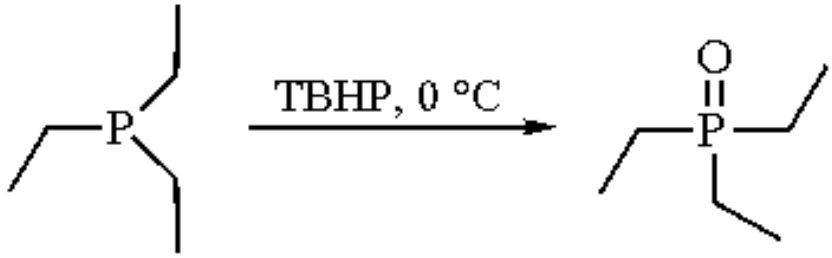

(36)

Oxidation of Selenides and Selenoxides.

Alkenes can be produced oxidatively from selenides, through the selenoxides and elimination. This is done by stirring TBHP with basic alumina and the appropriate selenide (eq 37).[51] This transformation can also be accomplished by treatment of the selenide with ***Hydrogen Peroxide***, ***Ozone*** followed by ***Triethylamine***, periodate, or peroxy acids.

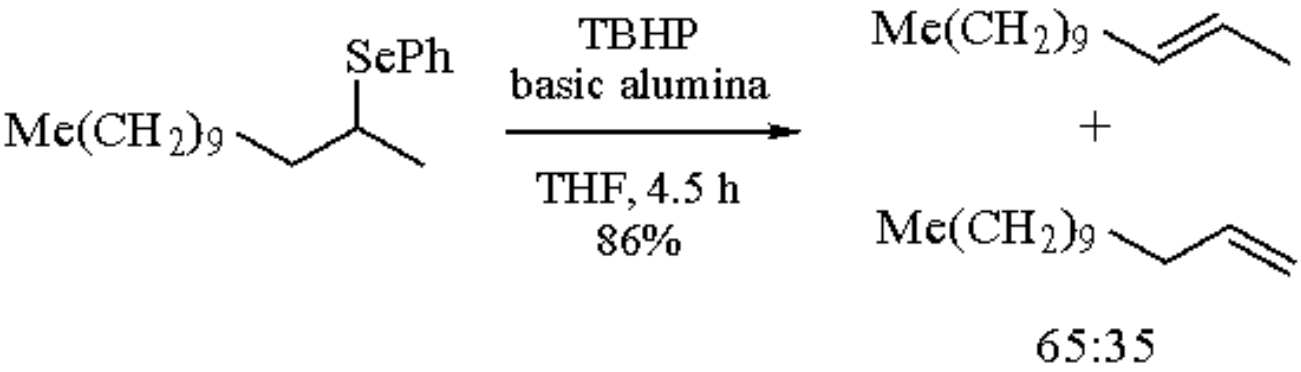

(37)

Oxidation of Nitrogen-Containing Compounds.[2]

Reactions of TBHP with compounds containing nitrogen have been used to effect a variety of oxidations, both of the nitrogen atom itself and of adjacent carbon atoms. Tertiary amines react with TBHP in the presence of vanadium and molybdenum catalysts to give amine oxides (eq 38).[52] This transformation can also be done with cumene and pentene hydroperoxides.

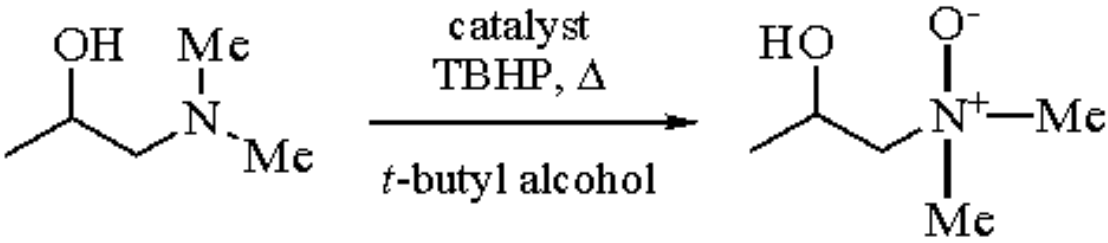

(38)

Secondary amines are oxidized to imines by TBHP in the presence of ruthenium(II) catalysts (eq 39).[53] Tertiary amines

are oxidized by TBHP in the presence of ruthenium catalyst to give α-(*t*-butyldioxy)alkylamines, which decompose to iminium ion intermediates when treated with acid (eq 40).[54] *N*-Methyl groups are selectively oxidized when other *N*-alkyl or -alkenyl groups are present.

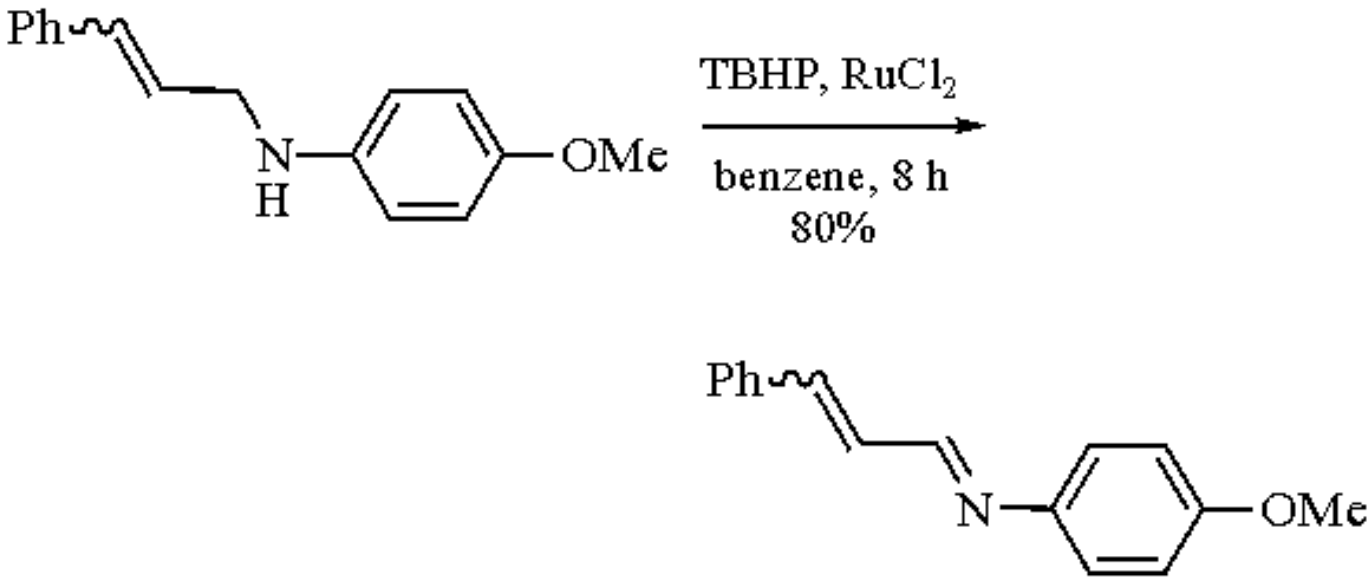

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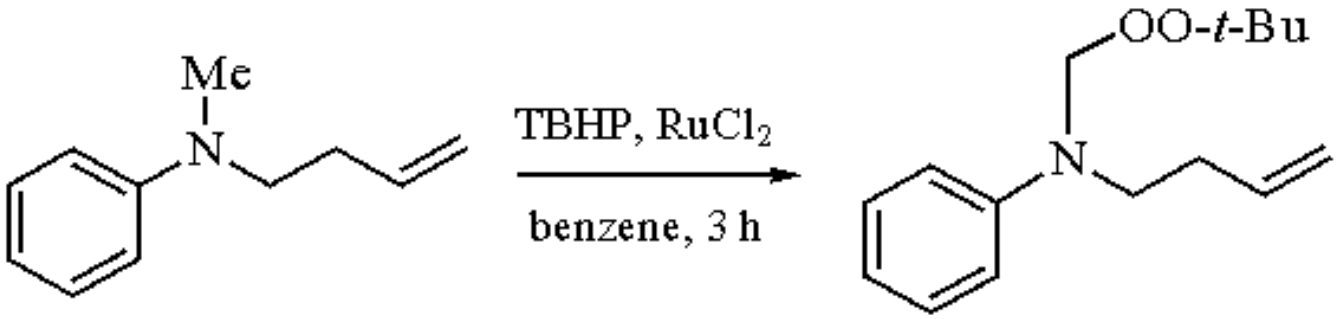

(40)

Amides are selectively oxidized to imides by TBHP, and other hydroperoxides, in the presence of cobalt or manganese salts as catalysts (eq 41).[55] The selectivity of this transformation is demonstrated by the oxidation of 3-ethoxycarbonyl-2-piperidone to the appropriate imide, with no other oxidation products. ***Peracetic Acid*** also effects this transformation, in many cases giving better yields and shorter reaction times, but the conditions for oxidation with TBHP are milder. Oxidation of amides with TBHP catalyzed by ruthenium gives the corresponding *t*-butylperoxy amide (eq 42).[56]

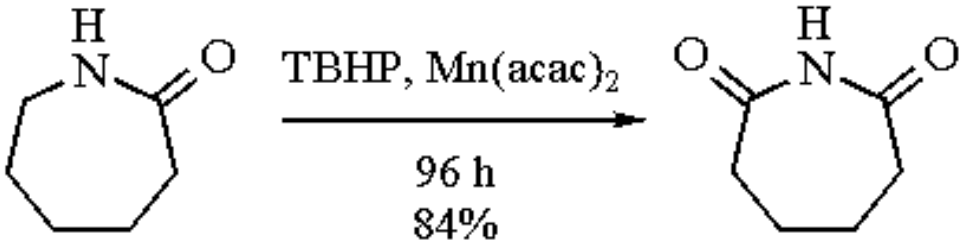

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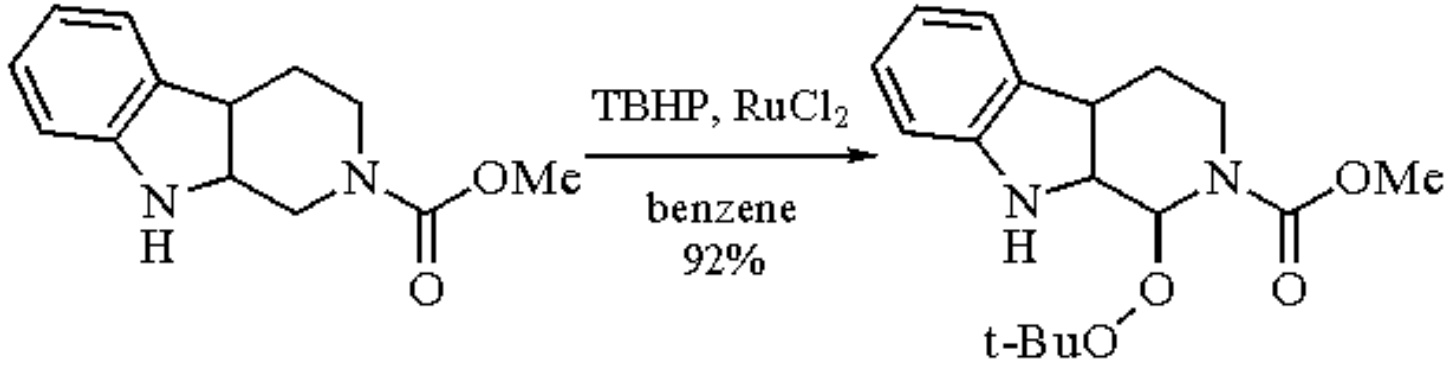

(42)

Nitronate anions, formed by deprotonation of nitro compounds, react with TBHP catalyzed by $VO(acac)_2$ or ***Hexacarbonylmolybdenum*** to give 1-hydroxy nitro compounds (eq 43). Analogous to α-hydroxyl carbonyl compounds, these collapse to give the carbonyl derivative and nitrous acid.[57]

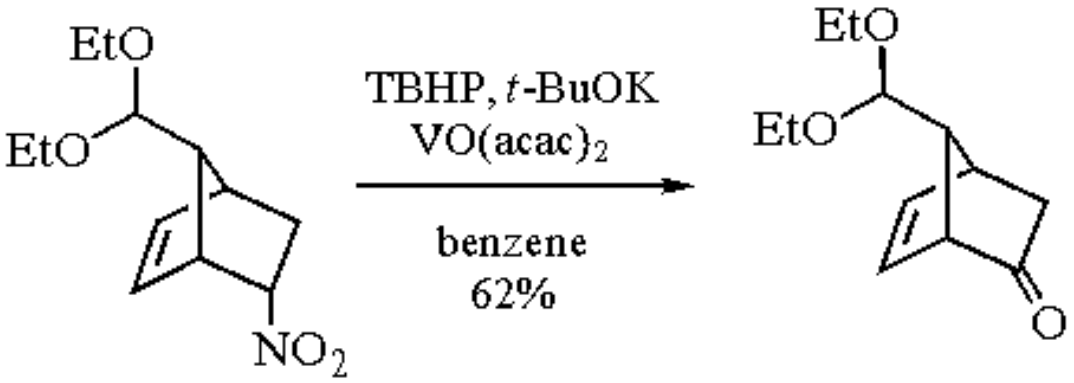

(43)

Introduction of Peroxy Groups into Organic Molecules.[58]

Using catalytic amounts of copper, cobalt, or manganese salts, TBHP reacts with molecules that contain a slightly activated carbon-hydrogen bond, replacing the activated hydrogen with a peroxy group. This transformation can also be accomplished with other hydroperoxides. Carbon-hydrogen bonds α to an alkene (eqs 44 and 45),[59,60,61] phenyl groups,[60] carbonyls,[61] nitriles,[62] oxygen,[60,61] or nitrogen (eq 46)[63] atoms are activated towards this reaction. The primary function of the metal salts in these reactions is to initiate decomposition of the hydroperoxide.

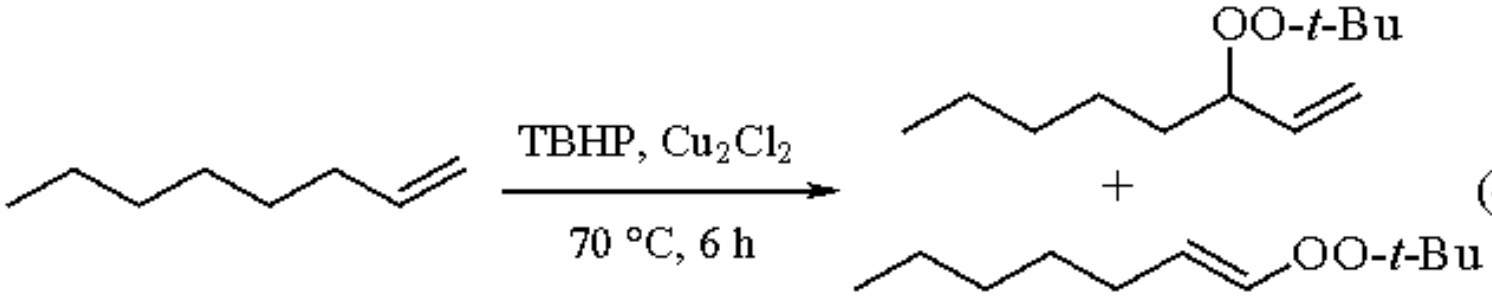

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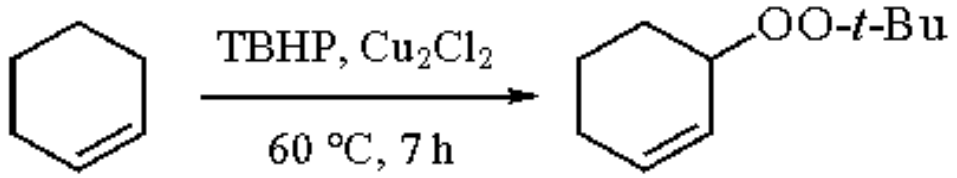

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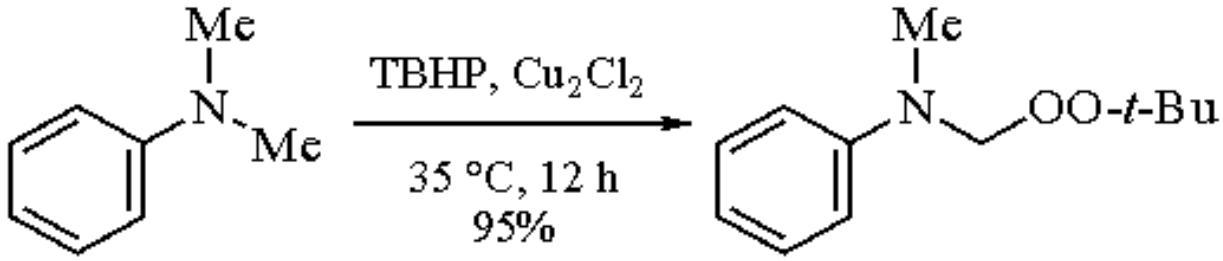

(46)

Peroxy groups may also replace alcohols (eq 47),[64] ethers,[65] or sulfates[66] directly, or be added to an alkene (with Markovnikov regioselectivity),[9] by reacting the functionalized organic compound with TBHP and concentrated sulfuric acid in acetic acid. Epoxides are transformed into β-hydroxy dialkyl peroxides using TBHP in the presence of base (eq 48).[67]

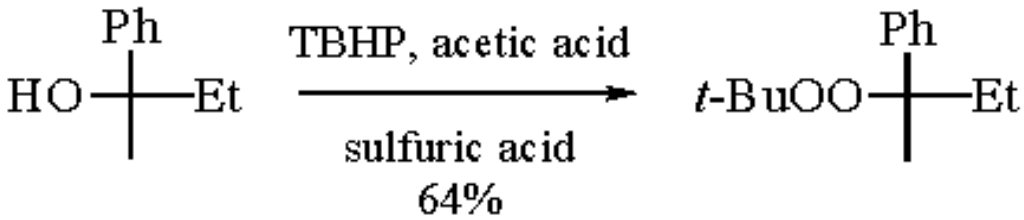

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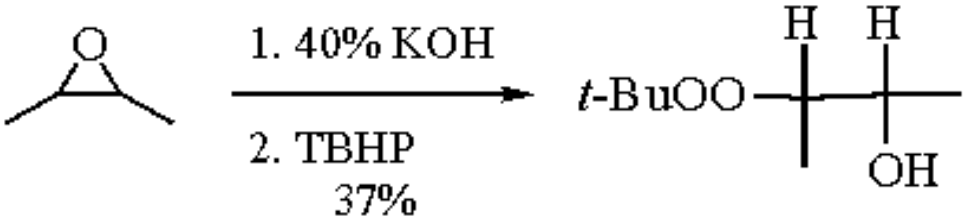

(48)

Peroxy *t*-butyl organosilanes can be prepared by reacting TBHP with the appropriate silyl chloride and pyridine, ammonia, or triethylamine (eq 49).[68] Peroxides of a number of other heteroatoms in organic compounds, such as germanium,[69] boron,[70] cadmium,[71] tin,[72] aluminum,[73] and mercury,[74] can also be synthesized using TBHP.

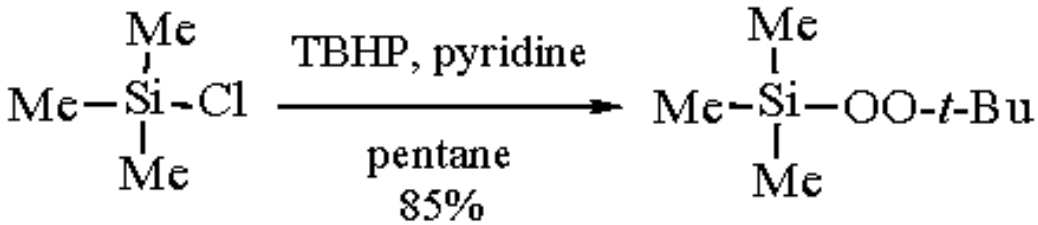

(49)

2,4,6-Substituted phenols react with TBHP to give 2- or 4-(*t*-butylperoxy)-2,4,6-trisubstituted quinones if the 4-substituent is not a methyl group, and 3,5,3´,5´-tetrasubstituted stilbene-4,4´-quinones if the 4-substituent is a methyl group (eq 50).[75]

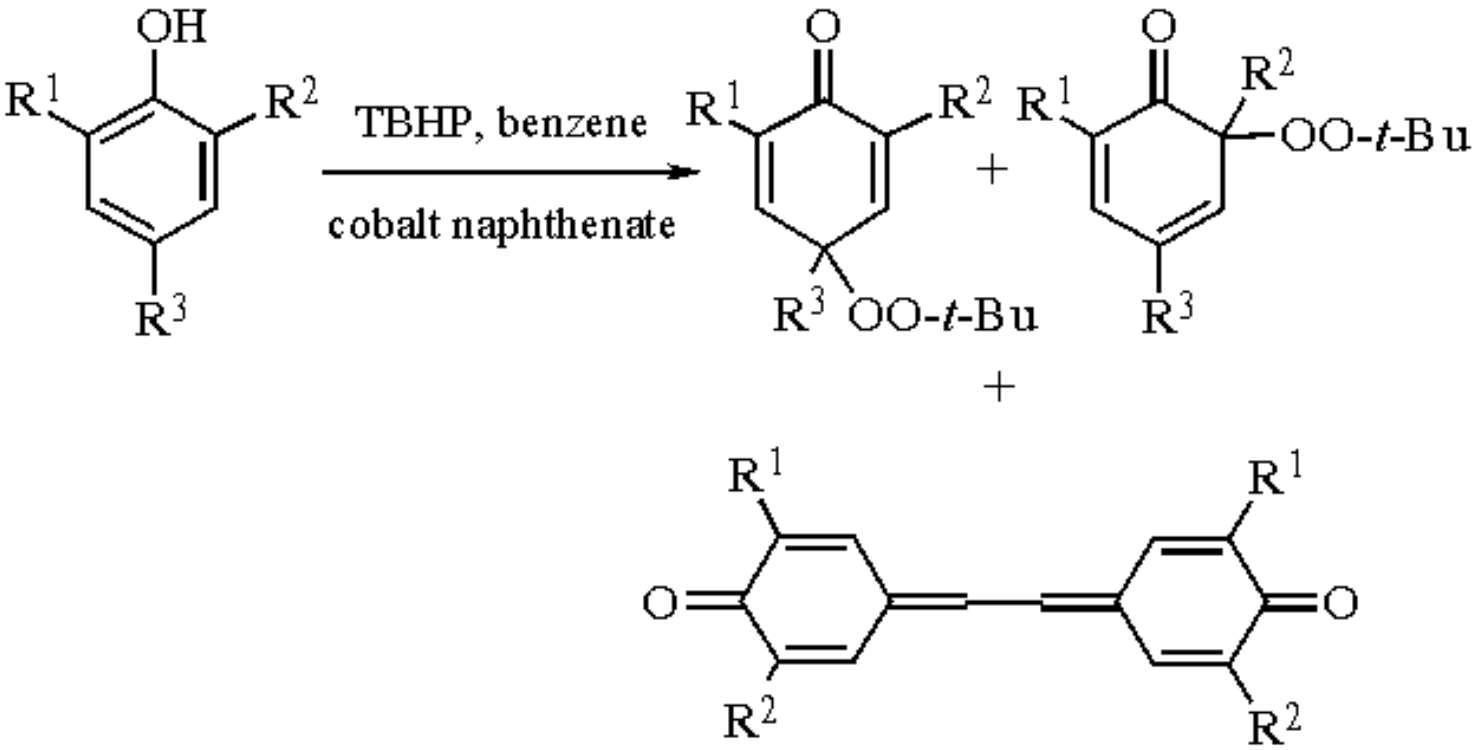

Reactions with Carbonyl Compounds.

Aldehydes react with TBHP in the presence of catalytic amounts of copper, cobalt, or manganese salts to give the *t*-butyl ester (eq 51).[76] In the absence of a metal catalyst, benzaldehyde will react with TBHP to give a mixture of the *meso* and racemic forms of benzopinacol dibenzoate.

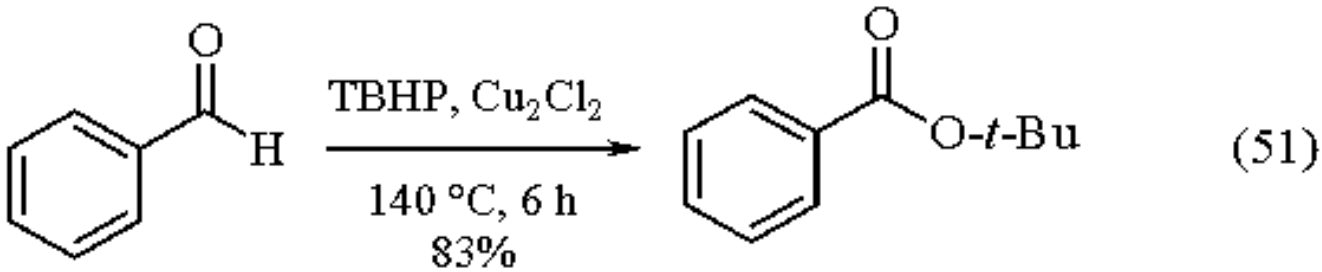

TBHP reacts with acid chlorides under basic conditions to give the appropriate *t*-butyl peroxy ester.[77] For small acids, 30% KOH is used, but for longer-chain acids, pyridine is substituted as the base (eq 52).[78] The use of pyridine as the base in this reaction allows the synthesis of carbamate peroxy esters from isocyanates and carbamic acid chlorides (eq 53).[79]

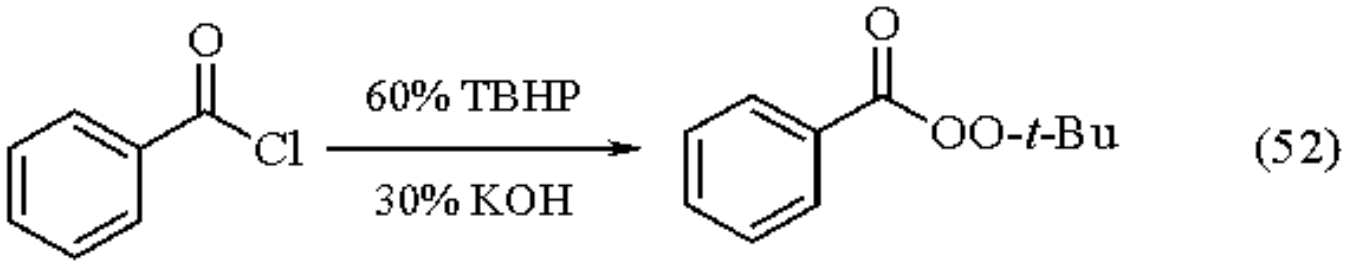

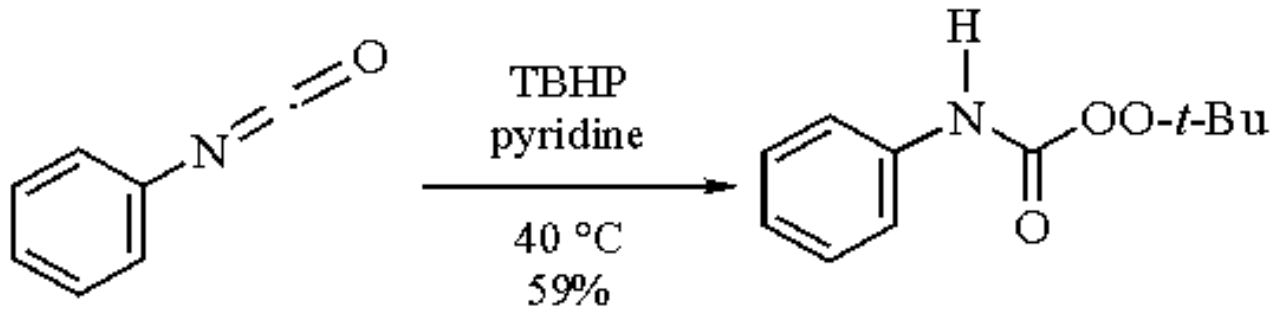

(53)

TBHP reacts with ketones or aldehydes in the presence of a strong acid catalyst to give products with diperoxy groups in place of the carbonyl (eq 54), or in the absence of the acid catalyst to give an α-hydroxyl *t*-butyl peroxide (eq 55).[80]

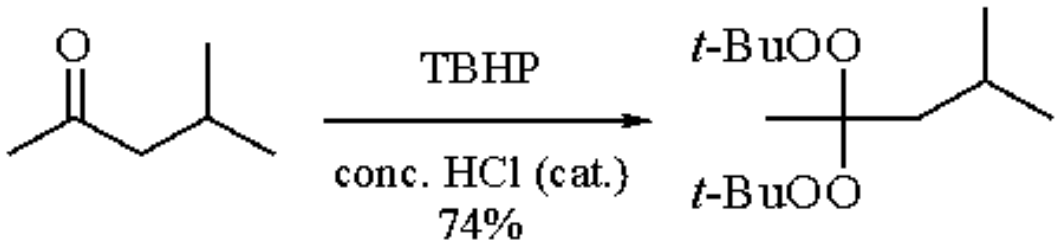

(54)

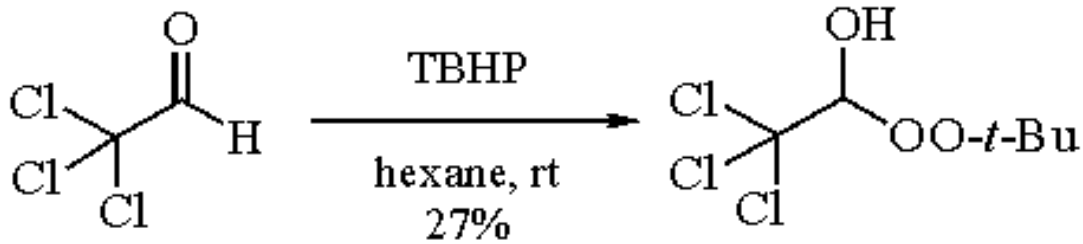

(55)

Conversion of Halides to Alcohols.

Grignard reagents react with TBHP to give the appropriate alcohol or phenol (eq 56).[81] This provides an alternative method for the conversion of halides to alcohols or phenols. Because the hydrogen of the peroxide is activated, either two equiv of Grignard reagent must be used or the magnesium salt of the hydroperoxide, prepared from the hydroperoxide and ethylmagnesium bromide.

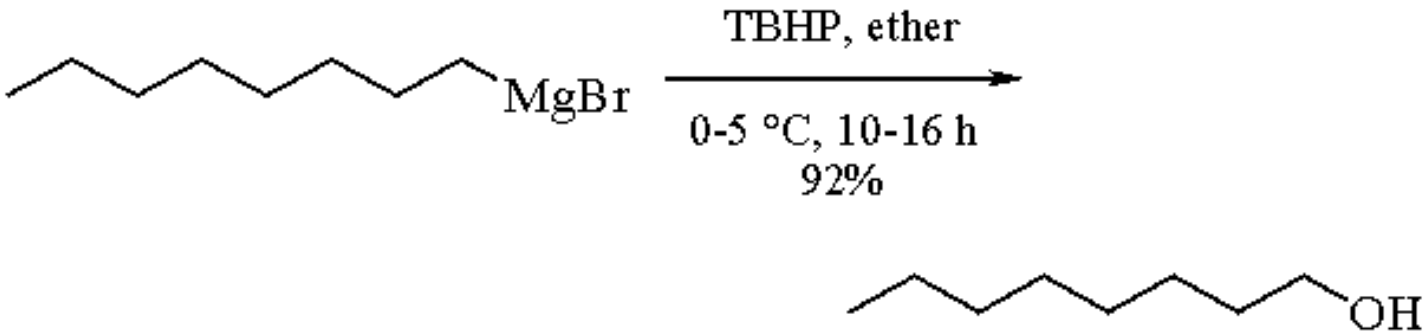

(56)

Conversion of Alcohols to Halides.

In cases where traditional methods fail, alcohols can be converted to halides by a radical chain reaction.[82] This is accomplished by transforming the alcohol into a chloroglyoxylate, reacting it with TBHP, and warming this in the presence of a halogen donor such as CCl_4 or $BrCCl_3$, to initiate a radical reaction where first a *t*-butoxyl radical is eliminated, then CO_2 is eliminated twice in succession, leaving an alkyl radical which then reacts with the halogen donor to give the halide (eq 57).

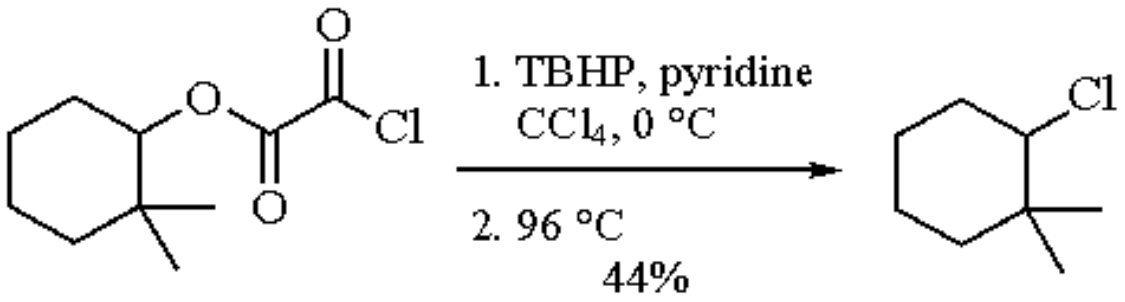

(57)

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N-t-Butylhydroxylamine[1]

***t*-BuNHOH**

[16649-50-6] · $C_4H_{11}NO$ · *N-t*-Butylhydroxylamine · (MW 89.14) (.HCl)

[57497-39-9] · $C_4H_{12}ClNO$ · *N-t*-Butylhydroxylamine Hydrochloride · (MW 125.60)

(condenses with a wide variety of aldehydes to afford *N-t*-butylnitrones;[2] condenses with alkynes to afford *N-t*-butylnitrones;[3] used with phenylacetyl chloride in the synthesis of aziridinones;[4] alkene amination[5])

Physical Data: mp 64-65 °C; hydrochloride, mp 183-185 °C.

Form Supplied in: available commercially as the hydrochloride salt.

Preparative Methods: nitro reduction;[6] oxaziridine hydrolysis;[7-9] amine oxidation.[10]

Purification: recrystallization from pentane.

Handling, Storage, and Precautions: hygroscopic; oxidizes slowly to the nitroso compound.

For a discussion of this reagent, see the entry for ***N-Cyclohexylhydroxylamine***.

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1. For a general review of hydroxylamines see: Roberts, J. S. In *Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D., Ed.; Pergamon: Oxford, 1979; Vol. 2, pp 185-217.
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t-Butyl Hypobromite[1]

***t*-BuOBr**

[1611-82-1] · C_4H_9BrO · *t*-Butyl Hypobromite · (MW 153.02)

(alkoxybromination of alkenes;[2] bromination of alkanes;[3] allylic bromination[4])

Physical Data: bp 44-45 °C/85 mmHg; mp -27 to -28 °C; *d* 1.33 g cm^{-3}.

Solubility: sol ether, CCl_4, CH_2Cl_2.

Analysis of Reagent Purity: the reagent can be assayed by thiosulfate titration of iodine liberated by the addition of the reagent to a solution of KI in aq HCl.[5]

Preparative Methods: prepared in 43% yield on a 0.18 mol scale by addition of *t*-butyl alcohol to a solution of Ag_2SO_4 and bromine in water.[3] The product is isolated by distillation. Since much material is lost during the distillation, many workers have found it more convenient to prepare and use the reagent in solution. In one procedure the reagent is generated in CH_2Cl_2 solution from Hg_2O, bromine, and *t*-butyl alcohol.[6] It has also been prepared from NaBr, NaOCl, *t*-butyl alcohol, and acetic acid.[2]

Handling, Storage, and Precautions: reported[3] to be stable for weeks at 0 °C in the dark. It decomposes at 85 °C, upon irradiation or by washing with 5% aq $NaHCO_3$ solution. It also decomposes upon repeated washing with water. Should be handled in a fume hood.

Alkoxybromination of Alkenes.

t-BuOBr has been used for the alkoxybromination of alkenes,[2,7] though there appears to be little advantage over the use of the more readily available ***Bromine*** or ***N-Bromosuccinimide***. For unsymmetrical alkenes the additions follow Markovnikov's rule. For terminal alkenes, selectivities are on the order of 2:1 (eq 1).

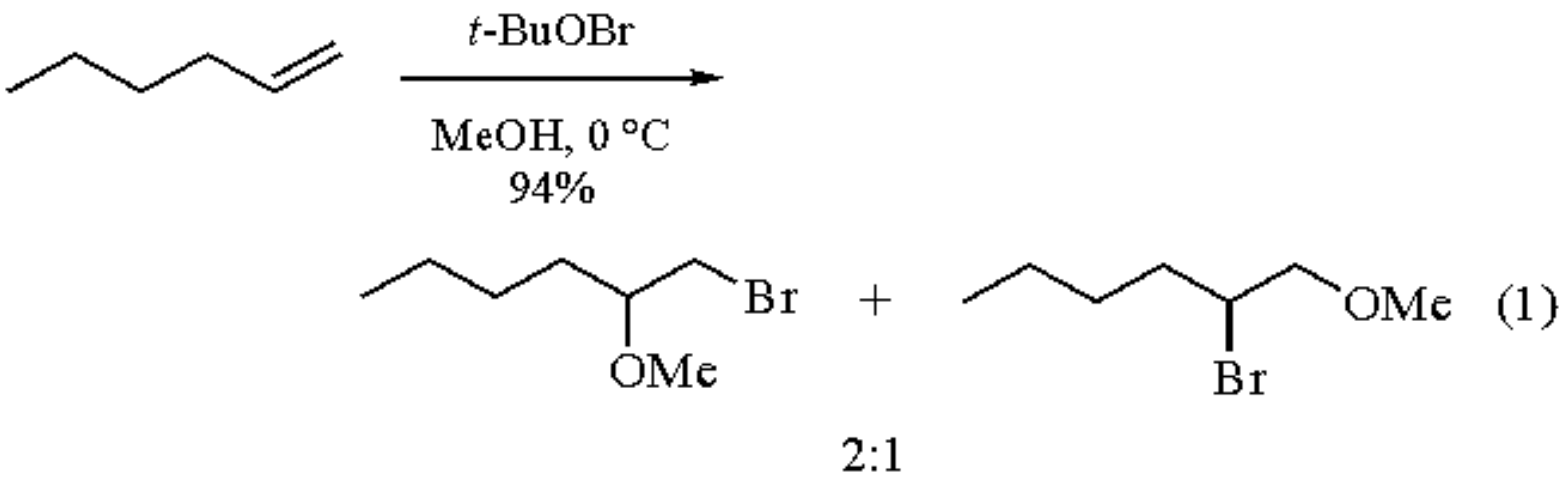

Substituted and unsubstituted 3,4-dihydro-2*H*-pyrans have been alkoxybrominated by this reagent (eq 2).[8] Little diastereoselectivity was seen in substituted examples.

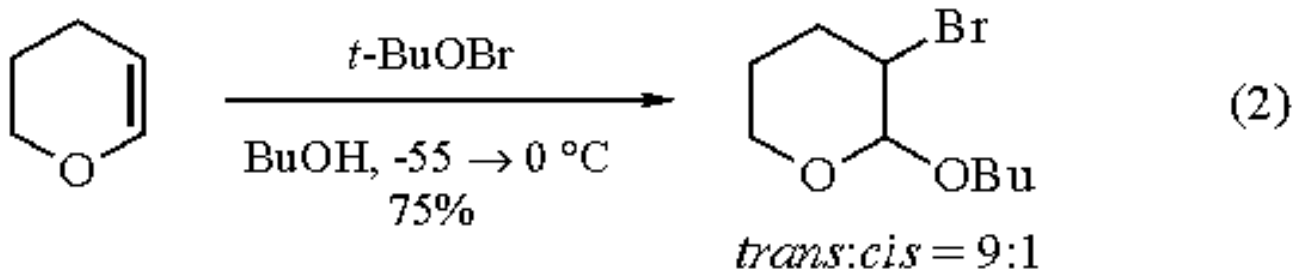

There are a few examples in the literature[9] of the preparation of β-bromo *t*-butyl ethers with this reagent. It has been proposed[10] that it would be possible to catalyze these reactions with ***Boron Trifluoride Etherate***, but no examples have been reported. The analogous chloro[10] and iodo[11] compounds have been prepared from the chloro and iodo reagents.

Bromination of Alkanes.

t-BuOBr has occasionally been used for the radical chain bromination of alkanes.[3] The radical chain carrier in these reactions is the *t*-butoxy radical. This radical is less selective than the bromine radical, and so these reactions often give a more random distribution of products than reagents such as NBS.[12]

Allylic Brominations.

t-BuOBr has occasionally been used for allylic bromination reactions. Alden and Davies reported[4] that the allylic bromination of 2-methylenebicyclo[2.2.1]heptane with *t*-BuOBr gives only the *exo* diastereomer (eq 3), whereas NBS gives *exo*/*endo* mixtures.

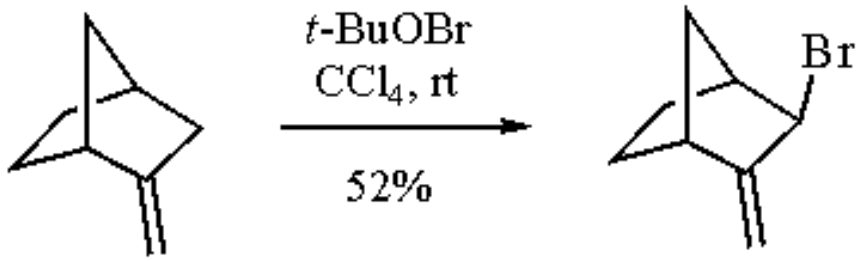

(3)

Other Applications.

t-BuOBr has been used to brominate nitroalkanes,[13] for aromatic bromination,[14] and for bromolactonizations.[15]

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Bruce L. Finkelstein

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t-Butyl Hypochlorite[1]

***t*-BuOCl**

[507-40-4] · C_4H_9ClO · *t*-Butyl Hypochlorite · (MW 108.57)

(reagent for ionic[2] or radical[3] chlorination of hydrocarbons; *N*-chlorination;[4] oxidation of alcohols,[5] sulfides,[6] and selenides[7])

Physical Data: bp 79.6 °C/750 mmHg; *d* 0.9583 g cm^{-3}.

Solubility: sparingly sol H_2O; sol alcohol, CCl_4, and $CHCl_3$.

Form Supplied in: commercially available as neat liquid.

Preparative Method: usually prepared by the method of Mintz and Walling.[8]

Purification: distillation is possible but can be hazardous, and is reported not to improve purity.

Handling, Storage, and Precautions: avoid exposure of the reagent to light; store protected from light in a refrigerator or freezer.

Radical Chlorination.

Under typical radical conditions, *t*-BuOCl can effect chlorination of a range of substrates, including alkanes, alkenes, ethers, epoxides, and aldehydes.[3] Reaction occurs by hydrogen abstraction from the substrate by the *t*-BuO&bdot; radical, this process showing the expected selectivity pattern of primary < secondary < tertiary (eq 1).[3a,c] The reaction can be initiated by irradiation or by the use of chemical initiators such as ***Azobisisobutyronitrile***[3a] or trialkylboranes.[3c] Reaction with alkenes results in allylic chlorination,[3d,e] whereas ethers[3b] and epoxides[3f] give products arising from attack at the position α to oxygen (eqs 2 and 3) and aldehydes give the corresponding acid chlorides (eq 4).[3b]

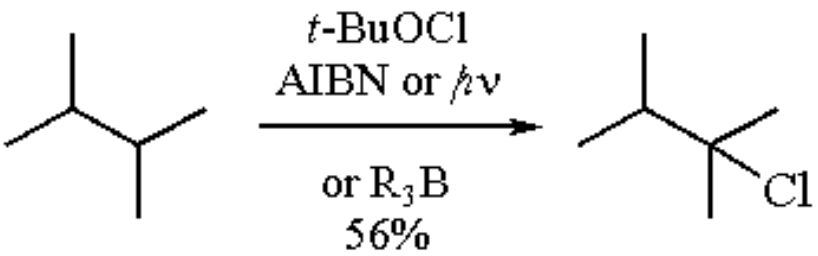

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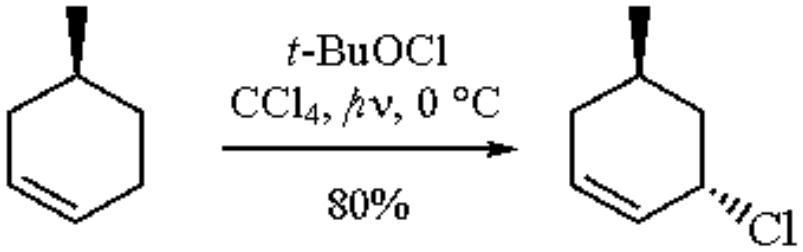

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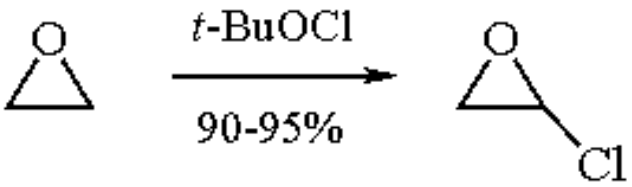

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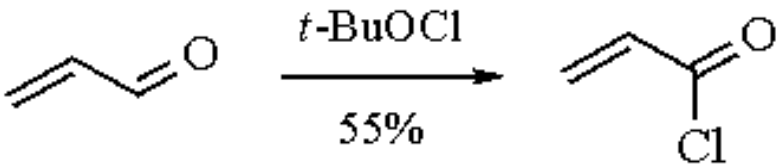

(4)

Ionic Reactions with Alkenes and Arenes.

Allylic chlorination with double bond rearrangement can also be effected by *t*-BuOCl under nonradical conditions in nonprotic solvents.[2] This process appears facile with particularly electron-rich alkenes, or if a catalyst such as ***Boron Trifluoride Etherate*** is employed (eq 5). If an alcohol is used as the solvent then β-chloro ethers are obtained via electrophilic addition (eq 6).[9]

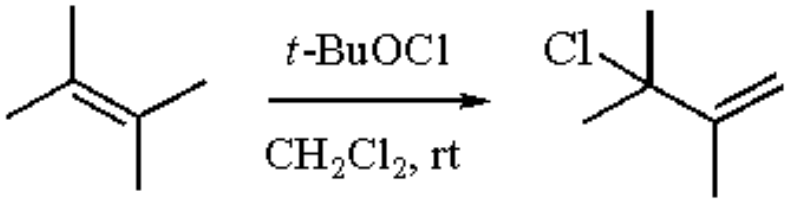

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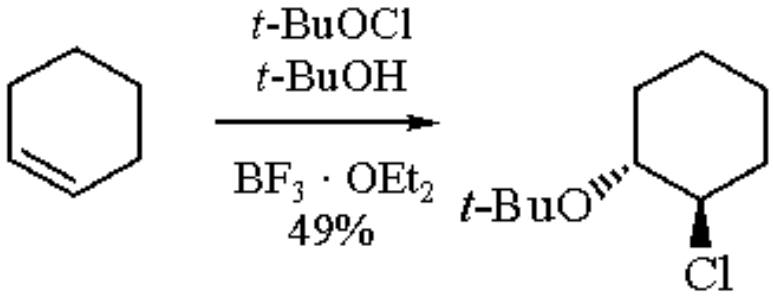

(6)

Chlorination of aromatics can also be effected by use of the *t*-BuOCl-BF_3.OEt_2 reagent combination,[9] or by the use of *t*-BuOCl in the presence of silica[10] or certain zeolites (eq 7).[11] Activated aromatics react with *t*-BuOCl alone, whereas deactivated systems do not react, even in the presence of catalysts under forcing conditions. The modified *o*/*p* selectivity in the presence of zeolite is notable. Chlorination of other types of systems, such as aminoquinones[12] and indoles,[13] has also been reported (eqs 8 and 9).

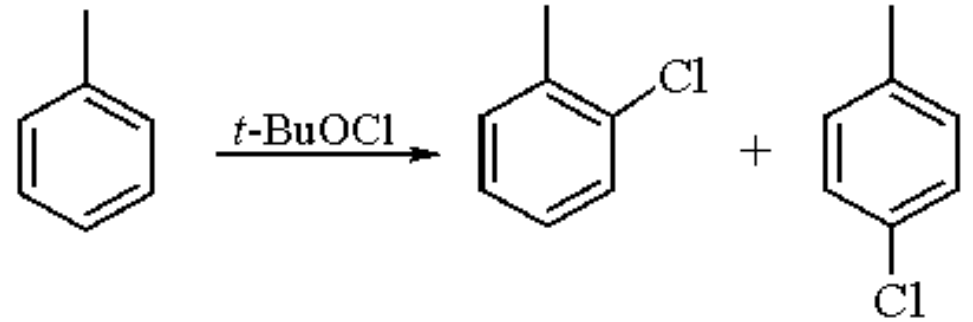

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silica, CCl_4	65:35	100%
H^+, Na^+ Faujasite X, CH_2Cl_2	9:91	88%

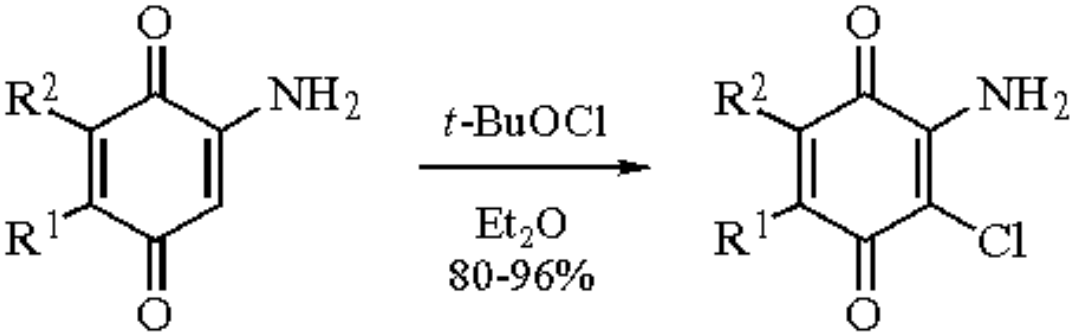

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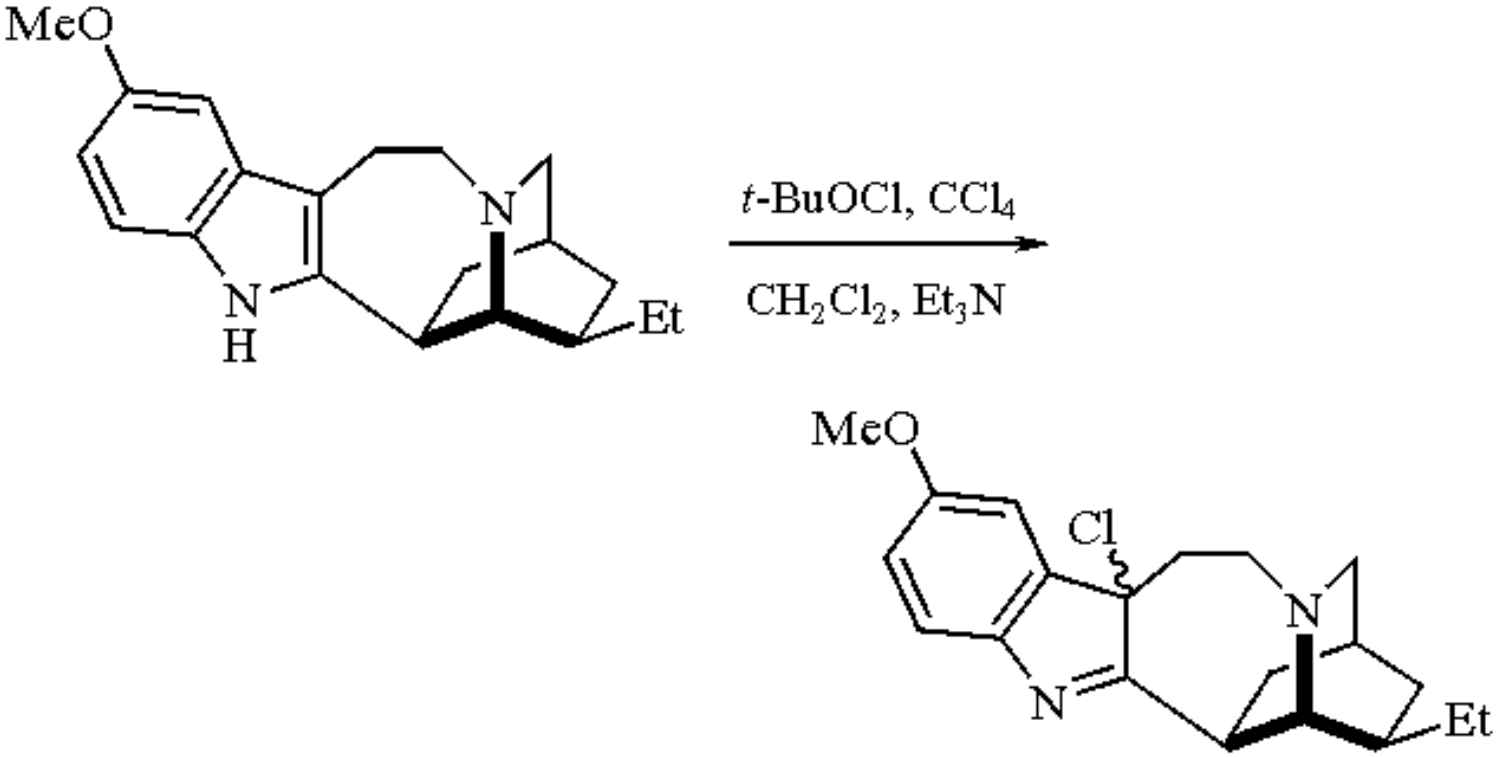

(9)

Chlorination at Nitrogen.

Chlorination of a wide range of nitrogen-containing systems to give chloroamines and related compounds, or products derived thereof, is an important use for *t*-BuOCl.[4] Examples include the hydroxylation of penicillins (eq 10)[4a-c] and a method for the asymmetric synthesis of amines via amino ester intermediates (eq 11).[4d] Both methods involve *N*-chlorination followed by dehydrochlorination and nucleophilic addition by the solvent.

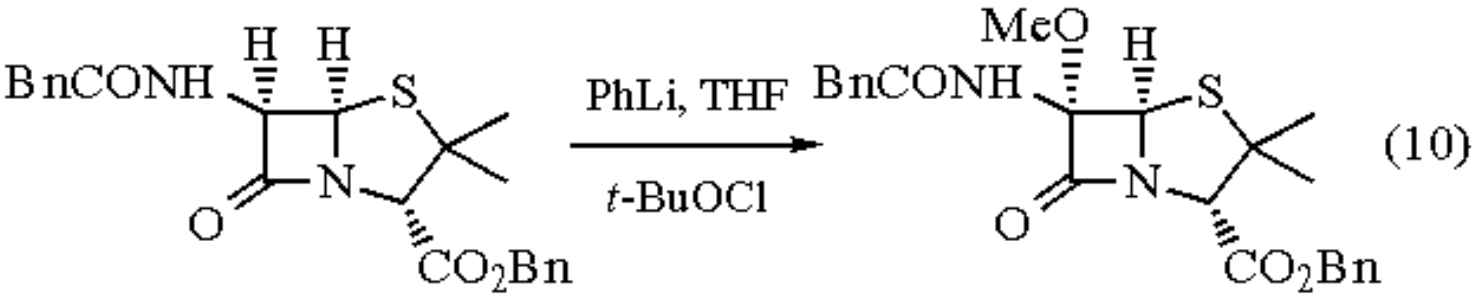

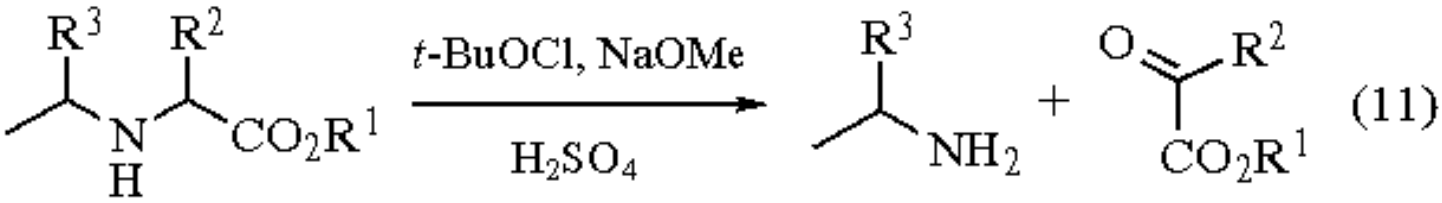

Oxidation Reactions.

The oxidation of secondary alcohols, using *t*-BuOCl in the presence of ***Pyridine***, gives high yields of the corresponding ketones (eq 12),[5] whereas in the absence of pyridine both the ketone and α-chloro ketone are usually formed (eq 13),[3b] the latter products probably arising from the initially formed ketones via chlorination by chlorine generated in situ.

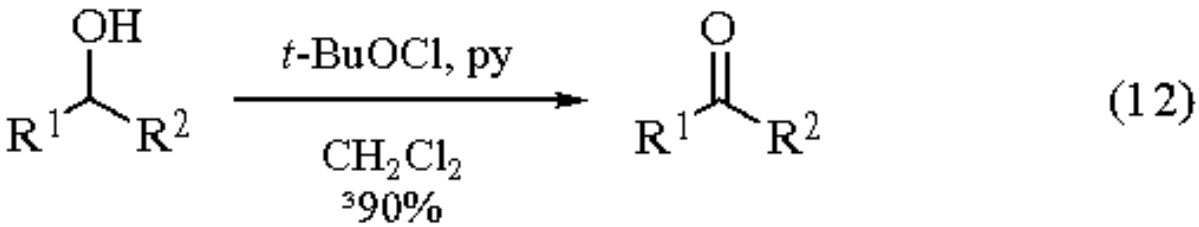

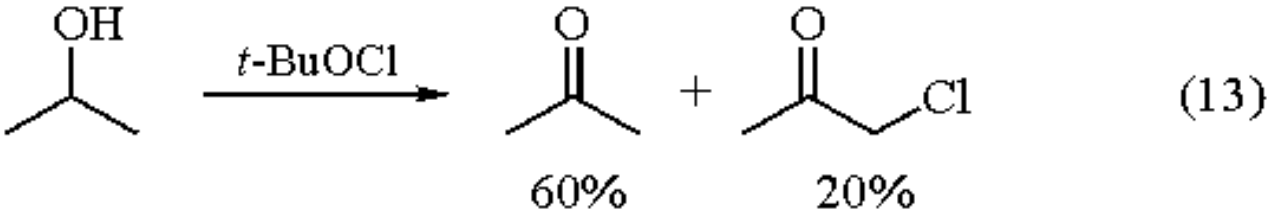

The oxidation of sulfoxides using *t*-BuOCl is very well established and can be used to prepare either *cis*- or *trans*-substituted thiane oxide products (eqs 14 and 15). Oxidation of selenides and tellurides is also possible in an analogous fashion, to give selenoxides and telluroxides (or their hydrates), respectively.[7]

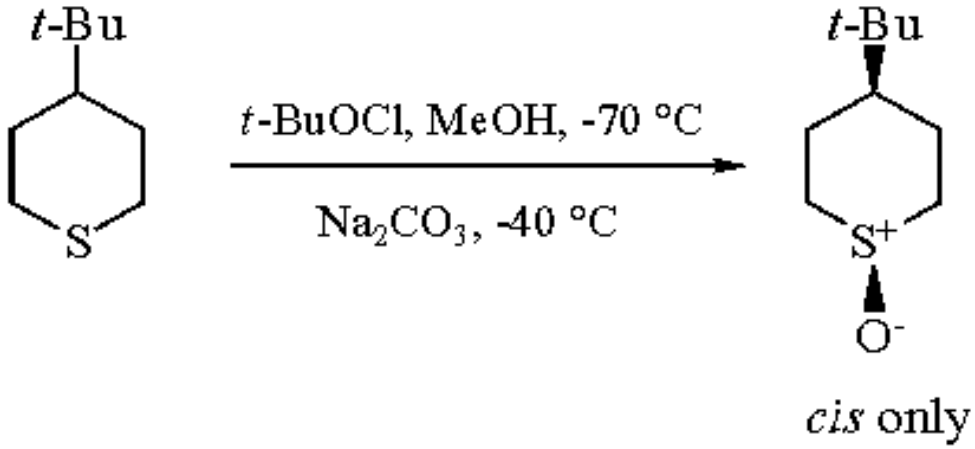

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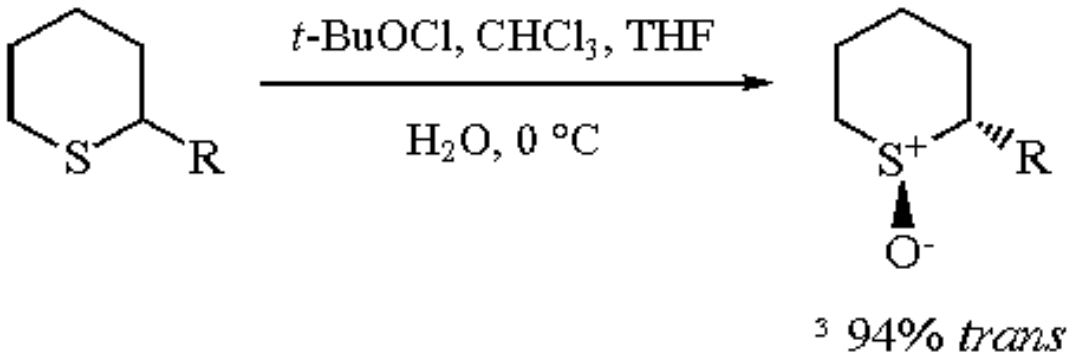

(15)

Other Applications.

Other types of reaction involving *t*-BuOCl which have been reported include cyclization of unsaturated peroxides to give chloroalkyl 1,2-dioxolanes (eq 16),[14] a ring expansion reaction of isopropenylcycloalkenols (eq 17),[15] and a dehydrogenation protocol for the synthesis of tetraethynylethylenes (eq 18).[16]

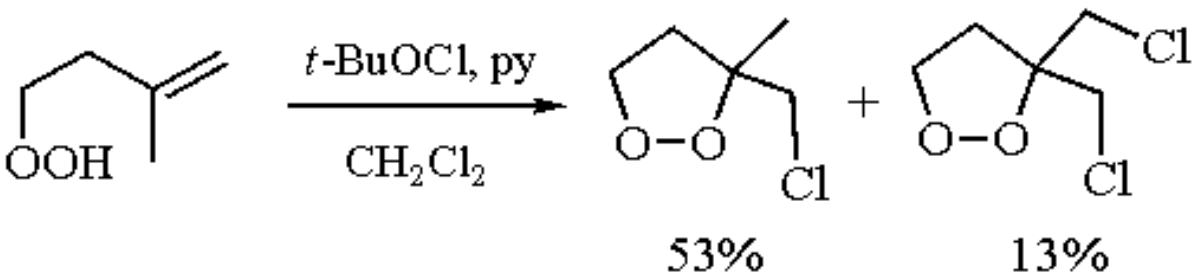

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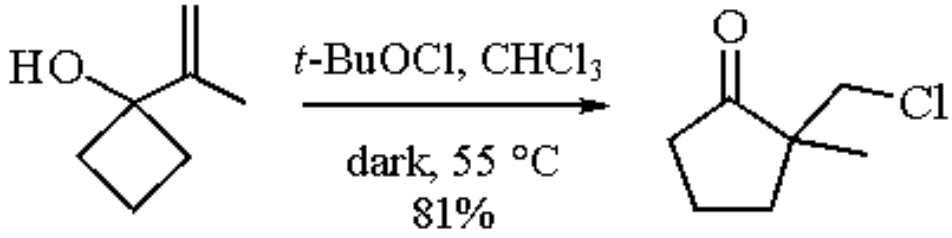

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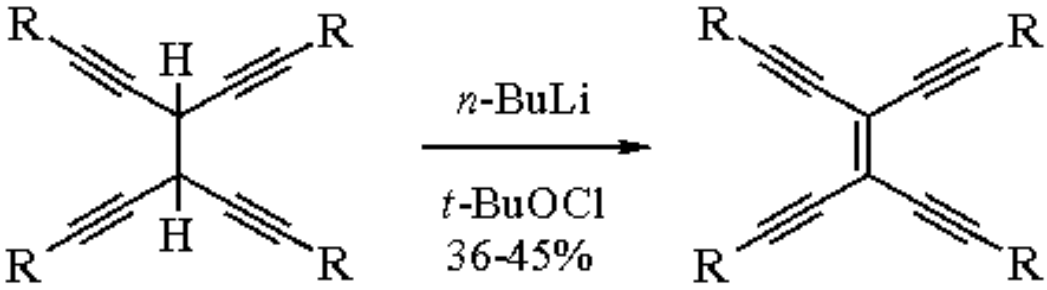

(18)

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t-Butyl Hypoiodite

_t_-BuOI

[917-97-5] · C_4H_9IO · *t*-Butyl Hypoiodite · (MW 200.02)

(reagent for radical and ionic iodinations)

Physical Data: orange-red solution, λ_{max} 515 nm.

Solubility: sol CCl_4 and benzene.

Form Supplied in: not commercially available.

Preparative Methods: the reagent has not been isolated in pure form and its precise nature is uncertain. Reagents considered to be *t*-butyl hypoiodite have been commonly prepared by the reaction of ***t-Butyl Hypochlorite*** with either ***Iodine*** or metal iodide salts, or by the reaction of ***Potassium t-Butoxide*** with iodine. Tanner and co-workers have shown that the reagent generated by the first of these methods is quite different to that formed by the other two methods.[1] Although the reagent formed by the latter two methods can be thought of as *t*-BuOI, the actual structure of the reagent is uncertain and there may be slight differences in the composition of different batches. This situation is amply illustrated for the reaction of *t*-BuOCl with AgI (eqs 1-4) The scheme adequately explains the spectroscopic and molecular weight measurements of the product formed in this way, and also the liberation of varying amounts of iodine (eq 4).

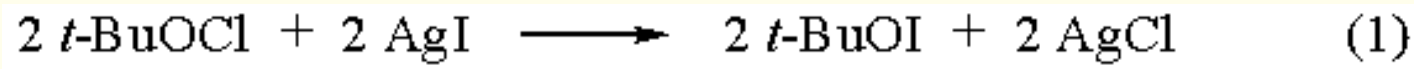

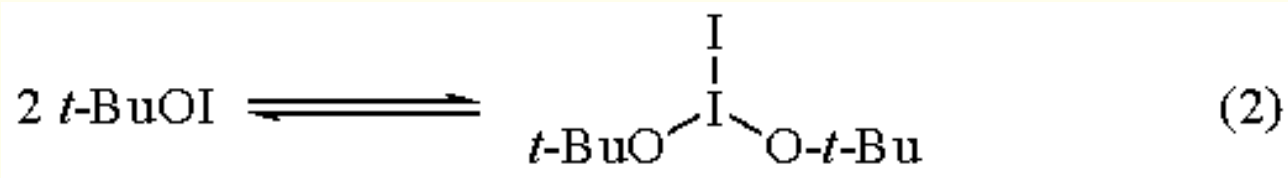

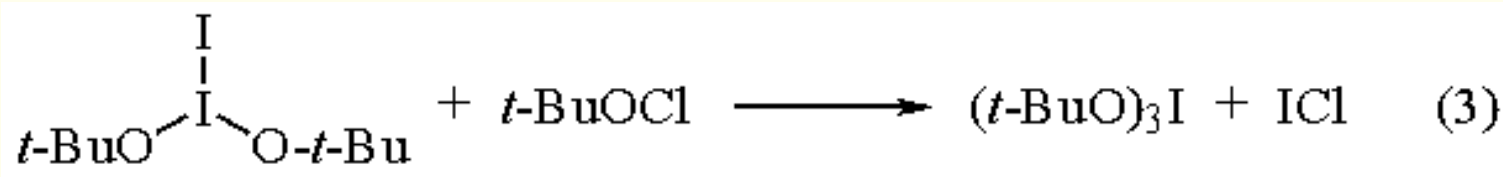

$$ICl + AgI \longrightarrow AgCl + I_2 \qquad (4)$$

Handling, Storage, and Precautions: reported to be very sensitive to moisture and is best generated in situ as required.

Iodination Reactions.

Barton and co-workers employed *t*-BuOI reagents, made by two of the above described methods, for a range of novel photochemical applications (eqs 5-7).[2-4]

$$RCO_2H \xrightarrow[h\nu,\ \text{benzene}]{t\text{-BuOK},\ I_2} R\text{-}I + CO_2 \qquad (5)$$

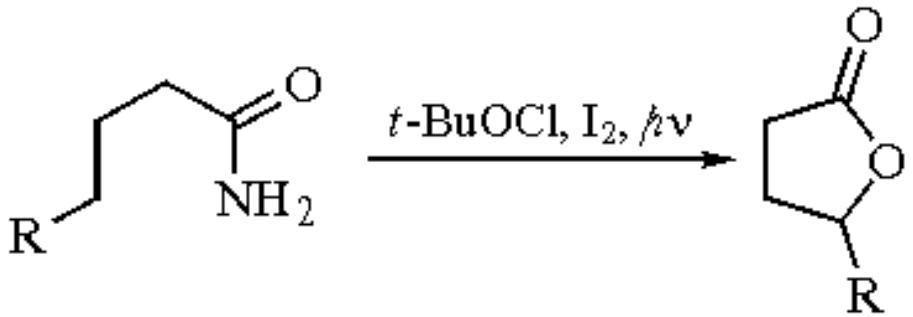

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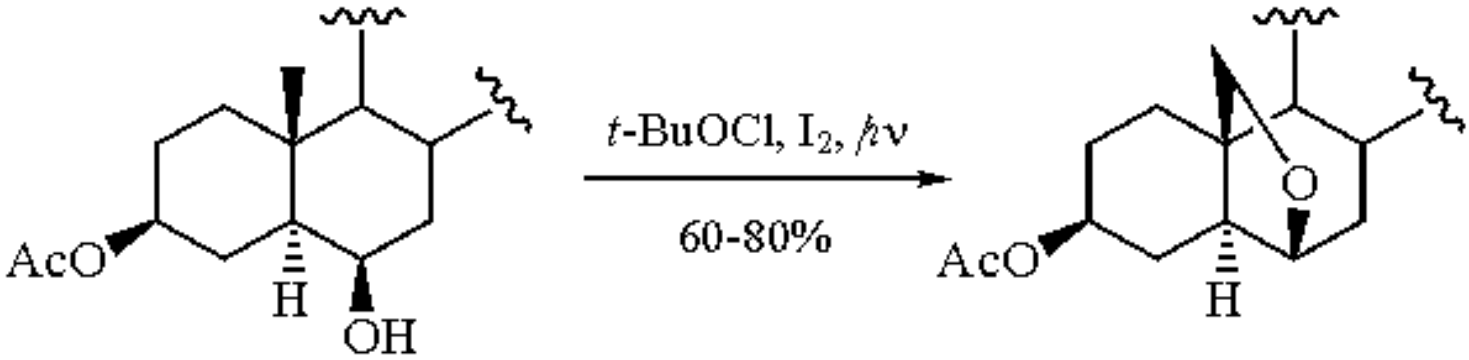

(7)

Irradiation of a benzene solution of a carboxylic acid and the reagent derived from *t*-BuOK and iodine results in efficient decarboxylation to form the one-carbon shortened alkyl iodide (eq 5).[2] This photochemical Hunsdiecker-type reaction presumably involves transformation of the starting carboxylic acid into the corresponding acyl hypoiodite, which then undergoes homolytic fission. This latter process is too facile to allow hydrogen atom abstraction by the carboxyl radical to compete. However, when amides are subjected to these reaction conditions, hydrogen atom abstraction can occur, resulting in a novel synthesis of lactones (eq 6).[3] Similar remote functionalization is possible in steroid systems via alkoxyl radicals, generated using either the *t*-BuOCl-I_2 or *t*-BuOK-I_2 combinations (eq 7).[4]

Reaction of carboxylic acids with excess alkyl iodide, in the presence of iodine and *t*-BuOCl, in the dark can give good yields of esters (eq 8).[5] Evidence points to this reaction proceeding via heterolytic S_N1 or S_N2 substitution, depending on the substrate structure.

$$R^1CO_2H + R^2I \xrightarrow{t\text{-BuOCl, } I_2} R^1CO_2R^2 \qquad (8)$$

Reagents derived from *t*-BuOCl and a metal iodide can be used to effect iodination of hydrocarbons and phenols (eqs 9 and 10).[6,7] The selectivities displayed by the radical hydrocarbon iodination led Tanner and Gidley to propose a chain reaction involving an iodonyl radical as the hydrogen atom abstracting species.[6]

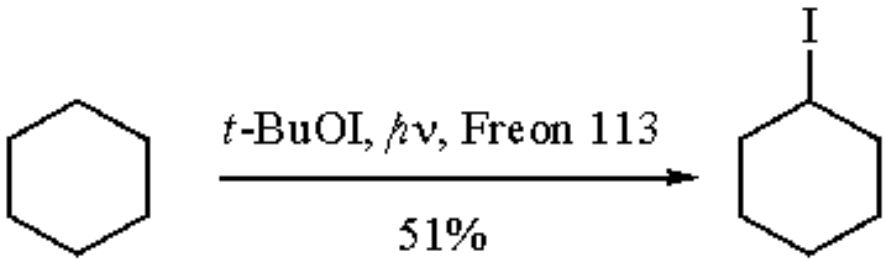

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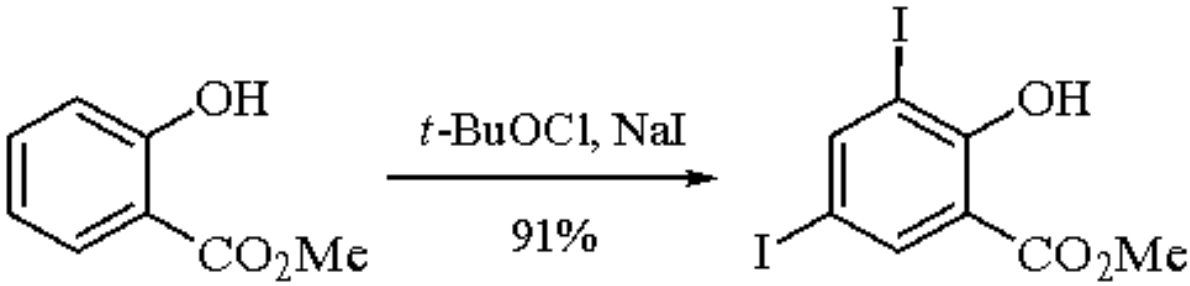

(10)

Addition reactions of *t*-BuOI (prepared from *t*-BuOCl and HgI_2) to alkenes can be carried out under radical or ionic conditions (eqs 11 and 12) with regiocomplementary results.[8] The additions catalyzed by BF_3 etherate were examined in detail and found to be stereospecific, probably involving *anti* addition.

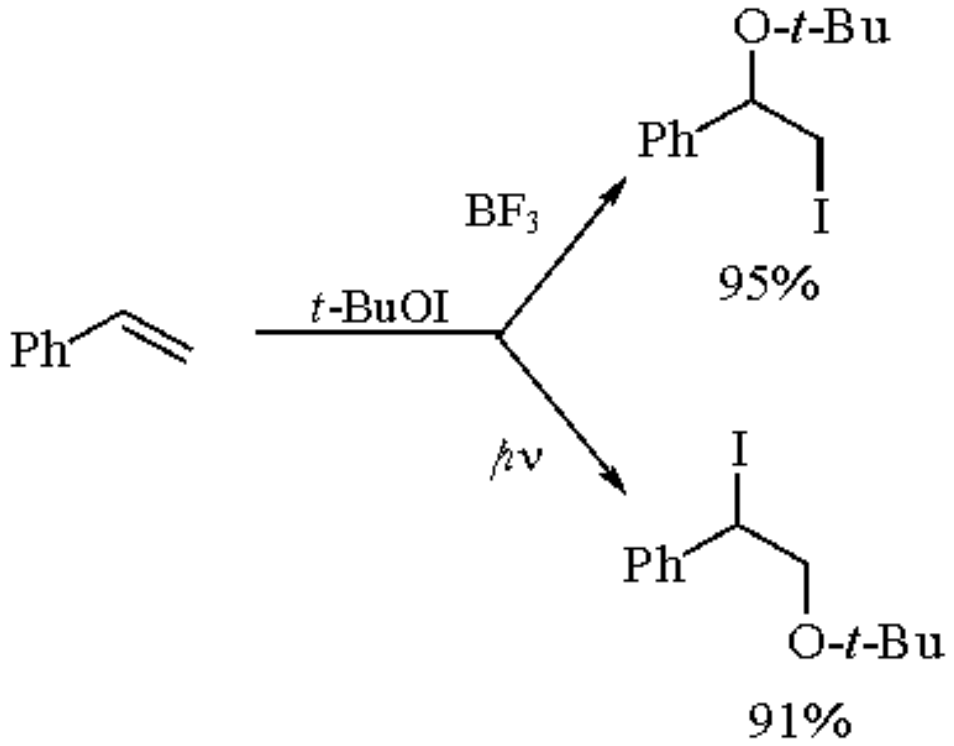

(11)

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t-Butyl (*E*)-4-Iodo-2-methyl-2-butenoate

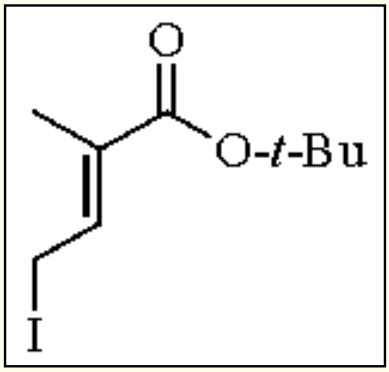

[53689-87-5] · $C_9H_{15}IO_2$ · *t*-Butyl (*E*)-4-Iodo-2-methyl-2-butenoate · (MW 282.12)

(regioselective annulations;[1] methyl vinyl ketone equivalent[2])

Alternate Name: *t*-butyl γ-iodotiglate.

Physical Data: bp 80 °C/0.005 mmHg.[1]

Preparative Method: treatment of ***Chloroacetaldehyde*** with the phosphorane shown in eq 1 followed by halogen exchange with ***Sodium Iodide***/acetone affords the title reagent in 76% overall yield.[1,2]

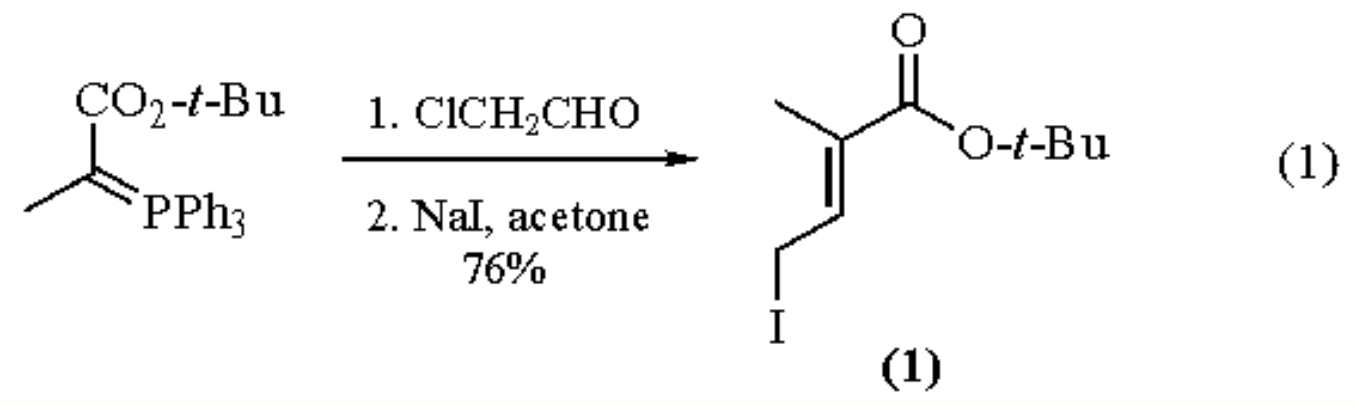

Cyclohexenone Annulation.

The title reagent is a ***Methyl Vinyl Ketone*** equivalent and has been employed in Robinson annulation reactions. A cyclohexanone derivative (lithium enolate or enamine) is alkylated with the iodobutenoate. Subsequent hydrolysis of the alkylated intermediate with ***p-Toluenesulfonic Acid*** affords the unsaturated carboxylic acid in 80-90% combined yield (eq 2).[1,2] An oxidative decarboxylation procedure (eq 3) via a Curtius rearrangement of the derived acyl azide

affords an ene carbamate. Basic hydrolysis of the carbamate followed by an in situ base-catalyzed aldol condensation completes the cyclohexenone annulation in 75-90% overall yield from the carboxylic acid intermediate.[1-3]

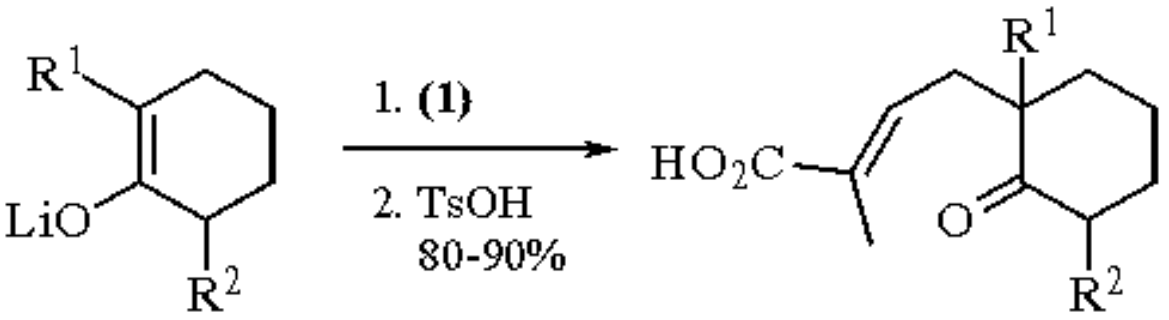

(2)

R = H or Me

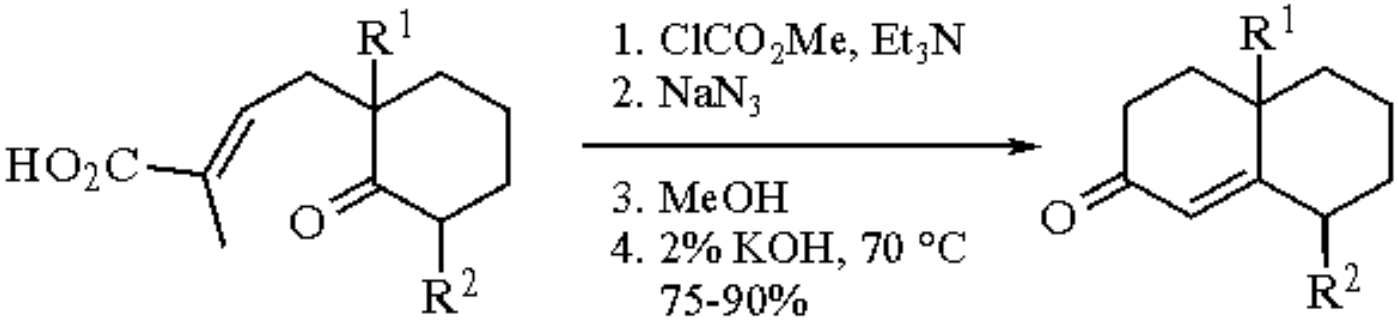

(3)

R = H, Me

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1. (a) Gawley, R. E. *S* **1976**, 777; (b) Hill, K. H. Ph.D. Thesis, University of Texas, Austin, TX, 1972.
2. (a) Stotter, P. L.; Hill, K. A. *TL* **1975**, *16*, 1679. (b) Stotter, P. L.; Hill, K. A. *JACS* **1974**, *96*, 6524.
3. Weinstock, J. *JOC* **1961**, *26*, 3511.

Jeffrey S. DePue

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t-Butyl Isocyanide[1,2]

***t*-BuNC**

[7188-38-7] · C_5H_9N · *t*-Butyl Isocyanide · (MW 83.13)

(reactive amphiphilic reagent for 1,1-additions to form various heterocyclic *N*-*t*-butylimines; asymmetric amino acid synthesis; fragment condensation of peptides; mild carboxylic acid esterifications; metal-catalyzed cyanation of acetals, α,β-enones, and 1-alkenes; other applications involving various iminyl 1,1-addition reactions[1,2])

Physical Data: bp 91 °C/38 mmHg; *d* 0.74 g cm^{-3}.

Solubility: sol most organic solvents, including methanol, ethanol, ether, toluene, dichloromethane.

Form Supplied in: pure liquid; commercially available.

Analysis of Reagent Purity: by gas chromatography.

Preparative Methods: dehydration of ***N-t-Butylformamide*** with ***Phosphorus Oxychloride***[3] and by the Hofmann carbylamine reaction.[4]

Handling, Storage, and Precautions: awful smelling liquid: should be stored and used in a fume hood; contaminated equipment should be washed with 5% methanolic sulfuric acid.

Heterocyclic Synthesis.

Silver(I) Cyanide catalyzes the formyl transfer from *t*-butyl isocyanide to 1,*n*-amino alcohols, diamines, and amino thiols.[5] An example is the conversion of γ-aminopropanol to 5,6-dihydro-4*H*-1,3-oxazine (eq 1). The reaction can be extended to *o*-aminophenol, *o*-phenylenediamine, and *o*-aminothiophenol, affording benzoxazole (54%), benzimidazole (64%), and benzothiazole (93%), respectively.

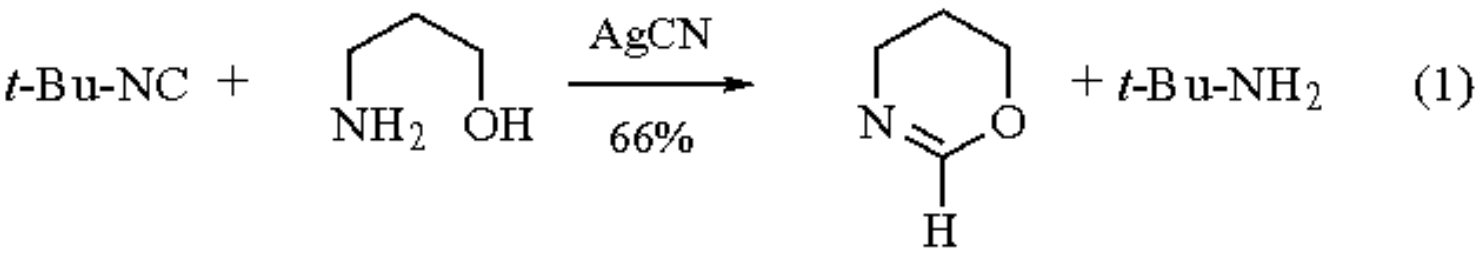

Four-membered ring formation of 2,3-bis(alkylimino)oxetanes can be performed in high yields from ketones and 2 equiv of *t*-butyl isocyanide (eq 2).[6] Iminodioxolane derivatives are available in excellent yield from *t*-butyl cyanoketene (eq 3).[7]

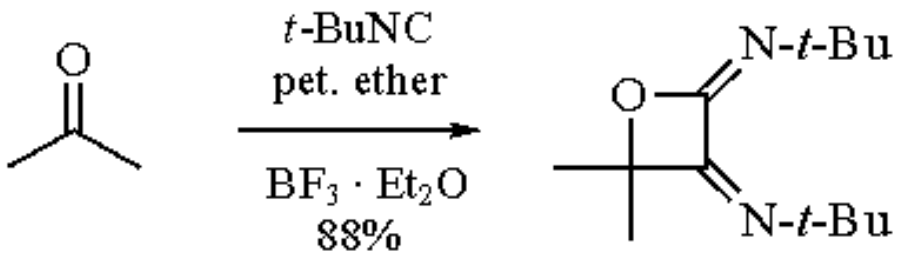

(2)

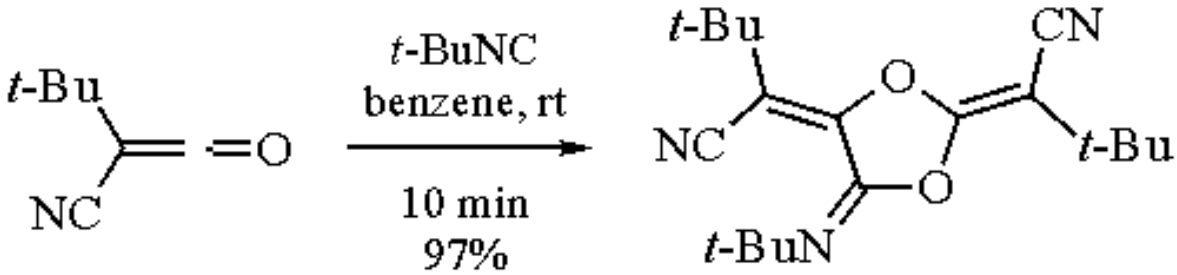

(3)

A spiro 1,4-dioxan-2-one is formed in a Lewis-acid catalyzed reaction in reasonable yields from cycloalkyl ethylene acetals, which are easily prepared from the ketone and ethylene glycol (eq 4).[8] [4 + 1] Cycloaddition of kinetically stabilized azetes with *t*-butyl isocyanide affords sterically hindered pyrrole imines (eq 5).[9] An intermediate ketenimine built from 3-aminoacrylamide reacts with *t*-butyl isocyanide, forming the diiminopyrroline system (eq 6).[10]

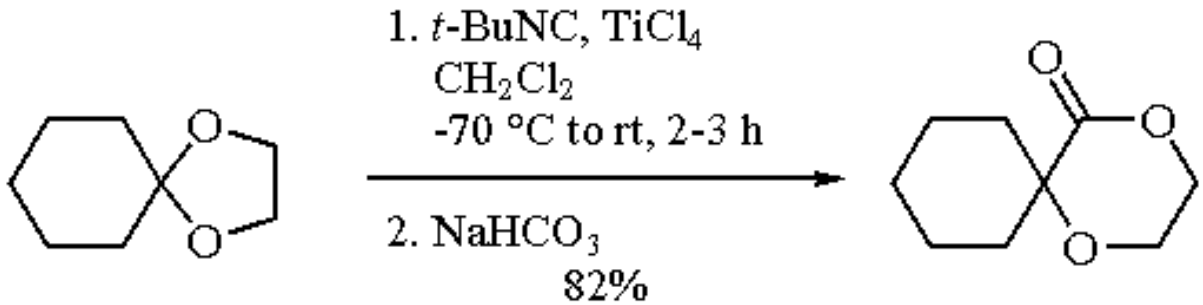

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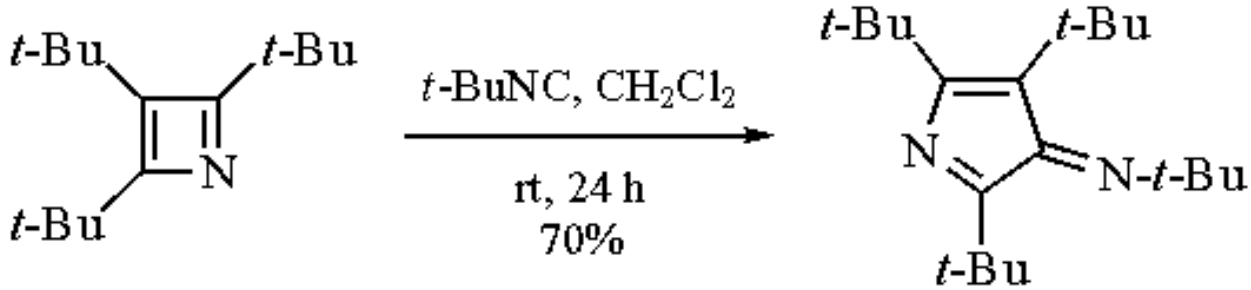

(5)

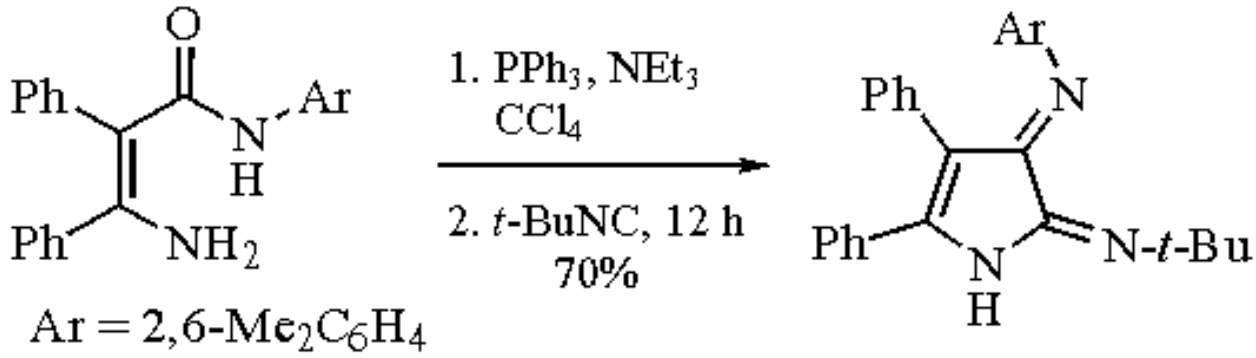

(6)

[4 + 1] Cycloaddition of 1,3-diaza-2-methylthiobutadienes with *t*-butyl isocyanide affords 4-imino-2-thioimidazolines (eq 7).[11] Isocyanides react with thiazolines, causing a ring transformation to imidazolines (eq 8).[12] In the presence of ***Boron Trifluoride Etherate***, *t*-butyl isocyanide dimerizes, forming pivalonitrile *N*-*t*-butylimine which reacts with *o*-phenylenediamine to afford 2-*t*-butylbenzimidazole (eq 9).[13]

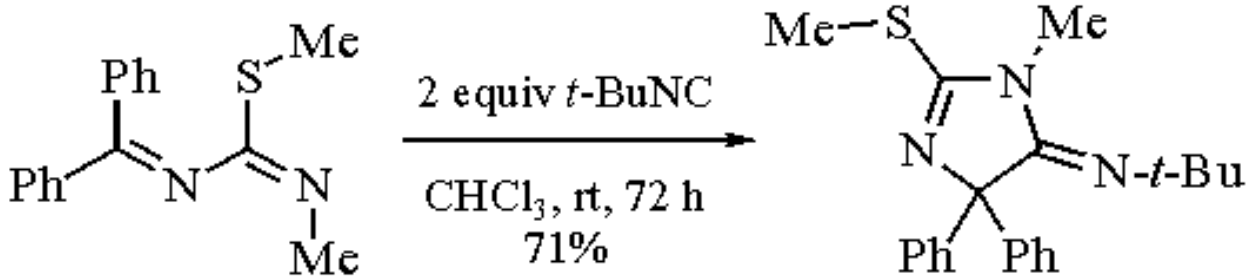

(7)

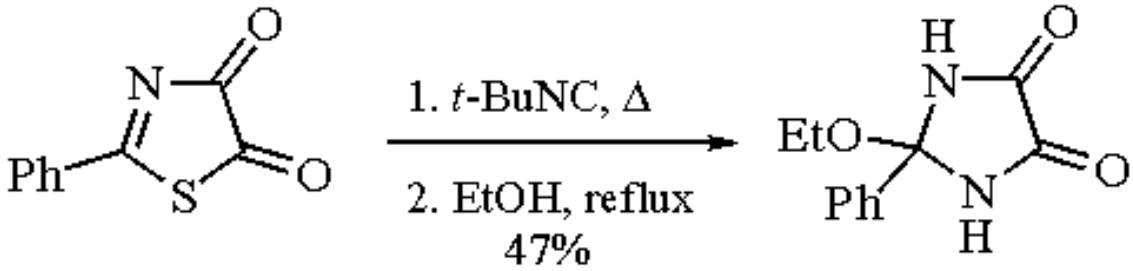

(8)

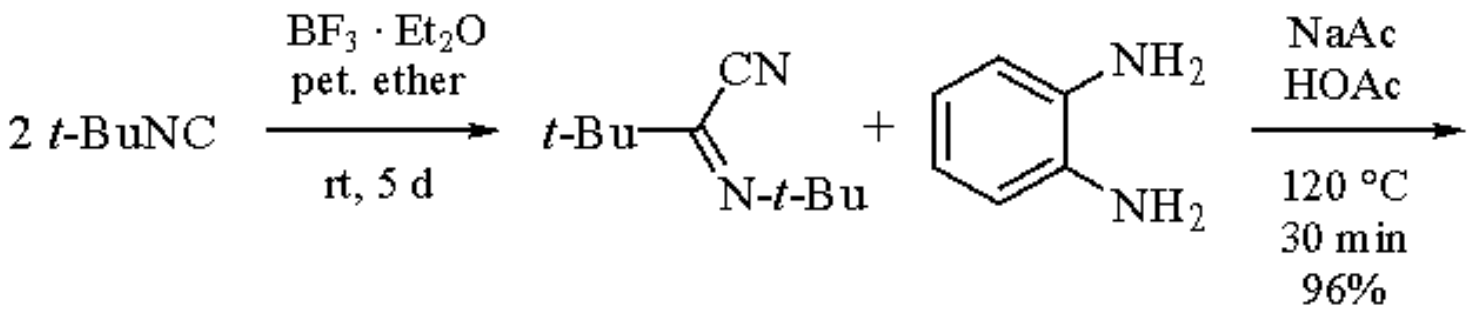

(9)

A structurally interesting boron heterocycle, namely a borapyrrole derivative, can be made by [4 + 1] cycloaddition plus alkyl tautomerization (eq 10).[14]

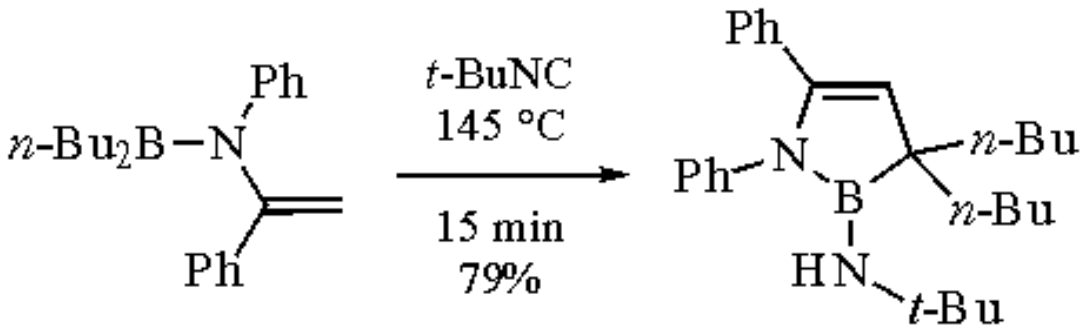

(10)

Asymmetric Synthesis of α-Amino Acids and Peptide Coupling.

Enantioselective formation of α-amino acids can be performed by asymmetrically induced Ugi reaction (eqs 11 and 12).[15,16]

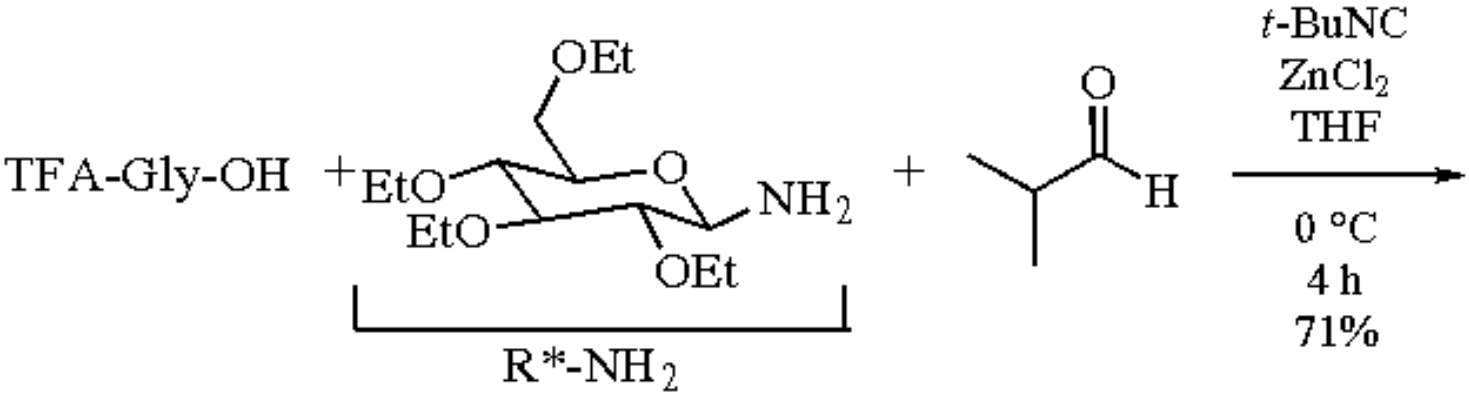

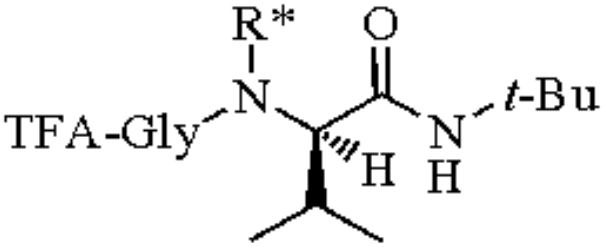

(11)

(*R*)

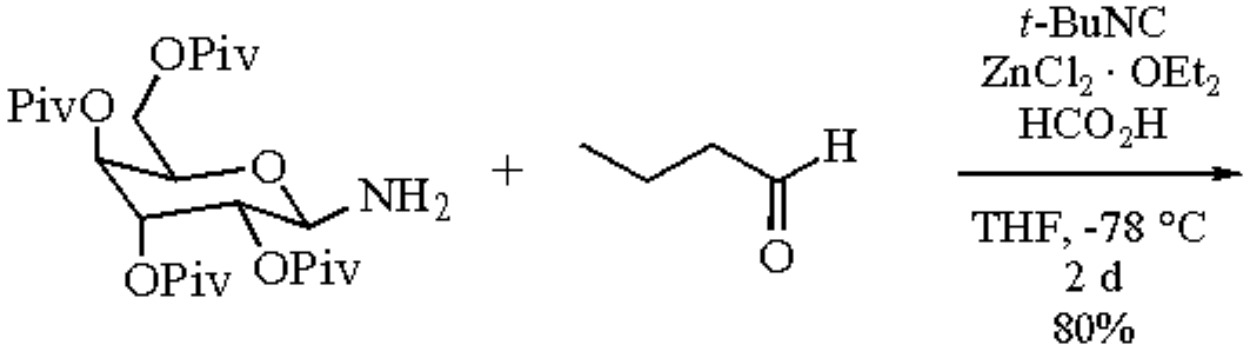

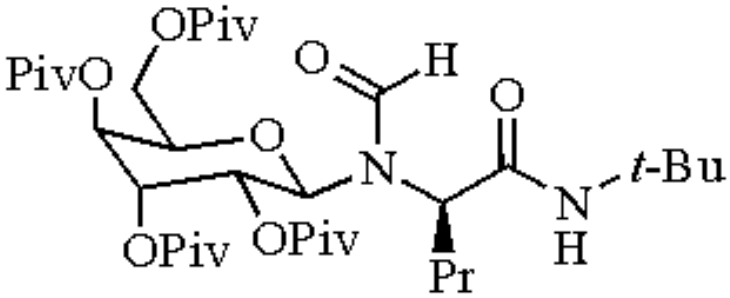

(12)

89% ee

The chiral auxiliaries in eqs 11 and 12 are aminopyranoses with protected hydroxy functions, derived from glucose and galactose respectively. Another effective auxiliary is (*R*)-α-ferrocenylisobutylamine.[17] In eq 13 chiral induction is nearly quantitative.

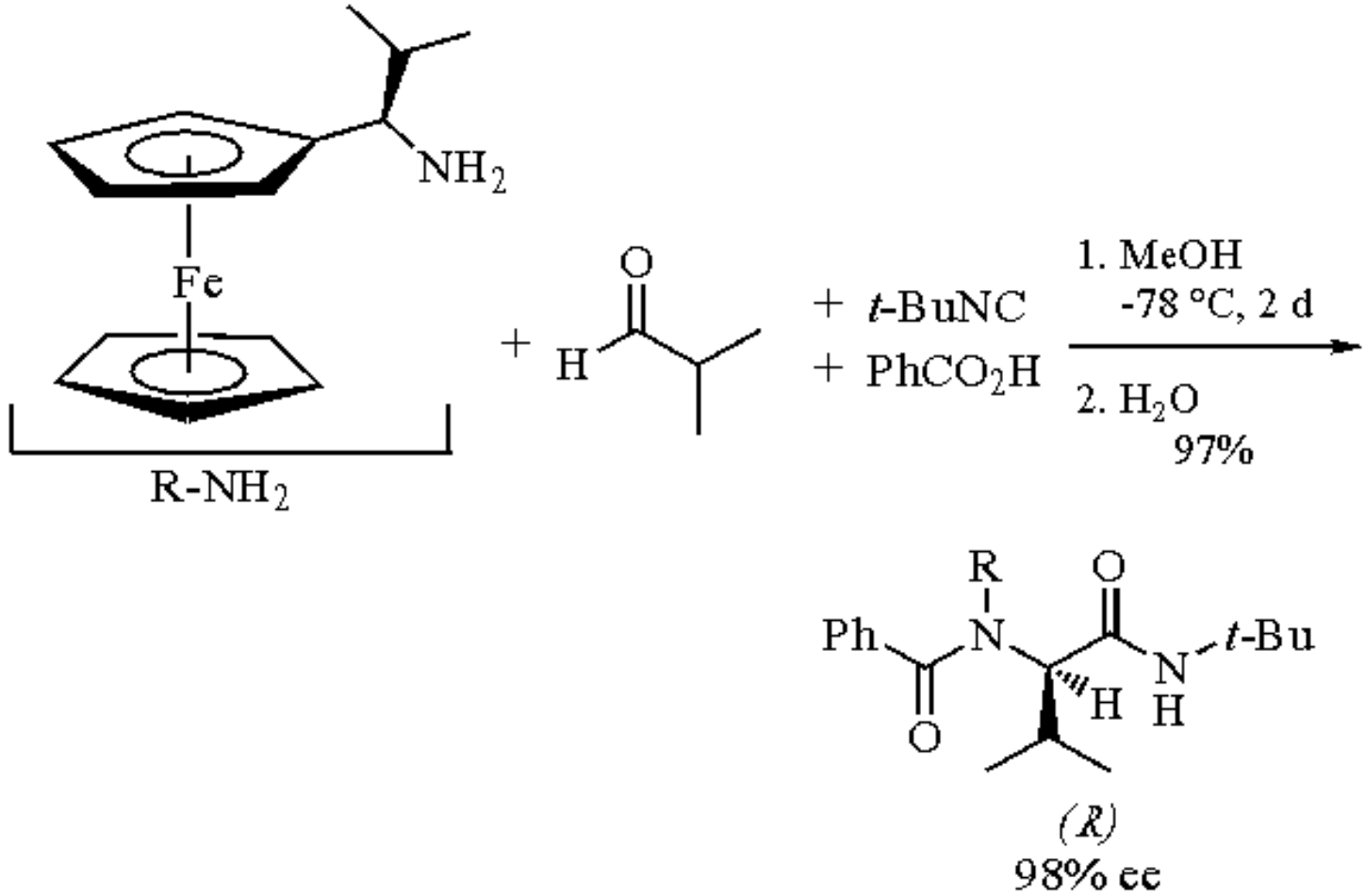

(13)

A method for fragment condensation of peptides involves using *t*-butyl isocyanide as coupling reagent (eq 14).[18]

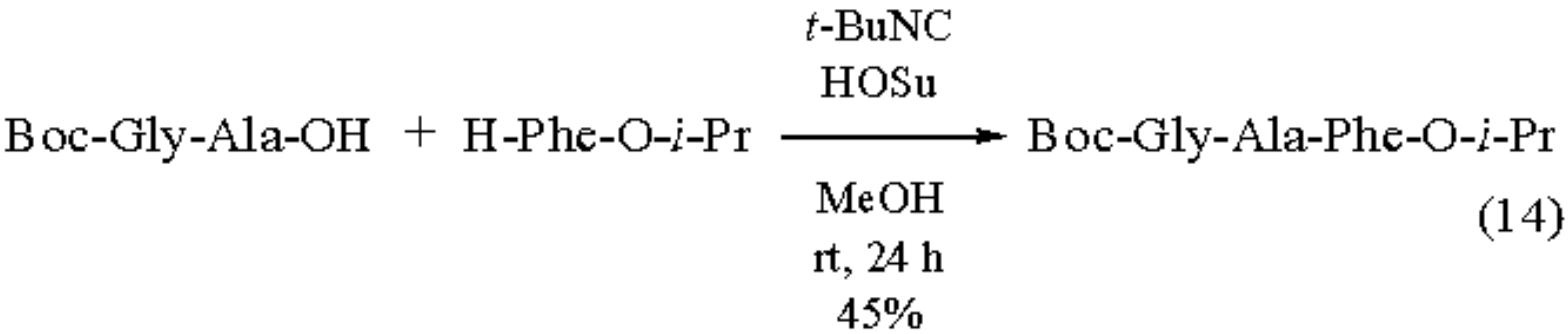

(14)

Mild Esterification.

In the chemistry of β-lactam antibiotics, especially of penicillins and cephalosporins, introduction of the ester group is often difficult. This problem can be solved by using the Passerini reaction with α-geminal polyhalogenated aldehydes and *t*-butyl isocyanide (eq 15).[19] The cleavage of β-haloalkyl esters can be performed under very mild conditions and regioselectively by cobalt(I) phthalocyanine anion without attack of the penicillin moiety.

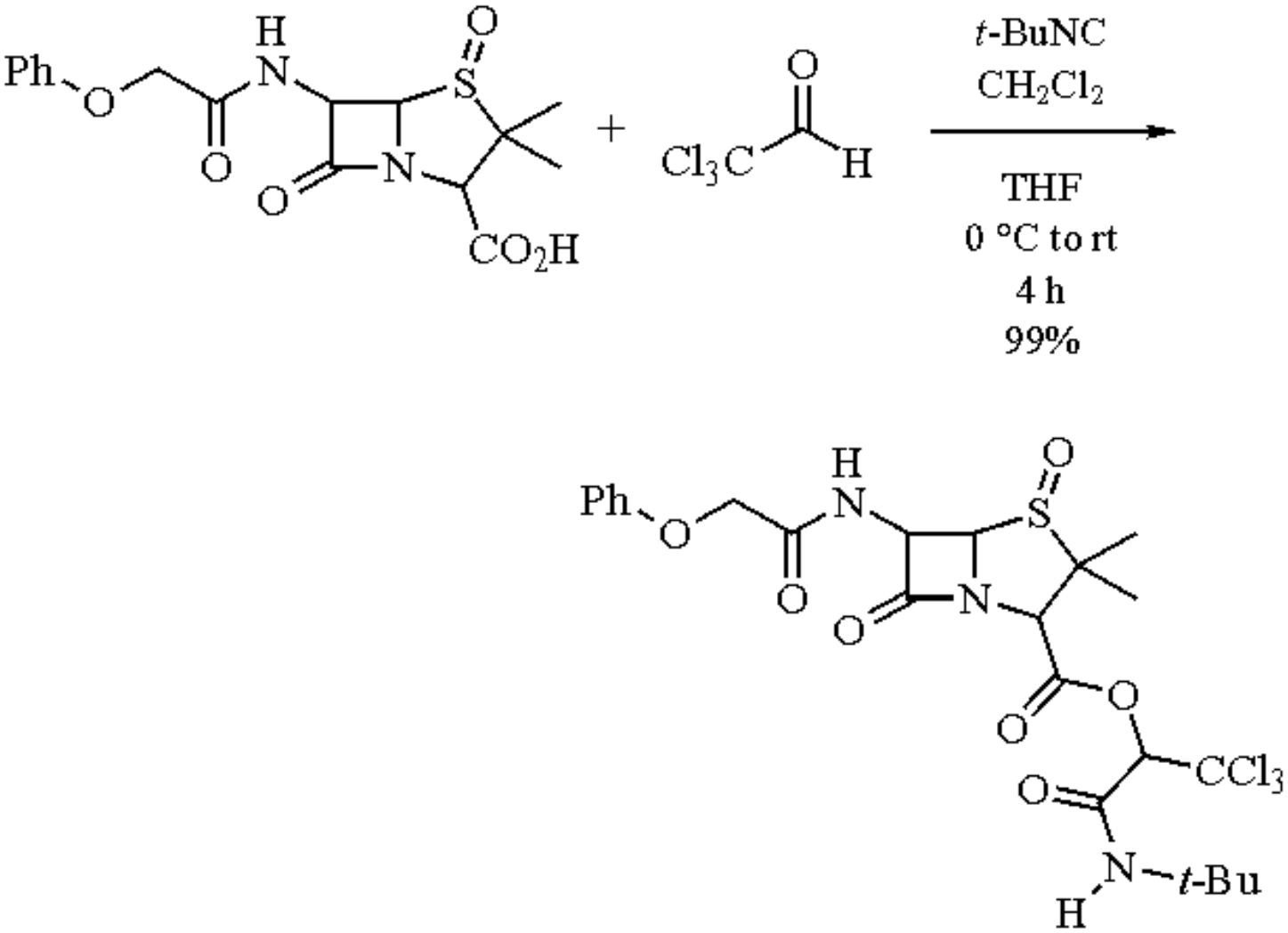

(15)

Esterification of carboxylic acids with absolute alcohols can be achieved under mild conditions using *t*-butyl isocyanide. Exceptionally high yields are achieved in forming dicarboxylic monoalkyl esters (eq 16).[20]

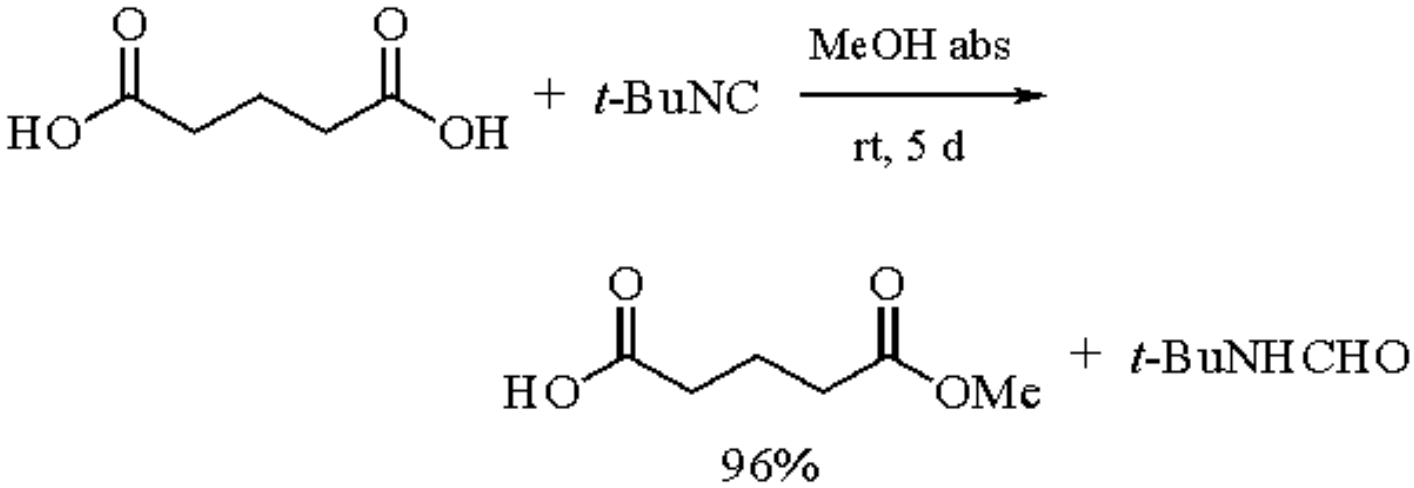

(16)

Cyanation Reactions.

α-Imino nitriles are accessible in excellent yield from aldehyde acetals and *t*-butyl isocyanide (eq 17).[21] *t*-Butyl

isocyanide serves as a cyanide source for cyanohydrin ether formation (eq 18).[8]

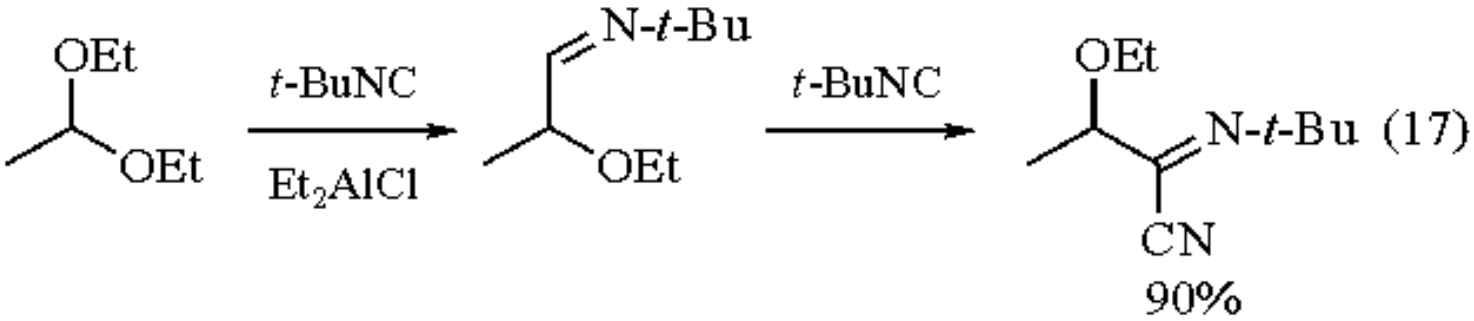

(17)

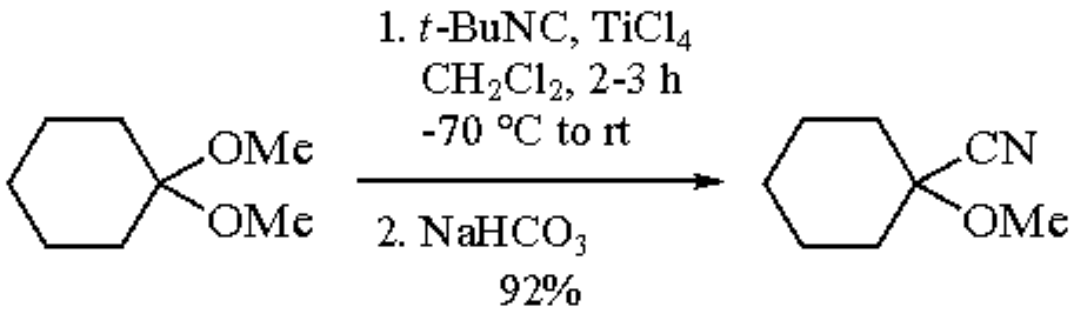

(18)

t-Butyl isocyanide undergoes formal [4 + 1] cycloaddition to α,β-enones in the presence of ***Diethylaluminum Chloride*** to give *N*-*t*-butylimines of β,γ-butenolides (~65%). Catalytic hydrogenation and hydrolysis afford γ-butyrolactones.[22a] This tertiary isocyanide donates cyanide for conjugate hydrocyanation of α,β-enones, producing β-cyano ketones (eq 19).[22b]

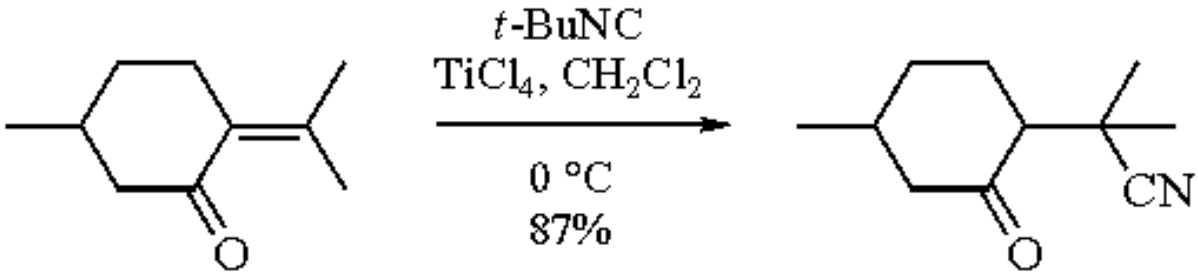

(19)

Regioselective hydrocyanation of terminal alkenes can be accomplished by hydrozirconation with Schwartz's reagent (***Chlorobis(cyclopentadienyl)hydridozirconium***), followed by imine insertion with *t*-butyl isocyanide and iodinolysis (eq 20).[23]

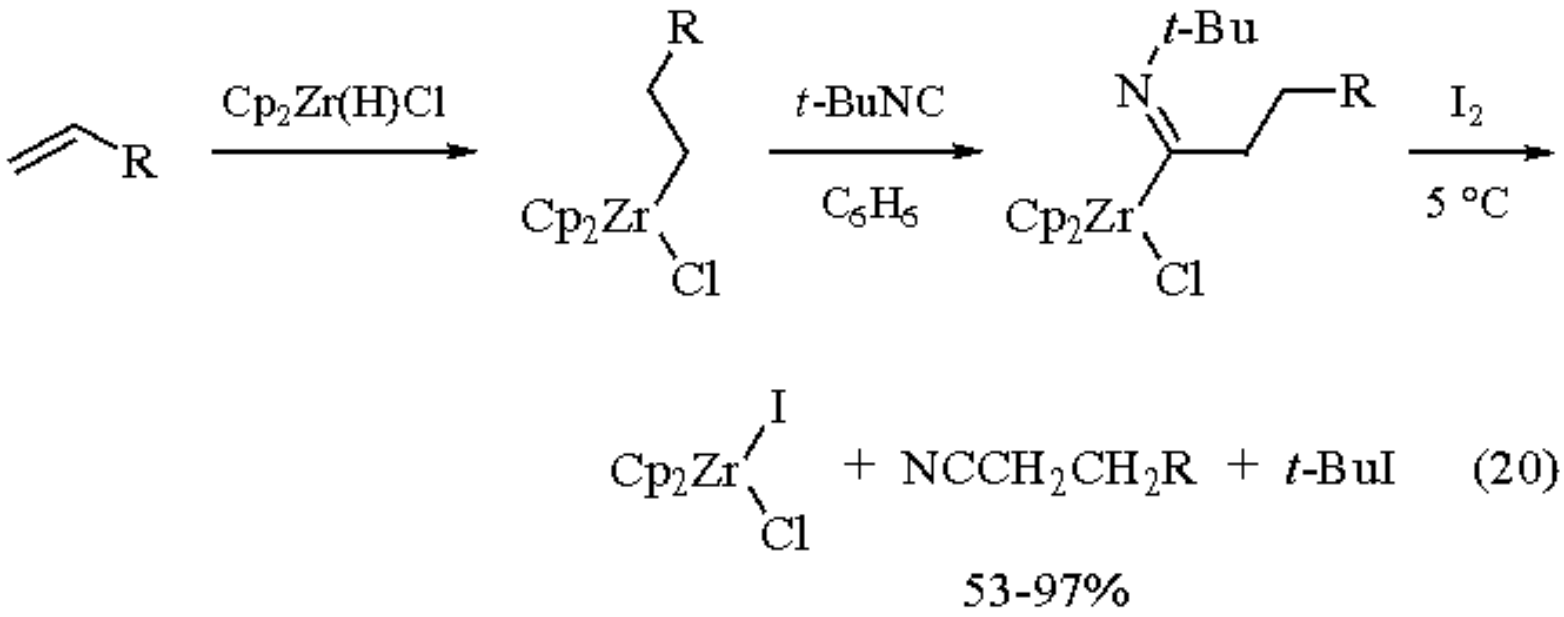

Other Applications.

Cyclohexenimines are accessible from ***Allyl Chloride***, ***Acrylonitrile***, and *t*-butyl isocyanide via *N*-*t*-butyl vinylketenimine in a [4 + 2] cycloaddition (eq 21).[24]

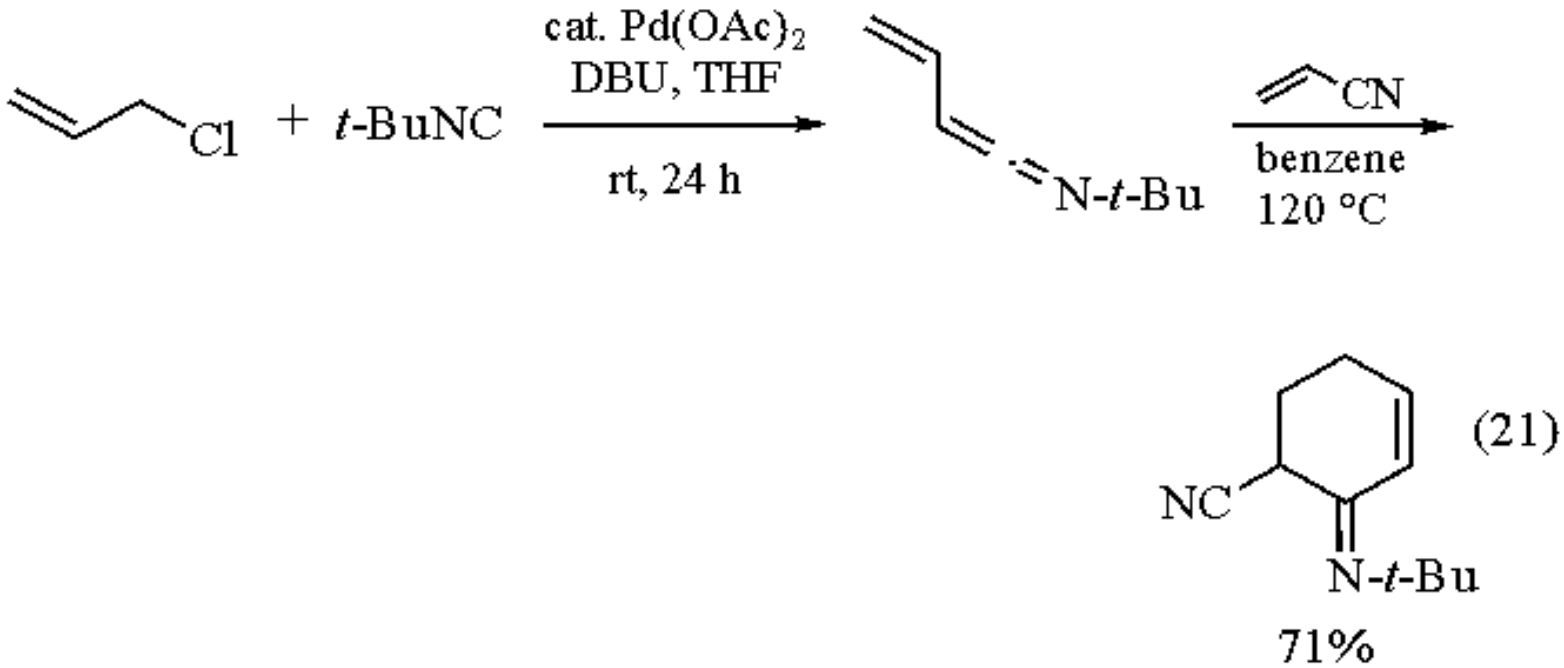

By a cross-coupling reaction of octyl-9-BBN, *t*-butyl isocyanide, and iodobenzene, an alkylarene ketimine is formed, which hydrolyzes by acid catalysis to the corresponding ketone (eq 22).[25] Unsymmetrical ketones may also be obtained by 1,1-addition of an alkyllithium reagent to *t*-butyl isocyanide, lithium-boron exchange with R_2BCl, thioglycolic acid-induced migration of one R group from boron to carbon, and alkaline oxidation (H_2O_2, OH^-)[26]

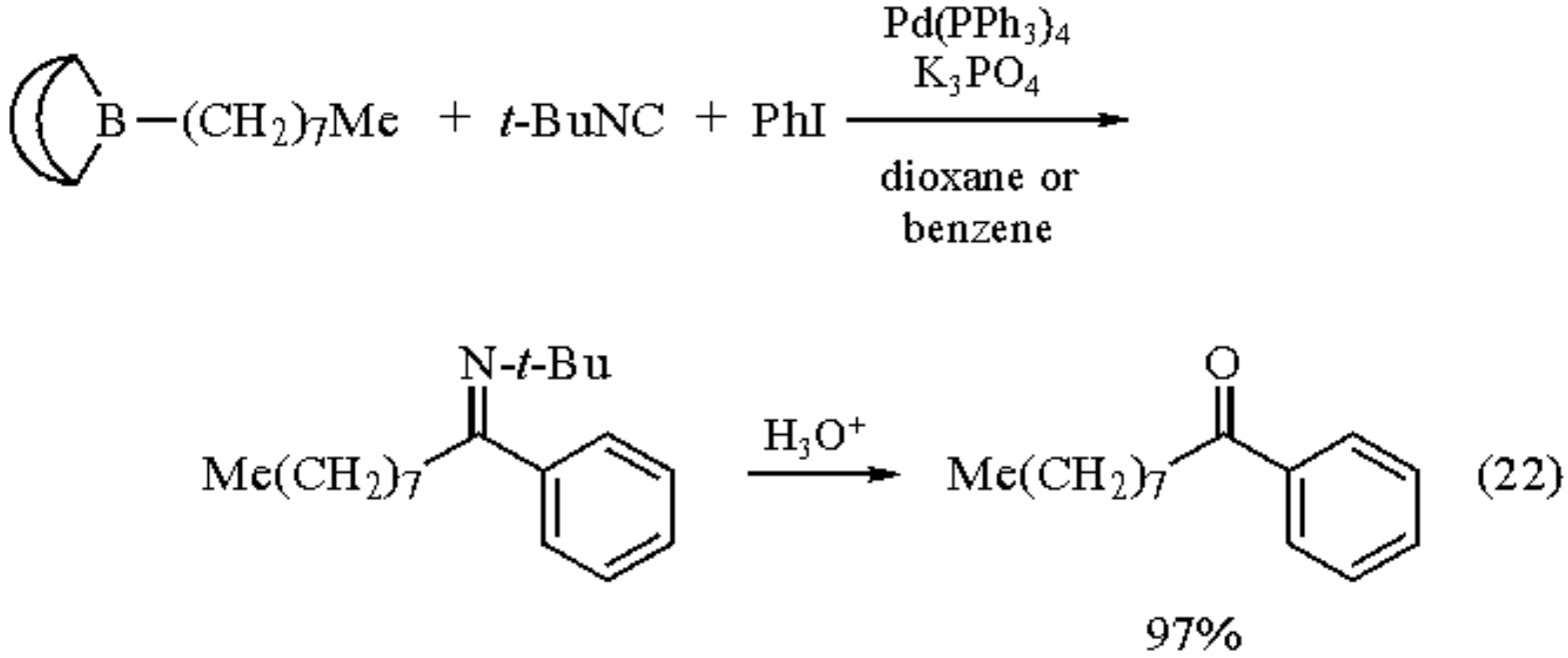

Arylimino esters are available by a palladium-catalyzed reaction of aryl halides with *t*-butyl isocyanide and ***Tri-n-butyl(methoxy)stannane***. The reaction conditions have been developed with great care (eq 23).[27] Cyclic imino esters are also formed by formal substitution of carbon monoxide with *t*-butyl isocyanide and 5-aryl-2,3-dihydro-1,3-furandiones via a ketene intermediate (eq 24).[28]

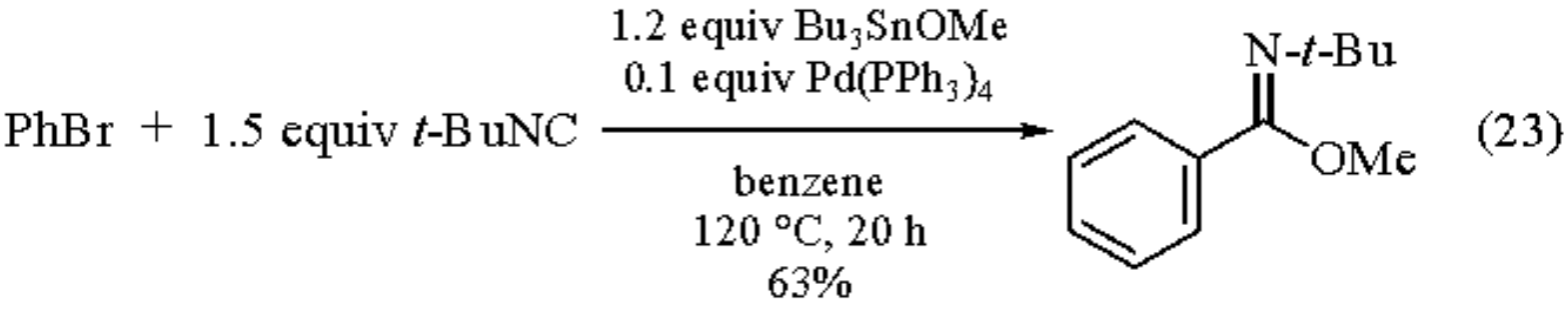

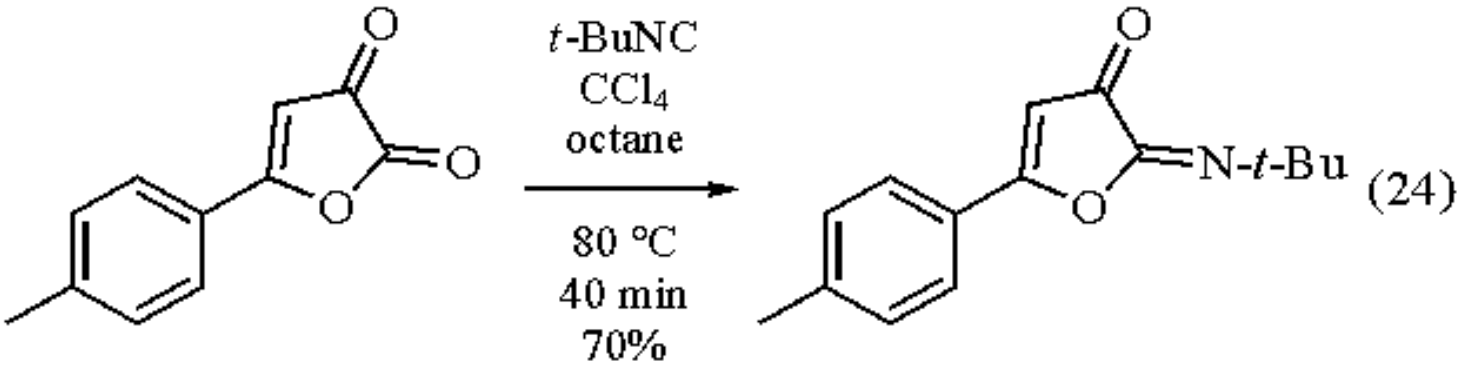

Radical carbon-carbon linkage of acrylonitrile and *t*-butyl isocyanide can be performed in acceptable yields by using ***Azobisisobutyronitrile*** as radical initiator and ***Tris(trimethylsilyl)silane*** (eq 25).[29]

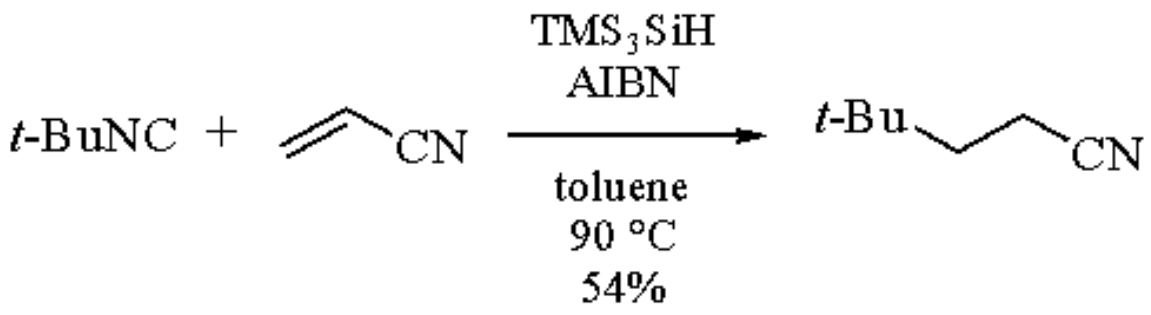

(25)

Isocyanides can insert at a benzylic carbon between a carbon-sulfur and a methoxycarbonyl bond to form a ketene *S,N*-acetal containing the isocyanide carbon (eq 26).[30]

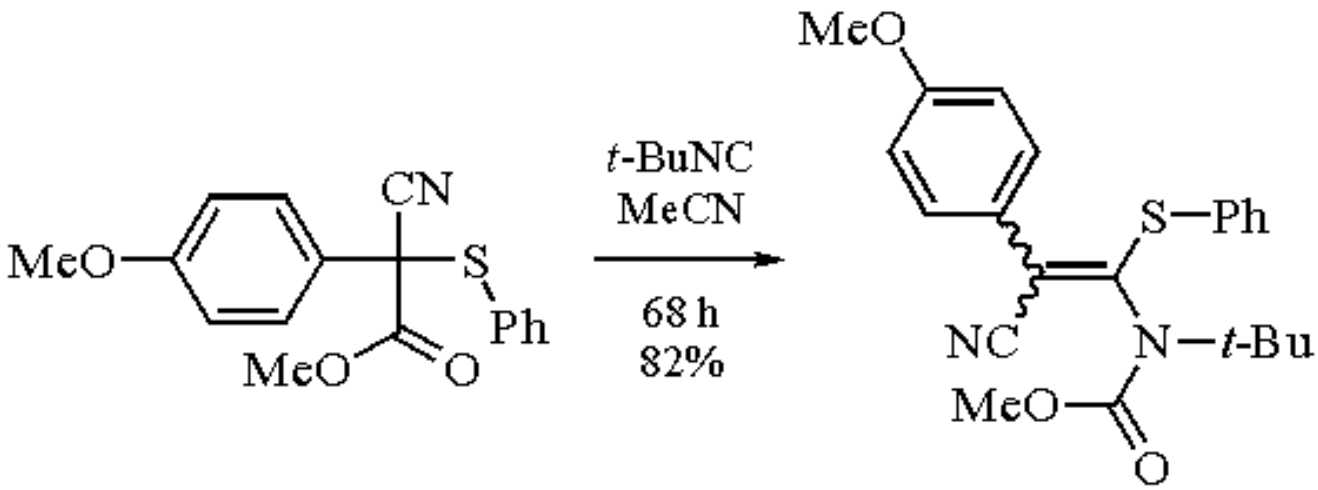

(26)

Polymerization of isocyanides under the action of Ni^{II} catalysis leads to helical polymethylenimines (eq 27).[31]

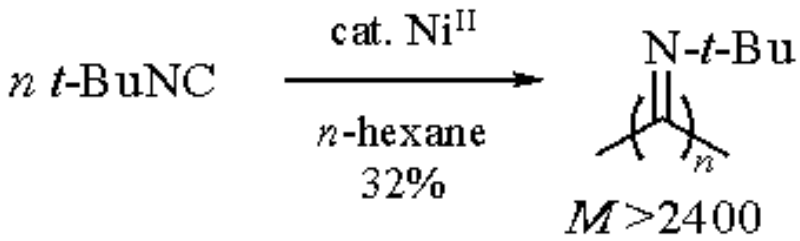

(27)

Oxidation of *t*-butyl isocyanide by elemental ***Sulfur*** with ***Tellurium*** as catalyst gives the corresponding isothiocyanate in reasonable yield (eq 28).[32] Direct oxidative addition to *t*-butyl isocyanide by elemental ***Selenium*** affords *t*-butyl isoselenocyanate.[33]

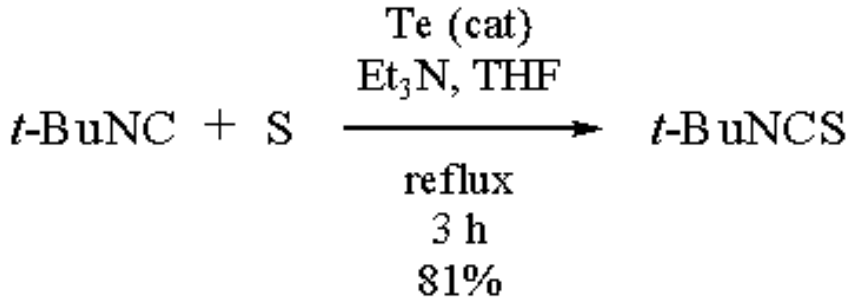

(28)

Related Reagents.

Copper(I) Oxide-t-Butyl Isocyanide; ***Cyclohexyl Isocyanide***; ***Ethyl Isocyanoacetate***; ***Methyl Isocyanide***; ***Phenyl Isocyanide***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***; ***Triphenylmethyl Isocyanide***.

---

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t-Butyl α-Lithiobis(trimethylsilyl)acetate

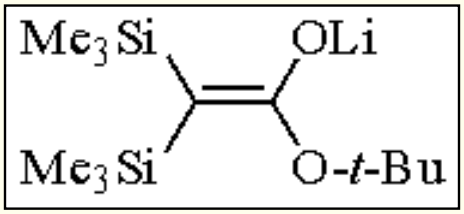

[62803-13-8] · $C_{12}H_{27}LiO_2Si_2$ · *t*-Butyl α-Lithiobis(trimethylsilyl)acetate · (MW 266.46)

(forms bis(trimethylsilyl)ketene at 25 °C; reacts with aldehydes to form α-silylated vinyl esters)

Preparative Method: an approximately 1 M solution in THF is prepared by addition of *t*-butyl bis(trimethylsilyl)acetate to a 1.0 M solution of ***Lithium Diisopropylamide*** maintained at -78 °C. The solution is stirred for 1 h at -78 °C following complete addition.[1] A simplified procedure utilizes ***n-Butyllithium*** in place of LDA and produces the amine-free reagent in THF/hexane.[2]

Formation of a Ketene.

Solutions of the reagent (**1**) decompose smoothly in THF at 25 °C to provide a useful synthesis of bis(trimethylsilyl)ketene (eq 1).[3]

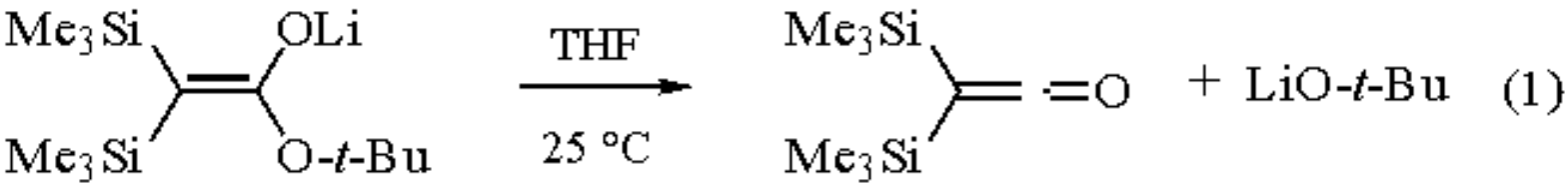

(1) 85% GLC; 60% isolated

Reaction with Aldehydes.

The reagent reacts via a Peterson alkenation process with aldehydes to give *t*-butyl 2-trimethylsilyl-2-alkenoates (**2**) (eq 2).[1,4] Only the 1,2-addition product is obtained with 2-butenal (eq 3). The reaction fails with ketones; only a proton transfer reaction to produce the ketone enolate is observed.

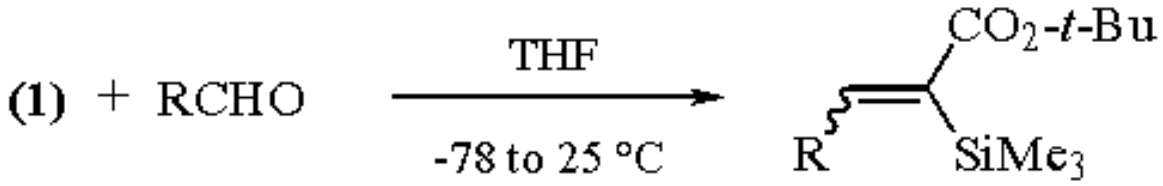

(2)

(2)

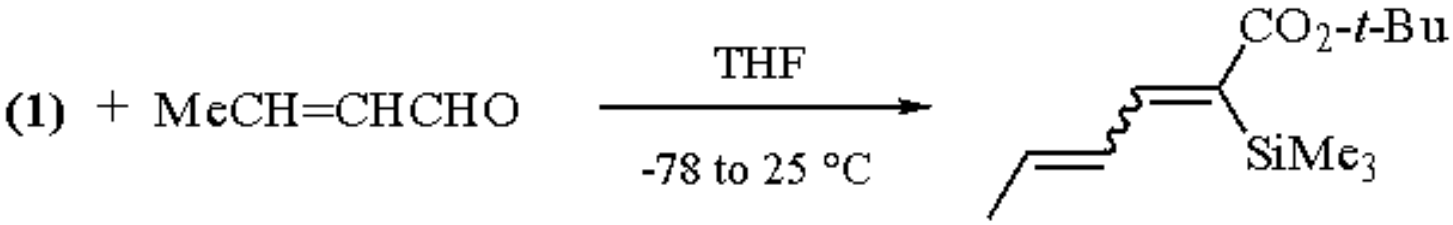

(3)

The (*E*) isomer of (**2**) is normally the favored product,[2,5] but selectivity for the (*Z*) isomer, especially with bulky aldehydes such as pivaldehyde, can be obtained by reaction in the presence of ***Magnesium Bromide*** or ***Diethylaluminum Chloride*** (eq 4).[5]

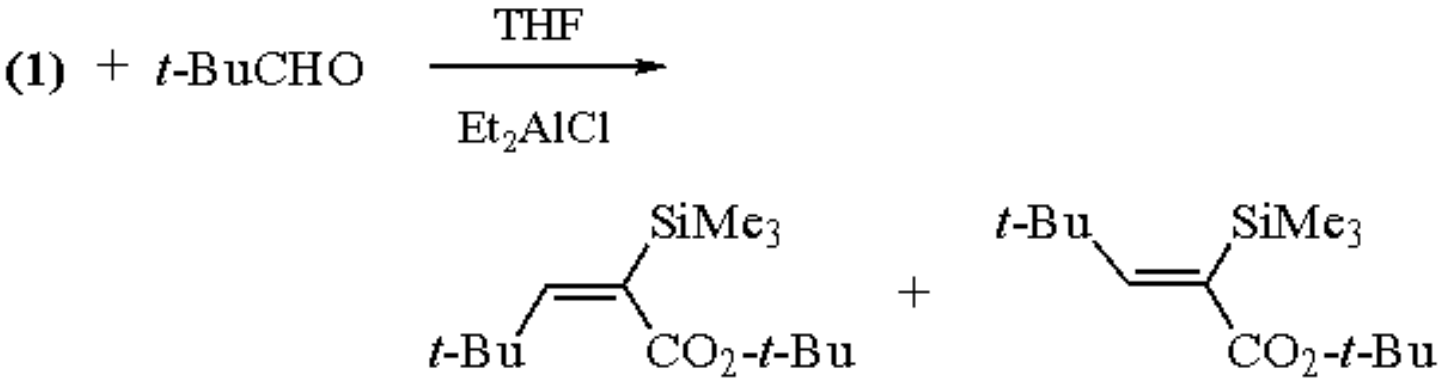

(4)

(*E*) (Z)

E:*Z* = 1:9; greater than 100:1 without Et_2AlCl

The products (**2**) are desilylated with ***Tetra-n-butylammonium Fluoride*** to produce an allenolate anion (**3**) which can be trapped in situ by protonation or reaction with aldehydes (eq 5).[2]

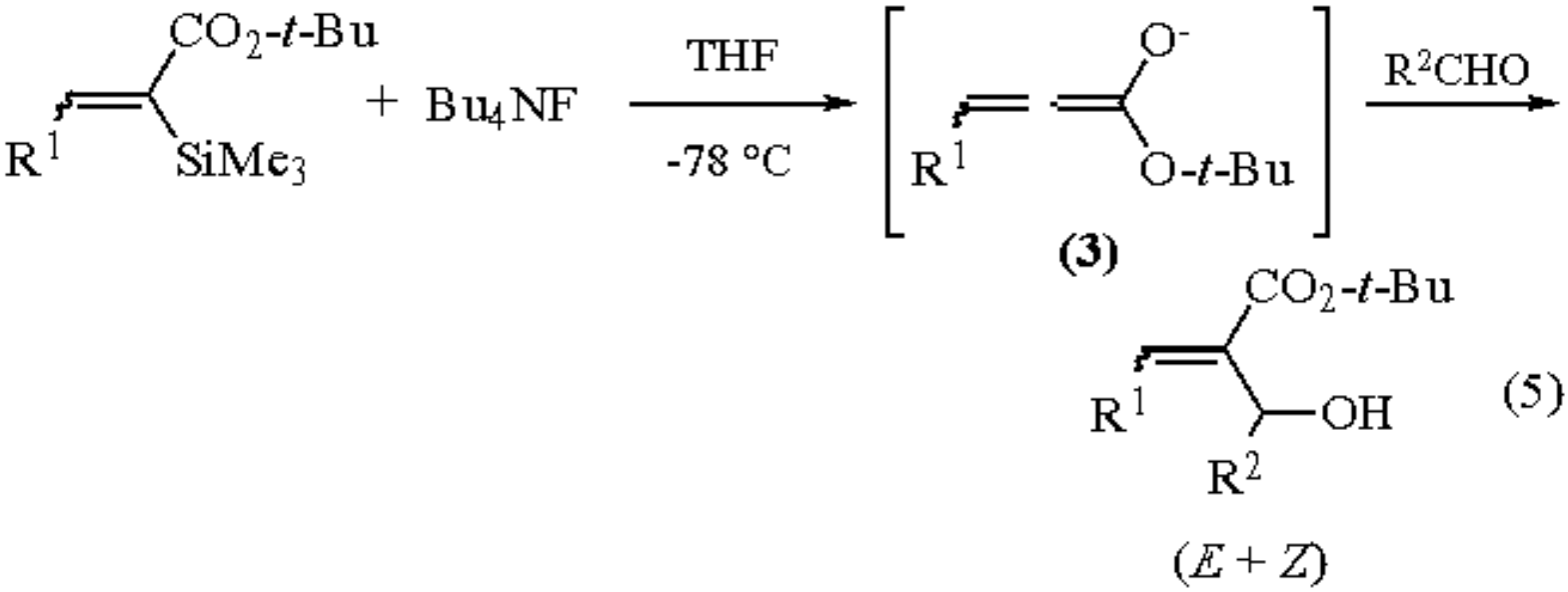

Related Reagents.

t-Butyl Trimethylsilylacetate; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***Ethyl Trimethylsilylacetate***; ***Methyl 2-Trimethylsilylacrylate***; ***Trimethylsilylacetic Acid***.

---

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t-Butyl α-Lithioisobutyrate

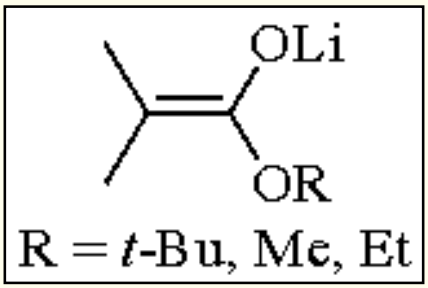

(R = *t*-Bu)

[54191-20-7] · $C_8H_{15}LiO_2$ · *t*-Butyl α-Lithioisobutyrate · (MW 150.15) (R = Me)

[35717-10-3] · $C_5H_9LiO_2$ · Methyl α-Lithioisobutyrate · (MW 108.07) (R = Et)

[53807-80-0] · $C_6H_{11}LiO_2$ · Ethyl α-Lithioisobutyrate · (MW 122.09)

(relatively stable ester enolates)

Physical Data: white solids. The X-ray crystal structure of the TMEDA complex (R = *t*-Bu) has been obtained.[1] The IR and ^1H, ^{13}C, and ^7Li NMR spectra for amine-free reagents have been reported.[2,3]

Solubility: sol THF; insol hexane and benzene (R = Me, *t*-Bu); the ethyl enolate (R = Et) is moderately sol benzene.[4]

Preparative Methods: for most transformations, a THF solution prepared by addition of the appropriate isobutyric ester to 1 equiv (or slight excess) of ***Lithium Diisopropylamide*** in THF at -78 °C is used directly. Solid reagents are prepared by addition of slightly less than 1 equiv of the ester (diluted 1:1 in toluene or benzene) to a 0.4 M solution of LDA in the same solvent at 10 °C. The precipitate is isolated by centrifugation and dried for at least 5 h at 1 mm (65% yield).[3]

Handling, Storage, and Precautions: the reagents react with air and moisture. Solutions of the amine-free reagents in THF slowly form β-keto esters with a half-life of 4200 min at 25 °C (R = Et).[4] The solid reagents are stable indefinitely at 25 °C.

Reactions.

The esters of isobutyric acid form relatively stable lithium enolates. Transformations of these enolates often occur in high yield, in part due to their greater stability and also because steric hindrance slows subsequent side reactions of the product.

Acylation with aroyl chlorides affords α,α-dimethyl β-keto esters which may be hydrolyzed and decarboxylated to isobutyrophenones.[5] Arylation of this stable enolate may be accomplished by reaction with arenechromium tricarbonyl complexes (e.g. anisole) and subsequent iodination (eq 1).[6] Vinylation may be effected by ***Nickel(II) Bromide*** catalysis.[7]

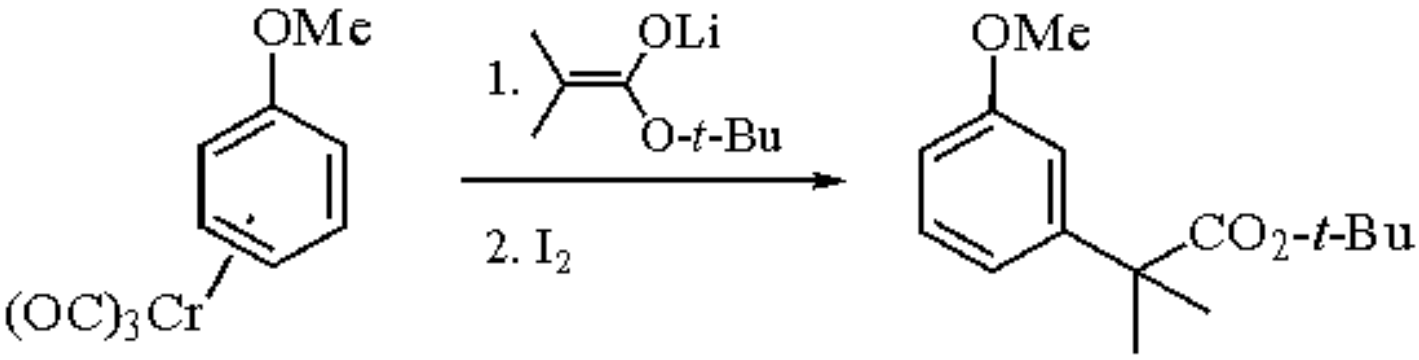

(1)

For other applications of these ester enolates, see the entry for ***Ethyl Lithioacetate***.

Related Reagents.

t-Butyl α-Lithiobis(trimethylsilyl)acetate; ***Dilithioacetate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***.

---

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Michael Rathke & Robert Elghanian

t-Butyl *N*-Lithio-*N*-(*p*-toluenesulfonyloxy)carbamate

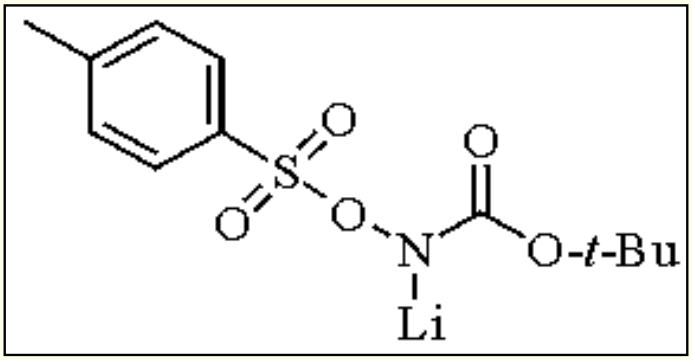

[134953-60-9] · $C_{12}H_{16}LiNO_5S$ · *t*-Butyl *N*-Lithio-*N*-(*p*-toluenesulfonyloxy)carbamate · (MW 293.26)

(electrophilic aminating agent for several carbanions;[1] can react with organoboranes to produce *N*-Boc protected primary amines[2])

Solubility: sol THF and diethyl ether.

Preparative Method: prepared from *t*-butyl *N*-(*p*-toluenesulfonyloxy)carbamate and ***n-Butyllithium*** at -78 °C in anhydrous THF.

Handling, Storage, and Precautions: should be used immediately as prepared for best results.

Electrophilic Amination.

t-Butyl *N*-lithio-*N*-(*p*-toluenesulfonyloxy)carbamate (**1**) is prepared from *t*-butyl *N*-(*p*-toluenesulfonyloxy)carbamate, which is easily obtained on a large scale by tosylation of the commercially available *t*-butyl *N*-hydroxycarbamate.[3] (**1**) is an electrophilic aminating reagent and a synthetic equivalent of $^{+}$NHBoc. It reacts with alkyllithium reagents (eq 1)[1a] or arylcopper reagents (eq 2)[1b] to provide primary amines in their *N*-Boc protected form.

$$\mathrm{RLi} \xrightarrow[\text{THF, -78 to 0 °C}]{\text{TsON(Li)Boc}} \mathrm{RNHBoc} \qquad (1)$$

R = Me, 60%; Bu, 71%; *s*-Bu, 42%

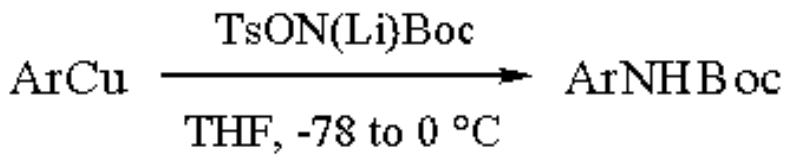

(2)

Ar = Ph, 51%; 2-anisyl, 73%; 2-pyridyl, 53%; 2-thienyl , 47%; 3-furyl, 48%

Zinc ester enolates react with (**1**) to give the corresponding *N*-Boc α-amino carboxylic esters in moderate yield (eq 3).[1a] In contrast, diethyl α-cuprophosphonates give *N*-Boc α-amino phosphonic esters in acceptable yields (eq 4).[1a]

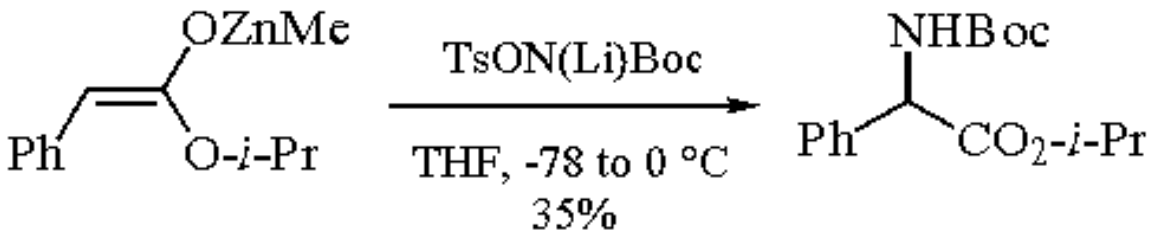

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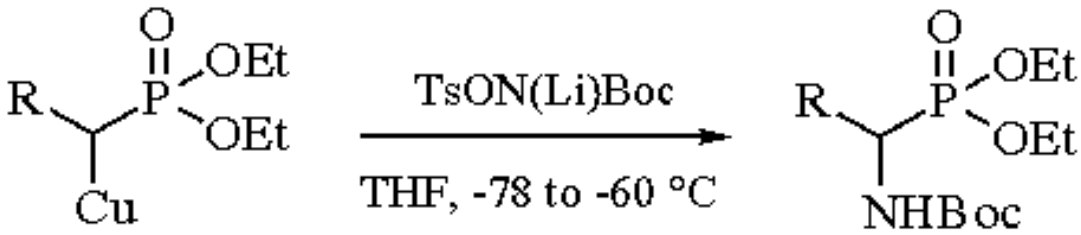

(4)

R = Me, 80%; Ph, 50%

Reaction with Organoboranes.[2]

Primary and secondary alkylboranes react rapidly at low temperature with (**1**) to give the corresponding *N*-Boc protected primary amines (eq 5). The reaction presumably proceeds via the anionotropic rearrangement of an organoborate complex (eq 6). *N*-Boc protected aniline is obtained from triphenylborane under the same conditions with a yield of 16%. This yield can be increased by using the potassium form of the aminating reagent, which is more reactive with organoboranes.

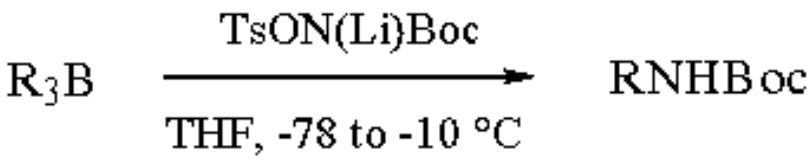

(5)

R = Bu, 81%; *s*-Bu, 30%

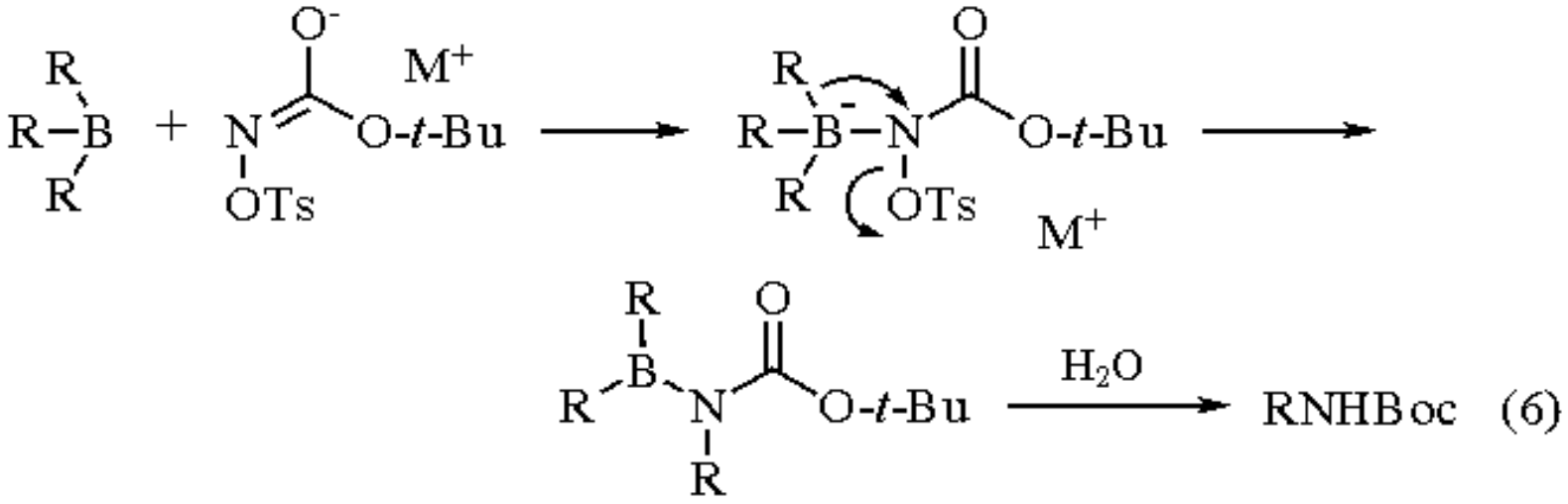

The reaction of alkyl derivatives of ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) with (**1**) results in migration of the *B*-cyclooctyl group, producing *N*-Boc-5-aminocyclooctanol (eq 7).

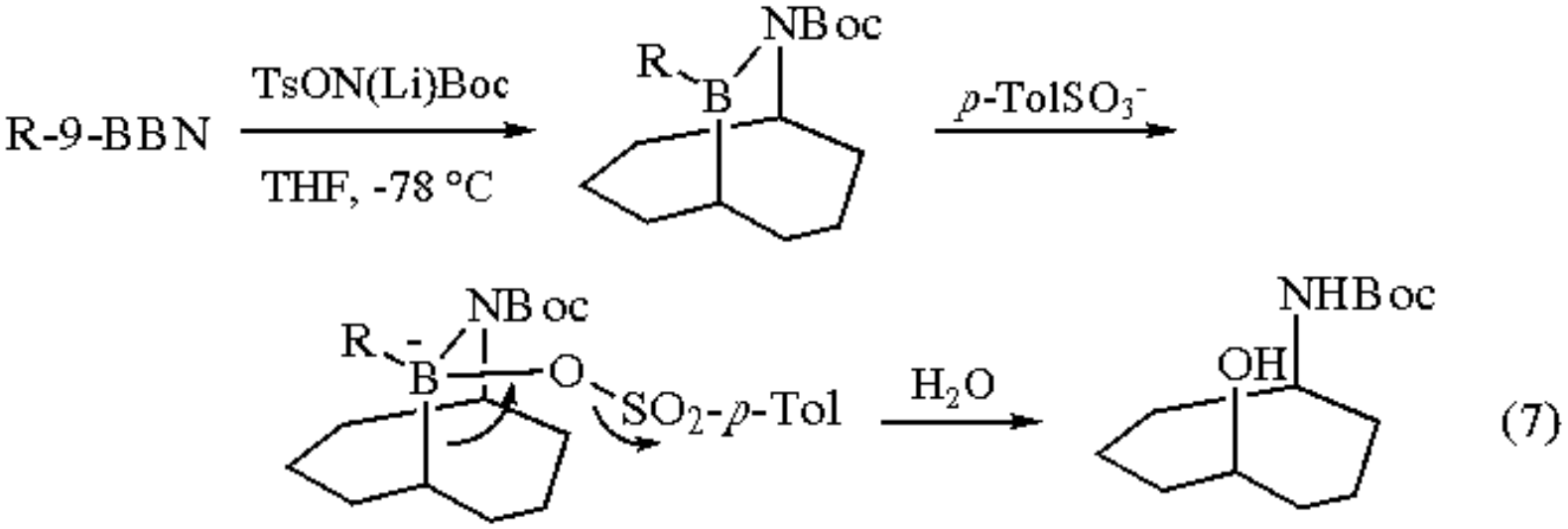

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n-Butyllithium[1]

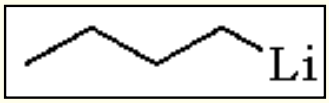

[109-72-8] · C_4H_9Li · *n*-Butyllithium · (MW 64.05)

(strong base capable of lithiating carbon acids;[1] useful for heteroatom-facilitated lithiations;[2,3] useful for lithium-halogen exchange;[1,4] reagent of choice for lithium-metal transmetalation reactions[1a,c,5])

Physical Data: colorless liquid; stable at rt; eliminates LiH on heating; d^{25} 0.765; mp -76 °C; bp 80-90 °C/0.0001 mmHg; dipole moment 0.97 D.[6] ^{13}C NMR, ^{1}H NMR, ^{6}Li NMR[8] and MS studies have been reported.[7-9]

Solubility: sol hydrocarbon and ethereal solvents, but should be used at low temperature in the latter solvent type: half-lives in diethyl ether and THF have been reported;[10] reacts violently with H_2O and other protic solvents.

Form Supplied in: commercially available as approximately 1.6 M, 2.5 M, and 10.0 M solution in hexanes and in cyclohexane, approximately 2.0 M solution in pentane, and approximately 1.7 M, and 2.7 M solution in *n*-heptane. Hexameric in hydrocarbons;[1c] tetrameric in diethyl ether;[1c] dimer-tetramer equilibrium mixture in THF;[11] when used in combination with tertiary polyamines such as TMEDA and DABCO, reactivity is usually increased.[1,12]

Analysis of Reagent Purity: since the concentration of commercial solutions may vary appreciably it is necessary to standardize solutions of the reagent prior to use. A recommended method for routine analyses involves titration of the reagent with *s*-butyl alcohol using 1,10-phenanthroline or 2,2´-biquinoline as indicator.[15] Several other methods have been described.[16]

Preparative Methods: may be prepared in high yield from *n*-butyl chloride[13] or *n*-butyl bromide[14] and ***Lithium*** metal in ether or hydrocarbon solvents.

Handling, Storage, and Precautions: solutions of the reagent are pyrophoric and the reagent may catch fire if exposed to air or moisture. Handling of the reagent should be done behind a shield in a chemical fume hood. Safety goggles, chemical resistant gloves, and other protective clothing should be worn. In case of fire, a dry-powder extinguisher should be used: in no case should an extinguisher containing water or halogenated hydrocarbons be used to fight an alkyllithium fire. Bottles and reaction flasks containing the reagent should be flushed with N_2 or preferably Ar and kept tightly sealed to preclude contact with oxygen or moisture. Standard syringe/cannula techniques for air and moisture sensitive chemicals should be applied when transferring the reagent. For detailed handling techniques see Wakefield.[1b]

Lithiations.

n-Butyllithium is a commonly used reagent for deprotonation of a variety of nitrogen (see ***Lithium Diisopropylamide***), oxygen, phosphorus (see ***Diphenylphosphine***), and carbon acids to form lithium salts. Compared to its *s*- and *t*-butyl analogs, *n*-BuLi is less basic[17] and less reactive but it is usually the reagent of choice for deprotonation of relatively strong carbon acids. These lithiations are most favorable when the conjugated bases are stabilized by resonance or when the carbanion forms at the sp hybridized carbon of a triple bond. Thus indene,[18] triphenylmethane,[19] allylbenzene,[20] and methyl heteroaromatics (e.g. ***Pyridine***, quinoline, and isoquinoline derivatives)[21] are readily lithiated with *n*-BuLi at the benzylic position. Allenes are lithiated at C-1 or C-3 depending on the number and size of the alkyl groups at these positions,[22] and terminal alkynes react with *n*-BuLi to give lithium acetylides.[4] Propargylic hydrogens can also be removed,[23] and treatment of terminal alkynes with 2 equiv of *n*-BuLi results in the lithiation of both propargylic and acetylenic positions (eq 1).[23a]

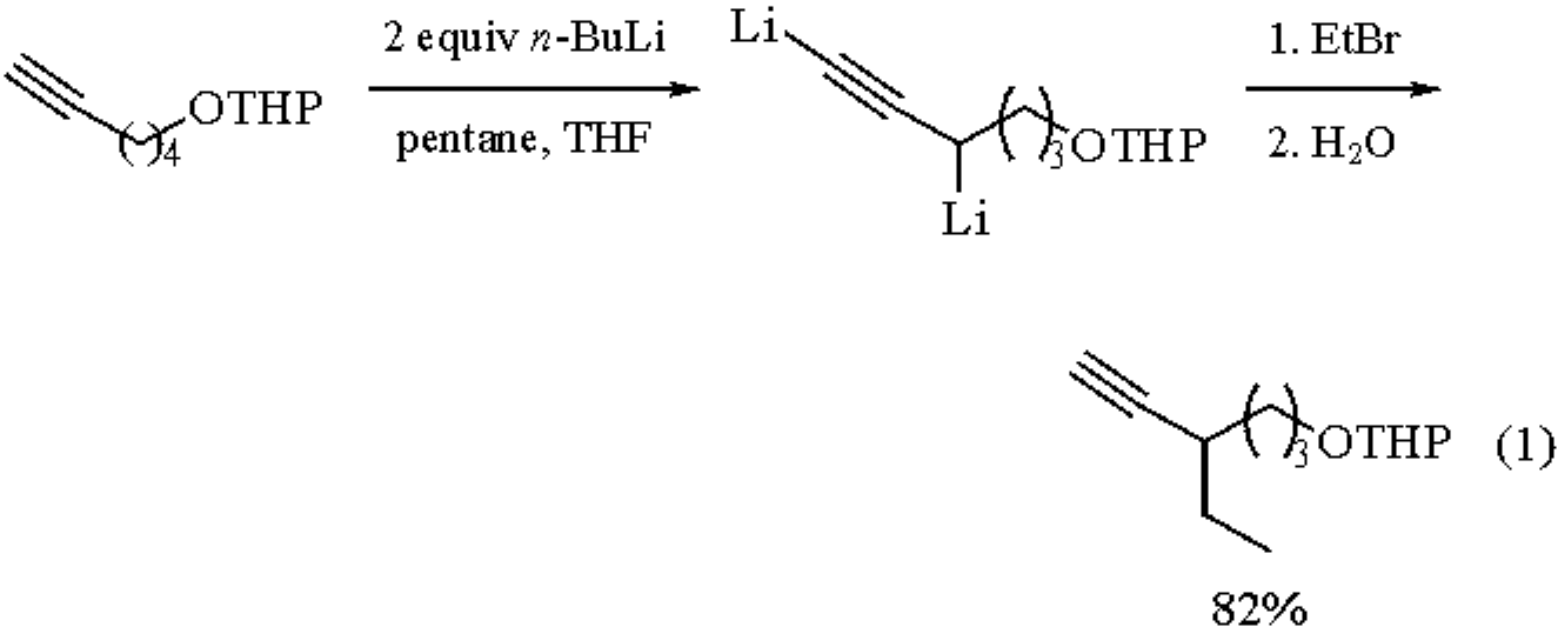

The metalating ability of *n*-BuLi (and other organolithiums) is greater in electron-donating solvents than in hydrocarbons. Electron-donating solvents such as diethyl ether or THF provide coordination sites for the electron deficient lithium and promote the formation of lower-order organolithium aggregates.[1a,c] These exhibit significantly higher levels of reactivity than do the higher-order oligomers present in hydrocarbon solvents. *n*-Butyllithium is often used in the presence of added lithium complexing ligands, such as ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) and ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO), which further enhance the reactivity of this reagent.[12] Many compounds, normally unreactive toward *n*-BuLi alone (e.g. benzene), are readily lithiated[24] and even polylithiated[25] by a combination of *n*-BuLi and one of these additives. Allylic[26,27] and benzylic sites bearing no additional activating groups at the α-position (e.g. toluene)[12c] are also lithiated in the presence of lithium complexing donors (eq 2).[26]

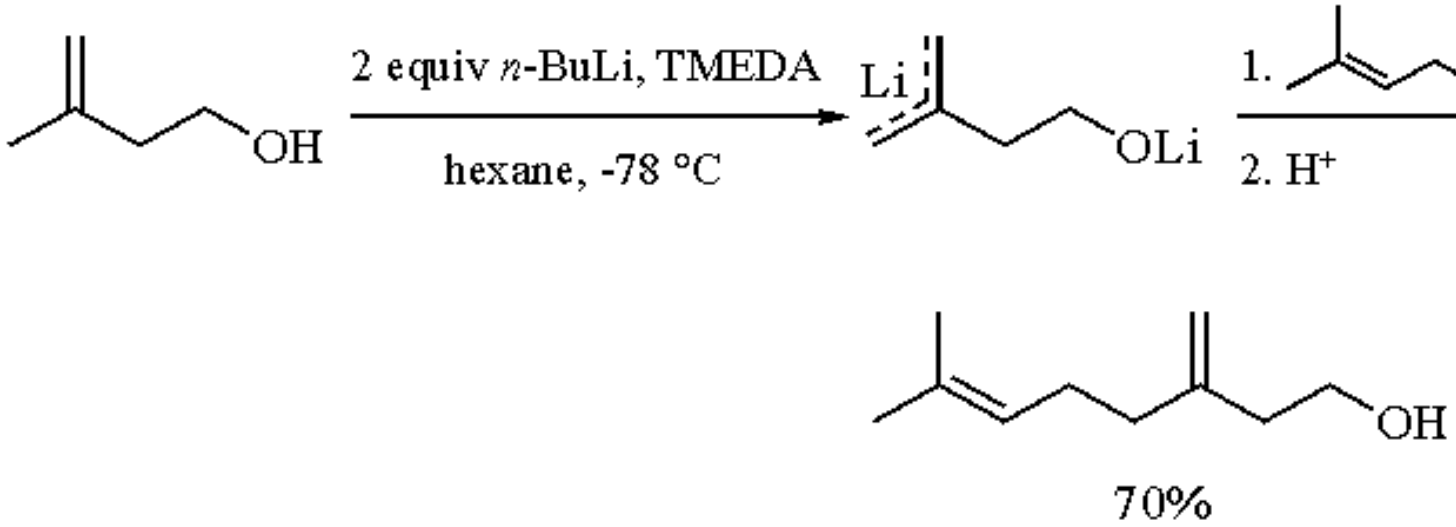

(2)

Metal alkoxides are often employed as additives to enhance the metalating ability of *n*-BuLi. Particular use has been made of the ***n-Butyllithium-Potassium t-Butoxide*** mixture,[28] which is capable of effecting rapid metalation of benzylic[29] and allylic[30] systems as well as aromatic rings.[28] Although the products of these metalations are not organolithium compounds they do, nevertheless, readily react with electrophiles. Alternatively, they may be converted into the corresponding organolithium derivatives by the addition of ***Lithium Bromide***.[30a,31] Using *t*-BuOK/*n*-BuLi for deprotonation, the one-pot synthesis of 2-(4-isobutylphenyl)propanoic acid (ibuprofen) from *p*-xylene, through a sequence of metalations and alkylations, has been achieved in 52% overall yield.[29] Dimetalation of arylalkynes with *n*-BuLi/*t*-BuOK followed by addition of electrophiles has been used as a route to *ortho*-substituted arylalkynes (eq 3).[31b]

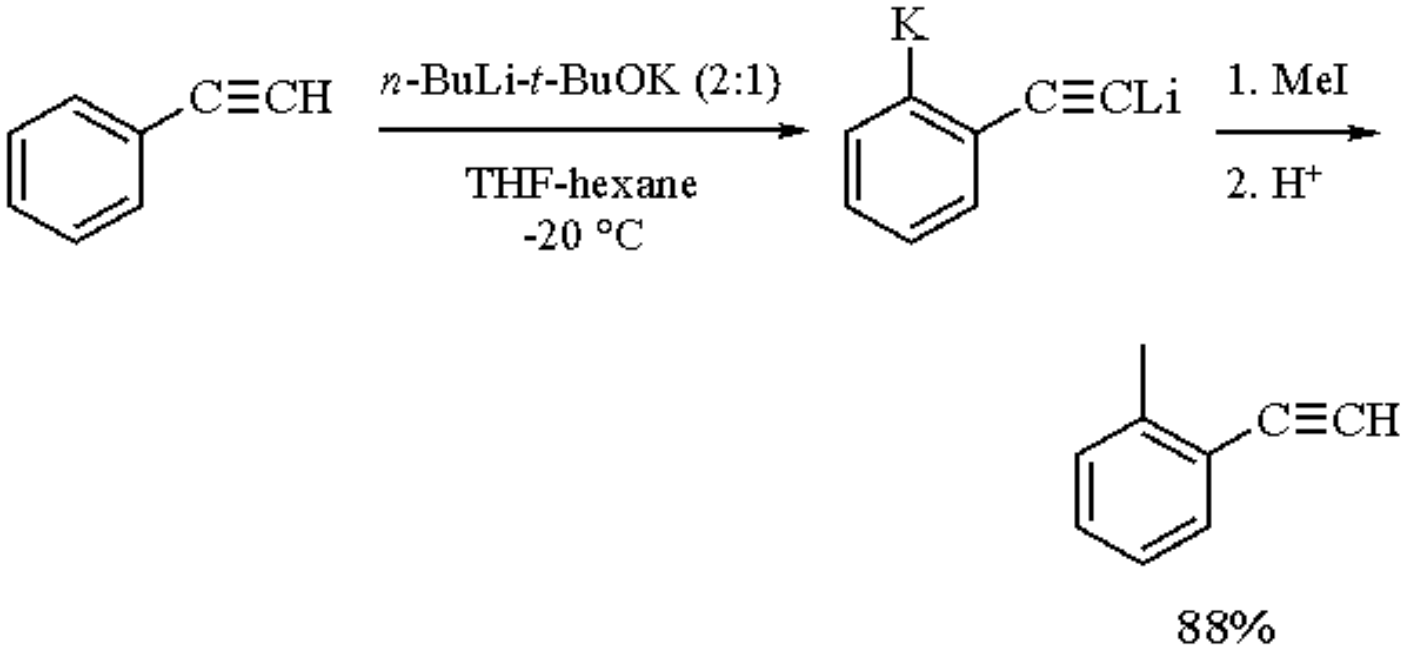

(3)

Facile and regioselective α-deprotonation is often effected by treatment of heteroatom-containing (e.g. oxygen, sulfur, nitrogen, and the like) compounds with *n*-BuLi, and these reactions have been extensively reviewed.[2,3,32,33] Thus sulfones,[34] certain sulfides,[35] and sulfoxides[36] can be lithiated adjacent to sulfur under various conditions, and α-heterosubstituted vinyllithium compounds are often available from the corresponding ethers,[37] thioethers,[38] chlorides,[39] and fluorides[40] via lithiation using *n*-BuLi. Isocyanides[41] and nitro compounds[42] have been lithiated adjacent to nitrogen with *n*-BuLi in THF at low temperatures (less than -60 °C) and the formation of various α-phosphorus

alkyllithiums has been reported.[43] Simple ethers are also susceptible to lithiation at the α site by *n*-BuLi, especially at elevated temperatures.[44] The initial proton abstraction in these systems is generally followed by various cleavage reactions resulting from α,β- and α´,β´-eliminations as well as the Wittig rearrangement.[45] Tetrahydrofuran, for example, is rapidly lithiated by *n*-BuLi at 35 °C ($t_{1/2}$ = 10 min) to give ethylene and the lithium enolate of acetaldehyde.[46]

Due to the stabilizing effect of two sulfur atoms, 1,3-dithianes are easily lithiated at the α-position on treatment with *n*-BuLi (see ***2-Lithio-1,3-dithiane***).[47] The 2-lithio-1,3-dithianes constitute an important class of acyl anion equivalents, permitting electrophilic substitution to occur at the masked carbonyl carbon.[47] Hydrolysis of the 1,3-dithiane functionality into a carbonyl group is effected in the presence of mercury(II) ion (eq 4).[48]

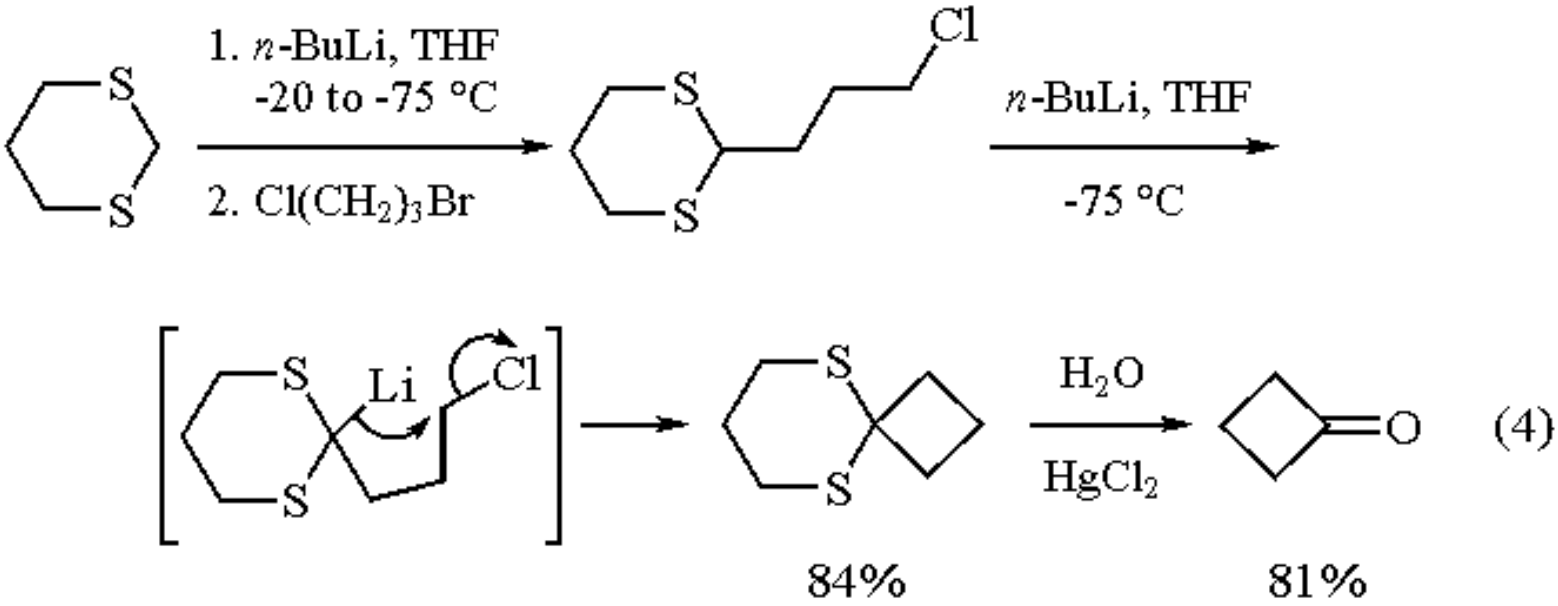

When conducted at sufficiently low temperatures (less than -78 °C), α-deprotonation can occur faster than nucleophilic addition to an electrophilic center present in the same molecule. This strategy, which involves initial lithiation followed by intramolecular nucleophilic addition of the newly generated C-Li bond to an electrophilic moiety, is useful for the construction of carbocycles including medium and large ring systems (eqs 5 and 6).[49,50]

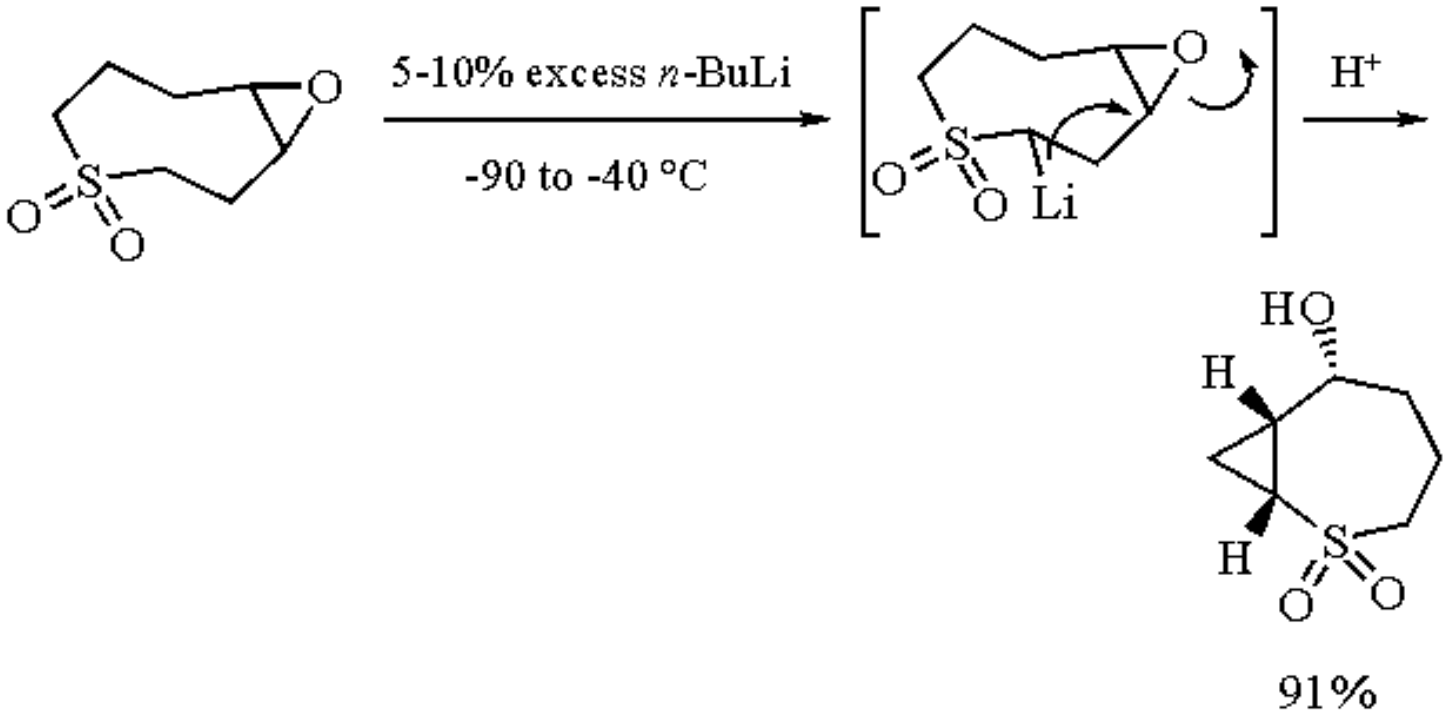

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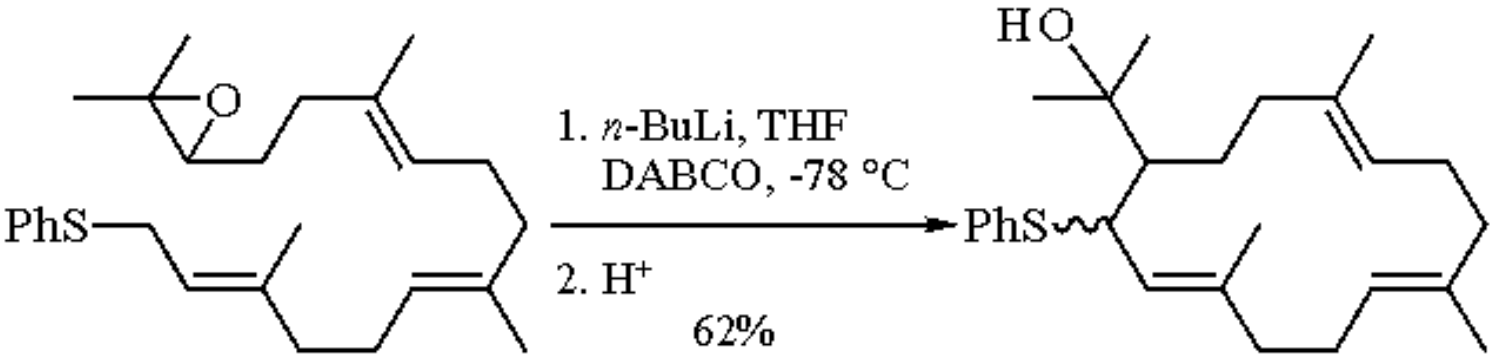

(6)

A large number of heteroaromatic compounds,[2] such as furans (see ***Furan***),[51] thiophenes (eq 7),[52] oxazoles,[53] and *N*-alkyl- and *N*-aryl substituted pyrroles (see ***2-Lithio-N-phenylsulfonylindole***),[54] pyrazoles,[55] imidazoles,[56] triazoles,[57] and tetrazoles,[58] are lithiated under various conditions α to the ring heteroatom using *n*-BuLi. However, pyridine and other nitrogen heteroaromatics bearing the pyridine, pyrimidine, or pyrazine nucleus are generally not lithiated. Indeed, they have a tendency to undergo nucleophilic addition reactions with this reagent[1b] (see ***2-Lithiopyridine***).

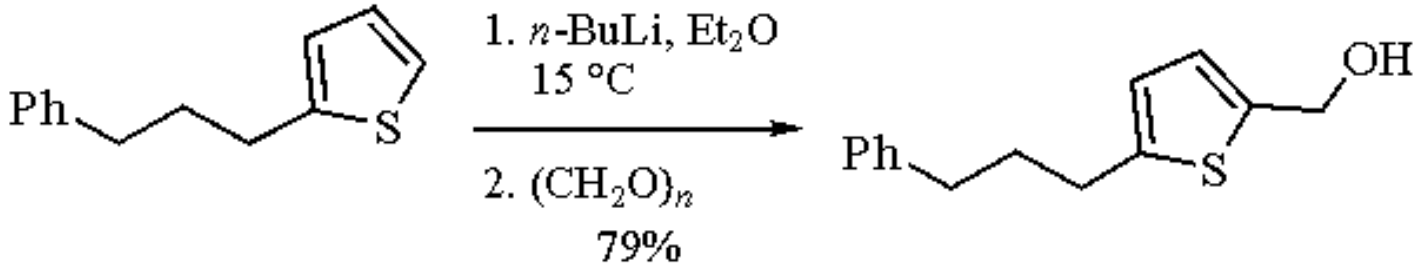

(7)

When the α-position is benzylic, propargylic, or allylic, deprotonation takes place more readily and *n*-BuLi is generally the reagent of choice for these reactions.[59,60] However, the more basic ***s-Butyllithium*** is a better reagent for deprotonation of alkyl allyl ethers[61] and certain alkyl allyl thioethers[62] which react slowly (if at all) with *n*-BuLi in THF at low temperatures (less than -65 °C).

Proton removal adjacent to a heteroatom is further facilitated if the lithium can be coordinated to proximate electron donors, such as a carbonyl oxygen, permitting the formation of dipole-stabilized carbanions.[33] Thus various 2-alkenyl *N*,*N*-dialkylcarbamates undergo rapid α-deprotonation adjacent to oxygen on treatment with *n*-BuLi/TMEDA at -78 °C.[63,64] The resulting dipole-stabilized lithium carbanions react with ketones and aldehydes in a highly regioselective fashion providing γ-hydroxyalkylated enol esters (eq 8) which, following cleavage of the carbamoyl moiety (***Titanium(IV) Chloride***/H_2O or MeOH), afford δ-hydroxy carbonyl compounds (homoaldols) as lactols or lactol ethers.[65] Similarly, aliphatic or aromatic amides[66,67] (eq 9),[67a] phosphoramides,[68] and some formamidine derivatives (e.g. 1,2,3,6-tetrahydropyridine,[69] thiazolidine,[69] 1,3-thiazine,[69] and tetrahydroisoquinolines[70]) are selectively lithiated α to the nitrogen at the activated position. Electrophilic substitution of the intermediate organolithiums followed by hydrolytic cleavage of the amide or formamidine group provides a synthetically valuable route to α-substituted (or γ-substituted[69]) secondary amines.[33] Use of the more basic *s*-BuLi (or ***t-Butyllithium***) is generally required for deprotonation of the analogous nonbenzylic or nonallylic systems.

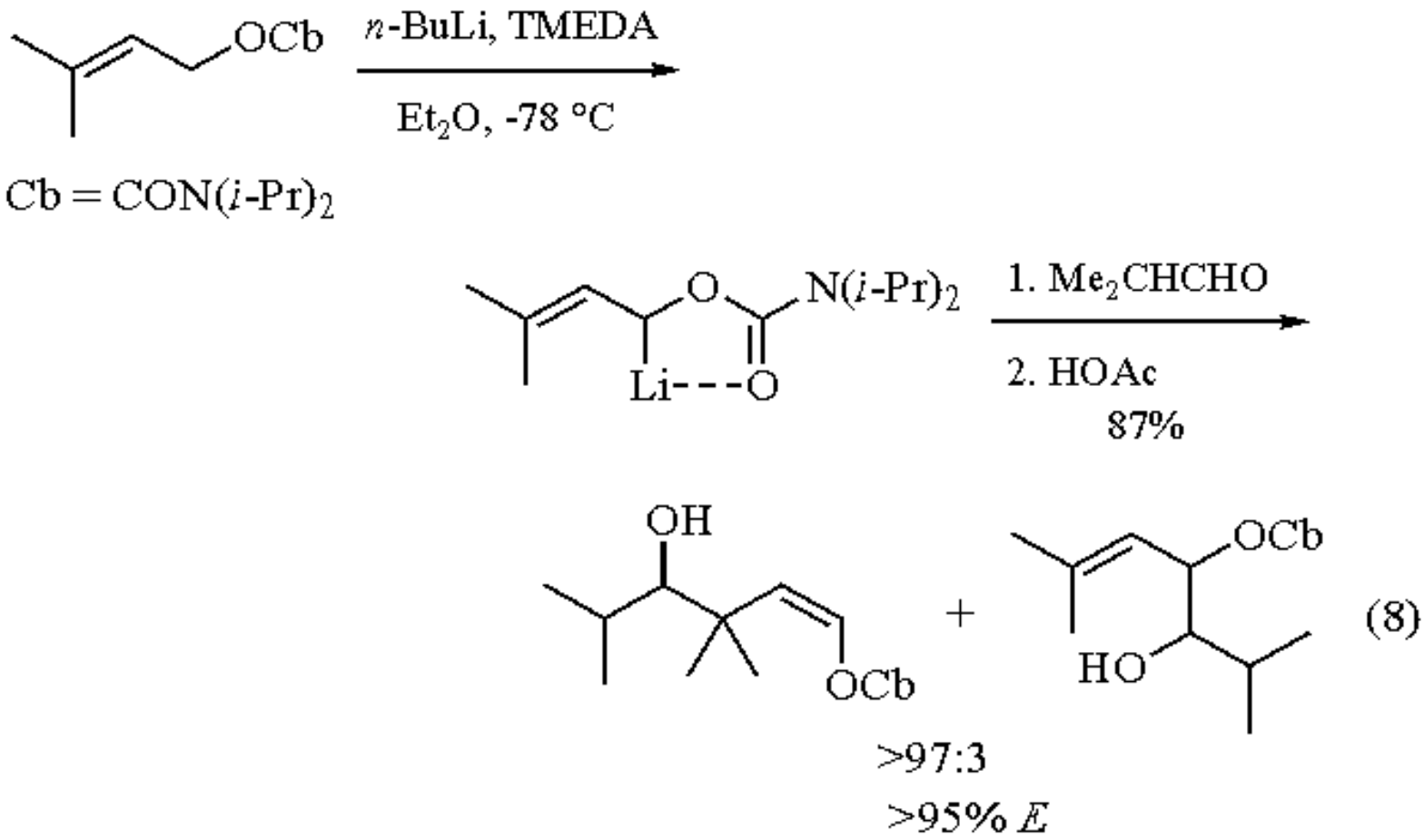

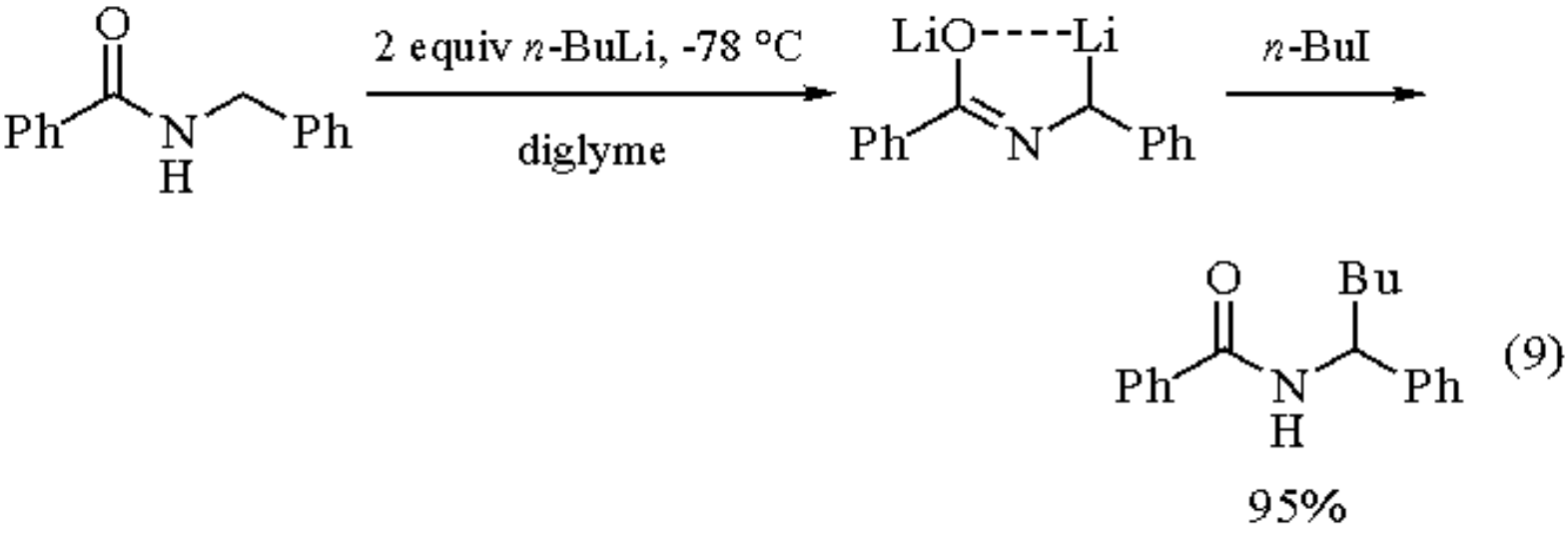

(9)

n-Butyllithium is also used for the stereoselective α-lithiation of chiral sulfonyl compounds,[71] chiral 2-alkenyl carbamates,[64,72] various heterocyclic amine derivatives with chiral auxiliaries appended on the nitrogen (e.g. oxazoline[73] or formamidine[74,75] groups) (eq 10),[75] and chiral oxazolidinones derived from benzylamines (eq 11).[76] These elegant reactions have been applied to the asymmetric syntheses of a number of natural products.[77,78]

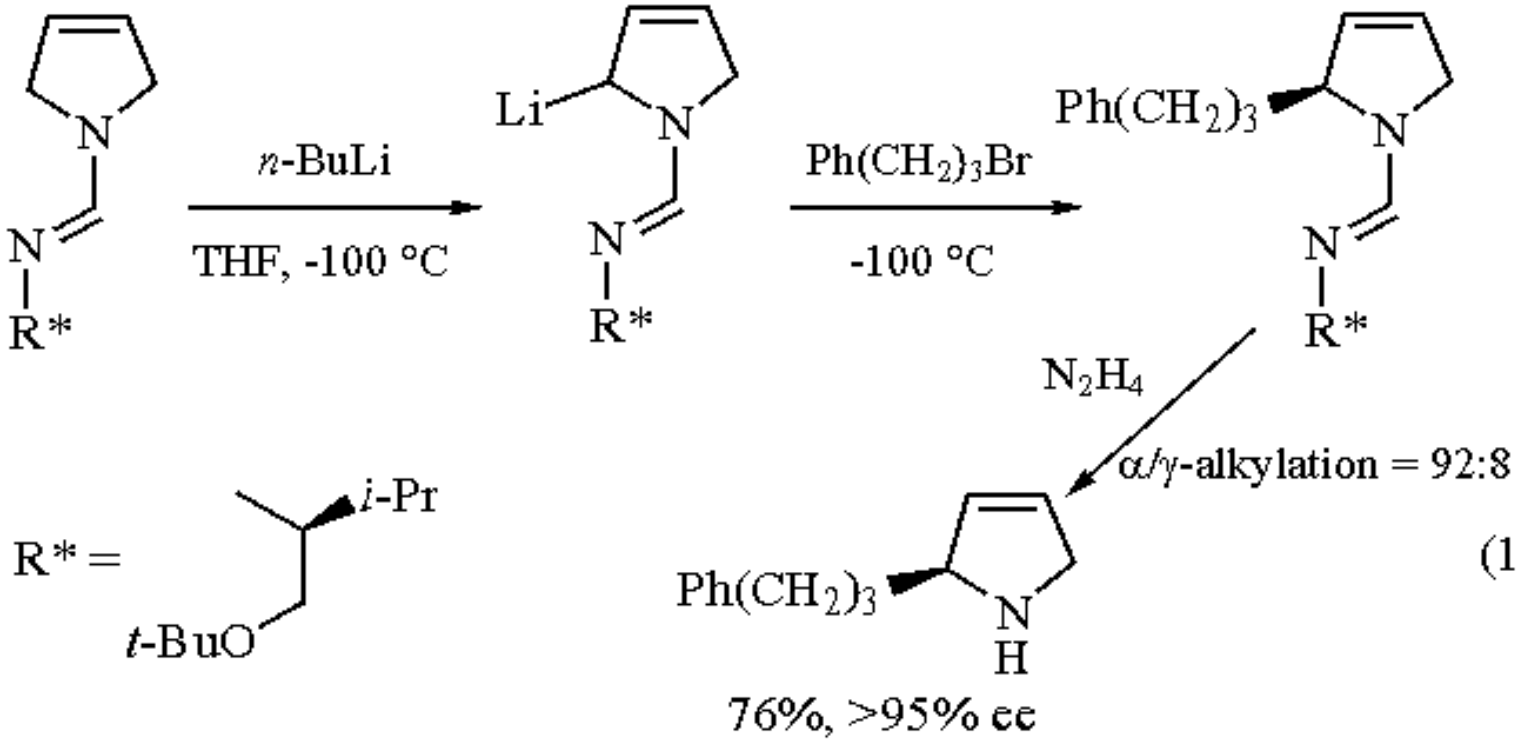

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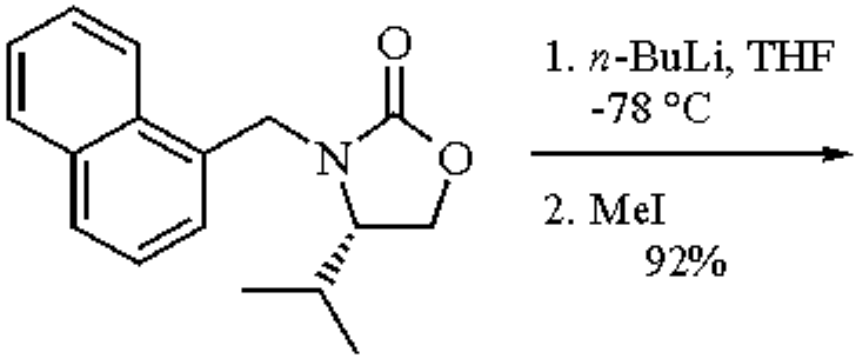

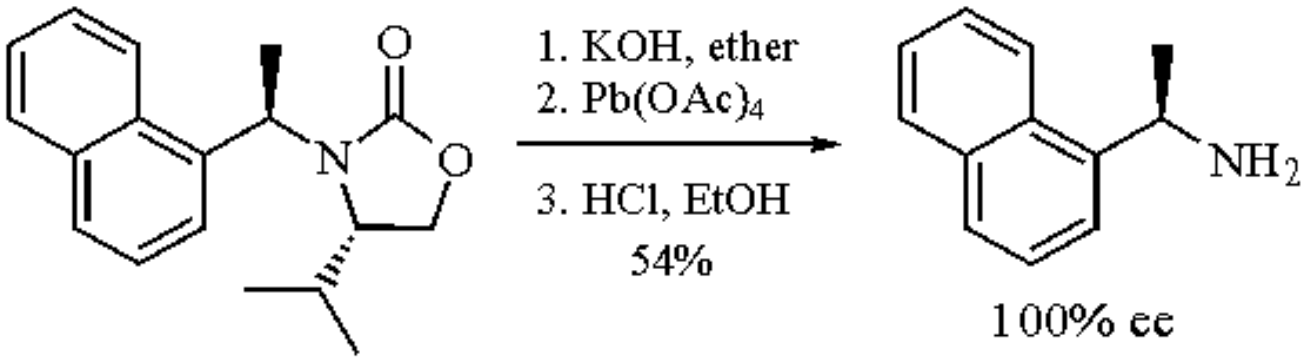

(11)

Ortho Lithiations.

Heteroatom-containing substituents on aromatic rings facilitate metalation by organolithium reagents and direct the metal almost exclusively to the *ortho* position. This effect, usually referred to as *ortho* lithiation, is of considerable synthetic importance and the topic has been extensively reviewed.[2,4,79] Although *n*-BuLi (typically in THF or Et_2O with added TMEDA)[80] is capable of effecting a large number of *ortho* lithiations, the use of this reagent is somewhat limited by its tendency to undergo nucleophilic carbonyl additions with some of the most potent and useful *ortho* directors, particularly tertiary amide and carbamate functionalities (e.g. $CONEt_2$ and $OCONEt_2$).[79,81] For example, *N*,*N*-dimethyl- and -diethylbenzamides afford primarily aryl butyl ketones upon treatment with *n*-BuLi (see ***2-Lithio-N,N-diethylbenzamide***).[82] The reagent of choice for these lithiations is ***s-Butyllithium***, which is less nucleophilic than *n*-BuLi and hence more tolerant of electrophilic functional groups.[79] There are, however, a variety of *ortho*-directing groups that are well suited for *n*-BuLi-promoted lithiations. These include NR_2,[80] CH_2NR_2,[80] $CH_2CH_2NR_2$,[80] OMe (see ***o-Lithioanisole***),[83] OCH_2OMe,[84] SO_2NR_2,[85] C=NR,[86] 2-oxazolinyl,[85,87] F,[88] CF_3,[80] and groups that contain acidic hydrogens and themselves undergo deprotonation prior to lithiation of the aromatic ring (thus requiring the use of 2 equiv of *n*-BuLi), e.g. CONHR,[89] CH_2OH,[80] NHCO-*t*-Bu,[90] and SO_2NHR[80] (eq 12).[91] *n*-Butyllithium is also used frequently for the *ortho* lithiation of heterocyclic aromatic rings,[2] including those that contain the pyridine nucleus (eq 13).[92]

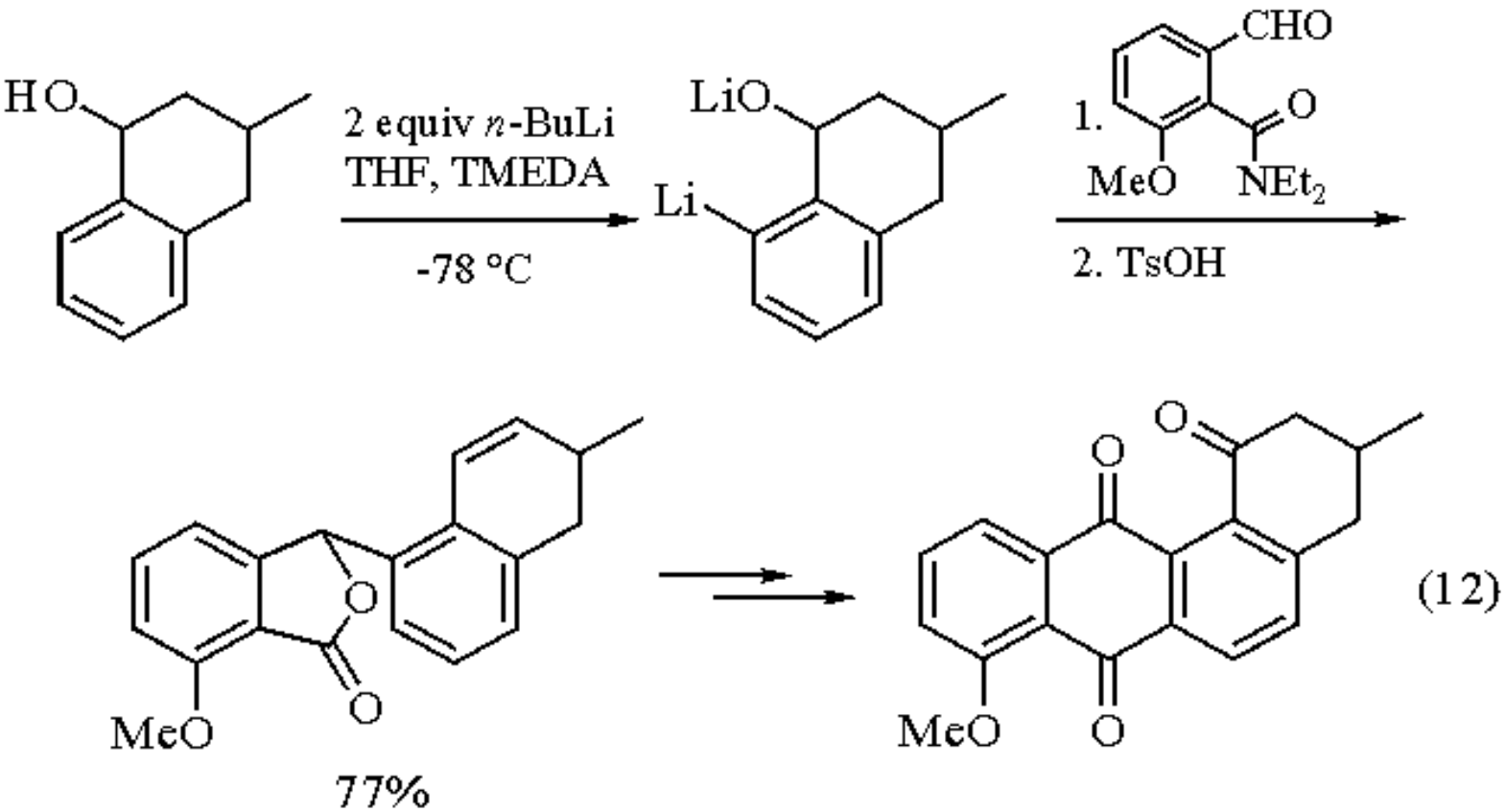

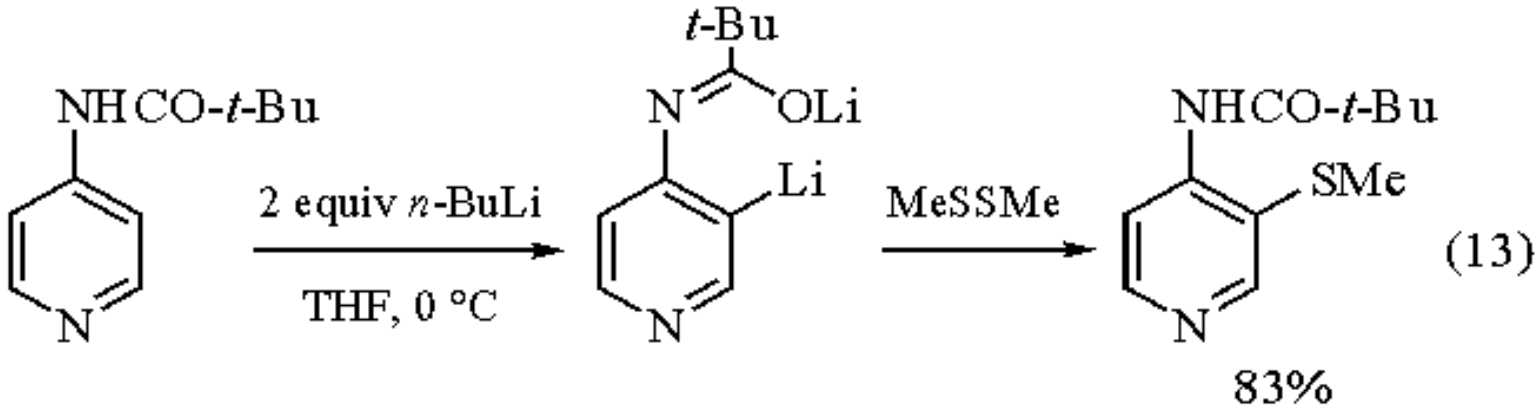

Formation of Enolate Anions and Enolate Equivalents.

Owing to its tendency to undergo nucleophilic addition with carbonyl groups and other electrophilic carbon-heteroatom multiple bonds (C=NR, C&tbond;N, C=S),[1] *n*-BuLi is usually not the reagent of choice for the generation of enolate anions or enolate equivalents from active hydrogen compounds. This is done most conveniently using the less nucleophilic lithium dialkylamides (e.g. ***Lithium Diisopropylamide*** (LDA), ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LiTMP), and ***Lithium Hexamethyldisilazide*** (LTSA)) prepared (often in situ) from sterically hindered secondary amines, typically by treatment with *n*-BuLi.[93] However, less reactive carbonyl compounds such as amides (eq 14)[94] and carboxylic acids[95] as well as those containing carbon-nitrogen or carbon-sulfur multiple bonds, e.g. imines,[96] oxazines,[97] nitriles,[98] some hydrazones,[99] and thioamides,[100] can be lithiated α to the electrophilic carbon with *n*-BuLi under various conditions. β-Keto esters can be alkylated at the α´-carbon using ***Sodium Hydride*** for the first deprotonation and *n*-BuLi for abstraction of the less acidic α´-proton followed by addition of alkyl halides.[101] Lithiation of unsymmetrical imines using *n*-BuLi takes place regioselectively at the most substituted α-carbon (eq

15).[96] In contrast, LDA directs metalation and subsequent alkylation predominantly to the less substituted α-position in similar systems.[102] Lithium enolates of camphor imine esters, prepared by addition of *n*-BuLi, undergo highly diastereoselective Michael additions with α,β-unsaturated esters (eq 16).[103] The tightly chelated structures of the intermediate enolates permit selective *re* face approach of the Michael acceptors, giving rise to the high degree of distereoselectivity observed.

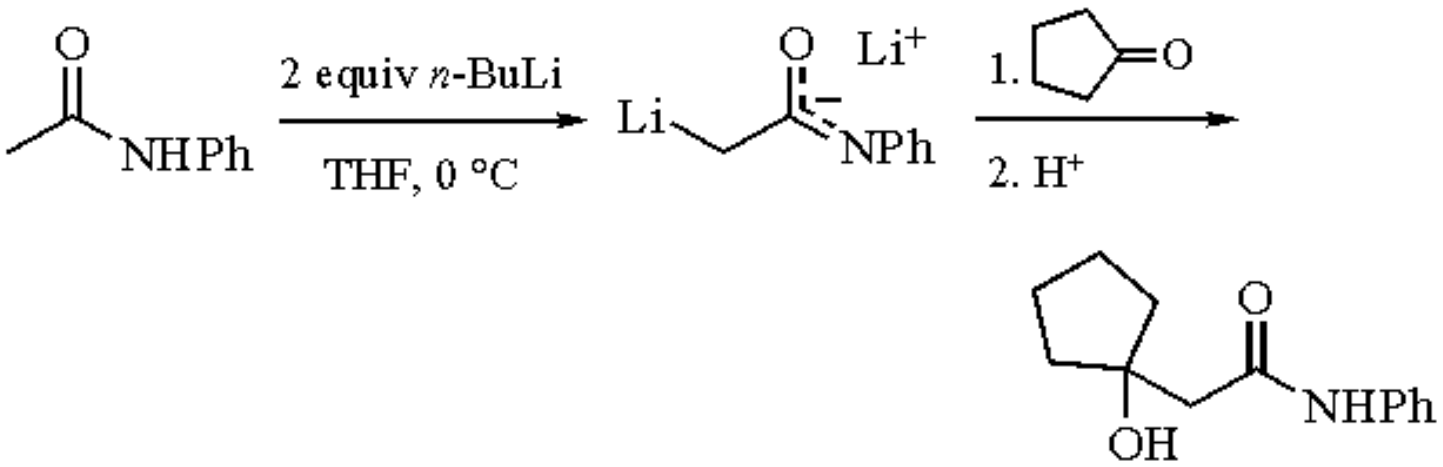

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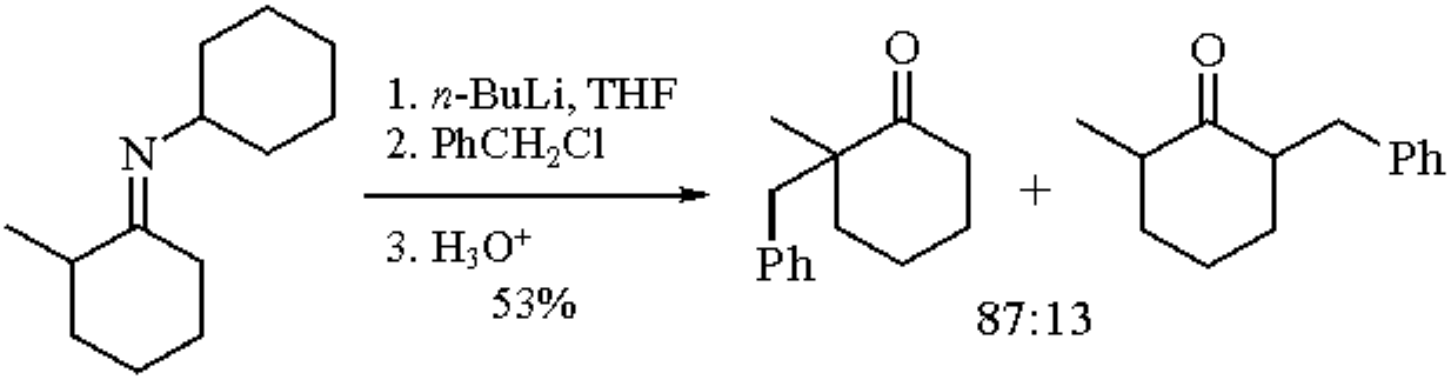

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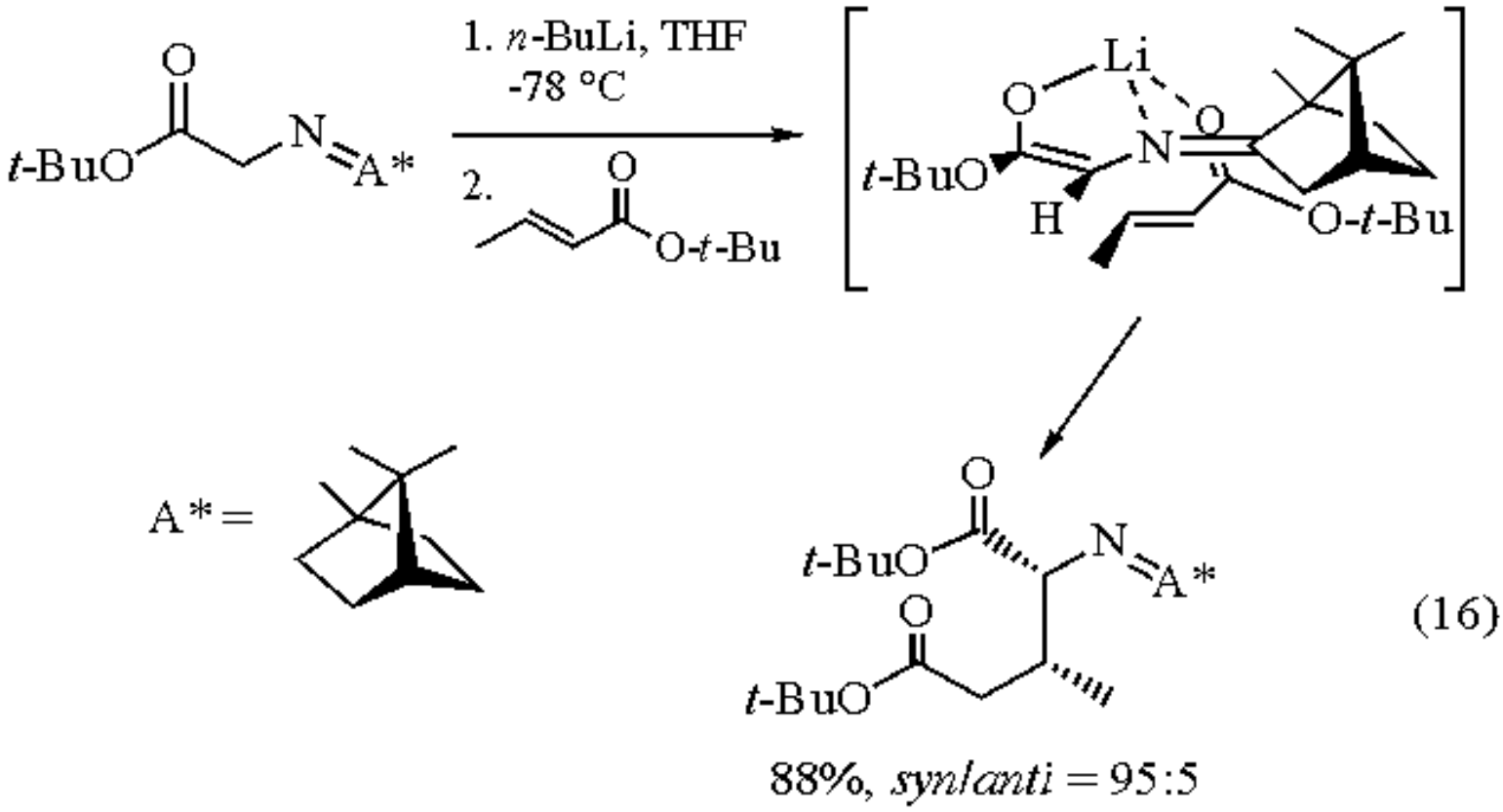

Metal-Halogen Interchange and Transmetalation Reactions.

The metal-halogen interchange reaction which involves the exchange of halogen and lithium atoms is an important method for the preparation of organolithium compounds not readily accessible through metalation. In particular, the generation of aryl-, vinyl-, and cyclopropyllithium derivatives from the corresponding bromides or iodides on treatment with *n*-BuLi (usually in ethereal solvents at or below -78 °C) is of considerable synthetic utility (eqs 17-19).[104-106] The relative rates of exchange depend on the halide and decrease in the order I > Br > Cl > F. Fluorides and chlorides, with the exception of some polychlorinated aliphatic[107] and aromatic compounds,[108] are quite resistant to lithium-halogen interchange; instead, they tend to promote *ortho* and α lithiations.[79]

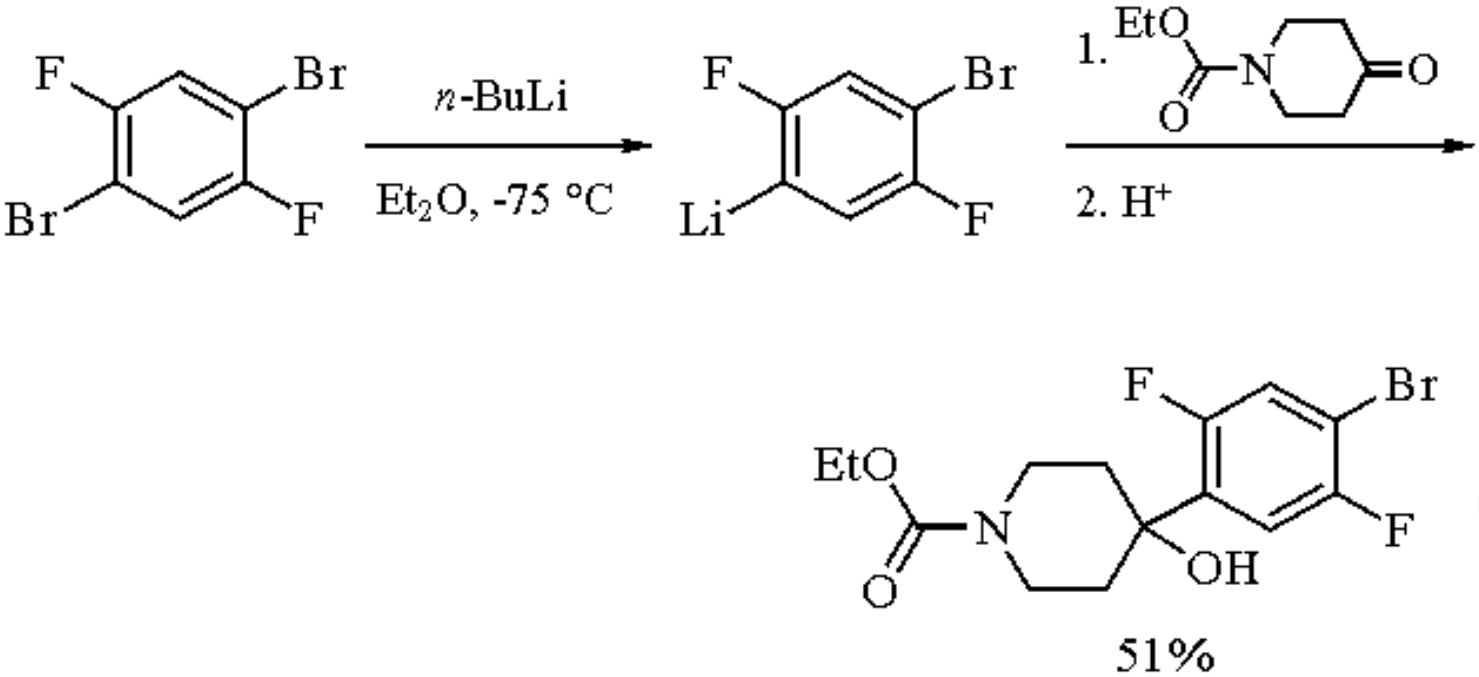

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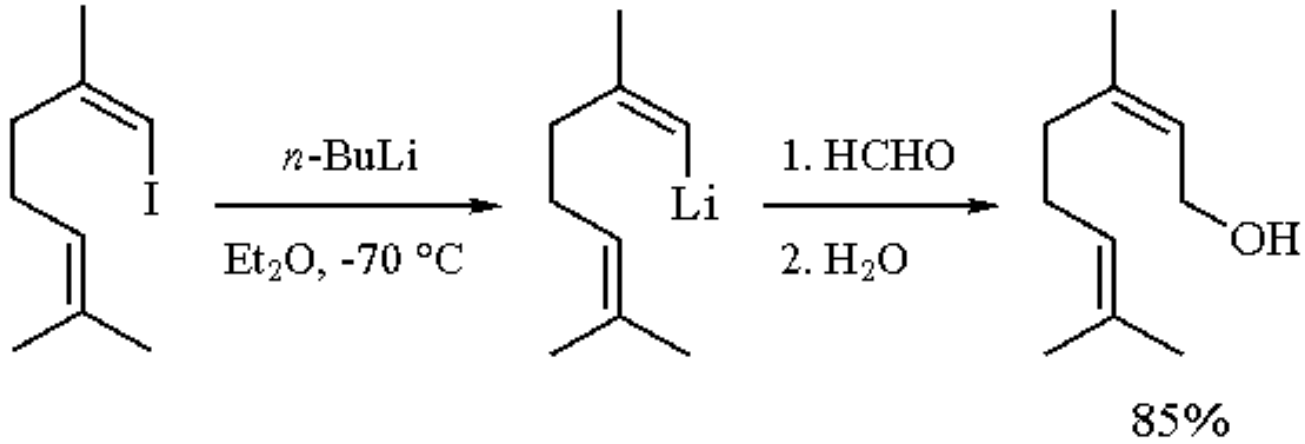

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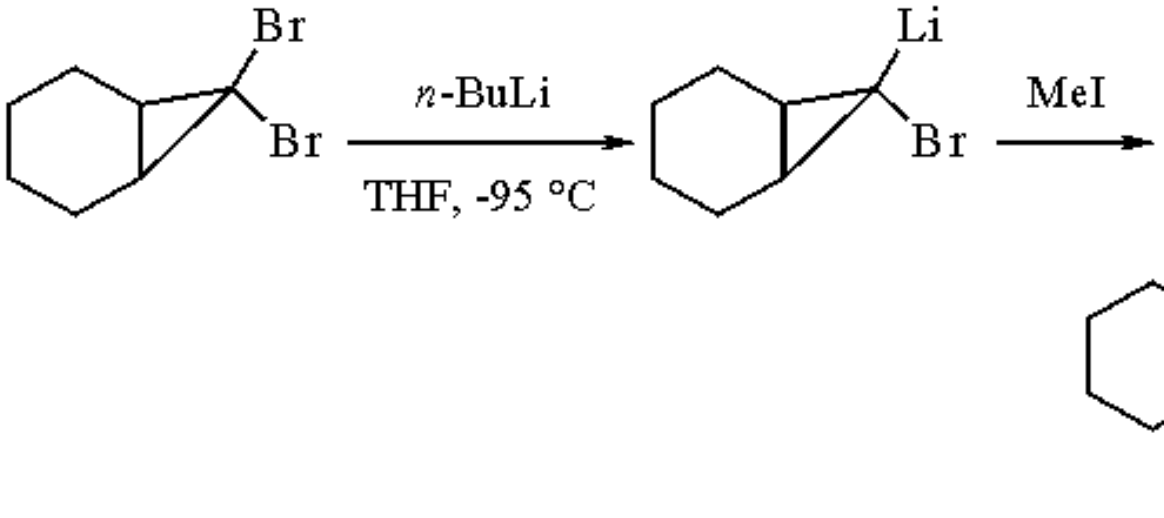

(19)

gem-Dihalocyclopropanes react with *n*-BuLi in a highly stereoselective fashion (eq 19), although subsequent isomerization can take place.[109] Alkyl-substituted vinyllithiums can be prepared with retention of configuration[105,110] and even aryl-substituted vinyllithium compounds retain their configuration under controlled conditions (<-78 °C in

THF or at rt in hydrocarbon solvents).[111] Simple alkyllithiums are generally not accessible by this route because of the unfavorable interchange equilibrium that ensues when primary or secondary halides are treated with *n*-BuLi, except in cases where the initially formed organolithium is rapidly consumed in a subsequent, irreversible reaction (eq 20).[112] Primary alkyllithiums may be prepared, however, from the corresponding alkyl iodides (but not from the bromides)[113] on treatment with the more reactive ***t-Butyllithium*** which renders the exchange operationally irreversible.[114]

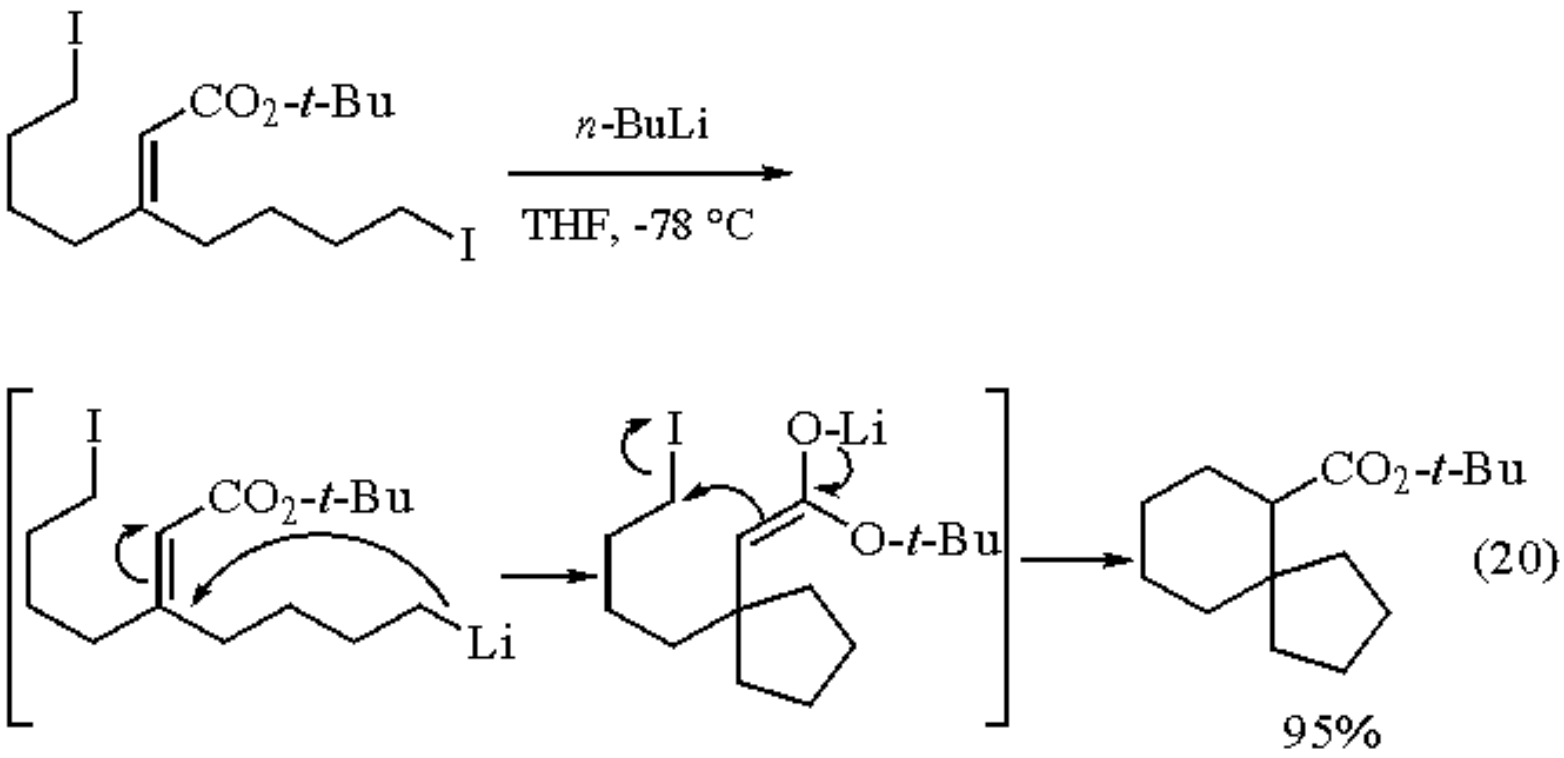

n-Butyllithium is the reagent of choice for effecting a number of transmetalation reactions involving the replacement of tin, selenium, tellurium, or mercury by lithium.[1a,1c,5] These reactions are typically conducted at low temperatures (less than -60 °C) in ethereal solvents, with THF being the most commonly employed reaction medium. The tin-lithium exchange is a particularly important operation, providing a convenient route to aryl- and vinyllithiums,[115] as well as functionalized lithio derivatives which are not readily accessible by other means, such as α-alkoxylithium compounds,[116] oxiranyllithiums,[117] and amino-substituted organolithiums.[118] The Sn-Li exchange in these systems and subsequent trapping of the intermediate lithio derivatives proceed stereoselectively with retention of configuration at the tin-bearing carbon (eqs 21 and 22).[116c,118c] Consequently, enantiomerically enriched functionalized products are available through this methodology from homochiral α-hetero-substituted stannanes.[119]

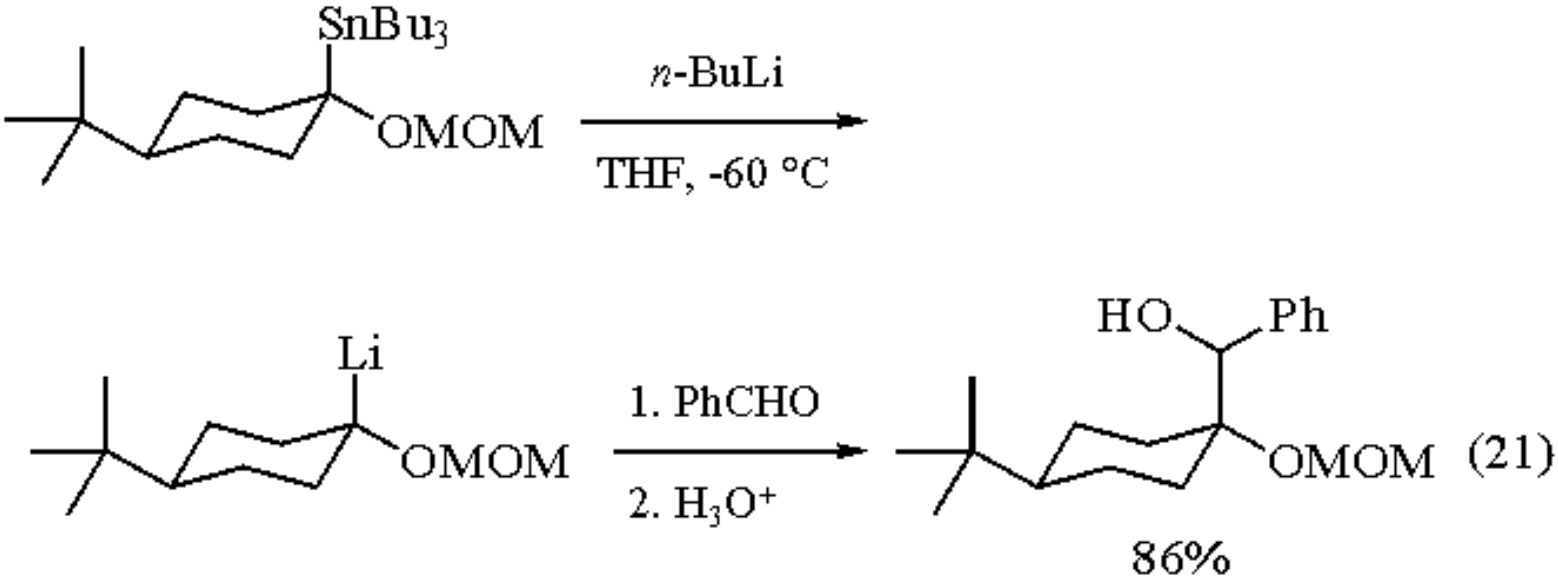

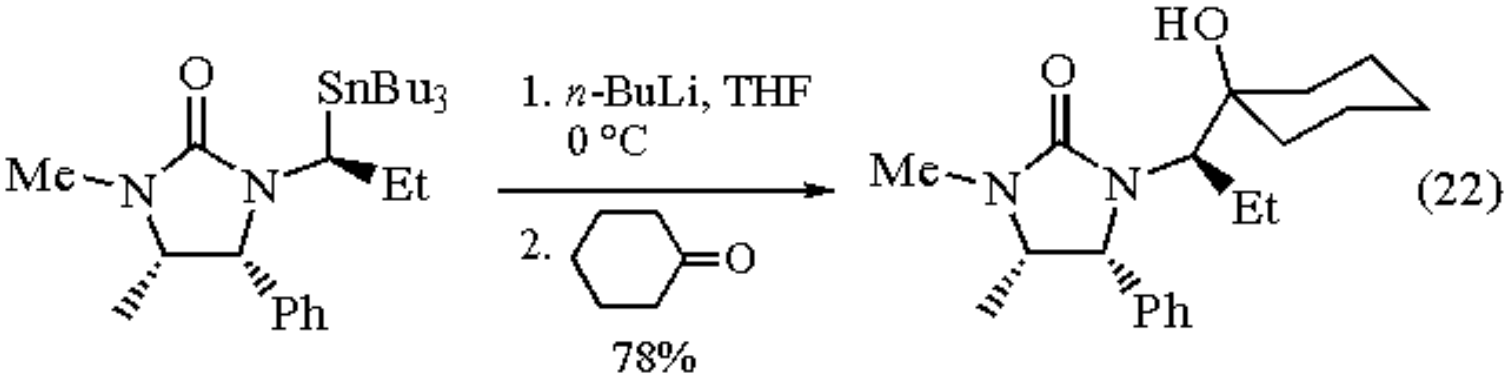

Appropriately substituted alkenic α-alkoxylithiums, derived from the corresponding tri-*n*-butyltin compounds on treatment with *n*-BuLi, have also been used to initiate 5-*exo*-*trig* cyclization reactions to give tetrahydrofuran derivatives (eq 23).[120] Other related ring-forming reactions have been reported.[121]

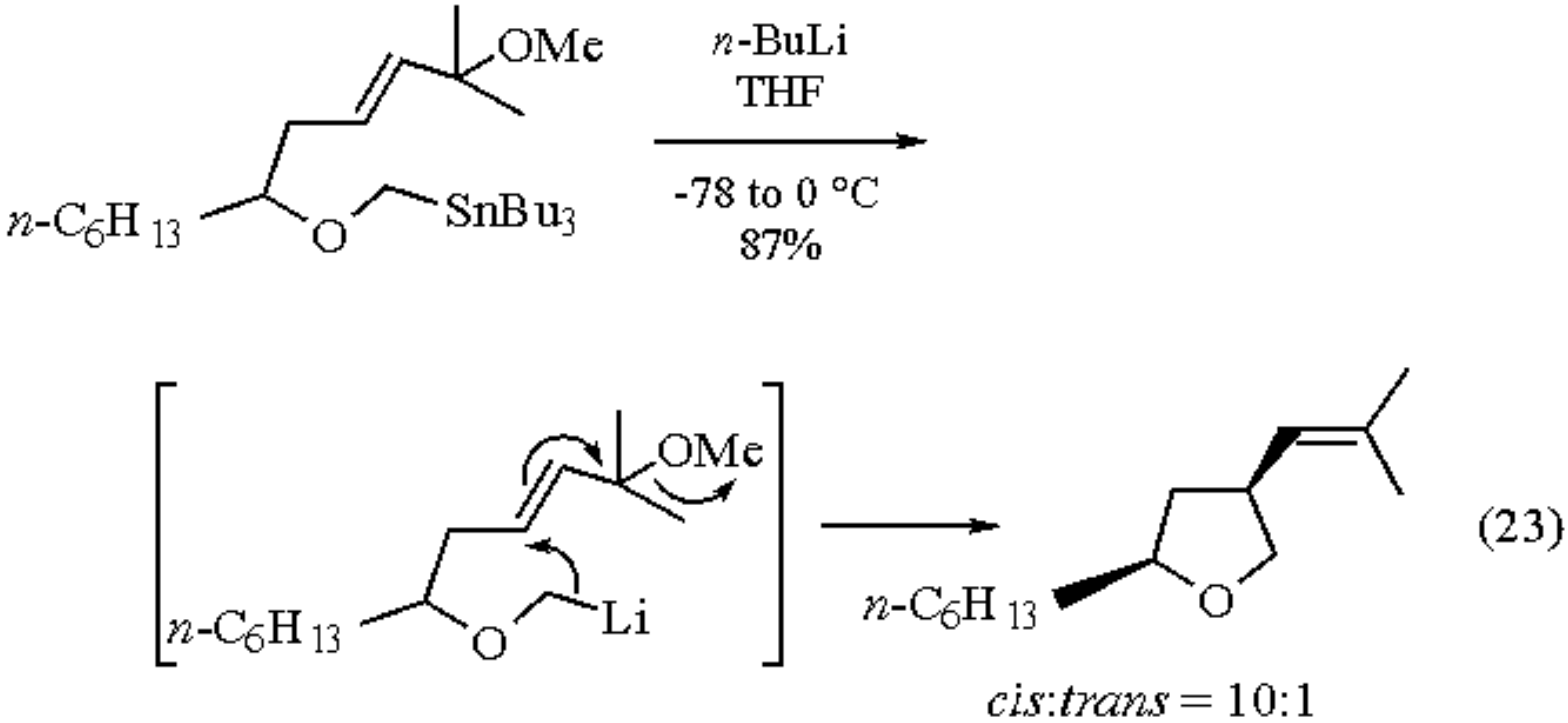

Organoselenium compounds, particularly selenoacetals or selenothioacetals, undergo facile lithium-selenium exchange reactions on treatment with *n*-BuLi, typically in THF at -78 °C.[122-124] The intermediate α-seleno organolithium derivatives formed in these reactions are readily trapped with electrophiles to afford a variety of synthetically useful α-functionalized selenide products[3,125] (eq 24).[126] Studies on cyclohexyl selenoacetals have shown that Li-Se exchange takes place almost exclusively at the axial position[123] and that equatorial α-lithio sulfides, derived from mixed Se,S-acetals by Li-Se exchange, epimerize within minutes at -78 °C to give the more stable axial lithio isomers.[124] *n*-Butyllithium may be used for the majority of Li-Se exchanges although selenoacetals derived from sterically hindered ketones react quite slowly with this reagent, and in these cases the use of the more reactive ***s-Butyllithium*** is warranted.[123]

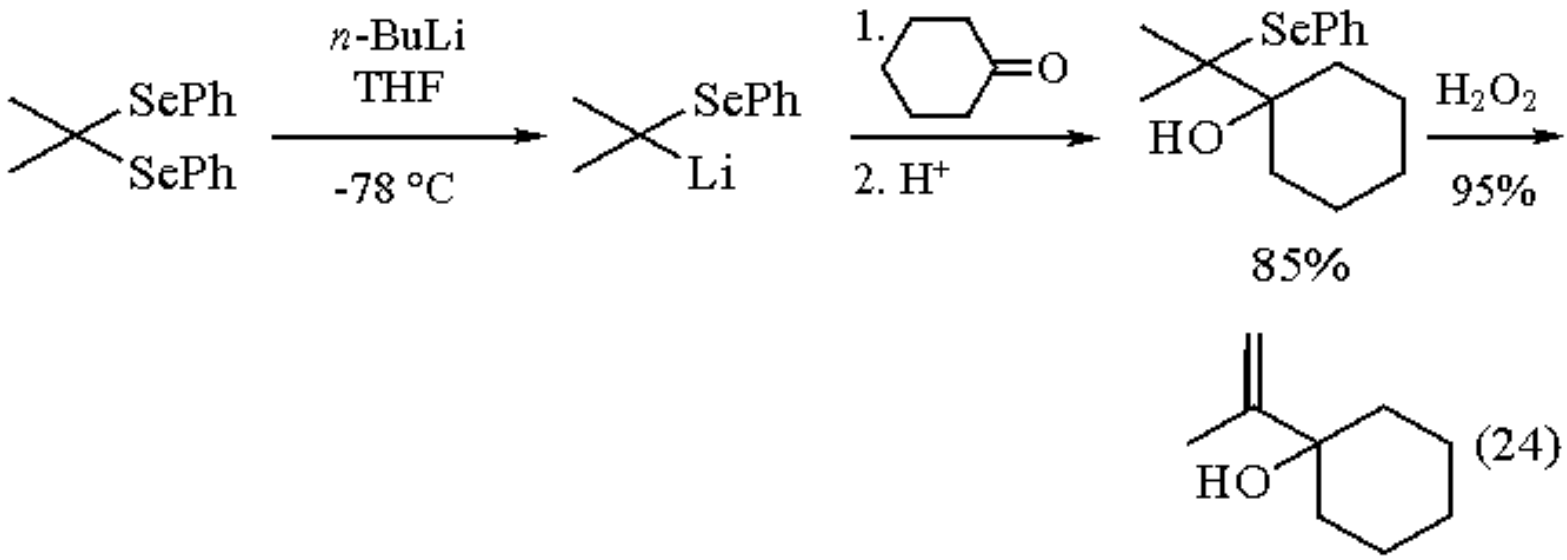

A variety of organolithiums, including benzylic, vinylic, alkynic, and 1-alkoxylithium compounds, are also accessible through the lithium-tellurium exchange, which involves the treatment of diorganotellurides with *n*-BuLi at -78 °C in THF (eq 25);[127] vinyllithium derivatives have been prepared from the corresponding organomercurials by essentially

the same methodology.[128]

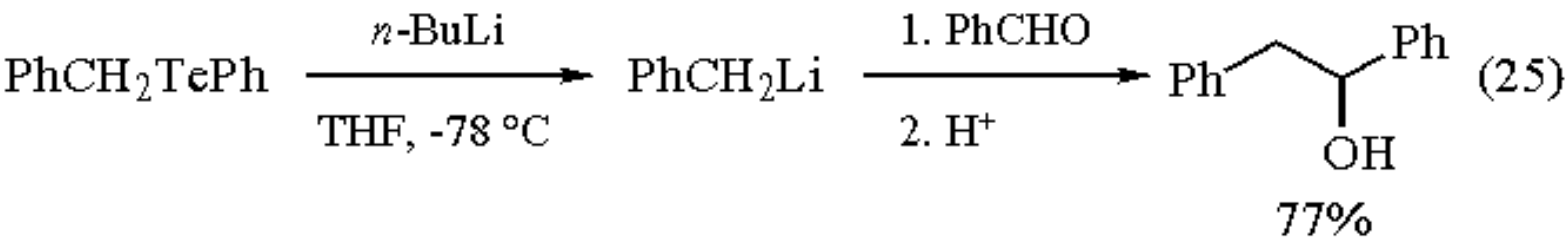

Rearrangements.

n-Butyllithium is used frequently to promote various anionic rearrangement reactions. 2,3-Wittig rearrangements are commonly effected by treatment of allylic and propargylic ethers with *n*-BuLi,[129] and 1,2-, 1,4-, as well as 3,4-rearrangements with similar systems are also known.[130] These reactions are most often initiated at low temperatures either by α-deprotonation adjacent to oxygen or via Li-Sn exchange, and the rearrangement occurs upon warming of the reaction mixture to 0 °C. Additional benzylic, propargylic, or allylic stabilization is necessary for deprotonation by *n*-BuLi; however, the Li-Sn method does not suffer from this limitation.[131] 2,3-Wittig rearrangements involving (*Z*)-allylic ethers proceed generally with high *syn* stereoselectivity (eq 26),[131] whereas the opposite tendency is observed with (*E*)-allylic ethers.[132] The regiochemistry of unsymmetrical bis-allylic ethers depends on the degree of substitution at the α- and γ-carbons, with the less substituted allylic position being the preferred site of deprotonation (eq 27).[133] The cyclic variant of the 2,3-Wittig rearrangement can be used for ring contraction reactions and it provides a useful method for the construction of macrocyclic ring systems (eq 28).[134]

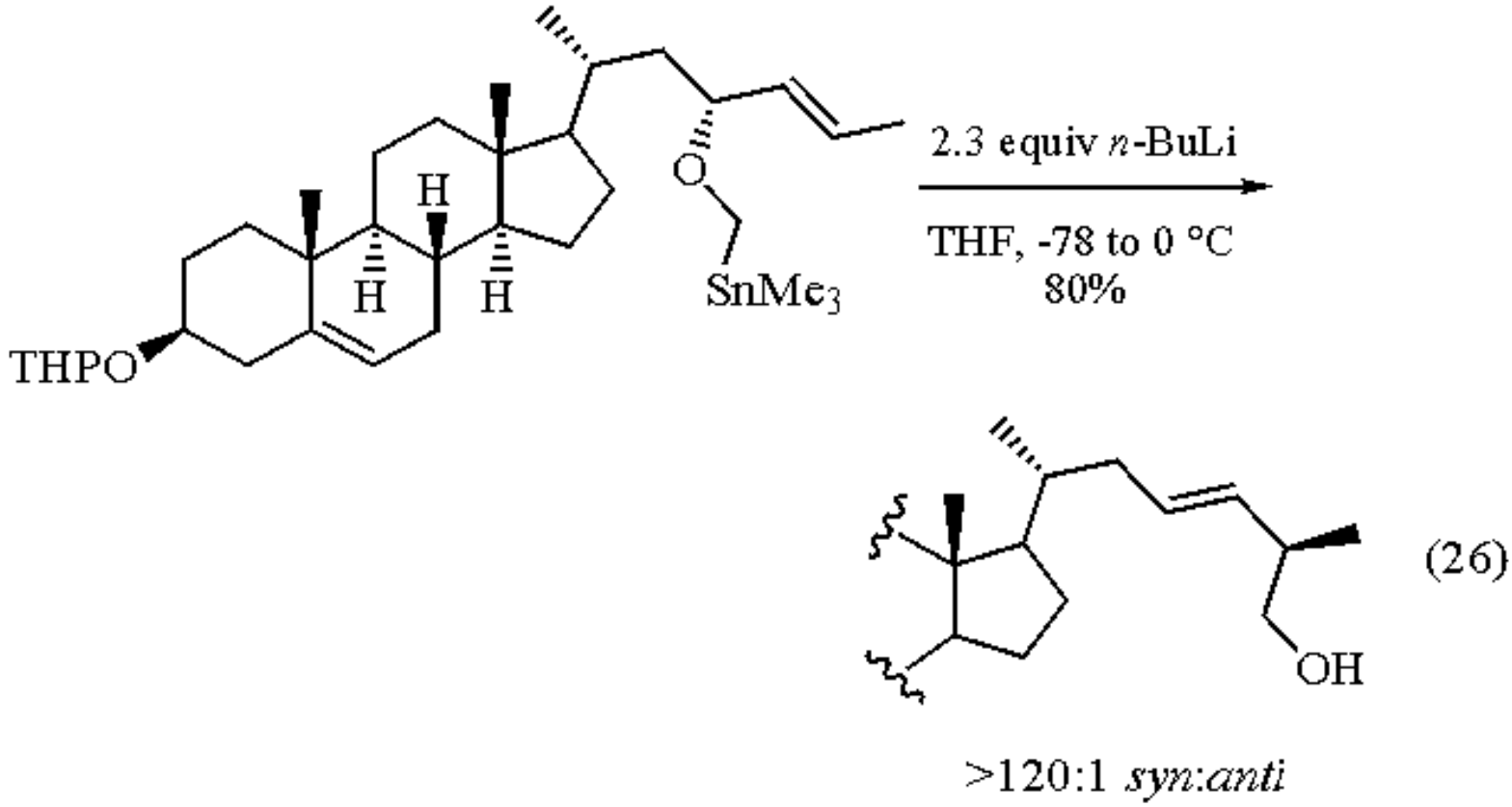

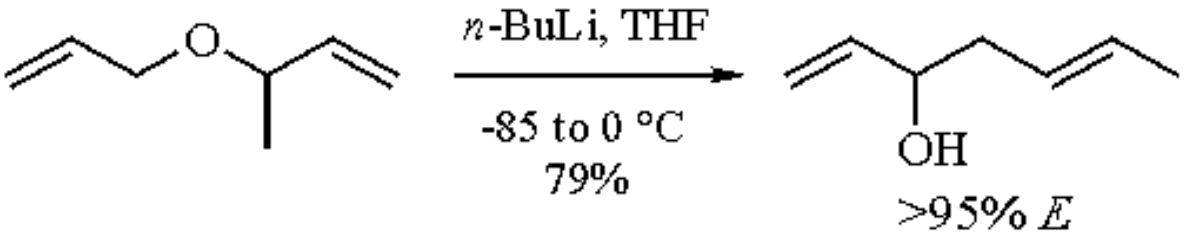

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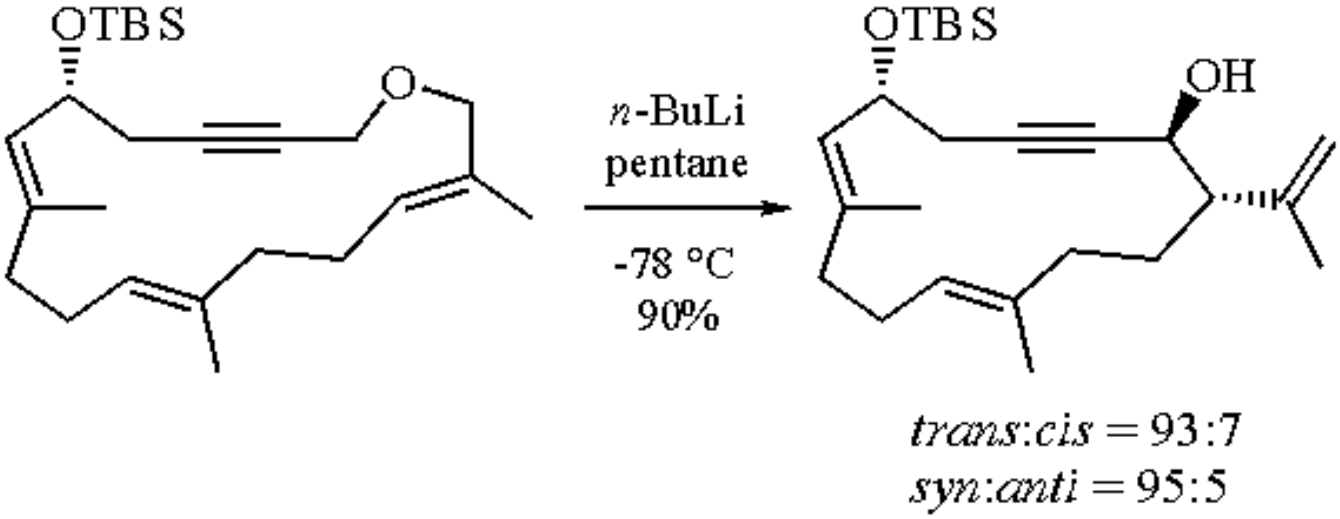

(28)

Secondary 1,2-epoxy alcohols may be prepared through the Payne rearrangement in aprotic media by treatment of primary 2,3-epoxy alcohols with *n*-BuLi in THF with catalytic amounts of ***Lithium Chloride***,[135] and α,β-unsaturated ketones are obtained from trimethylsilyl substituted propargylic alcohols through the Brook rearrangement followed by alkylation of the intermediate allenyllithium products and acidic workup (eq 30).[136] Quaternary ammonium salts, such as benzyltrimethylammonium ion, react with *n*-BuLi to deliver nitrogen ylides which can undergo either the Stevens rearrangement to give tertiary amines or the Sommelet-Hauser rearrangement to afford *ortho* alkyl-substituted nitrogen-containing aromatics, depending on the reaction conditions (eq 31).[137] Dibenzyl thioether has been reported to undergo a Sommelet-Hauser type rearrangement on treatment with *n*-BuLi/TMEDA in HMPA,[138] and appropriately substituted sulfonic ylides, prepared from sulfonium salts on treatment with *n*-BuLi, undergo 2,3-sigmatropic rearrangements (eq 32).[139]

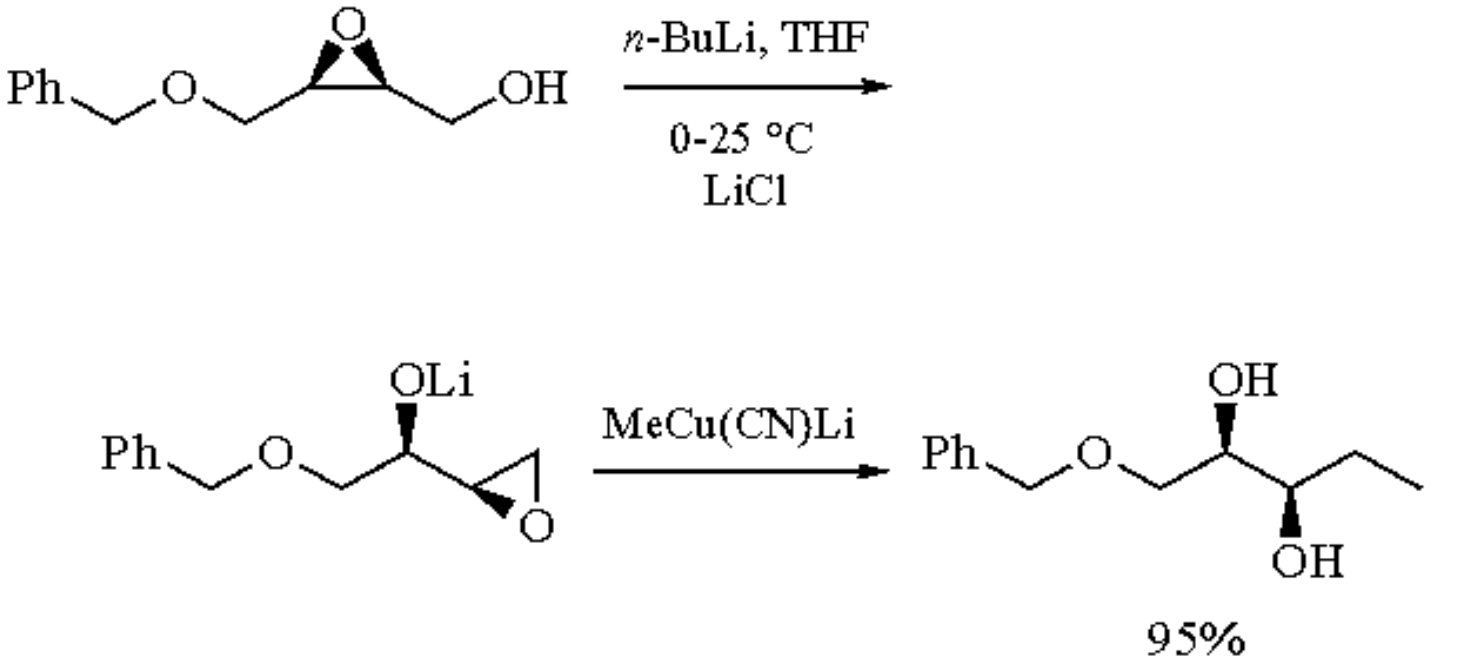
Ph
O
OH
n-BuLi, THF
0-25 °C
LiCl
OLi
MeCu(CN)Li
OH
95%

(29)

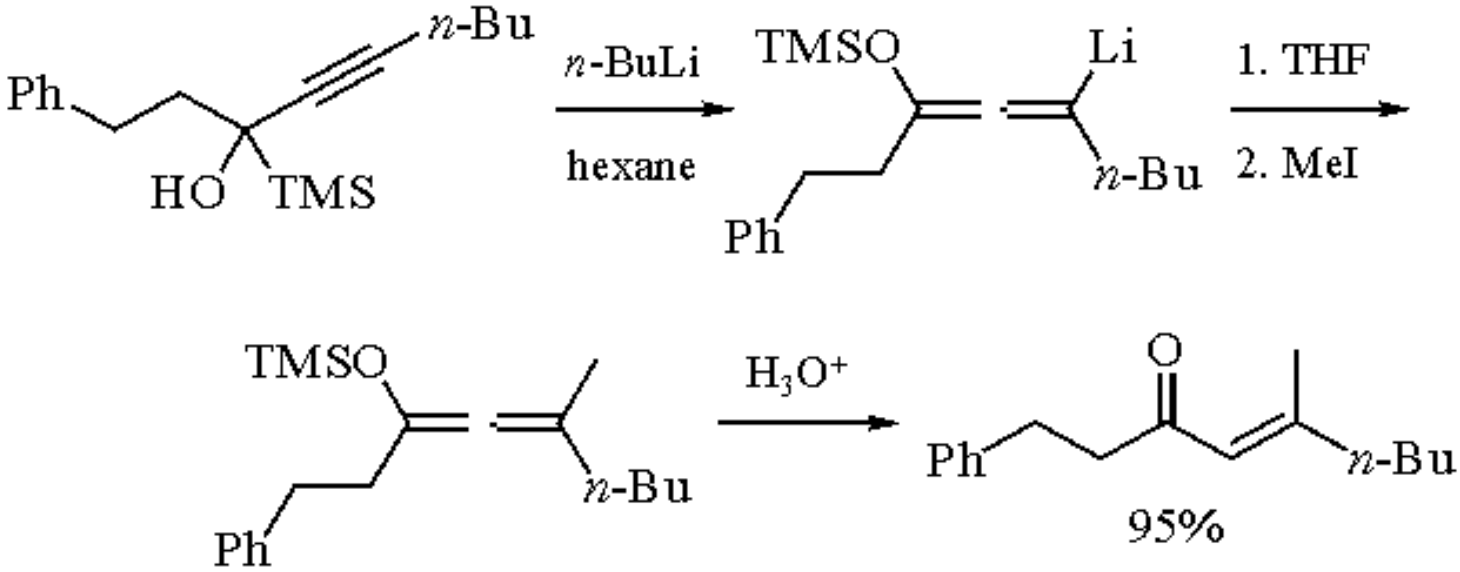
n-Bu
Ph
HO
TMS
n-BuLi
hexane
TMSO
Li
1. THF
2. MeI
H3O+
O
95%

(30)

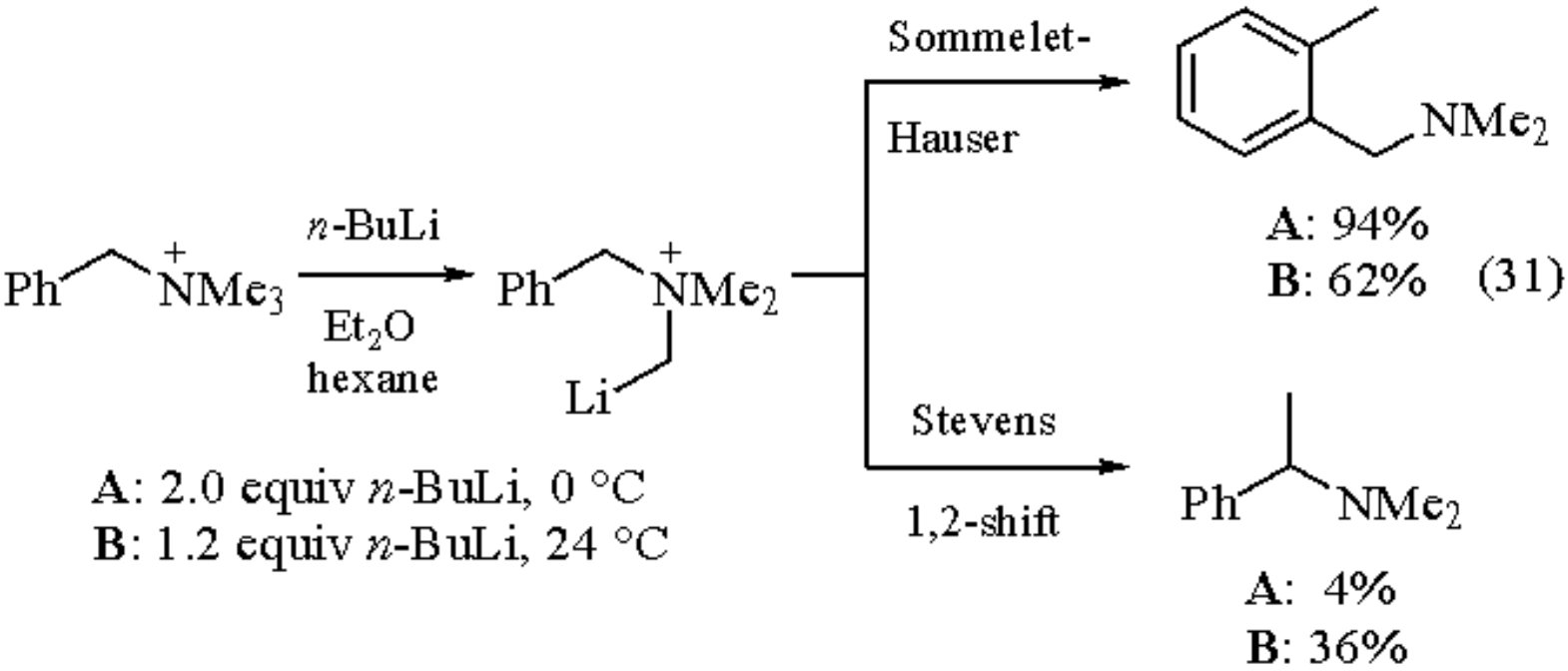

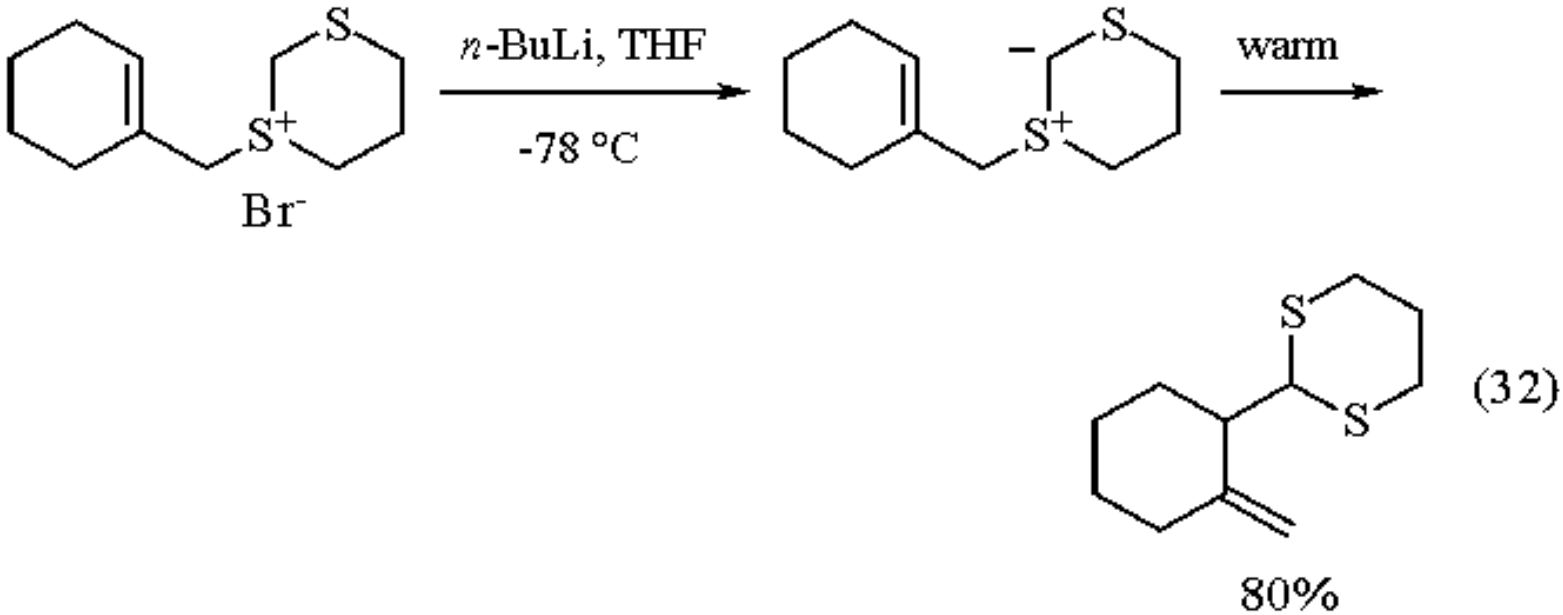

Elimination Reactions.

A number of eliminations can be effected using *n*-BuLi. The formation of phosphorus, nitrogen, and sulfur ylides[1a] and the generation of benzyne intermediates from aromatic halides[140] are well established processes, and α-eliminations resulting in the formation of carbenes have been used to prepare cyclopropanes,[141] oxiranes,[142] and other products via subsequent carbenoid rearrangements (eq 33).[143] Vinylidene dihalides undergo dehalogenation with concomitant formation of a triple bond on treatment with 2 equiv of *n*-BuLi.[144] The initial product of this reaction is a lithium acetylide which can be quenched with methanol to give a terminal alkyne or alkylated in situ by addition of alkyl halides to afford internal alkynes (eq 34).[145] The decomposition of (arylsulfonyl)hydrazones of aldehydes or ketones upon treatment with at least 2 equiv of *n*-BuLi (Shapiro reaction) is a useful method for the generation of vinyllithium compounds (eq 35).[146] In cases where two regioisomers can be produced, *n*-BuLi appears to promote the formation of the less substituted vinyllithium via deprotonation of the kinetically more acidic proton, whereas the use of *s*-BuLi

reportedly leads to the more substituted vinyllithium product.[147]

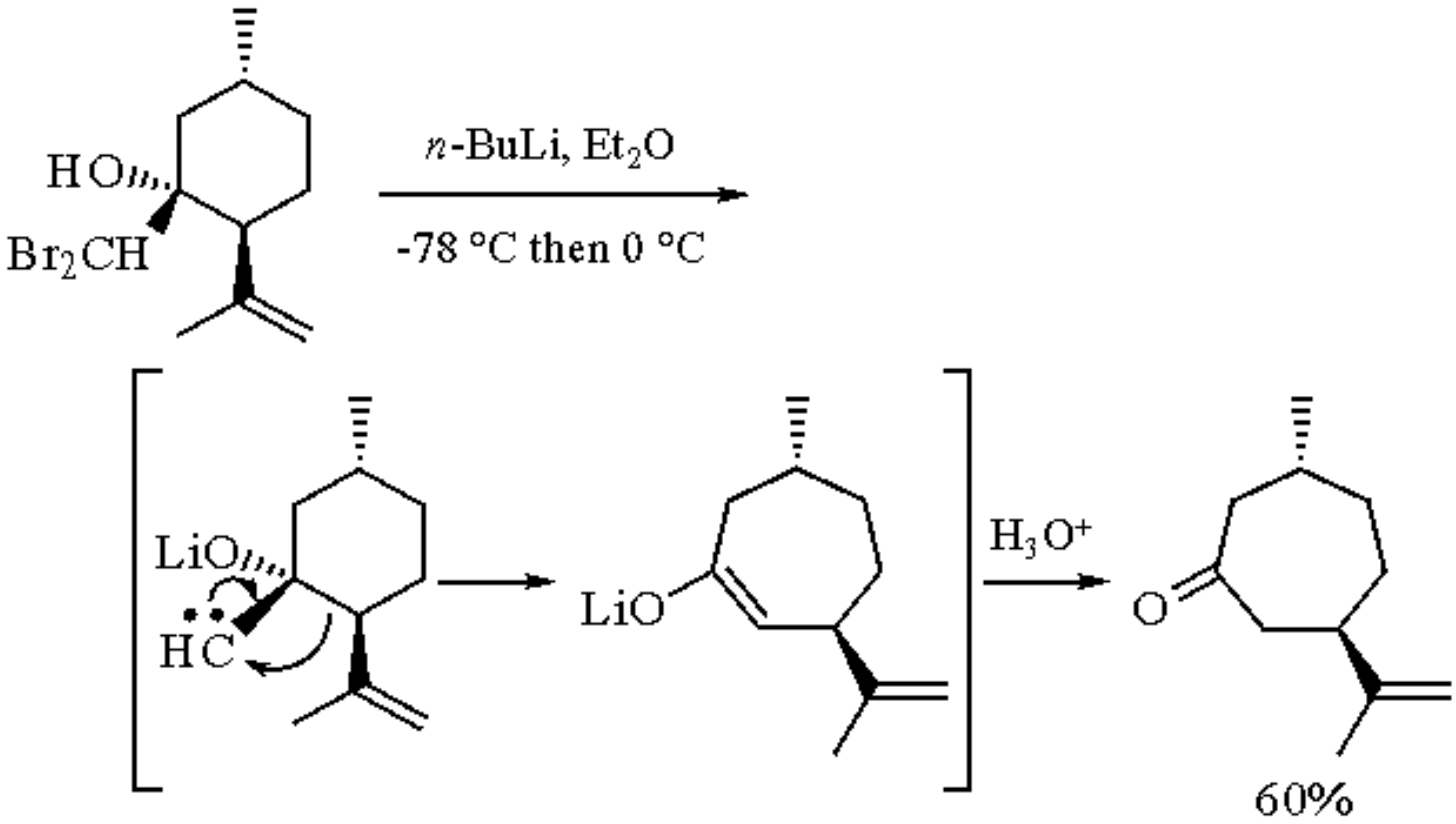

(33)

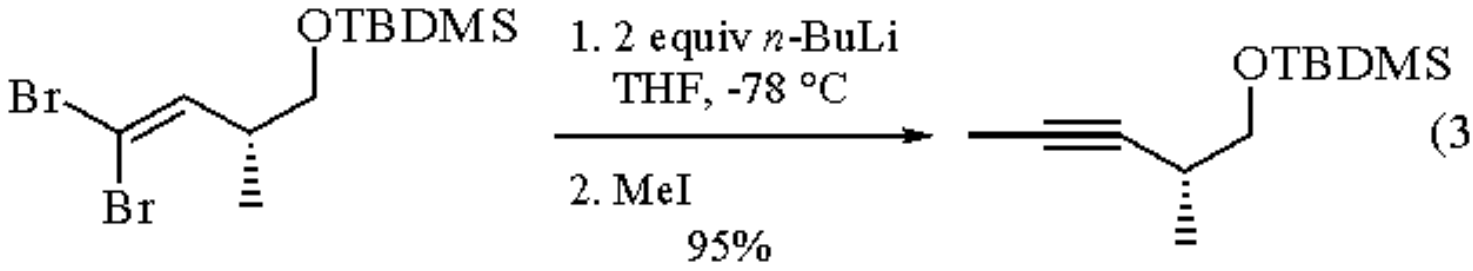

(34)

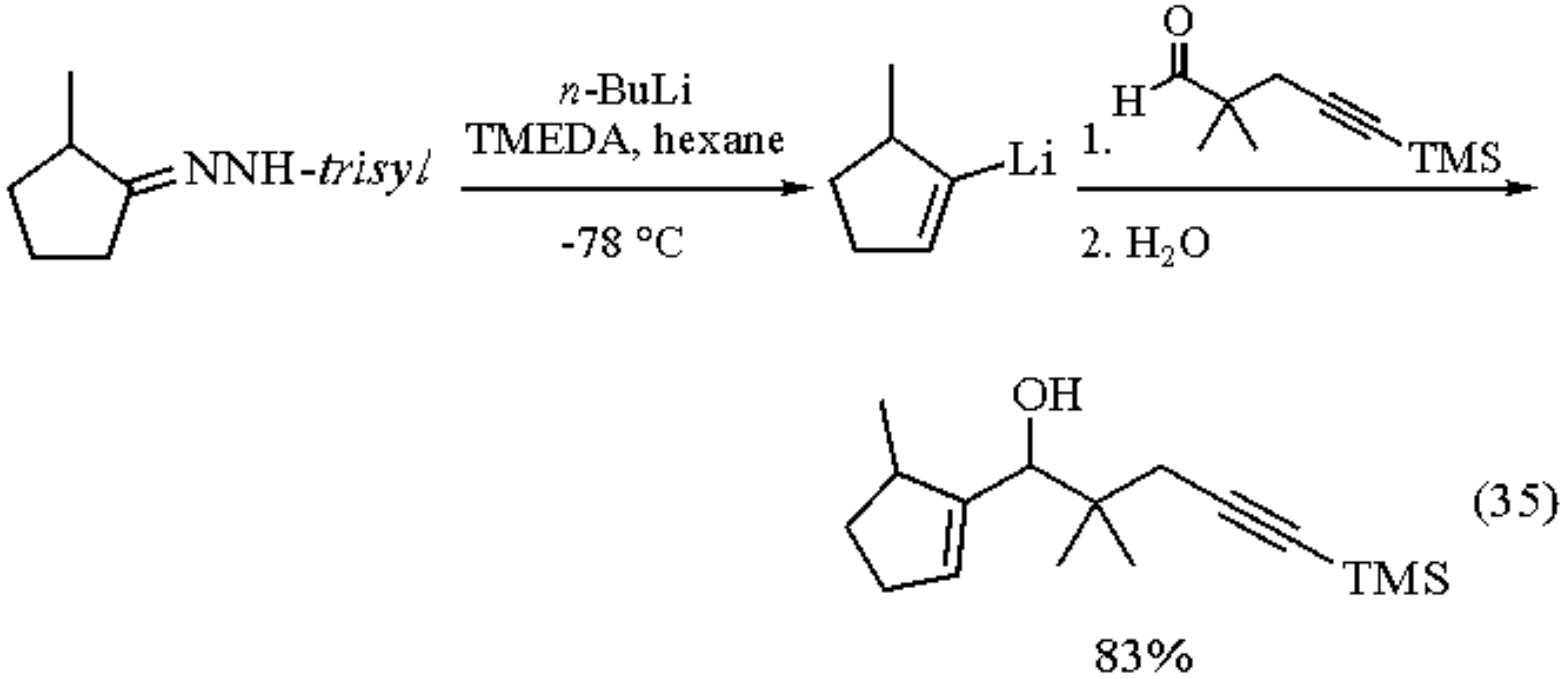

(35)

Related Reagents.

s-Butyllithium; ***t-Butyllithium***; ***n-Butyllithium-Boron Trifluoride Etherate***; ***n-Butyllithium-Potassium t-Butoxide***; ***Methyllithium***; ***Tungsten(VI) Chloride-n-Butyllithium***.

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t-Butyllithium[1]

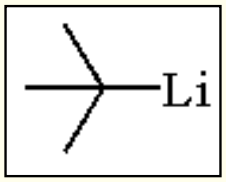

[594-19-4] · C_4H_9Li · *t*-Butyllithium · (MW 64.06)

(strong base capable of lithiating weak acids;[1] useful for heteroatom-faciliated lithiations;[2-4] reagent of choice for lithium-halogen exchange;[5] can add to π-bonds[1,6])

Physical Data: colorless solid; decomposes above 140 °C with loss of LiH; sublimes at 70 °C/0.1 mmHg. X-ray structures of the solvent-free tetramer and the ether-solvated dimer[7a] and ^{13}C NMR studies in hydrocarbon[8a] and ethereal solutions[7b] have been reported.

Solubility: sol hydrocarbon solvents, diethyl ether, and THF but should be used at low temperature; half-lives in various solvents have been reported;[9] reacts violently with H_2O and other protic solvents.

Form Supplied in: commercially available as an approximately 1.7 M solution in pentane or heptane. Tetrameric in hydrocarbons,[8] dimeric in diethyl ether,[7] monomeric in THF[10a] although earlier reported as dimeric.[1,10b] In combination with tertiary polyamines such as ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA), ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO), or ***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine*** (PMDTA), reactivity is often increased.[1,11]

Analysis of Reagent Purity: since the concentrations of commercial solutions vary appreciably, especially after the original seal is broken, it is necessary to standardize solutions of the reagent prior to use. The classical Gilman double titration method is described in detail by Wakefield.[1b] A particularly convenient method for routine analyses involves titration of the reagent with *s*-butyl alcohol using 1,10-phenanthroline or 2,2´-biquinoline as indicator.[13] A variety of other methods have been described.[14]

Preparative Method: the reaction of *t*-butyl chloride with 1-2% Na-Li alloy in dry pentane requires particular attention to detail to achieve a reasonable yield of the reagent. Detailed procedures should be consulted.[1b,12]

Handling, Storage, and Precautions: solutions of the reagent are pyrophoric and the reagent may ignite spontaneously upon exposure to air, producing a purple flame. It is prudent to conduct all operations involving *t*-BuLi behind a shield. In case of fire, a dry-powder extinguisher should be used: in no case should an extinguisher containing water or halogenated hydrocarbons be used to fight an alkyllithium fire. Bottles and reaction flasks containing the reagent should be flushed with N_2 or preferably Ar and kept tightly sealed to preclude contact with oxygen or moisture. The reagent may be cautiously transferred under an inert gas atmosphere using standard syringe/cannula techniques.[1b] Most reactions of *t*-butyllithium are exothermic

and for this reason are usually carried out at temperatures well below ambient. For detailed handling techniques see Wakefield.[1b]

Lithiations.

t-Butyllithium is less frequently used for proton abstraction than is ***n-Butyllithium*** or ***s-Butyllithium***. However, as it is more reactive and less nucleophilic than its isomers, *t*-BuLi may be the reagent of choice for the lithiation of relatively weak acids (eq 1). The addition of 1 equiv of a tertiary polyamine increases the metalating ability of the reagent.[1,11] Simple hydrocarbons, which are used as solvents, are generally inert to lithiation by *t*-BuLi. Although ethers and amines are often used as solvents in low temperature reactions involving *t*-BuLi, ethers,[15] THF,[16] and TMEDA[17] are readily lithiated by the reagent. Indeed, treatment of THF with *t*-BuLi has been reported to afford ethylene and the lithium enolate of acetaldehyde at temperatures as low as -78 °C.[16a]

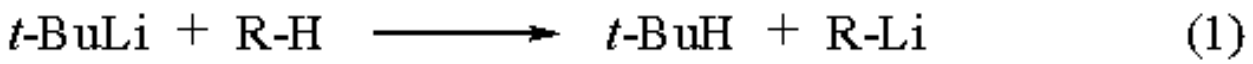

Monodeprotonation of terminal alkynes is conveniently accomplished with *n*-BuLi (see ***Propynyllithium***); the use of excess *t*-BuLi in hexane may lead to polylithiation.[18] For example, treatment of 1-butyne with 3 equiv of *t*-BuLi in hexane affords a mixture of allene and alkyne upon quench with an electrophile (eq 2).[19]

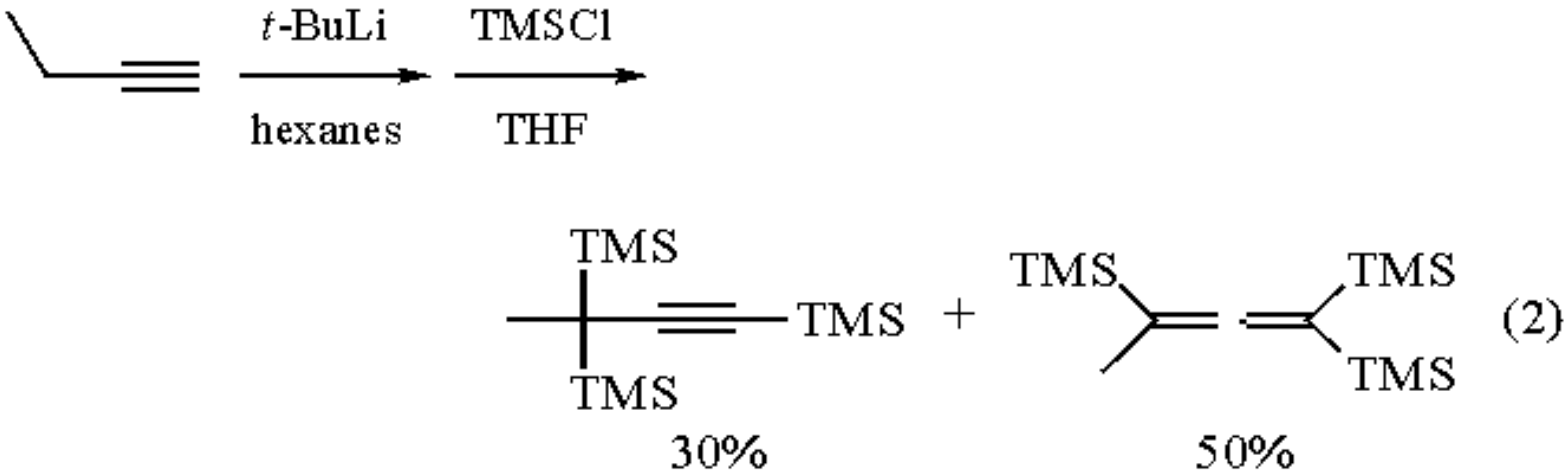

Highly regioselective proton abstractions may result when substrates containing such heteroatoms as oxygen, nitrogen, sulfur, and the like are treated with an organolithium. Several reviews of the topic[2-4,6,20] and a collection of detailed experimental procedures[21] are available. Two categories of heteroatom-facilitated lithiations are recognized: α-lithiation, involving removal of a proton from the carbon bearing the heteroatom, and β- (or *ortho*-) lithiation, involving abstraction of a proton from the β-position.[2,4] Lithiation of acyclic[22] (eq 3),[22a] cyclic (eq 4),[23] and conjugated enol ethers (eq 5)[24] using *t*-BuLi provides a simple route to readily functionalized α-lithio vinyl ethers (see ***1-Ethoxyvinyllithium***). Vinyl sulfides behave analogously[25] and sulfur appears to be a stronger α-director than is oxygen (eq 6).[26] Alkyl phenyl thioethers are α-lithiated by *t*-BuLi in the presence of ***Hexamethylphosphoric Triamide*** (eq 7).[27] Furans and thiophenes are readily α-lithiated by *t*-BuLi, but use of the less reactive *n*-BuLi is more convenient.[1,2,21] At temperatures below -100 °C, *t*-BuLi in THF regioselectively deprotonates enamines derived from β-acyl aldehydes in preference to 1,2- or 1,4-addition[28] (eq 8).[28a]

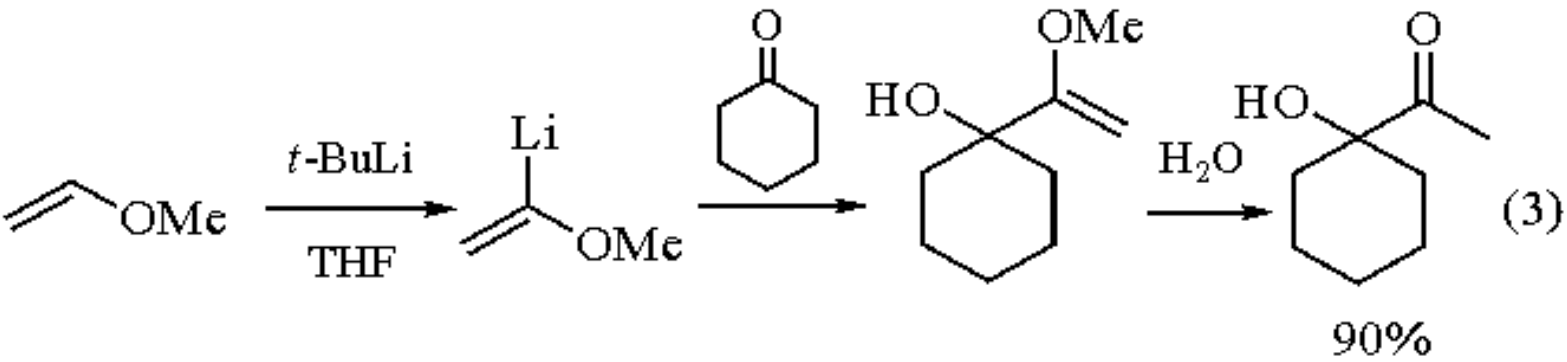
OMe
t-BuLi
THF
Li
OMe
O
OMe
HO
H2O
HO
O
90%

(3)

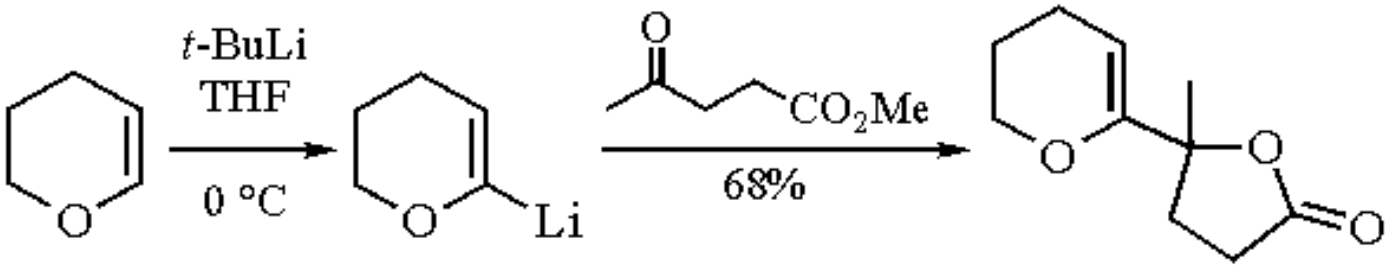
t-BuLi
THF
0 °C
O
Li
O
CO2Me
68%
O
O
O

(4)

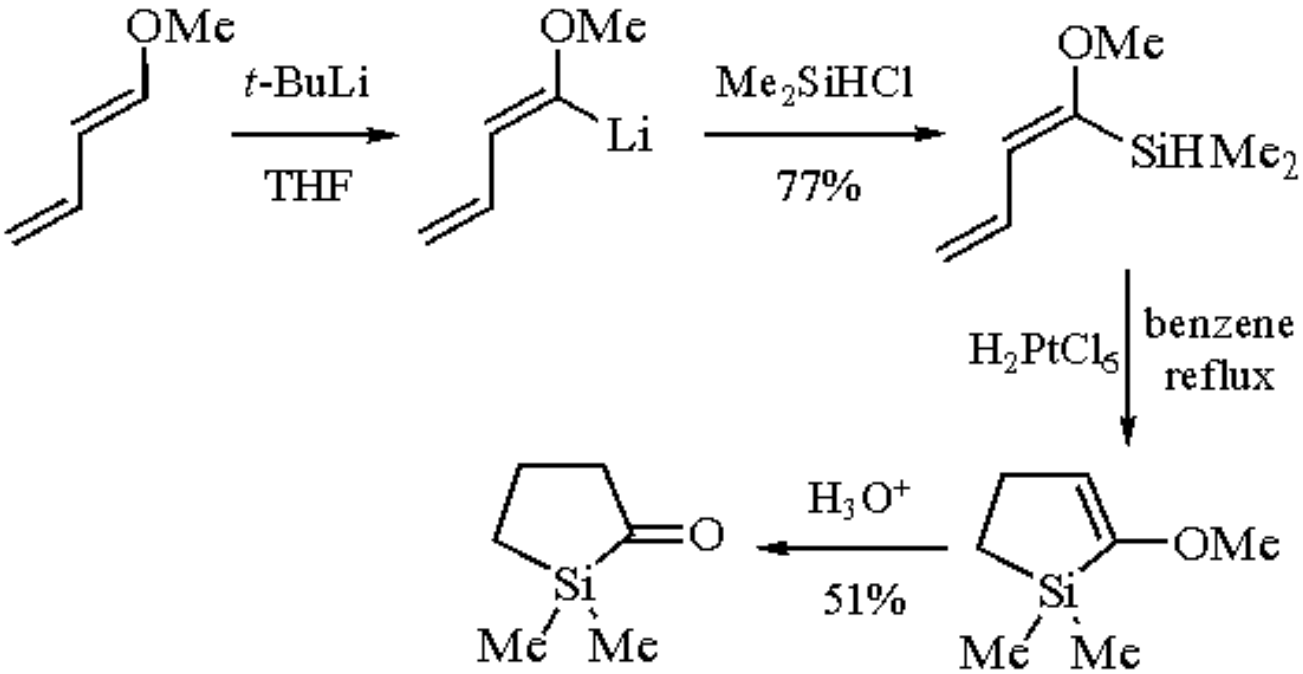
OMe
t-BuLi
THF
OMe
Li
Me2SiHCl
77%
OMe
SiHMe2
H2PtCl6
benzene
reflux
H3O+
51%
O
Si
Me Me
OMe
Si
Me Me

(5)

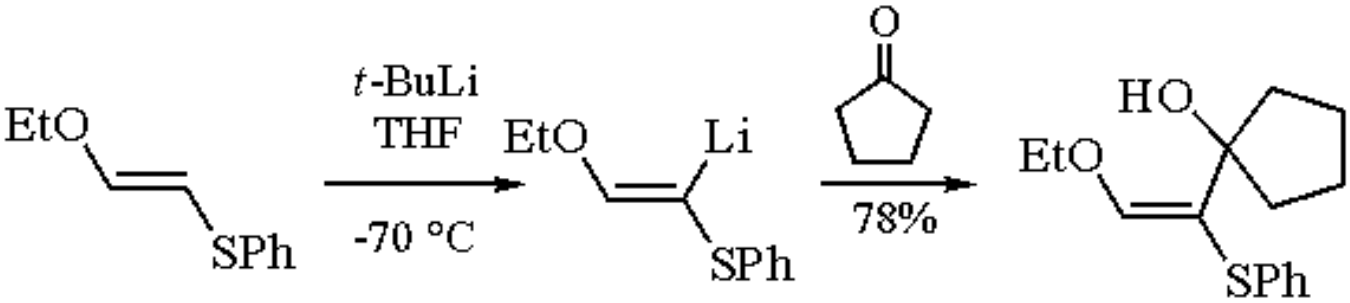
EtO
SPh
t-BuLi
THF
-70 °C
EtO
Li
SPh
O
78%
HO
EtO
SPh

(6)

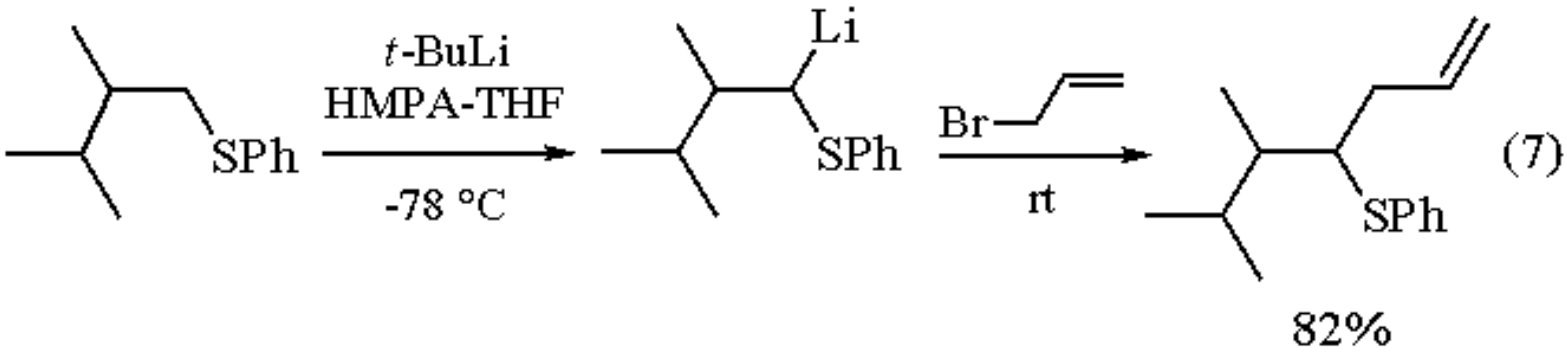

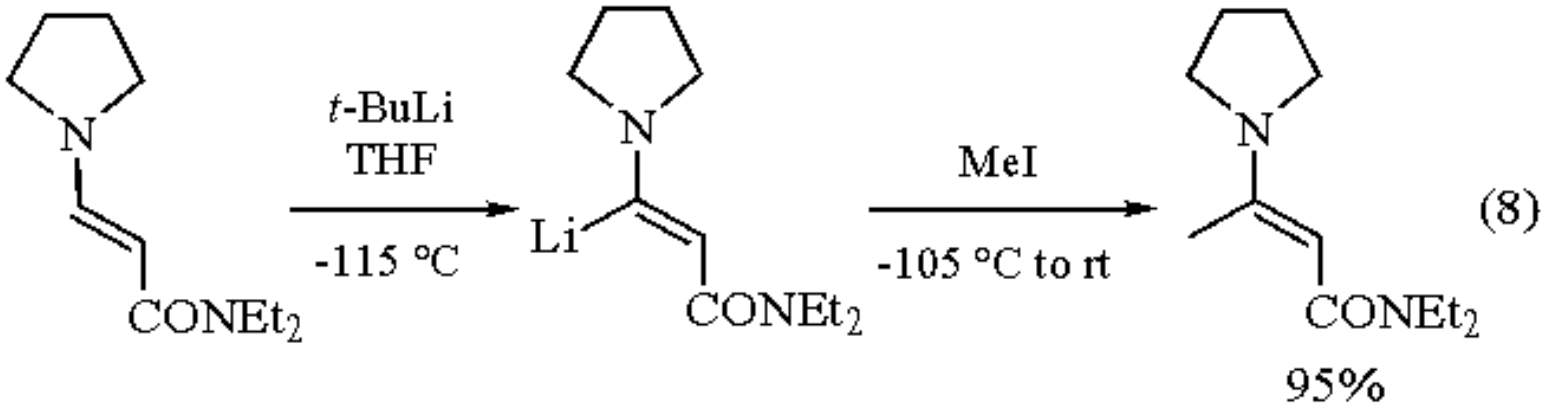

Heteroatom-directed *ortho* lithiations of aromatic compounds are most often accomplished with *n*- or *s*-BuLi, either alone or in combination with TMEDA.[4] Some benefit derives from the use of the bulkier and more basic *t*-BuLi for *ortho* lithiation of substrates bearing substituents susceptible to nucleophilic attack (eq 9)[29] or resistant to deprotonation by less reactive bases (eq 10)[9,30] The key step in a highly stereoselective asymmetric synthesis of chiral ferrocenes involves *ortho* lithiation of a ferrocenyl acetal at -78 °C using *t*-BuLi in THF (eq 11).[31]

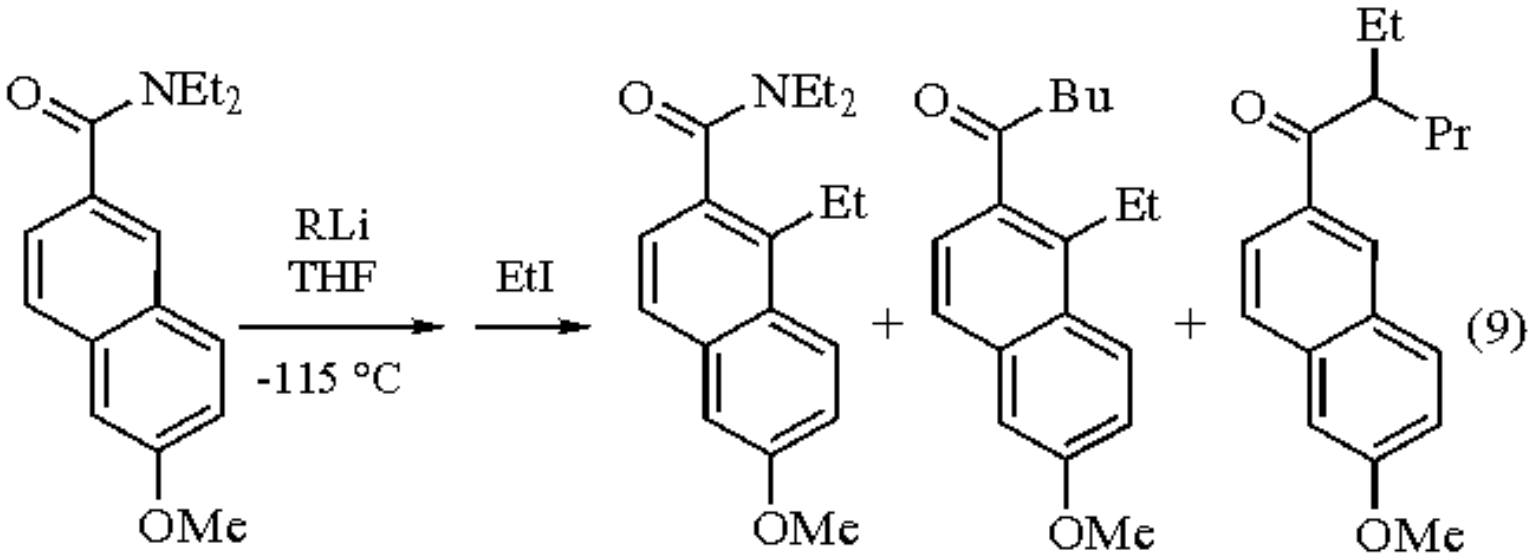

RLi			
n-BuLi	0	34%	38%
t-BuLi	68%	0	0

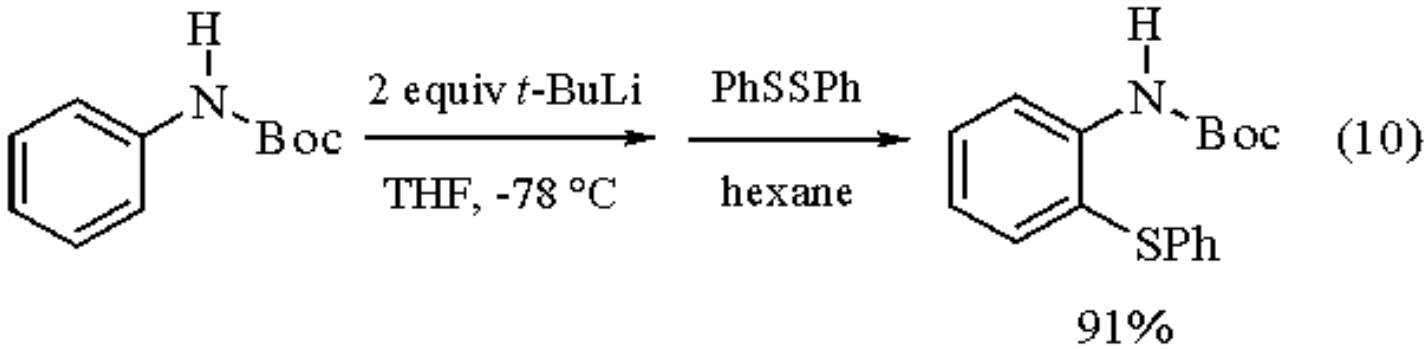

(10)

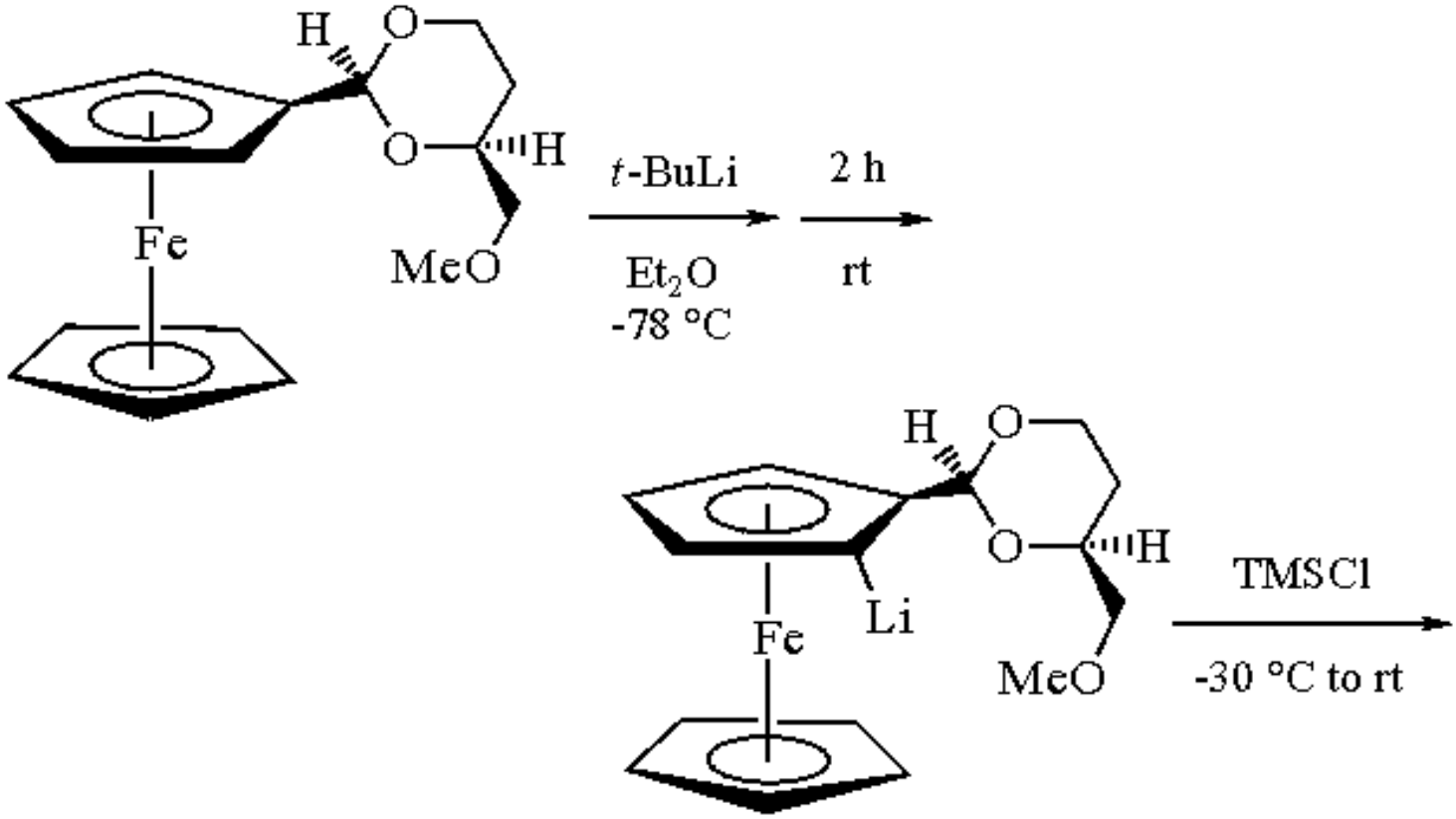

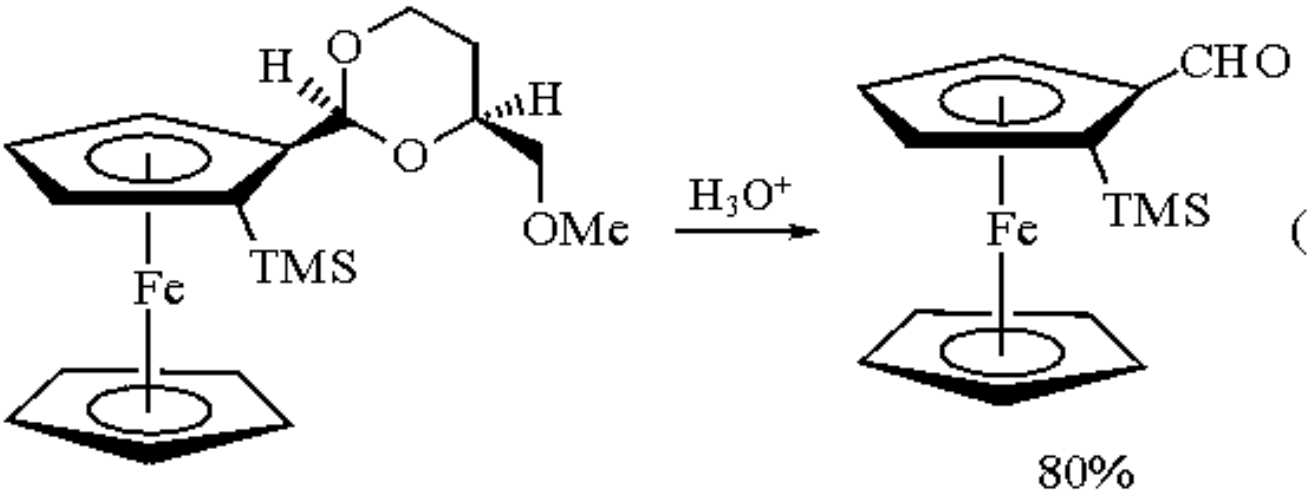

(11)

Lithium-Halogen Exchange.

t-Butyllithium is often the reagent of choice for the preparation of an organolithium by lithium-halogen exchange. The reversible metathesis (eq 12), most readily accomplished at low temperature with bromides and iodides, leads to an equilibrium mixture favoring the more stable organolithium.[1,32] The benefits of using *t*-BuLi (rather than *n*- or *s*-BuLi) for the preparation of organolithiums by lithium-halogen exchange derives from two considerations: (1) the interchange equilibrium is favorable when an aryl, vinyl, cyclopentyl, or primary-alkyl halide is treated with a tertiary organolithium,[33] and (2) the exchange may be rendered operationally irreversible by employing 2 equiv of *t*-BuLi since 1 equiv of the reagent rapidly consumes the *t*-butyl halide generated in the reaction to give isobutane, isobutene, and lithium halide (eq 13).[34]

$$R^1\text{-}X + R^2\text{-}Li \rightleftharpoons R^1\text{-}Li + R^2\text{-}X \qquad (12)$$

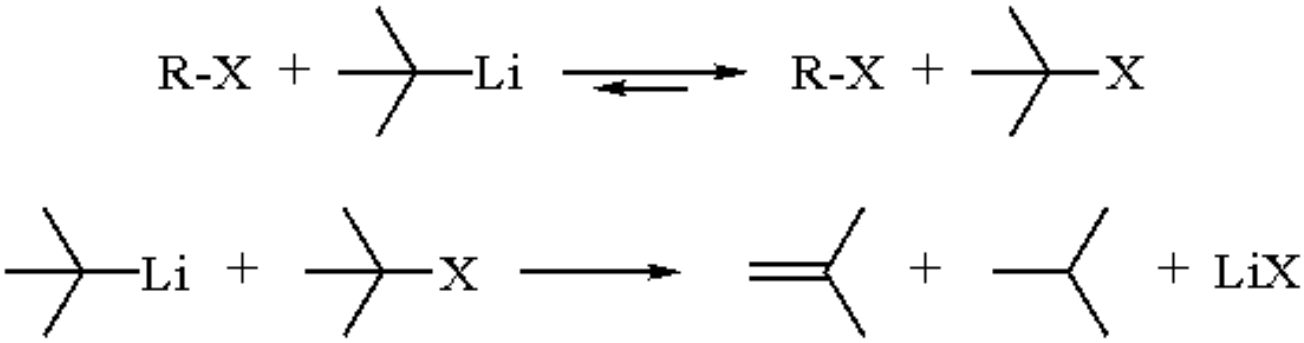

(13)

Aryl halides readily undergo lithium-halogen exchange with alkyllithiums in ethereal solvents at temperatures at or below -78 °C and the less expensive *n*-BuLi is often used for this purpose.[1,32] However, the presence of the *n*-butyl halide product can cause complications when the aryllithium is warmed since a coupling reaction may ensue[1,32] (for example, the reaction of ***Phenyllithium*** with *n*-butyl iodide in THF at -78 °C has a half-life of ~30 min). This potential problem is avoided when 2 equiv of *t*-BuLi are used for the generation of aryllithiums.

Vinyllithiums are readily prepared with retention of configuration from the corresponding vinyl bromides or iodides in a stereoselective exchange with 2 molar equiv of *t*-BuLi, provided that the reaction is conducted at temperatures below -110 °C.[35] The reactions are conducted most conveniently in the Trapp solvent,[36] a 4:4:1 mixture of THF, diethyl ether, and pentane (or hexane), by slow addition of 2 equiv of *t*-BuLi in pentane to a solution of the halide which is held at -110 to -120 °C. The preparation of (*E*)-1-hexenyllithium and its conversion to (*E*)-1-phenylthio-1-hexene is illustrative (eq 14)[35a] of the method, and detailed experimental procedures are available.[37] The stereoselective lithium-halogen exchange of vinyl halides is the key step in a highly diastereoselective metalla-Claisen rearrangement (eq 15)[38] and α-keto dianions may be prepared from the lithium enolates of α-bromo ketones by the exchange reaction with excess *t*-BuLi (eq 16).[39]

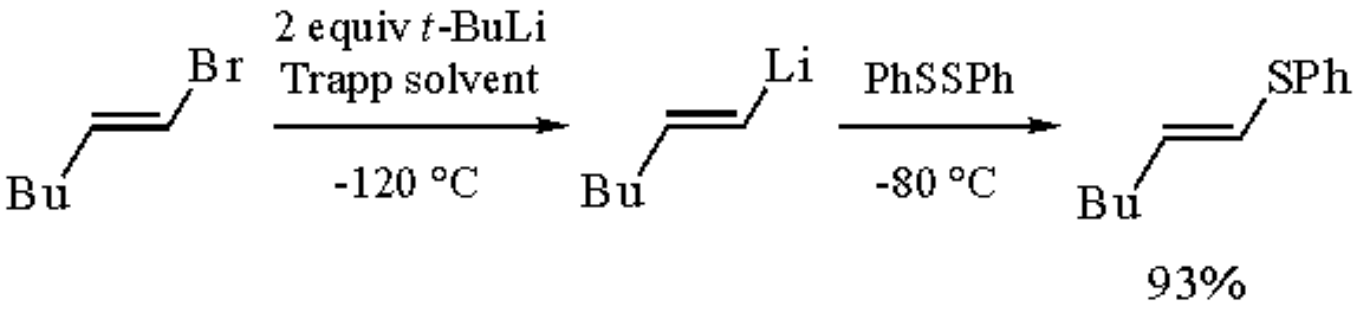

(14)

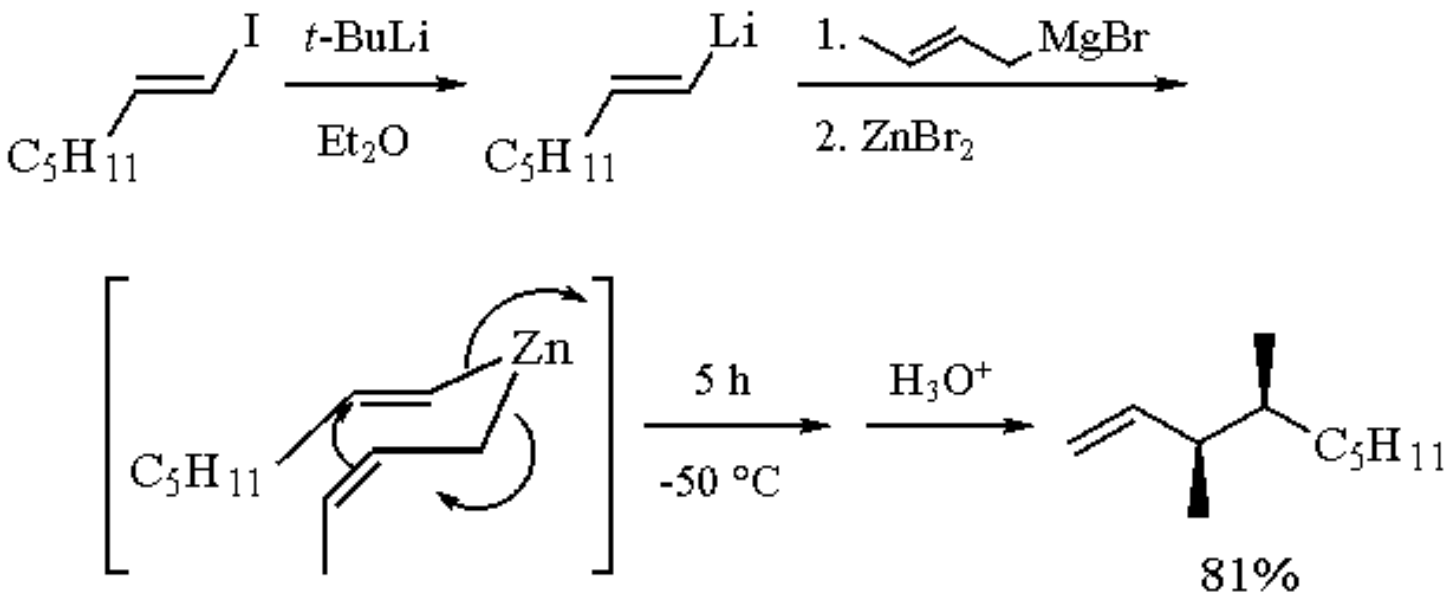

(15)

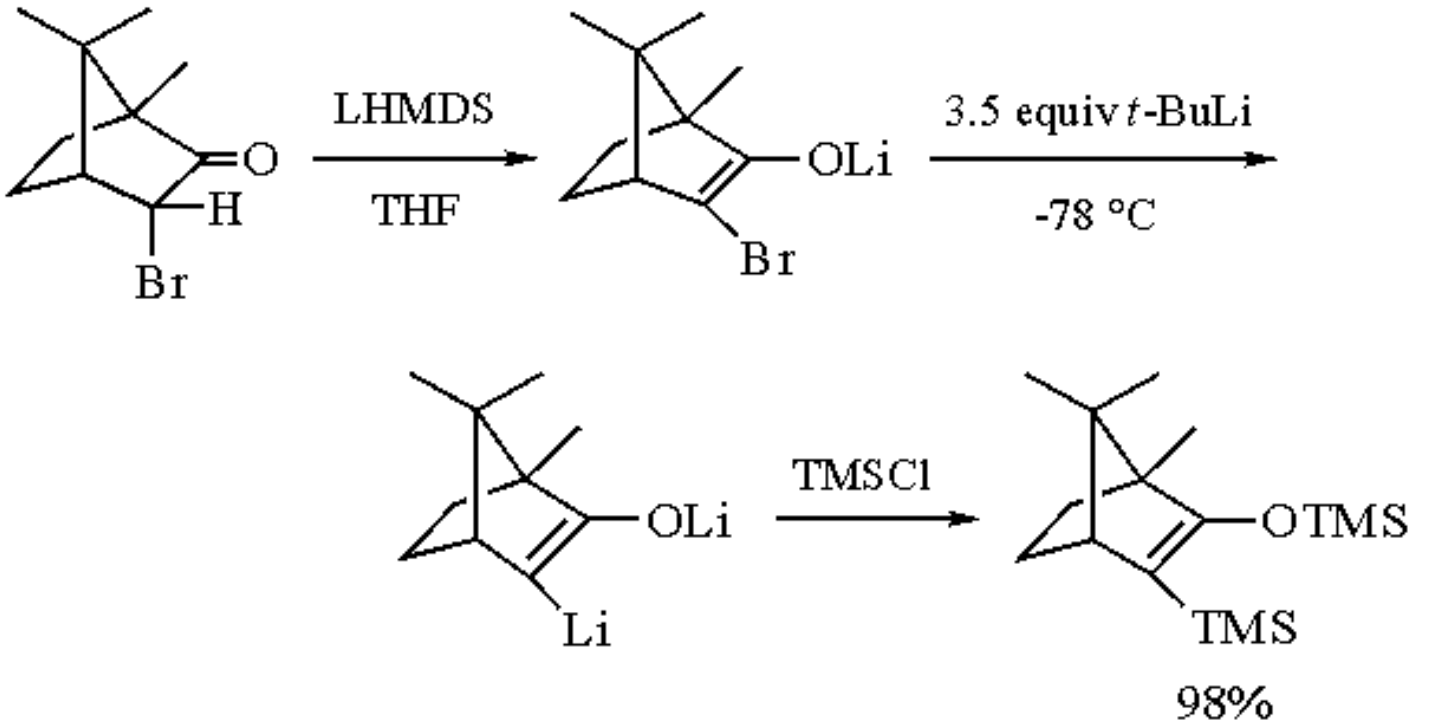

(16)

Cyclopropyllithiums (see ***Cyclopropyllithium***) are, in general, easily prepared from the corresponding bromides or iodides with retention of configuration by low-temperature lithium-halogen exchange using either *n*-BuLi or *t*-BuLi.[1,32] The more reactive *t*-BuLi was found to be superior for the generation of (1-ethoxycyclopropyl)lithium, a reagent useful for the preparation of cyclobutanones (eq 17).[40]

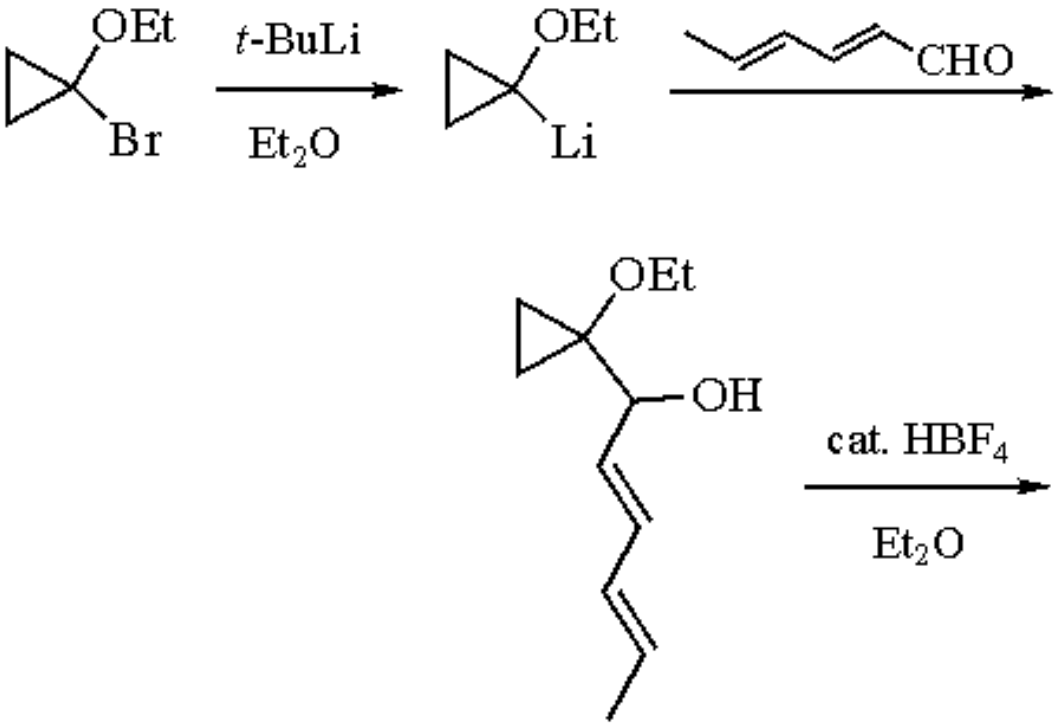

(17)

The early literature suggests that metal-halogen exchange between primary alkyl halides and alkyllithiums is not, in general, a preparatively useful reaction due to unfavorable equilibria (eq 12) and competition from coupling and elimination reactions.[1,32] However, more recent mechanistic studies of the exchange reaction[41,42] have revealed that virtually all of the difficulties historically associated with use of this method for the preparation of simple alkyllithiums can be overcome by the use of *t*-BuLi and judicious choice of experimental conditions.[5] Primary alkyllithiums are conveniently prepared at -78 °C (the exchange has been conducted at temperatures as low as -131 °C)[5a] by addition of 2.1-2.2 equiv of *t*-BuLi in pentane to a solution of primary alkyl iodide in pentane-diethyl ether (3:2 by vol).[5] Under these conditions (eq 18) the exchange is exceedingly rapid, the yield of alkyllithium is excellent,[5] and the only byproduct is a small quantity of easily removed hydrocarbon derived from formal reduction of the iodide via proton abstraction from the cogenerated *t*-BuI.[43] The alkyllithium may be used at low temperature but residual *t*-BuLi remaining in solution may complicate product isolation following addition of an electrophile to the cold reaction mixture, particularly if an excess of *t*-BuLi was employed. Any residual *t*-BuLi is easily removed by simply allowing solutions containing the primary alkyllithium and *t*-BuLi to warm to room temperature: the *t*-BuLi is rapidly consumed by proton abstraction from diethyl ether, leaving clean solutions of the less reactive primary alkyllithium.[5] The success of this route to primary alkyllithiums depends critically on the appropriate choice of both halide and solvent.[5] Alkyl iodides rather than alkyl bromides or chlorides must be used in the exchange: under the conditions of the reaction (eq 18), lithium-iodine exchange most probably involves rapid attack of *t*-BuLi on the iodine atom of the halide,[42,44] while lithium-bromine exchange occurs predominantly by a single electron transfer (SET) mechanism.[42] Alkyl chlorides are essentially inert to the action of *t*-BuLi under the conditions indicated in eq 18.[42] Moreover, it is advisable to run the reaction in a solvent system that contains diethyl or a similar ether; the use of THF or other strongly coordinating Lewis bases such as TMEDA should be avoided as elimination and coupling reactions may compete with exchange in these solvents.[5a]

$$\text{R-CH}_2\text{-I} \xrightarrow[\text{-78 °C, 5 min}]{t\text{-BuLi},\ n\text{-C}_5\text{H}_{12},\ \text{Et}_2\text{O}} \text{R-CH}_2\text{-Li} \xrightarrow{\text{E}^+} \text{R-CH}_2\text{-E} \qquad (18)$$

Low-temperature lithium-iodine exchange with *t*-BuLi has been used to prepare 5-hexenyllithiums from 6-iodo-1-hexenes.[43] When warmed, these alkenic alkyllithiums undergo highly stereoselective and totally regiospecific 5-*exo* cyclization via a cyclohexane chair-like transition state[45] to afford high yields of (cyclopentylmethyl)lithiums that may be functionalized by reaction with an electrophile[46] (eq 19).[46b] Such isomerizations have also been conducted in a tandem fashion to give polycyclic products[47] (eq 20).[47a] Alkynic alkyllithiums, which are prepared by lithium-iodine exchange with *t*-BuLi, cyclize in a stereoselectively *syn* fashion to four-, five-, and six-membered carbocyclic rings bearing an exocyclic lithiomethylene moiety[48] (eq 21).[48a] Related chemistry initiated by lithium-selenium exchange with *t*-BuLi has also been reported.[49]

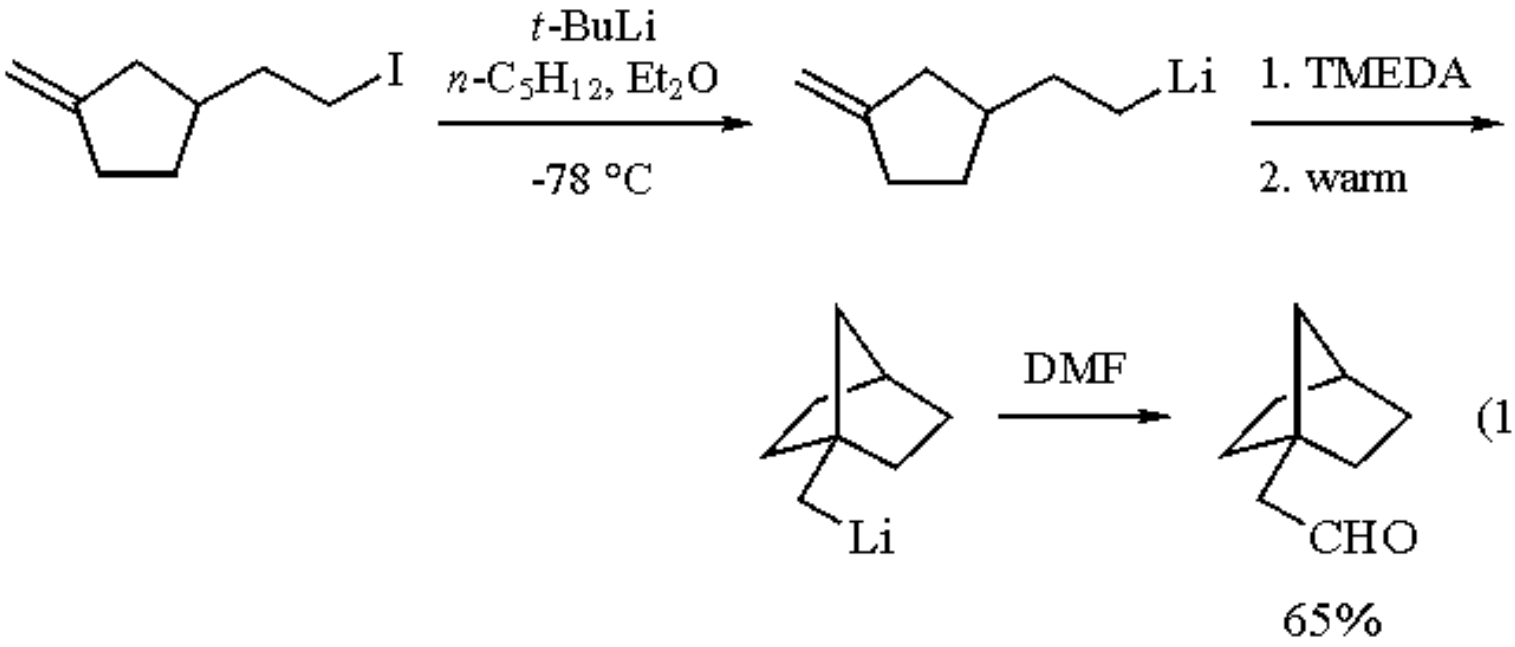

(19)

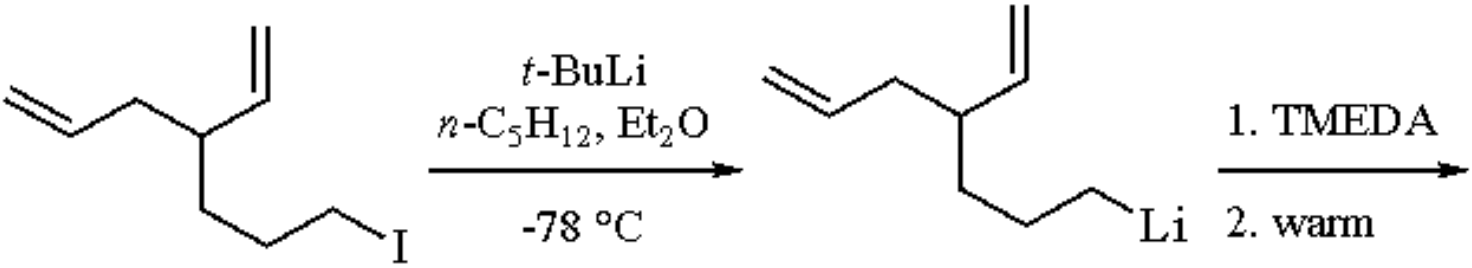

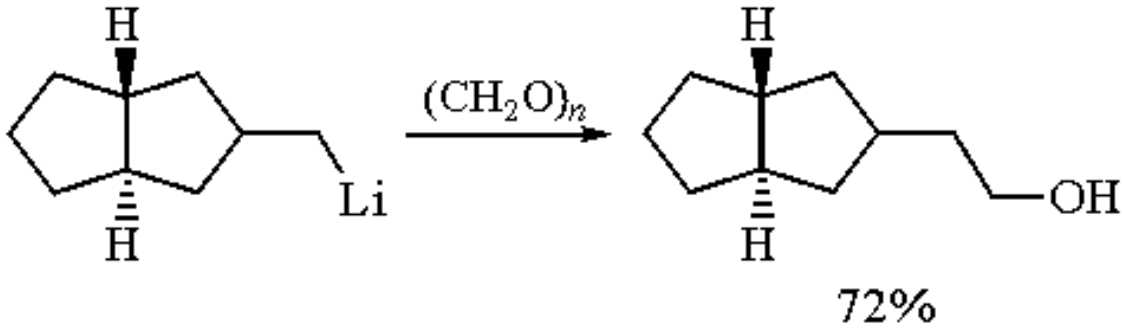

(20)

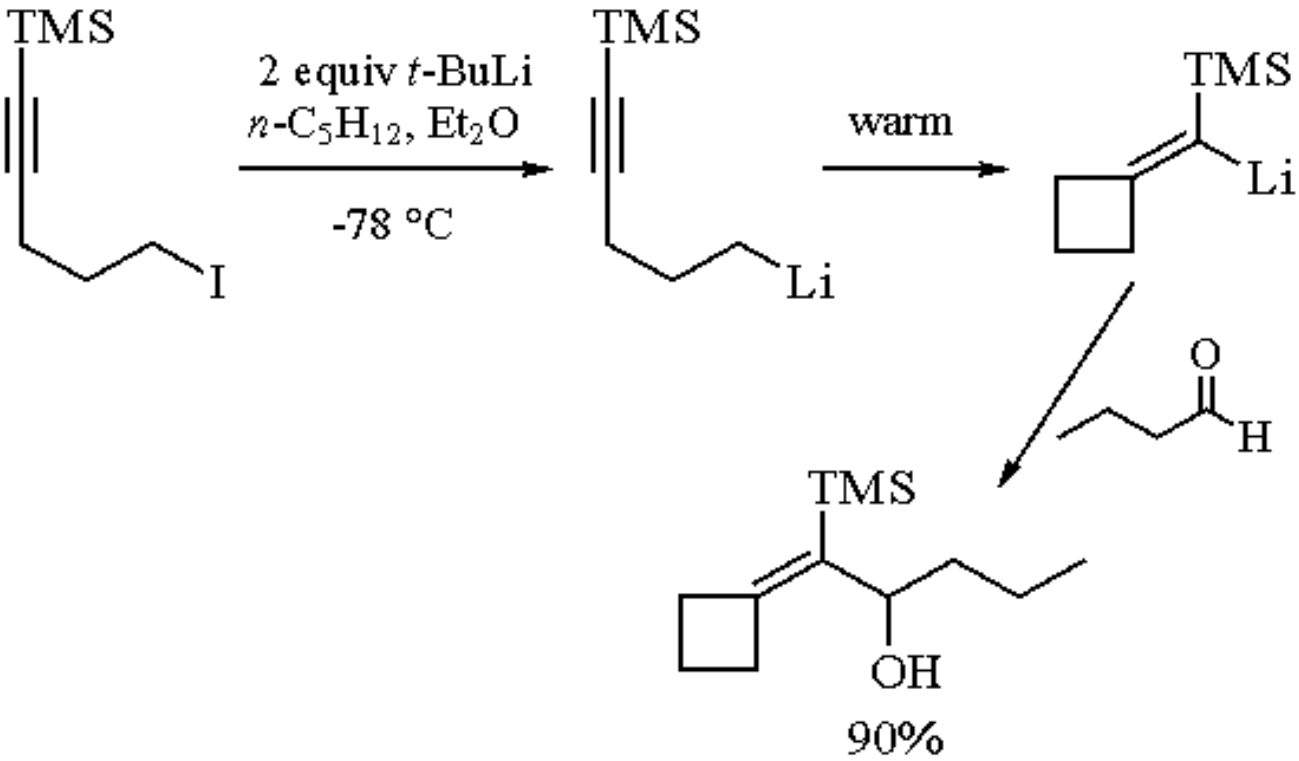

(21)

Reaction of 2 equiv of *t*-BuLi with α,o-diiodoalkanes at -23 °C affords nearly quantitative yields of three- through five-membered carbocyclic rings via cyclization of an intermediate α-lithio-o-iodoalkane (eq 22).[50] When 4 equiv of *t*-BuLi are used at -78 °C, α,o-dilithioalkanes such as ***1,4-Dilithiobutane***, ***1,5-Dilithiopentane***, and 1,6-dilithiohexane result.[5b]

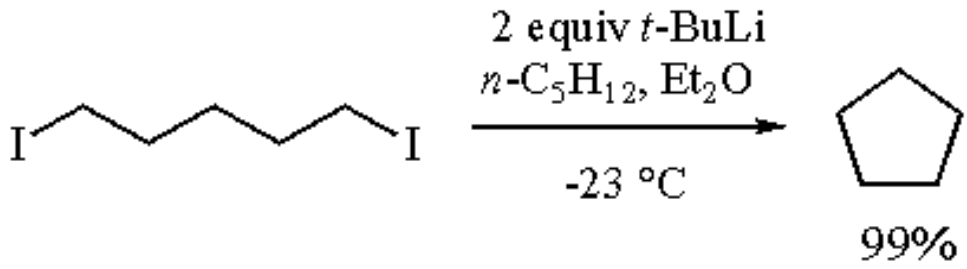

(22)

Low-temperature lithium-iodine exchange between *t*-BuLi and a primary alkyl iodide is more rapid than lithium-bromine exchange with aryl bromides.[51] Indeed, the iodine exchange reaction is so facile that it is sometimes possible to conduct preparatively useful lithium-iodine exchange in the presence of other reactive functional groups[1] such as ketones (eq 23).[52] Metal-halogen exchange-initiated intramolecular conjugate additions have also been reported[53] (eq 24).[53b]

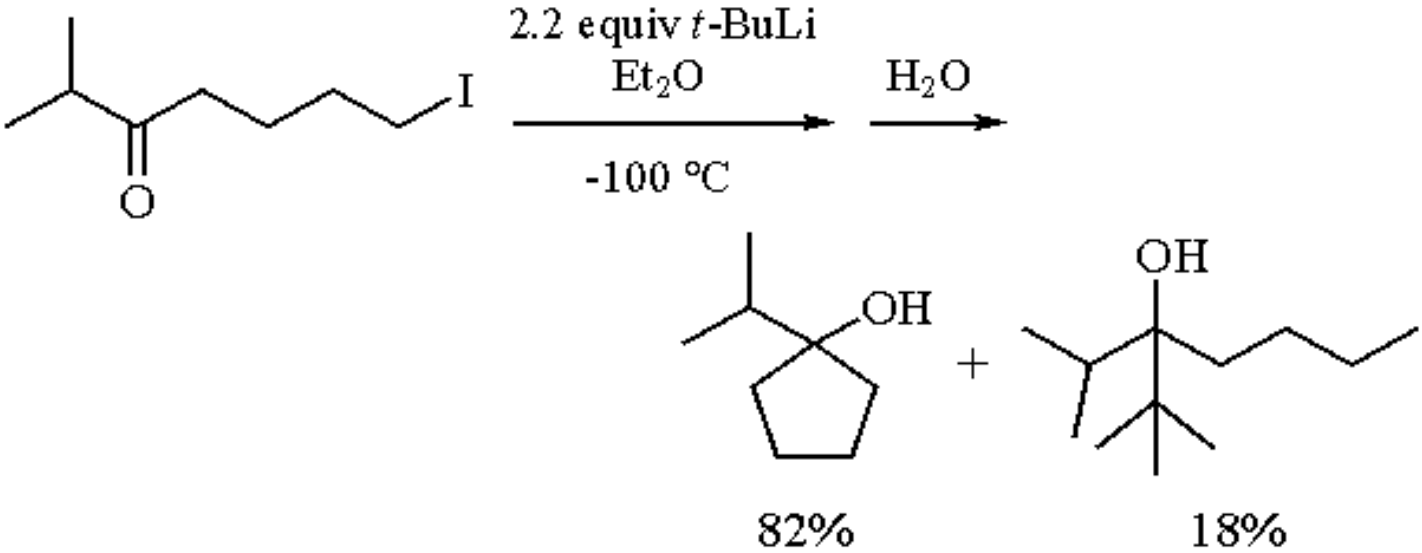

(23)

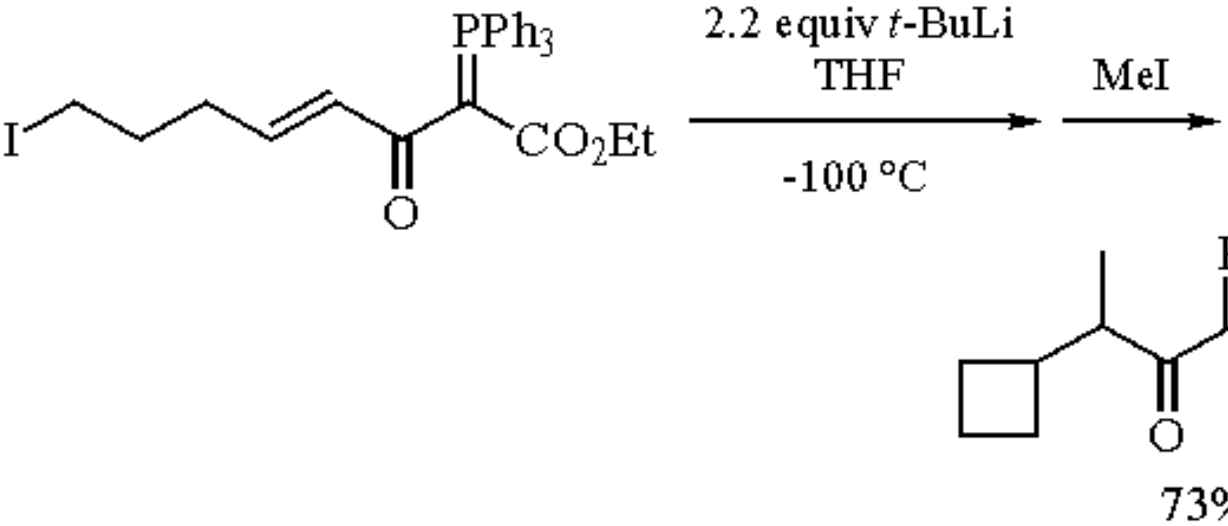

(24)

Dehalogenation of vicinal diiodides initiated by exchange with *t*-BuLi has been used to access highly strained alkenes[54] such as cubene (eq 25).[55]

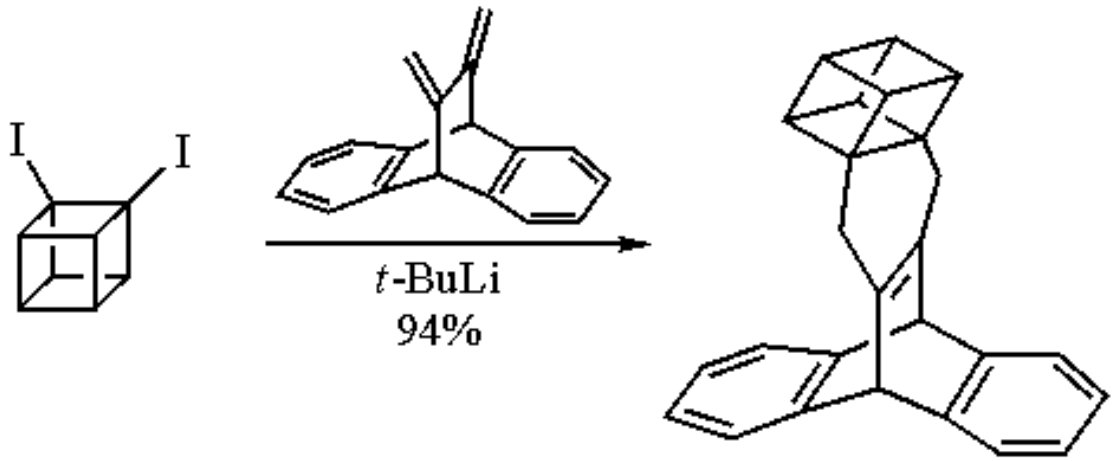

(25)

Addition of Carbon-Carbon Double Bonds.

In the presence of ethers or amines, *t*-BuLi adds rapidly to ethylene at -25 °C at 1 atm of pressure to give neohexyllithium (3,3-dimethylbutyllithium) in quantitative yield (eq 26).[56] It should be noted that neohexyllithium may unexpectedly result from addition of *t*-BuLi to the ethylene generated from the decomposition of diethyl ether[15] or THF[16] when these solvents are present in reaction mixtures containing *t*-BuLi.[56]

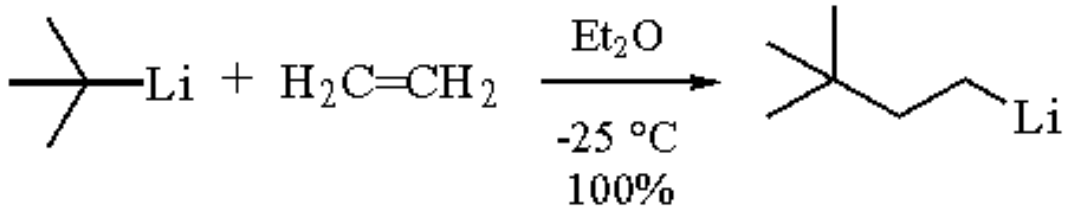

(26)

Addition of *t*-BuLi to other carbon-carbon double bonds is not a facile process unless: (1) the π-system is conjugated[1,57] (in which case anionic polymerization may result),[58] (2) the alkene is at least somewhat strained (eq 27),[59] (3) the resulting anion is stabilized as in vinylsilanes,[60] vinylphosphines,[61] and the like (eq 28),[62] (4) a good leaving group is present at the allylic position,[63] or (5) there is intramolecular assistance provided by a suitably placed heteroatom[6] (eq 29).[64]

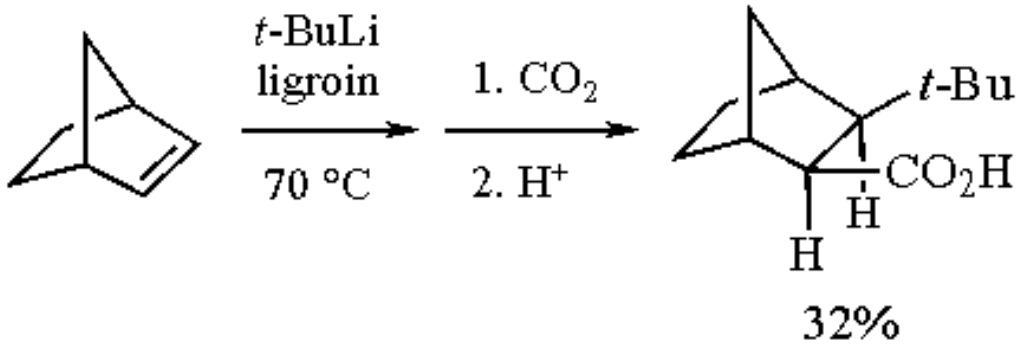

(27)

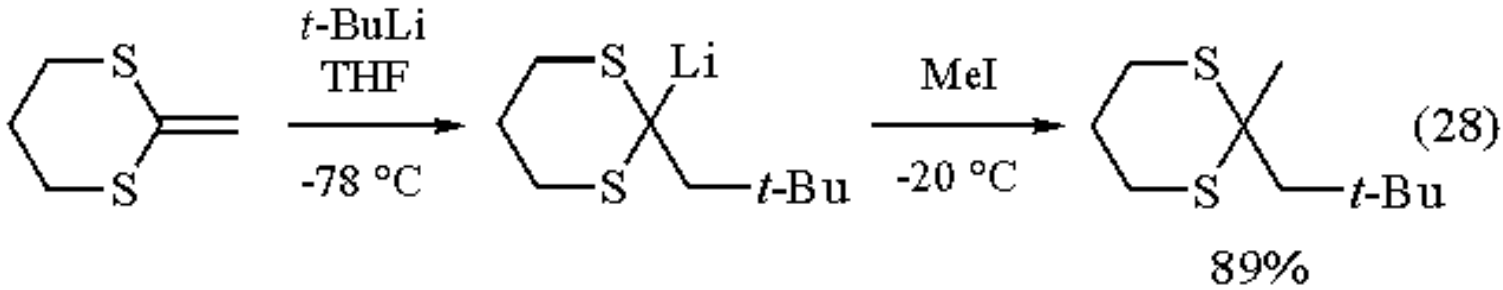

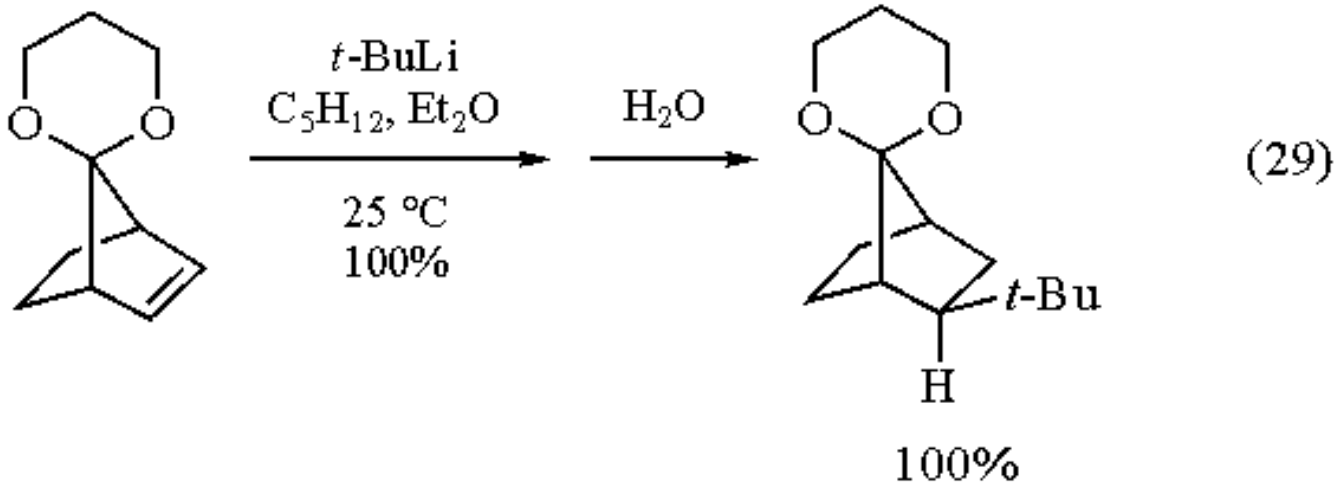

At high temperatures, alkyllithiums have been observed to alkylate aromatic rings by addition to the π-system and subsequent loss of LiH.[1,65] Of the butyllithiums, *t*-BuLi has been found to be more reactive than either of its isomers in the alkylation of naphthalene and other condensed aromatics.[66] Addition of *t*-BuLi, as well as other organolithiums, across the azomethine linkage of pyridine and similar nitrogen heterocycles is a facile process.[1]

Addition to Carbon-Heteroatom Multiple Bonds.

The behavior of *t*-BuLi in reactions with carbon-heteroatom π-bonds is relatively unremarkable and parallels that of other organolithium reagents.[1] Even in cases where steric hindrance might be expected to lead to difficulties, product yields are reasonable. Thus, for example, tri-*t*-butylcarbinol (3-*t*-butyl-2,2,4,4-tetramethyl-3-pentanol) may be prepared by addition of *t*-BuLi to di-*t*-butyl ketone (2,2,4,4-tetramethyl-3-pentanone), although there is a significant amount of reduction in this case,[67] and *N*-lithio-di-*t*-butylimines may be generated by addition of *t*-BuLi to *t*-butyl cyanide.[68]

Related Reagents.

n-Butyllithium; ***s-Butyllithium***.

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s-Butyllithium[1]

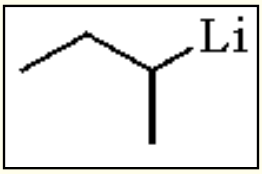

[598-30-1] · C_4H_9Li · *s*-Butyllithium · (MW 64.06)

(strong base capable of lithiating weak carbon acids;[1] useful for heteroatom-facilitated lithiations;[2-4] reagent of choice for *ortho* lithiations[5])

Physical Data: colorless to pale yellow liquid; slowly eliminates LiH; d^{25} 0.783; bp 90 °C/0.05 mmHg;[6,7] ^{13}C NMR, ^{1}H NMR, ^{6}Li NMR, and MS studies have been reported.[8-11]

Solubility: sol hydrocarbon and ethereal solvents, but should be used at low temperature in the latter solvent type: half-lives in ethereal solvents have been reported;[12] reacts violently with H_2O and other protic solvents.

Form Supplied in: commercially available as approximately 1.3 M solution in cyclohexane. Mostly tetrameric in hydrocarbons;[9,13] mostly monomeric in THF;[14] when used in combination with tertiary polyamines such as ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) and ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO), reactivity is usually increased.[1,15]

Analysis of Reagent Purity: since the concentration of commercial solutions may vary appreciably it is necessary to standardize solutions of the reagent prior to use. A recommended method for routine analyses involves titration of the reagent with *s*-butyl alcohol using 1,10-phenanthroline or 2,2´-biquinoline as indicator.[16] Several other methods have been described.[17]

Preparative Method: may be prepared in high yield from *s*-butyl chloride and ***Lithium*** metal in hydrocarbon solvents.[13]

Handling, Storage, and Precautions: solutions of the reagent are pyrophoric and the reagent may catch fire if exposed to air or moisture. Handling of the reagent should be done behind a shield in a chemical fume hood. Safety goggles, chemical resistant gloves, and other protective clothing should be worn. In case of fire, a dry-powder extinguisher should be used: in no case should an extinguisher containing water or halogenated hydrocarbons be used to fight an alkyllithium fire. Bottles and reaction flasks containing the reagent should be flushed with N_2 or preferably Ar and kept tightly sealed to preclude contact with oxygen or moisture. Standard syringe/cannula techniques for air- and moisture-sensitive chemicals should be applied when transferring the reagent.[18] For detailed handling techniques see Wakefield.[1b]

Lithiations.

s-Butyllithium is a powerful metalating agent which is used frequently to convert a variety of organic compounds into their lithio derivatives. The resulting organolithium products may be subsequently functionalized with a large number of electrophiles, hence allowing the preparation of, for example, alcohols, carboxylic acids, ketones, esters, organosilicon compounds, and other organometallic compounds.[1] The metalations of relatively strong carbon acids, such as terminal alkynes, triarylmethanes, and methyl heteroaromatics, may be regarded as simple acid-base reactions and these are done most conveniently using the less basic ***n-Butyllithium***,[19] which is also less reactive and easier to handle than *s*-BuLi. However, the use of *s*-BuLi is warranted for deprotonation of weaker carbon acids (e.g. preparation of aryl-,[15] vinyl-,[20,21] and certain allyllithiums,[15,21,22]) and those that require a less nucleophilic lithiating agent.[5,23]

Lithiations employing *s*-BuLi are most often conducted in electron-donating solvents such as Et_2O, THF, and DME which coordinate to lithium much more strongly than do the alkyl groups of hydrocarbon solvents and thus enhance the reactivity of the organolithium species. It is generally agreed that this effect is the consequence of the depolymerization of higher order organolithium aggregates (tetramers) into smaller units (dimers and monomers).[1] The increased reactivity of organolithiums in ether solvents can, in fact, lead to α-deprotonation of the solvent molecules at elevated temperatures; in diethyl ether, for example, *s*-BuLi has a maximum lifetime of about an hour at +20 °C and THF is attacked even more readily.[12] Hence, to ensure the integrity of the organolithium reagents in these solvents, the use of low-temperature conditions (typically -78 °C) is imperative.

s-Butyllithium is often used in the presence of various lithium complexing ligands such as ***Hexamethylphosphoric Triamide***, TMEDA, and DABCO, which serve to further enhance the reactivity of this reagent.[15] The *s*-BuLi/TMEDA complex is an extremely powerful lithiating agent, effecting rapid deprotonation of many compounds, e.g. benzene, tetramethylsilane, and propene (eq 1),[15] which are unreactive toward *s*-BuLi alone. Compared to the analogous *n*-BuLi/TMEDA complex, *s*-BuLi/TMEDA is considerably more potent as a metalating agent; e.g. the lithiation of Me_4Si proceeds ~1000 times faster with *s*-BuLi/TMEDA than with *n*-BuLi/TMEDA.[15a]

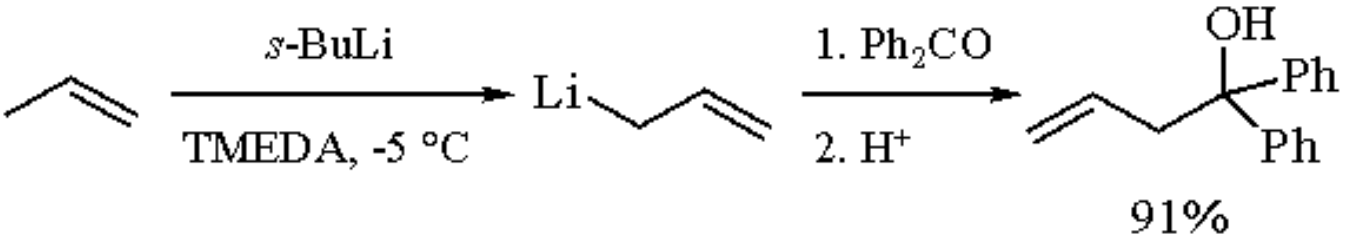

(1)

Metal alkoxides, such as ***Potassium t-Butoxide***, are also used in combination with *s*-BuLi to facilitate the metalation of weak carbon acids including aromatic compounds,[24] vinylic systems,[25] and others.[26,27] The products of these metalations are organopotassium derivatives, but they can be readily converted into the corresponding organolithium compounds by the addition of ***Lithium Bromide***.[26,27]

s-Butyllithium is often used to effect regiospecific and rapid deprotonation of heteroatom-containing compounds.[2-4,28,29] Heteroatoms such as oxygen, sulfur, nitrogen, phosphorus, and halogens enhance the acidity of α- or β-protons through either inductive or coordination effects and hence facilitate deprotonation. For example, the α-lithiation of vinyl thioethers,[30] vinyl chlorides,[31] and vinyl thioesters[32] is effected at low temperatures using *s*-BuLi in the presence of HMPA or TMEDA. The vinyllithium compounds derived from thioethers are important acyl anion equivalents which, after alkylation, are readily converted into substituted ketones (eq 2).[30]

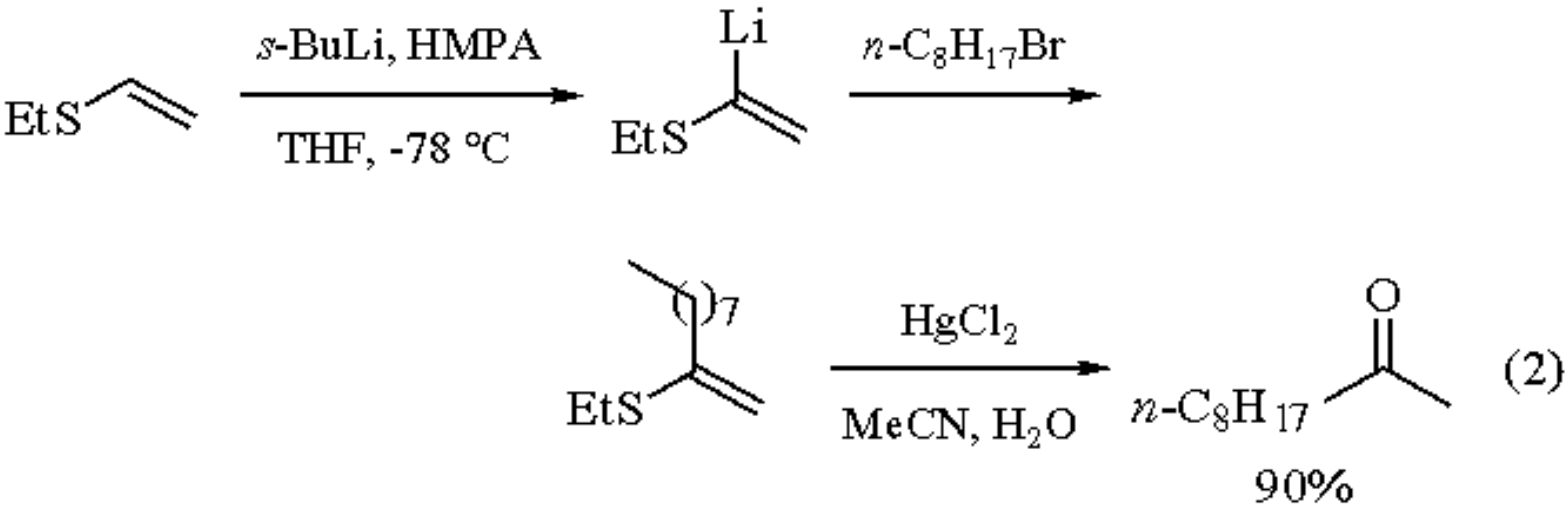

Lithiation of α-disubstituted alkenes is directed to the β-site in cases where the α-substituents are capable of activating the β-position through either inductive effects or chelation (eqs 3 and 4).[20,33] Internal coordination to the lithium by the electron-donating β-substituent in eq 4 permits deprotonation and subsequent electrophilic substitution to take place stereoselectively.[20]

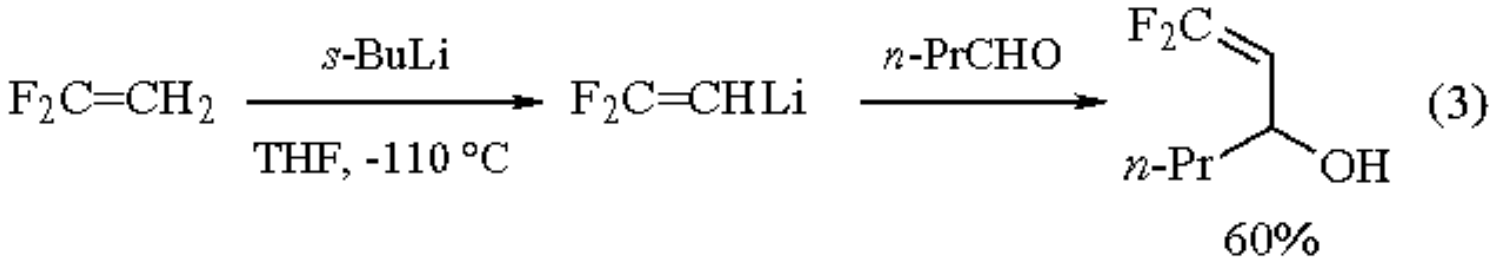

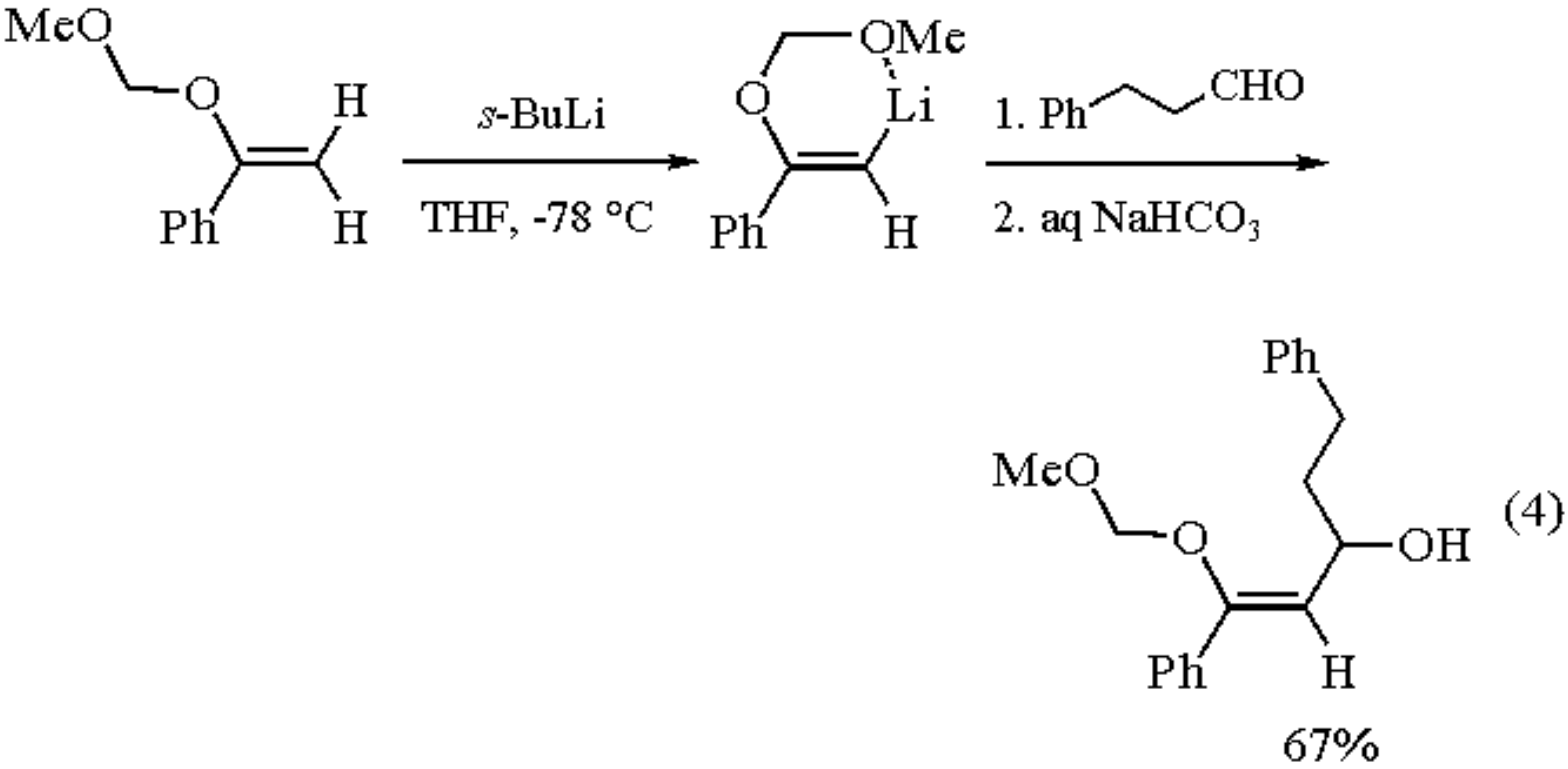

The preparation of a variety of α-heteroatom-substituted alkyllithiums is conveniently achieved using *s*-BuLi and in many cases this reagent exhibits highly original reactivity. ***(Methoxymethyl)trimethylsilane***, for example, undergoes facile lithiation on treatment with *s*-BuLi in THF at -78 °C to give $Me_3SiCHLiOMe$, which is readily hydroxyalkylated by the addition of aldehydes or ketones (eq 5).[34] With other butyllithium reagents, this reaction takes a completely different course: *n*-BuLi undergoes a nucleophilic attack on the Si atom with concomitant loss of the CH_2OMe group, and the use of ***t-Butyllithium*** gives $LiCH_2SiMe_2CH_2OMe$ through preferential deprotonation of one of the trimethylsilyl protons.[34] In a similar reaction, ***(Chloromethyl)trimethylsilane*** is lithiated α to the chlorine atom using *s*-BuLi to furnish synthetically useful α,β-epoxytrimethy lsilanes after treatment with aldehydes or ketones (eq 6).[23] Again, *s*-BuLi appears to be a superior reagent for this lithiation: the use of *n*-BuLi results in loss of the chloride anion, presumably through initial nucleophilic attack of this reagent upon the silicon atom and subsequent alkyl migration, and *t*-BuLi leads to the predominant formation of ***Trimethylsilylmethyllithium***, formally derived from Li-Cl exchange.[23] Selenide Bis(trimethylsilylmethyl) selenide,[35] ***Methylenetriphenylphosphorane***,[36] phosphonic acid triamides,[37] and 1,3-oxathianes[38] are also readily lithiated on treatment with *s*-BuLi. The final ketene *O*,*S*-acetal product in eq 7 is formed via the Peterson alkenation process after addition of 2-methylpropanal to the lithio intermediate.[38a]

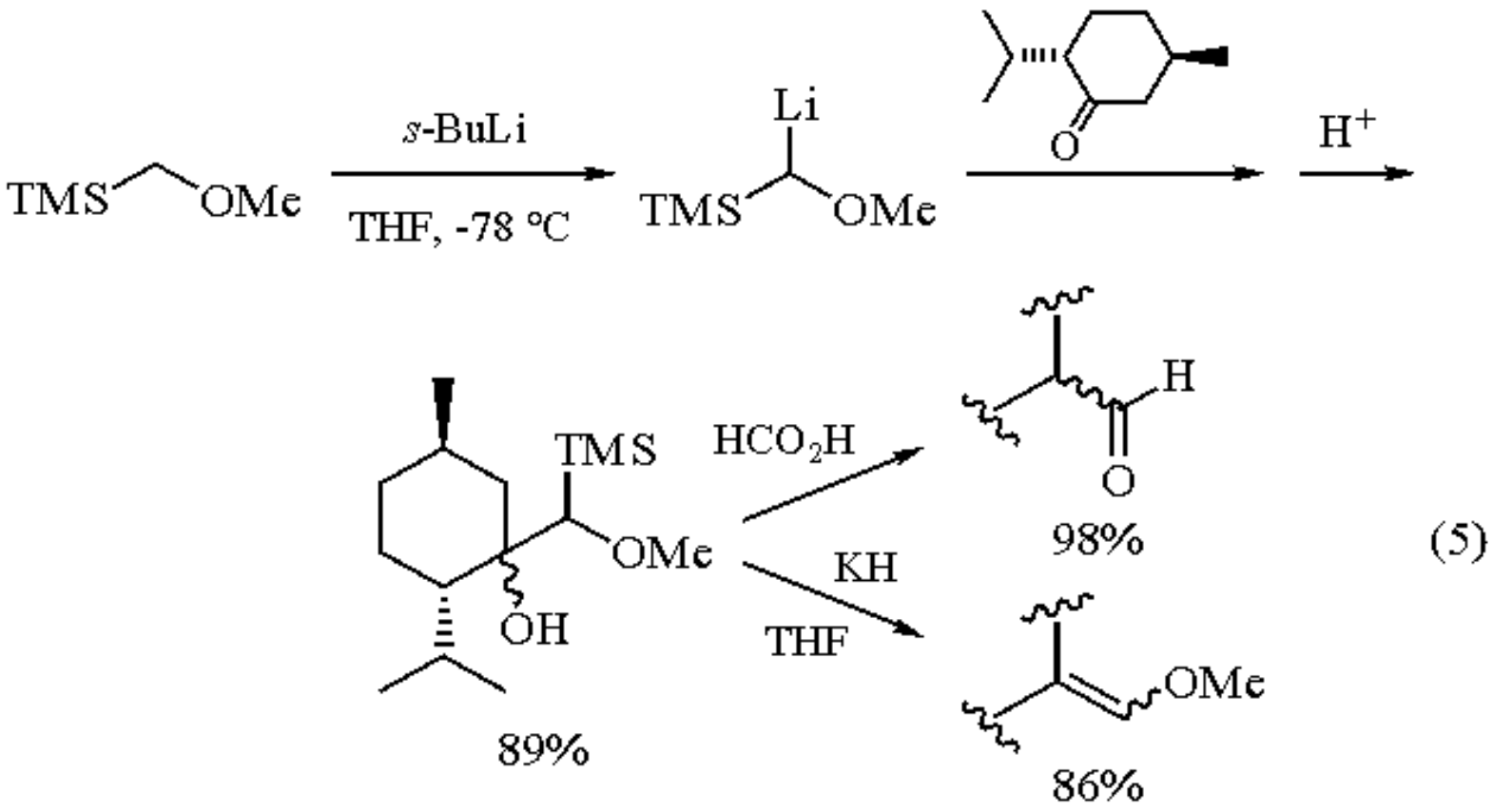

(5)

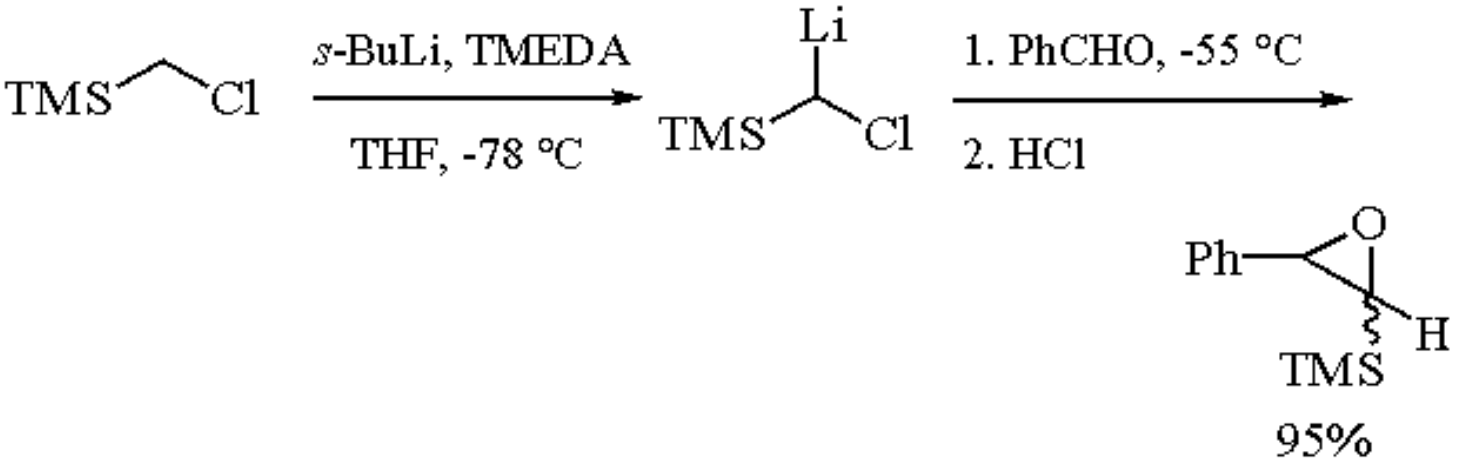

(6)

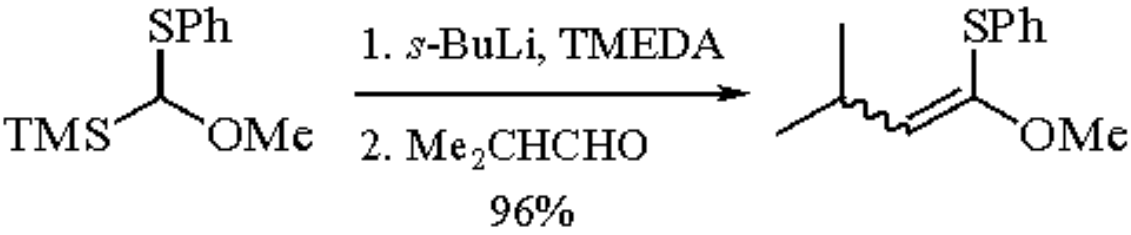

(7)

Metalation of *N*-methylpiperidine, *N*-methylpyrrolidine, and ***Trimethylamine*** takes place exclusively at the methyl group when *s*-BuLi is used in combination with *t*-BuOK (eq 8),[26] and the same mixture can be used to metalate *t*-butyl methyl ether (eq 9).[27] The intermediate organopotassium product in eq 9 is converted into the corresponding organolithium derivative by addition of LiBr to give *t*-BuOCH$_2$Li, the synthetic equivalent of hydroxymethyllithium (LiCH$_2$OH).[27]

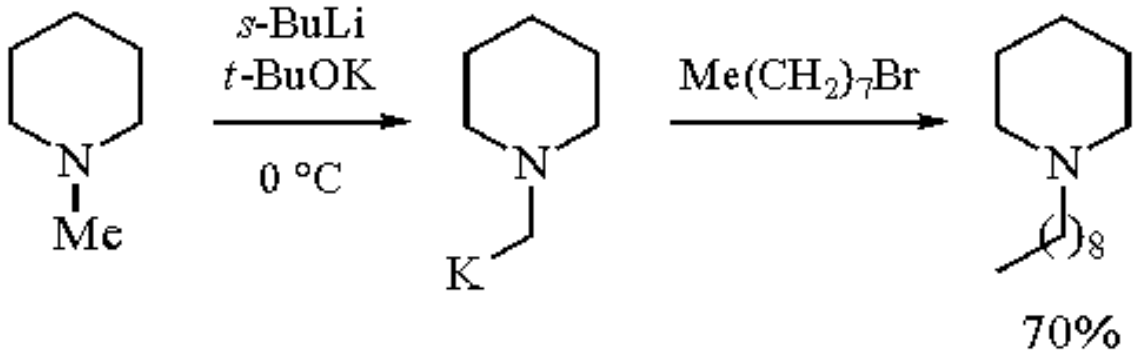

(8)

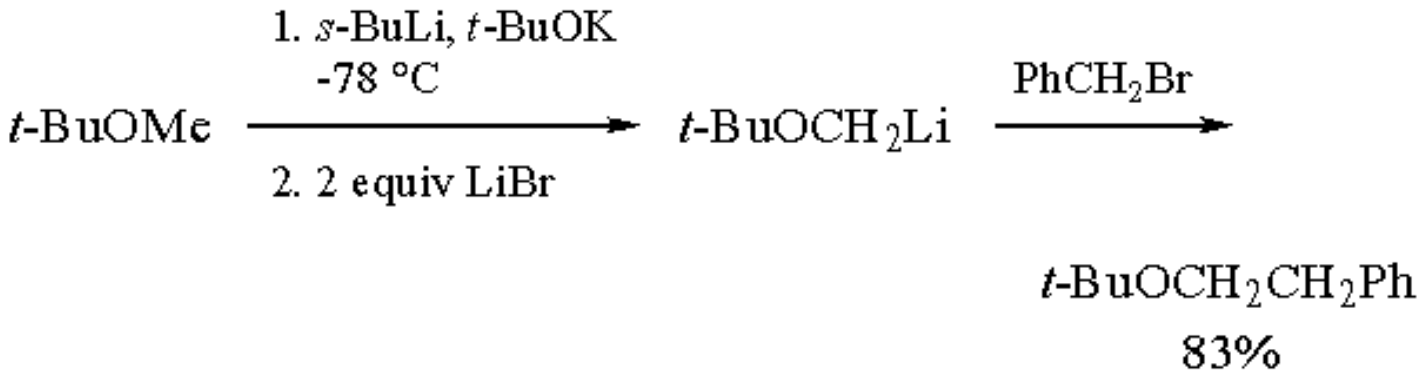

(9)

Many allylic or benzylic heteroatom-containing compounds are often lithiated more conveniently using the less reactive

n-BuLi rather than *s*-BuLi. However, the more basic *s*-BuLi is a better reagent for the deprotonation of alkyl allyl ethers[39] and certain allyl thioethers[21b] that react slowly (if at all) with *n*-BuLi in THF at low temperatures (<-65 °C). The allyllithium derivatives formed in these reactions may be alkylated or hydroxyalkylated either at the α- or the γ-position, depending on the electrophile and the structure of the allylic anion. With metalated allyl ethers, primary alkyl halides tend to attack the γ-position to afford alkylated enol ethers, but carbonyl compounds react to give products derived mainly from α-attack (eq 10).[39,40] The opposite tendency is generally observed with analogous lithiated allyl thioethers[21,41,42] which, upon addition of alkyl halides, give primarily α-alkylated products (eqs 11 and 12).[21b,42] Generally, soft electrophiles (e.g. RI) exhibit a higher propensity for γ-attack than do hard electrophiles (e.g. RCl).[42]

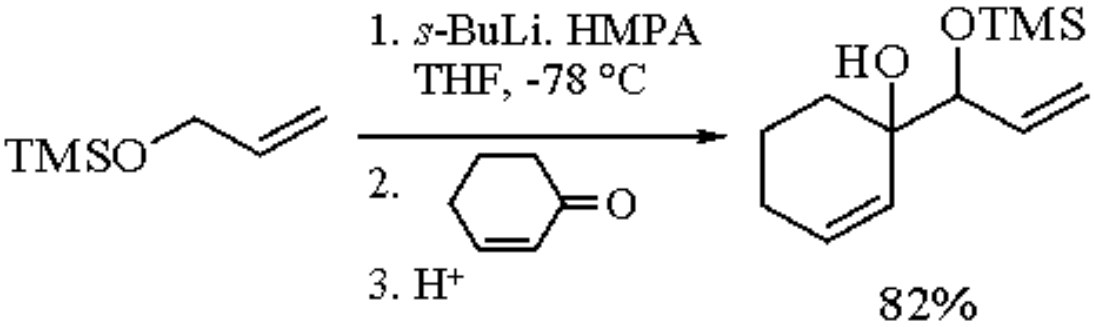

(10)

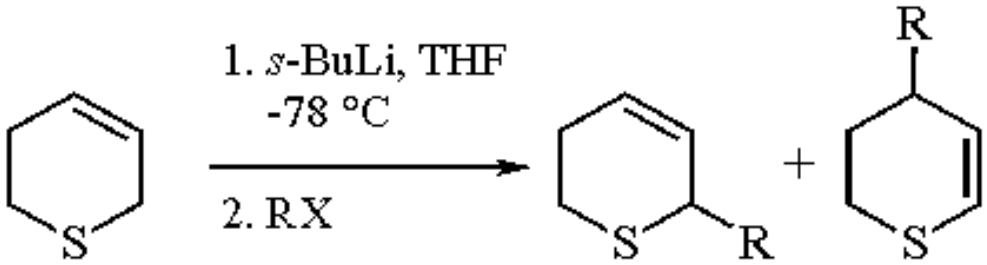

(11)

RX	α:γ	
n-BuCl	97:3	70%
n-BuBr	91:9	79%
n-BuI	70:30	100%

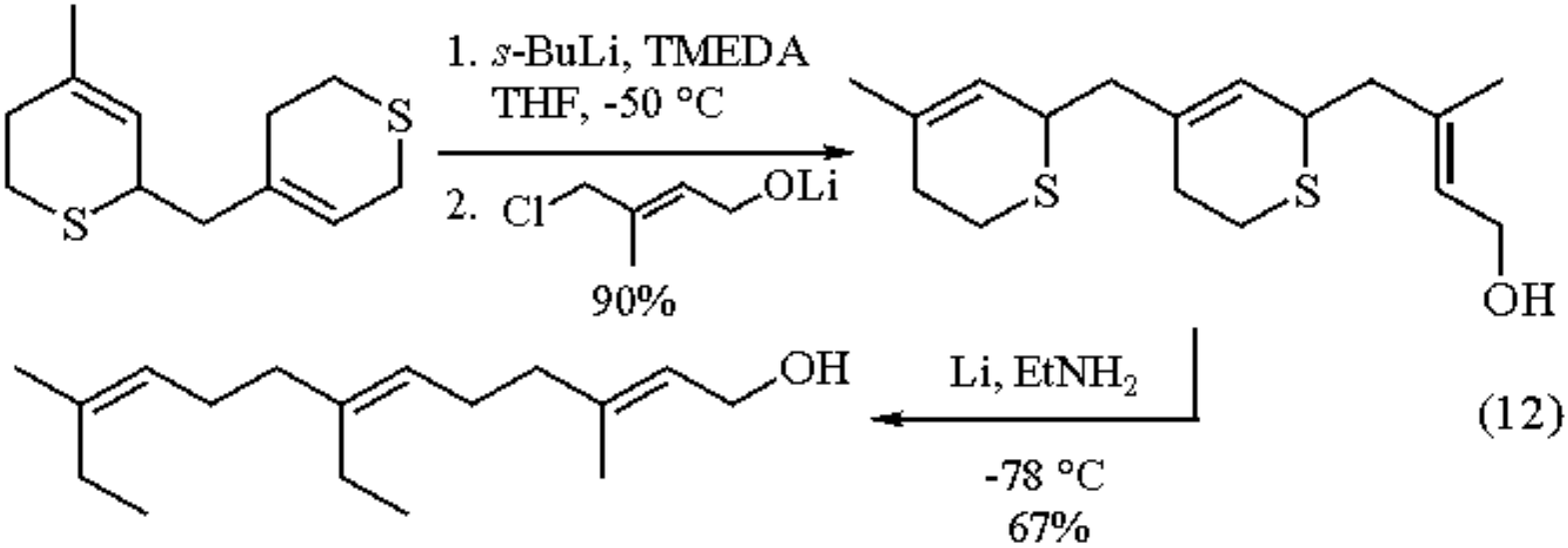

(12)

Proton removal adjacent to a heteroatom is further facilitated if the lithium can be internally coordinated to proximate electron donors, such as the carbonyl oxygen, permitting the formation of dipole-stabilized carbanions.[28] Thus lithiations of various amides,[43] thioamides,[44] imides,[45] esters,[46] Boc derivatives of cyclic amines (pyrrolidines, piperidines, and hexahydroazepines),[47] thioesters,[32] *N*,*N*-dialkylthiocarbamates,[32] and various formamidine derivatives[48] are achieved conveniently using *s*-BuLi (eqs 13-17).[32,43b,44,47a,48a] Subsequent addition of electrophiles followed by hydrolytic removal of the activating carbonyl, carbamoyl, or formamidine moiety provides a valuable synthetic route to a variety of α-substituted amines, alcohols, and thiols.[28,46] Successful alkylation of the dipole-stabilized carbanions may require the conversion of the initial lithio carbanions into their organocuprate derivatives, e.g. by the addition of *n*-PrC&tbond;CCu.[48a]

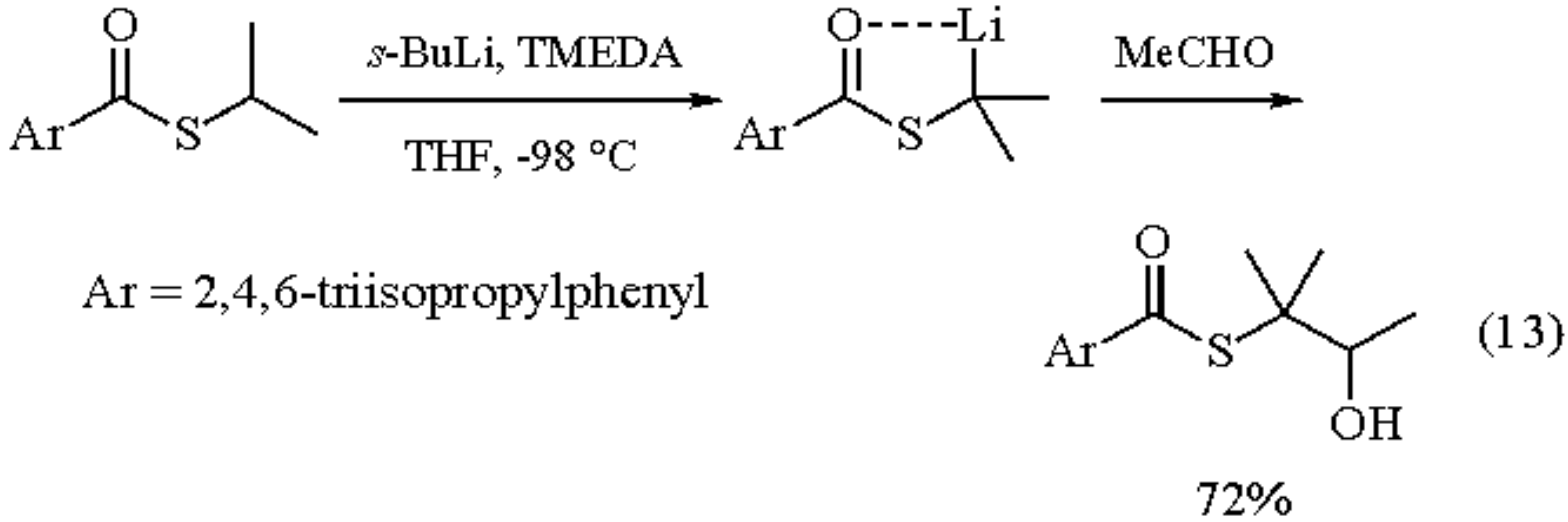

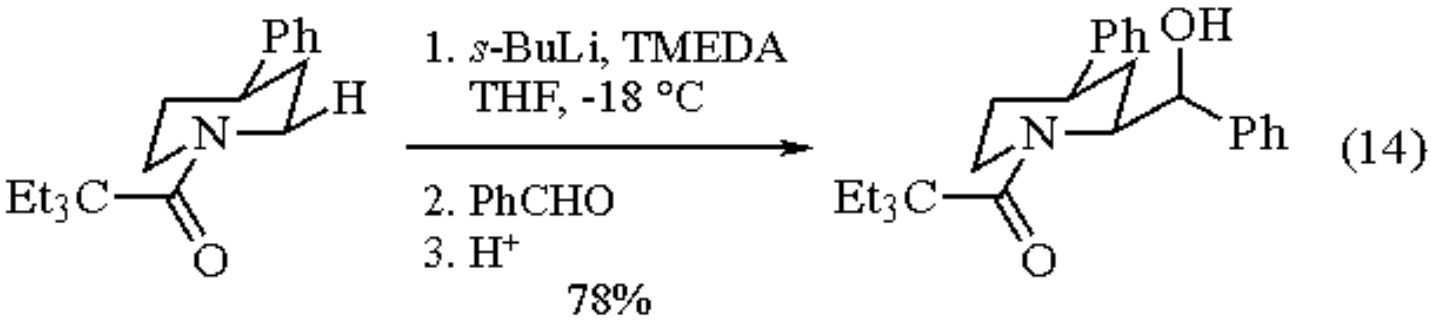

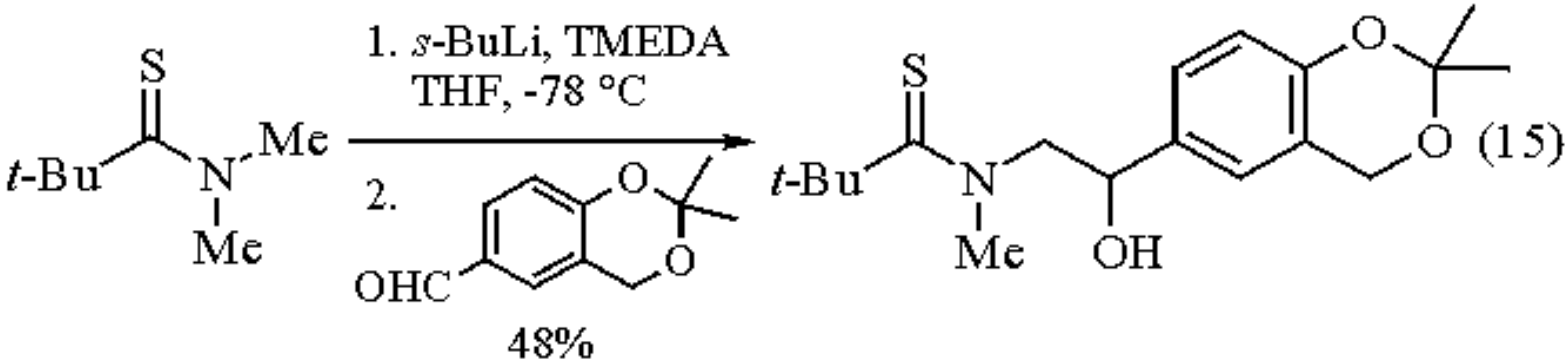

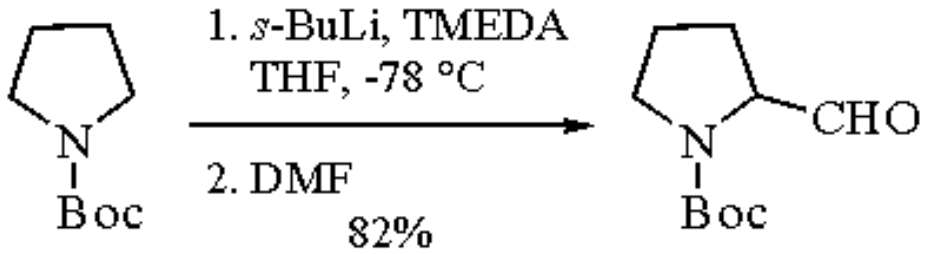

(16)

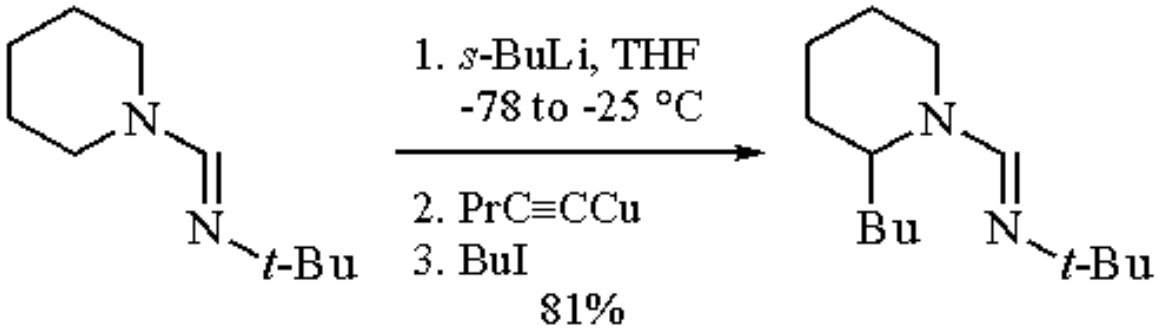

(17)

Lithiation takes place more readily if the dipole-stabilized anions are further activated by an adjacent aromatic ring or a double bond and, in fact, many such compounds are most conveniently deprotonated using the less reactive *n*-BuLi.[28]

Stereoselective *s*-BuLi-promoted α-lithiations have been accomplished with various piperidine and isoquinoline derivatives bearing chiral oxazoline or formamidine substituents on the nitrogen (eqs 18 and 19).[49,50] Asymmetric deprotonations α to oxygen in carbamates and α to nitrogen in Boc-protected pyrrolidines have been effected using *s*-BuLi in the presence of ***(-)-Sparteine***, which is a homochiral lithium-complexing ligand.[51,52] These deprotonations lead to the formation of chiral dipole-stabilized carbanions which react with electrophiles under strict stereocontrol to give substituted products in high enantiomeric excess, typically >95% ee. In the case of the *N*-oxazoline derivatives of piperidine and isoquinoline, enantiomerically enriched secondary amines are obtained upon hydrolytic removal of the oxazoline moiety.[49a] These reactions are of considerable synthetic value and this methodology has been successfully applied to the asymmetric synthesis of 2-piperidines[49] and 2-pyrrolidines (eq 20),[52] 2-alkanols,[51a] 2-hydroxyalkanoic acids,[51a] alkanediols,[51b,c] and lactones (e.g. (*R*)-pantolactone) (eq 21).[51b]

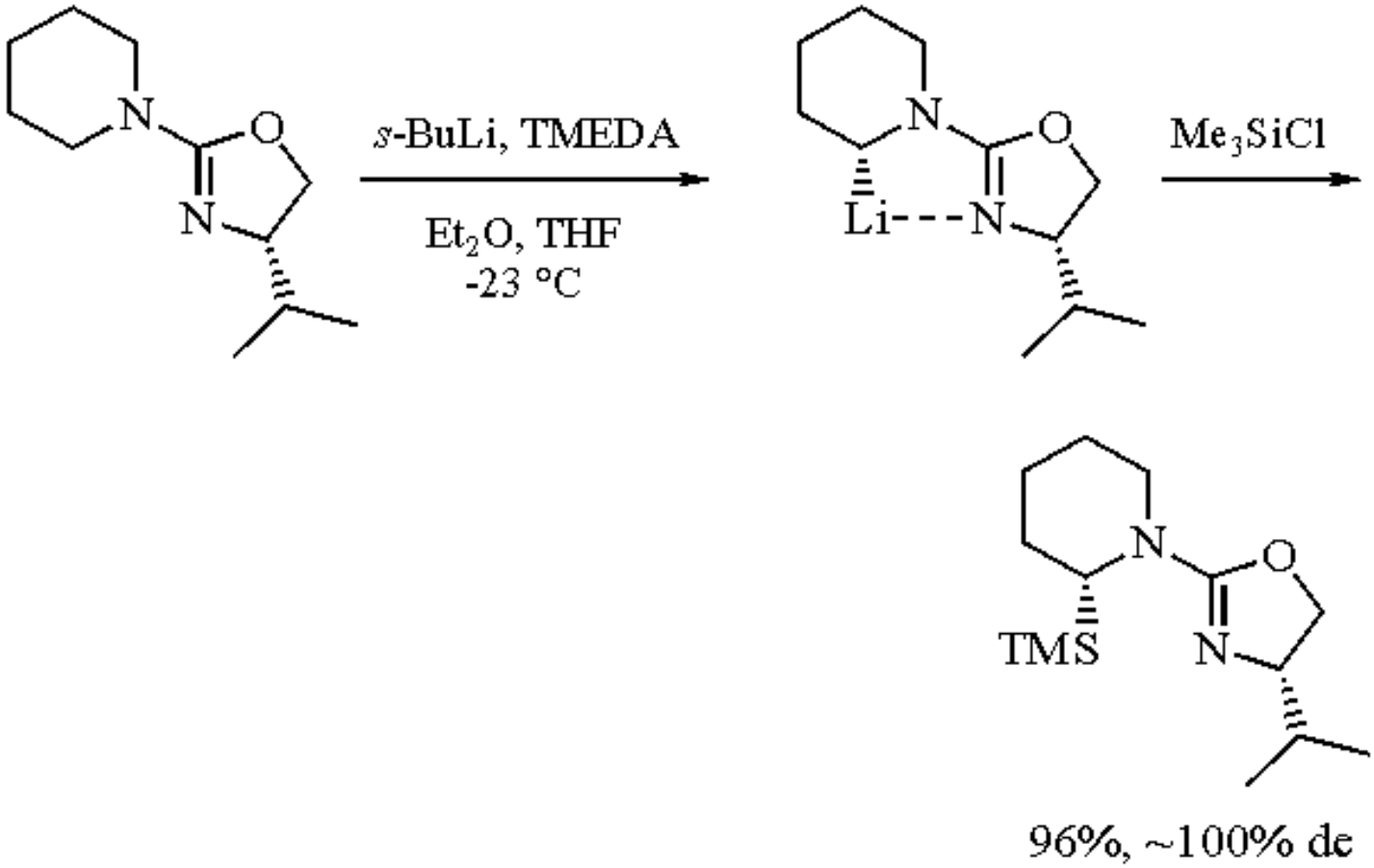
s-BuLi, TMEDA
Et2O, THF
-23 °C
Me3SiCl
TMS
96%, ~100% de

(18)

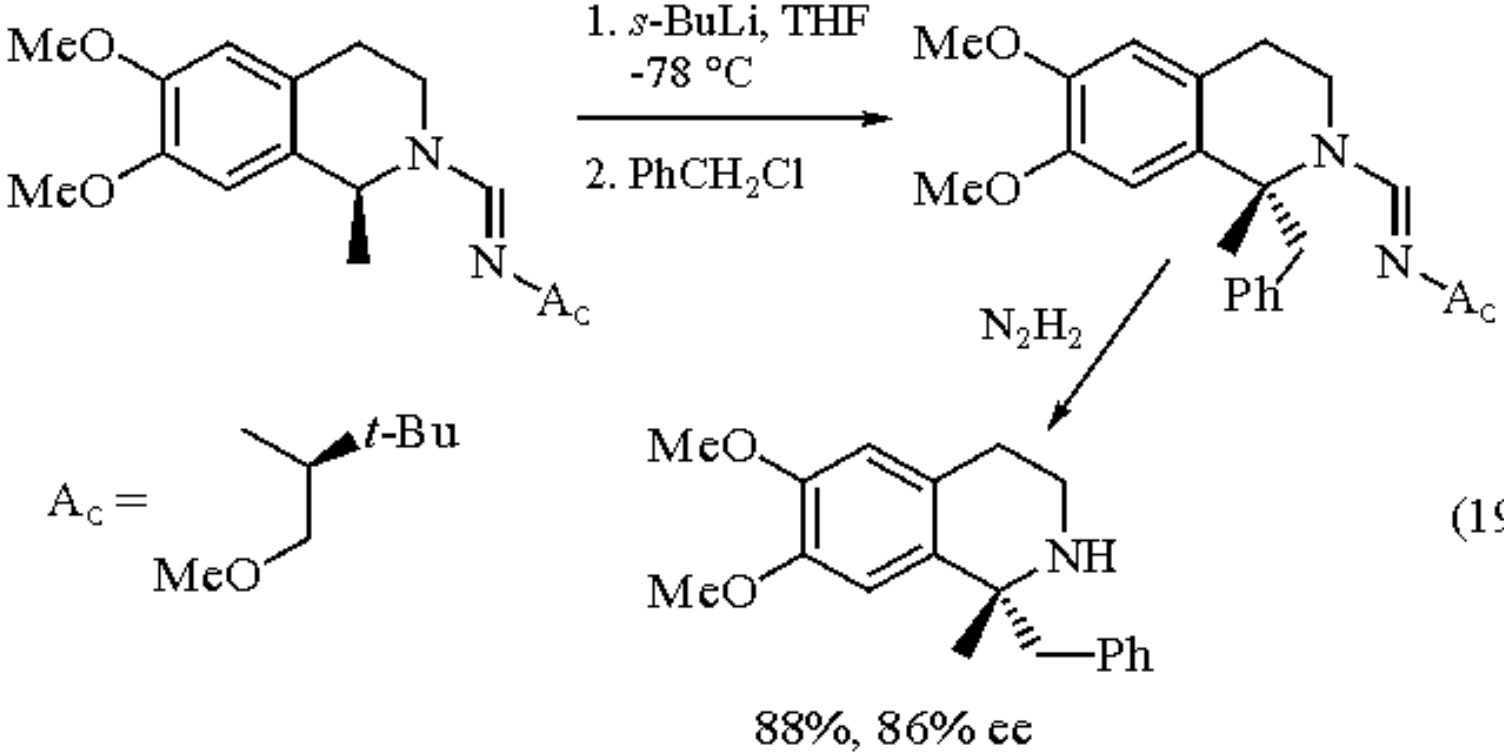
1. s-BuLi, THF
-78 °C
2. PhCH2Cl
MeO
MeO
Ph
N2H2
NH
Ac =
t-Bu
88%, 86% ee

(19)

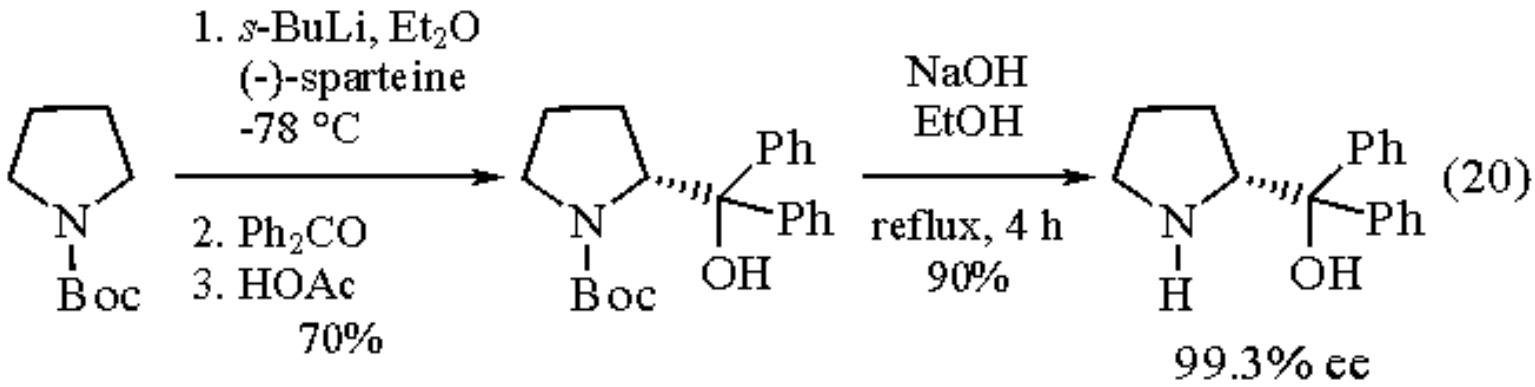

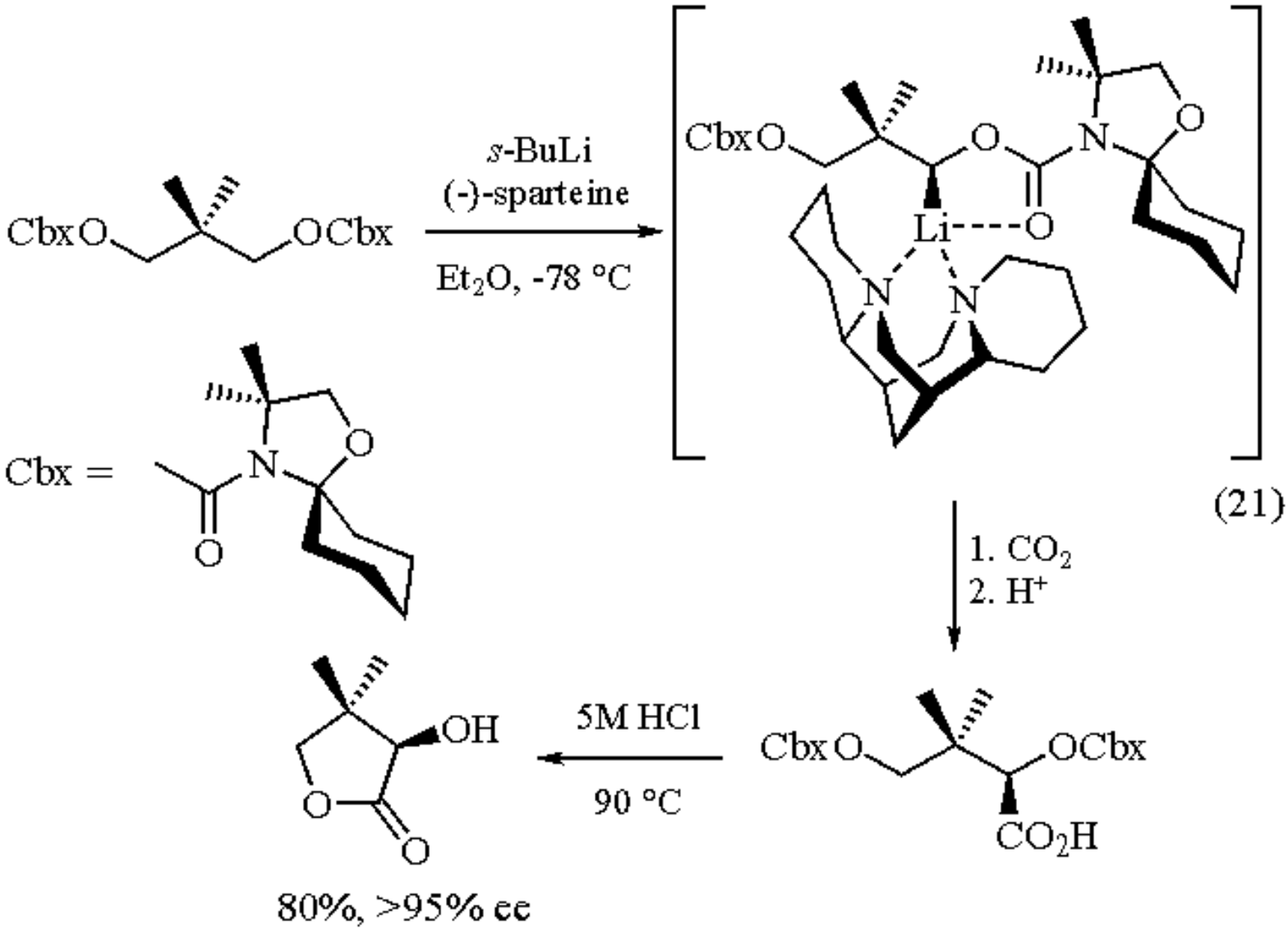

ortho Lithiations.

s-Butyllithium is a commonly used reagent for *ortho* lithiation of aromatic rings bearing heteroatom-containing substitutents. This methodology has been exploited extensively as a route to a wide variety of polysubstituted aromatic compounds, including natural products[53] (eq 22),[53e] and several excellent reviews have been published on the topic.[2,5,54] Included in the list of groups commonly used for *s*-BuLi-promoted *ortho* lithiations are OMe,[55] CH_2NEt_2,[55] NMe_2,[56] $CONEt_2$,[57] $OCONEt_2$,[57] SO_2NR_2,[58] 2-oxazolinyl,[57] and groups that contain acidic hydrogens and themselves

undergo deprotonation prior to ring lithiation, e.g. CONHR[57,58] and SO_2NHR.[57,58] Depending on the substituent, both inductive and coordination effects can be invoked to account for the observed regiochemistry.[2,59] Although a large number of *ortho* lithiations may be conducted with *n*-BuLi,[2] the use of *s*-BuLi is generally preferred, especially when the reactions involve aromatic tertiary amides or *O*-aryl carbamates which are susceptible toward nucleophilic additions with the latter. For example, *N*,*N*-dimethyl- and -diethylbenzamides have been shown to afford primarily aryl butyl ketones upon treatment with *n*-BuLi.[55,60] The recommended procedure for *ortho* lithiation involves slow addition of the aromatic substrate in anhydrous THF to a slight excess of 1:1 *s*-BuLi/TMEDA in THF at -78 °C.[55] Under these conditions, the lithiation is usually complete within 5 min.

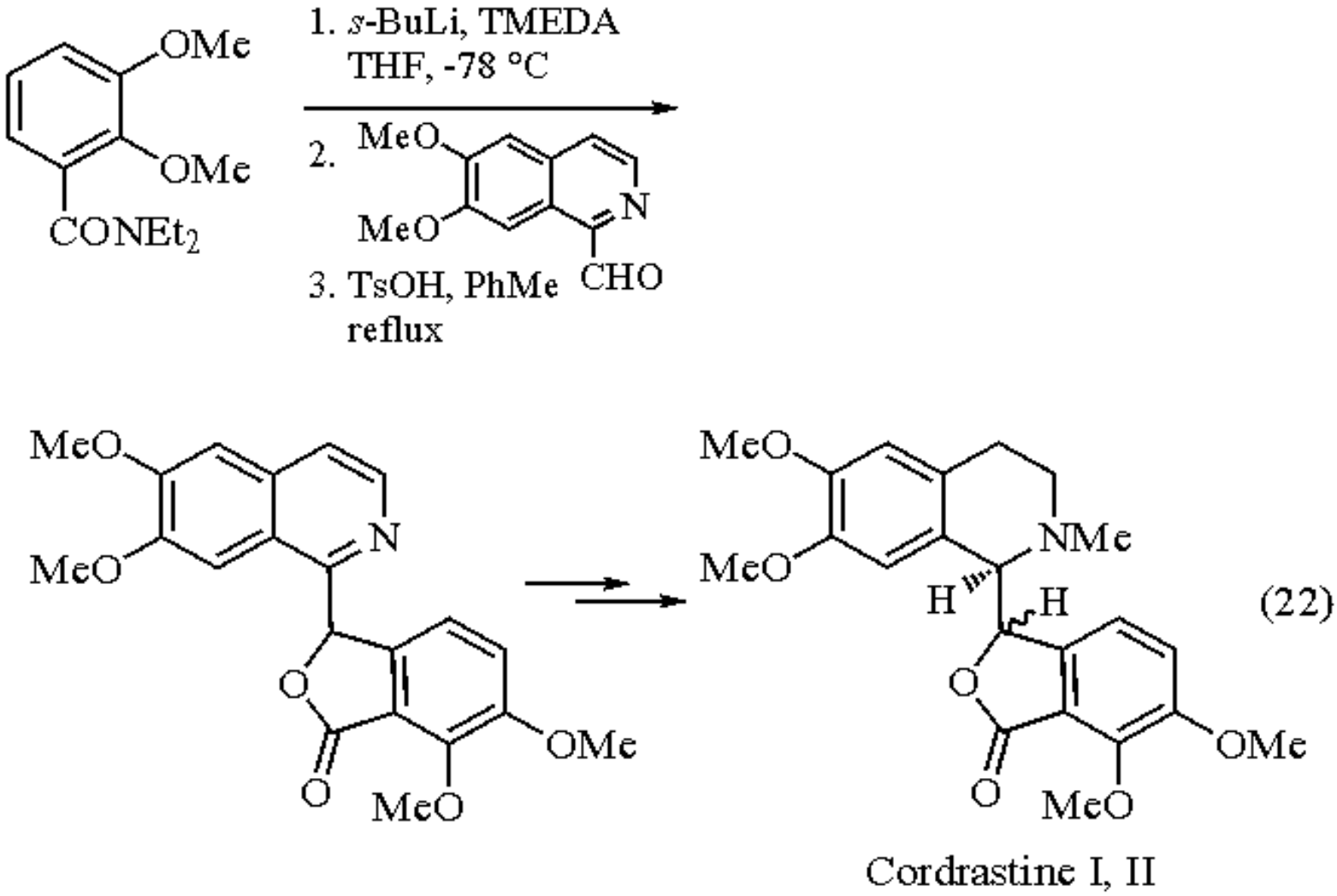

(22)

When two *ortho*-directing groups are in a *meta* relationship, lithiation is generally directed to their common site. Notable exceptions to this behavior are found in cases where $CONEt_2$, CONR, or oxazoline substitutents are *meta* to a dialkylamino group.[5] These systems exhibit nearly total reversal of the general trend and, as a result, almost exclusive metalation of the 6-position is observed (eq 23).[56] Considerable amounts of 6-substituted products are also obtained in cases where $OCONEt_2$ and OMe groups are in a *meta* relationship.[57] When two *ortho*-directing substituents are *ortho* or *para* to each other, the regiochemistry of the reaction depends on the relative directing abilities of these groups (eq 24).[57]

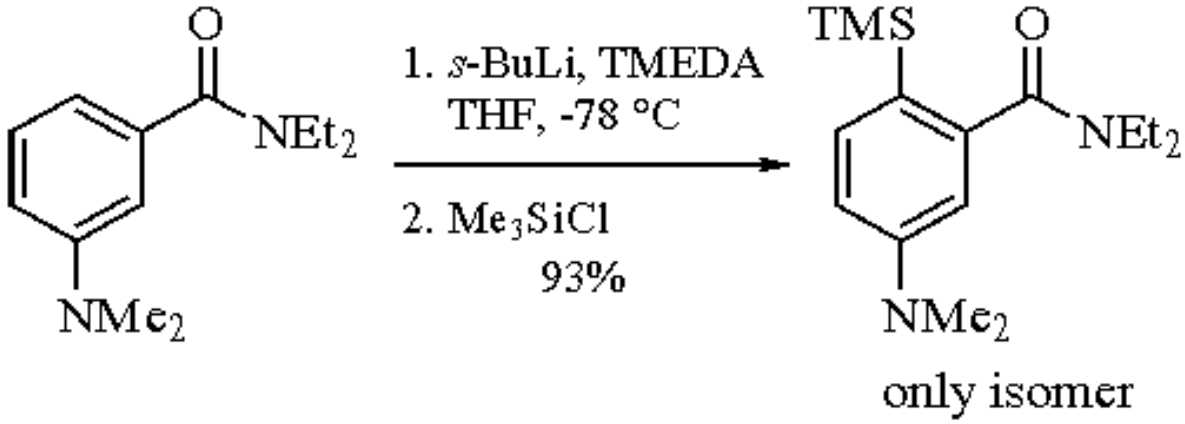

(23)

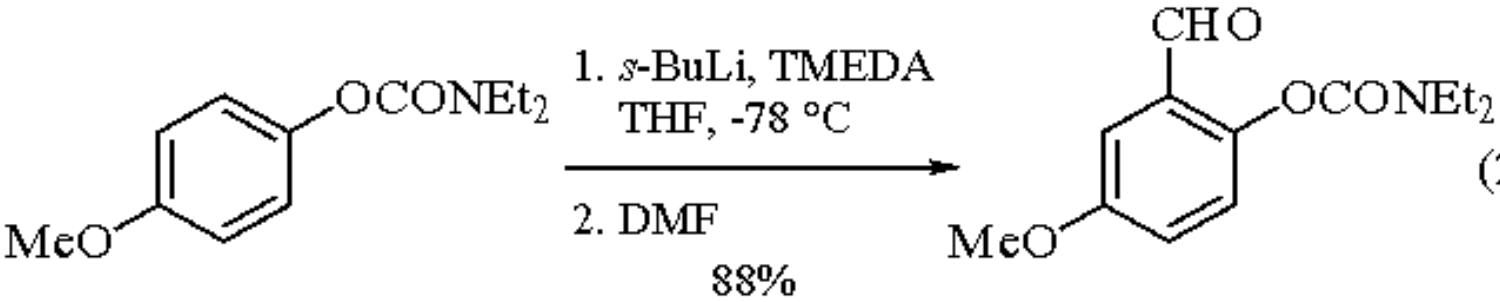

(24)

A large number of substituted polyaromatic and heteroaromatic compounds are also accessible through *s*-BuLi-induced *ortho* lithiation reactions. These include, for example, derivatives of naphthalene,[57] furan,[61] thiophene,[62] pyridine,[63] quinoline,[64] and N-protected imidazoles.[65] The smooth *ortho* lithiation of pyridyl (eq 25)[63] and quinolinyl systems is notable given the well-known tendency of organolithium compounds to undergo nucleophilic addition reactions with the pyridine nucleus.[1]

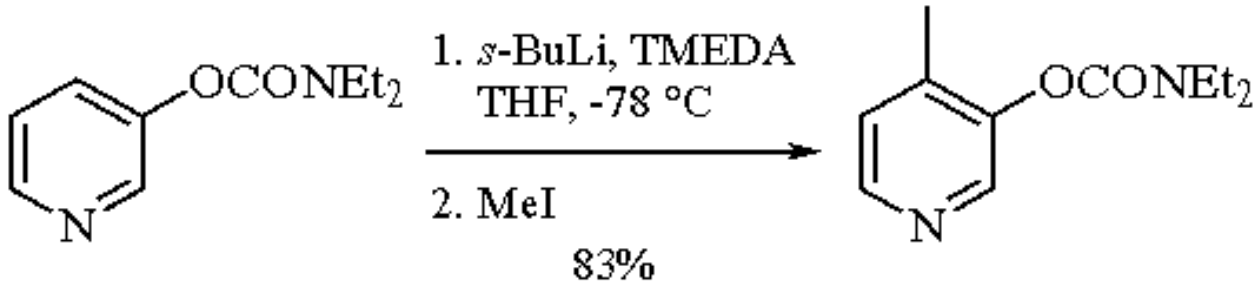

(25)

Lithium-Halogen Interchange and Transmetalation Reactions.

The lithium-halogen interchange involves the exchange of halogen by lithium in a reversible reaction, with the most stable organolithium species being favored at equilibrium. Hence, the most synthetically useful lithium-halogen exchanges take place between alkyllithiums and aryl halides, cyclopropyl halides, and vinyl halides. These reactions are accomplished most conveniently using *n*-BuLi rather than *s*-BuLi and, as a result, the latter has been employed only in a relatively few cases. However, the formation of select α-halo- and α-dihalolithiums,[66] aryllithium compounds,[67] and vinyllithium derivatives[68] using *s*-BuLi has been reported. The preparation of simple alkyllithium compounds by lithium-halogen exchange is usually limited to the generation of primary alkyllithiums from primary alkyl iodides by treatment with the more reactive tertiary alkyllithiums (such as *t*-BuLi).[69]

The lithium-selenium exchange has been exploited extensively for the generation of a variety of organolithiums from selenides, selenoacetals, and mixed *S,Se*-acetals, with *n*-BuLi being the most commonly employed reagent for these reactions.[3,70] Although *s*-BuLi can be used for all of these conversions, the primary role of this reagent is to provide a more reactive lithiating agent for the generation of synthetically useful[3,71] α-selenoalkyllithiums from selenoacetals of sterically hindered ketones.[72] For example, 2,2-bis(methylseleno)adamantane is completely unreactive toward *n*-BuLi in THF at -78 °C, but it undergoes a facile (30 min) Li-Se exchange on treatment with *s*-BuLi under identical conditions to afford the expected α-selenoorganolithium product in high yield (eq 26).[72]

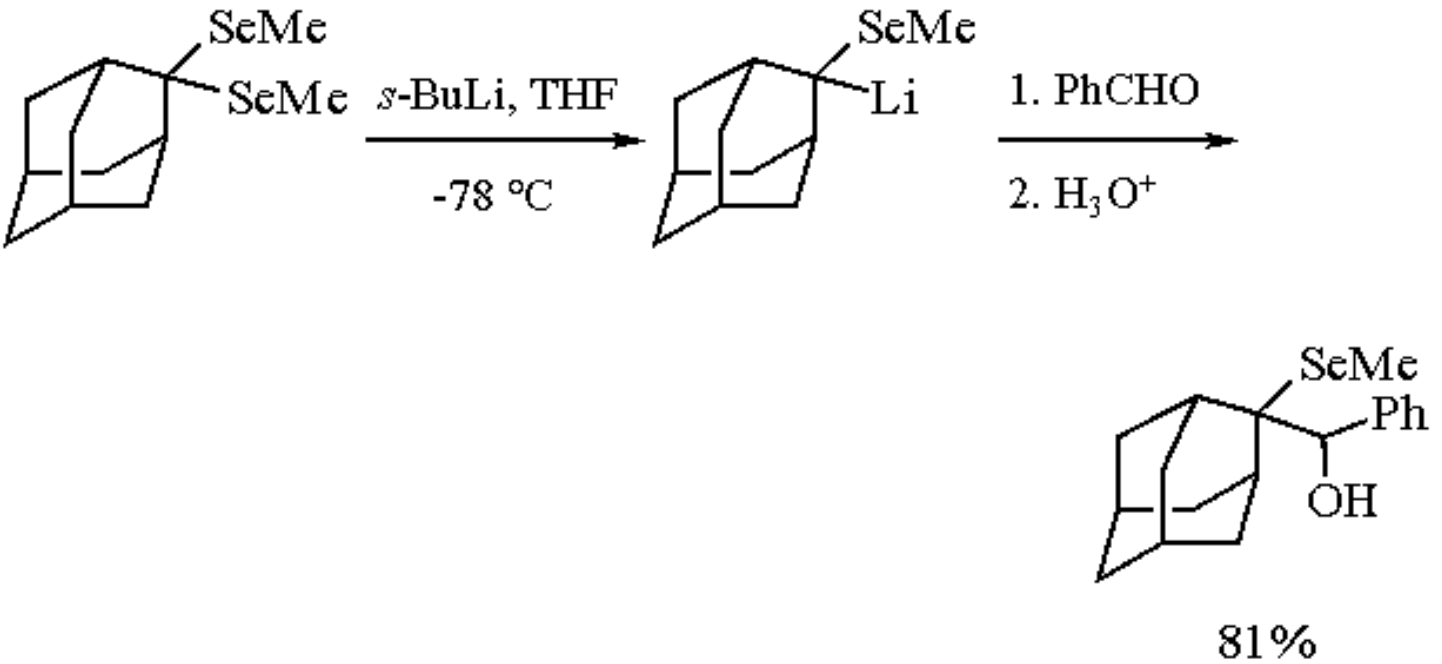

(26)

The following order of reactivity of organolithium reagents toward selenoacetals has been established: *t*-BuLi/THF-hexane &AApprox; *s*-BuLi/THF-hexane > *n*-BuLi/THF-hexane &AApprox; *s*-BuLi/ether-hexane >> MeLi/THF-ether > *t*-BuLi/hexane &AApprox; *n*-BuLi/hexane.[72] As seen from this order, the reactivity of *s*-BuLi in ether-hexane is comparable to that of *n*-BuLi in THF-hexane. The α-selenoalkyllithiums generated in ether-hexane are more stable than those prepared in THF. In this medium they also exhibit higher reactivity toward certain carbonyl compounds, especially hindered[73] or highly enolizable ketones.[74] The 1-methyl-1-phenylselenoethyllithium product in eq 27 (generated in ether-hexane) undergoes nucleophilic 1,2-addition with a cyclic α,β-unsaturated ketone to afford ring-expanded ketones after treatment with TlOEt.[75]

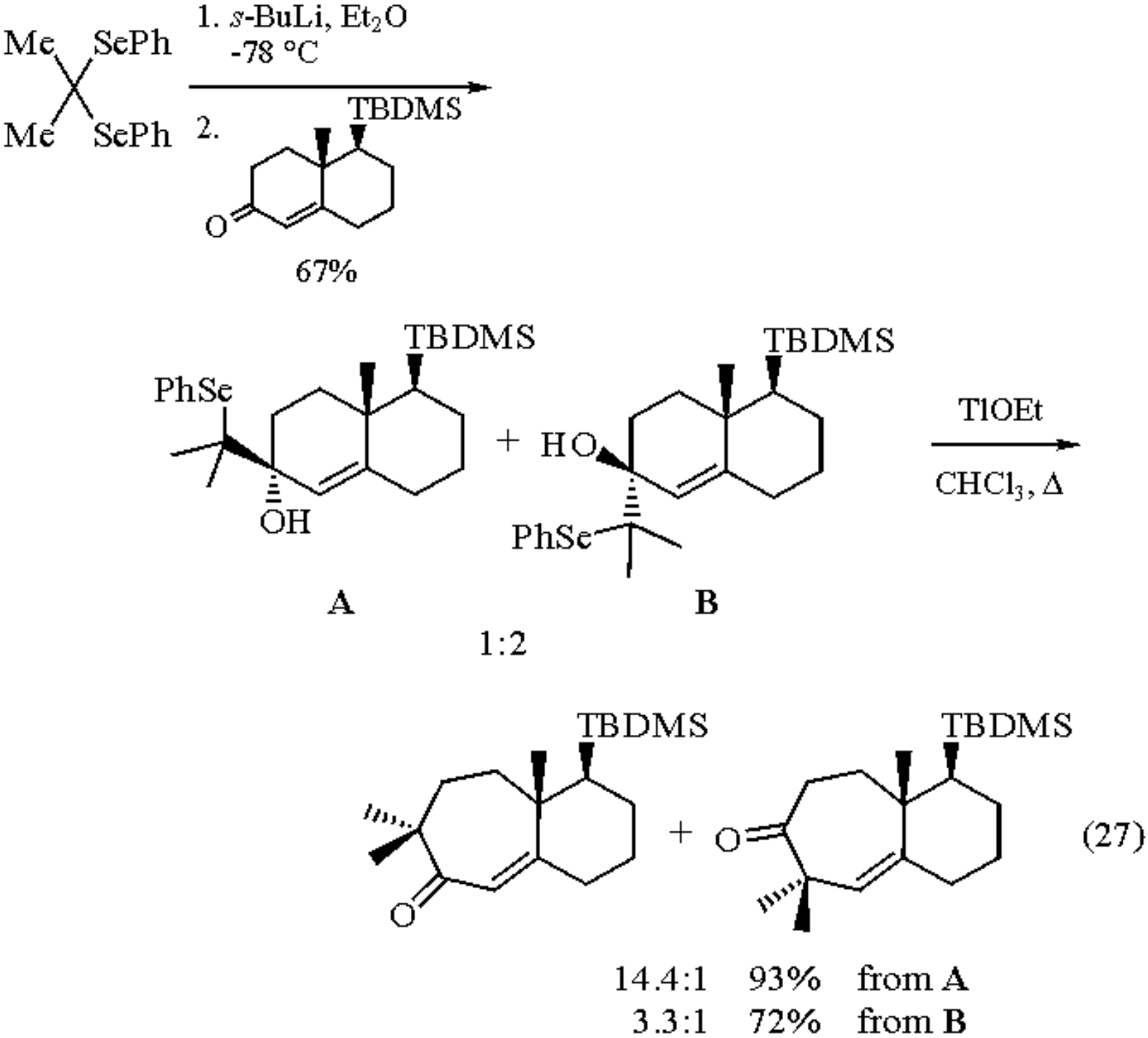

Organolithium compounds are also accessible through the replacement of tin and tellurium by lithium, with the various organotin compounds being particularly important precursors for otherwise inaccessible organolithium derivatives (e.g. α-amino- and α-alkoxy-substituted organolithiums). Although *s*-BuLi is well suited for these transformations,[52,76] most of the synthetic applications exploiting this methodology involve the use of *n*-BuLi.

Eliminations.

Arylsulfonylhydrazones undergo formal elimination reactions on treatment with 2 equiv of *s*-BuLi to give vinyllithium compounds.[77,78] Tosylhydrazones should be avoided with this reagent because they are susceptible to ring lithiation and benzylic deprotonation; instead, the use of hindered 2,4,6-triisopropylbenzenesulfonylhydrazones is recommended

(eq 28).[77] In cases where two regioisomers can be produced, *s*-BuLi appears to promote the formation of the more substituted vinyllithium compounds. In contrast, the use of *n*-BuLi leads to the less substituted vinyllithium product.[78] Other notable *s*-BuLi-induced elimination reactions are the α-eliminations involving bis(phenylthio)methyllithium-containing cycloalkanol derivatives, which have been exploited as a route to ring-expanded ketones (eq 29),[79] and β-eliminations of *ortho*-lithiated 2-carboxamide-substituted furan derivatives, which have been used to prepare ring-opened enyne products.[80]

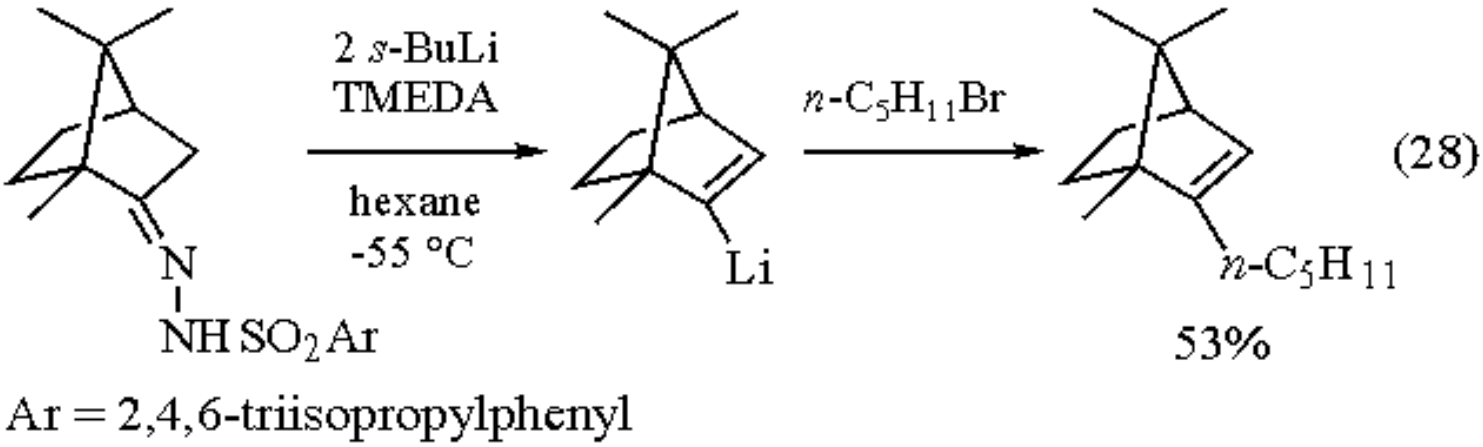

(28)

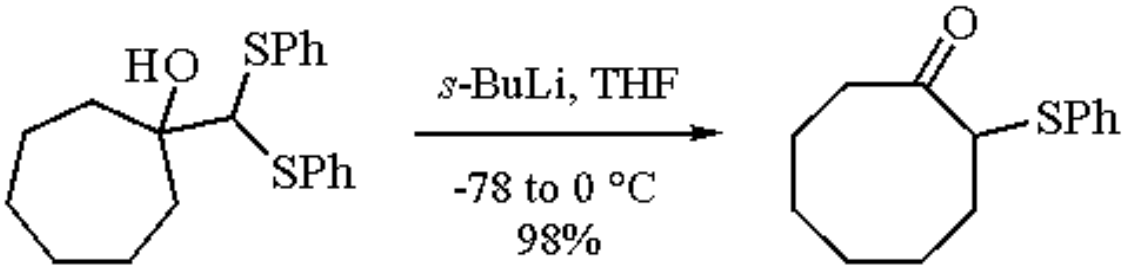

(29)

Formation of Enolate Anions and Enolate Equivalents.

s-Butyllithium may be used for the generation of enolate anions or enolate equivalents from active hydrogen compounds provided that nucleophilic addition of this reagent to the electrophilic carbon center is avoided. Thus the less reactive amides and imines are often suitable substrates for these reactions. For example, the bicyclic lactam in eq 30 undergoes two consecutive enolization/alkylation reactions in a highly diastereoselective fashion to afford a dialkylated product,[81] and the *N*-*t*-butylimine of 2-heptanone is deprotonated using *s*-BuLi to afford a mixture of two isomeric ketones after alkylation and hydrolysis (eq 31).[82] The less substituted ketone was obtained as the only isomer when *s*-BuLi was used with HMPA. Similar reactions have been reported for α-nitro imines,[83] and thiolactams.[84]

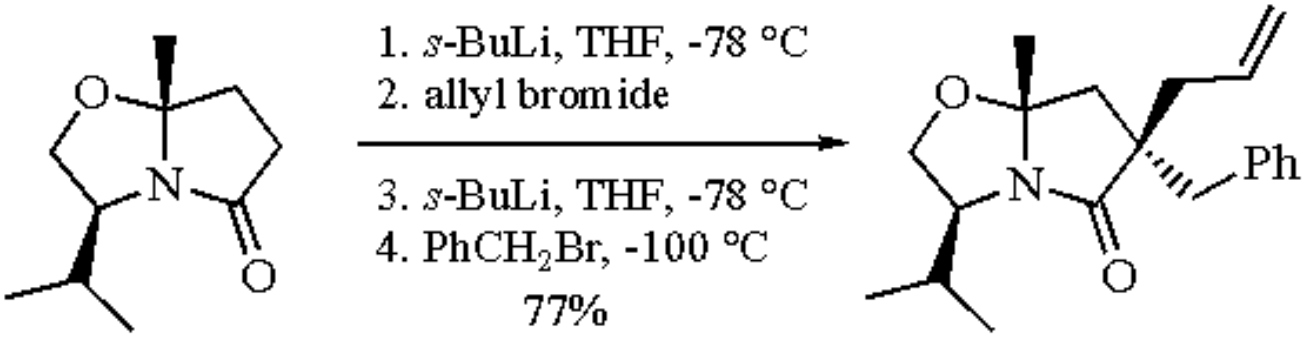

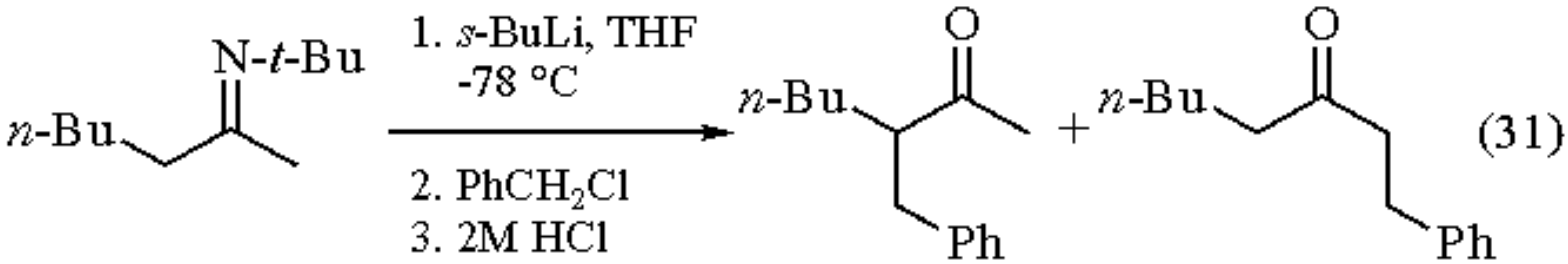

no additives	53:47	41%
HMPA added	100:0	61%

Rearrangements.

Salicylamides are available from various aryl carbamates, including those derived from ***Pyridine*** and naphthalene,[63] through the *s*-BuLi-mediated O-C 1,3-carbamoyl migration reactions (Snieckus rearrangement).[57] This regiospecific rearrangement is the anionic equivalent of the Fries rearrangement and it involves low-temperature (-78 °C) *ortho* lithiation of aryl carbamates with *s*-BuLi/TMEDA/THF followed by warming of the reaction mixture to rt (eq 32).[85] Benzylic carbamates rearrange to give products derived from either 1,4- or 1,2-carbamoyl migration (eq 33) following treatment with *s*-BuLi in THF,[86] and lithiated phenolic esters rearrange to furnish acyl phenols even at low temperatures (eq 34).[67] *s*-Butyllithium is also capable of initiating various Wittig rearrangements involving allylic ethers, but these reactions are done more conveniently using the less reactive *n*-BuLi.

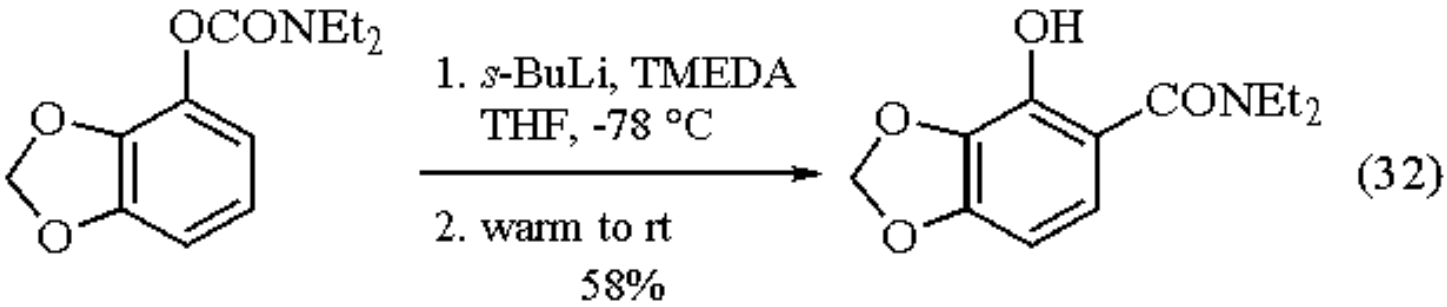

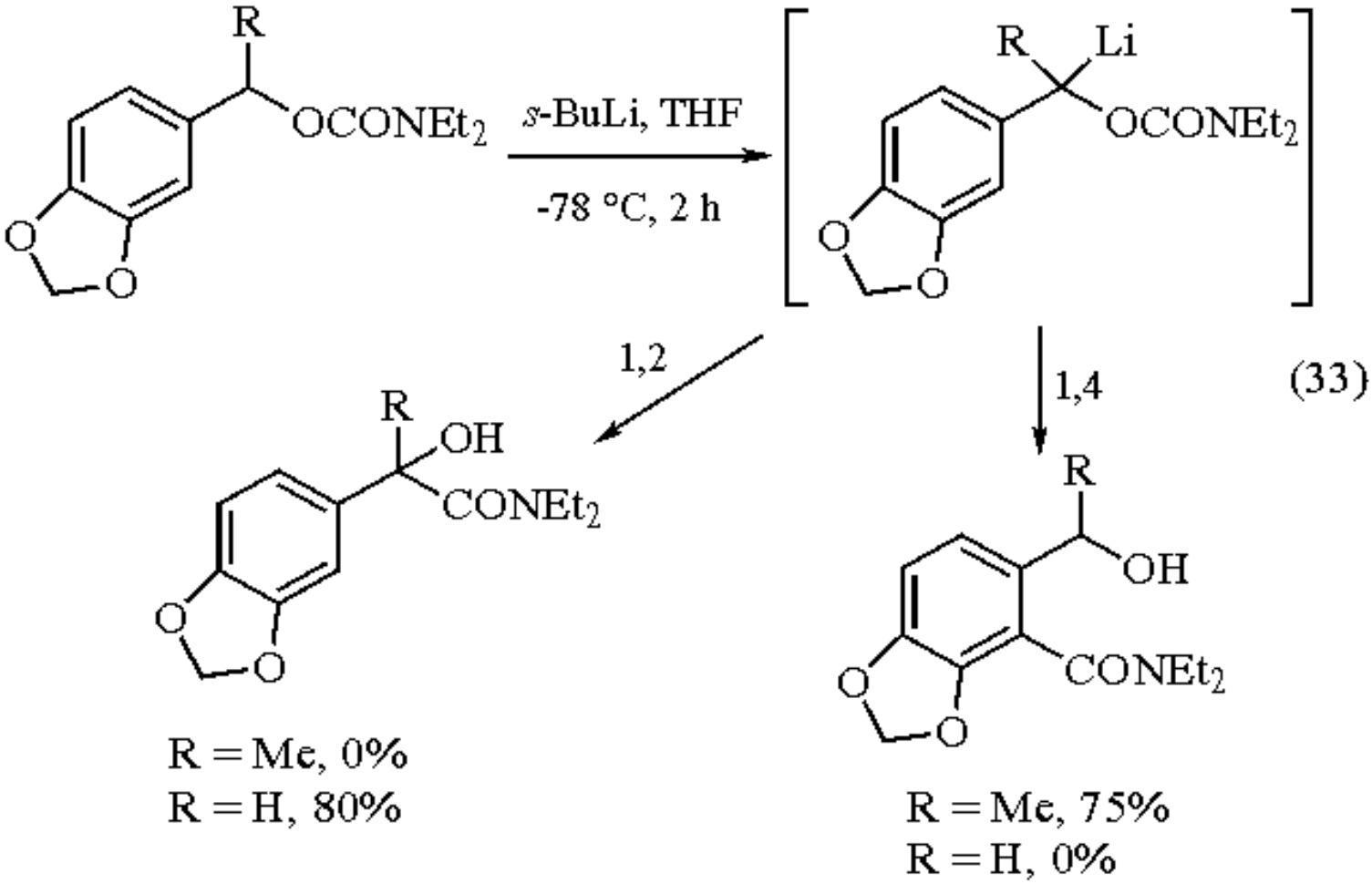

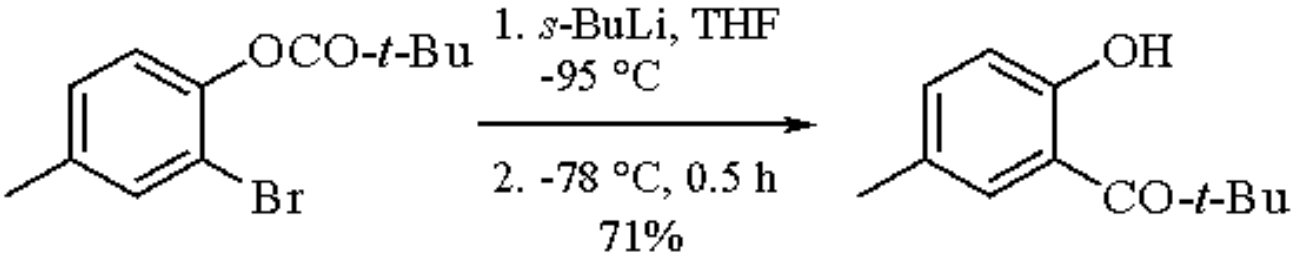

Related Reagents.

n-Butyllithium; ***t-Butyllithium***; ***Potassium Hydride-s-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine***.

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n-Butyllithium-Boron Trifluoride Etherate[1]

n-BuLi-BF_3.OEt_2

(*n*-BuLi)

[109-72-8] · C_4H_9Li · *n*-Butyllithium-Boron Trifluoride Etherate · (MW 64.06) (BF_3.OEt_2)

[109-63-7] · $C_4H_{10}BF_3O$ · *n*-Butyllithium-Boron Trifluoride Etherate · (MW 141.93)

(Lewis acid catalyst/strong base combination used to simultaneously generate an anion and activate an electrophile at low temperature, i.e. double activation[2])

Physical Data: see ***n-Butyllithium*** and ***Boron Trifluoride Etherate***.

Form Supplied in: the reagents are mixed with reactants in situ. BF_3.OEt_2 is supplied as a purified, redistilled liquid. *n*-Butyllithium is available as a 2 M solution in cyclohexane, 1.6 M, 2.5 M, and 10 M solution in hexanes, and a 2 M solution in pentane.

Handling, Storage, and Precautions: BF_3.OEt_2 is a fuming, corrosive liquid and is immediately hydrolyzed by moisture in air; *n*-butyllithium solutions are moisture sensitive and pyrophoric. Accordingly, both reagents should be stored and handled in the absence of moisture under N_2.[3]

Alkynyllithium Reagents and BF_3.OEt_2.

The most common use of the *n*-BuLi/BF_3.OEt_2 reagent combination is in the formation of lithium acetylides from terminal alkynes and their subsequent addition to a variety of electrophiles. While boron halides (BX_3) undergo rapid displacement with organolithiums (RLi) to furnish alkylhaloboranes (RBX_2 and R_2BX) and trisubstituted boranes (R_3B) at ambient temperatures,[4] it has been determined that organolithiums and BF_3.OEt_2 are stable together at low temperature and react independently.[5] Moreover, addition of BF_3.OEt_2 to lithium acetylides at -78 °C in THF affords an intermediate, lithium alkynyltrifluoroborate complex (**1**) (eq 1), which reacts smoothly with carboxylic acid anhydrides,[6] esters,[7] and tertiary amides[8] to give α,β-alkynic ketones in high yields (eqs 2-4). The acetylide-amide coupling can also be used with a subsequent ***Lithium Aluminum Hydride*** reduction to afford azacycloalkanes (eq 5).[8d]

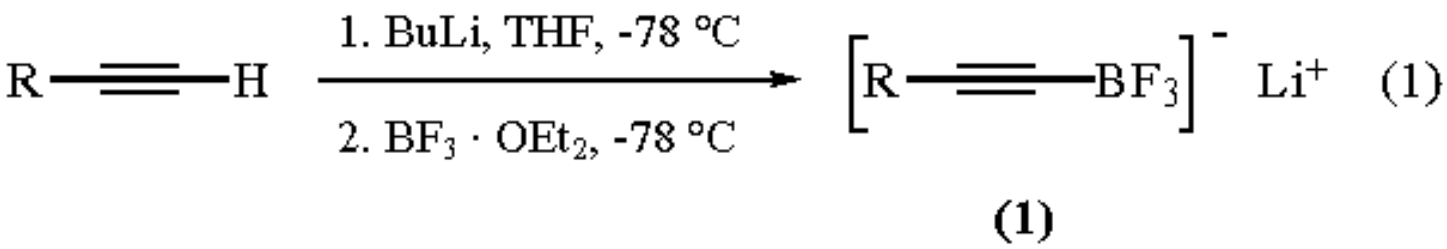

(1)

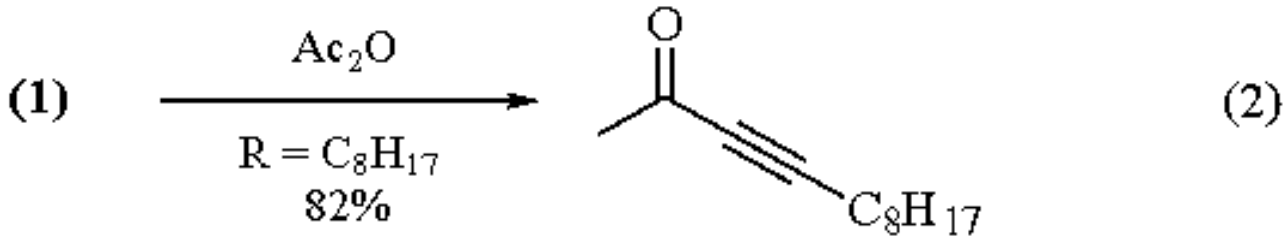

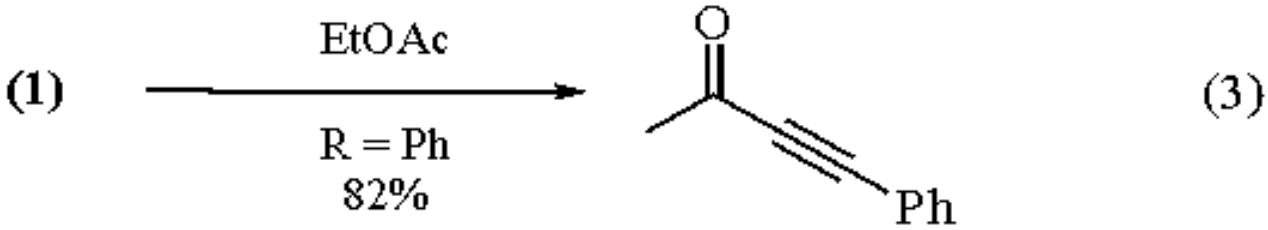

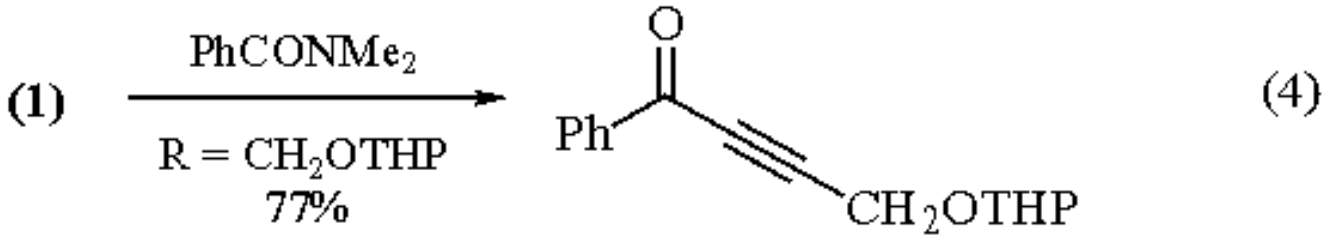

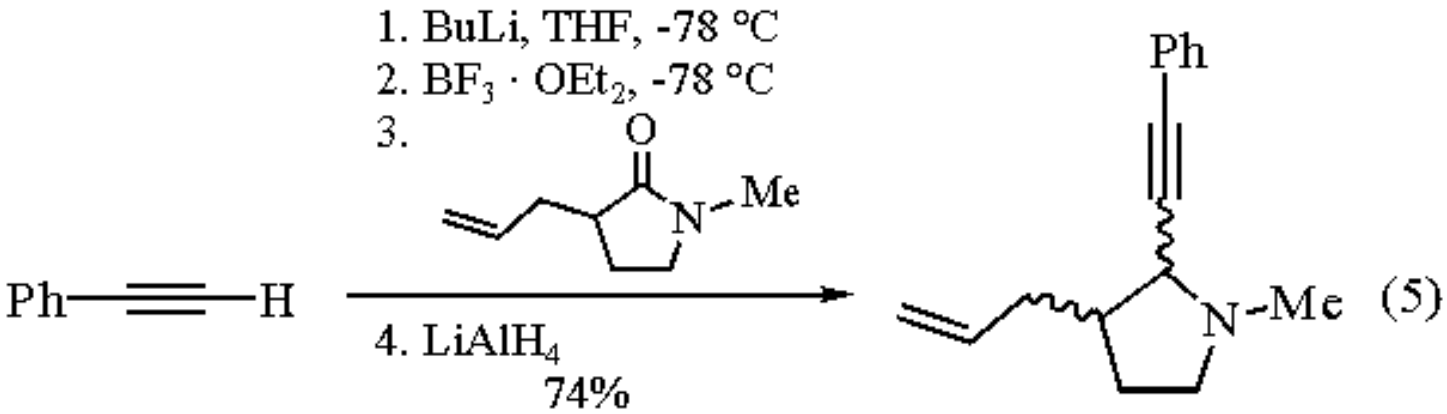

It has also been found that this complex cleaves epoxides to afford β-hydroxyalkynes in excellent yields (eq 6);[9] this method has been used extensively, as seen in the syntheses of FK 506,[10] okadaic acid,[11] lipoxin B,[12] *N*-acetylactinobolamine,[13] and leukotriene B_4.[14] The use of other metal acetylides for this transformation requires longer reaction times, higher temperatures and/or expensive catalysts, frequently resulting in low yields. Reaction of borate complex (**1**) (R = Ph) with (2*S*,3*S*)-3-phenylglycidol gave diol (**2**) with >99:1 diastereoselectivity, whereas the diethylaluminate complex afforded a 3:1 mixture (eq 7).[15] Borate complex (**1**) can also be used in the ring opening of

oxetanes to give γ-hydroxyalkynes (eq 8).[16]

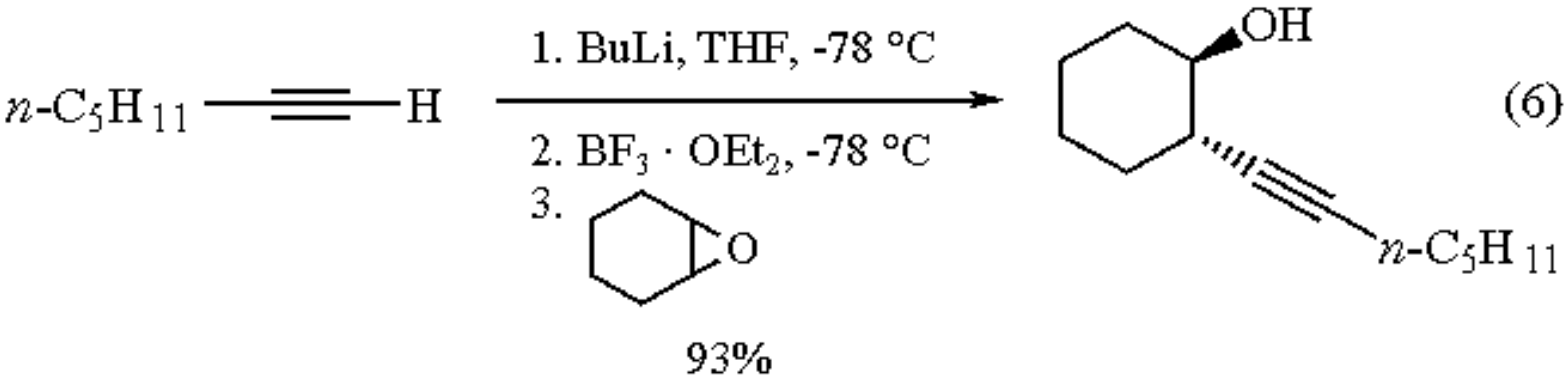

(6)

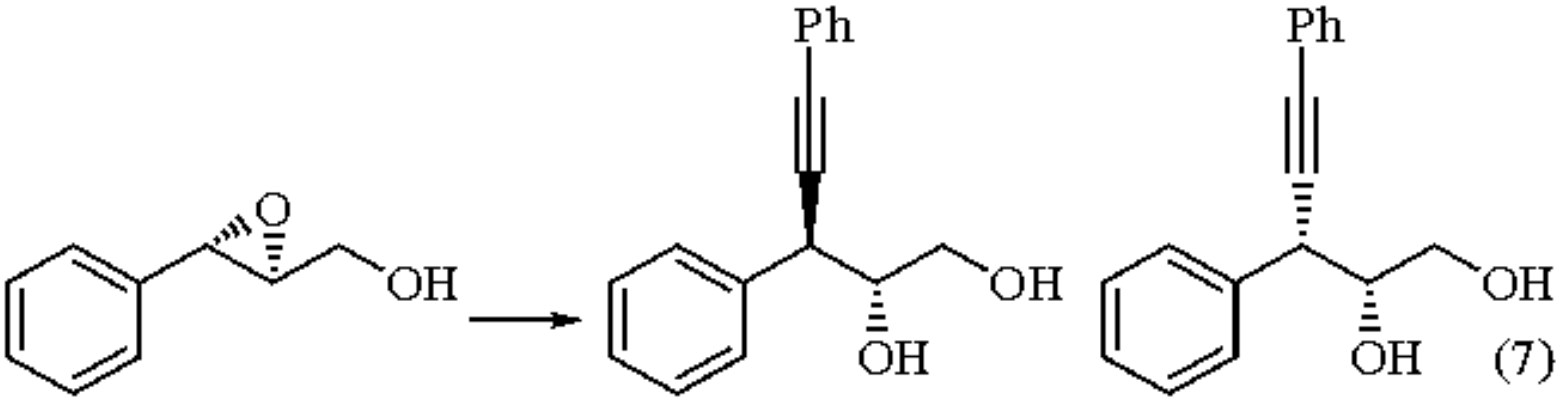

(7)

(2) **(3)**

PhCCLi, $BF_3 \cdot OEt_2$	>99:1
PhCCLi, Et_2AlCl	3.2:1

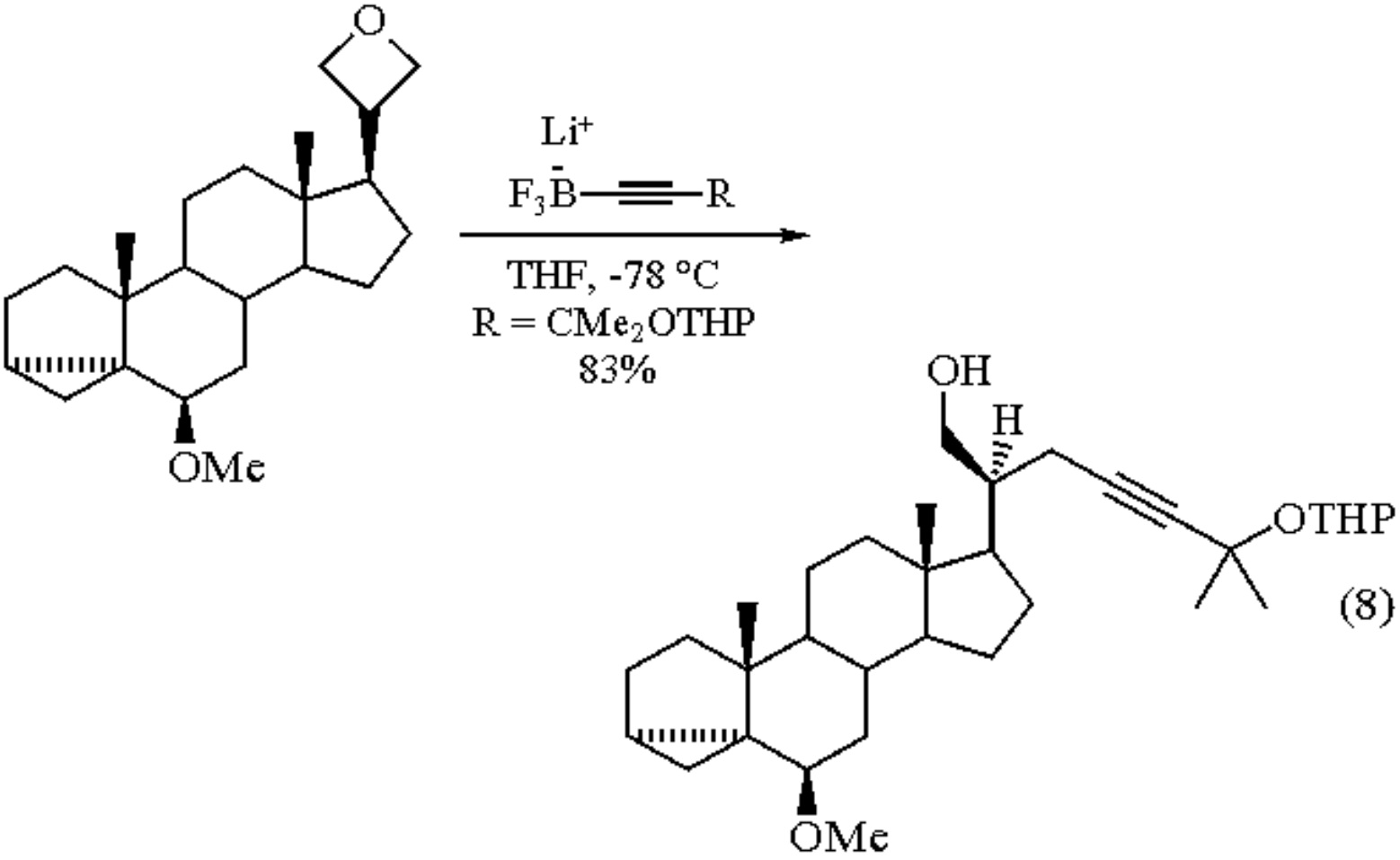

Borate complex (**1**; R = CH_2OTr) has also been added to an α-diazo ester to give a β,γ-alkynic ester as well as to an α-hydroxyaldehyde (**1**; R = CMe_2OTHP) to afford an α,β-dihydroxyalkyne.[17,18]

Lithium Enolates and Stabilized Alkyllithiums with $BF_3.OEt_2$.

The mechanisms by which $BF_3.OEt_2$ activates most of the following reactions remain unclear; while coordination of the Lewis acid with certain electrophiles prior to nucleophilic addition has been reported,[5] the possibility of BF_3/organolithium complexes cannot be precluded in all cases. It has been shown that the lithium enolates of amides[19] will cleave epoxides in the presence of $BF_3.OEt_2$ to afford γ-hydroxyamides, while the lithium enolates of both amides and esters will open oxetanes to give δ-hydroxy esters and δ-hydroxyamides in high yield (eq 9).[20] It was found that the lithium enolate of optically active iron acyl (**4**) would cleave *trans*-(±)-2,3-epoxybutane at -78 °C to afford γ-hydroxy product (**5**) as a 10:1 mixture of diastereomers (eq 10);[21] the enantiofacial recognition of this reaction allows for the synthesis of optically active β,γ-dimethyl-γ-lactones.

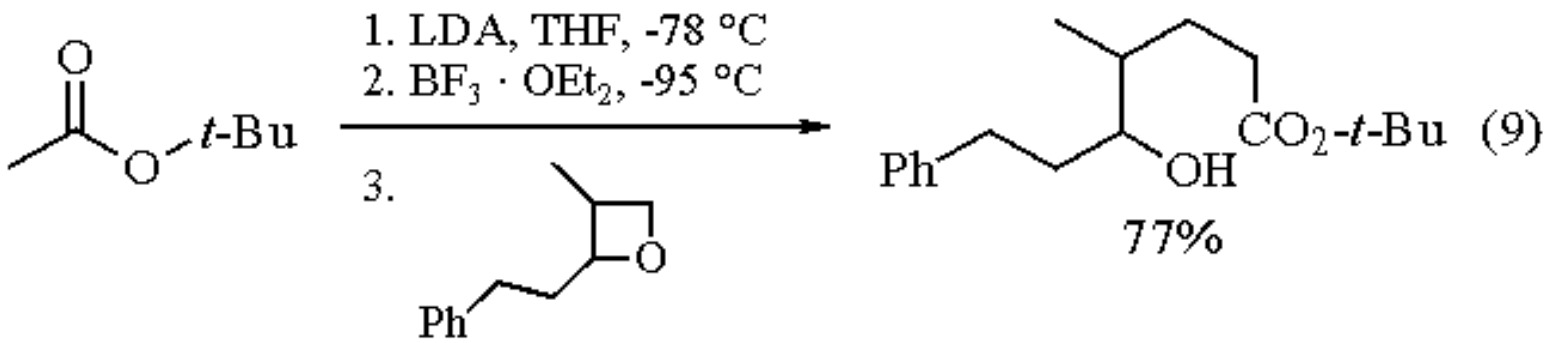

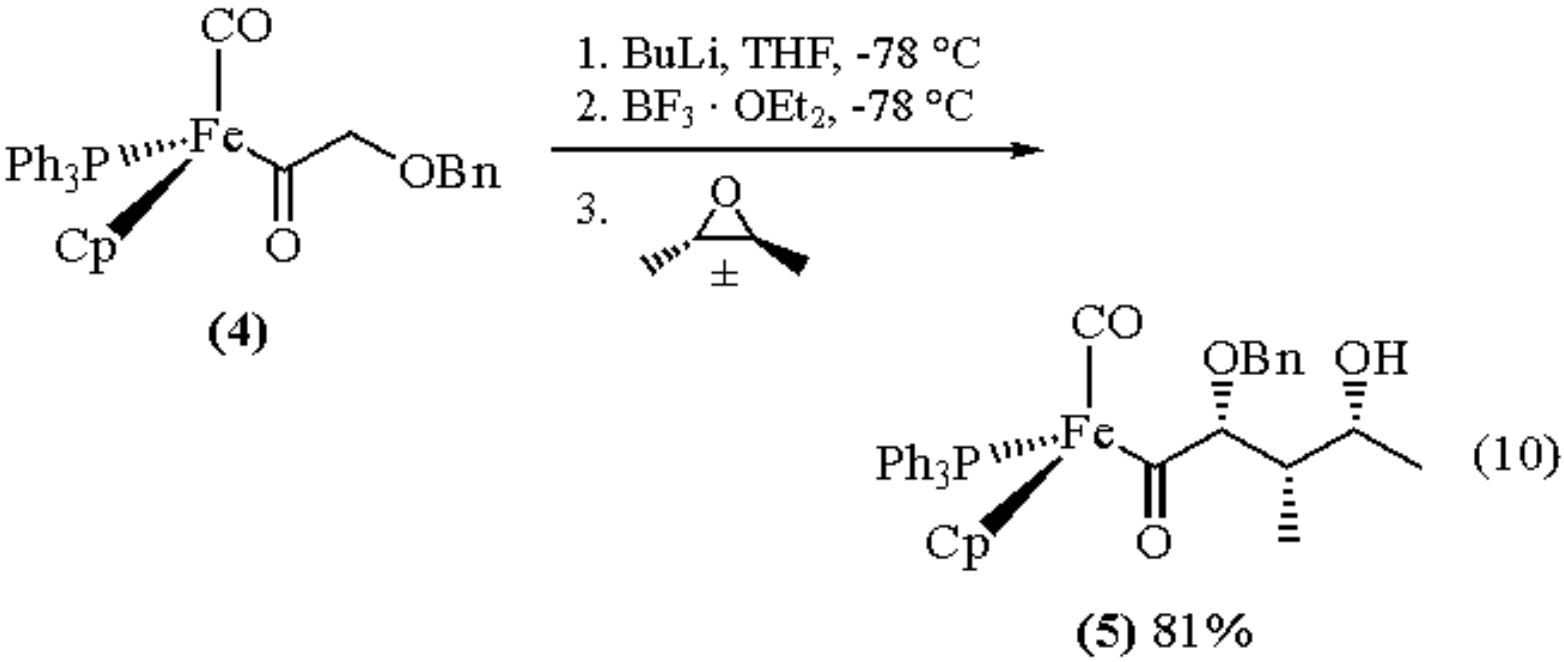

It also has been shown that the lithium enolates of ketones and esters can be added to $BF_3.OEt_2$-activated 3-thiazolines to give functionalized thiazolidines[22a] and trisubstituted thiophenes;[22b] lithium enolates of ketones can also be dialkoxymethylated using orthoformates in this manner.[23] In the presence of $BF_3.OEt_2$ the sodium-lithium dianion of β-keto esters will react with disubstituted epoxides to give tetrahydrofurans after acid-promoted cyclization,[24] as well as undergo Claisen condensations with tertiary amides.[25]

Concerning other stabilized organolithiums, α-lithiated sulfones can be treated with $BF_3.OEt_2$ activated aldehydes to afford *trans*-alkenes after reduction (Julia alkenation);[26] in addition, treatment with activated epoxides gives γ-hydroxy sulfones (eq 11) and α,β-unsaturated ketones after oxidation-elimination.[27] In the absence of $BF_3.OEt_2$ these processes suffer from low yields and/or long reaction times. In a separate example, it was found that when lithiated 2-styryl-1,3-dithiane was treated with aldehydes and ketones, a mixture of alcohols (**6**) and (**7**) would result (eq 12); however, treatment of the dithiane anion with $BF_3.OEt_2$ prior to the addition of carbonyl compound resulted in exclusive α-addition to give alcohol (**7**).[28]

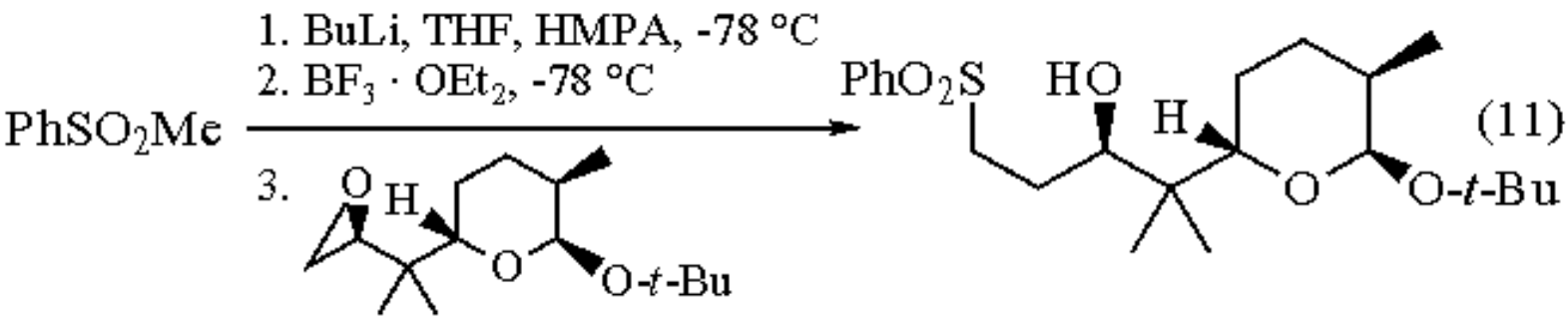

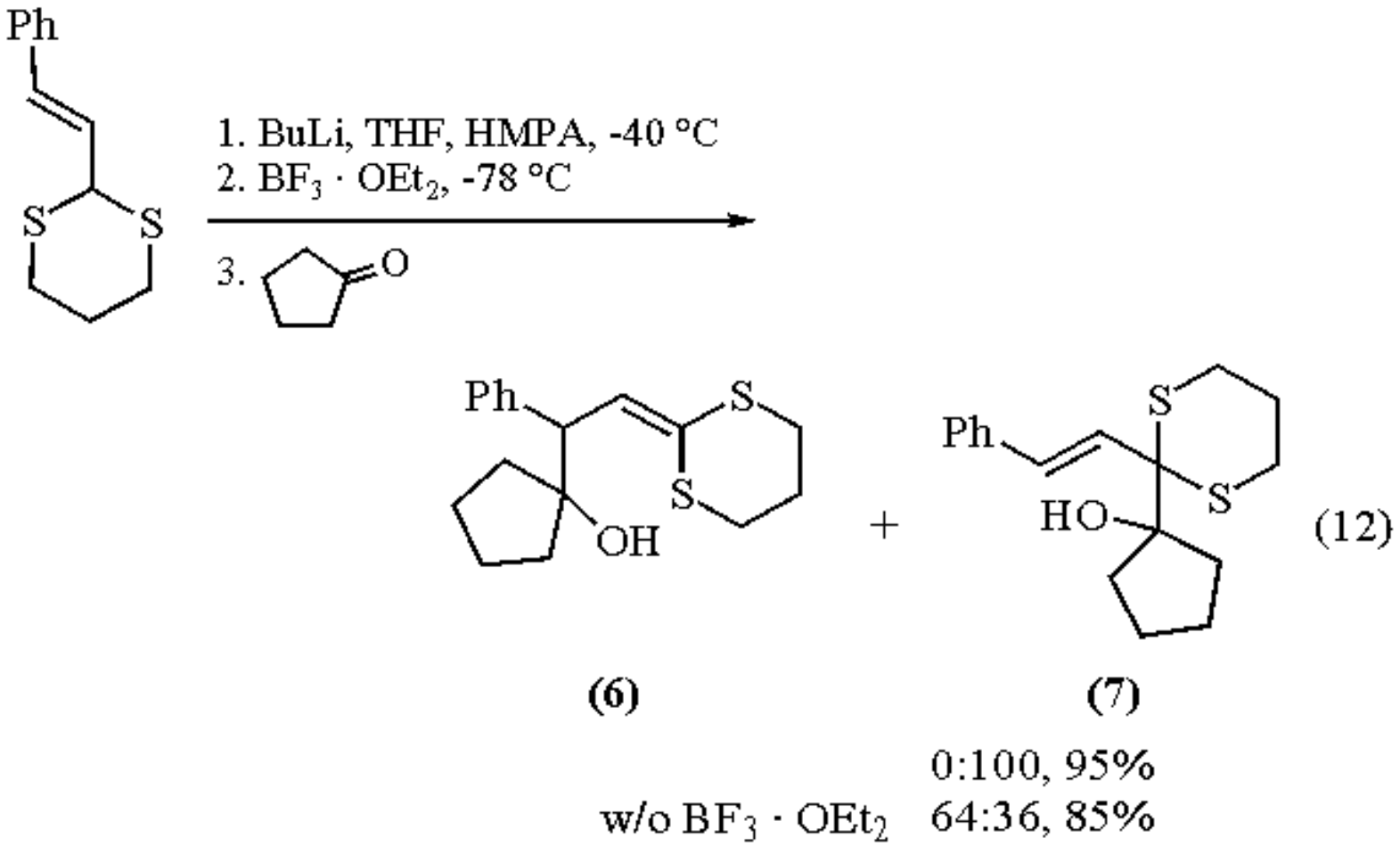

Other examples of reactions of stabilized organolithiums with $BF_3.OEt_2$ activation include the cleavage of a monosubstituted epoxide with an α-lithiophosphonate,[29] the addition of α-lithiated sulfoximines[30] to aldehydes and imines, and the cleavage of oxetanes with lithiomethylphosphonates (eq 13).[31]

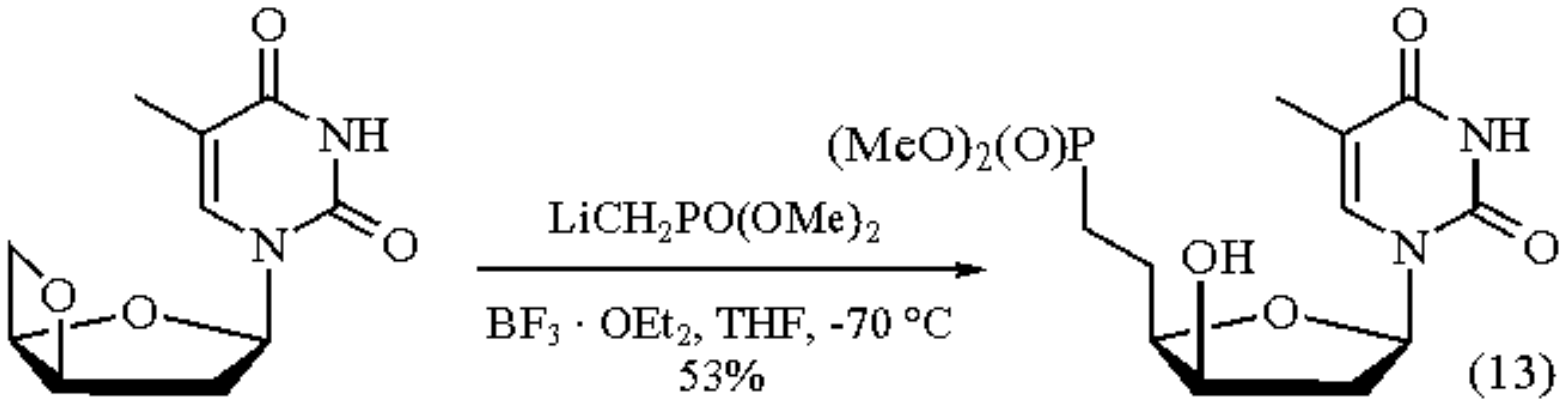

Nonstabilized Organolithiums with $BF_3.OEt_2$.

By far the most common reaction of nonstabilized organolithiums with $BF_3.OEt_2$ activation is the cleavage of epoxides. Examples include alkyl-, alkenyl-, and aryllithiums in both intra- and intermolecular variations; the mechanism of these reactions appears to include complexation of the Lewis acid at oxygen followed by nucleophilic attack of the carbon nucleophile on the resulting alkoxyboron trifluoride salt.[5] The organolithium reagents used include commercial reagents (***Methyllithium***, ***s-Butyllithium***, ***n-Butyllithium***, ***t-Butyllithium***, ***Phenyllithium***) as well as those prepared from alkylstannanes, alkenyl halides, aryl halides, furans, and indoles.

In one example it was found that in the presence of $BF_3.OEt_2$, diepoxide (**8**) could be treated with an excess of alkyl- and aryllithiums to afford symmetric 1,3-diols; more importantly, 1 equiv of organolithium reagent could be used to give C(2) differentiated epoxy alcohols which could be further elaborated with a second organolithium species (eqs 14 and 15).[32]

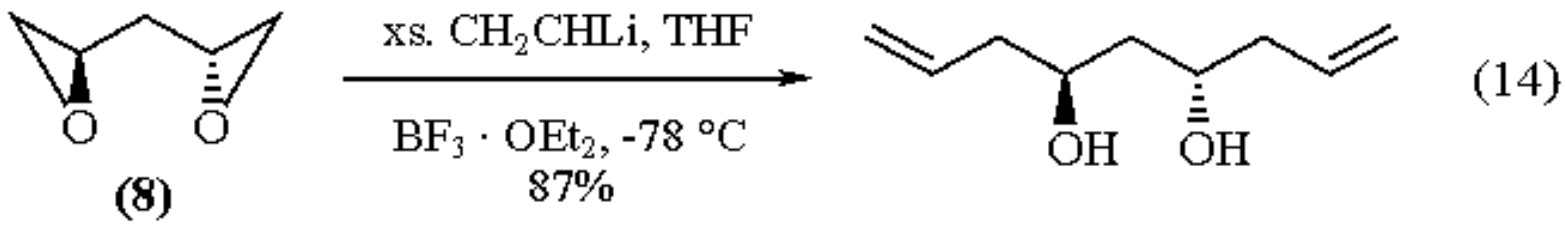

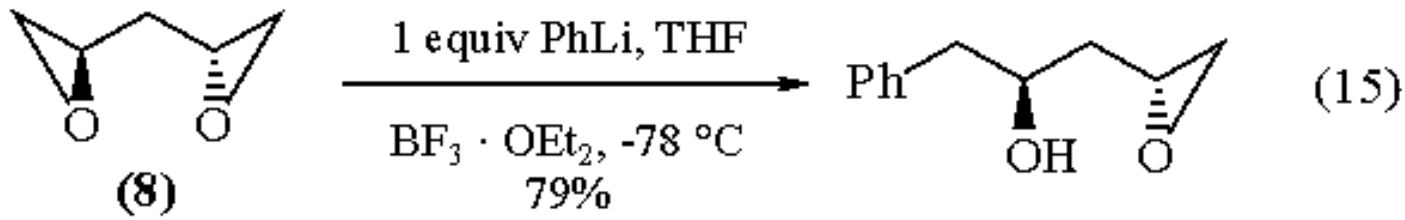

While vinyllithium reagents will cleave epoxides in good yields, a threefold excess of the reagent is required; it has been reported that this shortcoming can be avoided by the conversion of the lithium reagent to the corresponding alkenylaluminum species (see ***Diethylaluminum Chloride***) which will react smoothly under stoichiometric conditions in the presence of $BF_3.OEt_2$ to afford homoallylic alcohols in good yields.[33] Oxetanes are also cleaved by organolithium-BF_3 reagents.[5]

Other reactions of organolithiums utilizing $BF_3.OEt_2$ include those with: alkyl/aryllithiums and oxime ethers to give substituted *O*-alkyl hydroxylamines;[34] alkyl/aryllithiums and 2-isoxazolines to afford substituted isoxazolidines;[35] butenolide anions and orthoesters to give acylated butenolides;[2] alkyllithiums and imines to give α-alkylated amines;[36] an allenic zirconium species and aldehydes to afford β-alkynic alcohols;[37] and alkyllithiums with aldehydes/ketones to afford alcohols.[38]

---

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n-Butyllithium-Potassium *t*-Butoxide[1]

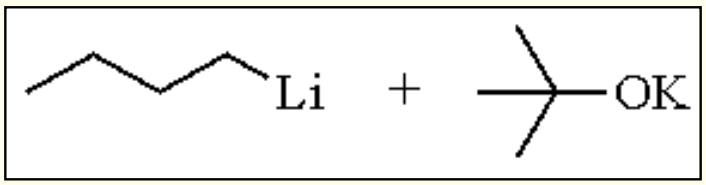

(*n*-BuLi)

[109-72-8] · C_4H_9Li · *n*-Butyllithium-Potassium *t*-Butoxide · (MW 64.06) (*t*-BuOK)

[865-47-4] · C_4H_9KO · *n*-Butyllithium-Potassium *t*-Butoxide · (MW 112.22)

(superbase for metal-hydrogen exchange of a carbon acid R-H;[2] can generate organopotassium compounds[3])

Physical Data: see ***n-Butyllithium*** and ***Potassium t-Butoxide***; NMR[4] and ESR[5] studies of the *n*-BuLi/*t*-BuOK mixture have been reported.

Solubility: see ***n-Butyllithium*** and ***Potassium t-Butoxide***.

Preparative Method: prepared in situ under nitrogen by addition of equimolar potassium *t*-butoxide to a solution of *n*-butyllithium at 0 °C.

Handling, Storage, and Precautions: use in a fume hood; must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture. Solutions in THF decompose above -40 °C.

Metal-Hydrogen Exchange.

Freshly prepared *n*-BuLi/*t*-BuOK is more basic than *n*-BuLi and *n*-BuK.[6] When treated with this superbase, hydrocarbons in the low acidity range of pK_a 35-50 undergo a clean metal-hydrogen exchange: benzene,[2] cyclopropane derivatives,[7,8] cumene,[7] a variety of 1- or 2-alkenes having allylic C-H bonds,[2,9-13] cyclohexene,[7,14] α-pinene,[15] conjugated dienes,[11,16-18] ene sulfides,[19] 4*H*-pyrans,[20] and 1,4-dihydropyridines.[20] *n*-BuLi/*t*-BuOK did not succeed in metalating saturated hydrocarbons such as octane and cyclohexane.

Benzene and substituted benzene, in the presence of *n*-BuLi/*t*-BuOK, undergo site selective metal-hydrogen exchange (eq 1). Best results are obtained in THF at -75 °C or -50 °C. Upon quenching with carbon dioxide, the corresponding acids are obtained in good to excellent yield.[21,22]

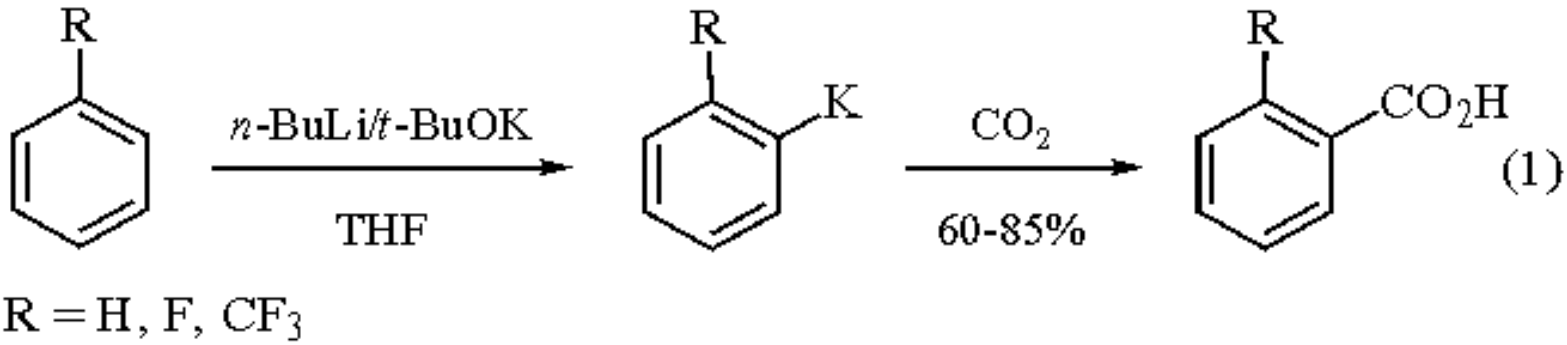

When alkenes are treated with *n*-BuLi/*t*-BuOK, the metalation occurs regioselectively: allylic methyl groups are much more readily attacked than methylene groups, which are less reactive than methine centers.[9,12] Furthermore, *cis*-2-alkenes generally react faster than their *trans* counterparts. This holds even for 4,4-dimethyl-2-pentene (eq 2).[23]

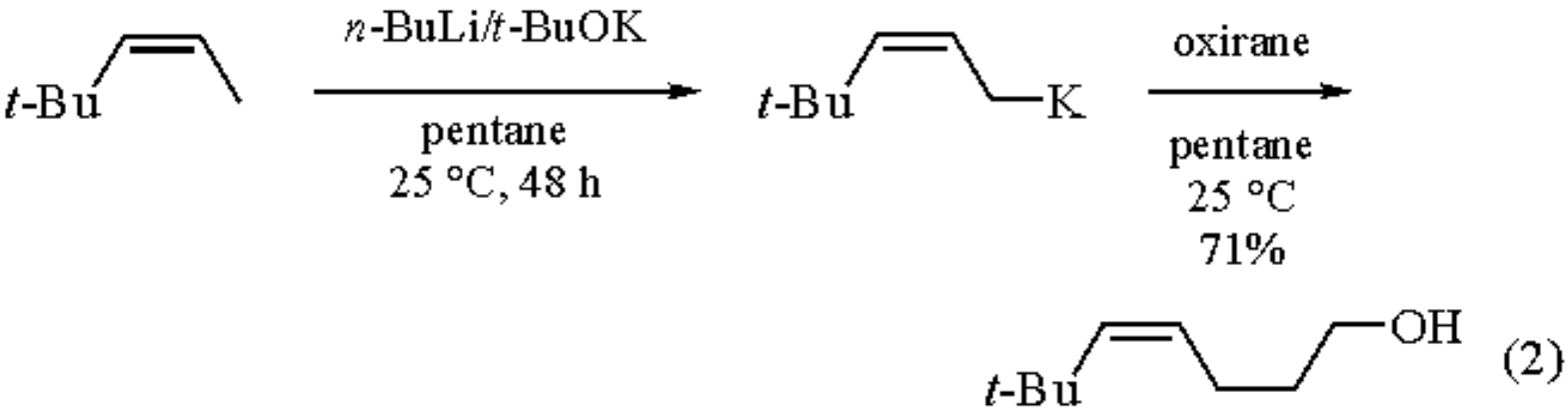

Above -60 °C, ethereal solvents are rapidly attacked by *n*-BuLi in the presence of *t*-BuOK.[6b] Nevertheless, acetal functions are suitable protecting groups for superbase metalations of alkenols.

The *n*-BuLi/*t*-BuOK mixture can convert 2-alkynyl ethers into allenic ethers and some α-substituted derivatives (eq 3).[24]

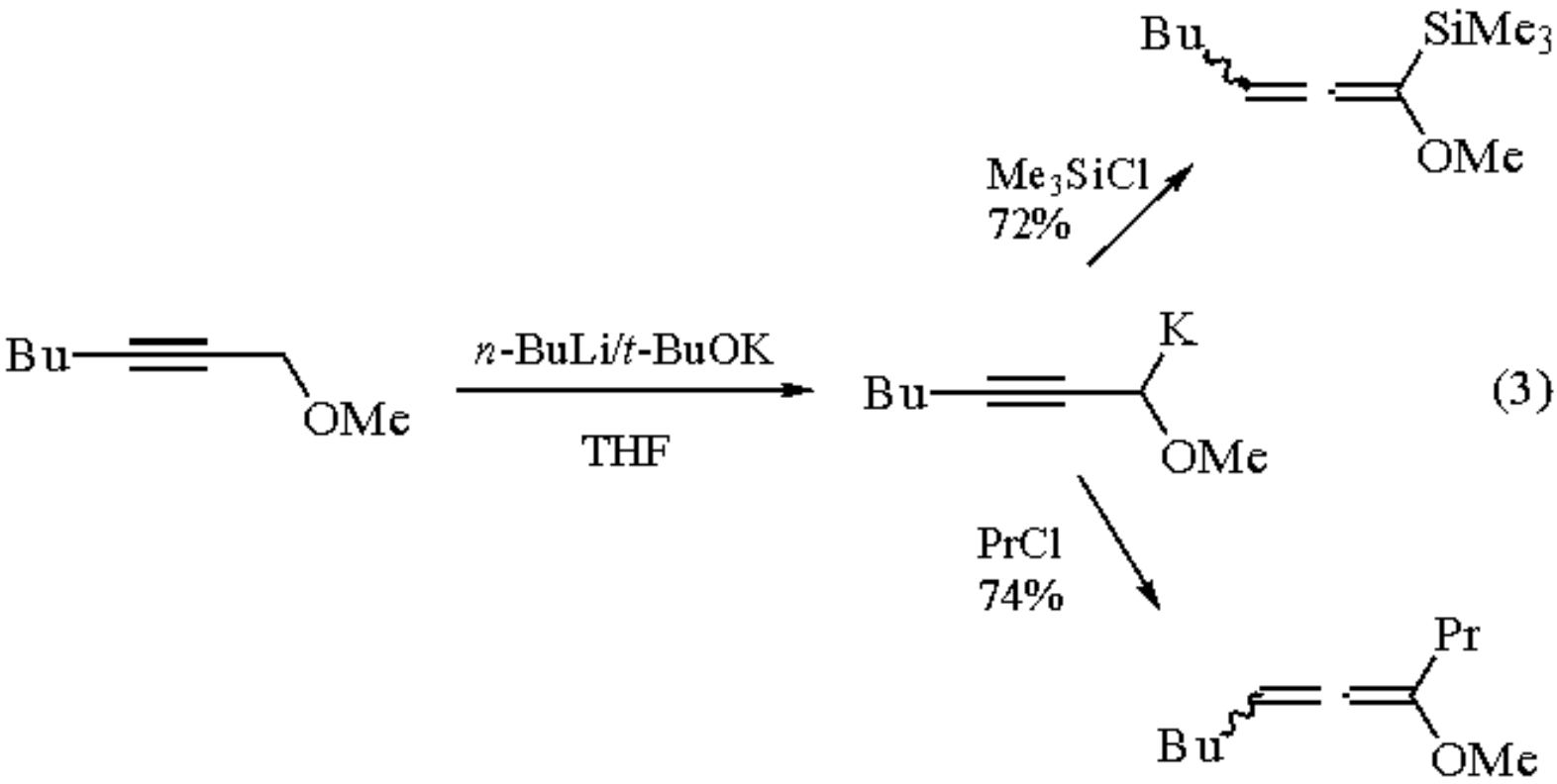

(3)

In the cases where metal-hydrogen exchange leads to a resonance-stabilized organometallic species, the intermediate organopotassium compounds precipitate.[3] Benzyl-, allyl-, pentadienyl-, and cyclooctadienylpotassium can be prepared in this way.[9,13,16] The accompanying lithium *t*-butoxide can be completely removed by washing with benzene or toluene. The resulting organopotassium can serve as a reagent of general applicability in preparing transition metal complexes through transmetalation (eq 4).[25]

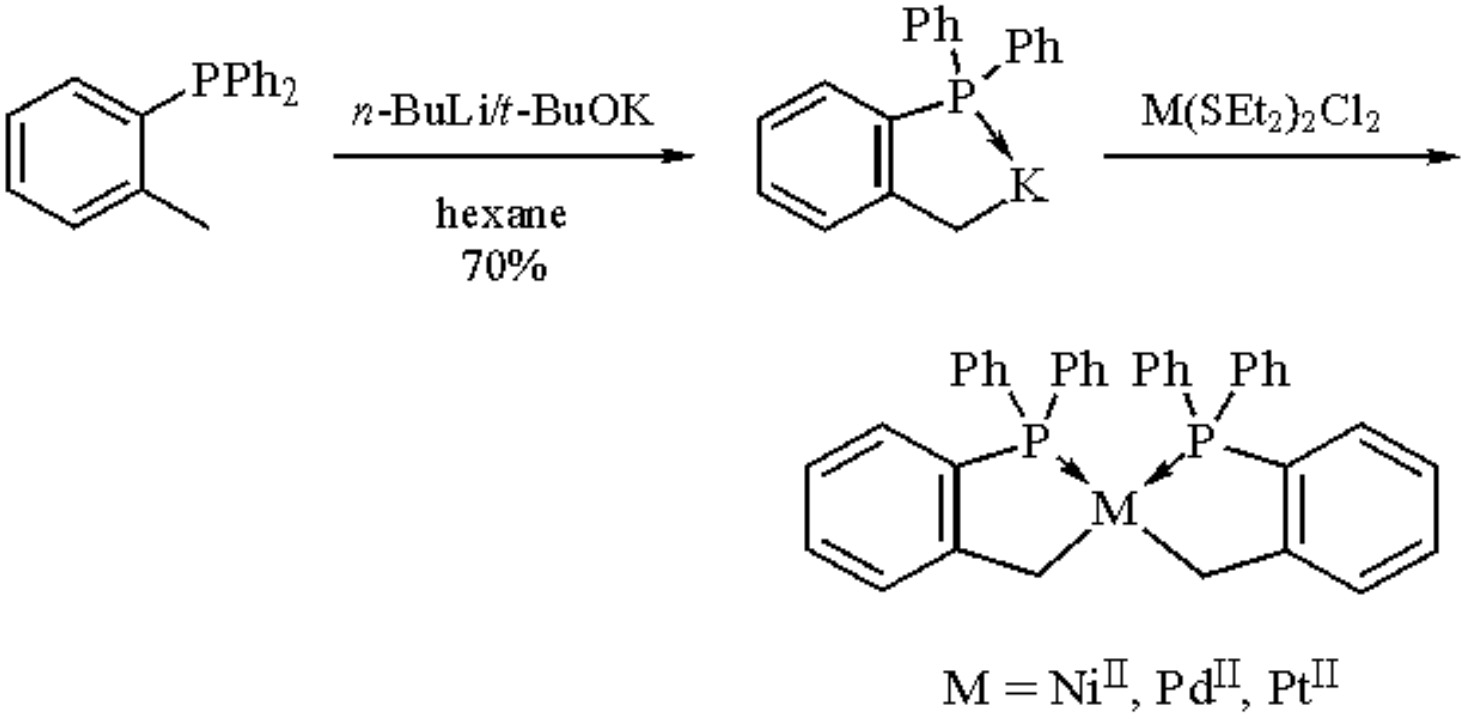

(4)

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t-Butylmagnesium Chloride[1]

***t*-BuMgX**

(X = Cl)

[672-22-5] · C_4H_9ClMg · *t*-Butylmagnesium Chloride · (MW 116.87) (X = Br)

[2259-30-5] · C_4H_9BrMg · *t*-Butylmagnesium Bromide · (MW 161.32)

(adds to many unsaturated functional groups; *t*-butyl can displace halide and like groups; can function as a strong base and a Lewis acid[1b-f])

Physical Data: NMR observations indicate that *t*-BuMgCl in Et_2O and THF and *t*-BuMgBr in THF are in fact mixtures of *t*-BuMgX, *t*-Bu_2Mg, and MgX_2.[2,3] Although essentially monomeric in THF, *t*-BuMgCl is mainly dimeric in Et_2O.[4] A solid of composition *t*-BuMgBr$(Et_2O)_2$, probably having a dimeric structure, has been isolated.[5]

Solubility: sol Et_2O and THF; insol hydrocarbons.

Form Supplied in: solutions of *t*-BuMgCl in Et_2O and THF are commercially available.

Analysis of Reagent Purity: see entry for ***Methylmagnesium Bromide***.

Preparative Methods: [1c,e,6] in spite of the commercial availability of *t*-BuMgCl solutions, *t*-BuMgCl[3,7] and *t*-BuMgBr are often prepared from reaction of a *t*-butyl halide and ***Magnesium***, usually in Et_2O or THF.

Handling, Storage, and Precautions: see entry for ***Methylmagnesium Bromide*** *t*-Butyl Grignard reagents do not significantly attack Et_2O or THF at normal reaction temperatures.

Preparation.

Side reactions in preparations of *t*-BuMgX and other tertiary alkyl Grignard reagents tend to be more significant than in preparations of less branched reagents. *t*-Butyl radicals, intermediates in the formation of the Grignard reagent, couple, disproportionate, and attack solvent molecules. Moreover, reaction of the Grignard reagent and unreacted alkyl halide is particularly significant with *t*-BuI. Because of side reactions, X generally exceeds *t*-Bu in the Grignard solutions. Yields generally seem to be improved by slow addition of the halide to the Mg and by use of activated[8] Mg (see the entry for ***Phenylmagnesium Bromide***). A considerable excess of *t*-BuX and Mg often is used to ensure that sufficient *t*-BuMgX is present for the subsequent reaction. When exact stoichiometry is important, determining the *t*-BuMg

concentration is important.

Structure.

See the entry for ***Methylmagnesium Bromide***.

Workup Procedures.

See the entry for ***Methylmagnesium Bromide***.

Representative Applications.[1b-f]

Also see the entry for ***Methylmagnesium Bromide***. A *t*-butyl Grignard reagent is used in reactions that result in attachment of its organic group to an electrophilic carbon atom of the substrate, most often of a carbonyl group, nitrile, or other unsaturated function. A generally unwanted reaction, reduction of such substrates by transfer of a β-H of the *t*-Bu or other tertiary or branched alkyl group, sometimes is more rapid. *t*-BuMgCl and di-*t*-butyl ketone, for example, normally furnish only di-*t*-butylmethanol.[9] The generation of a chiral sulfoxide (eq 1) exemplifies addition to a different unsaturated functional group.[10] Abstraction of a hydrogen α to unsaturated functions by a Grignard reagent, particularly a hindered one, may also compete with addition. Only abstraction is seen with the particularly acidic (**1**). Condensation with benzaldehyde (eq 2) does not occur when the anion is formed using an organolithium compound because equilibrium favors the anion and the aldehyde rather than their addition product.[11]

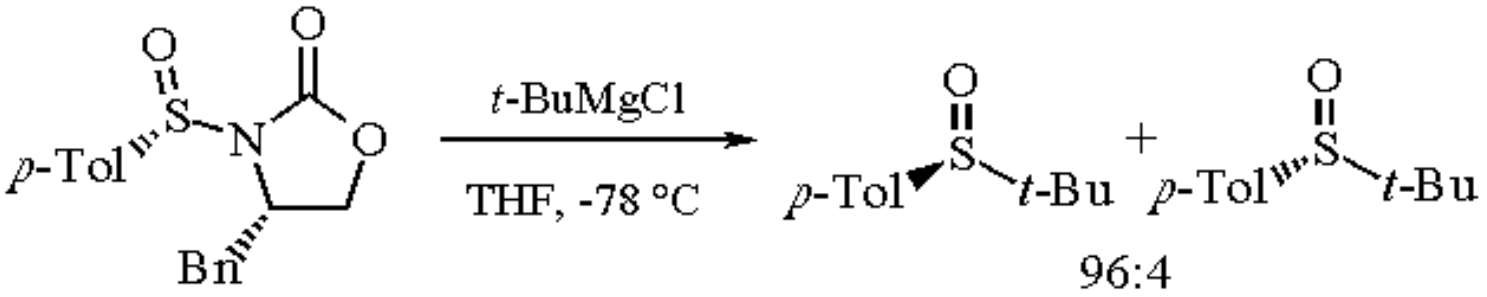

(1)

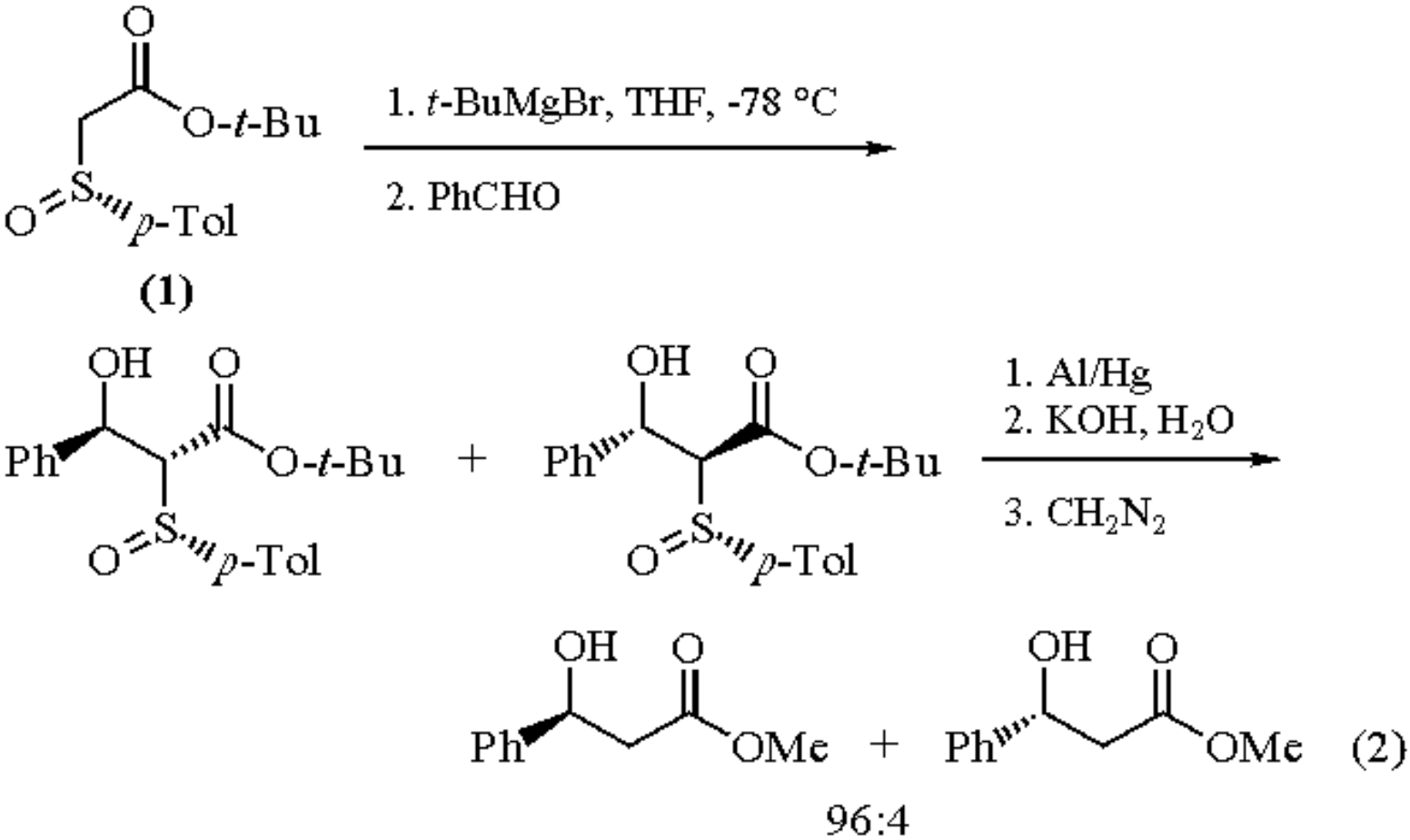

Related Reagents.

t-Butyllithium.

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n-Butylmagnesium Bromide-Methylcopper(I)[1]

_n_-BuMgBr-MeCu

[59532-66-0] · $C_5H_{12}BrCuMg$ · *n*-Butylmagnesium Bromide-Methylcopper(I) · (MW 239.90) (*n*-BuMeCu$^-$)

[70196-77-9] · $C_5H_{12}Cu$ · *n*-Butylmagnesium Bromide-Methylcopper(I) · (MW 135.70) (MgBr$^+$)

[43245-19-8] · BrMg · *n*-Butylmagnesium Bromide-Methylcopper(I) · (MW 104.21)

(serves as a butyl transfer reagent in substitution reactions)

Alternate Names: butylmethylcopper(I)magnesium bromide; bromomagnesium butylmethylcuprate.

Solubility: sol ether, THF.

Preparative Methods: a suspension of CuI (1.5 mmol) in THF (3 mL) is stirred at -78 °C and treated with a solution of salt-free MeLi (1.5 mmol) in ether. The resultant yellow precipitate of MeCu dissolves when a THF solution of *n*-BuMgBr (1.5 mmol) is added and a purple solution is formed.[2,3] In a similar fashion, the reagent is prepared from CuI, salt-free *n*-BuLi, and MeMgI.[3]

Handling, Storage, and Precautions: the reagent must be generated and immediately used in the absence of moisture and oxygen. Use in a fume hood.

Butylmagnesium bromide-methylcopper is a mixed lower order magnesium cuprate. It shows increased thermal stability in comparison to ***Lithium Di-n-butylcuprate***. The reagent selectively transfers the *n*-butyl group in reactions with acid chlorides (eq 1)[2] or 5-acetoxy-1,3-alkadienes (eq 2).[3]

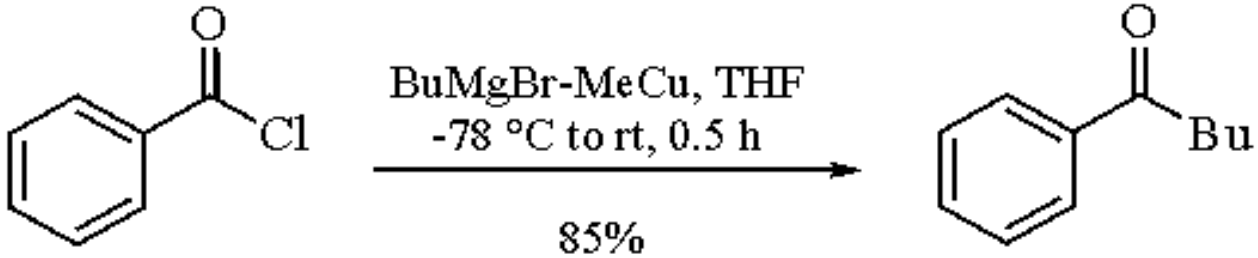

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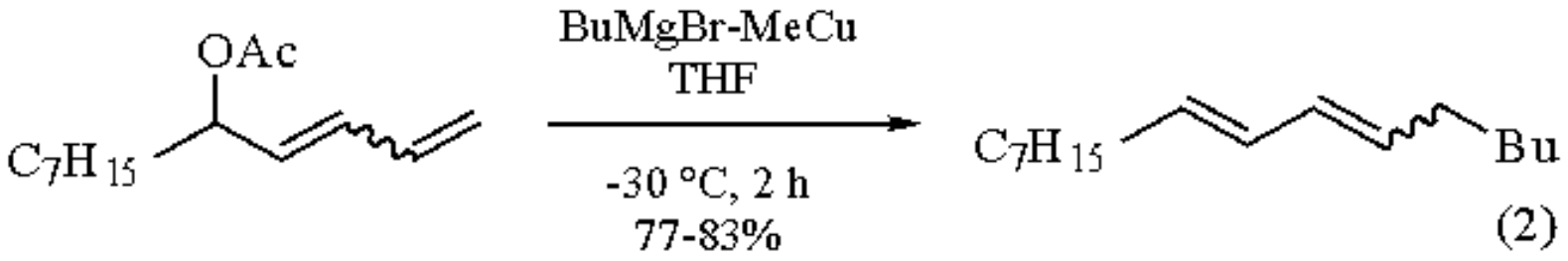

(2)

Related Reagents.

Lithium Di-n-butylcuprate; ***Vinylmagnesium Bromide-Methylcopper***.

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n-Butylmanganese Chloride

***n*-BuMnCl**

[88626-90-8] · C_4H_9ClMn · *n*-Butylmanganese Chloride · (MW 147.51)

(butylmanganese halides are especially interesting for their chemoselectivity; acylation,[1,2] carboxylation,[3] 1,2-addition to ketones and aldehydes,[4] 1,4-addition to conjugated unsaturated ketones,[5] aldehydes,[6] esters[7] and amides as well as alkylation of alkyl bromides[8] can be performed under mild conditions and in high yields)

Preparative Methods: [7b] BuMnCl can be prepared in THF, at 0 °C, by reaction of ***n-Butyllithium*** or BuMgX with ***Manganese(II) Chloride*** or, better, with the soluble ate complex $MnCl_4Li_2$. The latter is easily obtained by mixing $MnCl_2$ and ***Lithium Chloride*** (2 equiv) in anhydrous THF at rt until dissolution (about 1 h). BuMnBr can be obtained in ether or in THF, between -10 °C and 0 °C, from BuLi or BuMgX and $MnBr_4Li_2$ (prepared by mixing $MnBr_2$ + 2 LiBr in ether or THF at rt). BuMnI is prepared by adding BuLi or BuMgX to MnI_2 in ether or in THF between -10 °C and -20 °C. Organomanganese iodides are now of historical interest only since organomanganese chlorides in THF, or organomanganese bromides in ether, are both less expensive and more stable.

Commercial $MnCl_2$ and $MnBr_2$ must be dried by heating under vacuo before using (200 °C, 10^{-2} mmHg, 2 h). Anhydrous $MnBr_2$ can be conveniently prepared (>95%) by reaction of Br_2 with Mn (1.01 equiv, electrolytic grade) in anhydrous ethyl acetate. The reaction is exothermic and the temperature must be kept between 35 and 45 °C. Anhydrous MnI_2 is obtained by adding ***Iodine*** slowly (exothermic) to a suspension of Mn (1.01 equiv, electrolytic grade) in ether at rt. The use of manganese halides containing some impurities such as Ni, Fe, and Cu salts can strongly decrease the stability of BuMnX (and more generally of all alkylmanganese halides).

Handling, Storage, and Precautions: butylmanganese halide solutions must be handled under an inert atmosphere in the absence of moisture. In THF, BuMnX are stable at rt. In ether, BuMnI is stable at -10 °C and BuMnBr at 10 °C. These reagents are best generated in situ and used rapidly.

Acylation.[1]

BuMnI[1a,b] and BuMnBr[1f] (prepared in ether) react under mild conditions with a vast array of acylating agents (RCOCl, $(RCO)_2O$, RCO_2CO_2Et, etc.) to give the corresponding ketones in high yields (eqs 1 and 2); similarly, $ClCO_2Et$ leads to esters.[1c] BuMnCl prepared in THF is also acylated in high yield under mild conditions (eq 3).[1d]

$$\mathrm{BuMnX} + \mathrm{C_7H_{15}COCl} \xrightarrow[0\ ^\circ\mathrm{C\ to\ rt}]{\mathrm{ether}} \mathrm{BuCOC_7H_{15}} \qquad (1)$$

X = I, 91%; X = Br, 96%

$$\mathrm{BuMnI} + \mathrm{EtOCO(CH_2)_6COZ} \xrightarrow[0\ ^\circ\mathrm{C\ to\ rt}]{\mathrm{ether}} \mathrm{BuCO(CH_2)_6CO_2Et} \qquad (2)$$

Z = Cl, 96%; Z = OCO_2Et, 91%

$$\mathrm{BuMnCl} + \mathrm{PhCOCl} \xrightarrow[0\ ^\circ\mathrm{C\ to\ rt}]{\mathrm{THF}} \mathrm{BuCOPh} \qquad (3)$$

90%

In some cases the yield can be improved in the presence of copper salts (eq 4). A dramatic improvement is especially observed with *s*- or *t*-alkylmanganese chlorides (eq 5).

$$\mathrm{BuMnCl} + \mathrm{ClCO(CH_2)_5Br} \xrightarrow[0\ ^\circ\mathrm{C\ to\ rt}]{\mathrm{THF}} \mathrm{BuCO(CH_2)_5Br} \qquad (4)$$

no CuCl, 1.5 h: 85%
1% CuCl, 30 min: 92%

$$t\text{-}\mathrm{BuMnCl} + \mathrm{C_7H_{15}COCl} \xrightarrow{\mathrm{THF}} t\text{-}\mathrm{BuCOC_7H_{15}} \qquad (5)$$

no CuCl: 0%
1% CuCl: 96%

Interestingly, this acylation is highly chemoselective and numerous functional groups are tolerated;[1b,d] for example, halides, allylic halides, nitriles, esters, and even unprotected keto groups (eq 6).[1b] In addition, the reaction can be performed in the presence of various cosolvents which are not commonly used in organometallic chemistry, such as CH_2Cl_2 or EtOAc (eq 7).[1e]

$$BuMnCl + ClCO(CH_2)_3CO_2Et \xrightarrow[88\%]{THF} BuCO(CH_2)_3CO_2Et \quad (6)$$

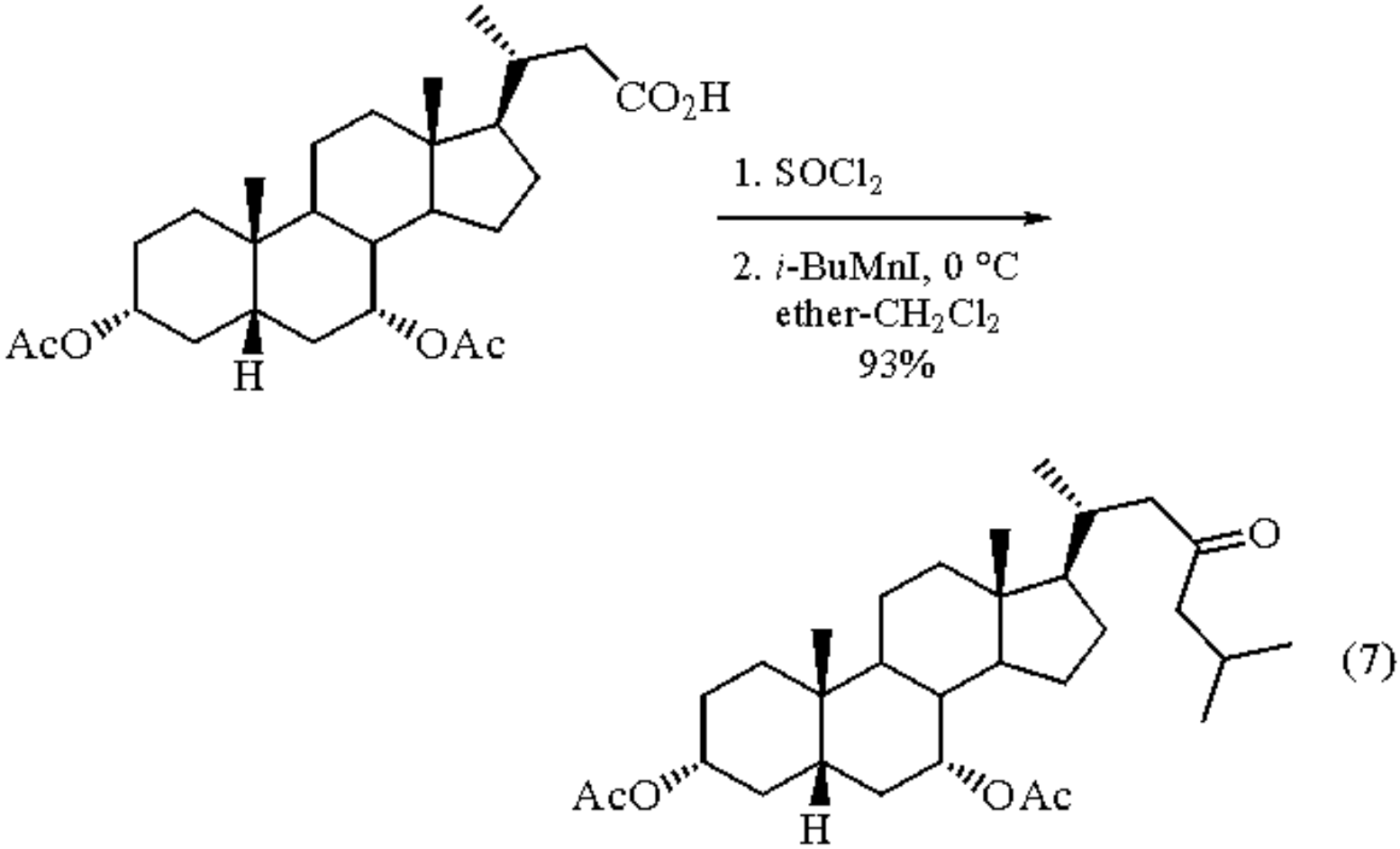

The acylation of organomanganese reagents is a very general reaction and numerous functionalized or polyunsaturated ketones can be prepared in high yields.

Acylation: Catalytic Procedure.[2]

Butylmanganese compounds are also involved in the Mn-catalyzed acylation of BuMgCl (eq 8). This procedure is very economic and easy to carry out; in addition, the chemoselectivity is generally excellent (eq 9).

$$C_7H_{15}COCl + 3\%\ MnCl_4Li_2 \xrightarrow[\substack{30\ min \\ 87\%}]{\substack{BuMgCl,\ THF \\ 0\text{-}10\ °C}} BuCOC_7H_{15} \quad (8)$$

$$EtCO(CH_2)_5COCl + 3\%\ MnCl_4Li_2 \xrightarrow[\text{45 min, 91\%}]{\text{BuMgCl, THF, 0-10 °C}} EtCO(CH_2)_5COBu \quad (9)$$

Carboxylation.[3]

Butylmanganese halides are easily carboxylated in ether or in THF to give the expected $BuCO_2H$ in good yields. Contrary to BuLi and BuMgX, butylmanganese halides smoothly react at room temperature (the exothermic effect is very limited) without side-reaction. Thus they do not add to the resulting $BuCO_2MnX$. The related lithium or magnesium tributylmanganates can also be carboxylated under similar conditions (eq 10).

$$Bu_3MnMgCl \xrightarrow[\text{2. } H_2O,\ \text{86\%}]{\text{1. } CO_2\text{, THF, 20 °C}} 3\ BuCO_2H \quad (10)$$

1,2-Addition.[4]

In ether, butylmanganese halides readily add to aldehydes and ketones at 0 °C, affording the corresponding alcohols in high yields (eqs 11 and 12).[1g,4a] However, they do not react with various less reactive carbonyl compounds such as amides and esters (except with formates).[3] It should be noted that BuMnX can be used in the presence of various amides (NMP, DMF) or ester (EtOAc) as cosolvent.

$$BuMnBr + HexCHO \xrightarrow[\text{0-20 °C, 98\%}]{\text{ether}} BuCH(OH)Hex \quad (11)$$

$$BuMnI + Pr_2CO \xrightarrow[\text{0-20 °C, 90\%}]{\text{ether}} BuPr_2COH \quad (12)$$

In THF, butylmanganese halides are less reactive towards carbonyl compounds.[4a] Thus they also add to aldehydes at rt in high yields (eq 13) but with ketones the reaction is slower and results in lower yields than in ether (from BuCOBu,

70% instead of 92%).

$$\text{BuMnCl} + \text{HexCHO} \xrightarrow[\text{0-20 °C, 95\%}]{\text{THF}} \text{HexCH(OH)Bu} \qquad (13)$$

Butylmanganese halides prepared from BuMgX are more reactive than those prepared from BuLi (electrophilic activation by MgX_2) (eq 14). In general, organomanganese reagents are of use when performing chemoselective 1,2-additions to functionalized ketones or aldehydes (eq 15).

$$\text{BuMnX} + \text{PrCOPr} \xrightarrow[\text{20 °C}]{\text{ether}} \text{BuPr}_2\text{COH} \qquad (14)$$

X = I, Br	10 min	30 min	6h
BuMnX, LiX	34%	53%	80%
BuMnX, MgX_2	81%	99%	-

$$\text{EtCO(CH}_2\text{)}_9\text{CHO} \xrightarrow[\text{20 °C}]{\text{BuMnX}} \text{EtCO(CH}_2\text{)}_9\text{CH(OH)Bu} \qquad (15)$$

BuMnBr, ether	90%
BuMnCl, THF	89%

A recent report[4b] showed that in THF, BuMnO(CO)-*t*-Bu adds more stereoselectively than BuMnBr to 4-*t*-butylcyclohexanone (axial preference) (eq 16).

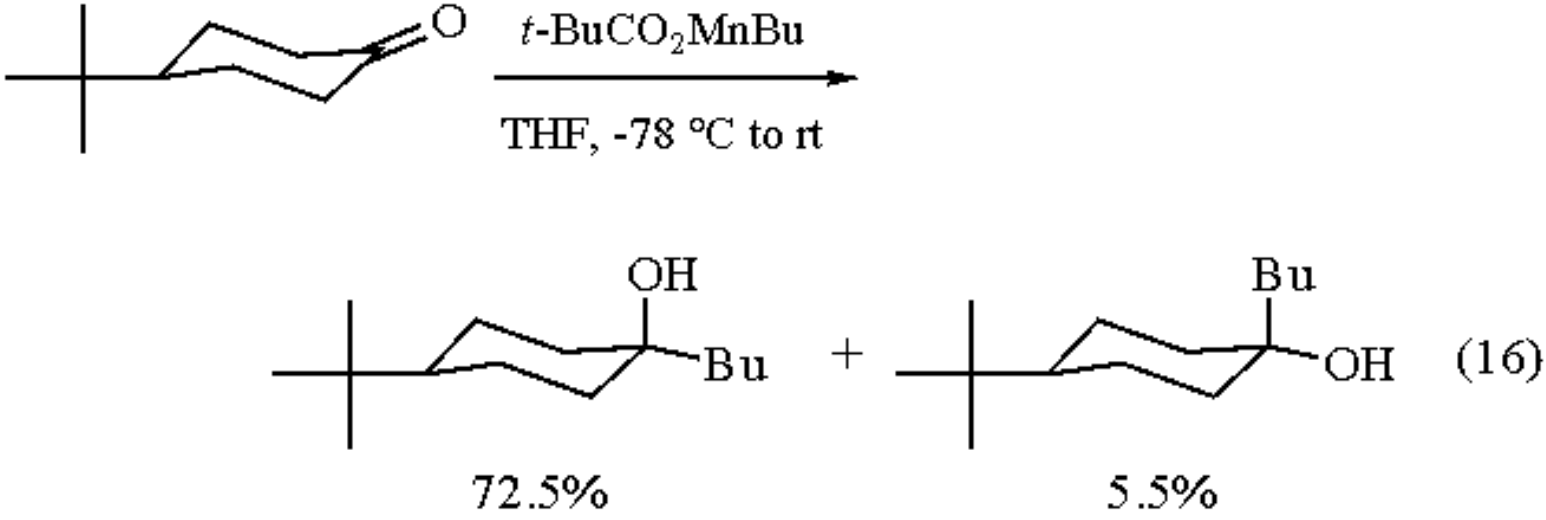

Conjugate Addition.[5-7]

BuMnCl readily adds to alkylidenemalonic esters to afford the conjugate addition products (eq 17).[7b]

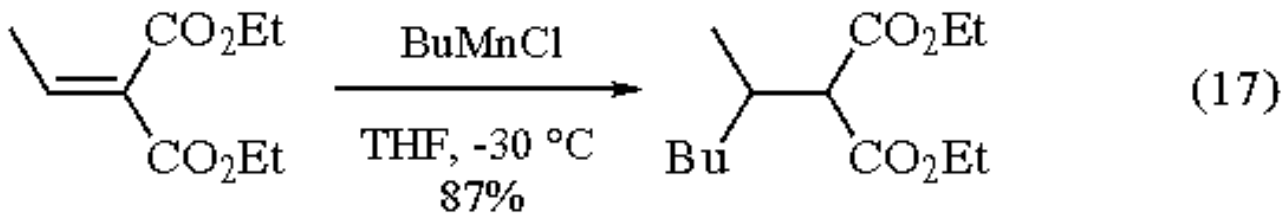

With the less reactive Michael acceptors, such as α,β-ethylenic ketones, the conjugate addition reaction does not occur or gives low yields. However, in the presence of ***Copper(I) Chloride*** as catalyst, the 1,4-addition product is obtained in high yields under very mild conditions (eq 18).[5] It is interesting to note that the conjugate addition reaction also takes place easily with the less reactive β-disubstituted enones (eq 19).

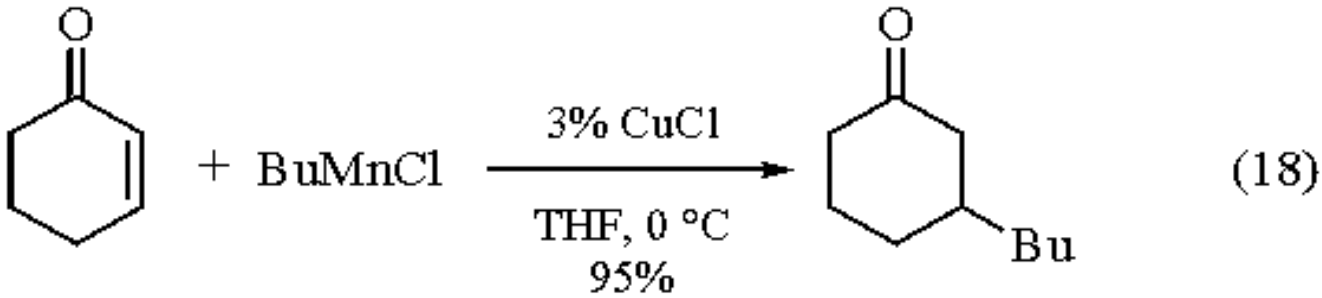

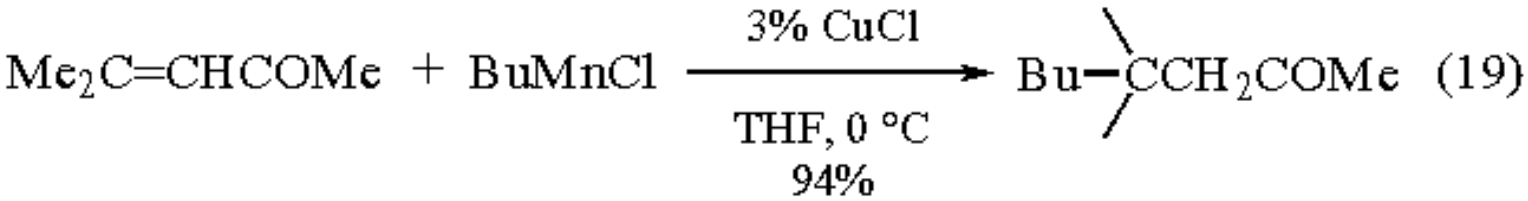

Butylmanganese compounds are also involved in the Mn-Cu-catalyzed conjugate addition of BuMgCl to enones (eq

20). The reaction has been successfully extended to α,β-ethylenic aldehydes (eq 21)[6] and, in the presence of Me_3SiCl, to α,β-ethylenic esters (eq 22)[7a] and amides.

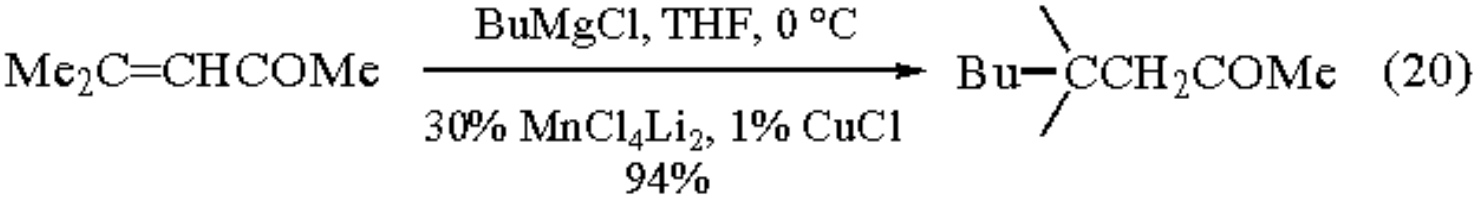

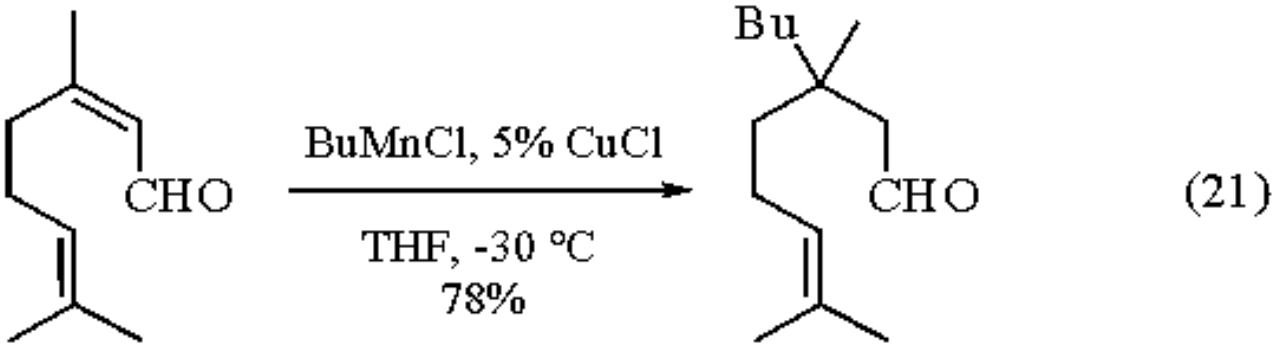

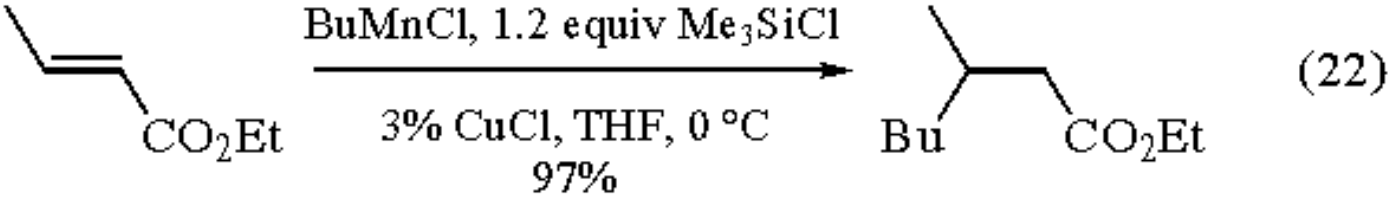

Generally, the Cu-catalyzed conjugate addition of organomanganese chloride reagents (as well as the Mn-Cu-catalyzed conjugate addition of RMgCl) gives higher yields and is easier to carry out than the classical organocopper procedures.[5]

Alkylation.[8]

Butylmanganese halides react only with a few very reactive alkylating agents such as ***Allyl Bromide***. In addition, even with this latter, the reaction is very slow and gives a moderate yield (~70%). However, BuMnCl prepared in THF can be easily alkylated at rt in the presence of both copper salt (CuCl) as catalyst and NMP as cosolvent. Under these conditions the alkylated products are generally obtained in excellent yields even from the less reactive alkyl bromides (eq 23).

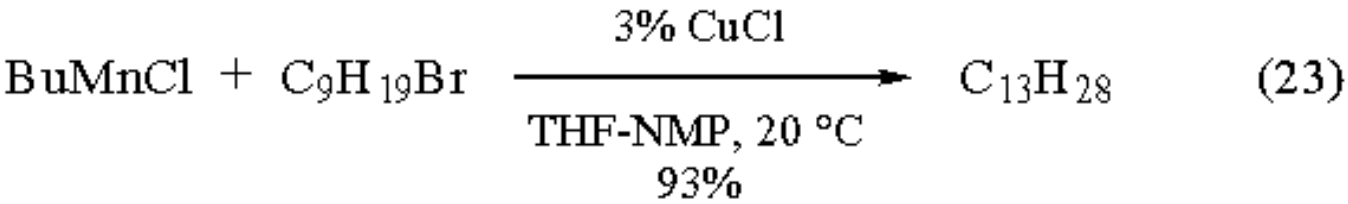

This procedure is as simple to carry out as the classical Cu-catalyzed Grignard reaction but the yields are very often better and the chemoselectivity is clearly superior. For example, in the case of eq 24, BuMgCl alone gives only a 45%

yield.

$$BuMnCl + Br(CH_2)_5COBu \xrightarrow[\text{THF-NMP, 20 °C}]{\text{3\% CuCl}} Bu(CH_2)_5COBu \quad (24)$$

90%

Related Reactions.

All the reactions described above for butylmanganese halides can be performed with *n*-, *s*-, or *t*-alkyl- as well as with alkenyl-, aryl-, and allylmanganese halides. Some examples are: acylation (eqs 25-27),[1d,2] one-pot acylation-alkylation (preparation of alcohols) (eq 28),[1i] conjugate addition (eqs 29-31),[5] 1,2-addition (eq 32),[4] and alkylation (eqs 33 and 34).[8]

$$Me_2C{=}CHCH_2MnCl + HeptCOCl \xrightarrow[\text{-10 to 20 °C}]{\text{THF}} Me_2C{=}CHCH_2COHept \quad (25)$$

89%

$$RMnCl + HeptCOCl \xrightarrow[\text{-10 to 20 °C}]{\text{THF, 1\% CuCl}} RCOHept \quad (26)$$

R = Me, 91%; *i*-Pr, 93%; $Me_2C{=}CH$, 87%; Ph, 92%

$$HeptCOCl + 3\%\ MnCl_4Li_2 \xrightarrow[\text{0-10 °C, 40 min}]{\text{PhMgCl, THF}} PhCOHept \quad (27)$$

85%

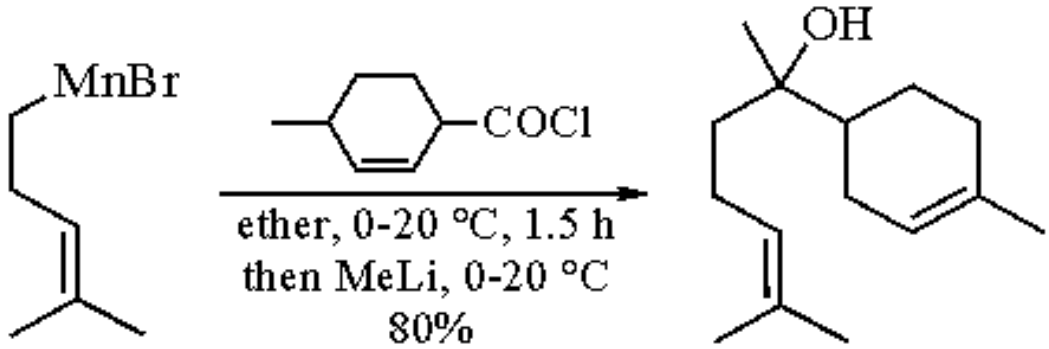

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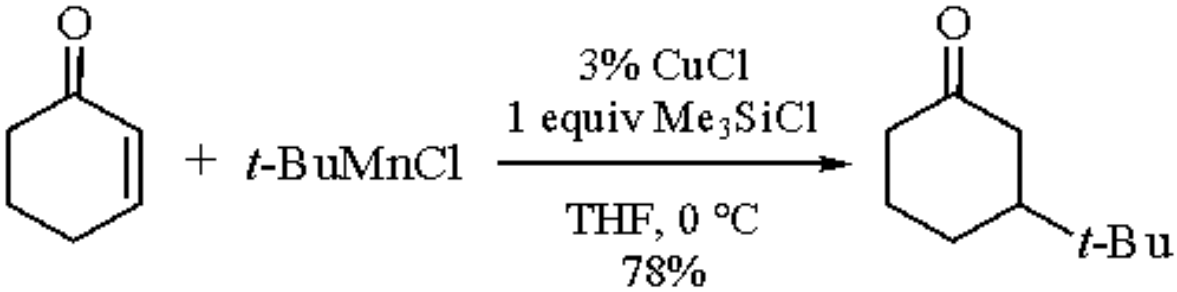

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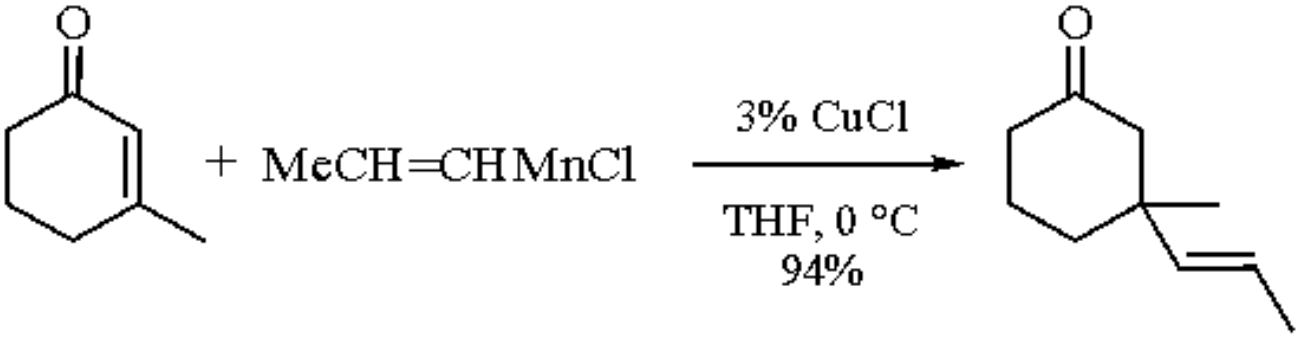

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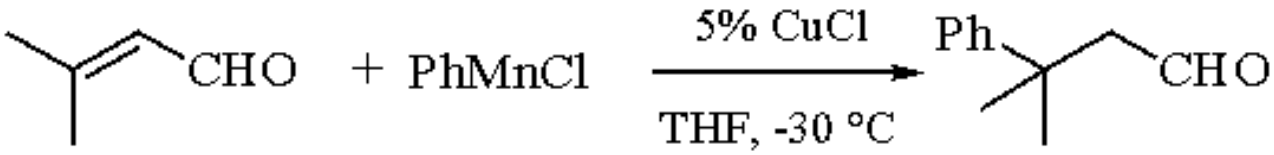

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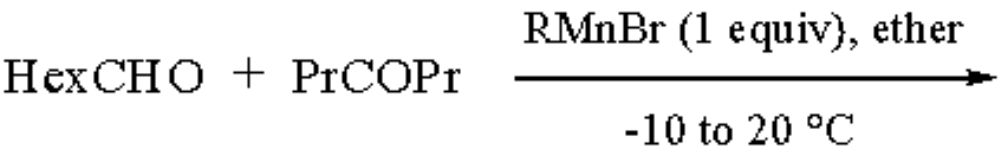

HexCH(OH)R (+ PrCOPr) (32)

PhMnBr	94%	selectivity > 99%
$Me_2C{=}CHMnBr$	98%	selectivity >99%

$$\mathrm{BuMnCl} + \mathrm{BuCO_2(CH_2)_2Br} \xrightarrow[\text{THF-NMP, rt}]{3\%\ \mathrm{CuCl_4Li_2}} \mathrm{BuCO_2(CH_2)_2Bu} \quad (33)$$

90%

$$t\text{-}\mathrm{BuMnCl} + \mathrm{C_9H_{19}Br} \xrightarrow[\text{THF-NMP, rt}]{3\%\ \mathrm{CuCl_4Li_2}} t\text{-}\mathrm{BuC_9H_{19}} \quad (34)$$

86%

Alkynylmanganese halides also react easily with various acylating agents to give the α,β-alkynyl ketones in excellent yields, and they add to carbon dioxide as well as to ketones or aldehydes (eqs 35-37).[1d,f,4] However, they cannot undergo the conjugate addition to α,β-unsaturated carbonyl compounds (except with the very reactive alkylidenemalonic esters)[7b] and they do not react with alkyl bromides under the conditions described above.

$$\mathrm{C_5H_{11}C{\equiv}CMnCl} + \mathrm{(CF_3CO)_2O} \xrightarrow[\text{20 °C}]{\text{THF}} \mathrm{C_5H_{11}C{\equiv}CCOCF_3} \quad (35)$$

84%

$$\mathrm{BuC{\equiv}CMnBr} + \mathrm{MeCH{=}CHCOCl} \xrightarrow[\text{20 °C}]{\text{ether}} \mathrm{BuC{\equiv}CCOCH{=}CHMe} \quad (36)$$

87%

$$\mathrm{C_6H_{13}CHO} + \mathrm{PrCOPr} \xrightarrow[\text{ether, 20 °C}]{\mathrm{BuC{\equiv}CMnBr\ (1\ equiv)}}$$

80%

$$\mathrm{BuC{\equiv}CCH(OH)C_6H_{13}}\ (+\mathrm{PrCOPr}) \quad (37)$$

selectivity > 99%

---

1. (a) Cahiez, G.; Bernard, D.; Normant, J.-F. *S* **1977**, 130. (b) Friour, G.; Cahiez, G.; Normant, J. F. *S* **1984**, 37; *S* **1985**, 50. (c) Cahiez, G.; Normant, J. F. *BSF(2)* **1977**, 570. (d) Cahiez, G.; Laboue, B. *TL* **1989**, *30*, 7369. (e) Cahiez, G. *TL* **1981**, *22*, 1239. (f) Cahiez, G.; Laboue, B. *TL* **1989**, *30*, 3545. (g) Cahiez, G.; Rivas-Enterrios, J.; Granger-

Veyron, H. *TL* **1986**, *27*, 4441. (h) Cahiez, G.; Chavant, P.; Métais, E. *TL* **1992**, *33*, 5245. (i) Cahiez, G.; Rivas-Enterrios, J.; Clery, P. *TL* **1988**, *29*, 3659.
2. Cahiez, G.; Laboue, B. *TL* **1992**, *33*, 4439.
3. Friour, G.; Cahiez, G.; Alexakis, A.; Normant, J. F. *BSF(2)* **1979**, 515.
4. (a) Cahiez, G.; Figadère, B. *TL* **1986**, *27*, 4445. (b) Reetz, M. T.; Haning, H.; Stanchev, S. *T* **1992**, *33*, 6963.
5. Cahiez, G.; Alami, M. *TL* **1986**, *27*, 569; *TL* **1989**, *30*, 3541.
6. Cahiez, G.; Alami, M. *TL* **1989**, *30*, 7365.
7. (a) Cahiez, G.; Alami, M. *TL* **1990**, *31*, 7423. (b) Cahiez, G.; Alami, M. *T* **1989**, *45*, 4163.
8. Cahiez, G.; Marquais, S. *SL* **1993**, 45.

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(*R*)-2-*t*-Butyl-6-methyl-4*H*-1,3-dioxin-4-one[1]

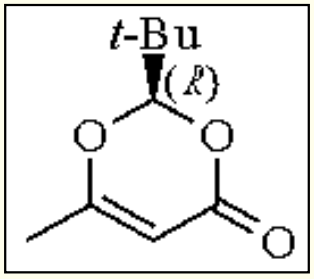

(*R*)

[107289-20-3] · $C_9H_{14}O_3$ · (*R*)-2-*t*-Butyl-6-methyl-4*H*-1,3-dioxin-4-one · (MW 170.21) (*S*)

[139973-88-9]

(enantiopure derivative of acetoacetic acid,[2-4] highly reactive Michael acceptor for Cu^I-doped Grignard and for Gilman reagents;[2,5] component for [2 + 2] photocycloadditions;[2] catalytic hydrogenation leads to the *cis*-disubstituted dioxanone;[2,5] the dienolate generated from the reagent can be used for chain elongations at the C(6)-Me carbon[6])

Physical Data: mp 59.8-60.2 °C; [α]rtD = -215° (*c* = 1, $CHCl_3$).

Solubility: sol most common organic solvents; poorly sol pentane at low temperature.

Preparative Methods: acid-catalyzed acetalization of ***Pivalaldehyde*** with (*R*)-3-hydroxybutanoic acid[8] gives the *cis*-1,3-dioxan-4-one (**2**) in 40% yield after recrystallization from ether/pentane. (Up to 60% yield can be obtained by using freshly loaded acidic ion-exchange resin and following the procedure of Seebach et al.[7b] Runs with up to 120 g hydroxy butanoic acid were performed in this way). Bromination with ***N-Bromosuccinimide*** leads to a mixture of brominated dioxinones which are debrominated hydrogenolytically to (**1**) (eq 1). The yield (**2**) -> (**1**) is ~45% after recrystallization from pentane/ether (50:3) at -20 °C.[4,7] The enantiomer *ent*-(**1**) is of course equally readily available from (*S*)-3-hydroxybutanoic acid.[9] Both enantiomers of 3-hydroxybutanoic acid are commercially available.

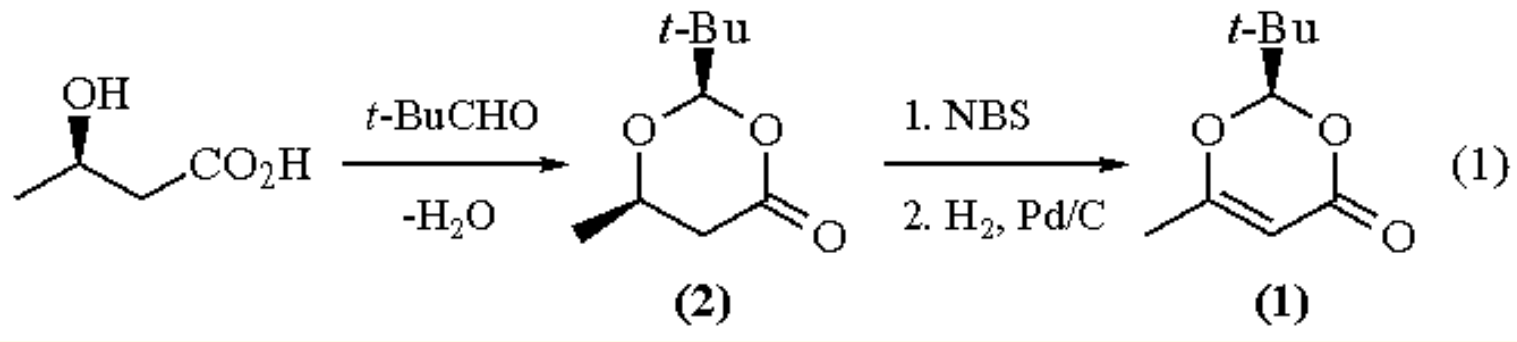

Handling, Storage, and Precautions: dioxinone (**1**) is commercially available and is indefinitely stable as a

crystalline solid stored in a dark bottle at rt.

Reactions of 4*H*-1,3-Dioxin-4-one (1).

The cuprate additions to (**1**) occur preferentially from the face *trans* to the *t*-Bu group. An example is the preparation of and correlation with mevalonolactone (**4**) in eq 2 by Michael addition of ***Lithium Diallylcuprate*** to give (**3**) and ozonolysis for degradation by one carbon.[5] Two examples of the use of the dienolate derived from dioxinone (**1**) are shown in eqs 3 and 4. The dienolate adds to aromatic aldehydes in a 1,2-fashion with reasonable diastereoselectivities at the exocyclic carbon atom. Oxidative degradation of the major diastereoisomer (**5**), obtained with benzaldehyde, leads to the β-hydroxy acid (**6**) of (*S*) configuration (eq 3).[6] With α,β-unsaturated aldehydes the exocyclic dienolate carbon reacts in a Michael addition. Thus the adduct (**7**) is isolated (53%) in a diastereomer ratio of 20:1 (eq 4).[6] Activation of the exocyclic methyl group in (**1**) is also realized by ***N-Bromosuccinimide*** bromination.[3,4,10] The resulting 6-bromomethyldioxinone has been employed in a vineomycinone B2 synthesis: see the intermediate (**8**) in eq 5.[11]

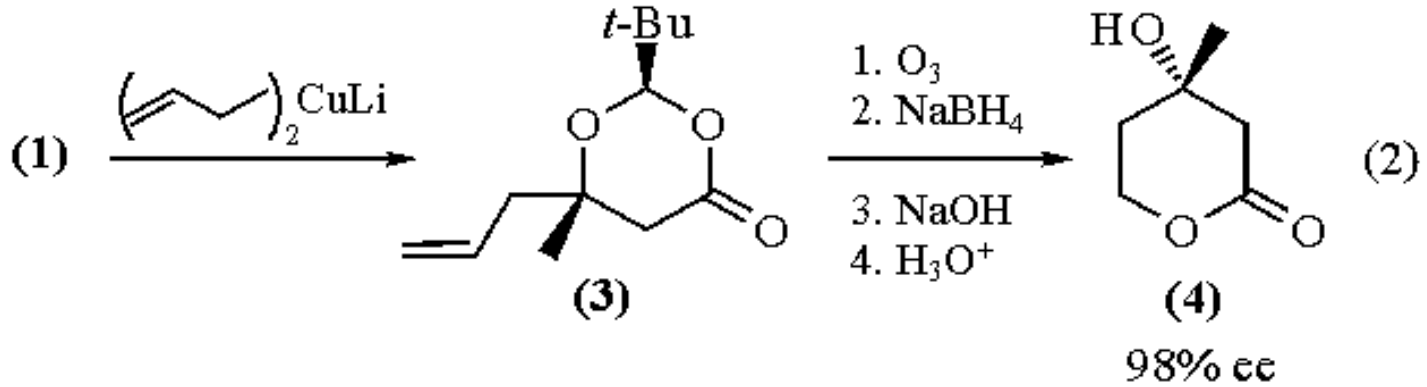

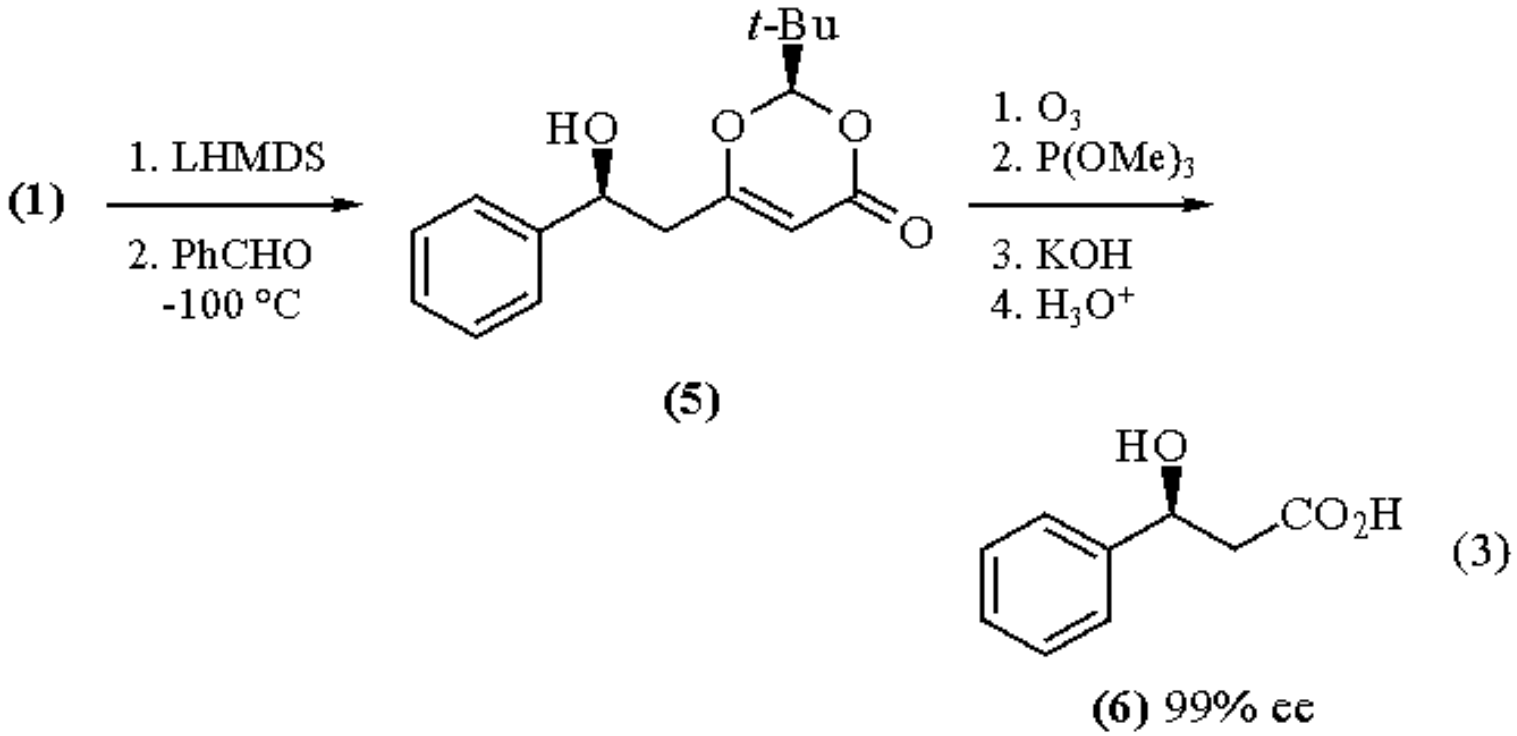

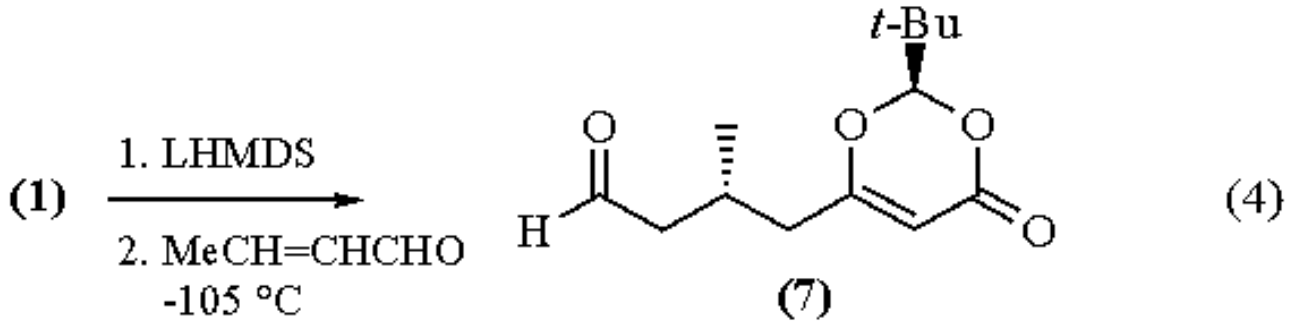

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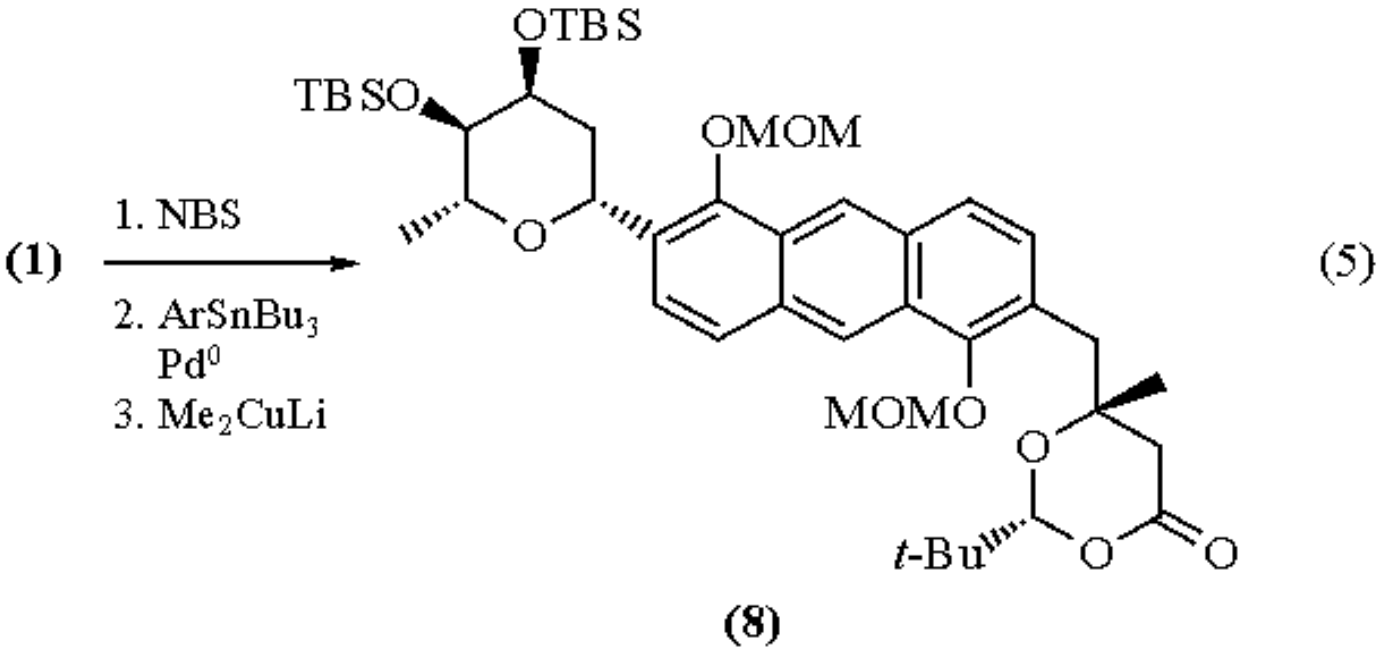

(5)

Other Enantiopure Dioxinones for Self-regeneration of the Stereogenic Center.

The principle of preparing dioxinones from enantiopure β-hydroxy acids was also applied to 3-hydroxypentanoic acid,[3,6] 4,4,4-trifluoro-3-hydroxybutanoic acid,[12] 4,4,4-trichloro-3-hydroxybutanoic acid,[13] and (*S*)-serine;[3,14] aldehydes other than pivaldehyde and ketones[15] may be used for dioxinone preparation as well. Furthermore, numerous other dioxinones have been prepared from the parent compound (**1**) (eqs 3, 4, 6 and 7). The dibromide intermediate (**9**) in the preparation of (**1**) can be converted to an aldehyde, which after undergoing Wittig alkenation, followed by catalytic hydrogenation, leads to the 3-hydroxyadipic acid derivative (**10**) shown in eq 6, in an overall yield of 55%.[10] Aldol condensations of dioxanone (**2**) with aldehydes and shift of the double bond from the exo- to the endocyclic position produce 2,5,6-trisubstituted dioxinones such as (**11**), which can be used for the preparation of 2,3-disubstituted β-hydroxycarboxylic acids: see (**12**) in eq 7.[16,17] Such compounds are not accessible by current enantioselective aldol addition methodology. An example of the preparation of a CF_3-branched 3-hydroxycarboxylic acid derivative is shown in eq 8; trifluoromethyldioxinone (**13**) and ***Lithium Di-n-butylcuprate*** give a dioxanone which is solvolyzed in methanol to the hydroxy ester (**14**).[12b]

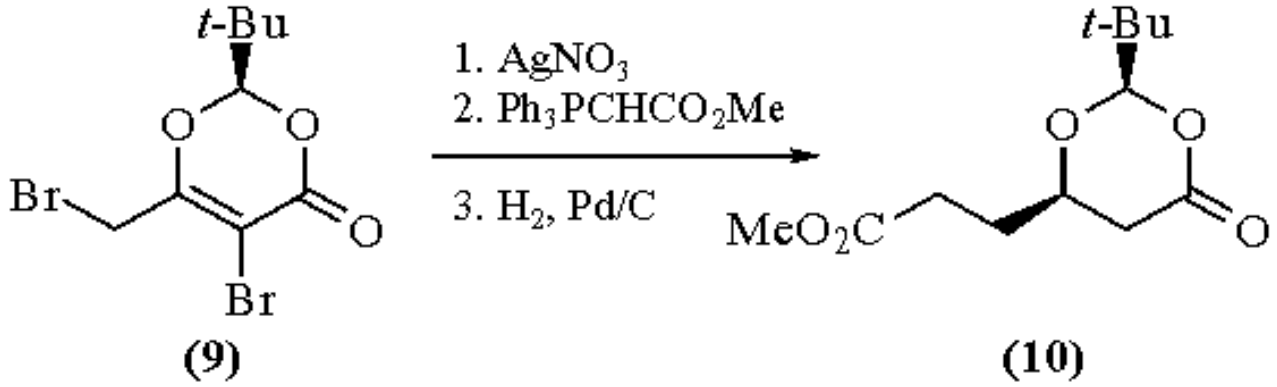

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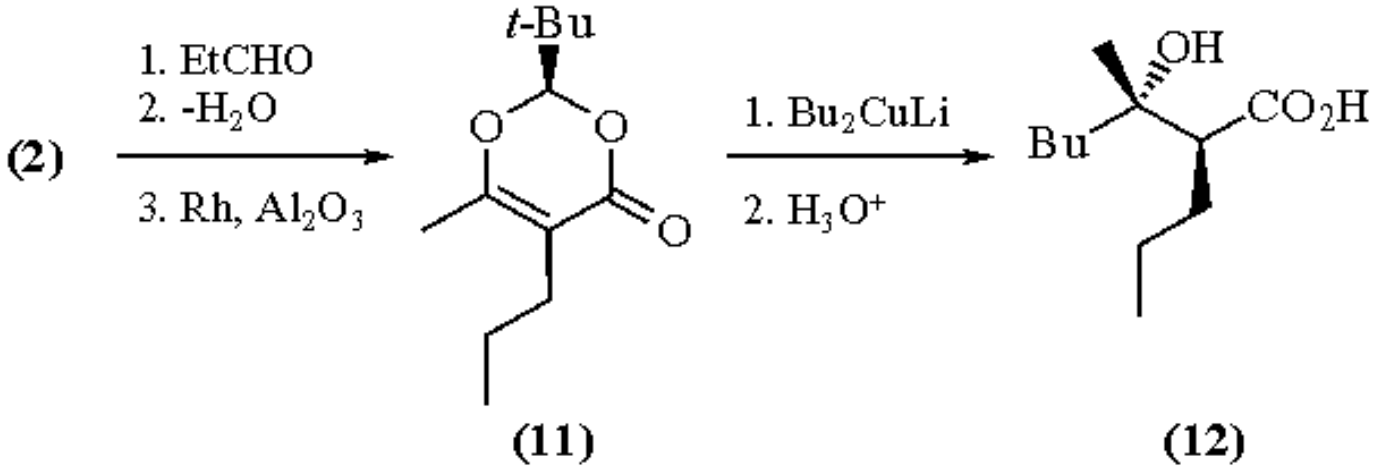

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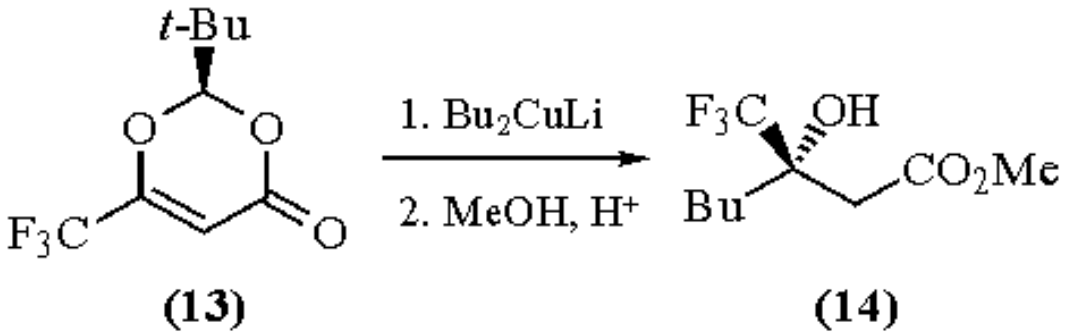

(8)

Dioxinones Obtained by Resolution or Prepared with a Chiral Auxiliary.

2-Phenyl-4*H*-1,3-dioxin-4-ones (**15**) derived from formylacetate or acetoacetate can be readily prepared in enantiopure form by preparative resolution[14,18] on cellulose triacetate.[18] These have been used for Michael additions and hydrolysis to long-chain β-hydroxycarboxylic acids, for example the tridecanoic acid (**16**) from (*R*)-(**15a**).[18] The cuprate adducts formed with the methylphenyldioxinone (*S*)-(**15b**) can be hydrogenolytically cleaved directly to β-branched β-hydroxy acids with benzyl protection of the hydroxy functional group; see (**17**) in eq 9.[18]

(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one

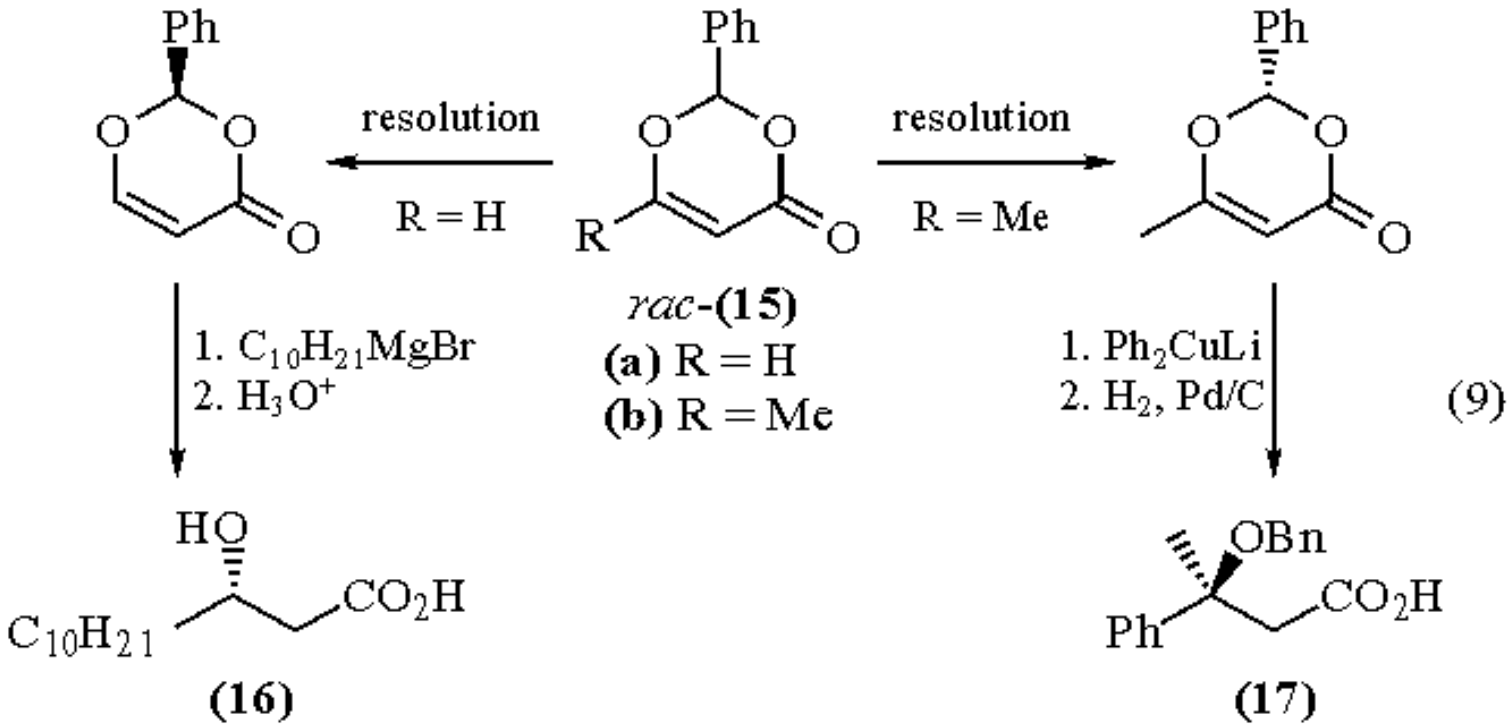

The chiral auxiliary approach involving dioxinones has been chosen by Demuth et al.[19] and, most extensively, by Kaneko and his collaborators.[20-22] They have used menthol esters (**18**) and (**19**) for typical diastereoselective reactions of dioxinones, with subsequent hydrolysis, for the preparation of various enantiopure products. For a review, also referring to the work of Winkler about photoreactions of *rac* or achiral dioxinones, see the articles by Kaneko.[23,24] For a table with enantiopure dioxinones as of mid-1991, see Kinkel et al.[14]

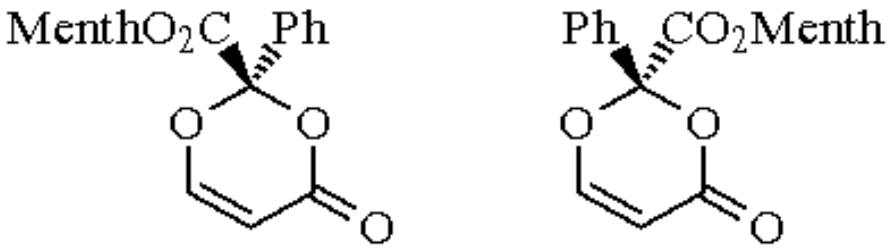

(18) *epi*-**(18)**

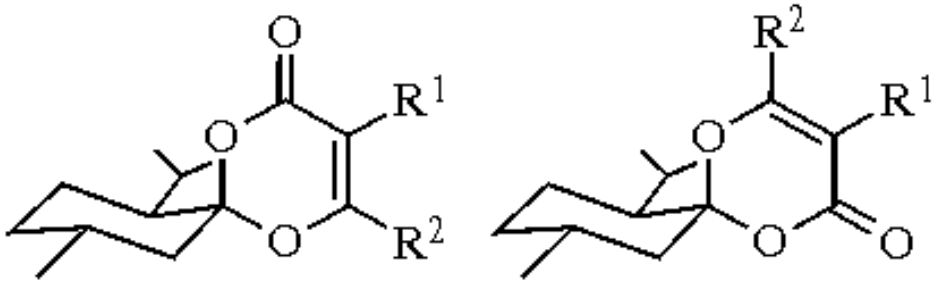

(19) *epi*-**(19)**

Related Reagents.

(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one; ***(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one***; ***10,2-***

(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one

Camphorsultam; ***10-Dicyclohexylsulfonamidoisoborneol***; ***(R,R)-2,5-Dimethylborolane***; ***Ethyl 3-Hydroxybutanoate***; ***2-Hydroxy-1,2,2-triphenylethyl Acetate***; ***(S)-4-Benzyl-2-oxazolidinone***; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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(*R*,*R*)-2-*t*-Butyl-5-methyl-1,3-dioxolan-4-one[1]

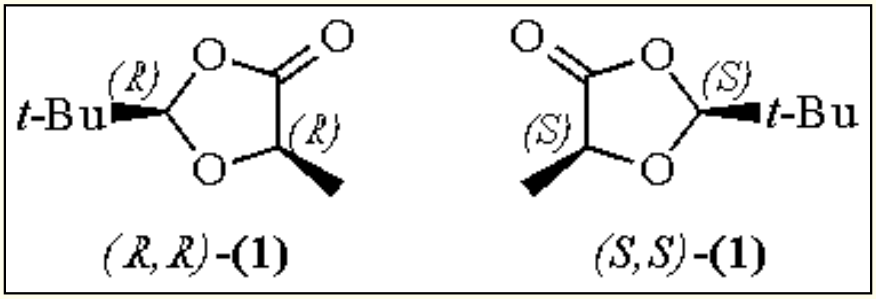

(*R*,*R*)

[104194-02-7] · $C_8H_{14}O_3$ · (*R*,*R*)-2-*t*-Butyl-5-methyl-1,3-dioxolan-4-one · (MW 158.20) (*S*,*S*)

[81037-06-1]

(cyclic acetals from (*R*)- and (*S*)-lactic acid and pivaldehyde;[1b,2-6] reagents for the preparation of enantiopure α-hydroxy-α-methyl carboxylic acids by alkylation of the corresponding lithium enolate with alkyl,[1b,2-4] allyl,[1b,2,7,8] and benzyl[1b] halides, by hydroxyalkylation with aldehydes and ketones,[1b,3,9,10] and by Michael addition to nitroalkenes;[9,11] precursor to the 5-bromo derivative used for radical reactions;[12,13] precursor to 2-*t*-butyl-5-methylene-1,3-dioxolan-4-one;[13-15] an acceptor for radical additions;[15,16] and an ene component for Diels-Alder reactions leading to cyclic, heterocyclic, and bicyclic α-hydroxy carboxylic acids[14,17-19])

Physical Data: mp ca. 5 °C; bp 80 °C/20 mmHg; $[\alpha]^{rt}_D$ = +44.8° (*c* = 1.83, $CHCl_3$) for (*S*,*S*)-(**1**) containing 4% (2*R*,5*S*) epimer after two recrystallizations from ether/pentane at -75 °C.

Solubility: good to excellent in all common organic solvents.

Preparative Method: on a 0.5 mol scale reagent (*S*,*S*)-(**1**) is prepared by condensation of ***Pivalaldehyde*** and (*S*)-lactic acid under acid catalysis in pentane, with azeotropic removal of the water formed. The crude product is distilled in vacuo to give 93% of a 4:1 *cis*/*trans* mixture. Two recrystallizations from pentane/ether at -75 °C furnish 60% (*S*,*S*)-(**1**) (*cis*/*trans* = 96:4).

Handling, Storage, and Precautions: stable for many months under an inert atmosphere in a refrigerator.

Reactions of the Enolate of (1) with Electrophiles.

Addition of the dioxolanones (**1**) to solutions of ***Lithium Diisopropylamide*** or ***Lithium Hexamethyldisilazide*** in THF at dry-ice temperature generates the corresponding enolates which react with alkyl halides,[1b,2-4,7,8] carbonyl compounds,[1b,3,9,10] and nitroalkenes[9,11] almost exclusively from the face remote from the *t*-Bu group to give products of type (**2**). These can be hydrolyzed to simple α-hydroxy-α-methyl carboxylic acids or further elaborated. Four examples are

(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one

shown in (**3**)-(**6**) in which the part of the molecule originating from lactic acid is indicated in bold.

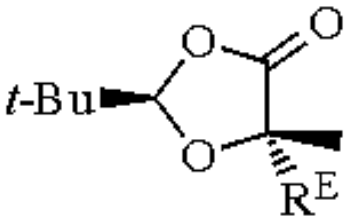

(2)

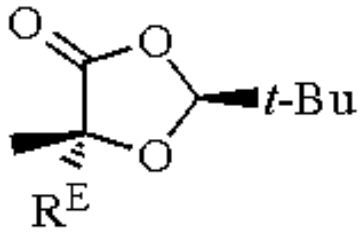

ent-**(2)**

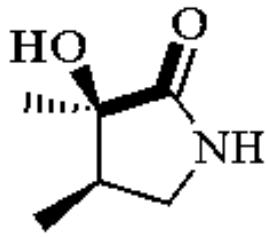

(3) γ-lactam from *(S)*-(+)-lactic acid

(4) *(S)*-(-)-Frontalin from *(R)*-(-)-lactic acid

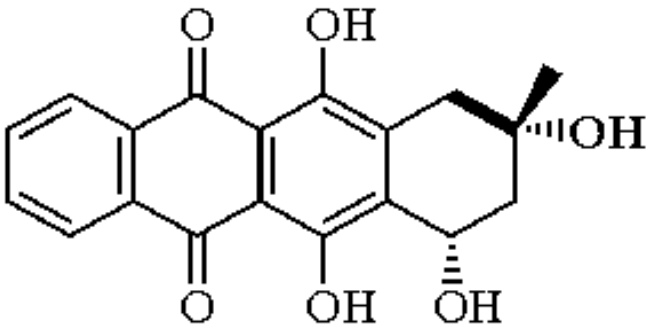

(5) 4-Demethoxyfeudomycinone C from *(S)*-(+)-lactic acid

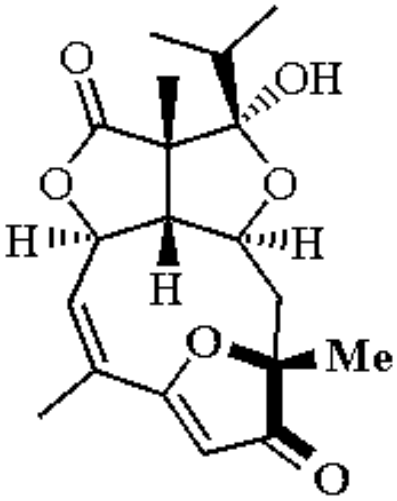

(6) (+)-Eremantholid A from *(S)*-(+)-lactic acid

Analogous Transformations with other α-Hydroxy Carboxylic Acids.

The conversion of lactic acid to products (**2**)-(**6**) is an example of the principle of self-regeneration of the stereogenic

centers (SRSC) which is also applicable to β-hydroxy-, α- and β-amino acids (see Related Reagents). Many α-hydroxy carboxylic acids occur naturally, and most α-amino acids can be converted to hydroxy acids by diazotization, with retention of configuration,[20] producing a host of readily available starting materials for this kind of conversion, for example in the synthesis of the antitumor alkaloid (**7**).[21] Table 1 lists various dioxolanones (**8**) made from the corresponding hydroxy acids and aldehydes or ketones, together with information on reactions carried out with them. This method is also applicable to α-mercapto carboxylic acids.[1,22]

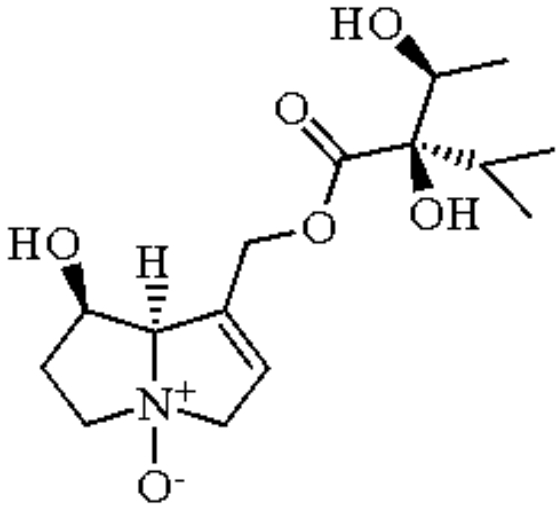

(7) (+)-Indicin *N*-oxide from *(S)*-2-hydroxy-3-methylbutanoic acid (from valine)

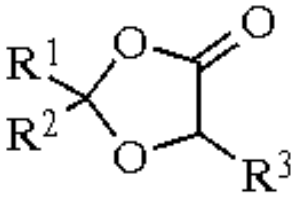

(8)

Table 1 Various Dioxolanones (**8**) Derived from the Corresponding a-Hydroxy Acids

R^1	R^2	R^3	Reported reaction
Me	H	Me	2
Ph	H	Me	6b
Cy	H	Me	6b
i-Pr	H	Me	6b
Me	Bu	Me	23
Me	Ph	Me	6a,23
t-Bu	Me	Me	6a
t-Bu	Ph	Me	6a
t-Bu	Ph	Me	Aldol addition[24]

t-Bu	Ph	Me	Aldol addition[24]
t-Bu	H	Et	Alkylation[7]
t-Bu	H	*i*-Pr	Aldol addition[21]
t-Bu	H	Bu	6b
t-Bu	H	*s*-Bu	6b
t-Bu	H	CH_2CO_2H	5
t-Bu	H	CH_2CO_2H	Alkylation[25]
t-Bu	H	CH_2CO_2H	Barton reaction[15]
t-Bu	H	CH_2SPh	Oxidation/elimination[17a]
Cy	H	CH_2SPh	Oxidation/elimination[17a]
t-Bu	H	Bn	6b
Me	H	Ph	6b
i-Pr	H	Ph	Alkylation[2]
t-Bu	H	Ph	5,6b
t-Bu	H	Ph	Alkylation[2]
Me	Me	Ph	23
$C(Me)=CH_2$	Me	Ph	23
Bu	Me	Ph	23
Ph	H	Ph	23

(*R*)- and (*S*)-*t*-Butyl-5-methylene-1,3-dioxolan-4-one, a Chiral α-Alkoxy Acrylate.

It is also possible to introduce an exocyclic double bond onto the dioxolanone ring, as in compounds (**9**)-(**11**), derived from lactic[13,14,17-19,26] and malic[12,27] acids. These α,β-unsaturated carbonyl derivatives are acceptors for radical additions[12,15,16] and undergo cycloadditions with dienes[14,17-19,26,27] and heterodienes.[18] The Diels-Alder adduct (**12**) of *ent*-(**9**) with cyclopentadiene is formed[14,17a,19] with *exo* selectivity (96:4) and serves as a precursor to norbornenone (**13**).[14,19] Cycloadduct (**14**), obtained from methylenedioxolanone (**9**) and an open-chain triene, is also the result of an *exo* addition and is used in tetronolide synthesis.[17b]

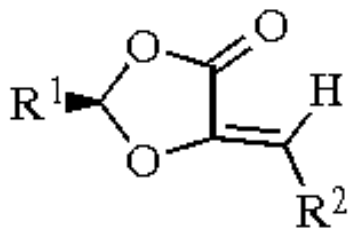

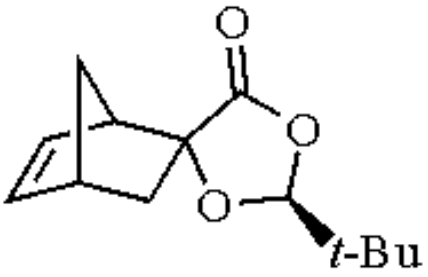

(9) $R^1 = t\text{-Bu}$, $R^2 = H$
(10) $R^1 = C_6H_{11}$, $R^2 = H$
(11) $R^1 = t\text{-Bu}$, $R^2 = CO_2Me$ or CO_2Et

(12)

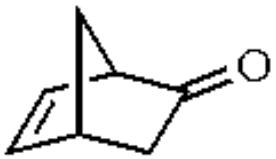

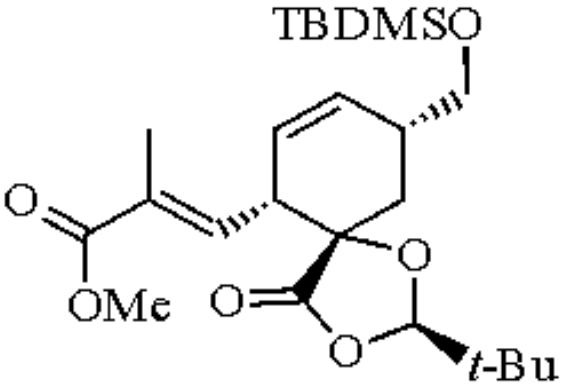

(13) **(14)**

Menthone-Derived Dioxolanones: Chiral Glycolic Acid Derivatives.[28]

Acetalization of menthone and phenylmenthone with glycolic acid leads to chromatographically separable mixtures of diastereoisomeric dioxolanones (**15**) and (**16**); they are precursors for chiral enolate derivatives of glycolic acid. Alkylations occur highly selectively, and the products can be solvolyzed with ethanol to give ethyl α-hydroxy carboxylates of either (*R*) or (*S*) configuration. Thus spiro compound (**16b**) gives the allylation product (**17**) (84%), from which pure ethyl (*R*)-2-hydroxypent-4-enoate is obtained.

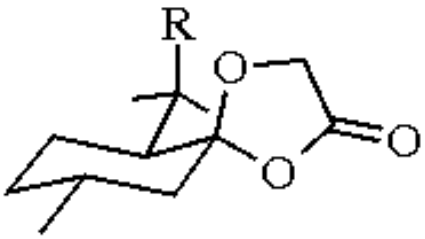

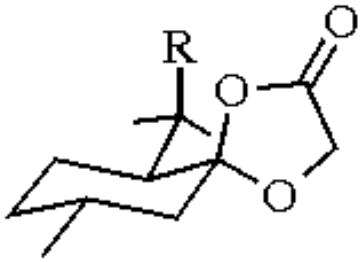

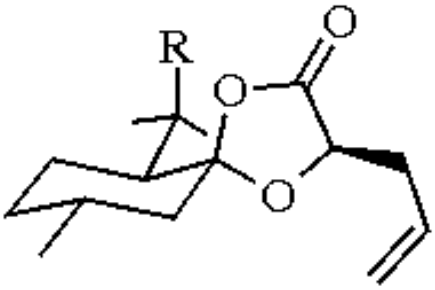

(15)
(a) R = H
(b) R = Ph

(16)
(a) R = H
(b) R = Ph

(17)
123:1 from **(16b)**

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***Ethyl 3-Hydroxybutanoate***; ***Ethyl Mandelate***; ***(R)-Methyl 2-t-Butyl-3(2H)-oxazolecarboxylate***; ***Methyl O-Methyllactate***; ***Phenoxyacetic Acid***; ***(-)-8-Phenylmenthol***.

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Eidgenössische Technische Hochschule Zürich, Switzerland

N´-t-Butyl-*N*-methyl-*N*-trimethylsilylmethylformamidine

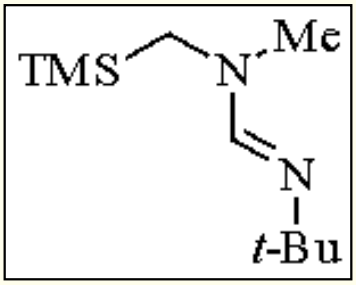

[80376-66-5] · $C_{10}H_{24}N_2Si$ · *N´-t*-Butyl-*N*-methyl-*N*-trimethylsilylmethylformamidine · (MW 200.40)

(conveniently effects the transformation of ketones and aldehydes to homologated nitriles,[1] amines,[2] aldehydes,[2] and ketones[3])

Alternate Name: TMS-Form.

Physical Data: bp 78-80 °C/7 mmHg.

Preparative Methods: easily synthesized by a two-step procedure (eq 1).[2] Initially, the condensation of ***t-Butylamine*** with either ***N,N-Dimethylformamide*** or dimethylformamide dimethyl acetal cleanly affords ***N´-t-Butyl-N,N-dimethylformamidine***. Subsequent lithiation and silylation with ***Chlorotrimethylsilane*** results in a 70% overall yield of the purified title reagent.

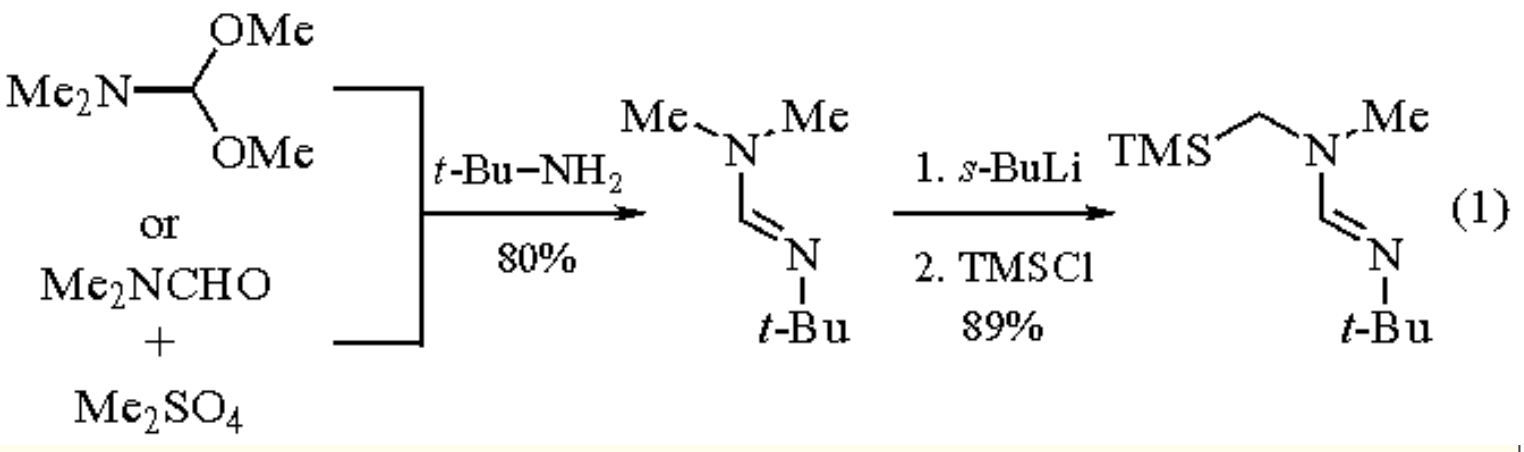

Handling, Storage, and Precautions: the reagent should be handled in a fume hood. Refrigeration should be used for prolonged storage.

Synthetic Utility.

The synthetic utility of TMS-Form has been demonstrated by the one-carbon homologation of a wide variety of ketones and aldehydes. The title compound is deprotonated with ***s-Butyllithium*** and then treated with a ketone to form an enamine by the Peterson alkenation (eq 2). A mixture of geometric isomers usually results; however, subsequent hydrolysis of the formamidine moiety affords a single compound. By varying the conditions under which the formamidine unit is destroyed, the corresponding homologated nitriles,[1] amines,[2] aldehydes,[2] and ketones[3] are obtained.

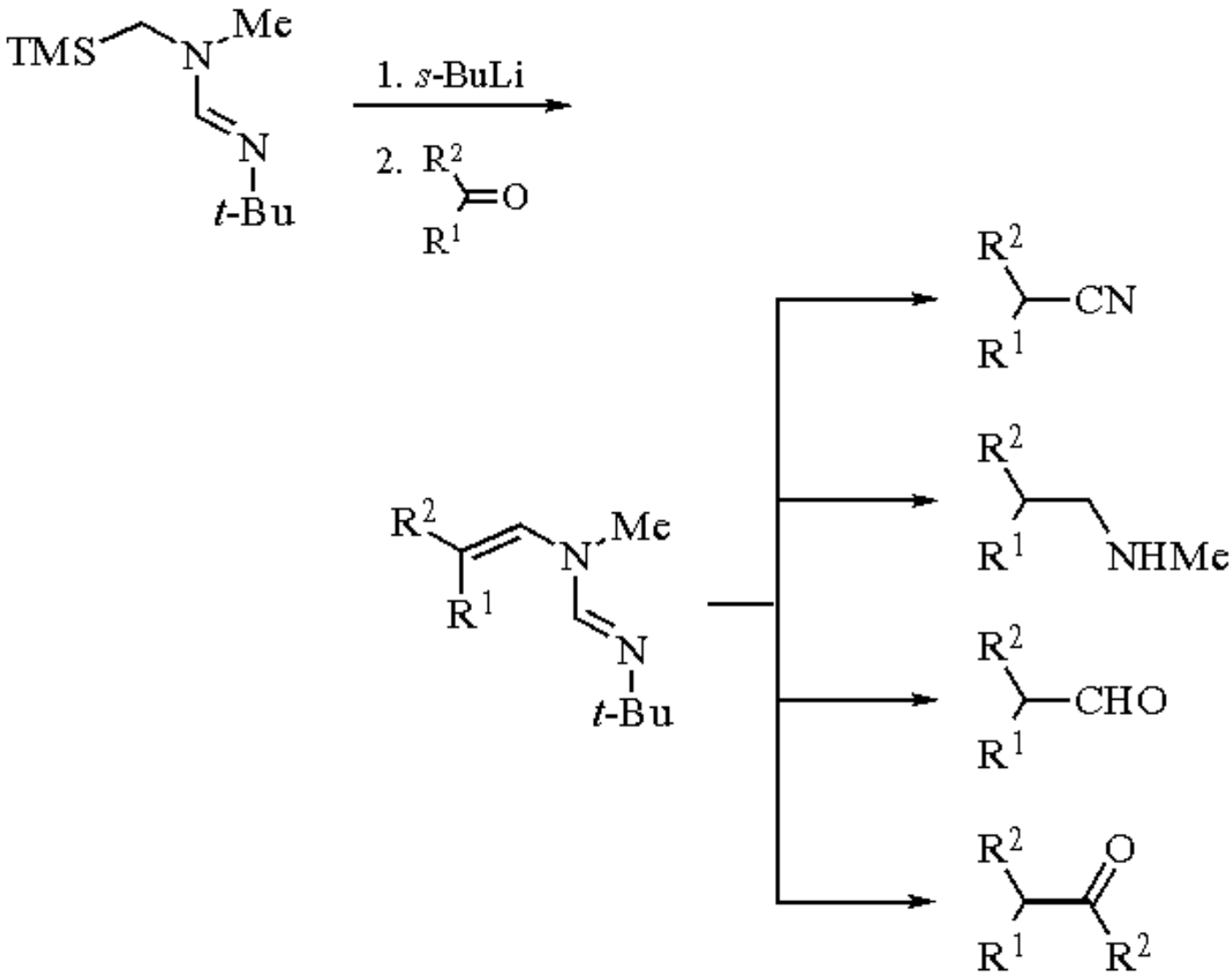

(2)

Homologation Processes.

The title reagent has recently been used for the homologation of ketones and aldehydes to nitriles.[1] The alkene formed from the previously described Peterson alkenation between the carbonyl compound and the anion of the title compound is treated with ***N,N-Dimethylhydrazine*** to form the corresponding hydrazone (eq 3). Quaternization with ***Iodomethane*** followed by methoxide-induced elimination affords the nitrile (65-89%).[1] Moreover, these nitriles can be prepared without purification or isolation of any intermediates. Thus 2-cyclohexen-1-one is transformed to the corresponding homologated nitrile in 66% yield (eq 4).

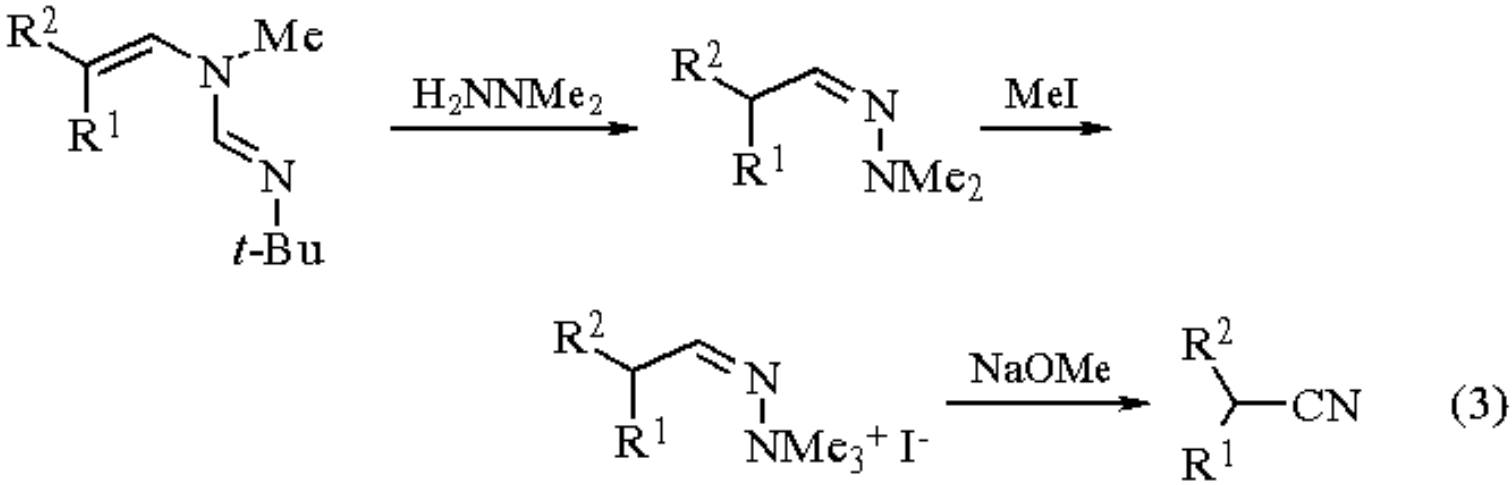

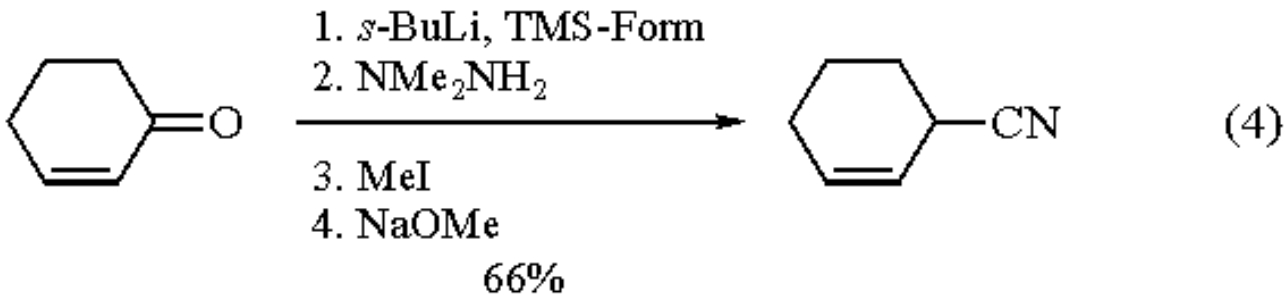

Alternatively, treatment of the intermediate hydrazone with ***Copper(II) Acetate*** easily affords the homologated aldehyde (55-84% from TMS-Form).[2] For example, α-tetralone is converted to the homologated aldehyde in 66% yield (eq 5).

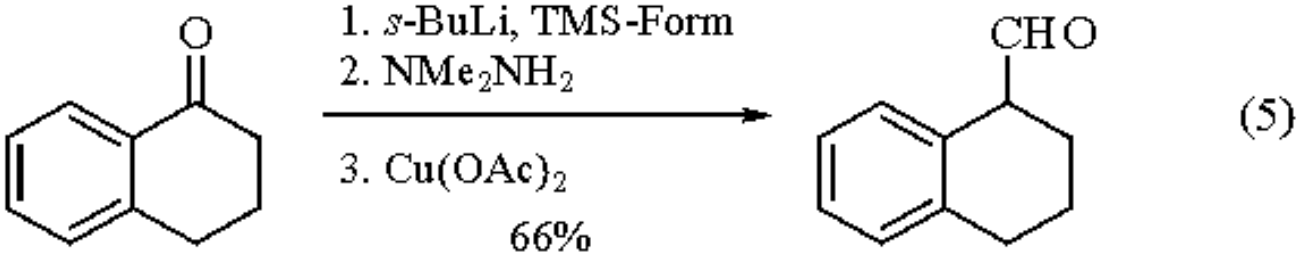

Reduction of the *N*-vinylformamidine with ***Sodium Borohydride*** in acidic media reduces both the imine and the enamine functionalities. The resulting aminal is then hydrolyzed to give the *N*-methylamine (52-70% from TMS-Form). For example, veratraldehyde affords the corresponding homologated *N*-methylamine in 67% yield (eq 6). In addition, homologated *N*-alkylamines are prepared by reaction of the initial *N´-t*-butyl-*N,N*-dimethylformamidine anion with an electrophile and then utilizing this newly prepared compound in the outlined protocol (eq 7).

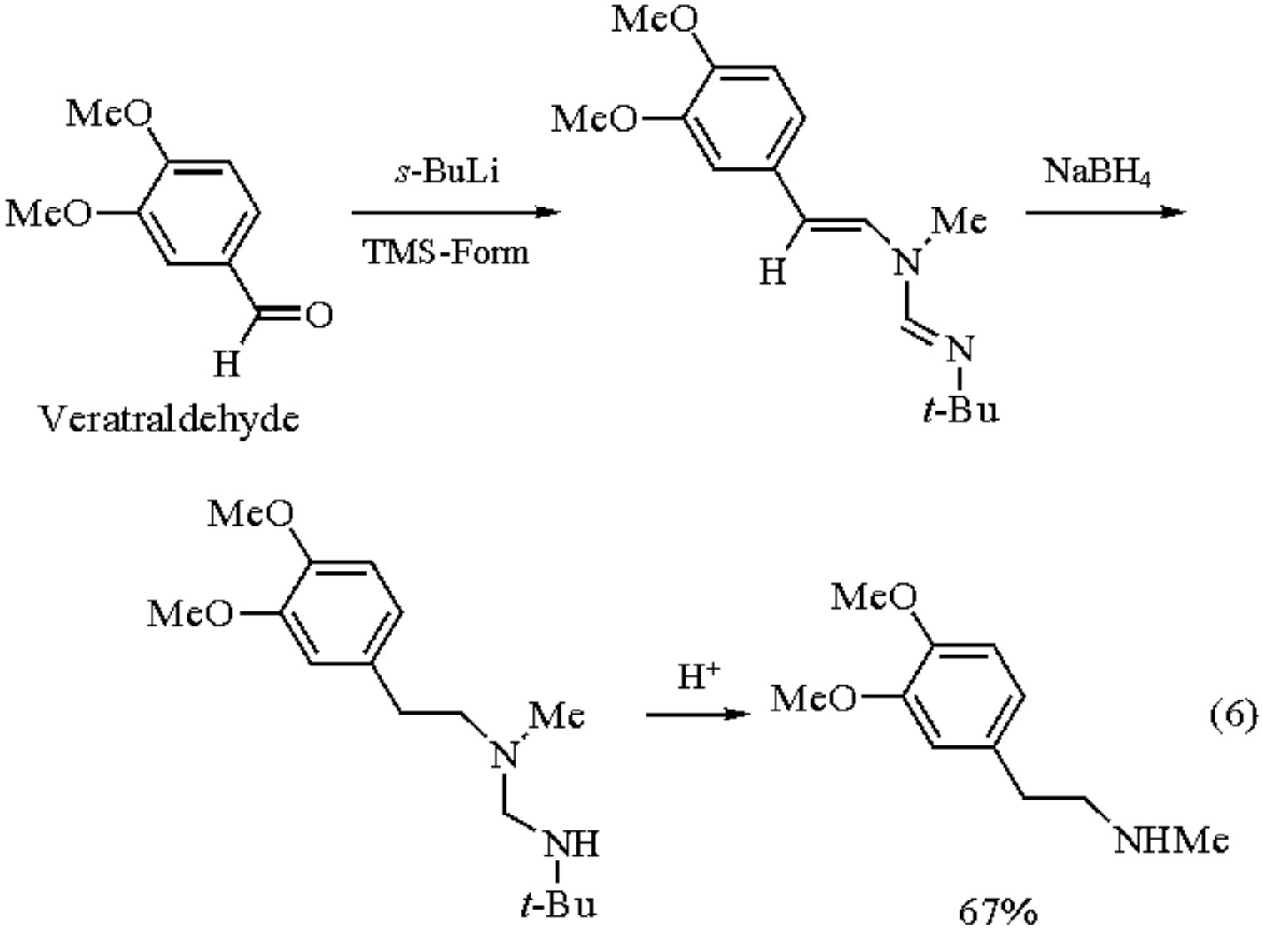

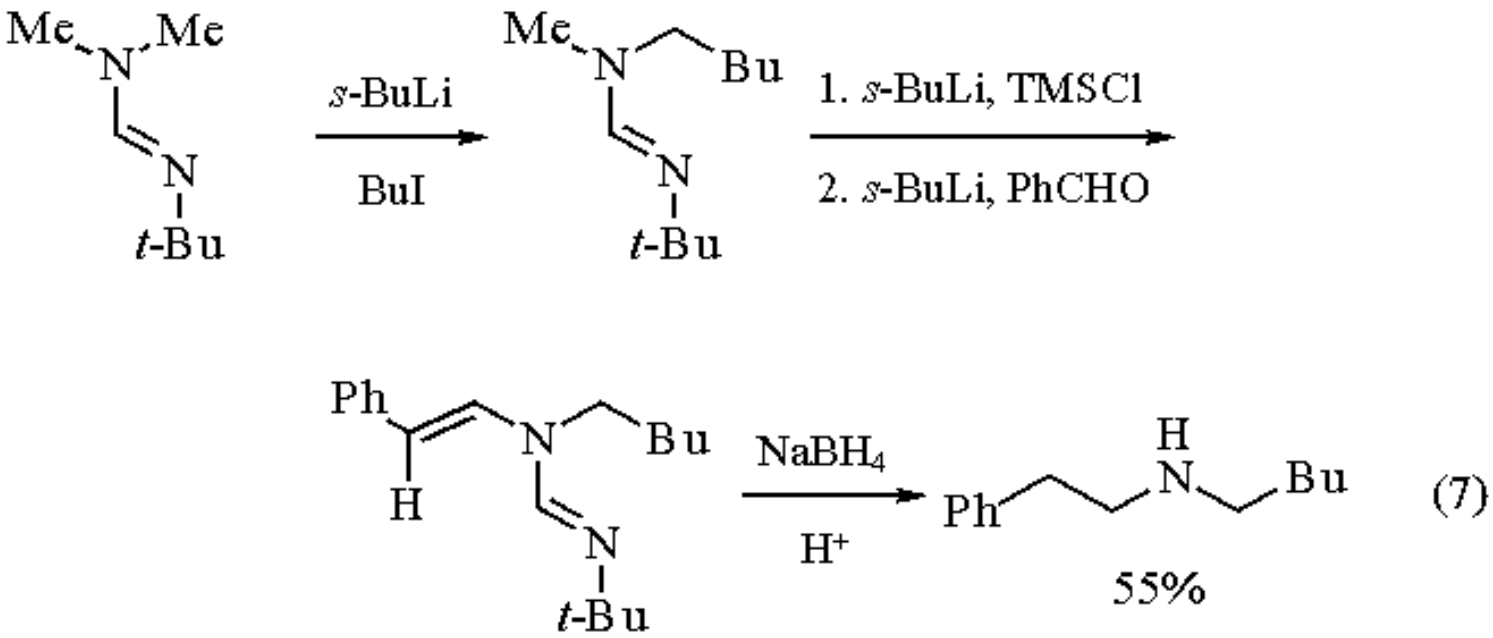

In a similar vein, the analogous *N*-butyl-*N*-(trimethylsilylmethyl)formamidine is converted to an alkene by the standard method (eq 8). Treatment with ***t-Butyllithium*** then forms the α-lithio enamine, which can be alkylated by a host of

electrophiles. Hydrazinolysis of the formamidine furnishes the homologated ketone or aldehyde. Some examples of this homologating nucleophilic acylation method are illustrated in Table 1.[4]

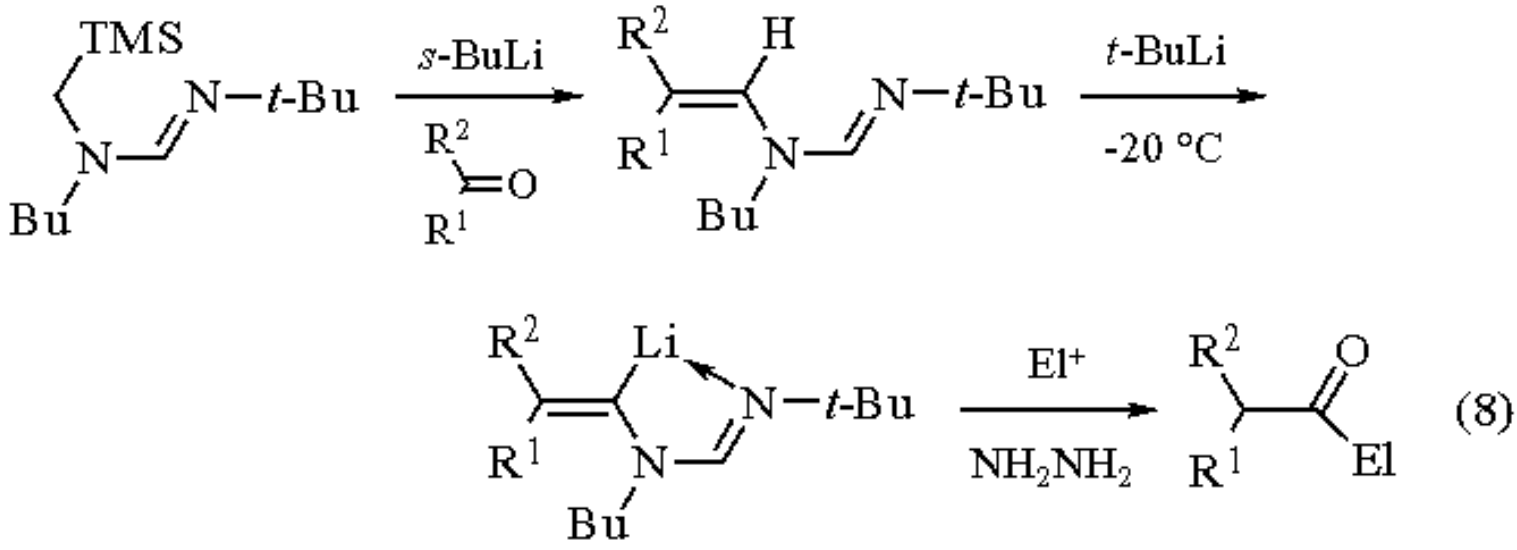

Table 1 Homologation of Carbonyls via Eq 8

Carbonyl	Electrophile	Product	Yield (%)
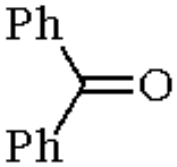	*n*-BuI	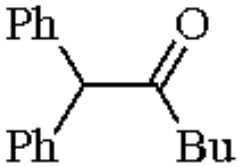	61
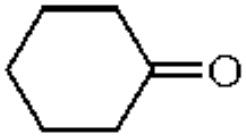	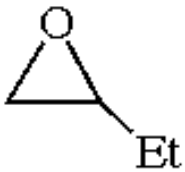	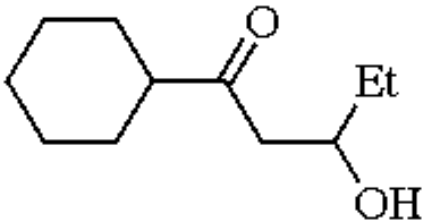	50
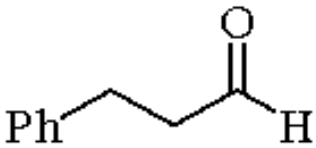	D_2O	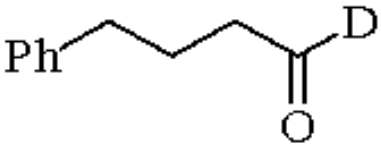	87

Related Reagents.

t-Butylamine; ***N´-t-Butyl-N,N-dimethylformamidine***; ***Chlorotrimethylsilane***; ***Diethyl N-Benzylideneaminomethylphosphonate***; ***Diethyl Isocyanomethylphosphonate***; ***Diethyl Morpholinomethylphosphonate***; ***(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine***; ***p-Tolylsulfonylmethyl Isocyanide***.

1. Santiago, B.; Meyers, A. I. *TL* **1993**, *34*, 5839.
2. Meyers, A. I.; Jagdman, G. E. *JACS* **1982**, *104*, 877.
3. Meyers, A. I.; Edwards, P. D.; Bailey, T. R.; Jagdman, G. E. *JOC*, **1985**, *50*, 1019.
4. Review on homologation of carbonyl compounds: Martin, S. F. *S* **1979**, 633.

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Colorado State University, Fort Collins, CO, USA

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n-Butyl Nitrite

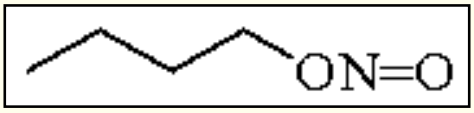

[544-16-1] · $C_4H_9NO_2$ · *n*-Butyl Nitrite · (MW 103.12)

(reagent for nitrosation[1-3,7] and oximation[4])

Physical Data: bp 78 °C; fp -13 °C.

Solubility: sol THF, propanol.

Form Supplied in: commercially available liquid.

Handling, Storage, and Precautions: nitrosation agents should be handled with care since products such as nitrosamines are extremely hazardous.

Ionic and Transition Metal Catalyzed Nitrosation.

n-Butyl nitrite has been widely employed as a nitrosation agent, particularly for the preparation of nitrosamines. Examples include the *N*-dealkylation-*N*-nitrosation of tertiary aromatic amines (eq 1)[1] and the deamination of aziridines (eqs 2 and 3).[2]

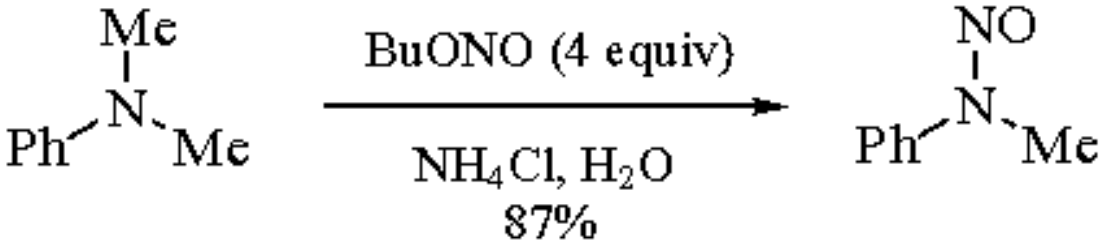

(1)

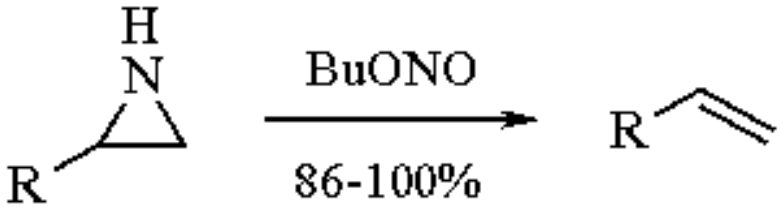

(2)

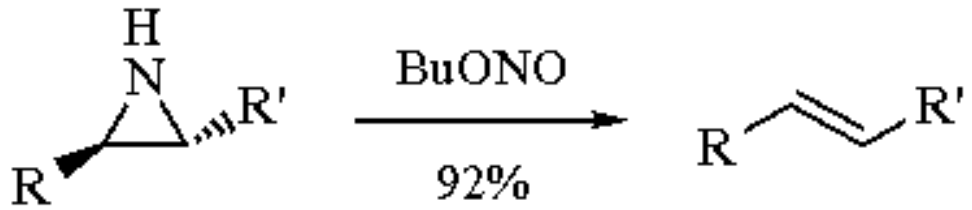

(3)

$R = Me, R' = C_5H_{11}$

In the first sequence (eq 1) little competing nitration of the aromatic ring was observed. The aziridine deamination occurs by a stereospecific loss of N_2O from an intermediate *N*-nitrosoaziridine. The method can be combined with an aziridine preparation to provide a means of interconverting the (*E/Z*) isomers of disubstituted alkenes.

Nitrosation of certain carbon electrophiles using butyl nitrite is also feasible, for example the conversion of sulfonamides into the corresponding α-oxime derivatives (eq 4).[3]

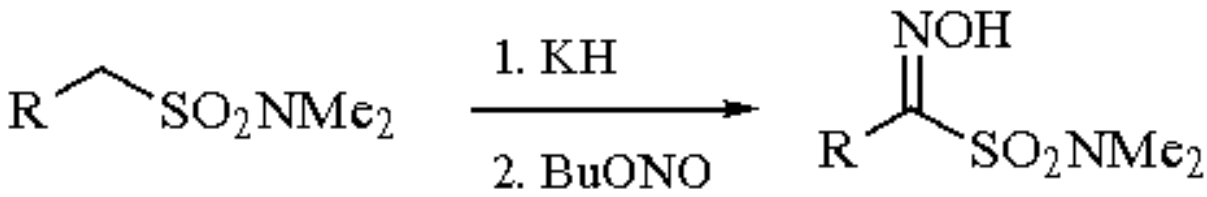

(4)

Transition metal catalyzed introduction of oxime (hydroxyimino) functionality into carbonyl compounds and nitriles may also be achieved starting with the corresponding α,β-unsaturated derivatives (eqs 5-7).[4] This reaction is thought to proceed via reaction of BuONO with an intermediate cobalt enolate, formed by metal catalyzed conjugate reduction of the starting material by the silane.

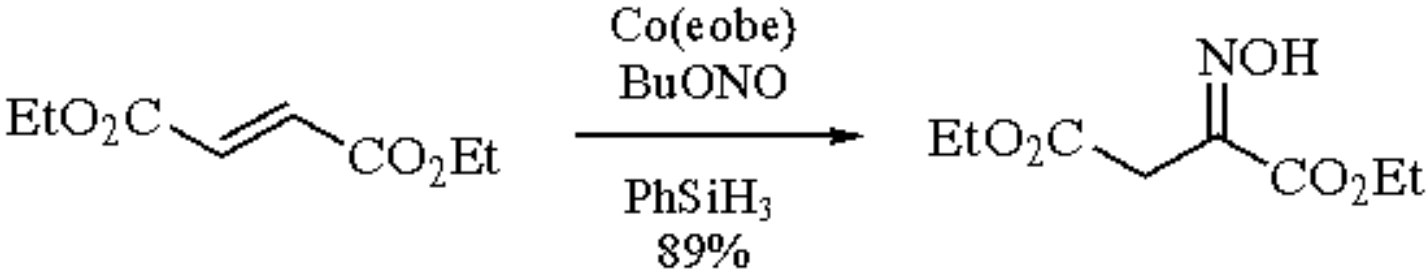

(5)

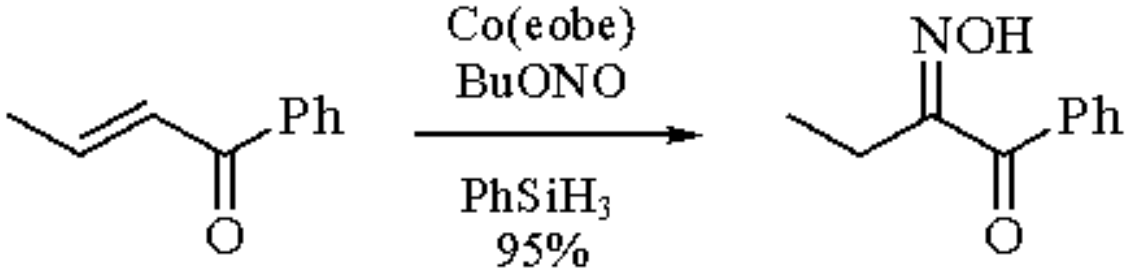

(6)

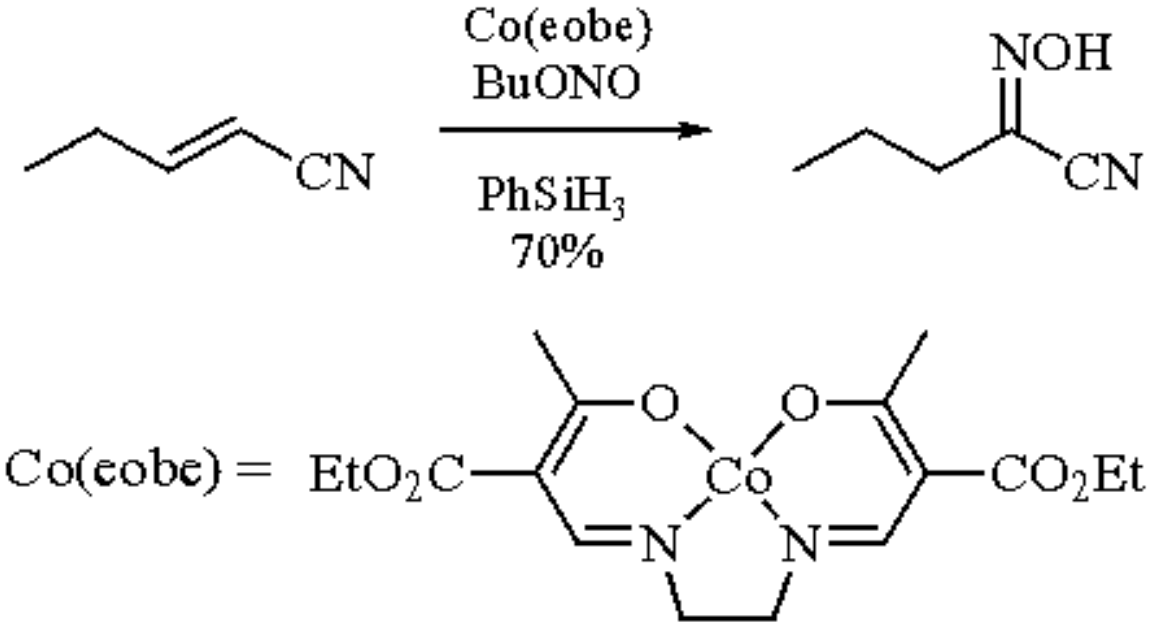

(7)

The same authors have described a related reaction which transforms simple alkenes into the corresponding nitrosoalkane dimers (eq 8)[5] (a radical synthesis of the nitroso alkane dimers is also possible by using *t*-BuONO).[6] This reaction is catalyzed by a number of iron complexes such as ***Tris(acetylacetonato)iron(III)***, and proceeds best when nitrogen monoxide, generated by the decomposition of BuONO, is removed from the reaction mixture by bubbling nitrogen gas.

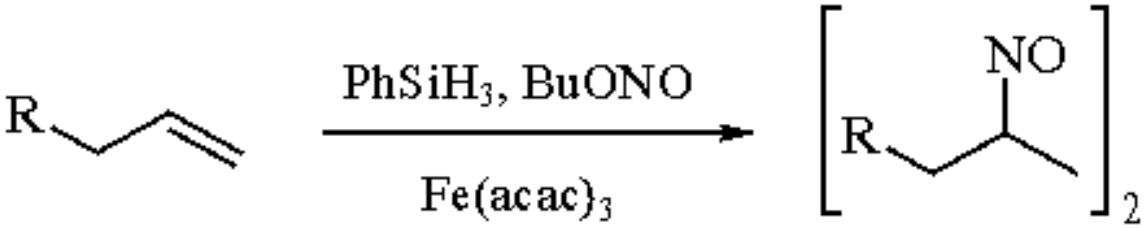

(8)

Other uses for butyl nitrite include the nitrosation of amino acid hydrazines,[7] used in the Rudinger modification for peptide synthesis, and the substitution of BuONO for other reoxidants in certain palladium-catalyzed reactions.[8]

---

1. Verardo, G.; Giumanini, A. G.; Strazzolini, P. *T* **1991**, *47*, 7845.
2. Carlson, R. M.; Lee, S. Y. *TL* **1969**, 4001.
3. Loev, B.; Dowalo, F. *TL* **1969**, 781.
4. Kato, K.; Mukaiyama, T. *BCJ* **1991**, *64*, 2948.
5. Kato, K.; Mukaiyama, T. *CL* **1992**, 1137.
6. Mackor, A.; De Boer, Th. J. *RTC* **1970**, *89*, 151.
7. (a) Hofmann, K.; Haas, W.; Smithers, M. J.; Wells, R. D.; Wolman, Y.; Yanaihara, N.; Zanetti, G. *JACS* **1965**, *87*, 620. (b) Honzl, J.; Rudinger, J. *CCC* **1961**, *26*, 2333.
8. Bréchot, P.; Chauvin, Y.; Commereuc, D.; Saussine, L. *OM* **1990**, *9*, 26.

t-Butyl (*E*)-3-Oxo-4-hexenoate

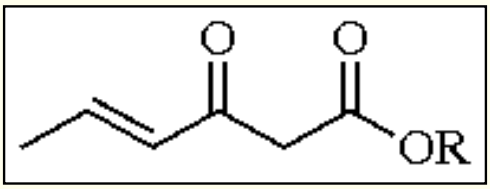

(**1**; R = *t*-Bu)

[132117-94-3] · $C_{10}H_{16}O_3$ · *t*-Butyl (*E*)-3-Oxo-4-hexenoate · (MW 184.23) (**2**; R = Et)

[25654-09-5] · $C_8H_{12}O_3$ · Ethyl (*E*)-3-Oxo-4-hexenoate · (MW 156.18) (**3**; R = Me)

[37734-08-0] · $C_7H_{10}O_3$ · Methyl (*E*)-3-Oxo-4-hexenoate · (MW 142.15)

(for base-catalyzed cycloaddition;[1] β-keto ester with additional enone reactivity for trapping intermediates)

Alternate Name: Nazarov reagent.

Physical Data: bp (**2**) 101 °C/15 mmHg; (**3**) 95 °C/14 mmHg.

Preparative Methods: the *t*-butyl ester has been prepared by reacting the Reformatsky reagent derived from *t*-butyl bromoacetate with (*E*)-***Crotonaldehyde***, followed by oxidation with ***Manganese Dioxide*** to afford the desired *t*-butyl (*E*)-3-oxo-4-hexenoate (**1**) in 55% overall yield.[1] In a similar way, the reaction of the lithium enolate of ethyl acetate with (*E*)-crotonaldehyde followed by Jones oxidation gave, after isolation by Kügelrohr distillation, a 50% overall yield of the ethyl ester.[2] This synthesis is amenable to scale-up and has been submitted to *Organic Syntheses*.[3] The enol content for this compound is 40% when neat and 60% in a CCl_4 solution. Mention should be made of the reported quantitative yield of the ethyl ester by reaction of the lithium enolate of ethyl acetate with (*E*)-crotonyl chloride.[4]

Handling, Storage, and Precautions: use in a fume hood.

Base-Catalyzed Cycloaddition.

These γ,δ-unsaturated β-keto esters are known as Nazarov reagents since they undergo Michael addition with enolizable ketones followed by an aldol condensation, accomplishing Robinson annulation. No example using the reagent (**1**) (or other esters) for this specific six-membered ring formation has been found in the literature. A very closely related transformation by base-catalyzed cycloaddition (or double Michael addition) of (**1**) with ***Methyl 6-Oxo-1-cyclohexenecarboxylate*** gave the corresponding *cis*-decalin, the *t*-butyl ester being selectively cleaved by acid with

concomitant decarboxylation (eq 1). High stereoselectivity in favor of the *exo* adduct is achieved using a nonpolar solvent. Several substituted 6-oxo-1-cyclohexenecarboxylates react similarly.[1] This methodology was applied to the synthesis of optically active 14β-hydroxy steroids.[5]

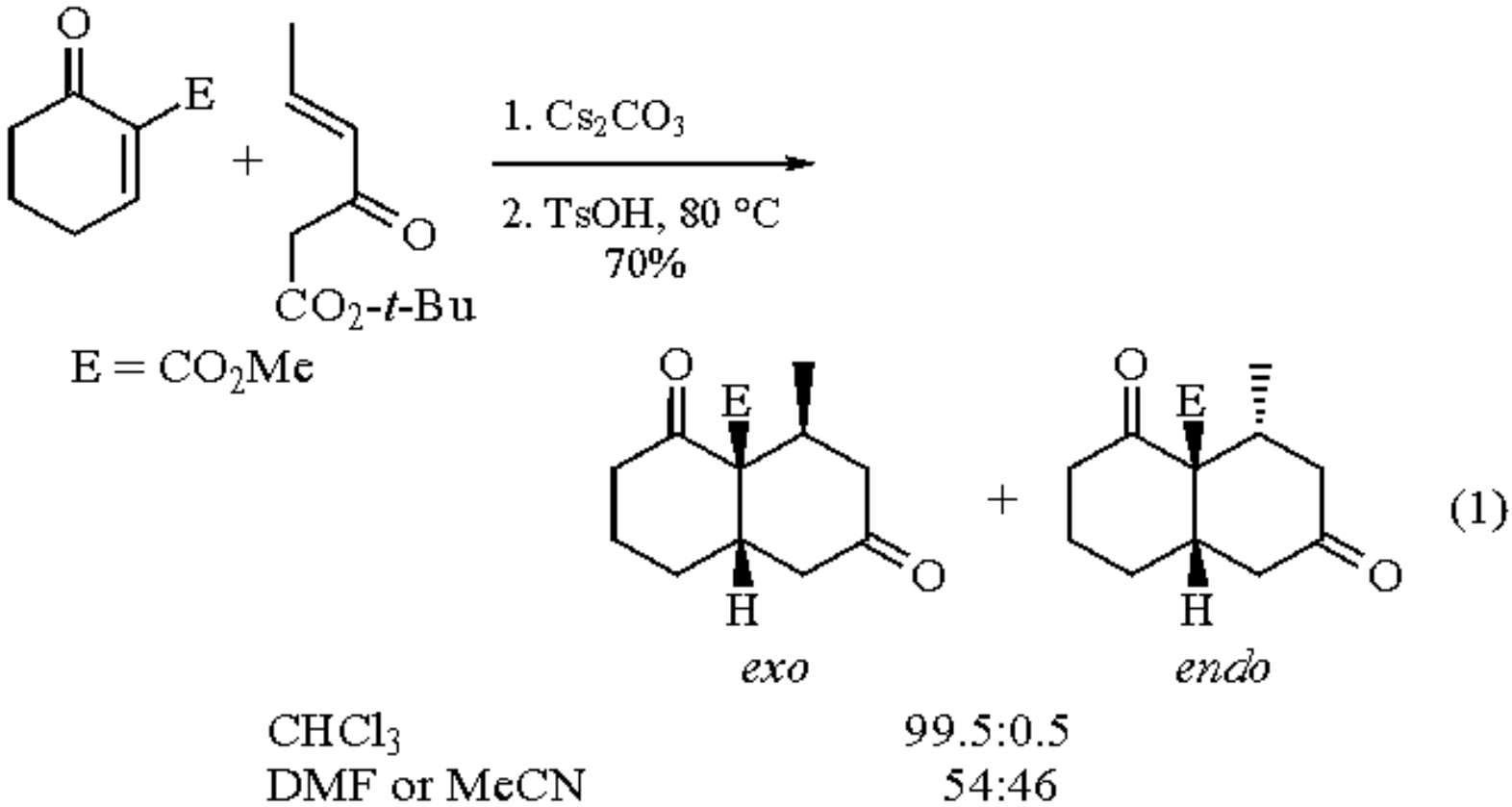

Pyranones.

3-(1-Oxo-2-propenyl)coumarins (benzopyran-2-ones) are easily prepared in one step by cyclocondensation of (**2**) with 2-hydroxybenzaldehyde, affording a divinyl ketone (eq 2)[6] susceptible to undergo double Michael addition and to be a good substrate for the Nazarov cyclization.[6] As a potential source of 3,5-bis(alkenyl)pyrazoles, 2,3-dihydropyran-4-ones were prepared by condensation of the ethoxymagnesio enolate of (**2**) with cinnamoyl or sorbitoyl chloride (eq 3).[7] After acylation, the enolic hydroxy group originating from the acyl chloride adds exclusively to the double bond. With (*E*)-3-chloroacryloyl chloride it is the enolic hydroxy group originating from the β-keto ester which undergoes conjugate addition, giving the 4*H*-pyran-4-one (eq 4).[8]

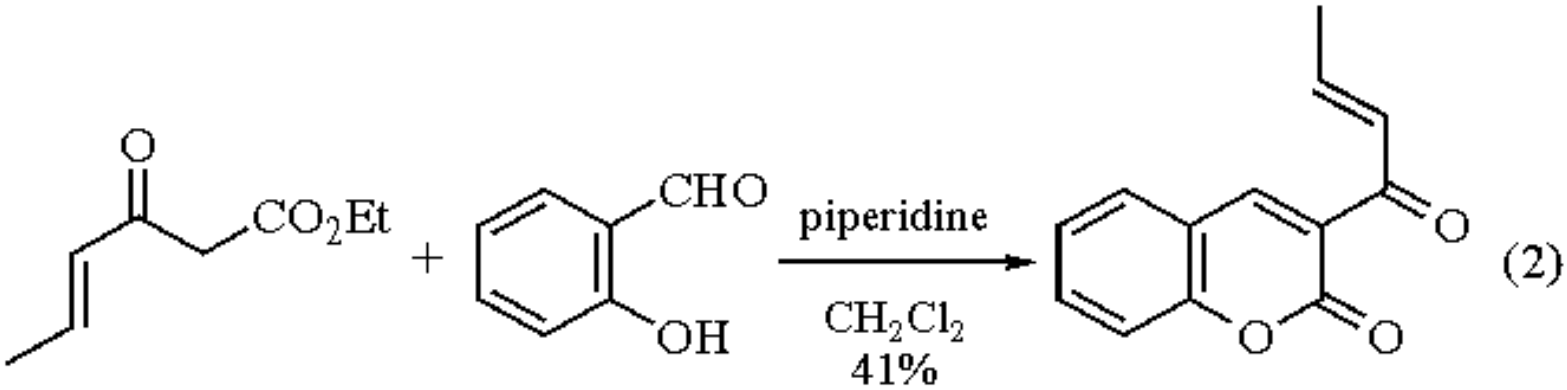

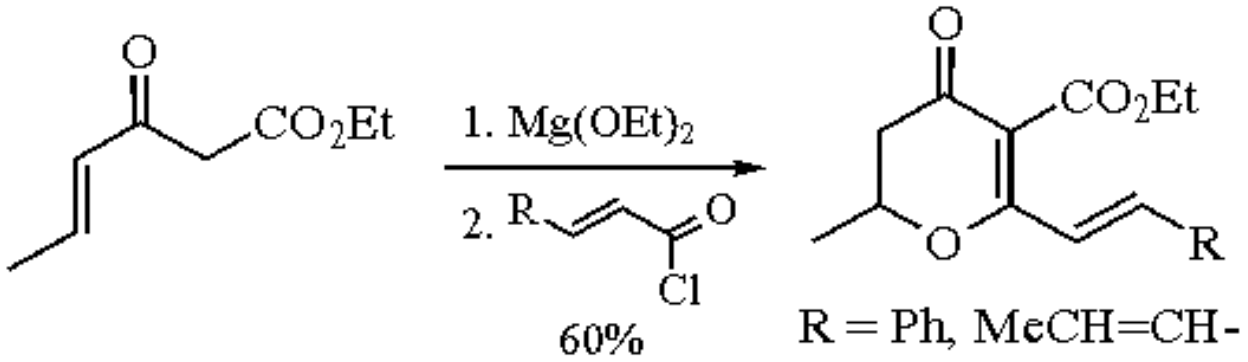

(3)

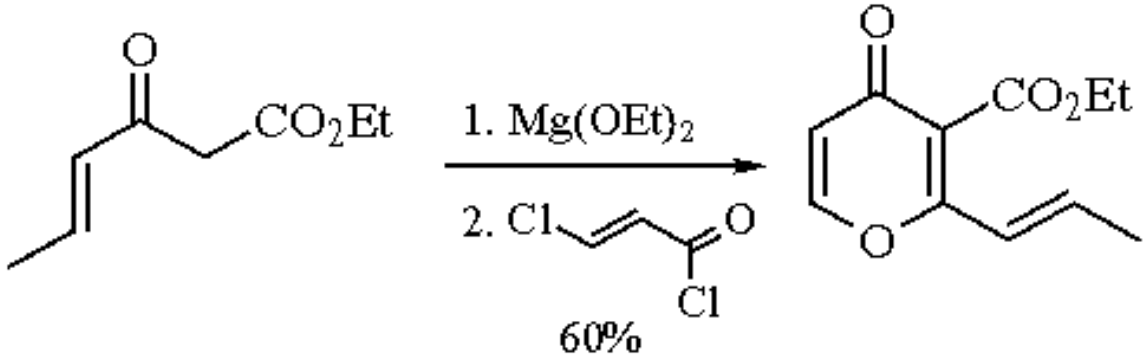

(4)

Other Heterocyclic Compounds.

In the pyranone synthesis (eqs 3 and 4) this reagent reacts like other β-keto esters, with the added advantage of having an enone for further reaction. This aspect was exploited in the synthesis of 1,4,5,6-tetrahydropyridazin-4-ones. Thus the reaction of (**2**) with a diazonium salt affords the α-hydrazone, which cyclized on heating (eq 5).[9] Also, condensation of (**2**) with dimethylformamide dimethyl acetal affords the enamine in almost quantitative yield. When treated with ***Phenylhydrazine*** in acetic acid, the pyrazole is obtained, while using DME instead of acetic acid resulted in the formation of the 1,4,5,6-tetrahydro-3-pyridinecarboxylate (eq 6).[10]

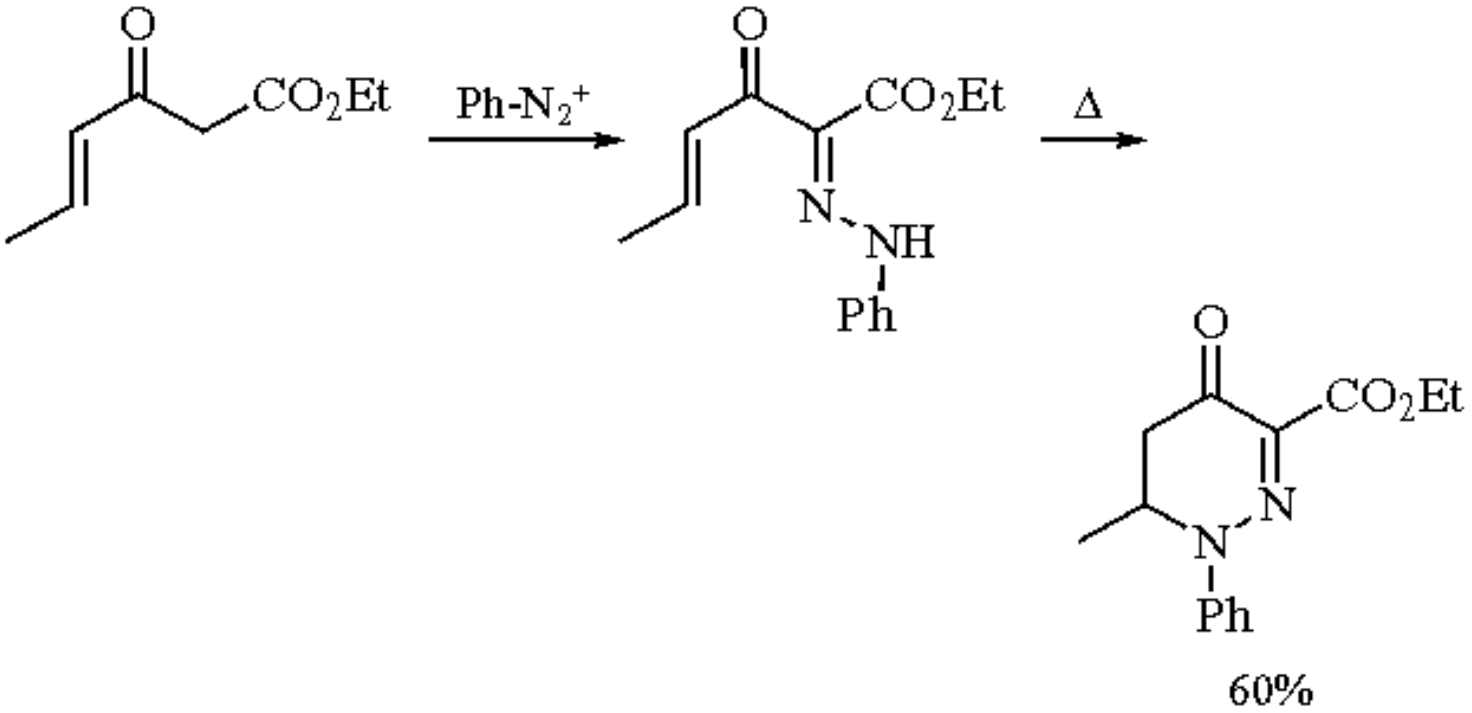

(5)

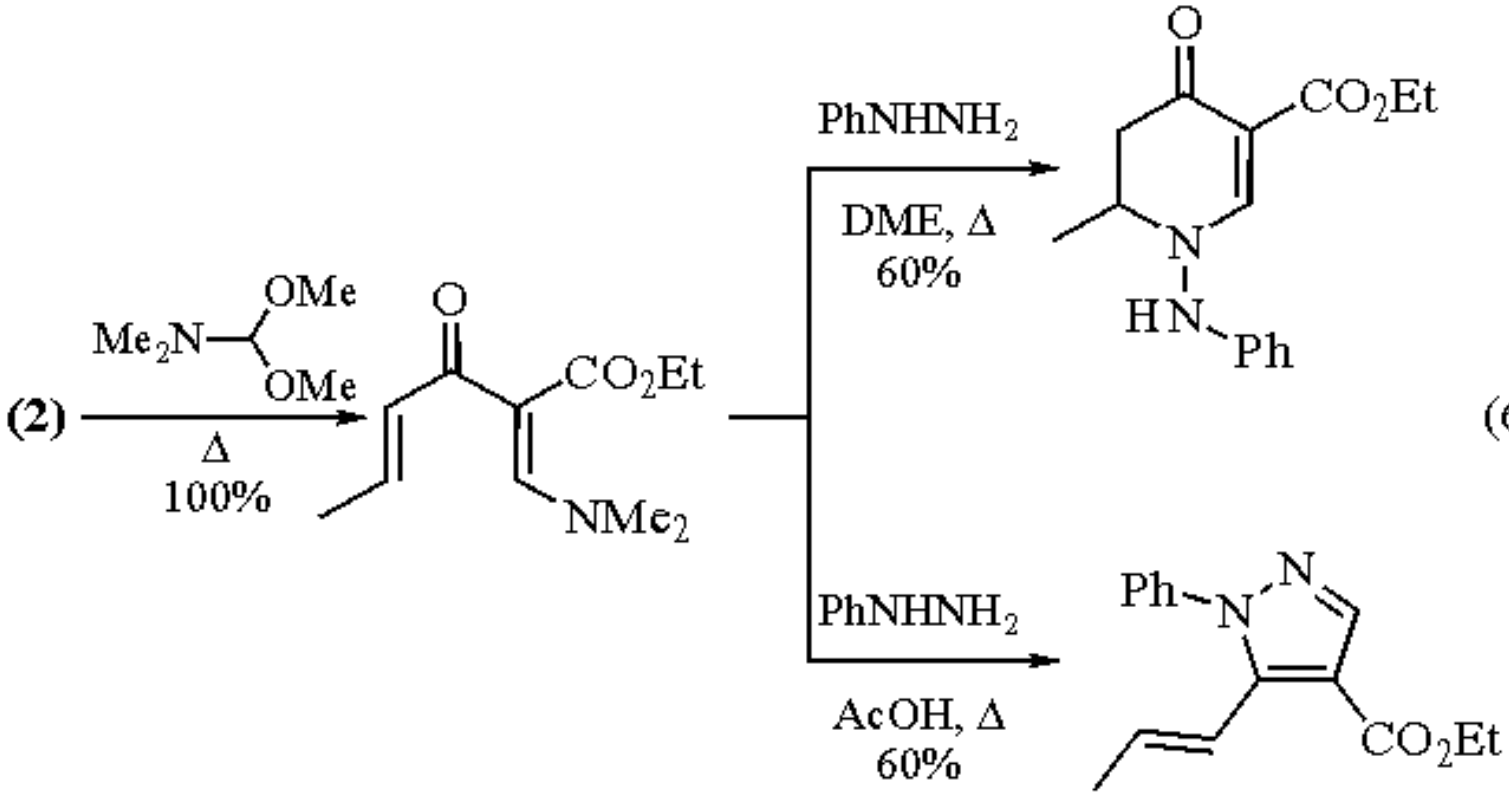

(6)

Related Reagents.

Ethyl 2-Methyl-4-oxo-2-cyclohexene-1-carboxylate; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***Methyl Dilithioacetoacetate***; ***Methyl 5-Methoxy-3-oxopentanoate***; ***Methyl 6-Oxo-1-cyclohexenecarboxylate***; ***Methyl 3-Oxo-4-pentenoate***; ***Methyl Vinyl Ketone***; ***trans-3-Penten-2-one***.

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t-Butyltetramethylguanidine

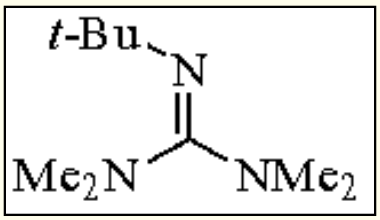

[88248-68-4] · $C_9H_{21}N_3$ · *t*-Butyltetramethylguanidine · (MW 171.29)

(strong base for formation of aziridines, alkylation, nitronation)

Physical Data: bp 80-82 °C/20 mmHg.

Form Supplied in: colorless liquid.

Preparative Method: prepared via reaction of ***t-Butylamine*** with the highly hygroscopic Vilsmeier salt obtained by reaction of *N,N,N´,N´*-tetramethylurea and ***Phosgene***.[1-3]

t-Butyltetramethylguanidine (**1**) is one of a range of hindered pentaalkylguanidines prepared by Barton for use as strong bases, and has been used in aziridine formation in a series of cholesterol derivatives (such as the conversion of (**2**) to (**3**), eq 1).[4]

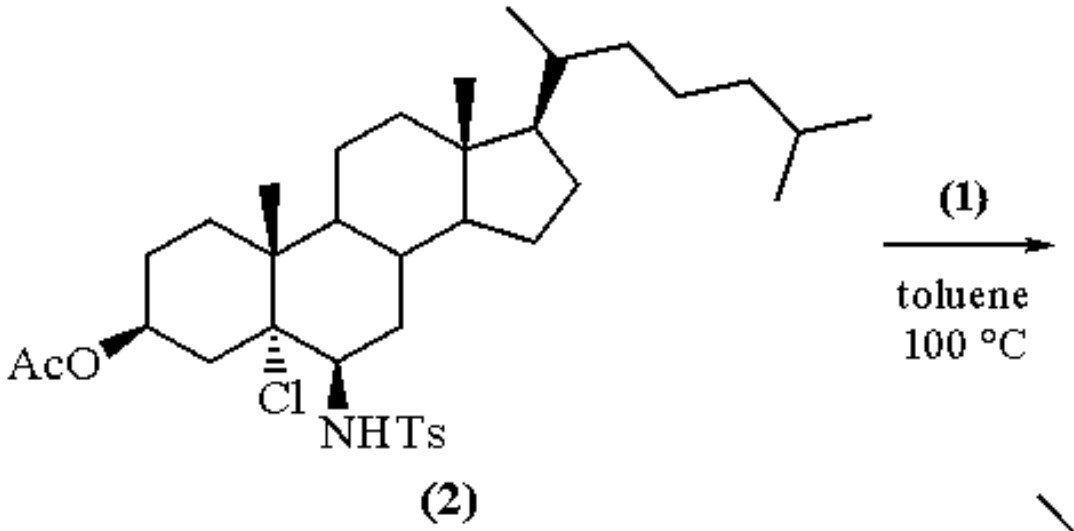

(2)

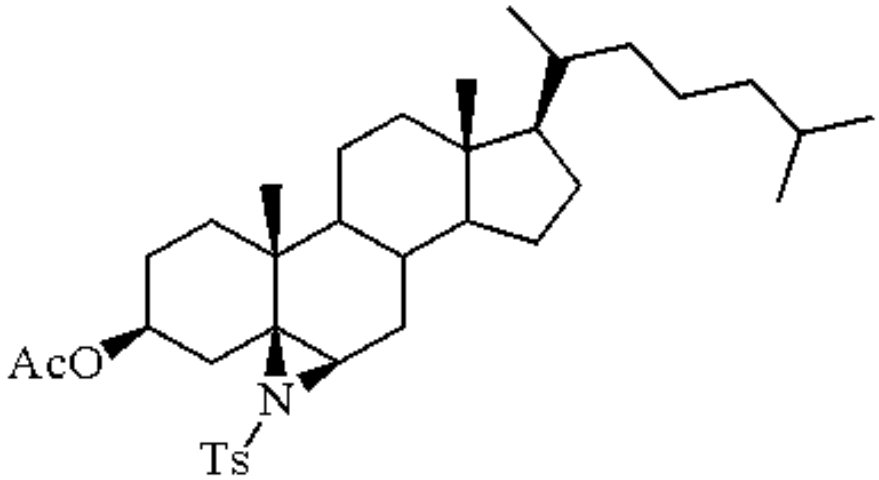

(1)

(3)

The reagent is particularly useful in the preparation of esters of sterically compromised acids via the alkylation of their carboxylate salts (eqs 2 and 3). Thus the extremely hindered carboxyl group of hederagenin is converted efficiently to its methyl ester (**4**).[3] Keto acid (**5**) is esterified in similarly productive fashion.[5]

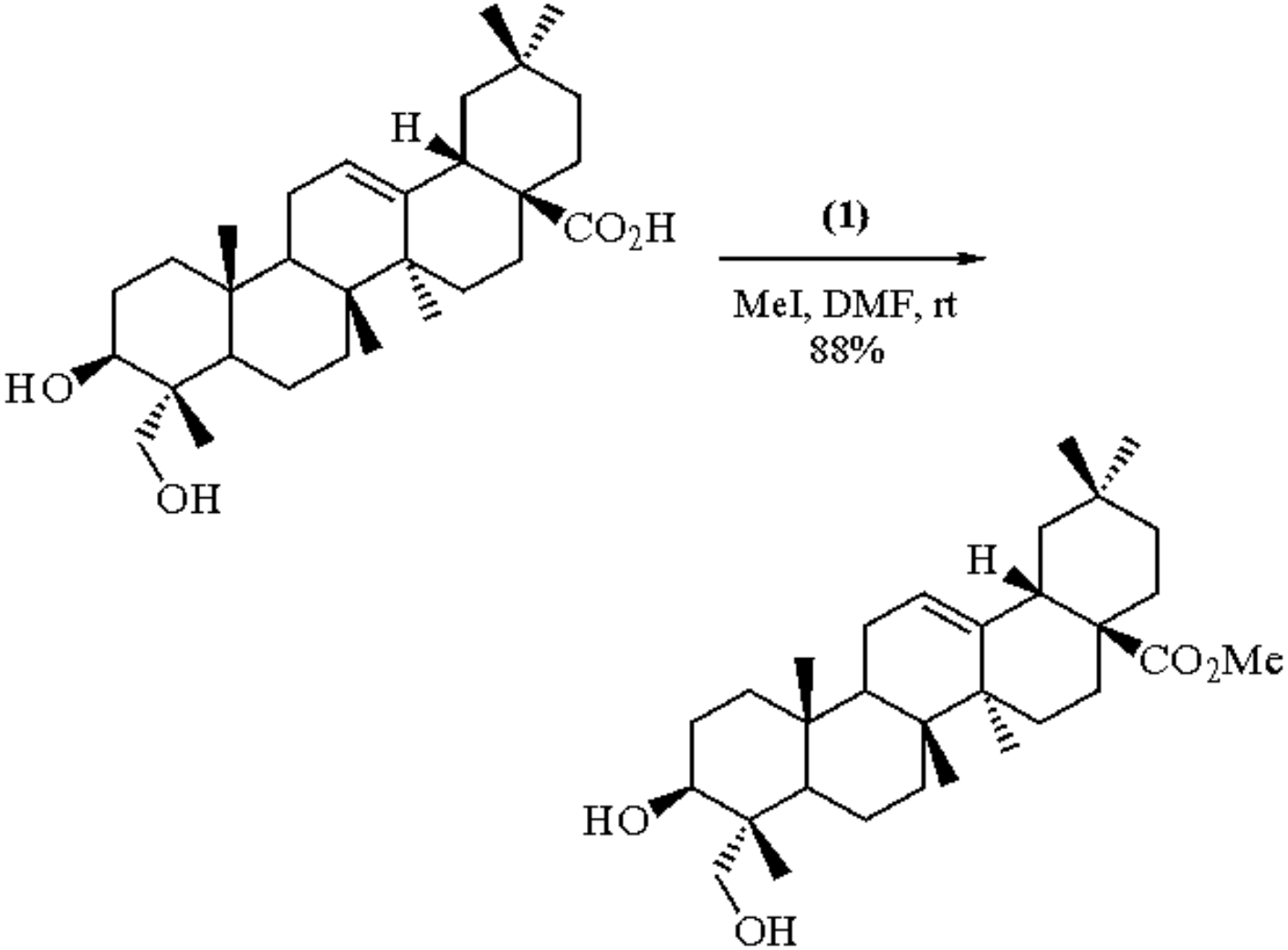

(2)

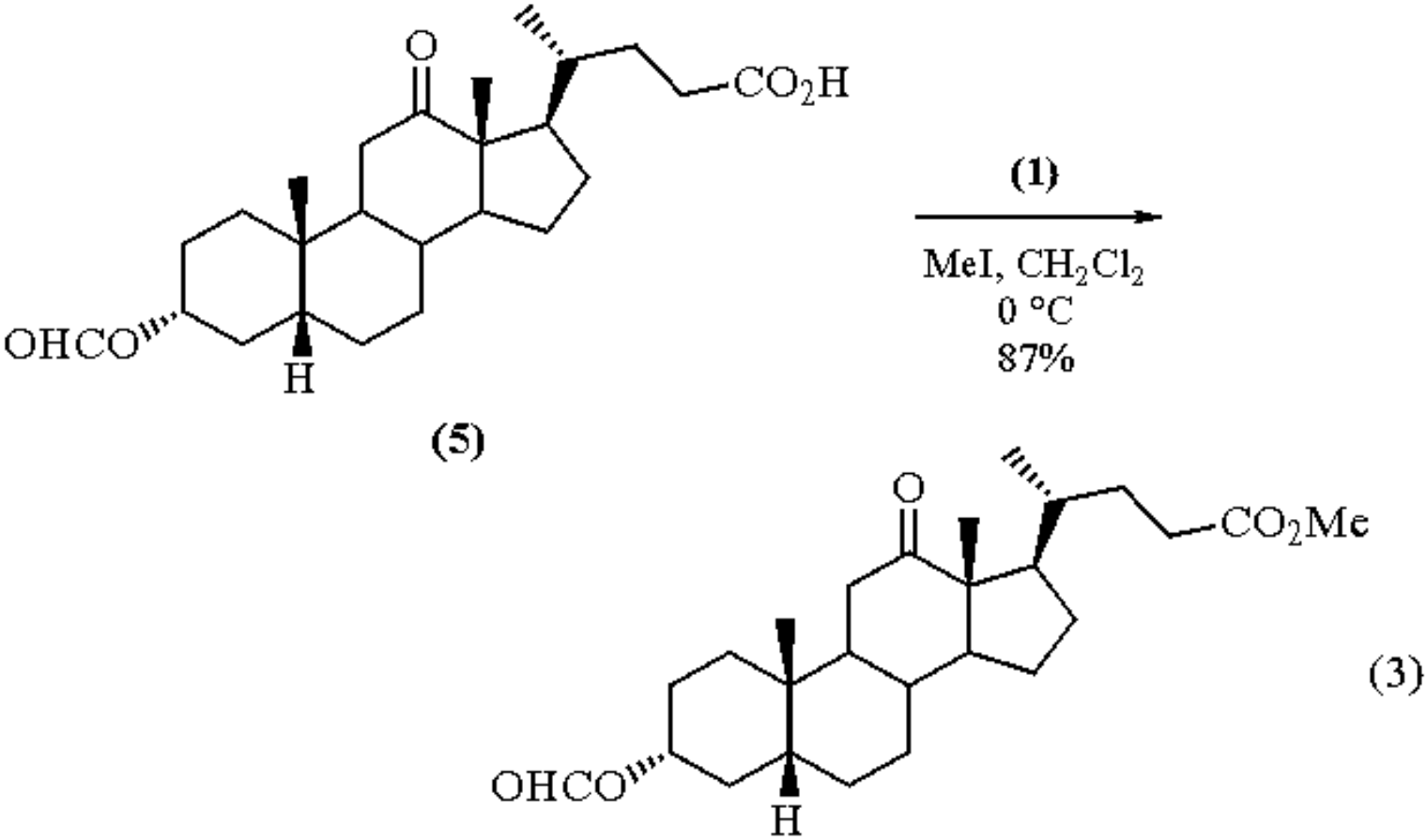

The reagent successfully effects monoalkylation of β-keto esters (eq 4). No *O*-methylation is observed in this reaction.[3]

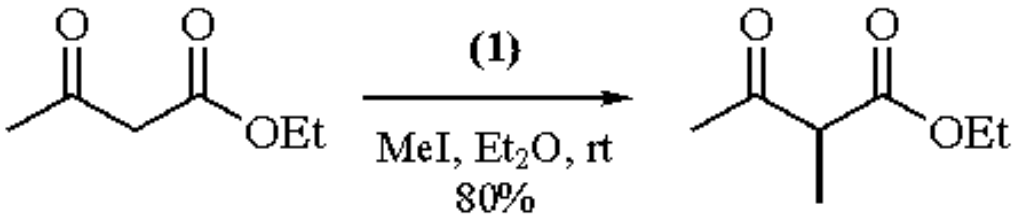

(4)

The conjugate addition of nitronate anions to oxidized naphthalenes such as (**6**) occurs smoothly in the presence of (**1**) (eq 5);[6] use of ***Triethylamine*** led to substantial decomposition of starting materials.

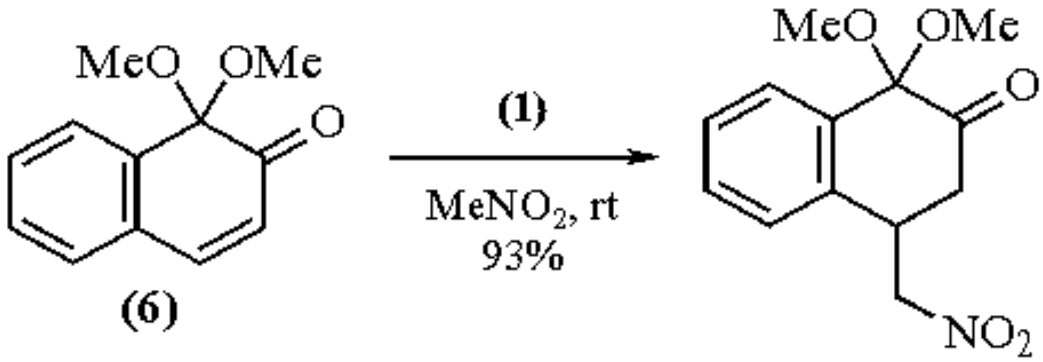

(5)

The reagent also proves significantly superior to triethylamine in the conversion of hydrazones to vinyl iodides (eq 6).[7]

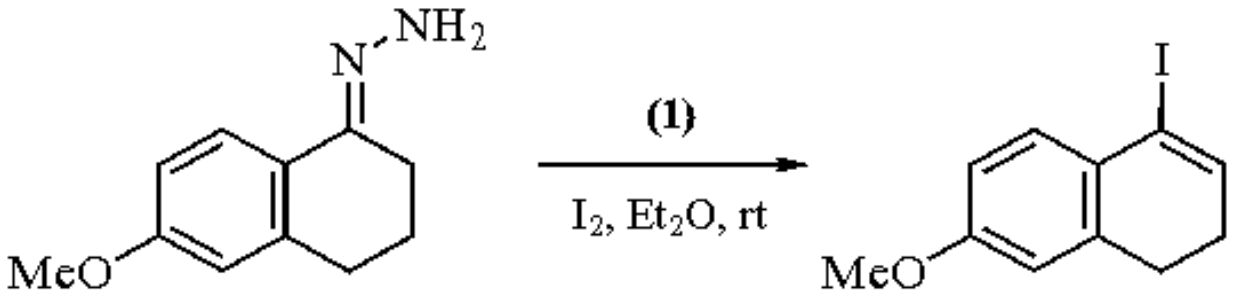

(6)

The above reaction was examined using a variety of bases (eq 7); use of (**1**) gave best overall yields of iodide (**7**) and also minimized formation of azine byproduct (**8**) (Table 1).[8]

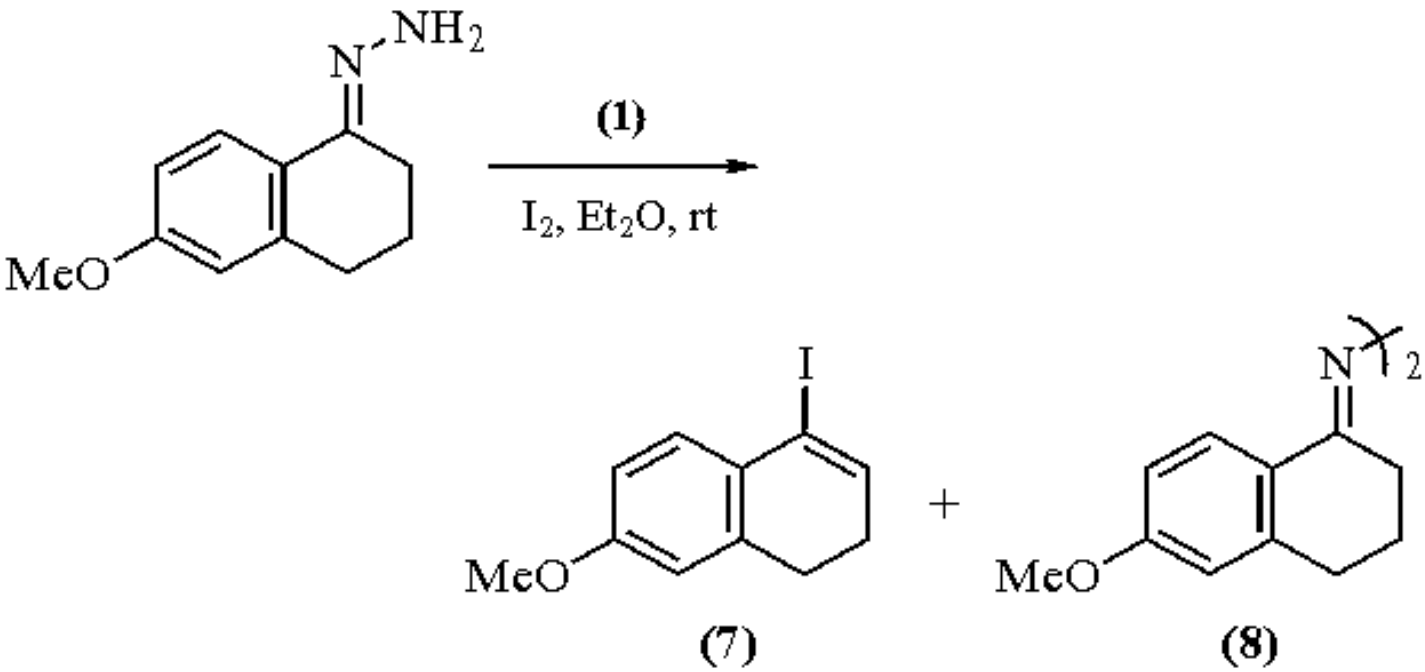

(7)

Table 1 Preparation of Vinyl Iodides from Hydrazones (eq 7)

Base	Yield of vinyl iodide (**7**) (%)	Yield of azine (**8**) (%)
DBN	55	8
Piperidine	35	18
N-Methylmorpholine	30	25
Butylamine	35	20
Triethylamine	38	20
(**1**)	70	15

In the reaction of camphor-derived hydrazones, the use of (**1**) was essential to prevent rearrangement (eqs 8 and 9).[8] When triethylamine was employed in place of (**1**), rearranged allylic iodide (**9**) became the major product.

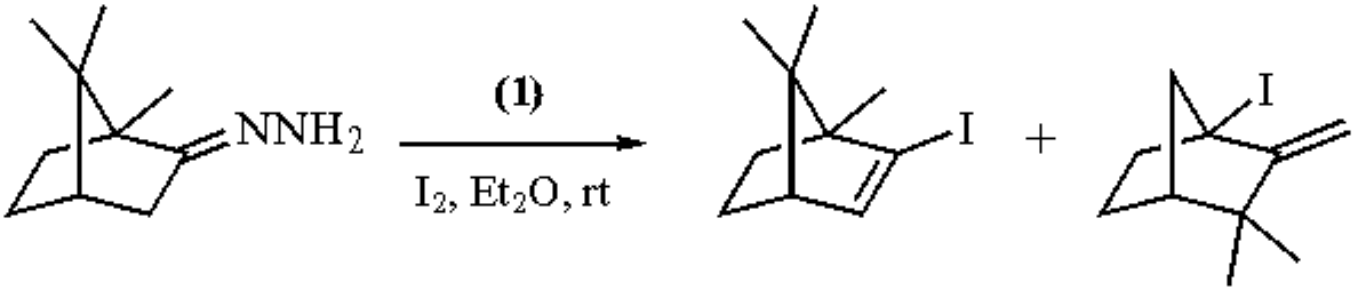

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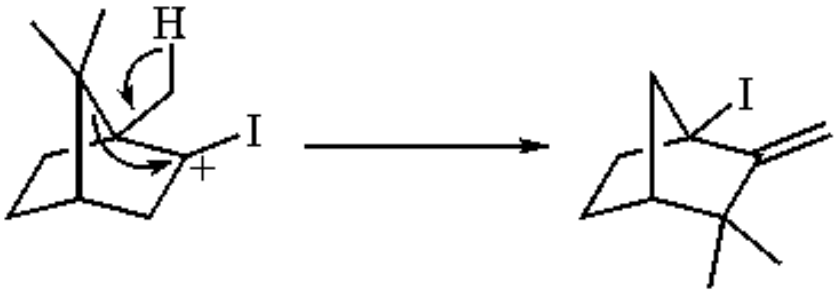

(9)

(9)

The use of (**1**) in the arylation of 2-naphthol using tetraphenylbismuth esters completely suppresses the *O*-arylation, which is otherwise a troublesome side reaction (eq 10).[9]

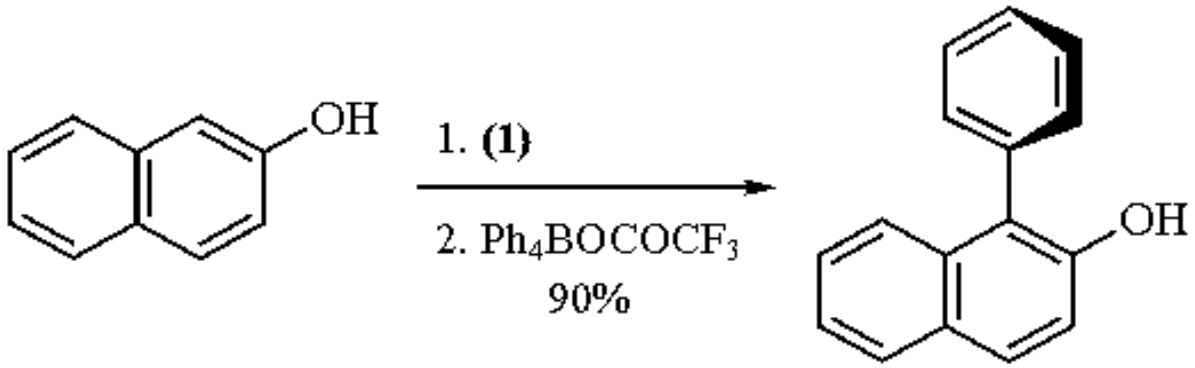

(10)

In the reduction of nitro compounds to oximes, the exceptional basicity of (**1**) is problematic (eq 11); for instance, the desired oxime (**10**) is obtained as the minor product (23%) and the major product is the nitrile (**11**), the product of over reaction.[10]

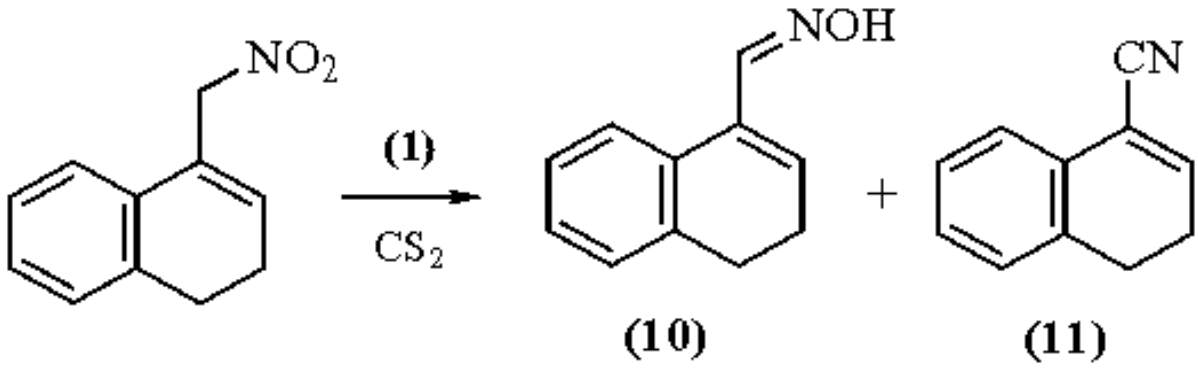

(11)

The reagent participates in a mild Nef reaction in the presence of ***Diphenyl Disulfide*** and a secondary nitroalkane such as (**12**) (eq 12).[11]

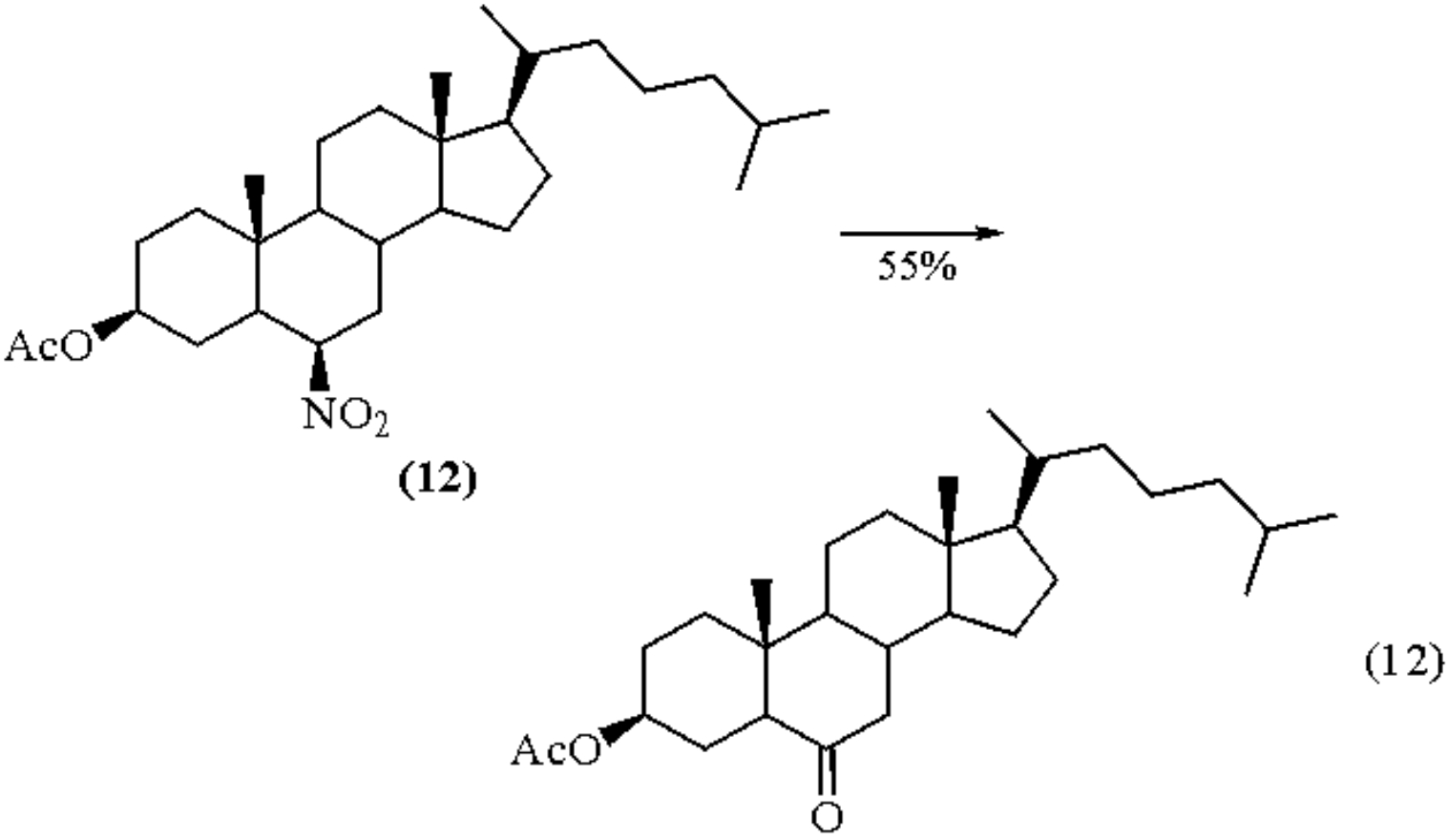

Nitroalkanes are again the substrates for the tetraalkylguanidine-mediated synthesis of trisubstituted pyrroles (**13**) invented by Barton et al (eq 13). The reagent gives better yields in a shorter reaction time than with ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.[12]

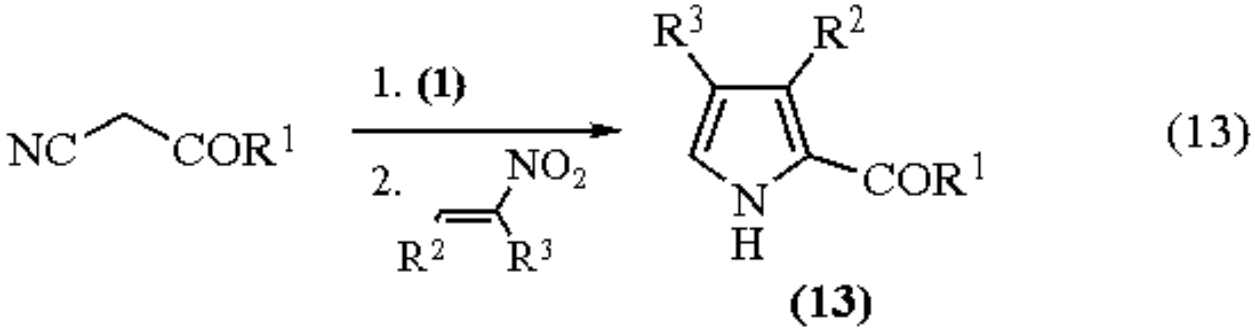

The salt (**14**) obtained from the reaction of (**1**) and *m*-iodoxybenzoic acid oxidizes nitronate anions at rt to give the corresponding carbonyl compounds (eq 14). Once again, DBU gives comparable results but the yields of the reaction are lower.[13] Salt (**14**) is also able to cleave glycols under extremely mild conditions.[14]

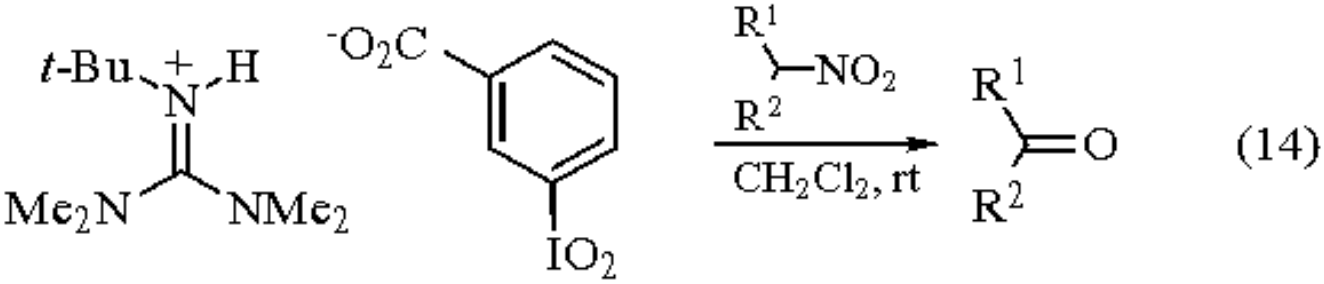

(14)

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1-*t*-Butylthio-1-*t*-butyldimethylsilyloxypropene[1]

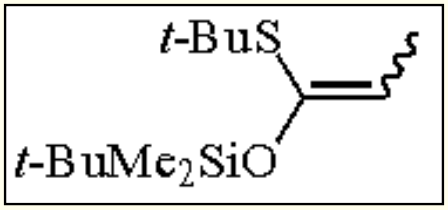

[102146-11-2] · $C_{13}H_{28}OSSi$ · 1-*t*-Butylthio-1-*t*-butyldimethylsilyloxypropene · (MW 260.51) (*E*)

[97250-84-5] (*Z*)

[97250-83-4]

(excellent reagent for Lewis acid-mediated aldol-type[2-9] and Michael additions,[17-21] under either stoichiometric or catalytic conditions)

Physical Data: colorless liquid.

Solubility: sol *n*-pentane, diethyl ether, dichloromethane, etc.

Analysis of Reagent Purity: (NMR) ^{1}H 0.15 (s, 6H), 0.95 (s, 9H), 1.30 (s, 9H), 1.65 (d, 3H, *J* = 6.7 Hz), 5.22 (q, 1H, *J* = 6.7 Hz) ppm (*Z* isomer). ^{1}H 0.18 (s, 6H), 0.95 (s, 9H), 1.30 (s, 9H), 1.60 (d, 3H, *J* = 6.8 Hz), 5.22 (q, 1H, *J* = 6.8 Hz) ppm (*E* isomer).

Preparative Methods: obtained by reaction of *t*-butyl thiopropionate with ***Lithium Diisopropylamide*** in THF and subsequent trapping with ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** (95% *Z* isomer),[2] or with LDA in THF/HMPT and subsequent trapping with ***t-Butyldimethylchlorosilane*** (95% *E* isomer).[2]

Handling, Storage, and Precautions: the reagent should be stored in the absence of moisture at -15 °C.

Enantioselective Aldol Additions.[1]

The reagent undergoes Lewis acid-catalyzed Mukaiyama-type additions to aldehydes to give *syn* α-methyl-β-hydroxy thioesters with good yields and remarkable enantioselectivities (eq 1).[3a-d] Slow addition of the aldehyde (3-4.5 h) in propionitrile is necessary for high enantioselectivity.[3b-d]

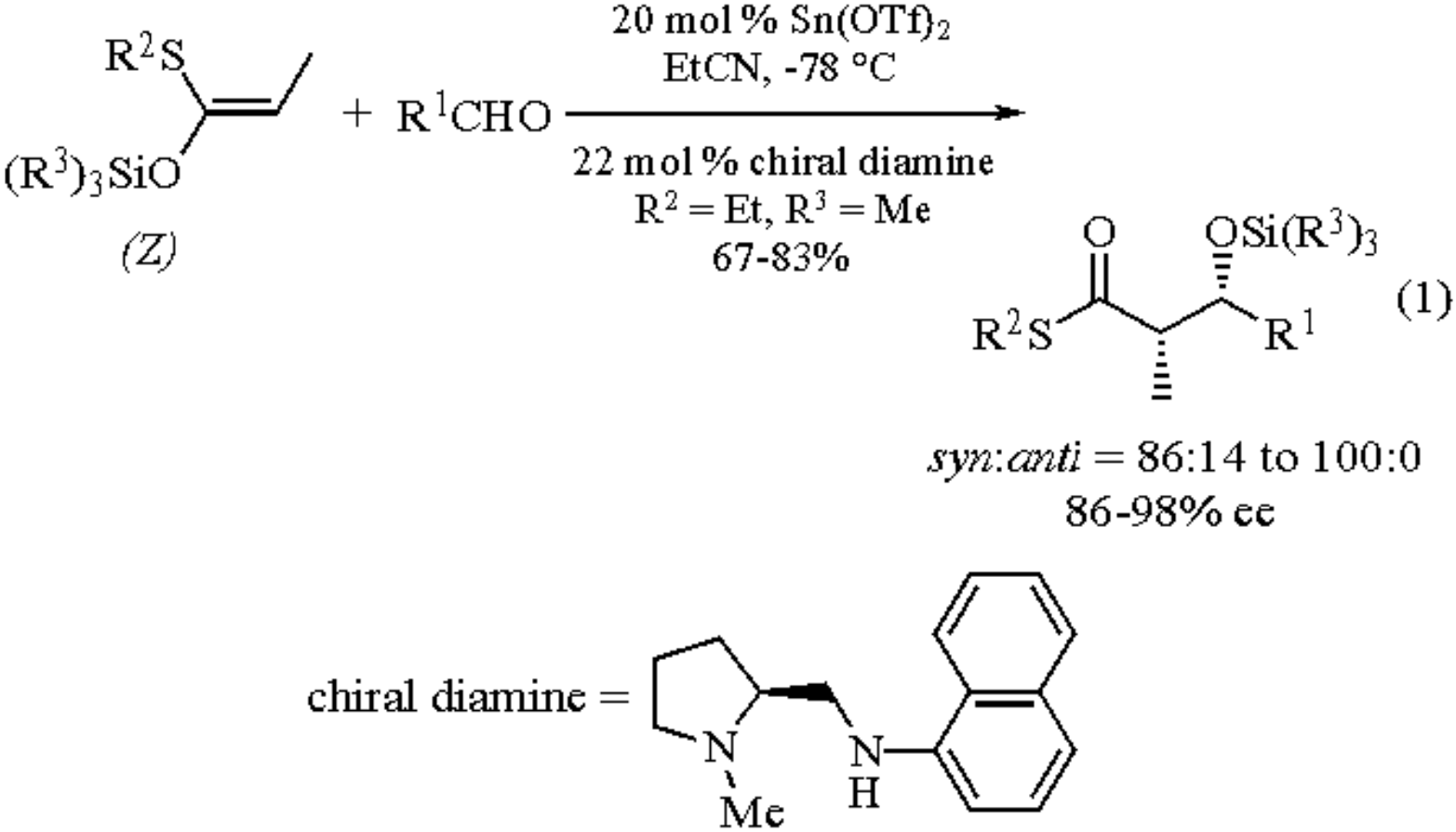

A similar version of the reaction makes use of 100 mol % tin(II) oxide, 65 mol % ***Trimethylsilyl Trifluoromethanesulfonate***, and 50 mol % chiral diamine under slow addition conditions (9 h), with slightly worse results (58-82% yield; *syn*:*anti* = 91:9-98:2; 68-94% ee).[3e] These reactions are the catalytic versions of the stoichiometric reaction outlined in eq 2.[3c,3d,3f-i]

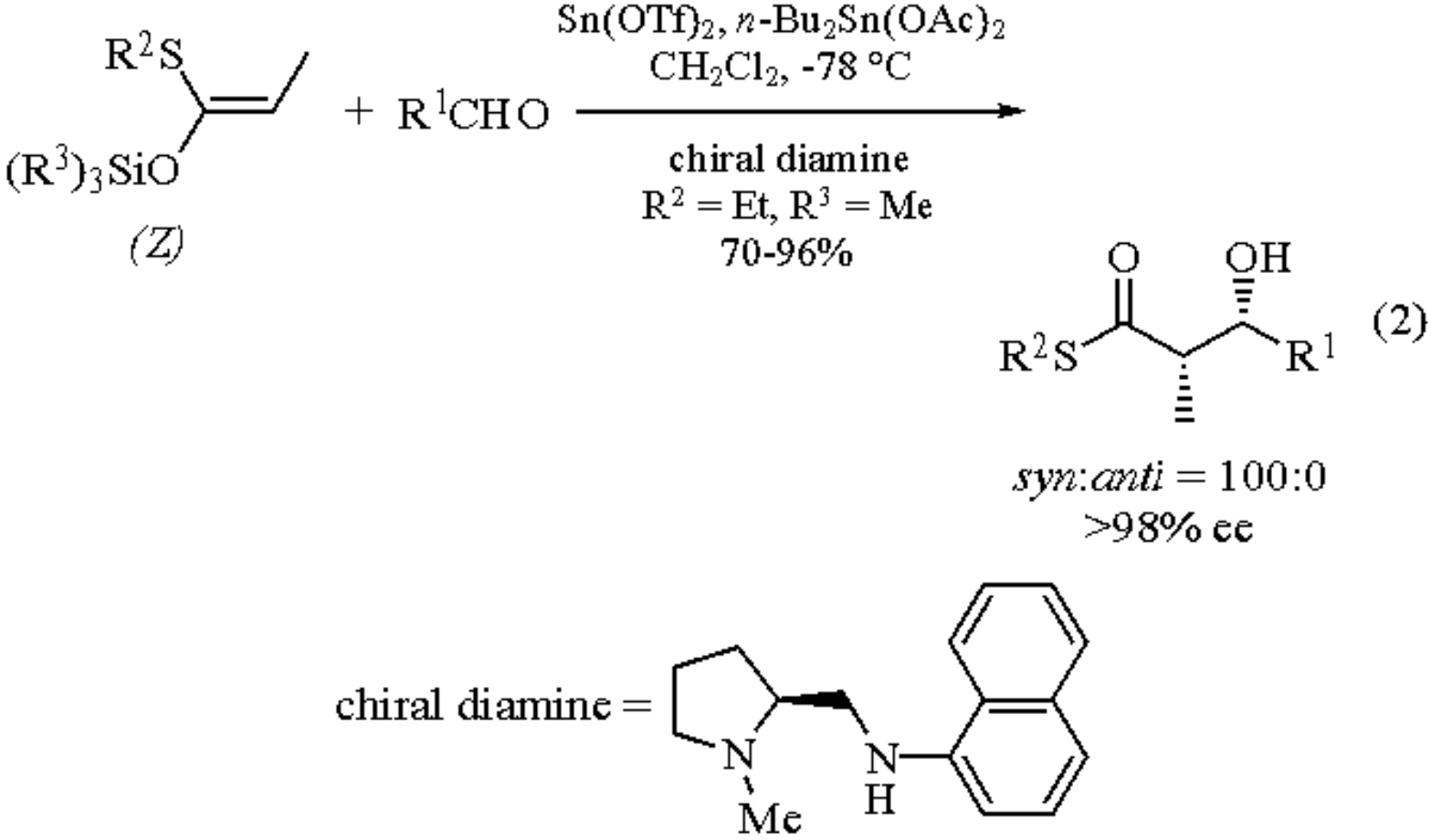

Under similar conditions to eq 2, the reagent adds to α-keto esters to give the corresponding substituted malates in good yield and high stereoselectivity (eq 3).[3j]

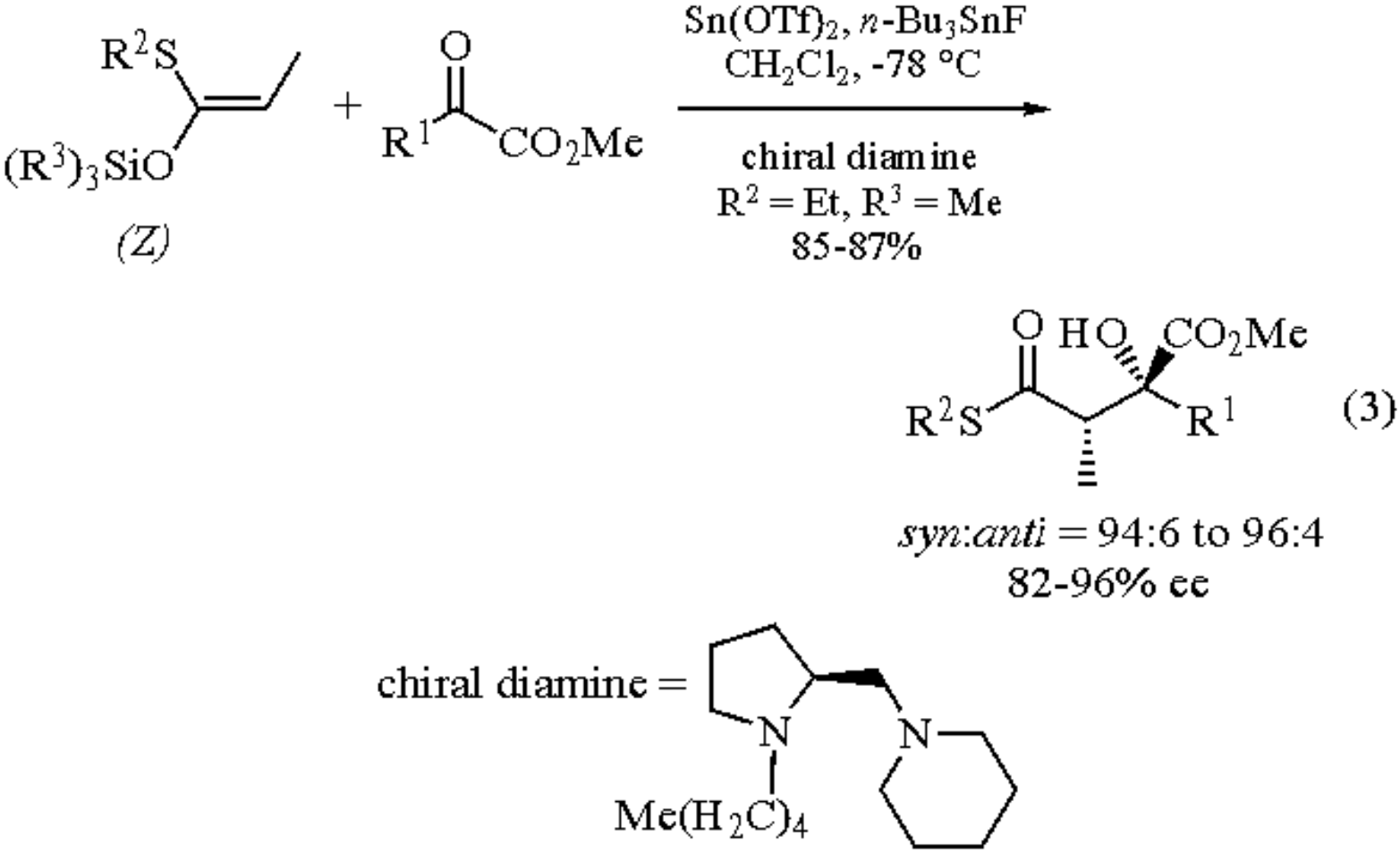

Under similar conditions to eq 3, silyl ketene acetals derived from α-benzyloxy thioesters[4a-c] or α-silyloxy thioesters[4d] add to various aldehydes to give either *anti* (91-99%) or *syn* (88-97%) α,β-dihydroxy thioesters, depending on the reagent used, in good yield (46-93%) and with high enantioselectivity (82-98% ee).

Another catalytic asymmetric aldol reaction is shown in eq 4. Slow addition of the aldehyde is again necessary for high selectivity.[5] Catalyst A is preferred in reactions with aromatic and unsaturated aldehydes, while catalyst B is employed in reactions with primary aldehydes.[5] In contrast to the catalysts mentioned above (eqs 1-3), both A and B give *anti* aldols as the predominant stereoisomers.[5]

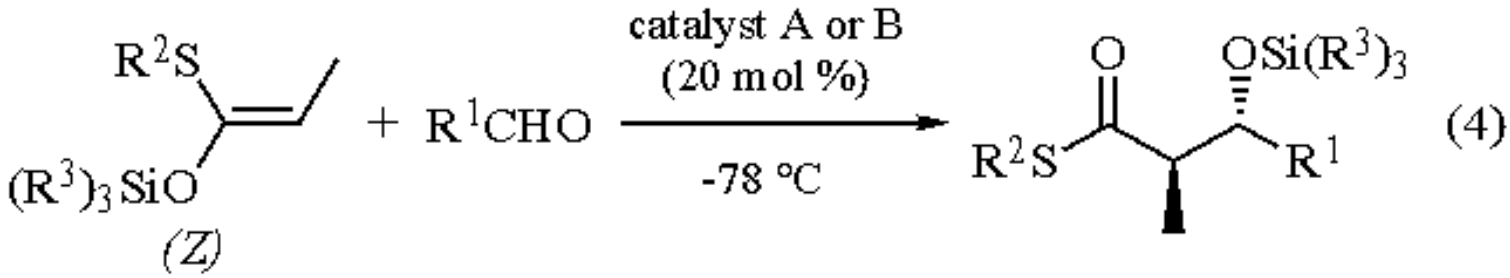

catalyst A	R^2 = Et, *t*-Bu; R^3 = Me	54-94% yield; 60-89% ee *anti*:*syn* = 66:33 to 94:6
catalyst B	R^2 = Et; R^3 = Me	81-85% yield; 70-82% ee *anti*:*syn* = 88:12 to 91:9

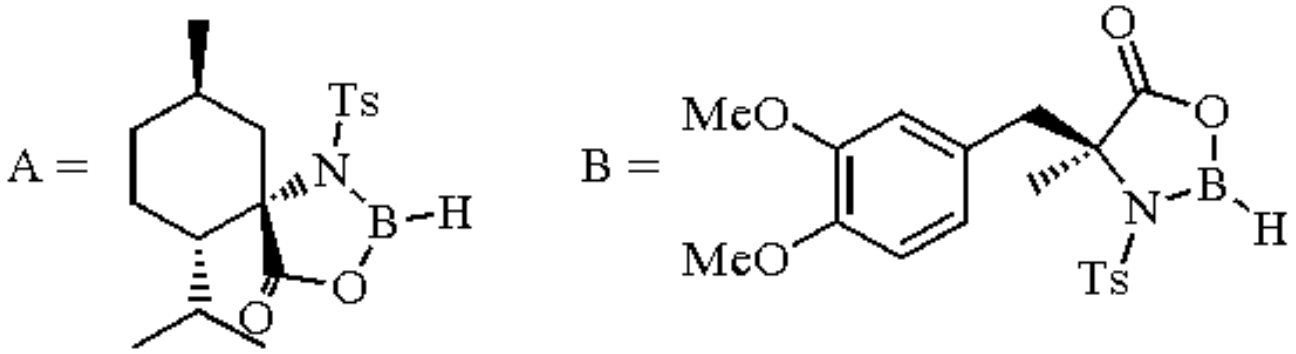

Diastereoselective Aldol Additions.[1]

Boron Trifluoride Etherate mediates the addition of both (*E*) and (*Z*) title reagents to various aldehydes to give the aldol products with high *anti* selectivity (*anti*:*syn* = 91:9-96:4) irrespective of the silyl ketene acetal geometry (eq 5).[2,6] *Syn* selectivity is obtained using the (*E*) isomer via fluoride-mediated addition to benzaldehyde (*syn*:*anti* = 95:5),[2] or via TMSOTf-catalyzed addition to benzaldehyde dimethyl acetal (*syn*:*anti* = 78:22).[7a-d] ***Titanium(IV) Chloride*** mediates the addition of both (*E*) and (*Z*) title reagents to propynals to give the aldol products with high *anti* selectivity (*anti*:*syn* &egt; 95:5) irrespective of the silyl ketene acetal geometry, while high *syn* selectivity (*syn*:*anti* &egt; 98:2) is obtained in the $TiCl_4$-mediated addition to cobalt-complexed propynals.[7e] High *syn* selectivity is obtained in the uncatalyzed reaction of either (*E*)- or (*Z*)-*O*-silacyclobutyl analogs via a direct silicon group transfer (eq 5).[8]

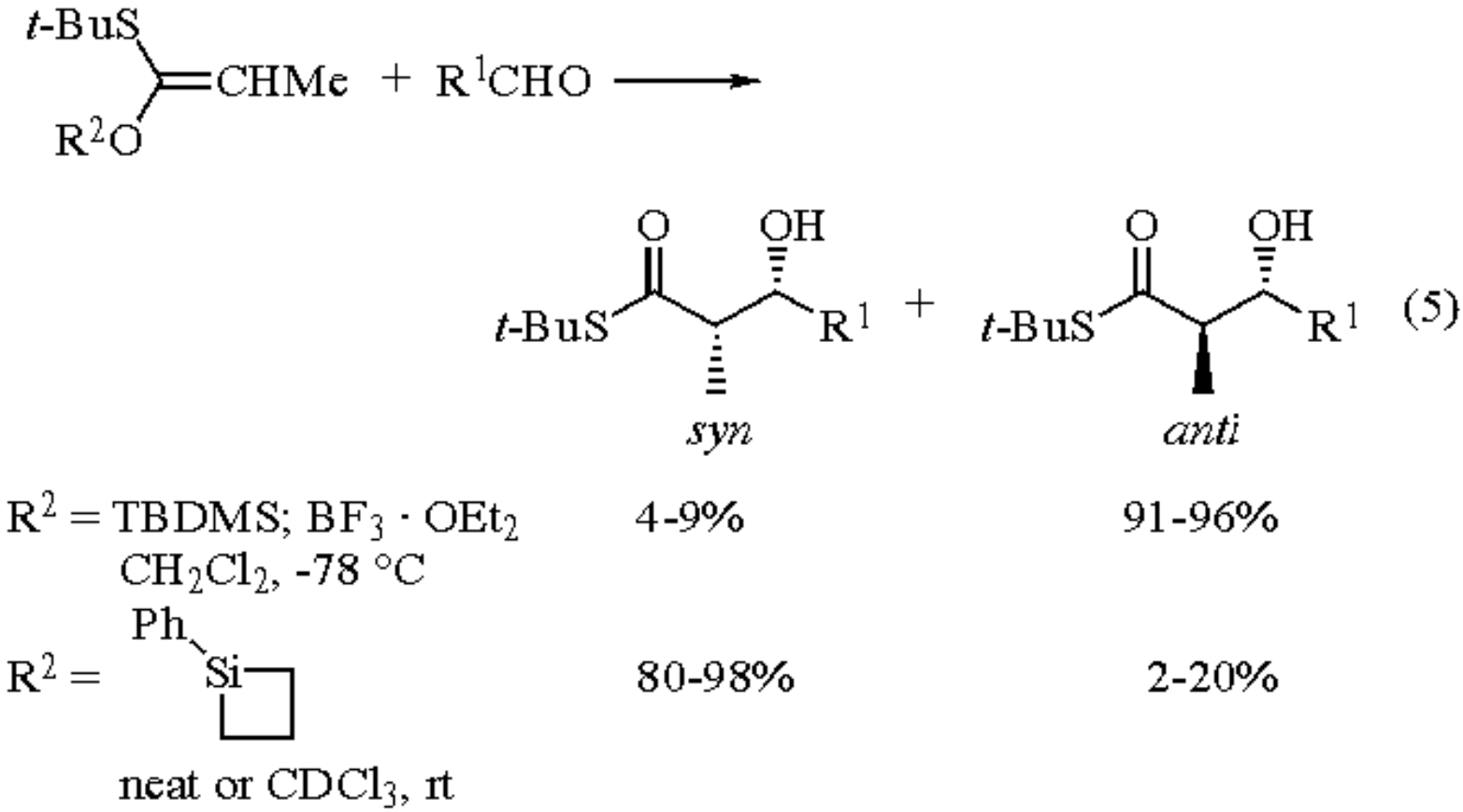

Simple stereoselectivity (*syn*:*anti* ratios) can be controlled in the $Sn(OTf)_2$-mediated addition of the reagent to α-keto esters by varying the silyl ketene acetal geometry (eq 6).[3j]

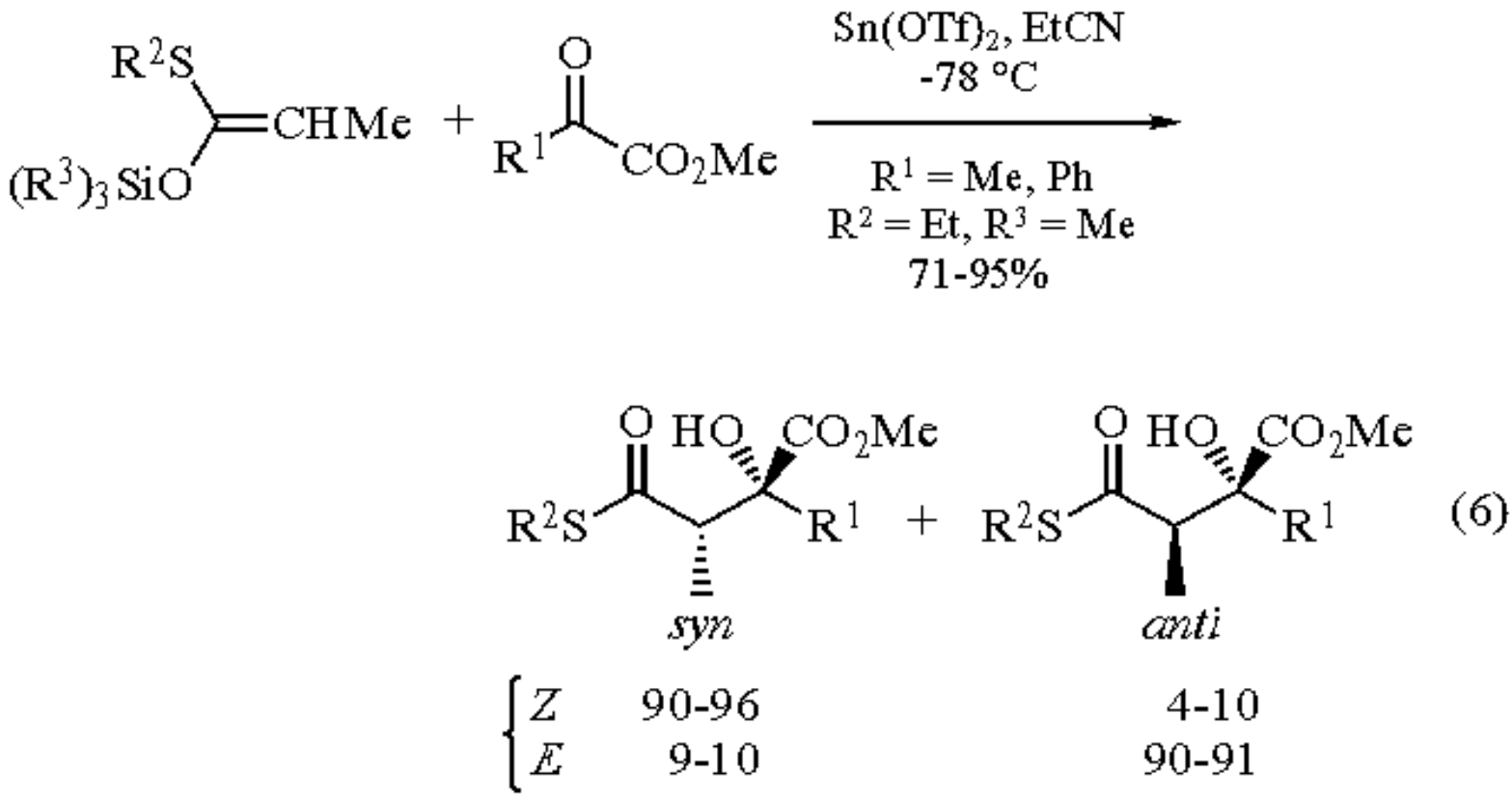

The reagent undergoes Lewis acid-promoted Mukaiyama-type additions[1] to chiral aldehydes with moderate to good stereocontrol (eq 7).[2,6,9a-d] It is remarkable that high diastereoselectivity (>99%) can be obtained using $TiCl_4$ due to chelation control, and that these results are independent of the silyl ketene acetal geometry.[2,9b] These reactions have been used for establishing three consecutive stereocenters in the total synthesis of several biologically interesting compounds.[10-13]

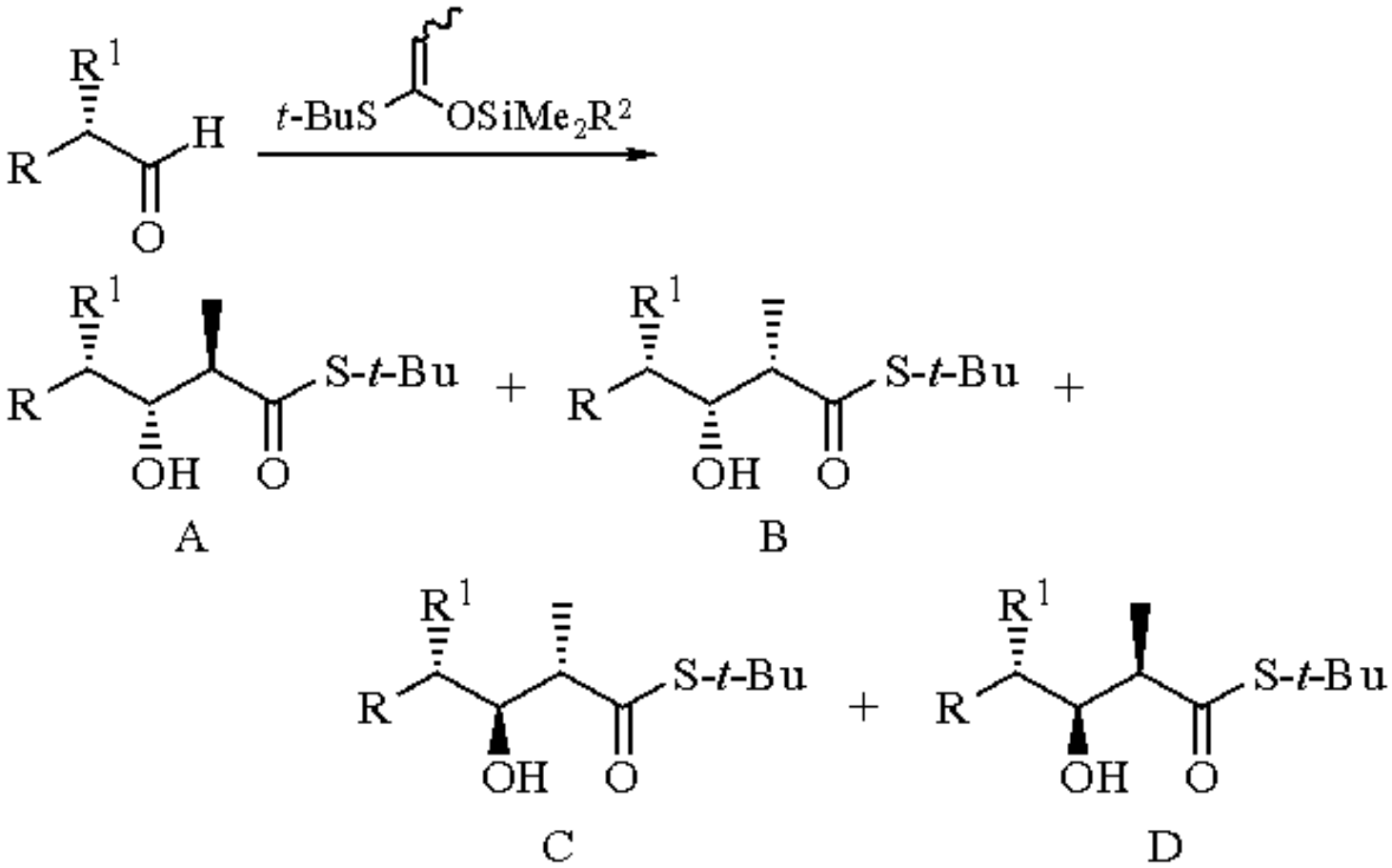

(7)

R	R^1	Promoter	(*E*):(*Z*)	Yield (%)	Ref.	Ratio A:B:C:D
Ph	Me	$BF_3 \cdot OEt_2$	95:5	75	2	91:7:2:0
Me	OBn	$SnCl_4$	95:5	89	2, 9a	3:97:0:0
Me	OBn	$SnCl_4$	5:95	90	2, 9a	24:76:0:0
Me	OBn	TBAF	93:7	72	2, 9a	3:16:8:73
Me	OBn	TBAF	10:90	68	2, 9a	3:13:12:72
Me	OBn	$BF_3 \cdot OEt_2$	93:7	57	2	22:6:60:12
$BnOCH_2$	OBn	$SnCl_4$	95:5	75	2	<5:>95:0:0
$BnOCH_2$	Me	$TiCl_4$	95:5	67	2, 9b	0:0:<1:>99
$BnOCH_2$	Me	$TiCl_4$	5:95	65	2, 9b	0:0:<1:>99
$BnOCH_2$	Me	$BF_3 \cdot OEt_2$	95:5	75	2, 9b	77:14:9:0
$BnOCH_2$	Me	$BF_3 \cdot OEt_2$	5:95	71	2, 9b	77:16:7:0
Et	SMe	$BF_3 \cdot OEt_2$	5:95	83	9c	0:0:91:9

Et	SMe	$BF_3 \cdot OEt_2$	5:95	83	9c	0:0:91:9
Et	SMe	$TiCl_4$	5:95	81	9c	0:100:0:0

Addition to Other Electrophiles.

Zinc Chloride catalyzes the addition to a chiral azetinone with good yield. The stereochemical outcome depends on the sulfur substituent (eq 8).[14]

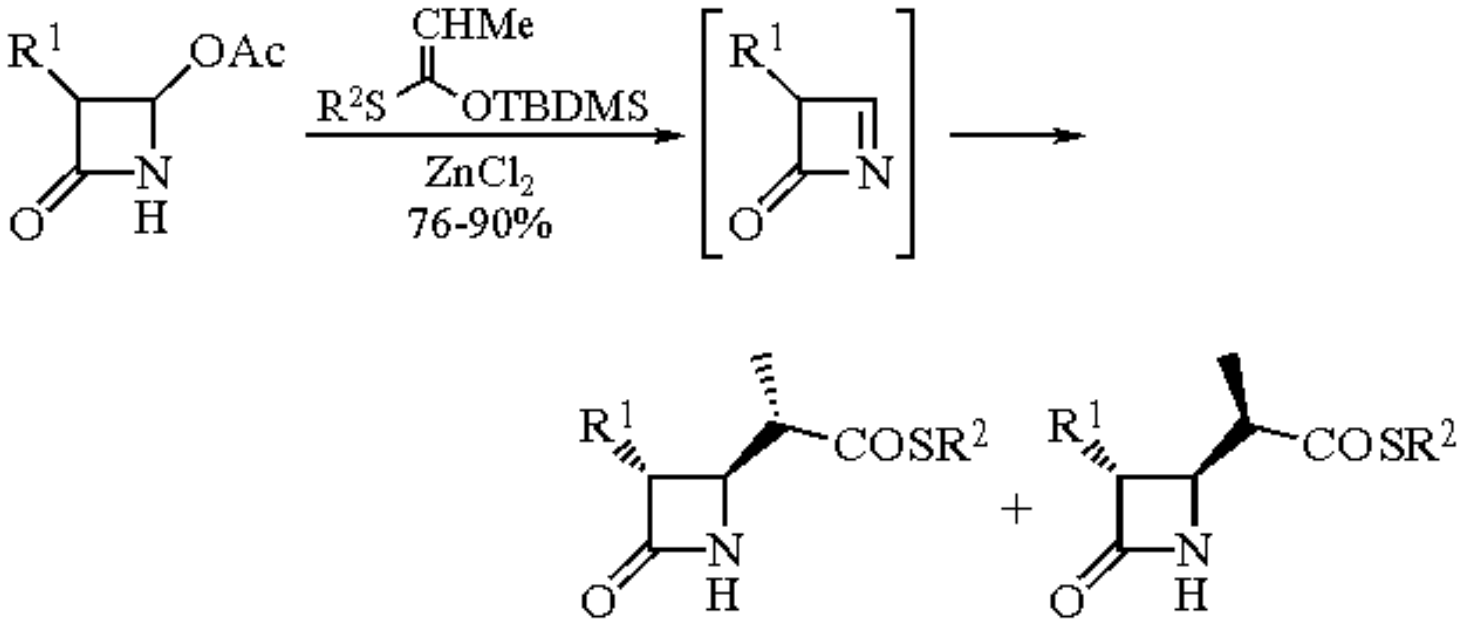

(8)

$R^2 = MeSCH_2$ 98:2
$R^2 = 2\text{-picolyl}$ 2:98

$TiCl_4$ mediates the addition of the title reagents to achiral and chiral thionium ions with good diastereoselectivity (eq 9).[15]

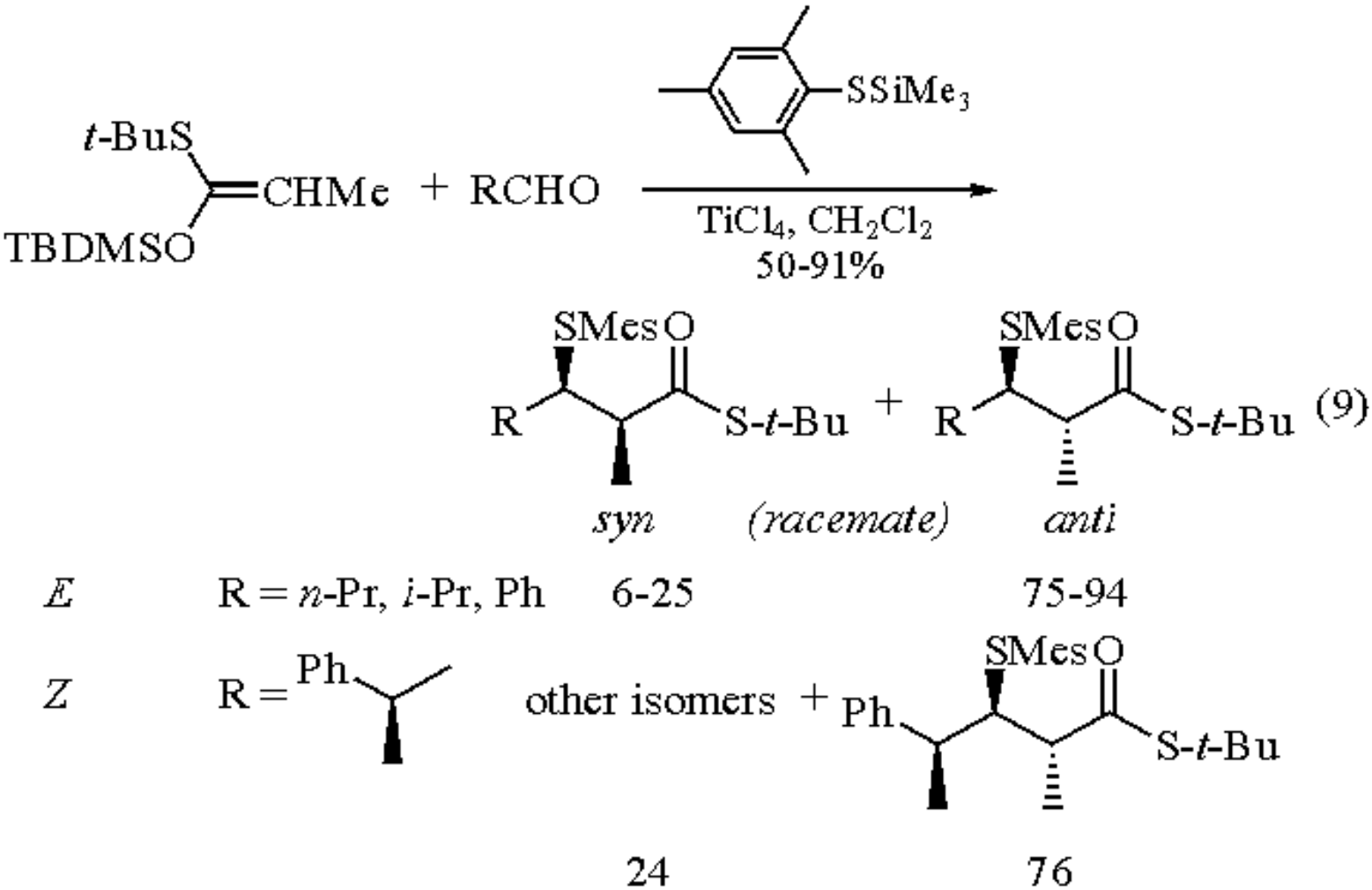

Tin(IV) Chloride or $BF_3.OEt_2$ mediate the addition of the title reagents to norephedrine-derived 2-methoxyoxazolidines; yields and diastereomeric ratios are independent of the silyl ketene acetal geometry (eq 10).[16]

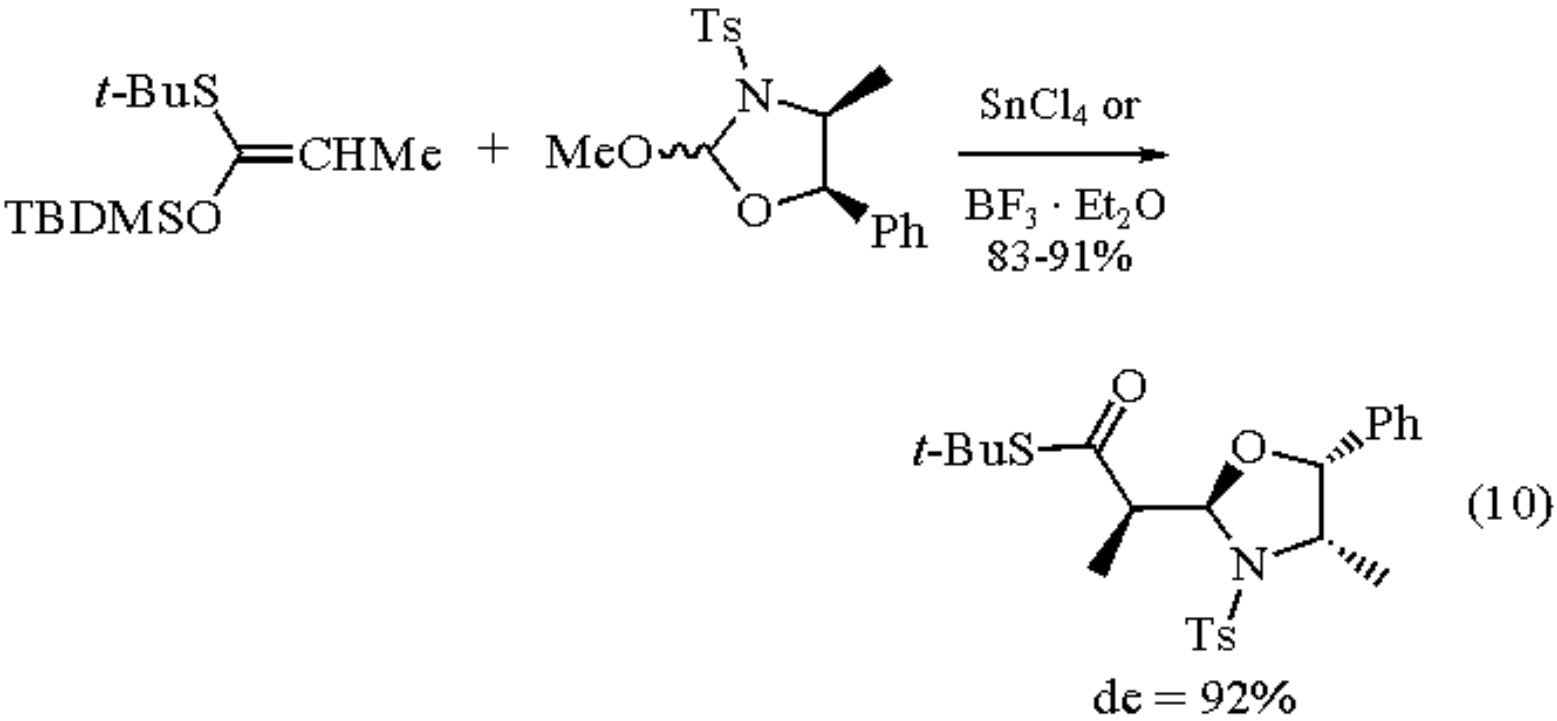

Michael Additions.

In the presence of a catalytic amount of trityl salts (2-3 mol %), thioester silyl ketene acetals react stereoselectively with acyclic α,β-unsaturated ketones to give the Michael adducts in high yield (eq 11).[17a]

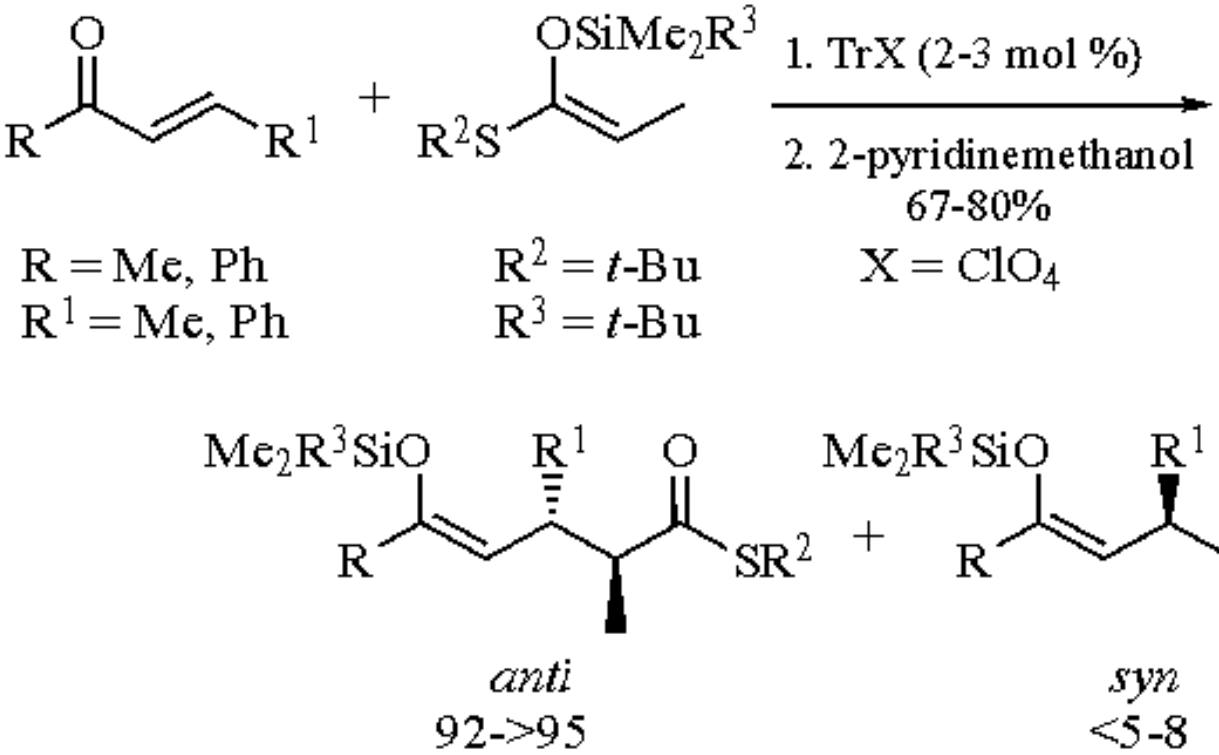

(11)

In the case of cyclic ketones, either the *syn* or the *anti* products can be obtained stereoselectively by varying catalyst and substituents (eq 12).[17a,b] For high *syn* selectivity the *t*-butyl thioester group (R^2 = *t*-Bu) is essential, while both the substituent on silicon (R^3) and silyl ketene acetal geometry have little effect on the diastereoselectivity.[17b]

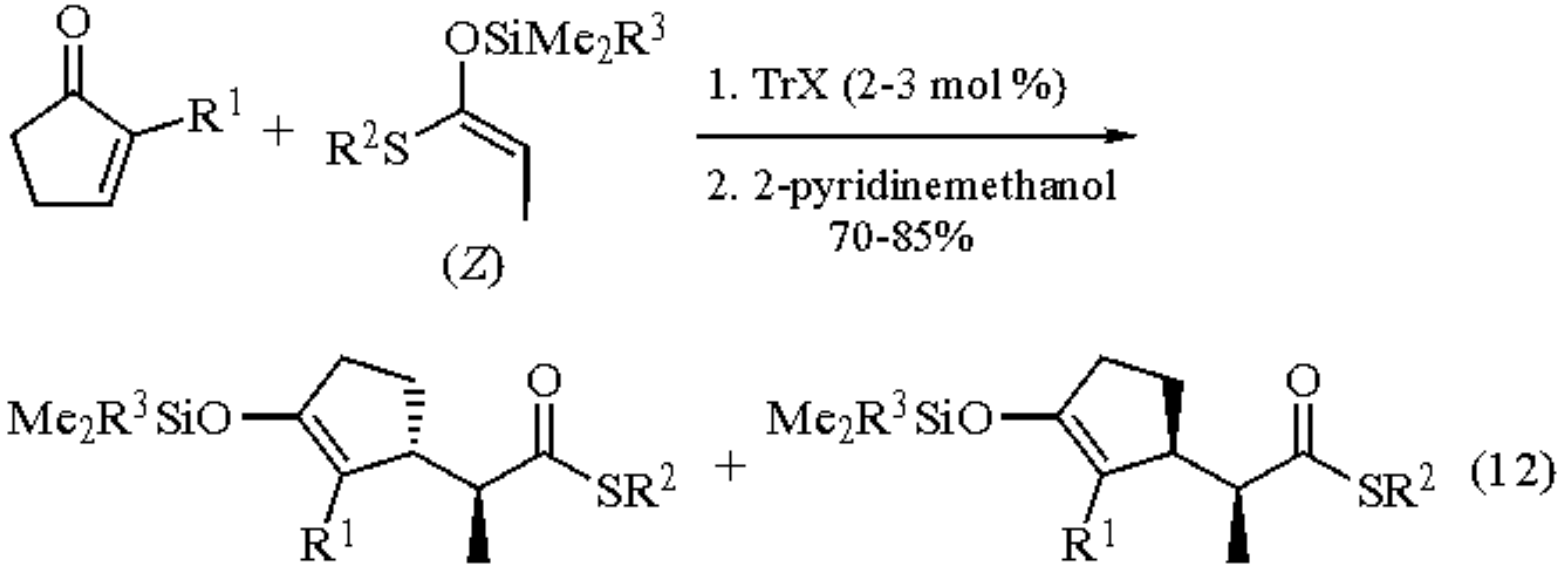

R^1	R^2	R^3	X	(*E*):(*Z*)	*anti*	*syn*
H	Et	Ph	$SbCl_6$	100:0	92	8
H	*t*-Bu	Me	OTf	0:100	21	79
Me	*t*-Bu	Me	$SbCl_6$	0:100	<5	>95
SPh	*t*-Bu	*t*-Bu	$SbCl_6$	0:100	<5	>95
CO_2Me	*t*-Bu	*t*-Bu	$SbCl_6$	0:100	10	90

Catalytic amounts (5 mol %) of trityl chloride and ***Tin(II) Chloride***,[18] or ***Antimony(V) Chloride*** and tin(II) triflate,[19] have also been used to promote the Michael additions, with stereoselectivity in favor of the *anti* isomers and slightly reduced ratios in comparison with the above results. No stereoselectivity was observed with catalytic amounts (10 mol %) of ***Ytterbium(III) Trifluoromethanesulfonate***.[20]

Using the Michael-aldol protocol, several key intermediates on the way to natural products have been synthesized, e.g. dehydroiridodiol,[17a] aromatin,[17b] and fastigilin-C (eq 13).[21]

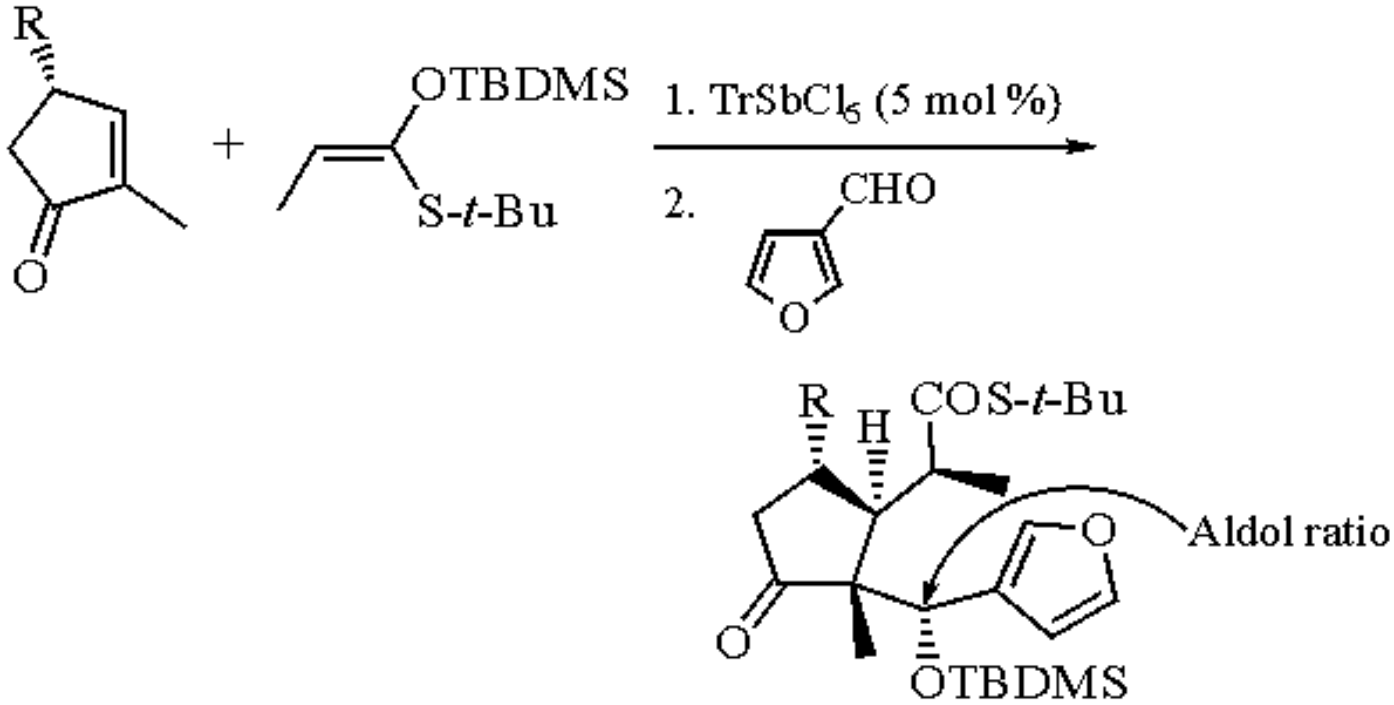

R = H	73%	Aldol ratio = 6:1 (-95 °C, CH_2Cl_2)
R = OMe	81-90%	Aldol ratio = 100:0 (-78 °C, CH_2Cl_2)

Related Reagents.

For comparisons and more details, see also those entries that deal with other silyl ketene acetals, in particular ***1-t-Butylthio-1-t-butyldimethylsilyloxyethylene***, ***Ketene t-Butyldimethylsilyl Methyl Acetal***, and analogs.

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Potenza, D. *TL* **1985**, *26*, 4129. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *JOC* **1992**, *57*, 456. (d) Yamazaki, T.; Yamamoto, T.; Kitazume, T. *JOC* **1989**, *54*, 83.
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1-*t*-Butylthio-1-*t*-butyldimethylsilyloxyethylene[1]

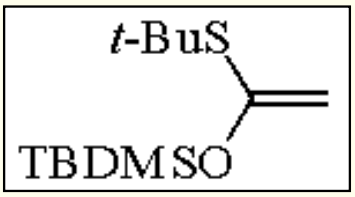

[121534-52-9] · $C_{12}H_{26}OSSi$ · 1-*t*-Butylthio-1-*t*-butyldimethylsilyloxyethylene · (MW 246.48)

(excellent reagent for Lewis acid-mediated aldol-type reactions,[2] under either stoichiometric[3c-e] or catalytic conditions[3a,b,4-6])

Physical Data: colorless liquid; bp 145 °C/20 mmHg.

Solubility: sol *n*-pentane, diethyl ether, dichloromethane, etc.

Analysis of Reagent Purity: (NMR) ^{1}H 0.20 (s, 6H), 0.96 (s, 9H), 1.39 (s, 9H), 4.68 (m, 2H) ppm.

Preparative Method: the reagent is obtained by reaction of *t*-butyl thioacetate with ***Lithium Diisopropylamide*** in THF/HMPT and subsequent trapping with ***t-Butyldimethylchlorosilane*** (75% yield).[2]

Handling, Storage, and Precautions: the reagent should be stored in the absence of moisture at -15 °C.

Enantioselective Aldol Additions.[1]

The reagent undergoes Lewis acid-catalyzed Mukaiyama-type additions to aldehydes to give β-hydroxy thioesters with good yields and remarkable enantioselectivity (eq 1).[3a,b] Slow addition of the aldehyde (3-20 h) is necessary for high enantioselectivity.[3a]

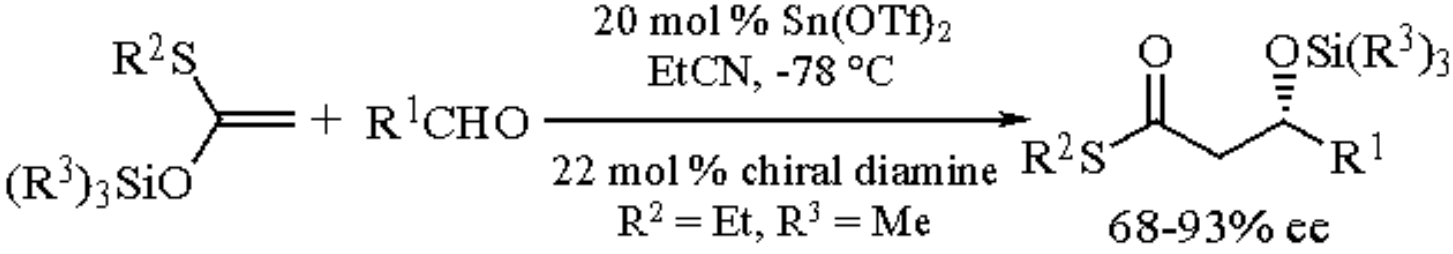

(1)

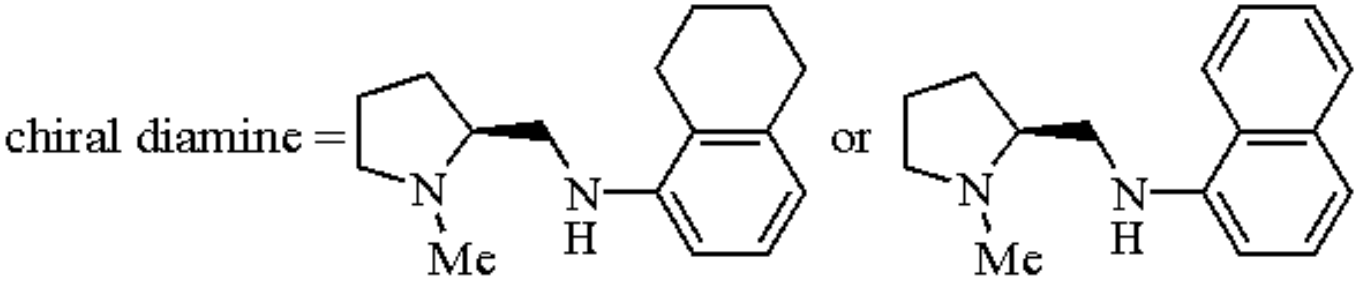

This reaction is the catalytic version of the stoichiometric reaction outlined in eq 2.[3c,d]

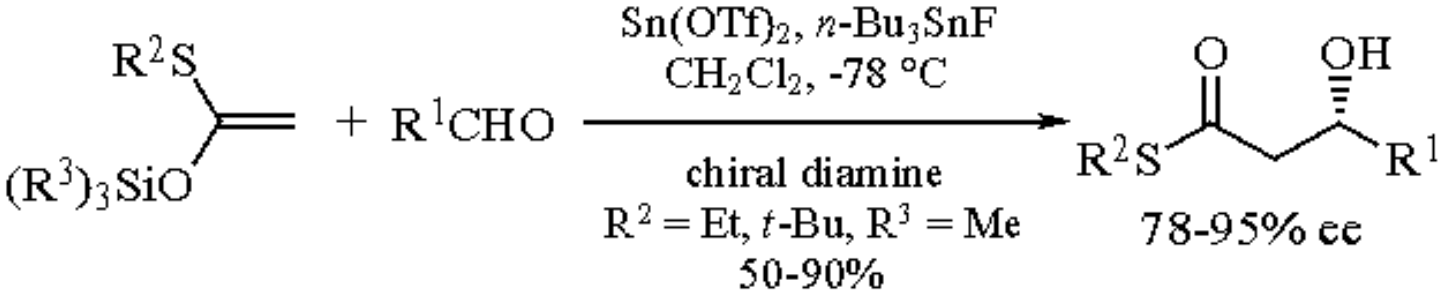

(2)

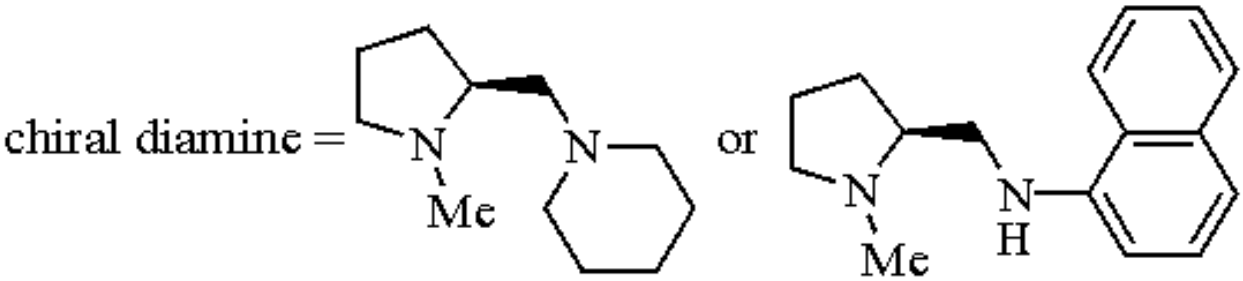

Under the same conditions as eq 2, the reagent adds to α-keto esters to give the corresponding 2-substituted malates in good yield (74-81%) and excellent enantiomeric excesses (92-98%).[3e]

Other catalytic asymmetric aldol reactions are shown in eq 3. Slow addition of the aldehyde is necessary for catalyst B[5] but not for A.[4]

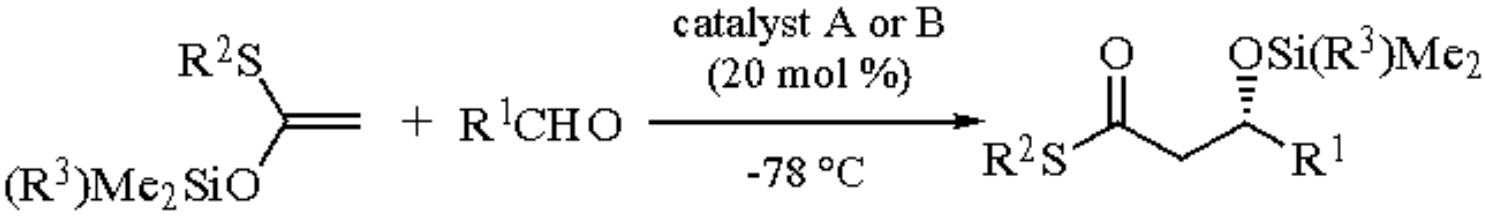

(3)

catalyst A	$R^2 = t$-Bu; $R^3 = t$-Bu	91-98% yield; 44-85% ee
catalyst B	$R^2 =$ Et, t-Bu; $R^3 =$ Me	75-98% yield; 81-92% ee

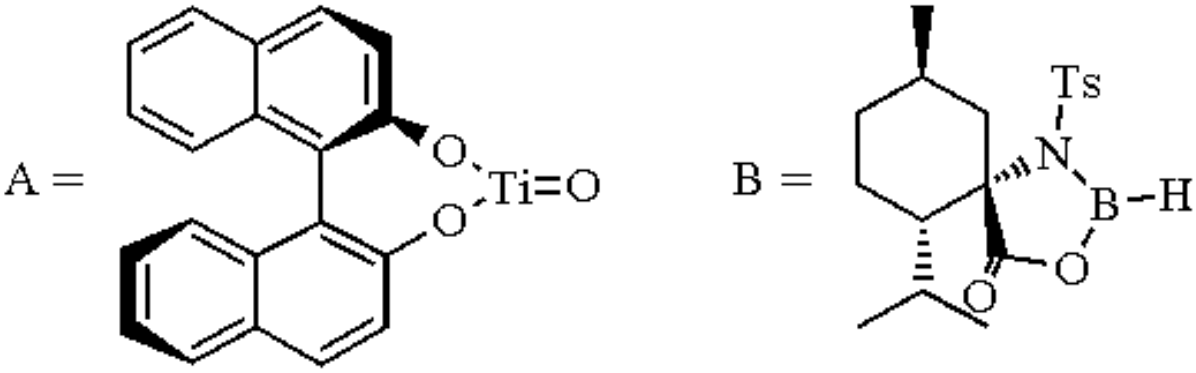

Under either the catalytic (eq 1) or the stoichiometric conditions (eq 2), the reagent undergoes addition to chiral aldehydes with complete reagent control, i.e. the stereochemistry of the aldol reaction is totally controlled by the chiral catalyst regardless of the inherent diastereofacial preference of the chiral aldehydes (eq 4).[6]

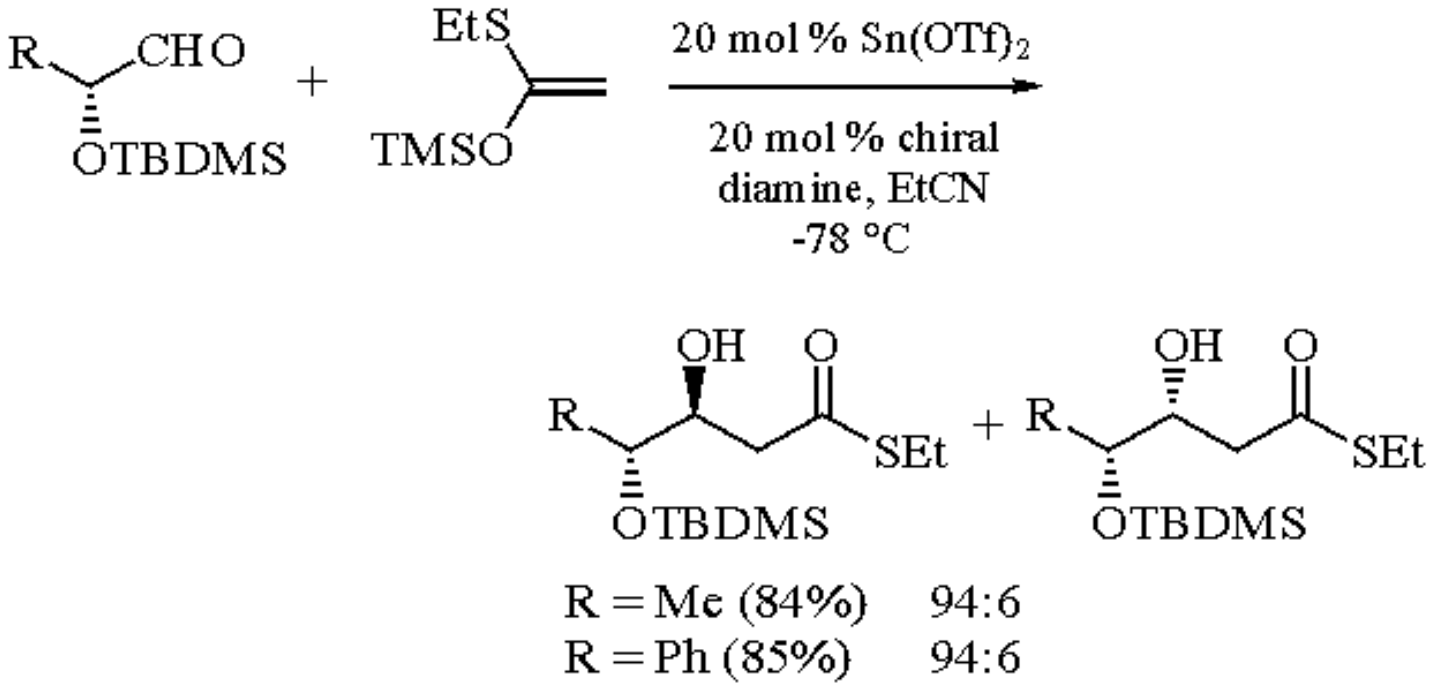

(4)

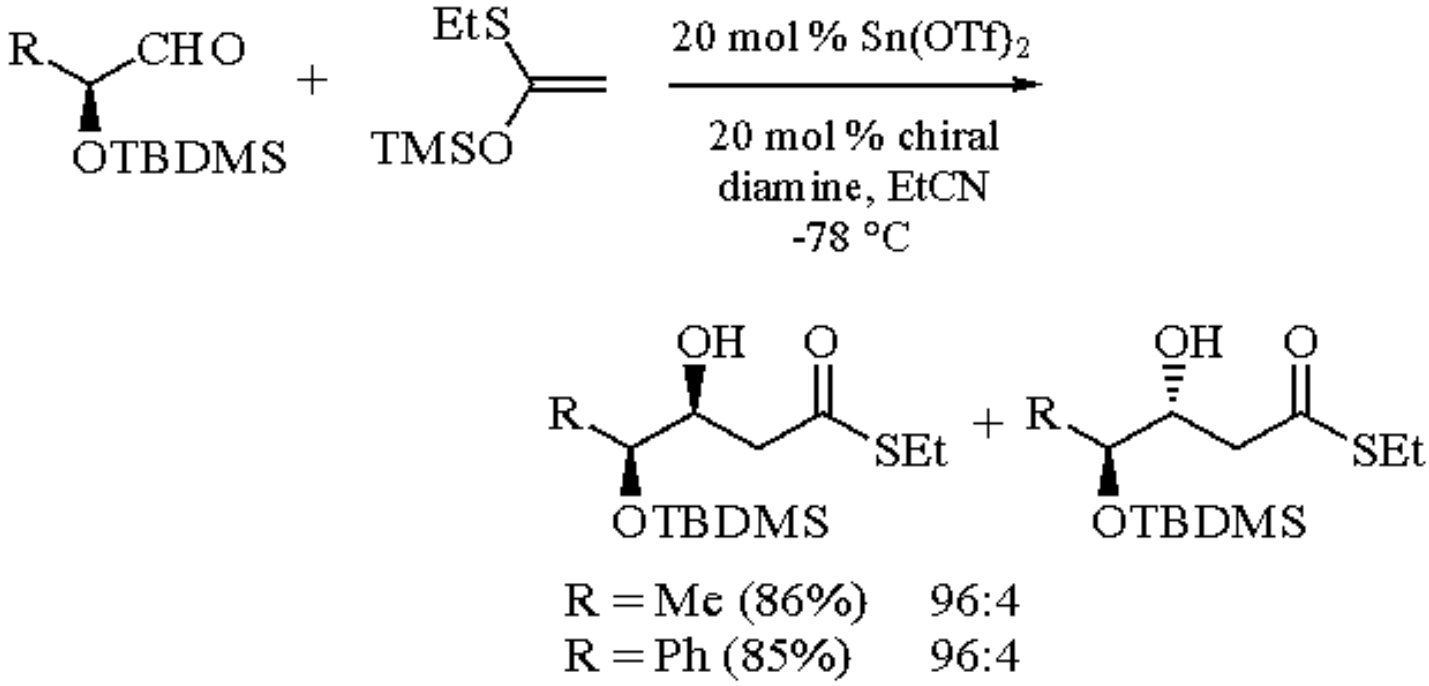

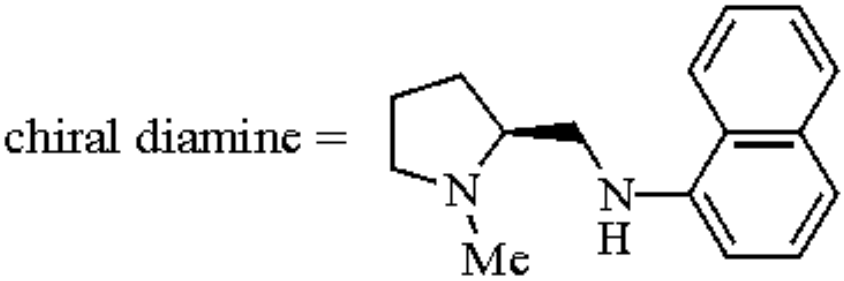

Titanium(IV) Chloride and ***Tin(IV) Chloride*** mediate the addition of the title reagent to chiral α-alkoxy aldehydes[2,7] and

β-alkoxy aldehydes[2] with complete chelation control (eq 5), whereas the corresponding silyl ketene acetal is unselective.[1,2]

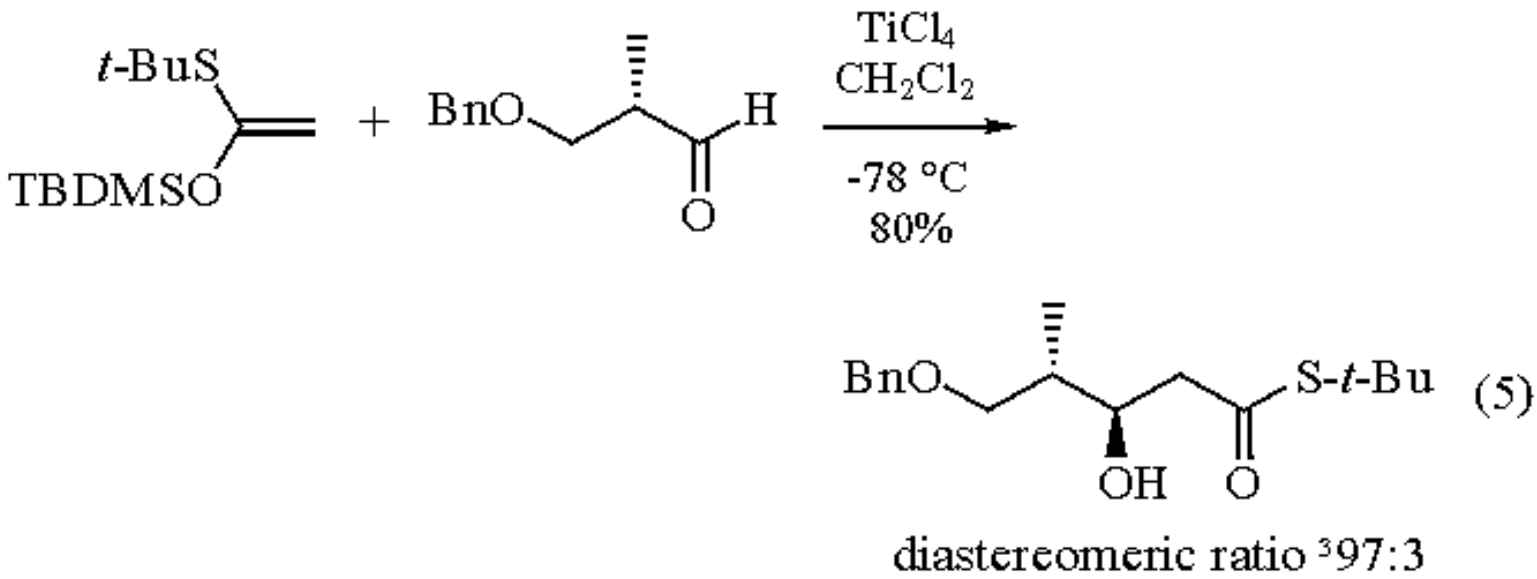

Addition to Other Electrophiles.

Trimethylsilyl Trifluoromethanesulfonate catalyzes the addition to a chiral iminium ion with good yield and complete stereoselectivity (eq 6).[8]

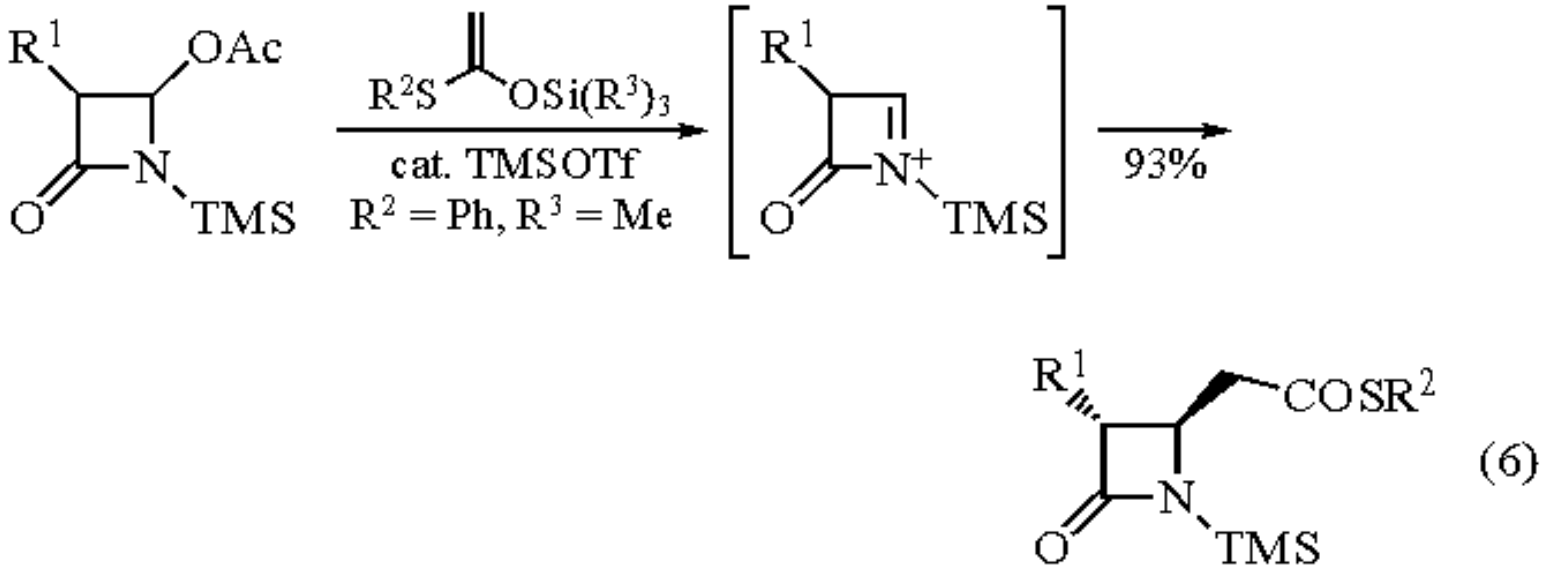

Chlorotrimethylsilane-$InCl_3$ catalyzes the addition to *O*-trimethylsilyl monothioacetals to afford the corresponding sulfide derivatives in good yield.[9] Titanium tetrachloride mediates the addition of the title reagent to a chiral acetal with high diastereoselectivity (eq 7).[10]

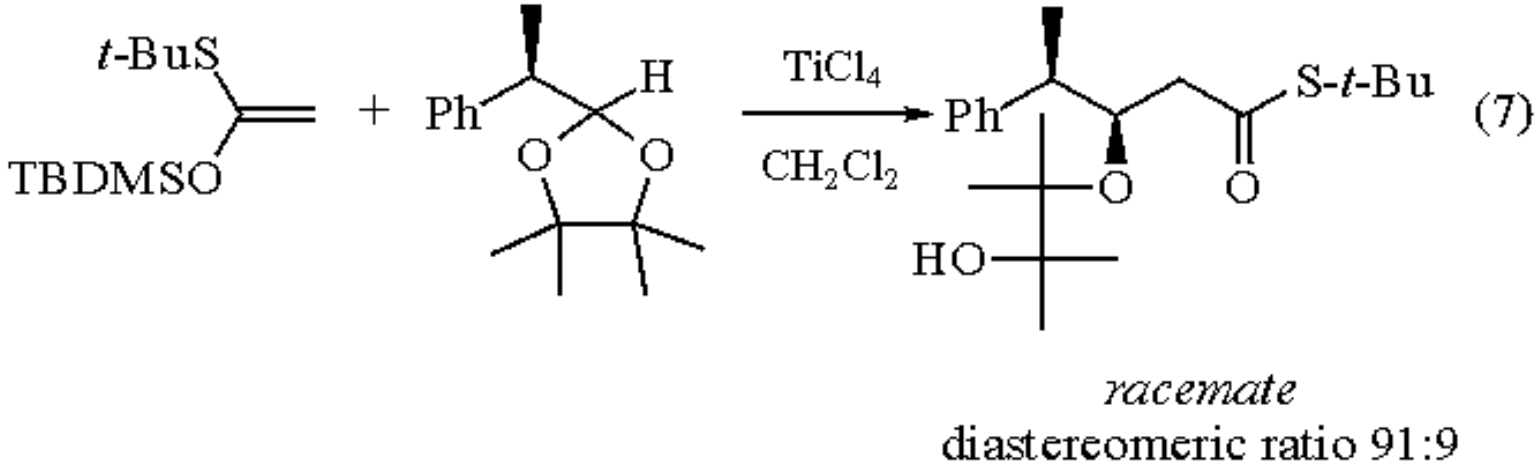

Related Reagents.

For comparison and more details, see also those entries that deal with other silyl ketene acetals, in particular ***1-t-Butylthio-1-t-butyldimethylsilyloxypropene***, ***Ketene t-Butyldimethylsilyl Methyl Acetal***, and analogs.

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n-Butyl *N*-(*p*-Toluenesulfonyl)iminoacetate[1]

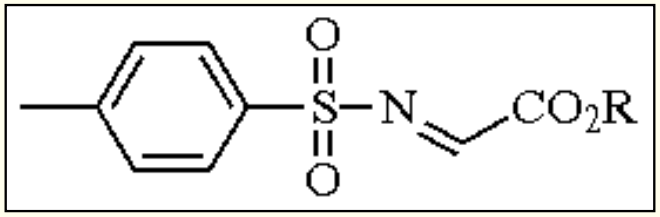

(R = Bu)

[2292-87-7] · $C_{13}H_{17}NO_4S$ · *n*-Butyl *N*-(*p*-Toluenesulfonyl)iminoacetate · (MW 283.34) (R = Me)

[89366-20-1] · $C_{10}H_{11}NO_4S$ · Methyl *N*-(*p*-Toluenesulfonyl)iminoacetate · (MW 241.26) (R = Et)

[83670-53-5] · $C_{11}H_{13}NO_4S$ · Ethyl *N*-(*p*-Toluenesulfonyl)iminoacetate · (MW 255.29)

(easily prepared *N*-tosyl imines of glyoxylate esters[2] are useful as enophiles in inter-[3,4] and intramolecular[5] imino ene reactions and as dienophiles in achiral[6] and asymmetric[7,8,20-23] hetero Diels-Alder reactions)

Physical Data: bp R = Bu, 130-135 °C/0.001 mmHg; R = Et, 145-150 °C/0.02 mmHg.

Solubility: sol various organic solvents, usually used in benzene or toluene; reactions often run without solvent.

Form Supplied in: viscous yellow oil.

Handling, Storage, and Precautions: usually prepared and distilled directly before use or generated and used in situ.

Preparations.

Although a variety of alkyl glyoxylates have been utilized for the preparation of *N*-tosyliminoacetates, the most widely used compound has been the butyl derivative (**1**). Albrecht and Kresze[1] published the first preparation of (**1**) in 1965, when butyl glyoxylate was found to react with ***N-Sulfinyl-p-toluenesulfonamide***[9] under Lewis acid catalysis to produce the *N*-tosyliminoacetate (**1**) (eq 1). This reaction presumably proceeds through an initial [2 + 2] cycloaddition, followed by extrusion of sulfur dioxide.

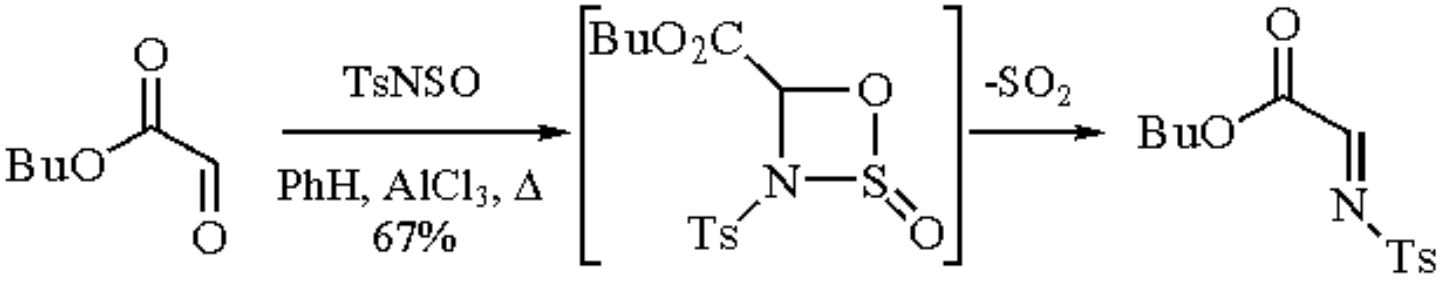

(1)

(1)

Two groups have independently published preparations of *N*-tolyliminoacetates by reactions of glyoxylates and ***p-Toluenesulfonyl Isocyanate***. Le Goffic and Baillarge[10a] found that Lewis acid catalysis of the reaction in refluxing benzene produced (**1**) in 95% isolated yield (eq 2). A few years later, Holmes and co-workers[10b] found that the reaction could be effected without catalysis in refluxing toluene to produce the corresponding methyl ester in good yield. The mechanism of this reaction is thought to parallel the pathway in eq 1.

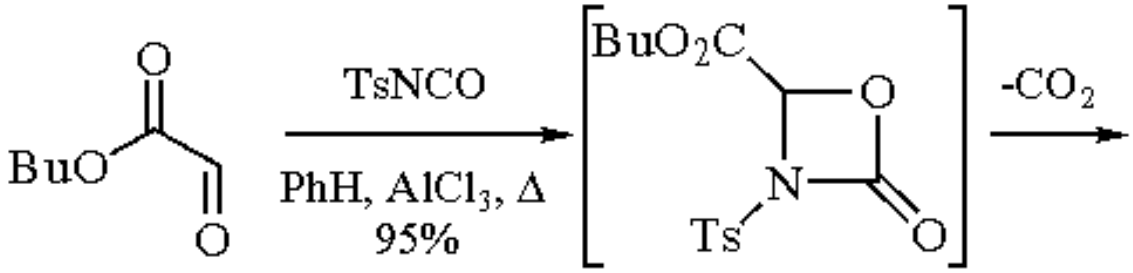

(1) (2)

Imino Ene Reactions.

The first report of an ene reaction of an *N*-tosylimine with an alkene appeared in 1976, when Achmatowicz and Pietraszkiewicz[3] showed that imino ene reactions could be effected thermally or under Lewis acid conditions to produce γ,δ-unsaturated amino acid derivatives (**2**) (eq 3).

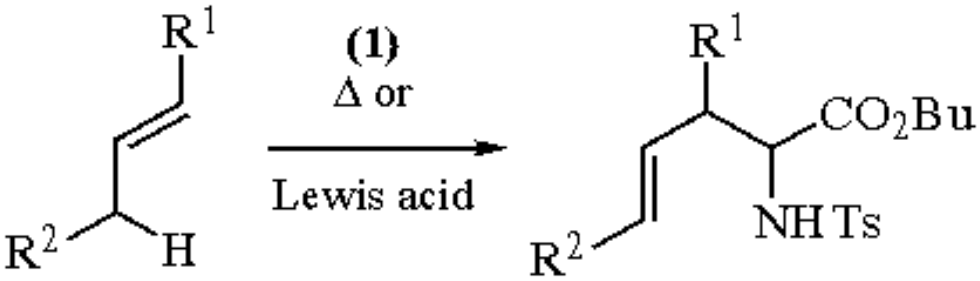

(3)

(2)

Interestingly, Kresze and Braxmeier[11] have found that the same ene reactions can be effected using *N*-perfluorobutylsulfonyliminoacetate (**3**), resulting in a reaction rate increase relative to (**1**) of approximately three orders of magnitude.

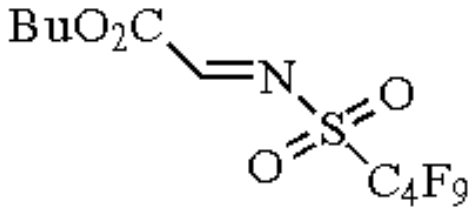

(3)

More recently, Weinreb and co-workers[4,5] investigated the stereochemical features of the intermolecular ene reaction of (**1**). It was found that the reactions are stereospecific when conducted thermally, apparently proceeding through a pericyclic mechanism. When ethyl *N*-tosyliminoacetate was heated at 170 °C with cyclohexene, only sulfonamido ester (**4**), derived from the *endo* transition state **A**, was isolated (eq 4). None of the diastereomer (**5**), derived from an *exo* transition state **B**, was detected. When the reaction was run under Lewis acid catalysis, however, a mixture of (**4**) and (**5**) was isolated. It is presumed that the addition of a Lewis acid induces a change in mechanism from a pericyclic to an ionic process.

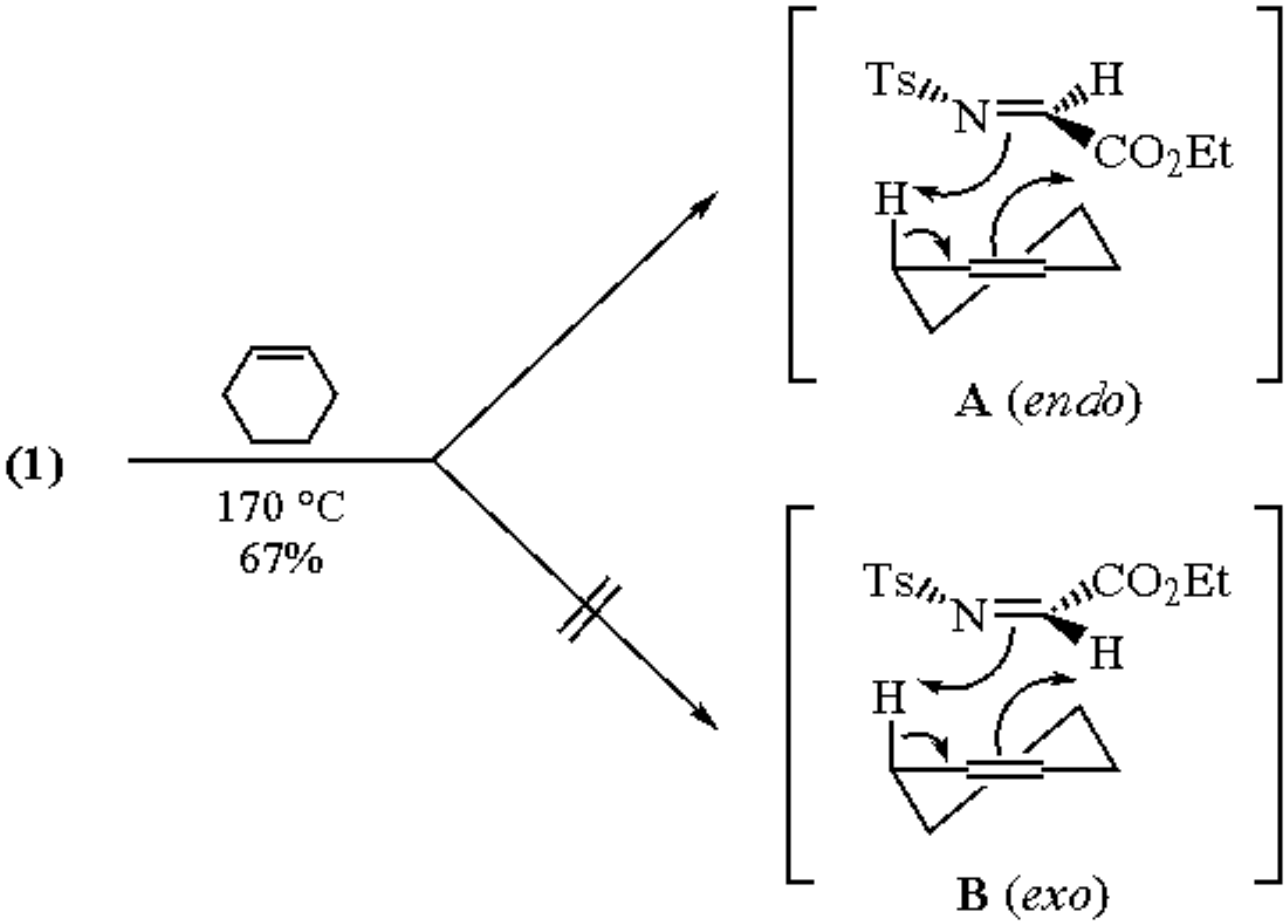

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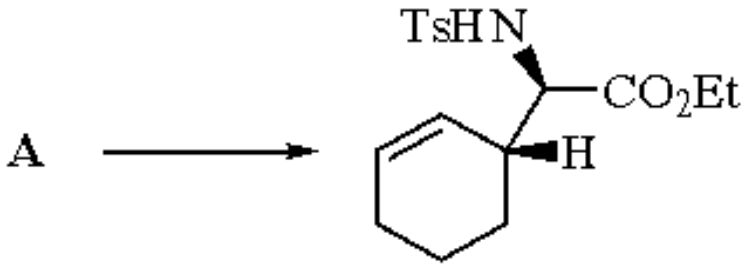

(4)

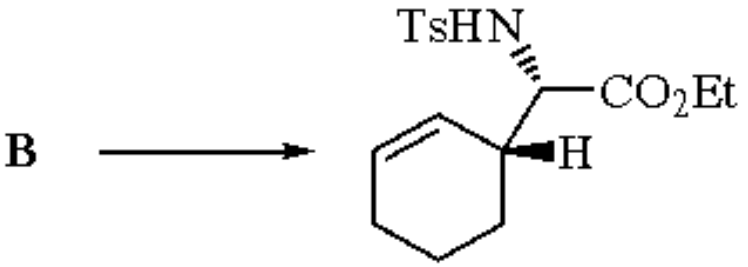

(5)

Weinreb and co-workers[5a,12] also found that ene reactions could be effected intramolecularly with unsaturated alkyl esters of *N*-tosyliminoacetates. The *N*-tosylimine derived from (*E*)-crotyl glyoxylate was prepared in situ and heated in *o*-dichlorobenzene to afford the single ene product (**7**),[13] arising from a cyclization through the intermediate *N*-tosylimine (**6**) (eq 5).

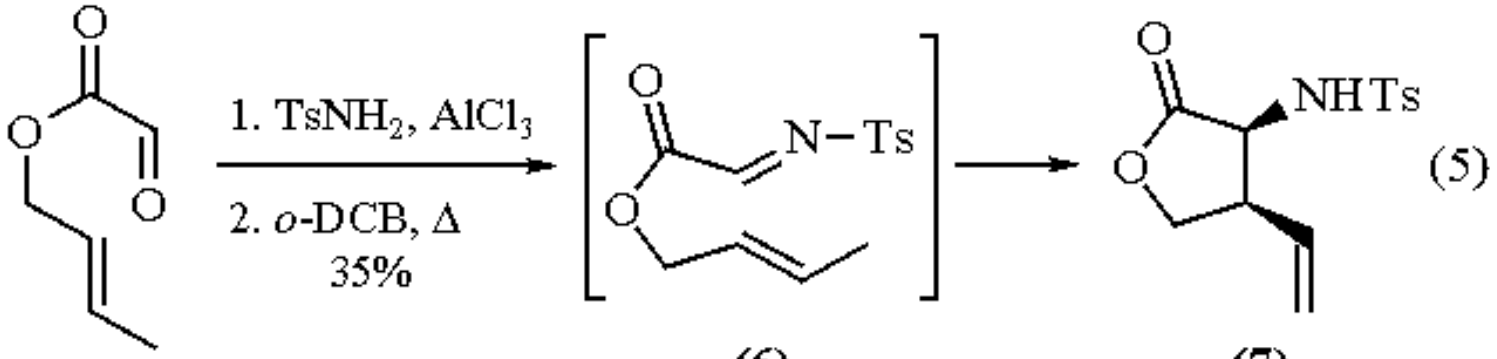

(6) (7) (5)

In an attempt to construct the framework of polyoxamic acid (**10**), Baumann and Duthaler[14] reacted ethyl *N*-tosyliminoacetate with methallene (eq 6). While only isolating minor amounts of the desired [2 + 2] adduct (**9**), a 33% yield of (**8**), derived from an imino ene reaction, was isolated.

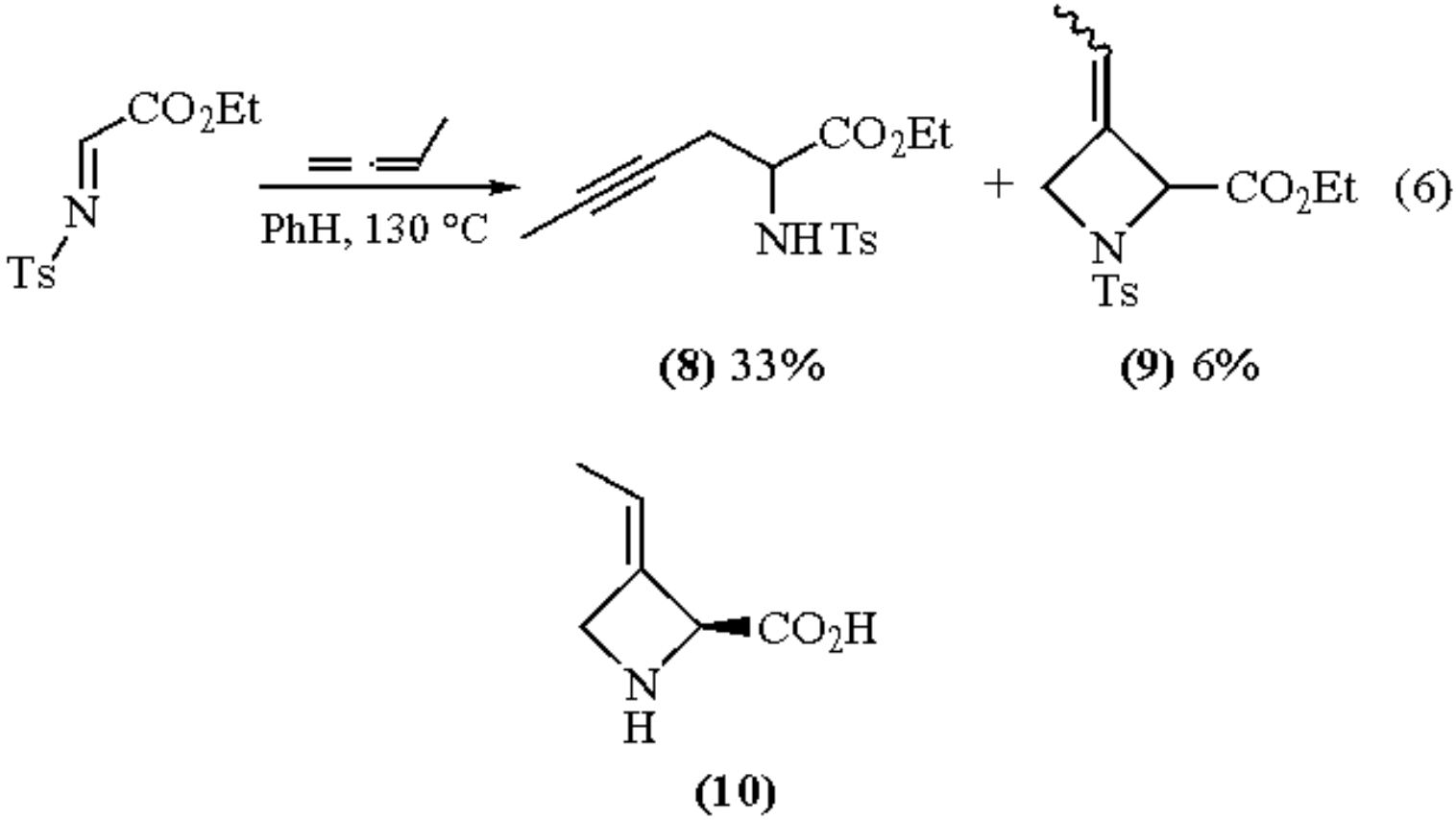

Hetero Diels-Alder Reactions.

The first example of an *N*-tosyliminoacetate as a dienophile was reported by Kresze[1] in 1965. The reaction was found to be generally regioselective (eq 7).

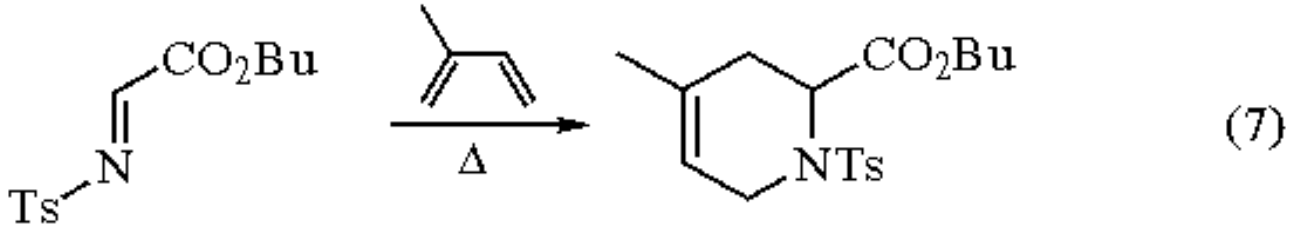

Other groups have explored the addition of (**1**) to cyclic dienes in a study of the stereochemistry of the reaction.[15] Barco and co-workers[16] found that when an *N*-tosyliminoacetate (**1**) was allowed to react with ***Cyclopentadiene***, only the *exo* adduct (**11**) was formed (eq 8). This compound was further elaborated upon to produce 8-aza-9,11-etheno-PGH_1, a prostaglandin endoperoxide analog.

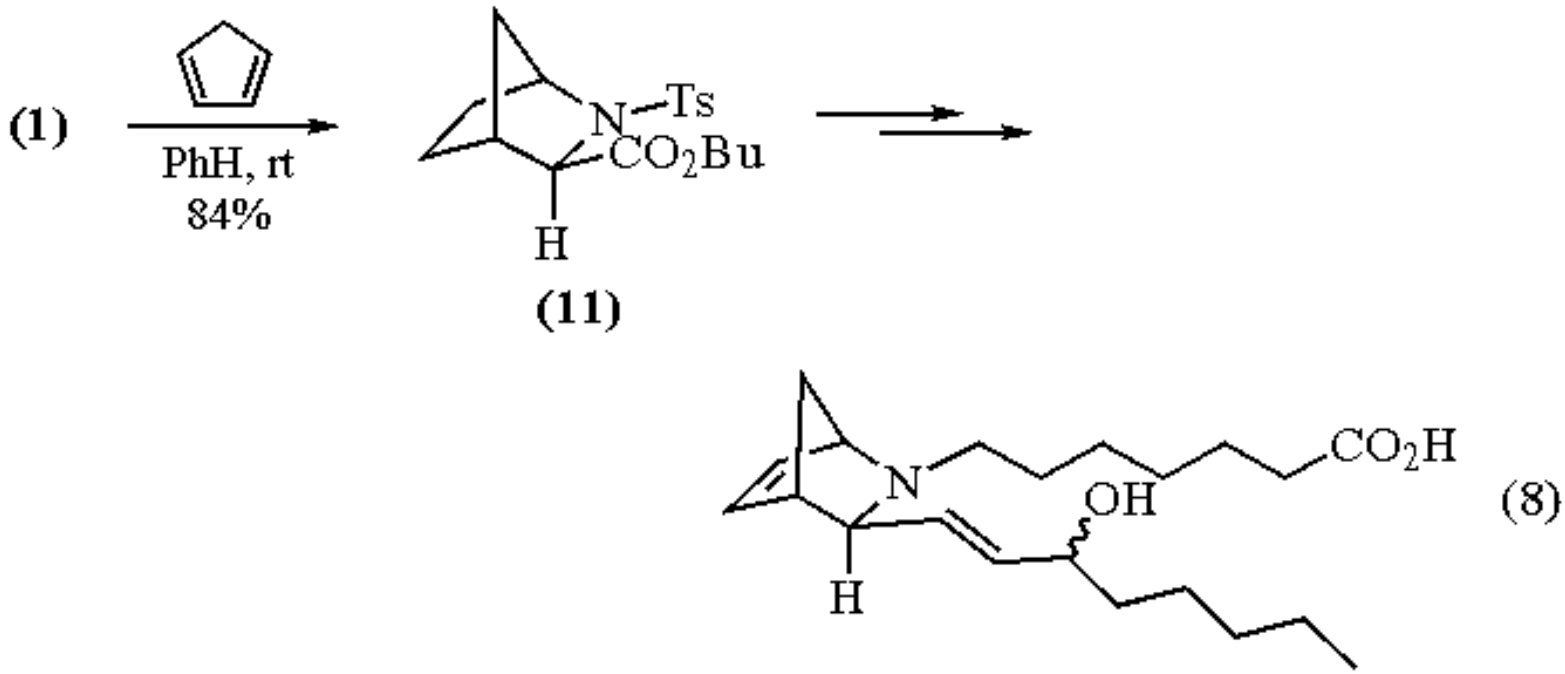

Holmes and co-workers[8,17] have studied the hetero [4 + 2]-reaction of *N*-tosyliminoacetates with various cyclohexadienes and have applied the adducts to natural product syntheses. Cyclohexadiene was found to afford only the expected *exo* isomer (**12**) when reacted with ethyl *N*-tosyliminoacetate (eq 9). This compound was further functionalized to provide (±)-actinobolamine.[17a]

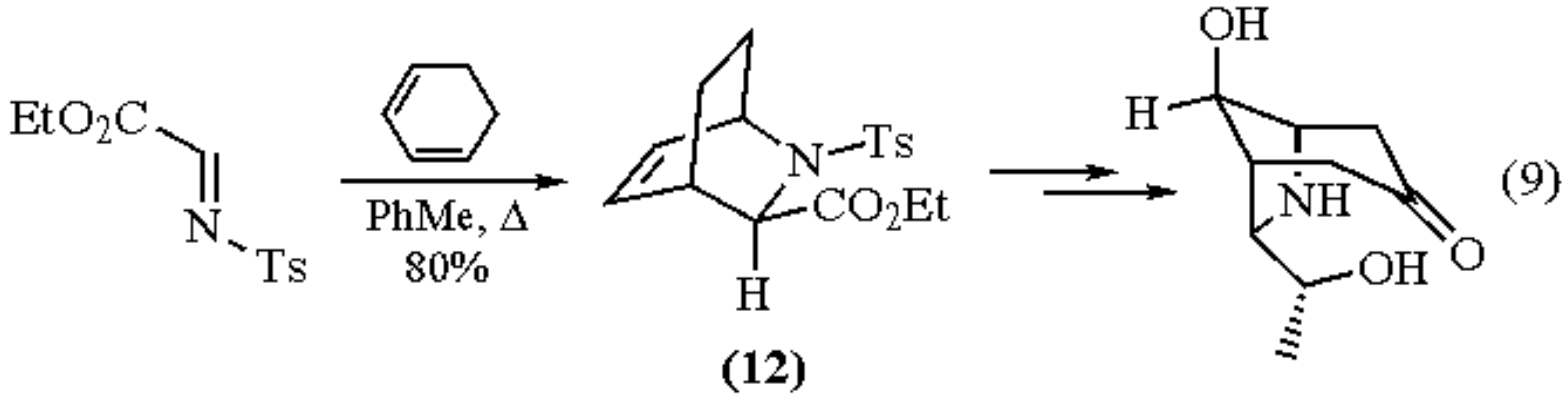

Advances have also been made toward asymmetric hetero Diels-Alder reactions using chiral ester derivatives of (**1**). For example, Holmes and co-workers[8] have employed the *N*-tosylimine glyoxylate derivatives of ethyl (*S*)-lactate (**13a**) and (*R*)-pantolactone (**13b**) (eq 10) in Lewis acid-catalyzed reactions with cyclopentadiene to produce only the *exo* isomers (**14**) and (**15**) with the diastereomeric ratios dependent upon the particular chiral auxiliary employed.

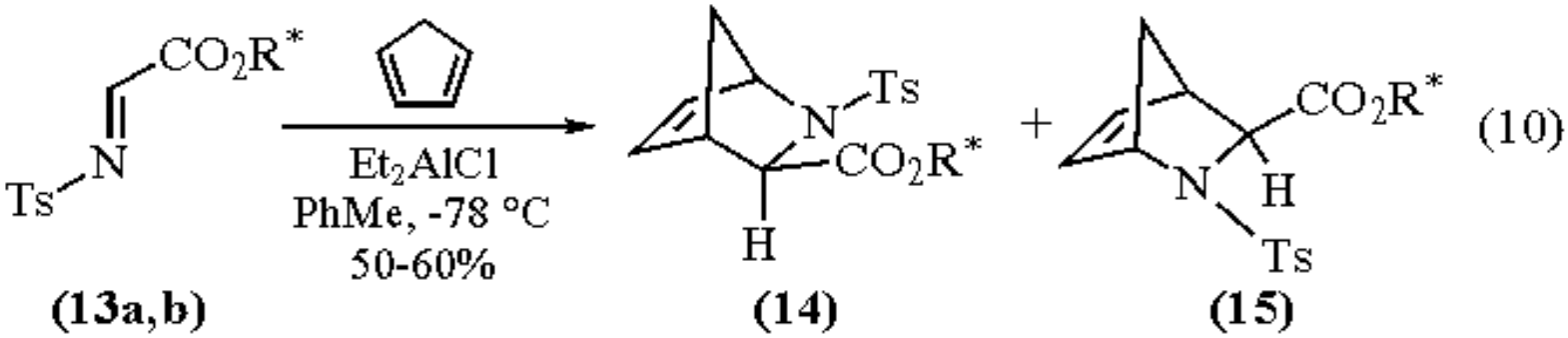

Chiral sulfonamide	Ratio **(14)**:**(15)**
(13a) $R^* =$ 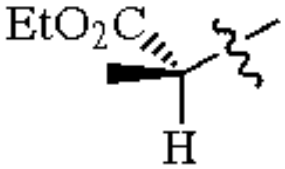	12:88
(13b) $R^* =$ 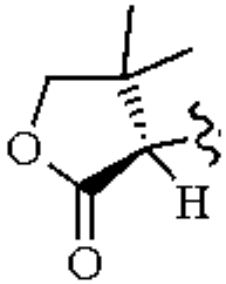	85:15

Hamada and co-workers[18] have recently reported a diastereoselective hetero Diels-Alder reaction between chiral diene (**16**) and (**1**) to produce the single diastereomer (**17**) in good yield (eq 11). This compound has been further elaborated to the alkaloid (-)-cannabisativine, the enantiomer of the natural product.[18b]

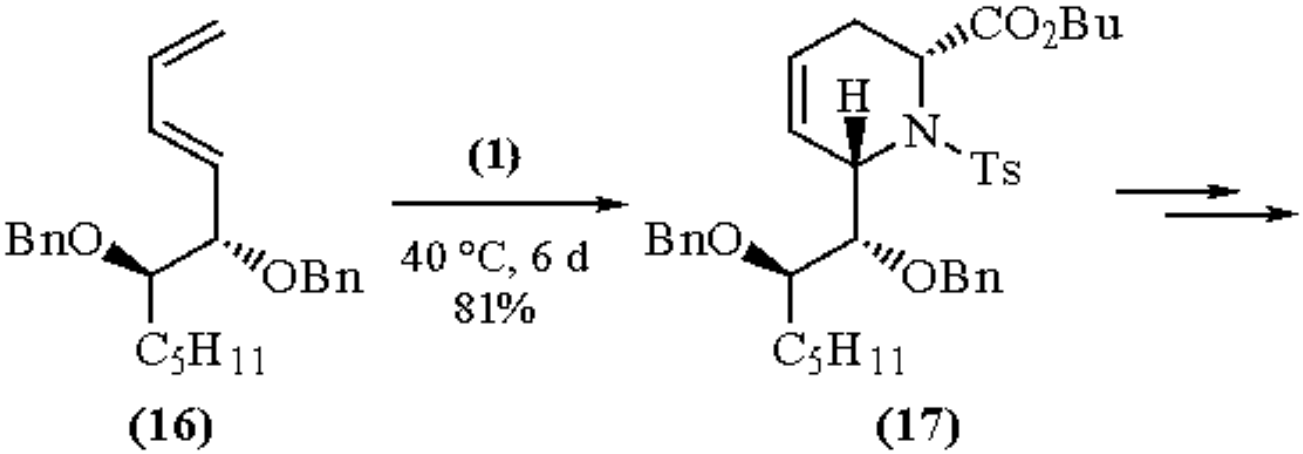

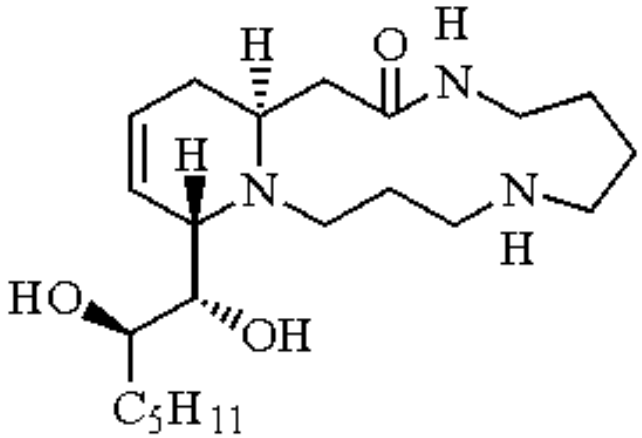

(11)

Recently, Whiting and co-workers[19] have achieved modest diastereoselectivity in a reaction of ethyl *N*-(1*R*)-camphorsulfonyliminoacetate (**18**) with Danishefsky's diene (***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***) (eq 12). Inseparable mixtures of tetrahydropyridone diastereomers were isolated in varying ratios under both thermal and Lewis acid-catalyzed conditions.

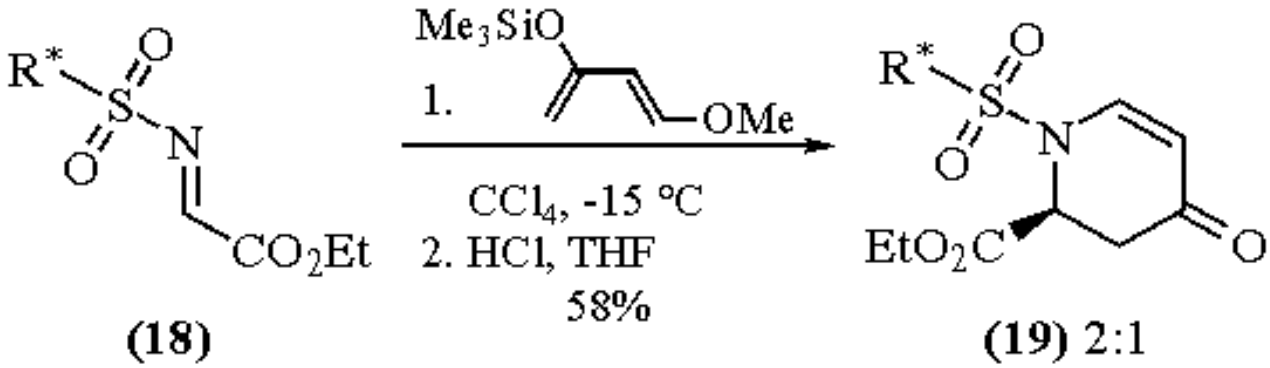

(12)

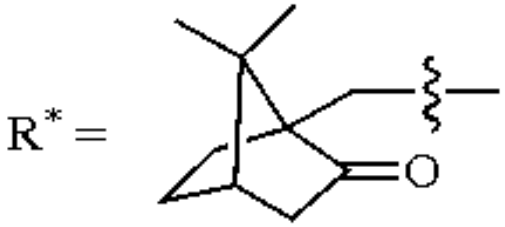

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20. Some chiral derivatives of *N*-alkyliminoacetate esters have also been employed in asymmetric hetero Diels-Alder reactions with excellent selectivity. Examples include α-methylbenzyl derivatives21,22 and α-amino acid derivatives.23
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(*R*)-(+)-*t*-Butyl 2-(*p*-Tolylsulfinyl)acetate

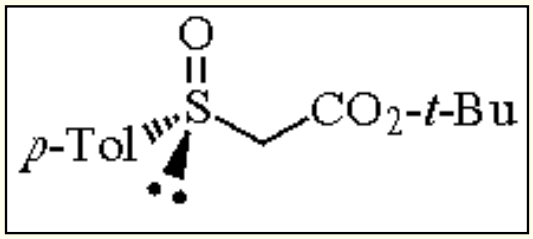

[58059-08-8] · $C_{13}H_{18}O_3S$ · (*R*)-(+)-*t*-Butyl 2-(*p*-Tolylsulfinyl)acetate · (MW 254.34)

(reagent for asymmetric aldol-type condensation;[1] used for the synthesis of sulfinyl dienophiles[13])

Physical Data: $[\alpha]_D^{20}$ = +149° (EtOH, *c* = 2.25)

Preparative Methods: conveniently prepared[2,3] by reaction of the magnesium enolate of *t*-butyl acetate (readily made with ***Bromomagnesium Diisopropylamide***) with ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate*** (eq 1). It was also made in 91% yield by reacting a solution of ***Lithium Diisopropylamide*** with (*R*)-(+)-methyl *p*-tolyl sulfoxide and *t*-butyl carbonate (eq 2).[4] It should be noted that asymmetric oxidation of *t*-butyl 2-(*p*-tolylsulfinyl)acetate with a modified Sharpless reagent gave a poor ee.[5]

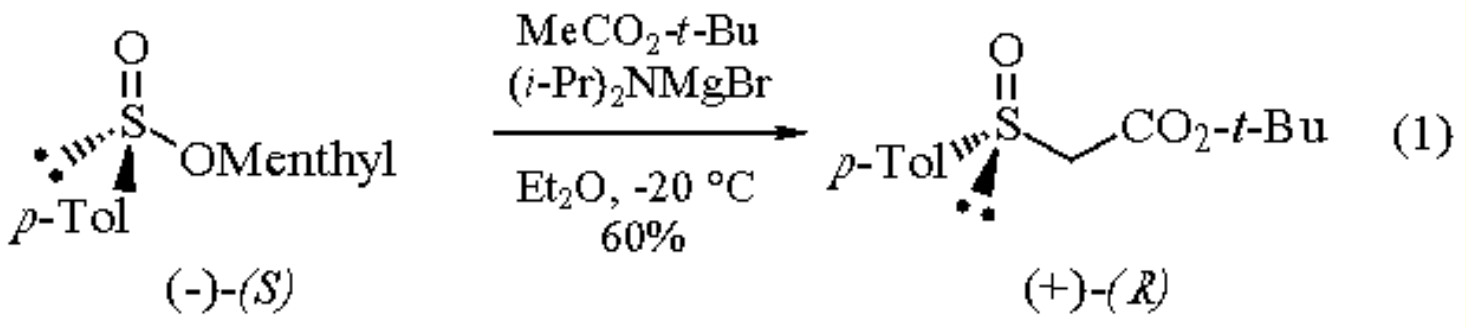

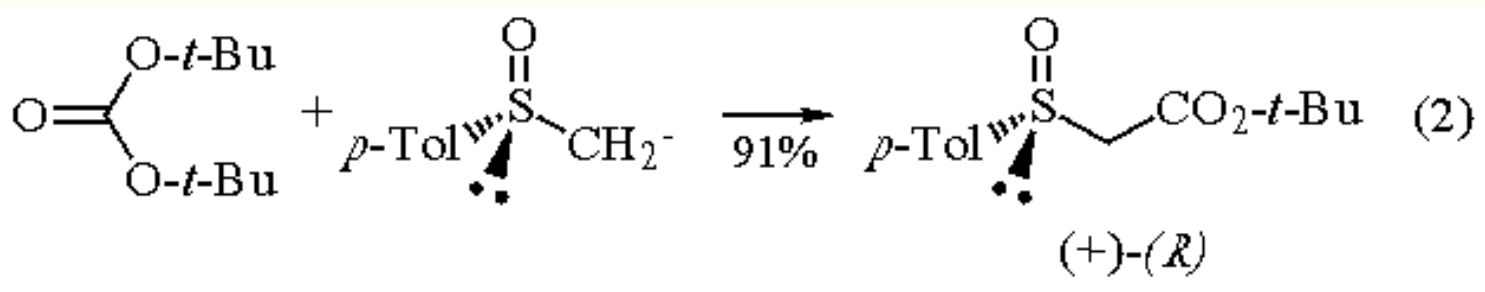

Aldol-Type Condensation.

Aldol-type condensation of the magnesium enolate of (*R*)-(+)-*t*-butyl 2-(*p*-tolylsulfinyl)acetate, prepared with *t*-butylmagnesium bromide, with aldehydes and ketones afforded, after desulfurization with ***Aluminum Amalgam***, β-hydroxy esters in very high diastereoselectivity (eq 3).[3,6,7] Two chiral centers are created in the first step with very high diastereoselectivity (mainly one diastereomer is formed). A model M based on the structure of the sulfinyl ester enolate (determined by ^{13}C NMR)[8] and on electrophilic assistance of magnesium to the carbonyl approach, was proposed to explain and predict the absolute configuration of the two created chiral centers.[3]

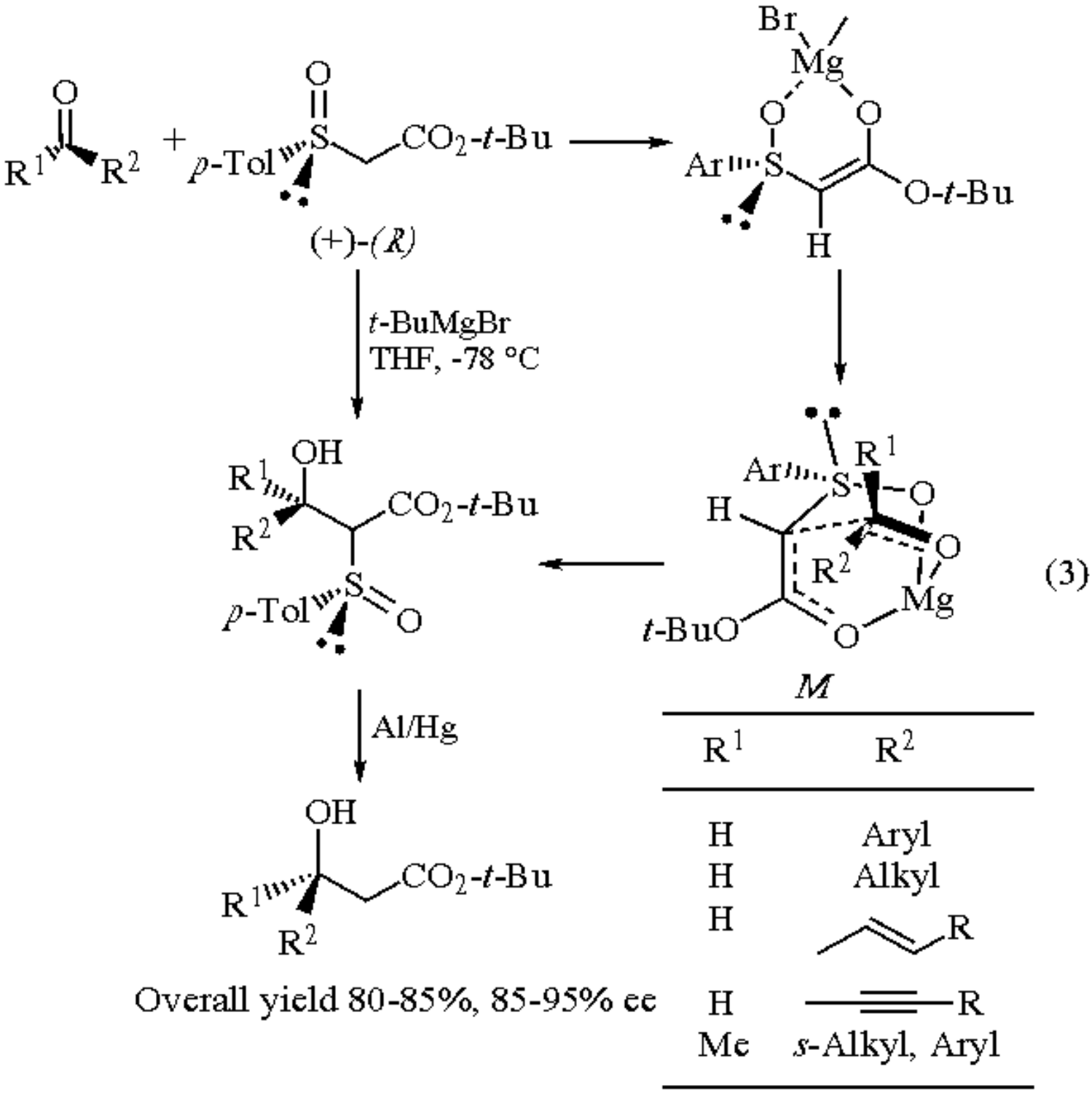

(3)

The first application of this aldol-type asymmetric synthesis was reported by Corey during the later stages of the total synthesis of maytansine.[9] This result (eq 4) showed that the *t*-butyl ester could be replaced by a phenyl ester as long as

the same base, *t*-BuMgBr, is used for the condensation. The reaction of the α,β-unsaturated aldehyde gave, after desulfurization, the corresponding β-hydroxy ester in 80% yield and 86% de.

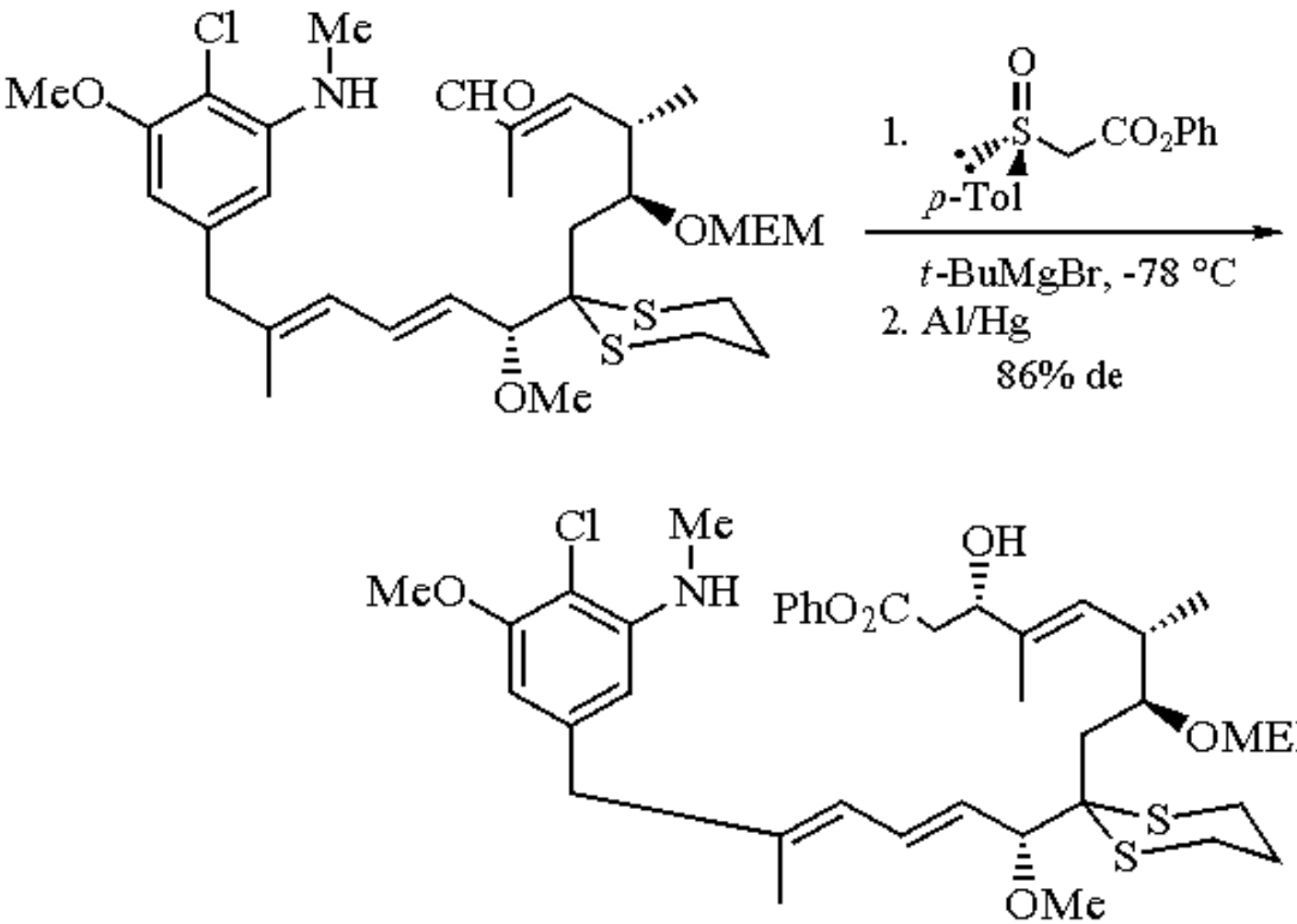

(4)

Optically active five- and six-membered lactones were also prepared by this aldol-type condensation (eq 5).[10]

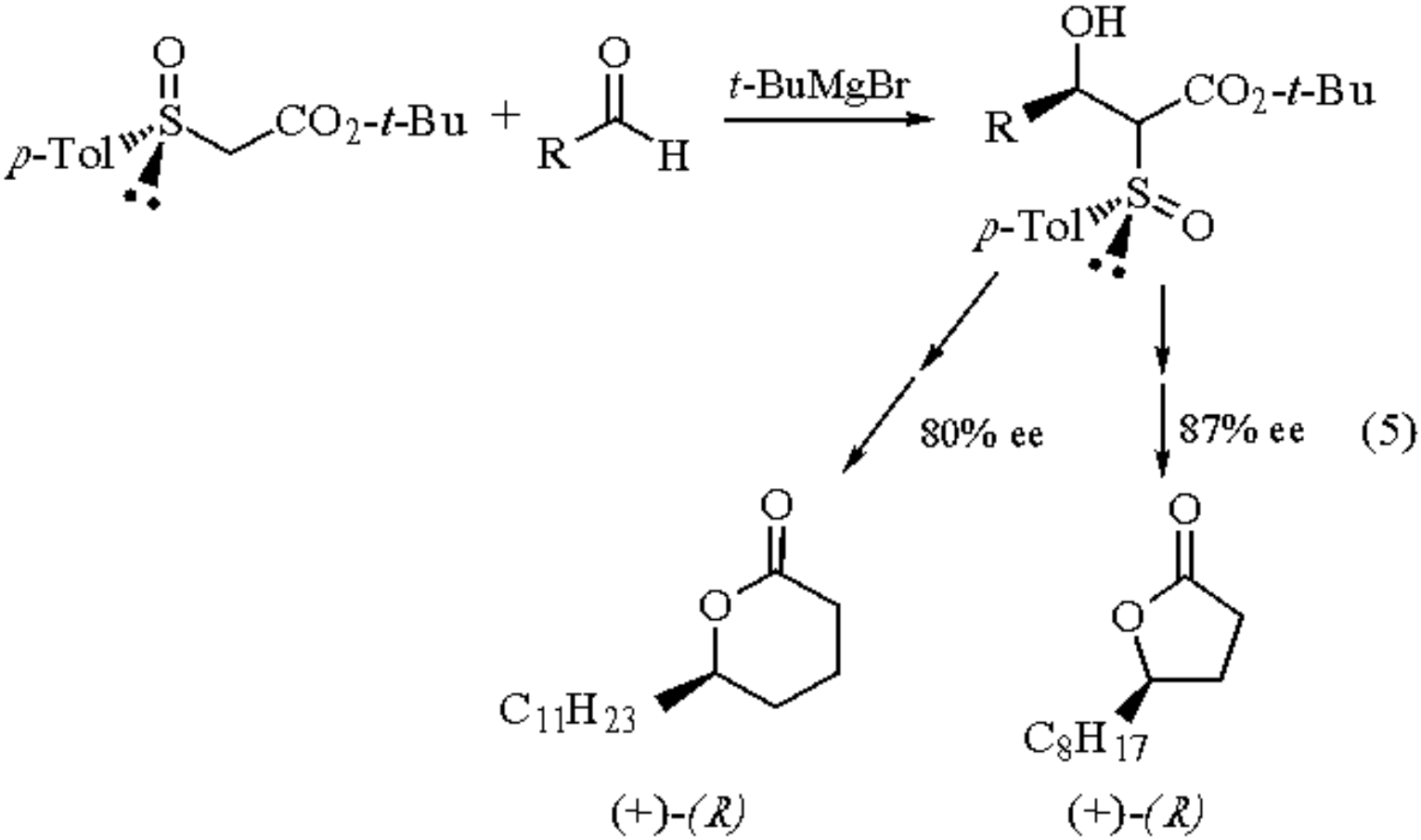

Propargylic aldehyde was also used to prepare, by condensation with (+)-(*R*)-*t*-butyl *p*-tolylsulfinylacetate, a precursor of the C-3-C-8 fragment of leukotriene B_4 (eq 6).[11]

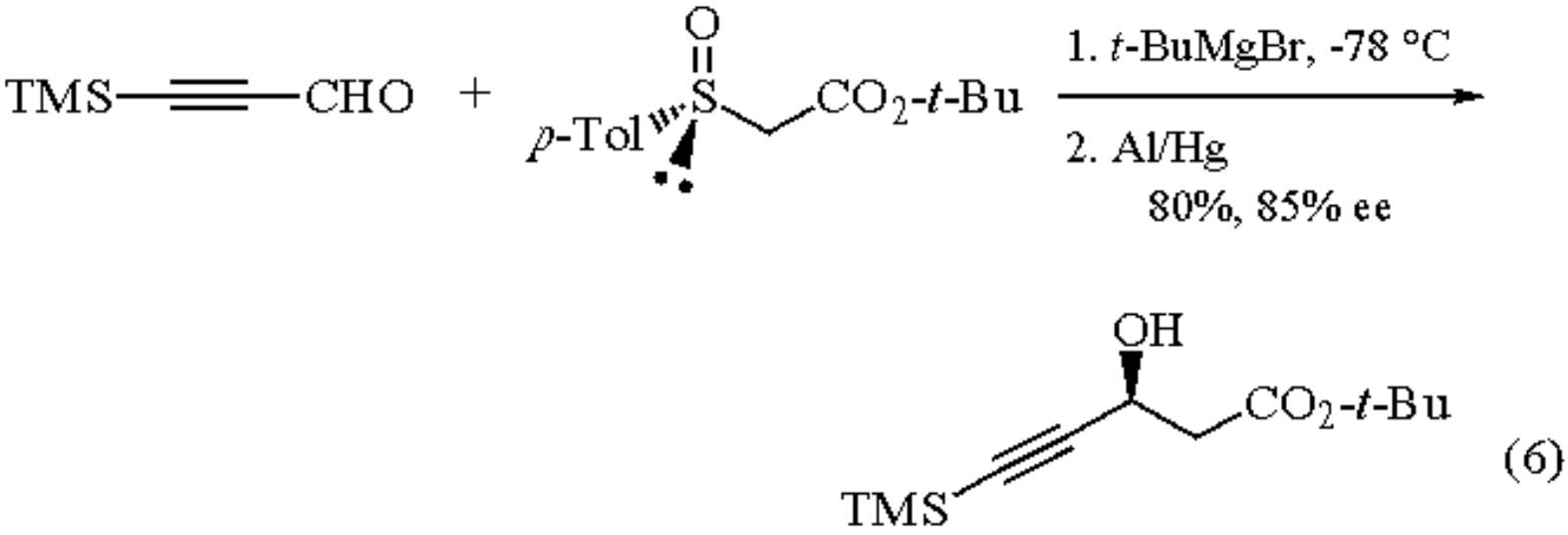

It should be noted that a poor ee was observed during the Michael addition of (+)-(*R*)-*t*-butyl *p*-tolylsulfinylacetate to an α,β-unsaturated ester.[12]

Preparation of Sulfinyl Dienophiles.

This sulfinyl ester was also used to prepare optically active sulfinyl dienophiles by a Knoevenagel-type condensation of ***Glyoxylic Acid*** (eq 7).[13,14]

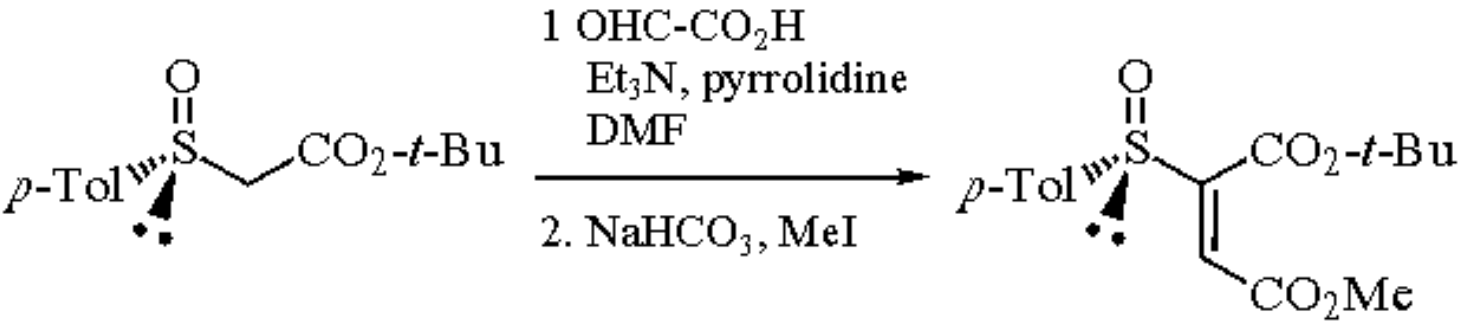

(7)

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(*R*)-(+)-*t*-Butyl 2-(*p*-Tolylsulfinyl)propionate

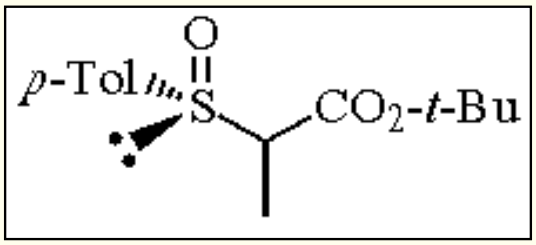

(*R*,*R*)

[83909-72-2] · $C_{14}H_{20}O_3S$ · (*R*)-(+)-*t*-Butyl 2-(*p*-Tolylsulfinyl)propionate · (MW 268.37) (*R*,*S*)

[83909-83-5]

(reagent for asymmetric aldol-type condensation)

Physical Data: $[\alpha]_D$ = +148° (EtOH, *c* = 0.3) for the 1:1 mixture of diastereomers.

Preparative Methods: the synthesis of this compound was first reported by methylation of ***(R)-(+)-t-Butyl 2-(p-Tolylsulfinyl)acetate*** via enolate generation with lithium bases such as ***n-Butyllithium*** or ***t-Butyllithium*** at 0 °C and with only ***Iodomethane*** as the alkylating agent (eq 1).[1] The diastereomeric ratio was shown by ^{1}H NMR to be 50:50 with BuLi and 42:58 with *t*-BuLi. The title compound was also prepared from ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate*** and the magnesium enolate of *t*-butyl propionate in 68% yield as a 1:1 ratio of the two possible diastereomers (eq 2).[1]

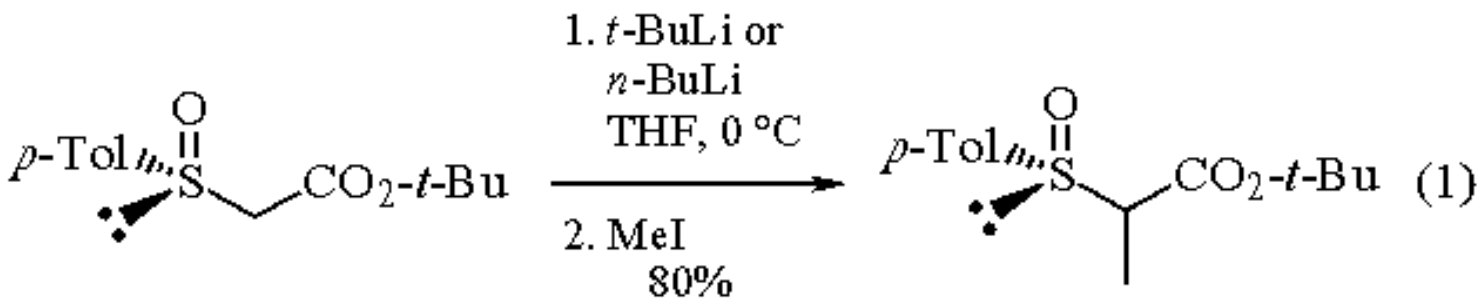

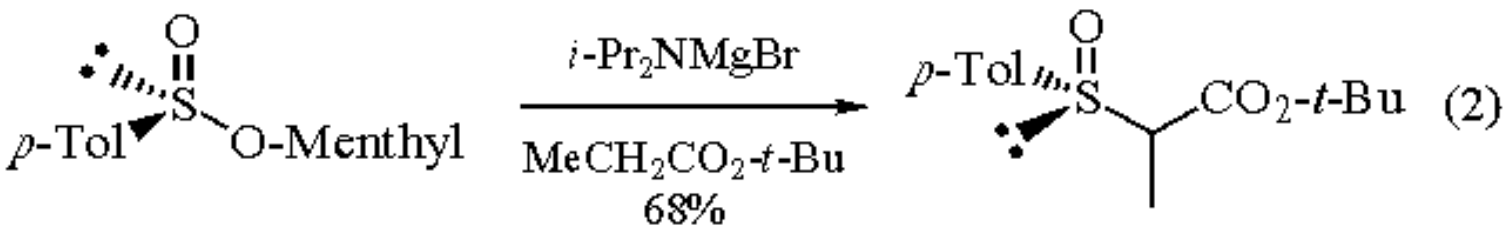

Aldol-Type Condensation.

The aldol-type condensation of the enolate anion of sulfinylpropionate, which was prepared as usual with the base *t*-butylmagnesium bromide, with aldehydes afforded after desulfurization with ***Aluminum Amalgam*** the corresponding β-hydroxy esters in high yield (90%) and, with aliphatic aldehydes, high diastereoselectivity (eq 3).[2,3] The amount of asymmetric induction was determined by transformation of the β-hydroxy esters to the corresponding isopropyl-substituted alcohols.

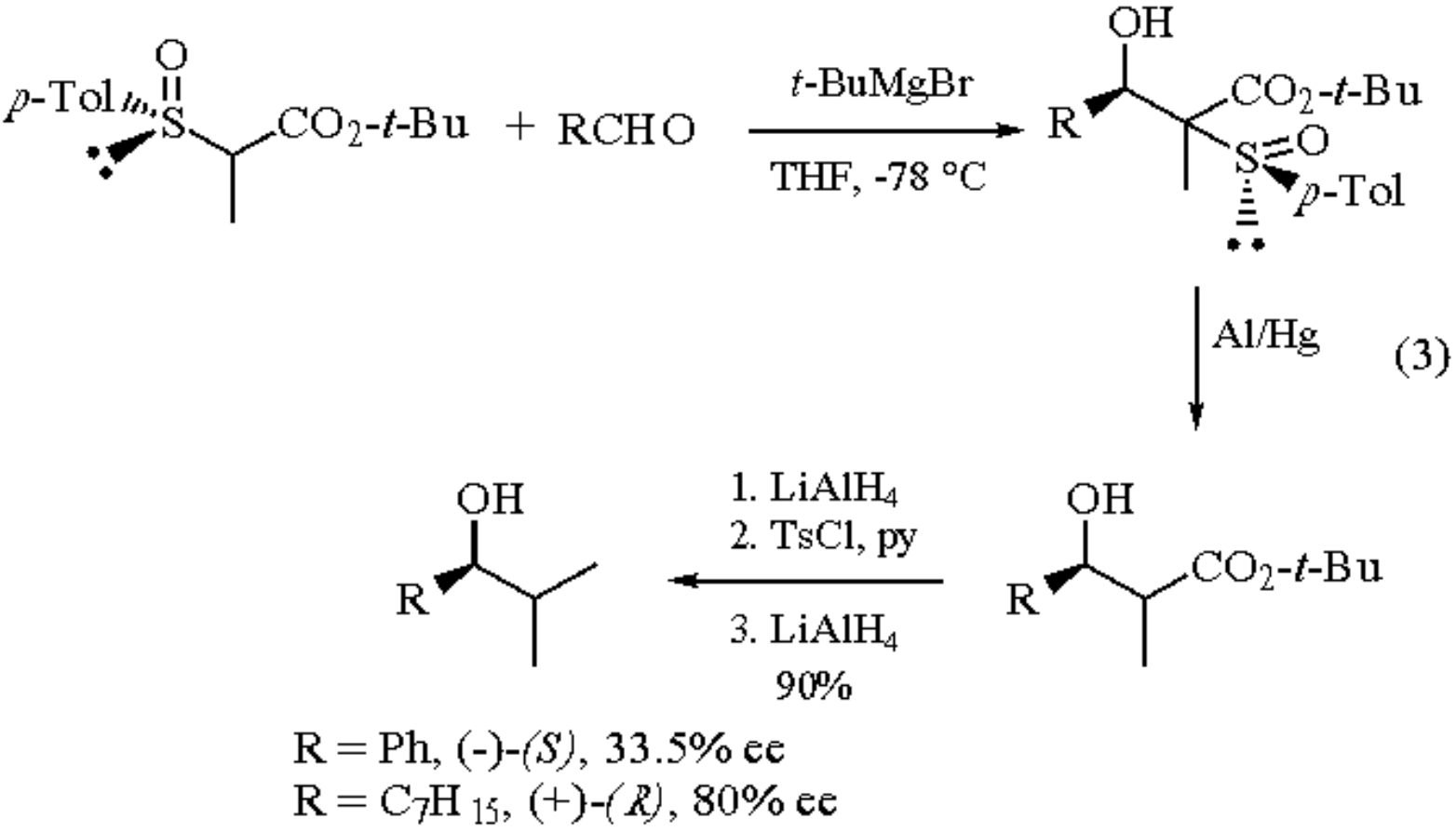

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3. Solladié, G. *S* **1981**, 185.

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t-Butyl 2,2,2-Trichloroacetimidate

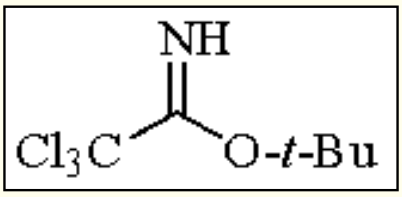

[98946-18-0] · $C_6H_{10}Cl_3NO$ · *t*-Butyl 2,2,2-Trichloroacetimidate · (MW 218.51)

(reagent for preparation of *t*-butyl esters and ethers,[1] and *t*-butylamines[5])

Physical Data: mp 21 °C;[1b] bp 65-69 °C/12 mmHg.[1a]

Solubility: sol organic solvents, preferably nonpolar ones especially cyclohexane (polar solvents promote ionization and decomposition).

Form Supplied in: white solid; commercially available in small quantities.

Preparative Methods: [1a] ***Potassium t-Butoxide*** (1.68 g, 15 mmol) was dissolved in *t*-butanol (30 mL) and this solution was added over 15 min to a stirred solution of ***Trichloroacetonitrile*** (21.6 g, 15 mL, 15 mmol) in dry diethyl ether (30 mL) cooled to 0 °C under nitrogen. The yellow mixture was allowed to warm to 20 °C over 1 h, and then heated to reflux for 1 h. After the reaction mixture had been cooled to rt, volatiles were removed on the rotary evaporator and the residual oil was dissolved in pentane (30 mL). The solution was filtered and the pentane was removed on the rotary evaporator. The residue was then distilled to yield 23 g (70%), bp 65-69 °C/12 mmHg, which solidified on storage.

Handling, Storage, and Precautions: the reagent is slowly hydrolyzed by water and thus should be stored cold under an inert atmosphere. The hydrolysis products are isobutene and trichloroacetamide. The use of polar solvents degrades the reagent more quickly due to decomposition in solvents that promote ionization.

t-Butyl Esters.

The facile preparation of (**1**) (eq 1) provides an easily handled reagent for formation of *t*-butyl esters (eq 2),[1a] extending the usefulness of trichloroacetimidates.[6] The typical previous method involved treatment of the acid with ***Isobutene*** and an inorganic acid catalyst under pressure.[2] The ***Boron Trifluoride Etherate*** catalyzed reaction in cyclohexane has the advantages of Lewis acid catalysis, easy reactions on small scales, and simple workup without water or base.[1,3] An instructive example is provided from the synthesis of dealanylalahopcin (eq 3).[3b] Yields are typically 70-90% with a simple nonaqeuous workup.

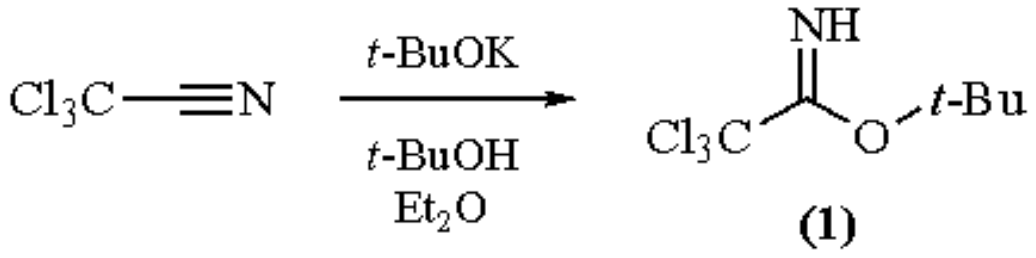

(1)

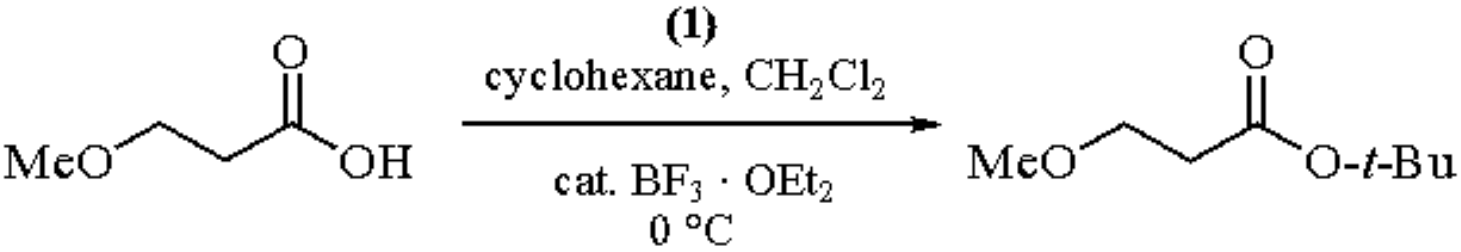

(2)

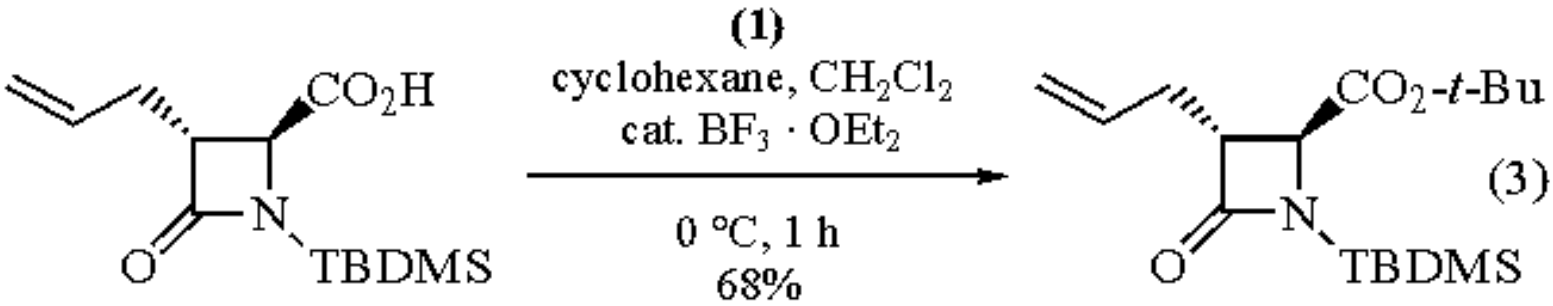

(3)

t-Butyl Ethers.

The methodology for preparing esters with reagent (**1**) has been extended to include ethers.[1a] In particular, this method has shown high selectivity for the formation of the less hindered ether (eq 4).[1a] Typical reactions are carried out in cyclohexane-dichloromethane mixtures for 16-20 h, giving 70% yields. Secondary alcohols require 2 equiv for effective reaction. These conditions compare favorably with the typical isobutene procedure.[4]

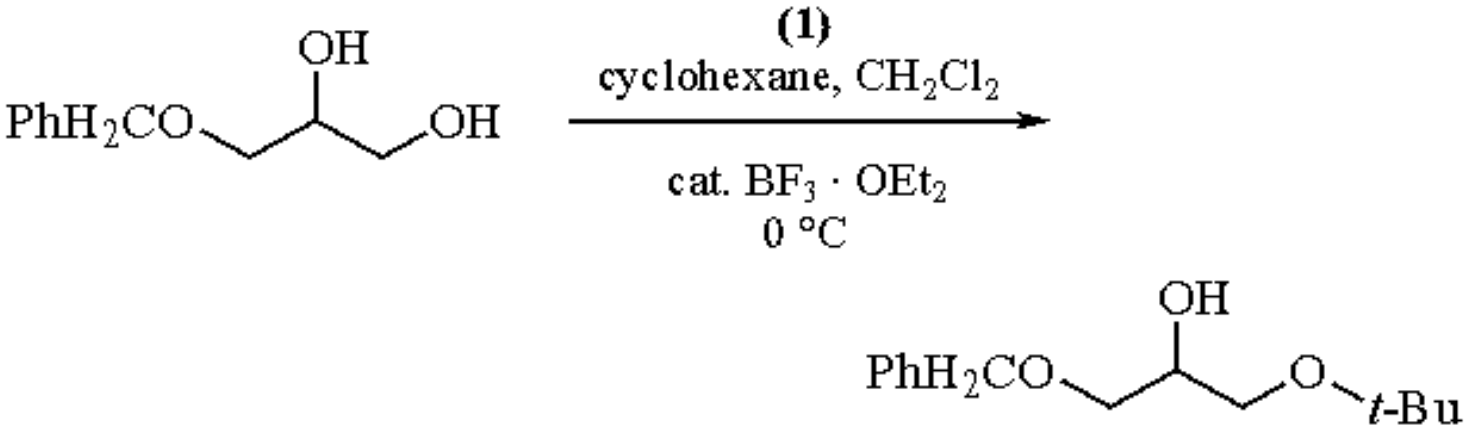

(4)

N-*t*-Butylanilines.

There is a single report of the very encouraging *t*-butylation of a nitrogen, in this case from the nonbasic hindered

aniline (**2**) (eq 5).[5]

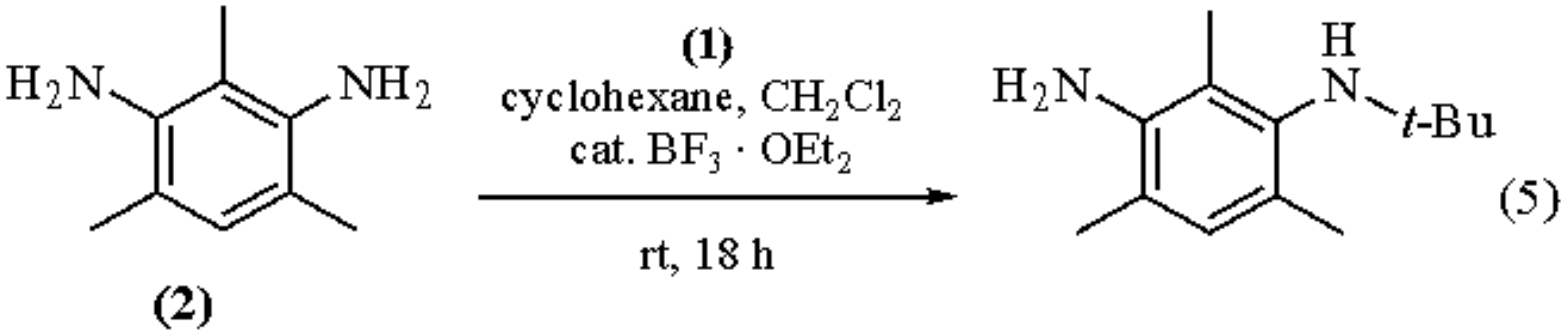

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t-Butyl 2,4,5-Trichlorophenyl Carbonate

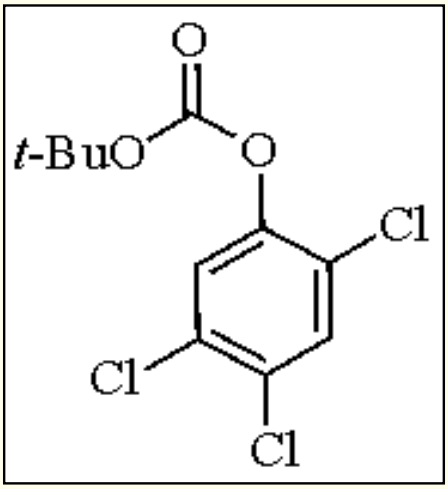

[16965-08-5] · $C_{11}H_{11}Cl_3O_3$ · *t*-Butyl 2,4,5-Trichlorophenyl Carbonate · (MW 297.57)

(reagent for the Boc protection of amino groups;[1] preparation of active esters for peptide synthesis[1])

Physical Data: mp 67-68.5 °C.

Form Supplied in: commercially available solid.

Preparative Method: reaction between 2,4,5-trichlorophenol and ***Phosgene*** in toluene at -10 °C in the presence of dimethylaniline gives 2,4,5-trichlorophenyl chloroformate. Treatment with *t*-butanol and quinoline in CH_2Cl_2 then affords *t*-butyl 2,4,5-trichlorophenyl carbonate.[1]

Purification: recrystallization from methanol/water (charcoal).

Preparation of Active Esters for Peptide Synthesis.

t-Butyl 2,4,5-trichlorophenyl carbonate (**1**) reacts with amino acids in the presence of ***Triethylamine*** to give the *N*-Boc-protected amino acid (**2**), along with 2,4,5-trichlorophenol (eq 1).[1] High yields are obtained (often 90-95%), except for the hydroxy amino acids. Reagent (**1**) is more easily prepared than ***t-Butyl Azidoformate***, commonly used for introduction of the Boc group, but seems otherwise to offer little advantage if protection is the only aim. The utility of (**1**) arises because (**2**) and the 2,4,5-trichlorophenol may be extracted together from the reaction mixture into ethyl acetate; addition of ***1,3-Dicyclohexylcarbodiimide*** then affords the *N*-Boc-protected 2,4,5-trichlorophenyl ester (**3**) of the amino acid. These activated esters may be employed for peptide synthesis; they are generally crystalline solids, stable in alcoholic solvents and on storage, and their reactivity towards amino groups is at least as high as that of the corresponding *p*-nitrophenyl esters (see also ***p-Nitrophenol***). Following peptide formation, the 2,4,5-

trichlorophenol coproduct is readily removed.

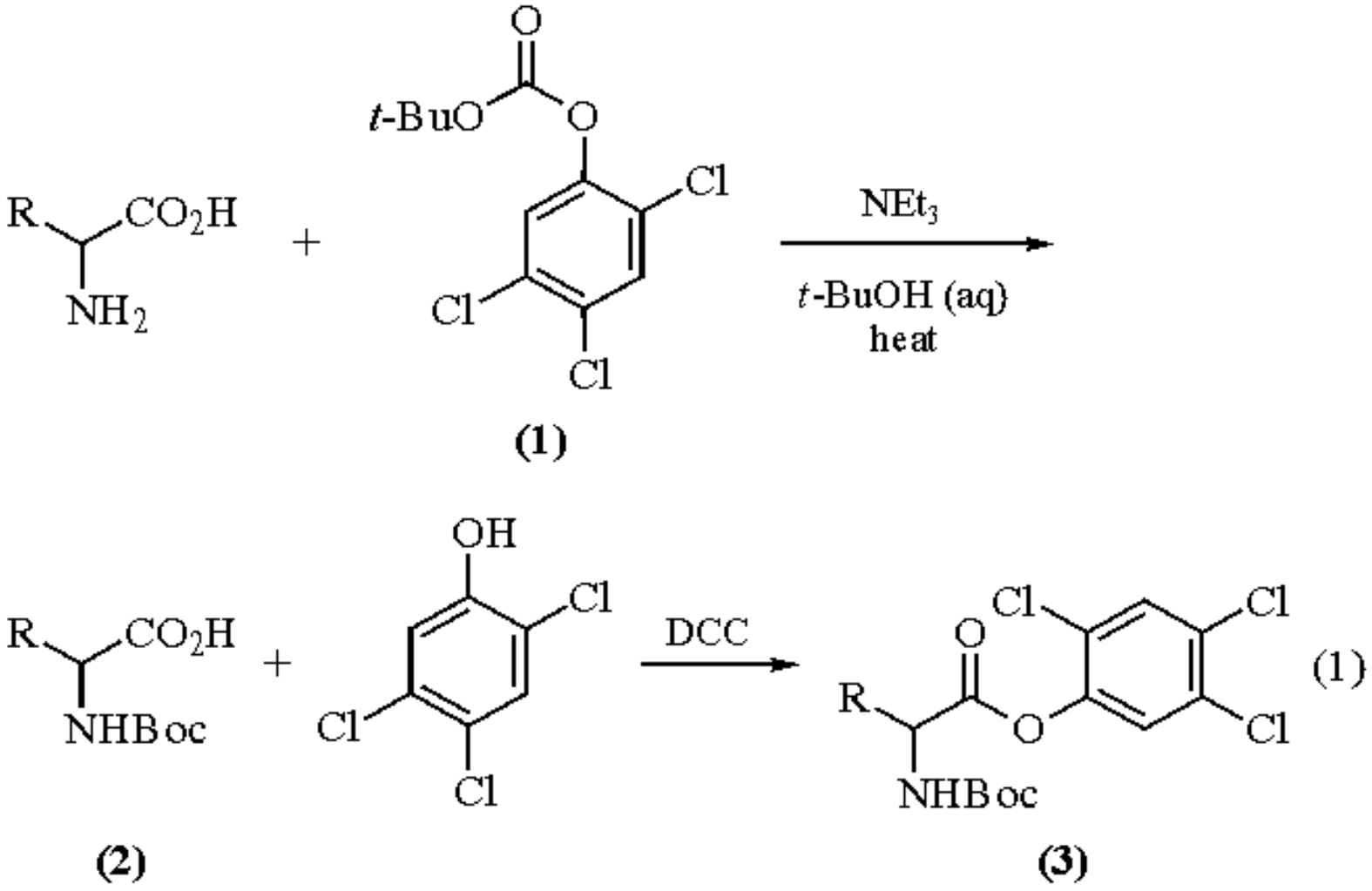

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Alan Armstrong

University of Bath, UK

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n-Butyltrichlorostannane[1]

n-BuSnCl$_3$

[1118-46-3] · $C_4H_9Cl_3Sn$ · *n*-Butyltrichlorostannane · (MW 282.16)

(Lewis acid catalyst for polymerization reactions, esterifications,[2] dehydration processes, acetalizations, and transacetalizations[3])

Alternate Names: butyltrichlorotin; butyltin trichloride.

Physical Data: bp 93 °C/10 mmHg; *d* 1.7 g cm^{-3}; n_D 1.5235.

Solubility: sol cold water, common organic solvents.

Form Supplied in: colorless liquid, widely available. *Drying:* the usual procedure is vacuum distillation. It dissolves in water to give strongly acidic, clear solutions. Hydrolysis is reversible: BuSnCl$_3$ may be recovered by distillation.[4]

Handling, Storage, and Precautions: storage of anhydrous BuSnCl$_3$ in a dark desiccator is recommended. It is reputed to be of low toxicity with respect to other organotins. Use in a fume hood.

Esterifications and Transesterifications.

Monoorganotin(IV) halides have been employed as esterification and transesterification catalysts.[1e] BuSnCl$_3$ shows fairly good activity in the reactions shown in eqs 1 and 2.[1e,2] BuSnCl$_3$ is also an effective esterification catalyst for fatty acids derived from palm oil.[2]

$$EtCO_2H + BuOH \longrightarrow EtCO_2Bu + H_2O \qquad (1)$$

$$EtCO_2Bu + MeOH \longrightarrow EtCO_2Me + BuOH \qquad (2)$$

Formation of Diallyl Ethers from Allylic Alcohols.

Butyltrichlorostannane catalyzes the dehydration of the following alcohols: (*E*,*Z*)-MeCH=CHCH$_2$OH, (*E*)-

MeCH=CHCH(OH)Me, $Me_2C=CHCH_2OH$, $MeCH=CHCH(OH)CH_2CH=CH_2$, and $MeCH=CHCH(OH)CH(R)CH=CH_2$ (R = Me, *n*-Pr) to give isomeric mixtures of diallyl ethers[5a] in high yields (80-90%). Three isomeric species are formed from dehydration of (*E*)-3-penten-2-ol (eq 3).

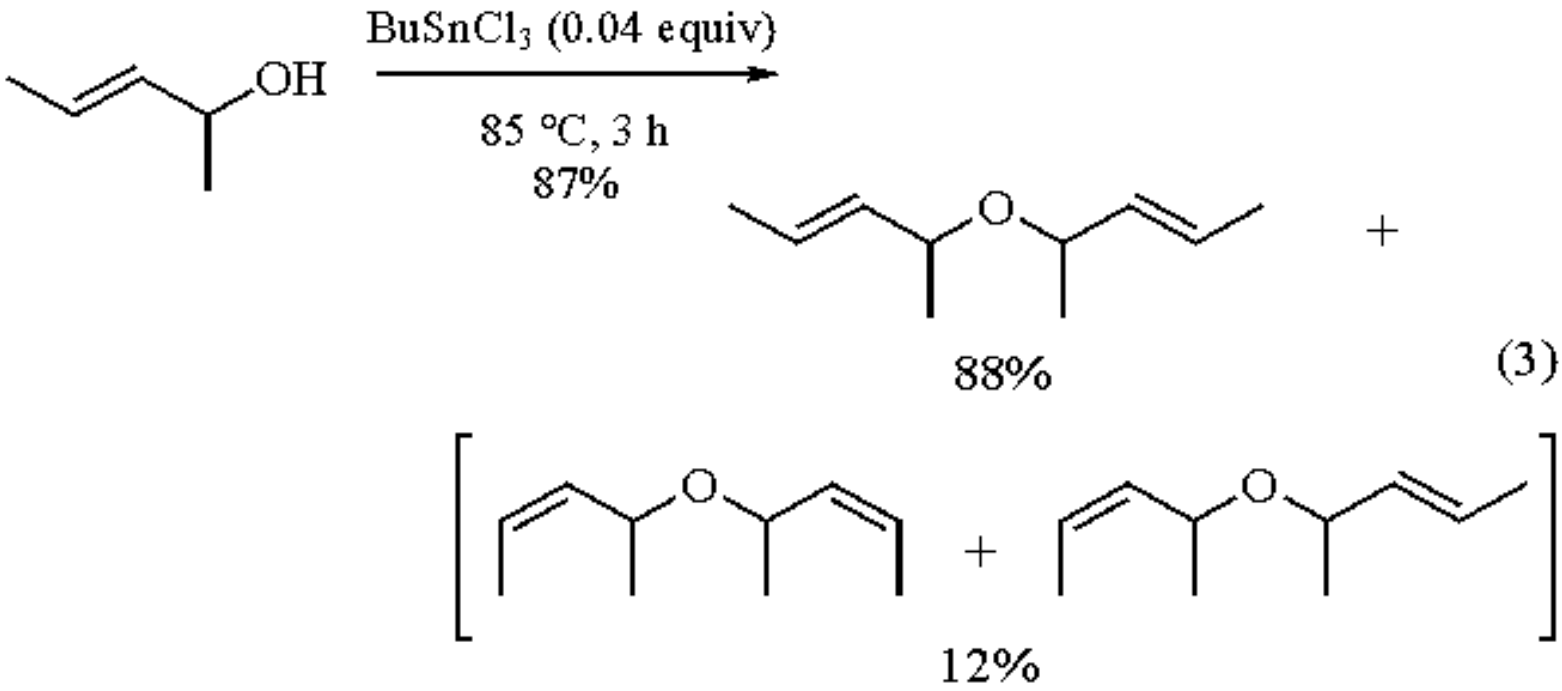

Formation of Cyclic Ethers from Diols and Triols.

Organotin halides catalyze the conversion of 1,*n*-diols (*n* = 4-6) to cyclic ethers[5] (eq 4); cyclizations of triols have been also described.[3,5b]

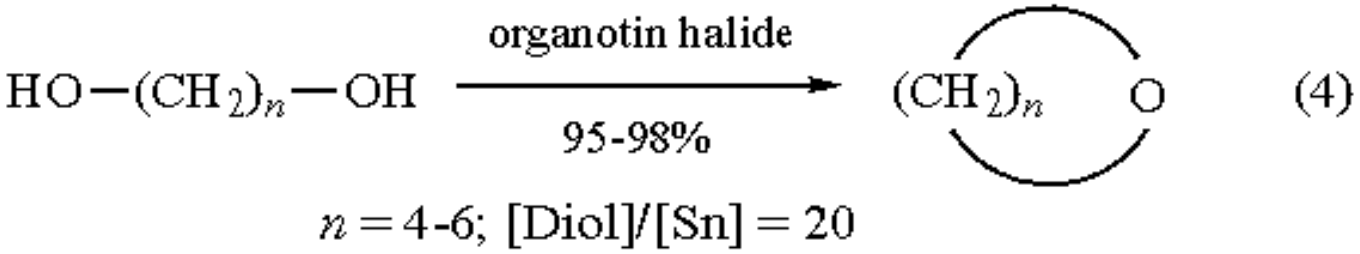

The catalytic activity of tin compounds is in the order $MeSnCl_3$ &egt; $PhSnCl_3$ &egt; $SnCl_4$ > $BuSnCl_3$ >> Me_2SnCl_2 > Bu_2SnCl_2 >> $(Bu_2SnCl)_2O$. $BuSnCl_3$ is preferred over ***Tin(IV) Chloride*** and other monoorganotin halides because it is easy to handle, is inexpensive, and it can be recovered unchanged after workup. The following cyclic ethers have been synthesized from the corresponding diols: THF, 2-methyl-THF, 2,5-dimethyl-THF, 2,5-dihydrofuran, THP, 2-methyl-THP, 2,4-diallyl-THP, and 1,4-dioxane. 3-Hydroxy-THF and 3-hydroxymethyl-THP are also prepared in 92% and 70% yield from 1,3,4-trihydroxybutane and 1,5,6-trihydroxyhexane.[3] A related cyclization is that of acetonylacetone to 2,5-dimethylfuran (eq 5).[5b]

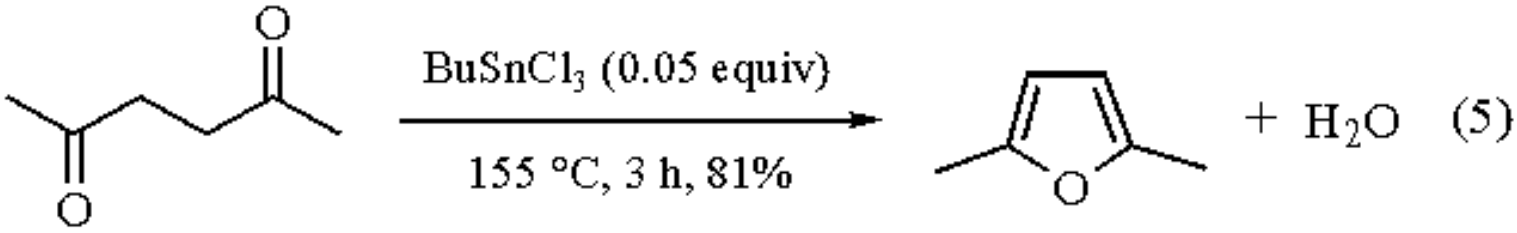

Dehydration of Cyclic Diols.

1,3-Cyclopentane-, 1,4-cyclohexane-, and 1,2-cyclooctanediol, when heated at 180-235 °C in the presence of $BuSnCl_3$ ([diol]/[Sn] in the range 20-40), give rise to mixtures of dehydrated products.[5b] 1,2-Cyclooctanediol yields a mixture of cyclooctanone, 1,4-epoxycyclooctane, and 1,3-cyclooctadiene (eq 6).[5]

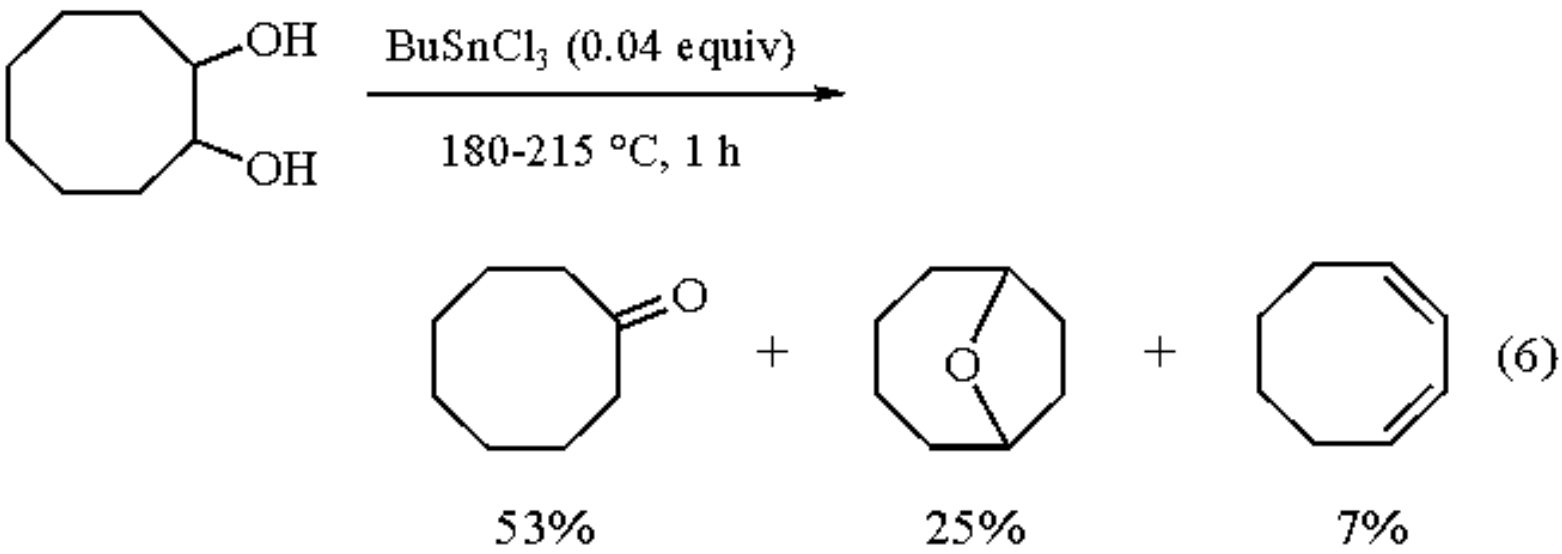

Acetalizations and Transacetalizations of Diols and Triols.

$BuSnCl_3$, which is able to act both as an acid and as a dehydrating agent, promotes acetalizations using diols and triols[6] with many advantages compared to other methods. Reactions occur under mild conditions, with very short reaction times and in absence of solvent. Even aqueous solutions of aldehydes can be used (eq 7).

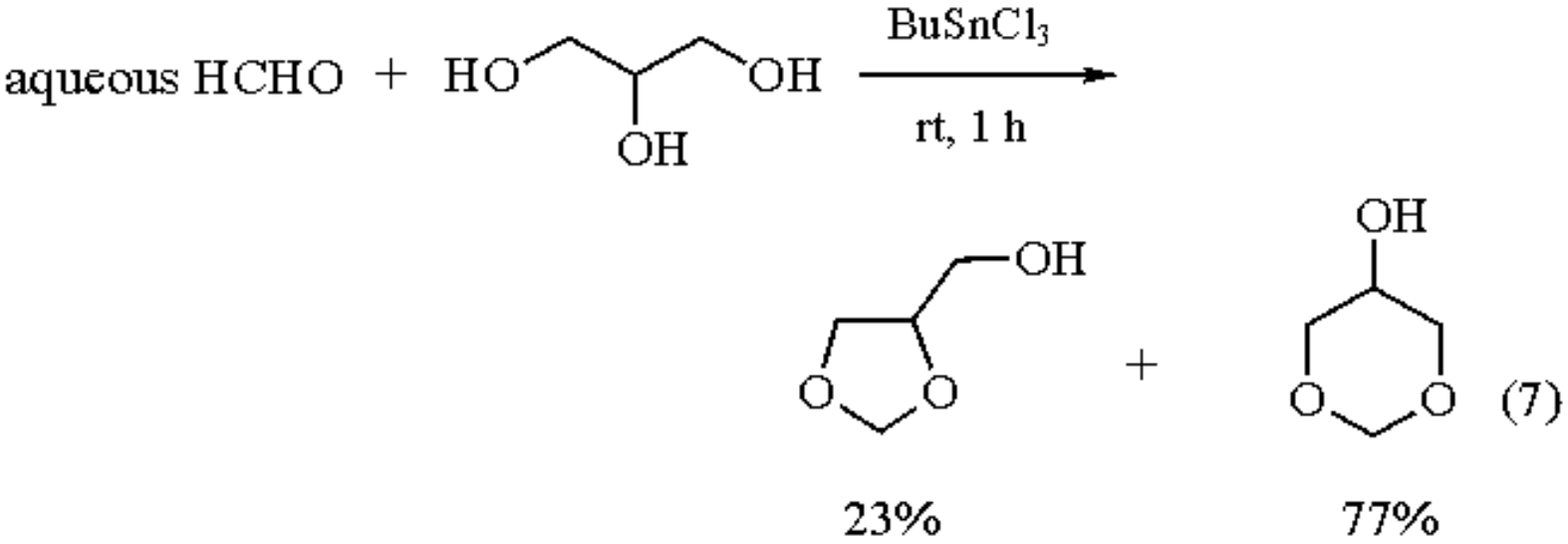

Transacetalizations of aldehyde dialkyl acetals, $R^1CH(OR^2)_2$, with diols and polyols can be carried out using $BuSnCl_3$ as the catalyst.[6b,c] As in acetalizations, reactions of glycerol with acetals provide mixtures of 1,3-dioxolanes and 1,3-dioxanes, the latter being the major products (eq 8).

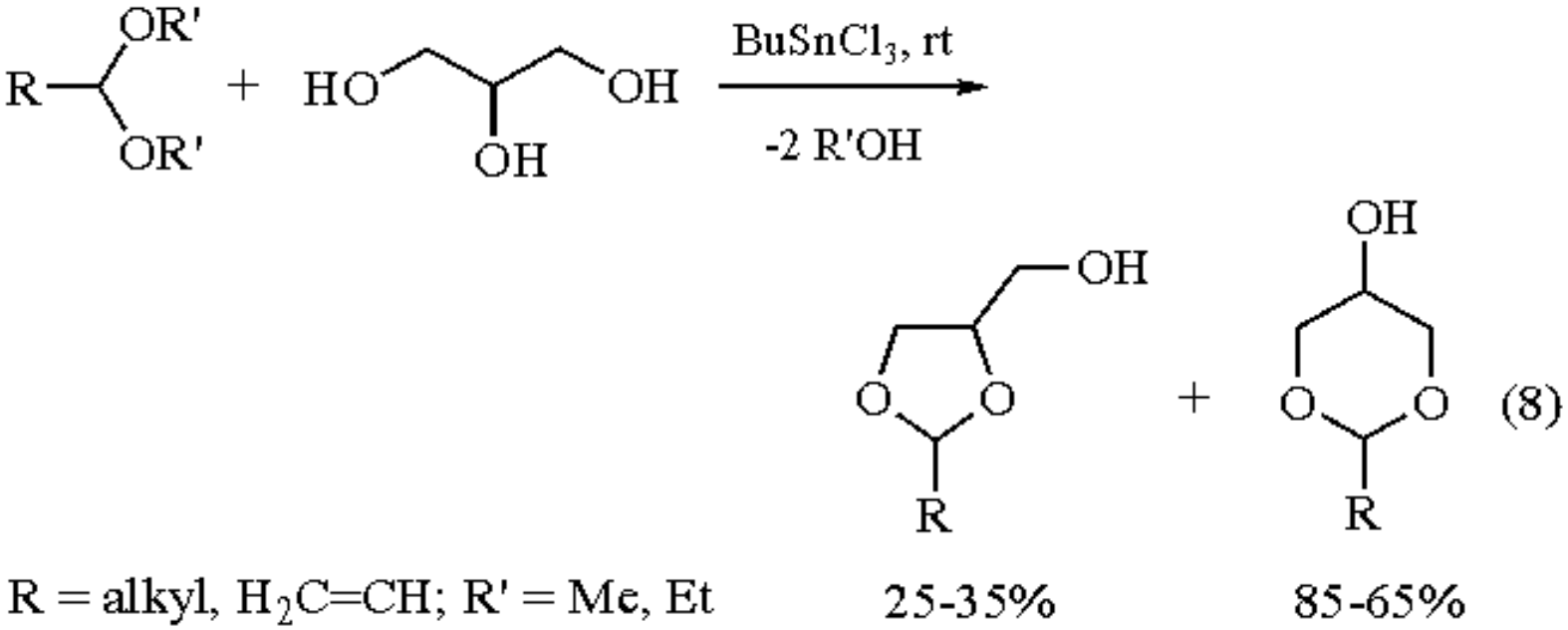

Several examples where $BuSnCl_3$ has been used as a catalyst for transacetalizations of 1,2-diols, 1,3-diols, 1,3-propanethiol, and 1,2,3-propane- and 1,2,4-butanetriols with ***2,2-Dimethoxypropane*** have been reported.[6d] The same catalyst has been employed for acetonation of the above alcohols using the enol ether ***2-Methoxypropene***.[6d]

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6. (a) Marton, D.; Slaviero, P.; Tagliavini, G. *G* **1989**, *119*, 359. (b) Marton, D.; Tagliavini, G. *Main Group Met. Chem* **1990**, *13*, 363. (c) Marton, D.; Slaviero, P.; Tagliavini, G.; Vanzan, N.; Zordan, M. *Chemistry and Technology of Silicon and Tin*; Kumar Das, V. G., Ed.; Oxford University Press: Oxford, 1992; p 277. (d) Carifiglio, T.; Marton, D; Stivanello, D..; Tagliavini, G. *Main Group Met. Chem.* **1992**, *15*, 247.

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t-Butyl Trimethylsilylacetate

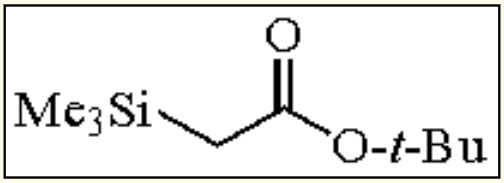

[41108-81-0] · $C_9H_{20}O_2Si$ · *t*-Butyl Trimethylsilylacetate · (MW 188.34)

(used to prepare lithium enolates which can be alkylated;[1,2] can be alkenated with aldehydes and ketones;[3] can be acylated;[4] can be reacted with Group 14 halides[5])

Physical Data: air stable, colorless liquid; bp 67 °C/13 mmHg; n^{20}_D 1.4184; ^{1}H NMR ($CDCl_3$, 90 MHz) 0.13 (s, 9H), 1.45 (s, 9H), 1.80 (s, 2H); IR 1710 cm^{-1}.

Preparative Methods: an advantage of *t*-butyl trimethylsilylacetate over its methyl and ethyl ester analogs is that it can be prepared by *C*-silylation of the lithium enolate of *t*-butyl acetate at -78 °C in THF (85-90% yield). Under the same conditions the enolates of methyl and ethyl acetate give primarily *O*-silylated products.[3] The reagent has also been prepared by a rapid ***Boron Trifluoride Etherate*** catalyzed reaction of ***Trimethylsilylketene*** with *t*-butyl alcohol.[6]

Lithium Enolate.

Most applications require initial formation of the enolate (**1**) (eq 1), which is obtained as a white solid suspended in THF, stable indefinitely at -78 °C.[1]

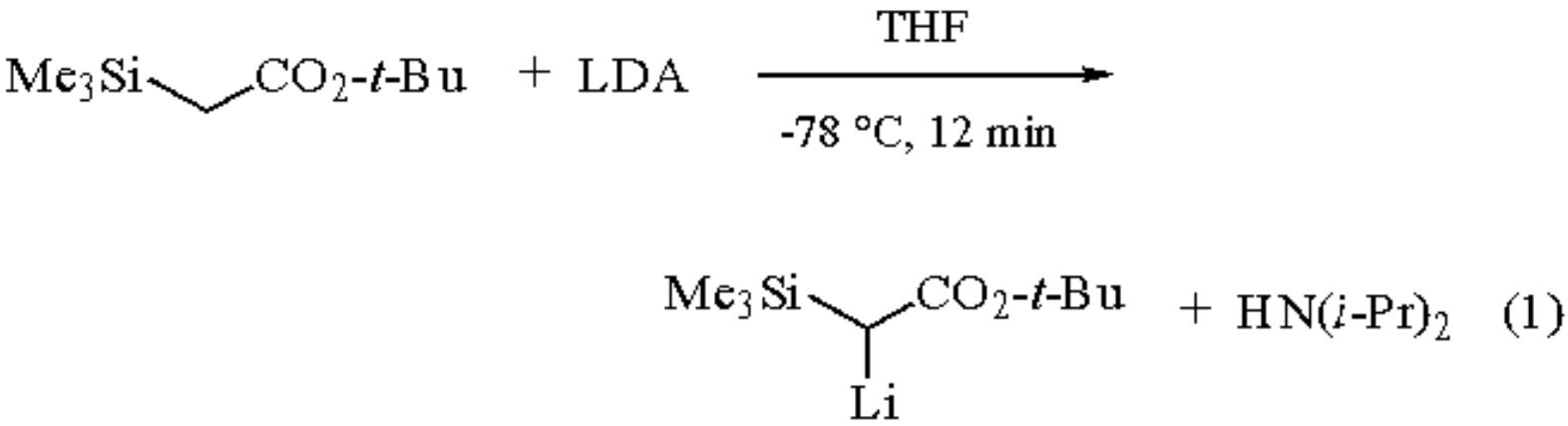

(1)

Alkylation Reactions.

Enolate (**1**) is readily alkylated with a variety of primary alkyl halides at -70 to 0 °C in THF,[2,7] usually in the presence of TMEDA or DMSO. The alkylation products may be desilylated (eq 2) to provide a two-carbon chain extension which is not prone to dialkylation or elimination side reactions.[7a]

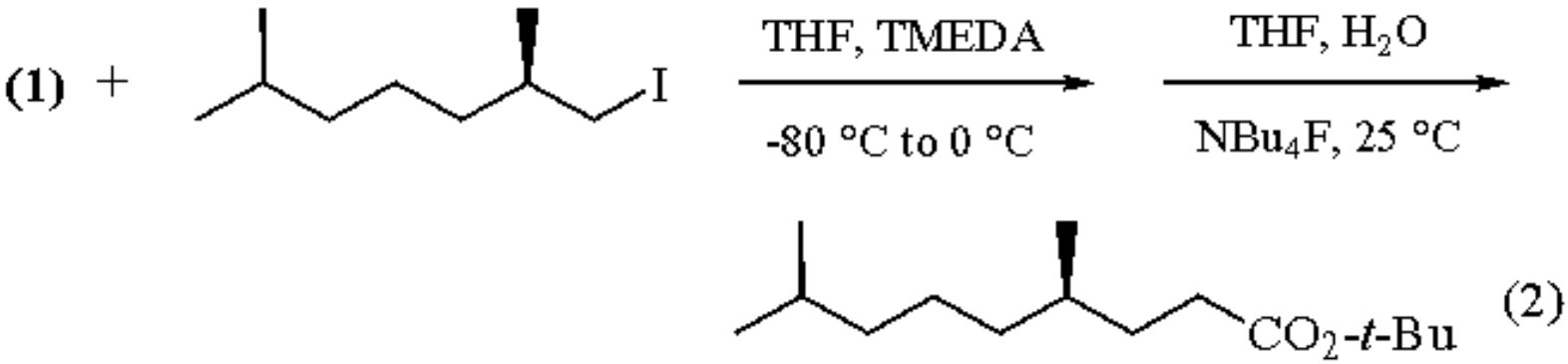

The reagent is spiroalkylated in two steps with 2-methyl-1,4-diiodobutane (eq 3).[7b]

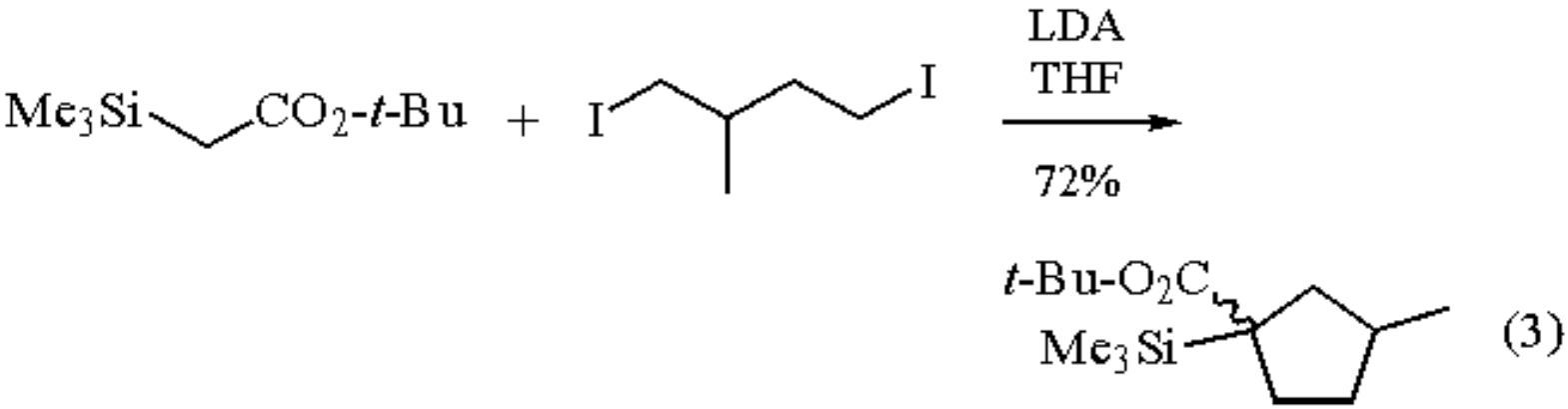

Enolate (**1**) can be vinylated with 2-bromopropene in the presence of a Ni catalyst.[7c]

Peterson Alkenation.[8]

Enolate (**1**) reacts with aldehydes or ketones to give α,β-unsaturated esters (eq 4).[1,8] In some cases (**1**) gives better yields and different *E*:*Z* ratios from the analogous Horner-Emmons reactions with phosphonoacetates.[9]

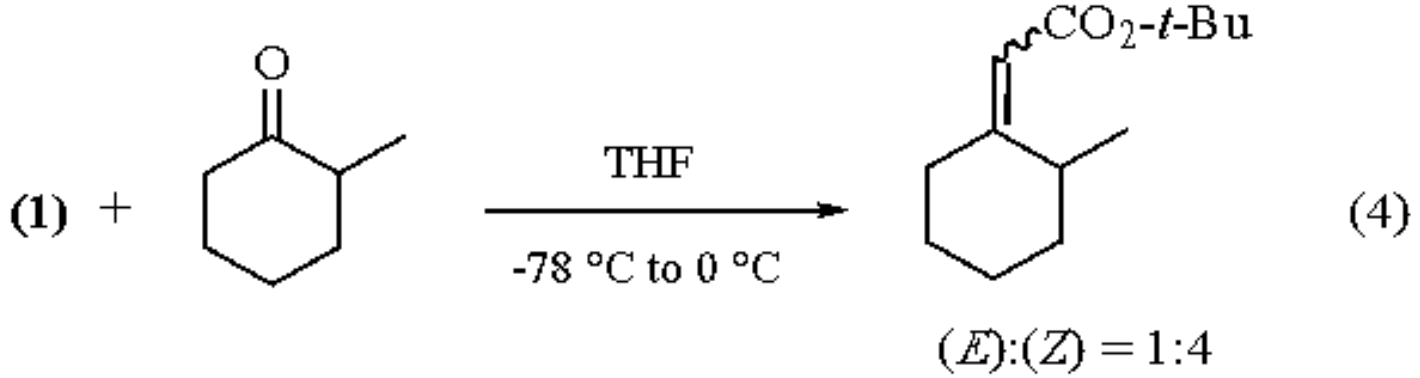

Reaction with Acyl Derivatives.

Enolate (**1**) does not react with ethyl acetate or *N*,*N*-dimethylacetamide, and gives a complicated mixture of products with acetyl chloride. However, (**1**) is acetylated with acetylimidazole to give the lithium enolate of *t*-butyl acetoacetate (eq 5).[4a]

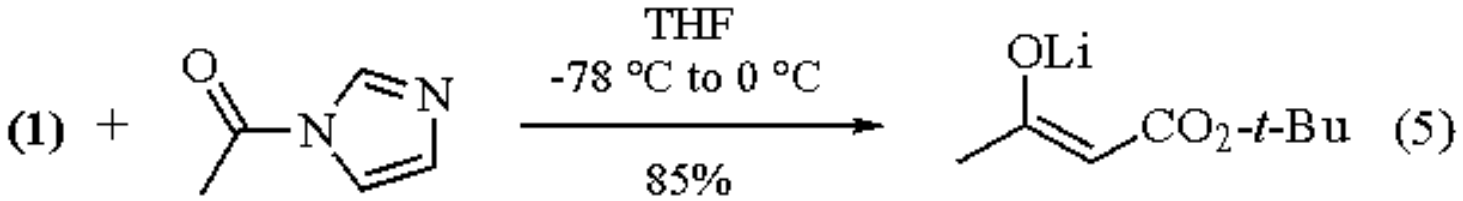

Protonation of the reaction mixtures obtained with a variety of acylimidazoles gives β-keto esters in 50-94% yields. Enolate (**1**) reacts with a variety of lactones to give Peterson alkenation products (eq 6).[4b]

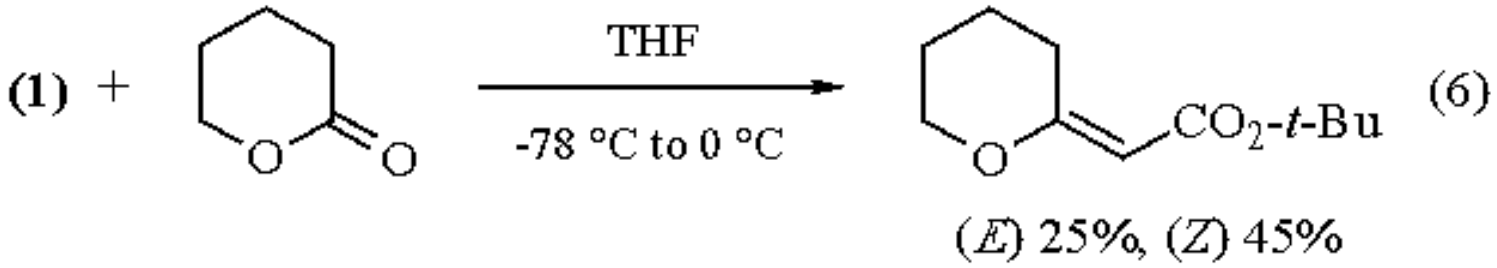

Enolate (**1**) reacts with some aromatic nitriles (but not with benzonitrile) to give *N*-silylenamines.[10]

Reaction with Group 14 Halides.

Enolate (**1**) reacts with ***Chlorotrimethylgermane*** or ***Tri-n-butylchlorostannane*** to give *t*-butyl (trimethylgermyl)(trimethylsilyl)acetate (83% yield)[5a] and *t*-butyl (trimethylsilyl)(tri-*n*-butylstannyl)acetate,[5b] respectively.

Related Reagents.

***t-Butyl* α*-Lithiobis(trimethylsilyl)acetate*; *Ethyl Lithioacetate*; *Ethyl Lithio(trimethylsilyl)acetate*; *Ethyl Trimethylsilylacetate*; *Triethyl Phosphonoacetate*; *Trimethylsilylacetic Acid*.**

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2-Butynoic Acid[1]

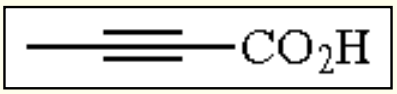

[590-93-2] · $C_4H_4O_2$ · 2-Butynoic Acid · (MW 84.07)

(dianion used in α- and γ-alkylation;[2] used in conjugate addition reactions and Diels-Alder reactions)

Physical Data: mp 78-80 °C.[3]

Preparative Methods: from 3-methyl-2-pyrazolin-5-one via bromination followed by basic hydrolysis;[3] via carboxylation of propynylsodium or ***Propynyllithium***.[4,5]

Purification: sublimation (60 °C/0.02 mm Hg).[3]

Handling, Storage, and Precautions: use in a fume hood.

Selective α- and γ-Alkylation.

The dianion of butynoic acid undergoes selective alkylation at the α- or γ-position depending on the reaction conditions (eq 1).[2] The original Pitzele procedure using ***Lithium Diisopropylamide*** in THF-HMPA or ***Lithium 2,2,6,6-Tetramethylpiperidide*** is not regioselective and leads to mixtures in favor of the alkynic derivative.[6] Reaction of aldehydes under the latter conditions also gives mixtures of alkynic and allenic derivatives.[7,8]

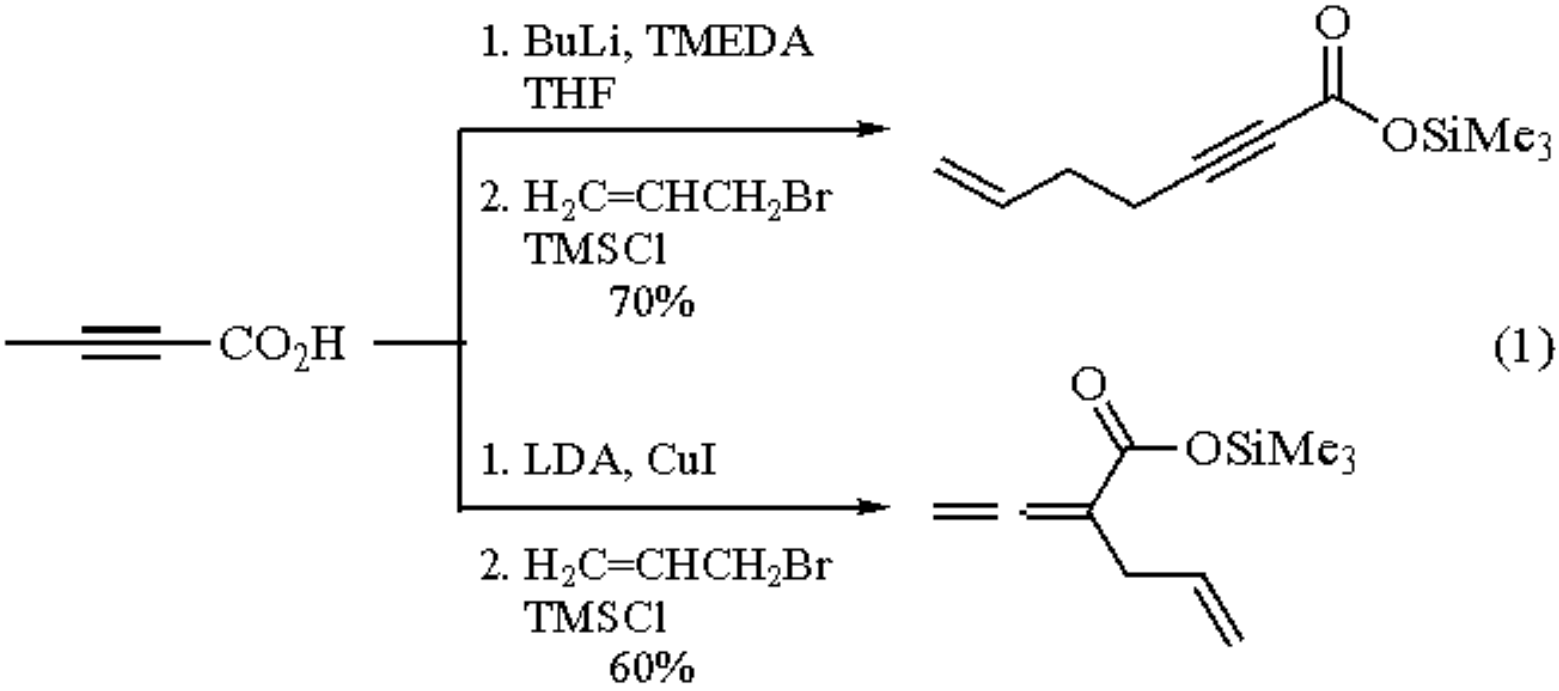

Conjugate Addition.

2-Butynoic acid undergoes conjugate addition with ***Phenylcopper*** or ***Lithium Diphenylcuprate*** to yield the (*E*) derivative with high stereoselectivity (eq 2).[9] Stereospecific *syn* addition is also observed with esters of 2-butynoic acid.[10]

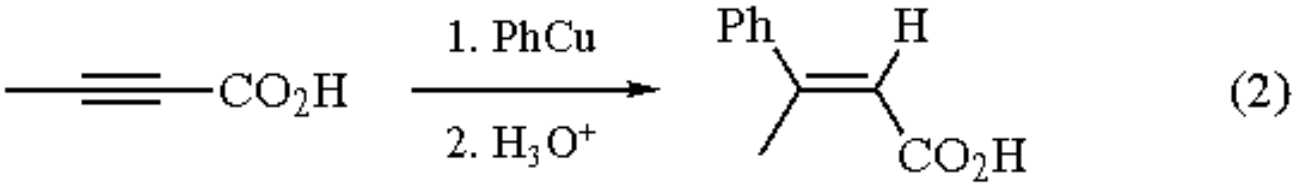

Cycloaddition.[11]

2-Butynoic acid undergoes Diels-Alder reactions with ***Cyclopentadiene*** (neat, 1 h, 185 °C; 68%).[12] The intramolecular version with a sorbyl ester is also known (eq 3).[13]

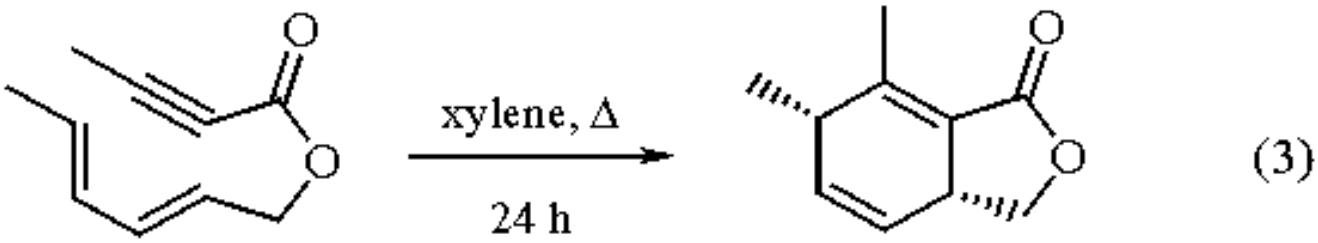

Related Reagents.

3-Butyn-2-one; ***3,3-Diethoxy-1-propyne***; ***Methyl Propiolate***; ***Propargyl Aldehyde***; ***3-Tetrahydropyranyloxy-1-propyne***; ***3-Tetrahydropyranyloxy-1-trimethylsilyl-1-propyne***.

---

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Pierre J. De Clercq & Frank Nuyttens

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3-Butyn-2-one

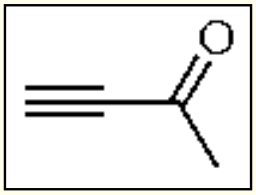

[1423-60-5] · C_4H_4O · 3-Butyn-2-one · (MW 68.08)

(conjugate acceptor, dienophile)

Physical Data: bp 85 °C; *d* 0.87 g cm^{-3}.

Solubility: sol chloroform, diethyl ether, ethanol.

Form Supplied in: neat liquid; widely available.

Preparative Methods: from 3-butyn-2-ol using oxidation[1,2] or catalytic isomerization.[3]

Handling, Storage, and Precautions: is a highly toxic, flammable liquid. It is also a severe lachrymator. It may be fatal if inhaled, swallowed, or absorbed through the skin. When handling this material, appropriate protective clothing, safety goggles, and an approved respirator should be worn. The material should be refrigerated when stored. Use in a fume hood.

3-Butyn-2-one has been employed successfully in Pictet-Spengler[4] reactions, Diels-Alder and ene reactions,[5] 1,3-dipolar cycloadditions,[6] and cyclotrimerizations.[7] A regioisomeric mixture of isoxazoles is produced when 3-butyn-2-one is reacted with bromonitrile oxide (generated in situ).[7] The major product is an intermediate in the synthesis of the β-agonist broxaterol.

A variety of nucleophiles successfully add to 3-butyn-2-one (and related alkynones).[8,9] Attempts to use 3-butyn-2-one in Robinson annulations have not been very successful.[10] Nitro-stabilized carbanions add well using phase transfer catalysis (eq 1), yielding preferentially the (*E*) isomer.[11]

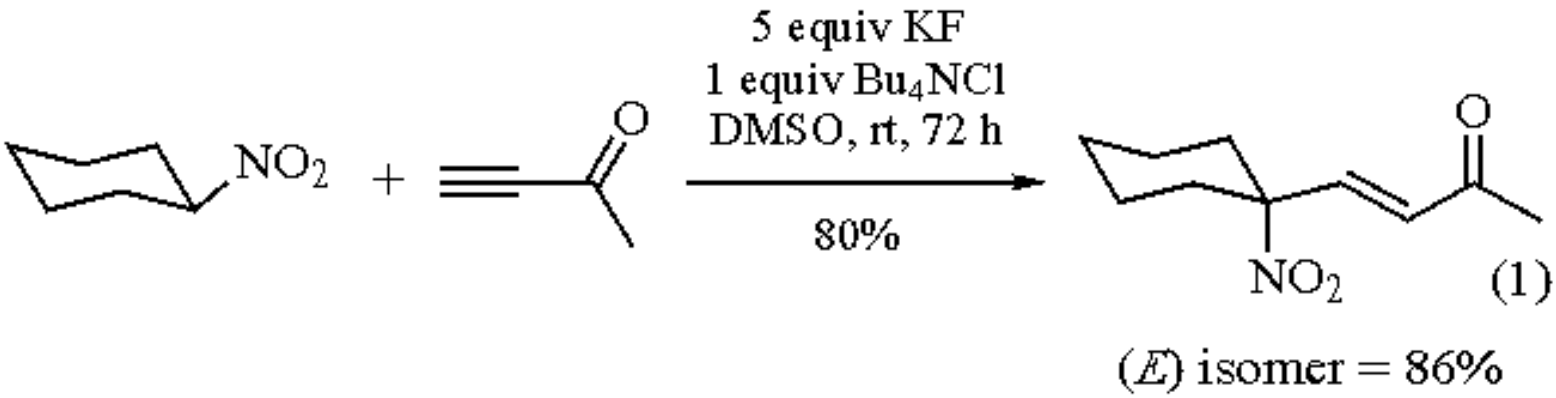

Trialkylboranes[12] and ***Tris(trimethylsilyl)aluminum***[13] efficiently transfer alkyl and trimethylsilyl groups, respectively, in a conjugate fashion.

Asymmetric reduction has been achieved using several different reagents.[14-17] Many other alkynones are reduced with high levels of asymmetric induction and the best result to date with 3-butyn-2-one was achieved using either Eapine- or Prapine-Borane.[14,18] For more sterically hindered alkynones, ***(+)-B-Chlorodiisopinocampheylborane*** works well.[14] Reduction of the tosylhydrazone of 3-butyn-2-one produces 1,2-butadiene in reasonable yield.[19]

Related Reagents.

4-Methoxy-3-buten-2-one; ***Methyl Vinyl Ketone***; ***Propargyl Aldehyde***.

---

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γ-Butyrolactone[1]

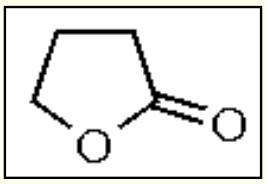

[96-48-0] · $C_4H_6O_2$ · γ-Butyrolactone · (MW 86.09)

(useful source of di- and trifunctional acyclic synthons; can be converted into various types of substituted γ-lactones and tetrahydrofurans)

Alternate Names: 4-hydroxybutyric acid γ-lactone; dihydro-2(3*H*)-furanone.

Physical Data: bp 204 °C; mp -43.5 °C; *d* 1.129 g cm^{-3}.

Solubility: misc with water; sol most organic solvents (e.g. CH_2Cl_2, Et_2O, benzene, THF, and MeOH).

Form Supplied in: colorless liquid (>99%); inexpensive.

Purification: hygroscopic; water can be removed by distillation from CaH_2, $CaSO_4$, or BaO under dry Ar. When the commercial reagent is distilled twice from CaH_2, the fraction boiling at 80-81 °C/11 mmHg contains 99.8% γ-butyrolactone.[2]

Handling, Storage, and Precautions: avoid contact with skin or eyes; do not inhale or ingest; vapor is irritating to the eyes and upper respiratory tract. Anhydrous γ-butyrolactone should be used immediately after distillation for best results. Use in a fume hood.

Formation of Halo Acid Derivatives.

The proclivity of lactones to undergo halide-assisted ring opening has often been exploited for easy access to valuable synthetic intermediates.[3] Thus alcoholysis in the presence of ***Hydrogen Bromide*** provides 4-bromobutyrates (eq 1).[4,5] Related procedures involving ***Bromotrimethylsilane***,[6] ***Boron Tribromide***,[7] or ***Phosphorus(III) Bromide***[3d] as the bromide source are also effective. Similarly, 4-iodobutyrates are obtained by using ***Iodotrimethylsilane***,[6a,8] BBr_3/***Sodium Iodide***,[7] or the ***Boron Triiodide***-*N*,*N*-diethylaniline complex (eq 2).[9] Alternatively, they can be prepared on a large scale from bromo or chloro esters by halogen exchange.[3f] The latter are readily available through alcoholysis of 4-chlorobutanoyl chloride (eq 3).[10]

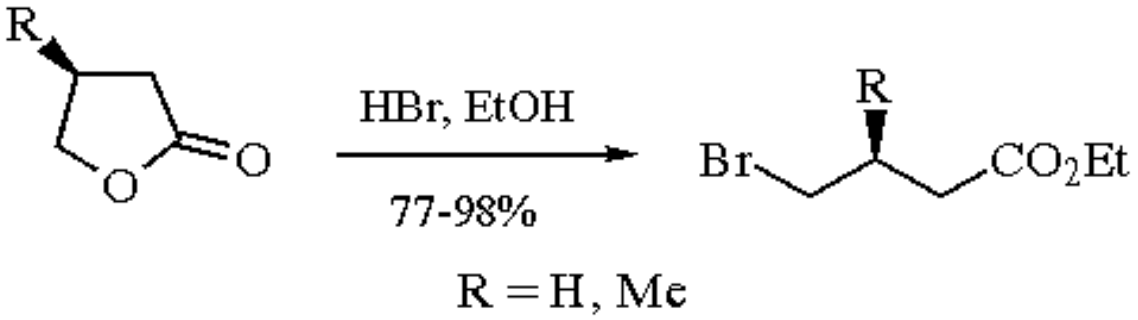

(1)

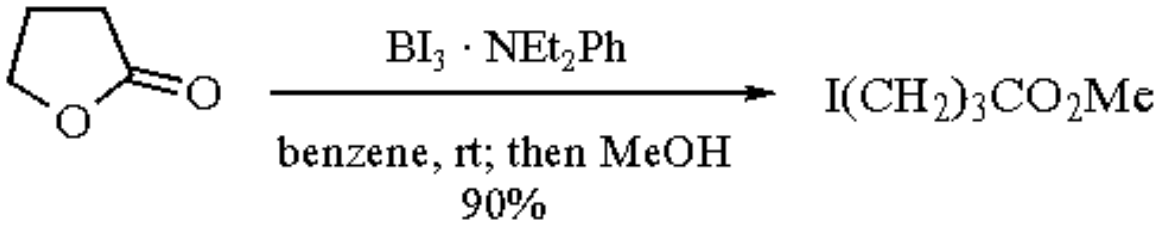

(2)

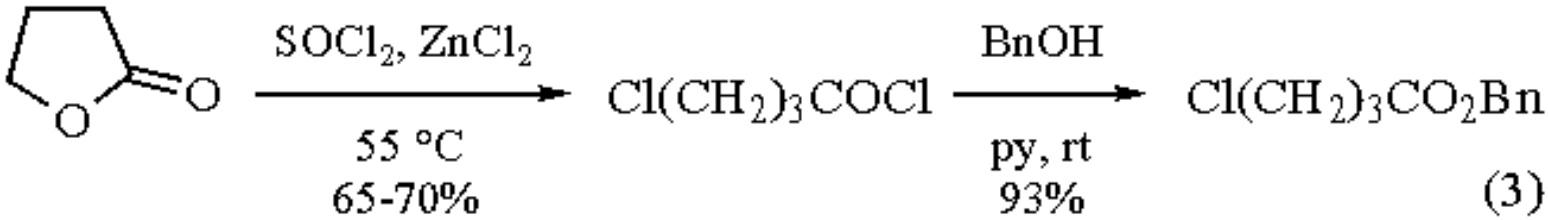

(3)

Reaction of γ-butyrolactone with 2.1 equiv of ***Bromine*** in the presence of red phosphorus affords α-bromo-γ-butyrolactone.[11] When 4 equiv of bromine are used, ring opening ensues to furnish 2,4-dibromobutyric acid bromide, which upon methanolysis affords methyl 2,4-dibromobutyrate in high overall yield (eq 4).[12] Dibromobutyrates are useful for preparing cyclopropanes (eq 4),[12] azetidines,[13] and β-lactams (eq 5).[14]

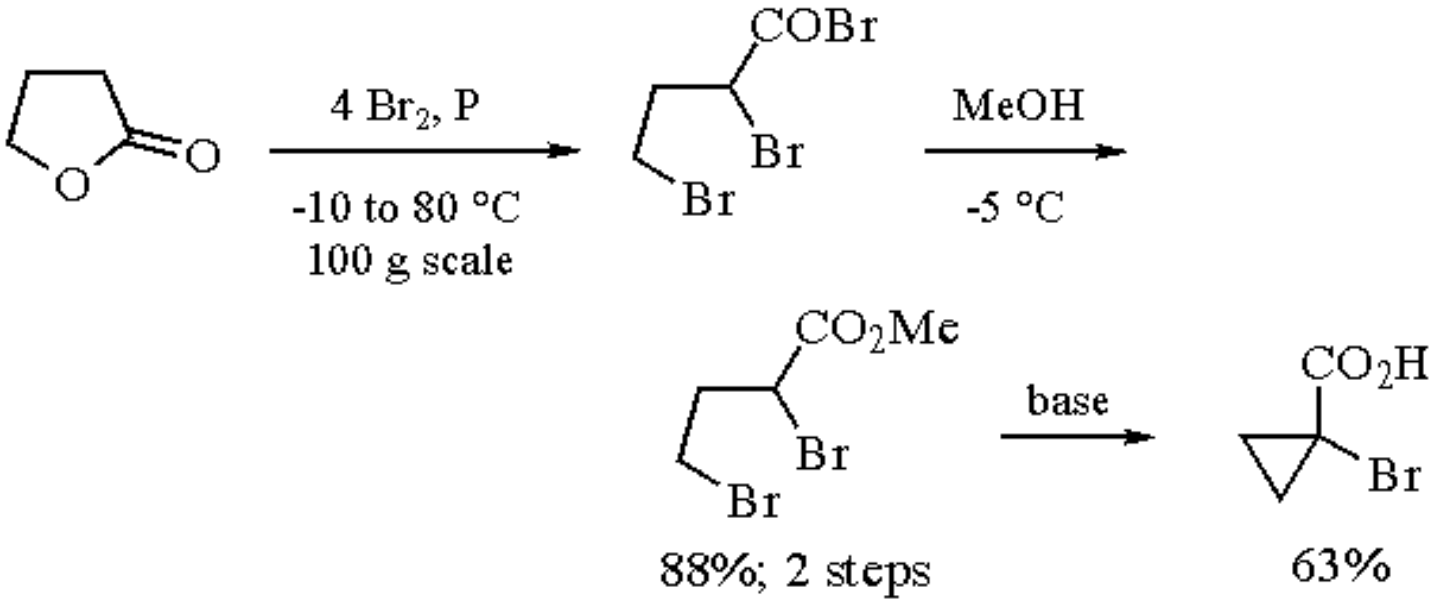

(4)

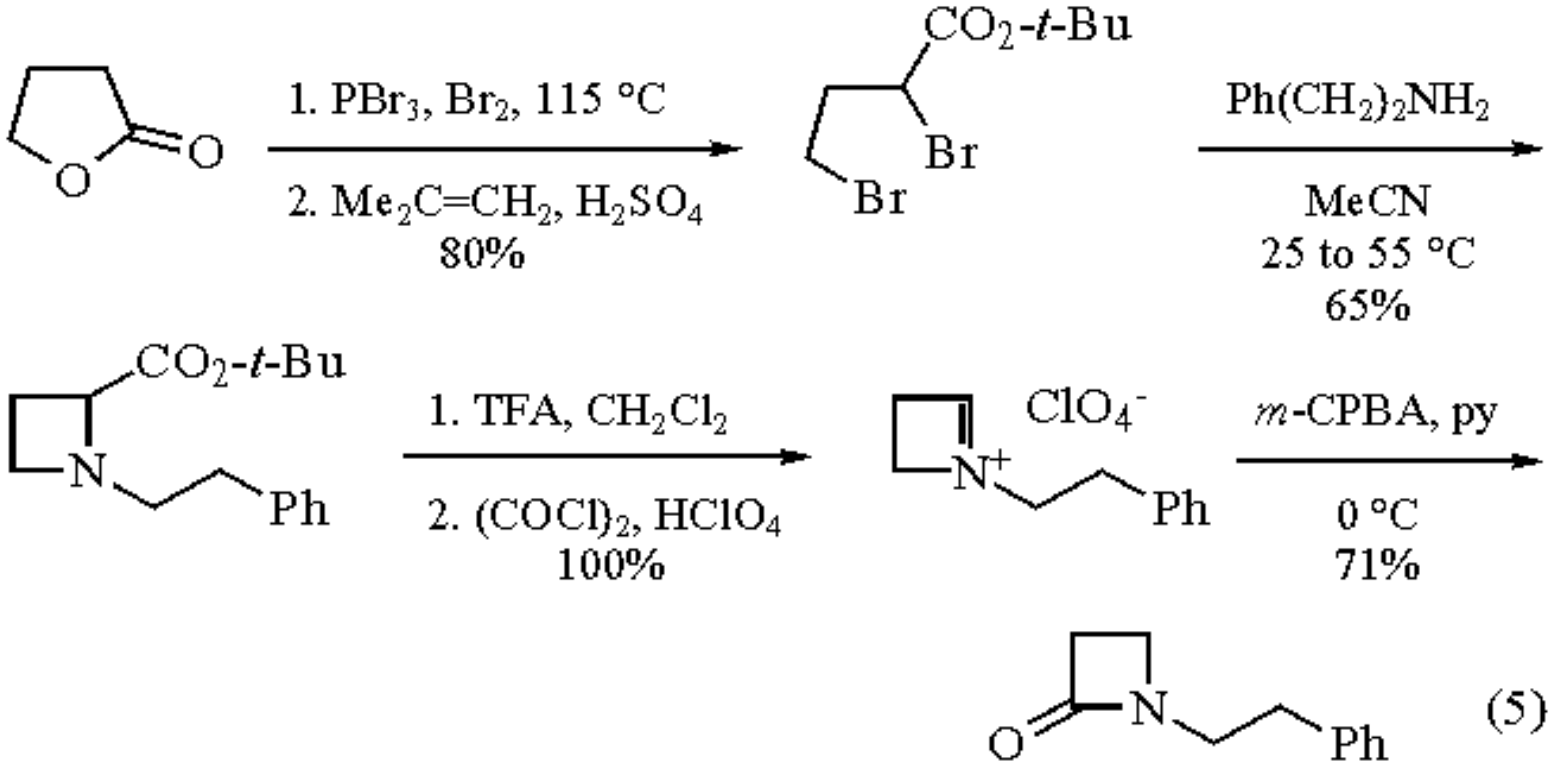

Aminolysis.

In the presence of an ***Aluminum Chloride-Triethylamine*** couple, lactones smoothly react with primary or secondary amines to give the corresponding o-hydroxyalkanamides (eq 6).[15]

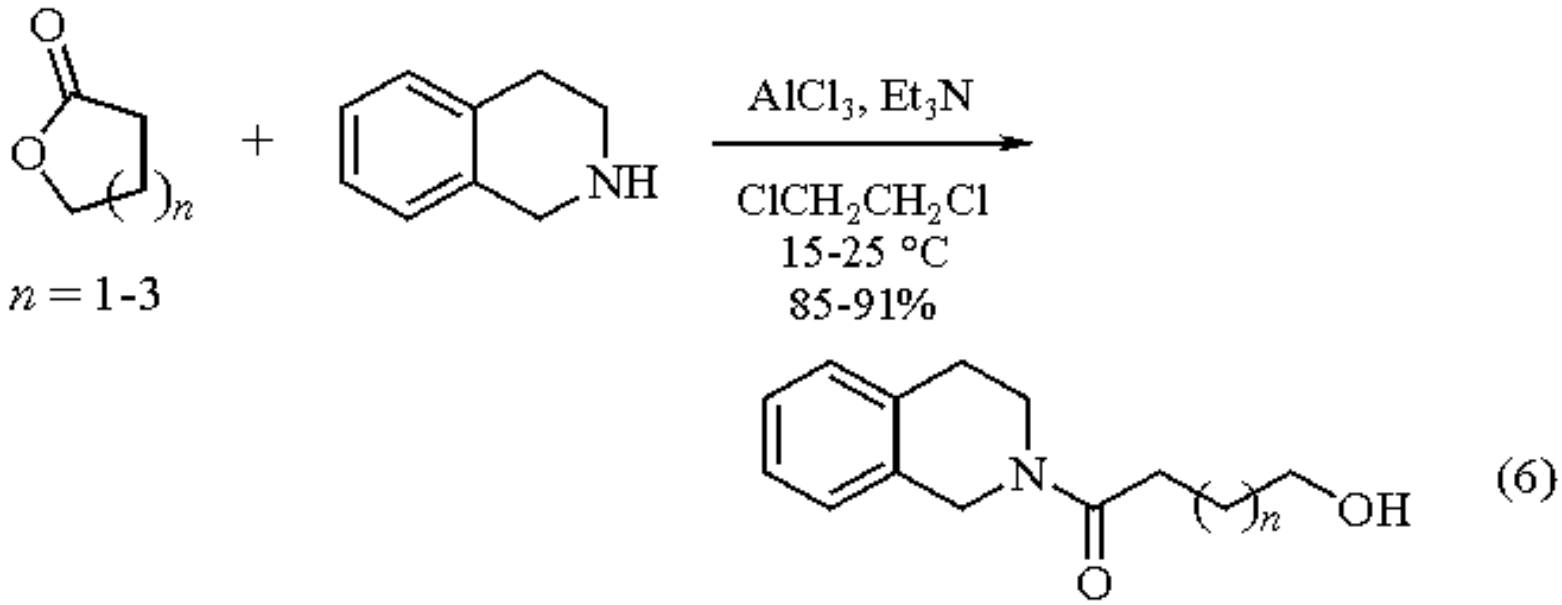

Lewis Acid-Induced Carbon-Carbon Bond Formation.

The outcome of the Friedel-Crafts reaction of γ-butyrolactone with benzene can be manipulated by simply varying the amount of $AlCl_3$ so that either 4-phenylbutyric acid or α-tetralone can be obtained at will (eq 7).[16] In the presence of

Triethylsilane and a catalytic amount of a trityl salt, lactones undergo condensation with silyl ketene acetals and in situ reduction of the resulting unsaturated esters to give α-substituted cyclic ethers (eq 8).[17] When a carbon nucleophile is used in place of Et_3SiH, α,α-disubstituted cyclic ethers are obtained.[17]

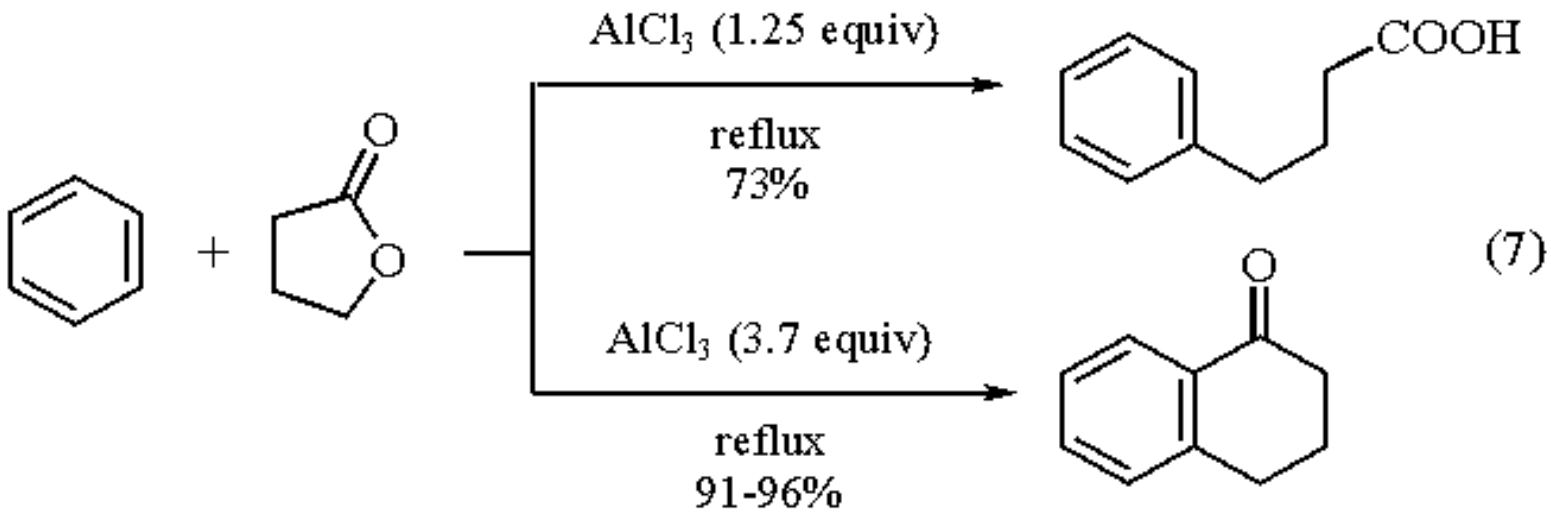

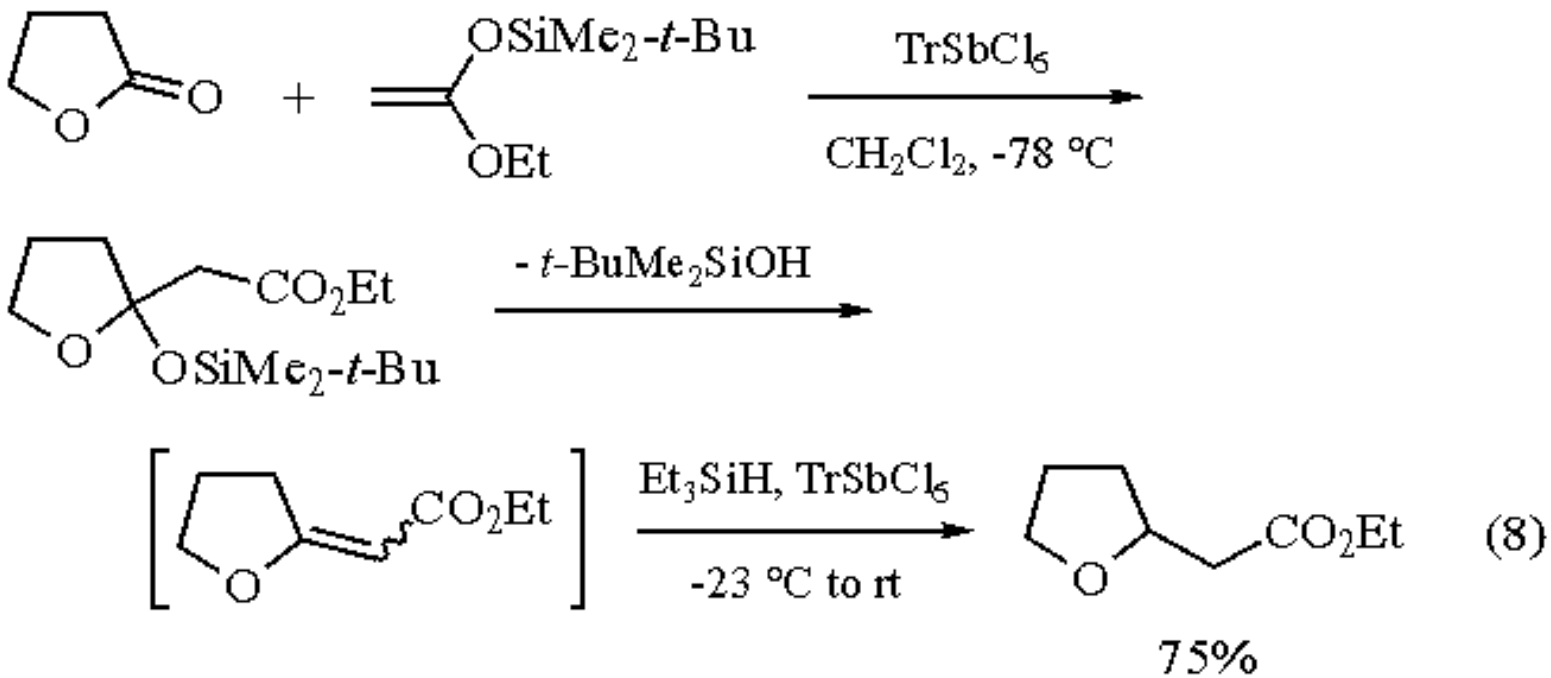

Formation of Hydroxy Esters.

Although 4-hydroxybutyrates may be prepared by acid-catalyzed alcoholysis of γ-butyrolactone, their isolation from the resulting lactone-hydroxy ester equilibrium is tedious and yields are low.[18] The practical alternative entails lactone saponification and subsequent reaction of the carboxylate with a suitable electrophile (eq 9).[19] Silyl esters can be prepared in a similar manner.[20]

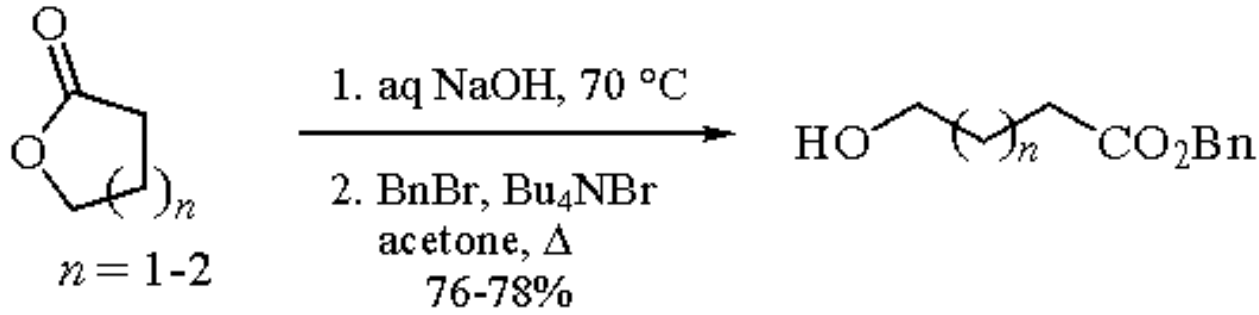

(9)

One of the most commonly used methods for converting lactones into acyclic compounds involves reduction with ***Diisobutylaluminum Hydride*** and Wittig homologation of the resulting lactol[21] (see also ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***). A related, more recent procedure[22] provides α,β-unsaturated esters in a single operation (eq 10).[23]

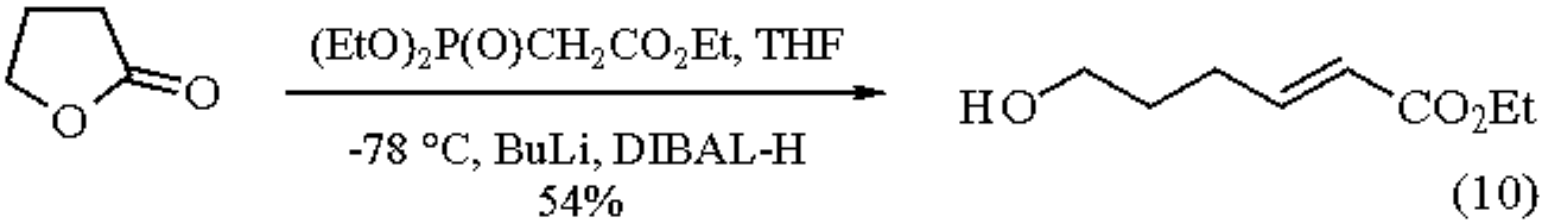

(10)

Reactions with Organometallics.

In general, unsubstituted lactones tend to undergo double attack by organometallics to give diols, whereas substituted lactones are more susceptible to monoaddition.[24,25] However, the outcome strongly depends on the nature of the organometallic reagent and reaction conditions.[24-26] Monoaddition can be achieved with organolithium compounds (eq 11),[24a] although yields of keto alcohols are rarely high.[27] Lithium acetylides have been widely exploited for the synthesis of natural spiroacetals,[28] such as the insect pheromone (**1**) (eq 12).[28a] The highly oxophilic organocerium reagents give superior yields of monoaddition products when compared to their lithium precursors (eq 13).[25] Organocerates are also advantageous for converting lactones into hydroxyallylsilanes (see also ***Cerium(III) Chloride***).[29]

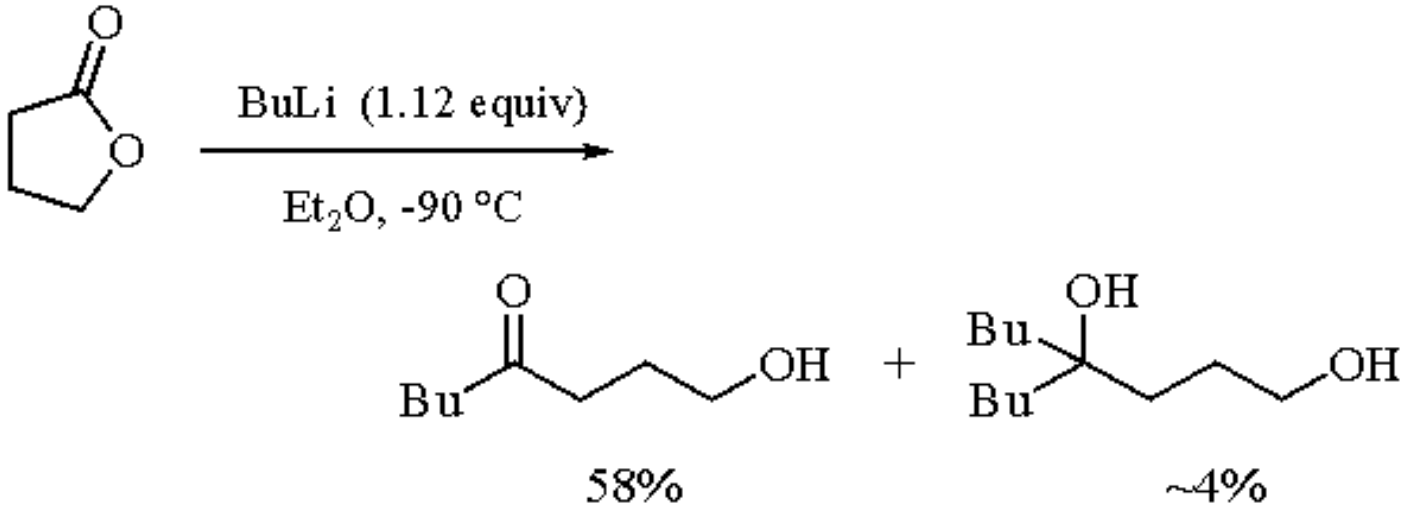

(11)

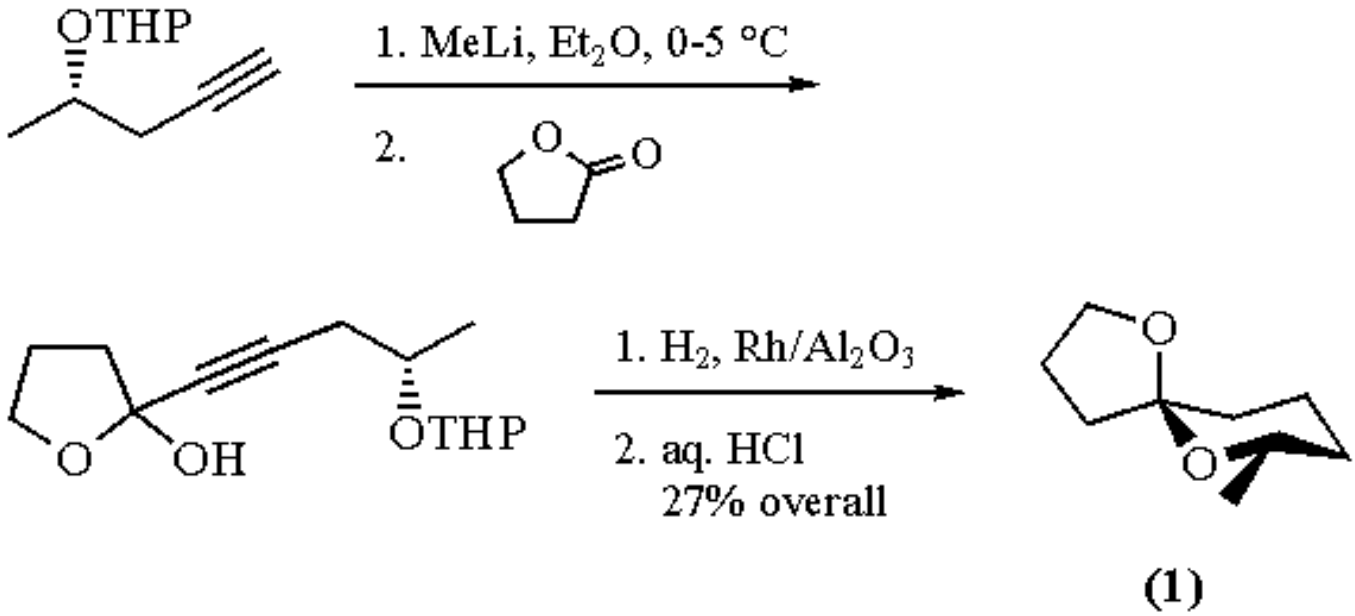

(12)

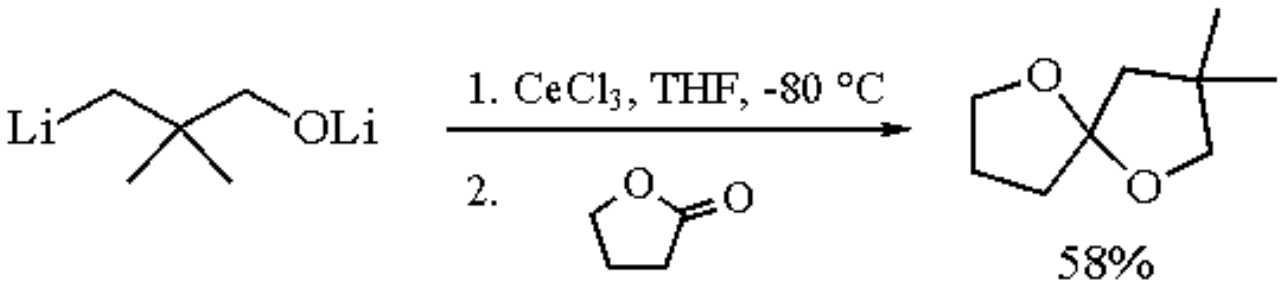

(13)

Grignard compounds exhibit an innate preference for double addition[24,30] giving high yields of diols which can be easily transformed into γ,γ-disubstituted-γ-butyrolactones (eq 14).[31] Analogously, α,o-di-Grignard reagents provide spirolactones (see also ***1,5-Bis(bromomagnesio)pentane***).[32]

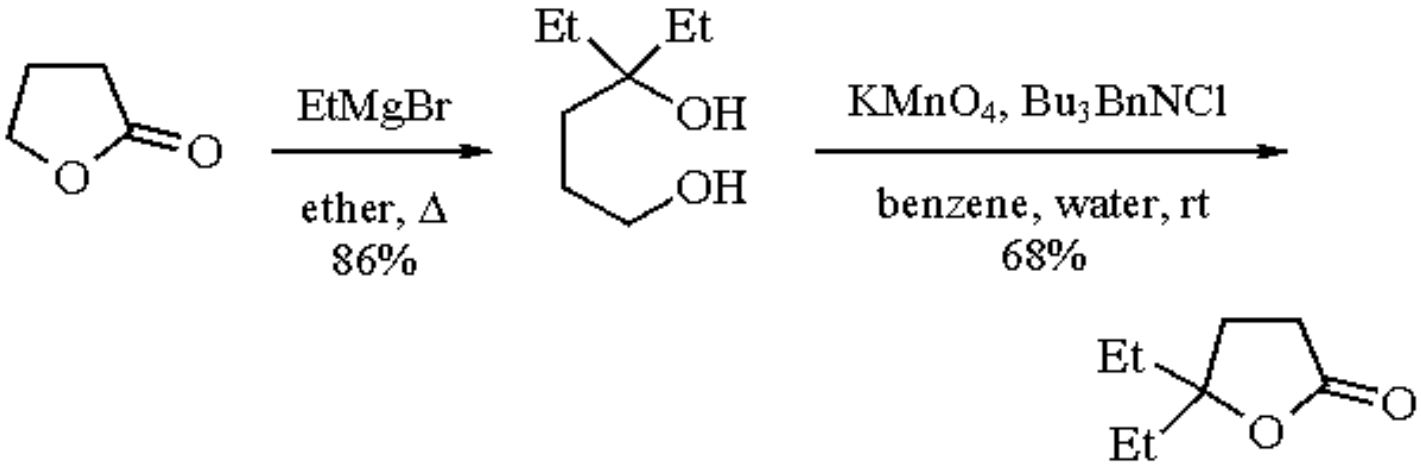

(14)

Alkylation and *C*-Silylation.

Clean α-monoalkylation of γ-butyrolactone is usually achievable by exposure to LDA and reaction of the enolate with a primary alkyl, allyl, or propargyl halide in the presence of HMPA (in the absence of HMPA, α,α-dialkylation is also observed).[33,34] An example is depicted in eq 15.[35] A highly effective but equally elaborate procedure, suitable for both

alkylation and acylation, utilizes a crown ether-potassium complex instead of LDA.[2] *C*-Silylation of γ-lactones can be realized in a highly selective fashion by using γ-***Butyrolactone*** as silylating agent. Addition of a Grignard reagent to the resulting α-silyl-γ-butyrolactone, followed by alkenation and eventual oxidation delivers 4-oxocarboxylic acids in good overall yields (eq 16).[36]

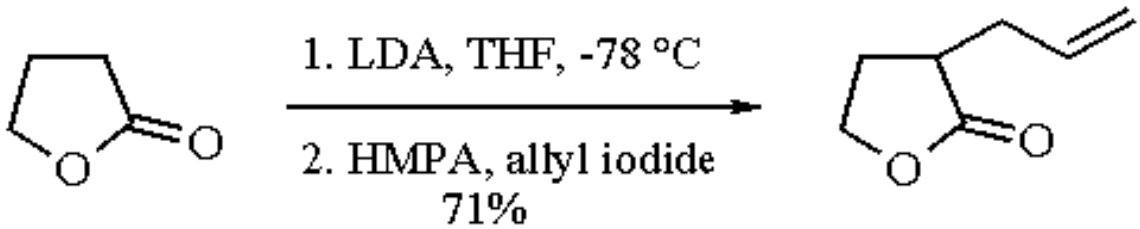

(15)

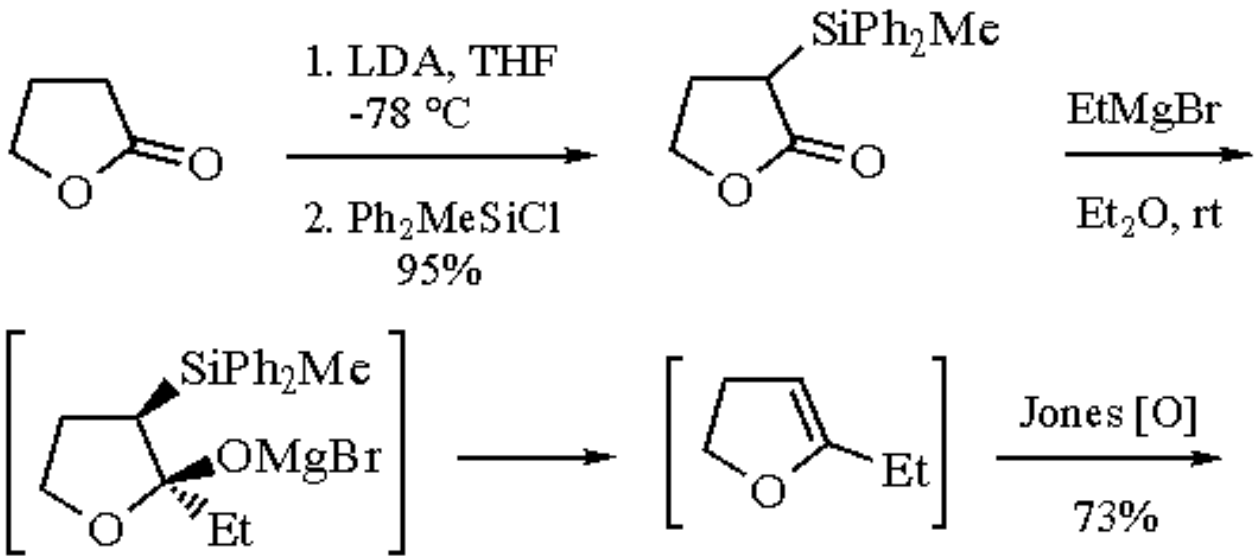

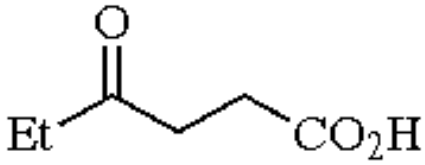

(16)

Aldol Reaction.

Generally speaking, lactone-derived enolates and silyl ketene acetals show poor simple diastereoselection.[37] Thus reaction of lithiated γ-butyrolactone with benzaldehyde provides a modest 30:70 ratio of *syn* and *anti* adducts which can be reversed by the intervention of ***Zinc Chloride*** (eq 17).[38] In the latter case a zinc enolate is involved. Higher *anti*-selectivity has been encountered with a sterically more demanding aldehyde.[39a] Useful levels of *syn* selectivity are conferred by Lewis acid-mediated aldol reaction of 2-(trimethylsilyloxy)-4,5-dihydrofuran[40] (prepared from γ-butyrolactone) with propynal-hexacarbonylcobalt complexes (eq 18).[41]

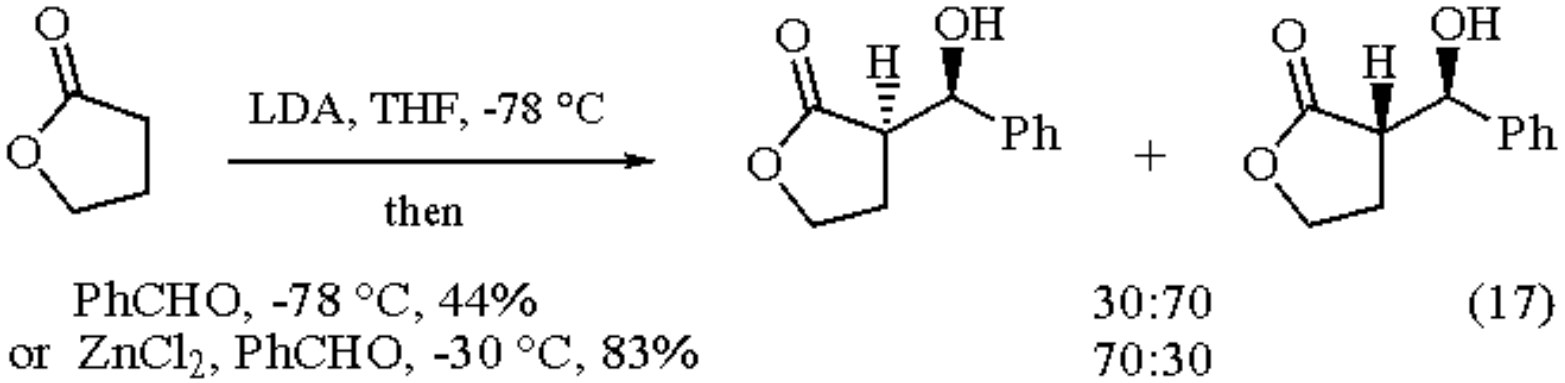

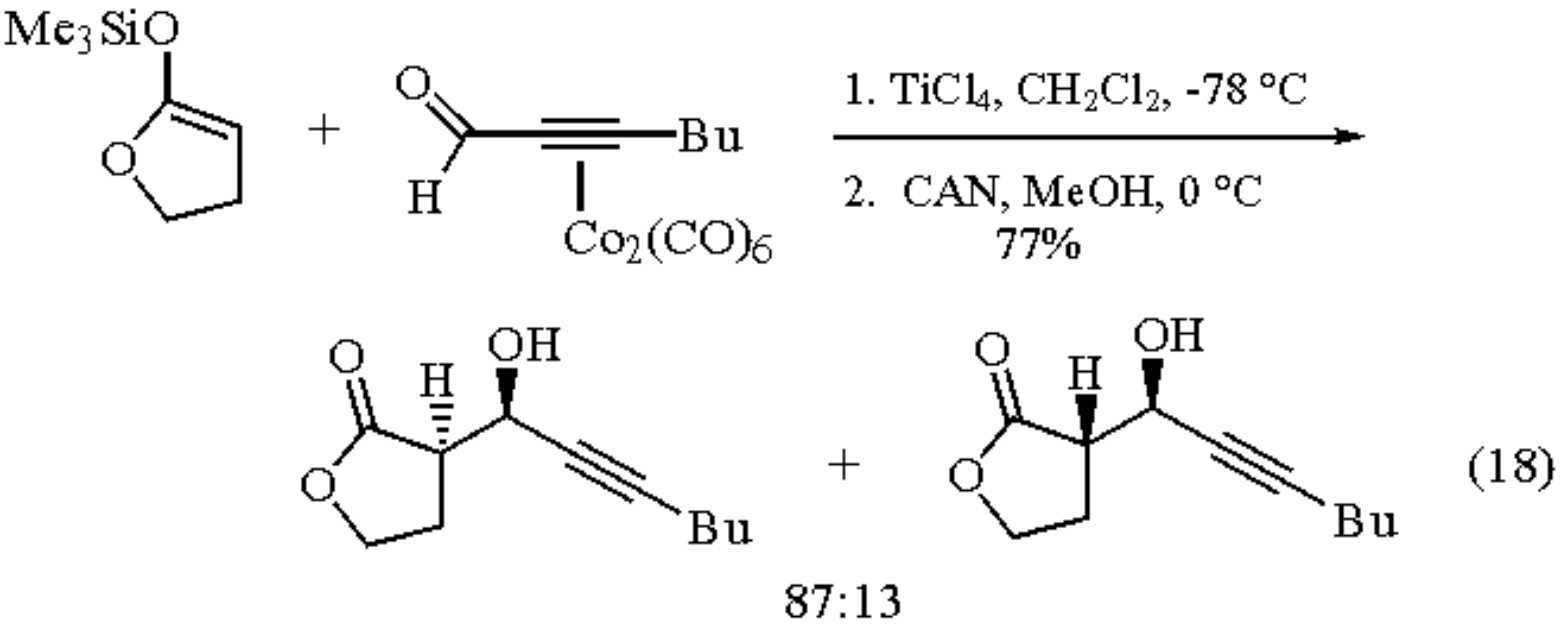

Exposure of the easily prepared α,α-bis(phenylthio)-γ-butyrolactone to ***Ethylmagnesium Bromide*** leads to a magnesium enolate which undergoes aldol reaction in excellent yields (eq 19).[42a] The resulting adducts can be transformed into 3-(1´-hydroxyalkyl)-2(5*H*)-furanones by oxidation of the phenylthio group and elimination of the resulting sulfoxide.[42] Alternatively, 3-(1´-hydroxyalkyl)-2(5*H*)-furanones are accessible in one step from butenolides (see also α,β-***Butenolide***).[43]

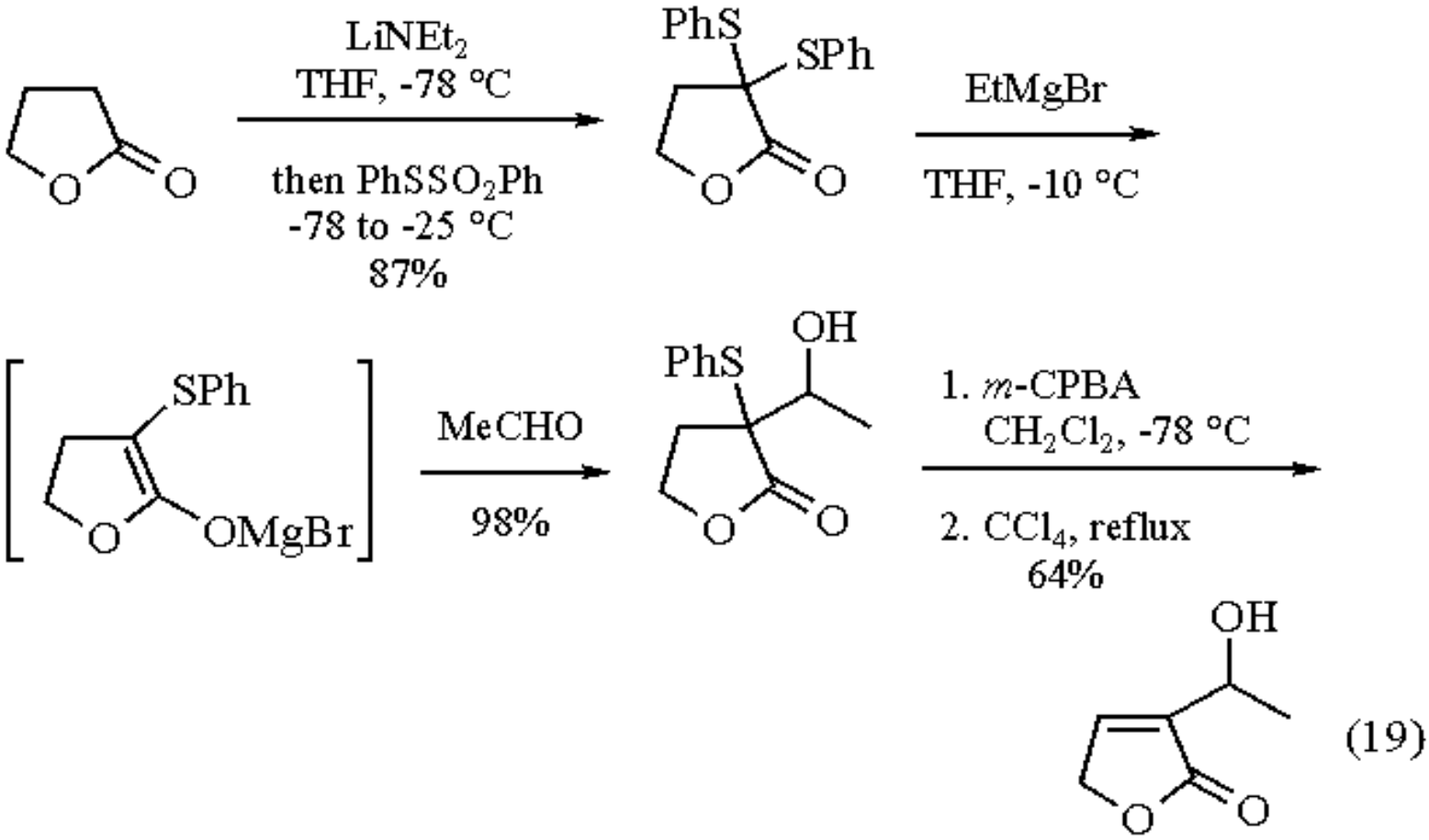

(19)

Alkylidenation.

Many methods exist for the α-methylenation[44,45] and α-alkylidenation[45a,46-48] of lactones. An appealing procedure for preparing α-methylene-γ-butyrolactone entails α-formylation and subsequent condensation with formaldehyde.[45a] (*E*)-α-Alkylidene-γ-butyrolactones, essentially free of their (*Z*) isomers, are available from γ-butyrolactone in high yields through the vinylogous carbamate (**2**) and α-butylthiolactone (**3**) (eq 20).[46] Usefully, α-alkylidene-lactones can be isomerized to 3-alkyl-2(5*H*)-furanones by heating with deactivated W-2 ***Raney Nickel***.[46]

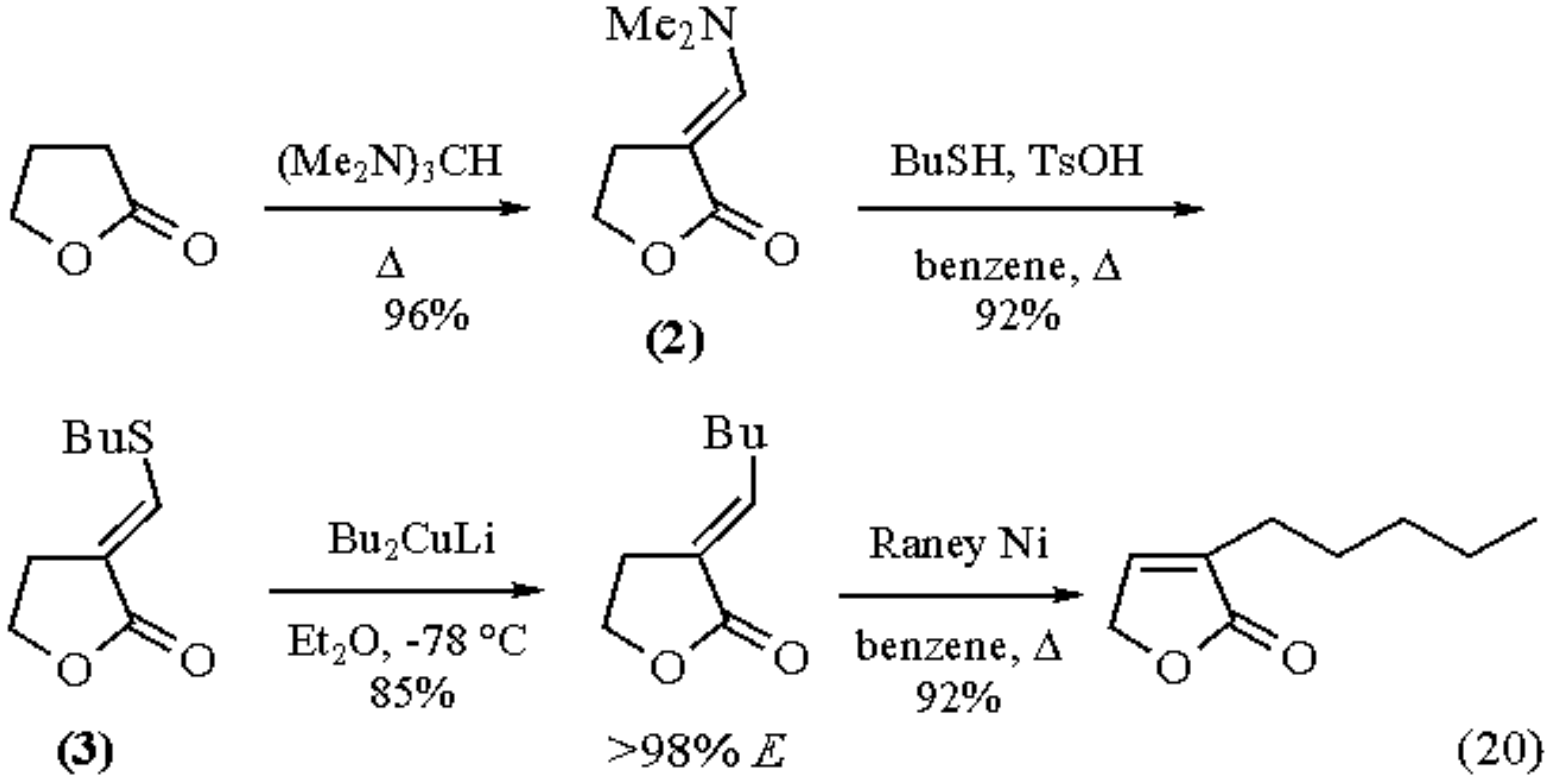

Sequential treatment of γ-butyrolactone with LDA and bis(methoxy(thiocarbonyl)) disulfide provides a lithium enolate which reacts with aldehydes to give preferentially either (*E*)- or (*Z*)-α-alkylidene-γ-butyrolactones, depending on whether $ZnCl_2$ is added before the aldehyde (eq 21).[47] Apparently, these reactions involve episulfides and the double bond geometry depends on the stereochemical outcome of the initial aldol process. Methylenation or alkylidenation of the lactone carbonyl group can be effected by using the Tebbe reagent (μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***) and its variants.[49]

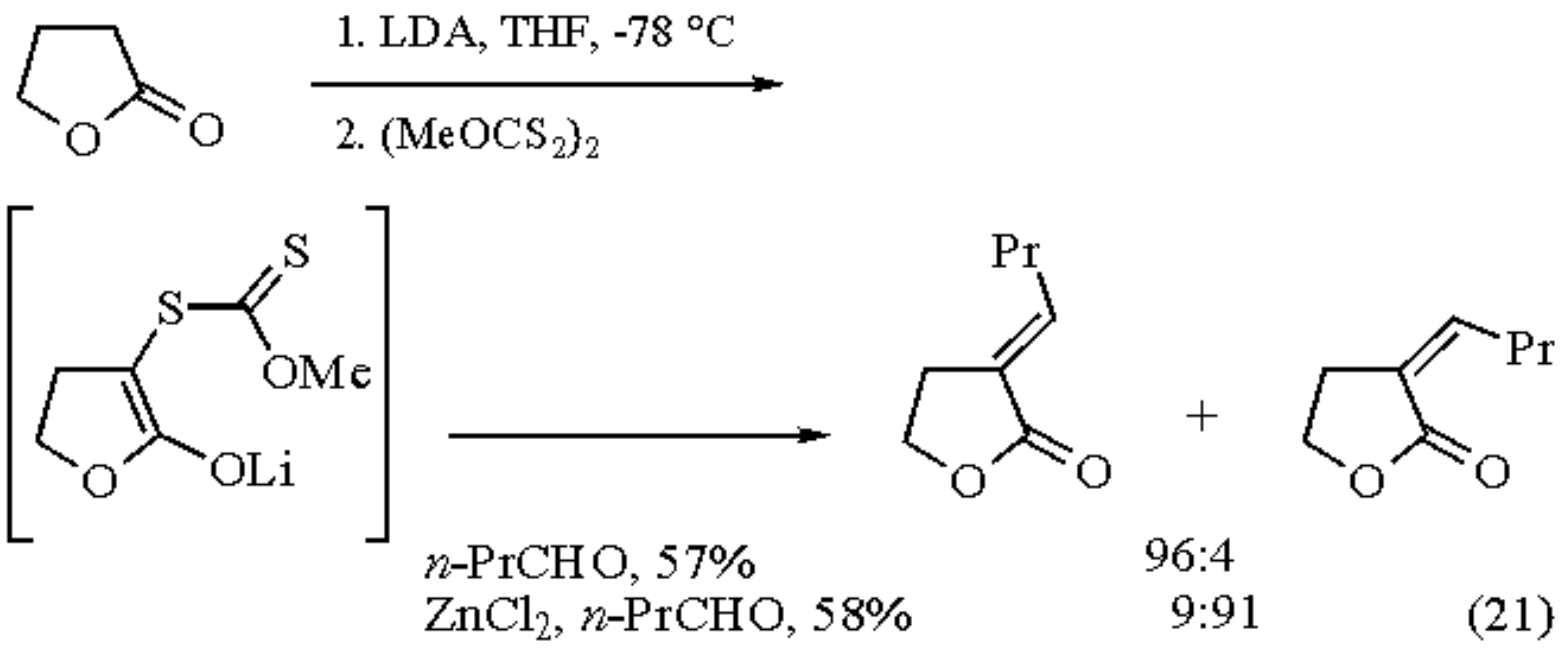

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Cadmium Carbonate

$CdCO_3$

[513-78-0] · $CCdO_3$ · Cadmium Carbonate · (MW 172.42)

(used in the preparation of aryl glycosides[1-8] and also for cleavage of thioacetals[9])

Physical Data: mp 357 °C; *d* 4.258 g cm^{-3}.

Solubility: sol concentrated ammonia and dilute acids.

Form Supplied in: white powder and chunks.

Handling, Storage, and Precautions: should be stored in a cool dry place. It is a carcinogen and hence should be handled carefully.

Synthesis of Glycosides.

$CdCO_3$ has been used as a catalyst in the Koenigs-Knorr synthesis of aryl glycosides.[1-3] Better yields are reported with $CdCO_3$ than with the usual catalyst, silver carbonate. For example, the 3-β-D-glucuronide triacetate methyl ester of estrone was prepared in 71% yield (eq 1), compared to 7% yield using silver carbonate.[1] Similar preparations of the β-D-glucuronides of 17β-estradiol,[1] estriol,[1,4] equilin,[1] equilenin,[1] phenolphthalein,[5] cholesterol,[6] and anthracyclines[7] are documented in the literature.

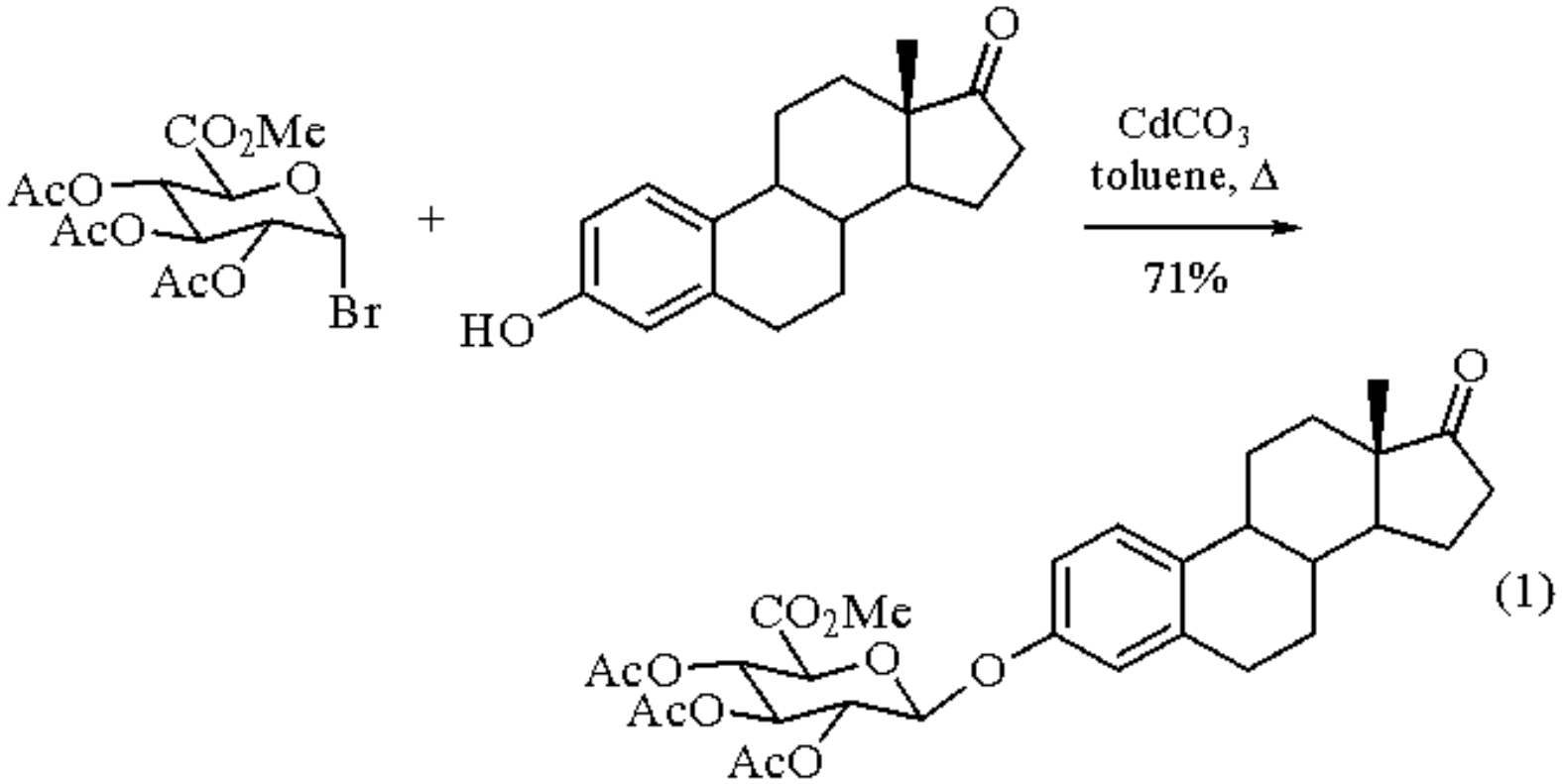

This methodology has also been used to prepare 2-aminoethyl glycosides (eq 2) for the preparation of carbohydrate-protein conjugates.[8]

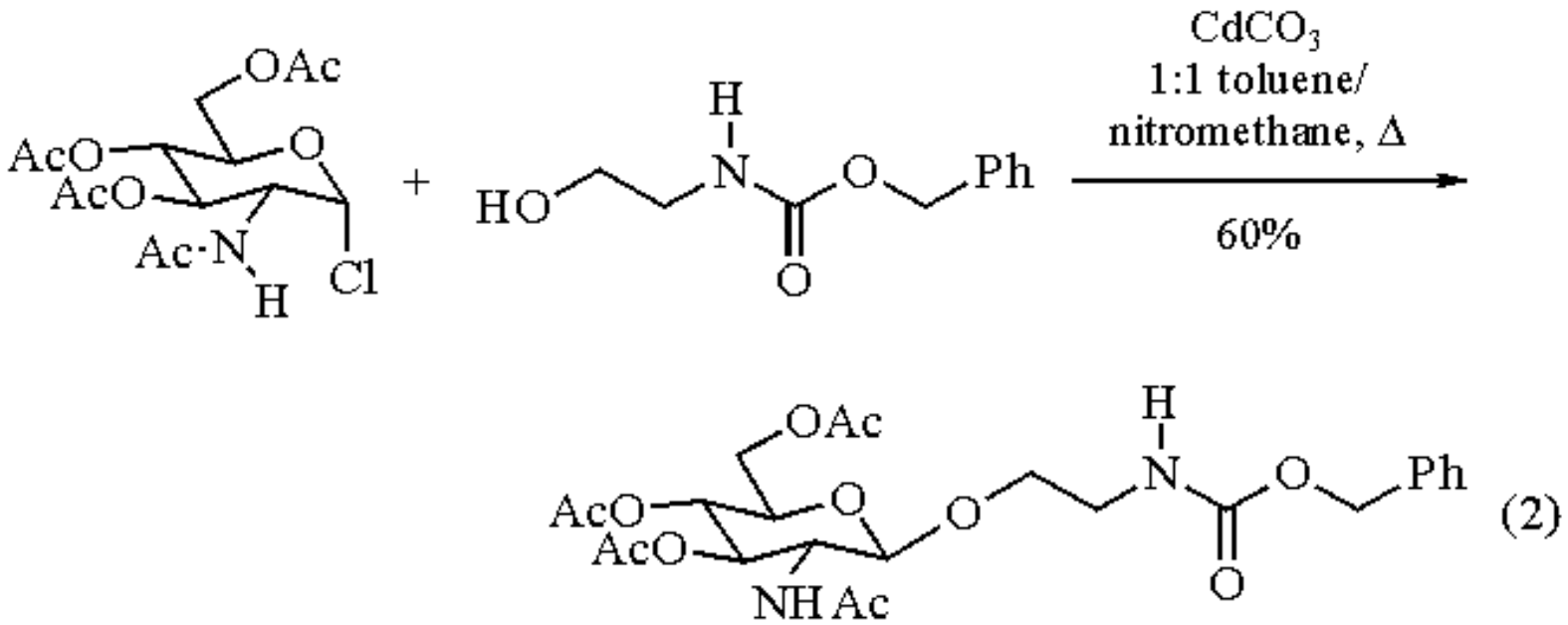

Cleavage of Thioacetals.

Thioacetals of aldosugars are cleaved by $CdCO_3$ in the presence of $HgCl_2$ (see ***Mercury(II) Chloride-Cadmium Carbonate***). This method has been used to prepare acyclic derivatives of monosaccharides (eq 3).[9]

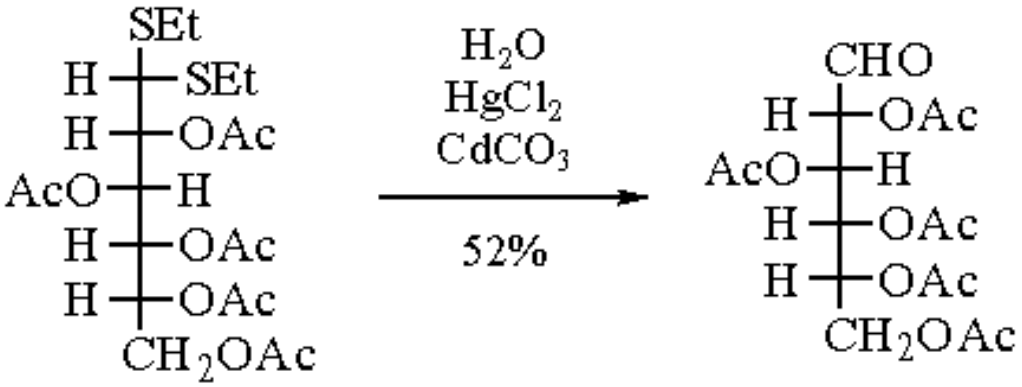

(3)

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Cadmium Chloride

$CdCl_2$

[10108-64-2] · $CdCl_2$ · Cadmium Chloride · (MW 183.31)

(organocadmium reagents are useful in the synthesis of keto esters,[2] in regioselective,[3] stereoselective[4] addition reactions, and in osmium-catalyzed hydroxylation;[5] $CdCl_2$ is useful in ring opening[6] and oxidation[7-11] reactions)

Physical Data: mp 568 °C; *d* 4.047 g cm^{-3}.

Solubility: insol ether; slightly sol methanol, ethanol; sol acetone; freely sol water.

Form Supplied in: white crystalline solid; widely available. *Drying:* for some applications the cadmium chloride must be anhydrous. The recommended procedure involves drying to a constant weight at 110 °C in an oven, grinding throughly, and storing in a desiccator.

Handling, Storage, and Precautions: should be stored in a dry place. It is a highly toxic cancer suspect agent and should be handled carefully.

Organocadmium Reagents.

Cadmium chloride is most often used to prepare organocadmium compounds. Use of organocadmium derivatives for the preparation of simple ketones was introduced as early as 1936.[1] Alkyl organocadmium derivatives, prepared by reaction of the corresponding RMgBr compounds with anhydrous $CdCl_2$ in ether, react with a variety of ester acid chlorides to give keto esters (eq 1).[2]

$$Me_2CHCH_2CH_2MgBr \xrightarrow[\text{2. } ClCOCH_2CH_2CO_2Me,\ C_6H_6]{\text{1. } CdCl_2,\ Et_2O} \underset{73\%}{} Me_2CHCH_2CH_2COCH_2CH_2CO_2Me \quad (1)$$

Lithium enolates of α,β-unsaturated esters condense cleanly with aldehydes, affording the α product exclusively. This

is in accordance with the normal regiochemical behavior of vinylogous anions. Use of organocadmium reagents prepared in situ from their lithium derivatives reverses the regioselectivity (eq 2).[3]

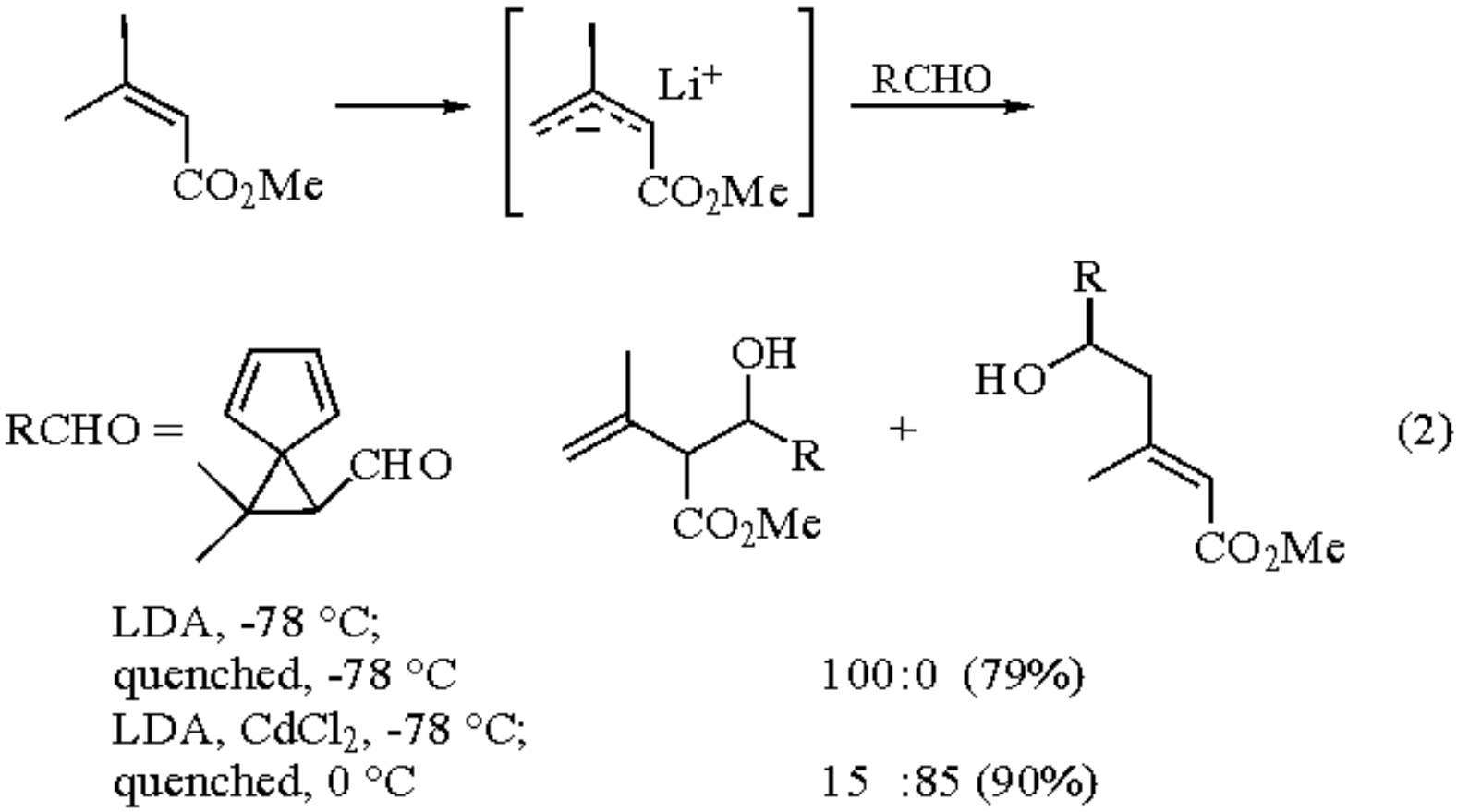

Cadmium chloride mediated addition of organometallics to chiral α-keto amides influences the stereochemistry of the reaction (eq 3).[4]

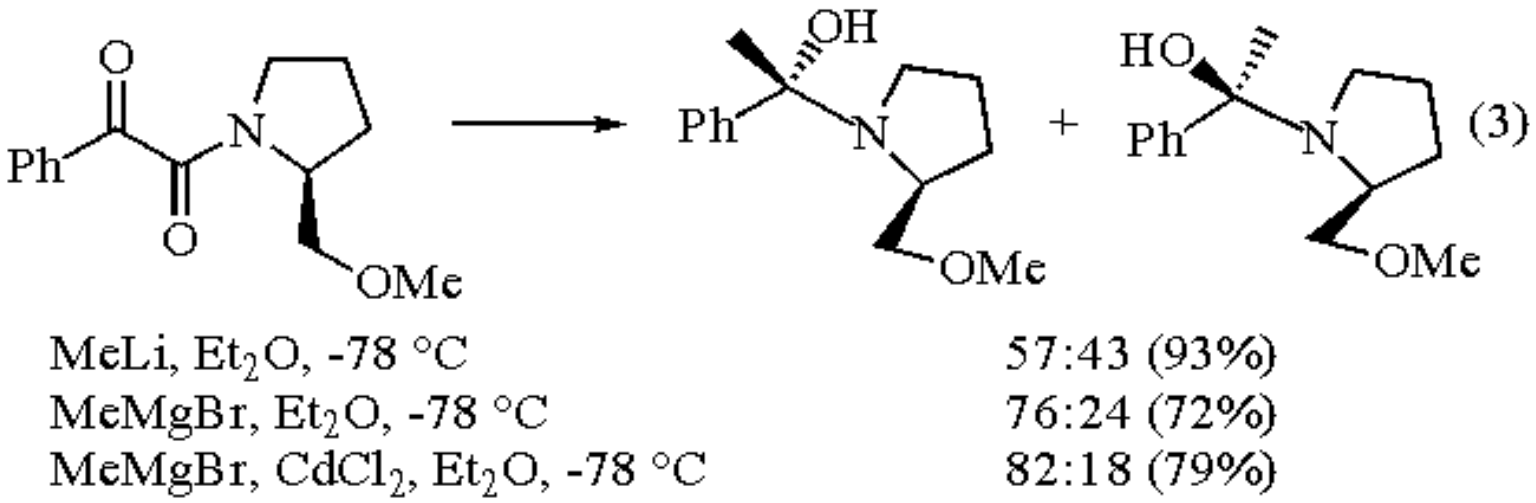

N-Chloro-*N*-cadmium carbamates can be generated in situ by reaction of the corresponding *N*-chloro sodiocarbamates with cadmium chloride in acetonitile. These organocadmium reagents are useful in an osmium-catalyzed procedure which effects *cis* addition of hydroxyl and carbamate moieties across an alkenic linkage (eq 4).[5]

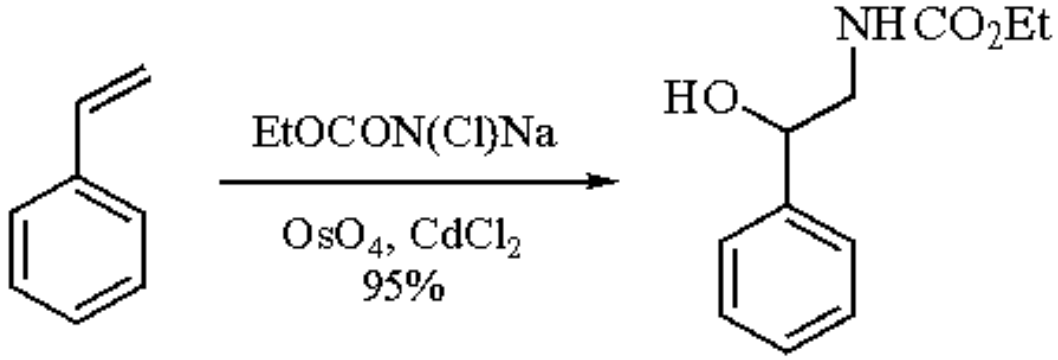

(4)

Synthetically useful cadmium homoenolates have been prepared by the heterometalation-type ring cleavage of electron-rich cyclopropanes by cadmium chloride under ultrasonic irradiation at room temperature (eq 5).[6]

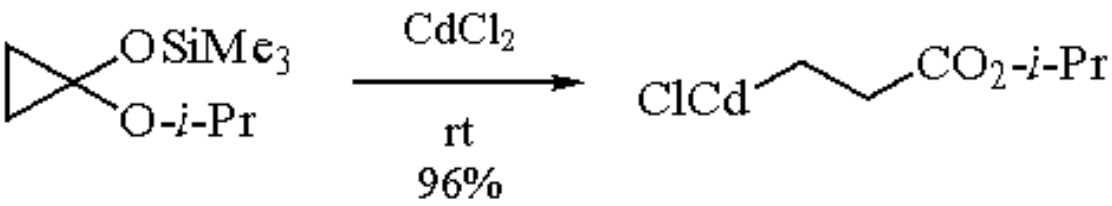

(5)

Oxidations.

In the synthesis of polycyclic aromatics, dehydrogenations are effectively carried out using cadmium chloride as an oxidizing agent (eqs 6 and 7).[7,8]

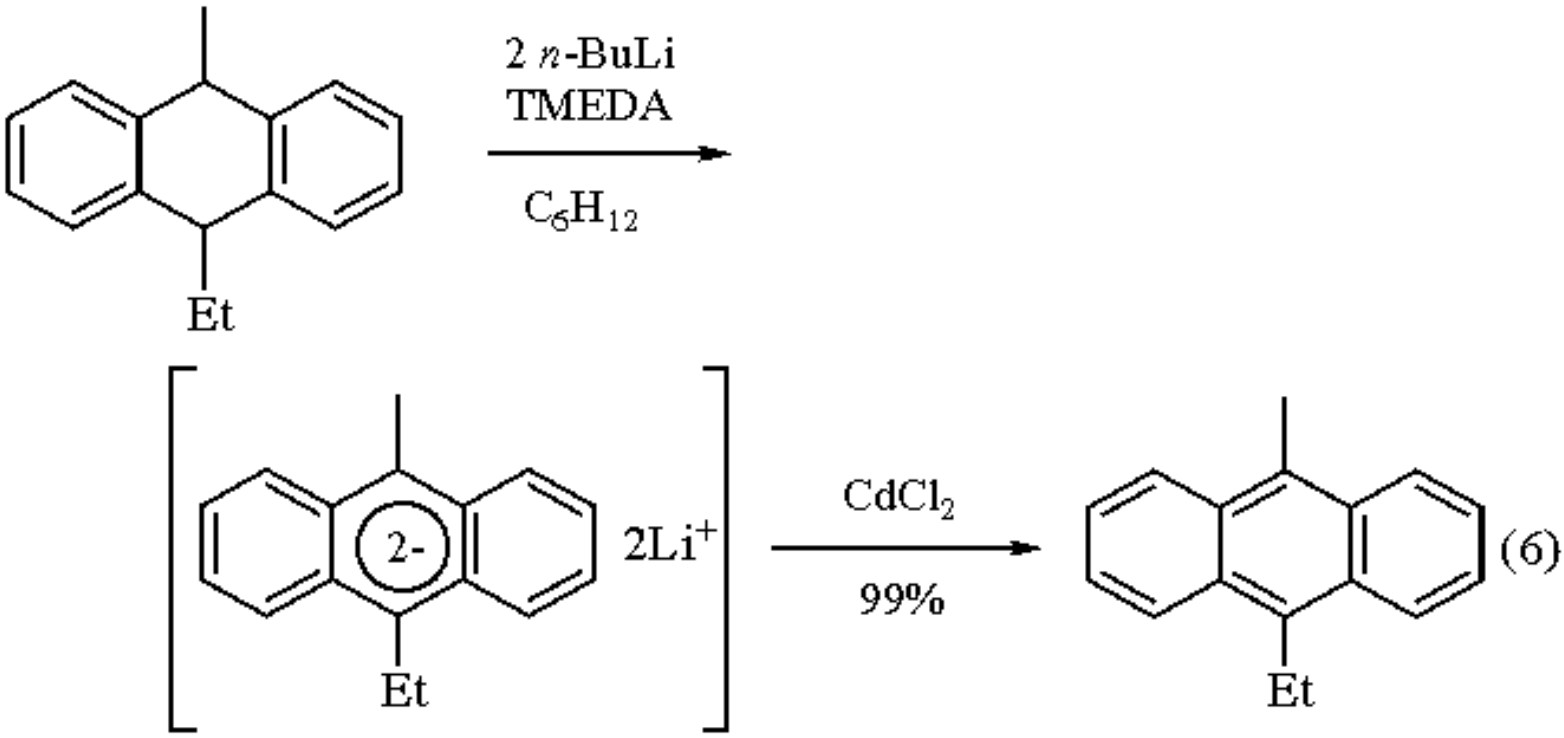

(6)

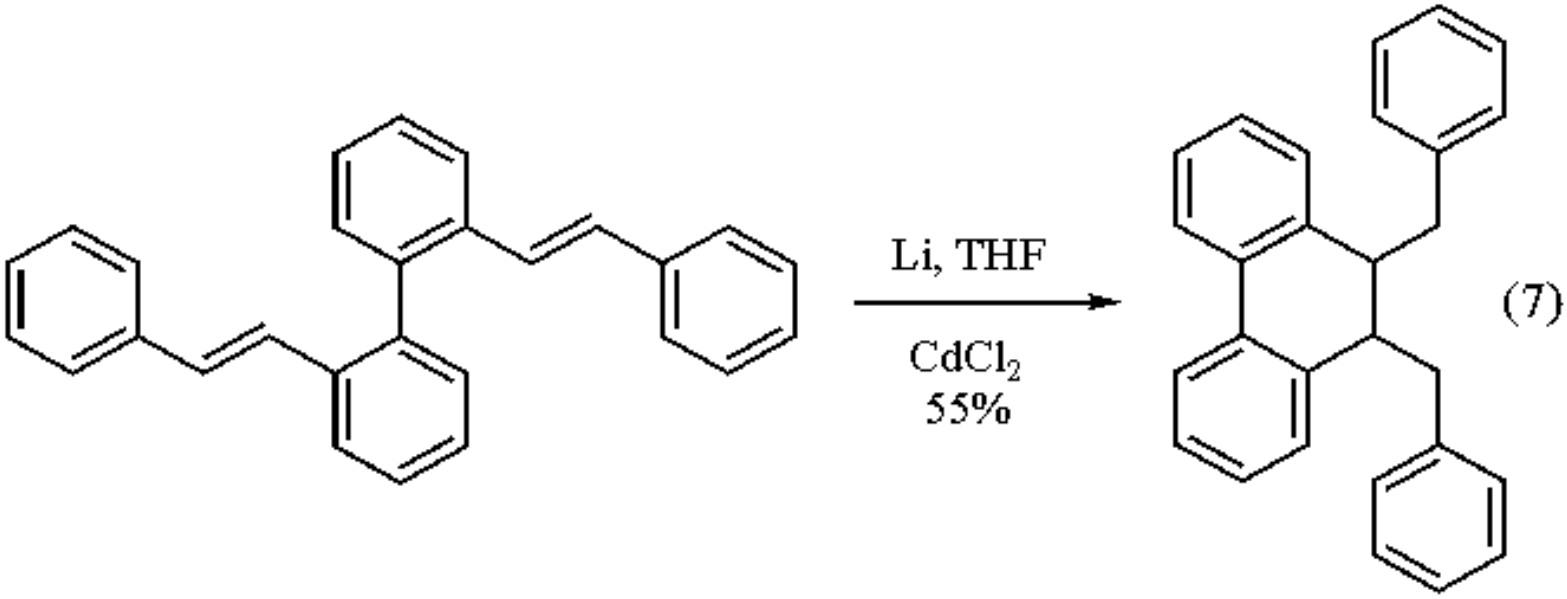

Cadmium chloride has been employed as an oxidizing agent in the conversion of 1,5-cyclooctadiene to cyclooctatetraene through the intermediacy of cyclooctatetraenyl dianion (eq 8).[9-11]

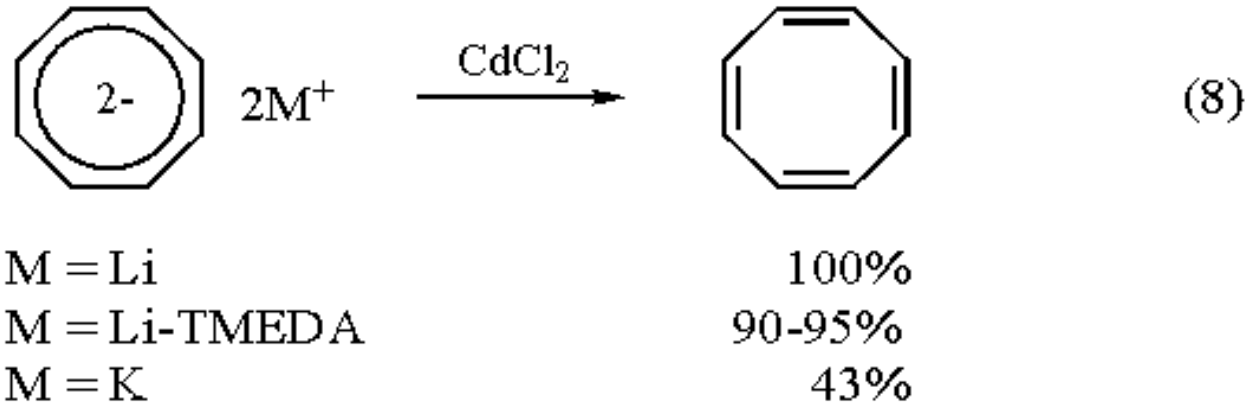

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Calcium-Ammonia[1]

Ca/NH_3

[7440-70-2] · Ca · Calcium · (MW 40.08)

[7664-41-7] · H_3N · Calcium · (MW 17.03)

(mild reducing agent capable of reducing double and triple bonds; moderately strong base)

Physical Data: Ca: mp 842-848 °C; bp 1240 °C; *d* 1.55 g cm^{-3}; NH_3: mp -77.7 °C; bp -33.35 °C; d_{-79} 0.817 g cm^{-3}.

Form Supplied in: Ca: silver, white, soft metal; NH_3: anhydrous gas or liquid in sealed ampules.
Drying: ammonia can be dried by passing the gas through a KOH drying tube prior to condensation.

Handling, Storage, and Precautions: calcium metal is a water reactive, flammable solid. In case of contact with water, the heat of the reaction may be sufficient to ignite the product hydrogen as well as the metal. Anhydrous liquid ammonia is corrosive, especially in contact with water. Although classified as a nonflammable gas, it will burn within certain concentration limits. The liquid may cause frostbite in contact with the skin. Use in a fume hood.

Reduction of Aromatic Hydrocarbons.

Although calcium in liquid ammonia, apparently in the form of $Ca(NH_3)_6$,[2] has long been known to convert aromatic hydrocarbons to unconjugated dienes and even monoalkenes,[3] alkali metals in ammonia or in ammonia/alcohol have generally been the reagents of choice, even though calcium is safer to handle. Thus benzene, toluene, and *o*- and *p*-xylene afford the corresponding monoalkenes in high yield after treatment with calcium hexamine after 24 hours (eq 1).[3] Similar reductions of bi- and terphenyl yield dihydro derivatives, while naphthalene gives 1,4-dihydronaphthalene at -75 °C and a mixture of the 1,4-derivative and 1,2,3,4-tetrahydronaphthalene at -33 °C (eq 2).[4]

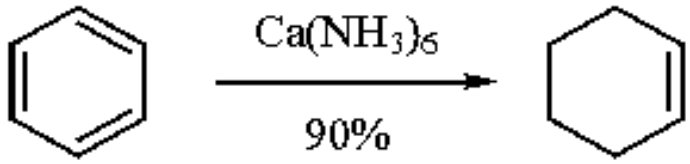

(1)

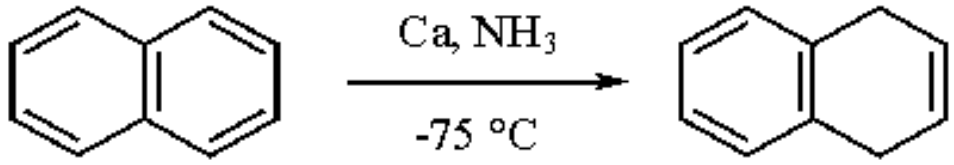

(2)

The reductions of aromatic hydrocarbons by calcium in liquid ammonia can be effected under two different conditions.[5] In the first case, the calcium is dissolved in ammonia and the latter is removed eventually with the aid of high vacuum to give solid calcium hexamine. In the second procedure, ammonia is added to a mixture of the calcium and the hydrocarbon. While the first method produced substantially higher yields of cyclohexene from benzene, nearly the same results were realized by both methods in the reduction of toluene.

Improved yields and cleaner products were realized by the use of calcium shot in ammonia with ether and HMPA.[6] For example, the reduction of *t*-butylbenzene by this method afforded 1-, 3-, and 4-*t*-butylcyclohexenes in yields of 56%, 34%, and 10%, respectively, results which are comparable to the better known lithium-amine system.[7] Calcium in methylamine/ethylenediamine was found to be an even better system, since substantially higher quantities of the more thermodynamically stable alkenes were formed from reduction of a large number of aromatic hydrocarbons.[8] Thus the yield of 1-*t*-butylcyclohexene in the reduction of the parent hydrocarbon was increased to 87% (eq 3).

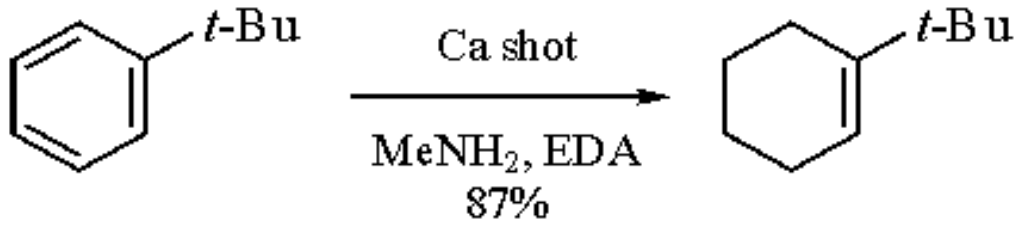

(3)

Birch-type products were obtained by effecting calcium reductions in butylamine/ethylenediamine in the presence of *t*-butyl alcohol.[9] The authors recommend that all such calcium reductions be run in the presence of white sand using a Hershberg stirrer to remove the insoluble coatings on the surface of the calcium metal. Use of this technique for the reduction of anisole provided the 2,5-dihydro derivative in 86% yield (eq 4).

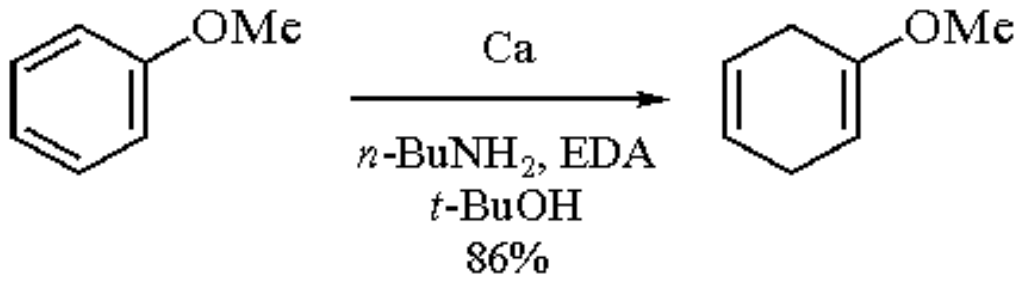

(4)

Reduction of Alkynes and Alkenes.

Dialkylalkynes have been reduced to *trans*-alkenes by calcium in ammonia[5] and by calcium in methylamine/ethylenediamine.[10] Thus, 2-nonyne, 3-nonyne, 4-nonyne, and 4-octyne gave the corresponding *trans*-alkenes in yields of 70-88% and purities of 72-91% (eq 5).[10] Similar reduction of 1-heptyne apparently gave substantial metalation unless a large excess of the metal was employed. In the latter case, the major product was heptane.

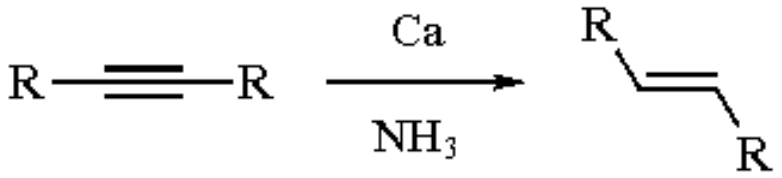

(5)

Arylated alkenes such as 1,1-diphenylethylene and 1,1,2-triphenylethylene have been reduced to the corresponding ethanes by calcium in ammonia.[11]

Reduction of Other Functional Groups.

Few functional groups other than those above have been reduced by calcium in liquid ammonia. The carbon-carbon double bond of several α,β-unsaturated ketones has been reduced by this reagent to give saturated ketones (eq 6).[12] In several cases, though, both the alkene and the ketone have been reduced to saturated alcohols (eq 7).[13]

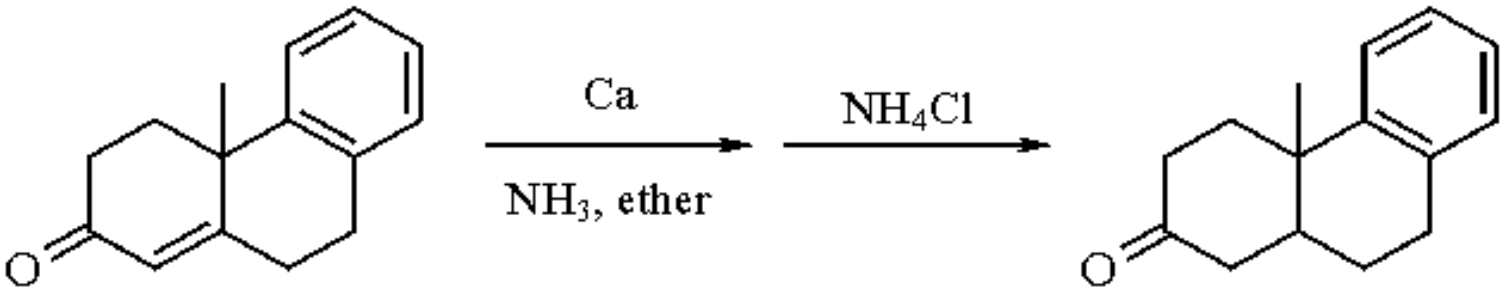

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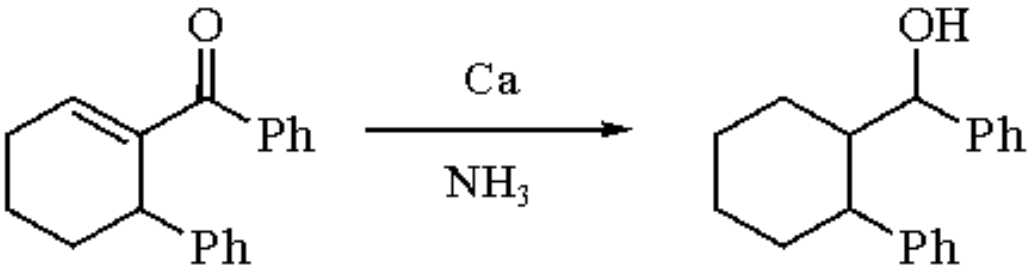

(7)

Calcium/ammonia solutions have been found to be useful when low basicity is desired, as in the conversion of both stereoisomers of the diacetoxy ketone (**1**) ($R^1 = R^2 = OAc$) to the corresponding ketone ($R^1 = OAc$, $R^2 = H$).[14] In this case, calcium was shown to be a better reagent than lithium for this reduction.

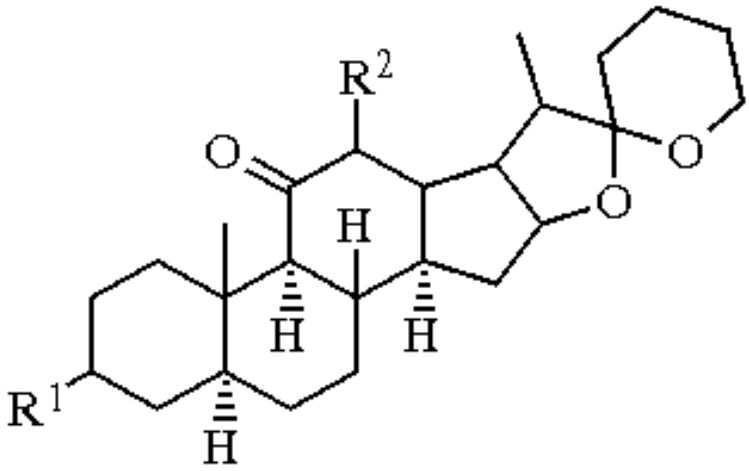

(1)

Calcium in ammonia offers better selectivity than lithium in the debenzylation of a variety of benzyl ethers containing other functional groups.[15] For example, in eq 8 the benzyl group of the alkynic ether is removed without concomitant reduction of the triple bond.

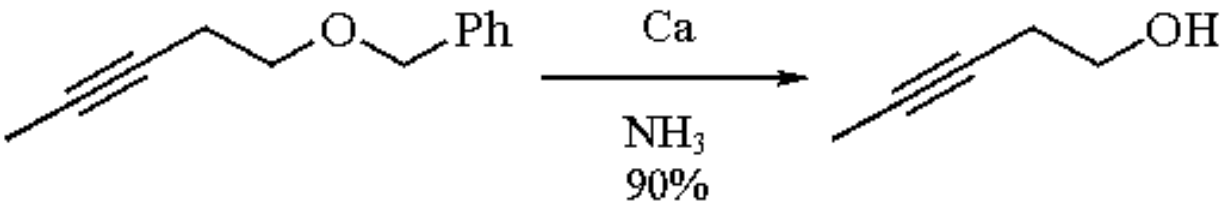

(8)

Epoxides have also been reduced to alcohols by calcium in ammonia (eq 9).[16] The results are similar to those realized by the use of lithium metal.

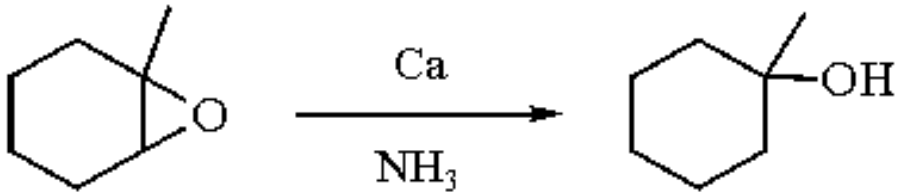

(9)

Calcium/Ammonia as a Base.

Although little used for many years, solutions of calcium in ammonia have been employed to convert certain active hydrogen compounds to their calcium salts. For example, calcium salts have been prepared from terminal alkynes,[17] alcohols,[18] nitrogenous heterocycles such as 1,2,4-triazole,[19] and other organonitrogen compounds, illustrated by dicyanodiamide.[20]

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Calcium Carbonate

$CaCO_3$

[471-34-1] · $CCaO_3$ · Calcium Carbonate · (MW 100.09)

(relatively insoluble white solid; a useful acid scavenger and stabilizing agent for acid sensitive compounds,[1] and a coreactant in reactions producing acidic byproducts.)

Physical Data: widely available as powder (reagent grade) or ppt powder (USP). Occurs naturally as limestone, marble, and chalk. Three crystal forms are known: (1) aragonite *[14791-73-2]*; mp 825 °C (dec); *d* 2.93 g cm^{-3}; water sol 0.0015 g/100 mL (at 25 °C); (2) calcite *[13397-26-7]*; mp 1339 °C (103 atm); *d* 2.71 g cm^{-3}; water sol 0.0014 g/100 mL (at 25 °C); (3) vaterite [*13701-58-1]*; found in N. Ireland and Israel.

Handling, Storage, and Precautions: none; nontoxic; generates calcium oxide and releases carbon dioxide on heating.

Elimination.

Halides (eq 1)[2] and sulfoxides (eq 2)[3] are converted to alkenes (or their tautomers) on heating with $CaCO_3$ in appropriate solvents. In the case of halo ketone eliminations (eq 3)[4] the methods of Holysz[5a] and Joly,[5b] employing lithium carbonate/lithium halide mixtures, appear to be more commonly used, and in some instances more effective (see ***Lithium Carbonate-Lithium Bromide***).[6]

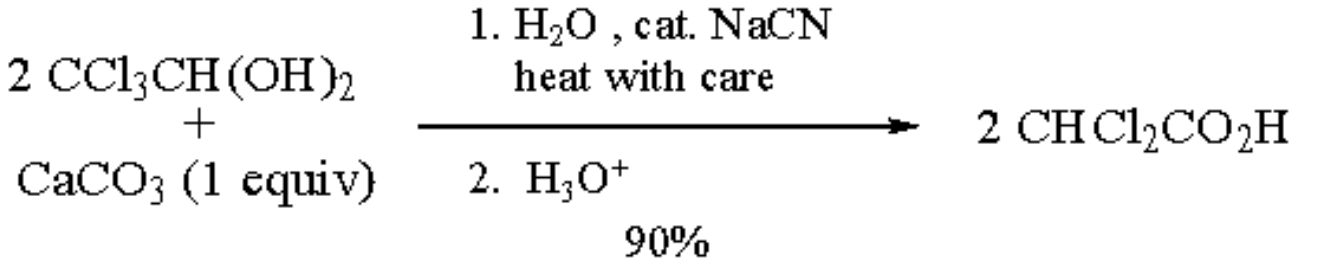

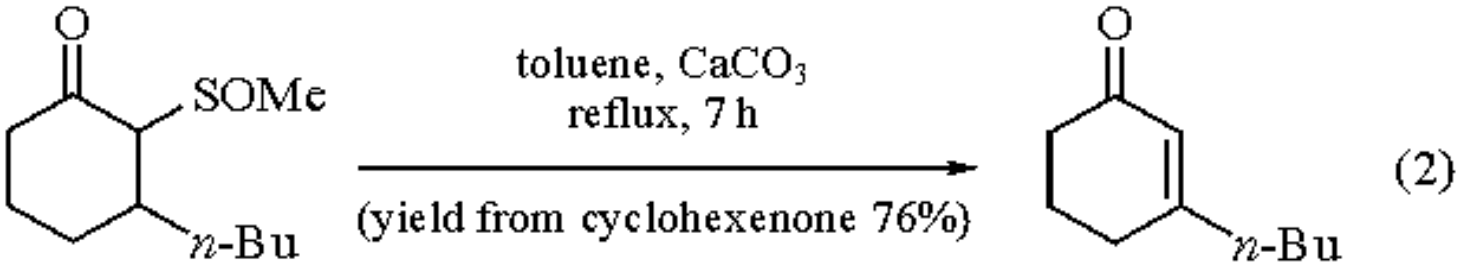

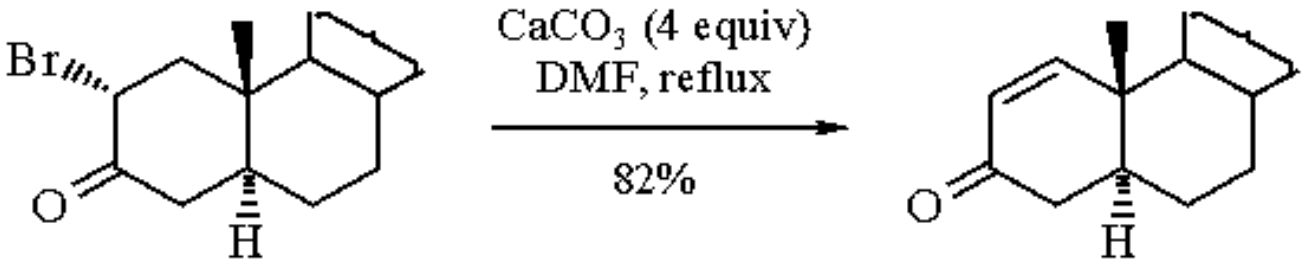

(3)

Halogenation.

Calcium carbonate is often used with reagents such as ***N-Bromosuccinimide*** (eq 4),[7] phosphorus halides,[8] and ***Benzyltrimethylammonium Dichloroiodate*** (BTMA) (eq 5).[9]

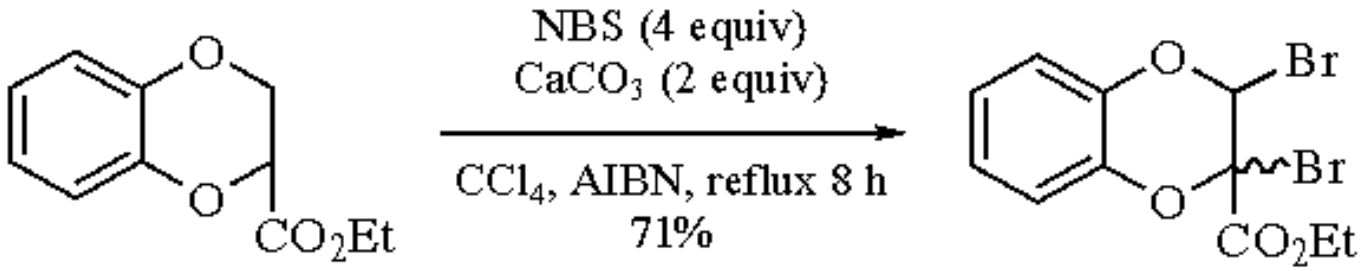

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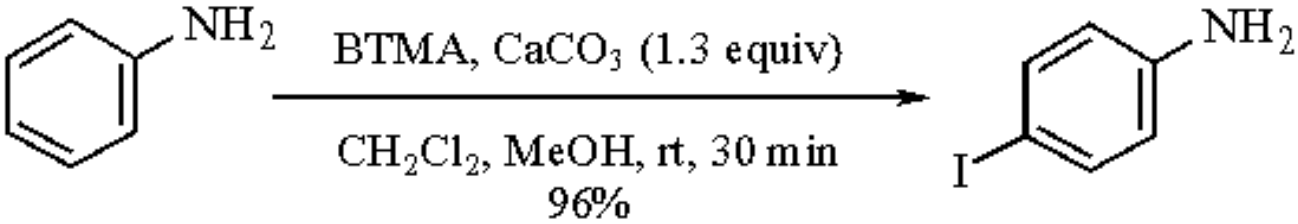

(5)

Substitutions.

Silver(I) Perchlorate promoted substitutions of reactive halides may be effected under mild conditions, as shown in eq 6[10] and eq 7.[11] This provides a useful alternative[12] to classical Friedel-Craft conditions.

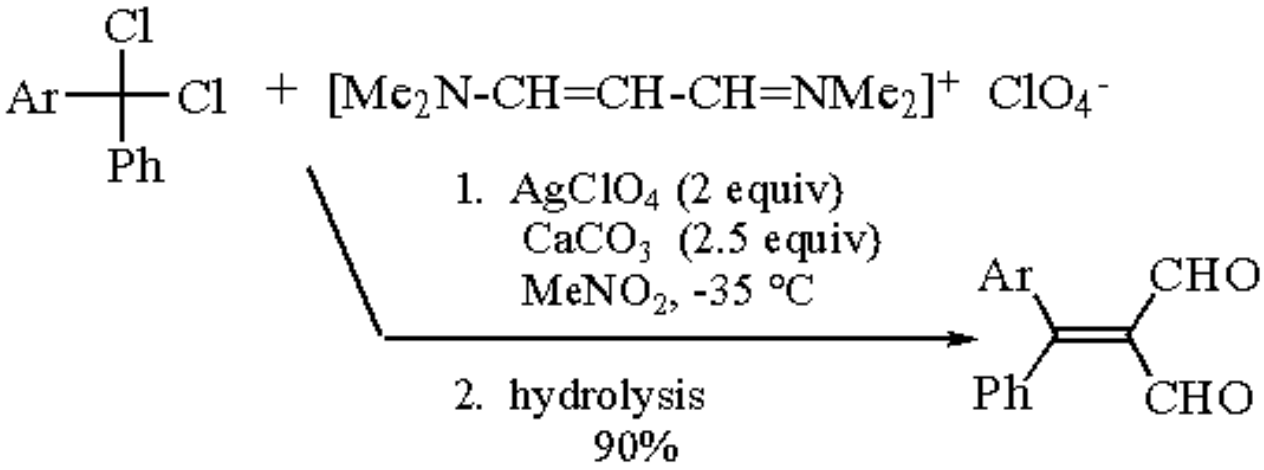

(7)

Pinacol Rearrangement.

Rearrangement of glycol monotosylates (eq 8)[13] is effected by the procedure of Corey.[14] Solvolysis of an analogous bicyclic epoxy tosylate in an aqueous suspension of $CaCO_3$ gave a 1,5-diketone in good yield (eq 9).[15]

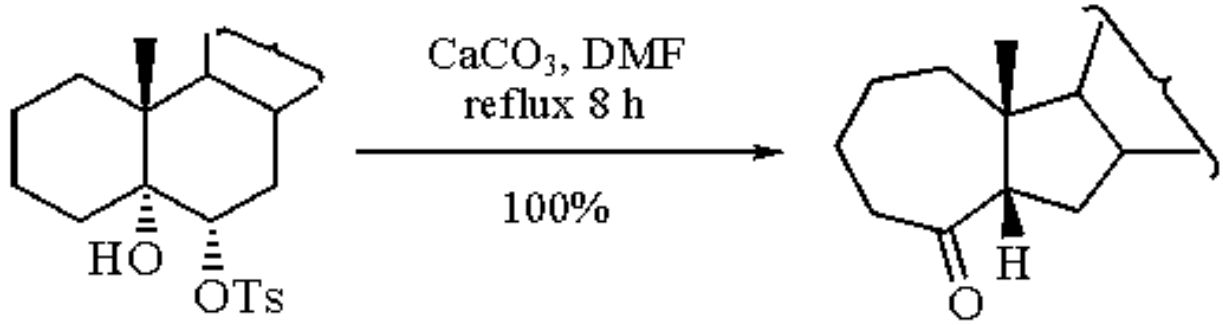

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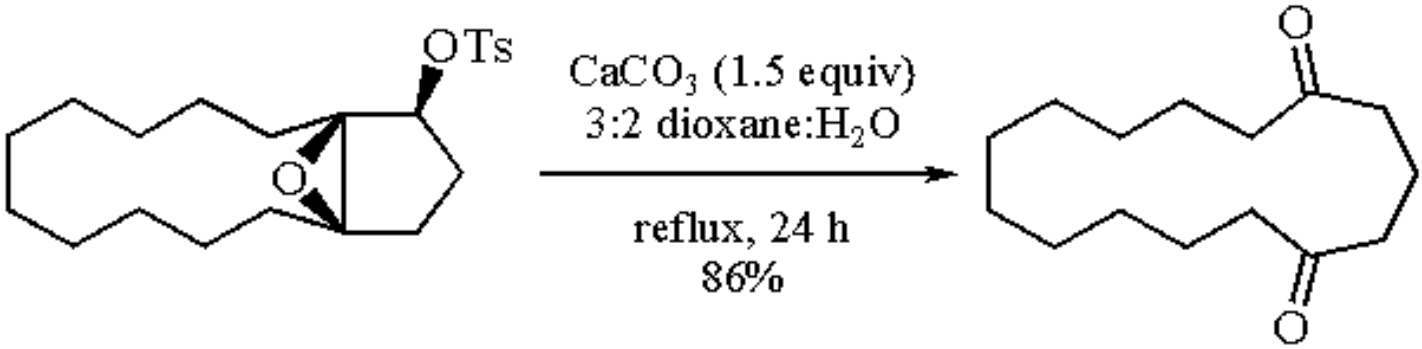

(9)

Thioether and Acetal Deprotection.

Mercury(II) Chloride induced cleavage of thioethers[16] and acetals (eq 10),[17] and their selenium analogs,[18] employs added $CaCO_3$.

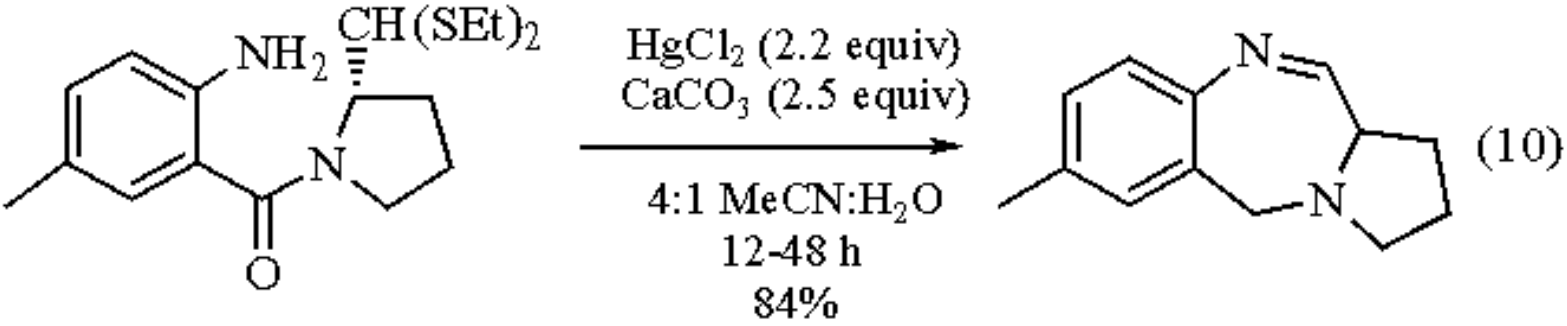

Cycloadditions.

Cycloaddition (eq 11)[19] and related reactions (eq 12)[20] have sometimes used $CaCO_3$ as a coreactant.

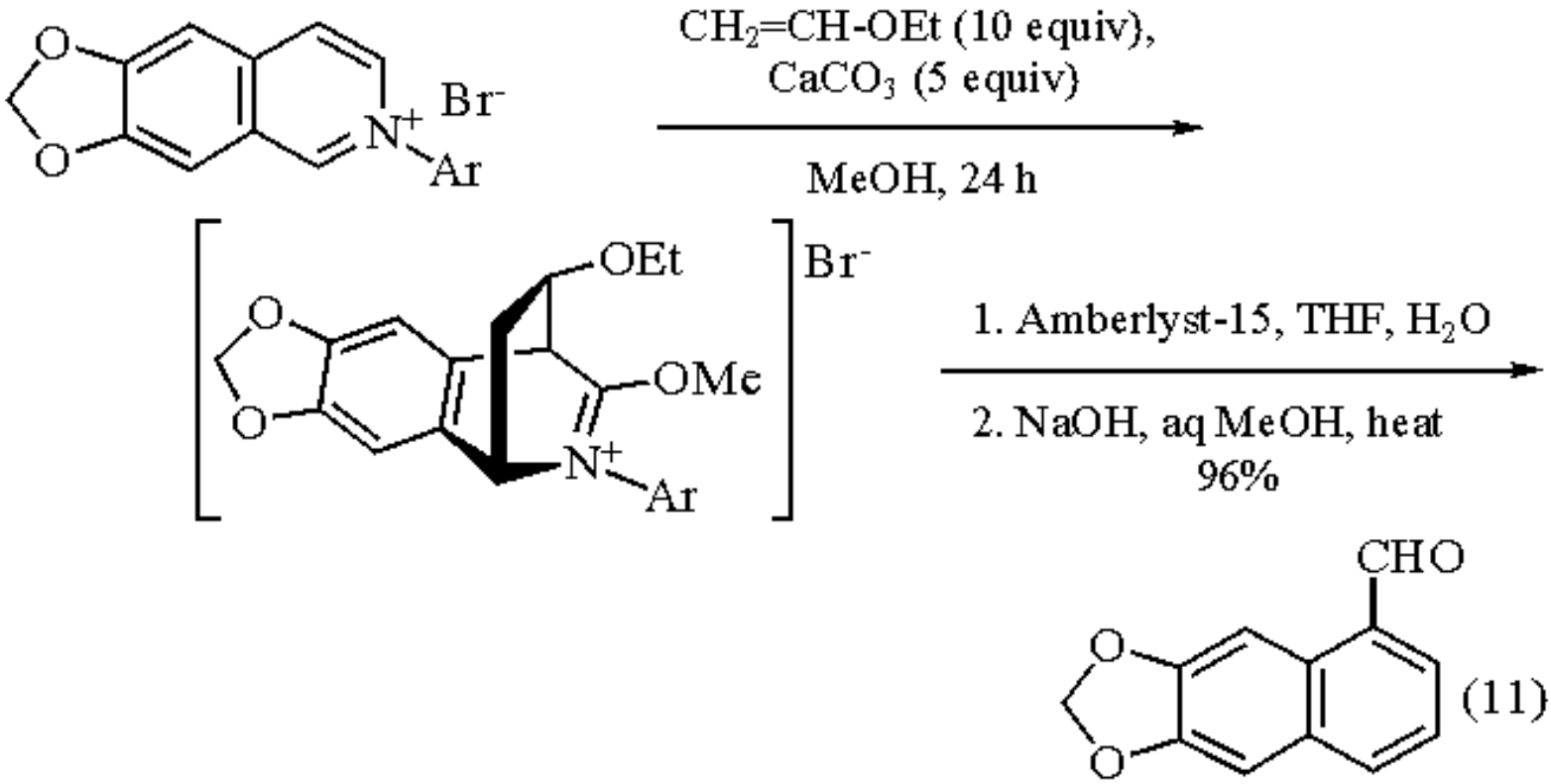

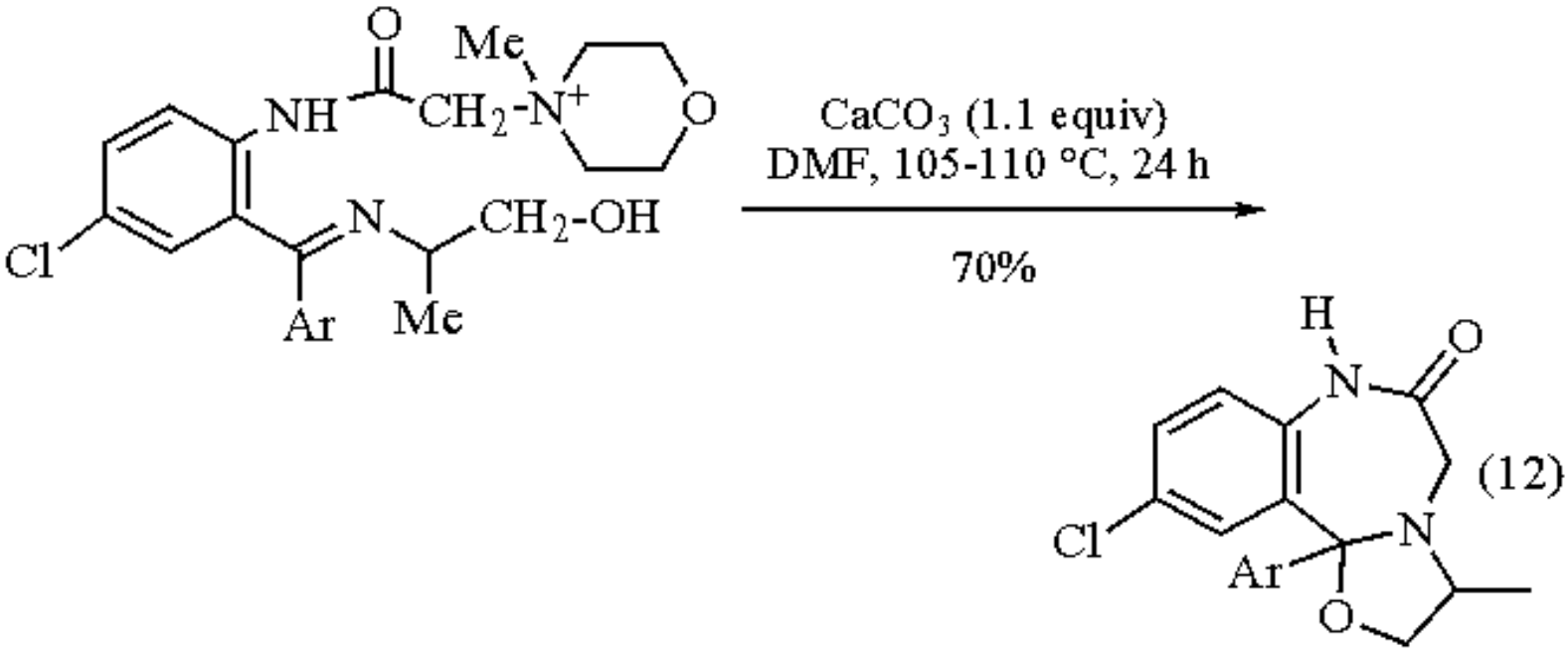

Other Divalent-Metal Carbonates.

Other divalent-metal carbonates related to calcium carbonate include $MgCO_3$ *[546-93-0]*, ***Zinc Carbonate*** *[3486-35-9]*, $SrCO_3$ *[1633-05-2]*, and $BaCO_3$ *[513-77-9]*. In general, these carbonates have not been widely used. Barium carbonate has served a similar role in halogenation and dehydrohalogenation reactions as the calcium salt. Since barium is more toxic than calcium, its equivalent use is not recommended. Calcium, strontium, and barium carbonates have all been used as supports for noble metal catalysts in hydrogenation reactions, and in some cases appear to give better selectivity than analogous carbon- or alumina-supported catalysts.[21]

A novel coumarin synthesis (eq 13), employing zinc or magnesium carbonate,[22] avoids the acidic conditions of the Pschorr synthesis.

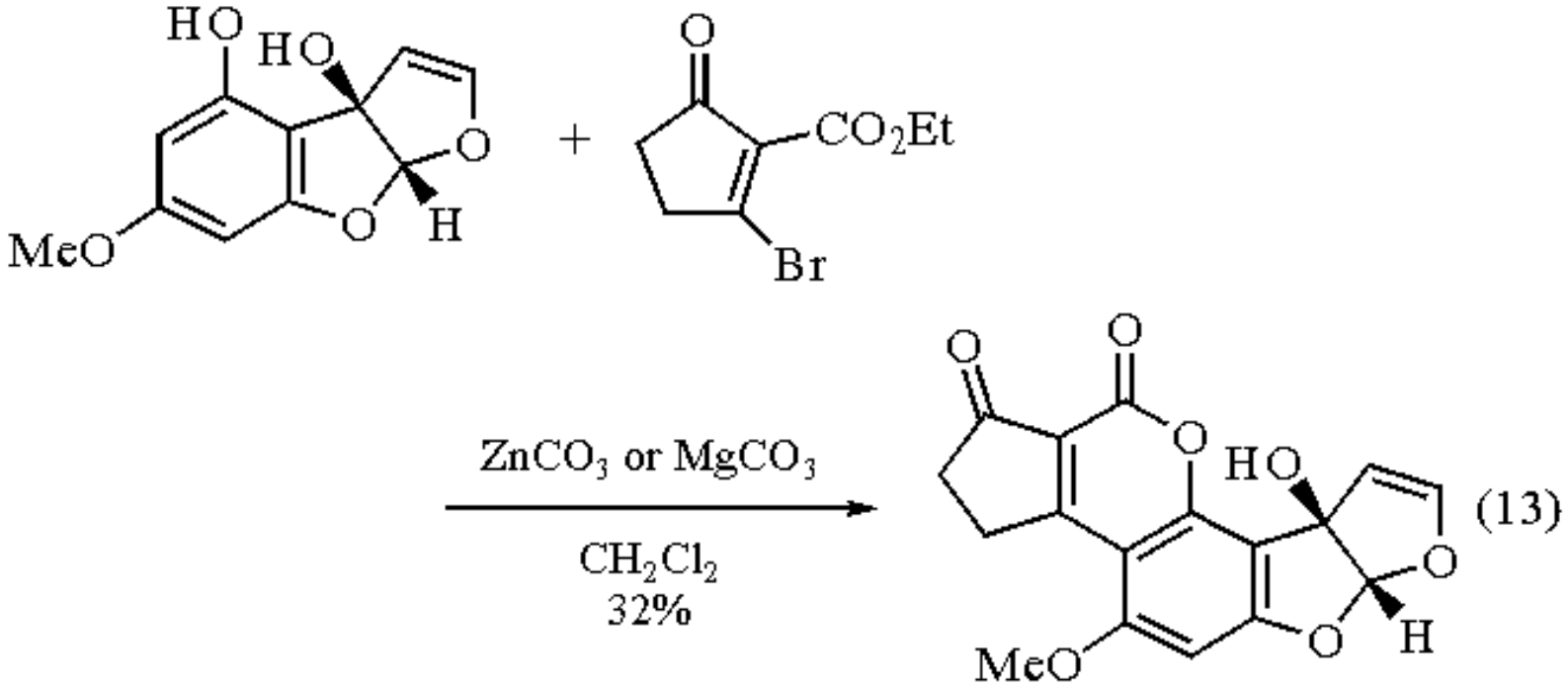

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Calcium Hydride[1]

CaH_2

[7789-78-8] · CaH_2 · Calcium Hydride · (MW 42.10)

(used as a drying agent for reagents and solvents, as a desiccant in reactions, as a base, and as a catalyst and cocatalyst)

Physical Data: mp 816 °C, *d* 1.902 g cm^{-3}.

Form Supplied in: gray orthorhombic crystals, fine ground powder, coarse ground powder, and granules/lumps.

Handling, Storage, and Precautions: moisture sensitive and pyrophoric. It reacts vigorously with water, and should be stored and handled under dry conditions (argon or nitrogen).

Calcium hydride reacts with water to form calcium hydroxide and hydrogen gas (eq 1). It reacts much more slowly than the other metal hydrides as a base (toward organic acids), and has therefore found its most widespread use as a drying agent. Thus it has been used to dry hydrocarbons, ethers, amines (including pyridine), esters, phosphites, and alcohols. A typical procedure is to stir the liquid containing approximately 5% w/v calcium hydride for a period of time (1-2 h at least; preferably 24 h), and decanting, filtering, or distilling the liquid away from the calcium salts.[2] Traces of water and cyanide may be removed from ***N,N-Dimethylformamide*** in this manner.[3]

$$CaH_2\,(s) + H_2O \longrightarrow Ca(OH)_2\,(aq) + H_2\,(g) \qquad (1)$$

Specific compounds dried with calcium hydride and analyzed for residual water content include benzene,[2] dioxane,[2] acetonitrile,[2,4] methanol,[5] ethanol,[5] 2-butanol[5] and *t*-butyl alcohol.[5] Benzene is dried to <=0.2 ppm and dioxane to <=50 ppm residual water.[5] Simply stirring acetonitrile over calcium hydride for seven days and distilling leaves 1900 ppm water.[5] A more rigorous drying protocol for acetonitrile has also been reported for electrochemical use.[4] Methanol and ethanol are dried to ~100 ppm residual water content,[5] in conflict with an early recommendation against using this drying agent.[6] Apparently, calcium hydride reacts with water considerably faster than with alcohols, making it an excellent drying agent for these compounds. On the other hand, perhaps the most convenient drying agent for the lower alcohols is 3°A molecular sieves (powdered sieves are best for all but methanol, where beads are best).[5] ***Molecular Sieves*** are as good as calcium hydride for methanol and ethanol, and superior for 2-butanol and *t*-butyl alcohol.[5]

Calcium hydride has also been used as a desiccant, removing water as it is formed in a reaction. For example, the condensation of methylboronic acid to trimethylboroxin (eq 2) proceeds in 58% yield in the presence of calcium

hydride. Note that the reverse reaction is exothermic and quantitative. Other desiccants are not as efficacious.[7] Similarly, calcium hydride removes the water formed in the condensation of methylboronic acid with pinacol (eq 3).[8]

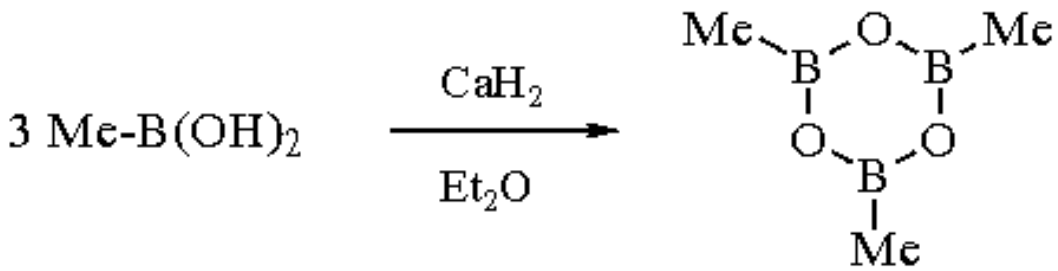

(2)

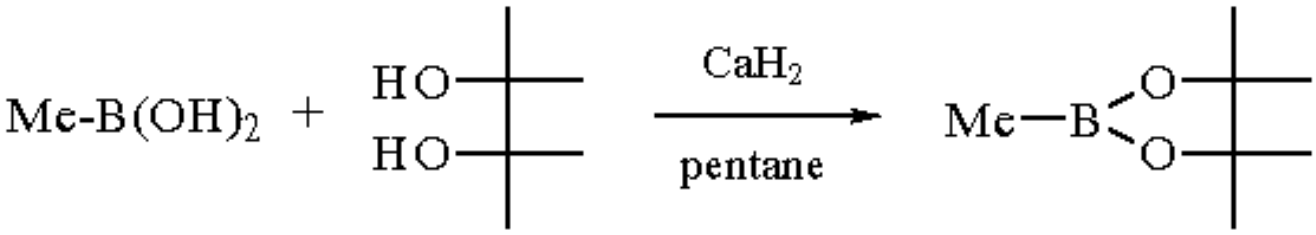

(3)

Two instances have been reported where calcium hydride has apparently been used as a desiccant for residual water in reagents such as tetrabutylammonium halides. For example, benzylation of an alcohol with ***Potassium Hydroxide***, ***Benzyl Bromide***, calcium hydride, and ***Tetra-n-butylammonium Iodide*** (eq 4) was used in a ganglioside synthesis.[9] Another such example is the S_N2 ring opening of an allylic ether, which required calcium hydride, probably as a desiccant (eq 5).[10]

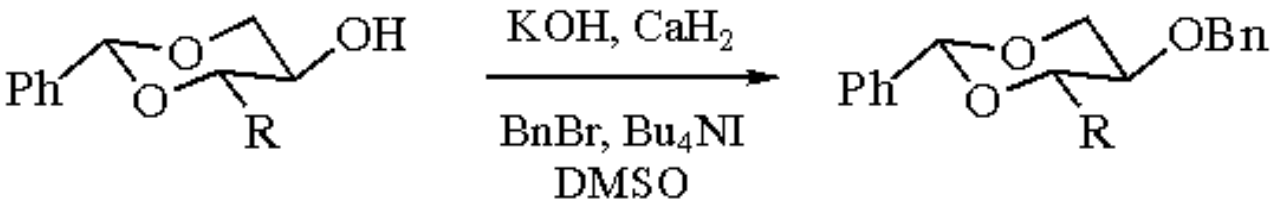

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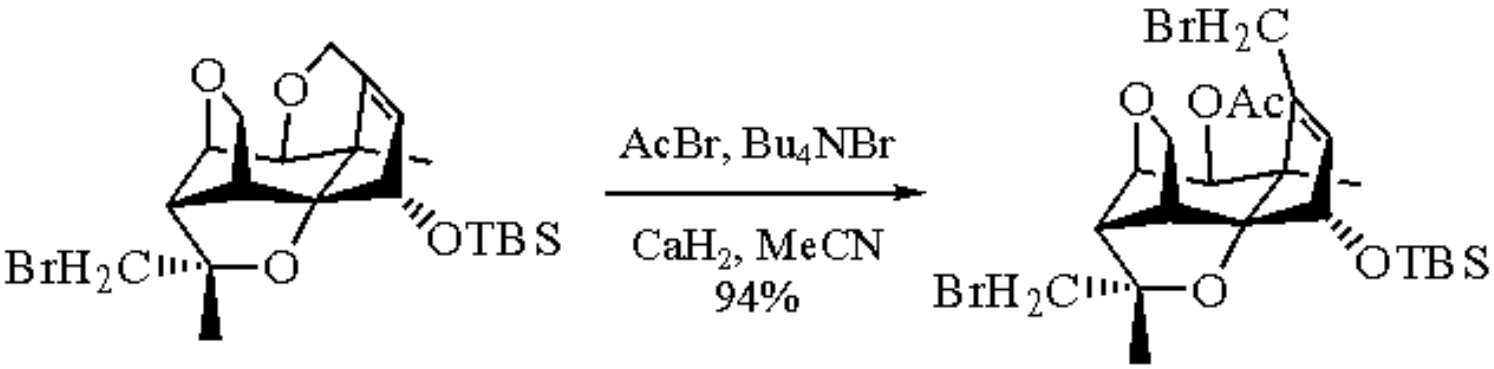

(5)

An early report describes calcium hydride as a basic catalyst for the 1,4-addition of 2-nitropropane to benzalacetophenone (eq 6).[11] In this reaction the methanol is essential (no reaction without it), and the order of addition is important (the calcium hydride must be added last).

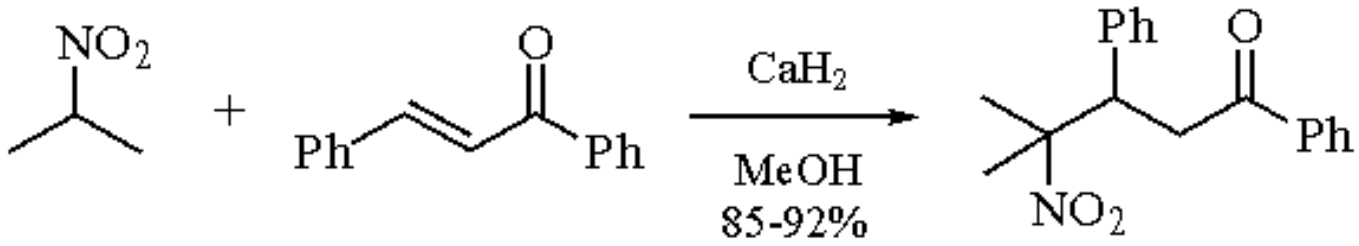

(6)

Calcium hydride assists in the acylation of alcohols (acting as a base), including tertiary ones, by anhydrides and acid chlorides (eq 7).[12,13]

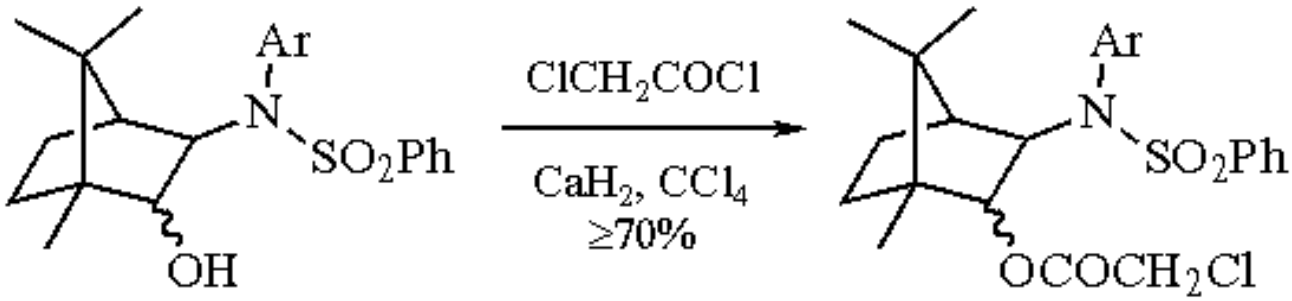

(7)

The site of methylation of 2-aminoethanol is influenced by the gegenion of the hydride used: ***Sodium Hydride*** affords 96% *O*-methylation while calcium hydride yields exclusive *N*-methylation (eq 8).[14]

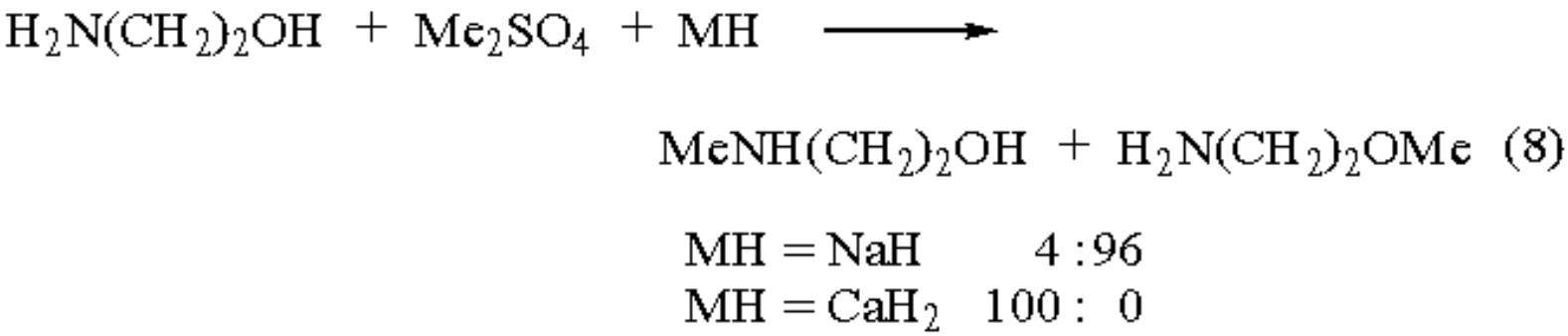

(8)

The Sharpless asymmetric epoxidation (SAE) is an extremely valuable technique for the synthesis of epoxy alcohols from allylic alcohols.[15] Although the asymmetric epoxidation gives good yields (76-80%) and high selectivities (&egt;90% ee), it may require a long reaction time. Wang and co-workers studied the effect of additives on the Sharpless epoxidation of (*Z*)-2-tridecen-1-ol.[16] Addition of silica gel alone did not affect the selectivity, the yield, or the reaction time. Addition of calcium hydride shortened the reaction time but decreased the selectivity. Addition of both, however, resulted in a reaction time shortened from 96 h to 8 h, with no loss of selectivity (eq 9). The calcium hydride/silica gel-modified Sharpless reagent has since been studied on a variety of allylic alcohols,[17] and has been used by other groups as well.[18]

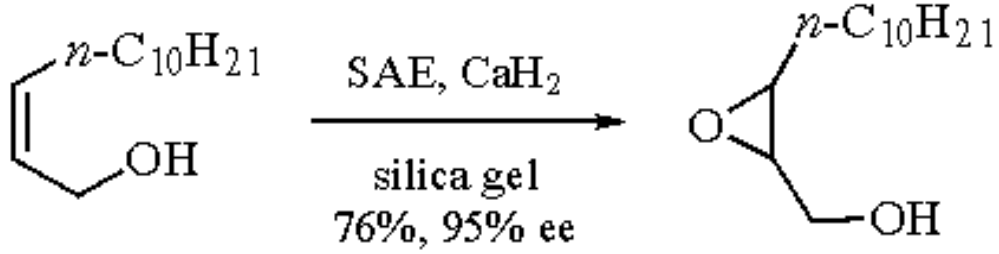

(9)

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Calcium Hypochlorite[1]

$Ca(OCl)_2$

[7778-54-3] · $CaCl_2O_2$ · Calcium Hypochlorite · (MW 142.99)

(oxidizing agent for the conversion of alcohols to aldehydes,[2] ketones,[3] carboxylic acids,[4] esters,[3] and methyl esters;[5] aldehydes to acids[6] and *t*-butyl esters;[5] ethers to esters,[3] and thioethers to sulfoxides;[7] for the C-C bond cleavage of 1,2-dioxygenated compounds;[8] for the chlorination of benzenoid compounds;[1] for the conversion of alkenes to chlorohydrins[9])

Alternate Names: calcium oxychloride; hypochlorous acid, calcium salt; B-K powder.

Physical Data: mp 100 °C; specific gravity 2.35.

Solubility: insol organic solvents; slightly sol H_2O (with decomposition); very sol H_2O with a few drops of HOAc; aqueous solutions of acetic acid, acetonitrile, acetone, MeOH, and *t*-butanol, and biphasic solutions of H_2O with EtOAc, CH_2Cl_2, ether, benzene, and CCl_4 are used for oxidations.

Form Supplied in: white or light yellow granular solid with strong chlorine odor; widely available.

Purification: composition is generally 60-70% $Ca(OCl)_2$ [$Ca(OCl)_2$, 65%; NaCl, 15%; H_2O, 10%; $Ca(OH)_2$, 4%; $CaCO_3$, 3%; $CaClO_3$, 1.5%; $CaCl_2$, 1%].[10]

Handling, Storage, and Precautions: commercially available $Ca(OCl)_2$ (65%) is easy to handle and may be stored in a desiccator without substantial decomposition.[11] Anhydrous $Ca(OCl)_2$ must be stored in a brown bottle kept away from sunlight and moisture. *It explodes when in direct contact with organic material, especially lubrication oils.* This reagent should be handled in a fume hood.

General Conditions of Use.

$Ca(OCl)_2$ is an inexpensive and broad-based reagent for the oxidation of a variety of functional groups.[1-9] Its advantage over ***Sodium Hypochlorite*** (NaOCl) is its relative stability at ambient temperature[11] and its ease of handling as a solid. NaOCl is commercially available in dilute aqueous solutions (usually about 3-5%) that deteriorate rather rapidly. Thus the solution must be frequently titrated to define the quantity of oxidant present. In addition, because of the low concentration of NaOCl in solution an excessive volume of solvent is usually present.[12] The major difficulty encountered with the use of $Ca(OCl)_2$ is that of solubility. It is insoluble in most common organic solvents and forms a

cloudy solution in water. However, complete solubility in water is attained by the addition of a few drops of acetic acid, giving a final oxidizing solution that is clear and light yellow. Aqueous organic biphasic solutions are also useful media in which to carry out the oxidations.

Oxidation of Alcohols, Ethers, Thioethers, and Aldehydes.

$Ca(OCl)_2$ efficiently oxidizes primary alcohols to esters[3] (eq 1), where both the acid and alcohol portion of the ester are derived from the alcohol. In the presence of ***Molecular Sieves*** and with excess MeOH, methyl esters[5] are obtained (eq 2), while with *t*-butanol, carboxylic acids[4] are generated (eq 3). A variety of substituted methyl benzoates are thus easily prepared from the corresponding benzyl alcohols by the former method, and *t*-butyl esters are available from aldehydes.[5] Aldehydes, which are easily oxidized to carboxylic acids[6] with $Ca(OCl)_2$ (eq 4), are themselves available in remarkably high yield from primary alcohols, in less than 15 min, when a catalytic amount of 4-(benzoyloxy)-2,2,6,6-tetramethylpiperidin-1-oxyl is added (eq 5).[2] (***Ruthenium(III) Chloride*** has also been used to catalyze this reaction.[13])

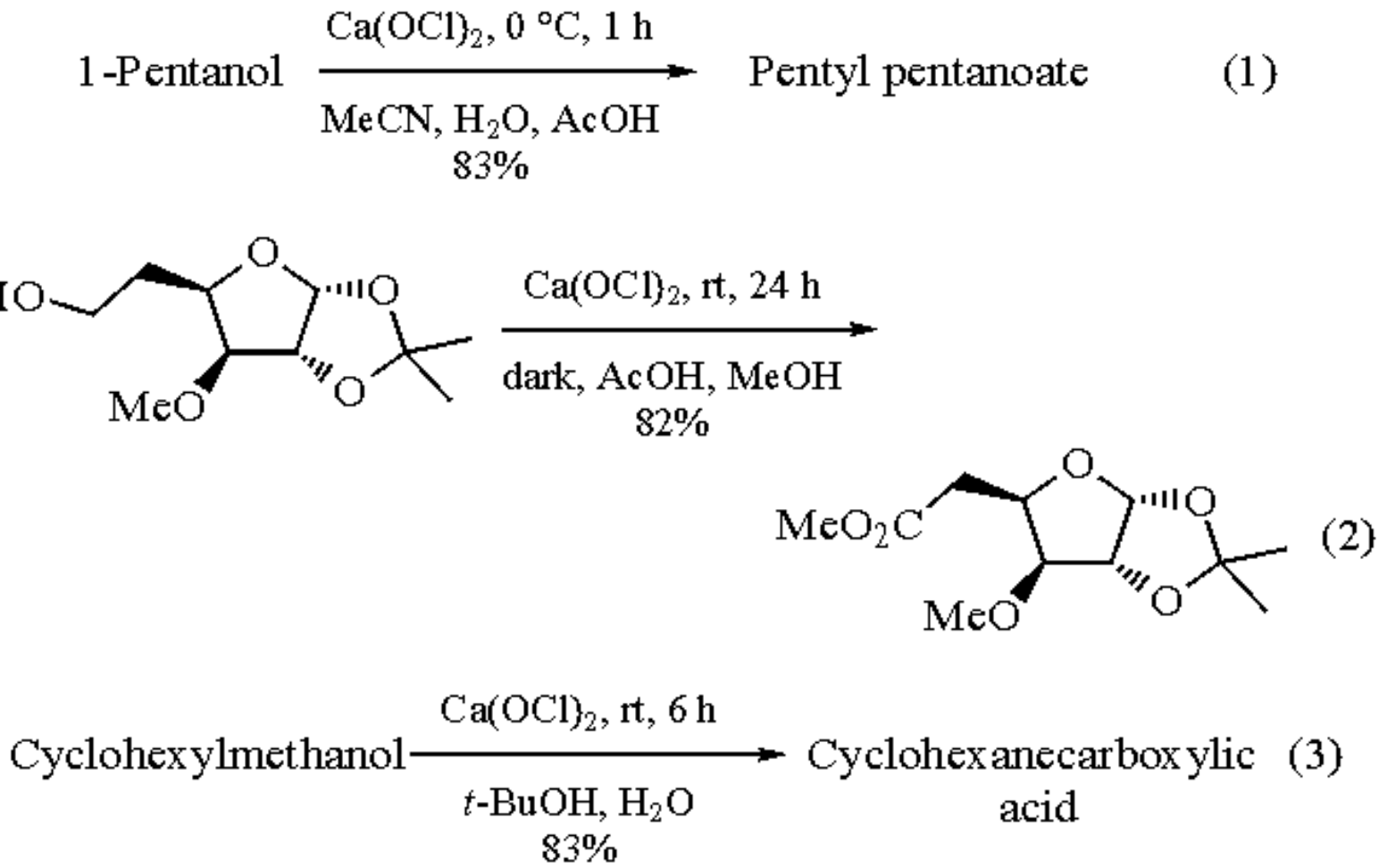

$$\text{RCHO} \xrightarrow[\text{MeCN, } H_2O\text{, AcOH}]{Ca(OCl)_2\text{, 0 °C, 1 h}} \text{RCO}_2\text{H} \qquad (4)$$

R = 3-pentyl	75%
R = *p*-ClC_6H_4	92%
R = *m*-$NO_2C_6H_4$	84%

$$\text{Me}(CH_2)_{10}\text{—}\equiv\text{—}CH_2OH \xrightarrow[\substack{CH_2Cl_2,\ H_2O,\ HCO_3^-,\ \text{cat.} \\ 96\%}]{Ca(OCl)_2\text{, 5 °C, 5 min}} \text{Me}(CH_2)_{10}\text{—}\equiv\text{—CHO} \qquad (5)$$

Secondary alcohols afford ketones[3] in high yield in aqueous media (eq 6), or in organic media (CH_2Cl_2, CCl_4, Et_2O, EtOAc) with a catalytic amount of hypochlorite resin (IRA 900)[14] using a triphasic system (liquid-solid-solid) (eq 7). Acyclic and cyclic ethers give esters (eq 8)[3] and lactones (eq 9),[3] respectively, although the yields are lower than for the oxidation of the other groups. A variety of alkyl and aryl-alkyl thioethers can be selectively oxidized to sulfoxides (eq 10)[7] in yields exceeding 70% however, dibenzyl sulfide is inefficiently converted to dibenzyl sulfoxide (25%).

$$\text{Borneol} \xrightarrow[\substack{\text{MeCN, } H_2O\text{, AcOH} \\ 98\%}]{Ca(OCl)_2\text{, 0 °C, 1 h}} \text{Camphor} \qquad (6)$$

$$\text{Cyclopentanol} \xrightarrow[\substack{CCl_4\text{, IRA 900} \\ 90\%}]{Ca(OCl)_2\text{, rt, 3 h}} \text{Cyclopentanone} \qquad (7)$$

$$(n\text{-Bu})_2\text{O} \xrightarrow[\substack{\text{MeCN, } H_2O\text{, AcOH} \\ 40\%}]{Ca(OCl)_2\text{, rt, 1 h}} \text{Butyl butanoate} \qquad (8)$$

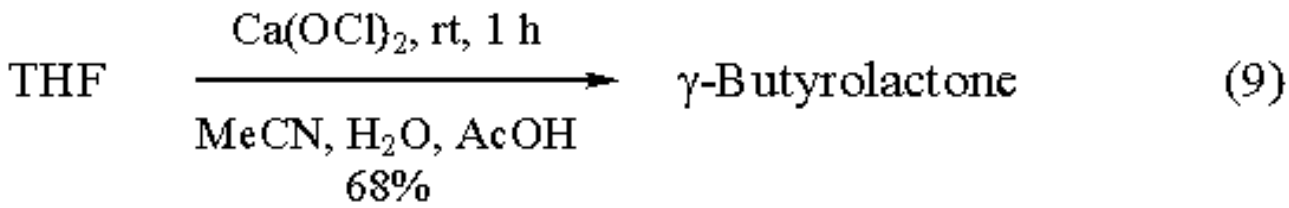

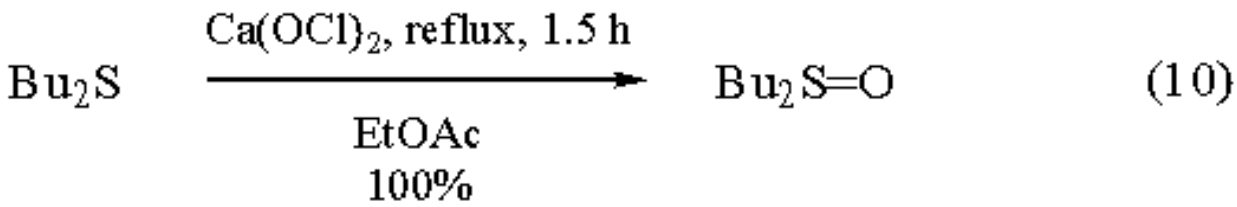

Carbon-Carbon Bond Cleavage Reactions.

α-Diols, α-diones, α-hydroxy ketones, and α-hydroxy and α-keto acids[8] are oxidatively cleaved with $Ca(OCl)_2$ (eqs 11 and 12). The yields are good to excellent and the products obtained (aldehydes, ketones, acids) depend on the oxidation state of the carbon atoms bearing the original oxygen groups. In an interesting two-step high-yield preparation of piperonal, the glycol obtained from electrochemical oxidation of isosafrole is converted to piperonal in near quantitive yield by glycol cleavage[15] when treated with $Ca(OCl)_2$ in benzene/H_2O (eq 13).

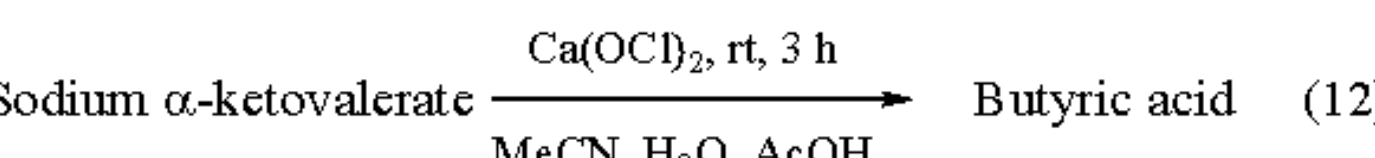

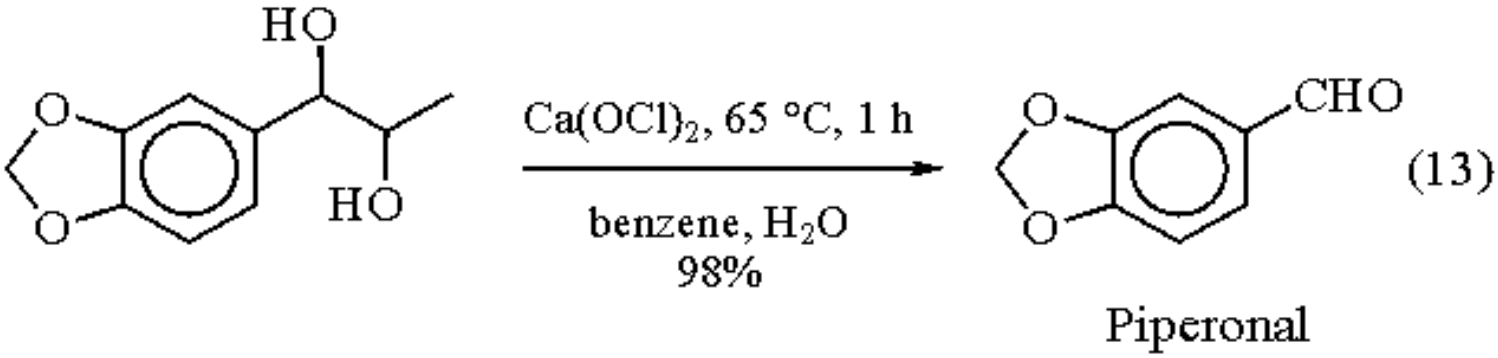

Chlorination of Benzenoid Compounds.

As depicted in eq 14, if the glycol of isosafrole is oxidized in $MeCN/CH_2Cl_2/H_2O$ at ambient temperature, ring chlorination[15] takes place instead of C-C bond cleavage to afford 1-[2-chloro-4,5-(methylenedioxy)phenyl]propane-1,2-diol (85%). $Ca(OCl)_2$ can thus be used for chlorination of aromatics (benzene, naphthalene).[1] While chlorobenzene, nitrobenzene, and 4-nitrotoluene do not react, good results are obtained when the substrate has strong electron-donating substituents (eqs 15-17).[1] Activated rings having oxidizable substituents will undergo chlorination and oxidation, depending on the reactivities of the groups and the number of equivalents of $Ca(OCl)_2$ used (eqs 18 and 19).

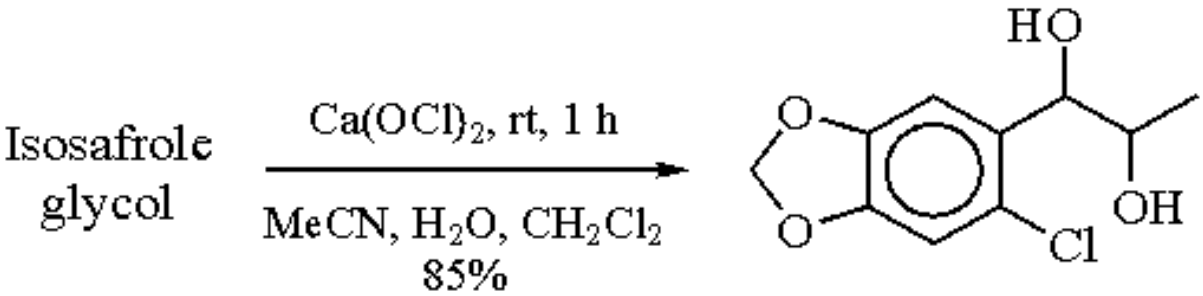

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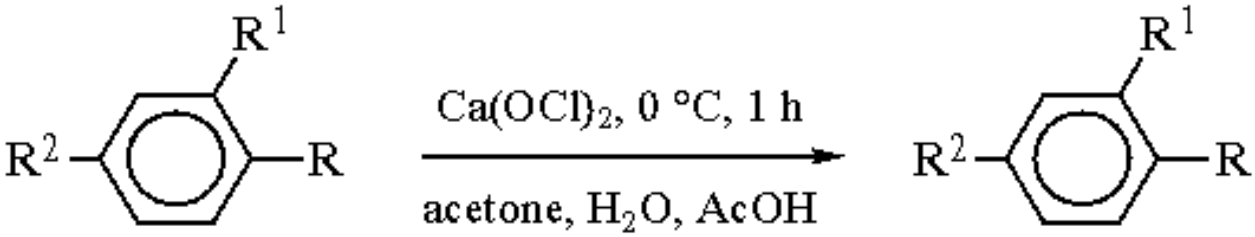

$R = Me, R^1 = R^2 = H$	50%	$R = Me, R^1 = H, R^2 = Cl$	(15)
$R = HNAc, R^1 = R^2 = H$	79%	$R = HNAc, R^1 = H, R^2 = Cl$	(16)
$R = OMe, R^1 = R^2 = H$	68%	$R = OMe, R^1 = H, R^2 = Cl$	(17)
$R = Me, R^1 = H, R^2 = CHO$	76%	$R = Me, R^1 = Cl, R^2 = CO_2H$	(18)
$R = OMe, R^1 = CHO, R^2 = H$	93%	$R = OMe, R^1 = CHO, R^2 = Cl$	(19)

Conversion of Alkenes to Chlorohydrins.

$Ca(OCl)_2$ converts mono-, di-, tri-, and tetrasubstituted, cyclic, and acyclic alkenes to the corresponding chlorohydrins[9] in good yield (eqs 20-23). The reactions are carried out under mild conditions and the expected regiochemistry is obtained.

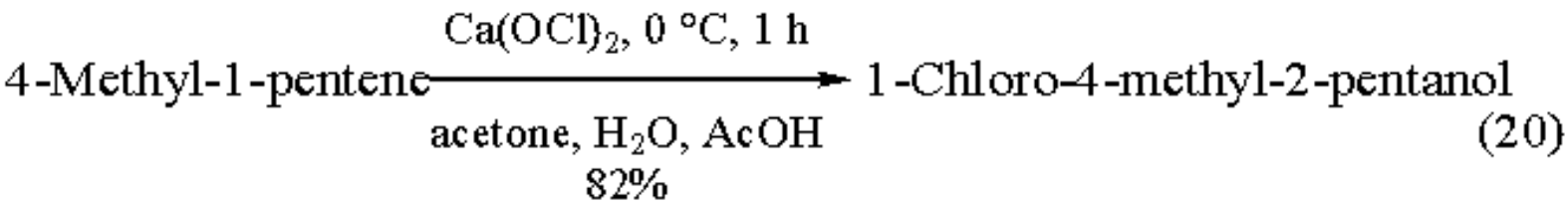

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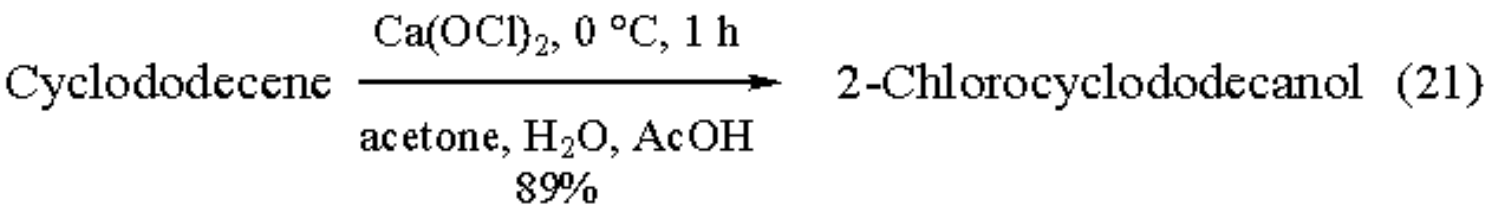

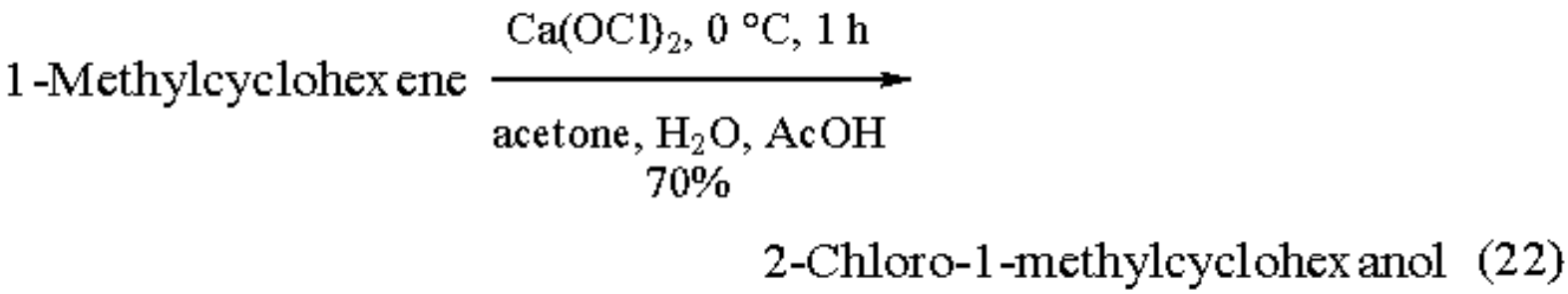

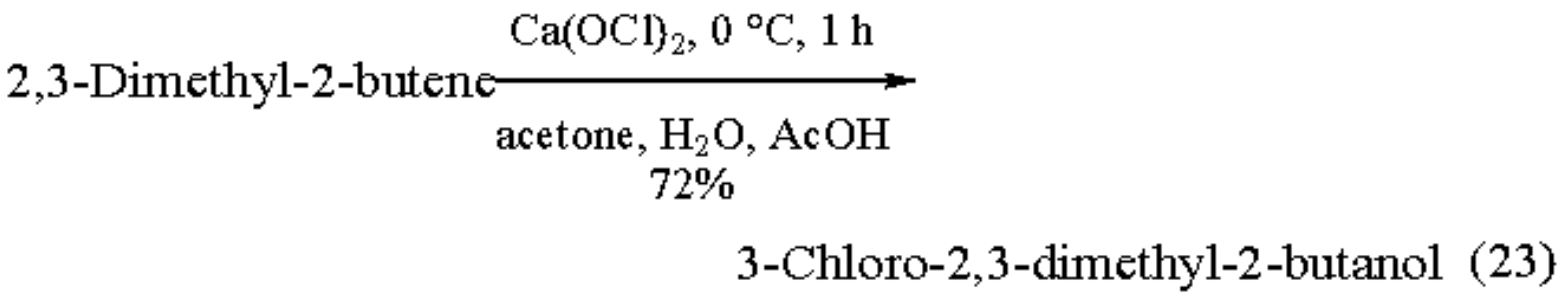

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(-)-(1*S*,4*R*)-Camphanic Acid[1]

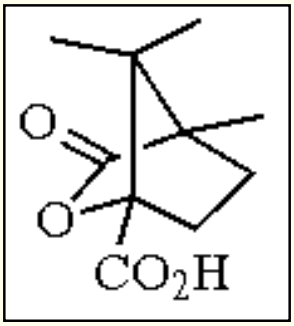

(1*S*)

[13429-83-9] · $C_{10}H_{14}O_4$ · (-)-(1*S*,4*R*)-Camphanic Acid · (MW 198.22) (1*R*)

[67111-66-4] (±)

[465-48-5]

(enantiomeric purity determination;[2] chemical resolution;[3] chiral auxiliaries[4])

Physical Data: mp 201-204 °C; (1*S*): $[\alpha]_D$ -20.4° (*c* 1.71, dioxane); $[\alpha]_D$ -18° (*c* 1, dioxane).

Solubility: sol EtOH, ether, boiling H_2O, and AcOH.

Form Supplied in: white solid.

Preparative Methods: commercially available. Alternatively, the acid can be prepared in two steps from camphoric acid (1. PCl_5; 2. H_2SO_4; 65% overall yield). The acid can be converted to the corresponding acid chloride upon treatment with ***Thionyl Chloride*** (99% yield).[1,5]

Purification: crystallized from hot toluene.

Handling, Storage, and Precautions: stable; no special precautions.

Analysis of the Enantiomeric Purity of Alcohols and Amines.

It has been shown that camphanic acid is an efficient chiral derivatizing agent for the determination of the enantiomeric purity of alcohols and amines.[2] A typical procedure involves mixing a solution of the amine or the alcohol (in CH_2Cl_2, py, or benzene) with camphanoyl chloride in the presence of a base (Et_3N, py, DMAP, or $NaHCO_3$). Alternatively, the substrate can be coupled directly with camphanic acid in the presence of DCC/DMAP. These conditions, however, can potentially lead to significant kinetic resolution.[6] Camphanic acid was initially developed for the analysis of the enantiomeric purity of α-deuterated primary alcohols[7] and amines.[8] Distinct signals by ^1H NMR for the two diastereomers can usually be observed upon addition of a chiral shift reagent or when using C_6D_6 as the solvent.[9] Since then, this chiral derivatizing agent has been widely used for measuring the enantiomeric excess of several classes of compounds such as α-monodeuterated glycine derivatives (**1**),[10] α-and β-amino acids (**2, 3**),[11,12] α,α-disubstituted α-amino acids (**4**),[13] secondary alcohols (**5**),[14] 1,2-amino alcohols (**6**),[15] and sulfoximines.[16]

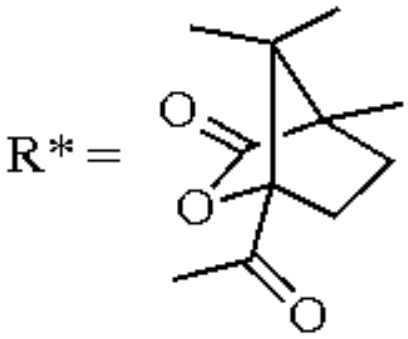

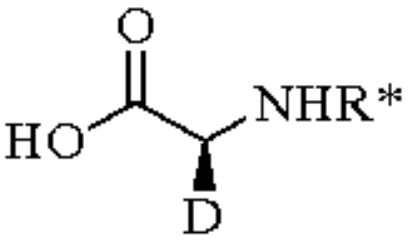

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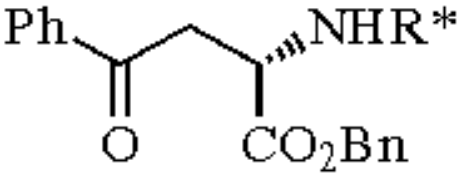

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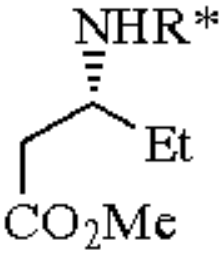

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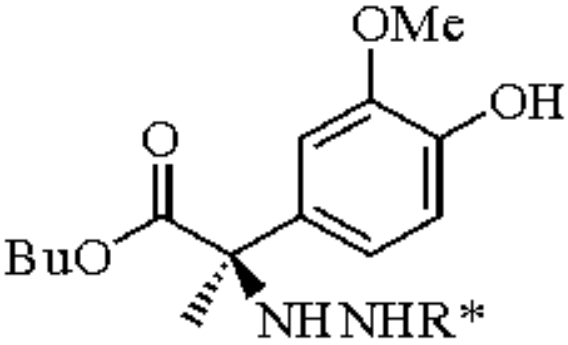

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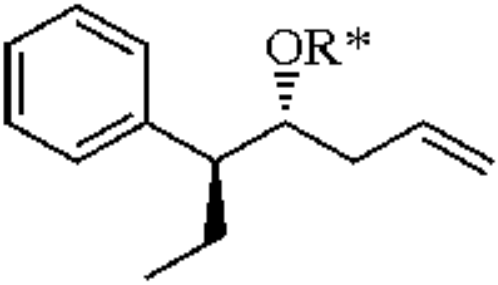

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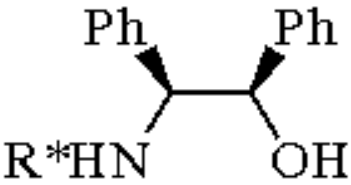

(6)

Resolution of Alcohols.

In addition to generally providing highly crystalline derivatives that are usually suitable for X-ray crystallographic studies,[17] diastereomeric esters derived from camphanic acid have been widely used in organic synthesis for the resolution of racemic alcohols by fractional crystallization or chromatography.[18] This is one of the methods of choice to resolve inositol derivatives.[19] Selected examples are shown in (**7**)-(**10**).[20]

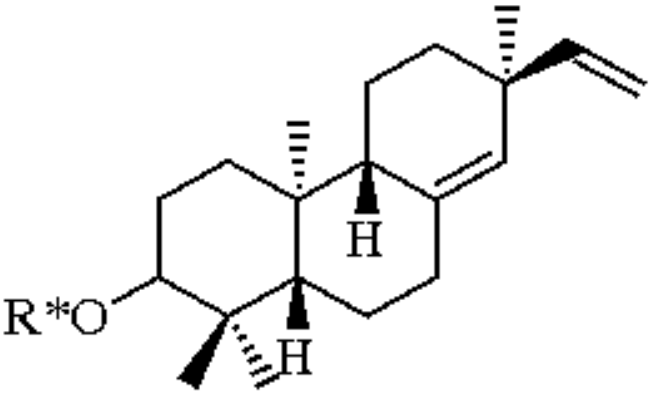

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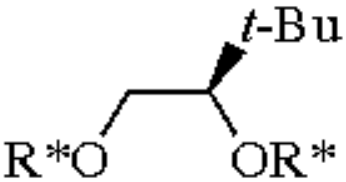

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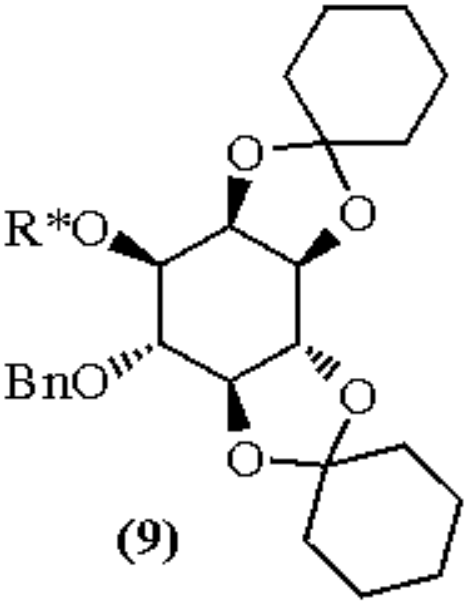

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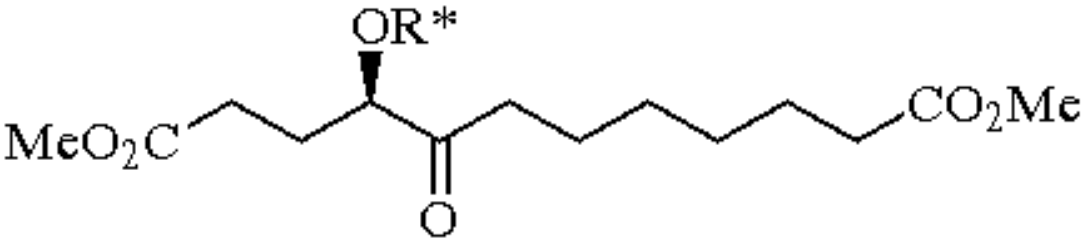

(10)

Chiral Auxiliary for Cycloaddition Reactions.

Camphanate ester (**11**) has been used as a chiral dienophile in cycloaddition reactions with substituted furans to produce 7-oxabicyclo[2.2.1]heptene derivatives (eq 1).[4,21]

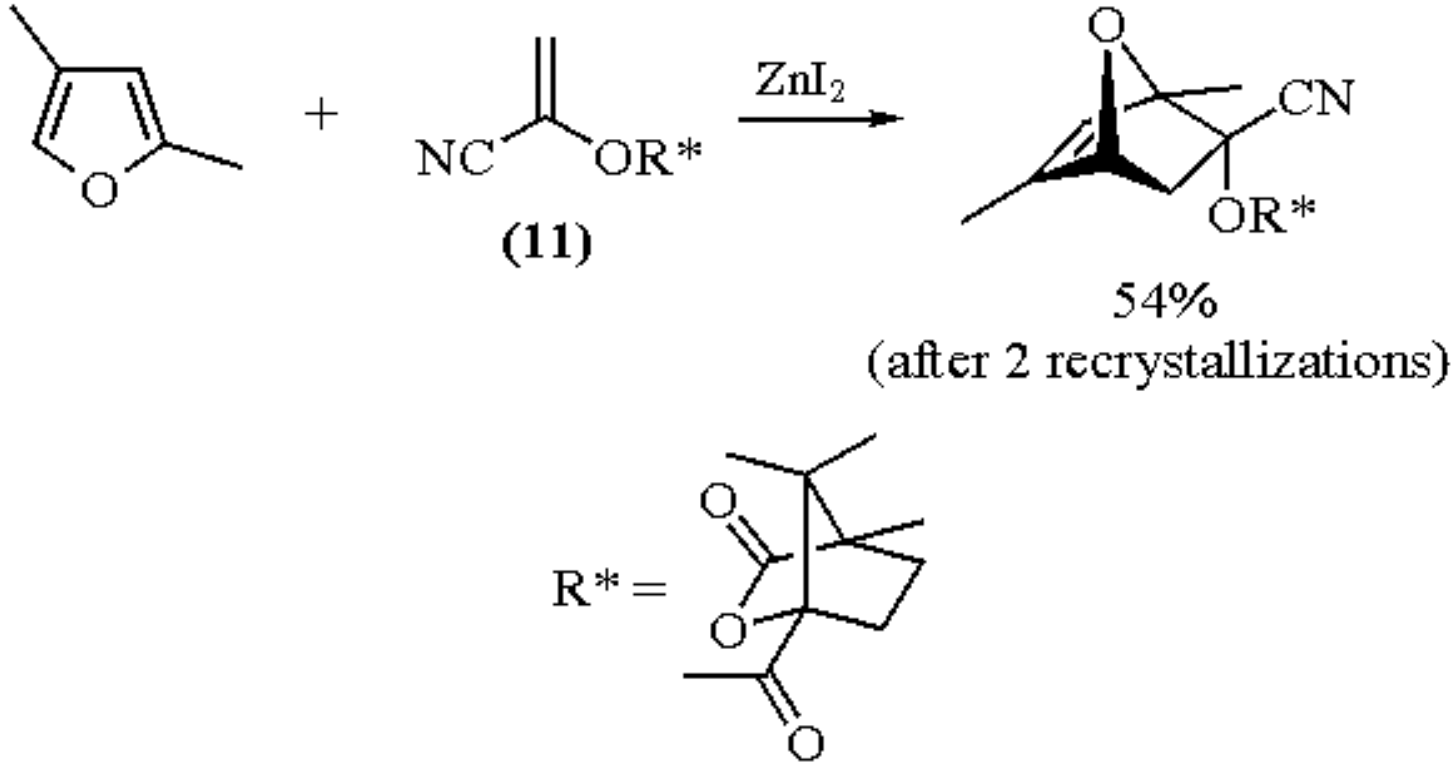

(1)

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10-Camphorsulfonic Acid

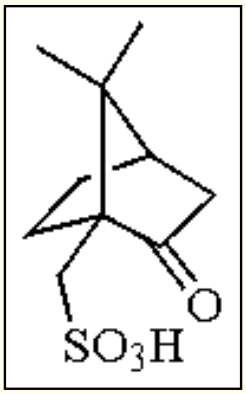

(1*S*)-(+)

[3144-16-9] · $C_{10}H_{16}O_4S$ · 10-Camphorsulfonic Acid · (MW 232.30) (1*R*)-(-)

[35963-20-3] (±)

[5872-08-2]

(acid catalyst,[1-8] resolving agent,[9,10] chiral auxiliary[11-20])

Physical Data: mp 203-206 °C (dec).

Solubility: sol dichloromethane, methanol, benzene; insol ether.

Form Supplied in: white crystals, racemic (±).

Analysis of Reagent Purity: melting point, NMR.

Preparative Methods: commercially available from several sources; can be prepared by sulfonation of camphor with acetic-sulfuric anhydride.[21]

Purification: recrystallize from ethyl acetate.

Handling, Storage, and Precautions: hygroscopic; corrosive.

Acid Catalyst.

Camphorsulfonic acid (CSA) has been used extensively in synthetic organic chemistry as an acid catalyst. It has particularly been used in protecting group chemistry. For example, hydroxyl groups can also be protected as tetrahydropyranyl (THP) ethers using dihydropyran and a catalytic amount of CSA (eq 1).[1] Both 1,2- and 1,3-diols can be selectively protected by reaction with orthoesters in the presence of camphorsulfonic acid to form the corresponding cyclic orthoester (eq 2).[2] This method of protection is particularly useful in that reduction of the orthoester with ***Diisobutylaluminum Hydride*** forms the monoacetal, which allows for preferential protection of a secondary alcohol in the presence of a primary alcohol. Ketones have also been protected using catalytic CSA (eq 3).[3]

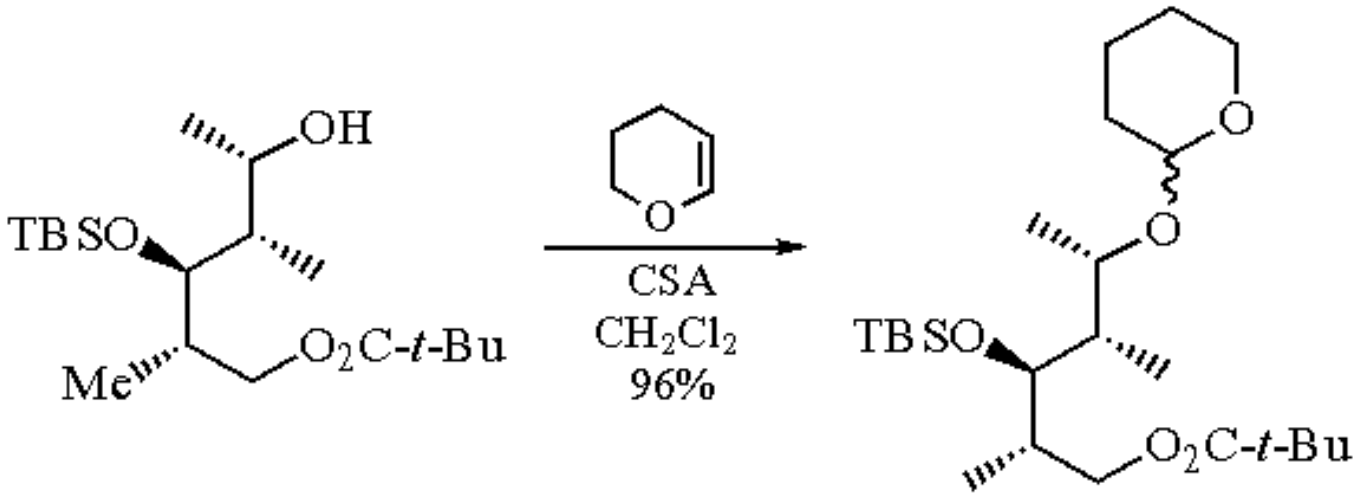

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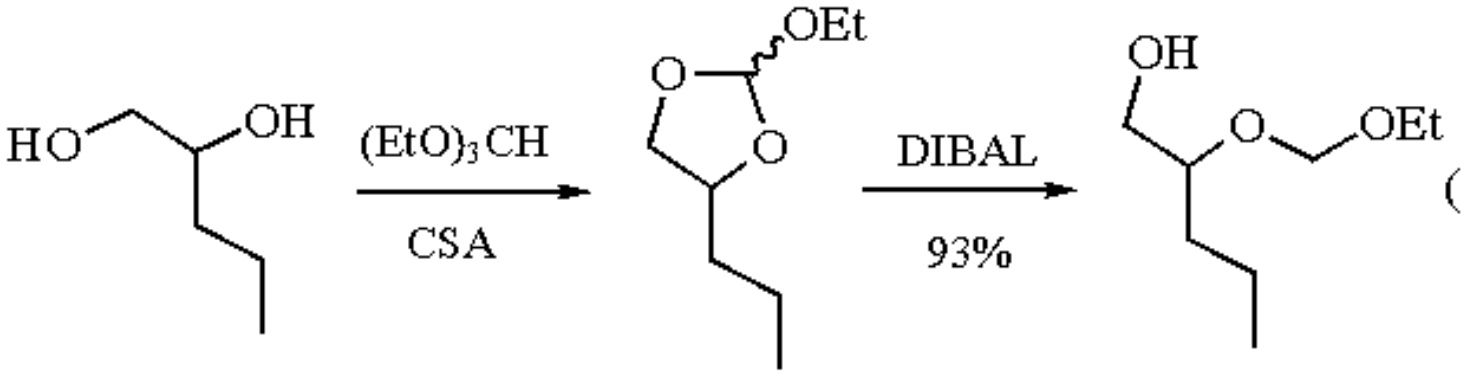

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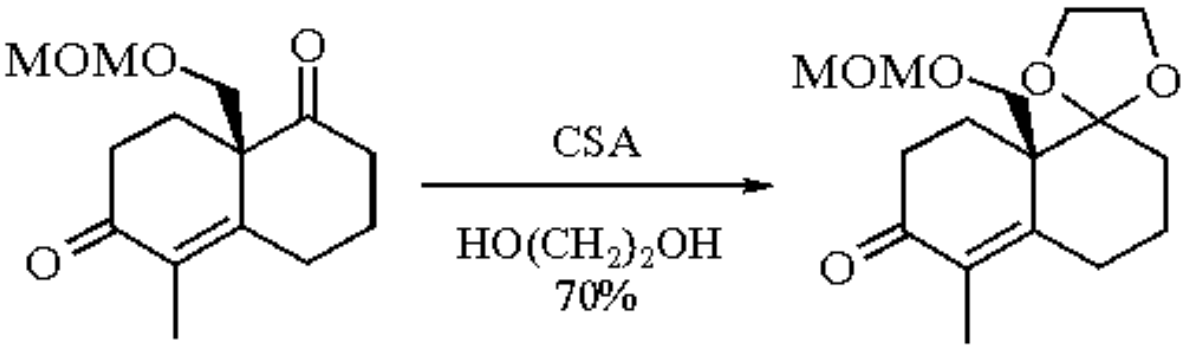

(3)

Overman has shown that camphorsulfonic acid can also be used in nucleophile-promoted alkyne-iminium cyclizations.[22] Alkylamines can react with formaldehyde and sodium iodide to yield piperidines in good yield. This methodology has been applied in the total synthesis of pumiliotoxin A (eq 4).[4]

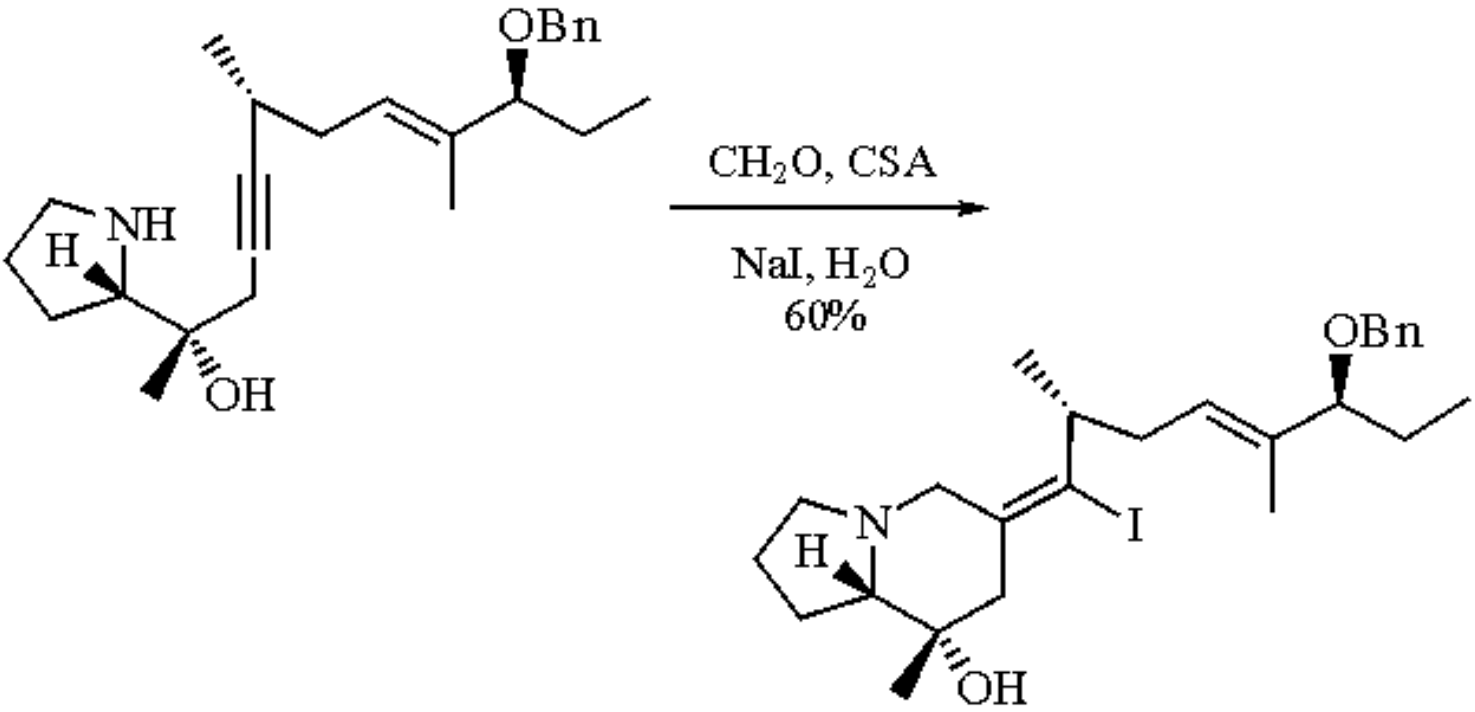

(4)

The most efficient catalyst for intramolecular opening of epoxides is CSA.[5,6] The formation of tetrahydrofurans or tetrahydropyrans is highly dependent on the structure of the hydroxy epoxide. The presence of a saturated chain at the secondary epoxide position leads to formation of tetrahydrofurans (eq 5)[5] via 5-*exo* ring closure, whereas an electron-rich double bond at this position gives tetrahydropyrans (eq 6)[6] via 6-*endo* ring closure. This methodology has also been extended to the synthesis of oxepanes (eq 7).[6]

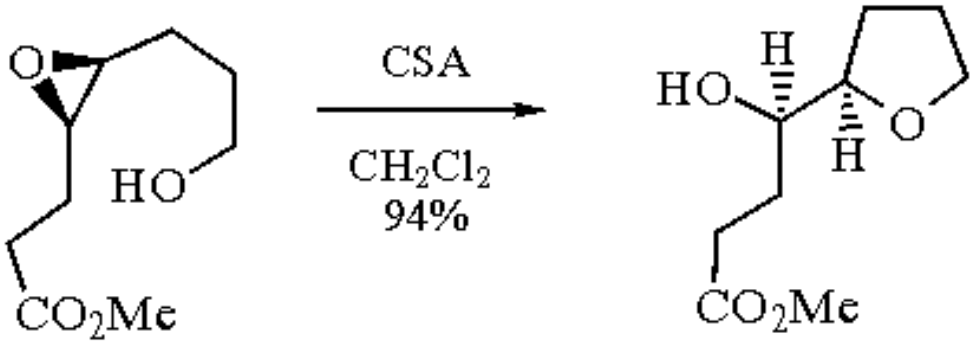

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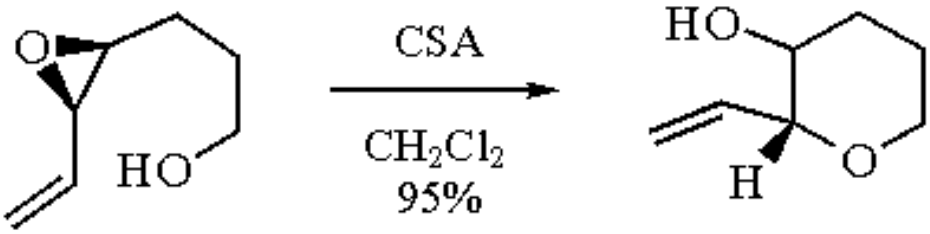

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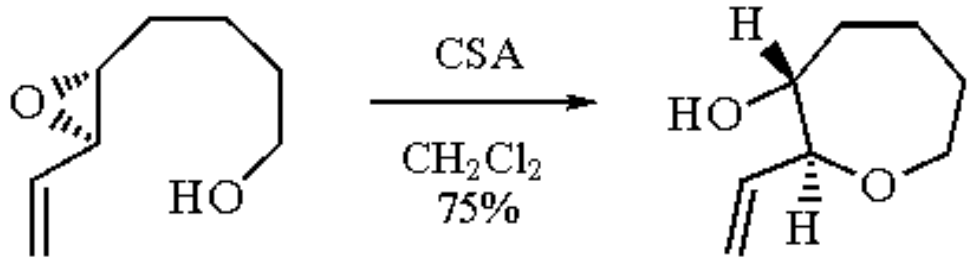

(7)

CSA is also the acid of choice for use in phenylselenation reactions.[7] It has been used as an acid catalyst in hydroxyselenation reactions of alkenes (eq 8)[7] and organoselenium-induced cyclizations (eq 9) using ***N-Phenylselenophthalimide*** (NPSP).[7]

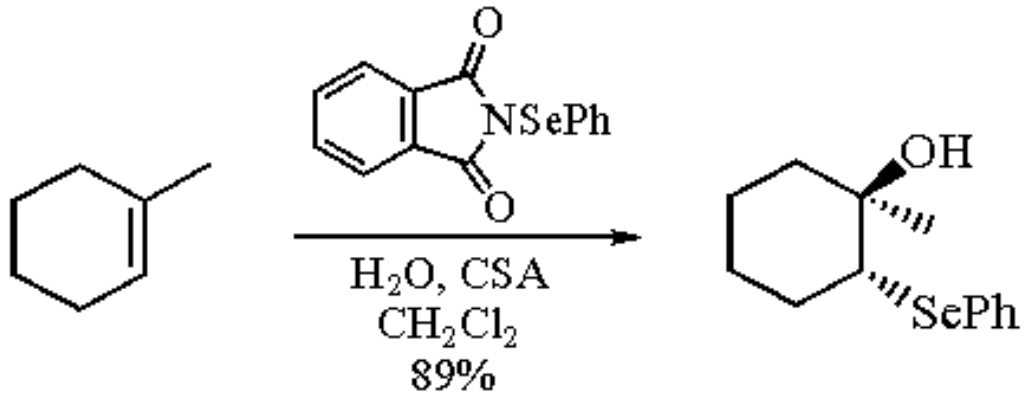

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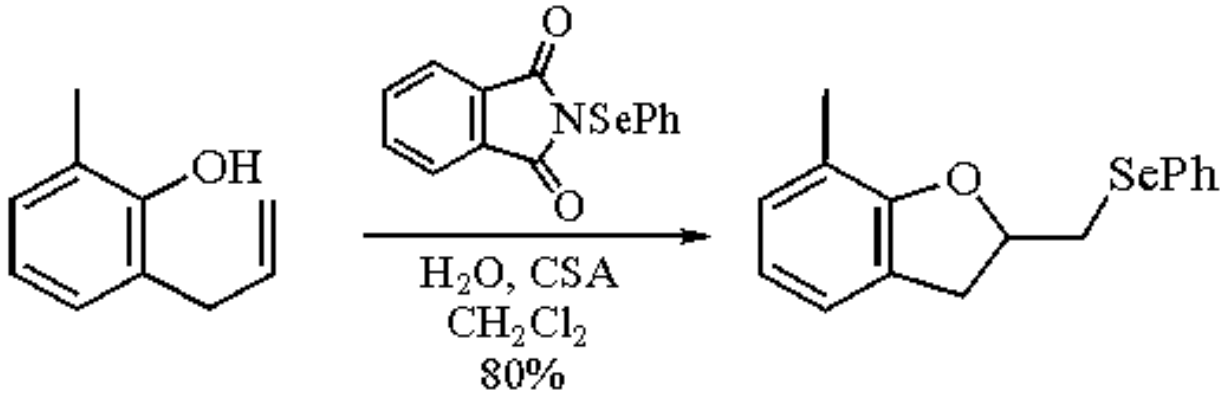

(9)

CSA has also been used to catalyze spiroacetalizations.[8,22] In Schreiber's approach to the talaromycins he utilized a CSA-catalyzed spiroacetalization (eq 10) and found that the use of different solvents led to varying percentages of isomeric products.[8] Other approaches to the talaromycins also utilize CSA for the required spiroacetalization.[23]

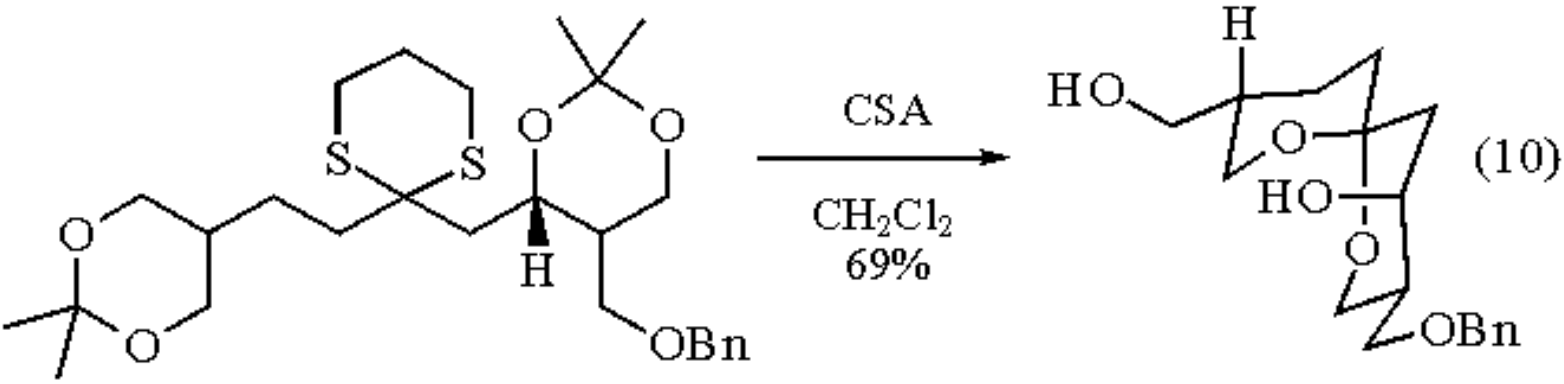

Resolving Agent.

Scalemic CSA has been used to resolve amines by forming diastereomeric salts which can be separated by fractional crystallization (eq 11).[9] In this instance, after obtaining the desired crystalline diastereomeric salt, the undesired diastereomer was completely transformed into the desired one by a resolution-racemization procedure (eq 12).[9] Additionally, racemic ketones can be resolved by forming enantiomeric iminium salts (eq 13).[10] Two different procedures have been devised depending on the ease of enamine formation.

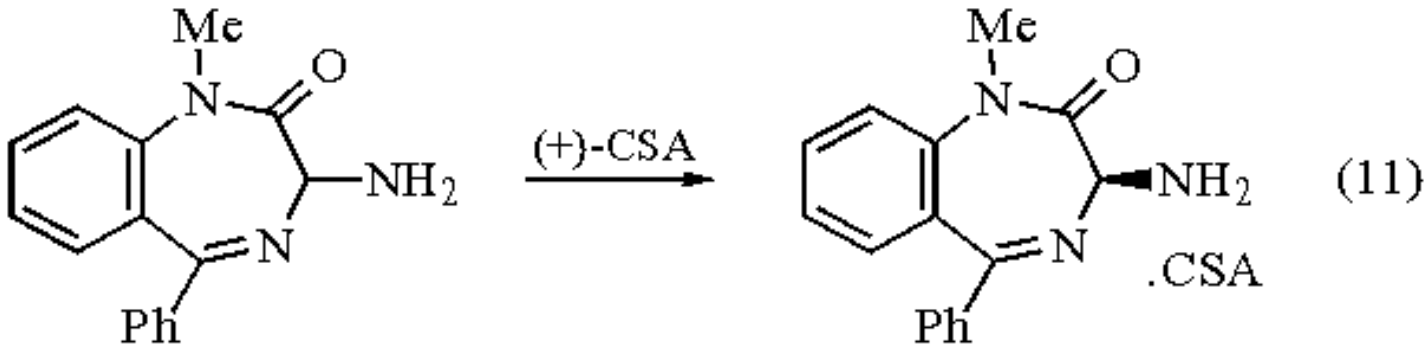

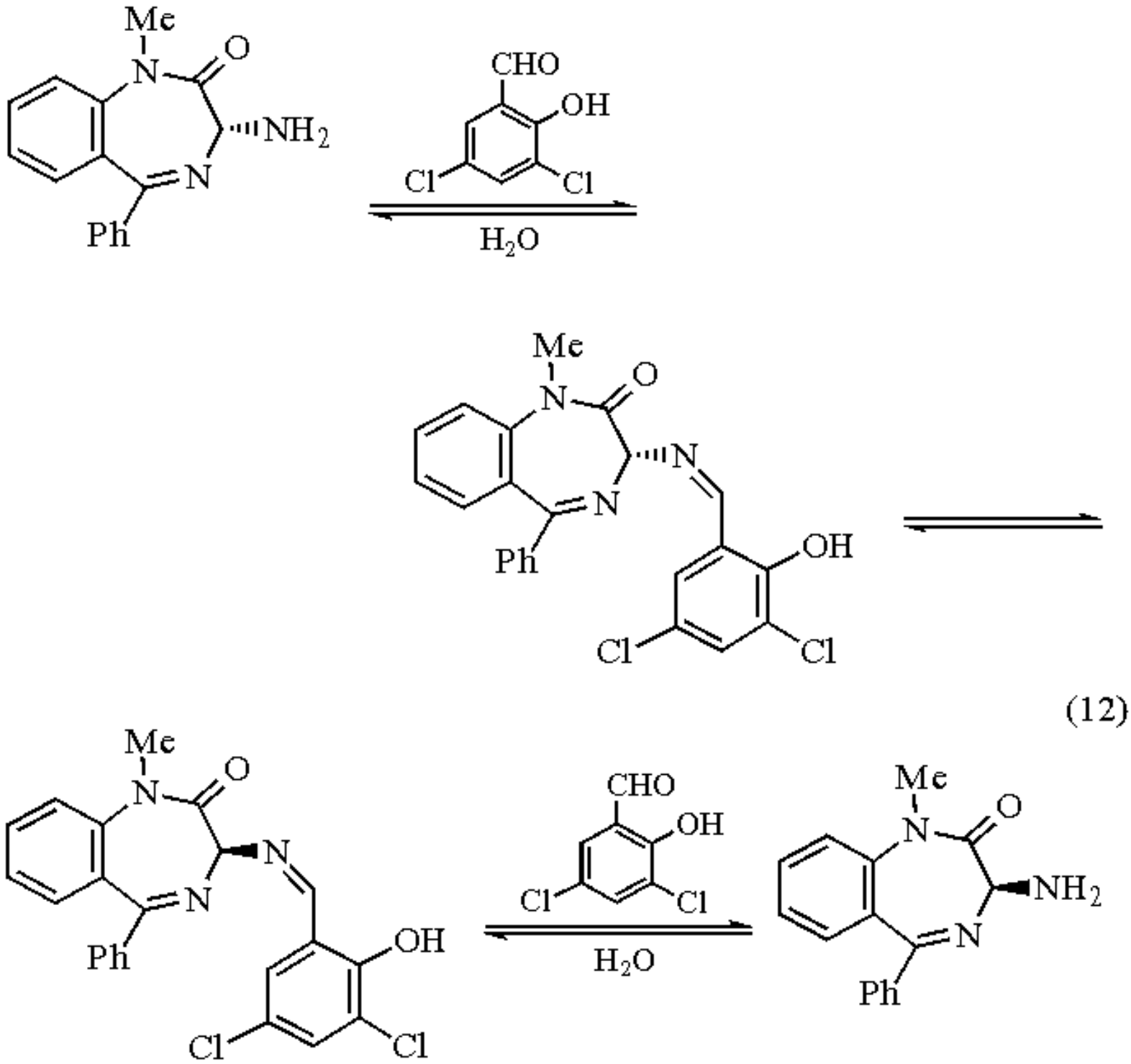
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(12)

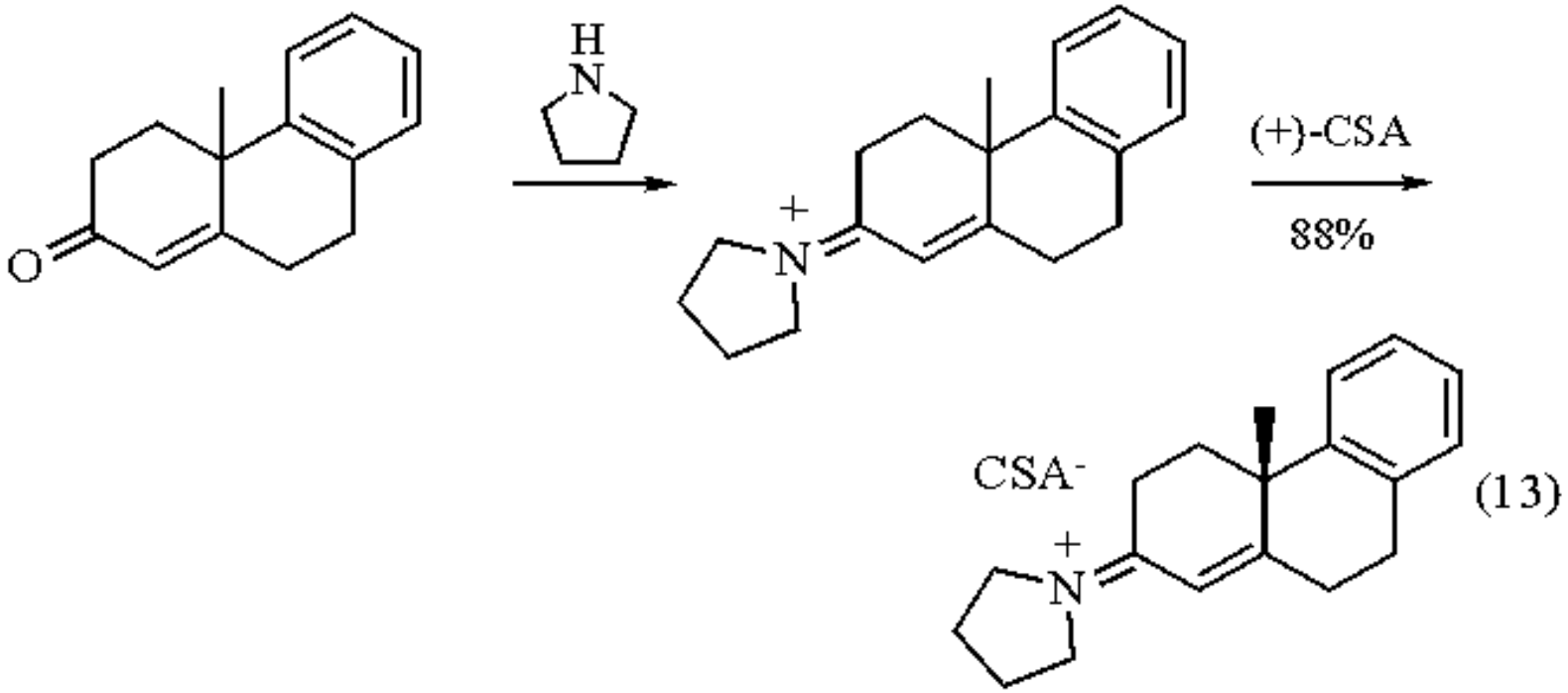

Chiral Auxiliaries.

Asymmetric Diels-Alder Reactions.

The commercial availability of either enantiomer of camphorsulfonic acid has made it quite useful in asymmetric Diels-Alder reactions. Reaction of the sultone (generated from CSA) with ***Lithium Diisopropylamide*** followed by esterification and β-elimination yields the crystalline acrylate (eq 14).[11] The Lewis acid-catalyzed [4 + 2] cycloaddition of 1,3-dienes with this acrylate affords the corresponding scalemic adduct which can be reduced with ***Lithium Aluminum Hydride*** to yield an enantiomerically pure alcohol (eq 15).[12]

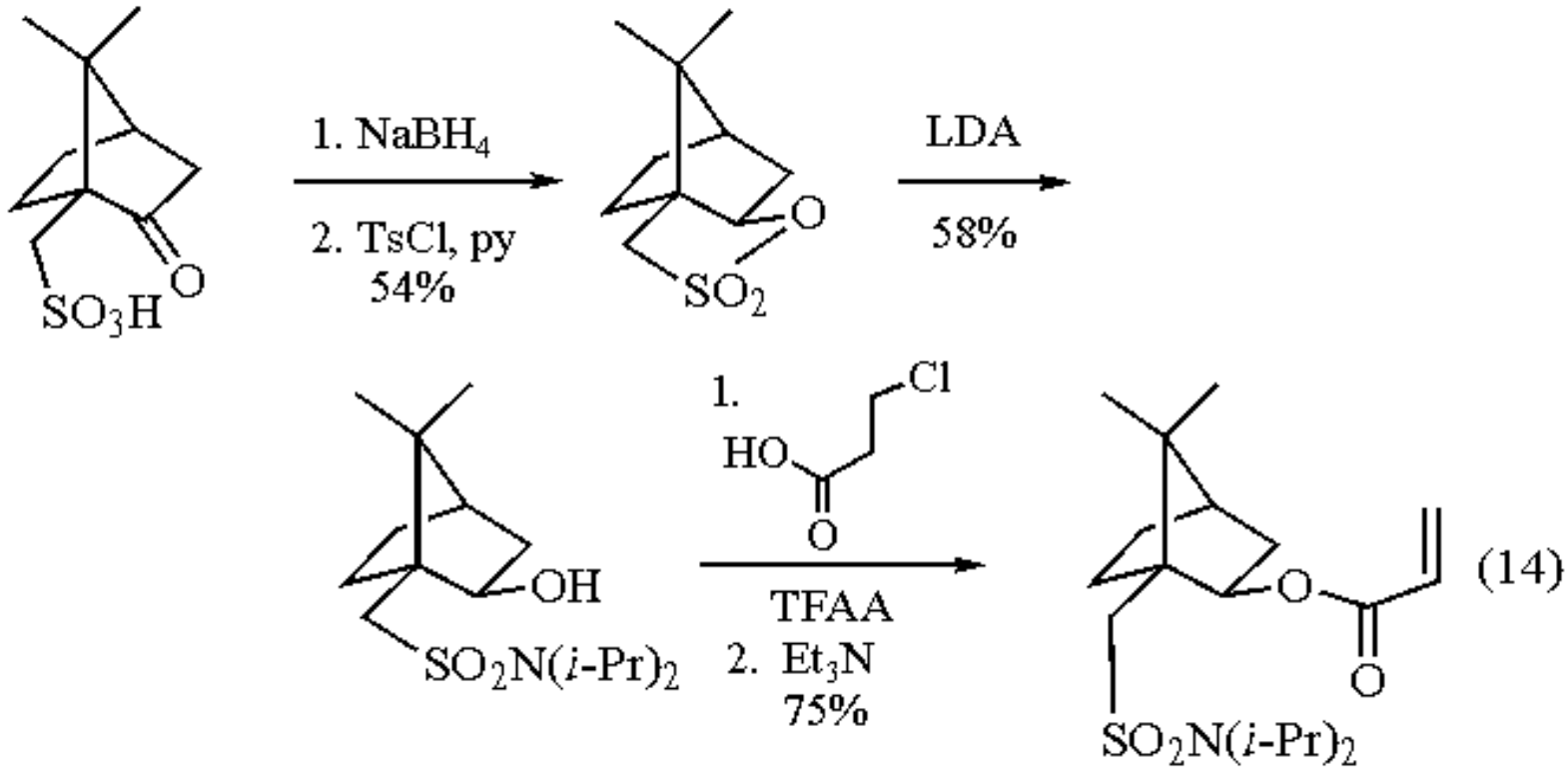

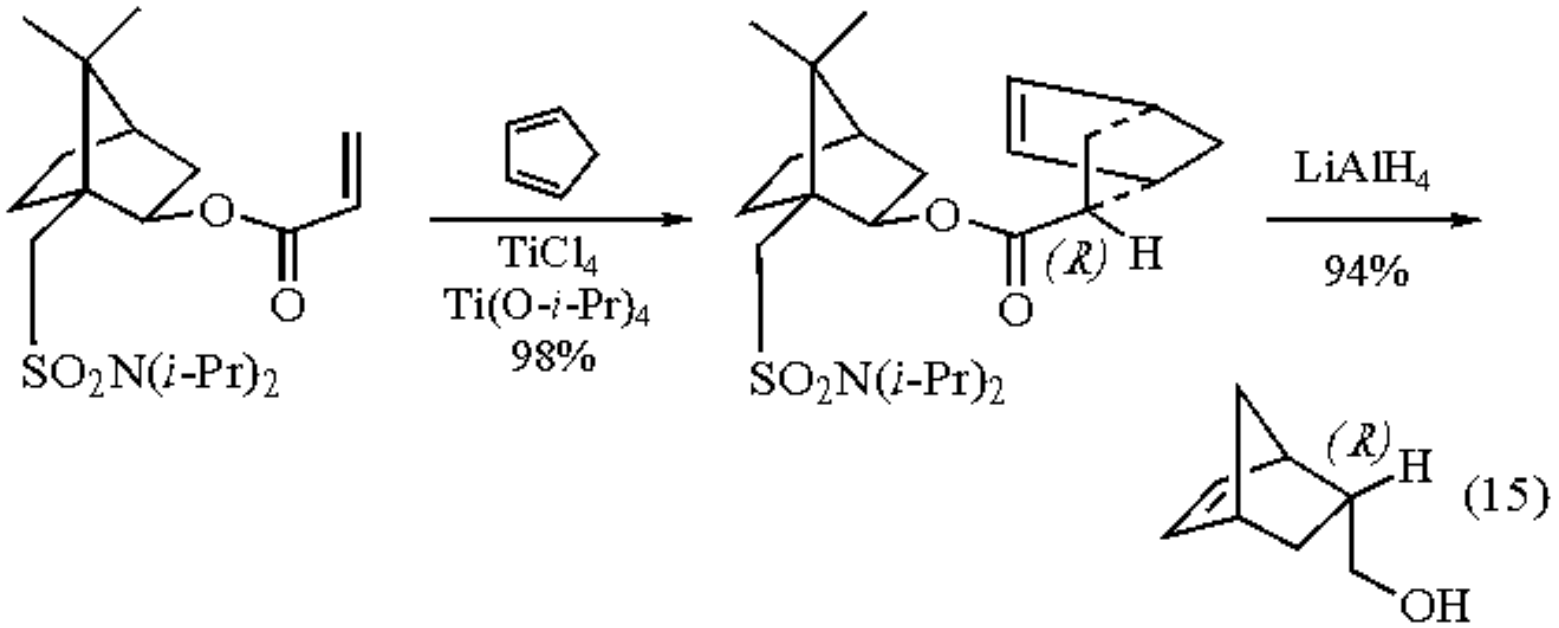

A different approach to the asymmetric Diels-Alder reaction involves the use of the sultam derived from CSA. Lewis acid-promoted reaction with dienes followed by reductive removal of the chiral auxiliary is analogous to that previously discussed for the sultone. Smith has successfully utilized this approach to synthesize the chiral acid used in the synthesis of the immunosuppressant FK-506 (eq 16).[13]

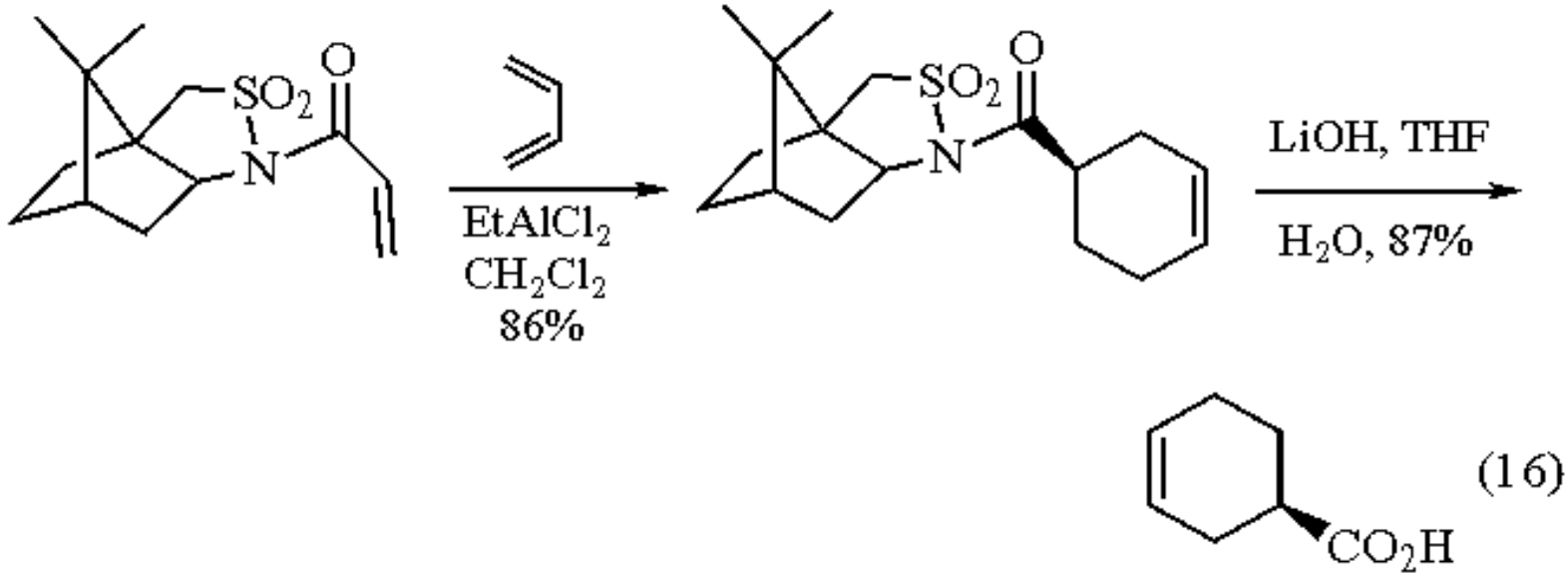

Oxaziridines.

Davis has developed the use of chiral 2-sulfonyloxaziridines derived from camphorsulfonic acid as chiral auxiliaries in the asymmetric oxidation reactions.[24] Although other oxaziridines may be preferable, the camphor-derived oxaziridines can be used for the oxidation of sulfides and disulfides to sulfoxides and thiosulfinates as well as for the epoxidation of alkenes.[24] On the other hand, the camphoryloxaziridines are the preferred reagents for hydroxylation of lithium enolates of esters, amides, and ketones, as utilized in the synthesis of kjellmanianone (eq 17).[14]

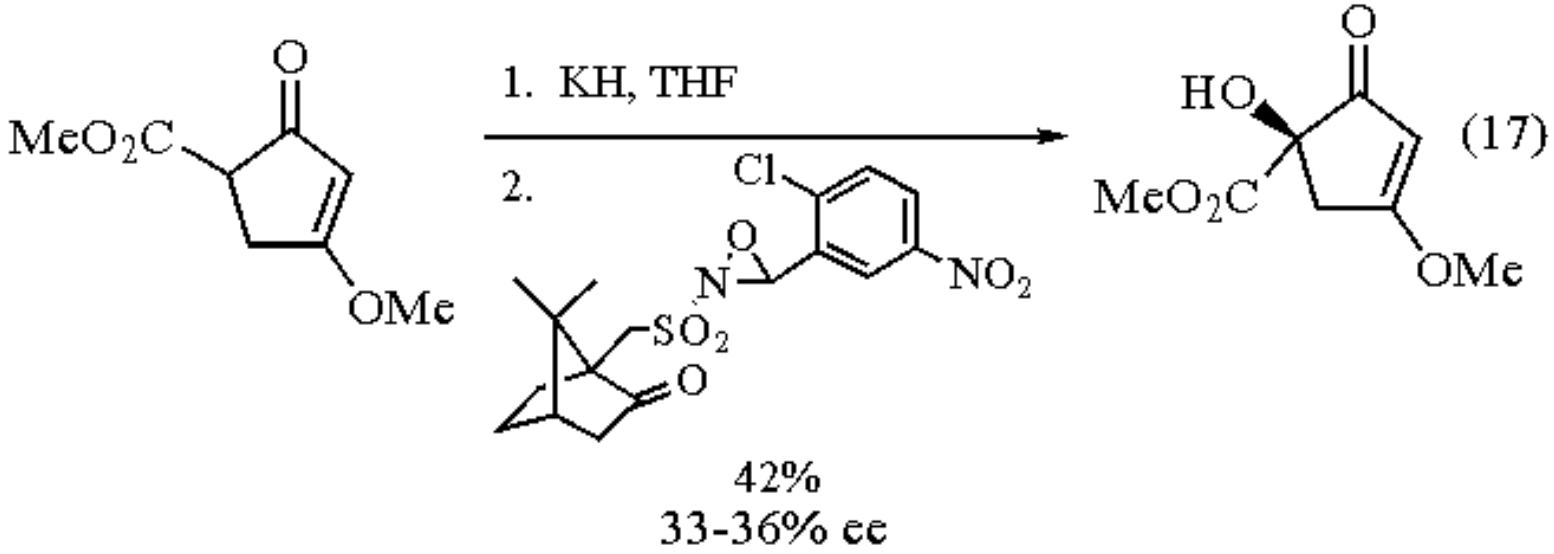

Chiral Sulfides.

Optically active sulfides prepared from (+)-CSA can be used to prepare optically active 1,2-diaryloxiranes (eq 18).[15]

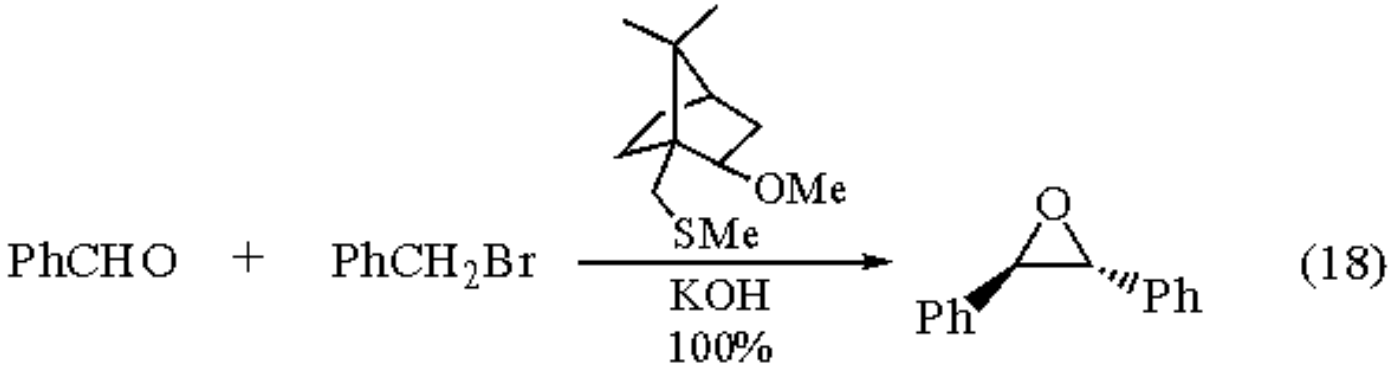

Grignard Addition to Enones.

The sultam generated from camphorsulfonic acid can also be used as a chiral auxiliary in the conjugate addition of Grignard reagents to enones. Simple alkylmagnesium chlorides add in a 1,4-fashion to afford imides (eq 19).[16]

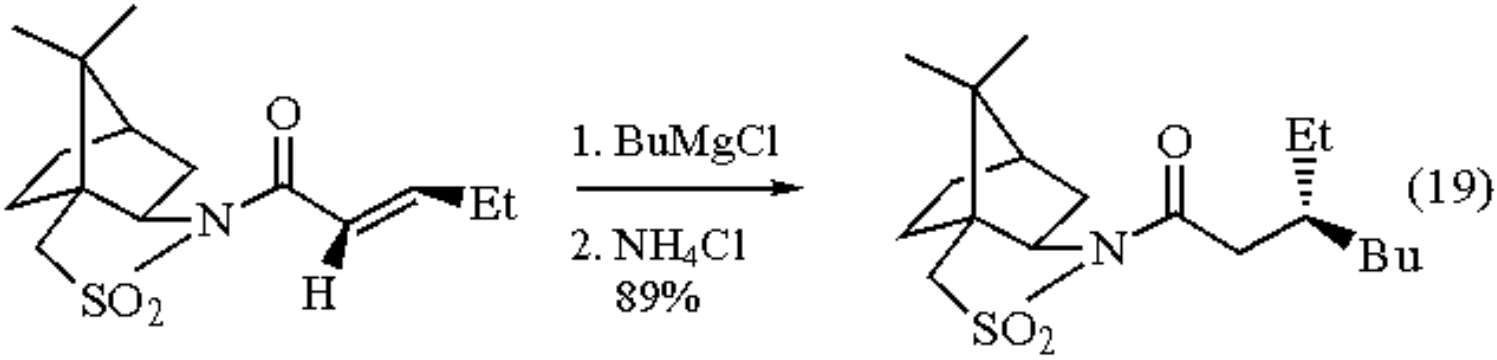

Asymmetric Hydrogenation of Camphor-Derived Sultamides.

The sultamide of CSA can be used as a chiral auxiliary for synthesis of β-substituted carboxylic acids (eq 20).[17]

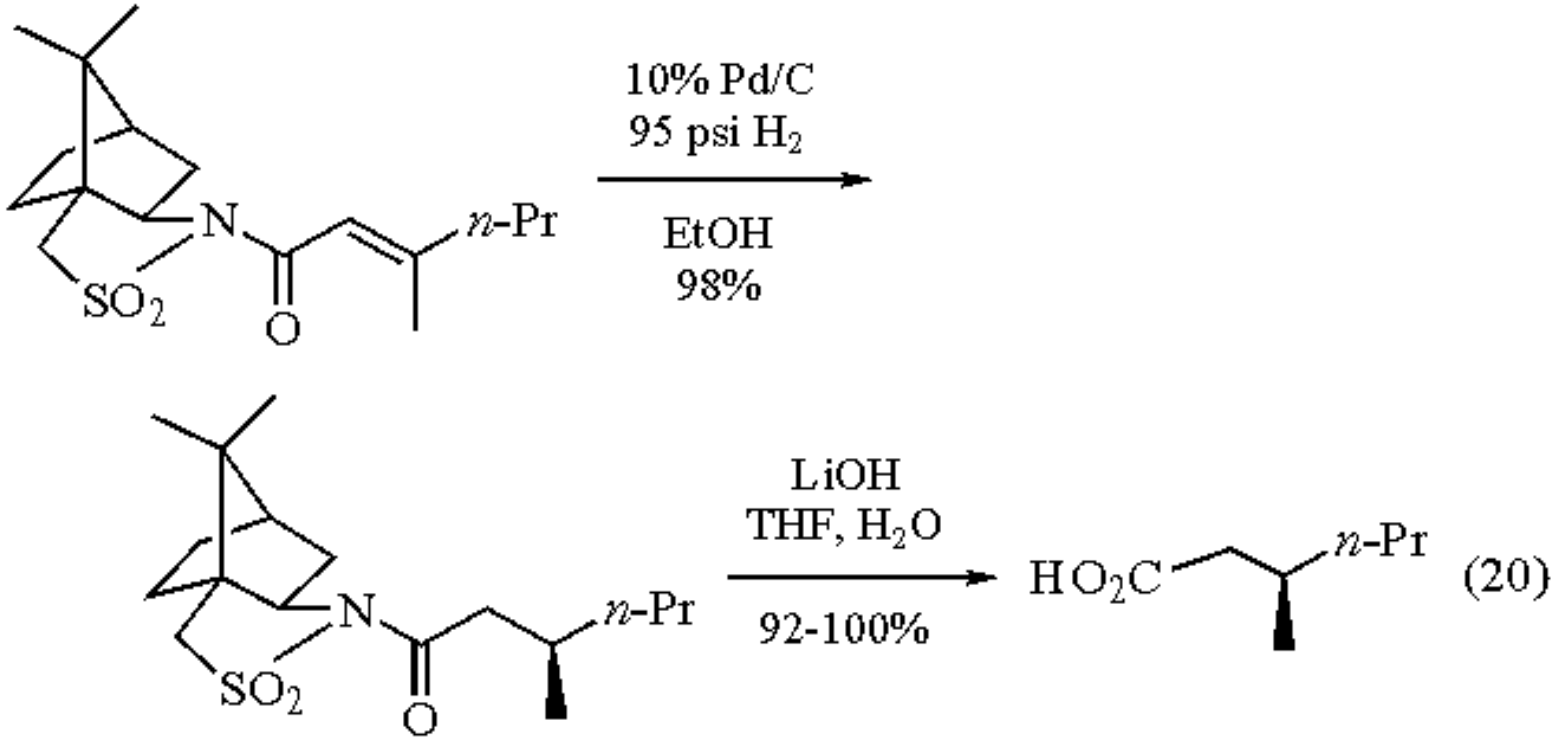

Asymmetric Acetoxylation of Esters.

The silyl enol ether derived from CSA reacts with ***Lead(IV) Acetate*** to yield the α-acetoxy ester with good diastereoselectivity. Hydrolysis of the chiral auxiliary gives the α-hydroxy acid, whereas reduction affords the terminal α-glycol (eq 21).[18]

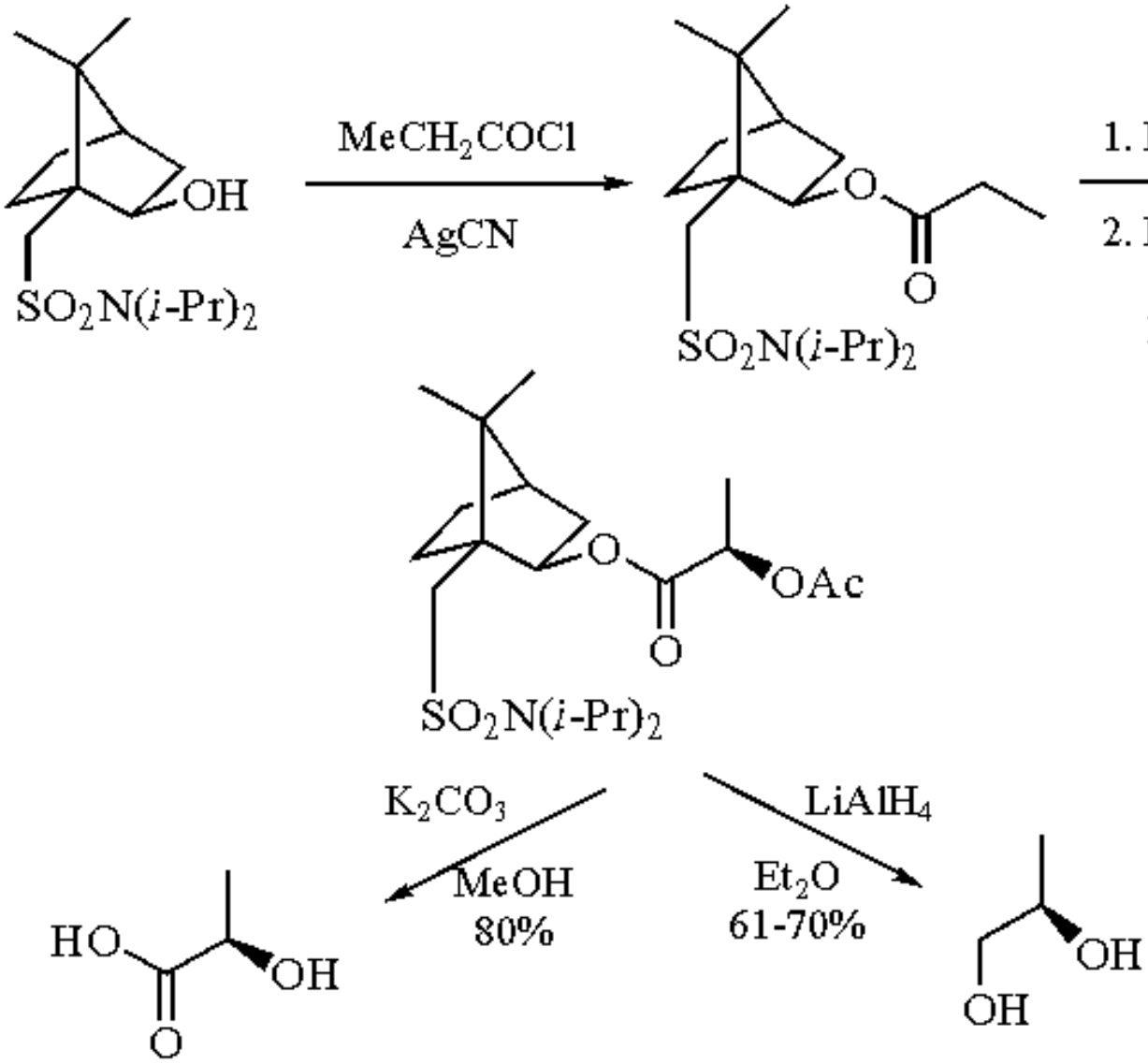

(21)

Allylation of Aldehydes.

Synthesis of enantiomerically pure allyl alcohols can be accomplished by catalytic asymmetric addition of divinylzinc to aldehydes using a camphorsulfonic acid-derived catalyst (eq 22).[19]

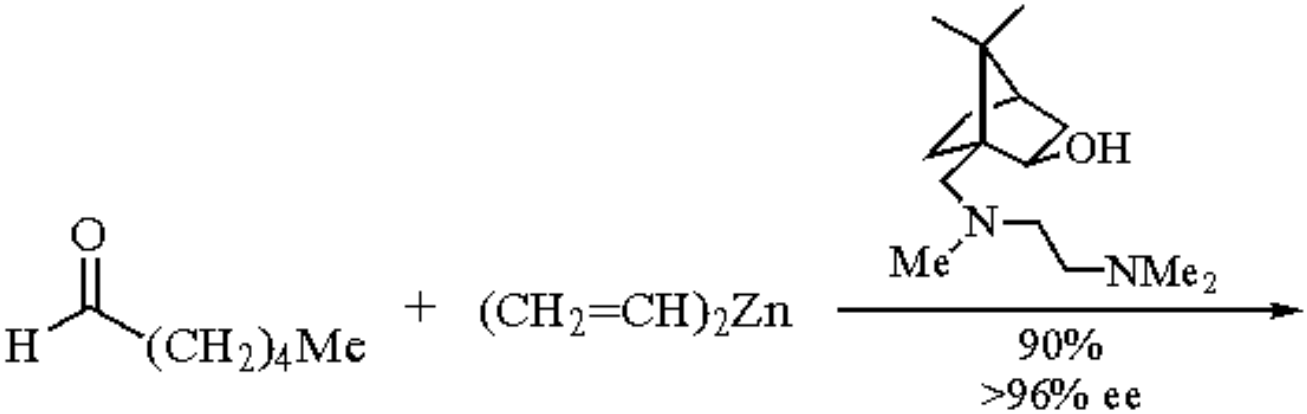

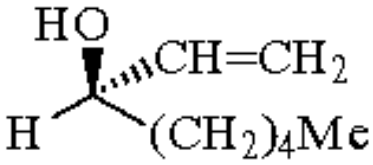

(22)

Synthesis of Epoxides from Chiral Chlorohydrins.

Asymmetric halogenation of CSA-derived esters allows for the formation of enantiomerically pure halohydrins and terminal epoxides (eq 23).[20]

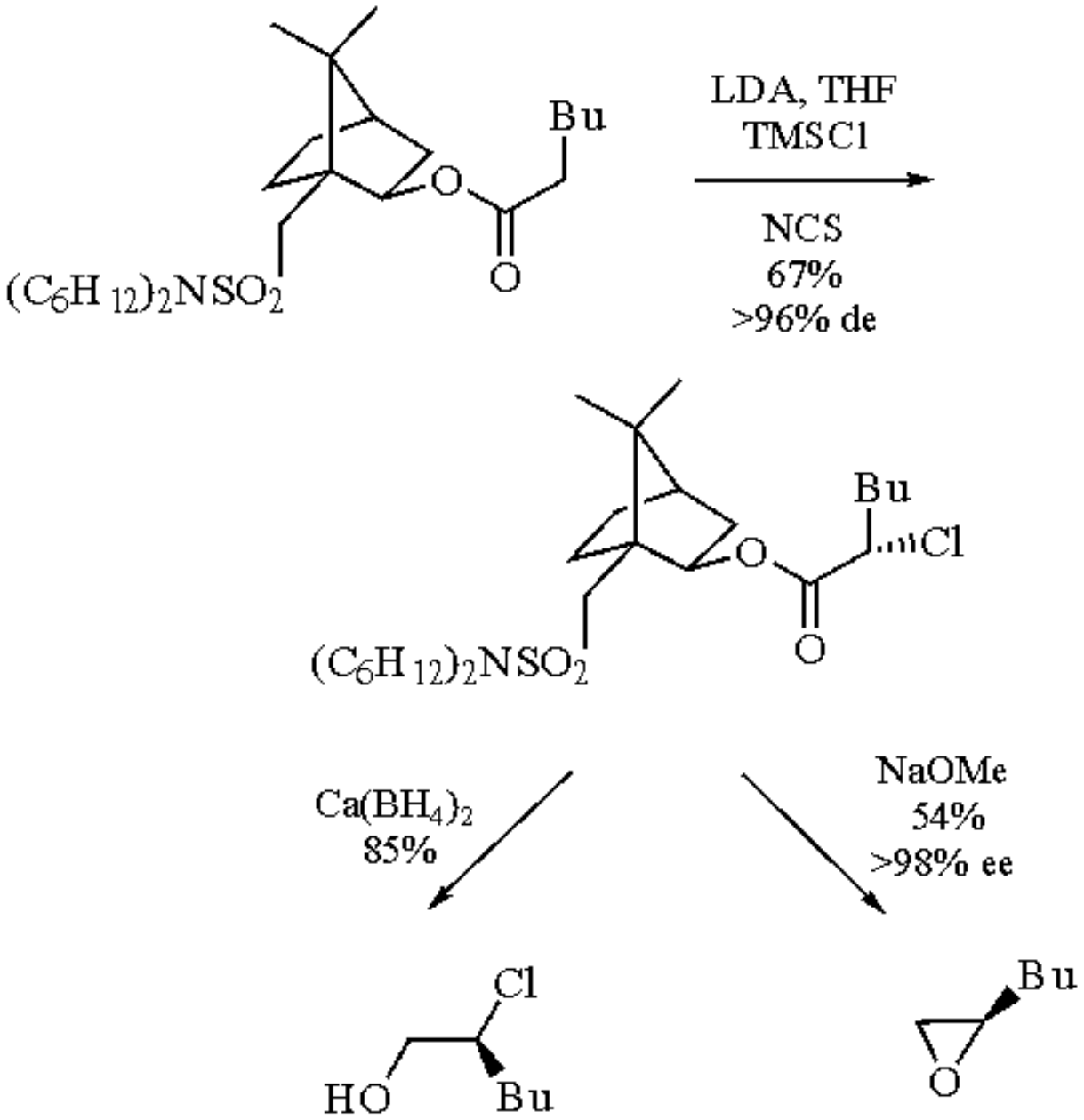

(23)

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10-Camphorsulfonyl Chloride[1]

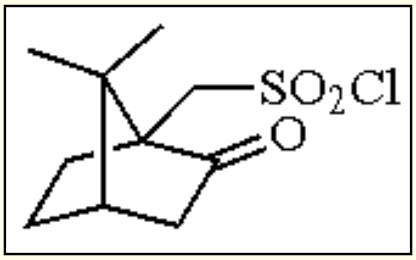

(1*R*)

[21286-54-4] · $C_{10}H_{15}ClO_3S$ · 10-Camphorsulfonyl Chloride · (MW 250.75) (1*S*)

[39262-22-1] (±)

[6994-93-0]

(enantiomeric excess determination;[2] chemical resolution;[3] synthesis of chiral auxiliaries;[4] chiral precursor for natural product synthesis;[1] synthesis of chiral reagents[5])

Physical Data: mp 65-67 °C; (1*S*)-(+): $[\alpha]_D$ + 32.1° (*c* 1, $CHCl_3$).

Solubility: sol CH_2Cl_2; slightly sol ether; insol H_2O.

Form Supplied in: both enantiomers and the racemic sulfonyl chloride are commercially available.

Preparative Methods: can be prepared from ***10-Camphorsulfonic Acid*** upon treatment with ***Phosphorus(V) Chloride*** or ***Thionyl Chloride***.[6]

Purification: crystallized from hexane or from MeOH.

Handling, Storage, and Precautions: corrosive and moisture-sensitive. This reagent should be handled in a fume hood.

Reagent for Determination of Enantiomeric Excesses and for Chemical Resolution of Alcohols and Amines.

10-Camphorsulfonyl chloride has been widely used as a chiral derivatizing agent for the assay of enantiomeric purity of alcohols and amines by NMR techniques.[2] A typical procedure for the preparation of the sulfonate ester or sulfonamide involves mixing a solution of the alcohol or amine in CH_2Cl_2 with camphorsulfonyl chloride in the presence of an amine base (Et_3N, py, or DMAP). This reagent has been particularly valuable for determining the enantiomeric purity of secondary alcohols (**1, 2**) and β-hydroxy esters (**3**).[7]

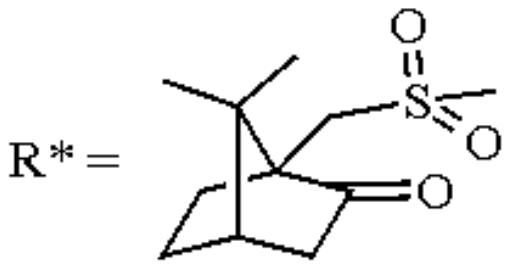

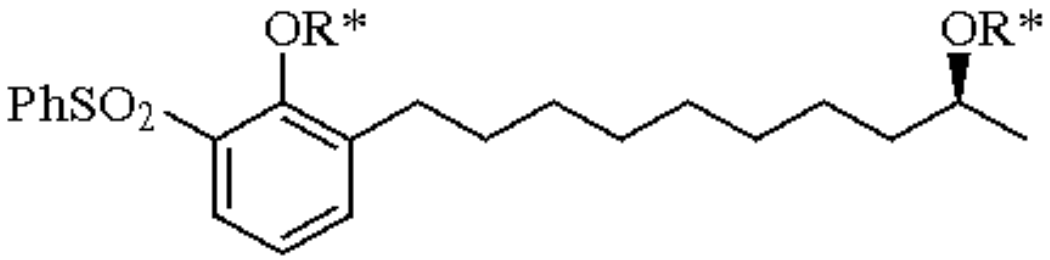

(1)

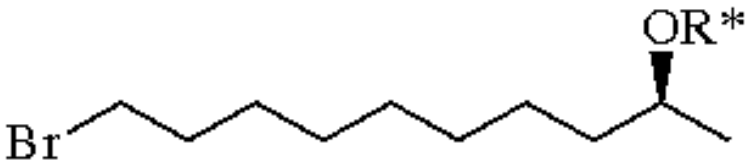

(2)

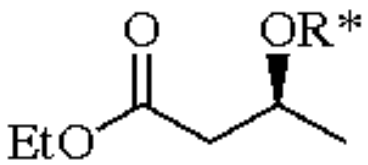

(3)

In some cases (**3**), the addition of a chiral shift reagent ($Eu(hfc)_3$) is necessary to obtain baseline separation of the signals corresponding to the β-proton of both diastereomers by ^1H NMR. Diastereomeric mixtures derived from secondary alcohols have also been analyzed by HPLC.[8] The resolution of a secondary alcohol (**4**) could be achieved by a selective crystallization of one of the two diastereomeric camphorsulfonate esters.[3]

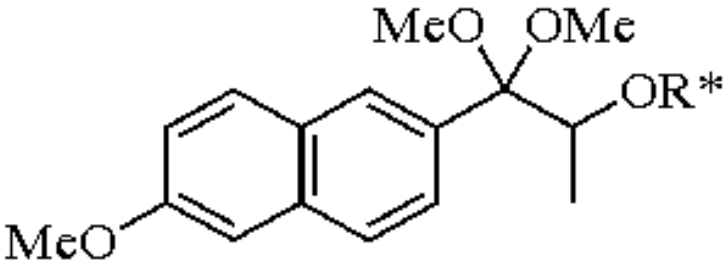

(4)

The enantiomeric purities of primary and secondary amines have also been established by ^{1}H NMR spectroscopy by their conversion into the corresponding sulfonamide. These derivatives often produce crystalline compounds that are suitable for X-ray crystallographic studies. For example, the enantiomeric purities of amines (**5**),[9] (**6**),[10] and (**7**)[11] were determined by ^{1}H NMR spectroscopy and the absolute stereochemistry of (**7**) was unequivocally established by X-ray crystallography.

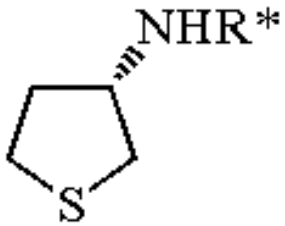

(5)

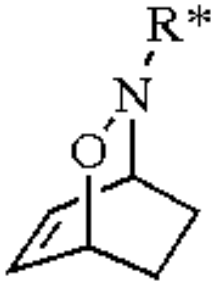

(7)

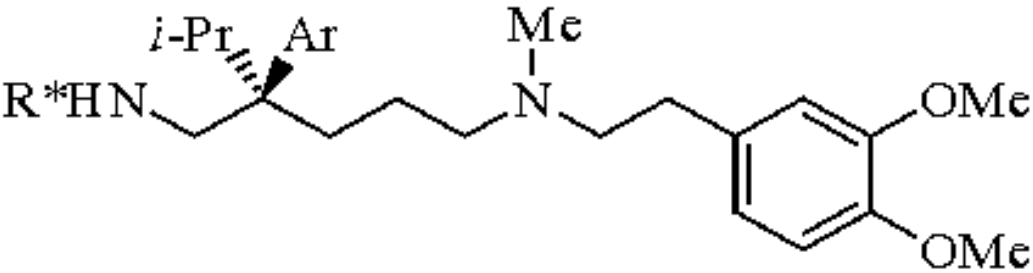

(6) Ar = 3,4-$(OMe)_2C_6H_3$

A general protocol for the HPLC separation of diastereomeric camphorsulfonamides[12] derived from racemic α-amino acids has been developed (eq 1).[13] More complex amino acids, such as (**8**), were successfully analyzed by this procedure.[14]

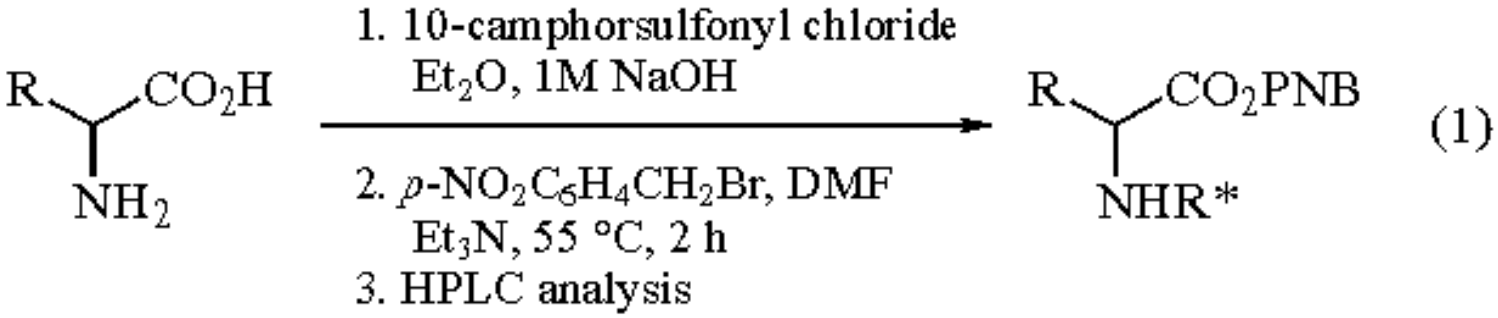

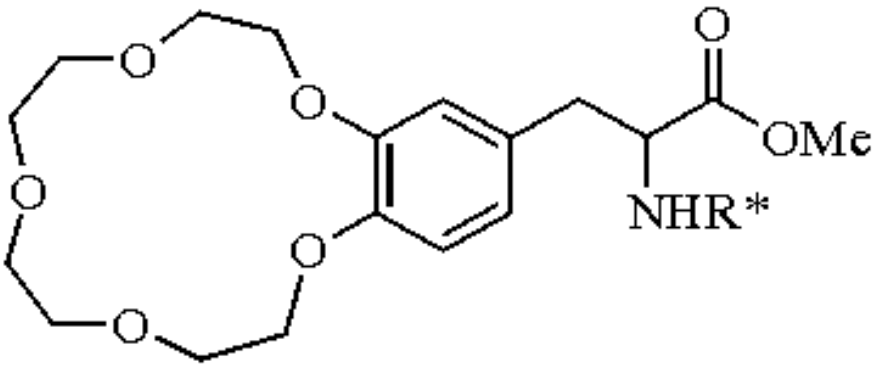

(8)

Synthesis of Chiral Auxiliaries.

Their availability and crystalline nature has made camphor derivatives the precursors of choice for the design and synthesis of chiral auxiliaries.[4] 10-Camphorsulfonyl chloride is the starting material for the synthesis of chiral auxiliaries (**9**)-(**12**) (eq 2). Sulfonamides (**9**) and (**10**)[15] have been used as chiral auxiliaries in a number of reactions, e.g. the Lewis acid-catalyzed Diels-Alder reaction, the [3 + 2] cycloaddition of a nitrile oxide to an acrylate, and the stereoselective conjugate addition reaction of organocopper reagents to α,β-unsaturated esters.[4]

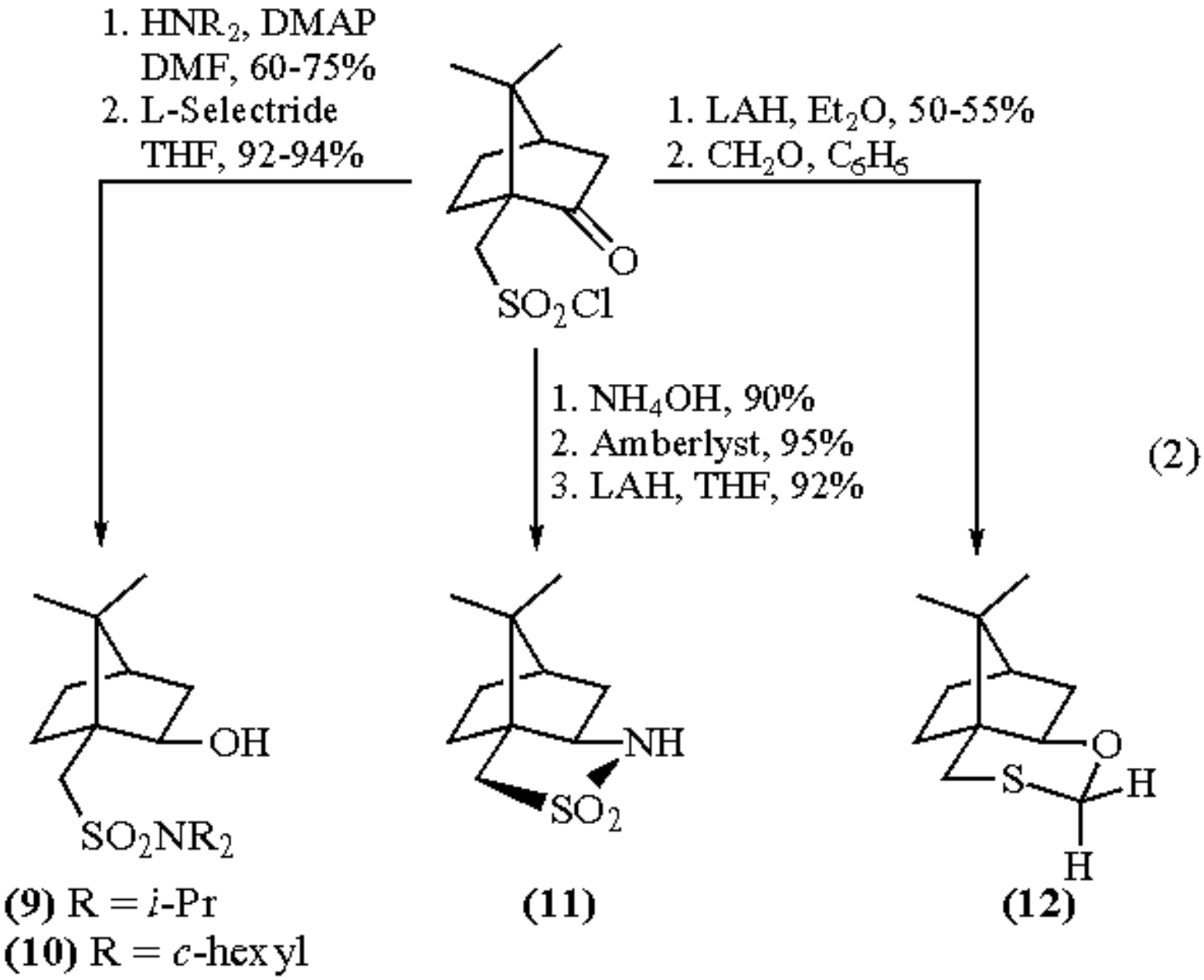

In addition to being an efficient chiral controller in a number of stereoselective transformations of chiral acrylates, (i.e. the Diels-Alder reaction,[4] the conjugate reduction,[16] the asymmetric dihydroxylation,[17] and the nitrile oxide cycloaddition[18]) the bornanesultam (**11**)[19] has been shown to be an exceptionally efficient chiral auxiliary for stereoselective aldol condensations (eqs 3 and 4). Depending upon the reaction conditions, *N*-propionylsultam can produce either the *syn* or *anti* aldol product with an excellent diastereoselectivity.[20] Furthermore, good diastereoselectivities are also observed for the corresponding acetate aldol reaction (eq 5).[21]

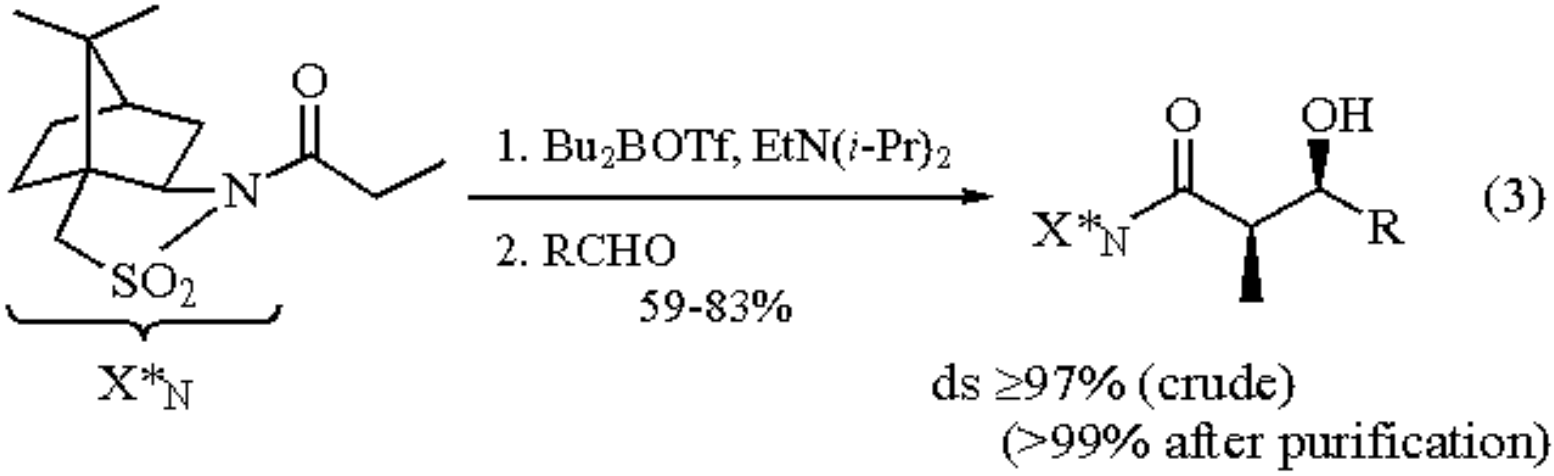

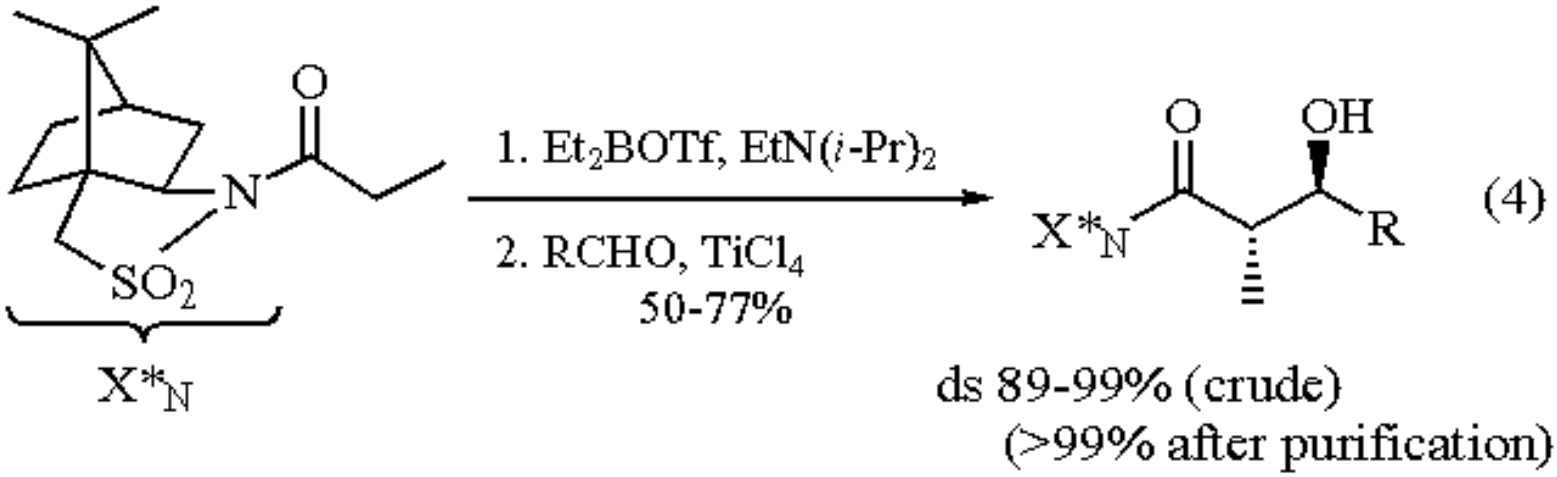

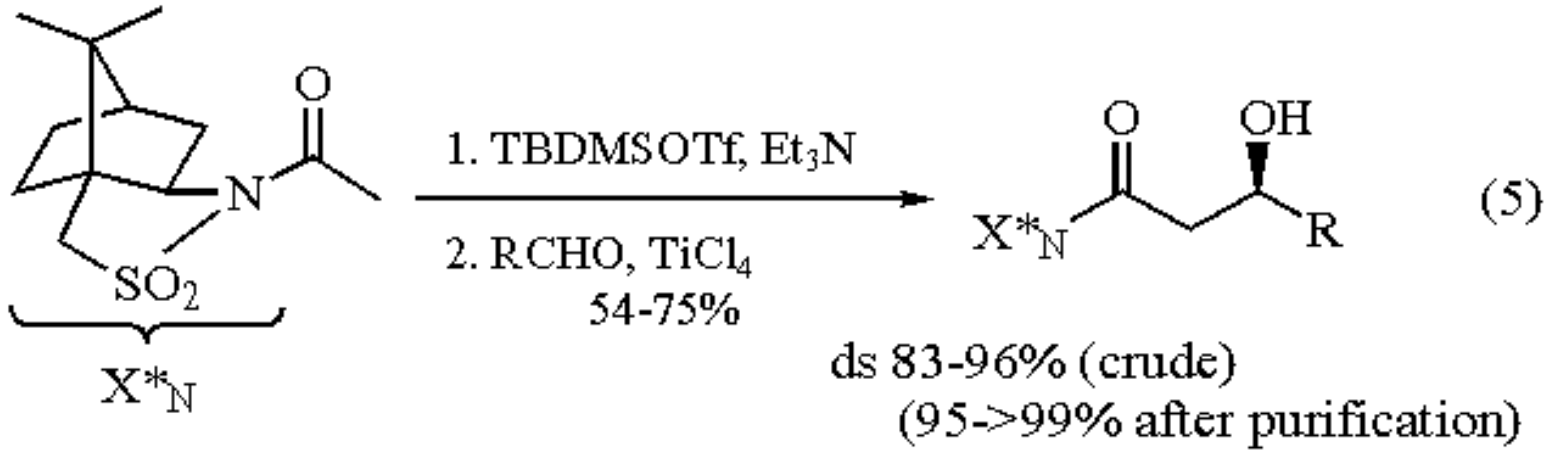

Oxathiane (**12**) has been shown to be an efficient chiral auxiliary in the nucleophilic addition to carbonyl compounds.[22]

10-Camphorsulfonyl chloride has also been widely used as a useful precursor to chiral dienophiles in hetero-Diels-Alder reactions.[23]

An elegant use of the chirality and the leaving group ability of the camphorsulfonate ester has been reported in the synthesis of a chiral C_2 symmetric cyclopentadienyl ligand (eq 6).[24]

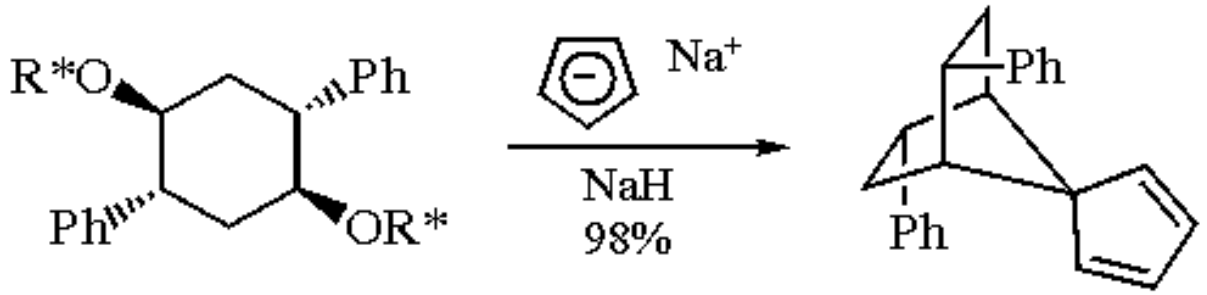

(6)

Synthesis of Chiral Reagents.

An efficient chiral α-chloro-α-nitroso reagent derived from 10-camphorsulfonyl chloride (1. Cy_2NH; 2. NH_2OH; 3. *t*-BuOCl; 70-78%) has been developed for the asymmetric α-amination of ketone enolates (eq 7).[25] The resulting β-keto *N*-hydroxylamine can be converted to the *anti*-1,2-hydroxyamine under reducing conditions ($NaBH_4$; Zn, HCl, AcOH).

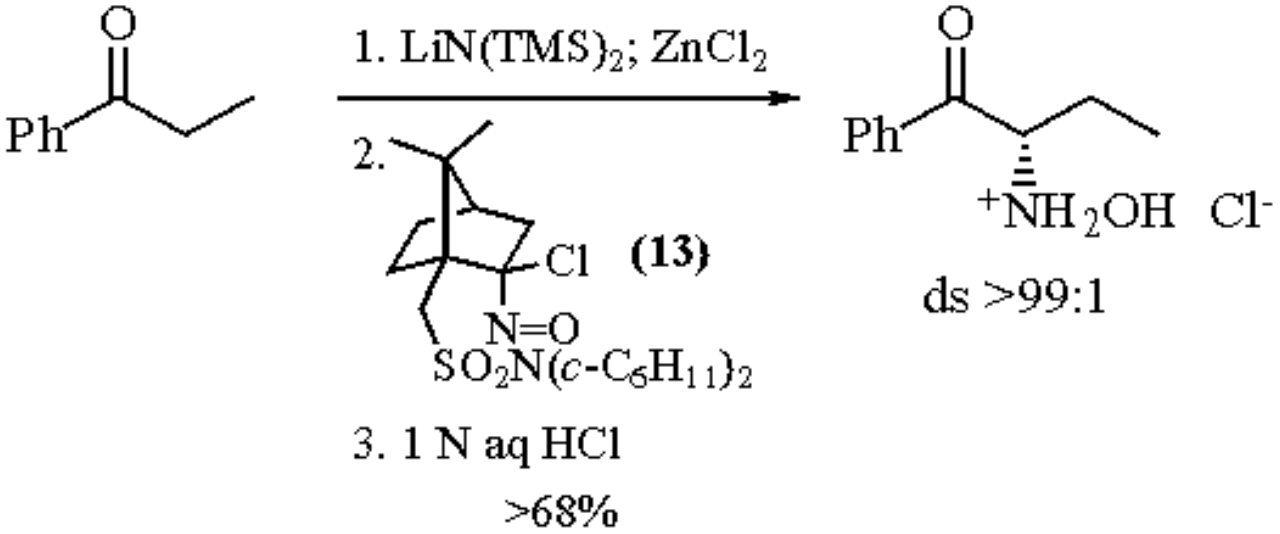

(7)

Several oxaziridines related to (**14**)[5] (eq 8) have been used, most notably in the enantioselective oxidation of sulfides to sulfoxides,[26] of selenides to selenoxides,[27] and of alkenes to oxiranes.[28] It is also the reagent of choice for the hydroxylation of lithium and Grignard reagents[29] and for the asymmetric oxidation of enolates to give α-hydroxy carbonyl compounds.[5,30] A similar chiral fluorinating reagent has also been developed.[31]

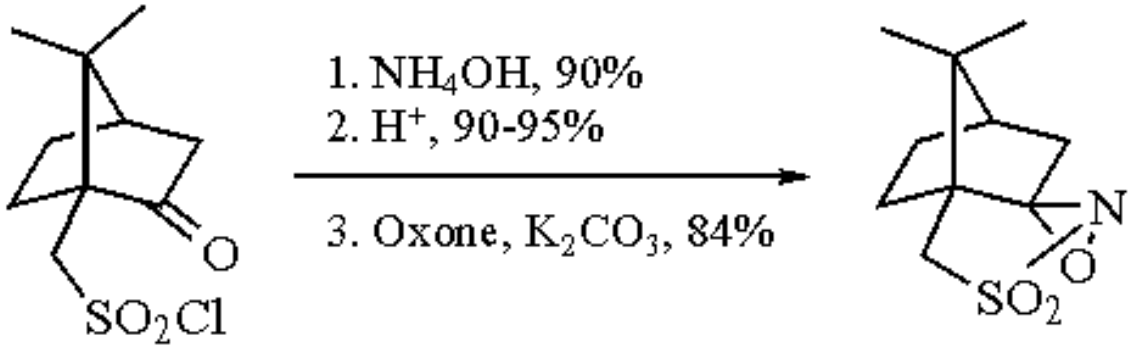

(8)

(14)

Chiral Precursor for Natural Product Synthesis.

10-Camphorsulfonyl chloride has been used as a chiral starting material for the synthesis of a number of products[1] such as ketopinic acid[32] (eq 9), which has been used to resolve alcohols[33] and hemiacetals.[34]

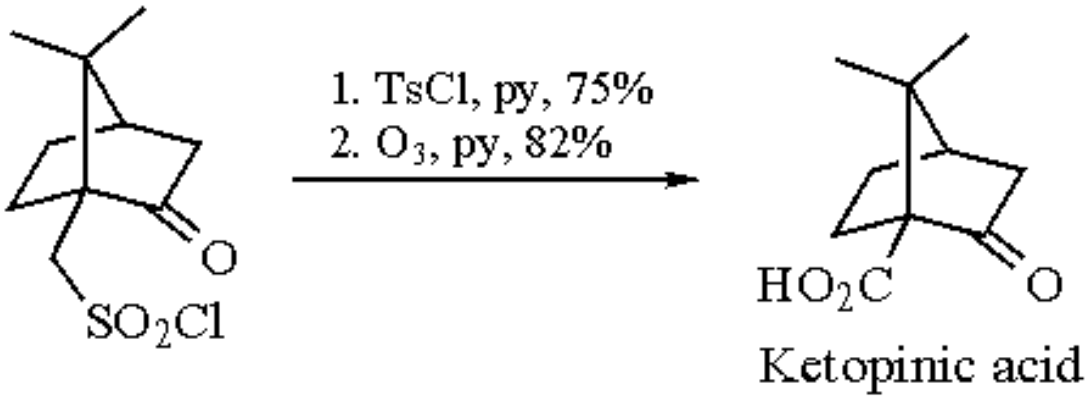

(9)

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(Camphorylsulfonyl)oxaziridine[1]

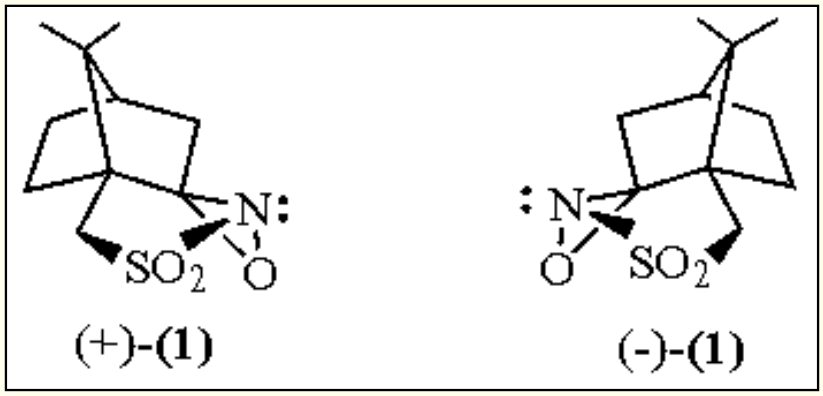

(+)-(**1**)

[104322-63-6] · $C_{10}H_{15}NO_3S$ · (Camphorylsulfonyl)oxaziridine · (MW 229.30) (-)-(**1**)

[104372-31-8]

(neutral, aprotic, electrophilic, and asymmetric oxidizing agents for the chemoselective oxidation of many nucleophilic substrates such as sulfides, enamines, enol esters, carbanions, and enolates[1])

Physical Data: (+)-(**1**): mp 165-167 °C, $[\alpha]_D$ +44.6° ($CHCl_3$, *c* 2.2); (-)-(**1**): mp 166-167 °C, $[\alpha]_D$ -43.6° ($CHCl_3$, *c* 2.2).

Solubility: sol THF, CH_2Cl_2, $CHCl_3$; slightly sol isopropanol, ethanol; insol hexane, pentane, water.

Form Supplied in: commercially available as a white solid.

Analysis of Reagent Purity: by mp and specific rotation determination.

Preparative Methods: the enantiopure (+)- and (-)-(camphorylsulfonyl)oxaziridines (**1**) and [(8,8-dichlorocamphor)sulfonyl]oxaziridines (**2**) are commercially available. They can also be prepared on a large scale via the oxidation of corresponding camphorsulfonimines with buffered ***Potassium Monoperoxysulfate*** (Oxone)[2] or buffered peracetic acid.[3] Since oxidation takes place from the *endo* face of the C=N double bond, only a single oxaziridine isomer is obtained. The precursor camphorsulfonimines can be prepared in 3 steps (>80% yield) from inexpensive (+)- and (-)-***10-Camphorsulfonic Acid***s. A variety of (camphorylsulfonyl)oxaziridine derivatives such as (**2**)-(**4**) are also readily available via the functionalization of the camphorsulfonimines followed by oxidation.[1,2-6]

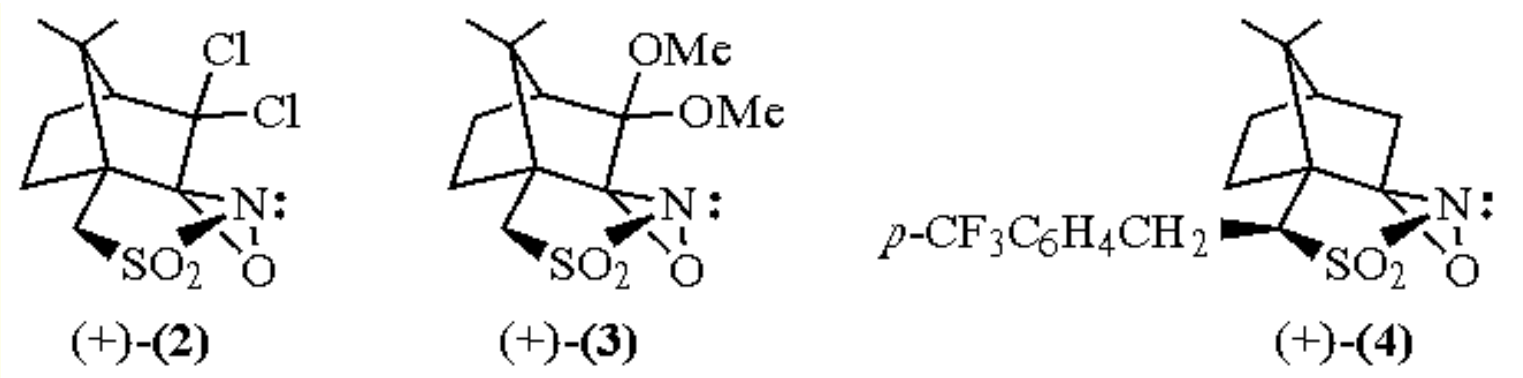

Purification: by recrystallization.

Handling, Storage, and Precautions: indefinitely stable to storage at room temperature and to exposure to air.

Asymmetric Oxidation of Sulfides.

Prochiral sulfides are oxidized by (camphorylsulfonyl)oxaziridine (**1**) to optically active sulfoxides. Over-oxidation to sulfones is not observed (eq 1).[7] However, the best chiral *N*-sulfonyloxaziridines for the asymmetric oxidation of sulfides to sulfoxides are the (+)- and (-)-***N-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine***s.[8]

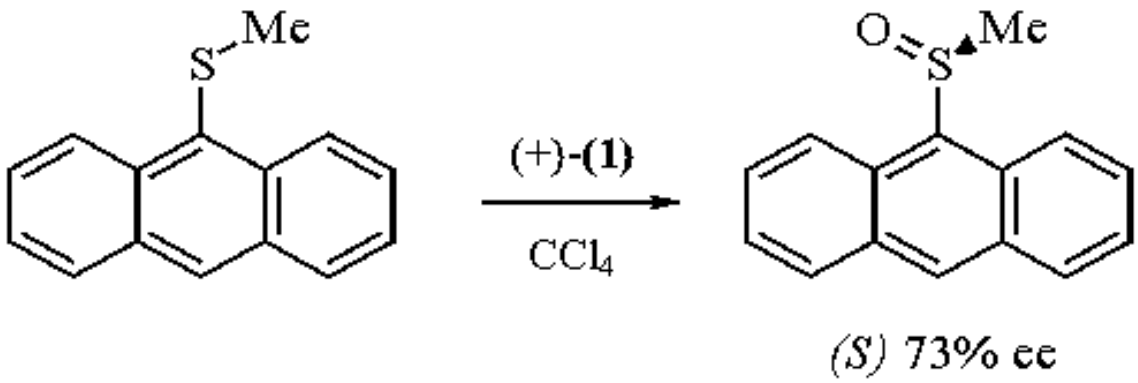

(1)

Oxidation of Enamines.

Enamines are rapidly oxidized by (+)-(camphorylsulfonyl)oxaziridine (**1**). Disubstituted enamines give rise to racemic α-amino ketones, while trisubstituted enamines afford, after hydrolysis, α-hydroxy ketones (eq 2).[9] A mechanism involving initial oxidation of the enamine to an α-amino epoxide is suggested to account for these products.

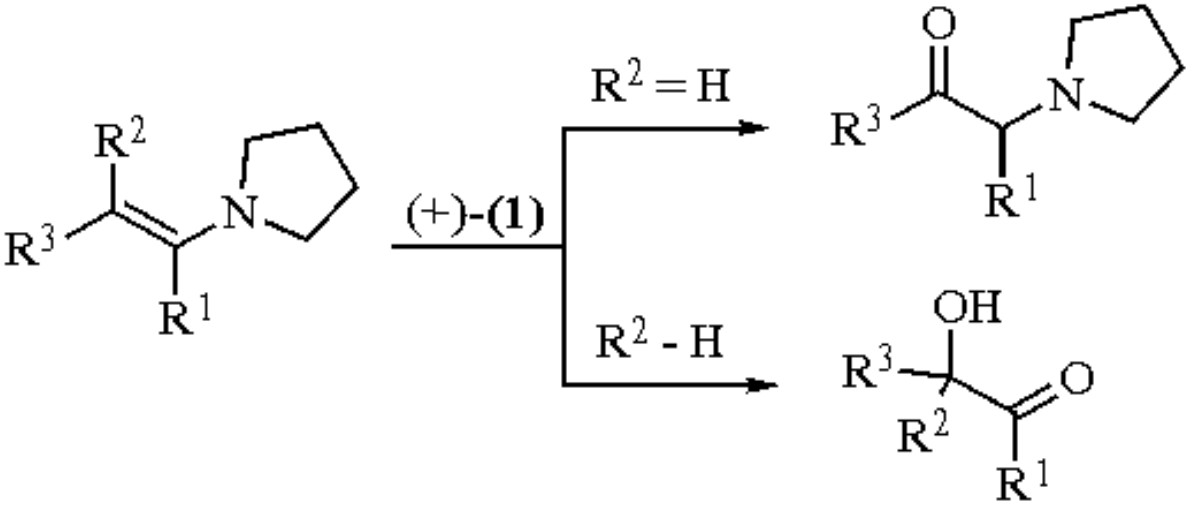

Oxidation of Oxaphospholenes.

Reaction of oxaphospholene (**5**) with (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**2**) affords β-hydroxy-γ-keto-phosphonate in 49% ee with undetermined absolute configuration (eq 3).[10] Higher temperatures accelerate the reaction but lower the stereoselectivity.

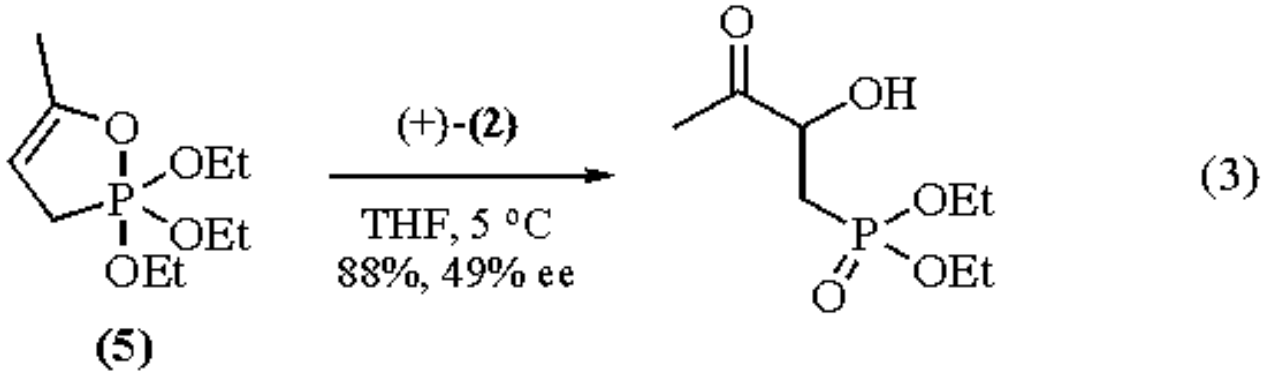

Oxidation of Organolithium and Organomagnesium Compounds.

Oxidation of phenylmagnesium bromide and phenyllithium with ***(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine*** or (camphorylsulfonyl)oxaziridine (**1**) gives phenol (eq 4).[11] Products are cleaner with the latter reagent because addition of the organometallic reagent to the C=N double bond of the imine is not observed. Oxidation of (*E*)- and (*Z*)-vinyllithium reagents with (+)-(**1**) affords enolates. The reaction is fast and represents useful methodology for the stereo- and regioselective formation of enolates.[12] While the enolates can be trapped with ***Chlorotrimethylsilane*** to give silyl enol ethers, better yields and higher stereoselectivity are obtained with ***Bis(trimethylsilyl) Peroxide*** (eq 5).[12]

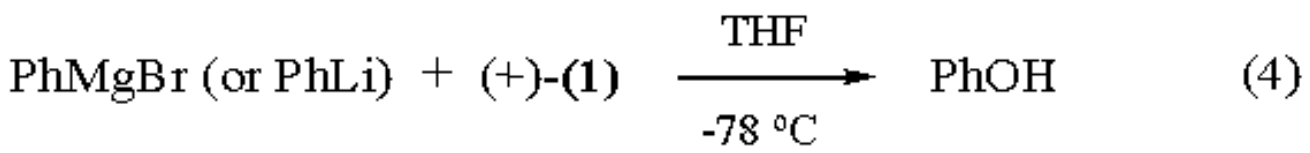

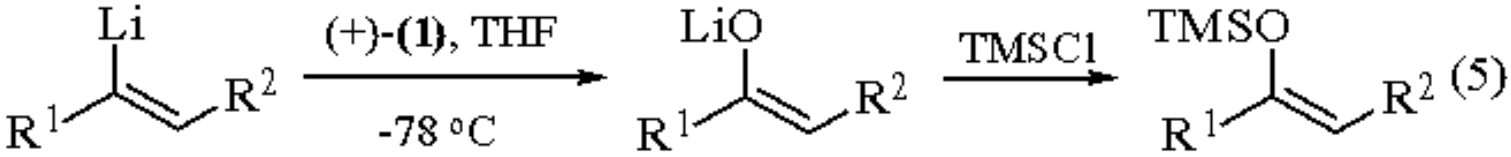

Oxidation of Phosphoranes.

Monosubstituted phosphoranes (ylides) are rapidly oxidized to *trans*-alkenes by (+)-(**1**), while disubstituted phosphoranes give ketones (eq 6). A mechanism involving initial attack of the carbanion of phosphorane to the electrophilic oxaziridine oxygen atom of (+)-(**1**) is proposed.[13]

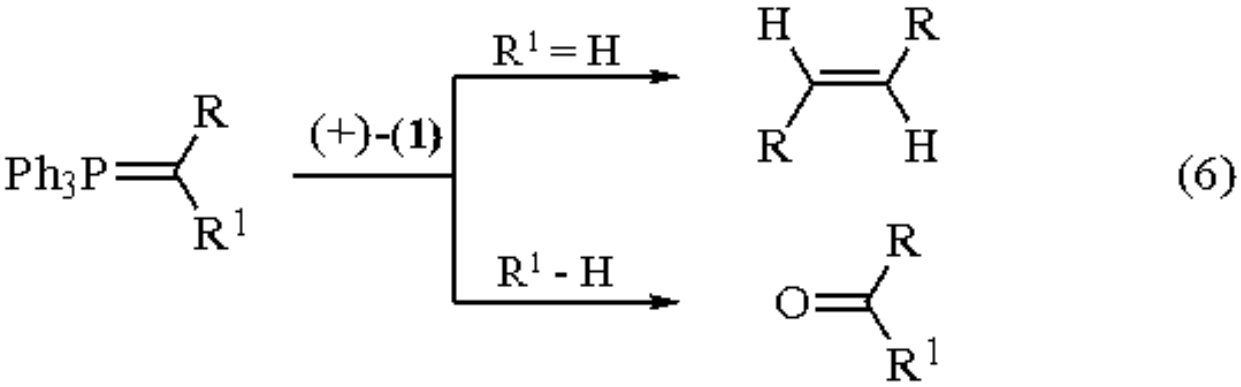

Asymmetric α-Hydroxylation of Enolates.

α-Hydroxylation of enolates represents one of the simplest and most direct methods for the synthesis of α-hydroxy carbonyl compounds, a key structural unit found in many natural products.[1b] Enolate oxidations using (+)- and (-)-(**1**) and their derivatives generally effect this transformation in good to excellent yields with a minimum of side reactions (e.g. over-oxidation). Furthermore, these reagents are the only aprotic oxidants developed to date for the direct asymmetric hydroxylation of prochiral enolates to optically active α-hydroxy carbonyl compounds.

By choice of the appropriate reaction conditions and (camphorylsulfonyl)oxaziridine derivative, acyclic α-hydroxy ketones of high enantiomeric purity have been prepared.[1] An example is the oxidation of the sodium enolate of deoxybenzoin with (+)-(**1**). The reaction proceeds very fast at -78 °C, affording (+)-(*S*)-benzoin in 95% ee. Both benzoin enantiomers are readily available by choice of (+)- or (-)-(**1**), because the configuration of the oxaziridine controls the absolute stereochemistry of the product (eq 7).[14] Detailed studies have indicated that the generation of a single enolate regioisomer is a pre-condition for high enantioselectivity, although this does not necessarily always translate into high ee's. Hydroxylation of tertiary substituted acyclic ketone enolates usually gives lower stereoselectivities due to the formation of (*E*/*Z*) enolate mixtures (eq 8).[14] In addition to enolate geometry, the molecular recognition depends on the structure of the oxidant, the type of enolate, and the reaction conditions.[1b] Generally the stereoselectivity can be predicted by assuming that the oxaziridine approaches the enolate from the least sterically hindered direction.

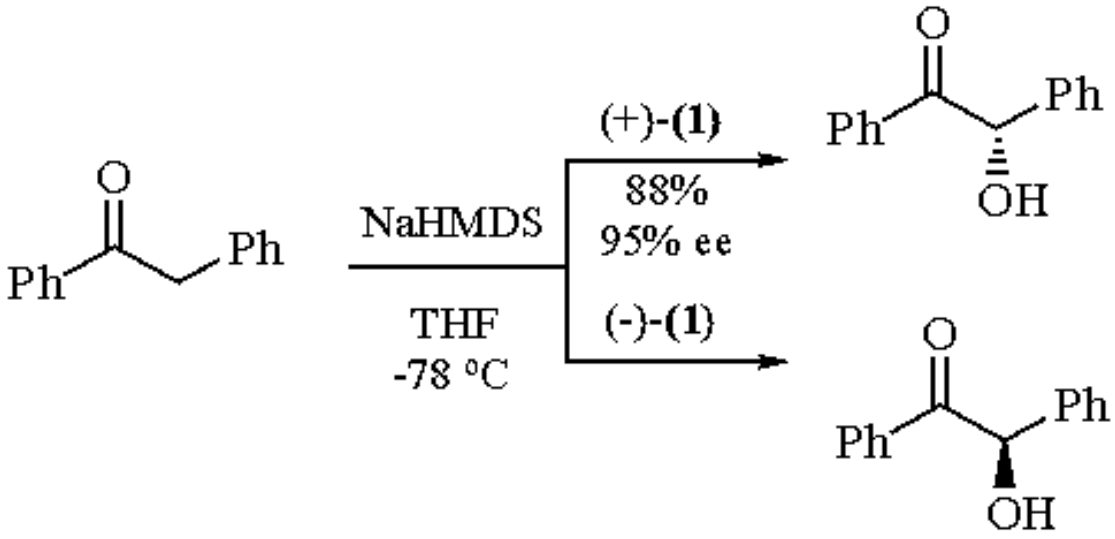

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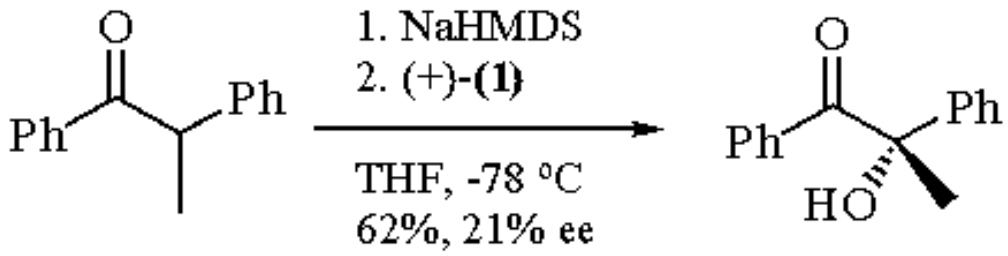

(8)

The asymmetric hydroxylation of cyclic ketone enolates, particularly the tetralone and 4-chromanone systems, has been studied in detail because the corresponding α-hydroxy carbonyl compounds are found in many natural products.[1b] Some general trends have been observed. 2-Substituted 1-tetralones having a variety of groups at C-2 (Me, Et, Bn) are best oxidized by chlorooxaziridine (**2**) in >90% ee (eq 9).[2c,15,16] However, substitution of a methoxy group into the 8-position lowers the stereoselectivity. For the 8-methoxytetralones, (8,8-dimethoxycamphorylsulfonyl)oxaziridine (**3**) is the reagent of choice. Similar trends have also been observed in 4-chromanones.[1b] Oxidation of the lithium enolate of (**6**) with (8,8-methoxycamphorsulfonyl)oxaziridine (**3**) affords 5,7-dimethyleucomol (**7**) in &egt;96% ee (eq 10).[17] Hydroxylation of the enolate of 1-methyl-2-tetralone (**8**) to (**9**) gives poor to moderate stereoselectivities. The optimum result, 76% ee, is obtained using the sodium enolate and oxaziridine (+)-(**1**) (eq 11).[15]

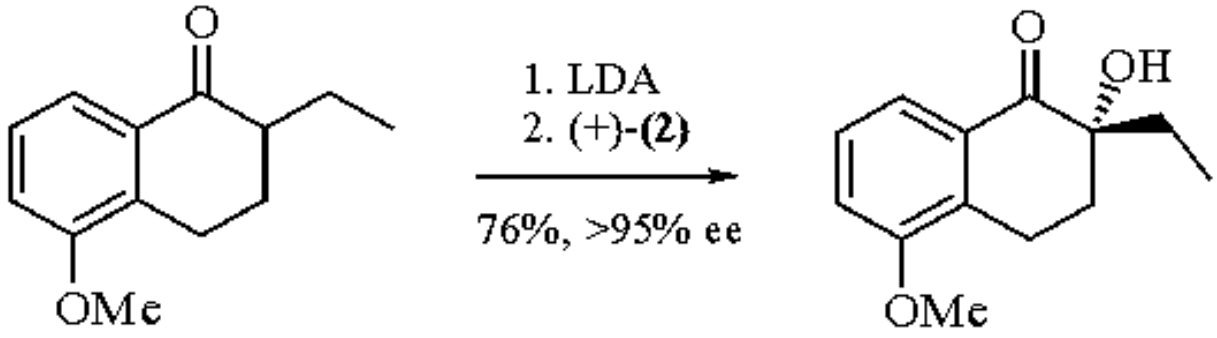

(9)

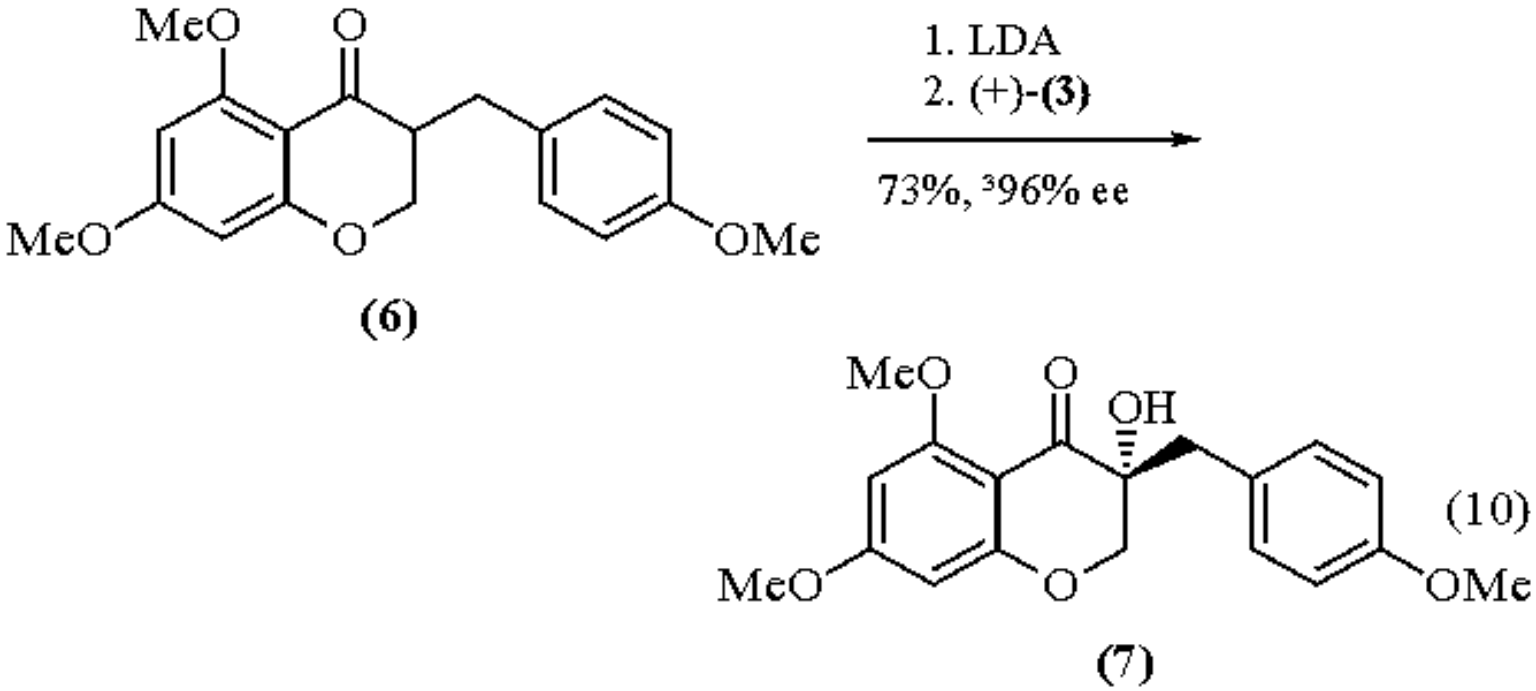

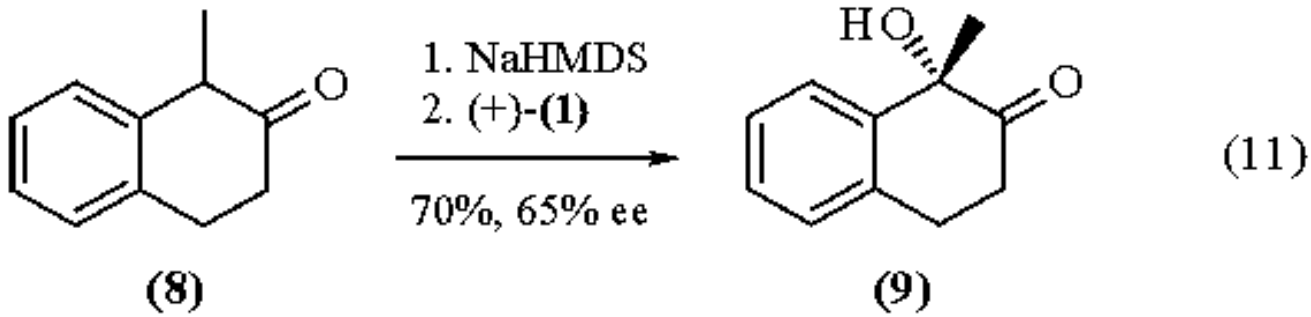

It should be pointed out that enolates are oxidized by the (camphorylsulfonyl)oxaziridine at a much faster rate than sulfides. An example is the preparation of α-hydroxy ketone sulfide (**9**), an intermediate for the total synthesis of (±)-breynolide (eq 12).[18]

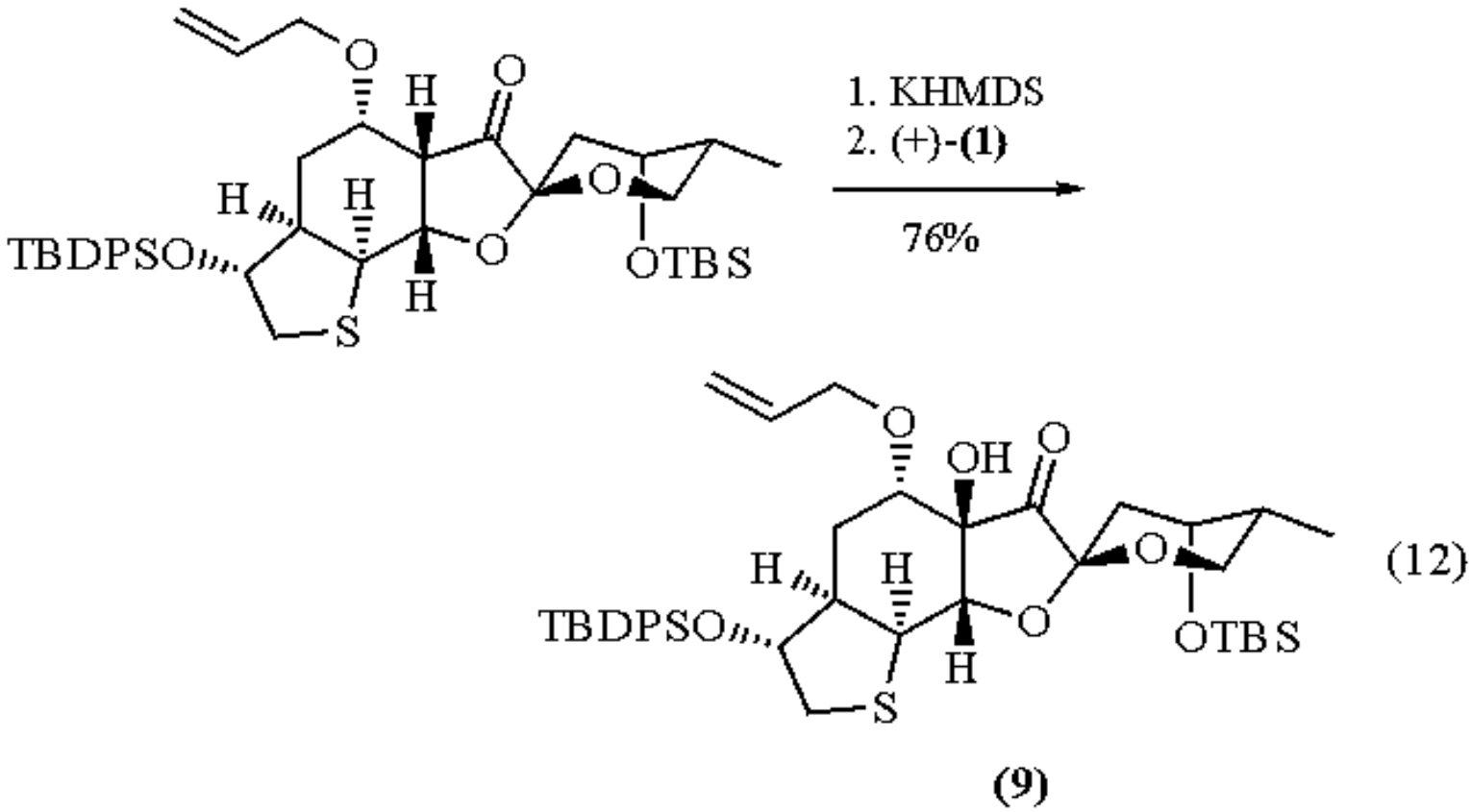

The asymmetric hydroxylation of ester enolates with *N*-sulfonyloxaziridines has been less fully studied.[1b] Stereoselectivities are generally modest and less is known about the factors influencing the molecular recognition. For example, (*R*)-methyl 2-hydroxy-3-phenylpropionate (**10**) is prepared in 85.5% ee by oxidizing the lithium enolate of methyl 3-phenylpropionate with (+)-(**1**) in the presence of HMPA (eq 13).[19] Like esters, the hydroxylation of prochiral amide enolates with *N*-sulfonyloxaziridines affords the corresponding enantiomerically enriched α-hydroxy amides. Thus treatment of amide (**11**) with LDA followed by addition of (+)-(**1**) produces α-hydroxy amide (**12**) in 60% ee (eq 14).[19] Improved stereoselectivities were achieved using double stereodifferentiation, e.g. the asymmetric oxidation of a chiral enolate. For example, oxidation of the lithium enolate of (**13**) with (-)-(**1**) (the matched pair) affords the α-hydroxy amide in 88-91% de (eq 15).[20] (+)-(Camphorsulfonyl)oxaziridine (**1**) mediated hydroxylation of the enolate dianion of (*R*)-(**14**) at -100 to -78 °C in the presence of 1.6 equiv of LiCl gave an 86:14 mixture of *syn*/*anti*-(**15**) (eq 16).[21] The *syn* product is an intermediate for the C-13 side chain of taxol.

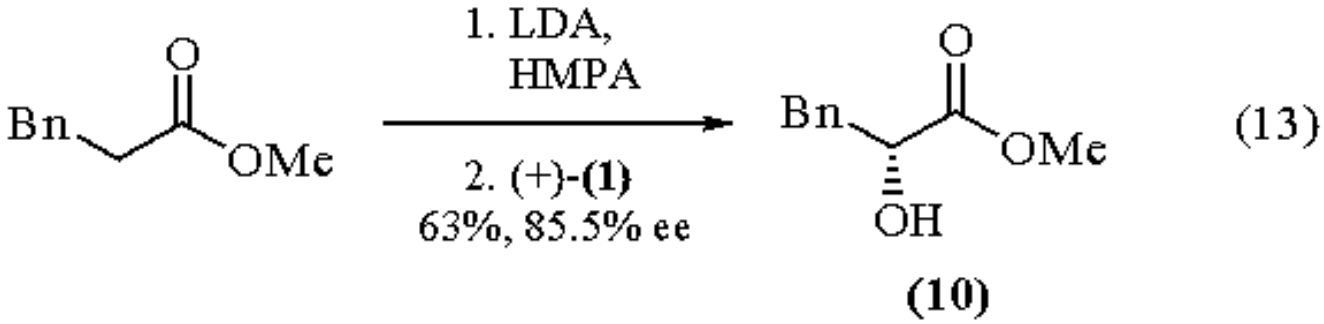

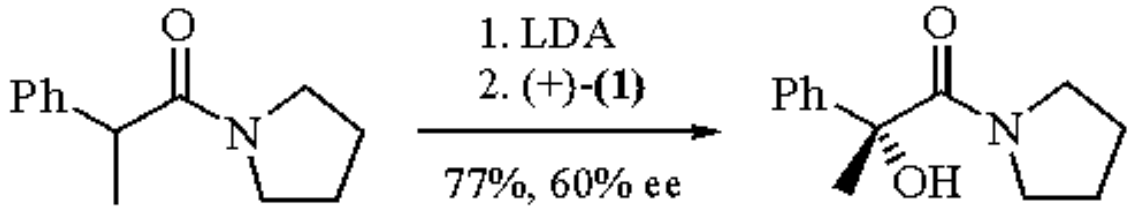

(14)

(11) (12)

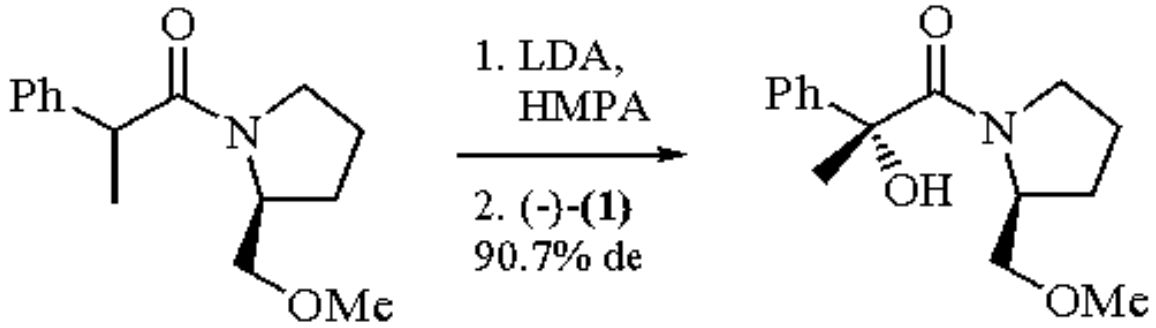

(15)

(13)

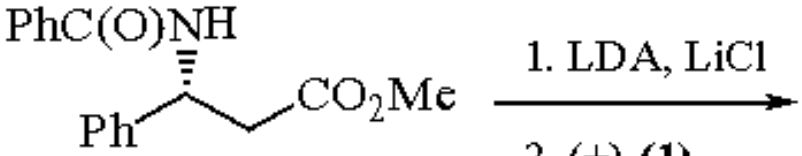

(*R*)-(**14**)

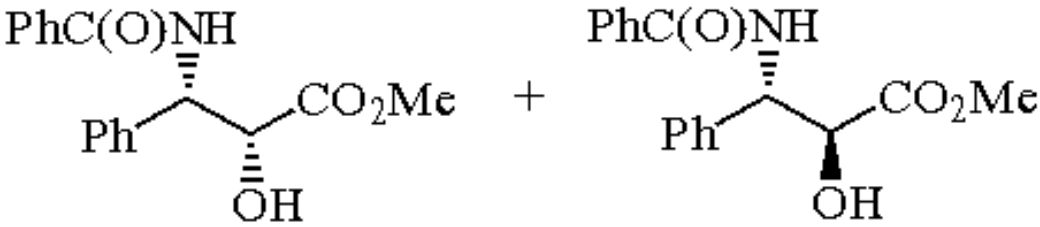

(16)

syn-(**15**) 85:15 *anti*-(**15**)

Hydroxylation of the sodium enolate of lactone (**16**) with (+)-(**1**) gives α-hydroxy lactone in 77% ee (eq 17).[15] Kinetic resolution and asymmetric hydroxylation with (camphorsulfonyl)oxaziridines has been applied to the synthesis of enantiomerically enriched α-hydroxy carbonyl compounds having multiple stereocenters, which may otherwise be difficult to prepare.[22] Thus hydroxylation of the enolate of racemic 3-methylvalerolactone with substoichiometric amounts of (-)-(**1**) affords (2*S*,3*R*)-verrucarinolactone in 60% ee (eq 18) which on recrystallization is obtained enantiomerically pure.[22]

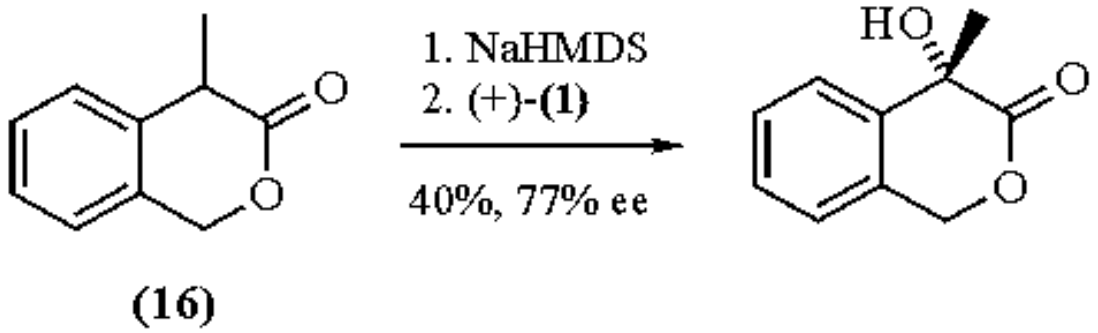

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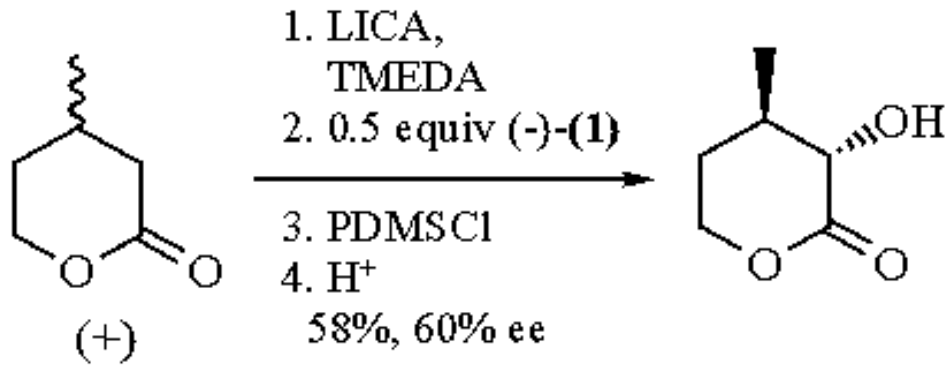

(18)

Oxidation of the dienolate of (**17**) with (+)-(**1**) affords α-hydroxy ester (**18**), a key intermediate in the enantioselective synthesis of the antibiotic echinosporin (eq 19),[23] whereas oxidation of enolates derived from 1,3-dioxin vinylogous ester (**19**) gives rise to both α´- and γ-hydroxylation depending on the reaction conditions (eq 20).[24] With (+)-(**1**) the lithium enolate of (**19**) gives primarily the α´-hydroxylation product (**20**), while the sodium enolate gives γ-hydroxylation product (**21**). Only low levels of asymmetric induction (ca. 16% ee) are found in these oxidations. Birch reduction products are also asymmetrically hydroxylated in situ by (+)-(**1**) (eq 21).[25]

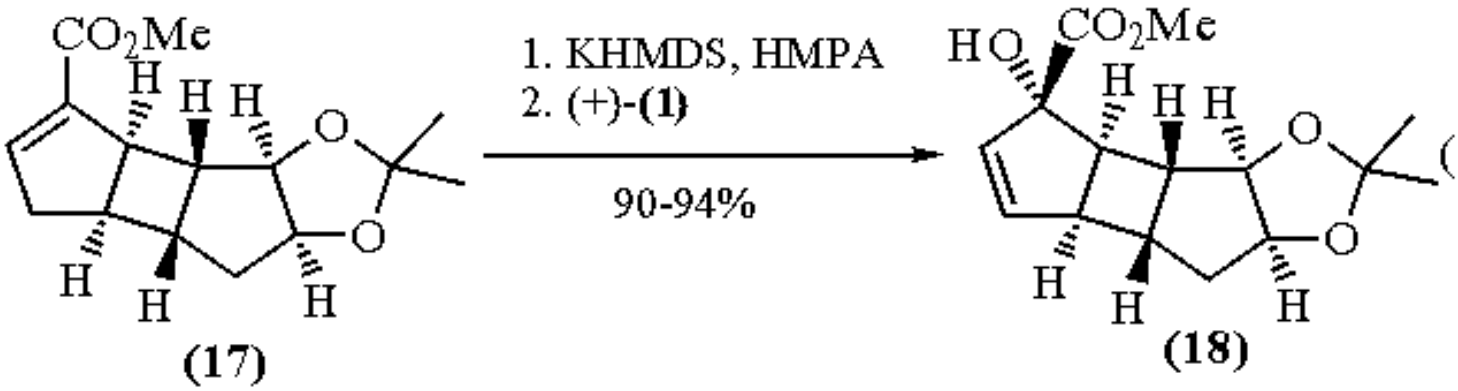

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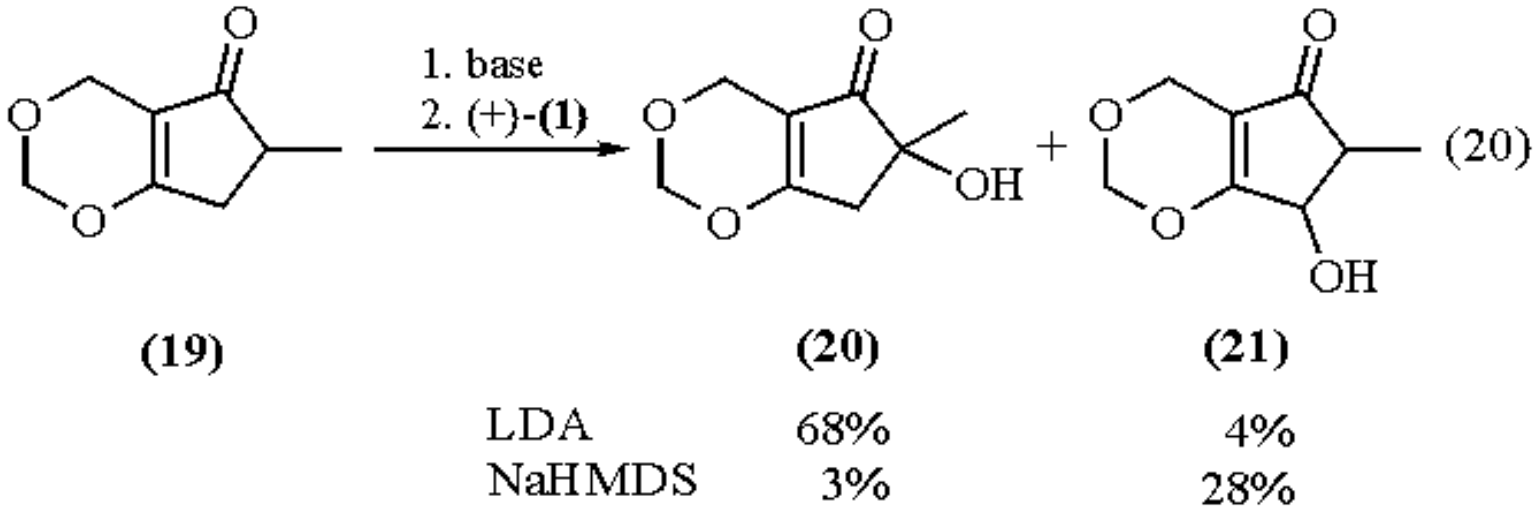

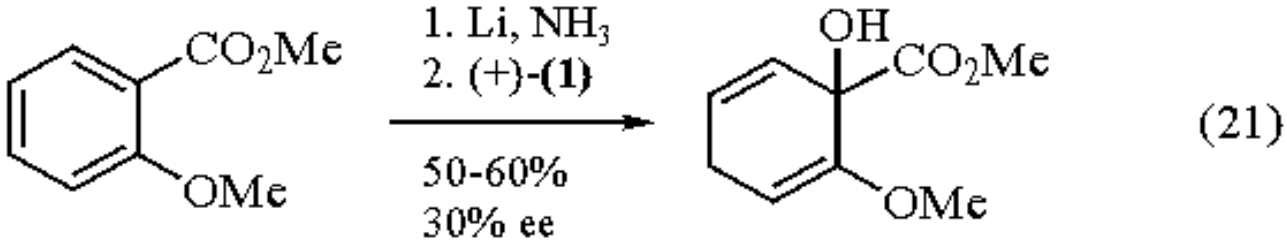

Few reagents are available for the hydroxylation of stabilized enolates such as β-keto esters, e.g. Vedejs' MoOPH reagent (***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)***) fails.[26] On the other hand, oxaziridines hydroxylate such enolates in good yield with good to excellent stereoselectivities.[1b] For example, enantioselective hydroxylation of the potassium enolate of the β-keto ester (**22**) with methoxyoxaziridine (-)-(**3**) affords (*R*)-(+)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**23**), a key intermediate in the asymmetric synthesis of the anthracycline antitumor agents demethoxyadriamycin and 4-demethoxydaunomycin (eq 22).[27] Hydroxylation of the sodium enolate of enone ester (**24**) furnishes kjellmanianone (**25**), an antibacterial agent isolated from marine algae (eq 23).[5] With (+)-(**1**) the ee's are modest (ca 40%), but improved to 69% ee with benzyloxaziridine (**4**).

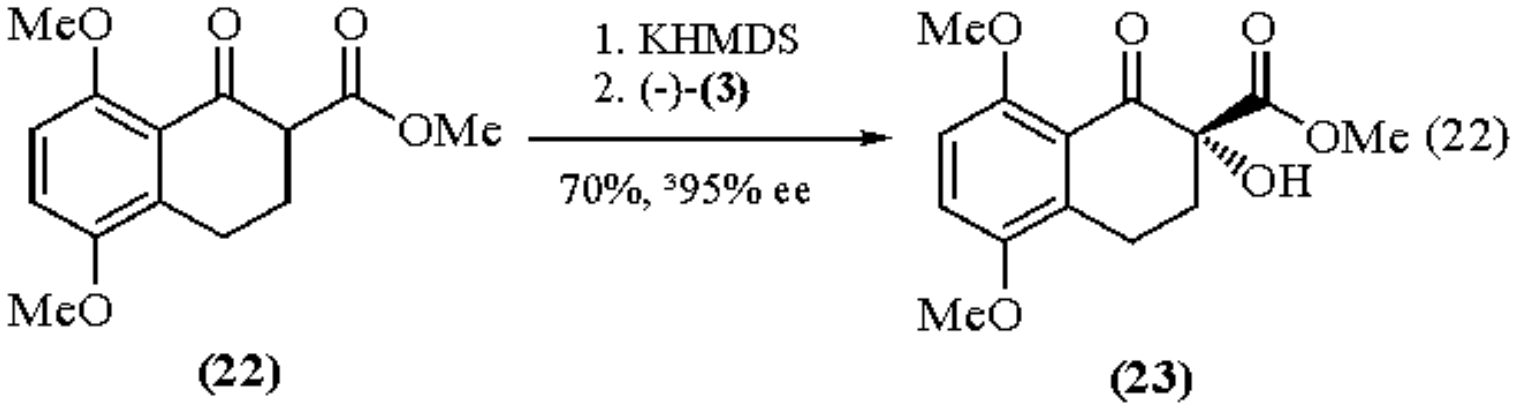

(Camphorylsulfonyl)oxaziridine

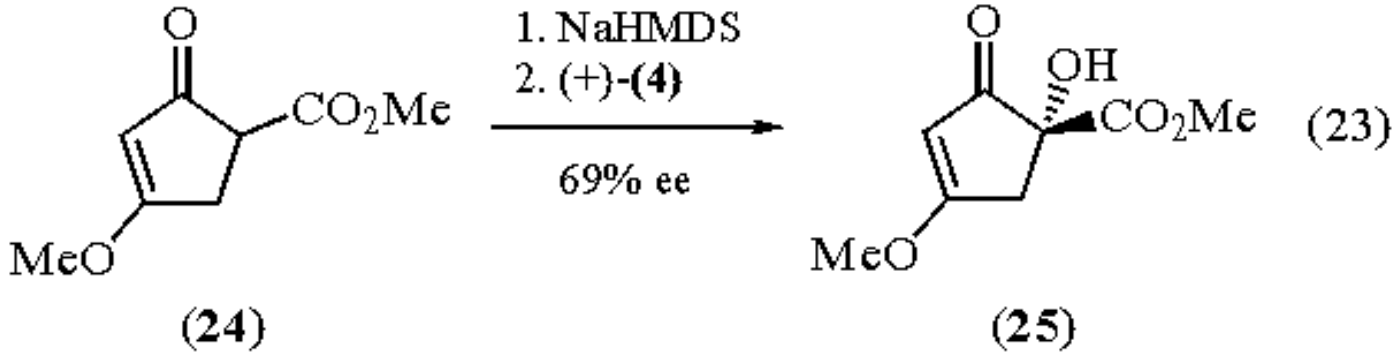

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Bang-Chi Chen

Bristol-Myers Squibb Company, Syracuse, NY, USA

10,2-Camphorsultam[1]

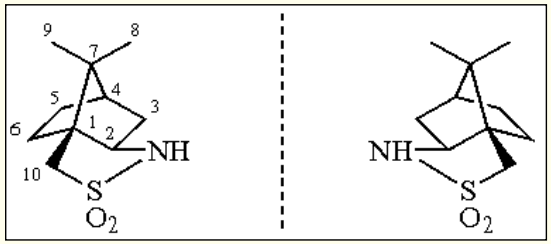

(-)-D-(2*R*)

[94594-90-8] · $C_{10}H_{17}NO_2S$ · 10,2-Camphorsultam · (MW 215.31) (+)-L-(2*S*)

[108448-77-7]

(versatile chiral auxiliary: *N*-enoyl derivatives undergo highly stereoselective [2 + 4] Diels-Alder[2] and [2 + 3][3] cycloadditions, cyclopropanations,[4] aziridinations,[5] dihydroxylations,[6] hydrogenations,[7] azido-iodinations[8] and conjugate hydride,[9] Grignard,[10] cuprate,[11] allylsilane[12] and thiolate[13] additions; radical additions[14] and S_N2' reactions[15] at the α-position also occur stereoselectively; enolates of *N*-acyl derivatives participate in highly stereoselective aldolizations,[16] alkylations,[17] halogenations, and aminations, the latter three types of reactivity being useful for α-amino acid preparation;[18] free radicals generated at the α-position of *N*-acyl derivatives participate in stereoselective intra- and intermolecular addition reactions;[19] the *N*-fluoro derivative functions as an enantioselective, electrophilic fluorinating reagent[20])

Alternate Name: bornane-10,2-sultam.

Physical Data: mp 183-185 °C (EtOH). (-)-D-(2*R*) enantiomer: $[\alpha]_D^{20}$ -31±1° ($CHCl_3$, *c* 2.3). (+)-L-(2*S*) enantiomer: $[\alpha]_D^{20}$ +34±1° (EtOH, *c* 1.00).

Form Supplied in: white crystalline solid; both enantiomers are commercially available (~same price) or may be readily prepared (3 steps, >70% overall yield) from ***10-Camphorsulfonic Acid***.[21]

Handling, Storage, and Precautions: stable indefinitely at ambient temperature in a sealed container; mild irritant.

Introduction.

Exploitation of chiral auxiliary controlled face discrimination in the reaction of a reactant with a prochiral molecule or functional group is a powerful strategy in asymmetric synthesis.[22] Clearly the choice of auxiliary for a desired chemical transformation is crucial for optimal synthetic efficiency. Hence, the ease with which the auxiliary can be introduced, the extent of stereoselection it imparts to the desired transformation, and the ease of its nondestructive removal are of critical importance. The 10,2-camphorsultam not only meets these criteria for a range of transformations, but also generally imparts crystallinity to all derived intermediates, thereby facilitating purification and isolation of enantiomerically pure products. Indeed, 10,2-camphorsultam derivatization alone allows for facile crystallographic determination of absolute configuration.[23]

Preparation of Derivatives.

N-Acyl- and *N*-enoylsultam derivatives are routinely prepared in good yields using either sodium hydride-acid chloride[16a] or trimethylaluminum-methyl ester[18g] single-step protocols. A variant of the former method employing in situ stabilization of labile enoyl chlorides with CuCl/Cu has also been reported.[3k] A two-step procedure via the *N*-TMS derivative (**1**) is useful when a nonaqueous work-up is desirable and for synthesis of the *N*-acryloyl derivative.[24] *N*-Enoyl derivatives may also be prepared via the phosphonate derivative (**2**) by means of an Horner-Wadsworth-Emmons reaction (eq 1).[2c,2d]

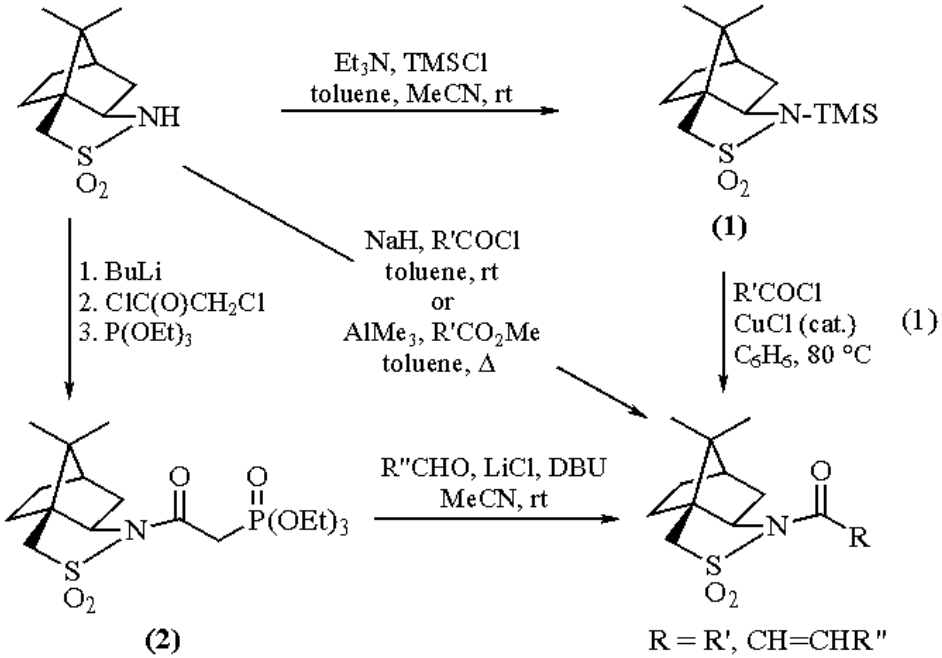

An *N*-acyl-β-keto derivative has been prepared by reaction with a diketene equivalent[17b] and the *trans*-N-cinnamoyl derivative by a Heck type coupling reaction.[4] The *N*-fluoro derivative (**3**) is prepared by direct fluorination (eq 2).[20]

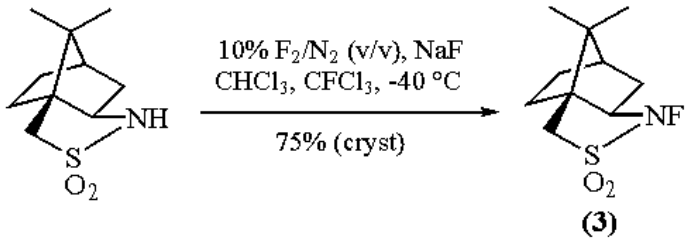

Reactions of *N*-Enoyl Derivatives.

[4 + 2] Diels-Alder Cycloadditions (Alkene -> Six-Membered Cycloadduct).[2]

N-Enoylsultam derivatives were originally devised as activated chiral dienophiles for stereoselective Diels-Alder reactions.[1,2a]

Thermal reactions of *N*-enoylsultams generally show only moderate *endo* and π-face selectivity, e.g. *N*-acryloyl- and *N*-crotonoyl-10,2-camphorsultams (**4**) and (**6**) with cyclopentadiene (eq 3, Table 1).[2g] The thermal hetero-Diels-Alder reaction of *N*-glyoxaloyl-10,2-camphorsultam with 1-methoxybuta-1,3-diene also proceeds with moderate *exo* and π-face selectivity (57% *exo*, 46% de).[2h] Thermal hetero-Diels-Alder reactions of *N*-acylnitroso-10,2-camphorsultam with cyclopentadiene and 1,3-cyclohexadiene, however, proceed with excellent selectivity (>98% ee, π-face selectivity not established).[2i]

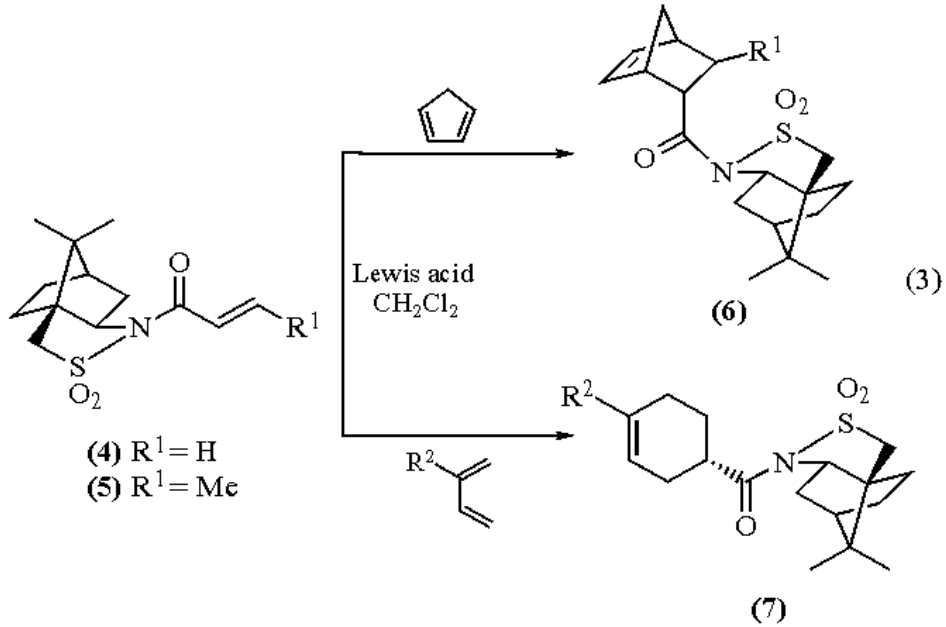

Table 1 Intermolecular Diels Alder Reactions of *N*-Enoylsultams (**4**)/(**5**) ® (**6**) and (**4**) ® (**7**)

Dienophile	Diene	Lewis acid[a]	Temp (°C)/time (h)	Adduct	Yield crude (cryst)[b] (%)	de crude (cryst) (%)
(**4**)	Cyclopentadiene	None	21 (72)	(**6**) R^1 = H	80[c]	66
(**5**)	Cyclopentadiene	None	21 (96)	(**6**) R^1 = Me	51[d]	52
(**4**)	Cyclopentadiene	$EtAlCl_2$	- 130 (6)[e]	(**6**) R^1 = H	96 (83)	95 (99)
(**5**)	Cyclopentadiene	$TiCl_4$	- 78 (1)	(**6**) R^1 = Me	98 (83)	93 (99)
(**4**)	1,3-Butadiene	$EtAlCl_2$	- 78 (18)	(**7**) R^2 = H	93 (81)	94 (99)
(**4**)	Isoprene	$EtAlCl_2$	- 94 (18)	(**7**) R^2 = Me	88 (68)	94 (99)

[a] $EtAlCl_2$ (1.5 equiv), $TiCl_4$ (0.5 equiv). [b] >98% *endo*. [c] 89% *endo*. [d] 79% *endo*. [e] EtCl as solvent.

Lewis acid-mediated reactions of *N*-enoylsultams, on the other hand, occur under very mild conditions and with high levels of *endo* and π-face selectivity (eq 3, Table 1).[2b,2g] Dicoordinate $TiCl_4$, $EtAlCl_2$, and Me_2AlCl are particularly effective and their role in the stereodifferentiating process, which results in almost exclusive C(α)-*re* face dienophile attack, has been rationalized.[2g] Both inter- and intramolecular reactions proceed well even on a preparative scale (e.g. >100 g), often requiring just a single recrystallization to furnish isomerically pure products, valuable as synthetic intermediates (eq 4, the key step in a synthesis of (-)-pulo'upone).[2d] The hetero-Diels-Alder reaction of *N*-glyoxaloyl-10,2-camphorsultam with 1-methoxybuta-1,3-diene also proceeds efficiently and with high *endo* and π-face selectivity in the presence of 2% $Eu(fod)_3$ (90% *endo*, 88% de).[2h] These levels of asymmetric induction compare very favorably with those obtained using alternative auxiliaries (see Related Reagents below) for most substrates.

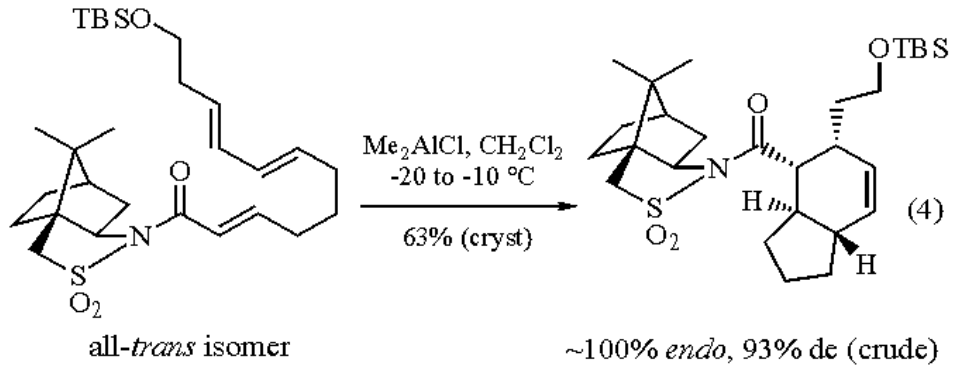

[3 + 2] Cycloadditions (Alkene -> Five-Membered Cycloadduct).[3]

The levels of selectivity found for 1,3-dipolar cycloaddition reactions are not as high as those obtained for Lewis acid-catalyzed Diels-Alder reactions. However, the 10,2-camphorsultam auxiliary can achieve synthetically useful levels of induction in these reactions, and this has been attributed to efficient enoyl conformational control by the sultam moiety leading to preferred C(α)-*re* face attack even in the absence of metal complexation.[1d]

The reactions of *N*-enoyl-10,2-camphorsultams with various nitrile oxides to give isoxazolines have been well studied.[3a-c] Indeed, the high regioselectivity and high π-face selectivity (62-90% de)[3a] observed in reactions with the *N*-acryloyl compound (**4**) have been exploited in synthesis (eq 5, the key step in a synthesis of (+)-hepialone[3b]), although related toluene-2,α-sultam auxiliaries provide still higher selectivity (see α-***Methyltoluene-2,α-sultam***). Isoxazolines may also be obtained by regioselective and similarly π-face selective cycloadditions of silyl nitronates followed by acid catalyzed elimination of TMS alcohol[3d-f] (eq 6, the key step in a synthesis of (+)-methylnonactate).[3f] A cyclic, photochemically generated azomethine ylide also participates in *exo* and π-face selective 1,3-dipolar cycloaddition with (*ent*-**4**), a reaction for which alternative auxiliaries were significantly less effective (eq 7, the key step in a synthesis of (-)-quinocarcin).[3g-i]

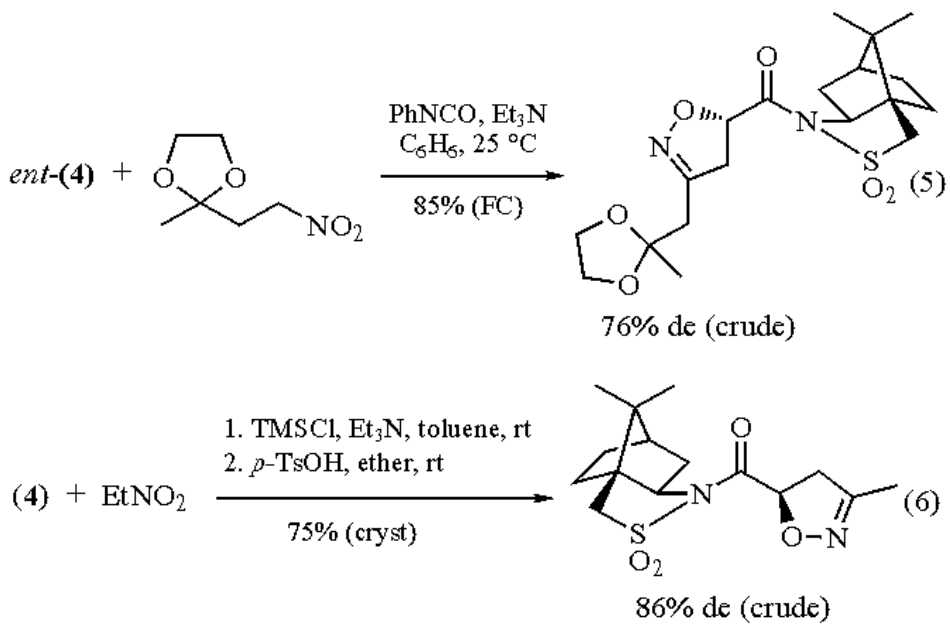

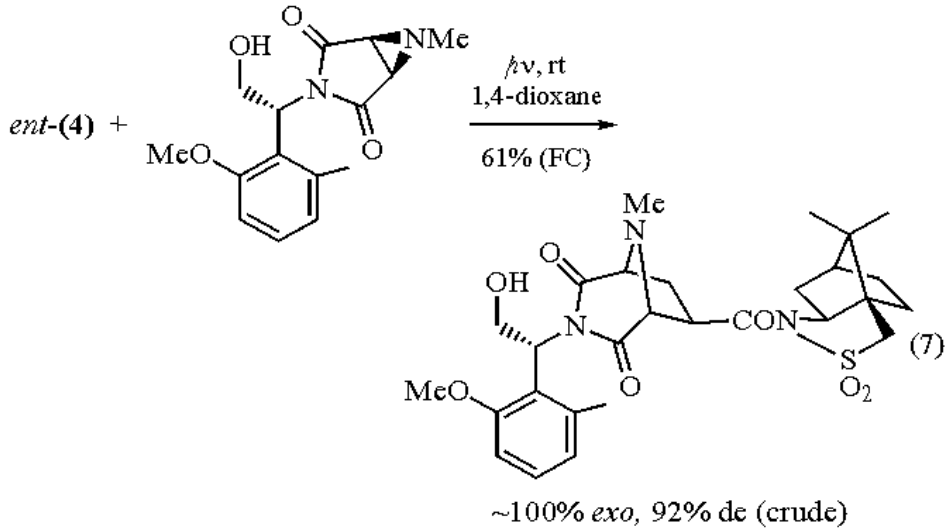

Nickel catalyzed [3 + 2] cycloadditions of methylenecyclopropane and 2,2-dimethylmethylenecyclopropane with (**4**) afford 3-methylenecyclopentane derivatives with extremely high π-face selectivities (91% and 98% de respectively); five alternative auxiliaries were found to be less effective.[3j,3k] Palladium catalyzed [3 + 2] cycloaddition of 2-(TMS-methyl)-3-acetoxy-1-propene with an *N*-enoylsultam, however, proceeds with disappointing selectivity (4-26% de).[3l] A norephedrine derived auxiliary ((4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone) was similarly ineffective in this instance.[3l]

Cyclopropanation and Aziridination (Alkene -> Three-Membered Cycloadduct).[4,5]

Cyclopropanation of various *trans*-*N*-enoyl derivatives using diazomethane with $Pd(OAc)_2$ as catalyst affords cyclopropyl products with good C(α)-*re* π-facial control (eq 8).[4] Similarly, aziridination with *N*-aminophthalimide-lead tetraacetate affords *N*-phthalimidoaziridines with variable but generally good π-face selectivity (33-95% de).[5]

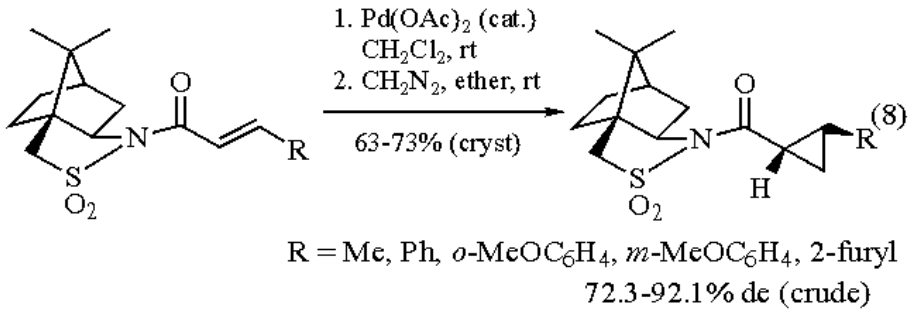

Dihydroxylation, Azido-Iodination and Hydrogenation (Alkene -> α,β-Addition Product).[6-8]

syn-Dihydroxylation of β-substituted *N*-enoylsultams using *N*-methylmorpholine with a catalytic amount of OsO_4 affords vicinal diol products with good C(α)-*re* π-facial selectivity (80-90% de) (eq 9, the key step in a synthesis of (+)-LLP 880β).[6a] Similar levels of selectivity but lower chemical yields are obtained using $KMnO_4$ and *N*-dienoylsultams.[6b] Regioselective but poorly stereoselective *trans* addition of iodine azide to *N*-crotonoyl- and *N*-cinnamoyl-10,2-camphorsultams has also been reported (34% and 47% de, respectively). The sense of addition corresponds to iodonium ion formation from the C(α)-*re* face followed by S_N2 attack of azide at the β-position.[8] Heterogeneous *syn* hydrogenation of β,β-disubstituted enoylsultams over Pd/C using gaseous hydrogen (100 psi) affords reduced products, again with excellent C(α)-*re* topicity (90-96% de).[7]

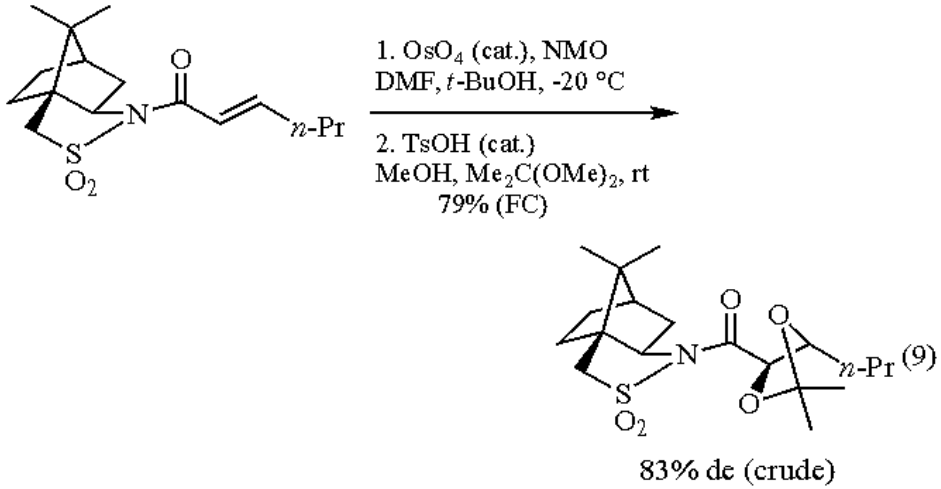

1,4-Hydride, Grignard, Cuprate, Allylsilane, and Thiolate Addition (Alkene -> β- or α,β-Functionalized Product).[9-13]

β,β-Disubstituted enoylsultams undergo efficient reduction with L-Selectride®.[9a] The *syn* hydrogenated products obtained result from conjugate hydride delivery (and protonation) on the opposite π-face [i.e. C(α)-*si*] to that from hydrogenation (90-94% de) (eq 10).[9b] Similarly, simple alkylmagnesium chlorides also undergo 1,4-addition-protonation with *trans*-β-substituted enoylsultams from this face (72-89% de).[10] Use of α-substituted *N*-enoyl substrates,[9a] or trapping of the intermediate aluminum or magnesium enolates with other electrophiles, allows creation of two asymmetric centers in one synthetic operation.[9a,10] The observed topicity is that of *syn* addition from the C(α)-*si* face. As PBu_3 stabilized alkylcopper reagents,[11a,11b] Grignard reagents (in the presence of copper salts),[11c] and cuprates (Gilman reagents)[11d] participate in analogous reactions but show reversed π-face selectivity, an appropriate 1,4-addition-trapping protocol can be devised to generate products with any desired configuration at both the α- and β-positions (eq 11).[11c] This complementarity has been rationalized.[11] Phosphine stabilized alkyl- and alkenylcopper reagents also add to *N*-(β-silylenoyl)sultams (giving aldols after C-Si oxidative bond cleavage). In this case, either π-face selectivity can be achieved, depending on the promoting Lewis acid employed.[11b] Similar Lewis acid dependent selectivity is observed for addition of allyltrimethylsilane to *N*-enoylsultams.[12]

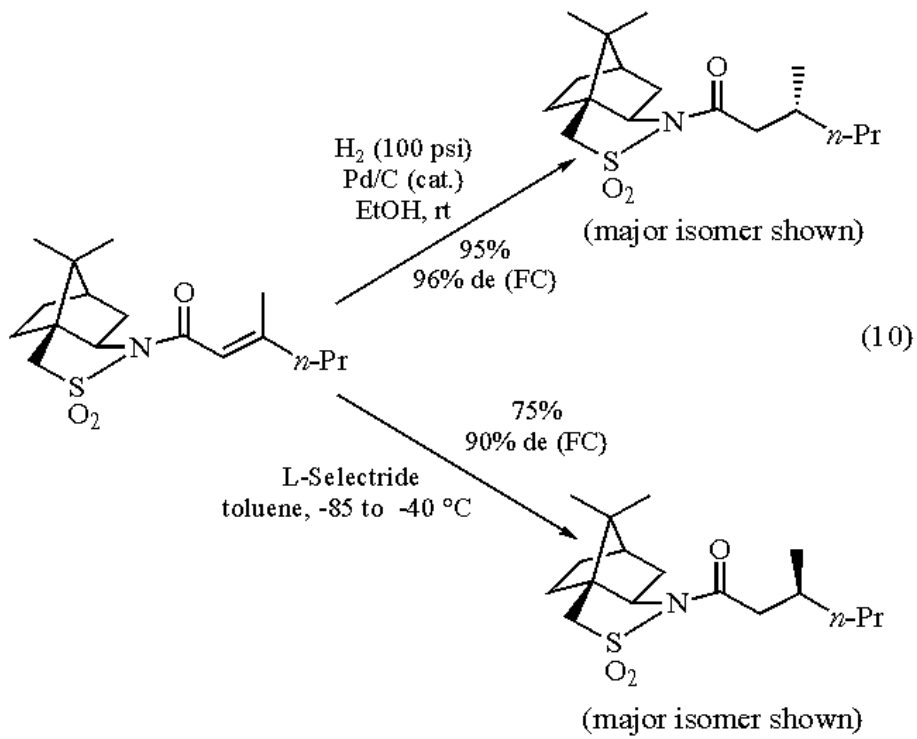

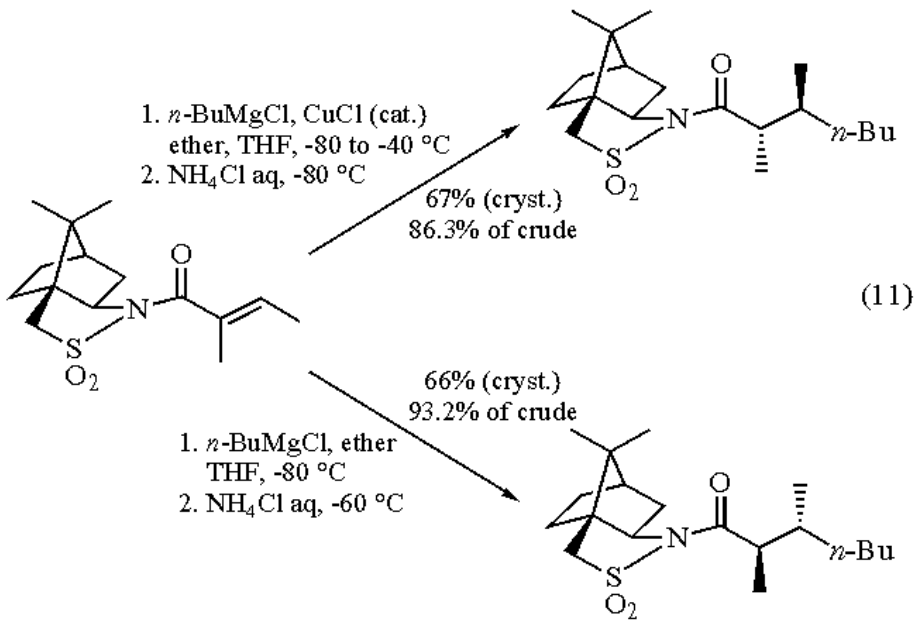

Stereoselective *anti* addition of thiophenol to *N*-[β-(*n*-butyl)methacryloyl]-10,2-camphorsultam [the key step in a synthesis of (+)-*trans* whiskey lactone] has been explained by a sulfur-induced, stereoelectronically directed protonation following C(β)-*re* face conjugate addition.[13]

Radical Addition and S_N2' Displacement (Alkene -> α-Functionalized Product).[14,15]

Stereoselective radical additions to *N*-enoylsultams occur at the α-position, while additions to the β-position are essentially nonselective.[1d,14] The S_N2' displacement of γ-bromo-*N*-enoylsultams with higher order cyanocuprates occurs with good π-face selectivity (90-96% de).[15]

Reactions of *N*-Acyl Derivatives.

Aldolization (Acyl Species -> β-Hydroxyacyl Product).[16]

Chiral oxazolidin-2-ones and 10,2-camphorsultams presently represent state of the art aldol reaction mediators. Both auxiliaries have similarly high π-facial preferences (totally overwhelming any modest facial preference of most chiral aldehydes), allowing the predictable formation of essentially one (of four possible) diastereomeric aldol type products by judicious choice of auxiliary antipode and reaction conditions.[16a] Although sultam mediated aldolizations generally require a 2-3 fold excess of aldehyde to go to completion (cf. 1-2 equiv when oxazolidin-2-one mediated), which is clearly wasteful when employing a valuable aldehyde, the superior crystallinity and cleavage properties of the sultam adducts makes the choice of auxiliary for a given aldolization dependent on the specific substrate.

syn-Aldols with (*R*) configuration at the α-position are obtained from boryl enolates of (-)-10,2-camphorsultam derivatives (**8**) on condensation with aldehydes.[16b] The observed topicity is consistent with C(α)-*si*/C=O-*re* interaction of the nonchelated (*Z*)-enolate and the aldehyde.[16b] *syn*-Aldols with (*S*) configuration at the α-position are obtained from lithium (BuLi-THF) or better tin(IV) enolates of the same derivatives (**8**), and this outcome is consistent with C(α)-*re*/C=O-*si* interaction of the chelated (*Z*)-enolate and the aldehyde.[16b] *anti*-Aldols with (*S*) configuration at the α-position are obtained from in situ prepared *O*-silyl-*N*,*O*-ketene acetals of sultams (**8**) on condensation with aldehydes in the presence of $TiCl_4$[16c] (Mukaiyama aldolization). This topicity arises from C(α)-*re*/C=O-*re* interaction of the *(Z)-N,O*-ketene acetal and the Lewis acid coordinated aldehyde (eq 12).[16c] These same *anti*-aldols can also be obtained from sultams (**8**) with similarly excellent stereocontrol using boryl enolates in the presence of $TiCl_4$, and this unique procedure is the method of choice when using crotonaldehyde or methacrolein.[16d] *anti*-Aldols with (*R*) configuration at the α-position should be obtained from sultams (*ent*-**8**) using the above Mukaiyama conditions. Enantiocontrolled synthesis of α-unsubstituted β-hydroxy carbonyl compounds from the *N*-acetyl derivative is best accomplished using the Mukaiyama conditions (58-93% de).[16e] The synthesis of beetle sex pheromone (-)-serricorole serves to highlight the power of the above methods.[16f,16g]

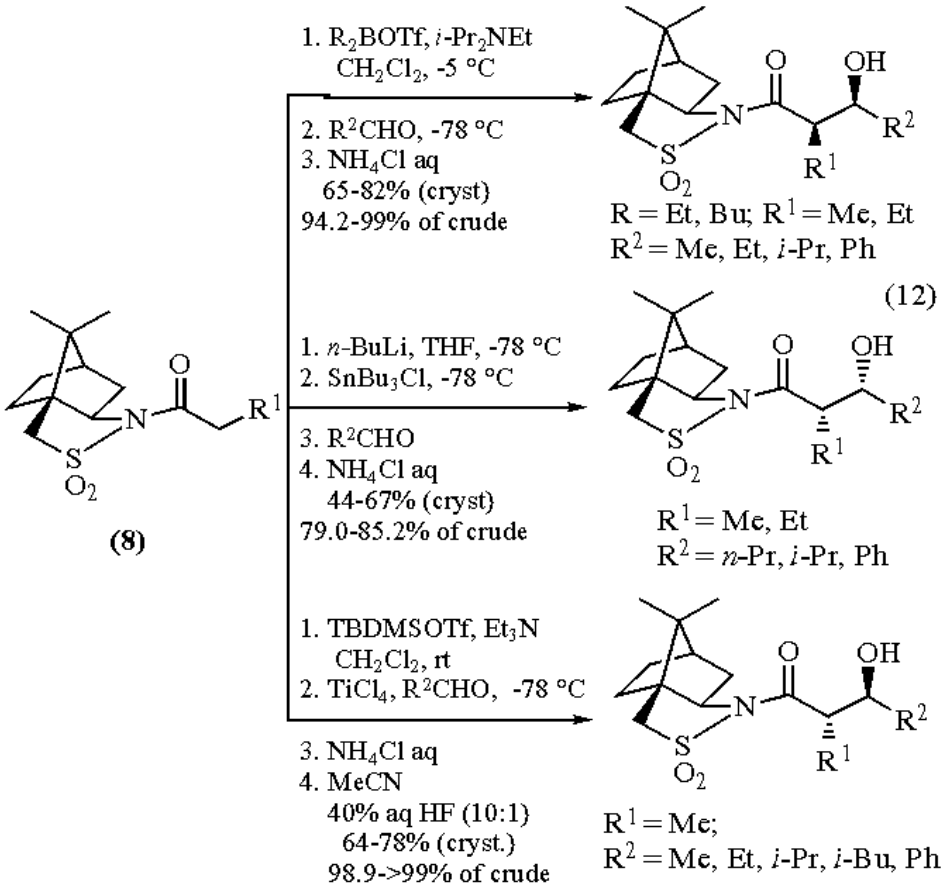

Alkylation (Acyl Species -> α-Alkylated Acyl Product).[17]

An efficient procedure for the C(α)-*re* alkylation of lithium and sodium enolates of *N*-acylsultams with various (even nonactivated) primary halides in the presence of HMPA has been developed (88.7-99% de).[17a] Alkylation with $ClCH_2NMeCO_2Bn$ enables a two-step β-lactam synthesis.[1c,17a] Michael-type alkylation of a β-keto derivative with arylidenemalononitriles in toluene containing piperidine has been reported to give 4*H*-pyrans (60-70% de).[17b]

α-Amino Acid Preparation.[18]

Three distinct strategies for the asymmetric preparation of α-amino acids using the 10,2-camphorsultam auxiliary have been developed. The first is a glycine anion strategy[18a] centered on alkylation, with excellent C(α)-*si* π-face stereocontrol, of lithium enolates of sultam derivative (**9a**) [mp 107-109 °C (EtOH)][18b,18c] to give adducts (**10**) (eq 13). α-Amino acids are obtained simply by Schiff base hydrolysis (0.5N HCl, rt) and auxiliary cleavage (LiOH, aq THF). Compound (**9b**) has also been reported to participate in analogous chemistry,[18d] but it is not crystalline and its derivatives require more vigorous hydrolysis. Commercially available (**9a**) is thus the preferred reagent, comparing favorably with other glycine anion synthetic equivalents (see ***4-t-Butoxycarbonyl-5,6-diphenyl-2,3,5,6-tetrahydro-4H-oxazin-2-one***). Promising preliminary results of deprotonation-alkylation of (**9a**) under phase transfer catalysis have also been disclosed.[1c,18c,18j]

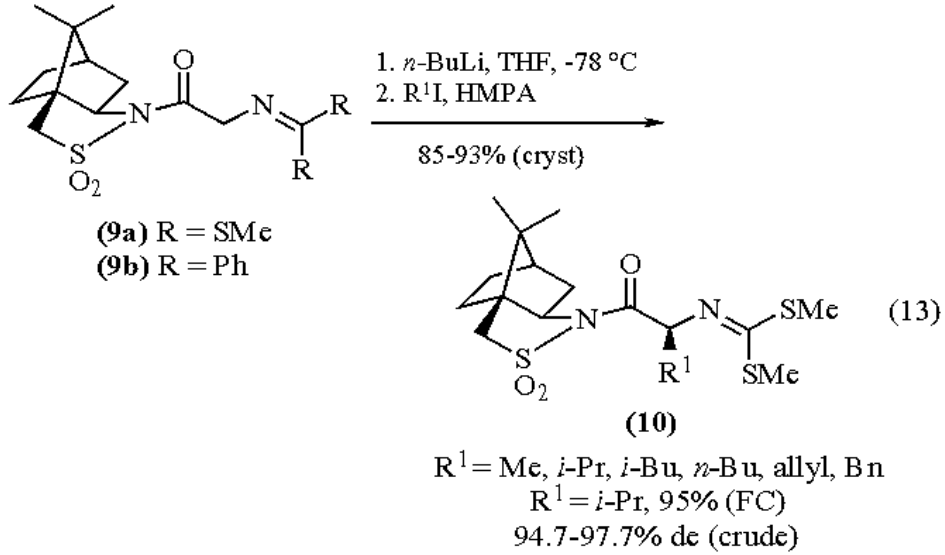

The second strategy involves a bromination-azide displacement-hydrogenolysis protocol. Treatment of boryl enolates of *N*-acylsultams (**8**) with NBS provides the key α-bromo derivatives (**11**) with good C(α)-*re* topicity (eq 14).[1c,18b] Stereospecific substitution with tetramethylguanidinium azide [$(Me_2N)_2C{=}NH_2^+N_3^-$], hydrogenolysis (H_2-Pd/C), and auxiliary cleavage provides α-amino acids in good overall yield.[1c,18b] As with the previous strategy, given that an appropriate derivative is crystallized to enantiomeric homogeneity, the enantiomeric purity of the product will reflect the extent of racemization during auxiliary hydrolysis (e.g. phenylglycine: 90.3% ee, isoleucine: >99% ee).[1c] This problem can be circumvented by the use of nonbasic Ti(O-*i*-Pr)$_4$ assisted transesterification with allyl alcohol then rhodium-catalyzed deprotection. This allows for the preparation of either free or *N*-Fmoc α-amino acids of excellent enantiomeric purity.[18e]

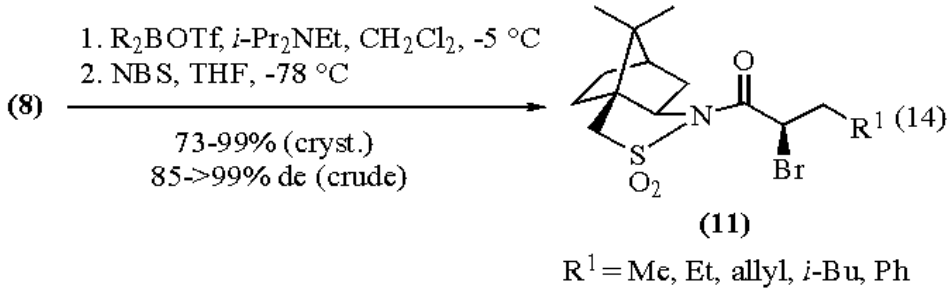

The third strategy involves electrophilic amination of sodium enolates of *N*-acylsultams (**8**) using ***1-Chloro-1-nitrosocyclohexane*** as an [NH_2^+] equivalent.[18f-i] The reaction proceeds via nitrone intermediates which are routinely hydrolyzed without isolation to give the key α-*N*-hydroxyamino derivatives (**13**) with outstanding C(α)-*re* π-facial control (eq 15). Nitrogen-oxygen bond hydrogenolysis (Zn, aq HCl, AcOH), then auxiliary cleavage, affords α-amino acids.[18f,18g] Omission of the hydrogenolysis step allows access to *N*-hydroxy-α-amino acids, which are extremely difficult to prepare by alternative means.[18f] The scope of the reaction has been extended to encompass the use of 1-chloro-1-nitrosocyclohexane as an electrophilic partner in conjugate addition-trapping reactions [allowing an expedient preparation of (2*S*,3*S*)-isoleucine],[18f,18g] *N*-alkyl-α-amino acid preparation,[18h] and homochiral α-substituted cyclic nitrone formation [giving a concise preparation of the piperidine alkaloid (-)-pinidine].[18i]

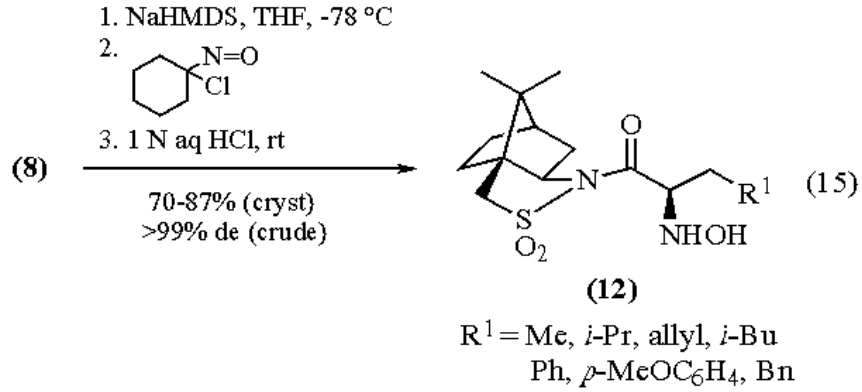

α-Radical Addition (Acyl Species -> α-Functionalized Acyl Product).[19]

Radicals derived from α-iodo-*N*-acylsultams give high levels of asymmetric induction in intramolecular addition reactions with allyltributylstannanes (85->94% de)[19a] and 5-*exo*-dig type cyclizations and annulations (eq 16).[19a] In addition, zipper type manganese(III) promoted oxidative radical cyclization of *N*-(*trans*-4-methyl-4,9-nonadienoyl)-10,2-camphorsultam gives a *cis*-fused hydrindane derivative with modest (50% de) selectivity at the α-center.[19b] All these reactions proceed at or above room temperature, making the levels of induction remarkable. Furthermore, effective alternative auxiliaries are scarce.[1d,14]

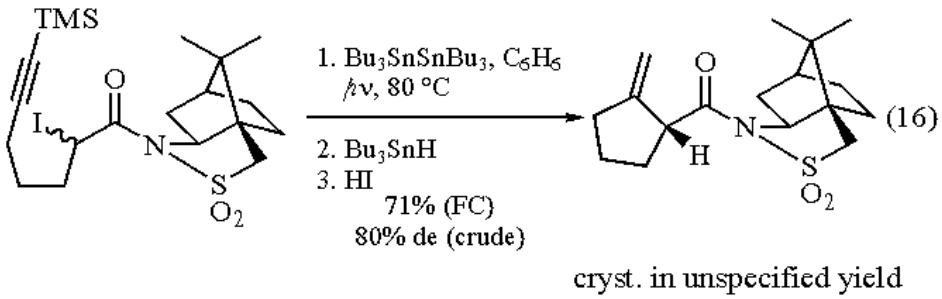

Nondestructive Auxiliary Cleavage.

One feature which makes the sultam chiral auxiliary, and to an even greater extent the related toluene-2,α-sultam auxiliaries (see ***α-Methyltoluene-2,α-sultam***), so versatile is the ease with which *N*-acyl bond fission occurs in derivatives. A great variety of extremely mild, bimolecular and intramolecular nondestructive cleavage protocols have been developed which tolerate a wide array of molecular functionality, simple extraction and crystallization usually providing almost quantitative auxiliary recovery without loss of enantiomeric purity.

Saponification with LiOH[6a] or H_2O_2-LiOH[16b] in aqueous THF is routinely employed for conversion of *N*-acylsultams to enantiomerically pure carboxylic acids. A variant conducted in aprotic media with phase transfer catalysis has also been reported.[18d] If base sensitive functionality is present, then the corresponding esters can be prepared by nonbasic titanium mediated alcoholysis. This can be accomplished with ethyl,[11b] benzyl,[4] or allyl[18e] alcohols, and in the latter two instances the carboxylic acids can be subsequently liberated by neutral hydrogenolysis or $RhCl(PPh_3)_3$ catalyzed hydrolysis,[18e] respectively. Lactones and esters can also be formed by intra-[18j] and intermolecular[2d] sultam cleavage with lithium alkoxides and bromomagnesium alkoxides.[11d] β-Lactams can be prepared by intramolecular ring closure of metallated β-aminomethyl derivatives[1b,17a] and an aluminum thiobenzyloxy ate complex has been used to obtain thioester derivatives.[13] Reductive cleavage of *N*-acylsultams using lithium aluminum hydride[2f] or L-Selectride®[3b,3f] in THF gives rise to the corresponding primary alcohols.

Auxiliary cleavage with concomitant carbon-carbon bond formation is a particularly attractive option, which has been demonstrated in a bimolecular sense using the dianion of methyl sulfone (giving a methyl ketone),[16f] and in an intramolecular sense using a Claisen-type condensation of a β-acetoxy enolate (giving a δ-lactone).[25] An interesting halolactonization procedure has also been devised; for certain α-aryl-bis-(γ-unsaturated)-*N*-acyl derivatives this allows for highly efficient auxiliary cleavage and asymmetric formation of two stereocenters, one of which is quaternary (eq 17), the key step in a synthesis of (-)-mesembrine).[26]

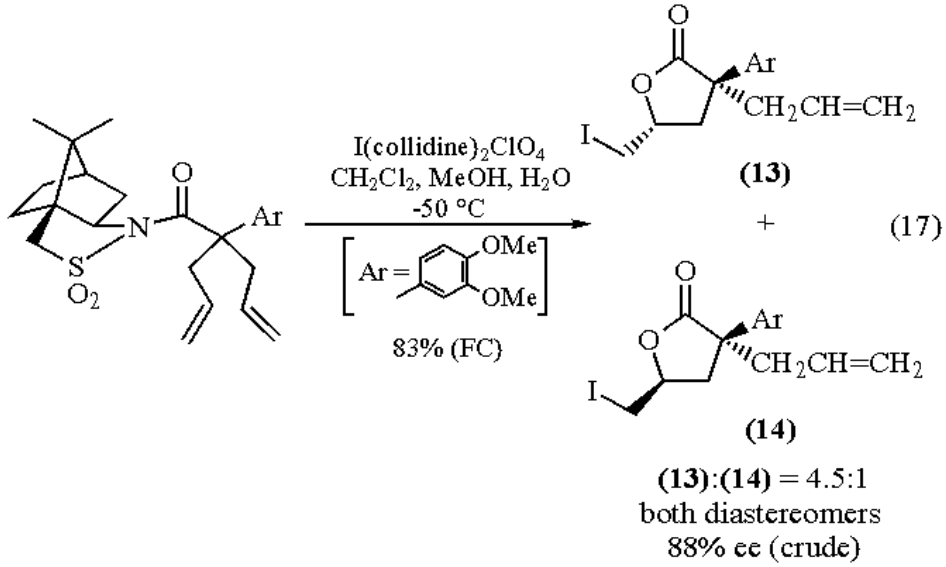

Enantioselective, Electrophilic Fluorination.

(-)-*N*-Fluoro-10,2-camphorsultam (**3**) [mp 112-114 °C (CH_2Cl_2-pentane)] is an enantioselective, electrophilic fluorinating agent.[20] Fluorination of stabilized enolates occurs with highly variable yield (5-63%) and stereoselectivity (10-70% de).

Related Reagents.

10-Dicyclohexylsulfonamidoisoborneol; ***2-Hydroxy-1,2,2-triphenylethyl Acetate***; ***(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline***; ***α-Methyltoluene-2,α-sultam***; ***(S)-4-Benzyl-2-oxazolidinone***.

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Carbon Dioxide[1]

O=C=O

[124-38-9] · CO_2 · Carbon Dioxide · (MW 44.01)

(agent for the carboxylation of phenols,[2] organometallic reagents[3] and various carbanions, and for the preparation of dialkyl carbonates, urethanes, and ureas[1])

Physical Data: bp -78.5 °C (sub); critical temp 31.06 °C; vapor pressure 6300 kPa at 25 °C; mp -56.6 °C (at 5.2 atm); density: solid: 1.56 g cm^{-3} (at -79 °C); liquid: 1.101 g cm^{-3} (at -37 °C); gas: 1.977 g L^{-1} (at 0 °C).

Solubility: 75.9 mL/100 mL in H_2O at 20 °C and 101.3 kPa; 31 mL/100 mL in EtOH at 15 °C.

Form Supplied in: solid pellets (dry ice); compressed gas or liquid. *Drying:* pass gas through conc H_2SO_4 or a column of anhydrous calcium sulfate.

Handling, Storage, and Precautions: colorless, odorless gas which is dangerous to respiration at high concentrations; TLV = 5000 ppm.

Carboxylation of Phenoxides.

The reactions of sodium or potassium phenoxides with carbon dioxide under pressure (the Kolbe-Schmitt reaction) or of phenols with anhydrous ***Potassium Carbonate*** (Marasse modification) are a very important source of hydroxy aromatic acids.[2] Carboxylation is favored at the *ortho* position, but *para* isomers may also be obtained at higher temperatures (eq 1). Depending on the reaction conditions, 2-naphthol may be converted into either the 1-carboxylic acid (<150 °C) or the 3-isomer (>200 °C) (eq 2). Carboxylation is retarded by electron withdrawing groups, but enhanced by electron releasing substituents. Resorcinol, for example, is carboxylated simply by bubbling CO_2 through an alkaline solution (eq 3).[4]

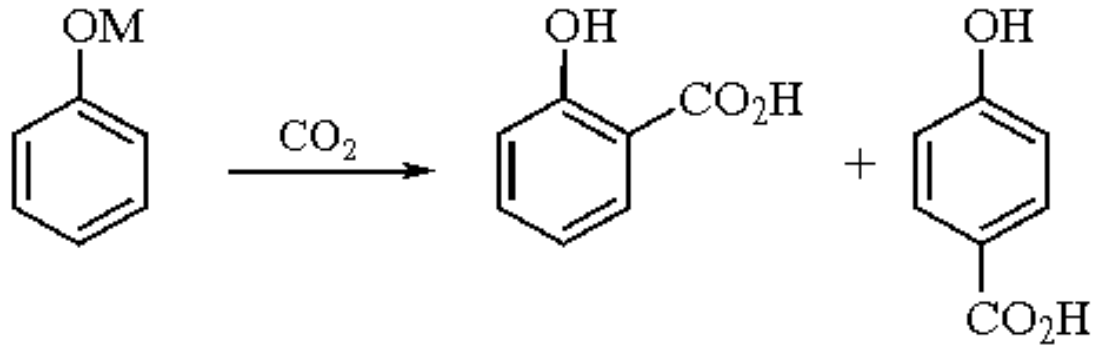

(1)

Na salt (150 °C, 80% yield) 97: 2
K salt (210 °C, 48% yield) 4:96

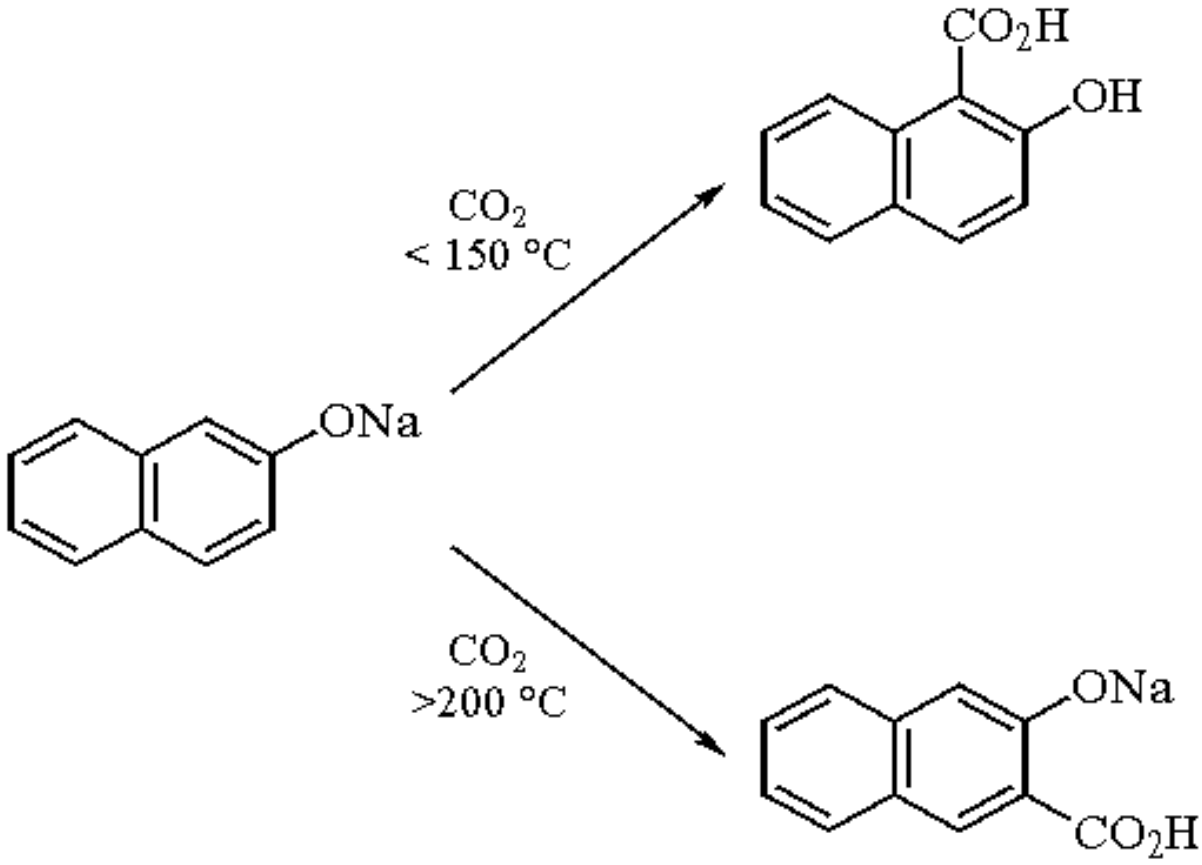

(2)

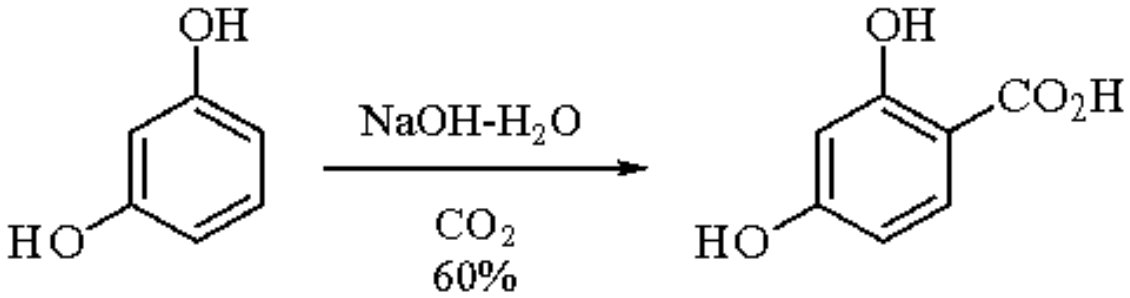

(3)

Carboxylation of Organometallic Derivatives.

Carbon dioxide inserts readily into metal-carbon bonds with two possible outcomes (eq 4).[5] By far the most familiar and common pathway is the formation of a new carbon-carbon bond leading to a carboxylic acid, as in the very familiar reactions[6] of Grignard reagents and organolithium compounds (eqs 5 and 6),[7,8] although care must be taken to use low temperatures and an excess of CO_2 in order to avoid further reaction of the product with additional reagent.

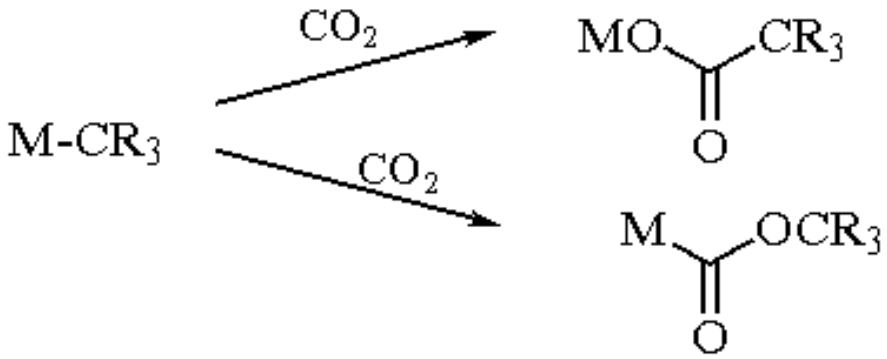

(4a)

(4b)

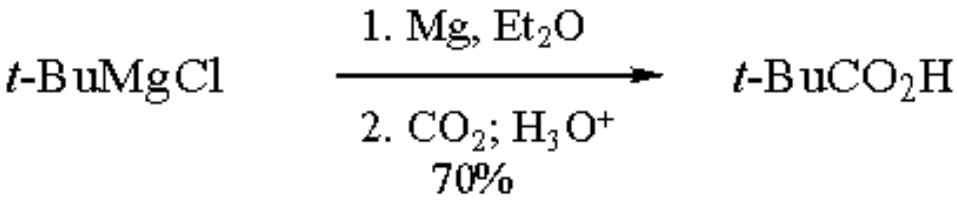

(5)

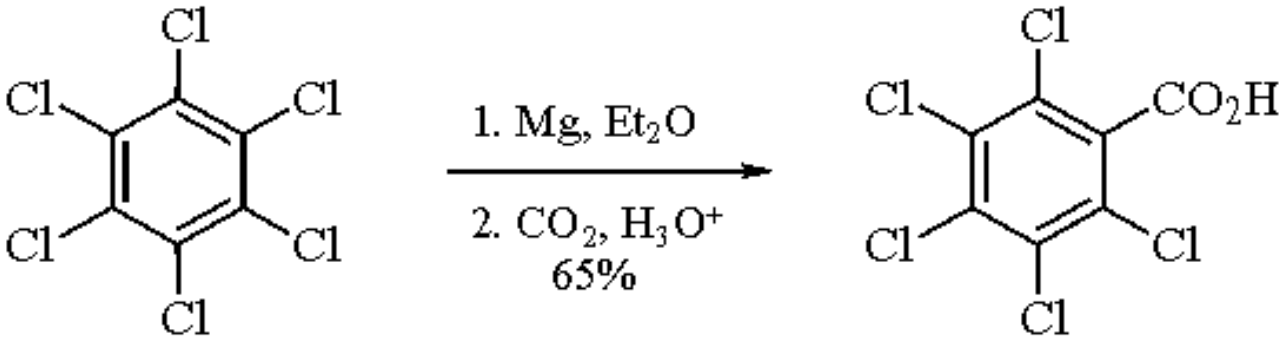

(6)

In a few special cases, however, carbon-oxygen bond formation may take place (eq 4b), as in the reaction of the cobalt complex (**1**) to form (**3**) in addition to the expected (**2**) (eq 7).[9] Treatment of (**3**) with ***Hydrogen Chloride*** afforded ethyl formate, while reaction with ***Iodomethane*** afforded ethyl acetate in high yield. Another example of carbon-oxygen bond formation was observed during the reaction of a methallyl palladium π-complex with CO_2 (eq 8), although this could be suppressed by the addition of ***1,2-Bis(diphenylphosphino)ethane*** (diphos).[10]

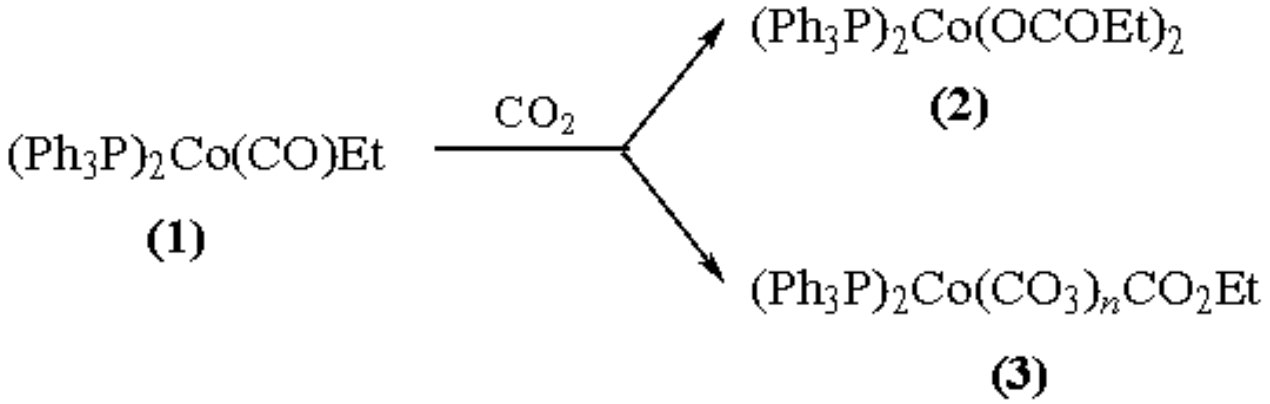

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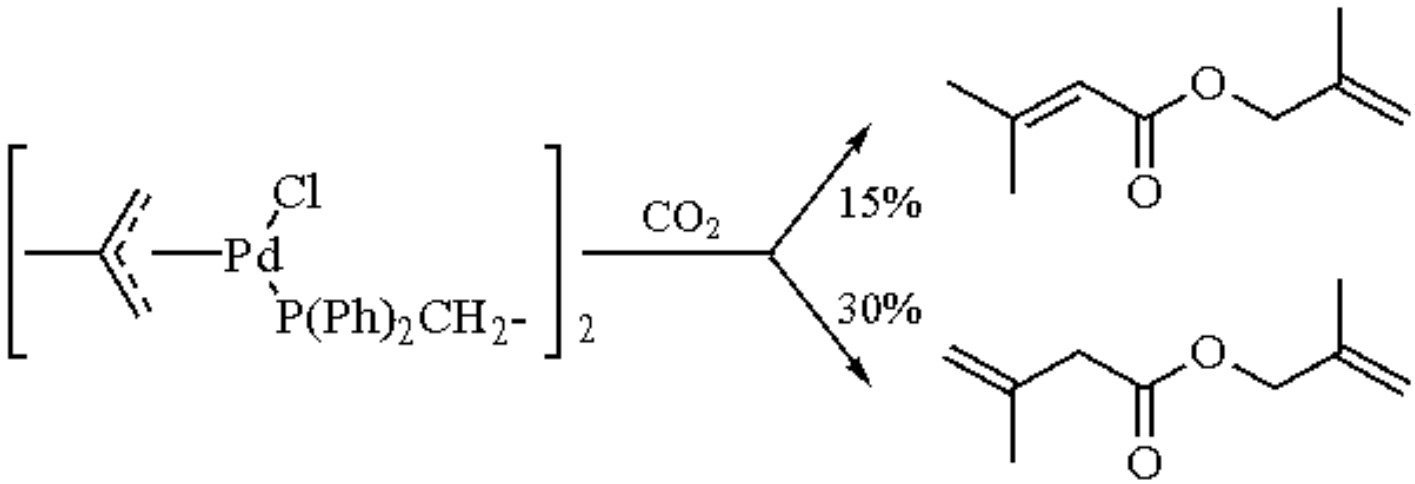

(8)

The reaction of diethylzinc with CO_2 is very slow, but it may be accelerated by ligands such as ***N,N,N´,N´-Tetramethylethylenediamine*** or ***N-Methylimidazole***.[11] Vinyl and aryl copper reagents are similarly unreactive, but again they may be activated by the addition of suitable ligands, as in the stereoselective synthesis of β-substituted acrylic acids from alkynes (eq 9).[12]

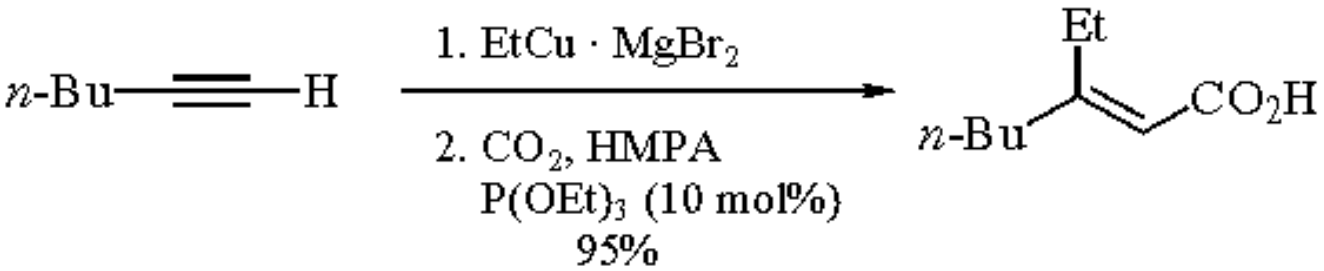

(9)

The heteroatom facilitated lithiation of sp^2 carbon, including the lithiation of heterocycles and the directed lithiation of aromatic compounds, is a powerful and flexible synthetic strategy.[13] The intermediates react with CO_2 in good to excellent yields to form carboxylic acids which, in many cases, could otherwise be obtained only with considerable difficulty. Carboxylation is strongly favored at C-2 in the common heterocycles: furan, pyrrole, thiophene, imidazole, oxazole, thiazole, pyridine, pyrimidine, benzofuran, indole, benzothiophene, and their derivatives.[14] For benzenoid aromatic derivatives, reaction occurs at *ortho* (eqs 10 and 11)[15,16] or benzylic sites (eq 12),[17] but neighboring positions in a second aromatic ring may also participate (eqs 13 and 14).[18]

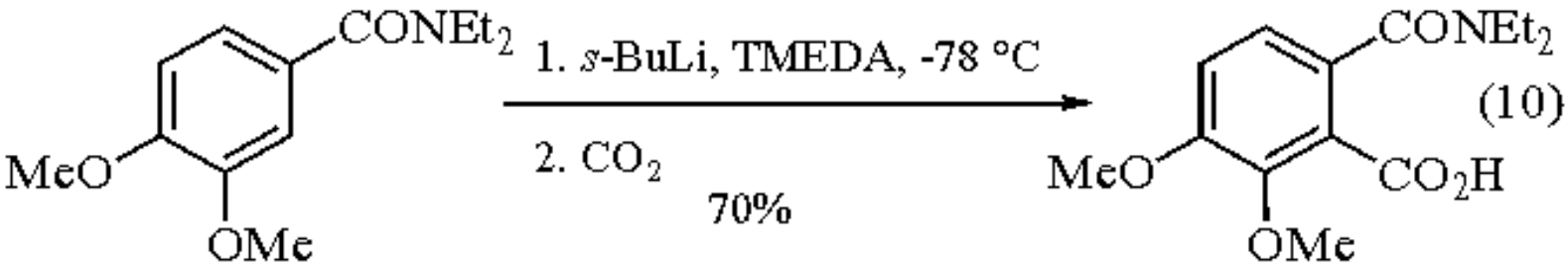
CONEt2
1. s-BuLi, TMEDA, -78 °C
2. CO2
70%
MeO
OMe
CONEt2
CO2H
MeO
OMe

(10)

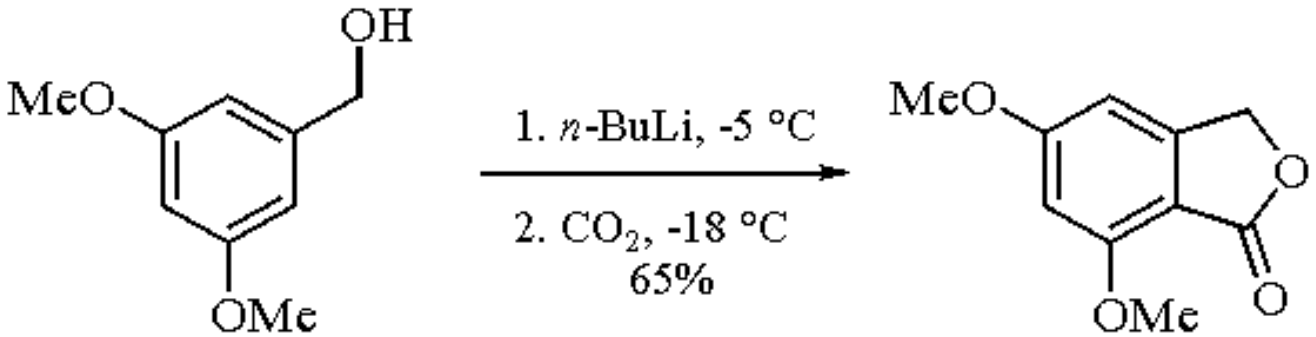
OH
MeO
OMe
1. n-BuLi, -5 °C
2. CO2, -18 °C
65%
MeO
O
O
OMe

(11)

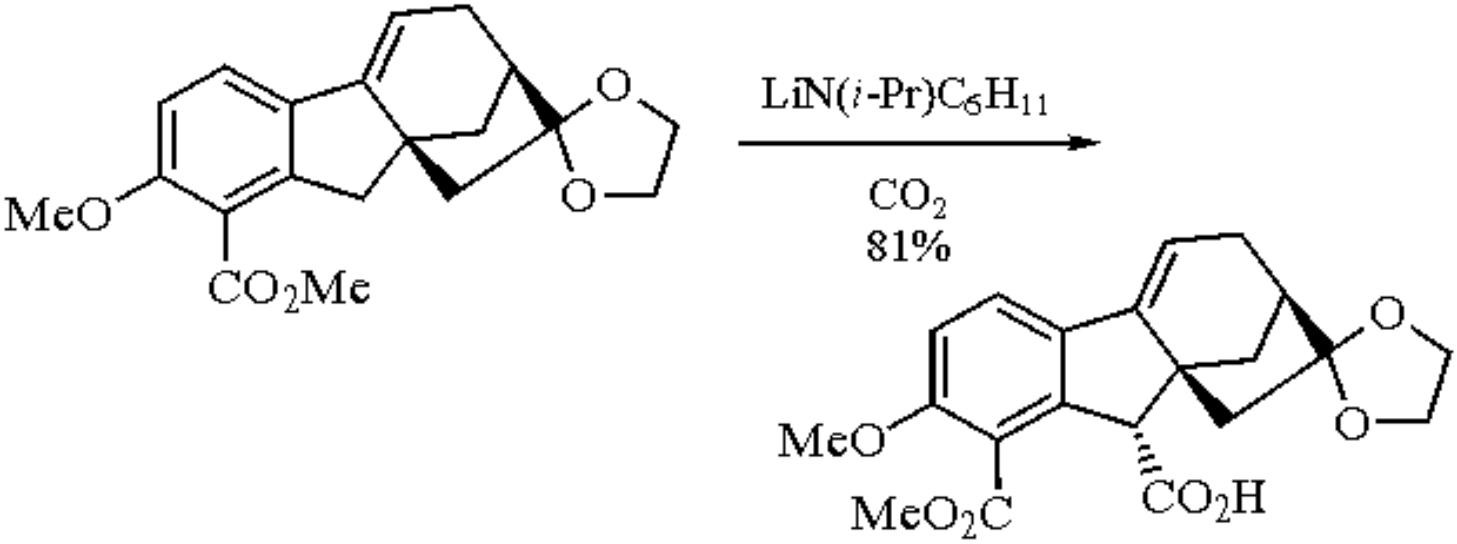
O
O
MeO
CO2Me
LiN(i-Pr)C6H11
CO2
81%
O
O
MeO
MeO2C
CO2H

(12)

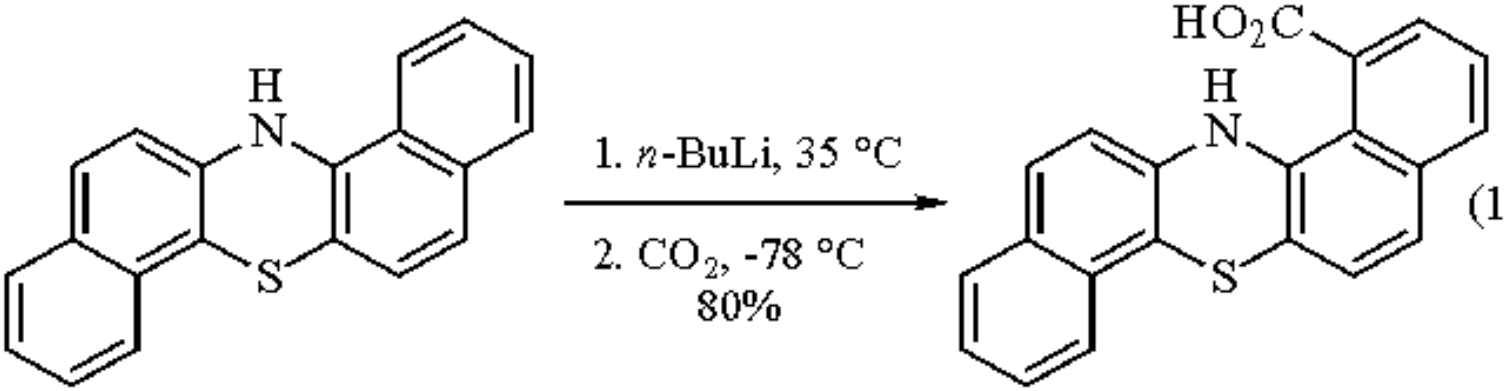
H
N
S
1. n-BuLi, 35 °C
2. CO2, -78 °C
80%
HO2C
H
N
S

(13)

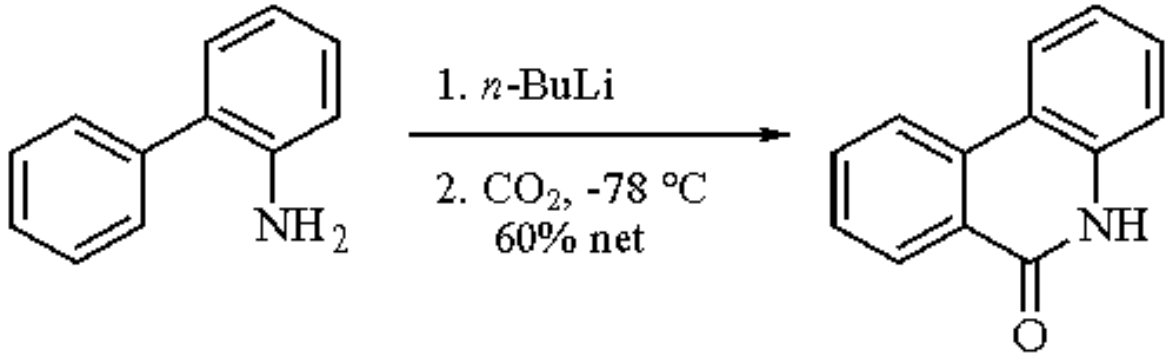

(14)

Carboxylation of Ketone Enolates and Other Carbanions.

Ketones may be converted into β-keto acids by treatment with CO_2 in the presence of a variety of bases, e.g. potassium phenoxide,[19] lithium 2,6-di-*t*-butyl-4-methylphenoxide,[20] ***Triethylamine-Magnesium Iodide***,[21] and ***1,8-Diazabicyclo[5.4.0]undec-7-ene***,[22] and with ***Methyl Magnesium Carbonate***.[23] Several urea-based magnesium complexes, inspired by the biotin carboxylases, have also been utilized.[24] There has been considerable interest in the trapping of preformed enolates with CO_2 (eqs 15 and 16),[25] especially under conditions of kinetic control.[26]

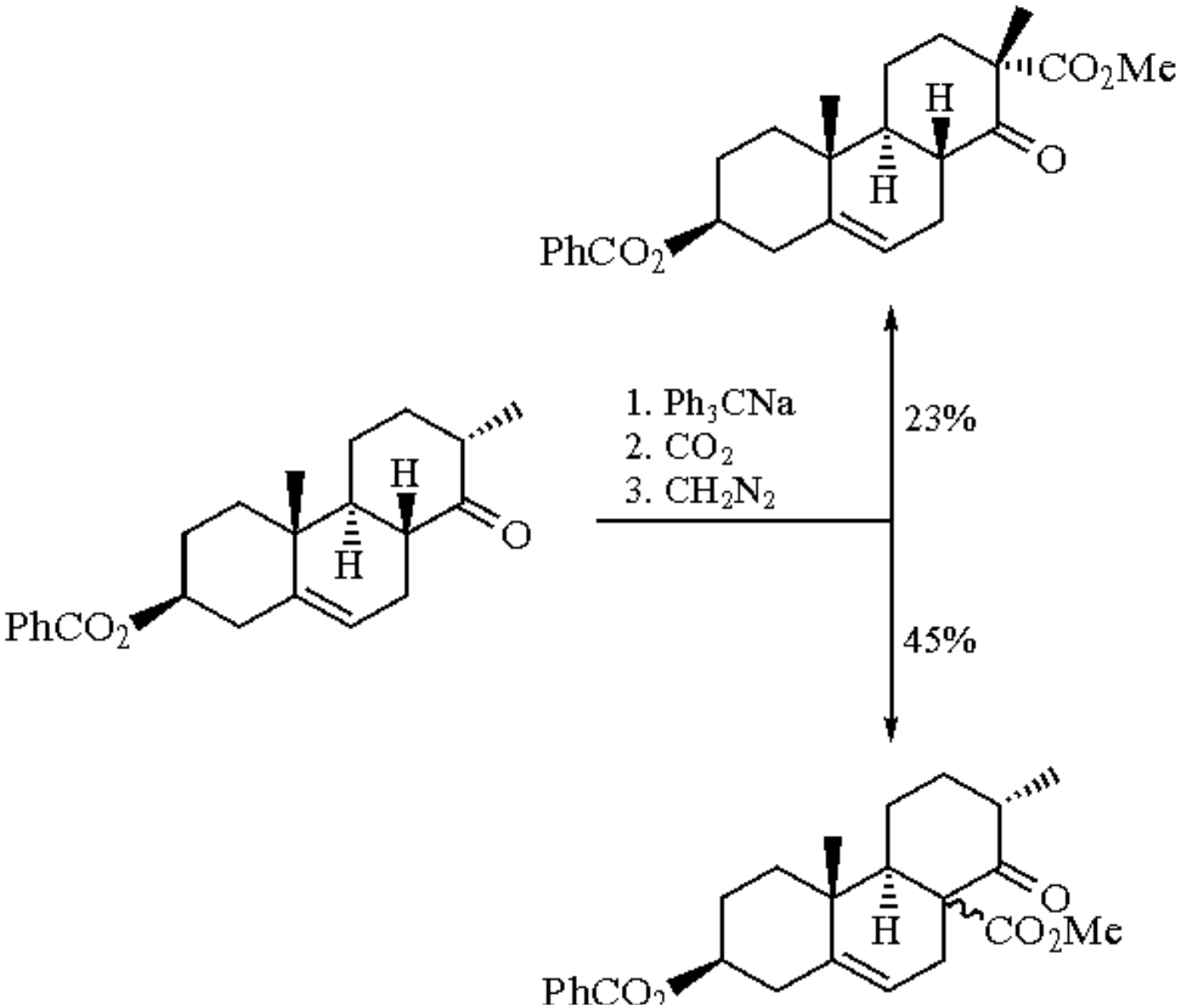

(15)

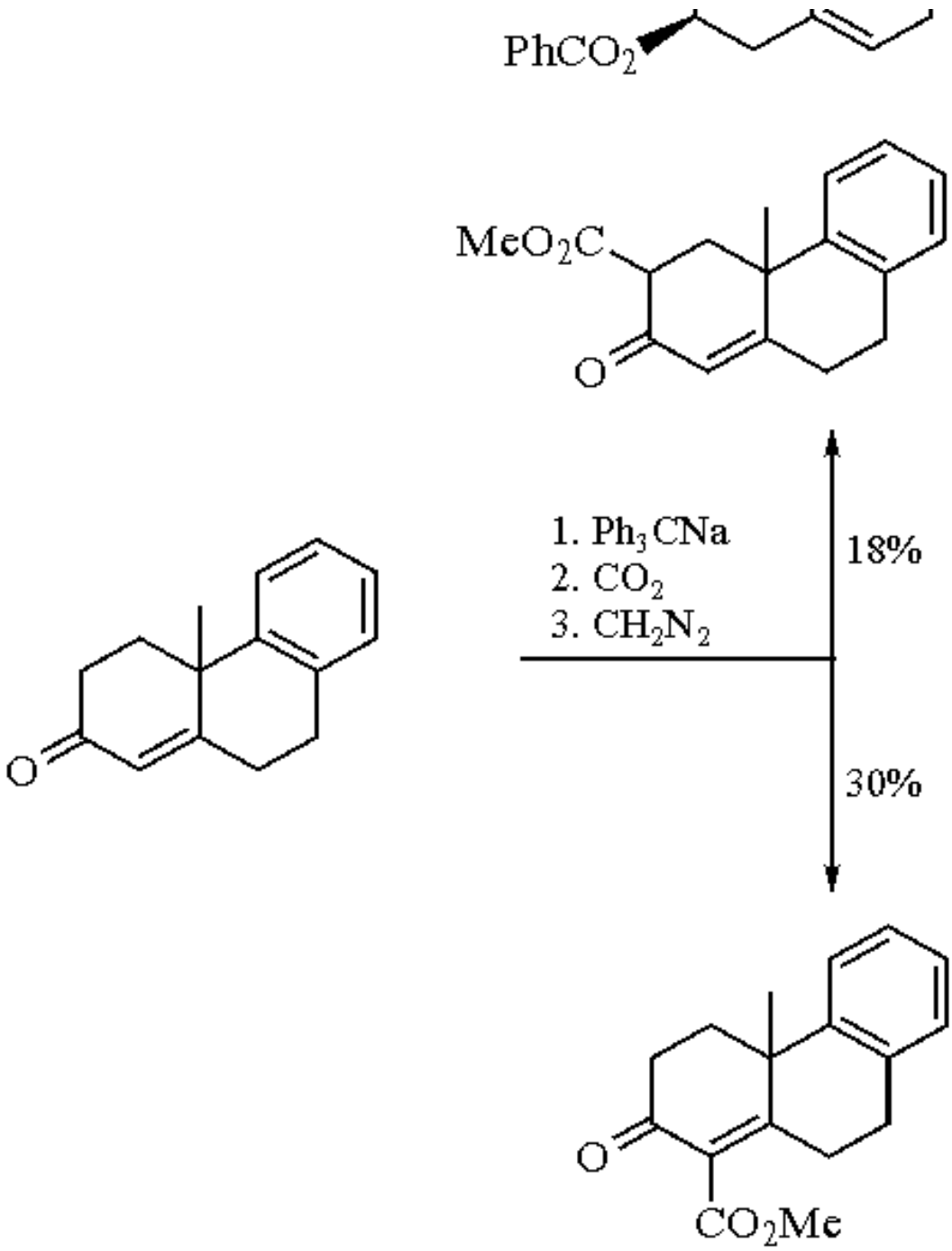

(16)

Yields are only poor to fair in most cases, probably because of the competing formation of enol carbonates[27] which decompose to the parent ketone on workup and/or the instability of the β-keto acid products. The successful trapping of enolates from Li/NH_3 reduction of enones (eq 17)[26,28] and *n*-butylthiomethylene ketones (eq 18)[29] has been reported.

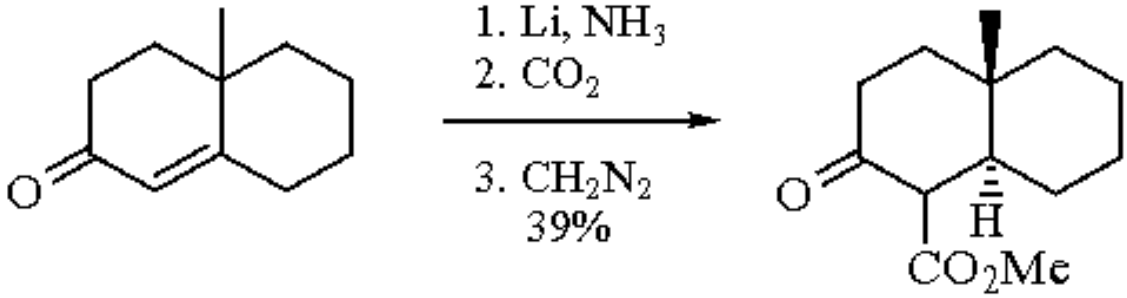

(17)

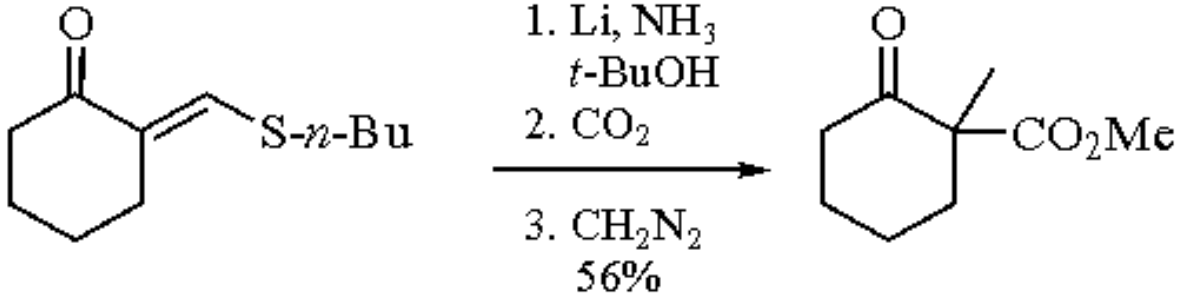

(18)

Carboxylation of Miscellaneous Carbanions.

In addition to ketones, various other carbanions have been carboxylated, including those from esters,[30] dithianes,[31] and aldimines,[32] as have phosphoranes.[33]

Preparation of Dialkyl Carbonates, Urethanes, and Ureas.

Alcohols may be converted into symmetrical dialkyl carbonates by reaction with a combination of CO_2, ***Triphenylphosphine***, and ***Diethyl Azodicarboxylate***,[34] while cyclic carbonates may be obtained from the reaction of epoxides with CO_2 with catalysis by a range of Lewis acids.[35] Allylic epoxides react with CO_2 and ***Palladium(II) Acetate*** plus ***Triisopropyl Phosphite*** to form cyclic carbonates with retention of configuration.[36]

Allylic and homoallylic alcohols may also be transformed into cyclic carbonates by conversion of the derived lithium alkoxides into hemicarbonates followed by in situ cyclization with iodine (eq 19).[37] Amines have been converted into urethanes by a mixture of ***Copper(I) t-Butoxide***, ***t-Butyl Isocyanide***, and CO_2[38] and into symmetrical ureas by treatment with Et_3N, ***1,3-Dicyclohexylcarbodiimide***, and CO_2.[39]

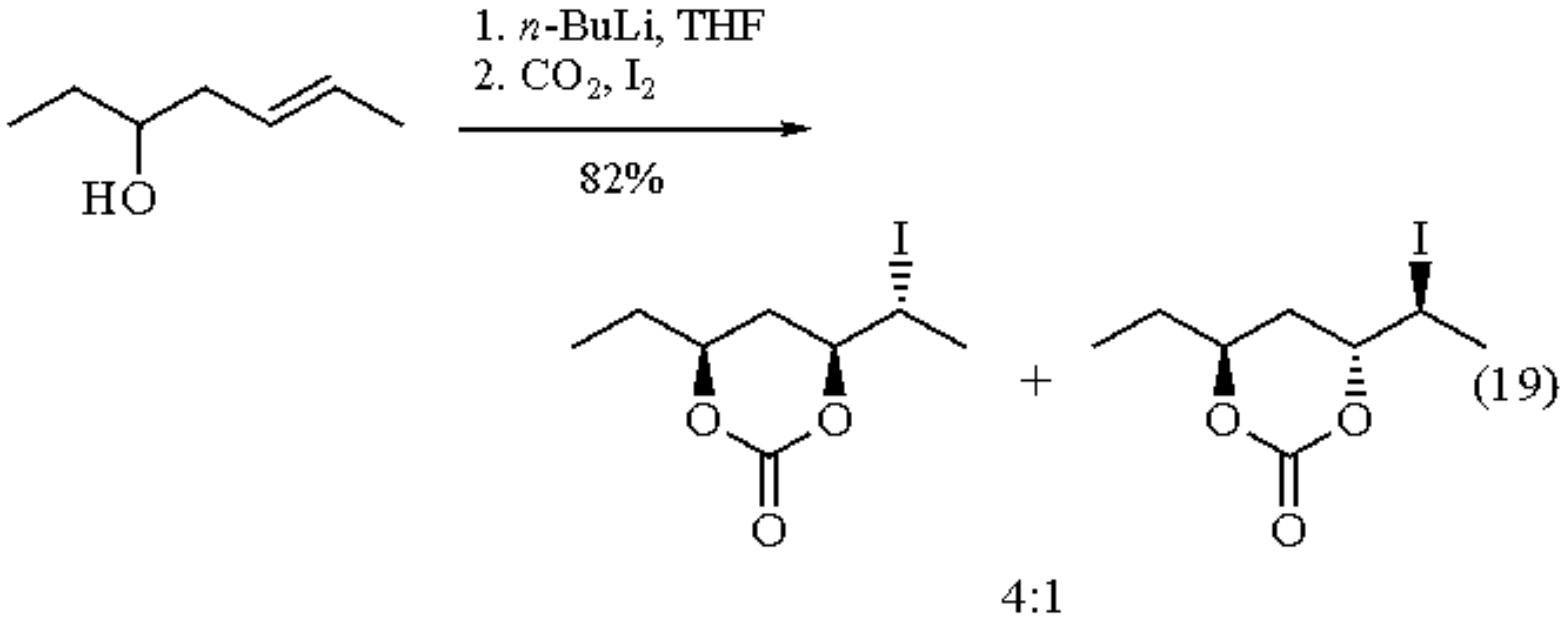

(19)

Related Reagents.

N,N´-Carbonyldiimidazole; ***Diethyl Carbonate***; ***Methyl Magnesium Carbonate***; ***Methyl Chloroformate***; ***Methyl Cyanoformate***.

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Carbon Disulfide[1]

CS_2

[75-15-0] · CS_2 · Carbon Disulfide · (MW 76.14)

(starting material for the synthesis of various sulfur and heterocyclic compounds;[1] protecting group for secondary amines[2])

Physical Data: mp -111.6 °C; bp 46.3 °C; *d* 1.26 g cm^{-3}; flashpoint -30 °C; fire point 102 °C.

Solubility: sol alcohol, ether, THF, benzene, CCl_4, $CHCl_3$; insol cold H_2O.

Form Supplied in: colorless liquid; discolors to yellow under influence of light.

Handling, Storage, and Precautions: should be stored in brown bottles in absence of light. CS_2 forms explosive mixtures with air (explosion limit 1-60 vol %). CS_2 is teratogenic. Constant inhalation or constant resorption through the skin cause chronic symptoms of poisoning, e.g. sight defects and headache. Inhalation of concentrated CS_2 vapor can be lethal. Use in a fume hood.

Reactions with Organometallic Compounds.

Grignard Reagents.

Treatment of CS_2 with Grignard reagents RMgX (**1**) leads to dithioesters (**2**) (eq 1).

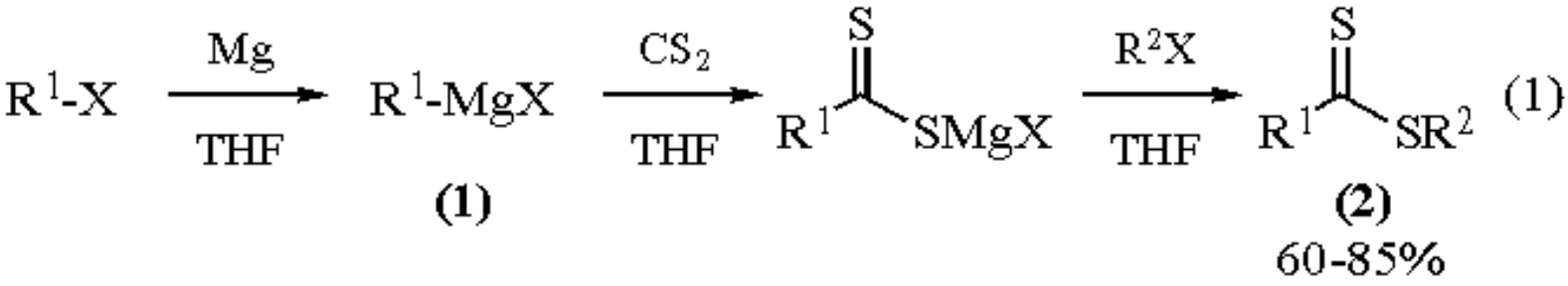

If THF is used as solvent, dithioesters can be obtained in 60-85% yield.[3] This method fails when *t*-alkyl- or cyclohexylmagnesium halides are used. With diethyl ether as solvent, the dithioesters are obtained in poor yields.[4] The reaction of CS_2 with an allylic Grignard reagent followed by methylation affords the dithioesters (**3**), bearing an

inverted allylic chain as expected.[5] Treatment of (**3**) with first ***Lithium Diisopropylamide***, then with ***Iodomethane***, leads to an isoprenic ketene dithioacetal (**4**) (eq 2).

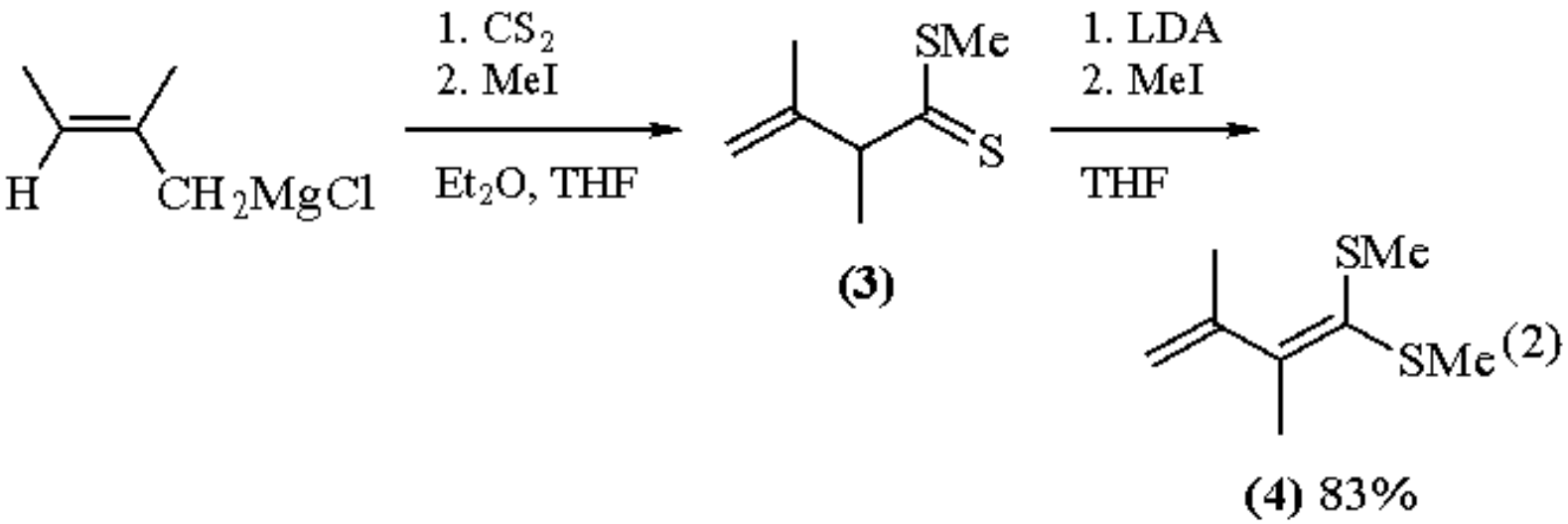

It is also possible to prepare various ketene dithioacetals in a one-pot synthesis with Grignard reagents and CS_2 as starting materials.[6]

Organocopper Reagents.

When catalytic amounts of ***Copper(I) Bromide*** are used, the reaction of CS_2 with Grignard reagents leads to dithioesters in 80-100% yield (eq 3).[7]

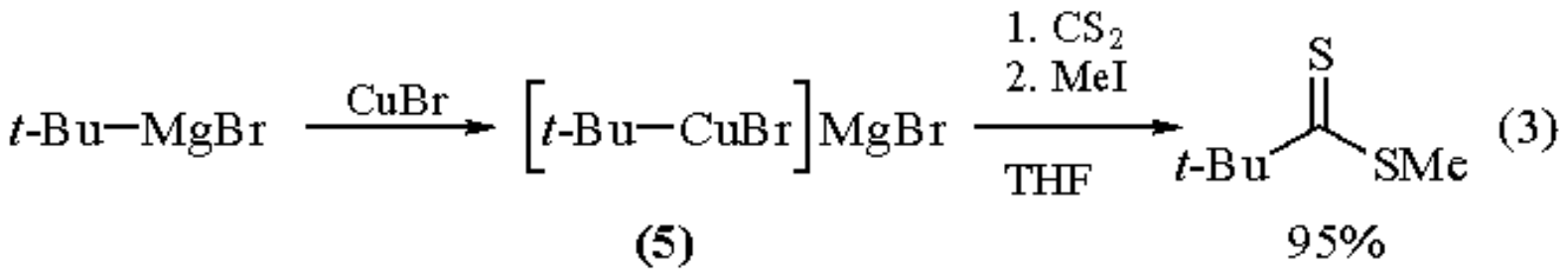

The organocopper(I) compound (**5**) is the reacting species.[7a] With this method, halides containing bulky groups can also be converted to dithioesters.

Reactions with Alcohols.

Treatment of alcohols with sodium hydroxide and CS_2 and subsequent reaction with an alkyl halide, usually methyl iodide, leads to *O*-alkyl *S*-methyl dithiocarbonates which can be pyrolyzed to alkenes (Tschugaeff reaction) (eq 4).[8]

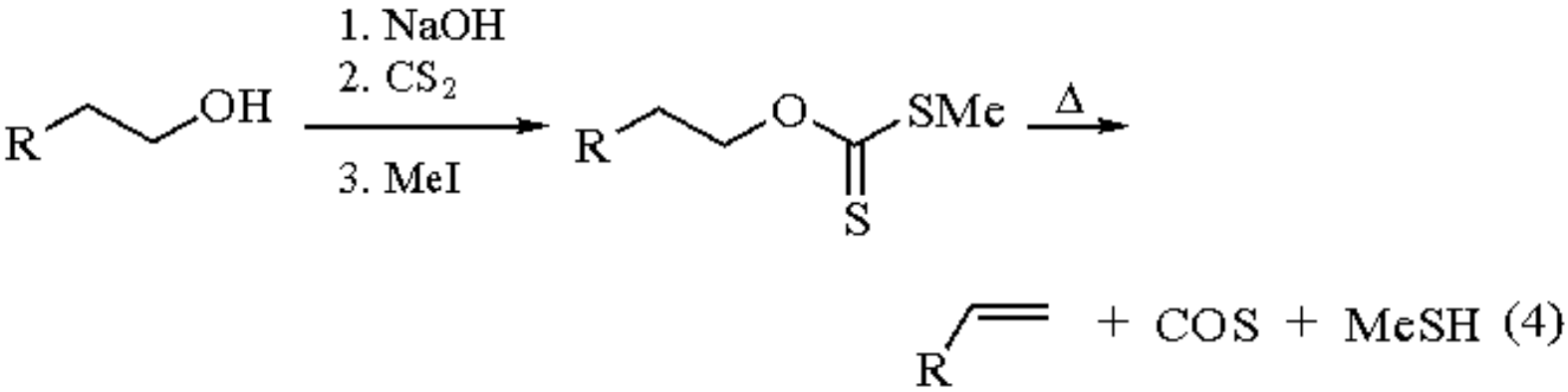

Formation of the metal salt of the alcohol can be difficult.[9] If ***Sodium Methylsulfinylmethylide*** in DMSO is used as base, the dithiocarbonates can be prepared in good yields.[10] The decomposition temperature is lowered when pyrolysis is also carried out in DMSO.[11]

Vicinal diols react with CS_2 under basic conditions, to give the corresponding bis-dithiocarbonates. Reduction with ***Tri-n-butylstannane*** in toluene[12] gives high yields of the alkenes.

Recently, a variety of reducing agents has been developed to convert dithiocarbonates derived from alcohols, especially secondary ones, to alkanes. The hydroxy function can be selectively replaced by hydrogen under mild conditions, with tri-*n*-butylstannane,[13a] tri-*n*-butylstannane/***Triethylborane***,[13b] or ***Tris(trimethylsilyl)silane***/***Azobisisobutyronitrile***[13c] as radical-based reducing agents.

Reaction with Amines.

Primary Amines.

Treatment of primary amines with base and CS_2 leads to isothiocyanates via the dithiocarbamate derivatives.[14] Alkyl or aryl amines which do not contain groups that react with butyllithium, can be converted in 55-99% yield to the corresponding isothiocyanates. The amines are treated with an equimolar amount of ***n-Butyllithium*** and CS_2 to give the lithium dithiocarbamate (**6**). Subsequent reaction with *n*-butyllithium and CS_2 forms the complex (**7**). Loss of Li_2CS_3 leads to an isocyanate (eq 5).[15]

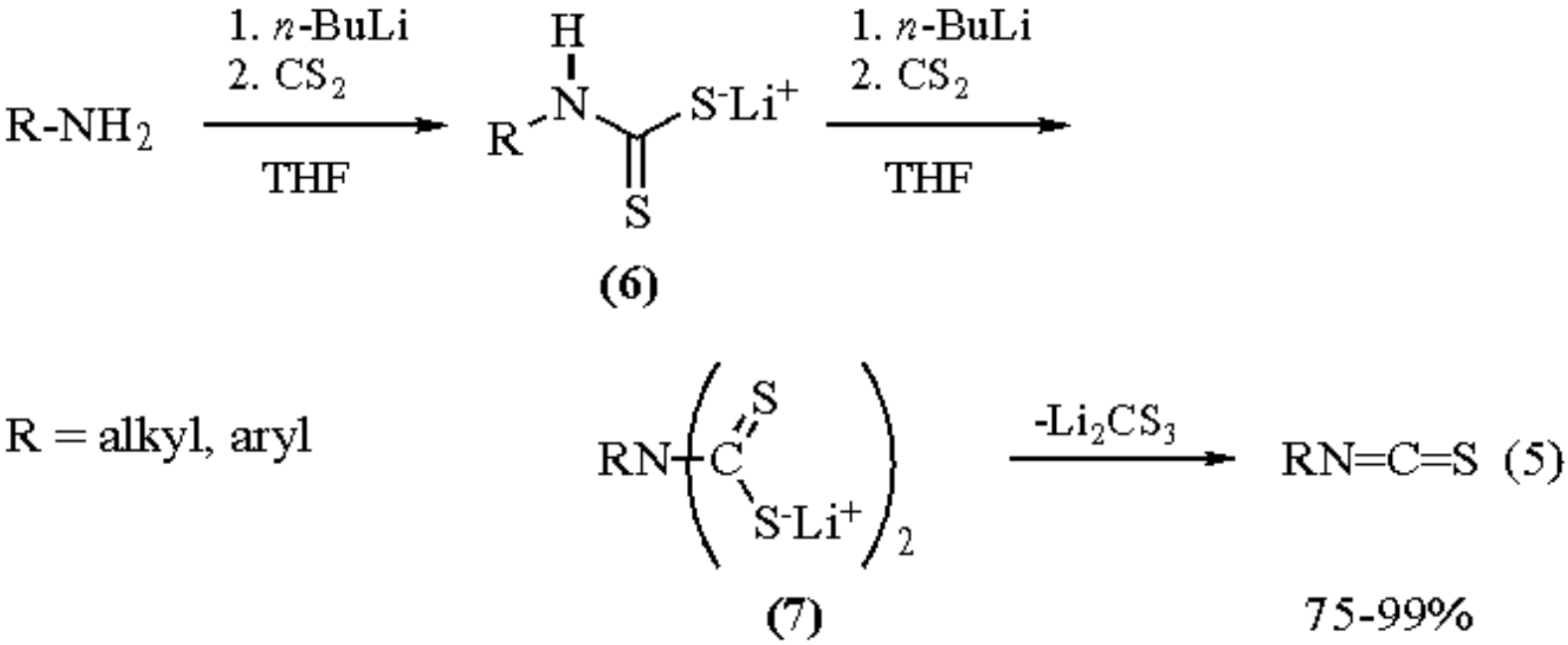

Diamines.

Aliphatic diamines react with CS_2 to give betaines (**8**). After pyrolysis of (**8**), cyclic thiourea derivatives are obtained (eq 6).[16]

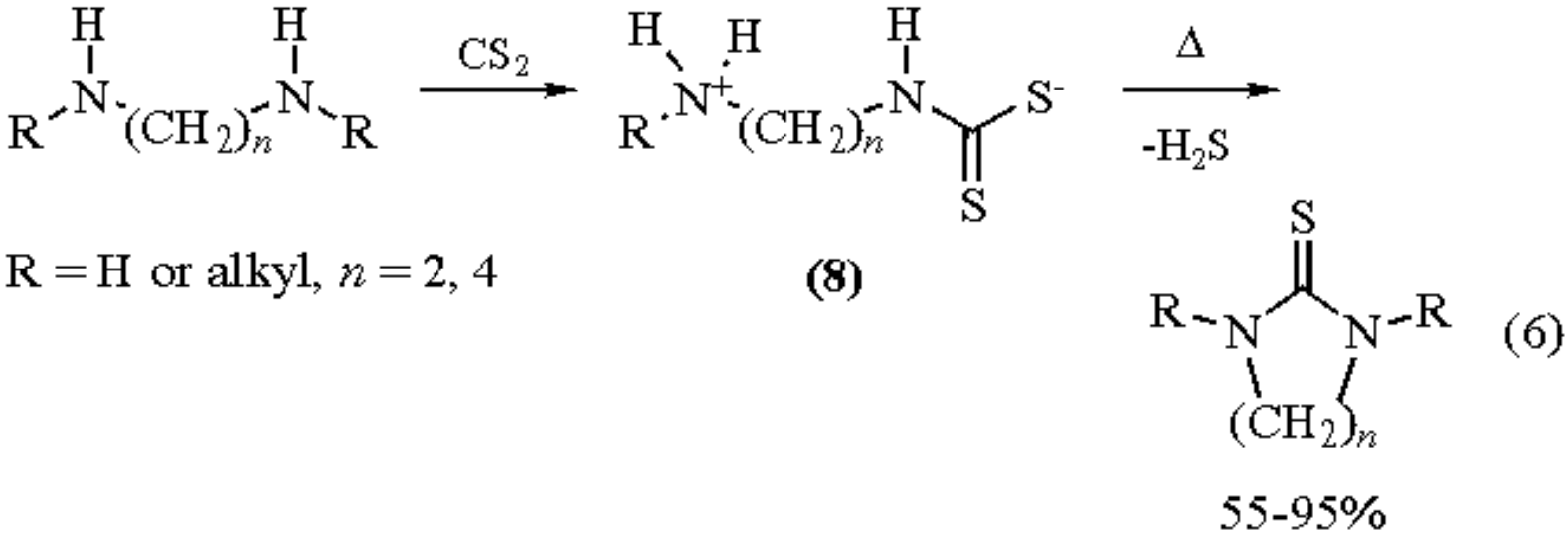

In the same way, 1,2-diarylamines and their hetero analogs can be converted to heterocyclic compounds.[17]

Secondary Amines.

Treatment of secondary amines with base and CS_2 leads to the corresponding dithiocarbamates.[18] Dithiocarbamates of functionalized secondary amines form heterocyclic compounds.[19] For example, monoalkylaminobutynes (**9**) react readily with CS_2 to give 4-methyl-3-alkyl-5-methylenethiazolidine-2-thiones (**10**) (eq 7).[20]

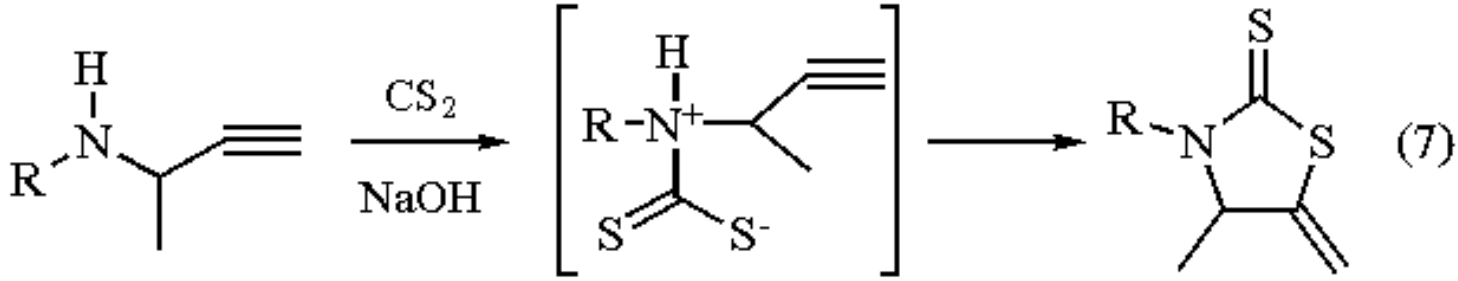

(9)
R = alkyl, benzyl

(10)
58-87%

Protecting Group.

As mentioned above, under basic conditions, secondary amines form with CS_2 dithiocarbamates. Subsequent reaction with an organometallic base and one equivalent of electrophile gives, in good yields, the secondary amines substituted in the α-position (eq 8).[2,21]

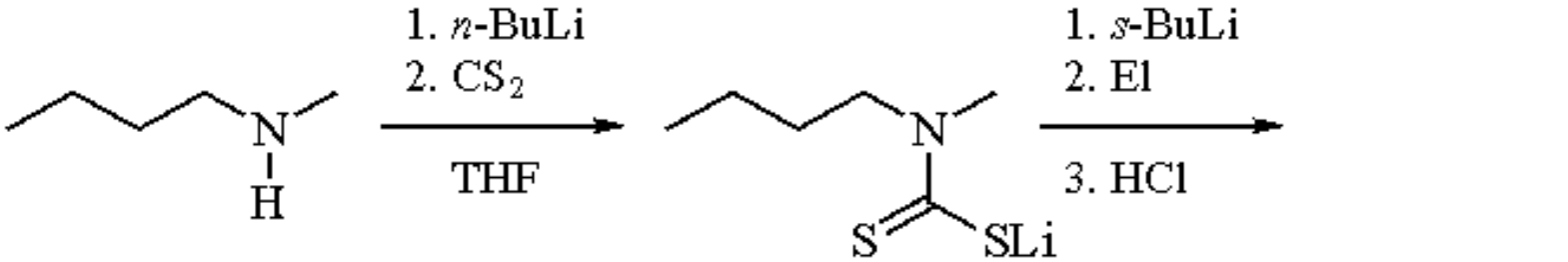

Electrophile (El) = alkyl halogenides, carbonyl compounds

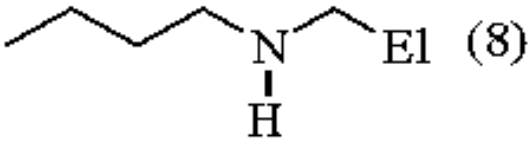

68-87%

The natural reactivity at α-position is umpoled.[22] This is a simple and versatile method for nucleophilic aminoalkylation[23] in a one-pot procedure. The reaction can be applied to numerous aliphatic and aromatic secondary amines.

Reactions with Enolizable Hydrogen Compounds.

Enamines.

Reactions of enamines with CS_2 afford several heterocycles.[24] Treatment of cyclic enamines with CS_2 leads to 1,4-dipoles (**11**) (eq 9).

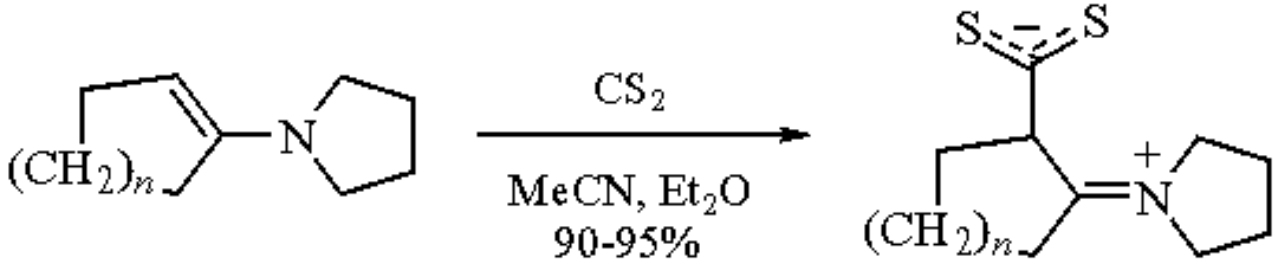

(9)

$n = 1, 2, 3$ **(11)**

In the absence of moisture the 1,4-dipoles (**11**) can be stored for several days at 0 °C. Further reactions with electrophiles lead to various heterocycles.[25]

Carbonyl Compounds.

In the case of aldehydes, only self-condensation products are obtained, whereas aliphatic ketones usually form the corresponding dithiocarboxylates or α-ketoketene dithioacetals.[26] If cyclic ketones are used, occurrence of carbon-carbon cleavage or formation of α-ketoketene acetals depend on the steric demands of the base. Treatment of cyclohexanone with lithium 4-methyl-2,6-di-*t*-butylphenoxide (**12**) (readily obtained by treatment of the phenol with *n*-butyllithium) and CS_2, followed by methylation, leads via the dithiocarboxylate ion (**13**) to the α-ketoketene dithioacetal (**14**) (eq 10).[27]

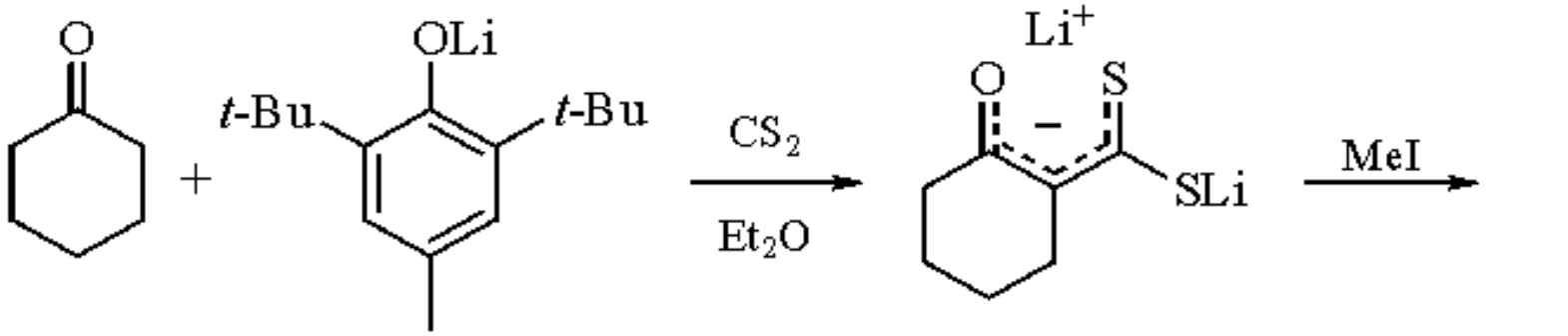

(12) **(13)**

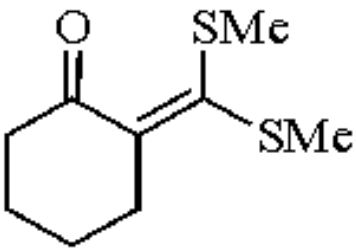

(10)

(14) 86%

If the reaction is carried out with lithium methoxide as base, 1,1-dithiodicarboxylic acid ester (**15**) is formed (eq 11).[28]

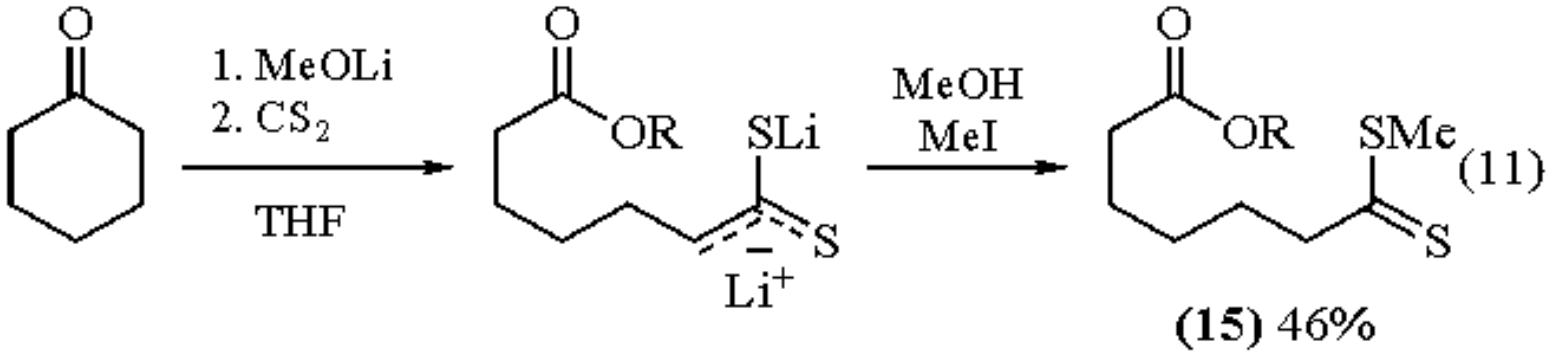

This carbon-carbon cleavage in cyclic ketones corresponds to an inverse Dieckmann-type reaction. Bulkier alkoxides like ethoxide or isopropoxide afford only α-ketoketene dithioacetals.[27]

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HCA **1980**, *63*, 102. (h) Seebach, D.; Yoshifuji, M. *HCA* **1981**, *64*, 643. (i) Beak, P.; Zajdel, W. J. *JACS* **1984**, *106*, 1010. (j) Gawley, R. E.; Hart, G.; Goicoechea-Pappas, M.; Smith, A. L. *JOC* **1986**, *51*, 3076. (k) Meyers, A. I.; Dickman, D. A. *JACS* **1987**, *109*, 1263. (l) Gawley, R. E. *JACS* **1987**, *109*, 1265. (m) Gonzales, M. A.; Meyers, A. I. *TL* **1989**, *30*, 43.
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Carbon Monoxide[1]

CO

[630-08-0] · CO · Carbon Monoxide · (MW 28.01)

(carbonylation of various organic compounds[1])

Physical Data: mp -205.0 °C; bp -191.5 °C; *d* 1.250 g L^{-1} (*d*04 at 760 mmHg).

Solubility: appreciably sol some organic solvents, such as EtOAc, $CHCl_3$, acetic acid.

Form Supplied in: cylinder types, valves, and pressure regulators.

Preparative Methods: may be generated by the dehydration of formic acid.

Purification: major impurities are CH_4 (~0.2%), N_2 (~0.5%), H_2, and O_2. O_2 can be removed from CO by passing the gas through a short bed of reduced Cu or MgO_2.

Handling, Storage, and Precautions: highly poisonous, odorless, colorless, and tasteless gas. All operations should be carried out in a fume hood.

Reactions with Carbocations.

The reaction of carbocations with CO leading to acylium cations is a key step in the Koch reaction. The Koch reaction produces tertiary carboxylic acids by treating alcohols with CO in a strong acid. It can be applied to alkanes, alkenes, and other compounds equivalent to alcohols under acidic conditions. A variety of acid systems, including Brønsted acids such as H_2SO_4, HF, and H_3PO_4, as well as in combination with Lewis acids such as BF_3, $AlCl_3$, $SbCl_5$, and SbF_5, are effective. The use of HCO_2H as a CO source is a practical method for laboratory scale reactions and this method is often used as an in situ preparation of CO. The treatment of alcohols, including secondary ones, with HCO_2H in 96% H_2SO_4 gives tertiary carboxylic acids (eq 1).[2] Adamantane is also carbonylated to 1-adamantanecarboxylic acid (eq 2).[3] Besides the HCO_2H method, the Koch synthesis can also be conducted at normal pressure of CO in the presence of copper or silver salts. Cyclohexene, for example, yields only 1-methylcyclopentanecarboxylic acid via ring contraction of the first-formed carbocation under 1 atm of CO (eq 3).[4] The Gatterman-Koch reaction[5] is the formylation of aromatic hydrocarbons with CO and HCl in the presence of $AlCl_3$ (eq 4).[6] Other catalytic systems such as HF/BF_3, HF/SbF_5, $HF/CF_3SO_3H/BF_3$, and CF_3SO_3H have been investigated and found to be effective for this reaction. Formylation and sulfonation take place when aromatic compounds are exposed to an atmosphere of CO at 0 °C in a

HSO_3F/SbF_5 system (eq 5).[7]

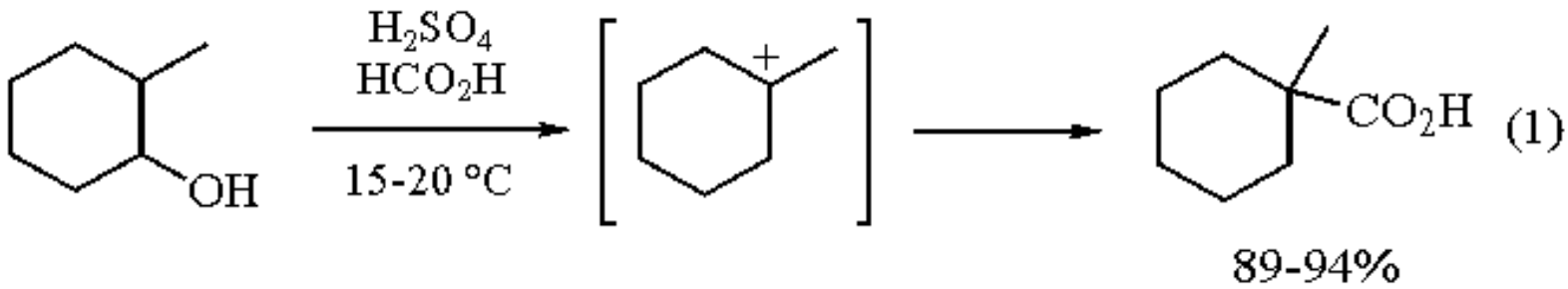

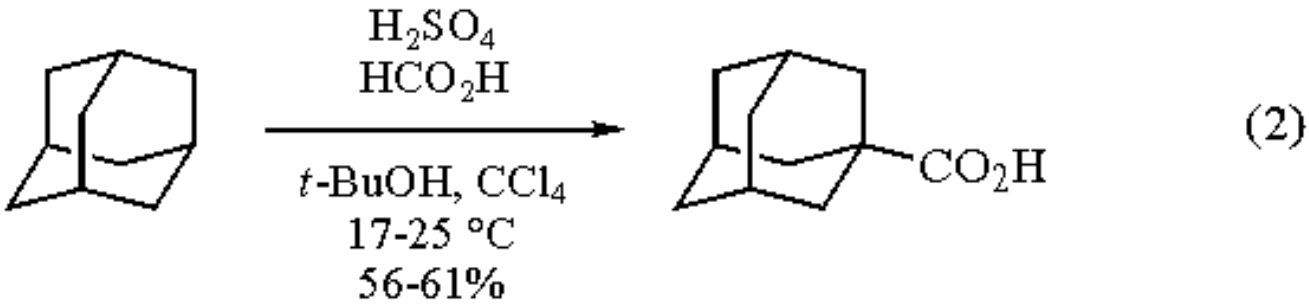

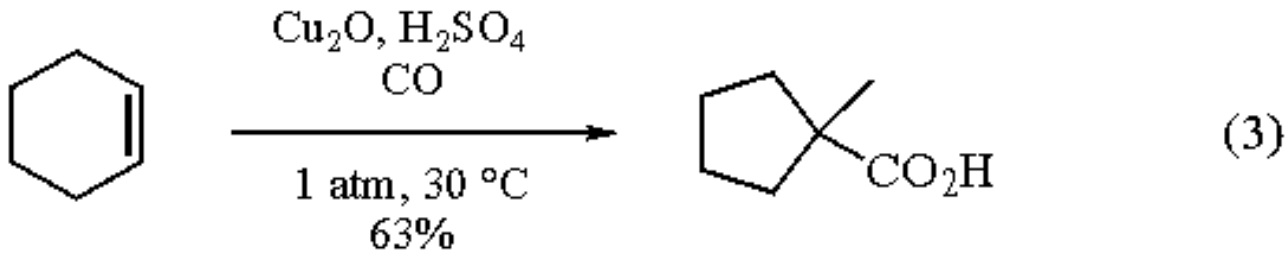

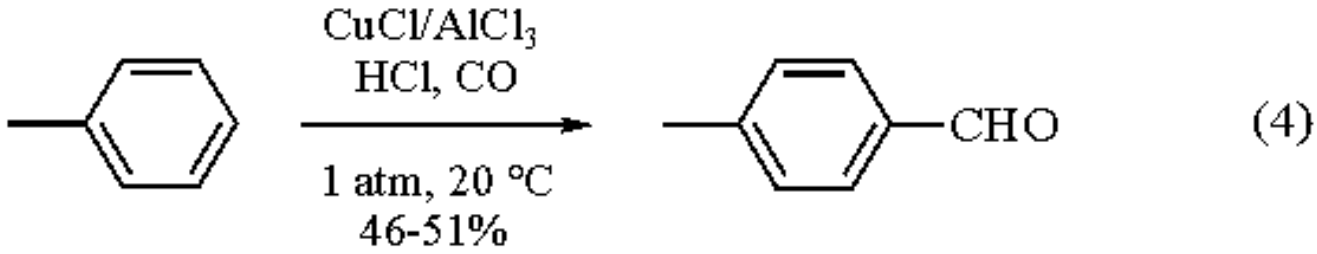

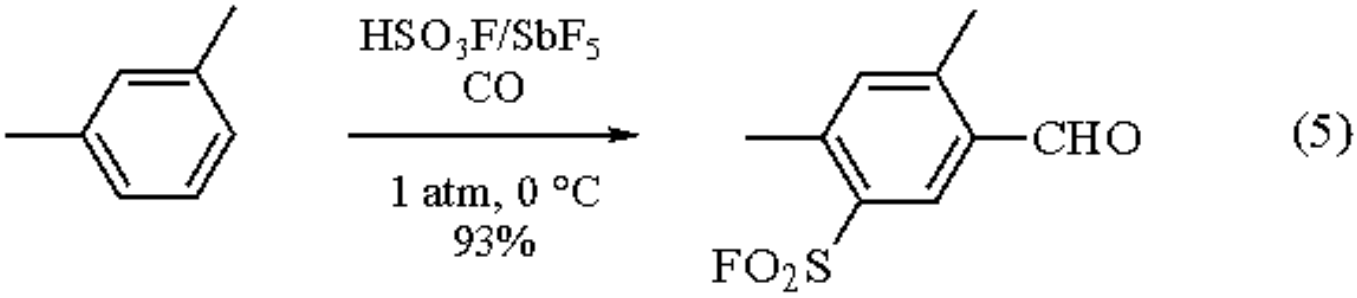

Reactions with Carbanions.

The reaction of organolithium reagents with CO gives carbonyl lithium reagents (acyllithium or aroyllithium), which

have not been utilized in practical synthetic reactions until recently. Difficulties in controlling the reaction of carbonyl lithium reagents are attributed to their extremely high reactivity. Acyllithium can be trapped by ***Chlorotrimethylsilane*** under extremely careful reaction conditions (eq 6).[8] A controlled, slow-rate addition of alkyllithium to a solution of Me_3SiCl saturated with CO at -110 °C is recommended. Direct nucleophilic acylation of ketones by in situ generated acyllithium reagents leading to α-hydroxy ketones has been described (eq 7).[9] The use of aldehydes,[10] lactones,[11] CS_2,[12] isocyanate[13] disulfide,[14] and carbodiimide[15] as trapping electrophiles has also been reported. Acylcuprate reagents successfully undergo nucleophilic 1,4-addition to α,β-unsaturated ketones and aldehydes (eq 8).[16]

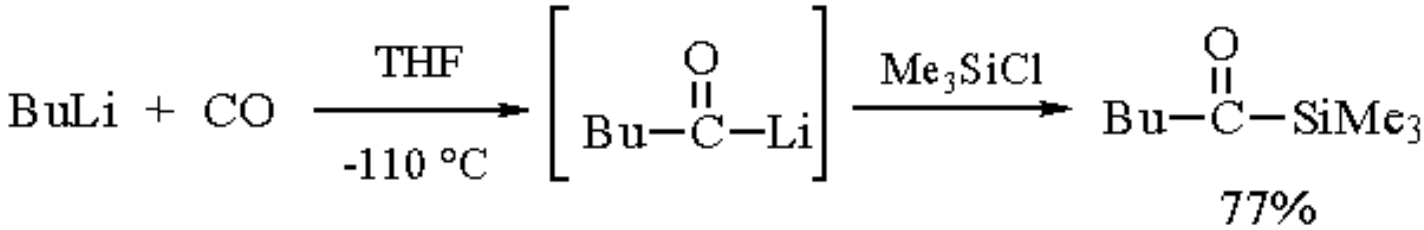

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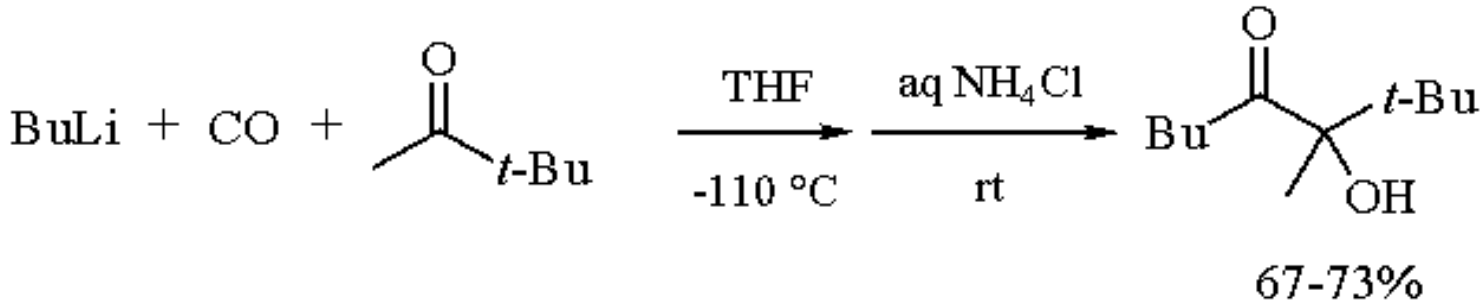

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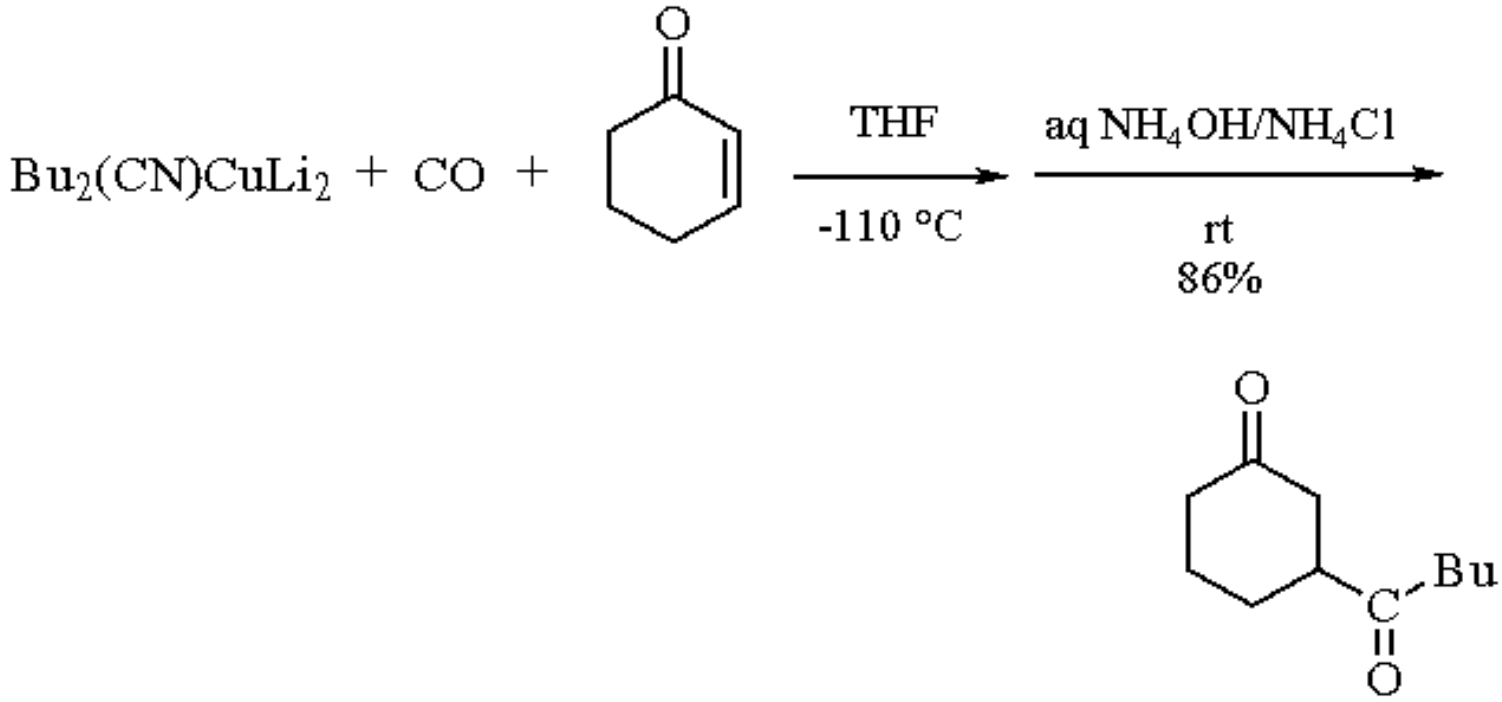

(8)

The reaction of an α-silylalkyllithium with CO is a convenient access to acylsilane enolates, which can be trapped by electrophiles such as H^+, Me_3SiCl, and benzaldehyde (eq 9).[17] The formation of the enolates takes place in a highly stereoselective manner to give (*E*) enolates.

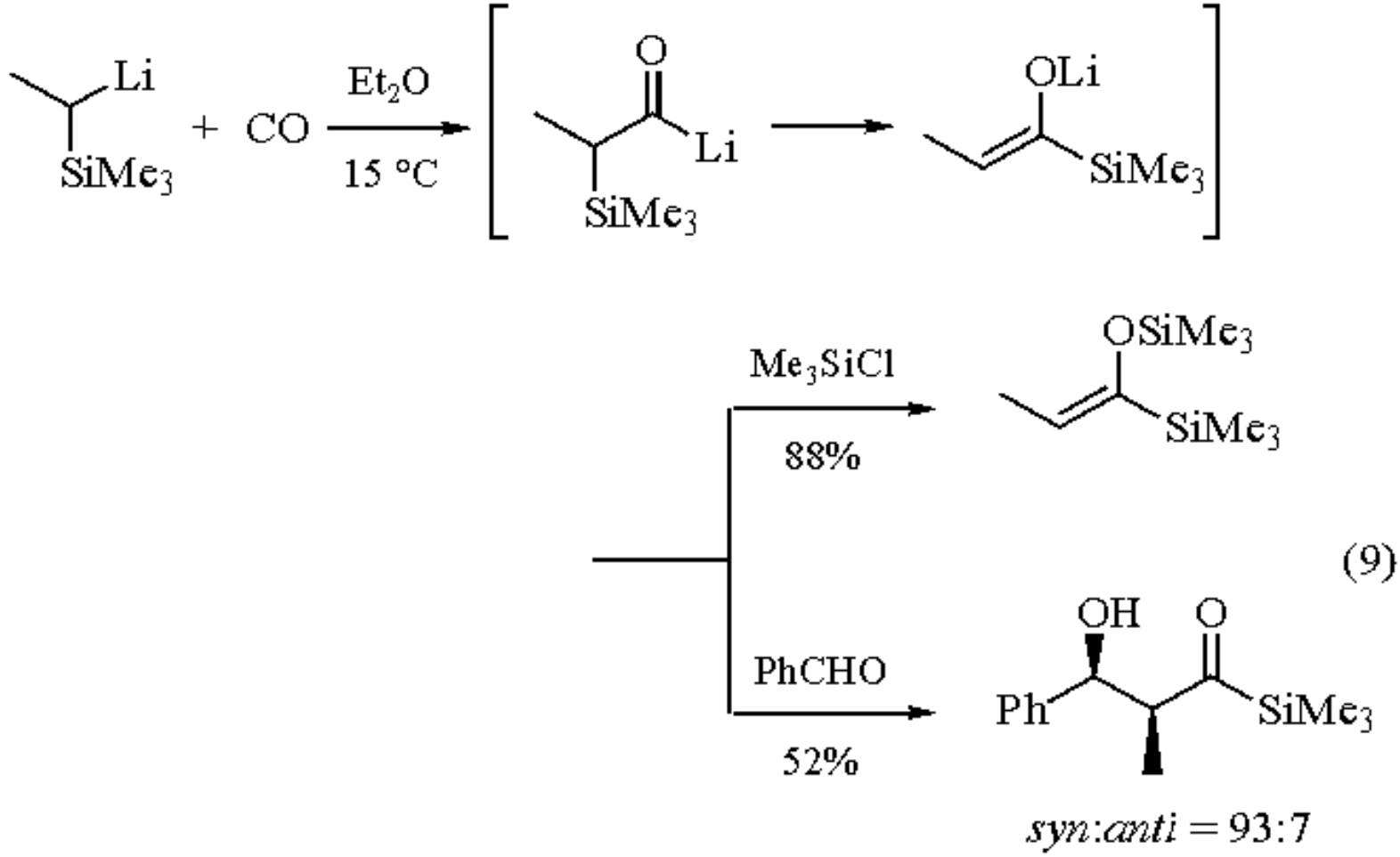

(9)

Reactions with Radicals.

The reaction of alkyl halides with ***Tri-n-butylstannane*** in the presence of ***Azobisisobutyronitrile*** (0.1-0.2 equiv) under CO pressure (65-80 atm) leading to aldehydes proceeds via the reaction of alkyl radicals with CO to give acyl radicals followed by abstraction of a hydrogen atom from $HSnBu_3$ (eq 10).[18] Aromatic halides can also be converted to aromatic aldehydes.[19] The use of ***Tris(trimethylsilyl)silane*** (TTMSS) in place of $HSnBu_3$ as a radical mediator permits the carbonylation under a lower pressure of CO (20 atm).[20] The radical carbonylation is applied to carbonylative cyclization of 4-alkenyl halides to cyclopentenes (eq 11).[21] The intramolecular trapping of acyl radicals by alkenes is utilized for the synthesis of functionalized unsymmetrical ketones.[22] The carbonylation of alkynes in the presence of thiols initiated by AIBN gives β-alkylthio-α,β-unsaturated aldehydes (eq 12).[23]

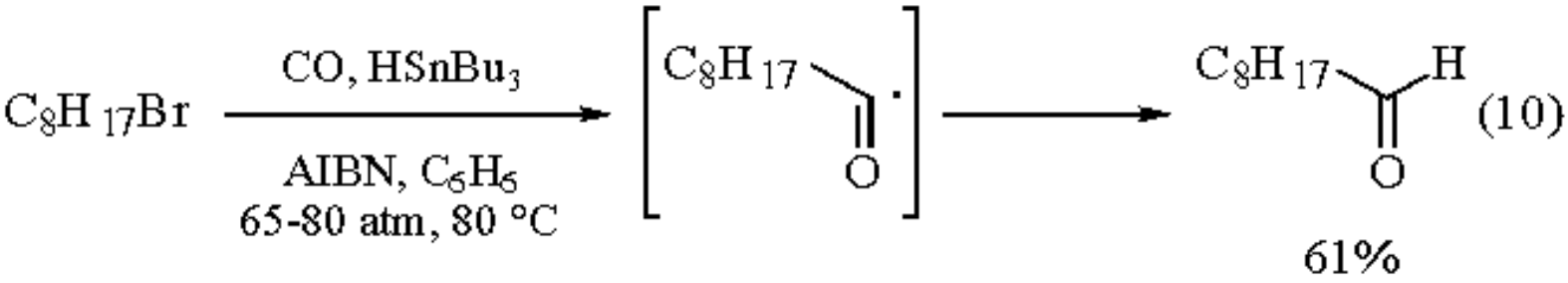

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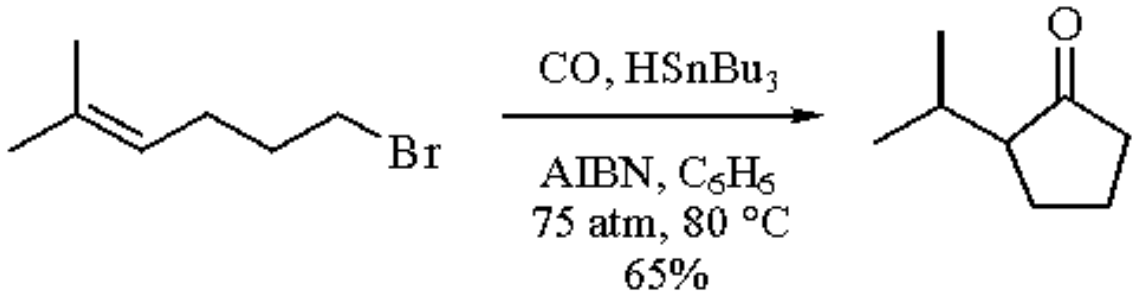

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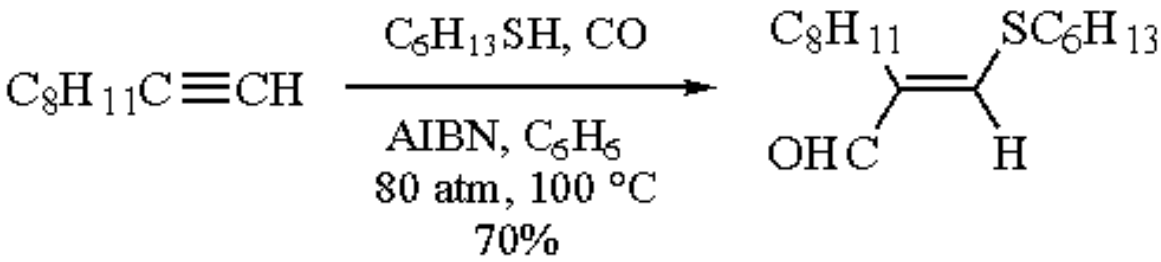

(12)

Transition Metal-Catalyzed Reactions.

Ring-opening siloxymethylation to 1,3-diol derivatives takes place in the reaction of cyclopentene oxide with $HSiEt_2Me$ and CO in the presence of $Co_2(CO)_8$ (eq 13).[24] The reagents $ML_n/HSiR_3/CO$ provide several important synthetic methods, which are covered under the reagent headings of ***Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide***, ***Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide***, and ***Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide***.

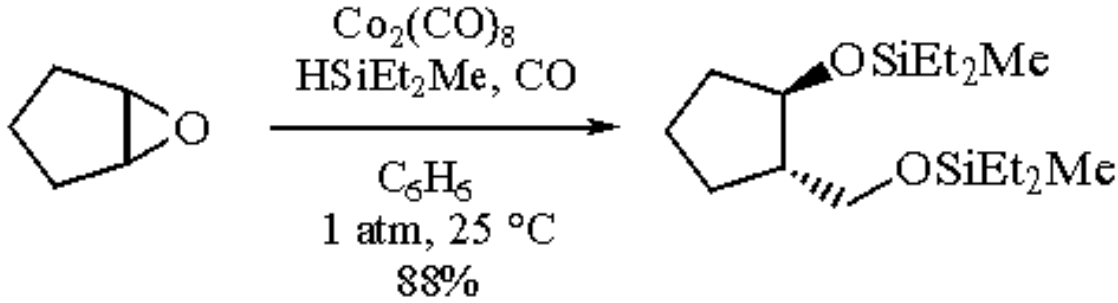

(13)

Hydroformylation has been an extremely important industrial process, and consequently has been the most extensively studied of all carbonylation reactions.[25] A wide variety of metals such as Pt, Co, Rh, Ir, and Ru exhibit catalytic activity for hydroformylation of alkenes. Among them, Rh has been preferred for laboratory use because of its higher activity (eq 14).[26] Various phosphine-modified catalysts such as $Co_2(CO)_8$/phosphine, (phosphine)$PtCl_2/SnCl_2$, and phosphine-modified Rh have been examined extensively to obtain high selectivity for the more desirable linear aldehydes. Practical, regioselective hydroformylation of functionalized terminal alkenes can be achieved by using a bis-organophosphite ligand (**1**).[27] Catalytic systems using diphosphines with natural bite angles near 120° increase regioselectivity for straight-chain aldehydes.[28] Highly selective formation of branched-chain aldehydes is attained by use of a zwitterionic Rh complex (eq 15).[29] Hydroformylation using $PtCl_2/SnCl_2$ in the presence of chiral ligands such as (-)-DIPHOS, (-)-DIOP, and chiraphos is reported to produce moderate enantioselectivity.[30] The highest level of enantioselective discrimination is realized with $PtCl_2/SnCl_2$ and (2*S*,4*S*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine ((-)-BPPM) in the presence of ***Triethyl Orthoformate***, which converts the product aldehyde to its diethyl acetal, although the branched/linear ratios are low.[31]

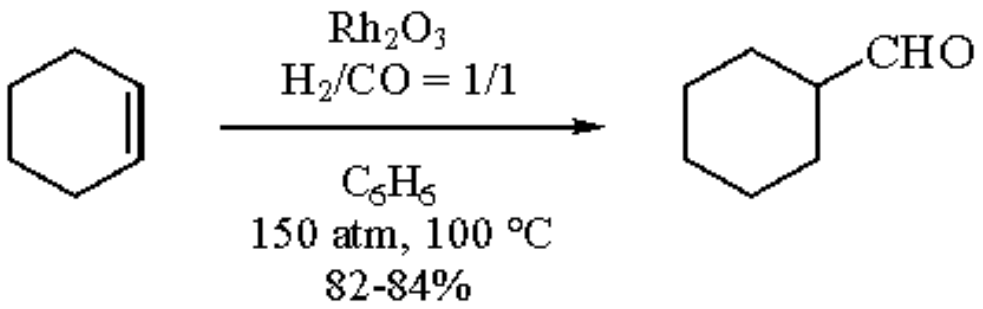

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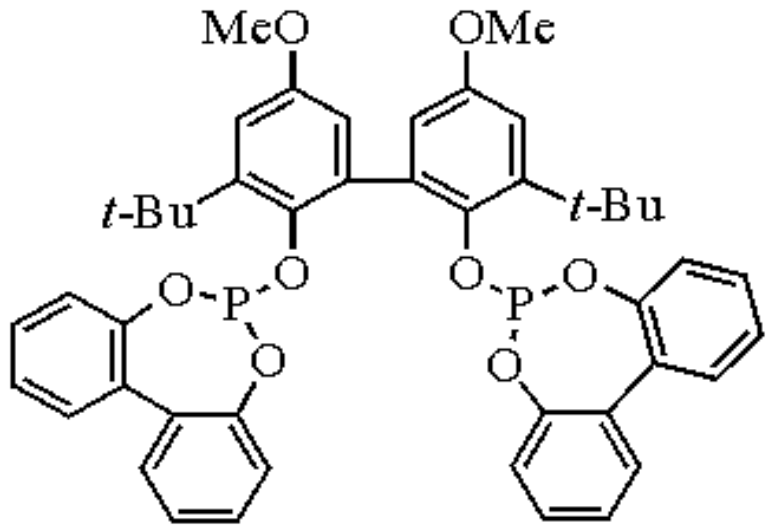

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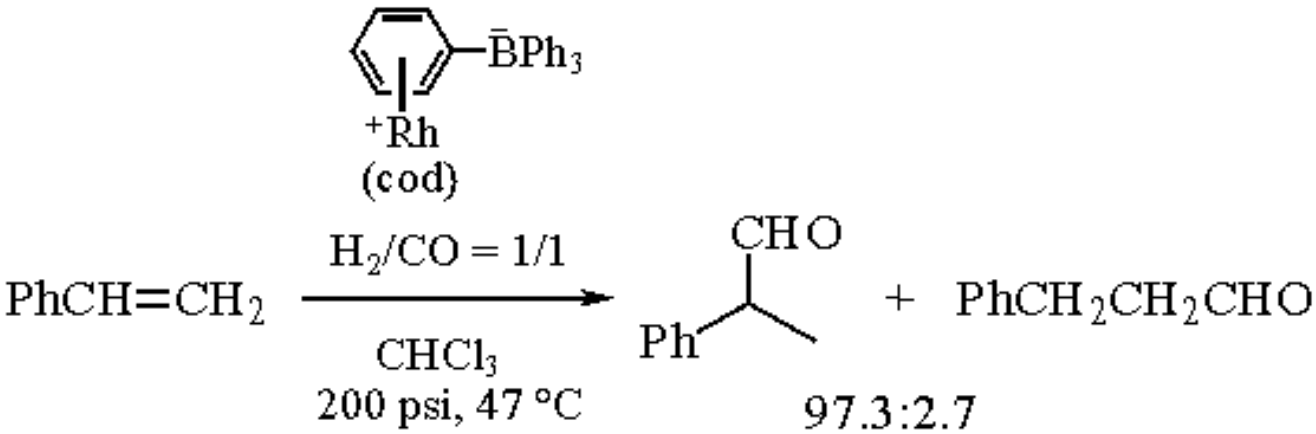

(15)

Hydrocarboxylation or hydroesterification is also an important process of CO. The asymmetric synthesis of (+)-ibuprofen and (+)-naproxen is attained based on asymmetric hydrocarboxylation of vinylarenes using (*S*)-(+)-1,1´-binaphtyl-2,2´-diyl hydrogen phosphate ((*S*)-BNPPA) (eq 16).[32]

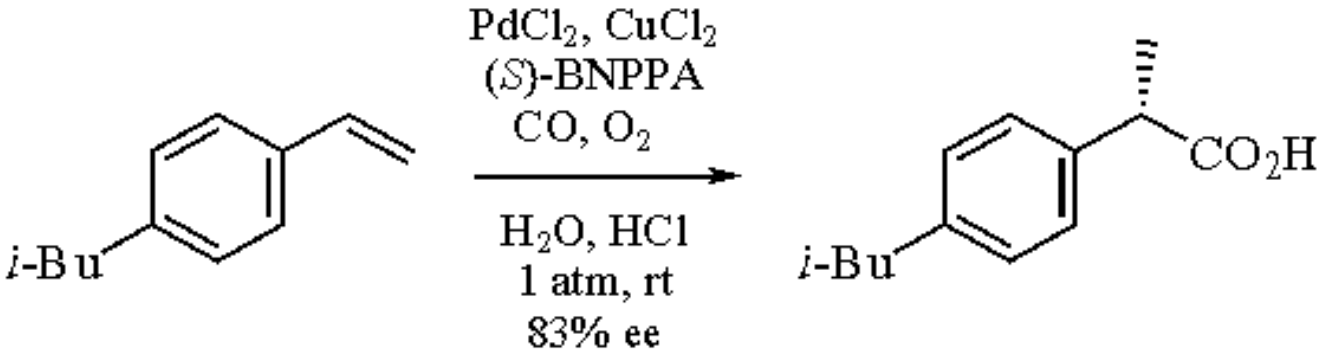

(16)

Terminal alkynes may be carbonylated to acetylenecarboxylic esters in the presence of $PdCl_2$ as catalyst and $CuCl_2$ as reoxidant in the presence of NaOAc (eq 17).[33] Hydroesterification of alkynes to α,β-unsaturated esters is catalyzed by $[P(p\text{-Tol})_3]_2PdCl_2/SnCl_2$,[34] $PdCl_2/CuCl/HCl/O_2$,[35] and $(PPh_3)_2PtCl_2/SnCl_2$.[36] Pd-catalyzed intramolecular carbonylation of alkynyl alcohols is an attractive route to α-methylene-γ-lactones (eq 18).[37]

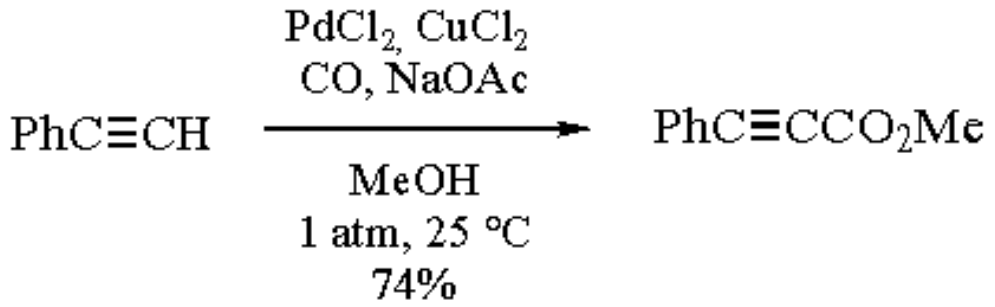

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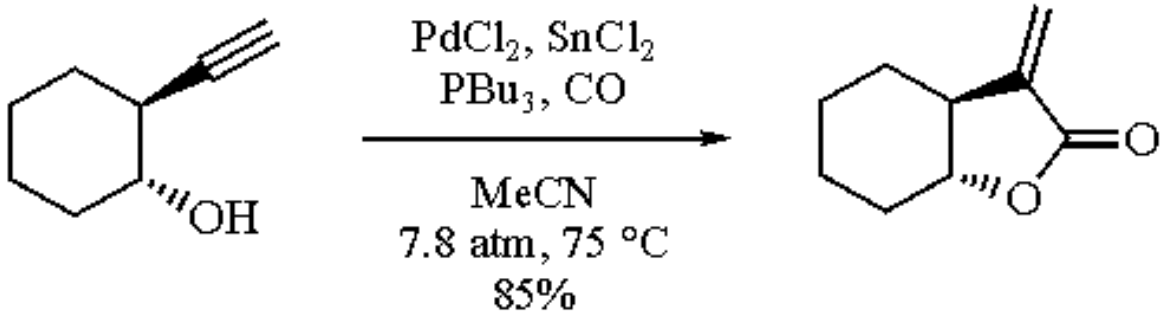

(18)

Ketones and aldehydes are formed using CO. Pd-catalyzed carbonylation of aryl or vinyl halides (or triflates) is an attractive method for a wide variety of carbonyl compounds. Carbonylation of aryl halides in the presence of hydrogen and a tertiary amine leads to the formation of aldehydes (eq 19).[38] Use of hydrogen donor such as HCO_2Na,[39] poly(methylhydrosiloxane) (PHMS),[40] $HSiEt_3$,[41] and $HSnBu_3$[42] also gives aldehydes. The Pd-catalyzed carbonylative coupling of aryl triflates with organostannanes is a potentially valuable route to unsymmetrical ketones (eq 20).[43] Organozinc reagents may be used in ketone syntheses.[44] Esters are obtained from aryl, vinyl, and heteroaryl halides (triflates) via the Pd-catalyzed carbonylation in the presence of alcohols.[45] The intramolecular version has been utilized for the preparation of α-methylene-γ-lactones from vinyl halides (eq 21).[46] The synthesis of lactams is also achieved in the presence of $Pd(OAc)_2/PPh_3$.[47] Aryl halides may be doubly carbonylated to α-keto amides in the Pd-catalyzed carbonylation of aryl halides with amines (eq 22).[48]

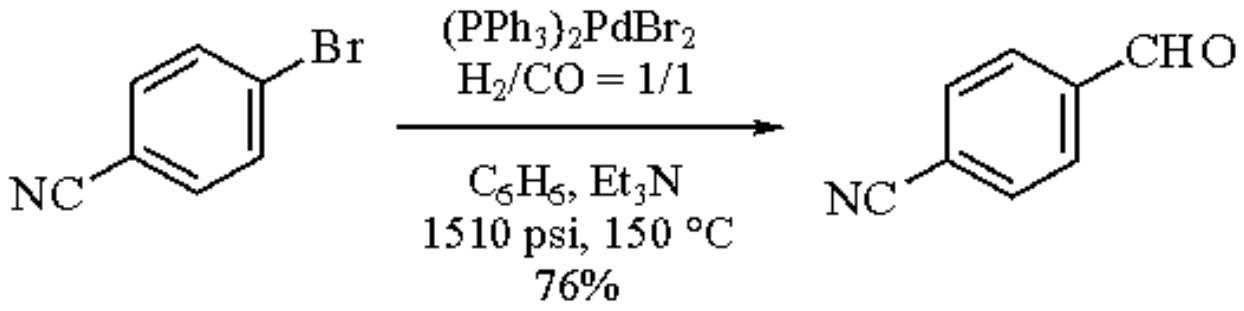

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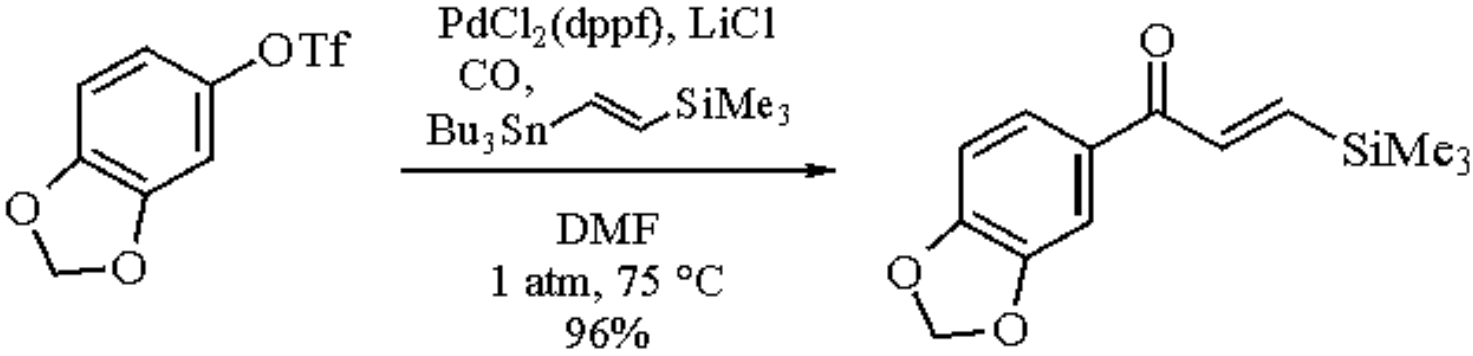

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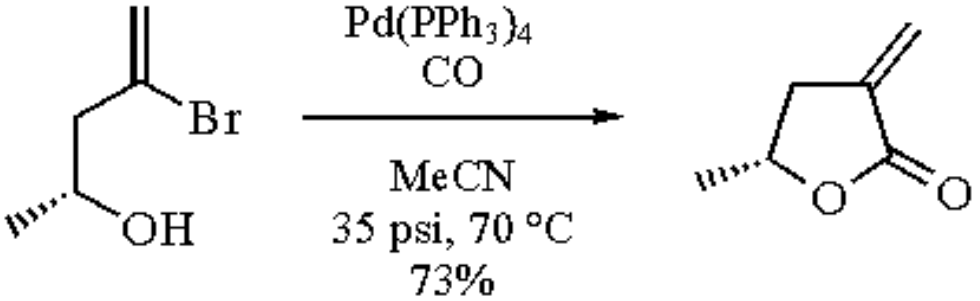

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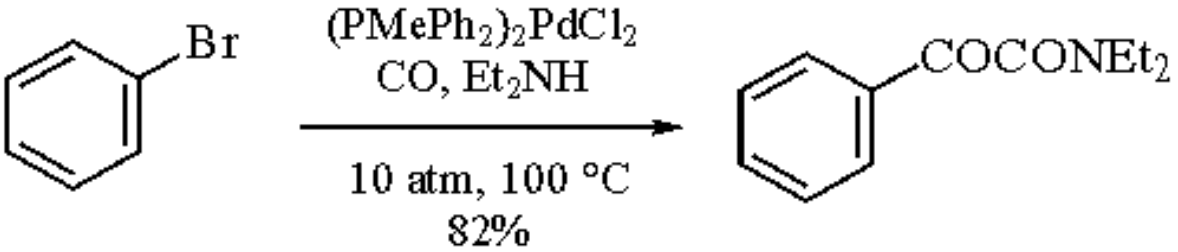

(22)

The catalytic carbonylation of benzyl chloride to arylacetic acid derivatives is shown to occur with Pd complexes as catalysts in the presence of a base under mild reaction conditions (eq 23).[49] $Co_2(CO)_8$-catalyzed carbonylation under phase transfer conditions (organic solvent/aq NaOH system containing catalytic amounts of quaternary ammonium salt) is also effective for the transformation of benzyl chlorides to arylacetic acids.[50]

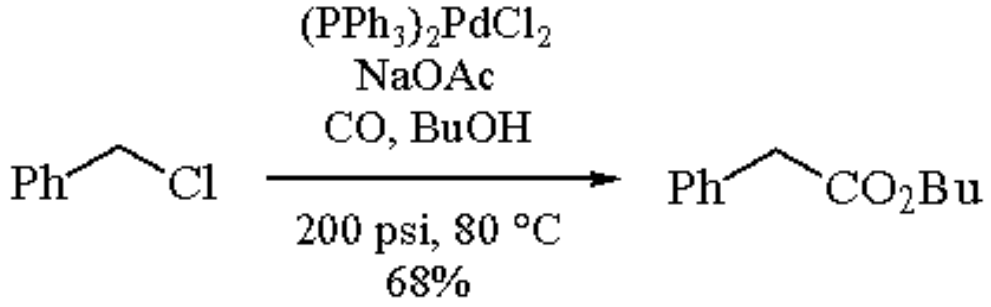

(23)

Pd-catalyzed cyclocarbonylation of aryl- or heteroaryl-substituted allyl acetates with Ac_2O gives bicyclic aromatic systems (eq 24).[51] Allylic phosphonates are cleanly carbonylated to β,γ-unsaturated amides in the presence of a catalytic amount of $Rh_6(CO)_{16}/NBu_4Cl$ (eq 25).[52] Use of NH_4Cl/Et_3N in place of $PhCH_2NH_2$ is found to be effective for the preparation of primary amides. Under more harsh reaction conditions (50 atm, 110 °C), allylamines may be carbonylated directly to β,γ-unsaturated amides in the presence of $Pd(OAc)_2$/dppp.[53] The Pd-catalyzed carbonylation of propargyl carbonates in MeOH affords allenic esters (eq 26).[54]

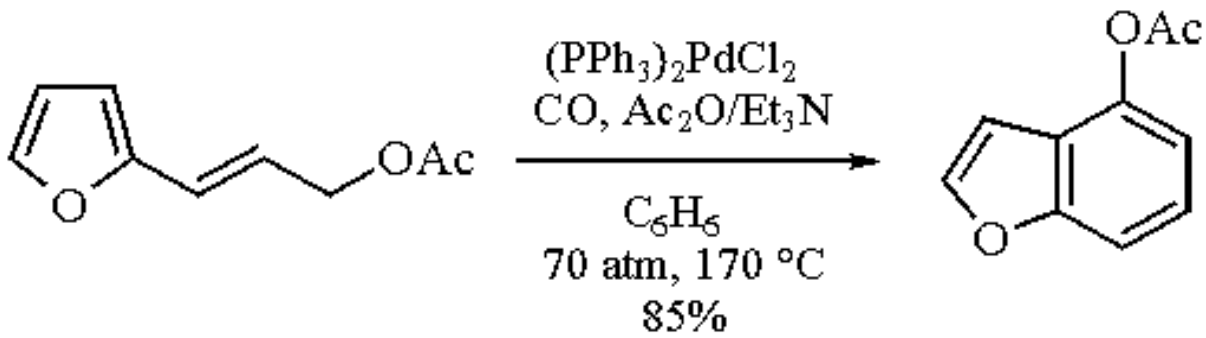

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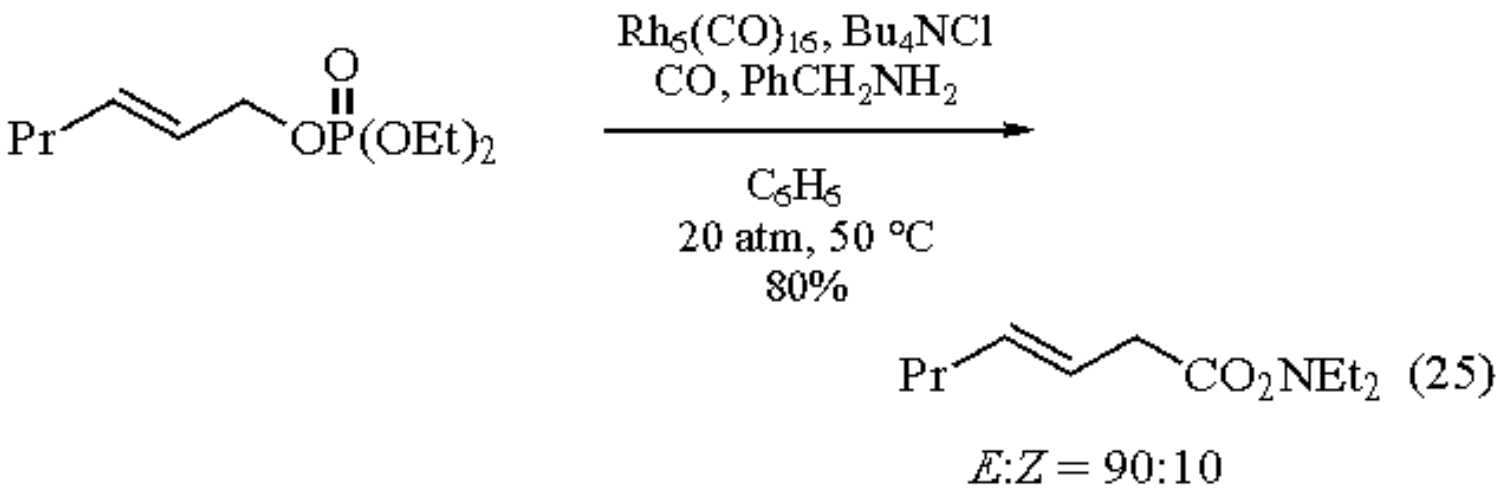

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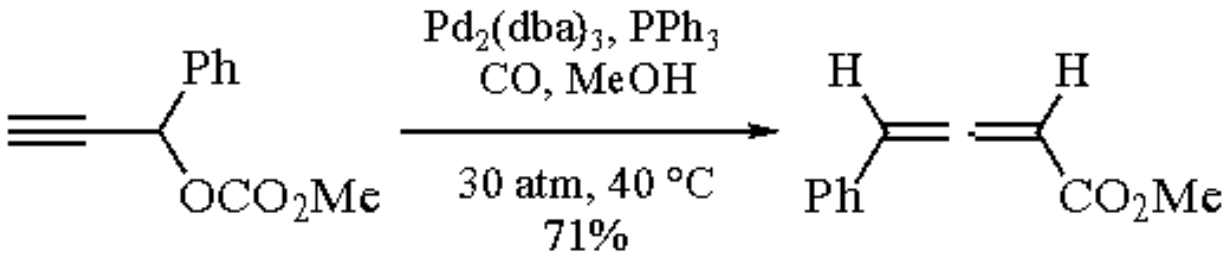

(26)

Exposure of an azirine to CO in the presence of $Pd(PPh_3)_4$ affords bicyclic β-lactams (eq 27).[55] 2-Arylaziridines are

carbonylated with retention of configuration in the presence of $[RhCl(CO)_2]_2$ to give monocyclic β-lactams (eq 28).[56] Similar carbonylative ring-expansion reactions are observed in the Rh-catalyzed reaction of azetidine-2,4-diones,[57] Co-catalyzed reaction of azetidines,[58] and Co/Ru-catalyzed reaction of oxetanes.[59]

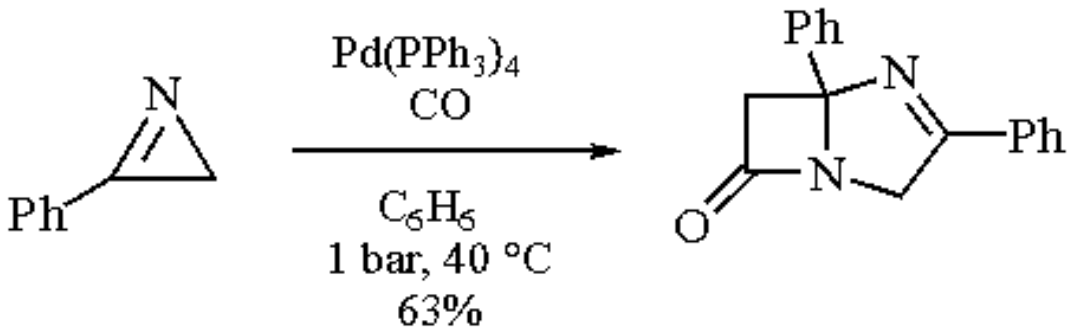

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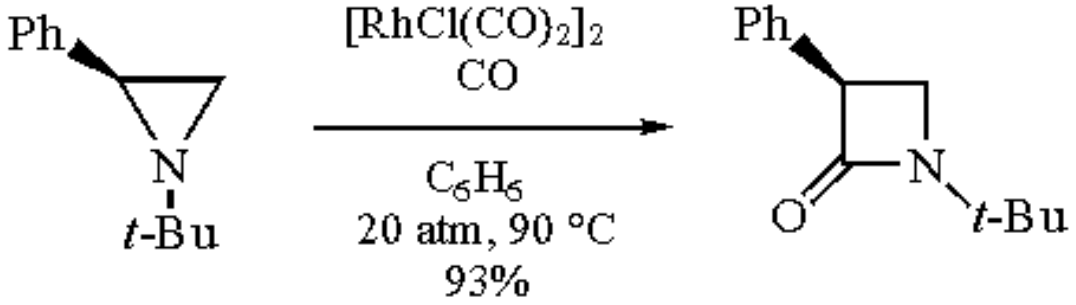

(28)

Cyclic ethers, including oxiranes, oxetane, and tetrahydrofuran, react with CO and *N*-(trimethylsilyl)amine in the presence of $Co_2(CO)_8$ to form siloxy amides (eq 29).[60]

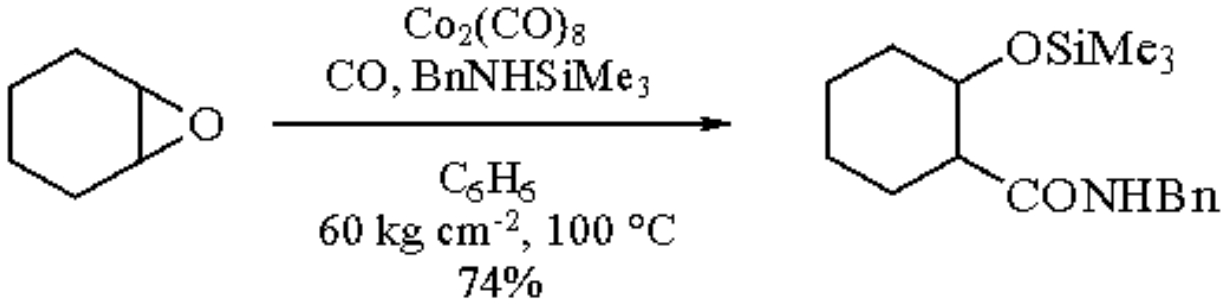

(29)

N-acyl-α-amino acids can be synthesized by amidocarbonylation of aldehydes with acetamide and synthesis gas (eq 30).[61] It is possible to achieve a direct, one-step synthesis of *N*-acyl-α-amino acids from precursors other than aldehydes themselves. For example, allyl alcohols can be converted to *N*-acyl-α-amino acids via isomerization of allyl alcohols to aldehydes followed by amidocarbonylation (eq 31).[62]

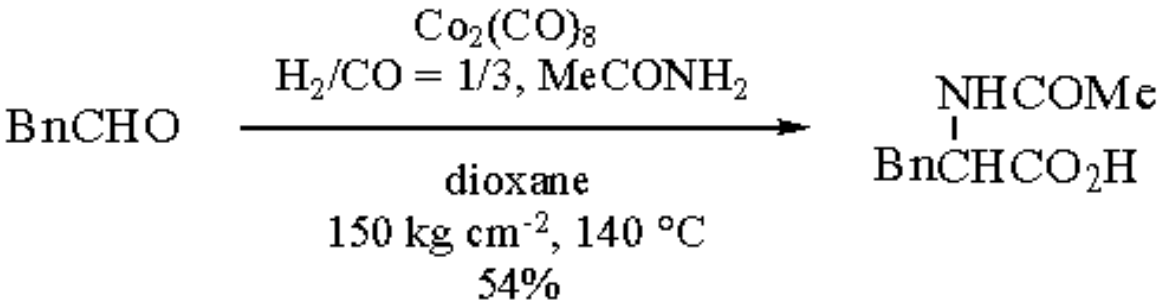

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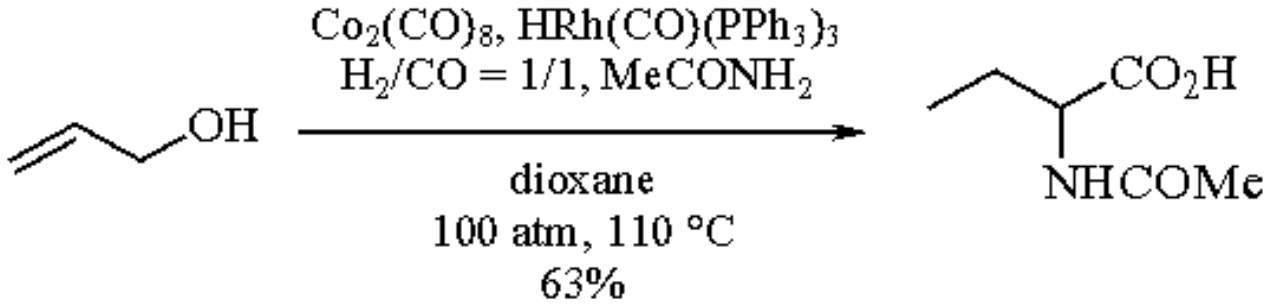

(31)

Heterocyclic rings can be constructed by oxidative carbonylation under mild reaction conditions. The formation of a pyran ring is achieved by oxidative carbonylation of hydroxy alkenes (eq 32).[63] Transformation of allenic amines to α-heterocyclic acrylic acid derivatives is also carried out under ambient conditions (eq 33).[64]

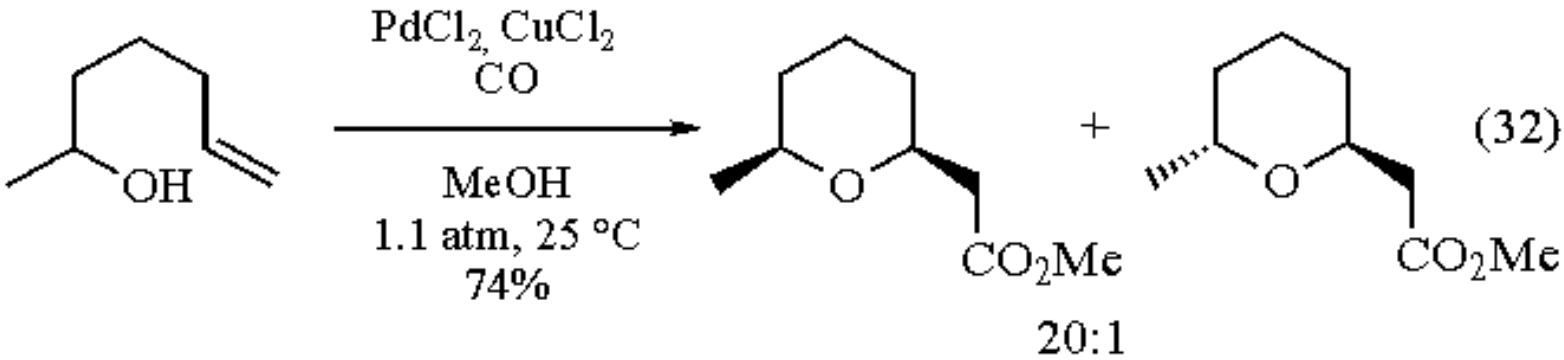

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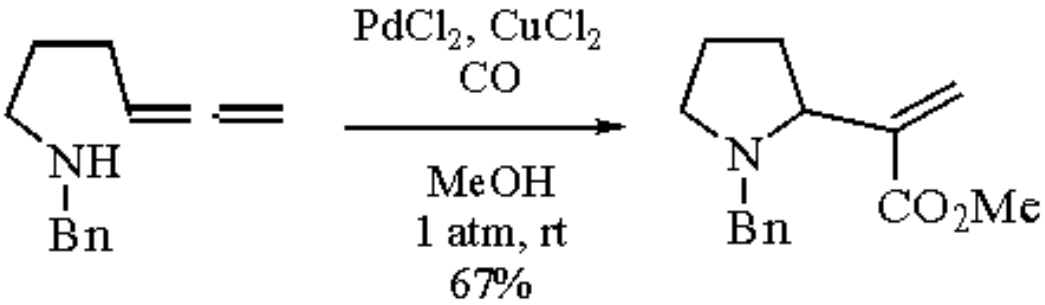

(33)

CO acts as reducing agent in the water gas shift reaction (WGSR).[65] Application of WGSR in organic synthesis includes hydrogenation, related reductions, and carbonylation. Ru-catalyzed reduction of aromatic nitro compounds to aromatic amines under mild reaction conditions (at rt under 1 atm of CO) has been achieved (eq 34).[66] Montmorillonite-bipyridine-$Pd(OAc)_2/Ru_3(CO)_{12}$ is an active catalyst for the reductive carbonylation of aromatic nitro compounds to urethanes (eq 35).[67] The reaction is highly selective and no side products such as azo, azoxytoluene, or *N*-methylanilines are detected.

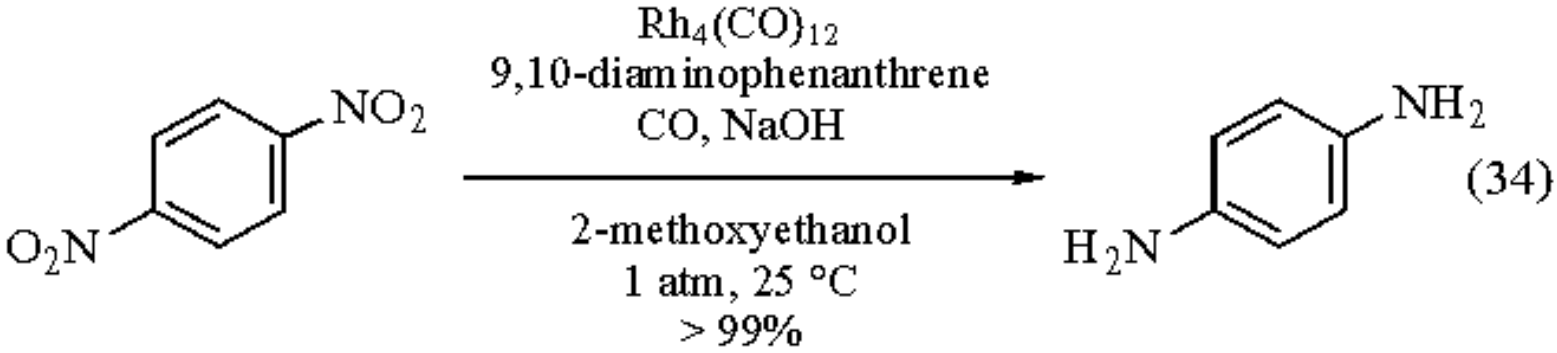

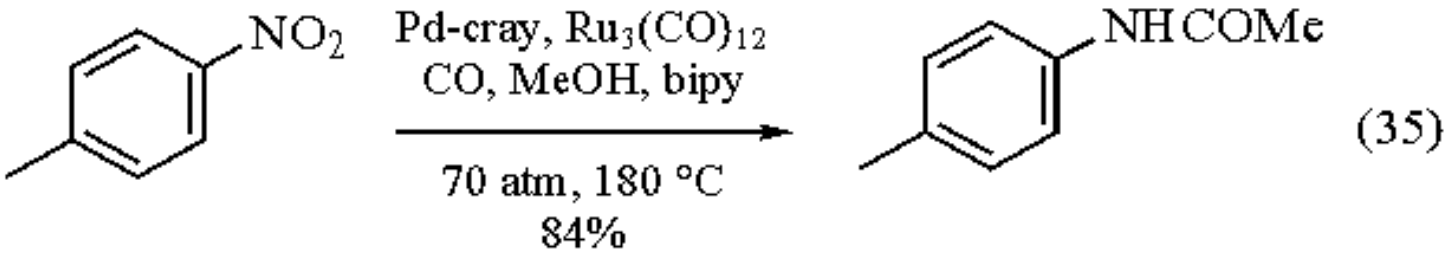

Miscellaneous.

Selenium effectively catalyzes the carbonylation of various amines with CO and O_2 to give urea derivatives quantitatively (eq 36).[68] Turnover numbers of Se reach 10^4 by using 0.8 mg of Se (0.01 mmol) for the carbonylation of benzylamine (200 mmol). The reaction can be applied to the synthesis of cyclic ureas.[69]

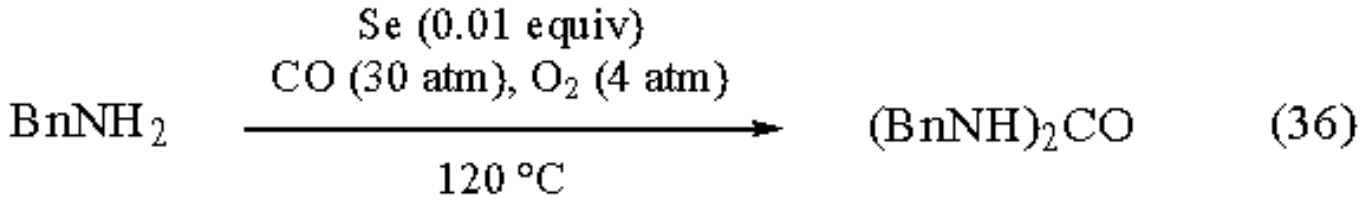

CO forms Lewis acid-base complexes with organoboranes. When the organoborane is heated with CO to 100-125 °C, a tertiary alcohol is obtained after workup by oxidation (eq 37).[70]

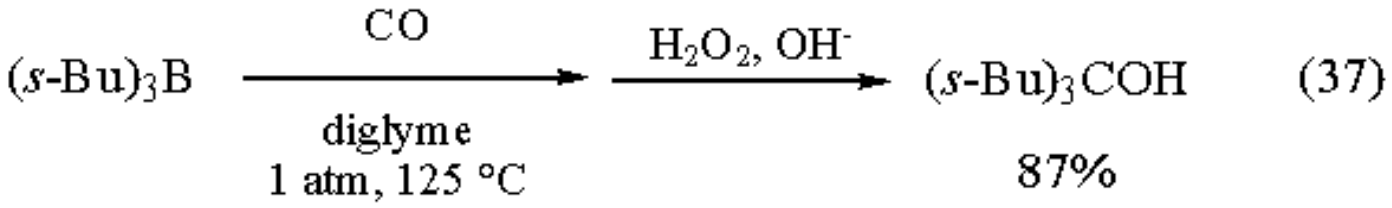

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Carbon Oxysulfide[1]

O=C=S

[463-58-1] · COS · Carbon Oxysulfide · (MW 60.07)

(agent for the thiocarboxylation of Grignard reagents,[2] enolates,[3] and other carbanions, and for the preparation of thiocarbonates,[1,4] ureas,[1] and various heterocycles[1])

Alternate Names: carbon oxide sulfide; carbonyl sulfide.

Physical Data: bp -50.2 °C; mp -138.2 °C; critical temp 105 °C; density (liquid) 1.25 g cm^{-3} at -87 °C; density (gas) 1.073 g L^{-1} at 0 °C.

Solubility: 54 mL/100 mL in H_2O at 20 °C; sol EtOH, CS_2.

Form Supplied in: compressed gas. *Drying:* pass gas through conc H_2SO_4.

Handling, Storage, and Precautions: carbon oxysulfide is a colorless, odorless, toxic gas. Use in a fume hood.

Reactions of Carbon Oxysulfide with Grignard Reagents, Enolates, and Other Carbanions.

Carbon oxysulfide reacts in a similar manner to carbon dioxide with a range of anionic substrates to form carbothioic acids [RC(=O)SH], with the option of in situ alkylation to carbothioic esters [RC(=O)SR´]. While overreaction of COS with Grignard reagents (eq 1) to afford trialkyl carbinols[2] appears to be more of a problem than with CO_2, the trapping of enolates with COS followed by methylation proceeds in high yield (eq 2)[3] and allows improved access (after Hg^{II} catalyzed transesterification) to β-keto esters,[5] compared with the more direct CO_2 based approach.[6]

$$\mathrm{PhMgBr} \xrightarrow{\mathrm{COS},\ H_3O^+} \underset{40\%}{\mathrm{PhCOSH}} + \underset{52\%}{\mathrm{Ph_3COH}} \qquad (1)$$

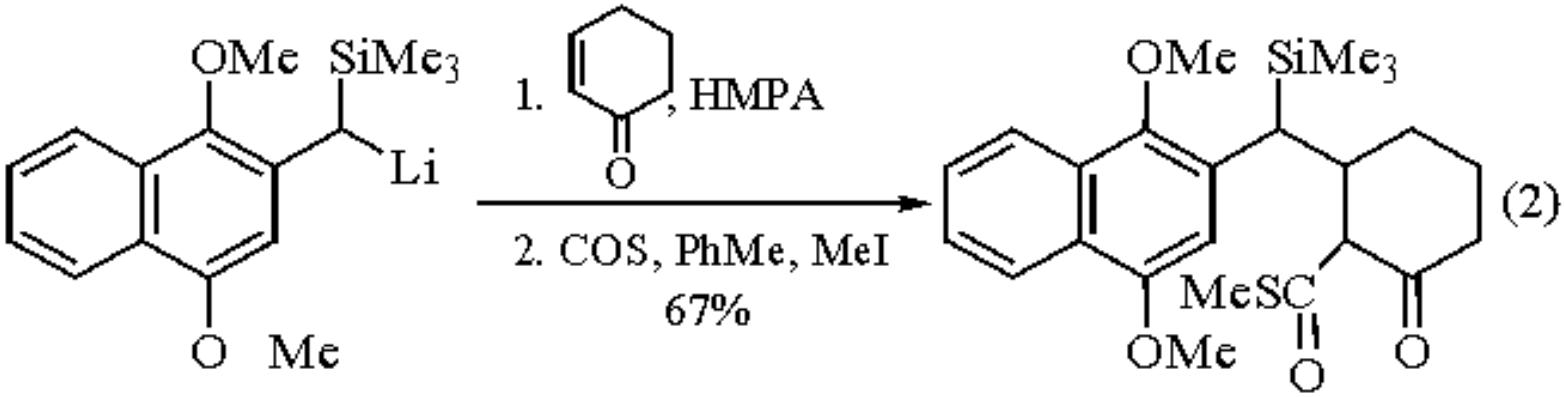

Acylation of thioenolate derivatives varies according to the substrate, occurring either on carbon (with *t*-butyl methyl thioketone) or sulfur (with diisopropyl thioketone).[7] Carbon oxysulfide has also been used to acylate phosphorus ylides[8] and acyllithium intermediates [RC(=O)Li].[9]

Reactions of Carbon Oxysulfide with Alkoxides, Phenolates, and Amines.

Carbon oxysulfide reacts extremely slowly with dry ethanol to form ethanethiol, but in the presence of KOH, potassium ethanethiocarbonate [KSC(=O)OEt] is formed.[1] Phenolate salts react similarly to give *O*-acylated products,[4] in contrast to the Kolbe-Schmitt reaction with CO_2.[10] Amines are converted by COS into thiocarbamates [$RNHC(=O)S^-$ RNH_3^+] which, on heating, decompose to ureas and H_2S.[1]

Heterocycle Formation.

Aminonitriles have been condensed with COS to afford thiazoles (eq 3),[11] and a thioxopyrimidine (eq 4). The latter process allowed access to a pyrrolopyrimidinone after a more direct approach based on ***Ethyl Chloroformate*** failed.[12]

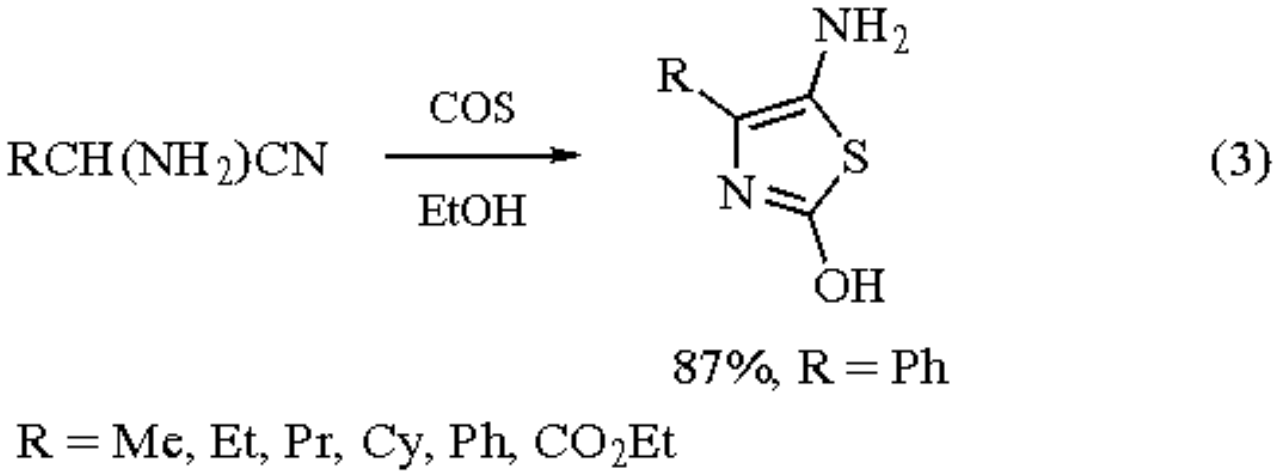

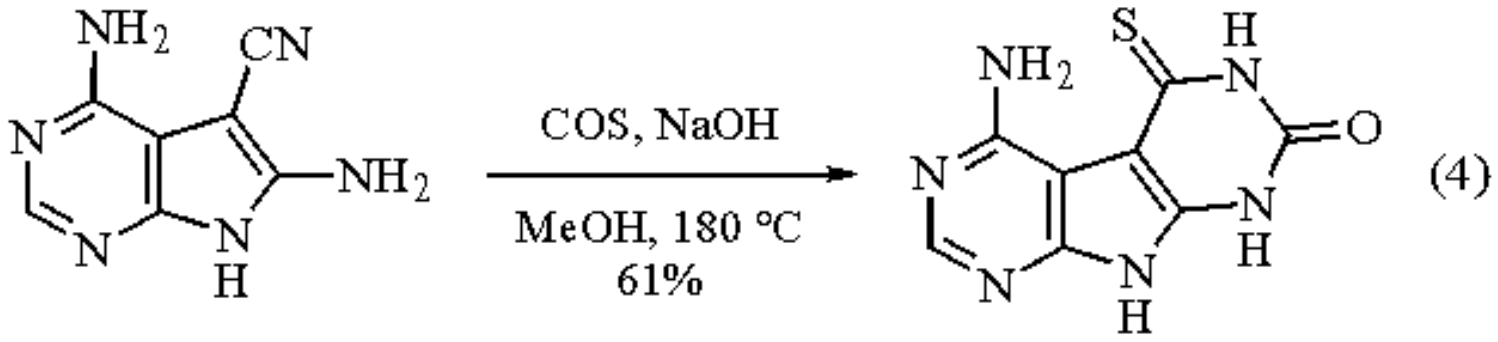

Related Reagents.

Carbon Dioxide; ***Carbon Disulfide***; ***Methyl Magnesium Carbonate***; ***Methyl Chloroformate***.

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Carbon Suboxide

O=C=C=C=O

[504-64-3] · C_3O_2 · Carbon Suboxide · (MW 68.03)

(1,3-dielectrophile used mainly for the synthesis of five- and six-membered heterocycles functionalized with oxo and hydroxy groups in the 1,3-position[1])

Alternate Name: 1,3-dioxo-1,2-propadiene.

Physical Data: mp -112.5 °C; bp 6.8 °C; *d* 1.114 g cm^{-3} (at 0 °C); 1.135 g cm^{-3} (at -12 °C); η_D 1.45384.

Solubility: sol ether, THF, benzene, etc.; reacts with H_2O and protic solvents.

Preparative Methods: for synthetic use, C_3O_2 can be prepared conveniently by three routes. (a) Pyrolysis of diacetyl tartaric anhydride at 770 °C under normal pressure.[1c] (b) Dehydration of malonic acid with P_4O_{10} at 150 °C.[1c,2] (c) Thermolysis of bis(trimethylsilyl) malonate in the presence of P_4O_{10} at 160 °C.[3] Good results[4] are also obtained by using method (b) and the apparatus as depicted in Birkofer and Sommer[3] (but also including a calcium oxide tube[1c] to absorb the acetic acid which is also formed by this most simple procedure). All three procedures can be adjusted to yield at least 7 g (>0.1 mol) of C_3O_2.

Handling, Storage, and Precautions: pure C_3O_2 is rather stable;[1b] nevertheless, it is advisable to use it within a few days after its preparation. Usually solutions of C_3O_2 in ether or THF are used in synthesis. An assay of the content of such solutions can be performed by adding an excess of aniline to an aliquot, and weighing the amount of malonic acid dianilide formed. *Caution*: Small amounts of C_3O_2 act as a lachrymator; in high concentrations it attacks eyes, nose, and respiratory organs, producing a feeling of suffocation. Use in a fume hood.

Reactions.

As an internal dianhydride, C_3O_2 represents the most electrophilic malonic acid derivative, but due to its value it is only used if other reagents fail. One typical example is the reaction of pyrazoles to yield cross-conjugated mesomeric pyrazolo[1,2-*a*]pyrazole betaines (eq 1).[5]

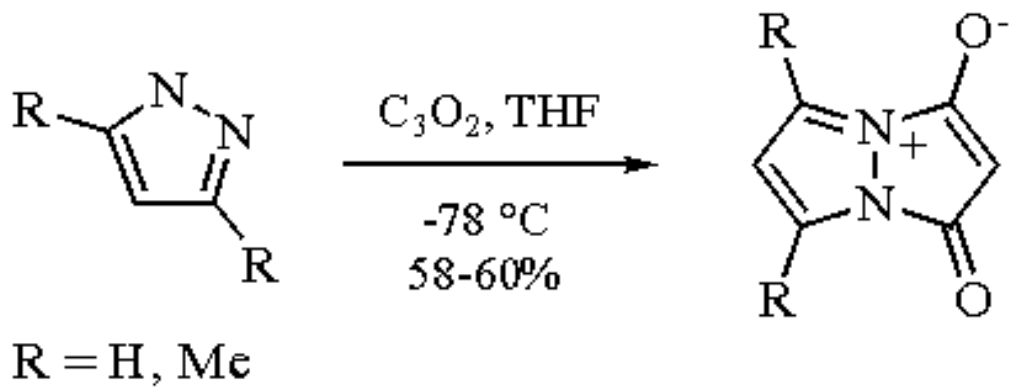

(1)

In a similar way amidine derivatives react with C_3O_2 to yield six-membered pyrimidine betaines (eq 2),[2,6] and *N*-substituted 2-aminopyridines[7,8] and pyrimidines[9] lead to bicyclic cross-conjugated betaines. 1,3-Dinucleophiles bearing only one hydrogen atom add C_3O_2 inevitably to zwitterionic compounds.[8]

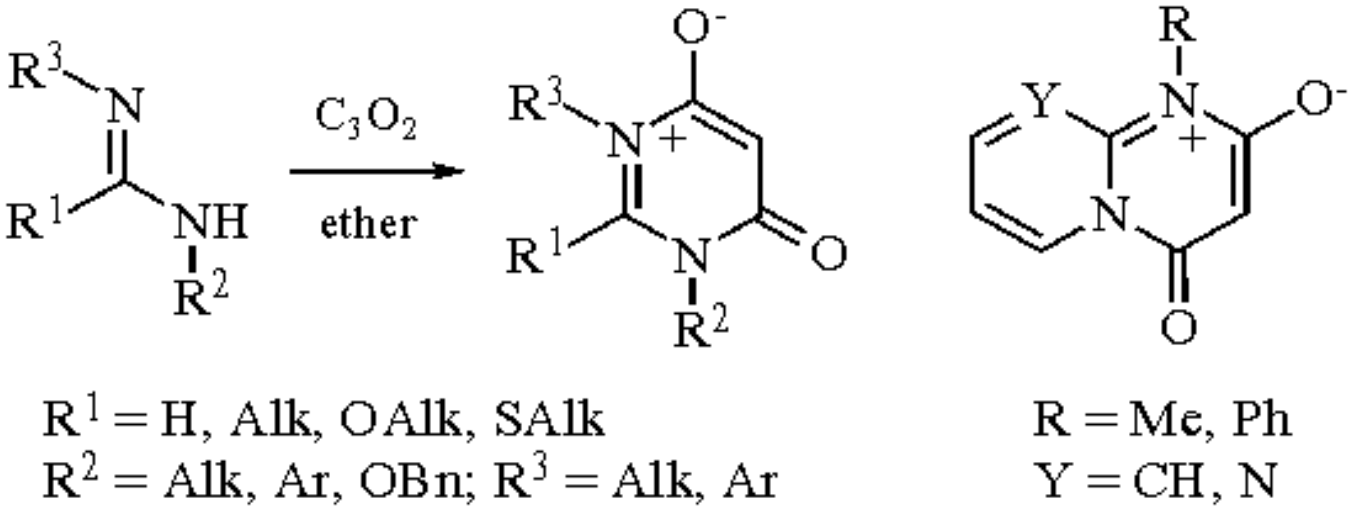

(2)

Another example is the synthesis of 4-hydroxy-2-pyrones (**1**), structural units found in many natural products. Silyl enol ether derivatives of aldehydes and ketones react smoothly with C_3O_2 to afford the trimethylsilyl ether of the target compounds, which are easily hydrolyzed to (**1**) (eq 3).[10] Ketones themselves react very sluggishly with C_3O_2 even if catalyzed by Lewis acids, and then they afford the pyronopyrones (**2**) in low yield by reaction of a second equivalent of C_3O_2 with (**1**) (eq 4).[11] The reason is that ketones are less nucleophilic than 4-hydroxy-2-pyrones. Thus acetone yields (**2**) (R^1 = H, R^2 = Me) in only 8% yield,[12] whereas triacetic acid lactone (**1**) (R^1 = H, R^2 = Me) affords the same compound (**2**) in 20% yield. The addition of 2 equiv of C_3O_2 to a substrate, leading to pyrono derivatives of the expected compound, is frequently observed in carbon suboxide reactions.[1]

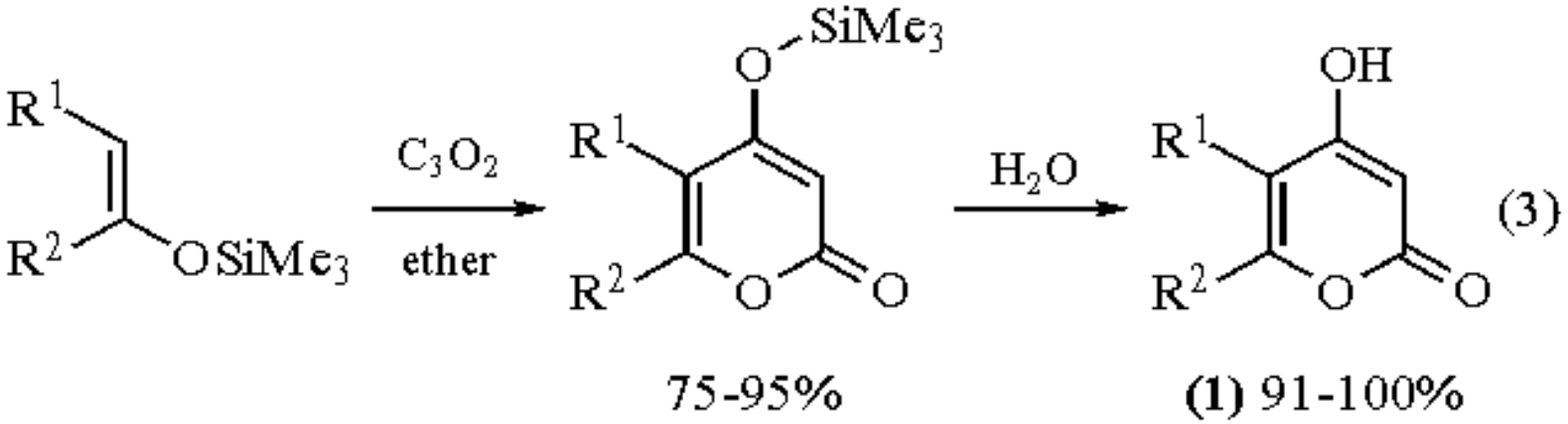

$R^1 = H$, Alk; $R^2 = H$, Alk, Ar; R^1-R^2 = -$(CH_2)_3$-

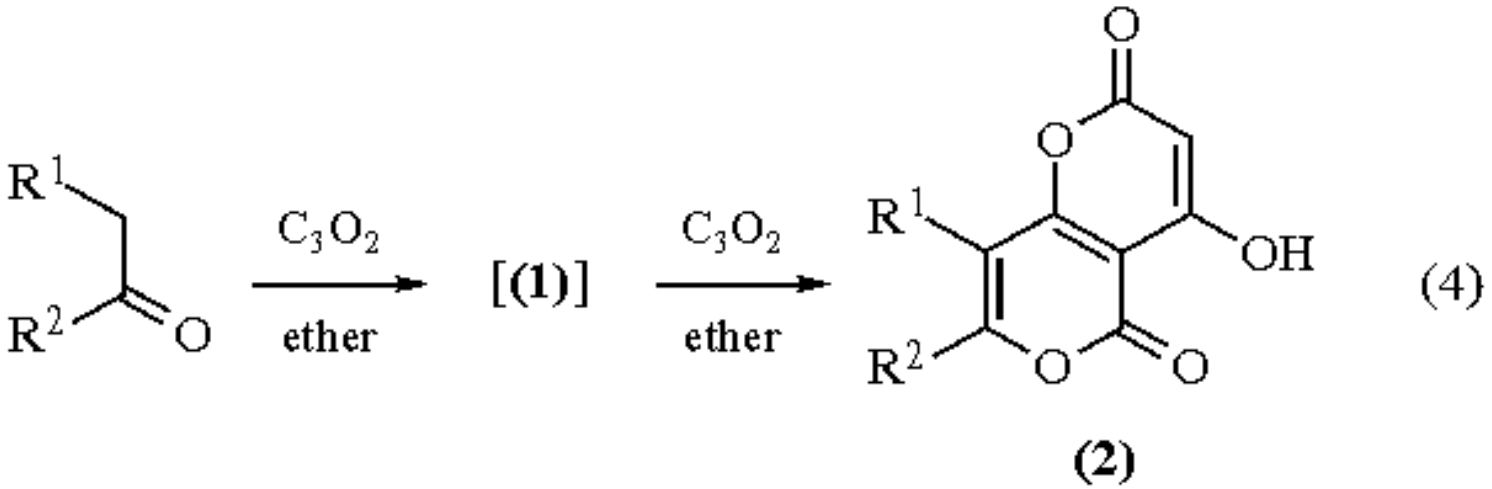

Alternatives.

Malonyl Chloride, ***Bis(2,4,6-trichlorophenyl) Malonate***, and even ***Diethyl Malonate*** may be used as substitutes. The reaction of trimethylsilyl enol ethers with malonyl dichloride (eq 3) may serve as an example since 4-hydroxy-2-pyrones are also formed with this reagent;[13] however, the yield is much lower and side products are formed. It has been shown that *N*-substituted 2-amino heterocycles form zwitterionic bicyclic pyrimido derivatives (eq 2) in good yields if heated with bis(2,4,6-trichlorophenyl) malonate (AME) to 160 °C for 3 minutes.[14] Heating of 2-phenylaminopyridine with diethyl malonate in tetralin forms the expected pyridopyrimidine betaine (eq 2) in 25% yield.[15]

Related Reagents.

Bis(2,4,6-trichlorophenyl) Malonate; ***Bis(trimethylsilyl) Malonate***; ***(Chlorocarbonyl)ethylketene***; ***Diethyl Malonate***; ***Malonic Acid***; ***Malonyl Chloride***.

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Carbon Tetrabromide

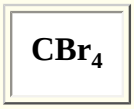

[558-13-4] · CBr_4 · Carbon Tetrabromide · (MW 331.65)

(brominating agent used in synthesis of α-acetoxycarboxylic acids[4] and allenes;[5-8] radical additions to alkenes[12-28]).

Alternate Name: tetrabromomethane.

Physical Data: shining plates, mp 88-90 °C; bp 190 °C (dec).

Solubility: insol in water, sol in organic solvents.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: FT-IR data.[1]

Preparative Method: carbon tetrabromide is most conveniently prepared by the exhaustive bromination of acetone in the presence of alkali.[2]

Purification: can be sublimed in vacuo; bromide removal via reflux with dil aq Na_2CO_3, followed by steam-distillation and EtOH recrystallization.[29]

Handling, Storage, and Precautions: safety data are available.[3]

Carbon Tetrabromide-Tin(II) Fluoride.

The reaction of aldehydes with CBr_4 and SnF_2 in DMSO at 25 °C gives 1-substituted 2,2,2-tribromoethanols in moderate to good yields. The acetate of the product can be hydrolyzed to an α-acetoxycarboxylic acid by $AgNO_3$ (eq 1).[4]

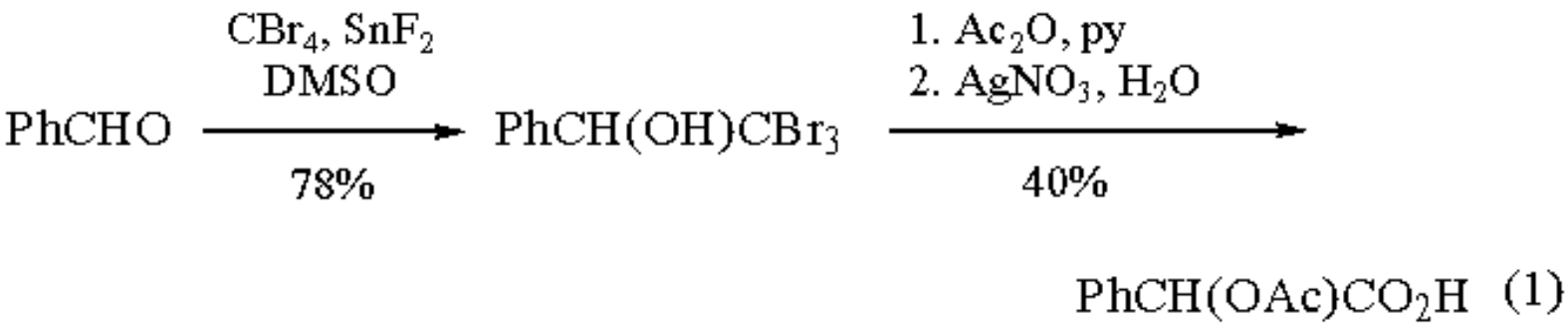

2,3-Diacetyl-D-erythronolactone[4] has been prepared in a similar fashion (eq 2).

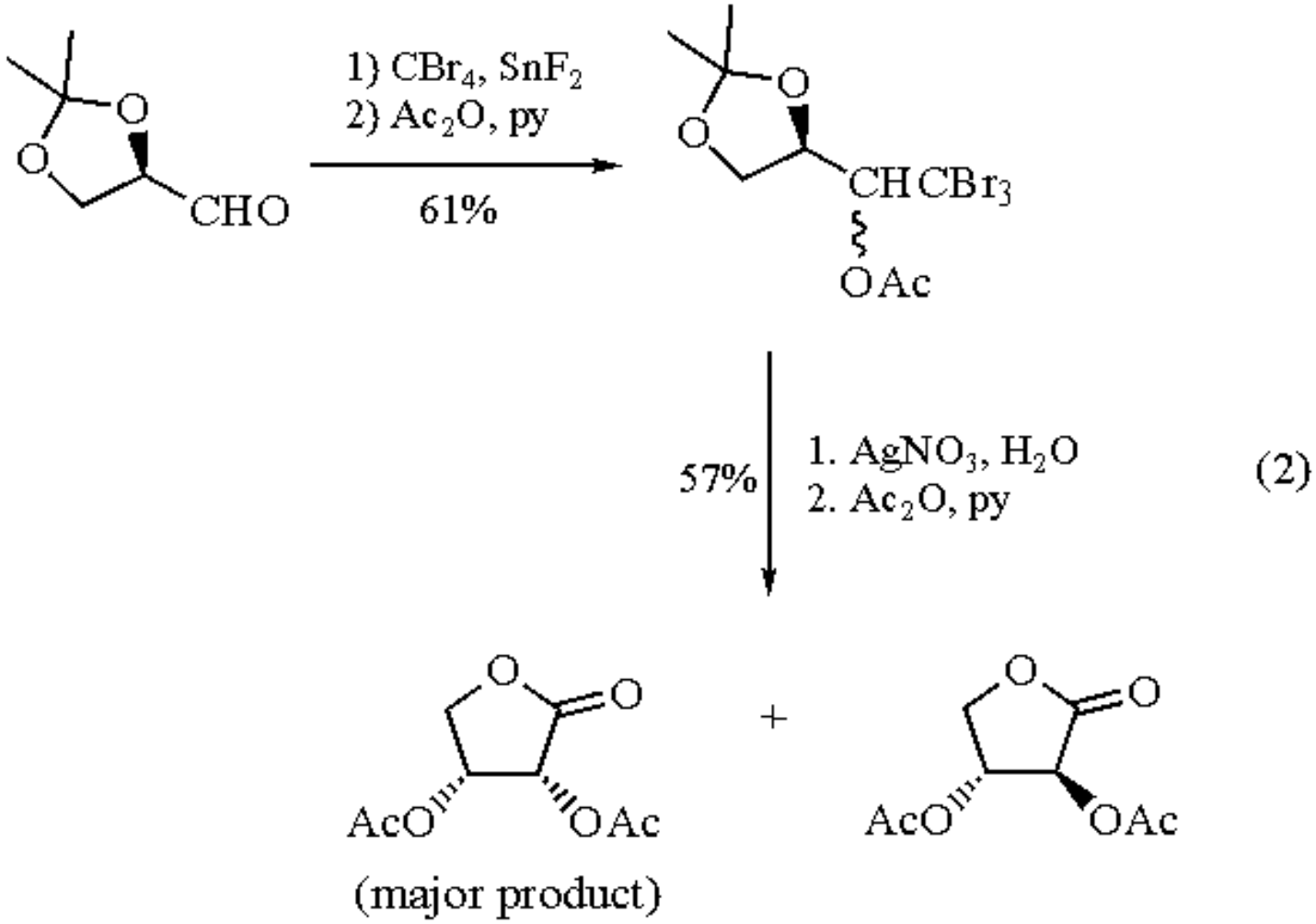

Allene Synthesis.

The system of carbon tetrabromide (1 equiv) with methyllithium (2 equiv) converts C_n alkenes into C_{n+1} allenes.[5-8] The synthesis of 1,2,6-cyclodecatriene from *cis,cis*-1,5-cyclononadiene[7] serves as an example (eq 3).

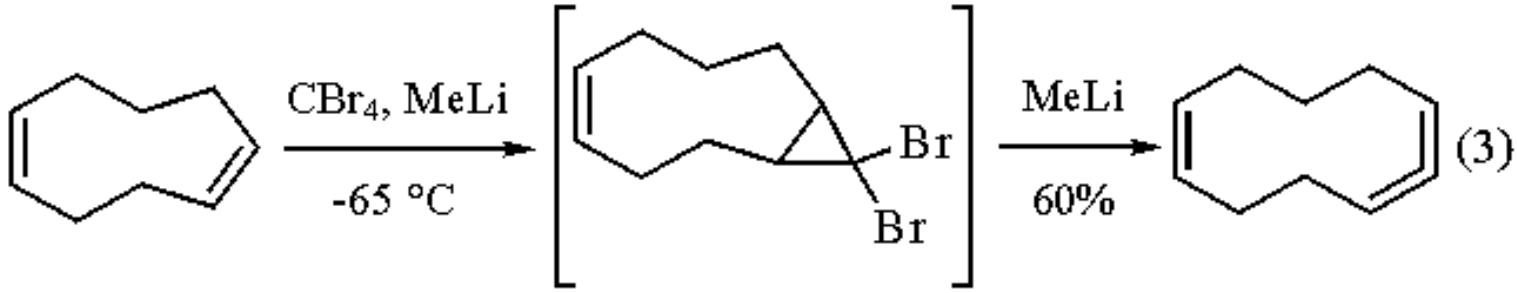

When 1 equiv of MeLi is used, the intermediate dibromocyclopropane can be isolated (eqs 4 and 5). Bicyclobutanes are the sole products when the resulting allene would be highly strained (eq 4),[9] or they are significant byproducts (eq 5) when the allene possesses two bulky geminal groups.[10]

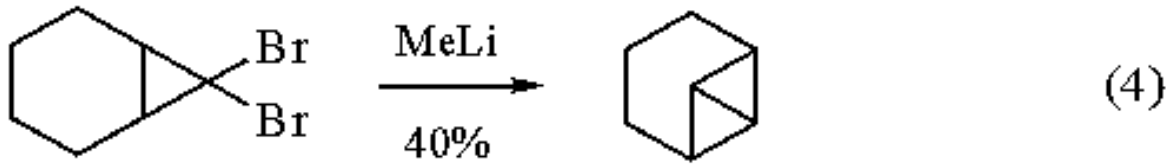

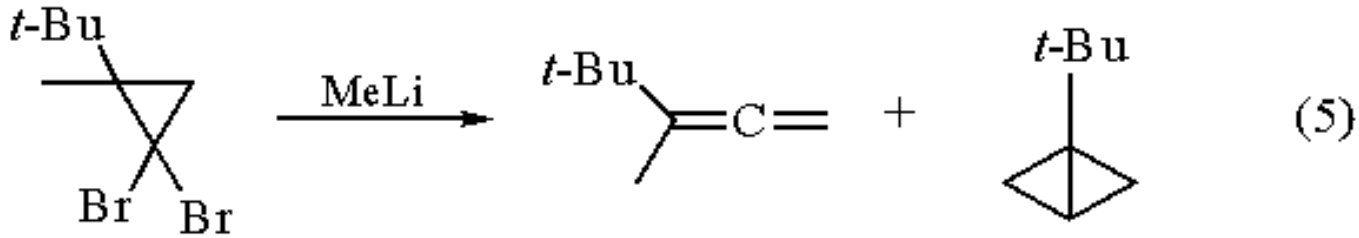

Dehalogenation of dibromocyclopropanes with an alkyllithium in the presence of (-)-sparteine gives optically active allenes of low optical purity.[11]

Radical Reactions.

The addition of CBr_4, or other halogenocarbons, to alkenes is known as the Kharasch reaction. The reactions of terminal alkenes furnish the addition products in the highest yields (eq 6).

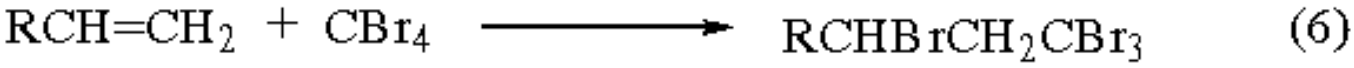

The reaction can be initiated by photoirradiation,[12] radical initiators,[13] inorganic salts,[14,15] ruthenium complexes,[16-19] other transition metal complexes,[20-24] samarium diiodide,[25] or by a manganic salt generated electrochemically in situ.[26] The scope and limitations of this reaction have been reviewed in two monographs.[27,28]

For related chemistry using CBr_4, see the entries ***Triphenylphosphine-Carbon Tetrabromide***, ***Triphenylphosphine-Carbon Tetrabromide-Lithium Azide***, ***Tribromomethyllithium*** and ***1,2-Bis(diphenylphosphino)ethane***.

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1,1´-Carbonylbis(3-imidazolium) Bis(methanesulfonate)

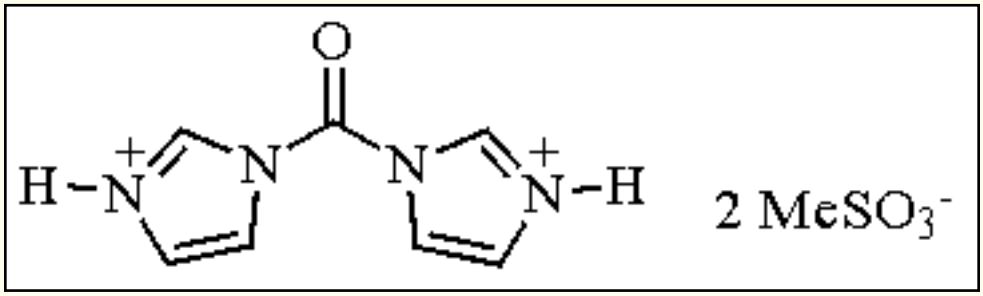

[82257-34-9] · $C_9H_{14}N_4O_7S$ · 1,1´-Carbonylbis(3-imidazolium) Bis(methanesulfonate) · (MW 354.33)

(dehydrating agent capable of preparing isocyanides under acidic conditions[2])

Preparative Method: freshly prepared by adding ***Methanesulfonic Acid*** to a solution of ***N,N´-Carbonyldiimidazole*** in acetonitrile.

The preparation of isocyanides from *N*-alkylformamides is typically accomplished with a dehydrating agent under basic conditions.[1,3] The preparation of isocyanides using ***Trichloromethyl Chloroformate*** (diphosgene)[4] and chlorodimethylforminium chloride[5] (Vilsmeier reagent) has been reported. The title reagent was developed to prepare chiral isocyanides from chiral *N*-formyl amino acids, with minimal racemization (eq 1). The other, more basic, reaction conditions had proven unacceptable.

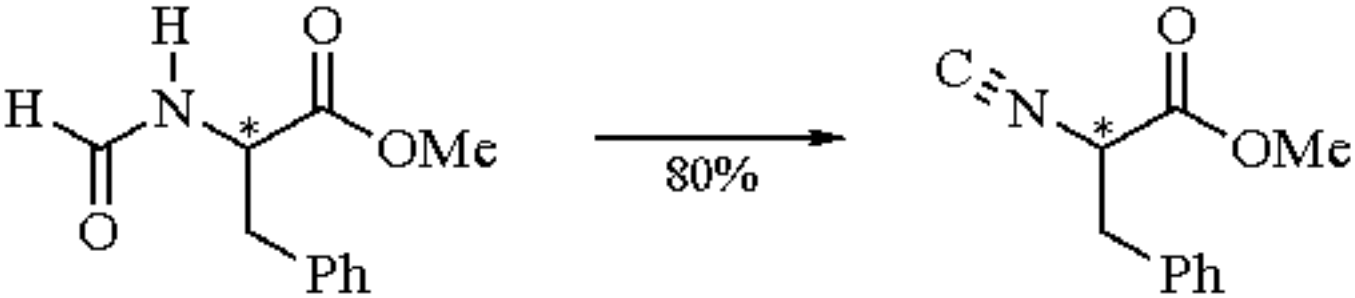

(1)

The reaction was carried out with freshly prepared carbonylbis(3-imidazolium) bis(methanesulfonate) in acetonitrile, at ambient temperature, over 4 h. Carbonyldiimidazole, without methanesulfonic acid, did

not effect the transformation. Cyclohexyl isocyanide (85%), *t*-butyl isocyanide (85%), and methyl-L-2-isocyanoisovalerate (90%) were prepared to further demonstrate the reagent. Carbonylbis-(3-imidazolium) bis(methanesulfonate) failed to prepare 2-nitro-5-methoxyphenyl isocyanide from the corresponding *N*-formylanilide. Carbonylbis-(3-imidazolium) bis(methanesulfonate) is conveniently prepared from readily available starting materials and avoids the problems associated with handling ***Phosgene*** or phosgene equivalents.

---

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1,1´-Carbonylbis(3-methylimidazolium) Bis(trifluoromethanesulfonate)[1]

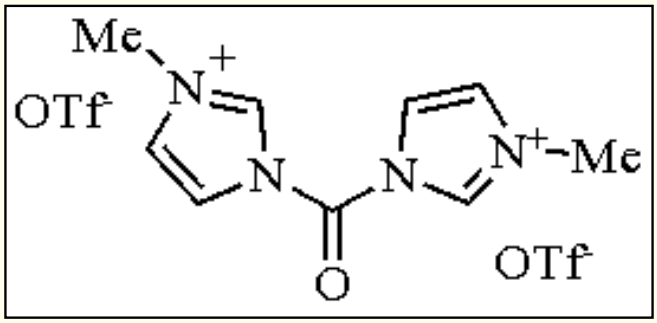

[120418-31-7] · $C_{11}H_{12}F_6N_4O_7S_2$ · 1,1´-Carbonylbis(3-methylimidazolium) Bis(trifluoromethanesulfonate) · (MW 490.36)

(versatile coupling reagent for aminoacylations[2])

Alternate Name: 1,1-carbonylbis(3-methylimidazolium) bistriflate.

Physical Data: pale white solid mp 78-80 °C; ^{1}H δ ($CDCl_3$) 8.86 (s, 2H), 7.44 (m, 2H), 7.16 (m, 2H), 4.00 (s, 6H).

Solubility: sol nitromethane, chloroform; insol ether; reacts with water.

Analysis of Reagent Purity: freshly prepared sample is treated with water: 200 mol % of *N*-methylimidazolium triflate is produced along with CO_2.

Preparative Methods: fresh methyl triflate is added to 1,1-carbonylbisimidazole in nitromethane at 10 °C. Solvent is then removed in vacuo, or the reagent used in situ.[2]

Handling, Storage, and Precautions: usually prepared under anhydrous conditions and used immediately. Can be stored in dry nitromethane solution or in solid state in absence of moisture. Preparation using aged methyl triflate should be avoided, owing to possible contamination of the coupling reagent with triflic acid.[2]

Coupling Reactions.

When *N*-Cbz derived amino acids are exposed to a freshly prepared solution of carbonylbis(3-methylimidazolium) triflate in nitromethane, coupling ensues with loss of CO_2 to give the derived amide and one equivalent of methylimidazolium triflate (eq 1).[2]

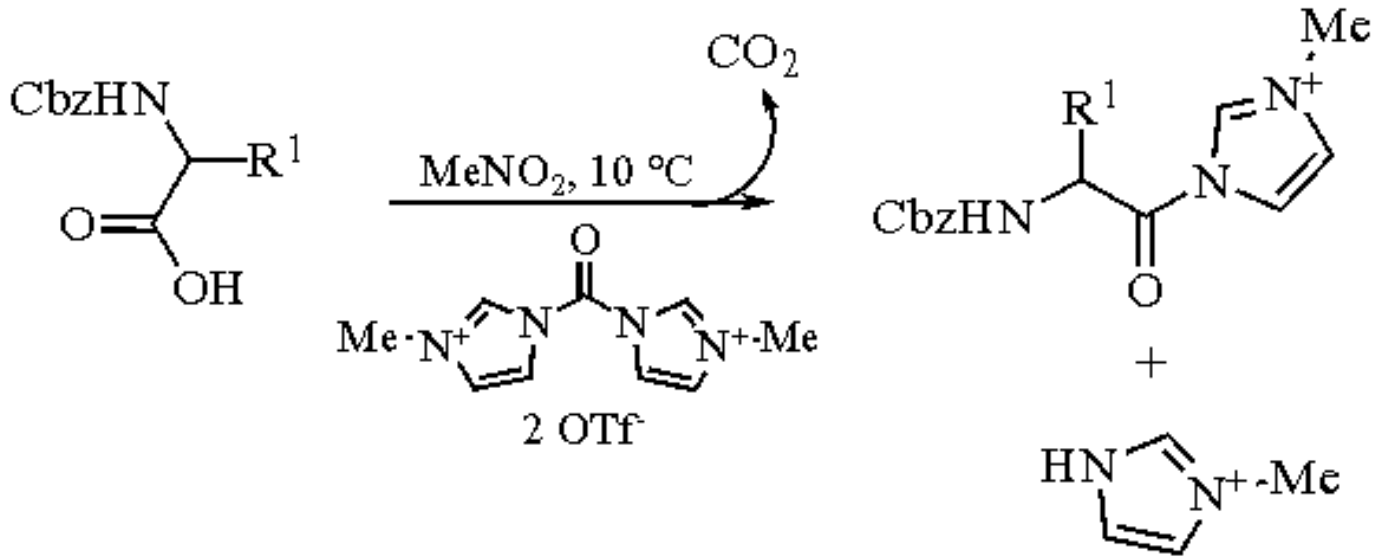

(1)

The acylated species so prepared can be coupled with alcohols to yield esters or with amines to form amides. The yields of coupled product are typically high and formation of the coupled products takes place within 15 min in the case of amides (eq 2) and within 3 h for esters.[2]

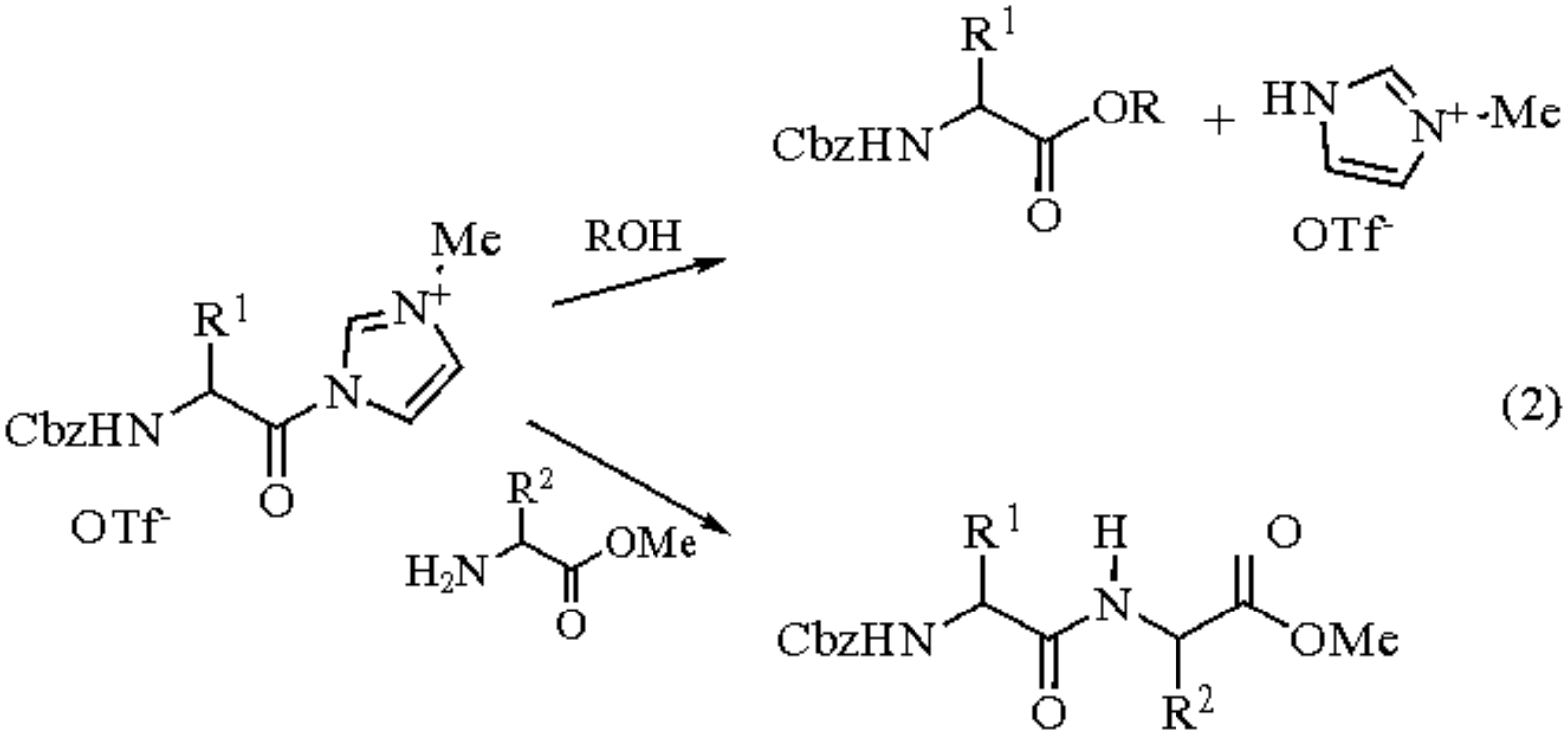

(2)

Of particular note is the fact that sterically hindered alcohols (e.g. menthol) couple in nearly quantitative yield (eq 3).

Racemization is not prevalent under these neutral conditions: routine analysis of the diastereomeric excess of coupled products revealed a >99.75:0.25 ratio, confirming both the mildness of the system and the near neutral conditions that persist during the coupling. The system compares most favorably against conventional coupling agents such as ***N,N´-Carbonyldiimidazole***,[3,4] where sluggish *O*-acylations are common[5] and racemization of the acyl component in the couplings has been observed.[6]

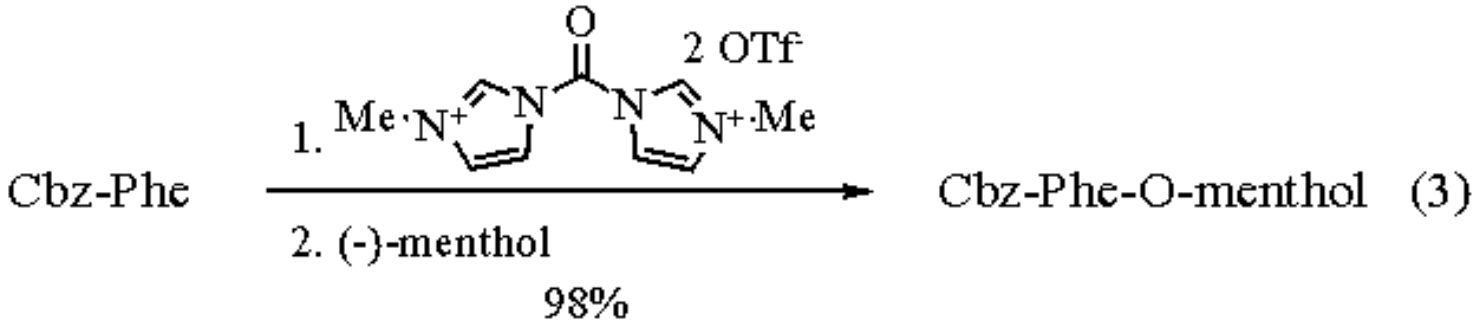

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trans-Carbonyl(chloro)bis(triphenylphosphine)iridium(I)[1]

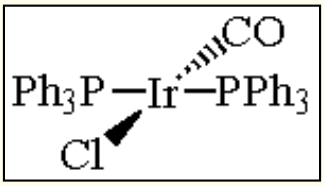

[14871-41-1] · $C_{37}H_{30}ClIrOP_2$ · *trans*-Carbonyl(chloro)bis(triphenylphosphine)iridium(I) · (MW 780.264)

(catalyst precursor for homogeneous hydrogenations,[2,3] decarbonylation of acyl halides,[10] and the hydrosilation[12] and hydroboration[13] of alkenes)

Alternate Name: Vaska's compound.

Physical Data: mp 327-8 °C (dec); ^{1}H NMR δ (C_6D_6) 6.6 (m);[15] IR νCO = 1953 cm^{-1} (nujol).

Solubility: sol toluene and chloroform; insol diethyl ether and alcohols.

Form Supplied in: yellow crystals, widely available.

Preparative Method: in a round-bottomed flask a mixture containing 3.52 g (10 mmol) of $IrCl_3.3H_2O$, 13.1 g (50 mmol) of PPh_3, 4 mL of aniline, and 150 mL of DMF is heated under nitrogen at reflux for 12 h. After filtering the resulting red-brown solution hot, 300 mL of warm methanol is added rapidly and the mixture stirred. Upon cooling in an ice bath, yellow crystals of *trans*-$IrCl(CO)(PPh_3)_2$ are collected on a filter and washed with 250 mL of methanol and then with 25 mL of diethyl ether (87-90%).

Handling, Storage, and Precautions: the compound is stable in air but readily takes up oxygen in solution.

Hydrogenation.

Although *trans*-$IrCl(CO)(PPh_3)_2$ was initially prepared by Angoletta[2] it was correctly formulated by Vaska[3] and henceforth has commonly been referred to as Vaska's compound. While a number of alkenes and activated alkynes can be hydrogenated in the presence of a catalytic amount of Vaska's compound, isomerization is frequently a faster pathway and during the course of the reaction a number of isomers can accumulate.[4] The catalyst precursor can be activated by weak UV radiation. Indeed, under these conditions 1,3-cyclohexadiene can be hydrogenated selectively (98%) to cyclohexene (eq 1), a reaction that does not take place thermally.[5] In a related study, butynediol is selectively hydrogenated during photolysis using Vaska's compound in toluene/trifluoroethanol (1:1).[7]

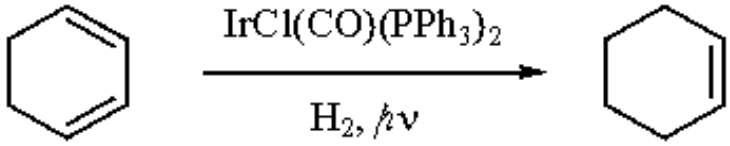

(1)

Hydrogen Transfer.

Selective hydrogen transfer from ***Formic Acid*** to α,β-enones can be accomplished with a catalytic amount of *trans*-IrCl(CO)$(PPh_3)_2$ (eq 2).[8] The polystyrene-supported reagent is an even more efficient catalyst for this transfer hydrogenation (with 70% conversion).[9]

$$RCH{=}CHCOR' + HCO_2H \longrightarrow RCH_2CH_2COR' + CO_2 \quad (2)$$

Decarbonylation.

Vaska's compound can also be used to catalyze the decarbonylation and dehydrohalogenation of aliphatic acid halides into mixtures of alkenes selectively and under mild conditions (yields ca. 75%).[10] Aromatic acid halides are not affected, making it possible to eliminate selectively one carbonyl functionality from the dichloride of 4-(*p*-carboxyphenyl)butyric acid, *p*-$ClOCC_6H_4(CH_2)_3COCl$. The resulting *p*-allylbenzoyl chloride is unstable, however, leading to extensive polymerization. Vaska's compound also catalyzes the decarbonylation of formate esters to alcohols and carbon monoxide.[11]

H-X Addition.

Vaska's compound catalyzes the regioselective hydrosilation of alkynes and styrenes with a number of silane reagents at high temperatures.[12] For example, addition of ***Triethylsilane*** to phenylacetylene using Vaska's compound in catalytic amounts affords the β_{trans} adduct in 88% yield. Photolysis of *trans*-IrCl(CO)$(PPh_3)_2$ leads to a moderately active catalyst for the hydroboration of 1-octene with ***Catecholborane*** (eq 3).[13] Unfortunately, no reaction is observed with styrenes under identical conditions. More active and selective rhodium catalysts for the hydroboration of alkenes are well established.[14]

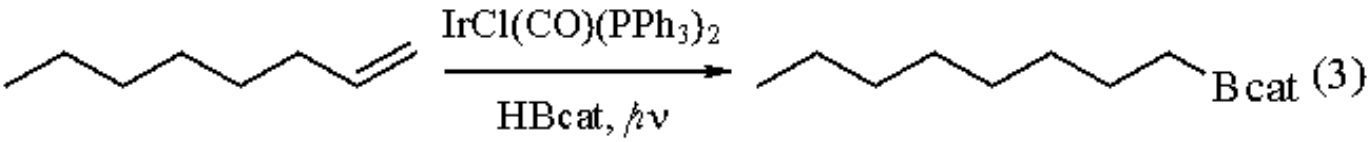

(3)

Related Reagents.

Carbonyl(chloro)bis(triphenylphosphine)rhodium(I); ***Chlorotris(triphenylphosphine)rhodium(I)***.

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Carbonyl(chloro)bis(triphenylphosphine)rhodium(I)[1]

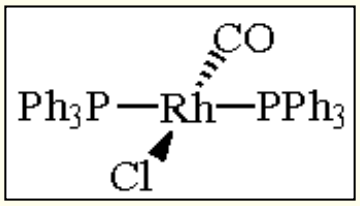

(*trans*/*cis*)

[13938-94-8] · $C_{37}H_{30}ClOP_2Rh$ · Carbonyl(chloro)bis(triphenylphosphine)rhodium(I) · (MW 690.96) (*trans*)

[15318-33-9] (*cis*)

[16353-77-8]

(catalyst for carbonylation,[2] decarbonylation,[3] carbonyl exchange,[4] reduction,[5] hydrometalation,[6] and C-H activation reactions;[7] reagent for alkylation of acid chlorides[8])

Physical Data: mp 209-210 °C (*trans* isomer), 204-205 °C (*cis* isomer), 195-197 °C (*trans*/*cis* mixture); IR carbonyl stretching 1970 cm^{-1} (nujol mull), 1977 cm^{-1} ($CHCl_3$).

Solubility: sol chloroform and dichloromethane; moderately sol aromatic hydrocarbons and CCl_4; insol ether, alcohols, and aliphatic hydrocarbons.

Form Supplied in: bright yellow crystalline solid, widely available.

Preparative Methods: to a solution of $RhCl_3.3H_2O$ (2 g, 7.6 mmol) in 70 mL of absolute ethanol is slowly added triphenylphosphine (7.2 g, 2.75 mmol) in 300 mL of boiling absolute ethanol. The solution becomes clear within 5 min, at which point sufficient (10-20 mL) 37% formaldehyde solution is added, causing the red solution to become pale yellow. After several minutes, yellow microcrystals precipitate. Upon cooling, the resulting crystals are washed with ethanol and diethyl ether, dried (4.5 g, 85%) and recrystallized from hot toluene.[1c]

Handling, Storage, and Precautions: the complex is air-stable as a crystalline solid and can be stored without special precautions. In solution it readily reacts with oxygen, which therefore must be excluded during preparation and use of this reagent.

Carbonylation Reactions.

Rhodium is the most widely used catalyst for the carbonylation of alkenes with CO and H_2.[1,2] Although $RhH(CO)_2L_2$ (L = PPh_3, PBu_3, etc.) is recognized as the actual species that reacts with alkenes in the ligand modified rhodium catalyst system, many other rhodium complexes can be utilized as precursors in the presence of suitable ligands (L), CO, and H_2. $RhCl(CO)(PPh_3)_2$ has been used as a catalyst precursor in the hydroformylation of alkenes and formaldehyde.[1b,2b]

Hydroformylation of terminal alkenes produces a mixture of regioisomeric linear and branched aldehydes. Triphenylphosphine-stabilized rhodium catalysts can be used to form linear, unbranched aldehydes from simple alkenes such as propene. The presence of

triphenylphosphine, however, gives poor results in the hydroformylation of $R_fCH{=}CH_2$ (R_f = perfluoroalkyl group), which with ***Dodecacarbonyltetrarhodium*** or ***Hexadecacarbonylhexarhodium*** produces the branched aldehydes $R_fCH(CHO)Me$ regioselectively and in good yields.[9]

Heterocyclic compounds have been obtained through rhodium-catalyzed hydroformylation of functionalized alkenes such as allylamines (eq 1),[10] 3-butenamides (eq 2)[11] and allyl alcohols.[12]

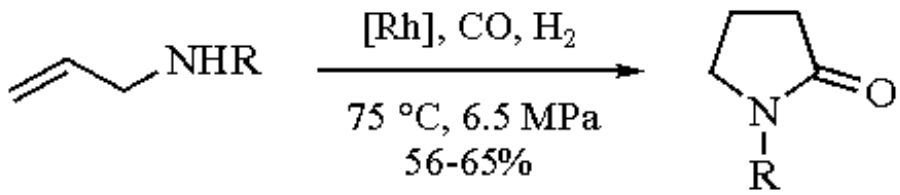

(1)

$[Rh] = RhCl(CO)(PPh_3)_2$ or $Rh(acac)CO(PPh_3)_2$

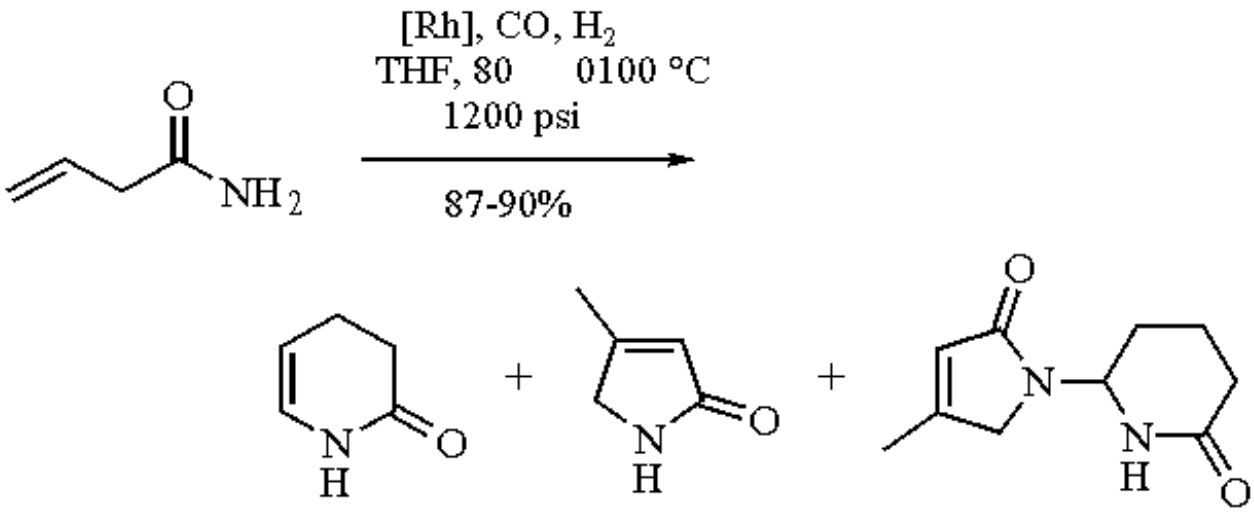

(2)

[Rh]	
$RhCl(CO)(PPh_3)_2$	53:47: 0
$RhH(CO)PPh_3)_3$-dppb	98: 2: 0
$RhCl(PPh_3)_3$	53:41: 6
$RhCl(PPh_3)_3$-10 $P(OPh)_3$	3: 3:94

Hydroformylation of formaldehyde has been extensively investigated because of its importance to the commercial production of ethylene glycol (eq 3).[1b,13] The $RhCl(CO)(PPh_3)_2$-***Triethylamine*** catalyst system produced a mixture of straight chain carbohydrates, from trioses to hexoses.[14] The hydroformylation in the presence of 3-ethylbenzothiazolinium bromide gives trioses selectively.

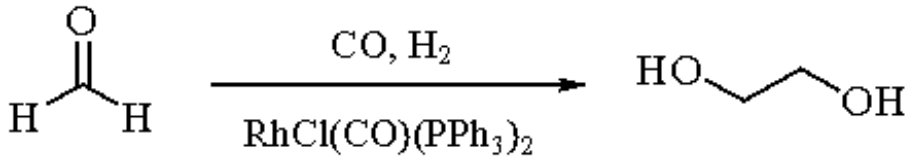

(3)

$RhCl(CO)(PPh_3)_2$ catalyzes the reaction of CO with epoxides (eq 4),[15] amines (eqs 5 and 6),[16,17] and azides (eq 7).[17]

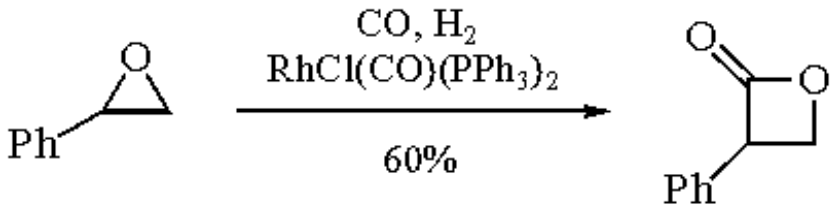

(4)

$$RNH_2 \xrightarrow{CO,\ [Rh]} RNHCHO + (RNH)_2CO \qquad (5)$$

$$ArNH_2 \xrightarrow[{[Rh]}]{CO,\ EtOH} ArNHCO_2Et \qquad (6)$$

$$ArN_3 \xrightarrow[{[Rh]}]{CO} ArNCO + N_2 \qquad (7)$$

$$[Rh] = RhCl(CO)(PPh_3)_2,\ [RhCl(CO)(dppe)]_2,\ [Rh(dppp)_2Cl]_2$$

Decarbonylation Reactions.

$RhCl(CO)(PPh_3)_2$ is a product of the stoichiometric decarbonylation of aldehydes with ***Chlorotris(triphenylphosphine)rhodium(I)*** (eq 8).[3b,18] However, at elevated temperatures $RhCl(CO)(PPh_3)_2$ is an effective catalyst for the decarbonylation of aroyl chlorides and aroyl cyanides (eq 9).[3a,19]

$$RCHO \xrightarrow{RhCl(PPh_3)_3} RH + RhCl(CO)(PPh_3)_2 \qquad (8)$$

$$ArCOX \xrightarrow[{50\text{-}95\%}]{RhCl(CO)(PPh_3)_2,\ 200\ ^\circ C} ArX + CO \qquad (9)$$

$$X = Cl,\ CN$$

Carbonyl Exchange (Isotope Labelling).

The carbonyl carbon of aroyl chlorides can be ^{13}C or ^{14}C labelled through acyl carbonyl exchange reactions with CO catalyzed by $RhCl(CO)(PPh_3)_2$ without formation of aryl chloride (ArCl) decarbonylation products (eqs 10 and 11).[4] Statistical distribution of ^{13}C is easily attained. The carbonyl group of aliphatic acid chlorides is also easily exchanged, but small amounts of decarbonylated products are formed.[4] Alkene migration or isomerization does not occur in the carbonyl exchange reactions of 3-butenoyl chlorides, although 1,3-scrambling of chlorine has been observed in the $RhCl(PPh_3)_3$-catalyzed decarbonylation of 3-butenoyl chlorides to allyl chlorides.[20]

$$\mathrm{ArCOCl} + {}^{13}\mathrm{CO} \xrightleftharpoons{\mathrm{RhCl(PPh_3)_3}} \mathrm{Ar}^{13}\mathrm{COCl} + \mathrm{CO} \quad (10)$$

$$\mathrm{PhCOCl} + \mathrm{Me}^{14}\mathrm{COCl} \xrightleftharpoons{\mathrm{RhCl(CO)(PPh_3)_2}} \mathrm{Ph}^{14}\mathrm{COCl} + \mathrm{MeCOCl} \quad (11)$$

Reduction Reactions.

The most widely studied homogeneous hydrogenation catalysts are all rhodium complexes. $RhCl(CO)(PPh_3)_2$ has been rarely used because of its low reactivity as a hydrogenation catalyst. The low reactivity, however, allows it to be a potentially useful catalyst for selective hydrogenation of terminal alkenes.[21] $RhCl(CO)(PPh_3)_2$-catalyzed reduction of diphenylacetylene with ***Sodium Borohydride*** gives (*Z*)-stilbene, whereas (*E*)-stilbene is formed with $RhCl(PPh_3)_3$ as the catalyst.[22]

Aromatic nitro compounds are reduced in good yields to aromatic amines with secondary alcohols as the reducing agent using the $RhCl(CO)(PPh_3)_2$-KOAc catalyst system (eq 12).[23]

$$\mathrm{ArNO_2} \xrightarrow[\text{120-150 °C}]{\mathrm{RhCl(CO)(PPh_3)_2},\ \mathrm{R_2CHOH}} \mathrm{ArNH_2} \quad (12)$$

Hydrometalation Reactions.

For the catalytic hydrometalation of alkenes, $RhCl(CO)(PPh_3)_2$ has no advantages over $RhCl(PPh_3)_3$ and its congeners, chloroplatinic acid (***Hydrogen Hexachloroplatinate(IV)***),[24] or radical catalysts.[25] The regioselectivity of hydrometalation of terminal alkynes depends on the ligands. For example, the hydrosilation and hydrogermylation of phenylacetylene in the presence of $RhCl(CO)(PPh_3)_2$ gives (*E*)-1-silyl- or 1-germyl-substituted 2-phenylethylene, whereas with $Rh[(CF_3CO)_2CH](C_2H_4)_2$ the isomeric 2-metalated 2-phenylethylenes are produced (eq 13).[26] In the hydrostannation of terminal alkynes, $RhCl(CO)(PPh_3)_2$ gives 2-stannyl-1-alkenes as the major product.[6]

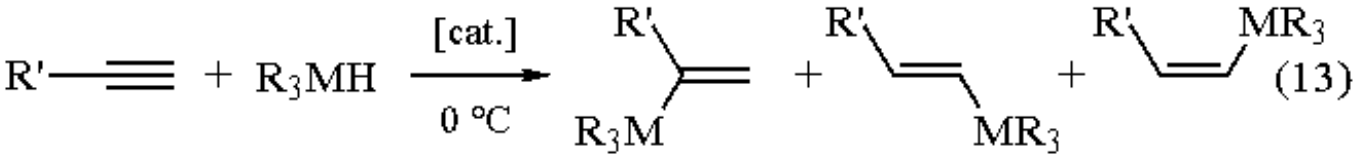

M	R'	R	[Cat]	Yield (%)	Isomer ratio
Si	Ph	Et	$RhCl(CO)(PPh_3)_2$	97	6:72:22
Si	Ph	Et	$Rh[(CF_3CO)_2CH](C_2H_4)_2$	93	96:4:trace
Ge	Ph	Bu	$RhCl(CO)(PPh_3)_2$	65	7:70:23
Ge	Ph	Bu	$Rh[(CF_3CO)_2CH](C_2H_4)_2$	85	95:4:1
Sn	Ph	Bu	AIBN, 80 °C	81	0:67:33
Sn	Ph	Bu	$RhCl(CO)(PPh_3)_2$	99	78:20:2
Sn	Ph	Bu	$RhCl(CO)(PPh_3)_2$, RI[a]	90	100:0:0
Sn	$AcOCH_2$	Bu	$RhCl(CO)(PPh_3)_2$	71	73:27:trace
Sn	$SiMe_3$	Bu	$RhCl(CO)(PPh_3)_2$	91	76:24:0

[a] RI = radical inhibitor, galvinoxyl

Hydrosilanes easily react with acylmetal complexes (metal = Fe, Mo, Mn) to form silyloxyalkyl metal complexes by using $RhCl(CO)(PPh_3)_2$ or $Rh(CO)(PPh_3)_3$ as catalysts.[27]

Hydrocarbon C-H Activation.

Under photochemical conditions, $RhCl(CO)(PPh_3)_2$ activates C-H bonds of aromatic and aliphatic hydrocarbons, leading to carbonylated products (eq 14)[7,28] and/or dehydrogenated products (eq 15).[29] UV irradiation of a solution of $RhCl(CO)(PPh_3)_2$ leads to the extrusion of CO to form a coordinatively unsaturated complex, $RhCl(PPh_3)_2$ (eq 16), which then inserts into the C-H bond of the hydrocarbon.[30] This photochemical reaction can be used for isotope labelling of aldehydes with ^{13}CO (eq 17).[28]

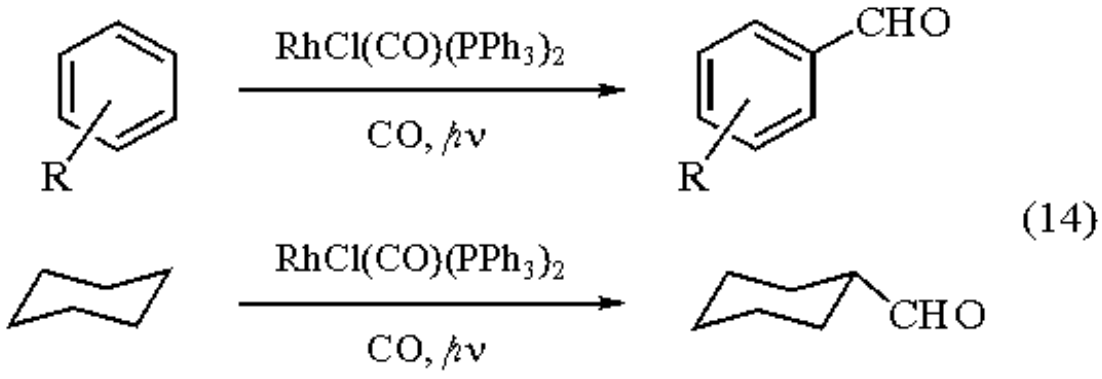

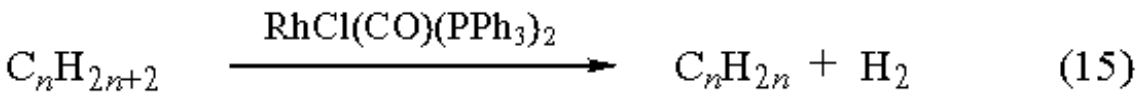

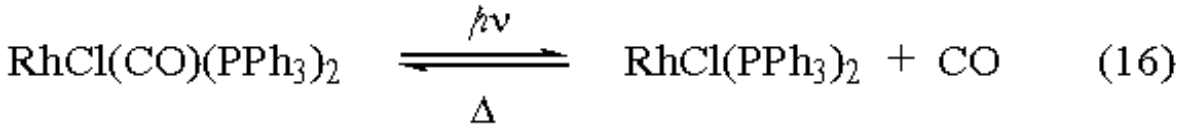

Alkylation of Acid Chlorides.

A number of rhodium complexes, including *trans*-RhCl(CO)$(PPh_3)_2$, facilitate the alkylation of acid chlorides, affording ketones in moderate to high yields.[8] This reaction proceeds by initial pretreatment of the catalyst precursor with an appropriate Grignard, organolithium, or organoytterbium[31] reagent to give an active alkylrhodium(I) species (eq 18). This reaction is specific for acid chlorides. Alkylation of ketones[32] and amines[33] can also be effected by *trans*-RhCl(CO)$(PPh_3)_2$ in a carbon monoxide-water system. In a more recent study,[34] nucleophilic addition of allylic stannanes to aromatic aldehydes has been accomplished by using derivatives of *trans*-RhCl(CO)$(PPh_3)_2$ in high yields (eq 19).

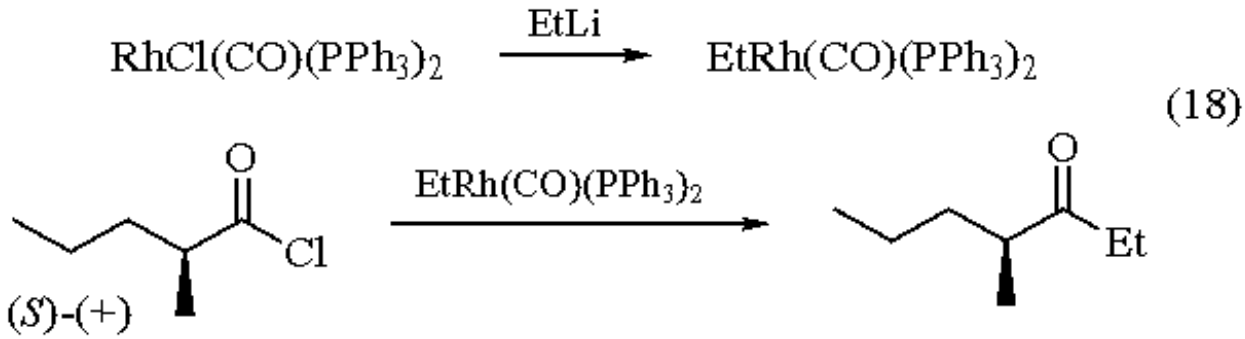

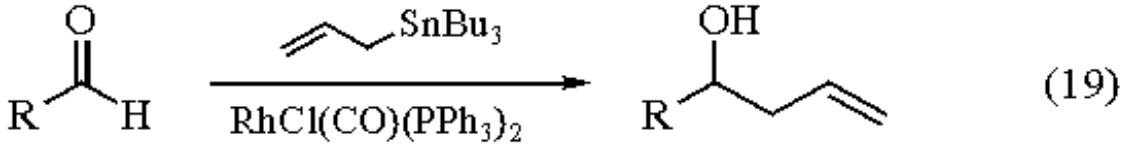

Oxidation Reactions.

The liquid phase oxidation of benzaldehyde to benzoic acid proceeds readily in the presence of a catalytic amount of *trans*-RhCl(CO)$(PPh_3)_2$ in benzene and under an atmosphere of oxygen (conversion is 78%).[35] Oxidation of terminal alkenes to methyl ketones also employs the use of a rhodium catalyst.[36]

Miscellaneous.

trans-RhCl(CO)$(PPh_3)_2$ is a moderately active catalyst precursor for the hydrosilation[37] and transfer hydrogenation[38] of imines. This rhodium complex is also used in the photochemical dehydrogenation of hydrocarbons,[39] and the thermal carbonylation of alkyl halides.[40]

The reaction of 1,5-dienes with hydrosilanes using *trans*-RhCl(CO)$(PPh_3)_2$ gives dehydrogenative silylation products, 1-silyl-1,5-dienes, in high yields (eq 20).[41]

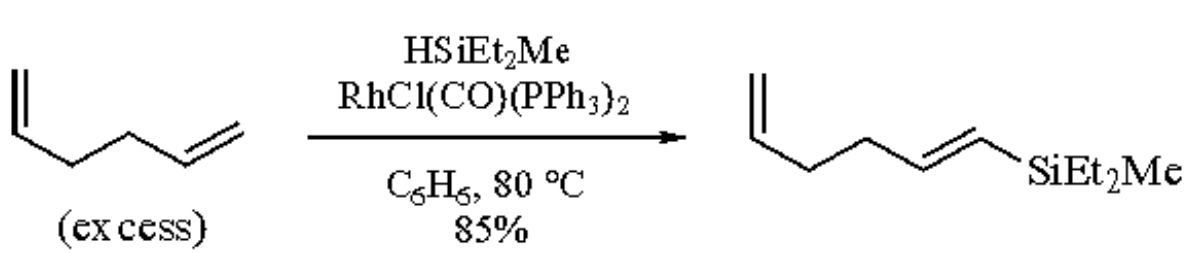

(20)

Related Reagents.

Carbonylhydridotris(triphenylphosphine)rhodium(I); ***Chlorotris(triphenylphosphine)rhodium(I)***.

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Carbonyl(cyclopentadienyl)(phthaloyl)cobalt[1]

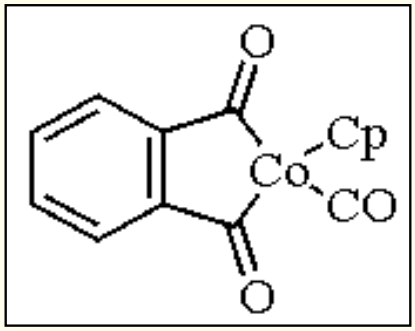

[99807-97-3] · $C_{14}H_9CoO_3$ · Carbonyl(cyclopentadienyl)(phthaloyl)cobalt · (MW 284.16)

(precursor to other cyclopentadienyl(phthaloyl)cobalt complexes which react with alkynes readily to give quinones or cyclopentadienylcobalt complexed quinones[1])

Physical Data: orange-yellow solid; mp 132-133 °C.

Solubility: very sol most organic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: ^{1}H NMR, IR, microanalysis.

Preparative Method: prepared in 98% yield by reaction of benzocyclobutenedione with commercially available dicarbonyl cyclopentadienylcobalt in xylene for 3.25 h at 160 °C.

Purification: flash chromatography on silica gel with petroleum ether.

Preparation of Phthaloyl- or Maleoyl(carbonyl)(cyclopentadienyl)cobalt Complexes.

Benzocyclobutenedione and 3,4-dimethylcyclobutenedione each react with ***Dicarbonyl(cyclopentadienyl)cobalt(I)*** in xylene to give carbonyl(cyclopentadienyl)cobalt complexes (**1**) and (**2**).[1] Analogously, they react with a mixture of ***Octacarbonyldicobalt*** and pentamethylcyclopentadiene to give carbonyl(pentamethylcyclopentadienyl)cobalt complexes (**3**) and (**4**) (eqs 1-4).[2-4]

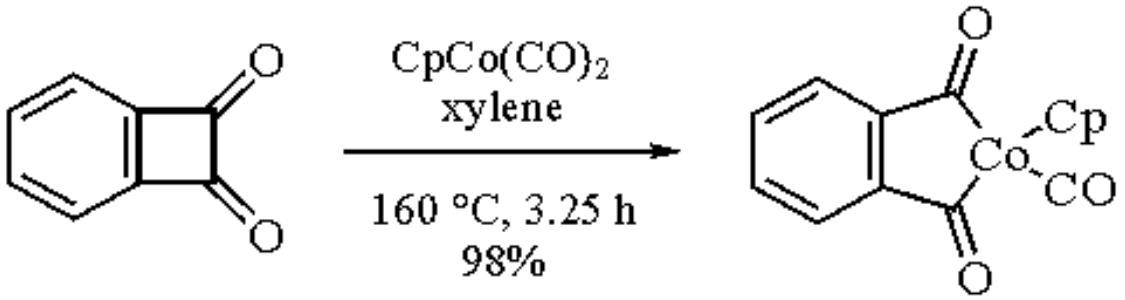

(1)

(1)
orange-yellow
mp 132-133 °C

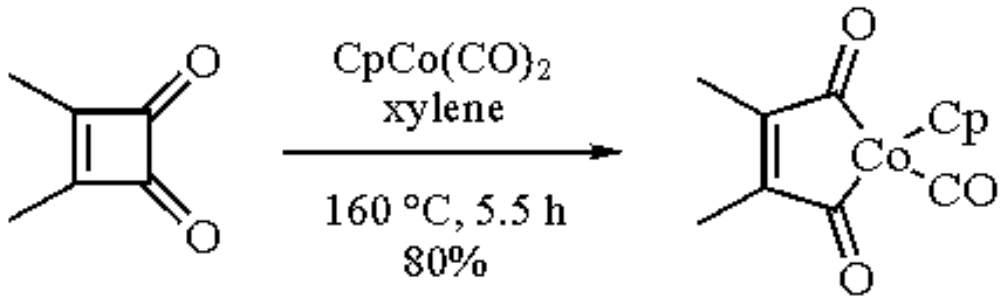

(2)

(2)
yellow
mp 80-81 °C

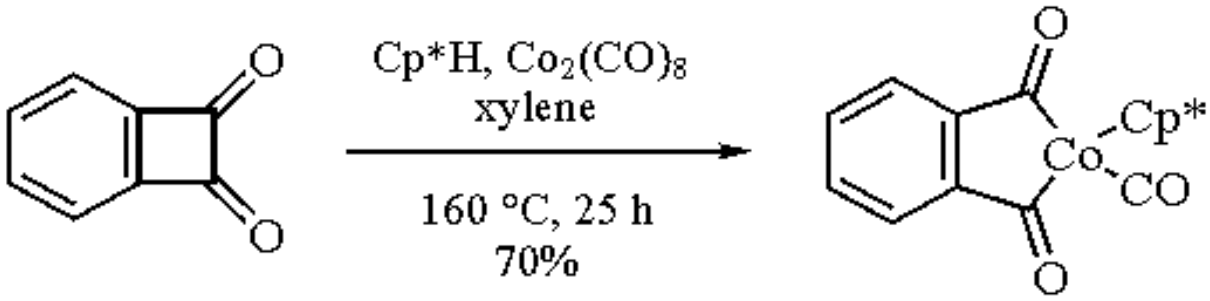

(3)

(3)
yellow-orange
mp 142-143 °C

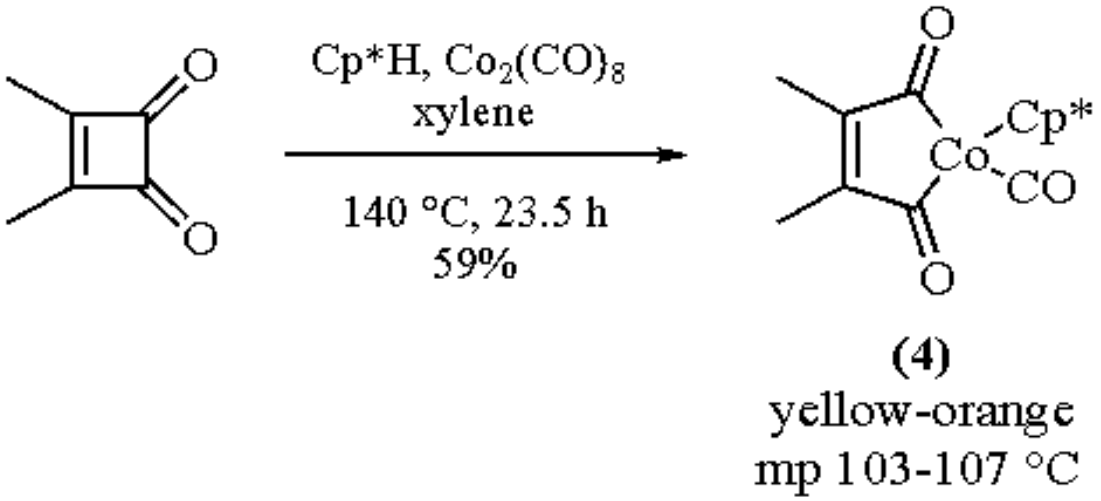

(4)

Synthesis of Quinones.

In general, phthaloyl and maleoyl transition metal complexes can be used in the synthesis of quinones[5,6] according to the following scheme: 1) an alkyne must coordinate to a free site on a coordinatively unsaturated metal center; 2) the alkyne must insert into the metal-carbonyl bond; and 3) the metal must reductively eliminate to give the quinone (eq 5).

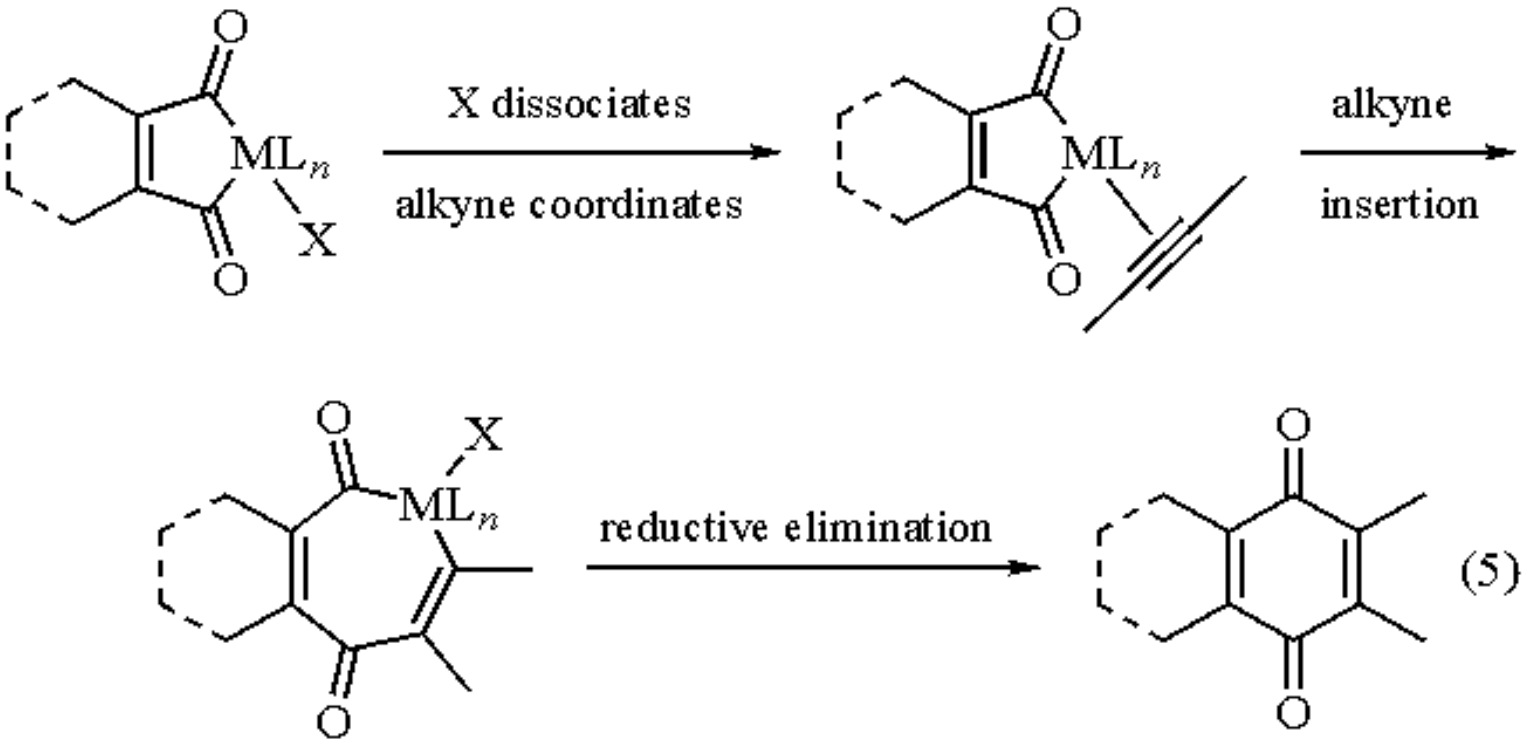

(5)

Complexes (**1**-**4**) do not react under thermal conditions (xylene, 120 °C) with alkynes. However, photolysis leads to dissociation of carbon monoxide, so when phthaloyl complex (**1**) is photolyzed in the presence of 3-hexyne it gives 2,3-diethyl-1,4-naphthoquinone (eq 6). However, when maleoyl complex (**2**) is treated under identical conditions, the cyclopentadienylcobalt complex of the corresponding benzoquinone is obtained (eq 7).[1] The 1,4-benzoquinones form more stable complexes with cyclopentadienylcobalt than the 1,4-naphthoquinones.

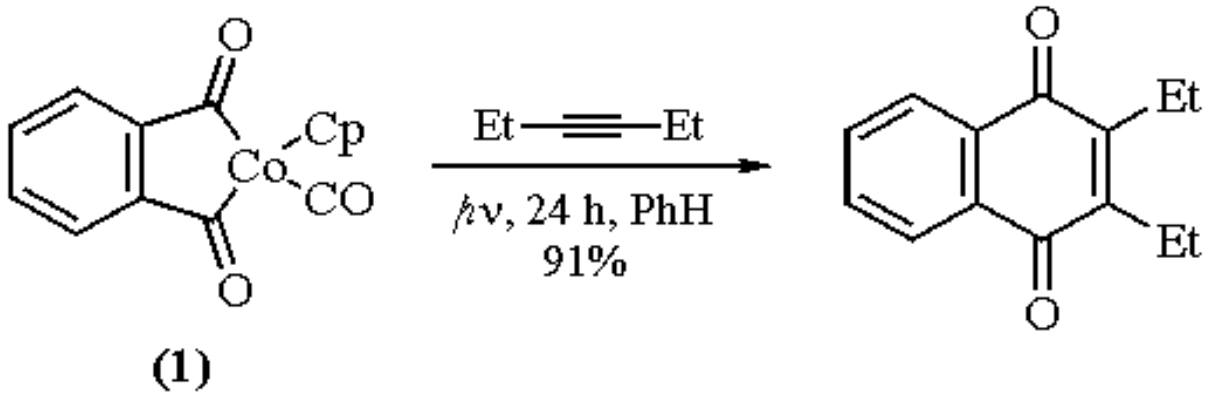

(1) (6)

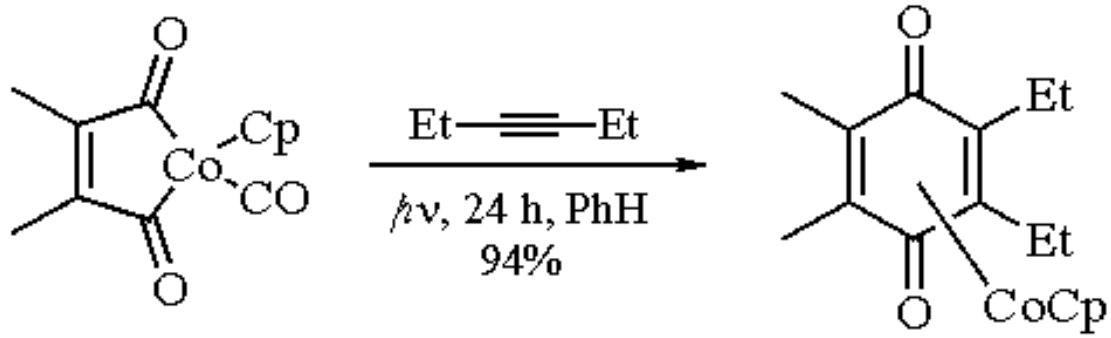

(2) (7)

Activation of complex (**1**) with ***Trimethylamine N-Oxide***, with acetonitrile as solvent, allows the isolation of the acetonitrile complex (**5**). This reacts with 3-hexyne to give the cyclopentadienyl(2,3-diethylnaphthoquinone)cobalt complex (**7**). Complex (**7**) can be formed in better yield under milder conditions by using the more labile benzonitrile complex (**6**) (eq 8).[1]

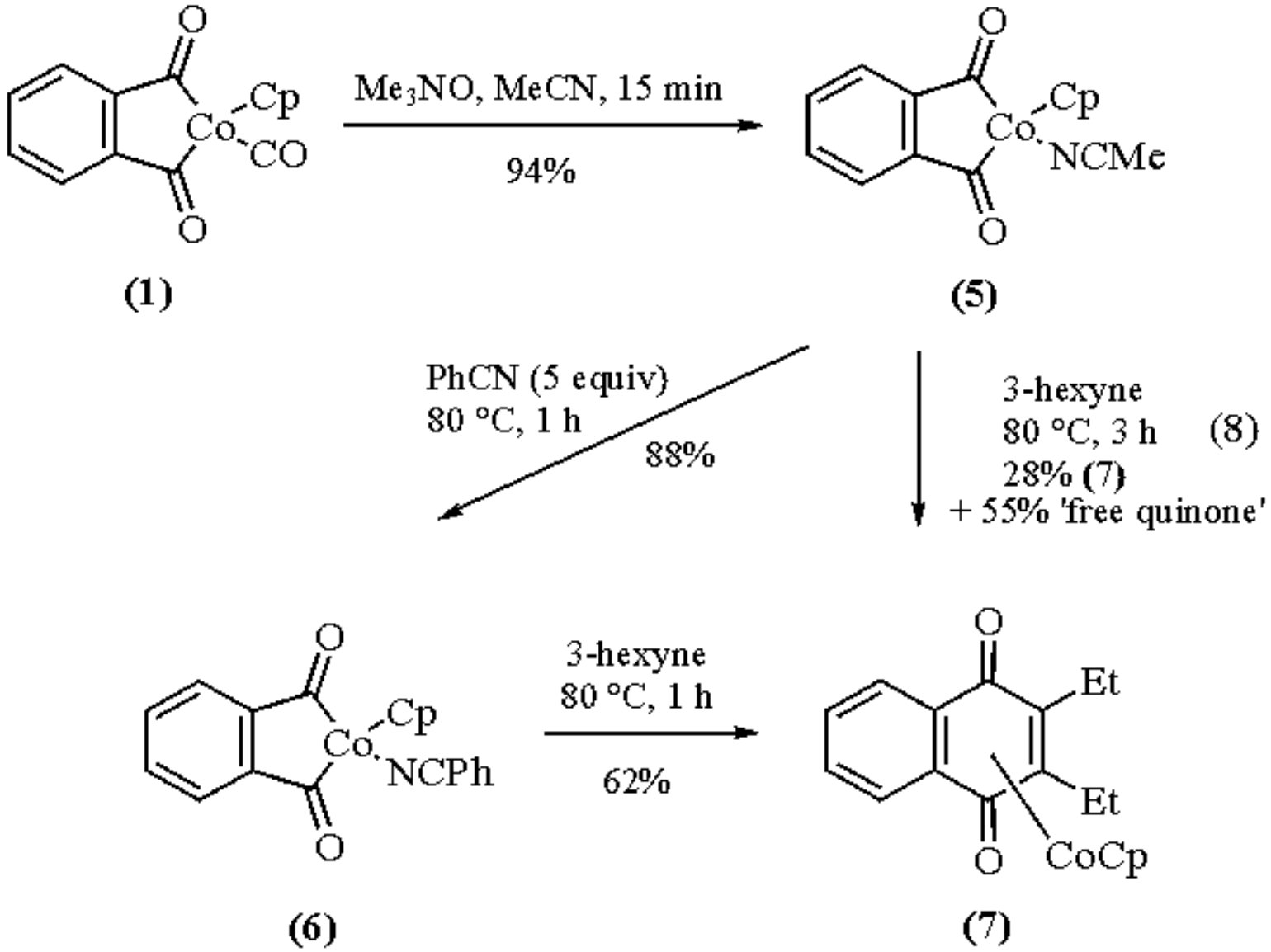

Naphthoquinone complexes such as (**7**) are very unstable. The analogous complex formed by reaction with the terminal alkyne, 1-hexyne, is not isolated under the conditions which give (**7**).[1] However, 1,4-naphthoquinone complexes are formed generally by reaction of the pentamethylcyclopentadienyl complex (**3**) with alkynes upon activation of the CO ligand with ***N-Methylmorpholine N-Oxide*** (NMMO) (Table 1).[3] The extra steric bulk of the pentamethylcyclopentadienyl ligand protects the 1,4-naphthoquinone complexes from decomplexation relative to the corresponding cyclopentadienyl complexes.

Table 1 Reaction of Complex **(3)** with Alkynes to give Cp*Co(naphthoquinone) Complexes

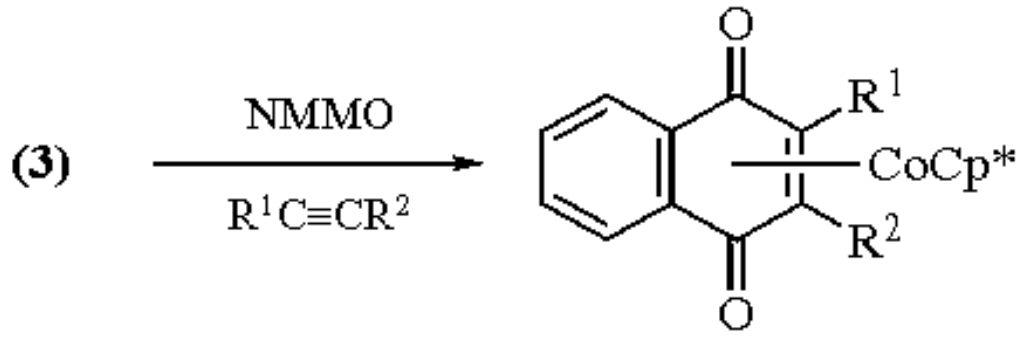

R^1	R^2	Yield (%)
Me	Me	83
Et	Et	61
H	*n*-Bu	61
H	Cy	58
Me	CO_2Et	86
Me	OEt	40
H	OEt	82
Me	CH_2OEt	70
H	CH_2OEt	75
H	Ph	58

The cyclopentadienylcobalt complexes of 1,4-benzoquinones are quite easy to form from reactions of cyclopentadienyl(maleoyl)cobalt complexes.[1] Photolysis of cyclopentadienyl(maleoyl)cobalt complex (**2**) in the presence of diethyl sulfide gives complex (**8**). This reacts with a wide variety of alkynes to give cyclopentadienyl(1,4-benzoquinone)cobalt complexes (Table 2).

Table 2 Reaction of Complex **(8)** with Alkynes to give CpCo(benzoquinone) Complexes

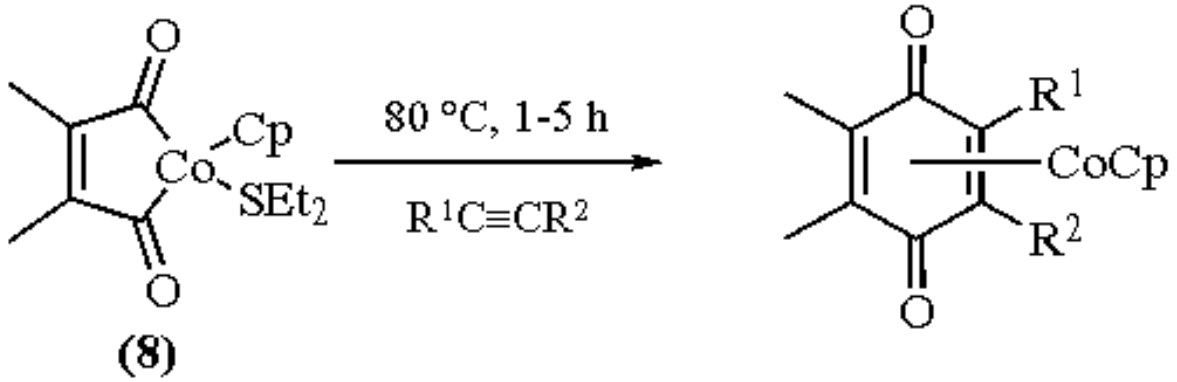

R^1	R^2	Yield (%)
Et	Et	90
H	Bu	96
OEt	Et	97
Et	COMe	90
Me	$C(Me)=CH_2$	91
H	CH_2Cl	97
H	CH_2NHBz	61
Me	CH_2OEt	80
H	CH_2OH	82

Photolysis of complex (**2**) in acetonitrile forms a red complex which on trituration with hexane is converted to the yellow cyclopentadienyl(dimethylbisketene)cobalt complex (**9**) (eq 9).[2] Complex (**9**) was reactive with alkynes to give cyclopentadienyl(1,4-benzoquinone)cobalt complexes at room temperature (Table 3).

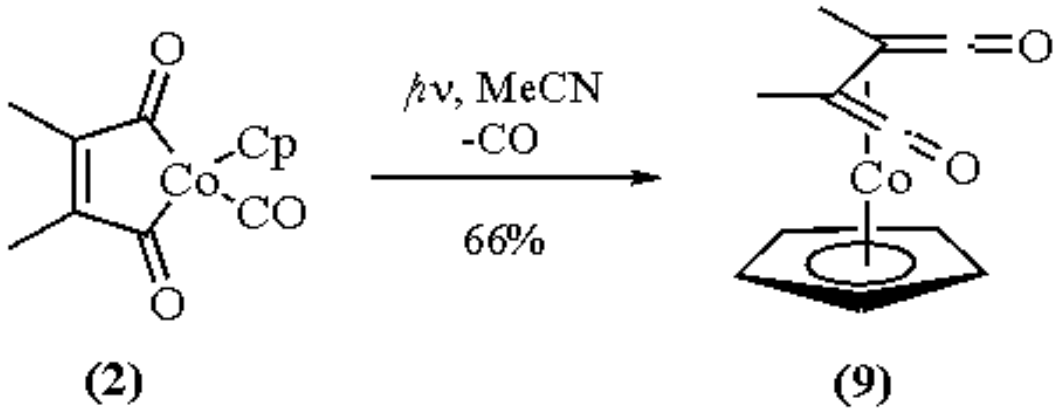

(9)

Table 3 Reaction of Bisketene Complex **(9)** with Alkynes to give CpCo(benzoquinone) Complexes

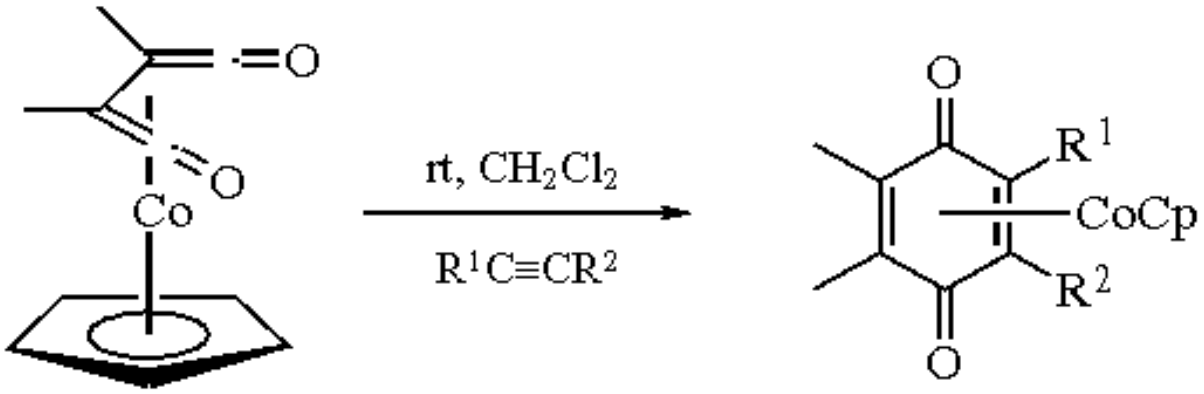

(9)

R^1	R^2	Reaction time (h)	Yield (%)
Pr	CH_2TBDMS	1	92
Me	CH_2Cl	6	86
Me	CO_2Et	6	93
H	$SiMe_3$	3	94

General Considerations.

The phthaloyl- and maleoyl(cyclopentadienyl)cobalt complexes should be compared to other phthaloyl- and maleoylcobalt complexes when being considered for use in the synthesis of quinones.[5,6] The main advantage of the cyclopentadienylcobalt complexes is the fact that quinone complexes can be obtained. This is currently the best method for making cyclopentadienyl(quinone)cobalt complexes.[3] Very limited work has been done on the application of these complexes in synthesis. Preliminary deprotonation/alkylation studies of maleoyl complexes (**2**) and (**4**) have been carried out but are only reported in dissertation form at this time.[4] This dissertation also contains some very preliminary work on the use of cyclopentadienyl(quinone)cobalt complexes in synthesis and the results are promising. The cyclopentadienyl ligand in these complexes makes them amenable to standard chromatographic purification, thus making the process of developing synthetic modifications of these complexes very feasible.

Related Reagents.

Phthaloylbis(triphenylphosphine)cobalt Chloride.

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1. Liebeskind, L. S.; Jewell, Jr., C. F. *JOM* **1985**, *285*, 305.
2. Jewell, Jr., C. F.; Liebeskind, L. S.; Williamson, M. *JACS* **1985**, *107*, 6715.

3. Cho, S. H.; Wirtz, K. R., Liebeskind, L. S. *OM* **1990**, *9*, 3067.
4. Jewell, C. F., Jr. Ph.D. Dissertation, Emory University, 1986.
5. Liebeskind, L. S. *T* **1989**, *45*, 3053.
6. Liebeskind, L. S.; Baysdon, S. L., South, M.; Iyer, S.; Leeds, J. P. *T* **1985**, *41*, 5839.

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N,N´-Carbonyldiimidazole[1]

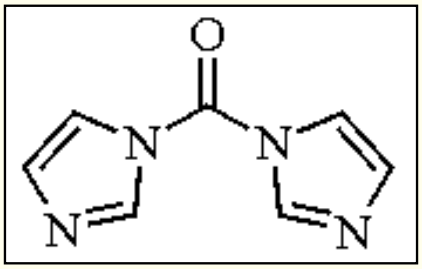

[530-62-1] · $C_7H_6N_4O$ · *N,N´*-Carbonyldiimidazole · (MW 162.15)

(reagent for activation of carboxylic acids;[1] synthesis of esters,[2] amides,[3] peptides,[4] aldehydes,[5] ketones,[6] β-keto thioesters,[7] tetronic acids;[8] ureas,[9] isocyanates,[10] carbonates;[9] halides from alcohols;[11] glycosidation;[12] dehydration[13-16])

Physical Data: mp 116-118 °C.

Solubility: no quantitative data available. Inert solvents such as THF, benzene, $CHCl_3$, DMF are commonly used for reactions.

Form Supplied in: commercially available white solid.

Analysis of Reagent Purity: purity can be determined by measuring the amount of CO_2 evolved on hydrolysis.

Preparative Methods: prepared by mixing phosgene with four equivalents of imidazole in benzene/THF.[17]

Purification: may be purified by recrystallization from hot, anhydrous THF with careful exclusion of moisture.[17]

Handling, Storage, and Precautions: moisture sensitive; reacts readily with water with evolution of carbon dioxide. May be kept for long periods either in a sealed tube or in a desiccator over P_2O_5.

Activation of Carboxylic Acids: Synthesis of Acyl Imidazoles.

N,N´-Carbonyldiimidazole (**1**) converts carboxylic acids into the corresponding acylimidazoles (**2**) (eq 1).[1] The method can be applied to a wide range of aliphatic, aromatic, and heterocyclic carboxylic acids, including some examples (such as formic acid and vitamin A acid) where acid chloride formation is difficult. The reactivity of (**2**) is similar to that of acid chlorides, but the former have the advantage that they are generally crystalline and easily handled. Isolation of (**2**)

is simple, but often unnecessary; further reaction with nucleophiles is usually performed in the same reaction vessel. Conversion of (**2**) into acid chlorides (via reaction with HCl),[18] hydrazides,[3] hydroxamic acids,[3] and peroxy esters[19] have all been described. Preparation of the more important carboxylic acid d erivatives is described below.

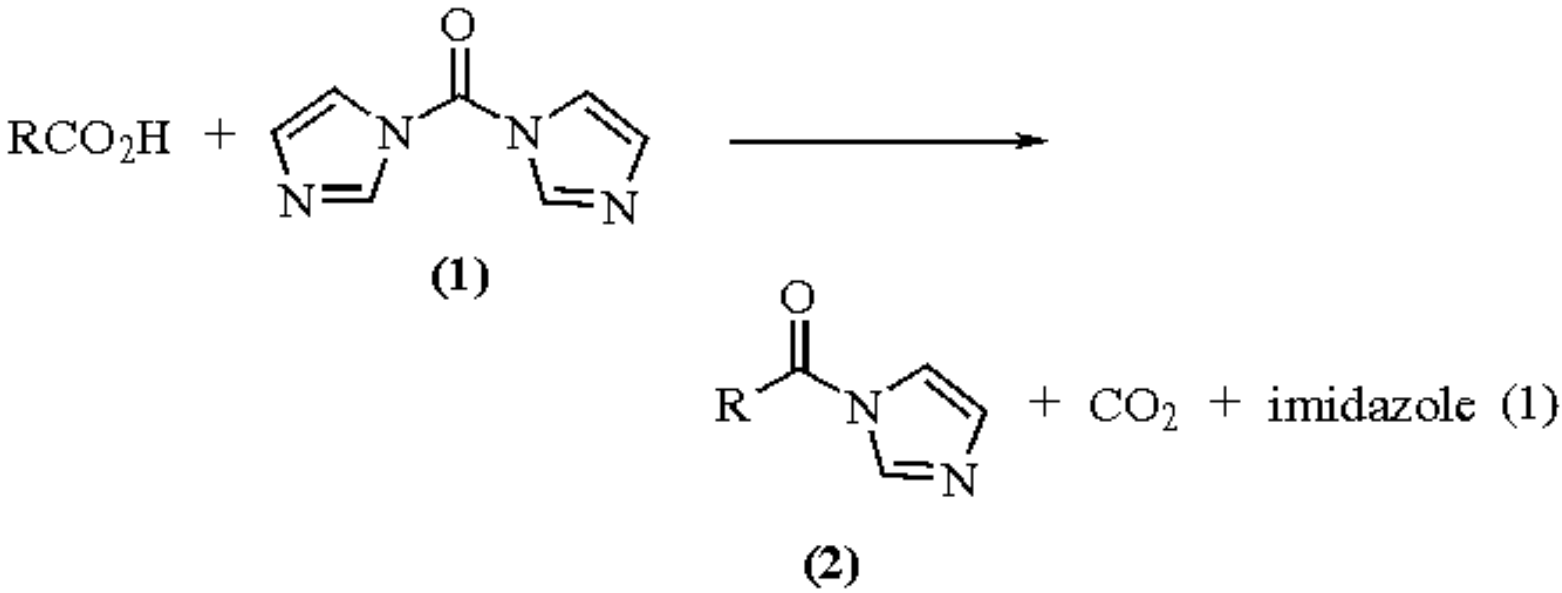

Esters from Carboxylic Acids.

Reaction of equimolar amounts of carboxylic acid, alcohol, and (**1**) in an inert solvent (e.g. THF, benzene, or chloroform) results in ester formation (eq 2). Since alcoholysis of the intermediate acylimidazole is relatively slow, the reaction mixture must be heated at 60-70 °C for some time. However, addition of a catalytic amount of a base such as ***Sodium Amide*** to convert the alcohol to the alkoxide, or a catalytic amount of the alkoxide itself, allows rapid and complete formation of the ester at room temperature.[2] The base catalyst must of course be added after formation of (**2**) from the acid is complete, as indicated by cessation of evolution of carbon dioxide.

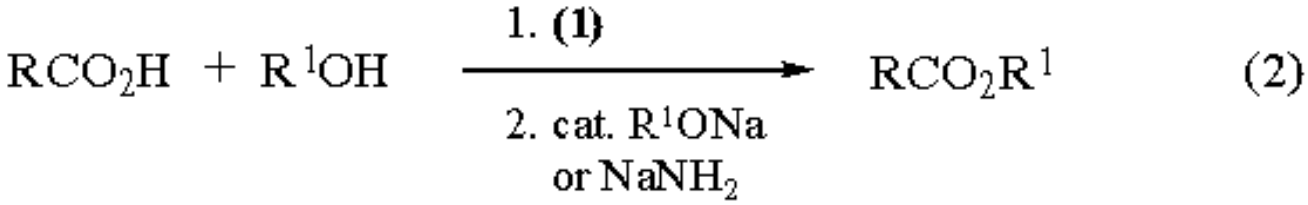

Esters of tertiary alcohols may not be prepared from carboxylic acids containing acidic α-protons using this modified procedure, since deprotonation and subsequent condensation, competes. However, the use of stoichiometric ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** as base has been shown to provide good yields of *t*-butyl esters even for acids with acidic α-protons (eq 3).[20] This procedure was unsuccessful for pivalic acid or for *N*-acyl-α-amino acids.

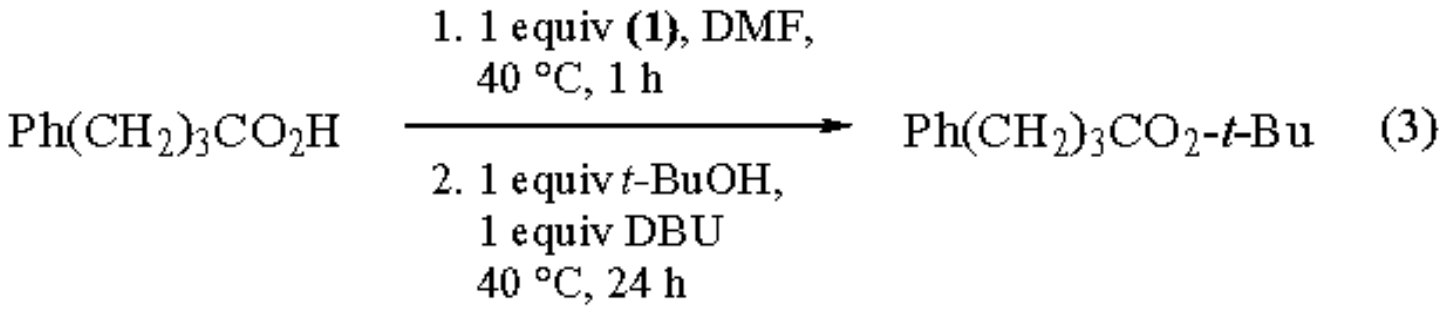

An alternative approach to increasing the rate of esterification is to activate further the intermediate (**2**). ***N-Bromosuccinimide*** has been used for this purpose,[21] but unsaturation in the carboxylic acid or alcohol is not tolerated. More generally useful is the addition of an activated halide, usually ***Allyl Bromide***, to a chloroform solution of (**1**) and a carboxylic acid, resulting in formation of the acylimidazolium salt (**3**) (eq 4).[22] Addition of the alcohol and stirring for 1-10 h at room temperature or at reflux affords good yields of ester in a one-pot procedure. These conditions work well for the formation of methyl, ethyl, and *t*-butyl esters of aliphatic, aromatic, and α,β-unsaturated acids. Hindered esters such as *t*-butyl pivalate can be prepared cleanly (90% yield). The only limitation is that substrates must not contain functionality that can be alkylated by the excess of the reactive halide.

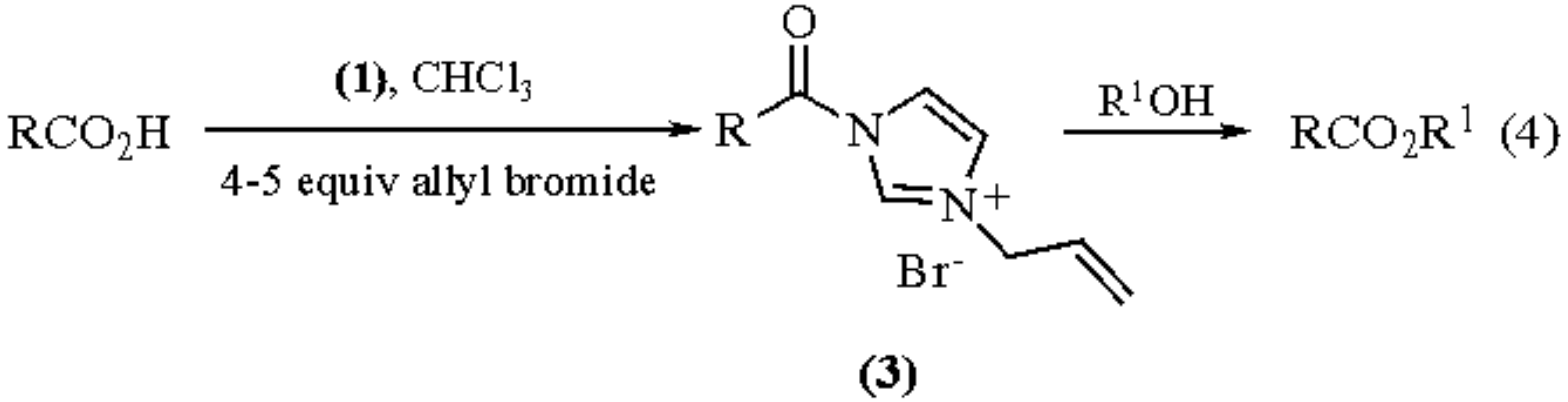

Since the purity of commercial (**1**) may be variable due to its water sensitivity, it is common to employ an excess in order to ensure complete conversion of the carboxylic acid to the acylimidazole. It has been suggested that alcohols react faster with residual (**1**) than with the acylimidazole (**2**), thus reducing the yield of ester. A procedure has been developed for removal of excess (**1**) before addition of the alcohol.[23]

Macrolactonization has been accomplished using (**1**).[24] Thiol and selenol esters can also be prepared in one pot from carboxylic acids using (**1**);[25] reaction of the intermediate (**2**) with aromatic thiols or selenols is complete within a few minutes in DMF, while aliphatic thiols require a few hours. Formation of the phenylthiol ester of *N*-Cbz-L-phenylalanine was accompanied by only slight racemization. ***N,N´-Carbonyldi-sym-triazine*** can be used in place of (**1**), with similar results.

Amides from Carboxylic Acids: Peptide Synthesis.

Analogous to ester formation, reaction of equimolar amounts of a carboxylic acid and (**1**) in THF, DMF, or chloroform, followed by addition of an amine, allows amide bond formation.[3] The method has been applied to peptide synthesis (eq 5).[4] One equivalent of (**1**) is added to a 1 M solution of an acylamino acid in THF, followed after 1 h by the desired amino acid or peptide ester. The amino acid ester hydrochloride may be used directly instead of the free amino acid ester. An aqueous solution of the amino acid salt can even be used, but yields are lower.

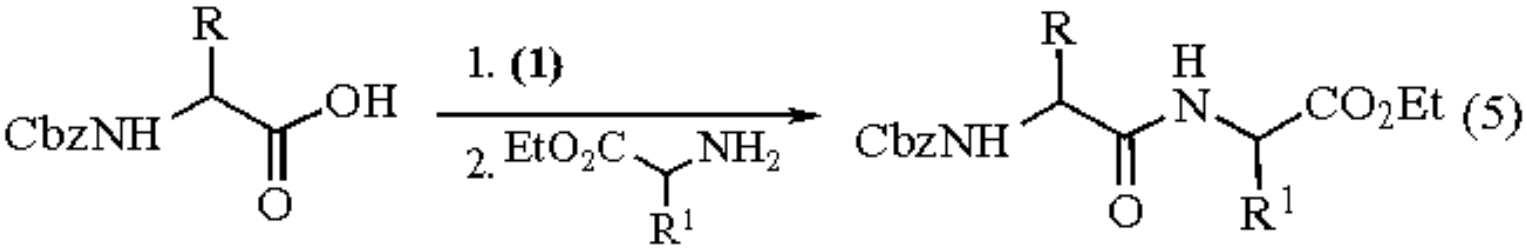

As is the case in esterification reactions, the presence of unreacted (**1**) can cause problems since the amine reacts with this as quickly as it does with the acylimidazole, forming urea byproducts that can be difficult to separate. Use of exactly one equivalent of (**1**) is difficult due to its moisture sensitivity, and also because of the tendency of some peptides or amino acids to form hydrates. Paul and Anderson solved this problem by use of an excess of (**1**) to form the acylimidazole, then cooling to -5 °C and adding a small amount of water to destroy the unreacted (**1**) before addition of the amine.[26]

For the sensitive coupling of Cbz-glycyl-L-phenylalanine and ethyl glycinate (the Anderson test), Paul and Anderson reported the level of racemization as 5% using THF as solvent at -10 °C, but as <0.5% in DMF.[4] Performing the same coupling reaction at room temperature, Beyerman and van den Brink later claimed that the degree of racemization in DMF was in fact as high as 17%, and reported better results (no detectable racemization) using the related reagent *N*,*N*´-carbonyl di-*sym*-triazine in place of (**1**).[27] In a comparative study of several reagents, Weygand and co-workers also observed extensive racemization using (**1**).[28] In the formation of tyrosine esters, Paul reported that the mixed anhydride method is to be preferred to use of (**1**), since *O*-acylation is a major side reaction with the latter.[29]

Aldehydes and Ketones from Carboxylic Acids.

Reduction of the derived acylimidazole (**2**) with ***Lithium Aluminum Hydride*** achieves conversion of an aliphatic or aromatic carboxylic acid to an aldehyde (eq 6).[5] ***Diisobutylaluminum Hydride*** has also been used, allowing preparation of α-acylamino aldehydes from *N*-protected amino acids.[30] Similarly, reaction of (**2**) with Grignard reagents affords ketones,[6] with little evidence for formation of tertiary alcohol.

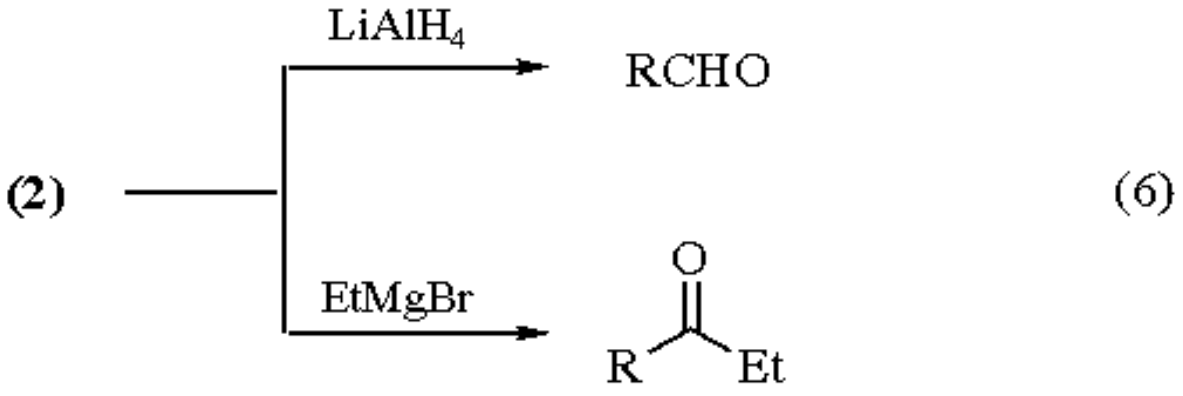

Reaction of acylimidazoles with the appropriate carbon nucleophile has also been used for the preparation of α-nitro ketones[31] and β-keto sulfoxides.[32]

C-Acylation of Active Methylene Compounds.

Treatment of an acylimidazole, derived from a carboxylic acid and (**1**), with the magnesium salt of a malonic or methylmalonic half thiol ester results in *C*-acylation under neutral conditions (eq 7).[7] The presence of secondary hydroxyl functionality in the carboxylic acid is tolerated, but primary alcohols require protection. Magnesium salts of malonic esters may be used equally effectively. Intramolecular *C*-acylation of ketones has also been reported.[33]

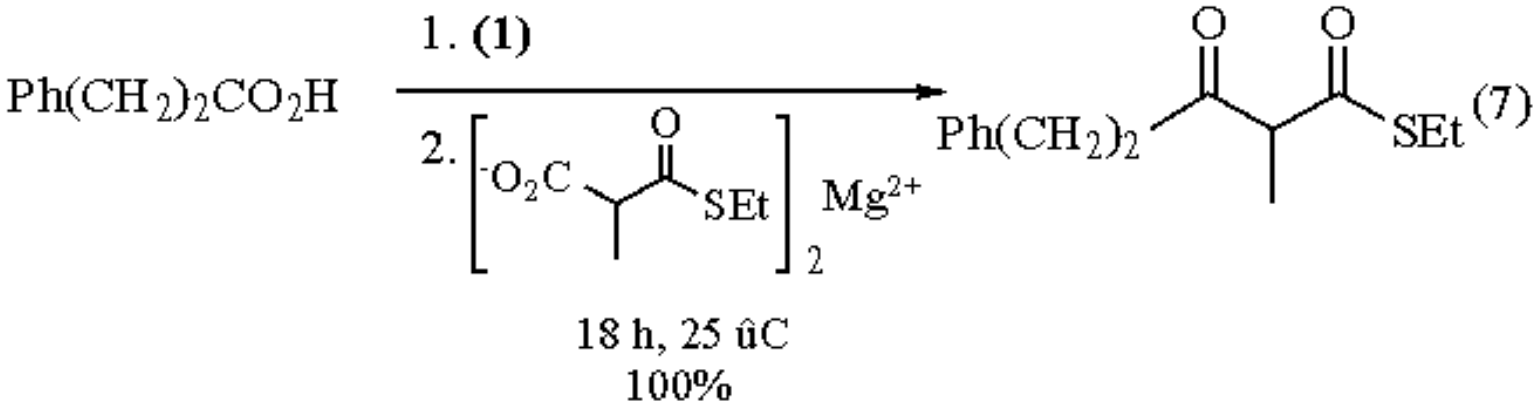

Tetronic Acids.

A synthesis of tetronic acids reported by Smith and co-workers relies on the reaction between (**1**) and the dianion derived from an α-hydroxy ketone (eq 8).[8] The reaction proceeds in moderate yield (31-57%).

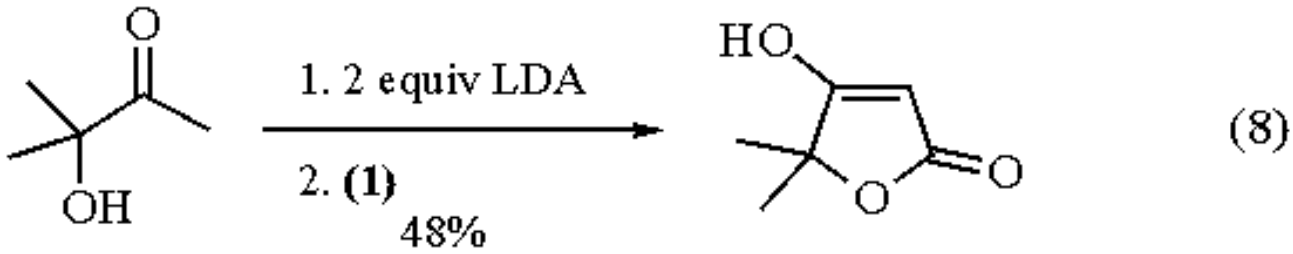

Ureas and Carbonates.

Reagent (**1**) may be used as a direct replacement for the highly toxic ***Phosgene*** in reactions with alcohols and amines. Reaction of (**1**) with two equivalents of a primary aliphatic or aromatic amine at room temperature rapidly yields a symmetrical urea (eq 9).[9] If only one equivalent of a primary amine is added to (**1**), then the imidazole-*N*-carboxamide (**4**) is formed (eq 10). These compounds can dissociate into isocyanates and imidazole, even at room temperature, and distillation from the reaction mixture provides a useful synthesis of isocyanates (eq 10).[10] Secondary amines react only at one side of (**1**) at room temperature, again giving the imidazole-*N*-carboxamide of type (**4**).

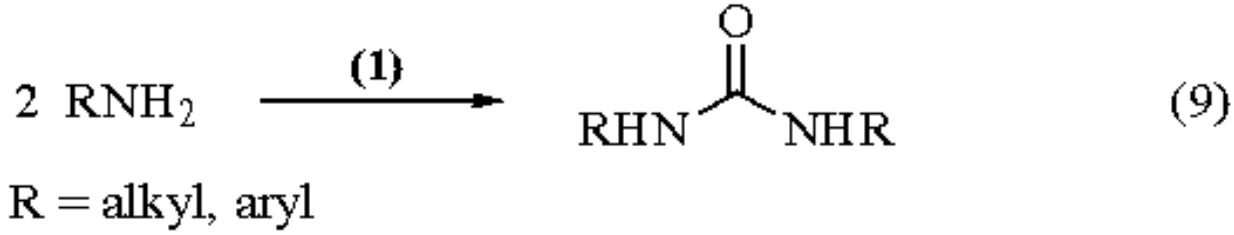

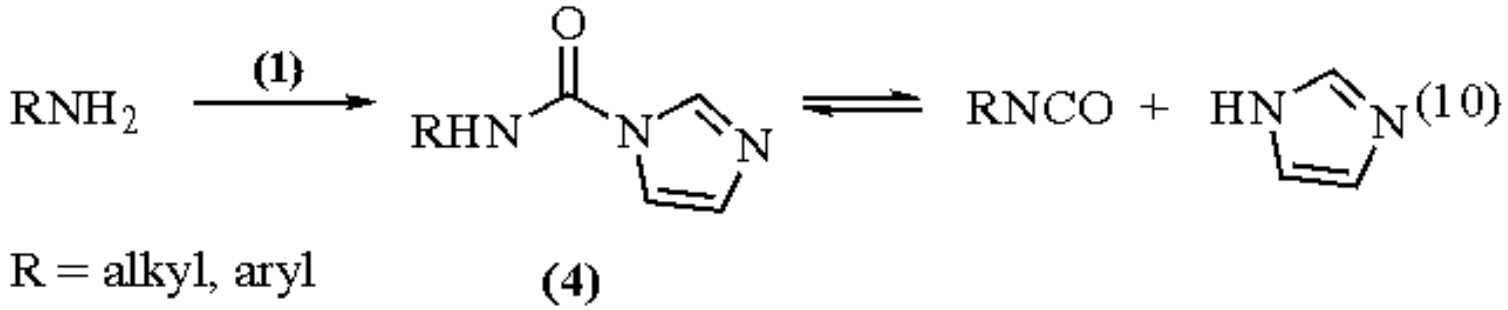

Reaction of (**1**) with one equivalent of an alcohol provides the imidazole-*N*-carboxylic ester (**5**) (eq 11).[34] Further treatment with another alcohol or phenol yields an unsymmetrical carbonate; alternatively, reaction with an amine affords a carbamate (eq 12).[34]

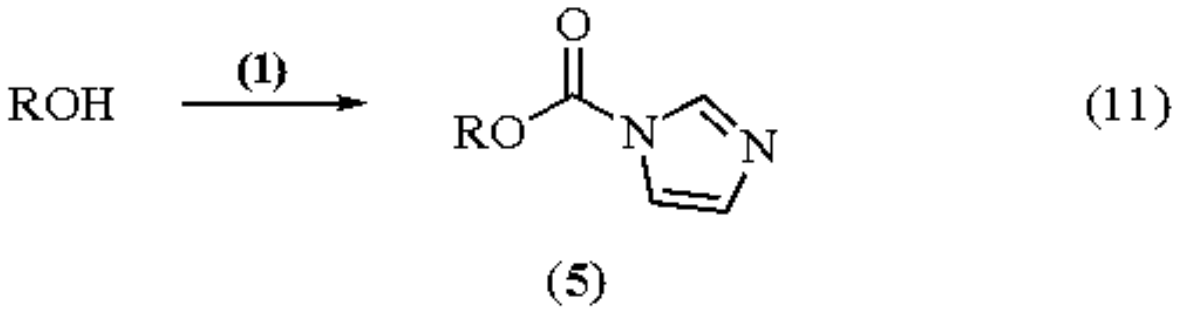

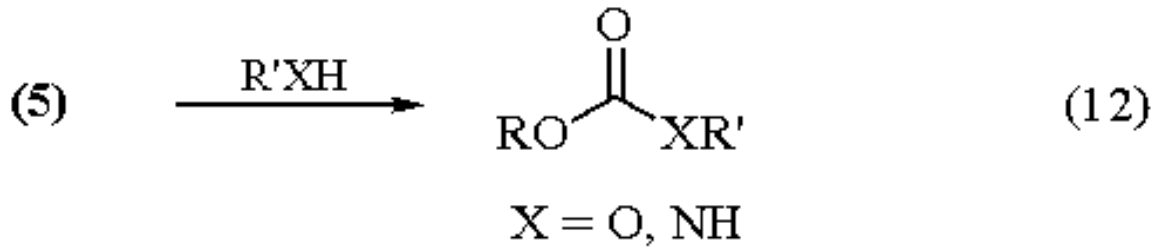

Heating (**1**) with an excess of an alcohol or phenol gives the symmetrical carbonate.[9] This reaction can be accelerated dramatically by the presence of catalytic base (e.g. ***Sodium Ethoxide***). Reaction under these conditions is so exothermic even at room temperature that only *t*-butanol stops at the imidazole-*N*-carboxylic ester stage.

1,2-Diamines, 1,2-diols, or 1,2-amino alcohols react with (**1**) to form cyclic ureas,[35] carbonates,[36] or oxazolidinones,[35] respectively. In the case of cyclohexane-1,2-diols, the *cis*-diol reacts much more rapidly than the *trans*, as would be expected.[36] Thiazolidinones can also be prepared using (**1**).[37]

Halides from Alcohols.

Treatment of an alcohol with (**1**) and an excess (at least three equivalents) of an activated halide results in its conversion to the corresponding halide (eq 13).[11] Any halide more reactive than the product halide may be used, but in practice ***Allyl Bromide*** or ***Iodomethane*** give best results as they are effective and readily removed after the reaction. Acetonitrile is the best solvent and yields are generally high (>80%). Bromide or iodide formation work well, but not chlorination. Optically active alcohols are racemized.

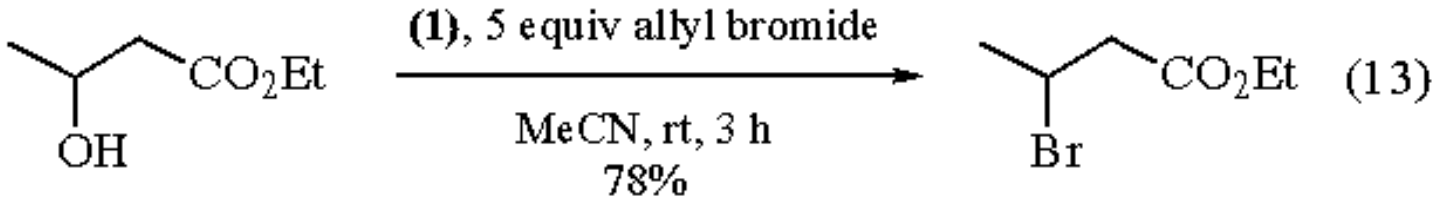

Glycosidation.

A mild glycosidation procedure involving (**1**) has been reported by Ford and Ley.[12] A carbohydrate derivative in ether or dichloromethane reacts with (**1**) through the anomeric C-1-hydroxyl to give the (1-imidazolylcarbonyl) glycoside (IMG) (**6**) (eq 14). Isolation of (**6**) is not usually necessary; treatment with one equivalent of an alcohol and two equivalents of ***Zinc Bromide*** in ether at reflux gives the glycoside. Generally, higher α:β ratios are obtained for more hindered alcohols and when ether is used as solvent rather than the less polar dichloromethane. Along with the fact that the α:β ratio is independent of the configuration of (**6**), this suggests an S_N1-type mechanism. In contrast, treatment of (**6**) with ***Acetyl Chloride*** provides the anomeric chloride with essentially exclusive inversion.

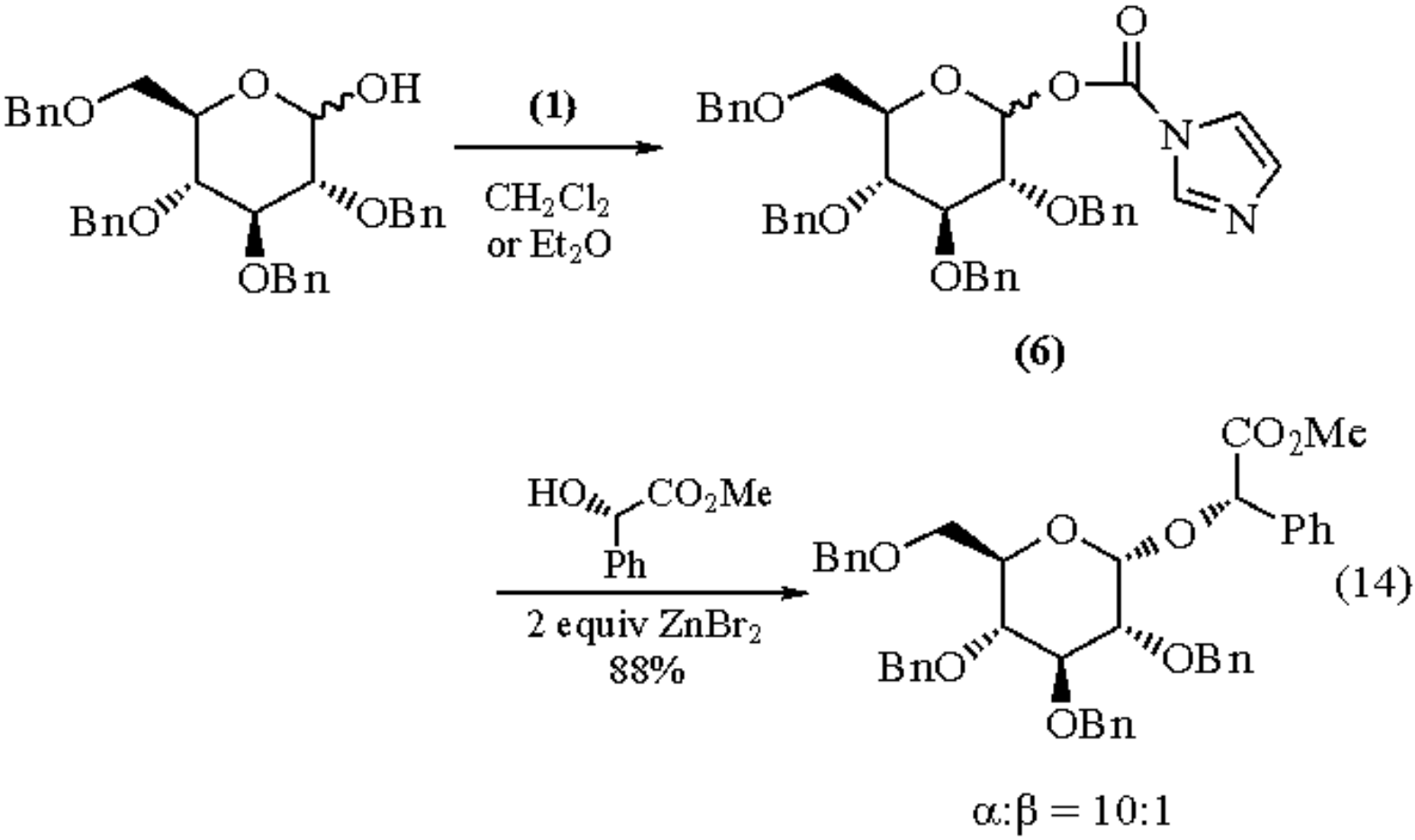

Dehydration.

Reagent (**1**) has been used for the dehydration of various substrates, including aldoximes (to give nitriles),[13] β-hydroxy amino acids,[14] and β-hydroxy sulfones.[15] 3-Aryl-2-hydroxyiminopropionic acids undergo dehydration and decarboxylation, to give 2-aryl acetonitriles, upon reaction with (**1**).[16]

1. Staab, H. A. *AG(E)* **1962**, *1*, 351.
2. Staab, H. A.; Mannschreck, A. *CB* **1962**, *95*, 1284 (*CA* **1962**, *57*, 5846d).
3. Staab, H. A.; Lüking, M.; Dürr, F. H. *CB* **1962**, *95*, 1275 (*CA* **1962**, *57*, 5908a).
4. Paul, R.; Anderson, G. W. *JACS* **1960**, *82*, 4596.
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N,N´-Carbonyldi-*sym*-triazine

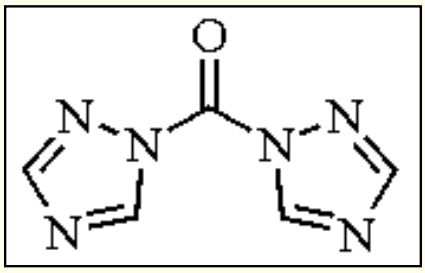

[41864-22-6] · $C_5H_4N_6O$ · *N,N´*-Carbonyldi-*sym*-triazine · (MW 164.13)

(reagent for peptide synthesis[1]; preparation of thiol or selenol esters[2])

Physical Data: mp 134-136 °C.

Solubility: no information available. Reactions are usually performed in DMF.

Analysis of Reagent Purity: purity has been determined by measuring the amount of CO_2 evolved on hydrolysis.

Preparative Methods: from triazole and phosgene in THF, in the presence of one equivalent of pyridine (80% yield).[1]

Purification: material prepared as above is 95% pure, and is generally used directly.

Handling, Storage, and Precautions: may be stored in a desiccator over P_2O_5 at room temperature for many months without apparent decomposition.

Peptide Synthesis.

N,N´-Carbonyldi-*sym*-triazine (**1**) may be used to effect activation of an *N*-protected amino acid towards amide bond formation, presumably via the acyltriazole intermediate (**2**) (eq 1).[1] Unlike the related reagent ***N,N´-Carbonyldiimidazole***, (**1**) may be used without problems in DMF, a suitable solvent for small and large peptides. Racemization is apparently lower when (**1**) is used rather than *N,N´*-carbonyldiimidazole; coupling of CbzGly-Phe-OH to glycine ethyl ester (the Anderson test) showed 17% racemization using *N,N´*-carbonyldiimidazole, whereas none was observed using (**1**) under strictly analogous conditions. This is presumably related to the fact that (**2**) reacts more rapidly with amines than does the corresponding acylimidazole, as expected based on consideration of the relative acidities of imidazole and triazole.

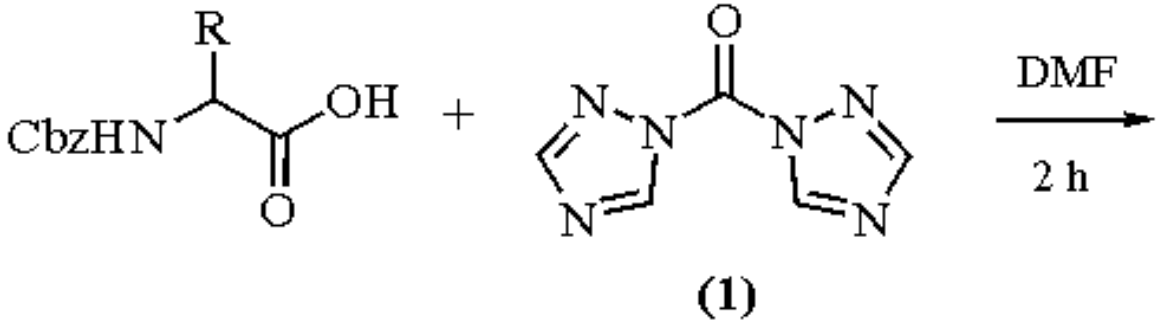

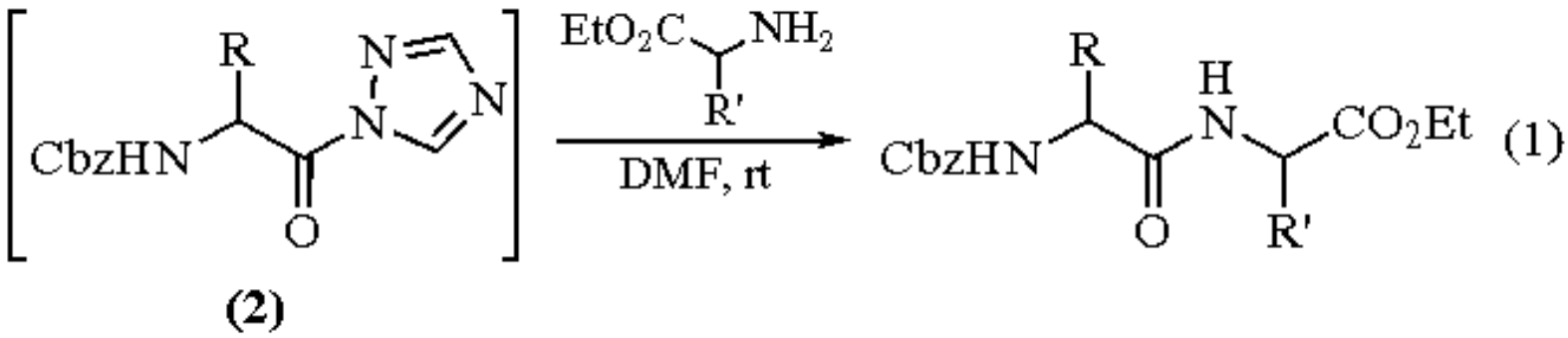

Thiol and Selenol Esters.

The acyltriazole resulting from activation of a carboxylic acid by (**1**) can be reacted without isolation with a thiol or selenol, affording a thiol or selenol ester, respectively.[2] Racemization is slight when the method is applied to *N*-protected amino acids (eq 2). *N*,*N*´-Carbonyldiimidazole can be used in place of (**1**), with similar results. Reaction with aromatic thiols or selenols is complete within minutes; alkyl thiols require a few hours. The 1,2,4-triazole formed is easily removed by extraction with water.

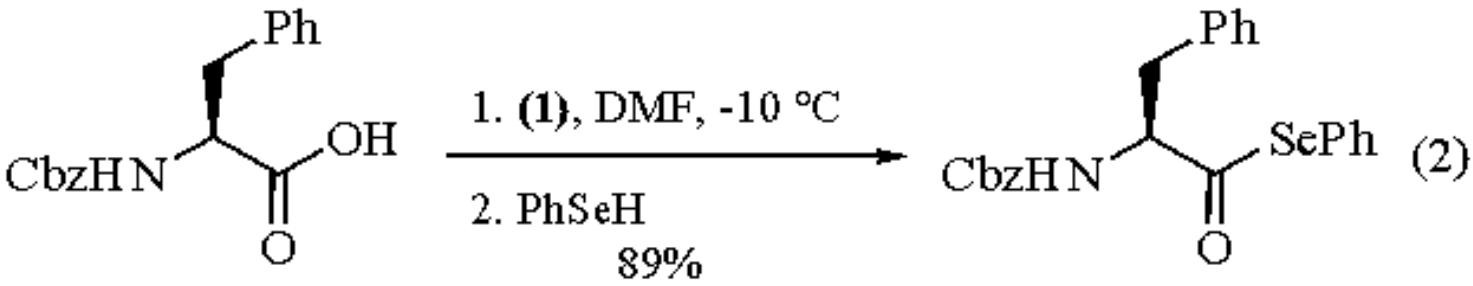

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Carbonylhydridotris(triphenylphosphine)rhodium(I)[1]

$RhH(CO)(PPh_3)_3$

[17185-29-4] · $C_{55}H_{46}OP_3Rh$ · Carbonylhydridotris(triphenylphosphine)rhodium(I) · (MW 918.79)

(catalyst for hydroformylation, hydrogenation, isomerization, and hydrosilylation of alkenes. It has also been used as a carbonylation catalyst and as a catalyst for the conjugate addition of activated Michael donors)

Alternate Names: hydridocarbonyltris(triphenylphosphine)rhodium(I); carbonyltris(triphenylphosphine)rhodium(I) hydride.

Physical Data: mp 172-174 °C (under N_2), 120-122 °C (in air).[2]

Solubility: moderately sol $CHCl_3$, CH_2Cl_2, and C_6H_6; sparingly sol cyclohexane; insol light petroleum and EtOH.[1,3]

Form Supplied in: yellow solid, widely available.

Preparative Methods: can be prepared from $RhCl_3.3H_2O$, PPh_3, and formaldehyde (see cautionary note below).[2,4] It can also be prepared from other rhodium complexes,[1] for example by the reaction of hydrazine with *trans*-carbonylchlorobis(triphenylphosphine)rhodium(I) in ethanolic solution.

Handling, Storage, and Precautions: is moisture sensitive and decomposes in many solvents above 80 °C. The preparation of the complex from $RhCl_3.3H_2O$, PPh_3, and formaldehyde (see above) results in the liberation of HCl which can react with formaldehyde to form the potent carcinogen bis(chloromethyl) ether.

Hydroformylation (Oxo Reaction).[1,5]

$RhH(CO)(PPh_3)_3$ has largely displaced cobalt-based catalysts in industrial hydroformylations. The aldehyde products are reduced to the corresponding alcohols for use in the plastics industry.[1] Whereas the earlier process involved operating at high temperatures and pressures, the use of $RhH(CO)(PPh_3)_3$ allows the reaction to occur at or below atmospheric pressure and at room temperature.[6,7] The catalyst is often added to reactions as a solid. However, it can also be generated in situ from other rhodium complexes under typical hydroformylation conditions. In all these cases $RhH(CO)(PPh_3)_3$ is the actual precursor to the active catalysts, $RhH(CO)(PPh_3)_2$ and $RhH(CO)_2PPh_3$ (eq 1).[8]

$$RhH(CO)(PPh_3)_3 \xrightleftharpoons{-PPh_3} RhH(CO)(PPh_3)_2 \xrightleftharpoons{+CO,\ -PPh_3} RhH(CO)_2(PPh_3) \quad (1)$$

For aliphatic alkenes, much emphasis has been placed on optimization of hydroformylation in favor of the linear product (eq 2) (R = alkyl). The best results are obtained by employing low gas pressures and a 1:1 ratio of H_2 to CO, in the presence of added ***Triphenylphosphine***.[1,9] Added diphosphines with bite angles near 120° also increase selectivity for the linear product.[10] Excess triphenylphosphine retards the rate of reaction and lower pressures of CO lead to competing hydrogenation and isomerization.[11]

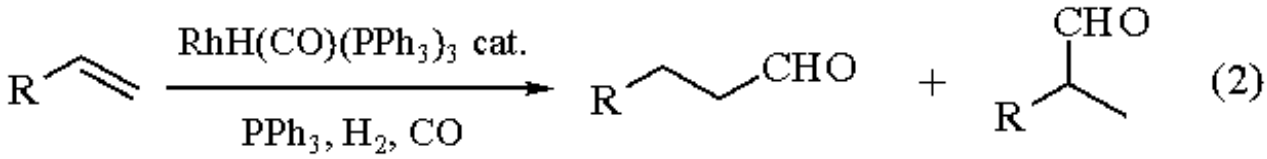

Steric hindrance in the alkene can lead to excellent regioselectivity as well as selectivity for a terminal alkene in preference to a trisubstituted alkene (eq 3).[12] A bulky silyl substituent also controls hydroformylation regioselectivity.[13] The use of a polymer-supported catalyst also leads to a high ratio of linear to branched product.[14]

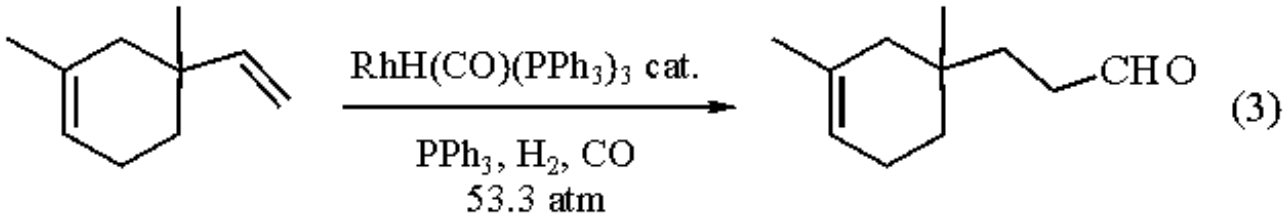

Hydroformylation of styrene is quite selective for the branched isomer. Reaction of the corresponding tricarbonylchromium complex, tricarbonyl(η^6-styrene)chromium, improves this selectivity dramatically (from 87:13 to >98:2, in favor of the branched isomer),[15] as does reaction with 1,2,3,4,5-pentafluorostyrene.[16] Addition of diphenylpyridinylphosphine also results in improved regioselectivity (as high as 94:6 in favor of the branched isomer) if the reaction is carried out under high pressure.[17]

The influence of chelation control on regioselectivity has been examined using phosphorus,[18,19] nitrogen,[20,21] and sulfur[22] substituents. In the case of nitrogen this has led to the synthesis of a variety of heterocycles, although often as isomeric mixtures (eq 4).[21]

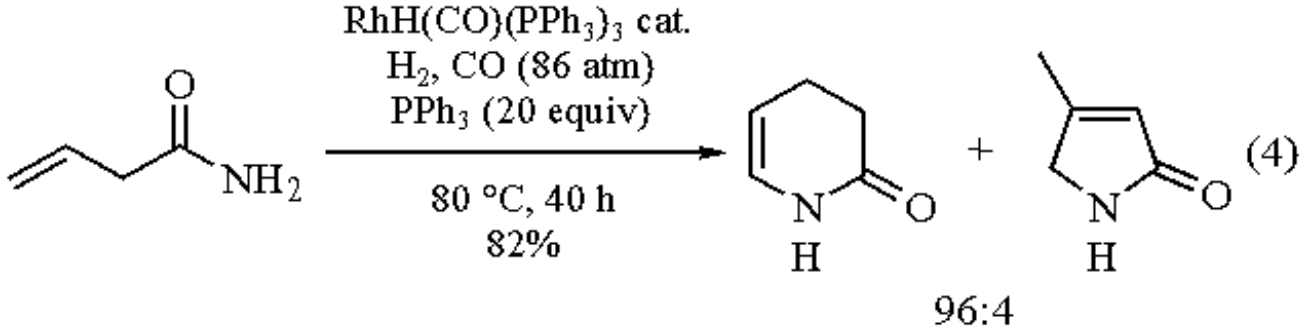

Carbonylation is sometimes a competing process. In reactions with alkenylamines, carbonylation is generally favored where the amine is unhindered and nucleophilic.[23,24] Double hydroformylations are also possible.[25,26] Alkynes are usually less reactive than alkenes under typical hydroformylation conditions.[23,27]

Many studies of asymmetric hydroformylations have been carried out using chiral rhodium-based catalysts. Rather than preparing pure, chiral catalysts it is often simpler to generate such catalysts in situ by adding chiral diphosphine ligands to $RhH(CO)(PPh_3)_3$ in solution.[28-32] Naturally, $RhH(CO)(PPh_3)_3$ is no longer the active catalyst in these reactions. Asymmetric hydroformylation of methyl 2-(acetylamino)acrylate using (-)-DIOP as the added chiral ligand provided the branched product with excellent regioselectivity and reasonable enantioselectivity (eq 5).[33]

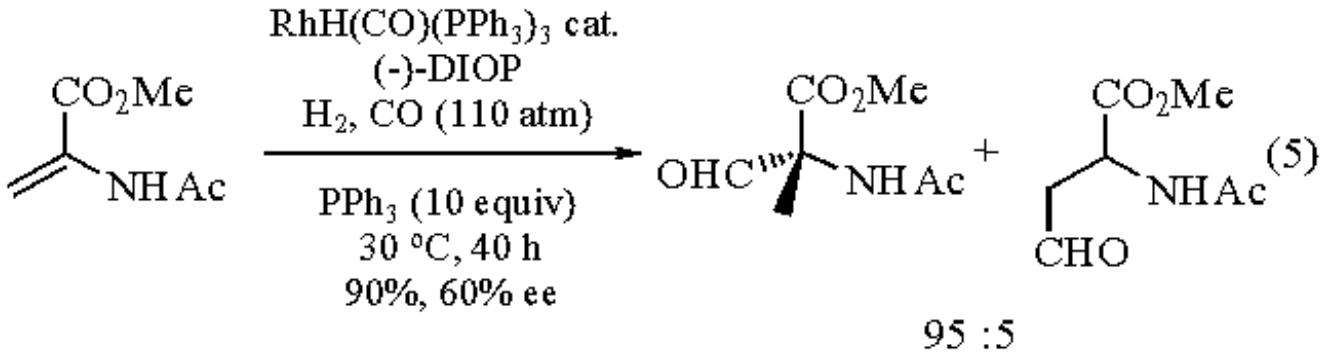

If an alkene such as ethylene is treated with $RhH(CO)(PPh_3)_3$ and CO only (i.e. no H_2) then co-oligomerization can occur, leading to polymers of the type H-$(CH_2CH_2CO)_n$-Et or H-$(CH_2CH_2CO)_n$-OR.[34] $RhH(CO)(PPh_3)_3$ also catalyzes hydroacylation[35] and silylformylation[36] of alkenes.

Hydrogenation.[37]

$RhH(CO)(PPh_3)_3$ is a hydrogenation catalyst selective for terminal alkenes. Under standard conditions, $RhH(CO)(PPh_3)_3$ is less efficient than the widely used Wilkinson's catalyst, ***Chlorotris(triphenylphosphine)rhodium(I)***. However, the selectivity of Wilkinson's catalyst derives from differences in double bond stereochemistry, with little difference in rate of hydrogenation of terminal, internal, or cyclic alkenes.[38] $RhH(CO)(PPh_3)_3$, on the other hand, can catalyze the hydrogenation of terminal alkenes at ambient temperature and pressure in the presence of internal, conjugated, or cyclic double bonds (eq 6).[38,39] At higher temperatures and pressures, internal[40] and cyclic alkenes[41] can also be hydrogenated.

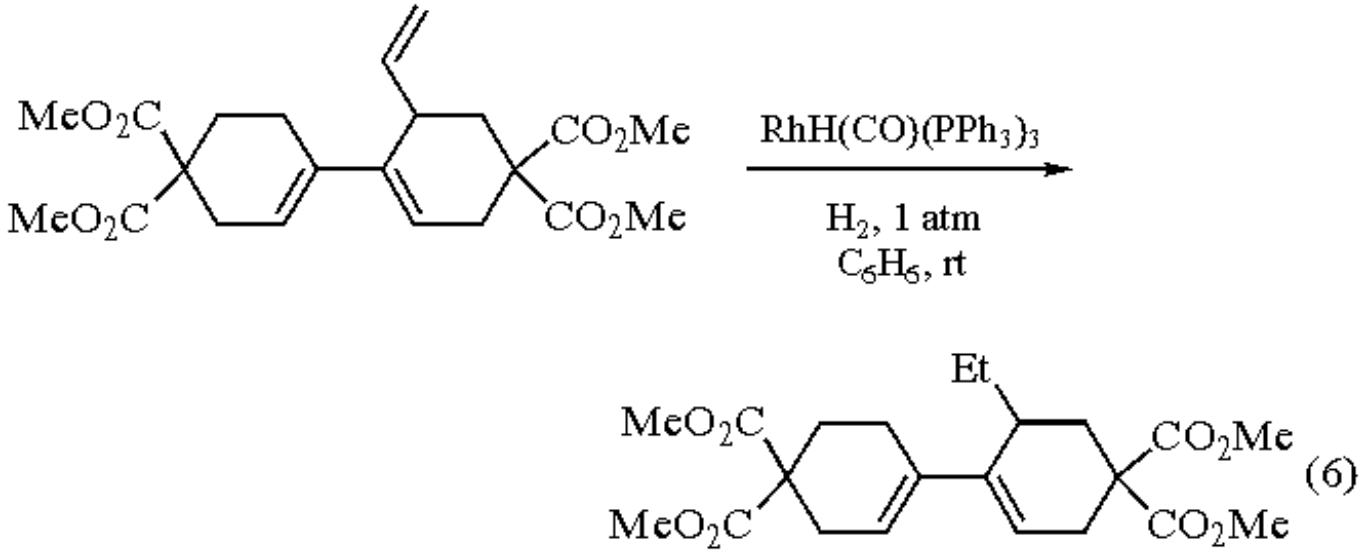

Functional groups such as keto, aldehyde, hydroxy, cyano, chloro, and carboxy are not reduced by the complex. $RhH(CO)(PPh_3)_3$ will not catalyze the hydrogenation of alkynes. However, it will react stoichiometrically with alkynes to give stable complexes.[42,43] Complexes generated from $RhH(CO)(PPh_3)_3$ (or $Rh_6(CO)_{16}$ or $Rh_4(CO)_{12}$) and diphosphines will catalyze the hydrogenation of α,β-unsaturated aldehydes.[44] In the presence of chiral diphosphines this reaction is enantioselective, as in the hydrogenation of neral to produce (+)-citronellal (eq 7).[44]

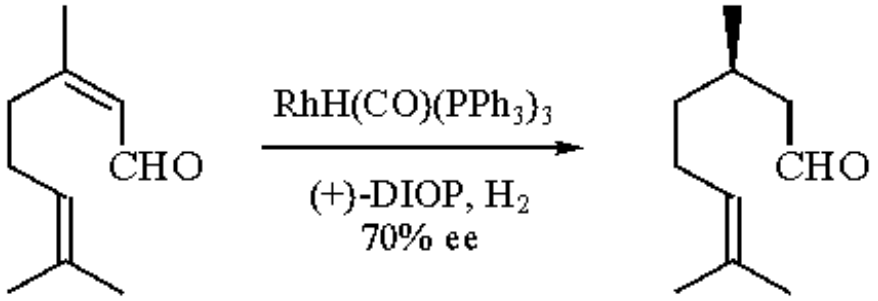

(7)

Isomerization.

$RhH(CO)(PPh_3)_3$ is a homogeneous catalyst for the isomerization of terminal alkenes to give the more stable internal alkene. Initially, the (*Z*)-2-alkene is formed and this is then slowly isomerized to the (*E*)-2-alkene.[45,46] The isomerization of 3-phenoxyprop-1-ene has been achieved with $RhH(CO)(PPh_3)_3$; however, the yields and selectivity are not as good as those obtained using ***Dichlorotris(triphenylphosphine)ruthenium(II)***.[47] The *exo*-methylene of a fused five-membered lactone has been isomerized in the presence of $RhH(CO)(PPh_3)_3$ to internalize the double bond.[48] Double bond migration has also been observed in nitrogen heterocycles, such that cyclic *N*-allylamides are isomerized to the cyclic enamide.[49] Allylic alcohols are isomerized to aldehydes in the presence of $RhH(CO)(PPh_3)_3$[50] and when chiral diphosphines are added a modest degree of enantioselectivity is observed.[51] β-Trimethylsilyl allylic alcohols have been isomerized to provide a stereoselective synthesis of trimethylsilyl enol ethers.[52] This reaction is believed to proceed via the α-trimethylsilyl ketone as the direct transformation of α-trimethylsilyl ketones into trimethylsilyl enol ethers has been demonstrated.[53] The stereoselective synthesis of α,β-unsaturated ketones has been achieved by the $RhH(CO)(PPh_3)_3$-catalyzed isomerization of vinyl epoxides.[54] Other Rh^I catalysts were also shown to catalyze this isomerization and the best yields and selectivities were obtained with ***Hydridotetrakis(triphenylphosphine)rhodium*** (eq 8).

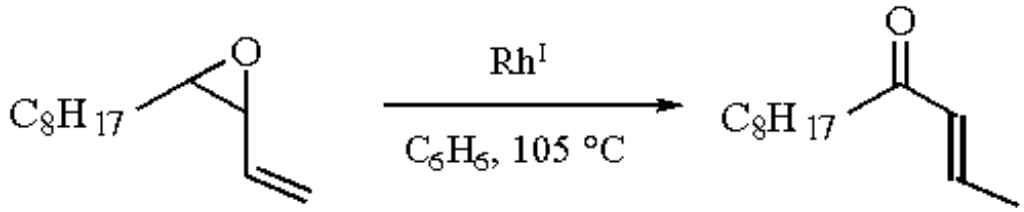

(8)

Rh^I	Yield (%)	(*E*):(*Z*)
$RhH(CO)(PPh_3)_3$	86	79:21
$RhH(PPh_3)_4$	91	100:1

An example of a catalytic isomerization in the presence of $RhH(CO)(PPh_3)_3$ that does not involve a double bond isomerization is the conversion of *cis*-2,3-epoxycyclohexan-1-ol to the *trans* isomer.[55]

Hydrosilylation.

As with many hydrogenation catalysts, the efficacy of $RhH(CO)(PPh_3)_3$ as a hydrosilylation catalyst has been investigated. $RhH(CO)(PPh_3)_3$ has been used in the hydrosilylation of a number of alkenic substrates, including 1-hexene,[56] styrene,[56,57] 1,3-butadiene,[58] and acrylonitrile.[59] In the first two examples, $RhCl(PPh_3)_3$ and $RhCl(CO)(PPh_3)_3$, respectively, were found to be superior catalysts. In the last two examples, under certain conditions, $RhH(CO)(PPh_3)_3$ proved to be the most effective of the catalysts that were investigated. Alkynes have also been hydrosilylated to produce both (*Z*)- and (*E*)-alkenes.[60]

Conjugate Addition.

In the presence of $RhH(CO)(PPh_3)_3$, activated Michael donors such as ethyl cyanoacetate, malononitrile, and benzyl cyanide undergo conjugate addition to α,β-unsaturated carbonyl compounds in high yield.[61] In the presence of the chiral *trans* chelating diphosphine ligand 2,2´´-bis(1-diphenylphosphinoethyl)-1,1´´-biferrocene (TRAP), and using α-substituted α-cyanocarboxylate as donor, this reaction proceeded with high enantioselectivity (eq 9).[62]

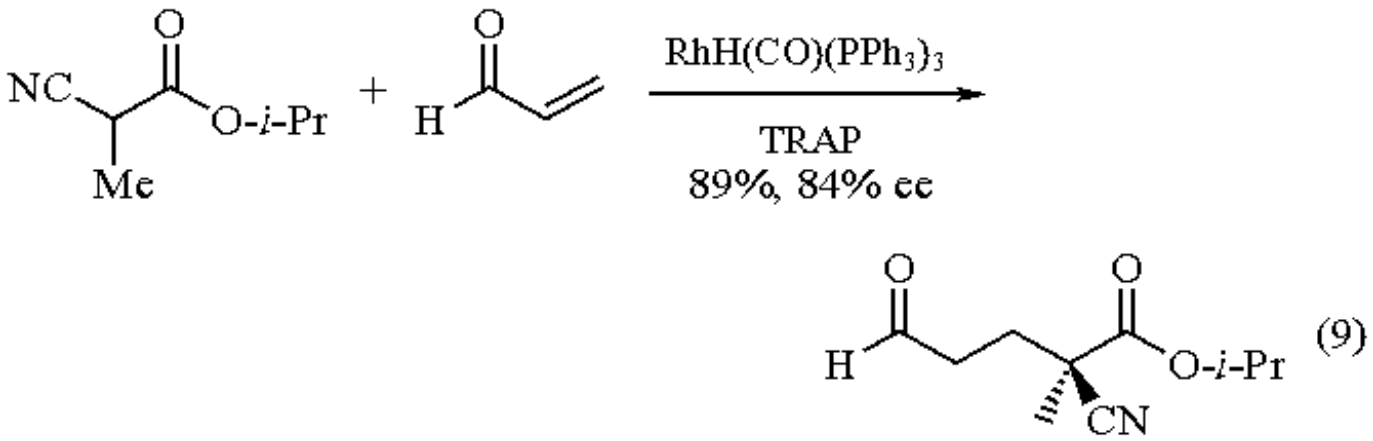

Miscellaneous.

$RhH(CO)(PPh_3)_3$ has been used in carbonylation reactions of amines[63] and alkenes[64] and in cross-carbonylation of alkynes and alkenes.[65] The complex has also been used as a decarbonylation catalyst,[66] although it does not perform as well as Wilkinson's catalyst in such reactions. $RhH(CO)(PPh_3)_3$ has been used, albeit less efficiently than Pd/Al_2O_3, to effect the rearrangement of tetrahydrofurylhydrosilane to give the corresponding oxasilacyclohexane in which the silicon had migrated into the ring.[67] The reduction of nitrobenzene by cyclohexanol in the presence of $RhH(CO)(PPh_3)_3$ has been reported,[68] although $Rh(CO)_2Cl_2$ was found to be a superior catalyst for this reaction. $RhH(CO)(PPh_3)_3$ also undergoes many inorganic ligand exchange reactions,[1] which are not detailed here as they are presently of little value to the synthetic chemist.

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Maree P. Collis & Patrick Perlmutter

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2-Carboxyethyltriphenylphosphonium Perbromide

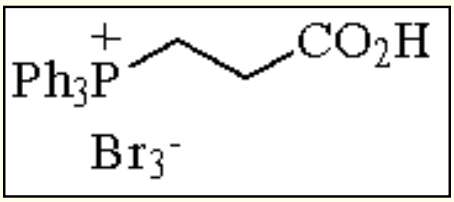

[55985-85-8] · $C_{21}H_{20}Br_3O_2P$ · 2-Carboxyethyltriphenylphosphonium Perbromide · (MW 574.93)

(bromine transfer agent for selective α-bromination of ketones[1] and ketone acetals[2] in the presence of double bonds,[1-3] activated aromatic rings,[2] esters[1] or another free enolic position[1,4])

Alternate Name: 2-carboxyethyltriphenylphosphonium tribromide.

Physical Data: mp 139-41 °C.

Solubility: sol THF (25 g/100 mL), dichloromethane; insol alcohol.

Form Supplied in: orange solid; not widely available; purity &egt;98%.

Analysis of Reagent Purity: identification in phosphonium salt mixtures by TLC/SIMS.[5]

Preparative Methods: Ph_3P (26.2 g, 0.1 mol), acrylic acid (7.2 g, 0.1 mol) and 49% HBr (50 mL) were stirred at rt until a homogeneous solution was obtained, then heated at 95-100 °C for 10 min, whereupon the mixture was cooled and glacial HOAc (240 mL) was added; bromine (9.8 mL) was added slowly with stirring to this mixture at 0 °C; after 0.5 h, the product was filtered and recrystallized from MeCN to give the perbromide (52.5 g, 91%);[1] a two step procedure involving bromination of the isolated intermediate monobromide can also be used.

Handling, Storage, and Precautions: irritant and moisture sensitive solid; store in a dry place. This reagent should be handled in a fume hood.

Saturated Ketones.

With this reagent, saturated ketones undergo α-bromination to give mainly the thermodynamically more stable

bromo ketone (eq 1).[1,4] No reaction was observed in the case of bicyclic ketones or camphor, or with esters under the above conditions.[1]

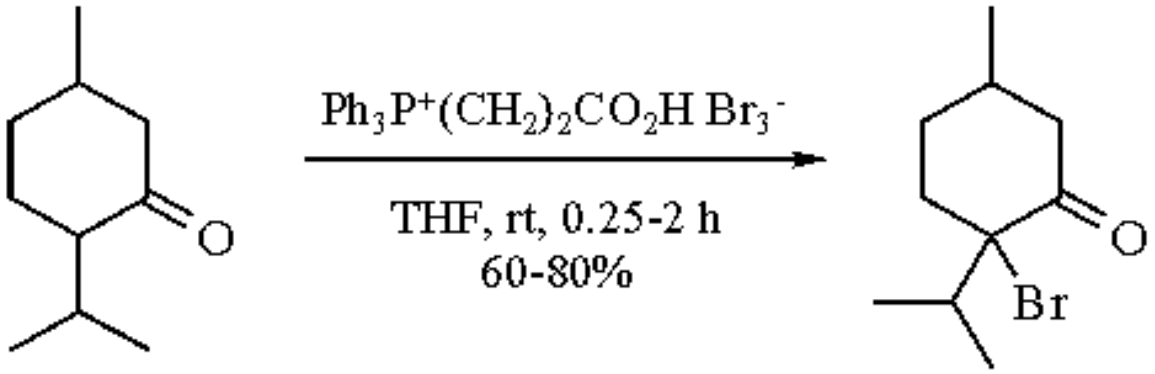

(1)

Unsaturated Ketones.

These are brominated without affecting the double bond to afford the desired α-bromo ketone (eq 2).[1,3]

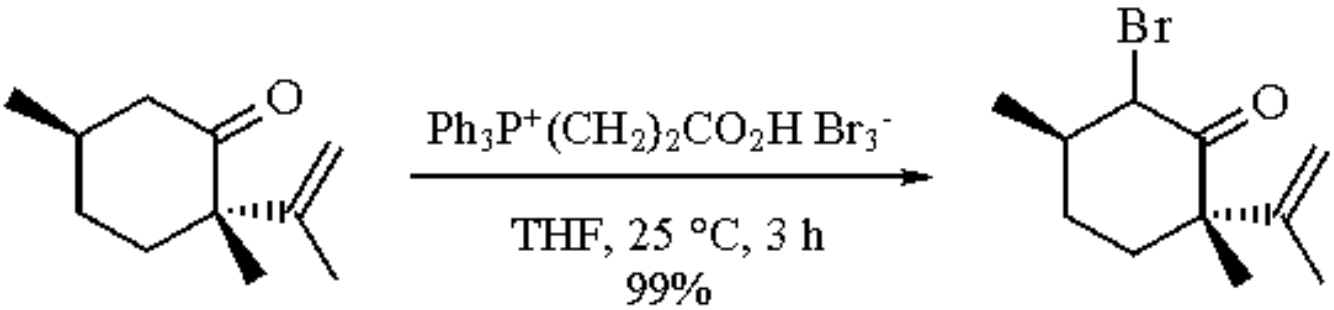

(2)

Aryl Alkyl Ketones.

Variable results are obtained with these compounds, depending on the activation level of the aromatic ring.[1,2] Either the nature of the solvent (dichloromethane, THF with or without H_2O) (eq 3) and/or the use of the one-pot acetalization-bromination procedure[2] also play a critical role in determining the distribution of the brominated products; these effects have not yet been optimized.

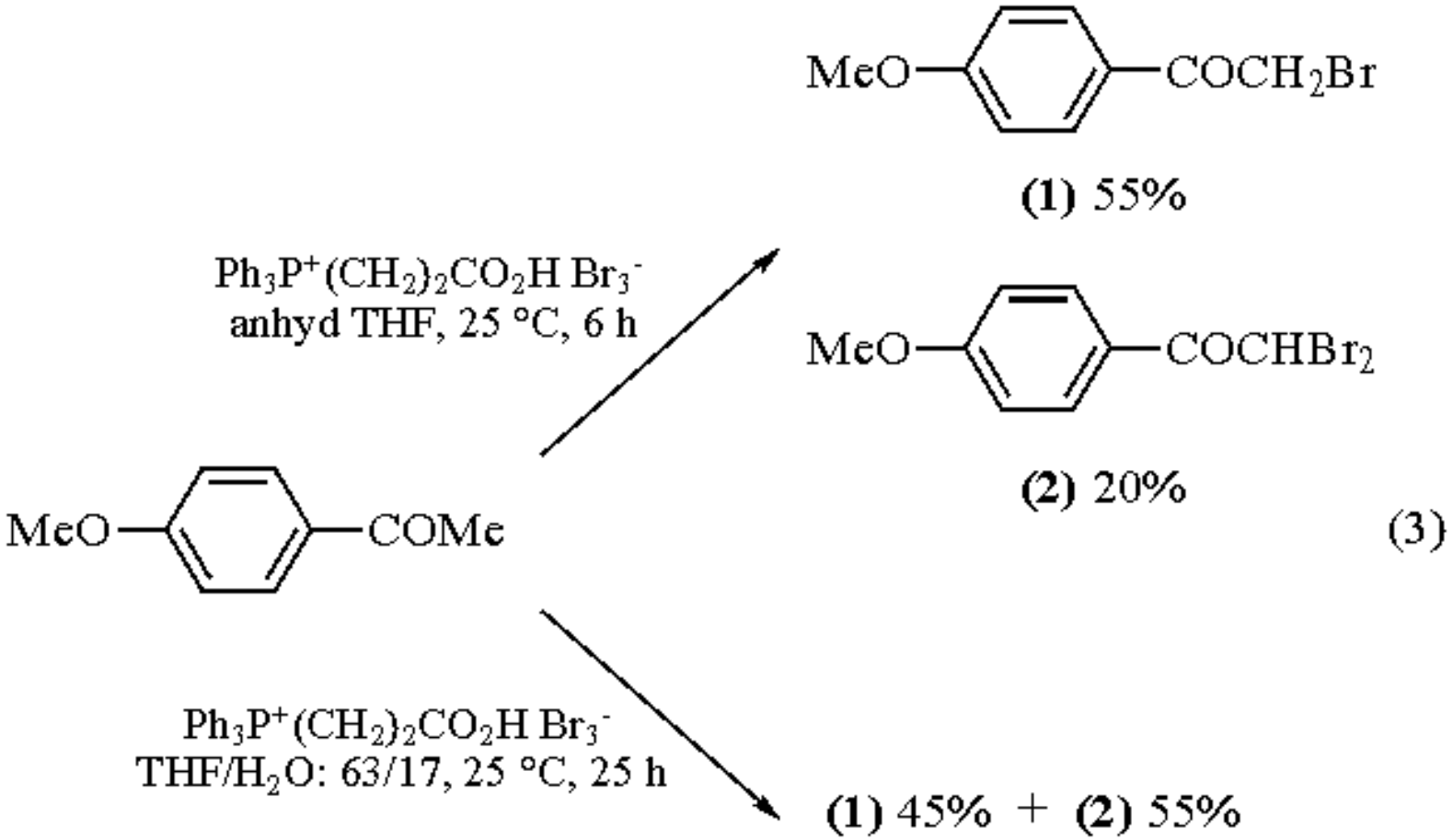

Note that recovery and reuse of the monobromide byproduct (after treatment with bromine) is possible.

For α-bromination of ketones this reagent often compares favorably with other ammonium or phosphonium salts.[2] Reagents for similar transformations include ***Pyridinium Hydrobromide Perbromide***,[6] ***Phenyltrimethylammonium Perbromide***,[7,8] ***2-Pyrrolidone Hydrotribromide***[9] and the phosphonium reagents described by Cristau et al.[2]

---

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Jean-Robert Dormoy & Bertrand Castro

SANOFI Chimie, Gentilly, France

(*E*)-(Carboxyvinyl)trimethylammonium Betaine

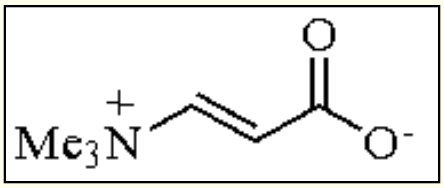

[54299-83-1] · $C_6H_{11}NO_2$ · (*E*)-(Carboxyvinyl)trimethylammonium Betaine · (MW 129.16)

(reaction of allylic alcohols with (*E*)-(carboxyvinyl)trimethylammonium betaine affords (*E*)-3-(allyloxy)acrylic acids, which on heating are transformed to γ,δ-unsaturated aldehydes via Claisen rearrangement/decarboxylation[8,9])

Physical Data: mp 176-177 °C (dec);[9] 240-245 °C (dec).[7]

Analysis of Reagent Purity: IR (KBr) cm^{-1}: 1665, 1600, 1360; ^1H NMR (D_2O, DSS ref) δ: 3.3 (br s, 9 H, Me_3N), 6.3 (br d, 1 H, *J* = 13, vinyl CH), 6.8 (br d, 1 H, *J* = 13, vinyl CH); elemental analysis.

Preparative Methods: A mixture of 25.0 g of ethyl propiolate, 14 mL of dichloromethane, and 440 mL of water is cooled to 5 °C and 90 mL of an aqueous 25% solution of trimethylamine is added with vigorous stirring over a period of 30 min. The mixture is then warmed to 25 °C for 3 h. The aqueous layer is separated and washed three times with 100 mL of dichloromethane. The aqueous solution is concentrated in vacuo at 45 °C. When the residue gives the appearance of a wet solid, it is treated with 150 mL of dioxane and concentrated as described above. The dioxane treatment-concentration procedure is repeated three times. The resulting yellow solid is triturated with acetonitrile until a white solid is obtained (25 g, 76% yield).

Purification: yellow impurities can be removed by trituration with acetonitrile to obtain a white solid. This is dried at 25 °C in vacuo (0.1 mmHg) for 14 h.

Handling, Storage, and Precautions: the reagent will slowly decompose at room temperature over a period of several months. Storage in a closed container at low temperatures is recommended. This reagent should be handled in a fume hood.

Synthesis of γ,δ-Unsaturated Aldehydes.

The Claisen rearrangement of allyl vinyl ethers[1] is a useful synthetic transformation. However, this synthetic method is limited due to the lack of efficient general methods for the preparation of allyl vinyl ethers. These intermediates are normally prepared by vinyl ether exchange with simple alkyl vinyl ethers and an allylic alcohol in the presence of a Lewis acid (usually mercury(II) acetate) or mineral acid.[2] Often yields in these reactions are low, and the use of mercury is

becoming unacceptable environmentally.

Useful modifications of the Claisen rearrangement have been reported (e.g. those of Johnson,[3] Ireland,[4] and Eschenmoser[5]); however, these methods give products at the carboxylic acid oxidation level, and additional steps are required if an aldehyde is the desired product.

The betaine (**1**)[6,7] can be used to convert primary and secondary allylic alcohols (**2**) to the corresponding γ,δ-unsaturated aldehydes (**3**) via allyloxyacrylic acids (**4a**).[8,9] The γ,δ-unsaturated aldehydes (**3**) obtained from the Claisen rearrangement-decarboxylation of (**4a**) are the same products that would be obtained from Claisen rearrangement of the corresponding allyl vinyl ethers. The basic conditions required for the addition of allyic alcohols to the betaine (**1**) complement the previous methods of allyl vinyl ether formation.

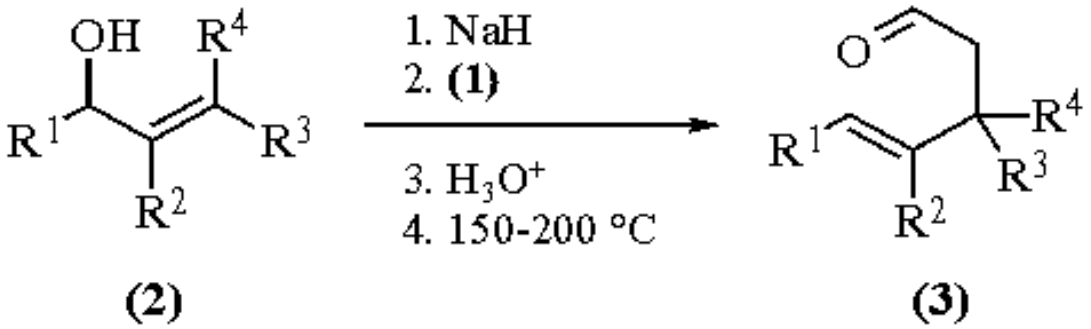

(2) (3) (1)

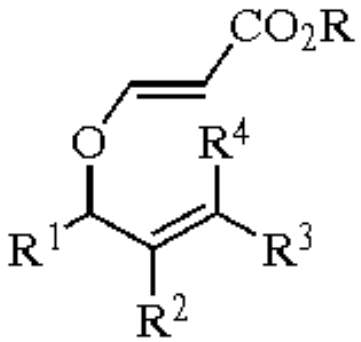

(4a) R = H
(4b) R = Na

Thus heating the sodium alkoxides of allylic alcohols with betaine (**1**) affords moderate to good yields of the corresponding *trans*-3-(allyloxy)acrylic acid sodium salts (**4b**). Aqueous solutions of the adducts (**4b**) are first washed with ether and then acidified to give the corresponding carboxylic acids (**4a**). These crude products are heated with a trace of hydroquinone at temperatures of 150-200 °C to give products (**3**) from Claisen rearrangement-decarboxylation of (**4a**).[10] Sealed tubes or other high-pressure vessels are not necessary since the acrylic acids (**4a**) have a much higher boiling point than the aldehydes (**3**). The acids are heated under the appropriate reduced pressure such that the product is removed rapidly from the reaction mixture. The aldehydes (**3**) are isolated in good to excellent yields often in analytically pure form (Table 1).

Table 1 Yields of Allyloxy Acrylic Acids (**4a**) and γ,δ-Unsaturated Aldehydes (**3**) from Allylic Alcohols Using Betaine (**1**)

Allylic alcohol (**2**)	Yield	Product (**3**)	Yield

Allylic alcohol (2)	Yield of (4a) (%)	Product (3)	Yield of (3) (%)
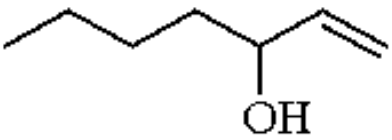	89	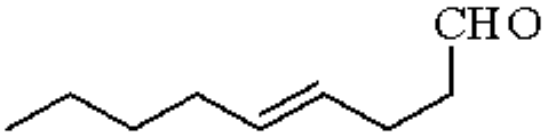	68
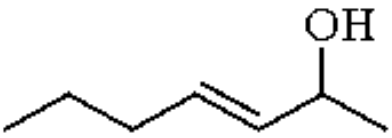	84	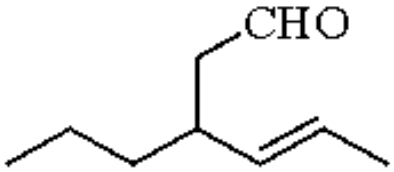	78
	92	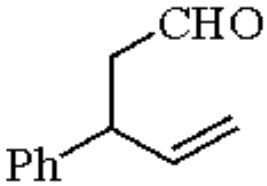	quant.
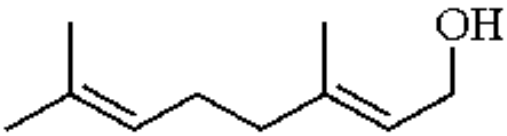	62		quant.
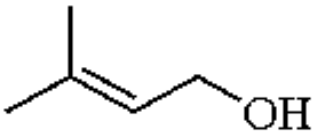	96	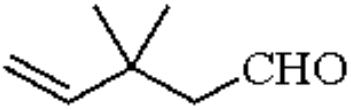	quant.
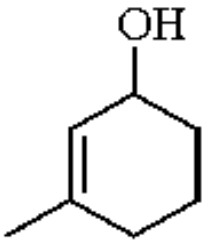	53, 77	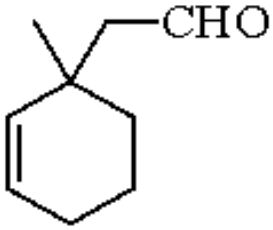	quant.
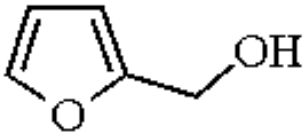	82	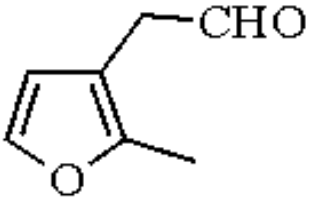	79
		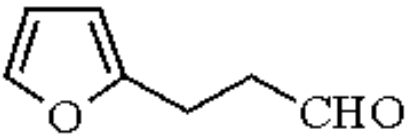	16

(E)-(Carboxyvinyl)trimethylammonium Betaine

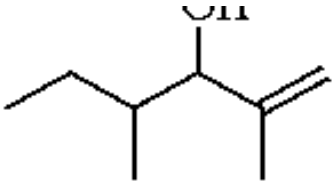

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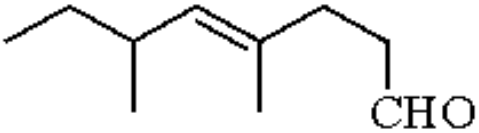

82

For a similar reaction useful for the preparation of ketones via Claisen rearrangement-decarboxylation, see Büchi and Vogel.[11]

---

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Dennis E. Vogel

3M Company, St Paul, MN, USA

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Catechol[1]

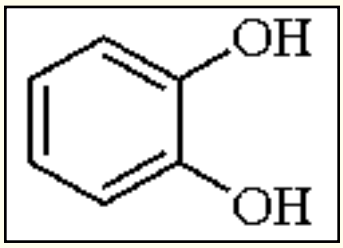

[120-80-9] · $C_6H_6O_2$ · Catechol · (MW 110.11)

(reagent for heterocycle synthesis; allylation catalyst; carbonyl protecting group; transition metal ligand)

Alternate Name: pyrocatechol.

Physical Data: mp 104-105 °C; bp 119-121 °C/10 mmHg; *d* 1.344 g cm^{-3}; sublimable (vp 1.0 mmHg, 75 °C); steam volatile.

Solubility: sol benzene, acetone, ether, ethanol, 2.3 parts water, pyridine, aqueous alkali; slightly sol chlorinated solvents.

Form Supplied in: colorless needles (or plates).

Purification: recrystallization from toluene; distillation.

Handling, Storage, and Precautions: toxic (readily absorbed through skin); irritant; causes burns. Light and air sensitive. Explodes on contact with conc. HNO_3.

Alkylation and Heterocycle Synthesis.

Catechol undergoes many of the reactions characteristic of phenols, and as such is used to prepare *o*-alkoxyphenols, *o*-dialkoxybenzenes, and heterocycles.[1] The high yield preparation of five-membered *o*-phenylene heterocyclic systems from catechol is particularly common, and includes 1,3,2-benzodioxaborole from diborane (eq 1) (see ***Catecholborane***),[2] methylenedioxybenzene from

diiodomethane,[3] *o*-phenylene carbonate from phosgene,[4] 1,3-benzodioxoles from allenic derivatives,[5] *o*-phenylene chloro- and bromoboronates from the respective boron trihalides,[6,7] and *o*-phenylene phosphorochloridite from phosphorus trichloride.[8] Larger heterocyclic ring systems, such as 1,4-benzodioxanes (eq 2)[9] and dibenzo- and dicyclohexyl-18-crown-6 polyethers[10] are prepared in good yields using alkylations of catechol.

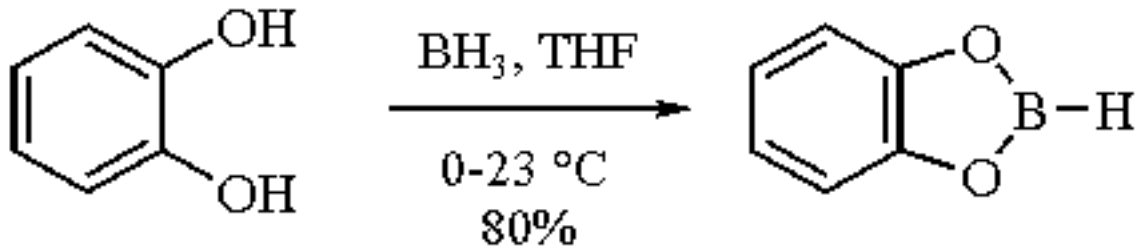

(1)

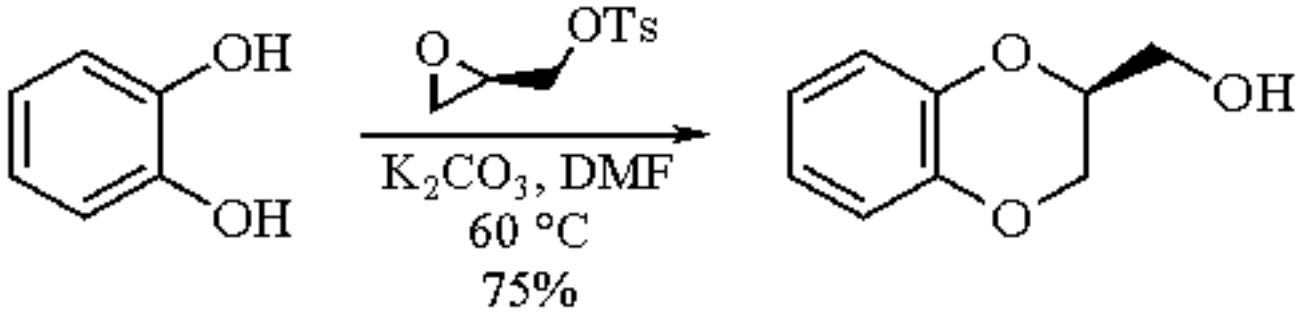

(2)

Allylation Catalyst.

Bis(catecholato)allylsiliconates, prepared in situ from catechol, triethylamine, and allyl(trialkoxy)silanes, are effective allylating agents for aldehydes (eq 3).[11] Good yields of homoallylic alcohols are obtained in a regiospecific manner.

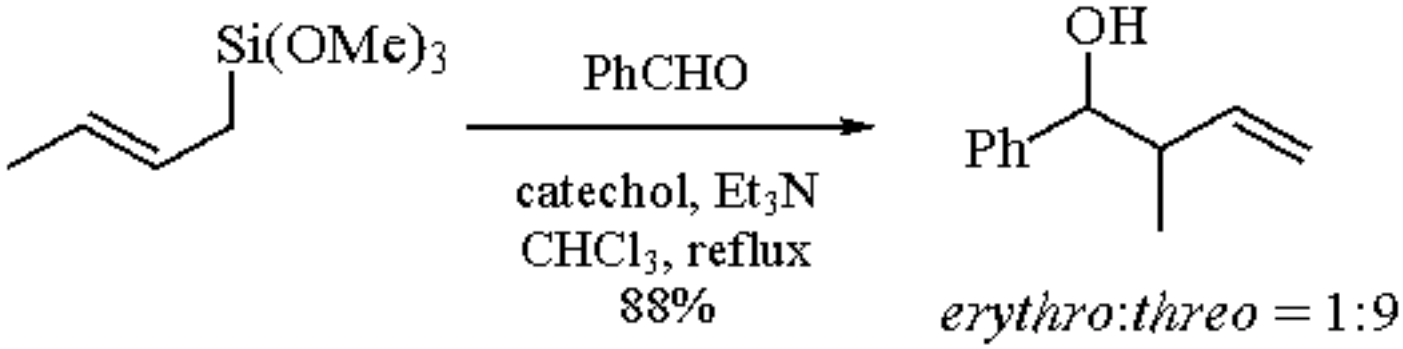

(3)

Carbonyl Protecting Group.

Ketones and aldehydes react with catechol under acidic conditions to form cyclic acetals (eq 4).[12] The acetals formed are more stable to acid than ethylene acetals.[13] Cleavage of the *o*-phenylene acetals of α-

unbranched and aromatic ketones with BBr_3 gives geminal dibromides and vinyl bromides, respectively (eq 5).[14]

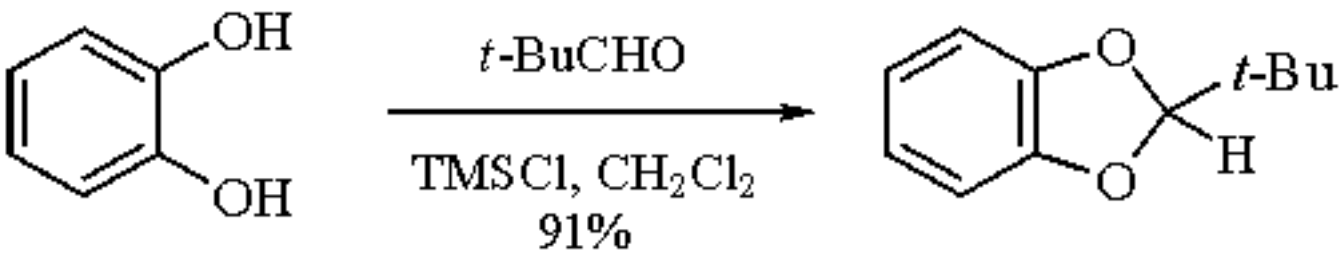

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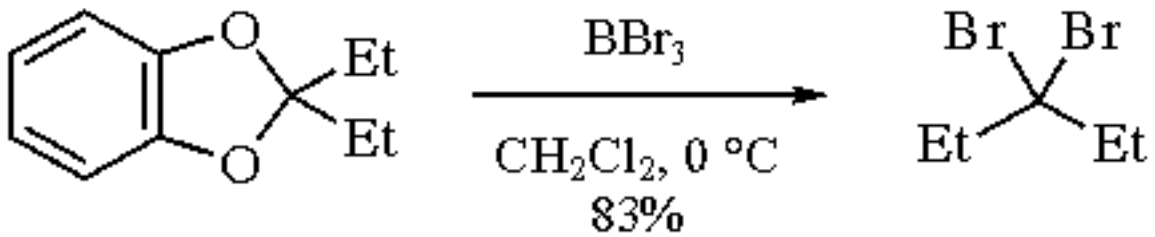

(5)

Transition Metal Ligand.

Catechol binds readily to virtually all transition metals, giving catecholato metal complexes.[15] The σ- and π-donating properties of catecholato ligands,[16] as well as other hydroxo ligands,[17] are postulated to stabilize unsaturated organometallic derivatives.

---

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Bruce A. Barner

Union Carbide Corp., South Charleston, WV, USA

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Catecholborane[1]

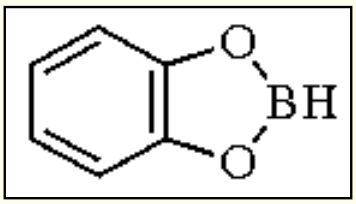

[274-07-7] · $C_6H_5BO_2$ · Catecholborane · (MW 119.92)

(reducing agent for several functional groups;[2] used to prepare alkyl- and alkenylboronic acids and esters via hydroboration of alkenes and alkynes;[3] can be used for synthesis of amides and macrocyclic lactams from carboxylic acids[4])

Physical Data: mp 12 °C; bp 50 °C/50 mmHg; *d* 1.125 g cm^{-3}.

Solubility: sol diethyl ether, THF, CH_2Cl_2, $CHCl_3$, CCl_4, toluene, and benzene; reacts readily with water and other protic solvents.

Form Supplied in: available as a colorless liquid; 1.0 M solution in THF.

Analysis of Reagent Purity: the technical bulletin *Quantitative Analysis of Active Boron Hydrides*, available upon request from the Aldrich Chemical Company, Milwaukee, WI, USA, describes methodology to determine reagent purity by hydrogen gas evolution.

Purification: the neat reagent may be purified by distillation at reduced pressure.

Handling, Storage, and Precautions: should be stored in a cold room or refrigerator, without exposure to atmospheric moisture; cold storage has been found to minimize loss of hydrogen activity as well as pressure build-up; the neat reagent may be stored as a solid at 0 °C; a sample stored over one year at 0-5 °C showed no detectable loss in hydride activity;[1a] syringe and double-tipped needle techniques are recommended for reagent transfer. Use in a fume hood.

Functional Group Reductions.

Catecholborane (CB) is one of the most versatile boron hydride reducing agents. This reagent possesses enhanced thermal stability and solubility characteristics as compared with other boron hydride reagents. Reductions can be carried out in several organic solvents including CCl_4, $CHCl_3$, benzene, toluene, diethyl ether, and THF, as well as in the absence of solvent.[1a]

Several functional groups do not react with catecholborane. Alkyl and aryl halides, nitro groups, sulfones, disulfides, thiols, primary amides, ethers, sulfides and alcohols are all inert toward the reagent. Nitriles, esters, and acid chlorides react slowly, while aldehydes, ketones, imines, and sulfoxides are readily reduced in a few hours at room temperature.[1a]

Catecholborane readily reduces tosylhydrazones[2] to the corresponding methylene derivatives (eqs 1 and 2). This mild method may be used to advantage with substrates possessing sensitive functional groups which preclude the use of the more conventional Wolff-Kishner and Clemmensen reductions.[5]

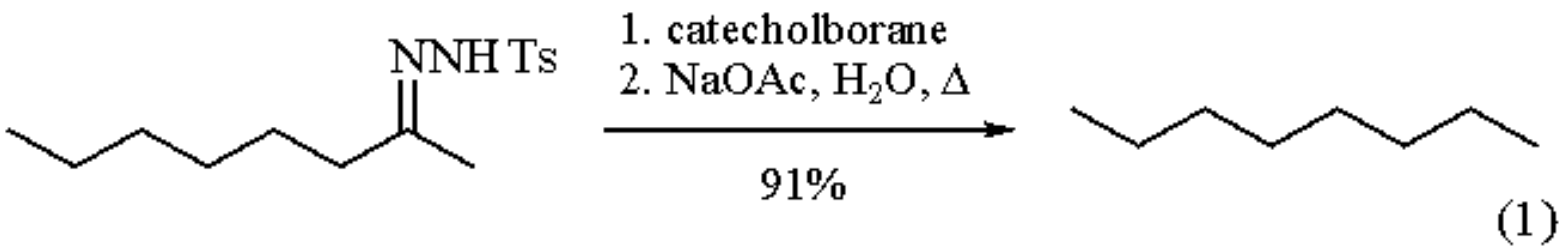

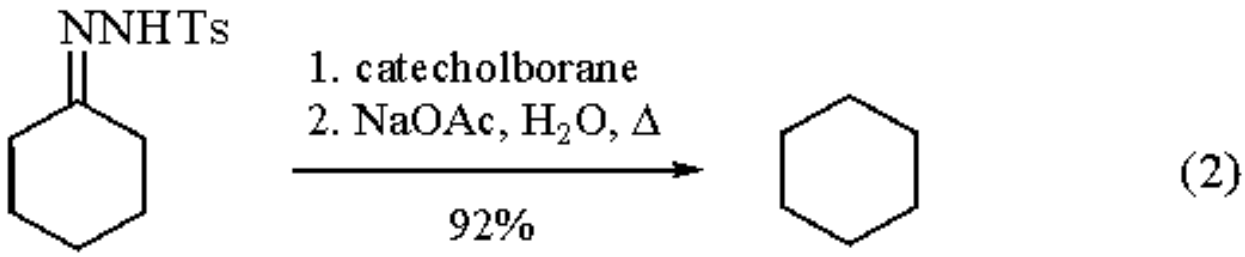

Evans[6a] has demonstrated that catecholborane will undergo conjugate reduction of α,β-unsaturated ketones at room temperature (eqs 3 and 4).[6,7] This reaction is limited to α,β-unsaturated ketones that can adopt an *s-cis* conformation, while α,β-unsaturated imides, esters, and amides are unreactive under these conditions. It was also determined that catalytic quantities of ***Chlorotris(triphenylphosphine)rhodium(I)*** greatly accelerate the 1,4-addition process such that reduction occurs readily at -20 °C.

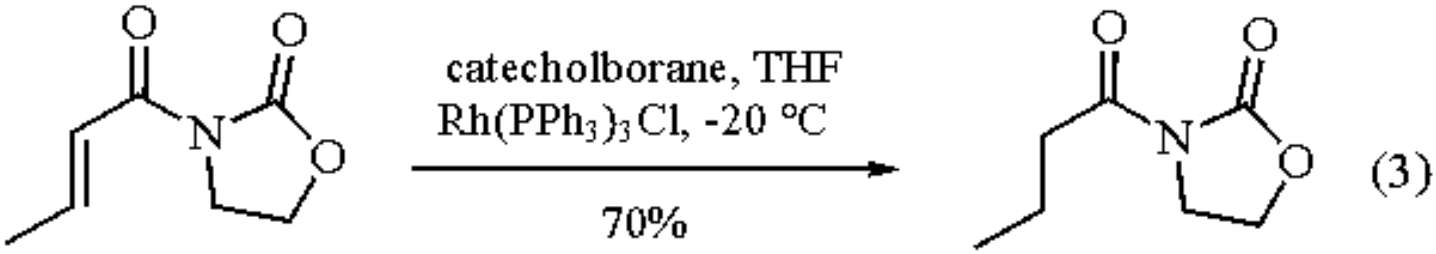

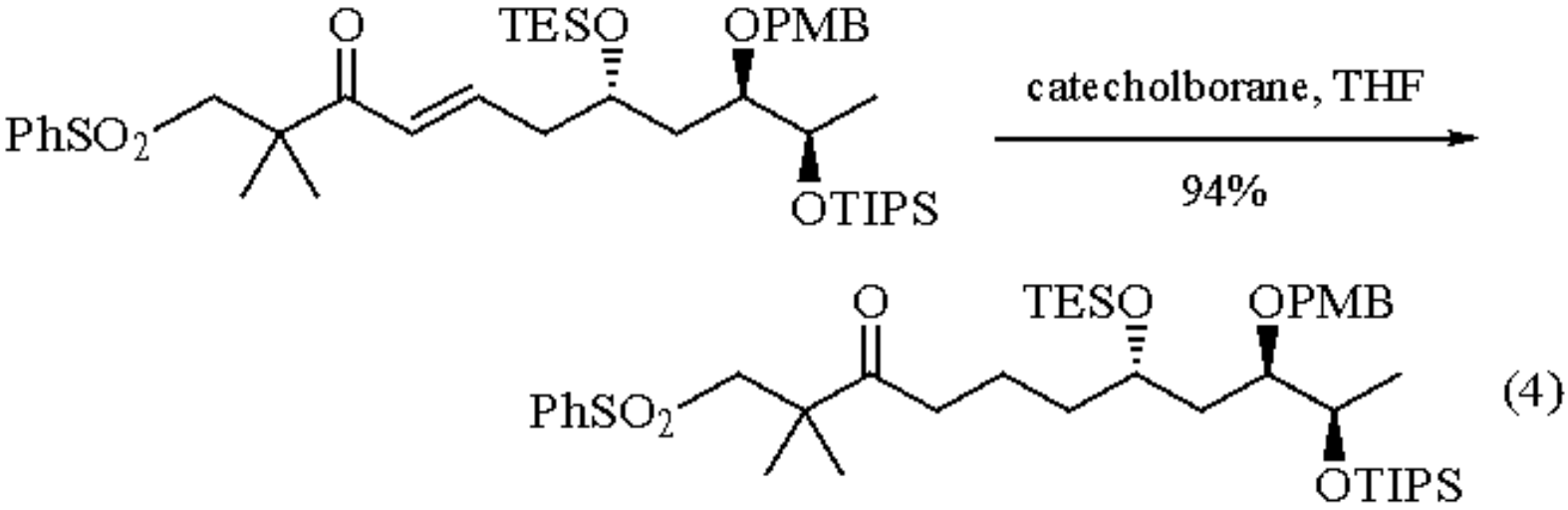

Cyclic enones bearing an endocyclic alkene, e.g. (**1**) and (**2**), do not undergo 1,4-addition but are instead reduced exclusively at the carbonyl group. It is also possible to selectively reduce *trans*-1,2-disubstituted enones in the presence of 1,1-disubstituted systems. The trapping of the intermediate boron enolate by aldehyde electrophiles has also been demonstrated.[6]

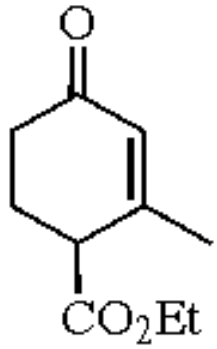

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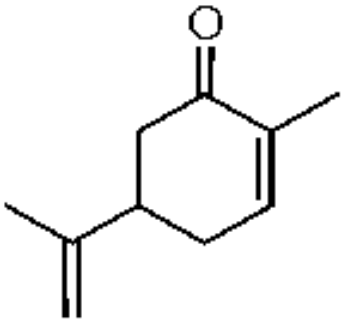

(2)

Several diastereoselective and enantioselective reductions of ketones mediated by catecholborane have also been reported. Acyclic β-hydroxy ketones are stereoselectively reduced to *syn* 1,3-diols by catecholborane (eq 5).[8] In several instances it was found that stereoselectivity could be enhanced by performing the reaction with Rh^{I} catalysis. The high levels of diastereoselectivity are believed to be due to the ability of catecholborane to preorganize the substrate prior to intermolecular delivery of hydride by a second molecule of catecholborane. The incorporation of a methyl group between the hydroxyl and carbonyl groups can affect the *syn* diastereoselectivity, the extent depending upon the stereochemical relationship between the two substituents (eqs 6 and 7).

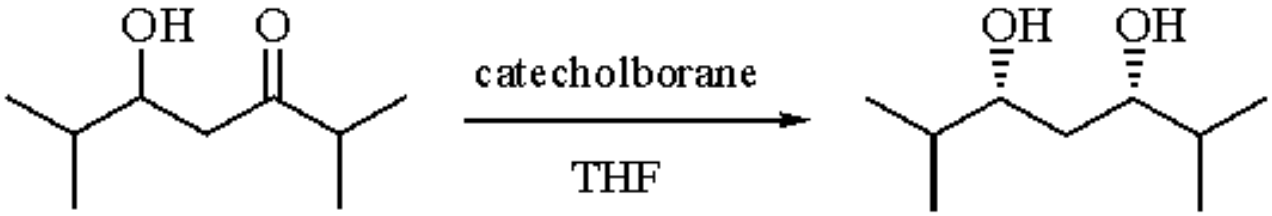

(5)

Conditions	Yield (*syn*:*anti*)
-10 °C	82% (10:1)
-10 °C, Rh^{I}	76% (12:1)
-35 °C	87% (6:1)
-35 °C, Rh^{I}	86% (20:1)

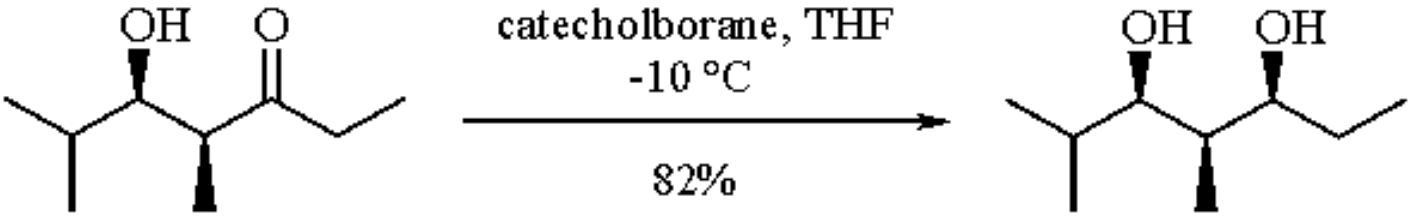

(6)

35:1

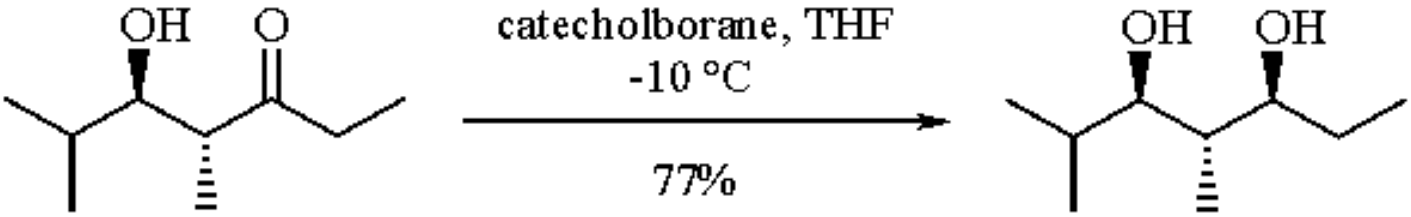

(7)

6:1

Chiral oxazaborolidines, initially reported by Itsuno[9] and later developed by Corey,[10] have been used for the enantioselective reduction of ketones. Corey has demonstrated that oxazaborolidine (**3**), prepared from ***α,α-Diphenyl-2-pyrrolidinemethanol*** and butylboronic acid, is a highly effective catalyst for the asymmetric reduction of ketones using catecholborane as a stoichiometric reductant. This system was also shown to be superior for the asymmetric 1,2-reduction of enones.

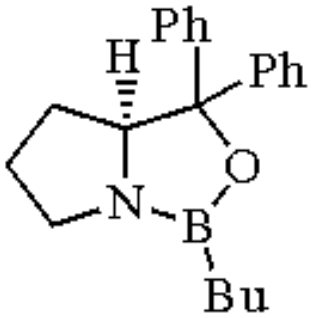

(3)

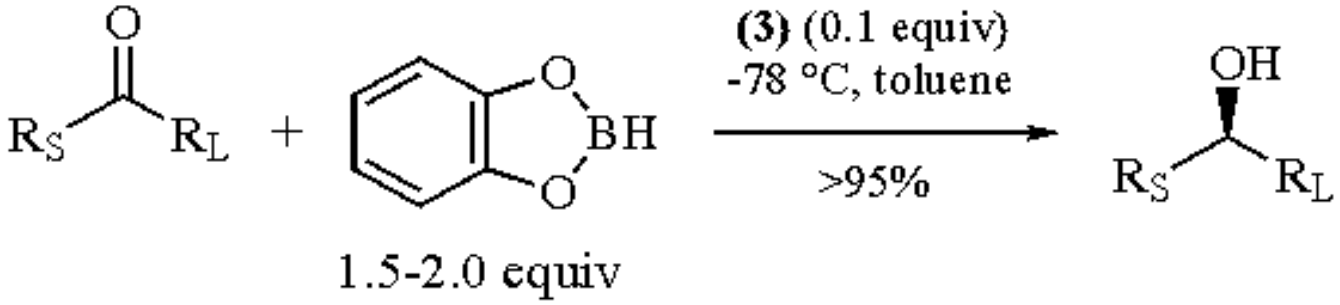

Substrate	Absolute configuration	Enantiomeric excess
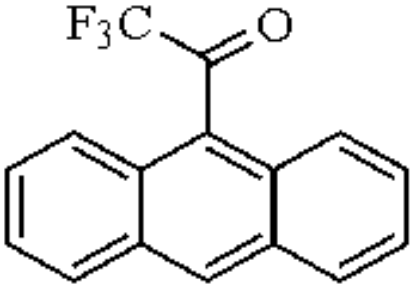	*R*	94%
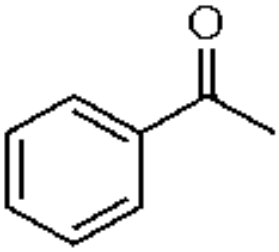	*R*	94%
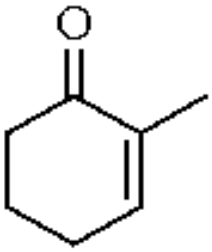	*R*	92%
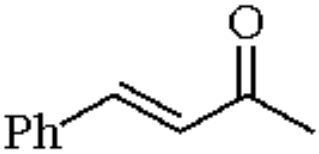	*R*	93%

Hydroboration of Alkenes.

Hydroborations of alkenes by catecholborane[3] are generally much slower than those employing dialkylboranes.[11] Elevated temperatures are usually required; however, the reaction rates may be enhanced by the use of Wilkinson's catalyst,[12] *N*,*N*-dimethylaniline-borane,[13] and ***Lithium Borohydride***.[14] The alkylboronic esters obtained are easily hydrolyzed to the corresponding alkylboronic acids or converted to aldehydes,[15] ketones,[16] carboxylic acids,[17] and alcohols.[3e,8] The esters may also be homologated, thus making possible the synthesis of substituted boronic esters, which have become increasingly useful as reagents for stereodirected synthesis.[18]

Catecholborane has been widely used for the transition metal catalyzed hydroborations of alkenes.[12,19] Both Rh^{I} and Ir^{I} have been used as the metal catalyst. Catalysis not only has a beneficial effect on rate, but has also been found to alter the chemo-, regio- and stereochemical course of the hydroboration when compared to the uncatalyzed reaction.[19]

Evans has established that the rate of the transition metal catalyzed hydroboration is very sensitive to the alkene substitution pattern.[20,21] Terminal alkenes undergo complete hydroboration within minutes at room temperature, while 1,1- and 1,2-disubstituted alkenes require several hours. Trisubstituted alkenes are unreactive. The sensitivity of the catalyzed reaction to steric effects affords the possibility for selective hydroboration of the less hindered of two alkenyl groups in a given substrate (eq 8).[20]

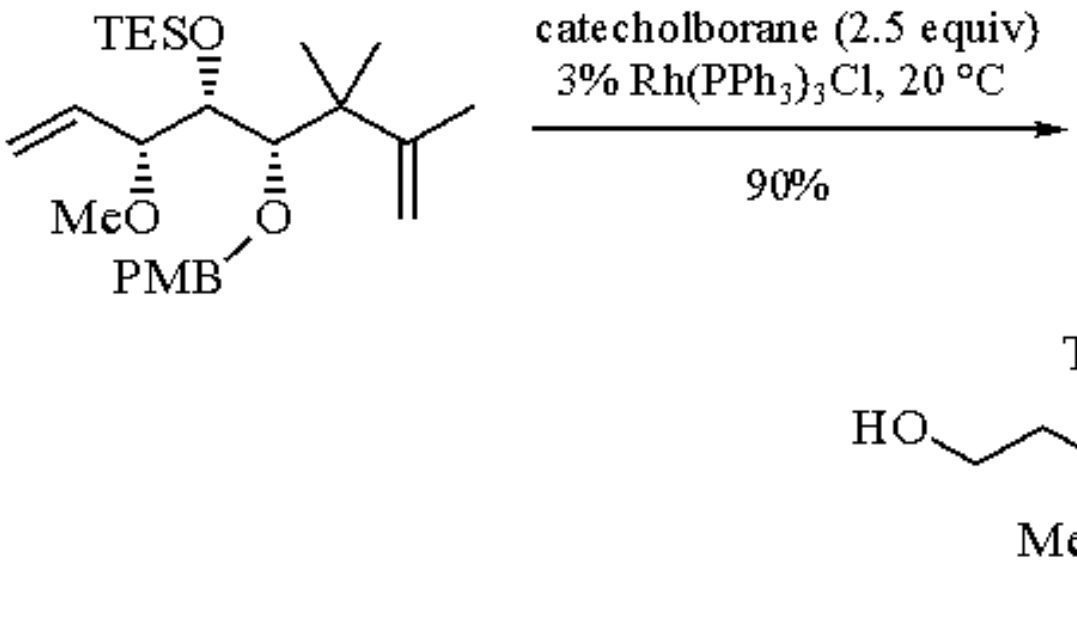

(8)

Good to excellent levels of 1,2-asymmetric induction are obtained in the catalyzed hydroboration of chiral 1,1-disubstituted alkenes with catecholborane (eq 9). The extent of asymmetric induction has been found to depend on the size of X and, to a lesser extent, the size of R´. The catalyzed and uncatalyzed reactions are stereocomplementary, with the former favoring the formation of products with *syn* stereochemistry while the latter favors products with *anti* stereochemistry.[20,22] Allylic and homoallylic diphenyl phosphinite and amide functional groups have also been used to direct the regiochemistry of the catalyzed hydroboration reaction. Examples of this methodology with both cyclic and acyclic substrates have been reported.[20,23]

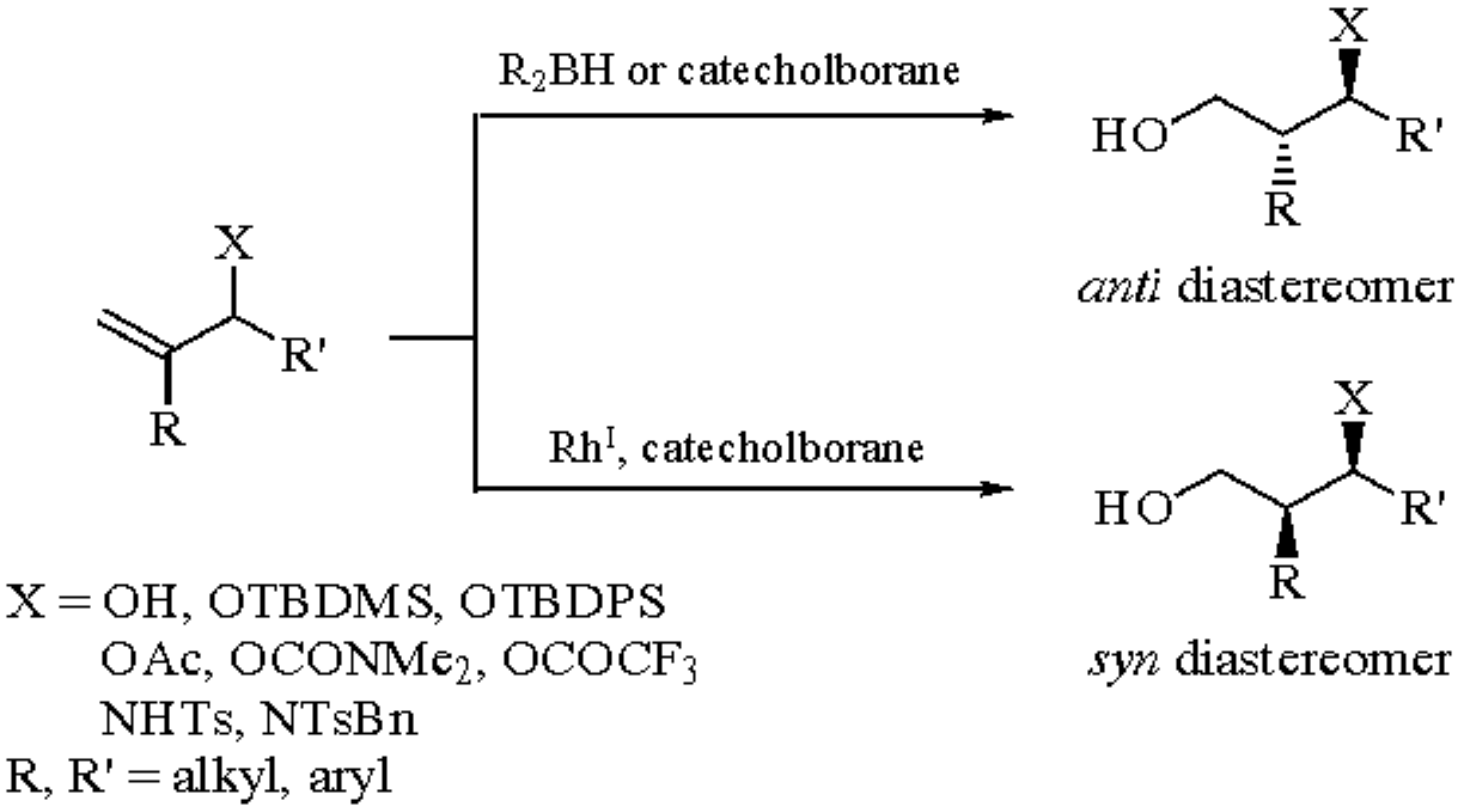

(9)

Several groups have reported catalyst systems for the asymmetric hydroboration of prochiral alkenes using the catalyzed hydroboration reaction with a chirally modified metal catalyst.[24] Most of the reactions employ a Rh^I catalyst modified with chirally modified bidentate phosphine ligands. Enantiomeric excesses obtained with several alkene substrates are in the good to excellent range.[24b,f]

Hydroboration of Alkynes.

The hydroboration of alkynes with catecholborane is an efficient route to alkenylboronic esters and acids. The regioselectivity of the addition to unsymmetrical alkenes is very similar to that displayed by ***Disiamylborane***.[3c-e] The rate of reaction can be enhanced through use of *N*,*N*-dimethylaniline-borane complex.[13]

The alkenylboronic esters and acids obtained have proven to be valuable synthetic intermediates. Perhaps the most widespread use of these intermediates has been in the Pd^0 catalyzed cross-coupling reaction with alkenyl, alkynyl, and aryl halides to give the corresponding alkenes (eq 10).[25]

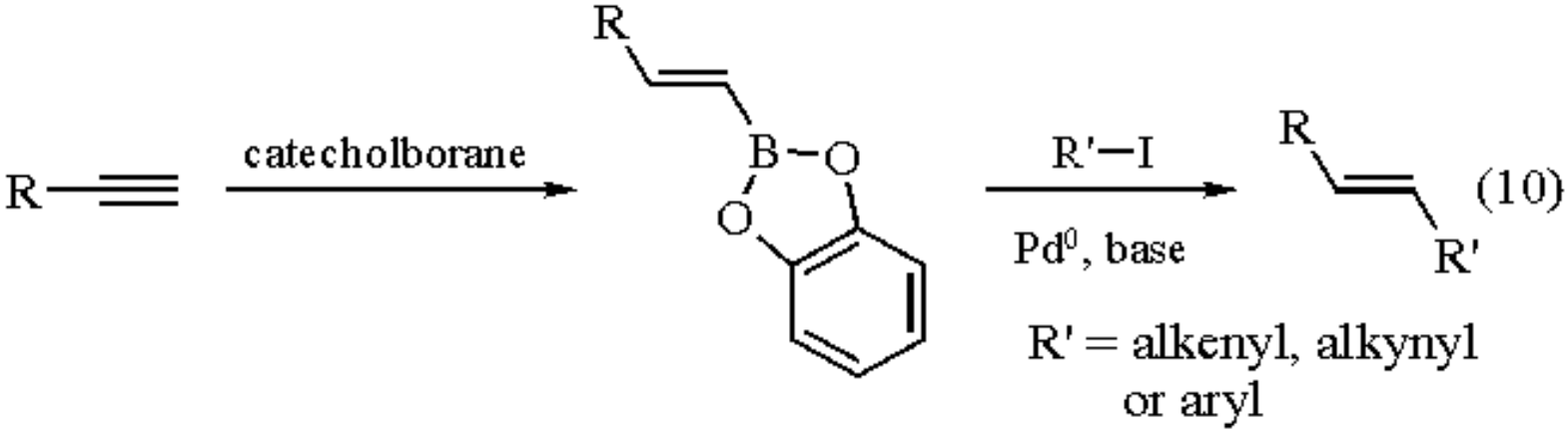

Protonolysis of alkenylboronic esters deriving from internal alkynes provides a route for the stereospecific synthesis of *cis*-disubstituted alkenes, while an oxidative workup will afford the corresponding ketone.[3d,e] Iodo- and bromoalkenes can also be prepared stereospecifically from alkenylboronic ester intermediates.[26] These compounds are useful in alkene cross-coupling reactions as well as in the preparation of alkenylmagnesium and alkenyllithium compounds. Haloalkenes may also be prepared from alkenylboronic acids via organomercurial intermediates (eq 11).[27]

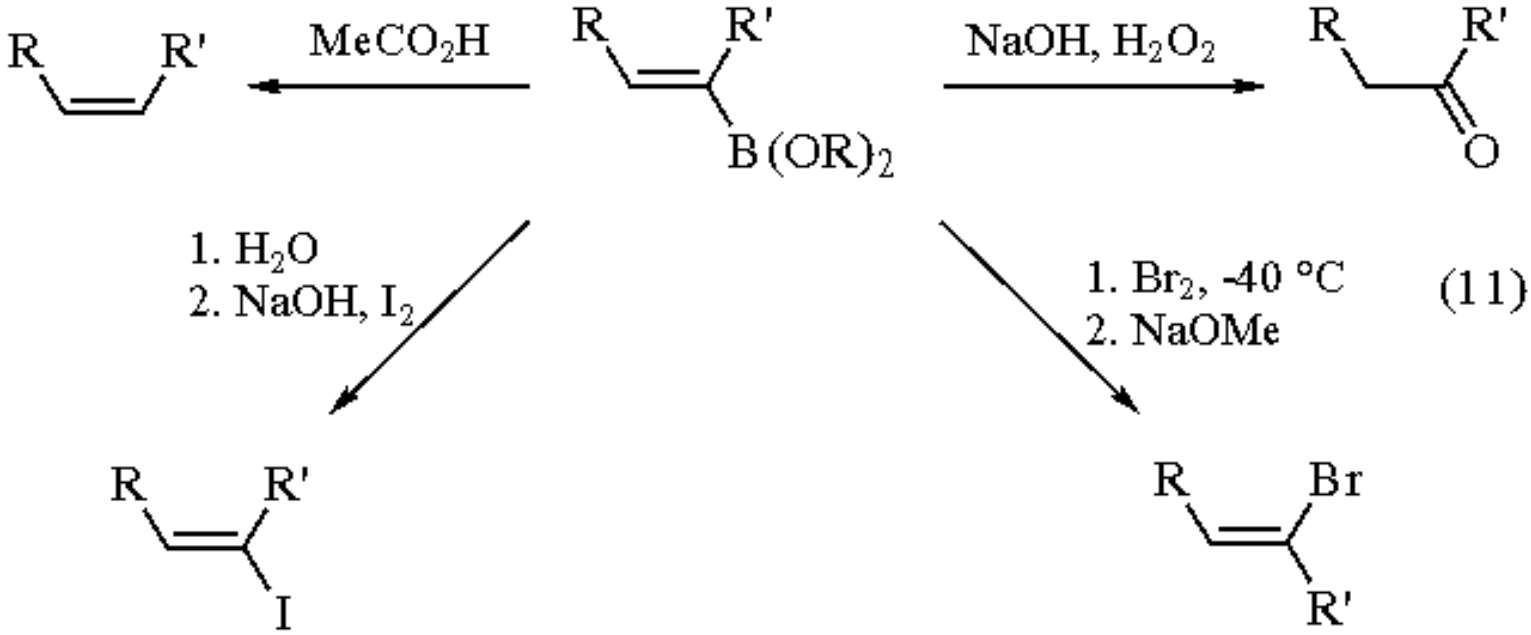

Reagent for Amide and Lactam Synthesis.

Carboxylic acids react rapidly with catecholborane to produce 2-acyloxy-1,3,2-benzodioxaborolanes, e.g. (**4**). This reaction has been used as the carboxyl activation step for the synthesis of amides and macrocyclic lactams (eq 12).[4]

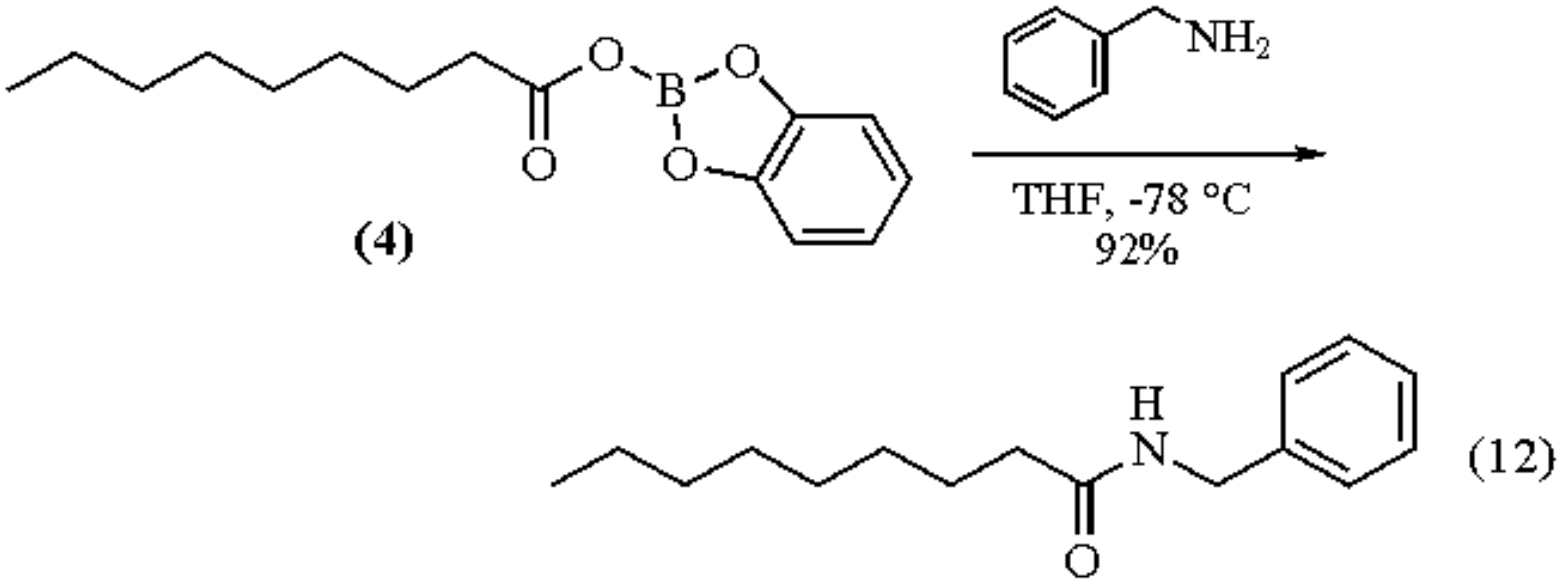

Related Reagents.

Bis(benzoyloxy)borane; ***Disiamylborane***.

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7. Other methods: (a) *COS* **1991**, *8*, Chapter 3.5, p 503 (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989, pp 8-17.
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Catechylphosphorus Trichloride[1]

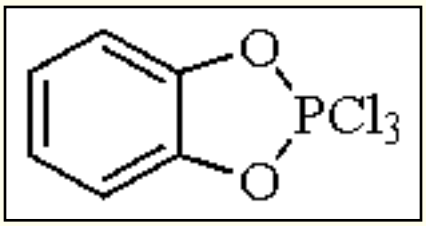

(trichloride)

[2007-97-8] · $C_6H_4Cl_3O_2P$ · Catechylphosphorus Trichloride · (MW 245.43) (tribromide)

[3712-44-5] · $C_6H_4Br_3O_2P$ · Catechylphosphorus Tribromide · (MW 378.81)

(chlorinating reagent; exchange of oxygen and sulfur to chlorine)

Alternate Names: CPT; 2,2,2-trichloro-2,2-dihydro-1,3,2-benzodioxaphosphole.

Physical Data: mp 61-62 °C; bp 132-135 °C/12 mmHg; ^{31}P NMR: δ -26 ppm.

Solubility: sol CH_2Cl_2, $CHCl_3$, CCl_4, Et_2O, benzene, hexane; reacts violently with H_2O and other protonic solvents, also with alcohols, acetone, DMF, THF.

Form Supplied in: pale yellow solid; commercially available.

Handling, Storage, and Precautions: the solid must be stored in absence of moisture; the dissolved solid is easy to handle; the substance is corrosive and toxic on contact. This reagent should be handled in a fume hood.

Reactions with catechylphosphorus trichloride (CPT) are normally carried out by heating (30 min, water bath) without solvents (other conditions are described, see equations). The products must be separated by distillation from the catechylphosphoryl (bp 120-122 °C/13 mmHg) or thiophosphoryl chloride (bp 114 °C/13 mmHg) also formed. Normally the boiling points of the products are lower than those of the byproducts.

Displacement of Double-Bonded Oxygen or Sulfur by Chlorine.

CPT converts carboxylic acids and dithiocarboxylic acids to acid chlorides (eqs 1 and 2).[1-3] Also sulfonic, phosphinic, and phosphonic acids react in the same way to give the corresponding acid chlorides (eqs 3-5; R´ = H).[1,4,5]

$$RCO_2H \xrightarrow{CPT} RCOCl \qquad (1)$$

$$RCSSH \xrightarrow{CPT} RCSCl \qquad (2)$$

$$RSO_3H \xrightarrow{CPT} RSO_2Cl \qquad (3)$$

$$R_2PO_2R' \xrightarrow{CPT} R_2POCl + R'Cl \qquad (4)$$

$$RPO_3R'_2 \xrightarrow{CPT} RPOCl_2 + 2\,R'Cl \qquad (5)$$

$$R' = H,\ Alk$$

Esters of phosphinic, phosphonic, and carboxylic acids were cleaved by CPT to alkyl chlorides and acid monochlorides or dichlorides (eqs 4-6; R´ = Alk).[1,5] Anhydrides of carboxylic acids also react with CPT to give acid chlorides (eq 7).[1,2]

$$RCO_2R' \xrightarrow{CPT} RCOCl + R'Cl \qquad (6)$$

$$(RCO)_2O \xrightarrow{CPT} 2\,RCOCl \qquad (7)$$

In all cases the yield of acid chlorides is higher than the yield of the reactions with PCl_5.

CPT converts alkyl formates to α,α-dichloromethyl alkyl ethers[1,2,6] and *N*,*N*-disubstituted formamides to the corresponding amide dichlorides (eqs 8 and 9);[1] in particular, dimethylformamide dichloride (Vilsmeier reagent) was obtained in high yield and very good purity.

$$\mathrm{OCHOR} \xrightarrow{\mathrm{CPT}} \mathrm{Cl_2CHOR} \qquad (8)$$

$$\mathrm{OCHNR_2} \xrightarrow[\mathrm{Et_2O,\ 0\ ^\circ C}]{\mathrm{CPT}} \mathrm{ClCHNR_2^+\ Cl^-} \qquad (9)$$

Both types of dichlorides are good chlorinating reagents. The reactions of unsubstituted amides, urethanes, and dithiocarbamides with CPT give nitriles,[1,2] isocyanates,[1,2,7] and isothiocyanates,[8] respectively, in good yields (eqs 10-12).

$$\mathrm{RCONH_2} \xrightarrow{\mathrm{CPT}} \mathrm{RCN} \qquad (10)$$

$$\mathrm{RNHCO_2R'} \xrightarrow{\mathrm{CPT}} \mathrm{RNCO} \qquad (11)$$

$$\mathrm{RNHCSS^-\ RNH_3^+} \xrightarrow{\mathrm{CPT}} \mathrm{RNCS} \qquad (12)$$

Displacement of Single-Bonded Oxygen or Sulfur by Chlorine.

CPT converts alcohols to alkyl chlorides[1,9] and cyclic ethers (e.g. THF or ethylene oxide) to α,o-dichloroalkanes (eqs 13 and 14).[1,2] Acetals and hemiacetals were cleaved by CPT to α-chloro ethers and alkyl chlorides and HCl, respectively (eq 15).[1,10] Trialkyl trithioorthoformate reacts with CPT to give the stable dialkyl chlorodithioorthoformate (eq 16).[11]

$$\mathrm{ROH} \xrightarrow{\mathrm{CPT}} \mathrm{RCl} \qquad (13)$$

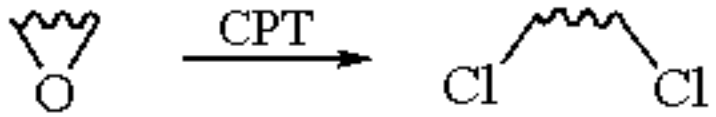

(14)

$$RCH(OR')OR'' \xrightarrow{CPT} RCH(OR')Cl + R''Cl \qquad (15)$$

$R'' = H, Alk$

$$CH(SR')_3 \xrightarrow{CPT} ClCH(SR')_2 + R'Cl \qquad (16)$$

CPT converts phosphites to chlorophosphites (eq 17);[1,12] it is the best method for the synthesis of pure diethyl chlorophosphite.[12] Silyl ethers or disiloxanes react with CPT to give silyl chlorides (eq 18).[1]

$$P(OR)_3 \xrightarrow{CPT} ClP(OR)_2 + RCl \qquad (17)$$

$$Me_3SiOR' \xrightarrow{CPT} Me_3SiCl + R'Cl \qquad (18)$$

$R' = Alk, Me_3Si$

Catechylphosphorus Tribromide.

This reagent reacts in the same way. It is particularly suitable for the synthesis of acid bromides from acids,[13] α,α-dibromomethyl alkyl ethers from alkyl formates,[14] and trimethylsilyl bromide from hexamethyldisiloxane.[15]

Related Reagents.

2-Chloroethyl Dichloromethyl Ether; ***Dichloromethyl Methyl Ether***; ***Dimethylchloromethyleneammonium Chloride***; ***Oxalyl Chloride***; ***Phosphorus(III) Chloride***; ***Phosphorus(V) Chloride***; ***Phosphorus Oxychloride***; ***Thionyl Chloride***.

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Catechol Sulfate

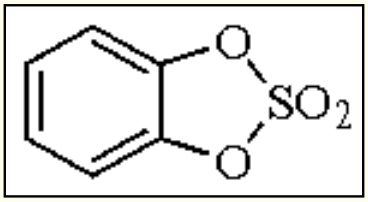

[4074-55-9] · $C_6H_4O_4S$ · Catechol Sulfate · (MW 172.16)

(selective reagent for the conversion of amines to sulfamate salts[4] and sulfamides;[9] mild reagent for sulfonation of carbon acids[16])

Alternate Name: pyrocatechol cyclic sulfate; 1,3,2-benzodioxathiole 2,2-dioxide.

Physical Data: mp 35.5-36 °C; bp 76-78 °C/1.25 mmHg.[4]

Solubility: Sparingly sol water and hexane; sol most organic solvents.

Form Supplied in: white solid or colorless needles.

Preparative Method: reaction of catechol with SO_2Cl_2.[4]

Purification: distillation and recrystallization (hexane).

Handling, Storage, and Precautions: stable indefinitely at ambient temp; no information available on toxicity.

The reactivity of catechol sulfate (CS) with hydroxide ion is anomalous relative to other sulfuric acid diesters. Surprising is the very high rate of cleavage[1] and that only S-O fission is observed.[2] X-ray crystal data suggest this unusual reactivity to be due to ring-strain effects and a distorted nonplanar conformation.[3]

Conversion of Amines to Sulfamate Salts.

Amines may be cleanly converted to catecholyl esters of sulfamic acids on reaction with CS.[4] These readily isolable esters may be efficiently hydrolyzed on mild alkaline treatment. This two-step process affords greater selectivity than possible with other reagents such as $ClSO_3H$ and SO_3 complexes,[5] fuming H_2SO_4,[6,7] and $SO_2Cl_2/SbCl_5$.[8] As example of the selectivity observed with CS, amine (**1**) is quantitatively converted to ester (**2**) which is then cleanly hydrolyzed to sulfamate salt (**3**) (eq 1). In contrast, while reaction of (**1**) with Me_3N/SO_3 gives (**3**) directly, it is formed as a minor

component (15-20%) of a complex mixture. Ester (**2**) is then cleanly converted to (**3**) by reaction with alkali.

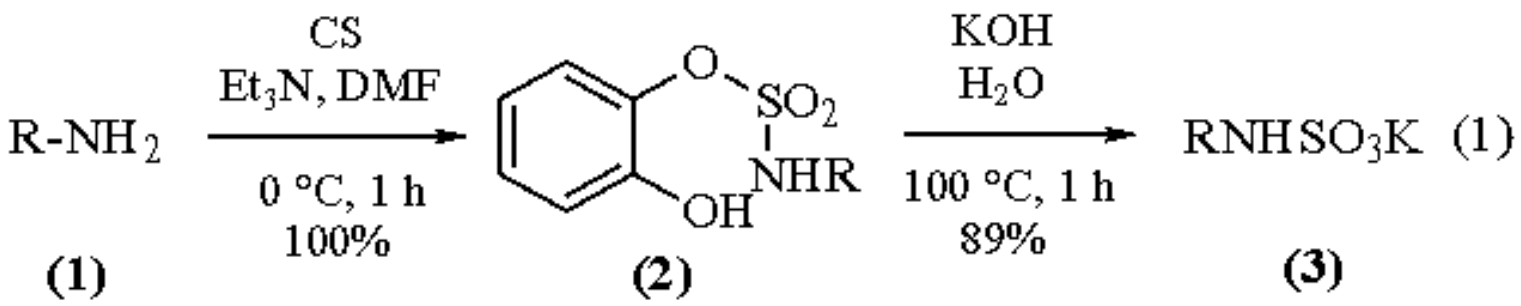

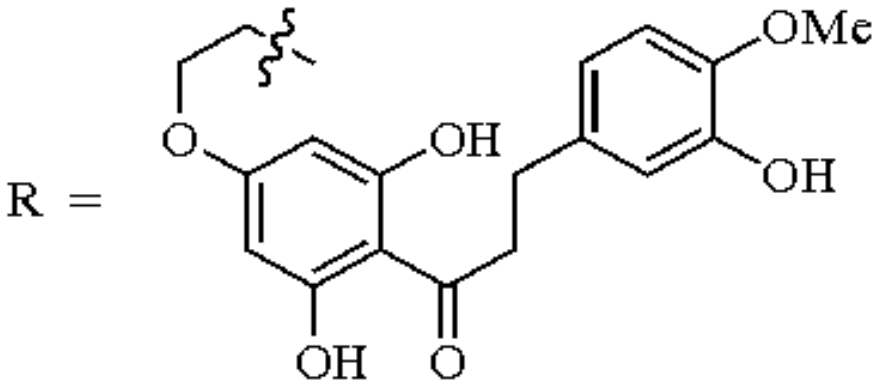

The CS sulfamation procedure is limited to primary aliphatic amines. Aromatic amines react only slowly with CS and secondary amine/CS condensation products are not cleaved by alkali.

Conversion of Amines to Sulfamides.

Catecholyl sulfamate esters, which are available as described above, may be combined with a second amine to provide sulfamides.[9] Other known procedures for sulfamide preparation employ strongly electrophilic agents such as SO_2Cl_2.[10-13] The two-step CS procedure is advantaged in its selectivity and in that either symmetrical or unsymmetrical sulfamides may be obtained. It is limited in that the amine which reacts with CS must be primary and thus tetrasubstituted products cannot be obtained directly. Sulfamides of the type $R^1R^2NSO_2NH_2$ have been prepared by using a primary amine in which the alkyl substituent is acid labile (e.g. 4-MeOPhCH_2).[14] Exemplary of the two-step CS sulfamide methodology is the preparation of (**4**) (eq 2).

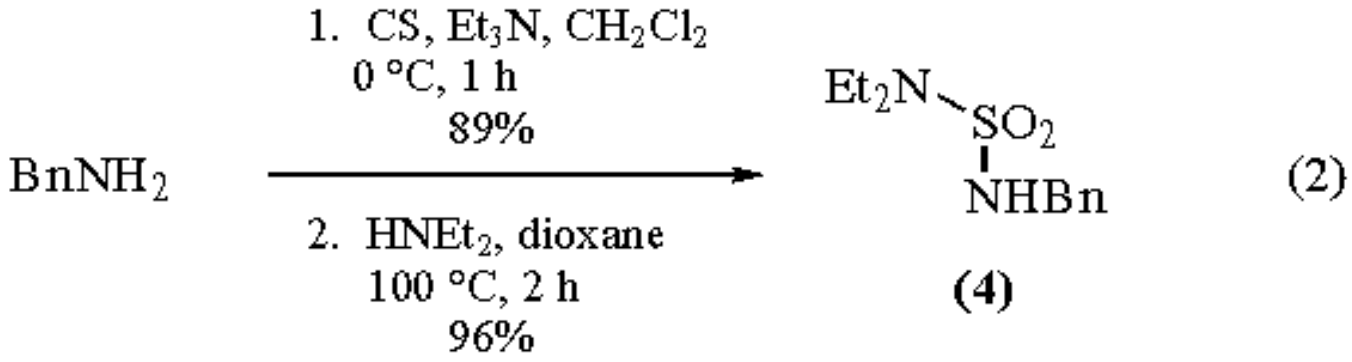

Conversion of Carbon Acids to Sulfonate Salts.

Reaction of a carbanion with CS yields the catecholyl ester of a sulfonic acid. The ester is easily hydrolyzed with alkali to give the desired sulfonic acid salt.[15] This procedure is selective and the intermediate esters may easily be isolated in pure form. Carbon acids may also be sulfonated by SO_3 and various of its complexes.[16] However, the yields are generally low and the desired products difficult to obtain in pure form. Exemplary of CS sulfonation is the preparation of substituted methionic acid (**5**) (eq 3).[15]

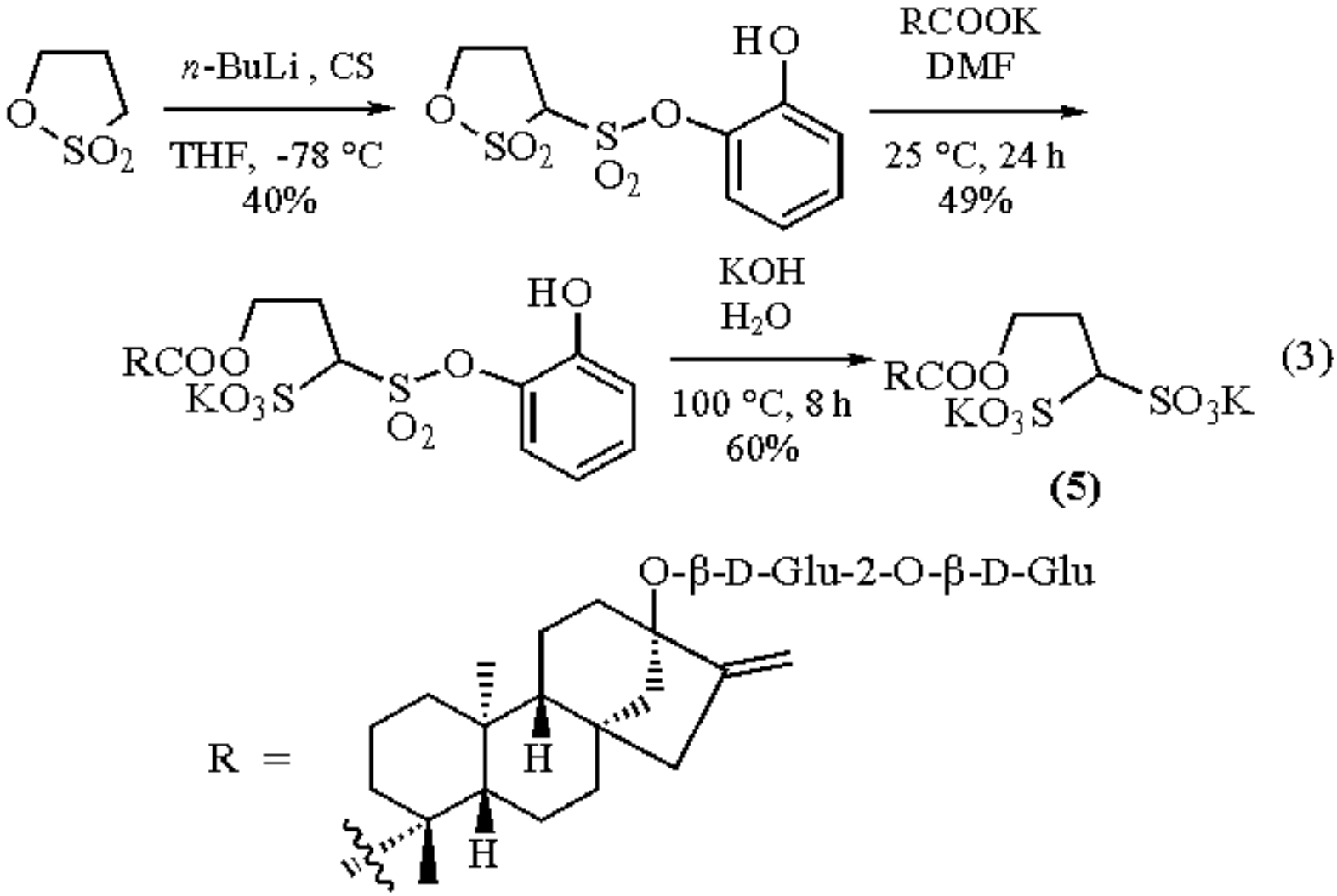

Related Reagents.

Chlorosulfonic Acid; ; ***Sulfur Trioxide***; ; ***Sulfuryl Chloride***.

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Grant E. DuBois

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Celite

[61790-53-2]

(diatomaceous, siliceous, or infusorial earth; filter aid; clarifying agent; adsorbent for reagents; chromatography[1])

Physical Data: inorganic solid, mainly SiO_2.

Solubility: insol H_2O, acid, or dilute base.

Form Supplied in: Celite® is a well known trademark of Manville, Filtration and Minerals; an off-white to white solid; widely available.

General Considerations.

Celite is composed of mostly SiO_2, and is known as diatomaceous earth or infusorial earth.[1] Celite is used in a wide variety of applications including, but not limited to, a filter aid, heat insulating material, clarifying agent, filler, adsorbent for dynamite, chromatography, and as a mild abrasive. It is useful for removal of finely divided particulate matter like decolorizing carbon, and adsorbance of colloidal substances. Future and current uses for Celite include immobilization of enzymes, spores, or cells for chemical transformations as well as reagent support in columns for microscale chemistry. The focus of this entry is the use of Celite as a surface for reagents or reactants in heterogenous reactions including oxidation, alkylation, and dehydration of organic compounds.

Chromium Oxidations.

Oxidations employing ***Chromium(VI) Oxide*** on Celite or ***Pyridinium Chlorochromate*** on Celite have been useful for oxidation of β-hydroxynitrosamines, β-hydroxynitrosoureas,[2] secondary alcohols (eq 1),[3] propargyl alcohols,[4] and primary alcohols to aldehydes (eq 2).[5]

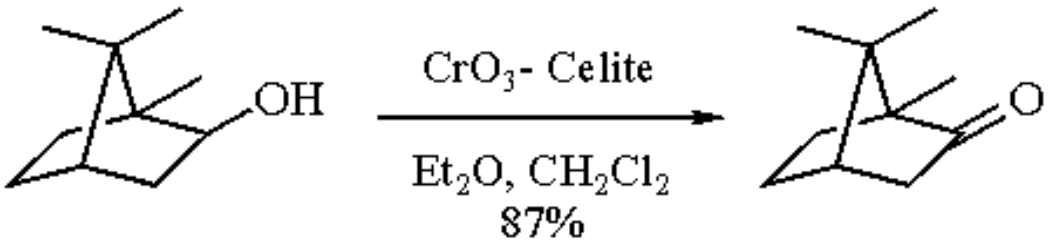

(1)

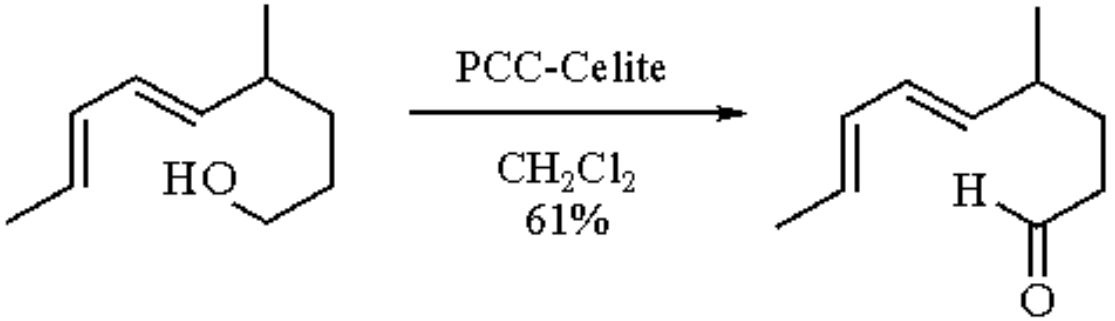

(2)

Potassium Fluoride.

Potassium Fluoride-Celite is a heterogenous catalyst that promotes an efficient cyclization that is useful in the synthesis of prenylated flavanones (eq 3).[6] Other studies include arylation reactions of 1,3-dicarbonyl compounds using fluoride ion by activation with iron,[7] *C*-, *N*-, *O*-, and *S*-alkylations with alkyl halides,[8] and KF/Celite alkylation reactions compared with other inorganic solid supports.[9]

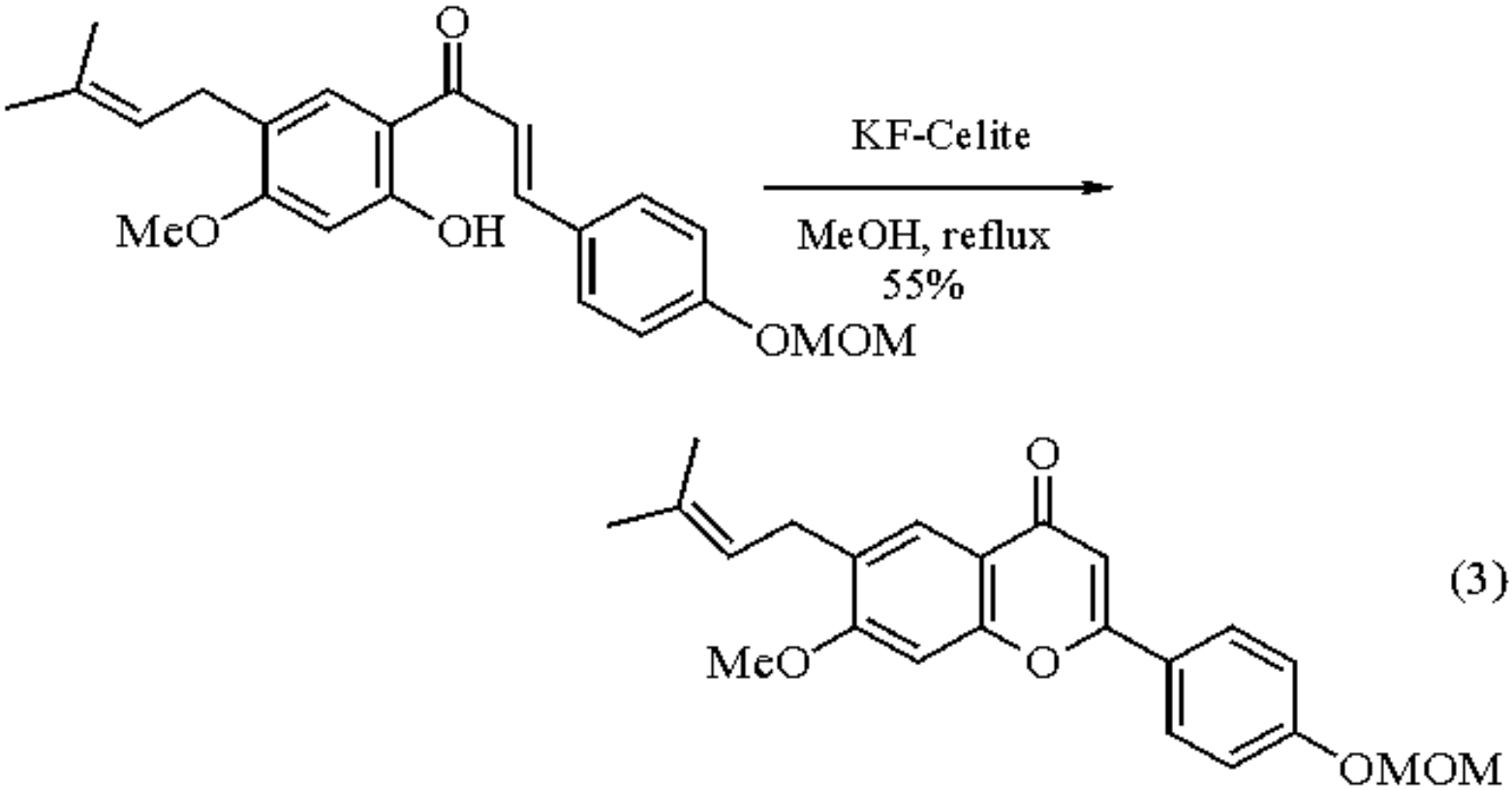

(3)

Silver Carbonate.

Perhaps the best known reagent employing Celite is Fetizon's reagent. ***Silver(I) Carbonate*** promotes reactions with phenols, amines, hydrazines, hydroxylamines, oximes, and fragmentations. An extensive review[10] describes selective oxidation of sensitive alcohols to aldehydes or ketones under neutral conditions, and includes a mechanistic discussion. Other studies include a series of papers on the oxidation of carbohydrates,[11] oxidative coupling of phenols (eq 4),[12] a mechanistic study,[13] and oxidation of allylic alcohols (eq 5).[14]

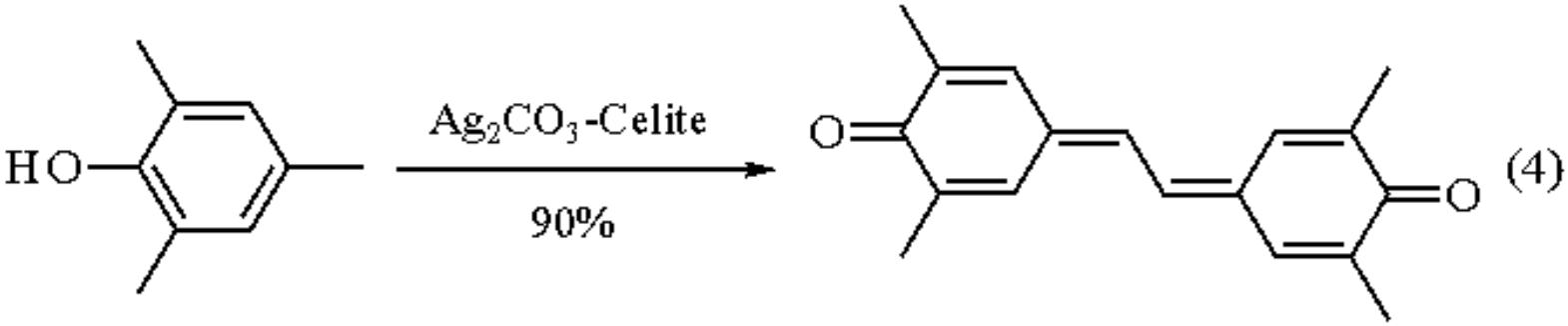

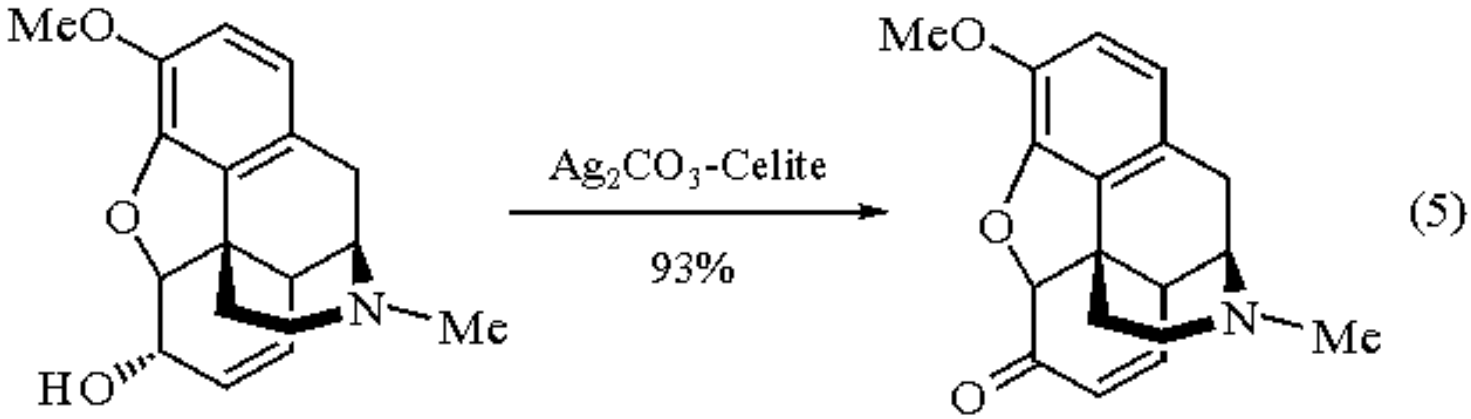

Phosphorus Pentoxide.

Phosphorus(V) Oxide/Celite has been used to mediate Bischler-Napieralski reactions (eq 6),[15] and has been used to dehydrate triflic acid to triflic anhydride in 70-90% yield (eq 7).[16]

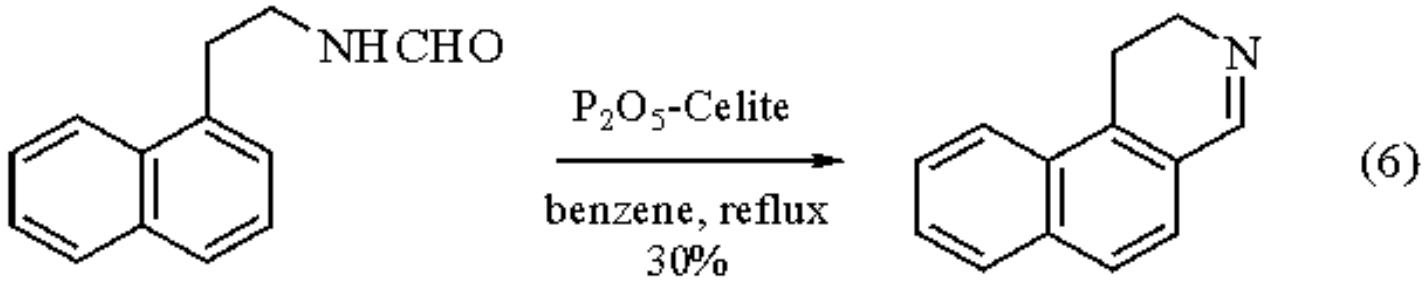

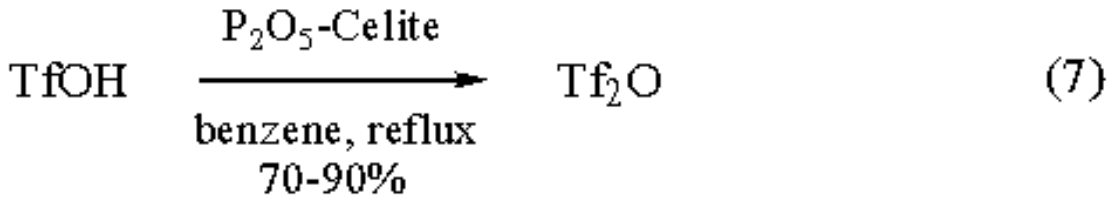

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Cerium

Ce

[7440-45-1] · Ce · Cerium · (MW 140.12)

(reagent for the Barbier and the Reformatsky reactions and pinacol coupling)

Physical Data: mp 804 °C; bp ca. 3470 °C; *d* 6.77 g cm^{-3}.

Form Supplied in: powder, chip, foil, and ingot are commercially available in 99.9% purity.

Handling, Storage, and Precautions: metallic cerium is sensitive to air and is stored in mineral oil or under argon. It readily burns in air from friction, and the preparation of cerium powder by scraping cerium ingots with a rasp should therefore be carried out in a glove bag or a dry box. Cerium is reputed to be of low toxicity.

Preparation of Organocerium Compounds.

Cerium powder or chips can be used for the Barbier reaction between alkyl halides and carbonyl compounds. Allylic and benzylic halides react most easily under mild conditions.[1,2] The reactions are chemoselective and additions to carbonyl compounds containing functional groups such as nitriles, nitro compounds, esters, and vinylic iodides are possible (eq 1).

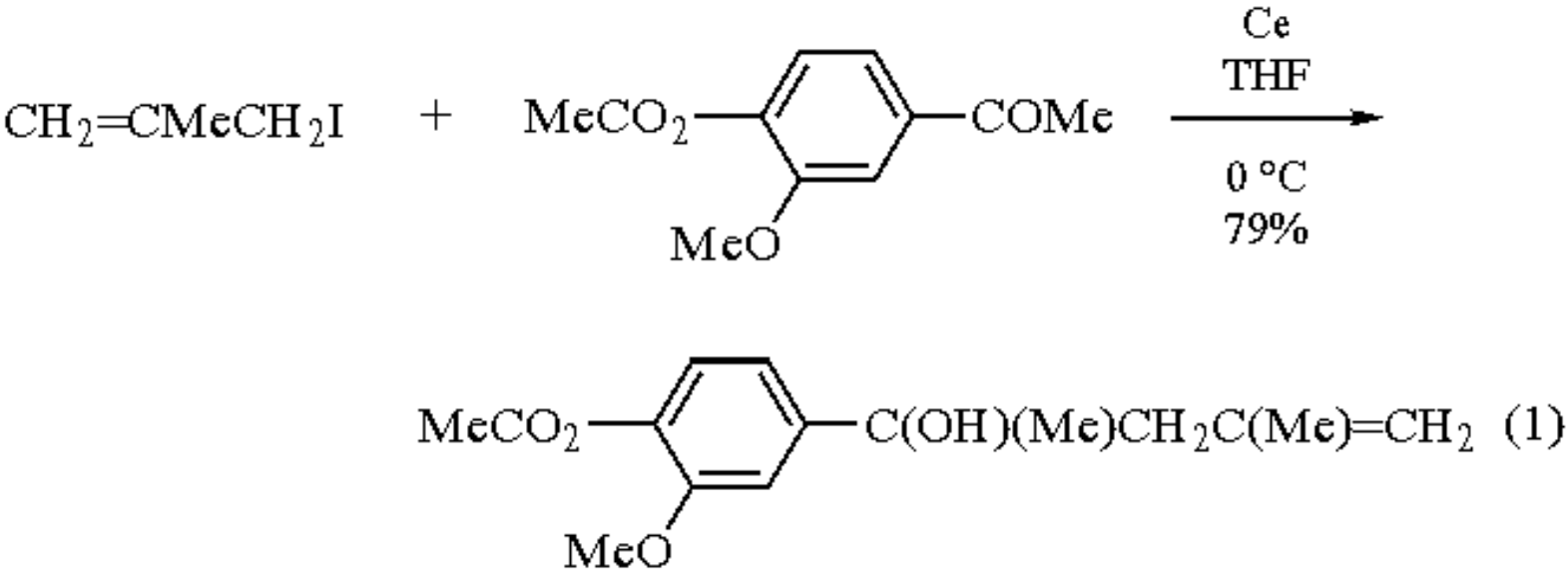

α-Halo esters undergo cerium-promoted Reformatsky reactions with carbonyl compounds. The reaction occurs even at -40 °C, and chemoselectivity is observed under these conditions (eq 2).[1] β-Halo esters also react with ketones in the presence of cerium to give γ-lactones together with pinacol coupling products (eq 3).[3]

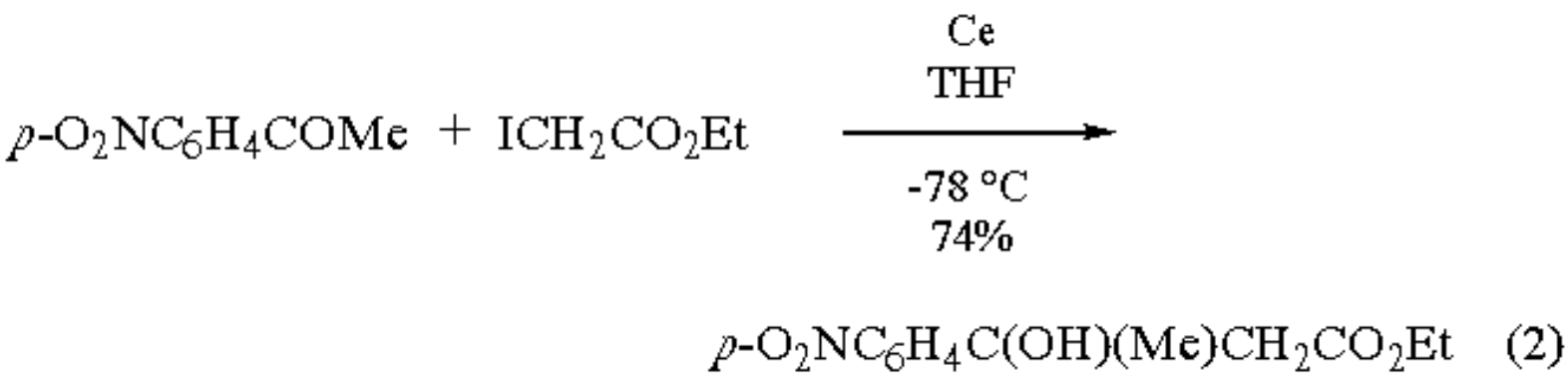

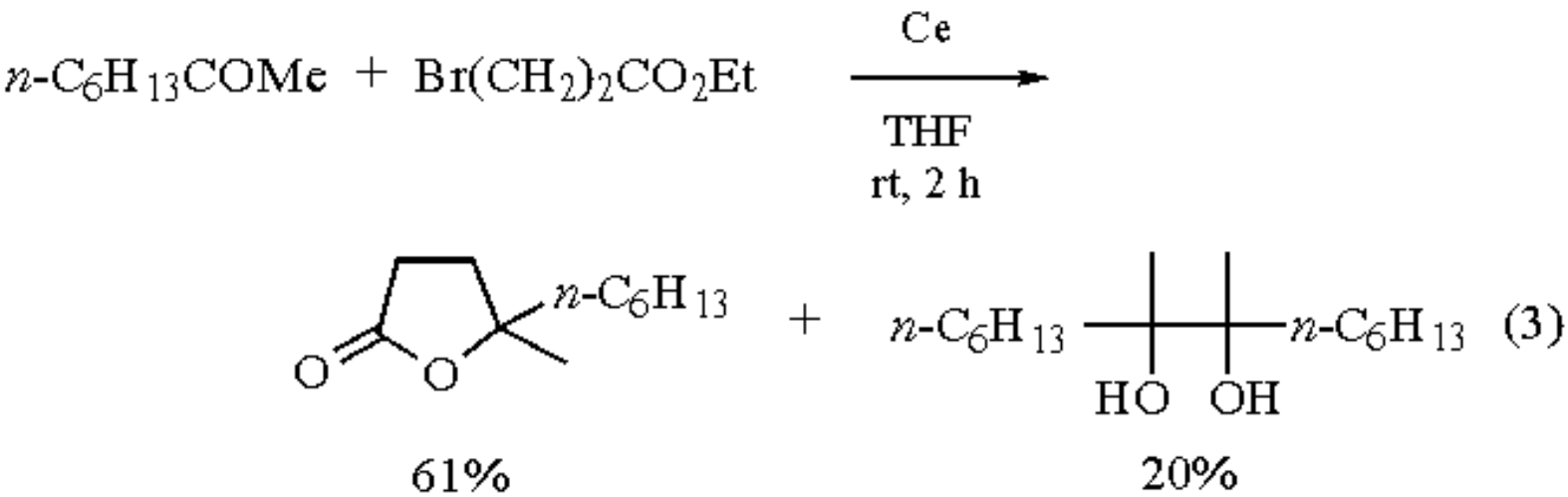

Cerium in combination with ***Iodine*** is used for reductive coupling of carbonyl compounds (eq 4).[4] Aromatic aldehydes and ketones (except benzophenone) are most easily dimerized to pinacols. On the other hand, the reactions of cyclic ketones depend on the ring size: 4-7 membered ketones undergo smooth dimerization, while cyclododecanone is subjected to reduction to give the corresponding secondary alcohol in 70% yield. Ester, nitrile, and vinyl halide moieties are not affected under these conditions, and over-reduction of the carbonyl substrate to generate alkenes is not observed with the cerium reagent. It is not clear whether this system has any advantages compared to the more widely used low-valent titanium reagents.

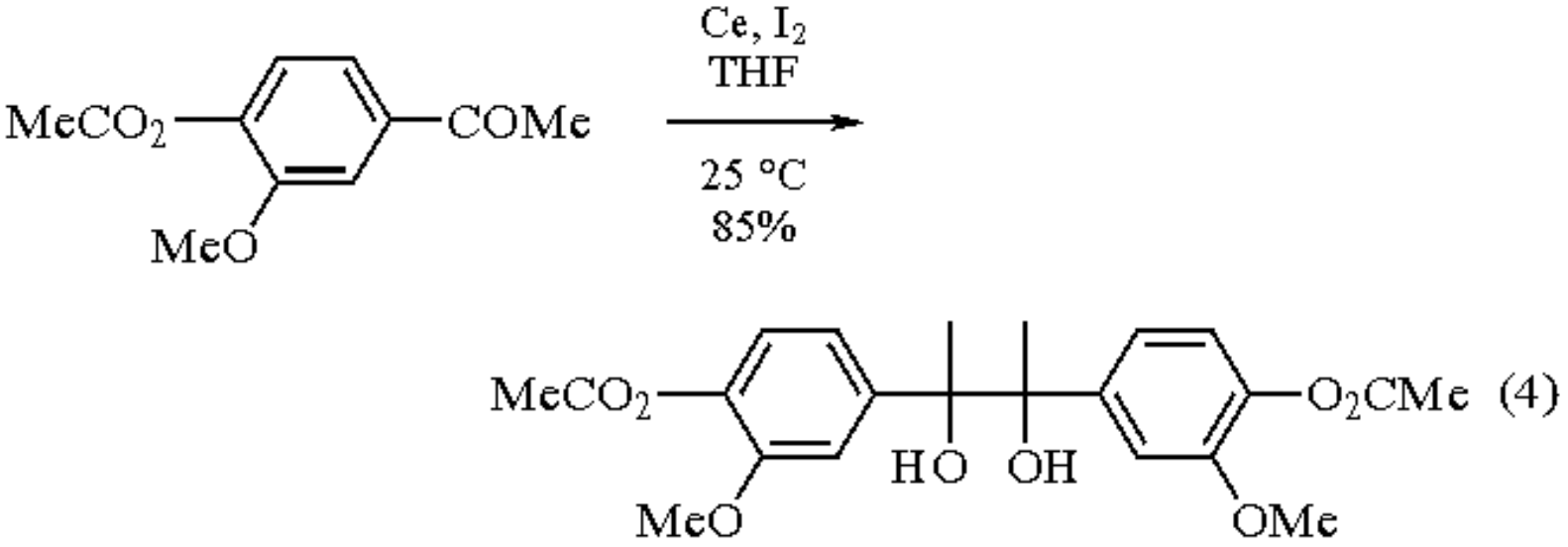

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Cerium(III) Acetate-Boron Trifluoride Etherate

$Ce(OAc)_3$-$BF_3.OEt_2$

($Ce(OAc)_3$)

[537-00-8] · $C_6H_9CeO_6$ · Cerium(III) Acetate-Boron Trifluoride Etherate · (MW 317.27) ($BF_3.OEt_2$)

[109-63-7] · $C_4H_{10}BF_3O$ · Cerium(III) Acetate-Boron Trifluoride Etherate · (MW 141.95)

(two-component Lewis acid catalyst system[1,2] for the cyclocondensation of aldehydes with siloxydienes[3])

Physical Data: complex generated in situ.

Solubility: slightly sol toluene.

Form Supplied in: generated in situ from anhydrous cerium(III) acetate and ***Boron Trifluoride Etherate***.

Preparative Methods: anhydrous $Ce(OAc)_3$ is required for the preparation of this Lewis acid system and is obtained by drying cerium(III) acetate hydrate at 100 °C under high vacuum for at least 3 h. This material is then slurried into toluene under an argon atmosphere for 30 min, cooled to -78 °C, and treated with freshly distilled $BF_3.OEt_2$ to give the title reagent.

Handling, Storage, and Precautions: this binary Lewis acid system is best used as prepared. Strictly anhydrous conditions are required. Cerium reagents are generally of low toxicity. $BF_3.OEt_2$ is extremely moisture sensitive. This reagent should be handled in a fume hood.

Cyclocondensation of Aldehydes with Siloxydienes.

Thus far, reported applications of $Ce(OAc)_3$-$BF_3.OEt_2$ have been limited to the area of Lewis acid-catalyzed cyclocondensation reactions of activated dienes with aldehydes.[1-3] In the context of efforts aimed at developing a fully synthetic route to tunicaminyl uracil, a subunit of the tunicamycins, Danishefsky and co-workers examined a number of Lewis acid promoters for the cyclocondensation of aldehyde (**1**) with the oxygenated diene (**2**).[1,4] They found that the binary Lewis acid $Ce(OAc)_3$-$BF_3.OEt_2$ (toluene, -78 °C, 2 h) afforded a 45% yield of a single diastereomeric product, dihydropyrone (**3**), along with ca. 20% of recovered aldehyde (**1**) (eq 1). The facial sense of the reaction can be rationalized by invoking chelation of the β-alkoxy aldehyde by the highly oxophilic[5] $Ce(OAc)_3$-$BF_3.OEt_2$, followed by α-face attack of the diene (**2**) on the chelated ensemble.[6] Apparently both oxygen atoms of the (benzyloxy)methoxy C-

5´ appendage play a role in the observed extraordinary diastereofacial selectivity.[2] The use of alternative Lewis acids, including those known to favor chelation control (e.g. $SnCl_4$), afforded (**3**) along with significant and varying amounts of two of the other three possible diastereomeric dihydropyrones.[1]

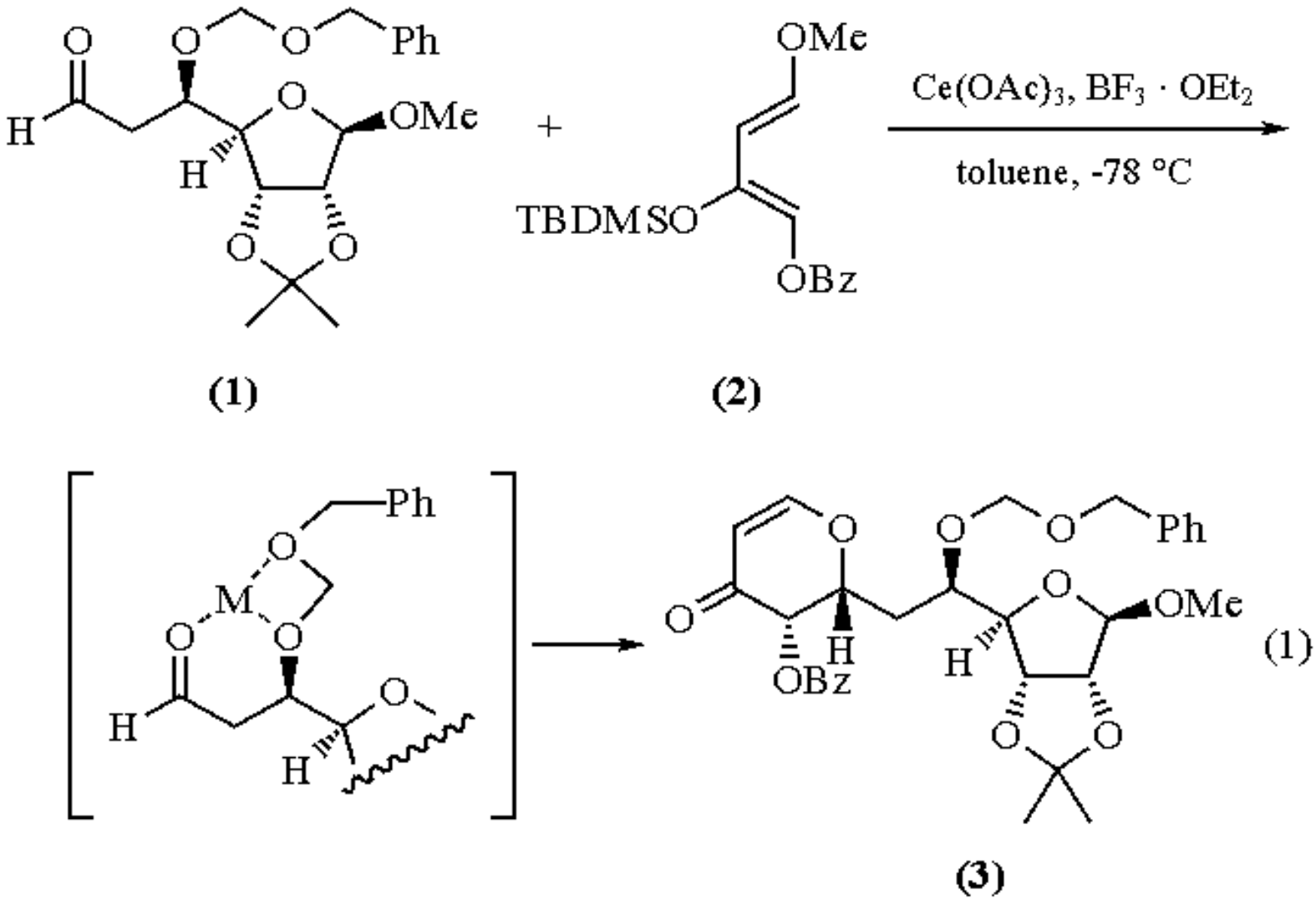

One limitation of the $Ce(OAc)_3$-$BF_3.OEt_2$ mediated cyclocondensation chemistry was found during attempts to extend the scope of the process to include aldehyde substrates incorporating a nucleoside subunit. For example, the aldehydes (**4**) failed to react with diene (**2**) to give the targeted dihydropyrones (**5**) (eq 2).[2] Evidently the two-component catalyst system is modified or destroyed by the uracil ring.

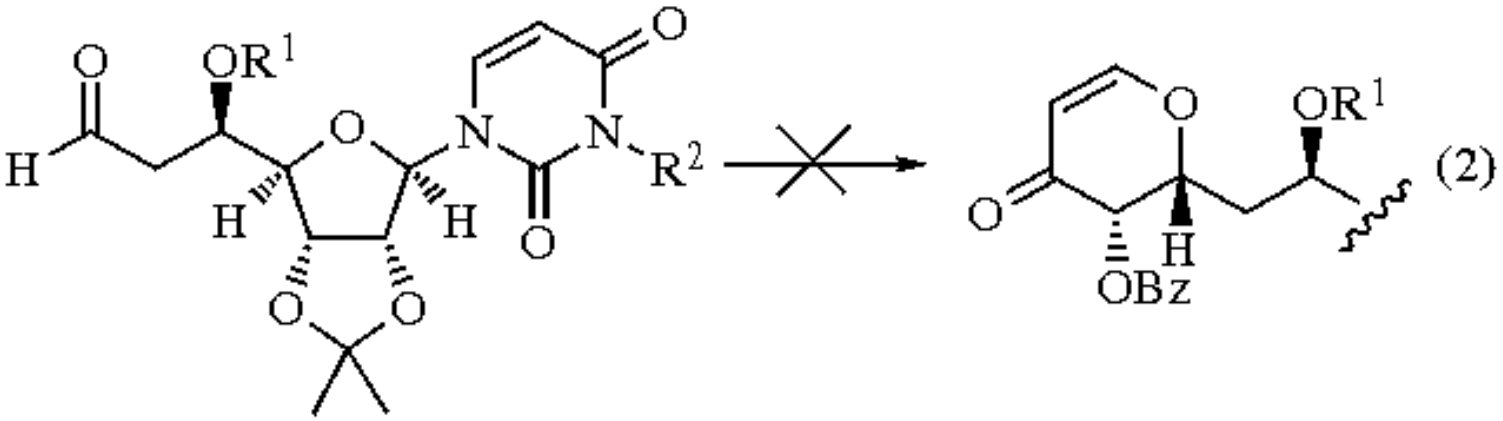

(4) **(5)**

$R^1 = Bn, MOM, BOM; R^2 = p\text{-}MeOC_6H_4CH_2$

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Cerium(IV) Ammonium Nitrate[1]

$(NH_4)_2Ce(NO_3)_6$

[16774-21-3] · $CeH_8N_8O_{18}$ · Cerium(IV) Ammonium Nitrate · (MW 548.26)

(volumetric standard oxidant;[2] oxidant for many functional groups;[1] can promote oxidative halogenation[3])

Alternate Name: ammonium cerium(IV) nitrate; ceric ammonium nitrate; CAN.

Solubility: sol water (1.41 g mL^{-1} at 25 °C, 2.27 g mL^{-1} at 80 °C); sol nitric acid.

Form Supplied in: orange crystals; widely available.

Handling, Storage, and Precautions: solid used as supplied. No toxicity data available, but cerium is reputed to be of low toxicity.

Functional Group Oxidation.

Ce^{IV} in acidic media is a stronger oxidant than elemental chlorine and is exceeded in oxidizing power only by a few reagents (F_2, XeO_3, Ag^{2+}, O_3, HN_3). The thermodynamically unstable solutions can be kept for days because of kinetic stability. CAN is a one-electron oxidant soluble in water and to a smaller extent in polar solvents such as acetic acid. Its consumption can be judged by the fading of an orange color to pale yellow, if the substrate or product is not strongly colored. Because of its extremely limited solubility in common organic solvents, oxidations are often carried out in mixed solvents such as aqueous acetonitrile. There are advantages in using dual oxidant systems in which Ce^{IV} is present in catalytic amounts. Cooxidants such as ***Sodium Bromate***,[4] ***t-Butyl Hydroperoxide***,[5] and ***Oxygen***[6] have been employed. Electrolytic recycling[7] of Ce^{IV} species is also possible.

Cerium(IV) sulfate and a few other ligand-modified CAN reagents have been used for the oxidation. The differences in their oxidation patterns are small, and consequently it is quite safe to replace one particular oxidizing system with another. More rarely employed is cerium(IV) perchlorate.

Oxidation of Alkenes and Arenes.

The outcome of the oxidation of alkenes is solvent dependent, but dinitroxylation (eq 1)[8] has been achieved. Certain arylcyclopropanes are converted into the 1,3-diol dinitrates.[9]

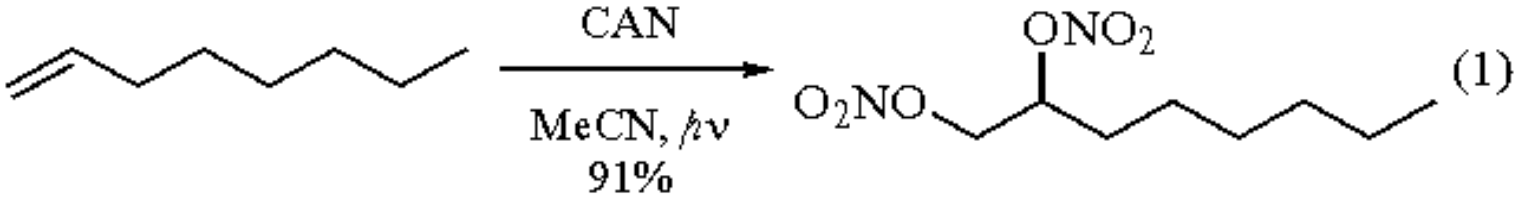

CAN promotes benzylic oxidation of arenes,[10] e.g. methyl groups are converted into formyl groups but less efficiently when an electron-withdrawing group is present in the aromatic ring. A very interesting molecule, hexaoxo[1_6]orthocyclophane in an internal acetal form (eq 2),[11] has been generated via CAN oxidation. Regioselective oxidation is observed with certain substrates, e.g. 2,4-dimethylanisole gives 3-methyl-*p*-anisaldehyde. Oxidation may be diverted into formation of non-aldehyde products by using different media: benzylic acetates[12] are formed in glacial acetic acid, ethers[13] in alcohol solvents, and nitrates[14] in acetonitrile under photolytic conditions.

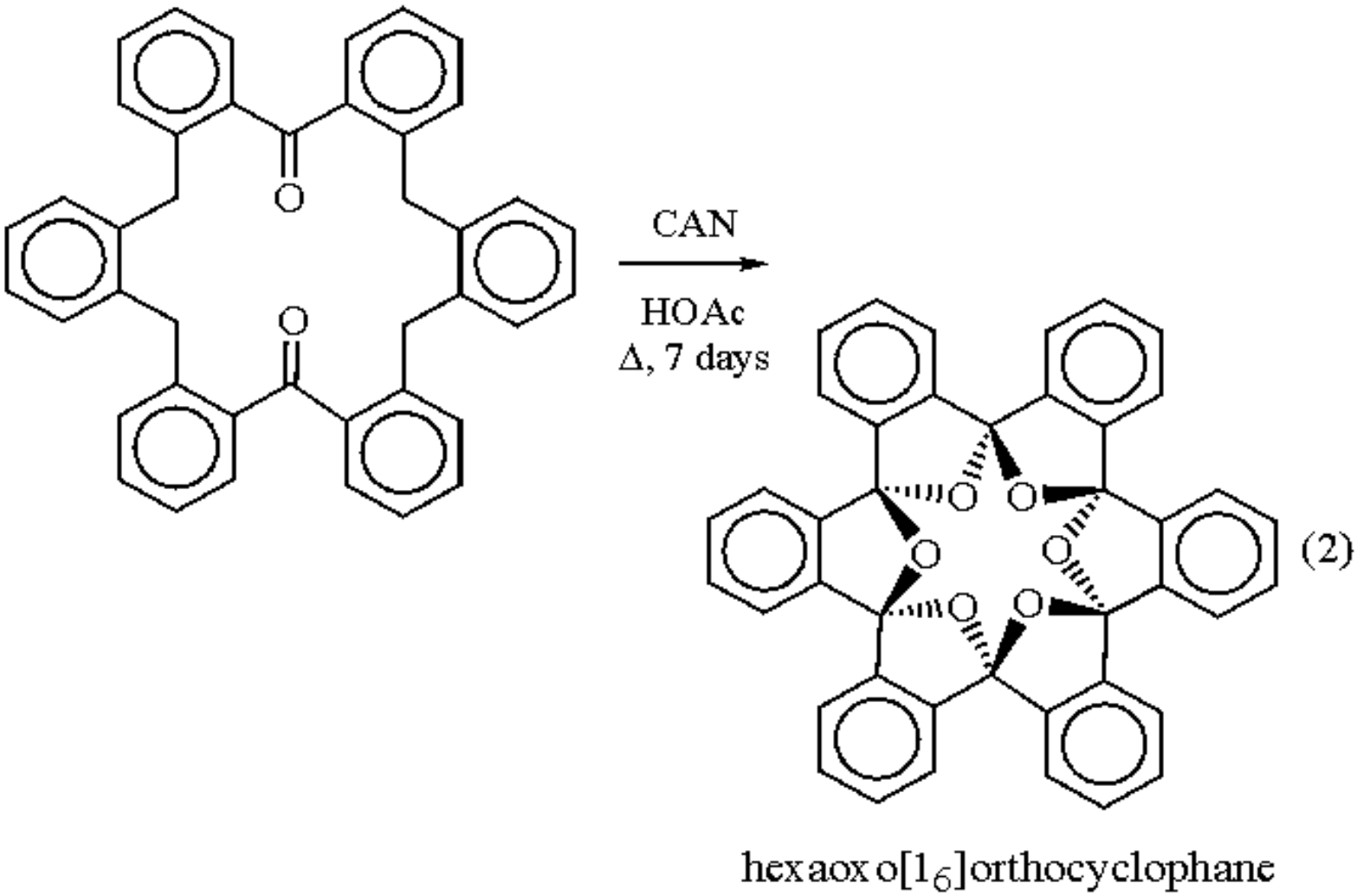

Polynuclear aromatic systems can be oxidized to quinones,[15] but unsymmetrical substrates will often give a mixture of products. It has been reported that mononitro derivatives were formed by the oxidation of polynuclear arenes with CAN adsorbed in silica,[16] whereas dinitro compounds and quinones were obtained from oxidation in solution.

Oxidation of Alcohols, Phenols, and Ethers.

A primary alcohol can be retained when a secondary alcohol is oxidized to ketone.[17] Tetrahydrofuran formation (eq 3)[18] predominates in molecules with rigid frameworks, which are favorable to δ-hydrogen abstraction by an alkoxyl radical.

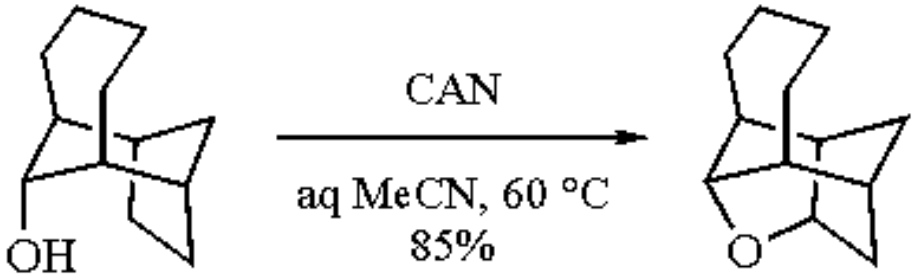

(3)

Tertiary alcohols are prone to fragmentation;[19] this process is facilitated by a β-trimethylsilyl group (eq 4)[20]. Other alcohols prone to fragmentation are cyclobutanols,[21] strained bicyclo[*x.y.z*]alkan-2-ols,[22] and homoallylic alcohols.[18d]

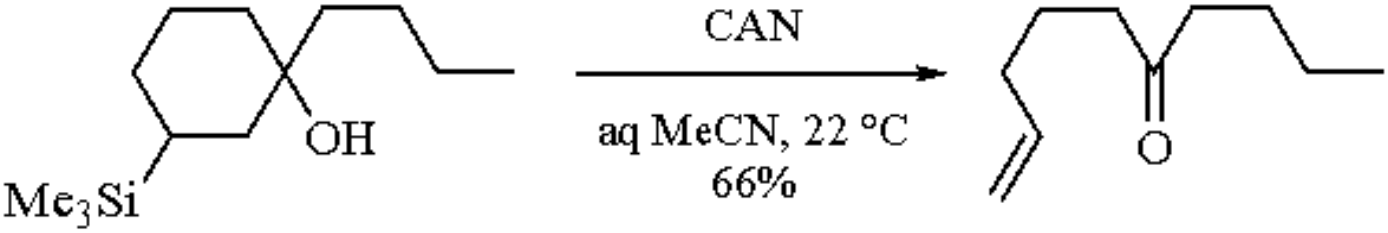

(4)

CAN converts benzylic alcohols into carbonyl compounds.[23] Even *p*-nitrobenzyl alcohol gives *p*-nitrobenzaldehyde in the catalytic oxidation system.[23c] Oxygen can be used[6] as the stoichiometric oxidant.

Catechols, hydroquinones, and their methyl ethers readily afford quinones on Ce^{IV} oxidation.[4,24] Partial demethylative oxidation is feasible, as shown in the preparation of several intramolecular quinhydrones (eq 5)[25] and a precursor of daunomycinone.[26] Sometimes the dual oxidant system of CAN-$NaBrO_3$ is useful. In a synthesis of methoxatin (eq 6)[27] the *o*-quinone moiety was generated from an aryl methyl ether.

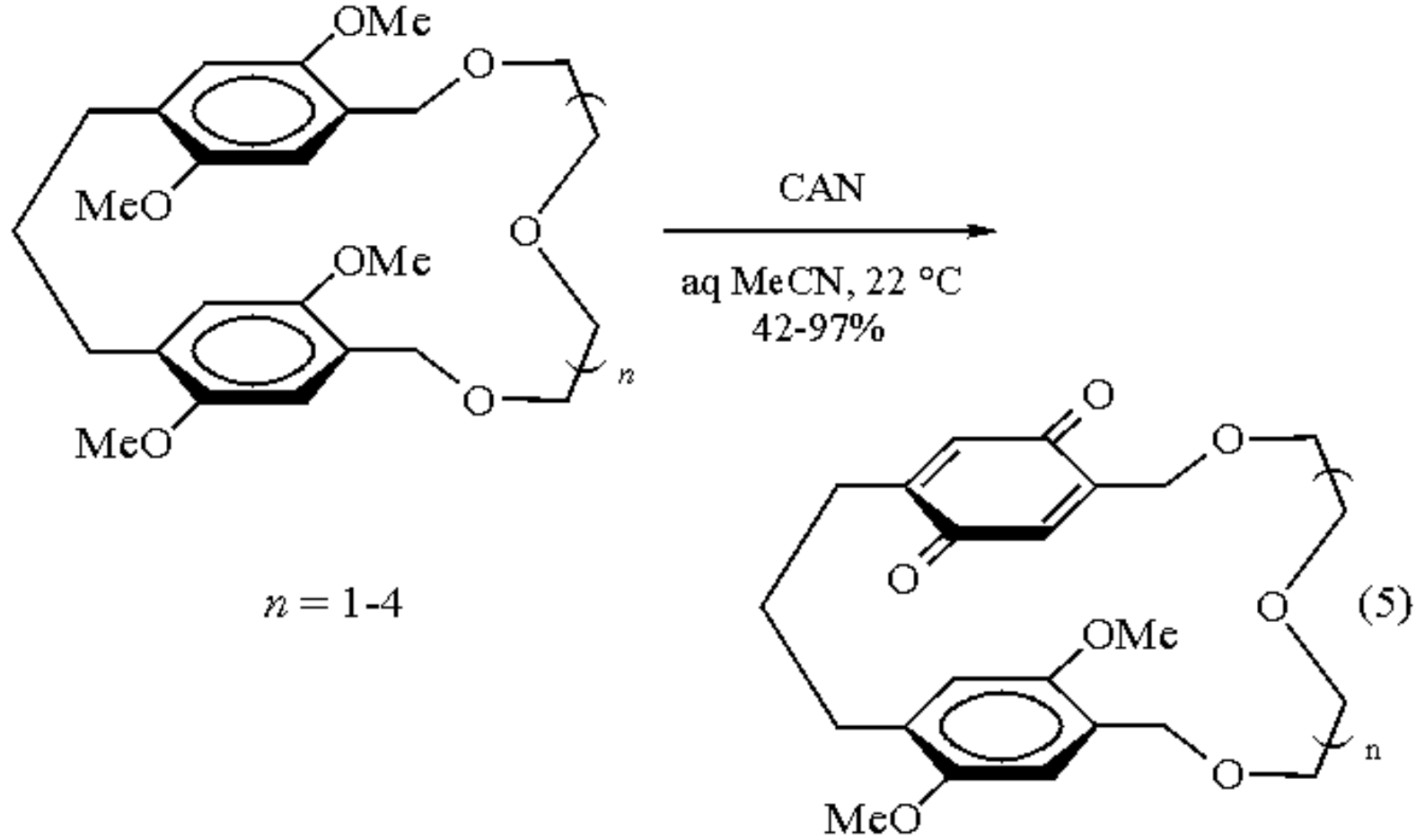

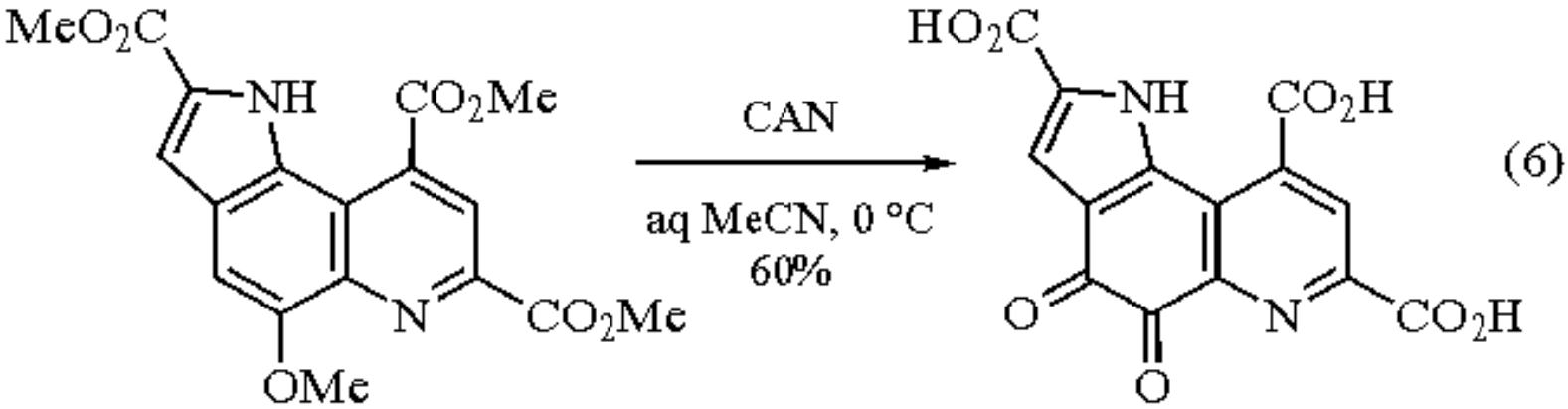

Oxidative regeneration of the carboxylic acid from its 2,6-di-*t*-butyl-4-methoxyphenyl ester[28] is the basis for the use of this auxiliary in a stereoselective α-hydroxyalkylation of carboxylic acids. The smooth removal of *p*-anisyl (eq 7)[29] and *p*-anisylmethyl[30] groups from an amidic nitrogen atom by Ce^{IV} oxidation makes these protective groups valuable in synthesis.

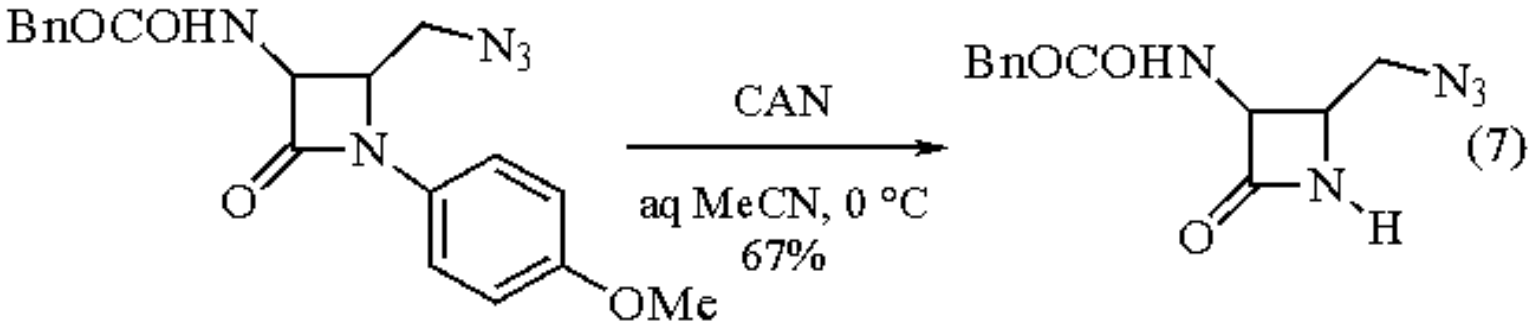

Simple ethers are oxidized[31] to carbonyl products and the intermediate from tetrahydrofuran oxidation can be trapped by alcohols.[32]

Vicinal diols undergo oxidative cleavage.[33] There is no apparent steric limitation as both *cis*- and *trans*-cycloalkane-1,2-diols are susceptible to cleavage. However, under certain conditions α-hydroxy ketones may be oxidized without breaking the C-C bond.[6]

Oxidation of Carbonyl Compounds.

The Ce^{IV} oxidation of aldehydes and ketones is of much less synthetic significance than methods using other reagents. However, cage ketones often provide lactones (eq 8)[34,35] in good yield. Tetracyclones furnish α-pyrones.[36]

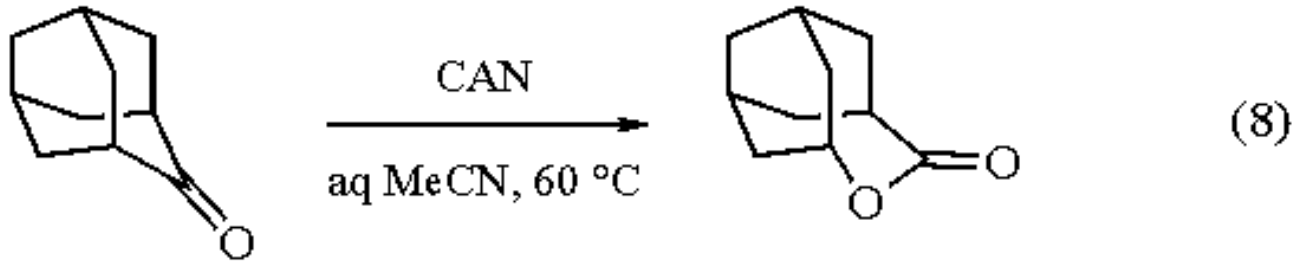

Concerning carboxylic acids and their derivatives, transformations of practical value are restricted to oxidative hydrolysis such as the conversion of hydrazides[37] back to carboxylic acids, transamidation of *N*-acyl-5,6-dihydrophenanthridines,[38] and decarboxylative processes, especially the degradation of α-hydroxymalonic acids (eq 9).[39] In some cases the Ce^{IV} oxidation is much superior to periodate cleavage. A related reaction is involved in a route to lactones.[40]

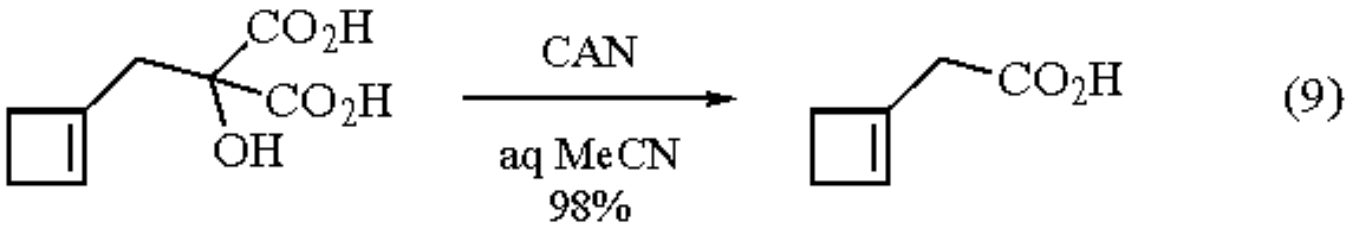

Nitrogenous derivatives of carbonyl compounds such as oximes and semicarbazones are oxidatively cleaved by Ce^{IV},[41] but only a few synthetic applications have been reported.[42]

Oxidation of Nitroalkanes.

Ce^{IV} oxidation provides an alternative to the Nef reaction.[43] At least in the case of a ketomacrolide synthesis (eq 10),[44] complications arising from side reactions caused by other reagents are avoided.

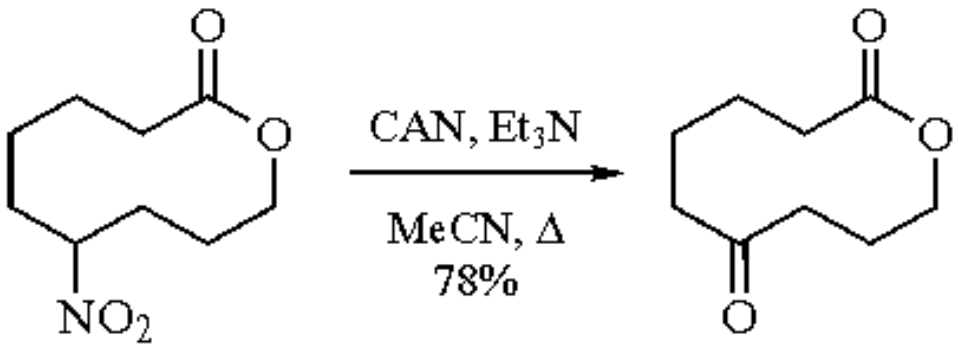

(10)

Oxidation of Organosulfur Compounds.

Thiols are converted into disulfides using reagents such as ***Bis[trinitratocerium(IV)] Chromate***.[45] Chemoselective oxidation of sulfides by Ce^{IV} reagents to sulfoxides[4,46] is easily accomplished. Stoichiometric oxidation under phase transfer conditions[46b] and the dual oxidant[4] protocols permit oxidation of a variety of sulfides.

The reaction of dithioacetals including 1,3-dithiolanes and 1,3-dithianes with CAN provides a convenient procedure for the generation of the corresponding carbonyl group.[47] The rapid reaction is serviceable in many systems and superior to other methods, e.g. in the synthesis of acylsilanes.[48] In a series of compounds in which the dithiolane group is sterically hindered, the reaction led to enones, i.e. dehydrogenation accompanied the deprotection (eq 11).[49]

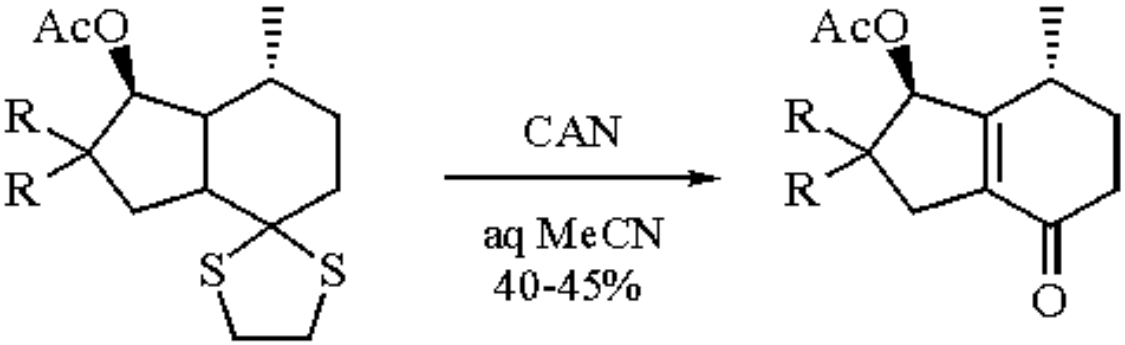

(11)

R = H, Me

Oxidative Cleavage of Organometallic Compounds.

Oxidative deligation of both σ- and π-complexes by treatment with CAN is common practice. Ligands including cyclobutadiene and derivatives (eq 12)[50] and α-methylene-γ-butyrolactone (eq 13)[51] have been liberated successfully and applied to achieving the intended research goals. In the recovery of organic products from a Dötz reaction, CAN is often employed to cleave off the metallic species.[52]

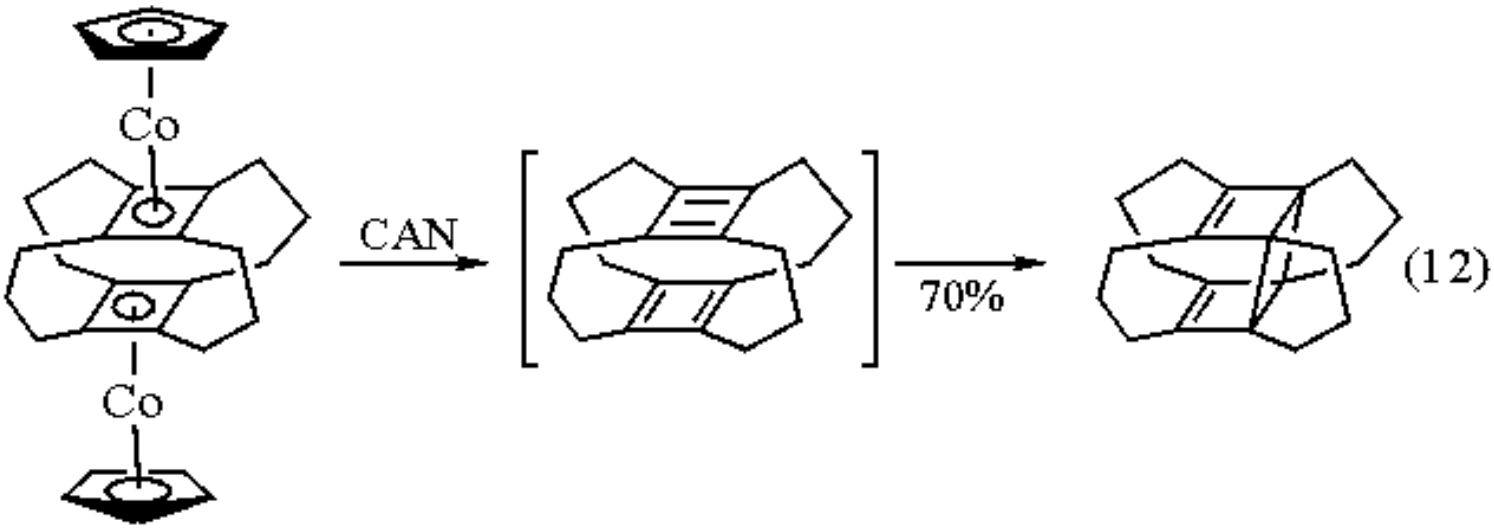

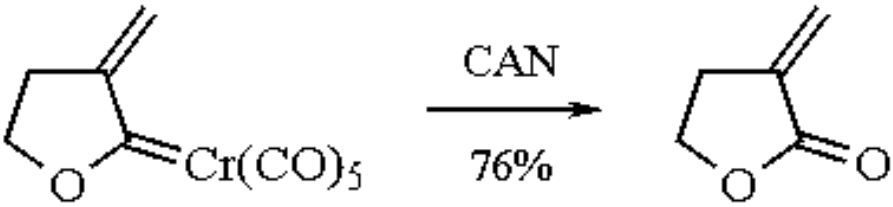

Generation of α-Acyl Radicals.

As a one-electron oxidant, Ce^{IV} can promote the formation of radicals from carbonyl compounds. In the presence of interceptors such as butadiene and alkenyl acetates, the α-acyl radicals undergo addition.[53] The carbonyl compounds may be introduced as enol silyl ethers, and the oxidative coupling of two such ethers may be accomplished.[54] Some differences in the efficiency for oxidative cyclization of δ,ε-, and ε,ζ-unsaturated enol silyl ethers using CAN and other oxidants have been noted (eq 14).[55]

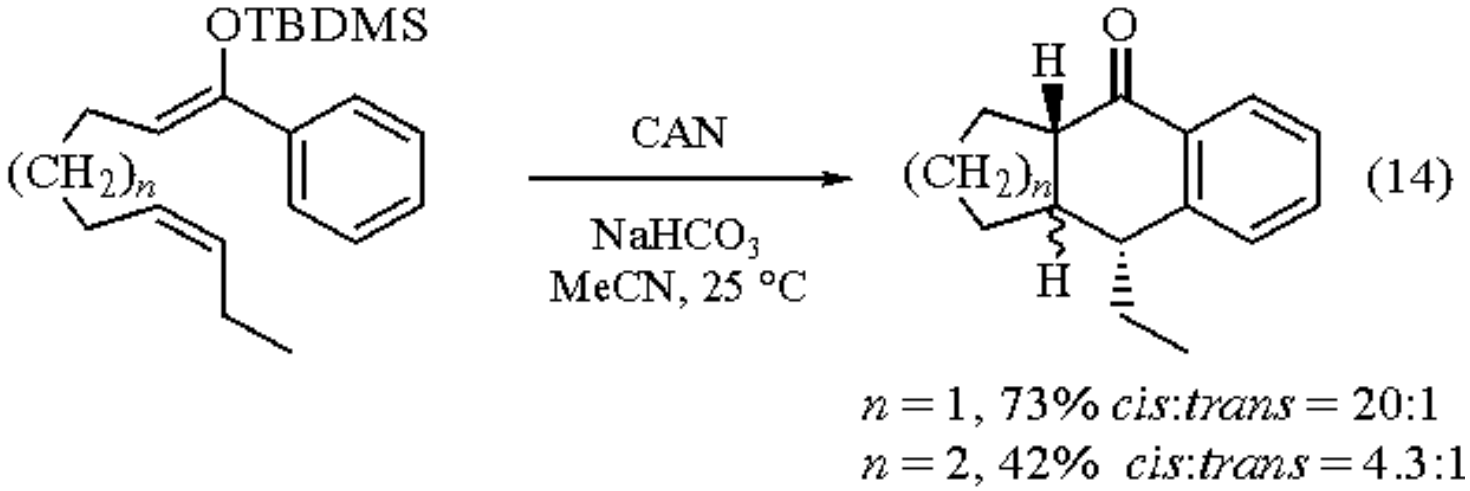

Oxidative Halogenation.

Benzylic bromination[56] and α-iodination of ketones[3a] and uracil derivatives[3b] can be achieved with CAN as in situ oxidant.

Related Reagents.

Cerium(IV) Ammonium Nitrate-Sodium Bromate; ***Iodine-Cerium(IV) Ammonium Nitrate***.

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Cerium(IV) Ammonium Nitrate-Sodium Bromate

$(NH_4)_2Ce(NO_3)_6$-$NaBrO_3$

($(NH_4)_2Ce(NO_3)_6$)

[16774-21-3] · $CeH_8N_8O_{18}$ · Cerium(IV) Ammonium Nitrate-Sodium Bromate · (MW 548.26) ($NaBrO_3$)

[7789-38-0] · $BrNaO_3$ · Cerium(IV) Ammonium Nitrate-Sodium Bromate · (MW 150.91)

(capable of selective oxidation of secondary alcohols, oxidative cleavage of alkyl and silyl ethers)
Cerium(IV) ammonium nitrate.

Solubility: very sol water.

Form Supplied in: small, orange-red, monoclinic crystals. Sodium bromate.

Physical Data: mp 381 °C (dec); *d* 3.34 g cm^{-3}.

Solubility: sol water (27.5 g/100 g at 0 °C; 90.9 g/100 g at 100 °C).

Form Supplied in: white granules or cryst. powder.

Handling, Storage, and Precautions: ingestion may cause vomiting, diarrhea, methemoglobinemia, renal injury. These reagents should be handled in a fume hood.

Oxidation of Alcohols.

Sodium Bromate oxidizes benzylic alcohols to the corresponding aldehydes or ketones under ***Cerium(IV) Ammonium Nitrate*** (CAN) catalysis (eq 1).[1] The reagent has been utilized for the oxidation of secondary alcohols to ketones. Primary/secondary diols can be oxidized selectively to afford hydroxy ketones in the presence of CAN or $Ce(SO_4)_2$ (eq 2).[2] Oxidation of a primary/primary 1,4-diol gives a γ-lactone (eq 3).[2] CAN catalyzes the oxidative cleavage of alkyl and silyl ethers to carbonyl compounds with $NaBrO_3$ (eq 4).[3]

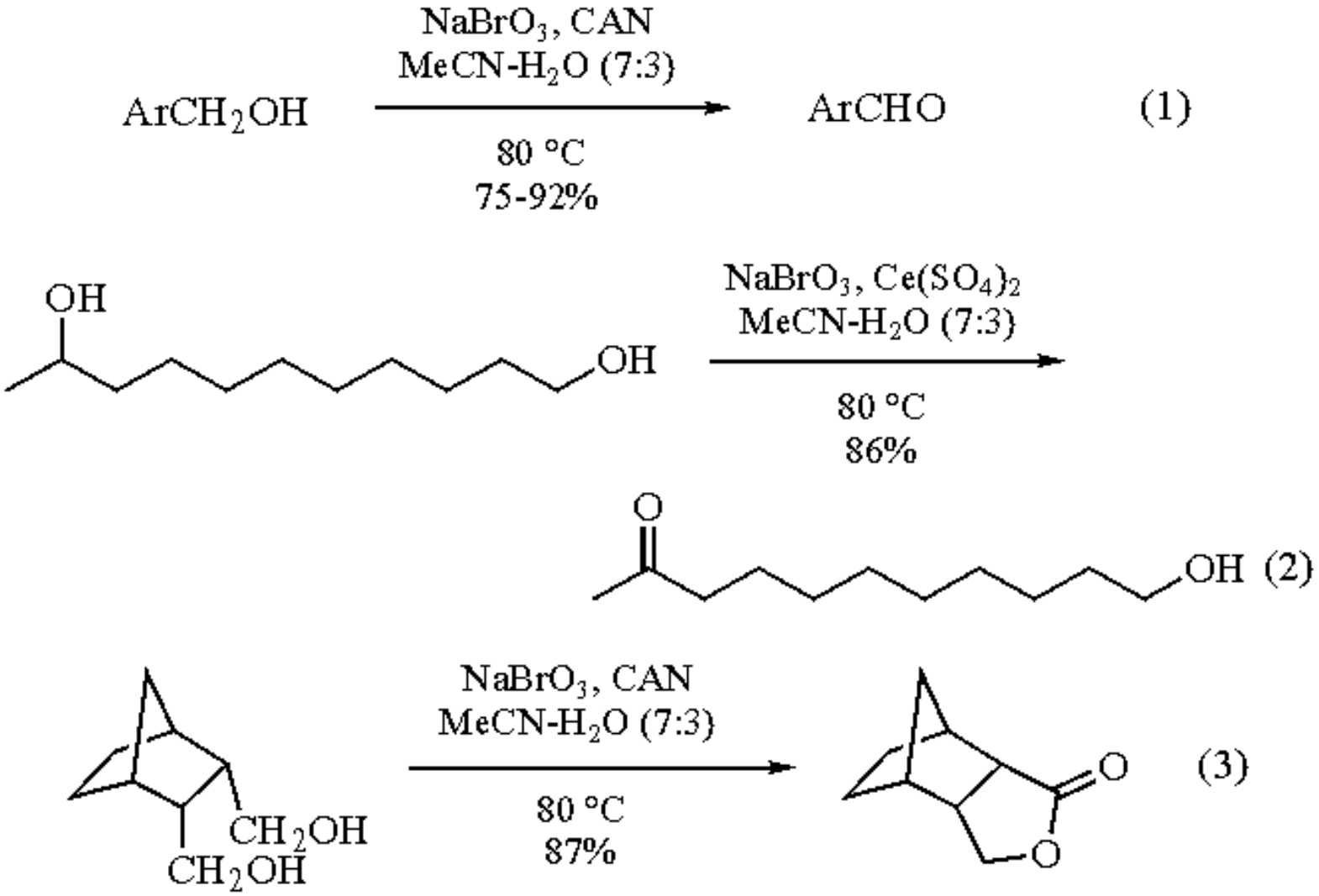

R^1 = alkyl, aryl; R^2 = H, alkyl, aryl;
R^3 = Me, Et, Me_3Si, *t*-$BuMe_2Si$

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Koichiro Oshima

Cerium(IV) Ammonium Sulfate[1]

$Ce(NH_4)_4(SO_4)_4.2H_2O$

[7637-03-8] · $CeH_{16}N_4O_{16}S_4$ · Cerium(IV) Ammonium Sulfate · (MW 596.52) (.$2H_2O$)

[10378-47-9] · $H_{20}CeN_4O_{18}S_4$ · Cerium(IV) Ammonium Sulfate · (MW 632.55)

(convenient reagent for oxidation of aromatic rings,[2] and halophenols to quinones,[6] for regioselective Baeyer-Villiger oxidation,[11] and oxidative aromatization[12])

Alternate Name: ceric ammonium sulfate; CAS.

Physical Data: mp 140 °C (dec).

Solubility: sol water, dil. H_2SO_4, dil. H_2SO_4-MeCN.

Form Supplied in: orange solid, widely available.

Handling, Storage, and Precautions: cerium(IV) ammonium sulfate is a stable reagent and precautions required for handling strong oxidizing agents such as ***Potassium Permanganate*** will be sufficient. Cerium is reputed to be of low toxicity.

Cerium(IV) ion is a potent one-electron oxidant.[1] ***Cerium(IV) Ammonium Nitrate*** (CAN), is the most widely utilized cerium(IV) oxidizing agent, but cerium(IV) ammonium sulfate (CAS) is a good substitute when complications due to the involvement of nitrate ligands occur, resulting in side products such as nitrate esters.[1]

Synthesis of Quinones by Oxidation of Aromatic Rings.

The most important application of CAS is in the oxidation of aromatic rings. CAN oxidizes polycyclic aromatic hydrocarbons only in moderate yields (20-60%),[1] and these reactions are often complicated by the formation of nitrate esters.[2] In contrast, CAS generally oxidizes aromatic hydrocarbons to quinones in good yields. For example, naphthalene is oxidized to 1,4-naphthoquinone in excellent yield by CAS in a dilute mixture of H_2SO_4 and MeCN (eq 1).[3]

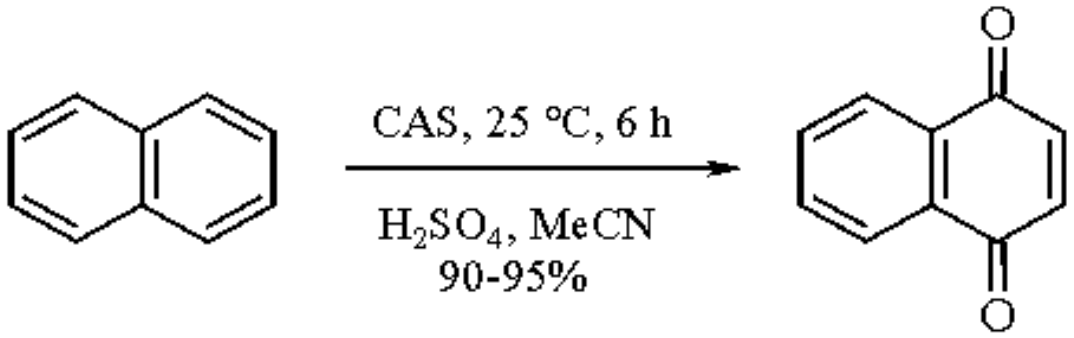

(1)

Other polycyclic aromatic hydrocarbons such as phenanthrene, anthracene, and fluoranthene are converted to the corresponding quinones on oxidation with CAS. Whereas 1-methylnaphthalene gives 1-naphthaldehyde under the conditions,[3] 1-phenyl- and 1-bromonaphthalene react to form some 2-substituted naphthoquinones through an interesting rearrangement (eq 2).[4]

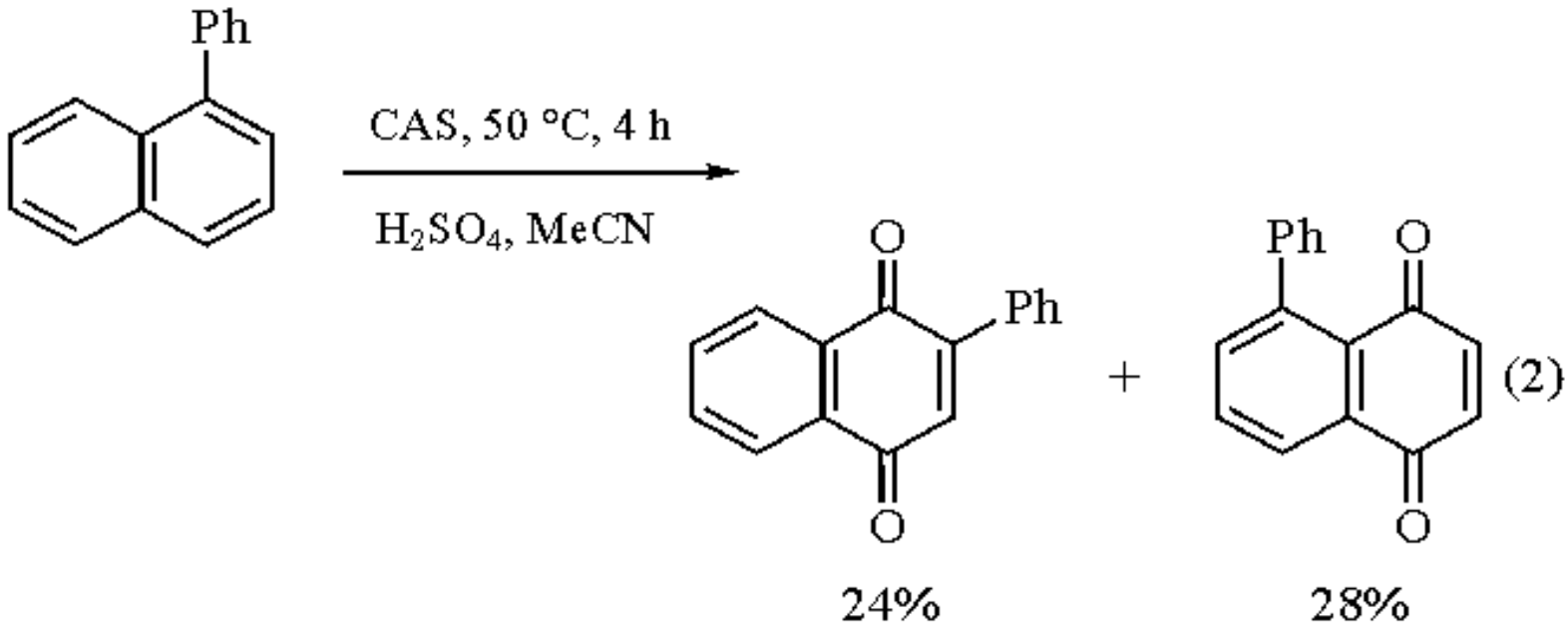

(2)

Oxidation of 1,4-diphenylnaphthalene gives 2,3-diphenyl-1,4-naphthoquinone or 4-hydroxy-2,4-diphenyl-1(4*H*)-naphthalenone, depending upon the reaction conditions (eq 3).[5]

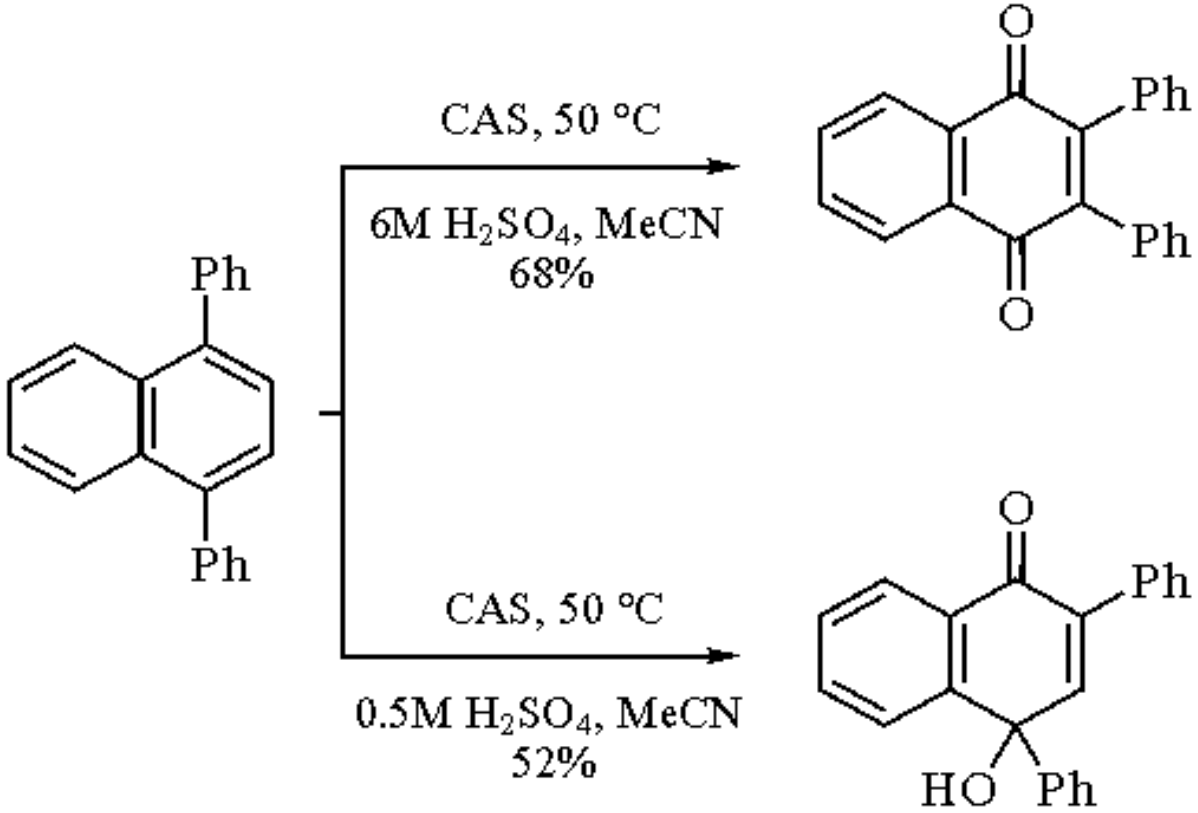

(3)

A process utilizing catalytic amounts of Ce^{IV} and Ag^{II} has also been reported (eq 4).[6]

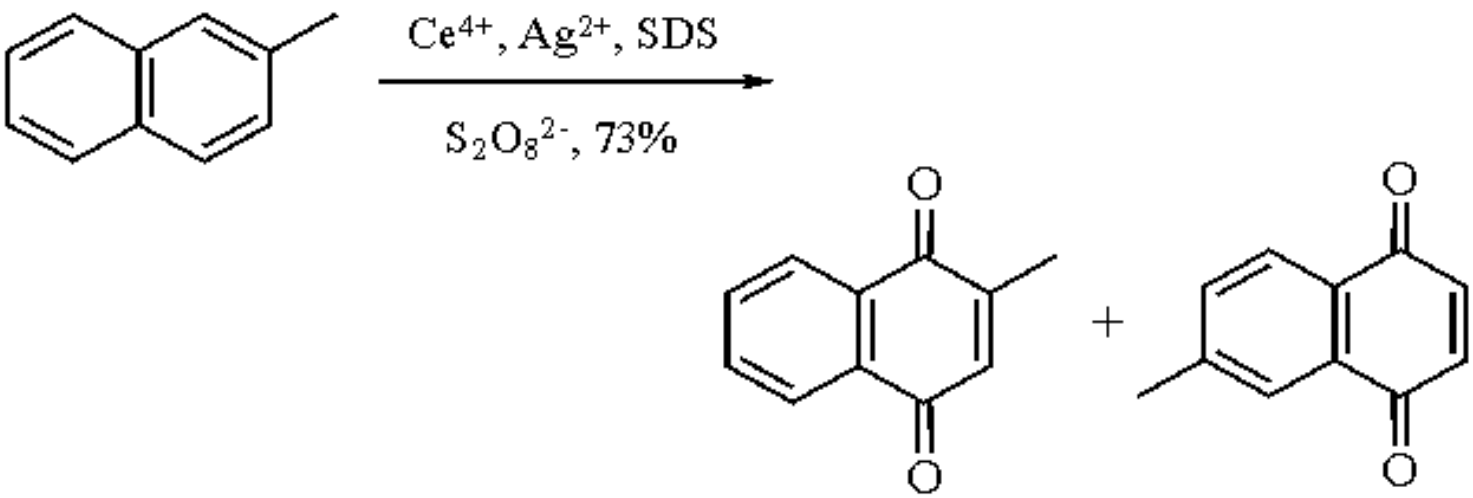

(4)

Unfortunately, this reagent system is not suitable for the oxidation of substrates of higher ionization potential nor for oxygen-substituted compounds.

The major product isolated from the reaction of CAS with benzo[*b*]fluoranthene is a lactone (eq 5).[7]

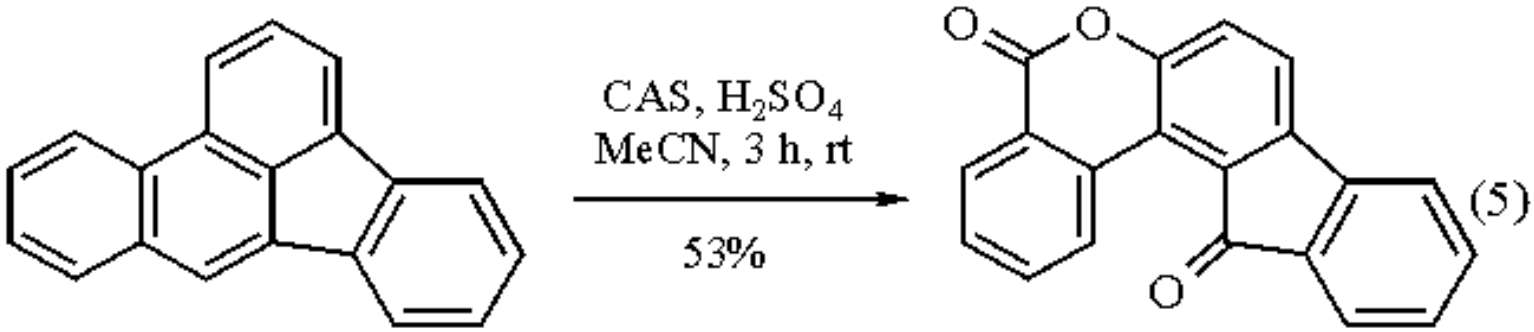

Oxidation of Phenols to Quinones.

Halophenols are conveniently oxidized by CAS to haloquinones in good yields (eq 6).[8] On oxidation with CAS, halonaphthols furnish 1,2-diones as minor products in addition to 1,4-quinones.

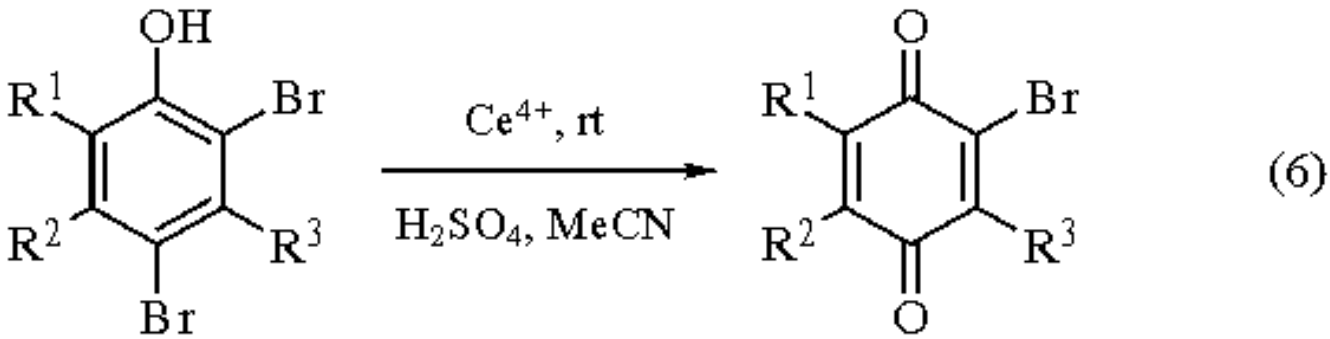

A direct and convenient route for the conversion of gentisic acid to the corresponding quinone has been developed through the use of CAS in $CHCl_3$ (10% within 15 min) (eq 7).[9]

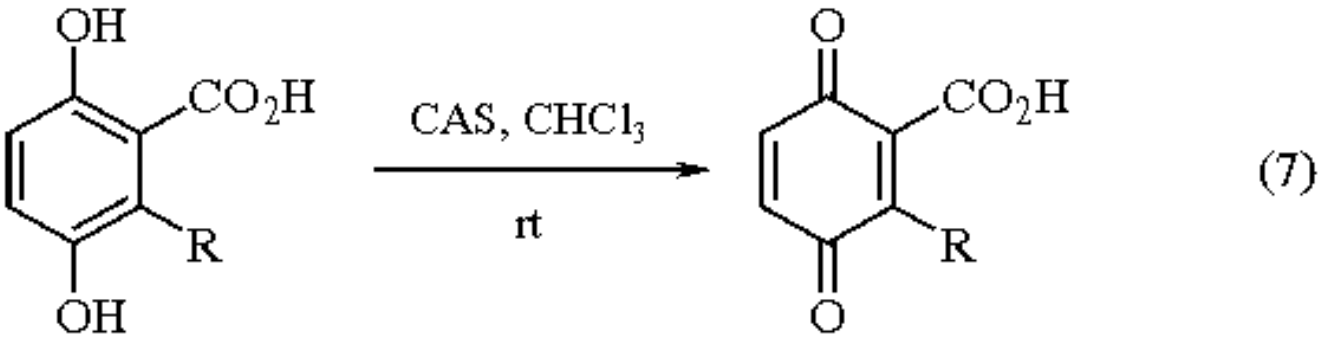

Baeyer-Villiger Oxidation.

Oxidation of 1,3-bishomocubanone with a slurry of CAS gives rise to the corresponding lactone (eq 8),[10] which is obtained only as a minor product in the peroxy acid Baeyer-Villiger oxidation conditions.

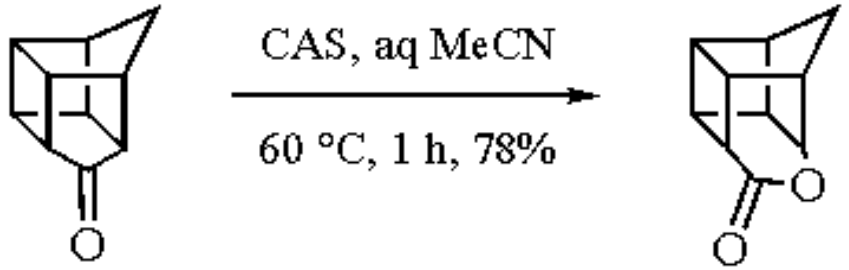

(8)

Oxidative Halogenation.

The reaction of RPh (R = H, Cl, Br, I, Me) with ***Potassium Iodide*** in CF_3CO_2H containing CAS gives a mixture of 2- and 4-RC_6H_4I. Oxidation of methyl 4-methylbenzoate with CAS under the reaction conditions gives exclusively methyl 3-iodo-4-methylbenzoate.[11]

Oxidative Aromatization.

A new type of oxidative aromatization of cyclohexenone with the CAS-***Iodine*** system has been developed (eq 9).[12]

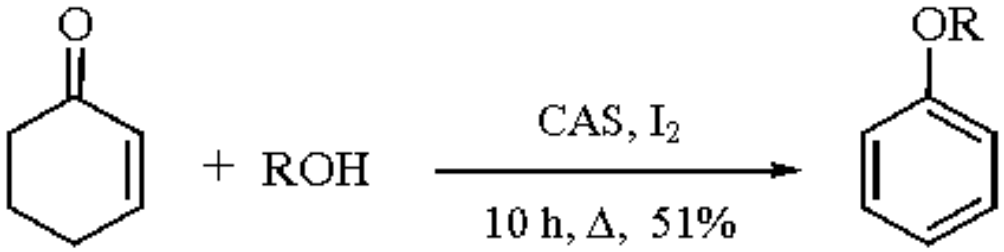

(9)

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Cerium(III) Chloride[1]

$CeCl_3.7H_2O$

[7790-86-5] · $CeCl_3$ · Cerium(III) Chloride · (MW 246.47) (.$7H_2O$)

[18618-55-8] · $H_{14}CeCl_3O_7$ · Cerium(III) Chloride · (MW 372.59)

(mild Lewis acid capable of selective acetalization;[2] organocerium reagents have increased oxo-[3] and azaphilicity[4] and greatly reduced basicity;[5] in combination with $NaBH_4$ is a selective 1,2-reducing agent[6])

Alternate Name: cerous chloride; cerium trichloride.

Physical Data: mp 848 °C; bp 1727 °C; *d* 3.92 g cm^{-3}.

Solubility: insol cold H_2O; sol alcohol and acetone; slightly sol THF.

Form Supplied in: white solid; widely available. *Drying:* for some applications the cerium trichloride must be strictly anhydrous. The following procedure has proven most efficacious: a one-necked base-washed flask containing the heptahydrate and a magnetic stirring bar was evacuated to 0.1 Torr and heated *slowly* to 140 °C over a 2 h period. At 70 and 100 °C, considerable amounts of water are given off, and these critical temperature zones should not be passed through too quickly. The magnetically stirred white solid is heated overnight at 140 °C, cooled, blanketed with nitrogen, treated with dry THF (10 mL g^{-1}), and agitated at rt for 3 h. To guarantee the complete removal of water, *t*-butyllithium is added dropwise until an orange color persists.

Handling, Storage, and Precautions: anhydrous $CeCl_3$ should be used as prepared for best results. Cerium is reputed to be of low toxicity.

Organocerium Reagents.

Organocerates, most conveniently prepared by the reaction of lithium compounds with anhydrous $CeCl_3$ in THF, are highly oxophilic and significantly less basic than their RLi and RMgBr counterparts. As a consequence, 1,2-addition reactions involving readily enolizable ketones are not adversely affected by competing enolization.[3] Well-studied examples of this phenomenon abound.[7] Although alkyl and vinyl cerates have most often been used,[3,5,7] Cl_2CeCH_2CN,[8] Cl_2CeCH_2COOR,[9] Cl_2CeC&tbond;$CSiMe_3$,[10] and $Cl_2CeCH_2SiMe_3$[11] are known to be equally effective. The last reagent has been utilized for the methylenation of highly enolizable ketones (eq 1)[11a] and for the

conversion of carboxylic acid halides, esters, and lactones into allylsilanes (eq 2).[11b-d] Amides and nitriles also condense with organocerates with equal suppression of enolization.[3,4] In general, high levels of steric hindrance in either reaction partner can be tolerated (eq 3). In select examples, the level of double stereodifferentiation can be impressively high.[5,7,12]

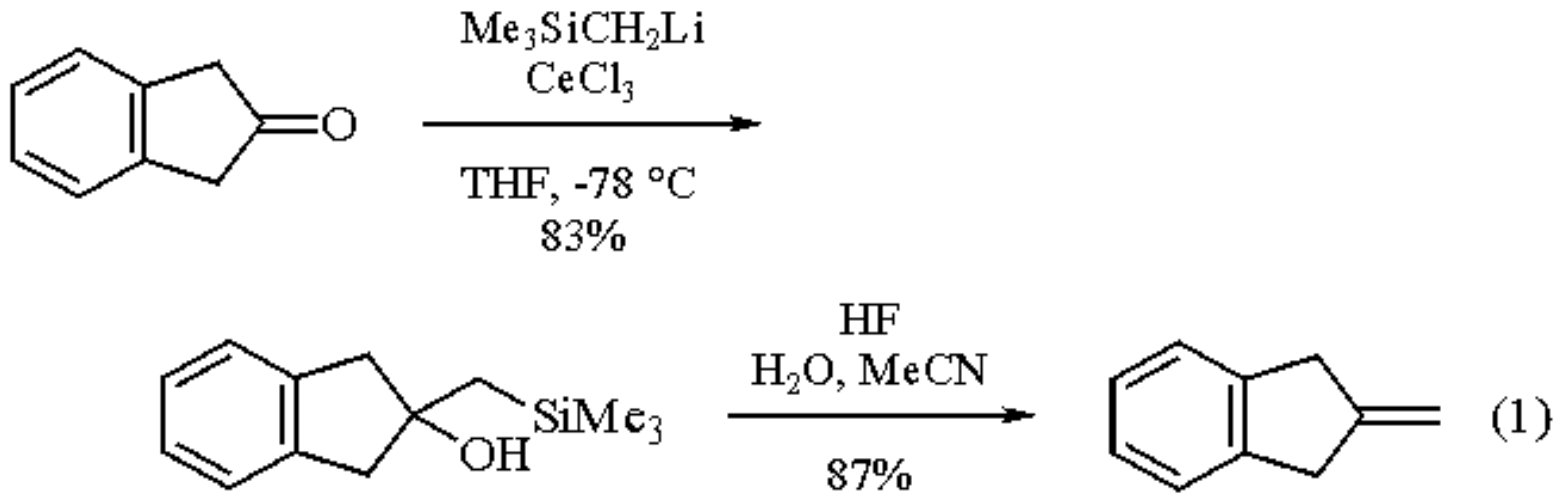

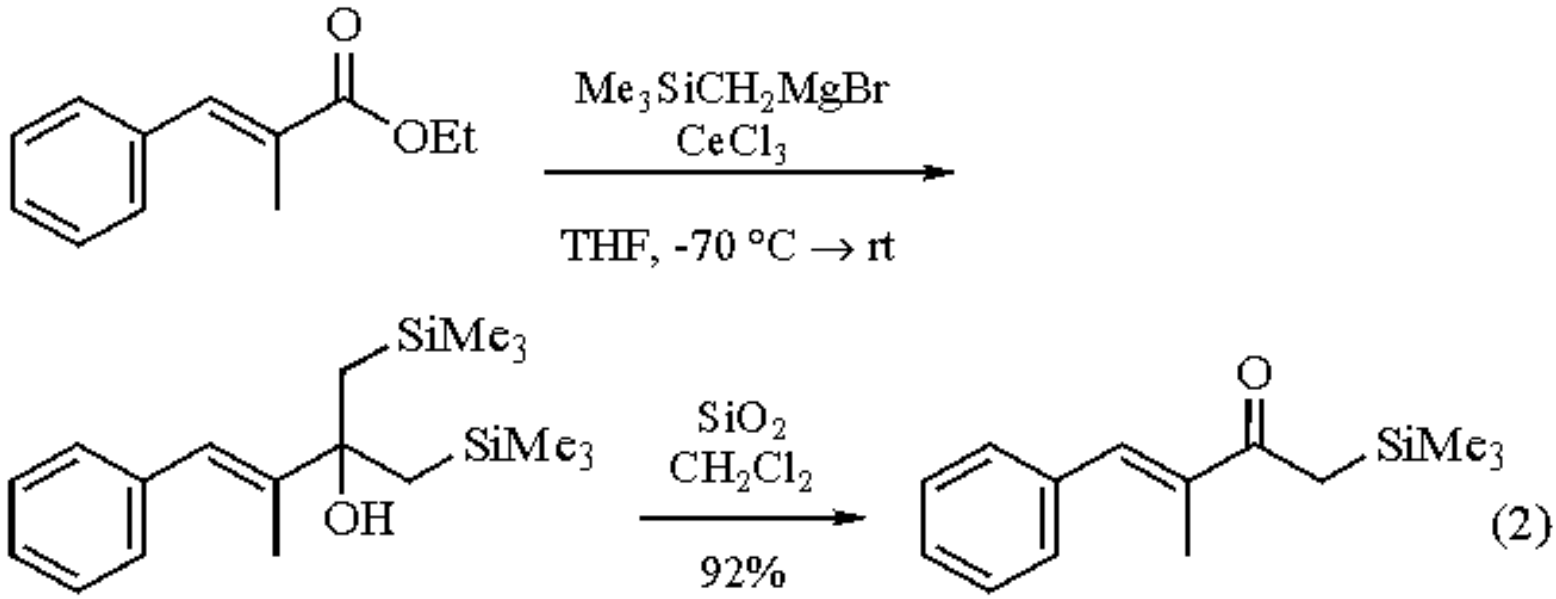

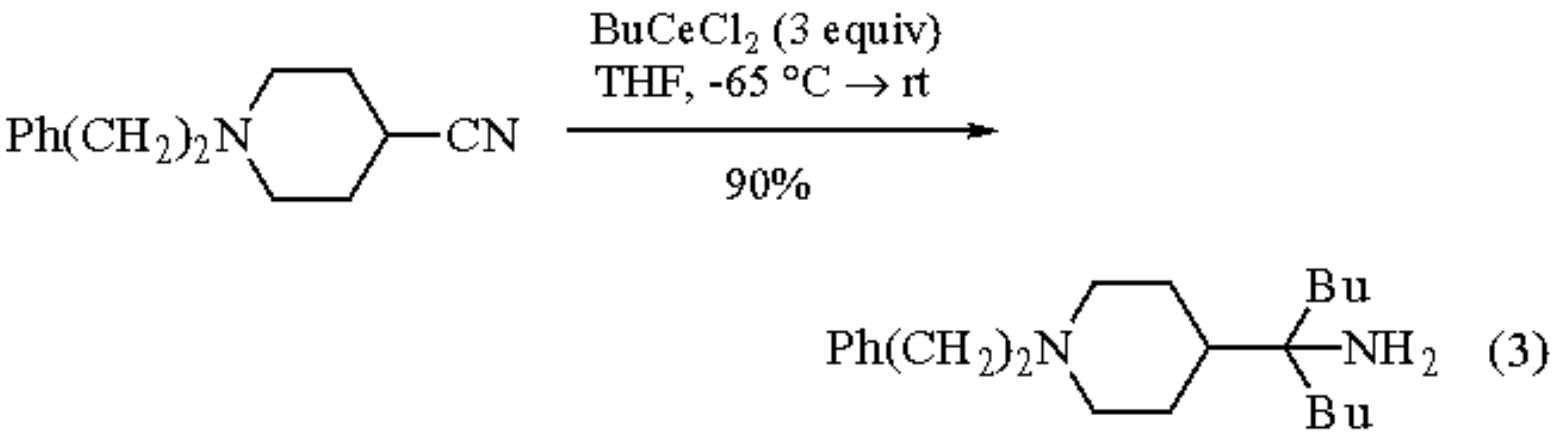

The discovery has been made that allyl anions produced by the reductive metalation of allyl phenyl sulfides condense cleanly with α,β-unsaturated aldehydes in 1,2-fashion at the more substituted allyl terminus in the presence of ***Titanium Tetraisopropoxide***.[13] Use of the allylcerium reagent instead reverses the regioselectivity. Further, the stereochemical preference is *cis* at -78 °C (kinetic control) and *trans* when warmed to -40 °C (eq 4).[14] Grignard addition reactions to vinylogous esters are improved if promoted by $CeCl_3$ (eq 5).[15]

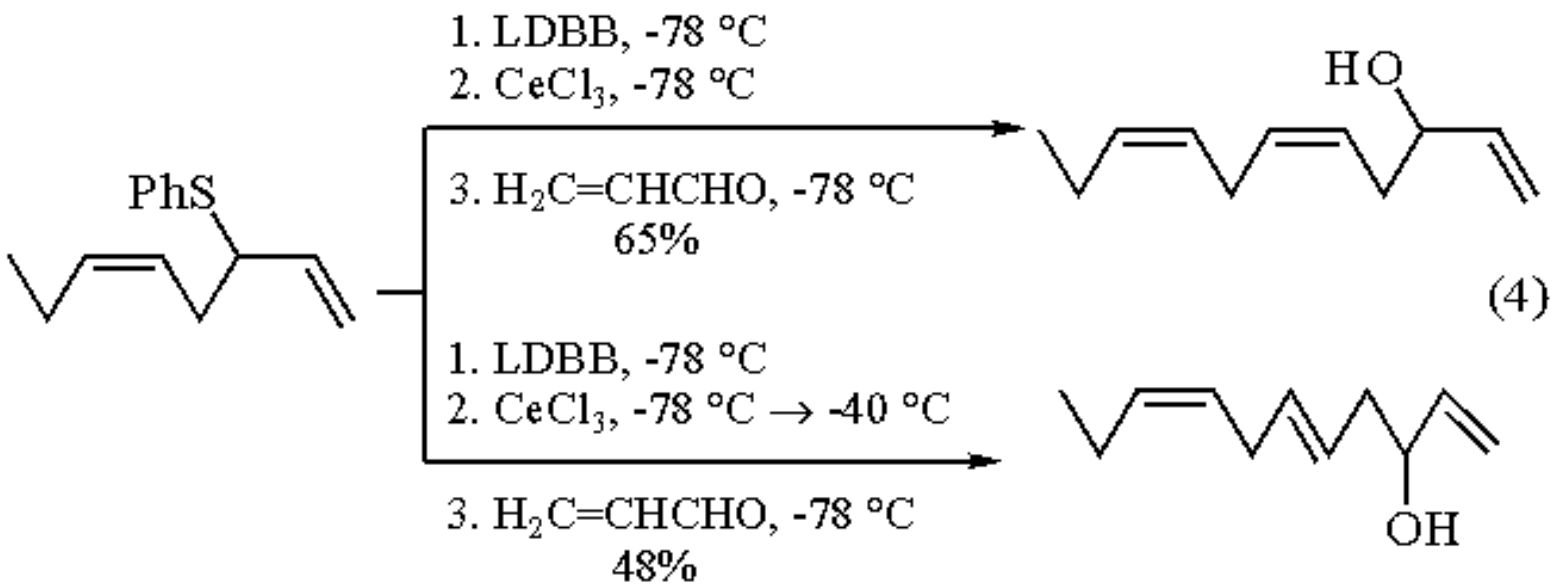

(4)

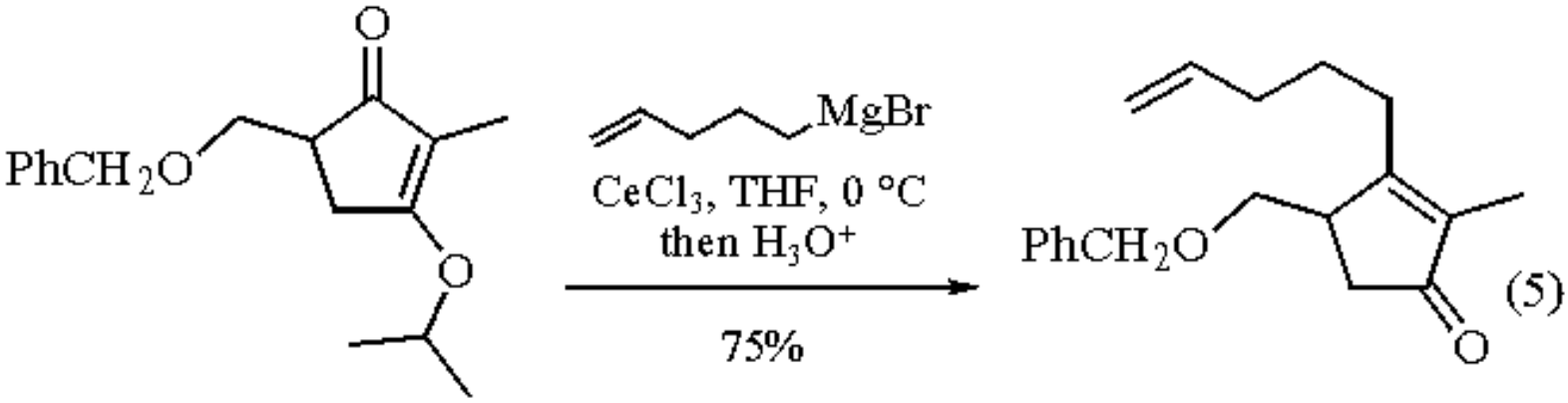

(5)

Stereodivergent pathways relative to other organometallics have surfaced in the addition of organocerium(III) reagents to chiral α-keto amides (eq 6)[16] and 2-acyloxazolidines (eq 7).[17] Applications of this type hold considerable synthetic potential not only in additions to carbonyl compounds,[18] but also to oxime ethers,[19] oxiranes,[20] and oxazolidines.[21]

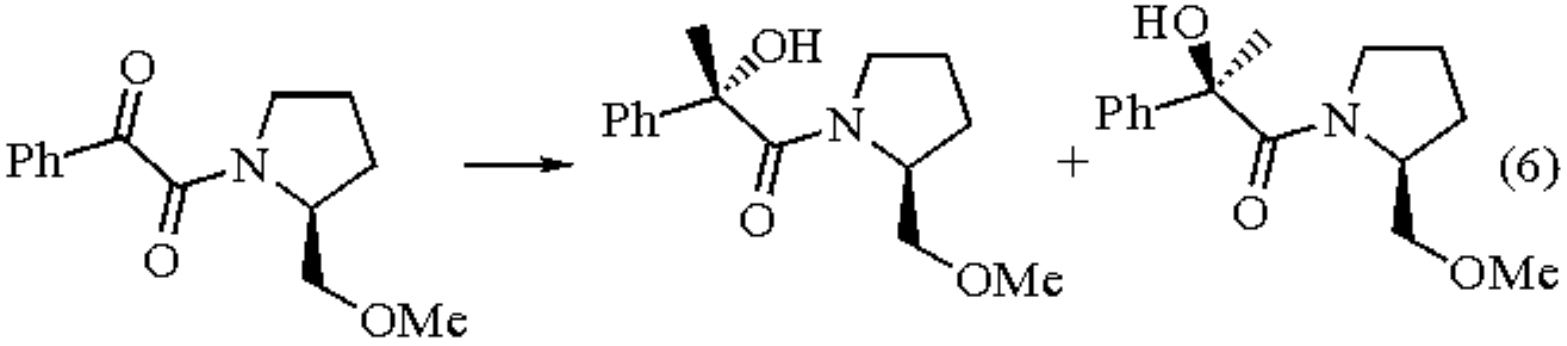

MeMgBr, Et_2O, -78 °C	76:24
MeMgBr, $CeCl_3$, THF, -78 °C	25:75

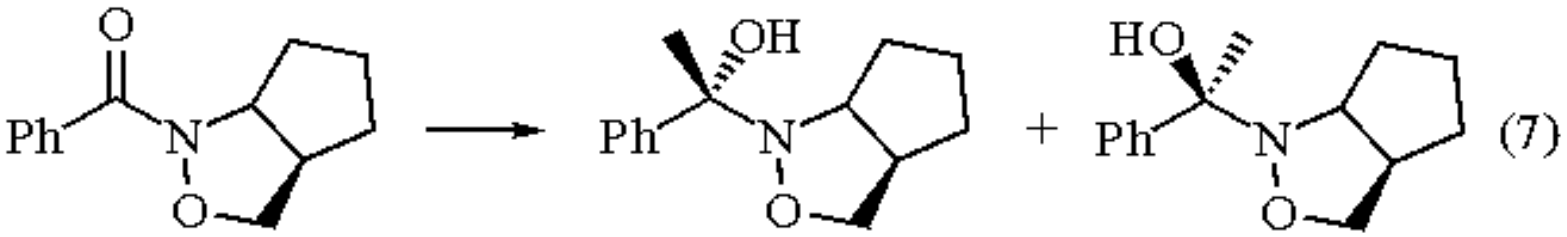

MeMgBr, Et_2O, -90 °C → -78 °C	94: 6
MeLi, $CeCl_3$, THF, -85 °C	16:84

The uniquely high reactivity of cerium reagents toward the often poorly electrophilic azomethine or C=N double bond of hydrazones has been extensively investigated. Smooth 1,2-addition occurs in good yield (67-81%) provided the air-sensitive hydrazones are acylated; when a chiral auxiliary is present, excellent diastereofacial control operates and enantiomerically enriched α-branched amines result (eq 8).[22] There appears to be a fundamental difference between warmed reagents (-78 °C -> 0 °C -> -78 °C) and those generated and used at -78 °C. Sonication appears to facilitate conversion to the organocerate.[23] For SAMP hydrazones and related compounds the condensation is accommodating of a wide range of substitution both in the hydrazone and in the nucleophile. Subsequent reductive cleavage of the N-N bond with preservation of configuration can be performed by hydrogenolysis over W-2 ***Raney Nickel*** at 60 °C (free hydrazones; less preferred because of competing saturation of aromatic substituents if present) or by treatment with ***Lithium*** in liquid ammonia (acylated hydrazines).[22c]

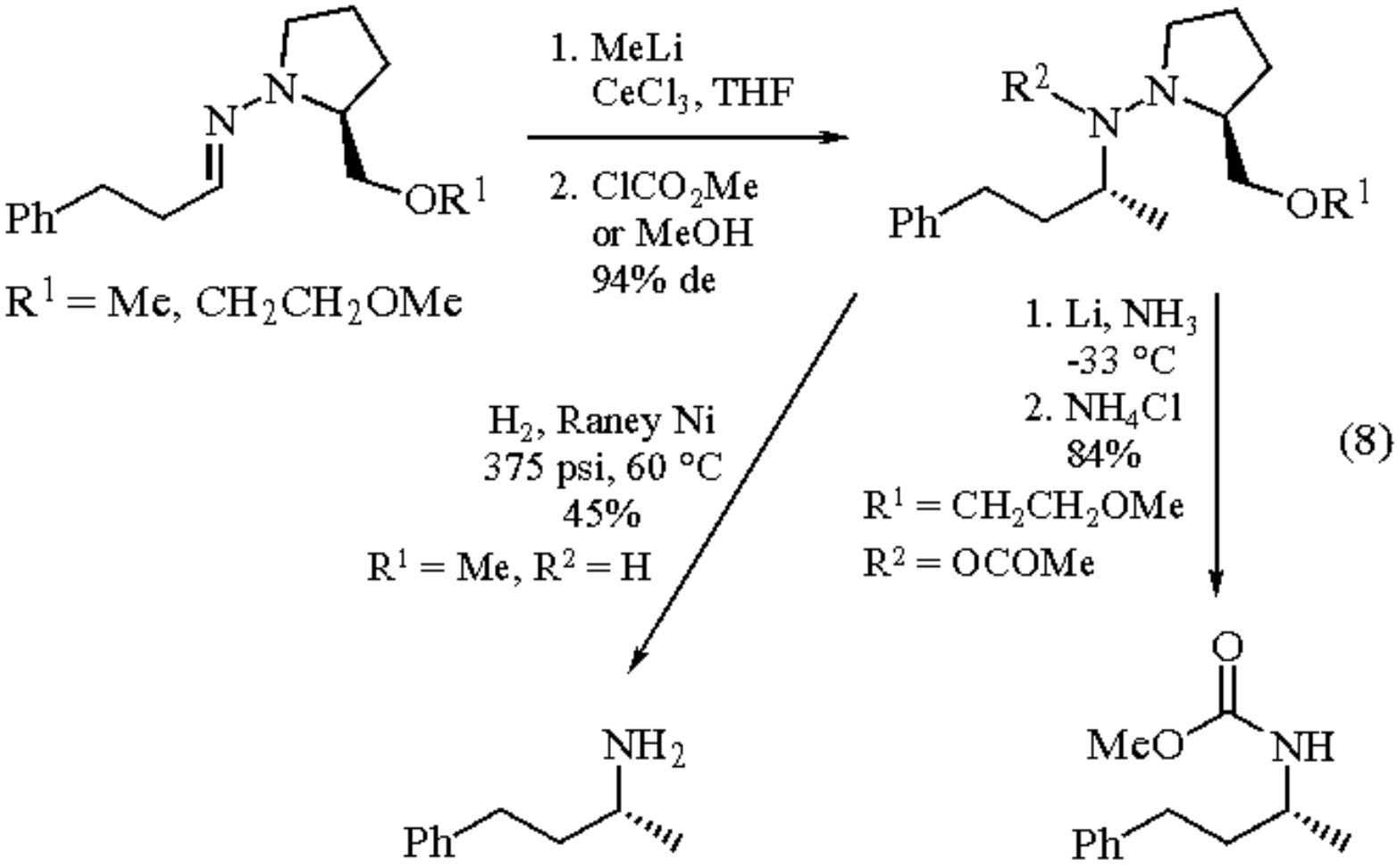

The preparation of (±)-1,3-diphenyl-1,3-propanediamine illustrates an alternative way in which this chemistry can be utilized (eq 9).[24] In all of the 1,2-addition reactions, the preferred reagent stoichiometry appears to be RLi:$CeCl_3$:hydrazone = 2:2:1. A detailed study of the consequences of varying the relative proportions of these constituents has indicated the optimal ratios of RLi:$CeCl_3$ to be 1:1, notwithstanding the fact that not all of the $CeCl_3$ is consumed in the transmetalation step.[25] The proposal has been made that the empirical formula of the cerate best approximates $R_3CeCl_3Li_3$.

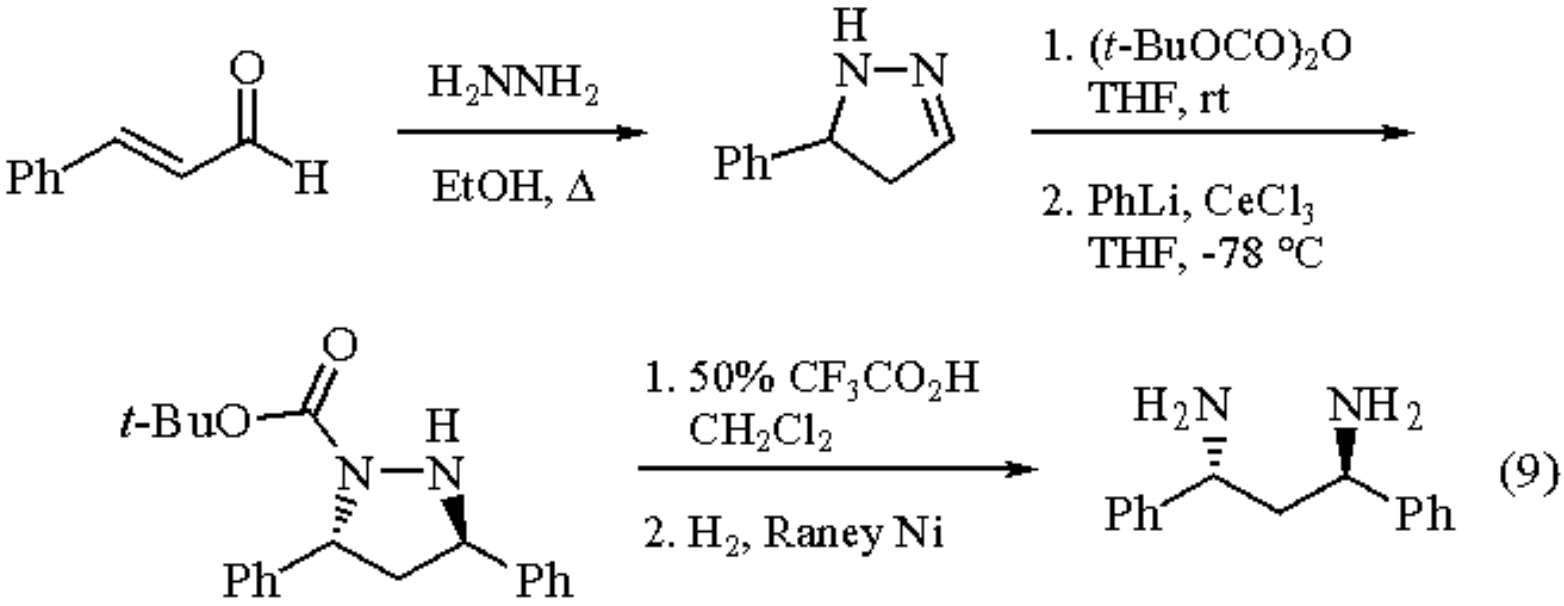

Cerium enolates, available by transmetalation of the lithium salts with $CeCl_3$ at -78 °C[26] or by reduction of α-bromo ketones with ***Cerium(III) Chloride-Tin(II) Chloride***,[27] give higher yields of crossed aldol products without altering the stereoselectivity. The $CeCl_3$-$SnCl_2$ reagent combination also acts on α,α´-dibromo ketones to give oxylallyl cations that can be captured in the usual way.[28]

Selective Reductions.

Equimolar amounts of ***Sodium Borohydride***$_4$ and $CeCl_3.7H_2O$ in methanol act on α,β-unsaturated ketones at rt or below to deliver allylic alcohols cleanly by 1,2-addition.[29] This widely used reducing agent[30] is not renowned for its diastereoselectivity[31] and asymmetric induction capabilities,[32] although exceptions are known.[33] Sometimes a stereofacial preference opposite that realized with other hydrides is encountered (eqs 10 and 11).[34]

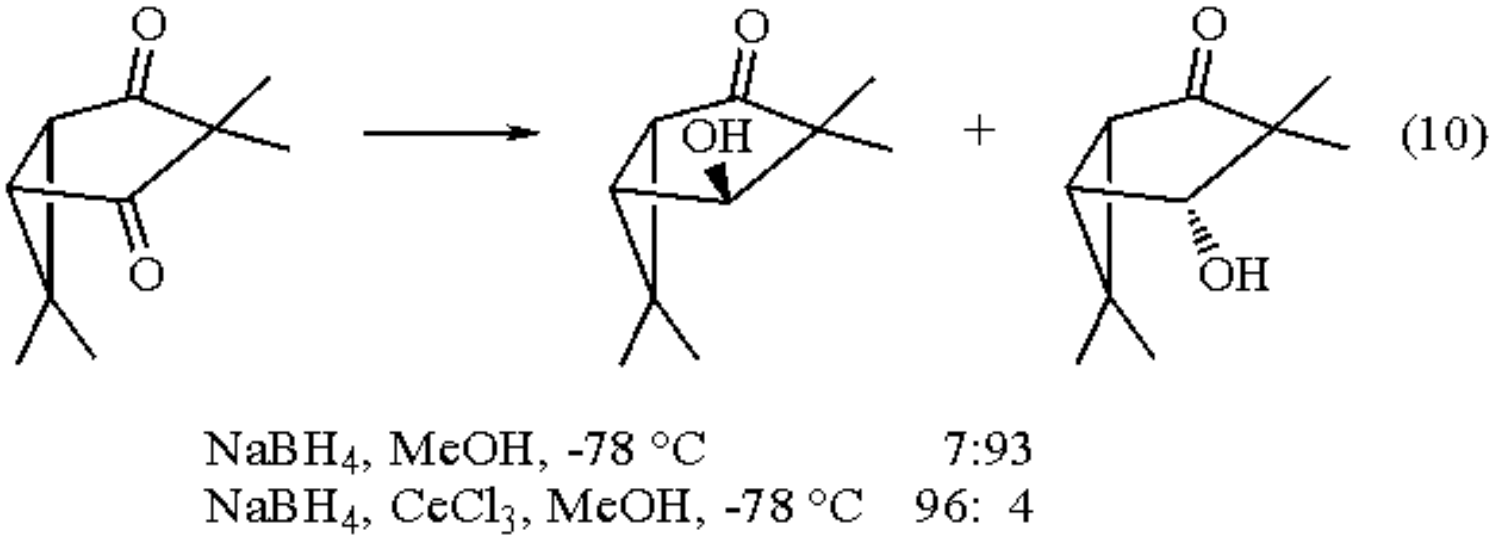

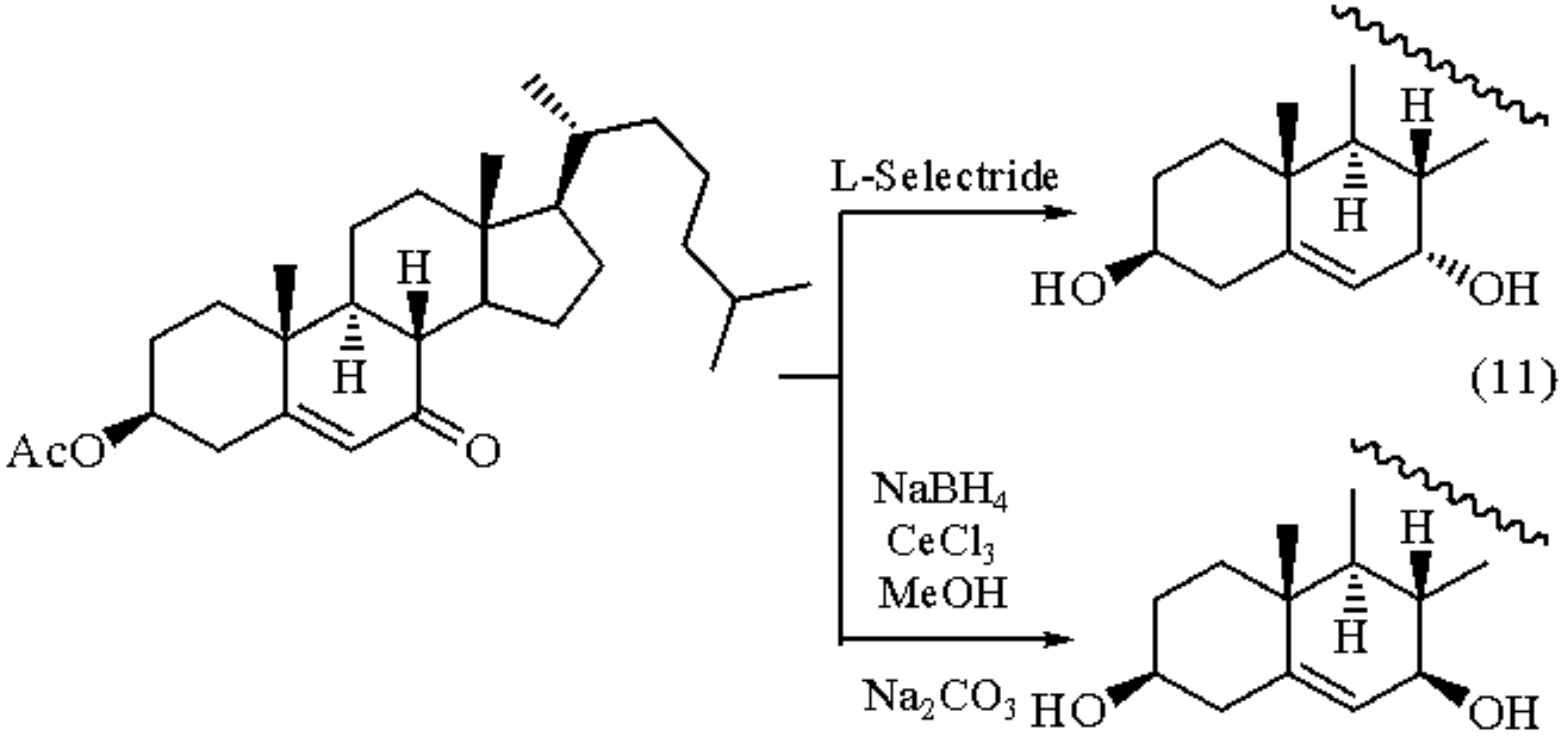

Allylic alcohol products that are especially sensitive are known to undergo ionization and solvent capture under these mildly acidic conditions (eq 12).[35] The Lewis acidic character of $CeCl_3$ has also been used to advantage in the selective acetalization[6] of saturated aldehydes under the Luche conditions, thereby preventing their reduction.[2] Since ketones and conjugated aldehydes are less responsive, these functionalities are not transiently protected and suffer reduction (eq 13).[36] $NaBH_4$-$CeCl_3$ in MeCN transforms cinnamoyl chlorides into cinnamyl alcohols,[37] while ***Lithium Aluminum Hydride-Cerium(III) Chloride*** in hot DME or THF can effectively reduce alkyl halides and phosphine oxides.[5]

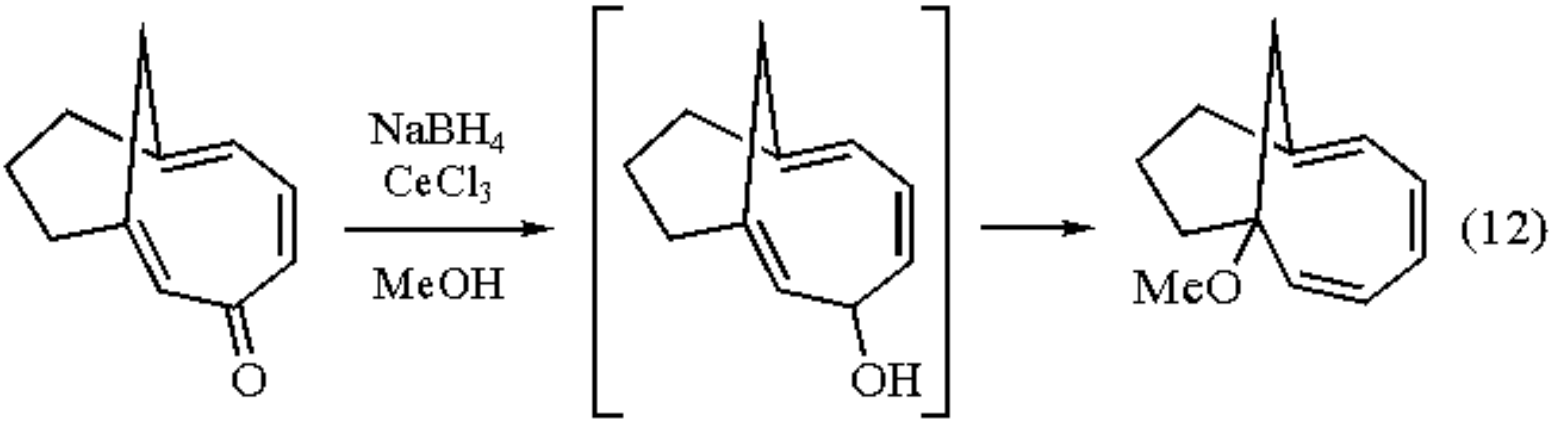

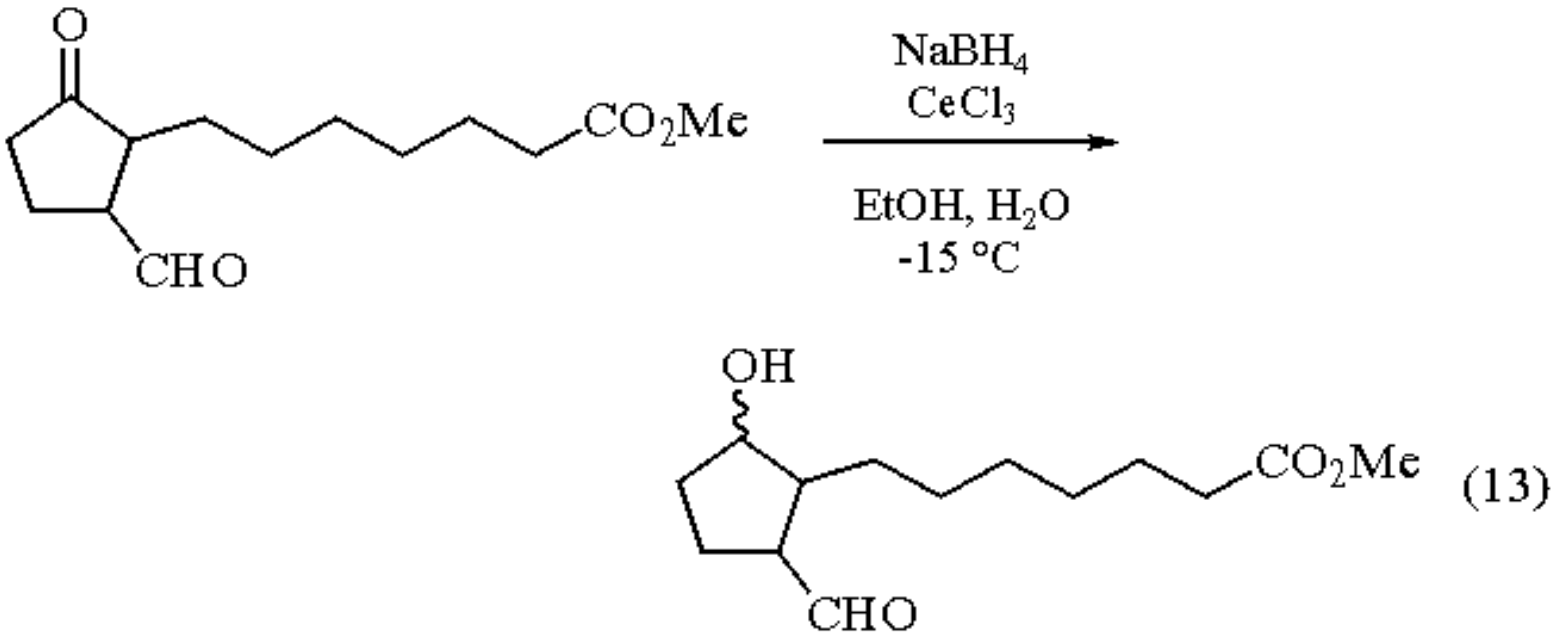

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Cerium(III) Chloride-Tin(II) Chloride

$CeCl_3$-$SnCl_2$

· $CeCl_3$ · Cerium(III) Chloride-Tin(II) Chloride · Cl_2Sn · Cerium(III) Chloride-Tin(II) Chloride

(combined reagent; reduces α-bromo ketones to yield cerium enolates which undergo cross-aldol reaction; reduces α,α´-dibromo ketones to yield oxyallyl cations which undergo [3 + 4] cycloaddition with 1,3-dienes)

Physical Data: see ***Cerium(III) Chloride*** and ***Tin(II) Chloride***.

Aldol Reactions with α-Bromo Ketones.[1]

The combination of cerium(III) trichloride-tin(II) chloride in conjunction with α-bromo ketones and carbonyl compounds in THF affords β-hydroxy ketones in good to excellent yields after aqueous workup (eq 1).

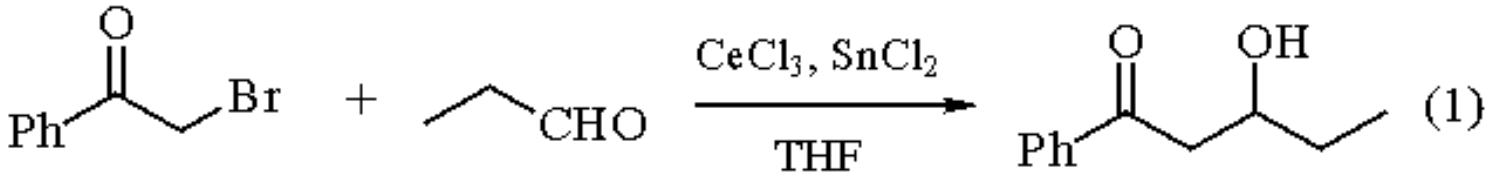

Carbon-carbon bond formation takes place regioselectively at the site of the bromine atom. Thus the reaction of 2-bromo-2-methylcyclohexanone or 2-bromo-6-methylcyclohexanone with benzaldehyde affords the corresponding β-hydroxy ketone without any contamination of the regioisomer (eq 2). This result indicates that no retro-aldol or cross-enolization processes occur in the reaction.

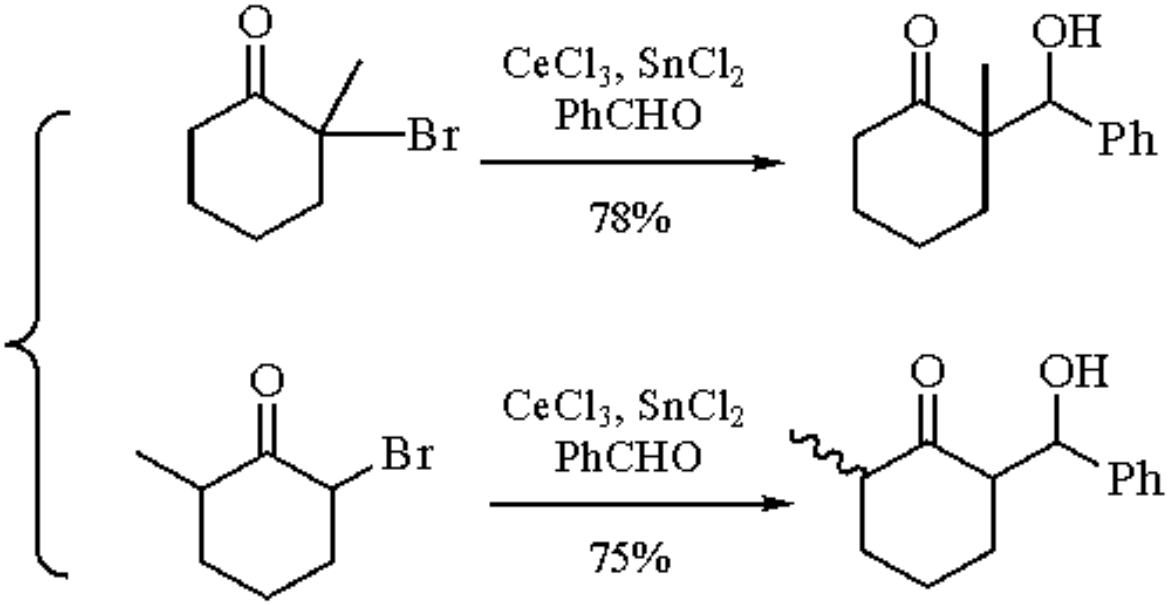

(2)

Reactions with ketones provide low yields (30-40%) of the desired aldol products compared with aldehydes. The difference in reactivity between aldehydes and ketones was successfully exploited in the chemoselective aldol condensation to 6-oxoheptanal (eq 3).

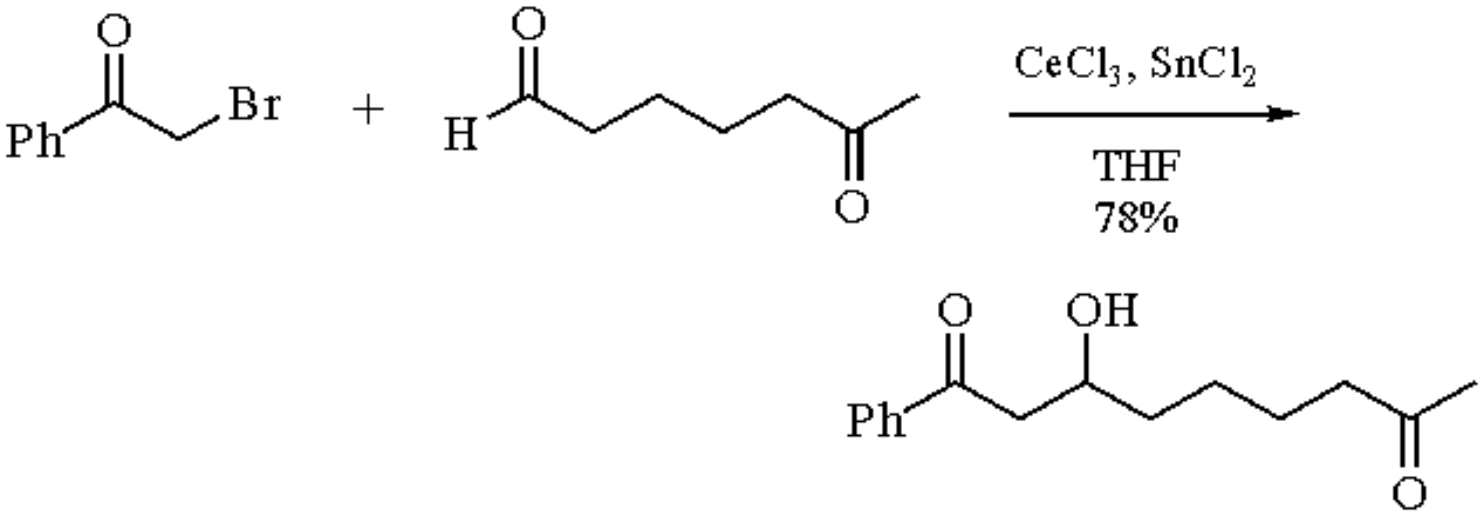

(3)

The success of this strategy for cross-aldol reaction is attributed to activation of carbonyl group by Lewis acidic $CeCl_3$ which promotes the reduction of bromine by $SnCl_2$ (eq 4). Neither $CeCl_3$ nor $SnCl_2$ alone gives the coupled products. A cerium enolate intermediate is implicated in the reaction since the tin enolate generated from 2-bromocyclohexanone and low-valent tin ($SnCl_2/LiAlH_4$) reacts with benzaldehyde to afford the *erythro* isomer predominantly,[2] while $CeCl_3$-$SnCl_2$ gives high *threo* selectivity in the same reaction (*erythro:threo* = 15:85-11:89) (eq 5).

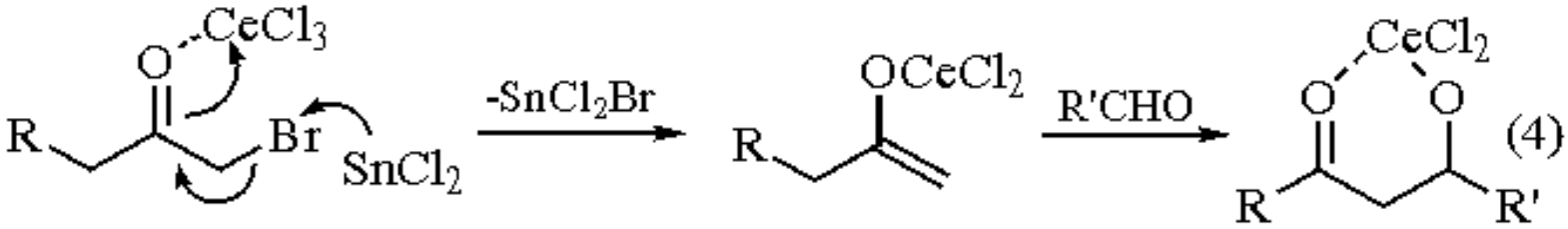

(4)

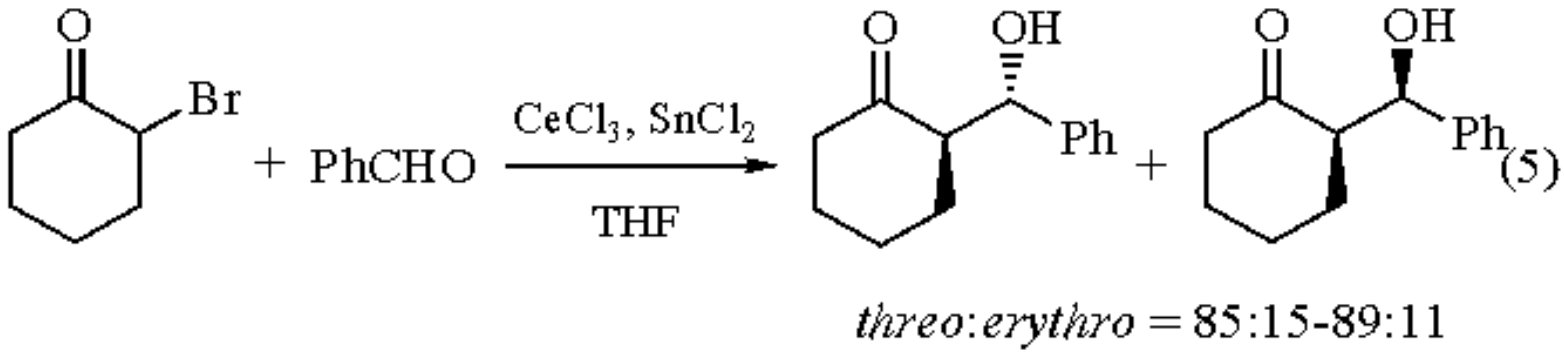

Reformatsky-type reactions cannot be carried out utilizing this combination of reagents,[3] and α-chloro ketones are also unreactive as cerium enolate precursors. Examples of related reagents include the organoaluminum system Et_2AlCl-$SnCl_2$.[4] This combination sometimes requires a Pd^0 complex, whereas the $CeCl_3$-$SnCl_2$ system functions effectively without palladium and is less sensitive to air and moisture contamination.

[3 + 4] Cycloadditions.[5]

The combined reagent $CeCl_3$-$SnCl_2$ promotes the [3 + 4] cycloaddition reaction of α,α´-dibromo ketones with 1,3-dienes in THF effectively under mild conditions (0 °C-rt, 2 h) (eq 6). Furan and cyclopentadiene provide very good yields of the expected cycloadducts. With acyclic 1,3-dienes, 4-cyclohepten-1-ones are produced in modest yields. It is noteworthy that the reaction of 2,4-dibromo-3-pentanone with isoprene gives both [3 + 4] and [3 + 2] cycloadducts. [3 + 2] Cycloaddition proceeds similarly with enamines to afford 2-cyclopenten-1-ones after treatment with 3% ethanolic NaOH solution.

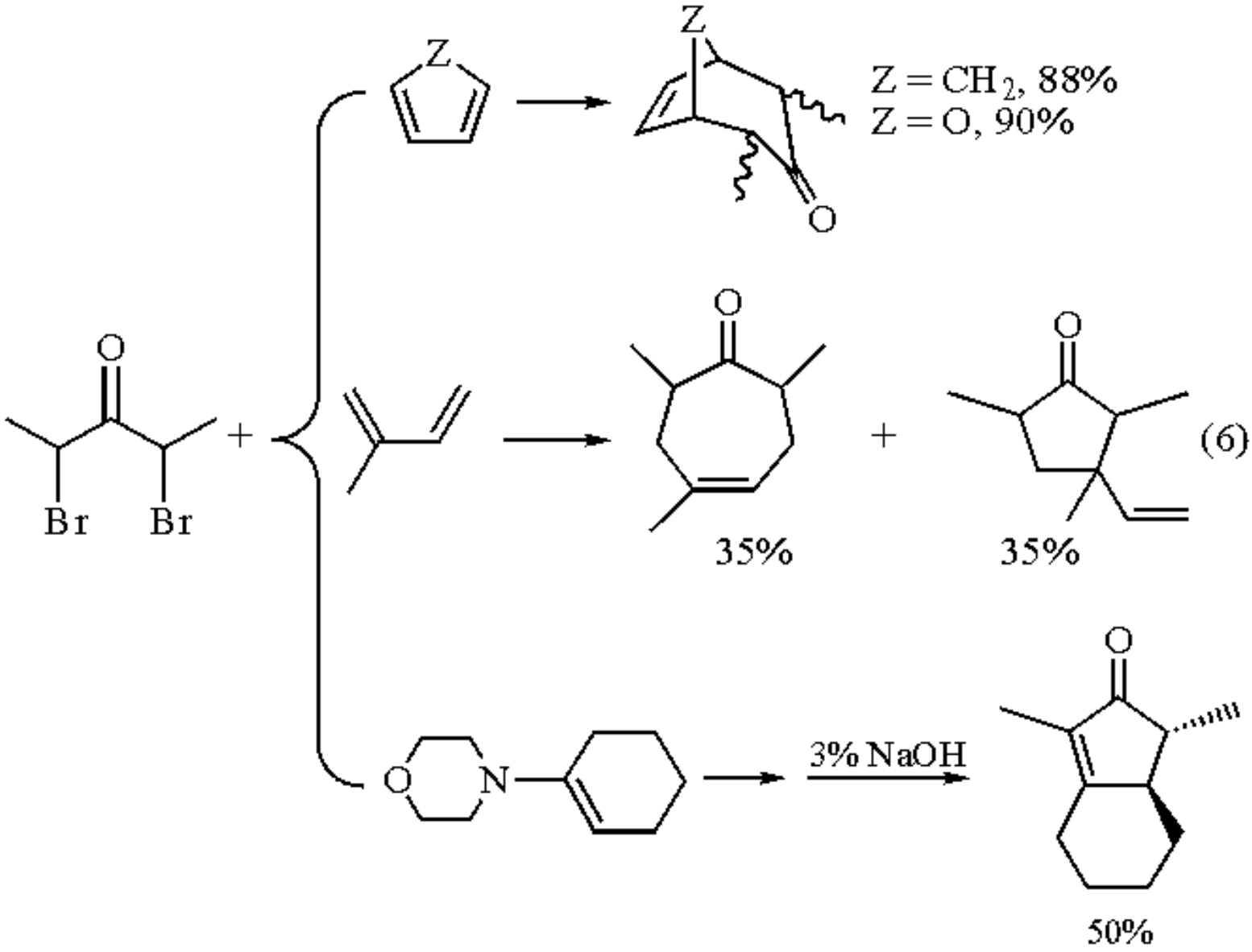

The $CeCl_3$-$SnCl_2$ reagent is a more convenient system for these cycloadditions compared to other procedures.[6] This reaction procedure is quite simple and is carried out at room temperature in air. The reaction involves reduction of an α,α´-dibromo ketone to afford an oxyallyl cation that can be captured by 1,3-dienes in the usual way.

---

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Cerium(III) Iodide

CeI_3

[7790-87-6] · CeI_3 · Cerium(III) Iodide · (MW 520.83)

(organocerium reagents prepared from cerium triiodide and organolithiums have reduced basicity and possess enhanced nucleophilicity toward the carbonyl group; promotes aldol reaction between α-halo ketones and aldehydes; in combination with $LiAlH_4$ is a selective 1,2-reducing agent)

Alternate Name: cerium triiodide

Physical Data: mp 752 °C.

Solubility: sol water, acetone.

Form Supplied in: bright yellow solid.

Preparative Methods: pure CeI_3 is prepared by the reaction of metallic cerium with iodine or mercury(II) iodide at high temperature.[1,2] Another method is to dissolve CeO_2 in aqueous HI solution, adding 12 moles of NH_4I per mole of CeO_2, and evaporating the mixture to dryness. The mixture is heated in vacuo at 300-350 °C to leave pure CeI_3.[3] CeI_3 is prepared in situ by the reaction of powdered cerium with iodine in THF.[4]

Handling, Storage, and Precautions: extremely hygroscopic and turns brown when exposed to air owing to the liberation of iodine. This reagent should be stored under nitrogen and handled in a glove bag.

Organocerium Reagents.

Organocerium reagents are prepared by the reaction of CeI_3 with organolithium compounds in THF.[4] The reagents possess reduced basicity and react with various carbonyl compounds to give the corresponding addition products, even though the substrates are susceptible to enolization, metal-halogen exchange, or 1,4-addition (eqs 1-3) (see also ***Cerium(III) Chloride***).[4,5]

$$Bn_2CO \xrightarrow[\text{THF, -78 °C}]{\text{BuLi, CeI}_3} Bn_2C(OH)Bu \qquad (1)$$

98%

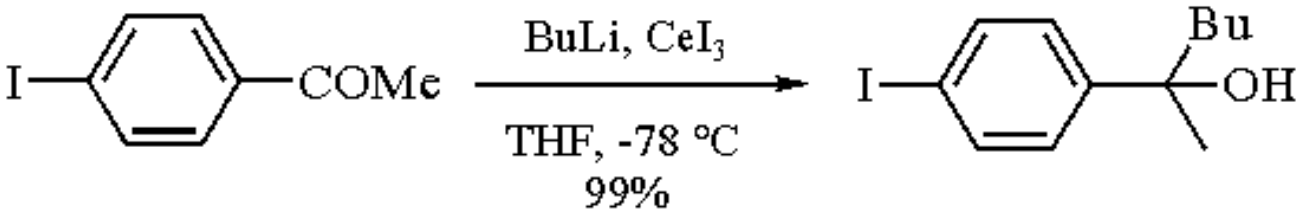

(2)

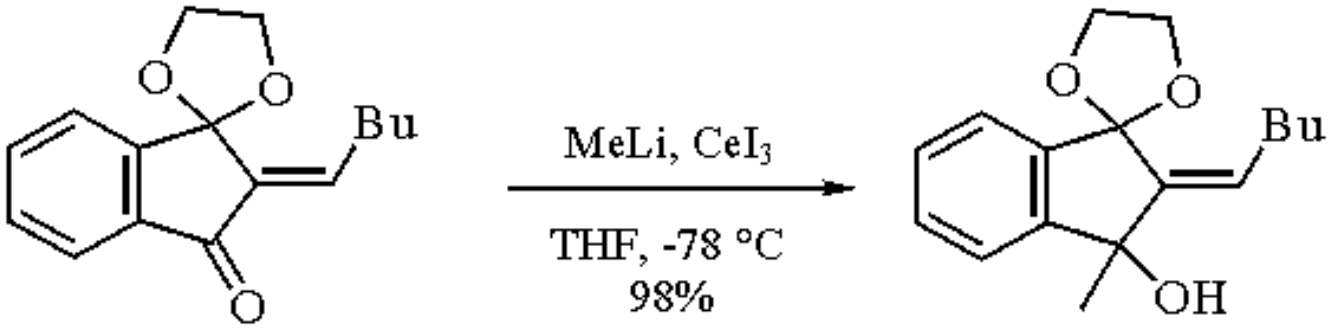

(3)

Aldol Reaction.

Cerium triiodide is used for cross-aldol reaction between α-halo ketones and aldehydes including α,β-unsaturated aldehydes.[6] The reaction proceeds in THF at room temperature to afford α,β-unsaturated ketones (eq 4); β-hydroxy ketones are not produced. Ketones, however, do not react under these conditions.

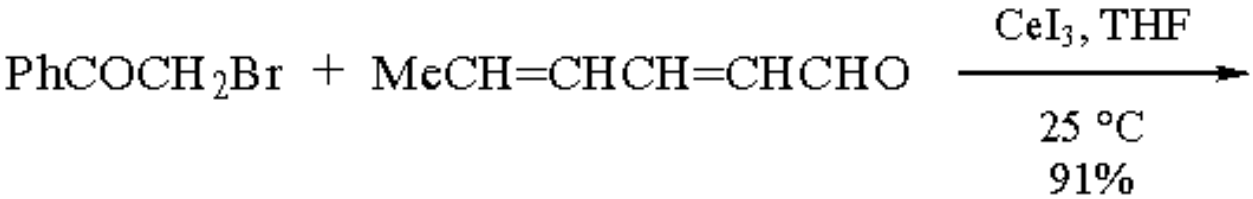

PhCOCH=CHCH=CHCH=CHMe (4)

Selective Reductions.

α,β-Unsaturated carbonyl compounds are subject to selective 1,2-reduction by ***Lithium Aluminum Hydride*** in combination with CeI_3 to give allylic alcohols.[7] This method is applicable to α,β-unsaturated aldehydes (eq 5), esters, and lactones that do not undergo selective 1,2-reduction with $NaBH_4$-$CeCl_3$ (see also ***Cerium(III) Chloride***).

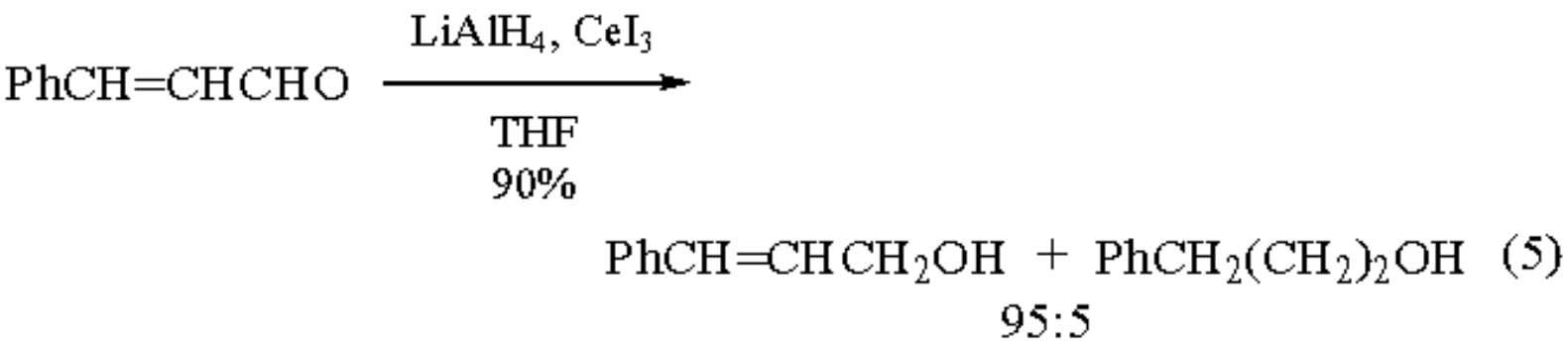

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Cerium(III) Methanesulfonate[1]

$Ce(OSO_2Me)_3$

[77998-20-0] · $C_3H_9CeO_9S_3$ · Cerium(III) Methanesulfonate · (MW 425.42) (.2H_2O)

[73640-09-2] · $C_3H_{13}CeO_{11}S_3$ · Cerium(III) Methanesulfonate · (MW 461.46)

(stable, soluble cerium(III) salt used as a mediator for organic oxidation)

Alternate Name: cerous methanesulfonate.

Physical Data: white crystalline solid.

Solubility: very sol water, aqueous methanesulfonic acid, and aqueous acetonitrile; sol methanol; insol acetone.

Preparative Methods: prepared by the reaction of methanesulfonic acid with an aqueous suspension of cerium(III) carbonate. Solids can be precipitated with acetone or a large excess of methanesulfonic acid.

Handling, Storage, and Precautions: best used in aqueous solution as prepared. Cerium(III) salts are generally believed to be of low toxicity.

Electrochemical Oxidation.

The methanesulfonate salt of cerium is a convenient mediator for these oxidations because of its high solubility, the stability of the mesylate anion to electrochemical and cerium(IV) oxidation, and the very limited reactivity of the anion with oxidized products or intermediates.[2] ***Cerium(IV) Trifluoromethanesulfonate*** also works well but is more expensive. A solution of cerium(III) methanesulfonate in aqueous methanesulfonic acid is oxidized to cerium(IV) at a platinum, RuO_2/Ti, IrO_2/Ti, or PbO_2/Ti anode.[3] Generally, protons are reduced to hydrogen at the cathode, which is isolated by a perfluorinated ion exchange membrane. Useful reductions can also be performed at the cathode,

such as the reductive coupling of formaldehyde to ethylene glycol.[4]

Oxidations which have been performed with cerium(IV) methanesulfonate in aqueous methanesulfonic acid include the oxidation of alkylaromatics to ketones or aldehydes,[2] polycyclic aromatics to quinones,[2,5] and alkenes to carboxylic acids.[6] The organic substrate is generally employed as a second phase, either as a pure liquid or dissolved in an inert solvent such as 1,2-dichloroethane.[2] This improves selectivity and aids in product separation. The aqueous Ce^{IV} solution can then be regenerated electrochemically. The oxidation of 4-fluorotoluene to 4-fluorobenzaldehyde was performed directly at the anode with cerium trifluoromethanesulfonate as the mediator.[7]

It is sometimes beneficial to modify the oxidizing solution so as to contain an organic cosolvent and/or comediators (catalysts). Thus the oxidation of highly reactive substrates such as 4-methoxytoluene to 4-methoxybenzaldehyde was best accomplished with acetonitrile as a cosolvent.[2] Also, the cerium(IV) oxidation of cyclododecene to dodecanedioic acid was performed with ***Ruthenium(VIII) Oxide***[6] and the oxidation of 2-methylnaphthalene to 2-methyl-1,4-naphthoquinone was performed with Cr^{VI} as comediator.[2]

A solid cerium(IV) material, $Ce(MeSO_3)_2(OH)_2$, can be conveniently prepared by electrochemical oxidation of Ce^{III} in dilute aq. $MeSO_3H$. This solid can be used directly or redissolved in water for organic oxidations.[2]

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Cerium(IV)-Nafion 511

(selective oxidation of secondary alcohols)

Physical Data: see ***Cerium(IV) Ammonium Nitrate***.

Form Supplied in: Nafion 511 is supplied as white granules 1 mm in diameter; Nafion® is a registered trademark of E. I. du Pont de Nemours & Co.

Preparative Methods: Nafion 511 (1.1 g) is stirred with a solution of $(NH_4)_2Ce(NO_3)_6$ (1.75 g) in 30 mL of deionized water for 36 h at 25 °C. The catalyst (cerium(IV)-Nafion 511, Ce/NAFK) is filtered, washed with water (10 mL × 5) and dried to constant weight. Titration of the polymer indicates capacity of 0.54 mmol of Ce^{IV} per gram, which corresponds to 71% of the theoretical capacity of a fully loaded resin (**1**).

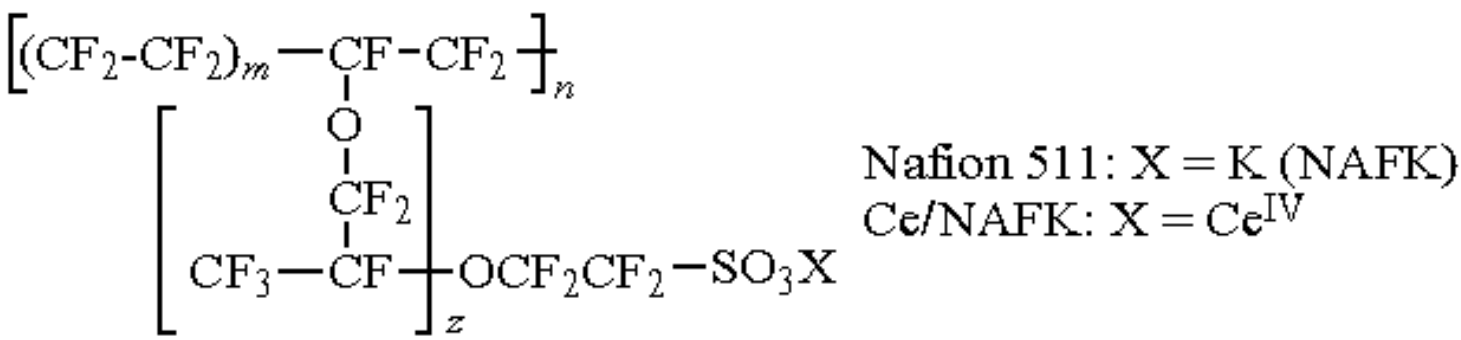

(1)

Oxidation of Alcohols.

t-Butyl Hydroperoxide can oxidize alcohols to carbonyl compounds in the presence of a polymer supported catalyst (Ce/NAKF).[1] In contrast to the ***Cerium(IV) Ammonium Nitrate-Sodium Bromate*** system, this method is not affected by the presence of carbon-carbon double bonds in the substrates. Thus 2-cyclododecen-1-ol and 11-dodecen-2-ol give the corresponding ketones in good yields (eq 1). Selective oxidation of secondary hydroxyls in the presence of primary ones has also been achieved (eqs 2 and 3). These reactions are performed with ***Sodium Bromate*** as a co-oxidant in AcOH at 55 °C. The catalyst is easily recovered and reused without loss of Ce^{IV} ion.

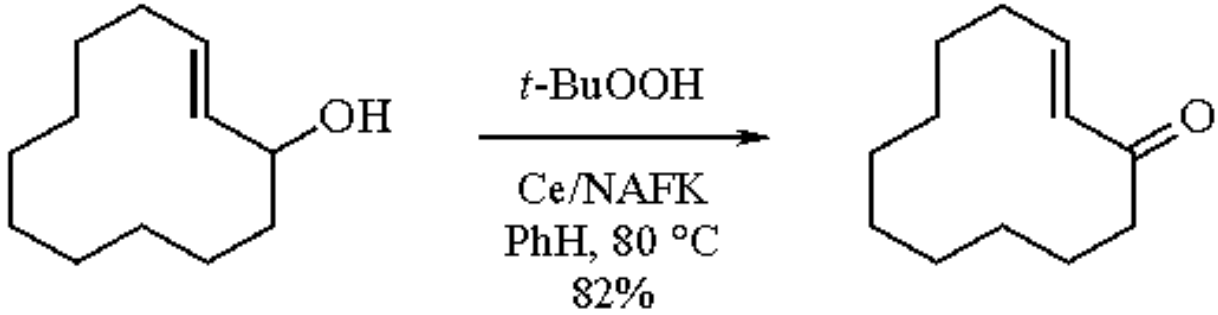

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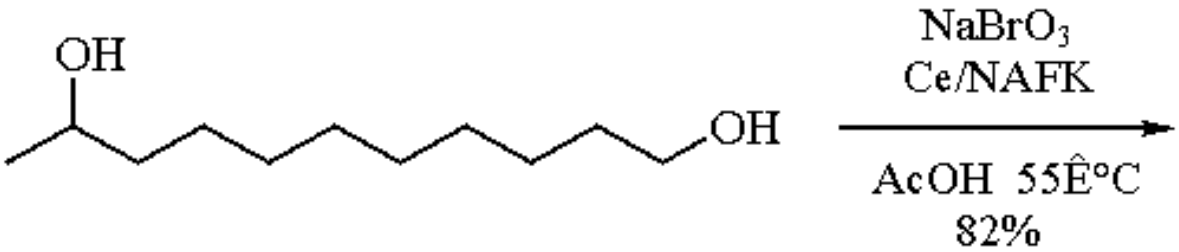

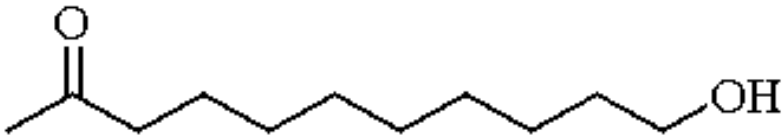

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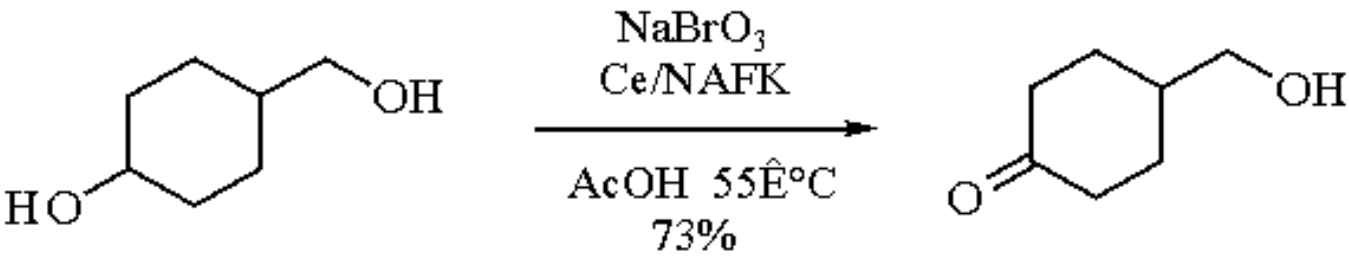

(3)

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Cerium(IV) Pyridinium Chloride

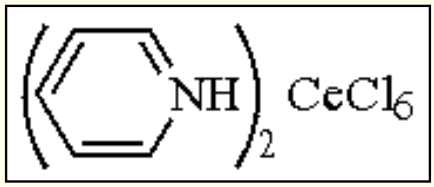

[40888-83-3] · $C_{10}H_{12}CeCl_6N_2$ · Cerium(IV) Pyridinium Chloride · (MW 513.06)

(oxidizing reagent for the direct preparation of amides from protected carboxylic acids;[1] for the functionalization of methyl-substituted aromatic compounds[2])

Alternate Name: dipyridinium hexachlorocerate(IV).

Solubility: sol acetonitrile, methanol, ethanol, and water.

Form Supplied in: yellow powder.

Analysis of Reagent Purity: elemental analysis.

Preparative Methods: by reaction of cerium(IV) hydroxide with anhydrous hydrogen chloride and pyridine.[3]

Purification: dry at 120 °C under reduced pressure (0.1 mmHg) for 3 h.[3]

Handling, Storage, and Precautions: hygroscopic, store under nitrogen and protect from exposure to moisture.

Preparation of Amides.[1]

Various amides are directly prepared from 5-acyl-5,6-dihydrophenanthridine carboxylic acid derivatives by reaction with primary amines in the presence of cerium(IV) pyridinium chloride and copper(II) oxide (eq 1). This reagent is far superior to ***Cerium(IV) Ammonium Nitrate*** (CAN) for this purpose. Employment of secondary amines did not give satisfactory results. 5-Acyl-5,6-dihydrophenanthridines with functional groups such as esters, carbonyls, or halogens in the same molecule are also converted to the corresponding amides. The benzoylation of α-amino ester proceeds without racemization.

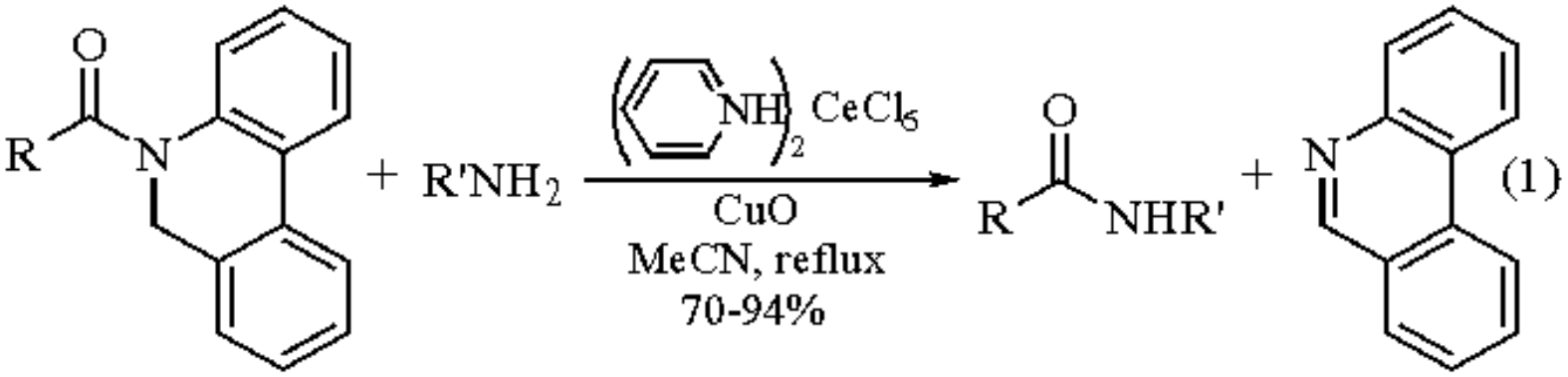

R = Ph, Ph(CH$_2$)$_3$-, MeCH$_2$CH(Ph)-, etc.
R' = Ph(CH$_2$)$_2$-, MeCH(Ph)-, etc.

Oxidation of Aryl Methyl Groups.[2]

Methyl-substituted aromatic compounds are oxidized to alkoxymethylbenzene derivatives by treatment with cerium pyridinium chloride in alcohol. Oxidation of hexamethylbenzene in ethanol proceeds at reflux temperature to afford the ethyl ether in good yield, while the reaction in methanol gives a 1:1 mixture of methyl ether and chloride (eq 2).

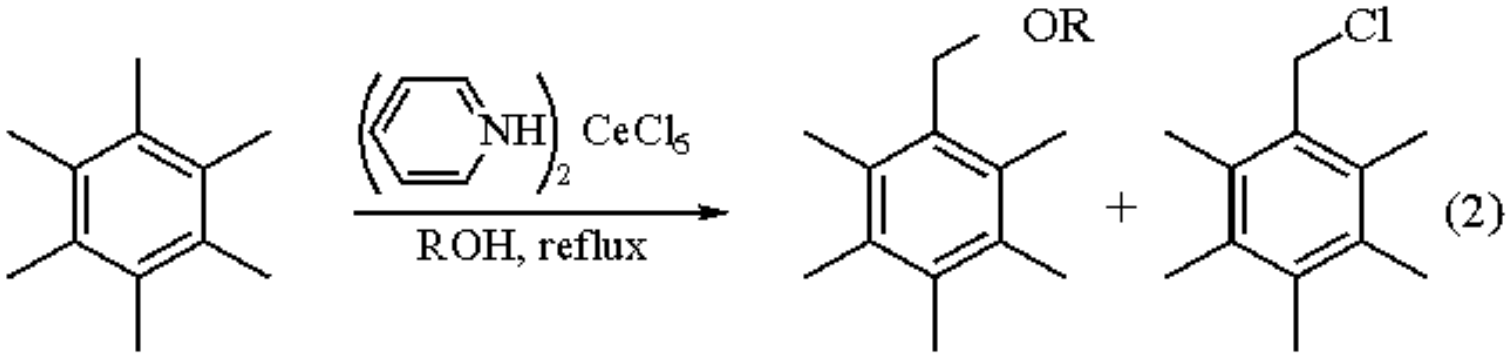

in MeOH	38%	36%
in EtOH	75%	-

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Cerium(IV) Trifluoromethanesulfonate

$Ce(OSO_2CF_3)_4$

[107792-63-2] · $C_4CeF_{12}O_{12}S_4$ · Cerium(IV) Trifluoromethanesulfonate · (MW 736.34)

(oxidizing agent for benzyl alcohols and toluenes)

Alternate Name: ceric triflate.

Solubility: sol water, THF, DME, dioxane; insol dichloromethane, hexane, benzene.

Form Supplied in: yellow solid.

Preparative Methods: by the reaction of trifluoromethanesulfonic acid with freshly prepared cerium(IV) carbonate.[1] The reagent can be prepared in situ by the electrochemical oxidation of $Ce(OTf)_3$ in aqueous trifluoromethanesulfonic acid.[2]

Purification: thus far the reagent has only been used in crude form as prepared above.

Handling, Storage, and Precautions: the reagent is extremely hygroscopic and should be stored under strict absence of moisture. This reagent should be handled in a fume hood.

Oxidation of Benzyl Alcohols and Aryl Methyl Groups.

Benzyl alcohols are readily oxidized by $Ce(OTf)_4$ in MeCN-H_2O at room temperature to the corresponding benzaldehydes (eq 1).[1] Under similar conditions, aryl methyl groups are converted to aldehydes in good yields (eq 2) (see also ***Cerium(IV) Ammonium Nitrate*** and ***Cerium(IV) Ammonium Sulfate***).[1] $Ce(OTf)_4$ appears to be more reactive as an oxidizing agent than CAN or CAS.

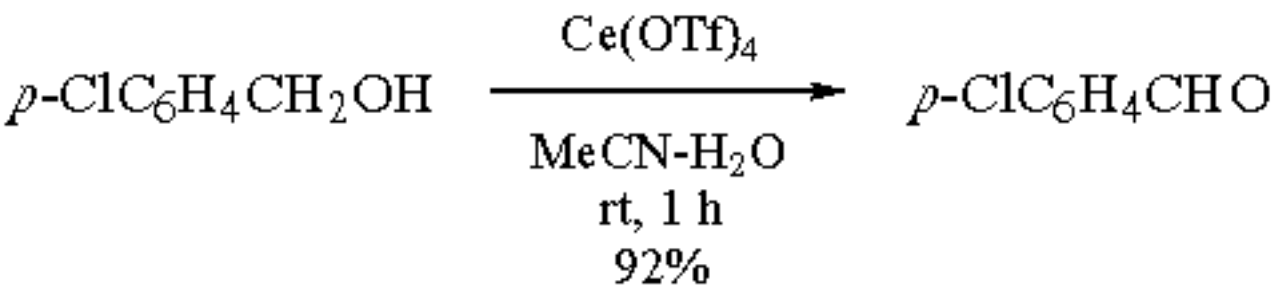

(1)

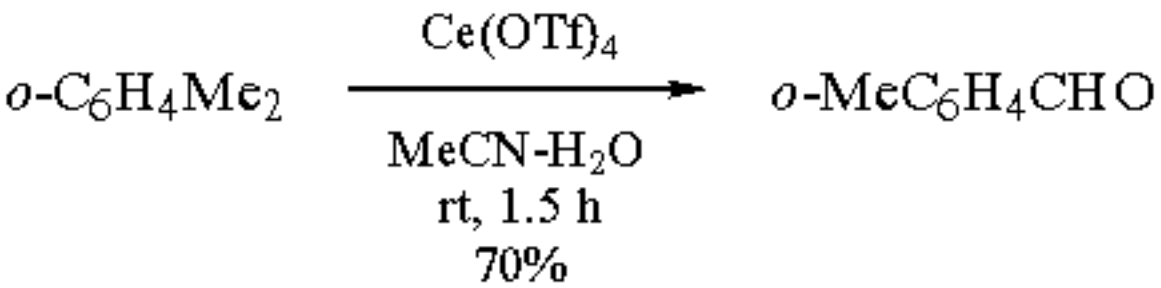

(2)

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Cerium(IV) Trifluoroacetate

$$Ce(O_2CCF_3)_4$$

[52118-96-4] · $C_8CeF_{12}O_8$ · Cerium(IV) Trifluoroacetate · (MW 592.17)

(oxidizing agent for aromatic hydrocarbons)

Solubility: sol acetone, DME, DMSO, acetonitrile, TFA containing lithium trifluoroacetate; insol chloroform, dichloromethane, benzene.

Form Supplied in: yellow solid.

Preparative Methods: by the reaction of cerium(IV) hydroxide with TFA to give the basic salt $Ce(OH)_2(O_2CCF_3)_2$, which on further treatment with TFA and its anhydride affords the desired reagent.[1] Thus far the reagent has only been used in the crude state without purification.

Handling, Storage, and Precautions: is sensitive to moisture and light and should therefore be stored under nitrogen and protected from light.

Oxidations of Arenes.

Cerium(IV) trifluoroacetate reacts instantaneously at room temperature with methylbenzenes to give coupling products.[1] For example, durene is oxidized rapidly in TFA containing cerium trifluoroacetate to give a diphenylmethane derivative (eq 1).

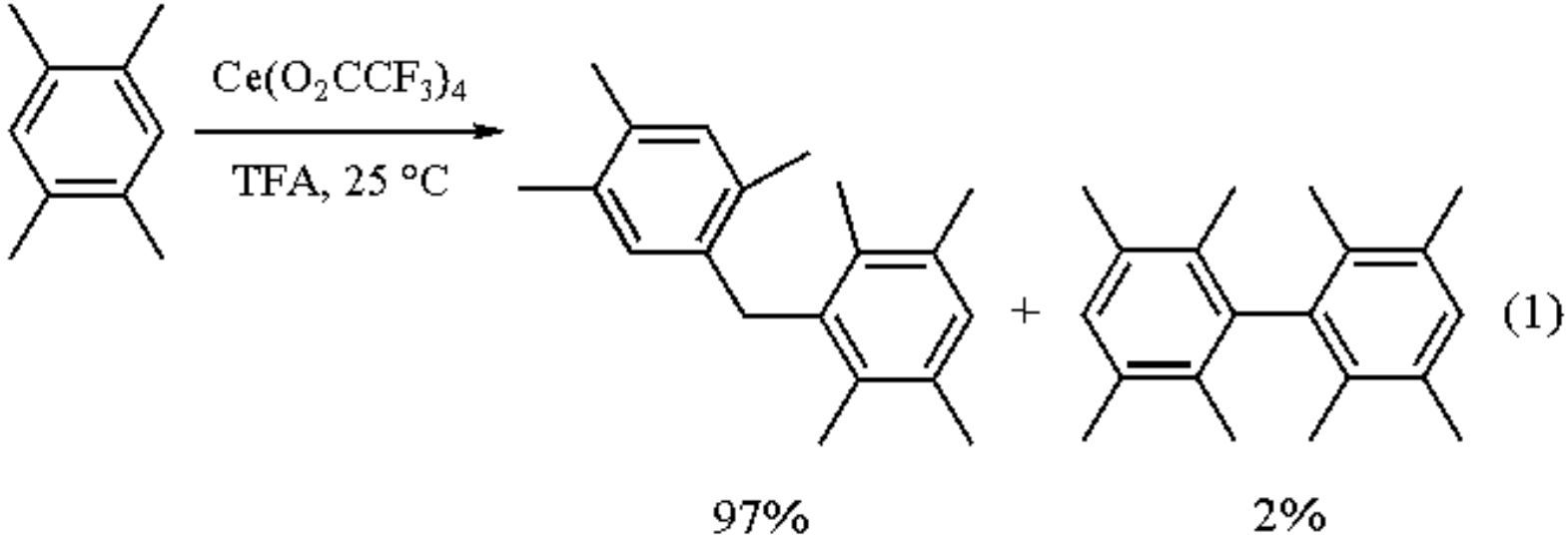

Reaction of anthracene with cerium(IV) trifluoroacetate in alcohols provides 9-alkoxyanthracenes (eq 2).[2] Use of lower alcohols affords the corresponding 9-alkoxyanthracenes in good yields, while reaction of higher alcohols results in poor yields of the products, a significant amount of anthraquinone being formed.

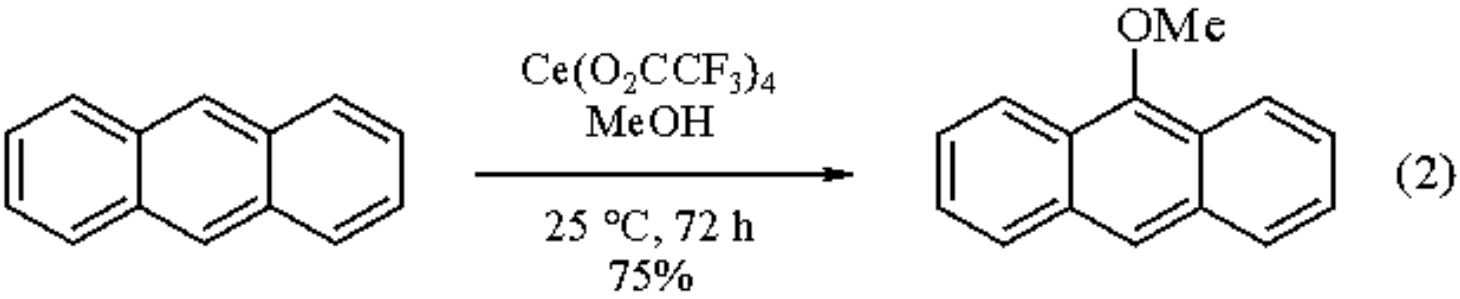

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Cerium(IV) Trihydroxide Hydroperoxide[1]

$Ce(OH)_3O_2H$

[93131-81-8] · CeH_4O_5 · Cerium(IV) Trihydroxide Hydroperoxide · (MW 224.12)

(mild oxidizing reagent for a variety of functional groups[2,3]

Solubility: insol H_2O, MeCN, EtOH, DMSO, THF.

Form Supplied in: orange-red solid, readily available.

Preparative Method: by the addition of 30% hydrogen peroxide solution (20 mL) to a solution of $CeCl_3.7H_2O$ (0.03 mol) in water (100 mol). Upon addition of conc NH_4OH (15 mL), precipitation of the reagent occurs, which is then washed with water, acetone, and dried in the air (95%).[2]

Handling, Storage, and Precautions: stable at high temperatures >180 °C and for months at rt. Cerium is reputed to have low toxicity.

Heterogeneous oxidations with this reagent (CTH) proceed in dry benzene under reflux. The oxidant is separated by filtration. Evaporation of the solvent and chromatography of the residue affords the oxidation product. Several drawbacks observed with Ce^{IV} oxidations[1a,4] are not encountered with CTH. Change of color from red-orange to pale yellow indicates the deactivation of the reagent, which can be regenerated by two consecutive washings with sodium hydroxide (54-10%) followed by hydrogen peroxide (30%) solutions.

Oxidations.

Allylic, propargylic, and saturated alcohols are not easily oxidized with this reagent, although benzylic alcohols are transformed to their aldehydes (eq 1).

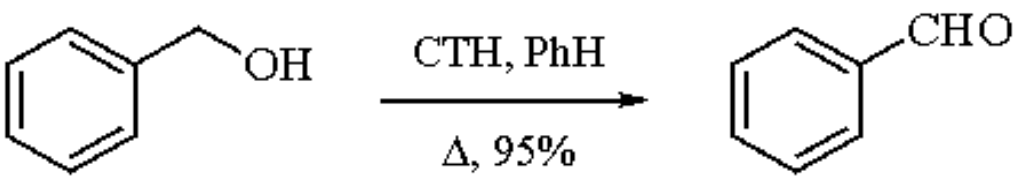

(1)

Benzoins are converted to the benzils (eq 2) and hydroquinones to quinones (eq 3) in high yields.

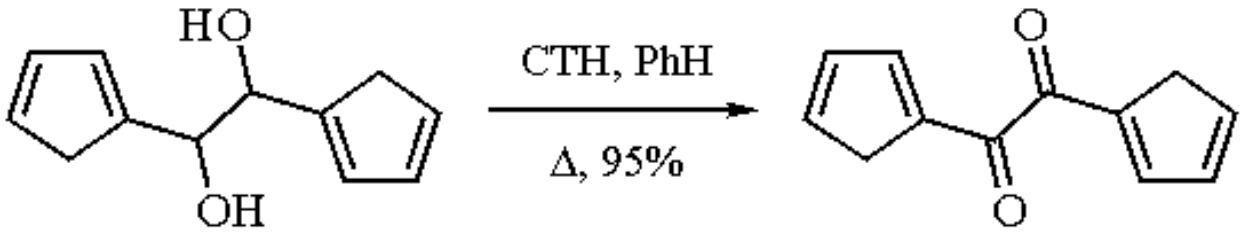

(2)

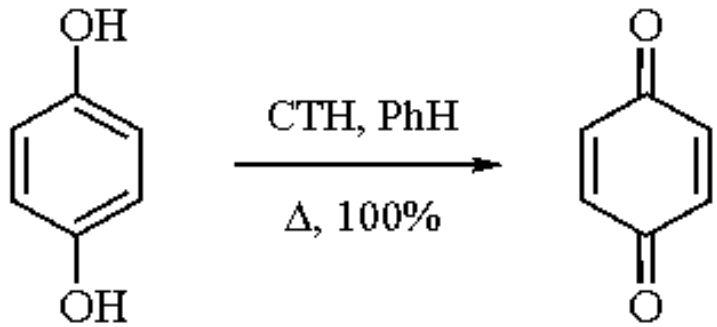

(3)

α-Hydroxycarboxylic acids are converted to carbonyl compounds with degradation (eq 4), and thiols are oxidized to disulfides (eq 5) in excellent yields.

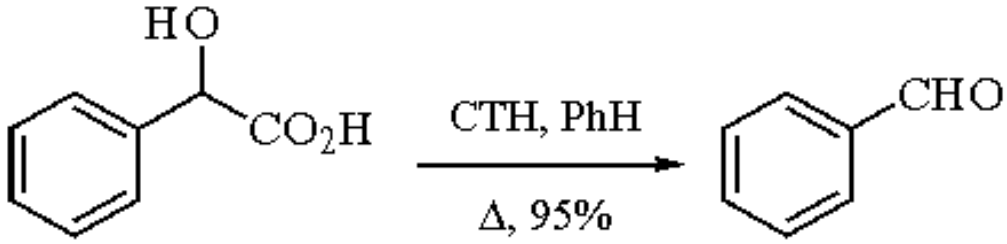

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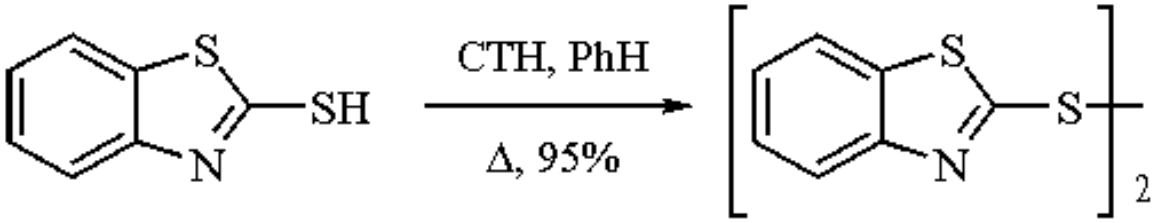

(5)

Aromatic amines are transformed to azo compounds (eq 6).

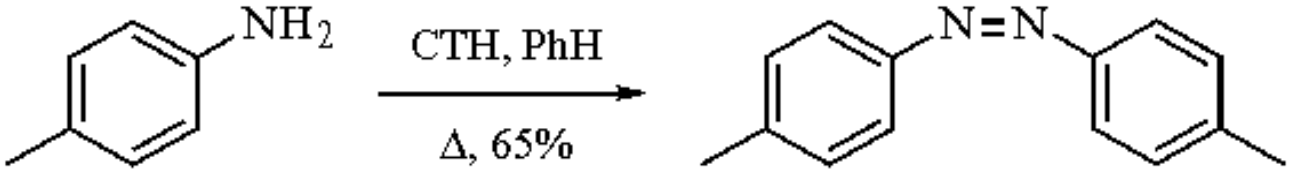

(6)

A comparison of CTH with ***Cerium(IV) Ammonium Nitrate*** (CAN),[4,5] ***Nickel(II) Peroxide*** (NP),[6] and 2,2´-bipyridylchromium peroxide (BPCP)[7] is shown in Table 1.

Table 1 Comparison of Oxidation Agents[a]

Substrate	Product	CTH	CAN	NP	BPCP
Benzyl alcohol	Benzaldehyde	95	94	91	95
Cinnamyl alcohol	Cinnamaldehyde	15		86	100
Furoin	Furil	95	5		90
2-Mercapto-benzothiazole	2-Benzothiazolyl disulfide	95			100
p-Toluidine	4,4¢Dimethyl-azobenzene	65		25	
Hydroquinone	Benzoquinone	90	83		95

[a] % yields given.

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Cesium Carbonate

Cs_2CO_3

[534-17-8] · CCs_2O_3 · Cesium Carbonate · (MW 325.82)

(used in the synthesis of crown ethers and macrocycles;[1] catalyzes the Horner-Emmons cyclization;[2] used as base for alkylations[3])

Physical Data: mp 610 °C (dec).

Solubility: sol water, alcohol, ether.

Form Supplied in: white powder; widely available.

Purification: crystallized from ethanol (10 mL g^{-1}) by slow evaporation.

Handling, Storage, and Precautions: irritant; handle with gloves; hygroscopic; keep away from moisture; flush eyes or skin with copious amounts of water in case of contact; possible mutagen; avoid inhalation.

Macrocyclization Reagent.

Crown ethers, generally used as ionophores for various applications, can be prepared by using Cs_2CO_3. This reagent serves as both a base and a cation template in the macrocylization of dicarboxylic acids and α,o-alkyl dihalides to generate crown ethers.[1,5] For example, a crown ether is produced in 85% yield when dicesium pyridine-3,5-dicarboxylate, generated from the acid and Cs_2CO_3, reacts with 1,11-dibromo-3,6,9-trioxoundecane in DMF upon heating the reaction mixture between 60-70 °C for 48 h (eq 1). Under similar conditions, aromatic dicarboxylic acids afford related crown ethers. This procedure also works well for crown ethers prepared from salicylic acid and bromopolyethylene glycols.[1]

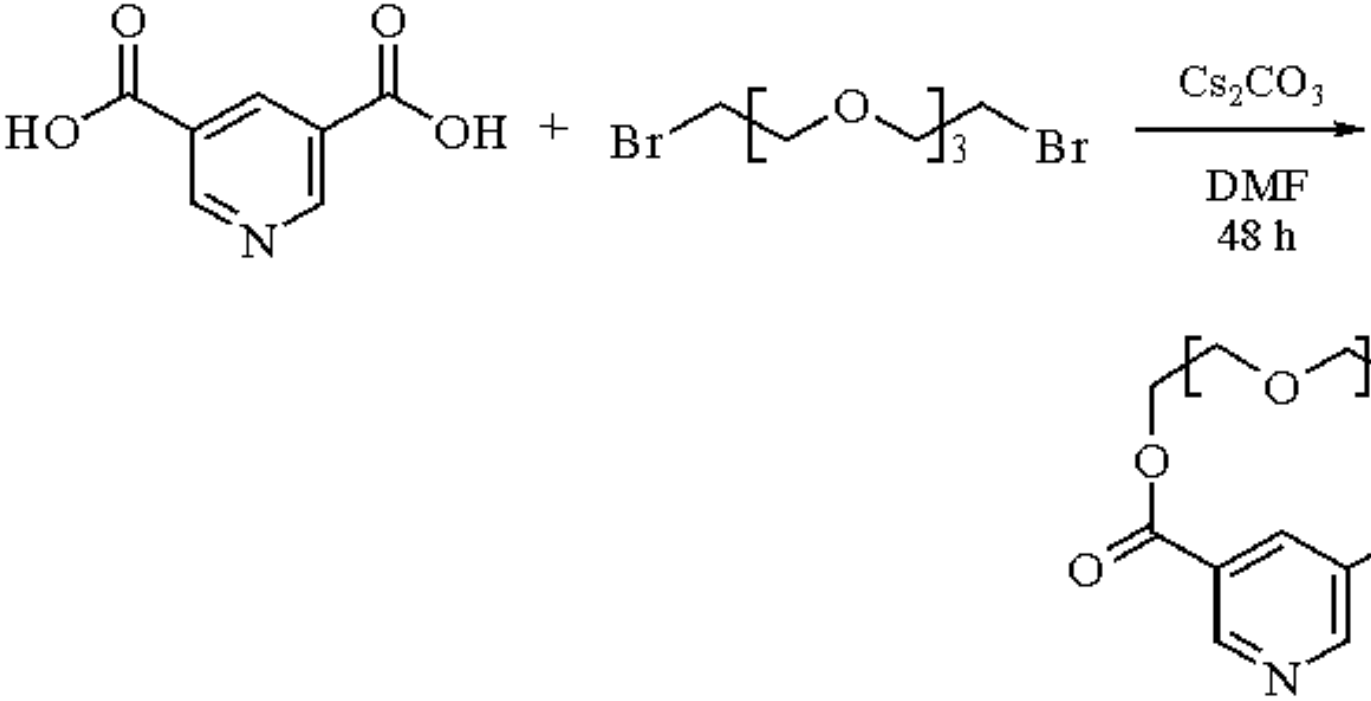

(1)

Thia crown ethers can also be prepared with Cs_2CO_3. Yields for these reactions are consistently good (45-95%) when the cesium salts of α,o-dithiols are treated with α,o-dihalides in DMF (eq 2).[5] Much lower yields (1-20%) are obtained if other methods, such as high dilution techniques, are used in the absence of a cesium counterion. Similar chemistry has been used to prepare functionalized cyclophane derivatives by replacing the α,o-dihalide with 1,3-dichloroacetone and using *o*-xylylenedithiol as the α,o-dithol.[6]

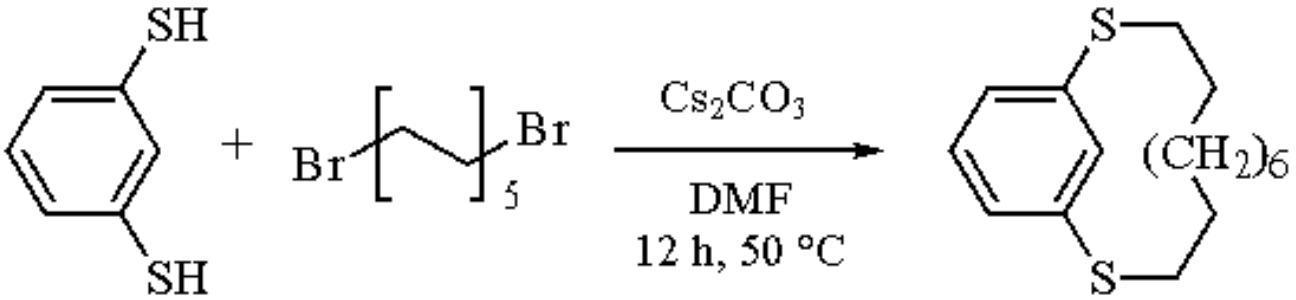

(2)

Chiral crown ethers have also been prepared by using Cs_2CO_3. A chiral diol and chiral ditosylate, both prepared from (*R*,*R*)-(+)-hydrobenzoin, have been coupled using NaH as a base and Cs_2CO_3 as a template in DMF (eq 3).[7]

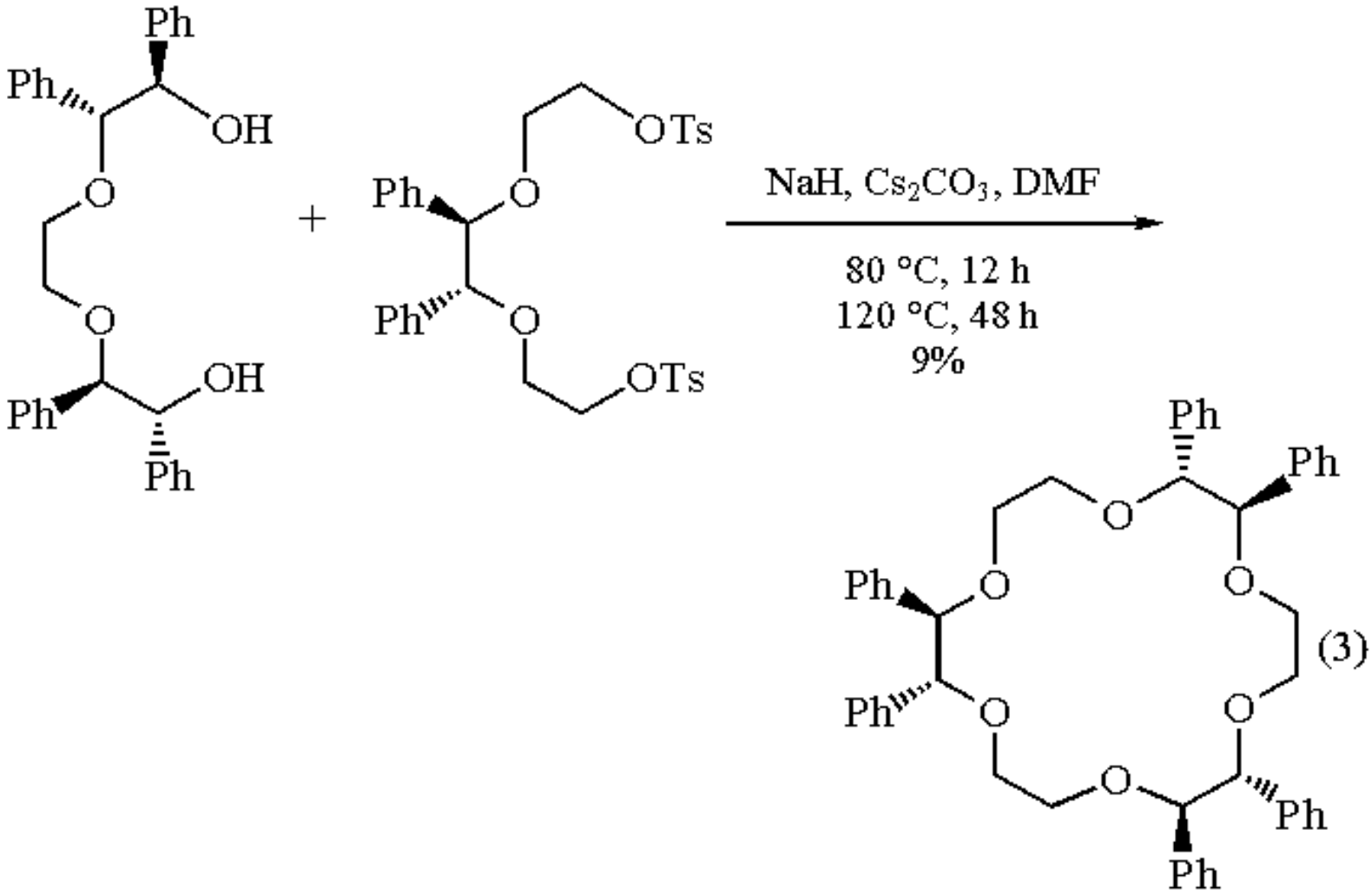

Tosylamides have been used to prepare aza macrocycles with Cs_2CO_3. The bicarbonate salt ($CsHCO_3$) is not basic enough to deprotonate ditosylamides.[8] Also, carboxamides and urethanes do not react as efficiently with Cs_2CO_3 as do tosylamides. Among the alkali bases, Cs_2CO_3 provided consistently higher yields than ***Lithium Carbonate***, ***Sodium Carbonate***, ***Potassium Carbonate*** and Rb_2CO_3. A typical example involved treating 1,10-bis[(*p*-tolylsulfonyl)amino]decane with two equivalents of Cs_2CO_3 in dry DMF followed by the addition of 1,6-dibromohexane and stirring the mixture at room temperature for 24 h to give the aza macrocycle in 72% yield. Reduction with sodium amalgam in buffered methanol gave the cyclic diamine (eq 4).

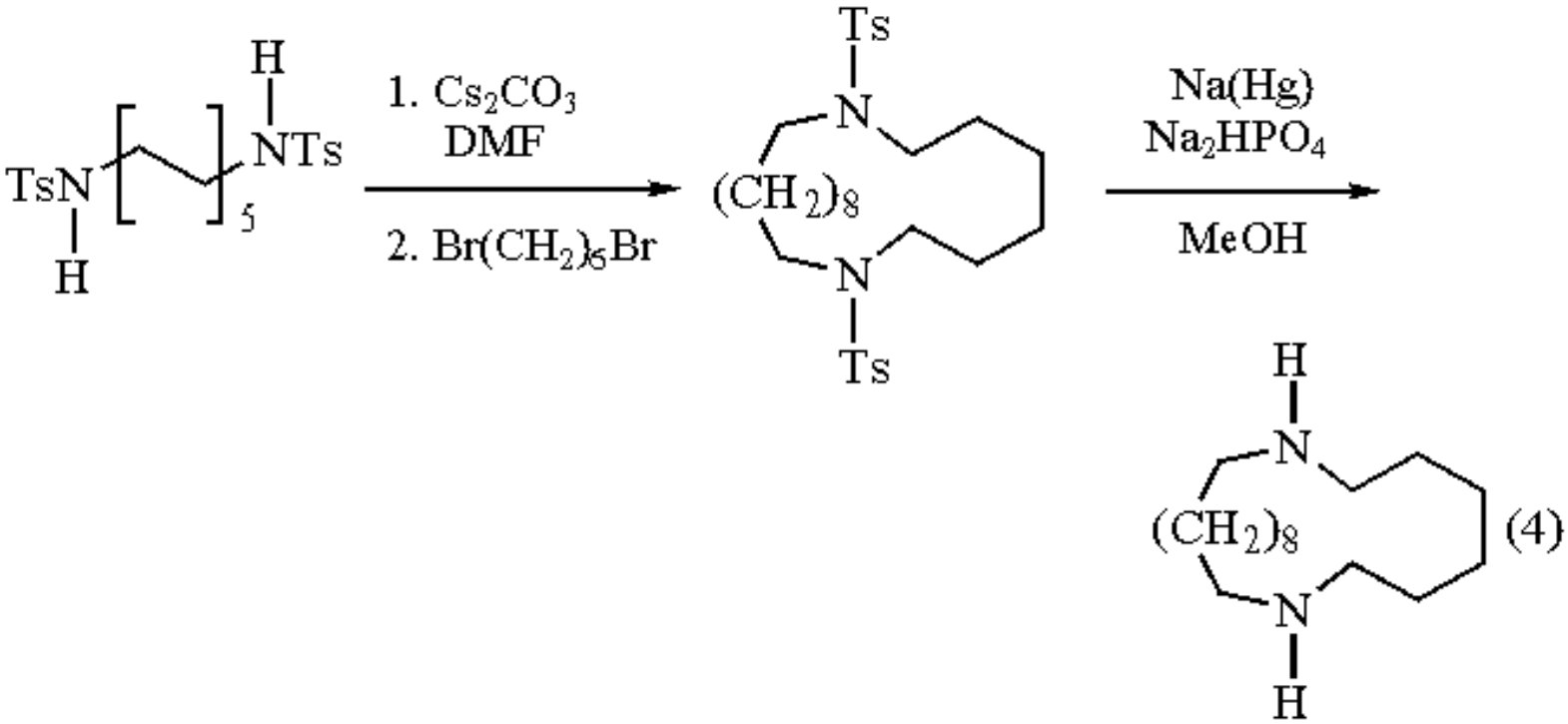

Cs_2CO_3 has been used to prepare derivatized calix[4]arenes for use as lipophilic, water-soluble, and ionophoric receptors.[9] The calix[4]arene cone structure depends on the type of base used for alkylation of the phenolic hydroxyl groups. For example, a cone is generated when NaH is the base during alkylation of the calix[4]arene with ethyl bromoacetate in acetone. When Cs_2CO_3 is used, a 1,3-alternate cone is obtained, whereas a partial cone is formed when K_2CO_3 is used.[9]

Carcerands and carceplexes have been prepared by using Cs_2CO_3. For example, mixing a tetrathiol, a tetrachloride, and pulverized Cs_2CO_3 in DMF/THF under high dilution conditions afforded the carcerand.[10] FAB-MS of the product indicated that the cesium ion served as a template.

Lactonizations can be accomplished using Cs_2CO_3 and o-bromocarboxylic acids at 40 °C in DMF.[4b,11] These conditions afford mixtures of lactones and diolides with their product distribution depending on the ring size. Cs_2CO_3 has been used in a macrocyclization reaction to generate steroids under anionic conditions.[12]

Horner-Emmons Base.

The Horner-Wadsworth-Emmons reaction is sensitive when the carbonyl component contains acidic hydrogens, such as hydroxyl groups. This problem can be circumvented by using Cs_2CO_3 as the base. The method is somewhat dependent on the type of solvent used and the degree of hydration of Cs_2CO_3 (eq 5).[2] NaH has also been replaced with Cs_2CO_3 in a synthesis of D-*erytho*-C_{18}-sphingosine using a Wittig-Horner reaction.[13] A tandem Wittig-Michael reaction in which a lactol is treated with dimethyl phosphonoacetate in the presence of Cs_2CO_3 has been reported (eq 6).[14] An intermolecular Michael addition of a cyclic β-keto ester to an α,β-ynone has been accomplished with Cs_2CO_3 in 89% yield.[15] An intramolecular Diels-Alder reaction using Cs_2CO_3 and paraformaldehyde in THF has been used to produce the neurotoxic toxin slaframine from an amide.[16]

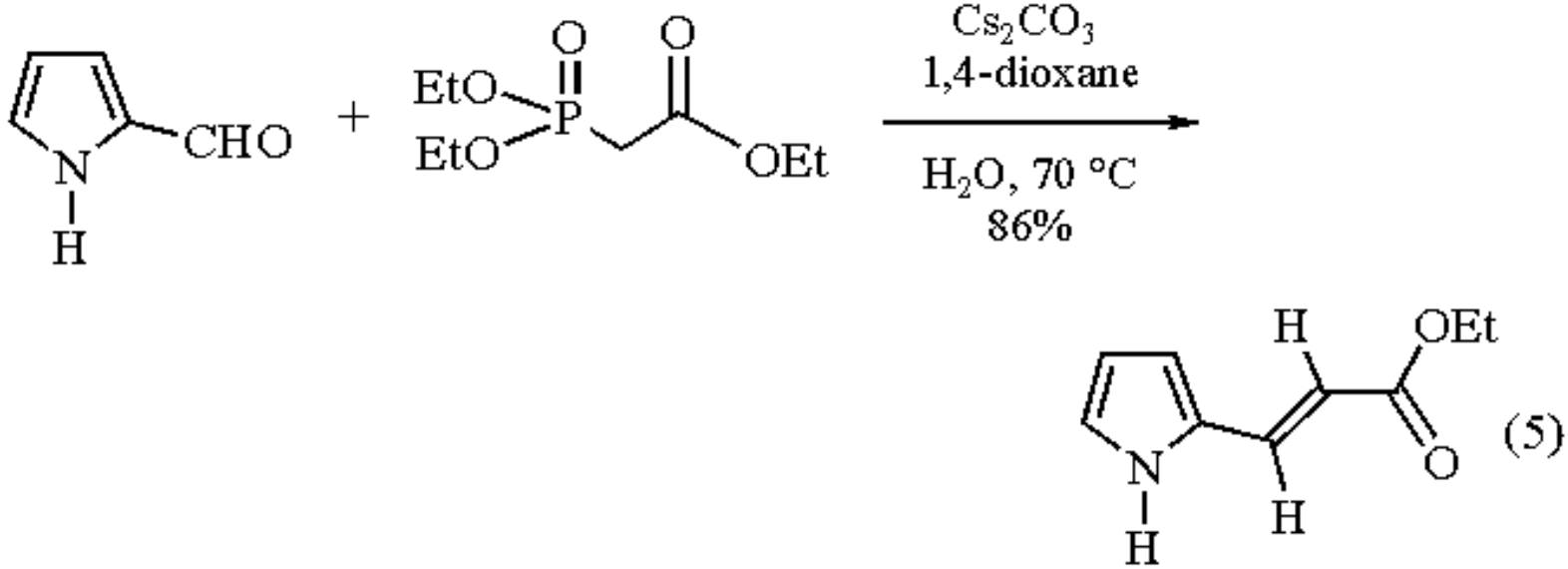

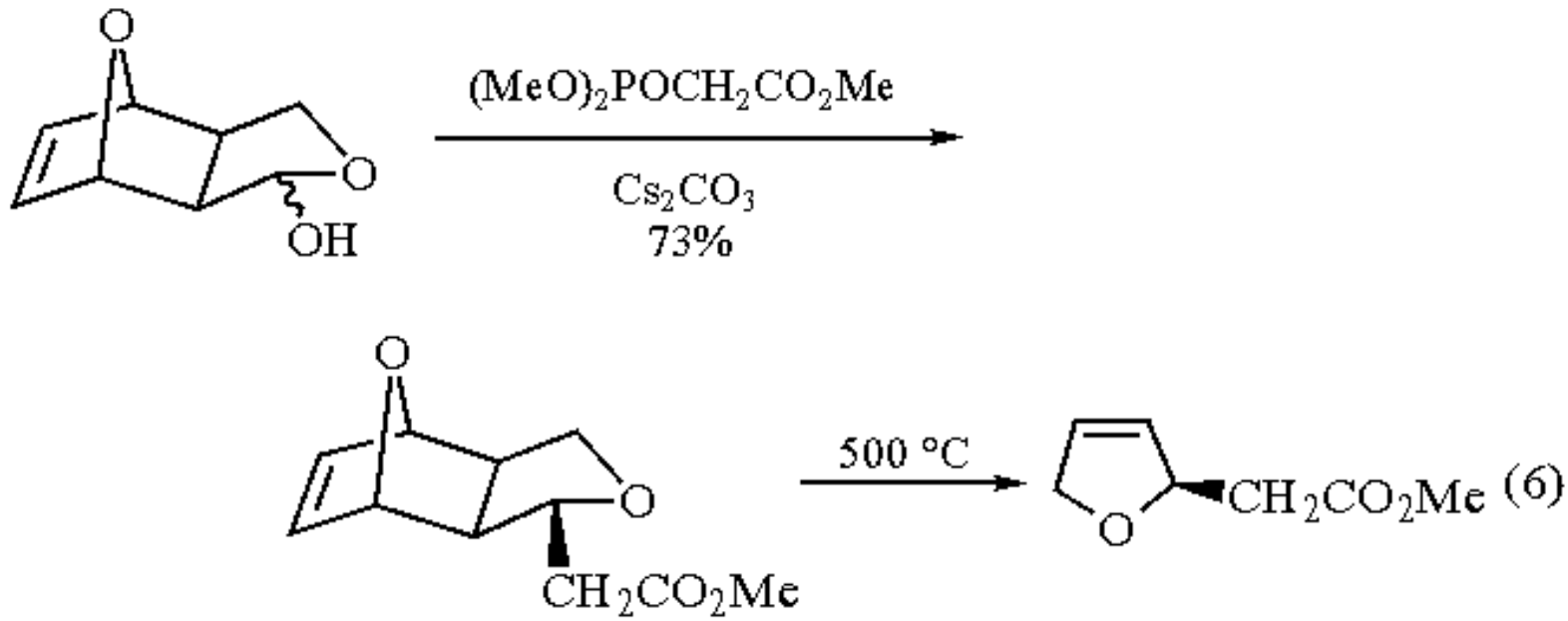

Alykylation Base.

Esterification under mild conditions can be accomplished with Cs_2CO_3 or $CsHCO_3$.[3] For example, amino acid and peptide esters can be made by generating the cesium salt of the corresponding carboxylic acid followed by treating the salt with an alkyl halide in DMF (eq 7).

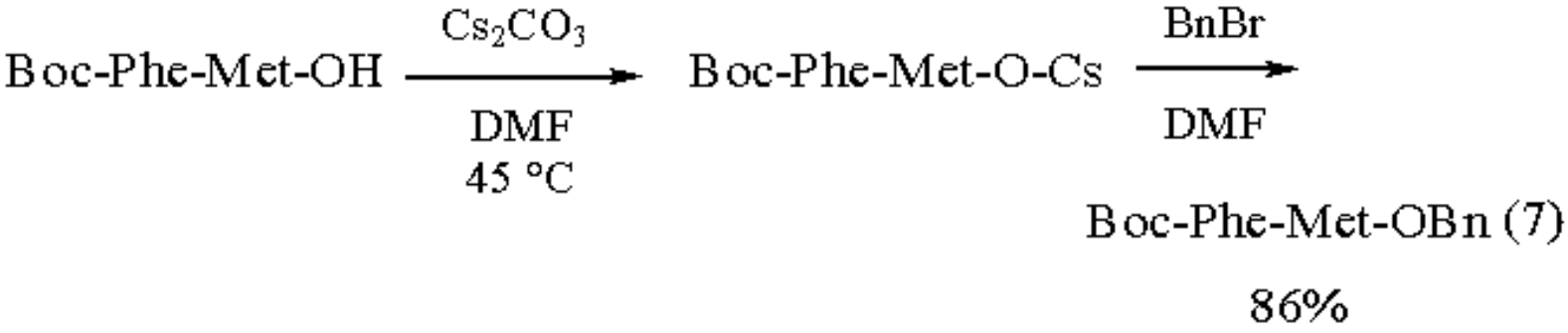

Mono-*C*-alkylation of β-dicarbonyl compounds is complicated by competitive *O*-alkylation and dialkylation reactions.[17] *C*-Alkylation of 2,4-pentanedione has been achieved with ***Iodomethane*** in 75% yield using K_2CO_3 as a base. The use of Cs_2CO_3 by itself, or in combination with K_2CO_3, allows for improved monoalkylation reactions using higher molecular weight alkyl halides (eq 8).[18] Phenolates generated with Cs_2CO_3 are alkylated with ***Dimethyl Sulfate*** in 94% yield.[19]

$$BrCH_2CO_2Et + (MeCO)_2CH_2 \xrightarrow[CH_2Cl_2]{Cs_2CO_3} \underset{92\%}{(MeCO)_2CHCH_2CO_2Et} + \underset{8\%}{MeCOCH{=}CMeOCH_2CO_2Et} + \underset{<1\%}{MeCOC(CH_2CO_2Et){=}CMeOCH_2CO_2Et} \quad (8)$$

Dibenzyl carbonate is prepared in 63-70% yield when Cs_2CO_3 is treated with ***Benzyl Chloride*** at 100-110 °C for 12 h.[20] Cs_2CO_3 has also been used to mediate Michael additions of glycine esters. Treating a Schiff base of glycine and an enone with 10 mol % Cs_2CO_3 gives substituted prolines in 60-78% yield after hydrogenation (eq 9).[21] Replacement of NaH with 5-10 mol% Cs_2CO_3 under standard Schmidt conditions in the preparation of trichloroacetimidates allows for large scale preparation of *O*-α-cellobiosyl trichloroacetimidate heptacetate in good yield.[22]

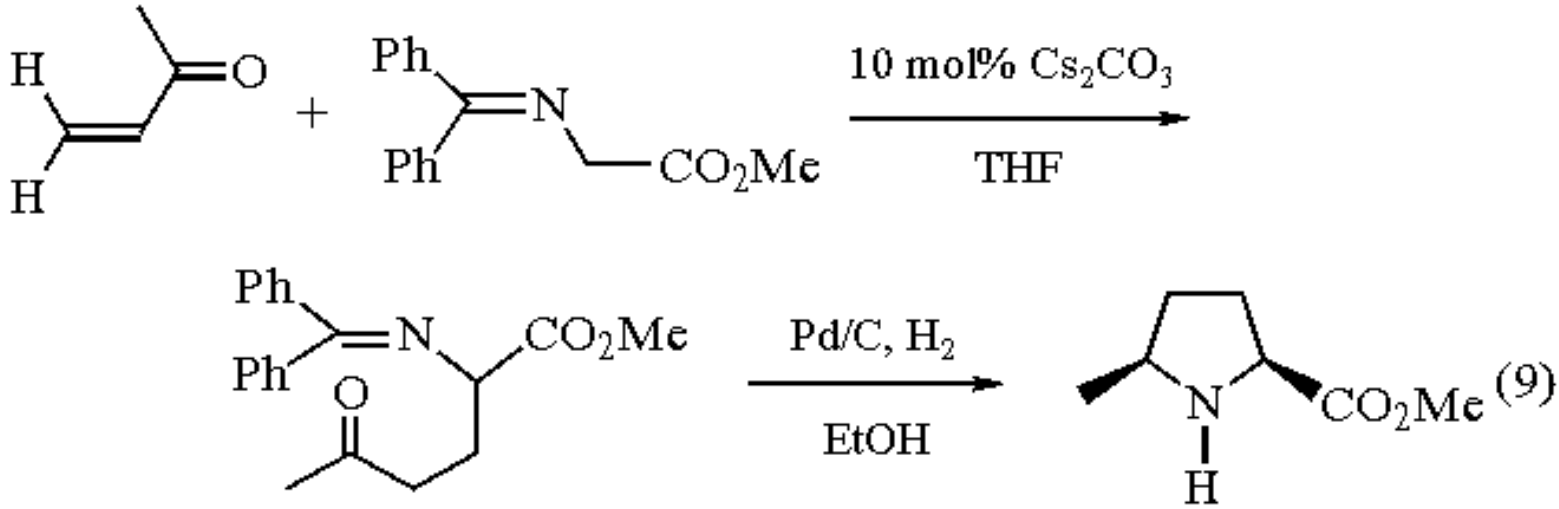

Cleavage of aryl esters has been accomplished using either Cs_2CO_3 or $CsHCO_3$. For example, refluxing resorcinol dibenzoate in DME for 24 h with 1.5 equiv Cs_2CO_3 produces the monobenzoate in greater than 95% yield.[23] Cs_2CO_3 and ***Di-t-butyl Dicarbonate*** cleave 2-oxazolidinones at 25 °C in MeOH to give Boc-amino alcohols in 70% yield (eq 10).[24]

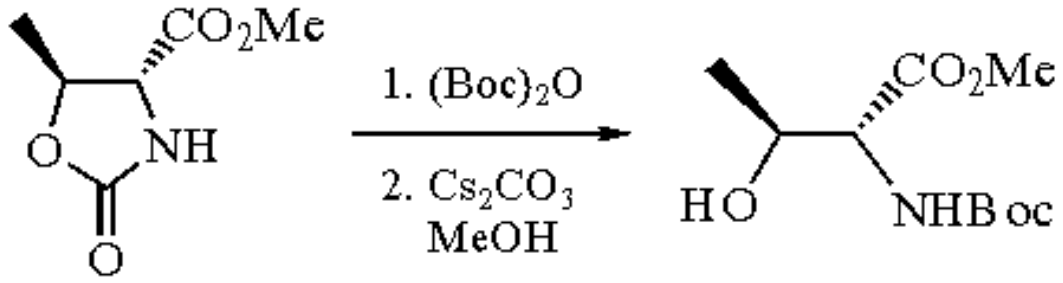

(10)

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Procter & Gamble, Cincinnati, OH, USA

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Cesium Fluoride

CsF

[13400-13-0] · CsF · Cesium Fluoride · (MW 151.90)

(fluoride ion source for removal of silyl protecting groups; reagent for mild desilylative anion and ylide formation; base catalyst; reagent for hydrogen bond-assisted alkylation; reagent for halide exchange)

Physical Data: mp 682 °C; bp 1251 °C; *d* 4.115 g cm^{-3}; refractive index 1.478 (18 °C).

Solubility: sol H_2O and MeOH; insol dioxane, pyridine.

Form Supplied in: white deliquescent crystalline powder.

Purification: dry by heating at 100 °C for 2 h in vacuo.[1]

Handling, Storage, and Precautions: hygroscopic. Keep container tightly closed. Harmful if inhaled or swallowed. Causes irritation of skin, eyes, and mucous membranes and may cause allergic reaction. Incompatible with acids: store away from acids. Use in a fume hood with safety goggles and chemically resistant gloves and clothing.

Catalysis of Condensations of Carbonyl Compounds.

Knoevenagel condensations of cyclohexanone and benzaldehyde with three active-methylene partners have been studied using various fluoride catalysts. Cesium and rubidium counterions lead to higher yields than the less soluble potassium, sodium, and lithium salts.[2] Silyl enol ethers react with aldehydes and ketones with CsF catalysis to form α,β-unsaturated ketones, or with unsaturated ketones by conjugate addition.[3] Trimerization of isocyanates occurs at 130 °C with CsF catalysis, forming aromatic isocyanurates in high yields.[4]

Desilylative Elimination and Carbanion Formation.

Fluoride ion desilylates compounds of the type C-Si, leading to useful carbanion-like reactivity, particularly when appropriate stabilizing substituents are present. When β-substituents are reasonable leaving groups, the expected eliminations occur. These types of reactions, with which water interferes, are particularly amenable to the use of CsF, since CsF can be made anhydrous much easier than the more commonly encountered ***Tetra-n-butylammonium Fluoride***.

Cyclopropenes have been prepared by desilylation of 1,1-dichloro-2-trimethylsilylcyclopropane with CsF in diglyme at 80 °C (eq 1).[5] A similar example of an advantage of CsF (and fluoride ion sources in general) - mild elimination conditions allowing isolation of unstable species - is seen in a synthesis of allene oxides. 1-(*t*-Butyl)allene oxide can be obtained in 55% yield by treating the precursor trimethylsilyloxirane with CsF (eq 2) and trapping the volatile products in a cold trap.[6] Desilylative 1,2-elimination from cyclohexadienes has been used to obtain the interesting benzene isomers 1,2,3-cyclohexatriene and cyclohexen-3-yne, which were trapped in situ by Diel-Alder reactions.[7] Sulfine, sulfene, and alkylsulfenes can be trapped as Diels-Alder adducts after their generation by desilylative 1,2-elimination from trimethylsilylmethanesulfinyl chloride, trimethylsilylmethanesulfonyl chloride, and trimethylsilylalkanesulfonic anhydrides, respectively.[8]

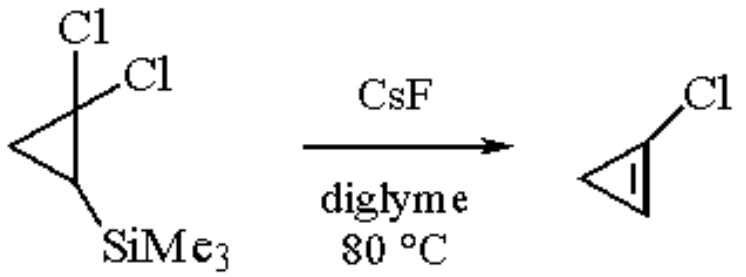

(1)

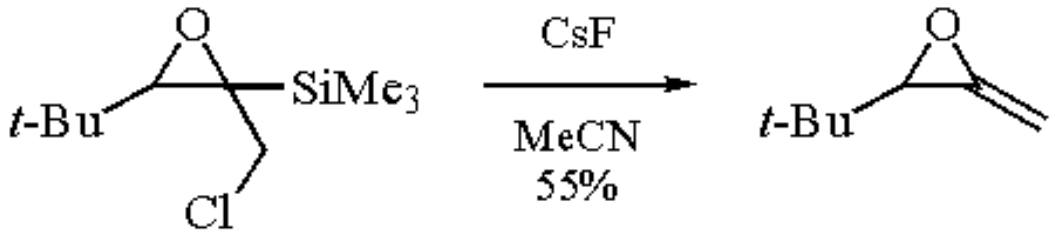

(2)

CsF-induced 1,4-elimination produces xylylene intermediates which undergo intramolecular cycloaddition with an alkene (eq 3).[9] Similar 1,4-elimination/Diels-Alder strategies have been used in the synthesis of other targets,[10] and in a cyclodimerization to give the bisthioacetal of [2,3:6,7]dibenzo-1,5-cyclooctanedione.[11]

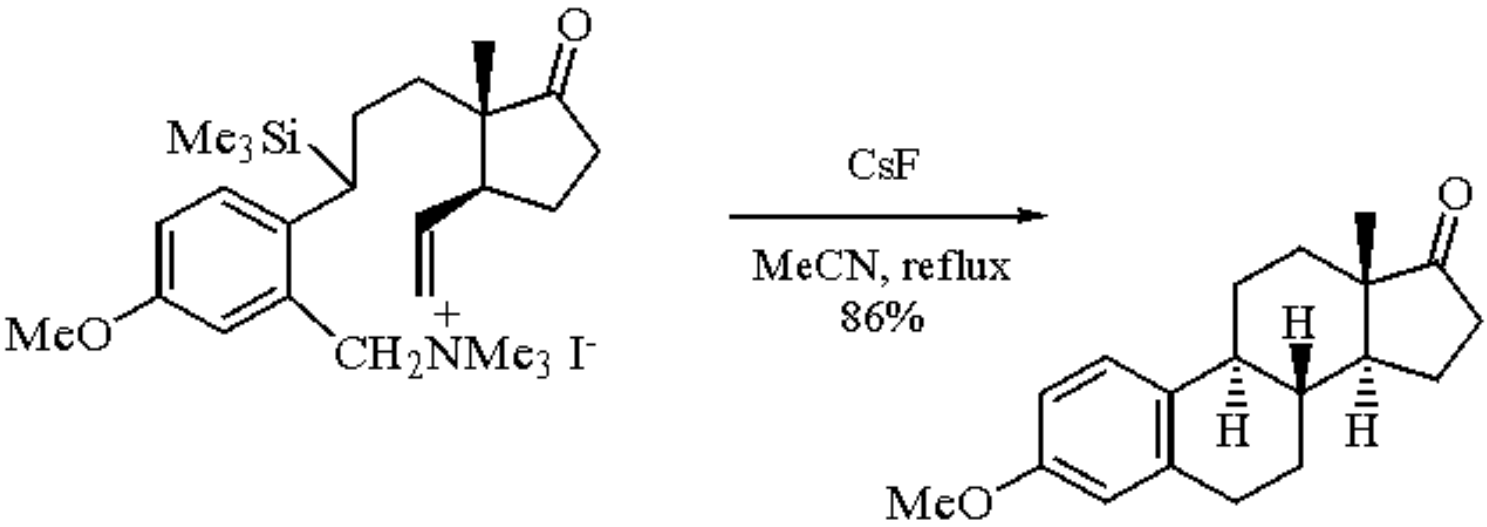

(3)

Stereoselective synthesis of 1,4-dienamine derivatives is achieved by CsF-induced desilylative ring-opening of tetrahydropyridinium salts. The diene is produced selectively as the (*Z*,*E*) diastereomer (eq 4). The authors contrast this behavior with that of an analogous tetrahydropyridine *N*-oxide, which undergoes spontaneous sila-Cope rearrangement to give the (*Z*,*Z*) diastereomer (eq 5).[12]

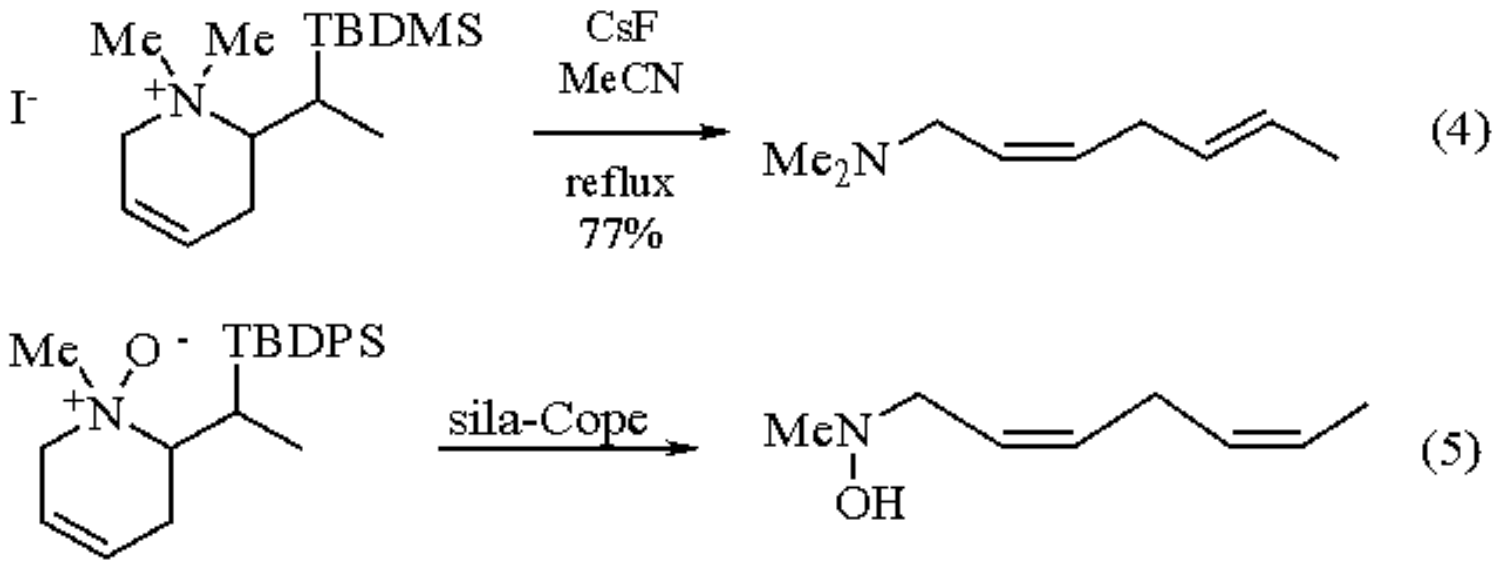

Numerous desilylative reactions of trimethyl(α-bromobenzyl)silanes with electrophiles are induced by CsF (eq 6).[13]

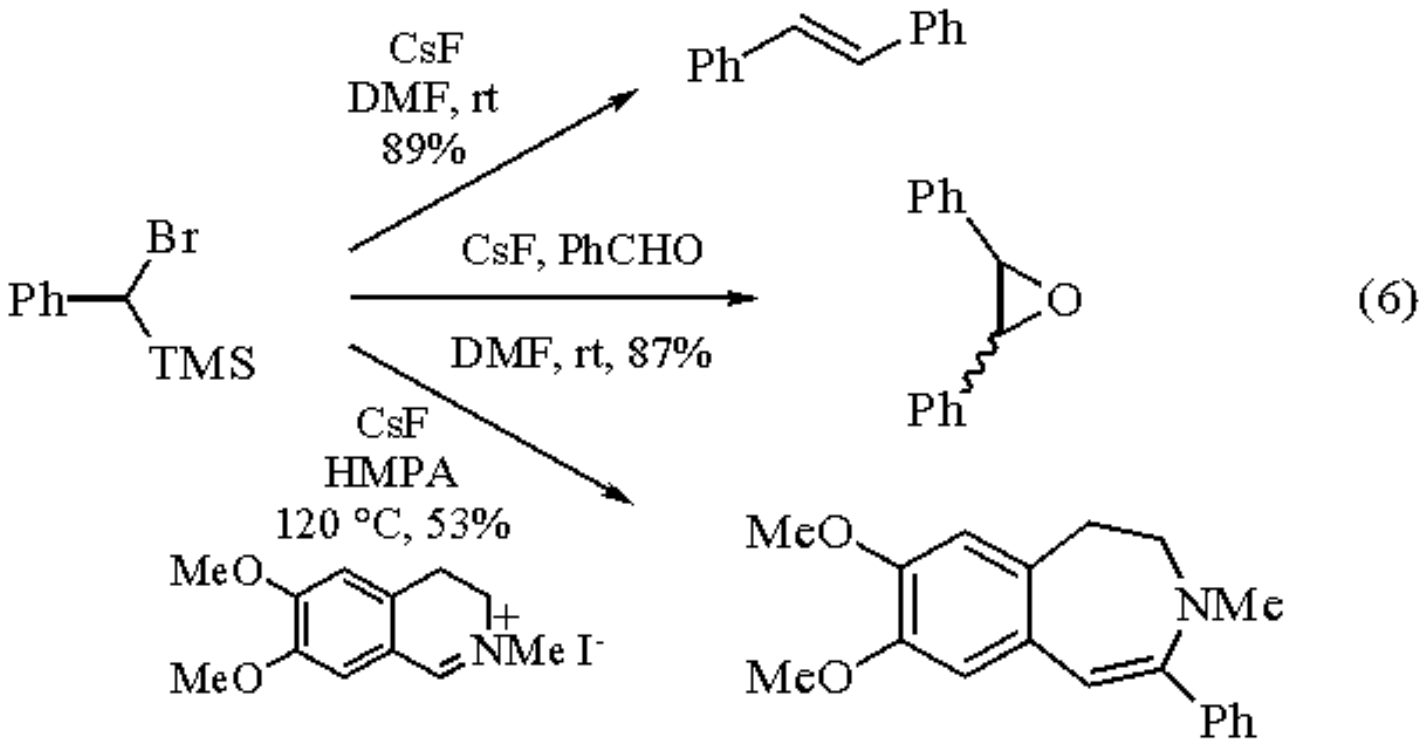

Acyl-, alkynyl-, benzyl-, allyl-, oxiranyl-,[14] heteroaryl-,[15] trichloromethyl-,[16] aryl-,[17] β-keto-,[18] β-sulfonyl-,[19] and cyclopropylsilanes[20] are useful carbanion precursors. When treated with CsF or other fluoride salts, they undergo desilylative addition to carbonyl compounds, including CO_2, aldehydes, ketones, and lactones; *C*-alkylation with ***Benzyl Bromide*** also can occur (eqs 7-11). Conjugate addition is also observed; nitroalkenes give 1,4-addition products, and reaction of allylsilane with cyclohexenone in the presence of CsF gives the 1,4-addition product selectively, whereas the presence of tetrabutylammonium fluoride leads to diallylated product.[21]

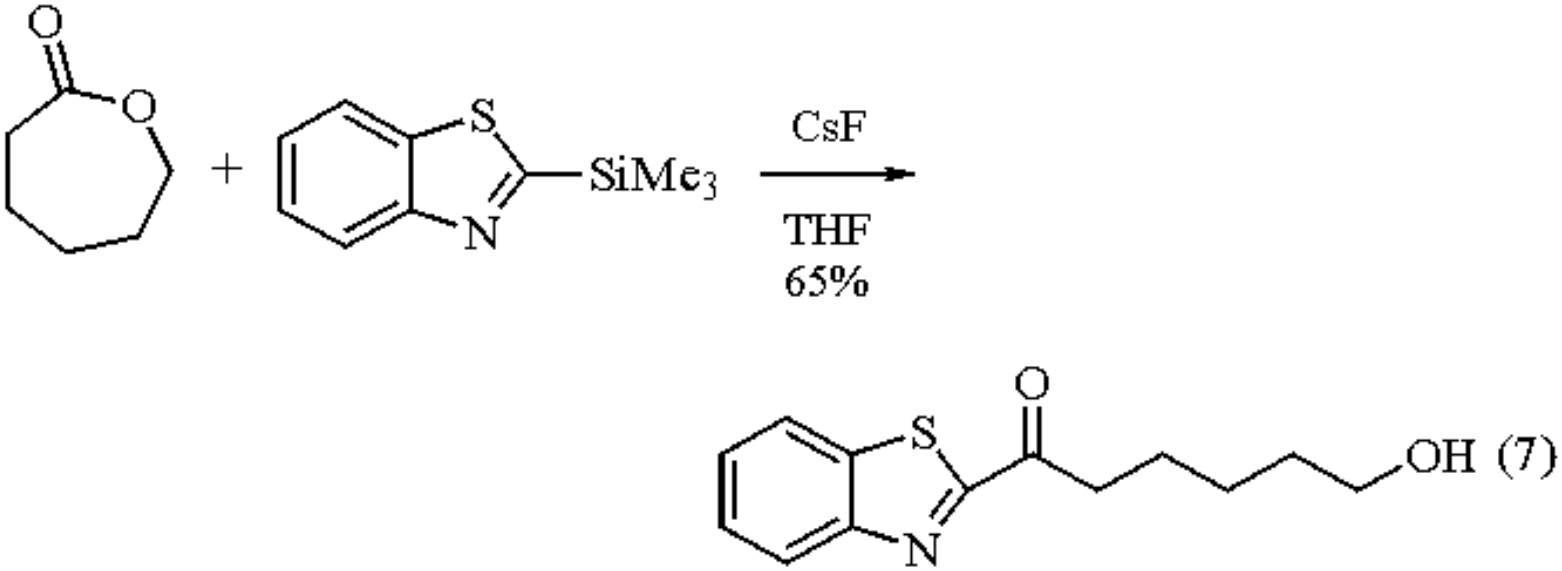
CsF
THF
65%
SiMe3
OH

(7)

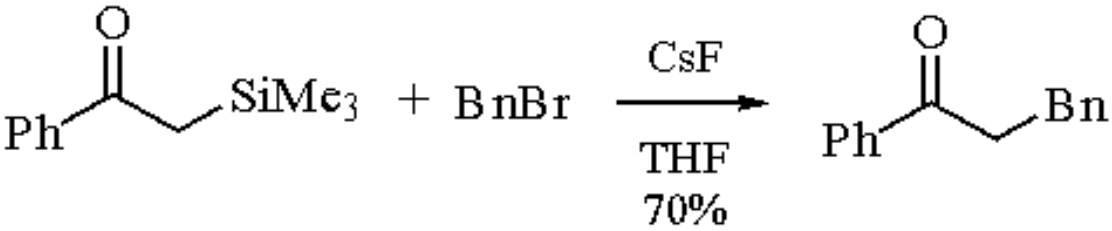
Ph
SiMe3
BnBr
CsF
THF
70%
Bn

(8)

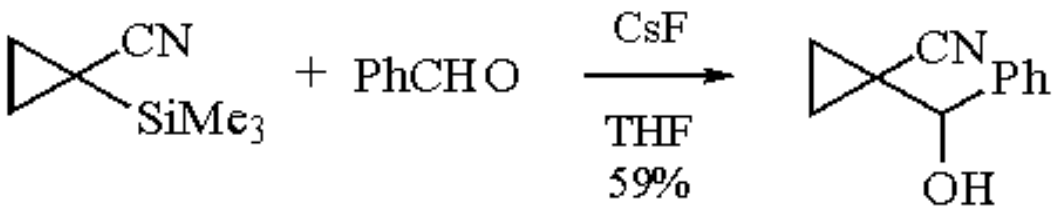
CN
SiMe3
PhCHO
CsF
THF
59%
CN
Ph
OH

(9)

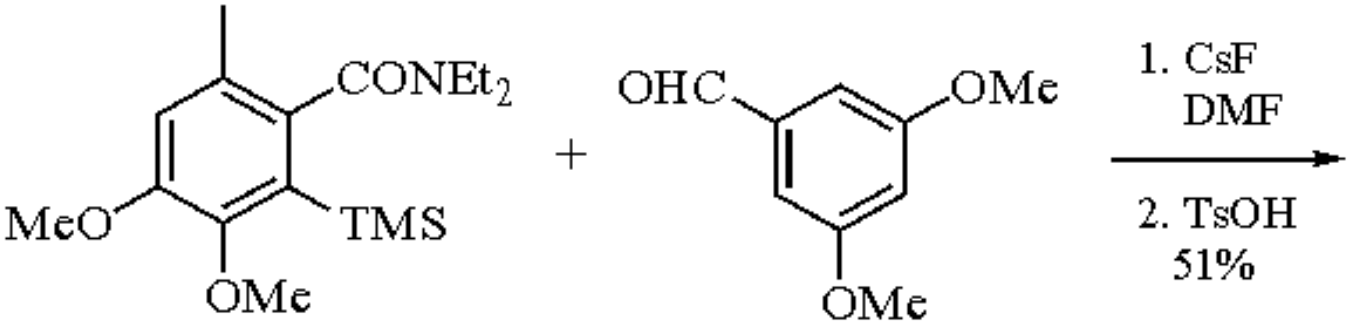

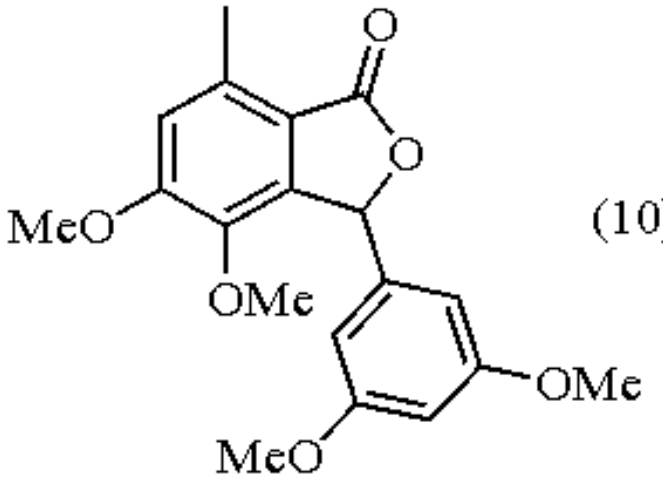

(10)

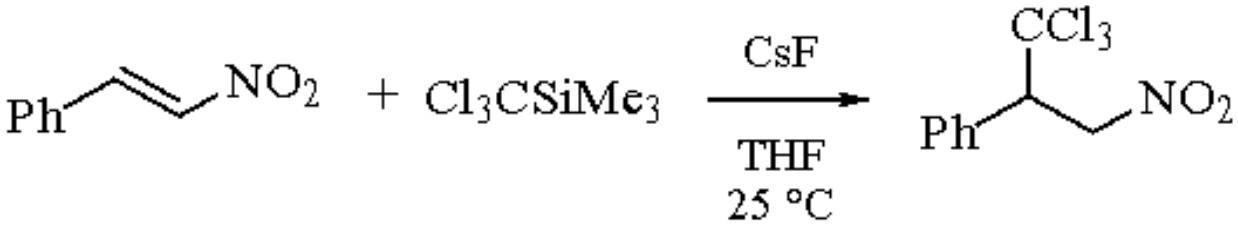

(11)

Cyclization of a carbanion produced by desilylation with CsF leads to 1,3-thiazolidines (eq 12).[22]

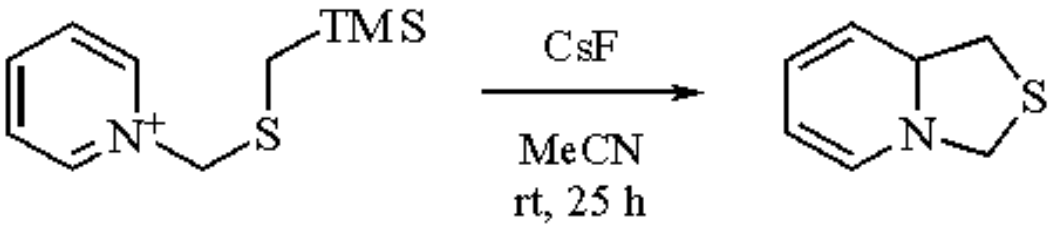

(12)

Anionic reactivity remote from the silyl bond cleavage site is observed when ketene bis(trimethylsilyl) acetals or α,β-unsaturated ketene bis(trimethylsilyl) acetals are treated with CsF and an aldehyde.[23] Complementary regioselectivity occurs with ***Titanium(IV) Chloride*** (eq 13).[24]

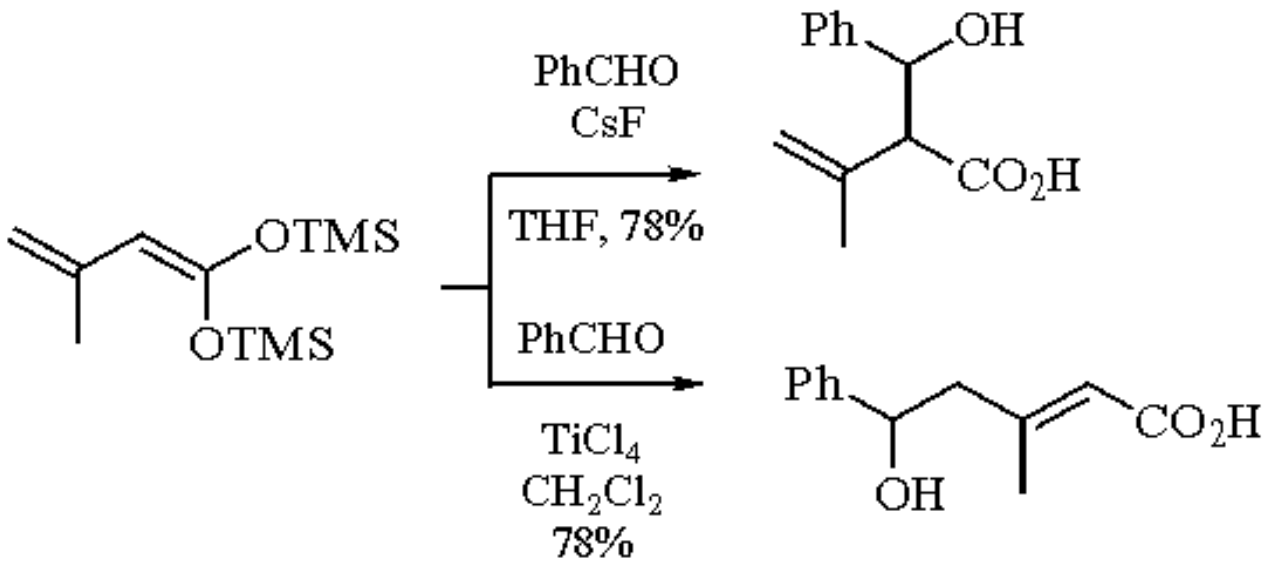

(13)

A novel method for the production of thiiranes from carbonyl compounds involves desilylation with CsF (eq 14).[25]

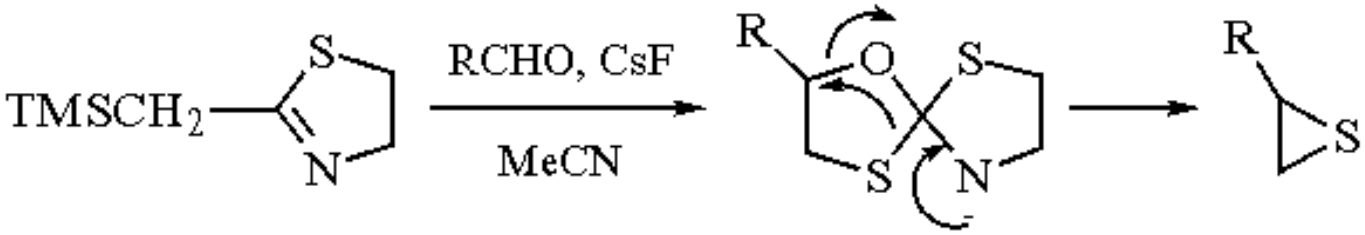

(14)

Stannyl Anion Generation.

By treatment of (trimethylsilyl)tributylstannane with CsF, a stannyl anion is formed. This method was used to achieve intramolecular reaction of a vinyl iodide with an ester, forming a spirocyclopentenone, which reacted further with the tributylstannyl anion under the reaction conditions (eq 15). Four subsequent steps completed a formal total synthesis of acorone.[26]

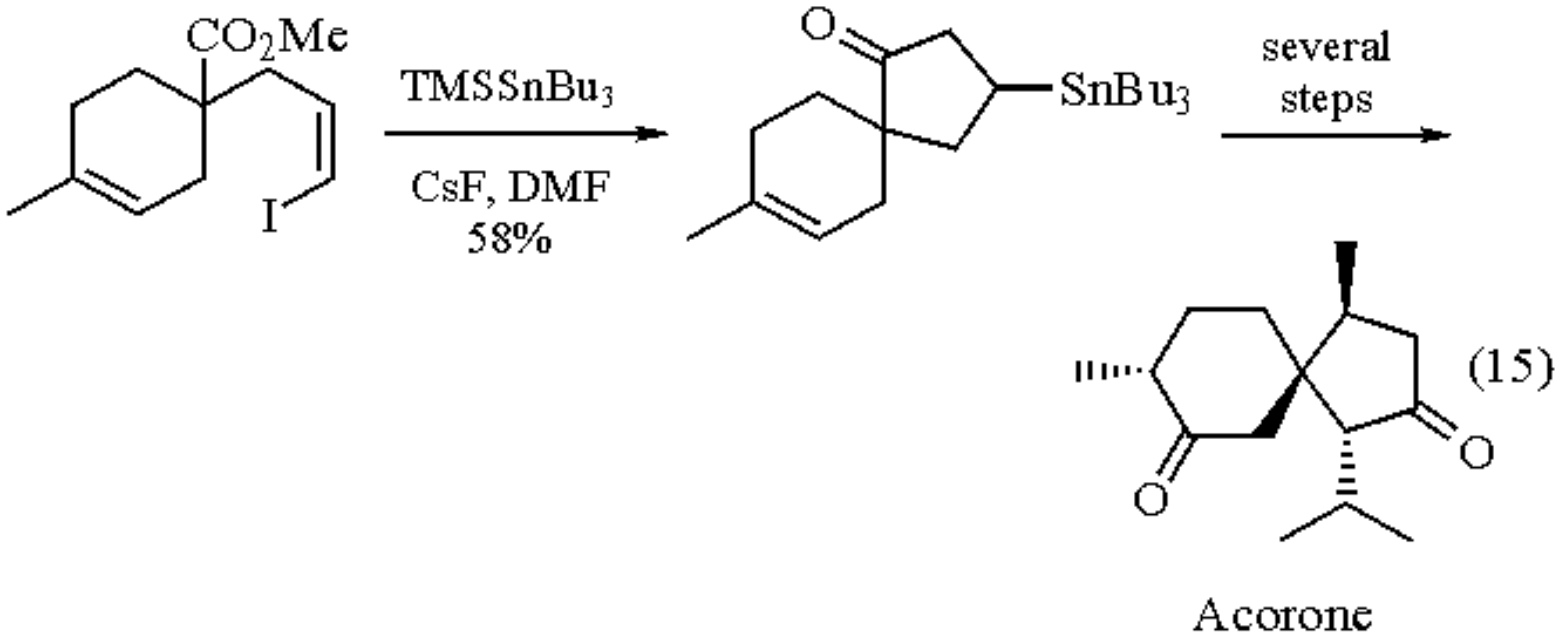

Ylide Formation.

Wittig reaction of a phosphonium salt with benzaldehyde is observed with CsF in DMF.[27] Similarly, CsF can be used to carry out Horner-Wadsworth-Emmons reactions.[28] Sulfonium, ammonium, and phosphonium ylides can be obtained by desilylation.[29] This ylide formation strategy has been used in a synthesis of the retronecine skeleton.[30]

Acylation and Transesterification.

Esters, amides, and thioesters are obtained in high yields under neutral conditions when the carboxylic acid is treated with the appropriate protic nucleophile, 1-ethyl-2-fluoropyridinium tetrafluoroborate, and CsF in methylene chloride (eq 16). *p*-Nitrophenyl esters of optically pure *N*-phthaloylamino acids are converted to methyl esters in MeOH/CsF without the racemization observed when triethylamine is employed.[31]

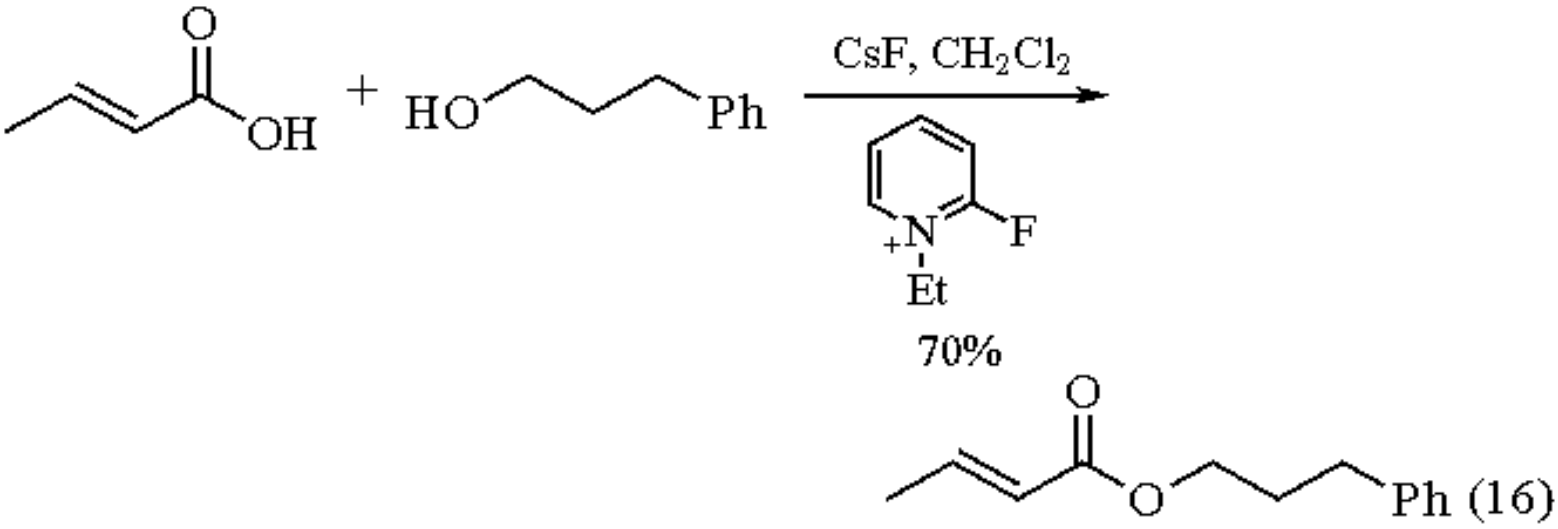

Acylations of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in quantitative yields are achieved with acyl fluorides and CsF

(eq 17). High ratios of either anomeric product can be obtained by changing the order of addition of the reagents.[32]

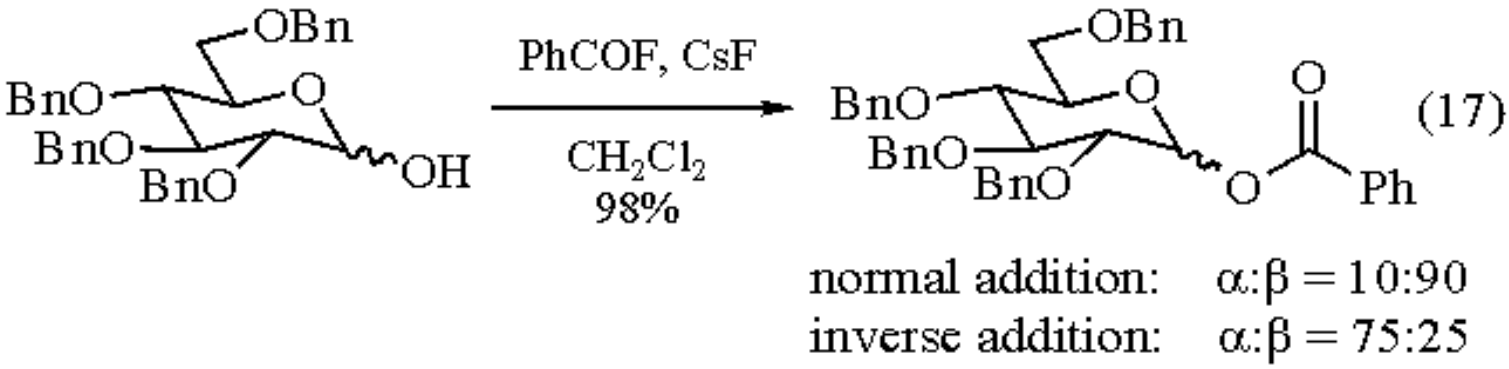

.

Phosphate esters can be transesterified in alcohols containing excess CsF.[33] This method has been used to advantage in the regioselective protection of hydroquinones by phosphorylation in the presence of CsF.[34] Ribooligonucleotides have also been synthesized by this approach.[35]

Acylation of alcohols is very efficient with acylthiazolidine-2-thiones and CsF in warm DMF. Benzyl 3-phenylpropionate was obtained in 99% yield by this method (eq 18).[36]

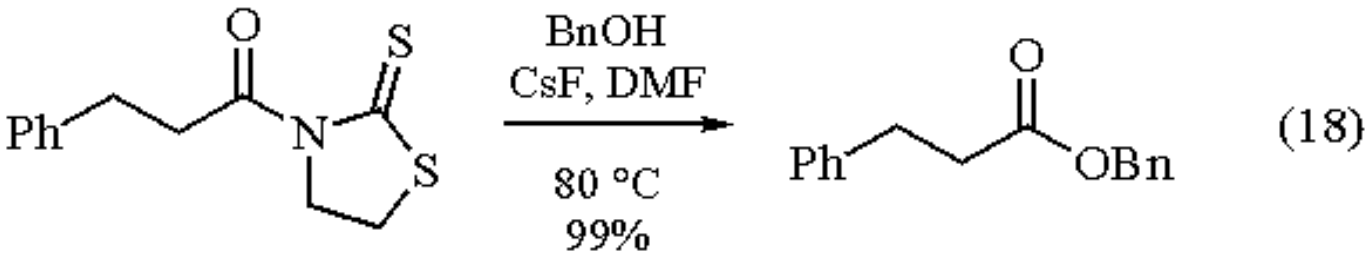

Hydrogen Bond-Assisted Halide Displacements.

Treatment of catechols with CH_2Cl_2 in the presence of CsF results in high yields of methylenated products (eq 19) with little competition from intermolecular condensations.[37] Hydrogen bonding of the catechol with fluoride has been demonstrated, and is thought to be responsible for the facilitation of the reaction. Numerous other H-bonding substrates are also alkylated more readily under the influence of fluoride (eq 20).[38] This alkylation promotion by CsF obviates prior conversion of phthalimide to its alkali metal derivative for use in the Gabriel synthesis (eq 21).[39] CsF leads to an order of magnitude in rate enhancement relative to ***Potassium Fluoride*** in some cases, although the higher expense of CsF may negate this advantage.

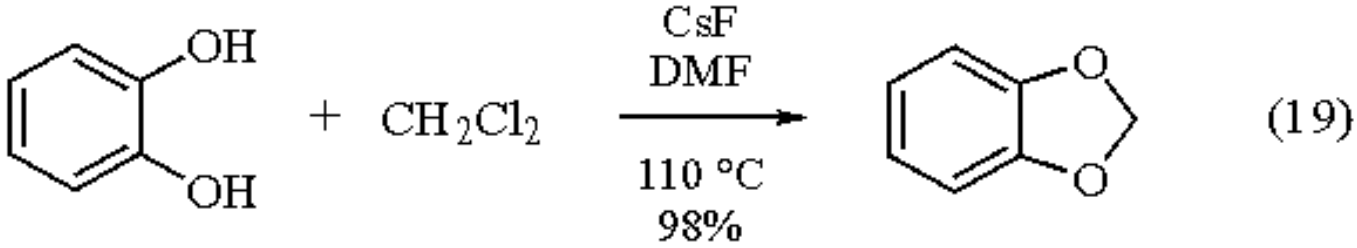

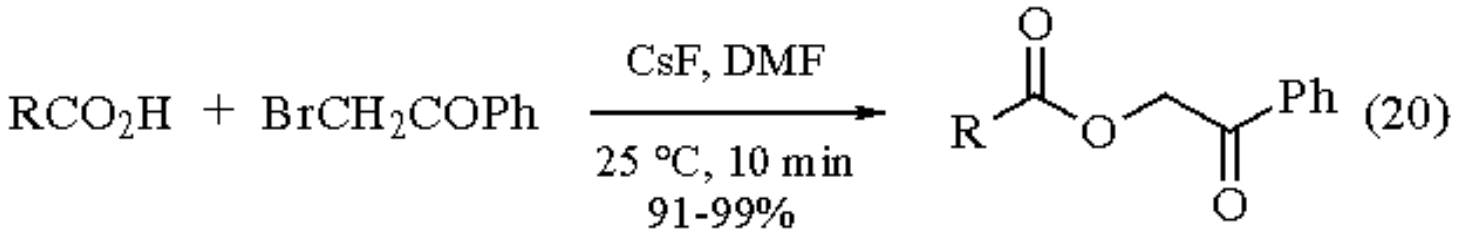

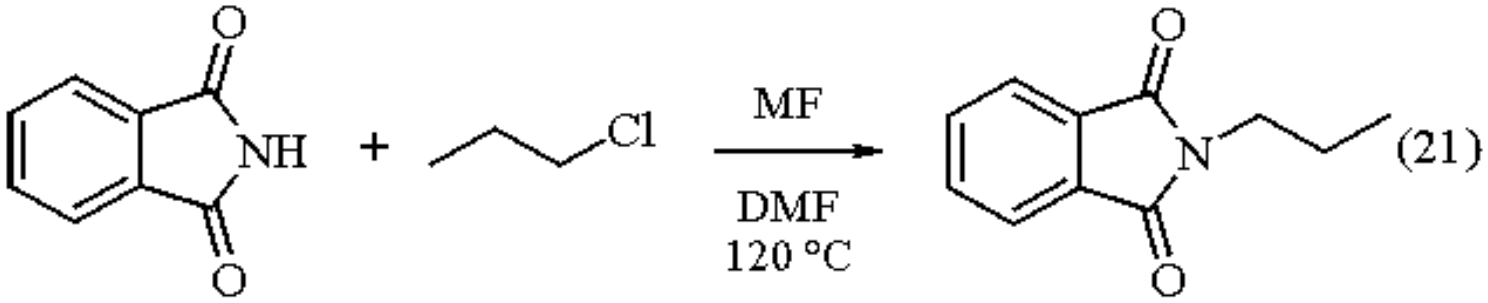

M	Time (h)	Yield (%)
K	4	73
Rb	1	82
Cs	0.2	82

1,2-Cycloalkanediols can also be methylenated under analogous conditions.[40] Glycols can be monoalkylated by treatment of their stannylene acetals with alkyl halides. CsF considerably improves the yields of these reactions.[41] Thus the dibutylstannylene acetal of dimethyl L-tartrate was monoalkylated with benzyl iodide and CsF in DMF at room temperature in 99% yield (eq 22), whereas the reaction without CsF required elevated temperatures and gave only a 13% yield. This method has recently been applied in syntheses of lepidimoide[42] and *myo*-inositol phosphates.[43] In a related reaction, glycol xanthates react with alcohols in the presence of CsF to provide monoalkylated glycols as a key step in syntheses of xylofuranosides.[44] Phosphoric acid alkylation by alkyl halides is catalyzed by CsF.[45] Several macrocyclic crown ethers have been prepared by reaction of ditosylated half-crowns with diol half-crowns in the presence of CsF.[46]

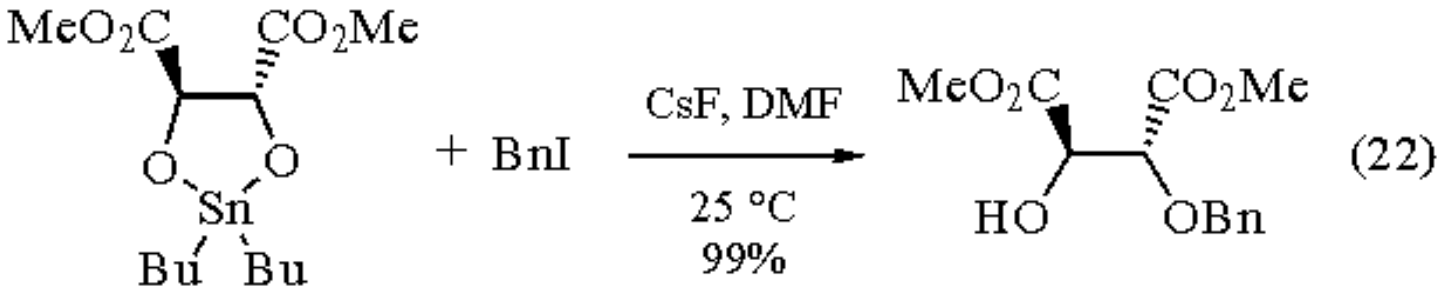

Synthesis of Acid Fluorides.

Organic halides can be converted to acid fluorides by metal-catalyzed (M = Pd, Pt, Co, Rh) carbonylation in the presence of fluoride salts (eq 23). CsF is superior to fluorides with other counterions.[47]

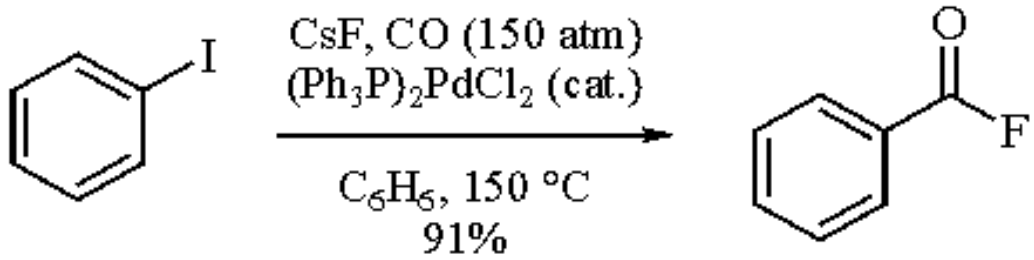

(23)

Preparation of Alumina-Supported Fluoride Reagents.

Mixing of aqueous CsF or KF with alumina followed by drying gave an effective base catalyst.[48] Its preparation was optimized by testing the activity in promoting Michael addition of nitroethane to buten-2-one and methylation of phenols with MeI.

Activation of Si-X Bonds.

Silicon-hydrogen, -oxygen, and -nitrogen bonds are activated by fluoride ions under heterogeneous conditions. ***Triethoxysilane*** is a mild, efficient and highly selective reducing agent in the presence of CsF, leading to quantitative yields of 1,2-reduction products from enones (eq 24). Other bifunctional compounds also can be reduced with quantitative regioselectivity.[49]

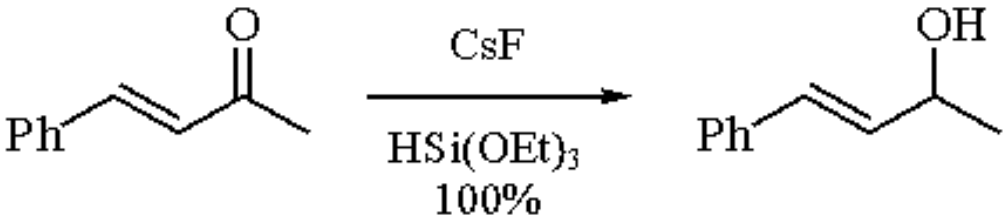

(24)

A system of CsF and $Si(OR)_4$ effects selective 1,4-addition in condensation of ketones with activated alkenes in good yield (eq 25). A silyl enol ether is formed in situ via reaction of CsF-activated $Si(OR)_4$ with the ketone.[49] This system has also been used to effect 1,4-addition to unsaturated amides.[50] Although bis(silyl)enamines undergo sluggish reaction, if any, with various electrophiles, the presence of CsF or tributylammonium fluoride allows high-yielding reactions with carbonyl compounds to afford 2-aza-1,3-dienes (eq 26).[51]

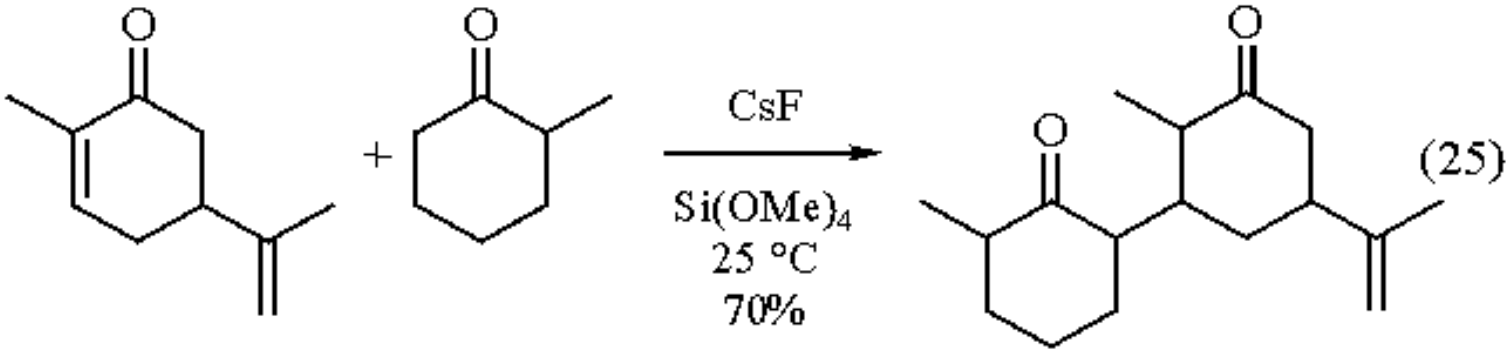

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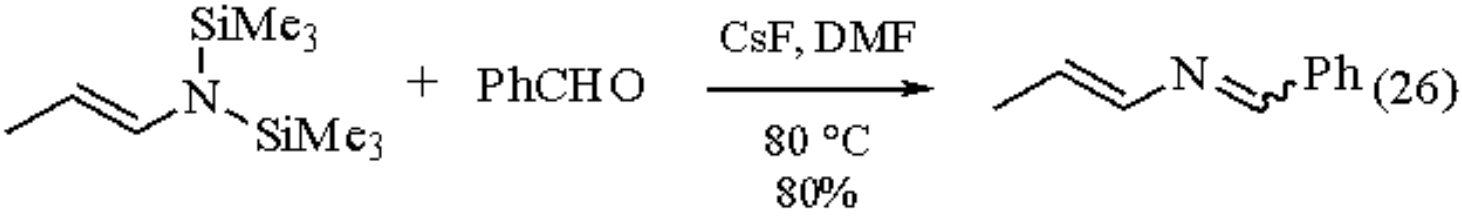

Benzostabase Protecting Group.

Aromatic and aliphatic primary amines have been protected as their benzostabase derivatives in high yield by heating with 1,2-bis(dimethylsilyl)benzene and CsF in polar aprotic solvents (eq 27).[52]

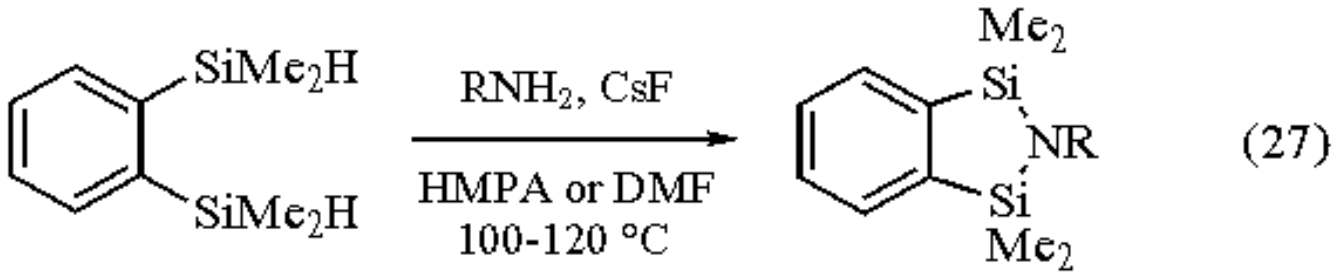

Desilylation of *O*-Silyl and *N*-Silyl Compounds.

O-Silyl compounds serve frequently as protecting functionalities in organic synthesis. CsF is sometimes used for cleavage of these Si-O bonds, but usually has no advantage over the more commonly used tetrabutylammonium fluoride. Cleavage of O-Si bonds with CsF has been used in the preparation of cesium selenocarboxylates.[53] CsF can be used to cleave *N*-trimethylsilyl groups from amides[54] and carbodiimides.[55]

Fluorodemetalation of Organogermanium, -tin, -lead, and -boron Compounds.

Cesium fluoride can be used to cleave C-M bonds; evidence for an associative mechanism in this process has been obtained.[56] Similar reactivity is observed in the reaction of organotin carboxylates and stannyl ethers with CsF and alkyl halides; the O-Sn bond is converted to O-C.[57] A borane-amine complex has been decomposed to the free amine by refluxing with CsF in Na_2CO_3/EtOH.[58]

CsF-Mediated Claisen Rearrangement.

Aryl propargyl ether Claisen rearrangement leads to an intermediate allene which undergoes intramolecular capture by the concurrently formed phenol to give a pyran or a furan. A comparison of the effects of various salts on the regioselectivity revealed that CsF promotes the furan formation, despite the fact that *both* CsCl and KF promote pyran formation. The reaction also was applied in a synthesis of chelerythrine (eq 28).[59]

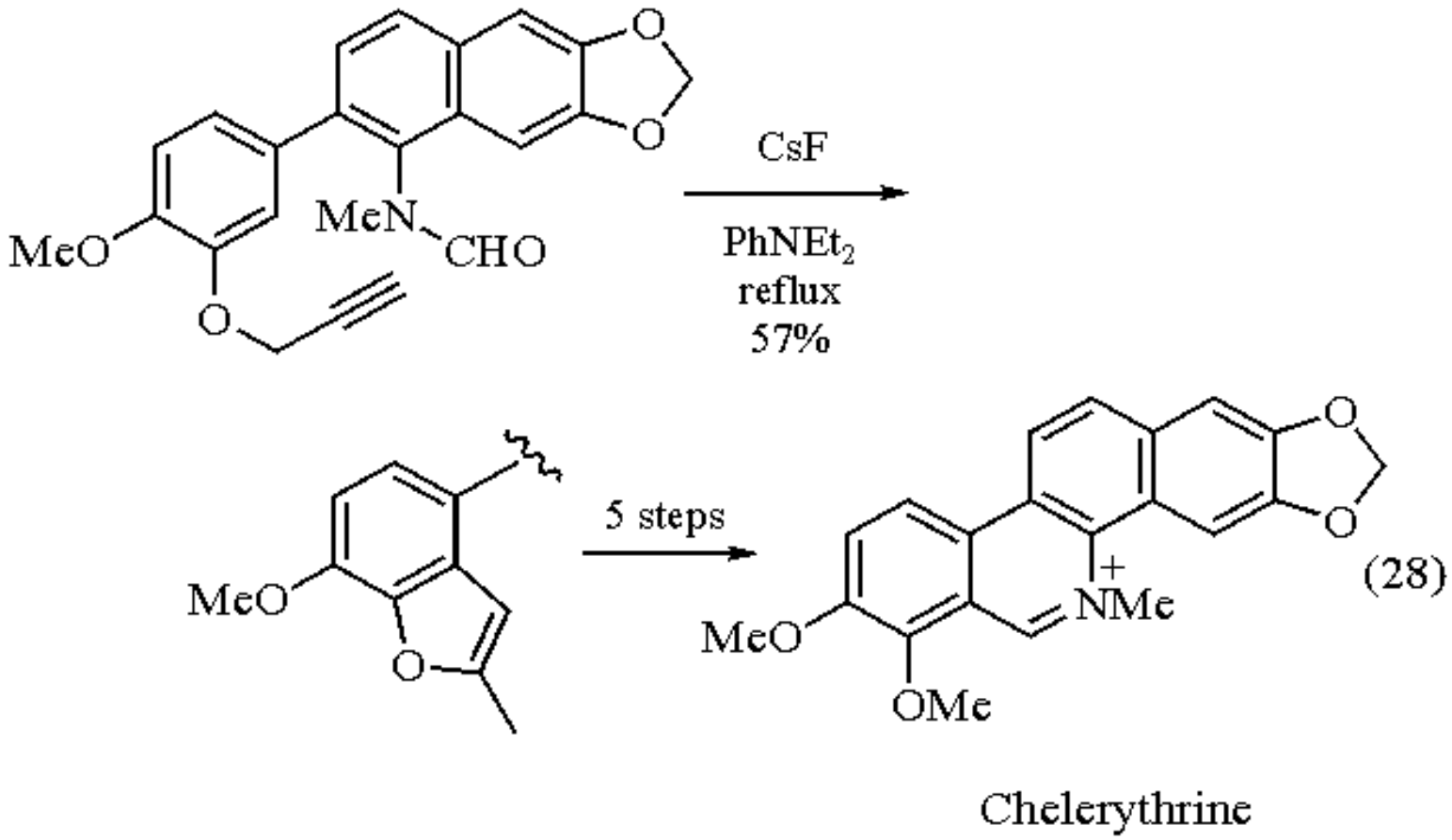

Alkyl Fluoride Synthesis.

n-Octyl fluoride has been made in 77% yield (along with 15% of *n*-octane) by treatment of *n*-octyl bromide with CsF and catalytic NBu_4Br at 85 °C.[60]

Related Reagents.

Diphenylsilane-Cesium Fluoride; ***Phenylsilane-Cesium Fluoride***; ***(Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride***.

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Cesium Fluoroxysulfate

$CsOSO_2OF$

[70806-67-6] · $CsFO_4S$ · Cesium Fluoroxysulfate · (MW 247.96)

(mild fluorinating agent capable of electrophilic addition to C=C bonds[1-3] and fluorofunctionalization of saturated hydrocarbons,[4,5] aromatics,[6-10] ketones and β-diketones,[11,12] enol acetates,[2,3,11,12] organosilicon[11] and organotin[13,14] derivatives, etc.)

Solubility: insol cold water; gives 0.07 M soln in acetonitrile.

Analysis of Reagent Purity: iodometric titration.[15]

Preparative Method: the reagent can be readily prepared from dilute fluorine and Cs_2SO_4: fluorine (20% mixture with nitrogen) was passed into Cs_2SO_4 in a polyethylene vessel with cooling to -4 °C. The yellowish-white precipitate is centrifuged, washed with a little water, and dried in vacuo.[8,15]

Handling, Storage, and Precautions: the synthesis of up to 200 g of $CsOSO_2OF$ has been described.[8] The reagent is easily handled, provided due care is taken not to cause detonation: avoid mechanical pressure (sharp strikes), any contact with a metallic spatula,[15] and do not heat. A protective shield should always be used. The reagent has been stored in a polyethylene vessel at 0 °C for 14 days without significant loss of activity.[8]

Fluorination.

The main result of $CsOSO_2OF$ reactions with various organic substrates is electrophilic fluorination, the hypofluorite moiety in the anionic fragment $FOSO_2O^-$ serving as the F^+ synthon.

Unsaturated compounds react readily with $CsOSO_2OF$ (**1**) to yield products of addition, of addition with incorporation of solvent or external nucleophile, and of addition-elimination, depending on the reaction conditions. The reactions of (**1**) with alkenes gives 1,2-addition products (**2**), which can be conveniently transformed into ethyl sulfates (**3**) by treatment with $Et_3O^+BF_4^-$ (eq 1).[1] The same reaction in the presence of methanol (rt, CH_2Cl_2) gives β-methoxyalkyl fluorides (**4**). Analogously, reactions in AcOH and HF give vicinal fluoroacetates (**5**) and difluorides (**6**), respectively (eq 2).[2,3] In some cases the reaction proceeds to give vinyl fluorides (**7**) (eq 3). For example, interaction of 1,1-diphenylethylene with (**1**) gives 2-fluoro-1,1-diphenylethylene.[2] Fluorination of norbornene gives a 1:1 mixture of 2-fluoronortricyclene and 7-*syn*-fluoronorbornene.[2]

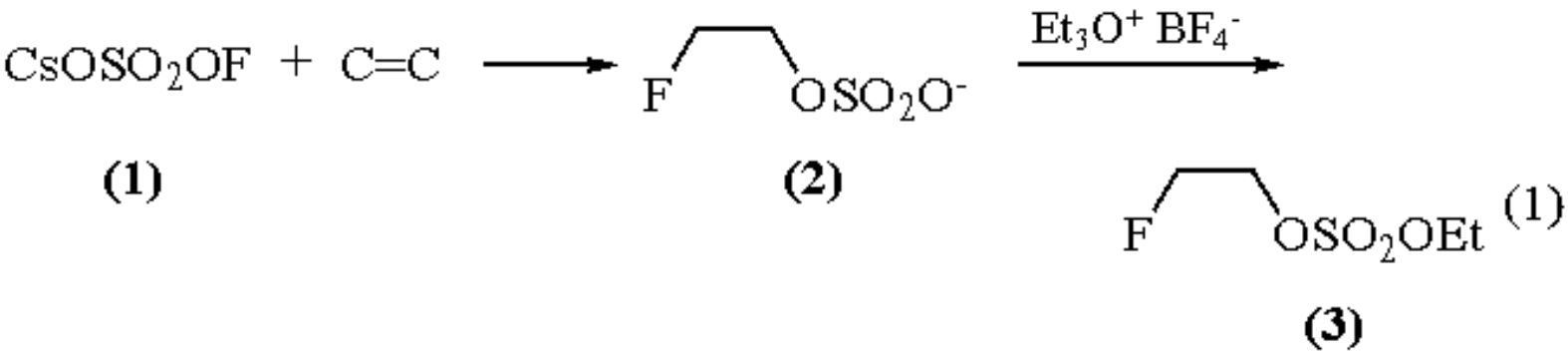

(1)

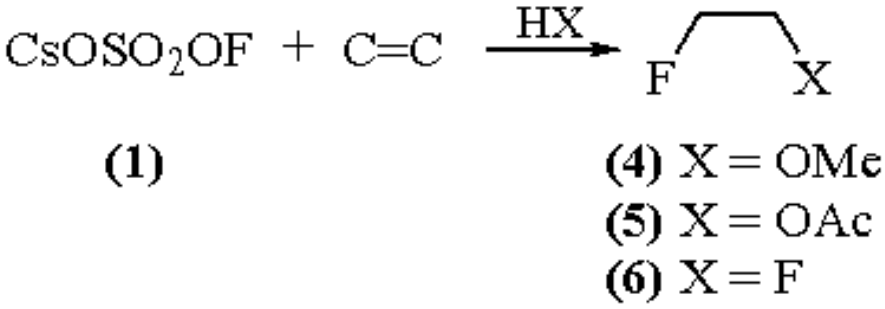

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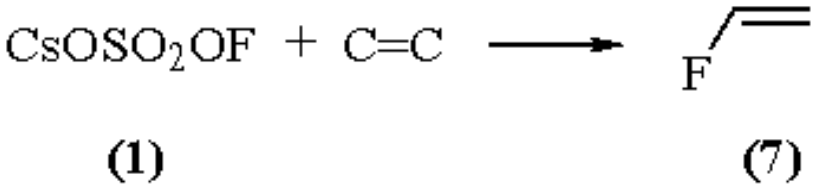

(3)

Reaction of the reagent (**1**) with 1,2-diphenylacetylene in methanol gives a mixture of 1,1-difluoro-2,2-dimethoxy-1,2-diphenylethane and 2,2-difluoro-1,2-diphenylethanone.[16]

Aromatic and aliphatic aldehydes react with $CsOSO_2OF$, giving acid fluorides in good yields, presumably via radical pathways (eq 4).[4]

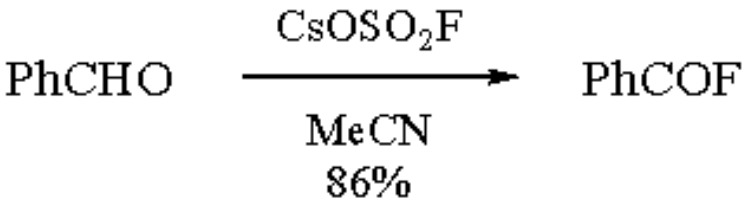

(4)

Room temperature fluorination of cyclic enol acetates by (**1**) gives α-fluorocycloalkanones in high yield (70-90%).[2] β-Diketones and barbituric acid give the corresponding *gem*-difluorinated derivatives.[11,12] Room temperature fluorination of uridine in methanol followed by treatment with Et_3N gives 5-fluorouridine (79%).[11] Similarly, 1,3-dimethyluracil gives the 5-fluoro derivative (89%).[11]

Cesium fluoroxysulfate is a mild fluorinating agent for activated aromatics,[6-10] such as phenols (eq 5), alkoxy-substituted benzenes, and naphthalenes. The reaction is catalyzed by HF, H_2SO_4, CF_3SO_3H, FSO_3H,[6] and BF_3.[9]

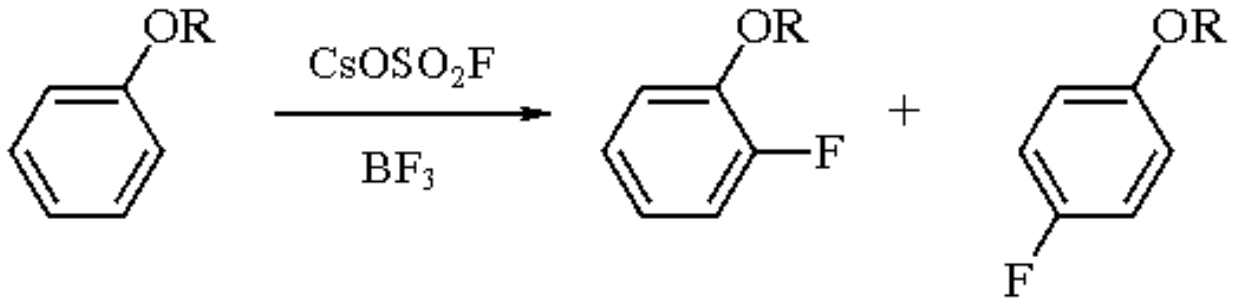

(5)

The reaction of toluene with $CsOSO_2OF$ in acetonitrile gives benzyl fluoride as the principal product,[7] but in the presence of catalysts, *o*- and *p*-fluorotoluenes (6:1) are produced.[6] In some cases of aromatic substitution the formation of fluorinated cyclohexadienones is observed (eq 6).[9]

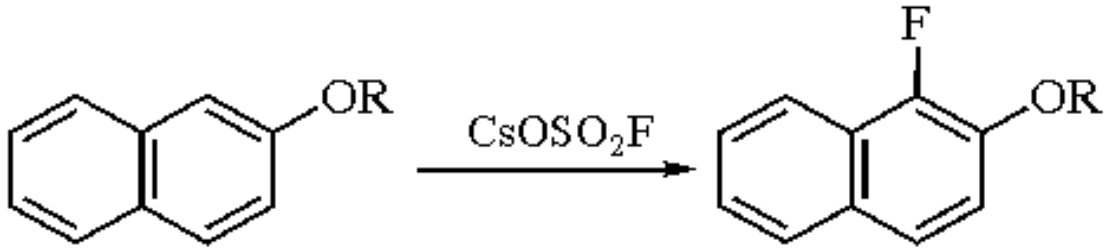

(6)

Trimethylchlorosilane reacts smoothly with $CsOSO_2OF$ to give trimethylfluorosilane.[11] Trimethyltin-substituted alkenes give fluoroalkenes (eq 7).[13]

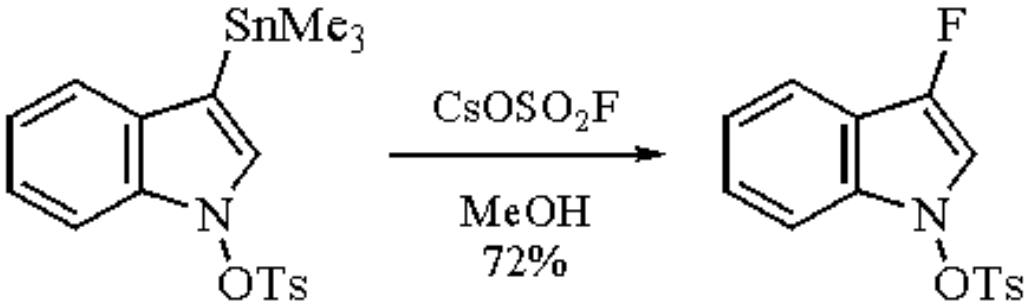

(7)

Oxidation.

The reagent (**1**) easily oxidizes secondary alcohols to ketones, and 1,2-dihydroxy-4-butylbenzene to the quinone derivative.[17] Ph_3P and dibenzothiophene are oxidized in room temperature reactions with $CsOSO_2OF$.[5,11]

Related Reagents.

Chlorine Fluoroxysulfate; ***(2-Chloro-1,1,2-trifluoroethyl)diethylamine***; ***Fluorine***; ***N-Fluoro-N-t-butyl-p-toluenesulfonamide***; ***Dibromomethane***.

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Chloral[1]

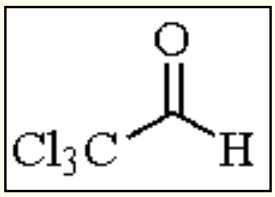

[75-87-6] · C_2HCl_3O · Chloral · (MW 147.39)

(electrophile which can react with a variety of nucleophiles,[1] insert into metal-C, -N, and -O bonds,[2] undergo ene and Diels-Alder reactions,[3] add to ketenes,[4] and function as a hydride acceptor[5])

Alternate Name: 2,2,2-trichloroacetaldehyde.

Physical Data: anhydrous: bp 98 °C; mp -57.5 °C; *d* 1.512 g cm^{-3}; refractive index 1.4557 (20 °C); hydrate [$Cl_3CCH(OH)_2$]: mp 57 °C; bp 96 °C; *d* 1.908 g cm^{-3}.

Solubility: anhydrous: sol CH_2Cl_2, $CHCl_3$, CCl_4, C_6H_6, Et_2O, THF, EtOAc, *n*-C_6H_{14}; sol and reacts with H_2O and alcohols; hydrate: sol H_2O, EtOH, Et_2O, C_6H_6.

Form Supplied in: anhydrous: colorless oily liquid, fairly widely available; hydrate: colourless crystals, widely available.

Analysis of Reagent Purity: various iodometric and colorimetric methods are available, but analysis by GLC offers the best discrimination.[1]

Purification: fresh commercial ~99% material is suitable for most purposes; chloral hydrate and polychloral are removed by distillation from P_2O_5.

Handling, Storage, and Precautions: toxic by inhalation, ingestion, and skin absorption. Irritating to the eyes, nose, throat, and skin; liquid and vapors are especially damaging to the eyes. Handle in an efficient fume hood and wear safety glasses, rubber or plastic gloves, and a laboratory coat. Bottles should be tightly sealed and refrigerated. Limited shelf life; hence may require redistillation from P_2O_5 before use. The hydrate, which is a powerful soporific, is much more stable but the same handling precautions apply. For small accidental spillages, (<~5 mL), flood with water and wash down the drain. Treat larger spillages with about 2-3 volumes of water and then adsorb onto proprietary spillage granules for disposal. Small quantities of unwanted reagent may be destroyed by hydrolysis to chloroform and sodium formate: add the chloral (*x* mol) slowly to a cooled (0 °C) and stirred solution of sodium hydroxide (1.5*x* mol) in water (100*x* mL). After 2 h, extract the chloroform layer with water and add to the departmental waste chlorinated solvent; the aqueous residues may be washed down the fume hood drain with plenty of water.

Introduction.

Chloral is an important source of dichloroacetic acid and its derivatives,[1] and the relative ease with which the Cl_3C-, $Cl_3CCH(OH)$- and Cl_2C= groups, derived from chloral by reaction, can be transformed into other types of functionality[1,3a] makes chloral a versatile synthetic reagent.

Formation of Hemiacetals and Acetals.

Anhydrous chloral reacts vigorously with a wide variety of alcohols to form hemiacetals.[1,6] Acetals are formed with acid catalysts and azeotropic distillation of water. Similarly, diols, hydroxy acids, and hydroxy ketones react to give cyclic acetals.[1,7] Chloral hydrate is usually used in combination with concentrated H_2SO_4.[1] Useful *erythro-threo* equilibration of lithium ketolates has been achieved through the formation of the chloral hemiacetal (eq 1).[8] Chloral adds ***Sodium Methoxide*** to form first the sodium salt of the hemiacetal which decomposes into dichlorocarbene, methyl formate and sodium chloride.[9a] ***Potassium t-Butoxide***, however, is usually preferred for generating **:**CCl_2 from chloral.[9b]

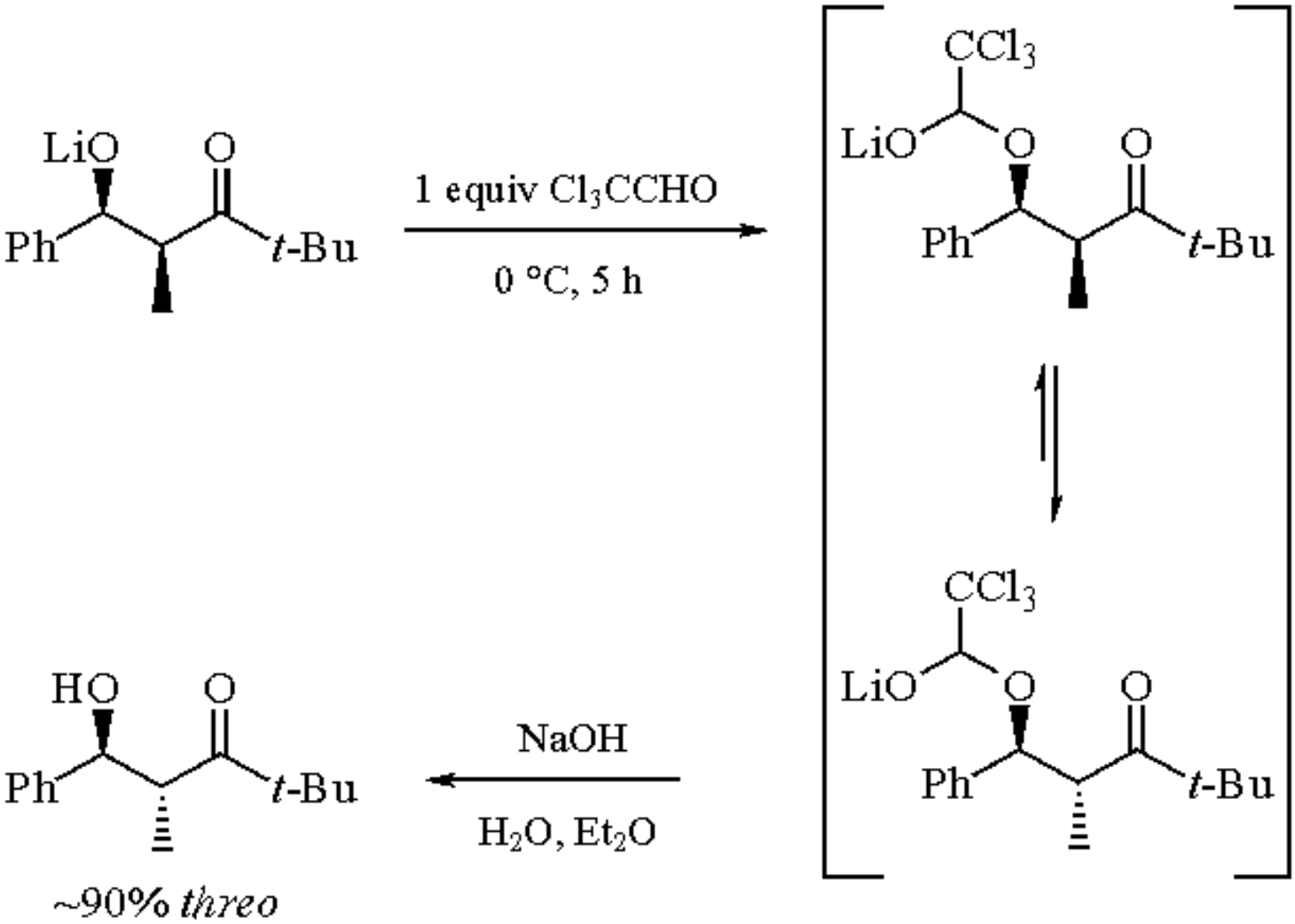

(1)

The hemiacetals formed from 2-alken-1-ols and chloral are cyclized in the presence of ***Mercury(II) Trifluoroacetate*** to the acetals. Demercuration and reductive cleavage gives *cis*-diols (eq 2).[10] The Hg^{II}-assisted addition of chloral to 1-penten-3-ol, followed by the electrophilic displacement of the mercury atom with iodine, gave a mixture of the stereoisomers of (**1**), which were used in a synthesis of the insect pheromone *exo*-brevicomin (**2**) (eq 3).[11] The transposition of the double bond and the hydroxyl group in 5-alkyl-4-hydroxycyclopentenones (in connection with a prostaglandin synthesis) has been achieved through a similar cyclic acetal formation (eq 4).[12]

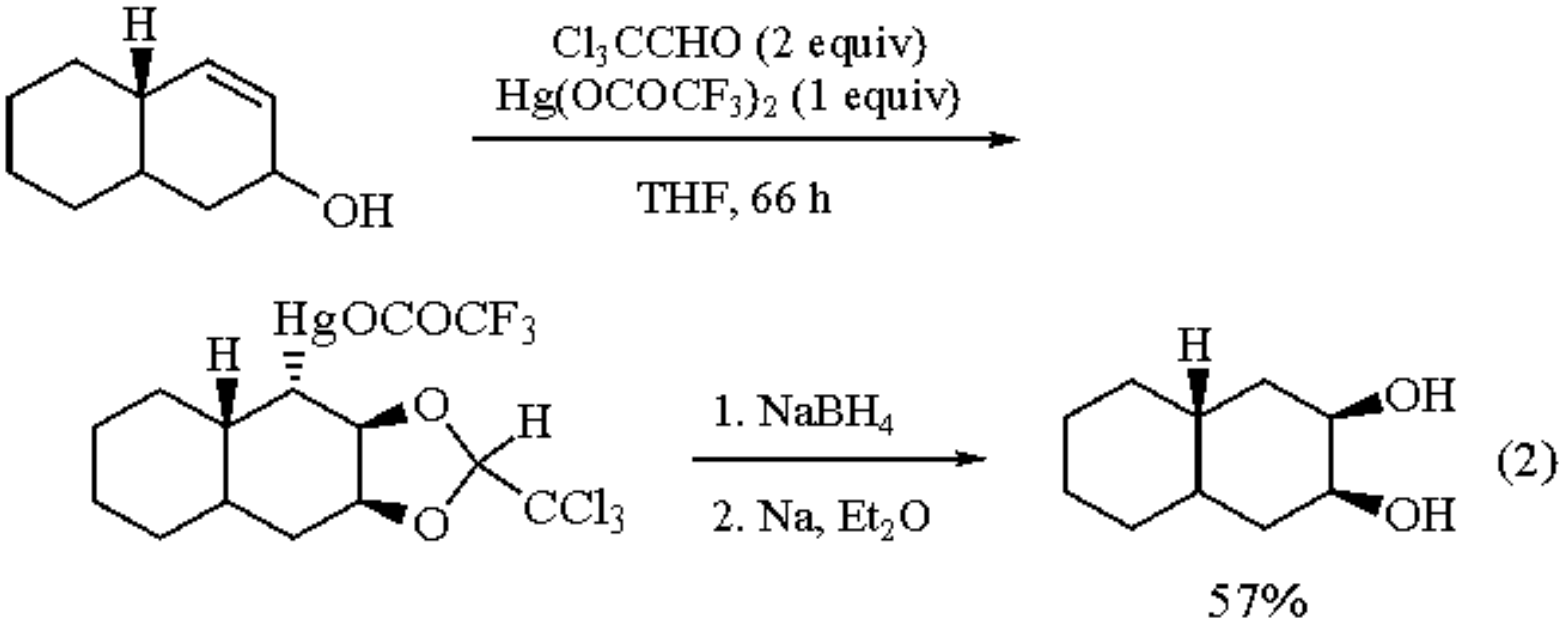

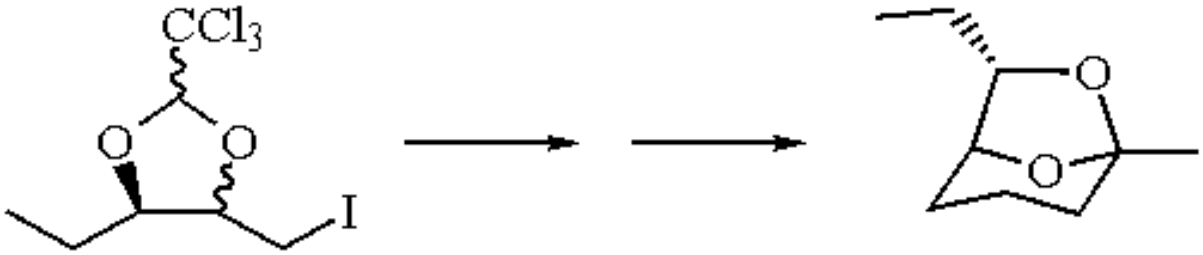

(1) **(2)**

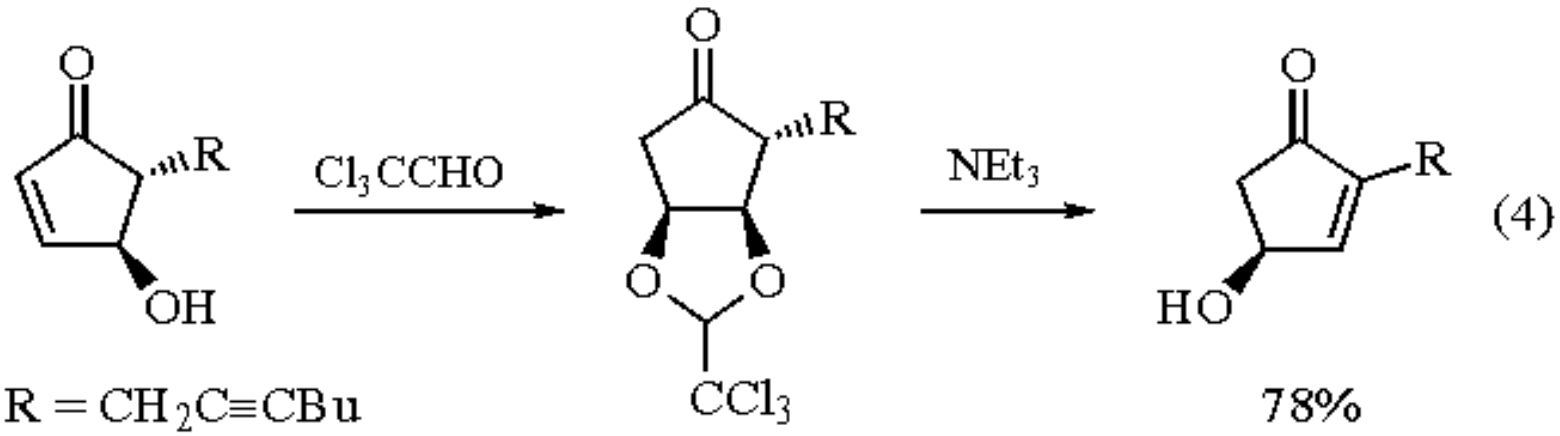

As an Alkylating and Acylating Agent for Amines and Amides.

Formylation (with simultaneous production of chloroform) of strongly basic primary and secondary amines and the esters of amino acids occurs in good yield on treatment with chloral.[1] Aromatic amines usually require the presence of Et_3N, otherwise hemiaminals or aminals may form.[1,13] Amides are formylated by chloral under alkaline conditions.[14] The hemiaminals formed from moderately nucleophilic amines may be dehydrated to afford chloral imines, or suffer elimination of chloroform to give the formyl derivative.[15] If the H-atom on the center adjacent to the N-atom of the chloral imine is acidic, then 1,4-elimination of HCl may be observed.[16] This chemistry has been used to convert the 7α-amino-1-oxacephem (**3**) into its 7β-epimer (57.5% overall) by the reduction (KBH_4, 0 °C) and hydrolysis (HCl, MeCN) of the intermediate (**4**) (eq 5).[17] Chloral catalyses the *N*-nitrosation of various secondary amines in the pH range 6.4-11.0 since the first-formed iminium ion is readily attacked by nitrite anion; the presumed adduct [R_2N-$CH(CCl_3)$-ONO] collapses to R_2NNO and chloral.[18]

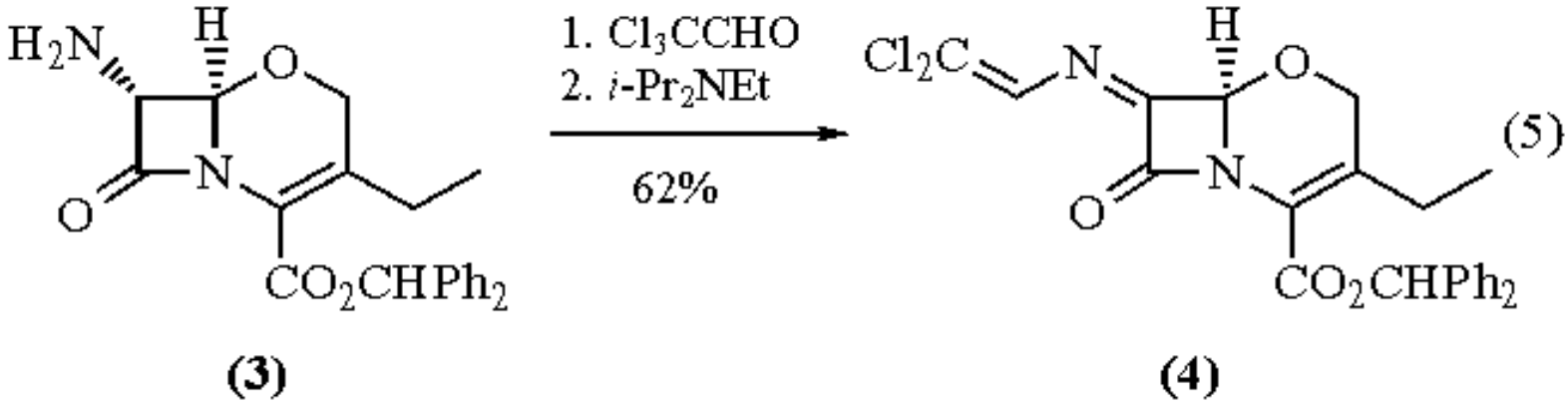

Aromatic amines condense with chloral hydrate and hydroxylamine to afford *N*-(hydroxy-iminoacetyl) derivatives which are readily cyclized in the presence of concentrated H_2SO_4 to provide a good route to isatin and its analogs (eq 6).[19] Acid hydrazides when refluxed with chloral in the presence of an alcohol are converted (70-80%) directly into the corresponding ester (eq 7).[20] The hydrazide to amide conversion can be made similarly.

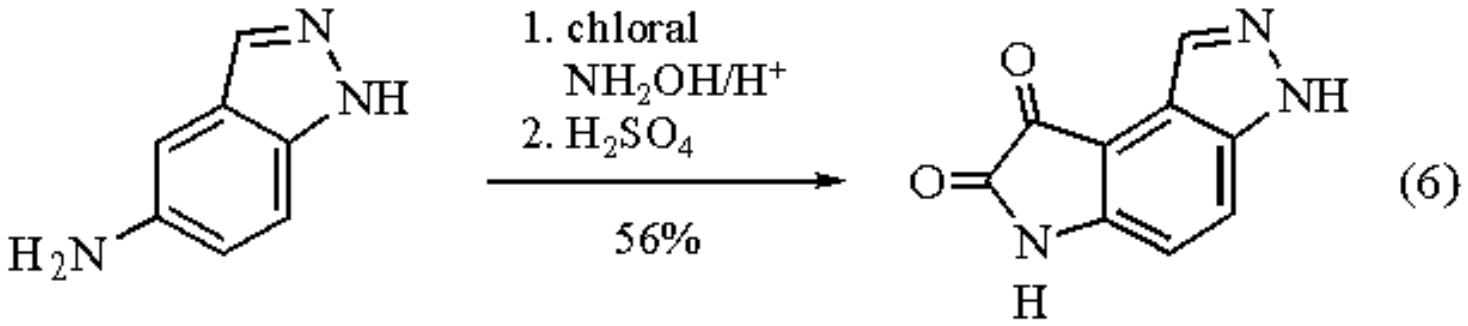

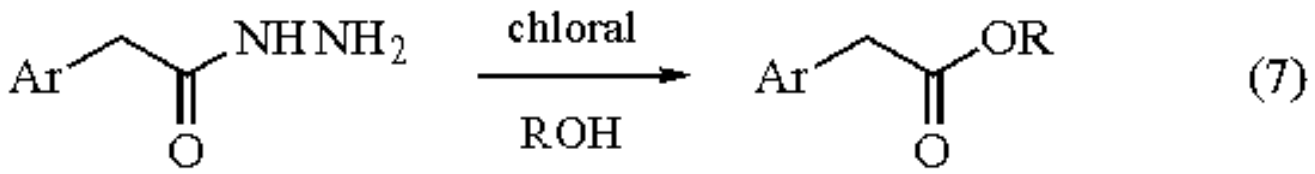

Aldol and Related Reactions.[1]

With aldehydes the best method for the directed cross-aldol condensation involves reaction of chloral with the TMS enolate of the aldehyde in the presence of ***Titanium(IV) Chloride*** (eq 8).[21] The TMS enolates of ketones react similarly to give the 1,1,1-trichloroethan-2-ols in excellent yields.[22] With simple methyl ketones, the condensation occurs at the methyl group.[23] Mesityl oxide affords (**5**) under buffered conditions (AcOH-NaOAc) (eq 9), whereas in the absence of the NaOAc the tetrahydro-1,4-pyranone (**6**) is formed.[23b]

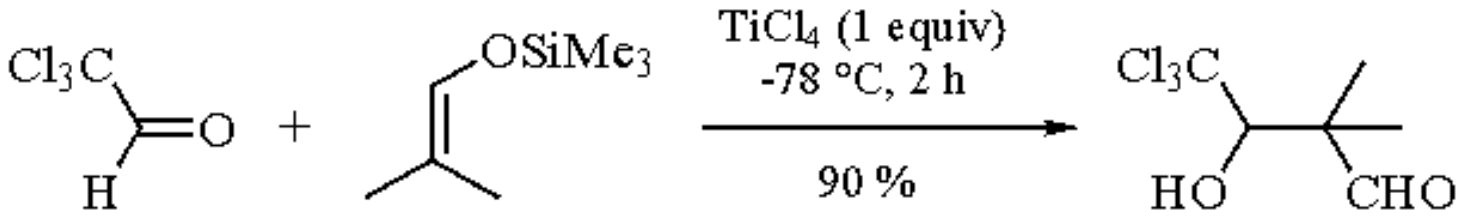

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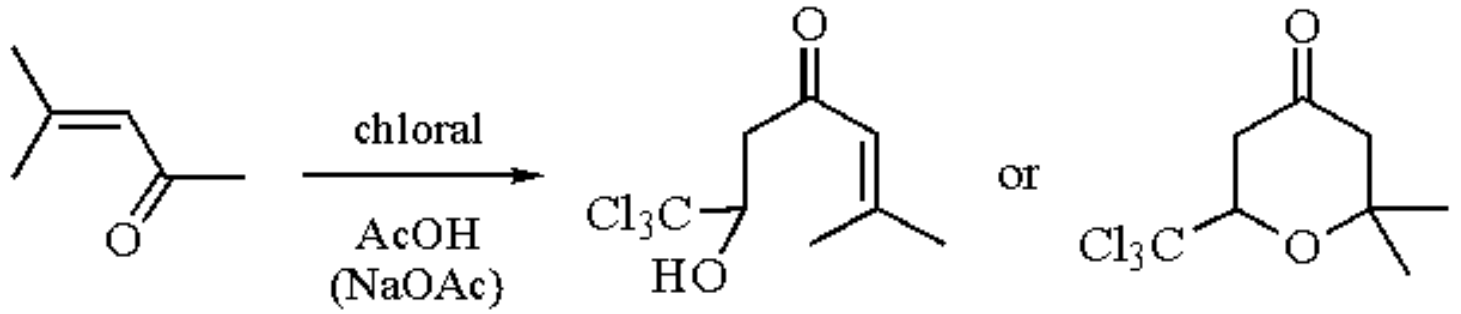

(9)

(5) **(6)**

The rather more stable enolate anions derived from β-diketones, α-cyanoacetates, α-nitroacetates, etc., are *C*-alkylated by chloral.[24-26] The 1,1,1-trichloro-2-hydroxyethyl derivative thus formed may be dehydrated under suitable conditions.[24d] When the condensation is performed with solid ***Potassium Carbonate*** in THF solution, β-diketones are deacylated. Thus acetylacetone is transformed into $Cl_3CCH{=}CHCOMe$ (74%)[25] and 2-acetylcyclopentanone is converted into (**8**) through a Favorskii rearrangement of the intermediate deacetylated product (**7**) (eq 10).[26] A 1,1,1-trichloro-2-hydroxyethyl derivative is also formed when chloral is allowed to react with various other anions (e.g. those derived from sulfones,[27] amides,[28] or 2-methylquinoline[29]). In this last case, chloral has been used as a convenient masked equivalent of glyoxylic acid (eq 11).[29]

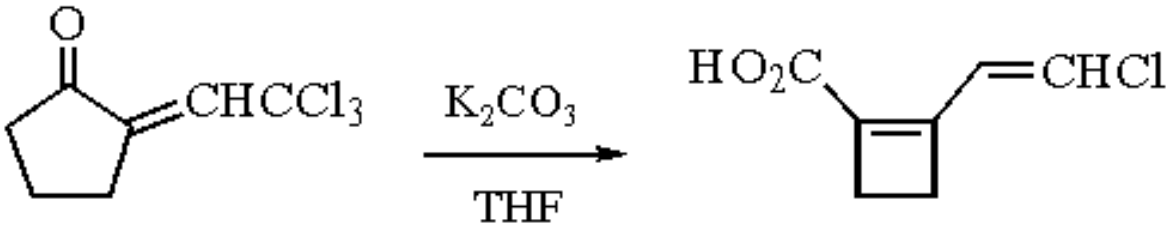

(10)

(7) **(8)**

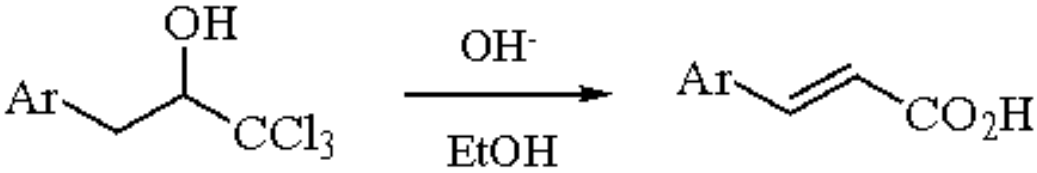

(11)

Electrophilic Aromatic Substitution.

Much research on chloral has been devoted to its use in electrophilic aromatic substitution reactions (promoted by acids or Lewis acids), not least because of the former importance of DDT.[1] Alkylation produces aryltrichloromethylcarbinols which may be transformed into aldehydes, α-hydroxy acids, and α-alkoxy acids.[30] The aryltrichloromethylcarbinols are oxidatively cleaved by alkaline ***Hydrogen Peroxide*** to afford carboxylic acids after acidification; yields are 85-98%.[31] Mild conditions (i.e. ***Zinc Chloride***) are necessary for furans, or a photochemical procedure can be employed.[32] The alkylation of dichloroaluminum phenolates with chloral is *ortho* selective. The products (**9**) are transformed by basic ***Alumina*** (decalin, reflux) into isoxindigos (**10**) (eq 12).[33] Asymmetric *o*-selective hydroxyalkyl ation of phenols occurs when chiral alkoxyaluminum chlorides are used as catalysts; the % ee's, however, are only poor to moderate.[34] Acrylate esters undergo formal electrophilic substitution at the α-position when treated with chloral in the presence of ***1,4-Diazabicyclo[2.2.2]octane*** as catalyst.[35]

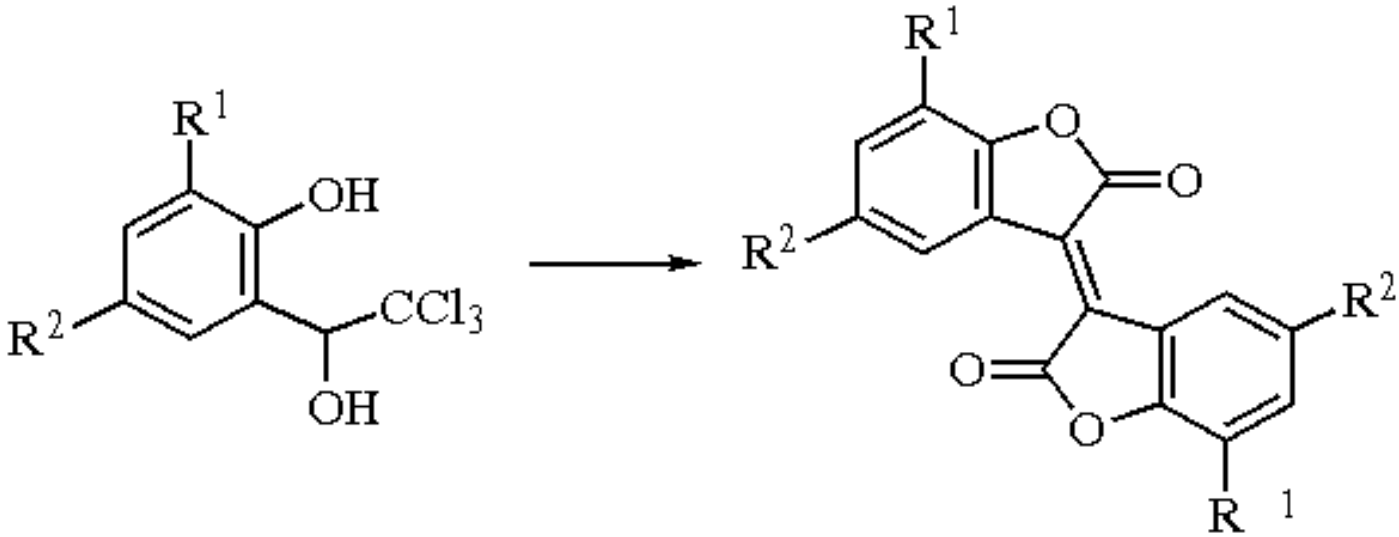

(12)

(9) **(10)**

Additions to Alkenes, Dienes, and Ketenes.

Anhydrous chloral affords formal ene adducts on reaction with suitable alkenes. Although chloral is a relatively reactive enophile, the thermal addition is really only successful with the more reactive (i.e. Type 1)[36] enes. The addition is strongly catalyzed by Lewis acids (e.g. $AlCl_3$, $SnCl_4$, $TiCl_4$, $FeCl_3$, etc.), such that a solvent (e.g. CH_2Cl_2, CCl_4) is necessary to moderate the room temperature reactions, and the useful reactivity range spans Type 1-Type 4 enes.[3a,b] The Lewis acid improves the yield and also has a profound effect upon the diastereoselectivity of the addition (eqs 13 and 14). Although the reactions with Type 1 enes appear to be concerted, the formation of significant byproducts with the less nucleophilic Type 2-4 enes points to an electrophilic addition pathway (eq 15).[3b,37,38] Chiral

alkoxyaluminum Lewis acid catalysts promote the asymmetric ene addition of chloral to 2-methylpropene with enantioselectivities of about 70-80% ee.[39] ***Aluminum Chloride***-promoted electrophilic additions of chloral to alkenes are also well documented.[1] For example, addition to 1,5-cyclooctadiene and to norbornadiene affords, respectively, the oxatricyclic compounds (**11**; 47%) and (**12**; 36%).[40] The cyclohexene-chloral ene adduct is rearranged by $AlCl_3$ into the oxabicyclo[3.2.1]octane (**13**)[3c] and not into an oxabicyclo[2.2.2]octane as thought previously.[41]

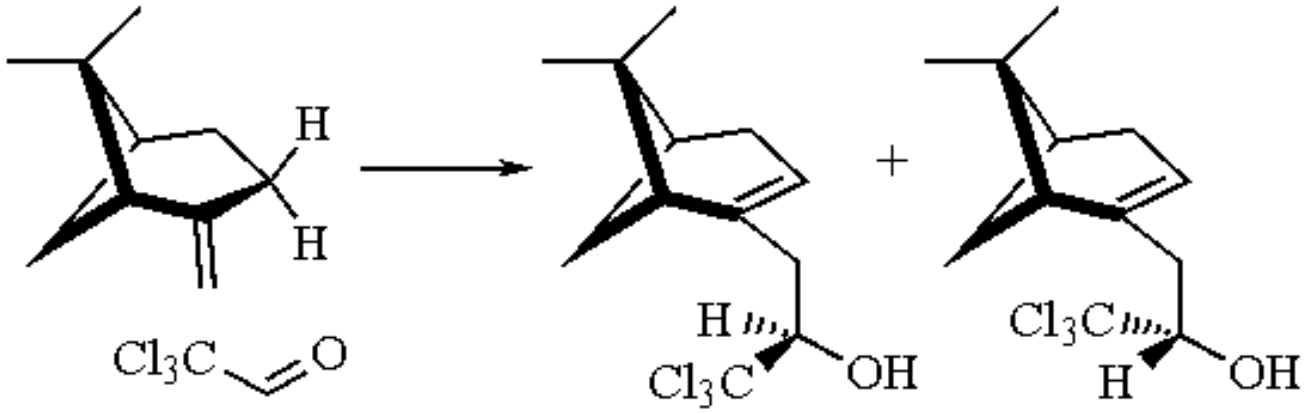

(13)

T (°C)	h	Solvent	Catalyst	R	S
95	18	-	-	83	17
20	0.5	CCl_4	$AlCl_3$ (2%)	24	76
20	0.5	CCl_4	$SnCl_4$ (2%)	10	90
20	0.5	CCl_4	$TiCl_4$ (2%)	0	100

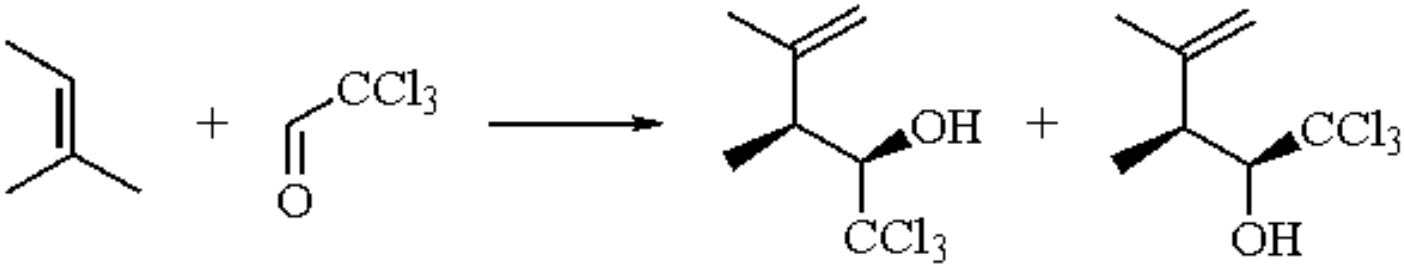

(14)

T (°C)	h	Solvent	Catalyst	$R,S + S,R$	$S,S + R,R$
130	72	-	-	16	84
20	3	CH_2Cl_2	$AlCl_3$ (2%)	85	15
20	3	CH_2Cl_2	$TiCl_4$ (2%)	70	30
20	3	CH_2Cl_2	$FeCl_3$ (2%)	60	40

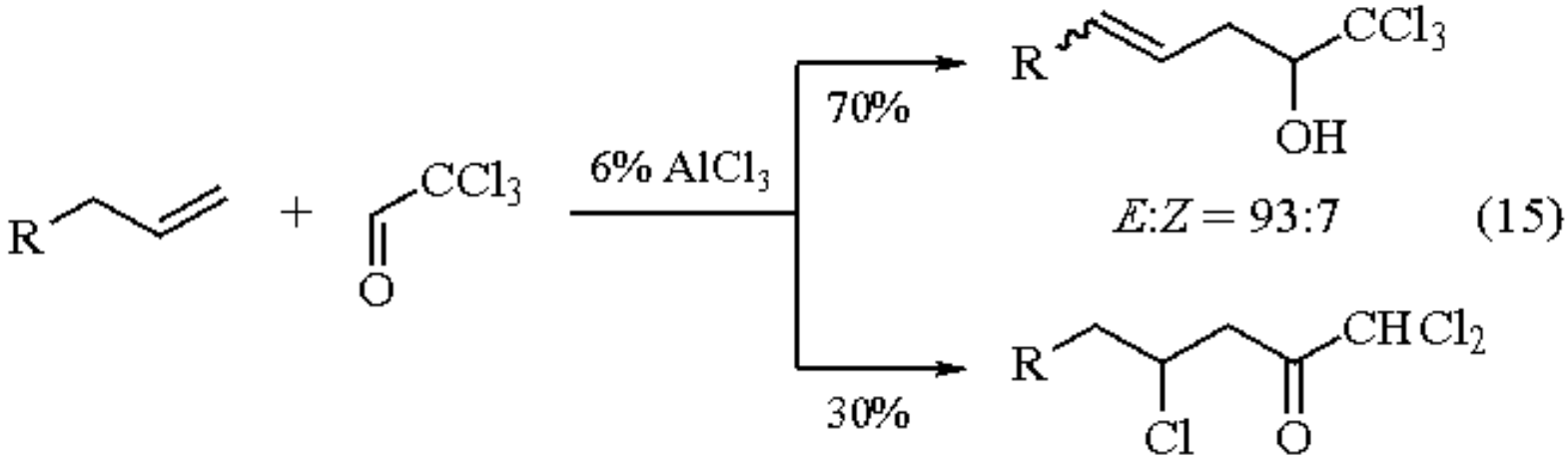

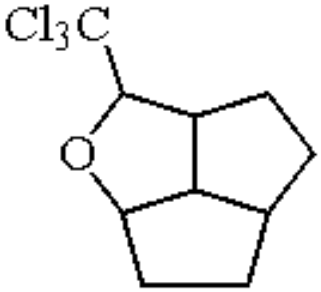

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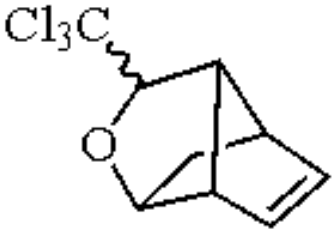

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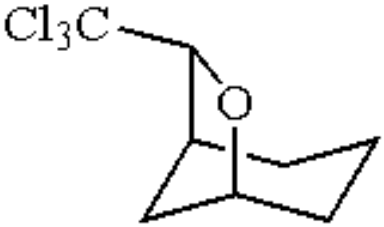

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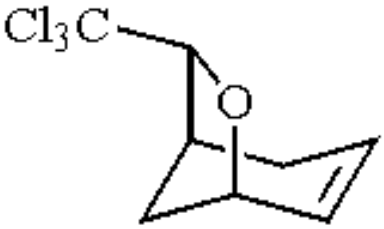

(14)

Thermal addition of chloral to isoprene yields the expected Diels-Alder adduct predominantly, whereas in the $AlCl_3$ catalyzed addition the ene adduct predominates.[3a,d] Thermal addition to 1,3-cyclohexadiene affords the oxabicyclo[2.2.2]octane only with pure reagents, otherwise rearrangement occurs to the oxabicyclo[3.2.1]octane (**14**).[3c] Chloral undergoes an exothermic formal [4 + 2] cycloaddition to the strained double bonds of *t*-butyl 2,3,4-tri-*t*-butylcyclobutadienecarboxylate,[42] successfully traps α-oxo-*o*-quinomethanes to give isocoumarins,[3e] but otherwise is not an especially versatile and reactive dienophile. It is, however, one of the few carbonyl acceptors for the carbon-carbon double bond of ketenes.[1,4a-d] Addition to ketene in the presence of quinidine as a chiral catalyst is highly enantioselective (98% ee) and affords (*R*)-3-trichloromethyl-2-oxetanone (**15**; 89% yield).[4c] Ketene acetals readily add chloral to give 2,2-dialkoxy-4-trichloromethyloxetanes under Lewis acid catalysis ($ZnCl_2$ or $EtAlCl_2$).[43]

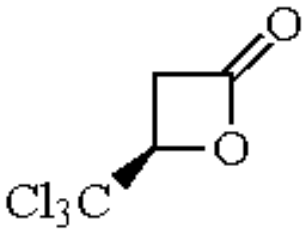

(15)

As a Hydride Acceptor.

Chloral on dehydrated chromatographic alumina transforms structurally diverse secondary alcohols (CCl_4 solution, 25 °C, 24 h) into ketones in good yields and some diols into the corresponding keto alcohols.[5a,44] The readily available β-hydroxy sulfides and selenides are chemoselectively oxidized to β-keto sulfides and selenides.[45] The method generally seems to be tolerant of a number of potentially sensitive functional groups, and product isolation simply involves filtration and evaporation. Aldehydes and ketones are also prepared in an Oppenauer oxidation of halomagnesium alkoxides using chloral as the hydride acceptor.[5b]

Insertion into Metal-C, -N, and -O Bonds.

Although chloral adds simple organometallic compounds (e.g. HC&tbond;C^-K^+, ArMgX) to form, after hydrolysis, the substituted trichloroethanol,[1,2a-e] it can be reduced by alkyl Grignard reagents (i.e. hydride transfer) or react at the Cl_3C- group with methyl- or phenyllithium.[1] The product distribution is often sensitive to reaction conditions and the order of addition of reagents. In the presence of a Lewis acid catalyst ($GaCl_3$, $InCl_3$ or $AlCl_3$) activated $RSiMe_3$ compounds (i.e. R = allyl, aryl, vinyl, ethynyl, or propargyl) add to chloral to give, after hydrolysis, the corresponding α-trichloromethylated carbinols [$RCH(OH)CCl_3$].[46] ***Crotyltributylstannane*** reacts with chloral at room temperature without the need for Lewis acid catalysis; the stereoselective substitution reaction occurs with an allylic shift (eq 16).[2f,47] Chloral also inserts readily into the metal-O bond of alkoxysilanes, -germanes, and -plumbanes,[2g,48] into the Si-N bond of trimethylsilyldimethylamine,[49] into the metal-C bond of silyl- and germylketene dimethyl acetals,[50] and into the Hg-C and Hg-Si bonds.[51]

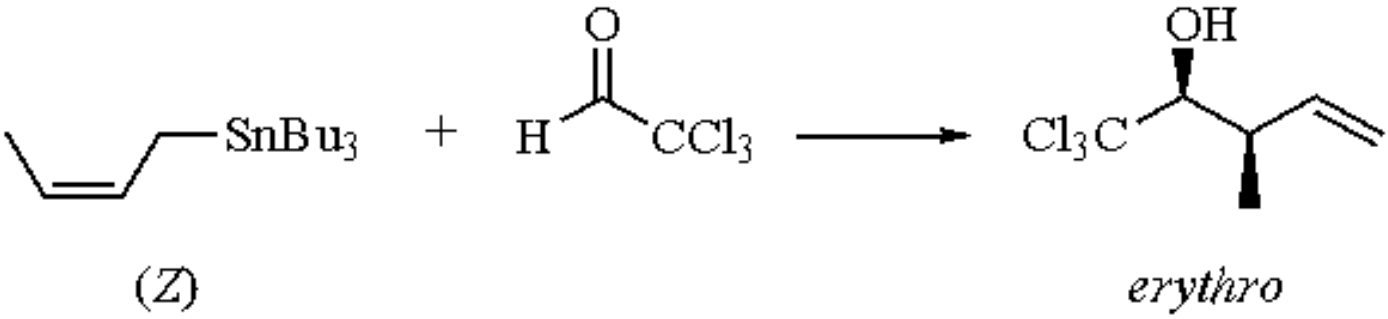

(16)

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Chloramine[1]

NH_2Cl

[10559-90-3] · ClH_2N · Chloramine · (MW 51.48)

(aminating agent; oxidizing agent)

Alternate Names: chloramide; monochloramine.

Physical Data: mp -66 °C.[2]

Solubility: sol H_2O, ether, methylene chloride, alcohol; slightly sol benzene, carbon tetrachloride.

Preparative Methods: prepared in situ by the reaction of aqueous NH_3 and NaOCl;[3] this aqueous solution [chloramine (aq)] can frequently be used for subsequent reactions; however, in many cases it is advisable to use an anhydrous ethereal solution of chloramine [chloramine (anhyd)];[4] chloramine (g) has been prepared by the gas phase reaction of Cl_2 with excess NH_3,[5] but this appears to be synthetically less useful.

Handling, Storage, and Precautions: although chloramine (aq or anhyd) is generally prepared immediately before use, storage at 0 °C for short periods of time (<=1 h) does not appear to be detrimental; only dilute solutions[4] should be prepared, as more concentrated solutions decompose readily to N_2, Cl_2, and NCl_3; use in a fume hood.

Amination of Organometallic Reagents.

Organoboranes react with chloramine (aq) under alkaline conditions to afford fair to good yields of primary amines, thus providing a convenient route to amines from alkenes (eq 1).[6] However, ***Hydroxylamine-O-sulfonic Acid*** (especially in DME) was found to be a more effective aminating agent, in terms of both yield and convenience.[7] ***Hydroxylamine*** and ***Hydrazine*** were ineffective, and *N*-chlorodimethylamine gave either chloroalkanes[8] or alkyldimethylamines,[9] depending on the reaction conditions (radical vs. polar mechanism).

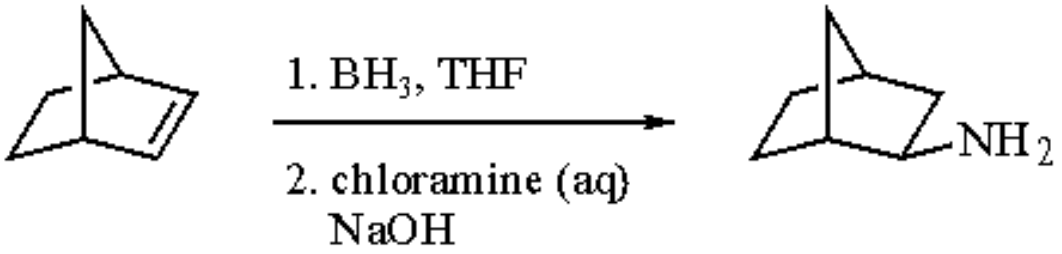

(1)

Chloramine (anhyd) reacts with Grignard reagents to furnish amines in poor to good yield.[10] Chloromagnesium Grignard reagents gave better yields than the bromo or iodo compounds, while the dialkylmagnesium reagents gave excellent yields.[11] Phenyl Grignard reagents gave poor yields of amines, the aromatic chlorides being obtained instead.[10b] Organolithium and organozinc reagents also react with chloramine (anhyd) to give amines.[12]

Reaction with Alcohol Anions.

Chloramine (anhyd) reacts with the sodium salts of aliphatic alcohols to give fair yields of the *O*-alkylhydroxylamines.[1a,13,14] The reaction with phenoxide anions, however, takes several different paths. While *ortho*-unsubstituted phenoxide ions give *o*-aminophenols (in poor yield) by simple *C*-amination, treatment of 2,6-disubstituted phenolic salts in molten phenols with <1 equiv of chloramine (anhyd) proceeds further with subsequent ring expansion to give 1,3-dihydro-2*H*-azepinones (eq 2).[15] Unsymmetrical 2,6-disubstituted phenols gave mixtures of the two possible ring expanded products, the ratios being governed primarily by steric control.[15d] Use of excess chloramine (anhyd) gave products due to oxidative coupling of the phenol.[16] Placement of a carbonyl group in the *ortho* position gave rise to 2-hydroxyanilides (eq 3).[17]

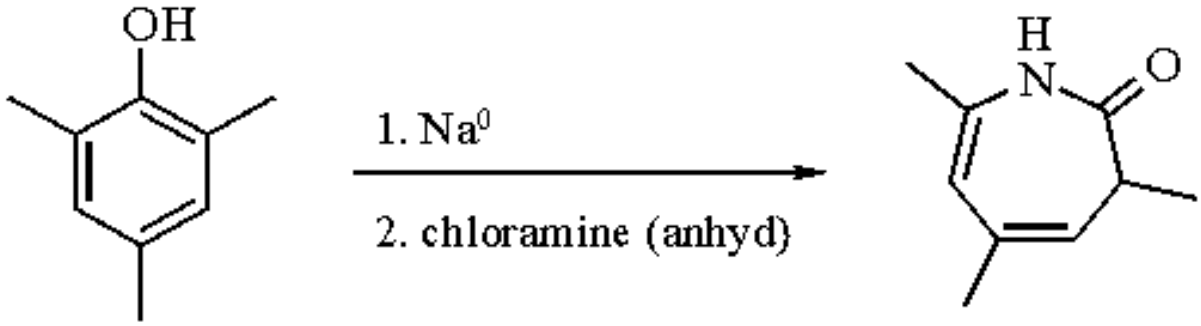

(2)

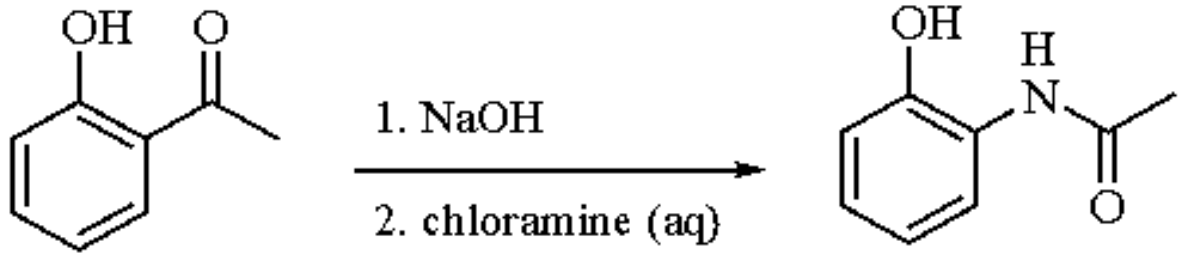

(3)

Reaction with Nitrogen-Containing Compounds.

Chloramine (aq) and substituted chloramines react with aliphatic amines to give hydrazines.[1a,1b,18] ***Hydroxylamine-O-***

sulfonic Acid, however, is often superior to chloramine (aq).[19]

α-Oximino ketones react with chloramine (aq) to give α-diazo ketones (Forster reaction).[20] When combined with a photolytic Wolff rearrangement, this provides a convenient, generally useful method of ring contraction.[21] This sequence of reactions has demonstrated great promise in the synthesis of nor-steroids (eq 4).[22]

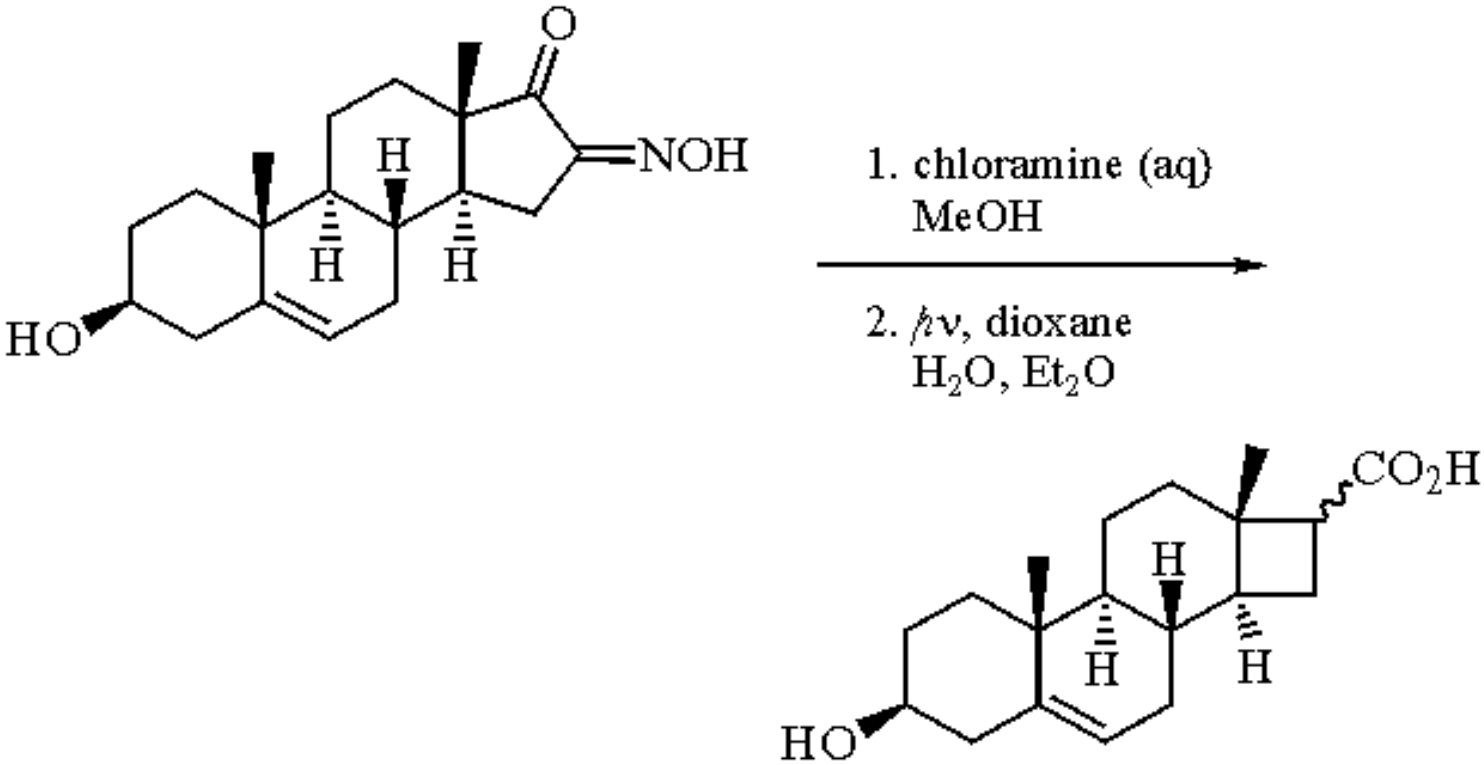

(4)

The reaction of chloramine (anhyd) with toluenesulfonamides provides a method for either hydrodeamination or halodeamination of primary amines (eq 5).[23] This method has demonstrated superiority to the related hydrodeamination using hydroxylamine-*O*-sulfonic acid in aqueous base.[24]

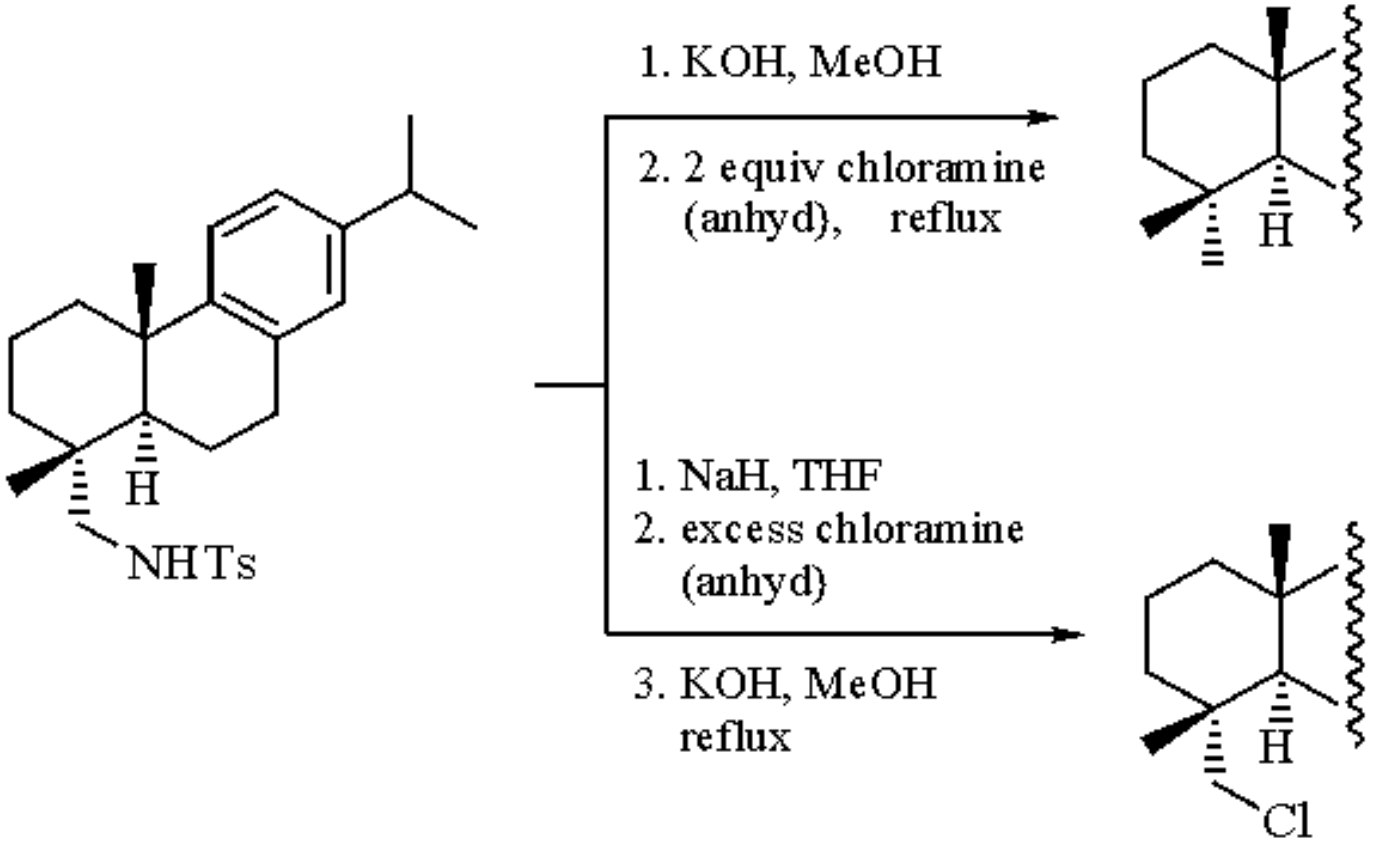

(5)

Oxidations.

Chloramine (anhyd) has been reported to oxidize anilines to mixtures of *cis*- and *trans*-azobenzenes.[4b] Although the yields were modest (20-50%), this method does provide access to the relatively rare *cis* isomers. Other oxidants (***Manganese Dioxide***, ***Lead(IV) Acetate*** or ***(Diacetoxyiodo)benzene***) give only the *trans* isomers.

Benzyl alcohols were also oxidized to carbonyl compounds in good to excellent yield, but this method has not been extended to aliphatic (nonbenzylic) alcohols.

Related Reagents.

Ammonia; ***Chloramine-Aluminum(III) Chloride***; ***Chloramine-T***; ***Hydrazine***; ***Hydroxylamine-O-sulfonic Acid***; ***Trichloramine***.

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Chloramine-Aluminum(III) Chloride

NH_2Cl-$AlCl_3$

(NH_2Cl)

[10599-90-3] · ClH_2N · Chloramine-Aluminum(III) Chloride · (MW 51.48) ($AlCl_3$)

[7446-70-0] · $AlCl_3$ · Chloramine-Aluminum(III) Chloride · (MW 133.34)

(reagent for aminating arenes, alkanes, and alkyl chlorides[1])

Physical Data: bp -66 °C.

Solubility: sol cold H_2O, ether, and methylene chloride; v sl sol CCl_4 and benzene.

Analysis of Reagent Purity: chlorine in chloramine is determined by iodometric titration.[8]

Preparative Methods: ***Chloramine*** can be prepared either by a gas phase or a liquid phase technique. In the gas phase technique, ammonia and chlorine are allowed to react and chloramine is collected in methylene chloride.[1-4] Since the gas phase technique is relatively cumbersome and provides only small amounts of the desired material, liquid phase techniques in which chloramine is extracted into an organic solvent from an aqueous phase are used. Sodium hypochlorite solution is added to aqueous ammonia at 0 °C; chloramine is distilled with water into cold ether[5-7] or extracted with methylene chloride.[1]

Handling, Storage, and Precautions: this reagent should be handled in a fume hood.

Amination.

Mono-, di-, and trichloramines in the presence of ***Aluminum Chloride*** have been reported to aminate various organic substrates, e.g. arenes, alkanes, and alkyl halides. Amination is carried out with an excess of the aromatic compound, a 1.7-2 molar ratio of $AlCl_3$/*N*-haloamine, and an aryl halide additive in the case of dichloramine at temperatures in the range -35 to -15 °C. Under these conditions the reaction of toluene with chloramine/$AlCl_3$ gives primarily *o*- and *p*-chlorotoluene, and only 13% of *m*-toluidine (eq 1).

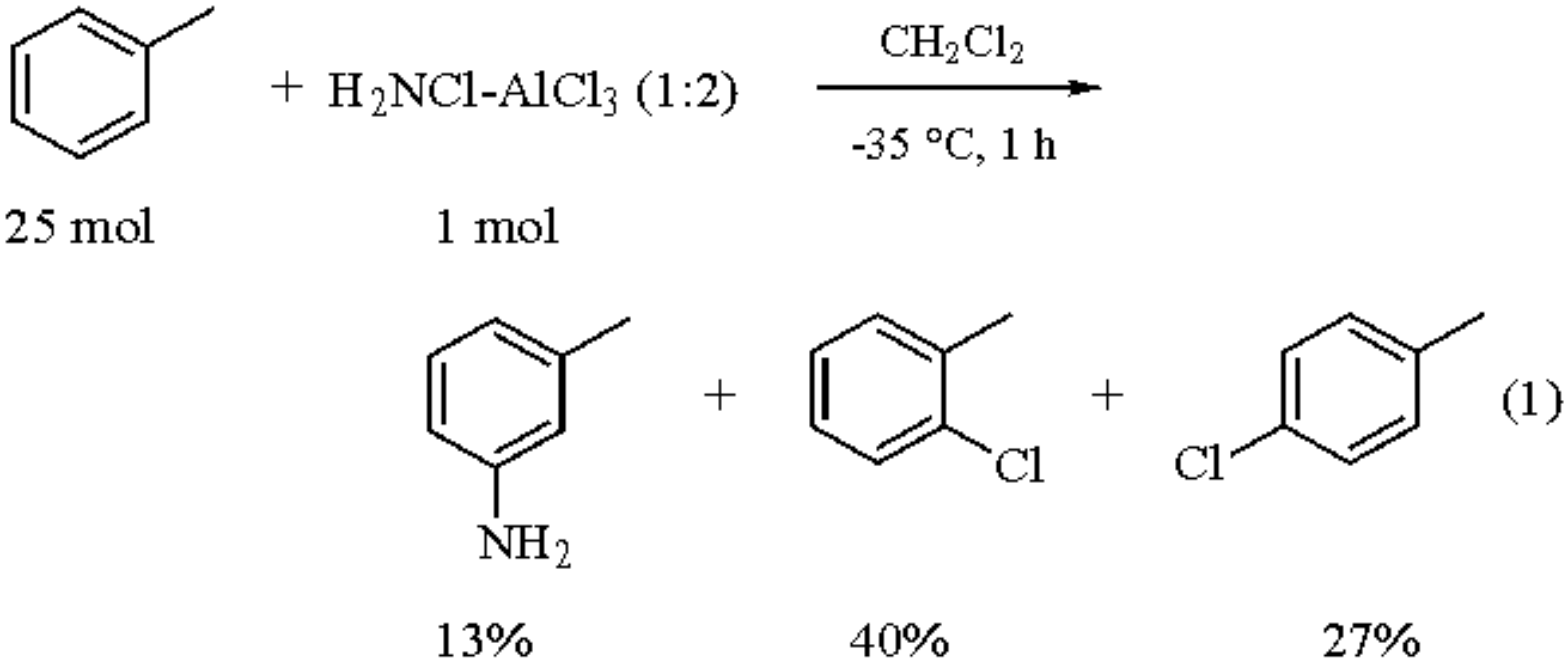

The reactions with trichloramine-aluminum(III) chloride and dichloramine/$AlCl_3$ give *m*-toluidine in 43%[1,9] and 25%[10] yields, respectively. Based on literature analogy involving the trichloramine/$AlCl_3$ system, a mechanistic scheme entailing addition-elimination is proposed for the *meta* substitution (eq 2).

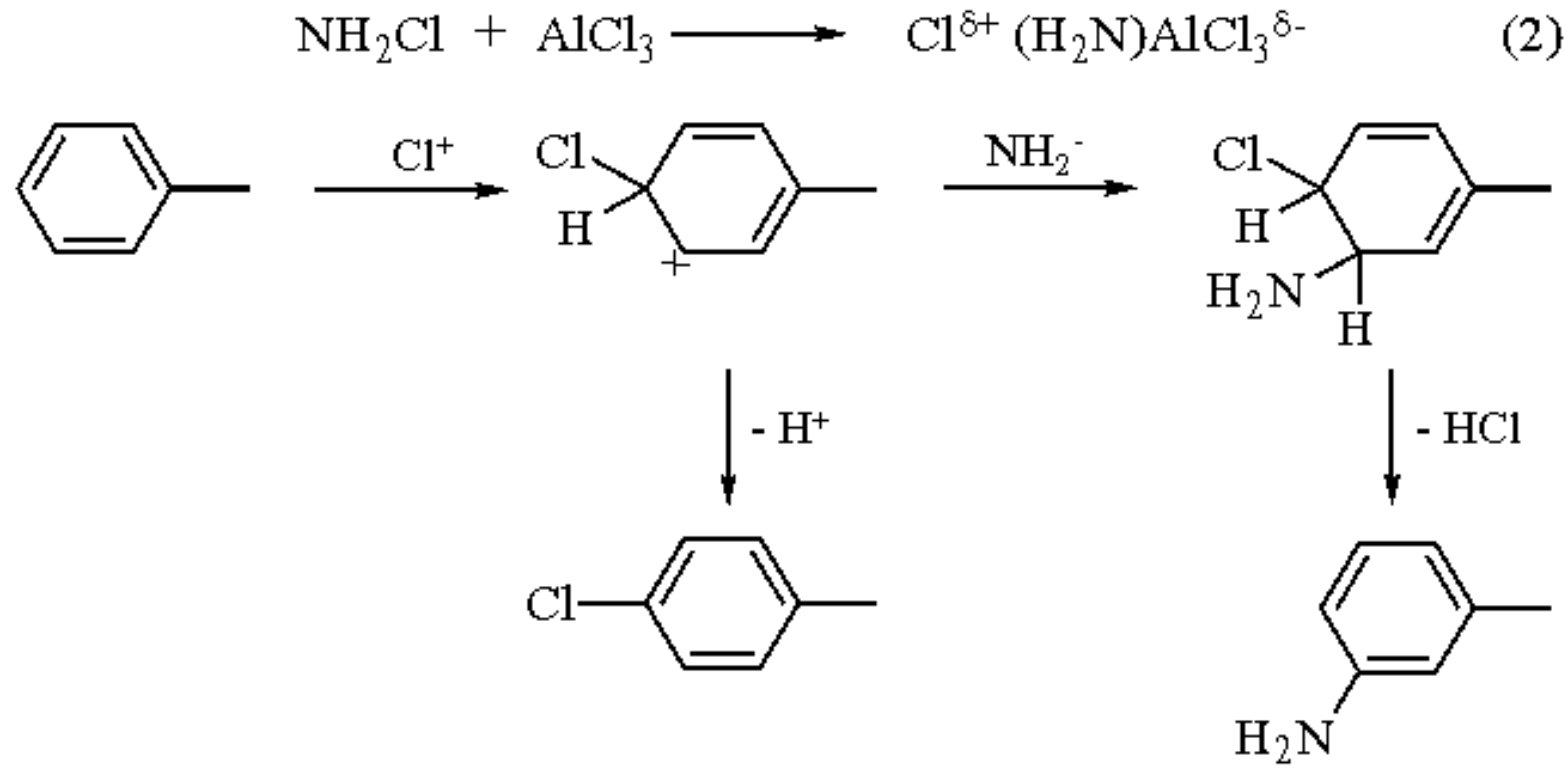

Amination of adamantane with chloramine/$AlCl_3$ gives 1-aminoadamantane (eq 3) in 40% yield, again in lower yield than that obtained with trichloramine/$AlCl_3$ (85% yield).[1,11,12]

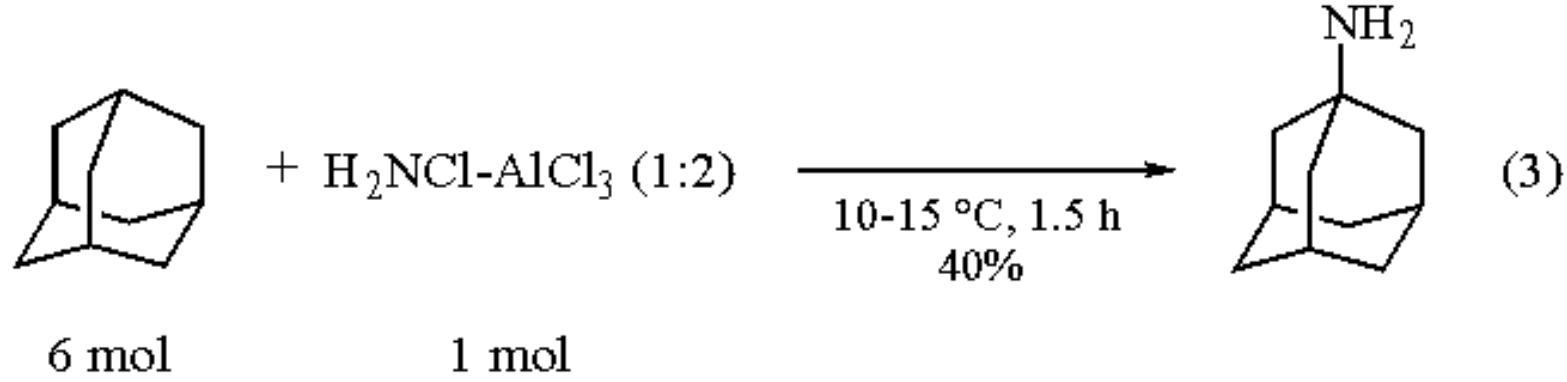

Amination of *t*-butyl chloride produces *t*-butylamine (eq 4) in 7-20% yield, which is much lower than that obtained with trichloramine/$AlCl_3$ (56% yield).[1,13]

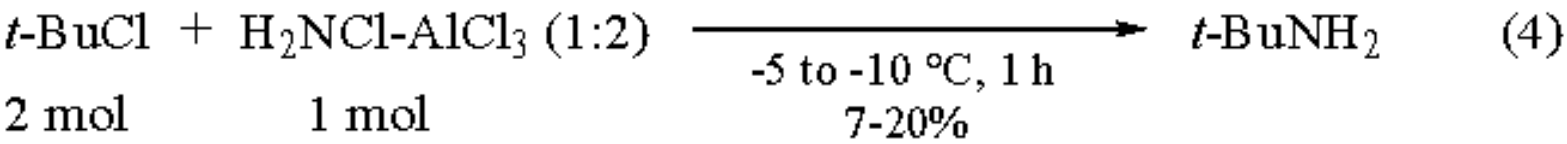

A possible rationalization for the lower yields with chloramine as compared to trichloramine in amination of the three organic substrates has been given.[1]

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Chloramine-T[1]

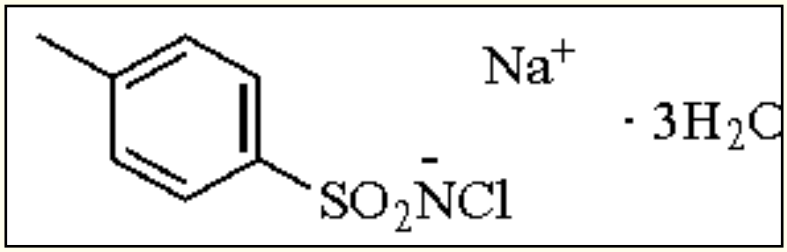

[127-65-1] · $C_7H_{13}ClNNaO_5S$ · Chloramine-T · (MW 281.69)

(source of chloronium cations and/or nitrogen anions; oxidizing agent; in conjunction with OsO_4 can hydroxyaminate alkenes)

Alternate Names: *N*-chloro-*N*-sodio-*p*-toluenesulfonamide.

Physical Data: mp 167-170 °C (dec).

Solubility: insol ether, benzene and chloroform; sol cold H_2O; v sol hot H_2O; dec in EtOH.

Form Supplied in: white or pale yellow solid; widely available. While other *N*-halo-*N*-sodiosulfonamides and -carbamates have been reported in the literature and used in organic synthesis, only chloramine-T and its demethyl analog, chloramine-B, are commercially available. *Drying:* in some reactions, anhydrous chloramine-T [chloramine-T (anhyd)] is required; the drying of the trihydrate at 80 °C under vacuum has been described,[2] although precautions should be taken (see below).

Analysis of Reagent Purity: by iodometric titration.[3]

Handling, Storage, and Precautions: irritant; keep containers tightly sealed and protect from light; although the trihydrate is stable, there have been reports of chloramine-T (anhyd) decomposing with explosive force;[2,4] to minimize potential risks it is advised that chloramine-T (anhyd) be prepared in minimal amounts and all manipulations be performed behind safety shields (full-face and free-standing); use in a fume hood.

Reaction with Chalcogens and their Derivatives.

Chloramine-T reacts with a variety of sulfur-containing compounds to form sulfur-nitrogen bonds.[1] A partial listing includes thiols, sulfides, sulfoxides, disulfides, sulfimides, xanthates, thioketones, sulfenyl chlorides, and sulfinyl chlorides. The reaction of chloramine-T with sulfides forms the basis for a deprotection of thioacetal groups. Thus 1,3-oxathiolanes,[5] 1,3-dithiolanes,[6] and 1,3-dithianes[7] are all cleaved by chloramine-T to regenerate the carbonyl compounds. However, with chloramine-T (anhyd), 1,3-dithianes yield ketene thioacetals (eq 1).[8]

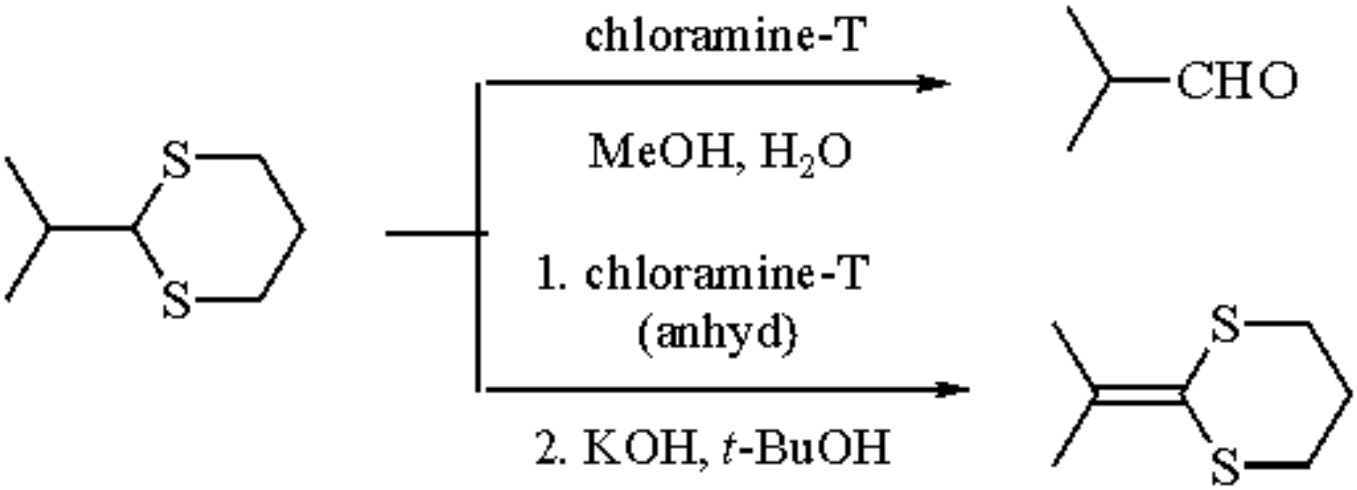

(1)

Selenides react with chloramine-T (anhyd) to give selenimides (eq 2).[9] In the case of primary alkyl phenyl selenides, the selenimide further undergoes β-elimination to give the terminal alkene (eq 3).[10] Tellurides behave similarly.[11] Allyl phenyl selenides can be converted to protected allylic amines via [2,3]-sigmatropic rearrangement of the selenimides (eq 4).[12]

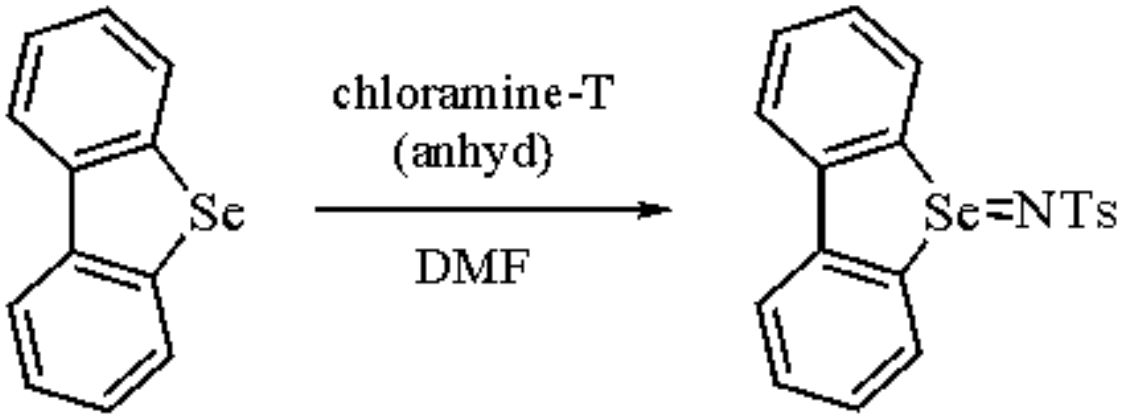

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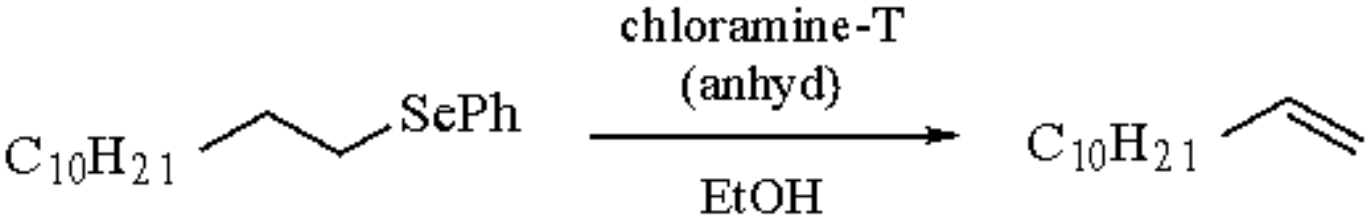

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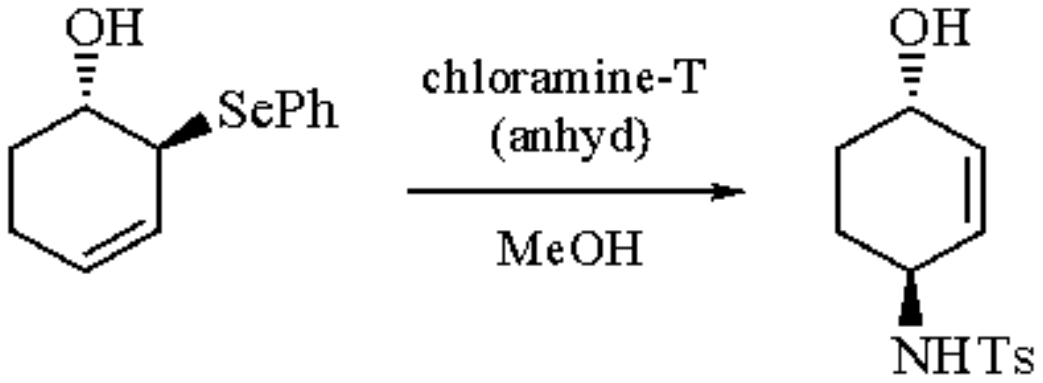

(4)

Diphenyl disulfide and diphenyl diselenide react with chloramine-T (anhyd) to give reagents that convert alkenes to *trans*-vicinal phenylthio(seleno)-*N*-tosylamines (eq 5).[13] Extension of this to the synthesis of α-phenylthio(seleno) ketones from silyl enol ethers has been reported.[14]

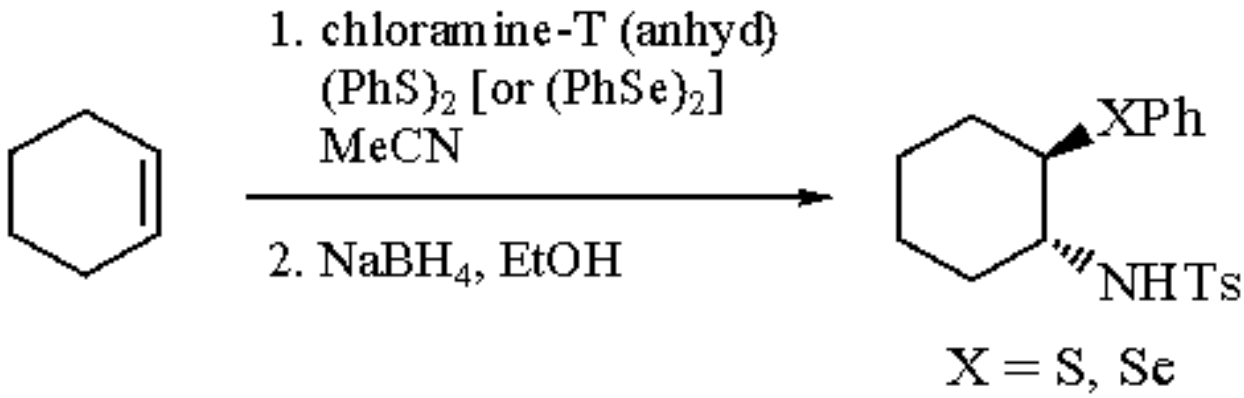

(5)

Chloramine-T (anhyd) converts selenium and tellurium metal to the diimide species (**1**) and (**2**), respectively. The selenium analog (**1**) has been used for the allylic amination of alkenes and alkynes (eq 6),[2,15] while its tellurium counterpart (**2**) has found utility in the synthesis of *N*-tosylimines from aldehydes.[16] Compound (**1**) has also been used in the 1,2-diamination of 1,3-dienes, but the yields were poor.[17]

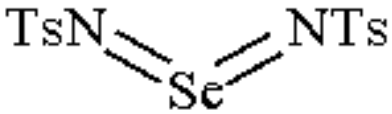

(1)

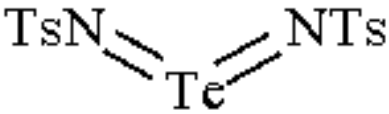

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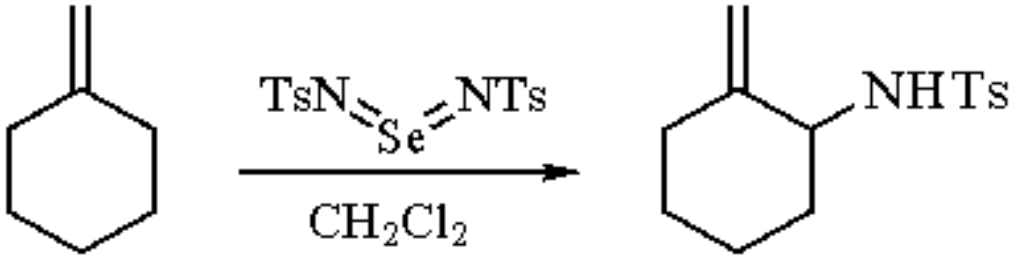

(6)

Other Reactions with Alkenes.

Chloramine-T, either alone or in conjunction with other agents, reacts with a variety of carbon-carbon double bonds to generate useful products. Under acidic conditions in aqueous acetone, alkenes give chlorohydrins,[18] while in an acetic acid medium the acetylated products are produced.[19] An intramolecular version allows for the synthesis of chlorolactones (eq 7).[20] Electron-rich alkenes, such as enamines, react to give α-aminated aldehydes (eq 8).[21] Vinyl ethers give the α-(*N*-tosylamino)aldehydes.

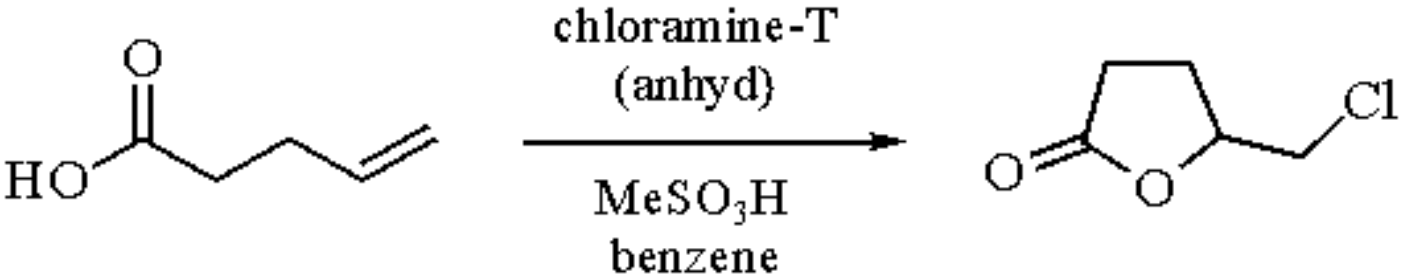

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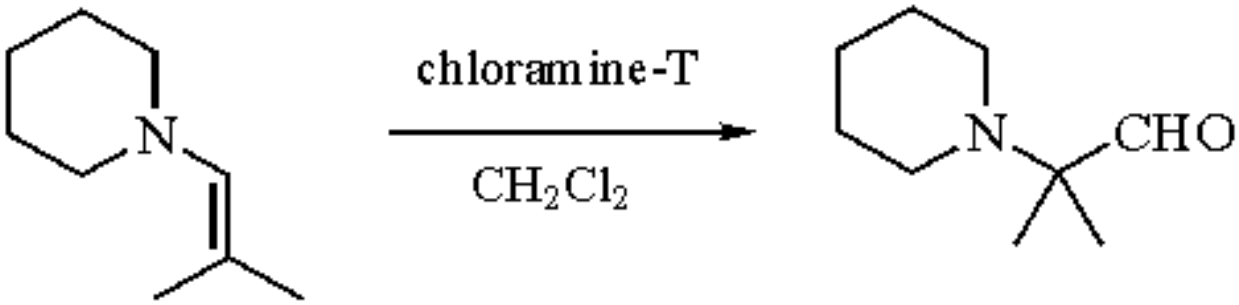

(8)

The reaction of alkenes with chloramine-T in the presence of catalytic amounts of ***Osmium Tetroxide*** provides a convenient and general method for the vicinal oxyamination of alkenes (eq 9).[22] Phase transfer conditions have also been employed.[23]

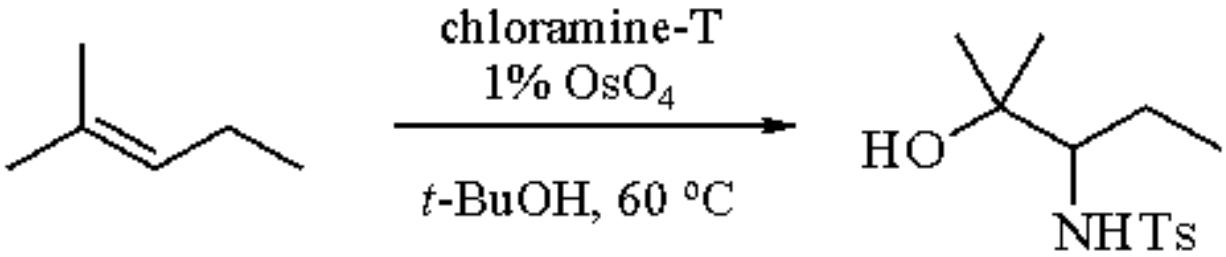

(9)

Other Oxidations.

Chloramine-T reacts with NaBr and NaI to provide a convenient method of generating BrCl and ICl, respectively, in situ (see ***Bromine Chloride***).[24,25] Chloramine-T has also been used to oxidize aldoximes to nitrile oxides as part of a synthesis of isoxazolines (eq 10).[26] A similar oxidation of aldehyde hydrazones to nitrilimines has also been reported.[27]

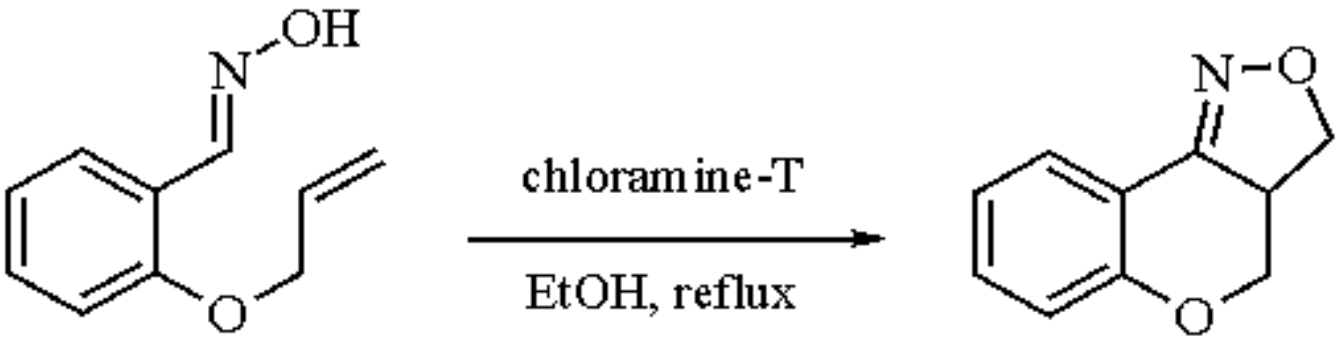

(10)

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R. Richard Goehring

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Chloranil[1]

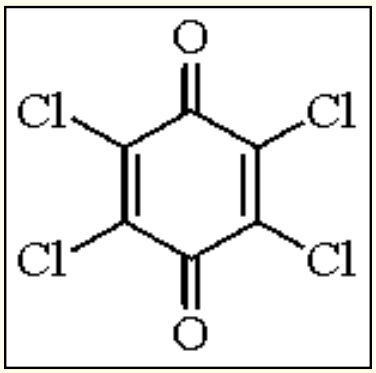

[118-75-2] · $C_6Cl_4O_2$ · Chloranil · (MW 245.89)

(oxidant, particularly useful for dehydrogenation to aromatic[1,2] and α,β-unsaturated carbonyl[2] compounds)

Alternate Names: 2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione; 2,3,5,6-tetrachloro-*p*-benzoquinone.

Physical Data: mp 290 °C; sublimes: E_0 742 mV (benzene).

Solubility: insol H_2O; sol ether; slightly sol alcohol, chloroform, CS_2, and light petroleum.

Form Supplied in: yellow solid.

Analysis of Reagent Purity: UV (λ_{max} 290 [log ε 4.34, cyclohexane]).

Purification: sublimation or recrystallization from benzene or acetic acid.

Handling, Storage, and Precautions: potential skin irritant; this reagent should be handled in a fume hood.

Dehydrogenation Reactions.

Chloranil and other quinones of high oxidation potential (see ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone***) are powerful oxidants which have found extensive application in dehydrogenation reactions.[1,2] Chloranil is particularly suitable for the aromatization of hydroaromatic substrates and has been used successfully in the synthesis of aromatic carbocycles[3] and nitrogen[4] and sulfur[5] heterocycles. The sequential aromatization of Diels-Alder adducts is an important application (eq 1).[6] Chloranil has also been used to facilitate the formation of α,*p*-dimethylstyrene from citral (eq 2), where its cheapness and efficacy makes it a preferred dehydrogenating reagent.[7]

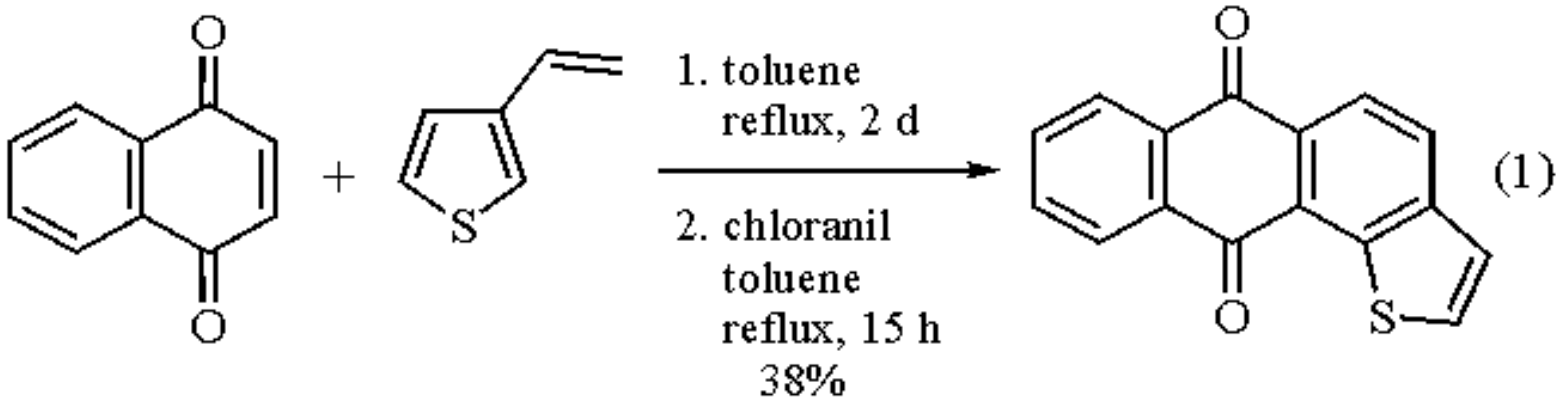

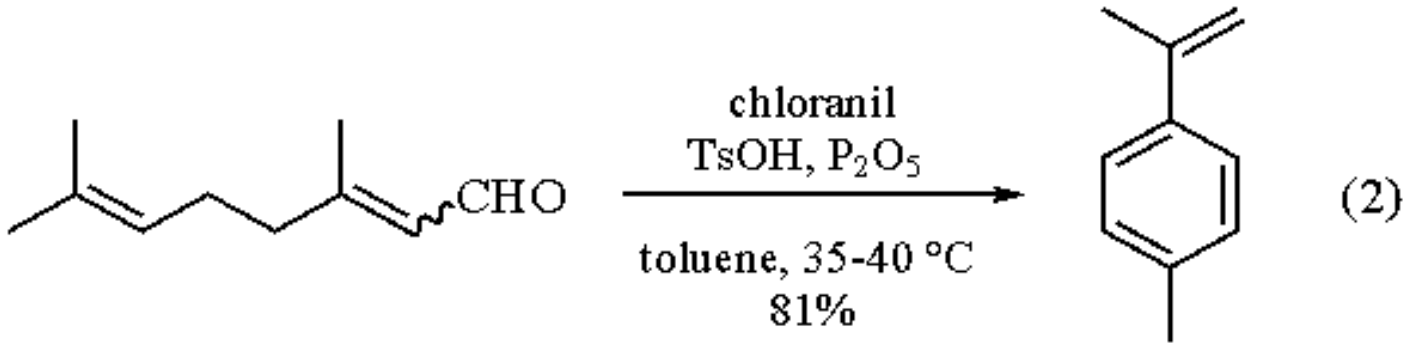

Dehydrogenation reactions have been shown to proceed faster in polar solvents such as alcohols and DMF and are enhanced by electron donating substituents in the ring system to be oxidized.[1]

Although skeletal rearrangements rarely occur during dehydrogenation reactions with quinones, Wagner-Meerwein rearrangements leading to alkyl group migration have been reported in the aromatization of cycloalkanes possessing *gem*-dialkyl substituents.[8] A somewhat more unusual oxidation of *gem*-dialkylpyrazolidines, which is markedly accelerated by the addition of chloranil, gives pyrazoles without rearrangement by C-C bond cleavage (eq 3).[9] Chloranil is also an effective reagent for the dehydrogenation of *N*-substituted dihydroquinolines[10] and -isoquinolines,[11] where high yields of quinolinium and isoquinolinium salts are formed (eq 4).

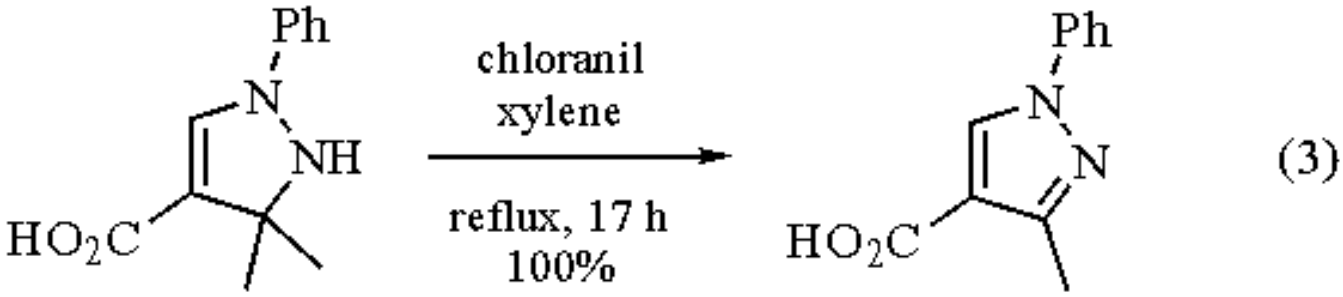

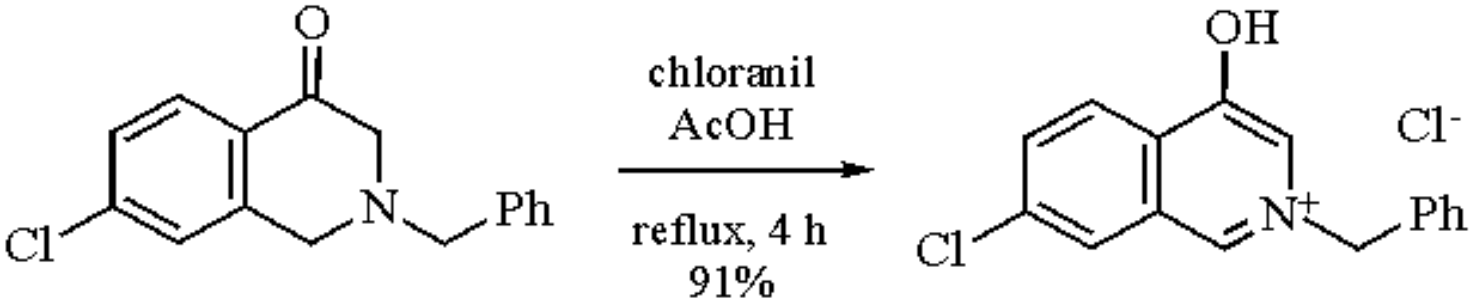

(4)

While quinones do not usually react directly with furans, oxidation of the intermediate hydroquinone by the addition of a high potential quinone such as chloranil results in the formation of 2-furylquinones in reasonable yield (eq 5).[12]

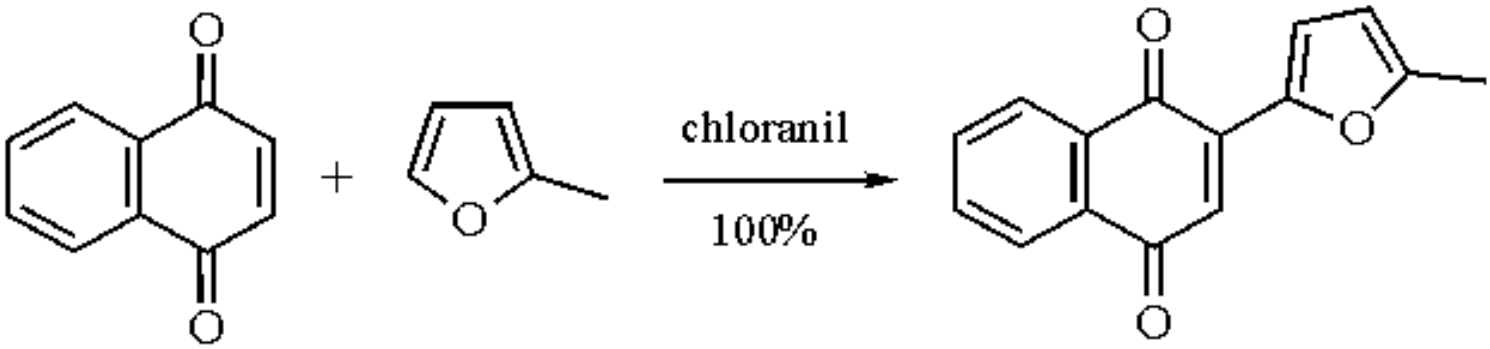

(5)

Chloranil and other high potential quinones have been extensively used in the dehydrogenation of cyclic carbonyl compounds,[2] particularly steroidal ketones.[2,13] One reaction of importance is the formation of 4,6-dien-3-ones from 4-en-3-ones (eq 6).[14] In certain instances, steroids may be fully aromatized using this procedure.[15]

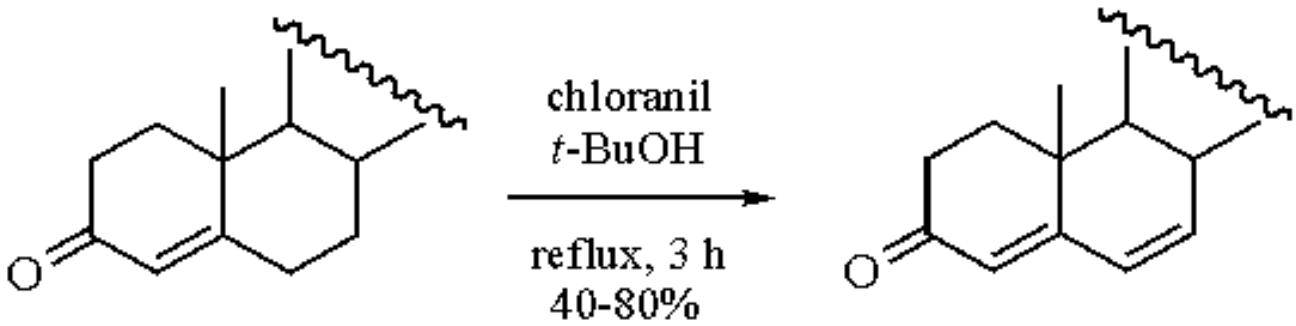

(6)

Other Oxidation Reactions.

In addition to dehydrogenation, quinones with high E_0 values effect various oxidation reactions.[1] Chloranil in particular is an effective electron acceptor photosensitizer for the oxidation of toluenes to benzaldehydes, where other classical photosensitizers have been shown to fail.[16]

Miscellaneous Reactions.

Chloranil undergoes facile nucleophilic displacement reactions with primary and secondary amines, leading to 2,5-bis-amino derivatives (eq 7).[17] Spectroscopic studies have demonstrated that with aliphatic amines at least, the reaction

proceeds via a one-electron oxidation of the amine.[18,19] Chloranil has also been shown to induce the dimerization of diaryldiazomethanes through a reaction believed to involve prior addition across the quinone carbonyl group.[20]

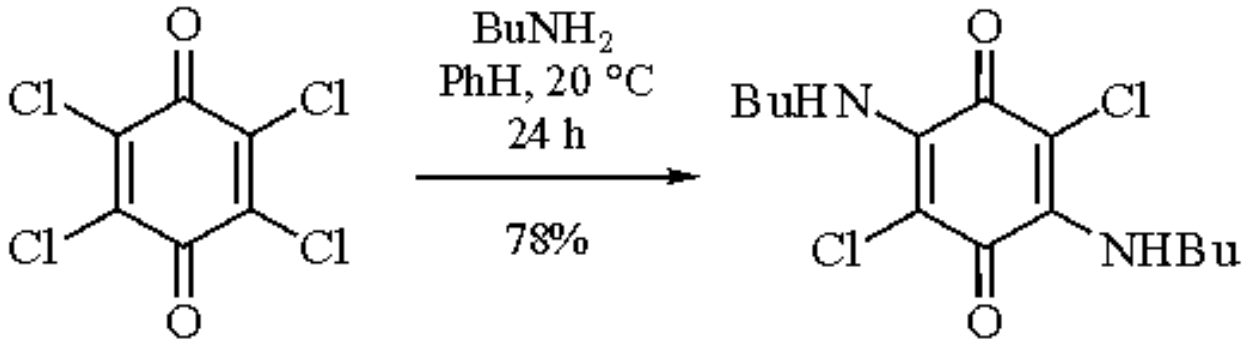

(7)

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Chlorine[1]

[7782-50-5] · Cl_2 · Chlorine · (MW 70.91)

(powerful oxidizing and chlorinating agent)

Physical Data: yellowish-green gas, mp -101 °C, bp -34 °C; *d* 3.21 g cm^{-3} (gas, rt), 1.56 g cm^{-3} (liq, -35 °C).

Solubility: sl sol water (0.7 g in 100 mL at 20 °C); sol acetic acid, benzene, aliphatic hydrocarbons, chlorinated solvents, DMF.

Form Supplied in: packaged in cylinders with stainless steel or monel regulators.

Preparative Methods: chlorine is commercially available, but small quantities can be generated in the laboratory. The most common procedure involves the treatment of solid $KMnO_4$ with conc HCl (0.89 g of $KMnO_4$ and 5.6 mL of conc HCl per g of chlorine required).[2] It is recommended that chlorine so generated be dried by passing in succession through gas-washing bottles containing H_2O (to remove HCl), concd H_2SO_4 (to remove H_2O), and glass wool (to remove spray).[3] Preparations using conc HCl/MnO_2[4] or by heating $CuCl_2$ (anhyd)[5] have also been reported.

Analysis of Reagent Purity: iodometric titration; the chlorine can be volatilized and the moisture and residue determined gravimetrically.[1a]

Purification: commercial chlorine should be purified with H_2SO_4, CaO, and P_2O_5 and subsequently condensed in a dry ice-acetone bath and vaporized, repeatedly, while the noncondensable gases are removed with a pump.[4]

Handling, Storage, and Precautions: [5] highly toxic, nonflammable gas. Forms explosive mixtures with hydrogen, acetylene, or anhydrous ammonia. It is corrosive when moist. Chlorine is a strong oxidant and reacts violently with combustible substances, reducing agents, organic compounds, phosphorus, and metal powders. Avoid skin contact. Use protective clothing and a full-face respirator equipped with a NIOSH-approved organic vapor-acid gas canister. Cylinders should be stored away from sources of heat. All reactions should be conducted in a well-ventilated fume hood. The amount of chlorine added to a reaction mixture can be determined by weighing the cylinder before and after addition, or by condensing the required volume into a calibrated vessel and subsequently allowing it to volatilize while connected to the reaction vessel, or by generation from a known quantity of $KMnO_4$.

Substitution Chlorination.

Chlorine atoms, obtained from the dissociation of chlorine molecules by thermal or photochemical energy, react with saturated hydrocarbons by a radical chain mechanism. Chlorine reacts with methane to form methyl chloride, methylene chloride, chloroform, and carbon tetrachloride.[1a] Trialkylboranes have also been used to induce the radical chlorination of alkanes, e.g. chloro-2,3-dimethylbutanes are produced from 2,3-dimethylbutane.[6] Ethers are also chlorinated by photoinduced radical substitution reactions (eq 1).[7a]

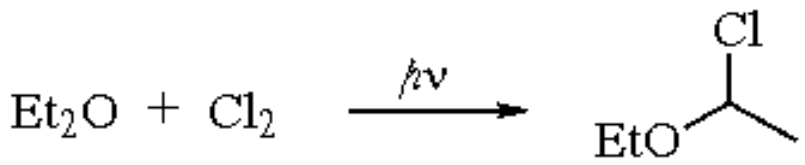

(1)

The chlorination of carboxylic acids with molecular chlorine is catalyzed by phosphorus and its trihalides.[7b] Chlorine has been used to chlorinate methyl esters of carboxylic acids to form monochloro esters.[8] Chlorinations with chlorine favor the (o - 1)-position rather than the (o - 2)-position obtained with ***Sulfuryl Chloride***.[8] Thus the chlorination of methyl heptanoate with chlorine results mainly in methyl 6-chloroheptanoate, whereas chlorination with sulfuryl chloride results mainly in methyl 5-chloroheptanoate.[8] Low temperatures are required for the chlorination of long-chain carboxylic acid methyl chlorides, as unsaturated compounds are formed at higher temperatures due to the elimination of HCl.

The main products of the chlorination of carbamates are the *N*-dichloro derivatives (eq 2).[7c]

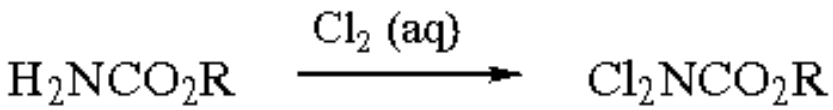

(2)

Aromatic amines react readily with chlorine, e.g. aniline is chlorinated to give 2,4,6-trichloroaniline in high yield (eq 3).[7d]

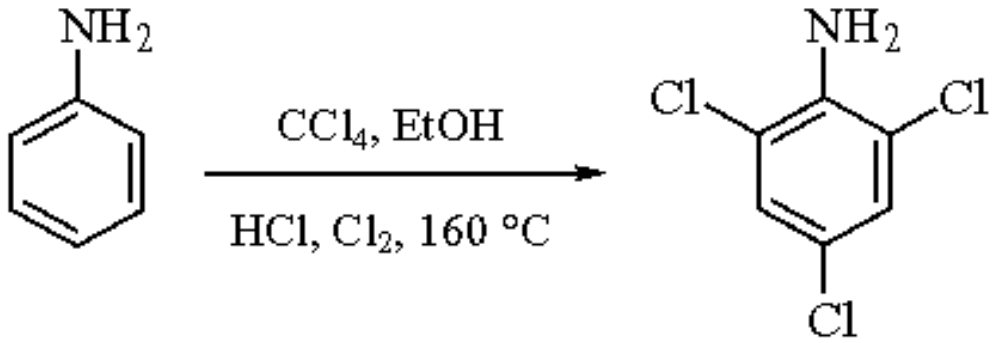

(3)

Primary and secondary amides react with chlorine to give *N*-chloroamides and HCl.[7e] The reaction is reversible, and the products are favored by highly polar solvents.

α-Chlorination of aliphatic acids has been achieved with chlorine using enolizing agents like chlorosulfonic acid, H_2SO_4, HCl, or $FeCl_3$ with a radical trapper like *m*-dinitrobenzene, oxygen, or chloranil.[9] The imidyl hydrogen atoms of aldazines can be substituted with chlorine (eq 4).[7f]

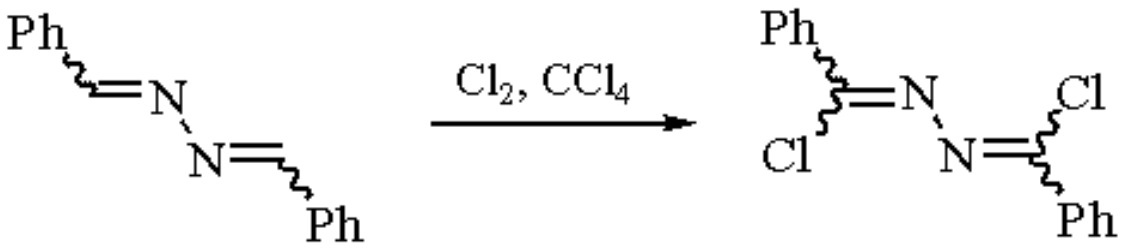

(4)

Addition Chlorination.

Saturated chlorides are formed when chlorine reacts with alkenes, e.g. chlorination of ethylene results in ethylene dichloride and chlorination of vinyl chloride gives 1,1,2-trichloroethane.[1a] These alkyl chlorides are important synthetic intermediates, e.g. 1,1,2-trichloroethane can be converted into vinylidene chloride in an alkaline medium.[1a] The addition of chlorine to 1-trimethylsilyl-1-alkenes in CH_2Cl_2 at low temperatures, followed by the elimination of Me_3SiX with methanolic sodium methoxide at 25 °C, produces vinyl chlorides in good yields (eq 5).[10]

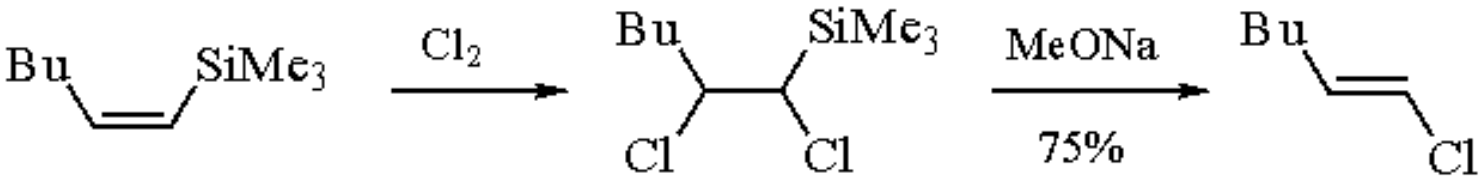

(5)

The radical chain addition reactions of chlorine are initiated by light or the walls of the reaction vessel and inhibited by oxygen. Some ionic addition reactions are accelerated by ***Iron(III) Chloride***, ***Aluminum Chloride***, ***Antimony(V) Chloride***, or ***Copper(II) Chloride***.[11]

Chlorination of Aromatics.

Aromatic compounds may be chlorinated in the presence of Lewis acids like iron and iron(III) chloride. Low temperatures favor monochlorination, while high temperatures (150-190 °C) favor dichlorinated products.[11] The chlorination of alkylbenzenes in alcoholic media can result in higher yields of monochloro derivatives than when $FeCl_3$ is used.[12] Chlorine diluted in water converts tyrosine into 3-chloro-4-hydroxybenzyl cyanide (eq 6);[13] larger amounts of chlorine give 3,5-dichloro-4-hydroxybenzyl cyanide and 1,3-dichloro-2,5-dihydroxybenzene. The latter product can be converted into 2,6-dichloro-*p*-benzoquinone with additional aqueous chlorine.

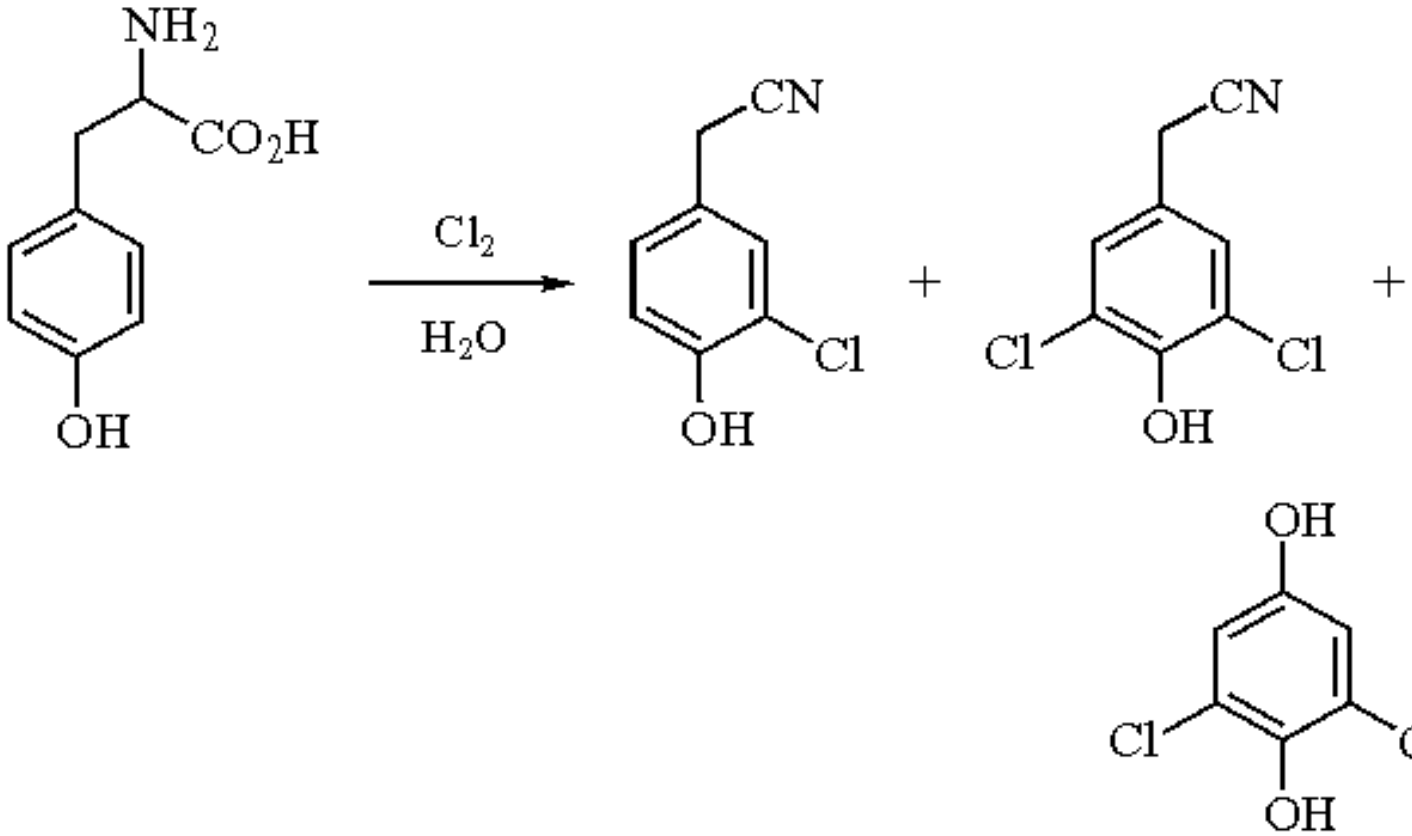

(6)

Toluene is chlorinated by the radical mechanism to give benzyl chloride, benzal chloride, and benzotrichloride.[11] Sulfuryl chloride, ***t-Butyl Hypochlorite***, ***Hydrogen Chloride*** (in the presence of a copper-salt catalyst), and ***N-Chlorosuccinimide*** have also been used to chlorinate aromatics.[11]

Chlorination of phenol yields 2-chlorophenol and 4-chlorophenol in a ratio of 0.45:0.49, which is higher than the *ortho*/*para* ratio obtained with *t*-butyl hypochlorite.[14] 4-Alkylphenols react with chlorine in various solvents to form mainly 4-alkyl-4-chlorocyclohexa-2,5-dienones (in yields of 19-100%) and substitution products.[15] Other chlorinating agents (alkyl hypochlorites, sulfuryl chloride, hypochlorous acid, and antimony pentachloride) have also been used, but they result in polychlorinated cyclohexadienones and cyclohexenones.[15] The chlorination of dimethylphenols with chlorine in acetic acid containing HCl results in polychlorinated cyclohexenones (eq 7).[16]

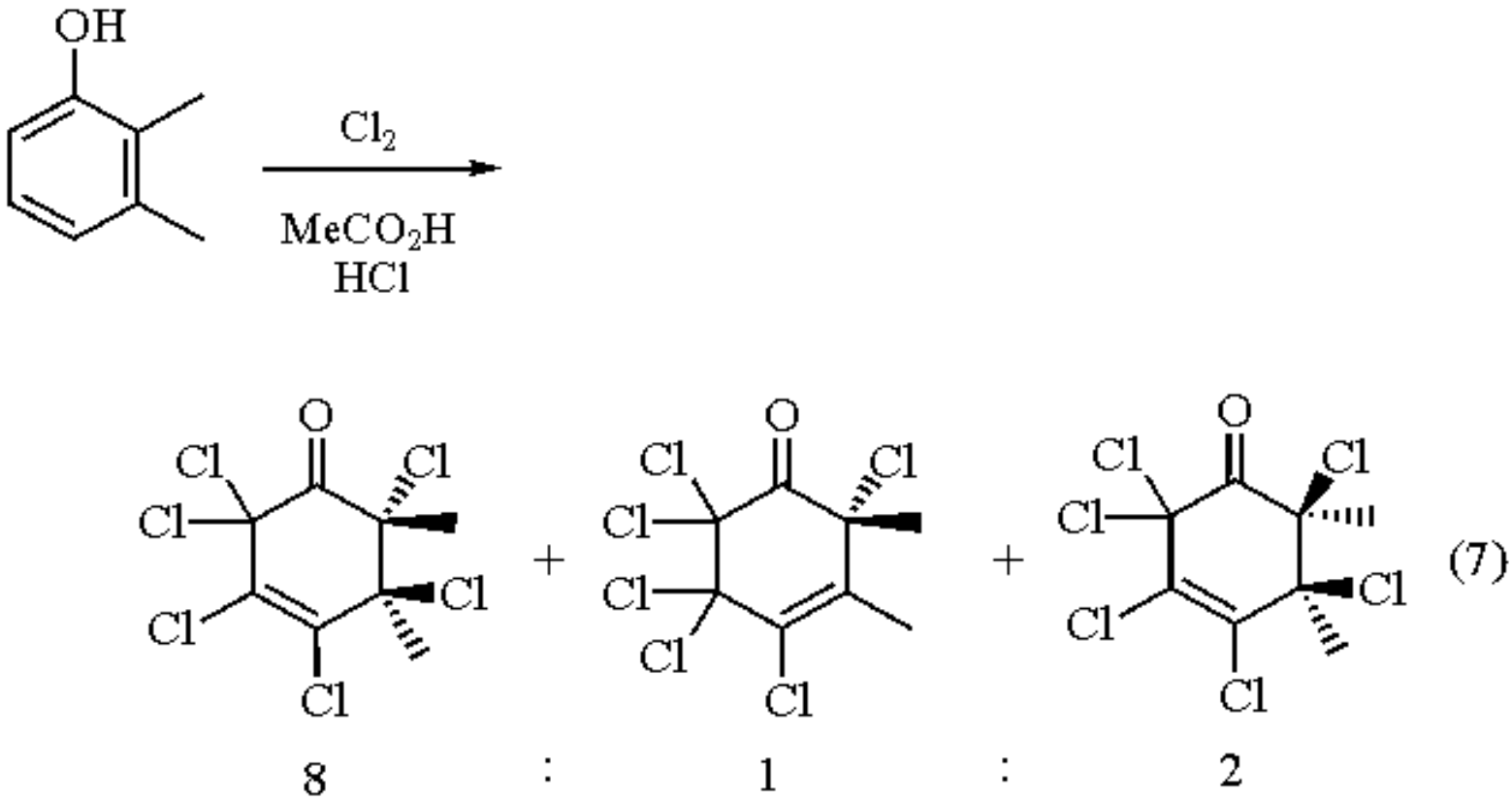

The α-monochlorination of alkyl aryl ketones by chlorine gas occurs readily in a variety of solvents (e.g. CH_2Cl_2, $CHCl_3$, CCl_4, HOAc).[17] α,α-Dichlorination of alkyl aryl ketones occurs with sodium acetate in refluxing acetic acid (5 h, 80-90% yield). Alternatively, DMF can be used as the catalyst (80-100 °C, 35-45 min) (eq 8).[18]

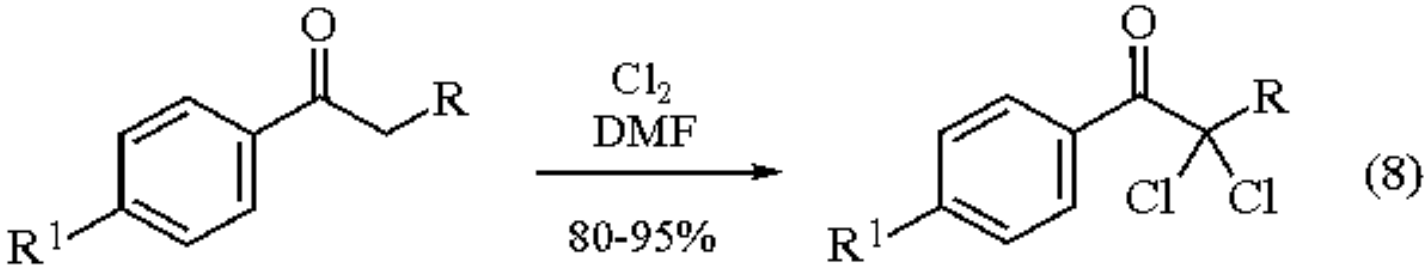

R = Me, Et, Pr, *t*-Bu, Ph; R^1 = H, Cl, Br, Me

Chlorination of phenylenedibenzenesulfonamides by chlorine in nitrobenzene results in the formation of a mixture of dichloro derivatives.[19] The more useful tetrachloro derivative can be prepared by successive oxidations and additions of HCl, or in one step using Cl_2 in DMF (eq 9).[19] The temperature must be kept below 60 °C when Cl_2/DMF is used, or a runaway thermal reaction can result.[20]

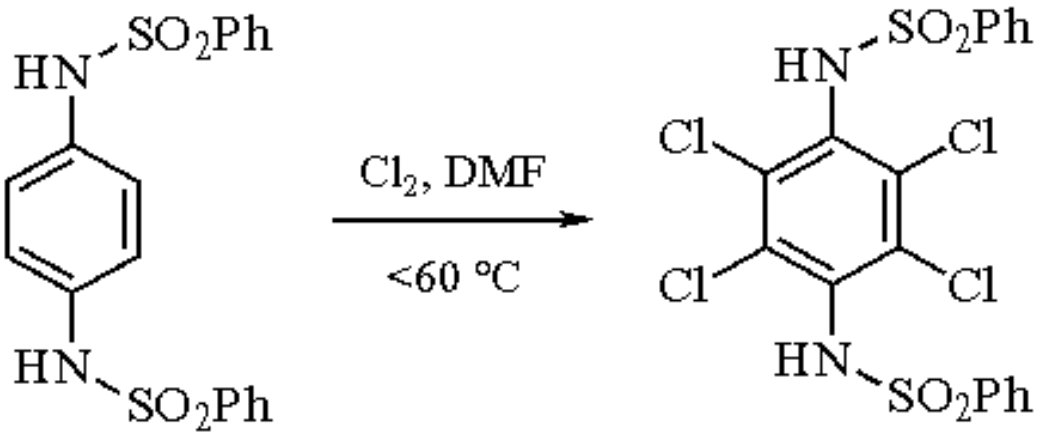

(9)

Chlorine has been used for the chlorination of heterocycles,[7i -k] but the varied reactivity of substrates makes discussion of these reactions too lengthy for this review.

Oxidation of Alcohols.

Alcohols have been oxidized with complexes of chlorine with dimethyl sulfide,[21] DMSO,[22] iodobenzene,[21] pyridine,[23] and HMPA.[21] Secondary hydroxyl groups are more readily oxidized than primary hydroxyl groups when the ***Chlorine-Pyridine*** (eq 10)[23] and chlorine-HMPA complexes[21] are used. The same results are obtained with 3-iodopyridine dichloride.[23]

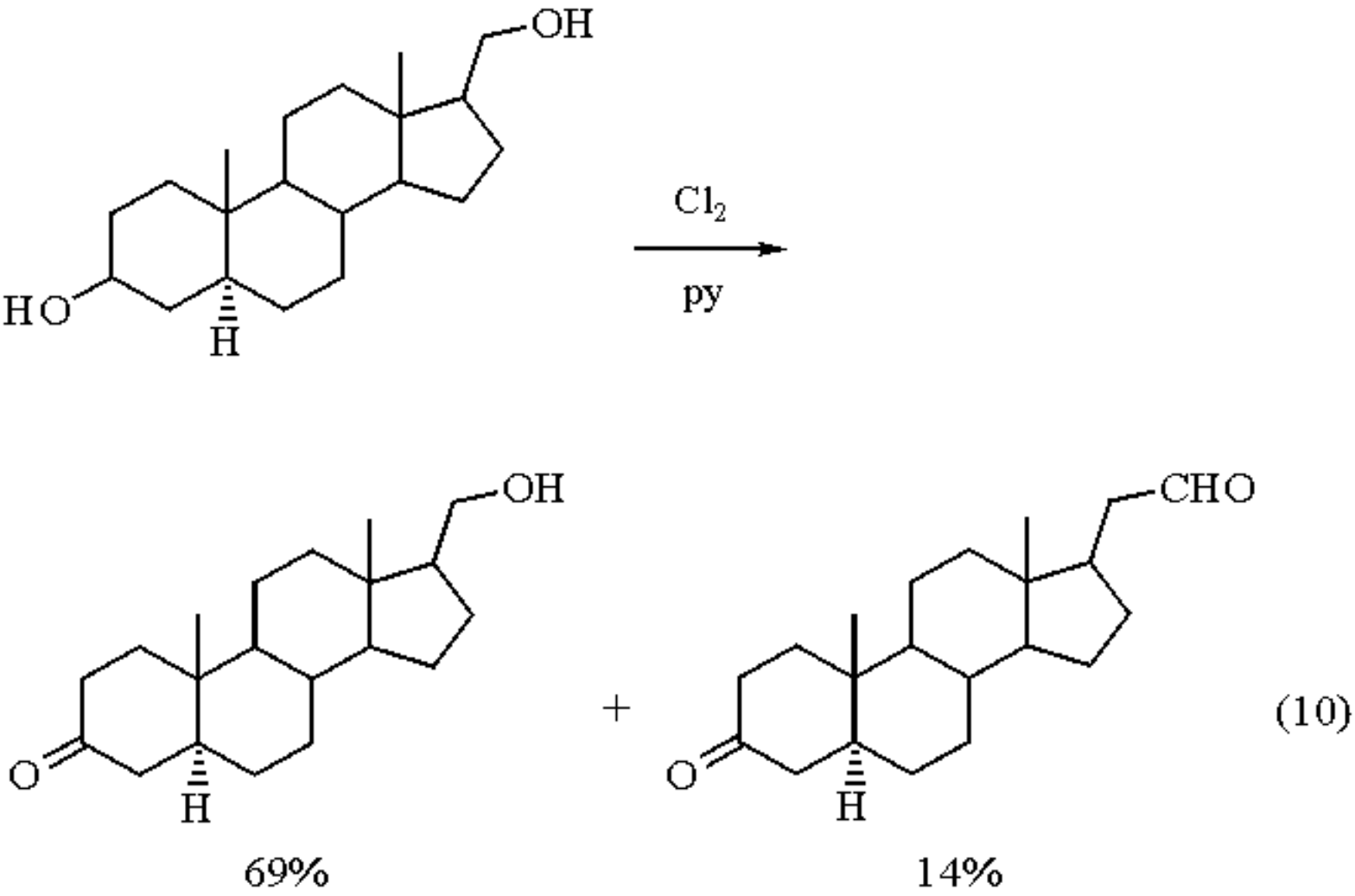

(10)

Hydroxythiols undergo chlorination reactions with Cl_2 in dichloromethane to form sultines and sulfinic esters after hydrolysis (eq 11).[24]

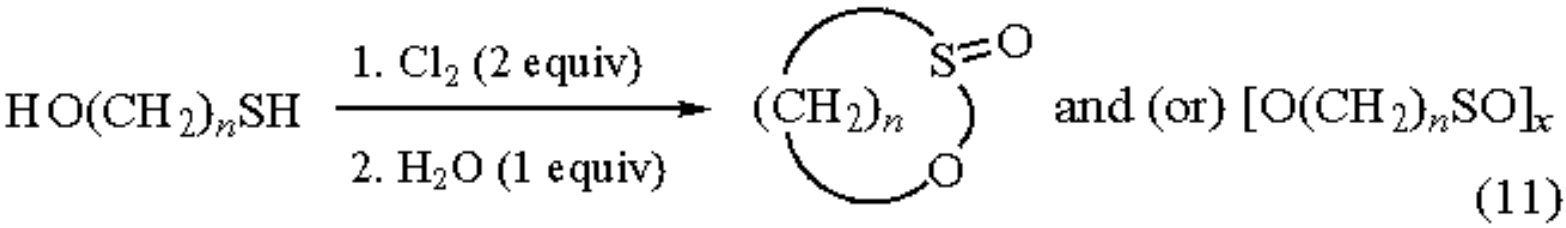

(11)

The oxidation of glycols usually results in C-C bond cleavage, but oxidation of the *s*-carbinol can be effected with a complex of a methyl sulfide (RSMe) and chlorine or NCS, or of DMSO and chlorine.[25] The tricyclic α-ketol (**2**) (eq 12) can be prepared from the glycol (**1**) using these reagents.[25]

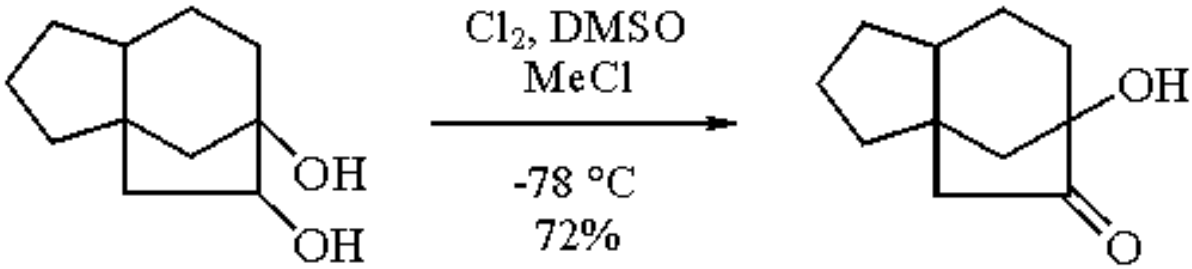

(12)

(1) (2)

Chlorinolysis.

The C-C bond of short-chain hydrocarbons (<C_3 and any partially chlorinated derivatives) can be cleaved by chlorine at high temperatures to give chlorinated products. 1,2-Dichloroethane and 1,2-dichloropropane are cleaved by chlorine to give carbon tetrachloride and tetrachloroethylene with HCl as a byproduct.[11]

C-S Bond Cleavage.

The benzylic group of alkyl benzyl sulfides can be selectively cleaved by chlorine in aqueous acetic acid to give alkanesulfonyl chlorides (eq 13).[26]

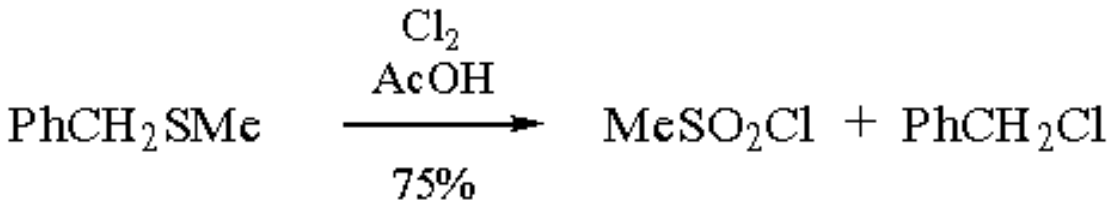

(13)

Excess chlorine has been used to cleave the secondary C-S bond in lactam (**3**) (eq 14) to give the azetidin-2-one (**4**) in nearly quantitative yield.[27] When *N*-acyl groups are present, as in eq 15, the nitrogen lone pair electrons are inhibited, so cleavage of the tertiary C-S bond is favored over the azetidine C-S bond.[27]

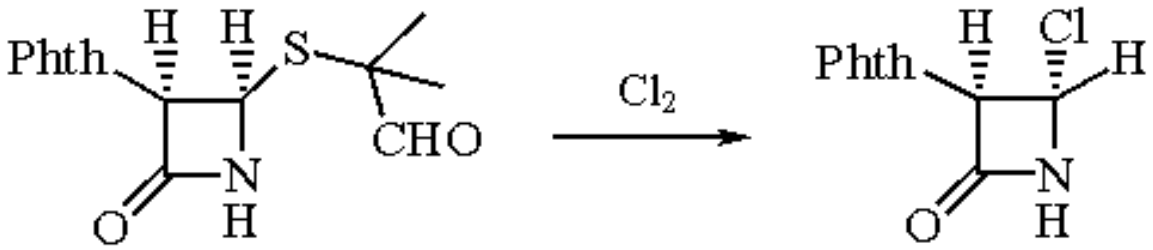

(14)

(3) (4)

Phth = phthalimido

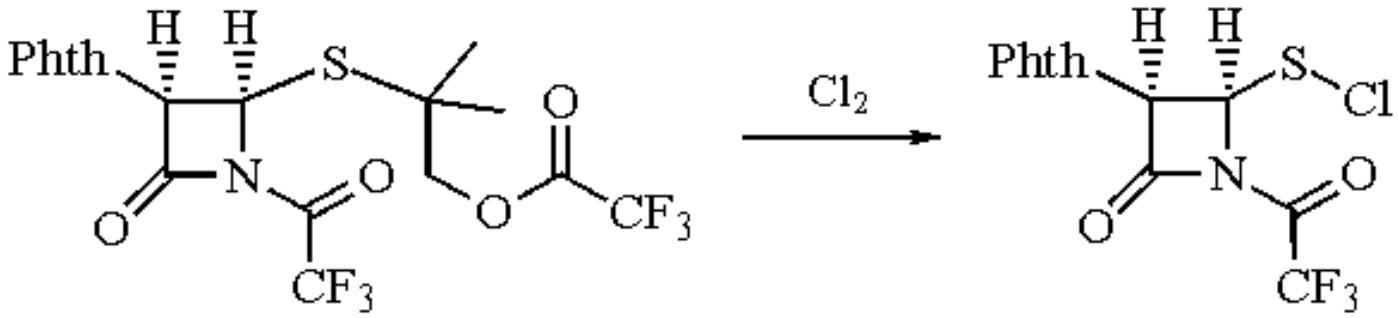

(15)

Other Reactions.

Chlorine and ***Sodium Bromide*** are used to produce ***Bromine Chloride***, which can be used in bromination reactions which are faster than those with elemental ***Bromine***, and which take place in aqueous solution rather than acidic solvents; the bromination of 4-nitrophenol to 2,6-dibromo-4-nitrophenol is one example.[28]

Thiocyanogen, prepared in anhydrous conditions from silver or lead thiocyanate and bromine, cannot be used for addition reactions with halogenated alkenes and is too expensive for most commercial processes.[29] Thiocyanogen can be prepared in a two-solvent system from ***Sodium Thiocyanate*** and chlorine.[29] The thiocyanogen is extracted into the toluene layer and can be used for addition reactions to vinyl halides in the synthesis of haloalkylene bisthiocyanates.

Several methods for the preparation of ***Phosgene*** are known, e.g. the gas-phase reaction of chlorine with carbon monoxide on activated carbon, the decomposition of trichloromethyl chloroformate, and the reaction of carbon tetrachloride with oleum.[30] Phosgene can be synthesized conveniently just before use by the reaction of chlorine with carbon monoxide in the presence of catalytic amounts of *t*-phosphine oxides, using carbon tetrachloride as the solvent.[30]

Chlorodimethylsulfonium chloride, generated in situ from ***Dimethyl Sulfide-Chlorine***, is a useful reagent for the conversion of epoxides to α-chloro ketones (eq 16)[31] and of aldoximes to nitriles,[32] in the presence of tertiary amines. Bromodimethylsulfonium bromide, generated in the same way, can be used to form α-bromo ketones, but the yields are lower than those obtained for α-chloro ketones.[31]

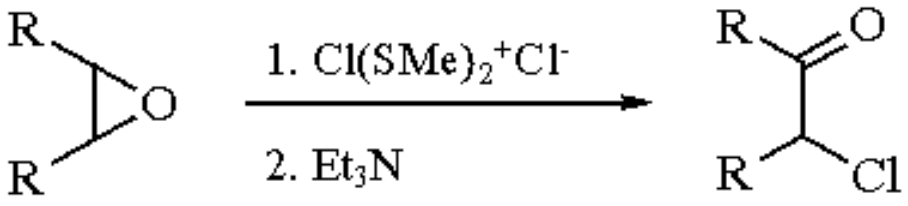

(16)

Chlorine and ***Triphenylphosphine*** are used in the synthesis of lactams from cycloalkanone oximes in high yields (eq 17).[33]

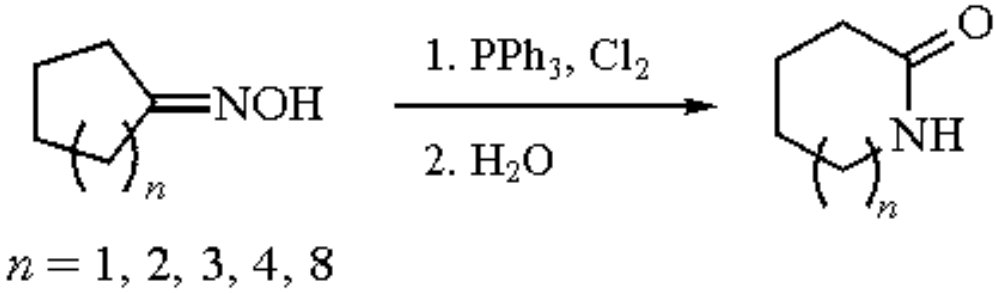

(17)

Alkanesulfonyl chlorides, which are useful reagents and intermediates in organic synthesis, can be conveniently produced from dithiocarbonic acid esters (eq 18).[34]

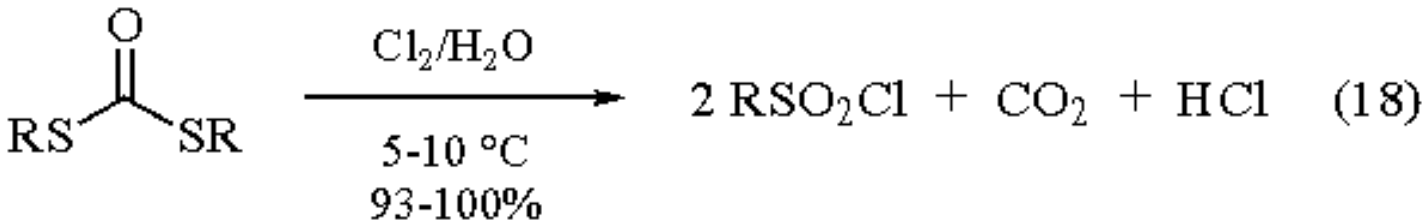

(18)

The indirect oxidation of trialkyl phosphites to trialkyl phosphates can be achieved in high yield and purity with chlorine in the corresponding alcohol (eq 19).[35] The indirect oxidation can also be effected by carbon tetrachloride, bromotrichloromethane, ***Carbon Tetrabromide***, ***Chloroform***, and hexachlorocyclopentadiene in alcohol.[35] Cyclic phosphites may undergo ring opening during reactions with chlorine, depending on the size of the ring and its degree of substitution.[7g]

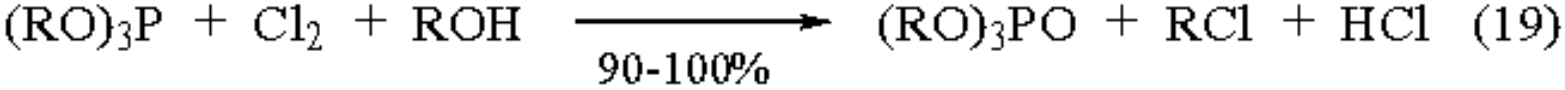

(19)

Cyclooctanone oxime can be synthesized from cyclooctane by a photochemical reaction with chlorine and nitrous oxide (eq 20).[36] The oxime hydrochloride intermediate is converted into the oxime by aqueous sodium hydroxide.

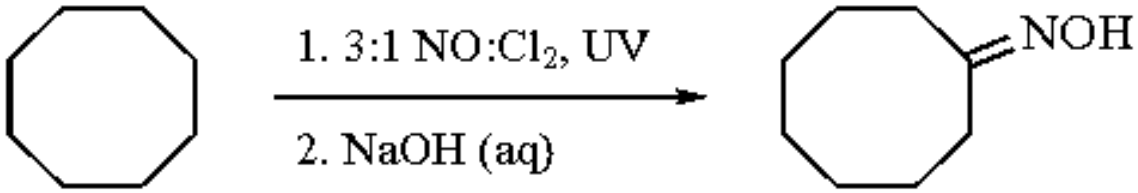

(20)

Chlorine can be used for the synthesis of hydrazines from ureas, via diaziridinone intermediates (eq 21).[7h]

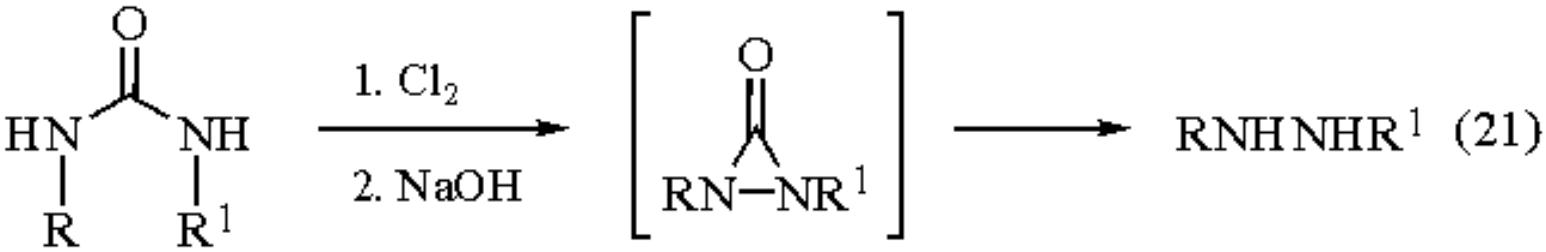

(21)

Related Reagents.

Bromine; ***Chlorine-Chlorosulfuric Acid***; ***Dimethyl Sulfide-Chlorine***; ***Chlorine-Pyridine***; ***Iodine***; ***Sulfuryl Chloride***.

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Chlorine-Chlorosulfuric Acid

Cl_2 + $ClSO_3H$

(Cl_2)

[7782-50-5] · Cl_2 · Chlorine-Chlorosulfuric Acid · (MW 70.91) ($ClSO_3H$)

[7790-94-5] · $ClHO_3S$ · Chlorine-Chlorosulfuric Acid · (MW 116.53)

(effective agent for α-halogenation of aliphatic acids; $ClSO_3H$ + Br_2 or $ClSO_3H$ + I_2 are similar)

Alternate Name: chlorine-chlorosulfonic acid.

Physical Data: $ClSO_3H$: mp -80 °C, bp 152 °C; *n*20D 1.433; *d* at 18 °C, 1.766 g cm^{-3}; for Cl_2 see ***Chlorine***.

Form Supplied in: transparent liquid; widely available.

Purification: commercial chlorosulfuric acid is usually contaminated with sulfuric acid and hydrogen chloride, and should be distilled before use (bp 86-88 °C at 33 mmHg).

Handling, Storage, and Precautions: chlorosulfuric acid is poisonous, and a strong oxidant and skin irritant: handle very carefully with gloves and a protective face shield; store in isolation from water, as it reacts to form H_2SO_4 and HCl; prolonged heating causes decomposition to H_2SO_4, SO_2, and Cl_2.

Chlorination of Carboxylic Acids.

Chlorine (or bromine or iodine) mixed with ***Chlorosulfonic Acid*** is conveniently used for the corresponding α-halogenation of aliphatic acids. The radical chlorination of aliphatic acids, e.g. photochlorination, occurs at random positions, while acid-catalyzed chlorination (e.g. the present reaction, as well as Hell-Volhard-Zelinsky procedures using PCl_3) gives exclusively α-chloro acids.[1,2] Molecular oxygen and ***Chloranil***,[3] as well as 7,7,8,8-tetracyanoquinodimethane,[4] are effective radical trappers. Chlorosulfuric acid is much more effective than sulfuric acid, as it forms homogeneous mixtures and has a stronger acidity.

The mechanism for the chlorosulfuric acid-mediated halogenation of an aliphatic acid involves the initial conversion of the aliphatic acid into an enolized monoacyl sulfate, followed by the addition of molecular halogen to give an α-haloacyl halide (eq 1).[5]

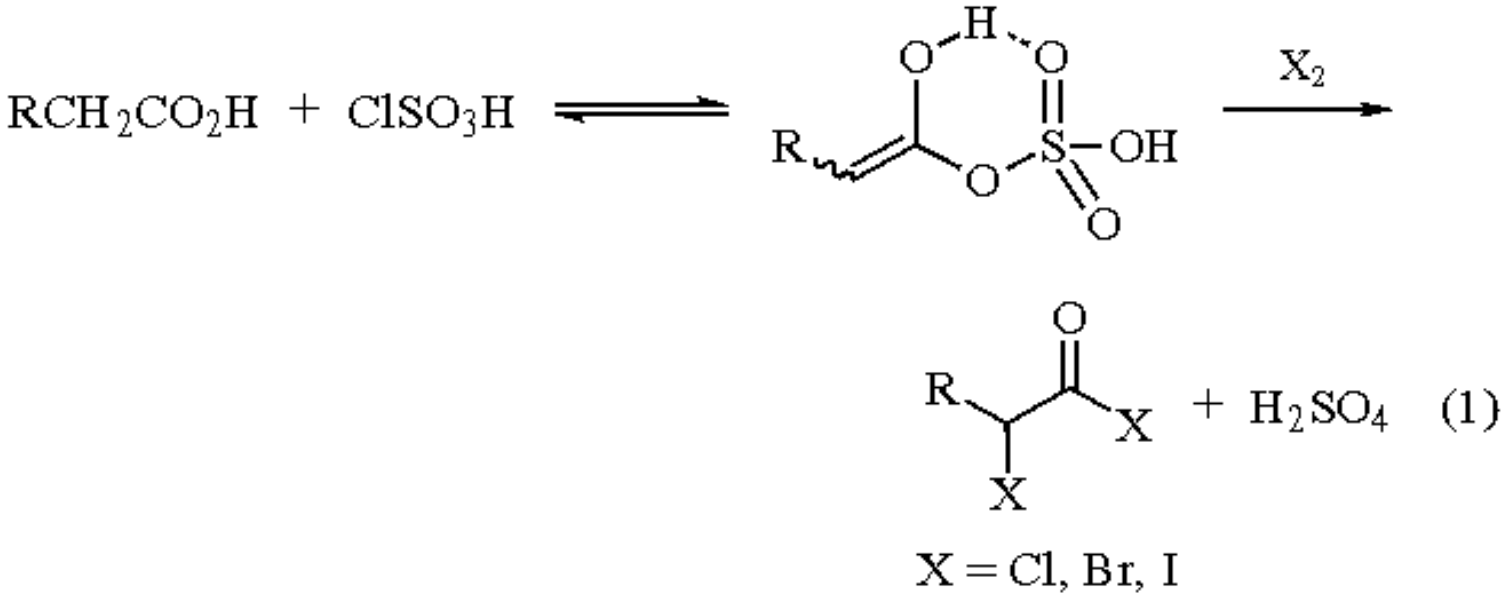

Examples of chlorination of aliphatic acids with 4:1 molar ratios of aliphatic acid:$ClSO_3H$ and with 2:1 molar ratios of Cl_2:O_2 are given in Table 1.[3,4,6,8,9]

Table 1 Chlorination of Aliphatic Acids with Cl_2-$ClSO_3H$

Acid	Conditions	Products, yield (%)	
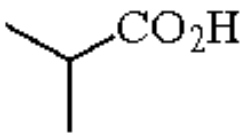	120 °C[3,6]	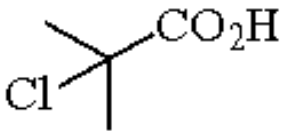 75	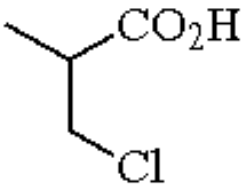 0.3
	120 °C[3]	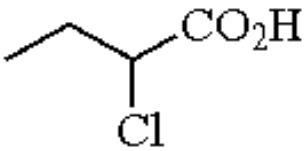 82	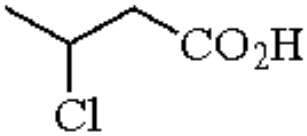 1.6
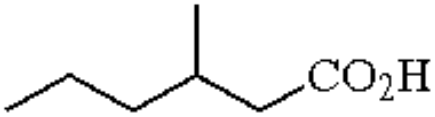	120 °C[3]	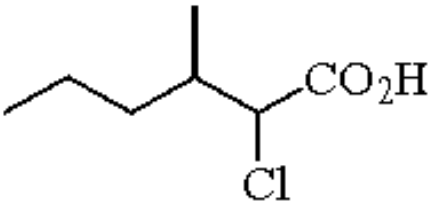 81	
		$Me(CH_2)_{14}$	

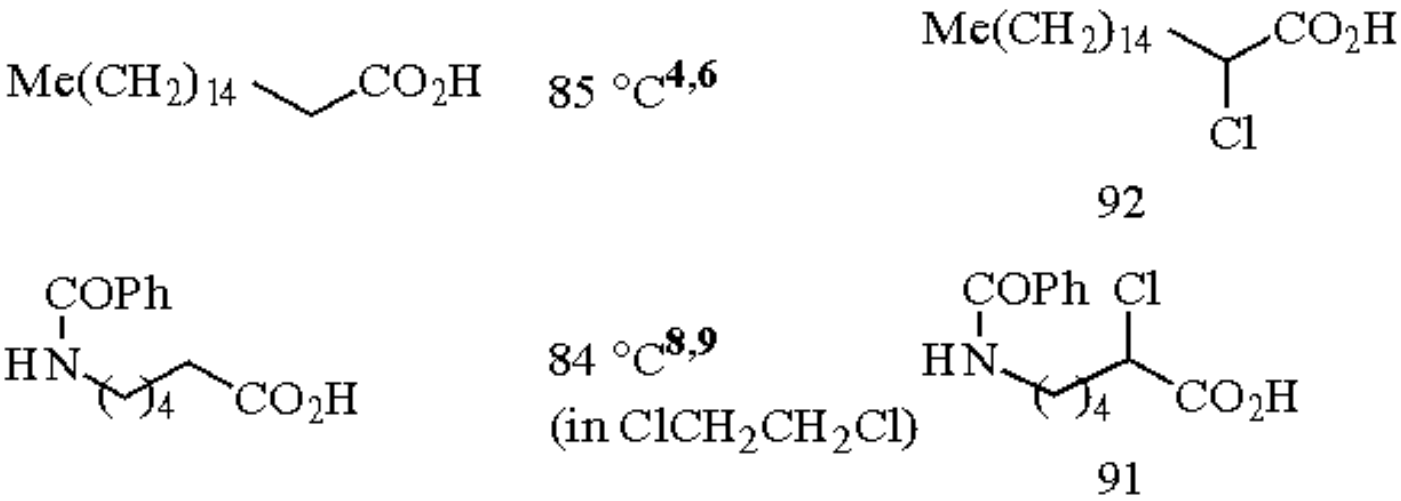

Bromine- or Iodine-Chlorosulfuric Acid Reagents.

Similarly, bromination or iodination of aliphatic acids is possible by using the reagents chlorosulfuric acid-halogen in dichloroethane without any radical trapper. Examples of brominations with 1:1:1 molar ratios of aliphatic acid:$ClSO_3H$:Br_2 are given in eqs 2 and 3.[10]

$$EtCO_2H \xrightarrow[78\%]{Br_2,\ ClSO_3H,\ ClCH_2CH_2Cl,\ 85\ °C} MeCHBrCO_2H \qquad (2)$$

$$i\text{-}PrCO_2H \xrightarrow[95\%]{Br_2,\ ClSO_3H,\ ClCH_2CH_2Cl,\ 85\ °C} Me_2CBrCO_2H \qquad (3)$$

Examples of iodination with molar ratios of 65:32:6.5 of aliphatic acid:$ClSO_3H$:I_2 are shown in eqs 4 and 5.[11] Here, excess $ClSO_3H$ converts the HI evolved to I_2, leading to the stoichiometry as shown in eq 6.[12]

$$EtCO_2H \xrightarrow[79\%]{I_2,\ ClSO_3H,\ ClCH_2CH_2Cl,\ 80\ °C} MeCHICO_2H \qquad (4)$$

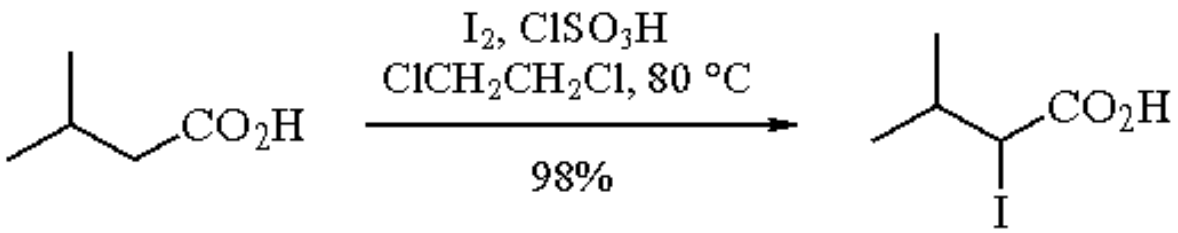

(5)

$$EtCO_2H + 0.5\ I_2 + ClSO_3H \longrightarrow MeCHICO_2H + HCl + 0.5\ H_2SO_4 + 0.5\ SO_2 \quad (6)$$

The similar oxidation of HBr to Br_2 is observed, but not that of HCl.[13] The yields for iodination of acetic acid (12%) and α,α-disubstituted acids (e.g. isobutyric acid, 14%) are poor, but in general acids give 93-98% yields.[11]

The effect of substituents on the relative rate constant k_{rel} of bromination and iodination fits the Taft equation (eq 7),[14] where ρ* is the polar reaction constant, &SSigma;σ* is the sum of polar substituent constants, δ is the steric reaction constant, and &SSigma;E_σ is the sum of steric substituent constants. The observed ρ* values are negative for both bromination and iodination, suggesting an electrophilic attack of the positively polarized halogen molecule on the double bond of the enol.

$$\log k_{rel} = \rho^*\Sigma\sigma^* + \delta\Sigma E_\sigma \quad (7)$$

Related Reagents.

Chlorine; ***Chlorosulfonic Acid***.

---

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Yoshiro Ogata

Chlorine Fluoroxysulfate[1]

$ClOSO_2F$

[13637-84-8] · $ClFO_3S$ · Chlorine Fluoroxysulfate · (MW 134.51)

(strong electrophilic chlorinating agent, capable of halogen abstraction reactions to give esters of fluorosulfuric acid,[1-7] of electrophilic additions[8-11] and substitutions[12-14])

Physical Data: colorless liquid; mp -84.3 °C; bp 45.1 °C.[1]

Preparative Methods: can be obtained either by the reaction of peroxydisulfuryl difluoride ($F_2S_2O_6$) with Cl_2[3,15] or by insertion of SO_3 into ClF.[16,17]

Handling, Storage, and Precautions: stable and is not explosive.[1] However, it can ignite organic materials upon contact (including nonperfluorinated grease).[4] It is hydrolyzed by water to give HCl and fluorosulfuric acid. This reagent should be handled in a fume hood.

Synthesis of Fluorosulfates.

The chemical behavior of $ClOSO_2F$ (**1**) is determined by its ability to serve as a Cl^+ synthon.[1] It smoothly substitutes halogen atoms (Cl, Br, I) for fluorosulfate groups (eq 1).[1-7]

$$\underset{\textbf{(1)}}{RX + ClOSO_2F} \longrightarrow ROSO_2F + XCl \qquad (1)$$

For example, 1,2-dichloroethane or alkylchloroacetates react with (**1**) at -40 °C to 0 °C to give the corresponding fluorosulfates (eq 2).[5]

$$ClCH_2CH_2Cl \xrightarrow{ClOSO_2F} ClCH_2CH_2OSO_2F$$

$$ClCH_2CO_2R \xrightarrow{ClOSO_2F} FSO_2OCH_2CO_2R \qquad (2)$$

Geminal chlorine atoms can be substituted to give *gem*-difluorosulfates, for example eq 3.[3]

$$CF_2ClCFCl_2 \xrightarrow{ClOSO_2F} CF_2ClCF(OSO_2F)_2 \qquad (3)$$

The addition of fluorosulfuric acid[2,3] or bromine[7] catalyzes the reactions. In the case of mustard gas and its analogs, $S[(CH_2)_nCl]_2$, the reaction with (**1**) gives the corresponding bis-fluorosulfates, while the sulfur atom undergoes chlorination to give $Cl_4S[(CH_2)_nOSO_2F]_2$.[6] Perfluoroalkyl bromides are also readily transformed into the corresponding fluorosulfates, R_fOSO_2F.[2,7] In the case of perfluoroalkyl iodides the relatively stable derivatives of type $R_fI(OSO_2F)_2$ can be isolated.[1,7]

Perfluoroalkenes, fluorochloroalkenes, and chloroalkenes react with (**1**) to give β-chlorofluorosulfates (eq 4).[8-11]

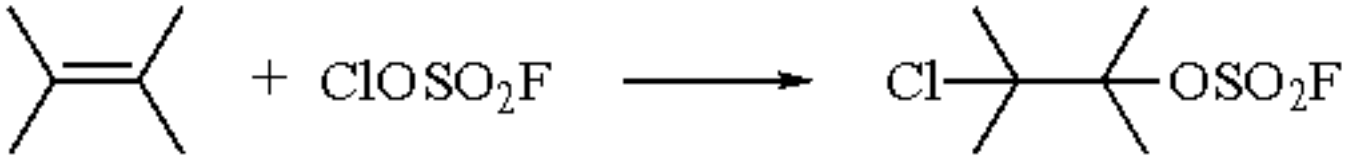

(4)

Hexafluorobenzene, C_6F_6, also gives a 1,4-addition product and then the 1,2,3,4,5,6-addition product.[9] Addition to the C&tbond;C bond gives mono- and diadducts.[11]

Nitrile groups can add 1 mol of (**1**) in accordance with eq 5.[4,18]

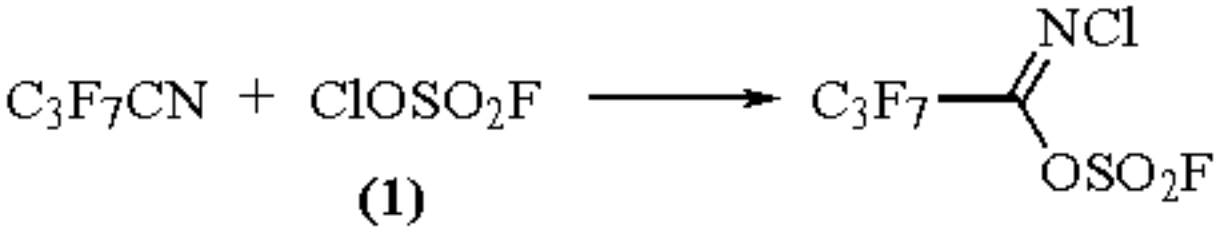

(5)

Reaction of (**1**) with *N*-chlorodifluoromethanimine gives the corresponding diazene (eq 6).[19]

$$F_2C{=}NCl \xrightarrow{ClOSO_2F} FSO_2OCF_2N{=}NCF_2OSO_2F \qquad (6)$$

Chlorination.

The electrophilic chlorination of various organic substrates is a typical reaction of (**1**), the reagent serving as the source of Cl^+. Alcohols and carboxylic acids react with (**1**) to give the corresponding hypochlorites (eq 7).[1] The reaction yields are variable and are determined by the stability of the final products.[1]

$$ROH + ClOSO_2F \longrightarrow ROCl \qquad (7)$$

$$R = \text{alkyl, acyl}$$

This process was applied to the synthesis of inorganic hypochlorites, for example TeF_5OH -> TeF_5OCl.[20]

Reagent (**1**) is also a powerful chlorinating agent for aromatic substitutions.[12,13] For example, benzene gives hexachlorobenzene even at -100 °C.[12] In the presence of SbF_5 the reagent (**1**) chlorinates the pentafluorobenzene, C_6HF_5, into chloropentafluorobenzene, C_6ClF_5.[14]

Perfluoronitroso compounds undergo substitution of the nitroso group by chlorine (eq 8).[21]

$$R_fNO + \underset{\textbf{(1)}}{ClOSO_2F} \longrightarrow R_fCl \qquad (8)$$

Related Reagents.

Peroxydisulfuryl Difluoride.

---

1. Fokin, A. V.; Studnev, Yu. N.; Kuznetzova, L. D.; Krotovich, I. N. *Usp. Khim.* **1982**, *51*, 1258 (*CA* **1982**, *97*, 181 258m).
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5. Fokin, A. V.; Studnev, Yu. N.; Krotovich, I. N.; Kuznetzova, L. D.; Verenikin, O. V. *IZV* **1979**, 806 (*CA* **1979**, *91*, 19 832y).
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11. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Verenikin, O. V. *IZV* **1985**, 1094 (*CA* **1985**, *103*, 214 819t).
12. Fokin, A. V.; Studnev, Yu. N.; Krotovich, I. N.; Kuznetzova, L. D.; Gukov, A. M. *IZV* **1977**, 2388 (*CA* **1978**, *88*, 89 228t).
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14. Fokin, A. V.; Studnev, Yu. N.; Krotovich, I. N.; Furin, G. G.; Yakobson, G. G. *IZV* **1981**, 927 (*CA* **1981**, *95*, 114 932x).
15. Gilbreath, W. P.; Cady, G. H. *IC* **1963**, *2*, 496.
16. Schack, C. J.; Wilson R. D. *IC* **1970**, *9*, 311.
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19. Zheng, Y. Y.; Bauknight, C. W., Jr.; DesMarteau, D. D. *JOC* **1984**, *49*, 3590.
20. Schack, C. J.; Christie, K. O. *JFC* **1982**, *21*, 393.
21. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Chilikin, V. G.; Verenikin, O. V. *IZV* **1984**, 832 (*CA* **1984**, *101*, 130 177c).

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Chlorine-Pyridine

$Cl_2.C_5H_5N$

[40007-00-9] · $C_5H_5Cl_2N$ · Chlorine-Pyridine · (MW 150.01)

(mild oxidizing agent)

Physical Data: [1] white crystals that decomposed rapidly when the solvent (CCl_4) was removed; mp <=47 °C.

Solubility: sol chloroform; insol carbon tetrachloride.

Form Supplied in: not commercially available.

Preparative Methods: although the chlorine-pyridine complex has been isolated,[1] the reagent is more conveniently prepared in situ.[2]

Handling, Storage, and Precautions: the same precautions associated with the use of ***Chlorine*** (protective clothing, respirator) should be followed; use in a fume hood.

The chlorine-pyridine complex has been used for the oxidation of alcohols.[2] Secondary alcohols are oxidized to ketones, while primary alcohols stop at the aldehyde stage. The faster rate observed for secondary alcohols (~20 min) vs. primary alcohols (~60 min) suggested that chlorine-pyridine might be useful in selective oxidations. In the oxidation of steroid diols and triols, chlorine-pyridine showed moderate to good selectivity (eqs 1-3).[2] Other reagents have been shown to be superior in effecting similar transformations.[3] However, these results may be misleading due to the problems that attend the oxidation of steroidal alcohols (axial vs. equatorial, adjacent to an angular methyl group, etc.). Thus chlorine-pyridine may be more selective than eqs 1 and 3 suggest. The usefulness of this reagent needs to be investigated further.

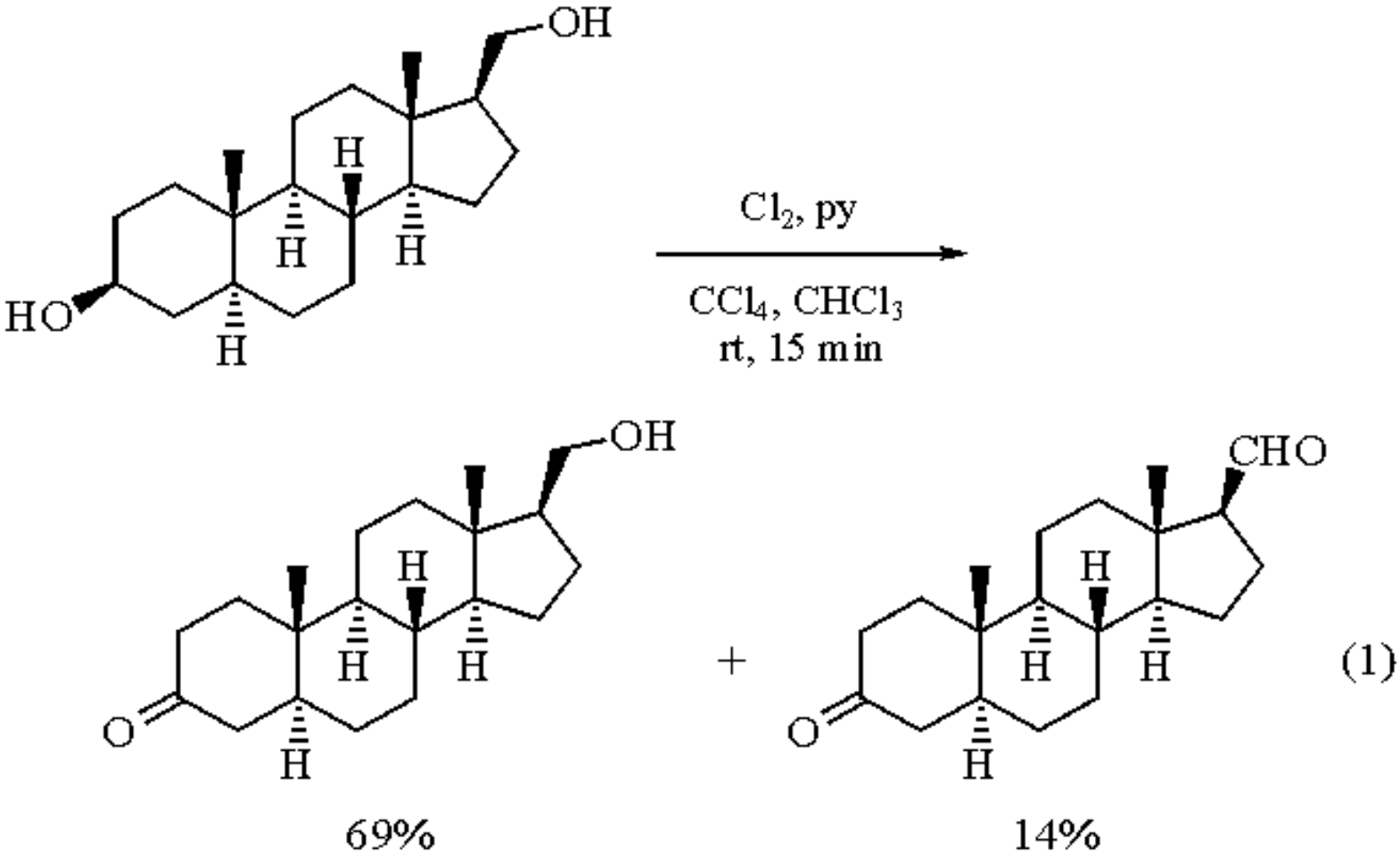
OH
H
H
H
HO
H
Cl2, py
CCl4, CHCl3
rt, 15 min
OH
H
H
H
O
H
+
CHO
H
H
H
O
H
(1)
69%
14%

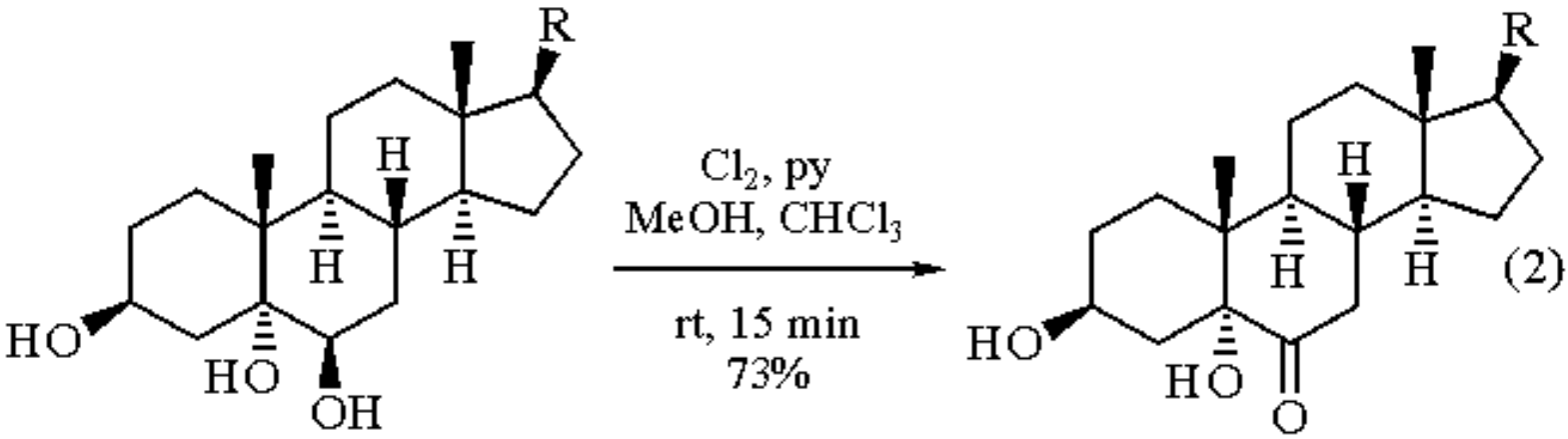
R
H
H
H
HO
HO
OH
Cl2, py
MeOH, CHCl3
rt, 15 min
73%
R
H
H
H
HO
HO
O
(2)

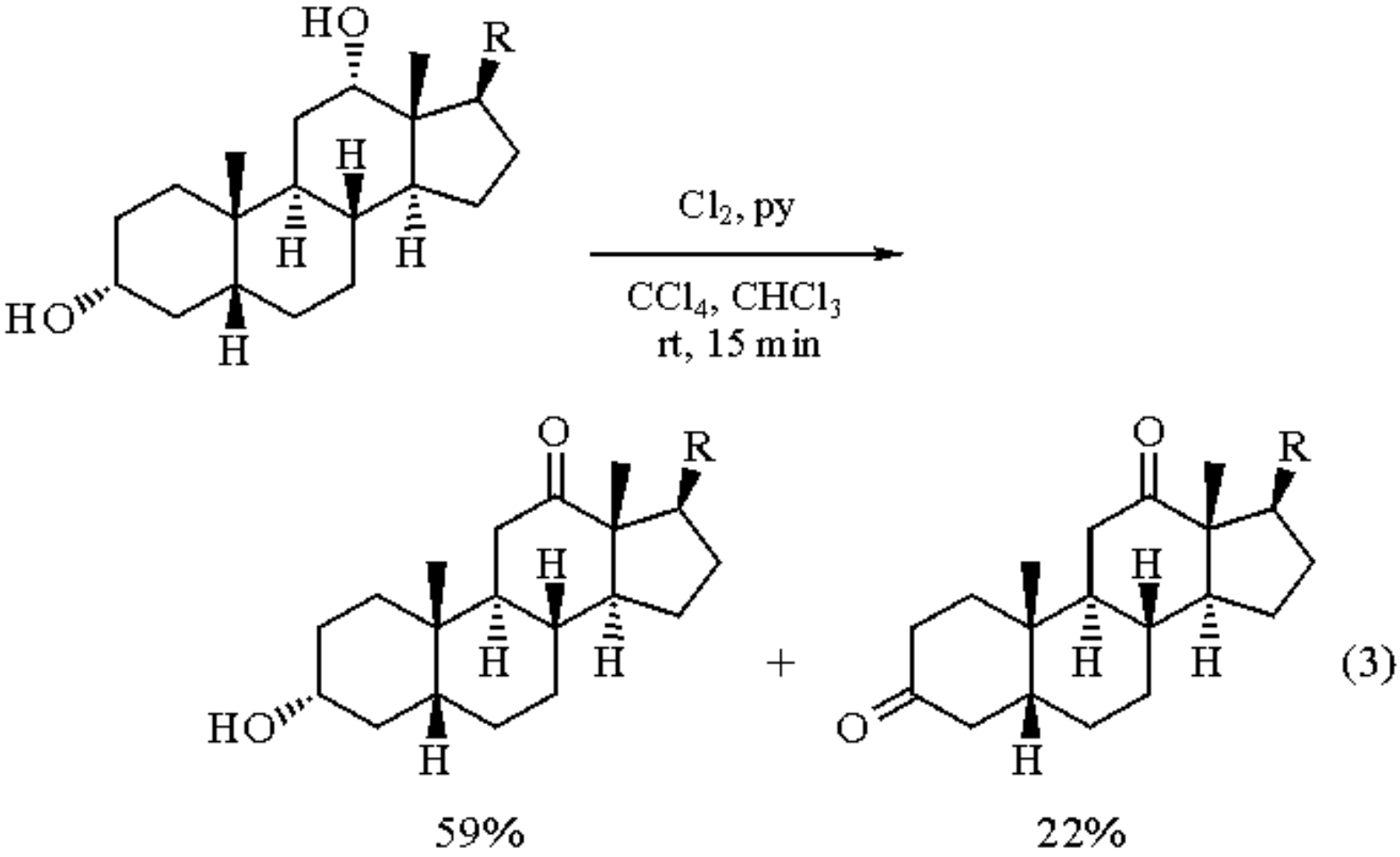

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1. Williams, D. M. *JCS* **1931**, 2783.
2. Wicha, J.; Zarecki, A. *TL* **1974**, 3059.
3. For other reagents that show selectivity in the oxidation of alcohols, see: Siedlecka, R.; Skarzewski, J.; Mlochowski, J. *TL* **1990**, *31*, 2177, and references cited therein.

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Chloroacetaldehyde

$ClCH_2CHO$

[107-20-0] · C_2H_3ClO · Chloroacetaldehyde · (MW 78.50)

(bifunctional electrophile; heterocycle building block;[4-10] α-chloro nitrone precursor[15])

Alternate Name: 2-chloroethanal.

Physical Data: bp 85-86 °C.

Solubility: sol water and most organic solvents.

Form Supplied in: aqueous solution (45-55%).

Analysis of Reagent Purity: oxime titration.

Preparative Methods: Water-free chloroacetaldehyde can be prepared by periodate oxidation of α-chlorhydrin[1] or through pyrolysis (200 °C) of 4-chloro-1,3-dioxolan-2-one.[2] Extraction of aqueous solutions of chloroacetaldehyde with organic solvents provides the hemiacetal.[3]

Handling, Storage, and Precautions: intensely irritating. Highly prone to polymerization, should be used immediately after preparation. This reagent should be used in a fume hood.

Heterocycles.

Chloroacetaldehyde is a building block for many types of heterocycles such as pyrroles,[4] furans,[5] thiophenes,[6] imidazoles,[7] thiazolines,[8] thiazoles,[9] or indoles.[10]

Wittig Reaction.

Alkoxycarbonylalkylidenephosphoranes react with chloroacetaldehyde in high yield to give γ-chlorotiglates. The *trans/cis* ratio is greater than 0.94 (eq 1).[11]

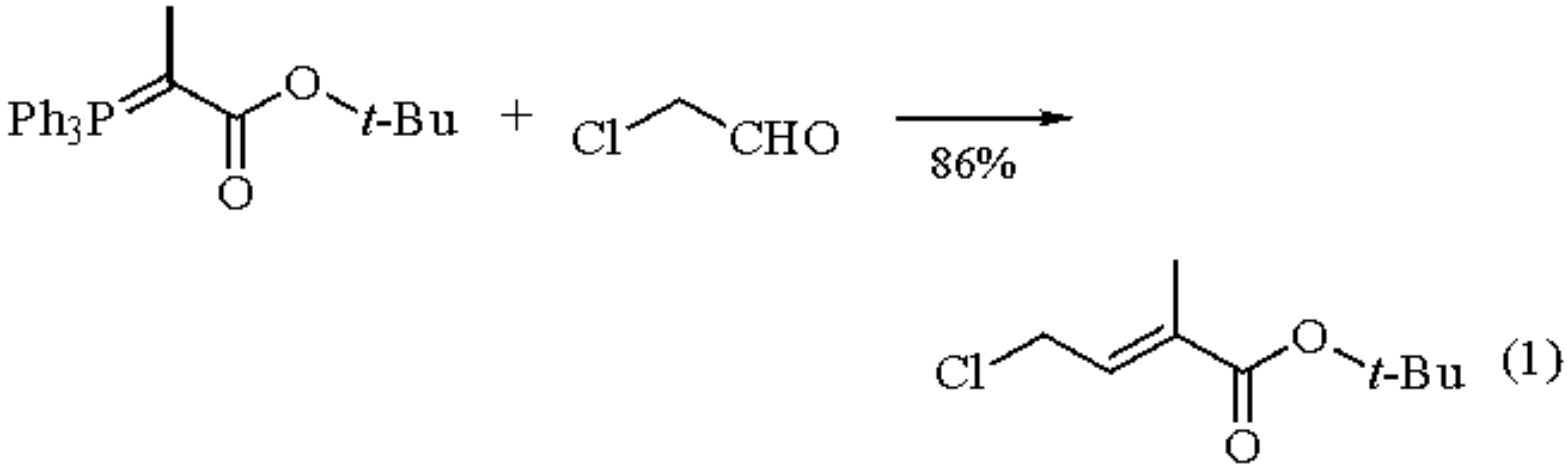

α-Cyanoenamines.

α-Cyanoenamines,[12] easily prepared from α-chloroacetaldehyde (eq 2), can be used for the synthesis of higher ketones,[13] 1,2-diketones,[13] 1,4-diketones,[14] and 1,5-diketones.[12]

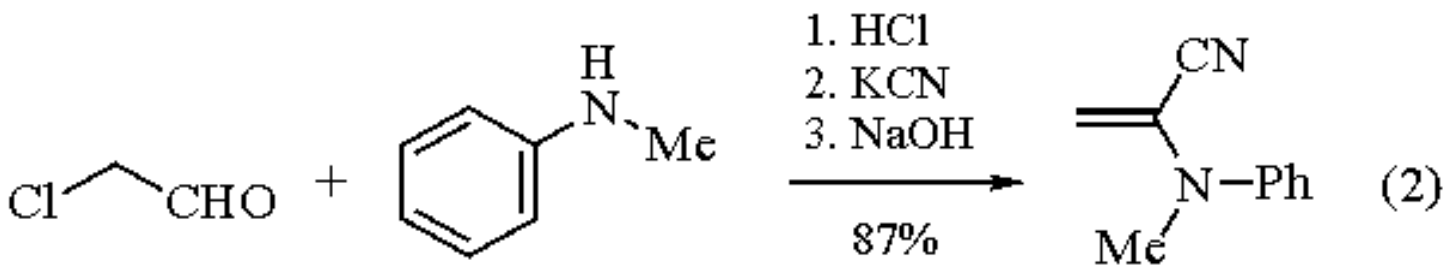

α-Chloro Nitrones.

α-Chloroaldehydes are easily converted into the corresponding α-chloro nitrones with various hydroxylamines. (eq 3).[15] The lower representatives (R = H, Me) are unstable and should be stored at -20 °C.

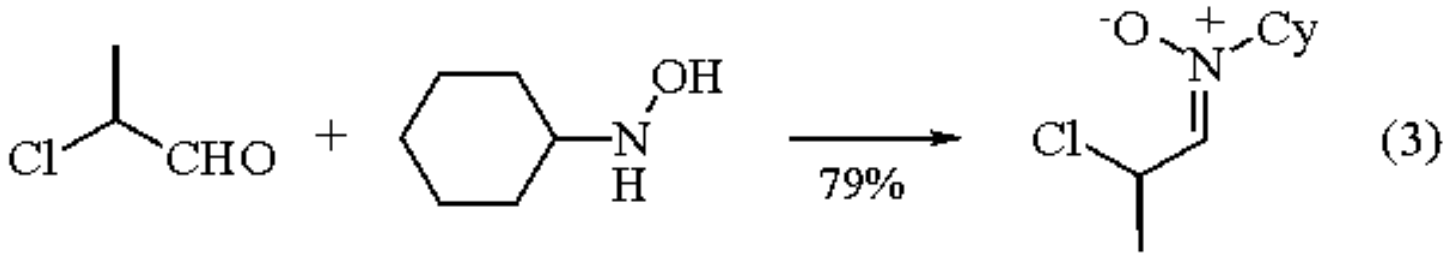

The Ag^+ mediated reaction of α-chloro nitrones with unactivated alkenes results either in a [4 + 2] cycloaddition (eq 4)[15 -19] or, especially in solvents like SO_2 or $MeNO_2$, in a substitution (eq 5).[16,17] Mono-, 1,2-di-, or tetrasubstituted alkenes predominantly react via cycloaddition, whereas with 1,1-di- or trisubstituted alkenes, substitution becomes the main reaction, thereby giving access to β,γ-unsaturated aldehydes. The configuration of the alkene is retained in both cases.

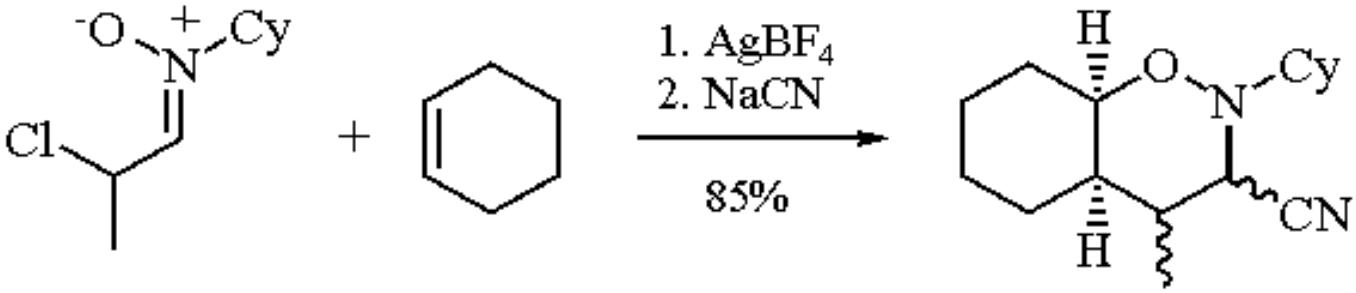

(4)

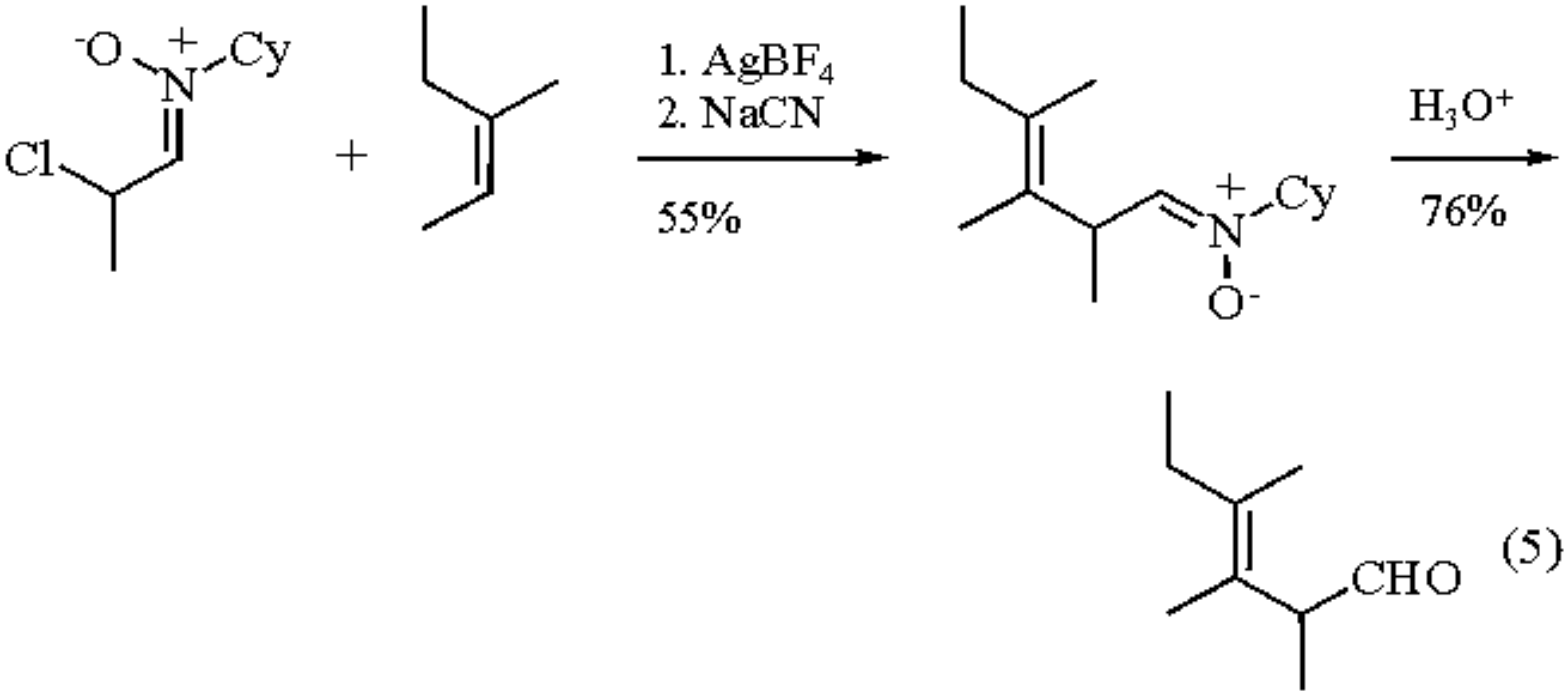

(5)

With strong bases, the cycloadducts are converted with potassium *t*-butoxide into iminolactones which upon hydrolysis furnish γ-lactones (eq 6).[16,17,19]

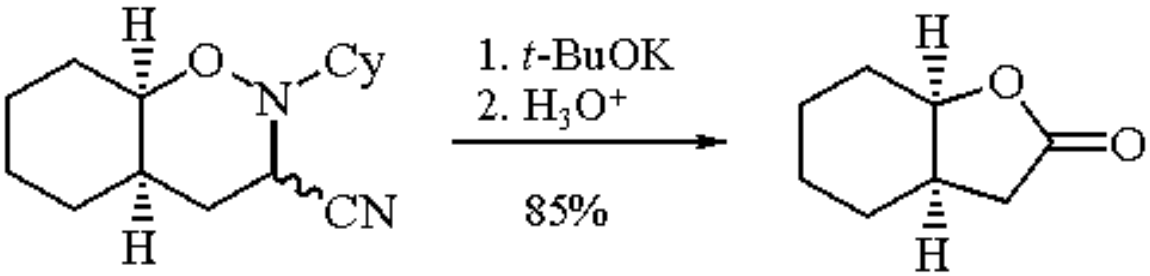

(6)

Treatment of the cyano 1,2-oxazine cycloadducts with Ag^+ followed by sodium tetraphenylborate results in the formation of easily crystallizable iminium salts.[15] Deprotonation of these salts with weak bases furnish tetrahydro-1,2-oxazines which undergo cycloreversion at slightly elevated temperature to give mono-α,β-unsaturated dialdehydes after hydrolysis (eq 7).[20]

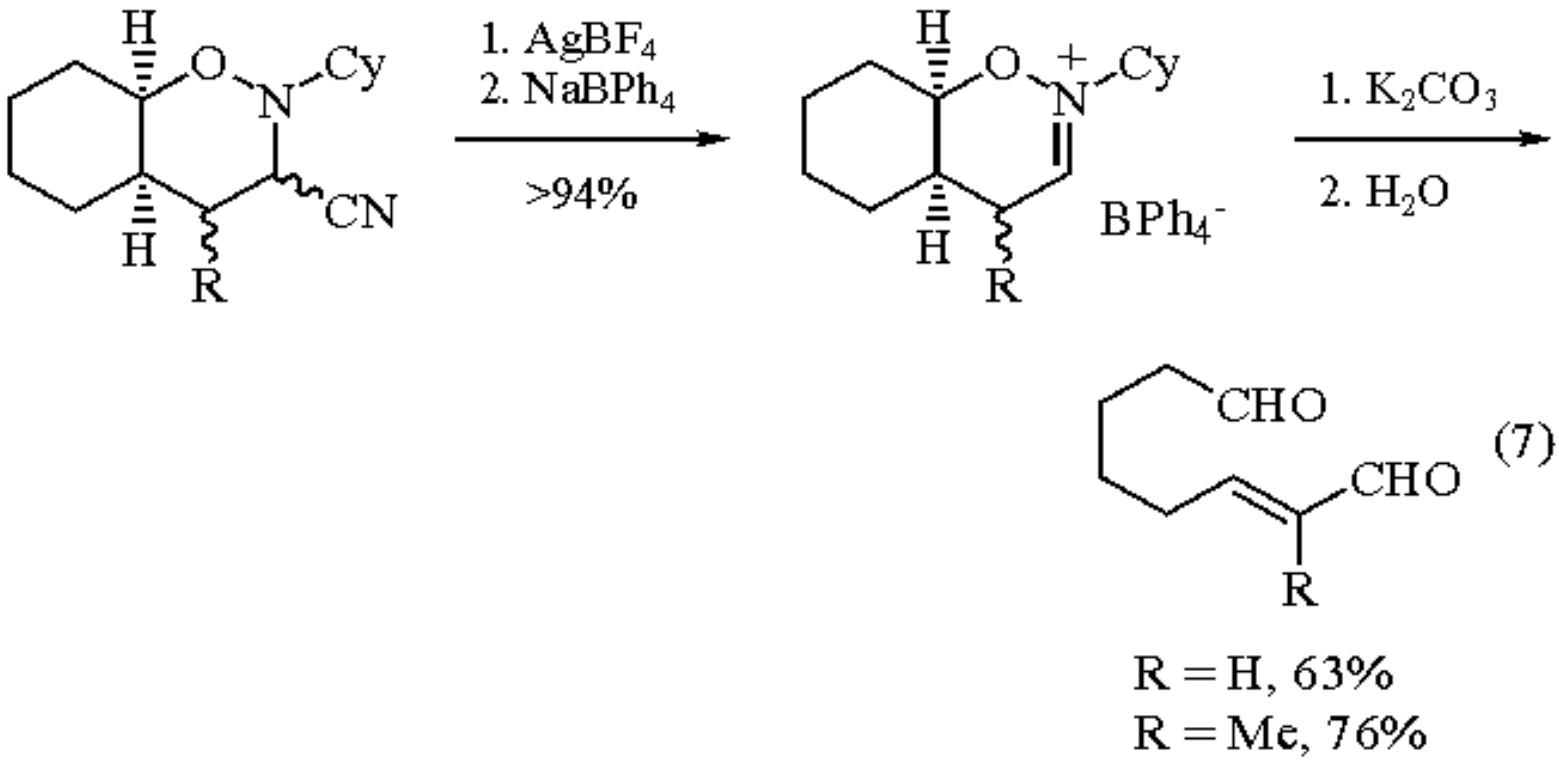

The cycloaddition-cycloreversion sequence has been used to synthesize indoles from 1,4-dihydro-5-nitronaphthalene.[21]

Slightly activated benzene derivatives furnish β-arylaldehydes upon treatment with α-chloro nitrones and $AgBF_4$ (eq 8).[18] Following the same procedure, *p*-cresol furnishes benzofurans (eq 9).[18] Electrophilic aromatic substitution reactions of chloro nitrones have also been described for furans[22] and indoles.[23]

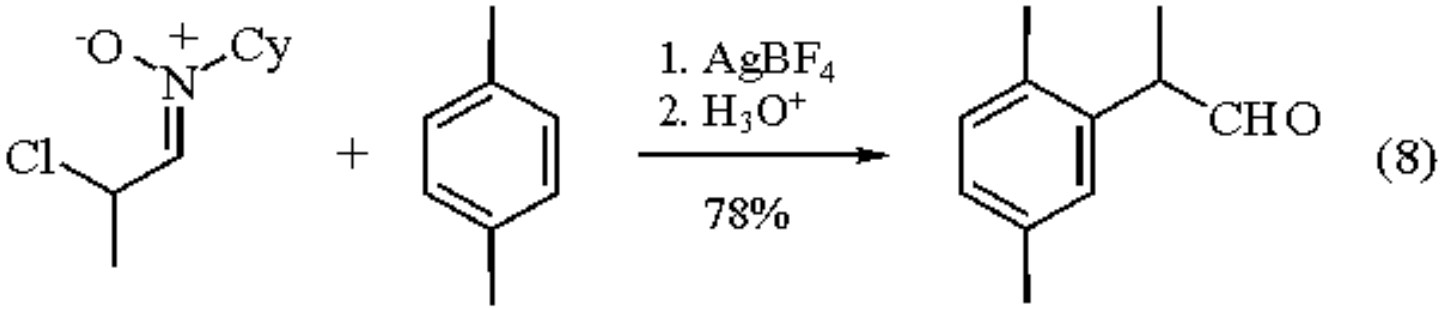

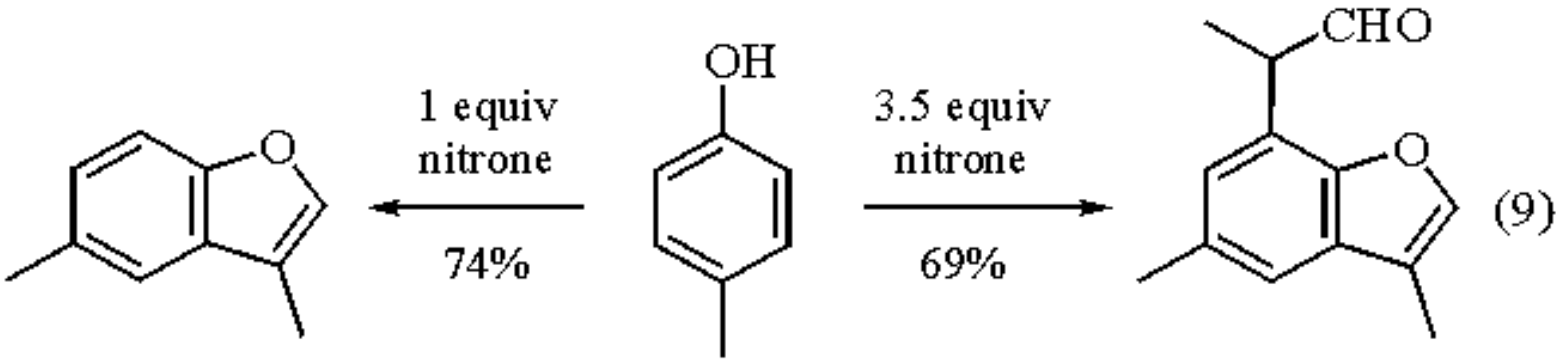

The Ag^+-induced cycloaddition of α-chloro nitrones to alkynes followed by chromatography through deactivated alumina furnishes α,β-unsaturated ketones (eq 10).[24]

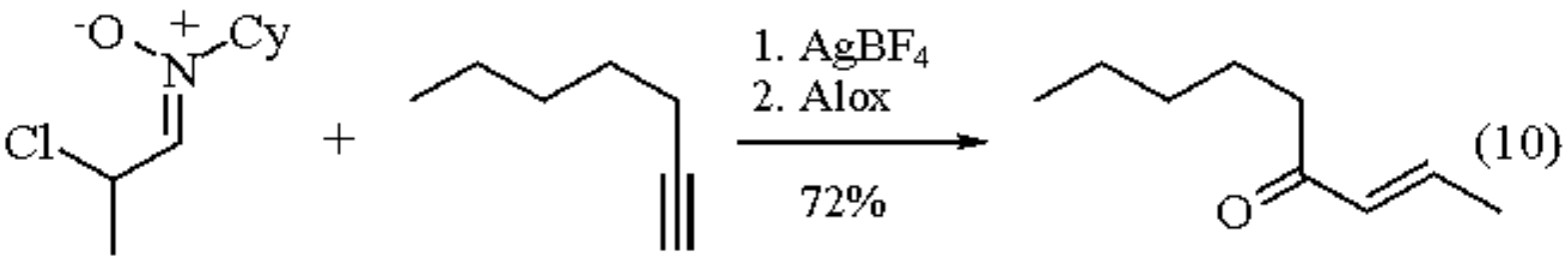

α-Chloro nitrones are alkylated by anions of dialkyl malonates, providing easy access to α-alkoxycarbonyl-β-formyl-carboxylic acid esters (eq 11).[25]

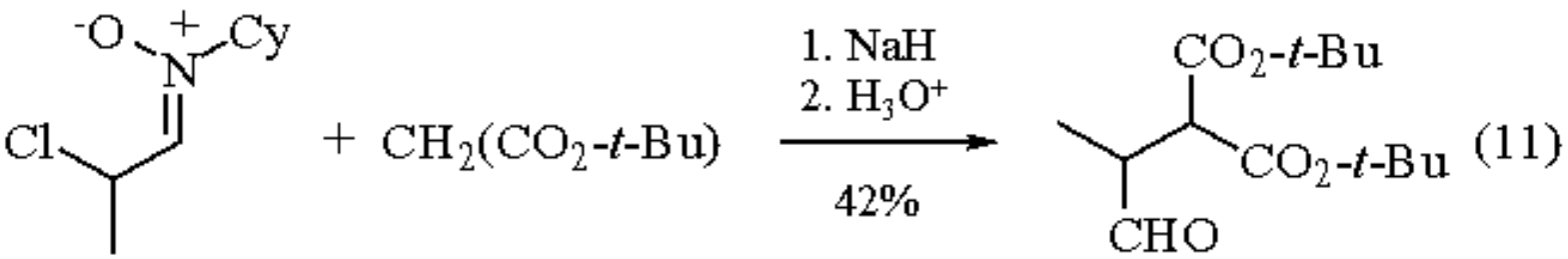

Related Reagents.

2,3-Dichloropropionaldehyde.

---

1. Hatch, L. F.; Alexander, H. E. *JACS*, **1945**, *67*, 688.
2. Weygand, C.; Hilgetag, G.; *Preparative Organic Chemistry*, 4th ed.; Martini, A.; Ed.; Wiley: New York, 1973; p 185.
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5. (a) Bisagni E.; Rivalle, C. *BSF* **1974**, 519. (b) Padwa, A.; Gasdaska, J. R. *T* **1988**, *44*, 4147. (c) Matsumoto, M.; Wanatabe, N. *H* **1984**, *22*, 2313.
6. (a) Hirota, K.; Shirahashi, M.; Senda, S.; Yogo, M. *JHC* **1990**, *27*, 717. (b) Waldvogel, E. *HCA* **1992**, *75*, 907.
7 (a) Kluge, A. F. *JHC* **1978**, *15*, 119. (b) Senga, K.; Robins, R. K.; O'Brien, D. E. *JHC* **1975**, *12*, 1043.
8. (a) Martens, J.; Offermanns, H.; Scherberich, P.; *AG* **1981**, *93*, 680. (b) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, p 314.
9. (a) Begtrup, M.; Hansen, L. B. L. *ACS* **1992**, *46*, 372. (b) Brandsma, L.; De Jong, R. L. P.; VerKruijsse, H. D. *S* **1985**, 948.
10. Wender, P. A.; White, A. W. *T* **1983**, *39*, 3767.
11. Stotter, P. L.; Hill, K. A.; *TL* **1975**, 1679.
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15. Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; Eschenmoser, A. *HCA* **1972**, *55*, 2187.

16. Das Gupta, T. K.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *HCA* **1972**, *55*, 2198.
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18. Shatzmiller, S.; Gygax, P.; Hall, D.; Eschenmoser, A. *HCA* **1973**, *56*, 2961.
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20. Gygax, P.; Das Gupta, T. K.; Eschenmoser, A. *HCA* **1972**, *55*, 2205.
21. Hattingh, W. C.; Holzapfel, C. W.; van Dyk, M. S. *SC* **1987**, *17*, 1491.
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25. Lidor, R.; Shatzmiller, S. *LA* **1982**, 226.

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Chloroacetonitrile

$ClCH_2CN$

[107-14-2] · C_2H_2ClN · Chloroacetonitrile · (MW 75.50)

(reagent for two-carbon homologation of alkenes via organoboranes;[1] useful in Wittig alkenation of ketones[2] and Darzens condensations[3])

Physical Data: bp 124-126 °C; *d* 1.193 g cm^{-3}.

Form Supplied in: colorless liquid, widely available.

Handling, Storage, and Precautions: highly toxic and a lachrymator; use in a fume hood.

Homologation of Alkenes via Organoboranes.

Organoboranes undergo a base-induced reaction with a variety of α-halo esters, ketones, and nitriles.[4] The reaction substitutes the α-halogen with an alkyl group from boron (eq 1).

$$R_3B + ClCH_2CN \xrightarrow{\text{base}} RCH_2CN \qquad (1)$$

The use of ***9-Borabicyclo[3.3.1]nonane*** provides for efficient use of the alkyl group on boron.[1] The two chlorines of dichloroacetonitrile may be successively replaced (eq 2).

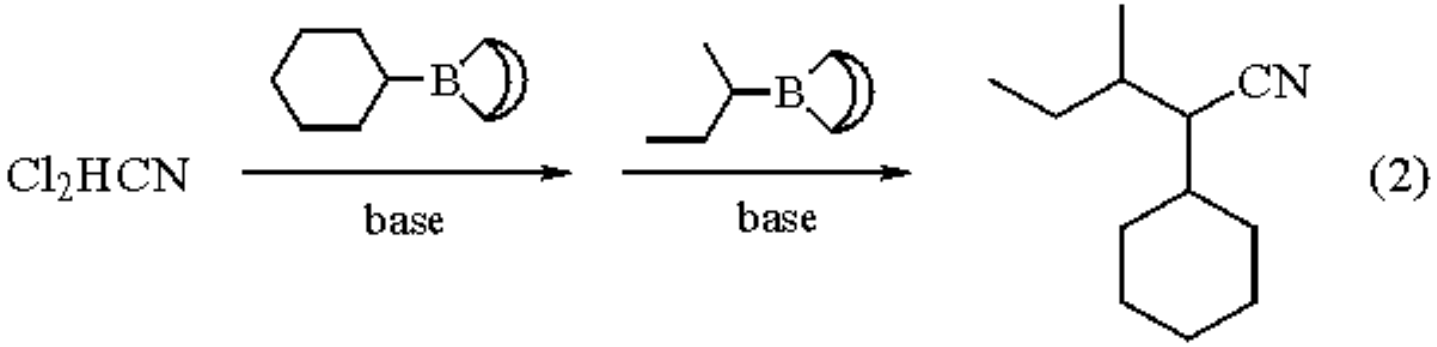

The reaction proceeds with retention of configuration of the original boron-carbon bond. This feature has been used

for the stereoselective construction of steroid side chains (eq 3).[5,6]

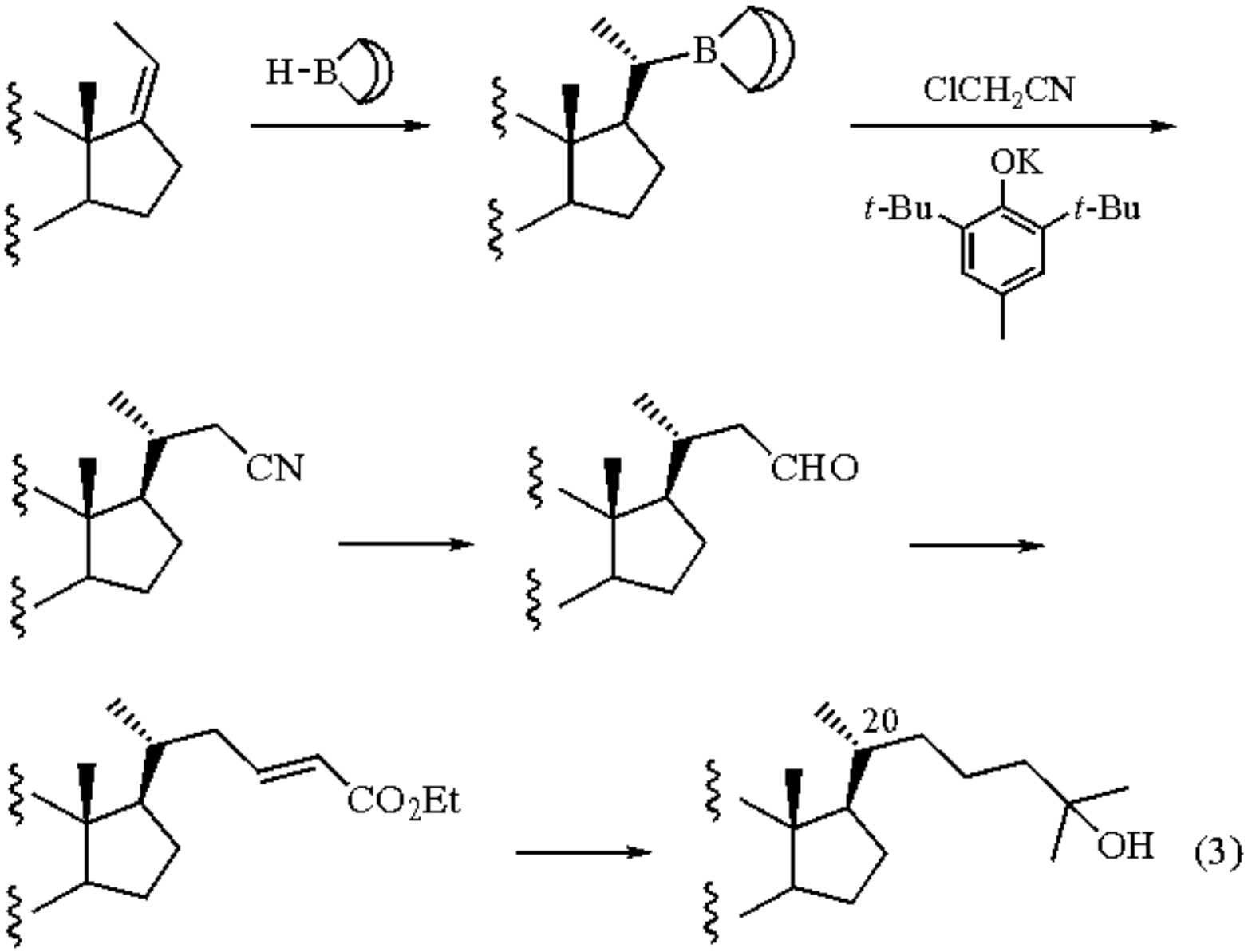

Either the natural or unnatural C-20 stereochemistry may be obtained (eq 4), depending on the configuration of the ethylidene unit.

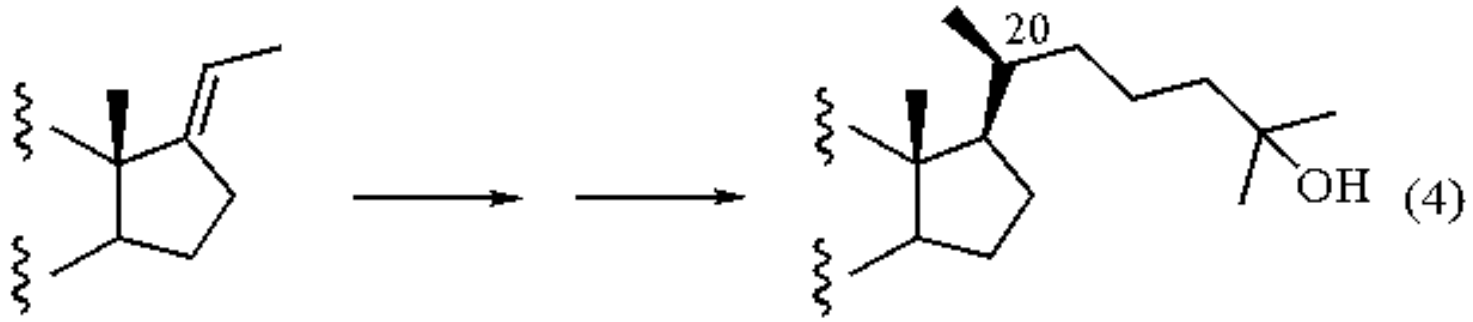

Wittig Alkenation of Ketones.

Ketones may be converted into α,β-unsaturated nitriles through a modified Wittig-Horner-Emmons reaction (eq 5).[2] The (*E*) isomer predominates.

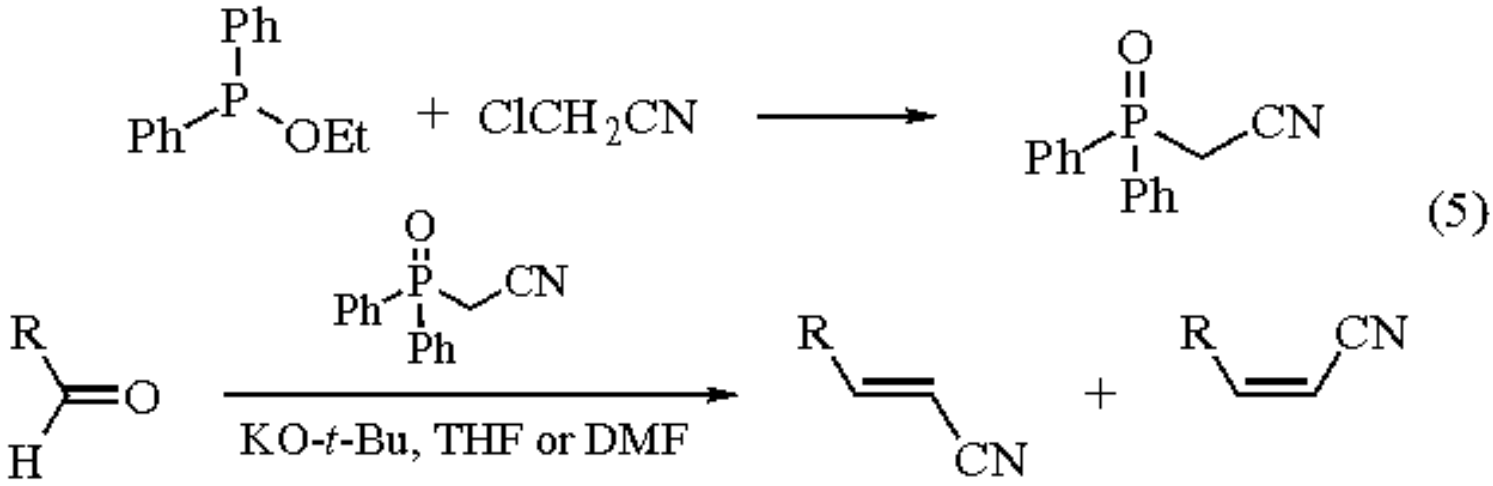

Darzens Condensations.

Glycidonitriles may be obtained by treating ketones with chloroacetonitrile and base (eq 6).[3] These glycidonitriles may be rearranged to carboxylic acids (eq 7).

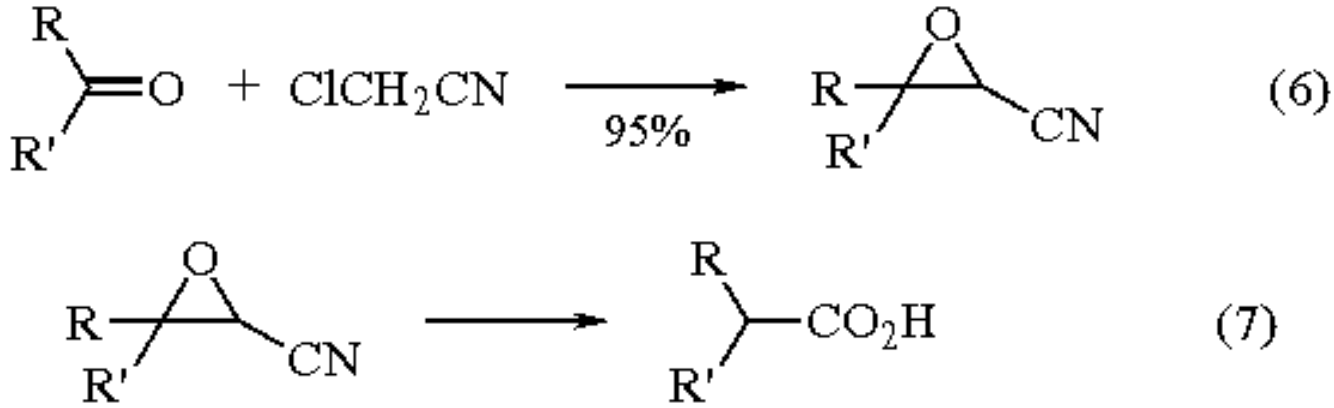

Related Reagents.

Dichloroacetonitrile; ***Iodoacetonitrile***; ***Methyl Bromoacetate***; ***Methyl Chloroacetate***.

---

1. Brown, H. C.; Nambu, H.; Rogic, M. M. *JACS* **1969**, *91*, 6854.
2. Loupy, A.; Gogadji, K.; Seyden-Penne, J. *S* **1977**, 126.
3. White, D. R.; Wu, D. K. *CC* **1974**, 988.
4. Brown, H. C.; Rogic, M. M. *Organomet. Chem. Synth.* **1972**, *1*, 305.
5. Midland, M. M.; Kwon, Y. C. *JOC* **1981**, *46*, 1227.
6. Midland, M. M.; Kwon, Y. C. *TL* **1982**, *23*, 2077.

Chloroacetyl Chloride

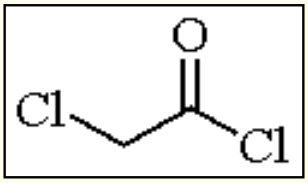

[79-04-9] · $C_2H_2Cl_2O$ · Chloroacetyl Chloride · (MW 112.94)

(acylating agent;[1-34] chlorinating agent;[39] a two-carbon building block for cyclization;[6,13,25-27,33] a precursor to monochloroketene[35-38])

Physical Data: mp -22 °C; bp 105-106 °C; *d* 1.418 g cm^{-3}.

Solubility: sol ether, acetone, and methylene chloride.

Form Supplied in: liquid; commercially available.

Handling, Storage, and Precautions: is corrosive and moisture sensitive. It should be used in an anhydrous atmosphere. Pure $ClCH_2COCl$ can be obtained by simple distillation of the commercial product. This reagent should be used in a fume hood.

Introduction.

Chloroacetyl chloride is a versatile reagent and has been extensively used in organic synthesis. It is primarily used as an acylating agent. The multi-functional nature of $ClCH_2COCl$ has made it a suitable two-carbon building block for cyclization. Numerous cyclic compounds, especially heterocycles, have been prepared through the use of the reagent. Chloroacetyl chloride is also a valuable precursor for monochloroketene and occasionally serves as a chlorinating agent.

C-Acylation.

Acylation of carbon functionalities using $ClCH_2COCl$ as an acylating reagent generally falls into two categories: acylation under Friedel-Crafts conditions and under anionic conditions. Friedel-Crafts acylation of arenes using $ClCH_2COCl$ as an acylating agent is usually carried out in CS_2, nitromethane, sulfolane, etc. solution with ***Aluminum Chloride*** as a promoter, although other Lewis acids have also been employed. Benzene, toluene, naphthalene, *s*-hydrindacene, fluorene, and fluorenone react readily with $ClCH_2COCl$ under the reaction conditions.[1] Heterocyclic arenes, phenols, and derivatives of phenols are also similarly acylated.[2,3] In the case of phenols, the major acylation

products are the *para* isomers (eq 1). However, excellent *ortho* regioselectivity can be achieved by combining $ClCH_2COCl$ with phenoxides of aluminum and magnesium (eq 2),[4] a condition similar to that used in the Kolbe-Schmitt reaction.[5]

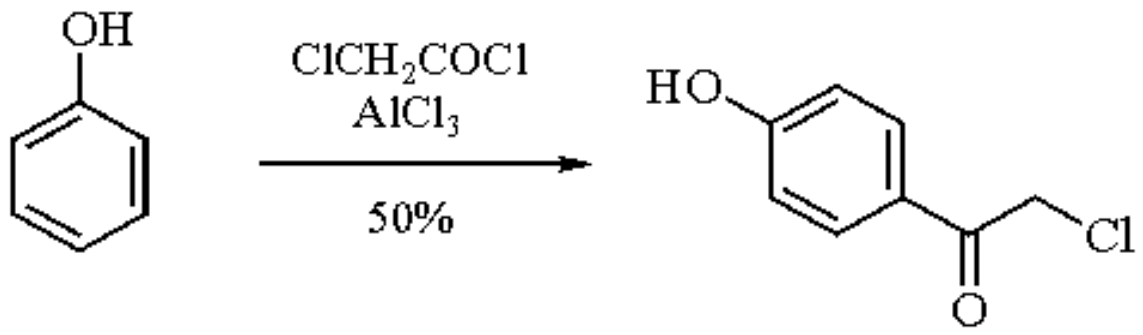

(1)

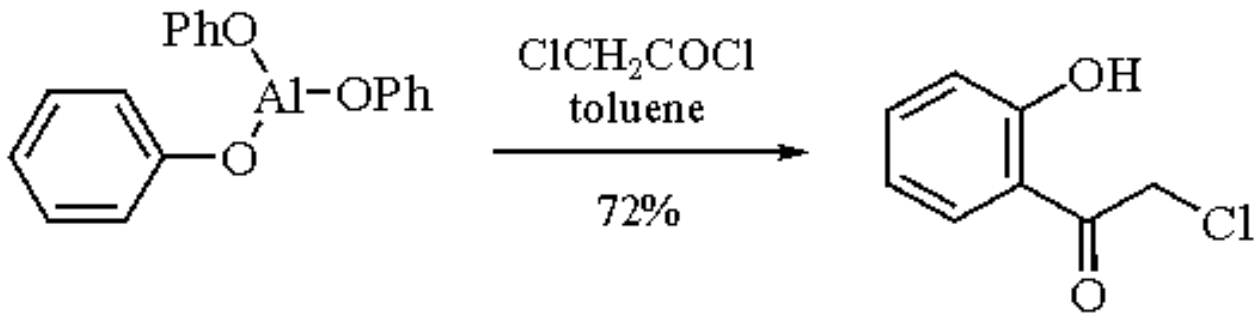

(2)

In the Friedel-Crafts reaction, both the acyl and the alkyl chloride functionalities of $ClCH_2COCl$ can react with an arene, resulting in the formation of a cyclic compound. For example, treatment of 1,2,3,4-tetrahydronaphthacene with $ClCH_2COCl/AlCl_3$ led to formation of 6-oxo-1,2,3,4,5,6-hexahydrobenz[*d*]aceanthrylene in 22% yield (eq 3).[6a] When 3,5-dimethoxytoluene is used as the substrate, a 2,3-dihydrobenzofuran-3-one is obtained almost quantitatively (eq 4).[6b,c] The carbonyl group of $ClCH_2COCl$ may also participate in cyclization under appropriate conditions.[6d,e] This behavior is illustrated by the formation of 2,7-difluoro-9-chloromethylenexanthene in the reaction of 4,4´-difluorophenyl ether with $ClCH_2COCl$ under $AlCl_3$ activation (eq 5).

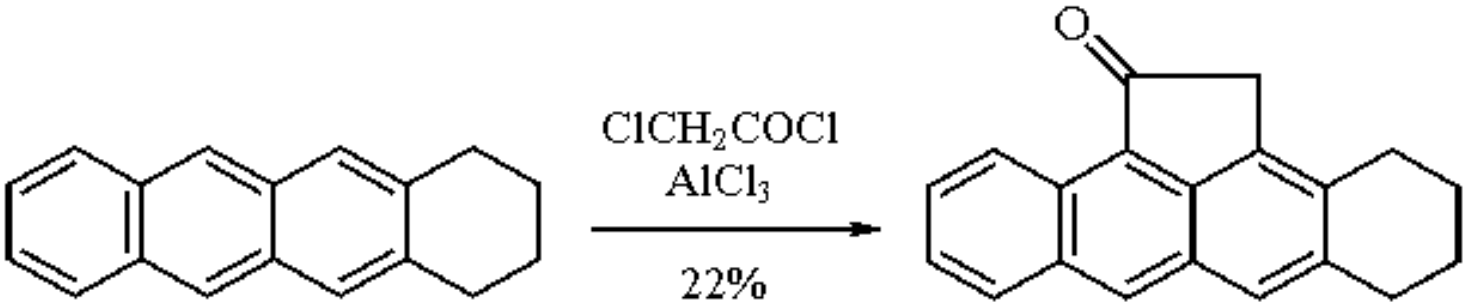

(3)

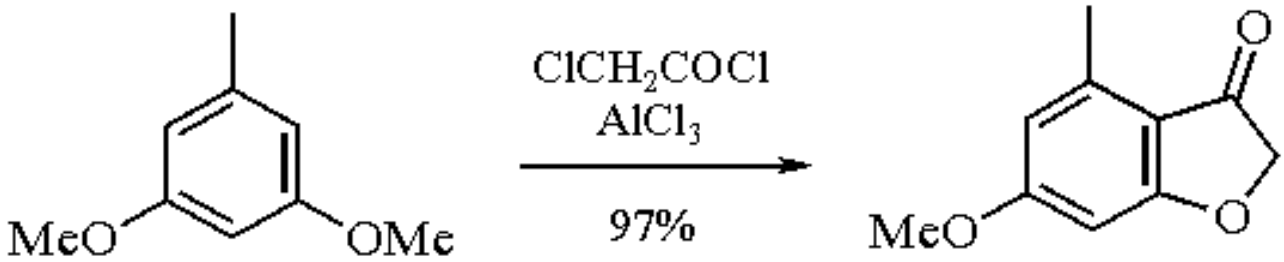

(4)

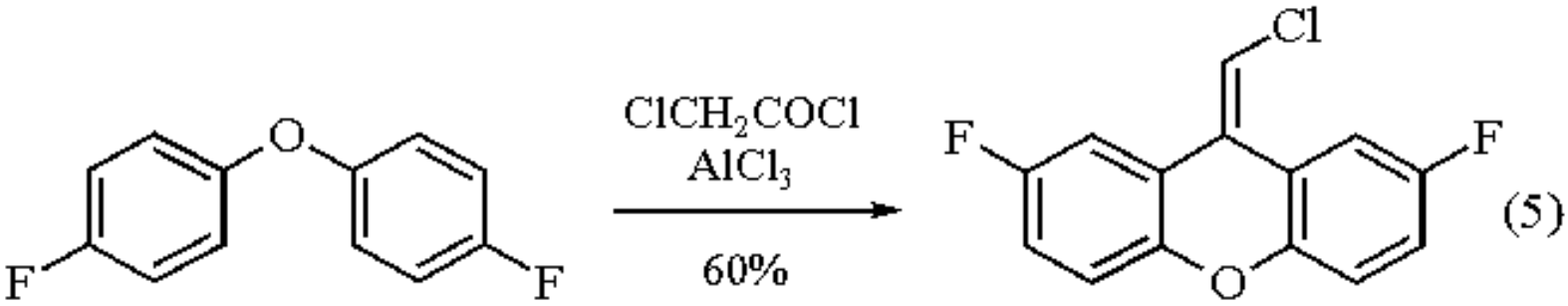

The Friedel-Crafts acylation reaction of $ClCH_2COCl$ has been extended to alkenes and alkynes.[7,8] When alkenes serve as substrates, addition or addition-elimination products can be obtained selectively depending on the reaction conditions. The addition-elimination reactions led to formation of α,β-unsaturated ketones (eq 6). In the case of 1,8-bis(trimethylsilyl)-2,6-octadiene acylation, using the $ClCH_2COCl$/***Titanium(IV) Chloride*** system at low temperature yielded chloromethylcyclopentanols (eq 7).[7e] When acetylene is treated with $ClCH_2COCl$ in the presence of $AlCl_3$, 1,4-dichlorobut-3-en-2-one was obtained in 75% yield (eq 8).[8a] In the presence of ***Sodium Tetracarbonylcobaltate***, alkynes were cyclized by $ClCH_2COCl$ (eq 9).[8b]

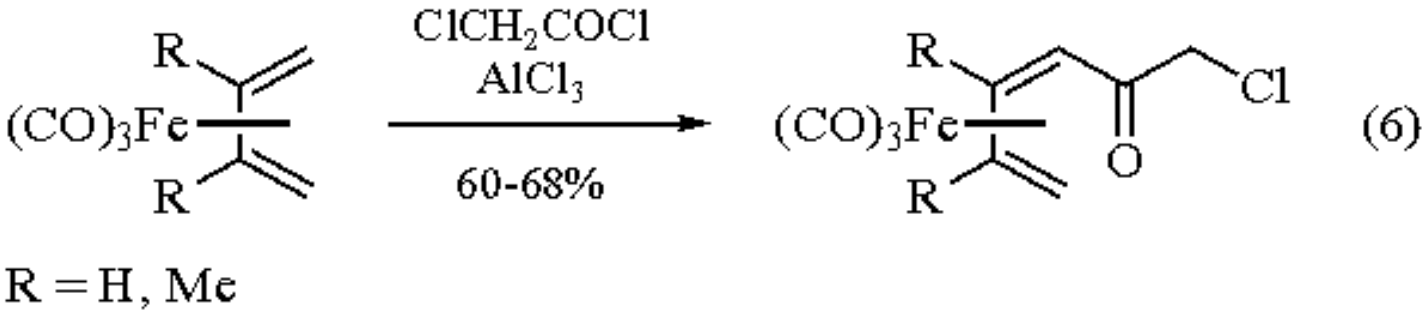

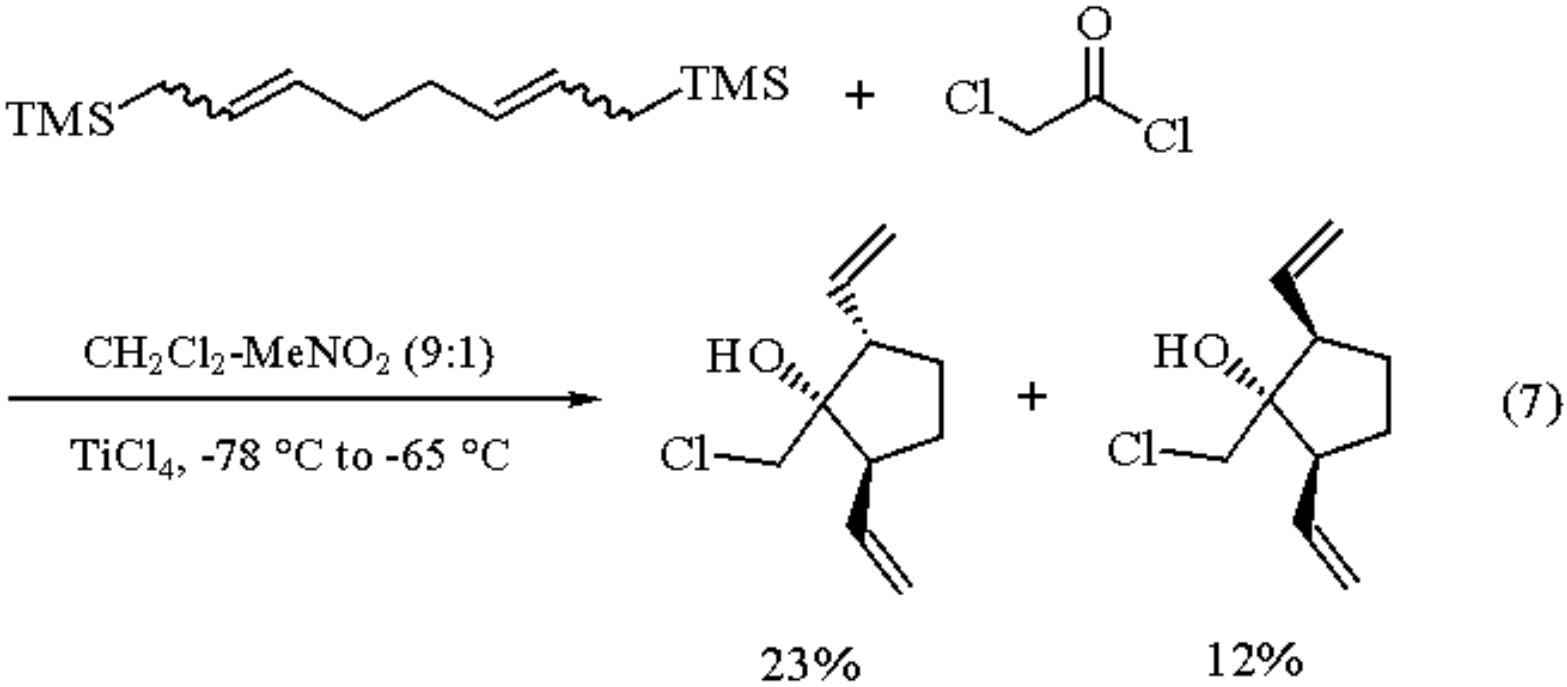

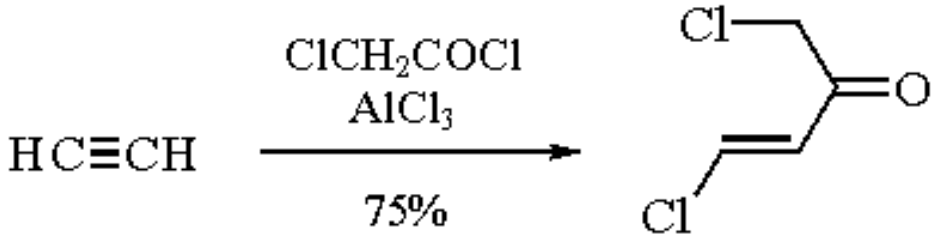

(8)

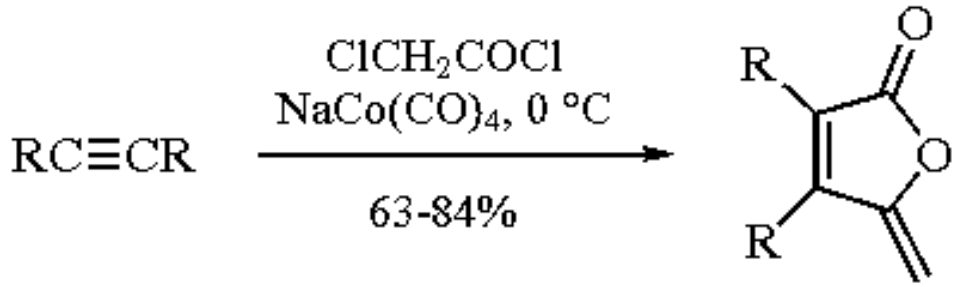

(9)

R = Et, *t*-Bu, CH_2SCN, TMS, CH_2OCH_2OMe

Organocadmium and organozinc compounds are generally the reagents of choice in the preparation of chloromethyl ketones from $ClCH_2COCl$,[9] even though Grignard reagents are sometimes also used for the preparation.[10] Strong bases such as ***Lithium Diisopropylamide*** (LDA) and ***Lithium Hexamethyldisilazide*** (LHMDS) have been introduced as deprotonation agents for the *C*-acylation reaction of a number of enolizable carbonyl compounds.[11] For the strongly acidic C-H bond of 1,3-cyclohexanedione, a weak base such as pyridine is sufficient to achieve this purpose.[12] An interesting reaction involving enolate *C*-acylation is the synthesis of 3-furanones by organocopper conjugate addition to α,β-unsaturated ketones. Trapping of the enolate with $ClCH_2COCl$ and subsequent base-promoted ring closure offers a very simple route to the construction of a furan ring (eq 10).[13]

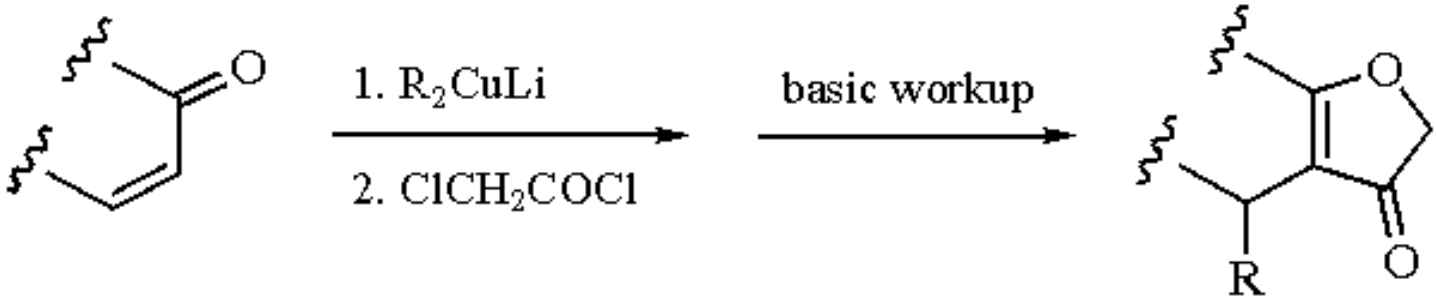

(10)

N-Acylation.

Acylation of nitrogen groups in organic compounds is the most frequently used reaction of $ClCH_2COCl$ in organic synthesis.[14-28] Primary and secondary amines react readily with $ClCH_2COCl$ to form amides.[14-17] In the case of diamines, both nitrogen atoms can be acylated. In fact, the diacylation has been utilized in the synthesis of cyclams[17a,b] and enantiomerically pure *trans*-2,3-diphenyl-DABCO.[17] Other nitrogen containing compounds such as *O*,*N*-dimethylhydroxylamine hydrochloride,[18a] benzyloxyguanidine,[18b] hydrazines,[18c] and amides[19] can also be acylated by $ClCH_2COCl$, under appropriate conditions. A one-pot procedure has been developed for reductive acylation of nitro compounds to chloroacetamides.[18d] If both amino and hydroxyl functionalities exist in the same

molecular, *N*-acylation generally proceeds preferentially.[20]

Chloroacetyl chloride is able to add across the C=N double bonds of imines to form *N*-chloroalkylchloroacetamide.[21] These addition products generally are unstable and are used for further reaction without isolation. The C=N double bonds of imines can be reductively acylated in the presence of ***Trichlorosilane***.[21f,g] The addition reaction is also applicable to carbodiimides[22] and other multiply bonded heteroatom functions such as P=N and S=N.[23]

1,3,5-Triisopropylhexahydrotriazine can undergo ring opening with $ClCH_2COCl$ in the presence of KSCN to form *N*-isopropyl-*N*-isothiocyanatomethylchloroacetamide in 67% yield (eq 11).[24]

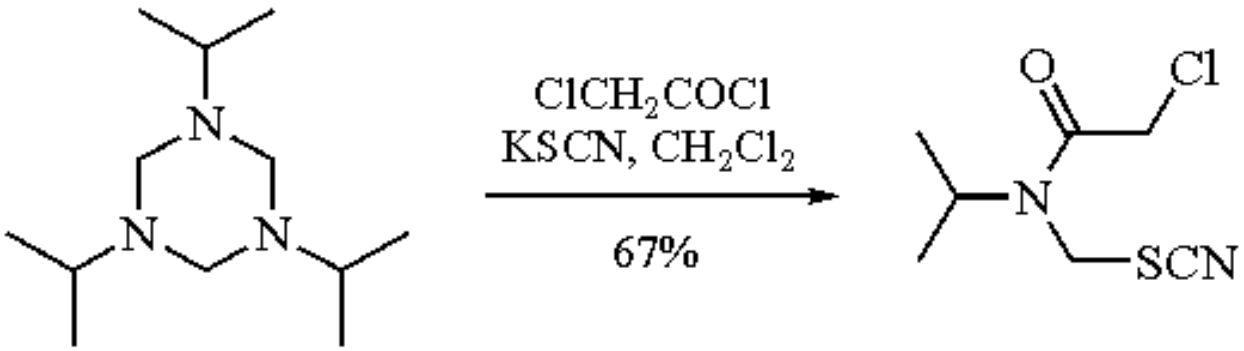

(11)

Similar to *C*-acylation, cyclocondensation can also proceed in *N*-acylation to form cyclic compounds.[25] The α-chlorine atom of $ClCH_2COCl$ is also reactive in this case.

The cyclization is not limited to the formation of only C-N and C-C bonds, but can also occur through forming C-N and C-N bonds.[26] This transformation was exemplified by the preparation of 3-hydroxy-1-phenylpyrido[1,2-*a*]pyrazinium chloride in the reaction of $ClCH_2COCl$ with phenyl(2-pyridyl)ketimine (eq 12).[26b] Besides the α-chlorine, the carbonyl group of $ClCH_2COCl$ can also be utilized for the cyclization.

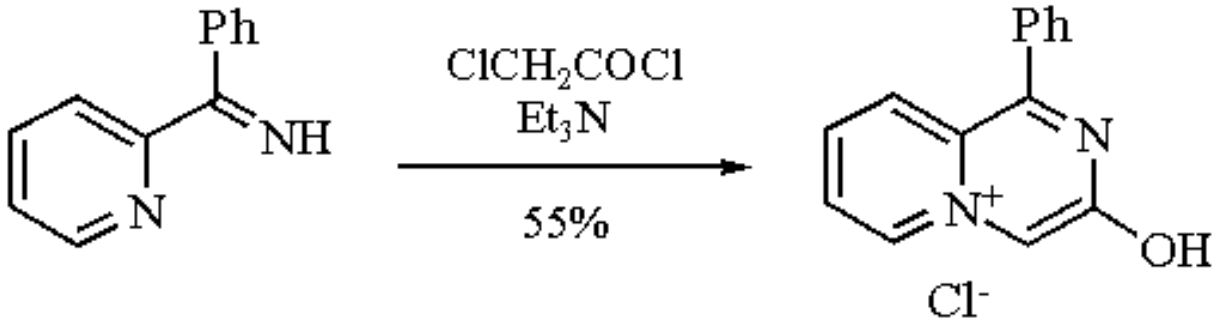

(12)

The chlorine atom at the α position of $ClCH_2COCl$ may also be displaced by an oxygen to form a ring containing both O and N atoms.[27] Cyclization of 4-amino-1-phenylisoquinolin-3-ol hydrochloride with $ClCH_2COCl$ generated 6-phenyl-2,3-dihydro-1*H*-[1,4]oxazino[2,3-*c*]isoquinolin-2-one in 40% yield (eq 13).[27b]

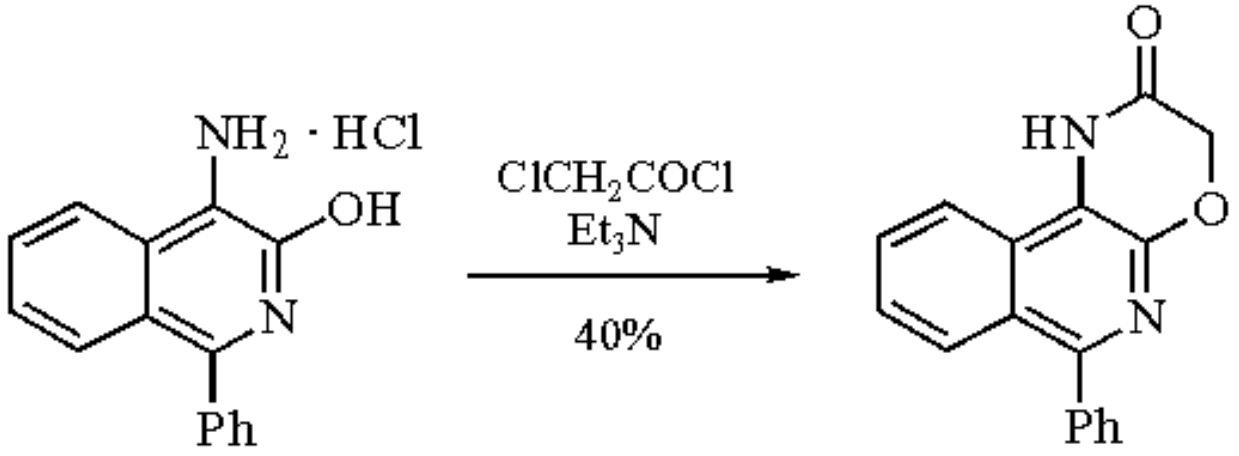

(13)

If a substrate has both N and S atoms, a heterocycle containing both atoms can be obtained upon treatment with $ClCH_2COCl$.[28] Preparation of thiazoles from thiobenzamide and $ClCH_2COCl$ has been accomplished through this process.[28c]

O-Acylation.

Like *N*-acylation, *O*-acylation using $ClCH_2COCl$ can be achieved either with or without a base.[29-33] Acylation has been successfully carried out with various hydroxy group-containing compounds such as alcohols,[29] phenols,[31] and saccharides[30] as substrates. Acylation of an enolate by $ClCH_2COCl$ has also been documented.[32] It is reported that treatment of salicylic hydrazide with $ClCH_2COCl$ in the presence of $MeSO_3H$ yielded 4,5-dihydro-5*H*-1,3,4-benzoxadiazepin-5-one in 59% yield (eq 14).[33]

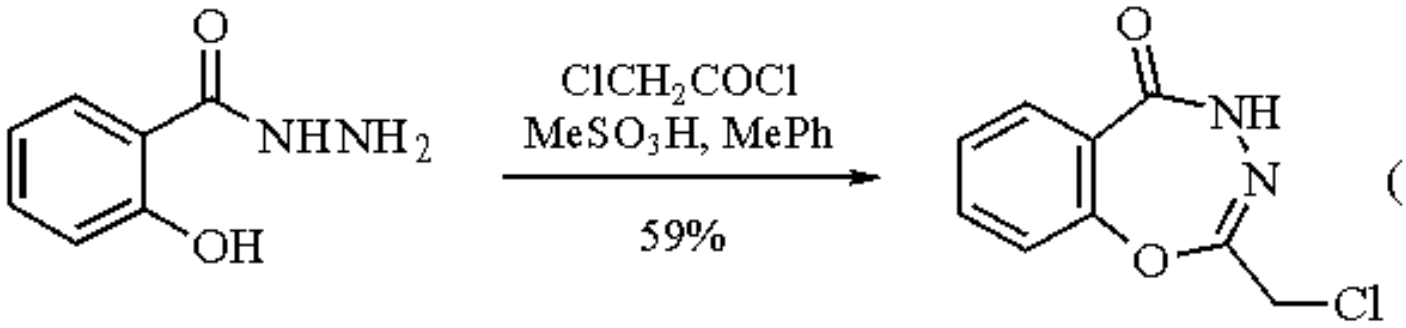

(14)

S-Acylation.

S-Acylation is a less well-studied reaction of $ClCH_2COCl$.[34] However, it has found use in the preparation of 2-oxo-1,4-dithiane and its derivatives, which can be further transformed to the analogs of tetrathiafulvalene for the study of conducting molecular solids.[34b,c]

Precursor to Monochloroketene.

By treatment with Et_3N, $ClCH_2COCl$ loses HCl to yield monochloroketene.[35-38] The ketene generated by this method has been extensively used to perform [2 + 2] cycloadditions. The most widely studied reaction is the addition of the

ketene to imines for the construction of the valuable β-lactam ring (eq 15).[35] This reaction proceeds readily with a wide range of imines with varying structures. Even diimines can be doubly cyclized. The in situ generated ketene was also trapped by allenes.[36a] An interesting method regarding the preparation of squaric acid is based the use of the monochloroketene.[36b]

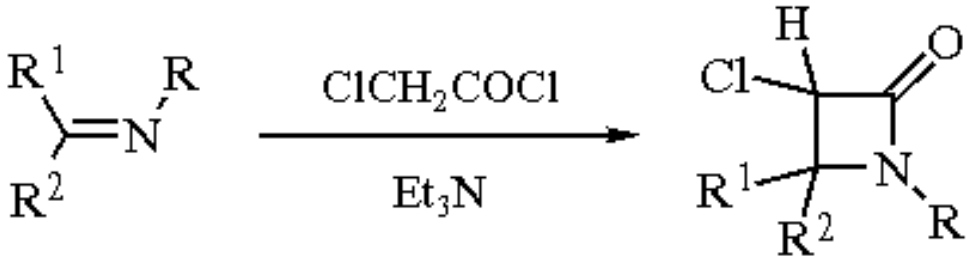

(15)

Beside [2 + 2] cycloadditions, [4 + 2] and [8 + 2] cycloadditions involving the in situ generated chloroketene have also been studied.[35a,37,38]

Chlorination.

Chloroacetyl chloride occasionally serves as a chlorinating agent.[39] 2,4-Pentanedione was chlorinated at the 1- and 5-positions upon treatment with $ClCH_2COCl/AlCl_3$ in the presence of $Cu(OAc)_2$.[39a,b] Chloroacetyl chloride has also been used to transform 2-picoline *N*-oxide and 2-oxo-2-dimethylamino-5-methyl-1,2-oxophospholane to 2-chloromethylpyridine and 2-oxo-2-chloro-5-methyl-1,2-oxophospholane, respectively.[39c,d]

Related Reagents.

Chloroacetyl Fluoride; ***Dichloroketene***.

---

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Chloroacetyl Fluoride

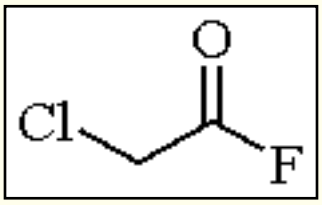

[359-14-8] · C_2H_2ClFO · Chloroacetyl Fluoride · (MW 96.49)

(acylating agent; a precursor to chloroacetylium ion)

Physical Data: bp 73-75 °C; d^{20} 1.379 g cm^{-3}.[1]

Preparative Methods: generally prepared by fluorination of $ClCH_2COCl$.[1] A variety of reagents has been employed for this transformation, including benzoyl fluoride/KH_2F,[2a] KHF_2,[2b] KF,[2c] KF/tetraalkylammonium chloride,[2d] and dialkylaminosulfur trifluoride.[2e] Preparation of $ClCH_2COF$ may also be accomplished from $ClCH_2CO_2H$ through the use of 2-chloro-1,1,2-trifluoroethyldiethylamine as the fluoride source.[3] Treatment of $ClCH_2CF_2CF_2OCH_3$ with SO_3 leads to the formation of $ClCH_2COF$ in 94% yield, which is the highest yield reported for the preparation of the reagent.[4]

Handling, Storage, and Precautions: is corrosive, moisture sensitive, and should be stored under anhydrous conditions. This reagent should be handled in a fume hood.

Chloroacetyl fluoride is less well studied compared to its analog ***Chloroacetyl Chloride***. The majority of the publications concerning $ClCH_2COF$ are centered on its structure and spectroscopic properties.[5] Regarding synthetic chemistry aspects, $ClCH_2COCl$ has mainly been used as an acylating agent. When $ClCH_2COF$ was treated with SbF_5 in SO_2 solution at low temperature, chloroacetylium ion was observed.[6a] Its stable hexafluoroantimonate salt has been isolated (eq 1) and used as chloroacylating agent for aromatic compounds (eq 2).[6b] Chloroacetylium hexafluoroantimonate reacts with benzene, toluene, *p*-xylene, and mesitylene to generate the corresponding chloroacylated products in high yields. In the case of toluene, a 7.7:3.4:88.9 isomer distribution ratio was obtained for the *ortho*, *meta*, and *para* isomers.

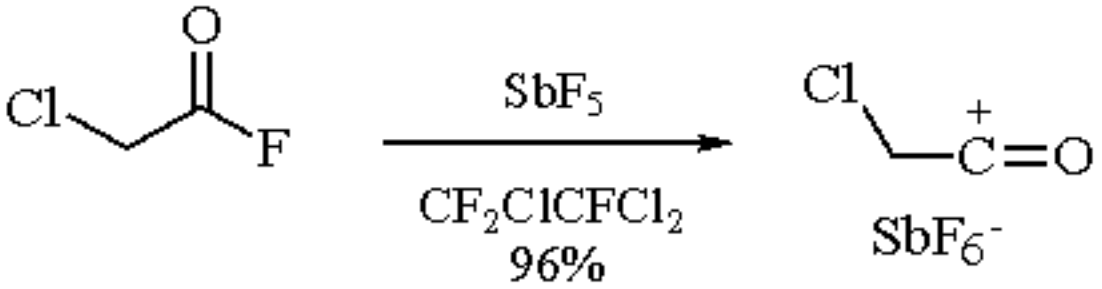

(1)

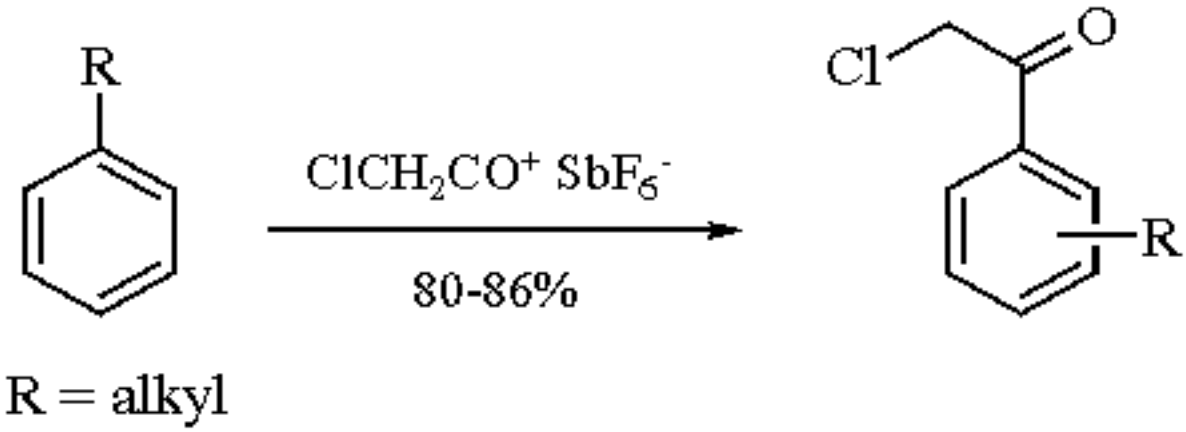

(2)

Reaction between $ClCH_2COF$ and diazomethane led to formation of $ClCH_2COCHN_2$, which was in situ converted to α-chloro-α´-fluoroacetone in 32% yield by the addition of HF (eq 3).[7]

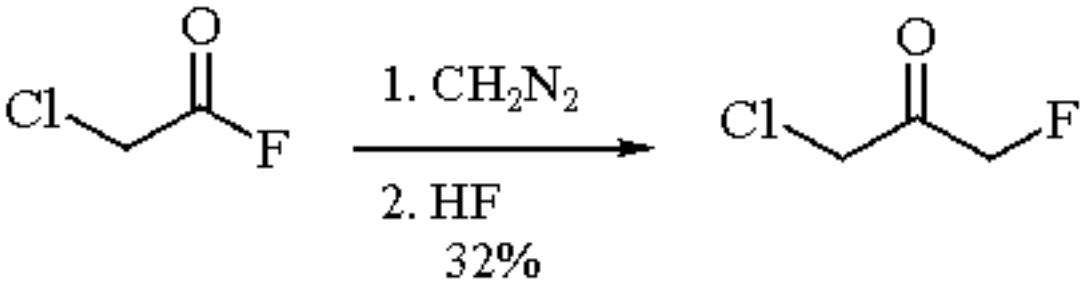

(3)

It was also reported that $ClCH_2COF$ can be electrochemically transformed into chlorofluoroacetic acids.[8]

Related Reagents.

Chloroacetyl Chloride.

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Chloroacetyl Isocyanate

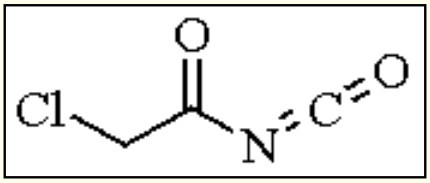

[4461-30-7] · $C_3H_2ClNO_2$ · Chloroacetyl Isocyanate · (MW 119.51)

(preparation of primary amides from Grignard reagents,[11] monosubstituted ureas from primary amines[12] and from β-lactams[13])

Physical Data: fp 61 °C; bp 50-55 °C/20 mmHg, 68-79 °C/70 mmHg; *d* 1.403 g cm^{-3}.

Solubility: sol benzene, THF, etc.

Form Supplied in: colorless-yellow oil, commercially available; can also be prepared in the laboratory.[1]

Handling, Storage, and Precautions: toxic, lachrymator, corrosive, reacts with moisture; refrigerate and store under nitrogen; should be handled in a fume hood.

Addition Reactions.

Chloroacetyl isocyanate (**1**) undergoes a variety of reactions, typical of the isocyanate class, including addition reactions with alcohols,[2] amines,[3] organic peroxides,[4] ketene silyl acetals,[5] hydrazines,[6] 2-pyrazolines,[7] and triazoline-3,5-diones.[8] In addition, the bifunctionality of this reagent endows it with specialized uses including the synthesis of heterocyclic rings[9,10] and polymers.[3,4]

Addition-Cleavage Reactions: *N*-Unsubstituted Amides and Ureas.

Grignard reagents add to reagent (**1**) to afford mixed imides.[11] These compounds may then be cleaved either reductively or hydrolytically at the chloromethyl-substituted carbonyl to give primary amides (eq 1).

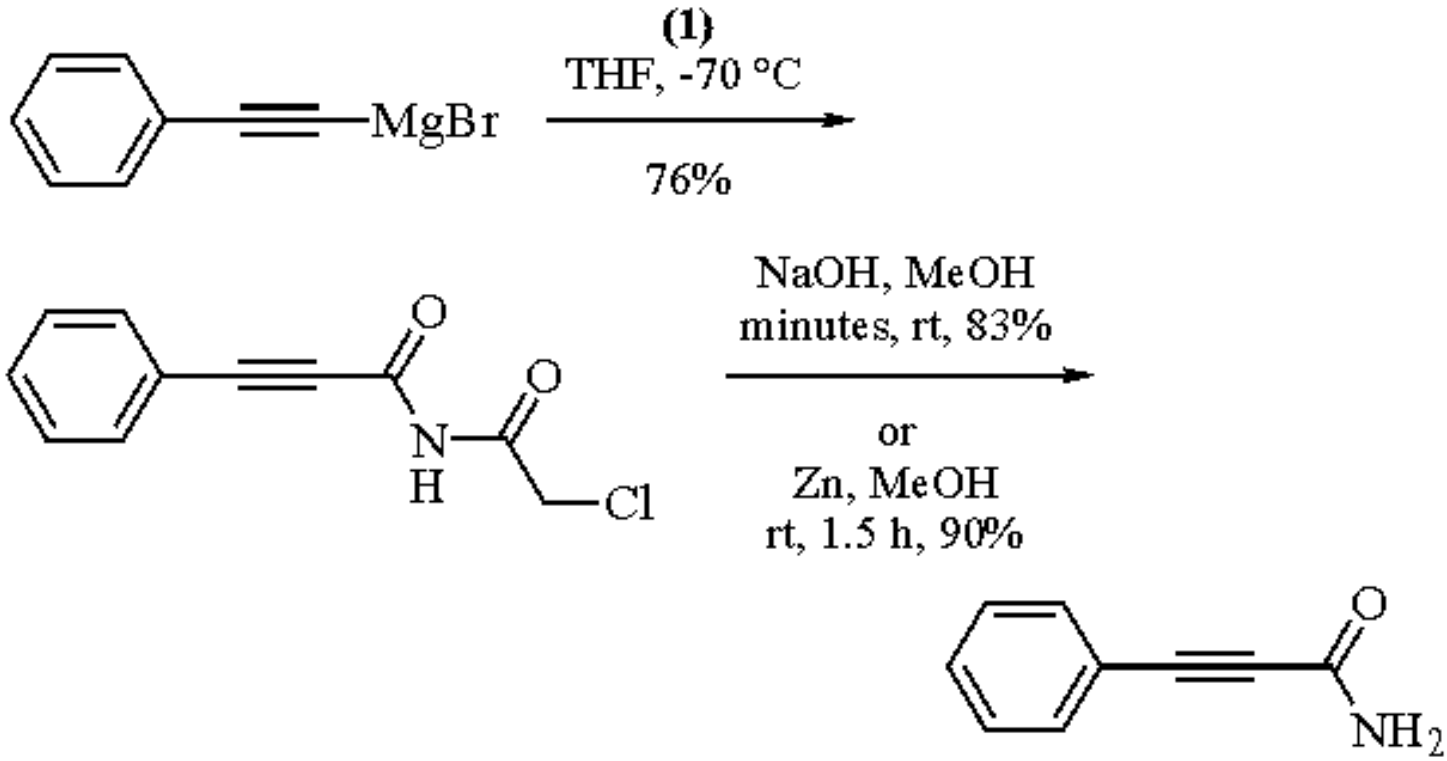

(1)

Likewise, chloroacetyl ureas derived from (**1**) and primary amines are subject to regioselective cleavage by nucleophiles to give *N*-monosubstituted ureas.[12]

Condensation of (**1**) with photopyridones (β-lactams, eq 2)[13] gave *N*-chloracetylcarbamoyl derivatives. Treatment of these compounds with ***Triethylamine*** in methanol gave the all-*cis*-1,2,3-trisubstituted cyclobutanes, whereas treatment with sodium methoxide in methanol afforded the *trans*,*trans*-cyclobutanes. The latter class of compounds provides an intermediate for the synthesis of oxetanosyl *N*-glycosides.

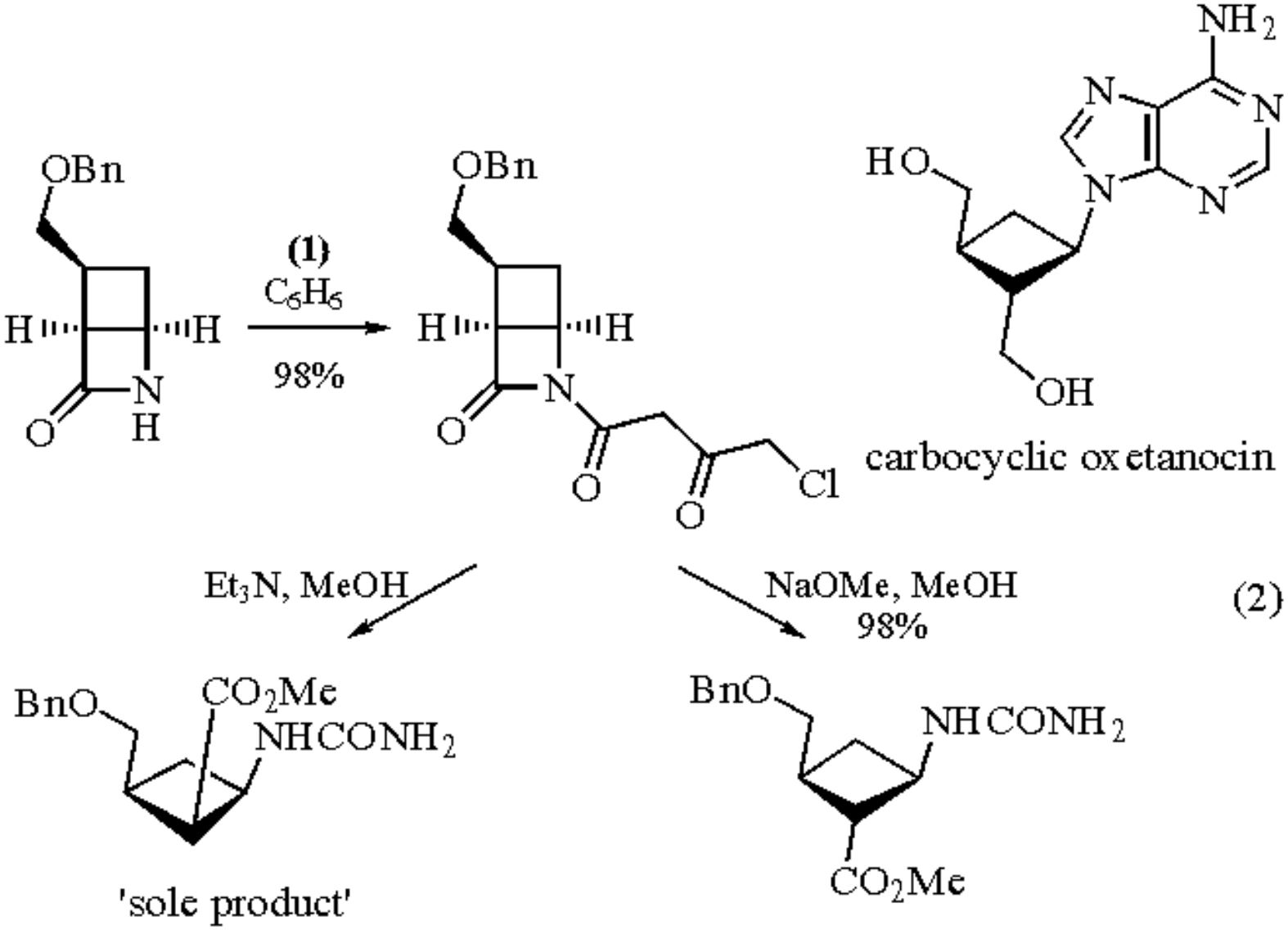

Related Reagents.

Chlorosulfonyl Isocyanate; ***Trichloroacetyl Isocyanate***.

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2-Chloroacrylonitrile

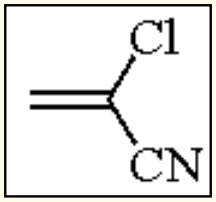

[920-37-6] · C_3H_2ClN · 2-Chloroacrylonitrile · (MW 87.51)

(ketene equivalent for use in the Diels-Alder reaction[1] and other cycloaddition reactions; undergoes Michael additions and radical additions)

Physical Data: mp -65 °C; bp 88-89 °C; *d* 1.096 g cm^{-3}.

Solubility: sol most organic solvents other than pure hydrocarbons.

Form Supplied in: neat colorless liquid.

Analysis of Reagent Purity: ^1H NMR, ^{13}C NMR.

Handling, Storage, and Precautions: highly toxic; use only in a fume hood. Reagent can be absorbed through the skin. Always wear gloves when handling this reagent.

[4 + 2] Cycloaddition Reactions.

2-Chloroacrylonitrile is a reasonably good dienophile for the Diels-Alder reaction. It reacts thermally with a variety of cyclic dienes such as cyclopentadiene[2] and cyclohexadiene.[2,3] Most often the initial cycloadducts are hydrolyzed immediately to produce the corresponding ketones (eq 1). In this fashion, 2-chloroacrylonitrile, along with ***2-Acetoxyacrylonitrile***, is one of the most popular ketene equivalents for use in the Diels-Alder reaction.[1] In the case of substituted cyclohexadienes the starting diene is often an unconjugated 1,4-diene which under the reaction conditions isomerizes to the reactive 1,3-diene and produces the desired Diels-Alder adduct (eq 2).[4]

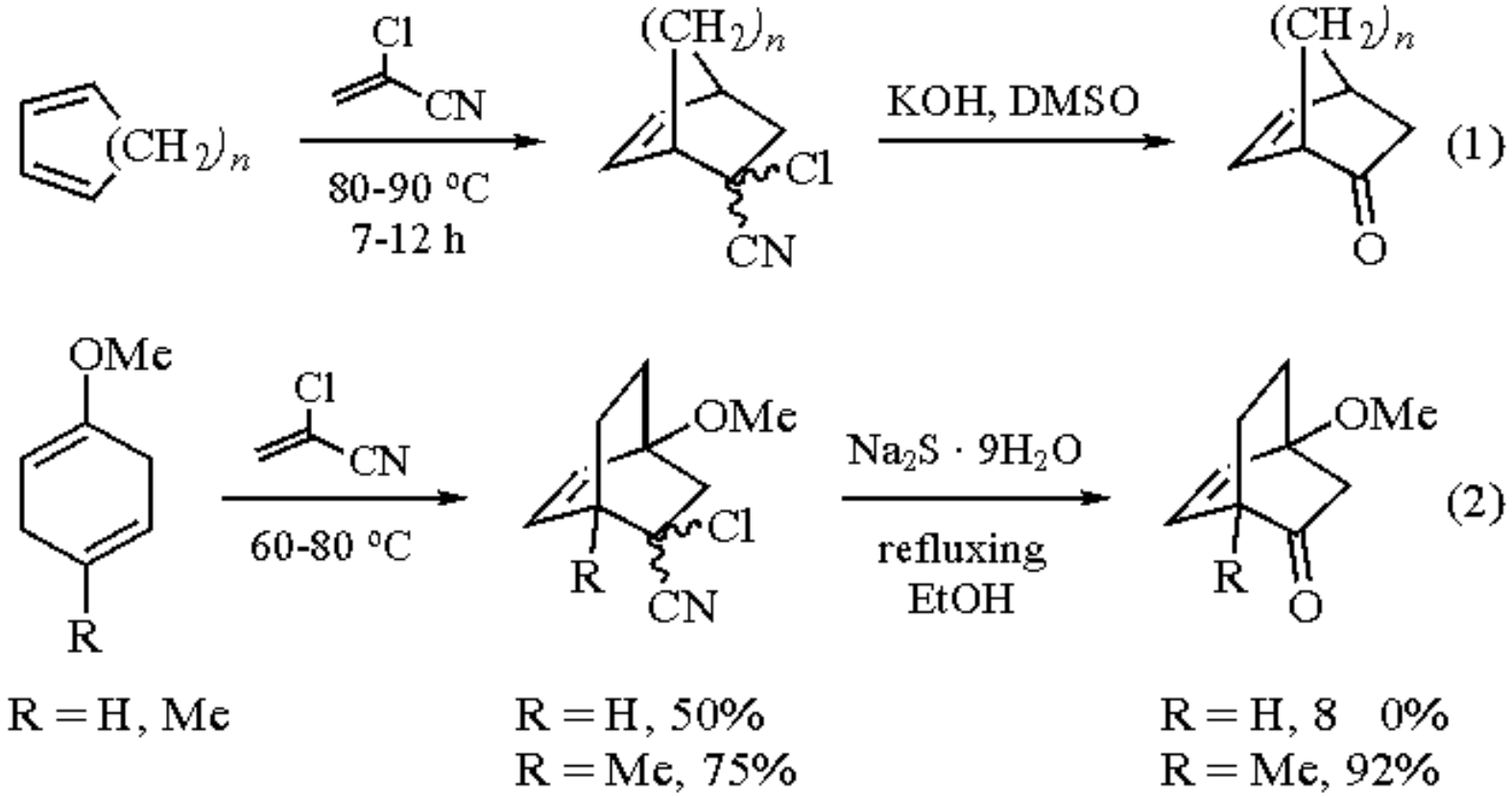

Once again the product α-chloro nitrile is hydrolyzed to produce the bicyclo[2.2.2]octanone. The hydrolysis reaction is usually carried out with either ***Potassium Hydroxide*** in DMSO[2,5] or with ***Sodium Sulfide*** in refluxing ethanol.[6]

Copper salts have been used to catalyze the Diels-Alder reaction of 2-chloroacrylonitrile.[6] Most notable is the successful cycloaddition of the thermally sensitive substituted cyclopentadiene (**1**) (eq 3).[6a,b] Use of copper(II) fluoroborate allowed the reaction to take place at 0 °C. This ultimately produced ketone (**2**), an important intermediate in the early syntheses of prostaglandins. Diels-Alder reactions between furans and 2-chloroacrylonitrile have also been achieved via copper catalysis (eq 4).[6d] Interestingly, the base-catalyzed hydrolysis of adduct (**3**) produced the amide (**4**) instead of the expected ketone. There have been other instances in which the intermediate α-chloronitrile yields products other than the hydrolyzed ketone.[7]

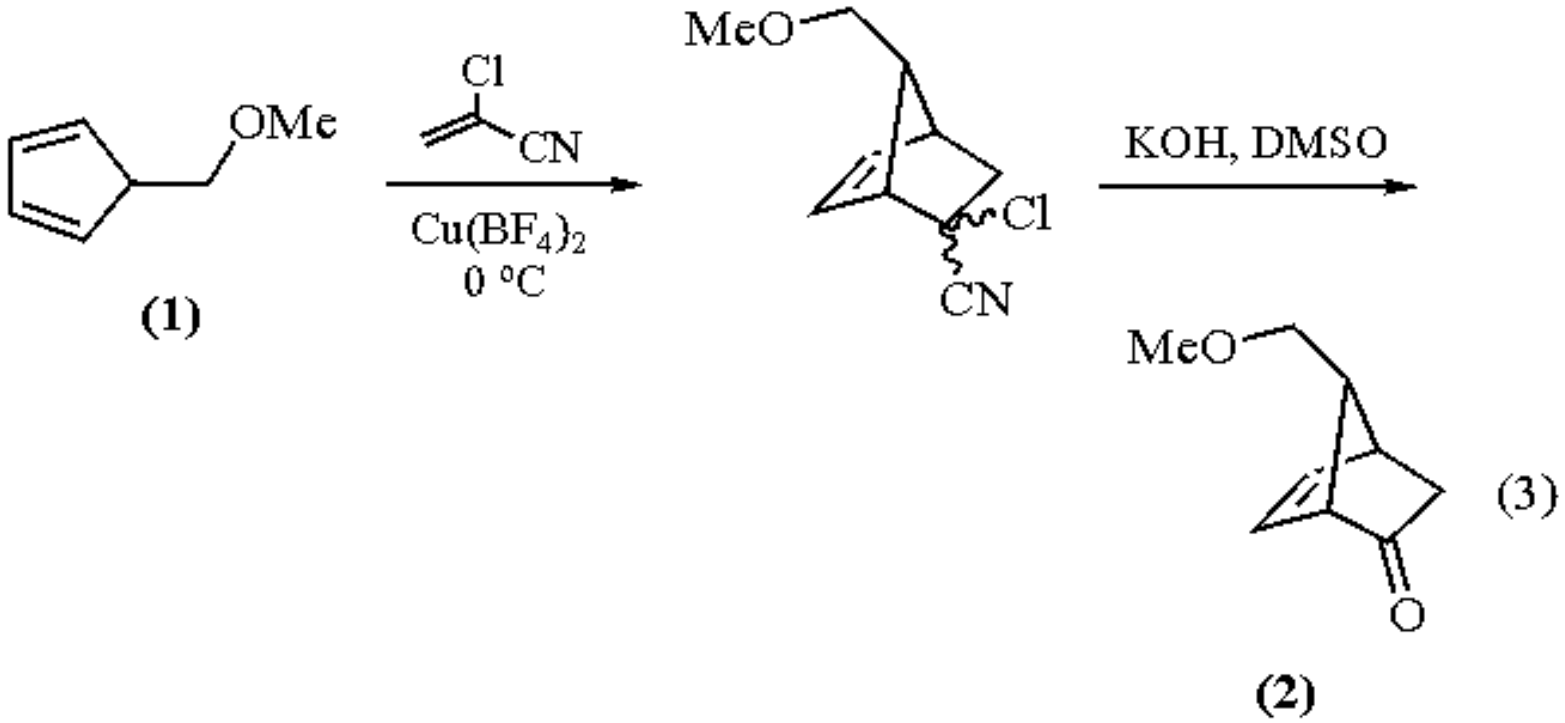

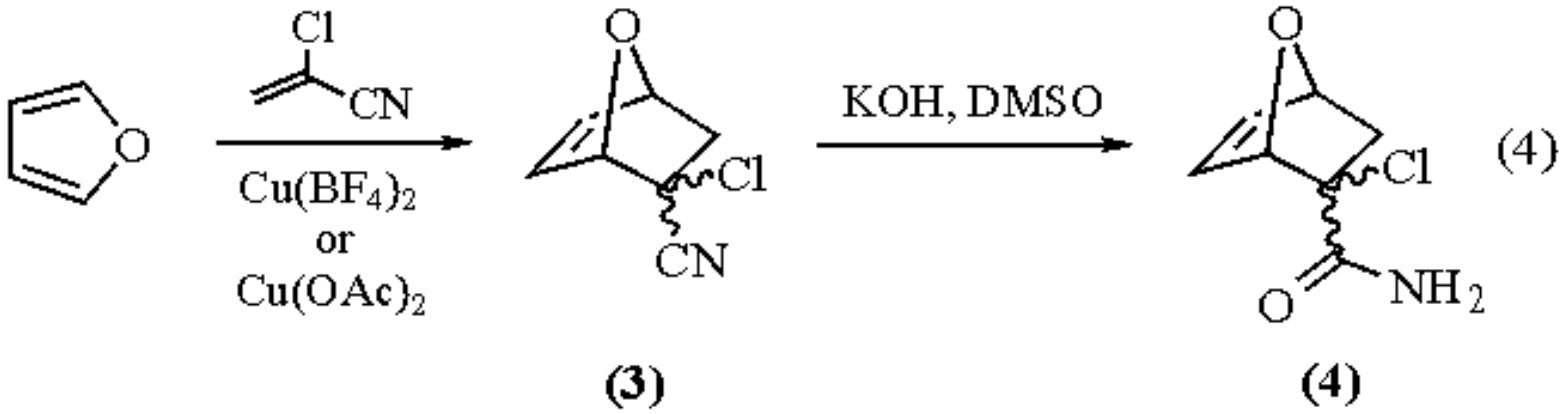

As seen from the above examples, cyclic dienes are usually used in conjunction with 2-chloroacrylonitrile.[8] Such dienes include substituted cyclohexadienes,[4,7a-d,9] substituted cyclopentadienes,[6a-c,7e] hydroxypyrones,[10] fulvenes,[11] furans,[6d,12] and isobenzofurans.[13] Other dienes which give [4 + 2] cycloadducts with 2-chloroacrylonitrile include vinyl heterocycles[14] and a few acyclic dienes.[15] It has been stated that thermal cycloadditions are limited to 140 °C due to polymerization of the chloroacrylonitrile above this temperature.[3] In addition to the aforementioned Cu^{2+} catalysis, ***Zinc Iodide***,[12b] triorganotin cations,[12e] and high pressure[12a,f] have been used to accelerate the cycloaddition reactions of 2-chloroacrylonitrile and furans.

In addition to 2-chloroacrylonitrile and ***2-Acetoxyacrylonitrile***, other ketene equivalents have been developed.[1] These include acrylonitrile,[2] 2-aminoacrylonitrile,[16a] 2-methylthioacrylonitrile,[16b] 2-chloroacryloyl chloride,[17a,b] 2-bromoacrolein,[17c] vinyl boronates,[4,18a] vinylboranes,[18b] nitroethylene,[19] and vinyl sulfoxides.[20] One comparative study found that 2-chloroacrylonitrile was both more reactive and more regioselective than either 2-acetoxyacrylonitrile or dibutyl vinyl boronate.[4] Chiral vinyl sulfoxides have been explored as possible chiral ketene equivalents.[17c,20]

Other Cycloaddition Reactions.

In addition to [4 + 2] cycloadditions, 2-chloroacrylonitrile also undergoes [2 + 3][21,22] and [2 + 2][23] cycloaddition reactions. In particular, 2-chloroacrylonitrile is a good dipolarophile and has produced cycloadducts with nitrones[21] and a number of different azomethine ylides.[22] In the case of nitrones the cycloadducts have been hydrolyzed to isoxazolidinones; thus 2-chloroacrylonitrile once again functions as a ketene equivalent in these reactions (eq 5).[21c] Chiral nitrones have been found to undergo stereoselective cycloaddition reactions and have been used in the synthesis of chiral amino acids[21c] and carbapenem derivatives.[21a]

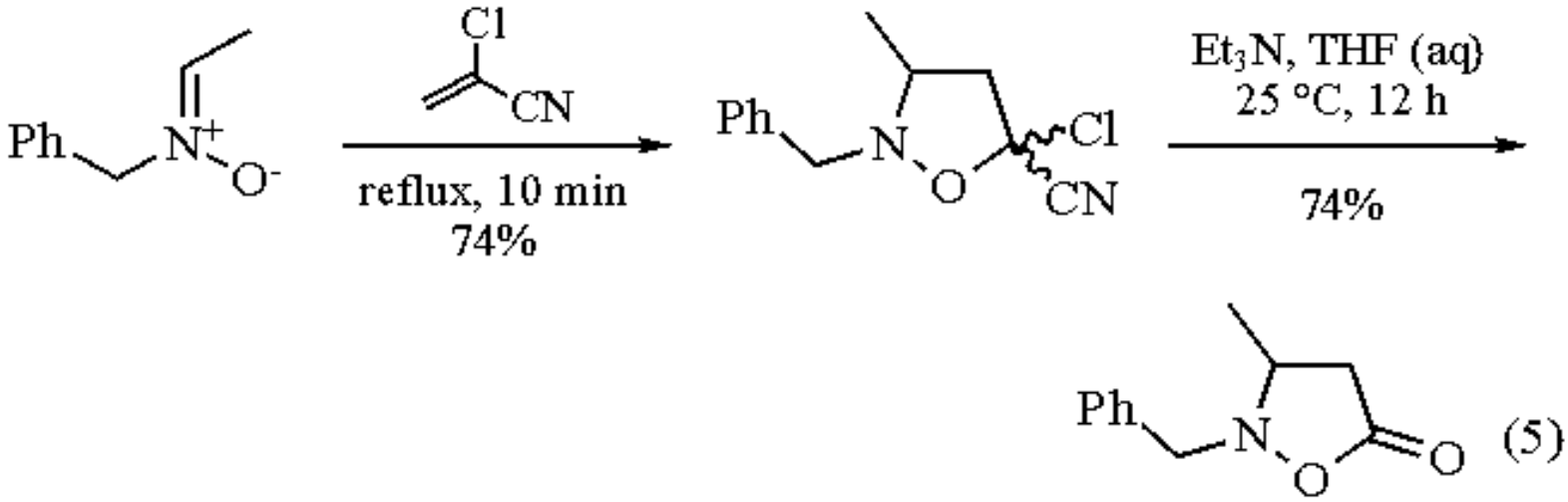

Michael Additions and Radical Additions.

As with other acrylonitriles, 2-chloroacrylonitrile is an excellent acceptor of nucleophiles[23e,24] and nucleophilic radicals.[25] In a number of instances[24a,b,25b,e] the initial addition product can undergo a further cyclization, in which case 2-chloroacrylonitrile functions as a convenient two-carbon annulating agent. Such an annulation is illustrated for both a polar addition (eq 6)[24b] and a radical addition (eq 7).[25b] 2-Chloroacrylonitrile has been used extensively in the homologation of nucleophilic radicals[25a,c,f] and, in keeping with the captodative effect,[25d] has been shown to react 10-15 times faster than acrylonitrile.[25a,d]

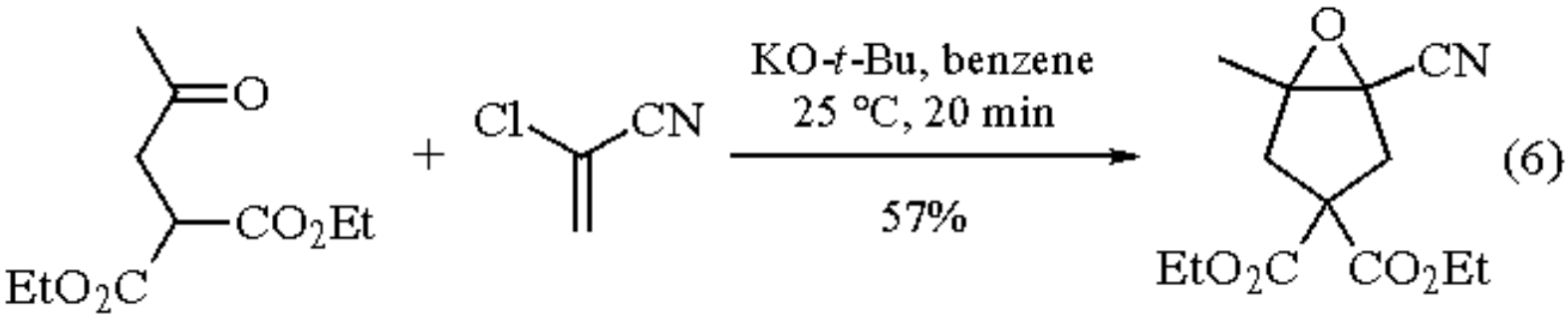

2-Chloroacrylonitrile

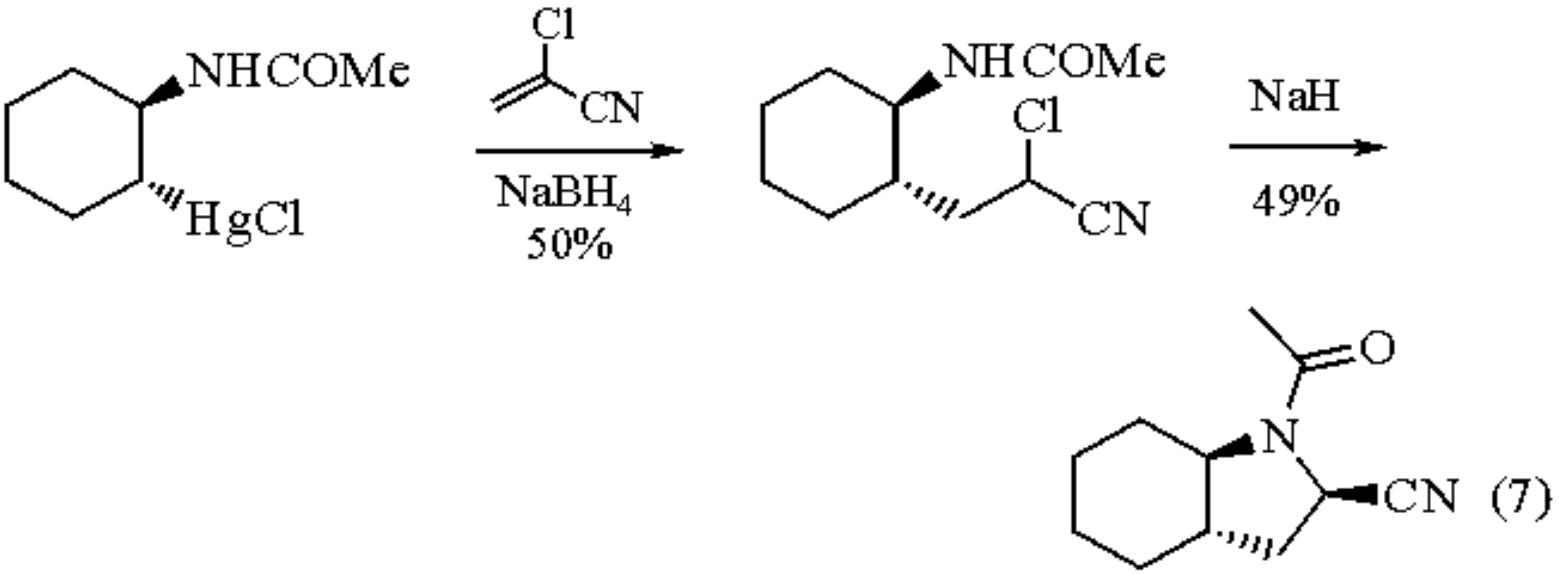

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1-Chloroallyllithium

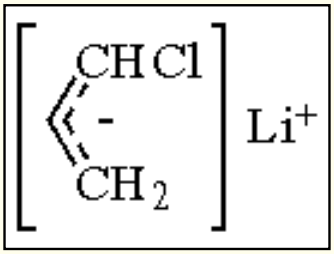

[80411-43-4] · C_3H_4ClLi · 1-Chloroallyllithium · (MW 82.46)

(reacts with substituted epoxides,[4] thiiranes,[5] esters,[1] alkyl bromides,[6] imines,[10] and azirines[10] in the α-mode; with carbonyl compounds[2] and alkyl halides[3] gives a mixture of α- and γ-adducts; 1-chloroallylzinc gives highly diastereoselective α-addition with aldehydes and ketones[7])

Solubility: sol diethyl ether, THF.

Handling, Storage, and Precautions: highly unstable; generated at -78 °C in the presence of electrophiles in an inert atmosphere.

Chloroallyllithium was first prepared[1] by treating γ-chloroallyltriphenyllead (**1**) with ***n-Butyllithium*** at -90 °C (eq 1). Reaction with various electrophiles gives products arising from both α- and γ-attack.[1-4] However, (**2**) displays exclusive α-selectivity in its reaction with epoxides to give either the corresponding β-chloro-γ-ethylenic alcohols (**3**) or a mixture of (**3**) and the cyclized products (oxetanes) (**4**) (eq 2).

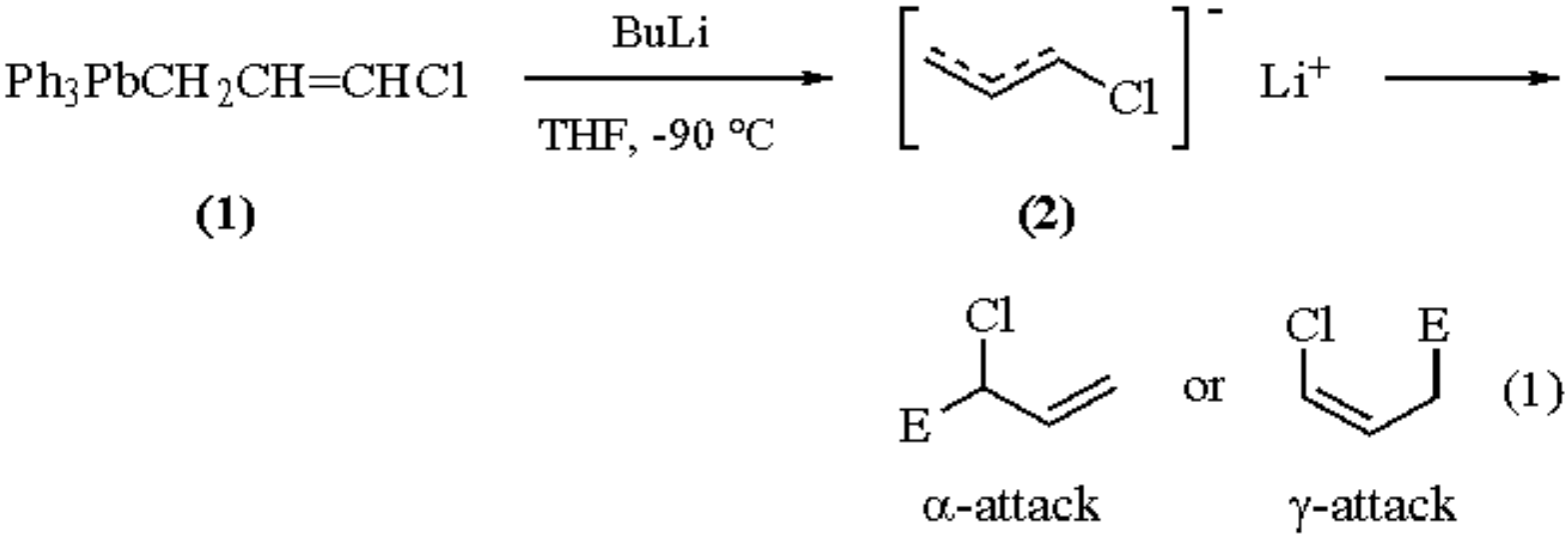

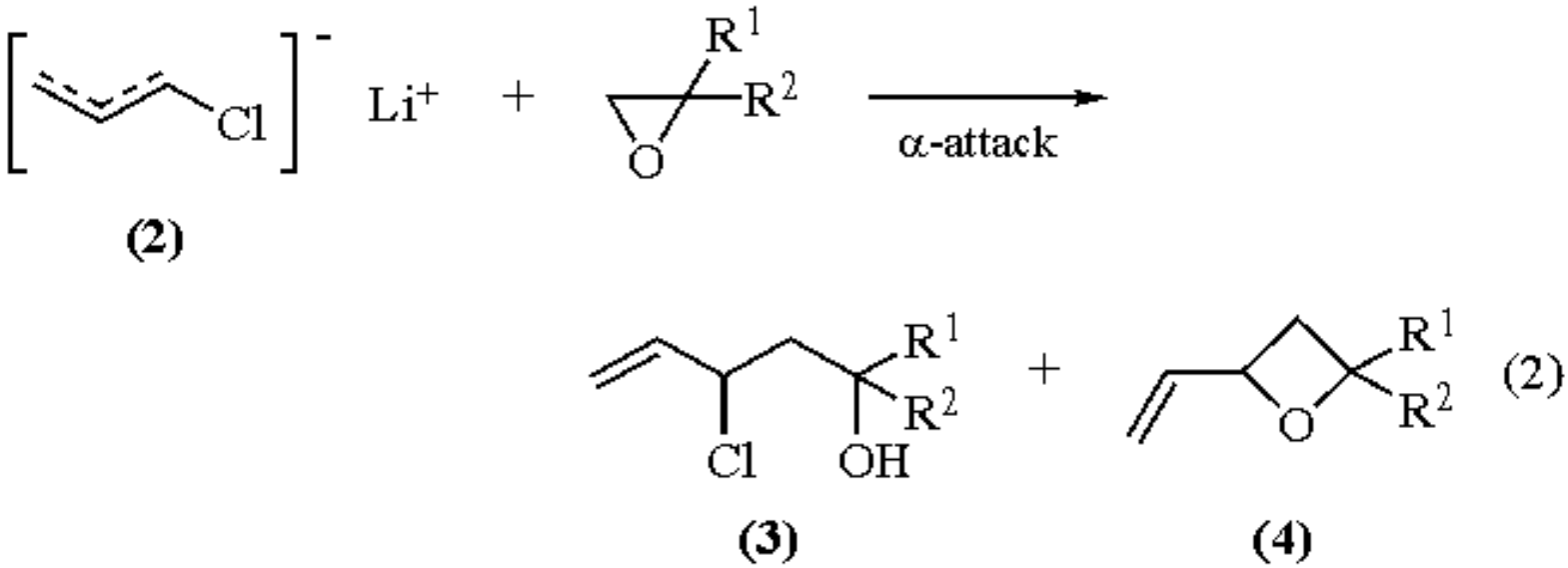

$R^1 = H, Me, Et, Ph, CH_2OH, CH_2OEt; R^2 = H$

$R^1 = R^2 = Pr, H_2C{=}CHCH_2CH_2$

Similarly, the reaction with thiiranes gave 2-vinylthietanes (**7**) by intramolecular cyclization of the initially formed β-chloro-γ-ethylenic thiolithium (**6**) (eq 3).[5] The α-regioselectivity was also observed in the acylation of (**2**) with esters (except with t-butyl carboxylate). α-Chloro-α,β-unsaturated ketones (**9**)[1] were formed by base-catalyzed isomerization of initially formed α-chloroacyl adducts (**8**) (eq 4).

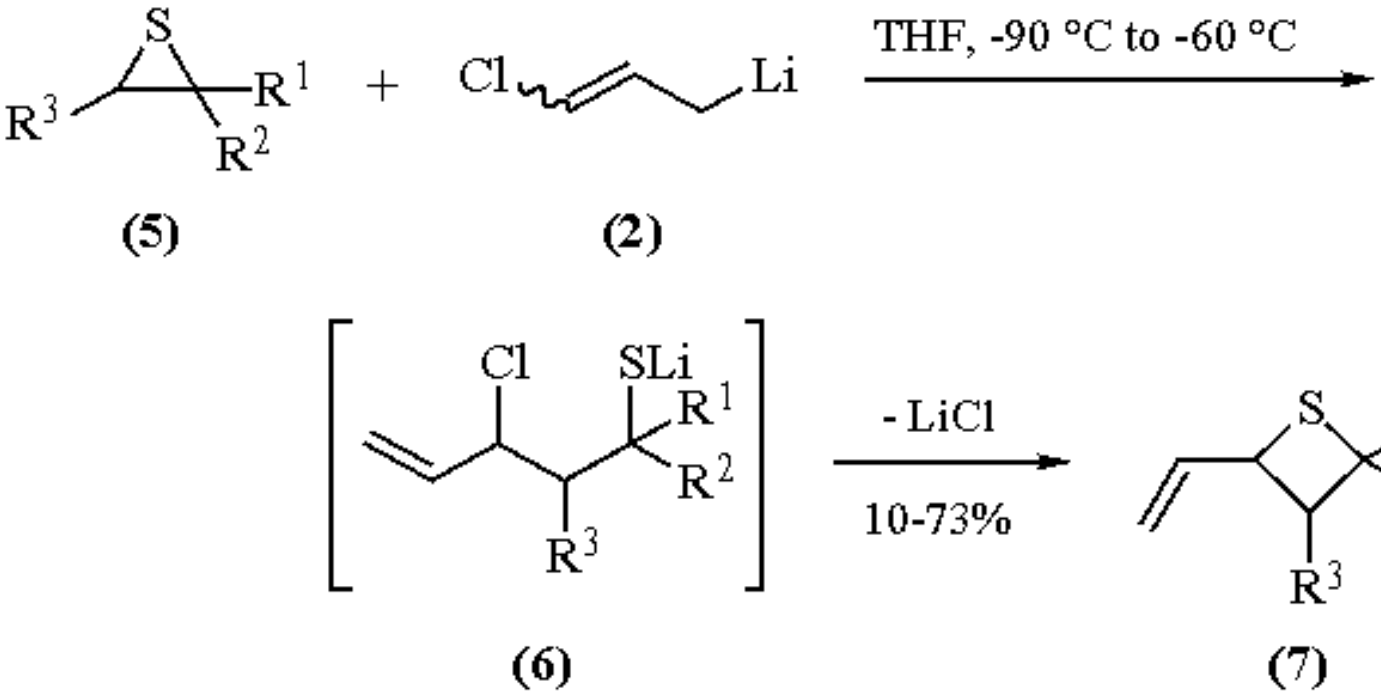

$R^1 = R^3 = H$; $R^2 = Et$, CH_2OEt, 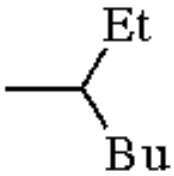

$R^1 = R^2 = Me$, Pr, CH_2-CH=CH_2; $R^3 = H$
$R^1 = R^2 = R^3 = H$
$R^1 = H$; $R^2 = R^3 = -(CH_2)_4-$

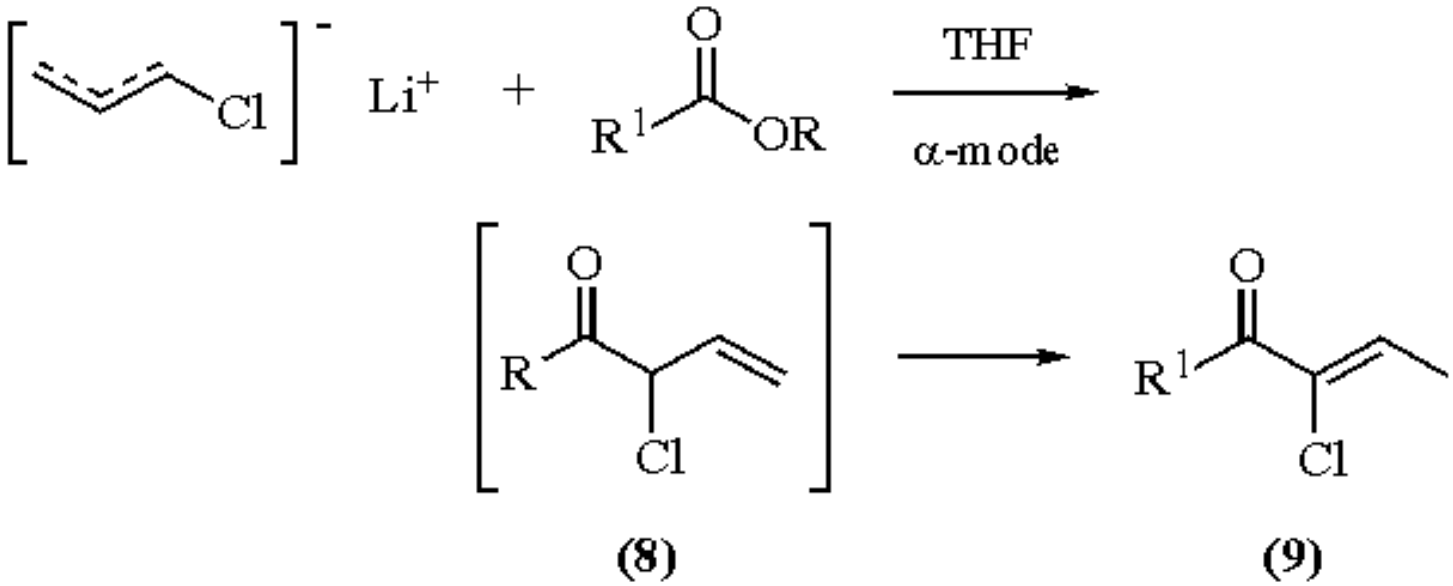

$R^1 = Et$, Pr, Bu, *i*-Pr, Ph, $MeOCH_2CH_2$

Alkylation of α-chloroallylithium gave mixtures of α- and γ-alkylated products (**10**) and (**11**) (eq 5).[3] However, with

a few alkylating agents, a high degree of α- (*n*-butoxymethylene chloride) or γ- (dimethylmethyleneammonium iodide) regioselectivity was observed. The γ-alkylated products are formed exclusively in the (*Z*) configuration, which is explained on the basis of transition state (**12**) (eq 5).

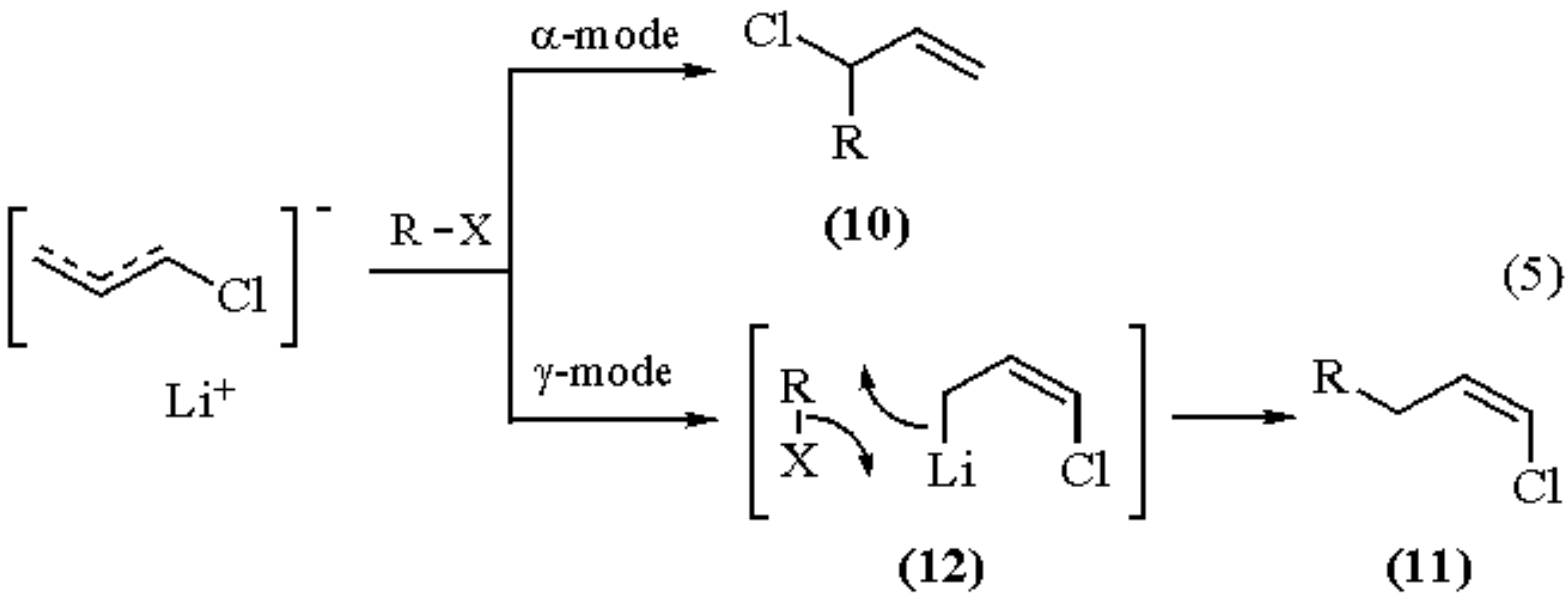

R = Bu; X = Br, Cl
R = C_6H_{13}, cyclo-C_6H_{11}, $PhCH_2$, $H_2C{=}CHCH_2CH_2$
$MeCH{=}CHCH_2$, $Me(CH{=}CH)_2CH_2$, $BuC{\equiv}CCH_2$

Subsequently, 1-chloroallyllithium was directly generated in situ by treating ***Allyl Chloride*** with ***Lithium Diisopropylamide*** at -78 °C and was shown to undergo alkylation with high α-regioselectivity with a variety of primary alkyl bromides.[6] The secondary allyl chloride intermediates (**13a**) and (**13b**) have been used as building blocks for the synthesis of disubstituted alkenic insect sex pheromones of *A. leucotreta* (**14a**) and *S. littoralis* (**14b**), respectively (eq 6). The α-alkylation/cuprate displacement sequence is also applicable to anions of methallyl and crotyl chloride and is a promising route for the synthesis of more complex systems (eq 7).[6]

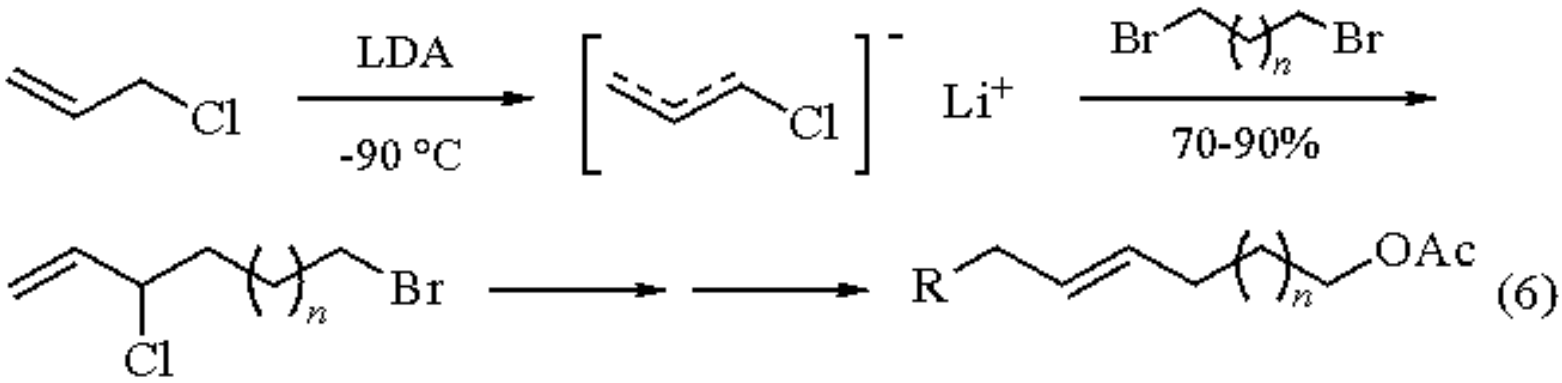

(13a) $n = 4$
(13b) $n = 8$

(14a) R = Pr, $n = 4$
(14b) R = Me, $n = 8$

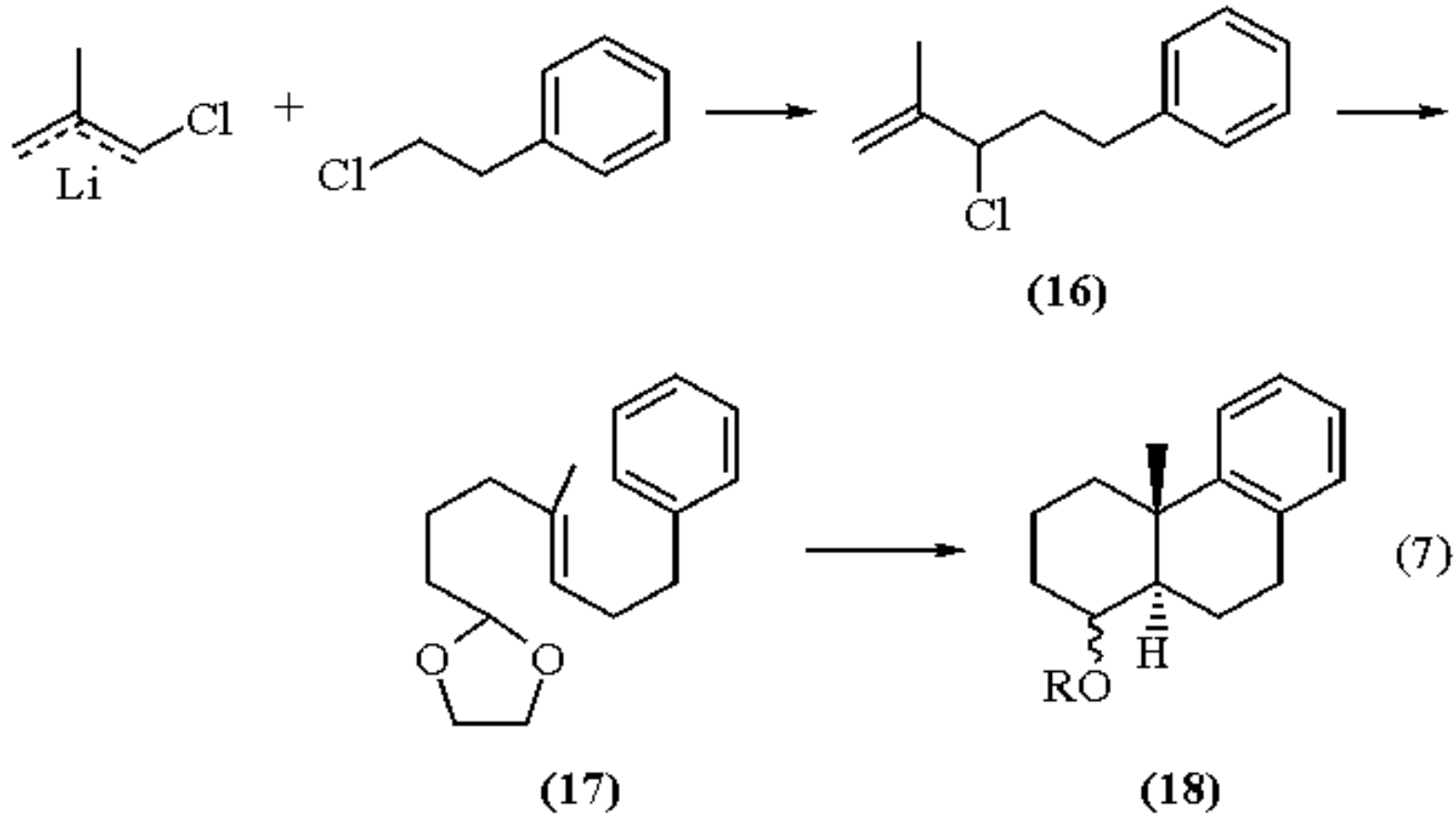

(7)

The chloroallyllithium (**2**) derived from (**1**) and butyllithium adds to carbonyl compounds to form products of both α- and γ-addition in varying proportions (eq 8).[2] The epoxides (**19**) thus obtained were a mixture of (*E*) and (*Z*) isomers, while the *cis* configuration was maintained in the γ-adducts (**20**), as observed earlier (eq 8).

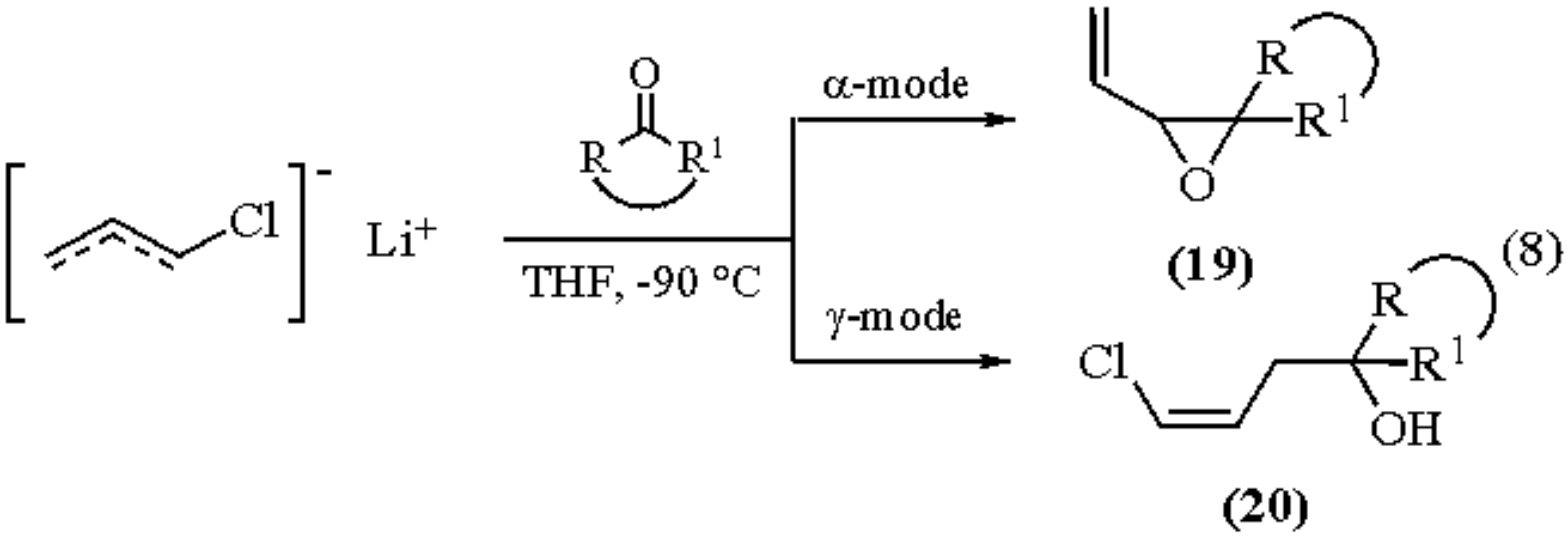

(8)

Interestingly, the anion (**21**) with a Zn^{2+} counterion reacts with aldehydes and ketones with exclusive α-addition and with high diastereoselectivity in the product chlorohydrins (eq 9).[7] No epoxides were formed with Zn^{2+} as counter cation. Treatment of the chlorohydrins (**22**) with potassium ethoxide gave *cis*-vinyloxiranes (**19**) in quantitative yields (eq 9). Chloroallyllithium (**2**) generated by direct deprotonation of allyl chloride with LDA, however, gave only γ-adducts (**20**) with aromatic aldehydes and ketones (eq 10),[7] in contrast to the ambident behavior of (**2**) generated from

1-Chloroallyllithium

(**1**).[2]

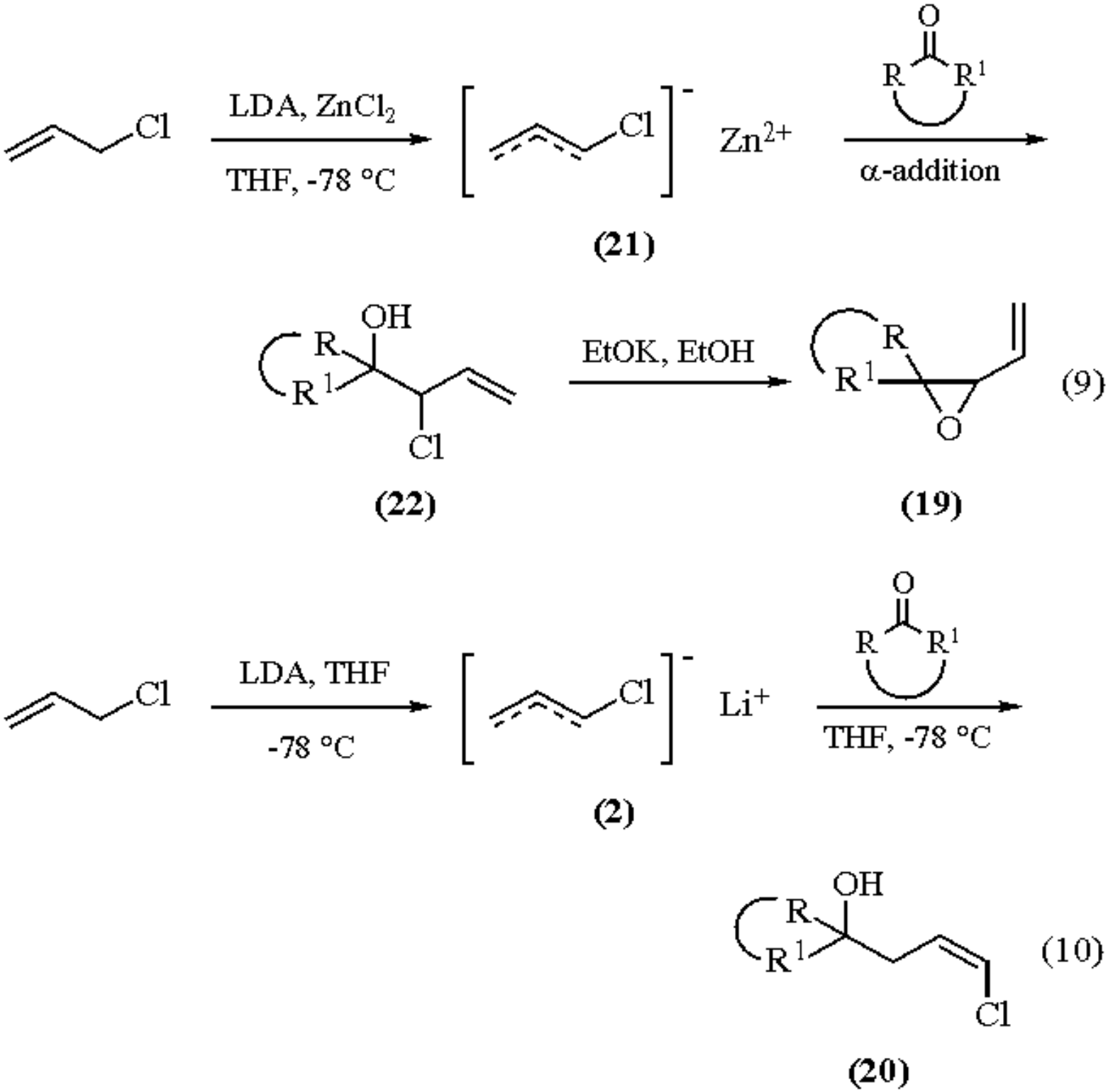

The anion (**2**) underwent regioselective α-addition with imines[8,9] and azirines,[10] followed by intramolecular cyclization to afford the corresponding vinylaziridines (**24**) (eq 11) and 2-vinylazabicyclobutanes (**26**), respectively (eq 12).

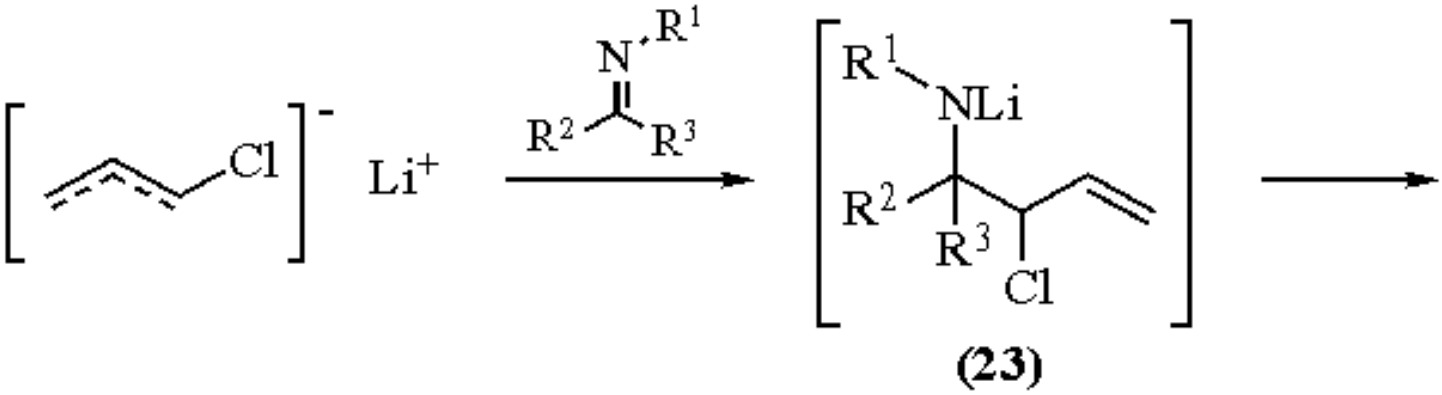

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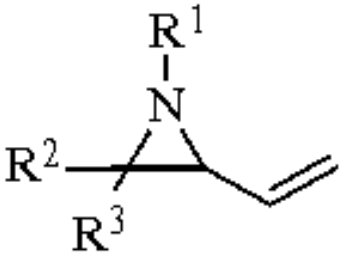

(11)

(24)

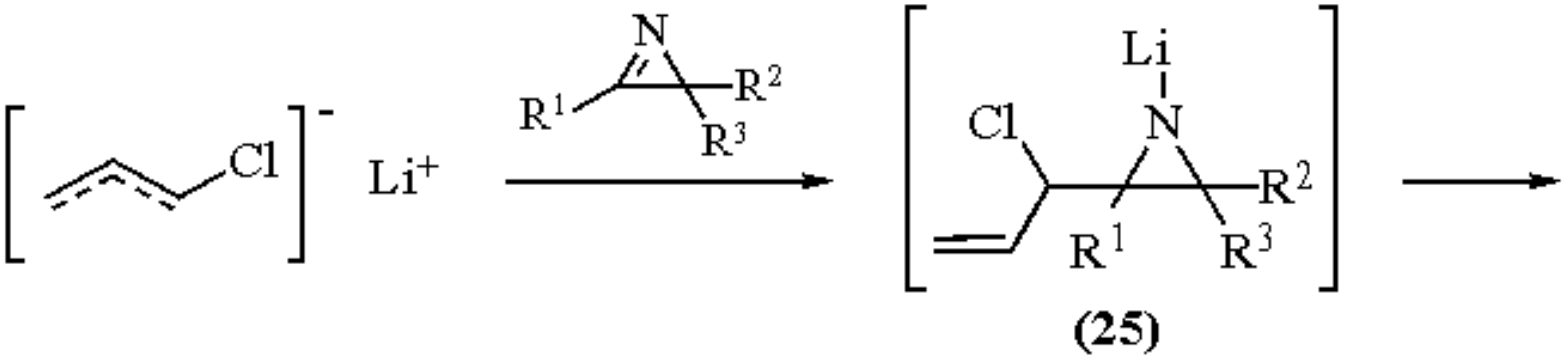

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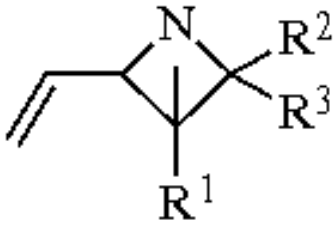

(12)

(26)

Related Reagents.

Allyllithium; ***Dibutyl Telluride***; ***1,1-Dichloroallyllithium***.

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1-Chlorobenzotriazole[1]

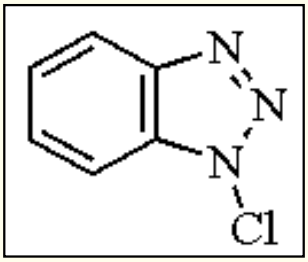

[21050-95-3] · $C_6H_4ClN_3$ · 1-Chlorobenzotriazole · (MW 153.57)

(positive halogen reagent for mild oxidations[2,3] and selective chlorinations[4])

Alternate Names: 1-chloro-1*H*-benzotriazole; *N*-chlorobenzotriazole; 1-CBT.

Physical Data: colorless needles; mp 104-106 °C; λ_{max} 252 nm.

Solubility: sol CH_2Cl_2, CCl_4, C_6H_6, MeCN, MeOH.

Analysis of Reagent Purity: solutions can be standardized by iodometric or potentiometric titration.[1]

Preparative Methods: treat benzotriazole with sodium hypochlorite in 50% aq acetic acid. The reagent quickly precipitates and is obtained in nearly quantitative yield after recrystallization from CH_2Cl_2/petroleum ether.[2a]

Handling, Storage, and Precautions: may ignite spontaneously;[5] *reacts explosively with DMSO;*[2b] light sensitive; stable to air and moisture in brown bottles; storage recommended at 0 °C; discard or repurify if discoloration occurs. This reagent should be handled in a fume hood.

Oxidation of Alcohols and Nitrogen Compounds.

1-Chlorobenzotriazole (1-CBT) behaves similarly to positive halogen compounds such as ***N-Bromosuccinimide***, ***N-Chlorosuccinimide***, and ***Chloramine-T***, acting as a source of halonium ion (Cl^+) or halogen radical (Cl&bdot;). The reagent is convenient to use and prepare, and in some applications gives higher yields than ***t-Butyl Hypochlorite***. Alcohols, hydrazones, 1,1- and 1,2-disubstituted hydrazines and aminobenzotriazoles are efficiently oxidized under extremely mild conditions by 1-CBT (Table 1).[2] Reactions are typically carried out by warming equimolar amounts of substrate and 1-CBT in CH_2Cl_2, CCl_4, or C_6H_6; reaction with hydrazines occurs readily in the cold. After a brief induction period a rapid exothermic reaction occurs, typical of a radical chain process, affording the oxidized product and benzotriazole hydrochloride which precipitates. Secondary alcohols are oxidized faster than primary alcohols, as is generally observed with *N*-halide oxidizing agents. Trace amounts of benzotriazole are easily removed from the product by washing with dilute aqueous sodium hydroxide.

Table 1 Oxidation of Alcohols and Nitrogen Compounds by 1-Chlorobenzotriazole

Starting material	Solvent	Product	Yield (%)
Benzyl alcohol	CH_2Cl_2	Benzaldehyde[a]	70
1-Phenylethanol	CCl_4	Acetophenone[a]	65
Cyclohexanol	CH_2Cl_2	Cyclohexanone[a]	70
Hydrazobenzene	CH_2Cl_2	Azobenzene	90
4,5-Diphenyl-pyrazolidin-3-one	CH_2Cl_2	*trans*-Stilbene	75
1-Aminobenzotriazole	CH_2Cl_2	Benzyne[b]	80

[a] Isolated as the 2,4-dinitrophenylhydrazone. [b] Isolated as tetraphenylnaphthalene after reaction with tetraphenylcyclopentadienone; two mols of oxidant required.

Reaction with Sulfides.

Sulfides are efficiently oxidized to sulfoxides by 1-CBT in methanol or methylene chloride at -78 °C.[3a] The reaction is very fast and clean, giving no overoxidation to sulfones as is often observed with peroxy acids (e.g. ***m-Chloroperbenzoic Acid***). The performance of the reagent is comparable to *t*-butyl hypochlorite. This transformation has been used in the conversion of steroidal thioacetals to ketones.[3b] The intermediate formed between 1-CBT and sulfides may also react with alcohols or primary and secondary amines. Treatment of the ensuing adduct with ***Silver(I) Tetrafluoroborate*** gives the corresponding amino- or alkoxysulfonium fluoroborate.[3c]

Chlorination of Heteroaromatics.

Indoles and other nitrogen heterocycles are selectively chlorinated by 1-CBT in high yield. This procedure often succeeds where the standard reagent *t*-butyl hypochlorite fails.[4] Multiple equivalents of chlorine may be selectively incorporated simply by adjusting the initial amount of 1-CBT used (eq 1).[4b] The chlorination of some indoles is better effected by using 1-chloroisatin.[4c]

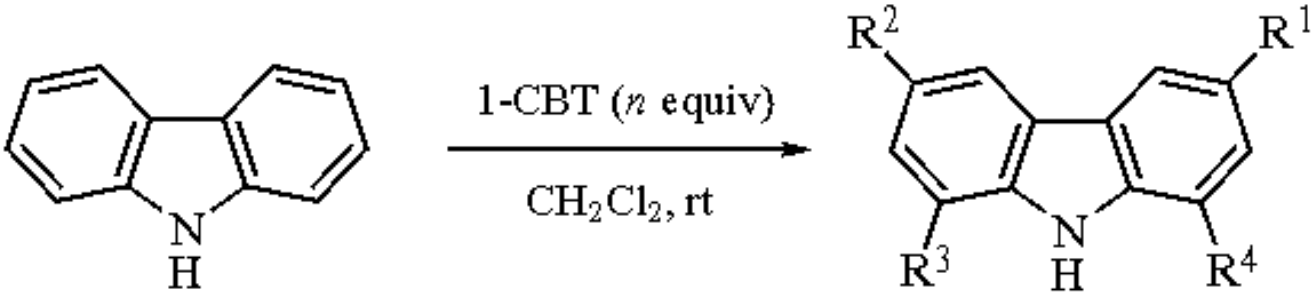

(1)

1-CBT (mol equiv)	Product	Yield (%)
1	$R^1 = Cl$; $R^2, R^3, R^4 = H$	79
2	$R^1, R^2 = Cl$; $R^3, R^4 = H$	64
4	$R^1, R^2, R^3, R^4 = Cl$	61

Other Applications.

The title reagent has been shown to undergo ready addition to alkenes, giving 1,2- and 2,2-chloroethylbenzotriazoles,[6] as well as to effect α-chlorination of ketones.[1] 1-CBT has also been used in the preparation of other benzotriazole derivatives (1-nitro-, 1-bromo-, and 1-iodobenzotriazoles),[7,8] as well as the selenium transfer reagent bis(1-benzotriazolyl) selenide.[9]

---

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μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium[1]

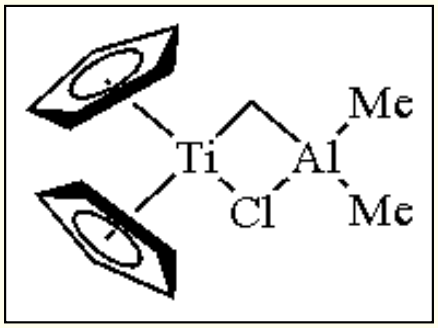

[67719-69-1] · $C_{13}H_{18}AlClTi$ · μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium · (MW 284.60)

(methylenating agent for alkenation of carbonyl compounds,[2-4] particularly esters, ketones, and aldehydes; of low basicity and functions without epimerization at α-chiral centers)

Alternate Name: Tebbe reagent.

Physical Data: red solid.

Solubility: highly sol toluene, benzene, or dichloromethane; will dissolve in THF at low temperature (but not stable for prolonged periods in ethereal solvents). Nearly insol saturated hydrocarbons.

Form Supplied in: may be purchased as the pure solid or prepared from titanocene dichloride and trimethylaluminum.

Handling, Storage, and Precautions: the dry solid is air-sensitive and may be pyrophoric in air, especially when impure; it must be handled under an atmosphere of nitrogen or argon. The reagent is most conveniently stored and handled as a toluene solution; in this form the reagent is somewhat pyrophoric in air and must be handled using syringe and cannula techniques as practiced when using Grignard or alkyllithium solutions.

Tebbe Reagent as a Source of $Cp_2Ti{=}CH_2$.

The complex $Cp_2TiCH_2.AlMe_2Cl$, commonly referred to as the Tebbe reagent,[5] is a source of the reactive titanium methylene species $Cp_2Ti{=}CH_2$ as shown in eq 1. The methylene intermediate, formation of which is greatly accelerated by bases such as THF or pyridine, is useful for the methylenation of carbonyl compounds in a process similar to Wittig alkenation; the driving force is the high oxophilicity of titanium. The scope of reactivity is greater than with the corresponding phosphoranes;[6] thus esters and amides are converted to vinyl ethers and enamines by the Tebbe reagent.[2,7] The lower basicity of the Tebbe reagent offers further advantages over the Wittig procedure (see below). Although many examples of methylenation of unsaturated

substrates are known, and carbon-carbon double bonds usually do not interfere, it should be noted that the Tebbe reagent will react with certain alkenes to form titanacyclobutanes.[8] These titanacycles, of importance as intermediates in degenerate metathesis of terminal alkenes and ring-opening metathesis polymerization of strained cyclic alkenes,[9] and as synthetic reagents themselves,[1b] have been studied in some detail. The most stable titanacyclobutanes are those derived from monosubstituted alkenes; even these will revert to free alkene and active methylene when heated to about 60 °C.[10] Therefore mild heating may be used to improve yields of irreversibly formed methylenation products for certain substrates.[3] Furthermore, use of excess Tebbe reagent will in certain cases lower the yield of alkene product.[3,11]

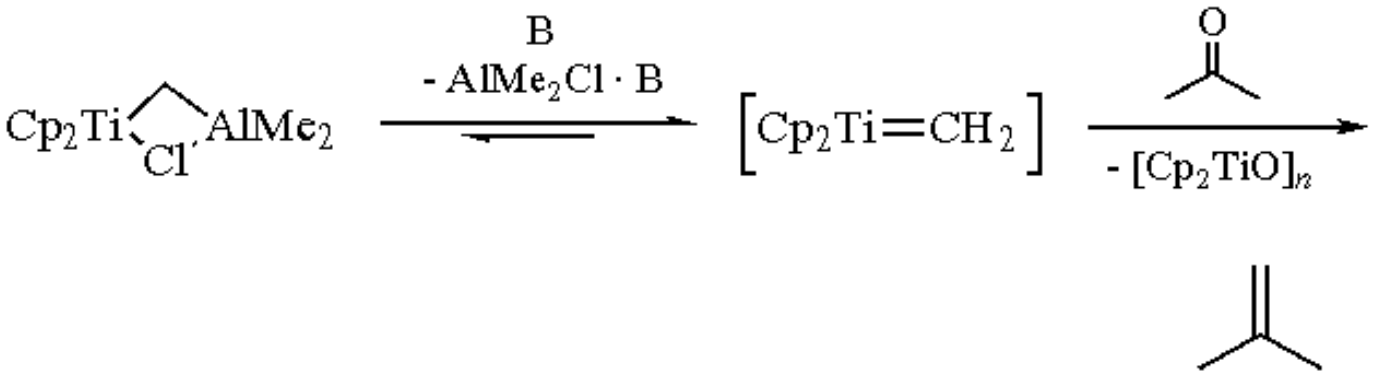

(1)

The reagent may be purchased as a pure solid, or synthesized as such using Schlenk line and glovebox techniques.[5a,12] Since isolation of the Tebbe reagent is time-consuming, in situ preparations of the complex have been developed.[3,13] It should be noted that in situ preparation produces a solution with one equiv of excess $AlMe_2Cl$ and often affords somewhat lower yields than the isolated reagent.[1a,13a] Typical conditions[2,13a] for use involve combining the reagent in toluene solution at low temperature with the substrate and a Lewis base such as THF and/or pyridine. After warming to room temperature, the solution is chilled and quenched with aqueous sodium hydroxide, diluted with ether, dried, filtered through Celite, and the product further purified, often by chromatography on neutral or basic alumina.

Tebbe methodology is specific for methylene transfer. However, approaches to analogous Group 4 metal reagents having substituted alkylidene units have been developed and show considerable promise.[1a,14] Several other titanium-based reagents for methylene transfer have been developed.[1a,15,16] A widely used system for methylenation of ketones[15a] is the still undefined mixture formed from $Zn/CH_2X_2/TiCl_4$. Also, thermolysis of Cp_2TiMe_2 provides a clean aluminum-free source of $Cp_2Ti{=}CH_2$ and shows considerable synthetic promise.[16] These various methylenation and alkylidenation processes have been comprehensively reviewed.[1a]

Methylenation of Aldehydes and Ketones.

The Tebbe reagent accomplishes methylenation of aldehydes and ketones.[4,5a,11,17-23] Table 1 shows some representative conversions with yields for the Wittig reagent included where available; the titanium reagent affords consistently higher yields and is less sensitive to steric crowding than ***Methylenetriphenylphosphorane***.[4] It is particularly useful in preparation of exocyclic alkenes (e.g. entries 2, 4, 5 and 8); only in extremely hindered substrates such as fenchone (entry 3) is the reagent ineffective. Also, the titanium complex efficiently methylenates such readily enolizable ketones as β-tetralone (entry 4).

Table 1 Methylenation of Ketones with $Cp_2TiCH_2 \cdot AlMe_2Cl$

Entry	Yield (%)	Substrate (X = O) and Product (X = CH_2)

X

1[4]	97; Wittig 46	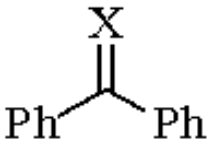
2[4]	96; Wittig 80	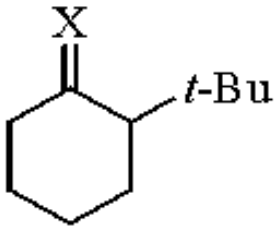
3[4,23]	16; Wittig 5	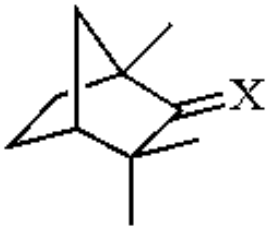
4[23]	84	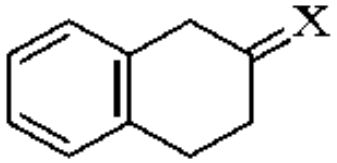
5[19]	55	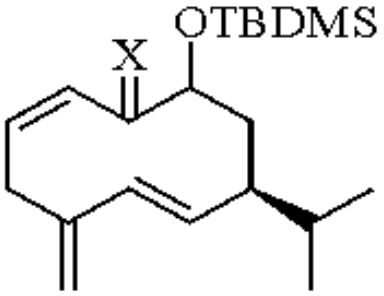
6[4]	77; Wittig 4	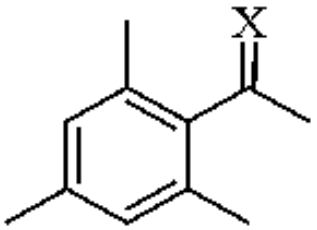
7[18]	93	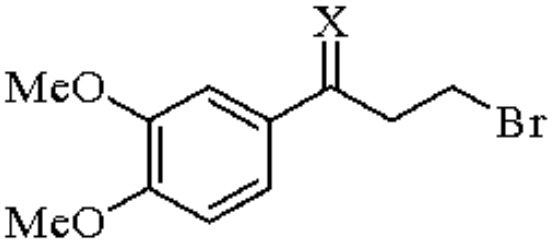

8[21]	63	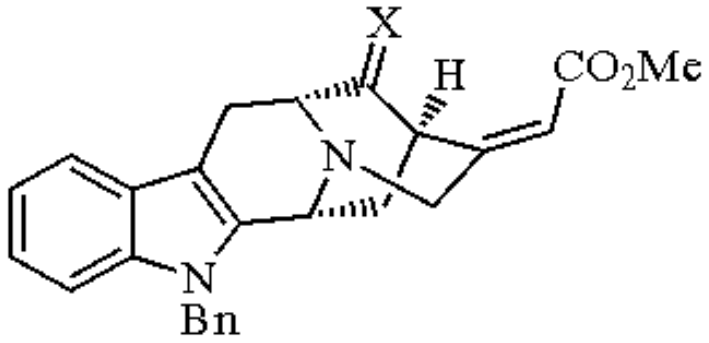

The Tebbe reagent will methylenate aldehydes and ketones without epimerization at α-chiral centers, as illustrated in eq (2).[22] The relatively low basicity of this reagent also permits conversions such as eq (3), which gives almost exclusively β-elimination across the C(1´)-C(2´) bond when attempted by the Wittig method.[11] When a large excess of Tebbe reagent is used in eq (3), *gem*-dimethylation occurs via a titanacyclobutane. Ketones with α,α-disubstitution (e.g. eq 4) will enolize rather than methylenate;[23] these titanium enolates are not active in the aldol reaction. The Tebbe reagent shows synthetically useful selectivity for ketones in preference to esters, as in the conversion of entry 8 (where 15% methyl ketone byproduct was observed), which was unsuccessful using $Zn/CH_2X_2/TiCl_4$ due to cyclopropanation. However, the $Zn/CH_2X_2/TiCl_4$ mixture is much more widely used for ketone methylenation since in certain preparations it will not react with esters.[1a]

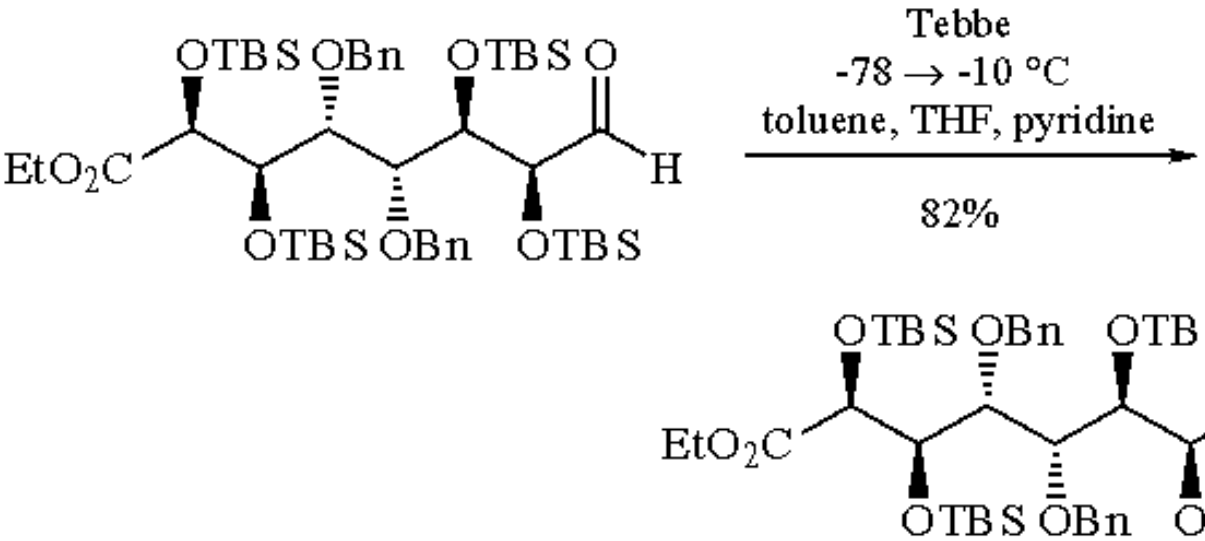

(2)

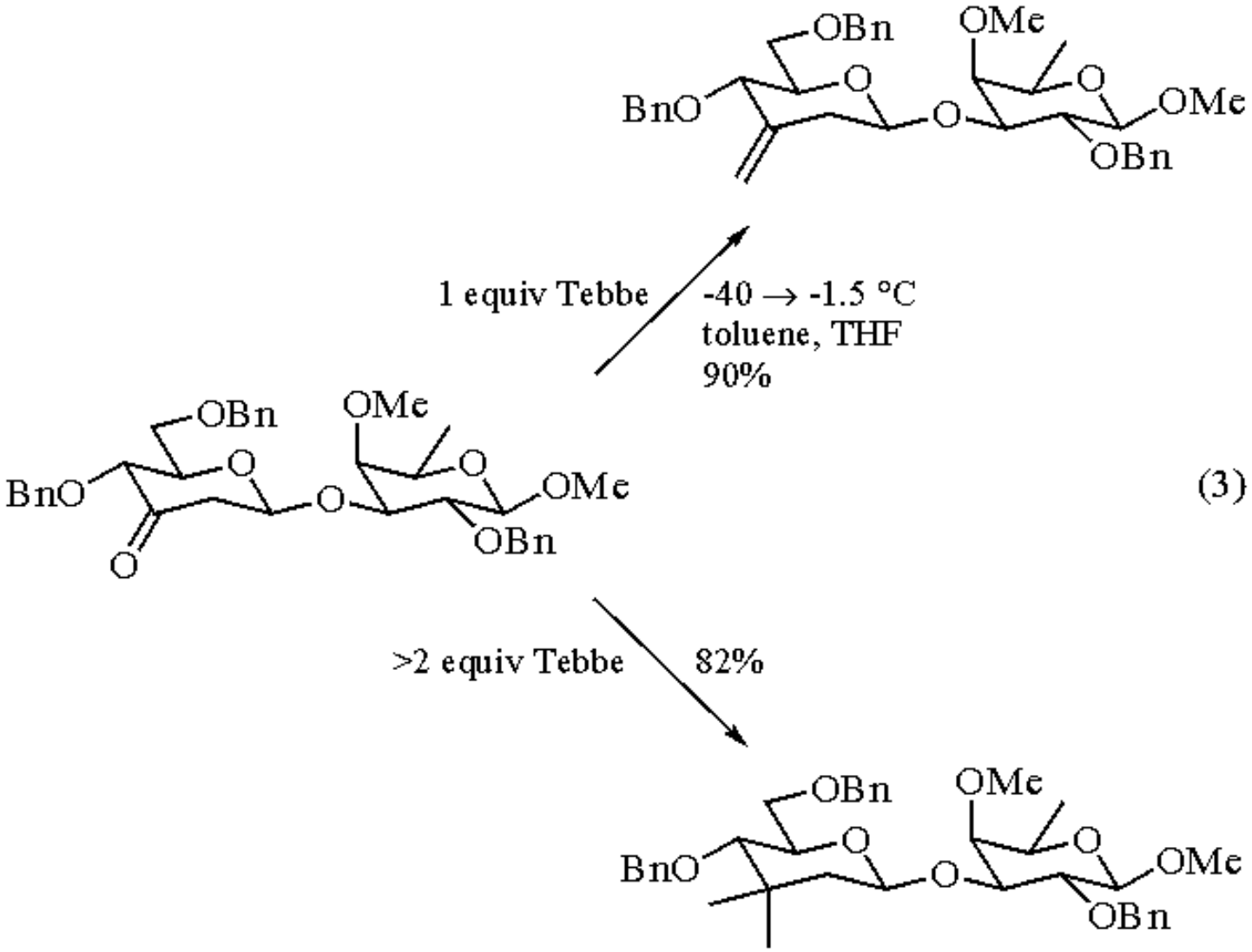

(3)

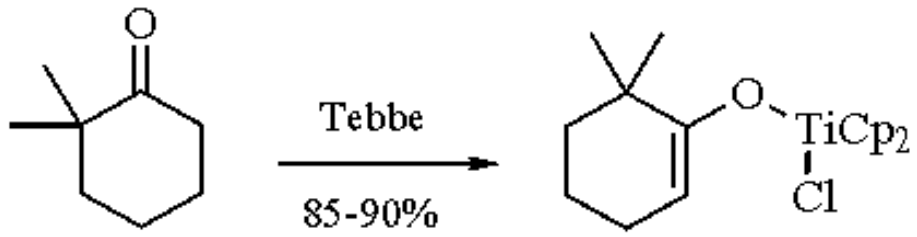

(4)

Methylenation of Esters and Lactones.

The greatest advantage of the Tebbe reagent is that, unlike phosphorous ylides, it may be used to convert esters and lactones to versatile enol ethers.[2] The reaction is quite general and typically proceeds in good to excellent yield.[3,7,24-50] Several representative conversions are presented in Table 2.

Table 2 Methylenation of Esters with $Cp_2TiCH_2 \cdot AlMe_2Cl$

Entry	Yield (%)	Substrate (X = O) and Product (X = CH_2)

X

1[7]	94	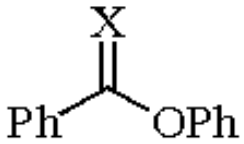
2[2]	87	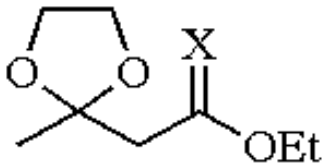
3[2]	97	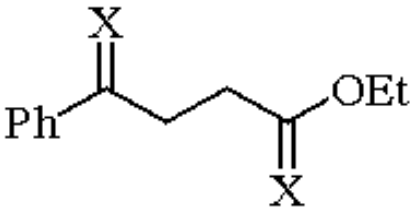
4[2]	96	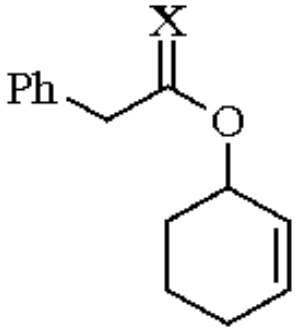
5[26]	85	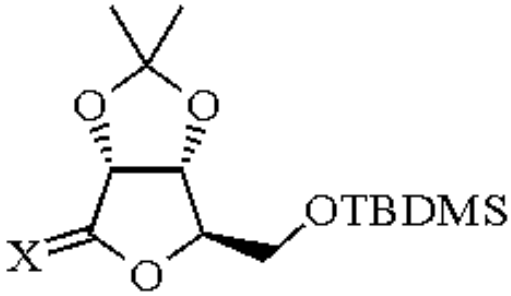
6[29]	R = Bn, 47 R = $CHPh_2$, 76 R = trityl, trace	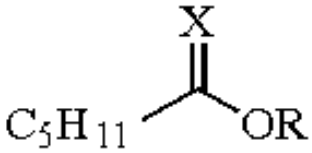
7[46]	76	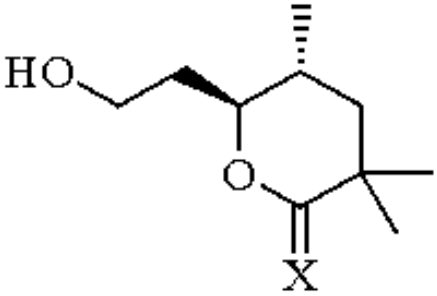

		$\ddot{X}$
8[2]	79	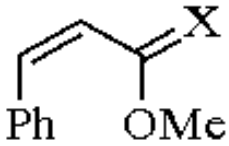
9[45]	-	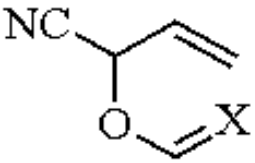
10[33]	R = Bn, 87-90	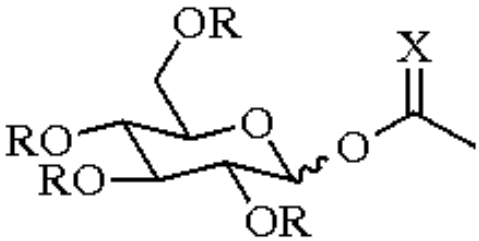
11[35]	R = Me, 95; R = Bn, 88	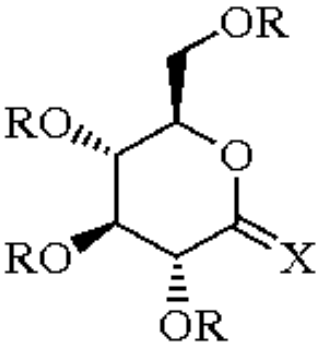
12[41]	ca. 50	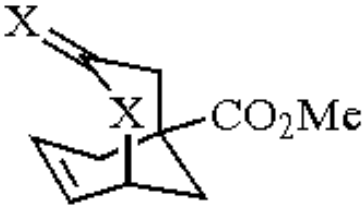

Table 2 Continued

Entry	Yield (%)	Substrate (X = O) and Product (X = CH_2)
13[43]	65	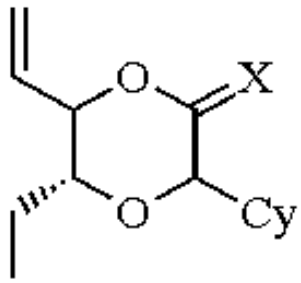
14[50]	94	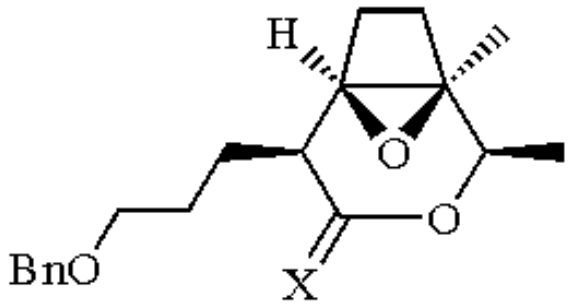

The procedure is tolerant of the acetal (entries 2 and 5) and cyano (entry 9) groups. Double bonds typically retain their stereochemistry (entry 8) and position. In a few instances, double bond migration has been reported upon workup;[30,47] precautions to minimize such rearrangement are described.[13a] Other compatible functionalities include various siloxy groups,[36,46] halide,[44,48] and thioacetal.[24] Ketone and ester groups may be simultaneously methylenated (entry 3), or a keto group may be preferentially methylenated with 1 equiv of reagent.[7,21] Literature estimates of ketone versus ester selectivity are given as 4:1 in general[2] and 25-30:1 for acetophenone against methyl benzoate.[23] It has been observed that yields may differ depending on whether isolated Tebbe reagent is used or if the complex is generated in situ; for example, 94% in entry 1 compared with 68-70% by in situ methods.[13a] Nonetheless, yields are often excellent using the in situ reagent (e.g. entry 11 and others[3,35]), which is considerably less expensive than the isolated complex. Since enol ethers are not known to form titanacyclobutanes on reaction with the Tebbe complex, *gem*-dimethylation does not occur when excess reagent is employed.[3]

Methylenation of allyl esters (Table 2, entries 4, 9, 12, and 13) affords allyl vinyl ethers[2,24,25,27,32,42-45,49] which are useful substrates for the Claisen rearrangement (e.g. eq 5[25] and eq 6[24a]). Although the methylene group of the Ti complex is mildly basic, solutions of the reagent are Lewis acidic, particularly when an extra equivalent of $AlMe_2Cl$ is present from in situ reagent preparation. The acidic character of the reagent has been used to advantage in a mild one-pot synthesis of 1,5-dienes from allyl esters in which a Claisen rearrangement occurs under Lewis acid catalysis (eq 6 and entry 12).[24a]

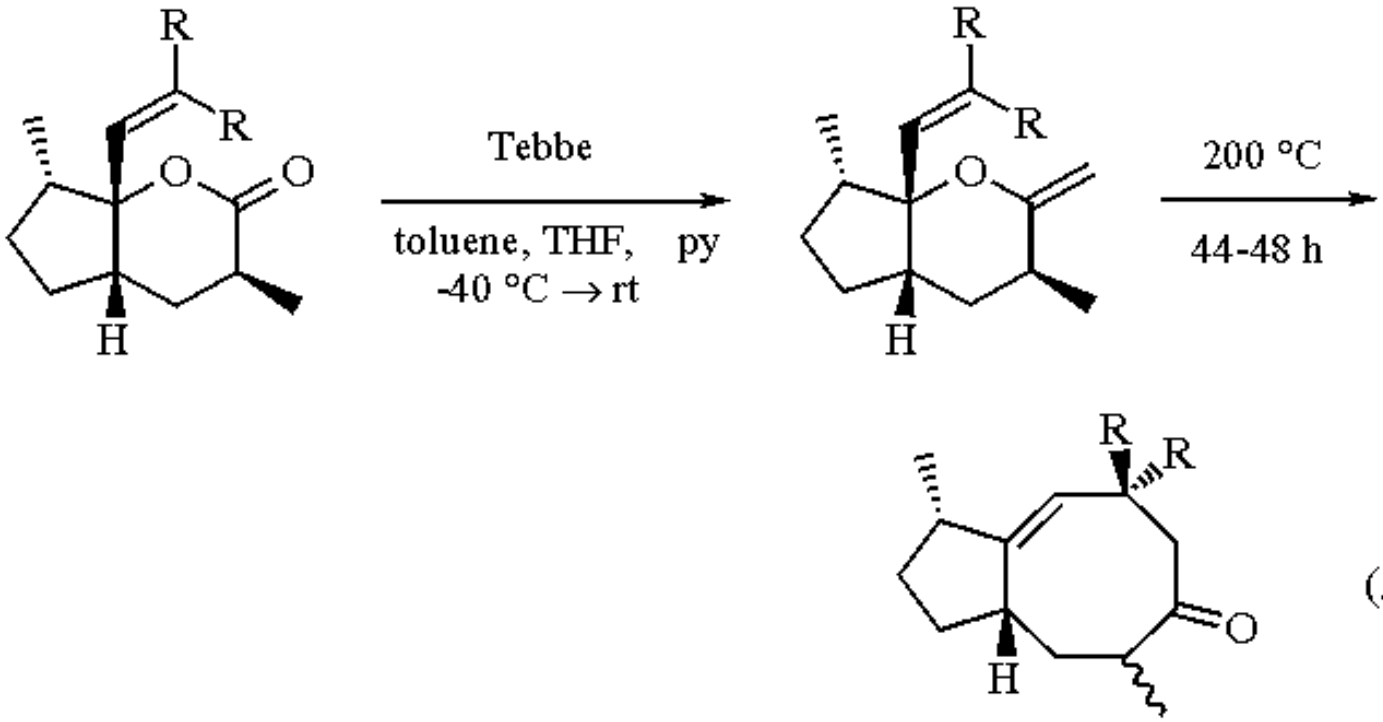

(5)

R = H, 91%; R = Me, 87%

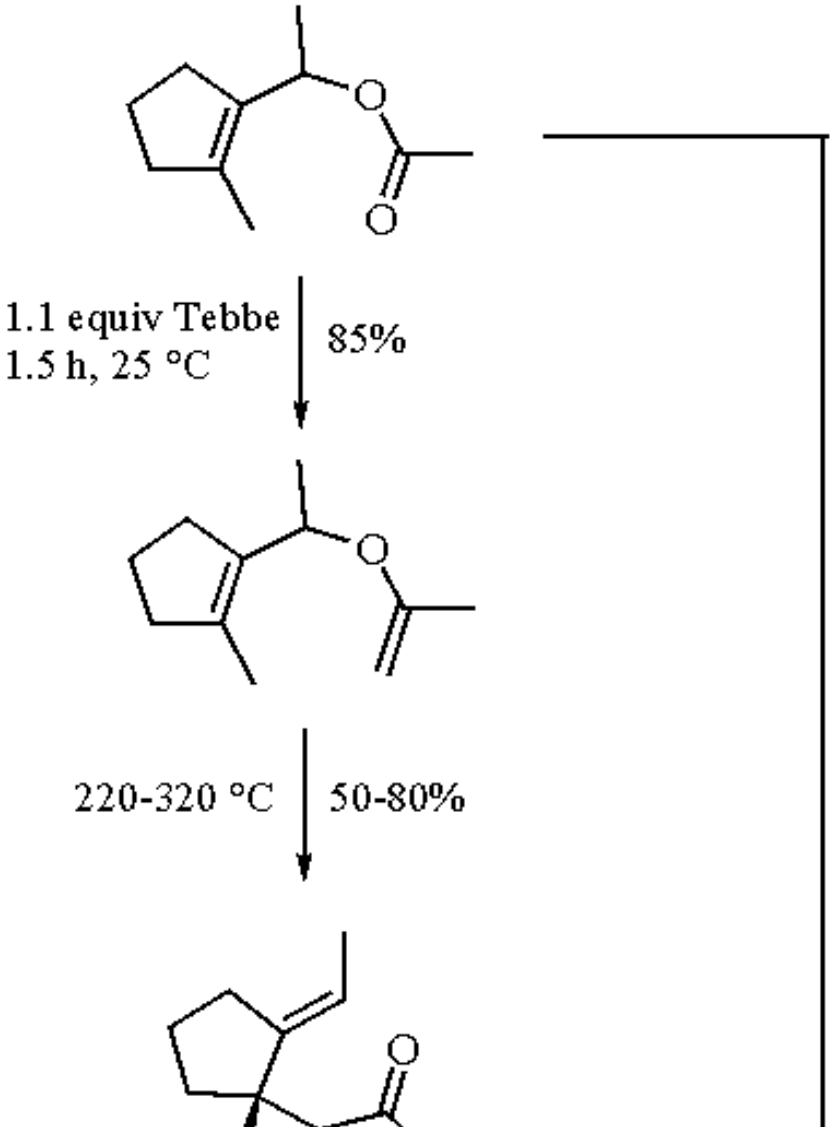

3 equiv Tebbe
12 h, 28 °C
75%

(6)

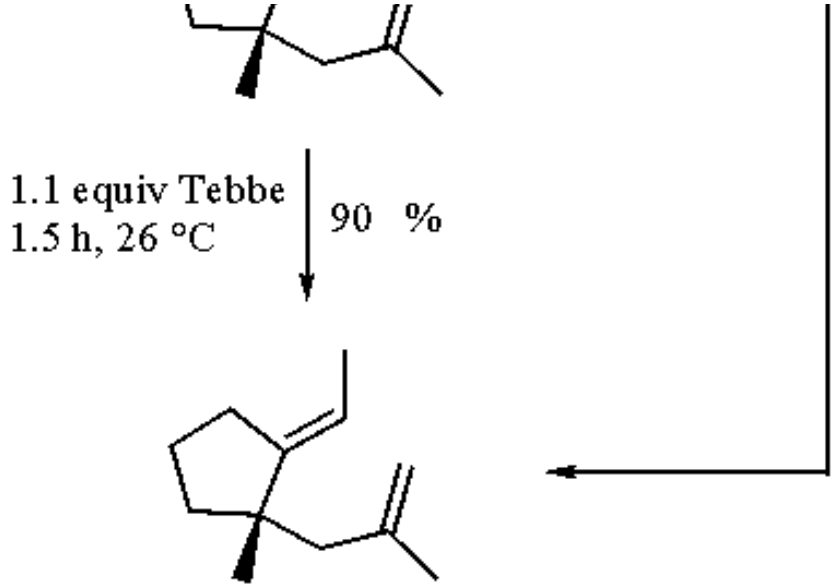

The Tebbe complex has found frequent application in carbohydrate chemistry.[26,31b,33,35,36]

The titanium reagent allows transformations of esters without epimerization at α-chiral centers, as is illustrated in the methyl ketone preparation of eq 7.[28b] Cyclic carbonates may be methylenated as well (eq 8).[1b]

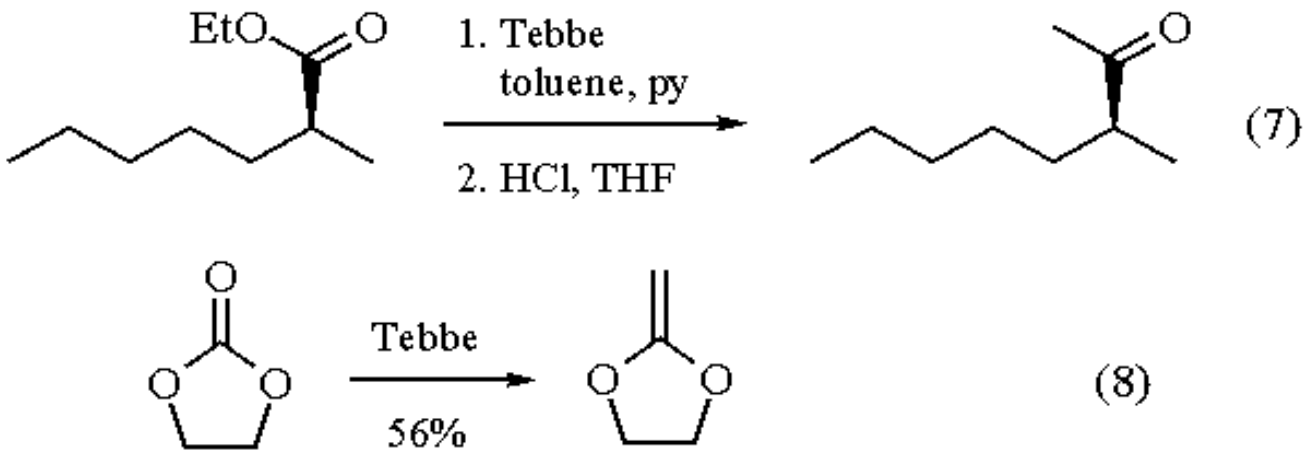

In at least one case where the Tebbe procedure is ineffective, presumably for steric reasons, an ester has been efficiently methylenated with $Zn/CH_2X_2/TiCl_4$.[38] However, hindered esters may be methylenated with the Tebbe reagent (e.g. entry 7).

Methylenation of Amides.

Amides have been converted to enamines of methyl ketones by the Tebbe reagent (eq 9).[1a,b,7,51] No added base is required. Isolation of enamines is possible, or in situ alkylation may be performed.[7] The reaction has been little developed.

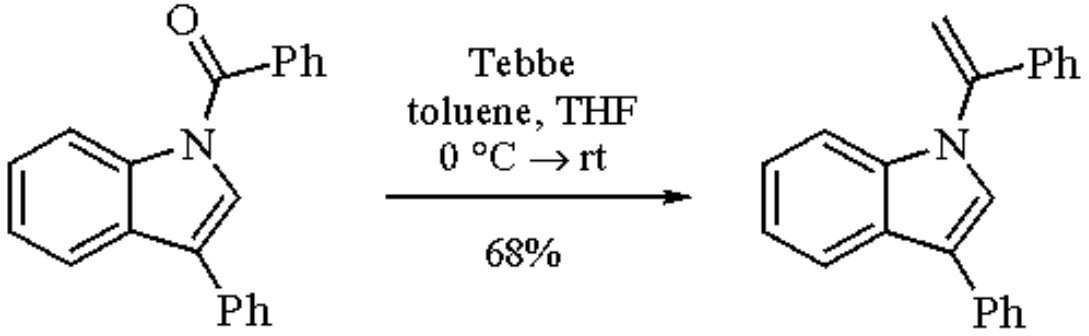

(9)

Titanium Enolates from Acid Chlorides.

Acid chlorides have been reported to react with the Tebbe reagent to afford titanium enolate complexes (eq 10),[52] although yields are much lower than those obtained using titanacyclobutane precursors.[53] These enolate complexes of methyl ketones are known to participate in aldol reactions.[53]

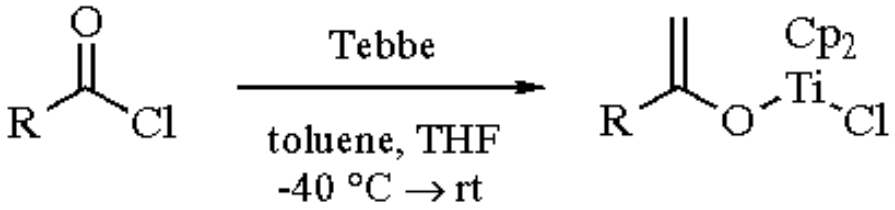

(10)

Other Reactions of the Tebbe Reagent.

Silyl esters and thioesters are methylenated by the Tebbe reagent.[1a] The complex is known to react with alkynes to give stable titanacyclobutenes.[54] Reaction with anhydrides gives enolate complexes which are not active in the aldol reaction.[55] By contrast, unhindered imides may be methylenated in good yield with excellent selectivity in unsymmetrical cases.[55] Nitriles react to afford vinylimidotitanium complexes, which have been studied in some detail.[56] The reagent has found application in the preparation of various organometallic complexes.[57]

Related Reagents.

Bis(*η^5*-cyclopentadienyl)(diiodozinc)(*μ*-methylene)titanium; ***Bis(cyclopentadienyl)dimethyltitanium***; ***Bis(cyclopentadienyl)-3,3-dimethyltitanacyclobutane***; ***Dibromomethane-Zinc-Titanium(IV) Chloride***; ***Diiodomethane***.

---

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Chlorobis(cyclopentadienyl)hydridozirconium[1]

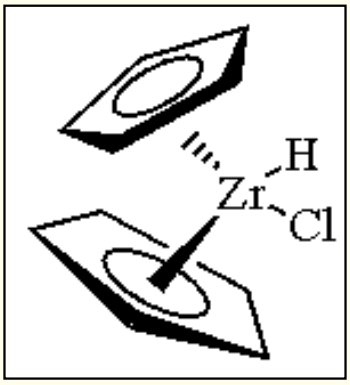

[37342-97-5] · $C_{10}H_{11}ClZr$ · Chlorobis(cyclopentadienyl)hydridozirconium · (MW 257.87)

(hydrozirconation reagent; reducing reagent of unsaturated compounds; starting material for organozirconium complexes)

Alternate Name: Schwartz's reagent.

Solubility: insol; hydrolyzed in water; very slowly converted by CH_2Cl_2 to Cp_2ZrCl_2.

Form Supplied in: commercially available as white powder (95%).

Analysis of Reagent Purity: IR (nujol) 1390 cm^{-1} (metal-hydrogen bond). The purity of $Cp_2Zr(H)Cl$ is measured by reaction with acetone. A small sample is assayed in a 5 mm NMR tube in C_6D_6 by treatment with a known amount of excess acetone, and the relative areas of the signal for the mono- and diisopropoxides are determined by ^1H NMR.[2,3]

Preparative Methods: $Cp_2Zr(H)Cl$ is prepared by the reaction of ***Dichlorobis(cyclopentadienyl)zirconium*** with ***Lithium Tri-t-butoxyaluminum Hydride***,[4,5] ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Vitride or Red-Al),[3] or ***Lithium Aluminum Hydride***.[2] Zirconocene dichloride (100 g, 0.342 mol) is dissolved in dry THF (650 mL, heating required) in a 1 L Schlenk flask under argon. To this solution (at or slightly above rt) is added dropwise, over a 45 min period, a filtered solution of $LiAlH_4$ in diethyl ether (prepared from 3.6 g, 94.9 mmol of 95% $LiAlH_4$ and 100 mL dry ether, followed by filtration using a cannula fitted with a piece of glass fiber filter; a Schlenk filtered or commercial clear solution would work as well). The resulting suspension is allowed to stir at room temperature for 90 min. It is then Schlenk filtered under argon using a D frit. The white solid is washed on the frit with THF (4 × 75 mL), CH_2Cl_2 (2 × 100 mL) with stirring or agitation of a stirbar immersed in the slurry and ether (4 × 50 mL). The resulting white solid is dried in vacuo to give a white powder: 65.5-81 g, 77-92% yield.[2]

Purification: over-reduction product Cp_2ZrH_2 reacts rapidly with methylene chloride to form $Cp_2Zr(H)Cl$.[2]

Handling, Storage, and Precautions: slowly develops a pink color when exposed to light and appears to be

photosensitive. This compound should be handled in a fume hood.

Hydrozirconation of Unsaturated Compounds.

Alkenes[6] react with $Cp_2Zr(H)Cl$ to give alkylzirconium complexes. Hydrozirconation of alkenes proceeds to place the zirconium moiety at the sterically least hindered position of the alkene as a whole. Formation of this product involves either the regiospecific addition of Zr-H to a terminal alkene or addition to an internal alkene followed by rapid rearrangement via Zr-H elimination and readdition to place the metal in the less hindered position of the alkyl chain (eq 1).[6,7] This is in sharp contrast to hydroboration or hydroalumination reactions. However, the tendency of zirconium to migrate towards the terminal position in the case of 1-arylalkenes is lower than simple alkenes.[8] Alkenes containing a heteroatom such as oxygen undergo C-heteroatom bond cleavage during the hydrozirconation reactions under some conditions (eq 2).[9] Alkylzirconium complexes obtained here are easily converted into alkanes,[10] alkyl halides (eq 3),[6] alcohols (eqs 4 and 5),[7] nitriles (eq 6),[11] aldehydes, carboxylic acids or esters (eq 7)[12] by hydrogenation (or hydrolysis), halogenation, oxidation, successive treatment with isocyanide and iodine, or carbonylation.

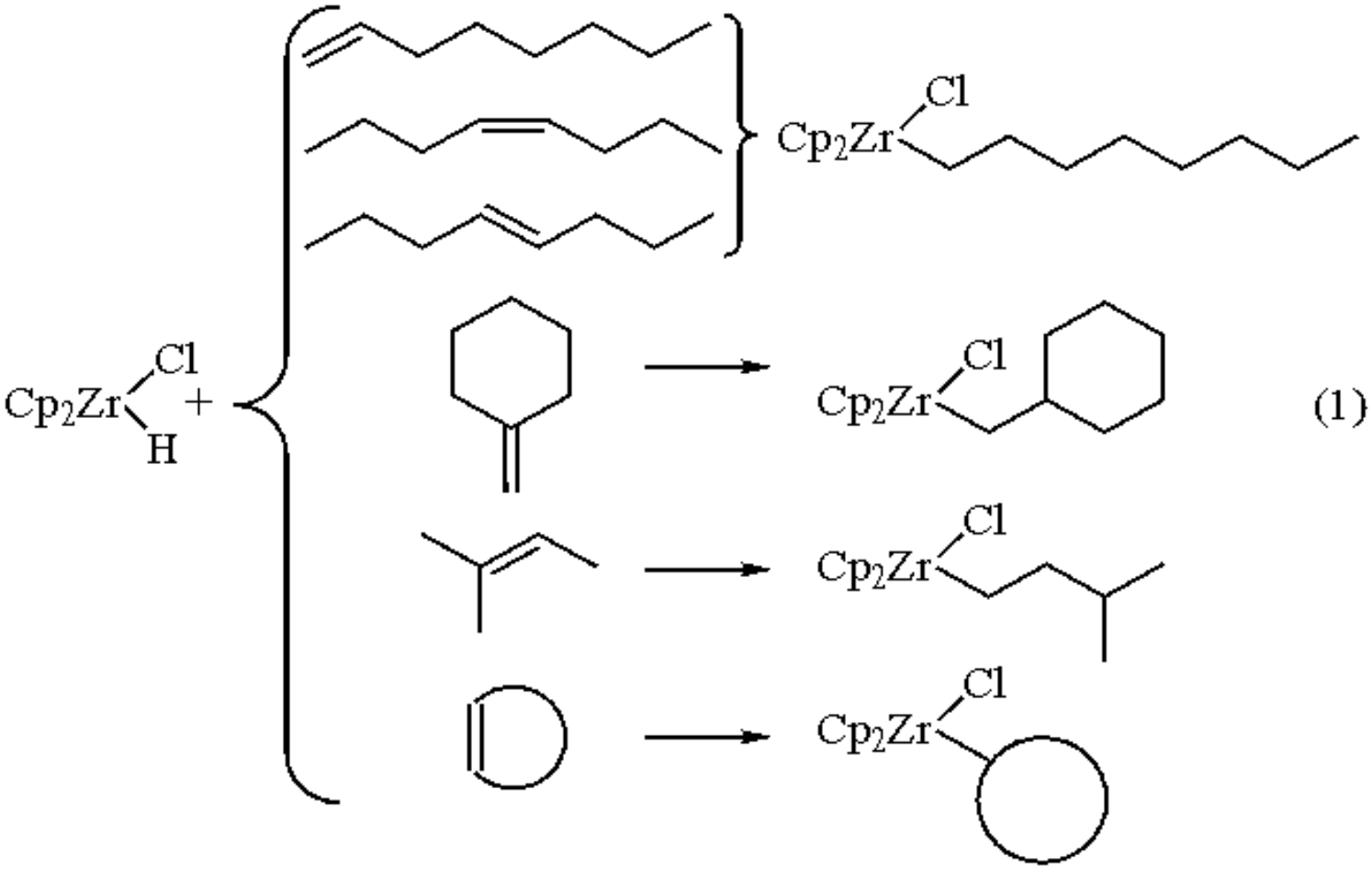

(1)

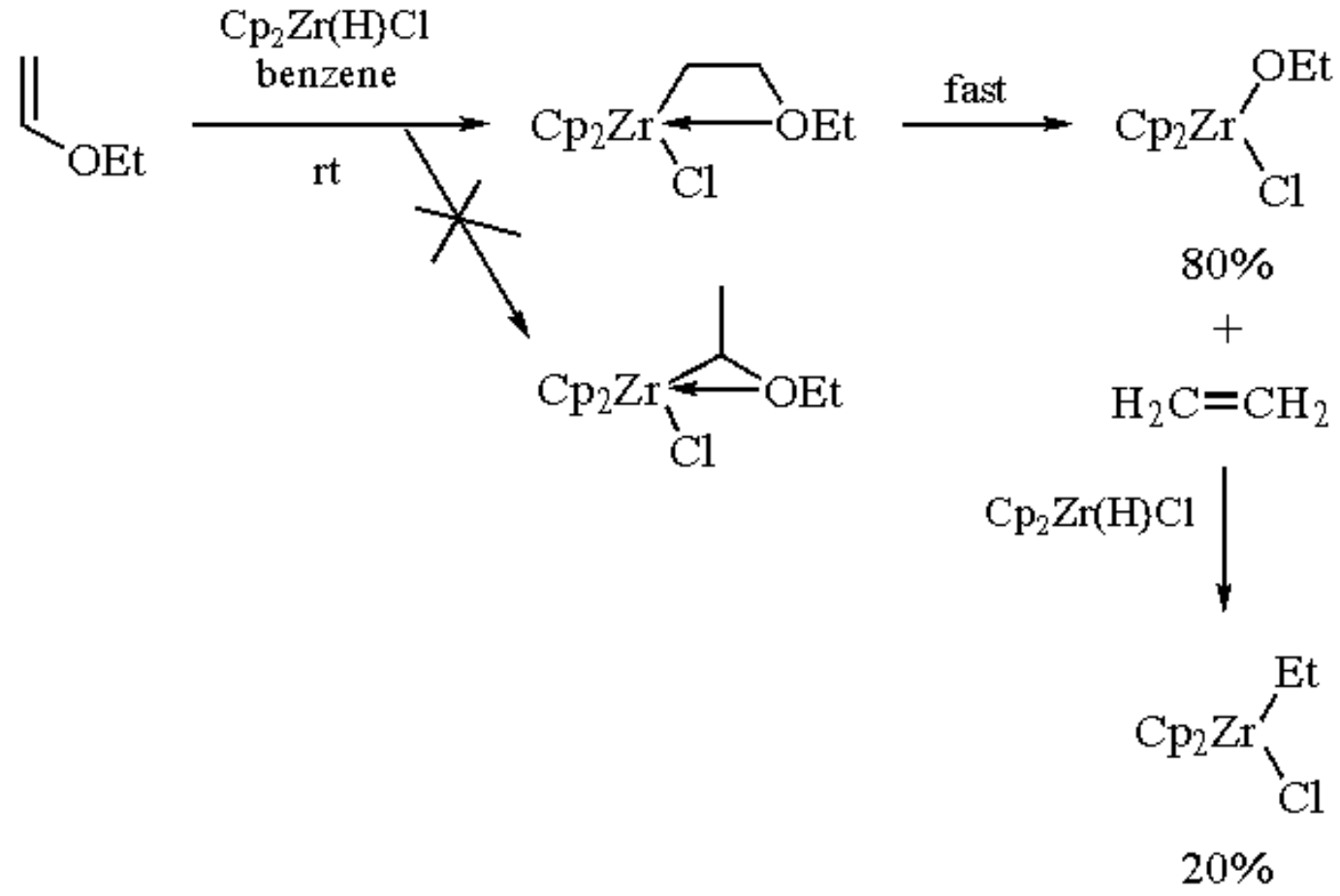
Cp2Zr(H)Cl
benzene
rt
OEt
Cp2Zr
Cl
fast
80%
+
H2C=CH2
Cp2Zr(H)Cl
20%
Et

(2)

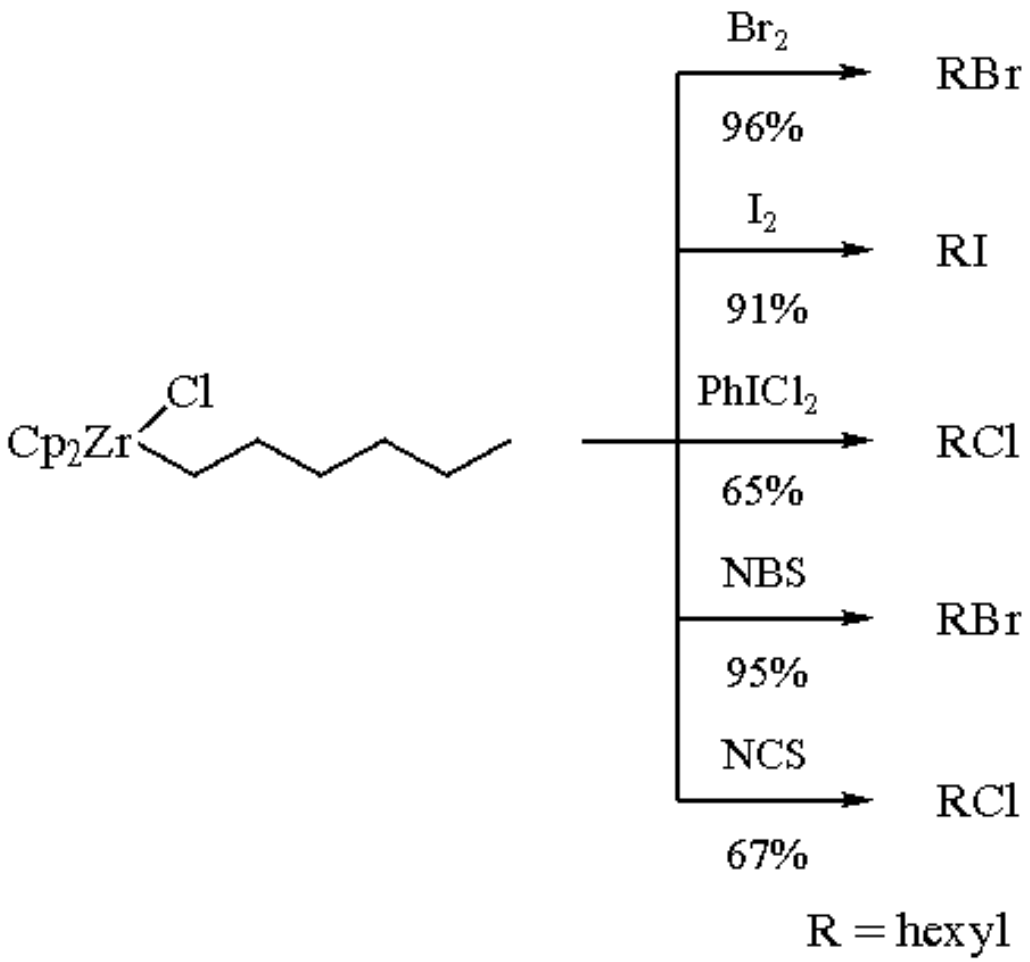
Cp2Zr
Cl
Br2
96%
RBr
I2
91%
RI
PhICl2
65%
RCl
NBS
95%
RBr
NCS
67%
RCl
R = hexyl

(3)

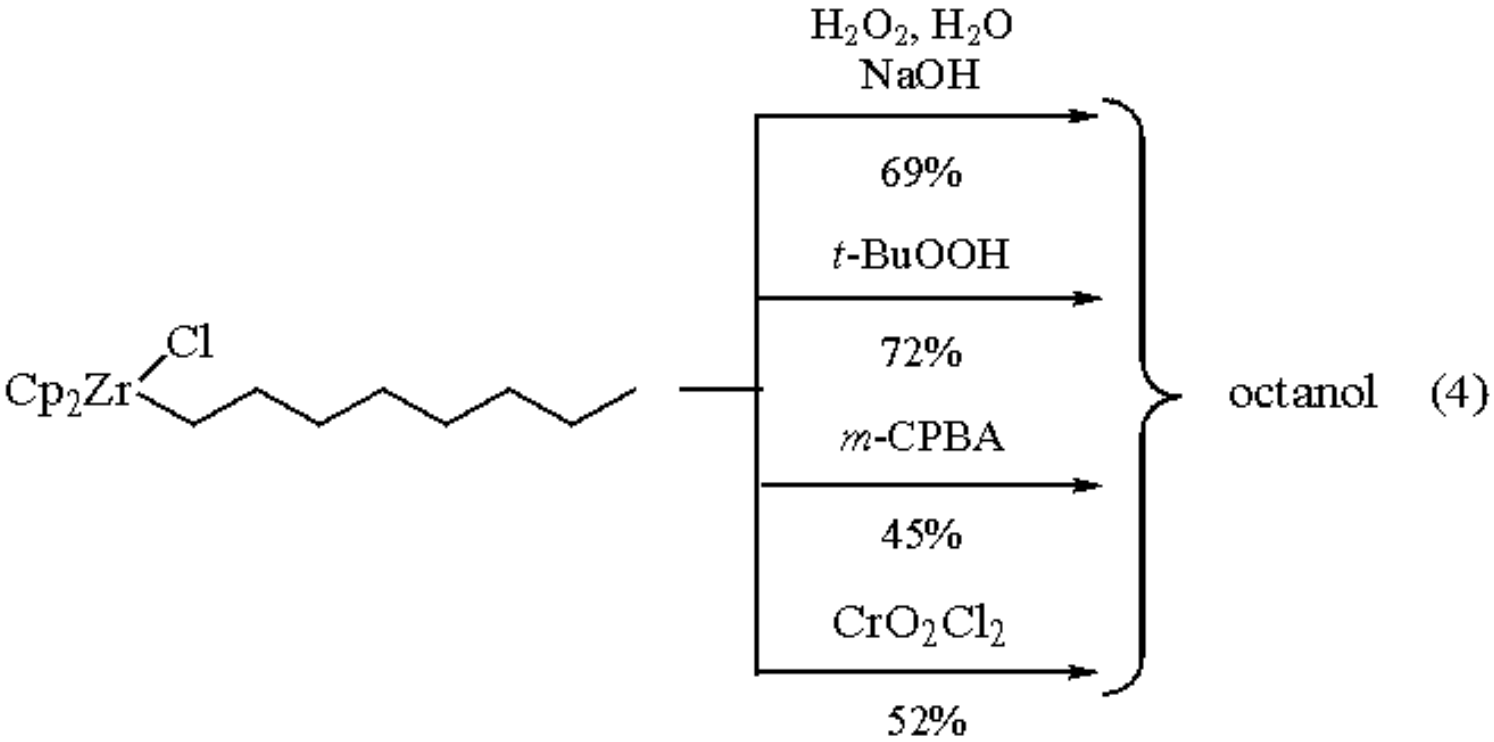
H2O2, H2O
NaOH
69%
t-BuOOH
72%
m-CPBA
45%
CrO2Cl2
52%
Cp2Zr
Cl
octanol
(4)

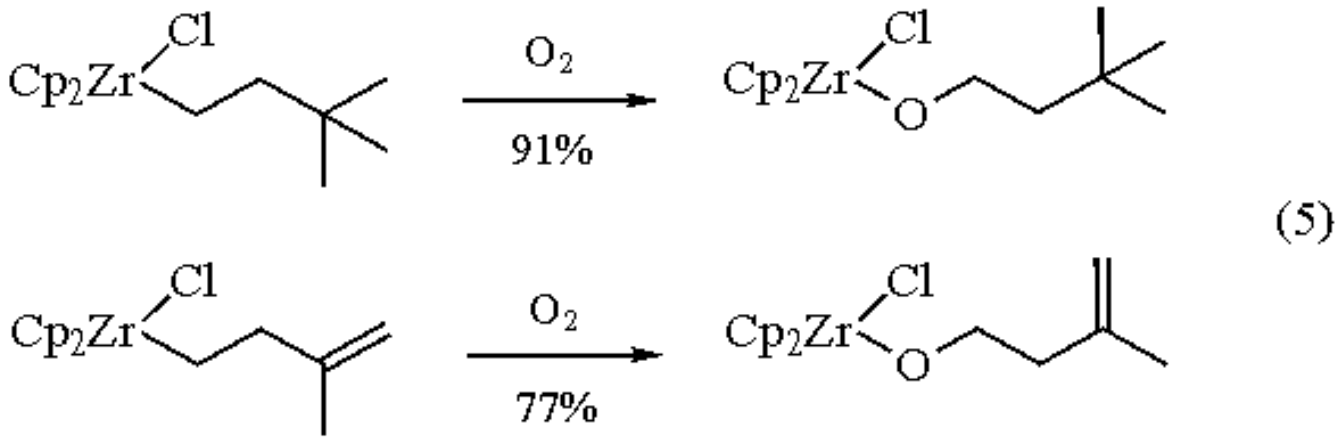
Cp2Zr
Cl
O2
91%
77%
O
(5)

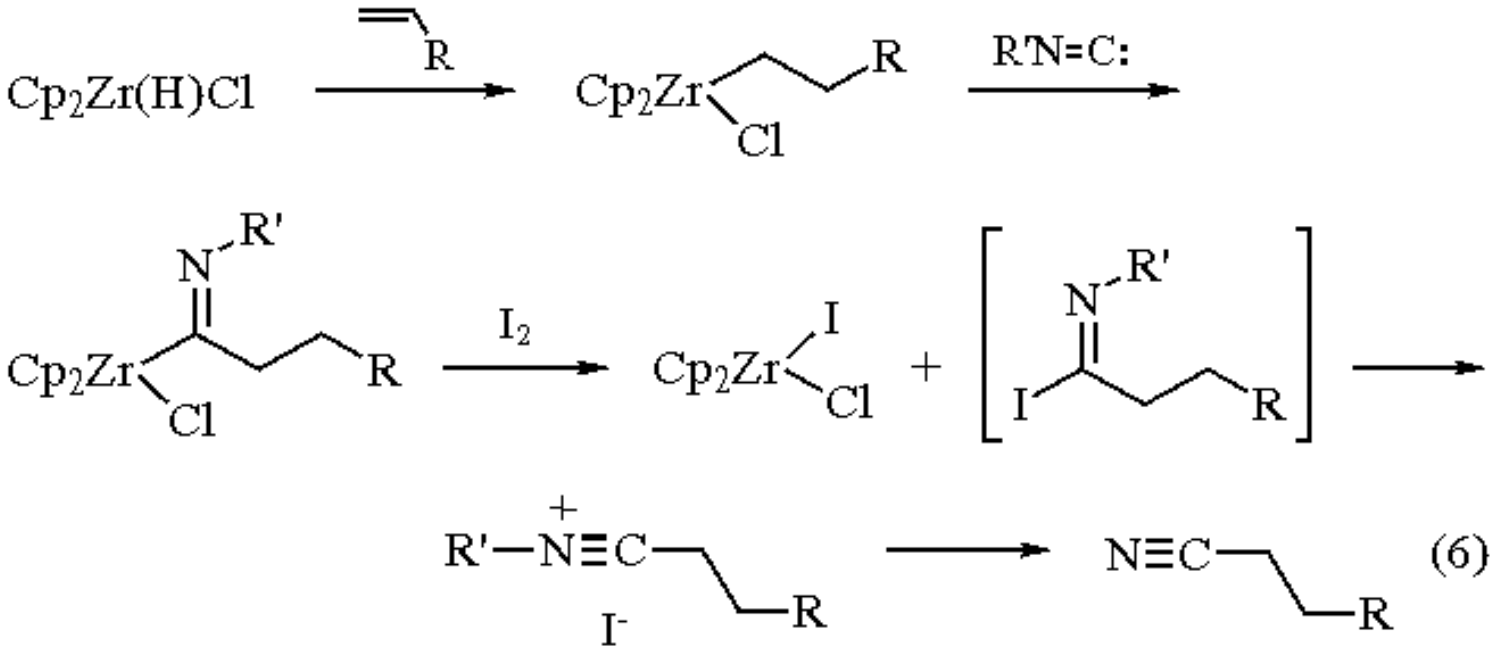

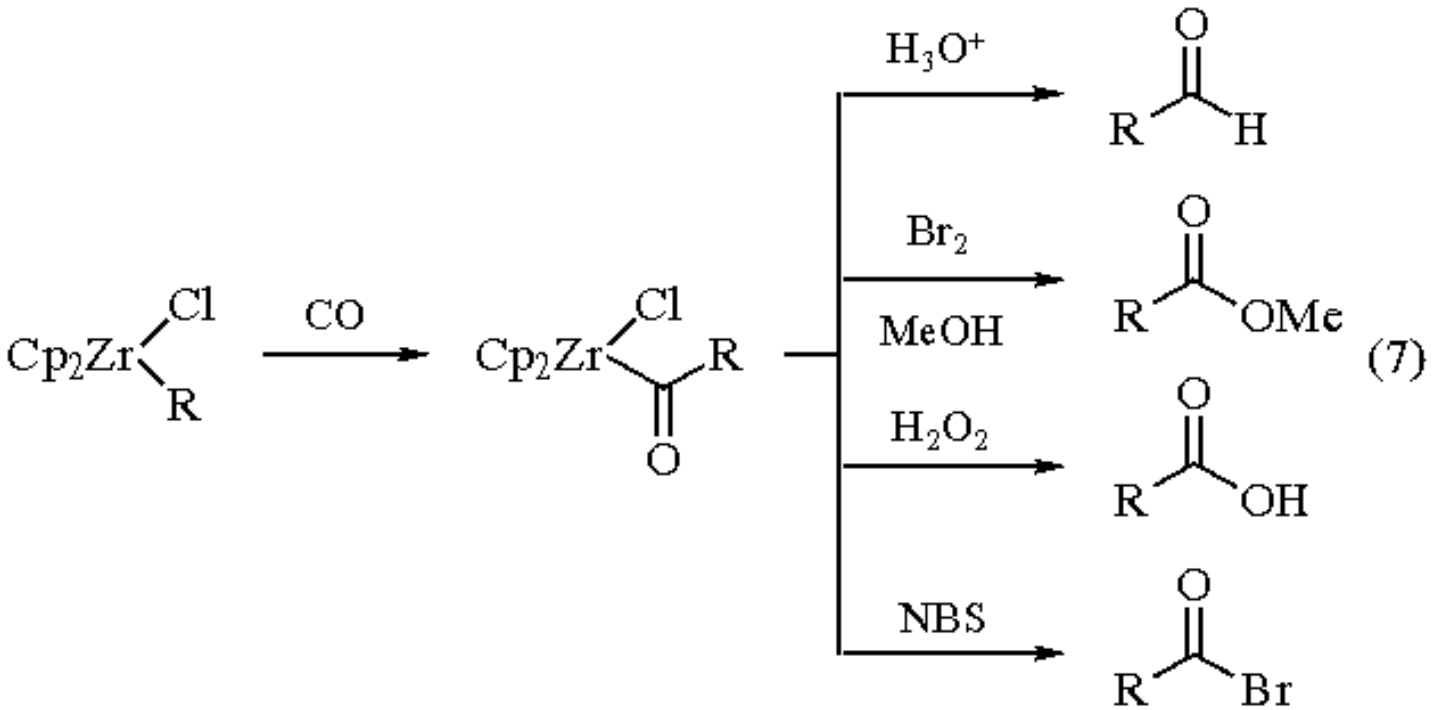

Hydrozirconation of alkynes gives alkenylzirconium complexes (eq 8).[13] Zr-H addition to the alkyne proceeds with *cis* stereochemistry. Hydrozirconation of various unsymmetrically disubstituted alkynes occurs readily to give a mixture of alkenylzirconium compounds. Over a period of several hours, this initial mixture of alkenyl species can be converted to one with higher regioselectivity, at room temperature, through catalysis with $Cp_2Zr(H)Cl$.[13] It is interesting to note that, whereas alkylzirconium complexes positionally rearrange rapidly, no such process occurs for purified alkenyl analogs. Alkenylzirconium complexes are also easily converted into alkenyl halides[13] and aldehydes (eq 9)[14] when they are treated with ***N-Bromosuccinimide*** and isocyanide/H^+, respectively.

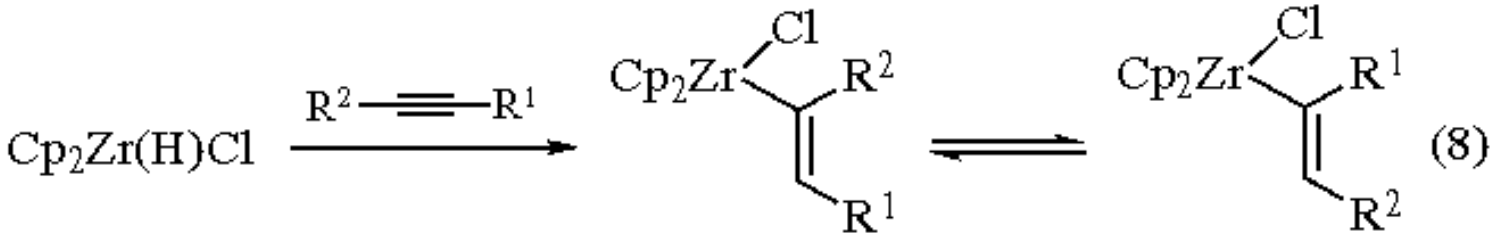

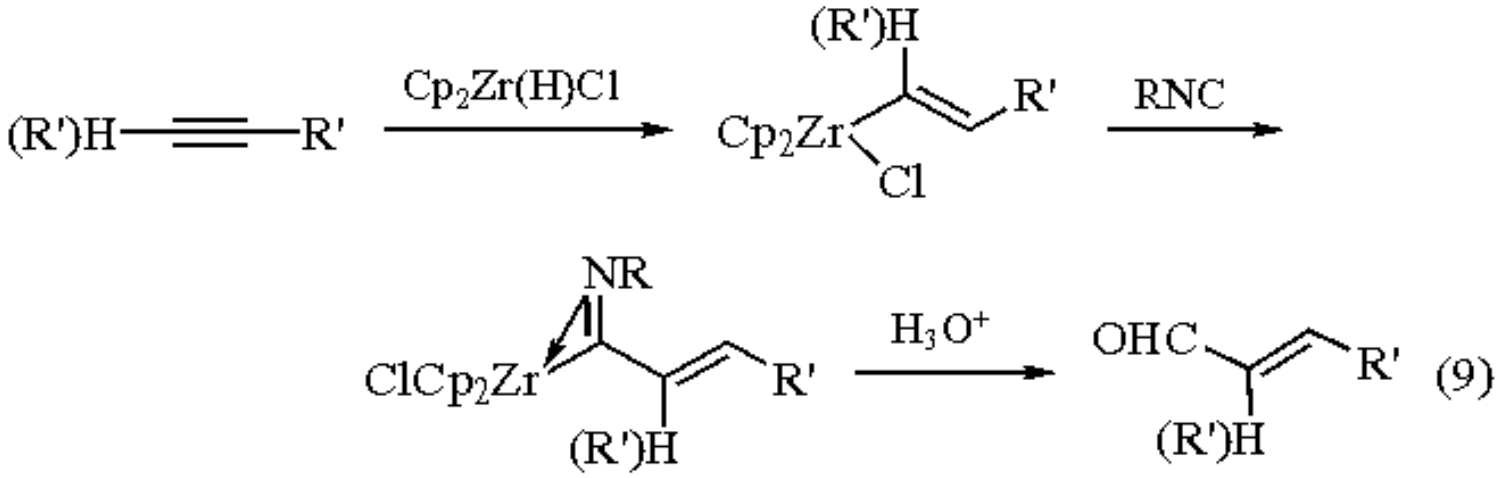

In situ generation of $Cp_2Zr(H)Cl$ or in situ hydrozirconation is practically useful. There are several in situ procedures which consist of ***Dichlorobis(cyclopentadienyl)zirconium***/***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al), Cp_2ZrCl_2/***t-Butylmagnesium Chloride***[15] or Cp_2ZrCl_2/***Lithium Triethylborohydride***.[16] Comparison of hydrozirconation using $Cp_2Zr(H)Cl$ and these in situ procedures is shown in Table 1.[15,16]

Table 1 Comparison of Hydrozirconation using Schwartz's Reagent and Various in situ Procedures[15,16]

Alkyne	Schwartz's reagent		Cp_2ZrCl_2 +		
			$LiEt_3BH$	Red-Al	*t*-BuMgCl
1-Octyne[a]	80	100	95	95	100
CH° C(CH$_2$)$_2$OTHP[b]	77		75	50	77[a]
1-Decyne[a]	80	100	88	80	95

[a] Isolated yield (%) of H^+ quenched materials. [b] Isolated yields.

$(MeC_5H_4)_2Zr(H)Cl$ reacts about seven times faster with 1-hexene or acetophenone than $Cp_2Zr(H)Cl$.[17] Hydrozirconation of other various unsaturated bonds such as Schiff bases,[18] ketones,[3,4,19] diazoalkanes,[20] nitriles,[21] carbon dioxide (eq 10),[22] 1-ene-3-ynes,[23] dienes,[24] phosphaimines,[25] thioketones,[26] carbon oxide,[27] and isocyanide[28] has been investigated.

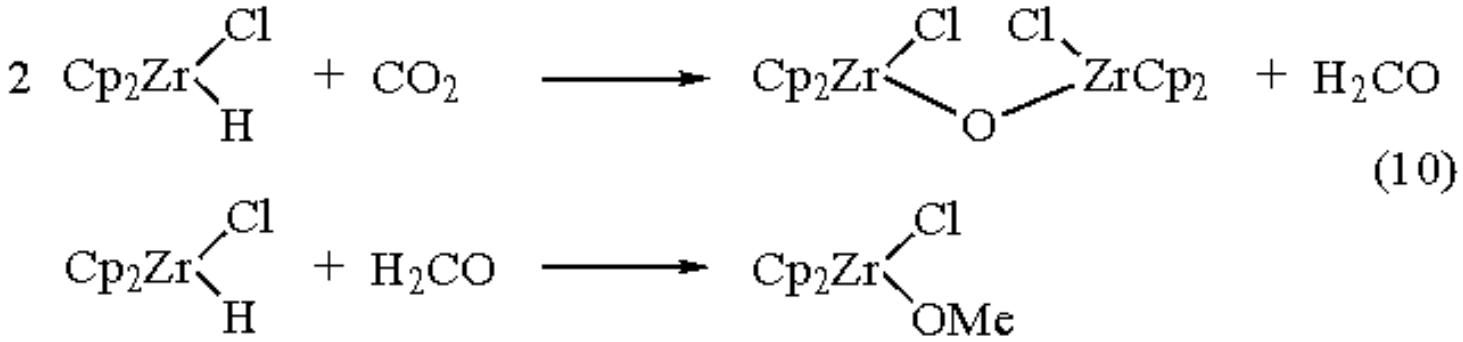

(10)

Hydrozirconation of unsaturated bonds attached to metals also proceeds. Alkenylzinc or alkynylzinc compounds react with $Cp_2Zr(H)Cl$ to give unstable 1,1-bimetallic reagents which can be used for highly stereoselective alkenation of aldehydes (eq 11).[29] Similarly, addition of $Cp_2Zr(H)Cl$ to a solution of (neohexenyl)diisobutylaluminum gives a 1,1-bimetallic complex.[30] Its structural analysis by X-ray clearly shows the 1,1-bimetallic system.[31] Reaction of stannylacetylenes with $Cp_2Zr(H)Cl$ seems to give 1,1-bimetallic compounds, since the iodination product is 1-iodo-1-stannylalkenes.[32] The regioselectivity of hydrozirconation of unsaturated bonds attached to metals is noteworthy. Hydrozirconation of an alkynyl ligand attached to Ru[33] or Zr,[34] and an alkenyl ligand attached to Zr,[35] shows the opposite regioselectivity to those described above, which give 1,1-bimetallic compounds (eq 12). However, the reaction of $Cp_2Zr(H)Cl$ with $Cp(CO)_2Re{=}CHR$[36] gives a 1,1-bimetallic intermediate with Zr and Re. An acyl ligand on zirconium also reacts with $Cp_2Zr(H)Cl$.[37] When $Cp_2Zr(H)Cl$ is treated with potassium allyl alkoxide or homoallyl alkoxide, intramolecular hydrozirconation seems to give oxazirconacycles.[38]

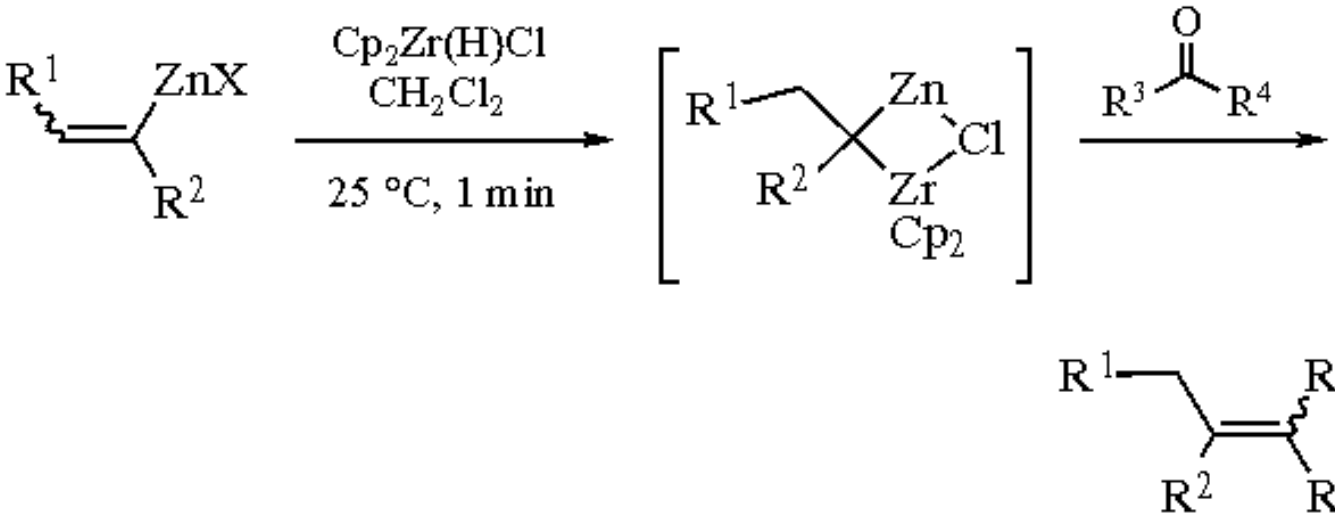

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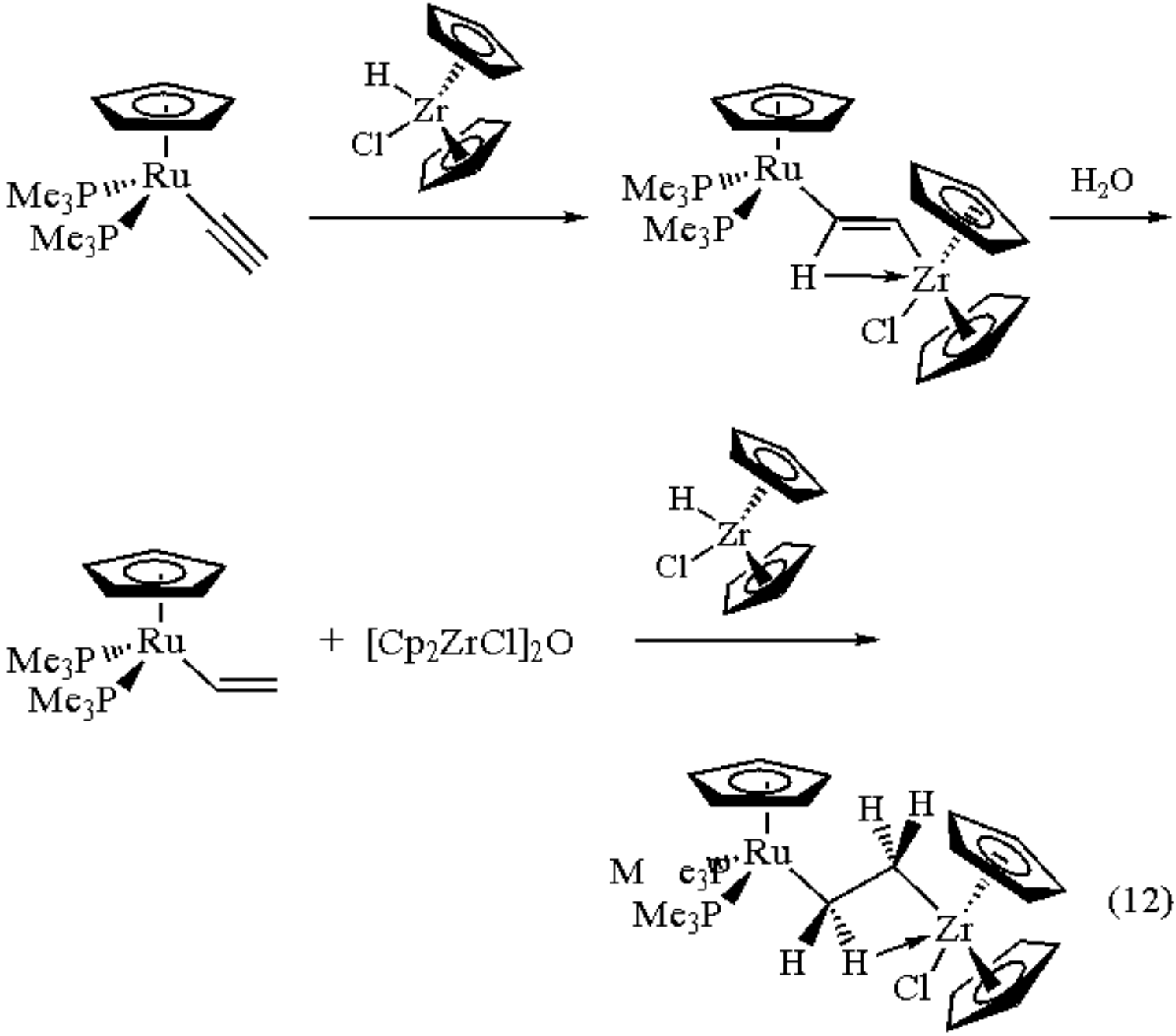

Carbon-Carbon Bond Forming Reactions of Hydrozirconation Products.

Hydrozirconation products of unsaturated compounds can be used for further C-C bond forming reactions. Since alkyl or alkenyl carbon attached to zirconium is not nucleophilic like Grignard, lithium, or aluminum reagents, the direct C-C bond formation is very limited. Only carbonylation (eq 7) and acylation with ***Acetyl Chloride*** can be used. However, transmetalation of the alkyl or alkenyl moiety from zirconium to other metals changes the situation. It provides a variety of C-C bond formation reactions of hydrozirconation products.

The alkyl or alkenyl moiety of hydrozirconation products are transferred from zirconium to aluminum when they are treated with ***Aluminum Chloride***. These organoaluminum dichlorides obtained here are converted into ketones or α,β-unsaturated ketones in high yields (eq 13).[39] Interestingly, since hydrozirconation of alkenes gives the terminal alkylzirconium exclusively, this method can provide a single ketonic product from a mixture of isomeric alkenes. For alkenylzirconium,

through this sequential use of two reactive organometallic species, the ketone is formed by overall *cis* addition of acyl-H to an alkyne.[39] Similar treatment of 1-(trimethylsilyl)-4-bromo-1-butyne with $Cp_2Zr(H)Cl$ followed by $AlCl_3$ affords 1-(trimethylsilyl)cyclobutene (eq 14).[40]

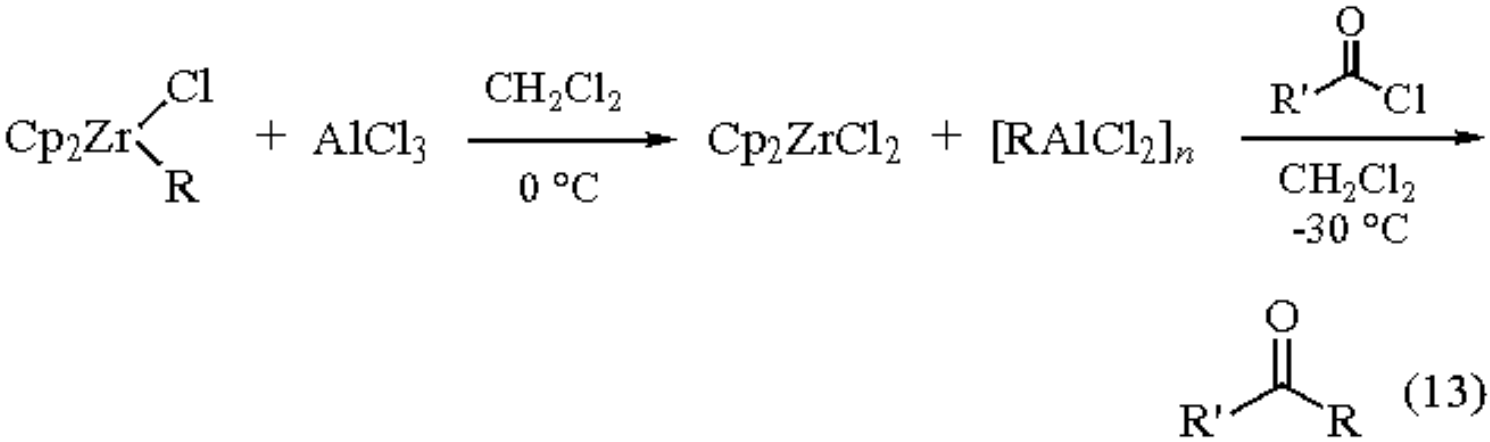

(13)

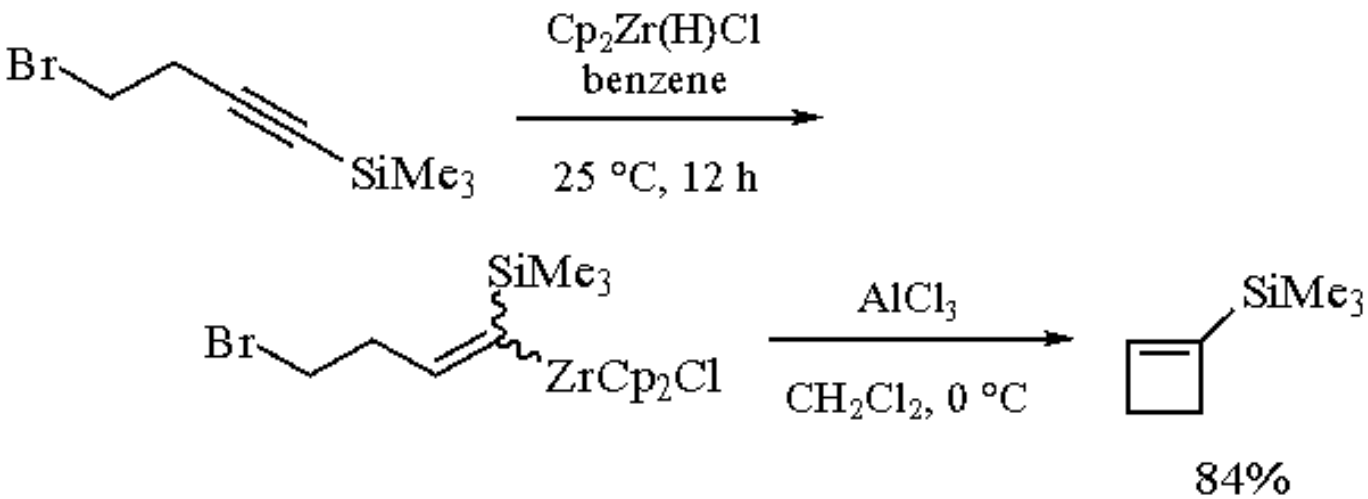

(14)

Transmetalation from Zr to Cu produces the corresponding organocopper compounds which can be used for addition to α,β-unsaturated ketones (eq 15).[41] It is noteworthy that functionalized lithiocuprates, which contain -CN, $-CO_2Si(i\text{-}Pr)_3$, -OCOPh, or Cl groups, are easily prepared by this method.[42]

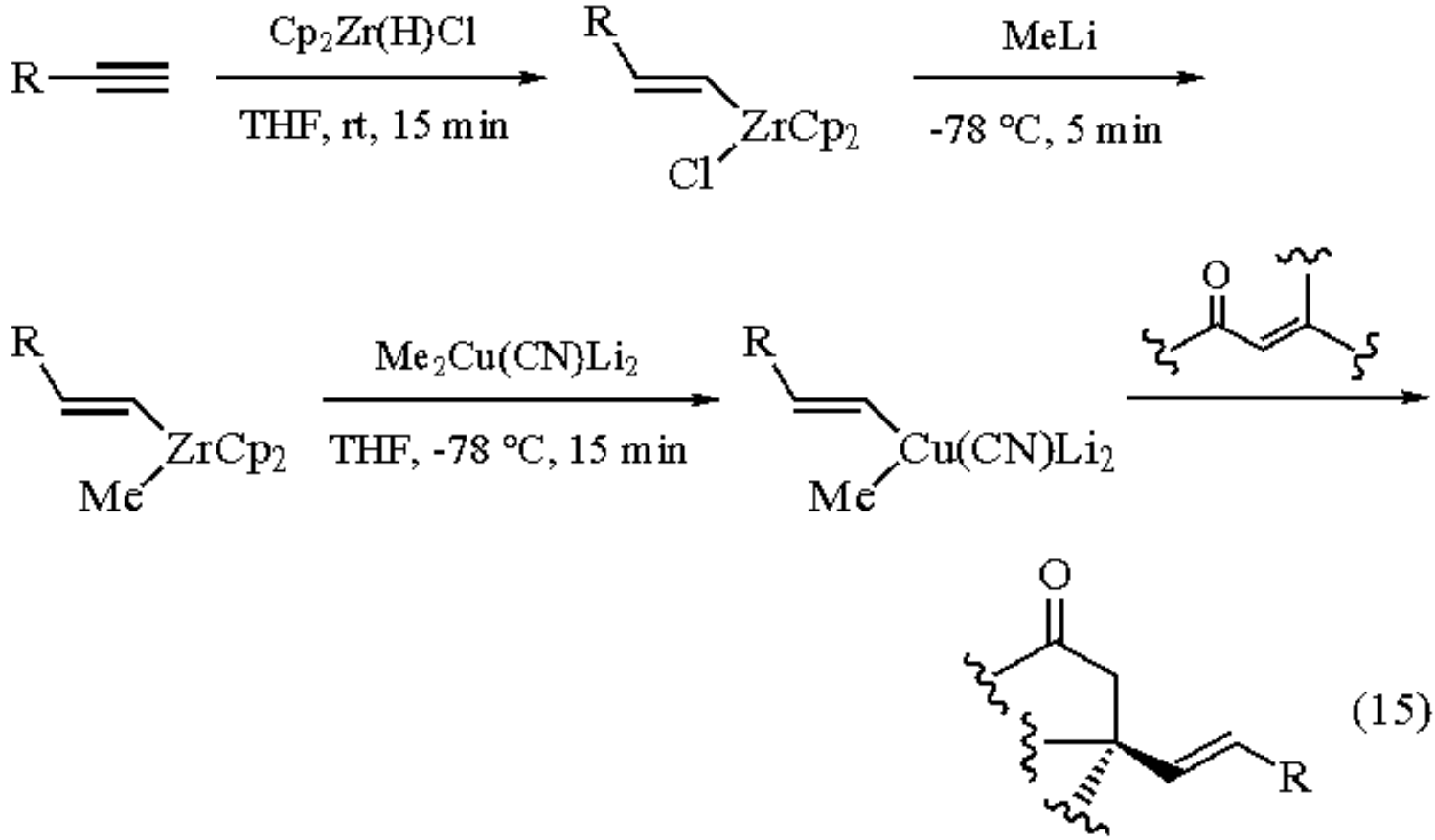

(15)

Migration of an alkenyl group from zirconium to boron (eq 16),[43] tin,[44] or selenium (eq 17)[44] also proceeds. Alkyltin compounds can be prepared from alkylzirconium and ***Tin(IV) Chloride***.[45] Imine transfer from zirconium to phosphorus or boron is also possible.[46]

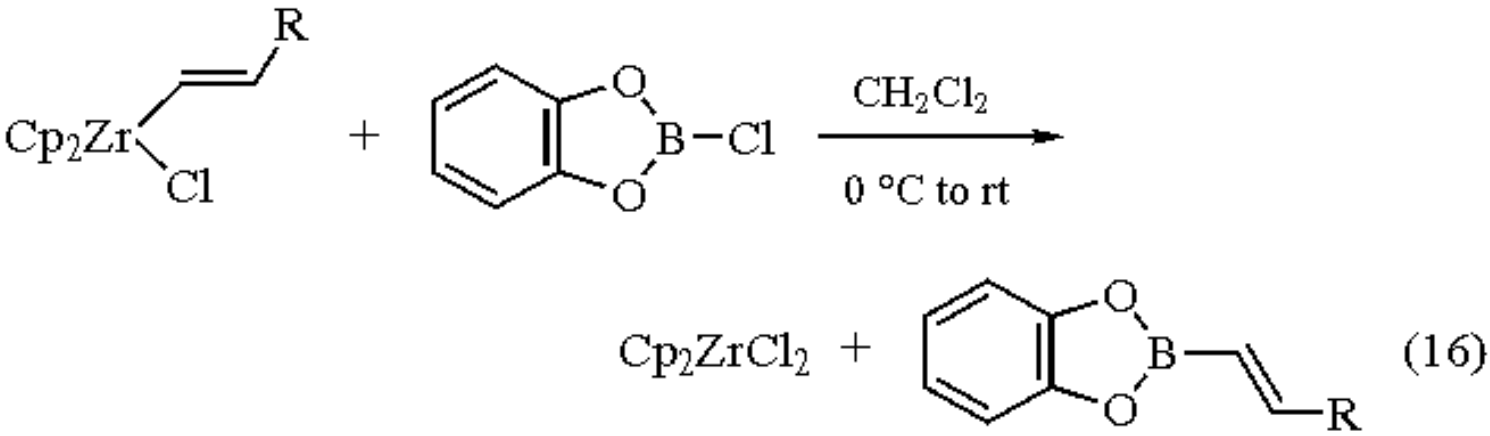

(16)

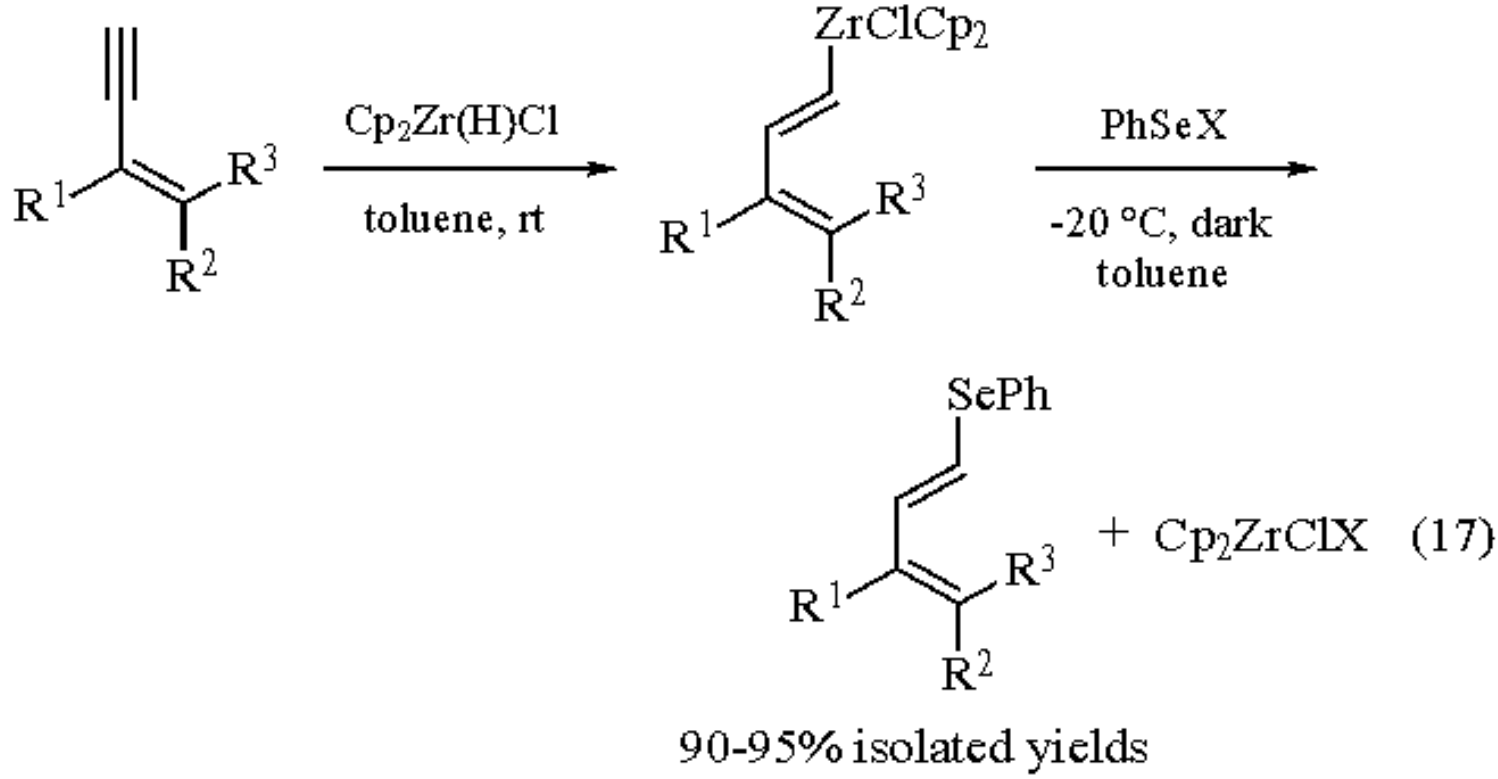

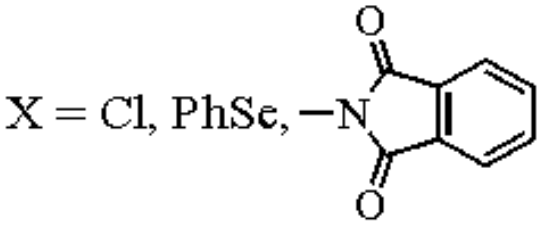

Catalytic reactions using transition metals have been investigated. Cross-coupling reaction of alkenylzirconium with aryl halides or alkenyl halides is catalyzed by Ni or Pd complexes (eq 18).[47] The effect of addition of metal salts such as ***Zinc Chloride*** and ***Cadmium Chloride*** is remarkable in this reaction.[48] Addition of alkenylzirconium to α,β-unsaturated ketones is also catalyzed by Ni (eqs 19 and 20).[49]

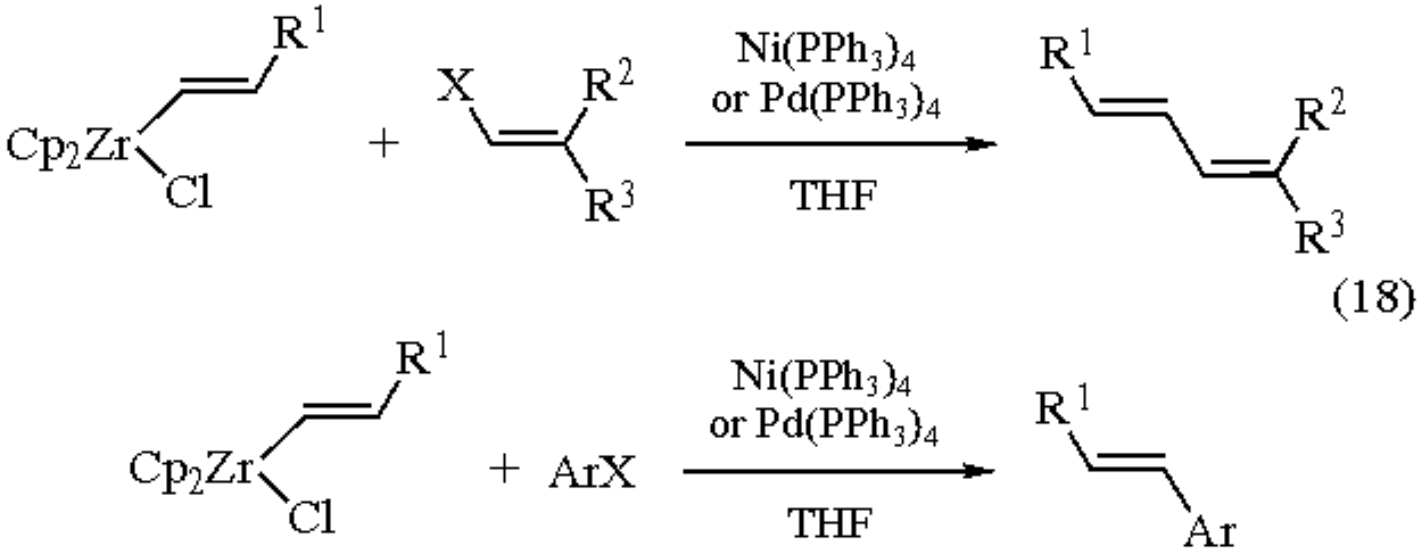

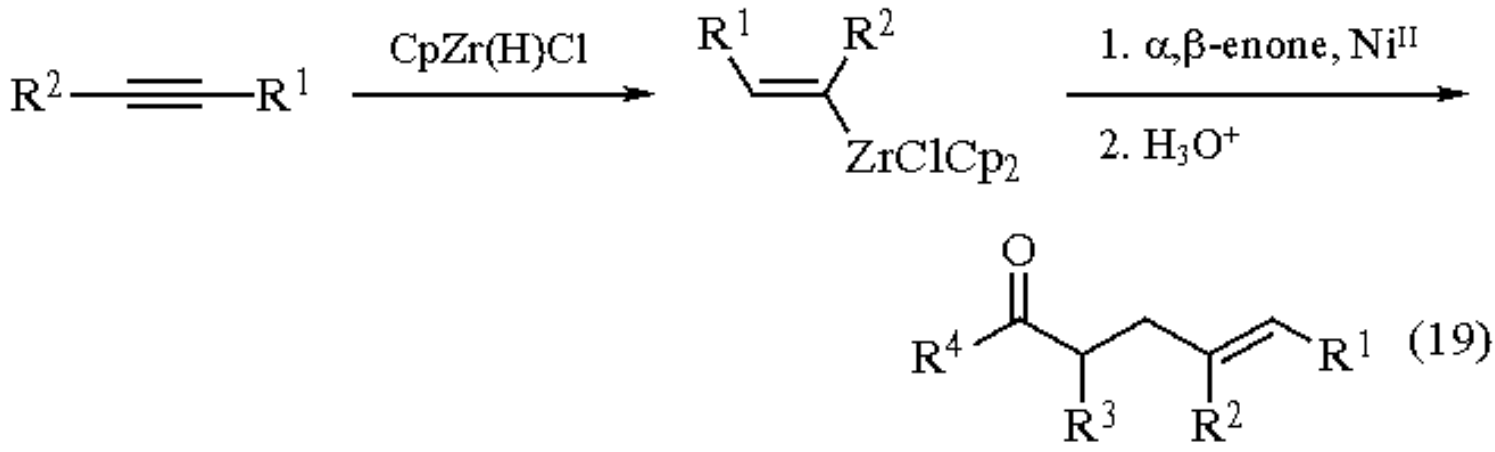

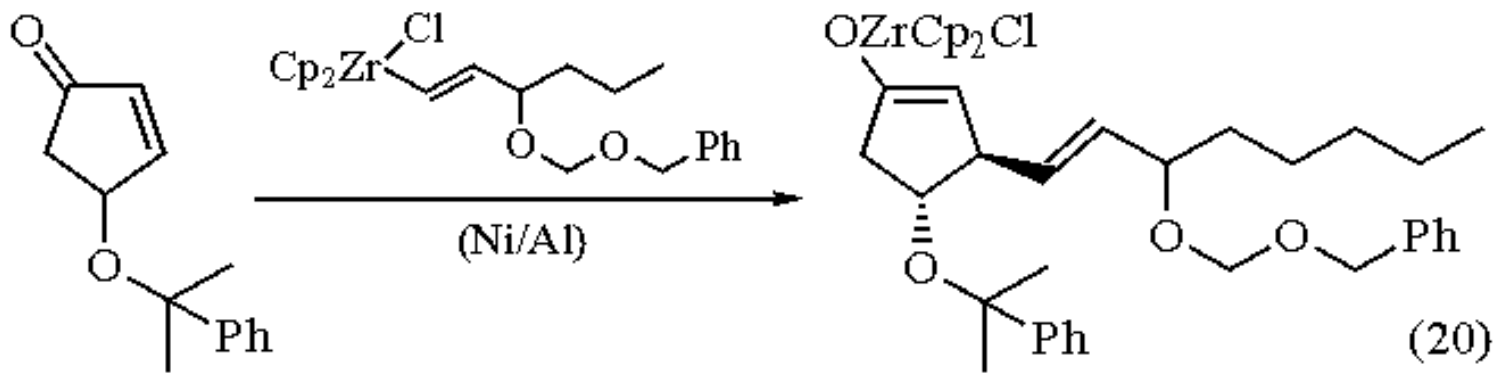

Alkylzirconium compounds react with α,β-unsaturated ketones (eq 21)[50] or ***Allyl Chloride***[51] in the presence of a catalytic amount of copper compound.

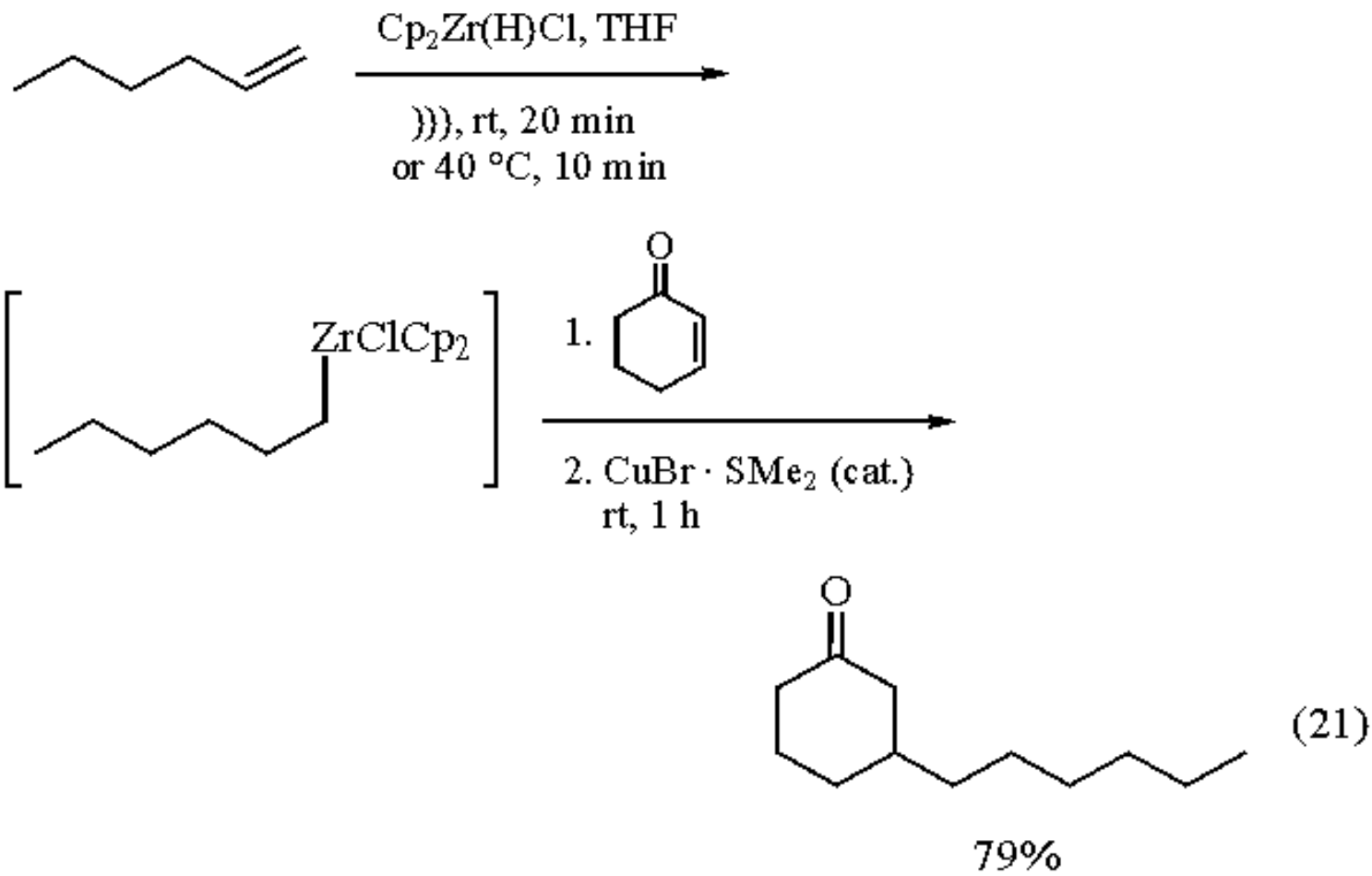

Formation of cationic species from alkyl- or alkenylzirconium compounds with a catalytic amount of ***Silver(I) Perchlorate*** is one method to make direct C-C bonds with aldehydes (eq 22).[52] Both alkyl and alkenyl groups attack aldehydes to give desired products in high yields. When 3-trimethylsilyl-1-propyne is used as a starting alkyne, (*E*)-selective terminal 1,3-dienes are formed.[53] Alkynes, 1-ethoxyethyne, and (*Z*)-1-methoxy-1-buten-3-yne give two- and four-carbon homologation of aldehydes, respectively, after treatment with an acid (eq 23).[54] A direct C-C bond formation of alkenylzirconium compounds with epoxides also proceeds in the presence a catalytic amount of $AgClO_4$.[55]

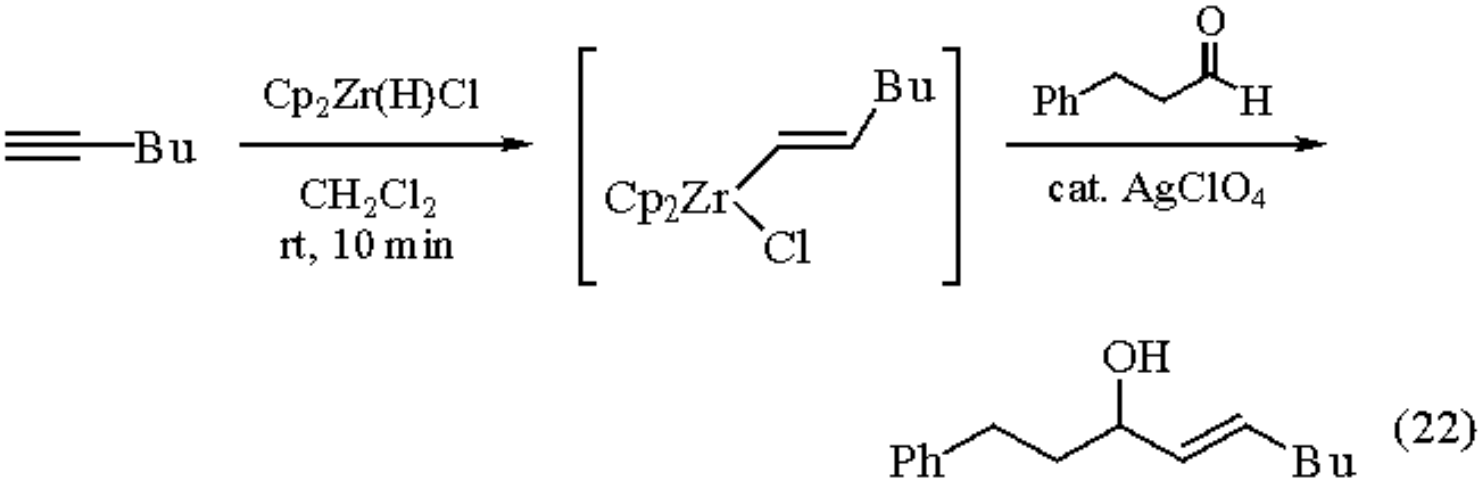

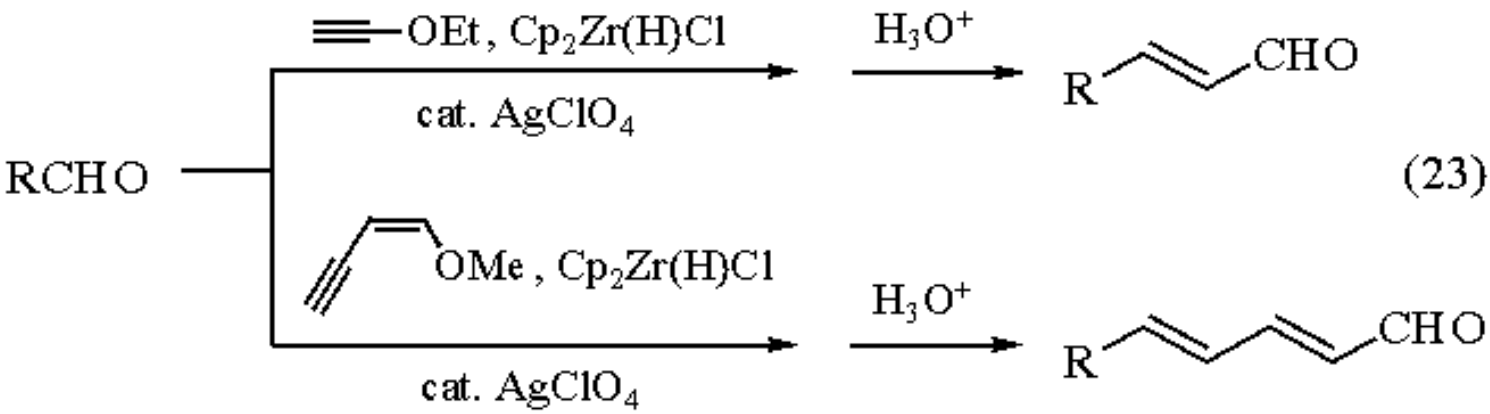

(23)

Organozirconium complexes, prepared by either hydrozirconation or the reaction of organolithium reagents with $Cp_2Zr(H)Cl$, can be converted into diene (eq 24),[56] alkyne (eq 25),[57] silanimine (eq 26),[58] and diazobenzene (or hydrazido(1-)) (eq 27)[59] Zr^{II} complexes which react with unsaturated compounds to afford various zirconacycles.

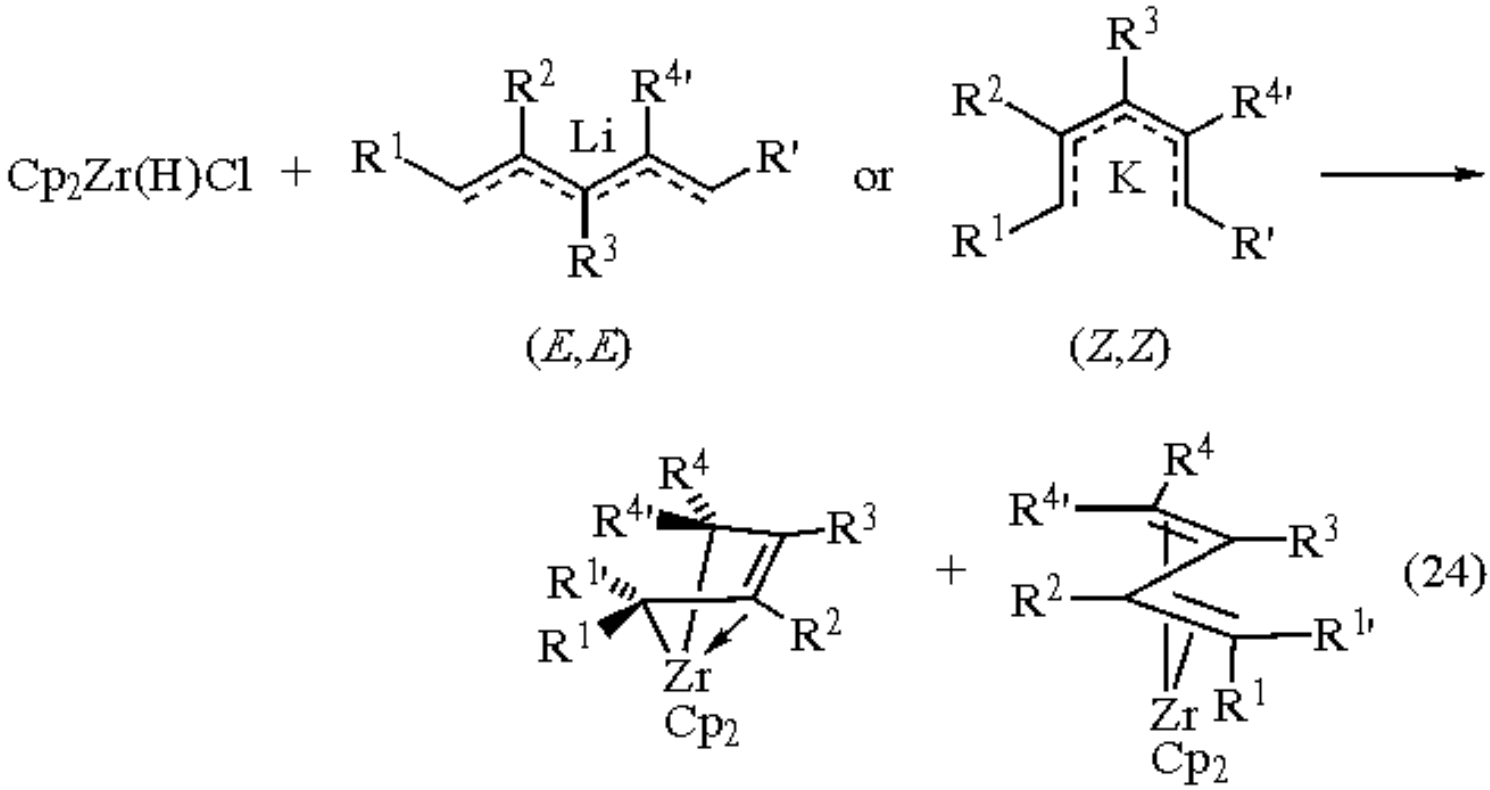

(24)

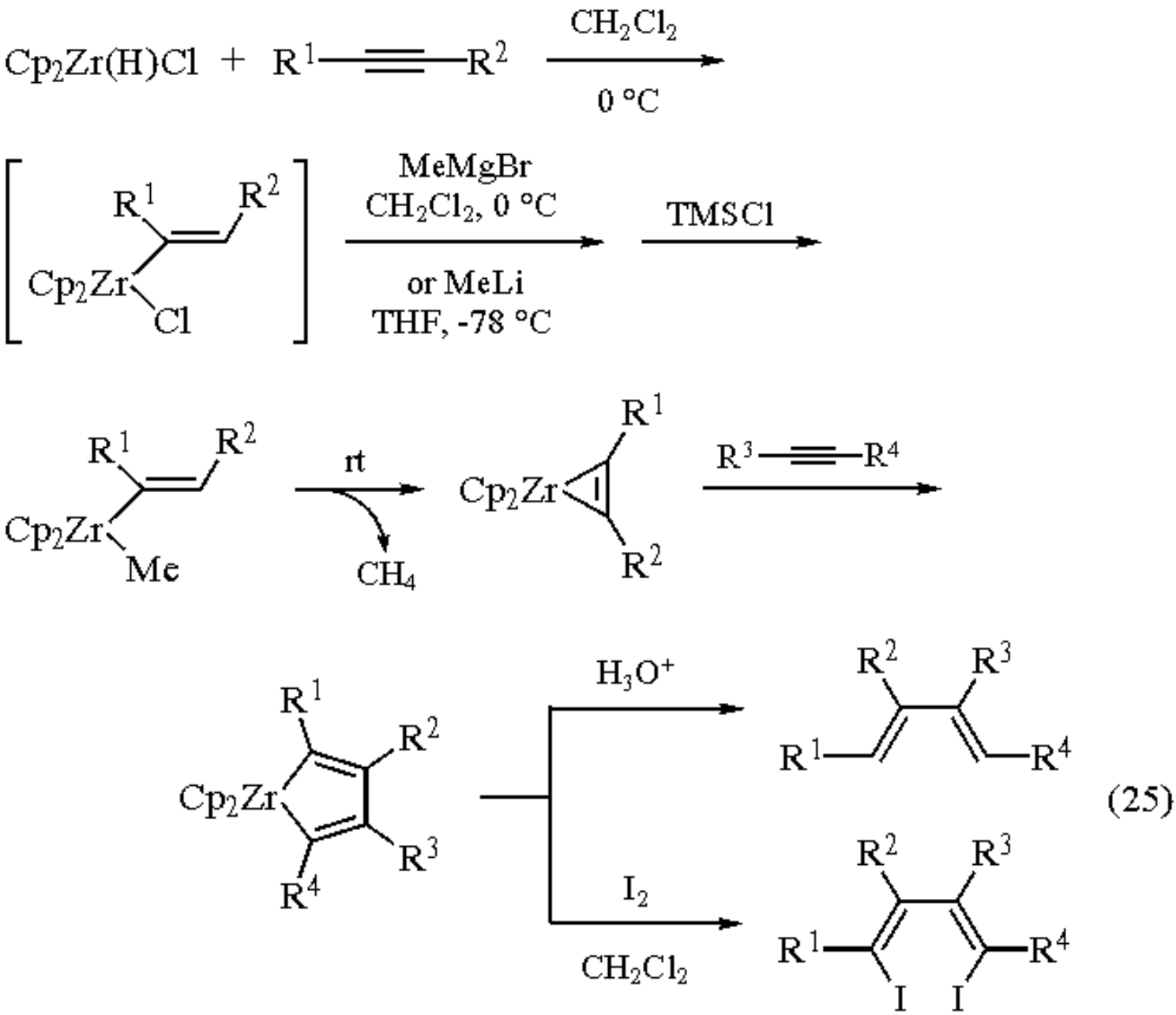
Cp2Zr(H)Cl + R1—≡—R2
CH2Cl2
0 °C
MeMgBr
CH2Cl2, 0 °C
or MeLi
THF, -78 °C
TMSCl
Cp2Zr
Cl
Me
rt
CH4
R3—≡—R4
H3O+
I2
CH2Cl2
(25)

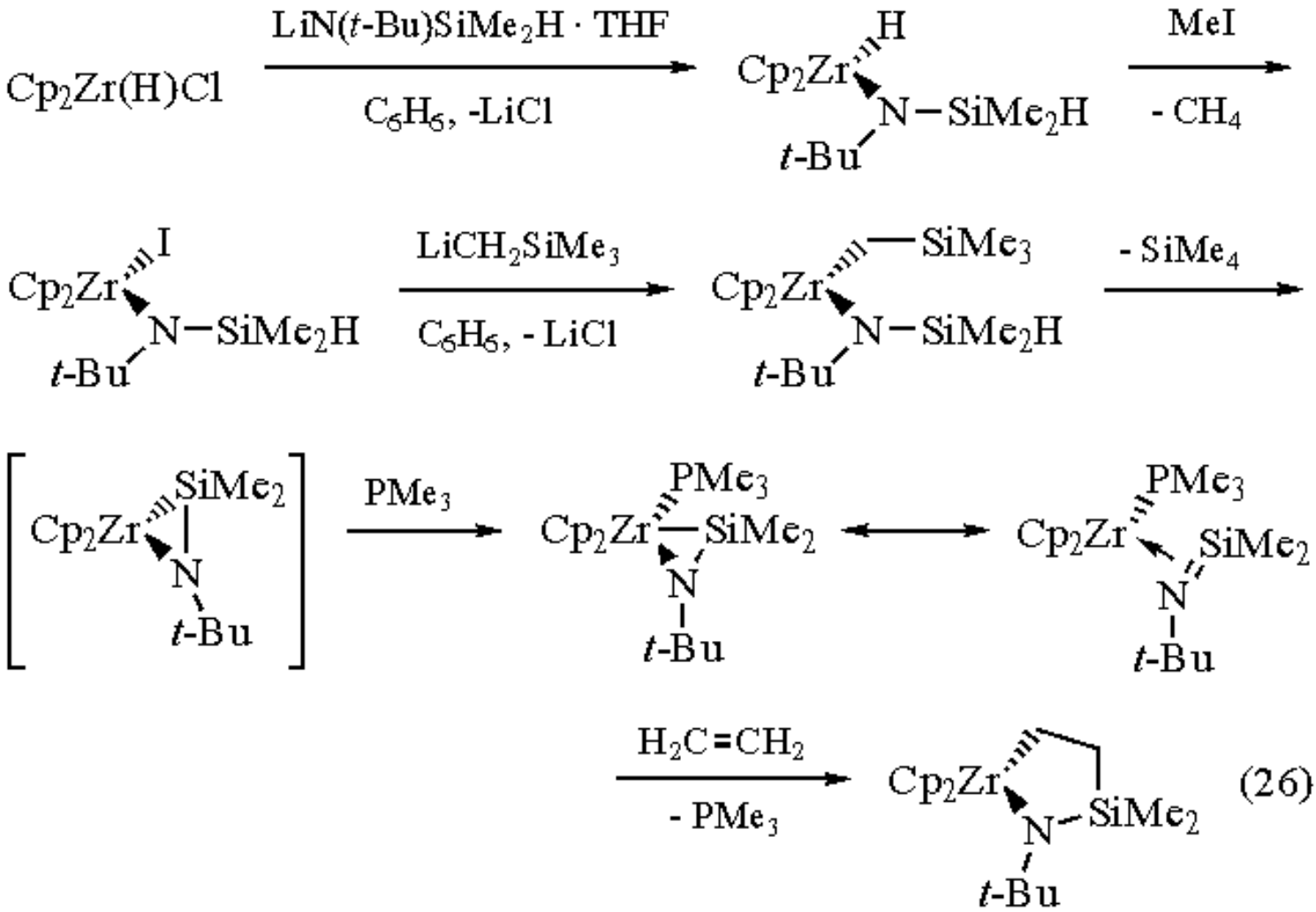

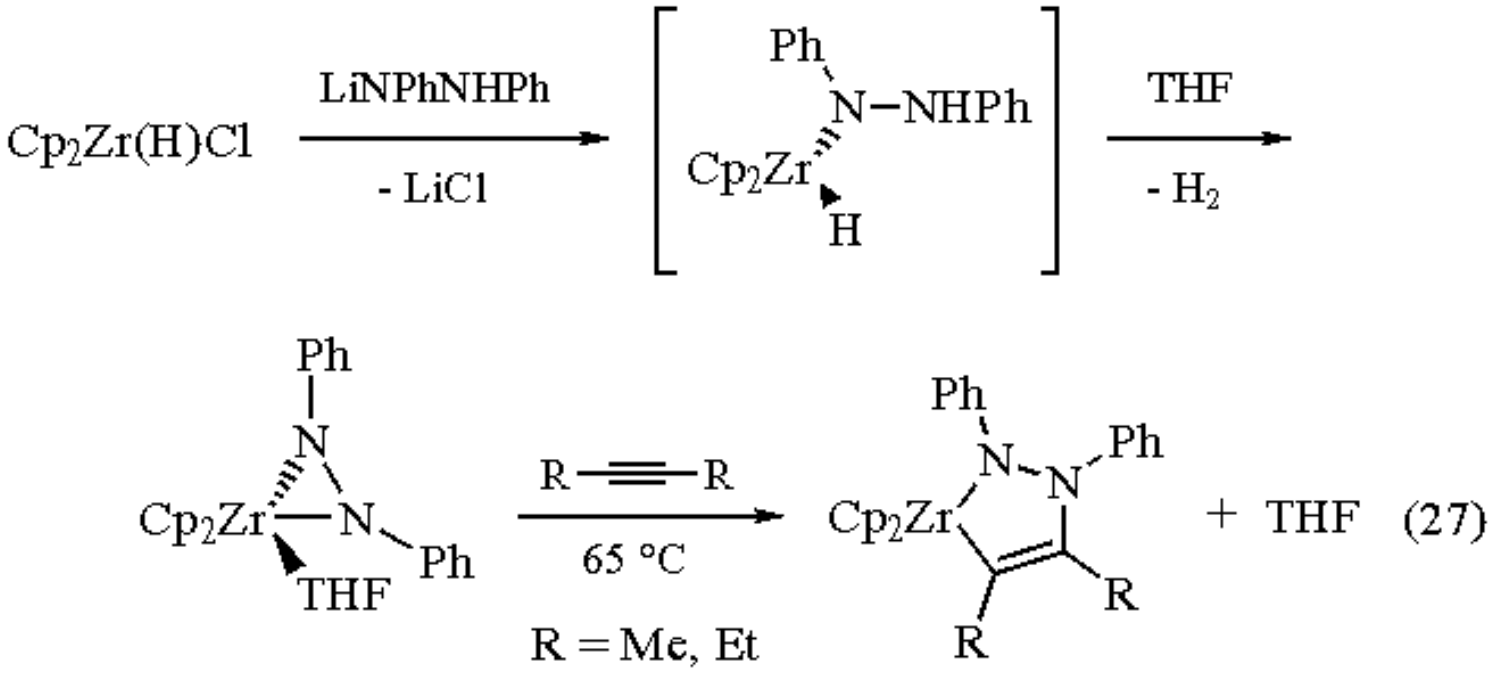

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L.; Riley, P. I. In *Comprehensive Organometallic Chemistry*, Wilkinson, G.; Stone, F. G. A.; Abel, E. W. Eds.; Pergamon: Oxford, 1982; Vol. 3, pp 549-633. (d) Negishi, E.; Takahashi, T. *Aldrichim. Acta* **1985**, *18*, 31.
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3. Carr, D. B.; Schwartz, J. *JACS* **1979**, *101*, 3521.
4. Wailes, P. C.; Weigold, H. *Inorg. Synth.* **1979**, *19*, 223.
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Chlorobis(cyclopentadienyl)methylzirconium[1]

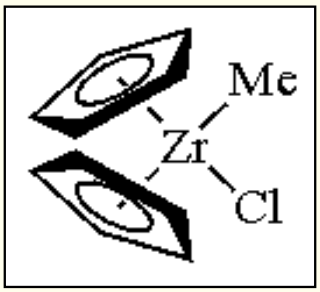

[1291-48-8] · $C_{11}H_{13}ClZr$ · Chlorobis(cyclopentadienyl)methylzirconium · (MW 271.90)

(used to generate zirconocene complexes with stable and unstable organic molecules;[2] catalyzes the carboalumination of R_3Al to terminal alkynes[3])

Physical Data: pale yellow crystals.

Solubility: sol aromatic solvents.

Analysis of Reagent Purity: ^1H NMR (benzene-d_6) δ 5.73 (s, C_5H_5), 0.32 (s, CH_3) in a ratio of 10:3.

Preparative Methods: can be prepared by the reaction of Cp_2ZrMe_2 with ***Dichlorobis(cyclopentadienyl)zirconium***. A 0.5 M solution of each reagent in toluene is heated to 130 °C for 35 h. $Cp_2ZrMeCl$ is isolated in >90% yield by recrystallization from toluene/hexanes.[4] Alternatively, it can be prepared in pure form by the treatment of $(Cp_2ZrCl)_2O$ with ***Trimethylaluminum***.[5] Although $Cp_2ZrMeCl$ is available in a reasonable quantity as mentioned, it is often convenient to generate an analog of $Cp_2ZrMeCl$ in the reaction media and use it in situ. Thus treatment of Cp_2ZrCl_2 with ***t-Butyllithium*** generates $Cp_2Zr(i\text{-Bu})Cl$ through β-hydride elimination and insertion. $Cp_2Zr(i\text{-Bu})Cl$ shows a comparable reactivity to $Cp_2ZrMeCl$.[6]

Handling, Storage, and Precautions: the dry solid is highly sensitive to moisture, forming $(Cp_2ZrCl)_2O$, and should be kept tightly sealed to preclude moisture. Use of this reagent immediately following preparation is recommended.

Formation of Cp_2Zr Complex.

$Cp_2ZrMeCl$ is a convenient reagent to produce mixed dialkylzirconocenes in the reaction with RLi (eq 1).[7] By the application of this method, zirconocene complexes of either unstable or stable organic molecules can be generated from $Cp_2ZrMeCl$.[8] The formation of zirconocene complexes is achieved by substituting the halogen atom of $Cp_2ZrMeCl$ with an alkyl or a vinyl organometallic reagent which possesses at least one β-hydrogen atom. Thermolysis then results in the

concomitant generation of methane. This procedure is complementary to Cp_2Zr-butene (zirconocene equivalent) promoted zirconocene complex formation of unsaturated molecules,[9] since the zirconocene equivalent does not allow the isolation of Cp_2Zr complexes from very unstable or very reactive organic molecules. This β-hydrogen abstraction process is reported to involve an interaction of a β-C-H bond with the empty orbital of the zirconium valence shell.[10] The general scheme for the formation of complexes of unstable organic molecules and the organic precursor required for their syntheses is shown in eqs 2-8.

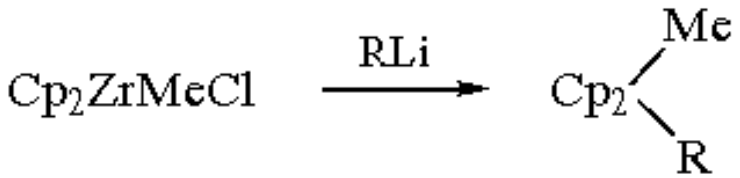

(1)

R = alkyl, alkenyl, aryl

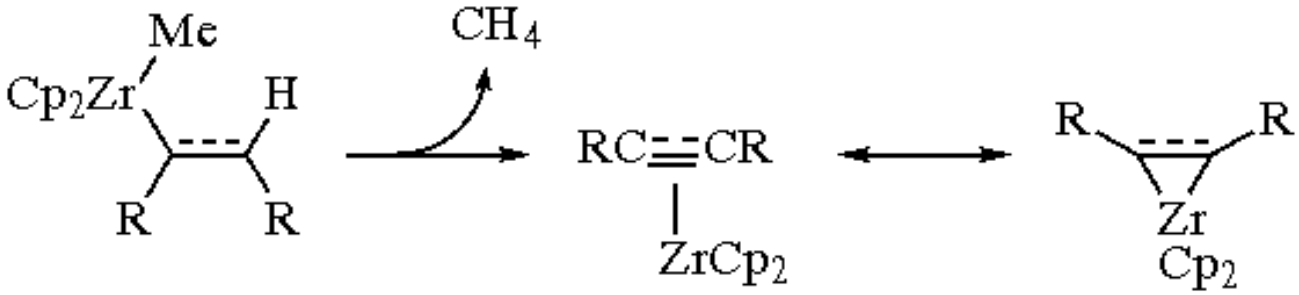

(2)

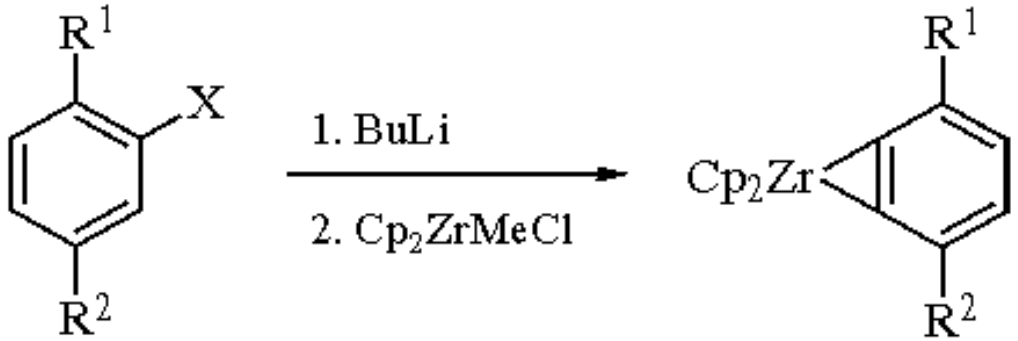

(3)

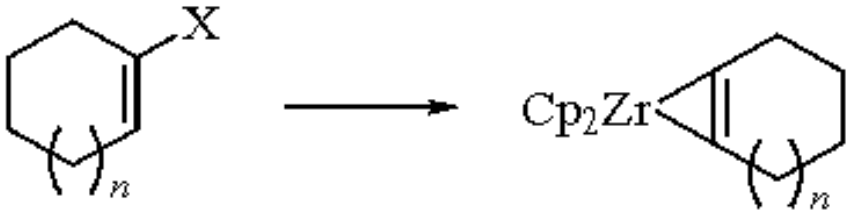

(4)

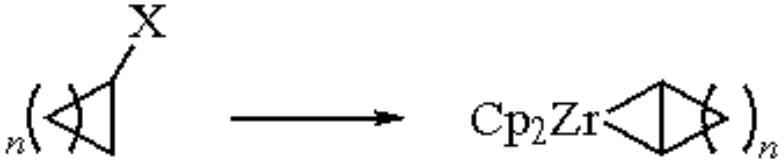

(5)

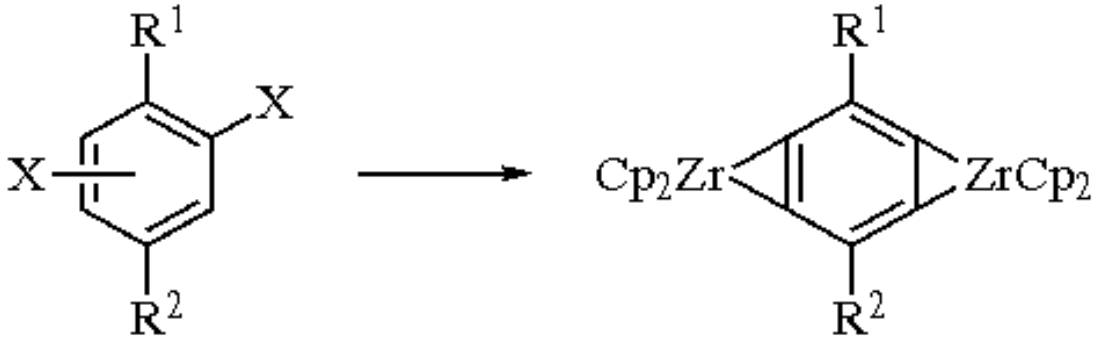

(6)

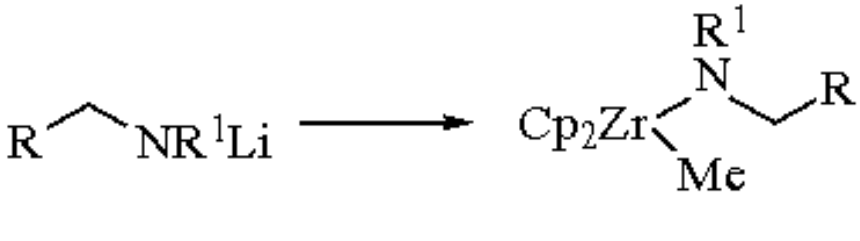

(7)

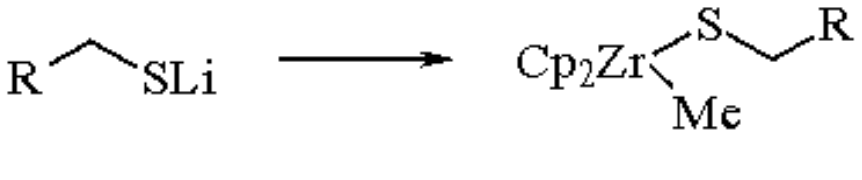

(8)

In each case, a metal-halogen exchange with an organolithium reagent followed by the addition of $Cp_2ZrMeCl$ produces the precursor for the zirconocene complex. Thermolysis of these precursors at temperatures ranging between 20-100 °C causes the evolution of methane to give the desired zirconocene complexes, which can be isolated as their trimethylphosphine adducts or trapped with an unsaturated compound. Through this procedure, Cp_2Zr complexes of arynes with a variety of substitution patterns (eq 3),[8a,11] cyclic alkynes containing five to eight membered rings (eq 4), cyclic alkenes (eq 5),[8b,c] benzdiynes (multiply unsaturated aromatic species) (eq 6),[12] imines (eq 7),[13] and thioaldehydes (eq 8)[14] have all been reported. Interestingly, methyl(2-norbornenyl)zirconocene is known to exist as a thermally stable complex (eq 9).[15] This stability is attributed to the strain and the bulkiness of the 2-norbornenyl ligand. Thermolysis of methyl(2-furyl)zirconocene, derived from $Cp_2ZrMeCl$ and 2-furyllithium, yields a ring-enlarged and methyl-migrated compound instead of a Cp_2Zr-heteroaryne complex (eq 10).[16]

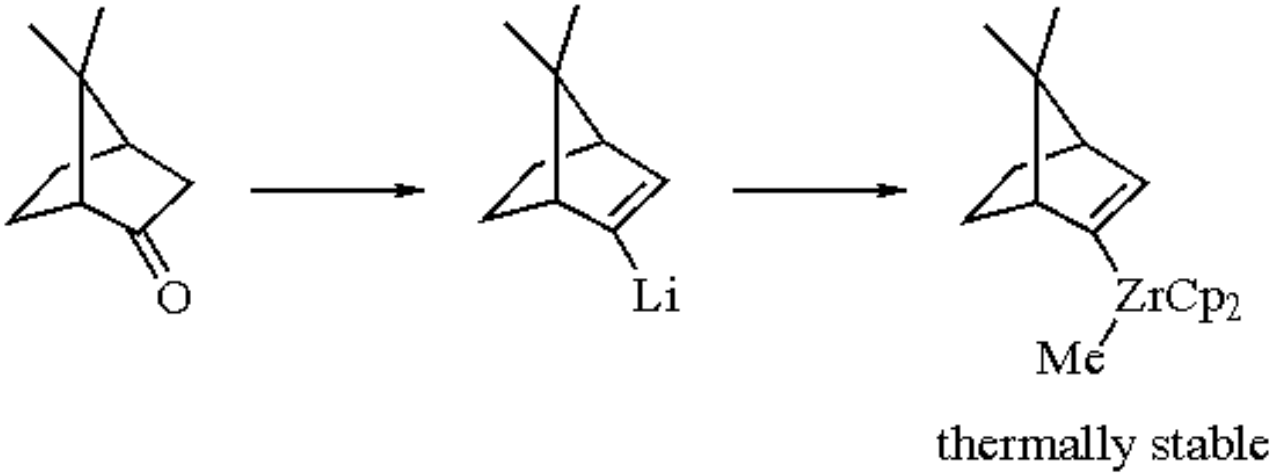

(9)

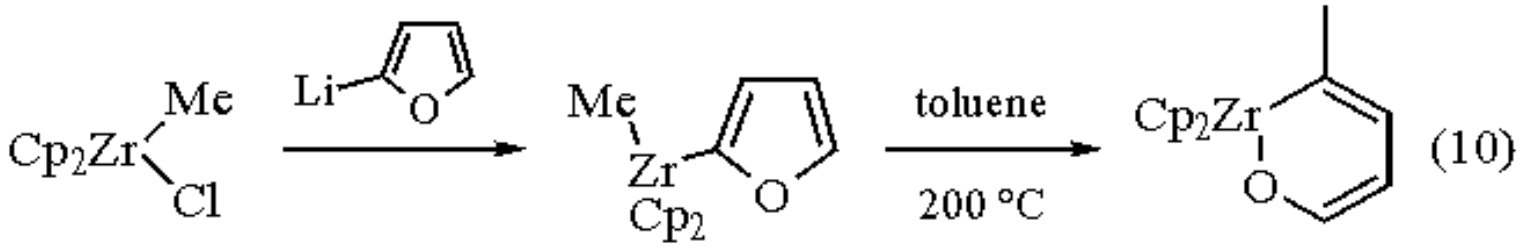

The reactions of Cp_2Zr complexes toward unsaturated molecules reveal their usefulness for preparing many functionalized compounds (eq 11). Thus the Cp_2Zr-benzyne complexes react with many unsaturated compounds to give benzo-fused compounds (eq 12).[8,17] A cyclopentyne-zirconocene complex has been used for the preparation of an optically active cyclopentenone derivative.[18] In this reaction the addition of an optically active allylic ether to the cyclopentyne complex proceeds with ~100% asymmetric induction (eq 13).

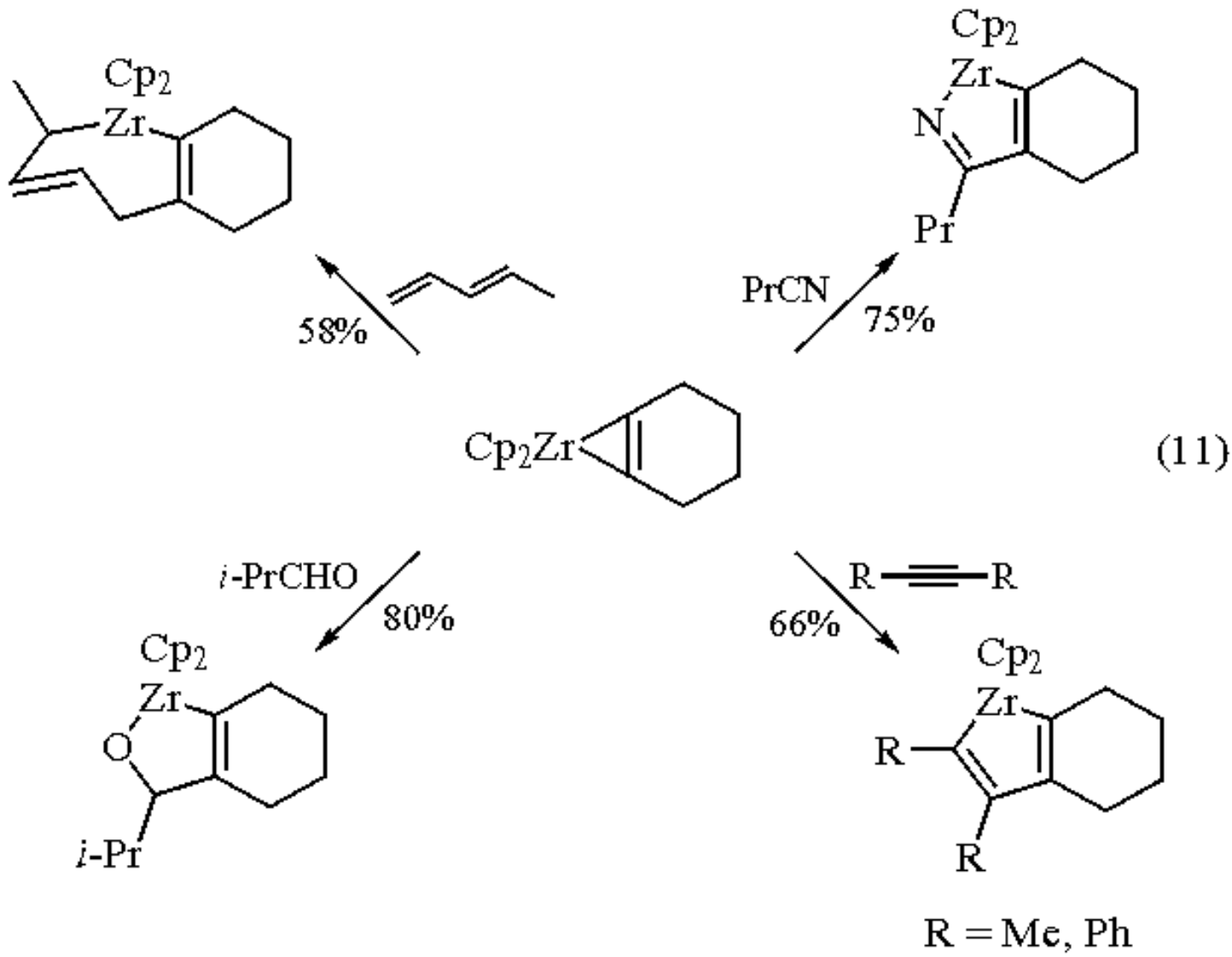

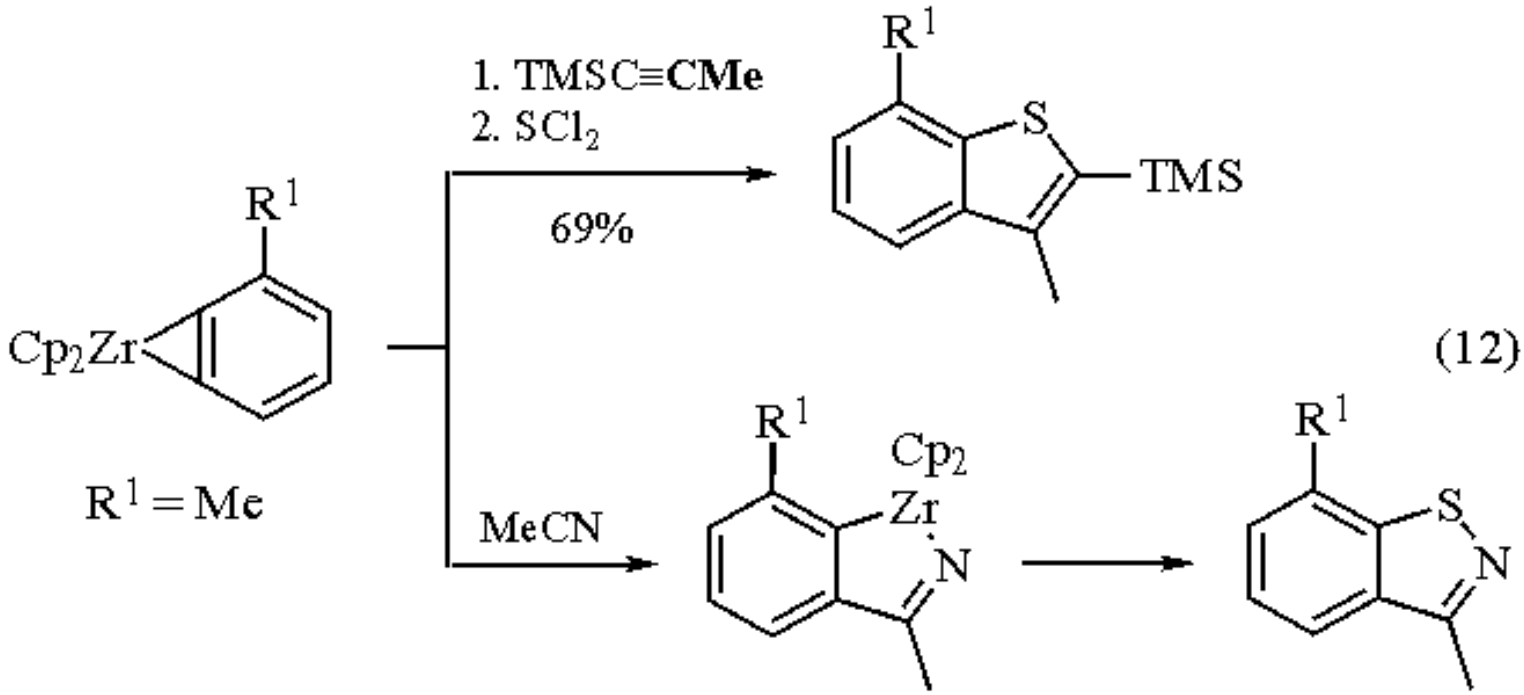

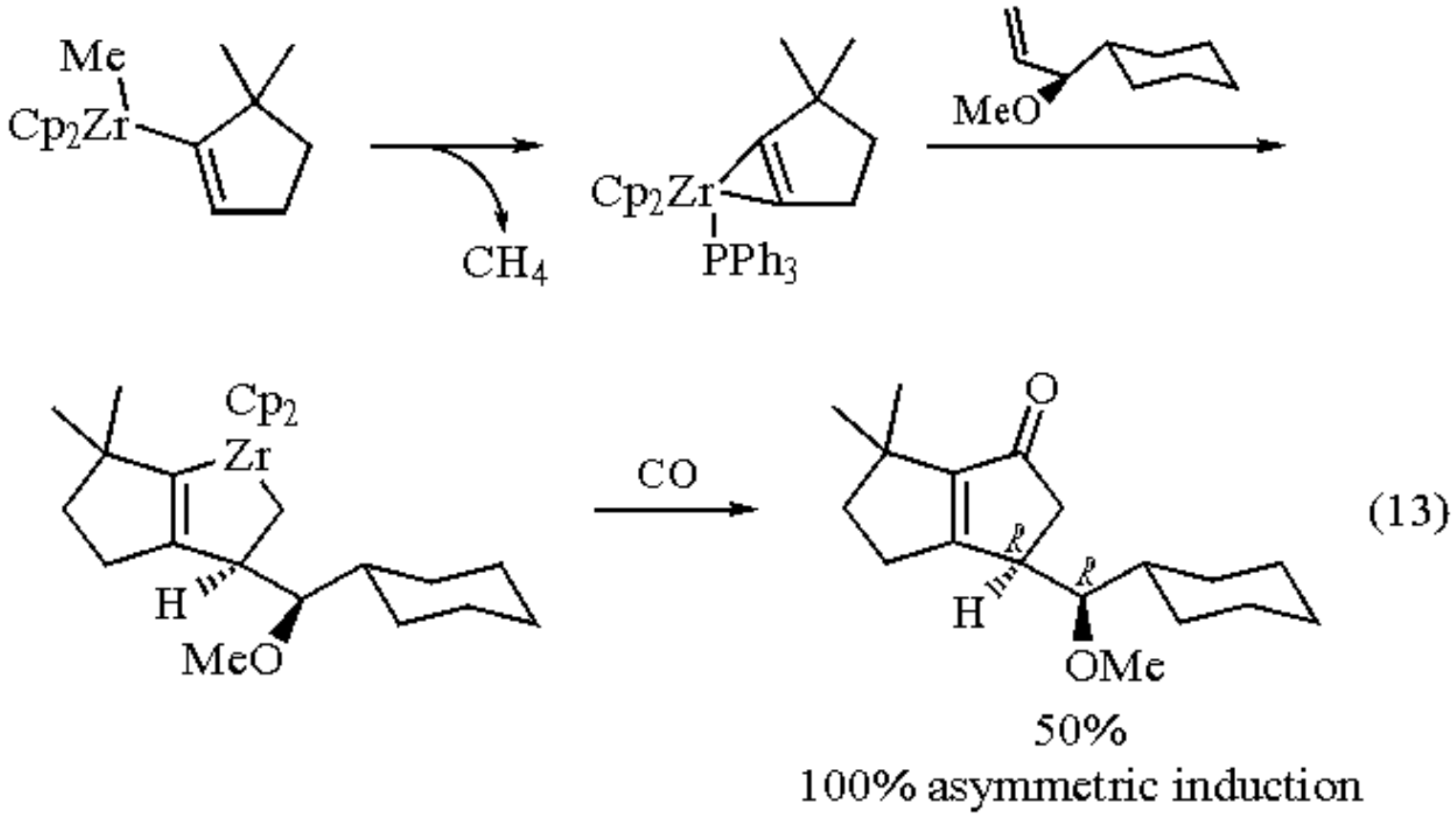

Reaction of $Cp_2ZrMeCl$ with lithium amide derivatives and the subsequent extrusion of methane through β-hydrogen elimination is a very efficient way of generating imine-zirconocene complexes, zirconaaziridines.[13] Zirconaaziridines, which can be isolated as trimethylphosphine adducts or THF adducts, have proven to be valuable intermediates in organic synthesis. These complexes react with carbonyl compounds or alkynes to give amino alcohols or allylic amines. When the azazirconacyclopentene prepared from zirconaaziridine and alkyne is treated with ***Carbon Monoxide*** under high pressure, di- and trisubstituted pyrroles are obtained in synthetically viable yields (eq 14).[13b] In a similar manner, reaction

of the lithium amide of an allylic amine with $Cp_2ZrMeCl$ when heated to 60 °C gives an azazirconacyclopentene, which is converted to a pyrrole when treated with an isocyanide.[13d] Notable and efficient application of the benzyne complex chemistry derived from $Cp_2ZrMeCl$ has been seen in the effective synthesis of the pharmacophore of potent antitumor antibiotics.[19]

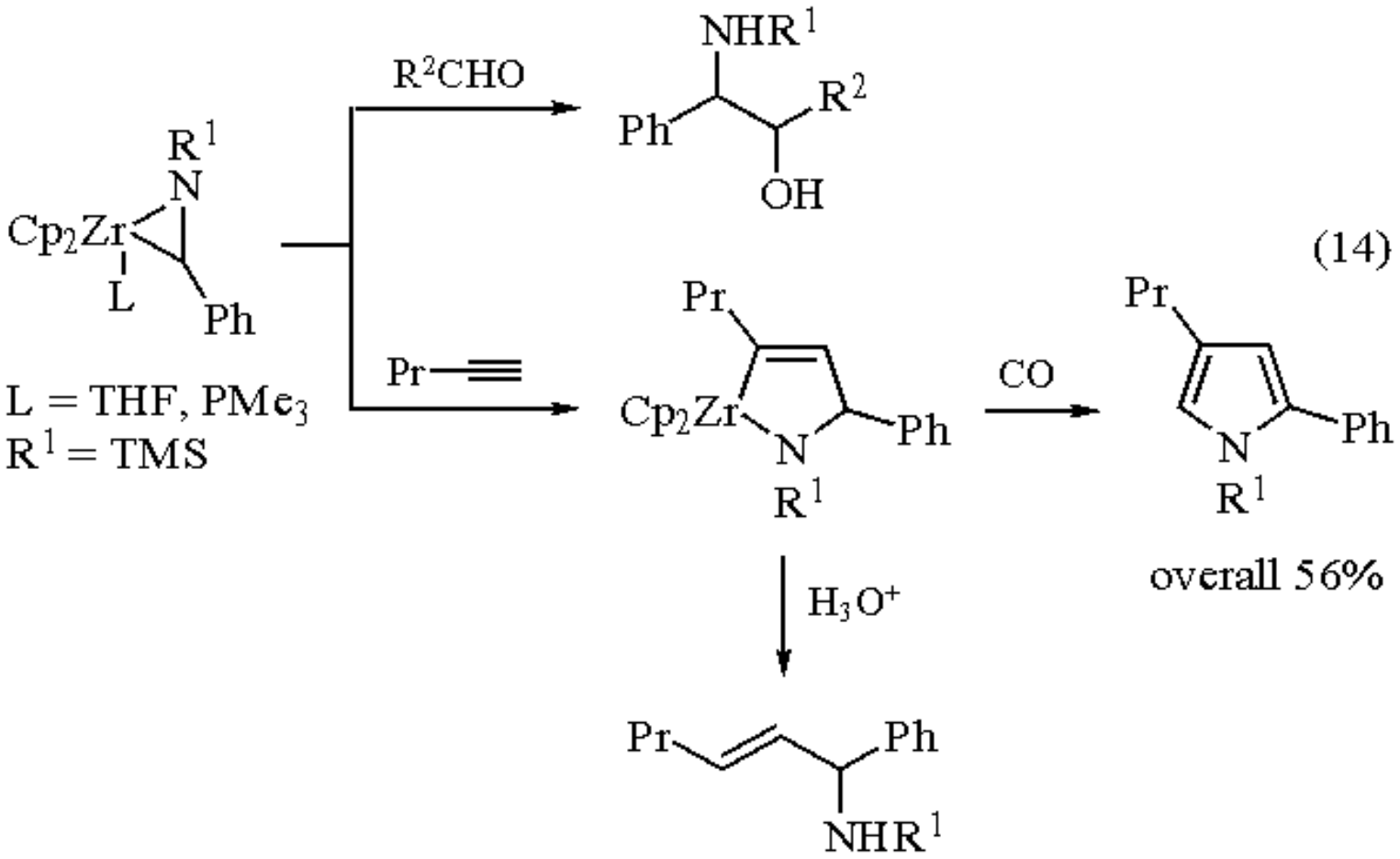

(14)

Hydroamination.

Imidozirconocene complexes[20] can be generated in situ by treating $Cp_2ZrMeCl$ with a lithium amide (which does not have β-hydrogen) followed by elimination of methane upon heating. This transient species reacts with an alkyne derivative to give an azazirconacyclobutene derivative which can be converted to a carbonyl compound via an enamine. Carbonyl compounds also react with imidozirconocene complexes giving imine compounds (eq 15).

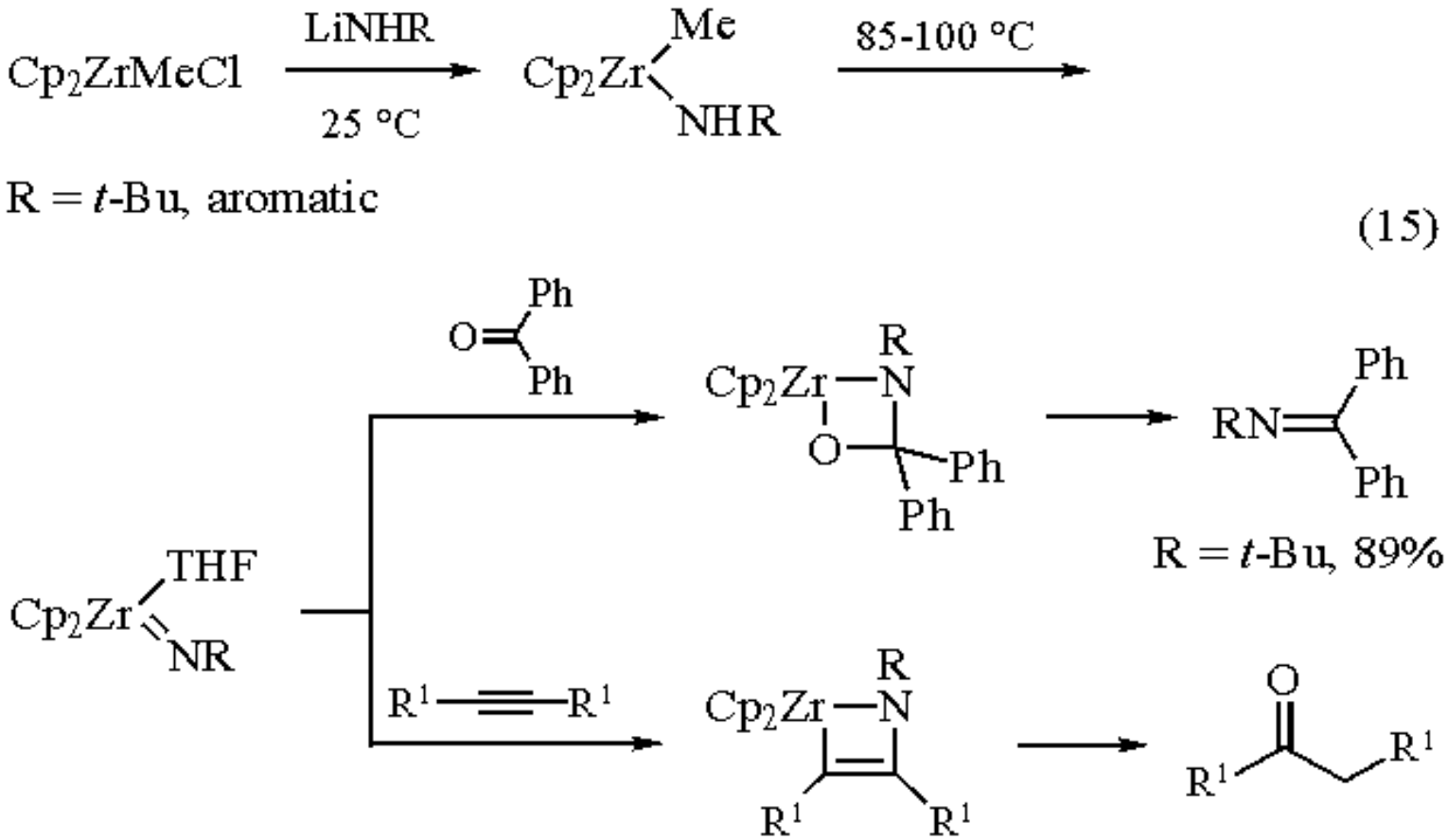

Carbometalation.

In the chemistry of carbometalation of alkylaluminum compounds mediated by zirconocene derivatives,[21] reaction of a stoichiometric amount of $Cp_2ZrMeCl$ with 1-pentynyldimethylalane is known to give an alkenylmetal species, which is converted to diiodo or 2-methyl-1-pentene in good yields upon treatment with excess iodine or water. This process is an Al-assisted direct addition of the Zr-carbon bond to the alkyne (eq 16). It is interesting to note that the $Cp_2ZrMeCl$-catalyzed R_3Al addition to alkyne is a Zr-assisted Al-carbon bond addition (eq 17).

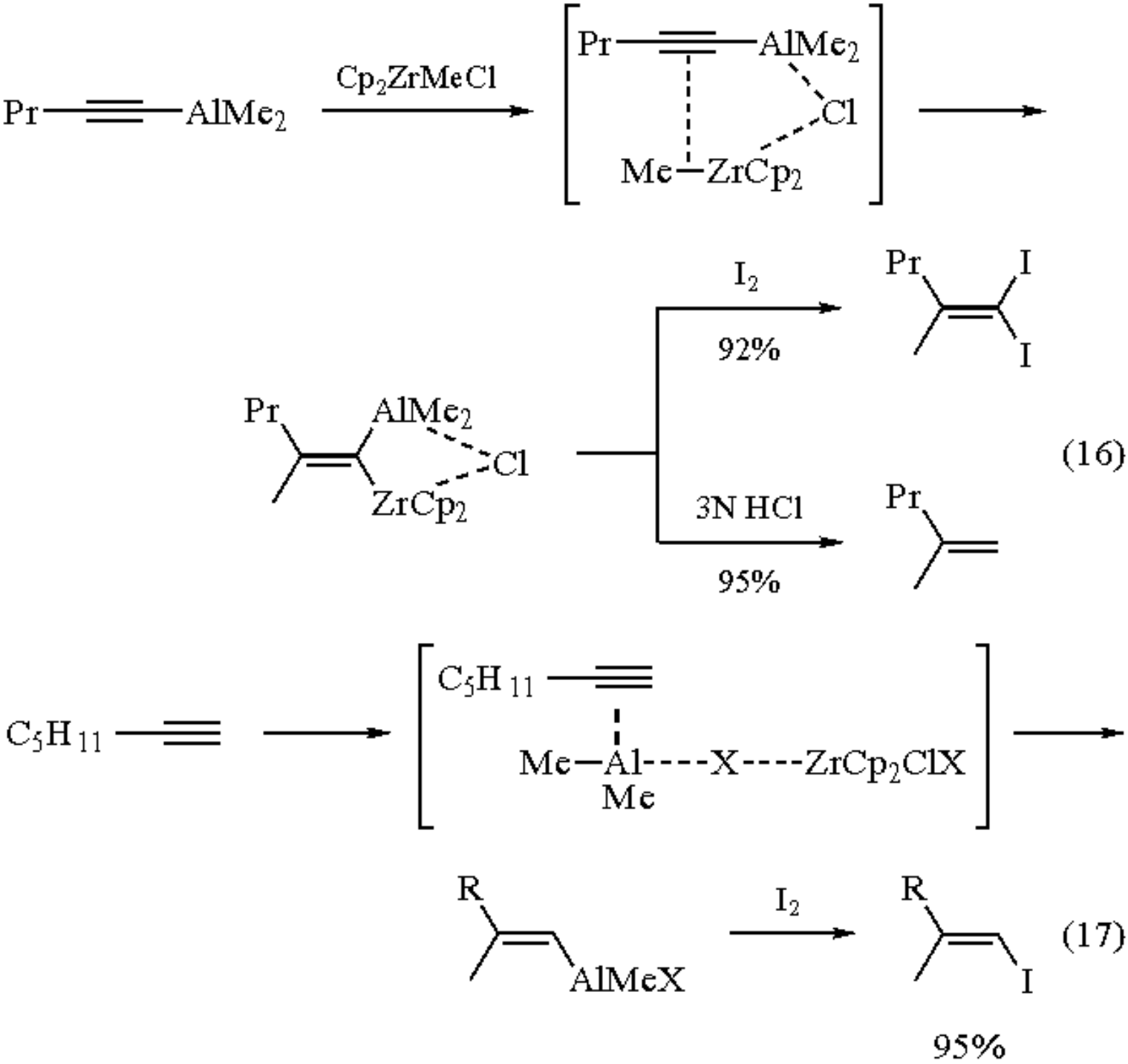

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Chlorobis(dimethylglyoximato)(pyridine)cobalt(III)[1]

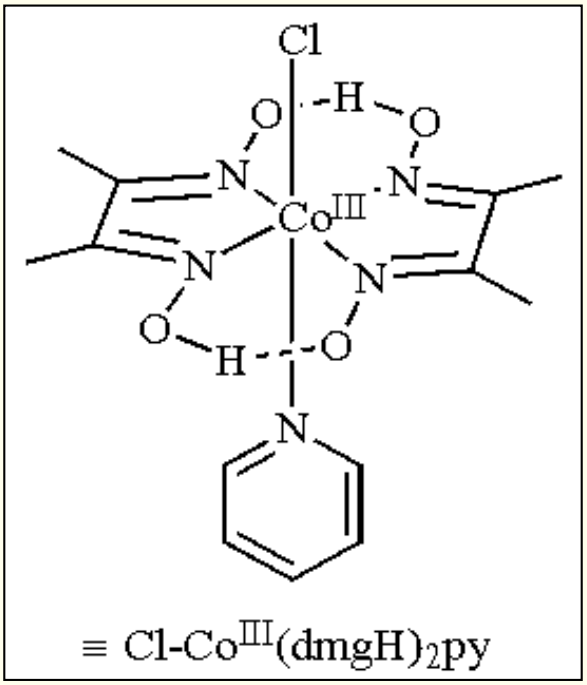

[23295-32-1] · $C_{13}H_{19}ClCoN_5O_4$ · Chlorobis(dimethylglyoximato)(pyridine)cobalt(III) · (MW 403.75)

(starting material for alkyl(pyridine)cobaloxime(III) complexes,[1] precursor for cobaloximes(II) and cobaloximes(I),[2] which have found widespread applications as catalysts for carbon-carbon,[3] carbon-oxygen,[4] carbon-nitrogen,[5] and carbon-hydrogen[6] bond formations)

Alternate Name: chloro(pyridine)cobaloxime(III).

Physical Data: mp 235 °C; polarographic half-wave potentials (acetonitrile solution, vs. $Ag/AgNO_3$ electrode): -0.65, -1.45, -2.42, -2.91 V.

Solubility: sol CH_2Cl_2; limited sol ethyl acetate, hot ethanol; sparingly sol most other organic solvents and water. Chloro(pyridine)cobaloxime(III) can be replaced without any change in reactivity by its 4-*t*-butylpyridine[7] derivative which has good solubility in toluene, carbon tetrachloride, alcohols and ethyl acetate.

Handling, Storage, and Precautions: forms brown, air stable crystals. The axial pyridine ligand can be removed by dilute acid extraction from ethyl acetate solutions of chloro(pyridine)cobaloxime(III). Due to their low solubility in common organic solvents, chloro(pyridine)cobaloxime(III) and -cobaloxime(II) (often the cobalt remainder in cobaloxime mediated transformations) are easily removed by adsorptive filtration of the reaction mixture on a short silica gel column. Acidic aqueous ethanol solutions of chloro(pyridine)cobaloxime(III) are photodecomposed when irradiated at wavelengths below 500 nm, yielding cobalt(II) salts, dimethylglyoxime, and pyridinium salts. For some applications the use of either iodo- or bromocobaloxime(III)[7] is advantageous, as activation of the halogen-carbon bond is essential for chlorocobaloxime(III) to be employed in organic synthesis. However, reduction potentials, bond strengths, and photostabilities increase on moving from the iodo to the chloro ligand,[8] so iodo(pyridine)cobaloxime(III) must be stored in tinted bottles.[9]

Inhalation of chlorocobaloxime(III) dust and contact with eyes should be avoided; wearing of protecting gloves for handling this compound is recommended. This compound should be handled in a fume hood.

Ligand Exchange Reactions.

Chlorocobaloxime(III) is a convenient source of the cobaloxime residue. It reacts with organomagnesium or -lithium compounds to yield the corresponding alkylcobaloximes(III).[1] This reaction is an efficient approach to arylcobaloximes which are otherwise difficult to obtain (eq 1).

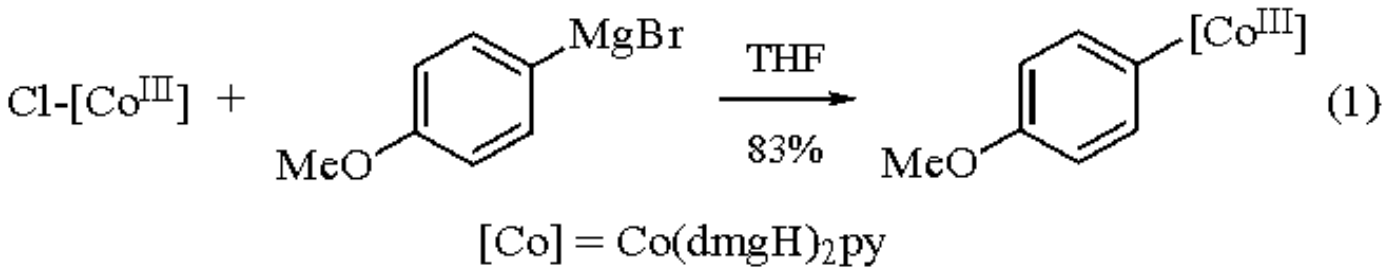

The chloro ligand can be substituted in the presence of metal ions (Ag^+, Hg^{2+}, Tl^{3+}) which form precipitating metal chlorides.[10] The entering ligand can be a solvent molecule that binds reversibly in a dynamic equilibrium, such as DMF, or an alkyl ligand that binds irreversibly. An example of the latter reaction is the formation of nitromethylcobaloxime which is formed from nitromethane, presumably via the nitronic acid (eq 2).

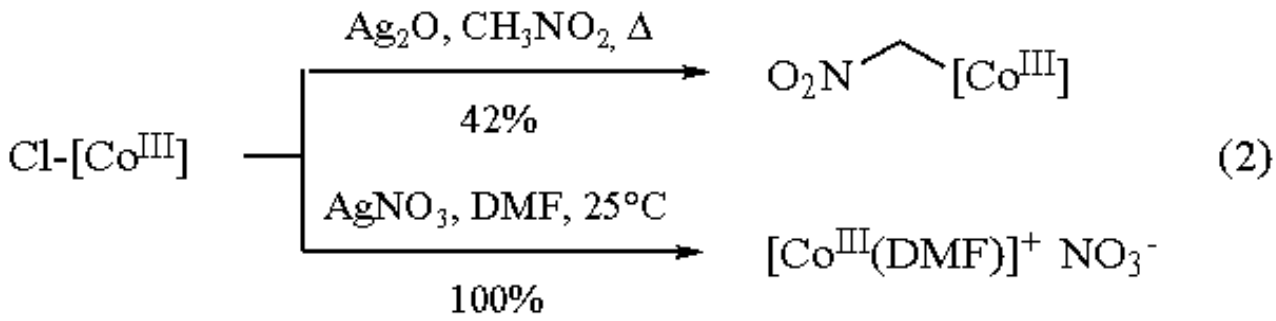

Upon reduction of chlorocobaloxime(III) by iron(II) salts,[11] ***Zinc*** in protic solvents,[12] ***Sodium Borohydride*** in alcohols,[1] ***Sodium Amalgam*** in THF, or on the surface of a cathode,[3a] the chloro ligand is removed from the complex and versatile catalytic properties of the cobaloxime moiety are unmasked. Hence immobilized derivatives of chlorocobaloxime(III) have been prepared by reaction of chloroaquacobaloxime with the copolymers of 4-vinylpyridine/styrene and 4-vinylpyridine/acrylamide (eq 3).[13]

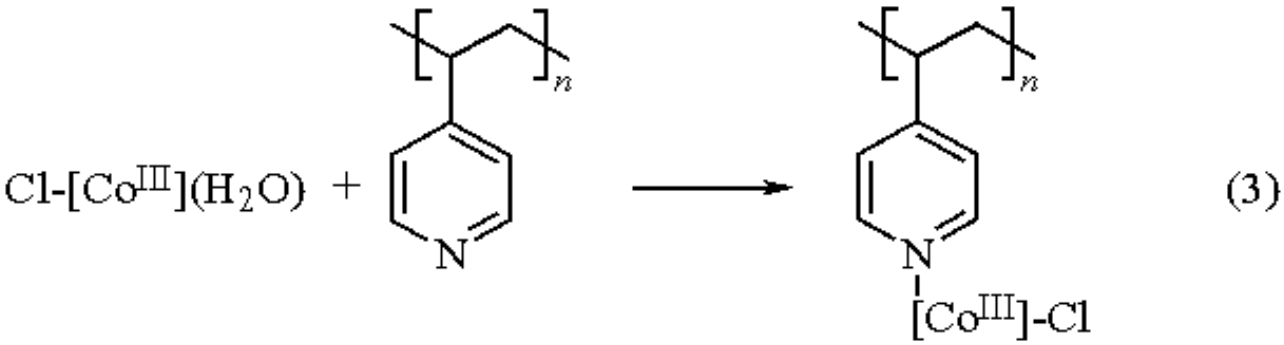

Carbon-Carbon Bond Formation.

In situ electrochemical reduction of chloro(pyridine)cobaloxime(III) to nucleophilic cobaloxime(I) allows carbon-carbon bond

formation. The example given in eq 4 illustrates this catalytic transformation for the conversion of a bromoacetal to hexahydrobenzofuran.[3] The key step of the reaction is a stereoselective cyclization of the intermediate alkoxyalkyl radical which is generated from an intermediate alkylcobaloxime. The alkene function which was present in the starting material is regenerated in the product via hydridocobaloxime elimination.

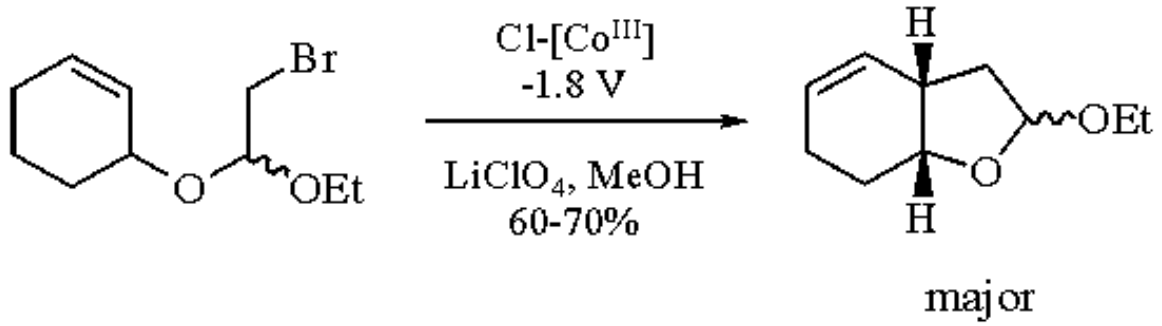

(4)

A combination of intramolecular 7-*endo* cyclization and intermolecular, cobaloxime-mediated, stereoselective alkyl-alkenyl cross coupling allows formation of the 5,7-fused bicyclic lactone from the linalool derivative in eq 5.

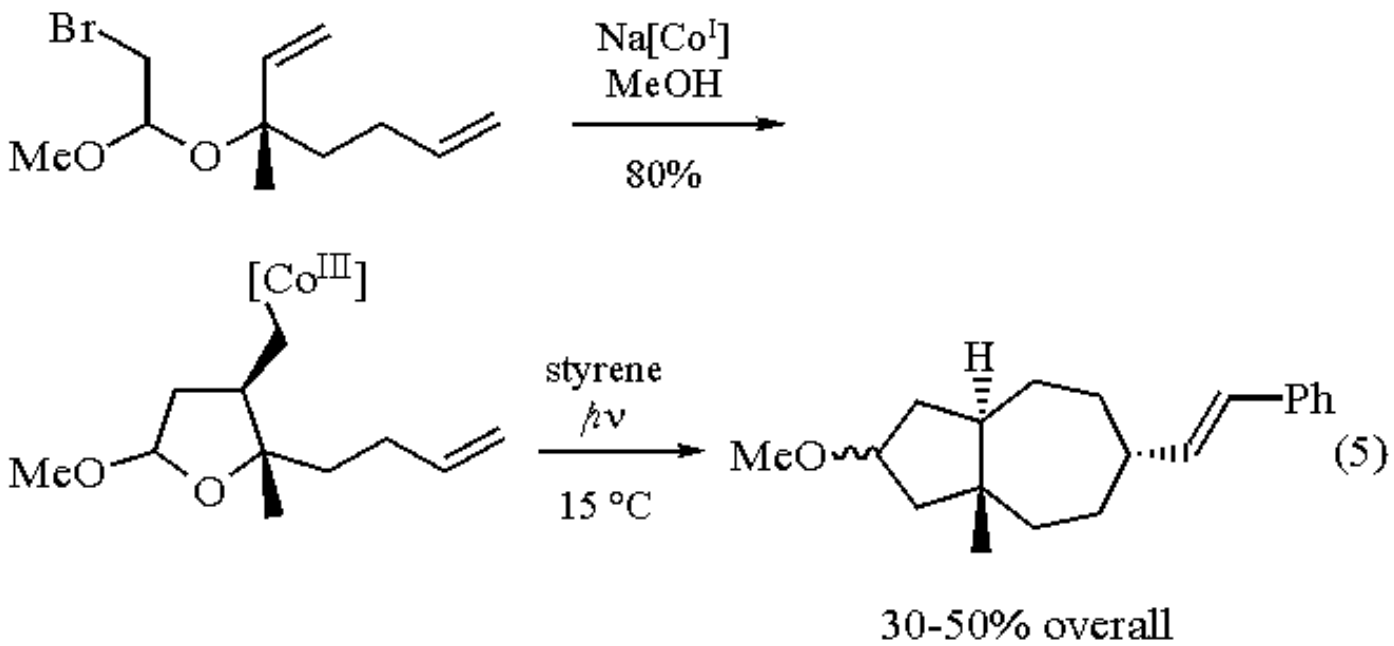

(5)

Alkyl-alkenyl cross coupling is a major area in alkylcobaloxime research.[3a,b] In contrast to the alternative carbon-carbon bond forming reactions via alkyl radicals under reductive conditions, application of the cobaloxime methodology allows the regeneration of the carbon-carbon double bond in the adduct. In particular photochemical alkyl-alkenyl cross couplings have been investigated under either stoichiometric or catalytic conditions. The stoichiometric reaction starts from an alkylcobaloxime(III) which is photolyzed in the presence of an alkene such as acrylonitrile or styrene. However, it should be noted that the solvent and the alkene used have a marked influence upon the yields and the product distribution of the reaction. The catalytic version requires in situ regeneration of cobaloxime(I). The adduct radical which is formed in the first step of the reaction can also be reduced to yield a carbanion which is then protonated. Aryl substituted alkenes are best suited for this transformation. Several usefully functionalized alkenes are simply reduced under these reaction conditions (eq 6).[3b] Application of this methodology to perfluoroiodides is straightforward and allows selective introduction of the perfluoroalkyl substituent, but bromocobaloxime(III) has been proven to be more efficient in this process than chlorocobaloxime (eq 7).[3c]

Chlorobis(dimethylglyoximato)(pyridine)cobalt(III)

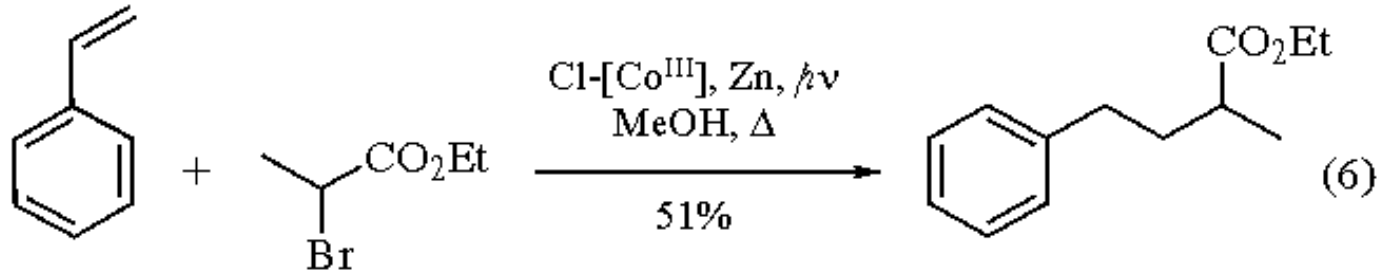

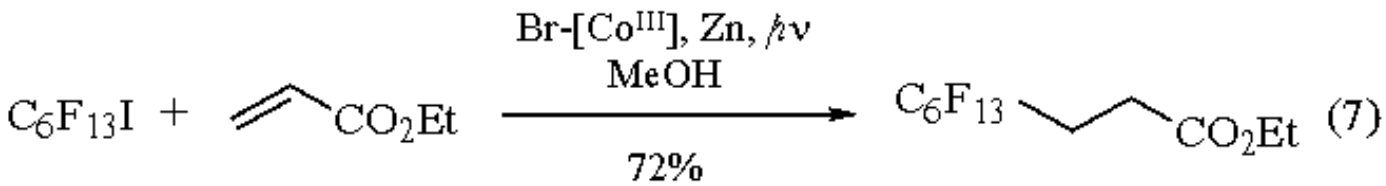

Carbon-Heteroatom Bond Formation.

Photolysis of solutions of alkylcobaloxime(III) in the presence of O_2 or NO yields alkylperoxycobaloximes(III) or oximes.[15,16] The former can then be transformed into products such as alcohols or substituted tetrahydrofurans, the latter then into amino sugars.[17] Catalytic versions of these processes require ***Sodium Borohydride*** as reducing agent. The scope of these reactions is still limited to aryl substituted alkenes (eqs 8-10).[4,5]

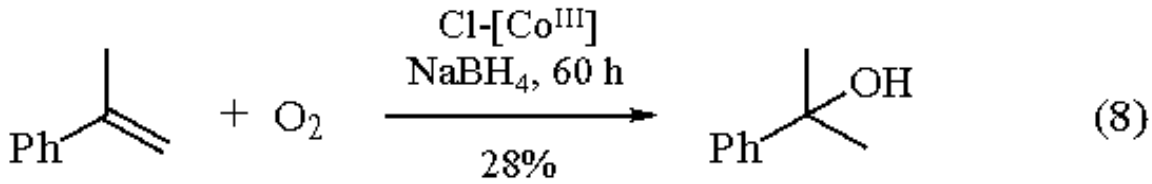

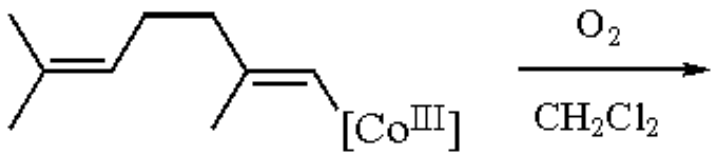

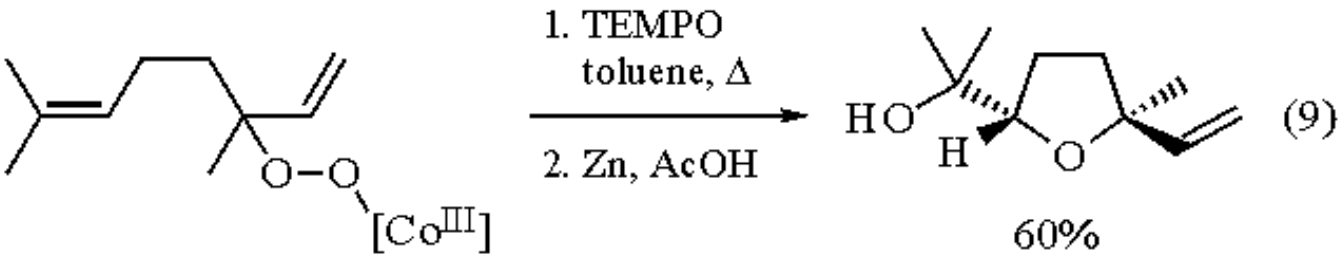

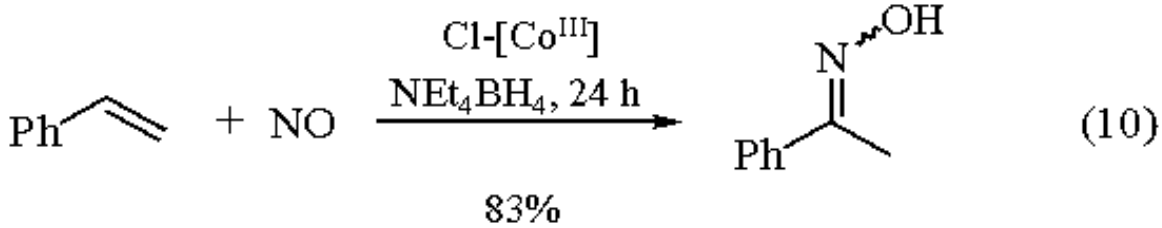

Carbon-Hydrogen Bond Formation.

Sodium borohydride reduction of chlorocobaloxime(III) under a hydrogen atmosphere leads to an efficient homogeneous hydrogenation catalyst which selectively reduces carbon-carbon bonds of substituted pyridines or acrylates.[6] Reduction of pyridinium salts to dihydropyridines requires the presence of a base such as ***Sodium Carbonate***, whereas sodium bicarbonate leads to significant amounts of tetrahydropyridines (eq 11).

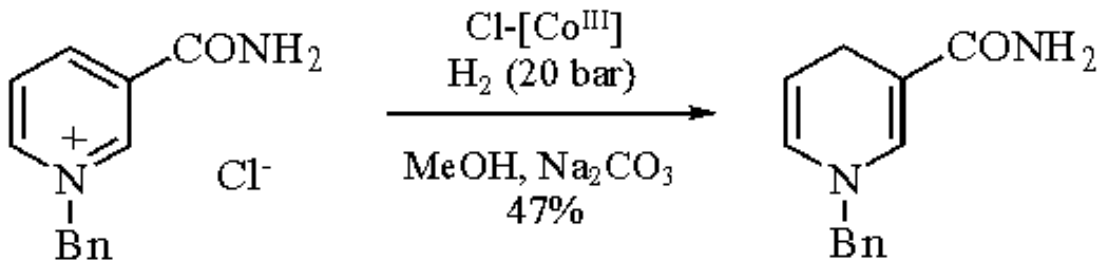

(11)

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4-Chloro-2-butanone

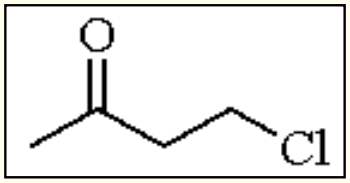

[6322-49-2] · C_4H_7ClO · 4-Chloro-2-butanone · (MW 106.55)

(reagent for Robinson annulation; often interchangeable with methyl vinyl ketone and the corresponding Mannich base 4-dialkylamino-2-butanone)

Alternate Names: 2-chloroethyl methyl ketone; 1-chloro-3-butanone.

Physical Data: bp 105-110 °C.

Solubility: sol most organic solvents.

Analysis of Reagent Purity: ^{1}H NMR data are available.[1]

Form Supplied in: liquid; commercially available.

Purification: by distillation.

Handling, Storage, and Precautions: use in a fume hood.

Annulation.

4-Chloro-2-butanone is one of three reagents commonly used for unsubstituted ring formation in the Robinson annulation. The other reagents are 3-buten-2-one (***Methyl Vinyl Ketone***, MVK) and the quarternary salt of the Mannich base 4-dimethylamino-2-butanone (or 4-diethylamino-2-butanone). The choice of reagent for the best yield from a specific substrate has to be determined empirically. MVK is the most difficult to handle because it can polymerize during preparation or annulation. Nevertheless, MVK has been widely used.[2]

One of the first annulations[3] with 4-chloro-2-butanone gave the product in a 70% yield, whereas only 12% was obtained from the corresponding Mannich base (eq 1). The acid-catalyzed annulation, first developed with 1-chloro-3-pentanone,[4,5] has been used with 4-chloro-2-butanone[6] to afford a much better yield (eq 2) than was obtained with MVK (12-34%).

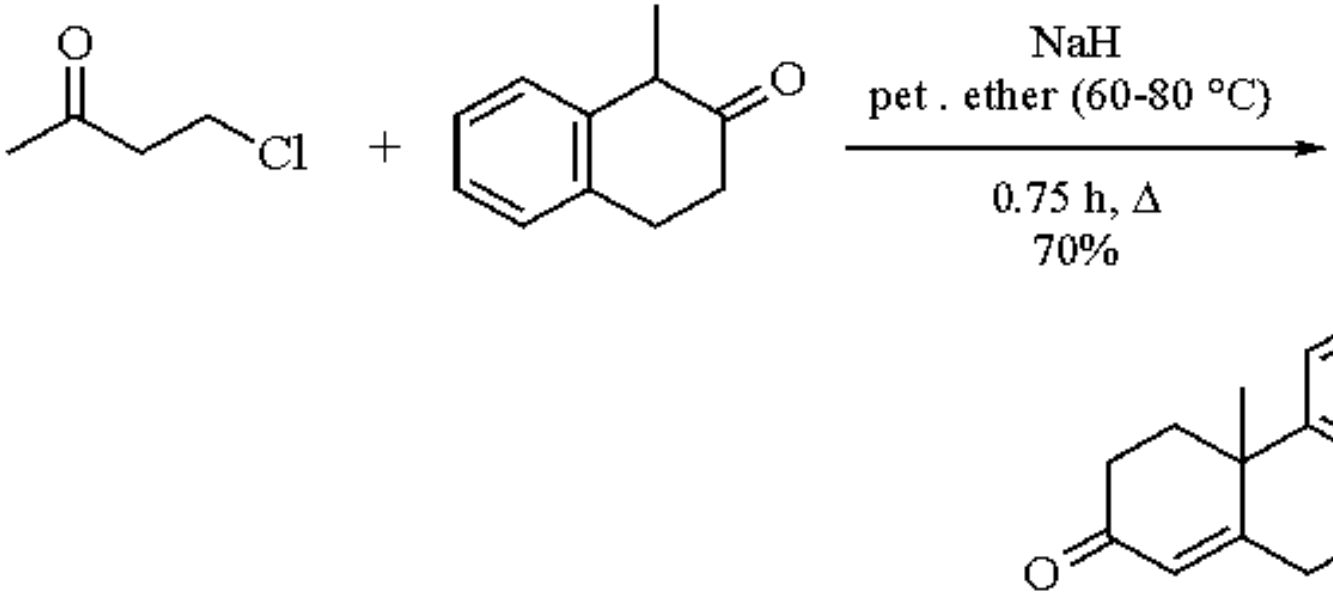

(1)

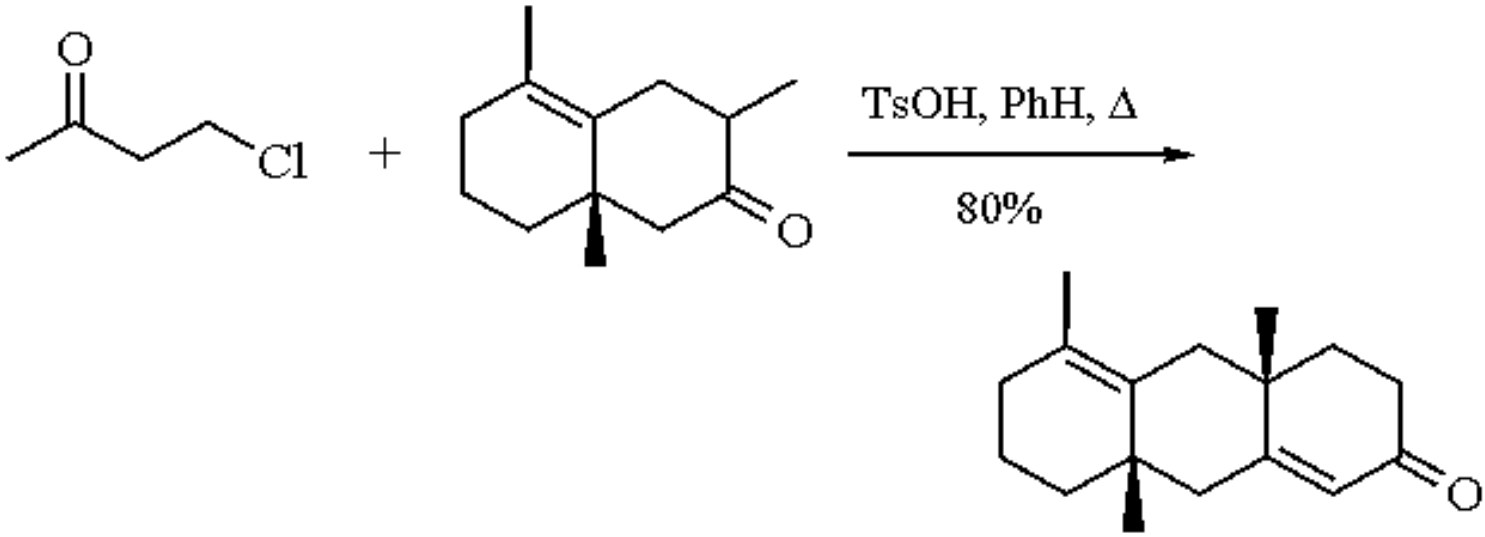

(2)

Annulation by Dialkylation.

The dimethylhydrazone of a cyclic 1,3-dione reacts regioselectively to give the dialkylated hydrazone, which can then be cyclized sequentially to the bicyclic and the tricyclic ketones (eq 3).[7] The reaction works equally well for 1,3-cyclohexanedione and 1,3-cyclopentanedione.

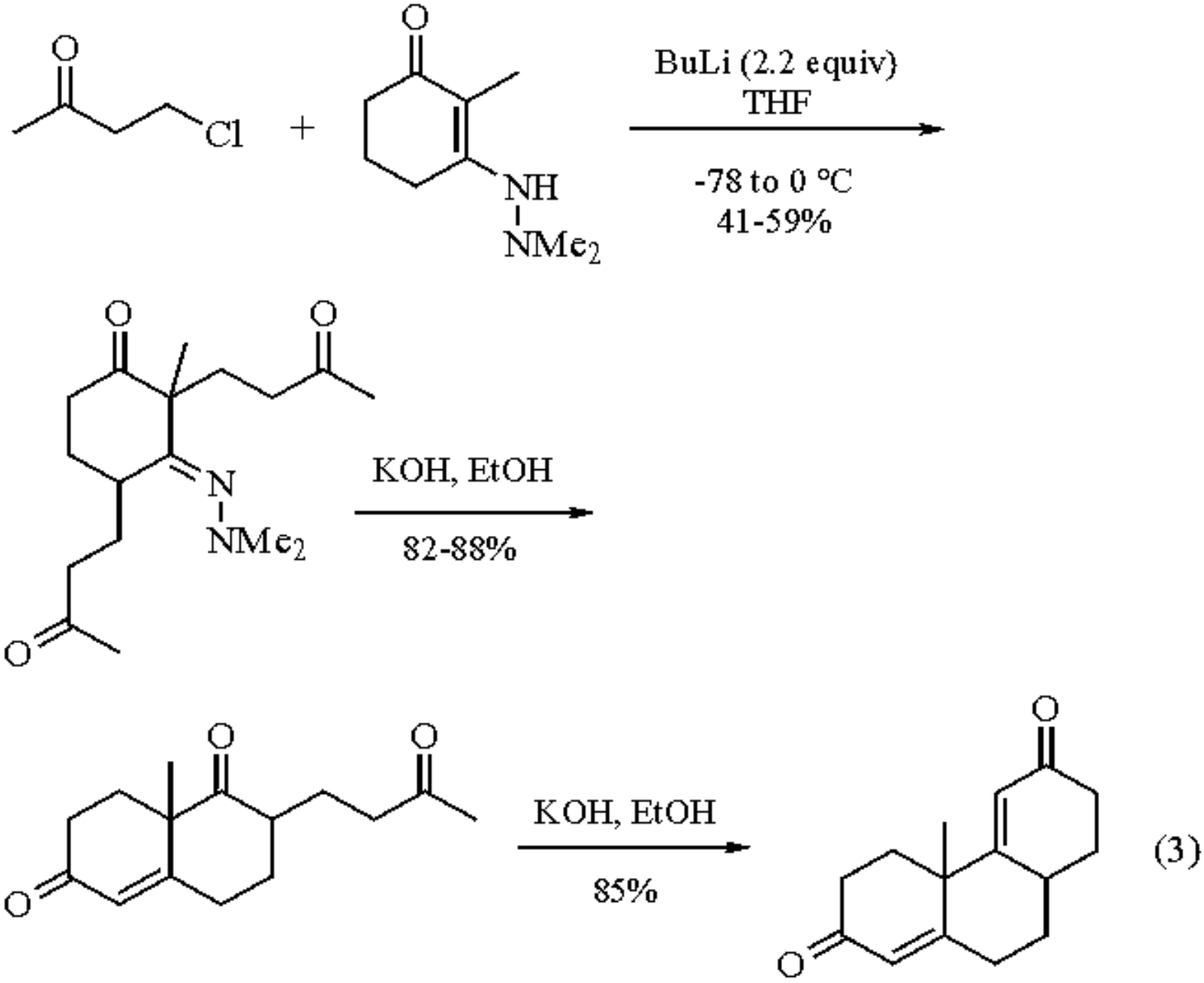

Stannylation.

The reagent reacts with ***Tin(II) Chloride*** to form the β-trichlorostannyl ketone, which can also be prepared (slightly faster) from $HSnCl_3$ and MVK as well as other vinyl ketones. The intermediate trichloro compounds can be converted to the tributylstannyl ketones (eq 4).[8]

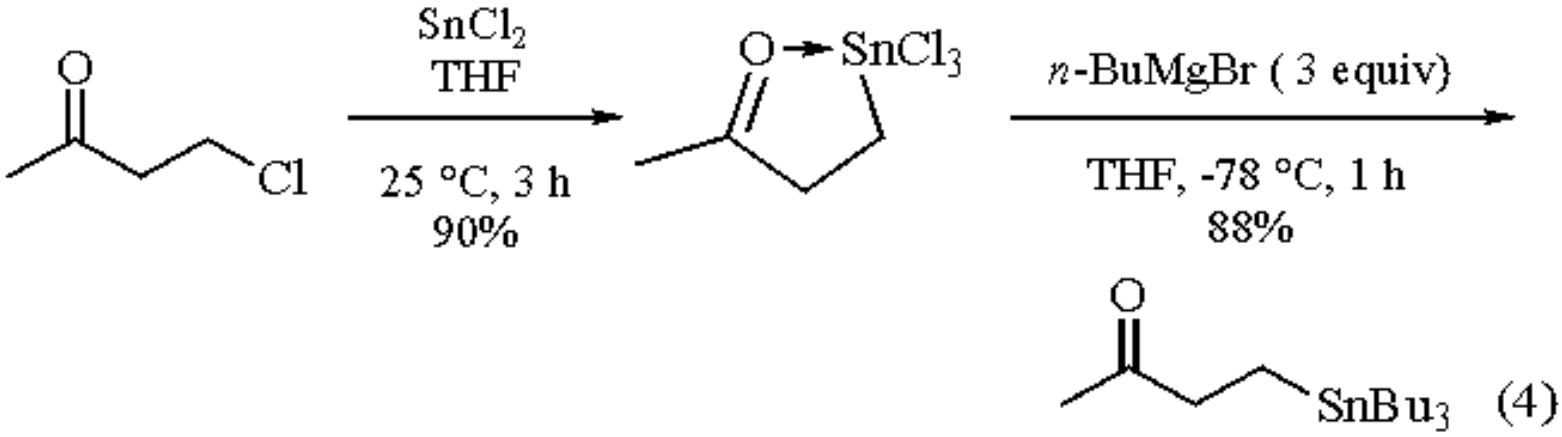

Alkynylsilane Functionalization.

Organometallic derivatives of propargylic silanes react with the reagent, as well as other α- or o-chlorocarbonyl compounds, to form homopropargylic alcohols (with the Zn reagent, eq 5)[9] or allenic alcohols (with the Al reagent, eq 6).[10] The products are used to form oxygenated heterocycles.[11]

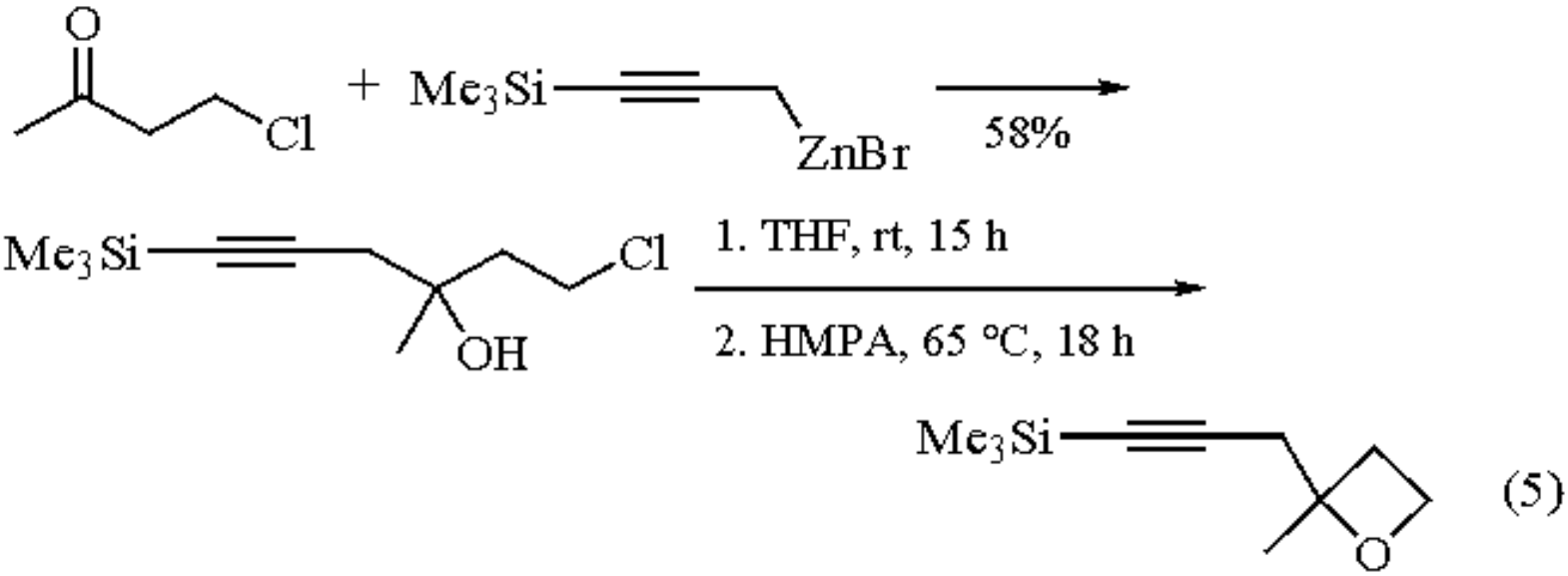

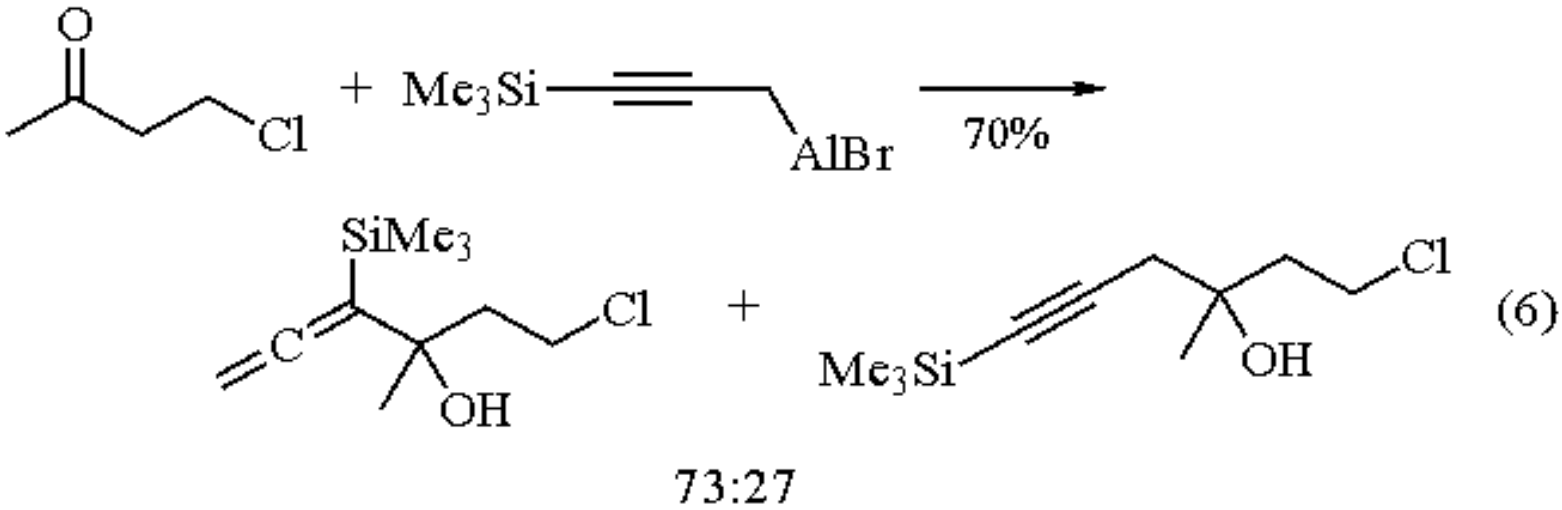

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Girts Kaugars

The Upjohn Company, Kalamazoo, MI, USA

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3-Chloro-1-butene

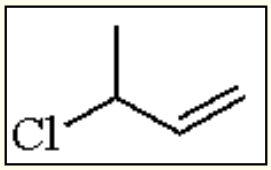

[563-52-0] · C_4H_7Cl · 3-Chloro-1-butene · (MW 90.55)

(alkylating agent[15,22] and organometallic precursor useful for introduction of 2-buten-1-yl (crotyl) and 1-buten-3-yl moieties)

Physical Data: bp 63.9-64.2 °C; *d* 0.900 g cm^{-3}; n_D^{20} 1.4155.

Solubility: insol water; sol all organic solvents.

Form Supplied in: colorless liquid.

Preparative Methods: from 1-buten-3-ol using PCl_3/py,[1] $SOCl_2$/HMPA,[2] Ph_3P/CCl_4,[3] Ph_3P/CCl_3COCCl_3,[4] $Me_2CC(Cl)NMe_2$,[5] or $PO(OPh)_2Cl$/LiCl;[6] from 2-buten-1-ol using $SOCl_2/FeCl_3$.[7]

Purification: by distillation.

Handling, Storage, and Precautions: stable at 0 °C in quartz;[8] flammable liquid and lachrymator.[9] Use in a fume hood.

Introduction.

This summary of 3-chloro-1-butene (**1**) chemistry focuses on the racemic reagent, although the (+)[1] and (-)[10] forms are known. 3-Chloro-1-butene is relatively stable at ambient temperature. However, it exists in equilibrium (eq 1)[11] with 1-chloro-2-butene (K_{eq} = 2.32; PhMe, 80 °C);[8] catalysis by UV light,[12] glass surfaces,[8] and by Ir, Rh, and Co coordination complexes[13] has been observed. Care must be taken that reactions with (**1**) are not complicated by the isomerization product. The thermolysis chemistry of (**1**) has been studied.[14]

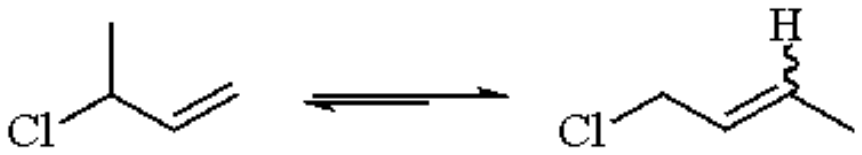

(1) (1)

The reactions of (**1**) in protic, dipolar aprotic, and nonpolar solvents in the presence and absence of nucleophiles (S_N1, S_N2, S_N2', E1, E2, and S_Ni) have been studied extensively and reviewed.[15] Friedel-Crafts alkylation of alkenes has also been studied.[16] Primarily, (**1**) has been used for electrophilic and nucleophilic introduction of 2-buten-1-yl (crotyl) and 1-buten-3-yl groups in organic synthesis. These reactions for (**1**) and other allylic compounds have been reviewed.[17]

Electrophilic Reactions.

3-Chloro-1-butene acts as an ambident electrophile at both α (S_N2) and γ (S_N2') positions in chloride displacement reactions. In early work, exclusive S_N2 reaction was reported with various nucleophiles (NaOEt/EtOH, KOAryl/Me_2CO, NaS-*n*-Bu/EtOH, $Me_4N^+OAc^-/Me_2CO$, and Kphthalimide/MeOH).[15] In later studies of the regioselectivity effects of counterion and solvent (EtO^-, PhS^-, and $(CO_2Et)_2CH^-$),[18] only modest changes were observed, all reactions strongly favoring the S_N2 pathway (83-95%). In contrast, the S_N2' reaction is a significant or dominant pathway with Et_2NH (100%),[19] Me_3N (70%),[20] and fluorenyl anions (30-100%).[21] In addition, the S_N2' reaction is strongly favored with many organometallic reagents, as is illustrated by the examples given in Table 1.

Table 1 Effects of Nucleophile and Solvent on the a:g Regioselectivity of Alkylations with 3-Chloro-1-butene

Reagent	Solvent	a:g Ratio
$4\text{-}MeOC_6H_4MgBr$[22]	Et_2O	14:86
n-BuMgCl[23]	THF	21:79
PhLi[24]	Et_2O	1:99
n-BuLi[23]	Et_2O	2:98
$LiCH_2C(NNMe_2)CO_2Li$[25]	THF HMPA	20:80
$Zn(CH_2CO_2\text{-}t\text{-}Bu)_2$[26]	THF	0:100
PhCu[23]	Et_2O	6:94
n-BuCu[23]	Et_2O	10:90
Ph_2CuLi[23]	Et_2O	19:81
$n\text{-}Bu_2CuLi$[23]	Et_2O	22:78
$n\text{-}BuCuBF_3$[23]	THF	0:100
$NC(CH_2)_3CuCNZnI$[27]	THF	4:96

Other chloride substitution reactions of (**1**) include the π-allyl complex reactions of Pd, Ni, and other transition metals. The $PdCl_2$ promoted reaction of (**1**) with NaOAc to give a 35:65 α:γ ratio of butenyl acetates is representative.[28] Additional

examples of palladium π-allyl complex reactions of (**1**) are 2,5-enyne (eq 2)[29] and 1,4-diene (eq 3)[30] syntheses. Both proceed with exclusive γ-substitution. Interestingly, it has been found in amination studies of the palladium π-allyl complex of (**1**) with Me_2NH that regioselectivity can be controlled by the charge on the complex.[31] Thus while γ-substitution is the normal product (α:γ = 10:90; 100%), α-substitution is dominant (α:γ = 71:22; 93%) if the reaction proceeds via a cationic complex generated by $AgBF_4$ precipitation of chloride.

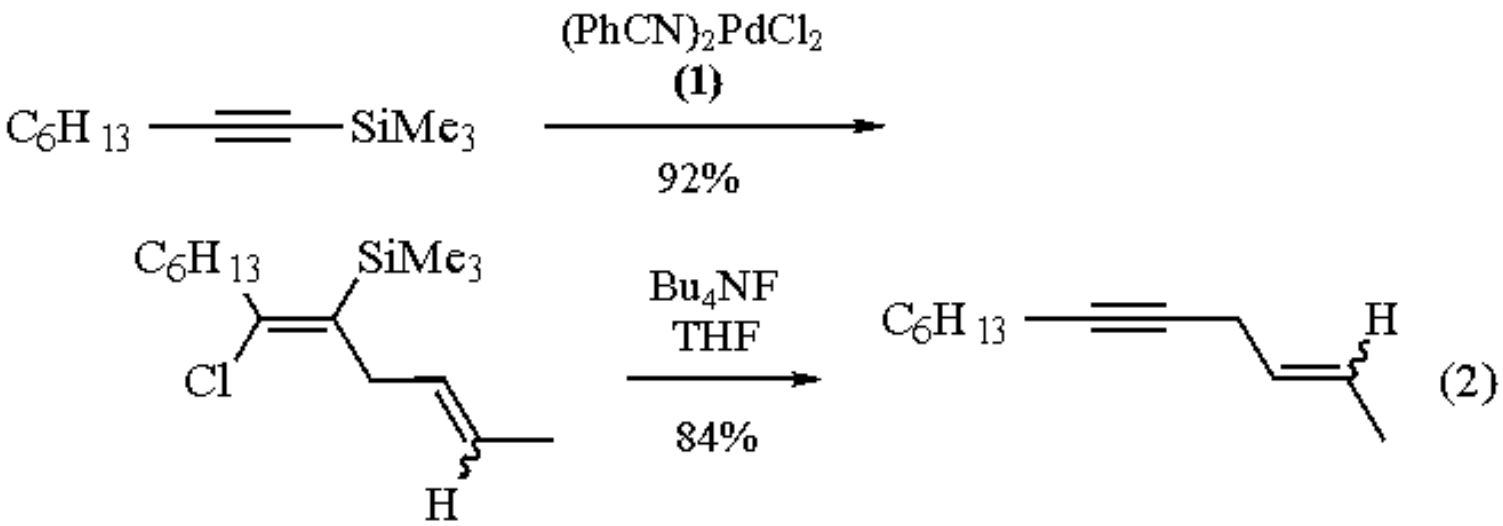

(2)

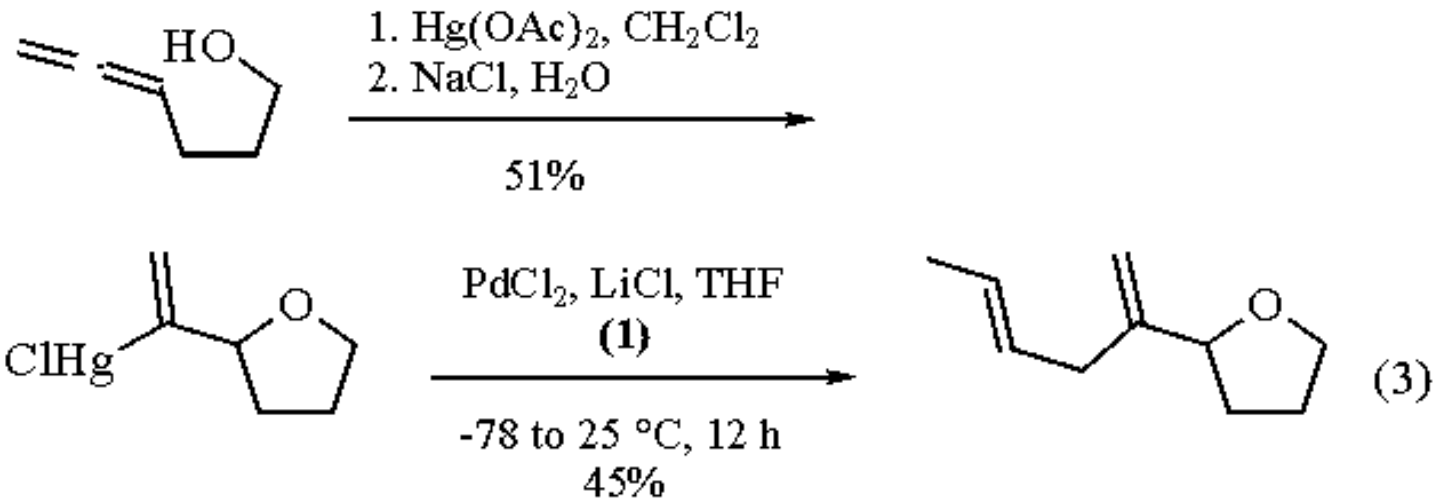

(3)

π-Allyl complex reactions of (**1**) with other metals are known. The nickel π-allyl complex-mediated carbonylative cycloaddition with alkynes is representative (eq 4).[32]

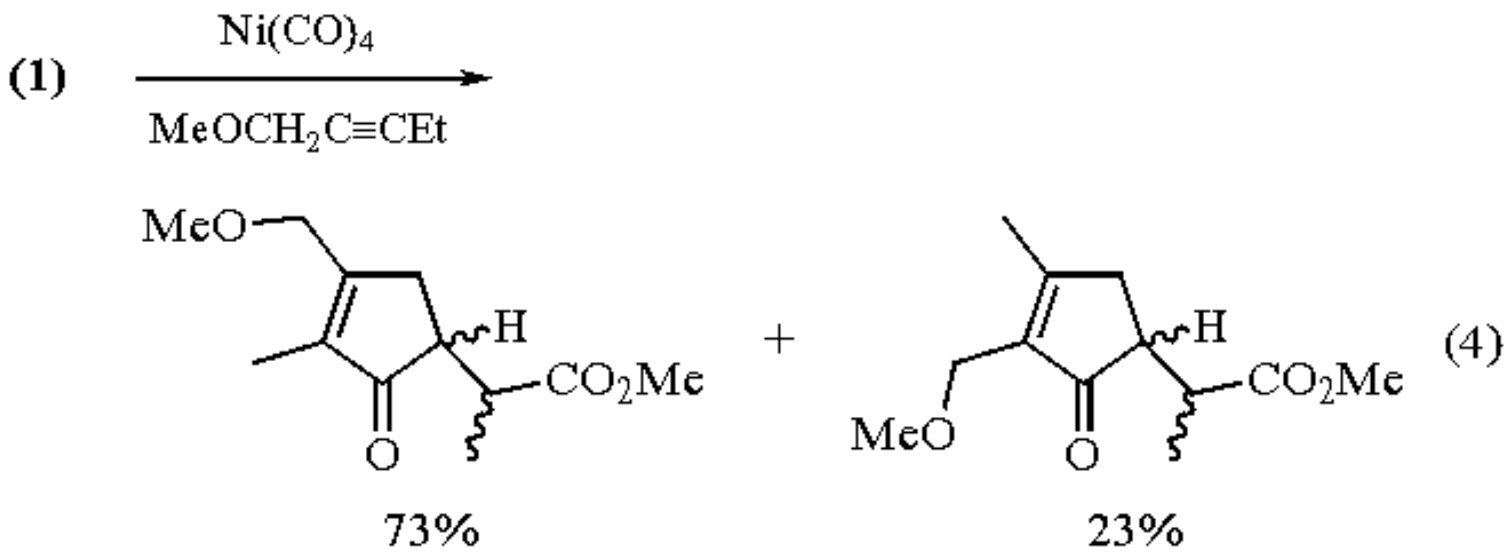

Nucleophilic Reactions.

A variety of organometallic reagents have been prepared from (**1**). These reagents undergo nucleophilic reactions with electrophiles at both α- and γ-positions. The chemistry of allylic organometallic reagents, including those derived from (**1**), has recently been reviewed.[33] The α:γ regioselectivity can be controlled during electrolytic coupling of (**1**) with acetone by choice of cathode (α:γ = 90:10 to 29:71).[34]

The reaction of 1-buten-3-ylmagnesium chloride with nitro compounds is representative of a general synthesis of secondary hydroxylamines.[35] Exclusive reaction at the secondary center of (**1**) is observed. On the other hand, reaction of the same reagent with $(ClCH_2)Me_2SiCl$ yields nearly equal amounts of α- and γ-products (eq 5).[36] Methoxide-induced rearrangement provides the homologation products in the same ratio.

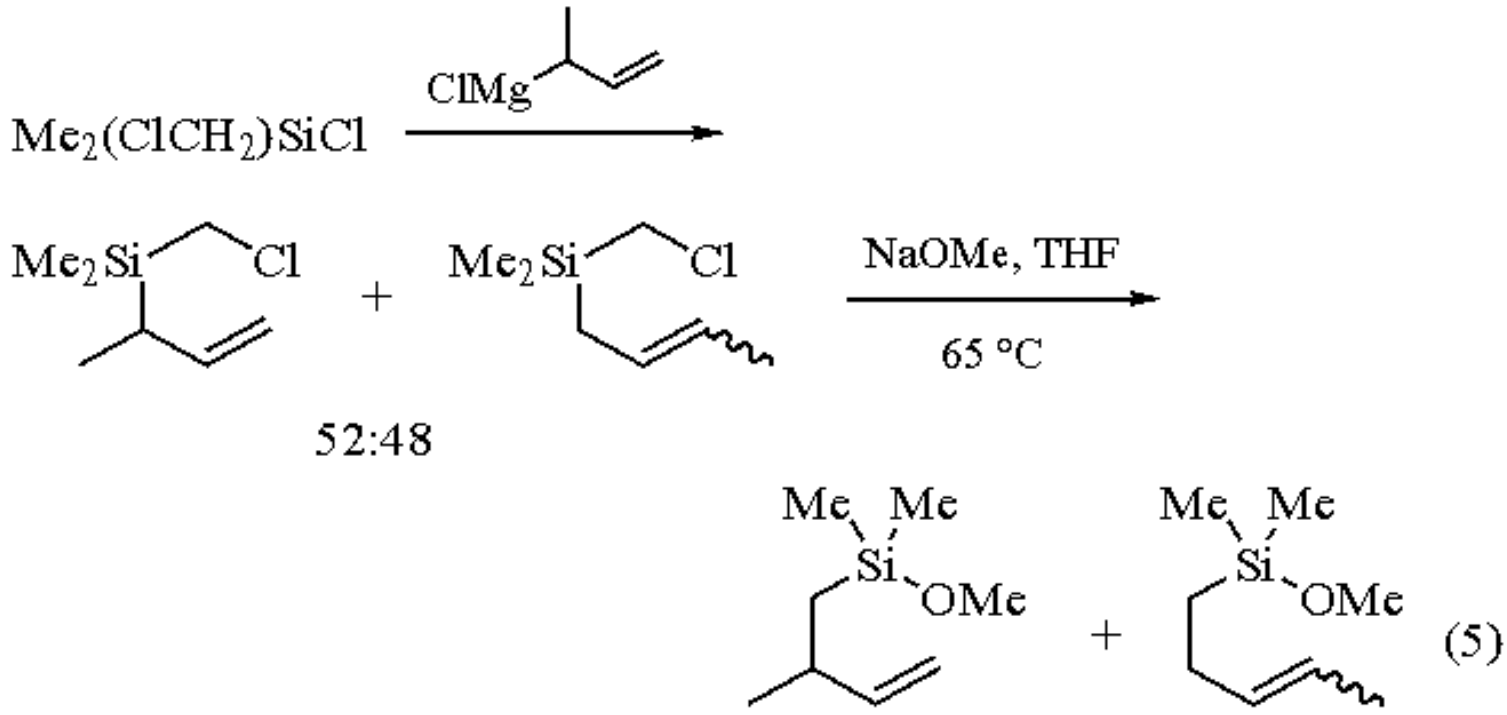

A mixed butenyl/butyl cuprate reagent is obtained on reaction of ***Lithium Di-n-butylcuprate*** with (**1**). This reagent

undergoes exclusive γ-butenyl transfer to a vinyl phosphate (eq 6).[37] In contrast, an organocopper reagent derived from (**1**) and Cu^0 gives exclusive α-coupling with PhCHO and PhCOCl (eq 7).[38] Similarly, organozinc compounds generated from (**1**) undergo exclusive α-coupling with aldehydes[39] and aldimines.[40] Interestingly, the aldehyde reaction was conducted in a two-phase aqueous/C-18 silica system, avoiding the need for an organic solvent.

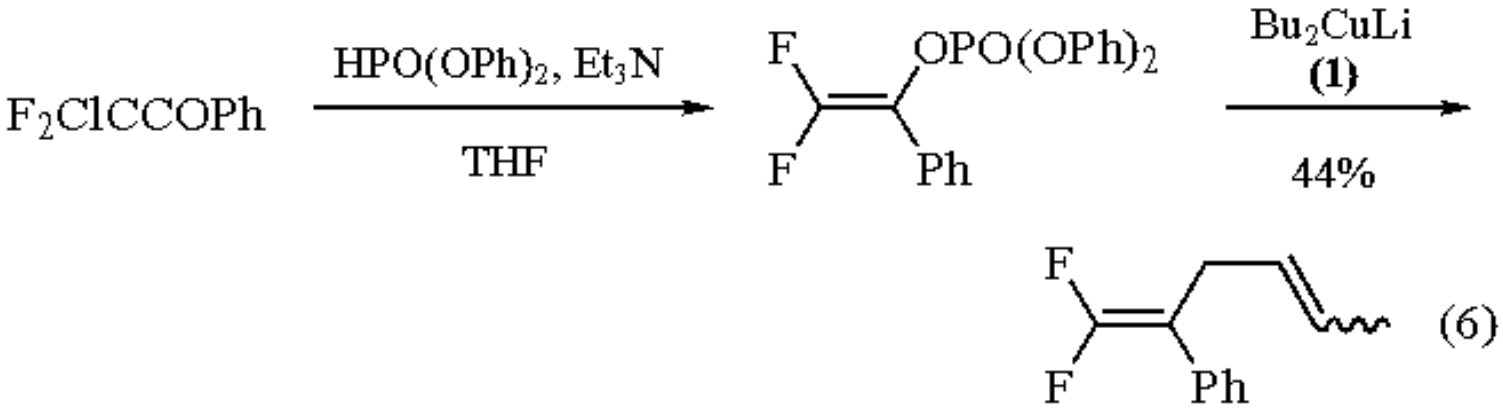

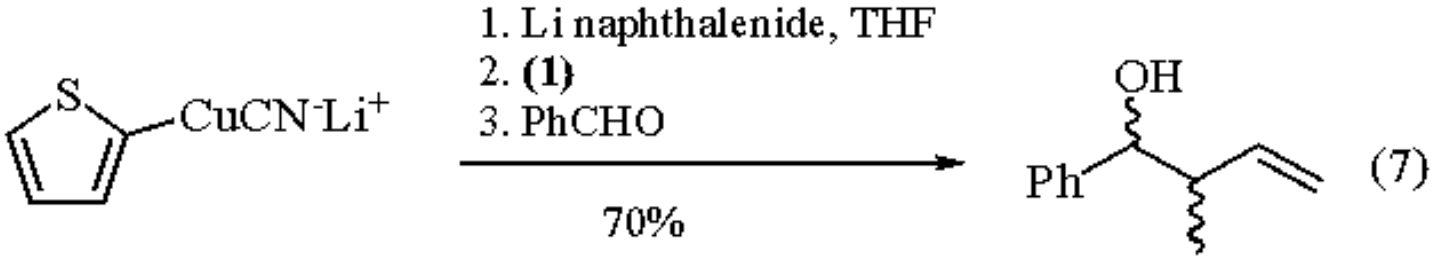

Related Reagents.

Allyl Chloride; ***Crotyl Chloride***; ***Methallyl Chloride***.

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(*E*)-4-Chloro-3-buten-2-one[1]

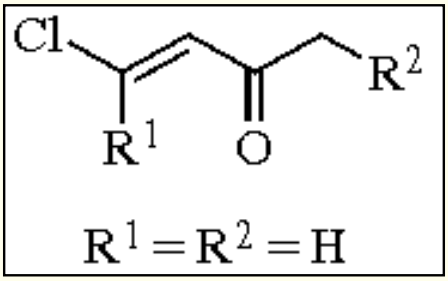

(**1**; $R^1 = R^2 = H$)

[7119-27-9] · C_4H_5ClO · (*E*)-4-Chloro-3-buten-2-one · (MW 104.52) (**2**; R^1 = Me, R^2 = H)

[57982-323-8] · C_5H_7ClO · (*E*)-1-Chloro-1-penten-3-one · (MW 118.56) (**3**; R^1 = H, R^2 = Me)

[105-32-8] · C_5H_7ClO · (*E*)-4-Chloro-3-penten-2-one · (MW 118.56)

(ketovinylation reagent which reacts with a variety of nucleophiles; used as a methyl vinyl ketone equivalent under aprotic conditions; precursor to dienol borinates)

Alternate Name: 2-chlorovinyl methyl ketone.

Physical Data: (**1**) bp 21 °C/21 mmHg; *d* 1.130 g cm^{-3};[2a] (**2**) bp 38-40 °C/11 mmHg; (**3**) bp 43-45 °C/14 mmHg; *d* 1.076 g cm^{-3}.

Solubility: insol water; sol most organic solvents.

Preparative Method: from acetylene and acetyl chloride catalyzed by aluminum chloride.[2]

Purification: distillation in vacuo.

Handling, Storage, and Precautions: the chloro enone is lachrymatory and corrosive to the skin. Therefore handling with gloves in a fume hood is essential. The compound has limited stability at room temperature and should be stored under nitrogen at 4 °C or lower; it solidifies at ca. 5 °C. Under these conditions, darkening and HCl loss is minimized, enabling the chloro enone to be stored for several weeks.

Ketovinylation of Carbonyl Compounds.

(*E*)-4-Chloro-3-buten-2-one (**1**) is a vinylogous acyl chloride and as such is highly reactive towards nucleophiles. Reaction with the enolates of substituted malonic esters, β-keto esters, and 1,3-diketones leads to highly functionalized products which may be utilized in a variety of synthetic schemes.[1a] For example, the enolates of substituted β-keto esters undergo conjugate addition to the chloro enone followed by loss of chloride ion to give ketovinyl substituted keto esters. Treatment of these products with ***Hydrochloric Acid*** in acetic acid with heating affords substituted α-pyrones (eq 1).[1a,3]

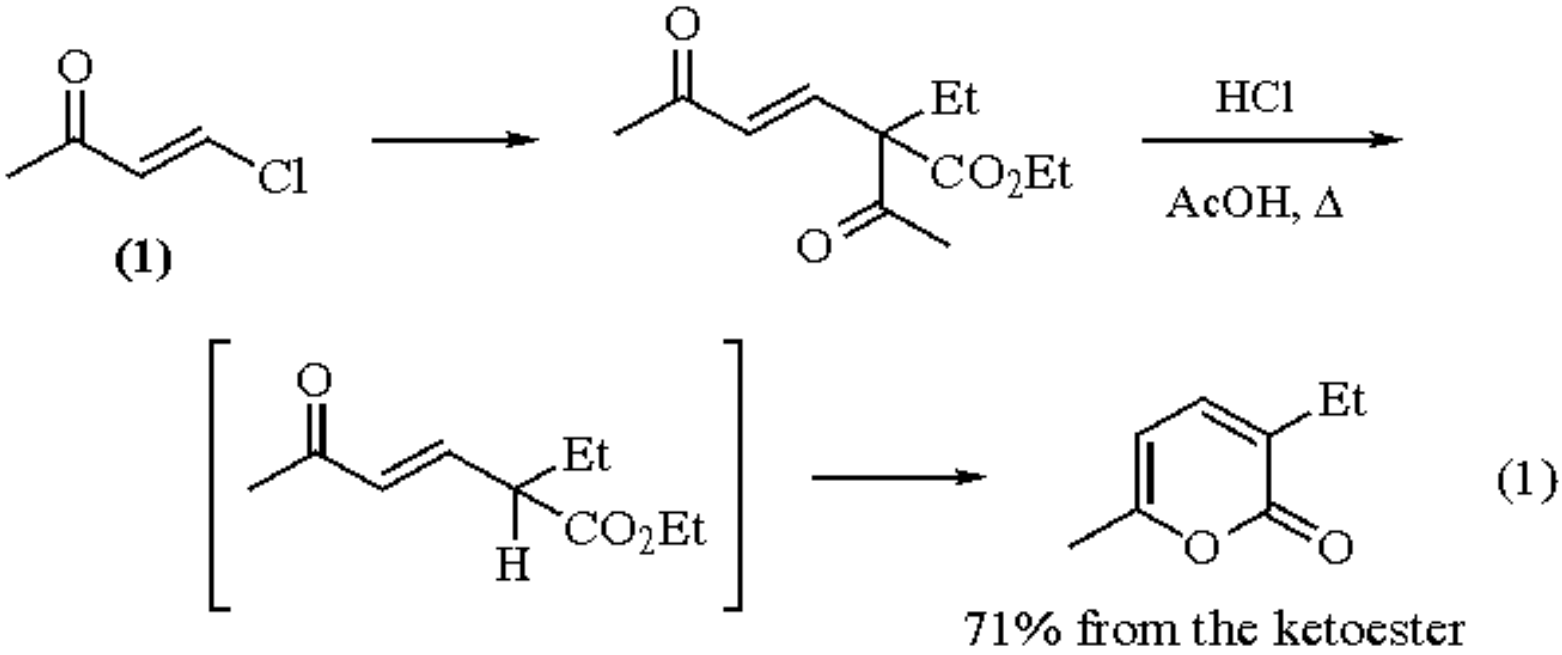

The ketovinylation of enolates derived from cyclic ketones[4] provides an alternative to the use of methyl vinyl ketone as an entry to 1,4-diketones required for the Robinson annulation.[5] For example, (**1**) efficiently traps the enolate derived from the conjugate addition of lithiated (*E*)-butenyl(*t*-butyl)phenyl phosphine oxide to 2-methylcyclopentenone. Hydrogenation of the double bonds followed by aldol cyclization affords hydrindenone precursors to vitamin D in 56% overall yield and with high diastereoselectivity (eq 2).[5b]

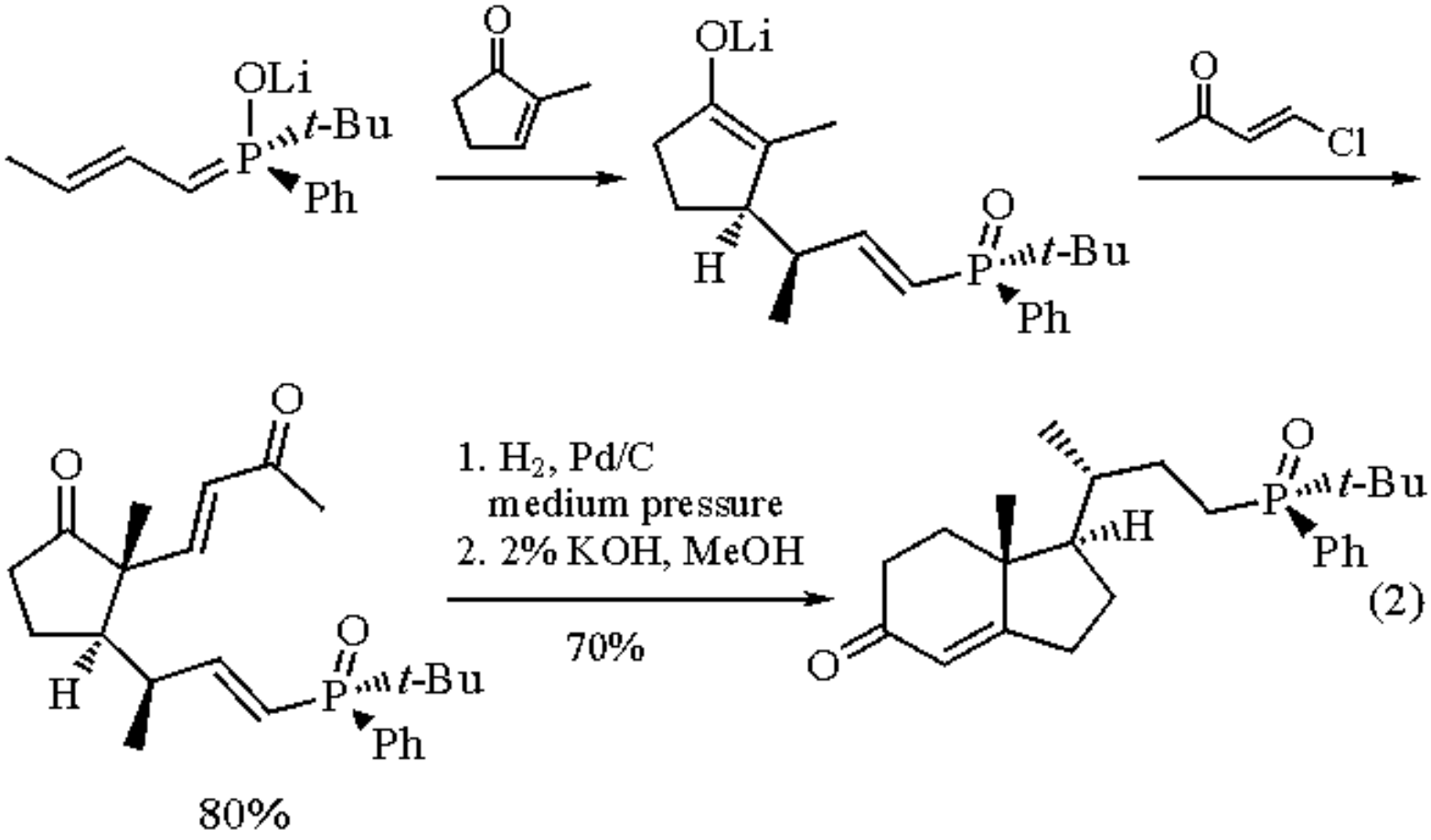

Substitution with Hetero Nucleophiles.

Chloride may be replaced by SR,[1c] NR_2, OR, $C_5H_5N^+Cl^-$,[4] and RNH in a conjugate addition-elimination.[6] In particular, (**1**) has been utilized extensively in synthetic approaches to the indole alkaloids in which the key step is vinylic substitution by tryptamine (eq 3).[6] The coupling of substituted homoallylic amines to 4-chlorobutenone followed by intramolecular photocycloaddition affords fused cyclobutanes, which undergo retro-Mannich fragmentation to ketoimines followed by Mannich ring closure to give perhydroindoles in good yields.[6b] By using this methodology, synthetic routes to mesembrine[6b] and vindorosine[6d] have been achieved.

(E)-4-Chloro-3-buten-2-one

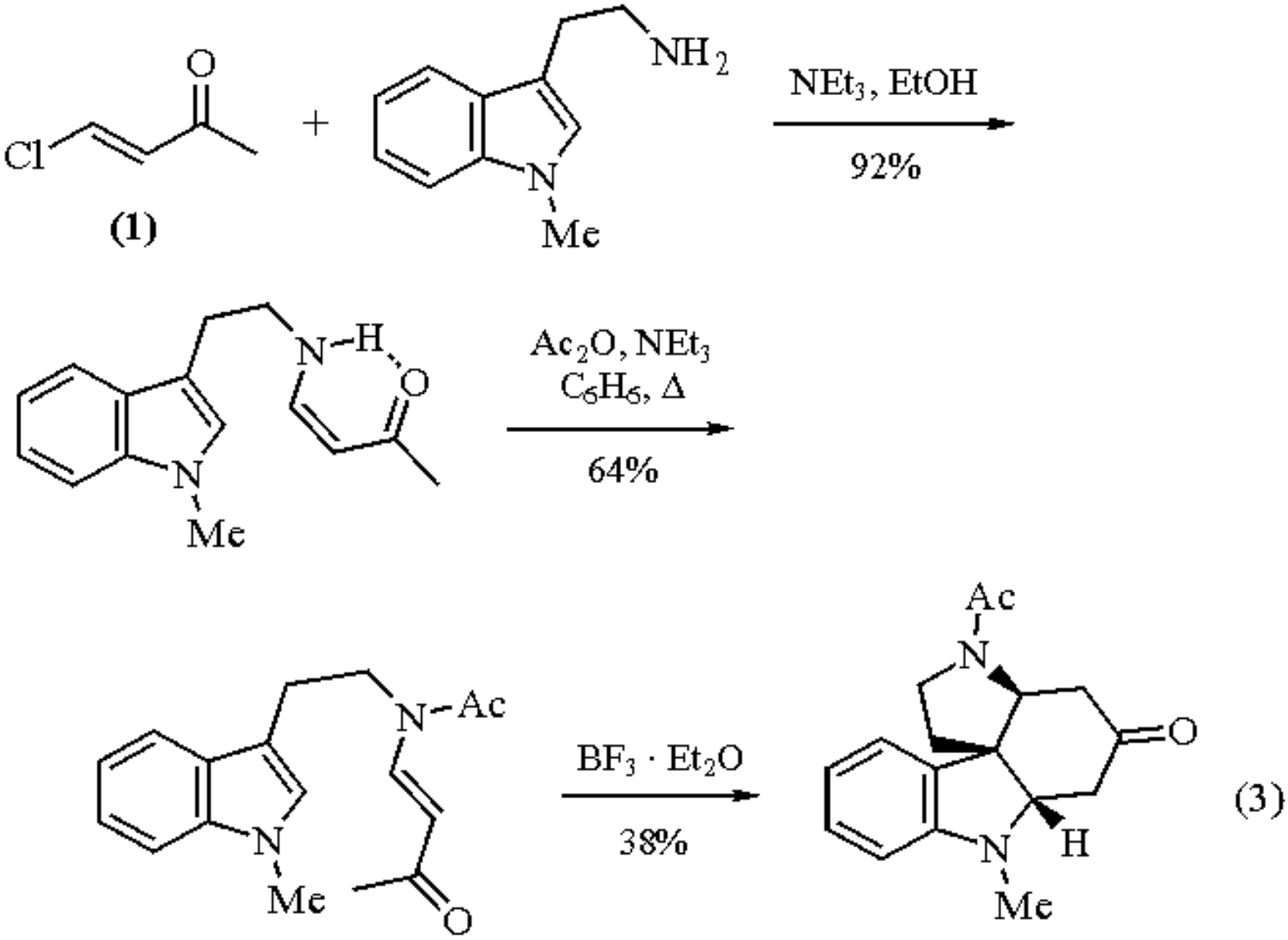

Substitution with Organometallic Reagents.

Lithium dialkylcuprates and organocopper reagents readily undergo conjugate addition to (**1**) with predominant retention of the double bond geometry.[7] For example, the conjugate addition of bis(trimethylsilylmethyl)copperlithium to (*E*)-4-chloropent-3-en-2-one (**2**) affords the silylmethyl derivative in 51% yield (*E*:*Z* = 74:26). Irradiation at -76 °C isomerizes the product to the (*Z*) isomer which upon heating at 38 °C undergoes a 1,5-shift of the silyl group to give a trimethylsilyloxy-substituted butadiene, a compound of general use in Diels-Alder chemistry (eq 4).[7a] Normally alkenylcopper reagents are too unreactive to add to β-chloro enones. However, in the presence of 3% ***Tetrakis(triphenylphosphine)palladium(0)*** coupling with (**1**) proceeds with high stereoselectivity and in high yield. For example, the formation of (*E*,*Z*)-dienones is readily achieved (eq 5).[7b]

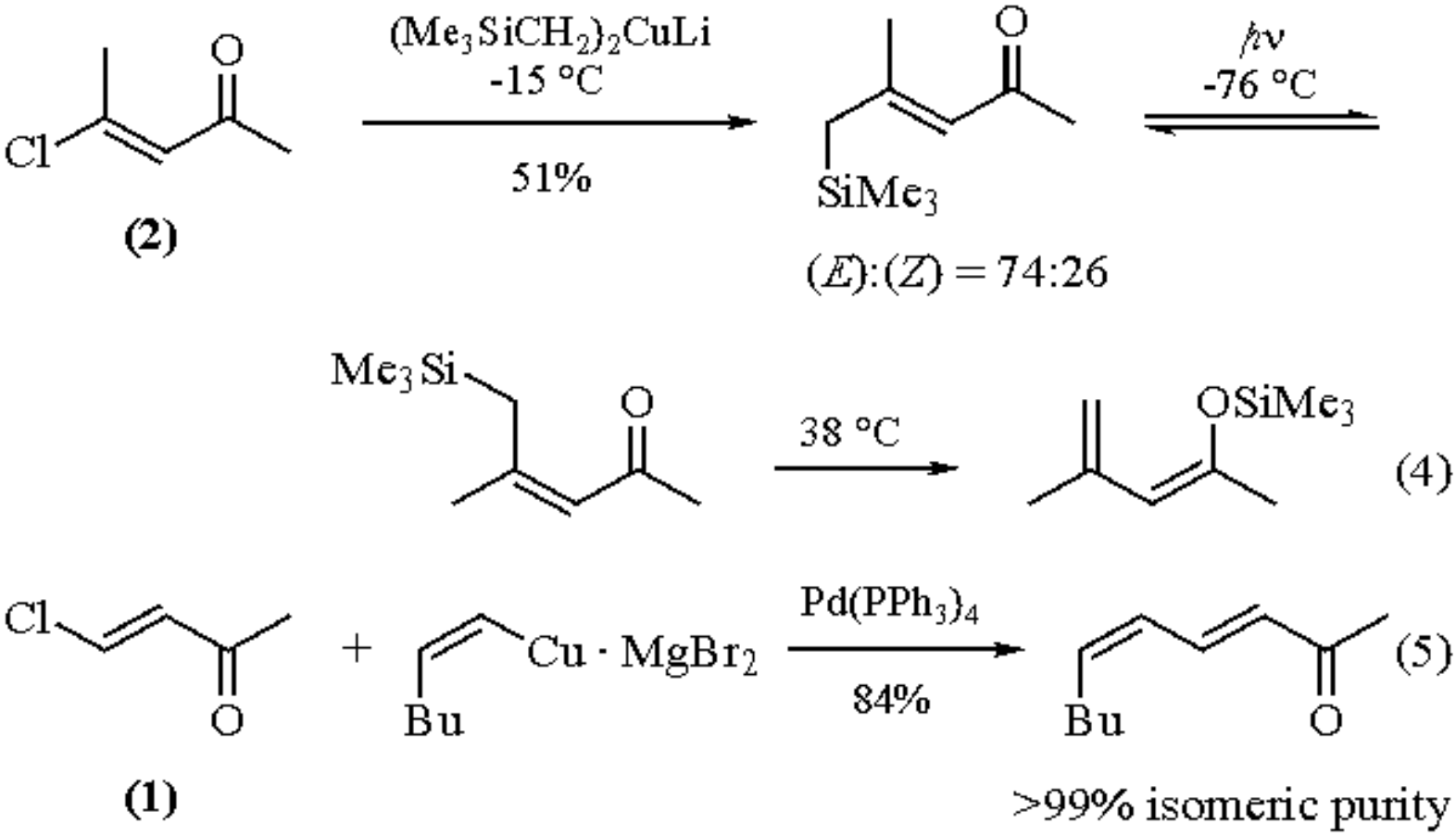

4-Chlorobut-3-en-2-one as a Bifunctional Reagent.

The ability to form dienol borinates while retaining the chloro functionality enables the reagent to react as a dipolar synthon. Thus treatment of the β-chloro enone (**3**) with ***Di-n-butylboryl Trifluoromethanesulfonate*** in the presence of ***Diisopropylethylamine*** generates the dienol borinate, which undergoes addition to aldehydes with high *syn* diastereoselectivity to give substituted hydroxy-β-chloro enones. These can then undergo an intramolecular conjugate addition in the presence of ***Trimethylsilyl Trifluoromethanesulfonate*** to afford dihydropyrones in good yields (eq 6).[8]

(E)-4-Chloro-3-buten-2-one

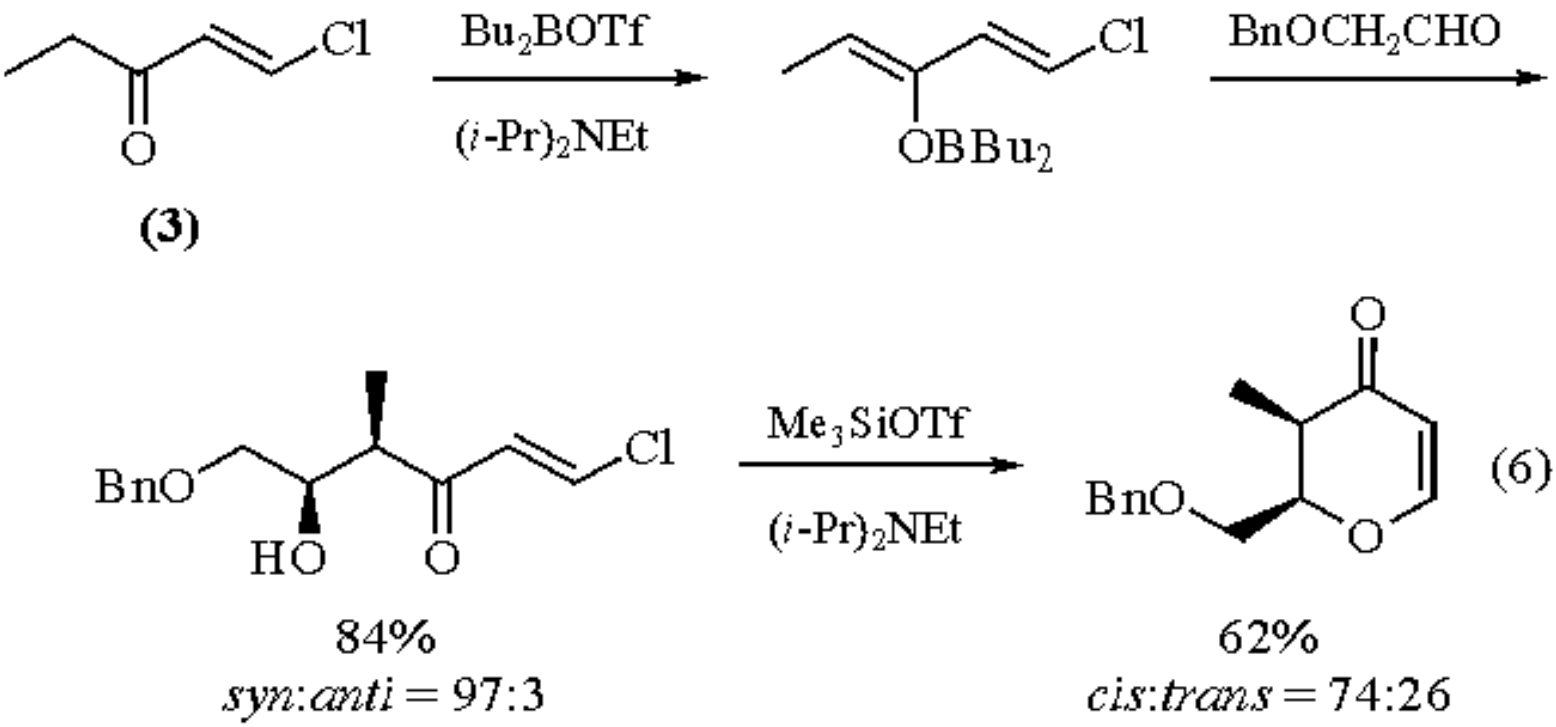

A route to α,β-unsaturated aldehydes has been reported in which the vinyl chloride moiety is converted into a dimethyl acetal and the carbonyl group can then react with Grignard reagents to form γ-hydroxy acetals. These are then hydrolyzed and dehydrated to the unsaturated aldehydes (eq 7).[2a]

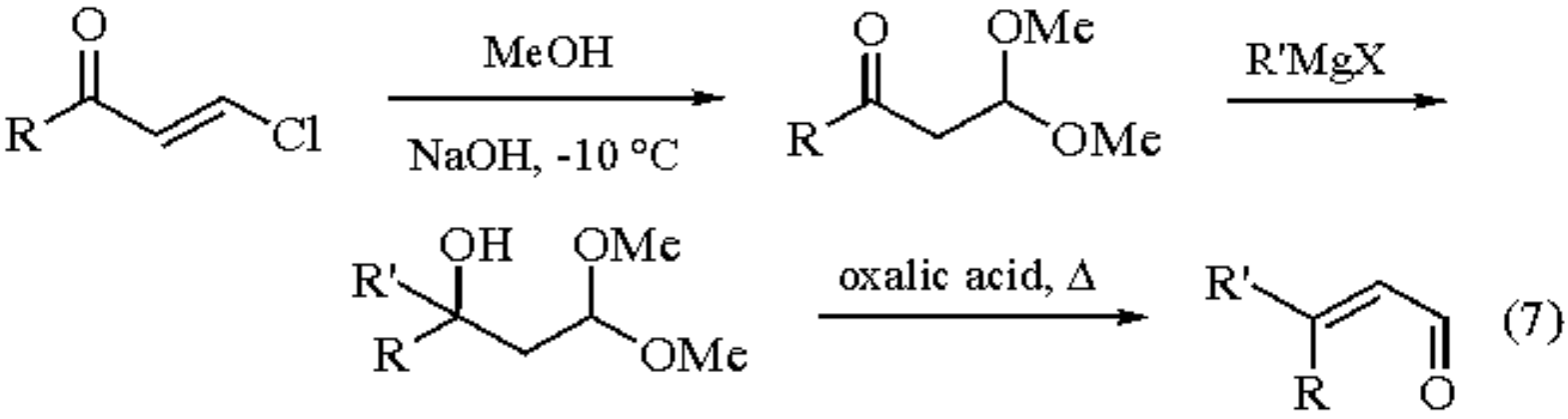

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1-Chlorocarbonylbenzotriazole

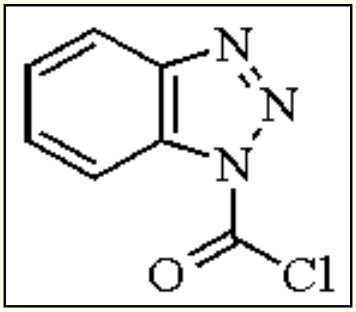

[65095-13-8] · $C_7H_4ClN_3O$ · 1-Chlorocarbonylbenzotriazole · (MW 181.58)

(formation of carbamates from alcohols;[1,2] peptide synthesis[3,4])

Physical Data: mp 54-55 °C.

Preparative Methods: by bubbling phosgene through a suspension of benzotriazole in toluene at 60 °C until a clear solution is obtained. Evaporation at reduced pressure gives (**1**) (99% yield); this crude material has mp 52-54 °C. Alternatively, an ethereal solution of benzotriazole may be added dropwise over 20 min to a 20% solution of phosgene in toluene (4 equiv); stirring until a clear solution is obtained followed by evaporation at reduced pressure gives 98% yield of (**1**) with mp 52 °C.[1]

Purification: recrystallization from light petroleum.

Preparation of Carbamates from Alcohols.

Reaction of 1-chlorocarbonylbenzotriazole (**1**) with an alcohol results in formation of the 1-alkoxycarbonylbenzotriazole (**2**). These compounds are stable to water or alcohols, but react with amines (or hydrazines) to give the carbamates (**3**) (eq 1).[1,2] Similarly, unsymmetrical ureas can be prepared if an amine is used rather than an alcohol in the first step.[5]

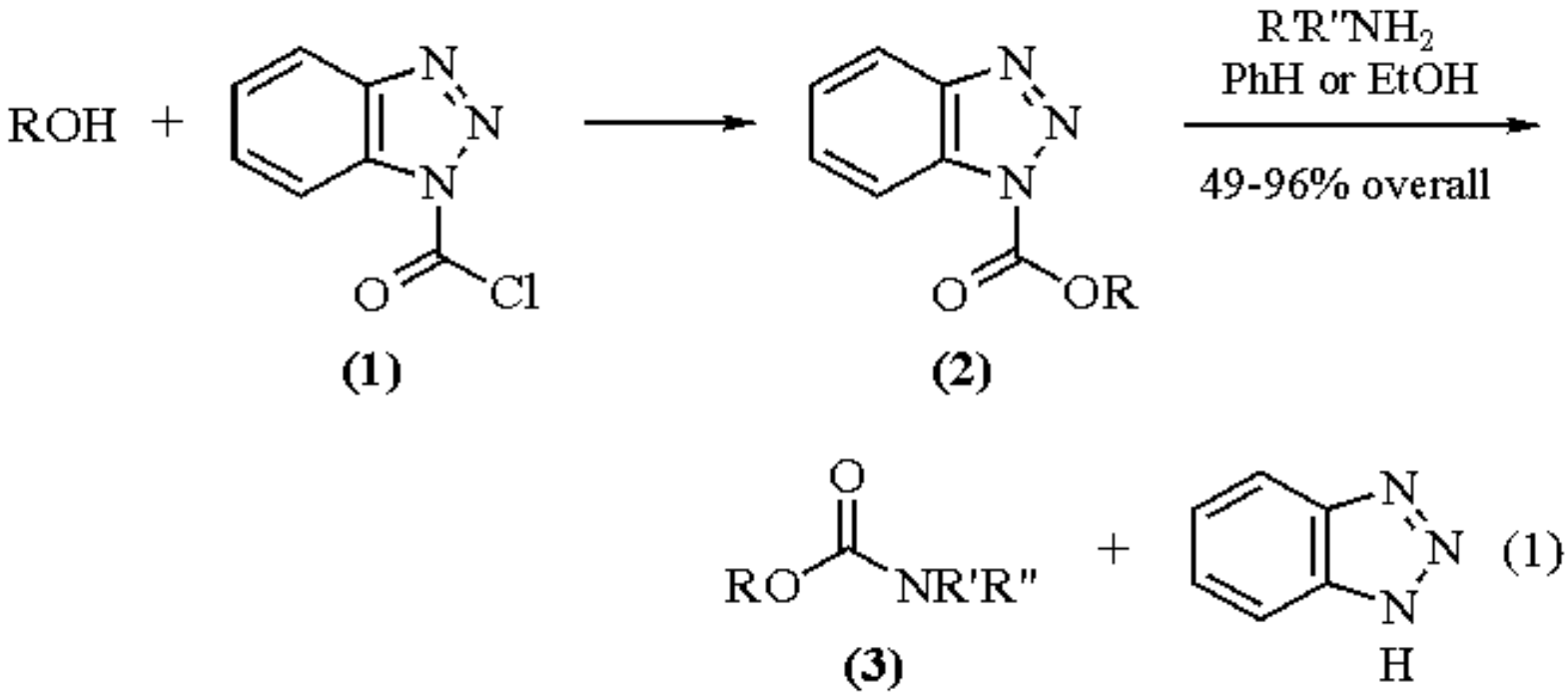

Peptide Synthesis.

(**1**) reacts with two equivalents of an amino acid in dioxane to give the *N*-(1-benzotriazolylcarbonyl) (Btc) amino acid (**4**) (eq 2), which separates almost quantitatively from the hydrochloride salt of the second equivalent of amino acid employed.[6]

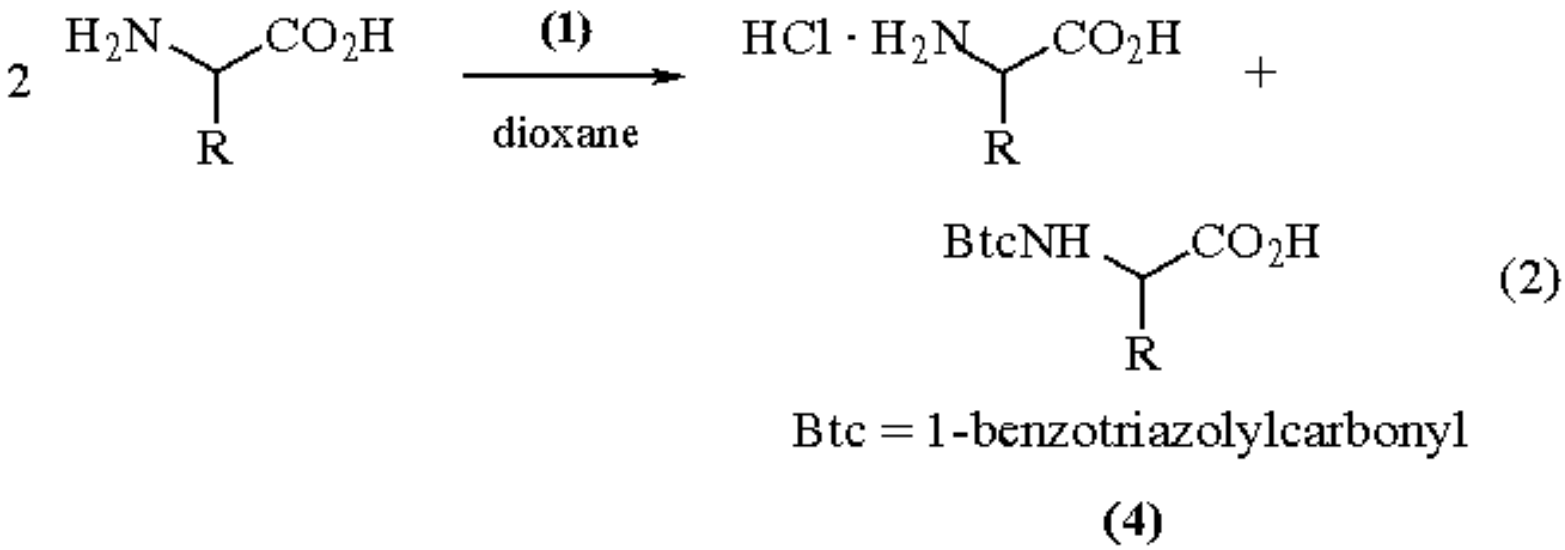

These Btc-amino acids can be used for peptide synthesis in two ways. Reaction of (**4**) with an amine or amino acid in acetonitrile or in aqueous acetone effects amide bond formation without racemization (eq 3).[3] Benzotriazole and CO_2 are the coproducts.

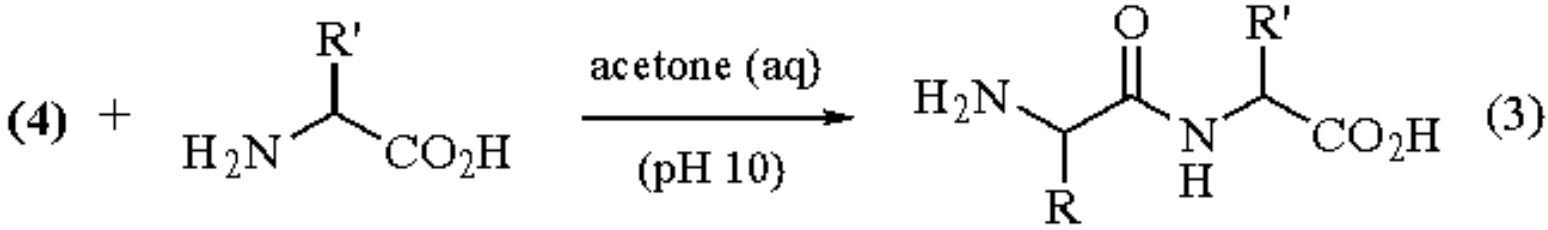

N-Activation can also be achieved. Treatment of the ester (**5**), derived from (**4**), with a Cbz-protected amino acid again results in loss of CO_2 and benzotriazole to form an amide bond (eq 4).[4] This procedure seems to offer little advantage over other methods of peptide synthesis, however.

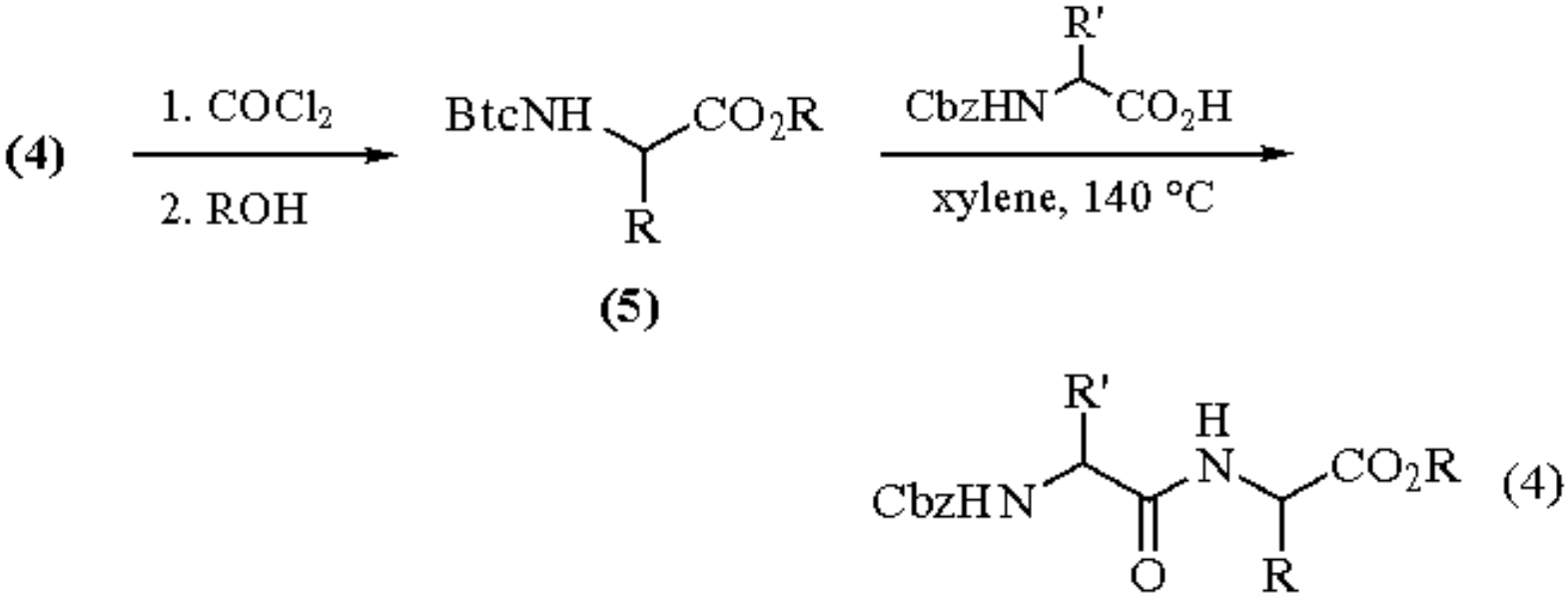

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(Chlorocarbonyl)ethylketene

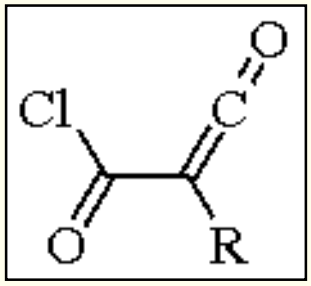

(R = Et)

[17423-43-7] · $C_5H_5ClO_2$ · (Chlorocarbonyl)ethylketene · (MW 132.55) (R = Ph)

[17118-70-6] · $C_9H_5ClO_2$ · (Chlorocarbonyl)phenylketene · (MW 180.59) (R = 2-ClC_6H_4)

[145004-66-6] · $C_9H_4Cl_2O_2$ · (Chlorocarbonyl)(2-chlorophenyl)ketene · (MW 215.04) (R = 3-$CF_3C_6H_4$)

[145020-10-6] · $C_{10}H_4ClF_3O_2$ · (Chlorocarbonyl)(3-trifluoromethylphenyl)ketene · (MW 248.59) (R = 2,4,6-$Me_3C_6H_2$)

[144758-26-9] · $C_{12}H_{11}ClO_2$ · (Chlorocarbonyl)(2,4,6-trimethylphenyl)ketene · (MW 222.67) (R = 4-*t*-BuC_6H_4)

[145004-67-7] · $C_{13}H_{13}ClO_2$ · (Chlorocarbonyl)(4-*t*-butylphenyl)ketene · (MW 236.68) (R = Bn)

[57421-93-9] · $C_{10}H_7ClO_2$ · (Chlorocarbonyl)benzylketene · (MW 194.62) (R = $PhCH_2CH_2$)

[57421-94-0] · $C_{11}H_9ClO_2$ · (Chlorocarbonyl)(2-phenylethyl)ketene · (MW 208.64)

(1,3-dielectrophiles used mainly for the synthesis of five- and six-membered heterocycles functionalized with oxo and hydroxy groups in 1,3-positions)

Alternate Names: chlorocarbonylketenes; α-carbonyl acetyl chlorides; CCKs.

Physical Data: R = Et, bp 75-78 °C/22 mmHg;[1] R = Ph, bp 84-85 °C/0.2 mmHg;[2] R = 2-ClC_6H_4, bp 93-95 °C/0.12 mmHg;[3] R = 3-$CF_3C_6H_4$, bp 65-69 °C/0.04 mmHg;[3] R = 2,4,6-$Me_3C_6H_2$, bp

96 °C/0.35 mmHg;[3] R = 4-*t*-BuC_6H_4, bp 105-110 °C/0.40 mmHg;[3] R = Bn, bp 110-112 °C/1.5 mmHg;[2] R = $PhCH_2CH_2$, bp 94-95 °C/0.7 mmHg.[2]

Preparative Method: substituted malonyl dichlorides lose HCl above 80 °C to form CCKs.[6] In order to avoid mixtures[7] of malonic acid dichlorides and CCKs, the crude product obtained from the reaction of malonic acid with $SOCl_2$ is heated at reflux in toluene at atmospheric pressure under a slow stream of nitrogen, prior to distillation at reduced pressure (Nakanishi-Butler procedure).[2]

The unsubstituted CCK (R = H) is unknown (and has so far not even been prepared by FVP). This compound, which is formed from the parent malonyl dichloride under very weakly basic conditions[4a] at rt, dimerizes rapidly in a [4 + 2] cycloaddition to yield 6-chloro-3-chlorocarbonyl-4-hydroxy-2-pyrone.[4,5]

Handling, Storage, and Precautions: use in a fume hood.

Reactions.

Reactions of CCKs with nucleophiles are performed in aprotic solvents either at reflux temperature, with evolution of HCl gas, or (usually at lower temperatures) with a base (in most cases ***Triethylamine***) as HCl scavenger. Thus a recent patent describes the reaction of several cyclic hydrazines with various CCKs in the presence of bases (eq 1).[3]

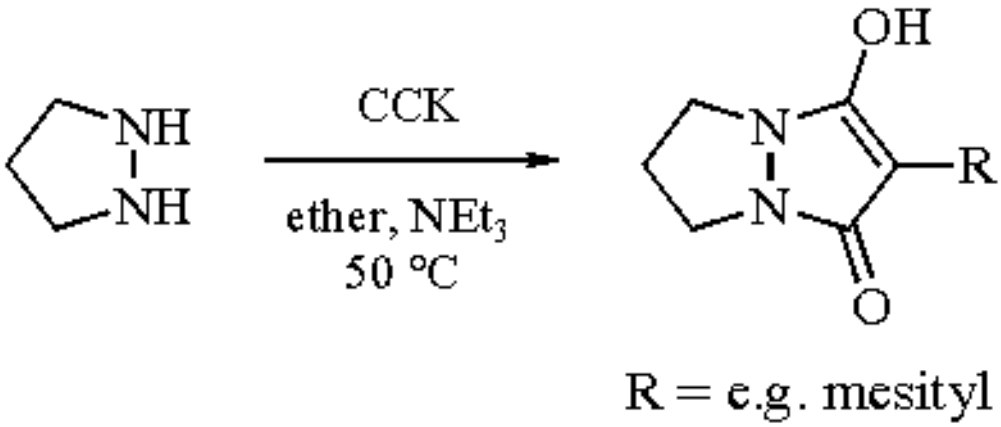

(1)

N-Substituted imidazoles (and benzimidazoles) undergo cycloaddition with CCKs, in the presence of Et_3N, to form zwitterionic pseudo-cross-conjugated mesomeric pyrrolo[1,2-*a*]imidazoles (eq 2).[8] Cross-conjugated mesomeric pyrazolopyrazole betaines of type (**1**) are readily prepared starting with pyrazoles;[8,9] for derivatives of (**1**) with R = H,[8] see ***Carbon Suboxide***.

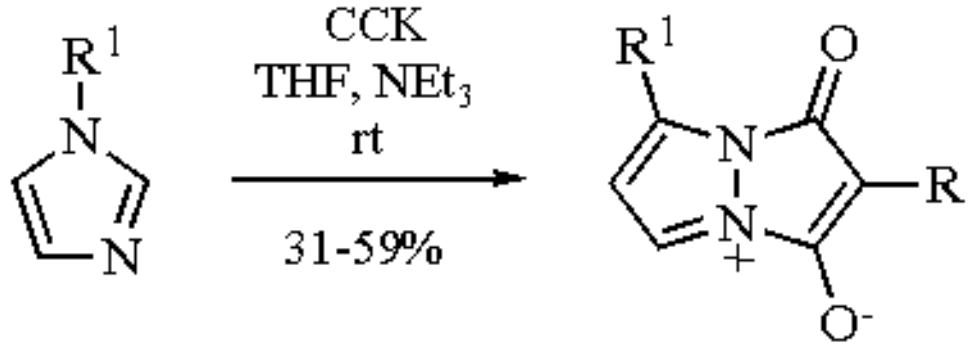

(2)

$R^1 = Me, Ph$ $R = Ph, PhCH_2$

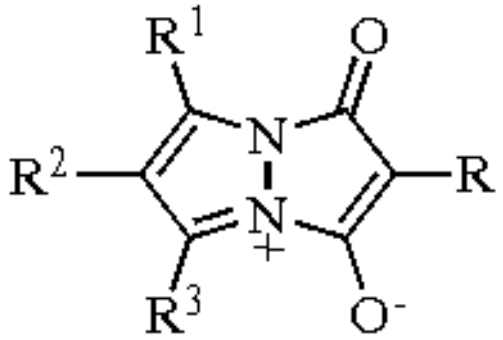

(1)

$R^1, R^2 = H, Me, Ph$

$R = Et, Ph$

Thioamides, and even amides, react as 1,3-dinucleophiles with CCKs to afford cross-conjugated mesomeric thiazine[10,11] or oxazine[1,11c,12,13] betaines (eq 3). Thiolactams[10,11] and lactams[1] lead to bicyclic thiazine and oxazine derivatives. Both zwitterionic thiazines and oxazines are good candidates for 1,4-dipolar cycloadditions with alkynic and alkenic bonds.[10b,11c,d] The intramolecular version,[11c] especially with bicyclic thiazines, has been introduced as a very valuable route to a variety of complex azapolycyclic ring systems found in Nature.[11d]

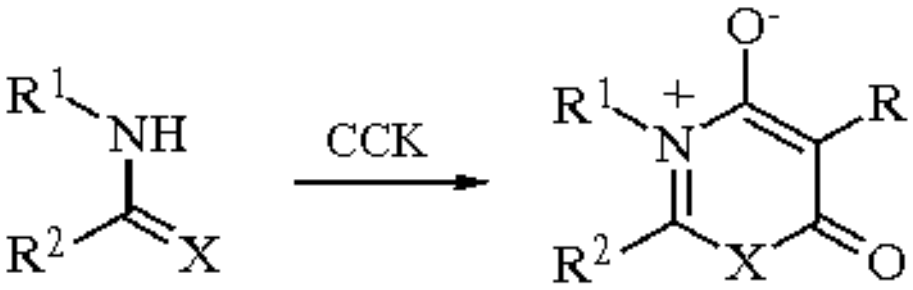

(3)

$X = S, O$

The cycloaddition of CCKs with cyanamides occurs at the C&tbond;N bond, leading to chlorooxazinones (eq 4).[13] Similar reactions with other nitriles[5b,14] (and other C=N bonds such as those in carbodiimides[15] and isocyanates[5b]) were reported earlier with substituted malonyl dichlorides, at a time when it was not yet recognized that redistilled dichlorides[2,7] are actually CCKs, and CCKs were postulated as intermediates only.

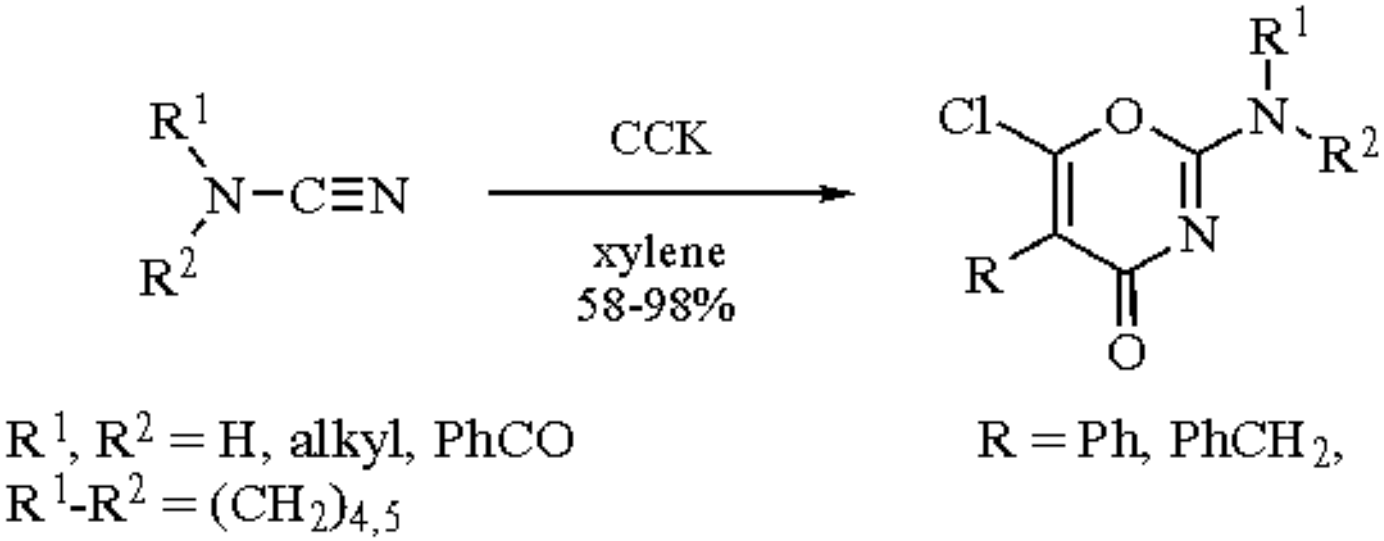

(4)

Alternatives.

CCKs represent a very valuable class of reactive malonic acid derivatives. Their advantages over ***Bis(2,4,6-trichlorophenyl) Malonate*** are (a) their much lower MW and (b) their reactivity at lower temperature. Thus the reaction of amidines (eq 3; X = NR^3, yielding zwitterionic pyrimidines, cf. AMEs) can be performed with both reagents. However, mesomeric thiazine and oxazine betaines rearrange or decompose at higher temperatures (>60-80 °C).[16] If the products (such as pyrazolopyrazoles, e.g. **1**) are stable at very high temperatures (>250 °C), they can be prepared simply by heating the substrates with the appropriate substituted diethyl malonate.[17]

Related Reagents.

Bis(2,4,6-trichlorophenyl) Malonate; ***Bis(trimethylsilyl) Malonate***; ***Carbon Suboxide***; ***Malonic Acid***; ***Malonyl Chloride***.

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6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole

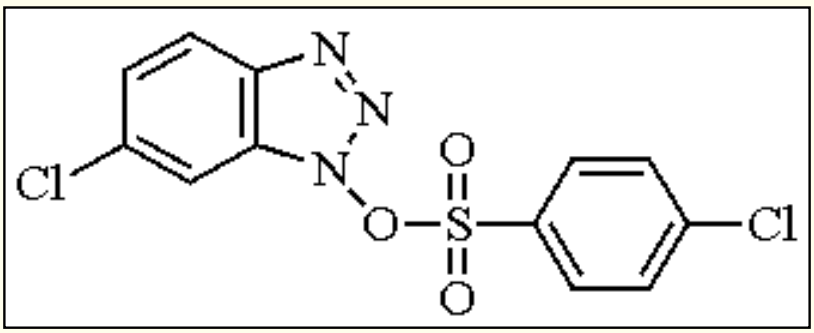

[57320-65-7] · $C_{12}H_7Cl_2N_3O_3S$ · 6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole · (MW 344.17)

(reagent for active ester formation;[1] synthesis of amides,[1] esters,[2] thiol esters[3] from carboxylic acids; peptide synthesis[1])

Physical Data: mp 125-127 °C.

Preparative Method: prepared by reaction of 6-chloro-1-hydroxybenzotriazole with *p*-chlorobenzenesulfonyl chloride in 1M aqueous NaOH/ether.

Purification: recrystallization from benzene/petroleum ether.

Handling, Storage, and Precautions: stable for long periods in the absence of moisture and light.

Active Ester Formation.

6-Chloro-1-(*p*-chlorobenzenesulfonyloxy)benzotriazole (**1**) converts carboxylic acids to the 1-acyloxybenzotriazole derivatives (**2**) in good yield (eq 1).[1] A study of several related reagents found (**1**) to be most suitable based on overall considerations of reactivity, stability, and accessibility. The reaction occurs rapidly (usually less than 1 h) in the presence of one equivalent of ***Triethylamine*** in $CHCl_3$ or EtOAc; the more polar solvent MeCN is required if ***Pyridine*** is used as base. The active esters (**2**) can generally be isolated as stable, crystalline solids.

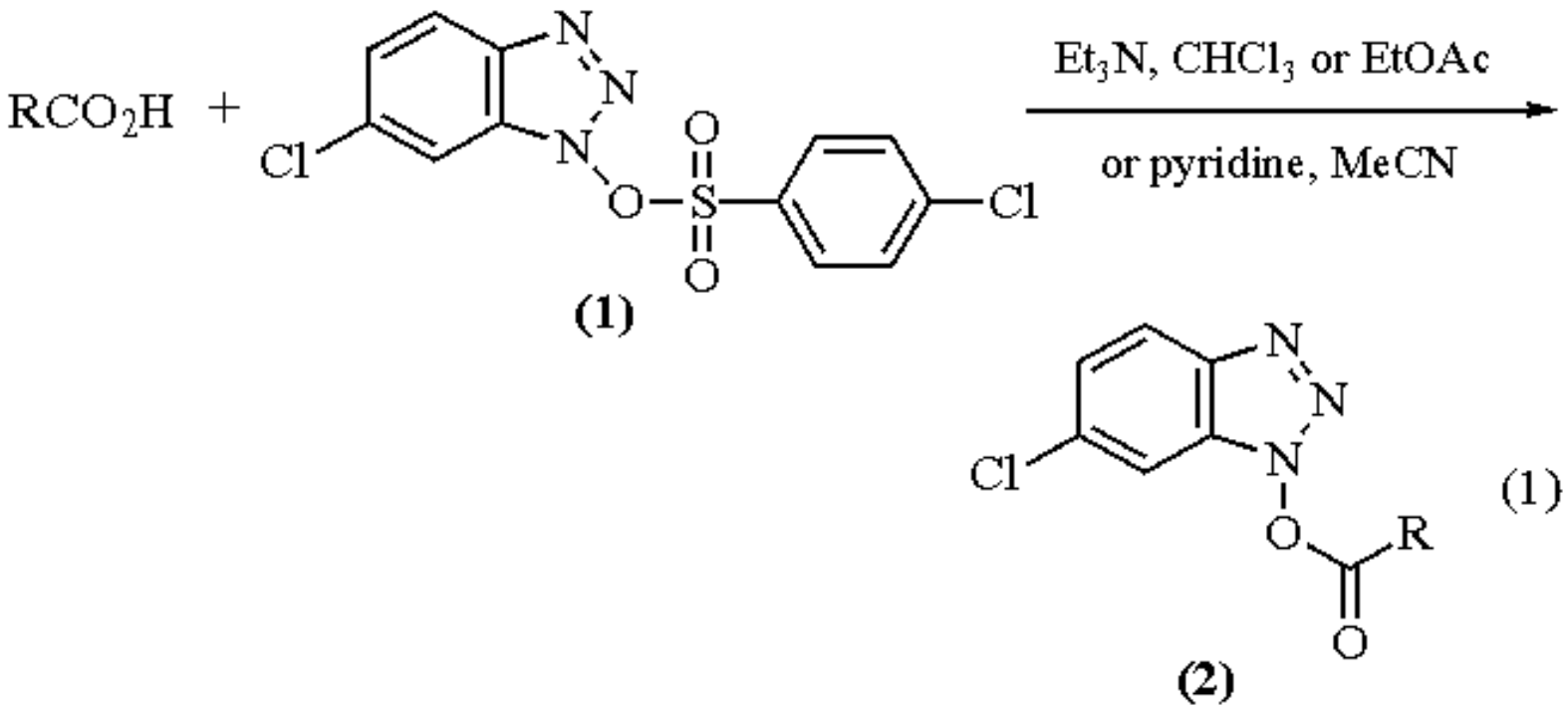

The active esters (**2**) react readily in the presence of base with amines,[1] alcohols,[2] and certain thiols[3] to provide amides, esters, and thioesters, respectively (eq 2). Aminolysis is generally rapid, as is reaction with primary alcohols; use of secondary alcohols such as *i*-propanol requires higher temperature (boiling $CHCl_3$), while no reaction is observed between (**2**) and *t*-butanol.

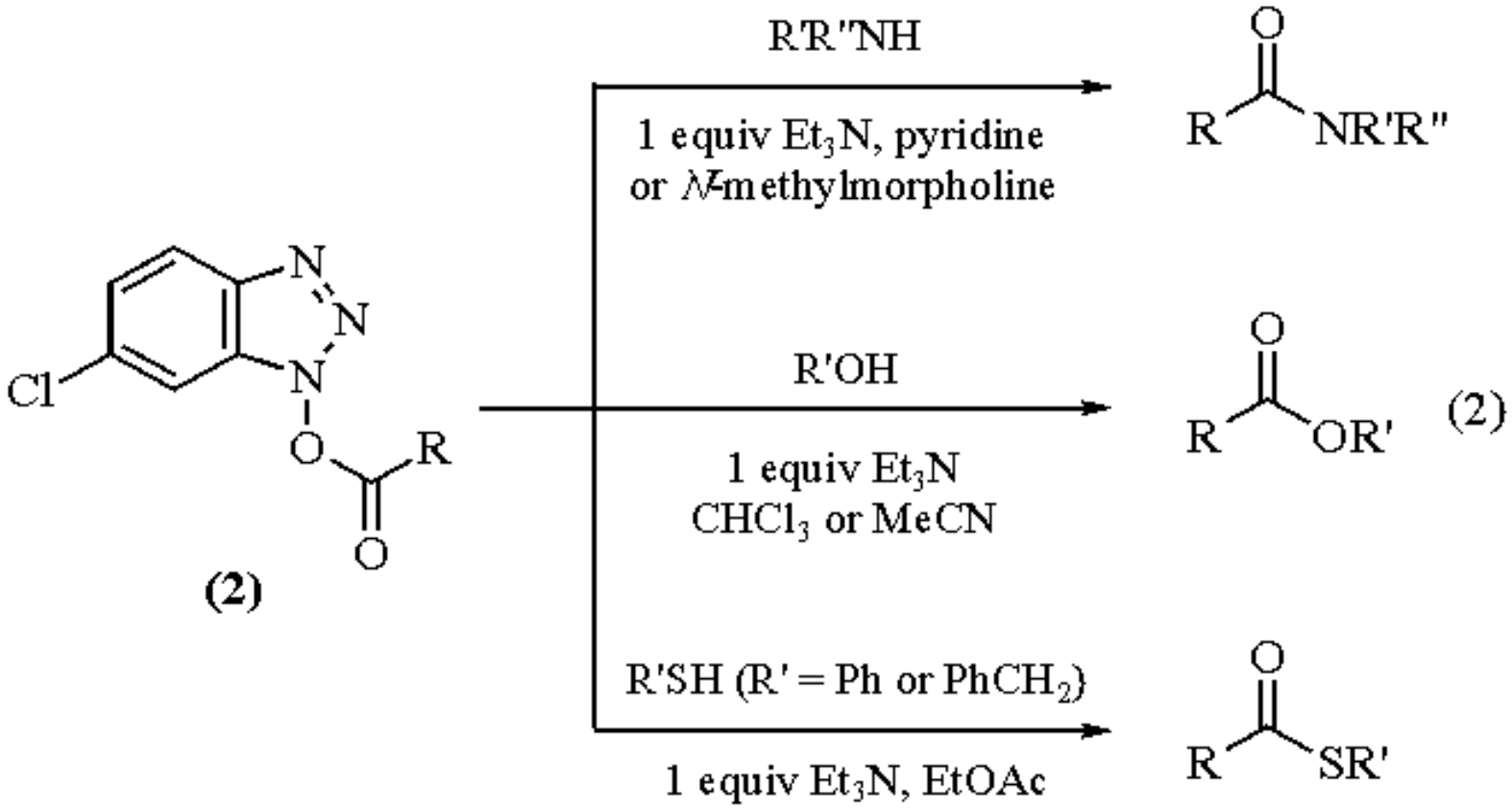

Ester formation may also be achieved without isolation of (**2**) by mixing a carboxylic acid and an alcohol with (**1**) in

the presence of two equivalents of base (eq 3).[2] Formation of the 1-alkoxy-6-chlorobenzotriazole as byproduct is suppressed by the use of ether as solvent rather than $CHCl_3$; use of pyridine in MeCN is also suitable.

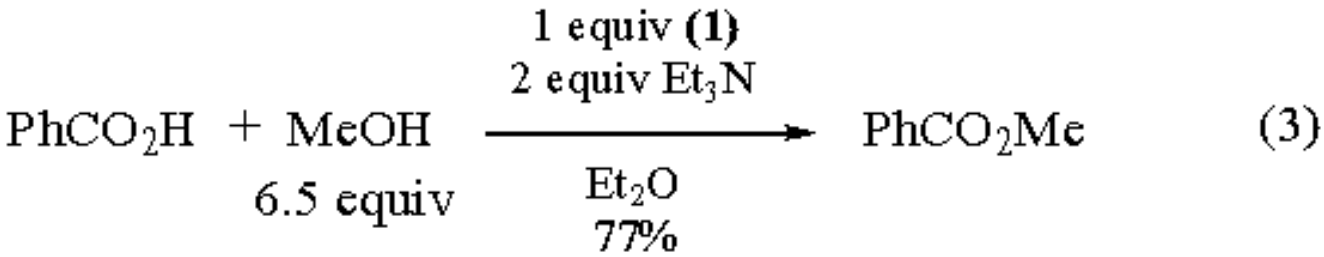

Similarly, one-pot amide synthesis is possible;[1] formation of sulfonamide by direct reaction of (**1**) with amine is avoided by using *N*-methylmorpholine or pyridine as base instead of Et_3N.[1a]

Peptide Synthesis.

This method of amide bond formation has been used for peptide synthesis; the active ester is usually reacted with the amino component in situ (eq 4).[1]

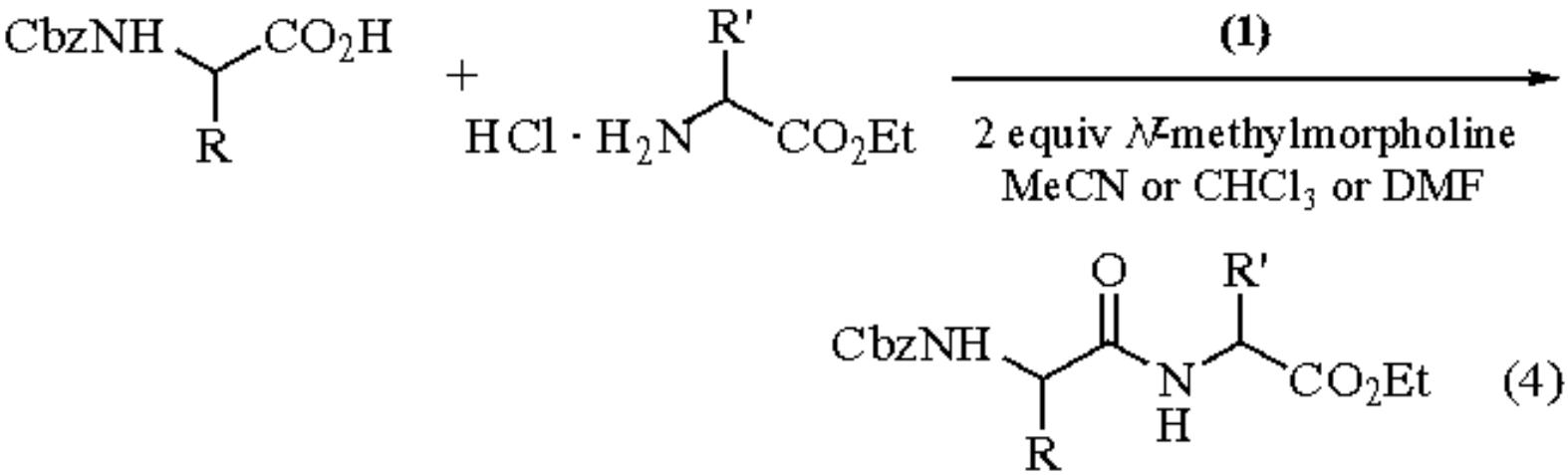

These reaction conditions have advantages over the popular ***1,3-Dicyclohexylcarbodiimide*** (DCC) method, not least that the sulfonic acid and hydroxybenzotriazole co-products can be washed out with aqueous sodium bicarbonate. In the coupling of *N*-protected L-asparagine or L-glutamine with amino components, no dehydration of the side-chain amide (to the nitrile) was observed. Free hydroxy or imino groups do not cause problems, as shown by the successful preparation of serine-, tyrosine- and histidine-containing peptides.

Using the coupling of Cbz-Phe-Ile-OH with H-Pro-OBn in DMF as a test, the degree of racemization using (**1**) with various bases was compared with other methods; less racemization occurred using (**1**) than with DCC.[1b] A more extensive comparison of degree of racemization has also been reported.[4]

---

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Chlorocyanoketene[1]

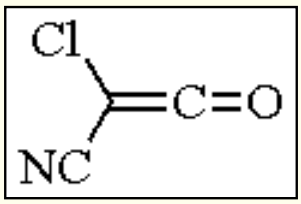

[60010-89-1] · C_3ClNO · Chlorocyanoketene · (MW 101.49)

(functions as a potent electrophile in reactions with a wide variety of ketenophiles including alkenes,[3] alkynes,[4] arylaldehydes,[5] and imines[6-8])

Alternate Name: CCK.

Preparative Methods: chlorocyanoketene readily undergoes self-condensation and must be generated in situ prior to usage. By generating the ketene in the presence of a ketenophile, concentration-related difficulties are circumvented and yields are greatly improved.[2] A most convenient route to the title compound is afforded by the thermal decomposition of pseudo esters of azidofuranones. Starting with commercially available mucochloric acid the desired furanone is synthesized in a two-step process: etherification and azidation (eq 1). Alcohols with at least three carbons, such as isopropanol, are desirable for the etherification in order to minimize the detonation capability of the subsequent azide.[2]

Cycloadditions to Alkenes.

Cycloadditions of chlorocyanoketene (CCK) to alkenes give good yields of the corresponding cyclobutanone and include additions to di-, tri-, and tetrasubstituted alkenes. The addition process is in complete accord with a concerted $_{\pi}2_s + {}_{\pi}2_a$ mechanism. Cyclobutanones (**1**), (**2**), and (**3**) are obtained by a highly stereoselective route as evidenced by the formation of their respective single diastereomers (eqs 2-7).

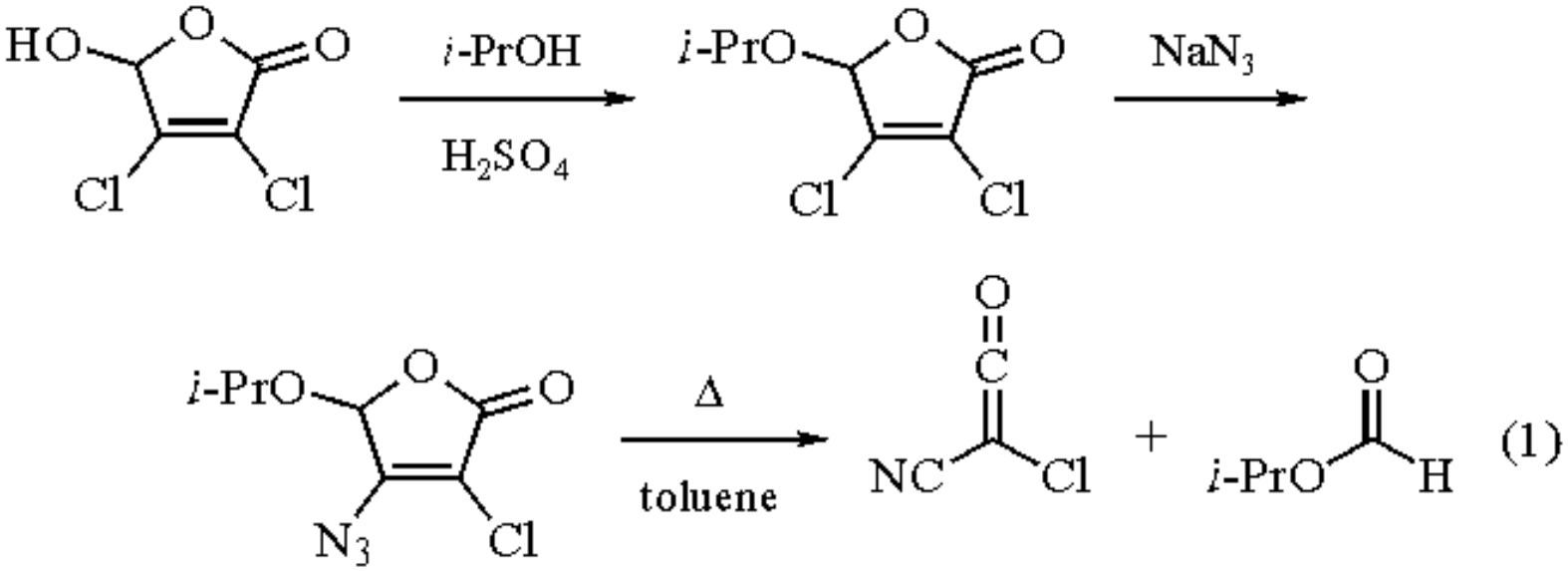
HO
O
O
Cl
Cl
i-PrOH
H2SO4
i-PrO
NaN3
N3
Δ
toluene
NC
C
Cl
+
i-PrO
H
(1)

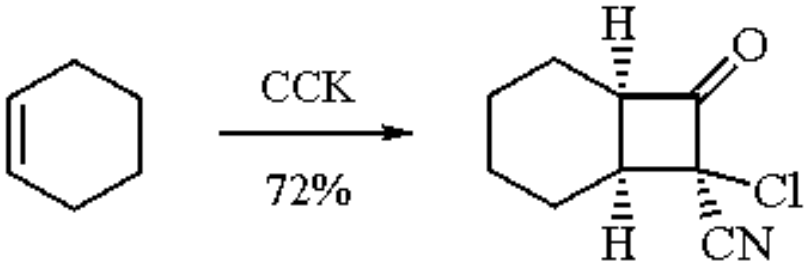
CCK
72%
H
O
Cl
CN

(2)

(1)

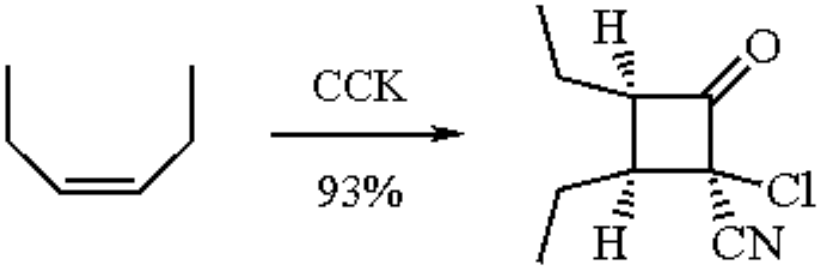
CCK
93%
H
O
Cl
CN

(3)

CCK
67%
H
O
Cl
CN

(4)

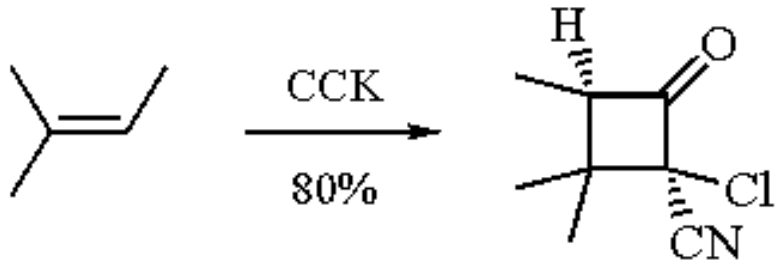

(2) (5)

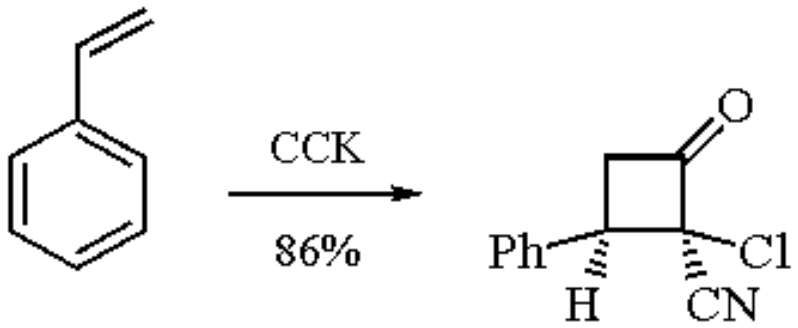

(3) (6)

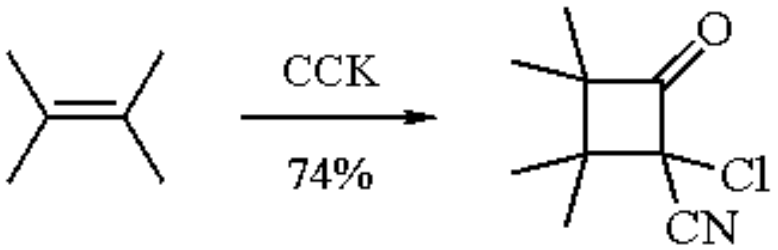

(7)

Alkenic ketenophiles with higher nucleophilic character react with CCK in a dipolar fashion. For example, treatment of cyclopentadiene with CCK gives a 55:45 mixture of diastereomers (eq 8). Further exemplifying this dipolar mode is the reaction of the ketene with dihydropyran (eq 9), whose product likely arises from a proton transfer process involving a zwitterionic intermediate.[3]

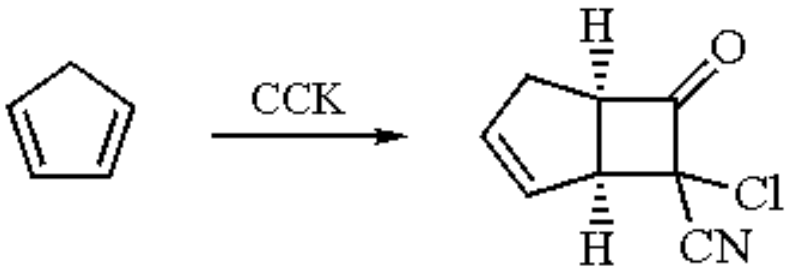

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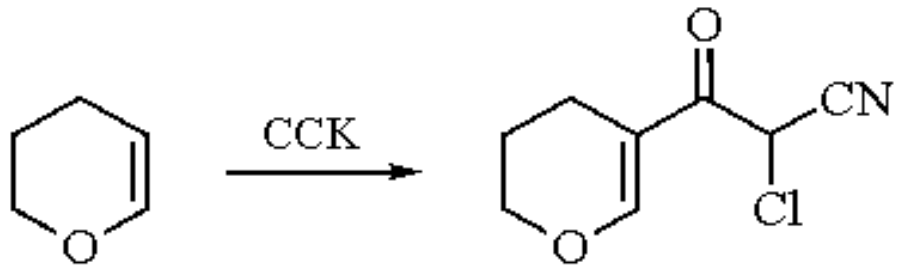

(9)

Cycloadditions to Alkynes.

CCK cycloadds to alkynes to give cyclobutenones. Reactions using terminal alkynes give complex mixtures, while employment of internal alkynes affords the corresponding cyclobutenones in good yields (eqs 10-13).[4]

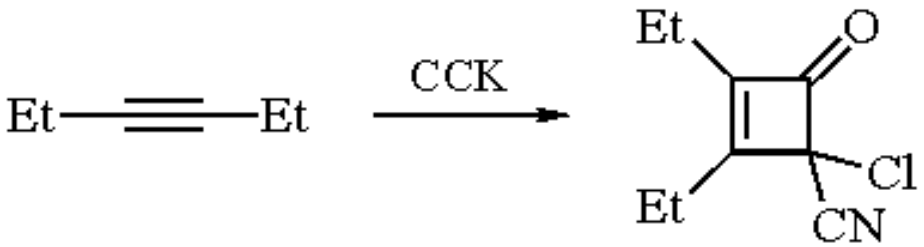

(10)

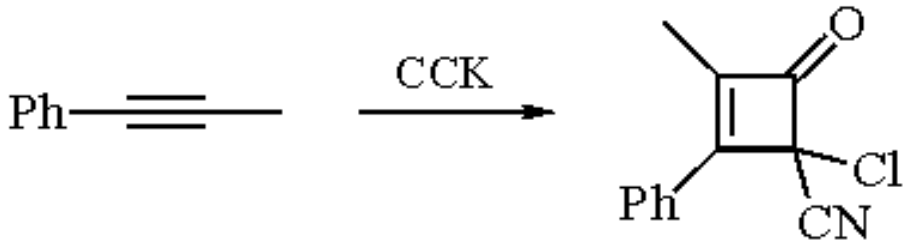

(11)

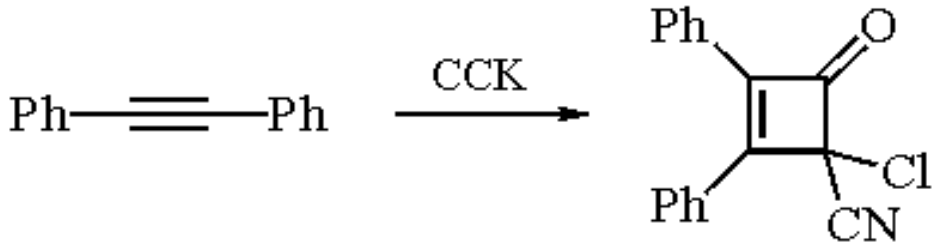

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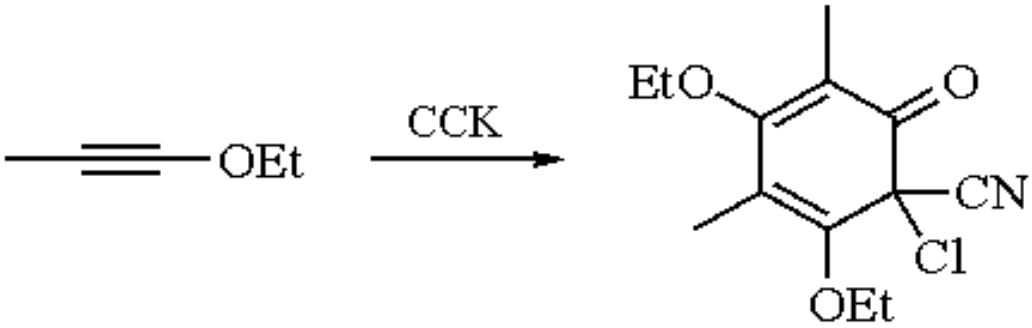

(13)

4-Chloro-4-cyanobutenones, by virtue of the initial cycloadditions, are in equilibrium with their respective vinylketenes at room temperature, and these reactive intermediates can be intercepted by other ketenophiles, as

exemplified in eq 14.[4]

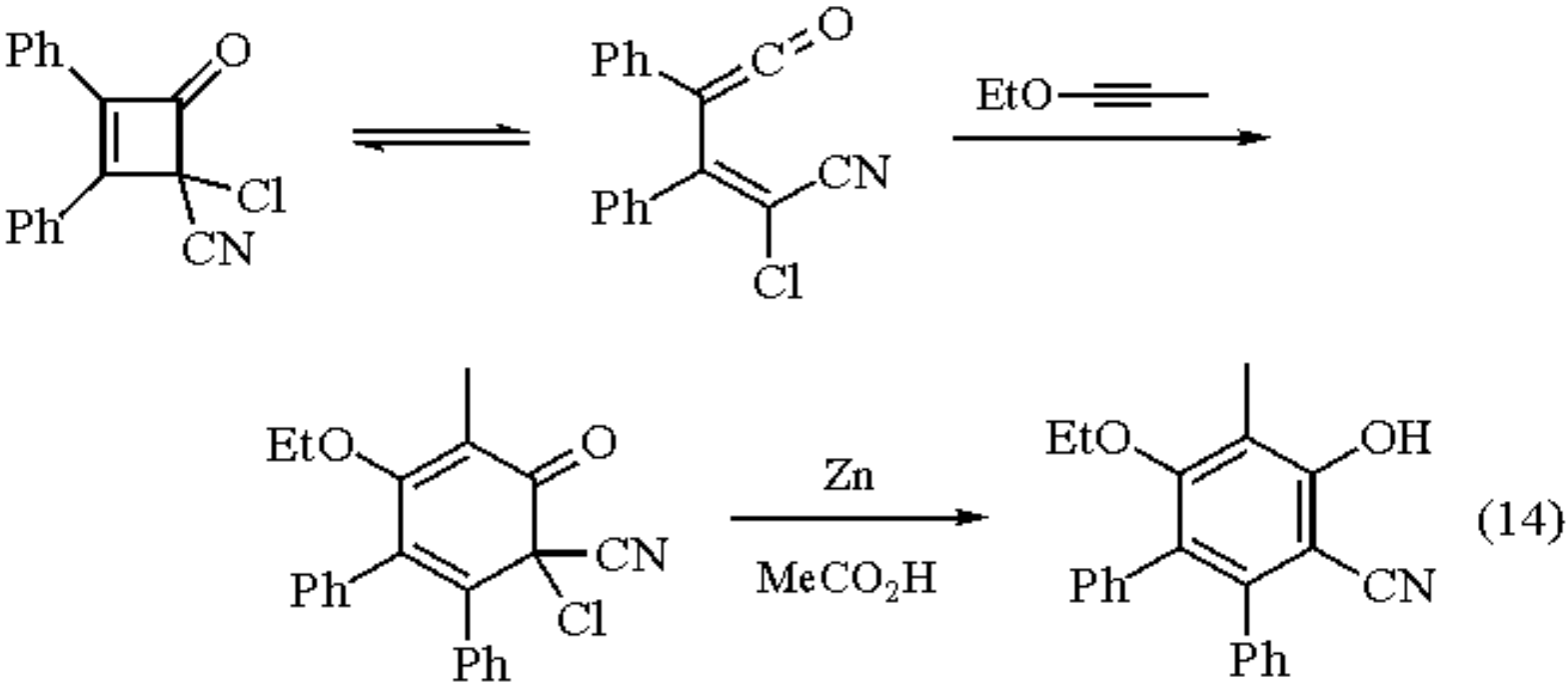

Cyclohexadienones are the result of trapping the vinylketenes with an alkyne. Reductive elimination of these products gives highly functionalized phenols.

Cycloadditions to Arylaldehydes.

Chlorocyanoketene cycloadds to arylaldehydes to form β-lactones which consequently decarboxylate under the reaction conditions to give exclusively the (*E*) isomer of 1-halo-1-cyano-2-phenylethylenes. The initial cycloaddition is a nonconcerted dipolar process in which the cyanoketene uniquely functions as an electrophile and the aldehyde as the nucleophile (eq 15).[5]

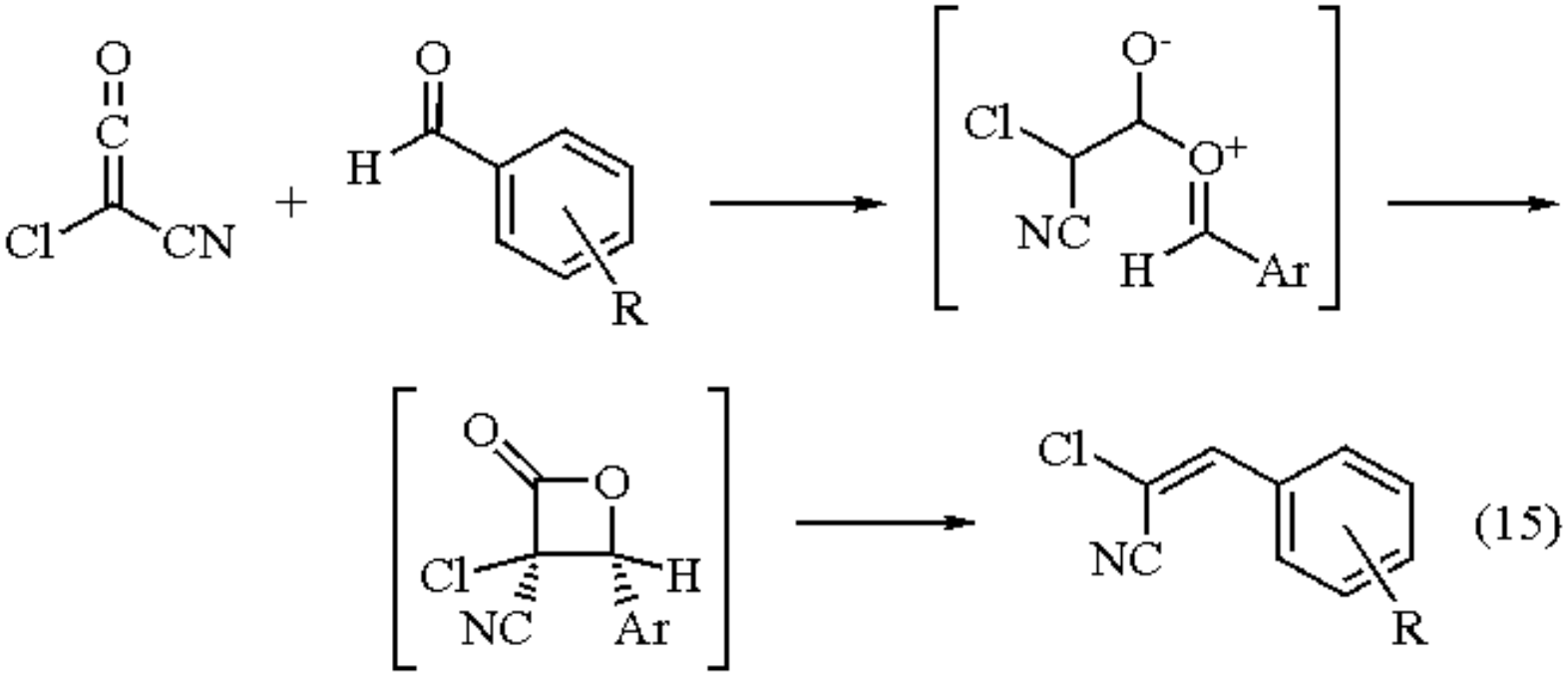

Cycloadditions to Imines.

CCK cycloadds to a variety of imines to form both β- and δ-lactams depending on the particular imine used.[6-8] Among the most studied imines are cinnamylideneamines and benzylideneamines. In the former series of cycloadditions, it is generally found that 2-azetinone formation is enhanced when the *N*-substituent of the imine is small. Stereochemical control is realized through the bulk of this substituent as well as the substitution pattern of the imine (eq 16). Within the benzylidene series, cycloadditions are stereospecific where the *N*-substituent is an aryl group resulting in a *trans* relationship between the 3-cyano group and the proton at the 4 position. The yield of corresponding *cis* diastereomer is progressively increased by increasing steric bulk (eq 17). As in the case with arylaldehydes, stereochemical outcomes in the cycloadditions of imines to CCK are best rationalized by invoking a dipolar intermediate.

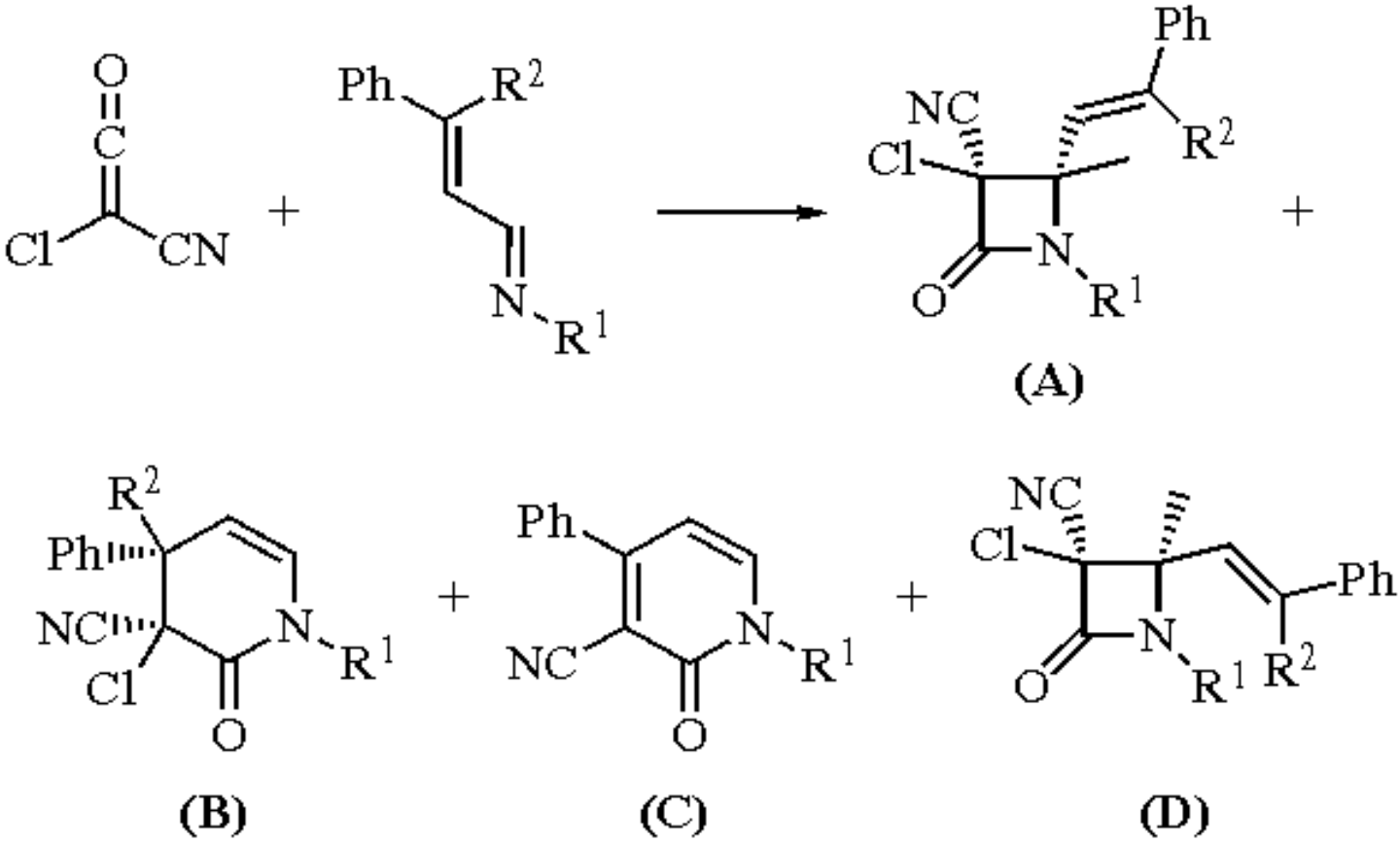

(16)

R^1	R^2	% (A)	% (B)	% (C)	% (D)
Ph	H	9	26	36	-
Bu	H	7	54	14	-
Cy	H	-	70	20	-
t-Bu	H	-	56	19	-
Ph	Ph	88	-	-	-
Bu	Ph	68	-	-	-
Cy	Ph	20	36	-	38
t-Bu	Ph	-	-	-	86

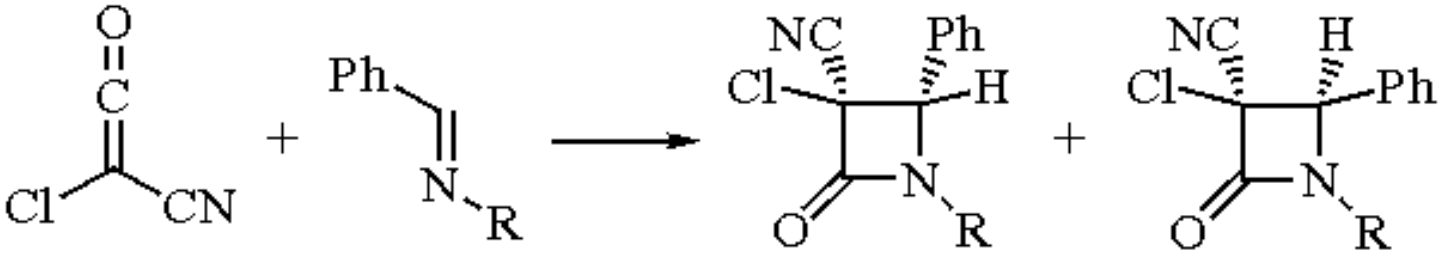

(17)

(E) (F)

R	% (E)	% (F)
Ph	88	-
Bu	92	-
Cy	81	19
t-Bu	-	88

Related Reagents.

2,5-Diazido-3,6-di-t-butyl-1,4-benzoquinone.

---

1. Moore, H. W.; Gheorghiu, M. D. *CSR* **1981**, *10*, 289.
2. Fishbein, P. L.; Moore, H. W. *OS* **1990**, *69*, 205.
3. Fishbein, P. L.; Moore, H. W. *JOC* **1984**, *49*, 2190.
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6. Moore, H. W.; Hughes, G.; Srinvasachar, K.; Fernandez, M.; Nghi, V.; Schoon, D.; Tranne, A. *JOC* **1985**, *50*, 4231.
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N-Chloro-*N*-cyclohexylbenzenesulfonamide[1]

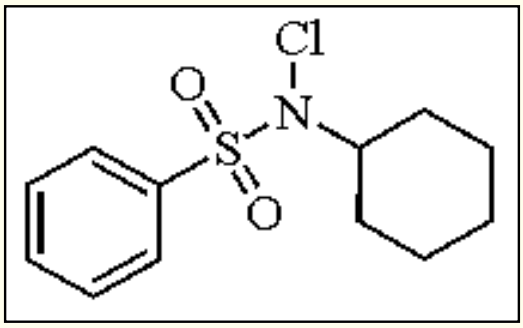

[15963-66-3] · $C_{12}H_{16}ClNO_2S$ · *N*-Chloro-*N*-cyclohexylbenzenesulfonamide · (MW 273.78)

(used for radical chlorination at allylic[1,4] or benzylic carbon[1])

Physical Data: mp 42 °C.

Solubility: sol benzene, CCl_4, $CHCl_3$, CH_2Cl_2; insol H_2O, petroleum ether.

Analysis of Reagent Purity: mp, NMR, combustion analysis.

Preparative Methods: *N*-cyclohexylbenzenesulfonamide can be prepared by addition of benzenesulfonyl chloride to a solution of cyclohexylamine in pyridine and purified by recrystallization from ethanol. *N*-Chlorination is accomplished by treating a solution of *N*-cyclohexylbenzenesulfonamide in dichloromethane with NaOCl solution at 0 °C followed by dropwise addition of glacial acetic acid.[1] Alternatively, a suspension of *N*-cyclohexylbenzenesulfonamide in acetic acid can be treated with NaOCl solution or powdered *N*-cyclohexylbenzenesulfonamide can be added to a solution containing $NaHCO_3$ and NaOCl.[2]

Purification: precipitation from $CHCl_3$ solution by addition of petroleum ether or trituration with petroleum ether.

Handling, Storage, and Precautions: to avoid decomposition, this reagent should be protected from prolonged exposure to light and moisture. Store under nitrogen in the dark. This toxic reagent should be handled in a fume hood.

Allylic Chlorination.

This reagent (**1**) has been used as a chlorine source in radical chlorination of allylic and benzylic positions. Treatment of alkenes bearing allylic carbon-hydrogen bonds with (**1**) in refluxing benzene in the presence of a radical initiator such as ***Dibenzoyl Peroxide*** results in the formation of allyl chlorides in good to moderate yields (eq 1).[1]

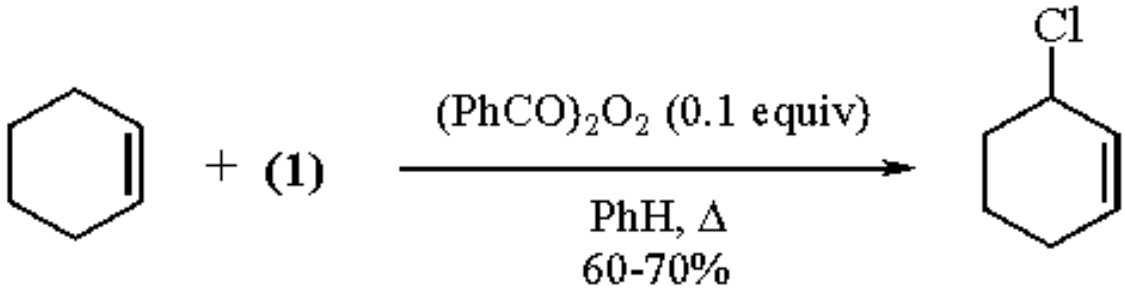

(1)

As with the more commonly used chlorinating agent ***N-Chlorosuccinimide***, this chlorination proceeds via a radical chain reaction in which Cl_2 is liberated and reacts with a carbon radical.[3] Consequently, isomeric mixtures are often obtained (eqs 2-4).[1,4]

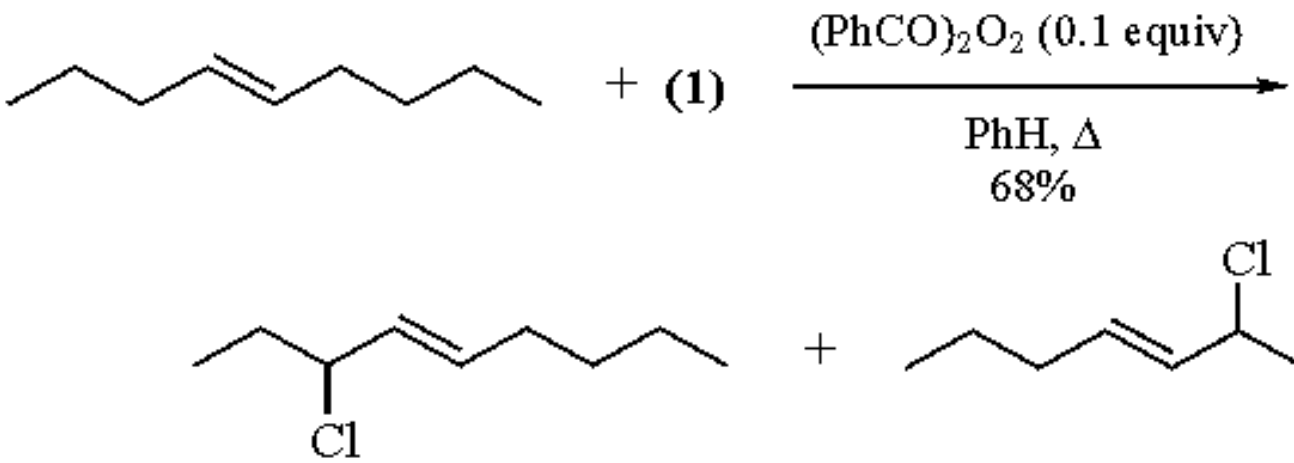

(2)

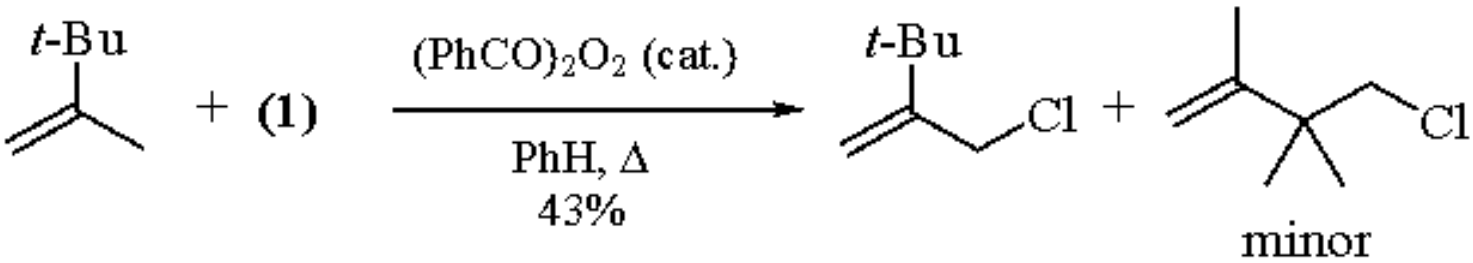

(3)

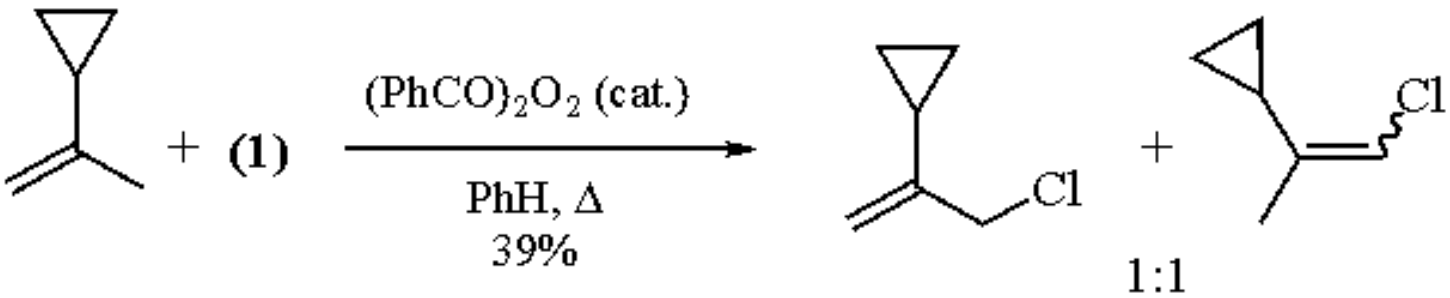

(4)

Separation of the resulting isomeric products is often difficult. For example, the isomeric chlorinated products in eq 4

were separated from one another using preparative gas chromatography.[4] *N*-Cyclohexylbenzenesulfonamide precipitates upon cooling of the reaction mixture and can be recovered by filtration.[1]

Chlorination at benzylic positions proceeds in good yields (eq 5).[1]

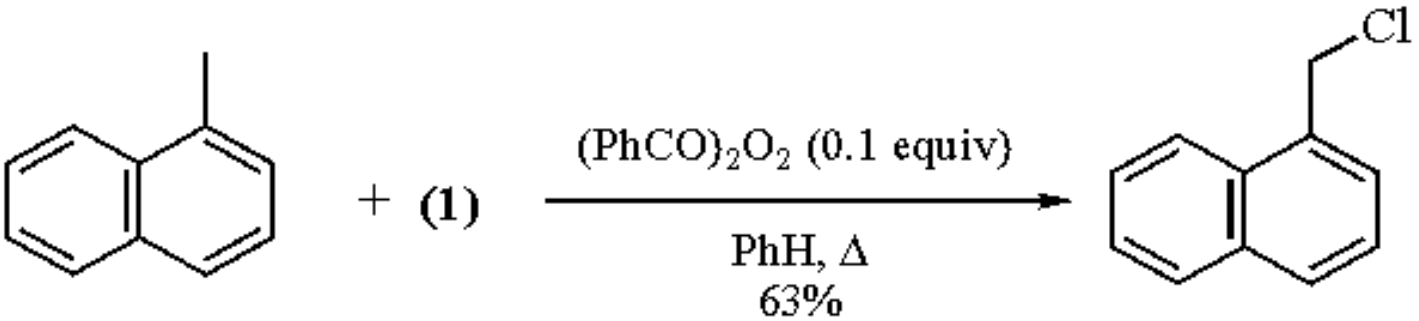

(5)

Related Reagents.

t-Butyl Hypochlorite; ***N-Chlorosuccinimide***; ***Hypochlorous Acid***; ***Phenylselenium Trichloride***.

---

1. Theilacker, W.; Wessel, H. *LA* **1967**, *703*, 34.
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3. Dauben, H. J.; McCoy, L. L. *JACS* **1959**, *81*, 4863.
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Chloro(η^5-cyclopentadienyl)[(4*R,trans*)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-*O*$^{\alpha}$,*O*$^{\alpha´}$]titanium

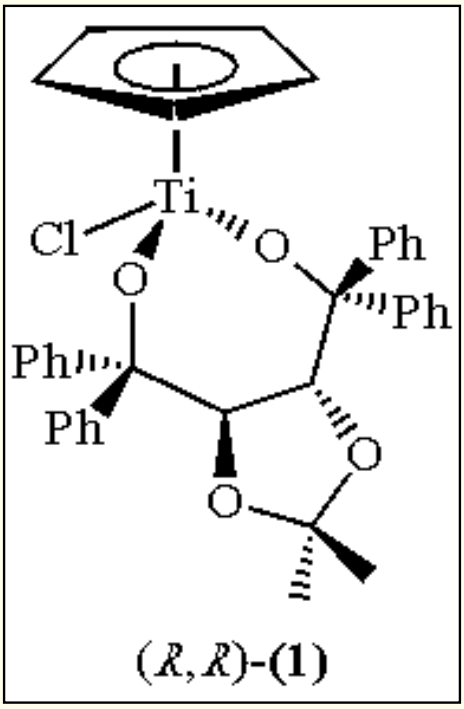

(4*R*,*trans*)

[132068-98-5] · $C_{36}H_{33}ClO_4Ti$ · Chloro(η^5-cyclopentadienyl)[(4*R*,*trans*)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-*O*$^{\alpha}$,*O*$^{\alpha´}$]titanium · (MW 613.0)

(highly enantio- and diastereoselective addition of allyl and terminally monosubstituted allyl groups to achiral and chiral aldehydes;[1] can also be used for enantioselective aldol reactions,[2] especially of glycine ester enolates[2a])

Physical Data: mp 214 °C (Mettler DSC); $[\alpha]_D$ = -243.4° (*c* = 1, $CHCl_3$); X-ray, ^1H, ^{13}C NMR.[1a]

Solubility: sol toluene (ca. 370 mg mL^{-1}), THF (ca. 470 mg mL^{-1}), diethyl ether (ca. 150 mg mL^{-1}).

Form Supplied in: pale yellow powder or crystals.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$);[1] may contain 1-5% of (4*R*,*trans*)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanol (but does not affect its efficiency).

Preparative Method: see ***Trichloro(cyclopentadienyl)titanium***.

Handling, Storage, and Precautions: the dry solid must be stored under exclusion of moisture and UV at rt (brown, tightly sealed bottle). It can, however, be handled quickly in the open, e.g. for weighing. Reactions should be carried out in dry equipment and with absolute solvents under argon or N_2.

Allyltitanation of Aldehydes.

The two-stage, one-pot procedure involves first the generation of the allyltitanium reagents (*R*)-(**2a-f**) (eq 1) by transmetalation of allyl-Grignard or allyl-Li compounds with a slight excess (1.2 equiv) of (*R*,*R*)-(**1**). It is advisable to analyze the content of the allylmetal precursor solution. Optimal conditions (time and temperature) of these transmetalations are preferably determined by test reactions with a simple aldehyde, assessing for maximal diastereo- and enantioselectivity. For stable allylmetal compounds, 1-3 h at 0 °C is usually sufficient. The allyltitanates (**2**) can be analyzed by ^{1}H and ^{13}C NMR.[1a] Fast allylic rearrangements are responsible for the formation of the thermodynamically most stable allyltitanium isomer with terminal substitution and *trans* double bond, irrespective of the nature of the organometallic precursor.

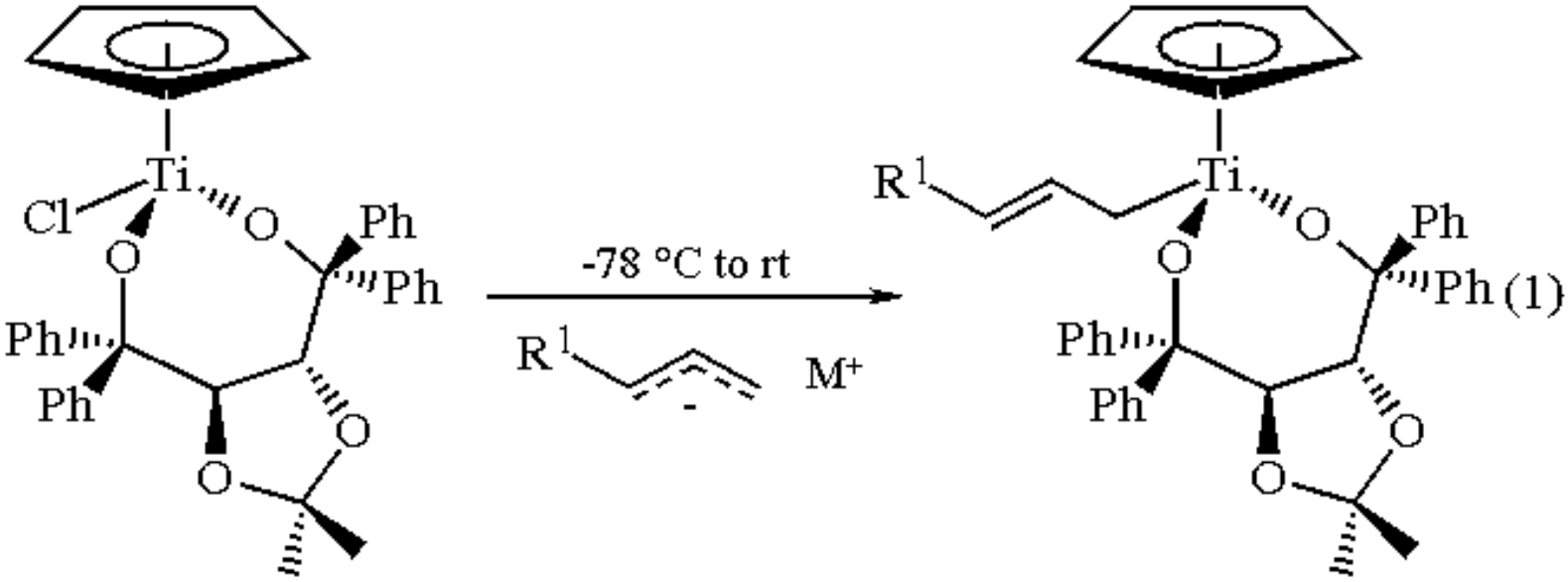

(*R*,*R*)-(**1**)

M =	MgCl	(*R*)-(**2a**), $R^1 = H$
	MgCl	(*R*)-(**2b**), $R^1 = Me$
	Li	(*R*)-(**2c**), $R^1 = CH{=}CH_2$
	Li	(*R*)-(**2d**), $R^1 = Ph$
	Li	(*R*)-(**2e**), $R^1 = SiMe_3$
	Li	(*R*)-(**2f**), $R^1 = 4\text{-}MeOC_6H_4O$

The second step, performed in situ, is the addition of ca. 0.75 equiv (based on **1**) of an aldehyde at -78 °C (eq 2). Most reactions are completed within 3 h and the resulting cyclopentadienyltitanium trialkoxides are hydrolyzed by stirring overnight with aqueous NH_4F (45%) at rt. The precipitated cyclopentadienyltitanium oxide (**3**) is removed by filtration and can be recycled to $CpTiCl_3$. The chiral ligand (**4**) and the product (**5**) are separated by crystallization or precipitation of (**4**) followed by distillation and/or chromatography.

The homoallylic alcohols (**5**) are isolated in fair to good yields. Their optical purity often exceeds 95% and the *anti* diastereomers are produced almost exclusively (&egt;98% ds). Exceptions with up to 33% *syn* epimer have, however, been obtained for (**2f**).[1b] The reagent controlled stereoselectivity of (*R*)-(**2**) and the enantiomers (*S*)-(**2**) is best documented by conversions with chiral aldehydes, examples being (**6**),[1a] (**7**),[1a] and (**8**).[1b]

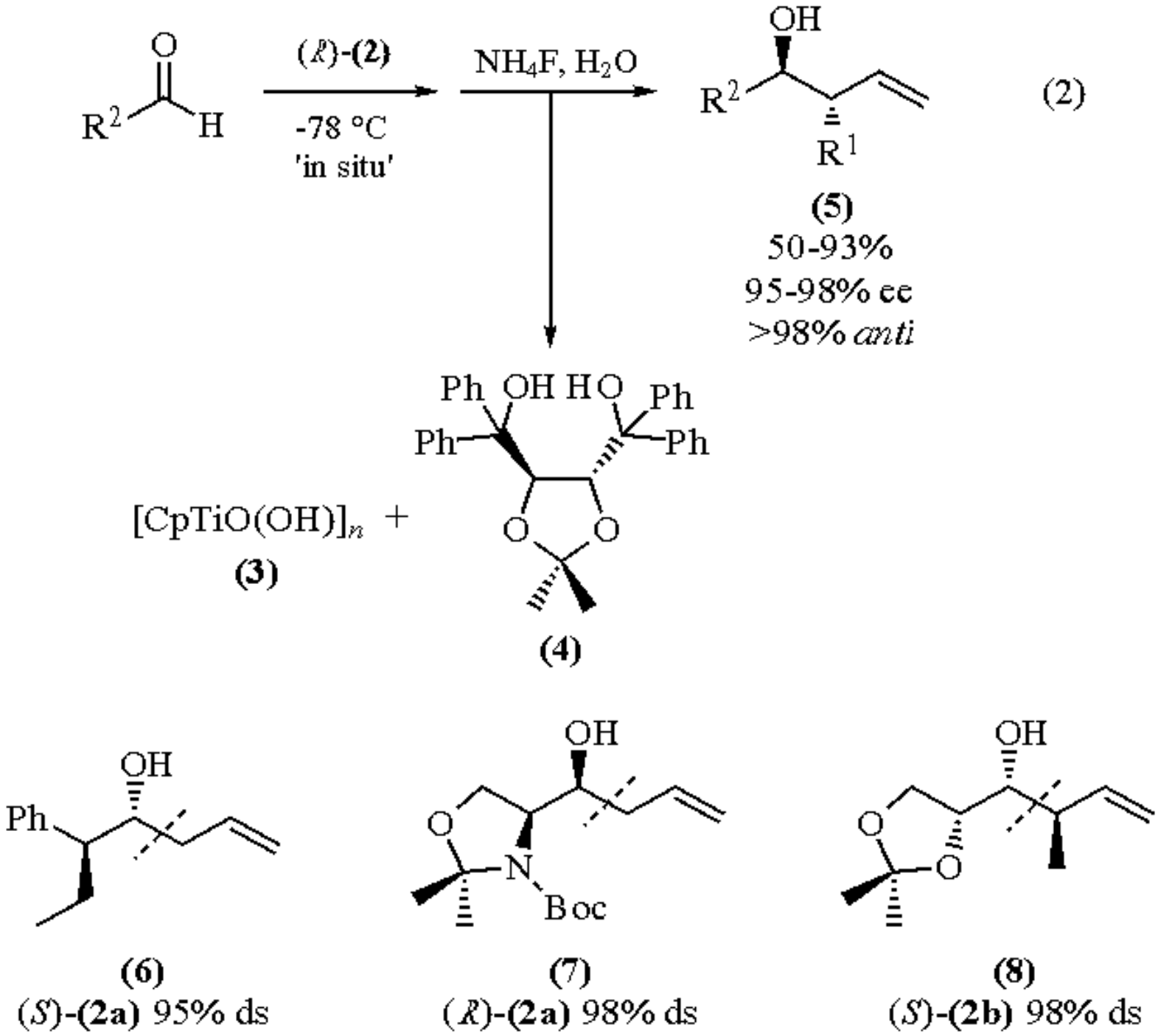

The allylation of (2*S*)-2-phenylbutyraldehyde to give (**6**) allows a comparison with other similar reagents. Whereas the transformation to (**6**) with (*S*)-(**2a**) (mismatched pair) proceeds with 95% ds, lower selectivity is observed for the allyltitanium reagent prepared analogously from ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium*** (79% ds) or from ***B-Allyldiisopinocampheylborane*** (74% ds).[3a] Due to the fast *E*/*Z* isomerization of (**2**), the *syn* isomers of (**5**) cannot be obtained as the major product by using allyltitanium compounds, e.g. (*R*)-(**2b**), derived from chloride (**1**). *Syn*-crotyl adducts are efficiently obtained with chiral allylboron reagents,[3] e.g. diisopinocampheyl-(*Z*)-crotylborane[3a,b] or diisopropyl tartrate (*Z*)-crotylboronate.[3c] Inferior stereoselectivity is also exhibited by 2-substituted and 1,3-disubstituted allyltitanium reagents derived from (**1**).[1,2b] The use of similar chiral titanium reagents[4] and stereoselective additions with other allylmetal compounds[5] have recently been reviewed. While all these methods rely on stoichiometric amounts of a chiral reagent, catalytic amounts of a chiral acyloxyborane complex mediate the enantioselective addition of allylsilanes[6a] and allylstannanes[6b] to aldehydes. Very recently, the addition of allyltributyltin was also found to be catalyzed by a complex formed from 1,1´-bi-2-naphthol and $TiCl_4$ (see ***(R)-1,1´-Bi-2,2´-naphthotitanium Dichloride***).[7]

Aldol Reaction.

In addition to the allyl derivatives (**2**) (eq 1), titanium ester enolates derived from chloride (**1**) react with aldehydes, affording aldol products after hydrolysis. Compared to the analogous reagents prepared from ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium*** the enantioselectivity of these enolates is only moderate, 78% ee for the enolate of *t*-butyl acetate[2] and 26-78% ee in the case of 2,6-dimethylphenyl propionate.[4] Better selectivity (81-94% ee) was, however, obtained for Ti enolates (**9**) derived from stabase-protected glycine esters (**10**) (eq 3).[2a] The primary *N*-bis-silyl-protected adduct (**11**) can easily be transformed to other *N*-derivatives, e.g. the *t*-butyl carbamate (**12**). This method thus gives access to L-*threo*-α-amino-β-hydroxy acids. Further details and references to other methods are provided in the entry for ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium***, an analogous reagent affording the enantiomer of (**12**).

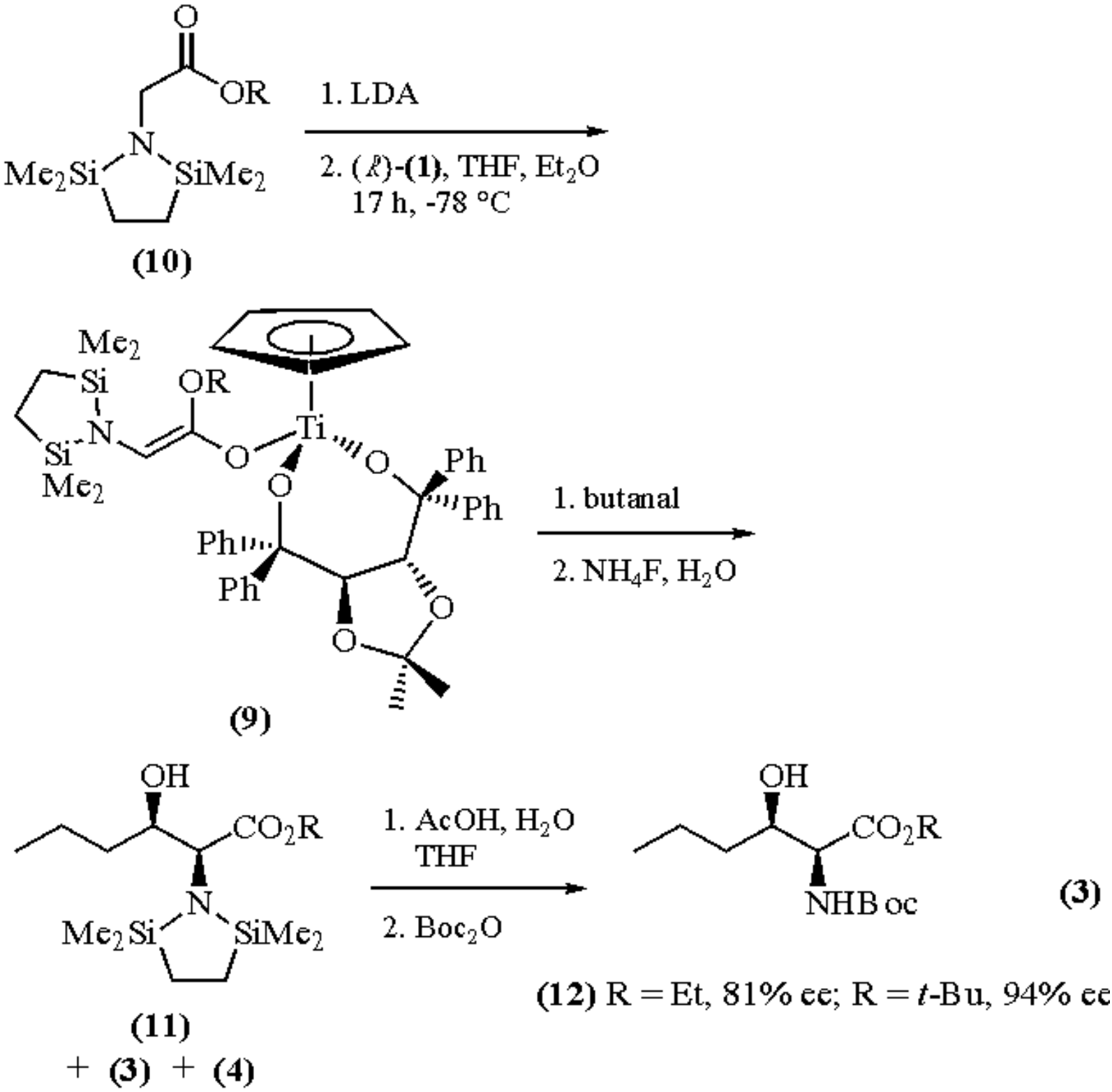

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1. (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *JACS* **1992**, *114*, 2321. (b) Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Rothe-Streit, P.; Rihs, G. *PAC* **1992**, *64*, 1897.
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3. (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *JOC* **1989**, *54*, 1570. (b) Racherla, U. S.; Brown, H. C. *JOC* **1991**, *56*, 401. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *JACS* **1990**, *112*, 6339. (d) Short,

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5. Yamamoto, Y.; Asao, N. *CRV* **1993**, *93*, 2207.
6. (a) Furuta, K.; Mouri, M.; Yamamoto, H. *SL* **1991**, 561. (b) Marshall, J. A.; Tang, Y. *SL* **1992**, 653.
7. (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *JACS* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *JACS* **1993**, *115*, 8467.

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1-Chloro-3-diazo-2-propanone

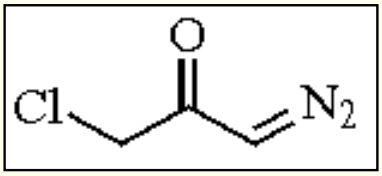

[20485-53-4] · $C_3H_3ClN_2O$ · 1-Chloro-3-diazo-2-propanone · (MW 118.53)

(undergoes Darzens condensation with aldehydes;[1,2] efficiently alkylates benzene;[3] forms a quaternary ammonium salt with trimethylamine;[4] undergoes P-H carbene insertion[5] with dimethyl phosphite; displaceable diazo moiety[6])

Alternate Name: chloromethyl diazomethyl ketone.

Physical Data: mp 3 °C; bp 75 °C/13 mmHg.

Preparative Method: prepared by reaction of chloroacetyl chloride with excess diazomethane. In most recent reports,[1] the crude material is purified by fractional vacuum distillation to furnish product as a yellow oil in 52% yield. In earlier references, isolation of pure material is accomplished by three-fold distillation under reduced pressure[8] or crystallization from diethyl ether at -80 °C.[7]

Handling, Storage, and Precautions: no difficulties have been reported. However, alkyl diazo compounds in general are considered explosive and appropriate precautions should be taken during handling and distillation of these materials. Use in a fume hood.

Darzens Condensation.

Darzens condensation[1,2] of 1-chloro-3-diazo-2-propanone (**1**) with aldehydes (**2a-e**) affords epoxy diazo ketones (**3a-e**) (eq 1). Treatment (stoichiometric quantities) of (**1**) and benzaldehyde (**2a**) in ice-cold methanol with an aqueous ***Sodium Hydroxide*** solution provides 1-diazo-3,4-epoxy-4-phenyl-2-butanone (**3a**) in 69% yield. In all cases the reaction is reported to proceed stereoselectively and affords epoxides which are exclusively of the *trans* configuration. Diadduct (**4**) is obtained on treatment of the diazo ketone with two molar equivalents of sodium hydroxide and a large excess of benzaldehyde.

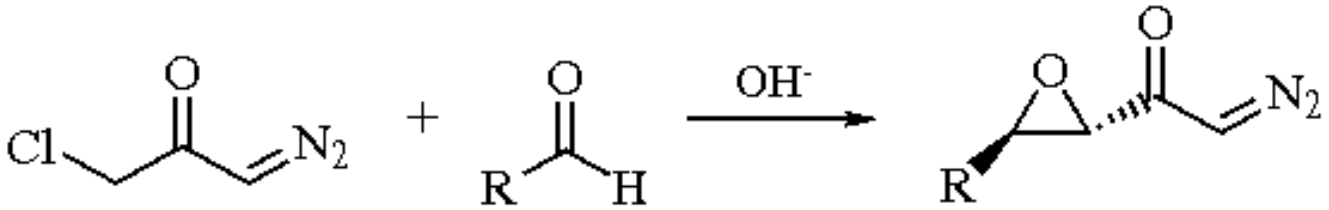

(1)

(1) **(2)** **(3)**

(**a**) R = Ph; (**b**) R = *p*-$NO_2C_6H_4$; (**c**) R = *p*-$MeOC_6H_4$; (**d**) R = *trans*-PhCH=CH; (**e**) R = 2-thienyl

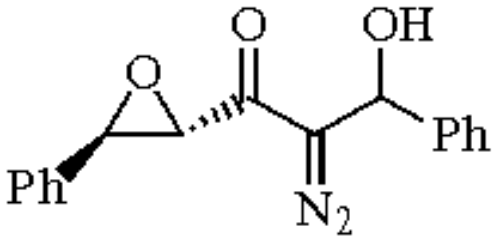

(4)

Alkylation of Benzene.

In a process reported to involve a cycloheptatrienyl intermediate, 1-chloro-3-diazo-2-propanone has been shown to alkylate benzene providing benzyl ketone (**6**).[3] The method employs sequential catalysis by rhodium(II) trifluoroacetate and ***Trifluoroacetic Acid***. Diazo ketone (**1**) is added to excess benzene containing a catalytic amount of rhodium(II) trifluoroacetate. Subsequent removal of excess benzene and treatment with trifluoroacetic acid in dichloromethane affords (**6**) in an 84% yield. Several α-diazo ketones were utilized to provide a variety of benzyl ketones, illustrating the scope and efficiency of this means of electrophilic aromatic alkylation.

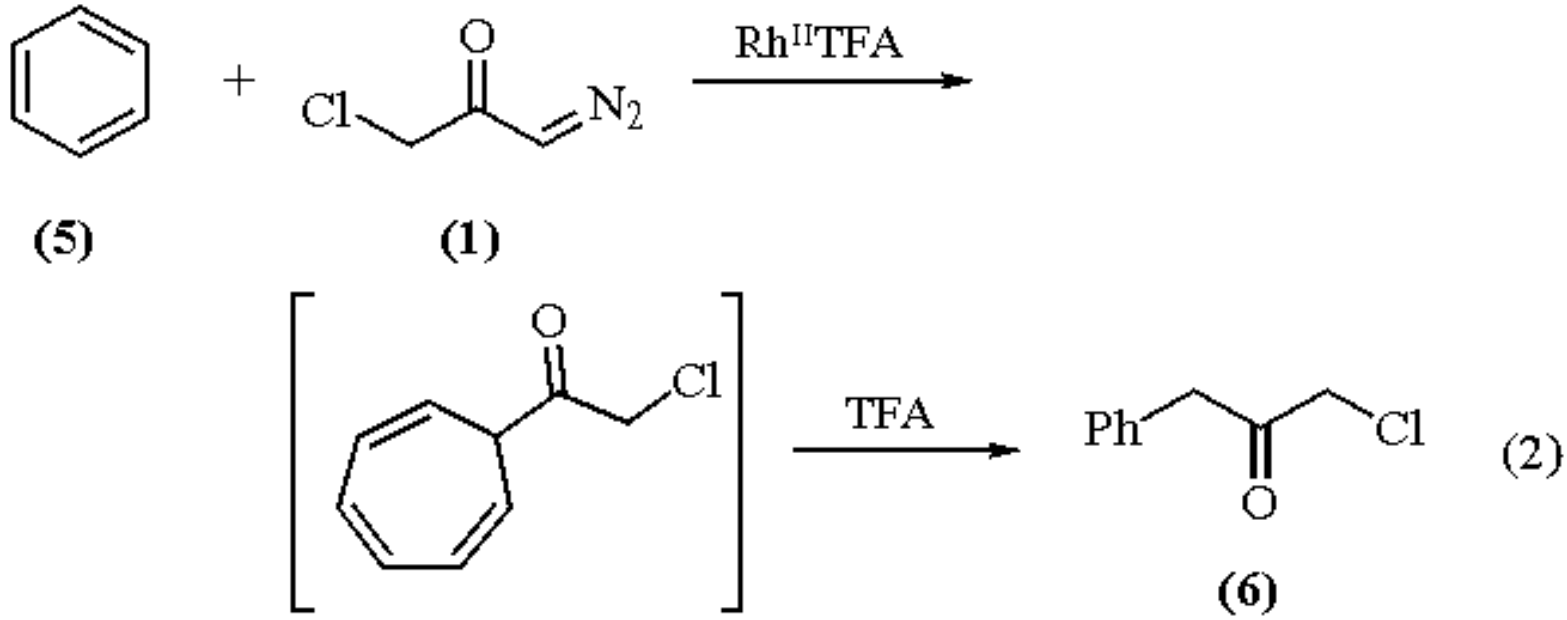

Quaternary Ammonium Salts.

1-Chloro-3-diazo-2-propanone reacts with ***Trimethylamine*** to form quaternary ammonium salt (**7**).[4]

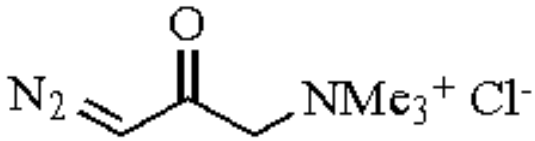

(7)

Phosphorus-Hydrogen Carbene Insertion.

In a ***Copper(I) Acetylacetonate*** catalyzed reaction, (**1**) and dimethyl phosphite form 3-chloro-2-oxopropylphosphonate (**8**) via P-H carbene insertion (eq 3).[5]

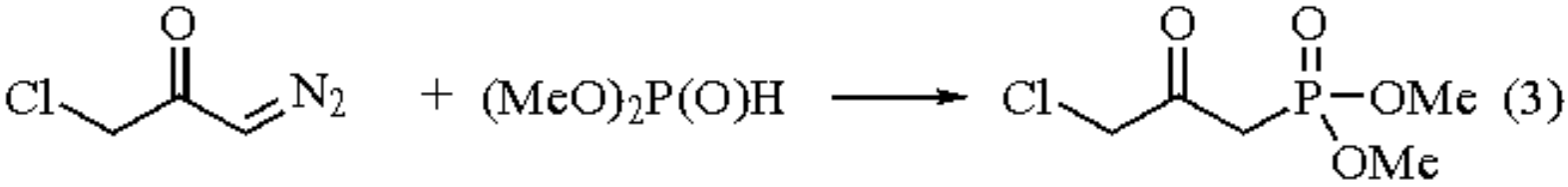

(1) (8)

Diazo Displacement.

Displacement of the diazo moiety in (**1**) with ***Phosphoric Acid*** furnishes 3-chloro-2-oxopropyl hydrogen phosphate

(**9**).[6]

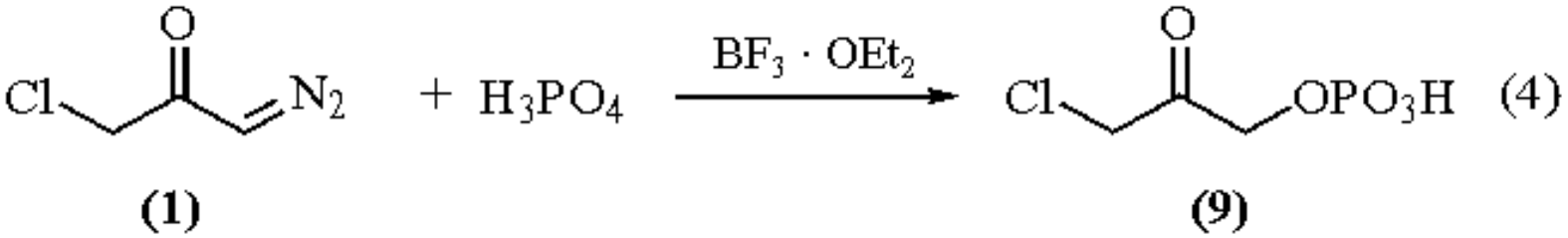

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2-Chloro-1,1-diethoxyethane

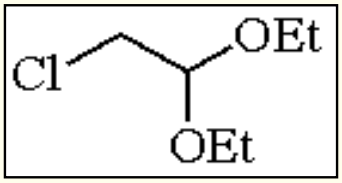

[621-62-5] · $C_6H_{13}ClO_2$ · 2-Chloro-1,1-diethoxyethane · (MW 152.62)

(versatile two-carbon synthon; forms carbocycles,[4] heterocycles;[14-18] used in the synthesis of alkynes[1,2] and alkenes[3,5,6])

Alternate Names: 1-chloro-2,2-diethoxyethane; chloroacetaldehyde diethyl acetal.

Physical Data: colorless liquid, bp 151 °C; *d* 1.018 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: neat liquid of high purity; readily available.

Handling, Storage, and Precautions: flammable, moisture sensitive. Use in a fume hood.

Alkoxyalkynes[1] and Alkynols.[2]

Sodium ethoxyacetylide is formed on treatment with ***Sodium Amide***/liq. NH_3, from which ethoxyacetylene, 1-ethoxyalkynes, or 1-ethoxyalkynols can be obtained by quenching the acetylide anion with the appropriate electrophile (eq 1).

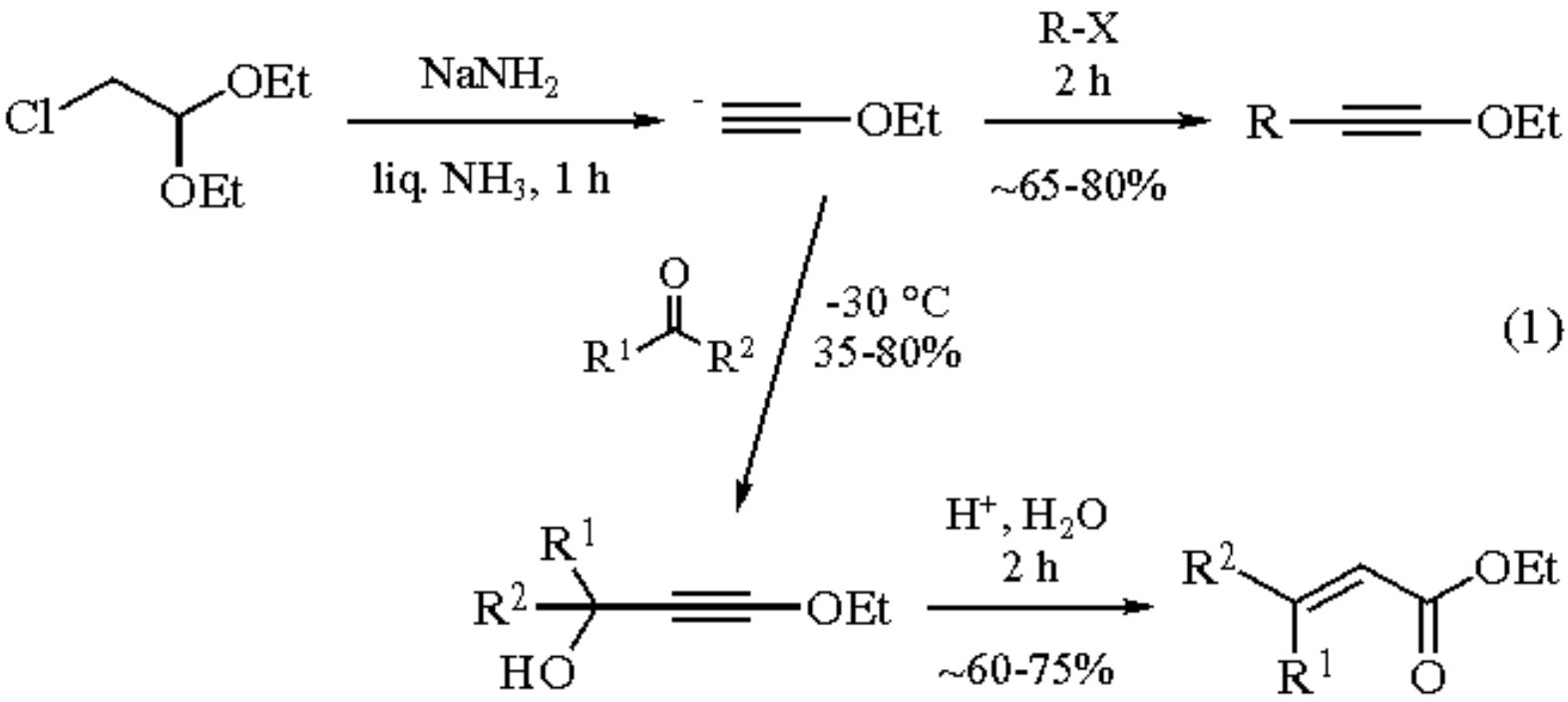

The alkoxyalkynols formed can easily be converted to α,β-unsaturated esters on acid treatment.[3]

Hydroxycyclopentenones.[4]

Biologically important 4-hydroxycyclopentenones are readily available in a high yielding route by reaction of 2-chloro-1,1-diethoxyethane with a dithiane (eq 2). It is noteworthy that yields are much lower with the corresponding bromoacetal.

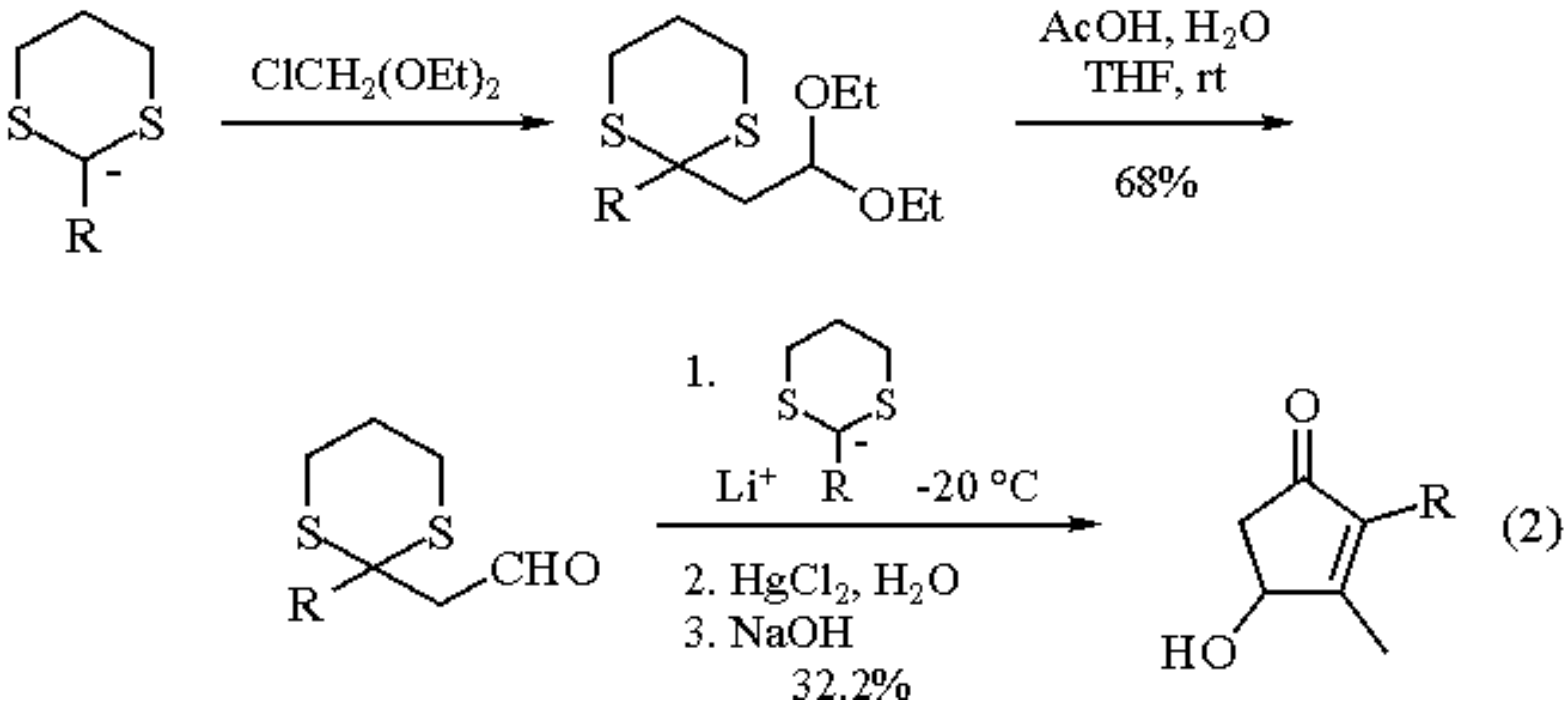

Functionalized Allylsilanes.[5]

With 1-ethoxy-3-trimethylsilyl-1-propyne, the reagent under ***Titanium(IV) Chloride*** catalysis affords 2-carbonylethoxyallyltrimethylsilane regio- and stereoselectively (eq 3).

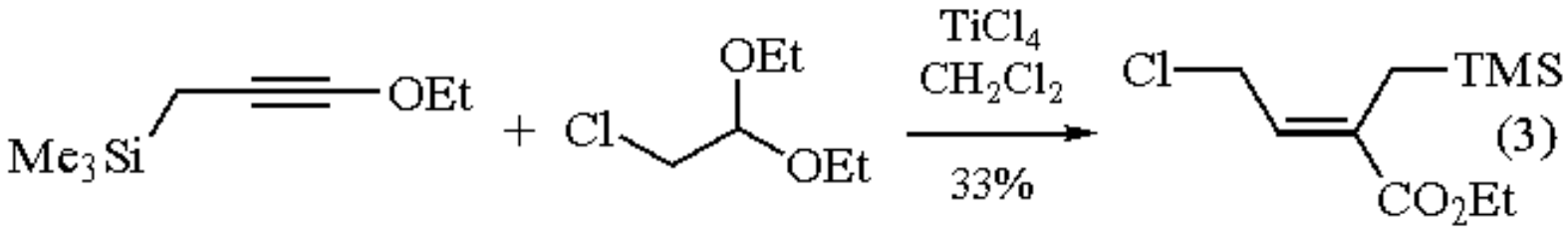

Vinylation of Enolates.[6]

An electrophilic species equivalent to a vinyl cation can be generated by treating the reagent with ***Sodium Dicarbonylcyclopentadienylferrate*** (eq 4).

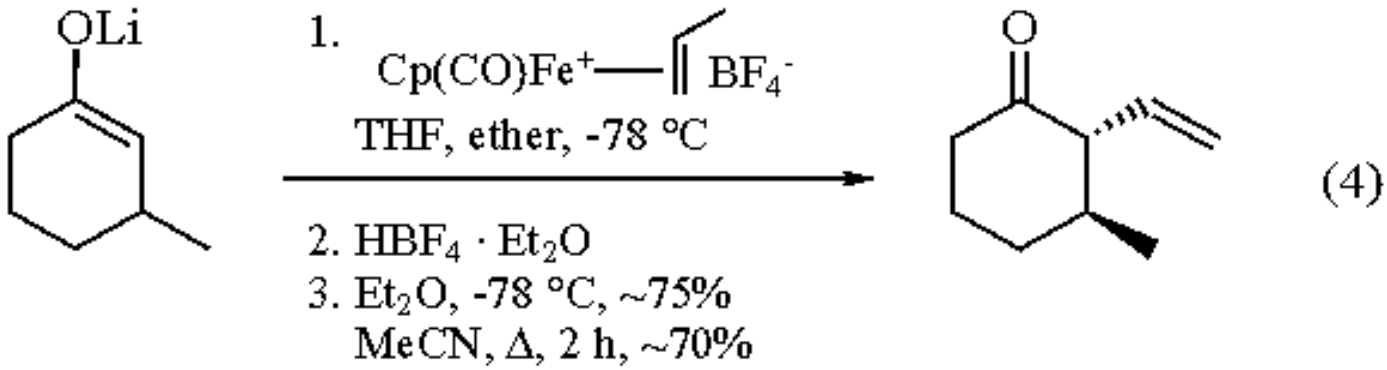

Isocytosine can be vinylated with 2-chloro-1,1-diethoxyethane to give the corresponding imidazolo[1,2-*a*]pyrimidine-5(1*H*)-one and -7(8*H*)-one (eq 5).[7] The process is reversable upon treatment with ***Lead(IV) Acetate*** and mild basic hydrolysis. Annulations to give six-membered ring systems containing a bridgehead nitrogen are also common.[8]

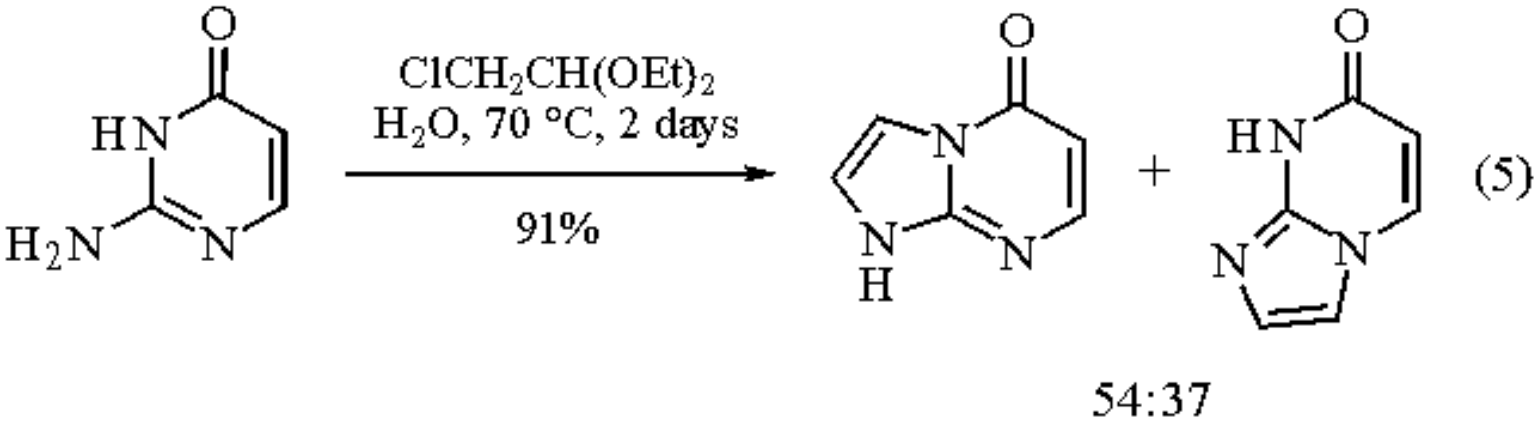

Miscellaneous applications include the synthesis of vinyl ethers[9] under acid catalysis and ketene acetals[10] under base catalysis; synthesis of sulfonic esters or sulfonyl ethers in reactions with a sulfinic acid in the presence of ***Boron Trifluoride Etherate***;[11] as a precursor to glycol aldehyde;[12] and use in the synthesis of *N*-nitrosamino aldehydes.[13] Among the heterocycles synthesized are imidazopyrazines,[14] imidazopyrazoles,[15] phenoxypyrimidinones,[16] 3-

substituted 1,5-dihydrobenzodithiepines,[17] *P*-functionalized phospholene oxides,[18] etc.

Related Reagents.

Chloroacetaldehyde; ***Ethoxyacetylene***.

---

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Chlorodiethylborane

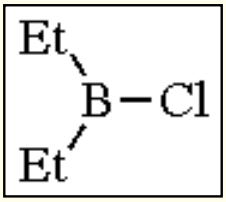

[5314-83-0] · $C_4H_{10}BCl$ · Chlorodiethylborane · (MW 104.39)

(reagent for the synthesis of organoboranes;[1] protection of sugars;[2] cleavage of strained ethers;[3] component of polymerization catalysts[4])

Physical Data: bp 81 °C.

Solubility: sol diethyl ether, THF, pentane, benzene.

Preparative Methods: chlorodiethylborane is conveniently prepared by the redistribution reaction of triethylborane and boron trichloride in the presence of a catalytic amount of tetraethyldiborane.[5] The product is isolated by distillation in 98% yield. Other methods are also known,[6-8] e.g. ^{10}B-labelled chlorodiethylborane is obtained by the reaction of ^{10}B-labelled triethylborane with antimony pentachloride.[6]

Handling, Storage, and Precautions: chlorodiethylborane is a colorless, mobile, thermally stable liquid. It is spontaneously flammable in air and should be handled and stored under nitrogen or argon. It reacts with alcohols and water.

Organoboranes.

Various diethylorganoboranes containing alkyl,[9] alkenyl,[10] alkynyl,[11] allylic,[12-16] aryl,[17,18] amino,[19-24] and other groups[25-30] are prepared by the transmetalation reaction of chlorodiethylborane with the corresponding alkali metal, tin, silver, or silicon derivatives. Allylic diethylboranes generated from alkenes via metalation are useful intermediates in the contrathermodynamic isomerization and allylic monodeuteration of alkenes (eq 1),[12,14] and the hydroxyalkylation, hydroxymethylation, acylation, and formylation of alkenes (eqs 2 and 3).[13,15,16]

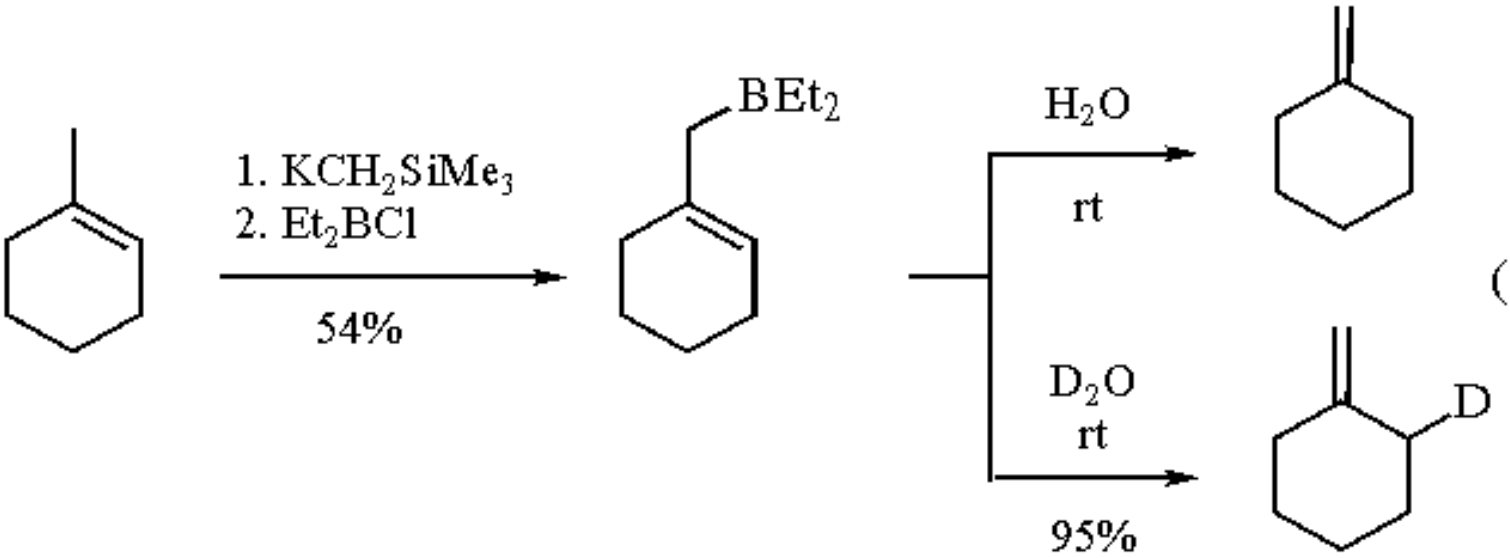
1. KCH2SiMe3
2. Et2BCl
54%
BEt2
H2O
rt
D2O
rt
95%
D

(1)

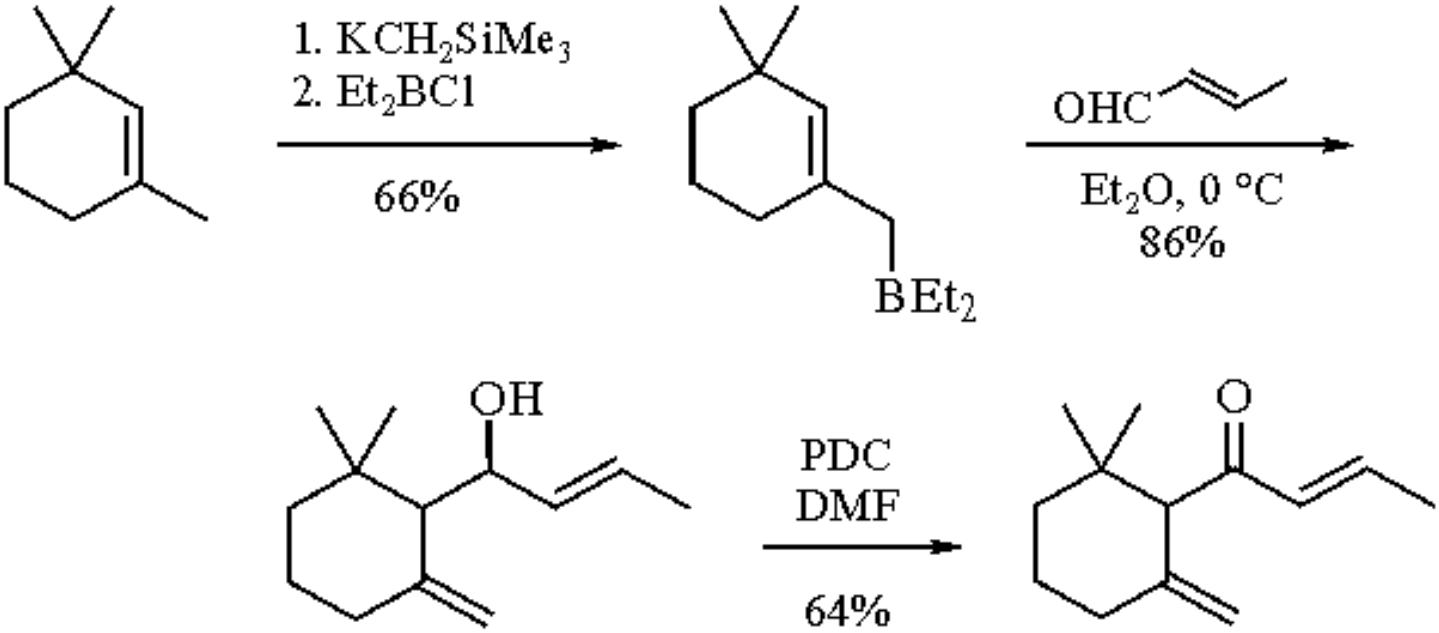
1. KCH2SiMe3
2. Et2BCl
66%
BEt2
OHC
Et2O, 0 °C
86%
OH
PDC
DMF
64%
O

(2)

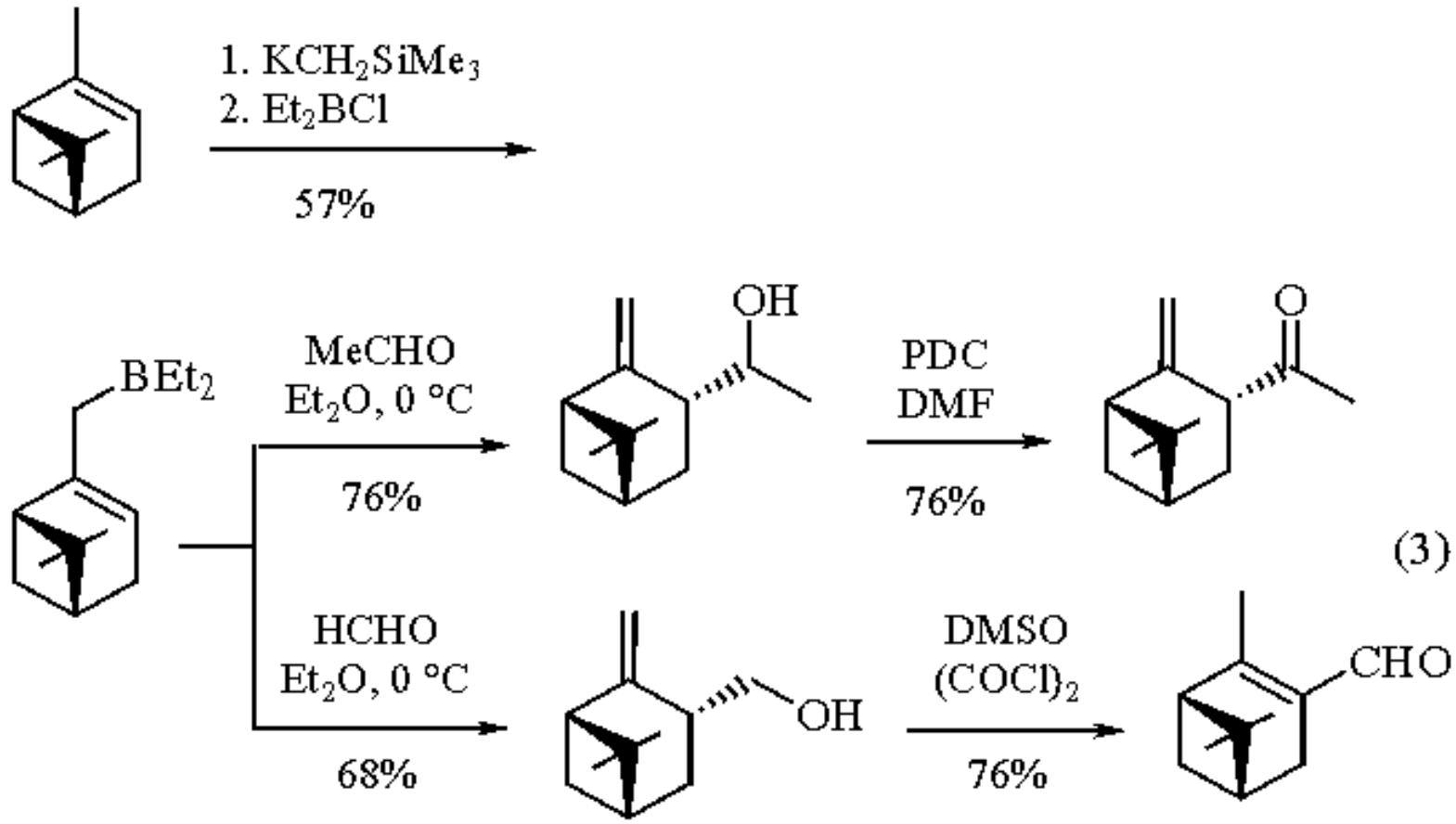

(3)

Bis(dialkylboryl)alkenes derived from l-alkynes are readily hydrolyzed to stereochemically pure (*Z*)-alkenes (eq 4).[10]

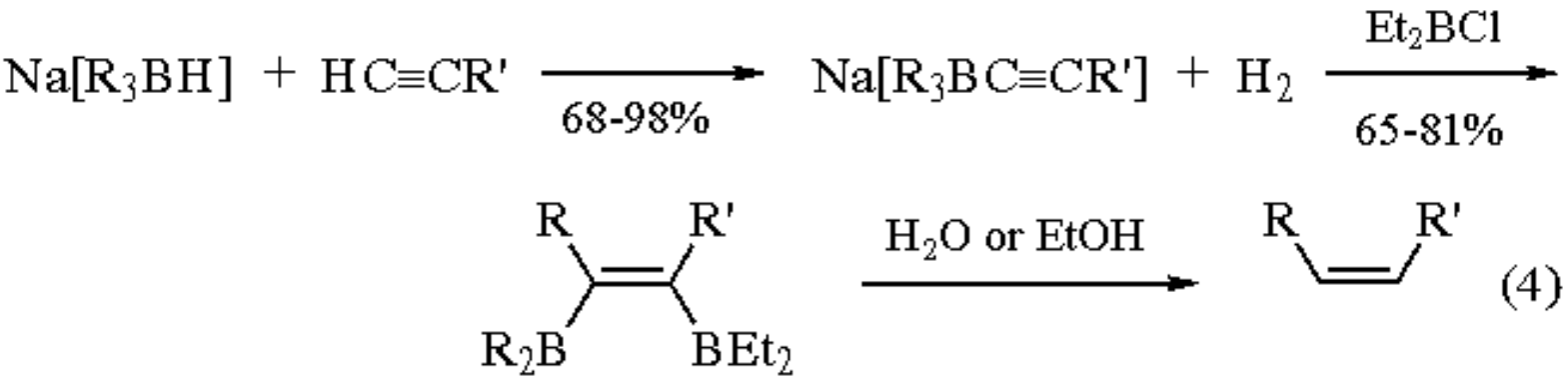

(4)

R = alkyl; R' = alkyl, Ph

The reduction of chlorodiethylborane with ***Lithium Aluminum Hydride*** affords tetraethyldiborane, a useful hydroborating agent, also available by other methods.[31-33] This method, however, initially generates a pure reagent. Deuterium labelled tetraethyldiborane is readily prepared (eq 5).[31]

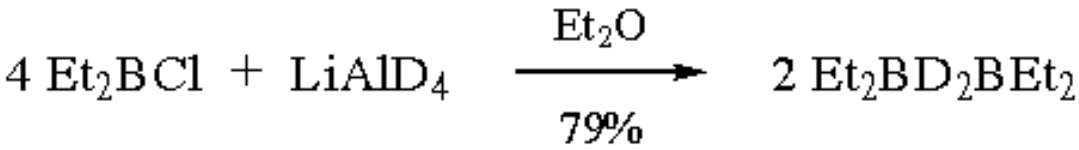

(5)

Tetraethyldiborane and other primary alkylboranes exist in equilibrium with alkyldiboranes and trialkylboranes. The mixtures have a mean composition corresponding to tetraalkyldiborane.[33]

The hydroxyl and carboxyl groups of sugars can be protected as diethylboryl derivatives with a mixture of chlorodiethylborane and triethylborane (eq 6).[2]

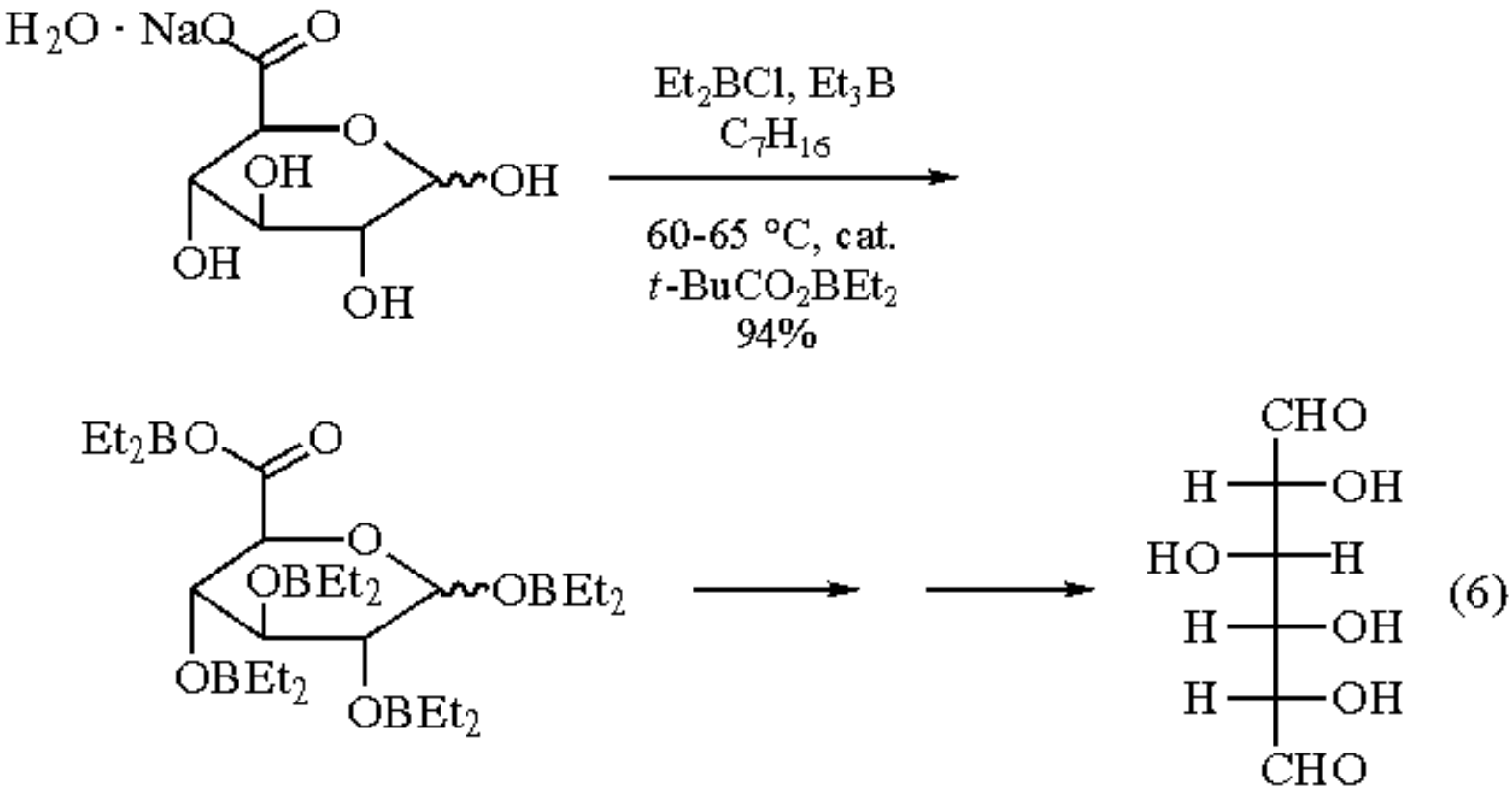

Cleavage of Ethers.[34]

Chlorodiethylborane cleaves strained cyclic ethers, e.g. oxetanes.[3] Dialkylbromoboranes, particularly *B*-bromo-9-borabicyclo[3.3.1]nonane, are more effective reagents.[35]

Polymerization Catalysis.

Chlorodiethylborane is applied in polymerization catalysis, e.g. regulating the alternation of copolymerization of methacrylate and styrene,[4,36,37] or as a component in Ziegler-Natta-type catalysts for polymerization of alkenes.

Related Reagents.

9-Bromo-9-borabicyclo[3.3.1]nonane; ***Bromodimethylborane***.

---

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Chlorodifluoromethane

$CHClF_2$

[75-45-6] · $CHClF_2$ · Chlorodifluoromethane · (MW 86.45)

(difluoromethylating reagent, can function as a precursor to difluorocarbene)

Physical Data: bp -40.8 °C.[1]

Solubility: sol ether, acetone, chloroform.

Form Supplied in: gas.

Preparative Method: prepared by the chlorination of CH_2F_2 with Cl_2;[2] by the hydrogenation of CCl_2F_2 in a Pt-lined tube at high temperature;[3] by the halogen-exchange reaction of $CHCl_3$ with HF and $SbCl_5$;[4] and by the reaction of HCF_2CO_2Ag with Cl_2.[5]

Handling, Storage, and Precautions: should be handled in a fume hood.

Reaction with Oxygen Nucleophiles.

Treatment of $CHClF_2$ with alkoxides in the corresponding alcohols gives alkyl difluoromethyl ethers.[6] Reaction of $CHClF_2$ with phenols in an aqueous dioxane solution and in the presence of an excess of ***Sodium Hydroxide*** produces aryl difluoromethyl ethers (eq 1).[7]

$$CHClF_2 + NaOR \longrightarrow ROCF_2H \qquad (1)$$

$$R = \text{alkyl, aryl}$$

Reaction with Phosphorus Nucleophiles.

Treatment of the anion of diethyl phosphite with $CHClF_2$ in hexane gives diethyl difluoromethylphosphonate (49%) (eq 2).[8] A modification of this route which employed THF as the solvent afforded the difluoromethylphosphonate in higher yield (77%).[9]

$$CHClF_2 + (RO)_2PONa \longrightarrow (RO)_2P(O)CF_2H \qquad (2)$$

Reaction with Sulfur Nucleophiles.

Reaction of $CHClF_2$ with sulfite in aqueous solution yields the difluoromethanesulfonate (eq 3).[10] Treatment of $CHClF_2$ with RSNa gives the difluoromethyl sulfide (eq 4).[6,11]

$$CHClF_2 + SO_3^{2-} \longrightarrow CF_2HSO_3^- \qquad (3)$$

$$CHClF_2 + RSNa \longrightarrow RSCHF_2 \qquad (4)$$

R = alkyl, aryl

Reaction with Carbon Nucleophiles.

Treatment of $CHClF_2$ with phosphonium ylides affords the corresponding 1,1-difluoroalkenes (eq 5).[12] Reaction of $CHClF_2$ with the carbanions of an alanine derivative or malonate affords the α-difluoromethylated alanine derivative[13] and the α-difluoromethylated malonate,[14,15] respectively (eq 6).

$$Ph_3P{=}CHR + CHClF_2 \longrightarrow F_2C{=}CHR \qquad (5)$$

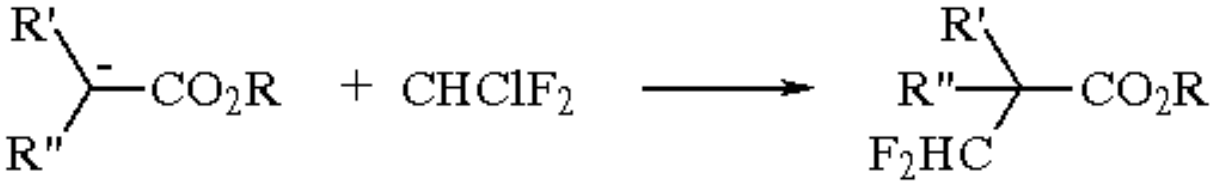

(6)

Reaction with Nitrogen Nucleophiles.

Treatment of $CHClF_2$ with 2-ethoxycarbonylindole gives the corresponding *N*-difluoromethyl-2-ethoxycarbonylindole in excellent yield (eq 7).[15] When the sodium derivative of carbostyril is treated with $CHClF_2$, however, a mixture of 2-difluoromethoxyquinoline (18-35%), *N*-difluoromethyl-α-quinolone (10-18%), and two other compounds is obtained (eq 8).[15]

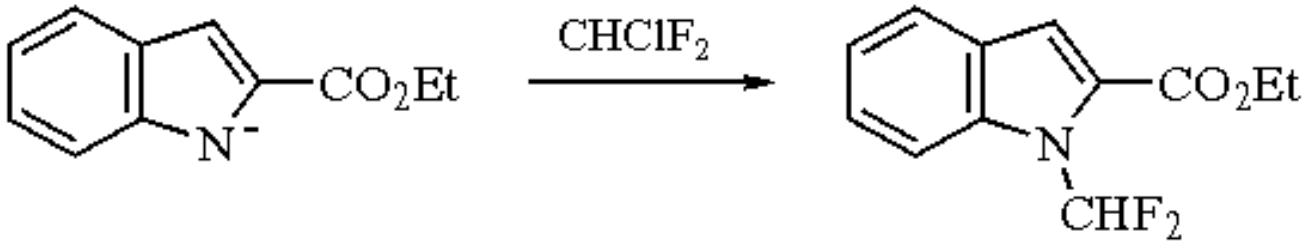

(7)

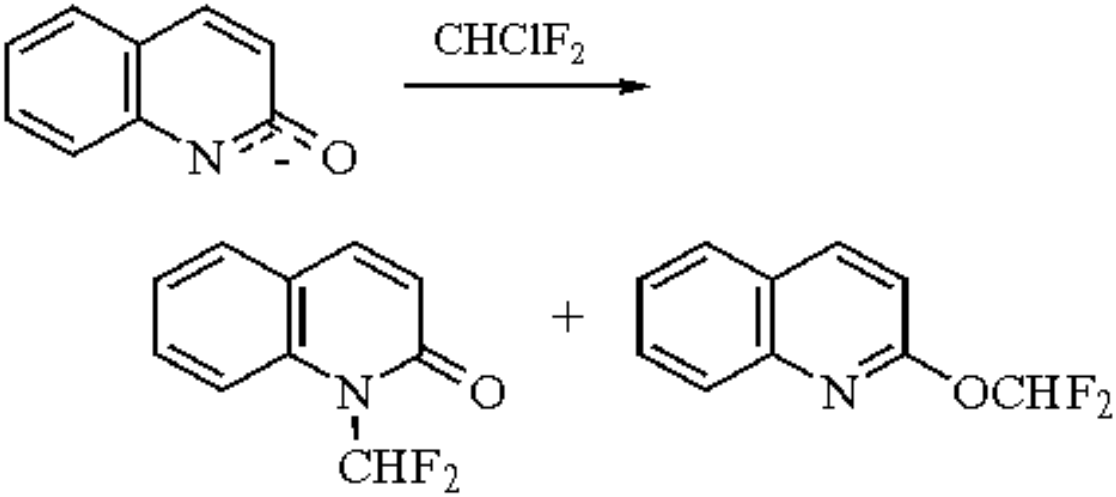

+ two others (8)

Difluorocarbene Formation and Reactions.

Difluorocarbene has been generated from $CHClF_2$ and base; it undergoes cycloaddition with alkenes to give the corresponding *gem*-difluorocyclopropane derivatives (eq 9).[16] Tetrafluoroethylene (TFE) is obtained by pyrolysis of $CHClF_2$ at high temperature (eq 10).[17]

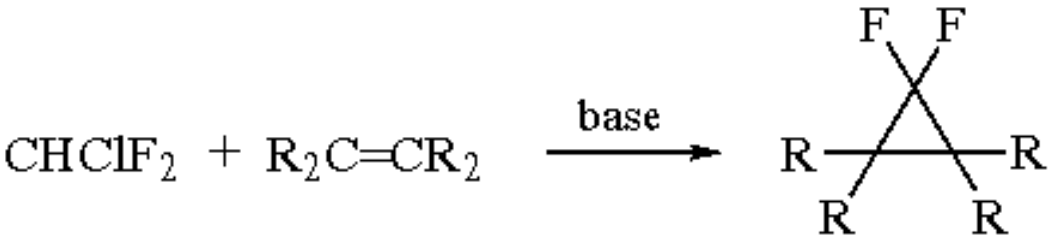

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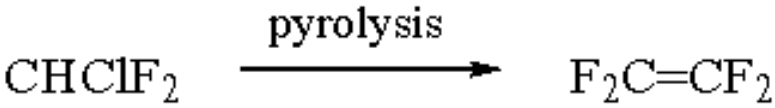

(10)

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Chlorodiiodomethane[1]

$CHClI_2$

[638-73-3] · $CHClI_2$ · Chlorodiiodomethane · (MW 302.27)

(carbenoid precursor used for formation of halo substituted cyclopropanes[2])

Physical Data: clear liquid, bp 200 °C (88 °C/30 mmHg);[3] *d* 3.17 g cm^{-3} at 0 °C.[4]

Solubility: sol CH_2Cl_2, benzene, hexane, dioxane, chloroform; insol water.

Preparative Methods: reaction of ***Iodoform*** with ***Mercury(II) Chloride***;[5] reaction of ***Chloroform*** with ***Ethyl Iodide*** in the presence of ***Aluminum Chloride***;[2] reaction of chloroform with ***Sodium Iodide*** and ***Sodium Hydroxide*** under phase transfer catalysis.[6] *Drying:* material is redistilled before use.

Analysis of Reagent Purity: bp and NMR (δ ^1H 6.18 ppm;[6] δ ^{13}C (calc. 60.6 ppm)).[7]

Handling, Storage, and Precautions: best kept in the dark for extended periods.

Halosubstituted Cyclopropanes.

Reaction of chlorodiiodomethane with alkenes under a variety of conditions gives rise to substituted cyclopropanes in reasonable yield. The additions, which have been proven to be electrophilic in nature, give product mixtures which are dependent on the conditions used. If hydroxide is used, under phase transfer conditions, chloroiodocyclopropanes result (eq 1). A wide range of alkene substituents has been studied.[8]

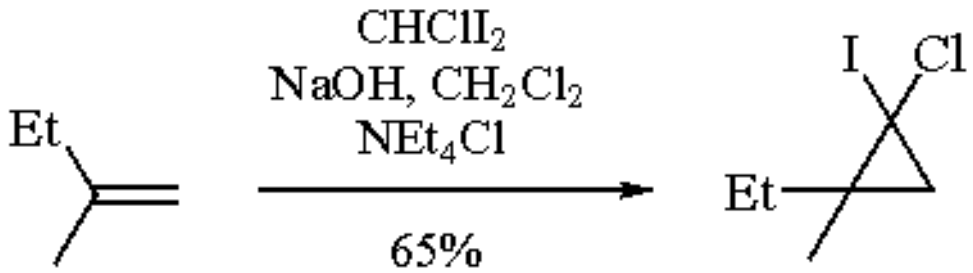

(1)

Reaction with alkenes in the presence of ***Diethylzinc***, however, gives rise to chloro-substituted cyclopropanes almost exclusively (eq 2).[9,10] The high *endo*:*exo* ratio is of note here (the analogous reaction with bromodiiodomethane gives the bromocyclopropane with a 2.8:1 *endo:exo* ratio).

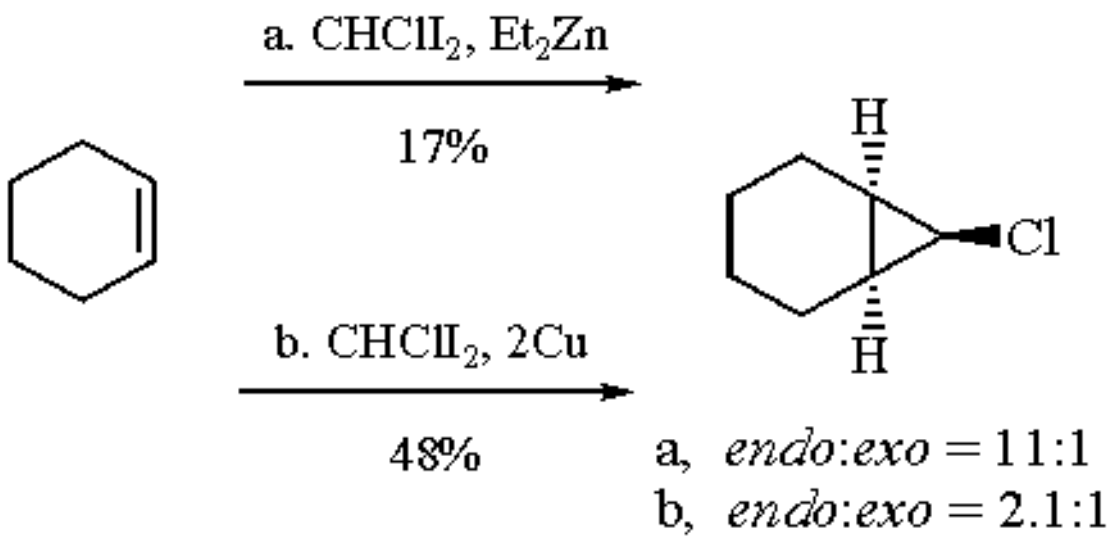

(2)

The most widely studied additions to alkenes are those using copper metal to generate the carbenoid species. Exclusive formation of chlorocyclopropanes ensues and the yields are often good. Addition to cyclohexene in the presence of ***Copper*** powder gives a 48% yield of product, but with a diminished *endo:exo* ratio (eq 2).[10] A similar addition to *cis*-cyclooctene gives a 50% yield of product with a 6.2:1 *endo:exo* ratio.[2] Application of this protocol to other alkenes was reported (eq 3).[2] The high *cis,cis:trans,trans* ratio for addition to (*Z*)-4-octene is complemented by the exclusive formation of the *cis,trans* adduct with (*E*)-4-octene. Addition to substituted styrenes has been studied in order to probe the electrophilic nature of the addition reaction (eq 4).[2] While the *cis:trans* ratios of the product cyclopropanes remained comparable, the rates of formation varied widely, allowing a Hammet ρ value of -1.13 for this reaction to be assigned. The relative stability of chlorodiiodomethane and related halomethanes to hydrolysis has been studied.[11]

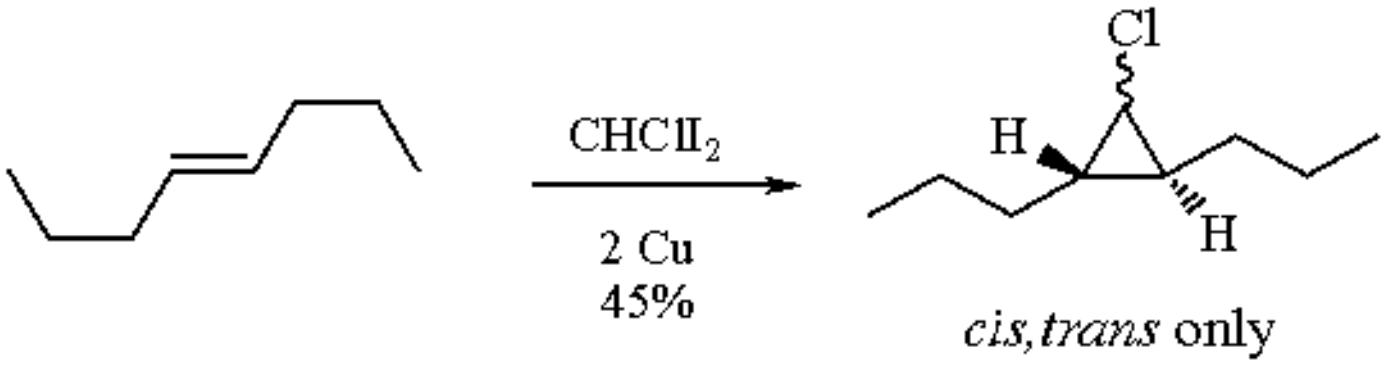

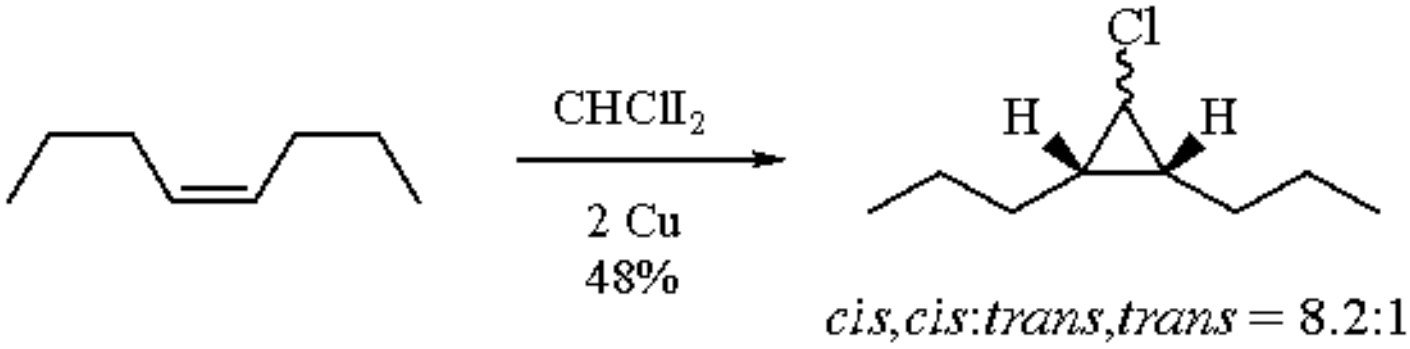

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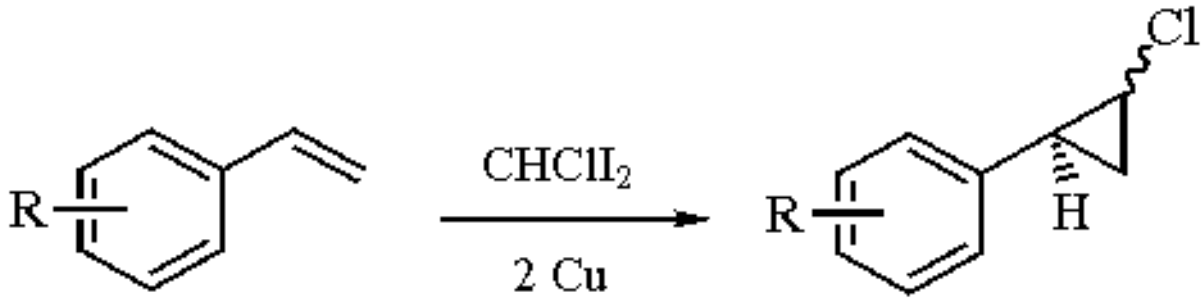

(4)

R = H, 41%, R = *p*-Br, 53%; R = *p*-Me, 56%, R = *m*-CF_3, 36%; R = *p*-Cl, 50%; R = *m*-Cl, 47%

Experiments conducted in the presence of *radical inhibitors* gave the most reproducible results for base hydrolysis in aqueous (dioxane/water) solution, exposing this potential source of side reaction.[11]

Related Reagents.

Bis(trichloromethyl)mercury; ***Bromoform***; ***Chlorodifluoromethane***; ***Chloroform***; ***Chloroiodomethane***; ***Phenyl(tribromomethyl)mercury***; ***Phenyl(trichloromethyl)mercury***.

---

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(+)-*B*-Chlorodiisopinocampheylborane

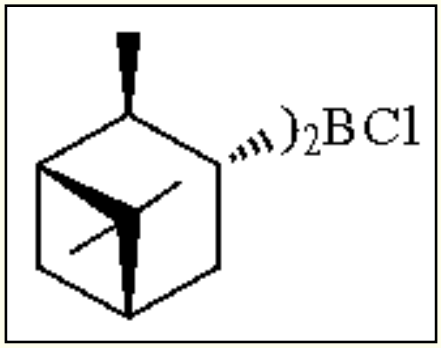

(+)

[112246-73-8] · $C_{20}H_{34}BCl$ · (+)-*B*-Chlorodiisopinocampheylborane · (MW 320.80) (-)

[85116-37-6]

(chiral reducing agent for various prochiral ketones;[1] reagent for asymmetric aldol condensation of methyl alkyl ketones;[2] reacts with *meso*-epoxides to give nonracemic chlorohydrins[3])

Alternate Name: (+)- and (-)-DIP-Chloride™.

Physical Data: mp 52-56 °C; (-)-DIP-Chloride $[\alpha]_D$ -67.07° (*c* = 13.5, CH_2Cl_2); ^{11}B NMR (diethyl ether) singlet at δ = 74 ppm (with reference to $BF_3.OEt_2$).

Solubility: sol in both polar and nonpolar aprotic solvents like diethyl ether, THF, methylene chloride, pentane, hexane, etc.

Form Supplied in: white crystalline solid, available commercially.

Handling, Storage, and Precautions: the dry solid and its solutions are moisture and air sensitive. The reagent reacts instantaneously with water and protic solvents to liberate HCl. Containers of DIP-Chloride should be stored in the absence of moisture. Cans or bottles of DIP-Chloride should be flushed with N_2 and kept tightly sealed to avoid contact of oxygen and moisture. The solid reagent should be crushed, transferred, or weighed only in glove bag or dry box under N_2 atmosphere. The reagent can be stored for several years under N_2 atmosphere below 25 °C. Use

in a fume hood.

Asymmetric Reduction of Ketones.

The reagent, developed by Brown and co-workers, is used primarily for the asymmetric reduction of a variety of prochiral ketones to form secondary alcohols with high enantiomeric purity.[1] It has been demonstrated that reduction of aryl alkyl ketones with DIP-Chloride proceeds with extraordinary consistency and predictable stereochemistry (eq 1).[4,5] Reduction of a variety of substituted aryl alkyl ketones demonstrates that representative aromatic substituents do not affect the stereochemical outcome.[1a] The reagent shows poor enantioselectivity with unhindered aliphatic ketones; however, hindered aliphatic ketones like 3,3-dimethyl-2-butanone provide the corresponding alcohol in 95% ee.[5,6] Bicyclic ketones like α-tetralone, 1-indanone, and 2´-acetonaphthone are reduced by the reagent in 87%, 97%, and 98% ee, respectively.[5] Substrates with heteroaromatic groups show some decrease in the enantioselectivity (e.g. 2´-acetylthiophene and 3-acetylpyridine are reduced in 91% and 92% ee, respectively).[5] The reagent has been recently applied to the reduction of fluoro ketones.[7] It has been shown that good enantioselectivity can be obtained if the reduction of fluoro ketones are carried out neat (without solvent) (eq 2). The reagent shows poor selectivity in the reduction of unhindered alkynic ketones. However, hindered alkynic ketones are reduced in relatively good optical purity (eq 3).[8] A variety of hindered alkynic ketones have been recently synthesized and converted by the reagent to the corresponding propargylic alcohol in high yields and in essentially optically pure form.[8] It has also been demonstrated that DIP-Chloride is a remarkably effective reagent for the asymmetric reduction of acylsilanes to form corresponding α-silyl alcohols in 96-98% ee (eq 4).[9]

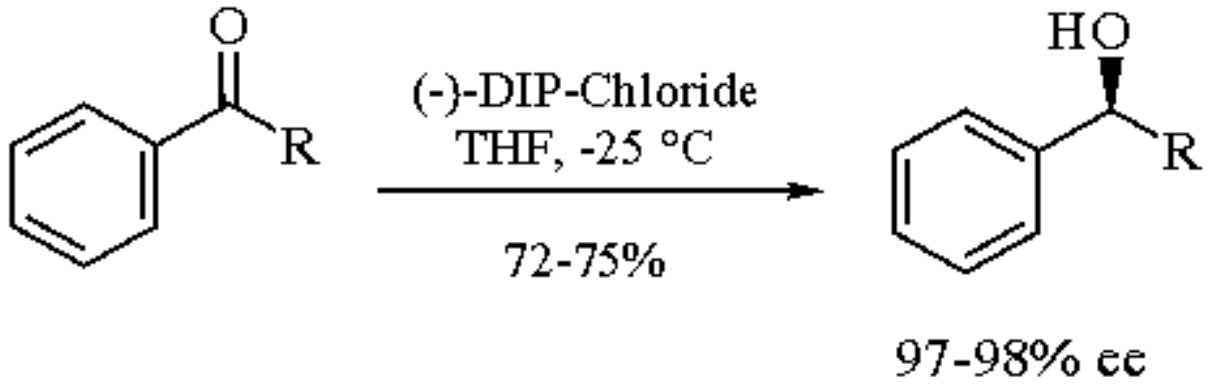

(1)

R = Me, Et, *n*-Pr, *n*-nonyl

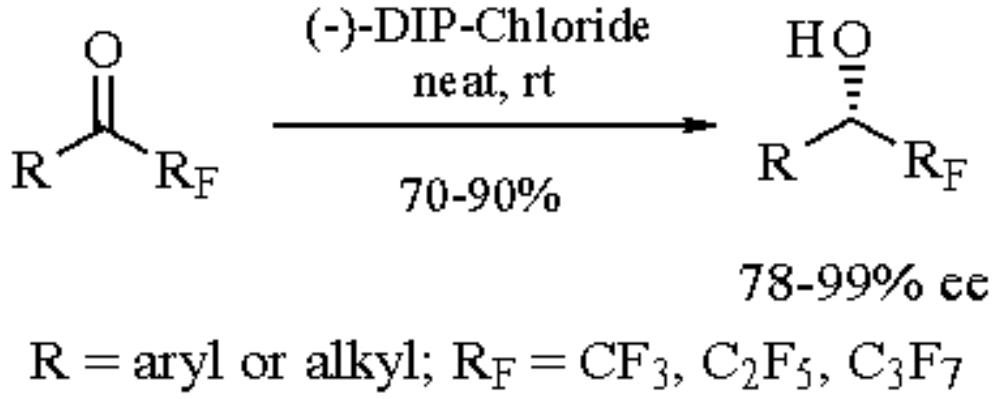

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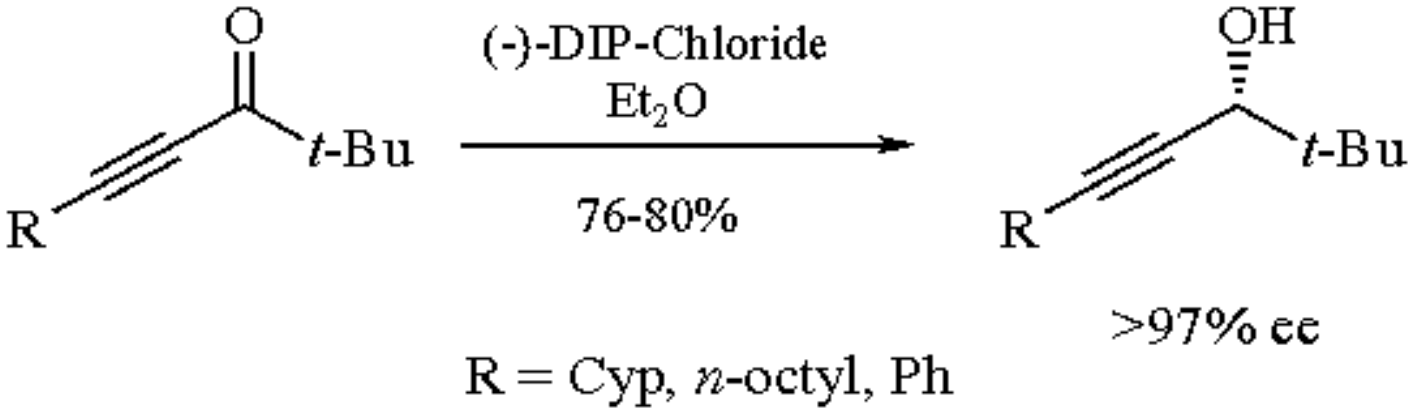

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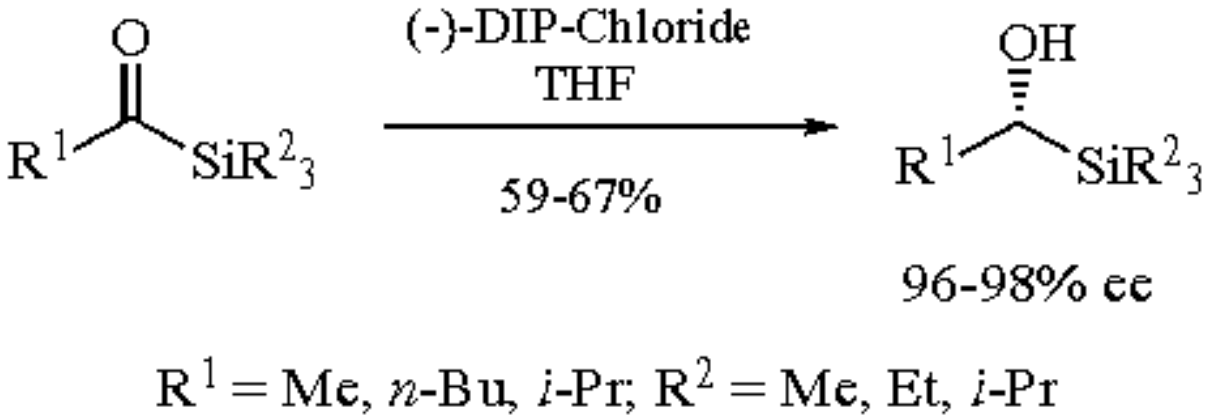

(4)

Chiral secondary alcohols are potentially of great importance in biological and medicinal science. For example, 3-chloro-1-phenyl-1-propanol, which is obtained in >99% ee via DIP-Chloride reduction of the corresponding ketone, provides access to a highly enantioselective synthesis of antidepressant agents such as Tomoxetine, Fluoxetine, and Nisoxetine.[10] Another representative application of DIP-Chloride is found in the synthesis of (1*R*,3*S*)-1-aminomethyl-3,4-dihydro-5,6-dihydroxy-3-phenyl-1*H*-2-benzopyran, a potent and selective D1 agonist.[11] The reagent has also been applied to the synthesis of a prostaglandin intermediate[1a] and for the synthesis of a dolaphenine intermediate which is the C-terminal unit of dolastatin (a promising anticancer agent).[12]

Enolboration of Ketones and Opening of *meso*-

Epoxides.

Methyl alkyl ketones have been successfully enolized by Ipc_2BX (X = OTf or Cl) in the presence of a tertiary amine. The corresponding enolborinates have been used in asymmetric aldol condensations (eq 5).[2] The reagent has also been applied to the enantioselective opening of *meso*-epoxides to form the corresponding nonracemic chlorohydrins (eq 6).[3]

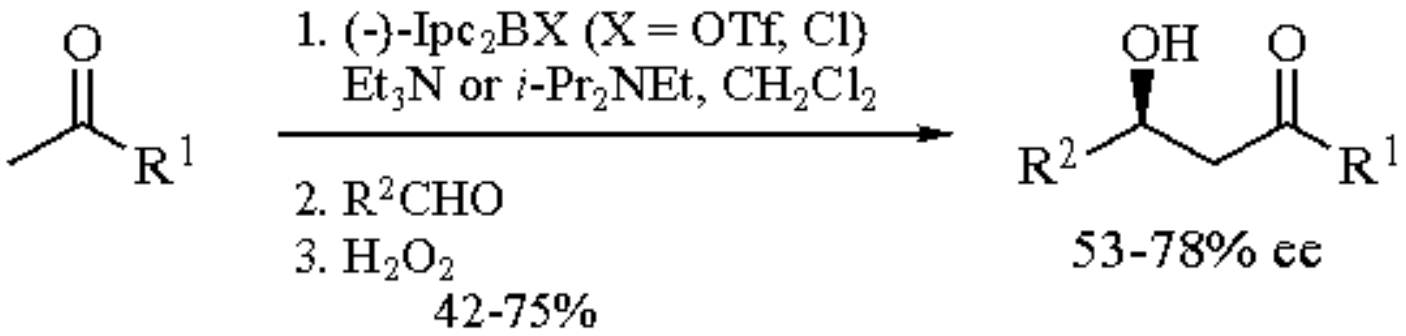

(5)

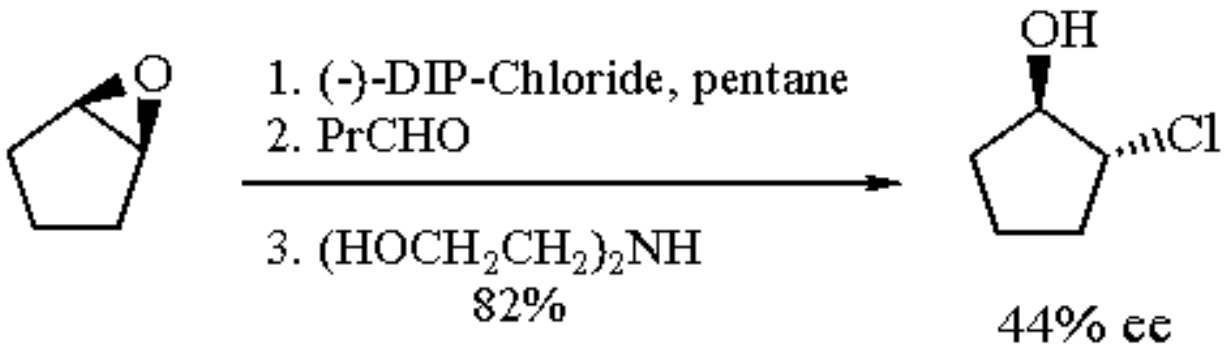

(6)

Related Reagents.

Diisopinocampheylboron Trifluoromethanesulfonate.

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Chlorodiisopropylsilane

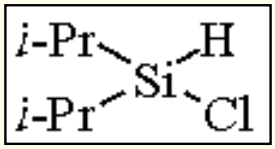

[2227-29-4] · $C_6H_{15}ClSi$ · Chlorodiisopropylsilane · (MW 150.73)

(reagent for the synthesis of *O*-diisopropylsilyl derivatives for intramolecular hydrosilylation reactions; used in a 1,3-*anti*-selective reduction of β-hydroxy ketones,[1-3] and in a mild method for reducing β-hydroxy esters[4])

Physical Data: bp 150-153 °C,[5] bp 54-55 °C/45 mmHg;[6] *d* 0.872 g cm^{-3}.[6]

Solubility: generally sol organic solvents; reacts with alcohols, ammonia,[6] and water.

Form Supplied in: neat liquid, commercially available.

Analysis of Reagent Purity: ^1H NMR δ($CDCl_3$) 4.35 (Si-H).[5] The most likely impurity is tetraisopropyldisiloxane, $(i\text{-}Pr_2SiH)_2O$, for which the corresponding signal is slightly upfield at 4.28.[7]

Preparative Method: obtained by reaction of trichlorosilane with isopropylmagnesium chloride;[6] the original yield of 45% may be raised to 70-80% by employing conc hydrochloric acid to quench the reaction.[2]

Purification: distillation at atmospheric or reduced pressure.

Handling, Storage, and Precautions: shelf-stable provided moisture is excluded. Corrosive; yields HCl on reaction with water. Use in a fume hood.

1,3-*Anti*-Selective Reduction of β-Hydroxy Ketones.

Treatment of β-hydroxy ketones (**1**) with chlorodiisopropylsilane in the presence of ***Pyridine***, or (more generally) ***Triethylamine*** with catalytic ***4-Dimethylaminopyridine***, gives β-diisopropylsilyloxy ketones (**2**) (eq 1).[1,2] These derivatives may be purified by chromatography on silica gel, and are obtained in yields of ca. 70-80%. Under the influence of Lewis acidic catalysts, most usefully ***Tin(IV) Chloride***, they undergo intramolecular hydrosilylation to give *trans*-siladioxanes (**3**), along with minor amounts of *cis* stereoisomers (**4**) (e.g. R^1, R^2 = *i*-Pr, diastereomer ratio (dr) = 120:1; R^1, R^2 = Bu, dr = 40:1).[1,2] After desilylation, *anti*-diols (**5**) may be isolated. The overall yields of (**5**)

from hydroxy ketones (**1**) are in the region 60-70%.[2]

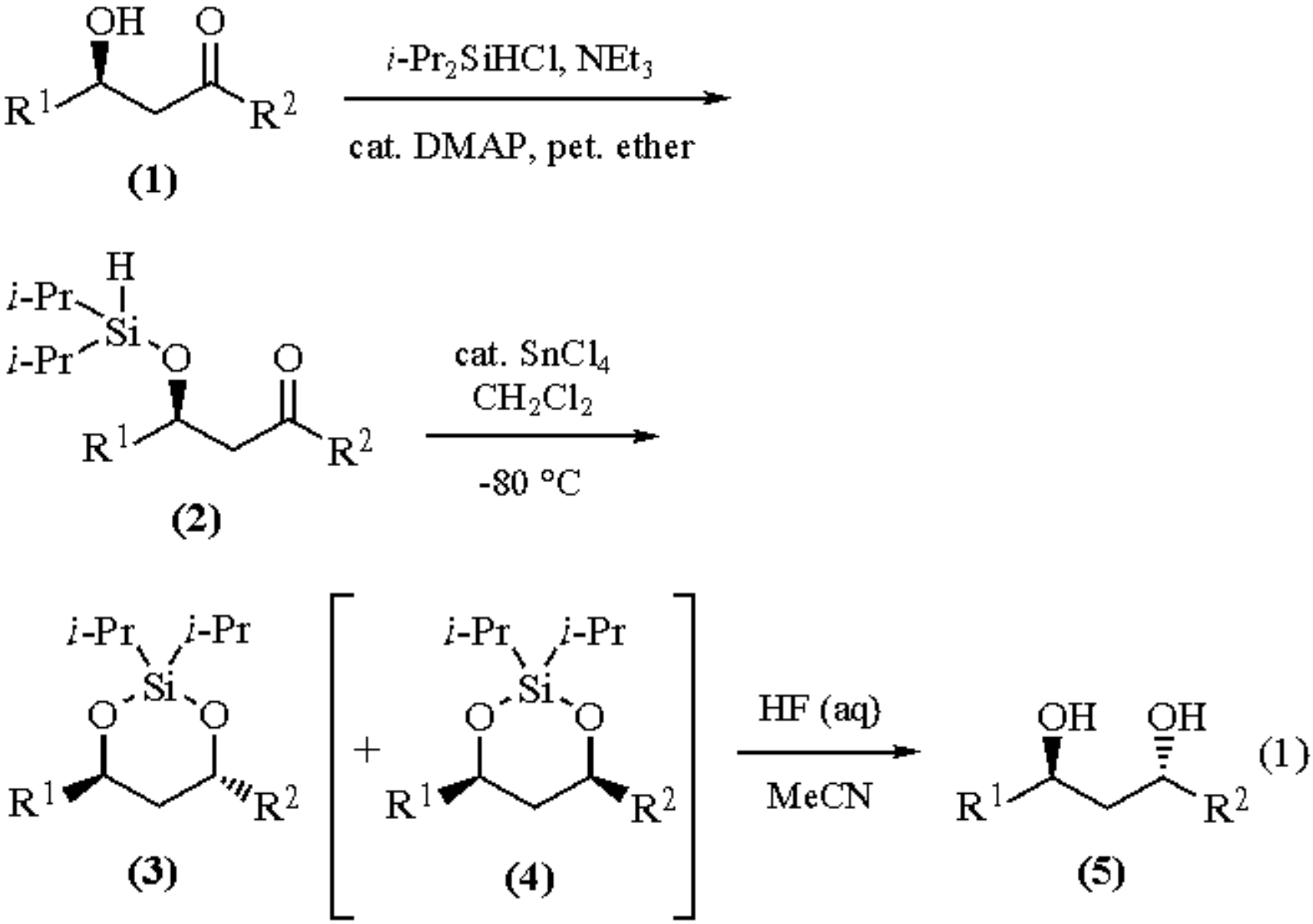

The hydrosilylation step is presumed to occur via six-membered cyclic transition state (**6**). The stereoselectivity results from (a) the equatorial disposition of R^1, and (b) steric and stereoelectronic effects (including possibly a C=O&dotbond;Si interaction) which promote the axial orientation for the carbonyl group. The dimethylsilyl derivative (**7**) has been used in similar sequences,[2] but selectivities were found to be lower and optimization was complicated by the hydrolytic instability of Me_2Si-O bonds.

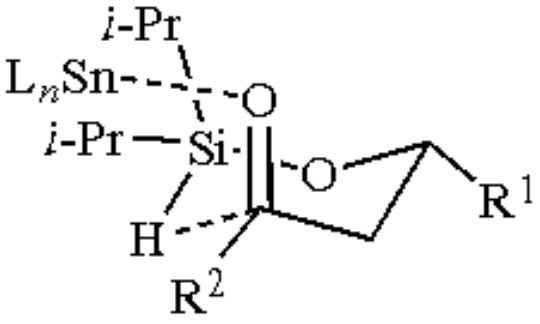

(6)

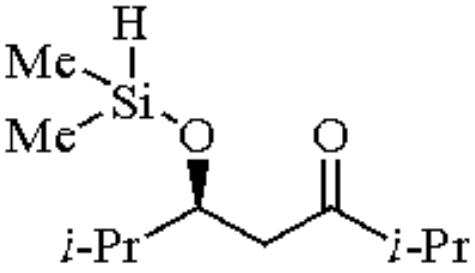

(7)

The 1,3-*anti* selectivity is maintained in the presence of an α-substituent, i.e. in substrates such as (**8**). Thus diisopropylsilylation/hydrosilylation of both diastereomers of (**8**) gave the 1,3-*trans*-siladioxane (**9**), with dr &egt; 250:1 (eq 2).[3] However, with the more challenging substrates (**10**) the α-position was found to have more influence. Both diastereomers gave principally the 1,2-*trans* product (**11**) (eq 3) but, while *anti*-(**10**) resulted in dr = 97:1, *syn*-(**10**) gave only dr = 5:1.

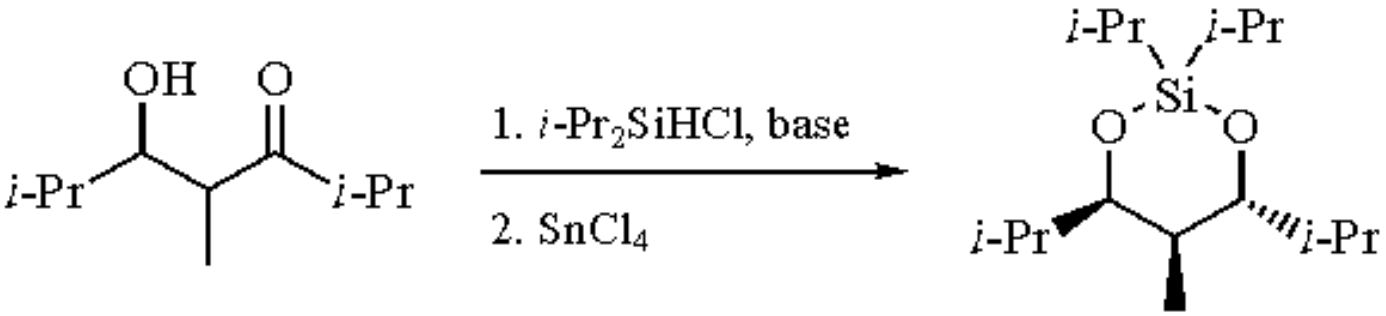

(2)

(8)
either diastereomer

(9)

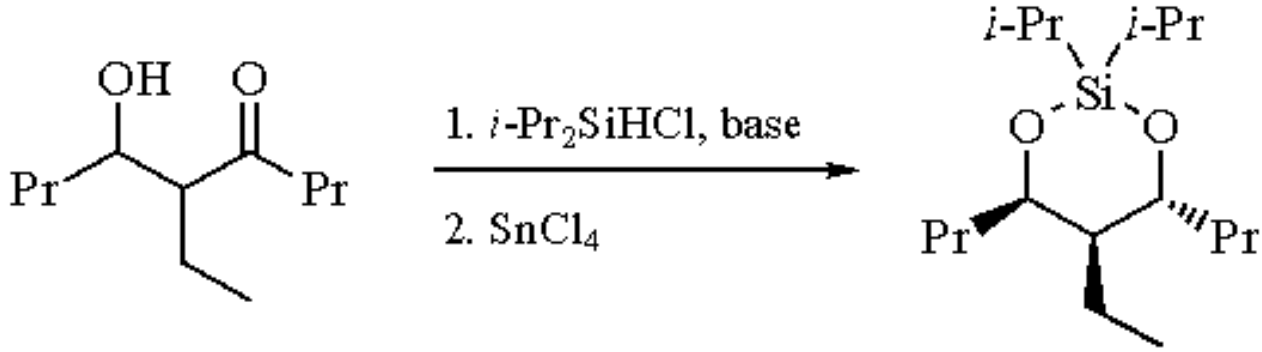

(3)

(10)
either diastereomer

(11)

As part of the above work it was found that the superacid $TfOH_2^+B(OTf)_4^-$ may also be used as the hydrosilylation catalyst.[3] In one case it gave superior results to those obtained with $SnCl_4$.

The 1,3-*anti*-selective reduction of β-hydroxy ketones may also be accomplished using ***Tetramethylammonium Triacetoxyborohydride***,[8] and the samarium-catalyzed intramolecular Tishchenko reduction.[9] The former gives the *anti*-diols directly, although with slightly lower stereoselectivity than the intramolecular hydrosilylation. The latter results in monoacylated products, and gives excellent yields and selectivities.

Intramolecular Reduction of β-Hydroxy Esters.

Intramolecular hydrosilylation is also possible within β-diisopropylsilyloxy esters (**13**), constituting an exceptionally mild method for reducing ester groups to the aldehyde oxidation level (eq 4).[4] The derivatives (**13**) may be synthesized from β-hydroxy esters (**12**) as described above for the analogous ketones. Treatment with fluoride ions

(but not Lewis acids) induces hydride transfer to give alkoxysiladioxanes (**14**) in excellent yields (&egt;95%). Although usually performed in dichloromethane, the hydrosilylation may also be accomplished with ethyl acetate as solvent, providing strong evidence for intramolecularity.

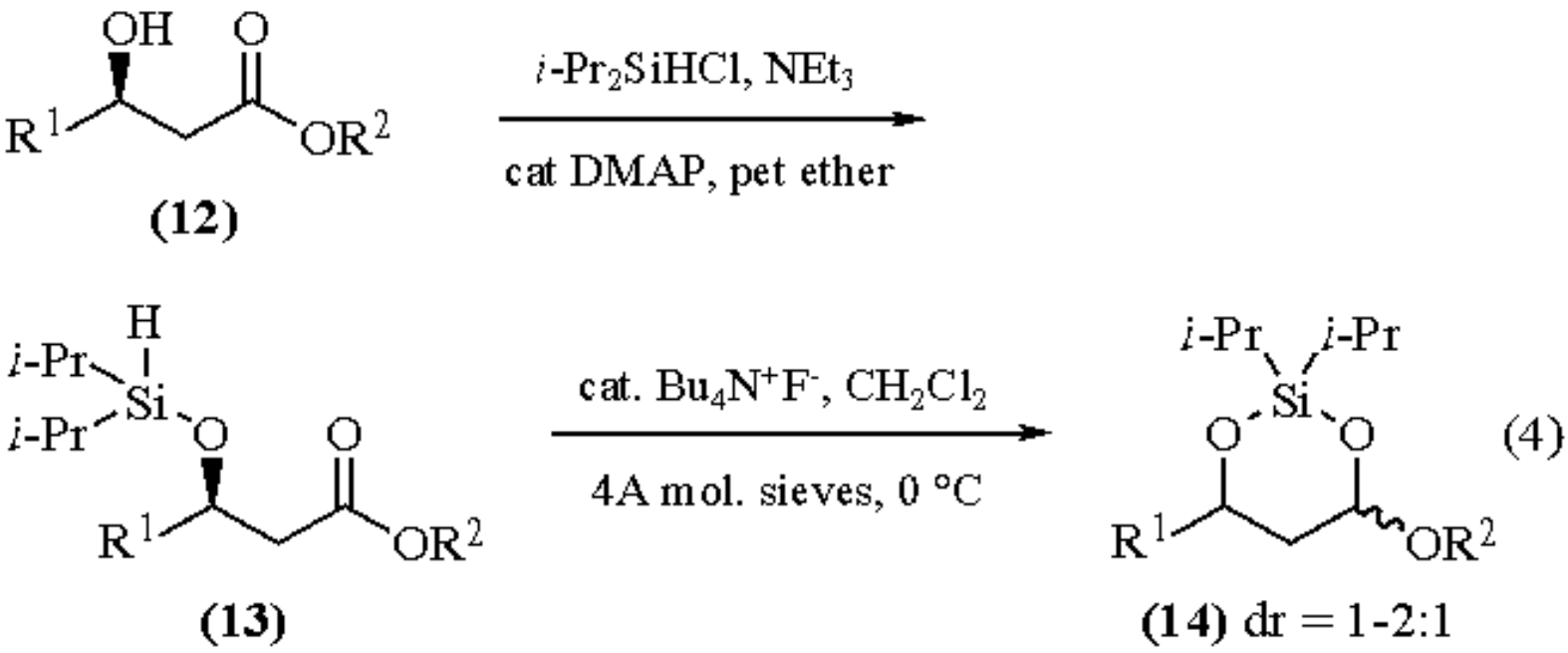

While the reduction in eq 4 is not stereoselective, the stereocontrolled elaboration of (**14**) may be achieved in principle via conformationally biased carbocations (**15**). This has been demonstrated for the allylation of (**14**) with ***Allyltrimethylsilane*** (eq 5).[4] The major products (**16**) appear to derive from axial attack on (**15**). The most effective catalyst was $TfOH_2^+B(OTf)_4^-$, which could be used at levels of 1-2 mol % and gave yields of 78-85% with dr &egt; 20:1. While it is possible that the superacid acts by protonation of the alkoxy oxygen in (**14**), it is probably more likely that the active species is the supersilylating agent $Me_3Si\ B(OTf)_4$,[10] derived from superacid and allylsilane.

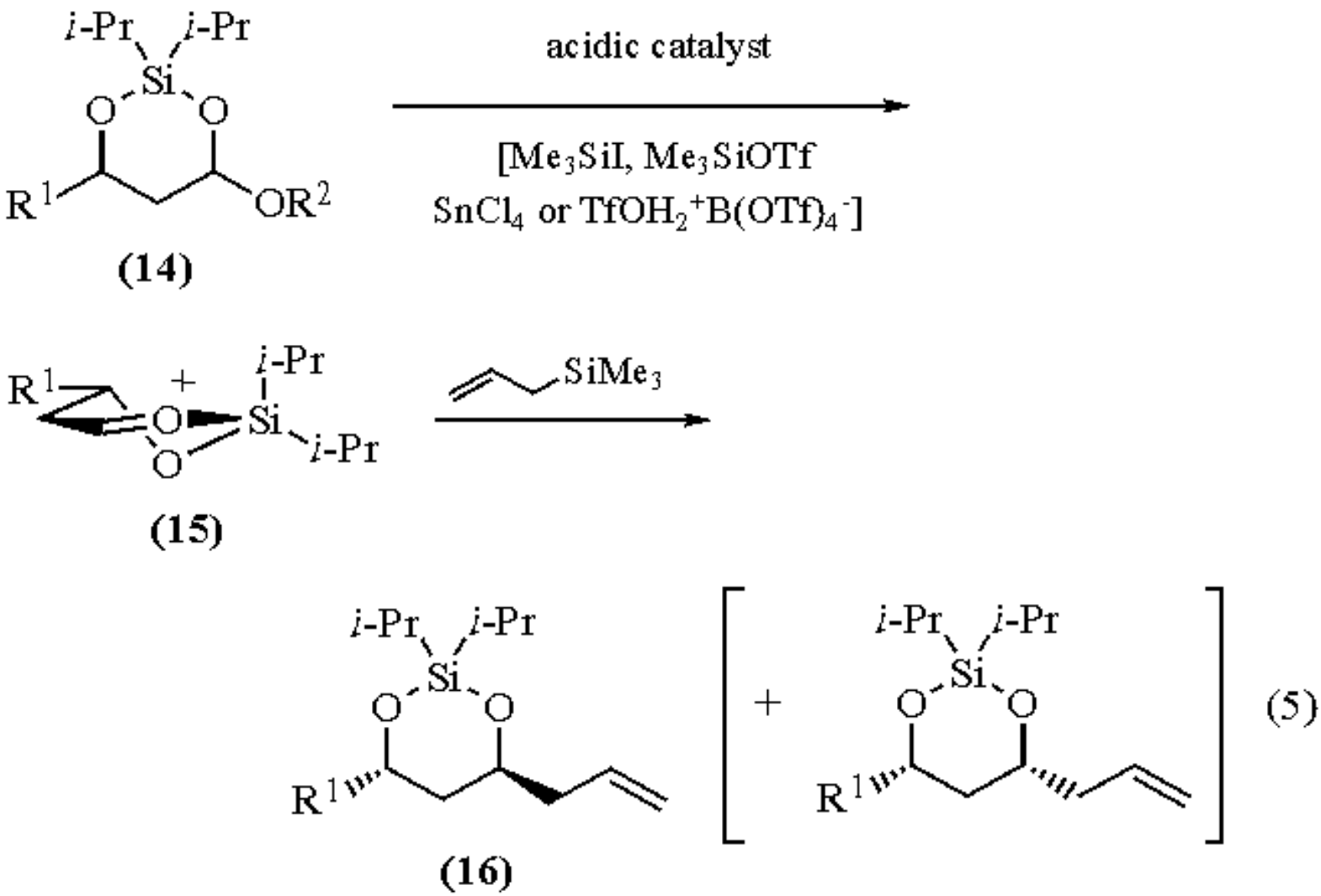

Intramolecular Hydrosilylation/Oxidation of Alkenols.

Since the advent of methods for the oxidative degradation of organosilicon compounds, it has been possible to develop controlled hydration methodology based on the hydrosilylation of C=C bonds. A useful variant involves the *O*-silylation of an alkenol with a dialkylsilylating agent R_2SiHX, followed by intramolecular hydrosilylation/oxidation to give a diol product.[11,12] Because of the intramolecular delivery of the Si-H moiety, these reactions often take place with excellent stereoselectivity. While most of this work has employed Me_2SiH as the internal reagent, the use of *i*-Pr_2SiH has been explored occasionally.[13,14] An example where it proved advantageous is the conversion of allylic alcohol (**17**) to *syn*-diol (**18**) (eq 6) in dr 30:1.[14] A related method involving dimethylsilyl groups gave dr of only 2.4:1 with this substrate.[12]

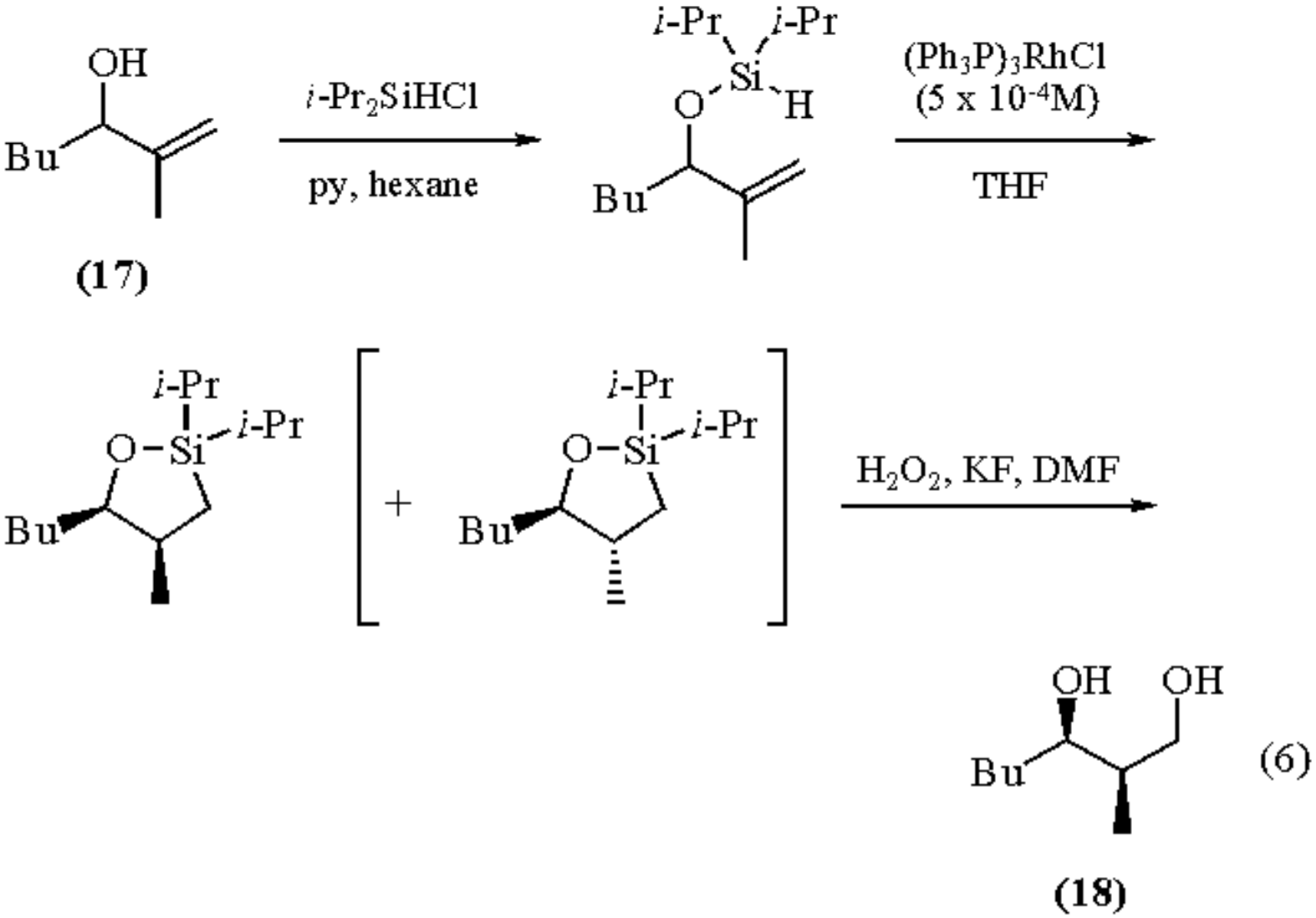

Synthesis of Other Organosilicon Reagents.

Aside from the direct applications referred to above, *i*-Pr_2SiHCl serves as an intermediate for the synthesis of certain other reagents. Examples are (a) *i*-$Pr_2Si(OTf)_2$, used for the protection of diols as diisopropylsilylene derivatives,[15] (b) dialkylarysilanes (**19**) for the introduction of a fluorescent *O*-protecting group,[16] and (c) the disiloxane (**20**), which may be converted to (**21**) (for diol protection)[7] or (**22**) (used in intramolecular ionic hydrogenation).[17]

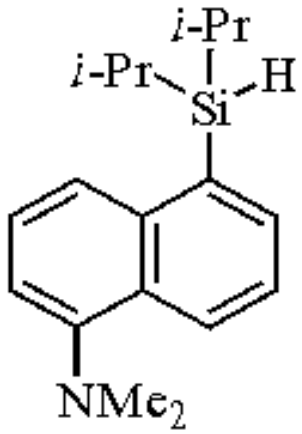

(19)

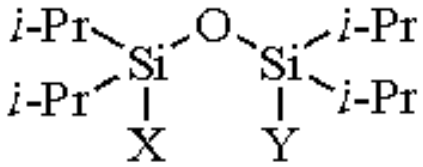

(20) X = Y = H
(21) X = Y = Cl
(22) X = H, Y = Br

Related Reagents.

Chlorodimethylsilane; ***Tetramethylammonium Triacetoxyborohydride***.

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Chlorodimethoxyborane[1]

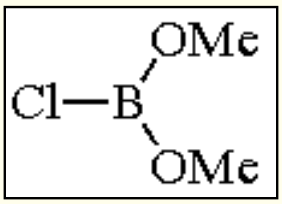

[868-81-5] · $C_2H_6BClO_2$ · Chlorodimethoxyborane · (MW 108.34)

(borylating reagent;[3,4] preparation of substituted allyl boronates;[5,6] preparation of enol borates[10,11])

Physical Data: mp -87.5 °C; bp 74 °C; *d* 1.079 g cm^{-3}.

Solubility: sol aprotic solvents (ether, THF, CH_2Cl_2, hydrocarbons); reacts with water and protic solvents.

Preparative Method: prepared from a 2:1 mole mixture of $B(OMe)_3$ and BCl_3.[2]

Handling, Storage, and Precautions: air and moisture sensitive; store and handle under an inert atmosphere.

Preparation of Organoboronates.

Chlorodimethoxyborane has been extensively used in organic synthesis for the preparation of boronic ester derivatives. Typically, $ClB(OMe)_2$ is allowed to react with an organolithium reagent at low temperatures in THF or ether to afford the corresponding organoboronates. The boronates obtained are then usually elaborated without isolation. Alkyl and allyl sulfones have been converted into ketones and aldehydes via the corresponding α-sulfonylboronic esters. The α-sulfonylboronic esters were synthesized via lithiation of the sulfone and subsequent reaction with $ClB(OMe)_2$ in THF (eq 1).[3] Use of $ClB(OMe)_2$ was critical for the borylation reaction, as both $FB(OMe)_2$ and trimethoxyborane gave unsatisfactory results. The efficiency of the chlorodimethoxyborane reagent has been attributed to the low solubility of LiCl in THF.[3] Similarly, 2-aryl- and 2-alkylfurans have been converted into 2(3*H*)-butenolides via the oxidation of boronic ester derivatives (eq 2).[4] The 5-furylboronate derivatives were prepared in a very efficient manner by reacting the corresponding lithiofurans with 1 equiv of $ClB(OMe)_2$ in trimethoxyborane (prepared in situ by reacting BCl_3 with an excess of $B(OMe)_3$). Yields for the corresponding reactions were poor when trimethoxyborane or fluorodimesitylborane were used.

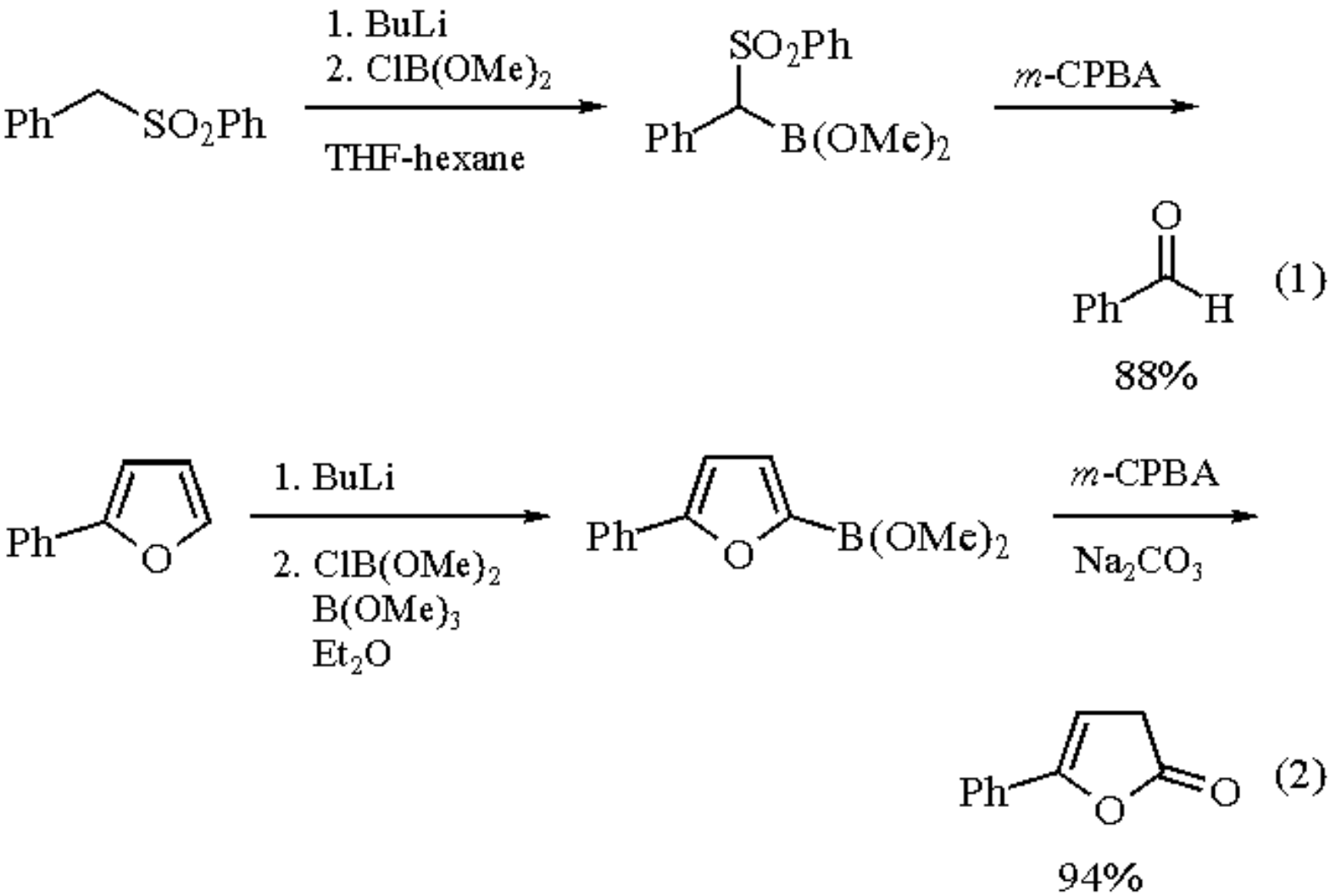

Preparation of Substituted Allylboronates.

The preparations of substituted allylboronic acid ester derivatives using halodialkoxyboranes,[5,6] trialkoxyboranes,[7] and halobis(dialkylamino)boranes[8] have been extensively studied in recent years. For example, a variety of γ-alkoxyallylboronates have been efficiently prepared via lithiation of allyl ethers and subsequent reaction with halodialkoxyboranes (eq 3).[5] Most notably, the preparation of (*E*)- and (*Z*)-crotylboronates has been thoroughly investigated. Reaction of (*E*)- or (*Z*)-crotylpotassium (see also Schlosser's base) with either $ClB(OMe)_2$[8b] or $F(BOMe)_2$[7a] affords the corresponding crotyldimethoxyborane. The crude boronate can be hydrolyzed to the boronic acid, which upon esterification can then be converted into a variety of crotylboronates, including the chiral diisopropyl tartrate (DIPT) modified crotylboronate reagents (eq 4).[6,7] However, the borylation reaction (especially when carried out on a large scale) is accompanied by the formation of methyl dicrotylborinate and tricrotylborane, resulting in lower yield and erosion of the isomeric purity (92-95%) of the crotylboronate. Use of $ClB(NMe2)_2$[8b] gave the crotylboronate in high isomeric purity; however, the yield was low. These problems can be overcome by using ***Triisopropyl Borate***, which gives the crotylboronate in high yield and >98% isomeric purity.[7a] Superior results were also obtained in the synthesis of alkyl boronic esters when $B(O\text{-}i\text{-}Pr)_3$ was used in place of $ClB(OMe)_2$.[9] For example, reaction of MeLi with $ClB(OMe)_2$ gave methyldimethoxyborane in 43% yield, whereas the corresponding reaction with $B(O\text{-}i\text{-}Pr)_3$ proceeded in 98% yield.[9]

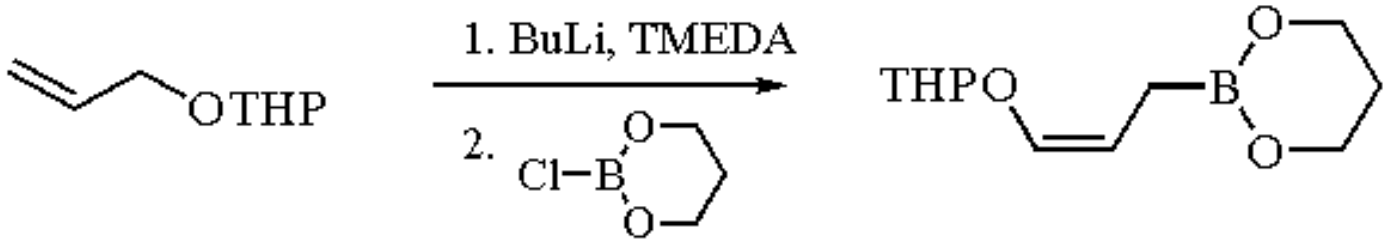

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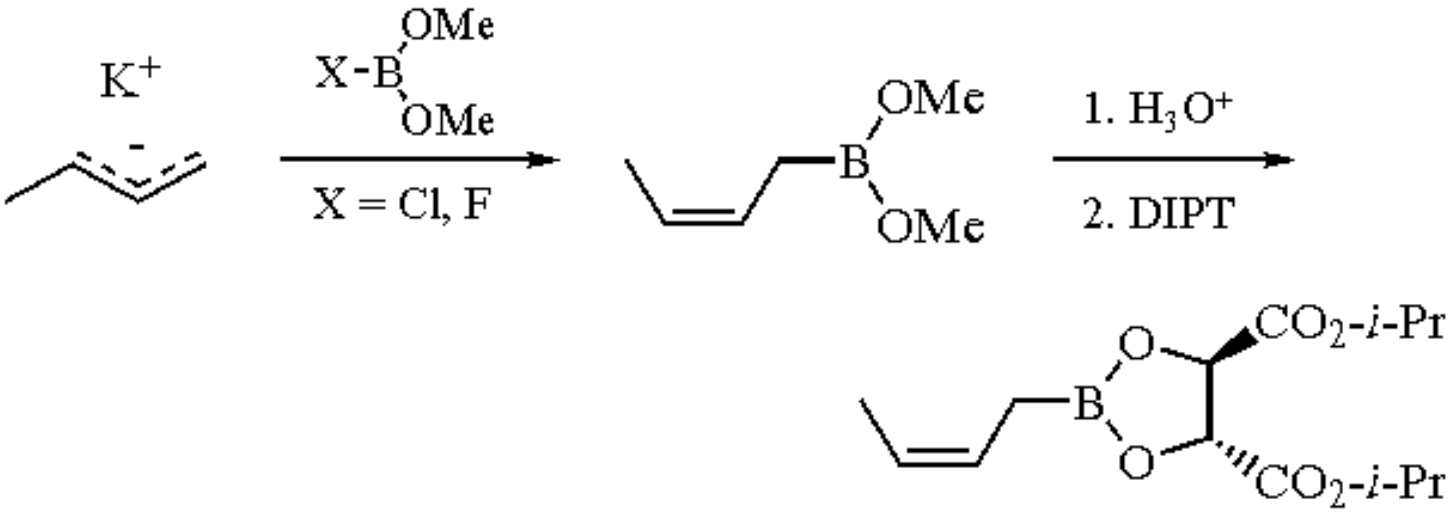

(4)

Preparation of Enol Borates.

Reaction of $ClB(OMe)_2$ with either lithium enolates[10] or trimethylsilyl enol ethers[11] affords the corresponding dimethyl enol borates. The enol borate (used without isolation) reacts with aldehydes to afford the dioxaborinane (**1**) (eq 5). The dioxaborinane (**1**) represents an internally protected aldol, which can be elaborated without the need for isolation and protection of the alcohol. Thus addition of an allyl metal such as allylmagnesium bromide affords the allylic diol (**2**) in good yield, albeit with low diastereoselectivity (eq 5).[10] Alternatively, the dioxaborinane can be reduced with ***Sodium Borohydride*** to the corresponding diol.[11]

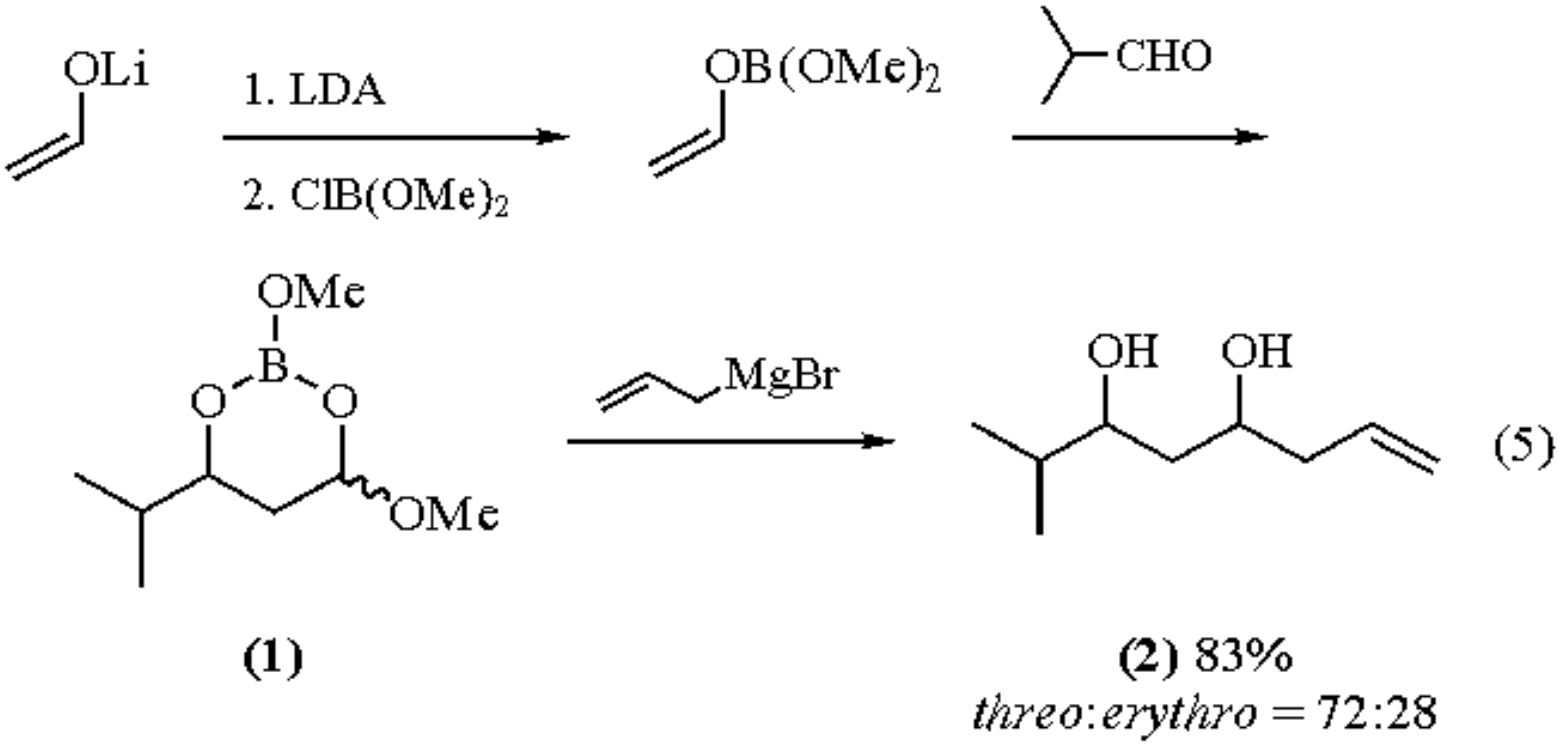

Related Reagents.

Triisopropyl Borate; ***Trimethyl Borate***.

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Chlorodimethylphenylsilane

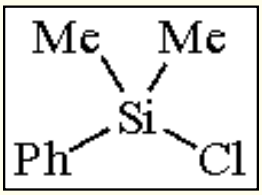

[768-33-2] · $C_8H_{11}ClSi$ · Chlorodimethylphenylsilane · (MW 170.72)

(nucleophilic silylation;[1] alcohol derivatization;[2] antenna chromophore;[3] enolate trapping;[4] Kumada-Fleming-Tamao oxidation[5])

Alternate Names: dimethylphenylsilyl chloride; DMPSCl.

Physical Data: bp 194-198 °C (63 °C/2 mmHg), d_4^{20} 1.026 g cm^{-3}; n_D^{20} 1.508.

Solubility: sol THF, ether, hexane.

Form Supplied in: liquid. Typical low-level impurities are metathesis products including dichloromethylphenylsilane (bp 205 °C).

Analysis of Reagent Purity: generally used as received. The methyl group appears at δ 2.4 and the silicon atom at δ 19.9 in the ^{1}H and ^{29}Si NMR spectra, respectively.[6]

Preparative Methods: widely available.

Handling, Storage, and Precautions: like other chlorosilanes, this compound can be destructive to tissue of the mucous membranes, upper respiratory tract, eyes and skin. Store in a cool dry place; the compound is moisture sensitive.

Chlorodimethylphenylsilane (DMPSCl) may be used in many of the same applications as chlorotrialkylsilanes, but in some cases the presence of the phenyl group on silicon offers advantages. For example, $Me_2PhSiLi$ is easier to prepare than Me_3SiLi.[7]

Nucleophilic Silation using Dimethylphenylsilylmetallics.

Several dimethylphenylsilylmetallics have been prepared (see Table 1). The most useful reaction in the class is conjugate addition of the silylcuprates to α,β-unsaturated esters and enones (eq 1).[1]

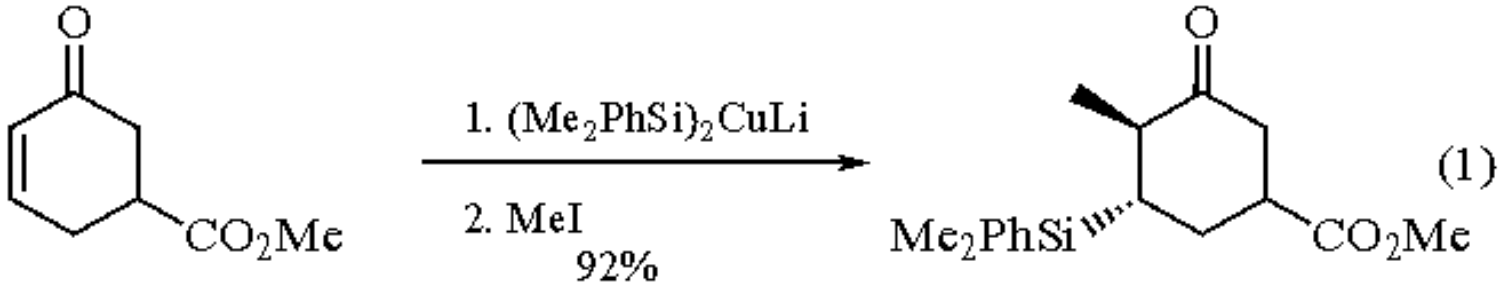

Table 1 Dimethylphenylsilylmetallic Reagents

Reagent	Reagent
$Me_2PhSiLi$[8]	$Me_2PhSiAlEt_2$[8]
Me_2PhSiK[9]	$Me_2PhSiMgMe$[12]
$(Me_2PhSi)_2CuLi$[10]	$(Me_2PhSi)_2Zn$[12]
$(Me_2PhSi)_2Cu(CN)Li$[1a,1b,11]	$Me_2PhSiCCl_2Li$[13]

Hydroxyl Derivatization.

Chlorodimethylphenylsilane is a useful derivatizing agent for alcohols.[2] DMPSCl derivatized monosaccharides may be analyzed chromatographically with UV detection.[14] A novel application of the UV-absorbing ability of the dimethylphenylsilyloxy chromophore uses 266 nm light absorbed by the DPS `antenna' in 3α-dimethylphenylsilyloxy-5α-androstane-11,17-dione for photolytic reduction of the C-17 keto group.[3] Photolysis with 308 nm light absorbed by the ketone moieties produces predominately D-ring epimerization.

Other Nucleophilic Reactions at Silicon.

DMPSCl may be used to trap ester enolates[4] (however, lactam enolates silylate at carbon).[15] Numerous *C*-silylations of organolithium compounds with DMPSCl have been reported (eq 2).[5,16] Other compounds derived from DMPSCl include the azide,[17] tributylstannane,[18] cyanide,[19] isocyanate,[20] and isoselenocyanate.[21]

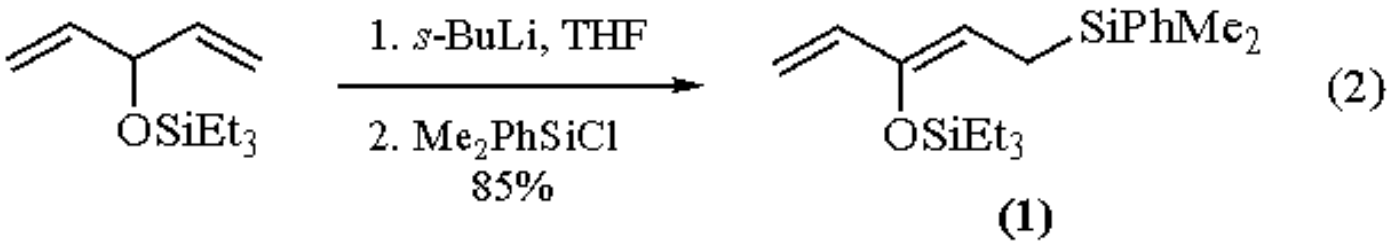

Protodesilation/Oxidation (Kumada-Fleming-Tamao

Oxidation).

Another advantage of the dimethylphenylsilyl group over trialkylsilyl is that the phenyl substituent may be readily removed by protodesilation.[7] Kumada-Fleming-Tamao oxidation converts *C*-silyl compounds into alcohols. Allylic dimethylphenylsilanes are preferred substrates for conversion to the corresponding allylic alcohols,[5] which is the basis for use of the β-silylethyl vinyl ketone (from **1**) as a β-hydroxyethyl vinyl ketone synthon in the Robinson annulation reaction.

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Chlorodimethylsilane

$ClMe_2SiH$

[1066-35-9] · C_2H_7ClSi · Chlorodimethylsilane · (MW 94.62)

(intramolecular hydrosilation of allyl alcohols, homoallyl alcohols, allyl amines, and α-hydroxy ketones for the regio- and stereoselective synthesis of polyols and amino alcohols)

Physical Data: bp 35-36 °C; mp -111 °C; *n*20D 1.3830; *d* 0.852 g cm^{-3}.

Solubility: sol common aprotic organic solvents.

Form Supplied in: neat liquid.

Handling, Storage, and Precautions: moisture sensitive and corrosive. Must be stored under nitrogen in a tightly capped bottle in a freezer and transferred or weighed quickly via syringe. This reagent should be handled in a fume hood.

Intramolecular Hydrosilation of Allyl and Homoallyl Alcohols.

For a detailed description of the intramolecular hydrosilation-oxidation sequence, see ***1,1,3,3-Tetramethyldisilazane***. 1,1,3,3-Tetramethyldisilazane and ***N,N-Diethylaminodimethylsilane*** are frequently employed for preparation of hydrodimethylsilyl ethers for the intramolecular hydrosilation of allyl and homoallyl alcohols. Chlorodimethylsilane in combination with a tertiary amine such as ***Triethylamine*** is another useful reagent for the synthesis of hydrodimethylsilyl ethers, especially for large scale preparations.[1]

Other chlorodiorganosilanes (ClR_2SiH) such as ***Chlorodiisopropylsilane*** ($Cl(i\text{-}Pr)_2SiH$),[2] ***Chlorodiphenylsilane*** ($ClPh_2SiH$),[3] and 1-chloro-1-silacyclohexane ($(CH_2)_5SiClH$),[4] are also useful reagents for intramolecular hydrosilation, including catalytic asymmetric intramolecular hydrosilation.[3,4] These bulky hydrosilanes have some advantages over $ClMe_2SiH$ in these reactions, since the silylated intermediates are less moisture sensitive, are more easily handled, and can lead to higher stereoselectivity in the alkene hydrosilation step.

Intramolecular Hydrosilation of Allyl Amines.

The amino group of an allyl amine is silylated with chlorodimethylsilane, and then the resulting silazane is subjected to standard platinum-catalyzed cyclization and oxidation steps to form a *syn*-2-amino alcohol (eq 1). Exclusive formation of the four-membered cyclic product and the high stereoselectivity should be noted.[5]

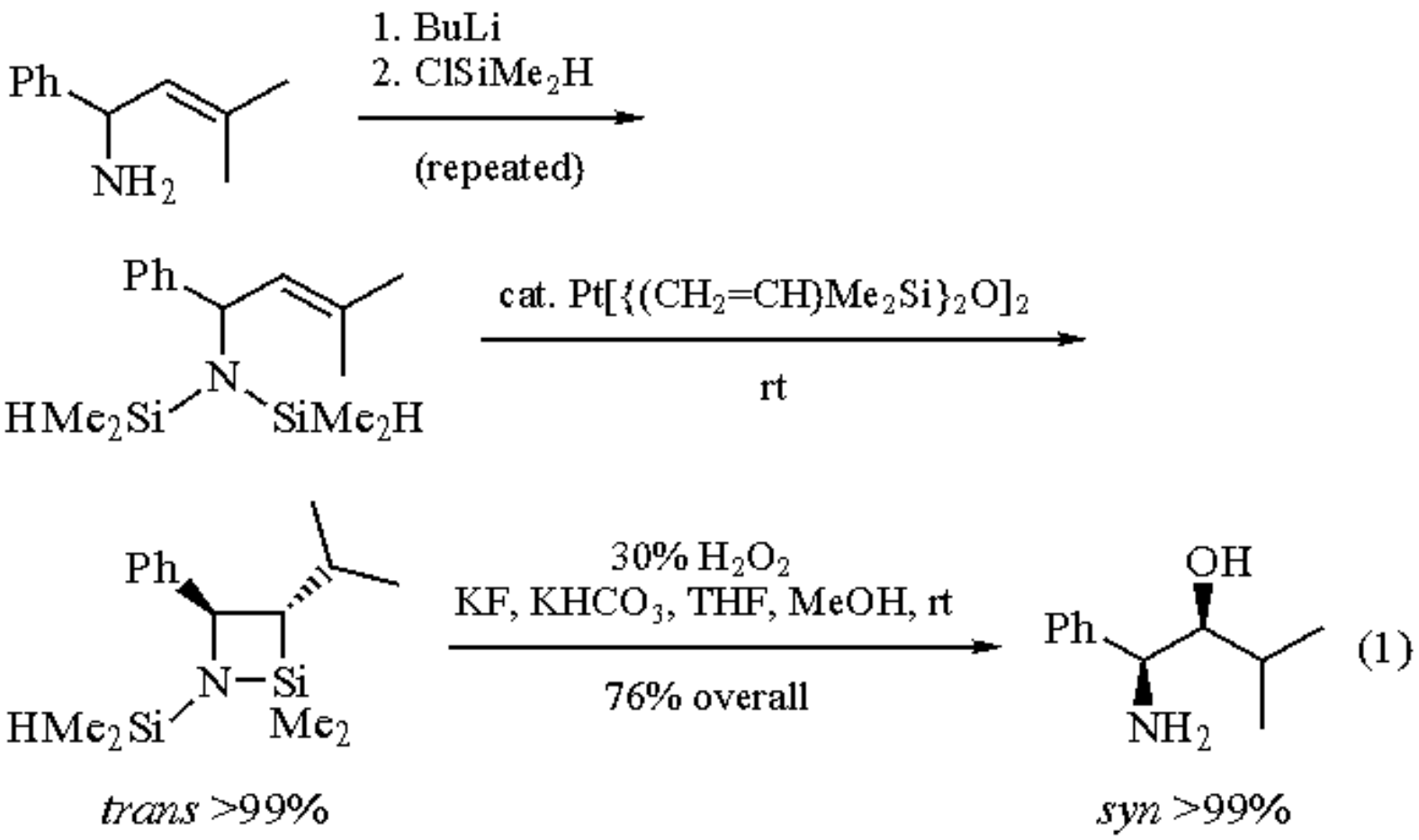

Intramolecular Hydrosilation of Carbonyl Groups.

Catalytic asymmetric intramolecular hydrosilation of the carbonyl group of an α-hydroxy ketone has been attained by using chlorodimethylsilane as the silylating agent and a rhodium catalyst containing an optically active bidentate ligand (eq 2).[6]

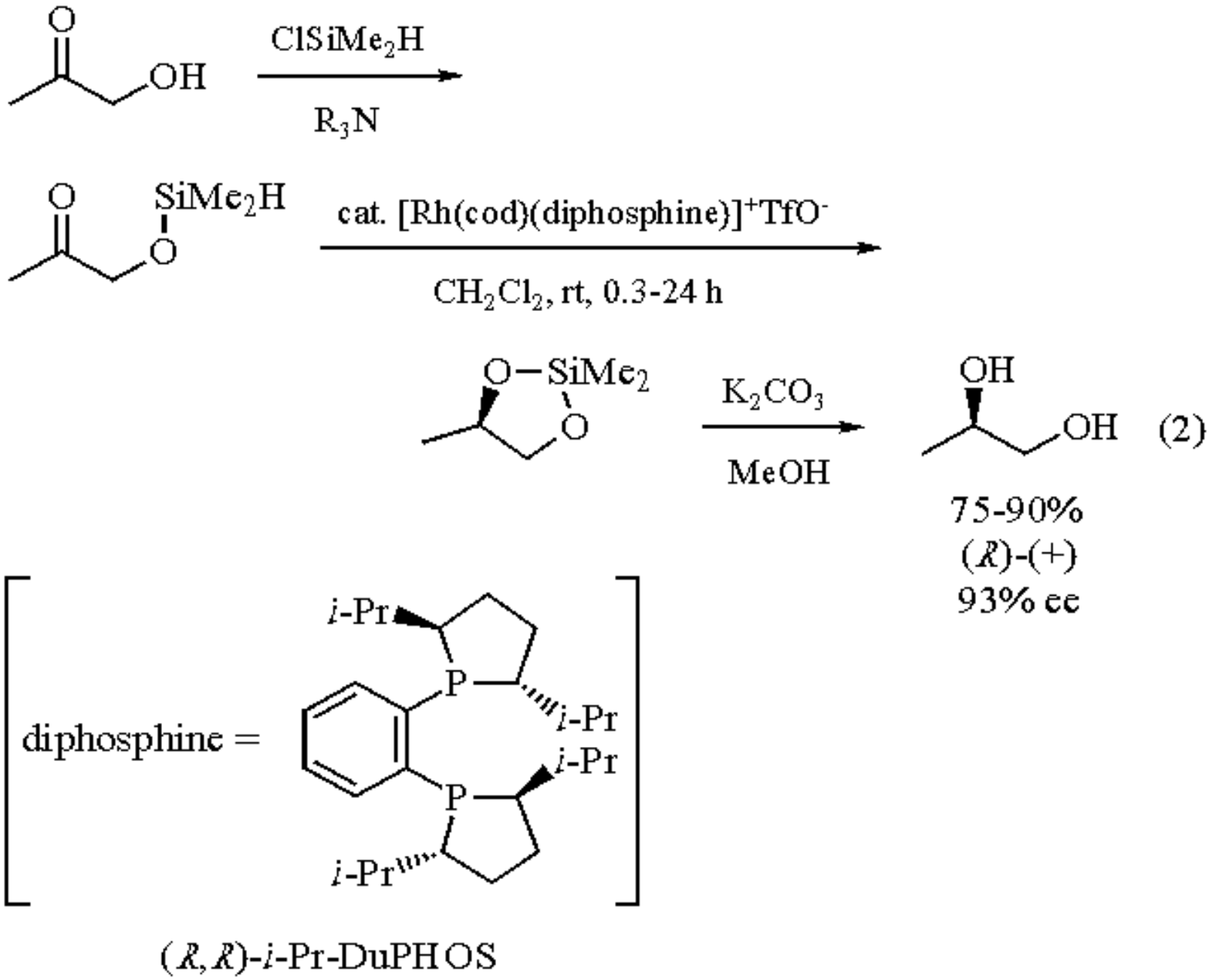

In addition, chlorodiisopropylsilane is a useful reagent for Lewis acid catalyzed intramolecular hydrosilation of β-hydroxy ketones[7] and for fluoride ion induced reduction of esters.[8] It may also be mentioned that chlorodi-*t*-butylsilane is used in highly stereoselective intramolecular ionic hydrogenations of hydroxy alkenes.[9]

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Chlorodiphenylphosphine

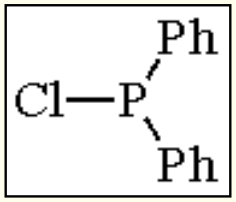

[1079-66-9] · $C_{12}H_{10}ClP$ · Chlorodiphenylphosphine · (MW 220.64)

(mild reagent for the halogenation of alcohols,[1] conversion of vicinal diols to alkenes,[2] transformation of sulfoxides to thioesters,[3] and formation of phosphines[4])

Physical Data: bp 320 °C; *d* 1.229 g cm^{-3}.

Form Supplied in: light-yellow liquid; widely available.

Handling, Storage, and Precautions: handle only in a chemical fume hood, wear respirator, chemical-resistant gloves, and safety goggles; do not breathe vapor, and avoid contact with eyes or skin. The compound is a corrosive lachrymator. It reacts violently with water to generate hydrogen chloride gas. It may be fatal if inhaled. See the material safety data sheet for first aid procedures.

Halogenation Reagent.

Primary and secondary alcohols can be converted to iodides and bromides in excellent yields employing chlorodiphenylphosphine, ***Imidazole***, and the appropriate halogen.[1] This reagent system is superior to most phosphorus-based reagents, which require the removal of triphenylphosphine and its oxide, because the phosphorus byproducts can be removed by basic aqueous extraction. Imidazole serves to neutralize the liberated halogen acids, enhances the reactivity, and can be washed away from the toluene phase during the extraction. Primary alcohols react at room temperature in less than 10 min (eq 1). Secondary alcohols require elevated temperatures and longer reaction times (eq 2). Competitive chlorination does not arise from the chloride anion generated during the reaction.

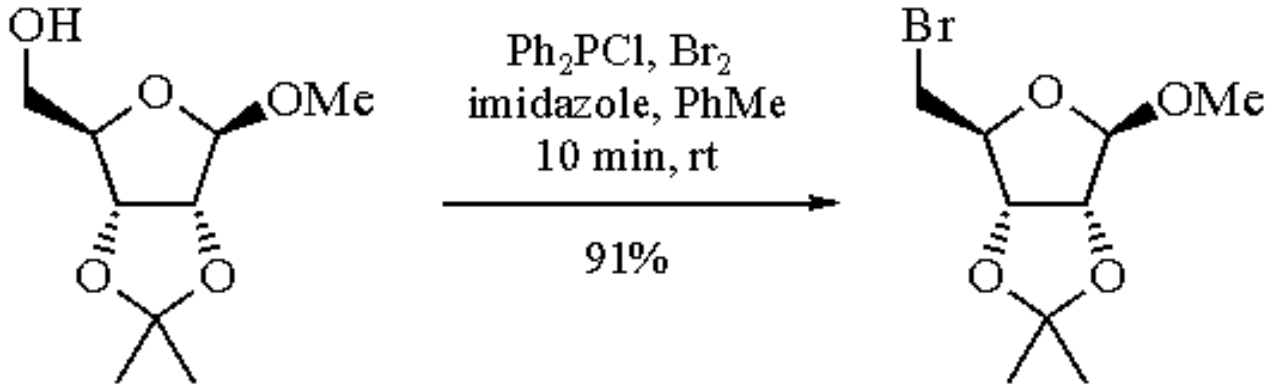

(1)

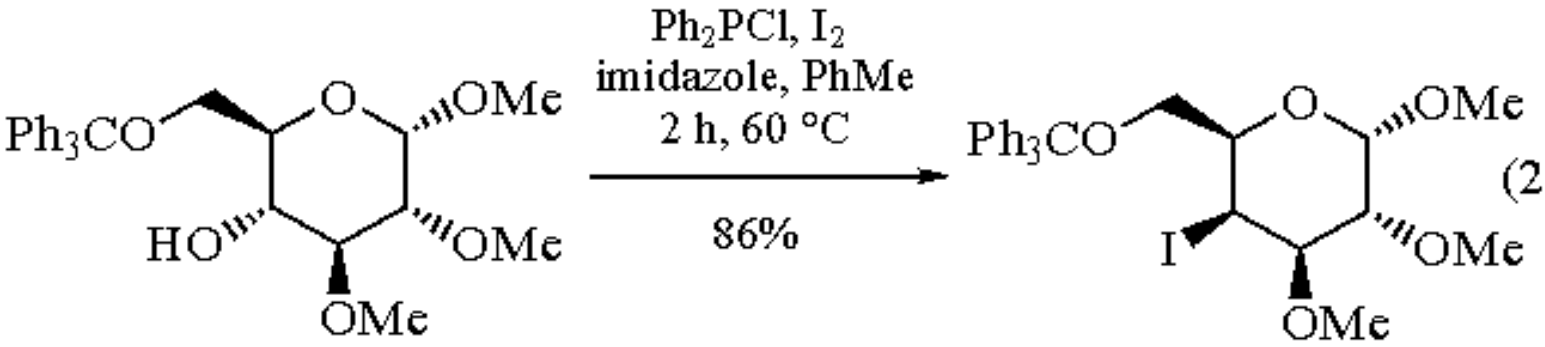

(2)

Alkenes from Vicinal Diols.

The same reagent system can be employed to convert vicinal diols to alkenes (eqs 3 and 4).[2] This single step procedure is more efficient than methods that require transformation of the diols to activated groups, such as disulfonates or cyclic thiocarbonates, which are subsequently converted into alkenes. The reaction proceeds through a vicinal iododiphenylphosphinate which can sometimes be isolated.

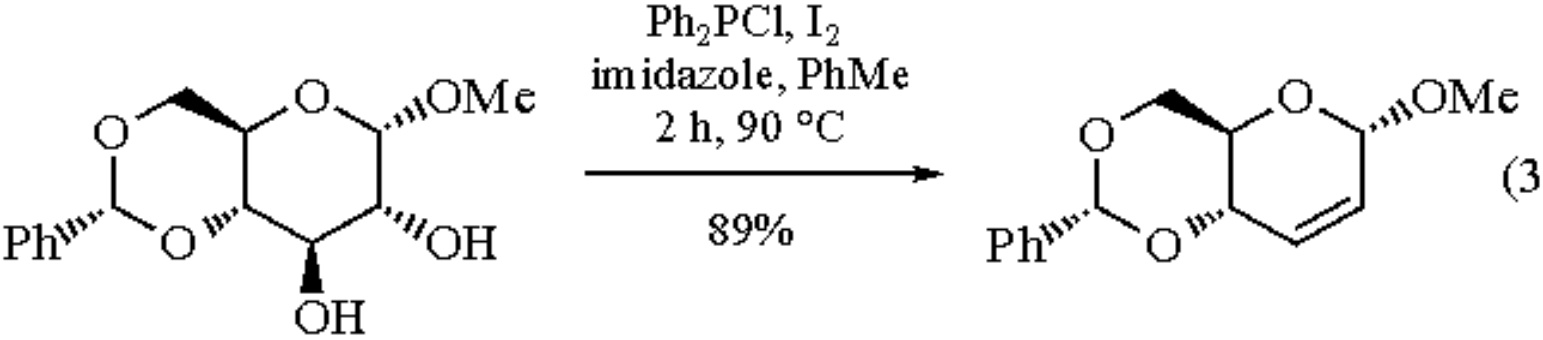

(3)

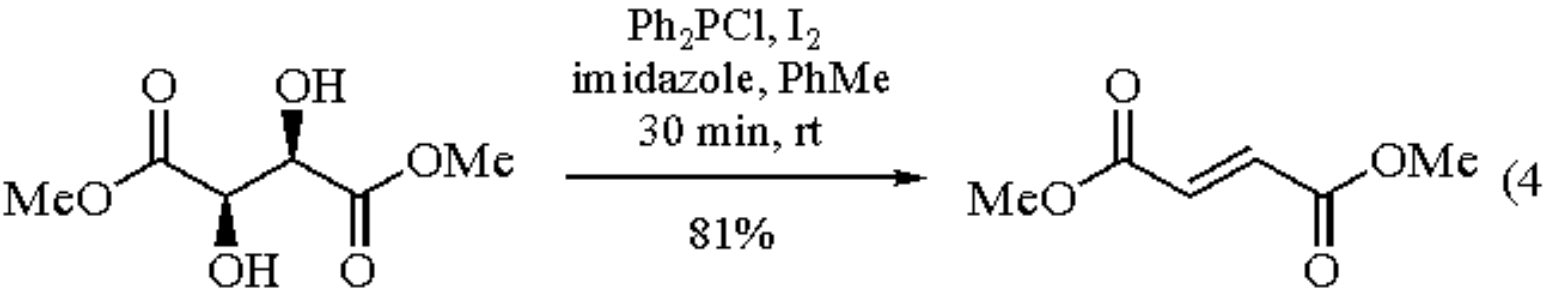

(4)

Thioesters from Sulfoxides.

Chlorodiphenylphosphine has been utilized to convert sulfoxides into thioesters (eq 5).[3] α-Lithio sulfoxides react with chlorodiphenylphosphine to provide α-sulfinylphosphines, which are rearranged by iodine to α-sulfenylphosphine oxides. Horner-Bestmann oxygenation gives the thioesters in good yields. This transformation has also been applied to cyclic sulfoxides to provide thiolactones (eq 6).[5]

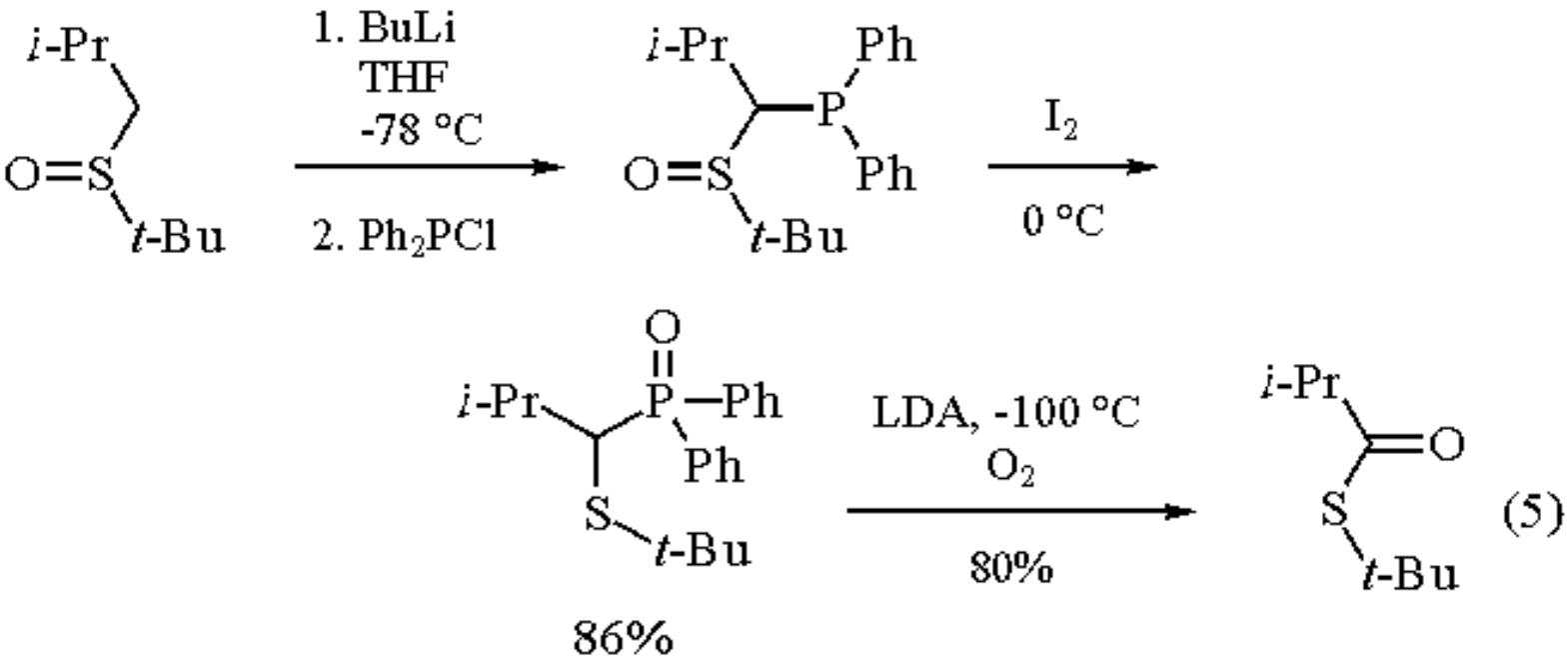

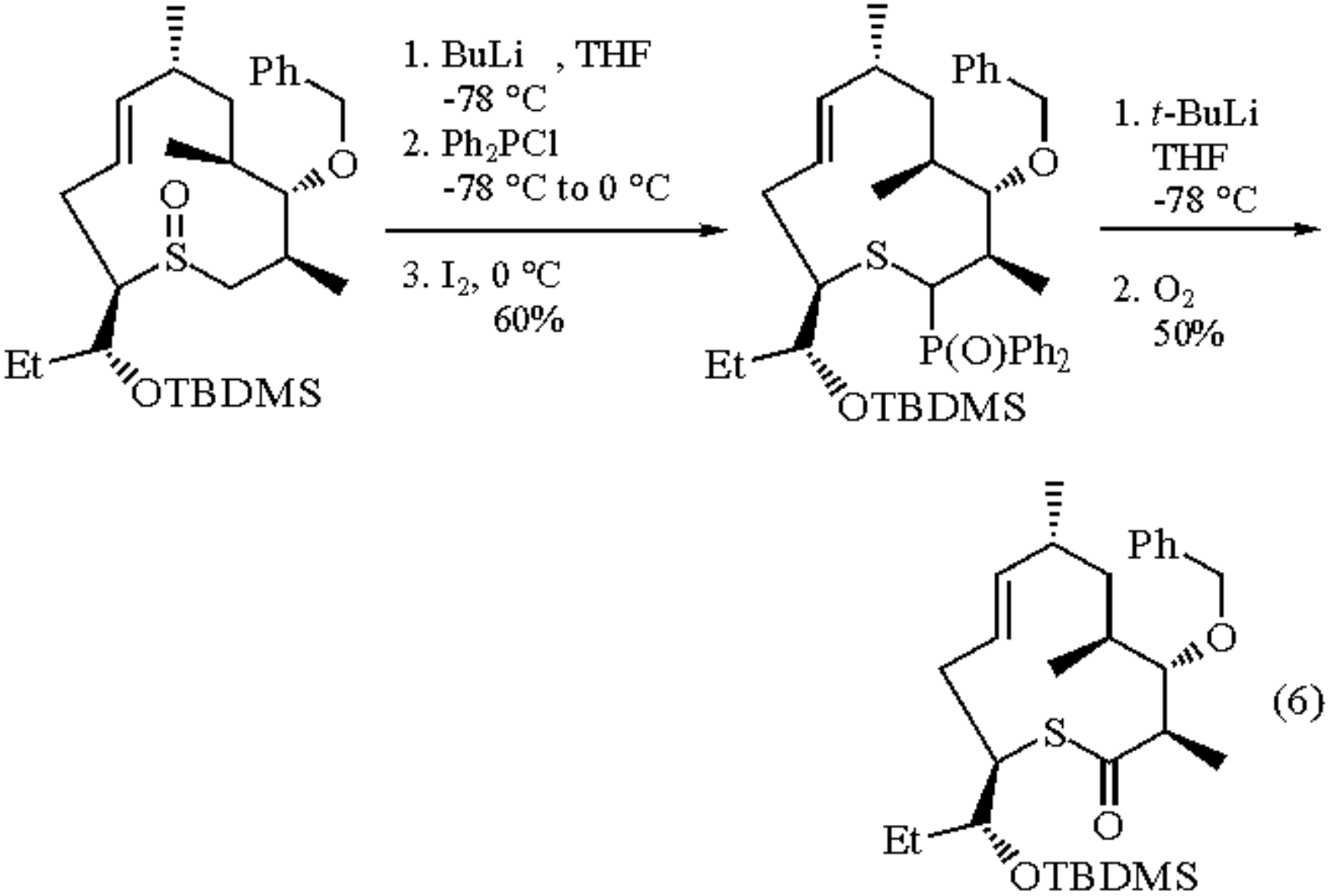

Phosphine and Phosphine Oxide Formation.

Chlorodiphenylphosphine has been electrochemically coupled with organic halides to generate phosphines.[4] It also reacts with anions to give alkyl- or arylphosphines which can be oxidized to phosphine oxides. This method has been used to form a bifunctional molecule capable of serving as a phase transfer catalyst and transition metal ligand (eq 7).[6]

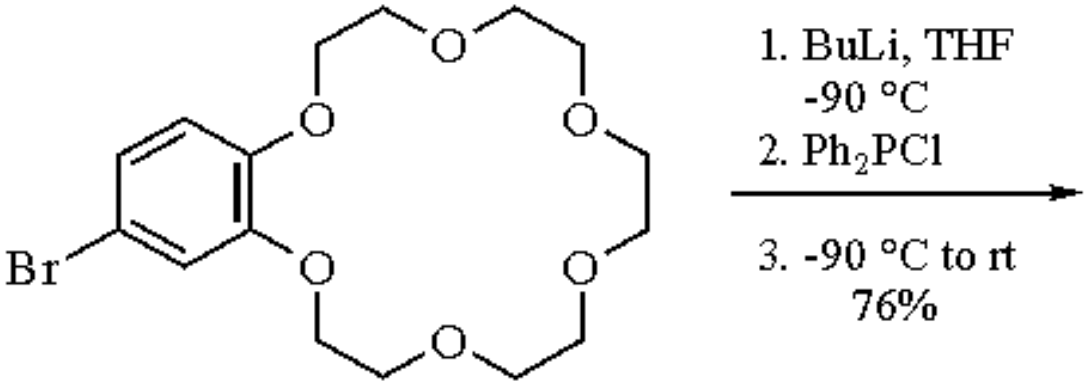

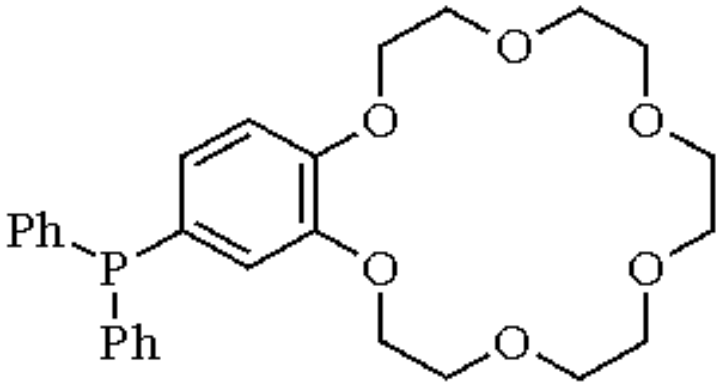

(7)

1,3-Dienylphosphines, bifunctional transition metal ligands, have been generated employing chlorodiphenylphosphine by two different routes. The first one involves hydrozirconation of conjugated enynes, followed by reaction with chlorodiphenylphosphine, to provide the dienylphosphines (eq 8).[7] In the other process, an in situ generated methylenephosphine phosphonate anion is alkylated with an α,β-enal to give the dienylphosphine (eq 9).[8] The second procedure is more versatile, because α,β-unsaturated aldehydes are more readily available than the corresponding enynes.

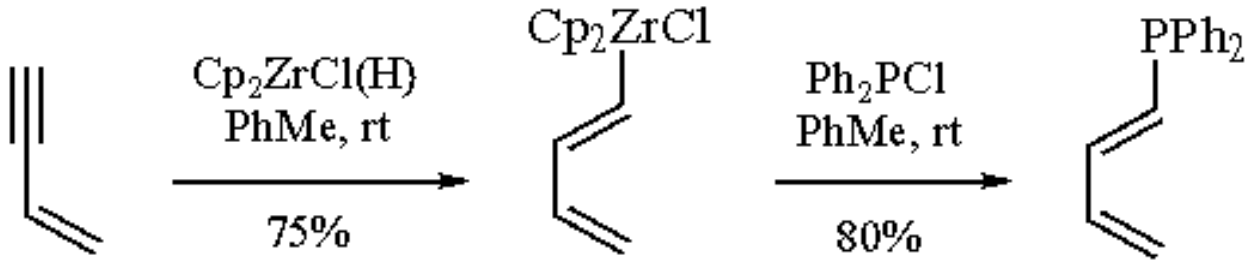

(8)

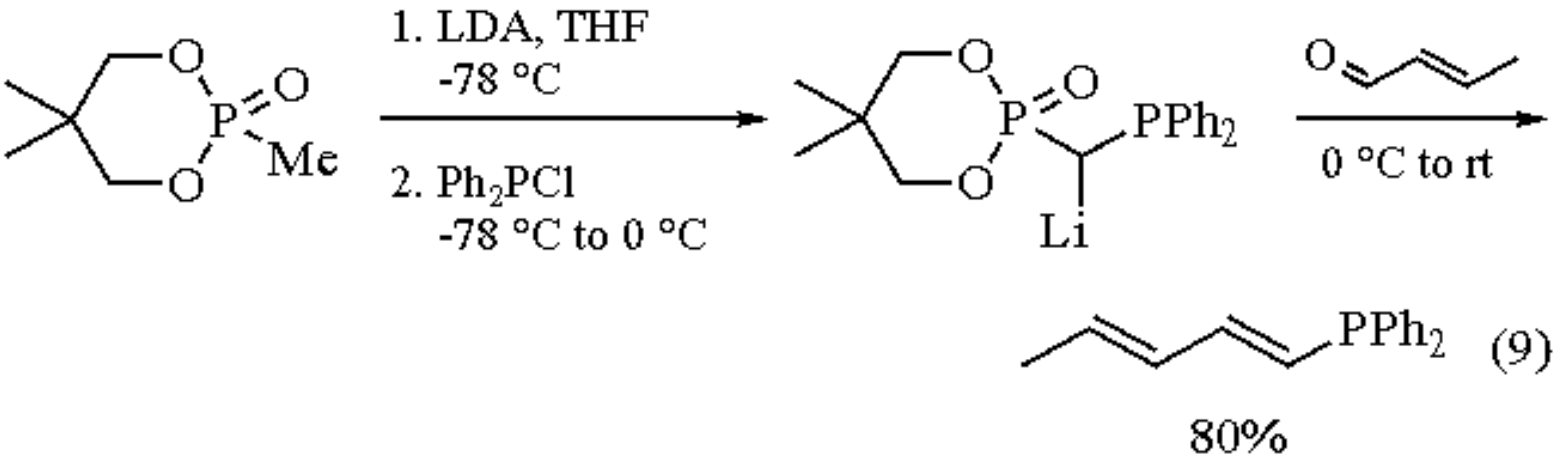

(9)

Ketones have been converted to vinylphosphine oxides (eq 10).[9] This process requires the conversion of the ketone to the trisylhydrazone. Subsequent formation of the vinyl carbanion, trapping with chlorodiphenylphosphine, and oxidation yields the vinylphosphine oxides.

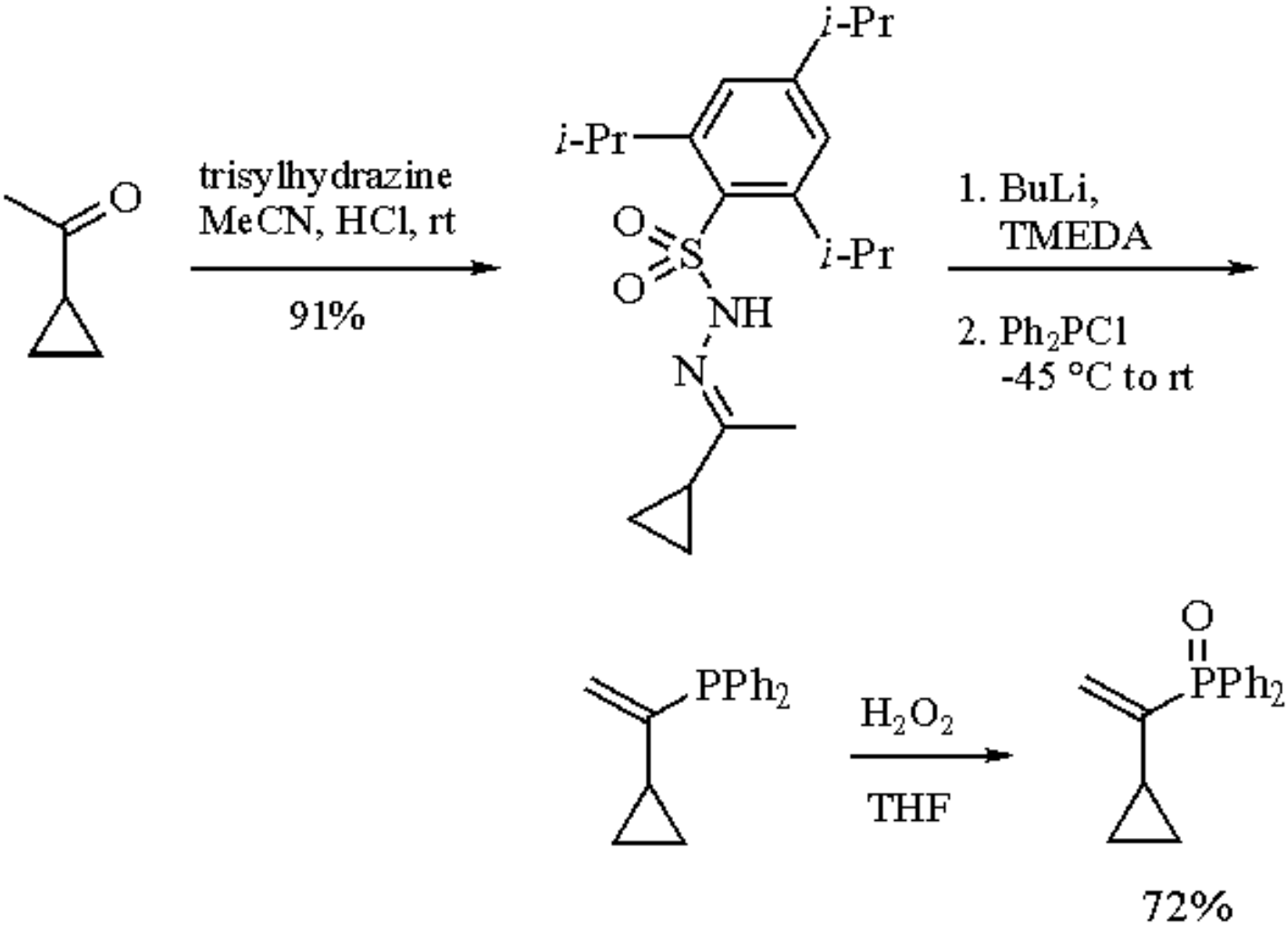

(10)

β-Ketophosphine oxides can be prepared from enolates by trapping with chlorodiphenylphosphine, followed by oxidation.[10] This sequence has also been applied to enolates generated from a Michael addition (eq 11).

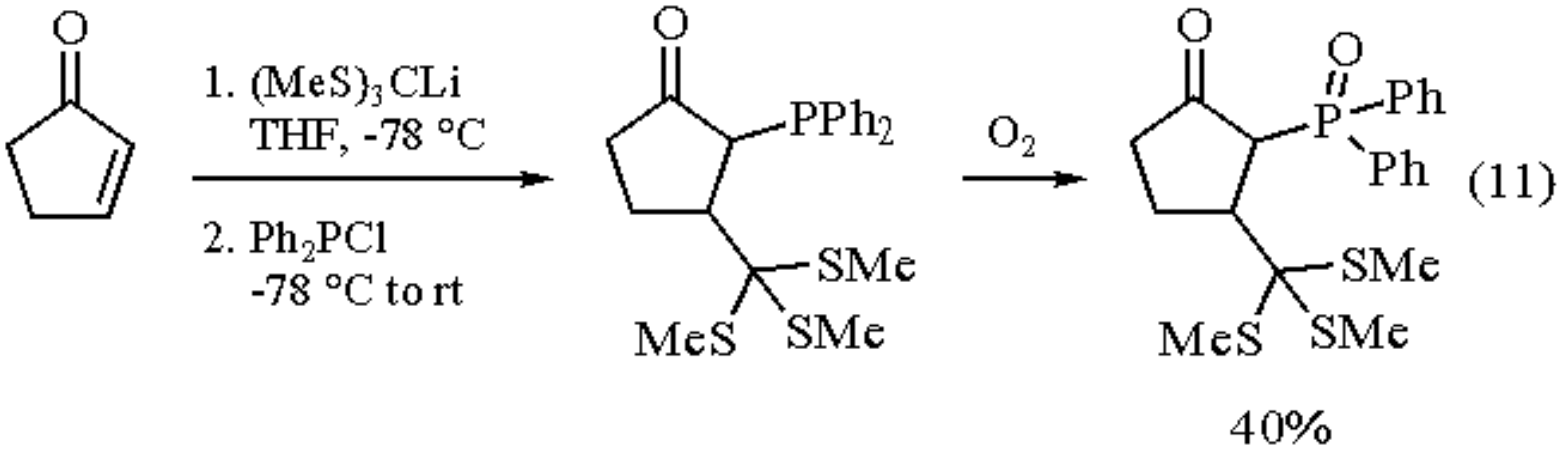

α-Functionalized phosphine oxides are versatile reagents for the formation of enol ethers, enamines, and vinyl sulfides via Horner-Wittig reactions.[11] α-Alkoxyphosphine oxides can be prepared by reaction of acetals with chlorodiphenylphosphine (eq 12). Ketene acetals can be generated from carbonyl compounds via the Horner-Wittig reaction with α,α-dialkoxyphosphine oxides made in a similar fashion to that of the previous equation from orthoesters and chlorodiphenylphosphine.[12] α-Aminophosphine oxides can be formed by reaction between chlorodiphenylphosphine and aminals in an analogous fashion.[13]

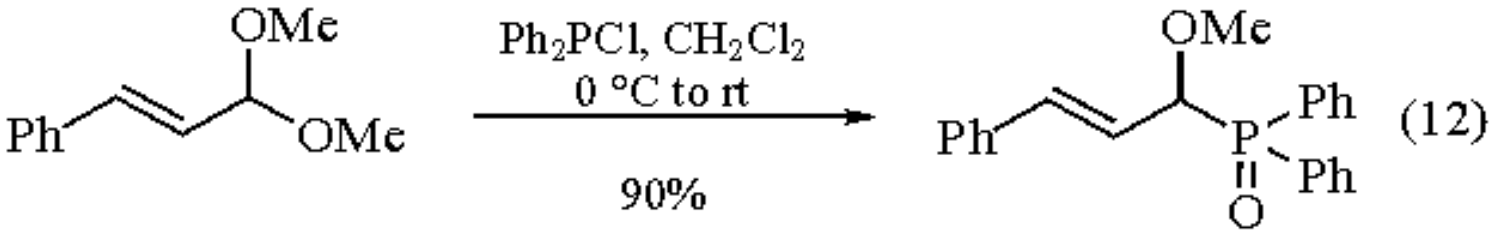

Propargylic alcohols react with chlorodiphenylphosphine to form phosphinite esters which subsequently undergo [2,3]-sigmatropic shifts to give allenylphosphine oxides.[14] This transformation has been coupled with an intramolecular Diels-Alder reaction to give vinylphosphine oxides (eq 13).

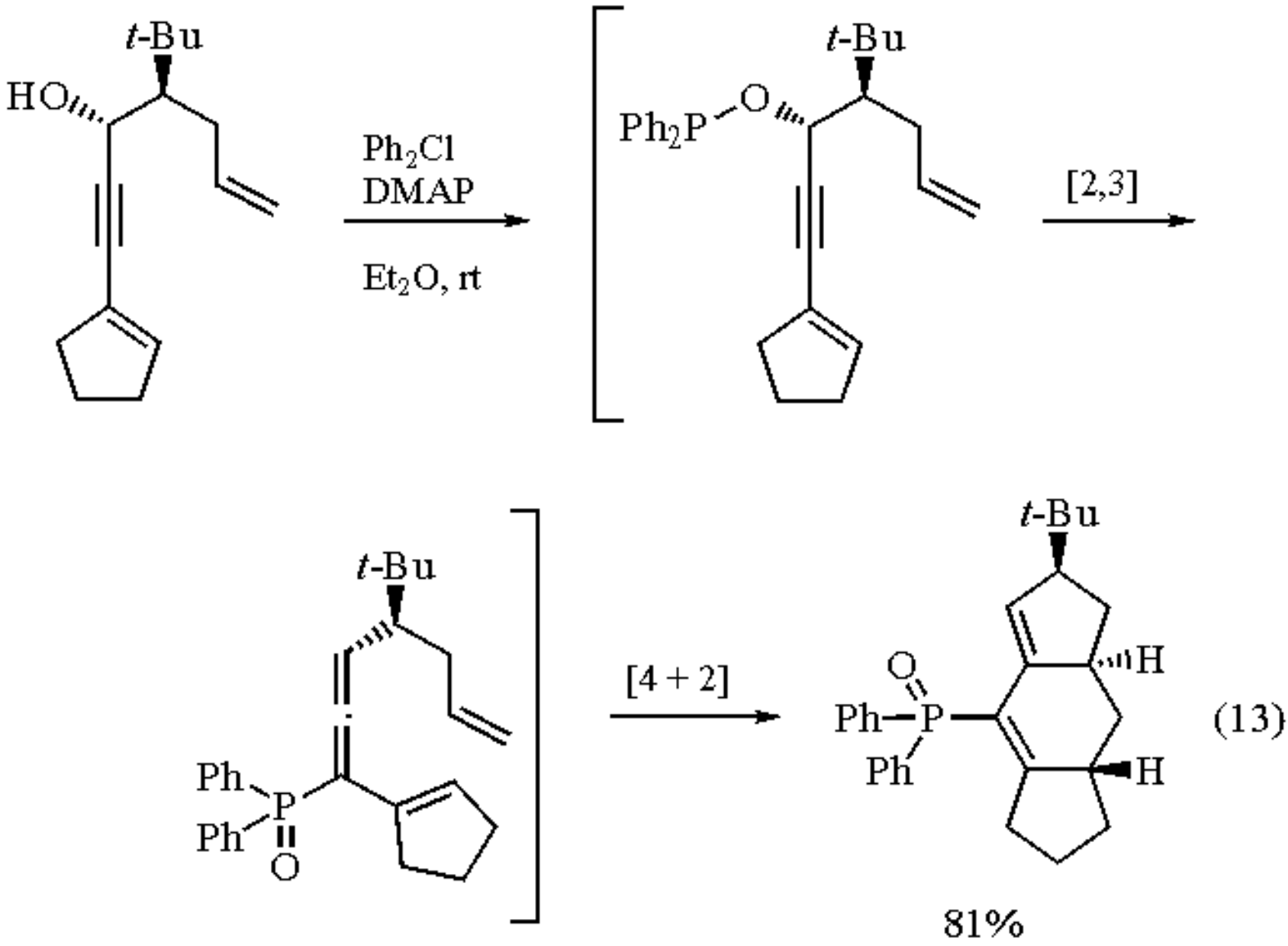

Other Applications.

Aldoximes and ketoximes react with chlorodiphenylphosphine to produce phosphinyloximes which undergo rearrangement to phosphinylimines.[15] This class of compounds can be reduced to provide protected amines, combined with organometallic reagents to give new amine derivatives, treated with hydrogen cyanide to yield α-aminonitriles, or reacted with diethyl phosphite to produce α-aminophosphonates (eq 14)

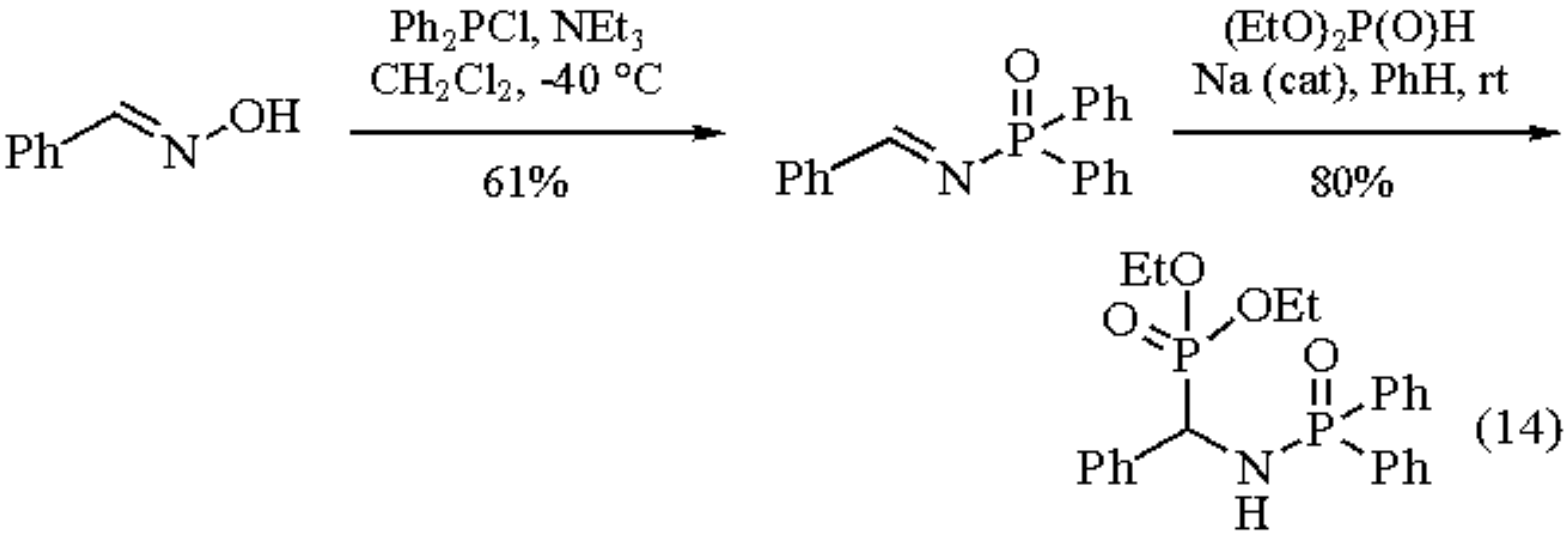

(14)

Lithium diphenylphosphide (Ph_2PLi) can be prepared from chlorodiphenylphosphine and lithium metal.[16] This is a versatile reagent for the dehydroxylation of α-hydroxy ketones and inversion of alkenes via epoxides.[17]

Chlorodiphenylphosphine can be oxidized with oxygen to form chlorodiphenylphosphine oxide.[18] This reagent can be utilized for the activation of carboxylic acids and protection of amines (see ***RC098-***).

Chlorodiphenylphosphine has been utilized as a reducing agent for diselenides and pyridine *N*-oxides.[19]

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Chlorodiphenylsilane[1]

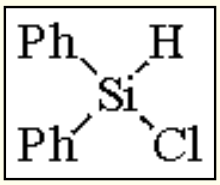

[1631-83-0] · $C_{12}H_{11}ClSi$ · Chlorodiphenylsilane · (MW 218.76)

(hydrosilylation;[1] precursor to alkyldiphenyl- and aryldiphenylsilanes[2])

Physical Data: bp 140-145 °C/7 mmHg (99-101 °C/1 mmHg; 83-85 °C/0.4 mmHg); *d* 1.137 g cm^{-3}; *n* 1.5845.

Solubility: sol benzene, chloroform, carbon tetrachloride, and ether.

Form Supplied in: liquid. Commercially available.

Preparative Methods: chlorodiphenylsilane may be prepared in high yield by treatment of diphenylsilane with triphenylmethyl chloride in refluxing benzene[3] or with PCl_5 at rt in CCl_4.[4]

Handling, Storage, and Precautions: moisture sensitive. Reactions are typically conducted under an inert atmosphere. The compound is corrosive and liberates HCl upon contact with moisture; may burn exposed skin and can be destructive to eyes, mucous membranes, and upper respiratory tract. Chemically incompatible with water, alcohols, and amines.

Hydrosilylation of Alkenes and Alkynes.

In the presence of a catalyst (typically chloroplatinic acid, H_2PtCl_2), chlorodiphenylsilane hydrosilylates double and triple bonds. As a difunctional reagent, chlorodiphenylsilane may be used in a reaction with an organometallic reagent (see the following section) to displace chlorine prior to the hydrosilylation reaction as in eq 1[5] or hydrosilylation may be conducted first with subsequent reaction at silicon as illustrated in eq 2.[6] The regiochemistry of the reaction has been reviewed.[7]

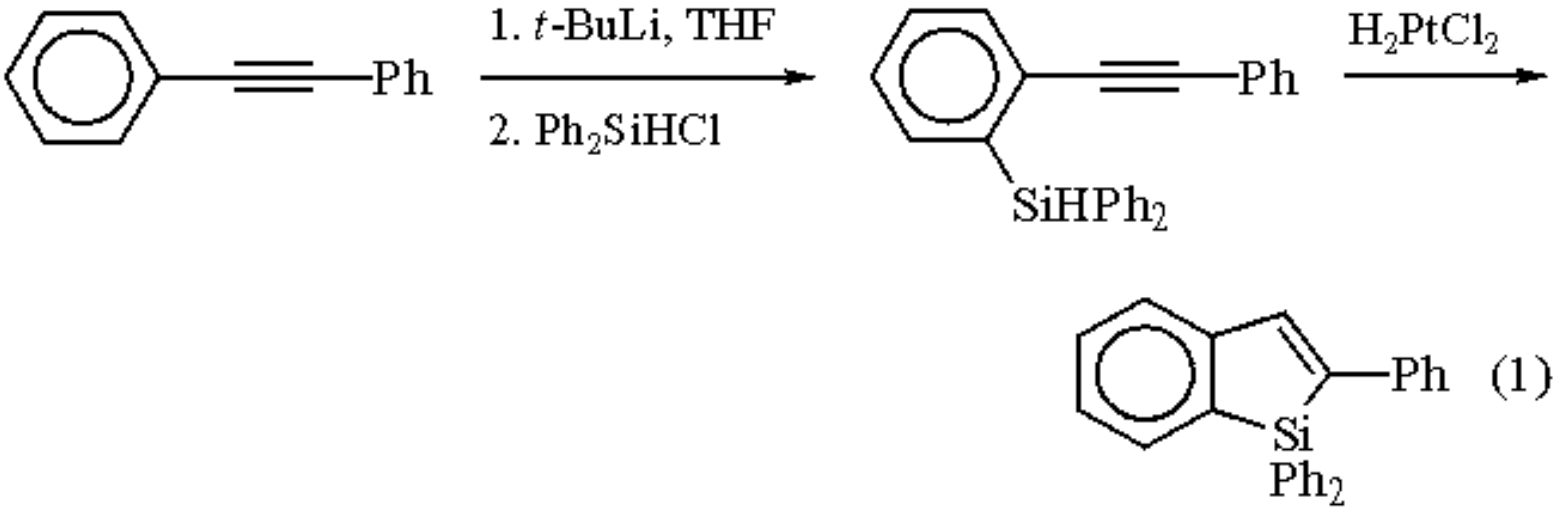

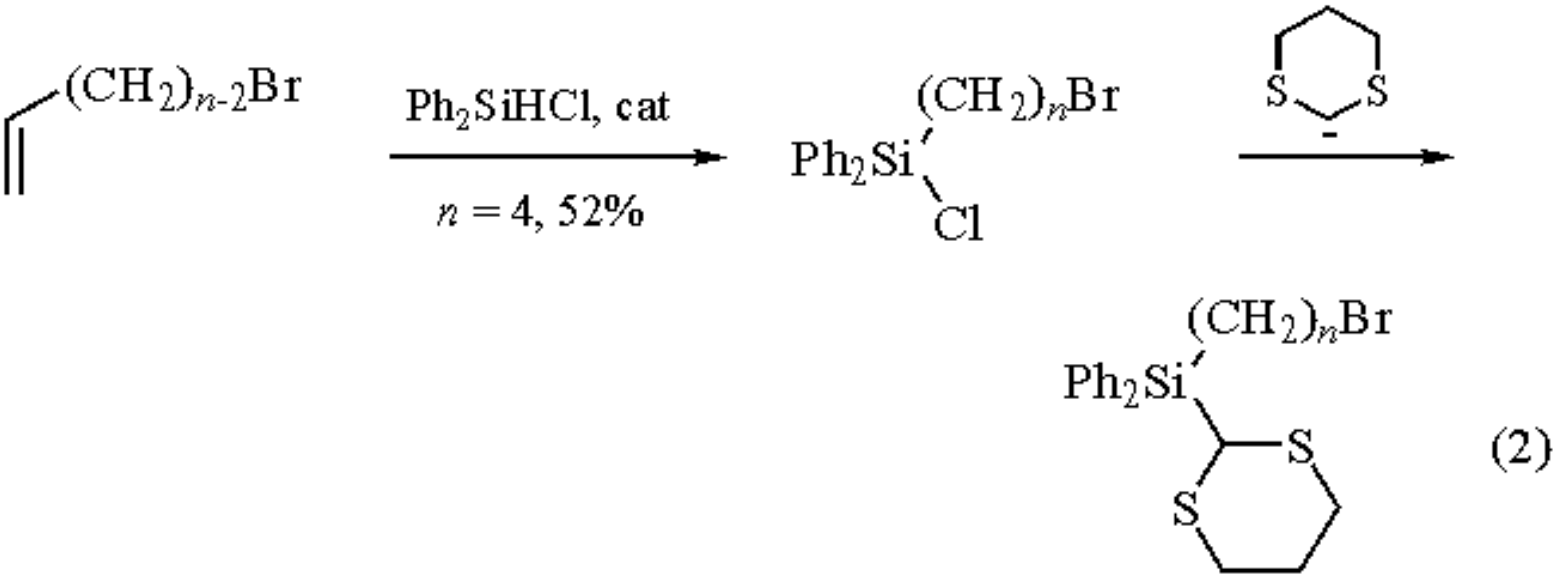

An enantioselective synthesis of chiral diols via intramolecular hydrosilylation using a chiral catalyst followed by oxidative cleavage of the Si-C bond (with retention of configuration) has been reported.[8] Intramolecular hydrosilylation/oxidation of allylamines provides a highly regio- and stereoselective synthesis of 2-amino alcohols (eq 3).[9]

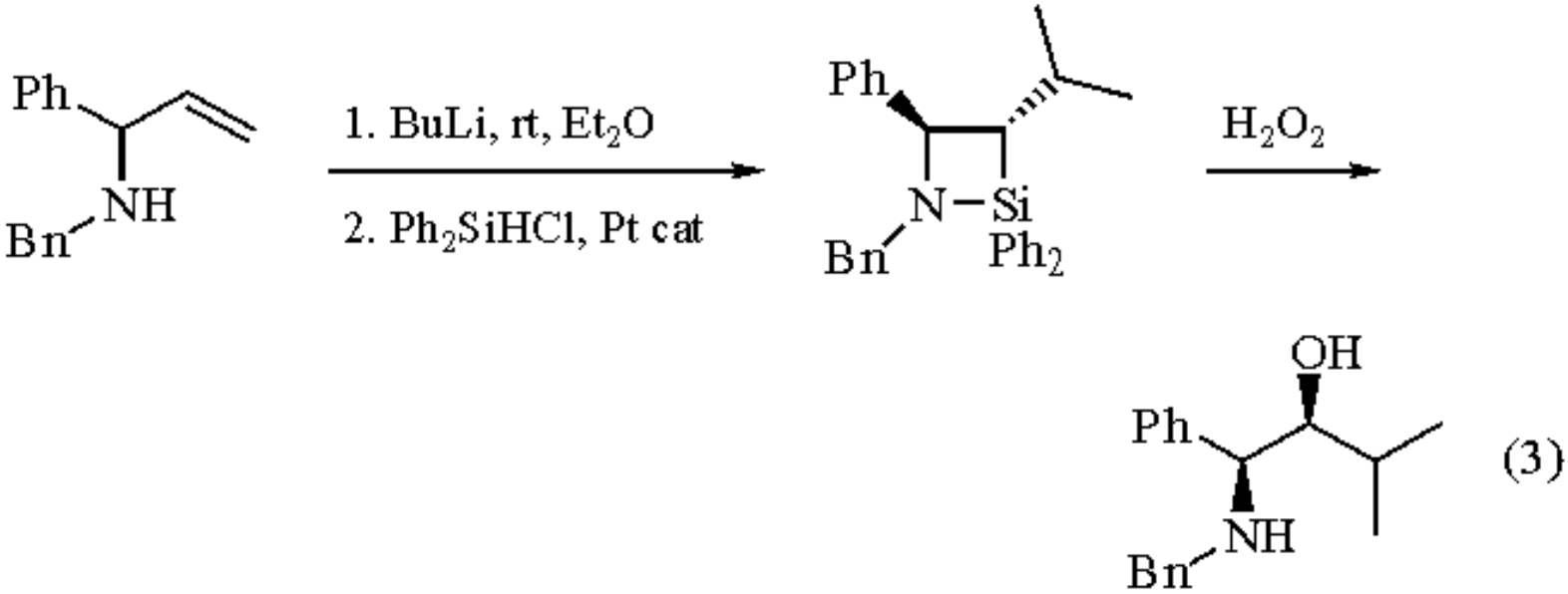

Chloride Displacement by Organometallic Reagents.

Organolithium and Grignard reagents react with chlorodiphenylsilane to produce substituted alkyl- or aryldiphenylsilanes (eqs 4 and 5).[2]

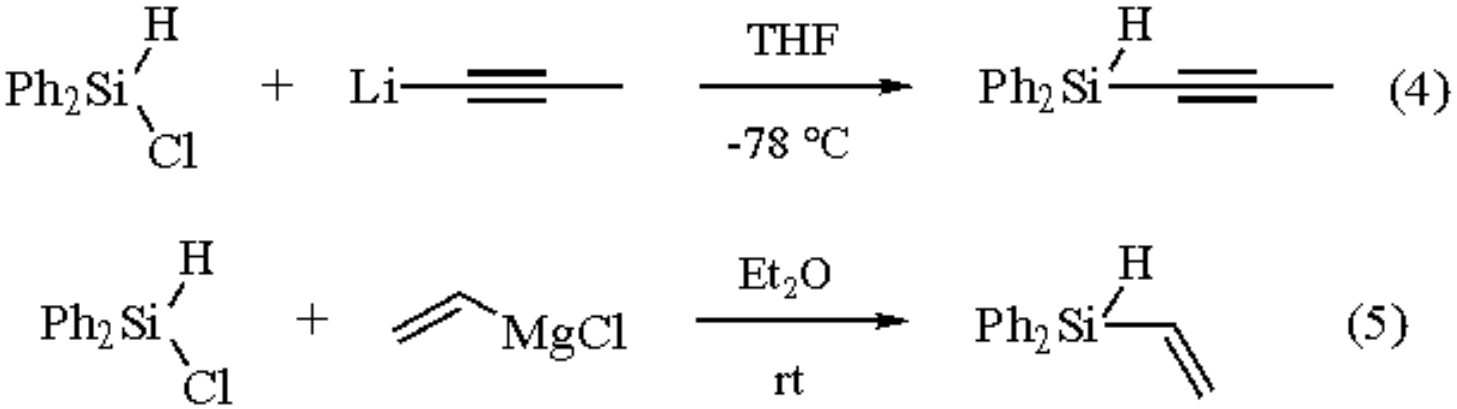

Related Reagents.

Triethylsilane.

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2-Chloro-1,3-dithiane

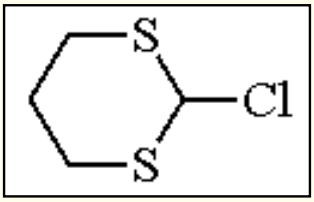

[57529-04-1] · $C_4H_7ClS_2$ · 2-Chloro-1,3-dithiane · (MW 154.69)

(readily accessible electrophilic 1,3-dithiane reagent; formyl cation equivalent; reacts with alkyl- and arylmagnesium halides,[1] enamines,[2] 1,3-dicarbonyl compounds,[1,2] electron-rich aromatics,[1,3] and with P,[4,5] N,[3] S,[3] and Se[6] nucleophiles)

Physical Data: mp 50 °C (dec).

Solubility: sol benzene, chloroform, THF, and ether.

Preparative Methods: the reagent can be easily obtained by chlorination of ***1,3-Dithiane***, either with ***N-Chlorosuccinimide*** (NCS) in benzene[3] or with ***Sulfuryl Chloride*** in chloroform.[5] The latter procedure generally gives a cleaner product[7] and is described here.

Sulfuryl chloride (11 mmol) in 5 mL of chloroform is slowly added to 1,3-dithiane (10 mmol) in 25 mL of chloroform at -40 °C in a nitrogen atmosphere. A white precipitate (chlorosulfonium salt) forms instantly. This precipitate gradually dissolves when the reaction mixture is allowed to warm to rt in 30 min. After stirring for an additional 30 min the solvent is evaporated at 0 °C and 1.55 g of 2-chloro-1,3-dithiane (**1**) of better than 95% purity (^{1}H NMR: C(2)-H δ 6.20) is obtained as a white or pale-yellow solid. A (minor) impurity is the sulfenyl chloride $ClCH_2S(CH_2)_3SCl$ (δ 4.80), formed by attack of chloride at the central carbon atom of the chlorosufonium salt.[5]

Handling, Storage, and Precautions: the reagent should be prepared shortly before use and rigidly protected against moisture, both in the solid form and in solution. Handle in a fume hood.

Reaction with Carbon Nucleophiles.

Organomagnesium (Aluminum) Reagents.

2-Chloro-1,3-dithiane (**1**) reacts readily with secondary and aromatic Grignard reagents,[1] thereby providing products such as (**2**), (**3**), and (**4**) that are not readily available by classical 2-lithio-1,3-dithiane chemistry.[8]

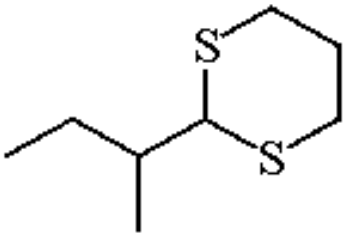

(2) 53%

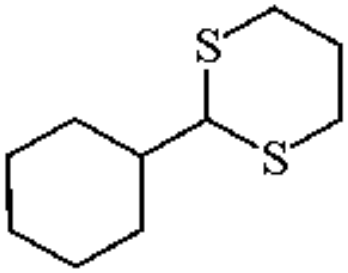

(3) 60%

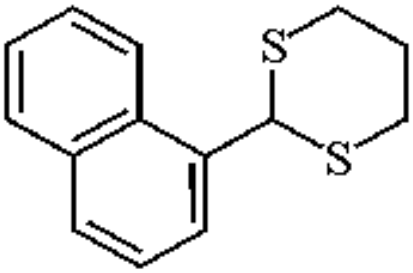

(4) 75%

Reaction with 3-substituted allylic aluminum reagents[9] affords dithianes (**5**), which arise from an allylic rearrangement, free of any other isomer (eq 1). Alkylation of 2-lithio-1,3-dithiane with allylic halides would give the isomeric, nonrearranged products.[8] The related reagent 1,3-dithienium tetrafluoroborate gives similar results in this reaction and affords better yields.[9]

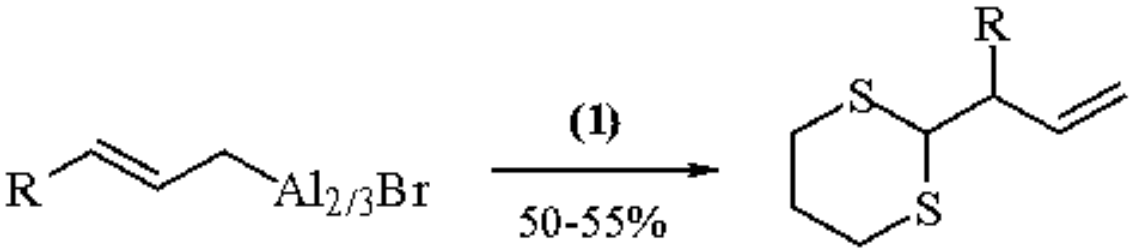

(1)

(5)

The aluminum derivative of 1-bromo-2-propyne affords (**6**) upon combination with (**1**).[9] The phenylacetylene derivative (**7**) had earlier been obtained by a Grignard reaction with (**1**).[10]

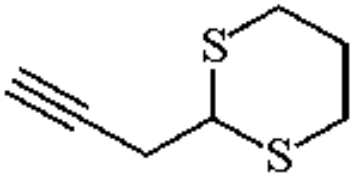

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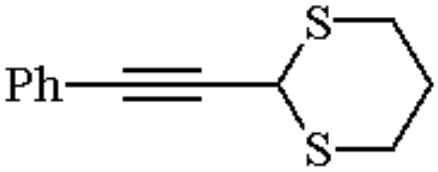

(7)

Reaction with Electron-Rich Arenes.

Reaction of (**1**), prepared with NCS, with phenol or dimethylaniline affords the crystalline 4-substituted 2-(1,3-dithianyl) derivatives (**8**) and (**9**), respectively.[3]

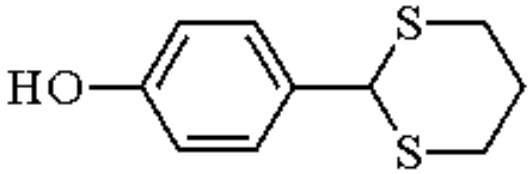

(8) 75%

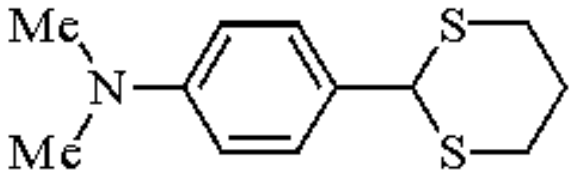

(9) 30%

Excellent yields of products (**10**), (**11**), and (**12**) are obtained by combining the corresponding phenols with (**1**), prepared with sulfuryl chloride.[1] In the reaction mixture obtained from phenol, 20% of the 2-substituted isomer was present (NMR).

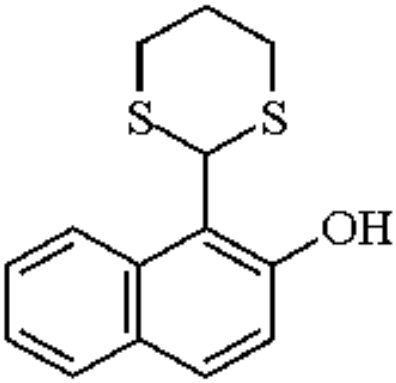

(10) 99%

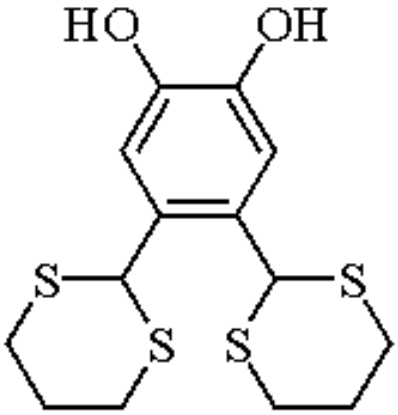

(11) 96%

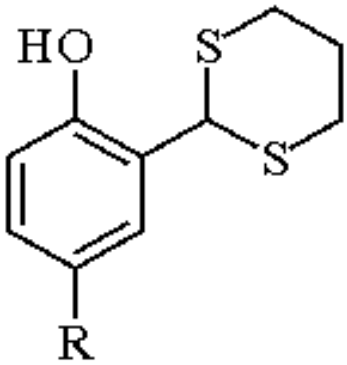

(12) R = OMe, 86%
R = Me, 85%
R = Cl, 81%

In a study of 1,3-benzodioxole derivatives, the 6-substituted 2-(1,3-dithianyl) compound (**13**), obtained from reaction of the diol with (**1**) in 79% yield, served as starting material for the corresponding 6-methyl compound (reduction with ***Raney Nickel***) as well as for the interesting 4,5-quinone (**14**) (eq 2).[11]

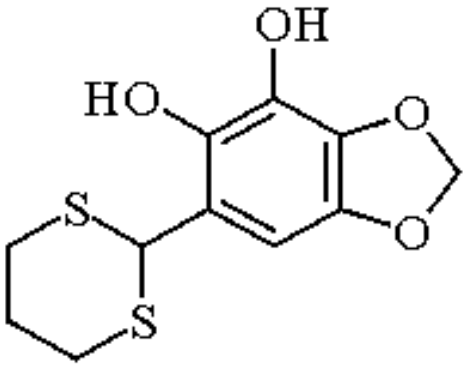

(13)

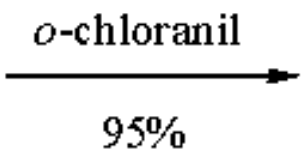

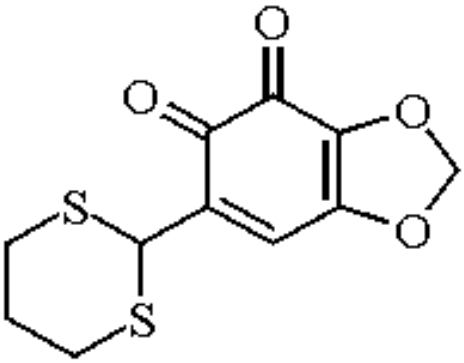

(2)

(14)

Reaction of the anion of *N*-(phenylsulfonyl)indole with (**1**) gives the 2-[2-(1,3-dithianyl)]indole (**15**) (65%) which, after deprotection, can be functionalized at C-2´ to give (**16**) (eq 3).[7]

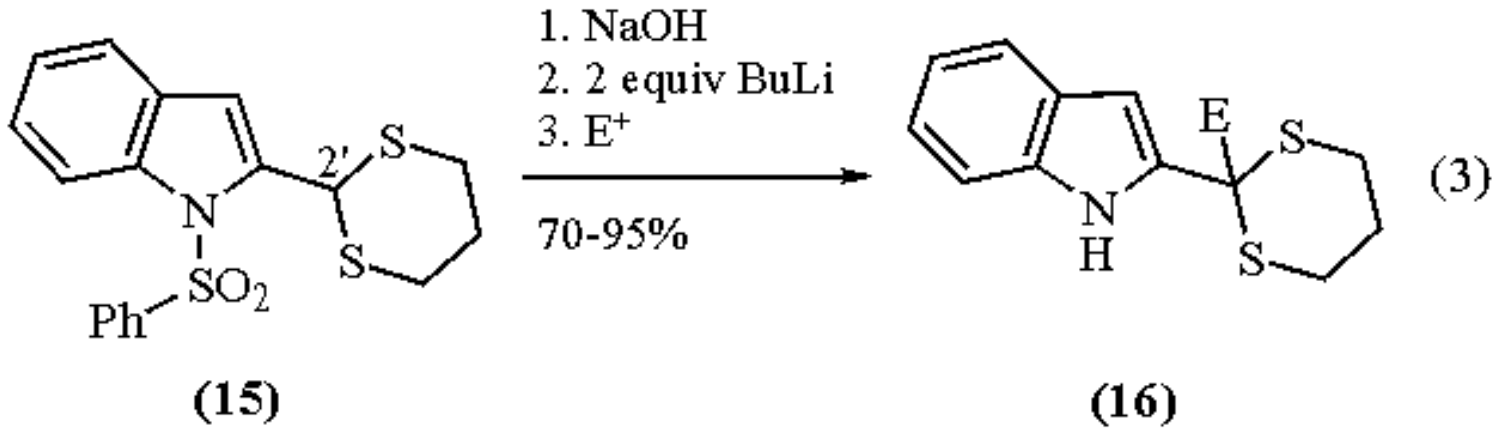

1,3-Dicarbonyl Compounds.

Reaction of (**1**) with the Na salts of malonic acid esters affords the 2-[2-(1,3-dithianyl)] derivatives (**17**) in excellent yields.[1] Danishefsky and co-workers have applied this procedure for the introduction of a critical C-1 unit in their approach towards the synthesis of naphthyridinomycin alkaloids.[12] Reaction of Na acetoacetic ester likewise affords (**18**).[2] These compounds can be deethoxycarbonylated by treatment with NaCl in DMSO.[2,13]

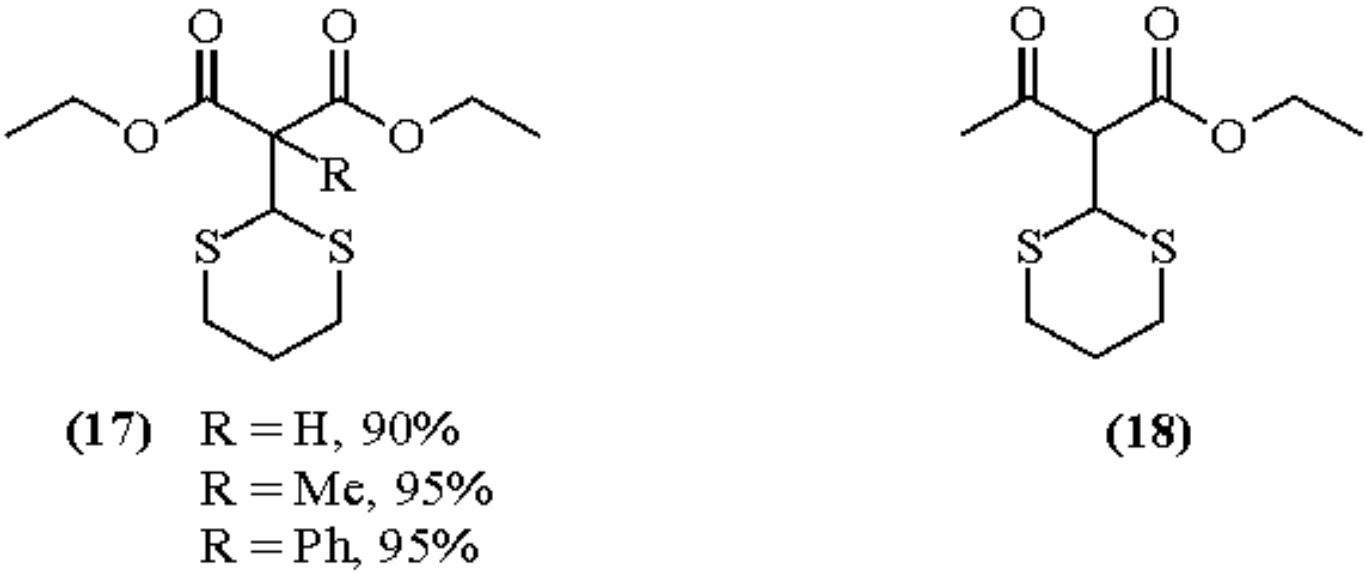

Enamines.

Taylor and LaMattina have reported the synthesis of 2-[2-(1,3-dithianyl)]aldehydes (**19**) (R = H) and ketones by reaction of (**1**) with morpholino enamines (eq 4).[2] This method has the advantage over classical methods for α-formylation of carbonyl compounds in that it directly introduces a base-stable protected formyl substituent.

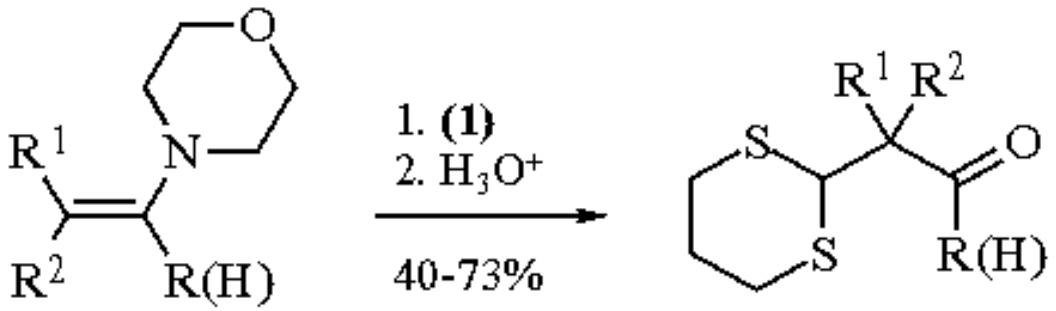

(4)

(19)

Reaction with Phosphorus Nucleophiles.

Reagent (**1**) reacts with ***Triphenylphosphine*** to give phosphonium salt (**20**) (78%)[5] and with ***Triethyl Phosphite*** to give diethyl phosphonate (**21**) (85%).[4,5] Both compounds are excellent reagents for the synthesis of ketene dithioacetals by the Horner-Wittig reaction. The reactions of (**20**) are restricted to aldehydes (eq 5);[5] however, (**21**) reacts well with both aldehydes and ketones (eq 6).[5,14,15]

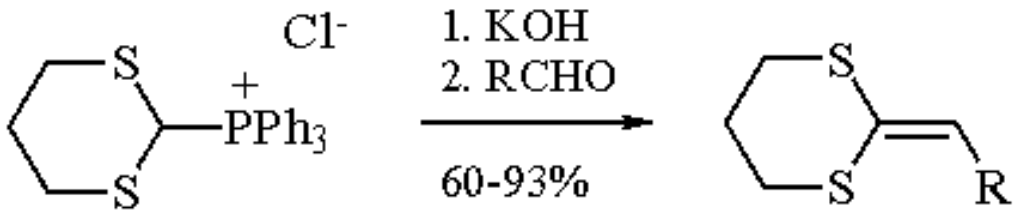

(5)

(20)

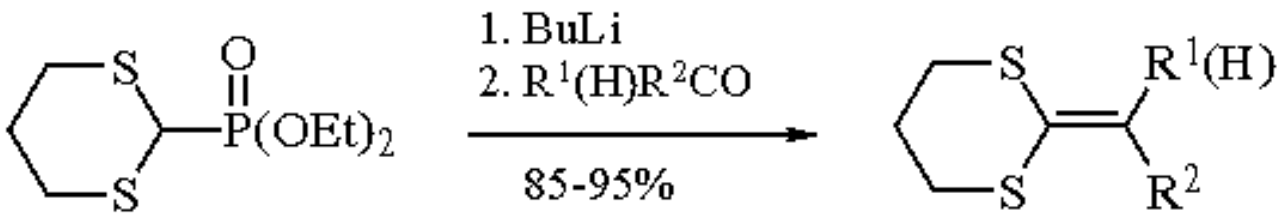

(6)

(21)

Reaction with S, Se, and N Nucleophiles.

Reaction of (**1**) with thiophenol affords 2-phenylthio-1,3-dithiane in 90% yield.[3] Reaction with ***Imidazole*** and with ***Succinimide*** affords the corresponding *N*-[2-(1,3-dithianyl)] compounds, also in excellent yields.[3a] Reaction of (**1**) with areneselenolate anions affords 2-arylseleno-1,3-dithianes (**22**) (eq 7).[6] These compounds, like the earlier studied (**7**)[10] and (**1**) itself,[3] show a strong anomeric effect in solution.[6]

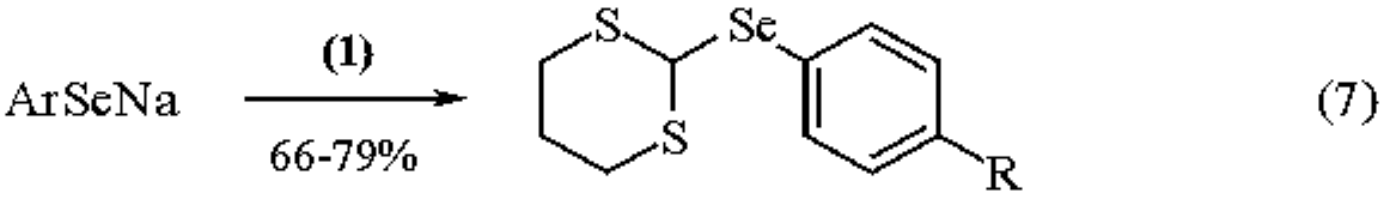

(22)

R = NMe_2, OMe, Me, H, I, Cl, CF_3, NO_2

Other Applications.

Reagent (**1**) has found use in the preparation of 2-(1,3-dithianyl)-substituted polycarbonyl-metal complexes of Cr,[16] W,[16] and Mn.[17]

---

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Leiden University, The Netherlands

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2-Chloro-3-ethylbenzoxazolium Tetrafluoroborate[1]

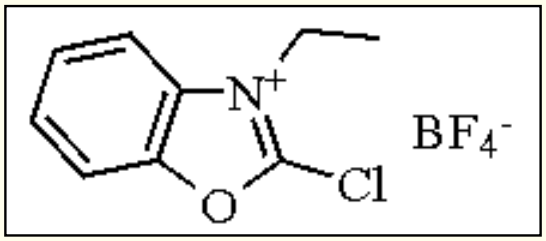

[63212-53-3] · $C_9H_9BClF_4NO$ · 2-Chloro-3-ethylbenzoxazolium Tetrafluoroborate · (MW 269.44)

(reagent for the conversion of alcohols to alkyl chlorides,[2,3] and preparation of isocyanides from formamides,[4] ketones from α-hydroxy carboxylic acids,[5] alkynes from aryl ketones,[6] and 1,2-*trans*-nucleosides from 1-hydroxy sugars[7])

Physical Data: mp 152 °C (dec).

Solubility: sol DMSO; slightly sol CH_2Cl_2, $CHCl_3$; insol Et_2O.

Form Supplied in: white solid.

Preparative Method: from *o*-aminophenol in three steps.[2] Commercially available.

Handling, Storage, and Precautions: hygroscopic and should be handled and stored under an argon atmosphere.

Synthesis of Alkyl Chlorides.

2-Chloro-3-ethylbenzoxazolium tetrafluoroborate (**1**) reacts with a variety of alcohols in the presence of tetraethylammonium chloride and triethylamine to afford the corresponding alkyl chlorides in high yields and generally with inversion of configuration.[2] 1-Hydroxy sugars are converted to the corresponding 1-chloro sugars with retention of configuration at the anomeric centers (eq 1). In reactions with alcohols, (**1**) is more reactive than the related reagents, 2-halopyridinium salts (**2**)[8] and 2-fluorobenzothiazolium tetrafluoroborate (**3**).[9]

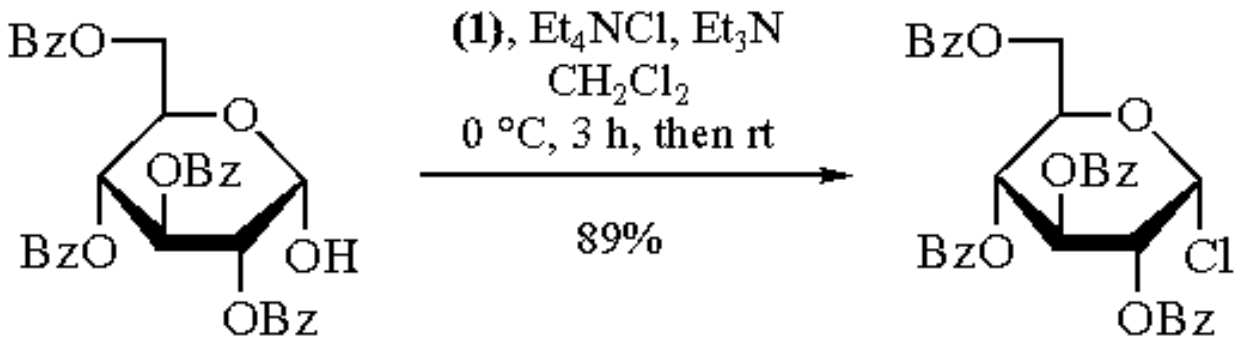

(1)

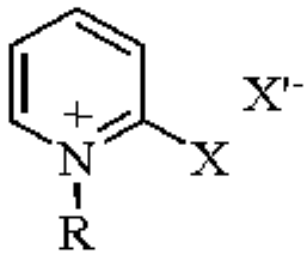

(2)

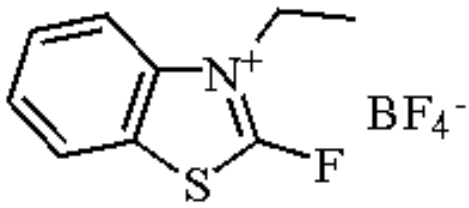

(3)

1,2-Dichloroalkanes are prepared from epoxides under similar reaction conditions (eq 2).[3]

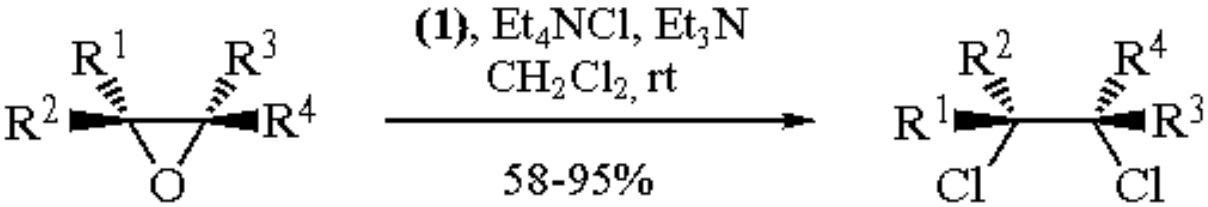

(2)

Synthesis of Isocyanides.

Isocyanides are useful intermediates in organic synthesis, and are frequently prepared via the dehydration of formamides.[10] Although several methods for achieving this transformation have been reported, rather drastic conditions, such as reflux in the presence of base, are often required.[11] As a useful alternative, dehydration of formamides proceeds smoothly in the presence of (**1**) and two equiv of triethylamine at room temperature; a variety of isocyanides can be prepared using this mild and simple procedure (eq 3).[4]

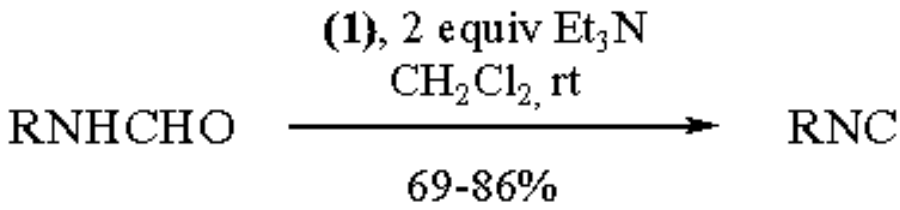

(3)

Synthesis of Ketones from α-Hydroxy Carboxylic Acids.

Treatment of α-hydroxy carboxylic acids, readily prepared from the corresponding carboxylic acids, with (**1**) and two equiv of triethylamine at room temperature affords ketones in good yields (eq 4).[5]

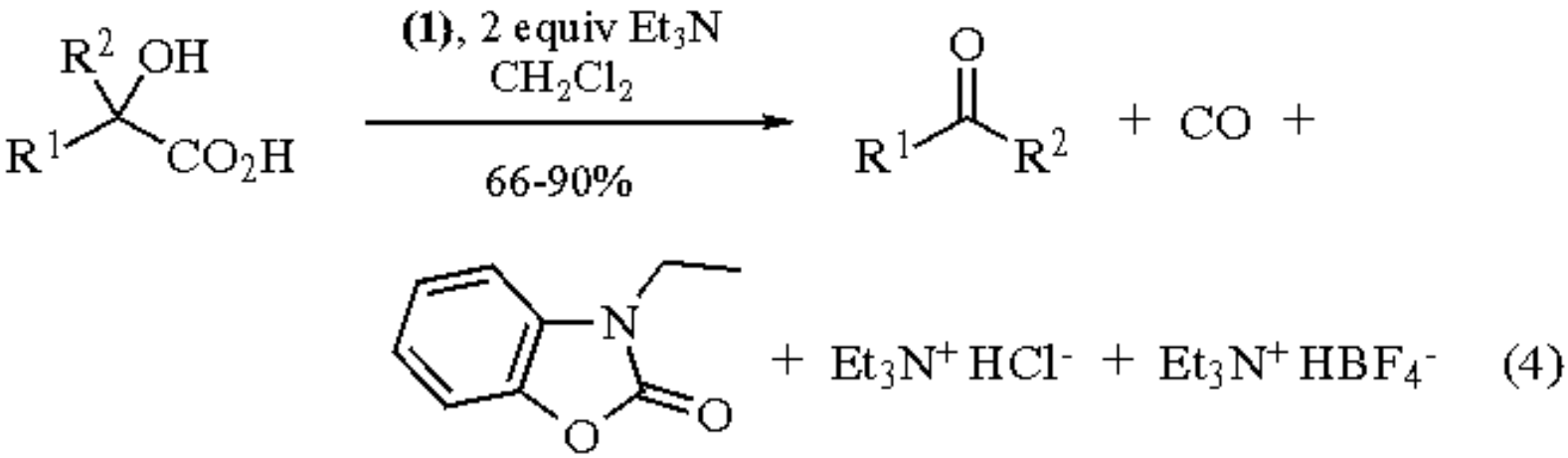

One-Step Formation of Arylalkynes from Aryl Ketones.

Aryl ketones are converted to the corresponding alkynes by treatment with (**1**) in the presence of a large excess of triethylamine at room temperature.

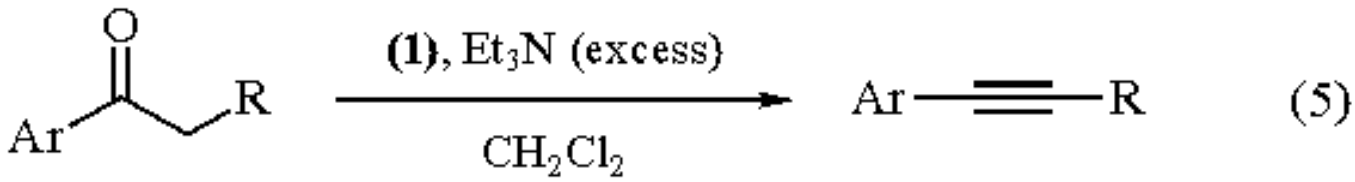

Synthesis of 1,2-*trans*-Nucleosides.

1,2-*trans*-Nucleosides are prepared from 1-hydroxy sugars and heterocycles by using (**1**) as a condensing reagent.[7]

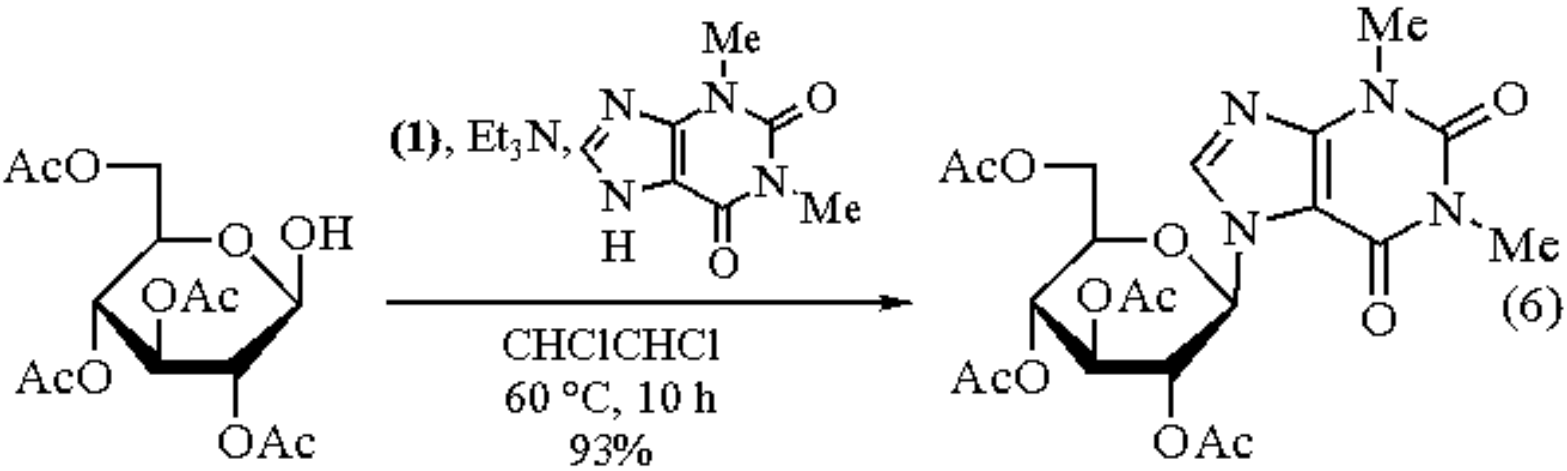

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1-Chloroethyl Chloroformate[1]

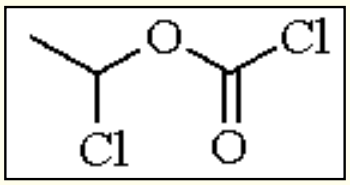

[50893-53-3] · $C_3H_4Cl_2O_2$ · 1-Chloroethyl Chloroformate · (MW 142.97)

(reagent for the *N*-dealkylation of tertiary amines[1,2])

Alternate Names: α-chloroethyl chloroformate; ACE-Cl.

Physical Data: bp 118-119 °C; *d* 1.325 g cm^{-3}; n_D^{20} 1.4230.

Form Supplied in: commercially available liquid.

Preparative Method: by stirring phosgene and acetaldehyde in the presence of benzyltributylammonium chloride, followed by distillation (96% yield).[2]

Purification: purified by vacuum distillation.

N-Dealkylation of Tertiary Amines.

1-Chloroethyl chloroformate (**1**) introduced by Olofson and co-workers, effects the selective, high yielding dealkylation of tertiary amines (eq 1).[2] Heating the amine (**2**) at reflux in 1,2-dichloroethane with 1 equiv of (**1**) for one hour results in formation of the ACE-piperidine (**3**). Evaporation of the solvent followed by heating the residue in methanol gives the hydrochloride salt of the secondary amine (**4**). Reagent (**1**) is preferred over the related reagent ***Vinyl Chloroformate*** for this application as the overall reaction conditions are milder and yields are higher.

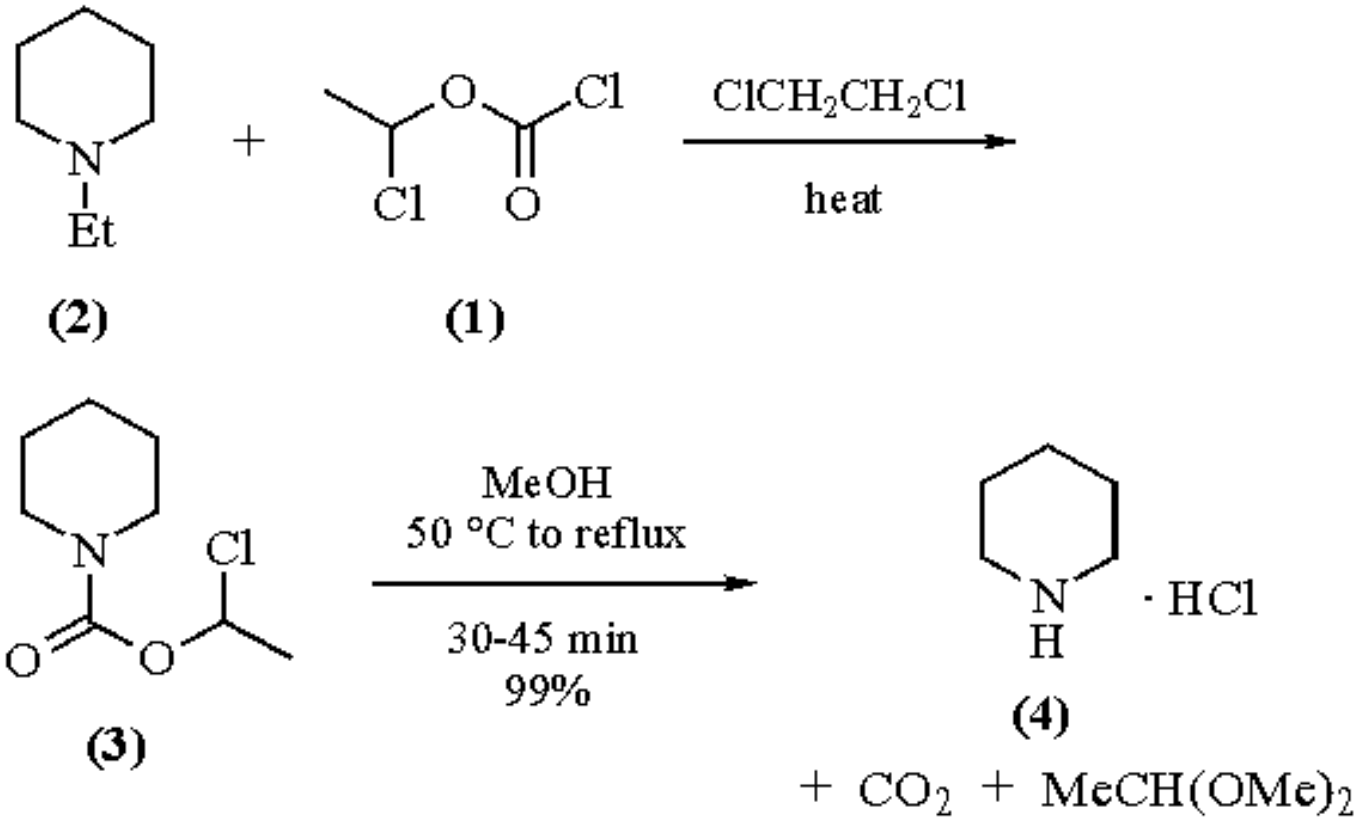

(1)

Ease of cleavage of *N*-substituents is observed to occur in the order $ArCH_2$ > allyl, *t*-alkyl >> *s*-alkyl > methyl > primary alkyl >> piperidine ring opening.[3] Dealkylation of aromatic amines can be achieved, but this requires higher temperatures. Acetoxy and alkoxycarbonyl groups are stable to the reaction conditions.

---

1. Olofson, R. A. *PAC* **1988**, *60*, 1715.
2. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *JOC* **1984**, *49*, 2081.
3. Olofson, R. A.; Abbott, D. E. *JOC* **1984**, *49*, 2795.

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2-Chloroethyl Chloromethyl Ether

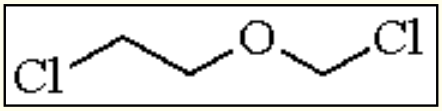

[1462-33-5] · $C_3H_6Cl_2O$ · 2-Chloroethyl Chloromethyl Ether · (MW 128.98)

(reagent for cyclopropanol synthesis;[1,2] formaldehyde equivalent in hydroxymethylation of Grignard reagents;[3] used for protection of indoles[4])

Alternate Name: 1-chloro-2-(chloromethoxy)ethane.

Physical Data: bp 145-147 °C (66-68 °C/22 mmHg);[3] *d* 1.28 g cm^{-3}.[5]

Solubility: sol most commonly used organic solvents including ethereal (THF, diethyl ether), halogenated (CH_2Cl_2, $CHCl_3$, CCl_4), and hydrocarbon solvents; incompatible with alcohol solvents.

Analysis of Reagent Purity: best ascertained by ^1H NMR [(300 MHz, $CDCl_3$/TMS) δ 3.96 (t, *J* = 5.7 Hz, 2 H), 3.96 (t, *J* = 5.7 Hz, 2 H), 5.53 (s, 2 H)].[3]

Preparative Method: most conveniently prepared by reaction of 2-chloroethanol and 1,3,5-trioxane with HCl(g) at 0 °C (1.0 mol scale, 66% yield).[3,6]

Purification: by distillation.

Handling, Storage, and Precautions: chloromethyl ethers are recognized carcinogens.[7] Preparation and handling of the reagent should be carried out in an efficient fume hood, and skin contact should be avoided. Chloromethyl ethers are also moisture-sensitive and should be stored and transferred under inert atmosphere. Excess reagent should be hydrolyzed in water before removing from the fume hood.[3]

Synthesis of Cyclopropanol Derivatives.

2-Chloroethyl chloromethyl ether serves as a precursor to (2-chloroethoxy)carbene[8] via deprotonation of the chloromethylene group with ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LiTMP) followed by α-elimination.[1] Trapping of the carbene intermediate with an alkene (excess) affords a 2-chloroethyl cyclopropyl ether. The corresponding cyclopropanol is obtained by cleavage of the 2-chloroethyl moiety upon treatment with ***n-Butyllithium***.[1,8] This methodology offers an efficient means for preparation of secondary cyclopropanols (eq 1),[8] but is not suitable for the synthesis of tertiary derivatives.

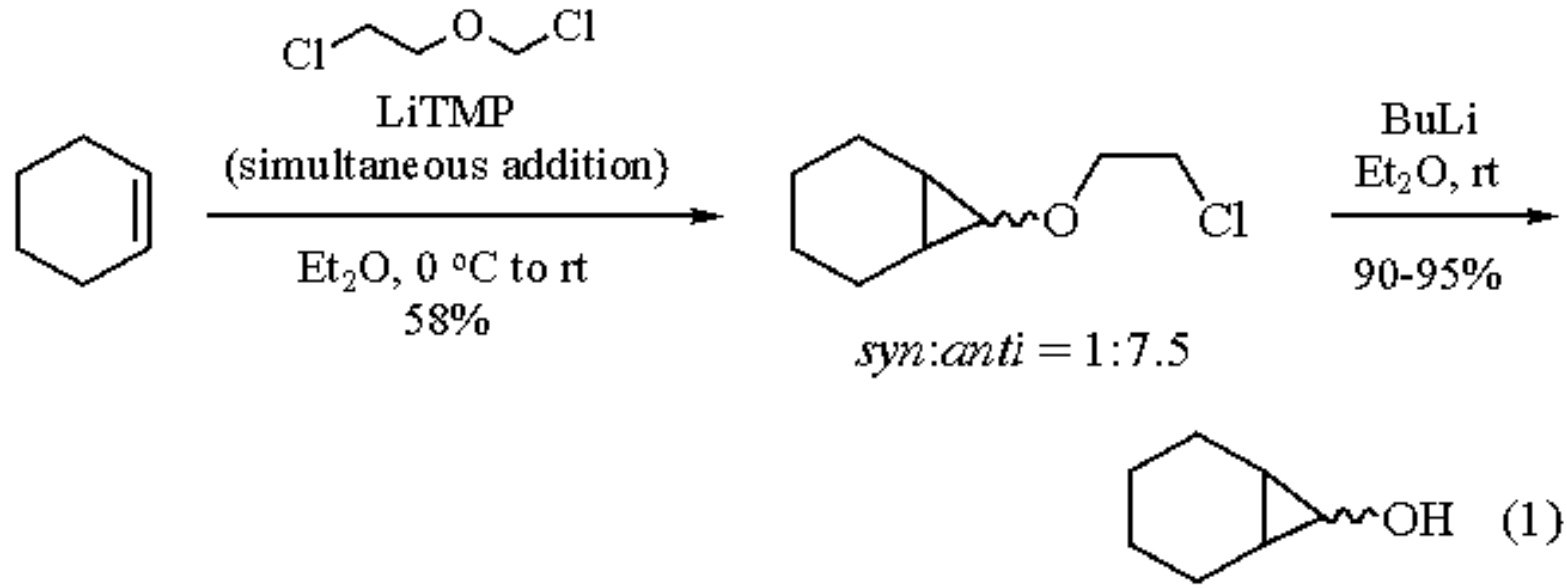

This reaction sequence has been applied by Danheiser and co-workers in the synthesis of cyclopentenols via an oxyanion-accelerated vinylcyclopropane rearrangement (eq 2).[2] In these cases the alkene is used as the limiting reagent in the cyclopropanation reaction. Upon treatment with *n*-BuLi the intermediate 2-vinylcyclopropanol alkoxides undergo an accelerated [1,3]-sigmatropic shift to afford the corresponding 3-cyclopentenols in a one-pot synthesis from the (2-chloroethyl) cyclopropyl ethers. The overall transformation is highly stereoselective and can be viewed as a [4 + 1] annulation proceeding via suprafacial *exo* addition of hydroxycarbene to a diene.

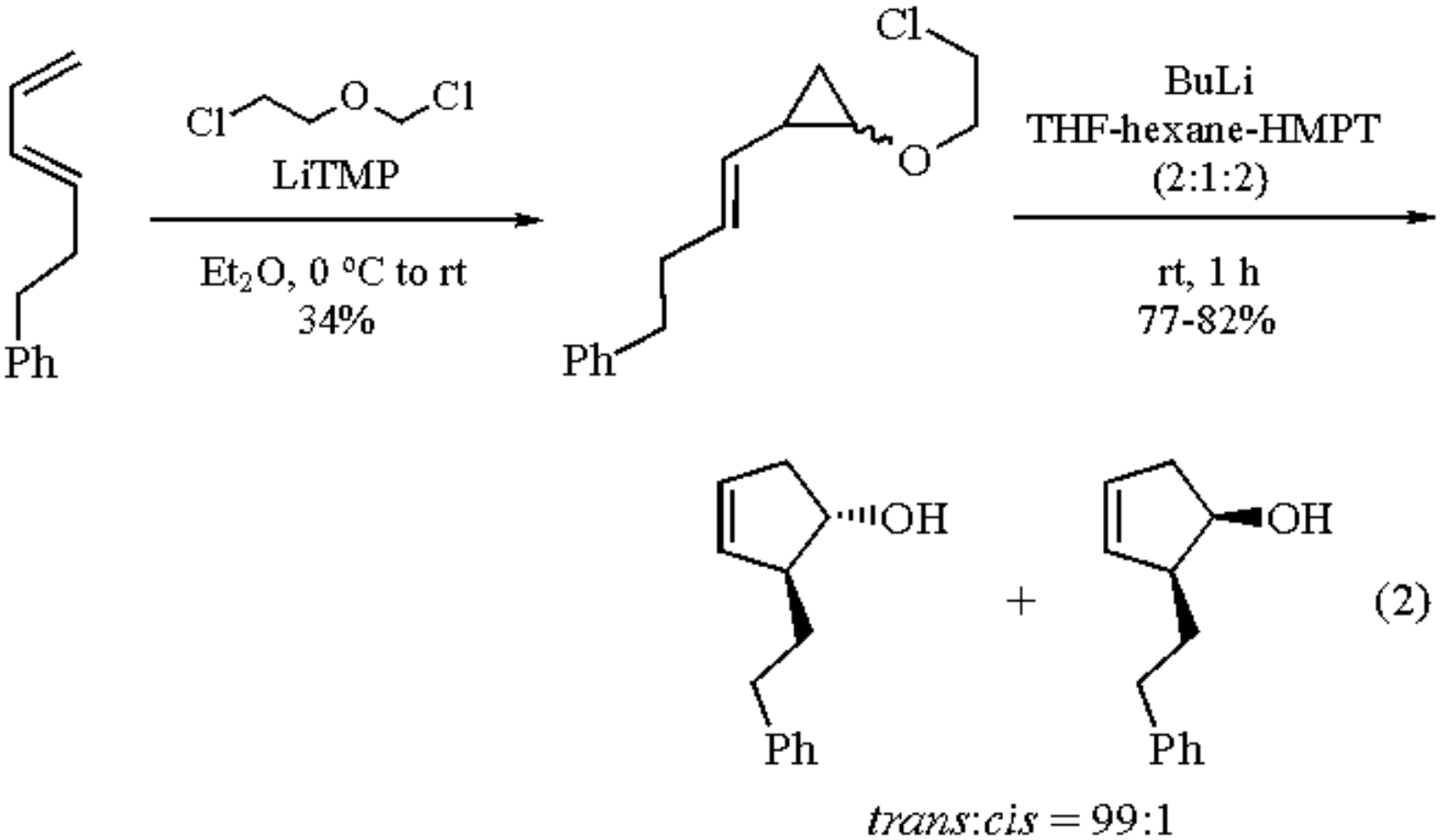

Hydroxymethylation of Grignard Reagents.

Hydroxymethylation of Grignard reagents via reaction with formaldehyde generally proceeds in only moderate yields and is complicated by difficulties in handling formaldehyde. Ogle and co-workers have developed a two-step, one-pot alternative procedure which involves reaction of Grignard reagents with 2-chloroethyl chloromethyl ether, followed by removal of the 2-chloroethyl group by treatment with ***Sodium-Potassium Alloy*** (eq 3).[3] Use of diethyl ether as solvent gives optimum yields. This two-step protocol can also be applied to alkynyllithium reagents to provide propargyl alcohol derivatives.

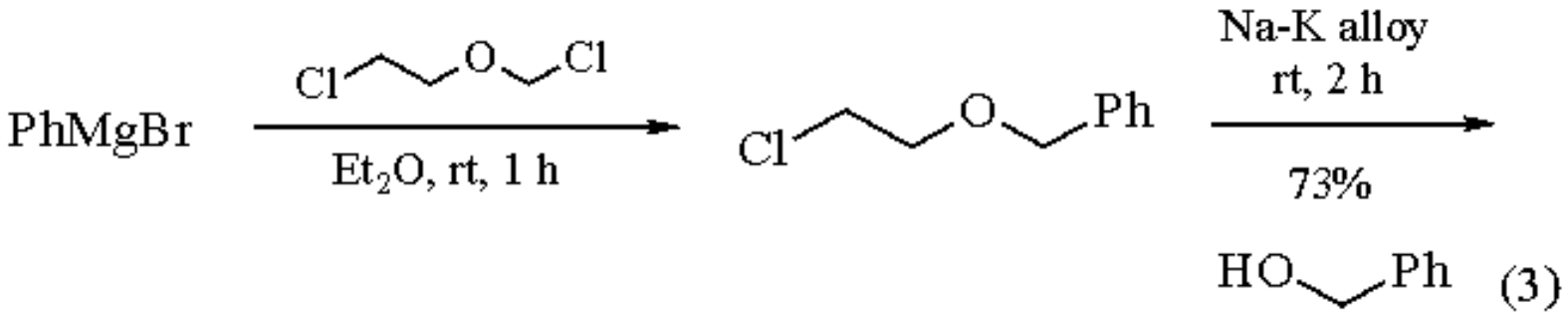

Protection of Indoles.

An example of protection of an indole with the 2-chloroethoxymethylene group was reported in the synthesis of (±)-austamide (indole derivative, $ClCH_2CH_2OCH_2Cl$, KH, DMF-THF, 50% yield).[4] Cleavage of this protecting group was effected by treatment with KCN in acetonitrile in the presence of ***18-Crown-6*** (84% yield).

---

1. (a) Barber, G. N.; Olofson, R. A. *TL* **1976**, 3783. (b) for a related example, see Dougherty, C. M.; Olofson, R. A. *OSC* **1988**, *6*, 571.
2. (a) Danheiser, R. L.; Martinez-Davila, C. E.; Morin, J. M. *JOC* **1980**, *45*, 1341. (b) Danheiser, R. L.; Martinez-Davila, C. E.; Auchus, R. J.; Kadonaga, J. T. *JACS* **1981**, *103*, 2443.
3. Ogle, C. A.; Wilson, T. E.; Stowe, J. A. *S* **1990**, 495.
4. Hutchison, A. J.; Kishi, Y. *JACS* **1979**, *101*, 6786.
5. Farren, J. W.; Fife, H. F.; Clark, F. E.; Garland, C. E. *JACS* **1925**, *47*, 2419.
6. For similar procedures, see ref 5 and Holy, A.; Rosenberg, I.; Dvorakova, H. *CCC* **1989**, *54*, 2190 (4.6 mol scale, 74% yield).
7. Olah, G. A.; Yu, S.; Liang, G.; Matseescu, G. D.; Bruce, M. R.; Donovan, D. J.; Arvanaghi, M. *JOC* **1981**, *46*, 571.
8. (a) Schöllkopf, U.; Paust, J.; Al-Azrak, A.; Schumacher, H. *CB* **1966**, *99*, 3391. (b) Schöllkopf, U.; Paust, J.; Patsch, M. R. *OSC* **1973**, *5*, 859.

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C-(1-Chloroethyl) *N*-Cyclohexyl Nitrone[1]

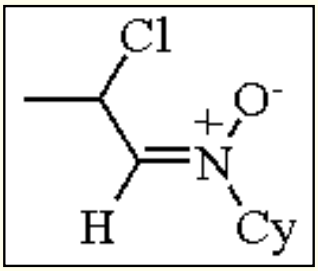

[37898-42-3] · $C_9H_{16}ClNO$ · *C*-(1-Chloroethyl) *N*-Cyclohexyl Nitrone · (MW 189.69)

(nitrone precursor of *N*-cyclohexyl-*N*-1-propenylnitrosonium cation, i.e. *N*-alkyl-*N*-vinylnitrosonium cations[1])

Alternate Names: α-(1-chloroethyl) *N*-cyclohexyl nitrone; α-chloro-*N*-cyclohexylpropanaldonitrone; *N*-(2-chloropropylidene-*N*-cyclohexylamine *N*-oxide.

Physical Data: mp 73-75 °C.

Solubility: sol ether, ethanol, dichloromethane, 1,2-dichloroethane, liquid sulfur dioxide.

Form Supplied in: not commercially available.

Preparative Methods: by condensation of freshly distilled 2-chloropropanal and *N*-cyclohexylhydroxylamine in anhydrous ether and dichloromethane in the presence of magnesium sulfate at 0 °C.[2a] Recrystallization is from a mixture of ether and pentane. *N*-Cyclohexylhydroxylamine hydrochloride is commercially available and the free base is easily liberated. The simpler aldonitrones, *C*-chloromethyl *N*-cyclohexyl and *N*-*t*-butyl nitrones, are made by chlorination of the appropriate *C*-methyl *N*-alkyl nitrone with *N*-chlorosuccinimide in carbon tetrachloride at 0 °C.[2a]

Handling, Storage, and Precautions: may be stored in a freezer under argon, but it slowly becomes yellow on standing at room temperature. For best results it should be used shortly after preparation.

[4 + 2] Cycloadditions.

Eschenmoser and co-workers introduced *N*-vinyl-*N*-alkyl-nitrosonium cations as heterodienes in reverse electron demand, Diels-Alder-type [4 + 2] cycloadditions in 1972.[2] *C*-α-Chloroalkyl *N*-cyclohexyl aldonitrones are the precursors which are treated with ***Silver(I) Tetrafluoroborate*** in 1,2-dichloroethane in the presence of a suitable alkene to produce 5,6-dihydro-4*H*-1,2-oxazin-2-ium tetrafluoroborate cycloadducts (eq 1).[2a] This salt may be used directly, but the usual workup is with aqueous ***Potassium Cyanide*** to give 3-cyanotetrahydro-2*H*-1,2-oxazines. Exchange to the

more stable tetraphenylborates is facile.[2a] The cycloaddition is regioselective with the oxygen of the *N*-vinylnitrosonium cation becoming attached to the carbon of the alkene which can best stabilize a positive charge (i.e. Markovnikov's r ule).

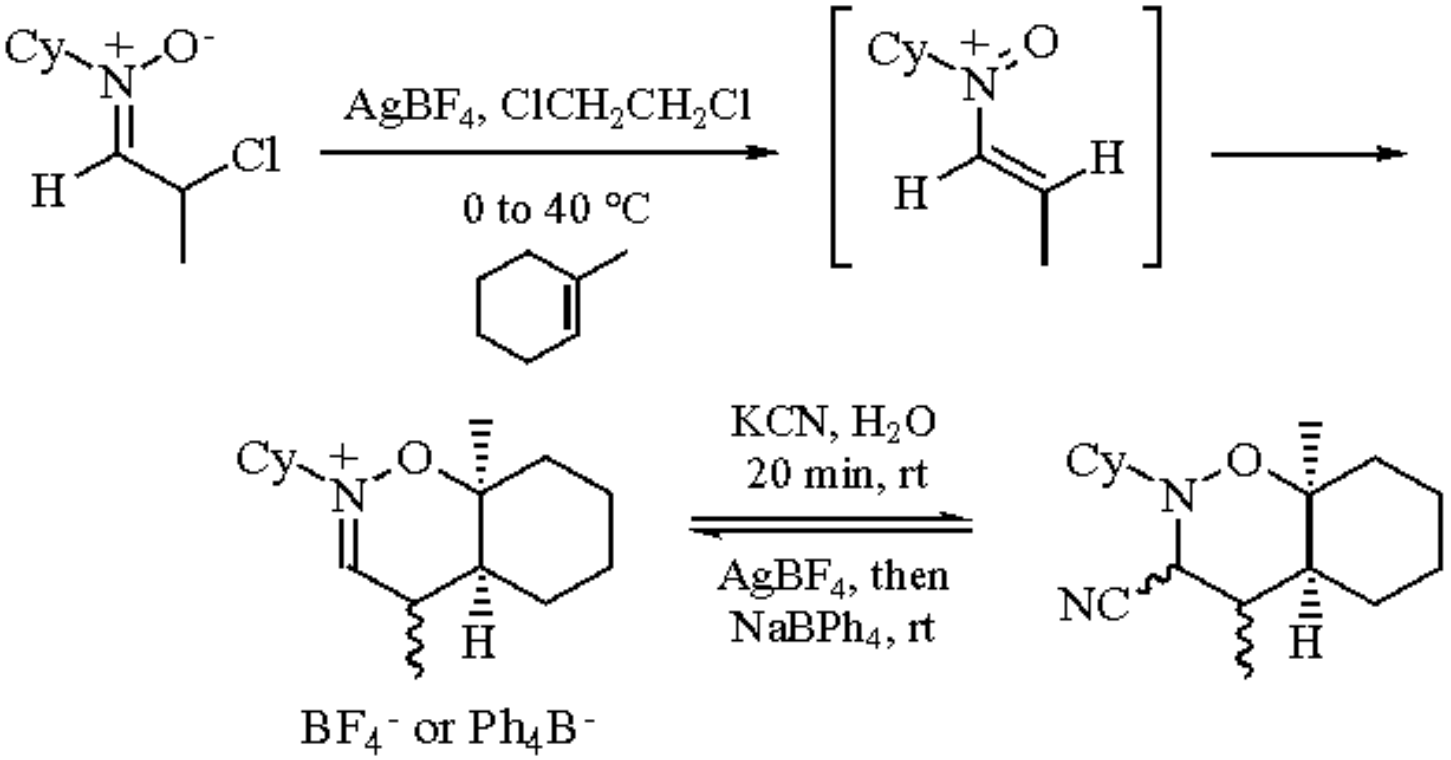

(1)

These cycloadducts, which may be derived from cyclic and acyclic di-, tri-, and tetrasubstituted alkenes, are useful synthetic intermediates. The preparation of γ-lactones is illustrative (eq 2[2b] and eq 3[3a]). The mechanism probably involves base-catalyzed rearrangement of the 3-cyano adduct to an iminolactone by elimination-addition with expulsion of hydrogen cyanide. Acid-catalyzed hydrolysis leads to the products. Propellane lactones have been prepared by this method.[4]

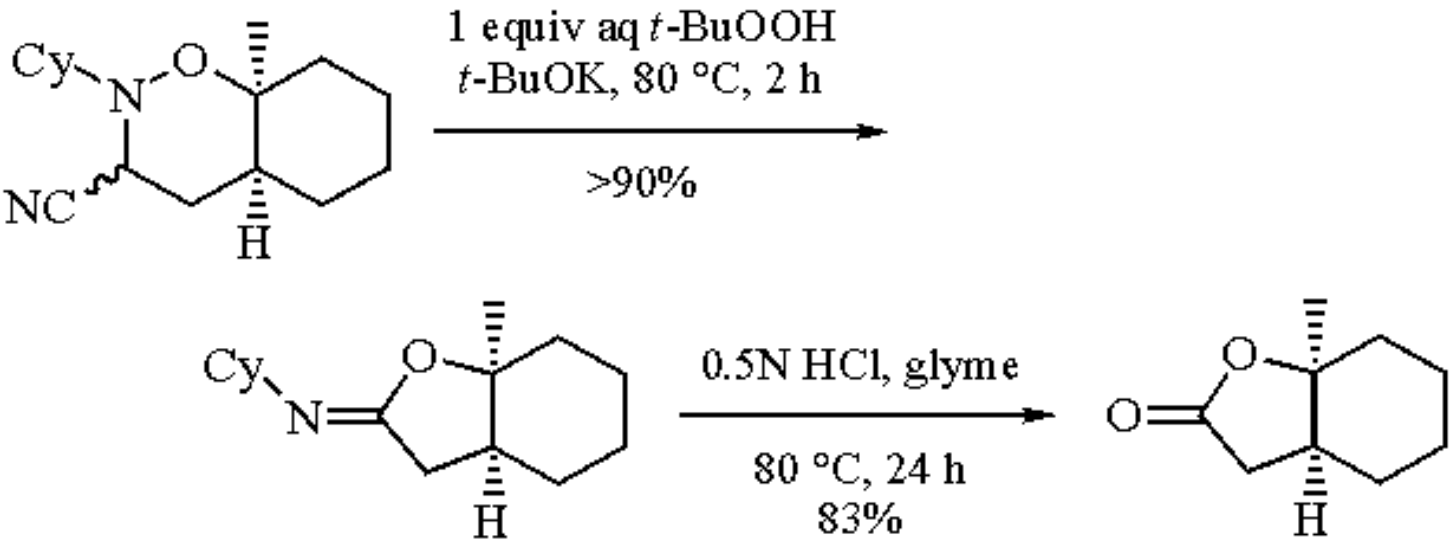

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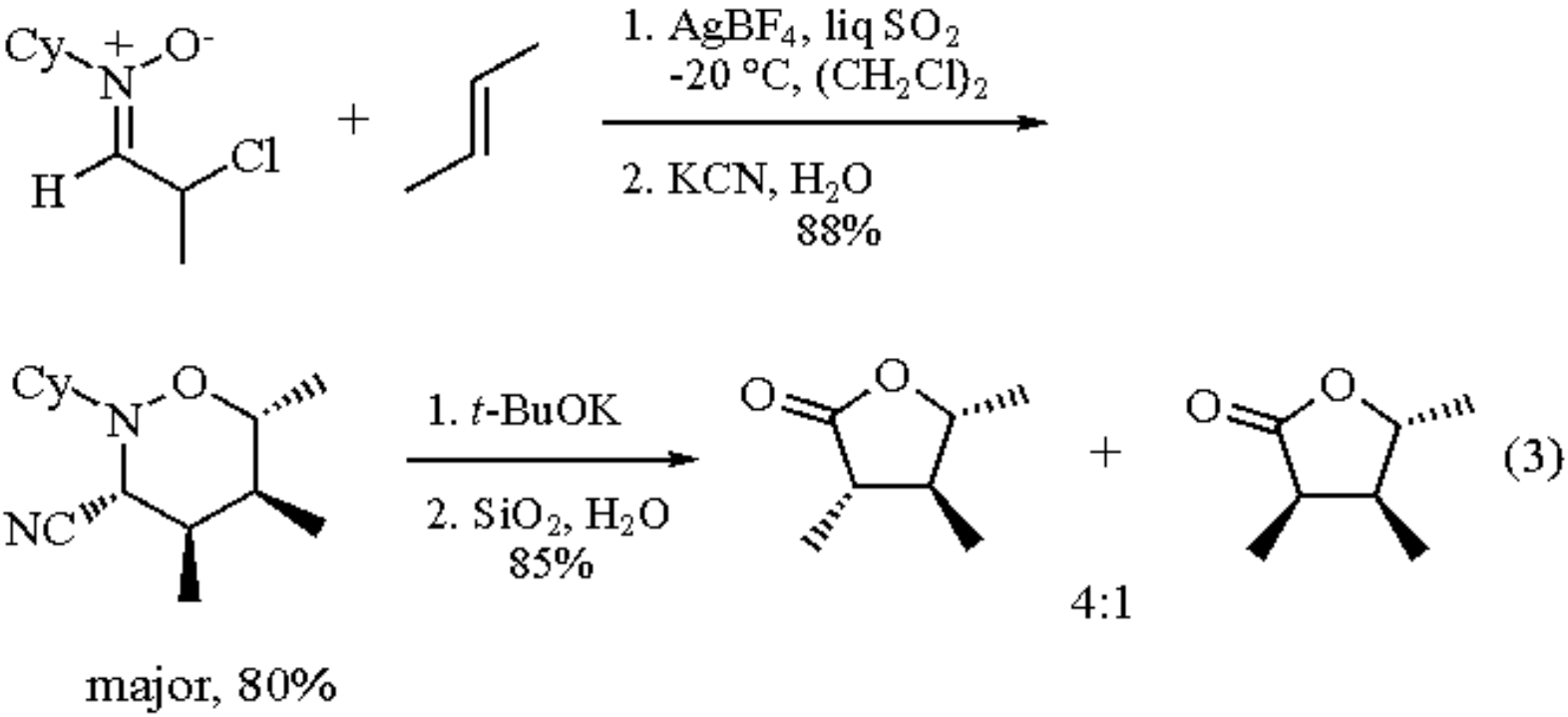

When *C*-α,β-dichloroethyl nitrones are used as starting materials, the identical sequence of reactions leads to α-methylene-γ-lactones via a 3-cyano-4-chloromethyl adduct (eq 4).[3a] Other contributions from the ETH laboratories have demonstrated that *C*-α,β-epoxy nitrones can be used for the same purpose. The reagent used to generate the vinylnitrosonium ion is a trialkylsilyl trifluoromethansulfonate, and the initially formed cyano-protected cycloadduct must be desilylated and converted to a mesylate before further reaction with base (eq 5).[5] The nitrone precursors for the reactions outlined in eqs 4 and 5 are easily prepared by condensation of 2,3-dichloropropanal and epoxypropanal, respectively, with *N*-cyclohexylhydroxylamine.

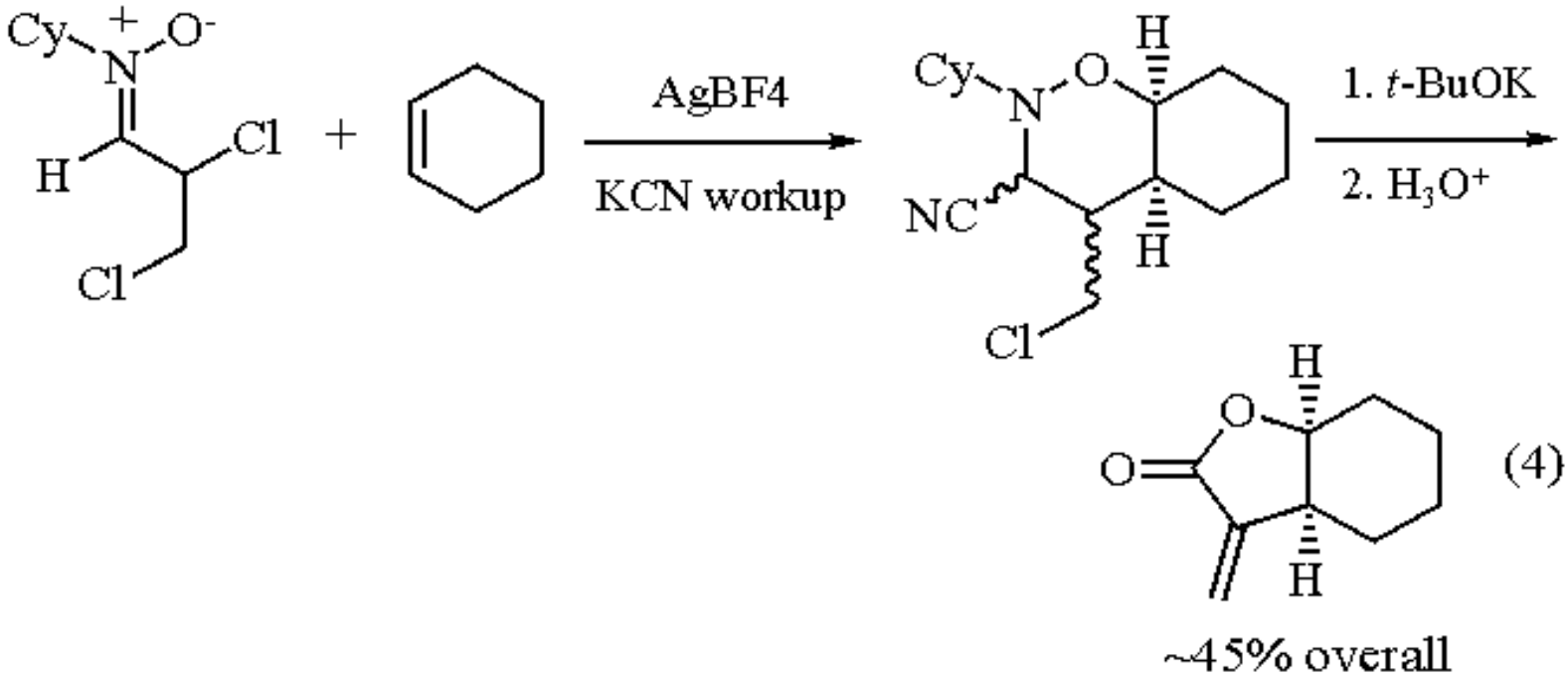

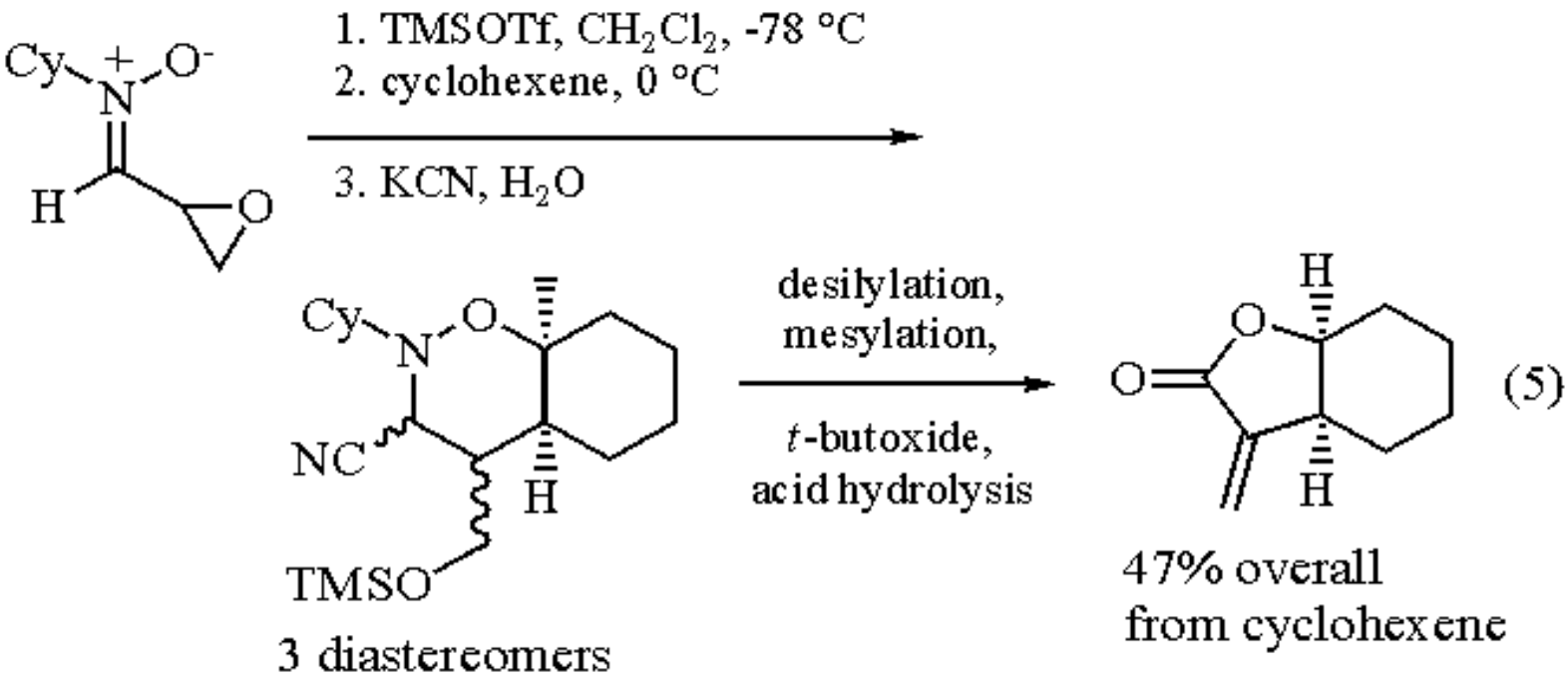

Intramolecular examples of the epoxy nitrone-alkene reaction are known (eq 6), but further conversion into useful products was not efficient.[6] Enol acetates also undergo the cycloaddition.[7]

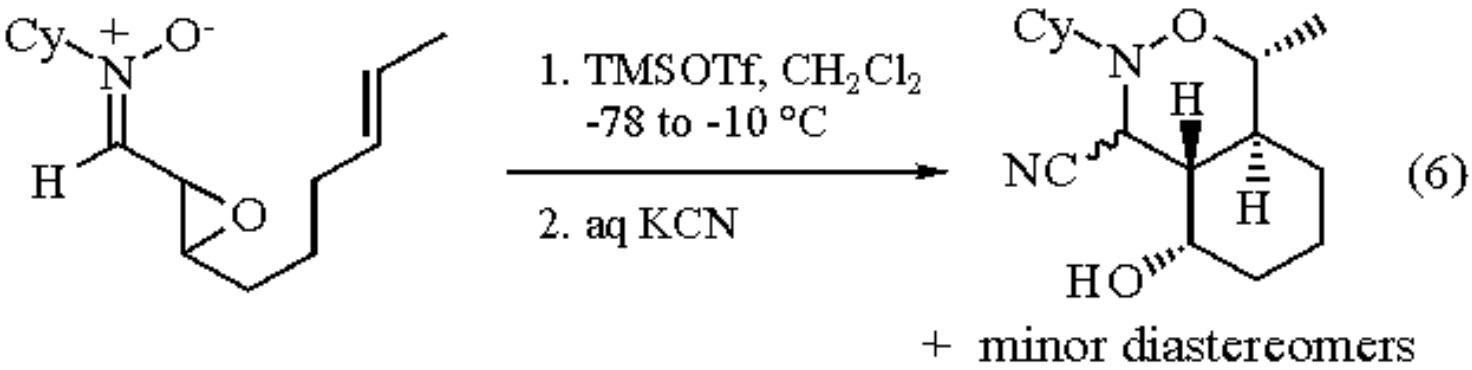

When the dihydro-4*H*-1,2-oxazin-2-ium tetraphenylborate is allowed to react with ***Potassium Carbonate*** in dichloromethane (or with ***Diisopropylethylamine***, Hunig's base), proton abstraction occurs to give a 5,6-dihydro-2*H*-1,2-oxazine which upon heating undergoes electrocyclic ring opening. The imine thus formed can be hydrolyzed, and an important synthesis of unsaturated dicarbonyl compounds is achieved (eq 7). The key feature of this sequence is that a cyclic alkene starting material is oxidatively cleaved (as in ozonolysis) to a product with carbonyl group and an extended alkylidene chain at the original alkenic carbon atoms (carboxolytic cleavage).[2a] A creative application of this method is the synthesis of a 4-prenylindole from 8-nitro-1,4-dihydronaphthalene.[8]

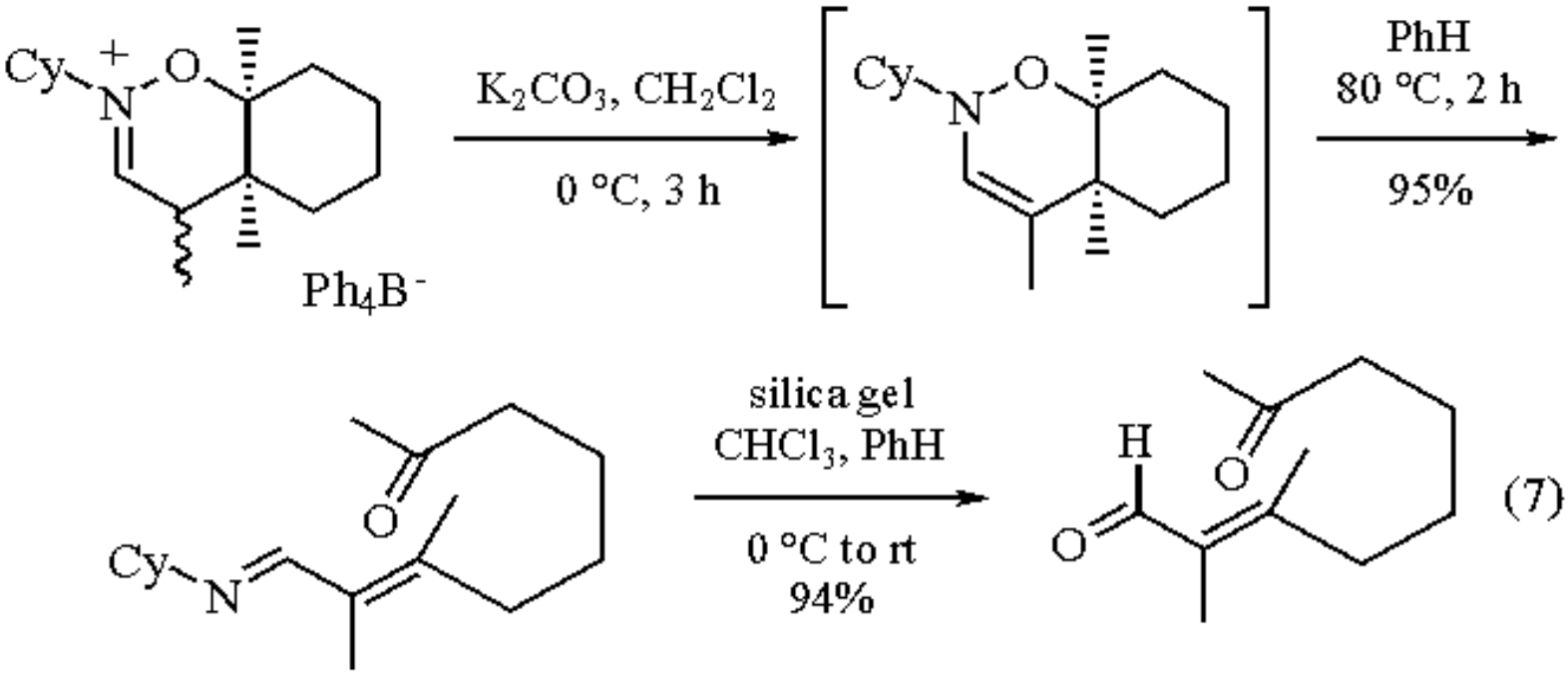

Enol ethers have proved somewhat problematic and unwanted side products often appear.[9] A bicyclic and several benzobicyclic enol ethers gave low yields of propellane-type nitrile adducts. The major products were keto alcohols thought to be formed from fragmentation of oxonium compounds. Nevertheless, the cycloadduct nitriles underwent further conversions in good yield to form macrocyclic lactones with a formylmethylene appendage.

There are reports of ketone carbonyl groups functioning as heteroenes in [4 + 2] cycloadditions with *N*-vinylnitrosonium salts.[10]

The *N*-vinylnitrosonium salts also undergo facile [4 + 2] cycloadditions with alkynes.[3c] The first-formed adducts are *N*-cyclohexyl-4*H*-1,2-oxazin-2-ium tetrafluoroborates and subsequent hydrolysis affords α,β-unsaturated ketones, a viable alternate route route to these common products (eq 8).

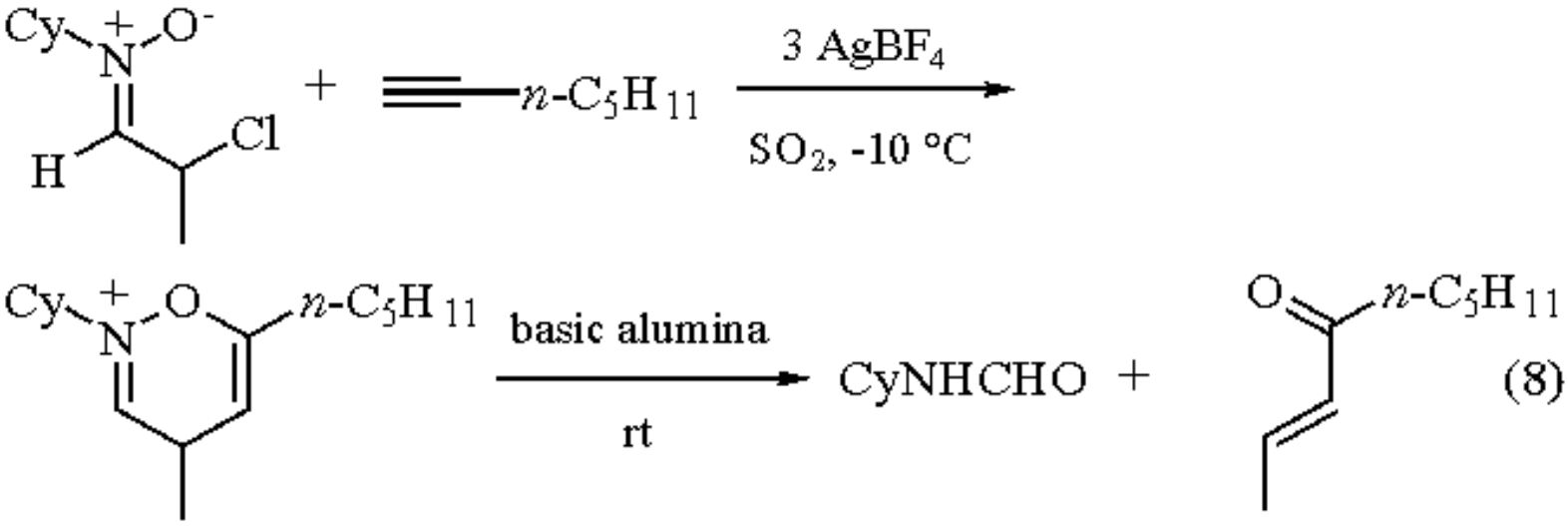

Electrophilic Substitution Reactions.

The *N*-vinylnitrosonium ions are strongly electrophilic and their interaction with alkenes often leads to substitution in competition with cycloaddition. For example, when the reaction is conducted with trisubstituted alkenes in a highly polar solvent, such as liquid sulfur dioxide, unsaturated nitrones are formed in addition to the dihydro-4*H*-1,2-oxazinium salts (eq 9).[3b] The stereochemistry of the alkene is retained. Mild acid hydrolysis of the nitrones affords β,γ-unsaturated aldehydes. Similarly, electron-rich aromatic compounds are alkylated and hydrolytic workup affords α-arylaldehydes (eq 10).[3b] The *N*-vinyl-*N*-cyclohexylnitrosonium ion is an α-acyl carbocation equivalent in these reactions. Analogous substitutions were successful with indole and *N*-methylindole, and they represent abbreviated pathways to *C*-(3-indolyl-1-ethyl) and *C*-(3-indolylmethyl) nitrones.[11]

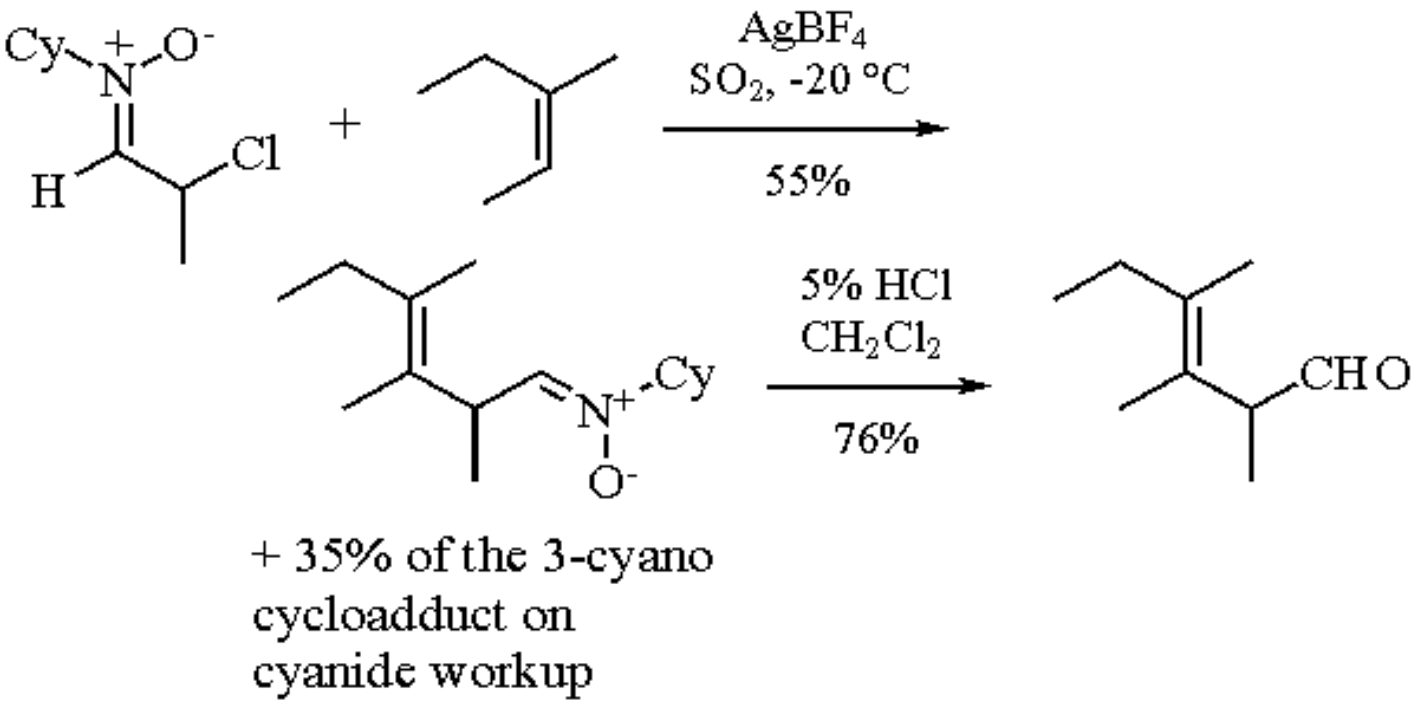

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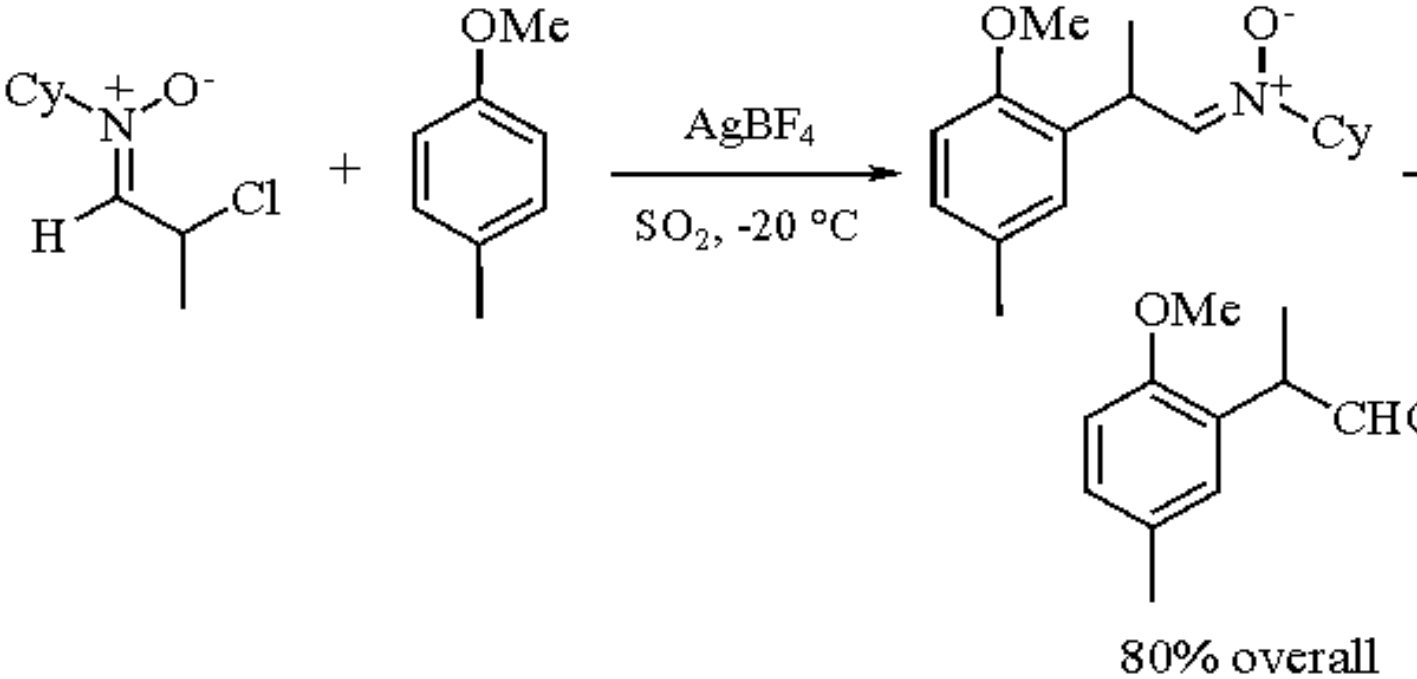

(10)

1. Breuer, E. In *Nitrones, Nitronates and Nitroxides*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1989; p 189.
2. (a) Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; Eschenmoser, A. *HCA* **1972**, *55*, 2187. (b) Das Gupta, T. K.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *HCA* **1972**, *55*, 2198. (c) Gygax, P.; Das Gupta, T. K.; Eschenmoser, A. *HCA* **1972**, *55*, 2205.
3. (a) Petrzilka, M.; Felix, D.; Eschenmoser, A. *HCA* **1973**, *56*, 2950. (b) Shatzmiller, S.; Gygax, P.; Hall, D.; Eschenmoser, A. *HCA* **1973**, *56*, 2961. (c) Shatzmiller, S.; Eschenmoser, A. *HCA* **1973**, *56*, 2975.
4. Ruttimann, A.; Ginsburg, D. *HCA* **1975**, *58*, 2237.
5. (a) Riediker, M.; Graf, W. *HCA* **1979**, *62*, 205. (b) Riediker, M.; Graf, W. *HCA* **1979**, *62*, 1586. (c) Riediker, M.; Graf, W. *HCA* **1979**, *62*, 2053. (d) Riediker, M.; Graf, W. *AG(E)* **1981**, *20*, 20.
6. Shatzmiller, S. *LA* **1982**, 1933.
7. Denmark, S. E.; Cramer, C. J.; Dappen, M. S. *JOC* **1987**, *52*, 877.
8. Hattingh, W. C.; Holzapfel, C. W.; van Dyk, M. S. *SC* **1987**, *17*, 1477.
9. Shalom, E.; Zenou, J.-L.; Shatzmiller, S. *JOC* **1977**, *42*, 4213. See also Levinger, S.; Shatzmiller, S. *T* **1978**, *34*, 563.
10. (a) Neidlein, R.; Shatzmiller, S.; Walter, E. *LA* **1980**, 686. (b) Hepp, L. R.; Bordner, J.; Bryson, T. A. *TL* **1985**, *26*, 595.
11. Holzapfel, C. W.; van Dyk, M. S. *SC* **1987**, *17*, 1349.

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2-Chloroethyl Dichloromethyl Ether

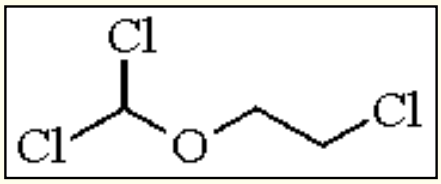

[13930-34-7] · $C_3H_5Cl_3O$ · 2-Chloroethyl Dichloromethyl Ether · (MW 163.44)

(reagent for forming cyclopropanols from alkenes[1])

Alternate Name: dichloromethyl 2-chloroethyl ether.

Physical Data: bp 106-110.5 °C/10 mmHg.

Solubility: sol most organic solvents.

Preparative Method: not commercially available. It can be prepared by the action of ***Phosphorus(V) Chloride*** on β-chloroethyl formate (eqs 1 and 2).[2,3]

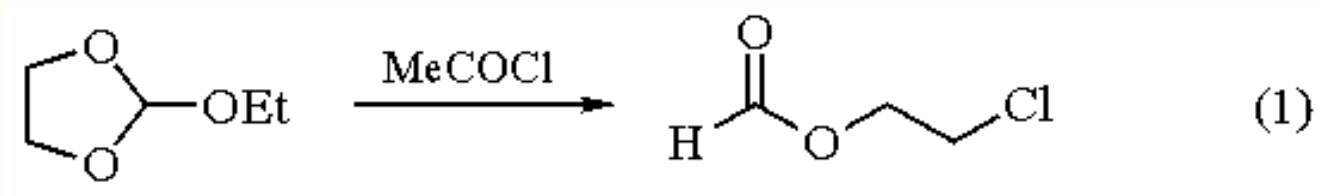

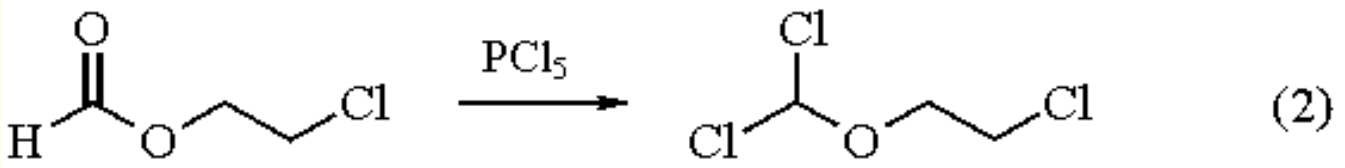

This is the reagent of choice for the preparation of cyclopropanols from alkenes. The method is very versatile and general in scope. It involves carbene insertion into an alkene to form the β-chloroethyl cyclopropyl ether (eq 3) which is then converted to the cyclopropanol (eq 4).[1]

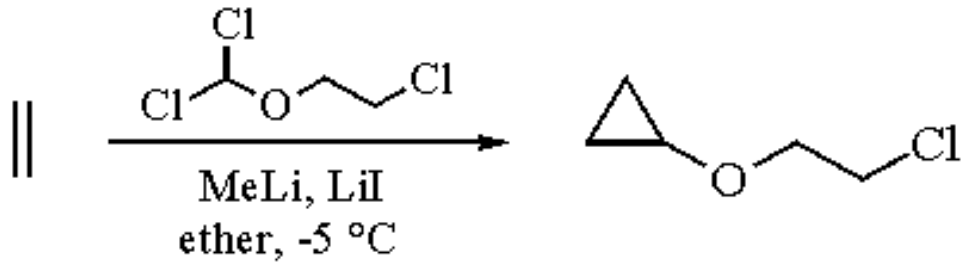

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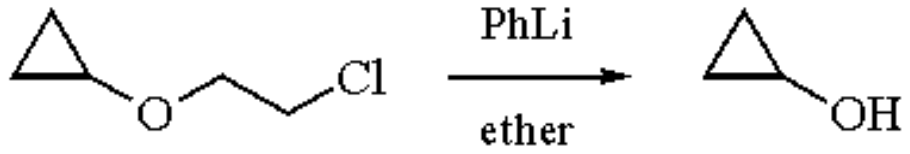

(4)

The alkenes employed ranged from monosubstituted to tetrasubstituted to give the cyclopropyl ethers in 23-86% yield (eqs 5-9).[1]

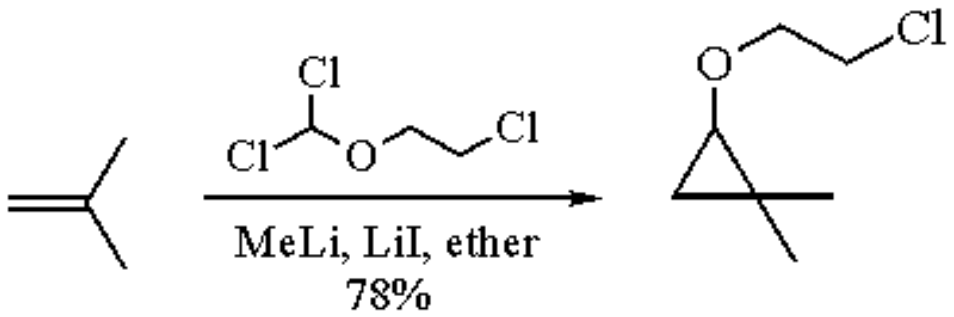

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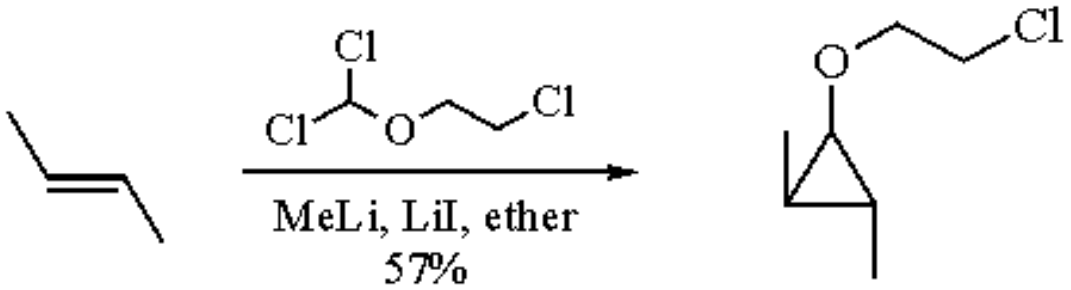

(6)

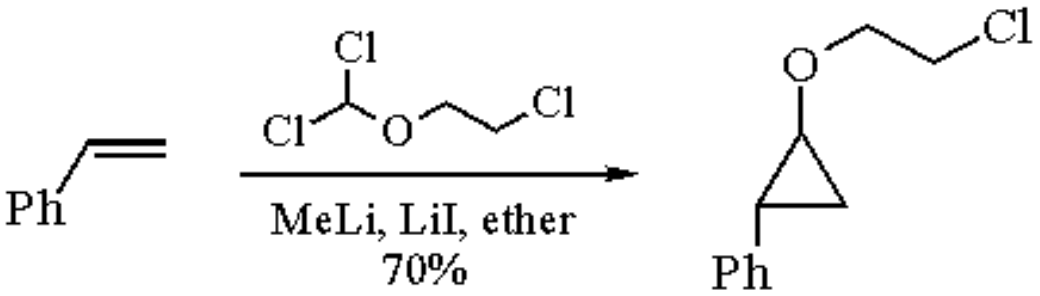

(7)

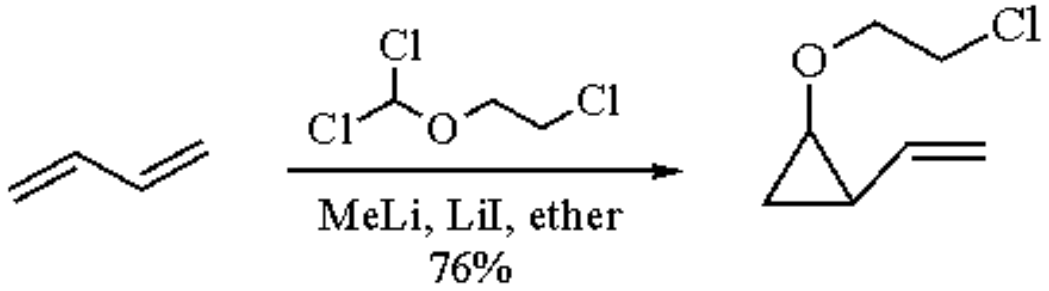

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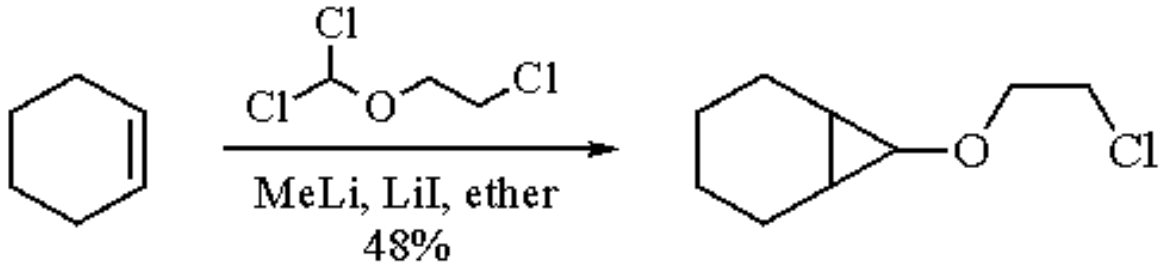

(9)

A more recent example yields an interesting spiro compound (eq 10).[4]

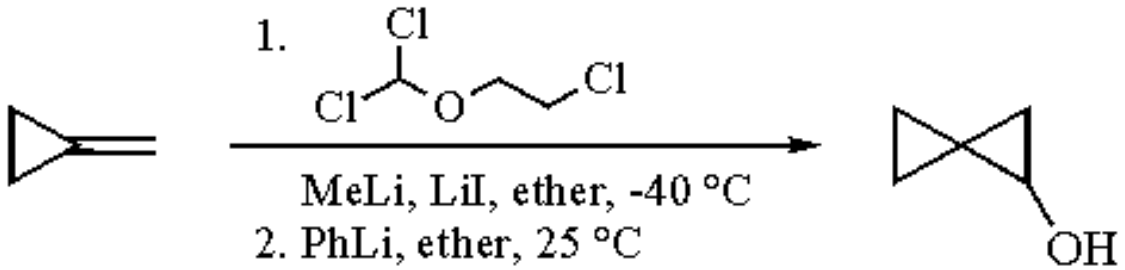

(10)

Cyclopropyl ethers have been prepared by a similar carbene insertion using 2-chloroethyl dichloromethyl ether as shown in eq 11.[5]

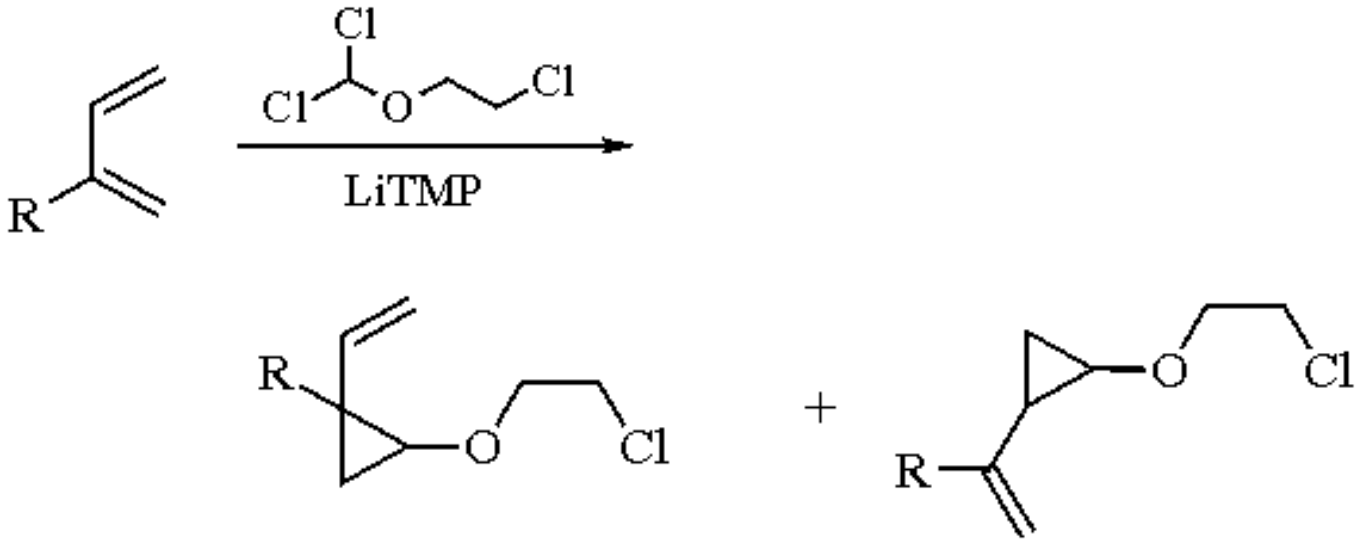

(11)

R = Ph, Me, *t*-Bu

1. Schöllkopf, U.; Paust, J.; Al-Azrak, A.; Schumacher, H. *CB* **1966**, *99*, 3391.
2. Baganz, H.; Domaschke, L. *CB* **1958**, *91*, 653.
3. Gross, H.; Rieche, A.; Höft, E. *CB* **1961**, *94*, 544.
4. Applequist, D. E.; Nickel, G. W. *JOC* **1979**, *44*, 321.
5. Danheiser, R. L.; Martinez-Davila, C.; Morin, Jr., J. M. *JOC* **1980**, *45*, 1340.

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1-Chloroethyltrimethylsilane

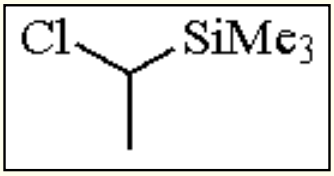

[7787-87-3] · $C_5H_{13}ClSi$ · 1-Chloroethyltrimethylsilane · (MW 136.72)

(nucleophilic addition of α-lithio derivative to aldehydes and ketones affords epoxysilanes, leading to methyl ketones)

Physical Data: bp 115-116 °C; *d* 0.862 g cm^{-3}.

Analysis of Reagent Purity: ^1H NMR.

Preparative Method: α-lithio derivative prepared from 1-chloroethyltrimethylsilane in THF and *s*-butyllithium (1.5 M in *n*-hexane or cyclohexane) at -78 °C, followed by warming to -55 °C.[1]

Form Supplied in: liquid; commercially available.

Handling, Storage, and Precautions: use in a fume hood.

Treatment of aldehydes and ketones with the α-lithio derivative of 1-chloroethyltrimethylsilane, prepared in situ, gives α,β-epoxytrimethylsilanes in moderate to high yields (35-96%) (eqs 1 and 2.[1,2]

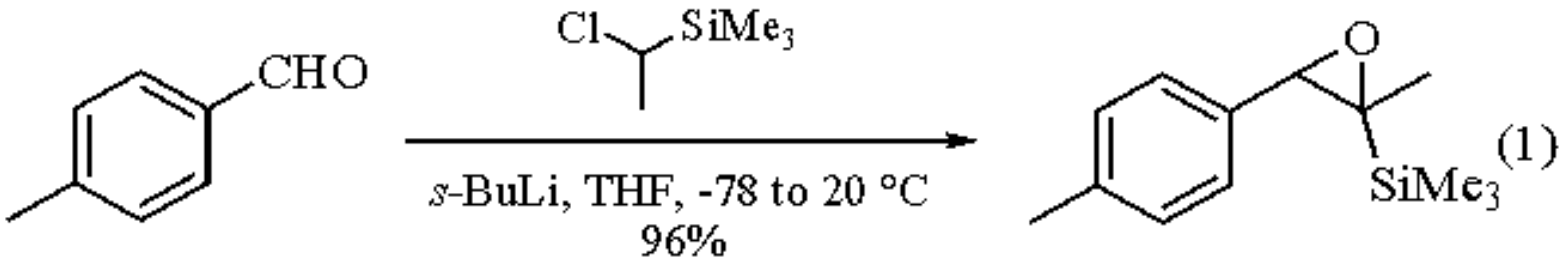

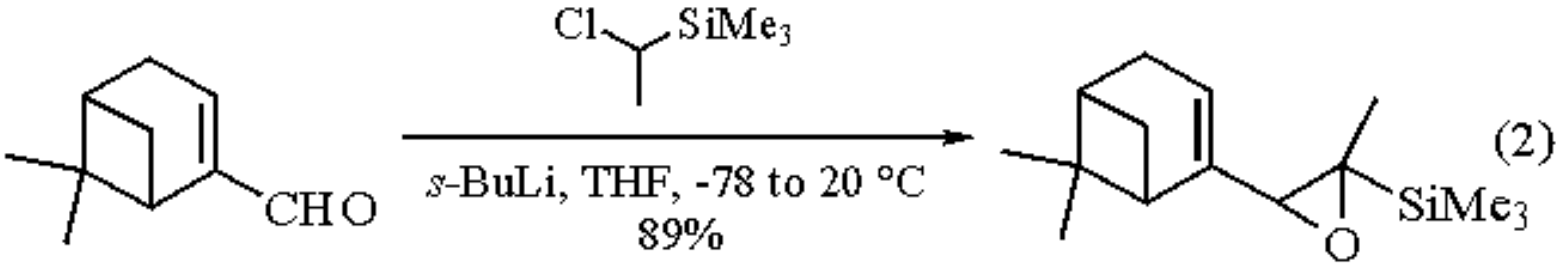

This bulky carbanion also reacts with sterically hindered ketones in moderate yields (eq 3).[1] It is speculated that this carbanion adds to hindered ketones via a single electron transfer mechanism.

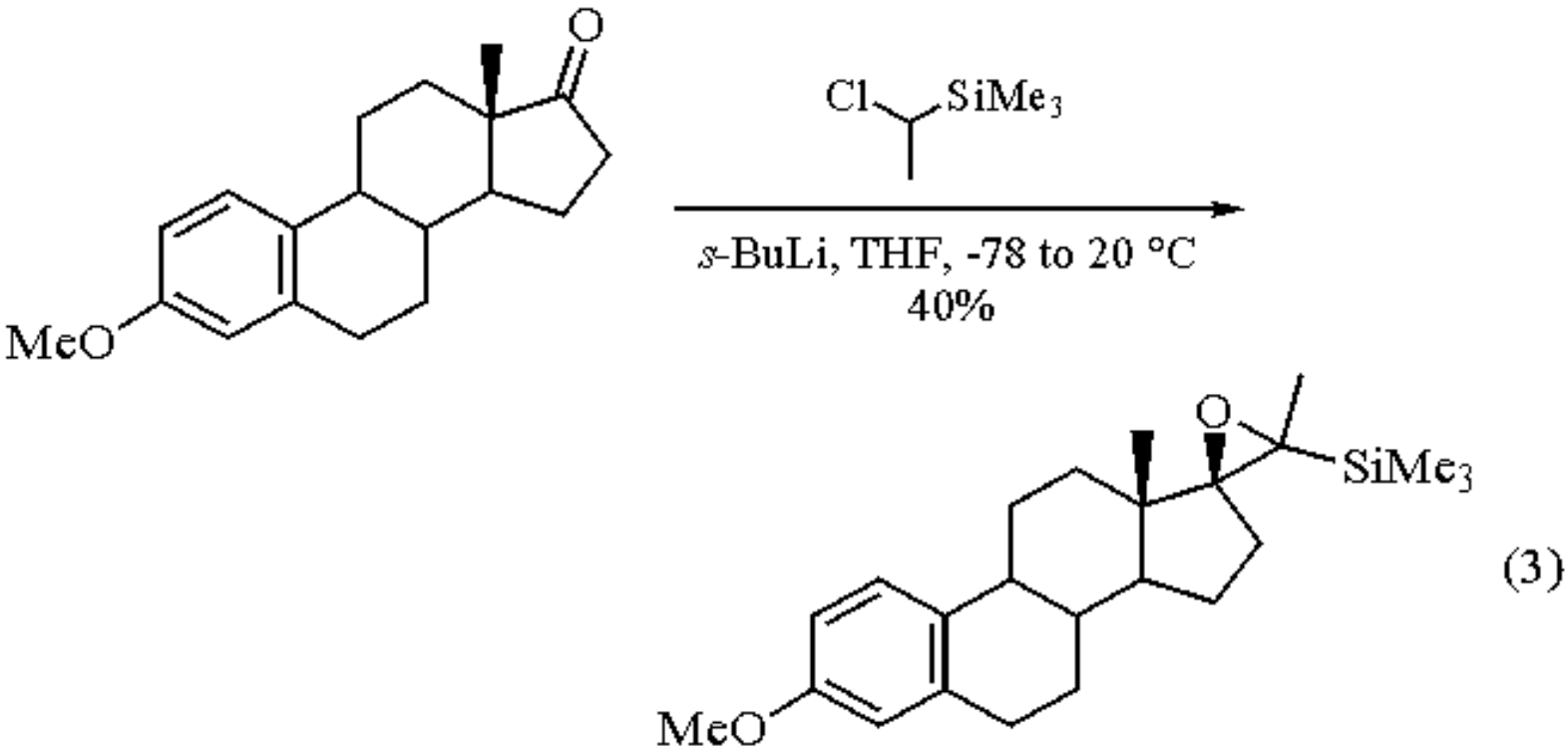

Acidic hydrolysis of the resulting α,β-epoxytrimethylsilanes yields homologated methyl ketones (eq 4).[3] The carbanion thus acts as a nucleophilic acylating species with reduction taking place at the original carbonyl group. This two-step sequence is more convenient than other methods for this type of homologation and proceeds under milder conditions.[4] The intermediate α,β-epoxytrimethylsilane can also be converted into an enol ether, enol acetate, alkenyl bromide, or enamide.[5]

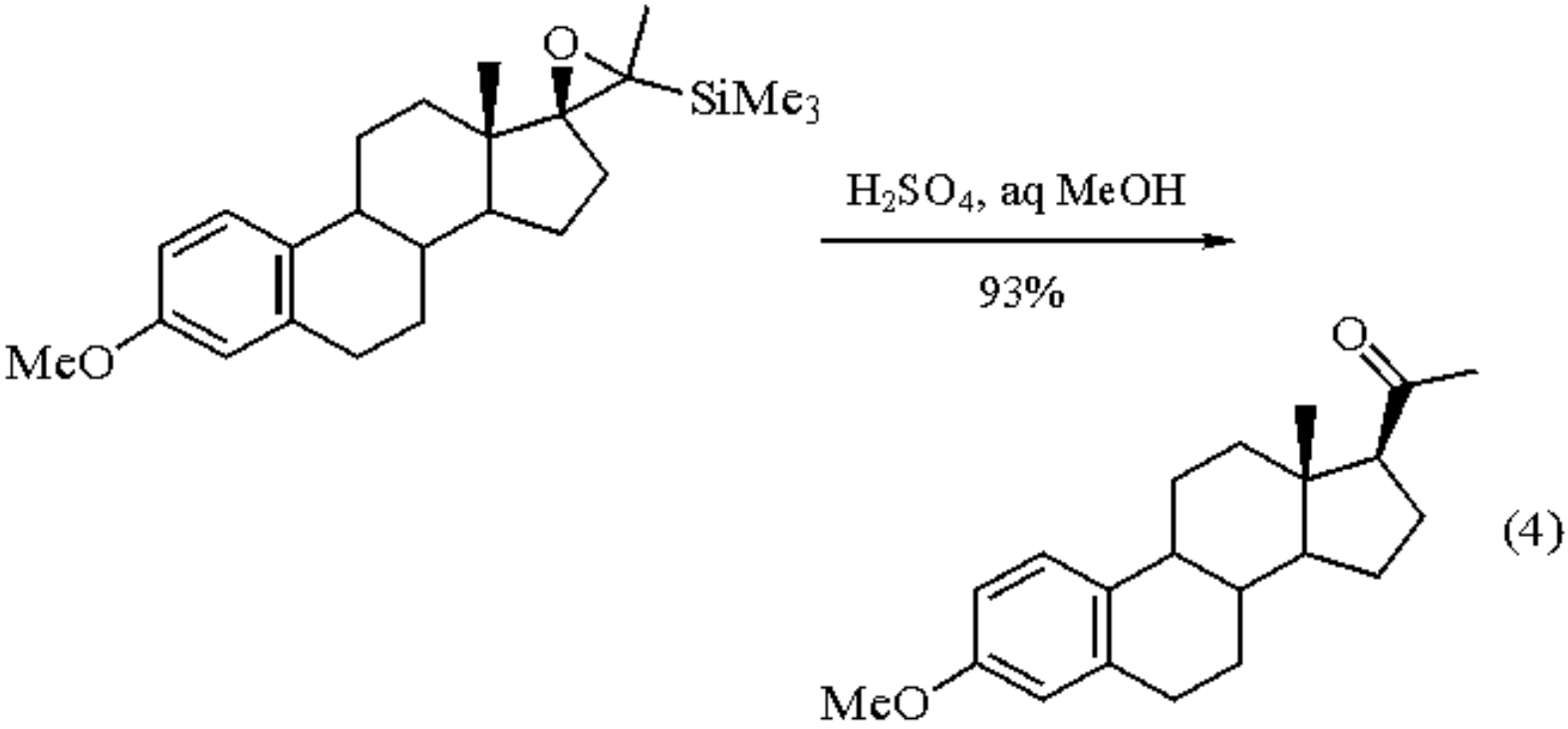

1. Cooke, F.; Roy, G.; Magnus, P. *OM* **1982**, *1*, 893.
2. (a) Cooke, F.; Magnus, P. *CC* **1977**, 513. (b) Magnus, P.; Roy, G. *CC* **1978**, 297.
3. Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *JACS* **1977**, *99*, 4536.
4. (a) Lever, Jr.; O. W. *T* **1976**, *32*, 1943. (b) Grobel, B.-T.; Seebach, D. *S* **1977**, 357. (c) Earnshaw, C; Wallis, C.J.; Warren, S. *JCS(P1)* **1979**, 3099.
5. Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *JACS* **1977**, *99*, 1993.

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Chloroform

$CHCl_3$

[67-66-3] · $CHCl_3$ · Chloroform · (MW 119.38)

(commonly a solvent in organic synthesis; also used in the preparation of dichlorocarbenes and α-trichloromethyl carbinols; and as a trichlorolithiocarbenoid precursor)

Physical Data: mp -63.5 °C; bp 61.7 °C; *d* 1.483 g cm^{-3}.

Solubility: very slightly sol water; sol ether, acetone, benzene, and ligroins.

Form Supplied in: colorless liquid with a sweet pleasant odor; available in high purity (99-99.9%).

Handling, Storage, and Precautions: oxidized by air and sunlight to phosgene. The addition of a small amount of alcohol or pentylenes prevents this. The solution should be handled with the usual precautions related to highly toxic substances; cancer suspect agent.

Formation of Dichlorocarbenes.

Chloroform reacts more rapidly with aqueous base than does dichloromethane or carbon tetrachloride (eq 1). The reaction proceeds by an S_N1cB mechanism[1] that involves the loss of a proton, followed by loss of Cl^-.[2] The dichlorocarbene is then hydrolyzed to formic acid or carbon monoxide.[3] Most reactions involving chloroform are based on its ability to form a dichlorocarbene in alkali media. The dichlorocarbenes are obtained by reacting $CHCl_3$ and OH^-, often under phase-transfer catalysis conditions,[4] and the dichlorocarbenes react with alkenes and nonalkene substrates.[5]

$$HCCl_3 \underset{}{\overset{OH^-}{\rightleftharpoons}} CCl_3^- \xrightarrow{-Cl^-} :CCl_2 \qquad (1)$$

Addition to Alkenes via Dihalocarbenes.

Dichlorocarbenes add to double bonds to give 1,1-dichlorocyclopropanes[6] that are versatile substrates for subsequent ring opening.[7] Dihalocyclopropanes are very useful compounds[8] that can be reduced to cyclopropanes, treated with ***Magnesium*** to give allenes, or converted to many other products. As an example, dichlorocarbene can be used as a

high yield two-step alternative to the Simmons-Smith reaction (eq 2).[9] It is also useful for the preparation of 2-chloronaphthalene derivatives (eq 3).[10]

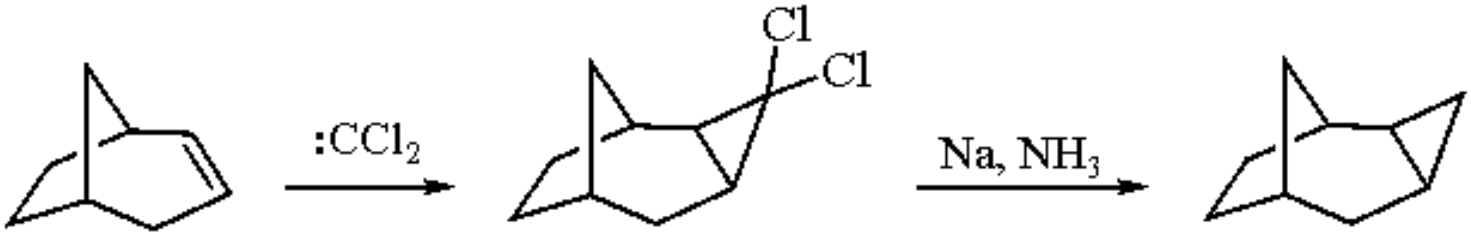

(2)

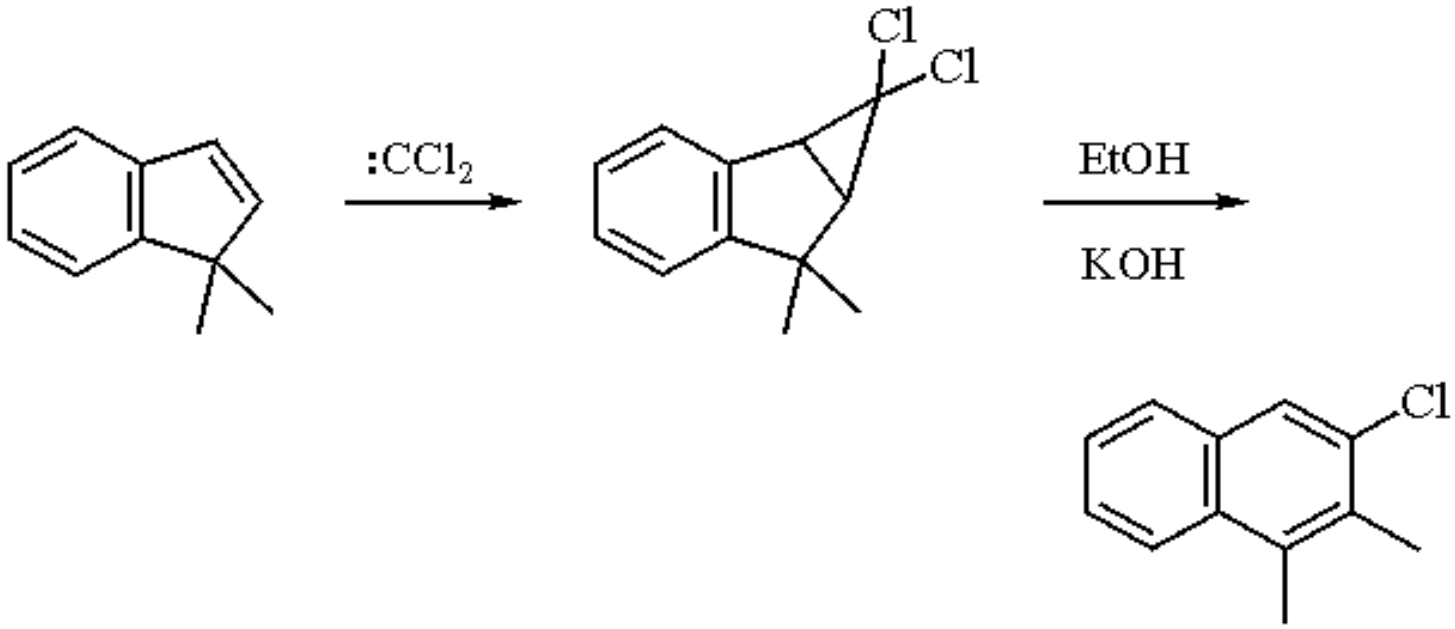

(3)

When more than one isolated double bond is present in a substrate, products of both mono and multiple cyclopropanation are isolated, unless a selective phase-transfer catalysis method is used. Dichlorocyclopropanation can be followed by rearrangement if the dichlorocarbene adduct is either strained or otherwise unstable (eq 4).[11] Another useful rearrangement involves the expansion of pyrroles and indoles to pyridines and quinolines derivatives, respectively (eq 5).[12]

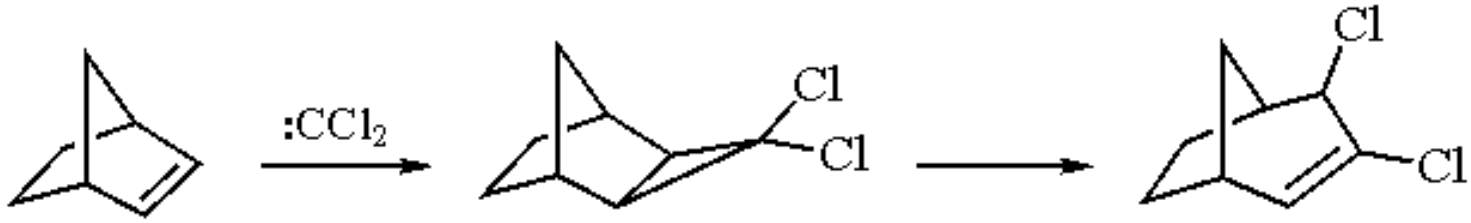

(4)

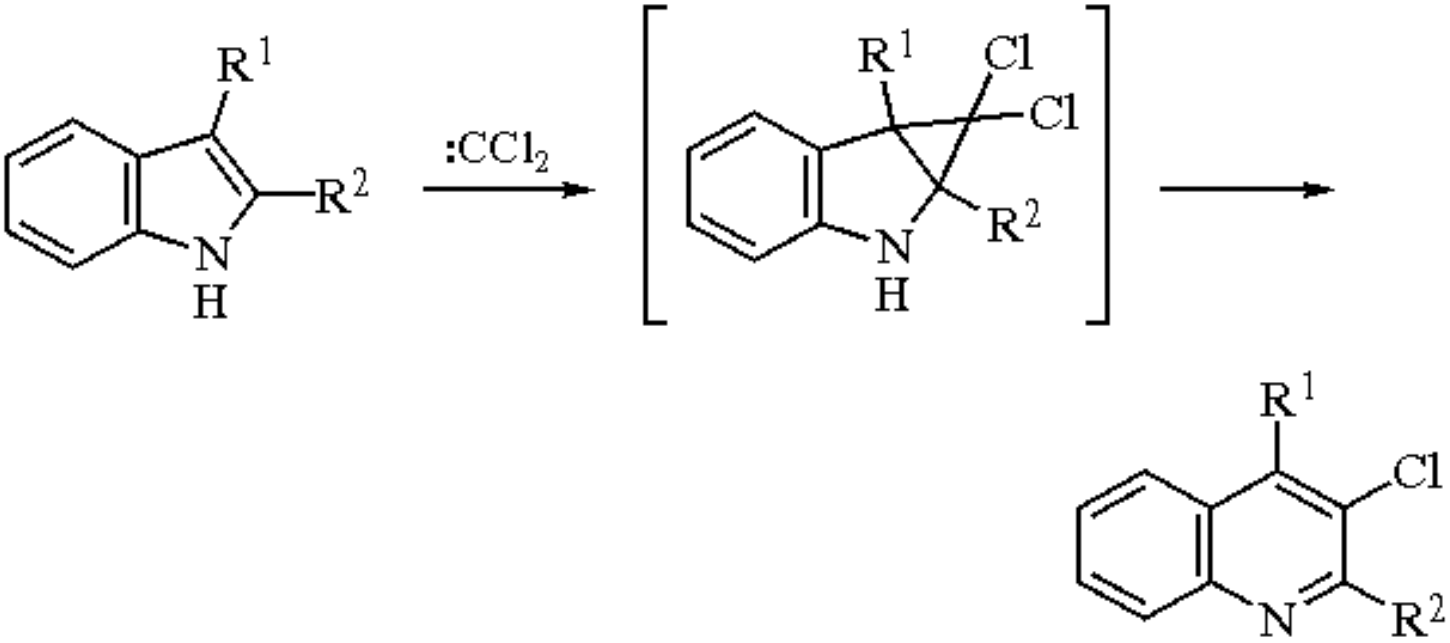

(5)

A similar rearrangement has been reported for the addition to furans, thiophenes, and polycyclic aromatics which, by loss of a proton, form expanded trienes with an exocyclic double bond (eq 6).[13] A second equivalent of dichlorocarbene can add to the exocyclic double bond, but in poor yield (eq 7).

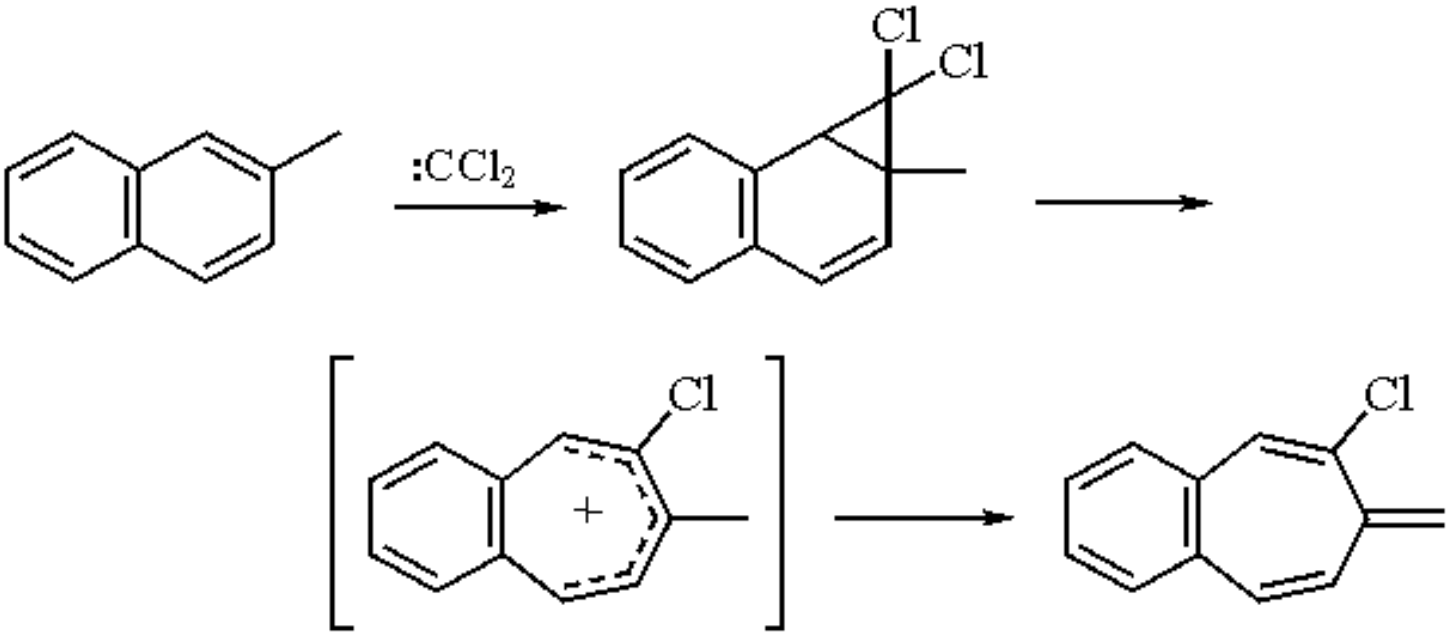

(6)

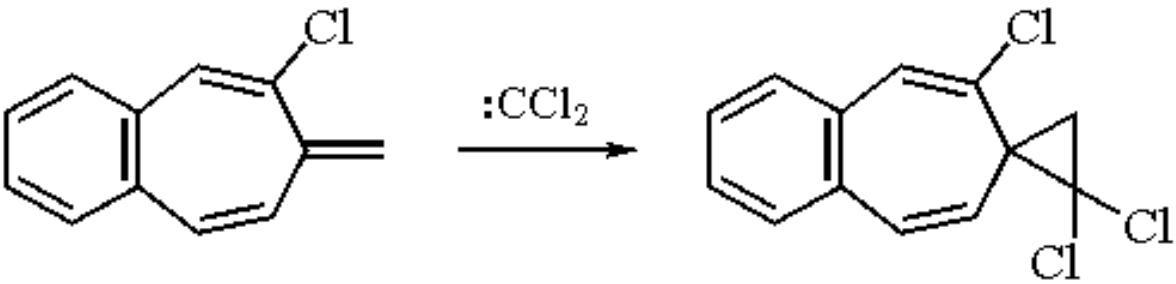

(7)

The formation of 1,1-dichlorocyclopropanes from allylic alcohols is of particular synthetic value because the initial

adducts can undergo rearrangement under acidic conditions to give good yields of cyclopentenones (eq 8).[14] If an electron-withdrawing group is present on the double bond, a Michael addition with trichloromethyl anion might occur (eq 9).[15]

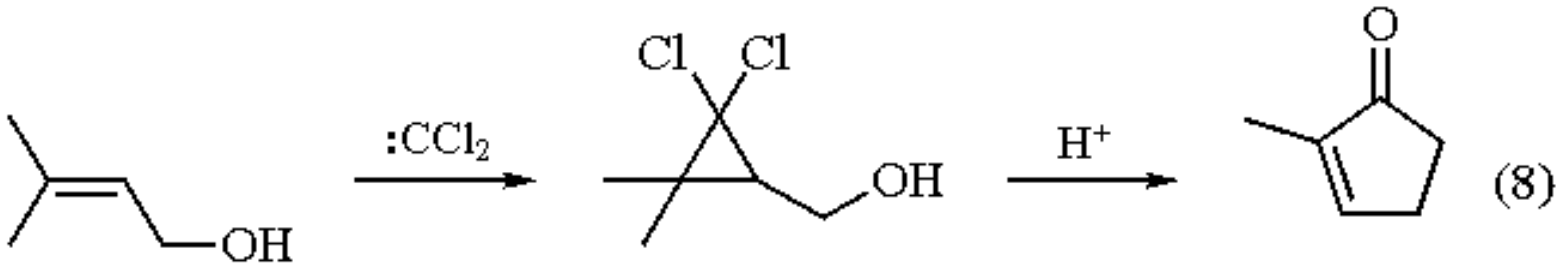

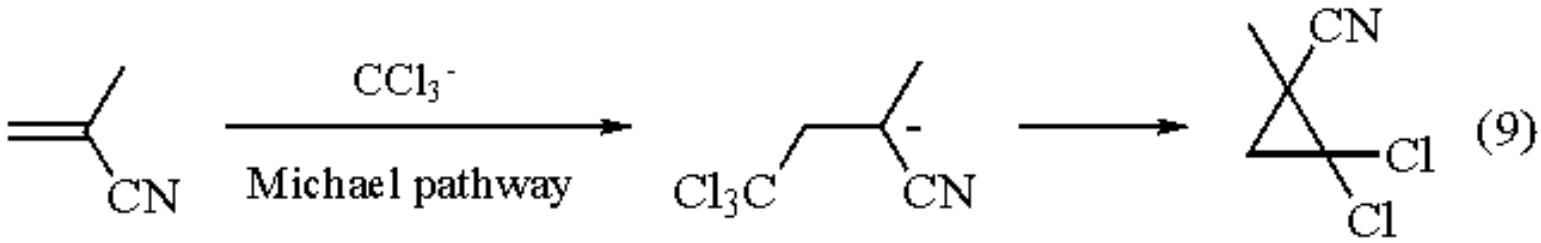

The most studied reaction of chloroform involving the formation of a dichlorocarbene is the Reimer-Tiemann reaction.[16] This reaction is commonly divided into normal and abnormal transformations, depending on the reaction products. A normal Reimer-Tiemann reaction is one in which a phenol (or electron-rich aromatic such as pyrrole) yields one or more aldehydes on treatment with chloroform and alkali (eq 10).[17]

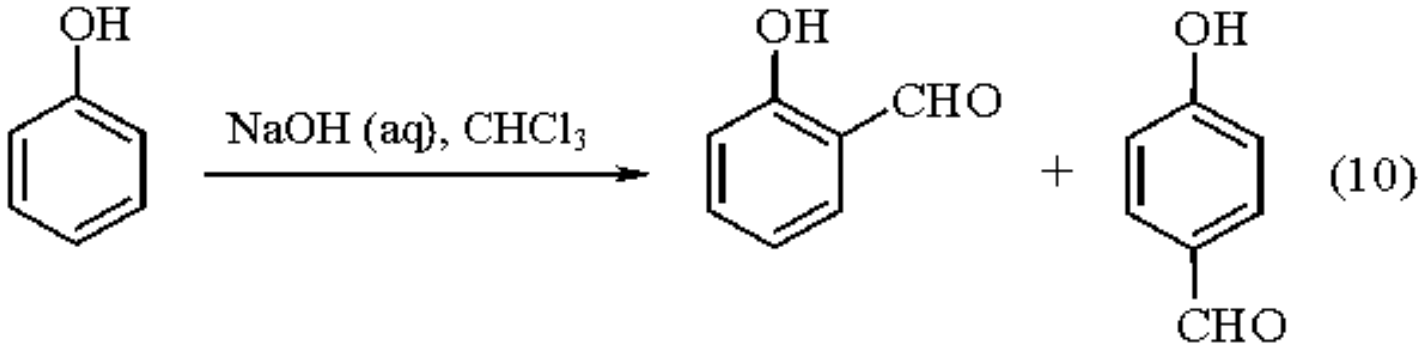

The abnormal Reimer-Tiemann reaction product can be subdivided further into cyclohexadienones and ring-expansion products. When *ortho*- or *para*-substituted phenols are subjected to the reaction, 2,2- or 4,4-disubstituted cyclohexadienones may be obtained, in addition to the normal product (eq 11).[18] With certain five-membered ring substrates, a ring expansion can also occur (eq 12).[19]

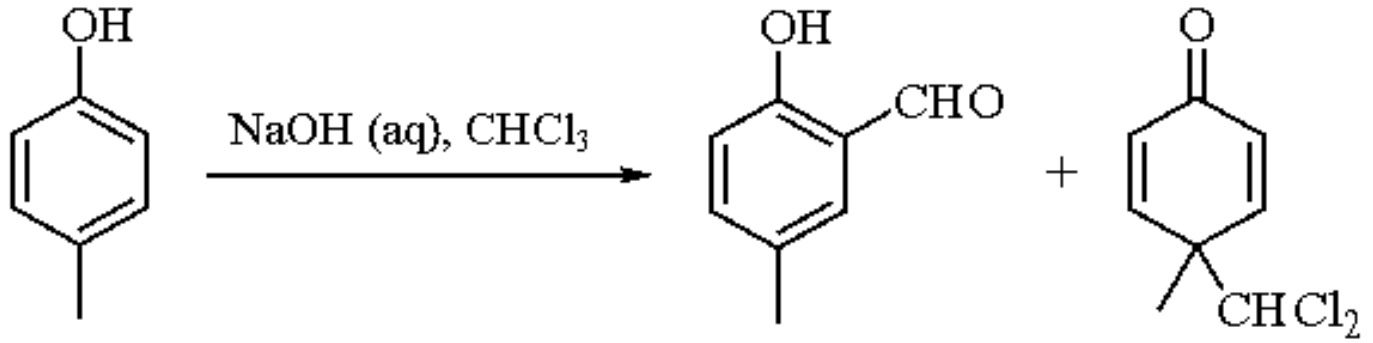

(11)

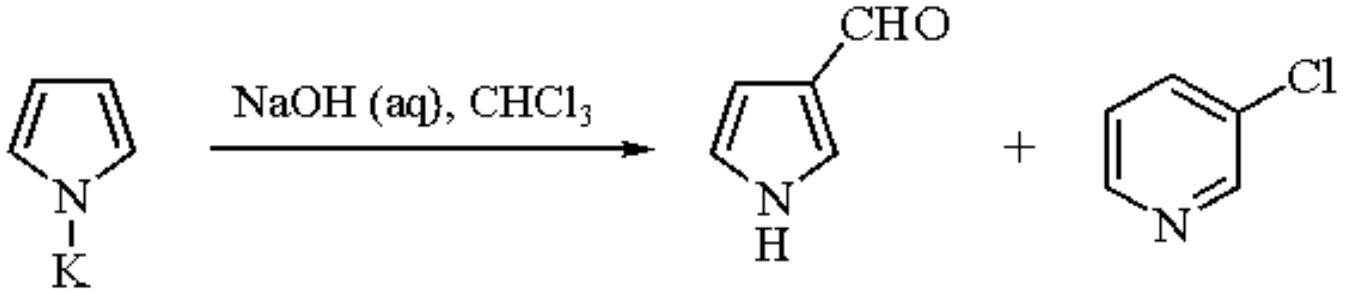

(12)

Several other methods for the direct introduction of an aldehyde group into an aromatic ring exist under acidic and/or anhydrous conditions.[20] The Reimer-Tiemann reaction is mainly useful for phenols[21] and certain heterocyclic compounds, such as pyrroles and indoles. Attempts to improve the procedure have focused on the nature of the base, the effect of the solvent, the use of phase-transfer catalysts,[22] the use of ultrasound,[23] cyclodextrins, and alternative precursors to dichlorocarbene.[24] No modification has led to a significant improvement in yield. However, alterations in *ortho/para* ratios and increased yields of abnormal products have been accomplished.[25]

Addition to Nonalkenic Substrates via Dihalocarbenes.

Halocarbenes insert much less readily than carbenes to C-H single bonds, though a number of instances have been reported (eq 13).[26]

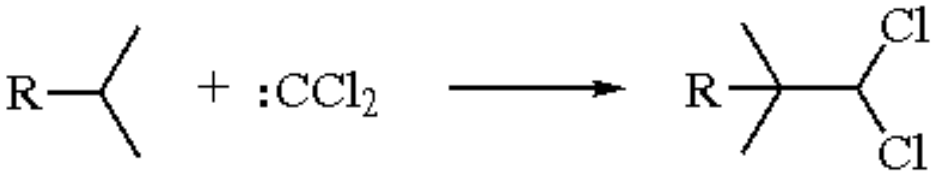

(13)

The reaction of dichlorocarbene with substrates other than hydrocarbons appears to be initiated by coordination of the electrophilic carbene with a Lewis basic site. Subsequent reactions that are attributable to differences in the basic functions or involvement with other reactive sites lead to differences in the chemistry of each substrate. The reactions of phase-transfer-generated dichlorocarbene with organic molecules possessing such heteroatoms as oxygen, nitrogen, and sulfur and no other more reactive functionality have led to a number of useful transformations. Alcohols react to give chlorides (eq 14).[27] Allylic alcohols that contain particularly reactive double bonds react preferentially at the alkenic sites.[28] In the absence of such complications, alcohols larger than about seven carbons react to yield chlorides, whereas small water-soluble alcohols generally yield the corresponding orthoformate in poor yield (eq 15).[29]

$$ROH + :CCl_2 \longrightarrow RCl + CO \qquad (14)$$

$$HCCl_3 + 3\,RO^- \longrightarrow HC(OR)_3 + 3\,Cl^- \qquad (15)$$

The facile addition of dichlorocarbenes under phase-transfer conditions has also been observed with imines[30] and can be a convenient pathway for the synthesis of some nitrogen-containing ring systems.[31] The hydrolysis of the *C,N*-diarylaziridines to the corresponding α-chloroacetanilides was also reported (eq 16).[32]

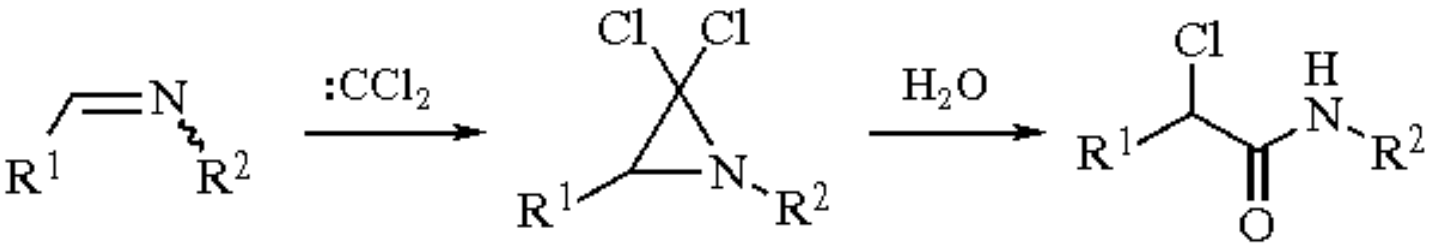

(16)

The reaction of chloroform under basic conditions is a common test for both primary aliphatic and aromatic amines (eq 17). The so-called Hofmann carbylamine reaction can also be used synthetically for the preparation of isocyanides, though yields are generally not high.[33] However, some improved procedures have been reported.[34] When secondary amines are involved, the adduct cannot lose two molecules of HCl; instead it is hydrolyzed to an *N,N*-disubstituted formamide (eq 18).[35] The reaction also yields imidazopyridines when α-(aminomethyl)pyridines are reacted with chloroform under phase-transfer catalysis conditions (eq 19).[36]

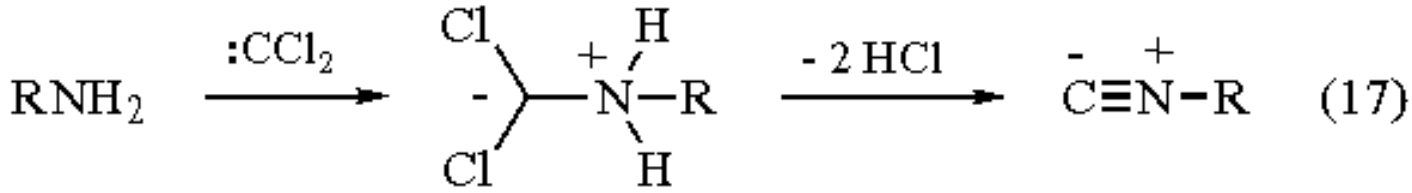

(17)

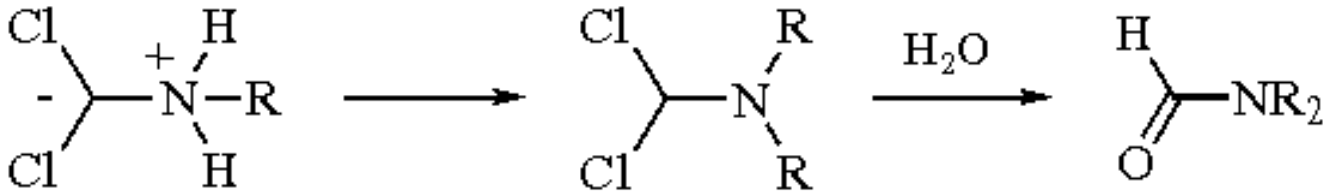

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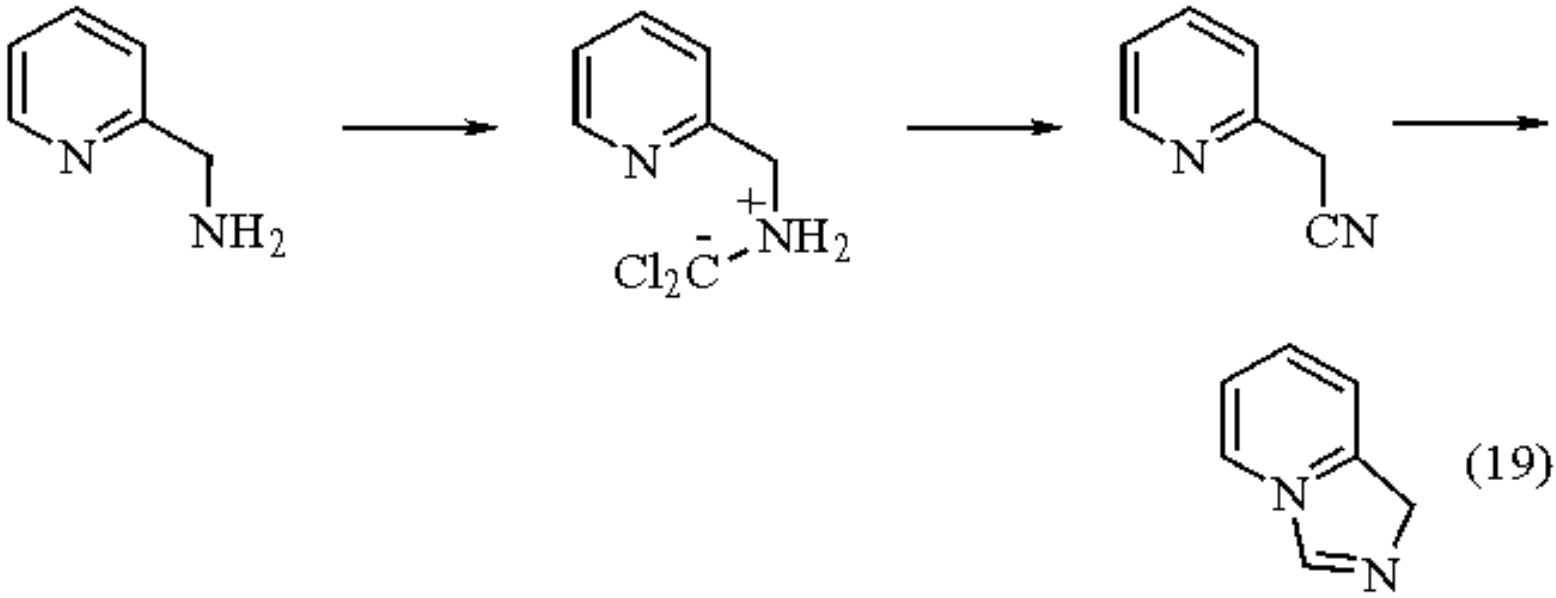

(19)

Dichlorocarbene can also be used as a dehydrating agent with primary amides, amidines, thioamides, and aldoximes, giving the corresponding nitriles (eq 20).[37]

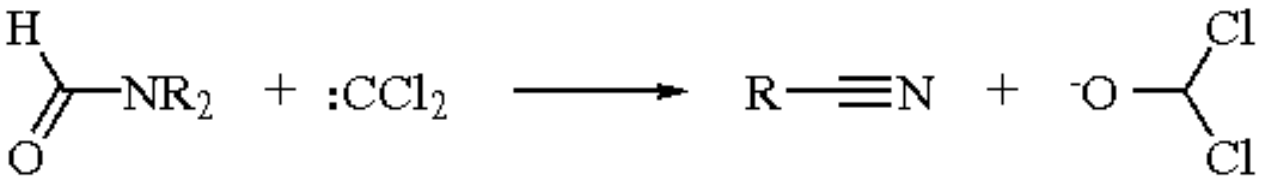

(20)

Friedel-Crafts Reaction.

Chloroform reacts with aromatics rings[38] to form di- and triarylmethanes (eq 21).[39] The coupling of the two phenyl rings to the methyl group can be followed by a Scholl condensation (eq 22).[40] The reaction can also be used for the high-yield synthesis of highly chlorinated mono-, di-, and triarylmethanes.[41]

$$C_6H_6 + CHCl_3 \xrightarrow{Al,\ CuCl} Ph_2CH_2 + Ph_3CH \qquad (21)$$

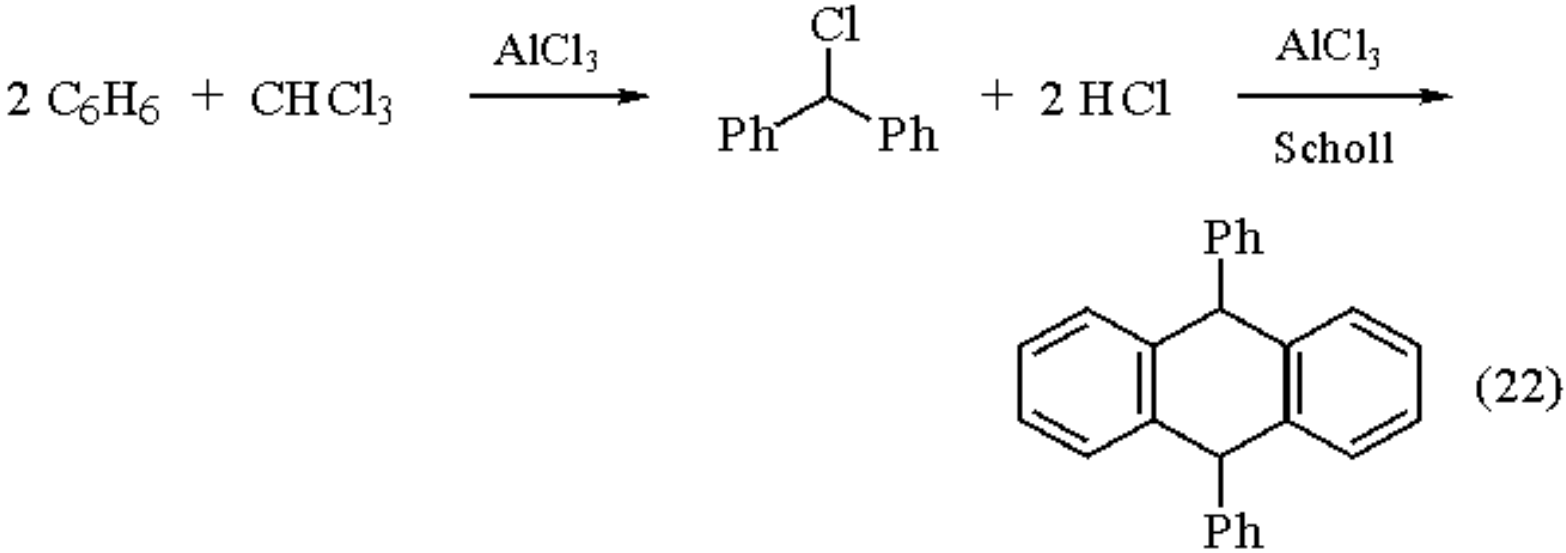

Addition to Aldehydes.

Chloroform can condense with aromatic aldehydes under basic conditions (or by cathodic reduction)[42] to produce aryl trihalomethyl-substituted methanols (eq 23).[43]

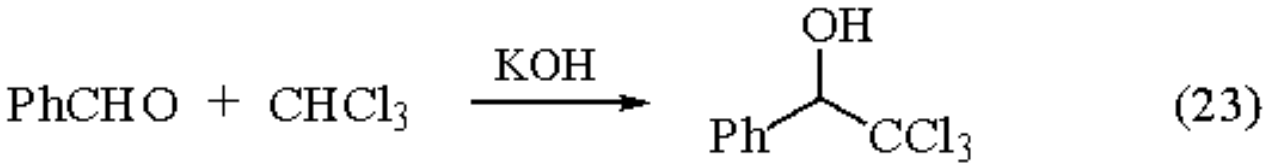

In the case of aliphatic aldehydes the reaction is not efficient due to the aldol condensation. However, a convenient general synthesis of α-trichloromethyl carbinols can now be used.[44] Condensation of chloroform with aliphatic ketones to form dialkyl(trichloromethyl) carbinols[45] can also be accomplished in lower yields, except in the case of cyclohexanone where the product was obtained in 92% yield.[46]

Trichloromethyl carbinols can be oxidized to ketones,[47] hydrolyzed to hydroxy acids,[48] condensed to diaryltrichloroethanes and related products,[49] or can be used for the preparation of ordinary derivatives of the hydroxy group, such as the chloride[50] or the acetate.[51] They can also be reduced to give (*Z*)-vinyl chlorides.[52] Secondary trichloromethyl carbinols are reduced by chromium(II) to form (*Z*)-monochlorovinyl compounds in one step; in the presence of a carboxy function in the α-position, an (*E*) double bond is formed. Tertiary carbinols favor the formation of dichlorovinyl compounds and rearranged carbonyl products (eq 24).

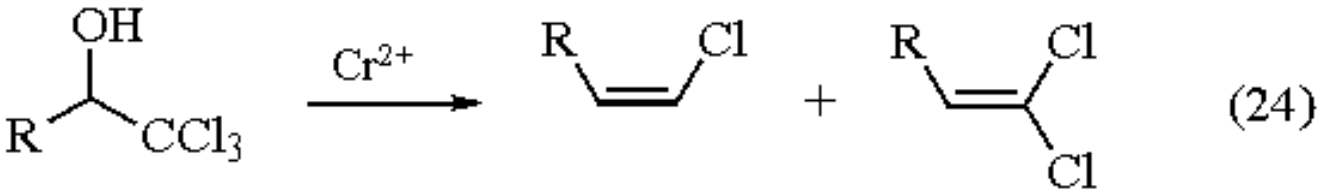

A variety of α-chloromethyl, α,α-dichloromethyl, and α,α,α-trichloromethyl ketones can also be synthesized from trichloromethyl carbinols utilizing cathodic reduction (eq 25).[53]

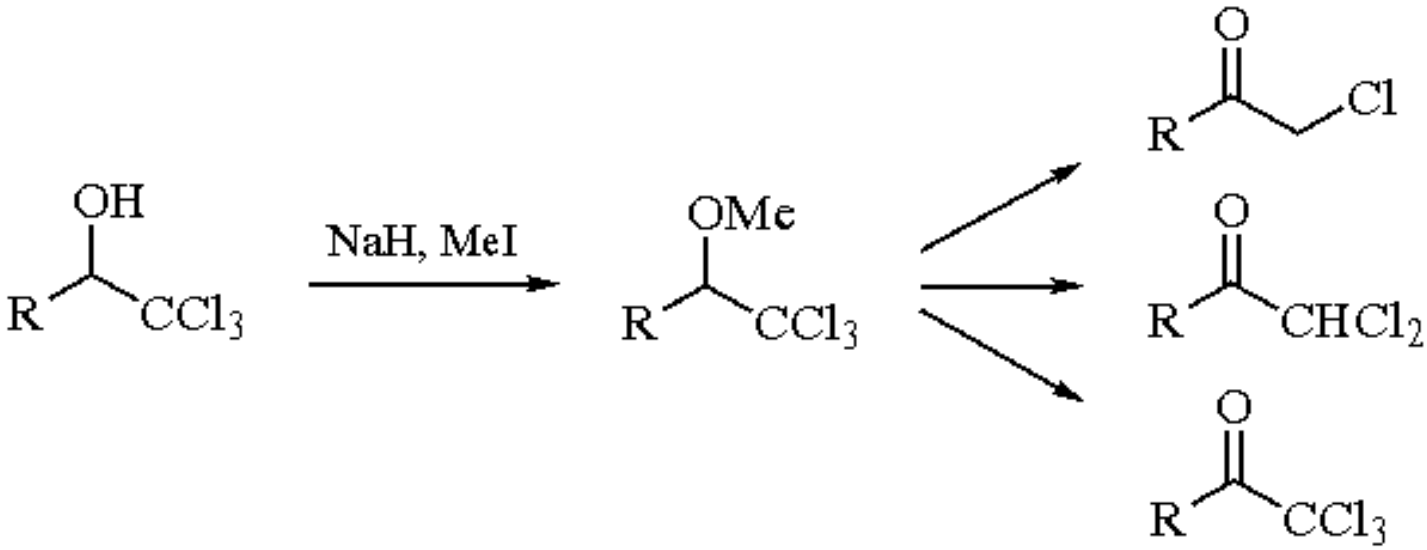

(25)

Another use of the reaction of the aryl trihalomethyl-substituted methanols involves their reaction with nucleophiles[54] under basic conditions, by forming first a dichloro epoxide, which in turn reacts with the nucleophile to form an acid chloride that gives rise to the final product (eq 26). This reaction is used for the preparation of α-substituted arylacetic acids, where the α-substituent is methoxy[55] (or alkoxy[56] in general), hydroxy,[57] amino,[58] and even chloro.[59] A method for the preparation of α-methoxy aliphatic acids has also been reported.[60]

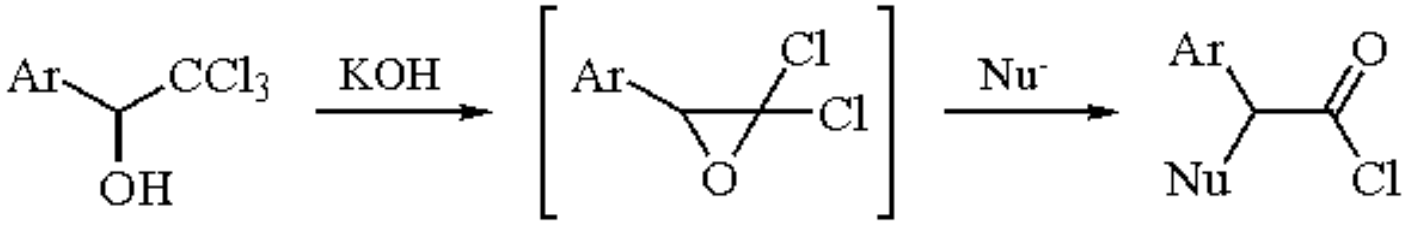

(26)

Reactions via Trichlorolithiocarbenoids.

Chloroform can be lithiated to form Cl_3CLi, a species that has proven to be a versatile synthon,[61] although other polyhalomethanes are sometimes preferred. Of particular interest is the reaction of Cl_3CLi with carbonyl functions (eq 27).[62]

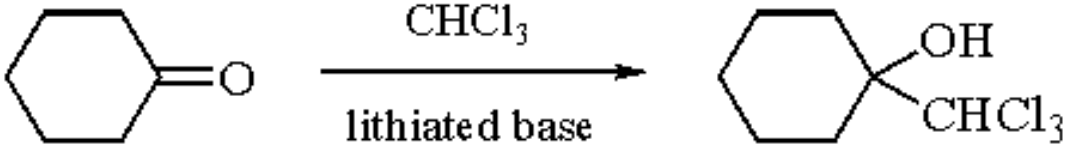

(27)

Polyhalomethyllithium carbonyl adducts may be easily converted to a variety of important structural classes, such as α-chloro ketones,[63] α,β-unsaturated aldehydes,[64] α-chloroaldehydes,[65] α-hydroxyaldehydes,[66] and dichloroalkenes.[67] Chloroform can readily give (trichloromethyl)alkenes by deprotonation with butyllithium and alkylation by iodoalkenes. The chloroalkenes generated can then undergo interesting transition metal catalyzed intramolecular cyclizations,[68] affording five- or six-membered rings (eq 28). Trichlorolithiomethane can also generate *gem*-dichloroalkenes by reacting with α-sulfonyl carbanions,[69] although their bromo analogs give better results (eq

29).

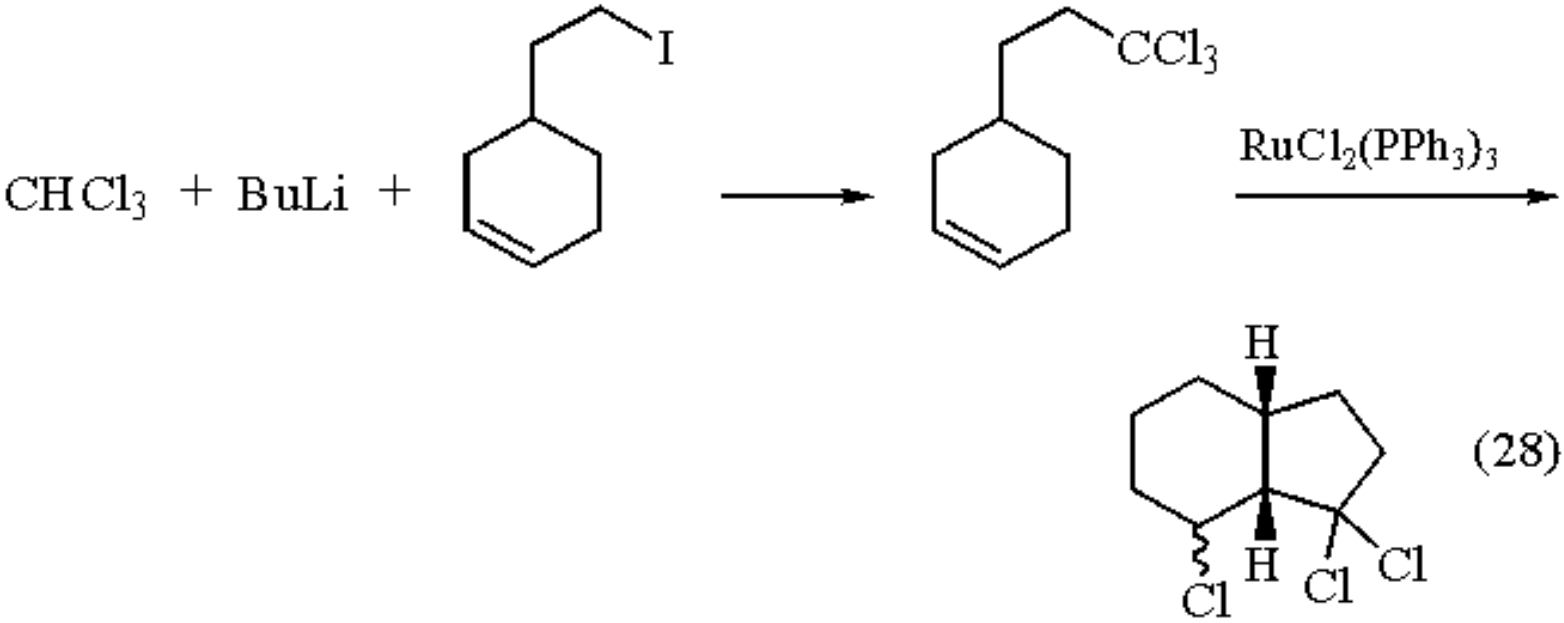

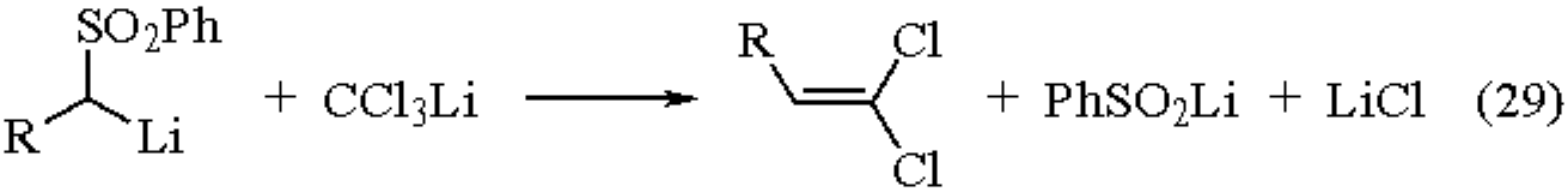

Chloroform in the presence of lithium triethylmethoxide can be used to convert organoboranes to the corresponding trialkyl carbinols (eq 30).[70] The reaction proceeds in good yield for tri-*n*-butylborane, but gives poor results when extended to tri-*s*-butylborane and other secondary, hindered organoboranes. ***Dichloromethyl Methyl Ether*** is a much more effective participant in this reaction.[71]

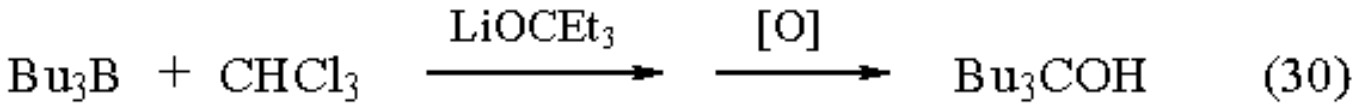

Related Reagents.

Bromoform; ***Phenyl(tribromomethyl)mercury***; ***Phenyl(trichloromethyl)mercury***.

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trans-Chlorohydridobis(triethylphosphine)platinum(II)

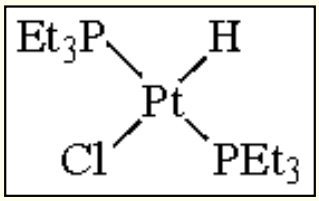

[20436-52-6] · $C_{12}H_{31}ClP_2Pt$ · *trans*-Chlorohydridobis(triethylphosphine)platinum(II) · (MW 467.87) (*trans*)

[16842-17-4]

(catalyst for nitrile hydration[1])

Physical Data: mp 81-82 °C; bp 130 °C/0.01 mmHg; sublimes at 75 °C/0.01 mmHg.

Solubility: sol organic solvents, incl. pentane (avoid chlorinated solvents).

Form Supplied in: white solid; commercially available.

Analysis of Reagent Purity: mp, NMR, IR.

Preparative Method: prepared in three steps from $PtCl_2$.[2]

Handling, Storage, and Precautions: air stable as the solid.

Nitrile Hydration.

The hydration of nitriles to amides is catalyzed by $(Et_3P)_2PtHCl$ (**1**) and the PMe_3 analog under mild conditions (80 °C) in the presence of one equivalent of ***Sodium Hydroxide*** per Pt (eq 1).[1] The maximum rate with acetonitrile occurs at about a 1:1 mixture of water to nitrile (70 and 178 moles amide per mol Pt per hour for Et_3P and Me_3P complexes, respectively). Phase transfer catalysts can be added to increase the rate with water-immiscible nitriles. Further addition of triethylphosphine also increases the reaction rate. In general, the trimethylphosphine analog appears to give higher rates than the triethylphosphine complex.

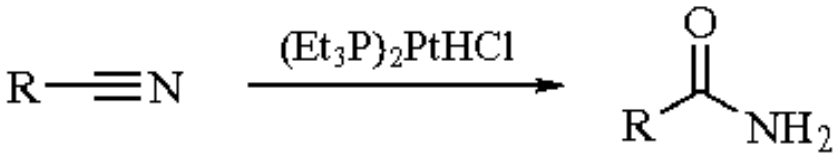

(1)

The title reagent might have particular value with hydrolysis-sensitive compounds, since the reaction conditions are much milder than those used with acid or base catalysts. The catalyst is particularly selective for hydrolysis of a nitrile in the presence of a conjugated double bond. For instance, conjugate addition of water to the alkenic double bond of acrylonitrile can be minimized, especially at lower temperatures. In addition, compounds which contain esters undergo selective nitrile hydrolysis (eq 2).

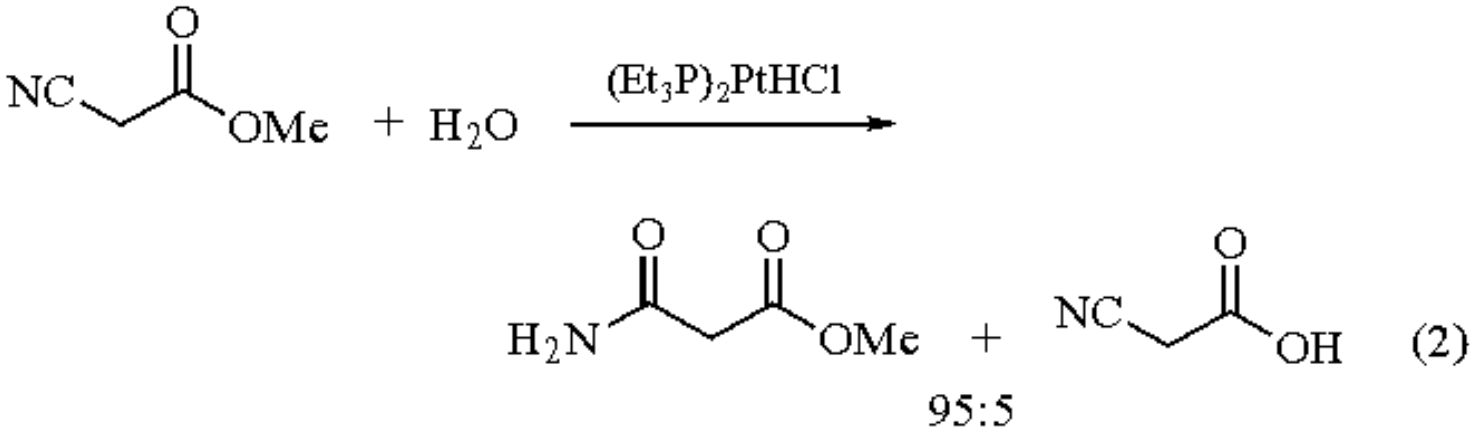

Methacrylate Polymerization.

Various *trans*-PtHX(PEt_3)$_2$ species catalyze the polymerization of methyl methacrylate in CCl_4.[3] The rate follows NO_3 > Cl > Br > NO_2 > CN. Co-polymerizations of methyl methacrylate with styrene have also been reported.[4] The monomer reactivity ratios were 0.50 and 0.65, respectively, and were suggested to proceed via a radical mechanism.

Alkene Hydrogenation.

Catalytic hydrogenation of simple alkenes, both terminal and internal, linear and cyclic, have been accomplished with (**1**) under ambient conditions in the presence of mineral acid.[5]

Alkene Hydroformylation.

In the presence of ***Tin(II) Chloride***, (**1**) catalyzes the hydroformylation of 1-hexene with moderate performance.[6]

Alkene Hydrosilation.

Complex (**1**) can function as an alkene hydrosilylation catalyst, but the activity is not as good as other catalysts.[7]

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Chlorohydridotris(triphenylphosphine)rhodium(III) Chloride

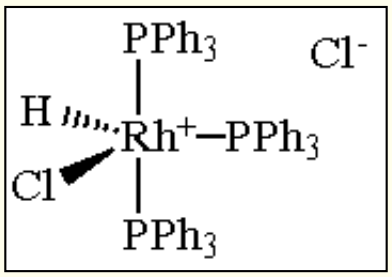

[12124-48-0] · $C_{54}H_{46}Cl_2P_3Rh$ · Chlorohydridotris(triphenylphosphine)rhodium(III) Chloride · (MW 961.72)

(catalyst for carboxamide decomposition,[2] chloroacetate carbonylation,[3] hydrogen transfer,[4] and hydrogenation[5])

Physical Data: α-form mp (dec) 160 °C; β-form mp (dec) 100 °C.

Analysis of Reagent Purity: elemental analysis.

Preparative Method: prepared from ***Rhodium(III) Chloride*** and ***Triphenylphosphine***.[1]

Carboxamide Decomposition.

The distillation of secondary carboxamides over this catalyst results in generation of nitriles (eq 1).[2] Higher yields are reported when ***Chlorotris(triphenylphosphine)rhodium(I)*** is employed for production of nitriles from carboxamides. Use of various iridium complexes, palladium complexes, and ruthenium complexes results in a less efficient process.

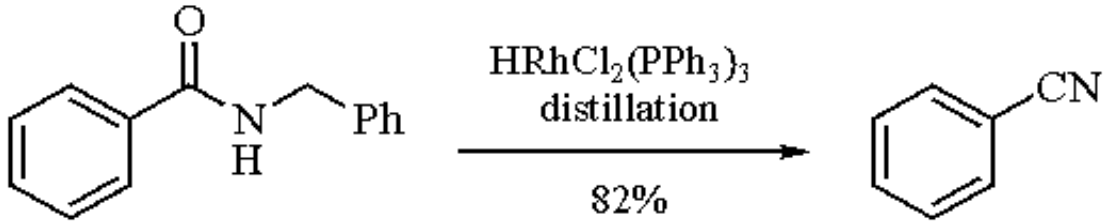

(1)

The title reagent also catalyzes the transformation of malonamides into acetamides (eq 2).[2] In this case, the activities of $RhCl(PPh_3)_3$ and $HRhCl_2(PPh_3)_3$ do not mirror one another with respect to substrate selectivity and rate. This disparate reactivity is probably a reflection of the different mechanistic pathways followed by these two catalysts: $RhCl(PPh_3)_3$ requires oxygen to be catalytically active while $HRhCl_2(PPh_3)_3$ does not.

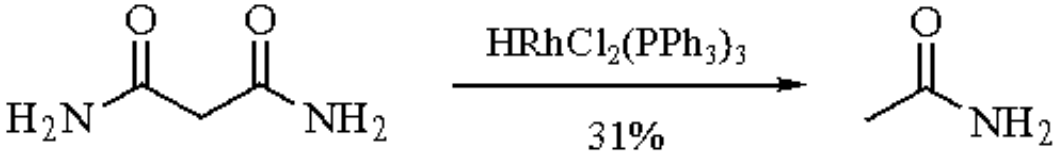

(2)

Carbonylation.

The carbonylation of chloroacetates has been effected using $HRhCl_2(PPh_3)_3$ adsorbed onto active carbon as a catalyst (eq 3).[3] When carbon monoxide pressures were less than 20 bars, lower product selectivities were observed. ***Rhodium(III) Chloride*** and $RhCl(PPh_3)_3$ can also function as catalysts for the carbonylation of chloroacetates.

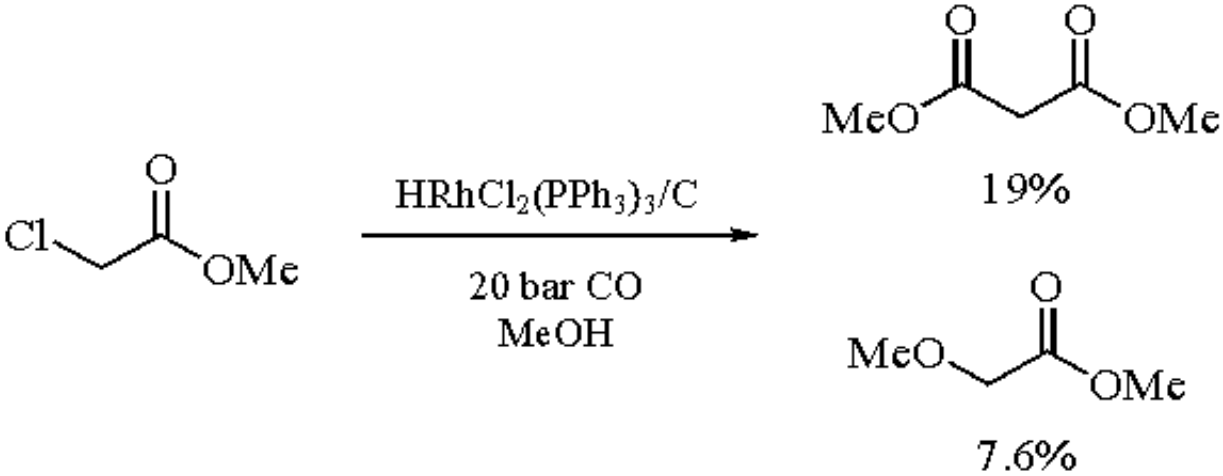

(3)

Alkene Isomerization.

Exposure of 1-pentene to $HRhCl_2(PPh_3)_3$ results in isomerization of the alkene to an internal position (eq 4).[4] Presumably this reaction occurs through the addition-elimination of a rhodium hydride species. Other catalysts that exhibit comparable activity in this type of isomerization are $RhCl_3(PPh_3)_3$ and $HRuCl(PPh_3)_3$.

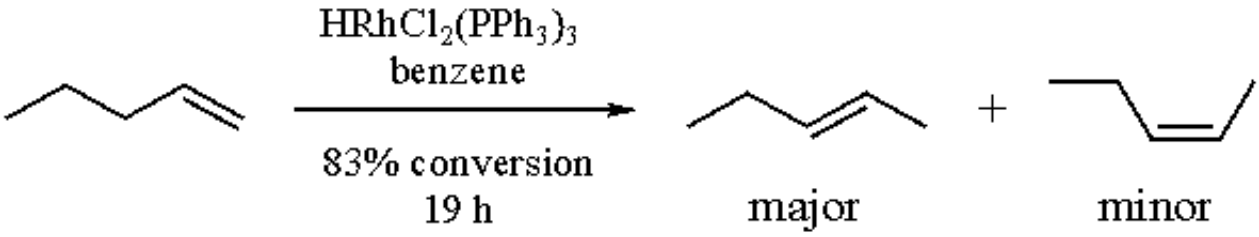

(4)

Hydrogenation.

$HRhCl_2(PPh_3)_3$ supported on silica can be used as a hydrogenation catalyst (eq 5).[5] In a comparison with other rhodium-based catalysts the following reactivity order emerges: $RhCl(PPh_3)_3 > H_2RhCl(PPh_3)_3 > HRhCl_2(PPh_3)_3$.

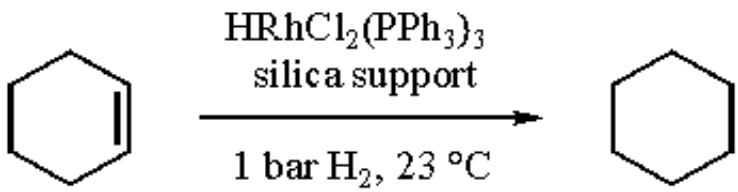

(5)

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3-Chloro-1-hydroxytetrabutyldistannoxane[1]

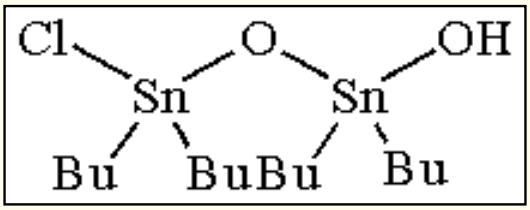

[95970-99-3] · $C_{16}H_{37}ClO_2Sn_2$ · 3-Chloro-1-hydroxytetrabutyldistannoxane · (MW 534.40)

(mild Lewis acid catalyst for urethane formation,[3] transesterification,[4c] esterification,[4c] acetalization,[6] deacetalization,[7] and deprotection of silyl ethers[7])

Alternate Name: CHTD.

Physical Data: mp 107-115 °C.

Solubility: insol H_2O, cold MeOH; sol most organic solvents.

Preparative Methods: a mixture of dibutyltin oxide (14.9 g, 60 mmol) and dibutyltin dichloride (6.07 g, 20 mmol) in 95% ethanol (200 mL) is heated under reflux. After 6 h the transparent solution is concentrated to give a white powder. This is pulverized, then exposed to ambient atmosphere overnight. The exposure to air converts partially formed ethoxydistannoxane to the corresponding hydroxydistannoxane. Recrystallization of the crude product from hot hexane affords pure 3-chloro-1-hydroxytetrabutyldistannoxane (15.1 g, 72%).

Handling, Storage, and Precautions: is extremely stable in air and to moisture and thus can be handled and stored in the open air. Because this compound is not volatile, it is virtually nontoxic under the usual conditions.

Urethane Formation.

CHTD catalyzes the reaction between isocyanates and alcohols much more efficiently than conventional organotin catalysts, and polyurethane formation from tolylene diisocyanate and poly(oxypropylene triol) is effected by 5×10^{-4} mol of CHTD per mol of -NCO.[2] The mechanism of the catalysis has been disclosed.[3]

Transesterification.[4]

Transesterification is catalyzed by CHTD (eq 1). The reaction is quite simple: a mixture of an ester and an alcohol is heated under reflux in toluene in the presence of the catalyst. The catalyst is surprisingly active; even 0.05 mol % catalyst is effective. The reaction proceeds under almost neutral conditions, and thus various functional groups remain intact during the reaction. Notably, β-keto esters are transesterified smoothly (eq 2), and transesterification of one of the acetoxy groups in 1,*n*-diol diacetates is realized in a highly selective manner (eq 3). The unique reactivities are ascribed to the template effects of the dimeric formulation shown in (**1**).

$$RCO_2R' + R''OH \longrightarrow RCO_2R'' + R'OH \qquad (1)$$

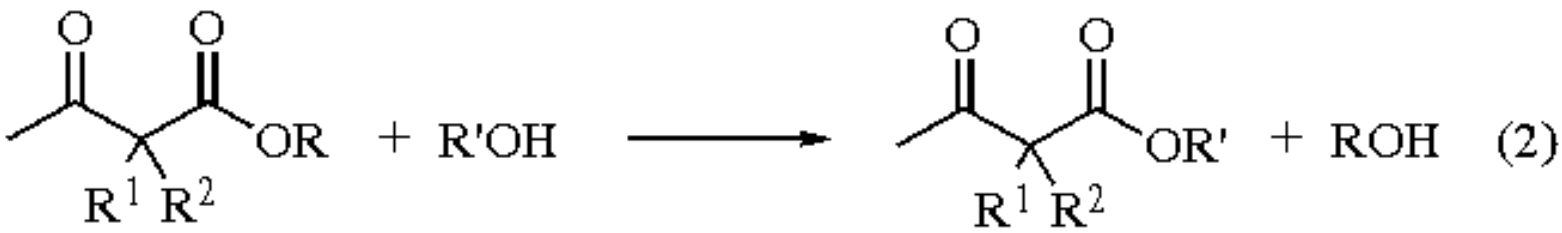

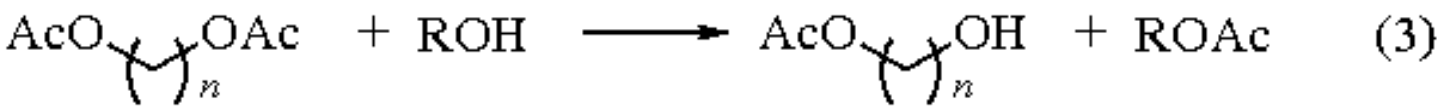

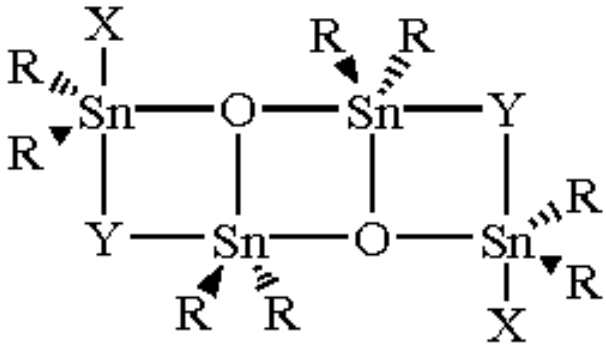

(1)

Esterification of Carboxylic Acids.[4c,5]

The CHTD catalyst is effective not only for intermolecular esterification of carboxylic acids (eq 4) but also macrolactonization of o-hydroxy acids (eq 5). Most significantly, the distannoxane-catalyzed esterification is free from the reverse reaction (hydrolysis). Simply heating the two reactants completes the reaction without the use of a Dean-Stark apparatus. The absence of hydrolysis is a consequence of the double-layered structure of CHTD, whose hydrophobic surface butyl groups prevent the water from approaching the catalytically important core sites, i.e. the tin atoms.

$$RCO_2H + R'OH \longrightarrow RCO_2R' + H_2O \qquad (4)$$

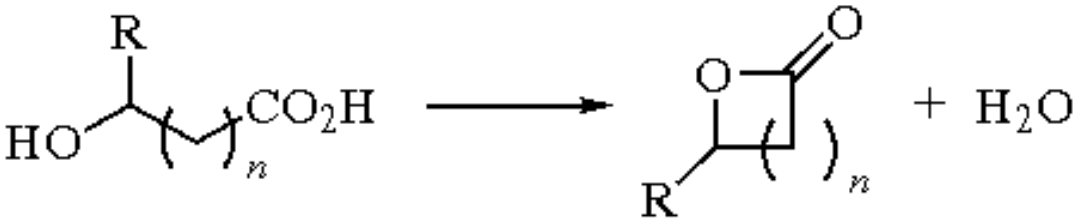

(5)

Acetalization of Carbonyls.[6]

Exposure of carbonyls to ethylene glycol in refluxing benzene, toluene, or methanol in the presence of a catalytic amount of CHTD affords the corresponding acetals in high yields. Mild reaction conditions allow facile preparation of products that are otherwise difficult to obtain. Ketones are acetalized more slowly than aldehydes. However, addition of an equivalent amount of aldehyde accelerates the reaction dramatically. A unique transcarbonylation mechanism is responsible for this acceleration.

Deprotection of Acetals and Silyl Ethers.[7]

Acetals are converted to parent carbonyls by treating with 1 mol % of CHTD in diethylene glycol dimethyl ether or dioxane-water at 100 °C. THP ethers are deprotected when heated in methanol or THF-H_2O under catalysis by CHTD. Silyl ethers are also converted to alcohols under analogous conditions.

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1-Chloro-2-iodoethane[1]

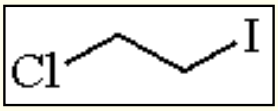

[624-70-4] · C_2H_4ClI · 1-Chloro-2-iodoethane · (MW 190.42)

(iodinating reagent for organometallic compounds[1,2] and carbanions;[3] alkylating agent[4])

Alternate Names: ethylene iodochloride; ethylene chloroiodide.

Physical Data: bp 38-40 °C/18 mmHg, 55-57 °C/37 mmHg, 140 °C/760 mmHg;[5] n_D^{25} 1.5636; *d* 2.12 g cm^{-3}.

Solubility: sol all common organic solvents; insol H_2O.

Analysis of Reagent Purity: VPC R_t 5.1 min (relative to air) on a 2 m × 6 mm 20% diethylene glycol succinate column at 125 °C;[6] NMR δ 3.7-3.4 (m, A_2B_2, CH_2I), δ 3.6-3.2 (m, A_2B_2, CH_2Cl).[6]

Preparative Methods: prepared in 76% yield by bubbling ***Ethylene*** gas into a CH_2Cl_2 solution of freshly redistilled ***Iodine Monochloride*** maintained at 30 °C by ice-cooling until the temperature begins to fall.[7] Other methods of preparation include reaction of ethylene, ***Copper(II) Chloride***, and ***Iodine*** at 75-85 °C in a pressure reactor;[6] reaction of excess 1,2-dichloroethane with ***Sodium Iodide*** in acetone[8] or with ***Aluminum Iodide*** in CS_2;[9] and by reaction of 2-iodoethanol with ***Thionyl Chloride***.[10]

Purification: material that is exposed to light and air develops a slight rose-colored tint due to the formation of I_2. It is usually suitable for use unless the color is very pronounced. The compound is purified by washing with aq thiosulfate and redistillation at reduced pressure.[7]

Handling, Storage, and Precautions: 1-chloro-2-iodoethane is a dialkylating agent and should be used only in an effective fume hood. Avoid inhalation of the vapor and contact of the liquid with the skin. The compound is light sensitive and should be stored refrigerated in the dark.

Iodinating Reagent.

1-Chloro-2-iodoethane is a selective reagent for the introduction of iodine atoms into organic molecules via carbanions or other organometallic species. It is only mildly electrophilic and can be used in the presence of many sensitive functional groups. The byproducts of the iodination reaction are ethylene and a metal chloride. In the syntheses of the

hydroquinoid fungal antibiotics Frustulosin[2] and Aurocitrin[1] the dimethoxyiodo vinyl ether was a crucial intermediate. It was readily prepared from an aryllithium which was available by direct metallation (eq 1).

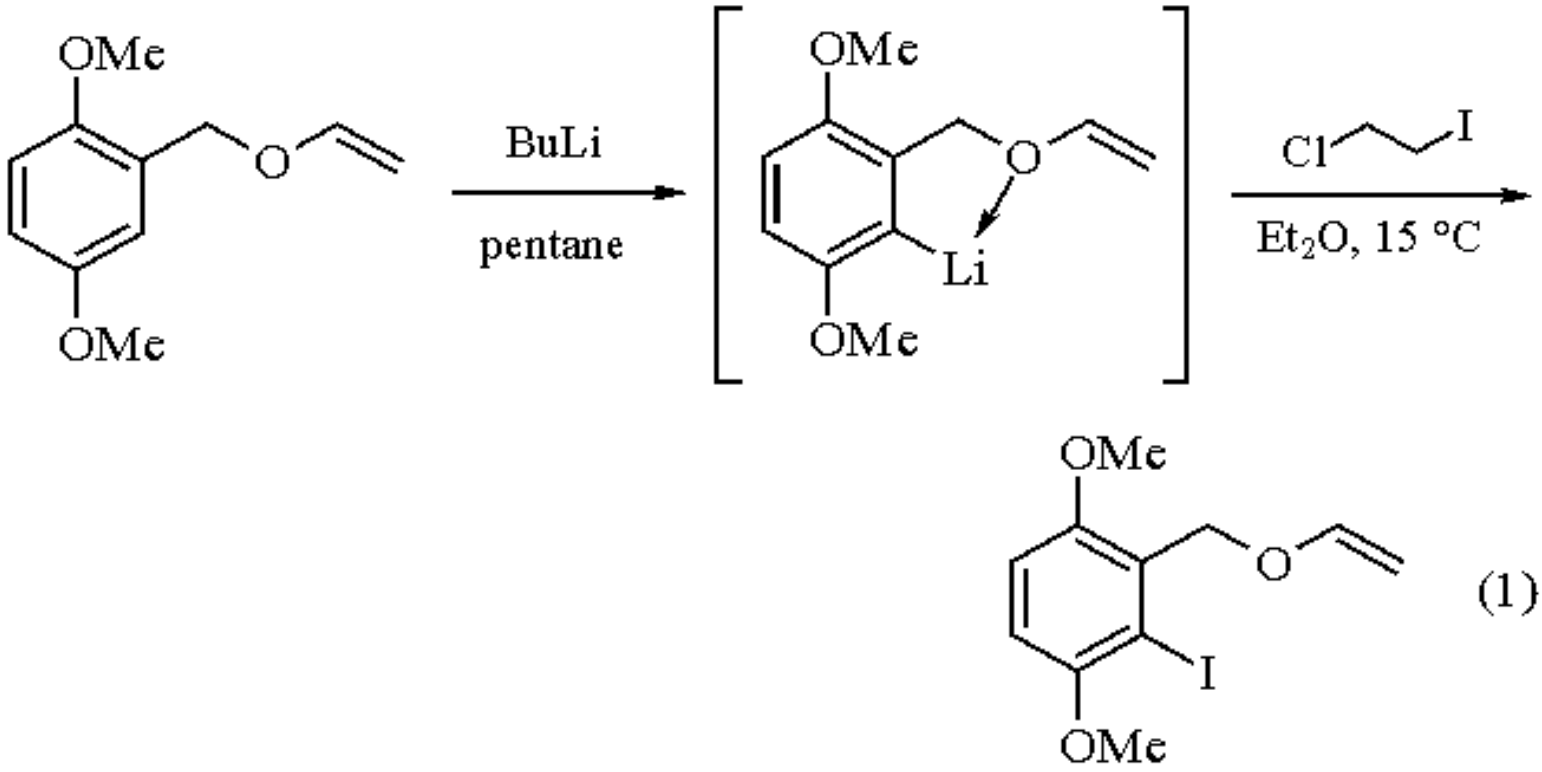

(1)

In their study of planar cyclooctatetraene analogs, Cracknell and co-workers[8] investigated a number of reagents to effect iodination of the metalated biphenylene and found that ethylene iodochloride was superior to both ***Iodine*** and ***Diiodomethane*** for preparation of the iodobiphenylene (eq 2). Similarly, it was shown to be an effective reagent for synthesis of iodobenzylic chlorides (eq 3).[11]

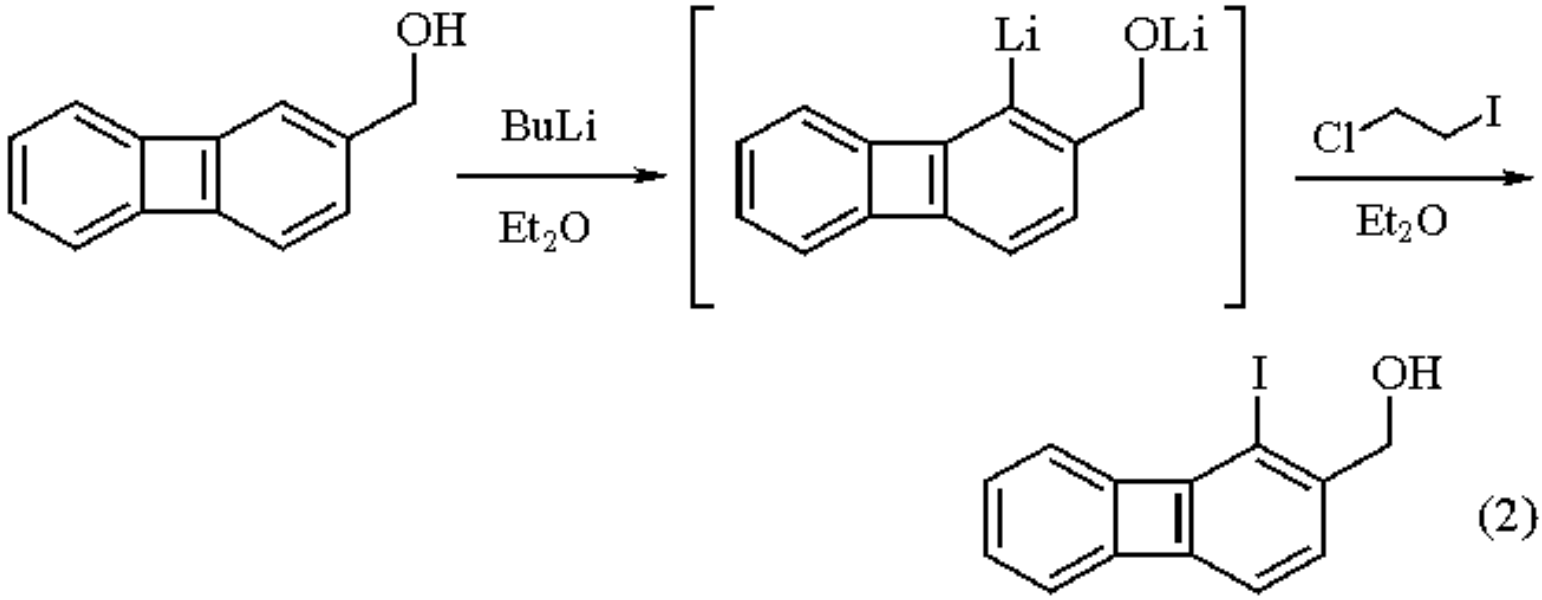

(2)

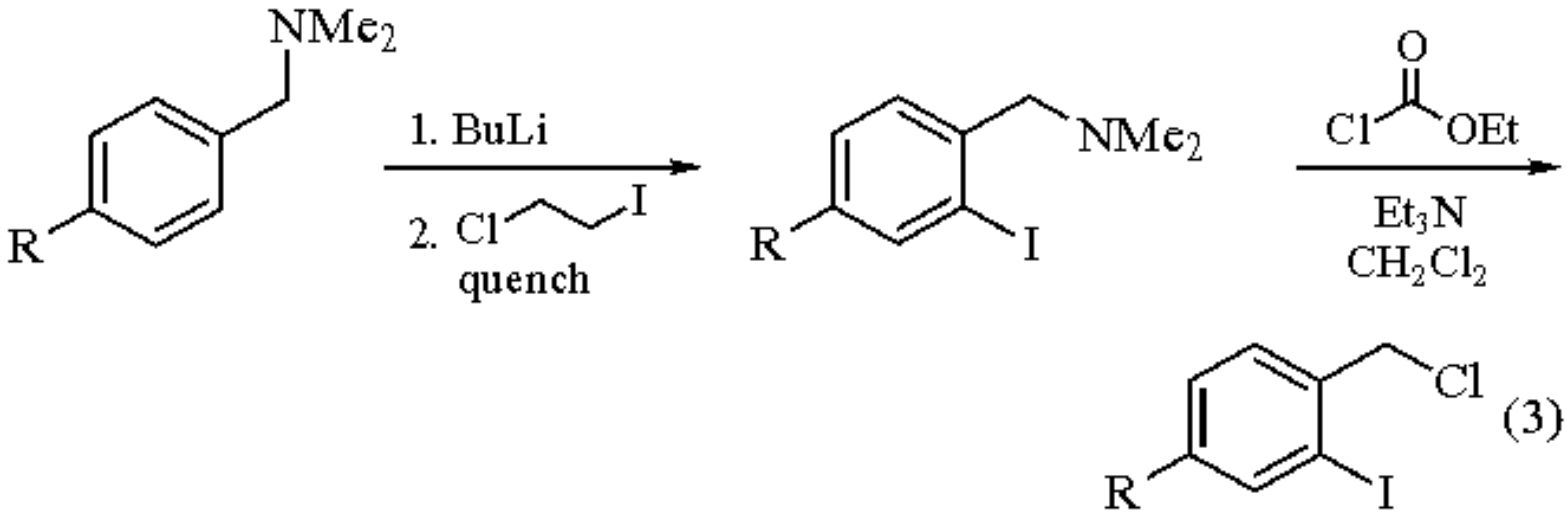

One of the principal uses of the reagent is to trap organometallic species as the iodides which can then subsequently be used to regenerate the carbanionic intermediates by halogen-metal exchange. This was shown to be especially effective by Fuchs and co-workers in their cytochalasin model studies where halogen-metal exchange on α-iodo sulfones in the presence of acid anhydrides effected acylation with <1% formation of butyl ketones (eq 4).[3]

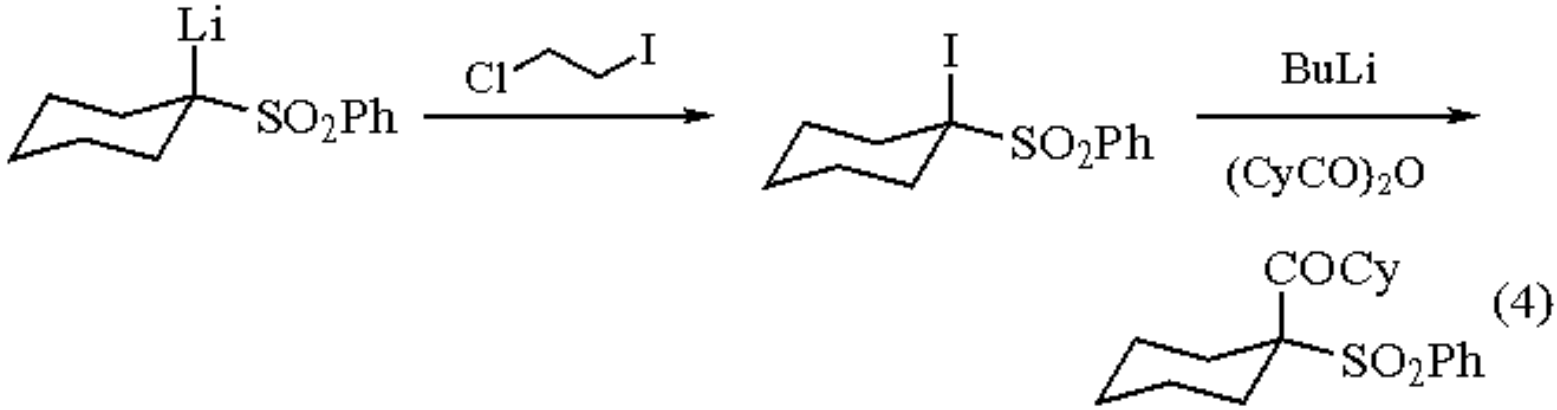

Alkylation Reactions.

1-Chloro-2-iodoethane tends to react by electron transfer mechanisms, which makes it an inefficient alkylating agent even with good nucleophiles. For example, even with Na_2S little or no alkylation was observed, and the products were ethylene and halide salts.[12] Similarly, treatment of anionic metal carbonyl complexes[13] resulted in dimerization (eq 5). With ***Chloroiodomethane*** these complexes alkylate normally (eq 6). This is probably a consequence of the weak C-I bond for which the activation energy for homolytic cleavage has been estimated to be as little as 30 kcal mol^{-1}.[14]

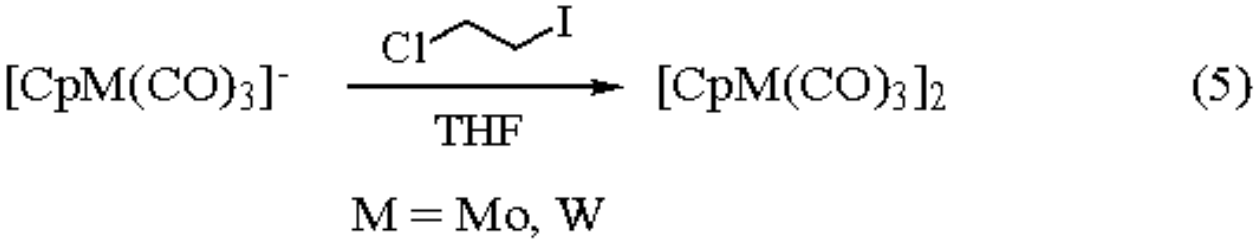

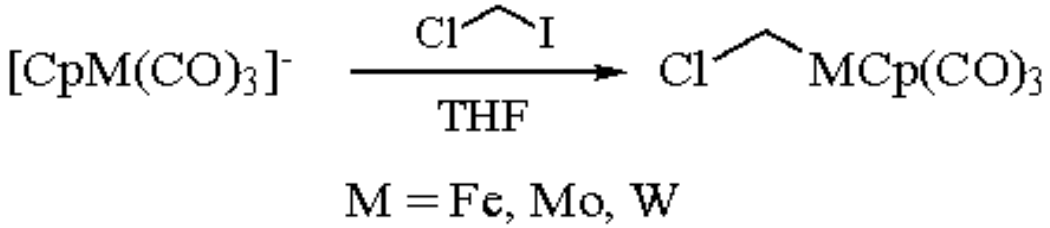

(6)

However, with extremely powerful nucleophiles, or nucleophilic atoms which are not easily oxidized, the reagent will function as a normal alkylating agent. Carboxylate salts react to form chloroethyl esters, and cyanamino-s-triazine salts are alkylated.[15] Collman has used the reagent with highly nucleophilic rhodium complexes to produce organometallic dimers linked by $-CH_2-CH_2-$ bridges (eq 7).

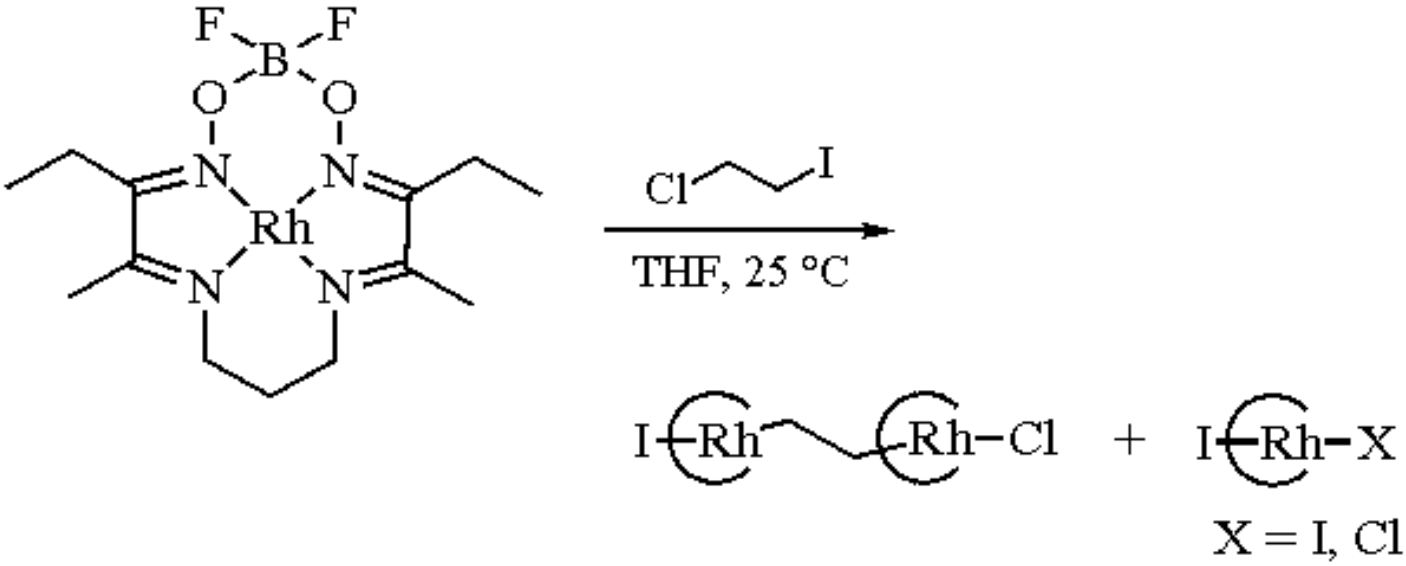

(7)

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Rob Ronald

1-Chloro-2-iodoethylene

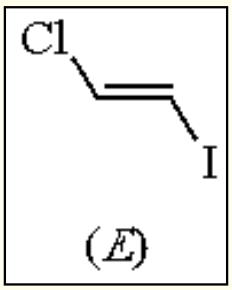

(*E*)

[28540-81-0] · C_2H_2ClI · 1-Chloro-2-iodoethylene · (MW 188.40) (*Z*)

[31952-74-6]

(cross-coupling reagent used as a precursor of chloroenynes, terminal, and unsymmetrical internal diynes)

Alternate Name: 1-chloro-2-iodoethene.

Physical Data: [1] (*E*), bp 113-114 °C; mp -41.0 °C, *d* 2.10 g cm^{-3}, bp of *n*-propanol azeotrope 87.5-88.5 °C. (*Z*), bp 116-117 °C; mp -36.4 °C, *d* 2.21 g cm^{-3}, bp of *n*-propanol azeotrope 93.6-94.0 °C.

Preparative Methods: 1-chloro-2-iodoethylene can be prepared by either chloromercuration of ***Acetylene***[2] followed by iodinolysis[3] or electrophilic addition of ***Iodine Monochloride*** to acetylene (eq 1).[1] The chloromercuration reaction is highly stereoselective and gives exclusively the (*E*) isomer, while the electrophilic addition of ICl has been reported to give a diastereomeric mixture (however, this reaction has also been reported to be stereoselective[4]). The (*E*)-alkenyl mercury intermediate can be isomerized[5] to an (*E*)/(*Z*) mixture by treatment with a catalytic amount of ***Dibenzoyl Peroxide*** at 100 °C in *p*-xylene. Its iodinolysis gives an (*E*) and (*Z*) mixture of 1-chloro-2-iodoethylenes.

Purification: stereoisomerically pure (*Z*)-1-chloro-2-iodoethylene can be obtained by azeotropic fractional distillation of stereoisomeric mixtures with *n*-propanol. Stereoisomerically pure samples can be isomerized to give a mixture of (*Z*) and (*E*) isomers upon long exposure to sunlight and should be stored accordingly.

Handling, Storage, and Precautions: use in a fume hood.

Cross-Coupling Reactions.

1-Chloro-2-iodoethylene can readily participate in selective mono-cross-coupling reactions because of the difference in reactivity between the two carbon-halogen bonds. Cross-coupling with alkylmercurials[6] is nonstereospecific because of its radical nature, and leads to a mixture of diastereomers in most cases. On the other hand, Pd-catalyzed cross-coupling[7] with alkynylzincs yields stereospecifically the corresponding (*E*)-chloroenynes (**1**) in good yields (eq 2).[4]

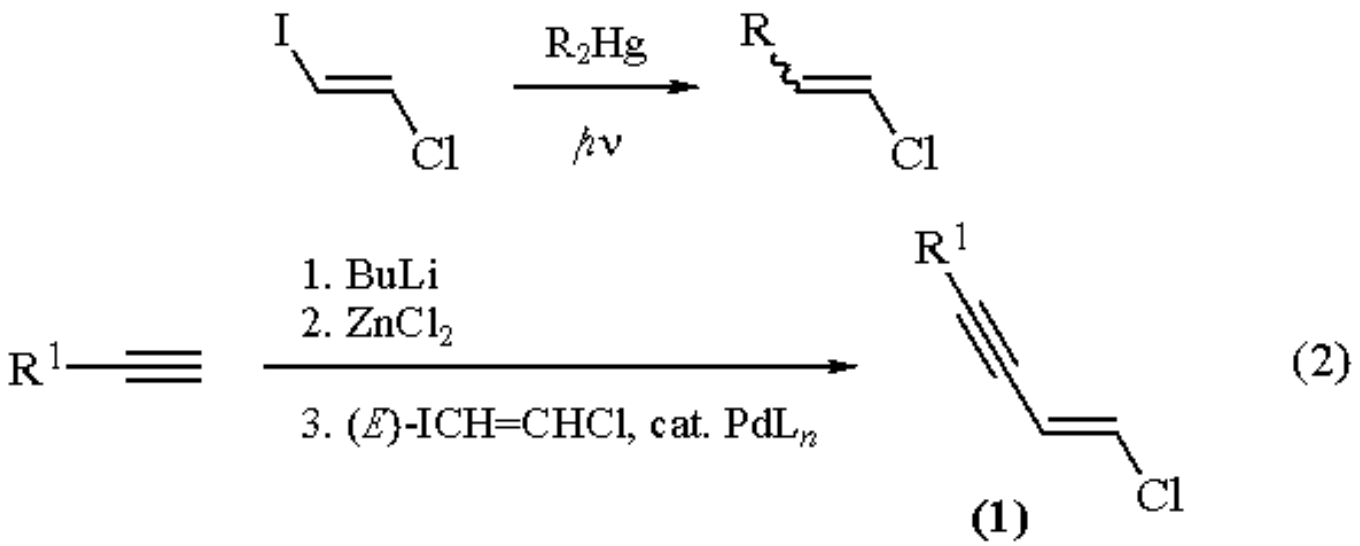

It is worth noting that the (*Z*)- or (*E*)-chloroenynes, e.g. (**1**) or (**2**), can also be stereospecifically prepared by Pd/Cu-catalyzed cross-coupling of alkynes with (*Z*)- or (*E*)-***1,2-Dichloroethylene*** (eq 3).[8] On the other hand, the corresponding reaction with 1,2-dibromoethylene gives a mixture of mono- and dialkynylated products.[9]

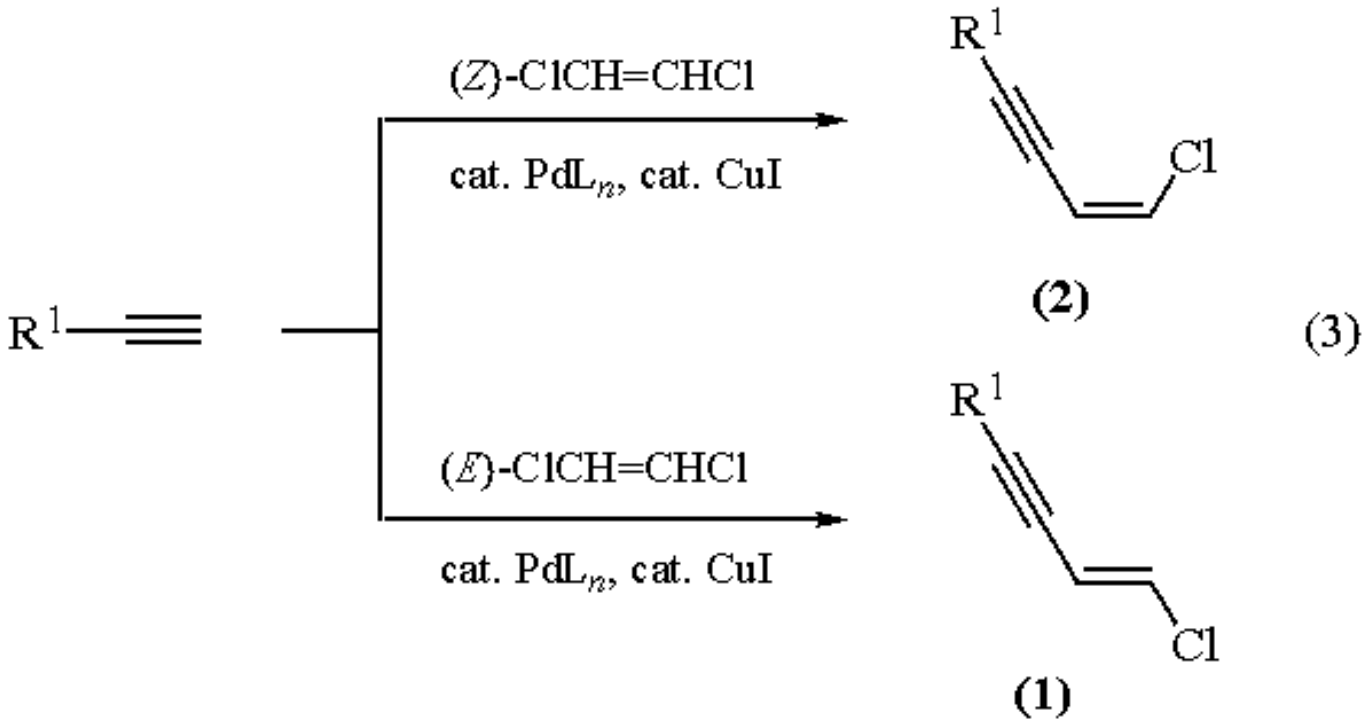

The chloroenynes (**1**) and (**2**) can readily participate in further cross-coupling reactions, and this methodology has been applied to the synthesis of a variety of natural products[10] and oligomeric unsaturated compounds.[11] Dehydrohalogenation

of the chloroenynes (**1**) with ***Sodium Amide*** in liquid ammonia can lead to 1-sodio-1,3-diynes which, in turn, can be further transformed into terminal and symmetrical or unsymmetrical internal diynes (eq 4).[4]

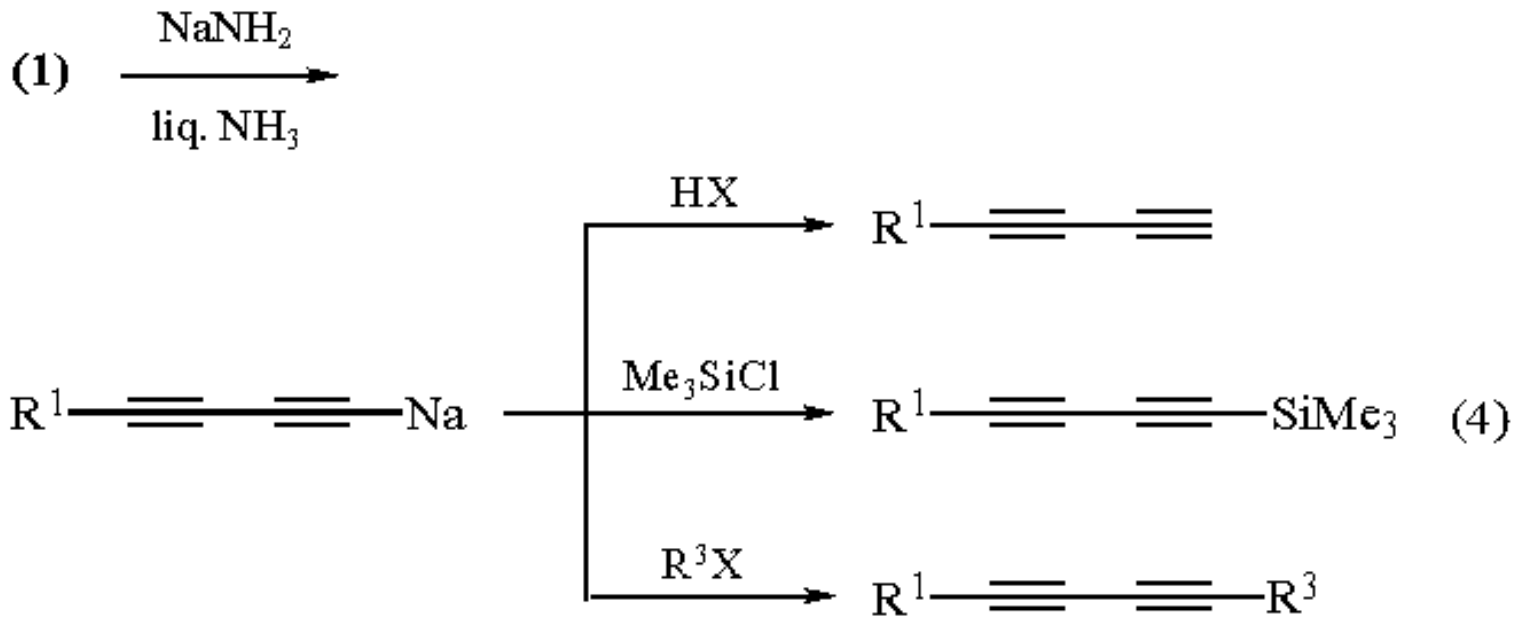

Related Reagents.

(E)-1-Bromo-2-phenylthioethylene; ***1,2-Dichloroethylene***.

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Chloroiodomethane[1]

$ClCH_2I$

[593-71-5] · CH_2ClI · Chloroiodomethane · (MW 176.38)

(chloromethylating agent for organozinc,[2] -lithium,[3] -phosphorus,[4] and -transition metal compounds,[5] and alkenes;[6] can generate *N*,*N*-dimethylmethyleneiminium iodide (Eschenmoser's salt) by reaction with *N*,*N*,*N´*,*N´*-tetramethylmethylenediamine[7])

Alternate Name: CIM.

Physical Data: bp 108-109 °C; *d*204 2.42 g cm^{-3}; *n*20D 1.582.

Solubility: sol ethers, acetone, polyhalomethanes, and benzene.

Form Supplied in: pale yellow oil; commercially available or readily preparable via halogen exchange of dichloromethane with iodide sources.[1,8]

Analysis of Reagent Purity: NMR (CCl_4/TMS), δ (ppm) 5.00.

Handling, Storage, and Precautions: should be stored over tin or silver wire in the dark.

Cyclopropanation of Alkenes.

The ***Diethylzinc***/chloroiodomethane (CIM) reagent system is a valuable alternative to Furukawa's version of the Simmons-Smith cyclopropanation reaction (eq 1).[2,9] The formation of the (chloromethyl)zinc species seems to proceed via a radical chain mechanism, considering the accelerating effect of oxygen and the retarding effect of radically polymerizable alkenes.[2] The samarium carbenoid generated from Sm(Hg) and CIM cyclopropanates allylic alcohols with high regio- and stereoselectivity via the directing effect of the hydroxyl function (eq 2).[10] Generally, CIM affords better results in these carbenoid reactions than ***Diiodomethane***.

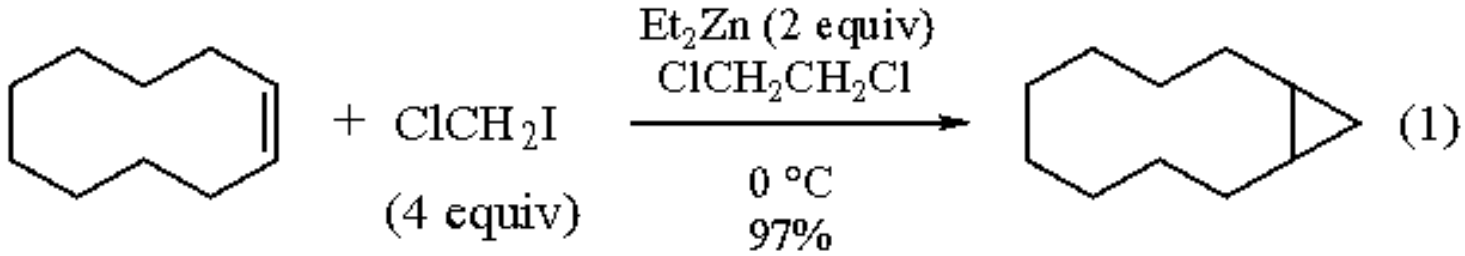

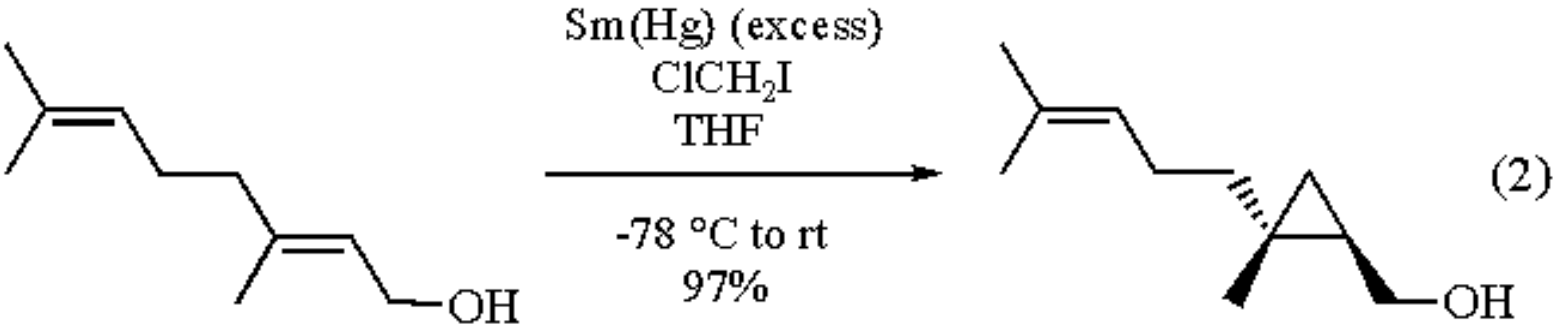

Generation and in situ Trapping of Chloromethyllithium.

The extreme thermal instability of ***Chloromethyllithium***[11] severely limits its synthetic applicability. A method has been devised to generate and trap (chloromethyl)lithium by reacting CIM with an alkyllithium in the presence of a substrate.[3a,12] Addition of ***n-Butyllithium*** to a mixture of a boronic ester and CIM in THF at low temperature yields the methylene insertion product with retention of the configuration of the alkyl moiety (eq 3).[3] Aldehydes and ketones can also capture the in situ generated carbanion species in THF at -78 °C.[12] The initial chloromethyl adducts are amenable to further reactions depending on the substrates and reaction conditions applied,[12,13] e.g. delayed hydrolytic workup yields the epoxides (eq 4).[12] The chlorohydrin products can be lithiated in situ to the β-oxidoalkyllithiums for further transformations (e.g. eq 5).[14]

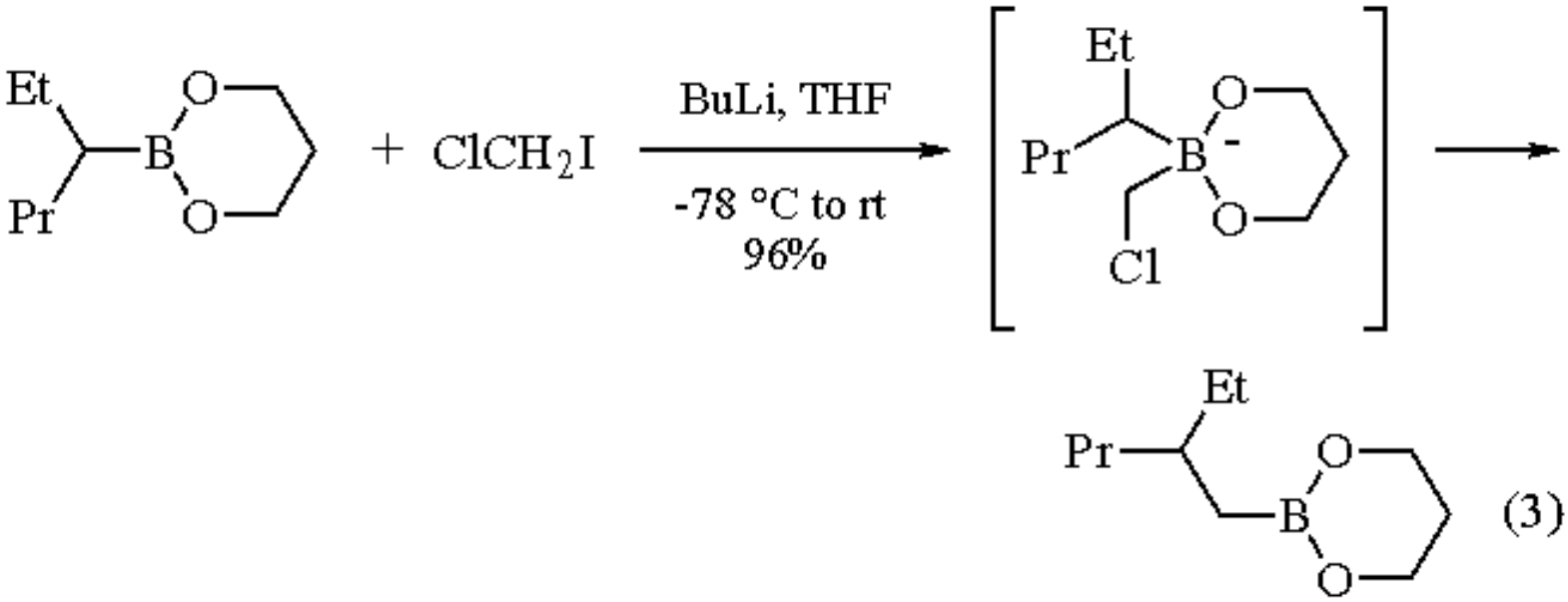

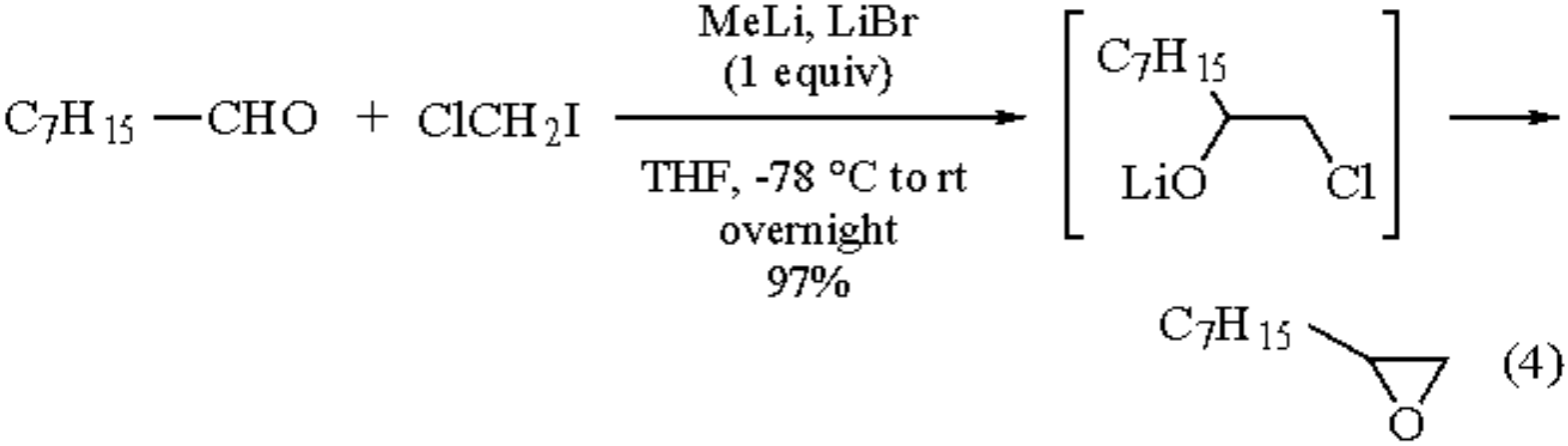

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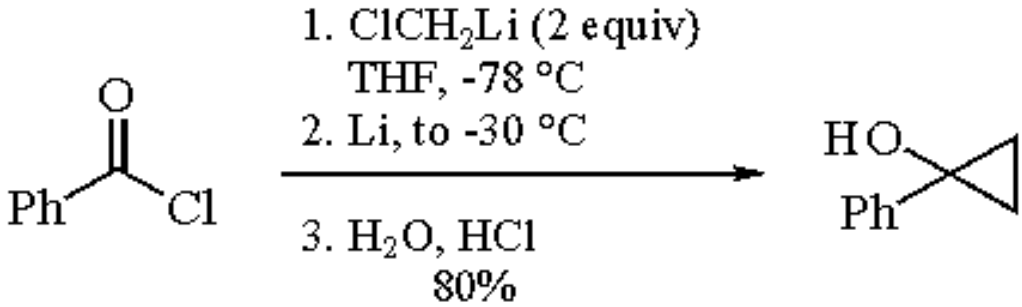

(5)

Wittig Chloromethylenation.

Treatment of ***Triphenylphosphine*** with CIM in THF at reflux forms the phosphonium iodide (**1**) in good yield, which in turn is transformed to the corresponding ylide by treatment with ***Potassium t-Butoxide*** and hence can chloromethylenate aldehydes and ketones (eq 6).[4,15]

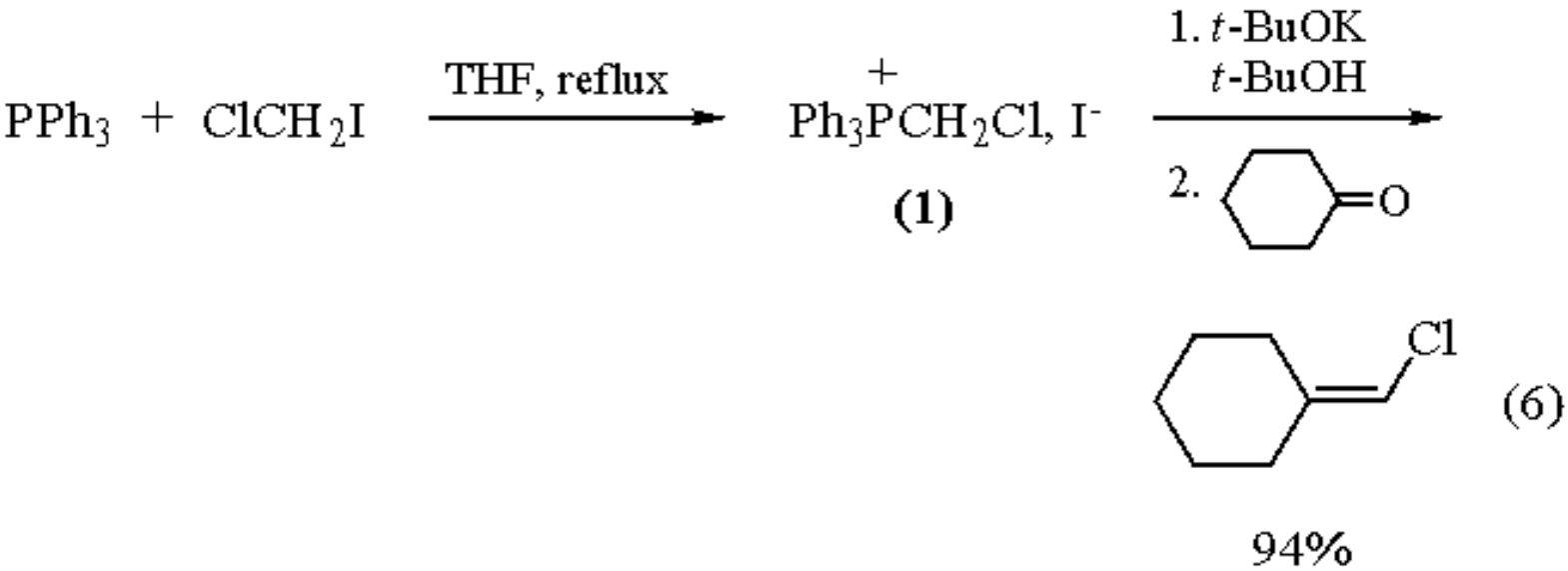

(6)

The Mannich Reaction.

The dimethylaminomethylation of carbonyl compounds is conveniently carried out via the enol trimethylsilyl ethers by a combination of CIM and *N,N,N´,N´*-tetramethylmethylenediamine (TMMD; ***Bis(dimethylamino)methane***) in

DMSO at ambient temperature (eq 7).[7] The reagent system CIM/TMMD also provides a convenient route to Eschenmoser's salt (**2**) (***Dimethyl(methylene)ammonium Iodide***) (eq 8).[7]

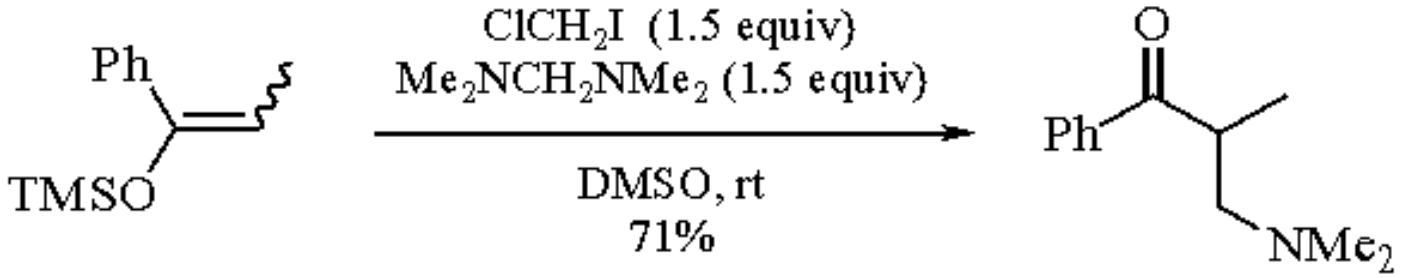

(7)

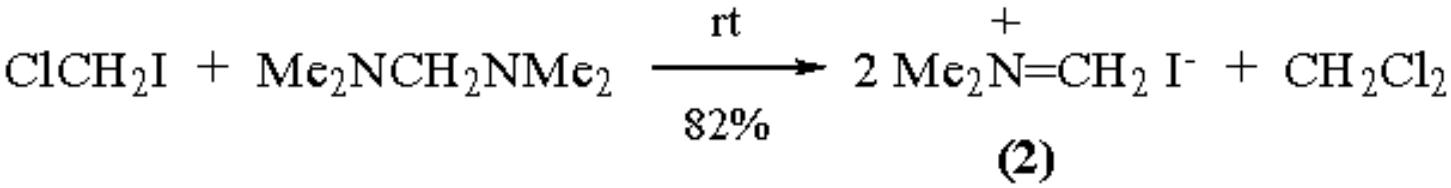

(8)

Related Reagents.

Chloroiodomethane-Zinc/Copper Couple.

---

1. Hahn, R. C. *JOC* **1988**, *53*, 1331.
2. (a) Miyano, S.; Hashimoto, H. *BCJ* **1973**, *46*, 892. (b) Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *S* **1977**, 700. (c) Miyano, S.; Hashimoto, H. *BCJ* **1973**, *46*, 1895.
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13. (a) Barluenga, J.; Llavona, L.; Concellón, J. M.; Yus, M. *JCS(P1)* **1991**, *297*. (b) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *JCS(P1)* **1989**, 77.
14. (a) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *JCS(P1)* **1988**, 3339. (b) Barluenga, J.; Fernández-Simón, J. L.; Concellón, J. M.; Yus, M. *S* **1987**, 584.
15. Matsumoto, M.; Kuroda, K. *TL* **1980**, *21*, 4021.

Chloroiodomethane-Zinc/Copper Couple

$ClCH_2I$-Zn(Cu)

($ClCH_2I$)

[593-71-5] · CH_2ClI · Chloroiodomethane-Zinc/Copper Couple · (MW 176.38) (Zn(Cu))

[12019-27-1] · Zn · Chloroiodomethane-Zinc/Copper Couple · (MW 65.39)

(used in the preparation of cyclopropanes[1], and alkenes from aldehydes[2])

Physical Data: $ClCH_2I$: bp 108-109 °C; *d* 2.422 g cm^{-3}. Zn(Cu): mp >400 °C; *d* ca. 7.14 g cm^{-3}.

Solubility: $ClCH_2I$: sol organic solvents; insol H_2O. Zn(Cu): insol organic solvents and H_2O.

Form Supplied in: $ClCH_2I$: colorless to brown liquid. Zn(Cu): reddish-brown or dark gray powder; often prepared directly before use.

Preparative Method: see ***Zinc/Copper Couple***.

Purification: chloroiodomethane can be purified by distillation.

Handling, Storage, and Precautions: chloroiodomethane is light sensitive and should be stored in the dark. It can be stabilized with copper wire. Zinc-copper couple deteriorates in moist air and should be stored under nitrogen. Very active zinc-copper couple is oxygen sensitive. It evolves hydrogen on contact with strong aqueous acids.

Chloroiodomethane reacts with zinc-copper couple to give chloromethylzinc iodide that will rearrange to iodomethylzinc chloride in ethereal solvents (eq 1).[3] The Schlenk equilibria favors the bis(halomethyl)zinc-ZnX_2, so the active species in solution are bis(chloromethyl)zinc-ZnI_2 (**1**), or bis(iodomethyl)zinc-$ZnCl_2$ (**2**). Except for the identity of the zinc salt, (**2**) is the same product formed from zinc-copper couple and diiodomethane, and its reactions parallel those of the Simmons-Smith reagent.[4]

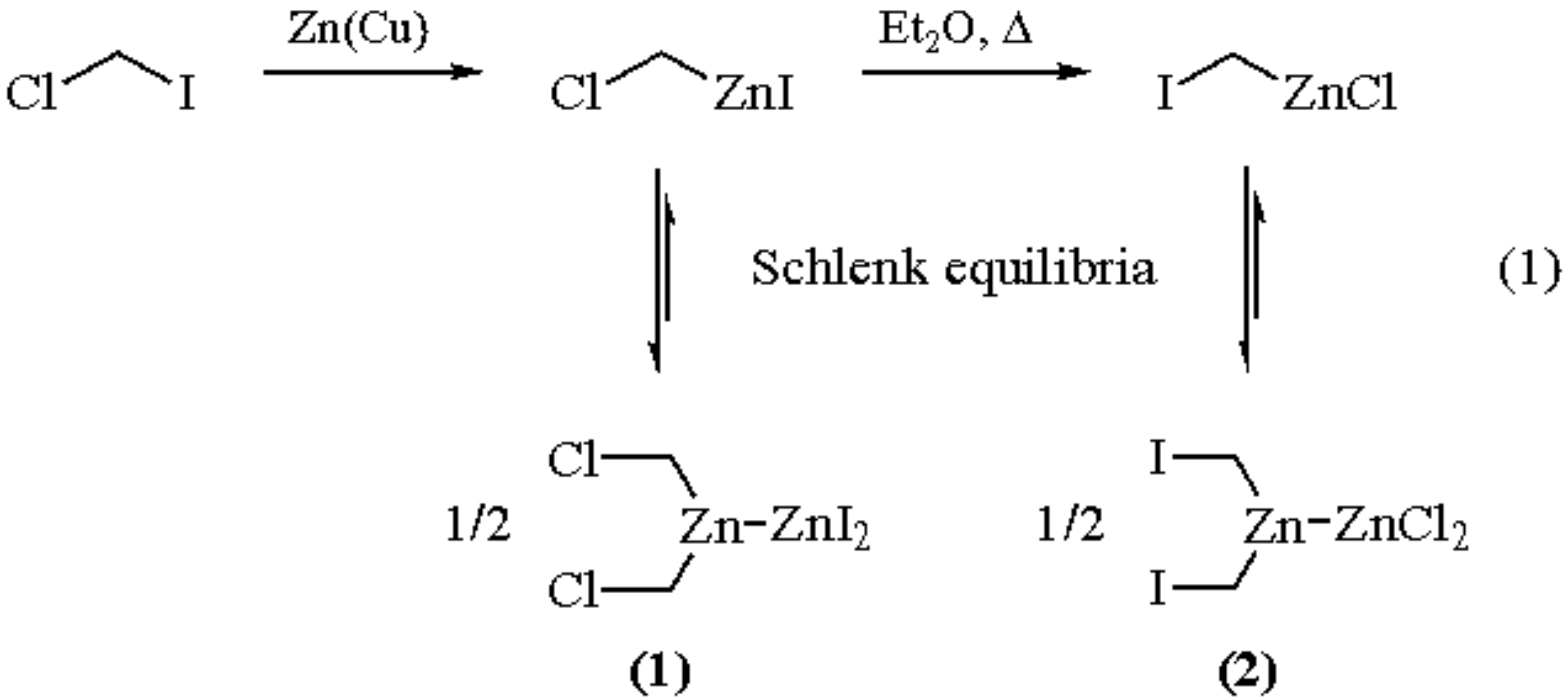

Chloroiodomethane and zinc-copper couple cyclopropanate alkenes and convert aldehydes to terminal alkenes (eq 2).[2] Chloroiodomethane works better than the other dihalomethanes, giving styrene in 80% yield compared to 72% with ***Diiodomethane***

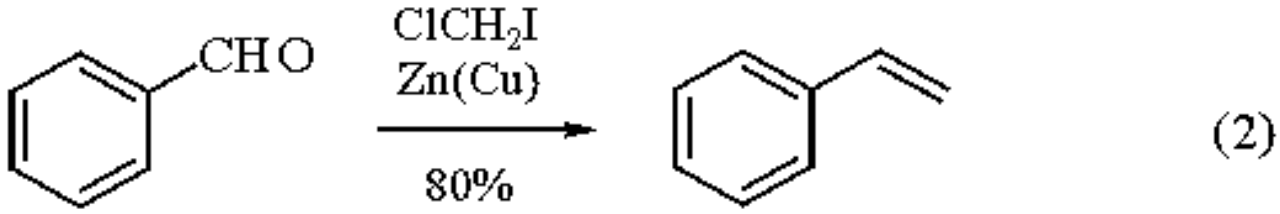

Chloroiodomethane and zinc-copper couple have not been used widely for cyclopropanation, but chloroiodomethane and diethylzinc have been used to generate $ClCH_2ZnEt$. This reagent was first prepared by Miyano[1] for cyclopropanations, and was reported to be superior to the Furukawa[5] reagent generated from diiodomethane and diethylzinc. Denmark found that *cis*-cyclodecene cyclopropanated in 94% (GC yield) using chloroiodomethane compared to 12% (GC yield) using diiodomethane under the same conditions (eq 3).[6] Miyano found that oxygen accelerated these reactions and proposed a radical mechanism for the formation of the chloromethylzinc intermediate, but Denmark found that the reagent prepared in 1,2-dichloroethane gave comparable results without oxygen.

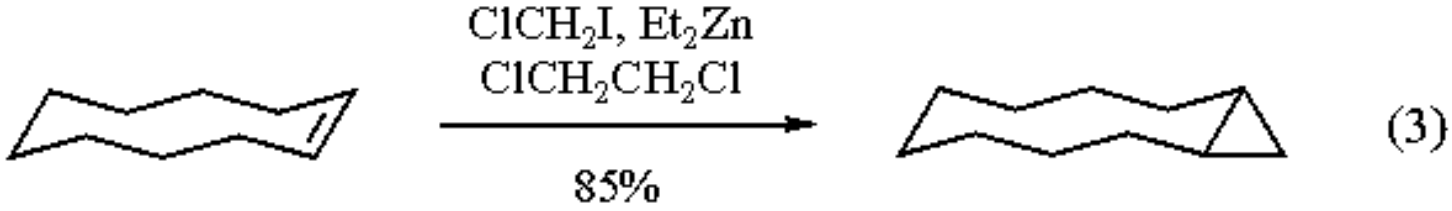

Related Reagents.

Diethylzinc; ***Diiodomethane***; ***Zinc/Copper Couple***.

---

1. (a) Miyano, S.; Hashimoto, H. *BCJ* **1973**, *46*, 892. (b) Miyano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H. *S* **1977**, 700.
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Chloromagnesium Dimethylcuprate[1]

$Me_2CuMgCl$

[67234-12-2] · $C_2H_6ClCuMg$ · Chloromagnesium Dimethylcuprate · (MW 153.39) (Me_2Cu^-)

[47942-29-0] · C_2H_6Cu · Chloromagnesium Dimethylcuprate · (MW 93.63) ($MgCl^+$)

[32195-53-2] · ClMg · Chloromagnesium Dimethylcuprate · (MW 59.76)

(methyl transfer reagent in conjugate additions)

Alternate Name: dimethylcoppermagnesium chloride.

Physical Data: prepared in situ.

Preparative Methods: methylmagnesium chloride (1 equiv) in THF is added dropwise to a rapidly stirred slurry of ***Copper(I) Iodide*** iodide (0.5 equiv) in anhydrous THF at -78 °C, and the resultant mixture is stirred at -78 °C for 15 min.[2] In a similar way, the reagent is generated using 0.5 equiv $LiCuBr_2$[3] (15 min, -60 °C) or ***Copper(I) Bromide***.[4]

Handling, Storage, and Precautions: the reagent must be generated and used immediately in the absence of moisture and oxygen. Handle in a fume hood.

Chloromagnesium dimethylcuprate seems to be a forgotten brother of its bromo analog. A few studies show some superior qualities in conjugate additions. In reaction with α,β-unsaturated aldehydes the reagent gives 1,4-adducts almost exclusively (eq 1);[4] it reacts readily at low temperature in a stereoselective manner with 2-alkyne nitriles without the need for a large excess of the reagent (eq 2).[5]

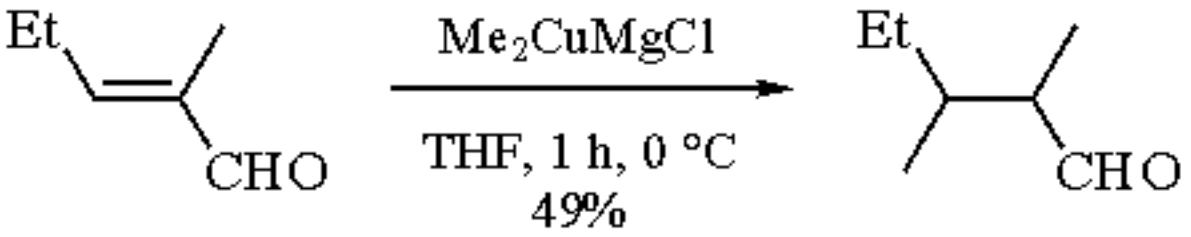

(1)

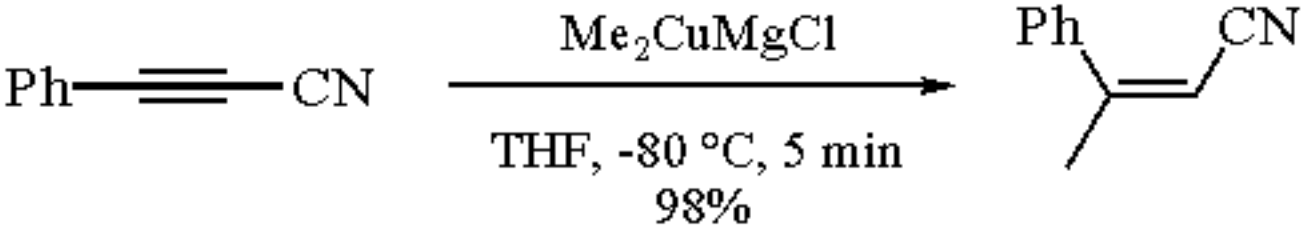

(2)

Related Reagents.

Methylmagnesium Iodide-Copper(I) Chloride; ***Vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Chloride-Copper(I) Chloride***.

---

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Chloromethane[1]

CH_3Cl

[74-87-3] · CH_3Cl · Chloromethane · (MW 94.95)

(methylating agent attacking C-, O-, N-, P-, S-, Se-, and Te-based nucleophiles; organometallic derivatives provide source of $Me^{\delta-}$ in reactions with >C=O, M-X, halogen, etc., and also as a base towards C-H; radical substitution of Me by C&bdot;, halogen, etc.)

Alternate Name: methyl chloride.

Physical Data: mp -97.7 °C; bp -24.22 °C; *d* 0.991 g cm^{-3} (-25 °C).

Solubility: miscible with most organic solvents, sparingly with aqueous media.

Form Supplied in: colorless gas.

Purification: gas passed through conc. H_2SO_4 then water, and dried with P_2O_5 and fractionally distilled.

Handling, Storage, and Precautions: usually available in cylinders. Potent alkylating agent; high toxicity. Use in a fume hood.

Methylating Agent.[2]

Nucleophilic displacement occurs readily at carbon (eq 1), often via anions as in the methylation of lithio-rhenocene ($LiReCp_2$)[3a] and the more classical methylation of acetoacetic, malonic, and cyanoacetic esters,[3] or in the alkylation of cyclopentadiene, or the α-attack of aliphatic ketones.[4] The Friedel-Crafts reaction with benzene may be modified to provide any or all of the possible polymethylbenzenes, as in the preparation of 1,2,4,5-tetramethylbenzene.[5] A range of Lewis acid catalysts have been applied[6a,6b] and the use of boron triflate exemplifies the introduction of more novel catalysts.[6c,6d] Methyl cyanate may be obtained from metal cyanates (MeCl, xylene-*N*,*N*-dialkylamide mixtures)[7] and dimethyl carbonate similarly from K_2CO_3 (phase-transfer catalysts; dipolar aprotic solvent).[8]

$$MeCl + X^- \longrightarrow MeX + Cl^- \qquad (1)$$

The carbonylation of MeCl leading to ***Acetyl Chloride*** is achieved in the presence of superacids or metal catalysts (eq 2).[9] Correspondingly, metal sulfites are advocated[10] as routes to ***Methanesulfonic Acid*** (eq 3). *N*-Methylation, either to

give more fully alkylated amines or to give quaternary ammonium salts, has been widely reported (eq 4).

$$MeCl + CO \longrightarrow MeCOCl \quad (2)$$

$$MeCl + SO_3^{2-} \longrightarrow MeSO_3^- + Cl^- \quad (3)$$

$$RNH_2 \longrightarrow RNHMe \longrightarrow RNMe_2 \longrightarrow RNMe_3^+ \quad (4)$$

In cases where the substrate is very susceptible to electrophilic attack, both methylation and formylation are observed when such reactions are carried out in DMF. The analogous reaction with phosphorus (R_3P, $(RO)_3P$) provides phosphonium salts, the deprotonation of which leads to synthetically useful phosphonium ylides (eq 5).

$$(RCH_2)_3P + MeCl \longrightarrow [(RCH_2)_3PMe]^+ Cl^- \longrightarrow [(RCH_2)_2PMe]^+ [CHR]^- \quad (5)$$

Reductive methylation is observed when Cl or another displaced group is removed by single-electron transfer to give Cl^- and, effectively, Me&bdot;. An example is the formation of Me_2SO_2 by the electrochemical reduction of MeCl in dipolar aprotic solvents containing SO_2.[11] Nucleophilic oxygen (e.g. OH^-, OR^-, RCO_2^-) and sulfur (e.g. S^{2-}, HS^-, RS^-, SCN^-, $S_2O_3^{2-}$, RSO_2^-, thiourea) are similarly methylated, while Te and Se show analogous chemistry. Halide ion exchange reactions (including N_3^-) are valuable routes between the various methyl halides and also allow the synthesis of labelled RCl (e.g. $Me^{36}Cl$).

Asymmetric methylation is achieved using chiral phase-transfer catalysts (e.g. *N*-benzylcinchoninium salts), as in the attack at C-2 of 2-phenyl-5-methoxy-6,7-dichloroindanone.[12]

Organometallics.

Methylmagnesium chloride (MeCl, Mg, Et_2O under dry, O_2-free conditions) provides a nucleophile capable of reacting with (i) metal halides in a transmetalation reaction, (ii) proton sources, including alcohols, phenols, amines, imines, and amides, (iii) electrophilic carbon, as in aldehydes, ketones, carboxylic acid derivatives, nitriles, and epoxides, and (iv) elements such as O_2, S_8, I_2, interhalogens such as CNCl, and species such as CO_2 and SO_2. While Grignard reactions give alcohols with many carboxylic acid derivatives, the reaction with RCOCl (eq 6) may be used to form methyl ketones in good yield (63-92%) by the presence of ***Tris(acetylacetonato)iron(III)*** (THF, rt).[13] Such a process replaces the older techniques which used $FeCl_3$, or the formation of organozinc or -cadmium intermediates.

$$MeCl + Mg \longrightarrow MeMgCl \xrightarrow{RCOCl} MeCOR + MgCl_2 \quad (6)$$

Substitution in the Alkyl Group.

Hydrogen abstraction provides a carbon-based radical which leads to substituted derivatives. Thus further chlorination of MeCl leads to CH_2Cl_2, $CHCl_3$, and CCl_4 (eq 7); fluorination of MeCl proceeds similarly.[14] Hydrogen isotope exchange may also be achieved in this way.

$$\mathrm{MeCl} + \mathrm{X_2} \longrightarrow \mathrm{H_2CXCl} + \mathrm{HX} \longrightarrow \mathrm{CHX_2Cl} \longrightarrow \mathrm{CX_3Cl} \qquad (7)$$

$$\mathrm{X = Cl, F}$$

Related Reagents.

Bromomethane; ***Iodomethane***.

---

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4-(Chloromethyl)-3,5-dimethylisoxazole[1]

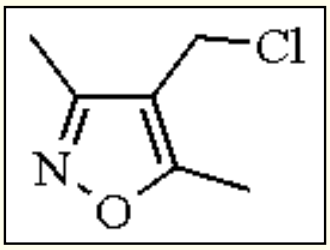

[19788-37-5] · C_6H_8ClNO · 4-(Chloromethyl)-3,5-dimethylisoxazole · (MW 145.59)

(annulation reagent used for the construction of cyclohexenones in the syntheses of steroids, terpenes, and alkaloids[2])

Physical Data: bp 87-88 °C/8 mmHg; *d* 1.173 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: liquid (97-98 + % pure).

Handling, Storage, and Precautions: light-sensitive lachrymator; refrigerate; handle and store under nitrogen.

The primary use for this reagent is in the isoxazole annulation.[2a,b] This procedure is related to the Robinson annulation.[1b] The method involves alkylation of a ketone, an α,β-unsaturated ketone, or an enamine with a latent 3-ketoalkyl synthon (eq 1).[2b]

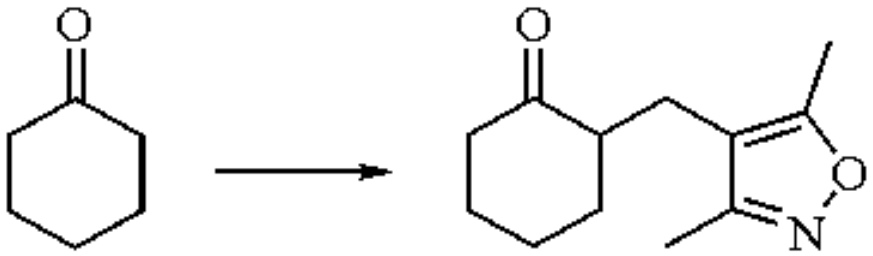

(1)

In Stork's original procedure, catalytic hydrogenation of the isoxazole unmasks the appended β-amino enone, which then cyclizes to a vinylogous carbinolamide. Subsequent methanolysis and hydrolysis furnishes a 1,5-diketone which cyclizes to a cyclohexenone (eq 2).

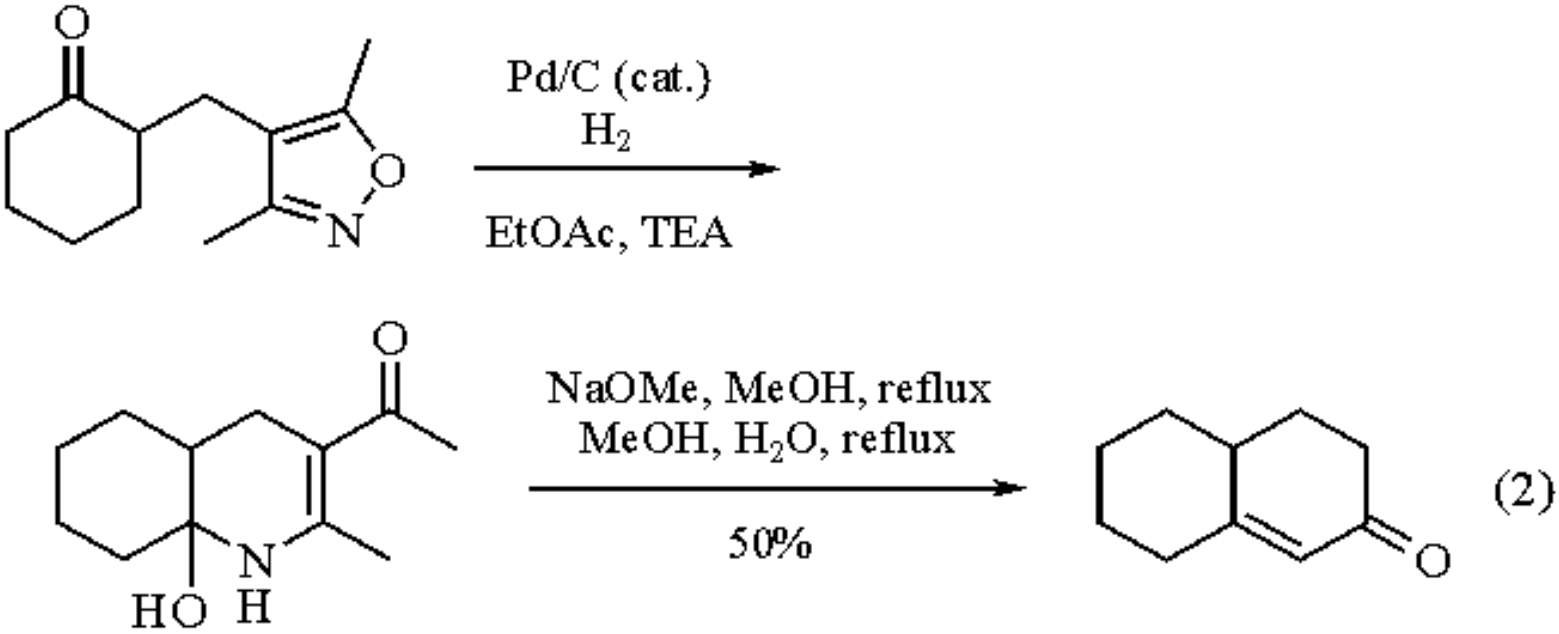

A limitation of the original Stork procedure involves the instability of the intermediate vinylogous carbinolamides. These intermediates may undergo dehydration to the corresponding dihydropyridines. These are sensitive intermediates which readily air-oxidize to β-acylpyridines. Based on this potential side-reaction, Stork reported a method for the synthesis of β-acylpyridines from intermediate carbinolamides (eq 3).[3]

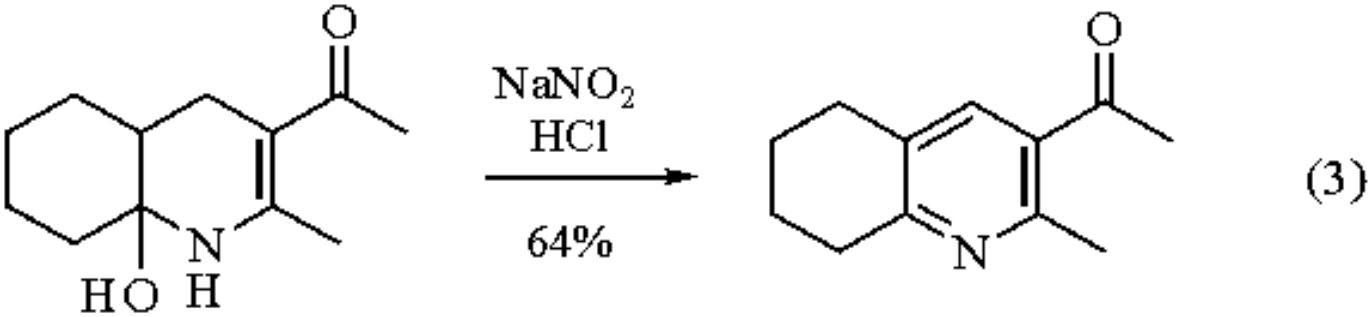

Scott, Banner, and Saucy have reported a modification of the original Stork procedure that moderately improves the overall yield of enone.[2f] The modification involves acetalization of the ketone prior to hydrogenation of the isoxazole, thus suppressing formation of the delicate vinylogous carbinolamides. Subsequent hydrogenation of the isoxazole provides a stable enamide which is directly converted to the corresponding 3-keto alkyl intermediate and cyclized to the desired enone in overall yields of about 65%.

An asymmetric isoxazole annulation for the formation of a chiral quaternary carbon has been reported.[2e] Alkylation of a diastereomeric pair of imines with 4-(chloromethyl)-3,5-dimethylisoxazole under appropriate conditions proceeded with diastereoselectivity, providing the corresponding isoxazolyl aldehyde in 70% ee. Unmasking of the keto functionality and subsequent cyclization provided the corresponding optically active cyclohexenone (eq 4).

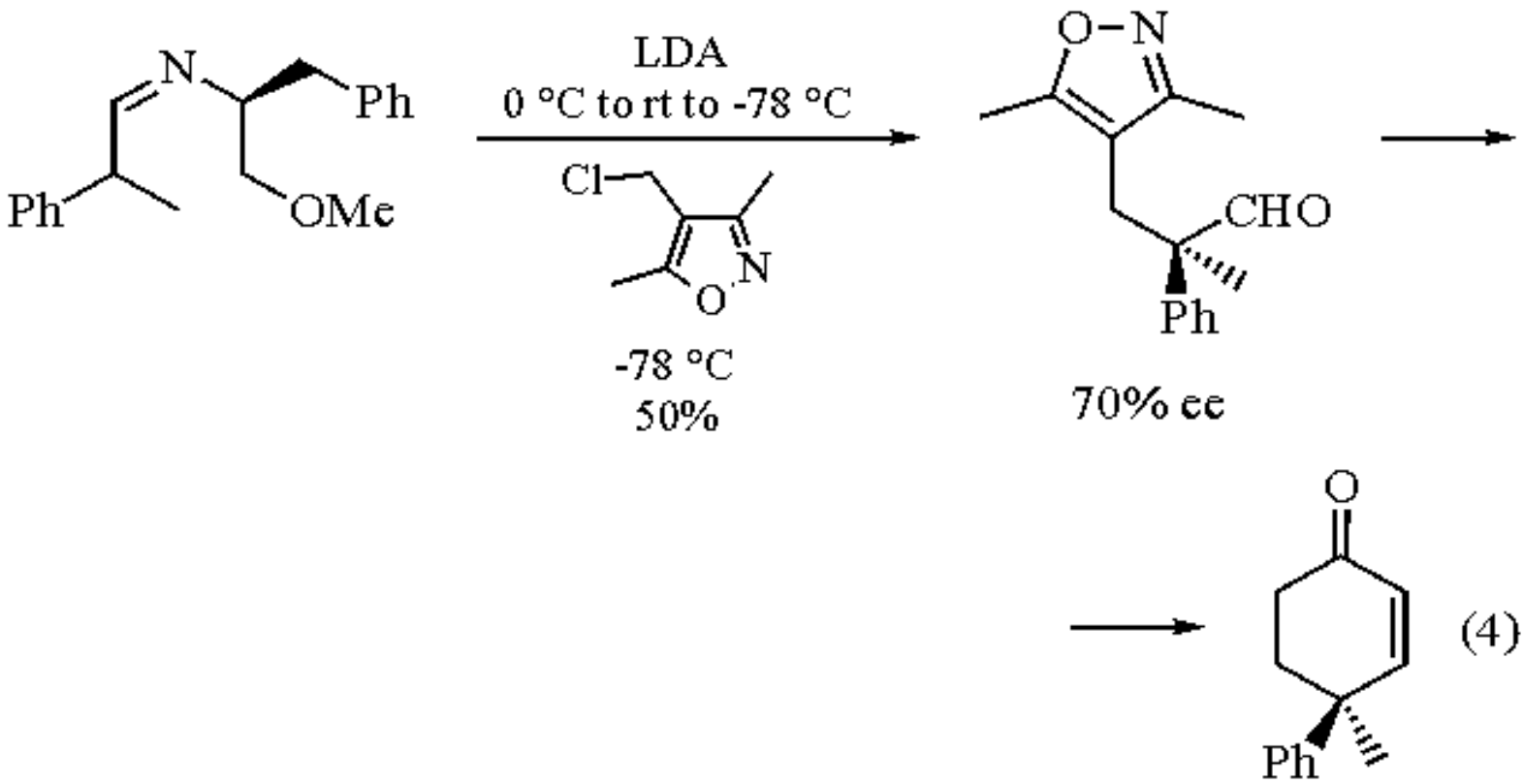

An alternative method for the reductive cleavage of isoxazoles using ***Samarium(II) Iodide*** has been reported and applied to the Stork isoxazole annulation.[4] Importantly, even delicate acetals survive the reduction, and subsequent cyclization efficiently furnishes the cyclohexenone in 78% overall yield (eq 5). The SmI_2 modification significantly enhances the yields of the enone obtained.

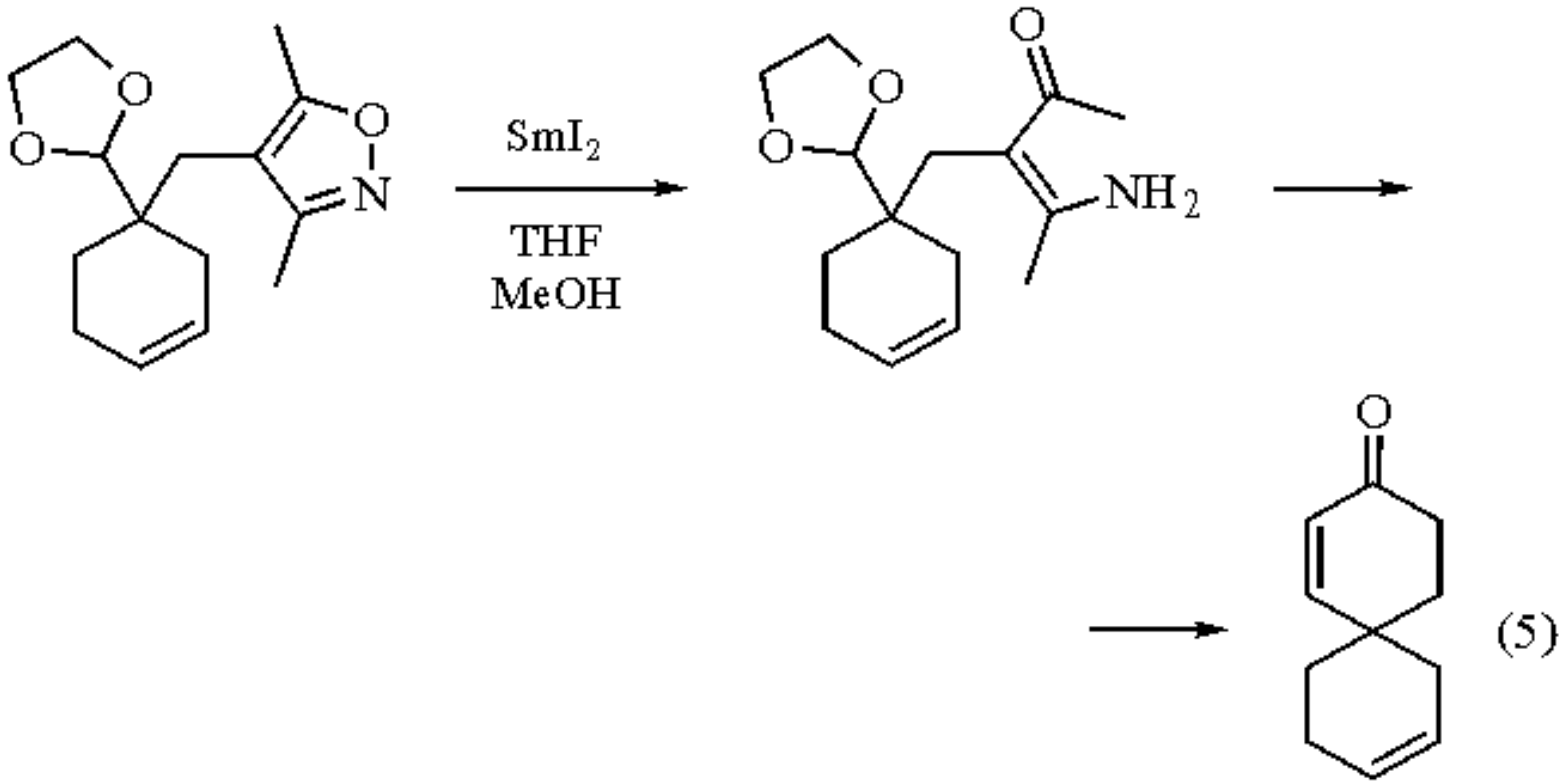

The Stork isoxazole annulation has been applied to the synthesis of steroids such as (±)-D-homotestosterone, (±)-progesterone, and $\Delta^{9(11)}$-dehydrotestosterone.[5,6] It has also been applied to the synthesis of substituted hydroazulenes, a ring system characteristic of the pseudoguaianolide family of sesquiterpenes.[7]

Recently, 4-(chloromethyl)-3,5-dimethylisoxazole has been transformed into a nucleophilic mercaptomethylisoxazole (eq 6). The mercaptomethylisoxazole has been used to open epoxides.[8]

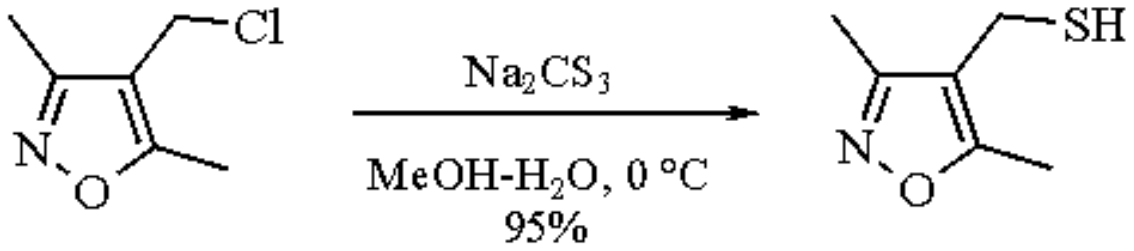

(6)

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Chloromethyldiphenylphosphine Oxide

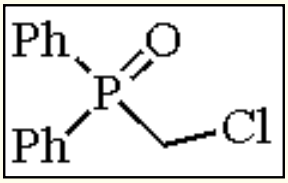

[89302-51-2] · $C_{13}H_{12}ClOP$ · Chloromethyldiphenylphosphine Oxide · (MW 250.66)

(useful reagent in the synthesis of phosphinylacetaldehydes which are stereoselectively transformed into 3,3-disubstituted allylic alcohols[5])

Solubility: sol THF.

Preparative Methods: chlorination of $Ph_2P(O)CH_2OH$[1] with ***Phosphorus(V) Chloride/Calcium Carbonate***[2] or reaction of ***Diphenylphosphinic Chloride/Aluminum Chloride*** with 1-1.1 mol % ***Paraformaldehyde*** and ***Hydrogen Chloride*** at 120-150 °C.[3] Reaction of $Ph_2P(O)SiMe_3$ with R^1CH_2Cl gives yields of 50-95%[4]

3,3-Disubstituted Allylic Alcohols via Phosphinoylacetaldehydes.

Condensation of chloromethyldiphenylphosphine oxide with ketones and subsequent treatment of the resultant epoxides (**1**) with ***Boron Trifluoride Etherate*** provides α,α-disubstituted (diphenylphosphinyl)acetaldehydes (**2**) (eq 1).

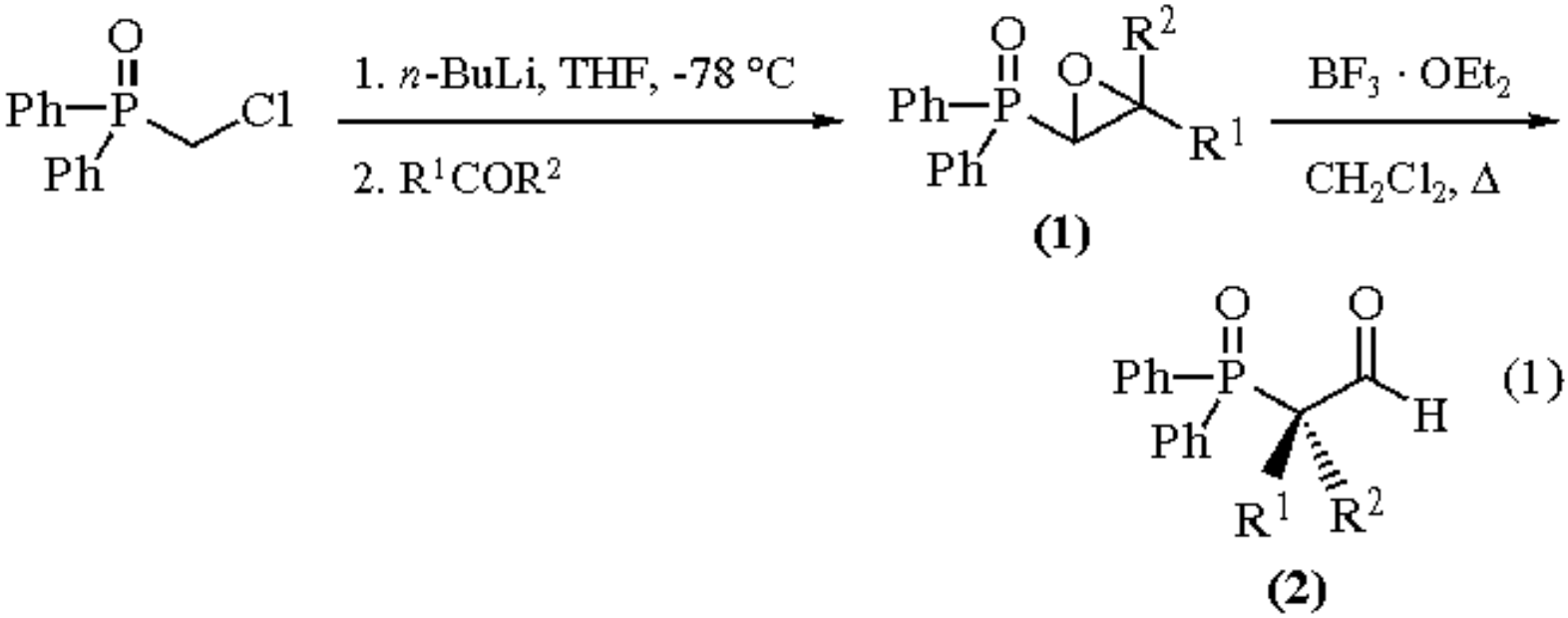

3,3-Disubstituted allylic alcohols are obtained from (**2**) via a vanadium(II)-mediated intermolecular pinacol cross-coupling[5] followed by Horner-Wittig elimination,[6] as shown in eq 2. The diols (**3**) are obtained stereoselectively through the chelation controlled pinacol coupling with *threo*/*erythro* ratios of 7.5-99:1.

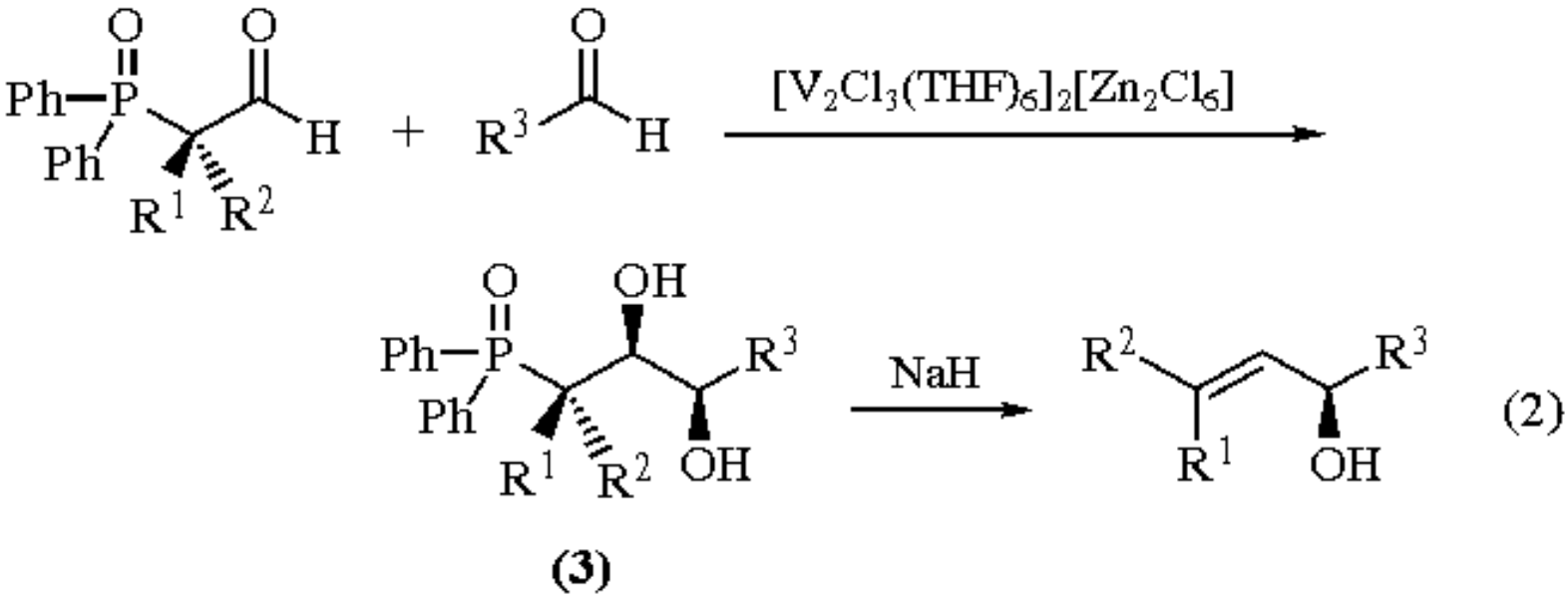

This methodology provides a general stereoselective route to allylic alcohols which are important synthetic intermediates[7] as well as constituents in many natural products.[8] Alternative phosphorus-based methods involving alkenation of ketones generally lack stereospecificity, especially when the two substituents are similar in size.[9]

Alternatives to phosphorus methods are the stereospecific carbometalation of terminal alkynes,[10] and the reaction of alkynic esters with cuprates and subsequent reduction or addition to the ester.[11] Both methods are limited by the organometallic reagents.

1. Marmor, R. S.; Seyferth D. *JOC* **1969**, *34*, 748.
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7. (a) Johnson R. A.; Sharpless, K. B. *COS* **1991**, *7*, 389. (b) Hoffmann, R. W. *CRV* **1989**, *89*, 1841.
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Brian E. Marron

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1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate)

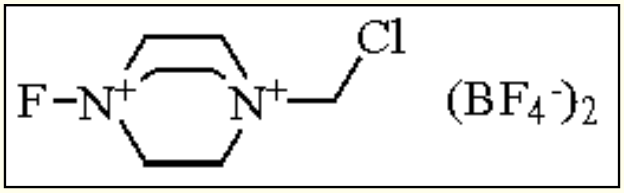

[140681-55-6] · $C_7H_{14}B_2ClF_9N_2$ · 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate) · (MW 354.26)

(easily handled, cost-effective, site-selective electrophilic fluorinating agent applicable to a wide variety of organic substrates possessing overt or masked carbanionic character[1-4])

Alternate Names: F-TEDA-BF_4; Selectfluor™.

Physical Data: apparent mp 190 °C (thermal behavior is complicated; exothermic decomposition can occur at temperatures >80 °C); *d* 1.731 g cm^{-3}.

Solubility: v sol cold H_2O (176 g L^{-1} at 20 °C), dil HCl (decomposed by dil NaOH); sol MeCN; sl sol MeOH, EtOH, Me_2CO; sol DMF (reacts slowly on heating), pyridine (reacts), and DMSO (reacts rapidly and exothermically).

Form Supplied in: free-flowing, virtually nonhygroscopic, white solid. Available commercially.

Analysis of Reagent Purity: NMR (^1H, ^{19}F; soln. in D_2O);[1] iodimetric titration [acidified (HCl) soln. in H_2O-Me_2CO (1:1) + excess KI; I_2 determined with thiosulfate/starch (1 I_2 &ident; 1 ^+NF)]. Note that the reagent (known as F-TEDA-BF_4;[3] TEDA = triethylenediamine) oxidizes aqueous bromide ion to bromine at rt but not chloride to chlorine.[5]

Handling, Storage, and Precautions: store below 38 °C (lower temperatures are advisable for bulk storage); use in solution or suspension; do not heat the solid reagent above 80 °C. Take standard precautions to avoid breathing dust or vapors (evolved during reaction), contact with eyes or skin (dust or its solutions), and contamination of clothing. F-TEDA-BF_4 is moderately toxic (male rat oral LD_{50} 640 mg kg^{-1}; female rat 350-500 mg kg^{-1}), and is an irritant to the eye and respiratory system. Always use approved dust mask (or respirator), gloves, and safety glasses when handling the solid. Carry out solubility tests on a sensible scale when seeking alternative solvents (note the problem with DMSO referred to above). An MSDS (Material Safety Data Sheet) and further information is available from Air Products and Chemicals, Inc., Speciality

Gases Dept., 7201 Hamilton Boulevard, Allentown, PA 18195-1501, USA.

Fluorination of Stabilized Carbanions.

Highly stabilized carbanions [e.g. alkali metal salts of substituted malonates (eq 1), phosphonates (eq 2)] react rapidly and efficiently with this reagent.[2-4] Only low yields (<20%) of α-fluoro ketones can be obtained from highly reactive ketone-derived metal enolates; this drawback can be overcome by using enol acetate or silyl enol ether derivatives of ketones as substrates (see below).[3]

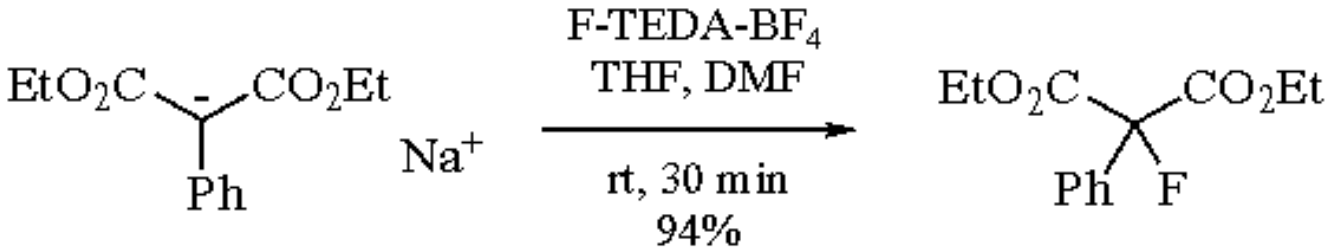

(1)

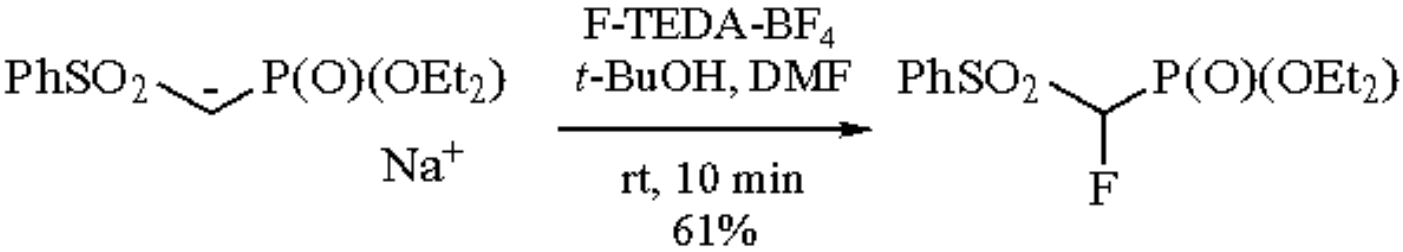

(2)

Fluorination of Enols, Enol Acetates, Silyl Enol Ethers, and Enamines.

Numerous enolizable substrates of the 1,3-dicarbonyl class ($RCOCH_2COR'$) have been monofluorinated efficiently under mild conditions with an equimolar proportion of F-TEDA-BF_4 (e.g. eqs 3-6); difluorination can be achieved (e.g. eq 6; yields here estimated by NMR), but efficient introduction of the second fluorine may require a two-step procedure (depending on the equilibrium enol content of the monofluoride) (eq 7).[4]

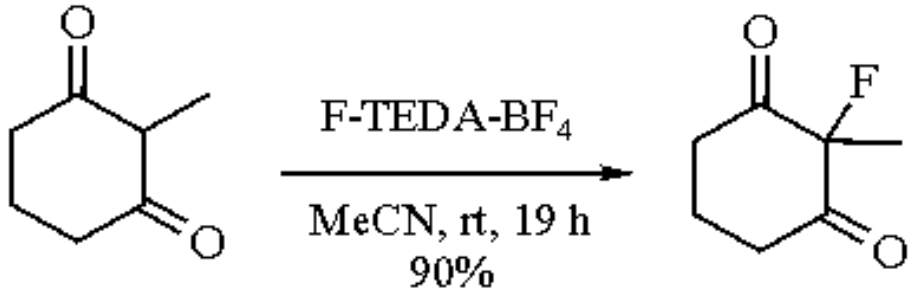

(3)

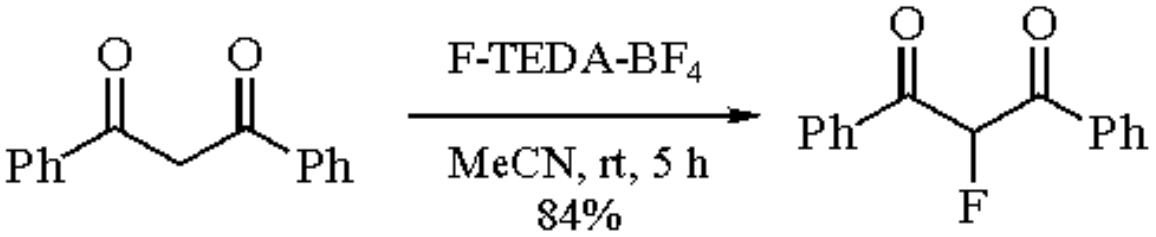
F-TEDA-BF4
MeCN, rt, 5 h
84%

(4)

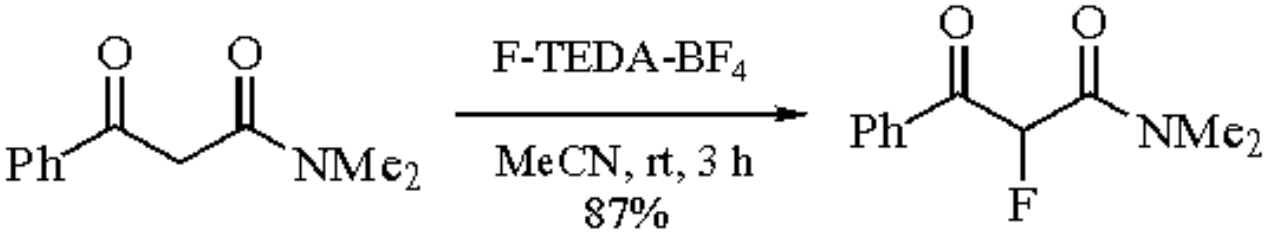
F-TEDA-BF4
MeCN, rt, 3 h
87%

(5)

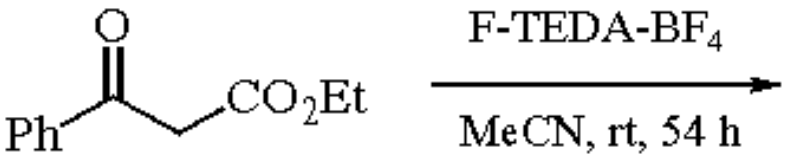
F-TEDA-BF4
MeCN, rt, 54 h

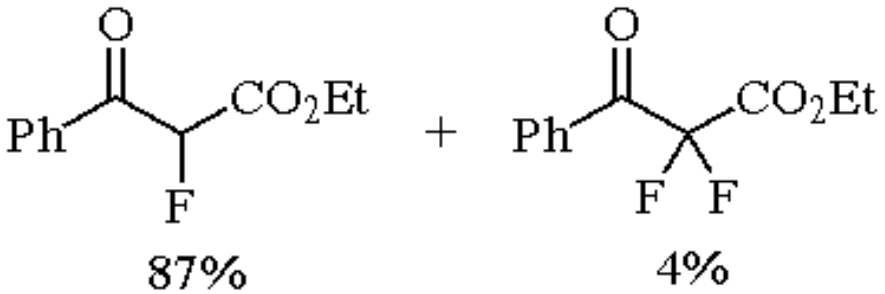
87%
4%

(6)

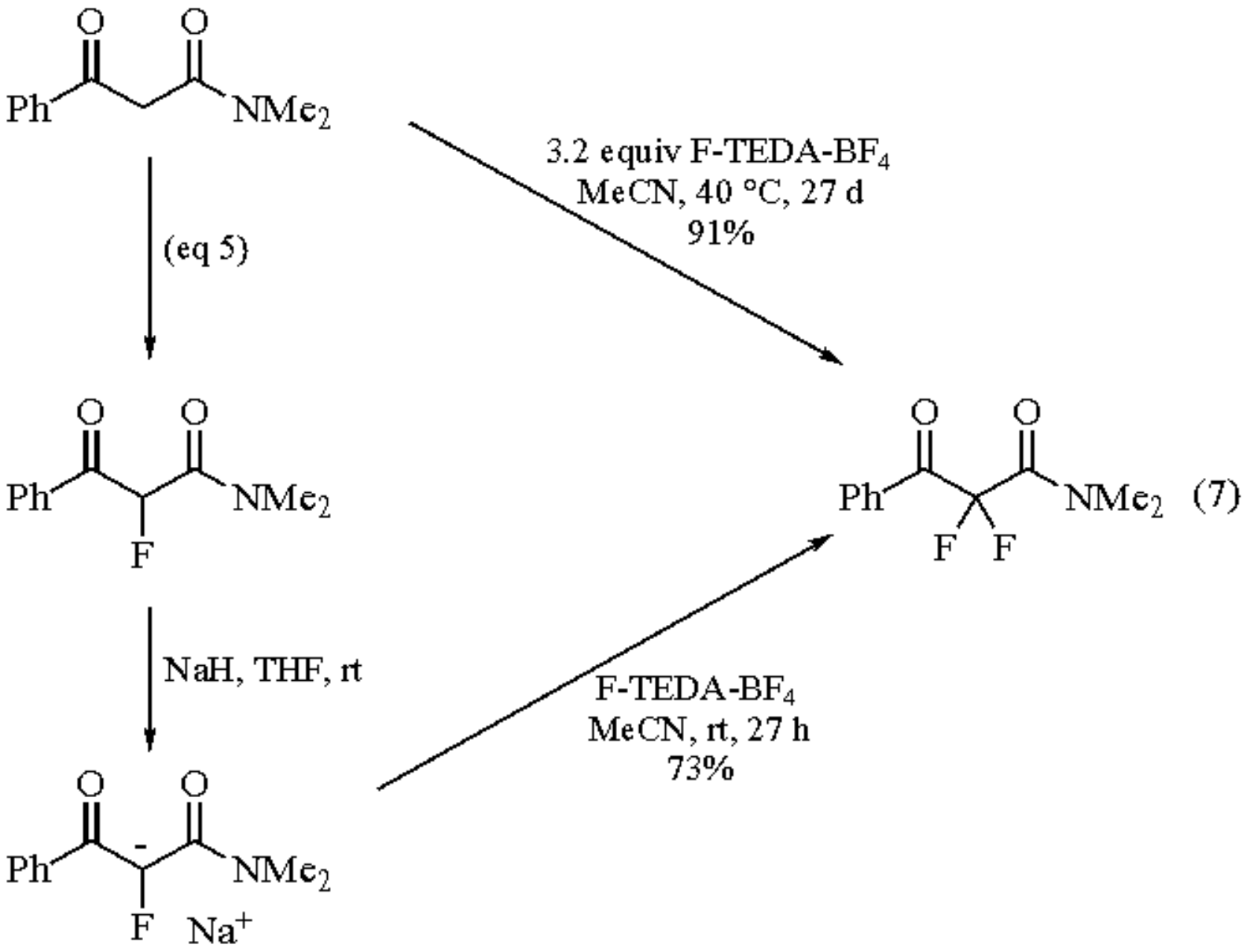

F-TEDA-BF_4 is highly effective for introducing fluorine selectively at positions 6 or 16 in steroids via attack on enol acetate or silyl enol ether derivatives.[2,3] High yields of 16-fluoro targets can be achieved with excellent stereoselectivity (e.g. eq 8). Fluorination at position 6 (e.g. eq 9) proceeds cleanly and more rapidly (typically, reactions are complete within 15 min at rt in MeCN).

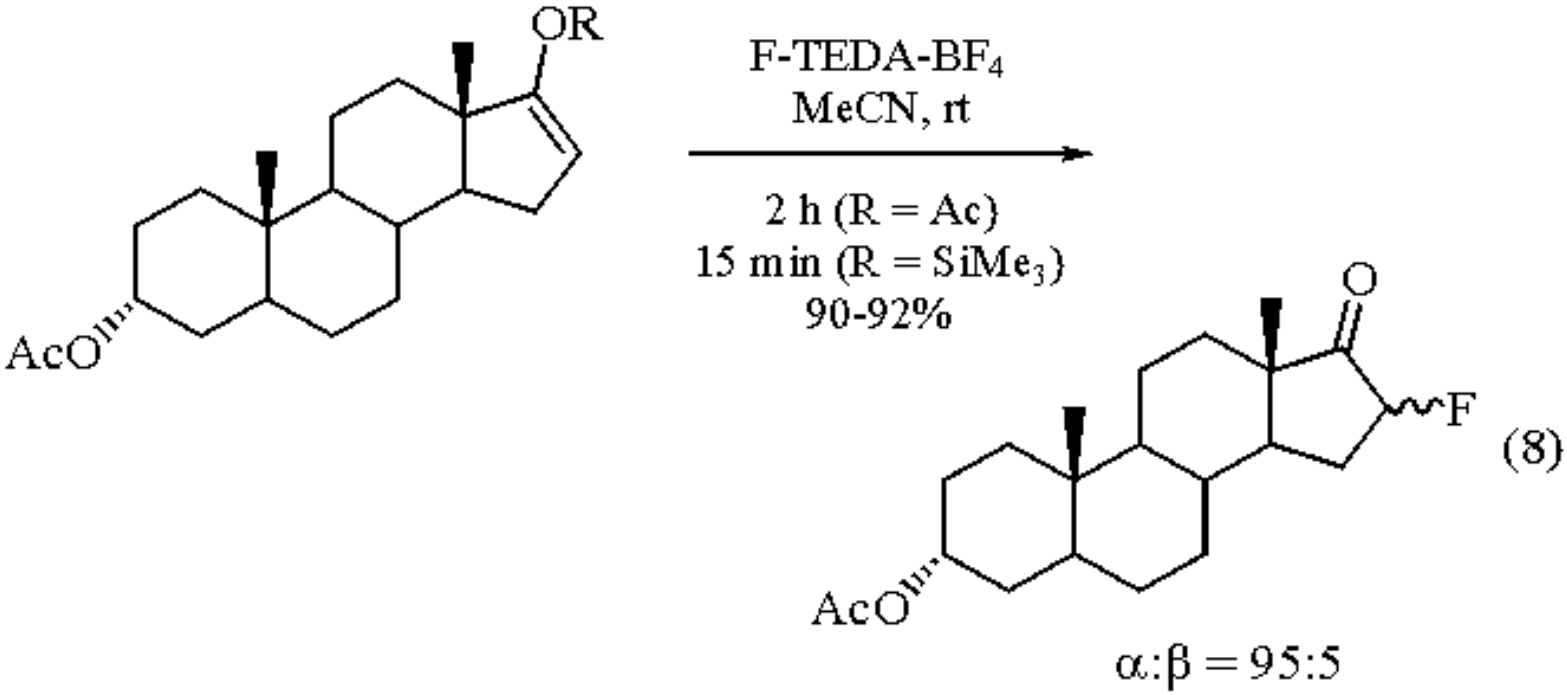

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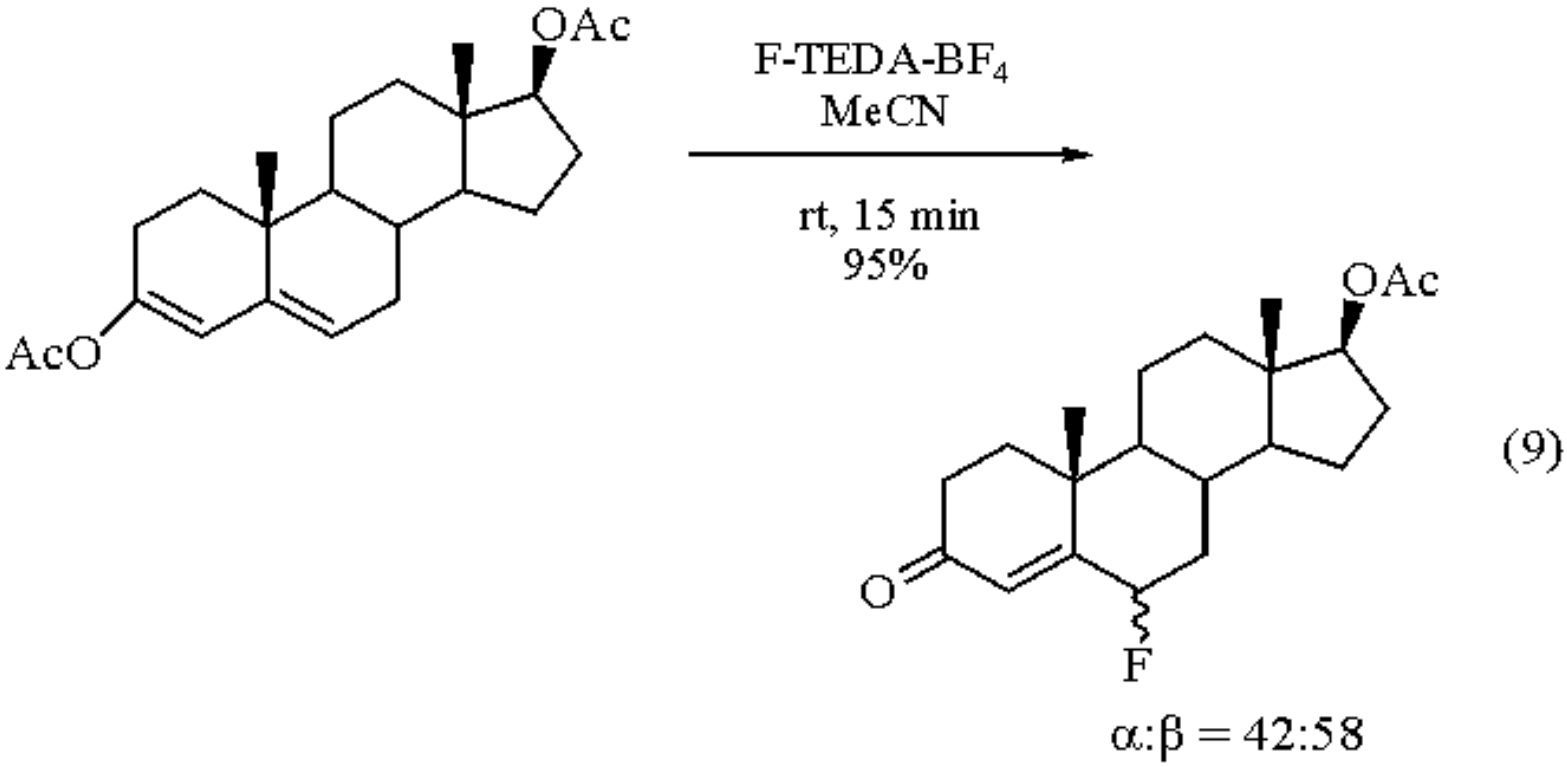

(9)

Fluorination of the prototypical enamine 1-morpholinocyclohex-1-ene with a suspension of the 1,1,1-trifluoroethyl analog of F-TEDA-BF_4, $CF_3CH_2{+}N(CH_2CH_2)_3{+}NF\ (CF_3SO_3^-)_2$,[1] in CH_2Cl_2 at 20 °C gives 2-fluorocyclohexanone in 81% yield.[2] [Note that within the *Selectfluor* range of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts, ease of F^+ transfer increases as the electronegativity of the 1-alkyl group increases (CF_3CH_2 > CH_2Cl > CH_3).[1]] Fluorination of enamines of Δ^4- or $\Delta^{1,4}$-3-keto steroids with F-TEDA-BF_4 is said to produce a mixture of 4-fluoro and 6-fluoro products.[3]

Fluorination of Alkenes.

Alkenes capable of producing highly stabilized carbocations through notional addition of F^+ (e.g. styrene, α-methylstyrene, *trans*-stilbene, 1-phenylcyclohexene) react smoothly with F-TEDA-BF_4 at room temperature in the presence of weak nucleophiles (e.g. H_2O, MeOH, AcOH, HF-pyridine) (e.g. eq 10).[3]

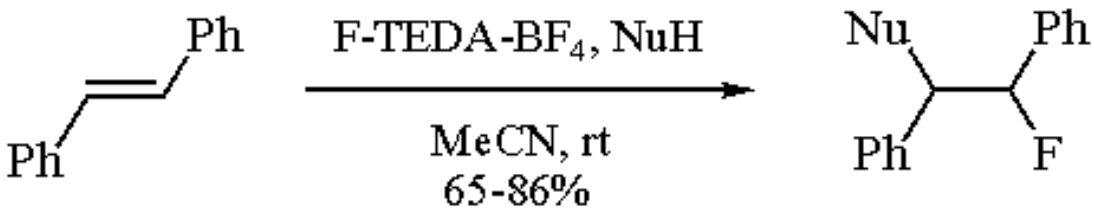

(10)

Nu = F, OMe, OAc, OH *erythro*:*threo* = 60-72:40-28

Fluorination of Aromatic Compounds.

Benzene resists attack by F-TEDA-BF_4 under normal conditions. The introduction of electron-releasing (+*I*, +*M*) ring substituents facilitates fluorination (e.g. eqs 11-13).[1,2,3,6]

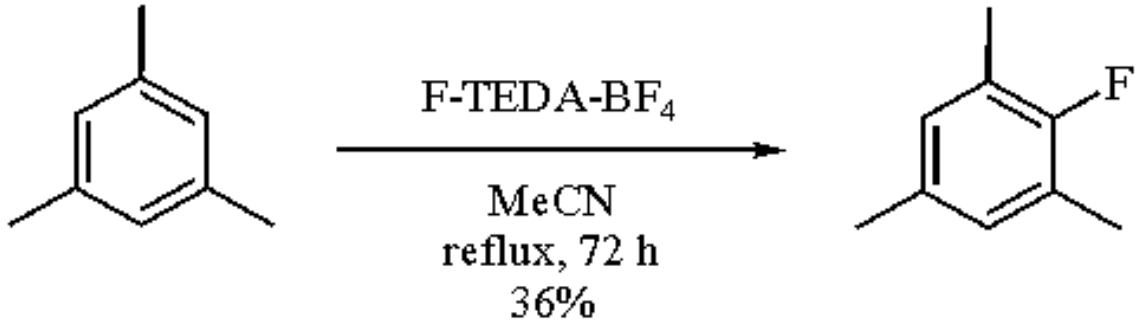

(11)

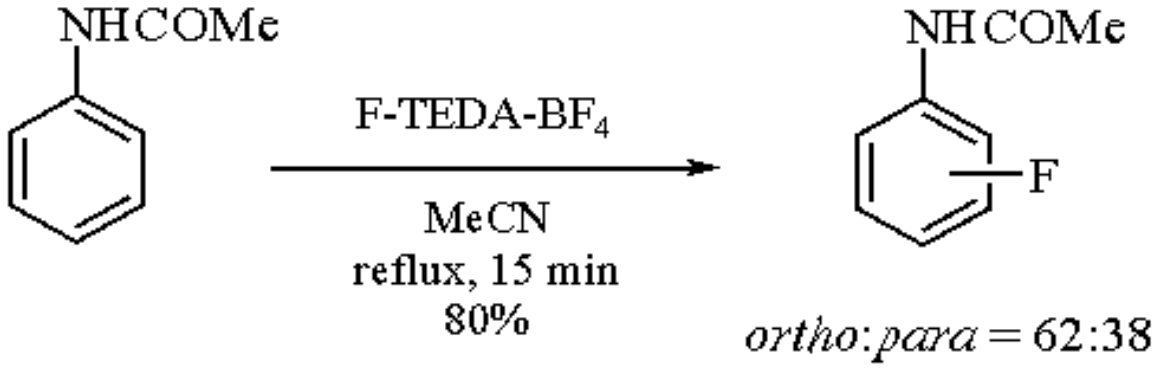

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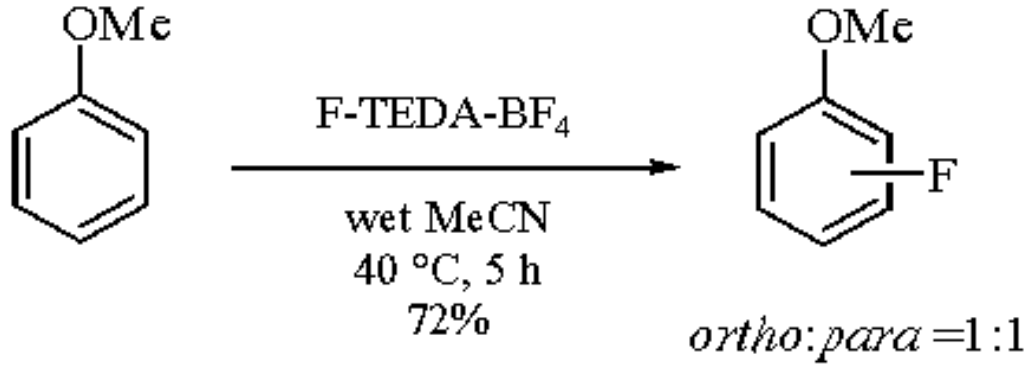

(13)

Organosulfur Compounds.

The first step in the sequence $RSCH_2R^1$ -> $R+S(F)CH_2R^1$ -> $RSCHFR^1$ -> $RS(O)_xCHFR'$ (x = 1, 2) can be effected smoothly with F-TEDA-BF_4, the Pummerer-like rearrangement of the fluorosulfonium salt (not isolated) being effected with a nitrogenous base (***Triethylamine*** or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***) (e.g. eqs 14-16).[3]

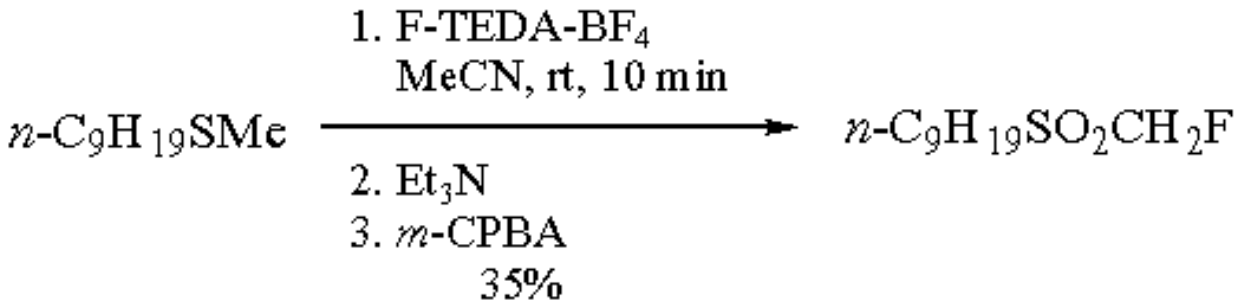

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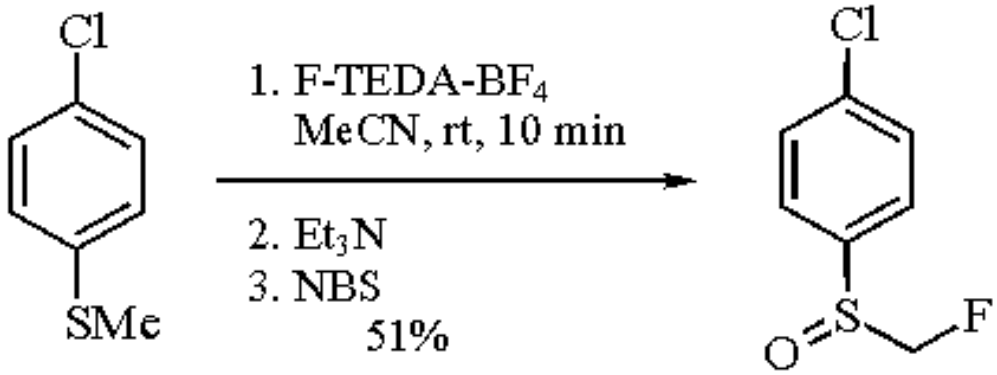

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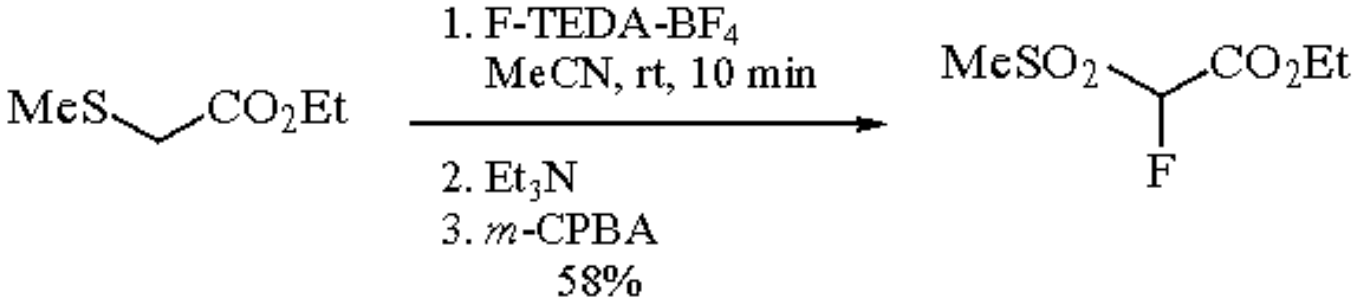

(16)

Fluorination of Carbon-Metal Bonds.

Grignard reagents react slowly with suspensions of F-TEDA-BF_4 in dry diethyl ether or THF at rt to provide the corresponding monofluorides (eqs 17 and 18).[3]

$$n\text{-}C_{12}H_{25}MgBr \xrightarrow[\text{Et}_2\text{O, rt}]{\text{F-TEDA-BF}_4} n\text{-}C_{12}H_{25}F \qquad (17)$$

58%

$$\text{PhMgBr} \xrightarrow[\text{Et}_2\text{O, rt}]{\text{F-TEDA-BF}_4} \text{PhF} \qquad (18)$$

61%

The availability of F-TEDA-BF_4 has at last made possible the synthesis of 5-fluorocyclopentadiene, the fugitive nature of which requires it to be trapped in situ (eq 19).[7] Treatment of ***Thallium(I) Cyclopentadienide*** with positive halogen sources such as NBS and NCS is a known route to other 5-halogenocyclopentadienes.

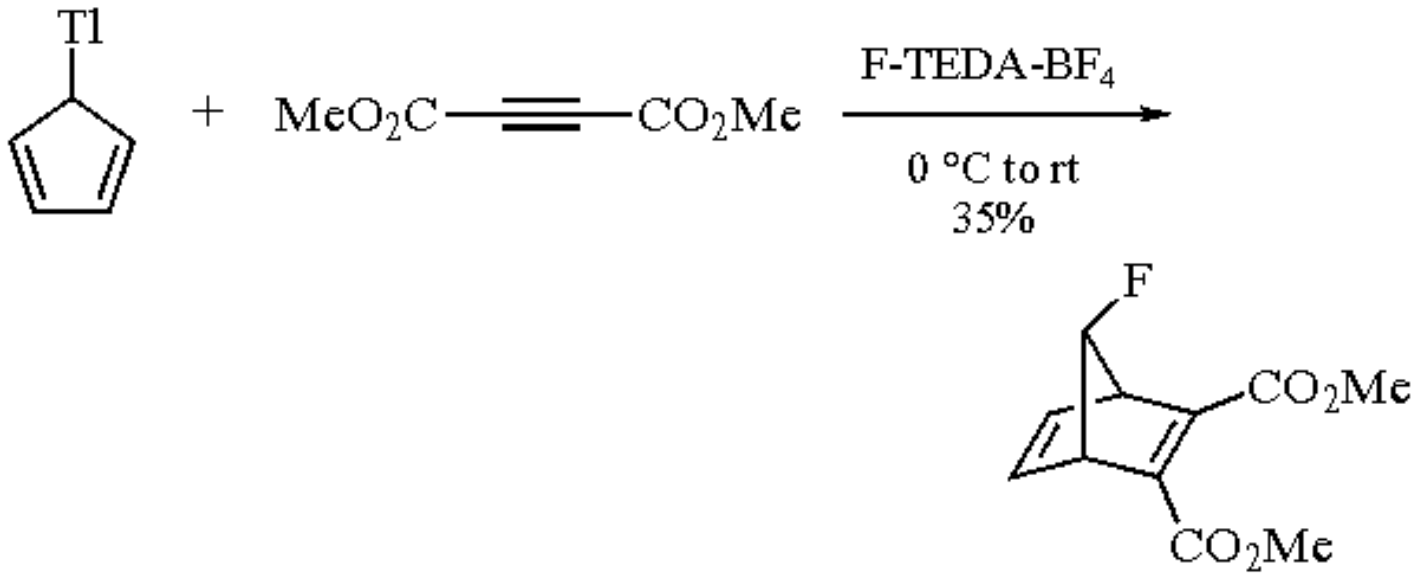

(19)

Electrophilic fluorination of vinylstannanes with F-TEDA-BF_4 provides easy access to fluoroalkenes carrying a variety of functional groups (e.g. eqs 20 and 21).[8]

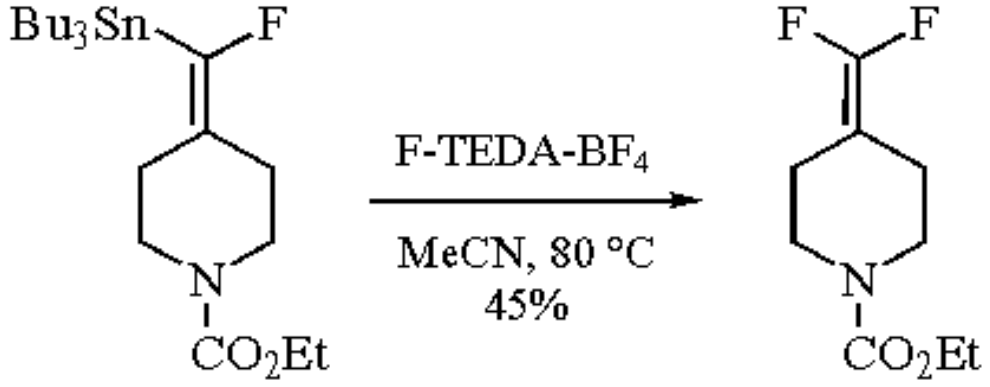

(20)

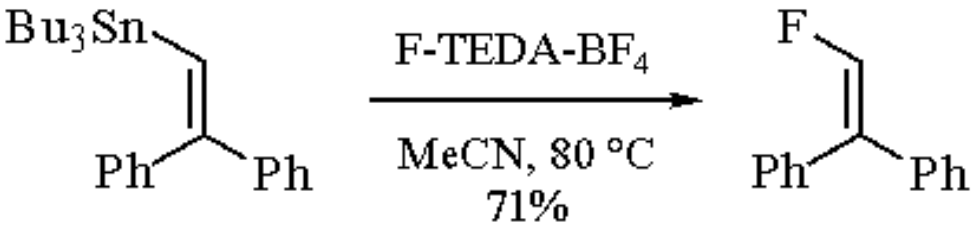

(21)

Fluorination of Quinuclidine.

Quantitative transfer of F^+ occurs from F-TEDA-BF_4 to quinuclidine at rt in acetonitrile (eq 22).[9] This method provides easy access to *N*-fluoroquinuclidinium tetrafluoroborate (NFQNBF_4), one of a family of *N*-fluoroammonium salts (fluoride,[10] triflate,[11] tetrafluoroborate,[11] perfluoroalkanecarboxylate[11]) originally developed in response to worldwide demand for more generally acceptable (less aggressive, nonexplosive, less toxic, inexpensive) site-selective electrophilic fluorinating agents than ***Perchloryl Fluoride***, O-F reagents (e.g. ***Trifluoromethyl Hypofluorite***, ***Cesium Fluoroxysulfate***), ***Xenon(II) Fluoride***, and ***Fluorine*** itself.[12]

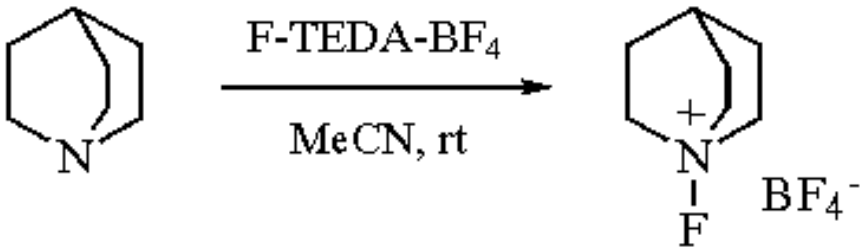

(22)

F-TEDA salts arose out of research aimed at the development of a similar yet more powerful family of *N*-fluoroammonium salts than NFQN salts; tunable fluorinating ability and considerably greater commercial prospects were also targets. [Fluorinating power can be adjusted via the electronegativity of the quaternizing alkyl group (see earlier).[2]] In-house synthesis of both NFQN and F-TEDA salts is an unwelcome prospect in many laboratories since fluorine is required;[1,10,11] the commercial availability of F-TEDA-BF_4 has resolved this major problem, making possible renewed interest in NFQN salts.

At present, not enough information is available to provide a proper appraisal of advantages to be gained by using an NFQN salt rather than its F-TEDA analog; given the current relative costs and availability of quinuclidine and TEDA, F-TEDA-BF_4 will normally be preferred. Limited data indicate that highly basic carbanions give better yields of C-F products with NFQN salts than with F-TEDA salts.

Some Comparisons.

Electrochemical measurements (reduction potentials),[5] supported by practical experience, indicate the following order of fluorinating power for *N*-fluoro reagents: $(CF_3SO_2)_2NF$, $ClCH_2{+}N(CH_2CH_2)_3{+}NF$ $(BF_4^-)_2$ (*F-TEDA-BF$_4$*; A), $Me{+}N(CH_2CH_2)_3{+}NF$ $(TfO^-)_2$, $HC(CH_2CH_2)_3{+}NF$ TfO^-, pyF^+ TfO^- (A), $(PhSO_2)_2NF$ (A), *p*-$MeC_6H_4SO_2NFMe$ (A) ($TfO^- = CF_3SO_3^-$; A = available commercially). The electrophilic fluorination power of F-TEDA-BF_4 falls not far short of that of the powerful so-called DesMarteau N-F reagent,[13] *N*-fluoro[bis(trifluoromethyl)sulfonyl]imide, $(CF_3SO_2)_2NF$, the only liquid in this group (bp 90-91 °C). This reagent is not available commercially, and its preparation entails a costly multistep synthesis terminating in a direct fluorination procedure [$(CF_3SO_2)_2NH + F_2$ -> $(CF_3SO_2)_2NF + HF$] requiring considerable expertise and special equipment.[14] Not all power-variable Meinert-Umemoto[15] *N*-fluoropyridinium salts (e.g. ***N-Fluoropyridinium Triflate***) are available commercially, and sensitivity to attack by moisture or bases can be a drawback.[16] *N*-Fluorobenzenesulfonimide, $(PhSO_2)_2NF$ (Differding's reagent),[17] and *N*-fluoro-*N*-alkylarenesulfonamides (Barnette reagents),[18] developed for the fluorination of carbanions, seem too unreactive to be viewed as general-purpose reagents.

Overall, F-TEDA-BF_4 is probably the best general-purpose electrophilic fluorinating agent available at the time of writing: it fluorinates a wide variety of electron-rich carbon centers rapidly under mild conditions with high efficiency and selectivity, and no special apparatus or handling techniques are required. Soluble in a number of useful reaction solvents (including aqueous systems), F-TEDA-BF_4 is compatible with common reactor materials and offers the additional advantage of being degradable into manageable waste products.[19] A most welcome alternative to the use of highly toxic and potentially explosive electrophilic fluorinating agents such as F_2, $FClO_3$, and CF_3OF, F-TEDA-BF_4 was already in commercial use just four years after its design and synthesis by Banks and Sharif.[2,19]

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(Chloromethyl)isopropoxydimethylsilane

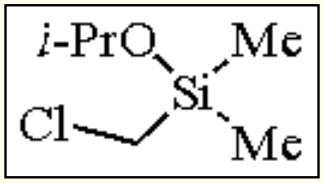

[18171-11-4] · $C_6H_{15}ClOSi$ · (Chloromethyl)isopropoxydimethylsilane · (MW 166.73)

(the Grignard reagent is a nucleophilic hydroxymethylating agent for aldehydes, ketones, epoxides, organic halides, and sulfoximines)

Physical Data: bp 64-66 °C/54 mmHg; *n*20D 1.4160; *d* 0.926 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: neat liquid.

Handling, Storage, and Precautions: moisture sensitive, but no special precautions are necessary for handling in the air for a short period of time. May be stored under nitrogen in a tightly capped bottle in a refrigerator.

The Grignard Reagent.[1,2]

The Grignard reagent, (*i*-PrO)Me_2SiCH_2MgCl, is readily prepared from (*i*-PrO)Me_2SiCH_2Cl by the reaction with ***Magnesium*** activated with ***1,2-Dibromoethane*** in THF in greater than 90% yield. It is sufficiently stable to be stored at room temperature for at least two days with little decrease in activity. The reagent is a versatile nucleophilic hydroxymethyl anion equivalent, in combination with ***Hydrogen Peroxide*** oxidation of the silicon-carbon bond (see also the diisopropoxy counterpart, ***(Diisopropoxymethylsilyl)methylmagnesium Chloride***) (eq 1).[3] The primary products, (*i*-PrO)Me_2SiCH_2E, are stable to weakly basic and acidic aqueous workup and silica gel chromatography. **Caution**: transition metal catalysts such as copper, nickel, and palladium, if used for any reactions with this reagent, should be removed prior to the subsequent oxidation, otherwise vigorous decomposition of hydrogen peroxide may occur.

$$(i\text{-PrO})Me_2SiCH_2MgCl + E^+ \longrightarrow (i\text{-PrO})Me_2SiCH_2E \xrightarrow{H_2O_2,\ F^-,\ \text{base}} HOCH_2E \quad (1)$$

The nucleophilic hydroxymethylation is applicable to aldehydes, including α,β-unsaturated aldehydes (eq 2)[4] and protected sugar derivatives (eq 3),[5] and ketones (eqs 4 and 5).[1,6] Following H_2O_2 oxidation, the corresponding 1,2-diols are obtained in high overall yields. It should be noted that the β-hydroxysilanes do not undergo β-elimination (Peterson alkenation) even under oxidation conditions which contain fluoride ion (eq 4).[1] A highly stereoselective hydroxymethylation of α-hydroxy ketones is also noted (eq 5).[6]

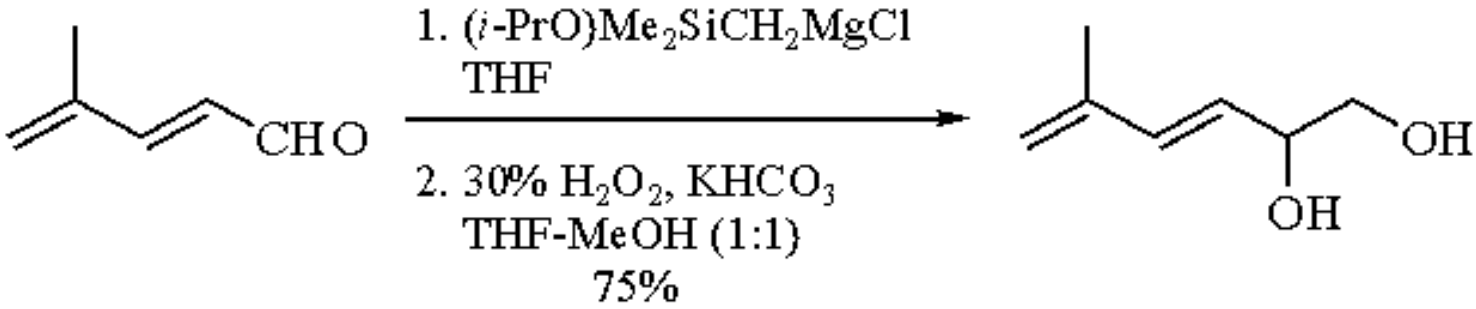

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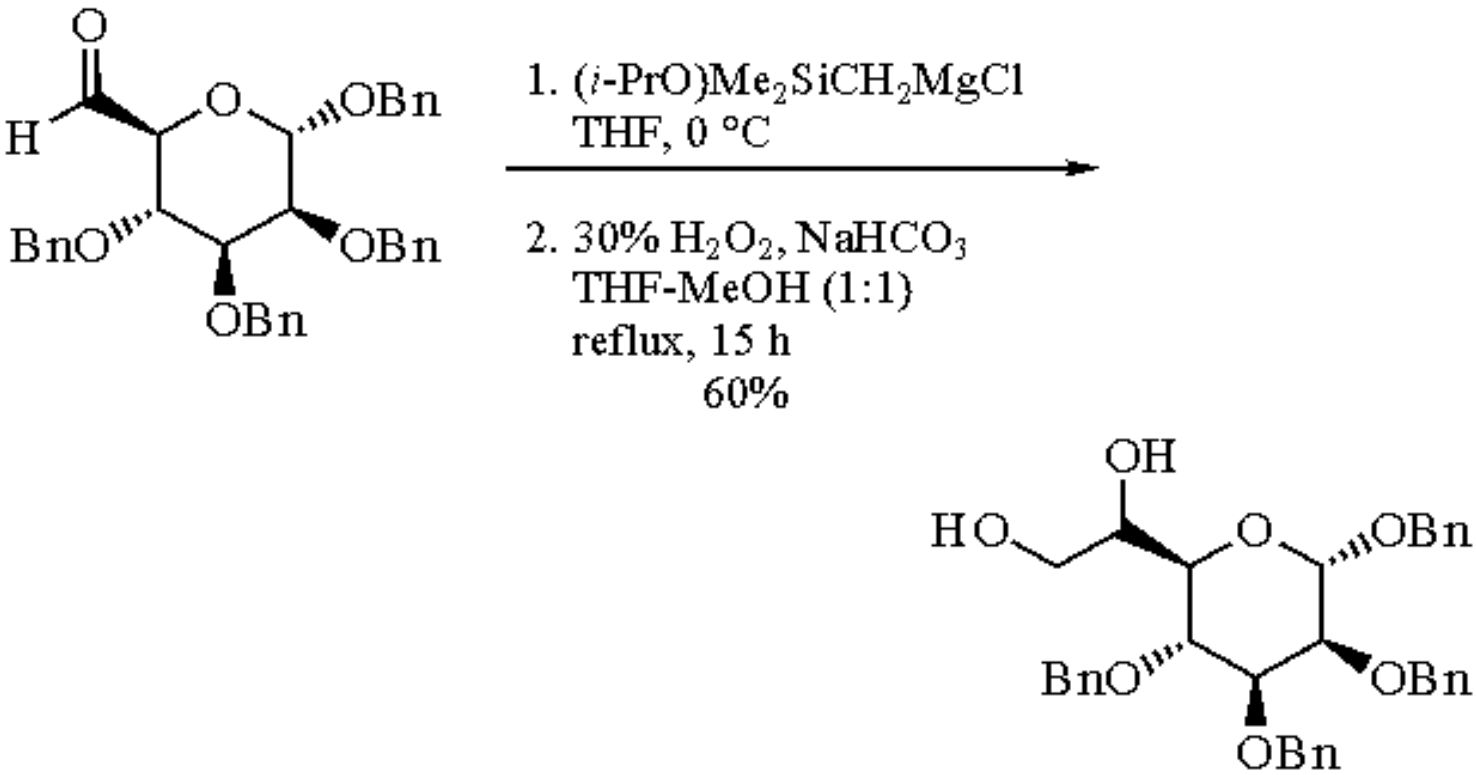

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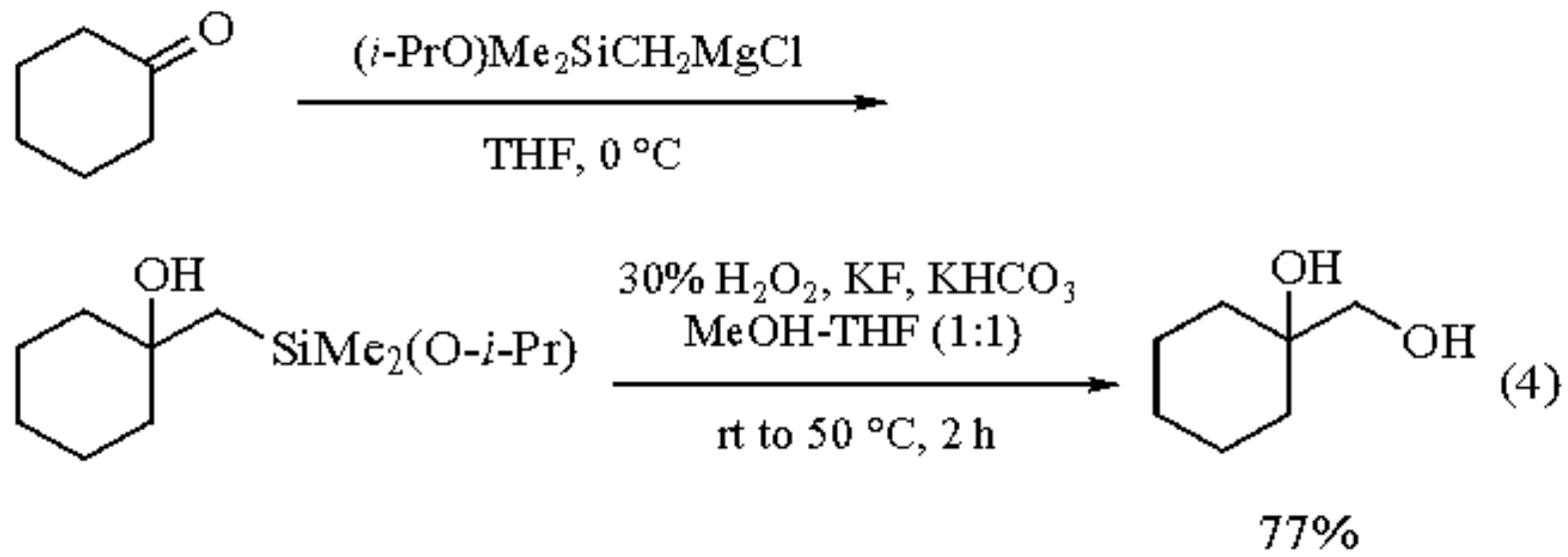

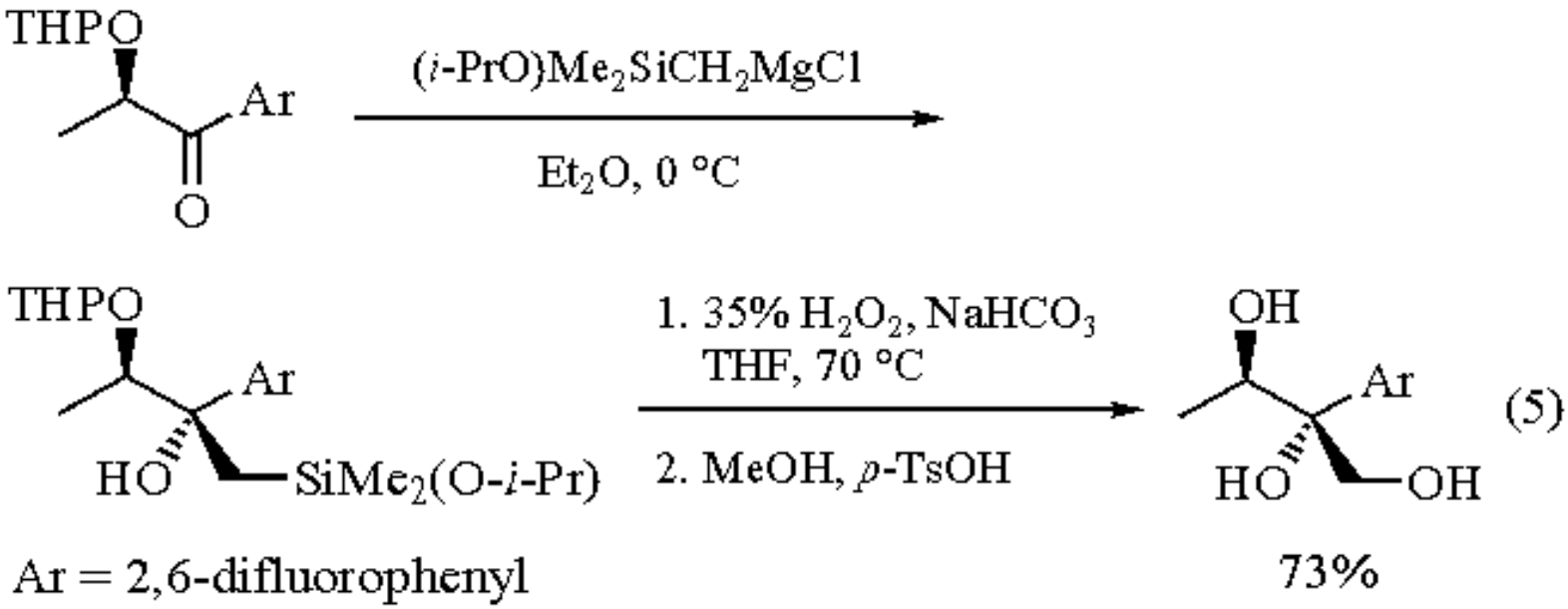

Epoxides are converted into 1,3-diols by a sequence involving copper-catalyzed Grignard addition, followed by oxidation of the five-membered cyclic alkoxysilane intermediates (eq 6).[7] Similarly, primary alcohols are homologated via the tosylates (eq 7).[7] Allylic halides are hydroxymethylated without isomerization or migration of the double bond (eq 8).[8] Alkenyl sulfoximines are also hydroxymethylated with retention of the alkene geometry, via nickel-catalyzed cross-coupling with the corresponding diorganozinc reagent in the presence of ***Magnesium Bromide*** as a co-catalyst, followed by oxidation (eq 9).[9]

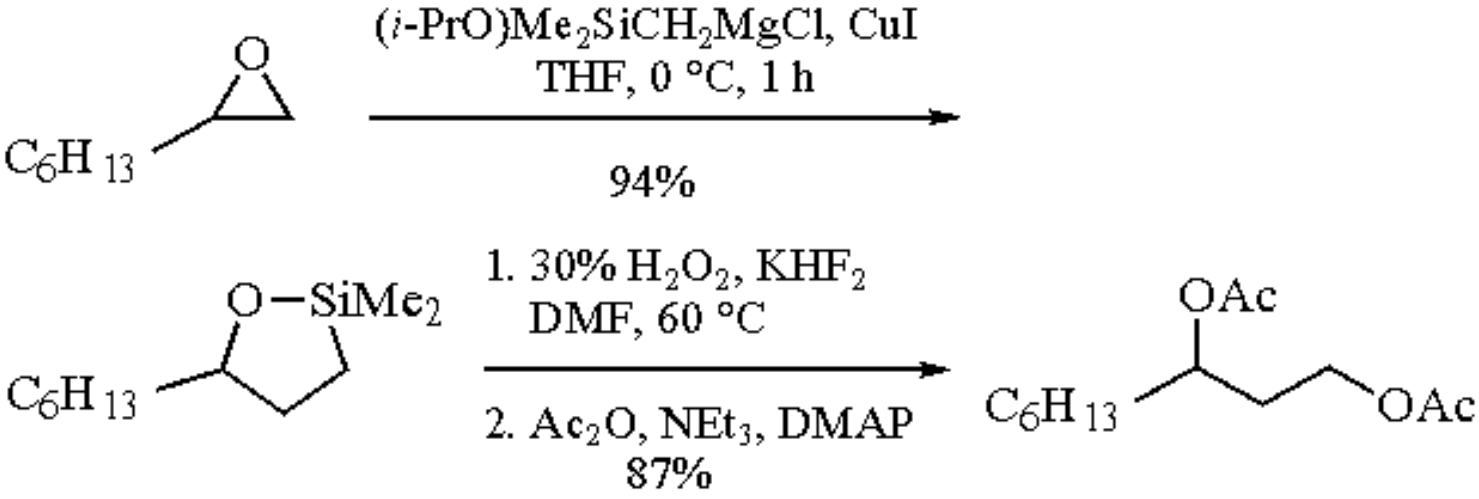
(i-PrO)Me2SiCH2MgCl, CuI
THF, 0 °C, 1 h
94%
C6H13
O
1. 30% H2O2, KHF2
DMF, 60 °C
2. Ac2O, NEt3, DMAP
87%
O—SiMe2
OAc
OAc
(6)

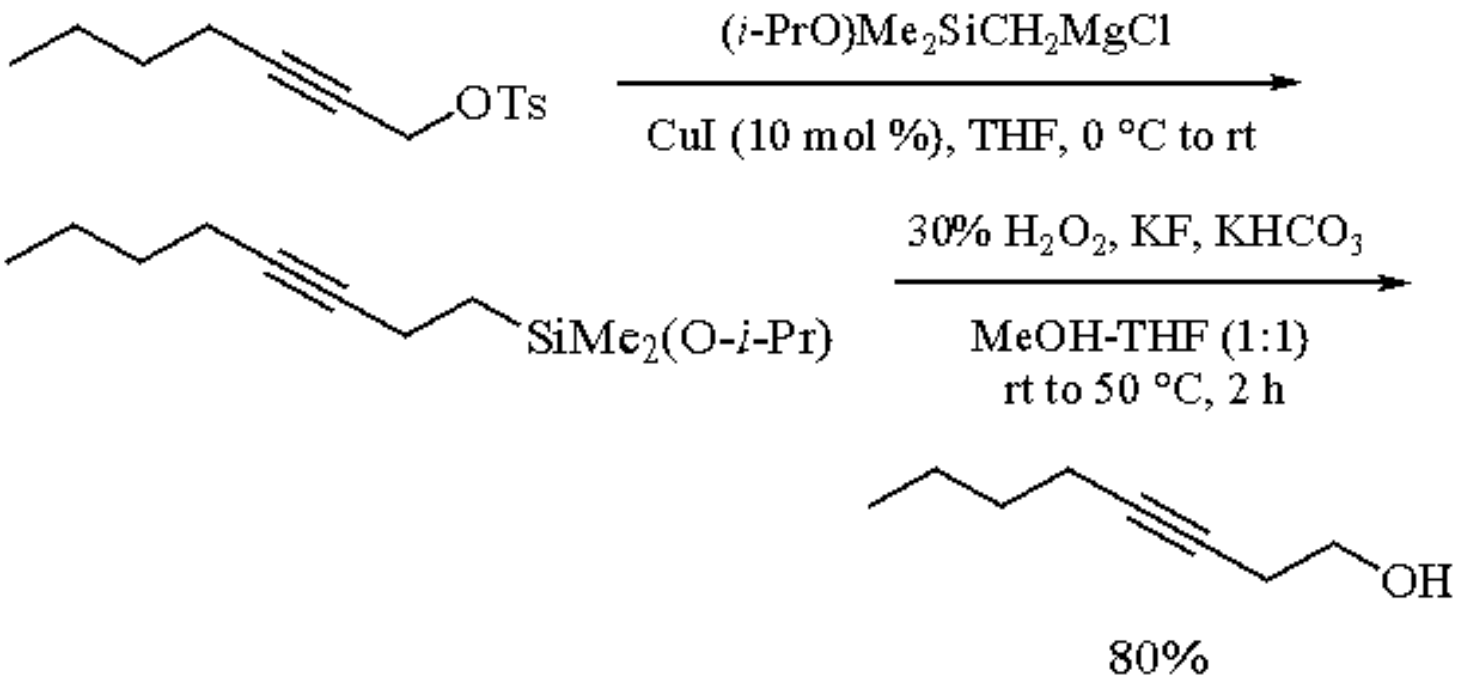
(i-PrO)Me2SiCH2MgCl
CuI (10 mol %), THF, 0 °C to rt
OTs
SiMe2(O-i-Pr)
30% H2O2, KF, KHCO3
MeOH-THF (1:1)
rt to 50 °C, 2 h
OH
80%
(7)

(Chloromethyl)isopropoxydimethylsilane

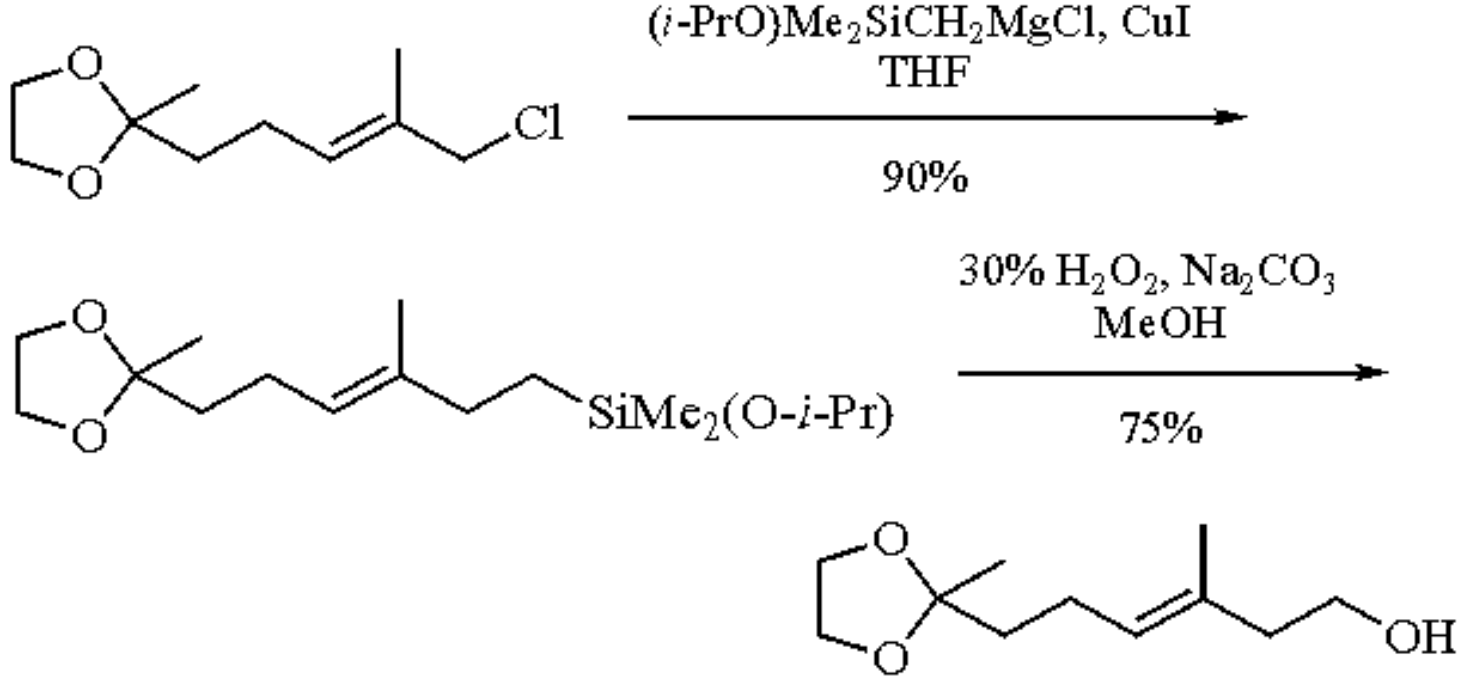

(8)

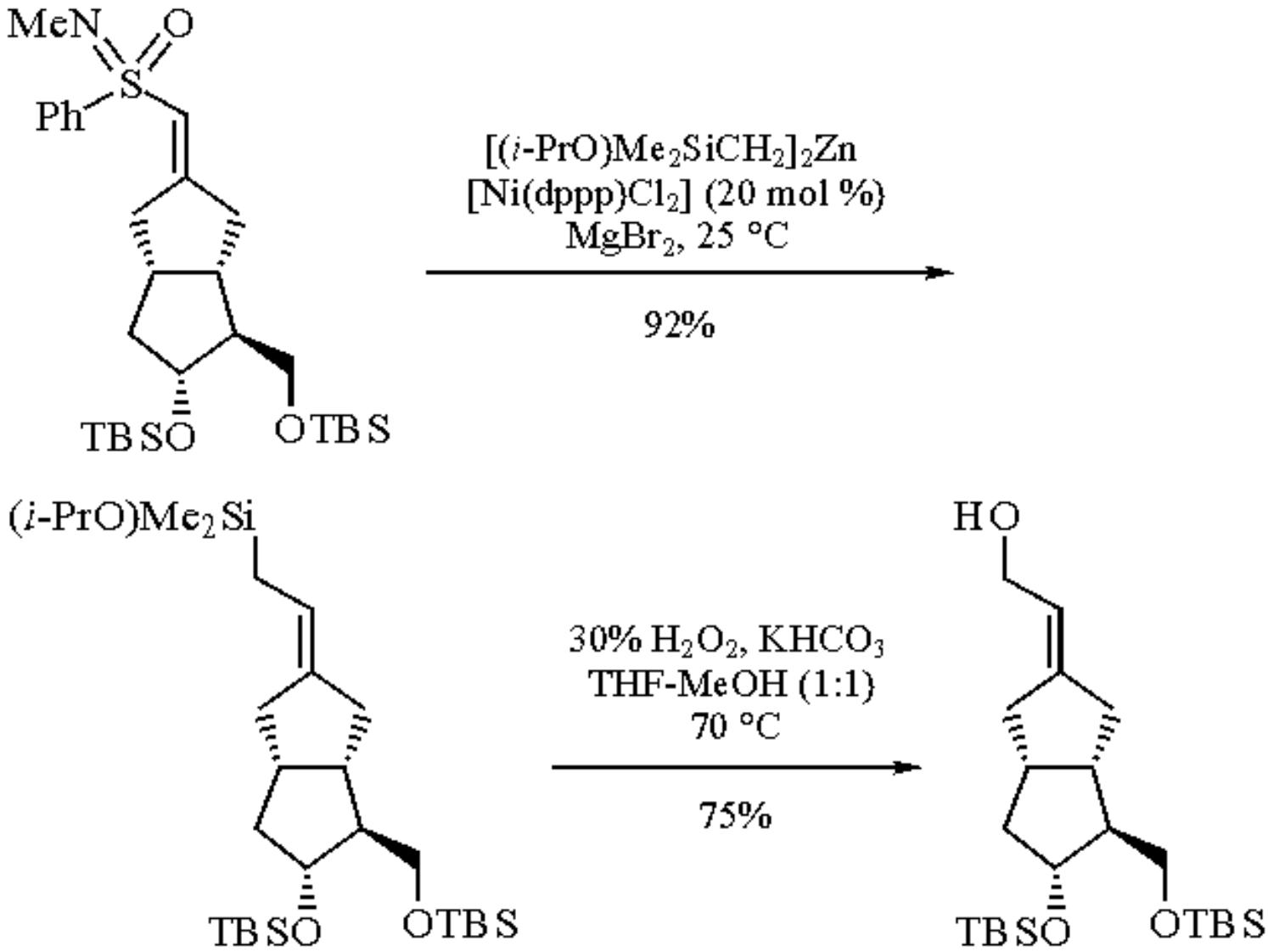

(9)

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Chloromethyllithium[1]

$ClCH_2Li$

[18645-12-0] · CH_2ClLi · Chloromethyllithium · (MW 56.42)

(converts aldehydes or ketones to chlorohydrins or oxiranes;[2-6] $R^1CO_2R^2$ to $RCOCH_2Cl$;[2] $B(OR)_3$ to $ClCH_2B(OR)_2$;[1,7] RBY_2 to RCH_2BY_2;[7-9] $ClSiR_3$ to $ClCH_2SiR_3$[10])

Physical Data: stable at -108 °C in the presence of LiBr; unstable at higher temperatures; unstable even at -130 °C in the absence of LiBr.[11]

Preparative Methods: preferably by addition of ***Methyllithium/Lithium Bromide*** or ***n-Butyllithium*** solution dropwise to a vigorously stirred solution of ***Chloroiodomethane*** and the substrate in THF cooled with a dry ice-acetone bath;[3,4] inexpensive $ClCH_2Br$ in place of $ClCH_2I$ is almost as efficient;[6,8] an alternative is ***Lithium*** wire, $ClCH_2Br$, and substrate in THF with sonication.[5]

Handling, Storage, and Precautions: see ***n-Butyllithium***; ***Chloroiodomethane***. The reagent must be generated under an inert atmosphere of nitrogen or argon.

Chlorohydrins.

O-Lithio chlorohydrins are the initial products of the reaction of $ClCH_2Li$ with carbonyl compounds.[2-6] If the reaction mixture is acidified promptly, before oxirane formation occurs, chlorohydrins can be isolated. The small body of literature data suggests that the most efficient and convenient procedure is the addition of an ether solution of methyllithium/lithium bromide to an equimolar mixture of chloroiodomethane and the carbonyl compound in THF at -78 °C (eq 1).[4] Although BuI can be less convenient than the more volatile MeI to separate, BuLi is otherwise a satisfactory alternative to MeLi and yielded 97% of isolated chlorohydrin from cinnamaldehyde.[4] Phenylacetaldehyde with its strongly acidic α-protons provided a severe test of generality and yielded 65% of chlorohydrin (eq 2).[4]

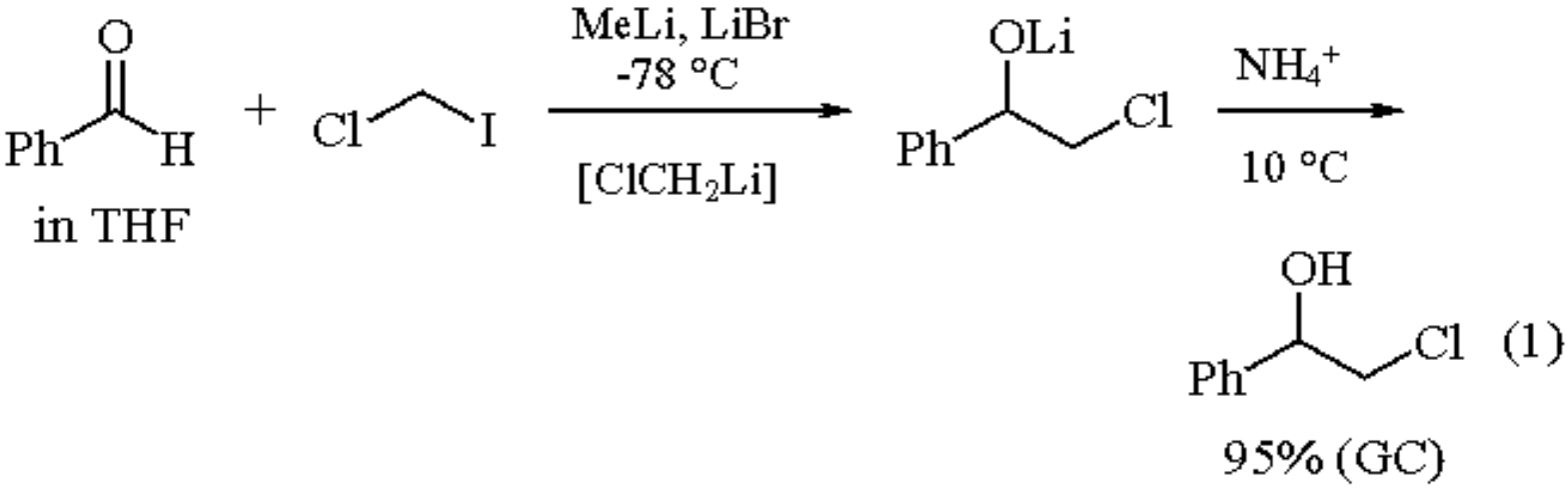

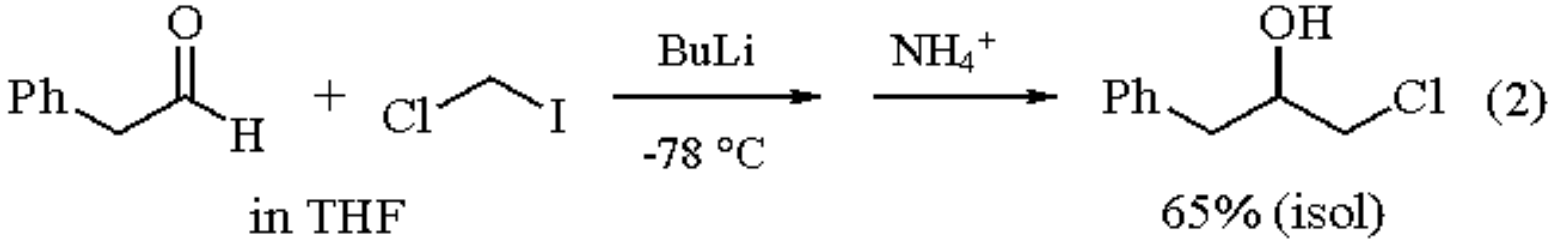

Sonication of benzaldehyde with lithium metal wire and $ClCH_2Br$ in THF at -50 °C has yielded 90% of the chlorohydrin (same transformation as eq 1).[5]

Although there is ordinarily no need to prepare the $ClCH_2Li$ in advance of adding the carbonyl reagent,[4] older chlorohydrin preparations were done with preformed $ClCH_2Li$ (eq 3).[2,3]

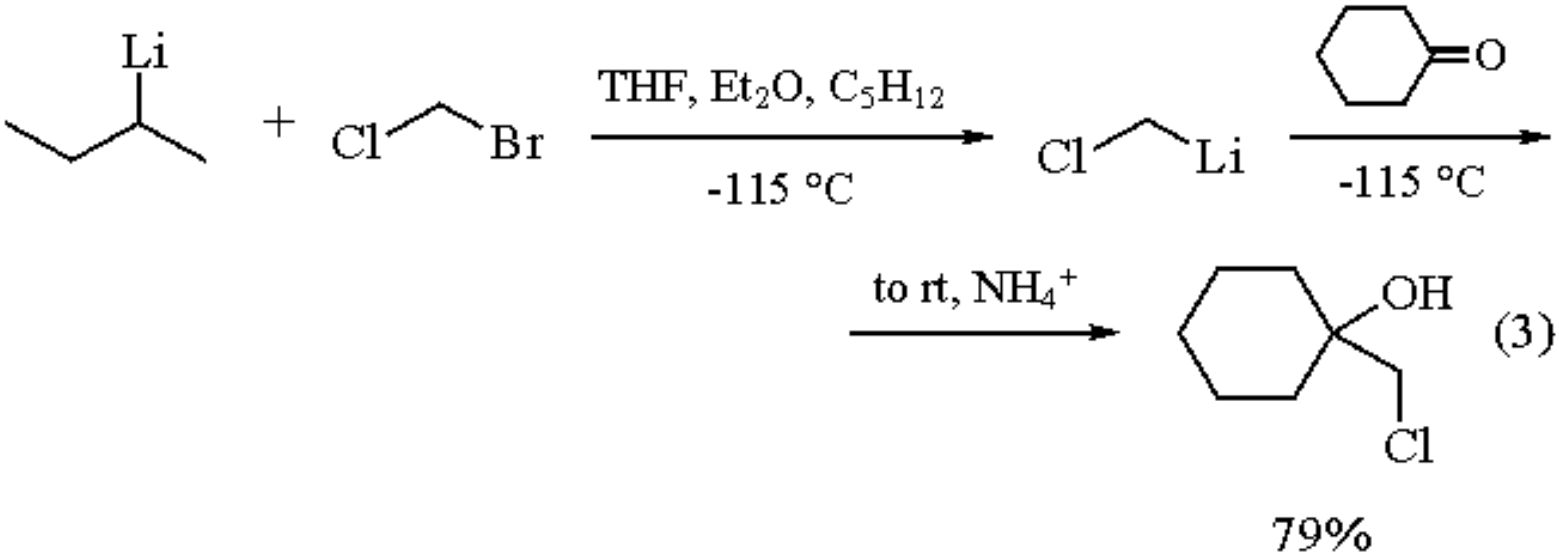

Preformed $ClCH_2Li$ has converted ethyl benzoate, $PhCO_2Et$, to chloroacetophenone, $PhCOCH_2Cl$ (61%).[2]

The reaction of BuLi with $ClCH_2Br$, as well as that of MeLi with $ClCH_2I$, in the presence of ketones has been used to produce *O*-lithio chlorohydrins, which were then lithiated and further transformed as described in the subsection β-

lithio lithium alkoxides below.[6]

Oxiranes.

If a solution of *O*-lithio chlorohydrin initially formed from $ClCH_2Li$ and a carbonyl compound is allowed to stand at rt for a sufficient time, generally a few hours, ring closure to the oxirane results.[2-6] These reactions are especially clean and nearly quantitative when $ClCH_2Li$ is generated from $ClCH_2I$ and MeLi/LiBr or BuLi in the presence of the carbonyl substrate in THF cooled with a dry ice-acetone bath (eqs 4-6).[4]

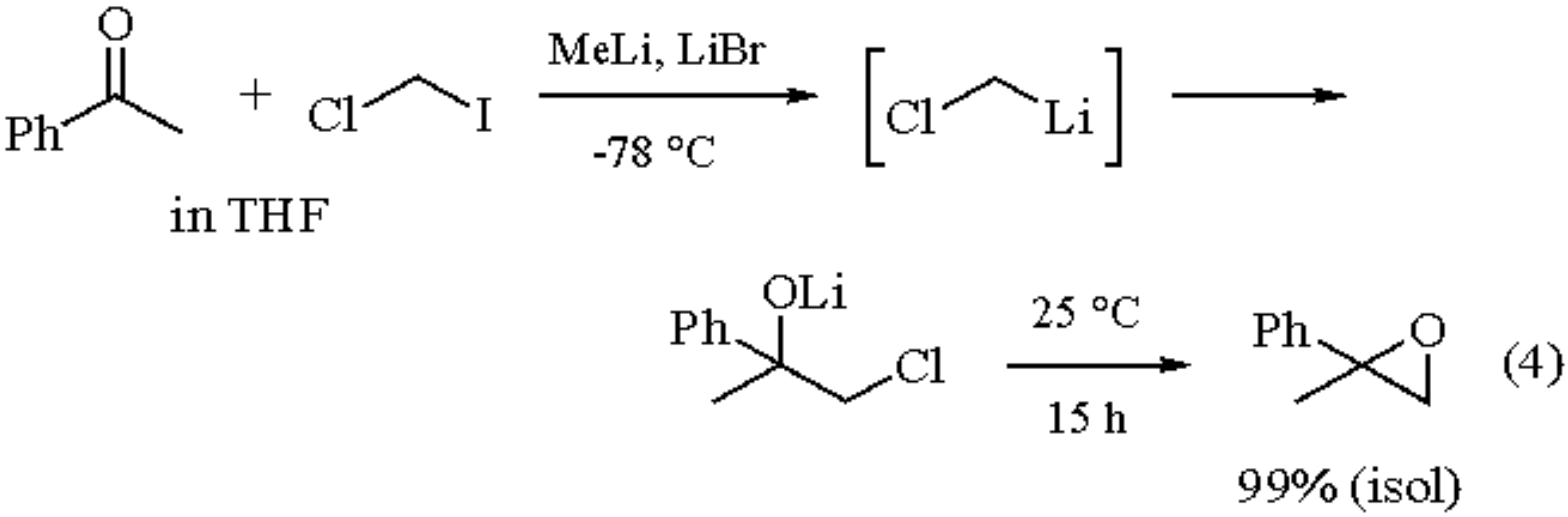

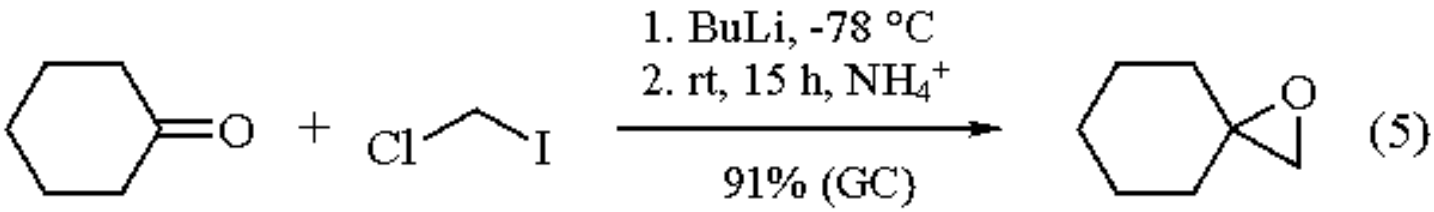

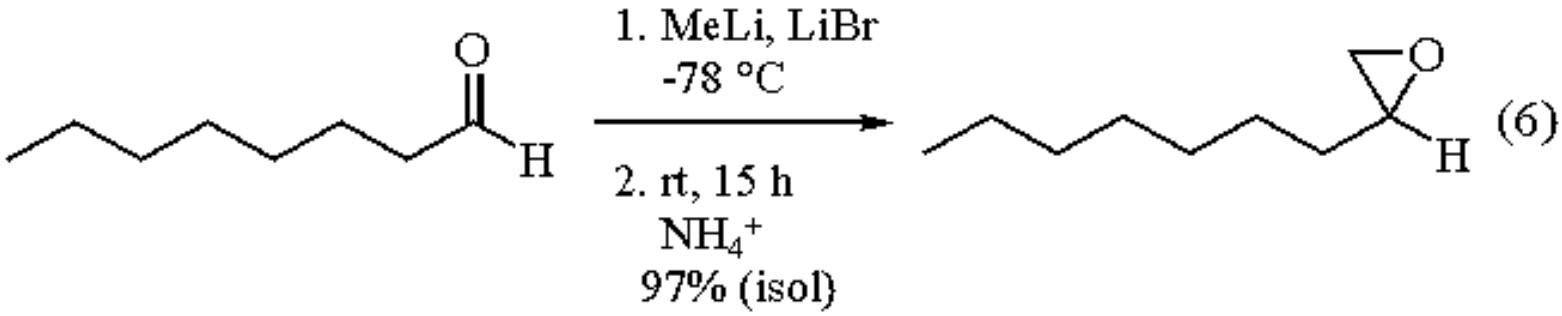

Sonication of acetophenone, $ClCH_2Br$, and lithium metal wire in THF has yielded 82% of the oxirane (same net transformation as eq 4).[6] Several other aldehydes and ketones were similarly converted to oxiranes in 72-91% yields. Reactions of ketones were carried out at -15 °C, aldehydes at -50 °C.

For an alternative reagent which costs less and converts carbonyl compounds to oxiranes faster and equally efficiently, see ***Bromomethyllithium***.

Boronic Esters.

Addition of butyllithium to ***Triisopropyl Borate*** and $ClCH_2I$ in THF at -78 °C followed by treatment with anhydrous HCl yields diisopropyl (chloromethyl)boronate (eq 7), a useful synthetic intermediate (see ***Pinacol (Chloromethyl)boronate***).[7]

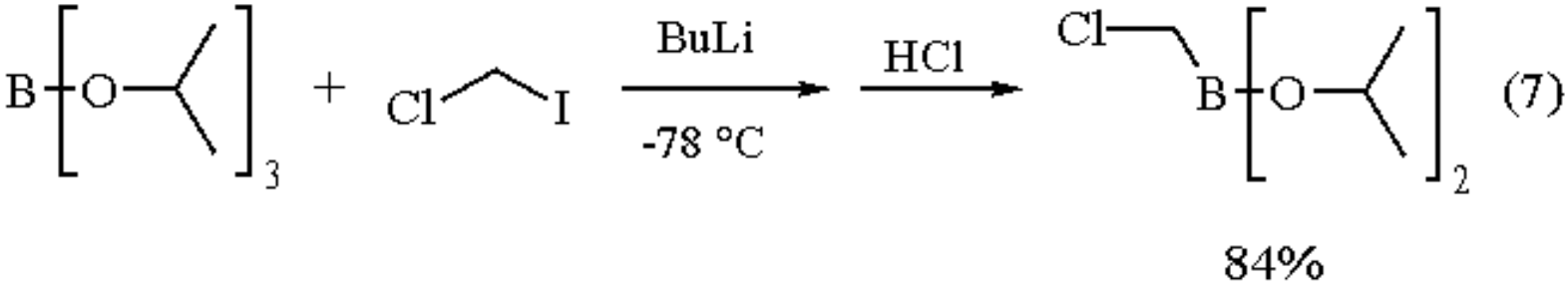

With boronic esters, $ClCH_2Li$ adds to the boron atom to form a borate complex, which on warming to rt rearranges to form the homologous boronic ester (eqs 8 and 9).[7] A chiral group was shown to migrate with retention of configuration (eq 10).[7]

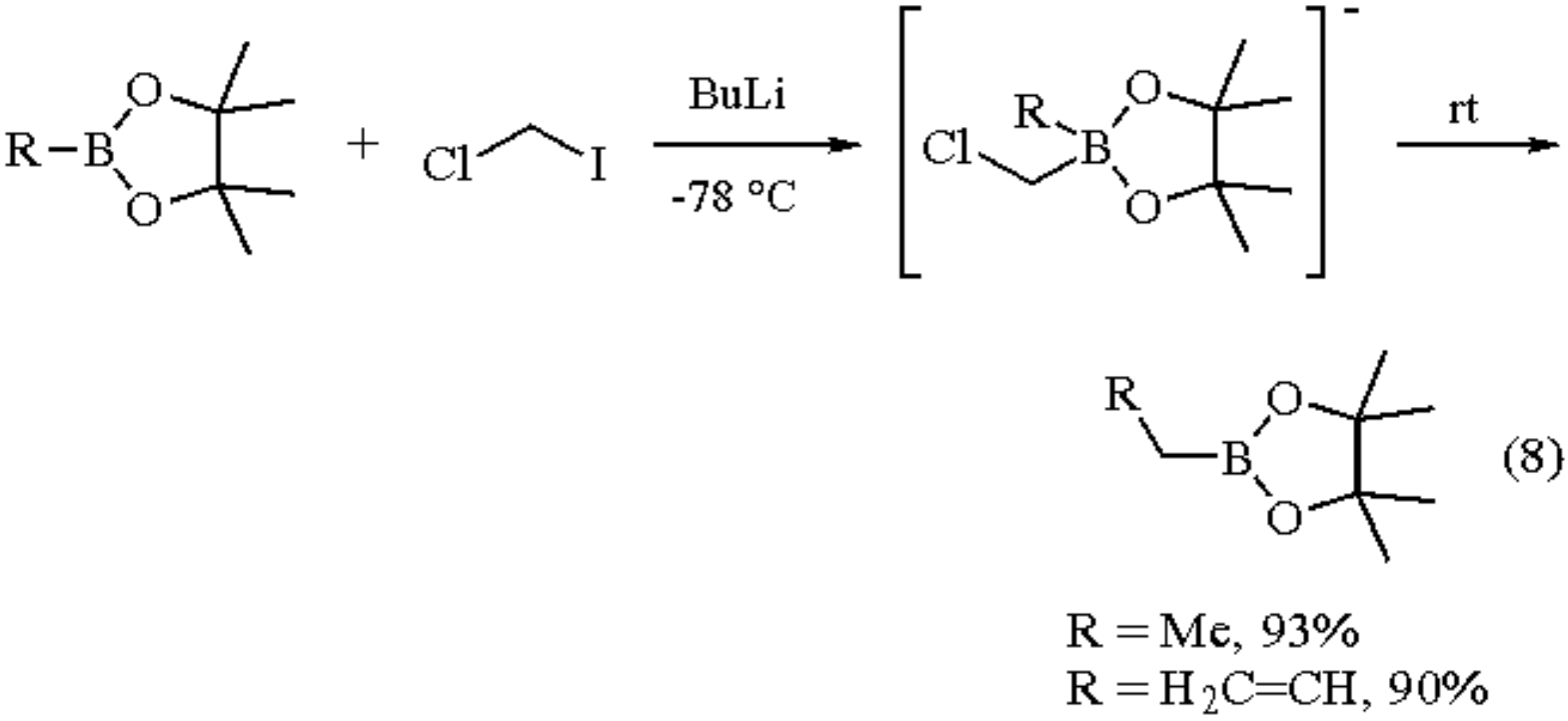

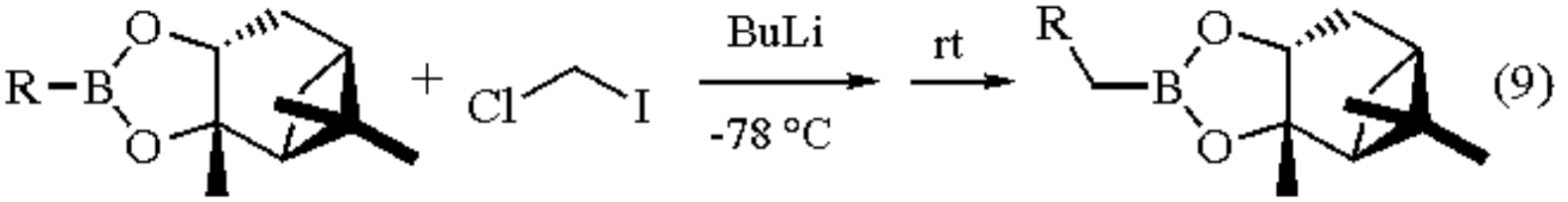

R = Me_2CH, 94%; R = Ph, 96%
R = $PhCH_2OCH_2$, 90%

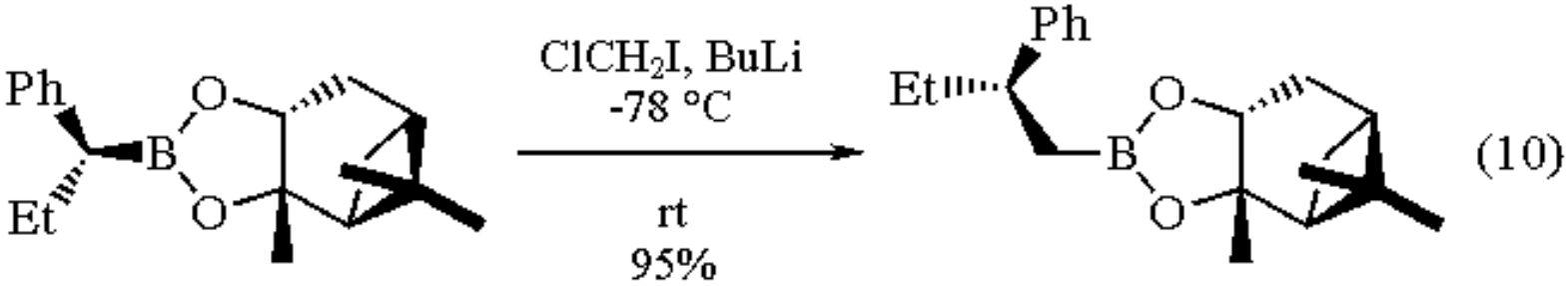

The conditions for in situ generation of $ClCH_2Li$ have been explored with boronic esters as substrates. Less expensive $ClCH_2Br$ was found to work almost as well as $ClCH_2I$ (eq 11).[8] It was also found that with $ClCH_2Br$ and R = 1-hexyl, addition of the BuLi at 0 °C resulted in a 47% yield, but temperatures between 0 °C and -78 °C were not tested.[8]

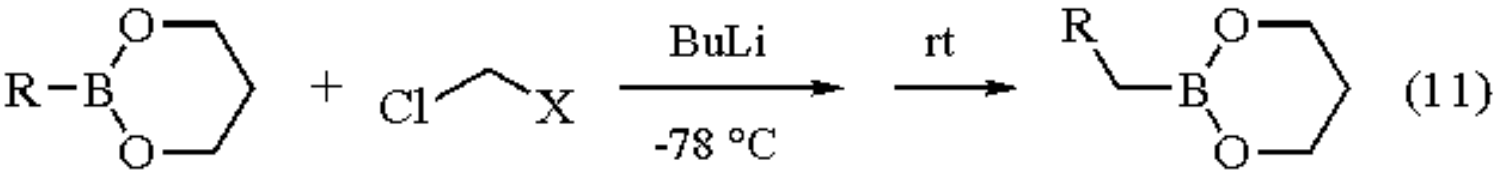

R = 1-hexyl: X = I, 97%; X = Br, 91%
R = 3-hexyl: X = I, 96%; X = Br, 89%

The reaction of eq 11 with $ClCH_2Br$ also yielded 89-91% with R = cyclopentyl, cyclohexyl, *trans*-2-methylcyclopentyl, *trans*-2-methylcyclohexyl, and *exo*-norbornyl.[8] However, in view of the possible problems in separating starting material and product that differ by only one methylene unit, the nearly quantitative conversions achieved with $ClCH_2I$ may justify the extra cost.

Boracyclane Ring Expansion.

Boracyclanes of ring sizes 5-11 undergo efficient ring expansion when treated with $ClCH_2Li$ generated in situ (eq 12).[9] Since these compounds are easily converted to carbocycles via the reaction with $LiCCl_2OMe$, which inserts a carbonyl group in place of BOMe, and since the 7-membered borepane can be prepared fairly directly from 1,5-hexadiene via a hydroboration route, this chemistry affords an efficient route to medium-sized rings.[9]

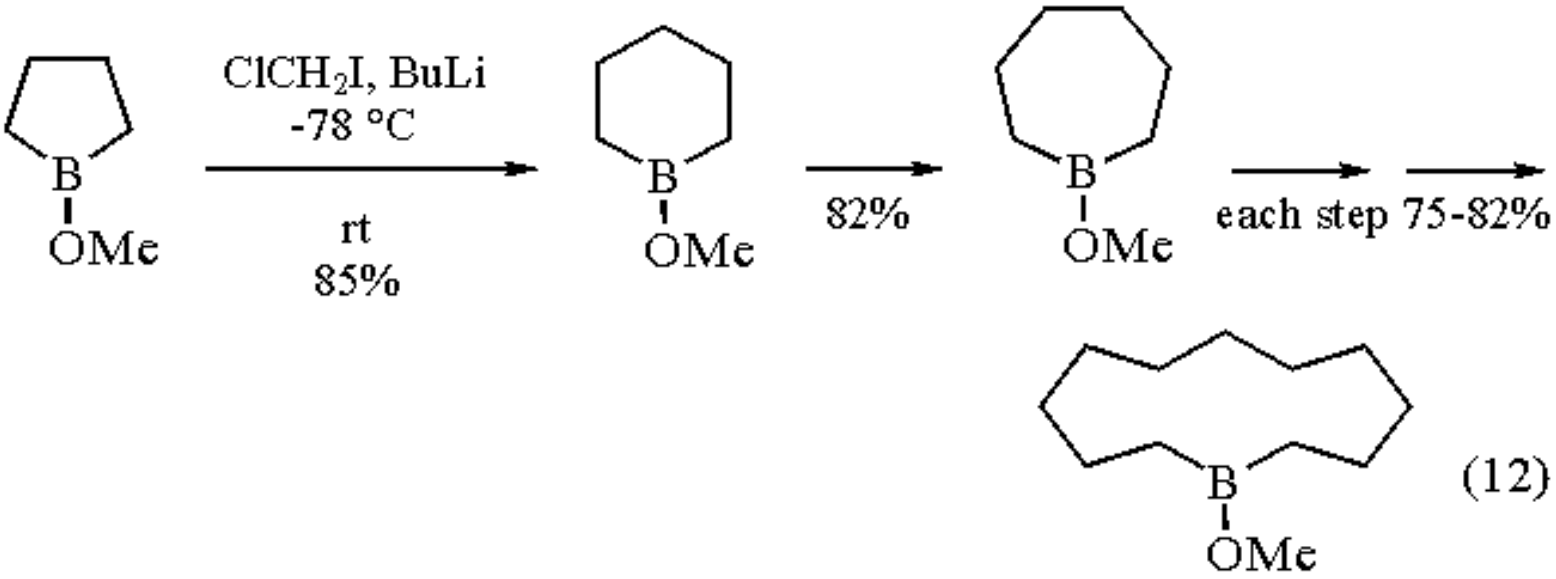

(12)

(Chloromethyl)silanes.

Addition of butyllithium to mixtures of $ClCH_2Br$ and various chlorosilanes in THF at -60 to -70 °C (-78 °C cooling bath) yields (chloromethyl)silanes.[10] A typical example is illustrated in eq 13. Similar conditions were used to prepare Ph_3GeCH_2Cl, Ph_3SnCH_2Cl, and Ph_3PbCH_2Cl.[10]

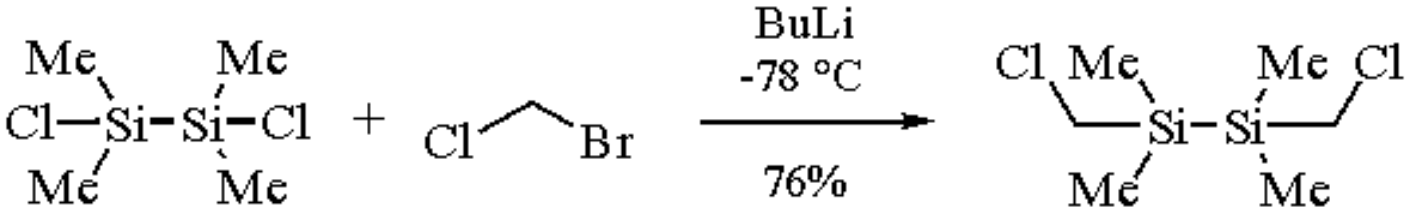

(13)

β-Lithio Lithium Alkoxides.

These are indirect derivatives of $ClCH_2Li$ and ketones which can be produced via lithiation of *O*-lithio chlorohydrins with ***Lithium Naphthalenide*** and related reagents (eq 14).[6] If warmed to rt, β-lithio lithium alkoxides eliminate Li_2O to form alkenes. At -78 °C, β-lithio lithium alkoxides react with variety of electrophiles EX to form *C*-substituted derivatives. Examples of EX and E included D_2O, D; MeSSMe, SMe; CO_2, CO_2H; $BrCH_2CH{=}CH_2$, $CH_2CH{=}CH_2$; and cyclohexanone, 1-hydroxycyclohexyl. Overall yields were generally in the useful range, 50-95%, for any of the processes described.[6]

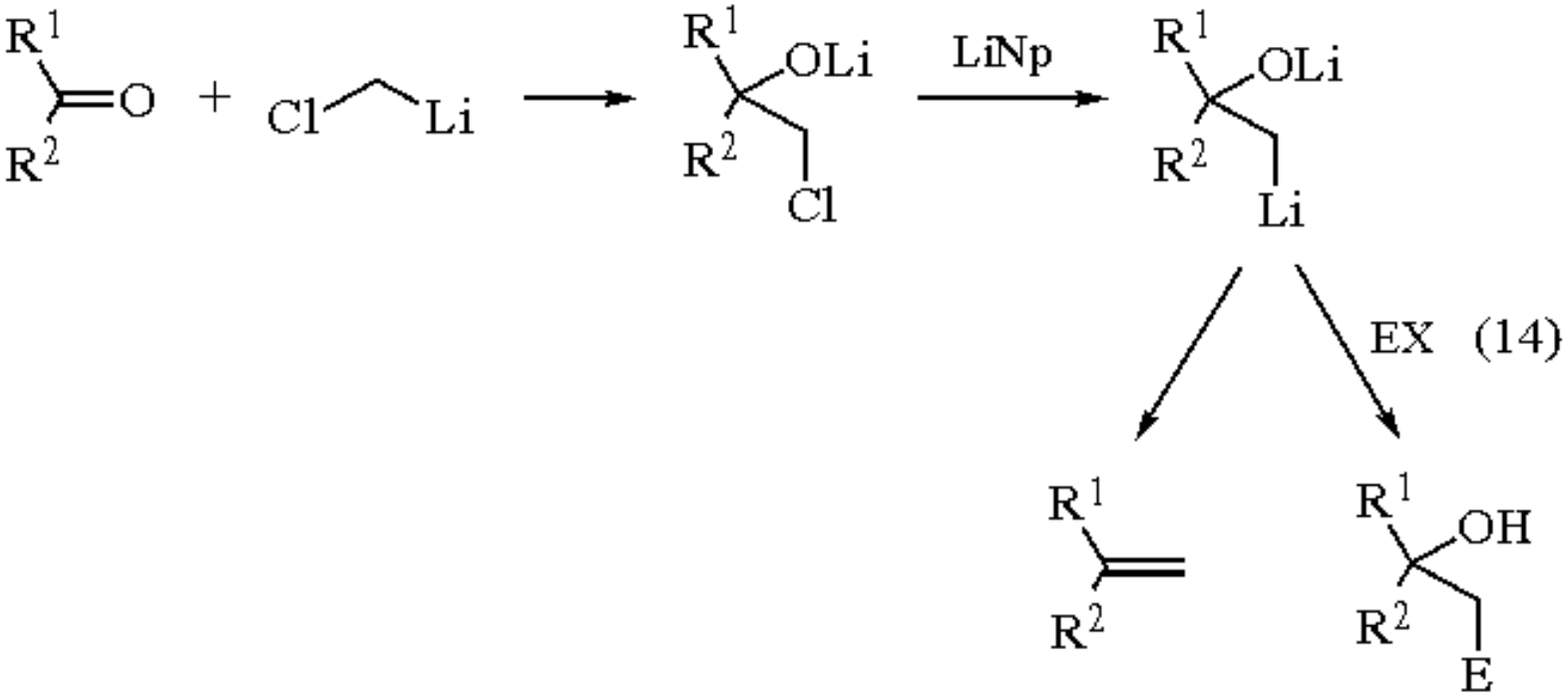

Related Reagents.

1-Chloroethyllithium has been prepared at -115 °C from MeCHClBr and *s*-BuLi and reacted with benzaldehyde to form the corresponding oxirane (60%, *cis/trans* ratio 2:1).[3] Similarly prepared $MeCH_2CHClLi$ with cyclohexanone yielded the chlorohydrin (70%), and Me_2CClLi with benzaldehyde yielded the oxirane (42%).[3] See also ***Bromomethyllithium***; ***Dimethylsulfonium Methylide***; ***Dibromomethyllithium***; ***Dichloromethyllithium***; ***Tribromomethyllithium***; ***Trichloromethyllithium***.

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Donald S. Matteson

Chloromethyl Methyl Ether[1]

$MeOCH_2Cl$

[107-30-2] · C_2H_5ClO · Chloromethyl Methyl Ether · (MW 80.51)

(used for the protection of alcohols, phenols, acids, amines, β-keto esters and thiols. A one-carbon synthon for alkylation of aromatics and active methylene derivatives)

Alternate Name: methoxymethyl chloride; MOMCl.

Physical Data: bp 55-57 °C; *d* 1.060 g cm^{-3}.

Solubility: sol nearly all organic solvents.

Form Supplied in: available as a technical grade liquid.

Preparative Methods: besides the original method[2] which uses HCl, formalin, and methanol, MOMCl can be prepared from methoxyacetic acid[3] or methylal (***Dimethoxymethane***).[4]

Handling, Storage, and Precautions: MOMCl is an OSHA-regulated carcinogen and depending on the method of preparation may contain bis(chloromethyl) ether, which is a more potent carcinogen. This reagent should be handled in a fume hood.

Protection of Alcohols.

Treatment of an alcohol with MOMCl and *i*-Pr_2NEt (0 °C, 1 h -> 25 °C, 8 h, 86% yield)[5] is the most commonly employed procedure for introduction of the MOM group. Formation of the sodium alkoxide and reaction with MOMCl is also very effective.[6] This method is particularly useful for the protection of the enol of β-keto esters.[7] Because of the carcinogenicity of MOMCl, a number of methods for the introduction of the MOM group have been developed which do not rely on the chloride. The methods are all based on the use of $CH_2(OMe)_2$ with various catalysts such as P_2O_5,[8] Me_3SiI,[9] Nafion H,[10] $CH_2{=}CHCH_2SiMe_3$/TMSOTf/P_2O_5,[11] $FeCl_3$,[12] Montmorillonite clay (H^+),[13] or TsOH/LiBr.[14] In the last case, 1,3-diols give methylene acetals. It is often difficult to achieve monoprotection of 1,3-diols but some success has been recorded, as illustrated in eqs 1-3.[15-17]

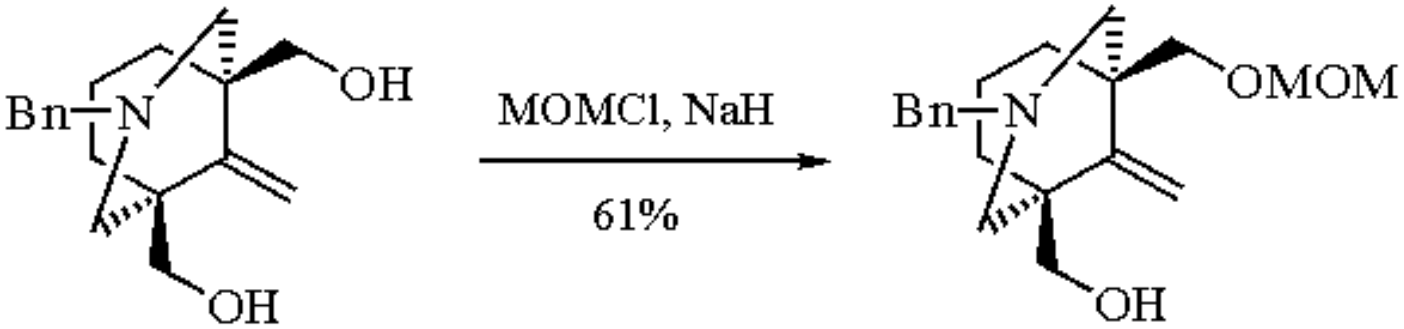

(1)

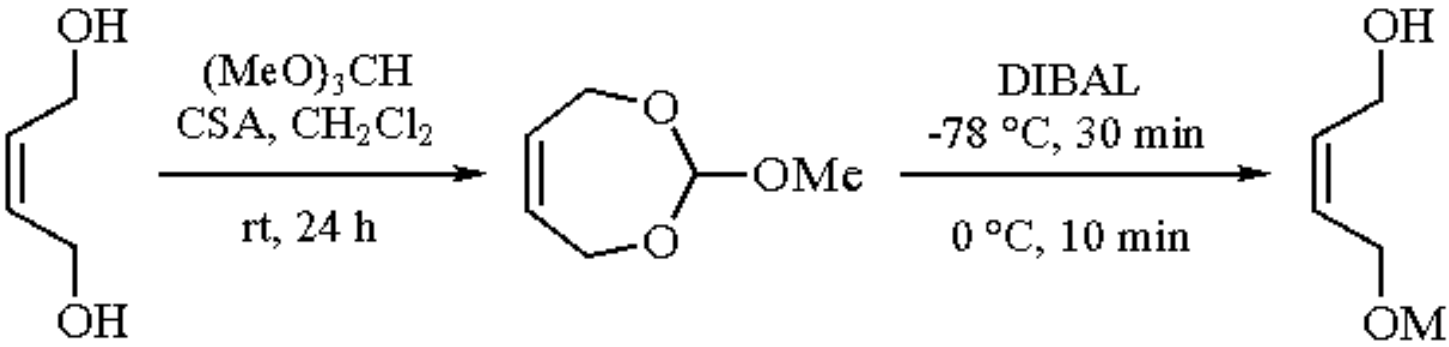

(2)

In the orthoester route when unsymmetrical diols are used, the most hindered alcohol is protected, in contrast to the normal methods which are expected to protect the least hindered alcohol. Diols capable of forming a stannylene derivative are efficiently monoprotected (eq 3).[17]

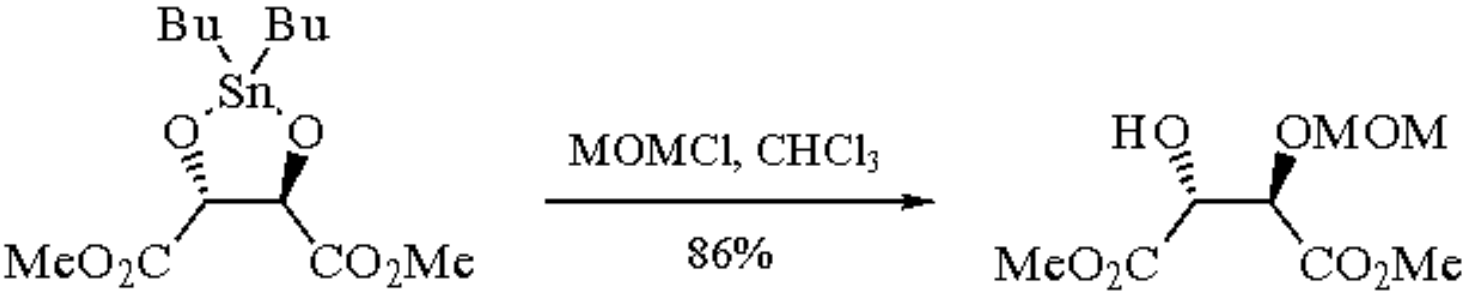

(3)

Cleavage of MOM Ethers.

Since the MOM group is an acetal, it can be cleaved using acid hydrolysis. In general, aqueous acid in an organic cosolvent has proven to be effective.[18-21] Use of the weak acid ***Pyridinium p-Toluenesulfonate*** in refluxing *t*-BuOH or 2-butanone is particularly effective for cleavage of MOM ethers of allylic alcohols.[22] MEM ethers are also cleaved under these conditions. Eq 4 shows that a MOM group can be cleaved with anhydrous ***Trifluoroacetic Acid*** in the presence of an acetonide which is normally cleaved with aqueous acid.[23]

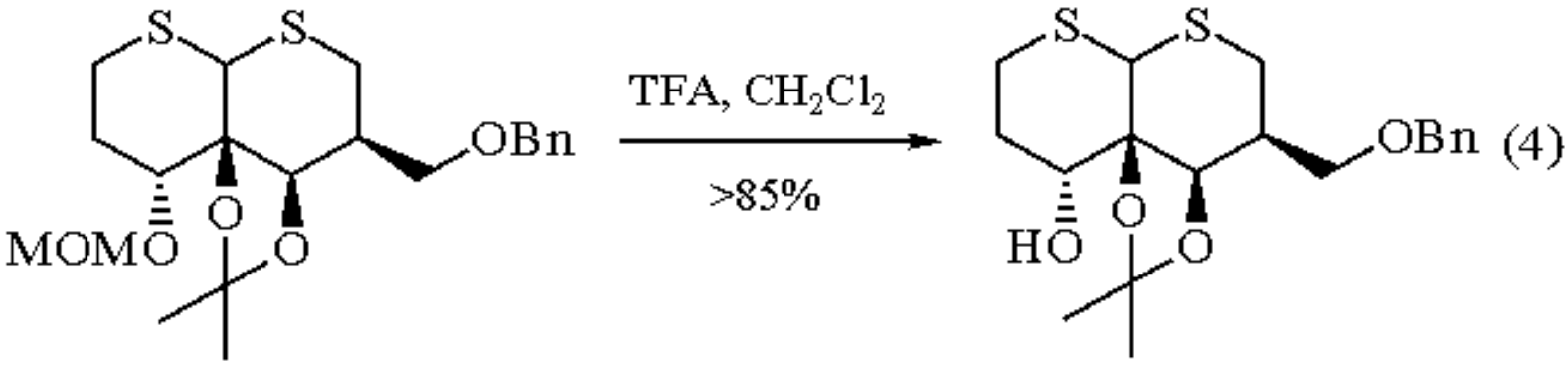

Catecholborane halides, particularly the bromide (***B-Bromocatecholborane***), are effective reagents for the cleavage of MOM ethers. The bromide cleaves the following groups in the order: MOMOR &AApprox; MEMOR > *t*-Boc > Cbz &AApprox; *t*-BuOR > BnOR > allylOR > *t*-BuO_2CR &AApprox; secondary alkylOR > BnO_2CR > primary alkylOR >> alkylO_2CR. The *t*-butyldimethylsilyl (TBDMS) group is stable to this reagent. The chloride is less reactive and thus may be more useful for achieving selectivity in multifunctional substrates. Yields are generally >83%.[24] A variety of other boron based reagents have been developed which are useful for MOM ether cleavage. The use of ***Bromobis(isopropylthio)borane*** (eq 5)[25] has the advantage that 1,2- and 1,3-diols do not give formyl acetals as is sometimes the case in cleaving MOM groups with neighboring hydroxyl groups.[26] The reagent also cleaves MEM groups and under basic conditions affords the *i*-$PrSCH_2OR$ derivatives. With ***Bromodimethylborane***, MEM and MTM ethers are also cleaved, but esters are not affected.[27]

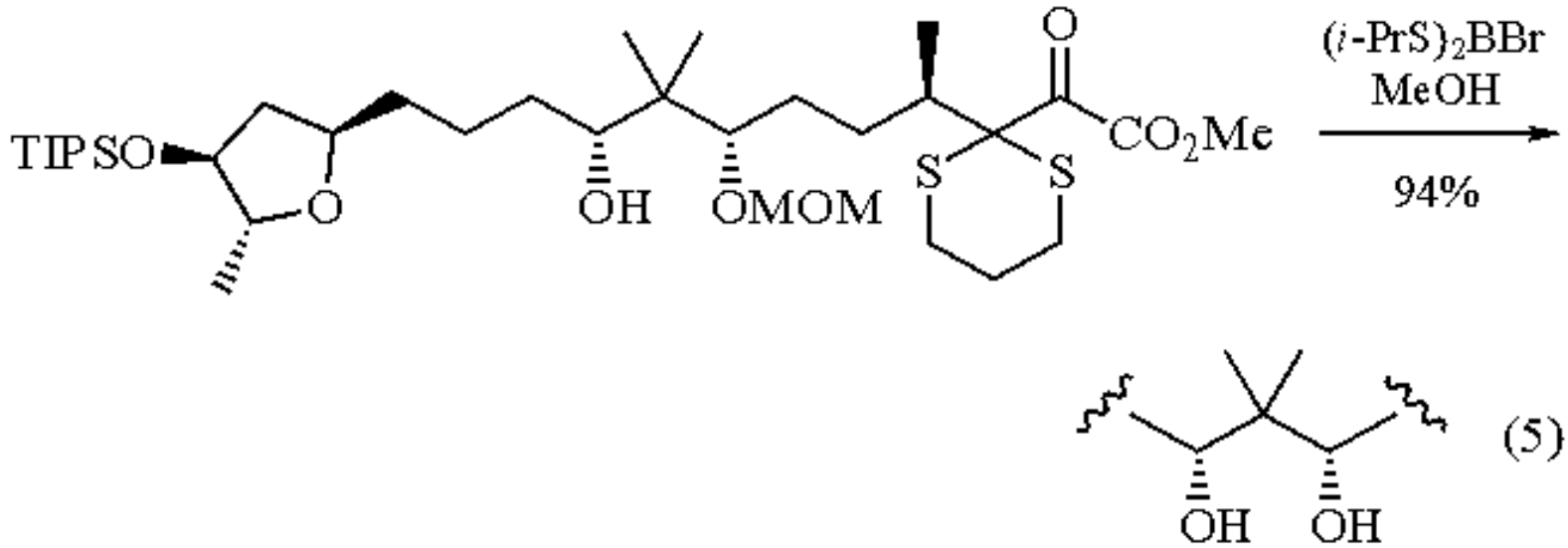

Bromotrimethylsilane, a reagent similar to but not as powerful as ***Iodotrimethylsilane***, will cleave MOM ethers as well as acetonide, THP, trityl, and *t*-$BuMe_2Si$ groups, but the reagent will not cleave esters, methyl and benzyl ethers, *t*-butyldiphenylsilyl ethers, and amides. One example is shown in eq 6.[28]

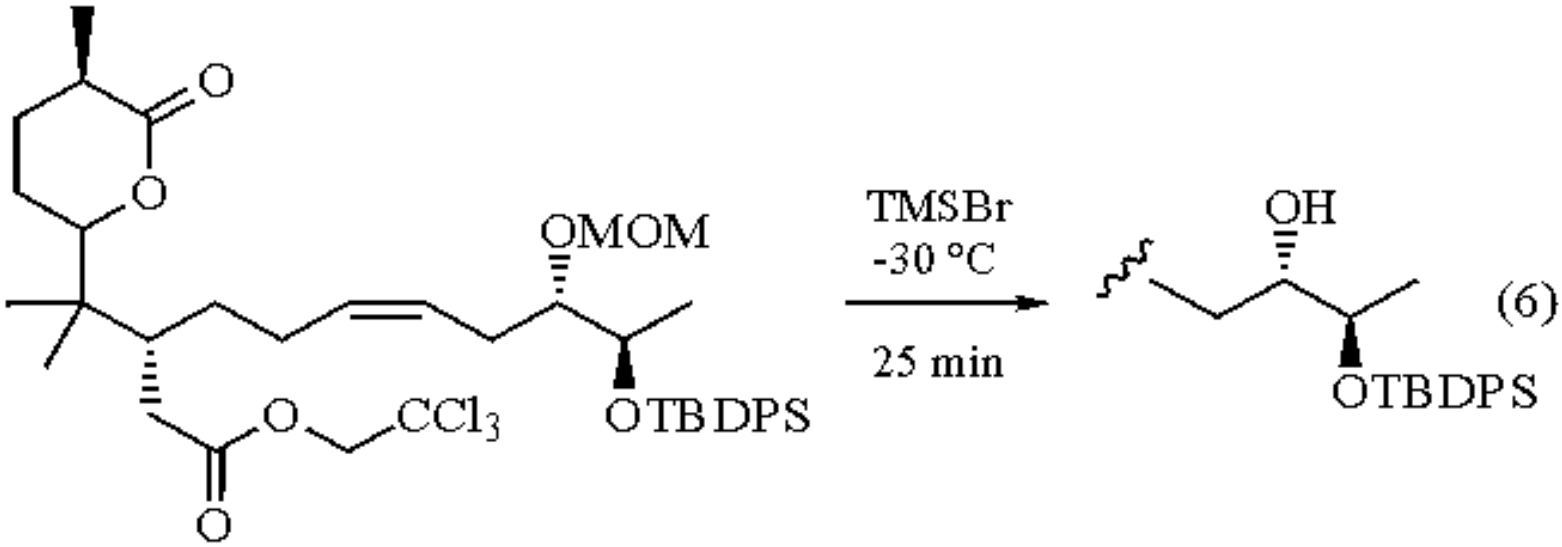

Boron Trifluoride Etherate in the presence of ***Thioanisole***,[29] ***Magnesium Bromide*** in the presence of butanethiol,[30] ***Triphenylcarbenium Tetrafluoroborate***,[31] and ***Lithium Tetrafluoroborate***[32] are also useful for cleavage of the MOM group. The action of lithium tetrafluoroborate is unique (eq 7) and the mechanism for cleavage is not well understood.

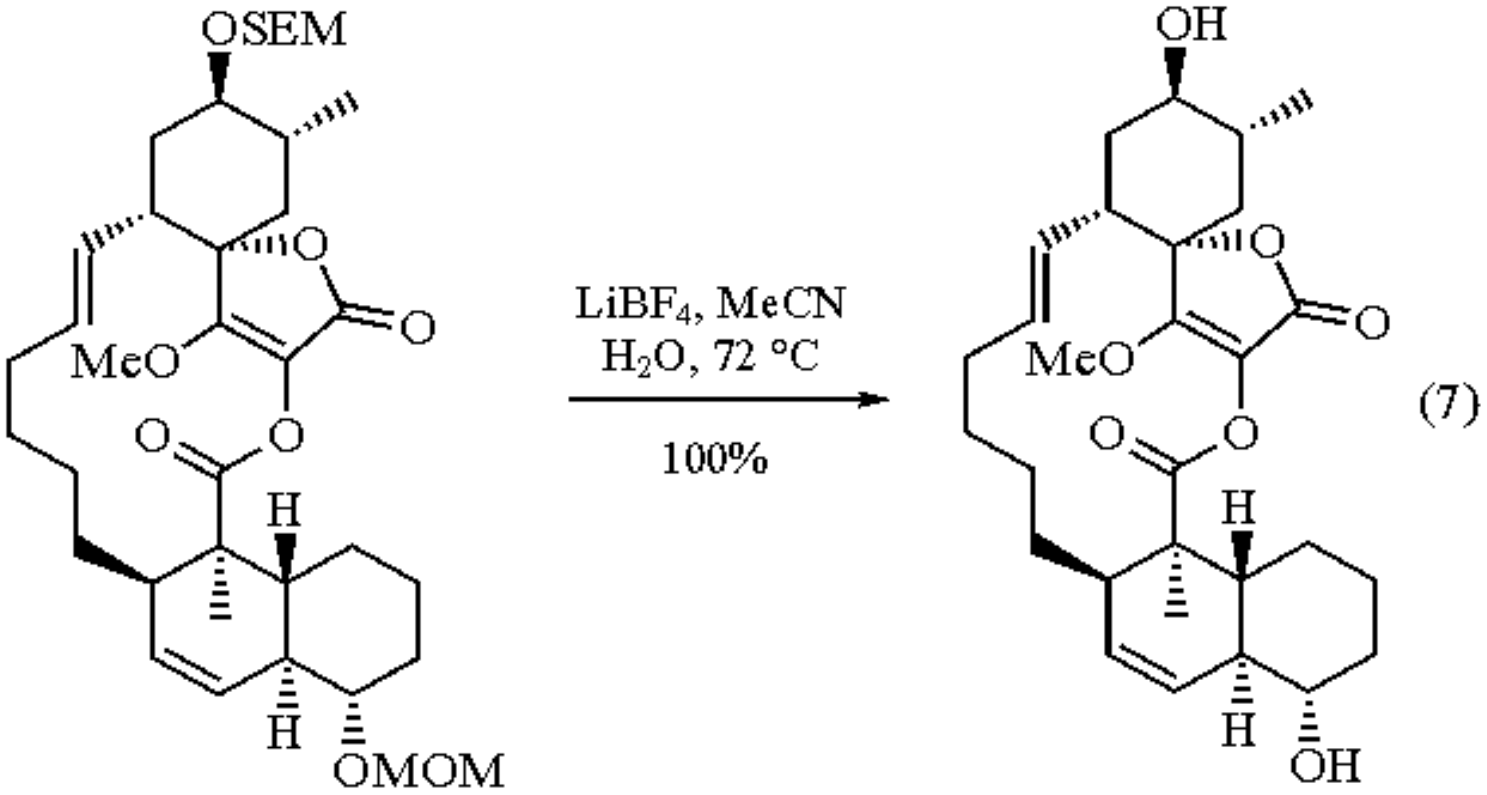

Protection of Phenols.

The reaction of MOMCl with a phenol under phase-transfer conditions works well to give phenolic MOM ethers[33] and will selectivity protect a phenol in the presence of an alcohol.[34] The more classical Williamson ether synthesis[35] also provides excellent results, but may require the addition of a crown ether to enhance the nucleophilicity of the

phenolate anion.[36] As in the case of alcohol protection, alternatives using methylal have been developed for phenol protection which do not rely on the carcinogenic MOMCl.[37] Phenolic silyl ethers can be converted directly to MOM ethers by reaction with TASF (***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate***) and MOMCl.[38]

Cleavage of Phenolic MOM Ethers.

Again, mild acid[37,39] is used for cleavage, but other alternatives such as ***Sodium Iodide***/acetone/cat. HCl/50 °C,[40] ***Diphosphorus Tetraiodide***/CH_2Cl_2/0 °C -> rt,[41] or TMSBr/CH_2Cl_2[42] are also effective.

Protection of Thiols.

Lithium[43] and potassium[44] thiolates react with MOMCl to form the thioethers. The use of MOMCl can be avoided by the reaction of the zinc thiolate with methylal.[45]

Protection of Acids.

The reaction of MOMCl with an acid in the presence of a base affords the MOM ester.[46-48] As with the thiols, the zinc carboxylate reacts with methylal to afford the MOM ester.[49] MOM esters are quite acid sensitive and are unstable to silica gel chromatography.[50] The MOM ester is easily cleaved with acid, $MgBr_2$,[51] or Me_3SiBr containing a trace of MeOH.[52]

Protection of Amine Derivatives.

Heterocyclic amines and amides are protected as their MOM derivatives by reaction of the amine or amide with MOMCl in the presence of a base such as ***Diisopropylethylamine***,[53] ***Sodium Hydride***,[54] LiH, ***Potassium t-Butoxide***,[55] or ***Sodium Hydroxide***.[56] These derivatives are cleaved with ***Hydrogen Chloride***/EtOH[53] or ***Boron Tribromide***.[55] To hydrolyze scopolamine without formation of the rearranged product (**1**) it was necessary to protect the amine nitrogen as the methoxy-methochloride as illustrated in eq 8.[57]

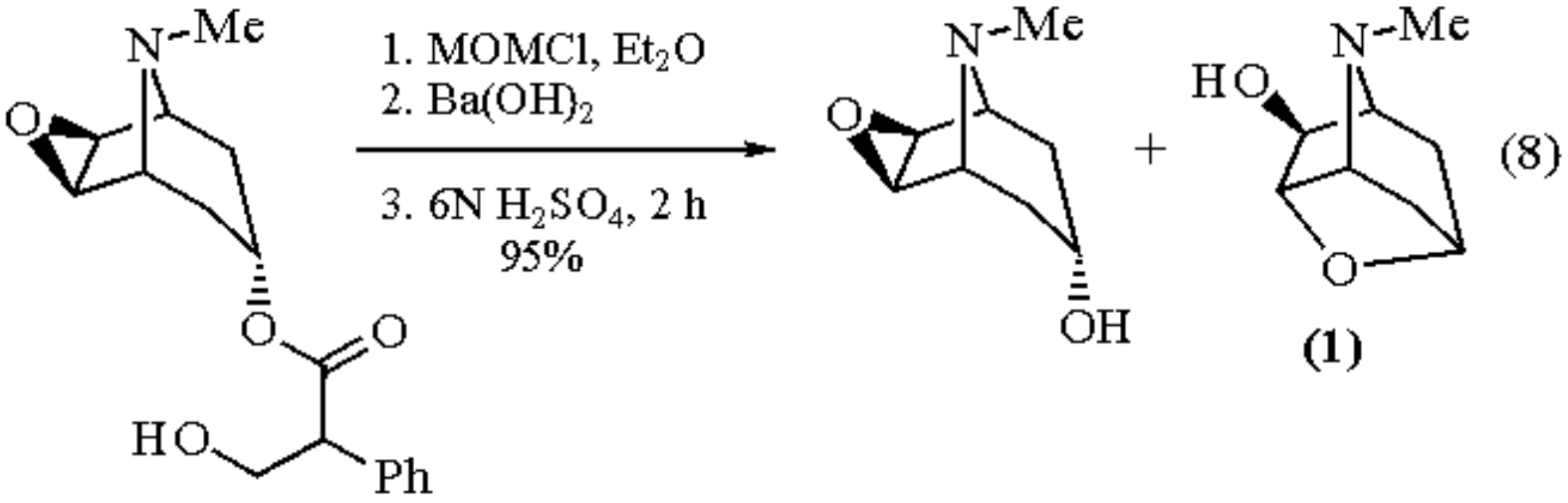

Use in C-C Bond-Forming Reactions.

Since MOMCl is an excellent electrophile it readily reacts with enolates[58] and other carbanions[59] and thus serves as an easily handled one-carbon synthon. Friedel-Crafts alkylation with MOMCl and a Lewis acid such as ***Tin(IV) Chloride***,[60] ***Titanium(IV) Chloride***,[61] ***Zinc Chloride***,[62] and ***Aluminum Chloride***[63] or ***Acetic Acid***[64] is a common method for introduction of a chloromethyl group onto an aromatic nucleus (eqs 9 and 10).[60,64] The reaction is quite general and tolerates a broad range of functionality.

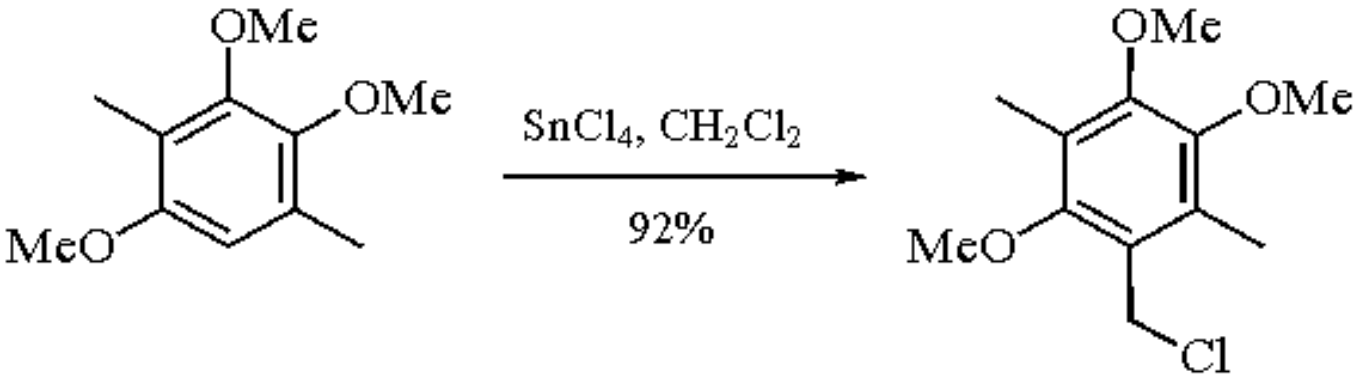

(9)

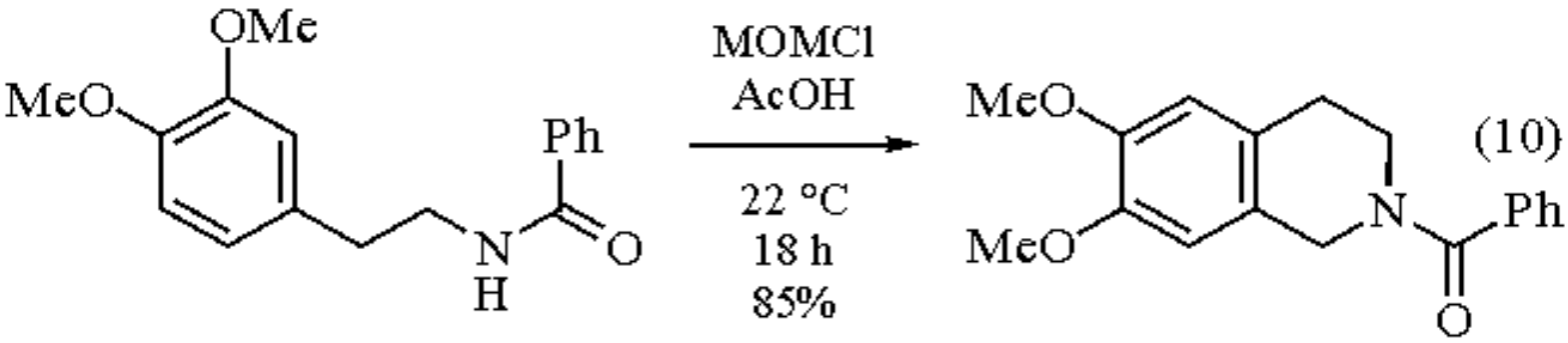

(10)

Alkenes react in a similar fashion giving methoxymethyl derivatives, but in this case the intermediate carbenium ion is trapped with methoxide or another nucleophile such as a nitrile to afford the methyl ether or amide in a Ritter-like reaction (eq 11).[65] In similar fashion, silyl enol ethers give ketones (eq 12),[66,67] allylsilanes afford homologated alkenes (eq 13),[68] and stannylalkynes are converted to propargyl ethers.[69]

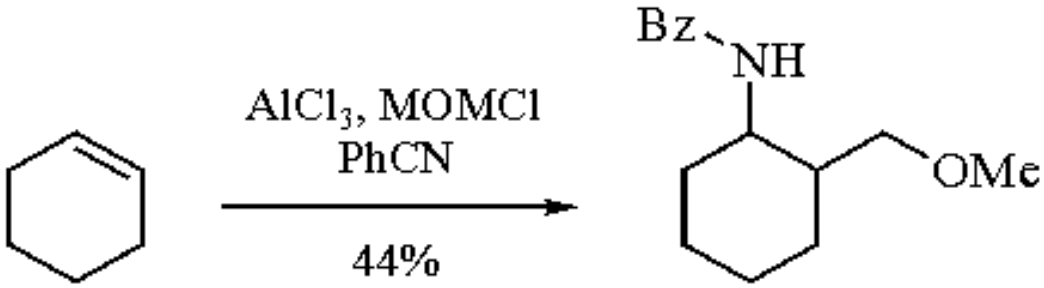

(11)

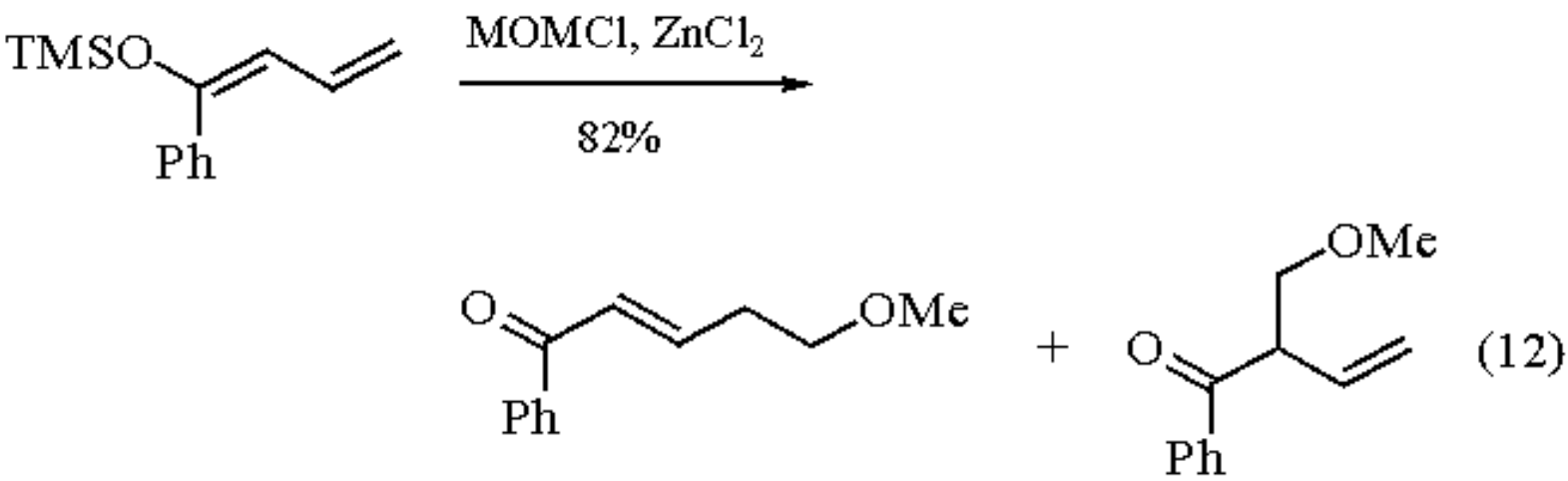

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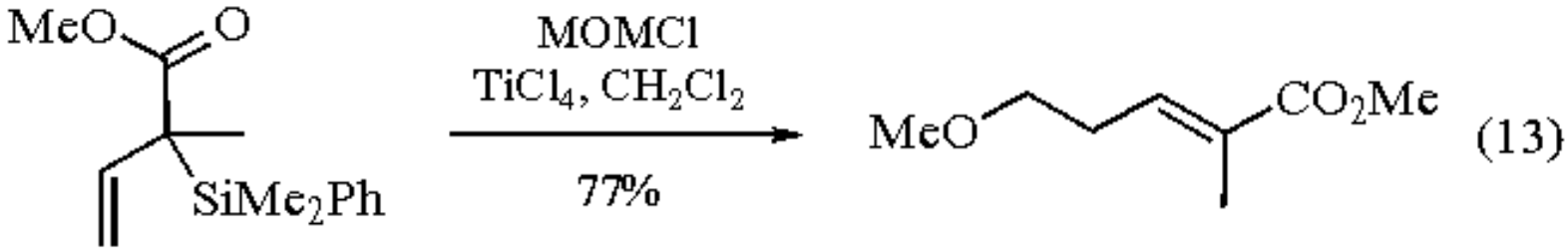

MOMCl can be converted to the Grignard reagent or the lithium reagent and used to introduce one carbon by nucleophilic attack on ketones and esters.[70] These reagents are best prepared in methylal.[71]

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Peter G. M. Wuts

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Chloromethyl Methyl Sulfide

$MeSCH_2Cl$

[2375-51-5] · C_2H_5ClS · Chloromethyl Methyl Sulfide · (MW 96.58)

(protection of carboxylic acids and alcohols;[1] introduces a methyl[2] or methylene[3] unit on carbon or nitrogen;[4] preparation of vinyl sulfides;[5] corresponding Grignard reagent reacts with various electrophiles;[6] oxidative additions with various metals[7])

Alternate Name: methylthiomethyl chloride; MTMCl.

Physical Data: bp 38 °C/55 mmHg, 52 °C/100 mmHg, 107 °C/750 mmHg; d^{20} 1.1773 g cm^{-3}.

Solubility: sol acetonitrile, ether, dichloromethane.

Form Supplied in: colorless liquid; commercially available.

Handling, Storage, and Precautions: hydrolyzes easily; flammable; exhibits obnoxious odor. Use in a fume hood.

Protective Group.

Carboxylic acids react with chloromethyl methyl sulfide (MTMCl) to give MTM esters (eq 1).[1,8-11] This protective group is stable for 1 h in contact with an aqueous solution of pH 0-15.[9] It is also stable to sodium borohydride and Zn-MeOH.[8] Primary and secondary alcohols[12,13] and phenols[14] react with MTMCl to yield the corresponding MTM ethers (eq 2). The MTM ether function is stable to basic, nucleophilic, and mild acidic conditions (aq AcOH).[12,14] Various mild conditions can be used for selective deprotection.[1]

$$RCO_2H \xrightarrow[\text{NEt}_3\ (1\ \text{equiv}),\ \text{MeCN}\ \text{reflux, 24 h}]{\text{MTMCl (1 equiv)}} RCO_2\text{-MTM} \qquad (1)$$

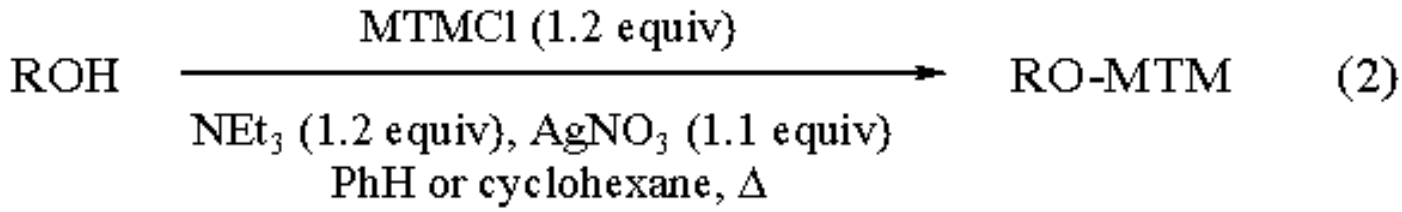

Electrophilic Reagent.

Silyl enol ethers react with MTMCl in the presence of ***Iodotrimethylsilane***[15] or ***Zinc Bromide***[3] to give methylthiomethylated products (eq 3).[3] The methylthio group can be removed reductively to accomplish an overall methylation. Oxidative removal of the methylthio group provides a way for α-methylenation of carbonyl compounds (eq 3).[3] Other carbon nucleophiles that react with MTMCl include aromatic compounds,[2] stabilized carbanions,[16,17] and organotin acetylides.[18] Similarly, introduction of the MTM group on nitrogen with MTMCl provides a way for eventual methylation[19] or methylenation.[4,20,21] Phosphonates (eq 4),[5,22] phosphine oxides,[23] or phosphorus ylides[24] derived from MTMCl have been used in the preparation of vinyl sulfides, which lead to the corresponding ketones after hydrolysis.[5]

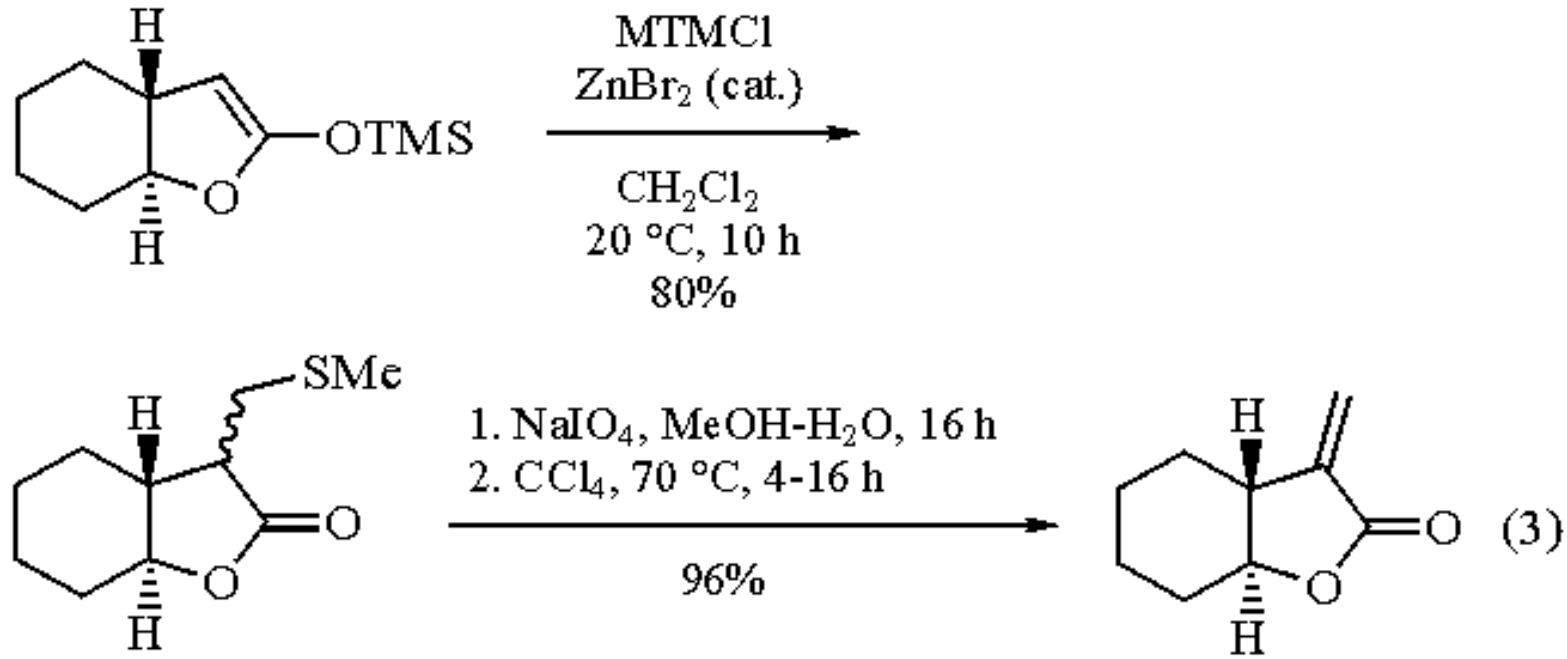

Reaction with Metals.

The Grignard reagent prepared from MTMCl reacts with various electrophiles (eq 5).[6] Oxidative additions of

transition metals (Pt, Pd, Ni, Fe) with MTMCl give organometallic compounds containing the methylthiomethyl ligand.[7,25-29] These compounds have been prepared because of interest in their structures and reactions.

$$\text{MTMCl} \xrightarrow[\text{10-20 °C}]{\text{Mg}} \text{MeSCH}_2\text{MgCl} \xrightarrow{\text{C}_{12}\text{H}_{25}\text{Br}} \underset{\text{76\%}}{\text{MeSC}_{13}\text{H}_{27}} \qquad (5)$$

Related Reagents.

Chloromethyl Phenyl Sulfide.

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Yeun-Min Tsai

2-Chloromethyl-4-nitrophenyl Phosphorodichloridate

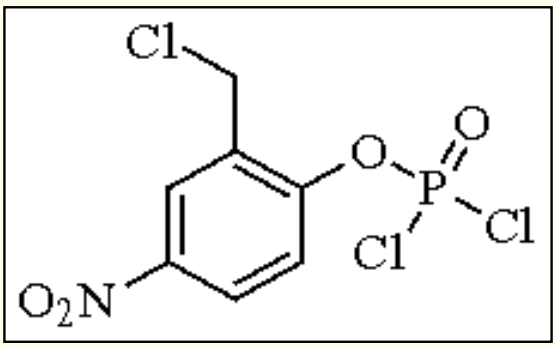

[23561-36-6] · $C_7H_5Cl_3NO_4P$ · 2-Chloromethyl-4-nitrophenyl Phosphorodichloridate · (MW 304.45)

(phosphorylation of alcohols[1,2])

Physical Data: bp 165-167 °C/0.2 mmHg; solidifies when chilled, mp 43-44 °C.

Preparative Method: by heating at reflux a mixture of 2-chloromethyl-4-nitrophenol and ***Phosphorus Oxychloride*** in the presence of a catalytic amount of KCl.[1]

Purification: by distillation.

Phosphorylation of Alcohols.[3]

Reaction of 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**1**) with one equivalent of an alkyl alcohol or phenol gives the alkyl or phenyl 2-chloromethyl-4-nitrophenyl phosphate (**2**) (eq 1).[1] Hydrolysis of (**2**) in aqueous pyridine affords the alkyl (phenyl) dihydrogen phosphates (**3**) (eq 2);[1] this is a useful method for the phosphorylation of valuable alcohols since only one equivalent of alcohol is required. Alternatively, (**2**) may be treated with a second alcohol in the presence of pyridine to provide a mixed diester (**4**) of phosphoric acid.[2]

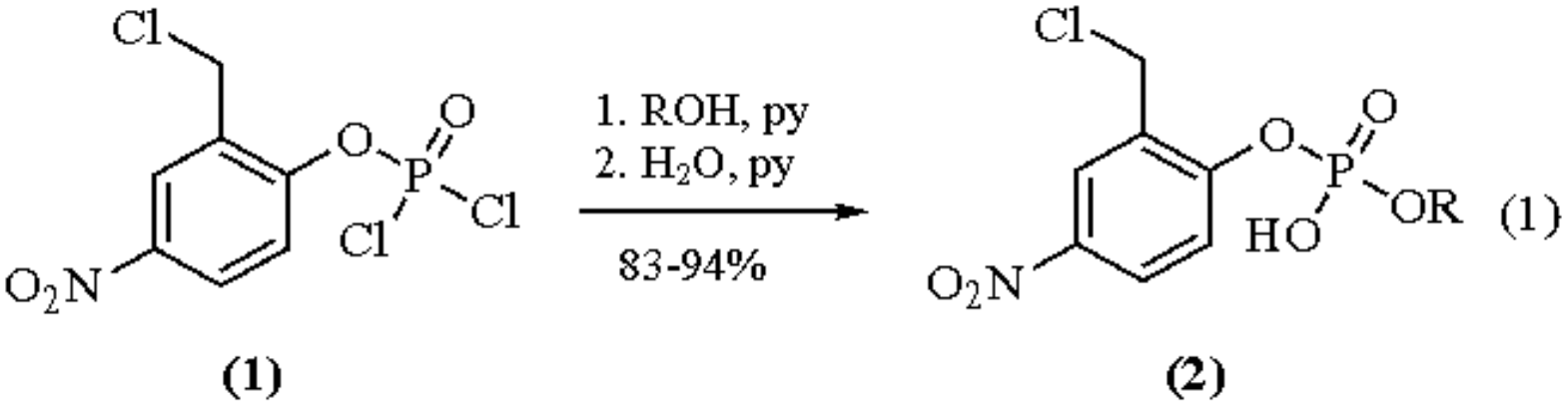

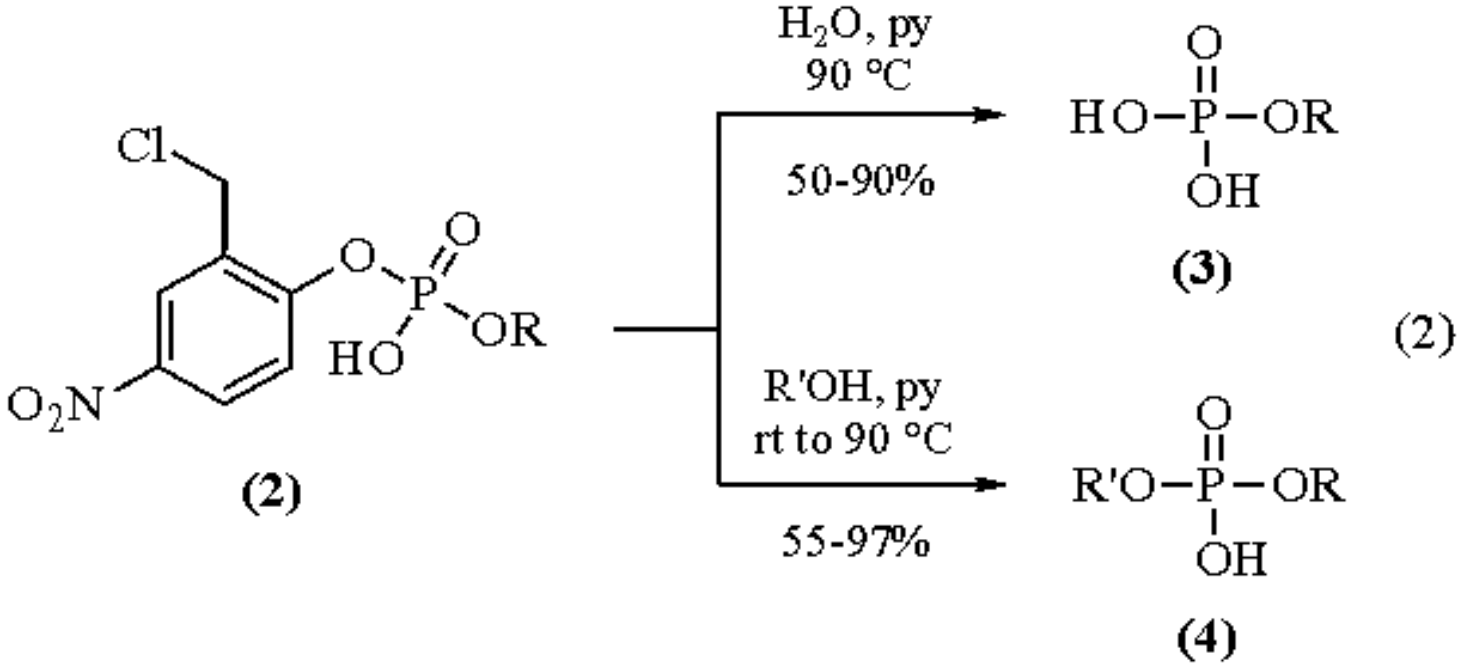

These transformations rely on the conversion of (**2**) to the inner salt (**5**), an active phosphorylating agent, upon reaction with pyridine. The 2-chloromethyl-4-nitrophenyl group therefore acts as an activatable protecting group. The reaction byproduct, the salt (**6**), is precipitated from the reaction mixture on addition of ethanol, and is readily removed by filtration.

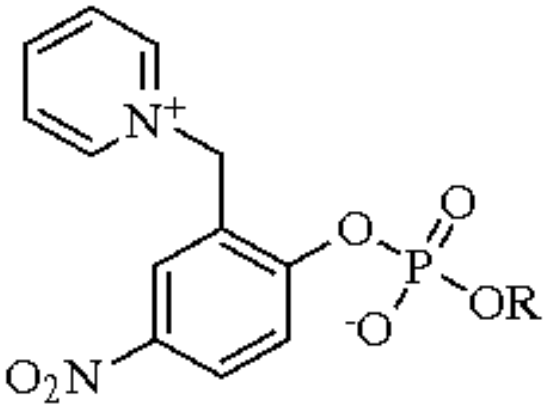

(5)

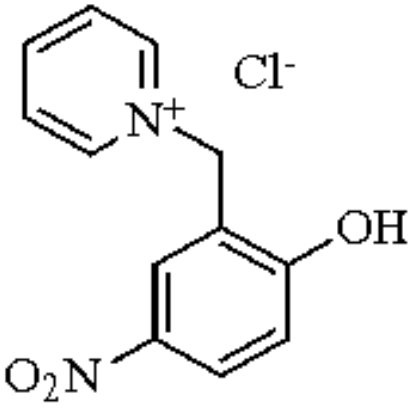

(6)

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Chloromethyl 4-Pentenyl Ether

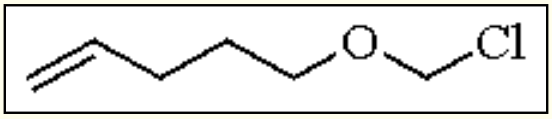

[98486-13-6] · $C_6H_{11}ClO$ · Chloromethyl 4-Pentenyl Ether · (MW 134.61)

(protection of alcohols[1])

Alternate Name: 4-pentenyloxymethyl chloride; POMCl.

Physical Data: bp 158-160 °C/760 mmHg, 34-38 °C/3.1 mmHg.

Solubility: sol dichloromethane.

Preparative Method: chloromethyl 4-pentenyl ether is prepared in 90-98% yield by treatment of a mixture of 4-pentenol and ***Paraformaldehyde*** (1.25 equiv) with ***Hydrogen Chloride*** gas at 0 °C. The crude product can be used directly or purified by distillation.[2,3]

Purification: by distillation.

Handling, Storage, and Precautions: potent alkylating agent; moisture sensitive. Use in a fume hood.

Protection of Alcohols.

Primary or secondary alcohols can be protected with the POM group upon treatment with POMCl (2 equiv) in the presence of Hünig's base (***Diisopropylethylamine***) (4 equiv) in dichloromethane (eq 1).[2] This protective group survives in 75% aqueous acetic acid but not in 5% aqueous hydrochloric acid.[4] Deprotection is performed with ***N-Bromosuccinimide*** (2.5 equiv) in 1% aqueous acetonitrile or a 1:1 mixture of 2% aqueous acetonitrile and dichloromethane.[4] The mild deprotection processes can tolerate many other protecting groups such as *t*-butyldimethylsilyl, benzyl, *p*-methoxybenzyl, acyl, allyl, and ethoxyethyl groups.[5]

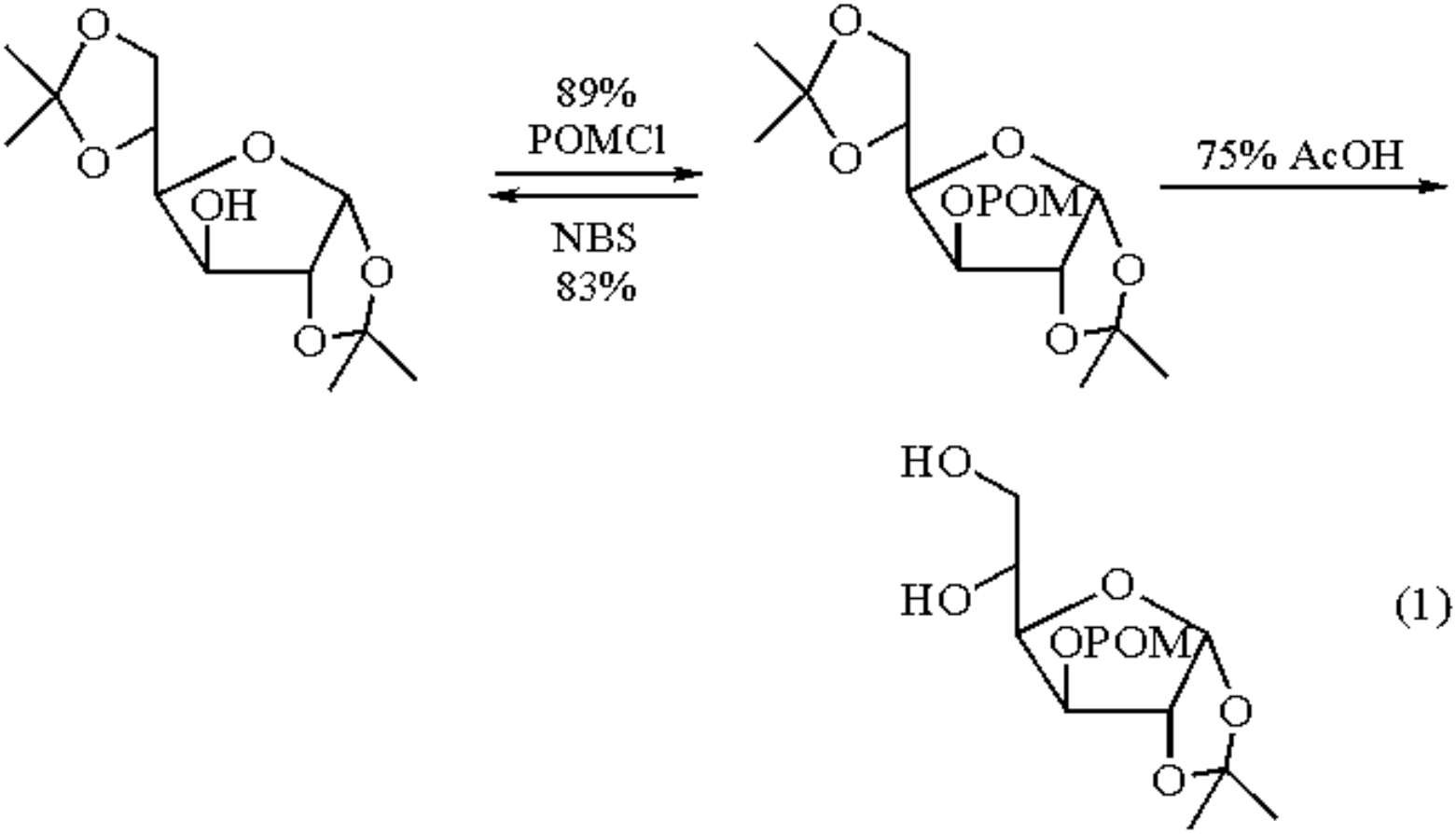

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Chloromethyl Phenyl Sulfide[1]

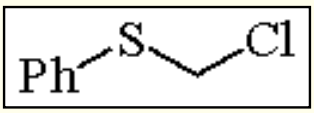

[7205-91-6] · C_7H_7ClS · Chloromethyl Phenyl Sulfide · (MW 158.65)

(reactive electrophile for many nucleophiles;[2] α-methylenating agent;[3] acyl carbanion equivalent;[4] phenylthiocarbene,[5a,b] phenylthiomethyl carbanion,[5c] and halomethyl phenyl sulfoxide precursors[6])

Physical Data: bp 66 °C/0.2 mmHg.

Solubility: sol most organic solvents; insol H_2O.

Form Supplied in: liquid; commercially available.

Preparative Methods: there are several preparative methods available.[1a,b] The two most convenient methods are the reaction of ***Thioanisole*** with ***Sulfuryl Chloride***[7] and the reaction of ***Thiophenol*** with bromochloromethane using ***1,8-Diazabicyclo[5.4.0]undec-7-ene***[8] or an alkali metal hydroxide as the base.[9]

Handling, Storage, and Precautions: stench; the material should be handled in a well-ventilated fume hood and kept cooled. Freshly prepared material can be stored at 0-5 °C without any appreciable decomposition. It is advisable to use freshly prepared or distilled material for reactions.

Alkylation Reactions.

The reagent reacts readily with silyl enol ethers of ketones, lactones, and esters in the presence of ***Zinc Bromide*** or ***Titanium(IV) Chloride*** as the Lewis acid. α-Methylated ketones,[10] α-methylenated ketones (eq 1),[3b,c] γ-lactones (eq 2),[3a] and esters (eq 3)[3a] can be synthesized by this method. The regioselectivity of the introduced substituents is controlled by the structures of the silyl enol ethers.

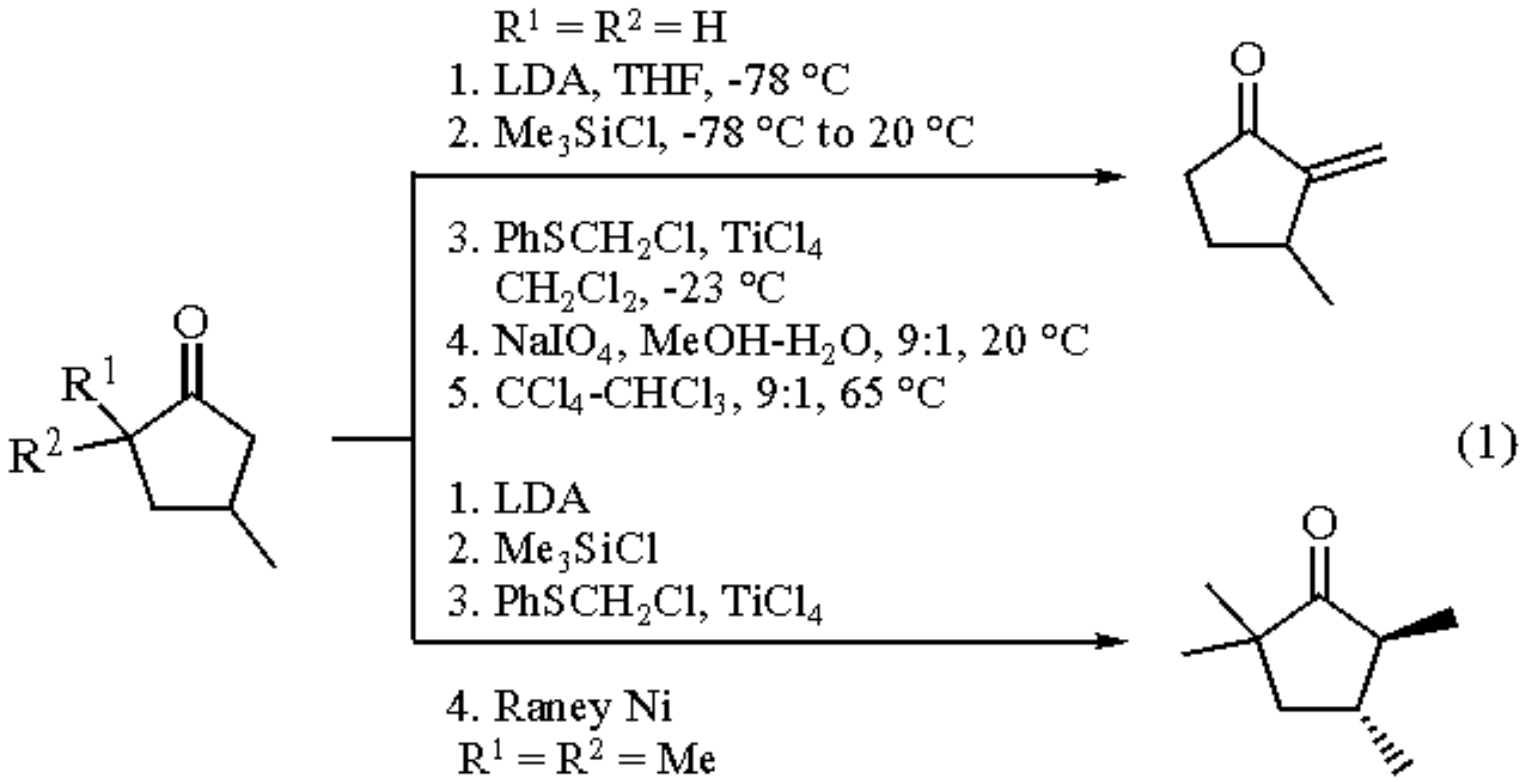

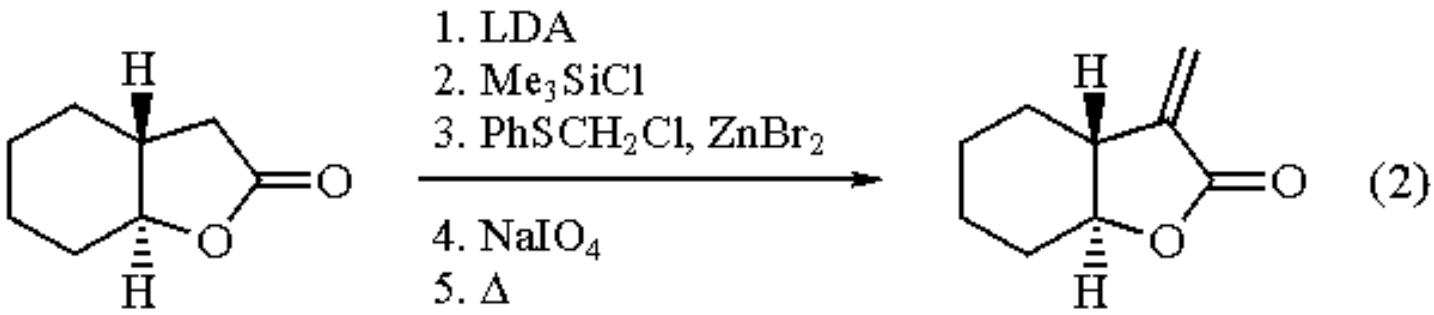

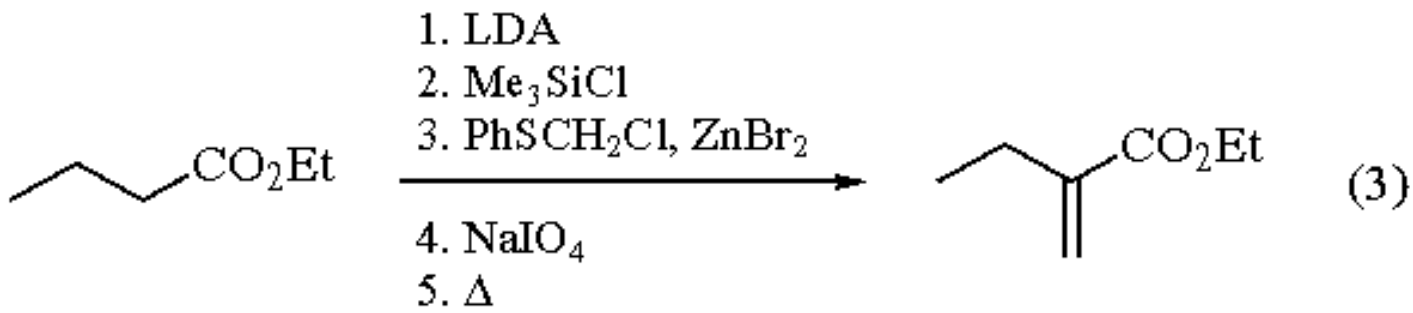

The α:γ ratios in phenylthiomethylation of silyl dienol ethers are controlled by the size of the substituents on the silyl atom and the substituents on the α- and γ-positions of the *O*-silylated dienolate (eq 4).[11,12]

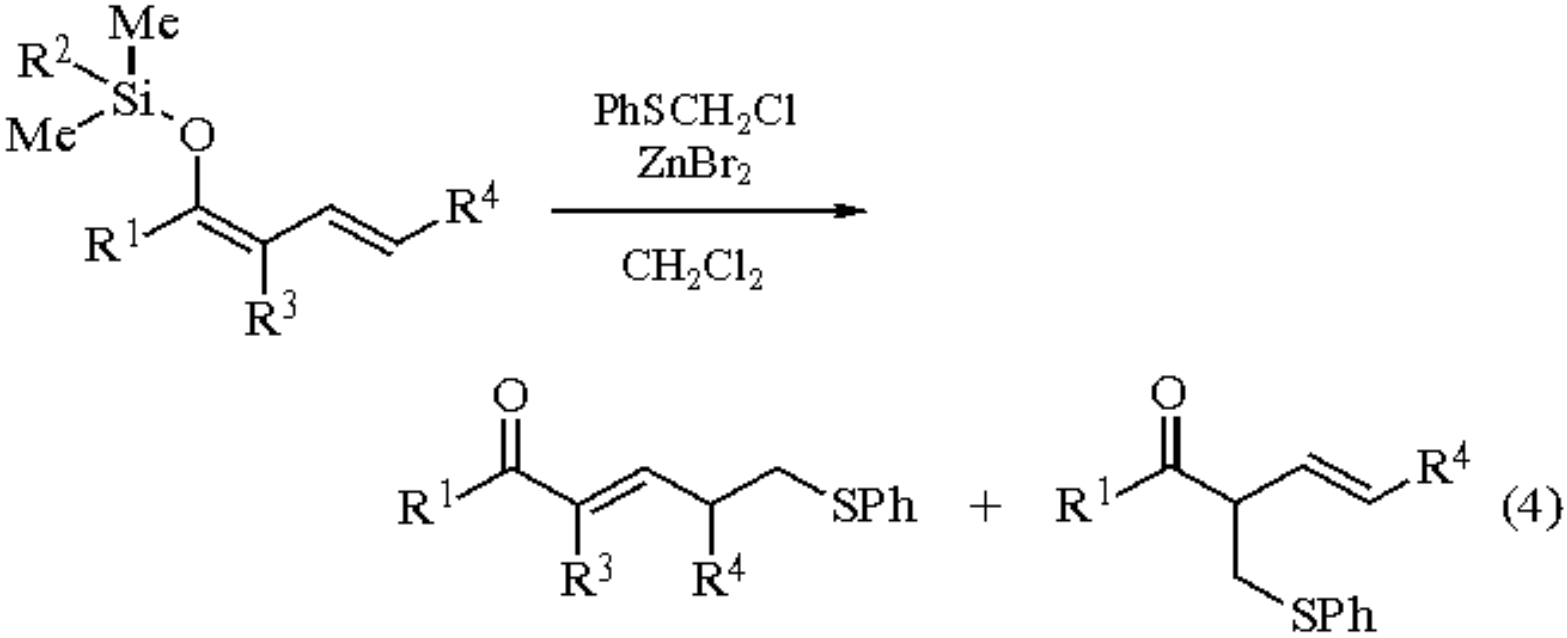

1. $R^1 = Ph$, $R^2 = Me$, $R^3 = R^4 = H$	45:55
2. $R^1 = Ph$, $R^2 = Ph$, $R^3 = R^4 = H$	85:15
3. $R^1 = Ph$, $R^2 = Me$, $R^3 = Me$, $R^4 = H$	31:69
4. $R^1 = Ph$, $R^2 = Me$, $R^3 = H$, $R^4 = Me$	74:26

Phenylthiomethylation-desulfurization of phenols yields *C*-methylated phenols in moderate yields. The *ortho*:*para* ratio is 3:1. A major useful byproduct in some cases, especially when only the *para* position is free, is a diphenylmethane. The Lewis acid of choice is ***Tin(IV) Chloride*** (eq 5).[2a] Phenylthiomethylation of aromatic hydrocarbons gives a low yield of the *C*-alkylated product.[13,14] Cationic polar [4 + 2] cycloaddition of the reagent with styrene using $SnCl_4$ as a Lewis acid gives a thiochroman (eq 6).[15] Allylic silanes can be alkylated by using $TiCl_4$ as a Lewis acid (eq 7).[16]

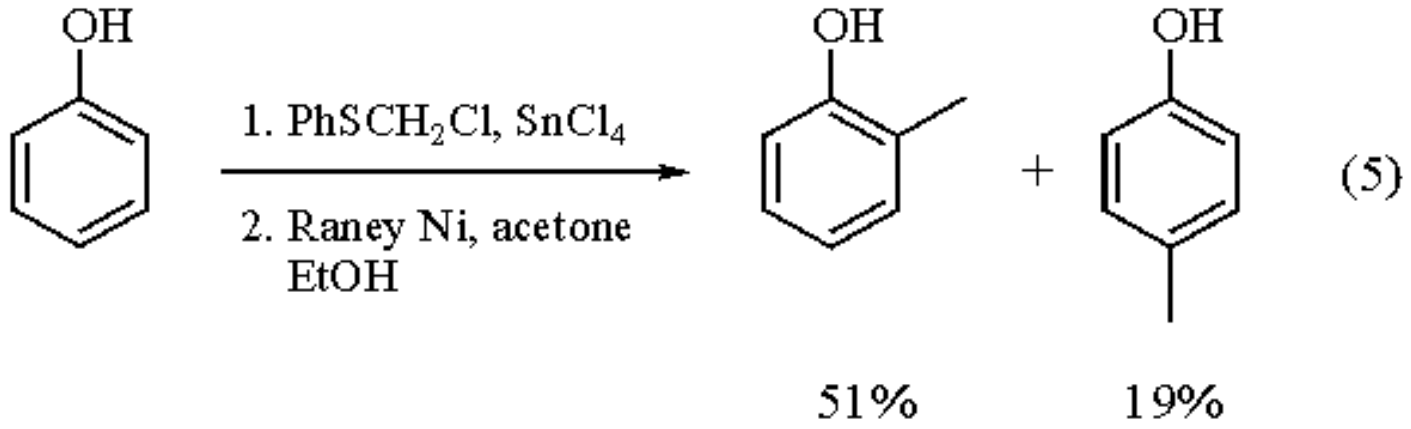

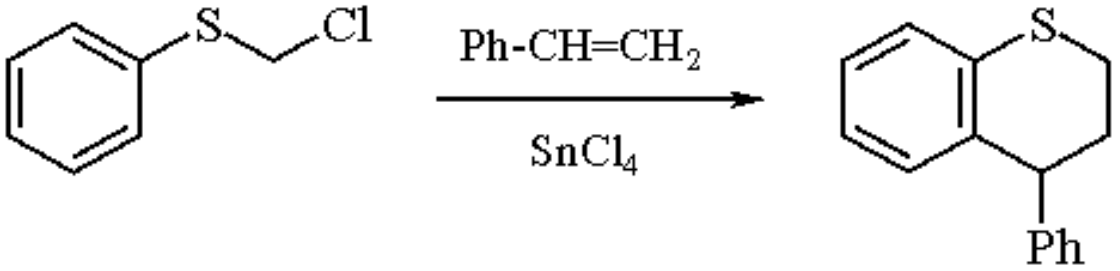

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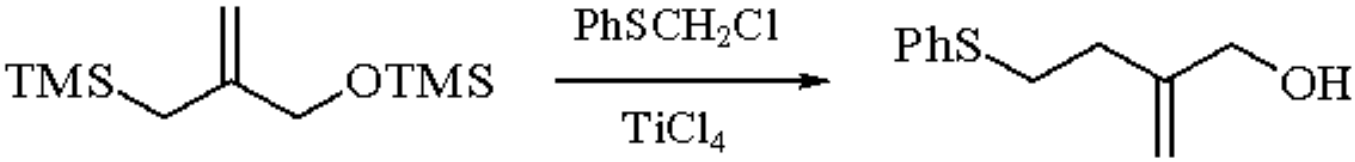

(7)

Phenylthiomethylation of metal enolates gives moderate yields of the *C*-alkylated products (eq 8).[17]

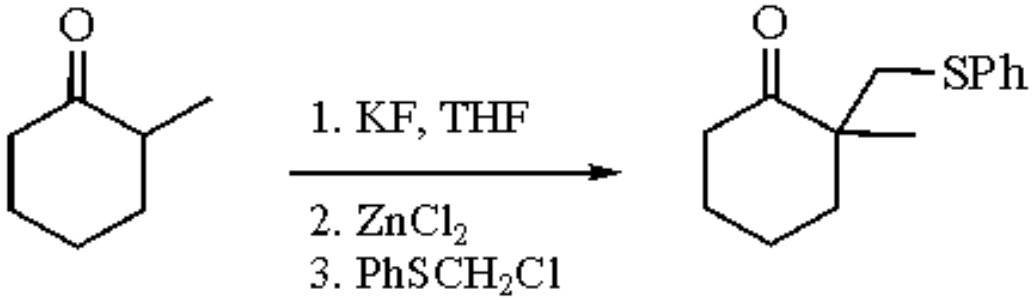

(8)

N-Alkylation.

Substituted methylene radicals can be generated from the substituted phenylthiomethylene group.[18] *N*-Alkylation of secondary amines,[18] sulfonamides,[18] imides,[19] and nitriles[20] gives the alkylated products. The *N*-phenylthiomethylated products can be transformed into pyrrolidine derivatives by radical cyclization with ***Tri-n-butylstannane-Azobisisobutyronitrile*** (eq 9).[18] Phenylthiomethylation of benzimidazole[2b] and benzotriazole[21] occurs at the *N*-1 position. The *N*-phenylthiomethylated benzotriazole can be readily alkylated and the product is a versatile 1,1-dipole synthon equivalent (eq 10).[21]

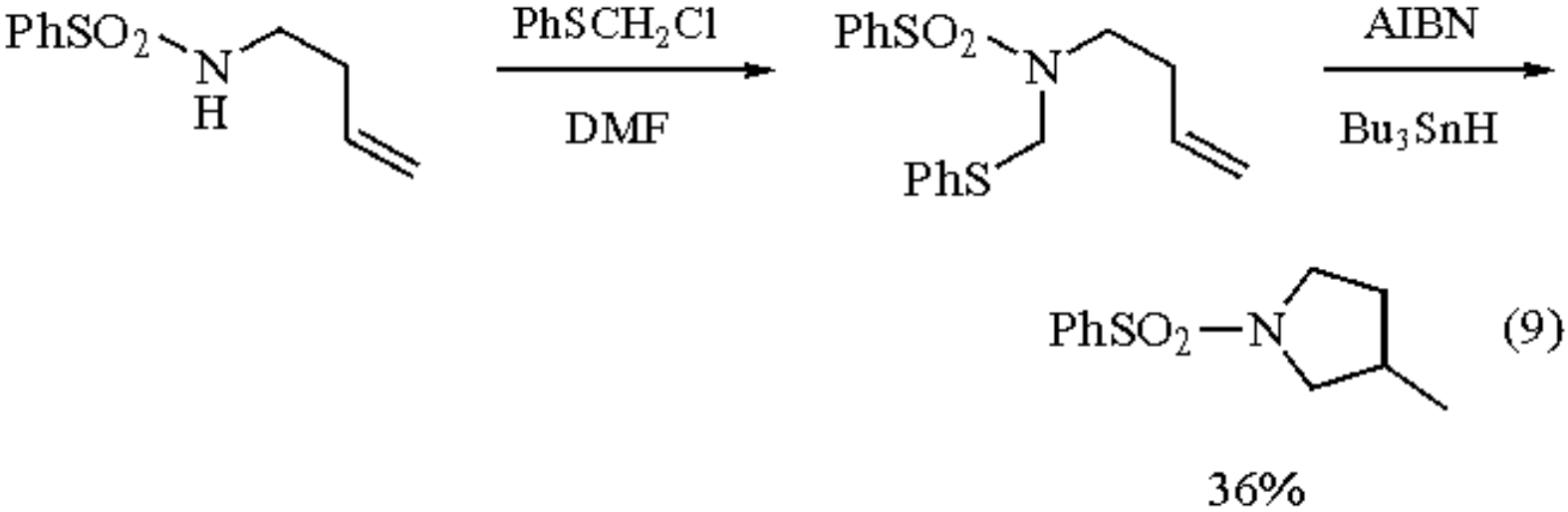

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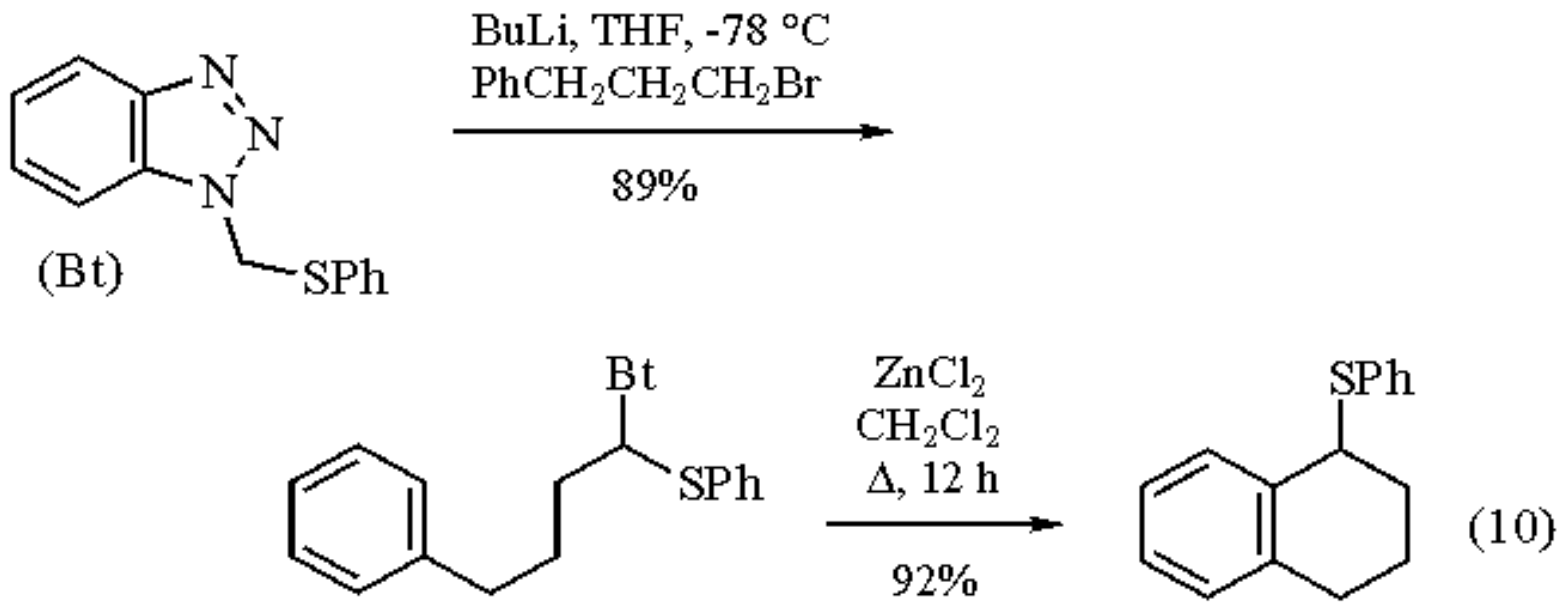

O-Alkylation.

The *O*-phenylthiomethylated products of phenols are utilized for the synthesis of aryl arylsulfonylmethyl ethers[22] and for protection of the phenol group; the protecting group is more resistant to hydrolysis by ***Mercury(II) Chloride*** in 4:1 acetonitrile-water than the methylthiomethyl group.[2g]

S-Alkylation.

A sulfonium salt is formed by the phenylthiomethylation of the reagent with sulfides. The appropriately substituted sulfonium salt can undergo [2,3]-sigmatropic rearrangement to a dithioacetal derivative,[23] which is a potentially useful isoprenoid synthon (eq 11).[24] The bis(phenylthio) acetal is a very useful acyl carbanion equivalent precursor.[2f,24,25]

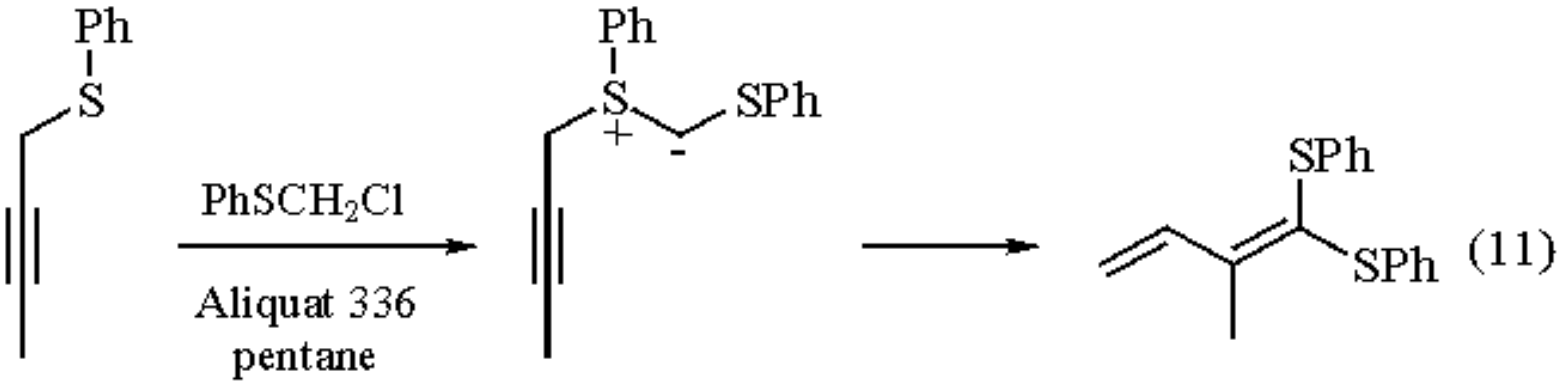

P-Alkylation.

Phenylthiomethylphosphonate and -phosphine oxide ylides, derived by deprotonation of the corresponding phosphorus derivatives obtained by phenylthiomethylation of the respective phosphorus compounds, undergo the

Horner-Wittig reaction with carbonyl compounds to give good yields of vinyl sulfides.[2c,4,26] Hydrolysis of the vinyl sulfides yields aldehydes and ketones.[4,24] The ylides are acyl anion equivalents (eq 12). Various carbonyl and ylide components are used for the synthesis of ketones and enones.[4]

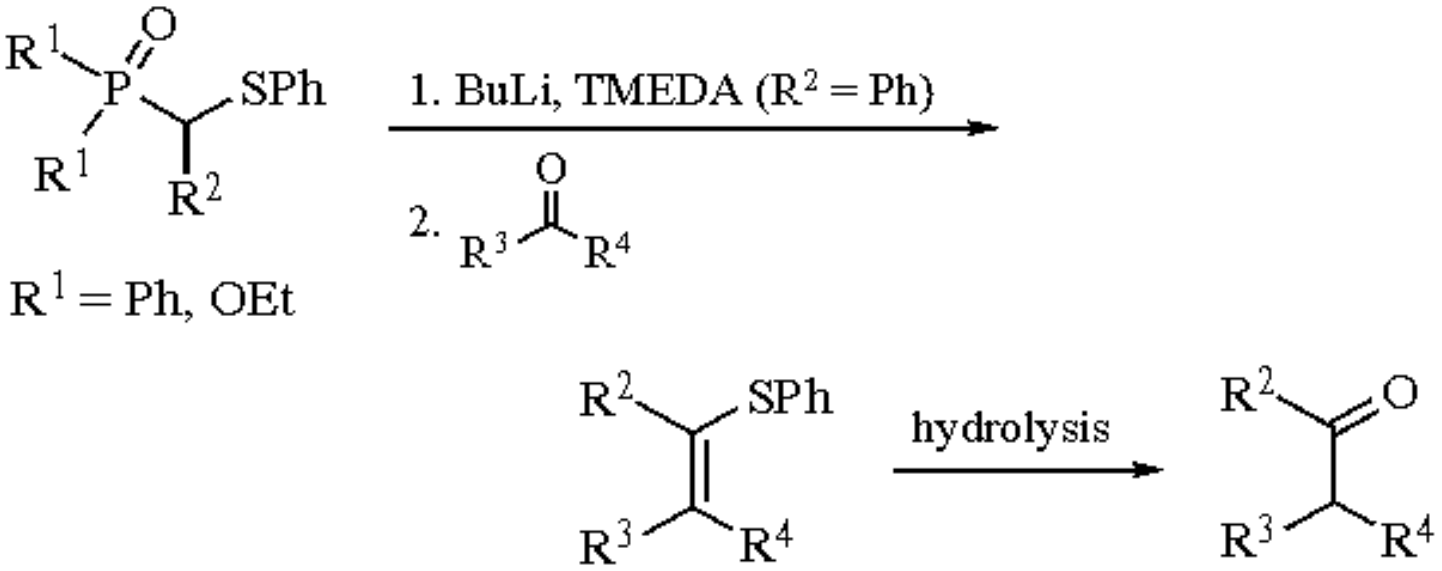

(12)

(Phenylthiomethylene)triphenylarsorane, derived by deprotonation (*n*-BuLi/THF) of the corresponding arsonium salt obtained from the reaction of chloromethyl phenyl sulfide and ***Triphenylarsine*** in the presence of ***Sodium Iodide*** in acetonitrile, reacts with aldehydes giving α-phenylthio epoxides in THF and vinyl sulfides in THF-HMPA. The α-phenylthio epoxides are rearranged with silica gel to α-phenylthio carbonyl compounds which upon desulfurization[10] yield methyl ketones. Hydrolysis of the vinyl sulfides gives aldehydes with one-carbon homologation (eq 13).[27]

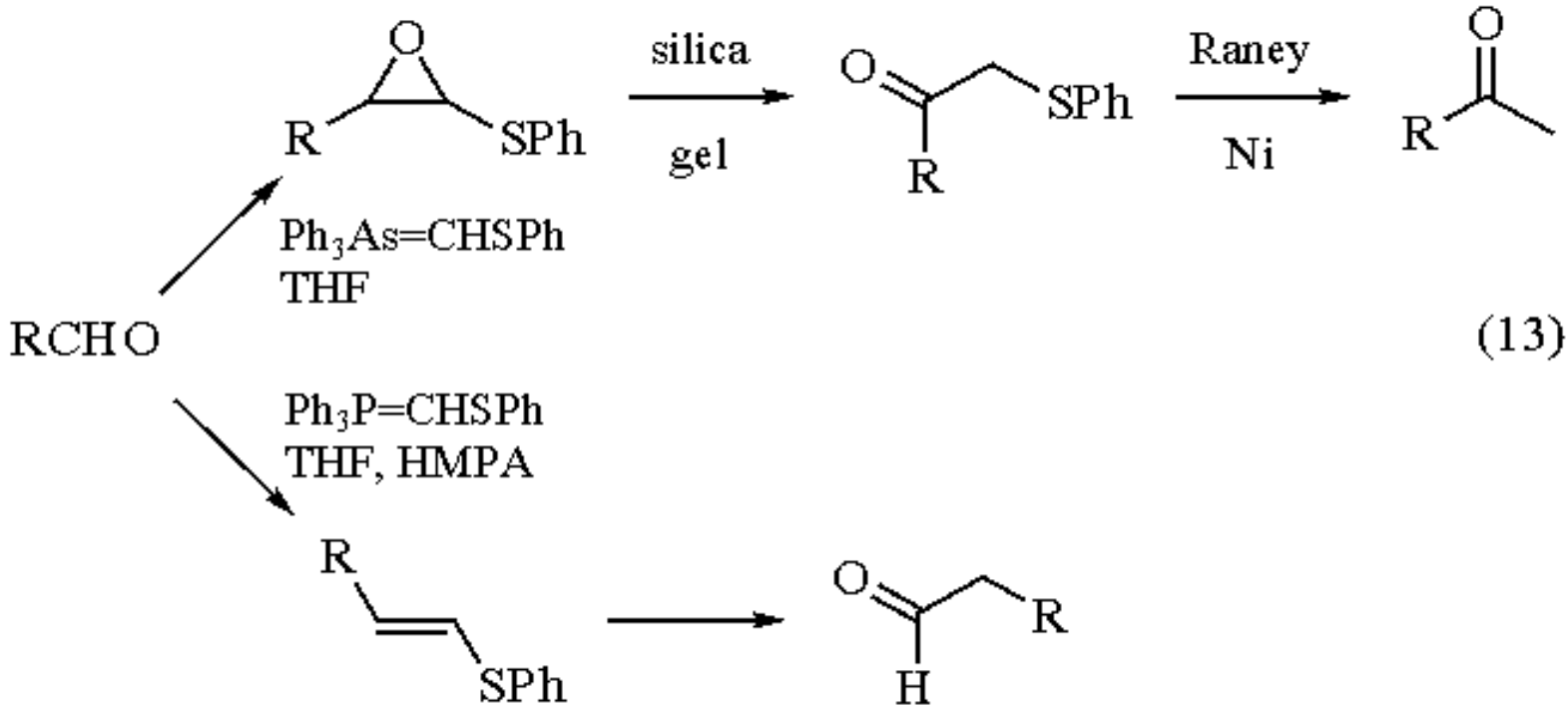

(13)

Thiocarbene Generation.

Phenylthiocarbene, generated by the reaction of chloromethyl phenyl sulfide with ***Potassium t-Butoxide*** in hexane[28] or with a phase transfer catalyst[5a,b] (***Benzyltriethylammonium Chloride*** and 50% ***Sodium Hydroxide***), adds to alkenes[5a,b] and 1,1-dimethylallene[28b] yielding phenylthiocyclopropanes and 2-(phenylthio)-1-methylenecyclopropane, respectively, in good yields (eqs 14 and 15). An alternative method for the generation of the phenylthiocarbene is by reaction of bis(phenylthio) acetals with organolithium reagents.[29] Phenylthiocyclopropane can also be prepared by the reaction of thiophenol with 1-bromo-3-chloropropane in aqueous potassium hydroxide followed by cyclization of the resulting 3-chloropropyl phenyl sulfide with ***Potassium Amide*** in liquid ammonia.[30] 1-Lithio-1-phenylthiocyclopropane, prepared by deprotonation of phenylthiocyclopropane, has numerous interesting applications in synthesis.[31-33]

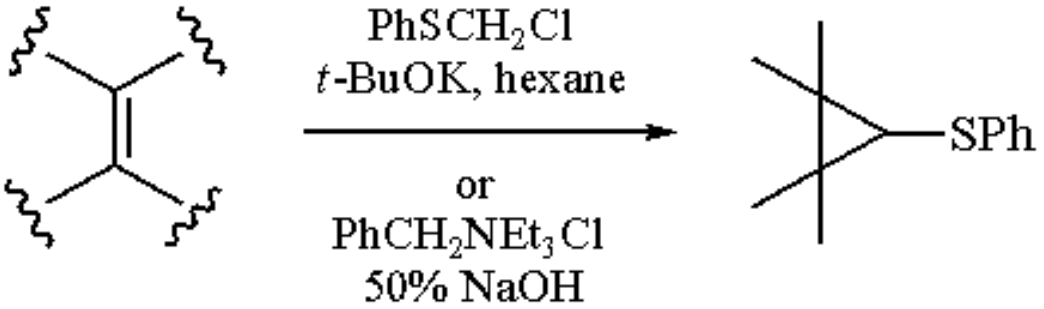

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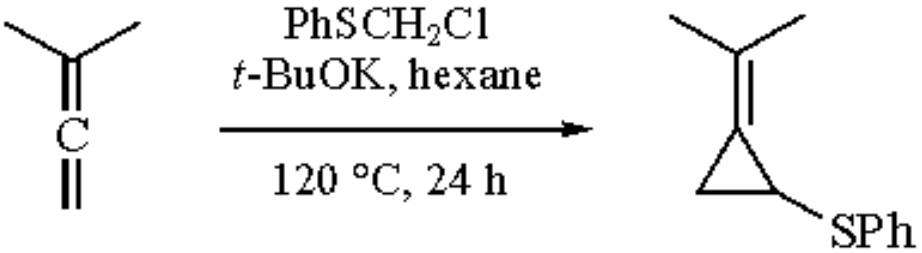

(15)

Reaction with Organometallic and Transition Metal Salts.

(η^5-Cyclopentadienyl)dicarbonyl(phenylthiomethyl)iron, $Cp(CO)_2FeCH_2SPh$, prepared from the reaction of ***Bis(dicarbonylcyclopentadienyliron)*** and chloromethyl phenyl sulfide, is used as a methylene transfer agent. Its reaction with *cis*-cyclooctene gives bicyclo[6.1.0]nonane.[34] Phenylthiomethyl carbanion[5c] is prepared by the reaction of chloromethyl phenyl sulfide with ***Chromium(II) Chloride*** and ***Lithium Iodide***[35] or with ***Samarium(II) Iodide*** (eq 16).[36] In the case of the [α-phenylthioalkyl)chromium compound], $PhSCHRCr^{III}$, *threo* selectivity is observed in the addition with aldehydes.

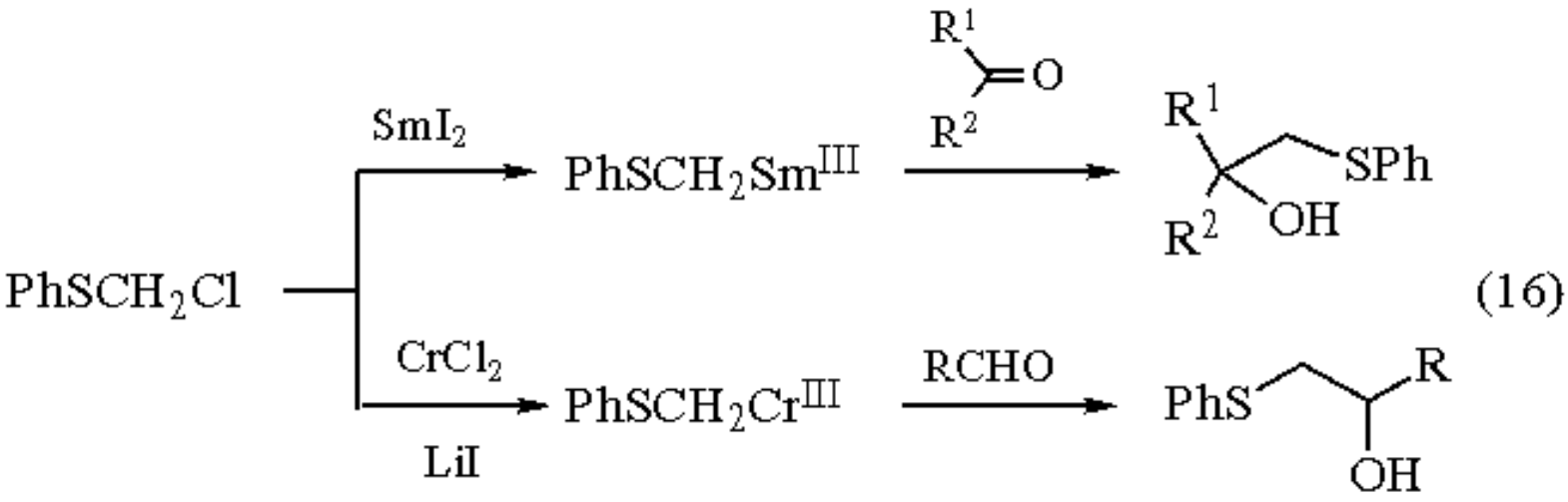

The coupling of organocuprates[37] and organotin compounds catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)***[38] with chloromethyl phenyl sulfide leads to carbon-carbon bond formation in good yields (eqs 17 and 18).

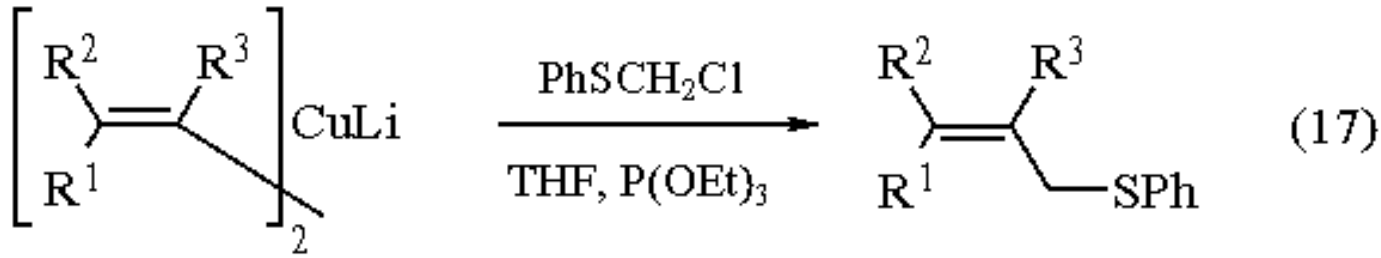

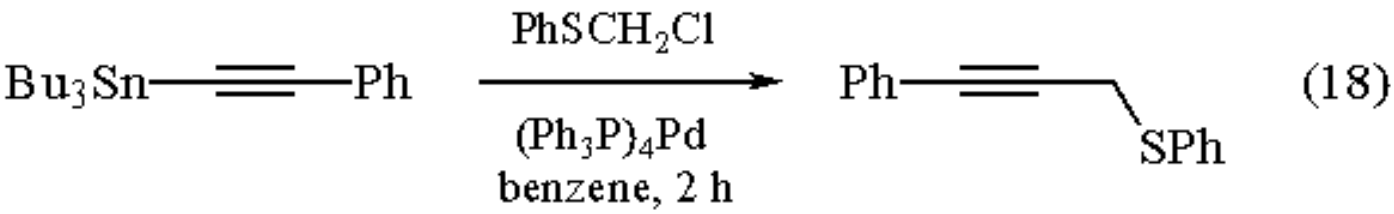

Oxidation Reactions.

Chloromethyl Phenyl Sulfoxide is prepared in good yield by the oxidation of chloromethyl phenyl sulfide with ***Sulfuryl Chloride*** and wet silica gel in methylene chloride (eq 19).[6a] ***Fluoromethyl Phenyl Sulfoxide*** is prepared by the oxidation of ***Fluoromethyl Phenyl Sulfide*** with NBS in aqueous MeOH; fluoromethyl phenyl sulfide is prepared from the reaction of chloromethyl phenyl sulfide using ***Potassium Fluoride*** and ***18-Crown-6*** in refluxing acetonitrile (eq 19).[6b]

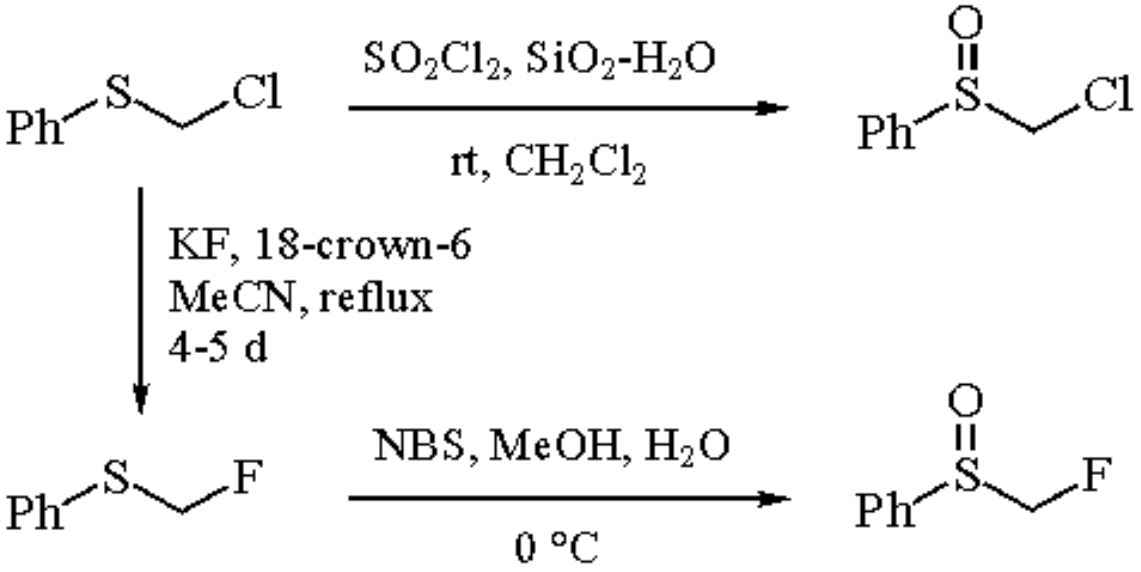

(19)

Related Reagents.

Benzyl Bromomethyl Sulfide; ***Benzyl Chloromethyl Sulfide***; ***Chloromethyl Methyl Sulfide***; ***Chloromethyl Phenyl Sulfone***; ***Chloromethyl Phenyl Sulfoxide***; ***Chloromethyl p-Tolyl Sulfide***.

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Mahidol University, Bangkok, Thailand

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Chloromethyl Phenyl Sulfone[1]

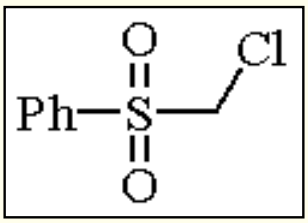

[7205-98-3] · $C_7H_7ClO_2S$ · Chloromethyl Phenyl Sulfone · (MW 190.65)

(synthesis of α,β-epoxy sulfones[1] and aziridines;[2] reacts with electrophilic arenes, heterocyclic arenes, and alkenes;[3] source of the α-phenylsulfonylmethyl radical[1a])

Physical Data: mp 52 °C.

Solubility: sol THF, $CHCl_3$, CH_2Cl_2, and most organic solvents.

Preparative Methods: several methods are available.[4] The most convenient is the reaction of ***Sodium Benzenesulfinate*** dihydrate with bromochloromethane in dimethyl sulfoxide.[4c]

Handling, Storage, and Precautions: use in a fume hood.

α,β-Epoxy Sulfones.

Epoxy sulfones are prepared by the reaction of the chloromethyl phenyl sulfone carbanion ($PhSO_2CHClM$) with carbonyl compounds. The one-step Darzens-type condensation can be effected by using a phase transfer catalyst, benzyltriethylammonium chloride in 50% sodium hydroxide (eq 1).[5] A less satisfactory two-step method involves the addition of α-lithiochloromethyl phenyl sulfone to carbonyl compounds at low temperature to give isolable β-hydroxy-α-chloro sulfones which are cyclized by ***Potassium Hydroxide*** in methanol (eq 2).[5c,6] The phase-transfer catalyst method gives *trans*-epoxy sulfones from aldehydes and mixtures of isomers from unsymmetrical ketones. In the two-step method the stereochemistry of the epoxy sulfones is not always determined by the stereochemistry of the β-hydroxy-α-chloro sulfones.[7] α,β-Epoxy sulfones can also be prepared by the epoxidation of α,β-unsaturated sulfones with alkaline ***Hydrogen Peroxide*** (giving *trans*-α,β-epoxy sulfones),[8] potassium chlorite (producing *cis*-α,β-epoxy sulfones),[9] ***1,1-Di-t-butyl Peroxide*** and alkyllithium (stereospecific),[10] ***t-Butyl Hydroperoxide*** (nonstereospecific),[10] and ***m-Chloroperbenzoic Acid***.[11]

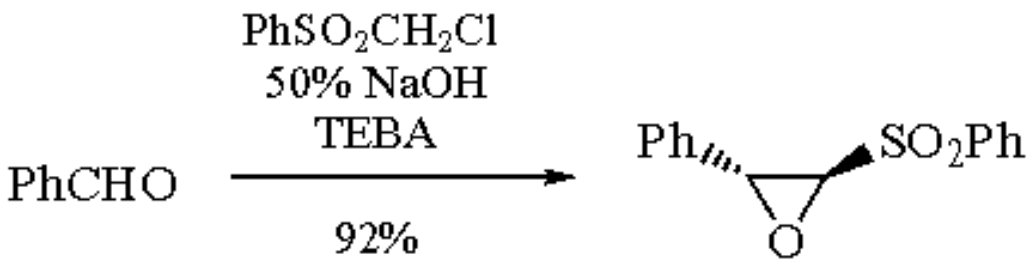

(1)

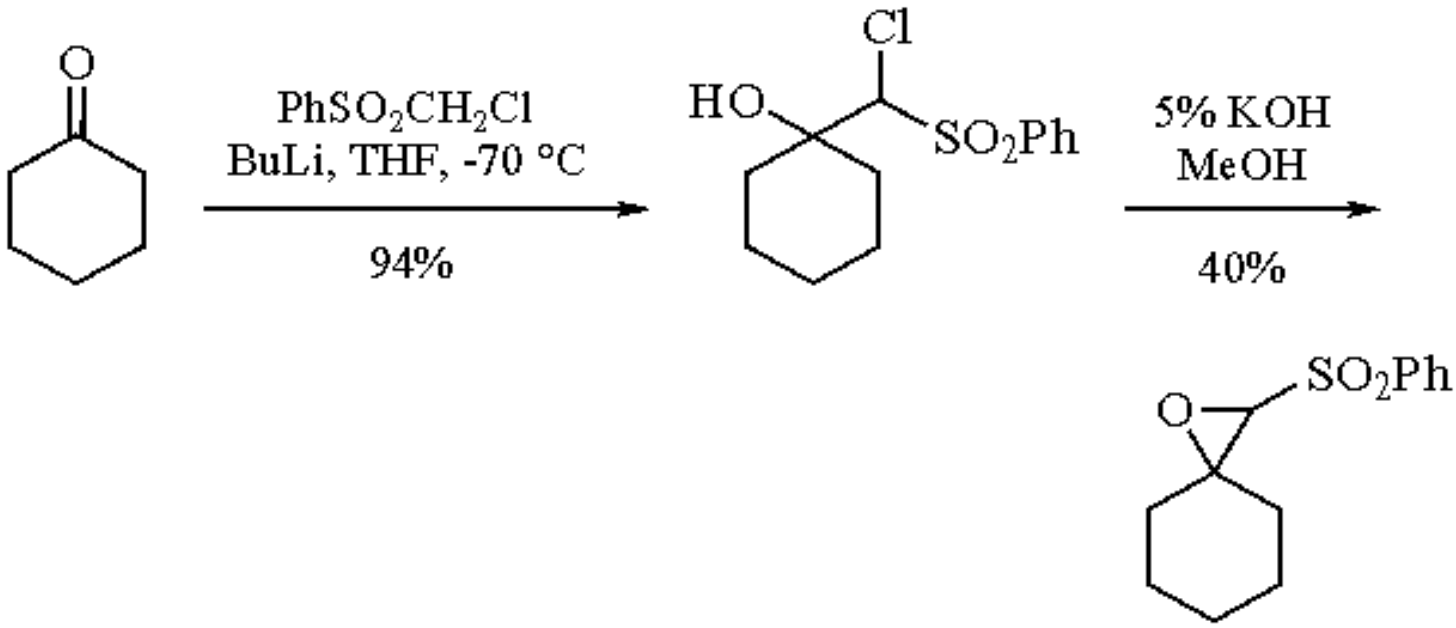

(2)

α,β-Epoxy sulfones undergo rearrangement-elimination either with ***Boron Trifluoride Etherate*** or thermally in a similar manner to α,β-epoxy sulfoxides. Normally, α-phenylsulfonyl carbonyl compounds or their mixture with the corresponding α,β-unsaturated carbonyl compounds are the final products (eq 3).[5c,6]

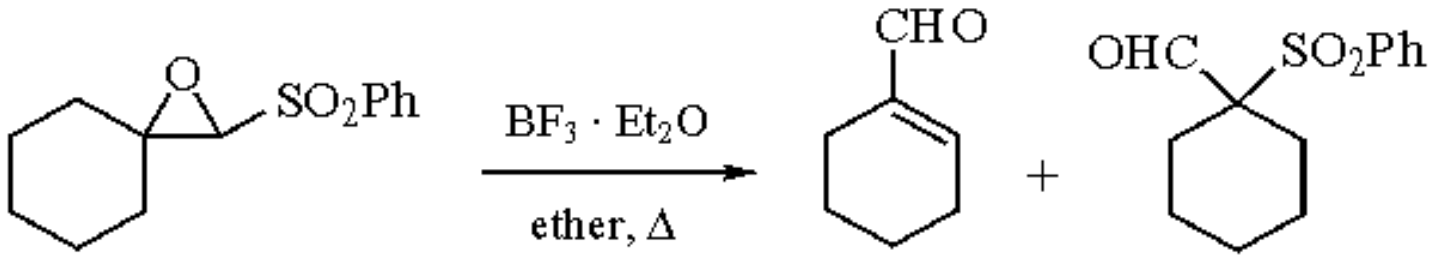

(3)

Reaction with a Lewis acid (i.e. ***Magnesium Bromide***) gives good yields of the α-bromo carbonyl compounds (eq 4).[5c,12]

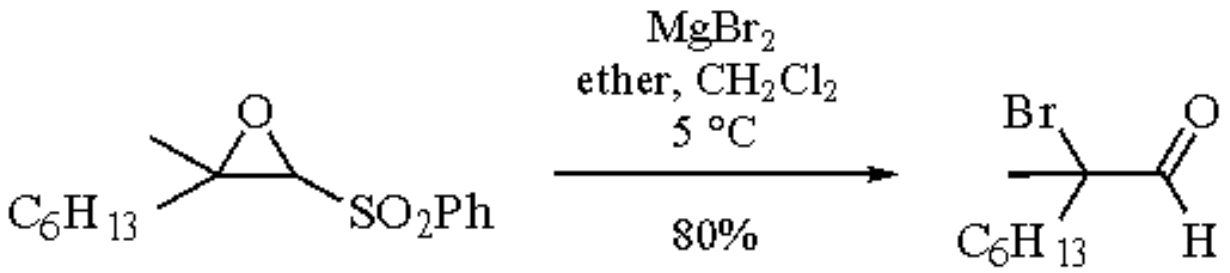

(4)

Ring opening of α,β-epoxy sulfones with ***Sodium Azide*** in DMF gives α-azido aldehydes which can be converted to α-azido nitriles by the Beckmann elimination (eq 5).[13] One-carbon homologation of ketones to α-hydroxy aldehydes is effected by the reaction of the α,β-epoxy sulfones with hydroxide ion generated by adding water to ***Potassium t-Butoxide*** (eq 6).[14] β-Keto phosphonates, valuable synthetic intermediates, are prepared by the reaction of α-substituted-α,β-epoxy sulfones with ***Diethyl Phosphonite*** (eq 7).[15]

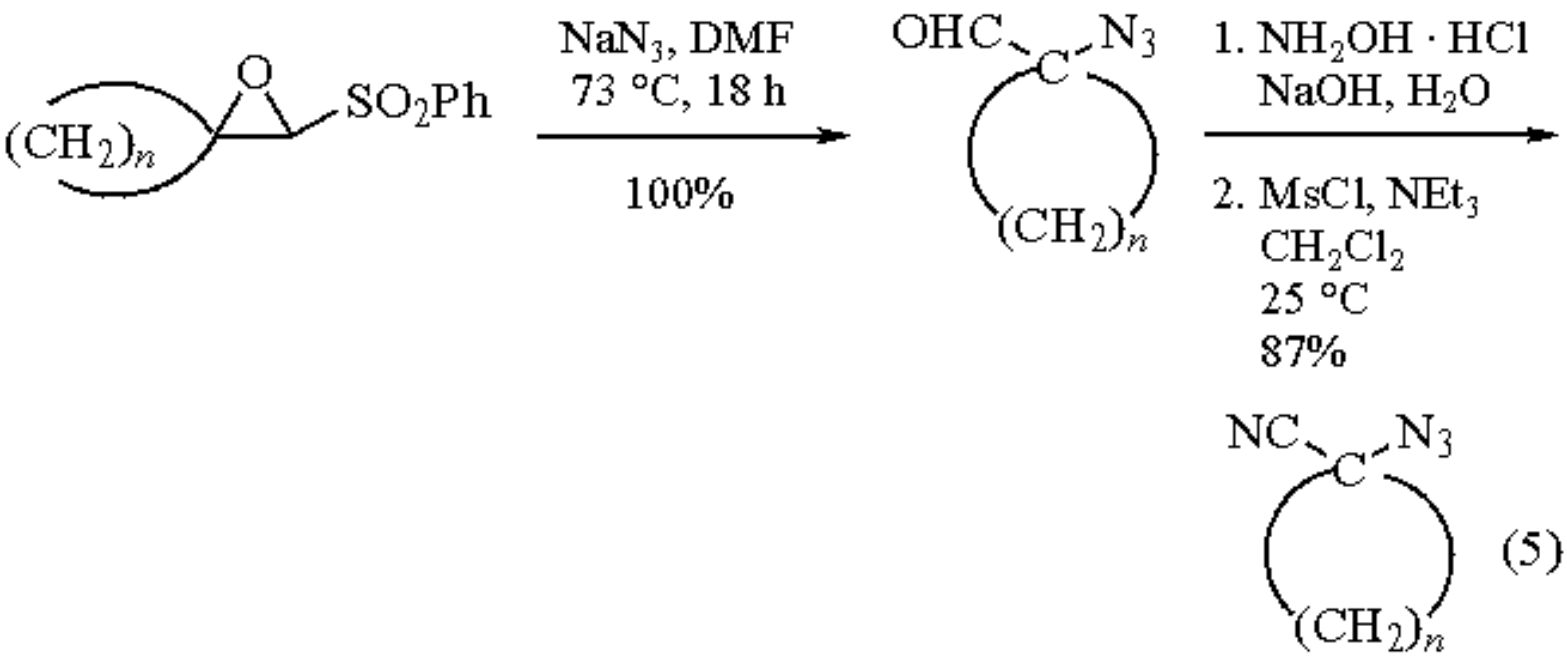

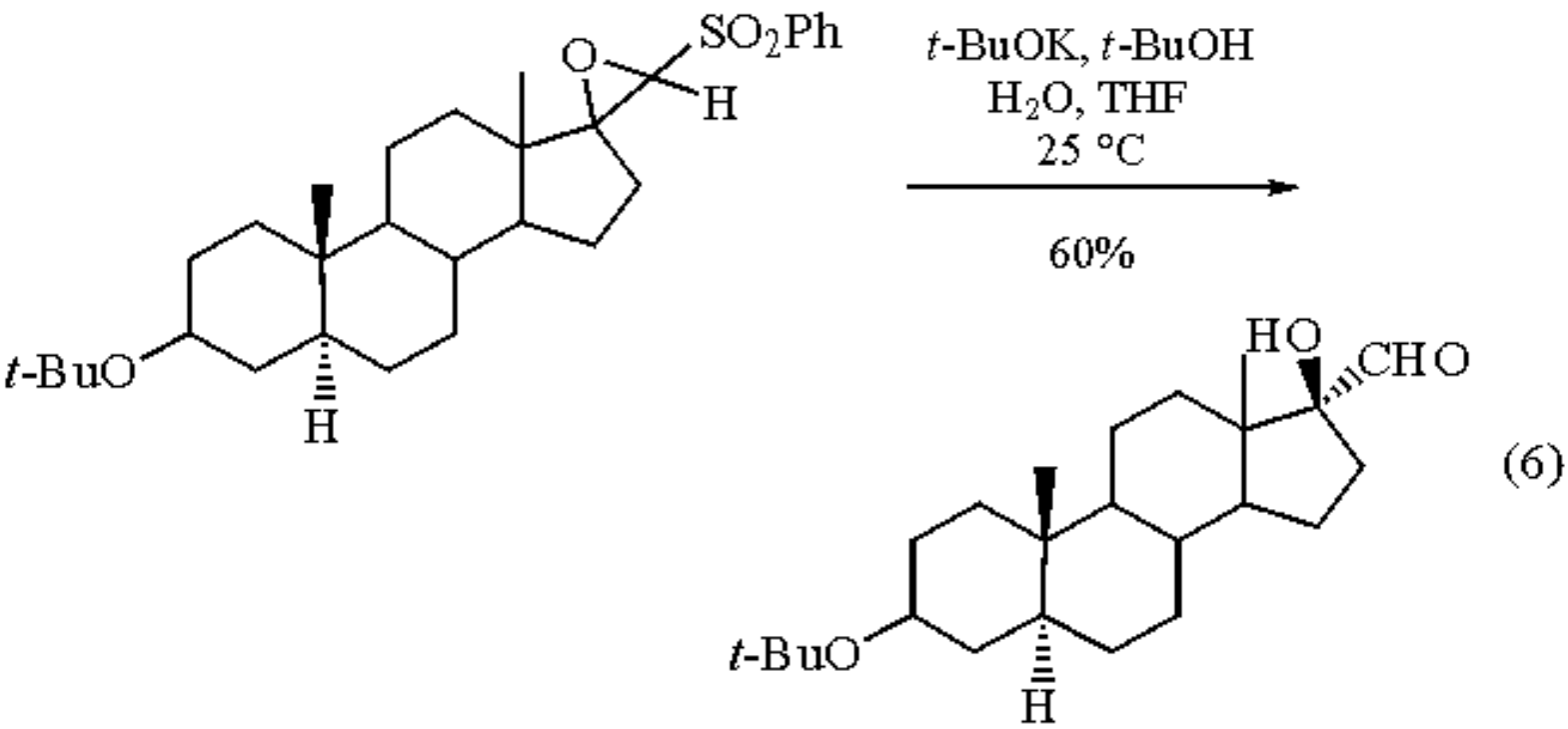

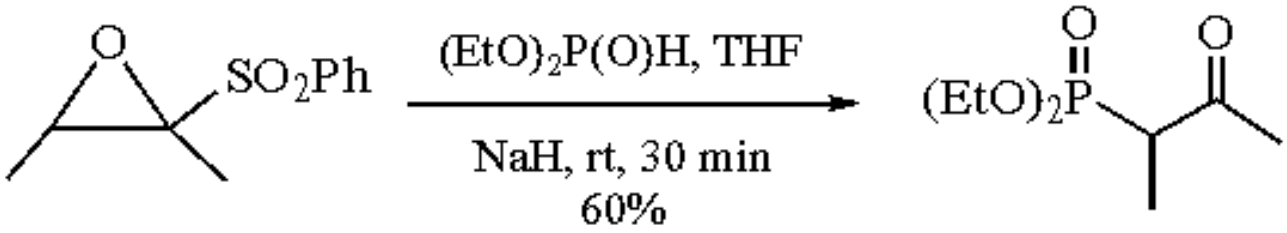

(7)

The acidic α-hydrogen of α,β-epoxy sulfones can be removed with ***n-Butyllithium*** at -102 °C to give the α-lithio-α,β-epoxy sulfone carbanion which reacts with ***Chlorotrimethylsilane***, aldehydes, ketones, and alkyl halides to give the corresponding adducts which can undergo further chemical transformations. This process demonstrates the equivalency of the α,β-epoxy sulfones to the acyl anion (eq 8).[16]

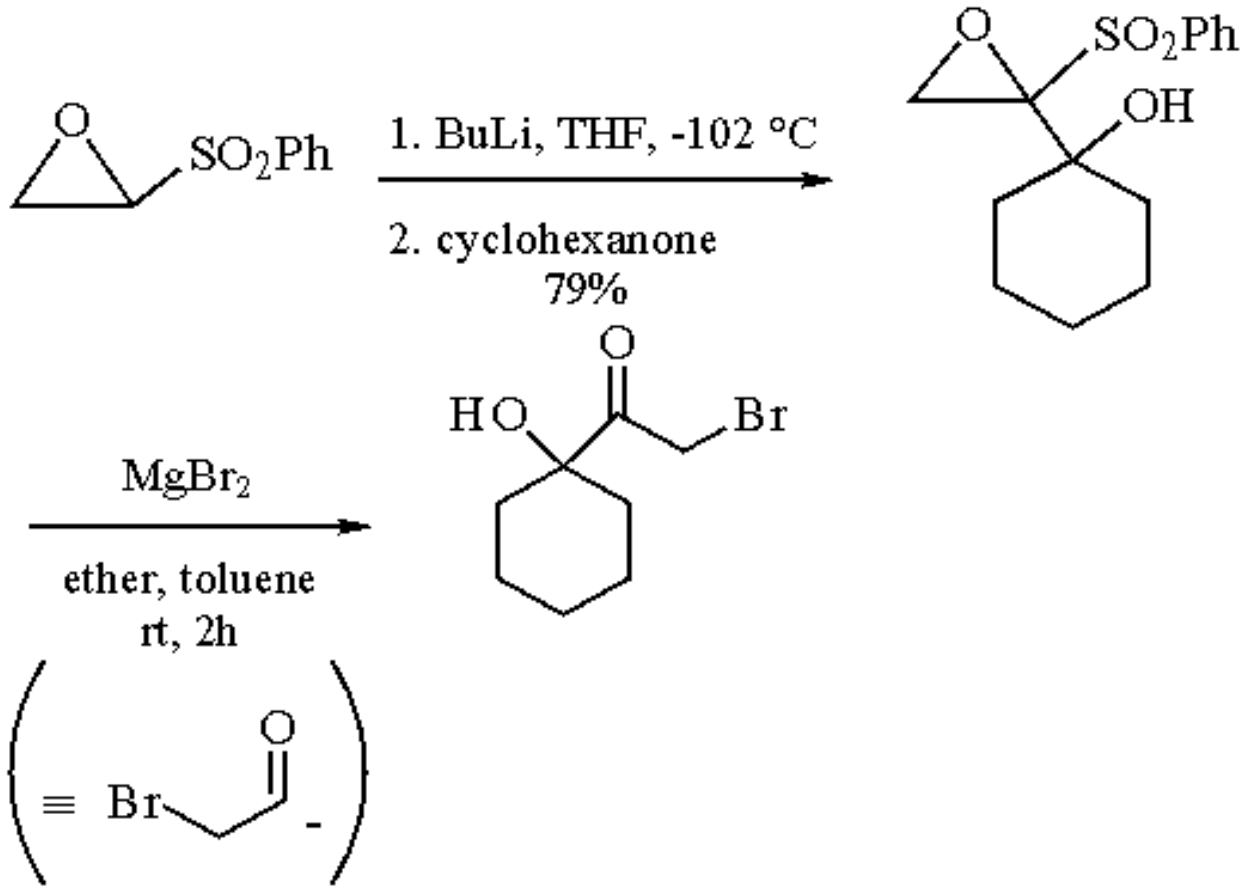

(8)

Addition to Imines.

N-Aryl(phenylsulfonyl)aziridines are prepared by the reactions of the α-lithiochloromethyl phenyl sulfone with diaryl imines. The aziridines and alkylated aziridines, formed by the alkylation of the α-lithio-*N*-aryl(phenylsulfonyl)aziridines, undergo [1,3]-dipolar cycloaddition with ***Dimethyl Acetylenedicarboxylate*** to give substituted pyrroles (eq 9).[2b] Bis(phenylsulfonyl)aziridine is formed by the reaction of the chloromethyl phenyl sulfone carbanion with quinazoline (eq 10);[2a] 1,5-, 1,6-, 1,7-, and 1,8-naphthyridines react similarly to give the corresponding phenylsulfonylaziridines.[2a]

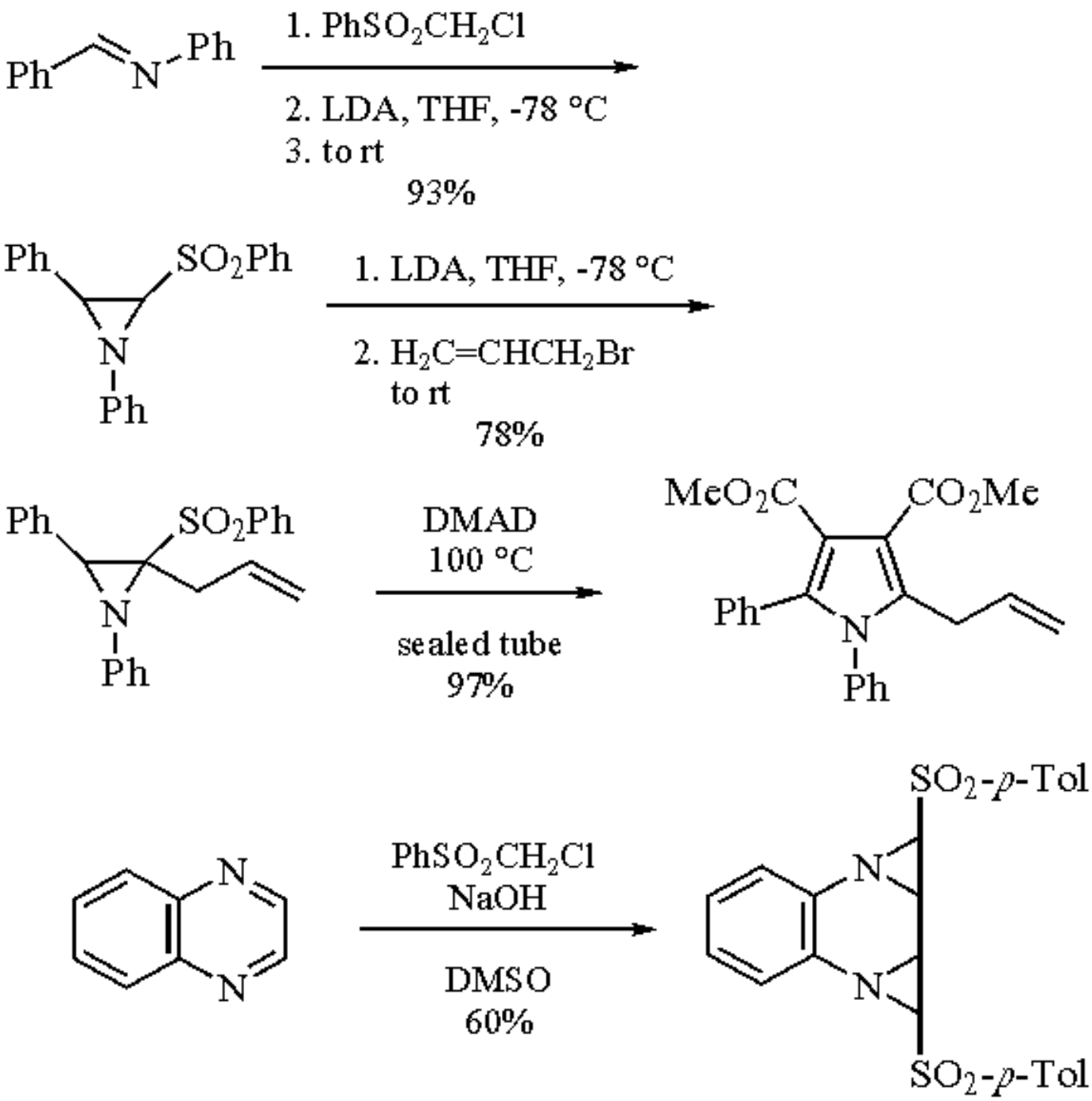

Vicarious Nucleophilic Substitution of Hydrogen (VNS).

The chloromethyl phenyl sulfone carbanion undergoes vicarious nucleophilic substitution of hydrogen (VNS) in electrophilic arenes, heterocyclic arenes, and alkenes[3] to give phenylsulfonylmethyl functionalized compounds. The most common starting aromatic compounds for this reaction are nitroarenes (eq 11).[17] The reaction can be applied to *ortho*-, *meta*-, *para*- and polysubstituted nitroarenes. The VNS reaction with electrophilic arenes is complementary to the Friedel-Crafts reaction.[3a]

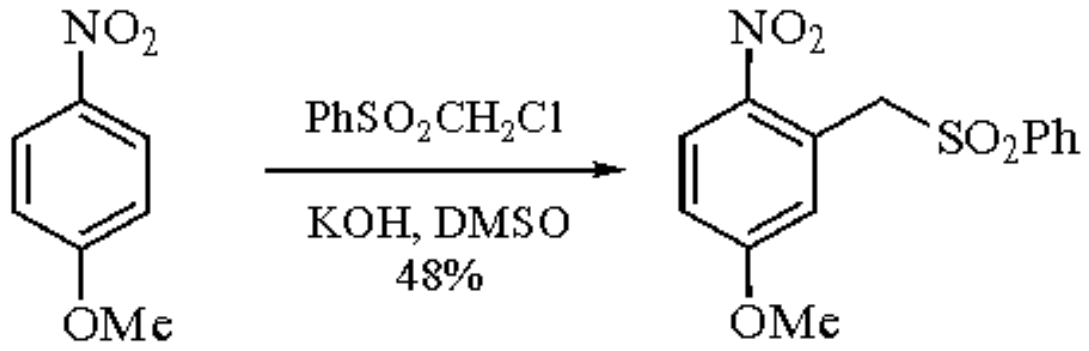

(11)

Electrophilic heterocyclic arenes (nitrothiophenes, 2-nitrofuran, *N*-protected nitropyrroles, *N*-protected nitroimidazoles, nitropyrazoles, nitropyridines, nitroquinolines, *N*-protected nitroindole, and 1,2,4-triazine)[18] undergo the VNS reaction with the chloromethyl phenyl sulfone carbanion (e.g. eqs 12 and 13).[3b,18] These reactions provide a convenient way to introduce the phenylsulfonylmethyl group into these compounds. Electrophilic alkenes with electron-withdrawing groups which can provide high stabilization of negative charge and β-substituents facilitating the abstraction of a geminal proton, can undergo the VNS reaction (eq 14).[19] The principle of the VNS reaction has been applied in the synthesis of a precursor of aklavinone, an anthracycline antibiotic (eq 15).[20]

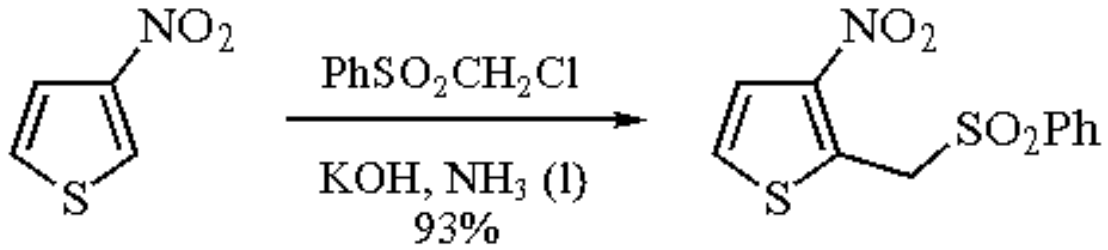

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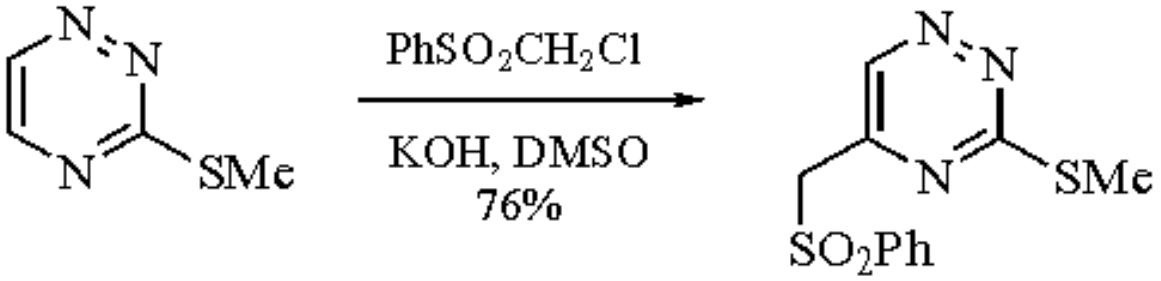

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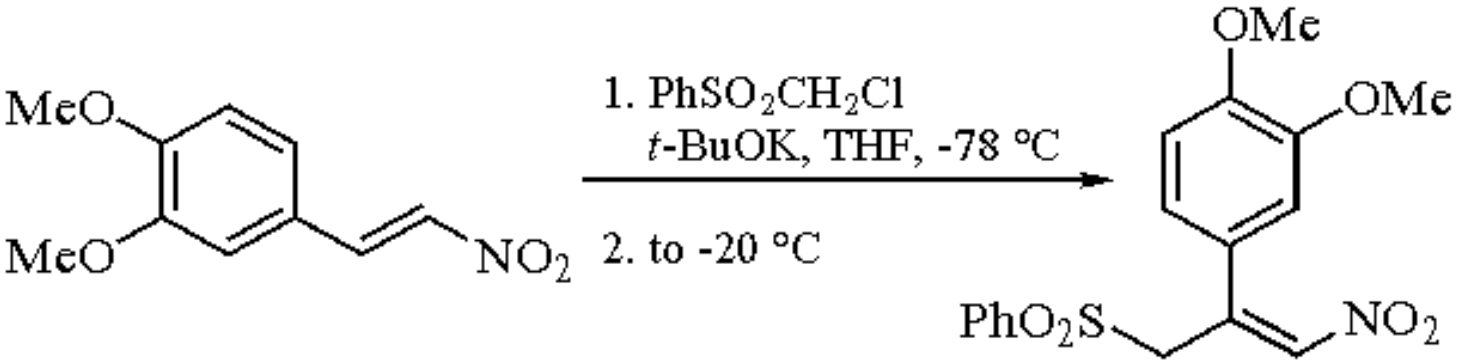

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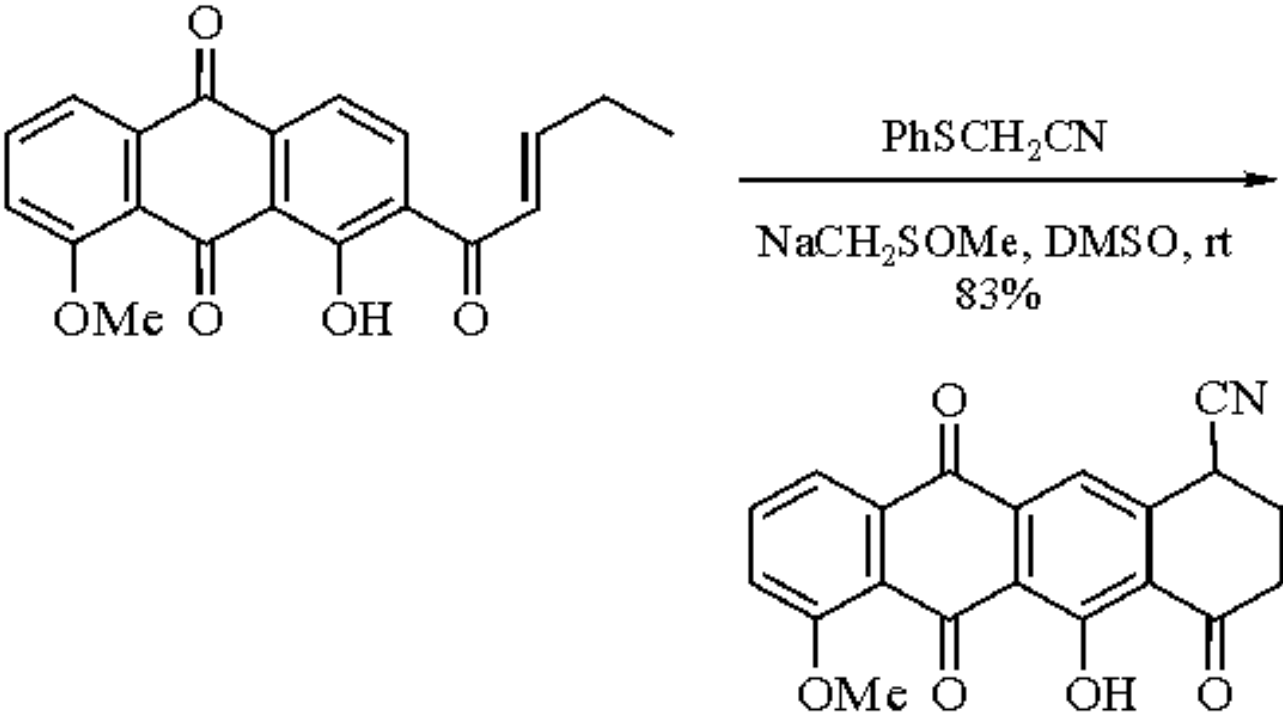

(15)

Radical Reaction.

The phenylsulfonylmethyl radical, generated by the reaction of chloromethyl phenyl sulfone with ***Tri-n-butylstannane*** and ***Azobisisobutyronitrile*** in refluxing benzene, adds diastereoselectively to enamines to give the *syn* adduct as the major product. The origin of the diastereoselectivity is explained on the basis of an allylic 1,3-strain model (eq 16).[1d,21]

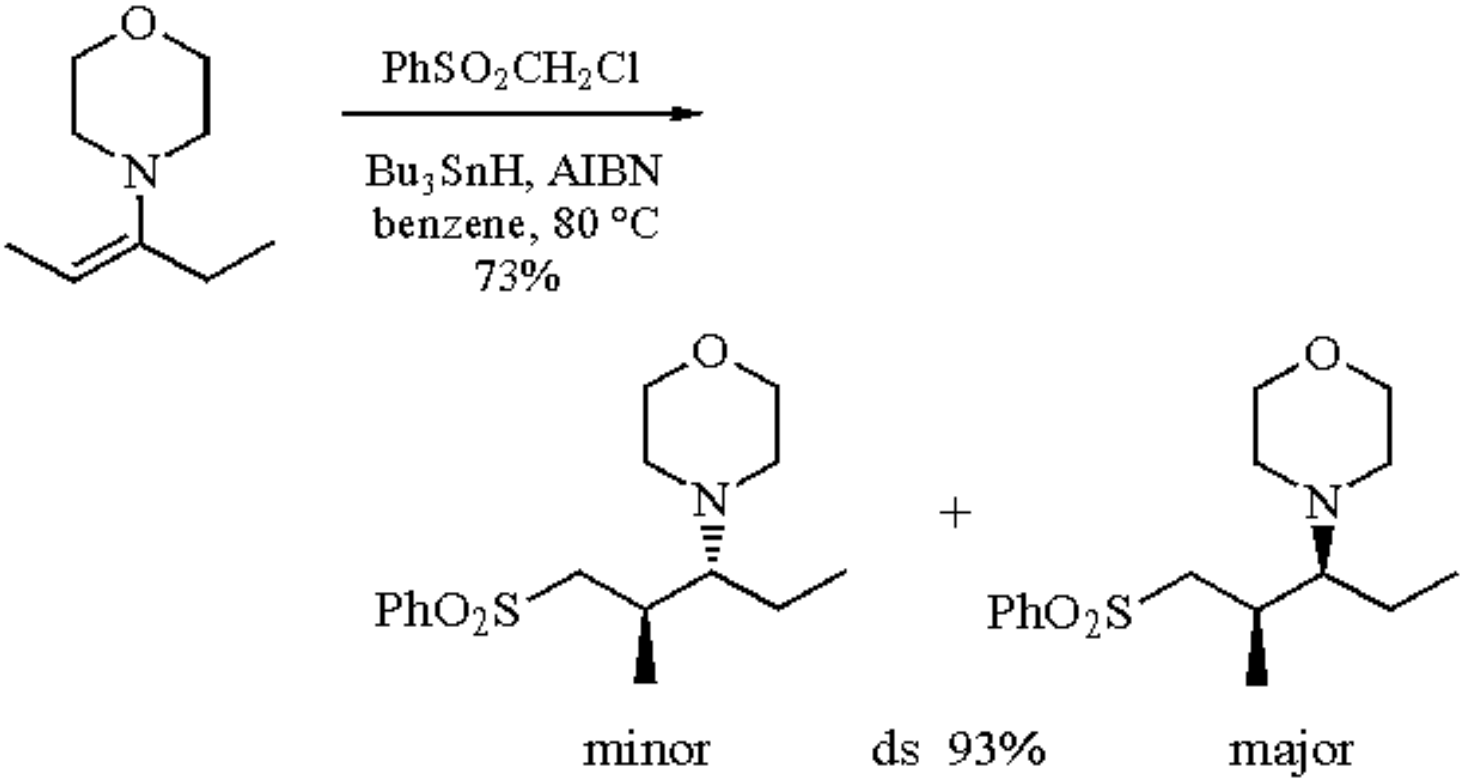

(16)

α-Alkyl phenylsulfonylmethyl radicals, generated from the corresponding α-bromo- or α-chloroalkyl phenyl sulfones, undergo tandem radical cyclization to cyclopentane derivatives (eqs 17 and 18).[22,23] The method provides a quick entry to these molecules.

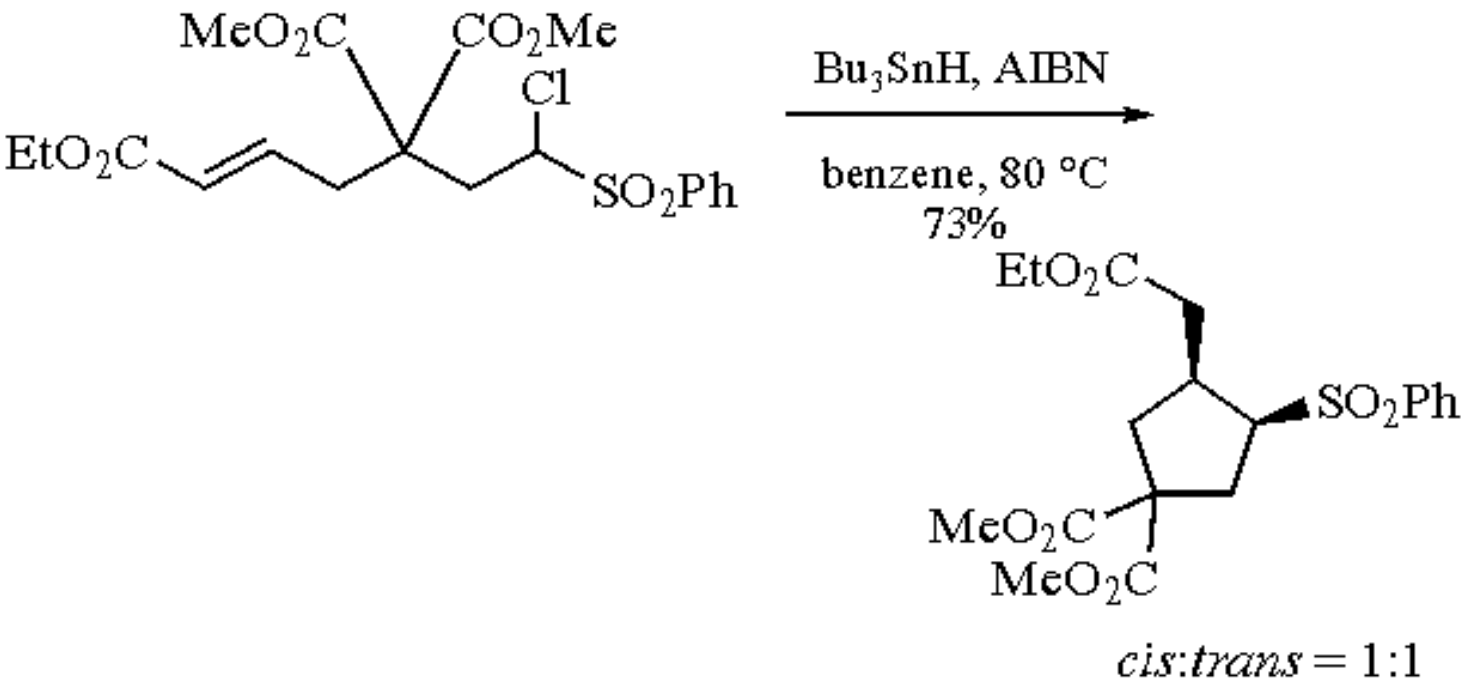

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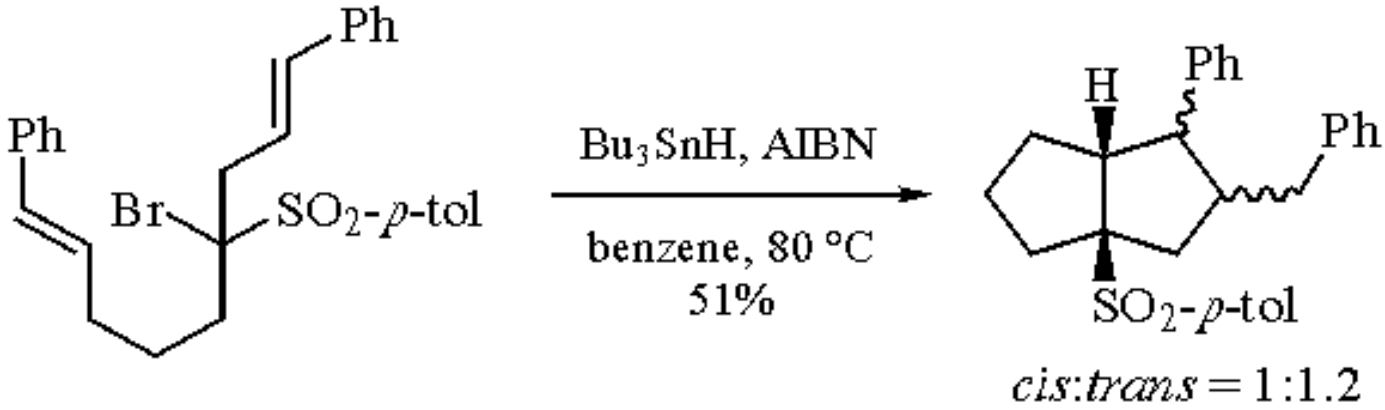

(18)

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Chloromethyl Phenyl Sulfoxide[1]

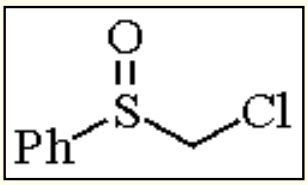

[7205-94-9] · C_7H_7ClOS · Chloromethyl Phenyl Sulfoxide · (MW 174.65)

(synthesis of α,β-epoxy sulfoxides;[2a-c] one-carbon homologating agent[3])

Physical Data: bp 120-121 °C/4 mmHg.

Solubility: sol $CHCl_3$ and THF.

Preparative Methods: chlorination of methyl phenyl sulfoxide with either ***Sulfuryl Chloride***[4] in methylene chloride or ***N-Chlorosuccinimide***[5] in chloroform gives a good yield of the product. A one-pot procedure starting with ***Thioanisole*** consists of chlorination with sulfuryl chloride in methylene chloride[6] followed by oxidation with the same reagent in the presence of wet silica gel.[7] Another alternative is to employ ***Silver(I) Nitrate*** and sulfuryl chloride in acetonitrile.[8]

Handling, Storage, and Precautions: use in a fume hood.

α,β-Epoxy Sulfoxides.

Epoxy sulfoxides are prepared by the reaction of the chloromethyl phenyl sulfoxide carbanion (PhSOCHClM) with carbonyl compounds. When ketones are used as electrophiles, either a one-step Darzens-type condensation using ***Potassium t-Butoxide*** in *t*-BuOH[2b,c] or a two-step route involving the addition of α-lithiochloromethyl phenyl sulfoxide (best generated by the reaction of $PhSOCH_2Cl$ with ***Lithium Diisopropylamide***; ***n-Butyllithium*** has been used, but caution should be taken due to the possible desulfinylation reaction) to ketones to give α-chloro-β-hydroxy sulfoxides (chlorohydrins), followed by treatment with ***Potassium Hydroxide*** in aqueous methanol (eq 1; R^1, R^2 = alkyl, aryl).[2a,3c]

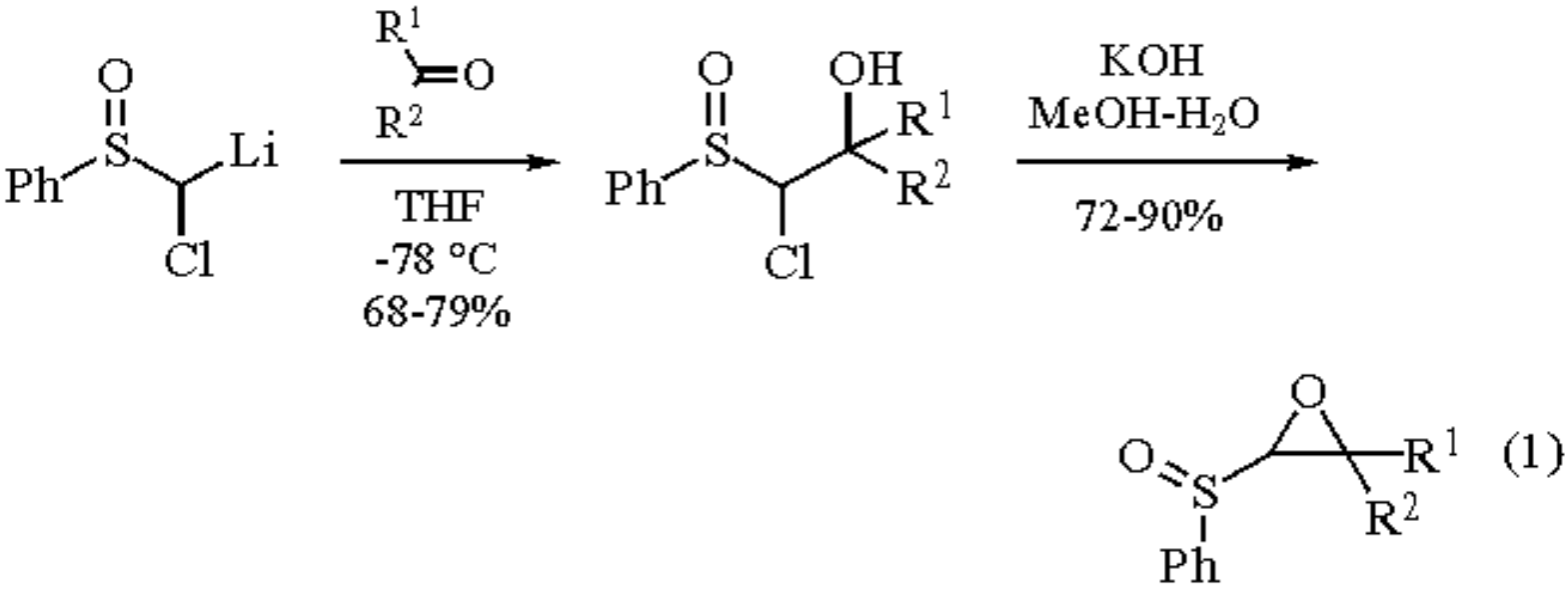

With aldehydes (eq 1; R^1 = H, R^2 = alkyl), only the two-step route can be used satisfactorily.[2b] A high degree of diastereoselectivity is observed in the formation of the chlorohydrins.[2a] Thermal[2b] or Lewis acid-catalyzed[3c] reactions of the epoxy sulfoxides (R^1 and/or R^2 = alkyl) give α,β-unsaturated aldehydes with one-carbon homologation. This process has been applied to the synthesis of (±)-suaveolin (eq 2).[9]

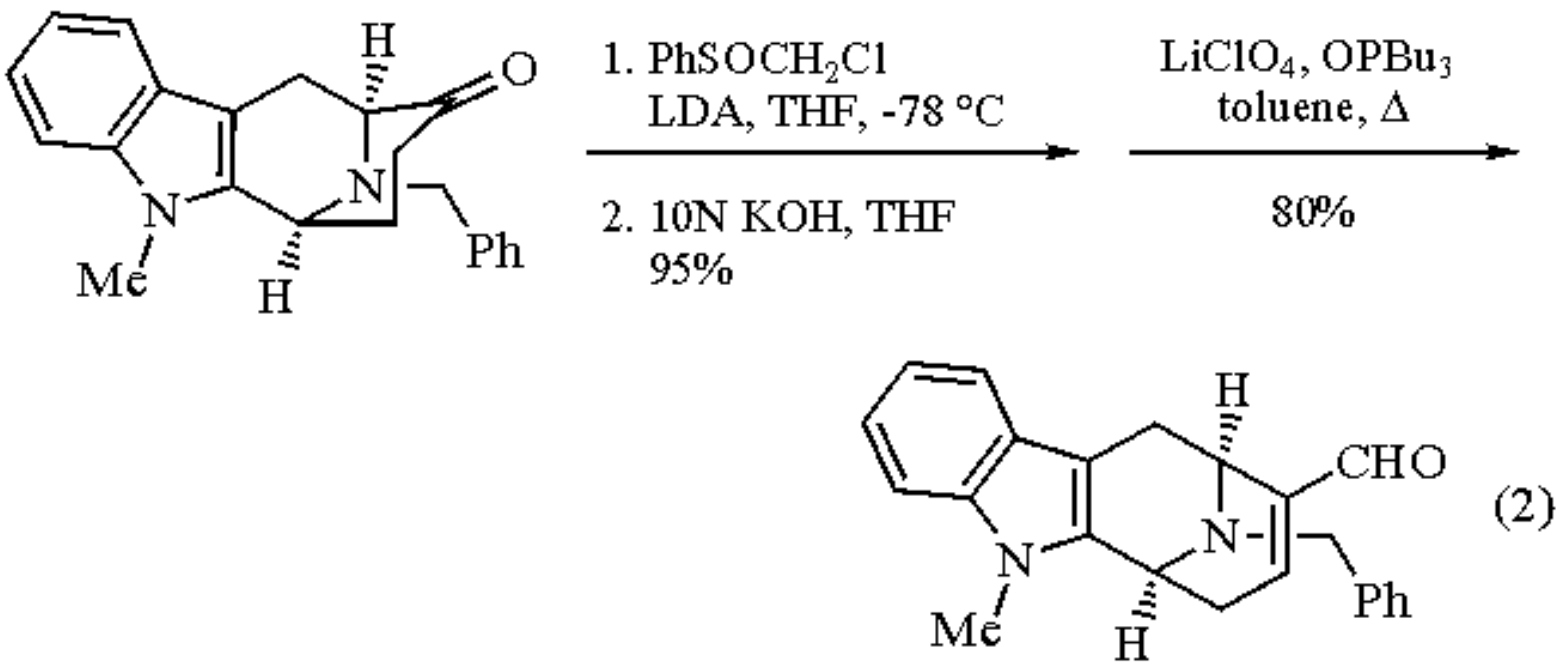

Thermal elimination of the chlorohydrins derived from aldehydes (R^1 or R^2 = H) provides chloromethyl ketones[10] in good yields (eq 3). One-carbon ring expansion[11] of the chlorohydrins derived from cyclic ketones can be induced by ***Lithium Diisopropylamide*** through an α-sulfinyl carbenoid intermediate (eq 3). Eliminative deoxygenation[3b] of the chlorohydrins with low-valent titanium gives vinyl sulfides (eq 3). 1-Chlorovinyl sulfoxides derived from the chlorohydrins undergo the Fritsch-Wiechell rearrangement with ***t-Butyllithium*** to give terminal alkynes (eq 4).[12]

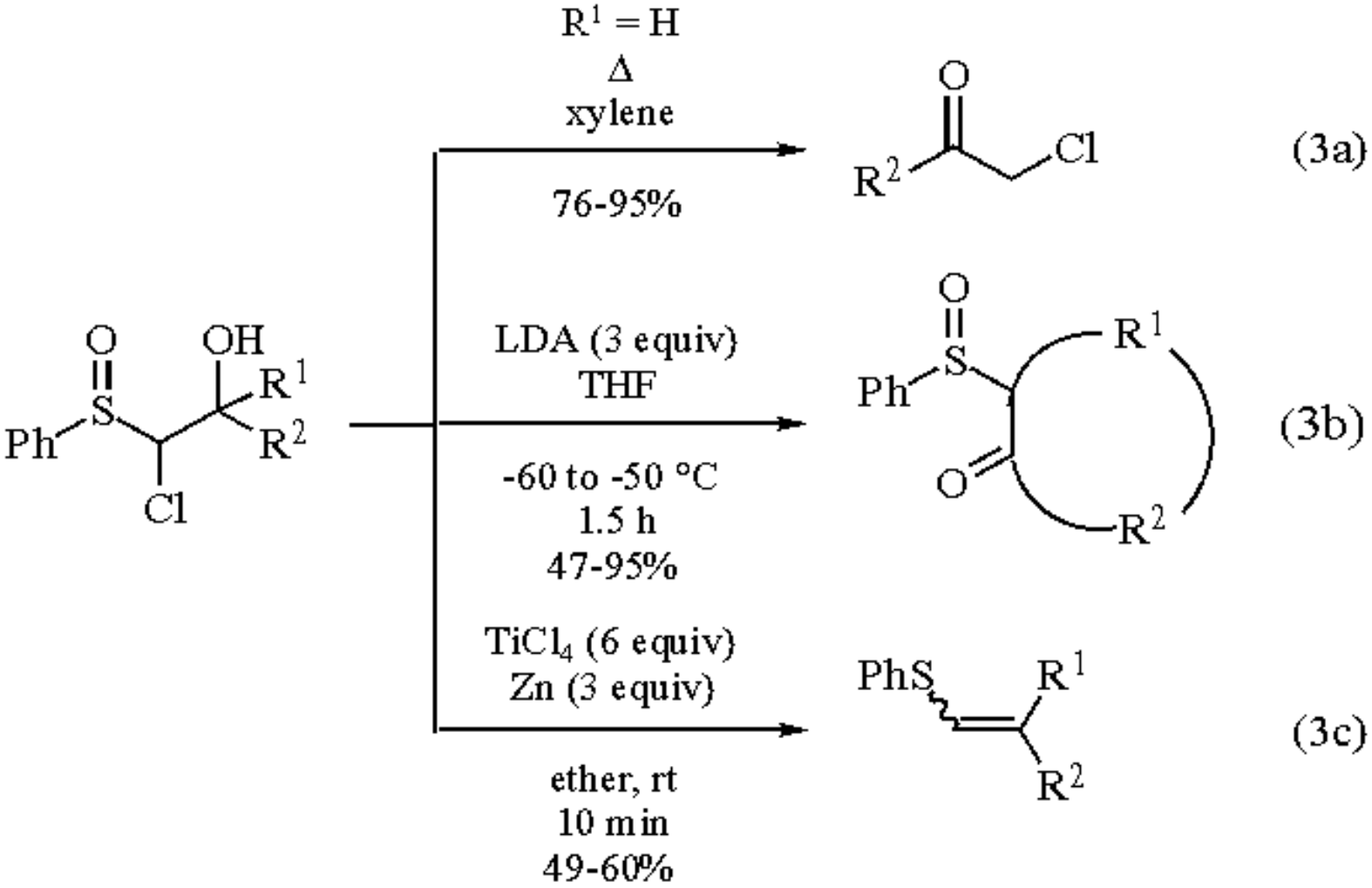

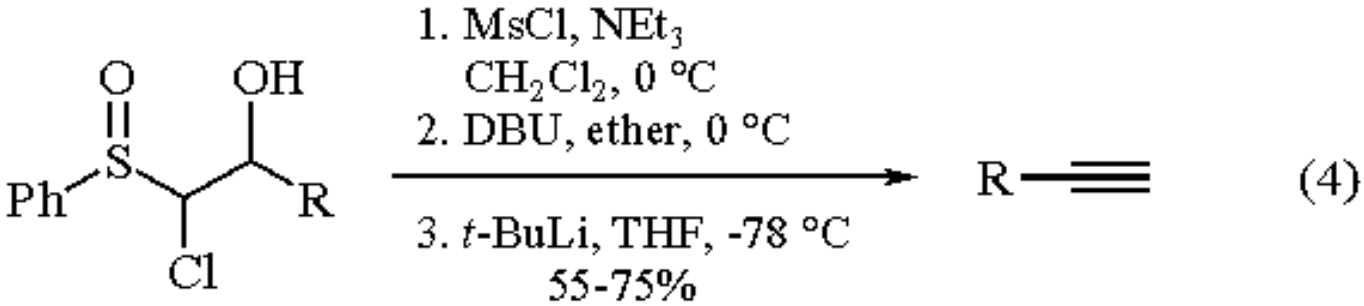

Lithiochloromethyl phenyl sulfoxide gives 1,2-addition products with enones.[13] The transformation of a chlorohydrin [R^1-R^2 = -$(CH_2)_3$-] to an α,β-unsaturated γ-hydroxycyclohexanecarbaldehyde[14] has been demonstrated (eq 5).

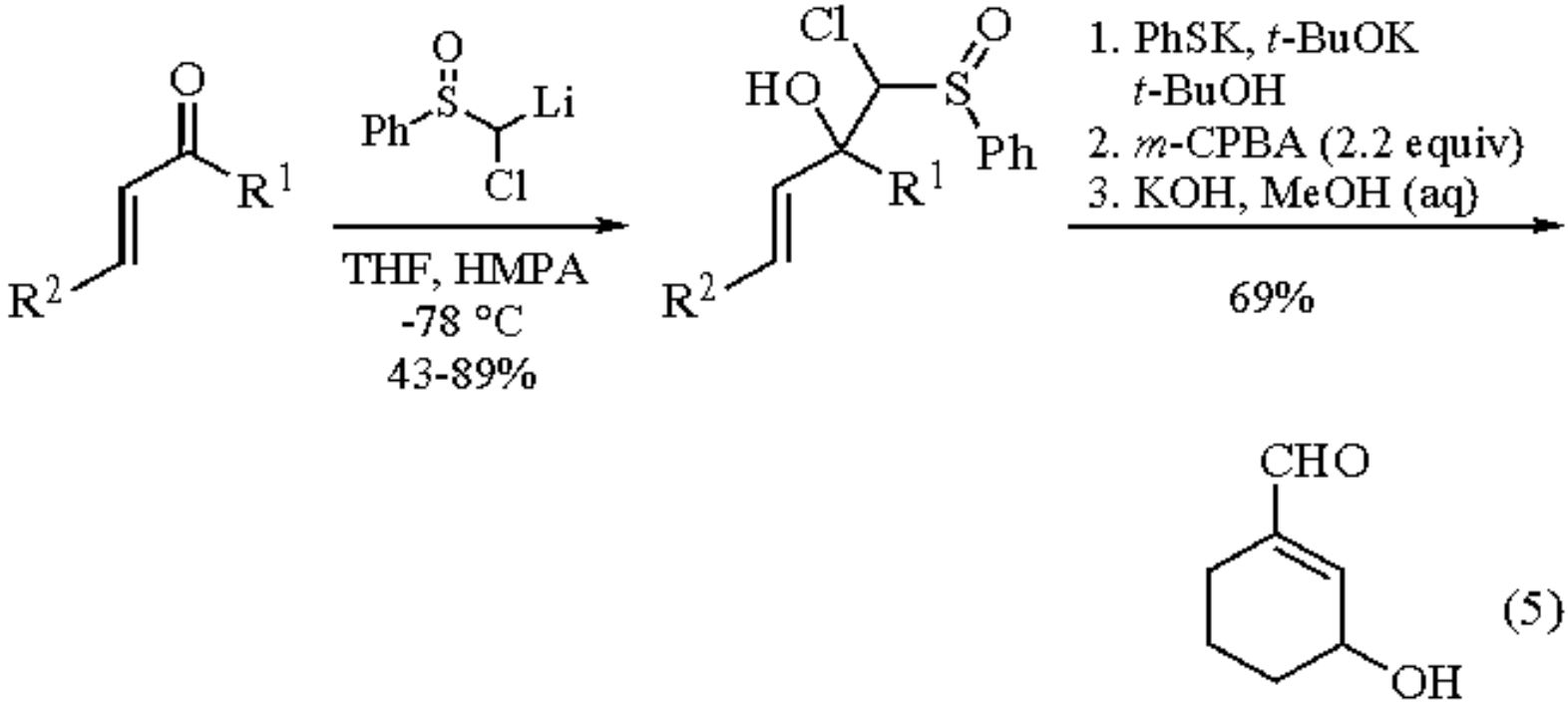

(5)

Addition to Imines.

The addition of lithiochloromethyl phenyl sulfoxide to aryl imines provides sulfinylaziridines as a mixture of *cis* and *trans* isomers which undergo 1,3-dipolar cycloaddition with ***Dimethyl Acetylenedicarboxylate*** (DMAD), giving *N*-aryl-2,3,4-trisubstituted pyrroles (eq 6).[15]

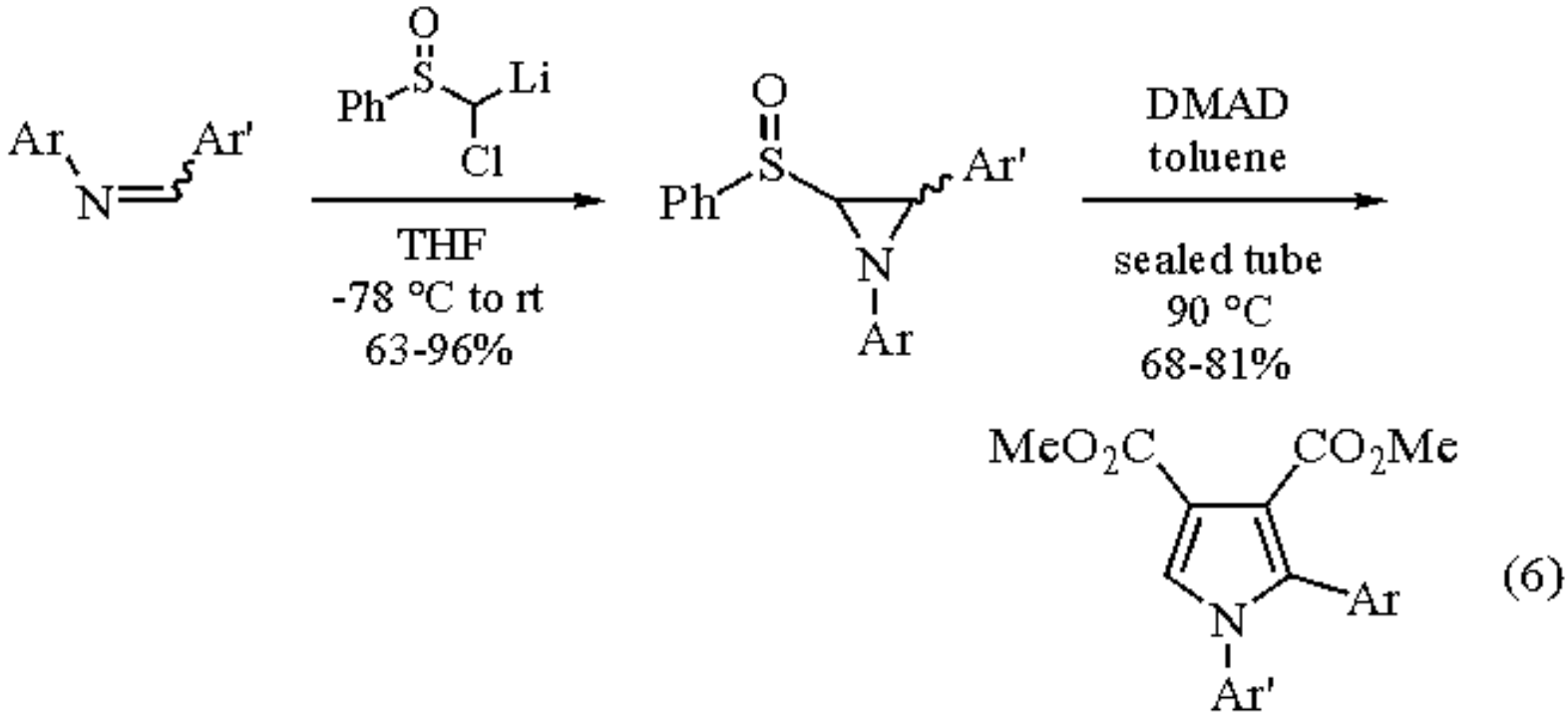

(6)

Alkylation with Alkyl Halides.

Chloroalkyl phenyl sulfoxides, available from alkylation of lithiochloromethyl phenyl sulfoxide with alkyl bromides or iodides, give high yields of terminal vinyl chlorides upon pyrolysis[16] and undergo the sila-Pummerer rearrangement with LDA and ***Chlorotrimethylsilane*** to yield thiol esters (eq 7).[17]

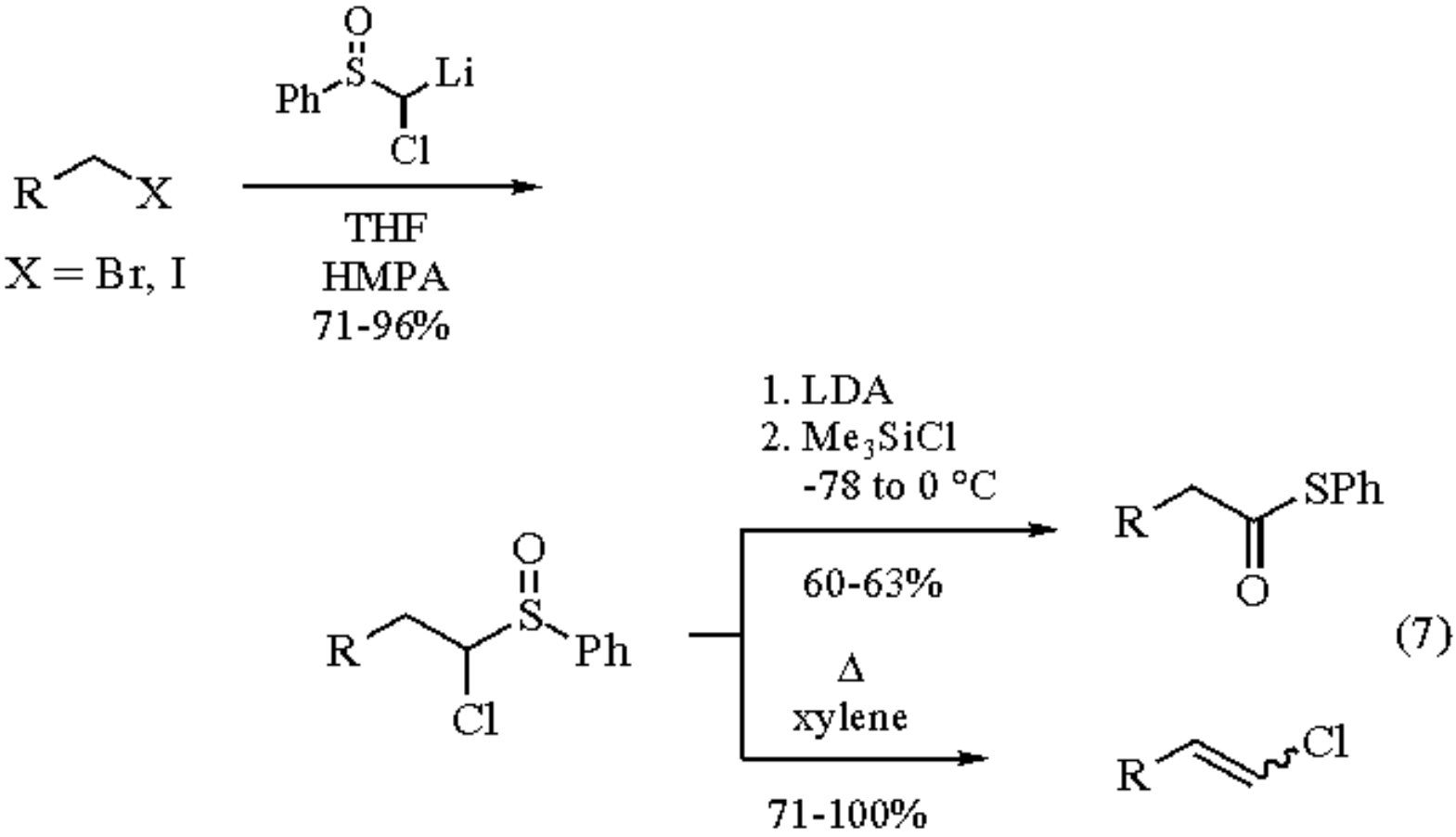

Direct chlorination of alkyl phenyl sulfoxides with NCS is a useful alternative method for the preparation of chloroalkyl phenyl sulfoxides.[18] Addition of lithiochloroalkyl phenyl sulfoxide to carbonyl compounds gives the chlorohydrins which can be transformed via α,β-epoxy sulfoxides into carbonyl compounds with one-carbon homologation,[19] α-sulfenylated ketones and aldehydes,[20] α-amino ketones and aldehydes,[21] α-acetoxy ketones,[22] alkyl vinyl ketones and divinyl ketones,[23] epoxides and allylic alcohols,[24] 2-acyl cyclic ethers and 3-keto cyclic ethers,[25] α-chloro and α-alkoxy ketones,[26] α,β-unsaturated ketones,[26] (*E*)-1-acylbutadienes,[27] 1,3-dihydroxy ketones,[28] functionalized cyclohexane derivatives,[29] spiro-methylenecyclopropanes,[30] and α-fluoro ketones.[31]

Eliminative deoxygenation of chloroalkyl phenyl sulfoxides using ***Trimethylsilyl Trifluoromethanesulfonate*** with ***Triethylamine*** as a base gives α-chlorovinyl phenyl sulfides.[32]

Bromomethyl and Iodomethyl Phenyl Sulfoxides.

α-Lithio anions derived from bromomethyl phenyl sulfoxide[33a-c] and iodomethyl phenyl sulfoxide[34a,b] react with carbonyl compounds and alkyl iodides in an analogous manner to the chloromethyl phenyl sulfoxide.[35a,b] α-Phenylsulfinyl radicals generated from either chloroalkenyl or bromoalkenyl phenyl sulfoxide undergo radical cyclization to cyclopentane derivatives together with the reduction products (eq 8).[36] Debromination of bromomethyl phenyl sulfoxide also occurs with ***Octacarbonyldicobalt*** on alumina.[37]

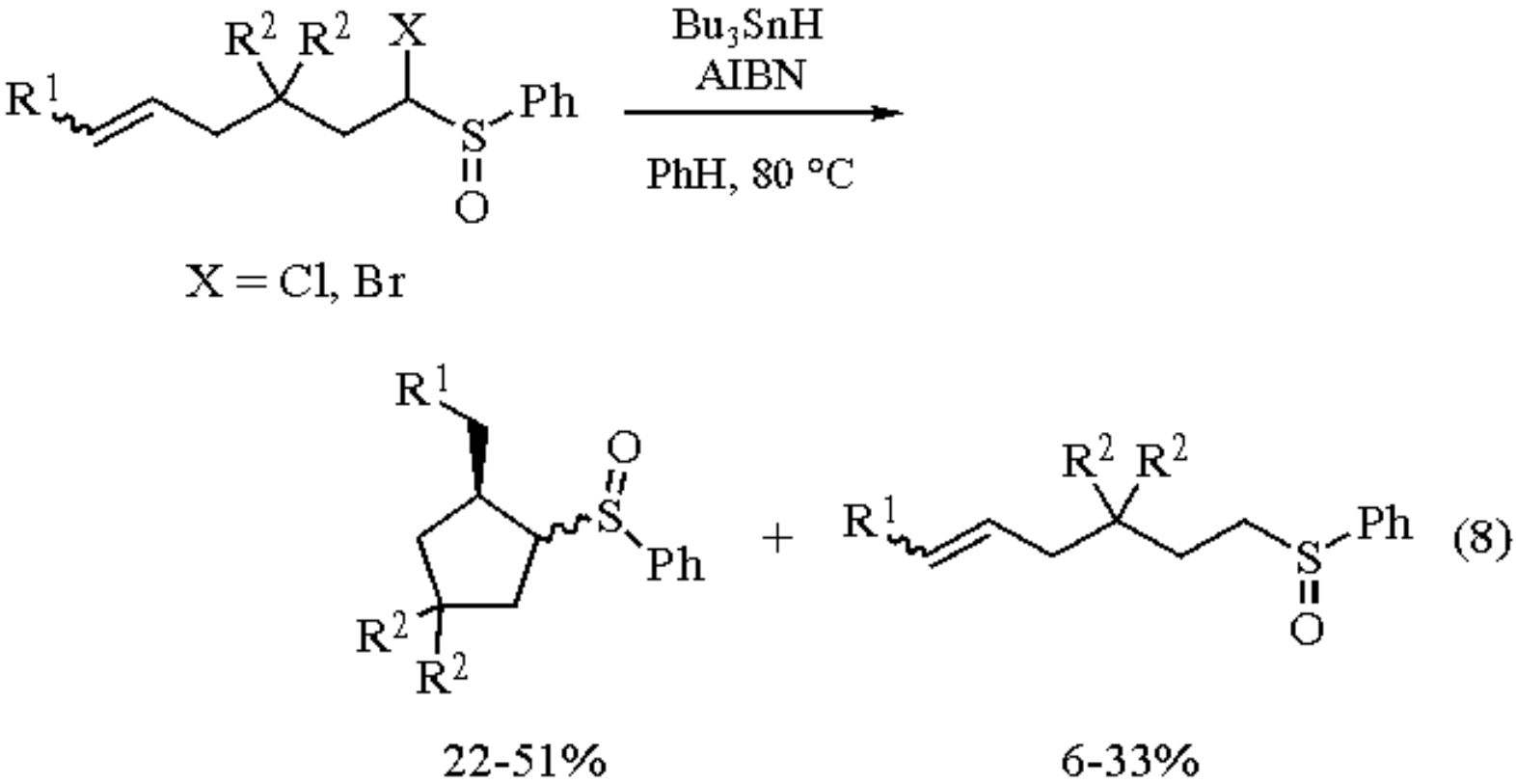

Pyrolysis of bromohydrins gives bromomethyl ketones.[35a] Solvolysis of iodohydrins of cyclic ketones with ***Silver(I) Nitrate*** in 95% ethanol provides vinyl sulfones, α-hydroxy sulfones, and/or one-carbon ring expansion products depending on the ring size, presumably through a common phenylsulfinyl carbenium ion.[35b,38]

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2-Chloro-2-methylpropanal *N*-Isopropylimine[1]

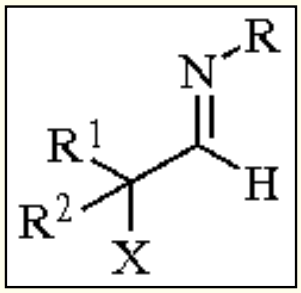

(R = *i*-Pr, R^1 = R^2 = Me, X = Cl)

[63364-30-7] · $C_7H_{14}ClN$ · 2-Chloro-2-methylpropanal *N*-Isopropylimine · (MW 147.64) (R = *i*-Pr, R^1 = R^2 = Me, X = Br)

[30453-45-3] · $C_7H_{14}BrN$ · 2-Bromo-2-methylpropanal *N*-Isopropylimine · (MW 192.12) (R = *t*-Bu, R^1 = R^2 = Me, X = Cl)

[56990-50-2] · $C_8H_{16}ClN$ · 2-Chloro-2-methylpropanal *N*-*t*-Butylimine · (MW 161.67) (R = Cy, R^1 = R^2 = Me, X = Cl)

[63364-31-8] · $C_{10}H_{18}ClN$ · 2-Chloro-2-methylpropanal *N*-Cyclohexylimine · (MW 187.70) (R = Bn, R^1 = R^2 = Me, X = Cl)

[63547-67-1] · $C_{11}H_{14}ClN$ · 2-Chloro-2-methylpropanal *N*-Benzylimine · (MW 195.68) (R = *t*-Bu, R^1 = Et, R^2 = Me, X = Cl)

[63364-32-9] · $C_9H_{18}ClN$ · 2-Chloro-2-methylbutanal *N*-*t*-Butylimine · (MW 175.69) (R = *t*-Bu, R^1 = R^2 = Et, X = Cl)

[63364-33-0] · $C_{10}H_{20}ClN$ · 2-Chloro-2-ethylbutanal *N*-*t*-Butylimine · (MW 189.72) (R = Cy, R^1 = R^2 = Et, X = Cl)

[63364-34-1] · $C_{12}H_{22}ClN$ · 2-Chloro-2-ethylbutanal *N*-Cyclohexylimine · (MW 215.76) (R = *t*-Bu, R^1R^2 = $(CH_2)_5$, X = Cl)

[63364-35-2] · $C_{11}H_{20}ClN$ · 1-Chlorocyclohexanecarbaldehyde *N*-*t*-Butylimine · (MW 201.73) (R = Cy, R^1R^2 = $(CH_2)_5$, X = Cl)

[63364-36-3] · $C_{13}H_{22}ClN$ · 1-Chlorocyclohexanecarbaldehyde *N*-Cyclohexylimine · (MW 227.77) (R = *t*-Bu, R^1 = Me, R^2 = Ph, X = Cl)

[63364-37-4] · $C_{13}H_{18}ClN$ · 2-Chloro-2-phenylpropanal *N*-*t*-Butylimine · (MW 223.73)

(synthesis of 1-aza-1,3-dienes,[2] α-amino acetals,[2,3] allylic amines,[4] α,β-unsaturated aldehydes,[5] α-alkoxy aldimines,[6,7] α-*t*-butyl aldimines,[7] α-sulfenylated aldimines,[8] 1,4-diimines,[9] α-cyano enamines,[10] β-chloro amines,[11] aromatic ketones,[12] aziridines,[13] 2-imidazolidinethiones,[14] 2-imidazolidinones,[15] α-aryl aldehydes,[16] 2-aza-1,3-dienes;[17,18] reductive dechlorination of α-halo aldehydes[18])

Alternate Name: *N*-isopropyl-α-chloroisobutyraldimine.

Physical Data: 2-chloro-2-methylpropanal *N*-isopropylimine (R = *i*-Pr, R^1 = R^2 = Me, X = Cl): bp 47-49 °C/24 mmHg; 2-bromo-2-methylpropanal *N*-isopropylimine (R = *i*-Pr, R^1 = R^2 = Me, X = Br): bp 58-61 °C/14 mmHg; 2-chloro-2-methylpropanal *N*-*t*-butylimine (R = *t*-Bu, R^1 = R^2 = Me, X = Cl): bp 50-52°/30 mmHg.

Solubility: sol most organic solvents; not compatible with aqueous acidic solutions; basic aqueous solutions cause a slow hydrolysis.

Form Supplied in: 2-chloro-2-methylpropanal *N*-isopropyl- and *N*-*t*-butylimines are commercially available as colorless liquids.

Analysis of Reagent Purity: GC, ^{1}H NMR.

Preparative Methods: aldimines, which are easily accessible from aldehydes and primary amines and which may be prepared in situ, react smoothly with ***N-Chlorosuccinimide*** in CCl_4 at room temperature to give α-chloro aldimines (eq 1).[2] Similarly, α-bromo[7] and the labile α-iodo aldimines[19] are accessible by reaction of aldimines with ***N-Bromosuccinimide*** and ***N-Iodosuccinimide***, respectively (eq 2). Alternatively, the condensation of α-chloro and α-bromo aldehydes with primary amines in the presence of magnesium sulfate,[18] ***Titanium(IV) Chloride***,[20] or ***Molecular Sieves***[28] as dehydrating agent affords the corresponding α-halo aldimines (eq 3).

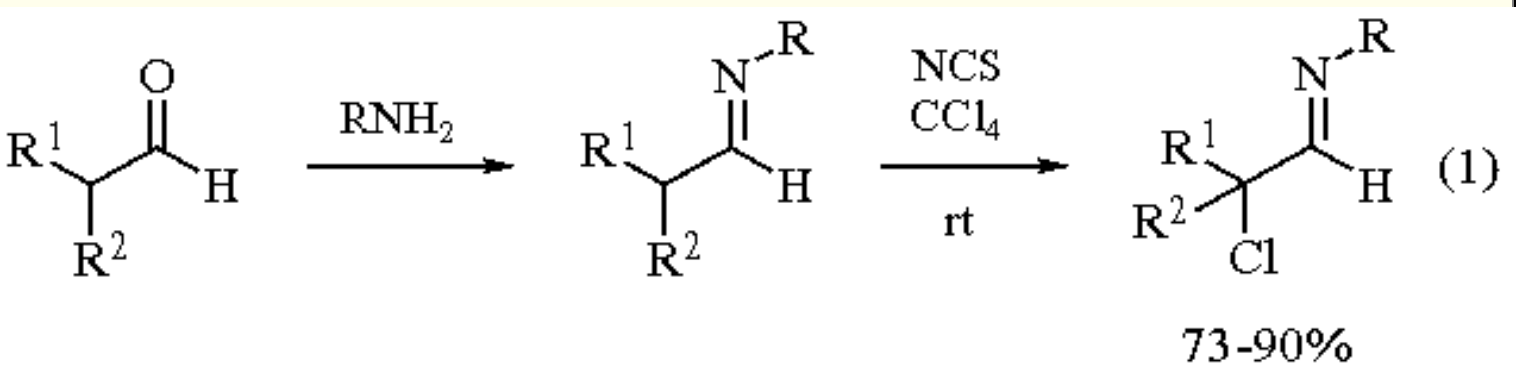

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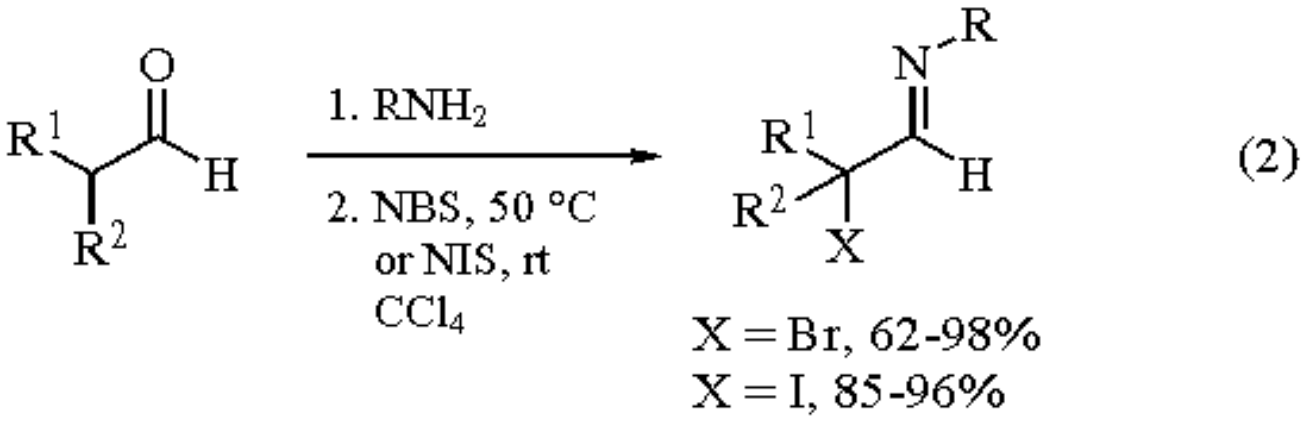

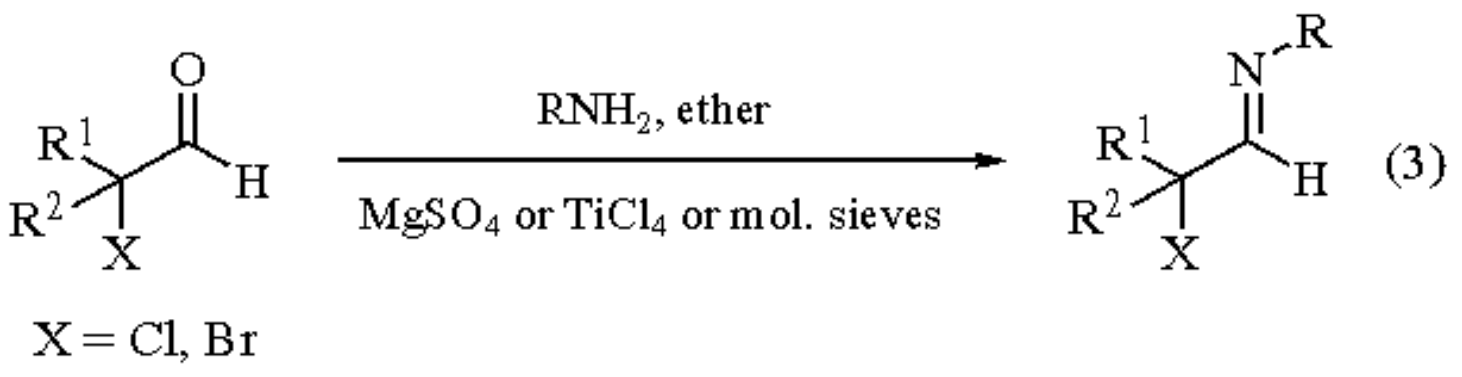

Handling, Storage, and Precautions: α-chloro aldimines are relatively stable bifunctional reagents which are preferably kept in the refrigerator, well-protected from moisture. α-Bromo aldimines are more labile and only readily accessible with *N*-*t*-butyl substituents. α-Iodo aldimines are best freshly prepared and used immediately. The use of α-halo imines in the presence of water is incompatible (except for a fast cyanation reaction; see below). Use in a fume hood.

α-Halo aldimines are protected or modified α-halo aldehydes, but their chemistry is quite different from that of α-halo aldehydes.[1,21,22] They are suitable building blocks for a variety of heterocycles and have a high synthetic potential for functional group transformations. Comparable reagents are β-haloenamines.[23]

Synthesis of 1-Aza-1,3-dienes, α-Amino Acetals, Allylic Amines, and α,β-Unsaturated Aldehydes.

α-Chloroisobutyraldimines react with ***Sodium Methoxide*** in methanol to give 1-aza-1,3-dienes and rearranged α-amino acetals (via a 2-methoxyaziridine intermediate) (eq 4).[2] Selective formation of 1-aza-1,3-dienes is obtained with ***Potassium t-Butoxide*** (eq 5),[4] while complete rearrangement into α-amino acetals is achieved by reaction with alcohols without added base (eq 6).[2,3] The α-amino acetals serve as precursors for α-(*N*-alkylamino) aldehydes (eq 6).[3] Higher analogs, having at least one α-methyl replaced by ethyl or higher alkyl, do not rearrange but are dehydrochlorinated on treatment with sodium methoxide or potassium *t*-butoxide (eq 7).[2,4] The resulting 1-aza-1,3-dienes are easily converted into allylic amines (eq 8)[4] and α,β-unsaturated aldehydes (eq 9).[5]

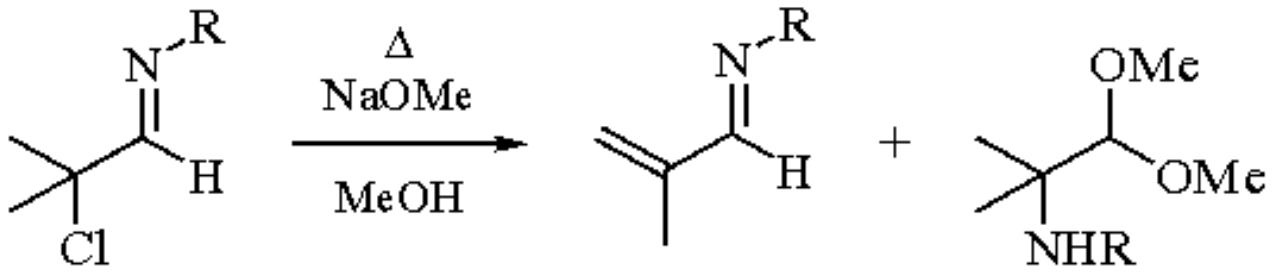

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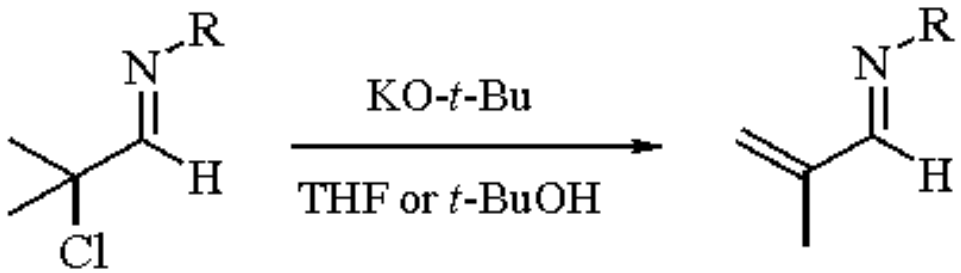

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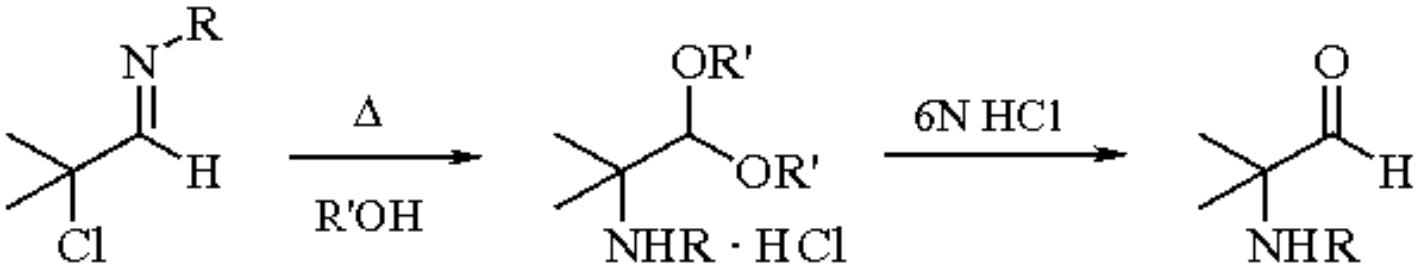

(6)

68-92%
R = *i*-Pr, *t*-Bu, Cy

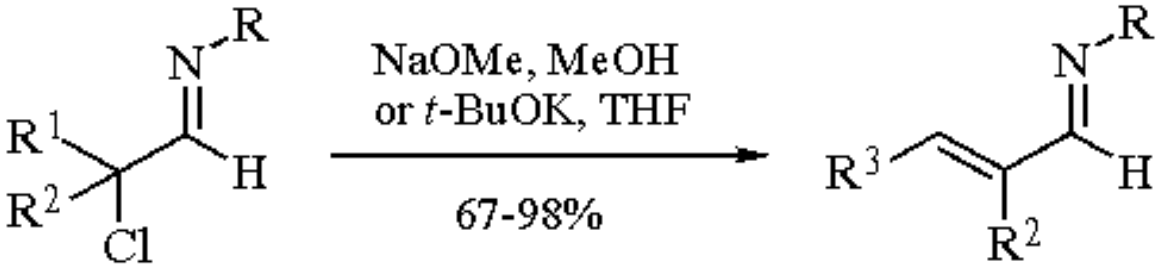

(7)

$R^1 = CH_2R^3$, $R^3 \neq H$, $R^2 = \text{alkyl}$

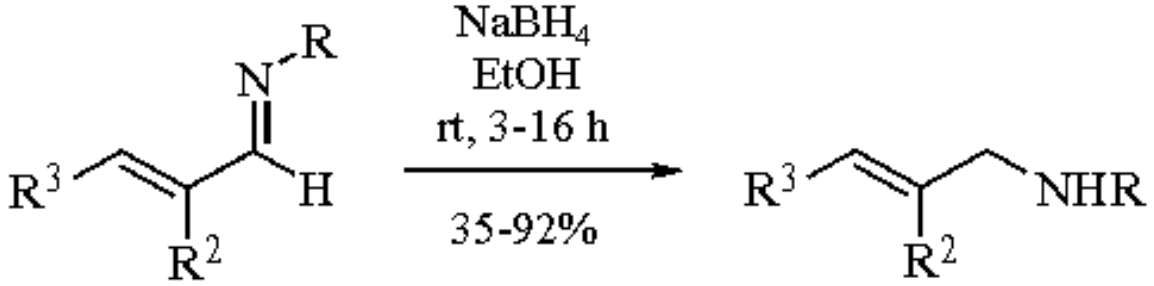

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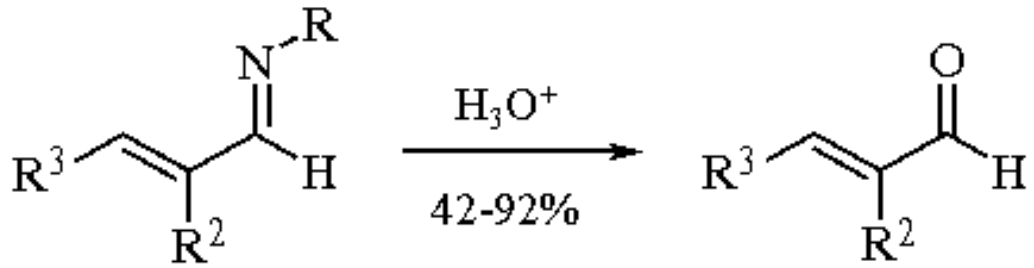

(9)

Synthesis of α-Alkoxy Aldimines, α-*t*-Butylaldimines, α-Sulfenylated Aldimines, and 1,4-Diimines.

While the reaction of α-bromo aldimines with alcohols produces rearranged α-amino acetals, the silver-induced alcoholysis affords α-alkoxy aldimines (eq 10).[6] In addition to oxygen nucleophiles, the α-halogen in α-chloro aldimines can be displaced by sulfur or carbon nucleophiles, e.g. thiolates (eq 12)[7,8] or ***t-Butyllithium*** (eq 11).[7] Coupling of α-bromo aldimines to give 1,4-diimines via captodative stabilized radical intermediates is accomplished with ***Lithium Diisopropylamide*** (eq 13).[9] A similar coupling of α-chloro aldimines by ***Methylcopper*** to give 1,4-diimines has been reported.[12]

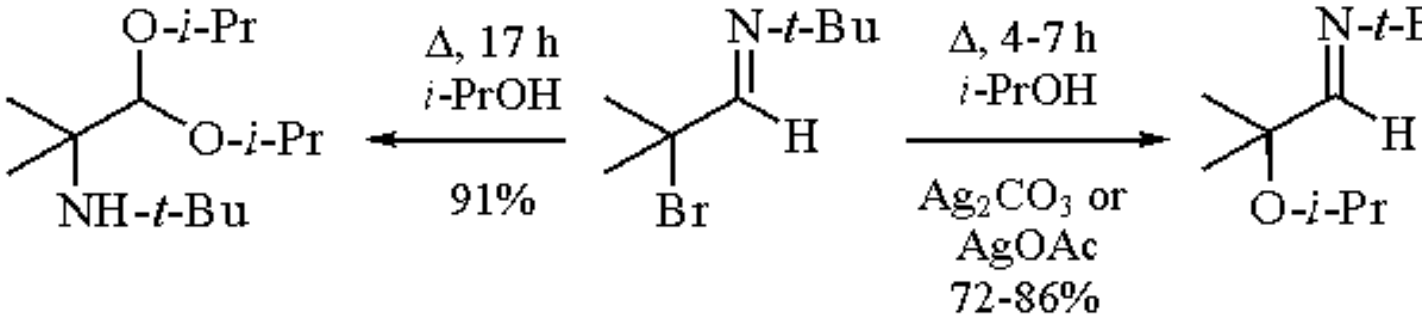

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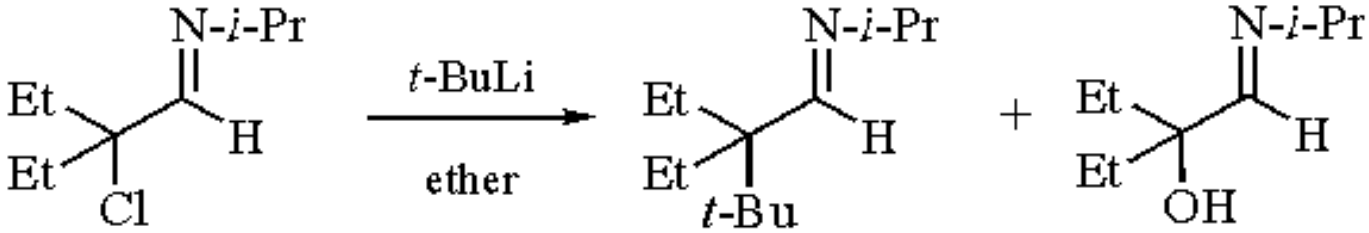

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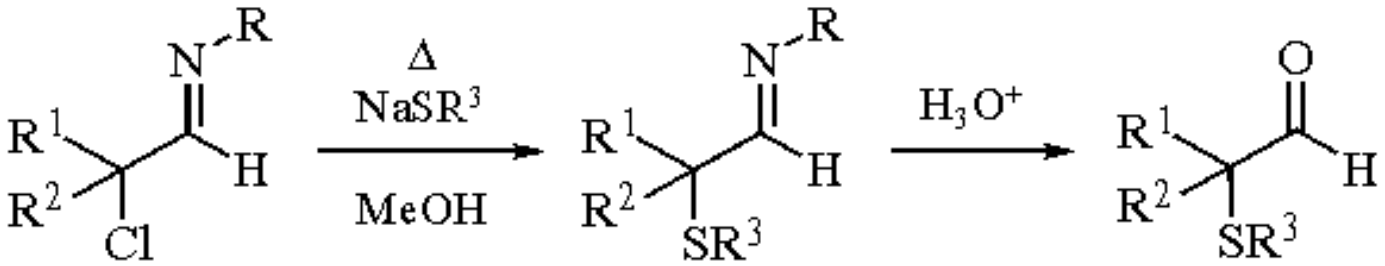

(12)

R = *i*-Pr, *t*-Bu, Cy; R^1, R^2 = Me, Et; R^3 = Pr, *i*-Pr, Ph, C_8H_{17}

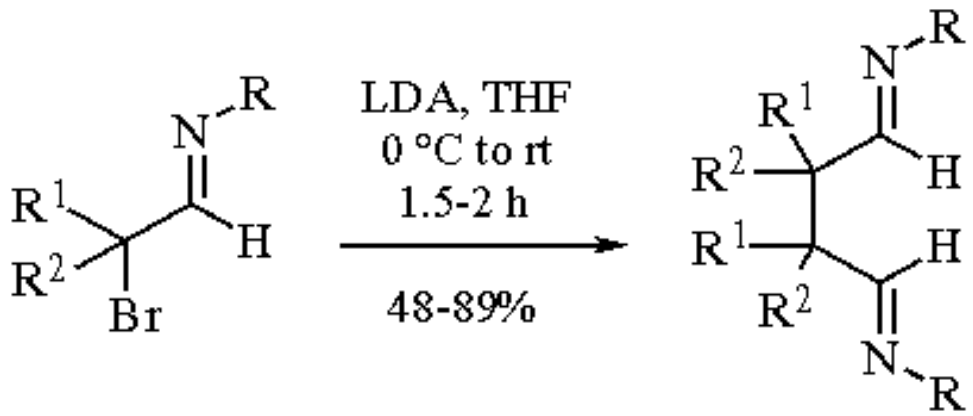

(13)

R^1, R^2 = $(CH_2)_5$; R^1 = R^2 = Me; R = *i*-Pr, *t*-Bu

Synthesis of α-Cyano Enamines,[11] Acylation of Arenes under Non-Friedel-Crafts Conditions, and Synthesis of β-Chloro Amines.

Cyanation of α-chloro aldimines leads to α-cyano enamines, which are potential building blocks (eq 14).[10] The conversion of α-chloro aldimines with ***Phenyllithium*** into alkyl phenyl ketimines and, after hydrolysis, into alkyl phenyl ketones constitutes a mild acylation of arenes under non-Friedel-Crafts conditions (eq 15).[12] Electrophilic reduction of α-chloro aldimines by the ***Borane-Dimethyl Sulfide*** complex is a route to sterically hindered β-chloro amines (eq 16).[11]

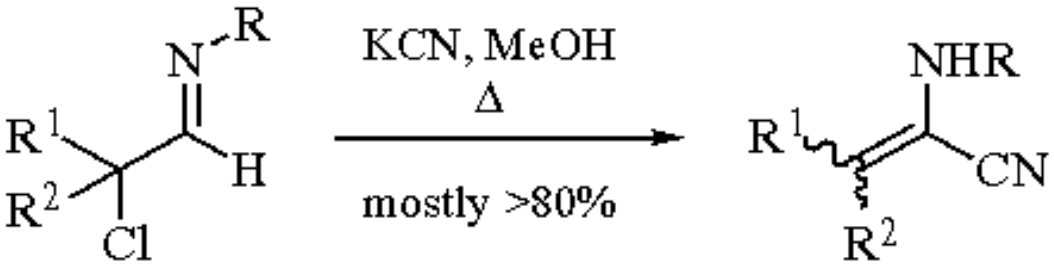

(14)

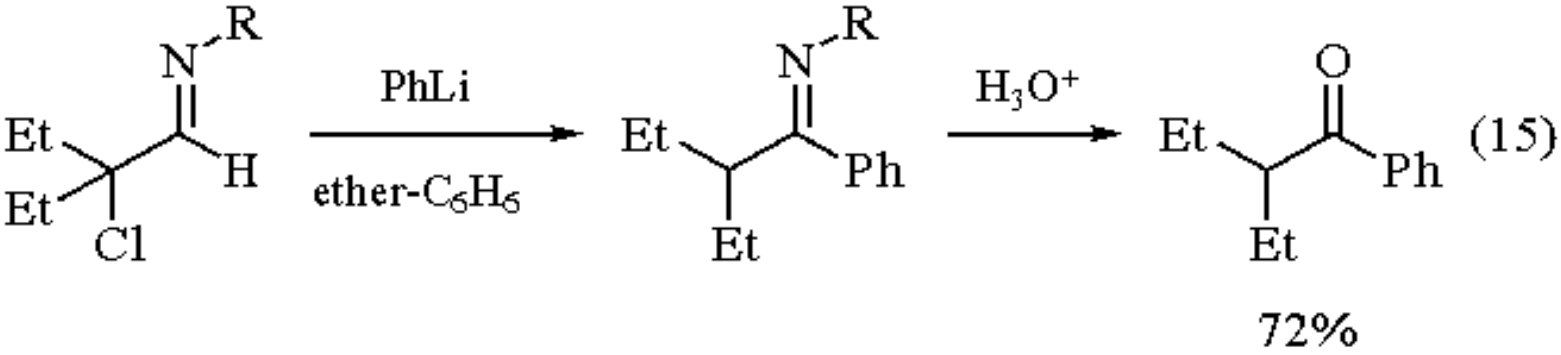

(15)

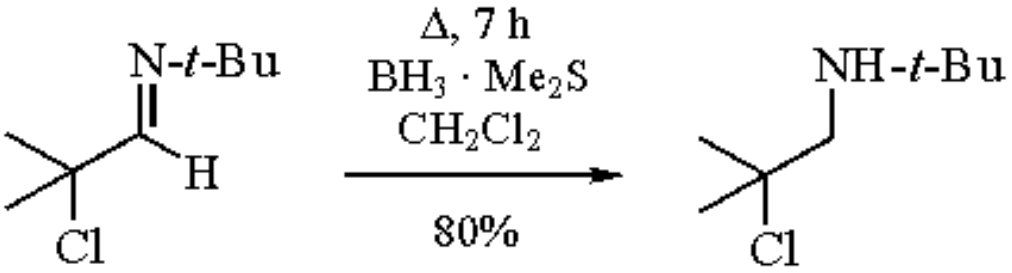

(16)

Synthesis of Aziridines, 2-Imidazolidinethiones, and 2-Imidazolidinones.

Nucleophilic reduction of α-chloro aldimines with ***Lithium Aluminum Hydride*** in ether gives ready access to aziridines (eq 17).[13] Ambident nucleophiles, such as ***Potassium Thiocyanate*** and potassium cyanate, react with α-chloro aldimines in methanol to produce 4-methoxy-2-imidazolidinethiones and 4-methoxy-2-imidazolidinones, respectively (eqs 18 and 19).[14,15] The latter heterocycles can be cleanly converted into the corresponding demethoxylated five-membered aza heterocycles,[14,15] 4-imidazolin-2-ones (eq 19),[24] or triimidazohexahydro[1,3,5]triazines (eq 18).[25]

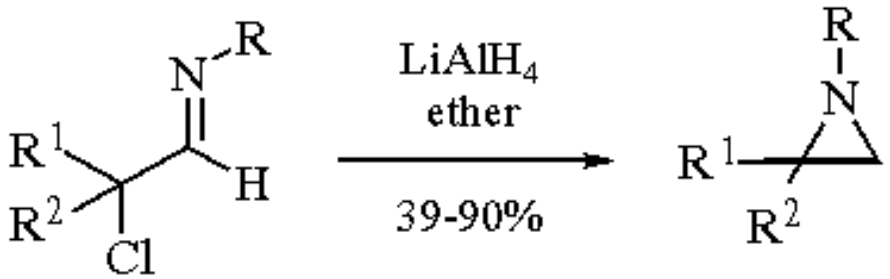

(17)

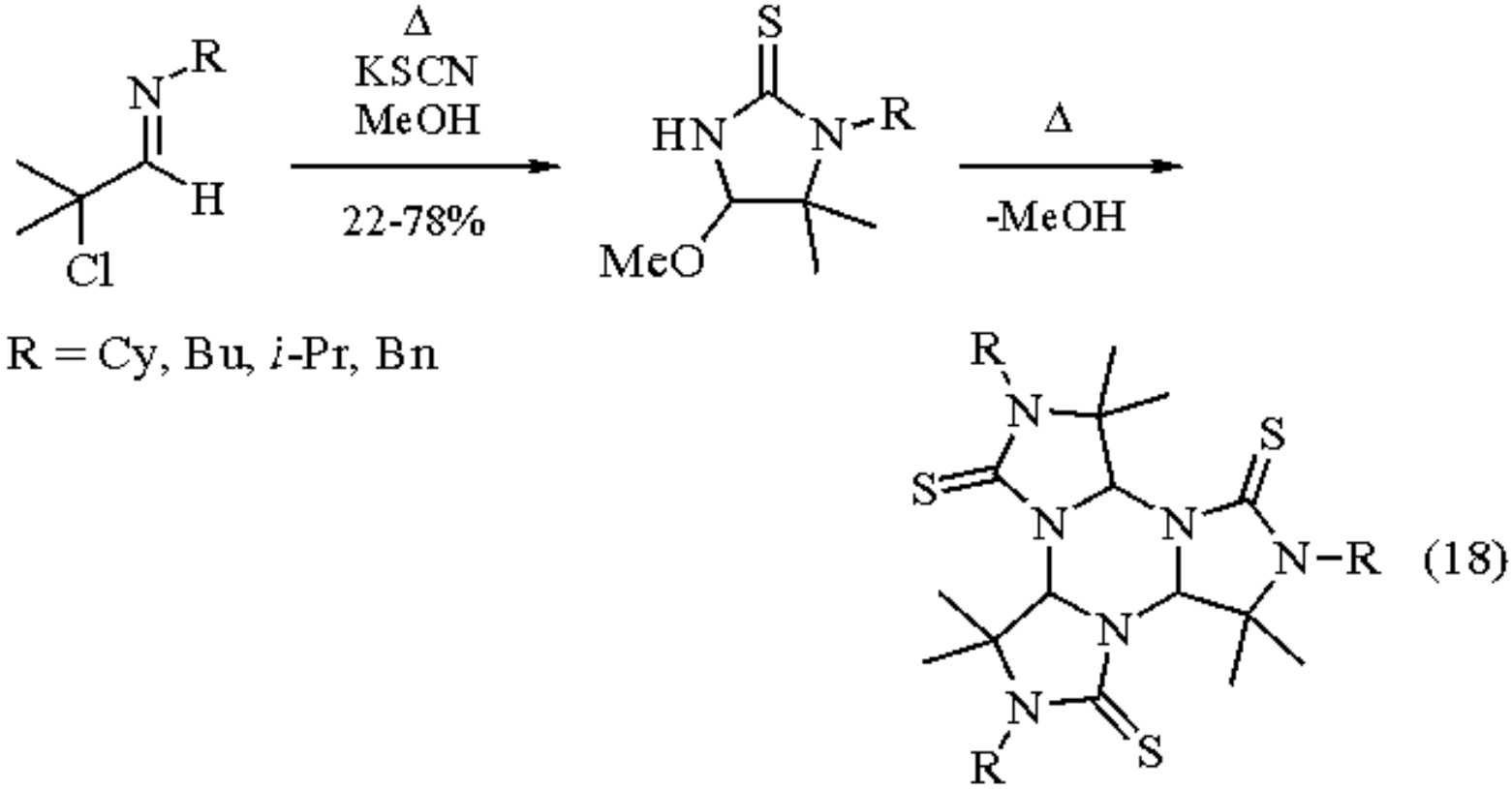

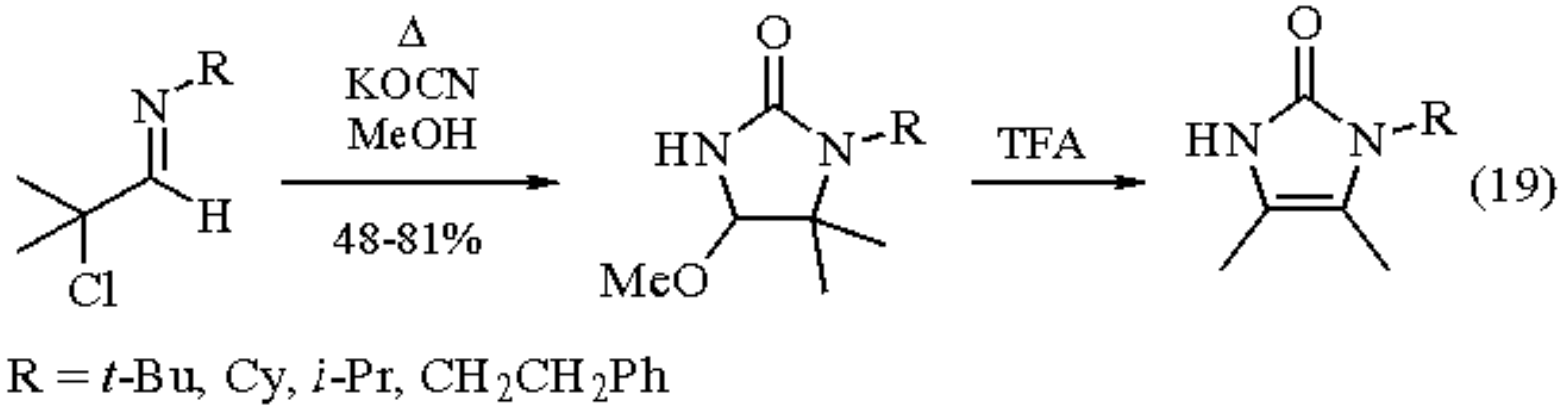

α-Arylation of Aldehydes, Synthesis of 2-Aza-1,3-dienes, Reductive Dehalogenation of α-Halo Aldehydes, and Synthesis of 3-(1-Chloroalkyl)oxaziridines.

The Friedel-Crafts-type arylation of α-chloro aldimines in the presence of ***Aluminum Chloride*** gives rise to α-aryl aldimines, which are hydrolyzed to α-aryl aldehydes (eq 20).[16] α-Substituents which stabilize the intermediate α-imidoylcarbenium ions, e.g. phenyl substituents, greatly enhance the yields of this reaction.[16,26] Higher alkyl analogs give lower yields of α-arylation products due to competing 1,2-dehydrochlorination to give α,β-unsaturated aldimines. When toluene is used as the arene, the *ortho*:*para* regiochemistry is about 7:93.[26] This reaction proceeds also with heteroaromatic compounds such as furan (eq 21).[26] The reductive conversion of α-halo aldehydes to aldehydes is not easy to accomplish due to the sensitivity of the carbonyl function for reductive processes. However, this conversion can be performed via *N*-benzyl α-halo aldimines, which undergo 1,4-dehydrohalogenation to give 2-aza-1,3-dienes

(eq 22).[17,18] The latter heterodienes are easily hydrolyzed to aliphatic and aromatic aldehydes (eq 22).[18]

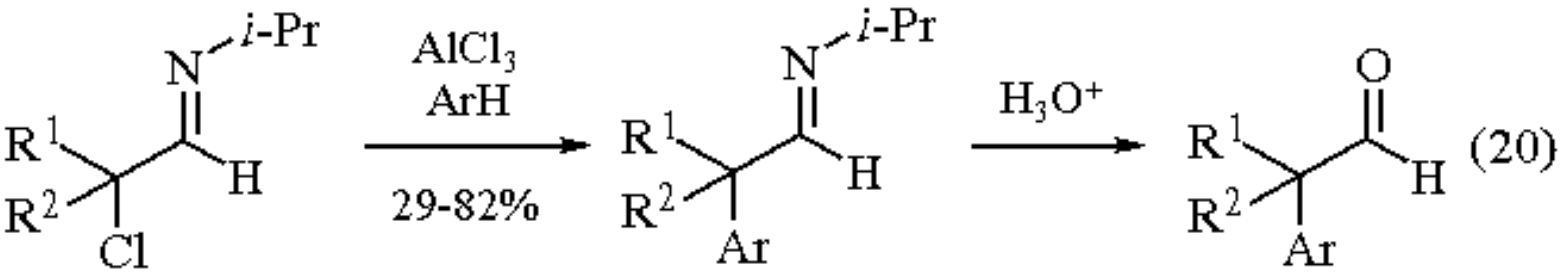

$R^1 = Me, Et; R^2 = Ph, Me, Et; Ar = Ph, 4\text{-}MeC_6H_4, 2,5\text{-}Me_2C_6H_3$

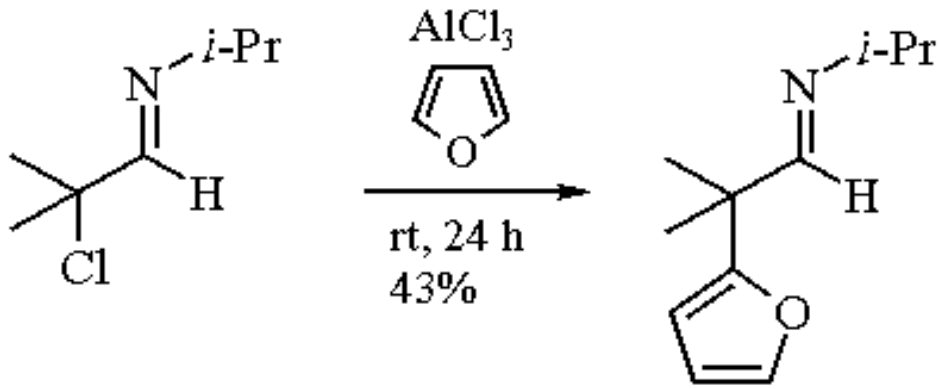

(21)

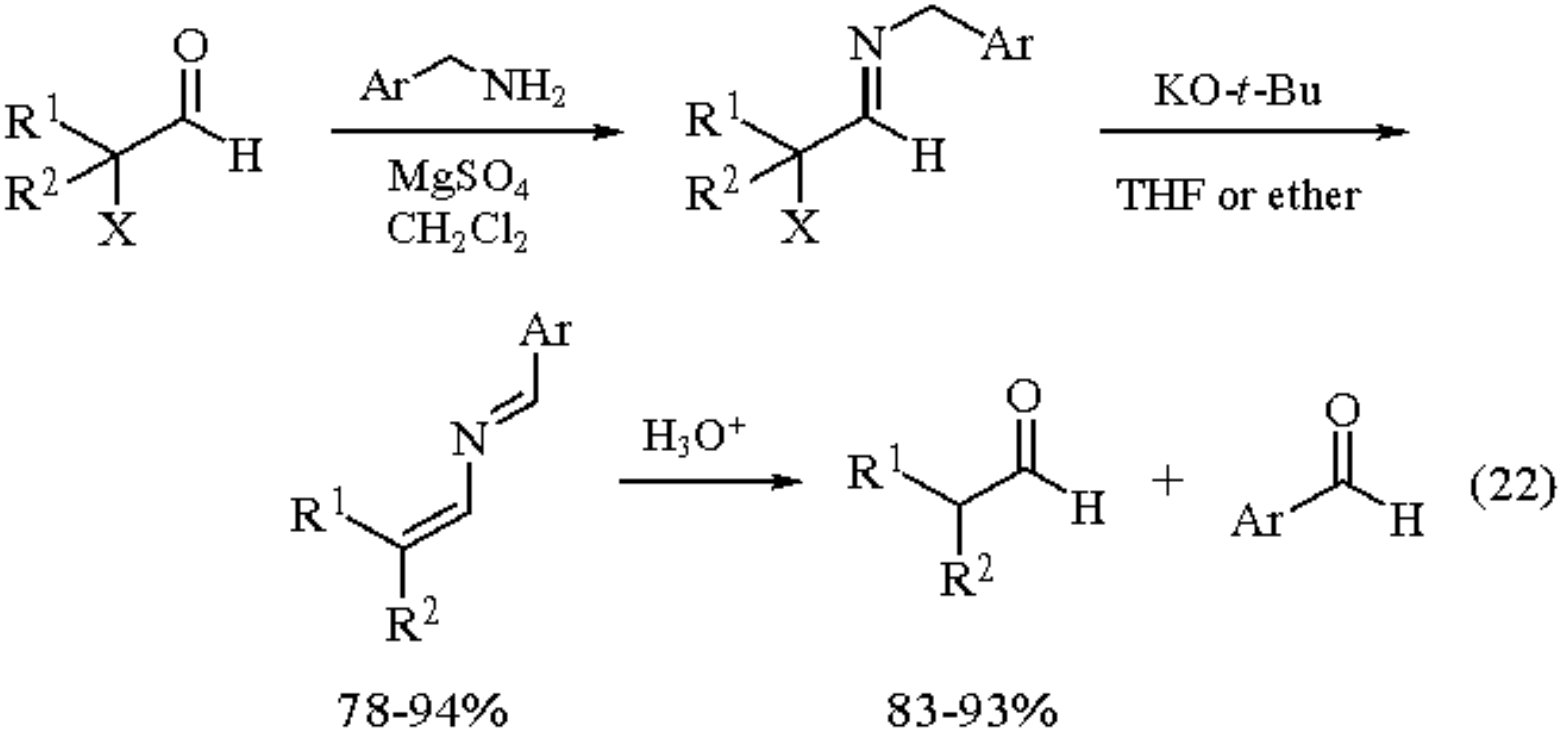

(22)

Oxidation of α-halo aldimines with ***m-Chloroperbenzoic Acid*** produces stable 3-(1-chloroalkyl)oxaziridines (eq 23), which undergo rearrangement with ***Methyllithium*** to α-(*N*-alkylamino) aldehydes (eq 24) and which oxygenate phenyllithium to phenol (eq 24).[27]

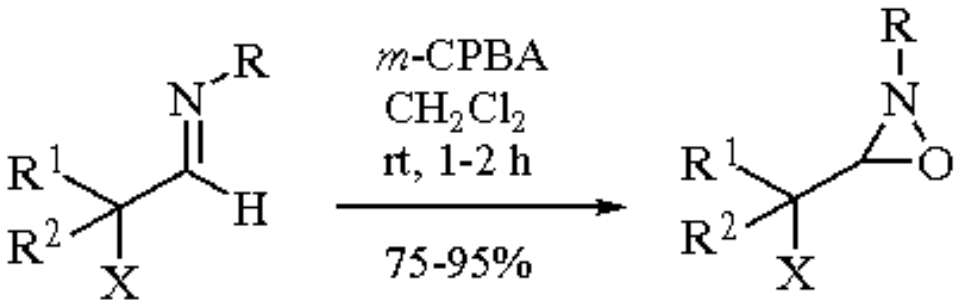

(23)

X = Cl, Br; $R^1 = R^2 = Me$; $R^1 = R^2 = (CH_2)_5$; R = *i*-Pr, *t*-Bu, Cy

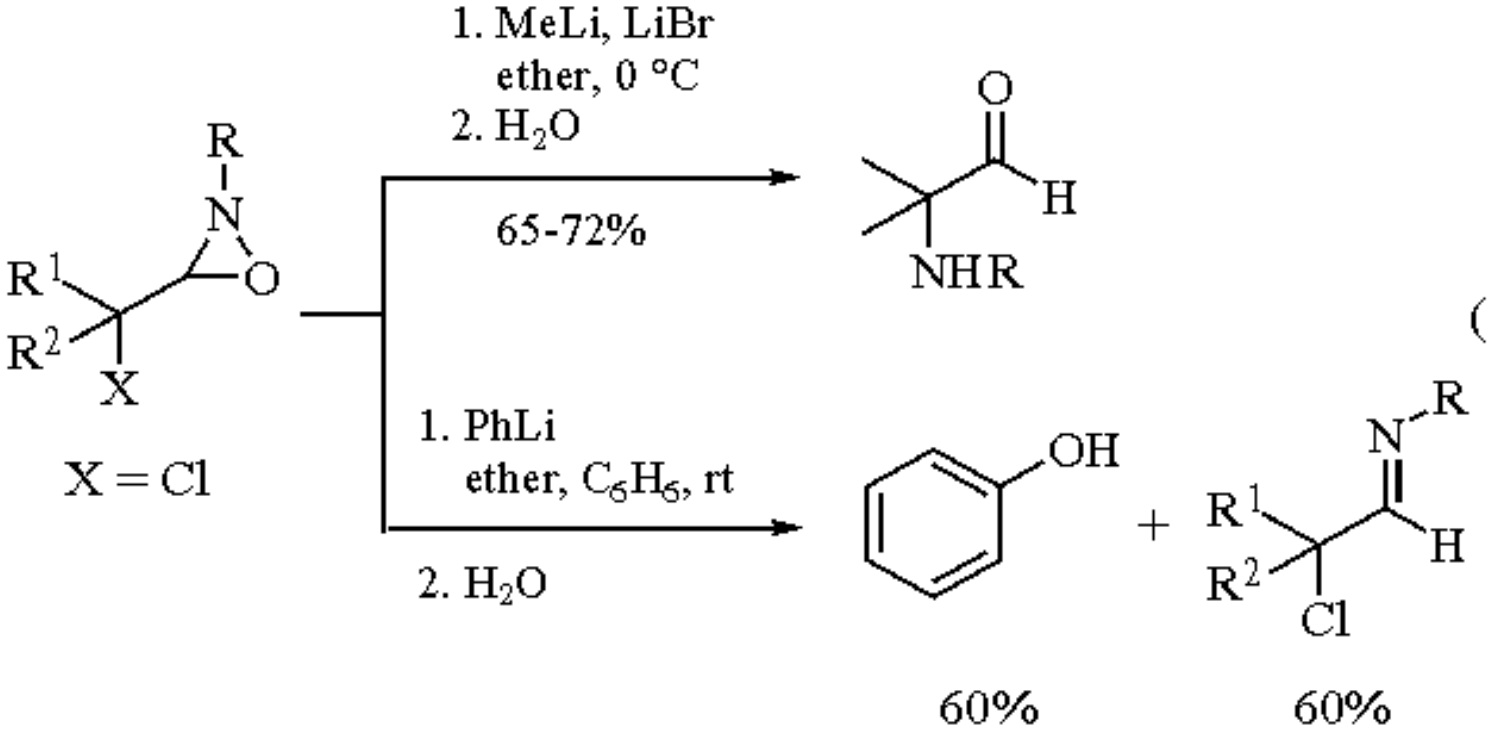

(24)

Related Reagents.

Acetaldehyde N-t-Butylimine; ***2-(t-Butylamino)-3-methyl-2-butenenitrile***; ***Chloroacetaldehyde***; ***1-(N,N-Dimethylamino)-2-methyl-1-propene***; α-***Methacrolein N-t-Butylimine***; ***Methacrolein Dimethylhydrazone***; ***Propionaldehyde t-Butylimine***.

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(*E*)-(3-Chloro-1-methyl-1-propenyl)trimethylsilane

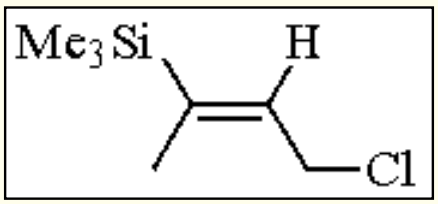

[116399-78-1] · $C_7H_{15}ClSi$ · (*E*)-(3-Chloro-1-methyl-1-propenyl)trimethylsilane · (MW 162.76)

(annulation reagent; alkylative equivalent of 3-buten-2-one; 3-oxobutyl synthon)

Alternate Name: (*E*)-1-chloro-3-trimethylsilyl-2-butene.

Physical Data: bp 92-94 °C/74 mmHg.

Solubility: freely sol organic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: $\delta_H(CCl_4)$ 0.0 (9H, s), 1.67 (3H, d, *J* 1.5 Hz), 3.93 (2H, d, *J* 7 Hz), 5.8 (1H, t of q, *J* 7 and 1.5 Hz).

Preparative Method: see ***1-Iodo-3-trimethylsilyl-2-butene***.

Basis and Example of Use.

This reagent acts as the alkylative equivalent of 3-buten-2-one (***Methyl Vinyl Ketone***), permitting regiospecific enolate alkylation under nonequilibrating conditions. As a vinylsilane it can be converted,[1] via the corresponding α,β-epoxy silane, into a 3-oxobutyl moiety, and hence used in an alkylative equivalent of Robinson annulation.[2] Application of such methodology can be seen (eq 1) in the preparation of bicyclodecenones via the alkylation of dihydrocarvone with this reagent.[3] Apart from this application, and its use in combination with potassium iodide[4] (see ***1-Iodo-3-trimethylsilyl-2-butene***), it has seen little use so far.

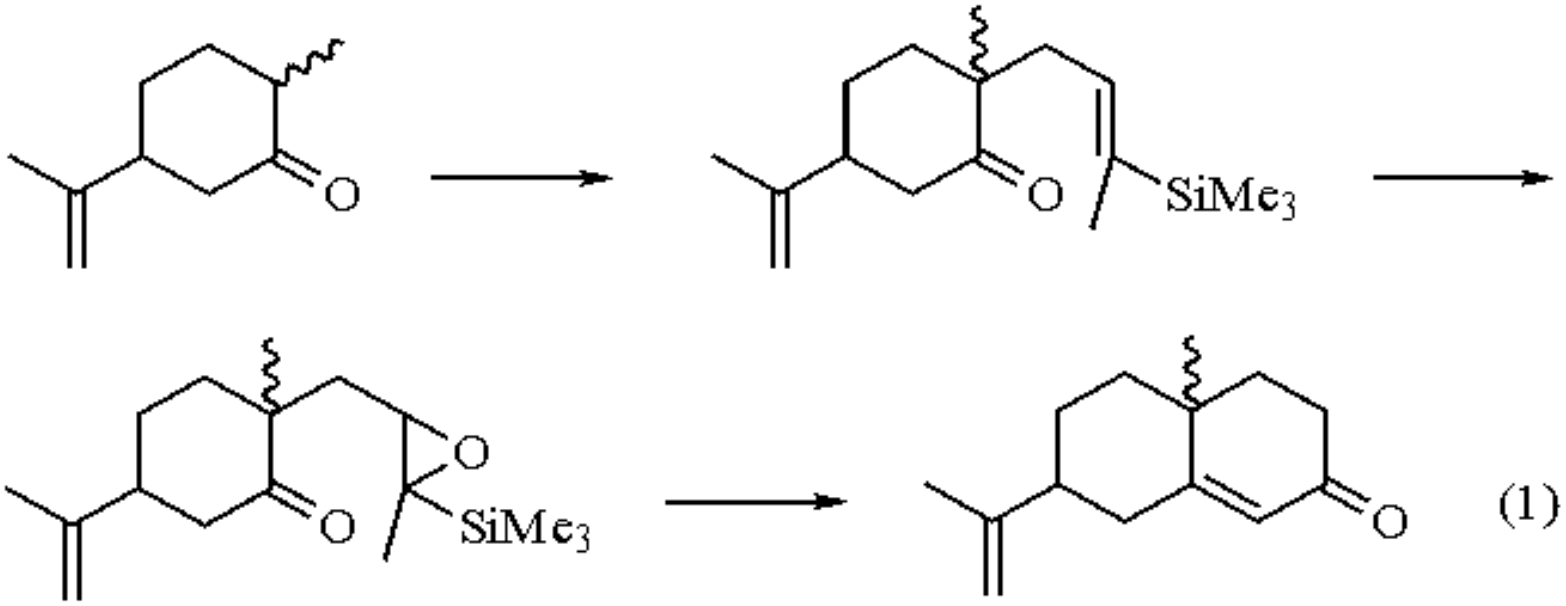

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2-Chloro-1-methylpyridinium Iodide[1]

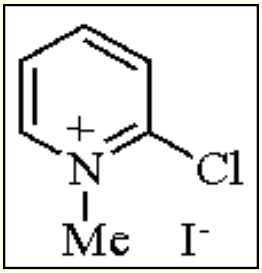

[14338-32-0] · C_6H_7ClIN · 2-Chloro-1-methylpyridinium Iodide · (MW 255.49)

(activation of carboxylic acids;[1] formation of esters[2] and amides;[3] lactonization;[4] ketene formation;[5] β-lactam synthesis;[6,7] carbodiimide synthesis[8])

Alternate Name: Mukaiyama's reagent.

Physical Data: mp 204-206 °C.

Form Supplied in: commercially available yellow solid.

Preparative Method: by reaction between 2-chloropyridine and ***Iodomethane*** in acetone at reflux.[9]

Purification: recrystallization from acetone.

Handling, Storage, and Precautions: hygroscopic.

Activation of Carboxylic Acids: Ester Formation.

2-Chloro-1-methylpyridinium iodide (**1**) reacts with a mixture of a carboxylic acid and an alcohol, in the presence of two equivalents of base, to form an ester (eq 1).[2] The pyridinium salt (**2**) is formed rapidly by displacement of chloride from (**1**) by the carboxylate; subsequent reaction with the alcohol results in formation of the ester, along with 1-methyl-2-pyridone (**3**). A variety of solvents may be employed, but yields are highest in dichloromethane or pyridine. ***Tri-n-butylamine*** or ***Triethylamine*** are often used as base. The co-product (**3**) is insoluble in dichloromethane and so precipitates from this solvent. Good results are obtained even for hindered carboxylic acids and alcohols.

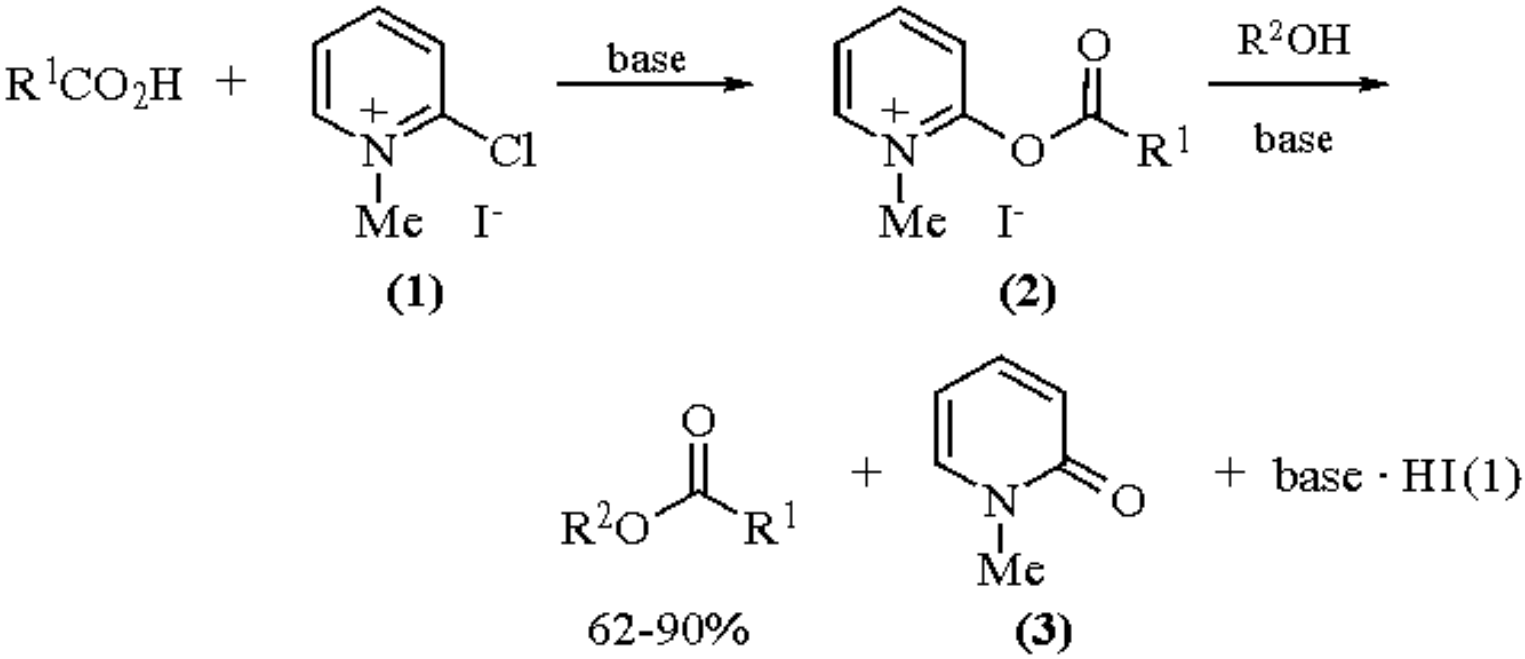

Amide Synthesis.

In a similar way, amides can be prepared efficiently by treatment of an equimolar amount of a carboxylic acid and an amine with (**1**) in the presence of base (eq 2).[3]

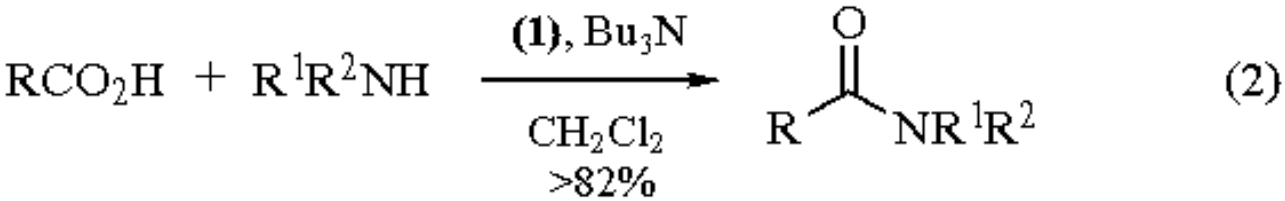

Lactone Formation.

The ester formation method has found widespread use in the synthesis of lactones by cyclization of hydroxy acids (eq 3).[4] The cyclization process is believed to be entropically favored because of the close proximity of all reactants to a central pyridinium salt (**4**). Optimum conditions for the process involve addition over 8 h of a solution of the hydroxy acid (0.0125 M) and triethylamine (8 equiv) in dichloromethane or acetonitrile to a solution of (**1**) (4 equiv; 0.04 M) in the same solvent at reflux. After a further 30 min at reflux, evaporation of the solvent and chromatography affords the lactone. Results of a study of the formation of lactones of various ring sizes are shown in Table 1. Good results are obtained for ring sizes 7 and &egt;12, but attempts to form 8- or 9-membered lactones result in substantial dimerization.

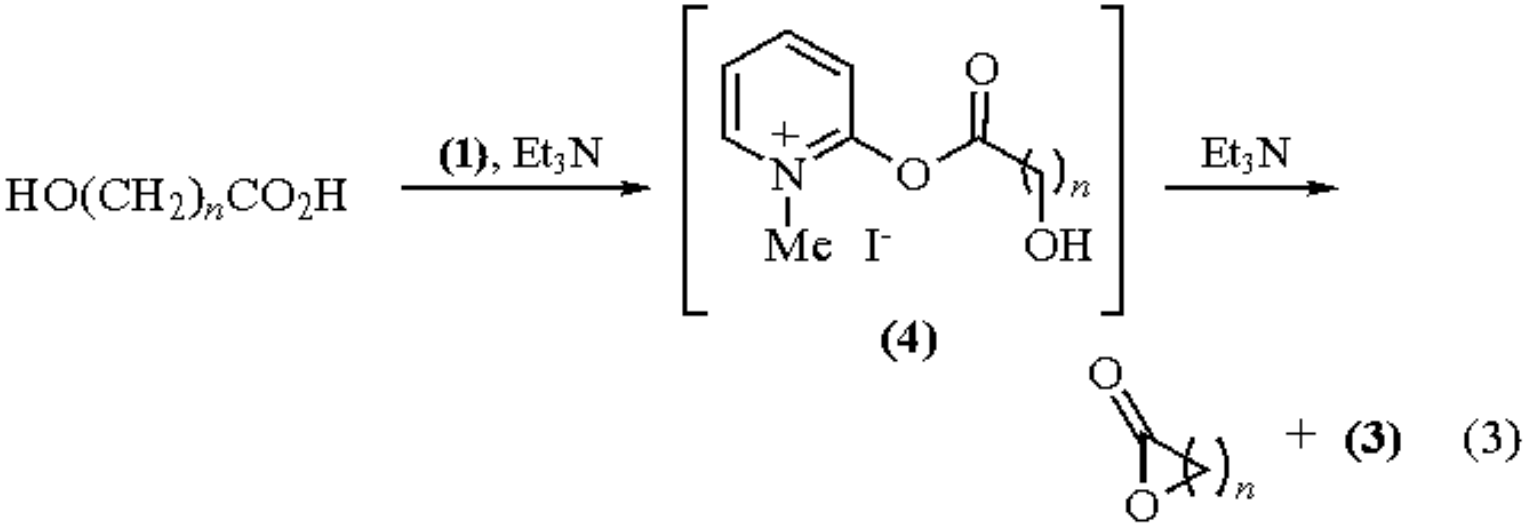

Table 1 Lactone Formation by Cyclization of Hydroxy Acids with Reagent (**1**)

Ring size	% Yield lactone	% Yield dimer
7	89	0
8	0	93
9	13	34
12	61	24
13	69	14
16	84	3

Cyclization of sensitive *trans*-γ-hydroxy acids to give strained *trans*-bicyclic γ-lactones of the type (**5**) is often problematic due to dehydration of the tertiary alcohol. A study showed (**1**) to be the reagent of choice for this transformation (eq 4).[10] Other reagents, such as ***1,3-Dicyclohexylcarbodiimide*/*Pyridine*** or ***2,2´-Dipyridyl Disulfide*/*Triphenylphosphine***, give far lower yields.

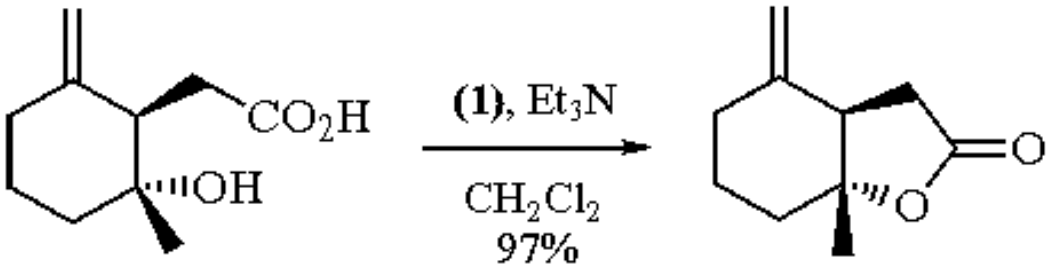

(4)

(5)

Ketene Formation.

There is evidence that the above esterification procedure may occur at least partly via formation of the ketene from the carboxylic acid.[5] If a carboxylic acid contains a suitably placed alkene, the resulting ketene can undergo intramolecular [2 + 2] cycloaddition (eq 5).[5] Benzene is the best solvent for this reaction, giving yields comparable to those obtained by ketene formation from the corresponding acid chloride.

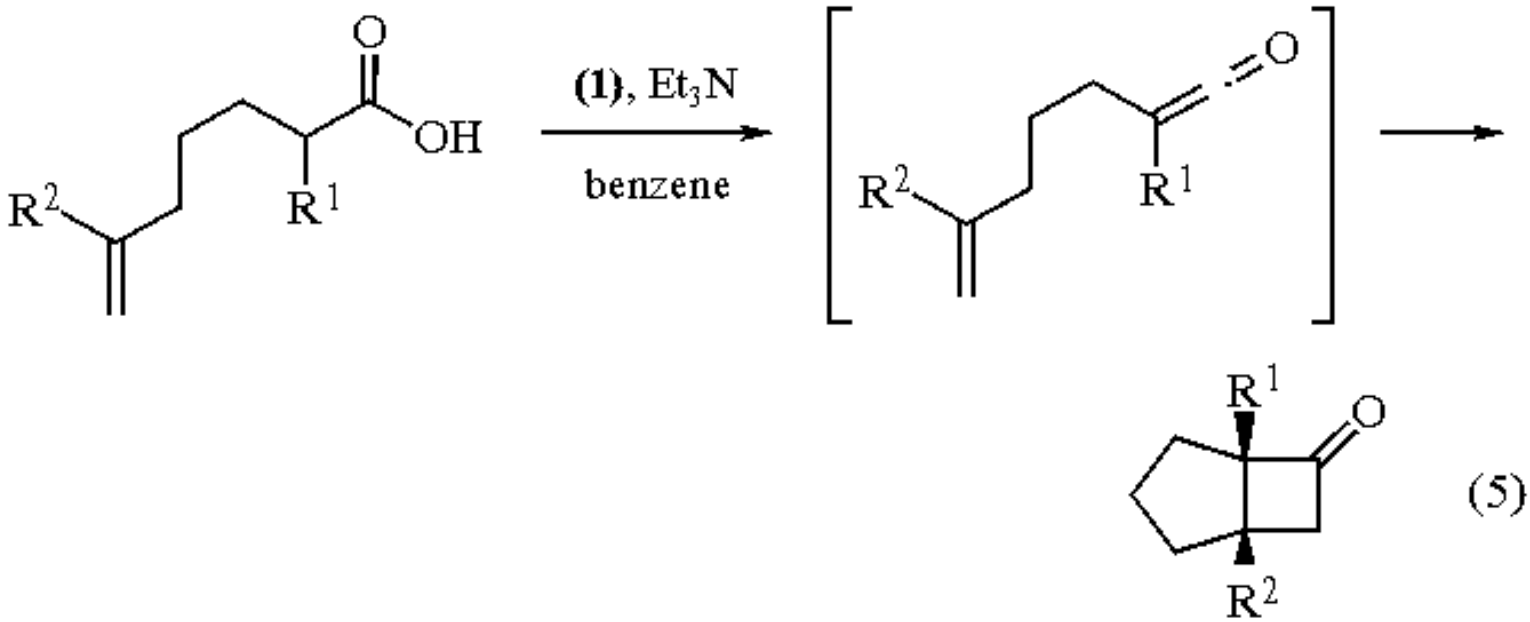

β-Lactam Synthesis.

Dehydration of β-amino acids to give β-lactams can be effected in high yield using (**1**) in CH_2Cl_2 or MeCN (eq 6).[6]

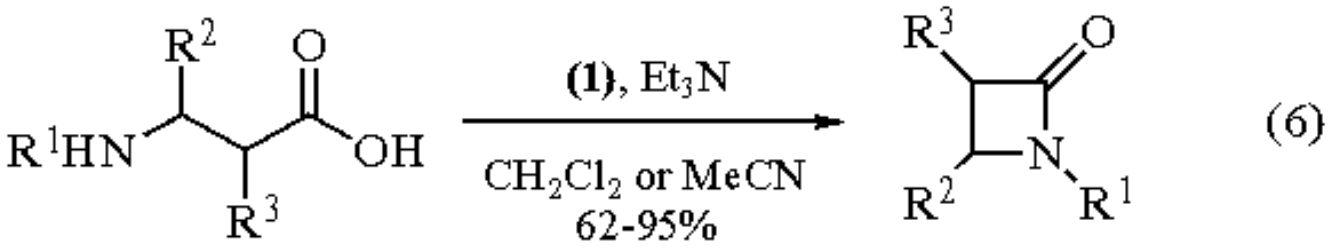

β-Lactams can also be prepared by the reaction of carboxylic acids, activated by (**1**), with imines; best results are obtained with ***Tripropylamine*** as base in CH_2Cl_2 at reflux (eq 7).[7]

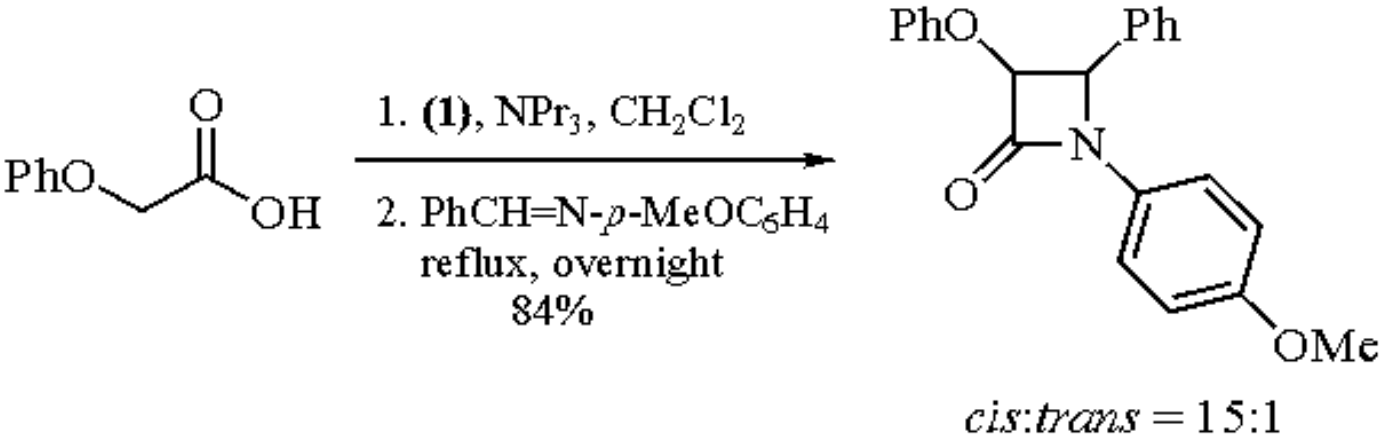

(7)

Carbodiimides from Thioureas.

Conversion of *N,N´*-disubstituted thioureas into carbodiimides can be effected by treatment with (**1**) and 2 equiv of base (eq 8).[8]

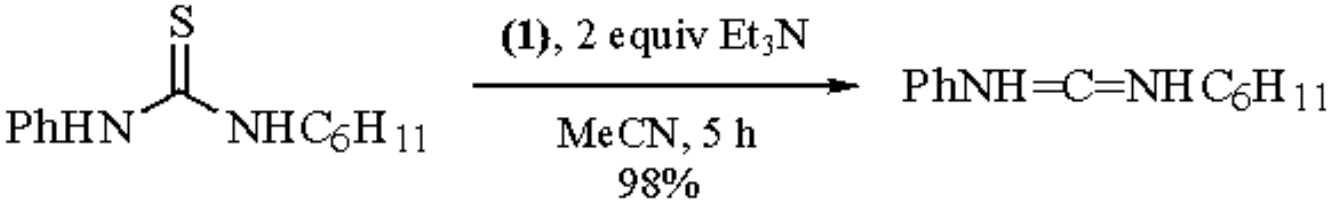

(8)

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10. Strekowski, L.; Visnick, M.; Battiste, M. A. *S* **1983**, 493.

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Chloromethyl *p*-Tolyl Sulfide[1]

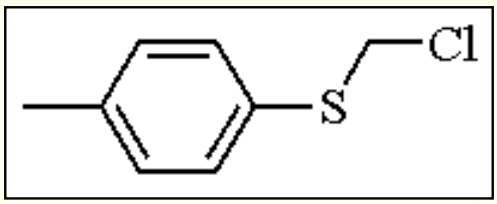

[34125-84-3] · C_8H_9ClS · Chloromethyl *p*-Tolyl Sulfide · (MW 172.68)

(source of the *p*-tolylthio carbanion[2] and reactive electrophiles;[1] starting material for the synthesis of 1-halomethyl *p*-tolyl sulfoxide[3])

Physical Data: bp 125-126 °C/15 mmHg.

Solubility: sol most organic solvents; insol H_2O.

Preparative Methods: several methods are available.[4] The most commonly used and convenient method is the chlorination of methyl *p*-tolyl sulfide with ***Sulfuryl Chloride*** in methylene chloride.[4a,b]

Handling, Storage, and Precautions: use in a fume hood.

Chloromethyl *p*-Tolyl Sulfide Carbanion.

The reaction of *p*-tolylthiochloromethylpotassium, generated by the reaction of chloromethyl *p*-tolyl sulfide with ***Potassium t-Butoxide*** in *t*-butanol in the presence of ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO), with benzaldehyde gives the corresponding α,β-epoxy sulfide as a mixture of isomers, the *cis* isomer being the predominant product. When ***Pivalaldehyde*** is used as the carbonyl component, only the *cis* isomer of the corresponding α,β-epoxy sulfide is formed. The *cis* isomers upon treatment with ***Boron Trifluoride Etherate*** rearrange to α-tolylthio aldehydes with the exclusive migration of the *p*-tolylthio group (eq 1).[2a] This type of rearrangement is analogous to the reaction of α,β-epoxy sulfoxides[5] (see also ***Chloromethyl Phenyl Sulfoxide***).

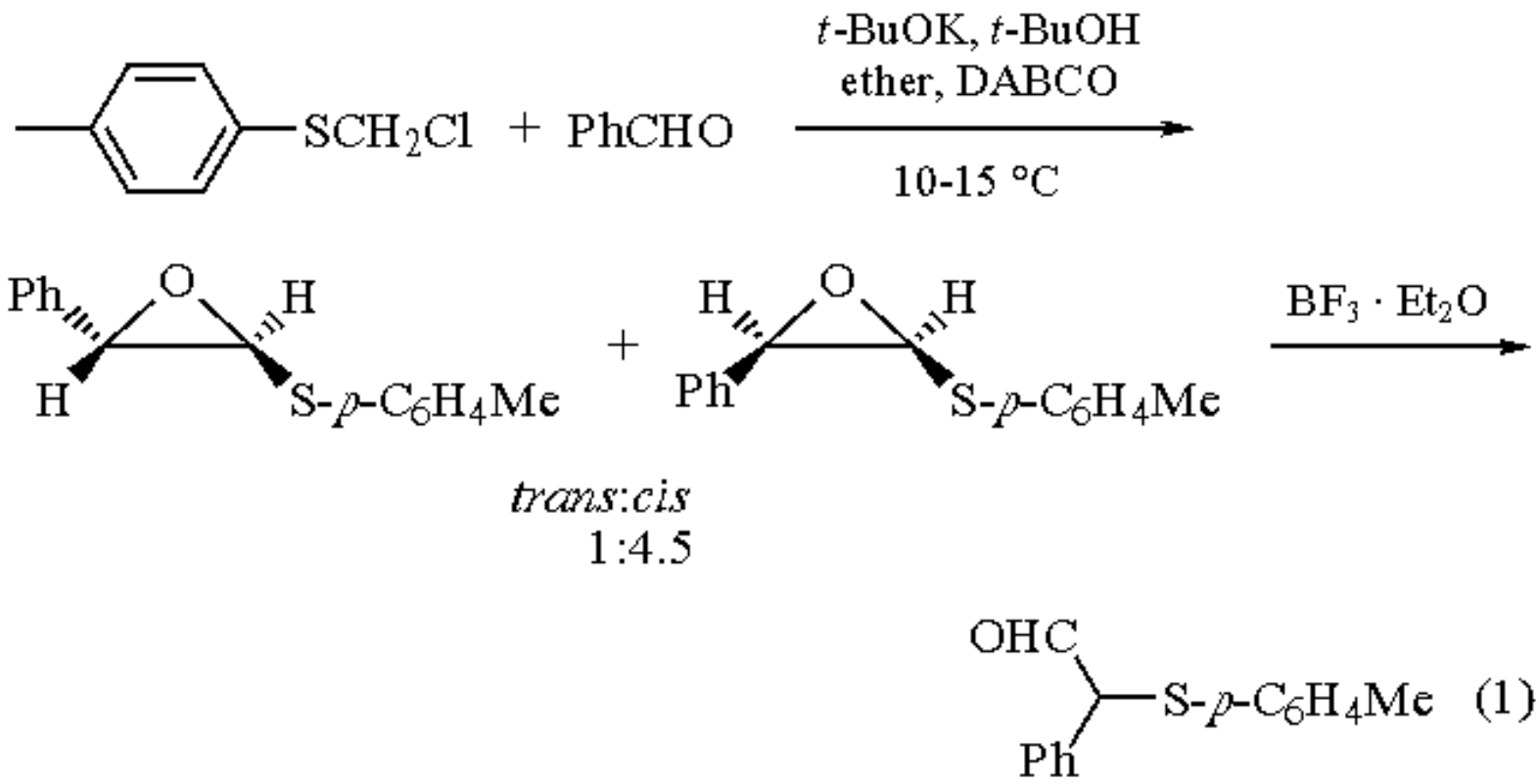

Attempts to generate *p*-tolylthiochloromethylpotassium with *t*-butoxide in *t*-butanol without DABCO in the presence of the carbonyl compounds gave only *trans*-1,2-bis(*p*-tolylthio)ethylene as a byproduct, presumably by a displacement-elimination reaction involving the *p*-tolylthiochloromethyl carbanion (eq 2).[2a]

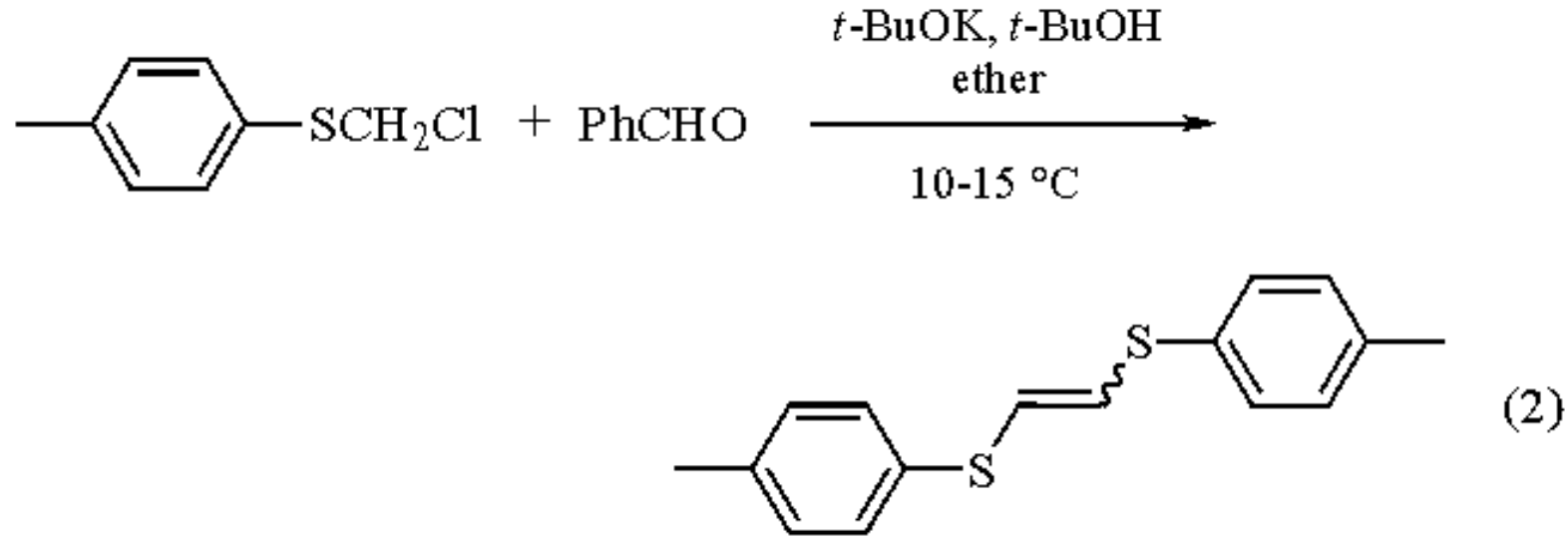

A low yield of β-hydroxy-α-chloro sulfide is obtained from the reaction of *p*-tolylthiochloromethyllithium with benzaldehyde, presumably due to the inefficient generation of the carbanion with *n*-butyllithium. The phenylthio analog of the α,β-epoxy sulfide is prepared by the reaction of bis(phenylthio)methyllithium with carbonyl compounds. The adducts, α-hydroxybis(phenylthio) acetals, on reaction with ***Copper(I) Trifluoromethanesulfonate*** (6 equiv) in benzene containing ***Diisopropylethylamine*** (4 equiv), give α,β-epoxy sulfides which are thermally labile and undergo thermal rearrangement to α-phenylthio ketones (eq 3).[6]

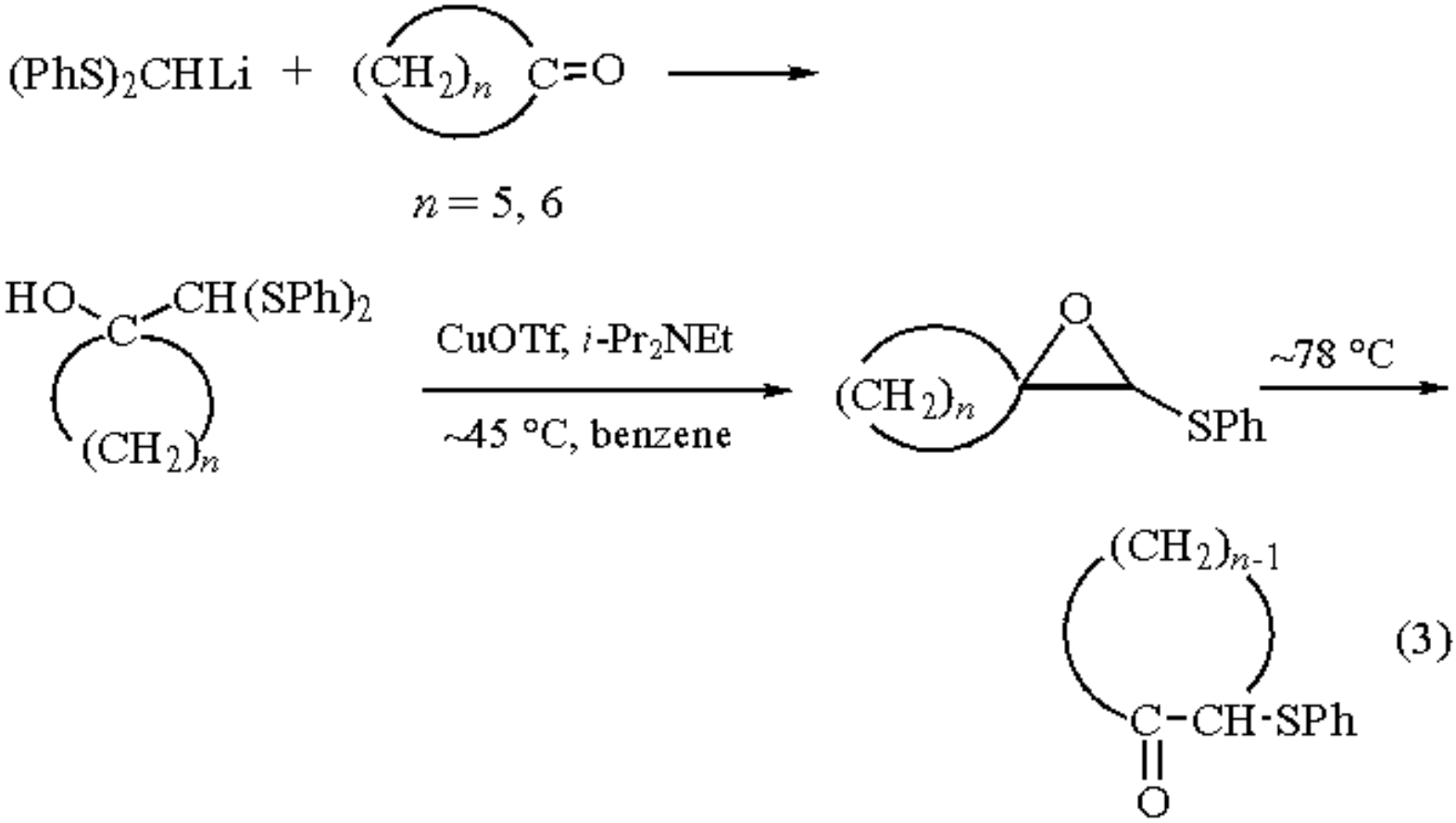

A high yield of a Grignard reagent, *p*-tolylthiomethylmagnesium chloride, is obtained by the reaction of chloromethyl *p*-tolyl sulfide with ***Magnesium*** in THF at 10-20 °C. The temperature is the crucial factor, and small amounts of ***Iodine*** and ***1,2-Dibromoethane*** are used to initiate the Grignard reaction. (+)-(*S*)-*p*-Tolyl *p*-tolylthiomethyl sulfoxide is formed in 81% yield with 88% optical purity upon reacting an equimolar amount of the Grignard reagent with (-)-(*S*)-menthyl *p*-toluenesulfinate (see ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***) (eq 4).[2b] This method is used for preparation of the chiral thioacetal monosulfoxide with a higher chemical yield but lower optical purity than the method reported earlier, which utilizes *p*-tolylthiomethyllithium as the carbanion partner.[7] The chiral thioacetal monosulfoxide is useful as a chiral synthon for the synthesis of chiral α-substituted aldehyde s (eq 5).[8]

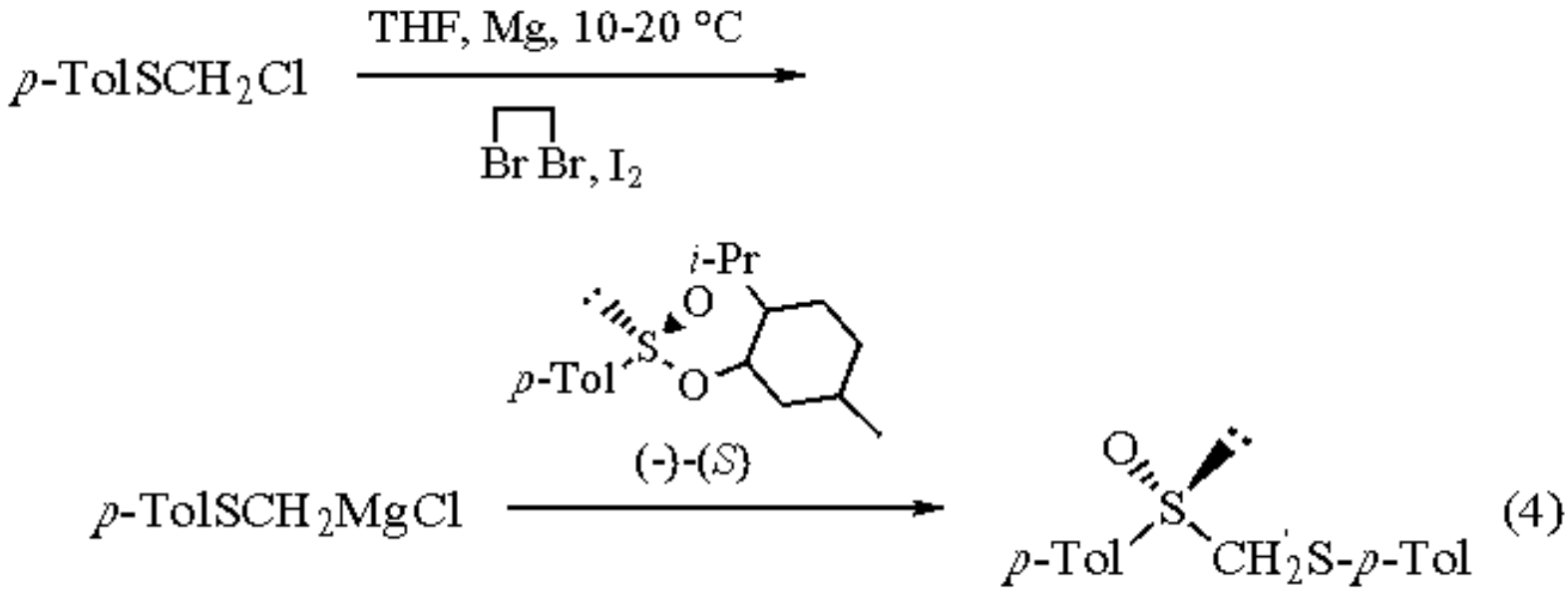

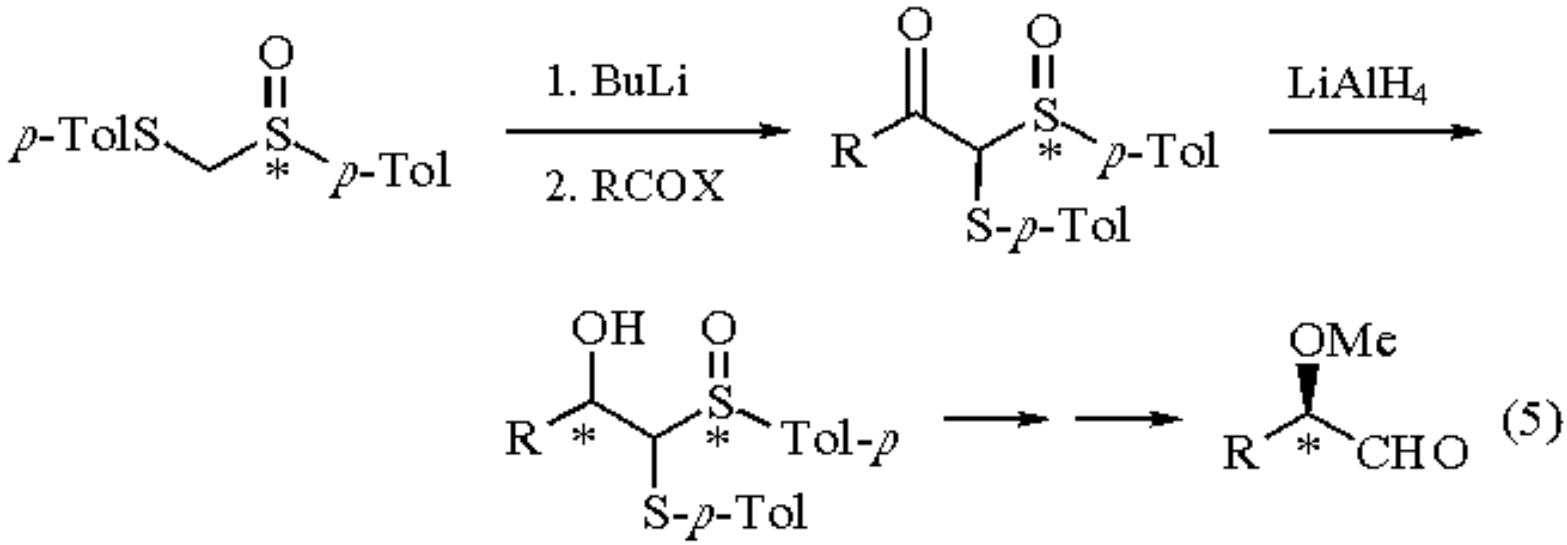

N-Alkylation.

2*H*-1,3-Benzothiazine derivatives, a group of compounds with significant pharmacological activities, are synthesized by *N*-alkylation followed by cyclization of aryl and alkyl nitriles using ***Antimony(V) Chloride*** as a Lewis acid (eq 6).[9]

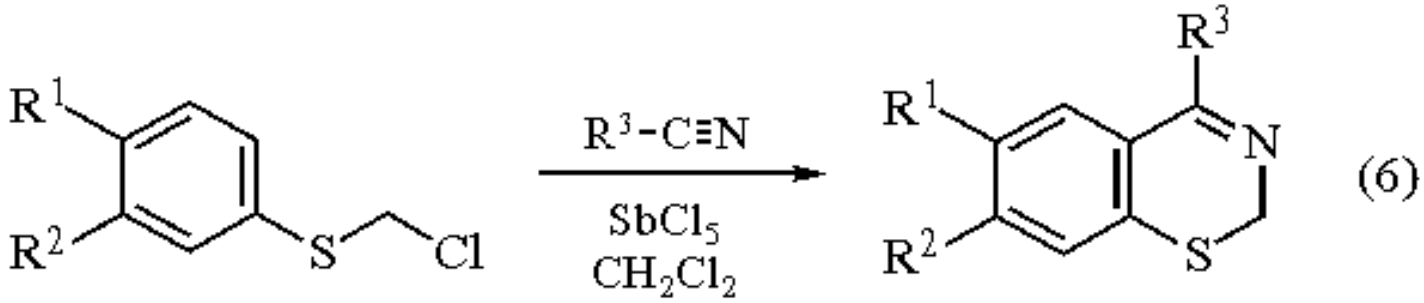

P-Alkylation.

The Michael-Arbuzov reaction of chloromethyl *p*-tolyl sulfide with ***Trimethyl Phosphite***[10] or ***Triethyl Phosphite***[11] yields dimethyl- or diethylphosphonylmethyl *p*-tolyl sulfides, which are important intermediates for the synthesis of vinyl sulfides and sulfoxides,[12] as well as for optically active derivatives of dimethylphosphonylmethyl *p*-tolyl sulfoxide (eq 7). This method of preparation of the chiral *p*-tolylthio monosulfoxide is complementary to the reaction using dimethylphosphonylmethyllithium and (-)-(*S*)-menthyl *p*-toluenesulfinate in which the (+)-(*R*) isomer is obtained in high yield and high optical purity (eq 8). The lithio dimethylphosphonylmethyl *p*-tolyl sulfoxide reacts with aldehydes and ketones to give the corresponding vinyl sulfoxides, which can be converted into optically active allylic alcohols (eq 9).[10,13]

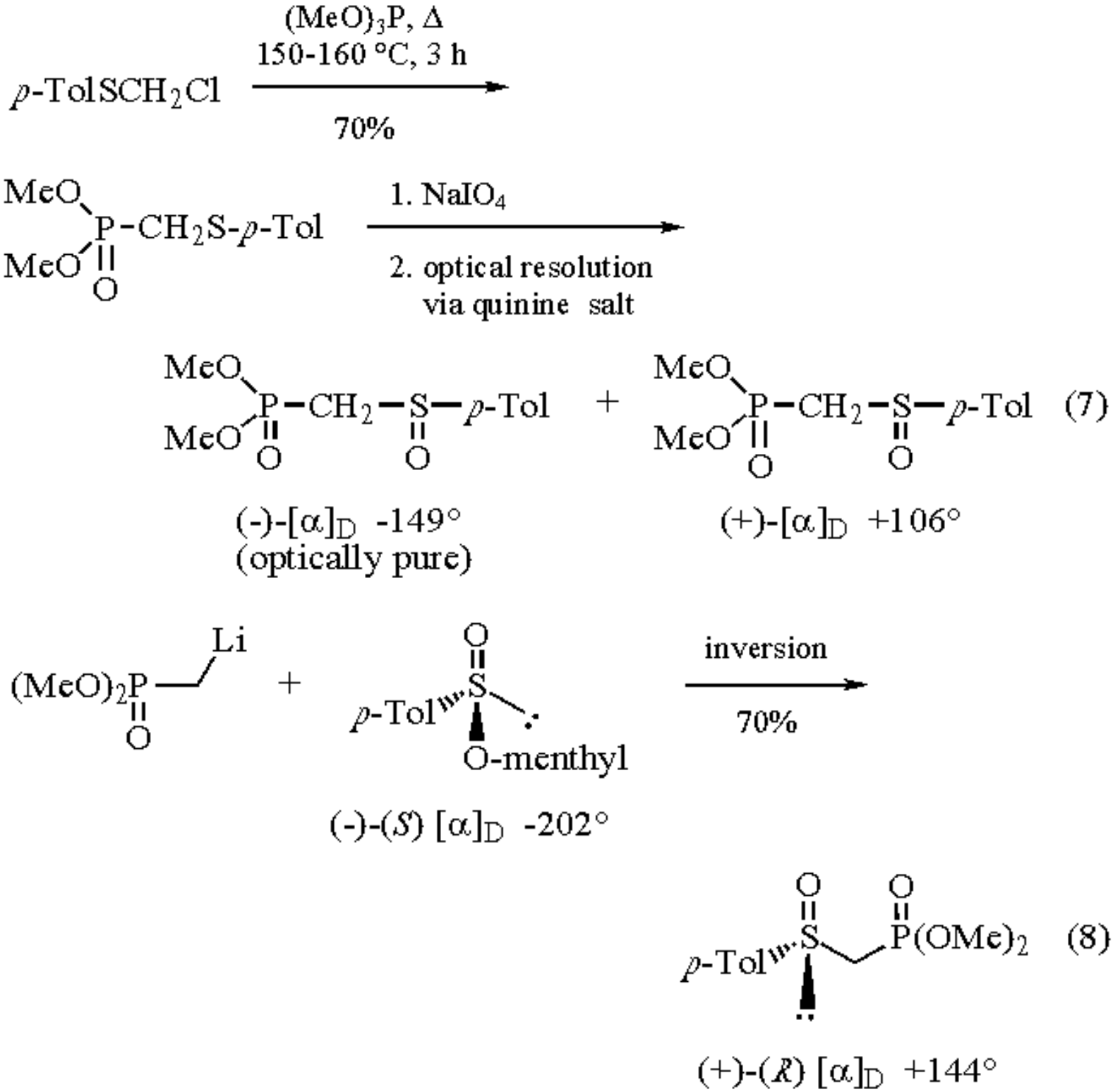
(MeO)3P, Δ
150-160 °C, 3 h
p-TolSCH2Cl
70%
MeO
MeO
P-CH2S-p-Tol
O
1. NaIO4
2. optical resolution
via quinine salt
MeO
MeO
P-CH2-S-p-Tol
O
O
+
MeO
MeO
P-CH2-S-p-Tol
O
O
(7)
(-)-[α]D -149°
(optically pure)
(+)-[α]D +106°
Li
(MeO)2P
O
+
O
p-Tol
S
O-menthyl
(-)-(S) [α]D -202°
inversion
70%
O
O
p-Tol
S
P(OMe)2
(8)
(+)-(R) [α]D +144°

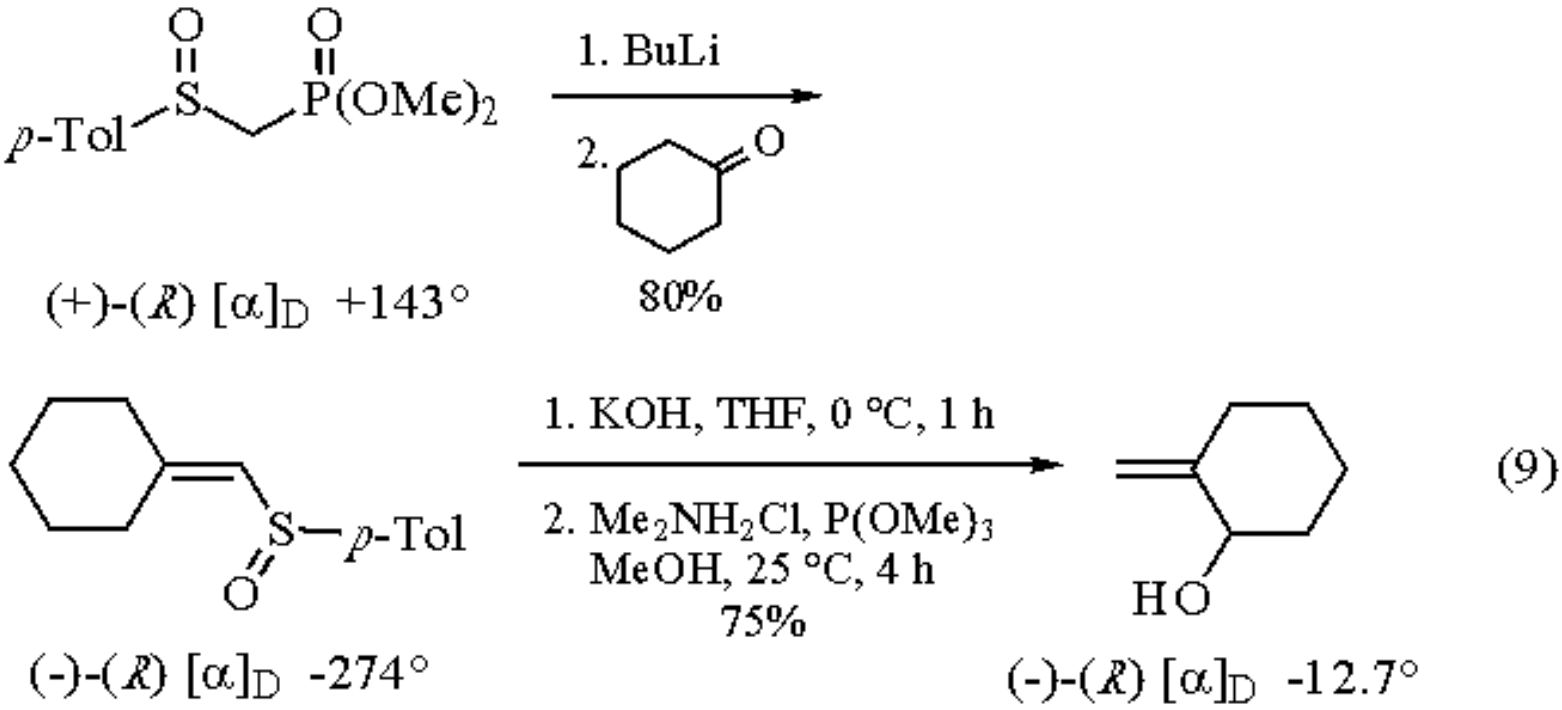

Self-Condensation.

Bis(*p*-tolylthio)methane, an important dithioacetal for nucleophilic alkylation,[14] is formed by self-alkylation of chloromethyl *p*-tolyl sulfide using neutral ***Alumina*** as a catalyst (eq 10).[15]

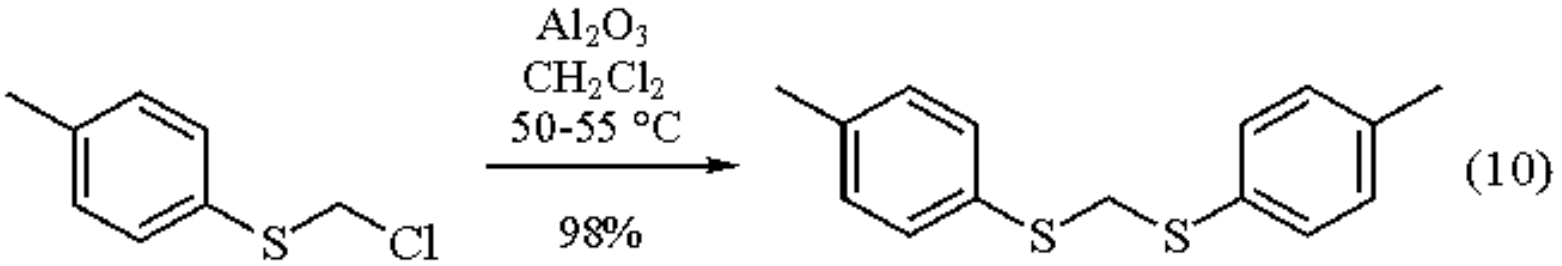

Oxidation.

Fluoromethyl *p*-tolyl sulfide, which can be oxidized to fluoromethyl *p*-tolyl sulfoxide with ***N-Bromosuccinimide*** in methanol, is synthesized by the reaction of chloromethyl *p*-tolyl sulfide with ***Potassium Fluoride*** in the presence of ***18-Crown-6*** (eq 11).[3b] Chloromethyl *p*-tolyl sulfoxide can be synthesized by a one-pot operation from methyl *p*-tolyl sulfide with ***Silver(I) Nitrate*** and ***Sulfuryl Chloride*** via the intermediacy of chloromethyl *p*-tolyl sulfide (eq 12).[3b,c]

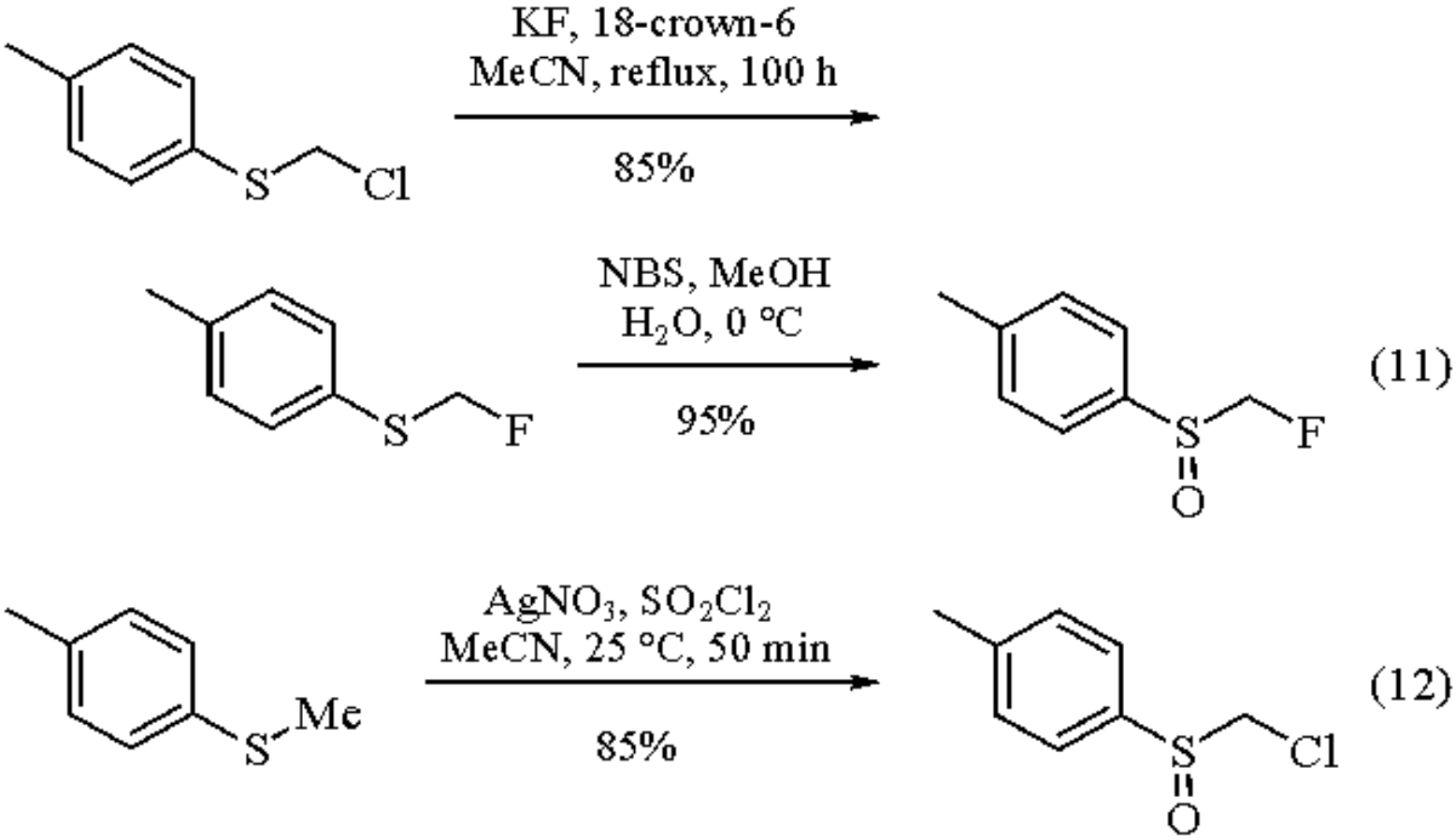

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12. (a) Mikolajczyk, M.; Grzejszczak, S.; Midura, W.; Zatorski, A. *S* **1975**, 278. (b) Mikolajczyk, M.; Grzejsczak, S.; Midura, W.; Zatorski, A. *S* **1976**, 396.
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14. Gröbel, B.-T.; Seebach, D. *S* **1977**, 357.
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Chloromethyl *p*-Tolyl Sulfone

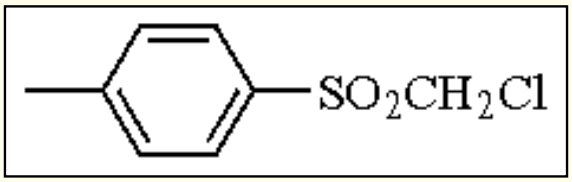

[7569-26-8] · $C_8H_9ClO_2S$ · Chloromethyl *p*-Tolyl Sulfone · (MW 204.68)

(synthesis of α,β-epoxy sulfones and alkylated sulfones;[1] reacts with electrophilic arenes and heterocyclic arenes;[2] source of α-*p*-tolylsulfonyl radicals[1a])

Physical Data: mp 81-82 °C.

Solubility: sol THF, $CHCl_3$, CH_2Cl_2, and most organic solvents.

Preparative Methods: by oxidation of the corresponding sulfoxide[3] or by reaction of sodium *p*-toluenesulfinate with bromochloromethane.[4]

Handling, Storage, and Precautions: use in a fume hood.

α,β-Epoxy Sulfones.

The chemistry of chloromethyl *p*-tolyl sulfone resembles that of chloromethyl phenyl sulfone (see ***Chloromethyl Phenyl Sulfone***). α,β-Epoxy *p*-tolyl sulfones derived from carbonyl compounds are conveniently prepared by a one-step Darzens-type condensation using ***Benzyltriethylammonium Chloride*** (TEBA) as phase-transfer catalyst, and 50% ***Sodium Hydroxide*** as a base (eq 1).[4a,5] *trans*-α,β-Epoxy *p*-tolyl sulfones, and a mixture of *cis* and *trans* isomers, are obtained from aldehydes and unsymmetrical ketones, respectively.

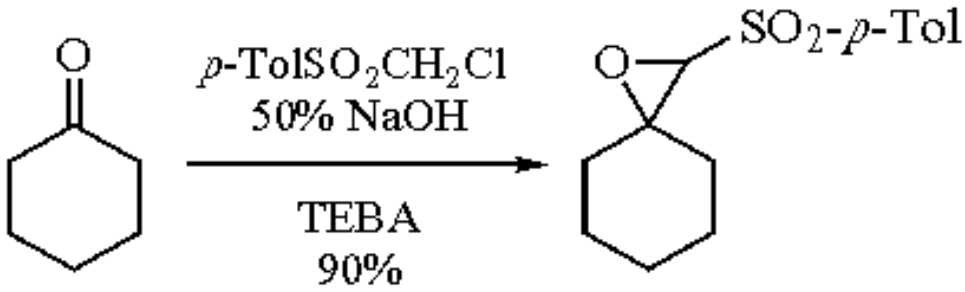

(1)

α,β-Epoxy *p*-tolyl sulfones can also be prepared by the epoxidation of α,β-unsaturated *p*-tolyl sulfones with alkaline ***Hydrogen Peroxide*** (giving *trans*-α,β-epoxy *p*-tolyl sulfones)[6] and potassium chlorite (producing *cis*-α,β-epoxy *p*-

tolyl sulfones).[7]

α,β-Epoxy *p*-tolyl sulfones undergo reactions similar to those of α,β-epoxy phenyl sulfones. Rearrangement with ***Boron Trifluoride Etherate*** gives the expected α-tolylsulfonyl substituted carbonyl products (eq 2).[5b] The reaction with sodium diethyl phosphite gives synthetically useful α-keto phosphonates (eq 3).[8]

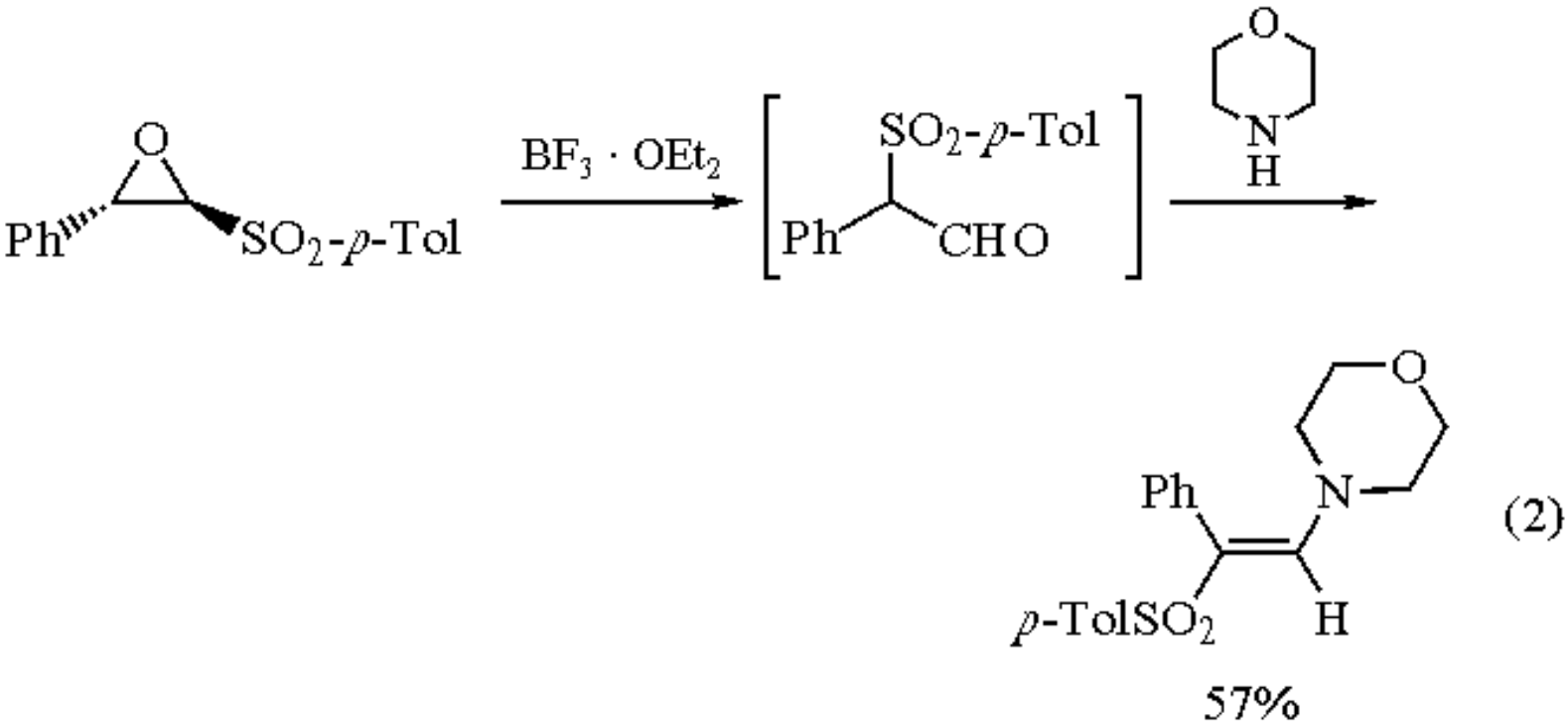

(2)

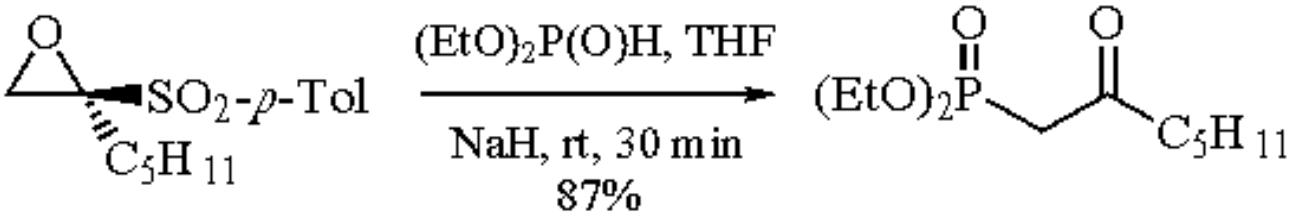

(3)

Alkylation Reactions.

Alkylation of chloromethyl *p*-tolyl sulfone with alkyl halides can be effected either by using a phase-transfer catalyst or ***n-Butyllithium*** as a base (eqs 4 and 5).[5a,9] *p*-Tolylsulfonylchloromethylmagnesium, prepared by the reaction with ***Ethylmagnesium Bromide***, is stable and undergoes normal Grignard reactions, e.g., carbonylation and carbonyl addition reactions.[10]

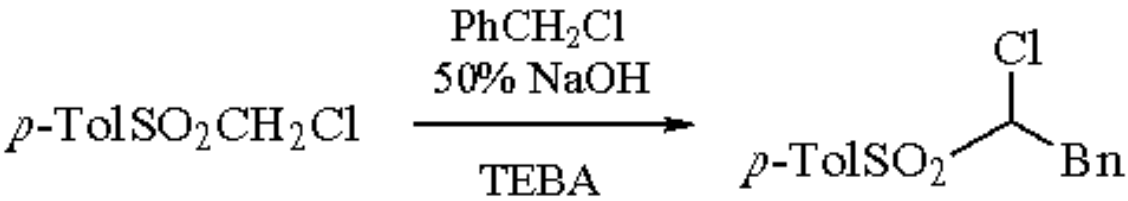

(4)

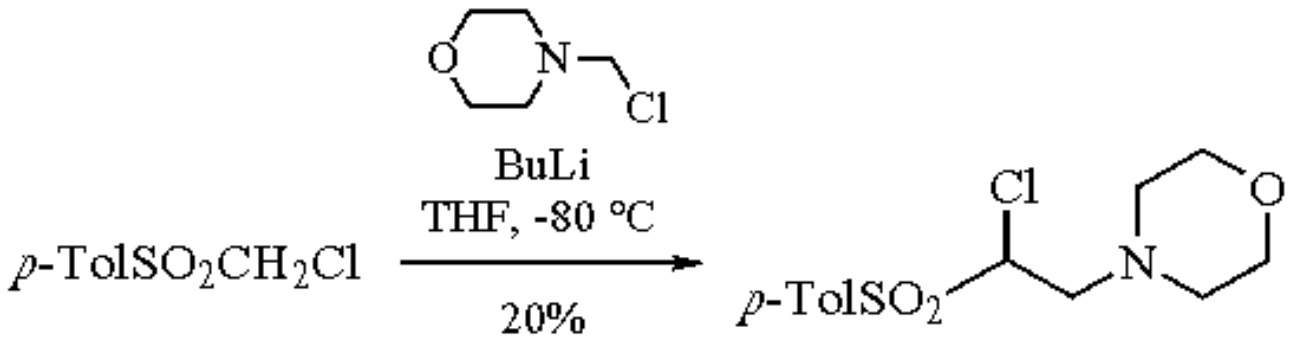

(5)

Reaction of α-Alkylated Sulfones.

Racemic and optically active α-chloro-β-keto *p*-tolyl sulfones, prepared by oxidation of the corresponding sulfoxides, undergo Favorskii rearrangement to give α-alkyl amides. This process can be used to synthesize optically active α-alkyl amides by the asymmetric Favorskii rearrangement (eq 6).[11] α-Chloro-α-alkyl-β-keto *p*-tolyl sulfones undergo metal-halogen exchange with *n*-butyllithium to give the corresponding enolates which can be protonated to give substituted α-*p*-tolylsulfonyl derivatives (eq 7).[12]

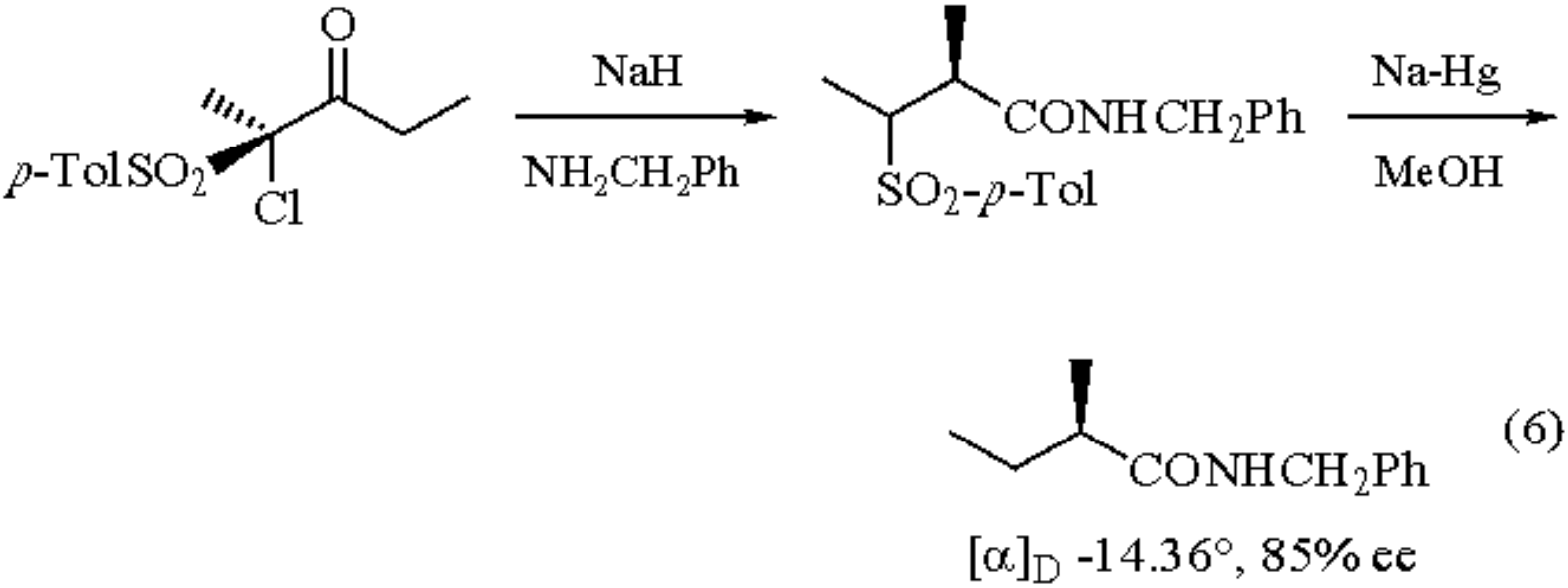

(6)

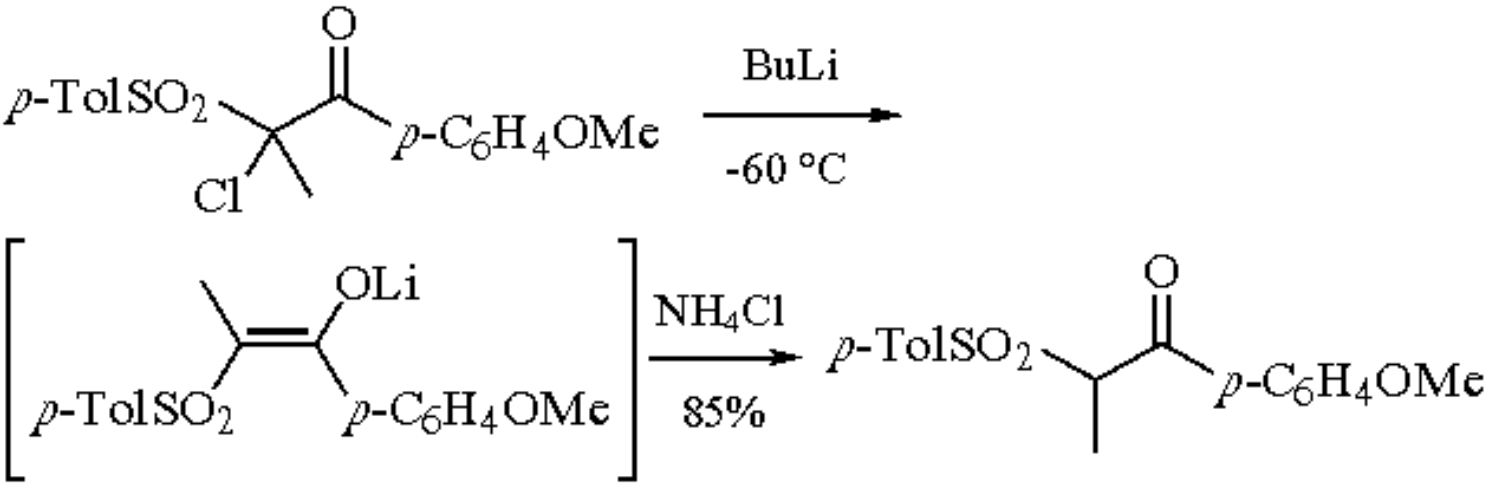

(7)

Vicarious Nucleophilic Aromatic Substitution of Hydrogen (VNS).

The chloromethyl *p*-tolyl sulfone carbanion behaves similarly to the corresponding phenyl analog in the vicarious nucleophilic substitution of hydrogen (VNS) with electrophilic arenes and heterocyclic arenes.[2] The reaction with 1,4-dicyanonaphthalene gives both the VNS product and the corresponding bis(cyclopropane) derivative (eq 8).[13] The reaction with 6-nitroquinoxaline gives the normal VNS product (eq 9),[13] whereas the reaction with 6-azaquinoxaline gives either VNS and/or the corresponding bis(cyclopropane) products depending on temperature, the base used and its concentration (eq 10).[14]

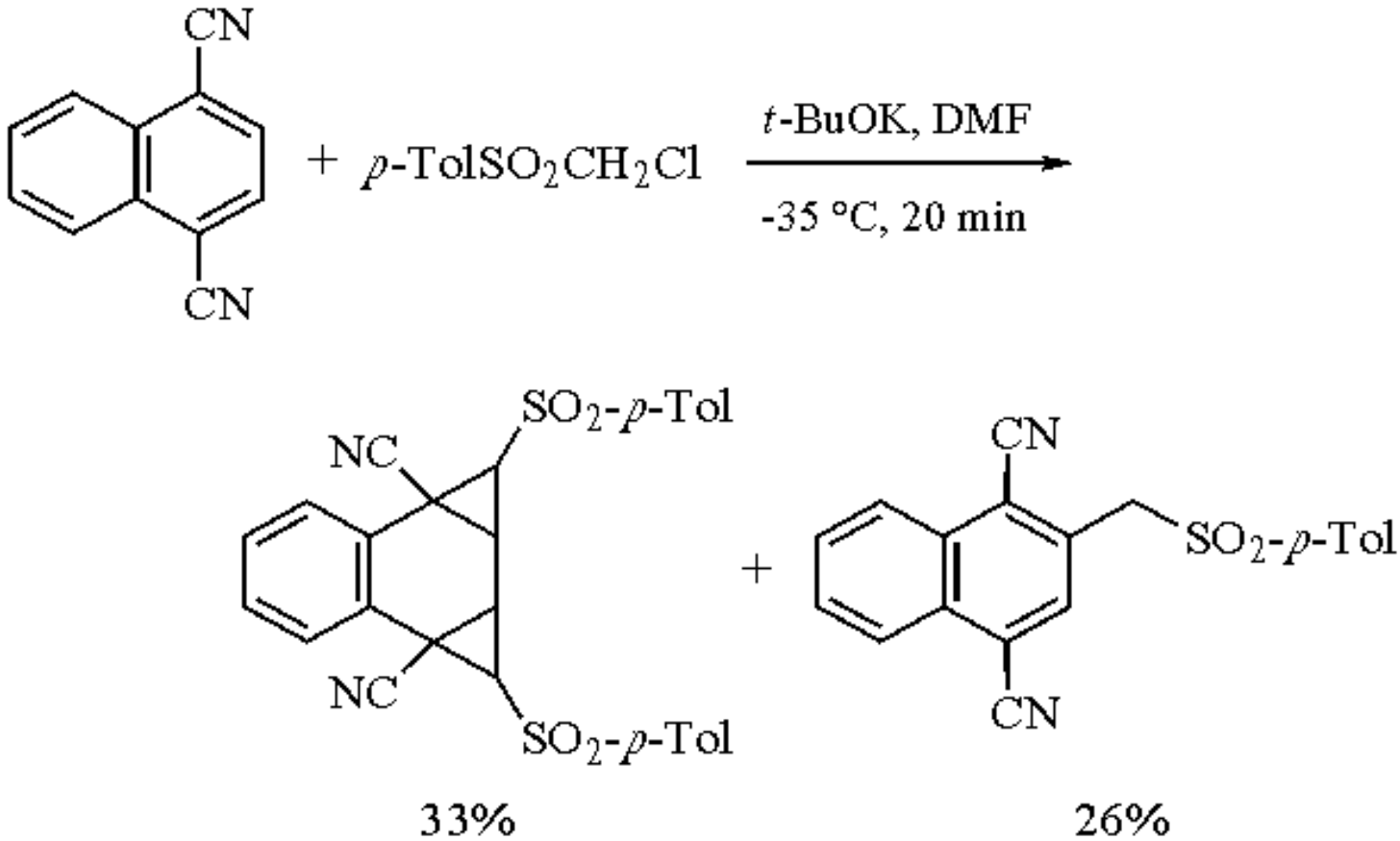

(8)

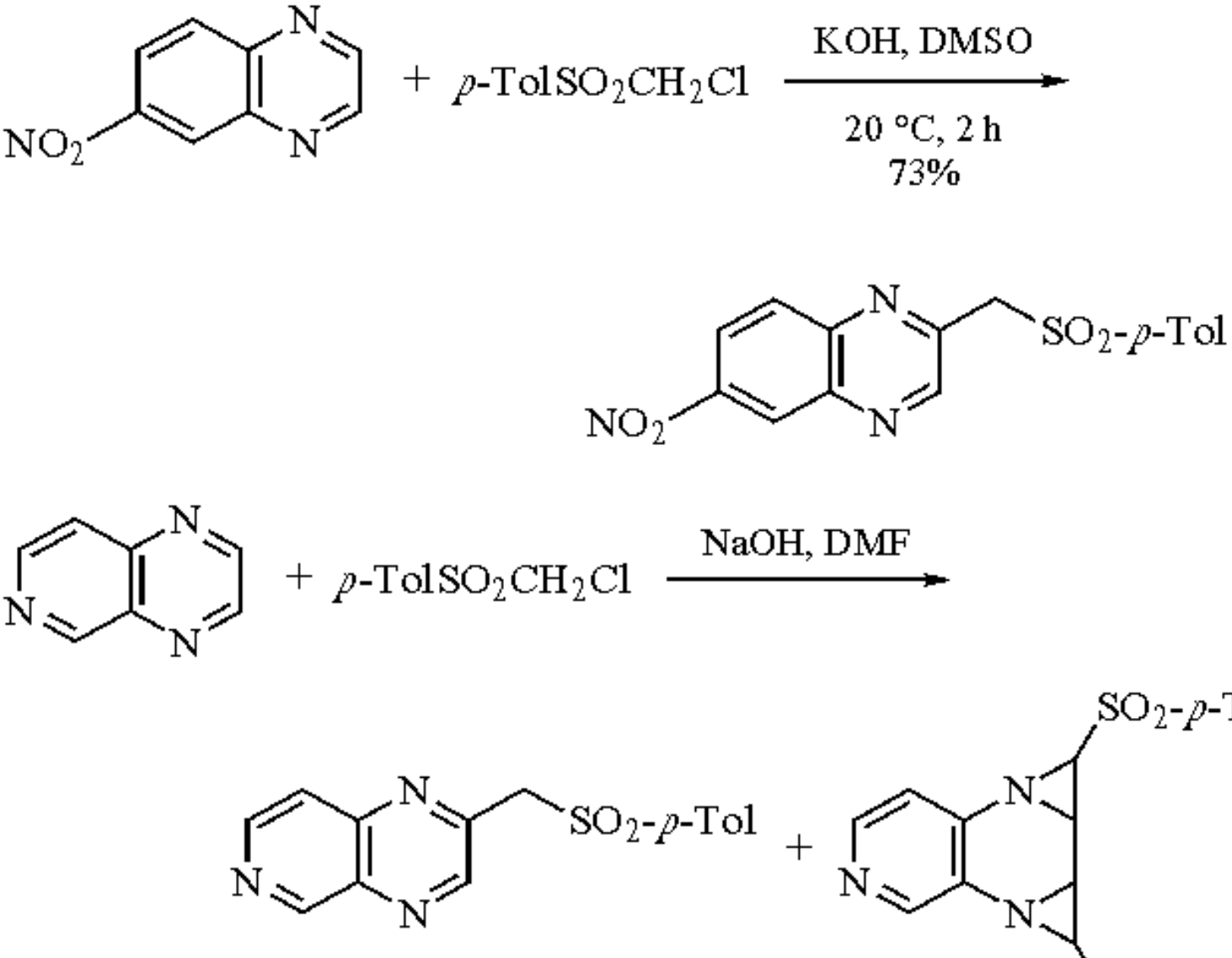

20 °C	0%	84%
-10 °C	25%	23%
-30 °C	44%	0%

Radical Reactions.

The α-*p*-tolylsulfonylmethyl radical, generated using either ***Tri-n-butylstannane***, ***Azobisisobutyronitrile***,[15] or ***Hexabutyldistannane*** with UV irradiation,[16] adds to enol ethers, enamines, and silyl enol ethers. The addition to enamines shows considerable *syn* diastereoselectivity which can be explained on the basis of an allylic 1,3-strain model (eq 11). When an alkenic or alkynic moiety is present in the α-substituent of the α-*p*-tolylsulfonylmethyl radical, cyclization can occur to give five-membered ring compounds (eqs 12 and 13).[15b,17]

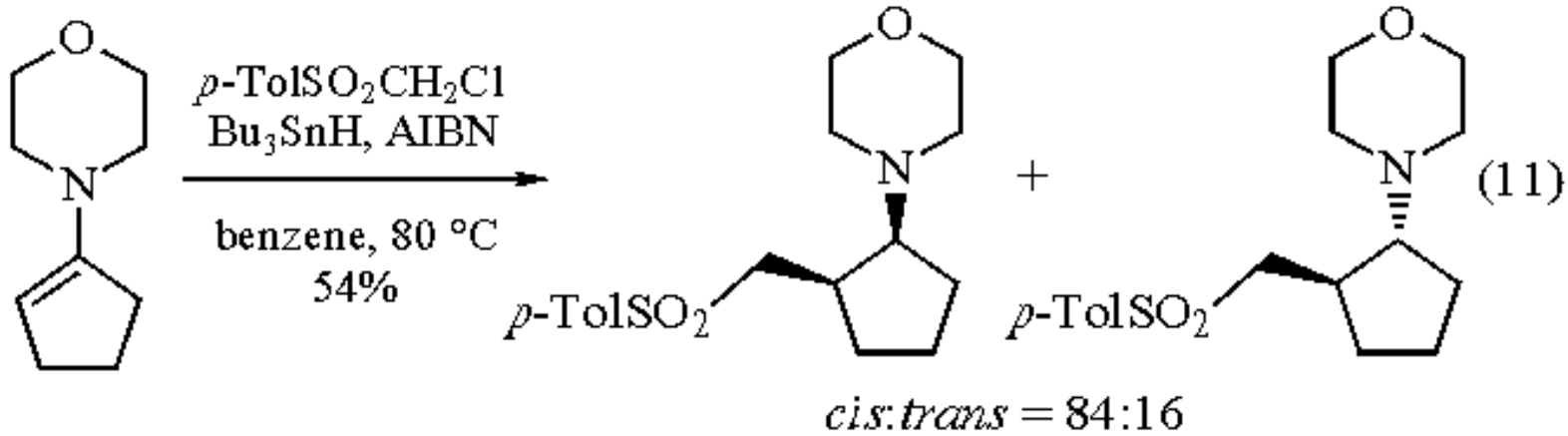

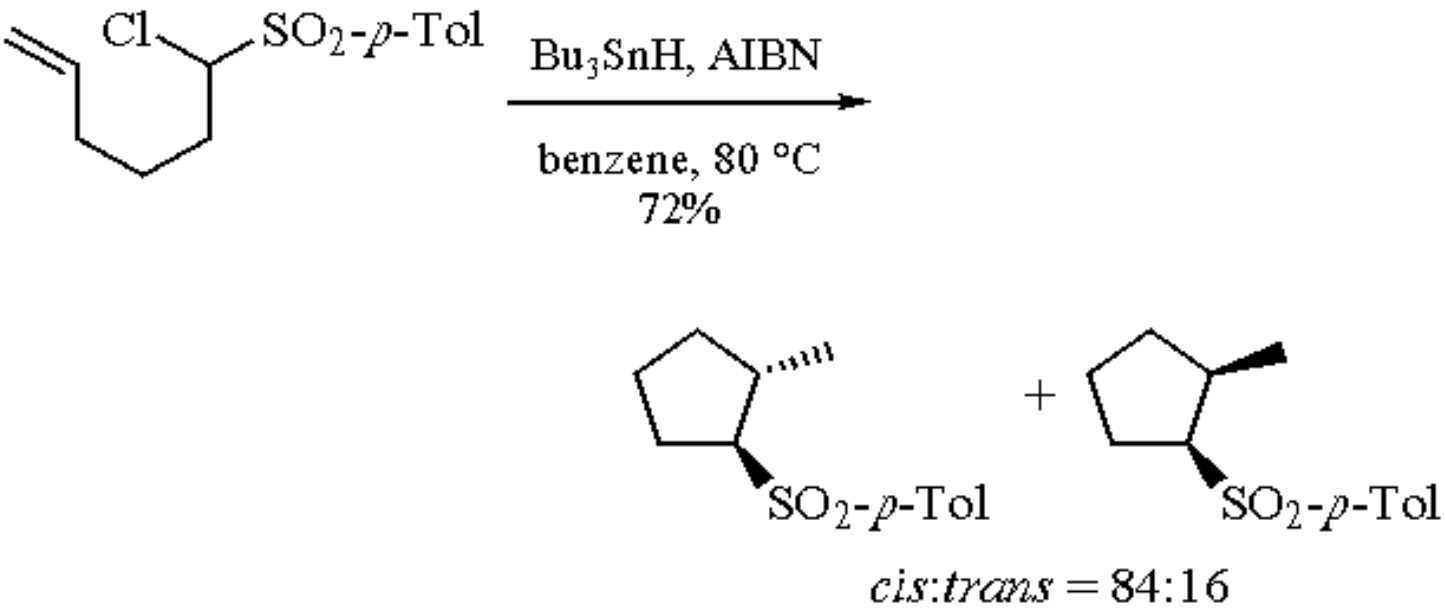

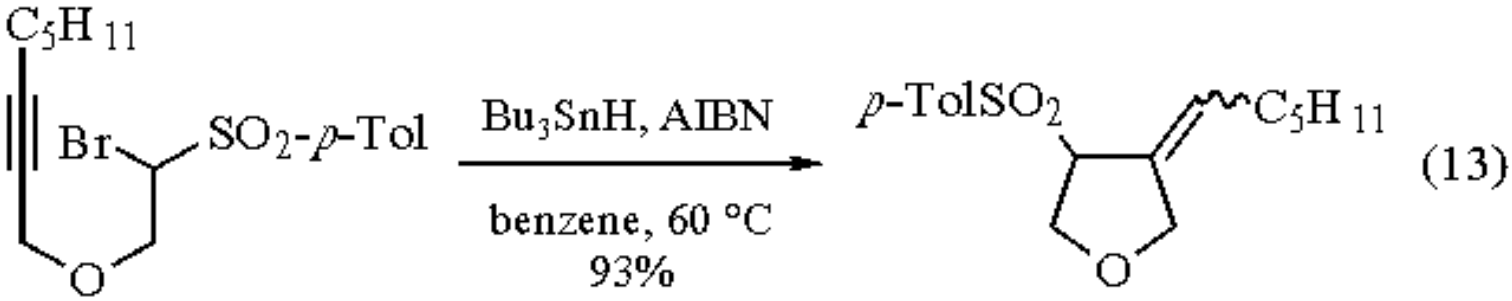

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(Chloromethyl)trimethylsilane[1]

Me_3SiCH_2Cl

[2344-80-1] · $C_4H_{11}ClSi$ · (Chloromethyl)trimethylsilane · (MW 122.67)

(reagent for direct alkene synthesis;[2] electrophile for the formation of a variety of functionalized synthetic intermediates for alkene synthesis;[3] alkylation adducts are frequently a source of fluoride-induced reactive intermediates;[4] readily undergoes metal-halogen exchange to generate a reagent for Peterson methylenation[5])

Alternate Name: trimethylsilylmethyl chloride.

Physical Data: bp 97-98 °C; *d* 0.886 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: highly flammable liquid; corrosive; irritant; use in a fume hood.

Reactions with Carbonyl Compounds.

Terminal alkenes are efficiently generated upon treatment of an aldehyde or ketone with Me_3SiCH_2Cl in the presence of ***Triphenylphosphine*** in a sealed tube (eq 1).[2] Reaction times are generally not more than 60 min, and the method is operationally simple, although use of this protocol for methylenation is limited to substrates which lack enolizable α-hydrogens, since in such cases studied, silyl enol ether formation is a competitive pathway.

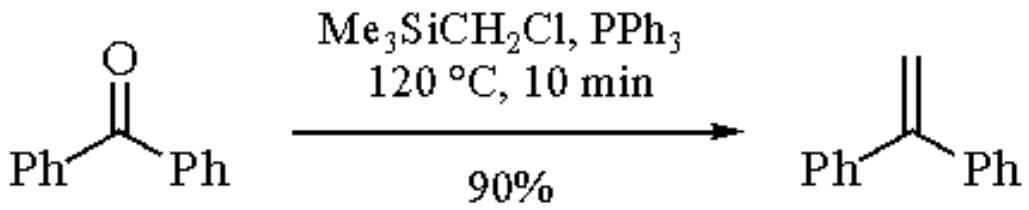

(1)

Conversion of aldehydes and ketones to α,β-epoxy trimethylsilanes is readily achieved by treatment of Me_3SiCH_2Cl with the appropriate alkyllithium reagent at low temperature, and subsequent quenching with the desired carbonyl compound.[6] It is critical that ***s-Butyllithium*** be used as the lithiating reagent, as use of ***n-Butyllithium*** results in attack at silicon and use of ***t-Butyllithium*** results in metal-halogen exchange. The resultant α,β-epoxy trimethylsilanes undergo facile hydrolysis under relatively mild conditions to provide the corresponding aldehydes in

good yields (eq 2). A variety of substrates have been successfully subjected to this sequence, including α,β-unsaturated carbonyl compounds and sterically congested aldehydes and ketones.

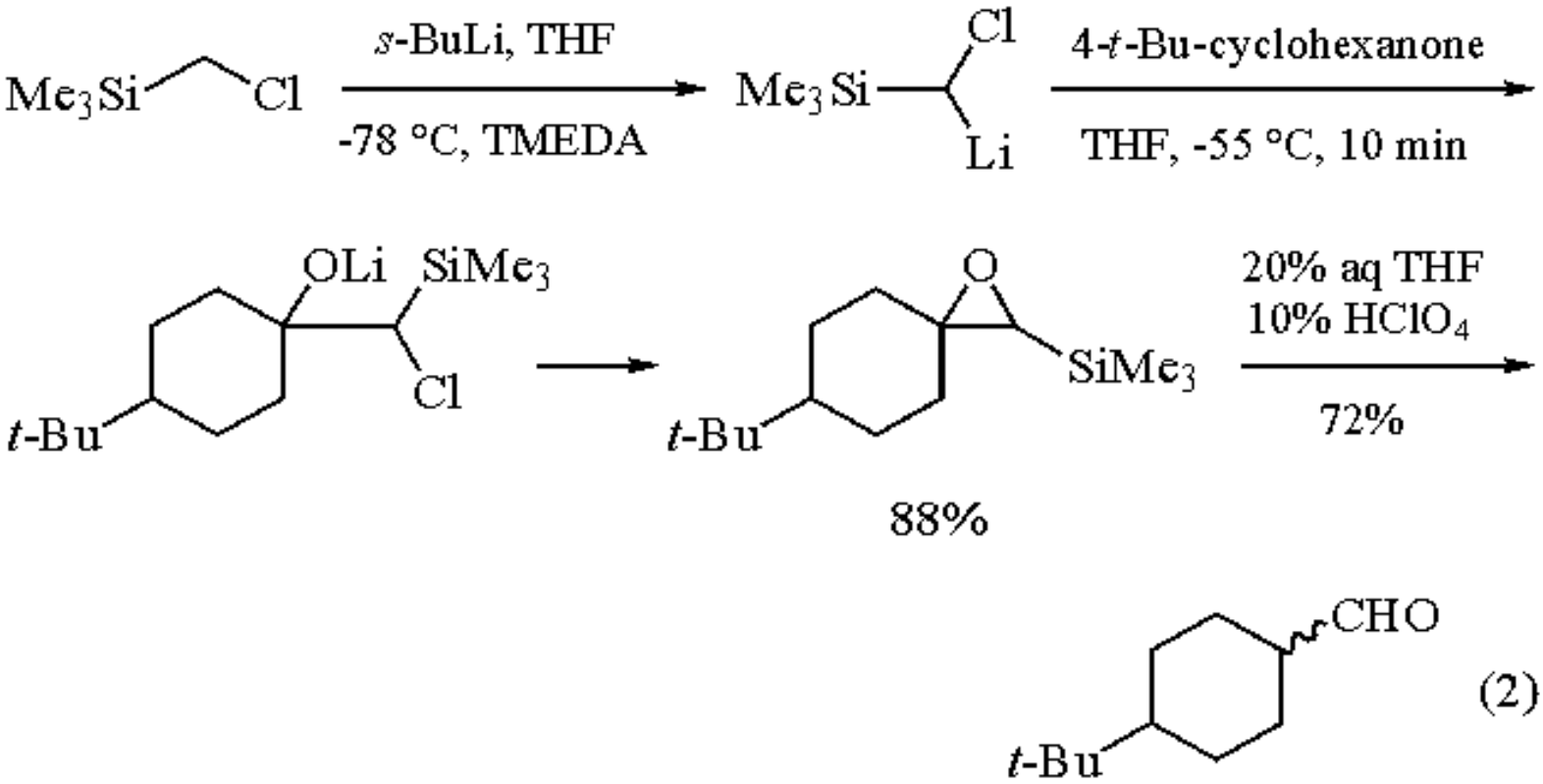

(2)

In the presence of ***Cesium Fluoride*** in DMF, Me_3SiCH_2Cl reacts with benzaldehyde to form phenyloxirane in 60% yield (eq 3);[7] this method has not yet proven to be a generally applicable route to epoxides.

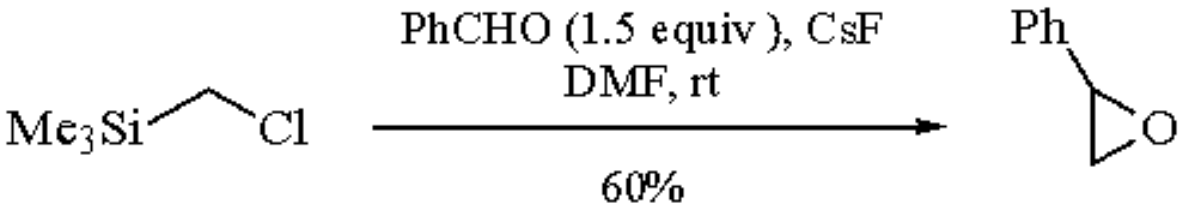

(3)

Electrophile for *O*-, *N*-, and *S*-Alkylations.

A novel method for phenol homologation utilizes Me_3SiCH_2Cl to trap phenoxides, forming trimethylsilylmethyl phenyl ethers which, upon treatment with *s*-butyllithium, undergo 1,2-Wittig rearrangement of the intermediate lithiated trimethylsilylmethyl species to produce trimethylsilyl-substituted benzyl alcohols in good yields. Subjecting these phenylsilylmethanols to basic hydrolysis with methanolic potassium hydroxide produces the homologated phenols (eq 4).[8]

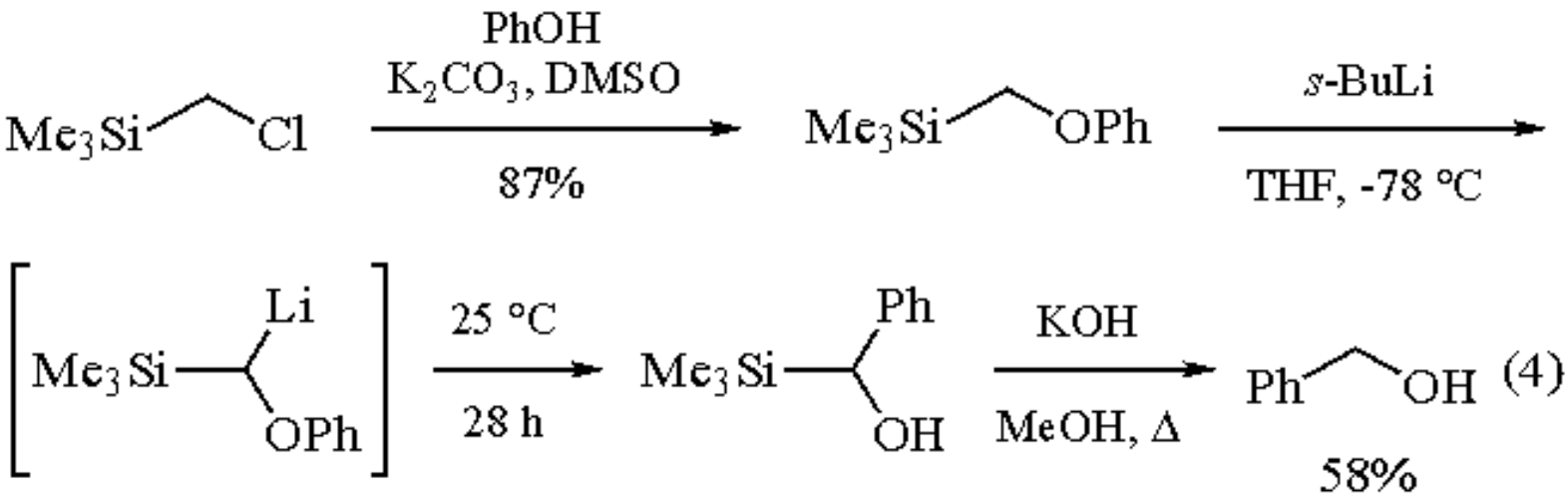

Much of the utility of Me_3SiCH_2Cl is derived from the lability of the methylene carbon-silicon bond in its alkylation products from nitrogen-containing nucleophiles. The subsequent, relatively mild conditions of fluoride treatment effect 1,3-dipole formation. This fluoride-promoted azomethine ylide generation methodology constitutes a highly stereoselective means for the synthesis of pyrroles by the trapping of the reactive intermediate with ***Dimethyl Fumarate*** or ***Dimethyl Maleate*** (eq 5).[4]

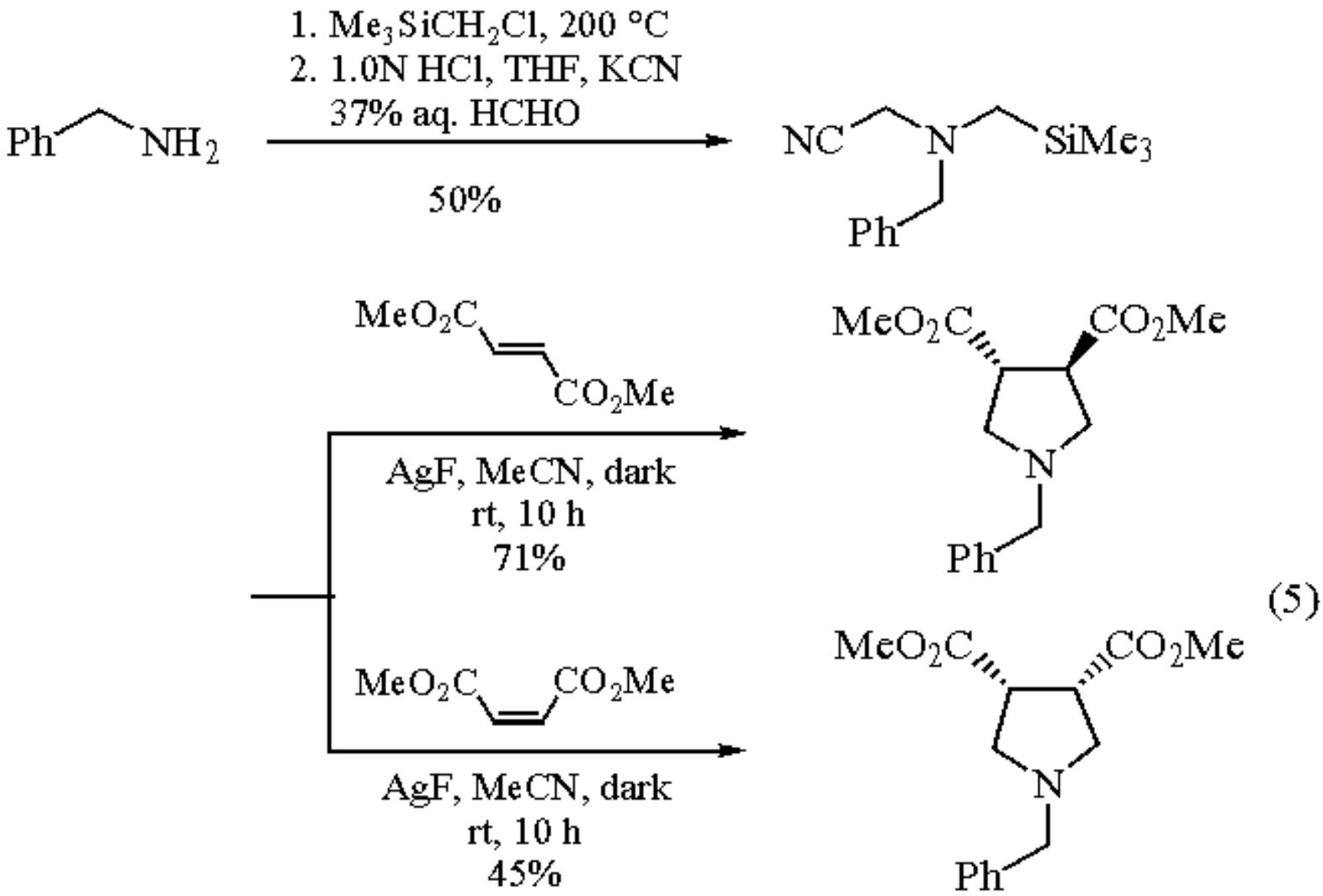

(Chloromethyl)trimethylsilane

Other dipolarophiles, including aldehydes, nitroalkenes, styrenes, and functionalized alkynes (eq 6), have also proven to be effective cycloaddition substrates for ylides generated in this fashion.[9]

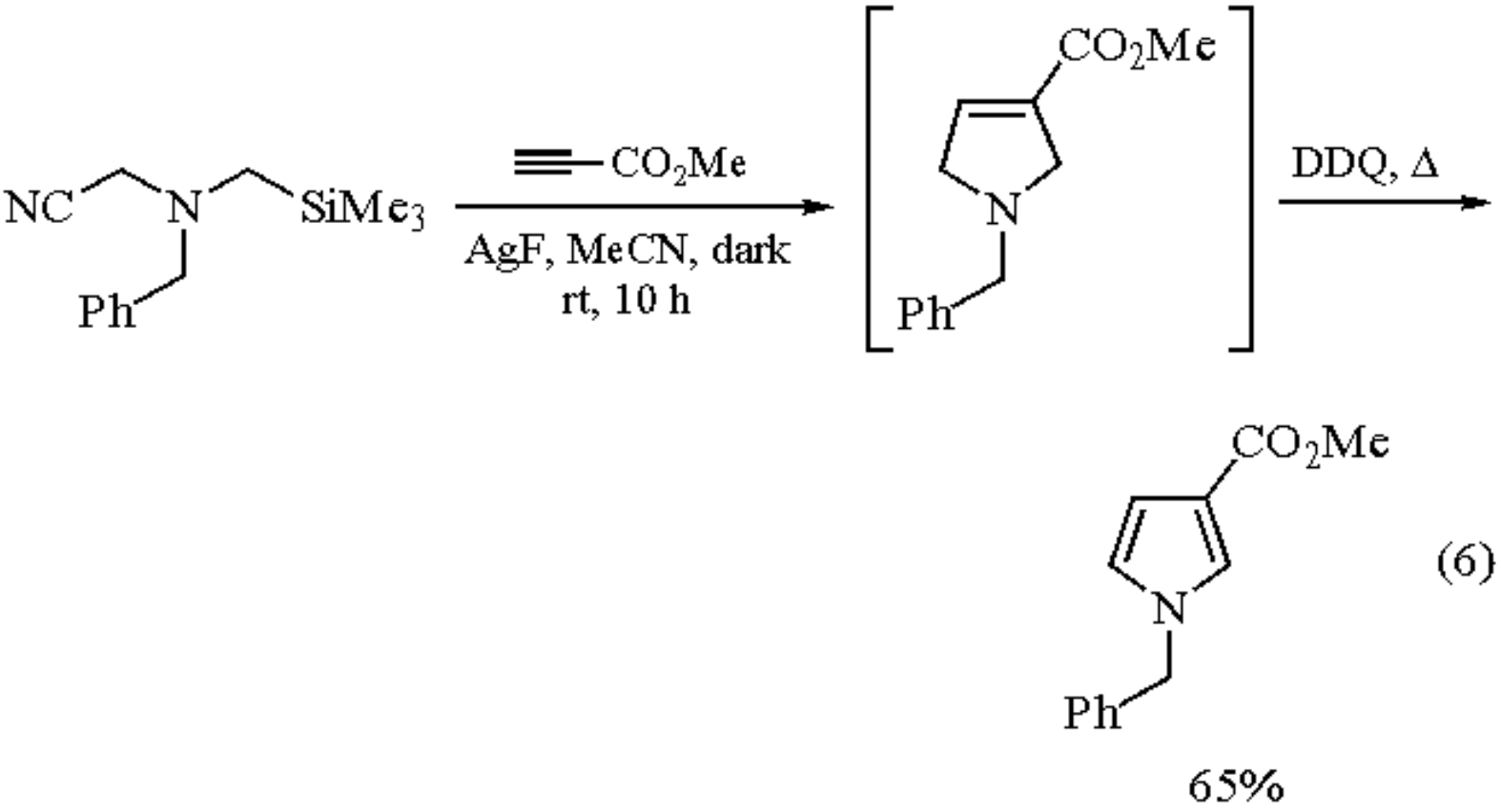

(6)

Intramolecular trapping of ylides derived from the Me_3SiCH_2Cl alkylation adducts of a variety of 3- and 4-substituted benzylamines proceeds through a Sommelet-Hauser pathway, providing the rearranged products in good yields (eq 7).[10]

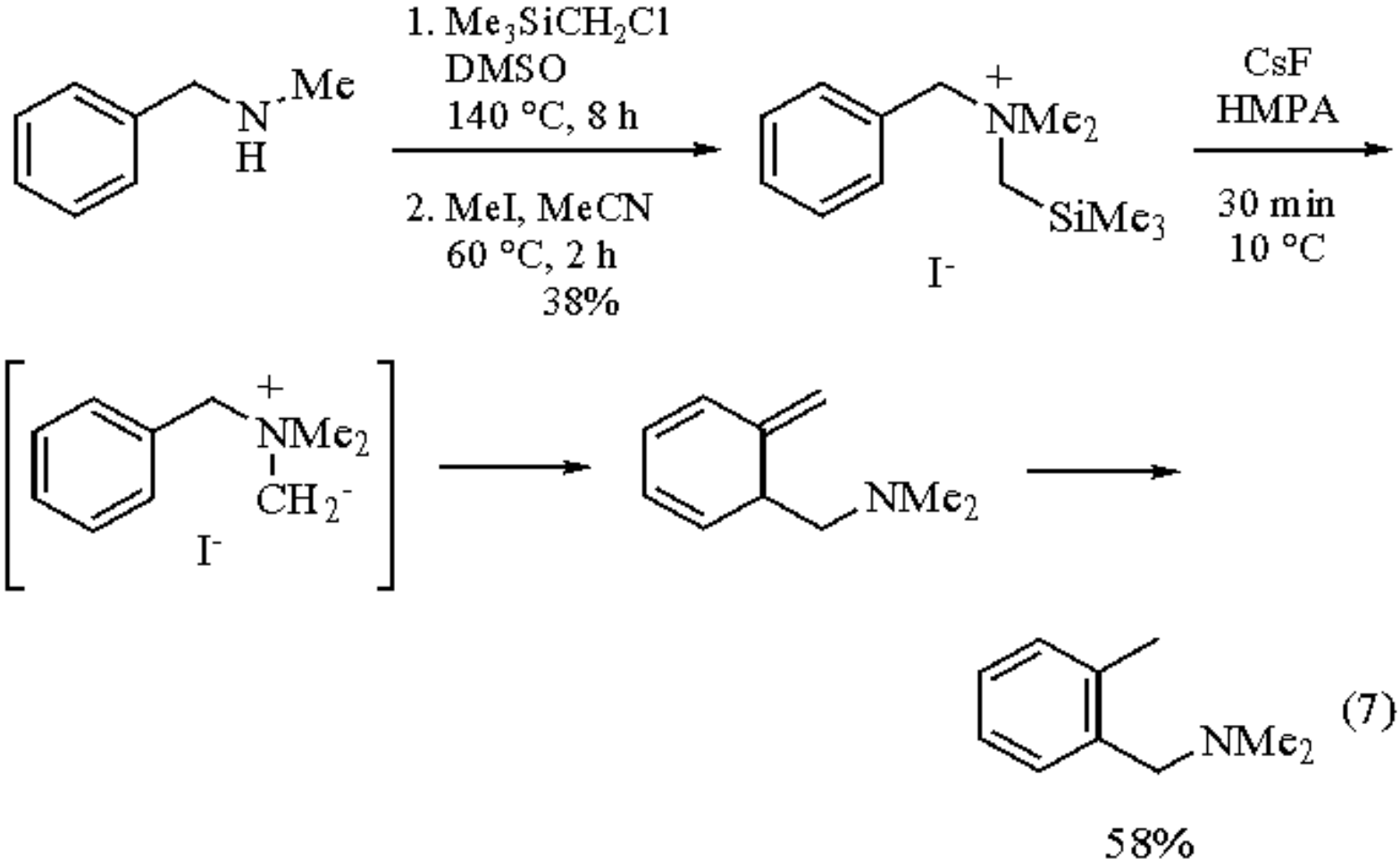

Azolylmethyl anions, generated by the fluoride-induced desilylation of Me_3SiCH_2Cl adducts of pyrroles, imidazoles, pyrazoles, triazoles, and tetrazoles, and azinonylmethyl anions similarly derived from (trimethylsilylmethyl)azinones, have demonstrated efficacy in the addition reactions to carbonyl compounds.[11]

Sulfur alkylation products of Me_3SiCH_2Cl have also been used as a convenient source of reactive intermediates. Lithiated (2-benzothiazolylthio)(trimethylsilyl)methane (eq 8) functions as a synthetic equivalent for the mercaptomethyl anion by (a) reaction with an electrophile, (b) fluoride-promoted desilylation/reaction with a carbonyl compound, and (c) alkyllithium addition to the benzothiazole 2-position.[12]

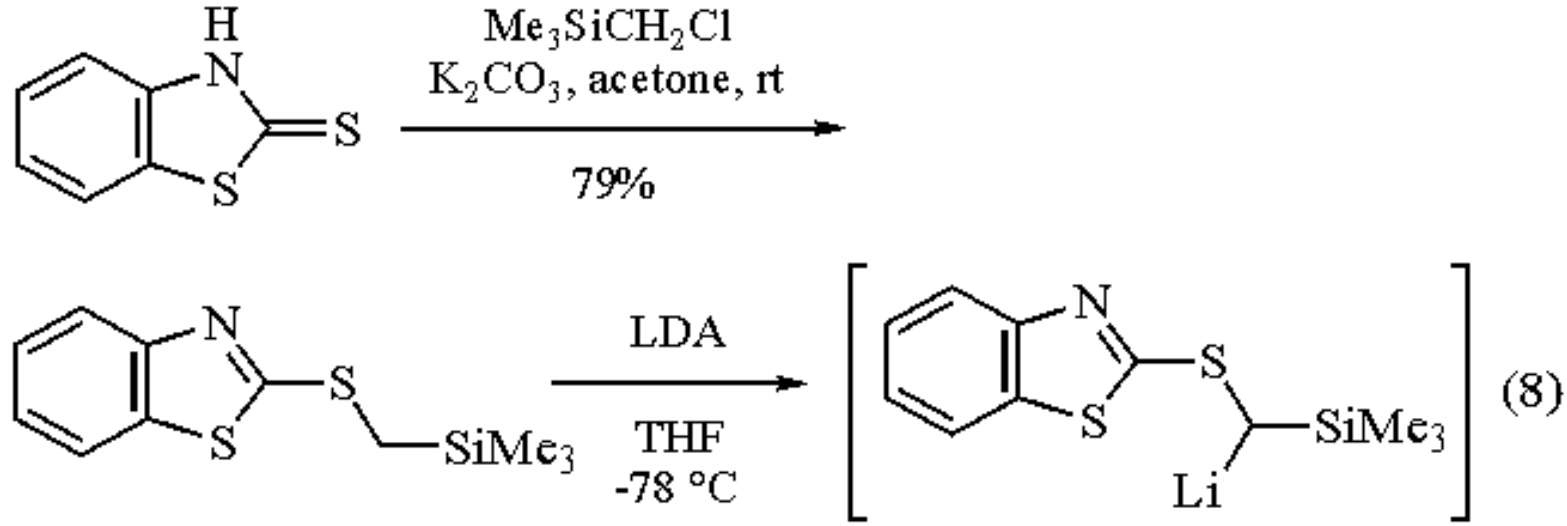

Thiiranes have been prepared by the reaction of aldehydes with *S*-methyl *S*´-trimethylsilylmethyl *N*-(*p*-tolylsulfonyl)dithioiminocarbonate in the presence of cesium fluoride (eq 9).[13] This novel route to thiiranes utilizes the 1,3-dipolar cycloaddition of the iminothiocarbonyl ylide derived from a Me_3SiCH_2Cl alkylated thiol to aldehydes.

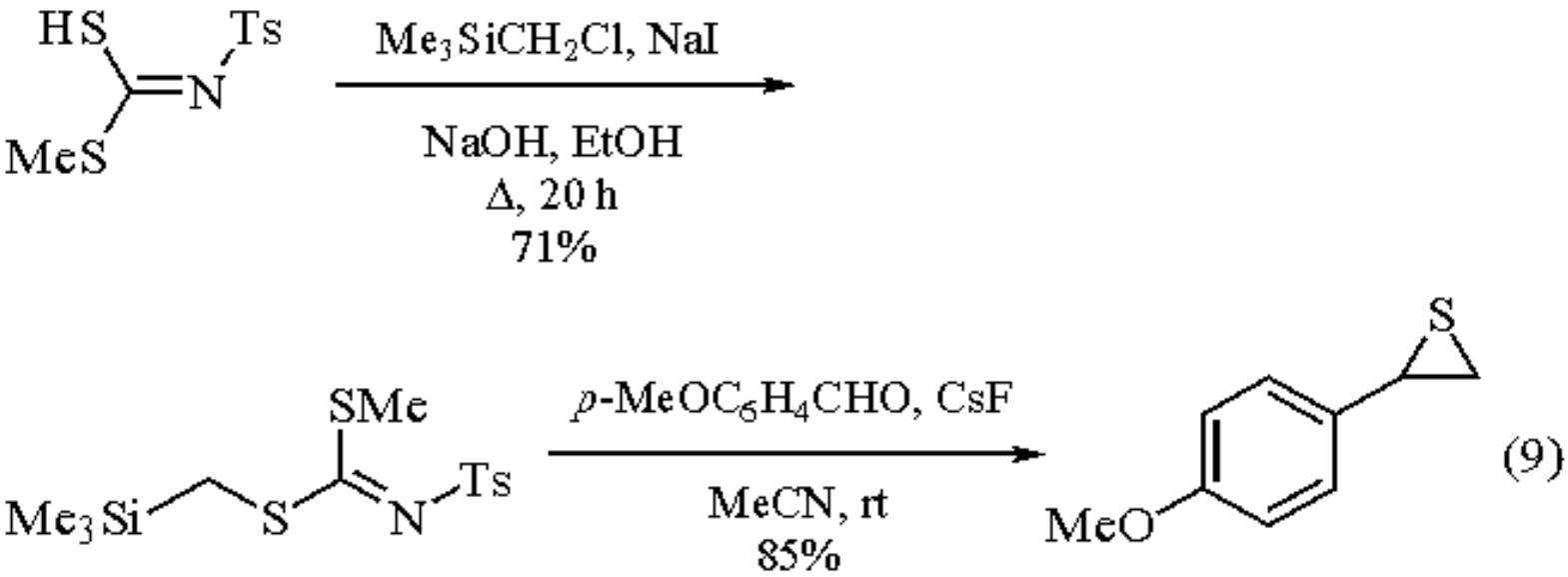

(9)

Preparation of Other Reagents.

One of the principal uses of this reagent has been for the formation of ***Trimethylsilylmethylmagnesium Chloride***, most often used for the methylenation of carbonyl compounds;[5] however, since both this reagent and the corresponding lithio reagent are now widely available commercially, its use in this capacity has diminished considerably. Similarly, chloromethyltrimethylsilane has been used to prepare many other now commercially available reagents, including trimethylsilylmethyl acetate, trimethylsilylmethyl isocyanide, ***Trimethylsilyldiazomethane*** and trimethylsilylmethyl trifluoromethanesulfonate, each useful for a variety of synthetic transformations.

Related Reagents.

(Iodomethyl)trimethylsilane; ***Trimethylsilylmethyllithium***; ***Trimethylsilylmethylmagnesium Chloride***; ***Trimethylsilylmethylpotassium***; ***Trimethylsilylmethyl Trifluoromethanesulfonate***.

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Chloromethyl Trimethylsilyl Ether

$ClCH_2OSiMe_3$

[23586-77-8] · $C_4H_{11}ClOSi$ · Chloromethyl Trimethylsilyl Ether · (MW 138.67)

(hydroxymethyl cation equivalent[1])

Physical Data: only characterized by ^1H and ^{13}C NMR at -50 °C.

Solubility: sol dichloromethane.

Preparative Method: prepared in situ under nitrogen by addition of a cooled (-78 °C) solution of ***Sulfuryl Chloride*** (1 equiv) in dry dichloromethane (2 M) to a solution of ethyl (trimethylsilyloxy)methyl sulfide in dichloromethane (1 M).[1]

Handling, Storage, and Precautions: low stability; best prepared in situ at low temperature.

Hydroxymethyl Cation Equivalent.

Chloromethyl trimethylsilyl ether, prepared in situ at -78 °C in dichloromethane, reacts with 1-(trimethylsilyloxy)cyclopentene (3 equiv) and a catalytic amount of ***Zinc Bromide*** (10 mol %) to give 2-hydroxymethylcyclopentanone in 71% yield (eq 1).[1] Since the preparation of chloromethyl trimethylsilyl ether generates an equivalent amount of ethylsulfenyl chloride, 2-ethylthiocyclopentanone is also obtained. Overall, this reagent provides a method for α-hydroxymethylation of carbonyl compounds.

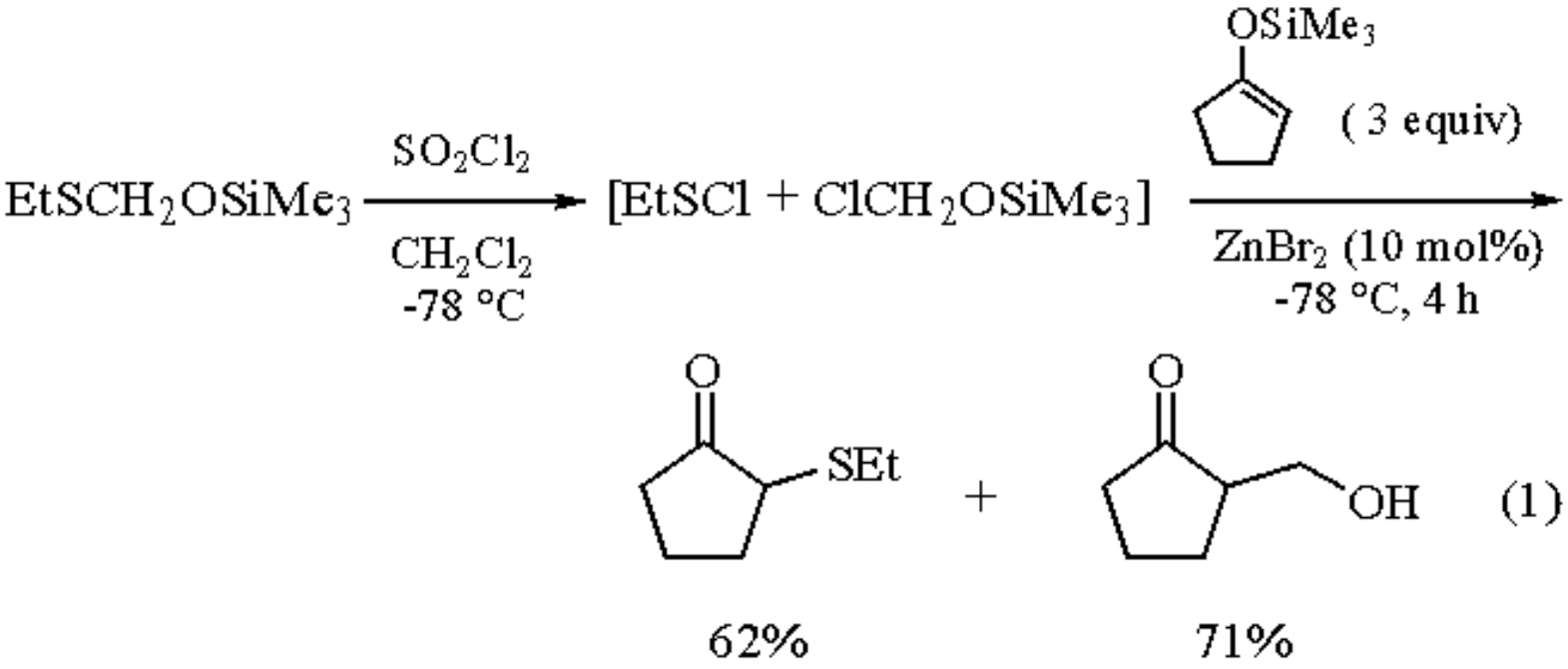

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Chloromethyl Trimethylsilylmethyl Sulfide

$ClCH_2SCH_2SiMe_3$

[105850-89-3] · $C_5H_{13}ClSSi$ · Chloromethyl Trimethylsilylmethyl Sulfide · (MW 168.76)

(thiocarbonyl ylide synthon[1])

Physical Data: bp 75 °C/20 mmHg.

Solubility: sol acetonitrile, THF.

Preparative Method: prepared in 69% yield by introducing dry ***Hydrogen Chloride*** into a mixture of trimethylsilylmethanethiol[2] and 1,3,5-trioxane (see ***Formaldehyde***) at temperature below 0 °C.[3]

Purification: by distillation.

Handling, Storage, and Precautions: potent alkylating agent; moisture sensitive; stench; use in a fume hood.

Stereospecific [3 + 2] annulation of chloromethyl trimethylsilylmethyl sulfide (**1**) with electron-deficient alkenes in the presence of ***Cesium Fluoride*** in acetonitrile at room temperature gives tetrahydrothiophenes in good yields (eq 1).[3] This reaction presumably goes through thiocarbonyl ylide intermediate (**2**).

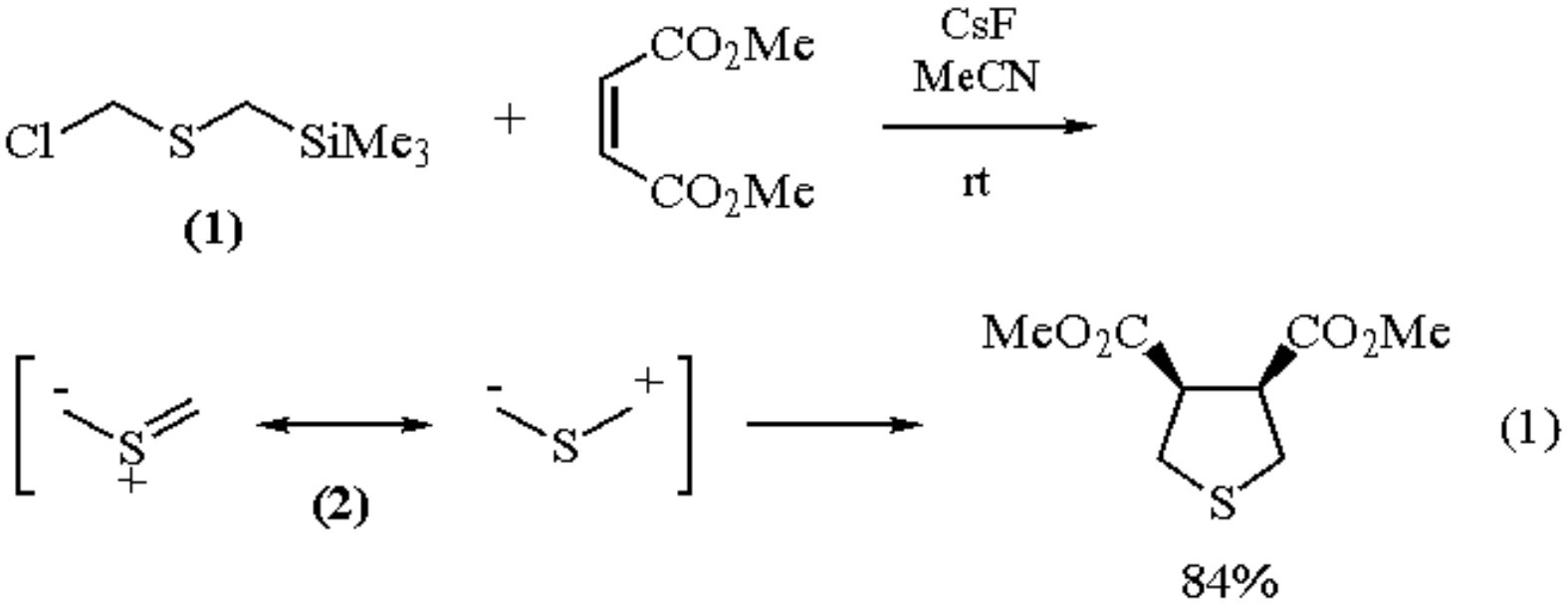

Sulfide (**1**) also reacts with acetylenedicarboxylate to give the corresponding dihydrothiophenes.[3] However, (**1**) is not reactive towards cyclic alkenes such as maleic anhydride.

The title reagent also reacts with aromatic aldehydes to yield the corresponding [3 + 2] cycloadduct 1,3-oxathiolanes (eq 2).[4] Simple ketones and oxoesters do not undergo this reaction.

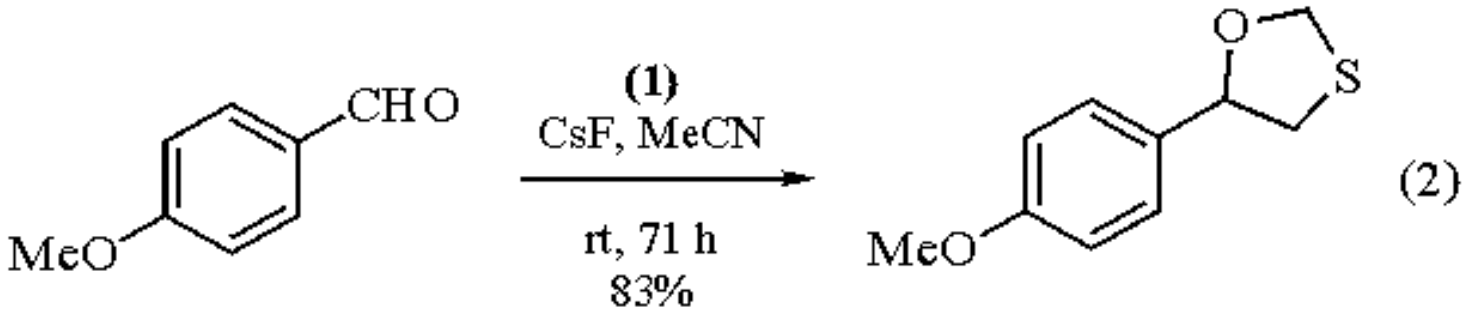

When sulfide (**1**) is heated with nitrogen-containing aromatic heterocycles followed by treatment with cesium fluoride in acetonitrile, various 1,3-thiazolidines are obtained (eq 3).[1] This is formally a [3 + 2] cycloaddition between the thiocarbonyl ylide (**2**) and the carbon-nitrogen double bond.

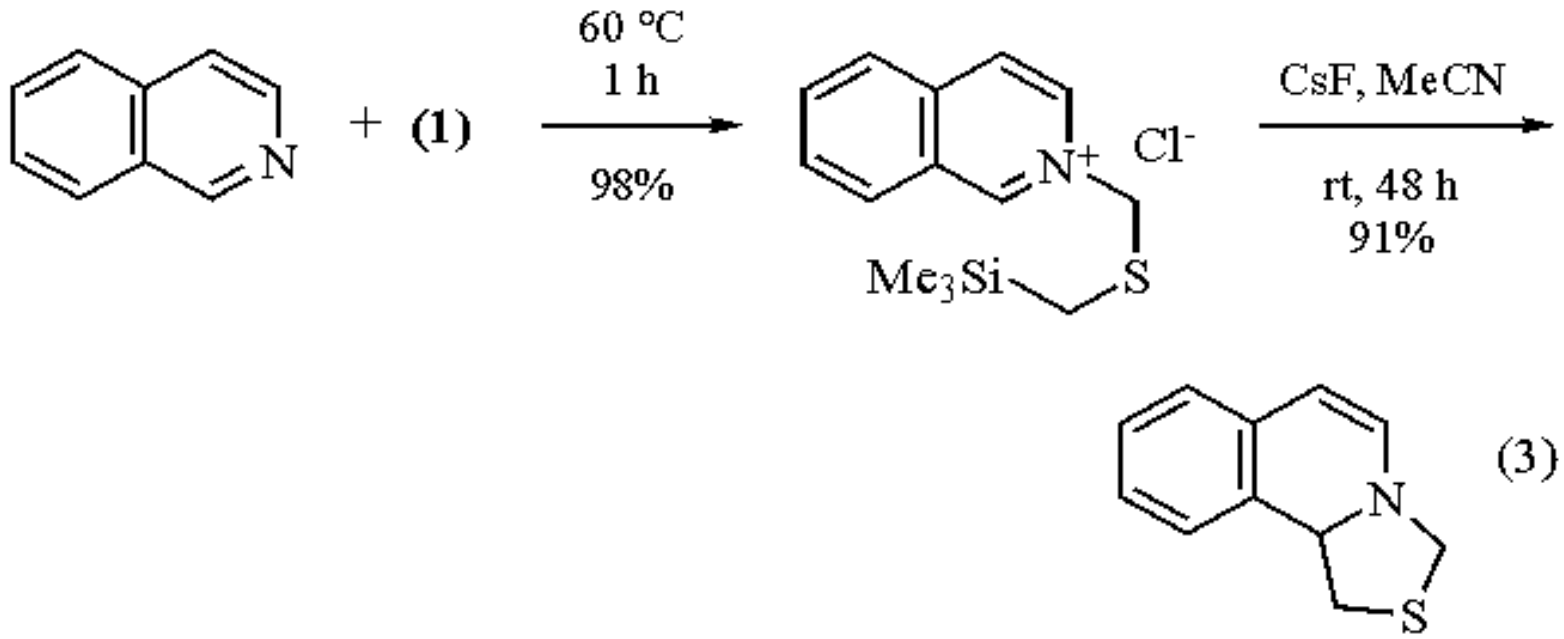

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3-Chloro-3-methyl-2-trimethylsilyloxy-1-butene

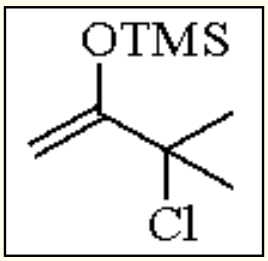

[69875-71-4] · $C_8H_{17}ClOSi$ · 3-Chloro-3-methyl-2-trimethylsilyloxy-1-butene · (MW 192.76)

(allyl halide, precursor of 2-oxyallyl cation with the aid of $AgClO_4$; precursor of silyl vinyl ether)

Physical Data: bp 74-75 °C/90 mmHg.

Solubility: sol common organic solvents; insol and slowly decomposed in H_2O.

Form Supplied in: oil.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$-Me_4Si) δ 0.18 (s, 9H), 1.95 (br s, 3H), 4.23 (br s, 1H), 4.40 (s, 1H), 4.87 (br s, 1H), 5.30 (m, 1H).

Preparative Method: [1] a mixture of 3-chloro-3-methyl-2-butanone (**1**),[2] ***Chlorotrimethylsilane***, and ***Triethylamine*** in DMF is heated at 85-90 °C for 18 h. The mixture is diluted with petroleum ether, washed with cold water, and dried over Na_2SO_4. Solvent is evaporated, and the remaining oil is fractionated under reduced pressure to give 3-chloro-3-methyl-2-trimethylsilyloxy-1-butene (**2**) in 52% yield (eq 1). A byproduct, 2-methyl-3-(trimethylsilyloxy)-1,3-butadiene, is isolated in foreruns (54-55 °C/95 mmHg, 9%).[1]

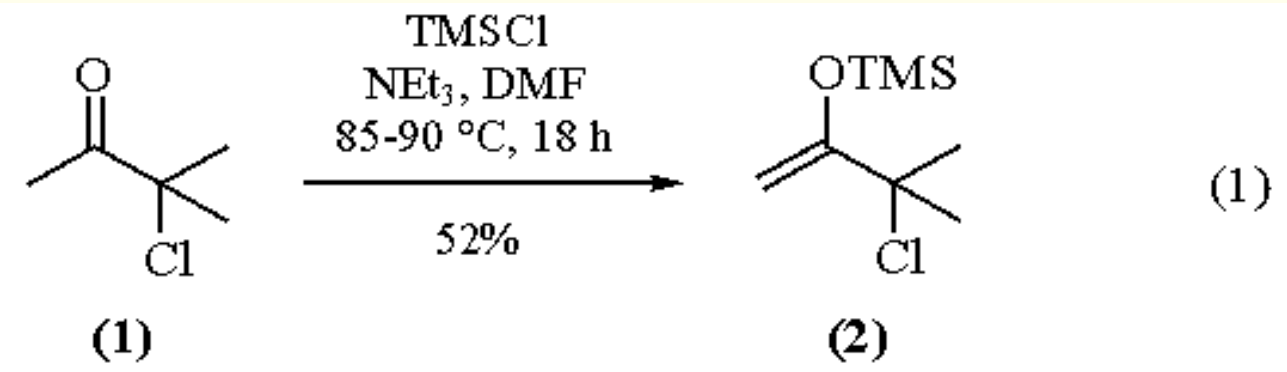

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; use only in a chemical fume hood; recommended to distill just prior to use.

2-Trimethylsilyloxyallyl Cation.[1,3-5]

Reaction of 3-chloro-3-methyl-2-trimethylsilyloxy-1-butene (**2**) with ***Silver(I) Perchlorate*** produces 3,3-dimethyl-2-trimethylsilyloxyallyl cation (**3**), which reacts with cyclopentadiene, furan, or alkenes to give 2,2-dimethylbicyclo[3.2.1]oct-6-en-3-one (**4**), 2,2-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**5**), or 2,2-dimethylcyclopentanone derivatives (**6**), respectively (eqs 2 and 3). The reaction with furan in nitromethane is assumed to be a concerted reaction which gives the tricyclic ketone as the sole product. The one in THF/Et_2O results in a stepwise reaction to give 2-(1,1-dimethyl-2-trimethylsilyloxy-3-chloro-2-butenyl)furan.

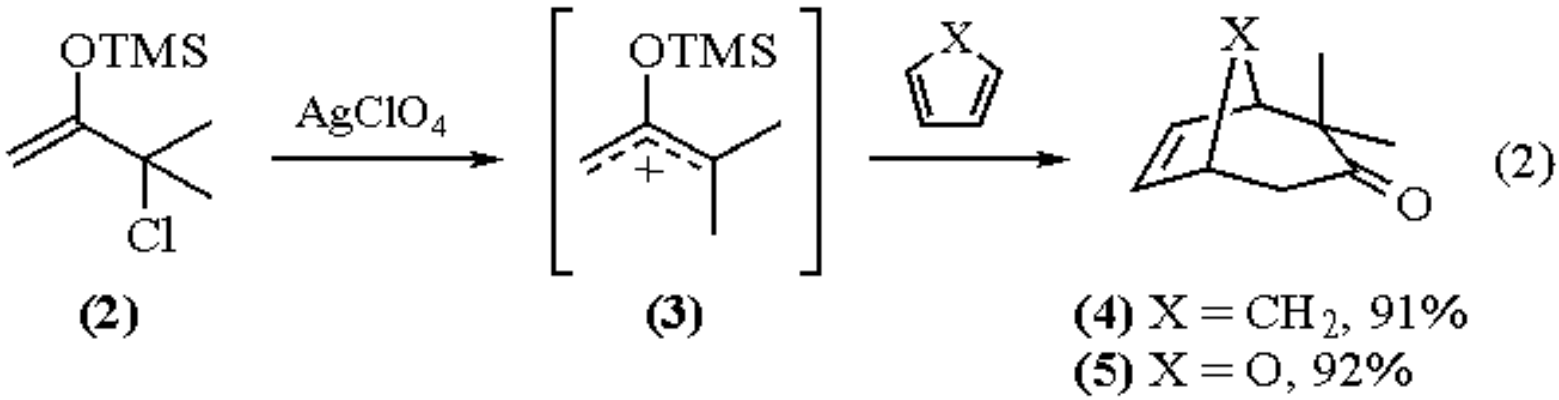

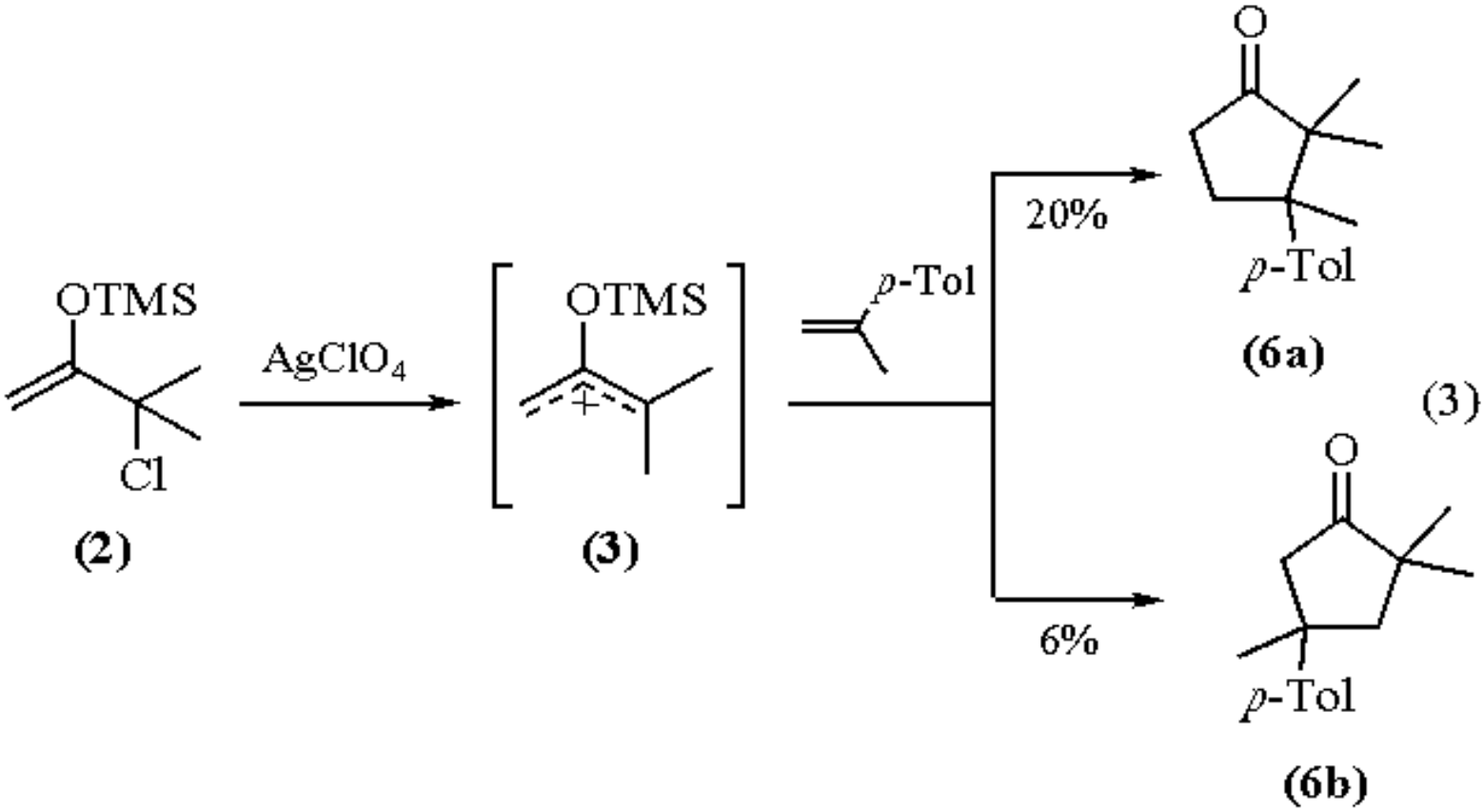

In general, the reaction of 2-oxyallyl cation with furans is either concerted or stepwise (Scheme 1). Concerted reaction of the 2-oxyallyl cation species (**3**) with the furan follows the [3 + 4] manner to give 8-oxabicyclo[3.2.1]oct-6-en-3-ones (**9**). Stepwise reaction of the allyl cation first produces a 2-substituted furyl cation intermediate (**8**) which then cyclizes to give the same products (**9**) or undergoes intermolecular reaction with a nucleophile to give a mixture of dihydrofurans (**10**) and (**11**). Alternatively, deprotonation of the intermediate cationic species affords 2-substituted furans (**12**).

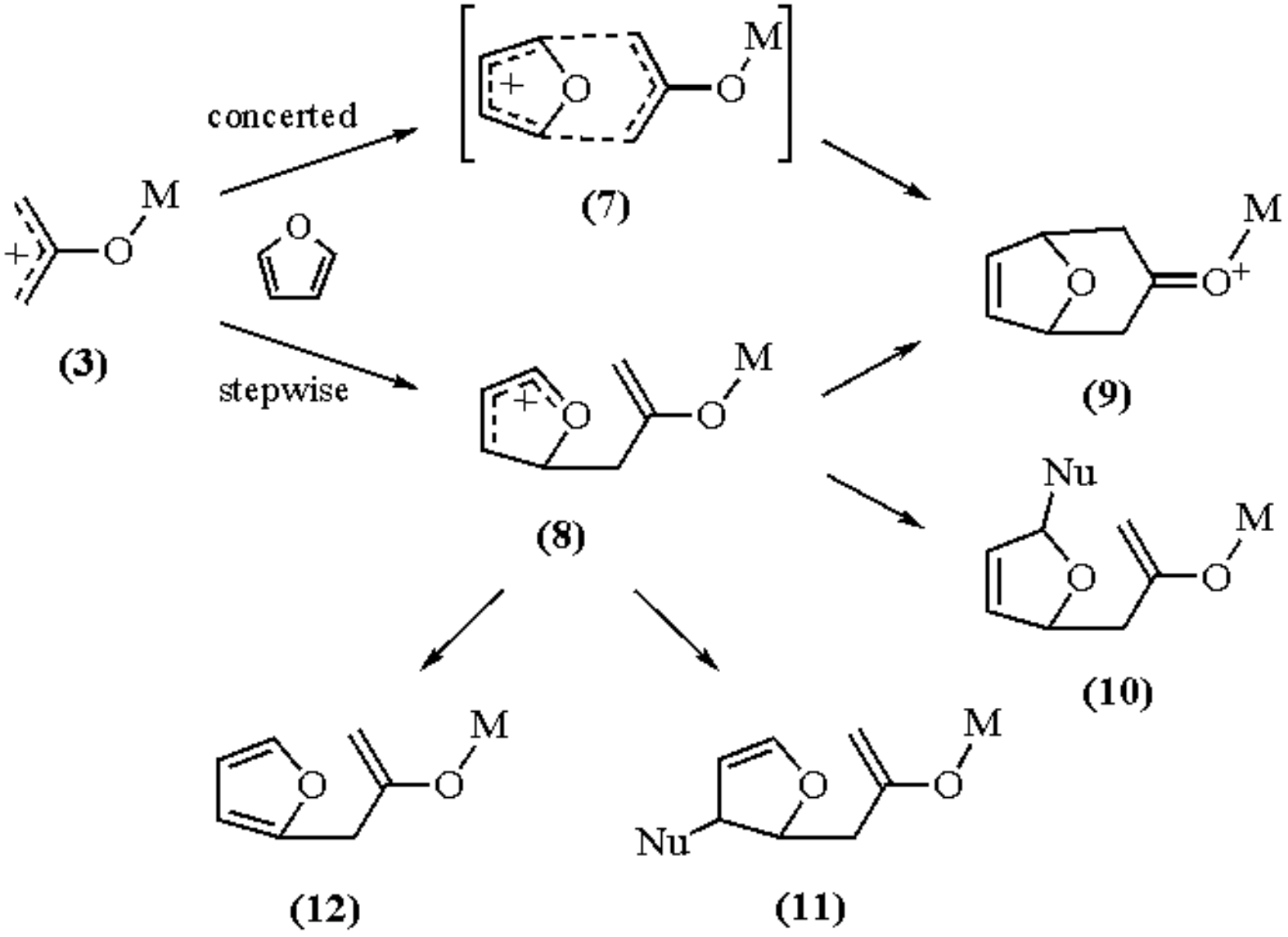

Scheme 1

Similar 2-oxyallyl cation species are generated from α-halo ketones with ***Triethylamine*** or from α,α´-dihalo ketones with ***Zinc/Copper Couple*** or ***Pentacarbonyliron***. Cycloaddition reactions of 2-oxyallyl cation species have been reviewed.[3]

The electrophilicity of the oxyallyl intermediates decreases in the order of M = FeX > SiR_3 > ZnX > Li > Na. The allyl cation of high electrophilicity favors stepwise reaction pathways, while less electrophilic 2-oxyallyl cations needs more nucleophilic furans to afford [3 + 4] cycloaddition products.

Regioselective Synthesis of Silyl Vinyl Ethers.[6]

Reaction of (**2**) and its derivatives with lithium dialkyl- or diarylcuprate proceeds in an S_N2' fashion to give 4-substituted 2-methyl-3-trimethylsilyloxy-2-butenes (**13**) (eq 4). This method can be applied to the synthesis of the silyl vinyl ethers that are inaccessible by other methods.

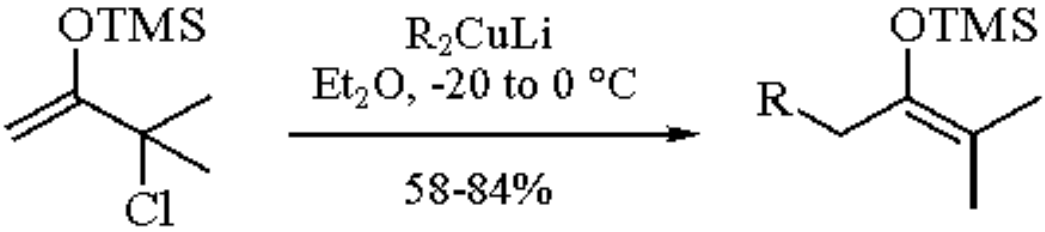

(4)

(2) R = alkyl, aryl **(13)**

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2. Wyman, D. P.; Kaufman, P. R. *JOC* **1964**, *29*, 1956.
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2-Chloromethyl-3-trimethylsilyl-1-propene

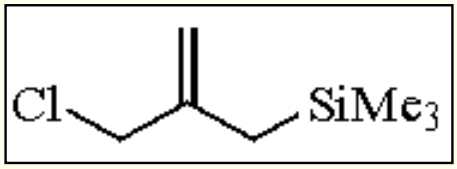

[18388-03-9] · $C_7H_{15}ClSi$ · 2-Chloromethyl-3-trimethylsilyl-1-propene · (MW 162.73)

(bifunctional electrophilic and nucleophilic reagent displaying reactions characteristic of both allylsilanes and allyl halides; useful for exomethylene annulation reactions)

Physical Data: bp 162-163 °C/768 mmHg; *d* 0.899 g cm^{-3}; *n* 1.4540.

Solubility: insol water; miscible with organic solvents.

Form Supplied in: colorless liquid; commercially available.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$) δ 4.99 (s, 1H), 4.75 (s, 1H), 3.96 (s, 2H), 1.68 (s, 2H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 143.0, 112.3, 49.9, 23.6, -1.5.[1]

Preparative Methods: from 3-chloro-2-methyl-1-propene,[2] from ***(Iodomethyl)trimethylsilane***,[3] from 2-(hydroxymethyl)-3-trimethylsilyl-1-propene,[4] from 3-chloro-2-(chloromethyl)-1-propene and ***Trichlorosilane***,[5] and from ***Methyl Chloroacetate***.[1,6]

Handling, Storage, and Precautions: flammable liquid (flash point 43 °C). Storage at 4 °C under N_2 advised. Handle under N_2. May be harmful by inhalation, ingestion, or skin absorption. Vapor or mist is irritating to the eyes, mucous membranes, and upper respiratory tract. Causes skin irritation. Toxicological properties not thoroughly investigated. Use in a fume hood.

Characterization of Reagent.

This reagent, 2-chloromethyl-3-trimethylsilyl-1-propene (**1**), at once an allyl chloride and allylsilane, is best considered as a synthetic equivalent of the zwitterion (**2**).

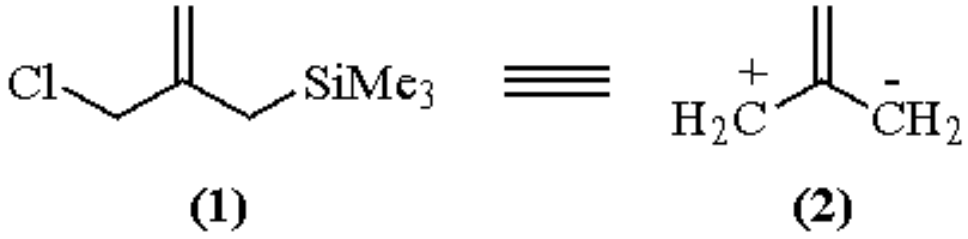

Methylenecyclopentane 3,4-Annulation with Enones.

By virtue of the fact that the electrophilic and nucleophilic reactivities of (**1**) are triggered under well differentiated conditions, this reagent has found some utility for cyclopentane annulation in which the ring is invariably constructed by a two-step process. This was first demonstrated by Knapp et al. with the methylenecyclopentane annulation of cyclic enones (**3**) (eqs 1 and 2).[3,7]

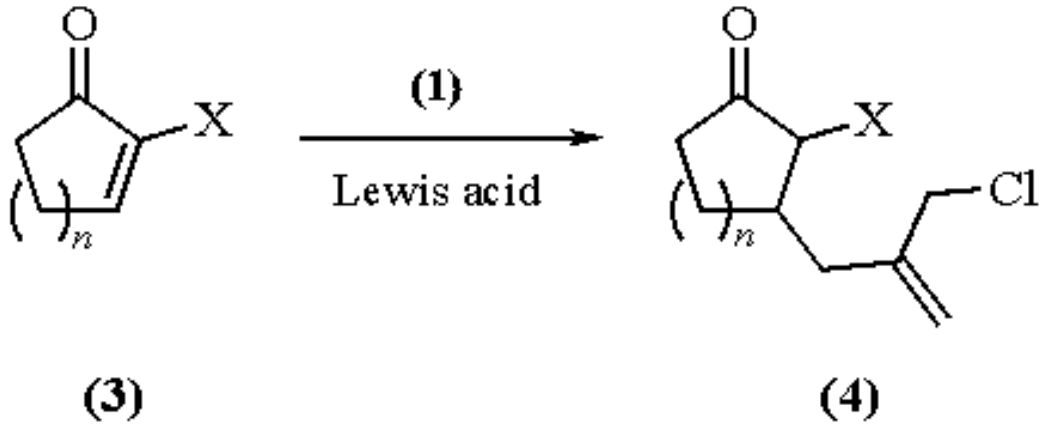

(1)

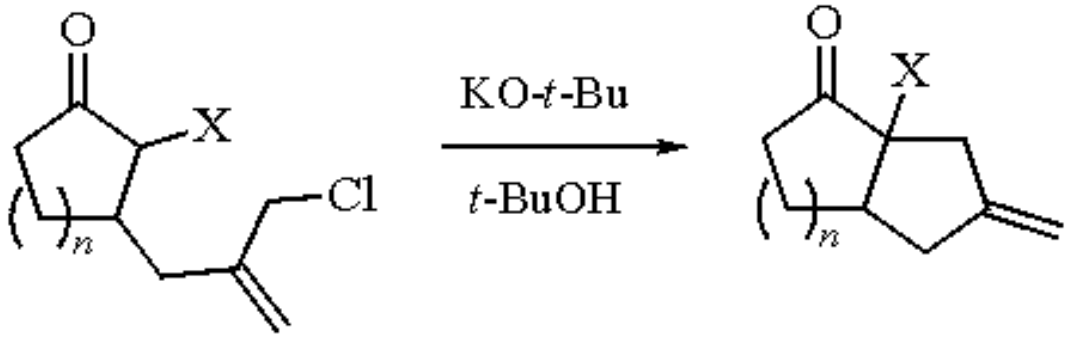

(2)

(4) **(5)**

	n	X	Lewis acid		Yield (%)		Yield (%)
(3a)	1	H	$TiCl_4$	**(4a)**	8	**(5a)**	-
(3b)	1	SPh	Et_2AlCl	**(4b)**	63	**(5b)**	73
(3c)	2	H	$TiCl_4$	**(4c)**	80	**(5c)**	60
(3d)	2	SPh	Et_2AlCl	**(4d)**	80	**(5d)**	79

This sequence makes use of the ability of allylsilanes to undergo the Michael reaction with α,β-unsaturated ketones under Lewis acidic conditions (eq 1) (see ***Allyltrimethylsilane***). Best results are achieved with α-phenylthio substitution; the sensitive cyclopentenone (**3a**) suffers extensive polymerization during this step. Cyclization is then achieved by base treatment (eq 2). In the case of (**4c**) a 3:1 mixture of isomers results, but the predominant diastereoisomer of (**5c**) is not characterized. These results contrast with those obtained by Trost and Chan with the trimethylenemethane complex (**6**) (eq 3).[8] This reagent generated in situ from ***3-Acetoxy-2-trimethylsilylmethyl-1-propene*** in the presence of a palladium catalyst accomplishes the methylenecyclopentane annulation with a variety of activated alkenes in one step under mild conditions (eqs 3 and 4).[9] A good yield (60%) is obtained in this concerted reaction with cyclopentenone, although poor yields are observed with cyclohex-2-enone and cyclohept-2-enone, in contrast to Knapp's two-step sequence.[7,9-11]

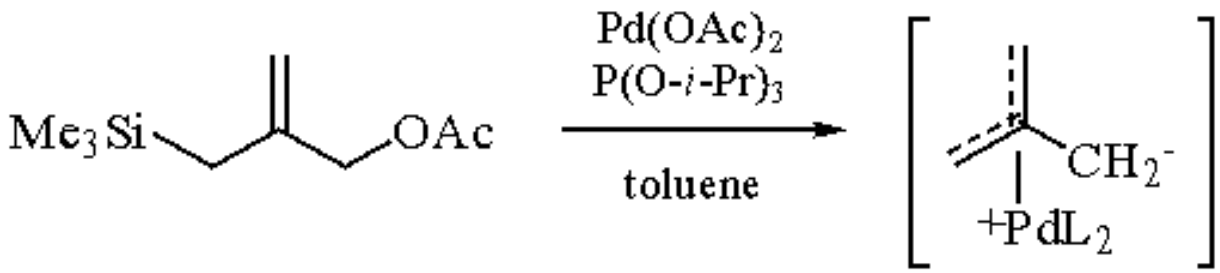

(3)

(6)

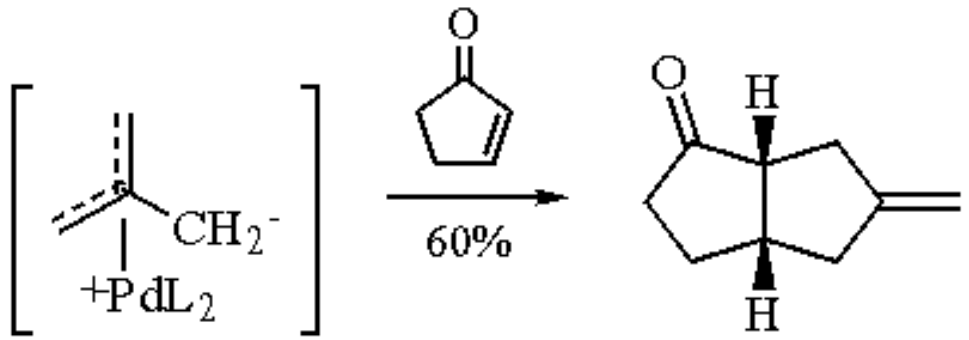

(4)

(6)

1,2-Aldehyde Addition Reactions.

The allylsilane reactivity of (**1**) with aldehydes under Lewis acid conditions (eq 5) forms the basis of another mode of annulation, furnishing either 3-methylenetetrahydrofurans (**8**) (eq 6) or α-methylenebutyrolactones (**9**) (eq 7).[12]

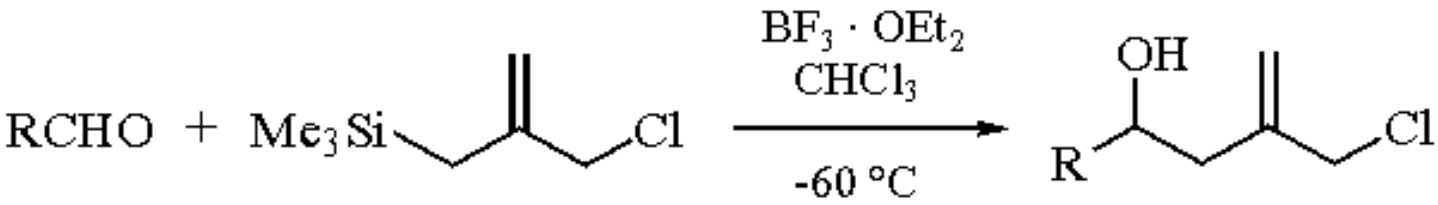

(5)

(10)

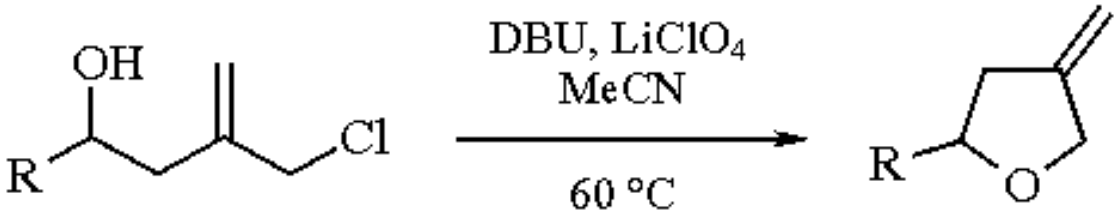

(6)

(8)

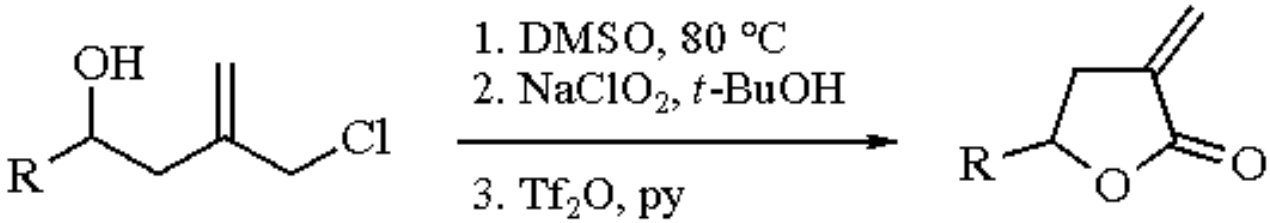

(7)

(9)

The first step proceeds under catalysis by ***Boron Trifluoride Etherate*** in the preferred solvent chloroform to give homoallyl alcohols (**10**) in good yield (eq 5). Cyclization to the ether (**8**) is accomplished by treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) in the presence of ***Lithium Perchlorate*** (eq 6). The equivalent transformation has been more commonly achieved in one step in generally high yields by use of 3-acetoxy-2-trimethylsilylmethyl-1-

propene (eq 8)[13,14] or 2-trialkylstannylmethyl-3-trimethylsilyl-1-propene in the presence of a palladium catalyst.[15,16]

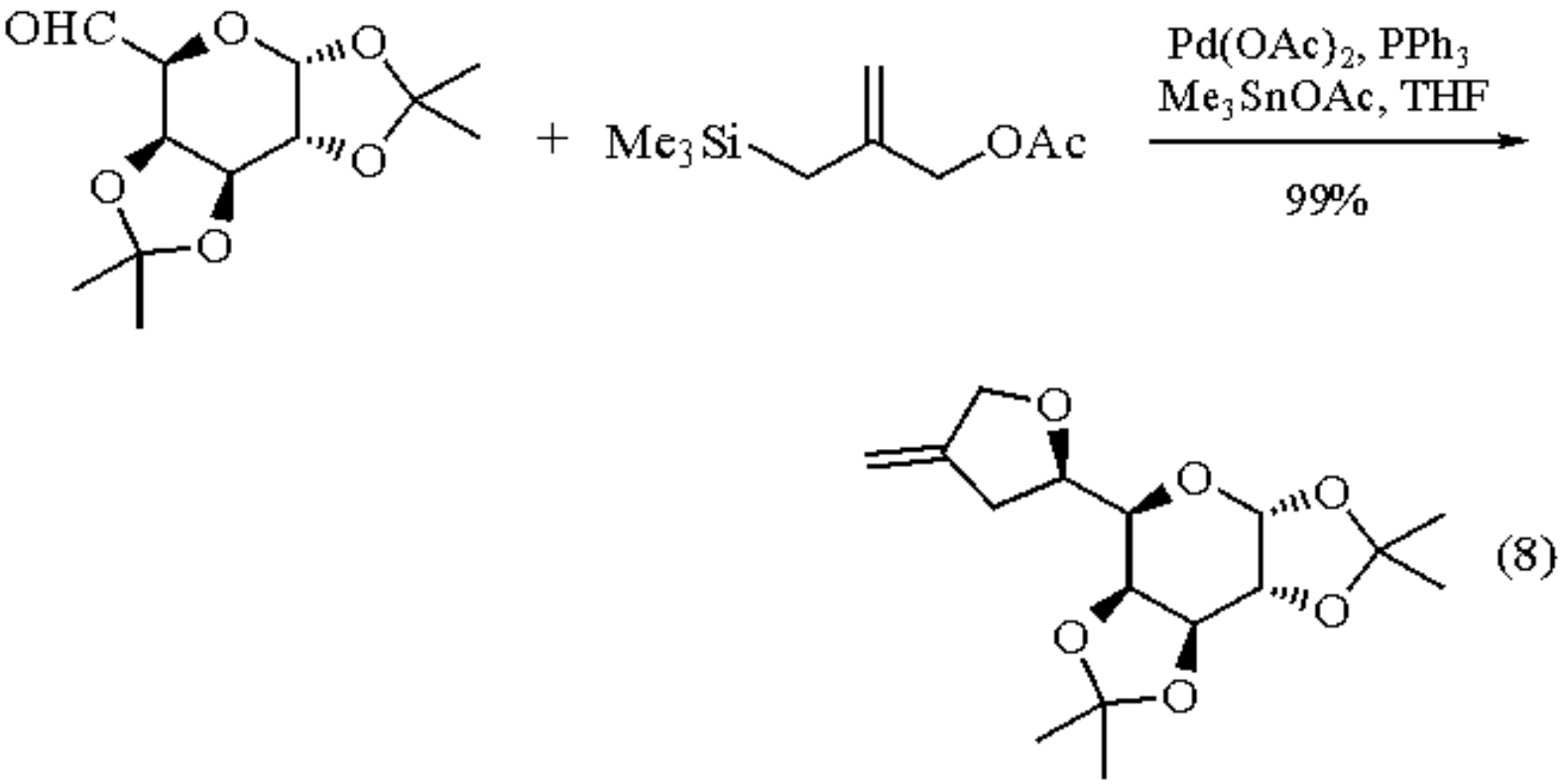

(8)

Alternatively, (**10**) may be oxidized to a carboxylic acid; cycloesterification with ***Trifluoromethanesulfonic Anhydride*** then yields α-methylenebutyrolactones (**9**) (eq 7).[12] This same transformation has also been demonstrated in one step using 2-(bromomethyl)acrylic acid[17b] or its ethyl ester under reducing conditions (eq 9).[17]

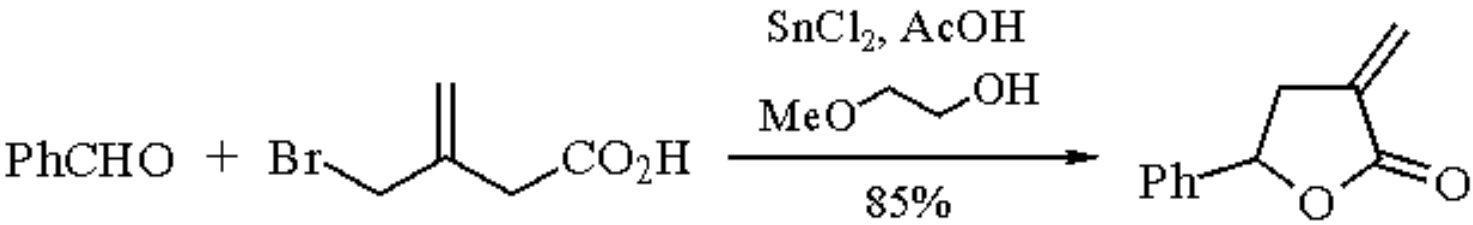

(9)

The same authors have described the addition of (**1**) to protected α-aminoaldehydes to give amino alcohols with high levels of diastereoselectivity in moderate to good yields (eq 10).[18,19] They report isolation of a single diastereoisomer following chromatographic purification.

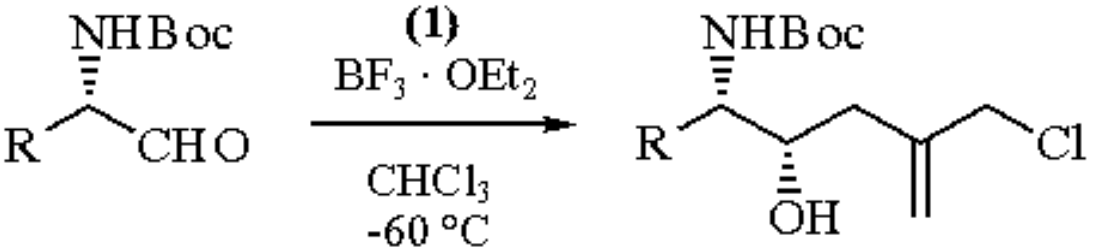

(10)

Alkylations.

An interesting example of the use of (**1**) for the construction of a six-membered ring has been demonstrated by Guiles and Meyers (eq 11).[20] Tetrahydroisoquinoline alkylation with (**1**) occurred with high enantioselectivity. Following deprotection, cyclization was initiated in the presence of fluoride ion with formaldehyde. A racemic product was obtained due to the reversible aza-[3,3]-sigmatropic rearrangement of the iminium ion intermediate.

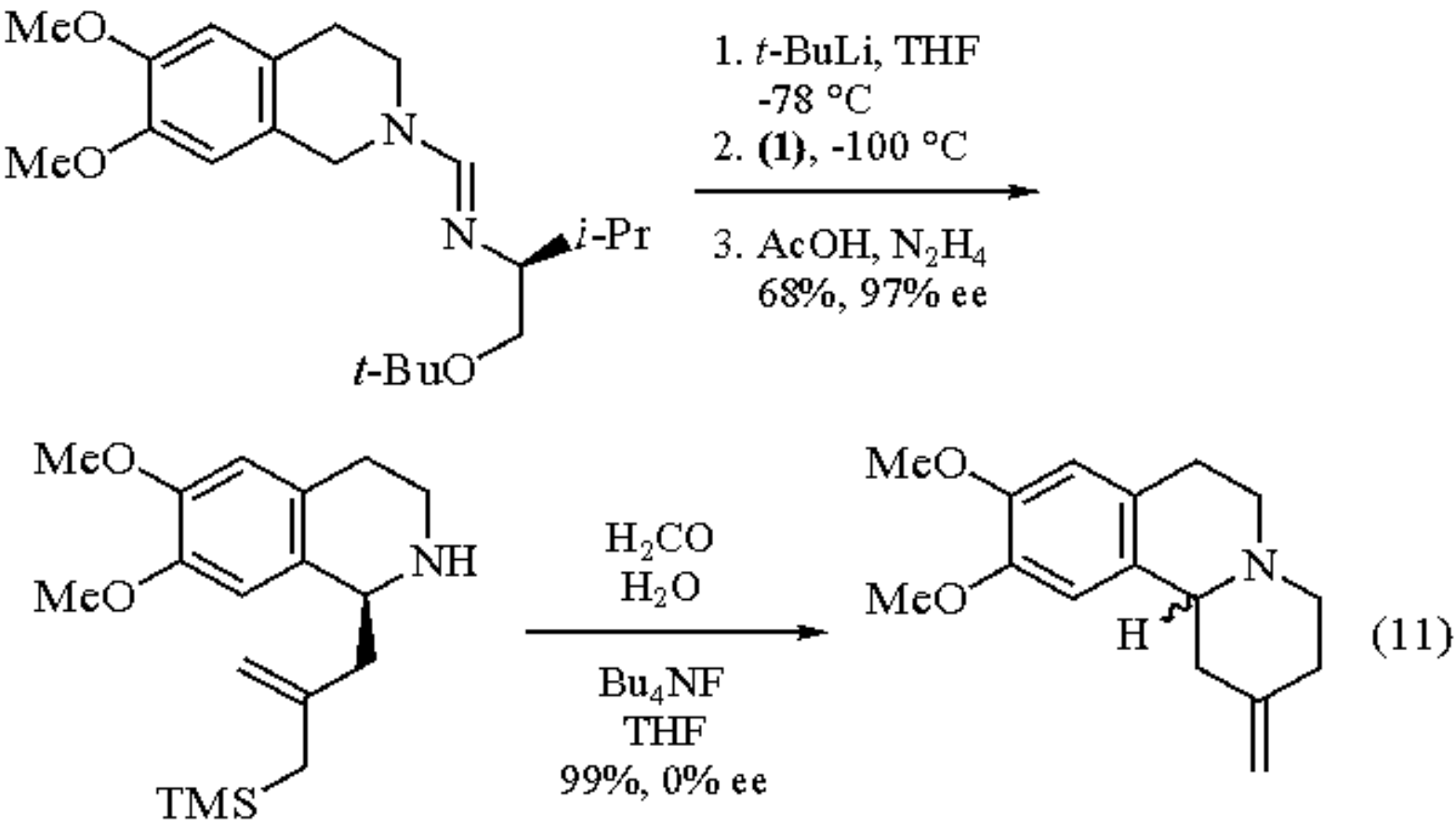

A few examples have appeared in the literature in which solely the electrophilic character of (**1**) has been utilized;[21-23] in this respect, 2-mesyloxymethyl-3-trimethylsilyl-1-propene has found more general usage.[11]

---

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Chloromethyltriphenylphosphonium Chloride[1]

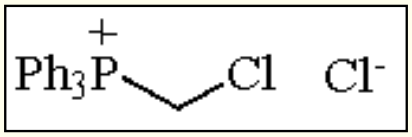

[5293-84-5] · $C_{19}H_{17}Cl_2P$ · Chloromethyltriphenylphosphonium Chloride · (MW 347.22)

(precursor to the chloro-substituted ylide for Wittig reactions with aldehydes and ketones to form 1-chloroalkenes and, after elimination of HCl, terminal alkynes)

Physical Data: mp 260 °C.

Solubility: suspensions in most organic solvents can be treated with base to form the soluble phosphorus ylide.

Form Supplied in: white powder, available commercially (chloride or iodide salt) or synthetically from ***Triphenylphosphine*** and ***Chloroiodomethane***.[2]

Handling, Storage, and Precautions: for best results the anhydrous salt should be used. The ylide, formed from the salt and strong base, will react with air, water, or other acidic protons.

Preparation of the Ylide and Stereoselectivity.

The Wittig reaction of chloromethylenetriphenylphosphorane forms chloroalkenes from carbonyl compounds with complete regioselectivity. The ylide is prepared by treating a suspension of dry phosphonium salt under N_2 with a strong base. ***n-Butyllithium*** has often been used, but the chloroalkene products are usually obtained as (*E*)/(*Z*) mixtures,[3,4] and side reactions have occasionally been reported.[2,3] Better results are obtained with bases such as ***Potassium Hexamethyldisilazide***,[5] ***Potassium t-Butoxide***,[2] or ***Sodium Amide***.[6] Although stereoselectivity for this ylide is often low (even in the absence of Li cation),[2] several (*E*)- or (*Z*)-selective reactions have been reported. Reaction of the chloro-substituted ylide, prepared from KHMDS in toluene, with an α-keto amino acid derivative (eq 1) gave an 85:15 (*Z*)/(*E*) ratio of chloroalkenes in 85% yield.[5]

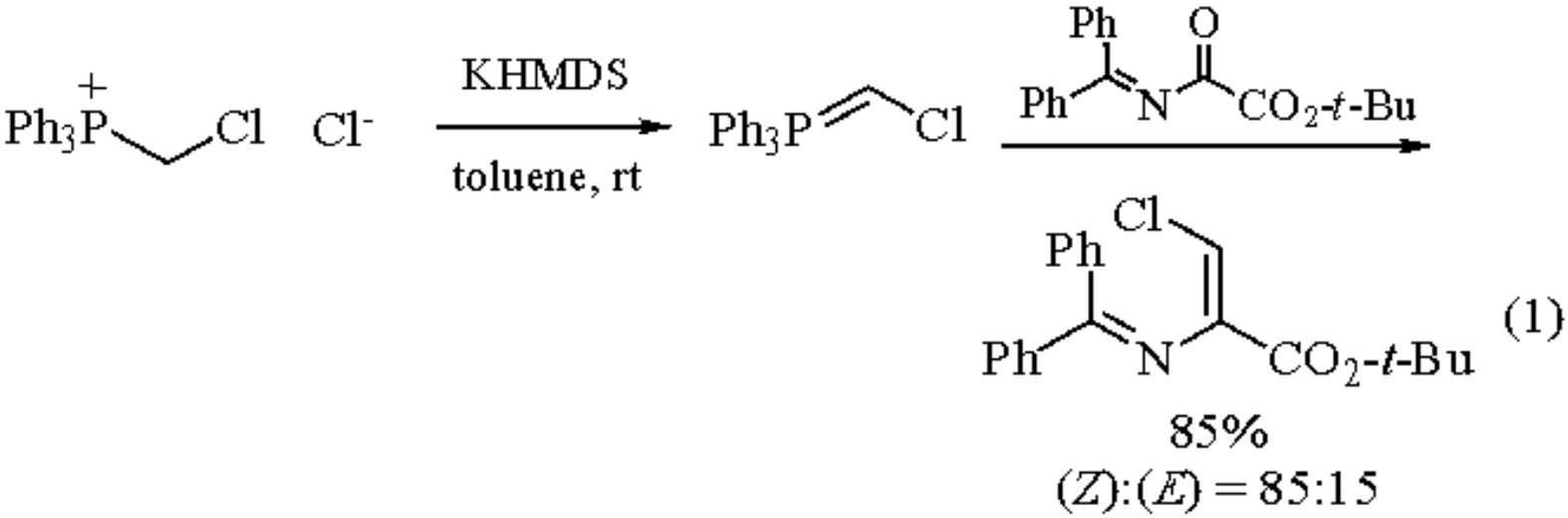

High (*E*) selectivity was obtained in the reaction of this ylide (generated from the salt and *t*-BuOK in *t*-butanol) with benzaldehyde. A 1:1 mixture of chlorostyrenes was formed at rt, but 100% (*E*)-alkene was produced after refluxing the reaction for 4 h (eq 2).[2]

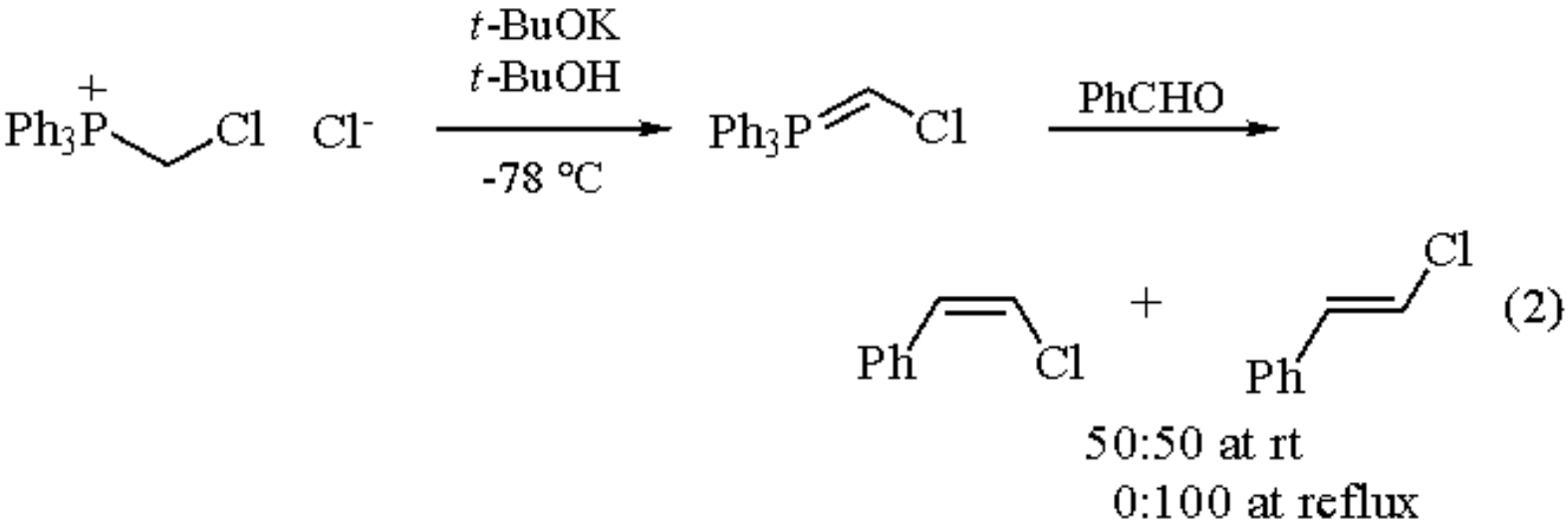

Synthesis of Alkynes.

Synthetically, the most common use for the chloroalkene products is the preparation of alkynes. Dehydrohalogenation of the vinyl chlorides with an excess of strong base (***n-Butyllithium*** or ***Lithium Diisopropylamide***) gives terminal alkynes in good yield. This methodology has been used in the synthesis of alkynyl steroids (eq 3)[7] and carbohydrate derivatives (eq 4).[8] The transformation of RCHO to RC&tbond;CH has also been performed in the synthesis of lycopene isomers,[9] and derivatives of vitamin D[10] and retinal.[11]

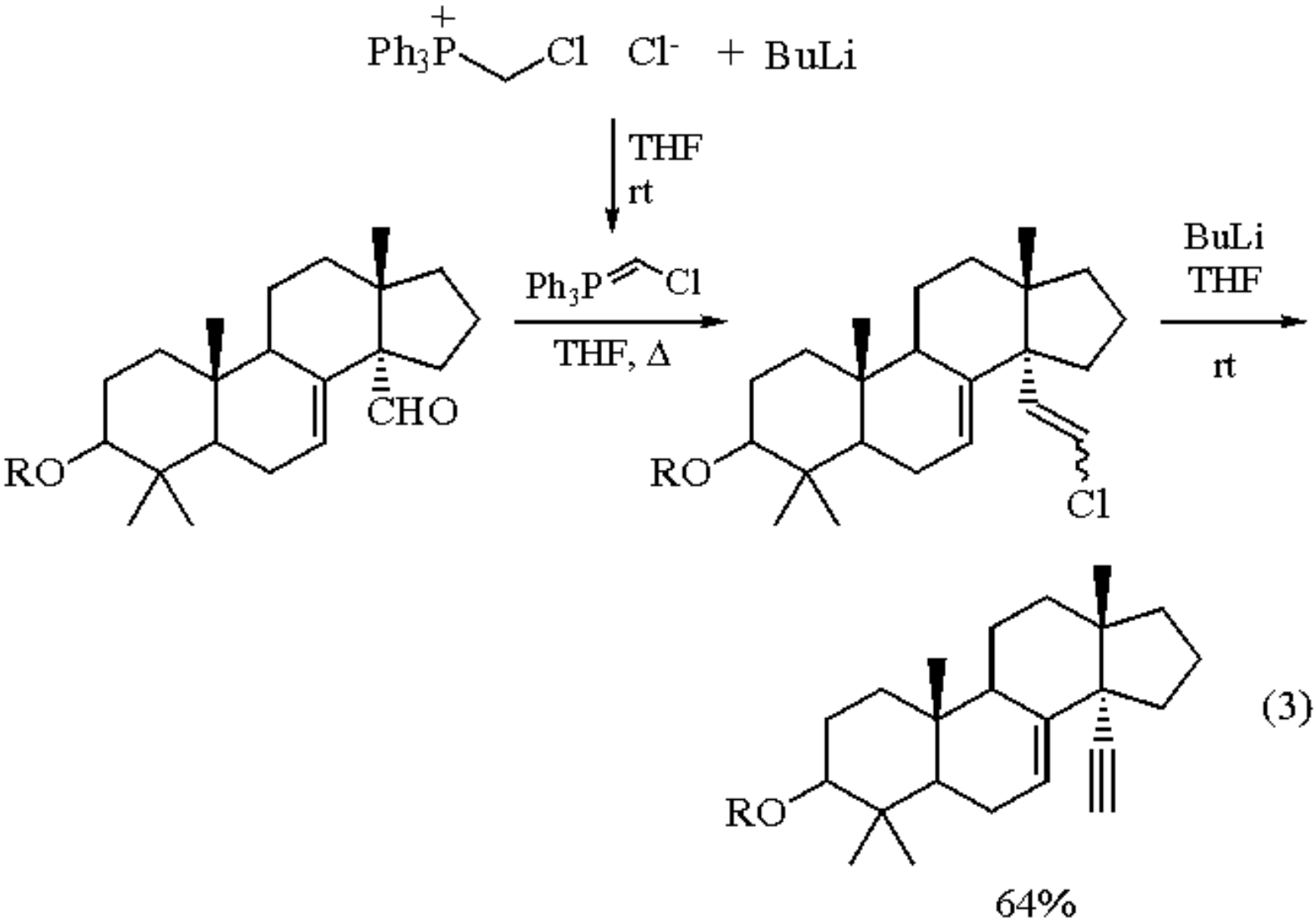

(3)

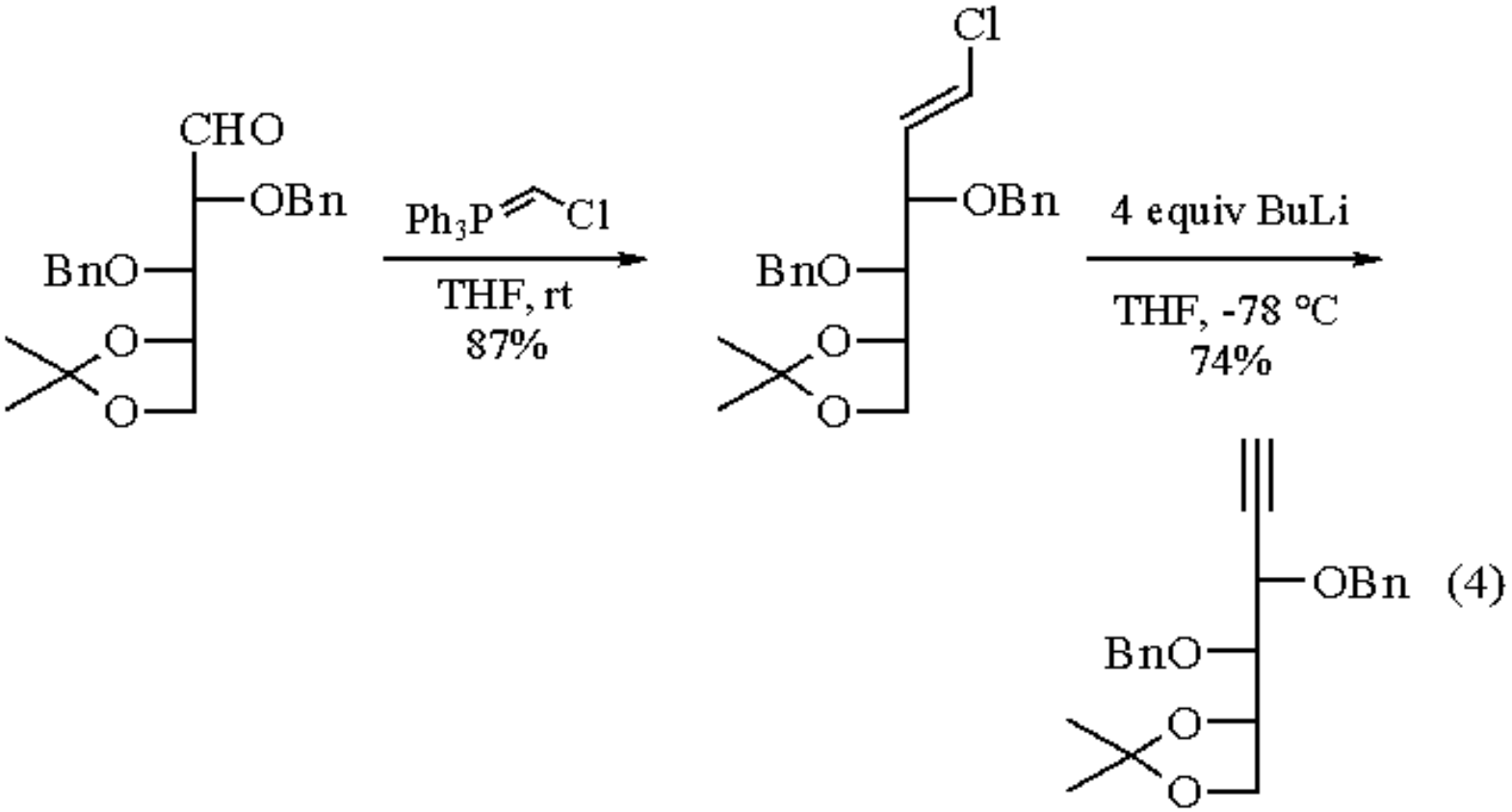

A useful alternative to the Wittig reaction for vinyl halide synthesis is the ***Chromium(II) Chloride*** mediated reaction of an aldehyde and chloroform.[12] The organochromium intermediate forms 1-chloroalkenes from aliphatic and aromatic aldehydes with high (*E*) selectivity in yields of 55-75%. The procedure, however, requires 6 equiv of the expensive chromium reagent. Other alkene-forming reactions, such as the Peterson alkenation[13] and the Tebbe reaction,[14] are not useful for the preparation of vinyl chlorides.

---

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14. Pine, S. H. *OR* **1993**, *43*, 1.

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N-Chloromorpholine

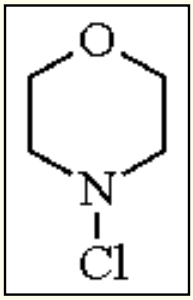

[23328-69-0] · C_4H_8ClNO · *N*-Chloromorpholine · (MW 121.57)

(useful reagent for selective and efficient chlorination of activated aromatics[1])

Alternate Name: NCM.

Physical Data: bp 63-64 °C/36-38 mmHg.[1]

Solubility: sol diethyl ether, trifluoroacetic acid, carbon tetrachloride.

Preparative Methods: not commercially available; prepared from ***Morpholine*** and aqueous ***Sodium Hypochlorite*** at <10 °C, followed by ether extraction, concentration below 30 °C, and vacuum distillation.[1,2]

Analysis of Reagent Purity: can be determined iodometrically.[3]

Handling, Storage, and Precautions: lachrymatory liquid; begins to decompose at ambient temperature within hours, or on distillation at atmospheric pressure.[4] Preferably used immediately after distillation; however, can be stored at -18 °C for several weeks with limited decomposition. Solid which forms on standing (morpholine hydrochloride) can be removed by filtration just before use.[1] Store under inert atmosphere. This reagent should be handled in a fume hood.

Chlorination of Activated Aromatics.

Phenol, anisole, and related activated aromatic compounds are selectively chlorinated by *N*-chloromorpholine (NCM) in the *para* position in high yield, with formation of only small amounts of the corresponding *ortho* isomers. For example, 2-chloroanisole and NCM afford 2,4-dichloroanisole in 80% yield (eq 1). Less than 1% each of 2,6-dichloroanisole and 2,4,6-trichloroanisole are obtained under these conditions.[1]

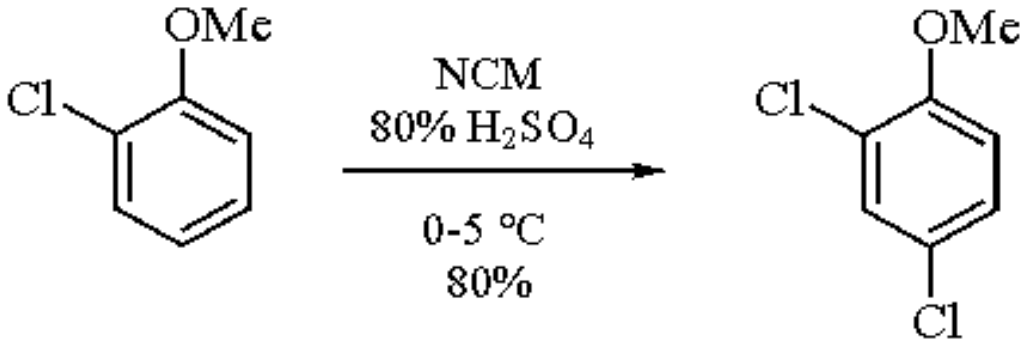

(1)

Salicylic acid and NCM also give chlorination mainly *para* to the phenolic hydroxyl group (eq 2).[5]

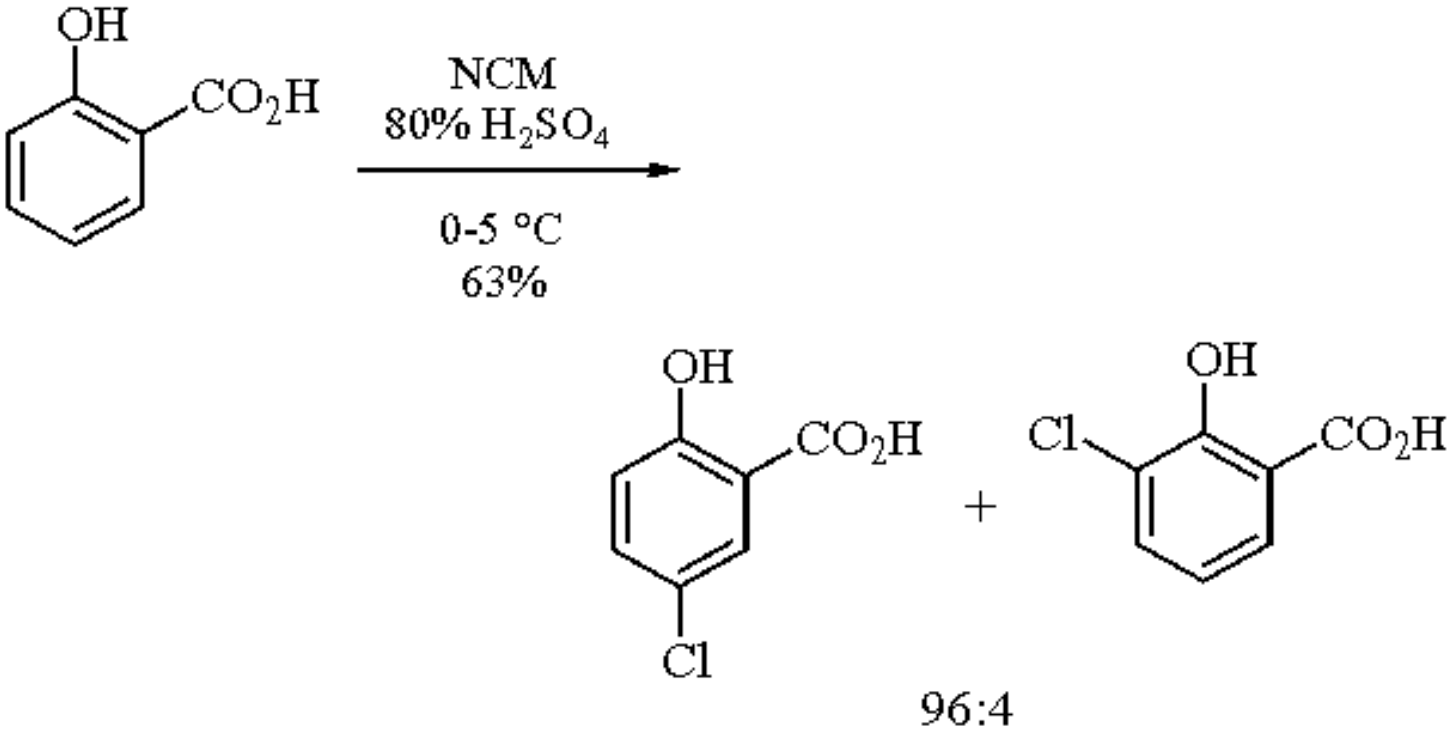

(2)

These chlorinations are usually carried out in either trifluoroacetic acid or 80% aqueous sulfuric acid. In the latter solvent, highly activated substrates such as phenols can undergo ring sulfonation. Such side reactions can generally be minimized by keeping the reaction mixtures cold and employing short reaction times.[1,5]

Other structurally similar chlorinating agents, such as *N*-chloropiperidine (NCP), have also been used for selective *para* chlorination of activated aromatics. There appears to be no strong preference for use of NCM over NCP or related compounds, as overall yields and isomer ratios are generally excellent with each of these reagents.[1] Mechanistic details of these transformations have been published.[6]

Unfortunately, NCM as well as other reagents in this family chlorinate less activated aromatics such as alkylbenzenes relatively unselectively, to afford mixtures of 2- and 4-substituted products.[7] The isomer ratio can be affected by changing the acid strength of the solvent,[7a] or by use of added silica gel;[3] however, only limited specificity for one isomer can be obtained in this fashion.

Chlorodealkylation of Alkyl Phenols.

t-Butyl substituted phenols react with NCM to substitute chlorine for the *t*-butyl group (eq 3).[5]

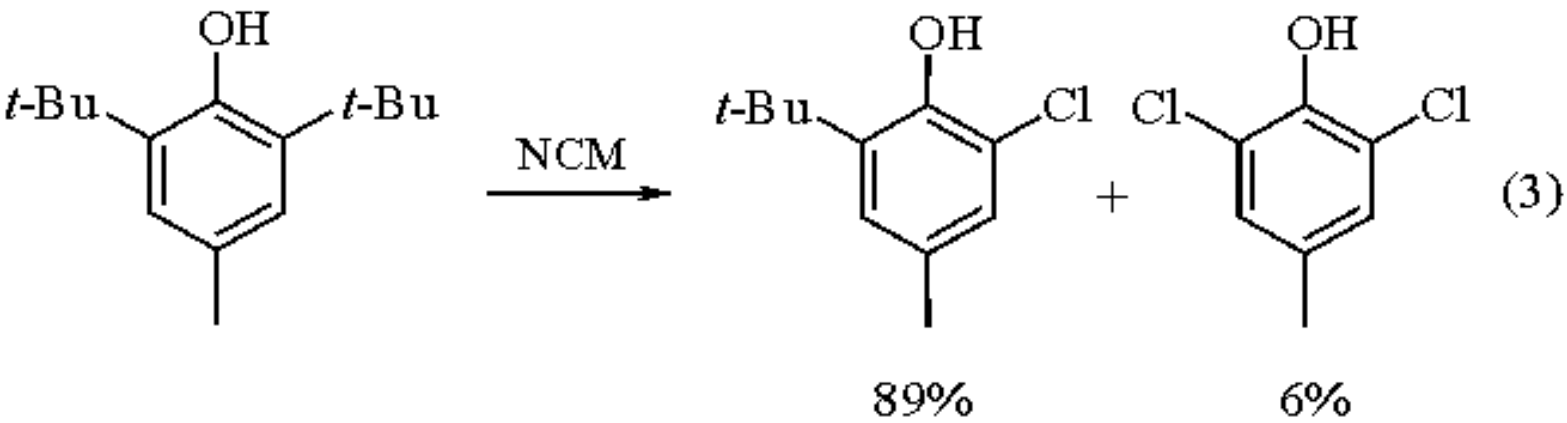

Other Reactions.

NCM can be used to prepare morpholino-substituted sulfenamides[8] and selenamides[9] upon reaction with alkyl sulfides and selenides, respectively. Such amides have been used as vulcanization accelerators in the rubber industry.

---

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1-Chloro-1-nitrosocyclohexane

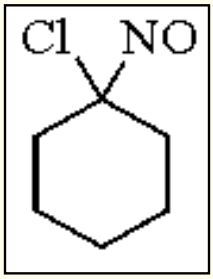

[695-64-7] · $C_6H_{10}ClNO$ · 1-Chloro-1-nitrosocyclohexane · (MW 147.5)

(electrophilic [NH_2^+] for alkenes and can function as a dienophile for [4 + 2] reactions)

Physical Data: bp 52 °C/12 mmHg.

Solubility: sol in wide range of organic solvents.

Form Supplied in: solid; widely available.

Preparative Methods: the most commonly used method is the reaction of cyclohexanone oxime with a chlorinating agent such as ***t-Butyl Hypochlorite*** in trichlorofluoromethane (eq 1).[1]

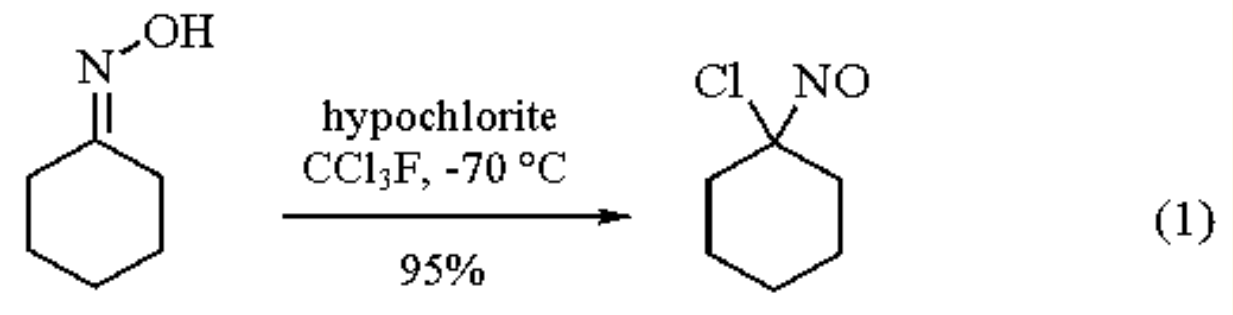

1-Chloro-1-nitrosocyclohexane shows a wide range of reactivity towards different functional groups. Deboer first demonstrated the reactivity of this reagent by reacting it with allylic alkenes such as phenylpropene to give cyclohexylidene-*N*-(2-phenyl)-prop-1-en-3-yl nitrone hydrochloride in 76% yield (eq 2).[2]

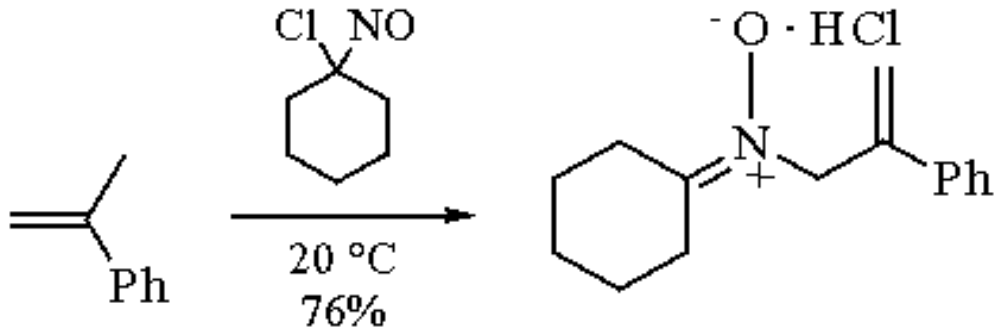

(2)

Other authors have shown that this reagent can be used effectively in the synthesis of polyhydroxylated cyclohexyl derivatives, alkaloids, and amino acids. 1-Chloro-1-nitrosocyclohexane reacts with 1,3-butadiene in ethanol to give 3,6-dihydro-1,2-dioxine (eq 3).[3] Kresze in 1981 reported a synthesis of polyhydroxy amino compounds by utilizing the reactivity of 1-chloro-1-nitroso compounds towards dienes such as *trans*-1,3-cyclohexadien-5,6-diyl diacetate (eq 4).[4] In 1984, Kibayashi reported a facile route to naturally occurring tropane alkaloids.[5] The approach employs a Diels-Alder cycloaddition of cyclohepta-1,3-dienes with nitroso compounds followed by an intramolecular C-N bond formation (eq 5).

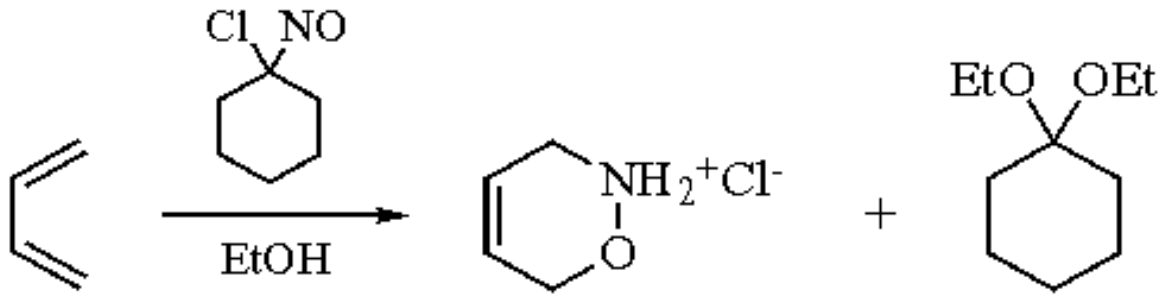

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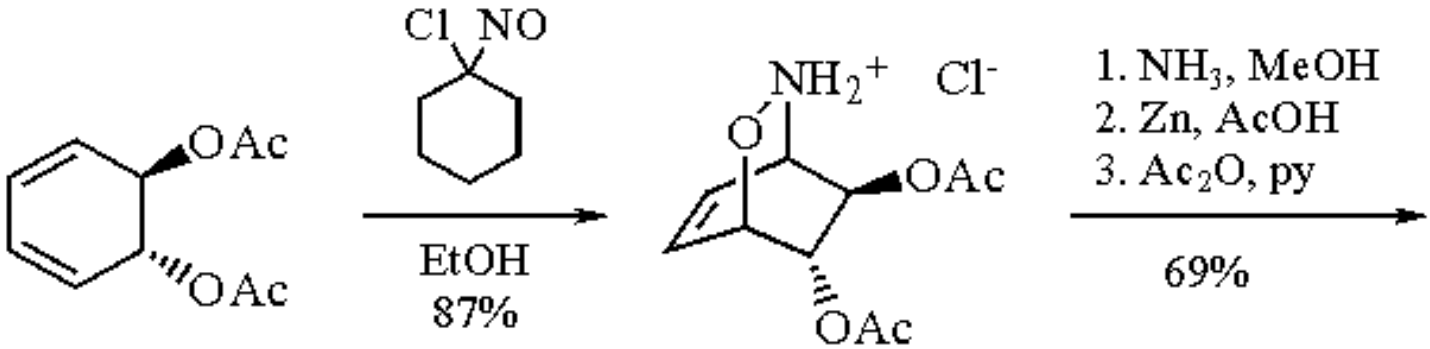

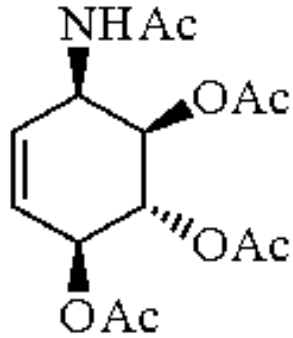

(4)

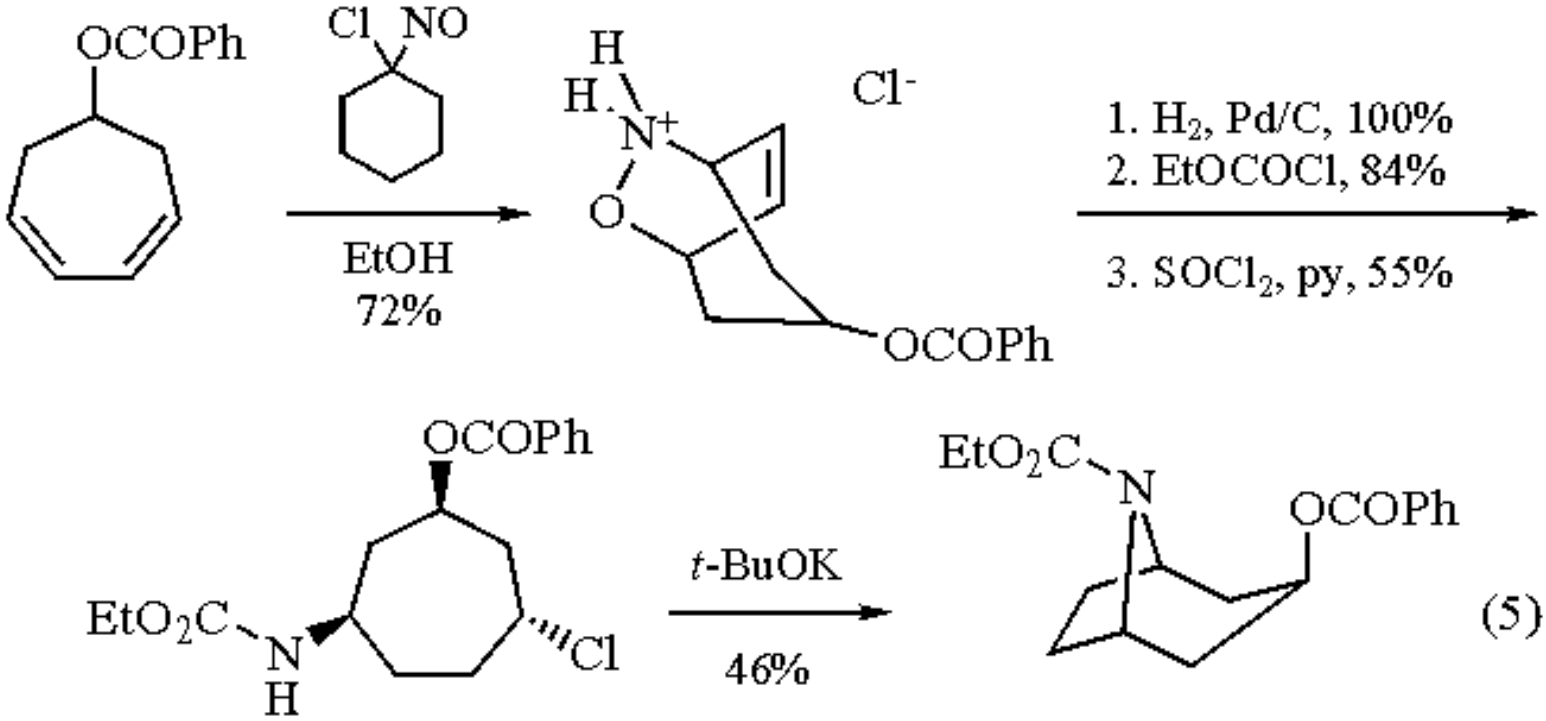

(5)

Recently, Oppolzer demonstrated the use of 1-chloro-1-nitrosocyclohexane as a convenient electrophilic nitrogen source in the asymmetric synthesis of amino acids and α-hydroxyamino acids.[6] Treatment of an *N*-alkylsultam with ***Sodium Hexamethyldisilazide*** followed by 1-chloro-1-nitrosocyclohexane gave diastereomerically pure crystalline *N*-hydroxy amino acids (eqs 6 and 7).

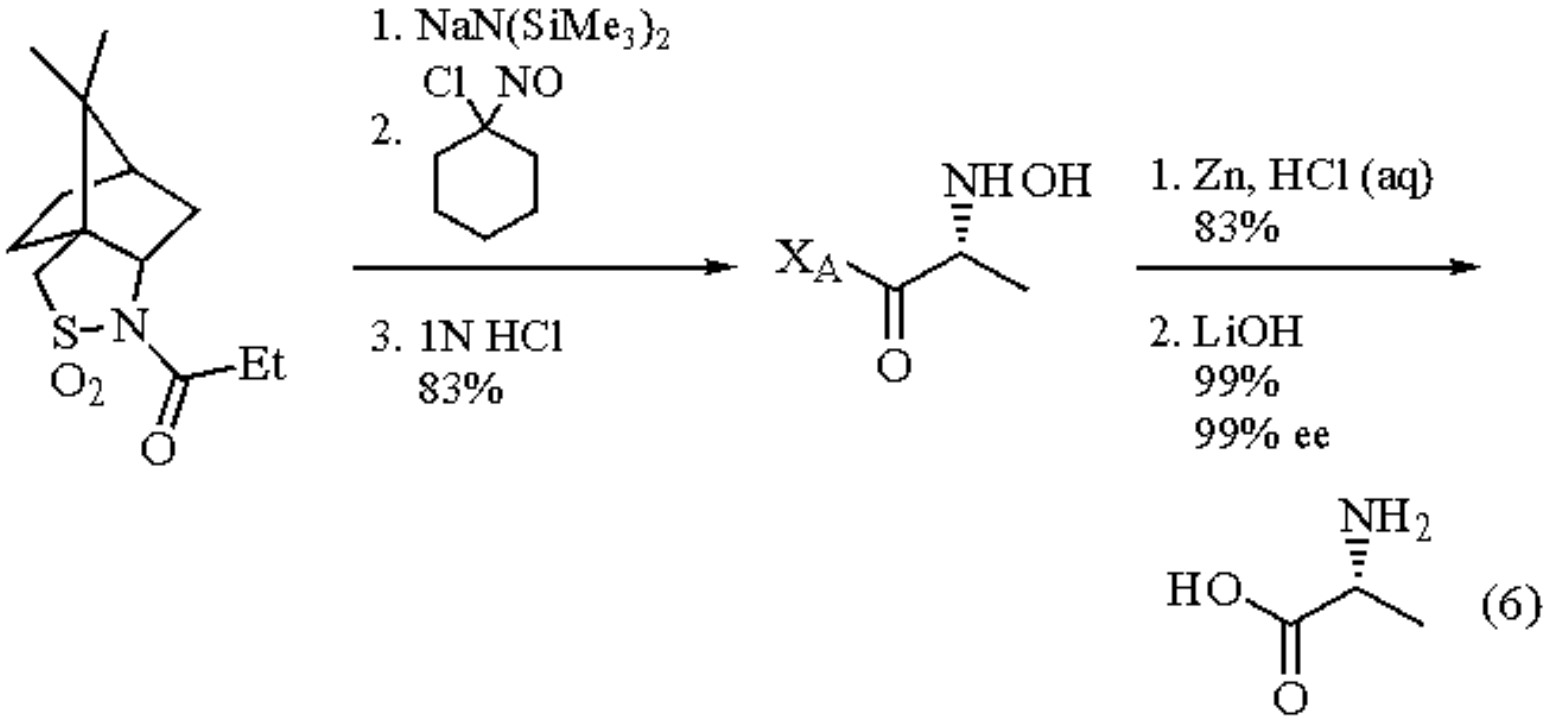

(6)

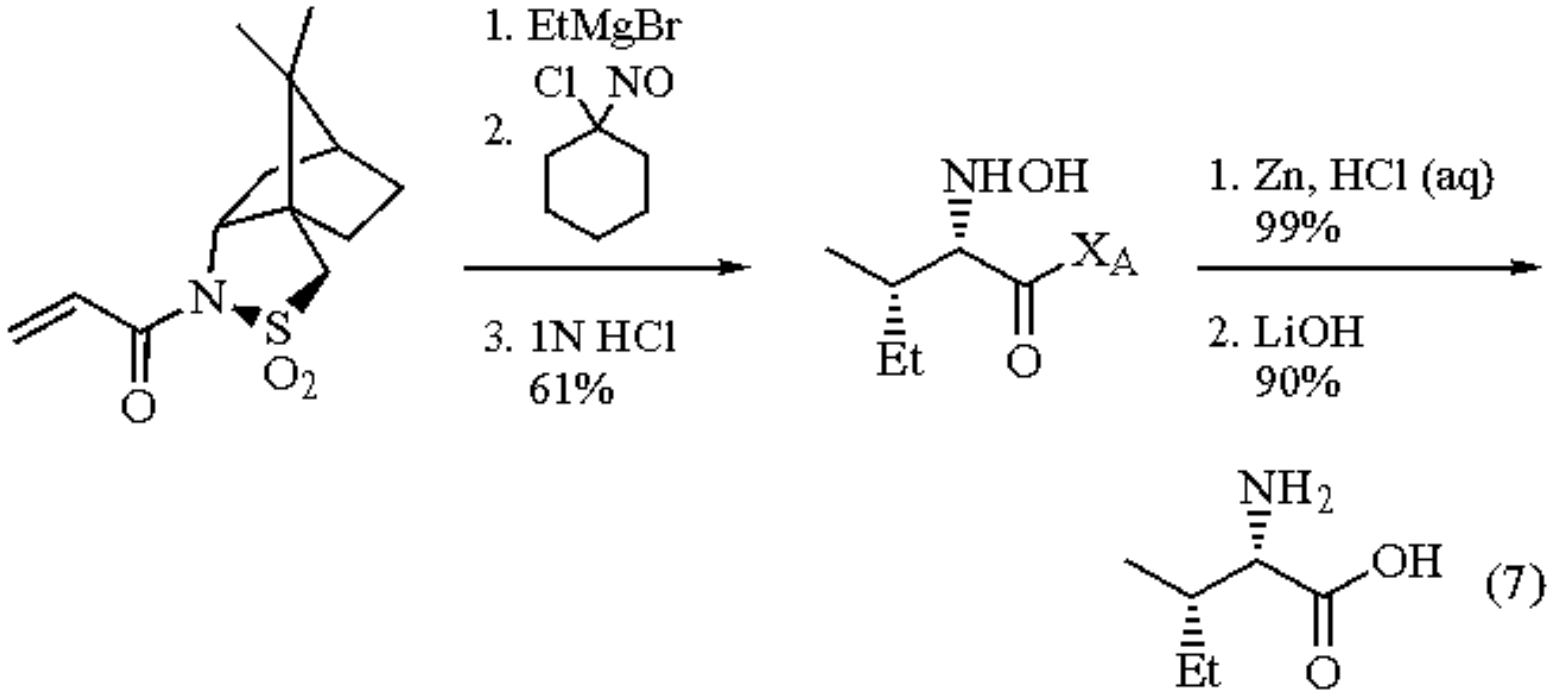

1. Luttke, W.; Diekman, H. *AG(E)* **1968**, *7*, 387.
2. Schenk, C.; DeBoer, T. J. *TL* **1979**, *35*, 147.
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5. Kibayashi, C.; Watanbe, Y.; Iida, H. *TL* **1984**, *25*, 5091.
6. (a) Oppolzer, W.; Tamura, O.; Deerberg, J. *HCA* **1992**, *75*, 1965. (b) Oppolzer, W.; Tamura, O. *TL* **1990**, *31*, 991.

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2-Chloro-2-oxo-1,3,2-benzodioxaphosphole

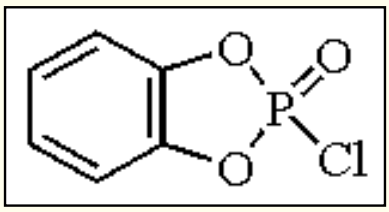

[1499-17-8] · $C_6H_4ClO_3P$ · 2-Chloro-2-oxo-1,3,2-benzodioxaphosphole · (MW 190.52)

(phosphorylation of alcohols;[1] peptide synthesis,[2] β-lactam synthesis[3])

Alternate Name: *o*-phenylene phosphorochloridate.

Physical Data: mp 59-61 °C; bp 80-81 °C/1.2 mmHg.

Form Supplied in: commercially available as a white to off-white solid.

Preparative Method: prepared by heating 2,2,2-trichloro-1,3,2-benzodioxaphosphole with a slight excess of acetic anhydride.[1]

Purification: purified by distillation.

Handling, Storage, and Precautions: moisture sensitive, but may be kept indefinitely in a sealed vessel.

Preparation of Monophosphate Esters from Alcohols.[1,4]

2-Chloro-2-oxo-1,3,2-benzodioxaphosphole (**1**) is an extremely active phosphorylating agent for alcohols, reacting rapidly and quantitatively even with hindered alcohols such as *t*-butanol.[1] The resulting phosphotriesters (**2**) (eq 1) need not be isolated, and are hydrolyzed in the presence of base to the stable, often crystalline, *o*-hydroxyphenyl phosphates (**3**). Oxidation to the monoalkyl phosphates (**4**) may conveniently be accomplished using buffered bromine water or with aqueous periodic acid. Where the original alcohol contained unsaturation, however, these conditions are unsatisfactory and the transformation may be achieved with ***Lead(IV) Acetate*** in dioxane.[1] Reductive conditions (H_2/Adams catalyst) have also been employed.[5]

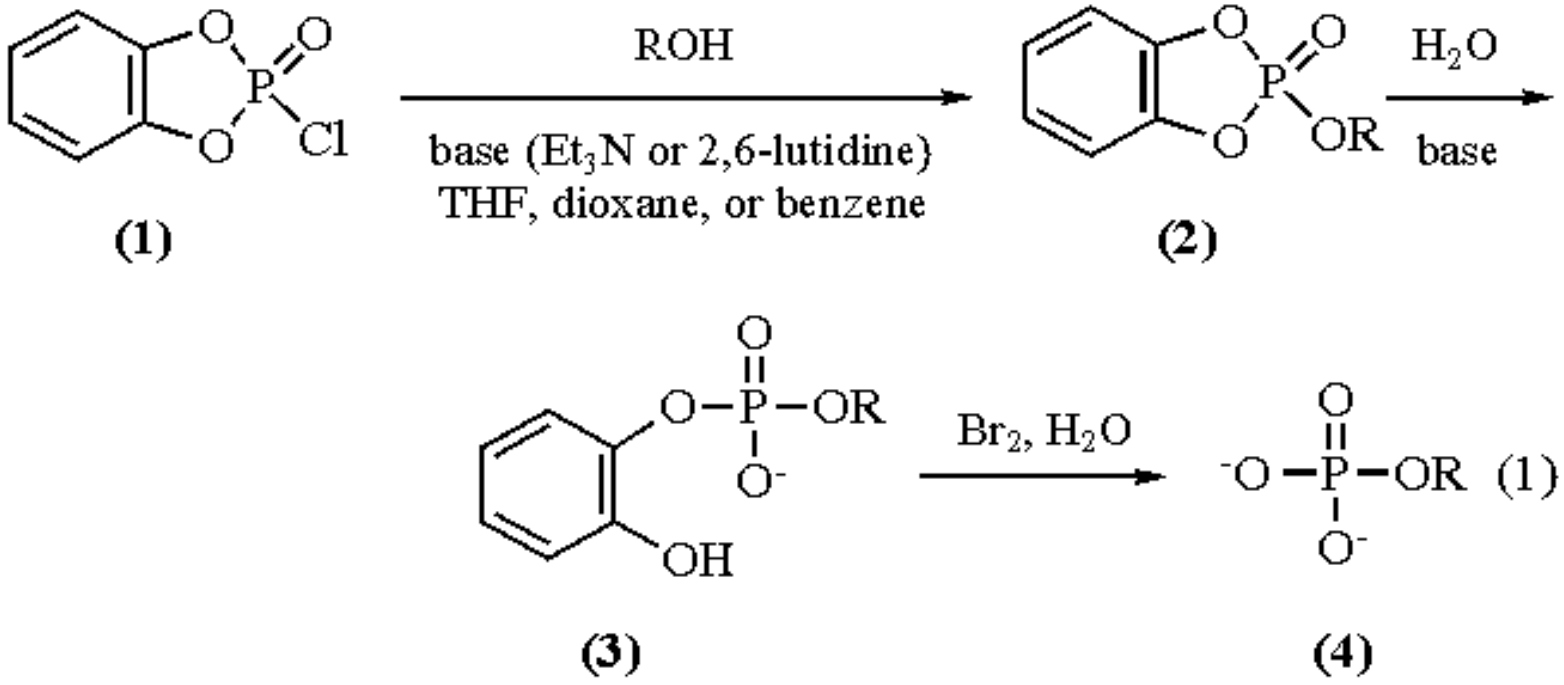

The overall procedure is of great utility for the phosphorylation of alcohols, including tertiary alcohols, and has been applied to the phosphorylation of nucleosides.[6] The phosphates (**4**) are generally isolated as their barium salts, free of inorganic phosphate, and indeed are often analytically pure before recrystallization.

Peptide Synthesis.

Treatment of (**1**) with an amine and a carboxylate salt results in amide bond formation, via the phosphoramidate intermediate (**5**) (eq 2).[2] No racemization was observed for the example shown (the Anderson test).

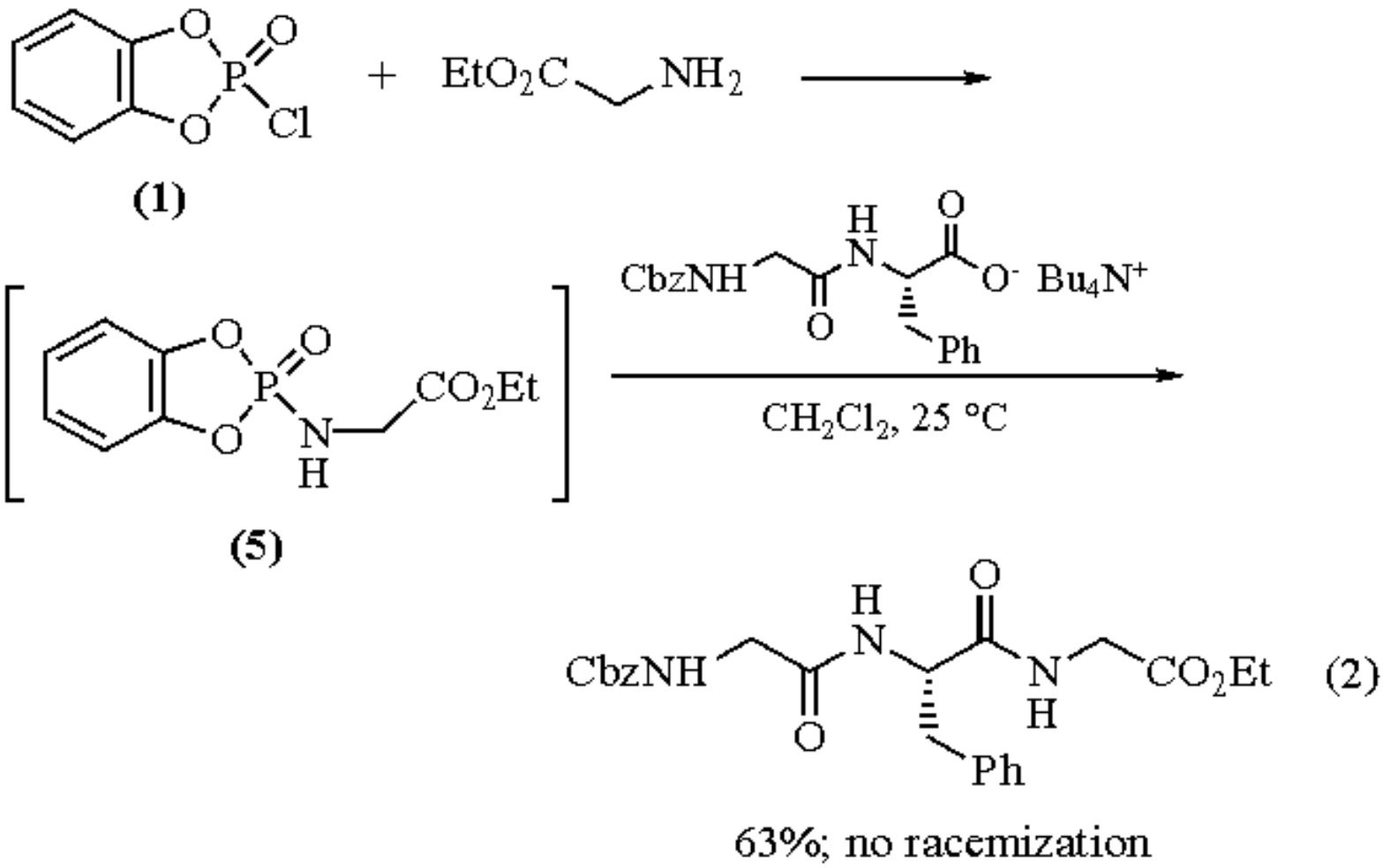

β-Lactam Synthesis.

Reagent (**1**) has been used for the condensation of carboxylic acids with amines to give β-lactams (eq 3).[3] The *trans* isomer predominated in this example.

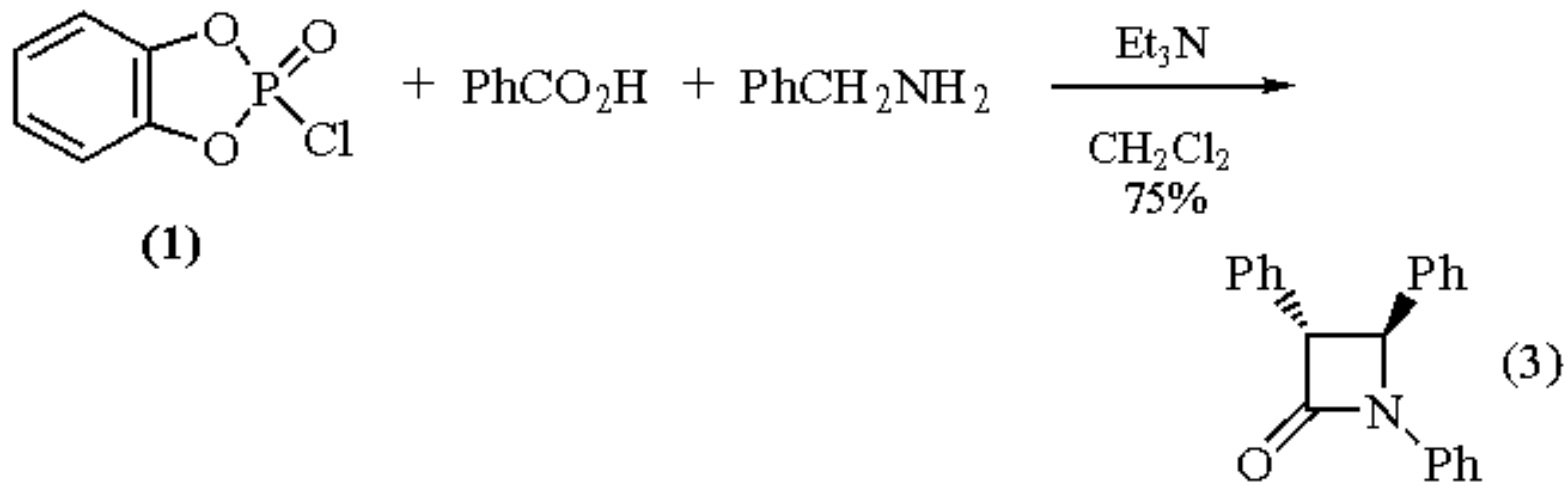

1. Khwaja, T. A.; Reese, C. B.; Stewart, J. C. M. *JCS(C)* **1970**, 2092.
2. Wakselman, M.; Acher, F. *TL* **1980**, *21*, 2705.
3. Manhas, M. S.; Lal, B.; Amin, S. G.; Bose, A. K. *SC* **1976**, *6*, 435.
4. For a review of phosphorylation methods, see: Slotin, L. A. *S* **1977**, 737.
5. Calderón, J.; Moreno, G. *CA* **1957**, *51*, 11273f.
6. Khwaja, T. A.; Reese, C. B. *T* **1971**, *27*, 6189.

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1-Chloro-3-pentanone

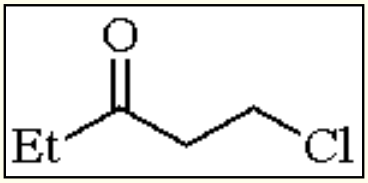

[32830-97-0] · C_5H_9ClO · 1-Chloro-3-pentanone · (MW 120.58)

(reagent for Robinson annulation; often interchangeable with 1-penten-3-one and the corresponding Mannich base 1-dialkylamino-3-butanone)

Alternate Name: 2-chloroethyl ethyl ketone

Physical Data: bp 62-65 °C/15 mmHg; *d* 1.042 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: liquid; commercially available.

Purification: by distillation.

Annulation.

The reagent is the synthetic equivalent of 1-penten-3-one (ethyl vinyl ketone) and the quaternary salt of the Mannich base 1-dimethylamino-3-butanone in the Robinson annulation. The use of the reagent in this annulation has been briefly reviewed.[1,2] The reagent is believed to generate the vinyl ketone.[3] Although most annulations are done with base in organic solvents, the reagent can also be used with acid in organic[4] and in aqueous solution. In water, it reacts as expected with 2-methylcyclopentane-1,3-dione (eq 1).[5]

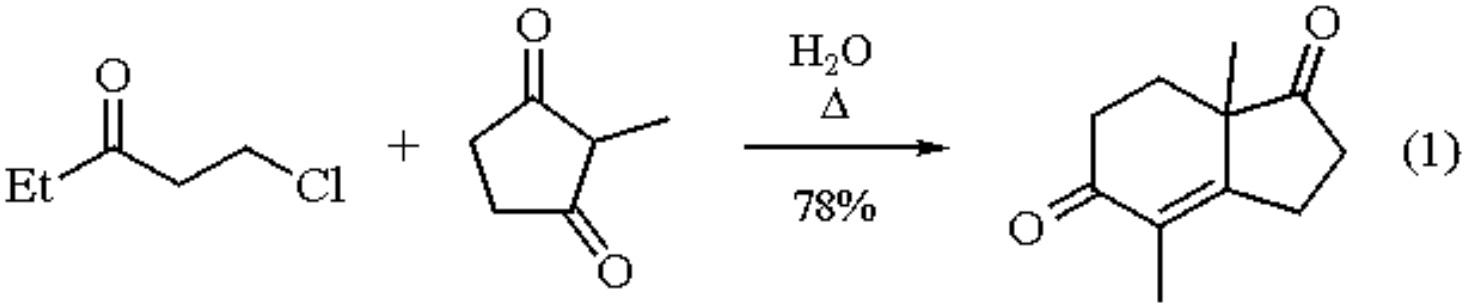

(1)

However, the corresponding cyclohexane derivative gives an acid as the major product, which presumably results from opening of a bridged aldol intermediate (eq 2).[5]

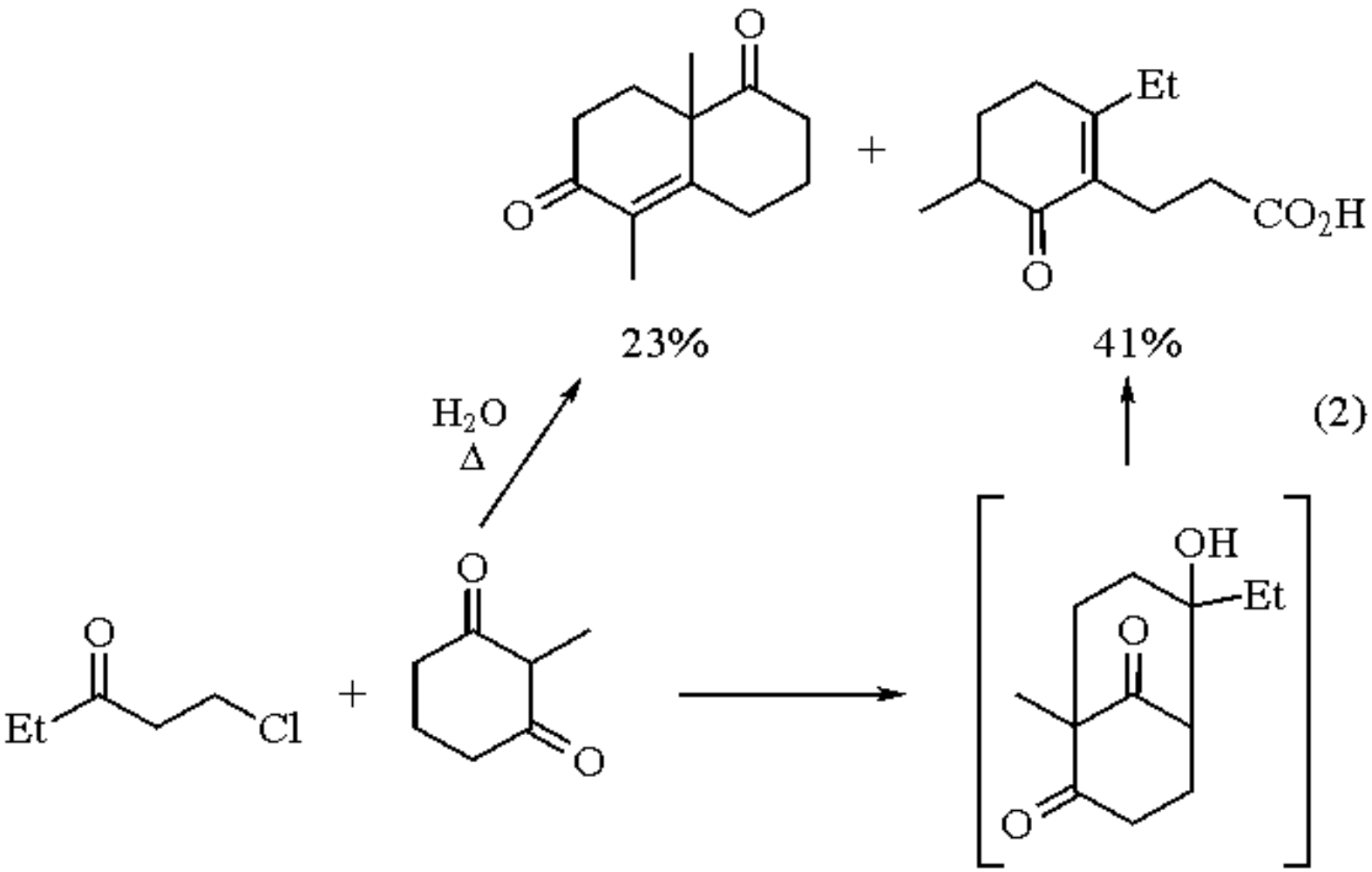

Careful examination of products shows that often both mono- and bis-annulation products are formed (eq 3).[6] The bis-annulation can give two intermediate products, which converge to one (eq 4).[6] The bis-annulation can also be done without isolation of the intermediates (eq 5).[7]

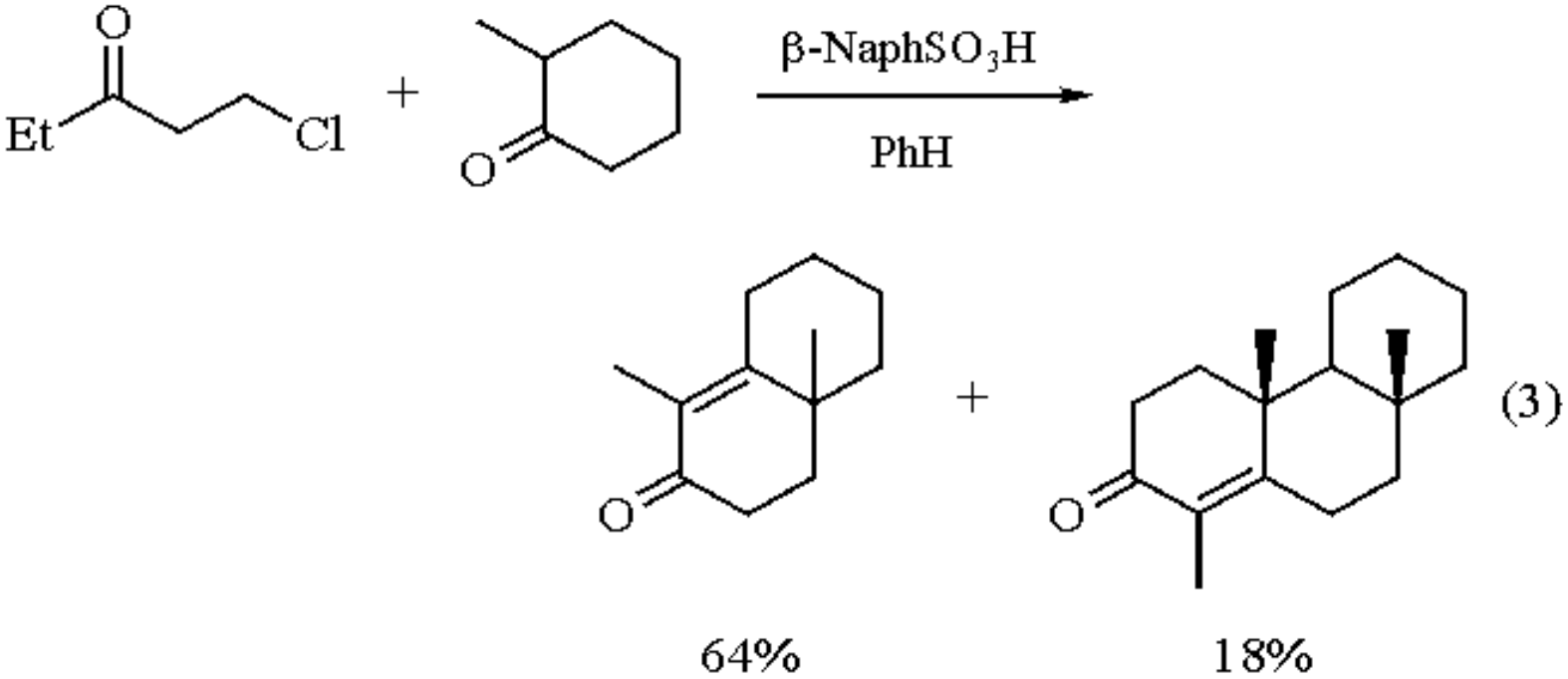

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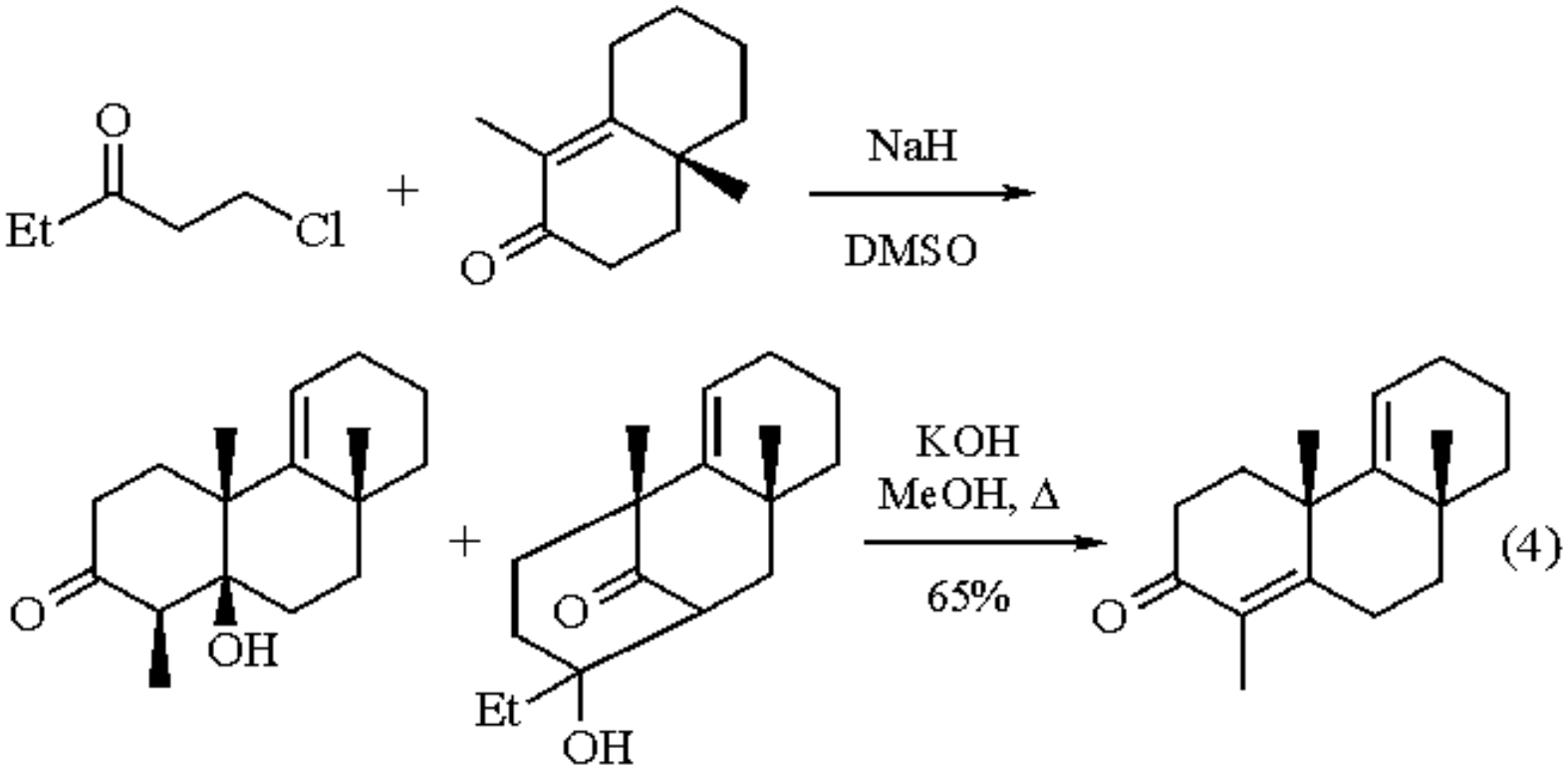

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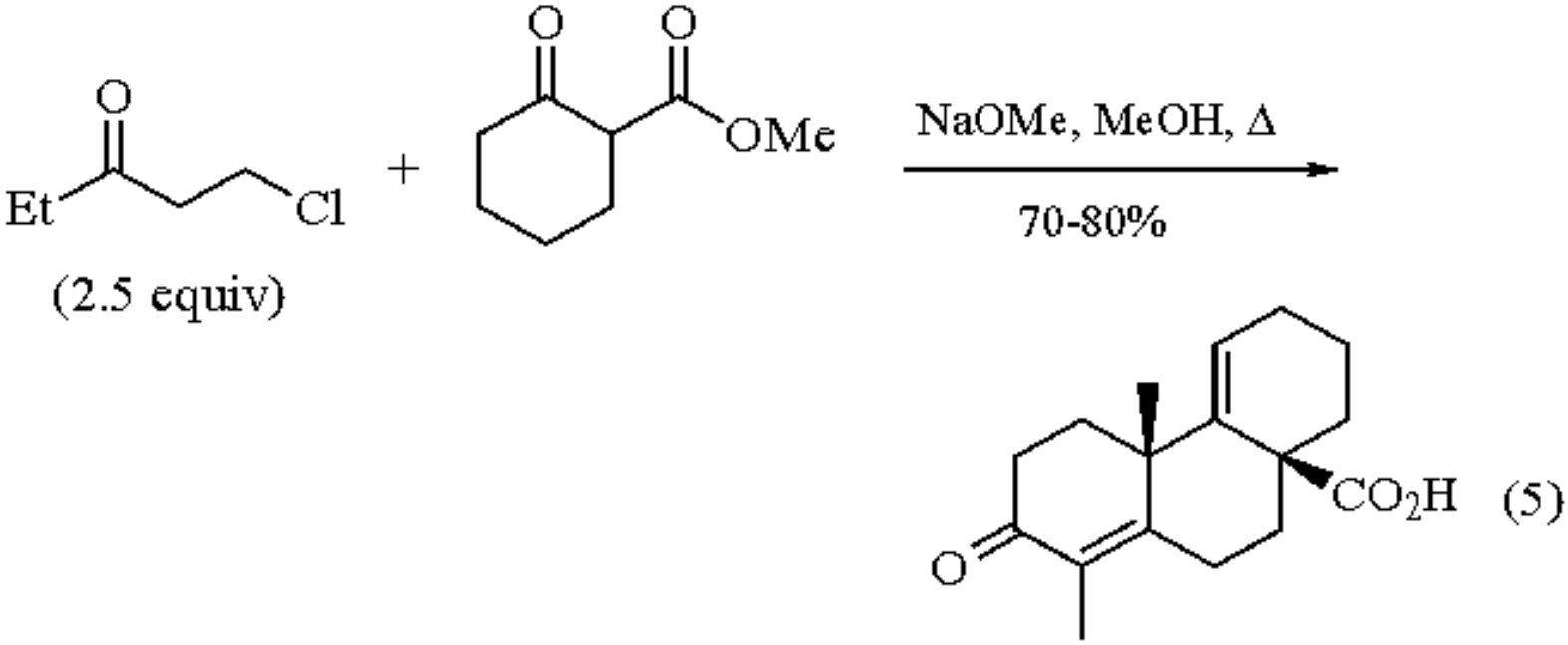

While most of the annulations have been done with a strong base, the reactions with 1,3-dicarbonyl compounds are efficient with ***Triethylamine*** in boiling EtOAc (eq 6).[8] This method has been applied to synthesis of spiroenediones (eq 7).[9]

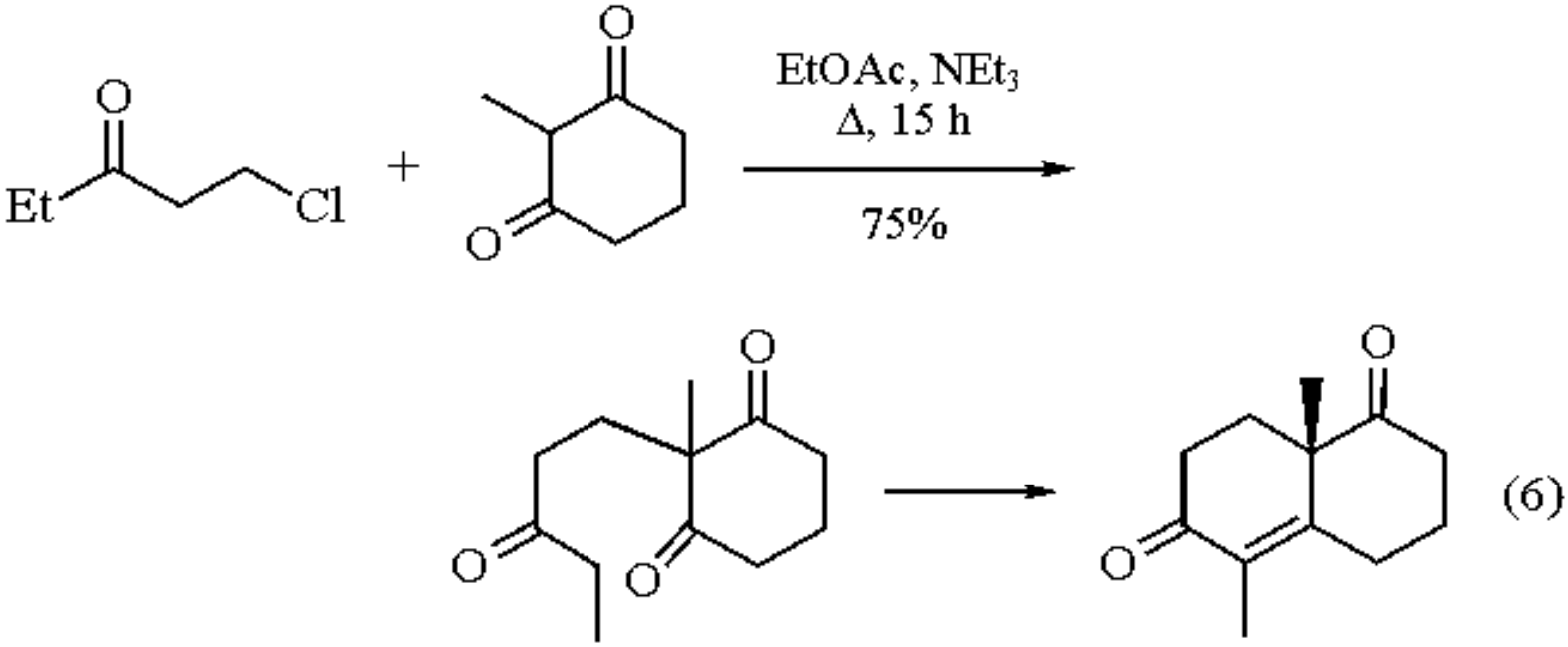

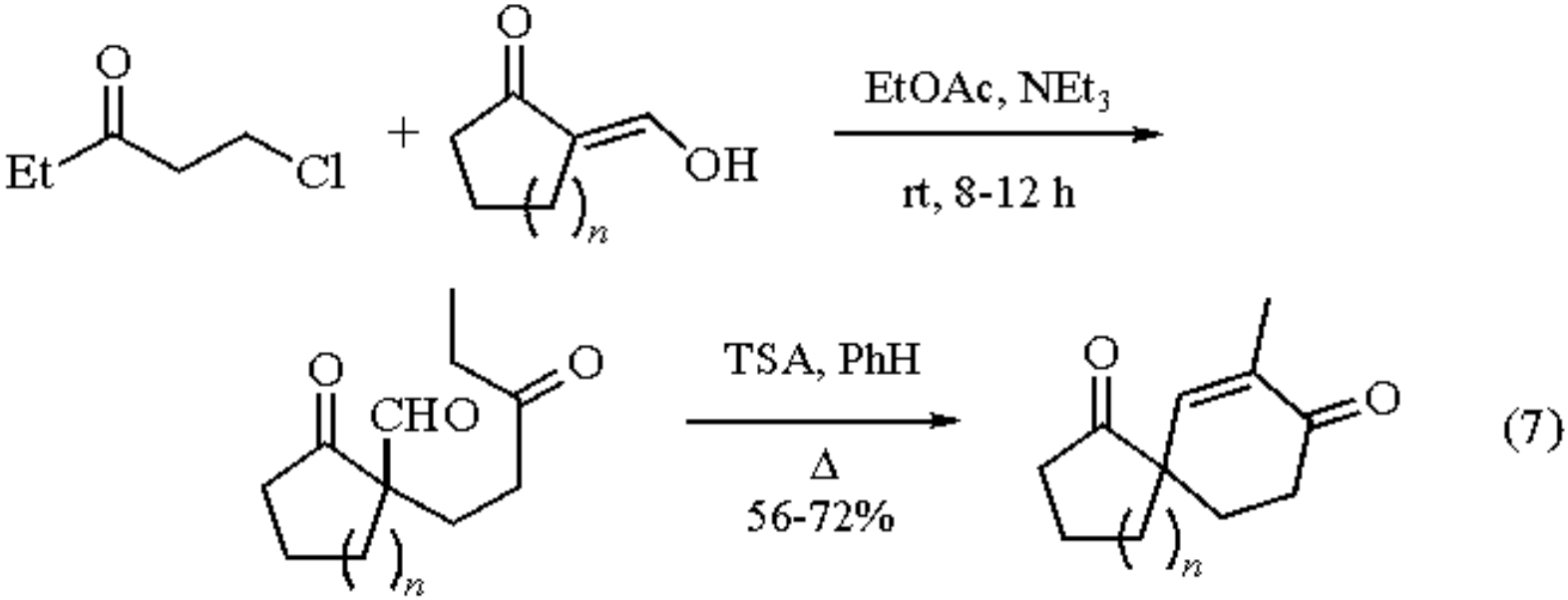

(7)

Quinoline Synthesis.[10]

The reagent was used to prepare a quinoline by a Skraup-type reaction (eq 8). Although the yield is low, it is comparable to the yields from the α,β-unsaturated aldehydes or ketones, which usually are in the 20-30% range.[11]

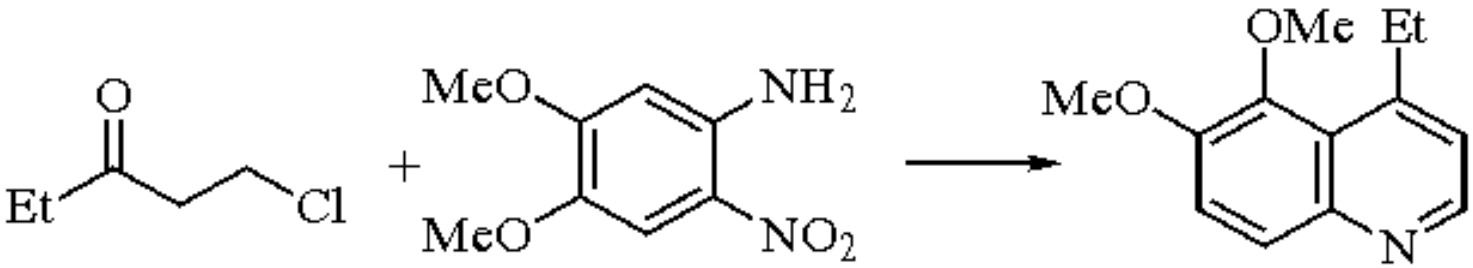

(8)

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The Upjohn Company, Kalamazoo, MI, USA

5-Chloro-1-penten-3-one

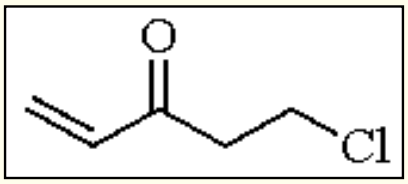

[20757-87-3] · C_5H_7ClO · 5-Chloro-1-penten-3-one · (MW 118.56)

(reagent for the construction of fused ring systems and polyketones with 1,4- and 1,5-carbonyl relationships)

Physical Data: bp 25 °C/0.08 mmHg.

Solubility: sol most organic solvents.

Analysis of Reagent Purity: ^{1}H NMR data are available.[1]

Preparative Method: not commercially available; prepared in a two-step sequence from β-chloropropionyl chloride and ethylene to give 1,5-dichloro-3-pentanone in 95% yield,[2] which is then monodehydrochlorinated in 83% yield;[3] earlier preparations[4,5,6] of 1,5-dichloro-3-pentanone gave much lower yields.

Handling, Storage, and Precautions: use in a fume hood.

Condensations.

The reagent is used to generate a 2,6,10-triketone, which can be condensed to a tricyclic system[1] by multiple intramolecular aldol condensations (eq 1). It is the synthetic equivalent of ***Divinyl Ketone***; however, it allows sequential Michael addition of two different carbonyl compounds to produce an unsymmetrical 2,6,10-triketone, a procedure which is unsuccessful if used with divinyl ketone.

5-Chloro-1-penten-3-one

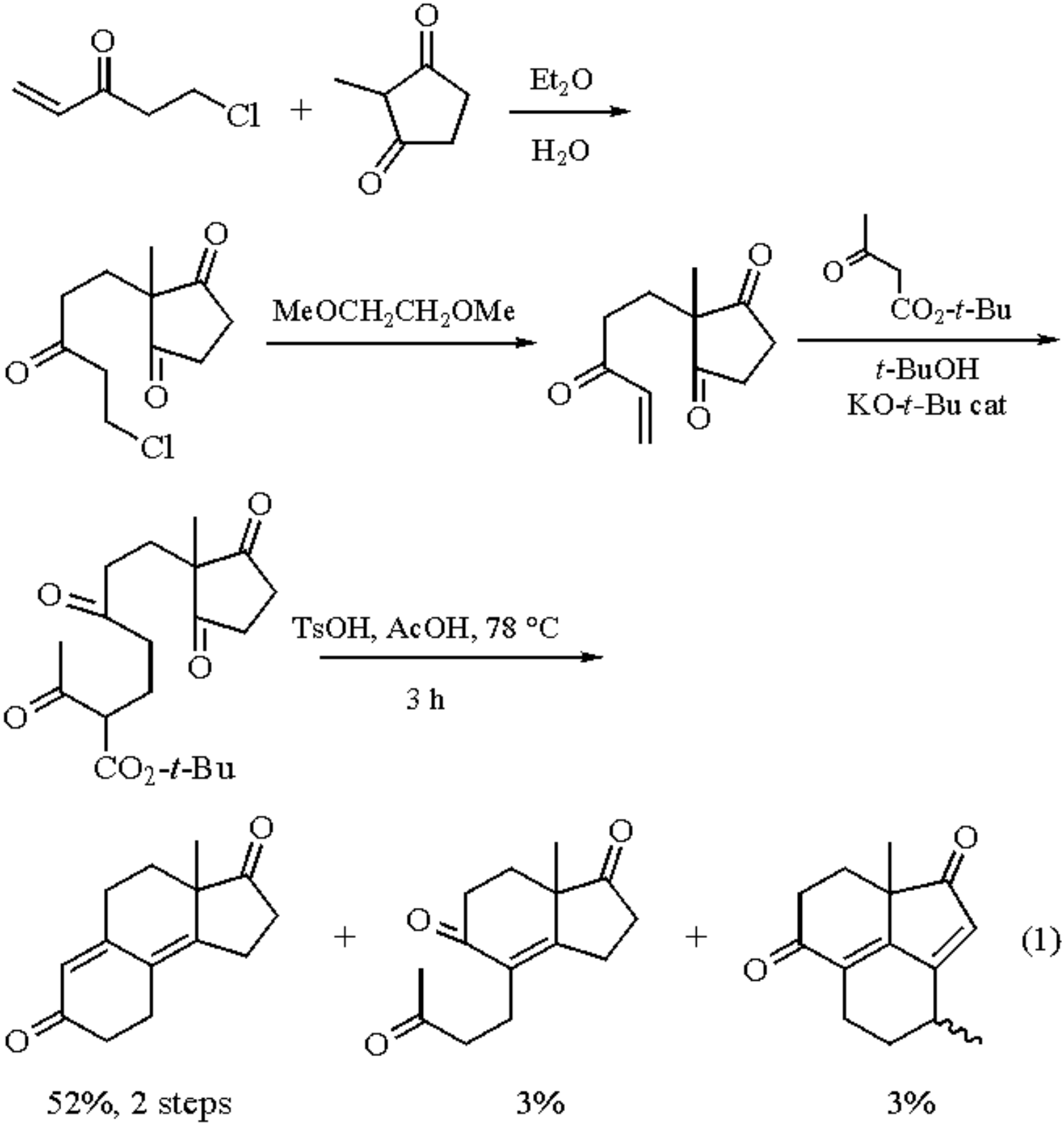

Diels-Alder Reaction.

The reagent undergoes a Diels-Alder reaction to yield β-chloro ketones, which can be dehydrohalogenated to the vinyl ketones. Thiazolium salt catalyzed additions of aldehydes to the vinyl ketones lead to 1,4-diketones, which can be further elaborated by repeated sequences of the same type to 1,4,7-triketones and 1,4,7,10-tetraketones (eq 2).[3]

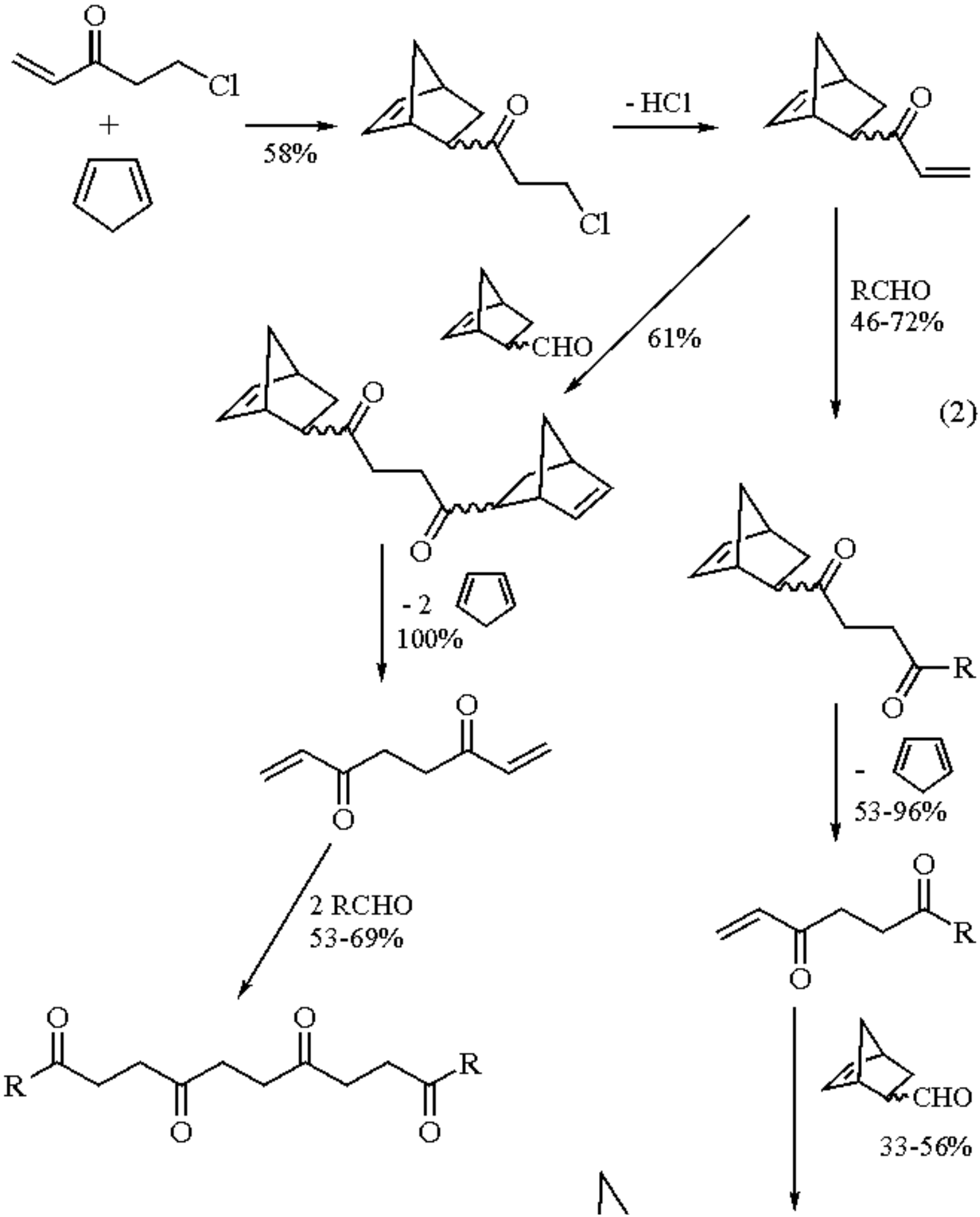
O
Cl
+
58%
O
Cl
- HCl
O
RCHO
46-72%
CHO
61%
O
O
- 2
100%
O
O
2 RCHO
53-69%
O
R
O
O
R
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O
R
O
R
O
R
O
R
O
CHO
33-56%

(2)

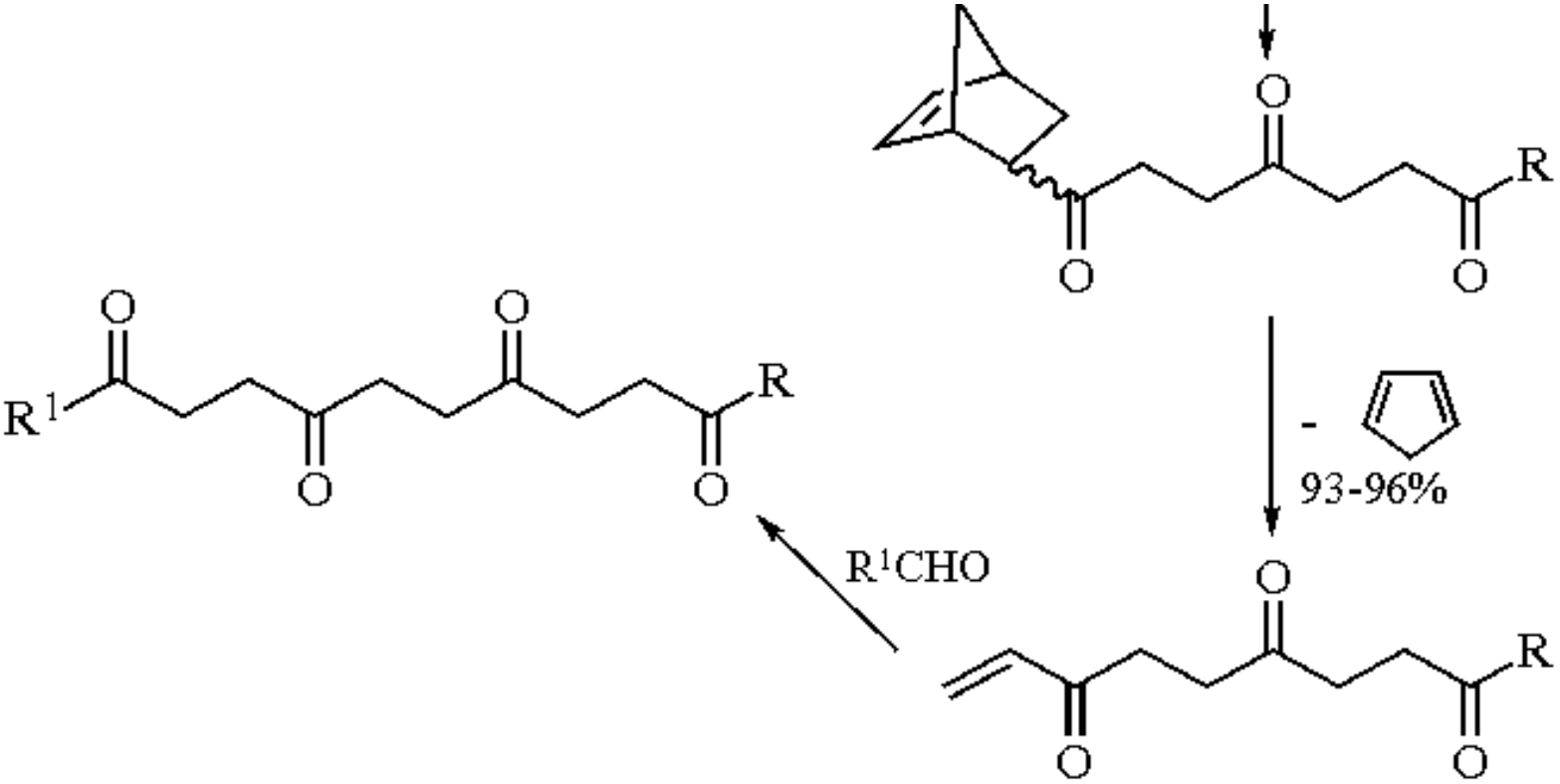

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m-Chloroperbenzoic Acid[1]

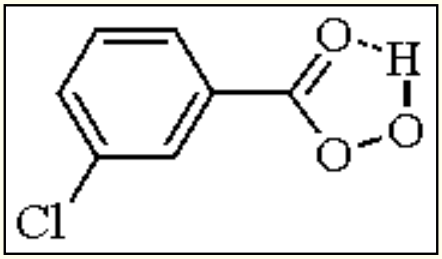

[937-14-4] · $C_7H_5ClO_3$ · *m*-Chloroperbenzoic Acid · (MW 172.57)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes, sulfides, selenides, and amines)

Alternate Name: m-CPBA; MCPBA.

Physical Data: mp 92-94 °C.

Solubility: sol CH_2Cl_2, $CHCl_3$, 1,2-dichloroethane, ethyl acetate, benzene, and ether; slightly sol hexane; insol H_2O.

Form Supplied in: white powder, available with purity of 50%, 85%, and 98% (the rest is 3-chlorobenzoic acid and water).

Analysis of Reagent Purity: iodometry.[2]

Purification: commercial material (purity 85%) is washed with a phosphate buffer of pH 7.5 and dried under reduced pressure to furnish reagent with purity >99%.[3]

Handling, Storage, and Precautions: pure *m*-CPBA is shock sensitive and can deflagrate;[4] potentially explosive, and care is required while carrying out the reactions and during workup.[5] Store in polyethylene containers under refrigeration.

Functional Group Oxidations.

The weak O-O bond of *m*-CPBA undergoes attack by electron-rich substrates such as simple alkenes, alkenes carrying a variety of functional groups (such as ethers, alcohols, esters, ketones, and amides which are inert to this reagent), some aromatic compounds,[6] sulfides, selenides, amines, and N-heterocycles; the result is that an oxygen atom is transferred to the substrate. Ketones and aldehydes undergo oxygen insertion reactions (Baeyer-Villiger

oxidation).

Organic peroxy acids (**1**) readily epoxidize alkenes (eq 1).[1b] This reaction is *syn* stereospecific;[7] the groups (R^1 and R^3) which are *cis* related in the alkene (**2**) are *cis* in the epoxidation product (**3**). The reaction is believed to take place via the transition state (**4**).[8] The reaction rate is high if the group R in (**1**) is electron withdrawing, and the groups R^1, R^2, R^3, and R^4 in (**2**) are electron releasing.

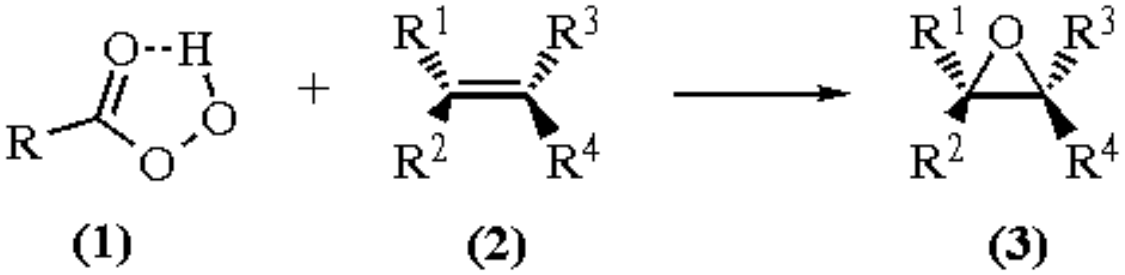

(1)

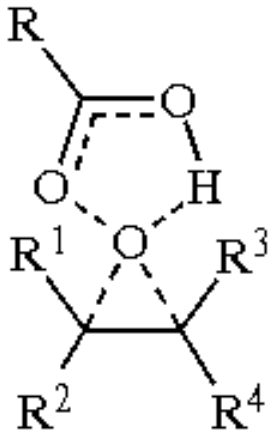

(4)

Epoxidations of alkenes with *m*-CPBA are usually carried out by mixing the reactants in CH_2Cl_2 or $CHCl_3$ at 0-25 °C.[9] After the reaction is complete the reaction mixture is cooled in an ice bath and the precipitated *m*-chlorobenzoic acid is removed by filtration. The organic layer is washed with sodium bisulfite solution, $NaHCO_3$ solution, and brine.[10] The organic layer is dried and concentrated under reduced pressure. Many epoxides have been purified chromatographically; however, some epoxides decompose during chromatography.[11] If distillation (*caution*: check for peroxides[12]) is employed to isolate volatile epoxides, a trace of alkali should be added to avoid acid-catalyzed rearrangement.

Alkenes having low reactivity (due to steric or electronic factors) can be epoxidized at high temperatures and by increasing the reaction time.[13] The weakly nucleophilic α,β-unsaturated ester (**5**) thus furnishes the epoxide (**6**) (eq 2).[13b] When alkenes are epoxidized at 90 °C, best results are obtained if radical inhibitor is added.[13a] For preparing acid-sensitive epoxides (benzyloxiranes, allyloxiranes) the pH of the reaction medium has to be controlled using $NaHCO_3$ (as solid or as aqueous solution),[14] Na_2HPO_4, or by using the *m*-CPBA-KF[9a] reagent.

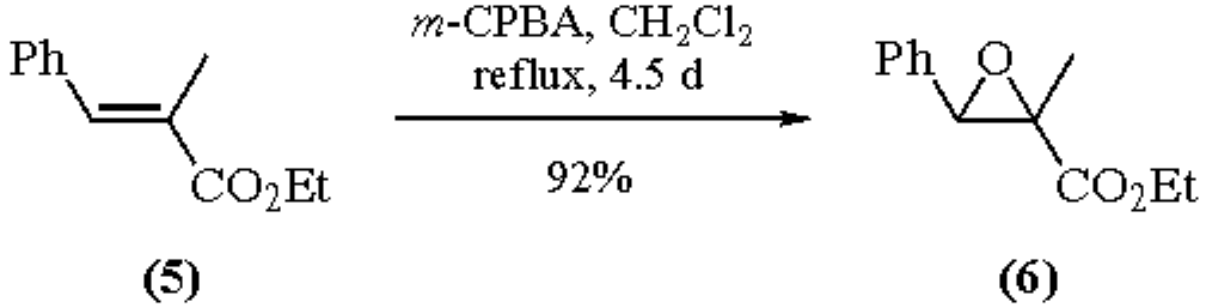

(2)

Regioselective Epoxidations.

In the epoxidation of simple alkenes (**2**) (eq 1), due to the electron-releasing effect of alkyl groups the reactivity rates are tetra- and trisubstituted alkenes > disubstituted alkenes > monosubstituted alkenes.[1a] High regioselectivity is observed in the epoxidation of diene hydrocarbons (e.g. **7**) having double bonds differing in degree of substitution (eq 3).[15] Epoxidation takes place selectively at the more electron-rich C-3-C-4 double bond in the dienes (**8**)[16] and (**9**).[17]

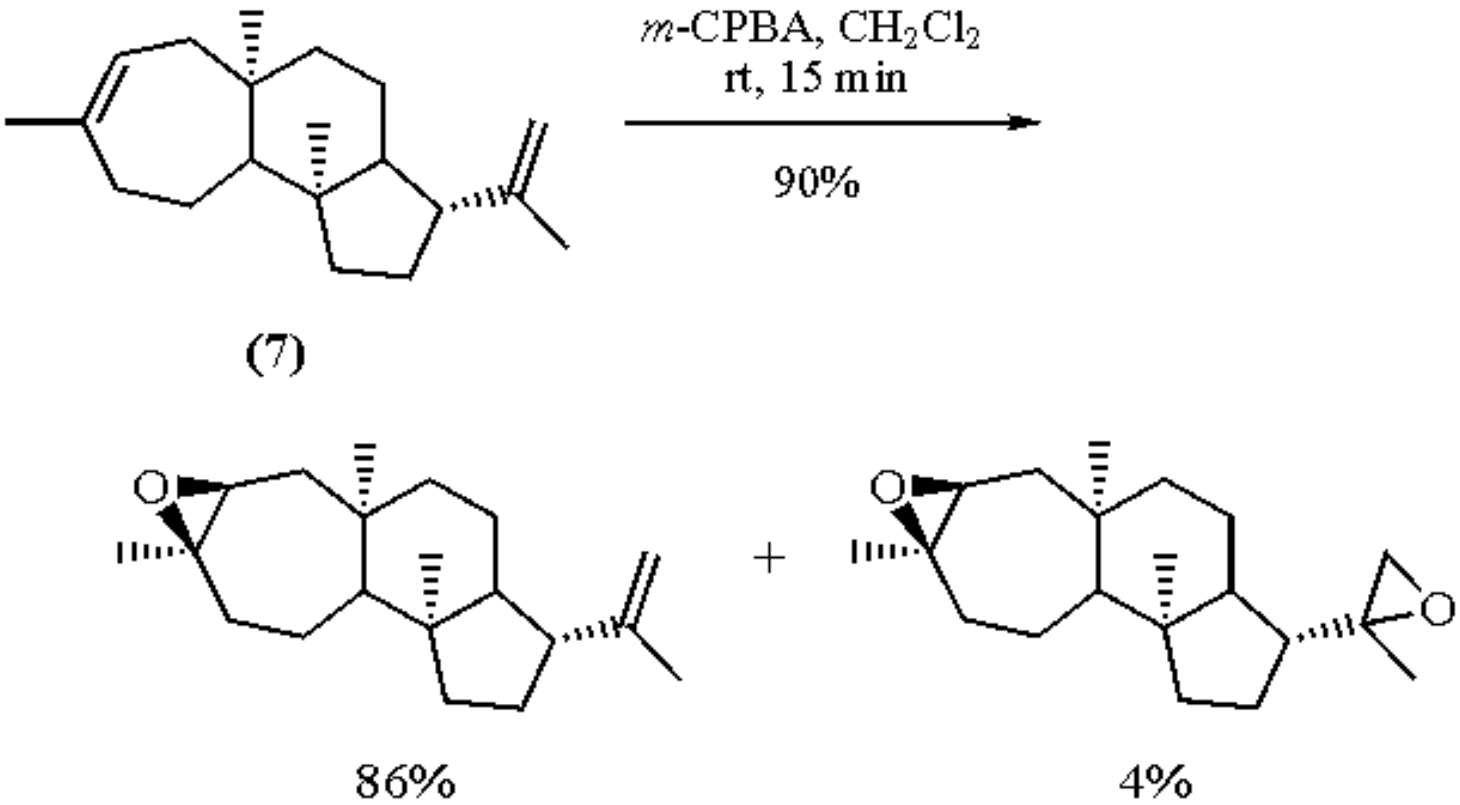

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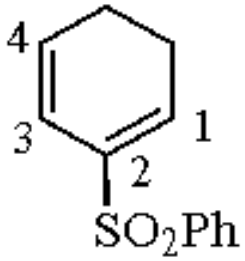

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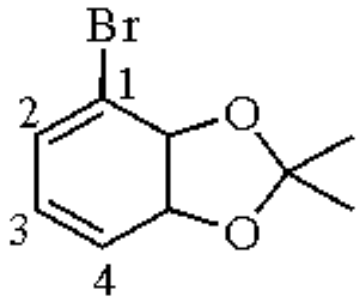

(9)

Diastereoselective Epoxidation of Cyclic Alkenes.

π-Facial stereoselectivity (75% *anti*) is observed in the epoxidation of the allyl ether (**10a**) since reagent approach from the α-face is blocked by the allylic substituent; a higher diastereoselectivity (90% *anti* epoxidation) is observed when the bulkier O-*t*-Bu is located on the allylic carbon (eq 4).[18] Due to steric and other factors, the norbornene (**11**) undergoes selective (99%) epoxidation from the *exo* face.[19] In 7,7-dimethylnorbornene (**12**), approach to the *exo* face is effectively blocked by the methyl substituent at C-7, and (**12**) is epoxidized from the unfavored *endo* face, although much more slowly (1% of the rate of epoxidation of **11**).[19] The geminal methyl group at C-7 is able to block the approach of the peroxy acid even when the double bond is exocyclic to the norbornane ring system (for example, epoxidation of (**13**) proceeds with 86% *exo* attack, while (**14**) is oxidized with 84% *endo* attack). Folded molecules are epoxidized selectively from the less hindered convex side; *m*-CPBA epoxidation of the triene lactone (**15**) takes place from the α-face with 97% stereoselectivity.[20] The triepoxide (**16**) has been obtained in 74% yield by epoxidizing the corresponding triene;[21] in the epoxidation step, six new chiral centers are introduced stereoselectively as a result of steric effects.

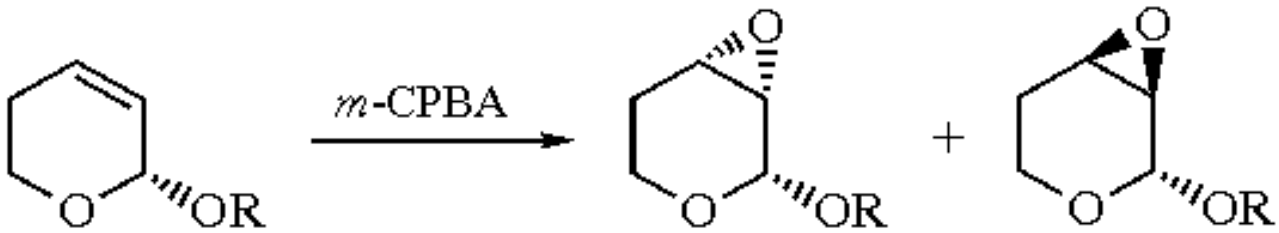

(4)

(10)

(a) R = Me 1:3
(b) R = *t*-Bu 1:9

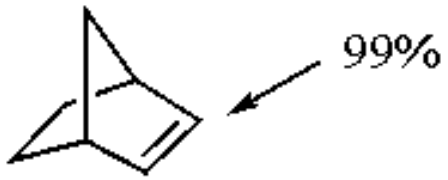

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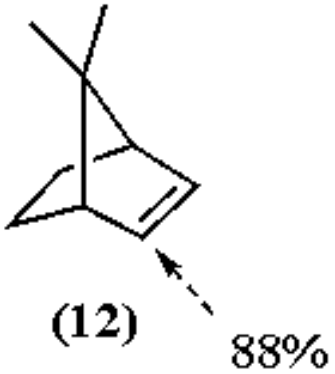

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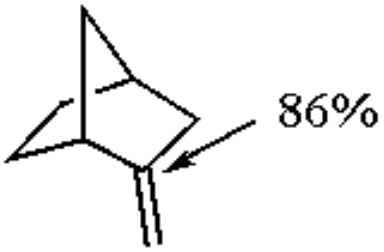

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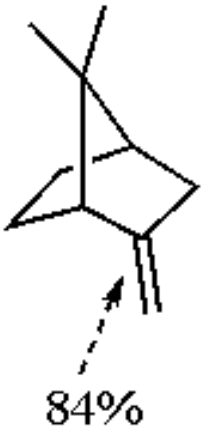

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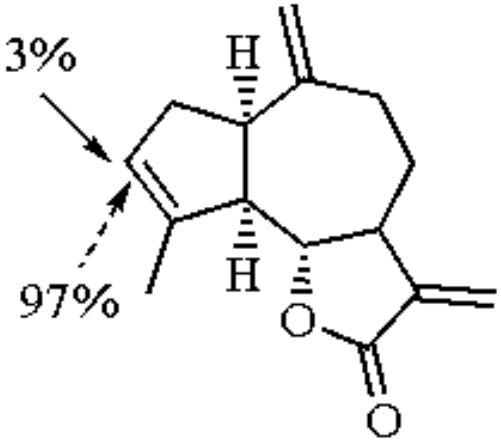

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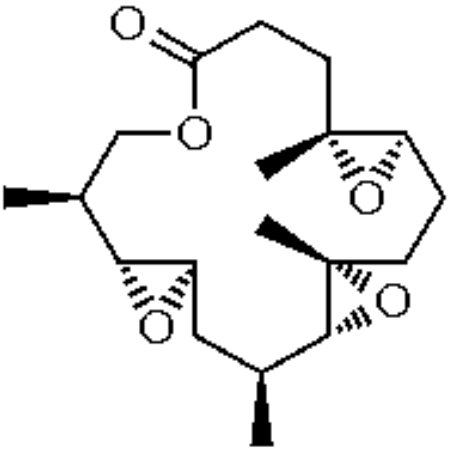

(16)

Unhindered methylenecyclohexanes and related compounds show a moderate preference for axial epoxidation. In the epoxidation of (**17**) the ratio of axial:equatorial attack is 86:14;[22] for the alkene (**18**) the ratio is 75:25.[23]

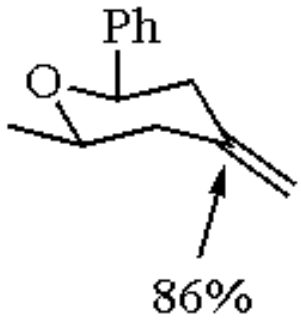

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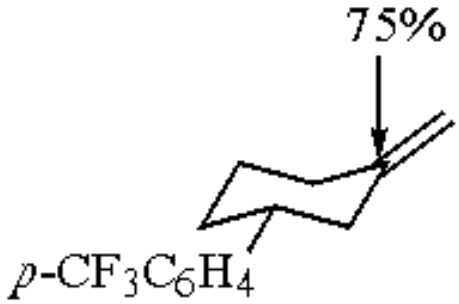

(18)

Epoxidation of Cyclic Alkenes having Directing Groups.

Henbest showed that in the absence of severe steric interference, allylic cyclohexenols are epoxidized stereoselectively by organic peroxy acids to furnish *cis*-epoxy alcohols;[24a] a large number of *cis*-epoxy alcohols have been prepared by epoxidizing allylic cyclohexenols.[7] A mixture (5:1) of labile bisallylic alcohols (**19**) and (**20**) was reacted with *m*-CPBA (eq 5); from the reaction mixture diepoxide (**21**) was isolated as a single isomer.[25] Epoxidation of (*Z*)-cyclooct-2-en-1-ol (**22**) furnishes exclusively (99.8%) the *trans*-epoxide (**23**) (eq 6).[24b] Similar observations have been made subsequently.[26] This result, as well as the stereoselectivity observed during the epoxidation of other allylic alcohols, both cyclic and acylic, has been rationalized on the basis of transition state models.[24,27]

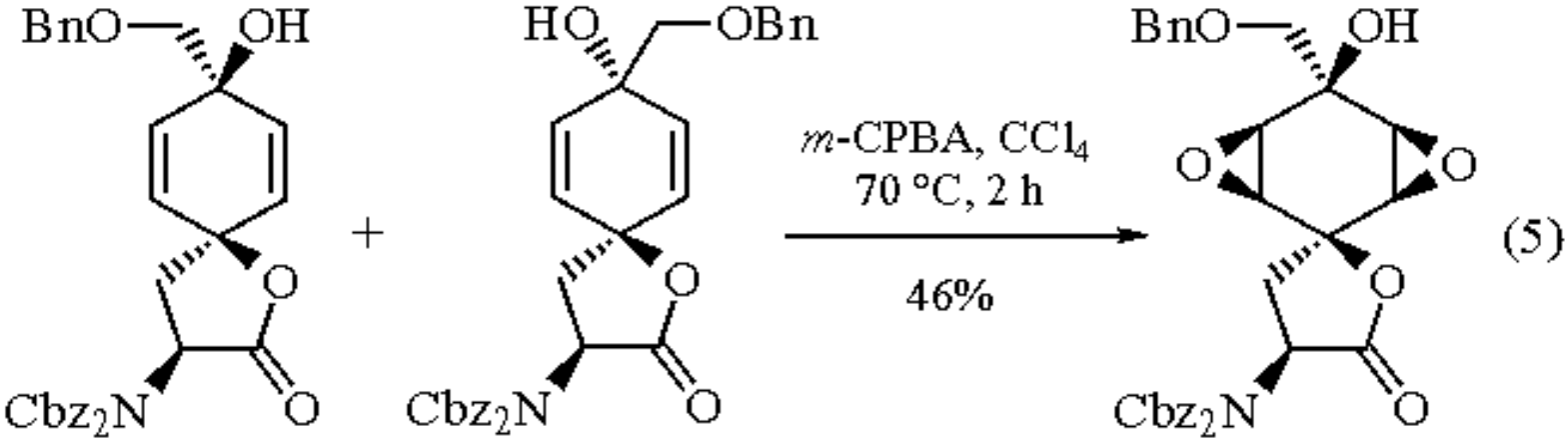

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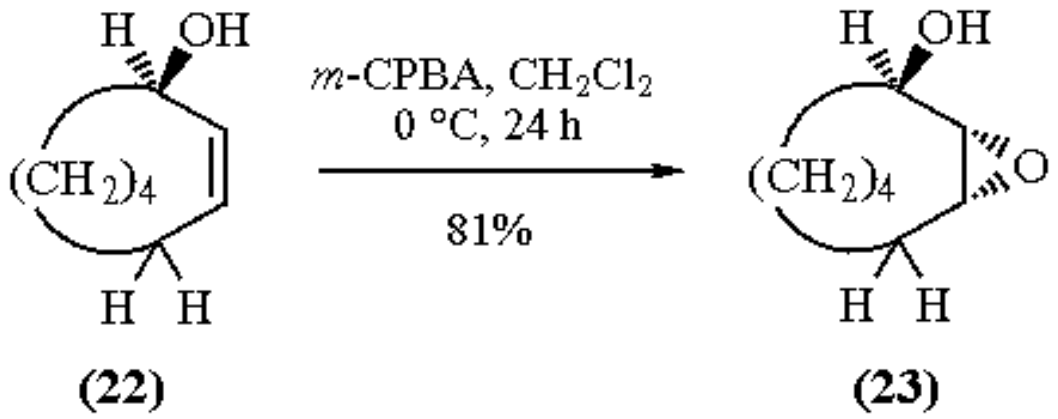

(6)

Stereoselectivity has been observed during the peroxy acid epoxidation of some homoallylic and bishomoallylic alcohols,[28] and the epoxidation of the allylic carbamate (**24**) is *syn* stereoselective (eq 7).[28]

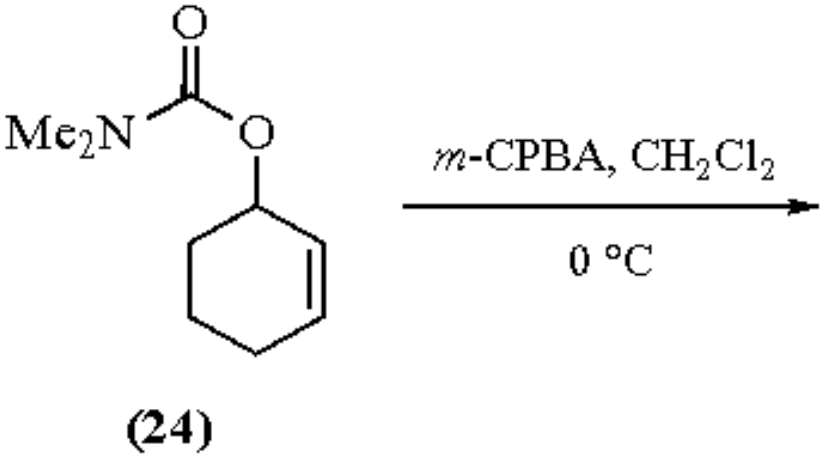

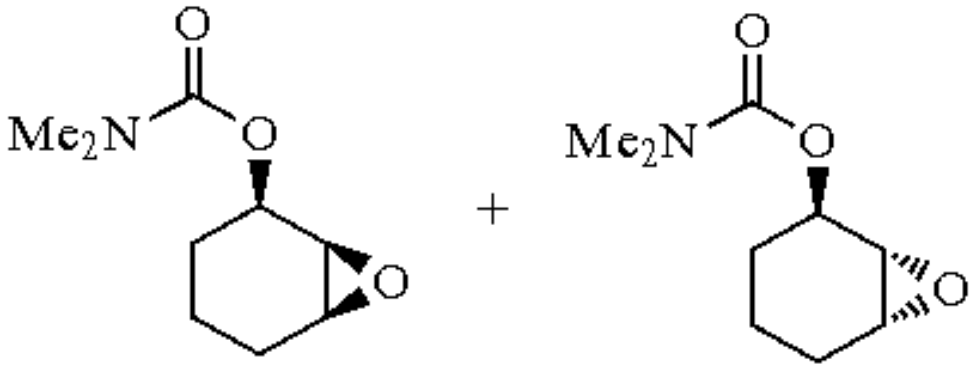

(7)

cis:*trans* = 10:1

Epoxidations of Acyclic Alkenes.

Since acyclic systems normally are not rigid, high stereoselectivity has been observed only when special structural features are present. The presence of functional groups (OH, NH, CO, and ether) which form hydrogen bonds with the peroxy acid can facilitate stereoselective epoxidations by imparting rigidity to the system. High *anti* selectivity (>95%) has been observed in the epoxidation of both (**25**) and (**26**) each of which has a branched substituent adjacent to the carbon carrying the silicon group.[29] High *anti* selectivities have been noted during the epoxidation of (**27**)

(95%),[30] (**28**) (96%),[31] (**29**) (95%),[32] and (**30**) (96%).[33] High *syn* selectivity has been observed in the reactions of (**31**) (98%)[33] and (**32**) (93%).[34] When the allyl alcohol (**28**) reacts with *m*-CPBA, in the transition state the reagent is hydrogen-bonded to the ether oxygen as well as to allylic hydroxyl. The high selectivity is due to the cooperative effect of the hydroxyl group and the ether oxygen.[31]

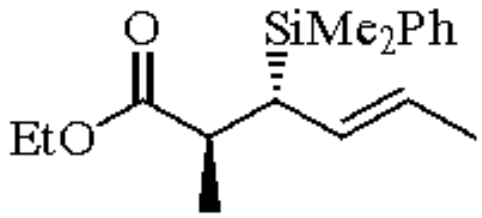

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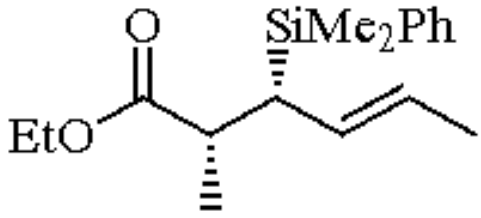

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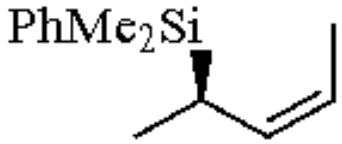

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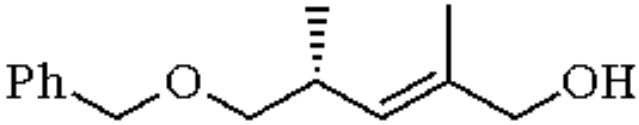

(28)

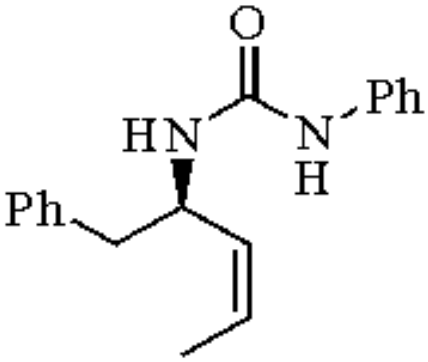

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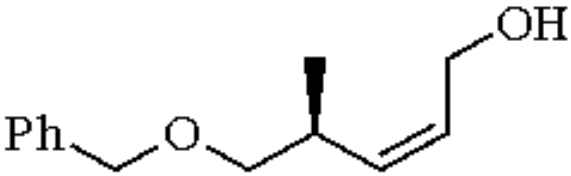

(30)

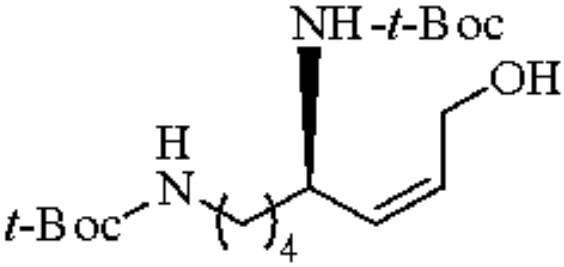

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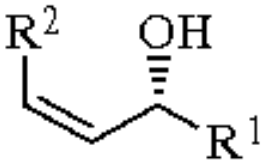

(32) $R^1 = (CH_2)_6CO_2Me$
$R^2 = (CH_2)_5Me$

High stereoselectivity has also been observed in the epoxidation of some acyclic homoallylic alcohols.[35]

Oxidation of Enol Silyl Ethers and Furans.

Epoxides of enol silyl ethers undergo facile ring opening and only in rare cases have stable epoxides been isolated.[36] α-Hydroxy enones have been prepared in two steps from α,β-unsaturated ketones; the enol silyl ether (**33**) prepared from the corresponding enone is treated with *m*-CPBA and the resulting product reacts with triethylammonium fluoride to furnish an α-hydroxy enone (**34**) (eq 8).[37] This method has also been used for the preparation of α-hydroxy ketones,[38] α-hydroxy acids,[39] and α-hydroxy esters. As illustrated in (eq 9), aldehydes have been converted to protected α-hydroxy aldehydes in a similar fashion.[40] Epoxidation of enol silyl ethers according to eq 10 has been used in synthesizing α,α´-dihydroxy ketones from methyl secondary alkyl ketones; the silyl ether (**36**) furnishes the corresponding dihydroxy ketone quantitatively upon brief acidic treatment.[41] Peroxy acid oxidation of furfuryl alcohols yields pyranones according to eq 11.[42,43] Furfurylamides also react similarly.[44]

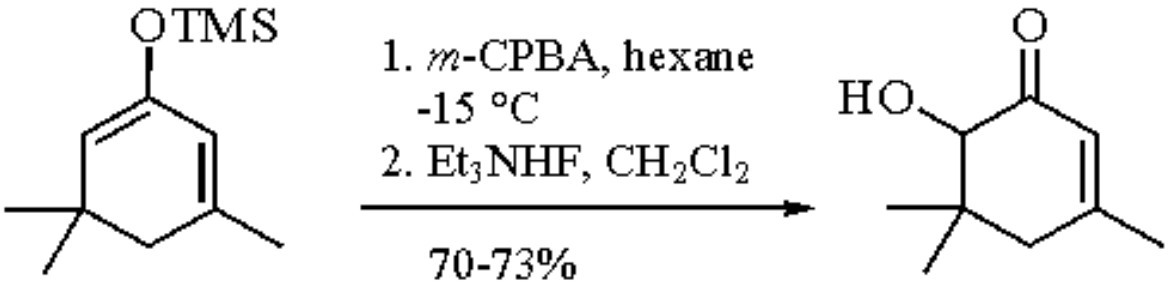

(8)

(33) **(34)**

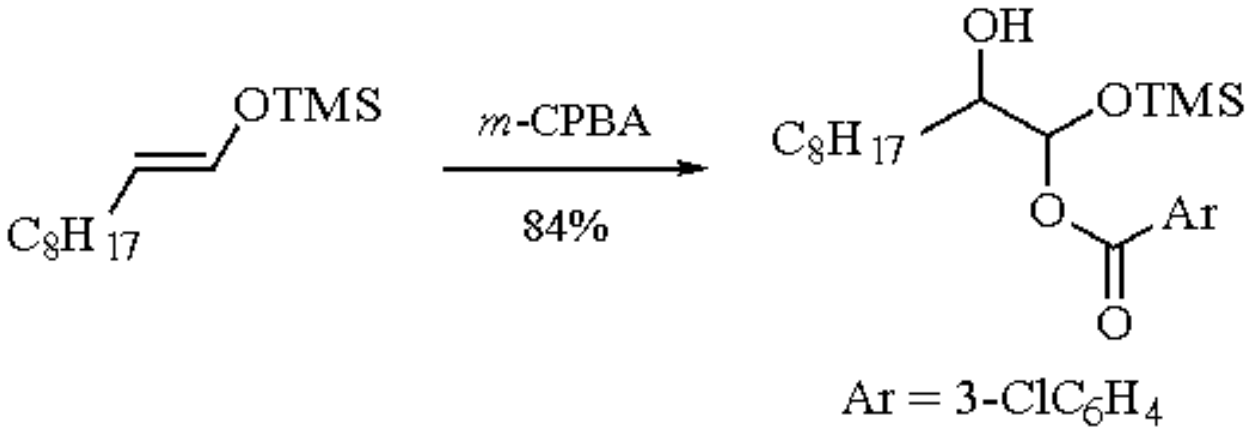

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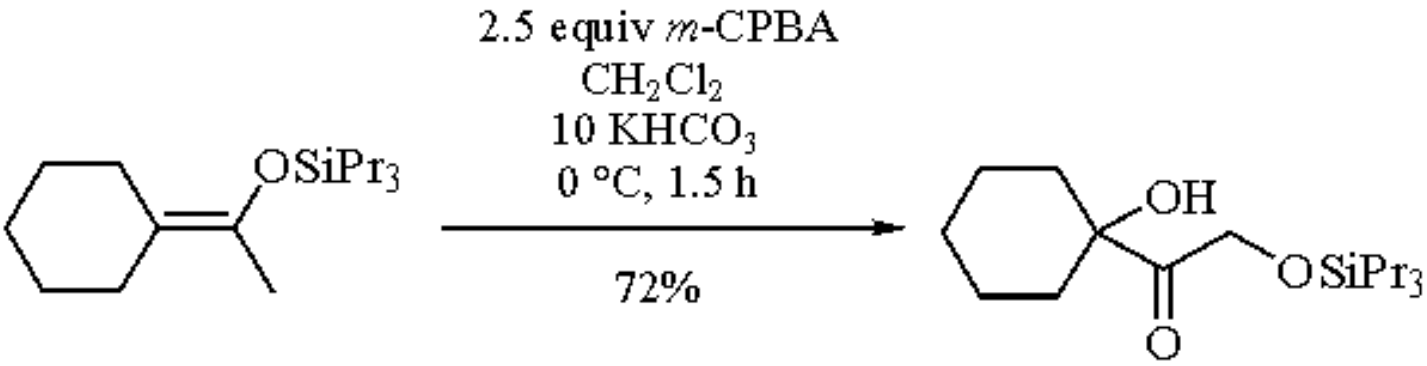

(10)

(35) **(36)**

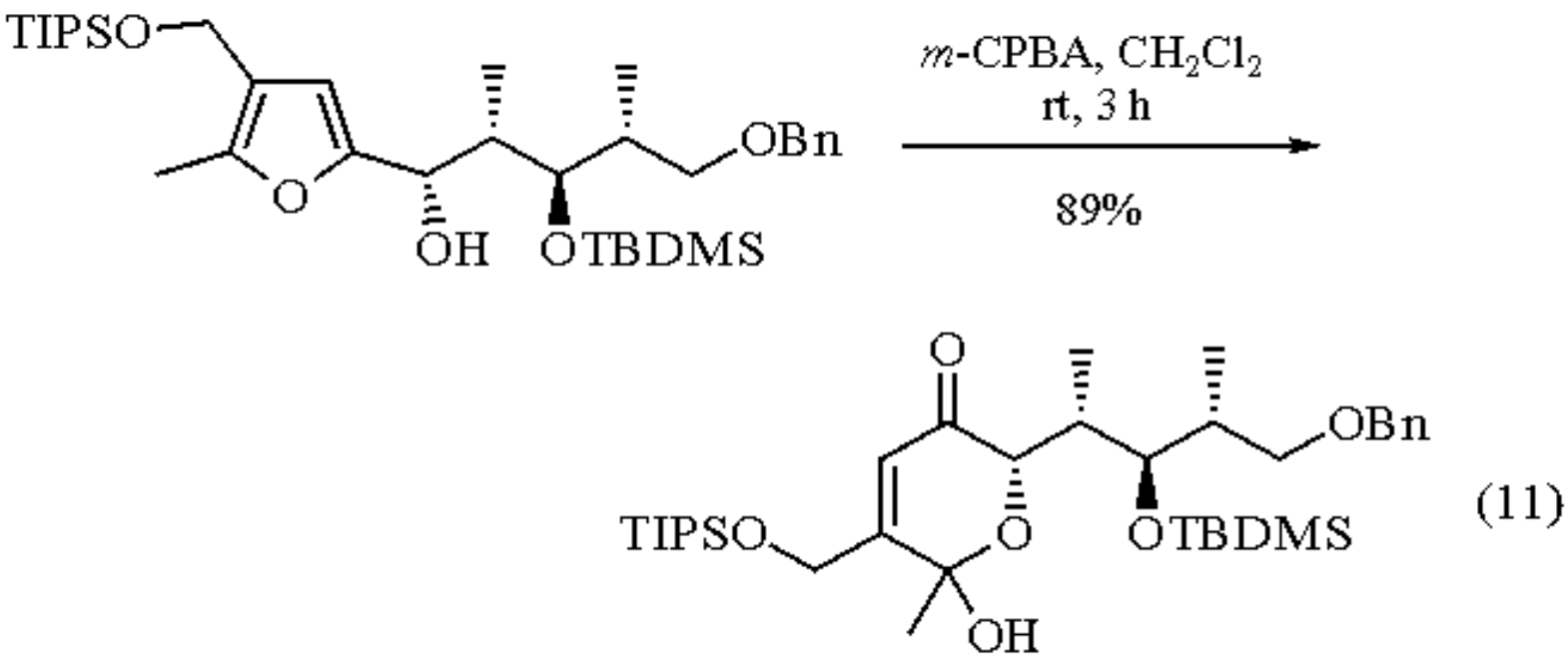

Baeyer-Villiger Rearrangement.

Reaction of a ketone (**37**) with peroxy acid results in oxygen insertion to furnish the esters (**38**) and (**39**). This reaction, known as the Baeyer-Villiger rearrangement, has been reviewed recently.[45] Cyclobutanones undergo very facile rearrangement with peroxy acids, as well as with ***Hydrogen Peroxide*** in presence of base. The cyclobutanone (**40**) reacted readily with *m*-CPBA to furnish regio-, stereo-, and chemoselectively the lactone (**41**) (eq 12),[38b] which was elaborated to gingkolide. Baeyer-Villiger reaction of (**40**) with H_2O_2/base furnished a γ-lactone which was the regioisomer of (**41**). When 1,2,3,8,9,9a-hexahydro-1-methyl-3a,8-methano-3a*H*-cyclopentacycloocten-10-one, which has double bonds as well as a keto group, was treated with *m*-CPBA, exclusive alkene epoxidation was observed.[46] Ketones having stannyl groups on the β-carbon undergo a tin-directed Baeyer-Villiger reaction.[47]

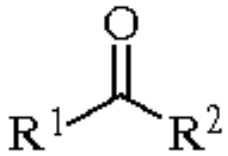

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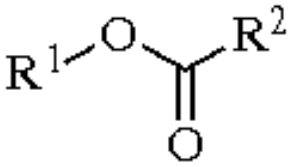

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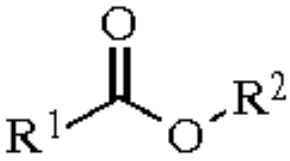

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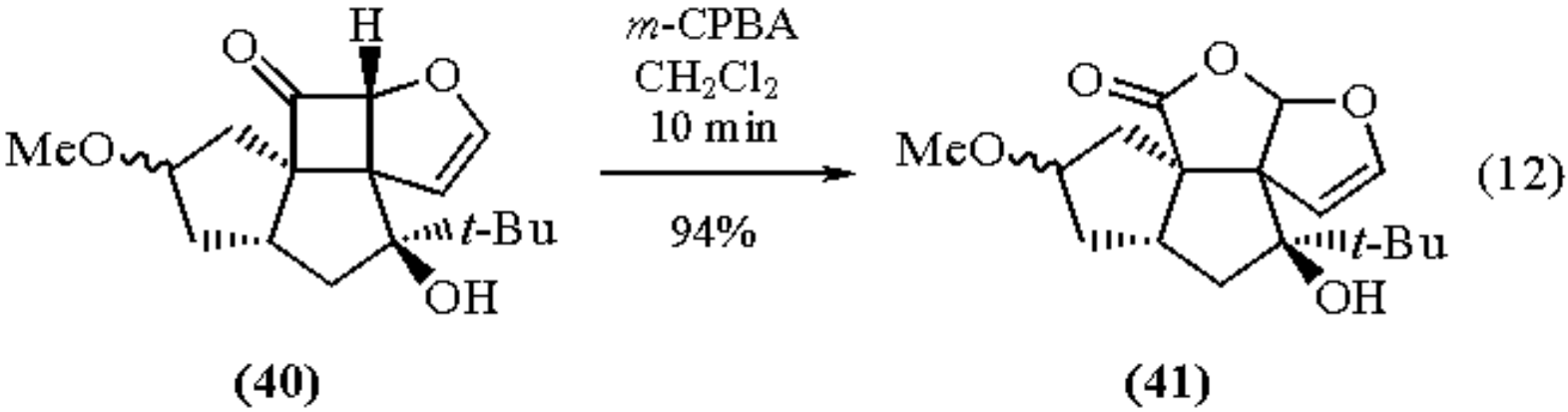

Oxidation of Nitrogen-Containing Compounds.

Primary amines are oxidized by *m*-CPBA to the corresponding nitro compounds. One of the intermediates formed in this reaction is the corresponding nitroso compound, which reacts sluggishly with the reagent. High yields are obtained by carrying out the reaction at a high temperature (~83 °C) and increasing the reaction time (3 hours). For example, *n*-hexylamine is oxidized to 1-nitrohexane in 66% yield.[48] When a substrate having the amino group at a chiral center was oxidized, the nitro compound was formed with substantial (~95%) retention of configuration.[49]

m-CPBA oxidation of the sulfilimine (**42**) prepared from 2-aminopyridine, furnished 2-nitrosopyridine (**43**) (eq 13).[50]

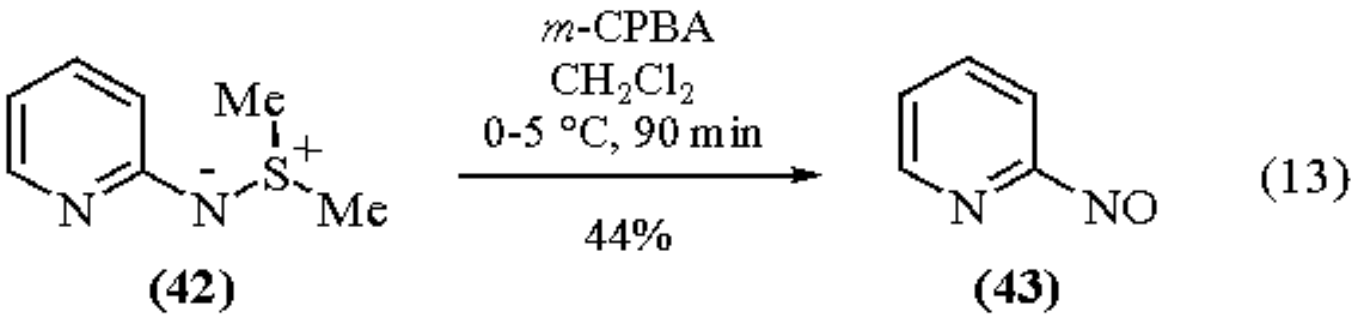

Secondary amines have been oxidized to hydroxylamines with *m*-CPBA.[26b] In this reaction, substantial amounts of nitrone as byproduct are expected. (The best method for the preparation of hydroxylamines is to oxidize the secondary amine with 2-(phenylsulfonyl)-3-aryloxaziridine (see e.g. ***(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine***) to the nitrone, and then to reduce the nitrone with ***Sodium Cyanoborohydride***).[51]

m-CPBA oxidation of N-heterocycles furnishes in high yields the corresponding *N*-oxides.[52] Several tertiary *N*-oxides have been prepared by the reaction of tertiary amines with *m*-CPBA in $CHCl_3$ at 0-25 °C and employing chromatography on alkaline alumina; for example, trimethylamine *N*-oxide was obtained in 96% yield.[53] When the optically pure tertiary amine (**44**) is oxidized with *m*-CPBA, the initially formed amine oxide rearranges to the hydroxylamine (**45**) with complete 1,3-transfer of chirality (eq 14).[54]

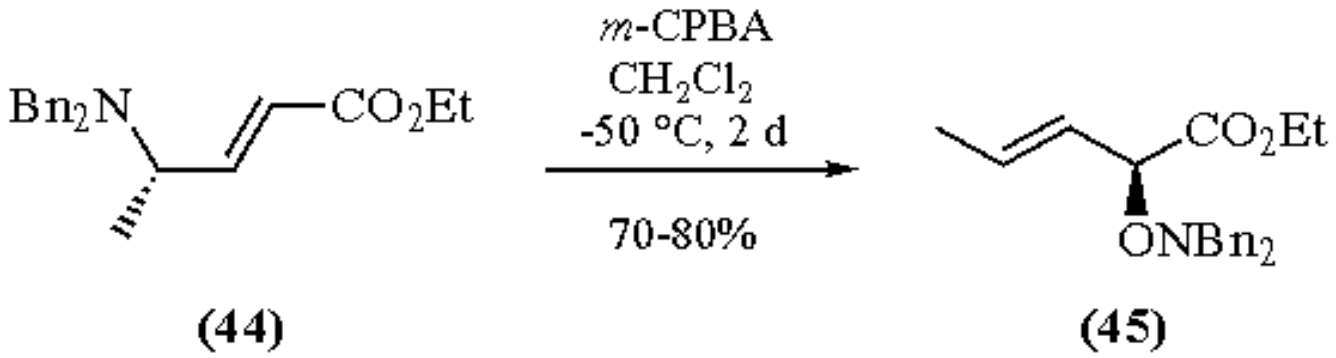

(14)

Reaction of *m*-CPBA with the isoxazole (**46**) furnishes the nitrone (**47**) (eq 15).[55] *m*-CPBA oxidation of (-)-isoxazole (**48**) and subsequent workup results in the formation of the (-)-cyclopentanone (**49**) (eq 16);[56] the initially formed nitrone is hydrolyzed during workup. The oxaziridine (**51**) has been prepared by epoxidizing the sulfonimine (**50**) (eq 17).[57]

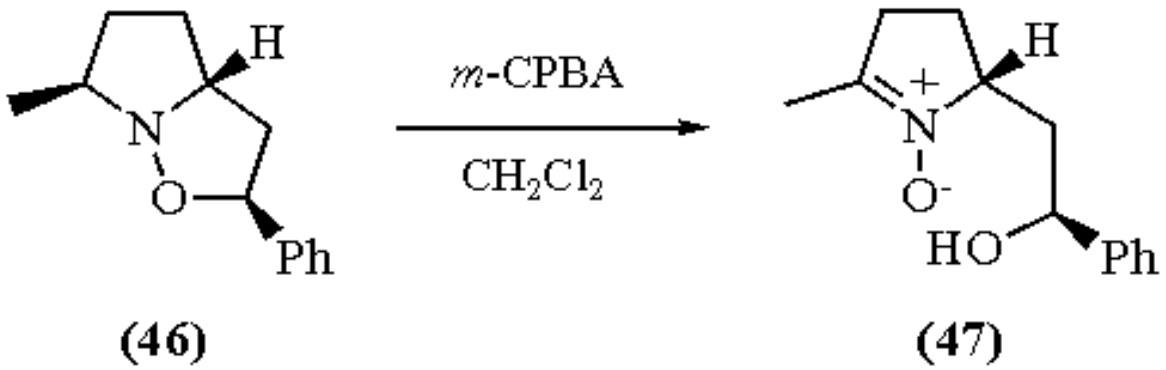

(15)

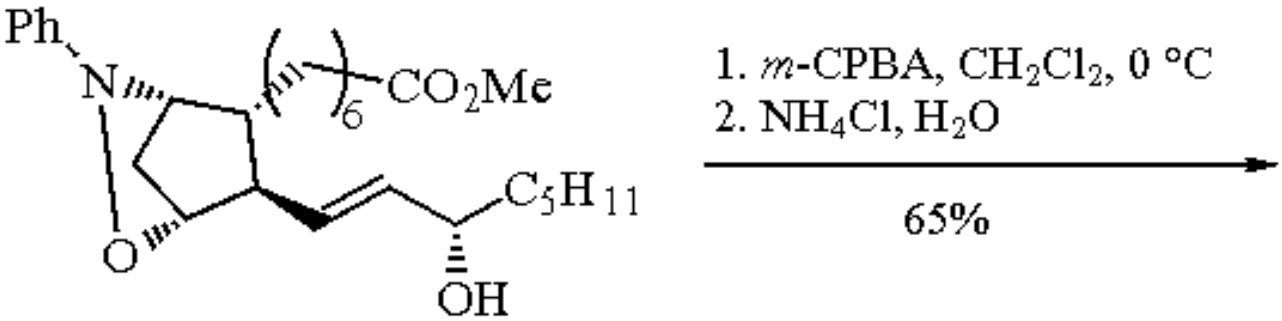

(-)-(**48**) 86% ee

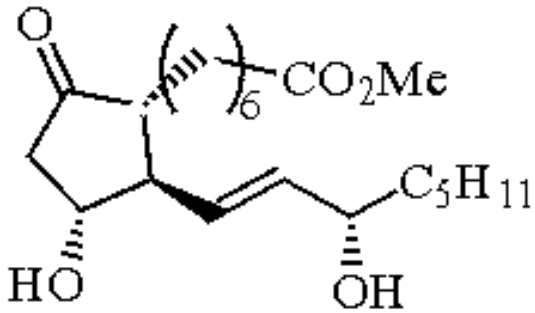

(16)

(-)-(**49**) 86% ee

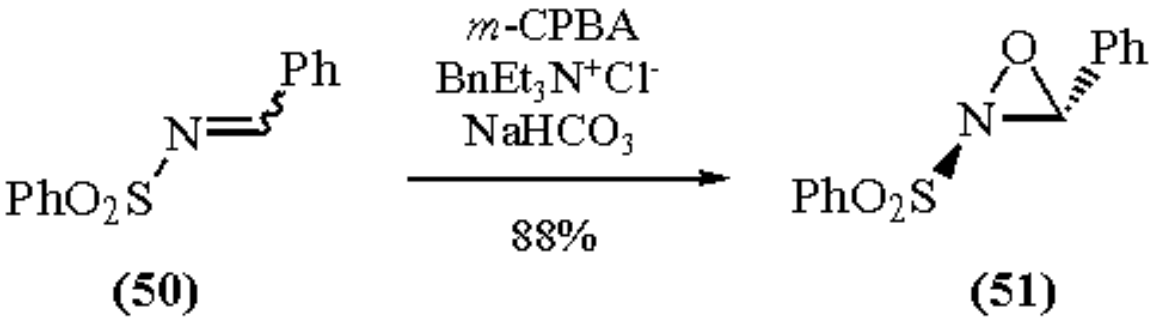

(17)

The cleavage of the *N*,*N*-dimethylhydrazone (**52**) proceeds rapidly in the presence of *m*-CPBA, even at low temperatures, to furnish the ketone (**53**), without isomerization to the more stable *cis* isomer (eq 18).[58]

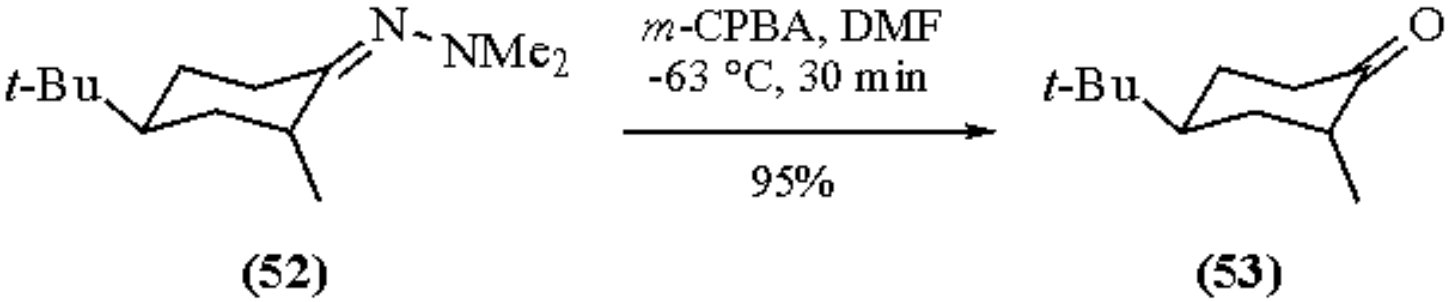

(18)

Oxidation of Phosphorus-Containing Compounds.

m-CPBA oxidation of the phosphite (**54**) is stereospecific; it furnishes the phosphate (**55**) (eq 19).[59a] However, aqueous ***Iodine*** is the reagent of choice for the oxidation of nucleotidic phosphite triesters.[59b] *m*-CPBA oxidation of thiophosphate triesters furnishes the corresponding phosphate esters with retention of configuration.[60]

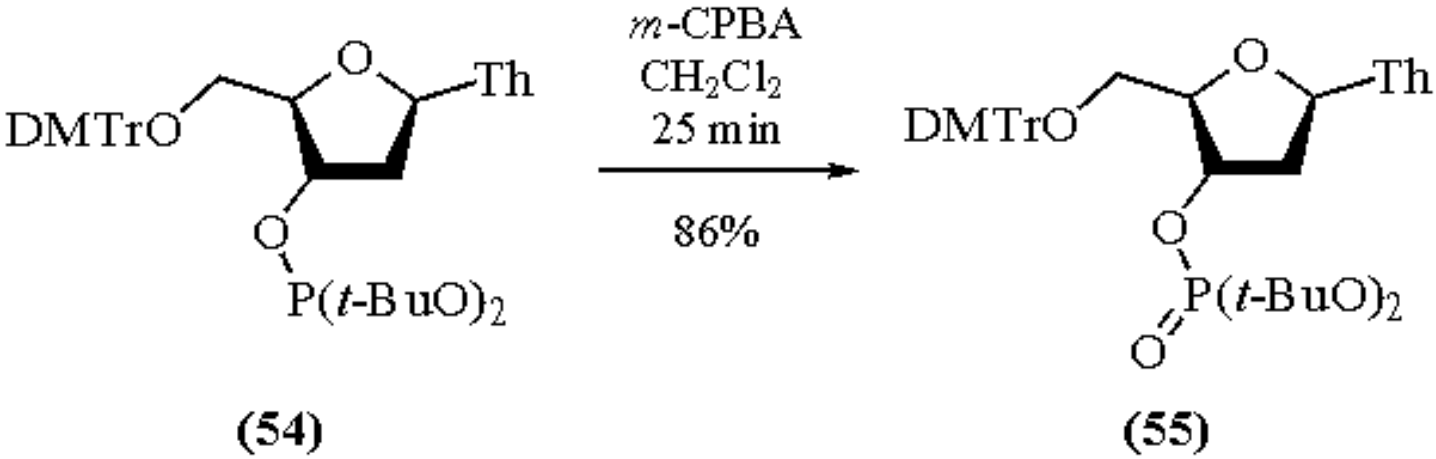

(19)

Oxidation of Sulfur-Containing Compounds.

n-Butanethiol is oxidized by *m*-CPBA in CH_2Cl_2 at -30 °C to furnish in 82% yield *n*-butanesulfinic acid (*n*-$BuSO_2H$); other thiols react similarly.[61] Sulfides are oxidized chemoselectively to sulfoxides by *m*-CPBA; the reaction is fast even at -70 °C, and the product is free from sulfone.[62] Three reagents (*m*-CPBA, ***Sodium Periodate***, and

Iodosylbenzene) are regarded as ideal for the oxidation of sulfides to sulfoxides.[63] Good diastereoselectivity has been observed in the oxidation of the sulfide (**56**) (eq 20).[64] Sulfides carrying suitably located hydroxyl groups are oxidized diastereoselectively, due to the directing influence of the hydroxyl group.[65] A phenyl sulfide carrying a variety of functional groups (epoxide, hydroxyl, ether, carbamate, and enediyne) has been chemoselectively oxidized in 99% yield to the corresponding sulfone.[52]

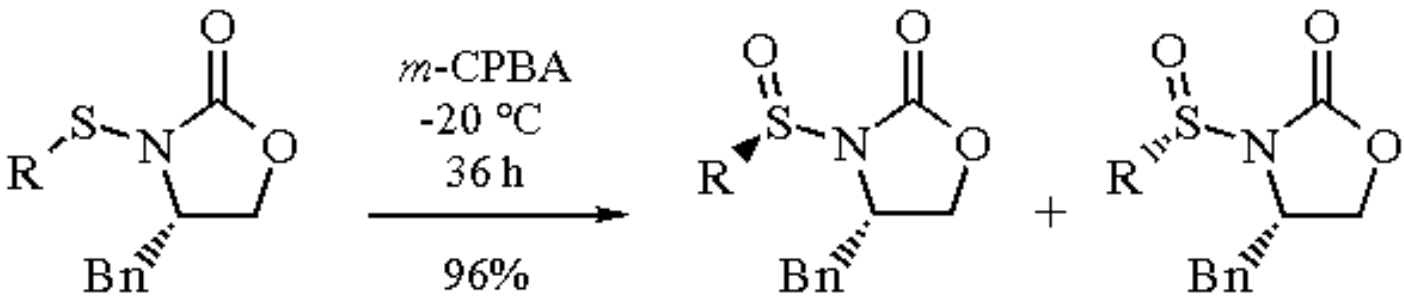

(20)

(56) R = Ph

Allenyl chloromethyl sulfoxide (**57**) reacts with *m*-CPBA to furnish allenyl chloromethyl sulfone (**58**) (eq 21).[66] The enethiolizable thioketone (**59**) has been oxidized to the (*E*)-sulfine (**60**) (eq 22).[67] The 2´-deoxy-4-pyrimidinone (**62**) has been prepared by reacting the 2-thiopyrimidine nucleoside (**61**) with *m*-CPBA (eq 23).[68] Thioamides have been transformed to the amides in high yields.[69]

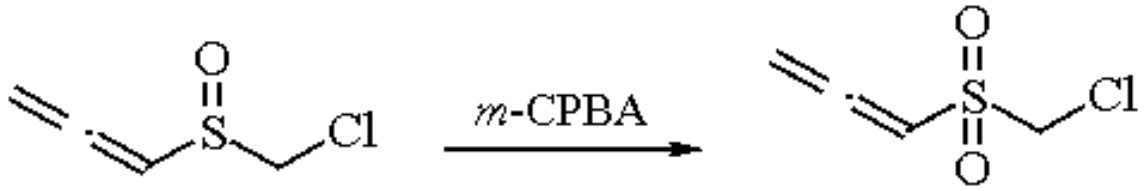

(21)

(57) **(58)**

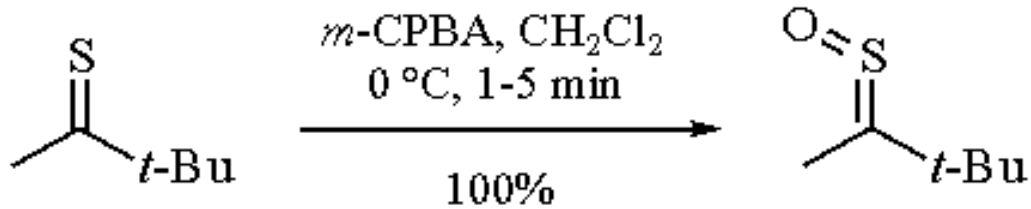

(22)

(59) **(60)**

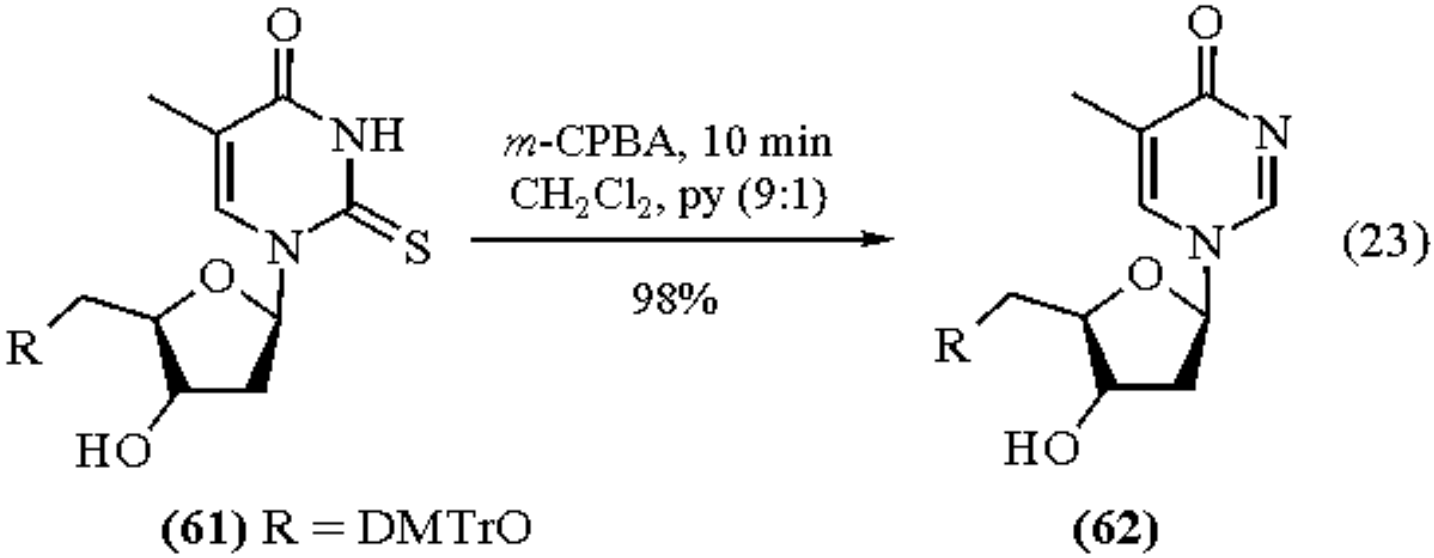

Oxidation of Selenides.

Phenyl selenides react rapidly with *m*-CPBA at -10 °C to form phenyl selenoxides,[70a] which on warming to 0 °C or at rt undergo facile *cis* elimination. This procedure for introducing unsaturation under mild conditions has been used in the synthesis of thermally sensitive compounds; for an example see eq 24.[70b] The selenonyl moiety is a good leaving group, and its generation in the substrate can lead to the formation of cyclic compounds. The oxazoline (**64**) has been synthesized through oxidation of the selenide (**63**) and treatment of the oxidized material with base (eq 25).[71]

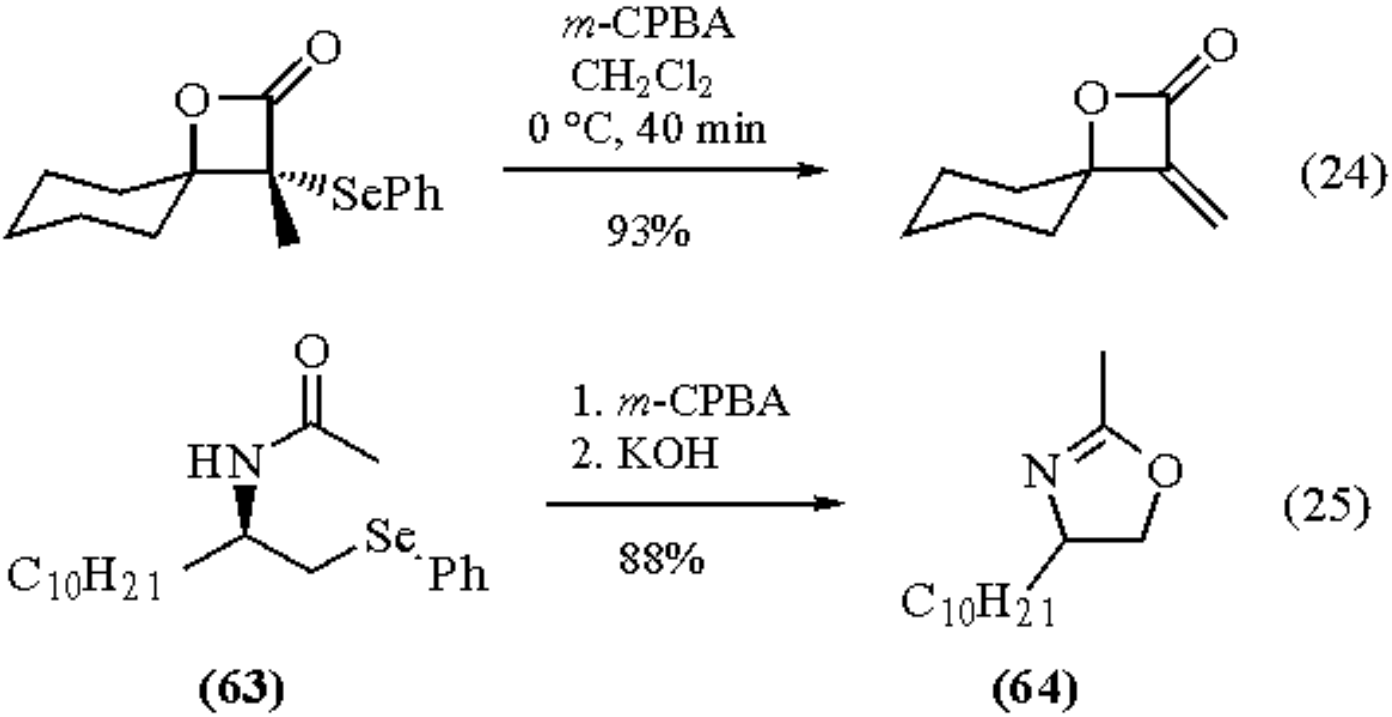

Oxidation of Allylic Iodides.

m-CPBA oxidation of the primary allylic iodide (**65**) furnishes the secondary allylic alcohol (**66**) (eq 26);[72] this

involves rearrangement of the iodoxy compound formed initially.

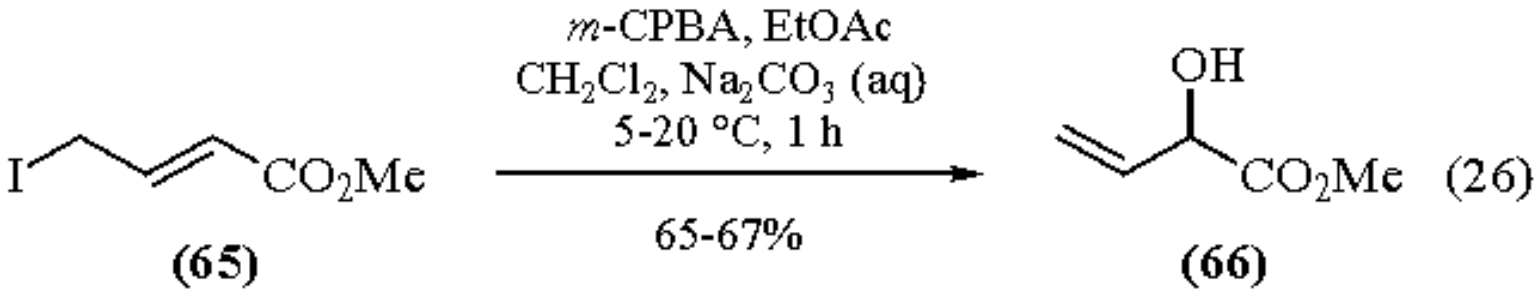

Comparison with Other Reagents.

To effect epoxidation, the most commonly used reagents are *m*-CPBA, ***Peracetic Acid*** (PAA), and ***Trifluoroperacetic Acid*** (TFPAA). TFPAA is not commercially available. *m*-CPBA is more reactive than PAA and is the reagent of choice for laboratory-scale reactions. For large-scale epoxidations the cheaper PAA is preferred. The highly reactive TFPAA is used for unreactive and heat-sensitive substrates; its reactivity permits the use of low reaction temperatures. The recently introduced reagent magnesium monoperphthalate (MMPP) (see ***Monoperoxyphthalic Acid***) is more stable than *m*-CPBA and has many applications.[4]

Epoxidations of hydroxyalkenes have been carried out with ***t-Butyl Hydroperoxide***/vanadium (TBHP/V). *m*-CPBA epoxidation of (*Z*)-cyclooct-2-en-1-ol is *anti* selective; with TBHP/V it is *cis* selective.[24b] Similar differences have been noticed in some acyclic systems.[27c] Since the directing effect of the hydroxyl group is larger in the TBHP/V system it is a better reagent for hydroxyl-directed regioselective epoxidations of polyunsaturated alcohols;[73] the TBHP/V system also exhibits higher hydroxyl-directed selectivity in highly hindered allylic alcohols.[74]

m-CPBA epoxidation of hindered alkenes takes place selectively from the less hindered side; the epoxide of opposite stereochemistry can be prepared by a two-step procedure involving initial preparation of bromohydrin, followed by base treatment.[28]

For the epoxidation of extremely unreactive alkenes[38b] and for the preparation of epoxides which are highly susceptible to nucleophilic attack, ***Dimethyldioxirane*** is the reagent of choice.[75] Electron-deficient alkenes such as α,β-unsaturated ketones are usually oxidized with ***Hydrogen Peroxide***/base.

Related Reagents.

m-Chloroperbenzoic Acid-2,2,6,6-Tetramethylpiperidine Hydrochloride.

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m-Chloroperbenzoic Acid-2,2,6,6-Tetramethylpiperidine Hydrochloride

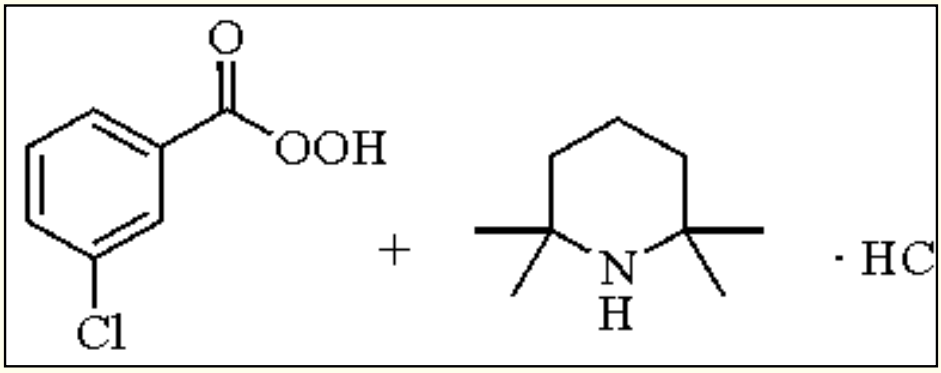

[937-14-4] · $C_7H_5ClO_3$ · *m*-Chloroperbenzoic Acid-2,2,6,6-Tetramethylpiperidine Hydrochloride · (MW 172.57)

[935-22-8] · $C_9H_{20}ClN$ · *m*-Chloroperbenzoic Acid-2,2,6,6-Tetramethylpiperidine Hydrochloride · (MW 177.75)

(reagent for the oxidation of alcohols at rt;[1] when used in combination with other oxidizing properties of *m*-CPBA this reagent can effect conversion of alkenic alcohols to epoxy ketones or secondary alcohols to esters or lactones[2])

Solubility: sol CH_2Cl_2, $CHCl_3$, diethyl ether, THF.

Form Supplied in: for *m*-CPBA, see ***m-Chloroperbenzoic Acid***; 2,2,6,6-tetramethylpiperidin-1-oxyl is a red solid, mp 36-38 °C and is available commercially.

Preparative Method: 2,2,6,6-tetramethylpiperidine hydrochloride is prepared by passing dry HCl into a cold solution of ***2,2,6,6-Tetramethylpiperidine*** in ether.

Oxidation of Alcohols.

Secondary alcohols are oxidized to ketones at room temperature by *m*-CPBA in the presence of catalytic (1-2%) quantities of 2,2,6,6-tetramethylpiperidine-1-oxyl, and HCl.[1] The nitroxide can be conveniently generated in situ from 2,2,6,6-tetramethylpiperidine hydrochloride (**1**), which also provides the requisite HCl (eq 1). The reaction can be conducted in CH_2Cl_2, $CHCl_3$, or ether solvents. In practice a slight excess of *m*-CPBA is used to offset its slow decomposition catalyzed by the nitroxide. Workup simply involves removal of the *m*-CPBA by filtration and/or extraction with base followed by removal of solvent. Yields of ketones are generally quite high (75-95%).

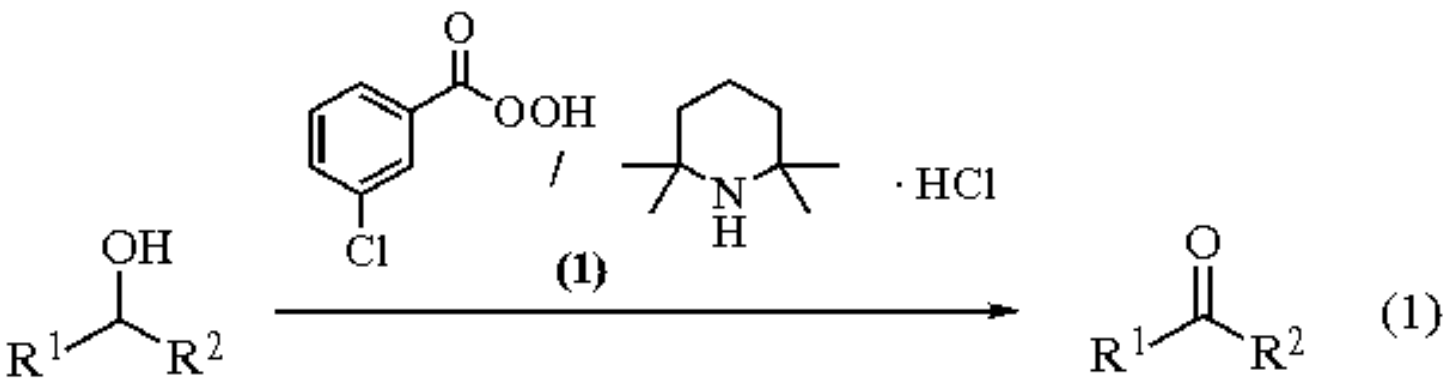

Primary alcohols are oxidized to aldehydes by this reagent, but further oxidation of the aldehydes to carboxylic acids by *m*-CPBA is sometimes observed. The oxidation is tolerant of any functional groups stable to *m*-CPBA and dilute mineral acid. Combining this oxidation procedure with other oxidizing properties of *m*-CPBA enables a range of unique transformations to be effected in a simple manner.

Preparation of Epoxy Ketones.

Epoxy ketones are conveniently prepared from alkenic alcohols in a one-pot procedure by epoxidation of the alkene using slightly more than 2 equiv of *m*-CPBA followed by addition of TMP.HCl to the reaction mixture to effect oxidation of the alcohol.[2] The procedure is particularly advantageous for the preparation of sensitive epoxy ketones. For example, (**2**) is prepared in 86% yield from norbornenol by this procedure (eq 2), compared to a 31% yield obtained by the ***Dipyridine Chromium(VI) Oxide*** oxidation of the same substrate.[3]

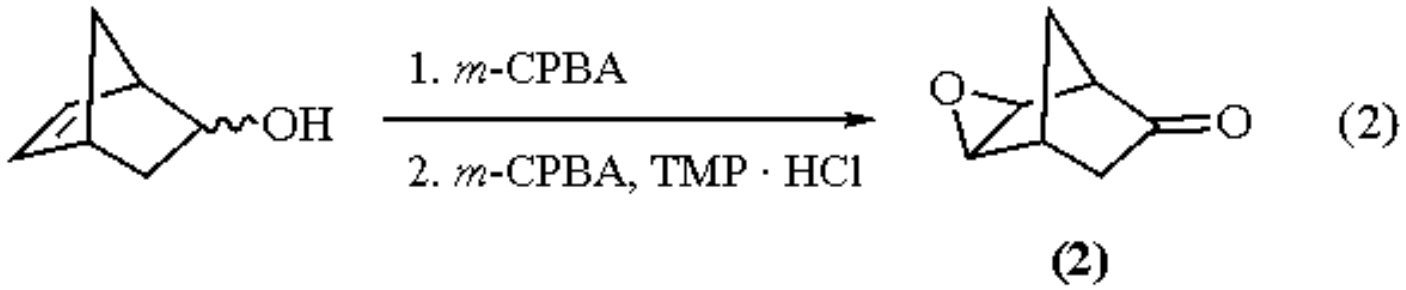

Combining this procedure for preparing epoxy ketones from allylic alcohols with the hydrazine-induced Wharton rearrangement[4] provides a convenient sequence for the transposition of allylic alcohols, as exemplified by the conversion of (**3**) to (**4**) (eq 3).

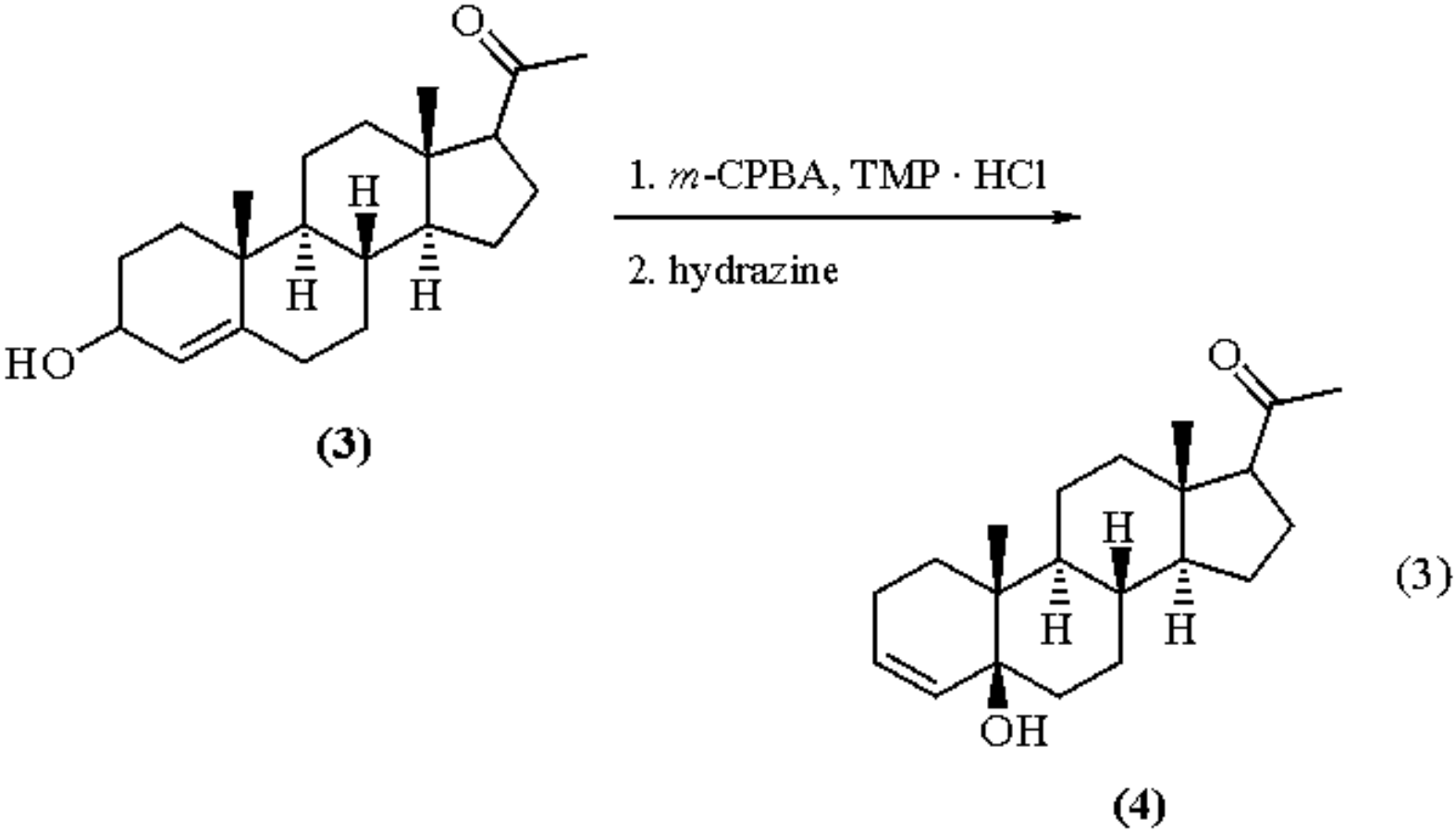

Preparation of Esters and Lactones from Secondary Alcohols.

Although under ordinary conditions the Baeyer-Villiger oxidation does not interfere with the peracid-mediated alcohol oxidation, under more forcing conditions the reactions can be coupled to afford esters and lactones directly from secondary alcohols.[2] Phenyl-2-propanol was converted to benzyl acetate in 90% yield by this process (eq 4). To accomplish this two-step sequence, a large excess of *m*-CPBA (3.5-4.0 equiv) is required; even under these conditions yields vary, depending on the reactivity of the ketone product to the Baeyer-Villiger reaction. Use of more reactive peracids (such as trifluoroperacetic acid or permaleic acid) was ineffective as these were rapidly degraded by the nitroxide catalyst.

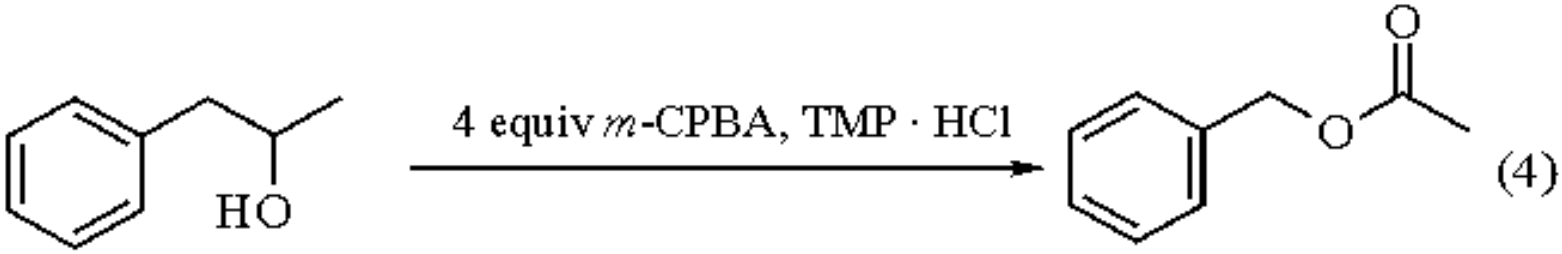

Related Oxidants.

The oxoammonium ion (**5**) is believed to be the species responsible for alcohol oxidation in this system, and several related methods for oxidizing alcohols involving generation of this intermediate from the nitroxide using chlorine,[5] bromine,[5] copper(II) salts,[6] sodium hypochlorite,[7] or electrochemically[8] have been reported. Acid-catalyzed oxidation of alcohols by *m*-CPBA alone has also been reported.[9]

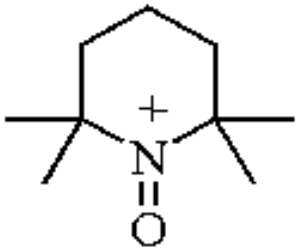

(5)

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1-Chloro-2-phenylacetylene

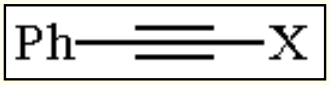

(X = Cl)

[1483-82-5] · C_8H_5Cl · 1-Chloro-2-phenylacetylene · (MW 136.57) (X = Br)

[932-87-6] · C_8H_5Br · 1-Bromo-2-phenylacetylene · (MW 181.03) (X = I)

[932-88-7] · C_8H_5I · 1-Iodo-2-phenylacetylene · (MW 228.03)

(reacts with tertiary enolates to form phenylethynyl adducts; starting material for the preparation of ynamines, ynehydrazines, alkynylphosphonates, and alkynyl ethers)

Alternate Name: (chloroethynyl)benzene; phenylchloroethyne.

Physical Data: X = Cl: bp 78 °C/20 mmHg;[3] X = Br: bp 40-41 °C/0.1 mmHg, *d* 1.456 g cm^{-3}; X = I: bp 115-117 °C/16 mmHg, *d* 1.75 g cm^{-3}.

Preparative Methods: the method of choice is by reaction of phenylacetylene with sodium hypochlorite;[1] it can also be prepared by reaction of sodium phenylacetylide with *p*-toluenesulfonyl chloride[2] or lithium phenylacetylide and *N*-chlorosuccinimide.[3]

Handling, Storage, and Precautions: use in a fume hood.

Phenylethynylation.

1-Chloro-2-phenylacetylene reacts with tertiary ketone or ester enolates to give phenylethynyl adducts (**1**) and (**2**) in 70-95% yields. Hydration of the ethynyl group leads to dicarbonyl systems (**3**).[4] Additional enolate addition/elimination reactions with chloroacetylenes to yield alkynyl derivatives (**4**) and (**5**) have been reported for dichloroacetylene (see ***Trichloroethylene*** and 1-chloro-2-phenylthioacetylene.[4] This method is limited to tertiary enolates. Similar alkynylations have been reported for tertiary β-dicarbonyl enolates using alkynyl lead triacetates[5] or alkynyl iodonium tetrafluoroborates.[6]

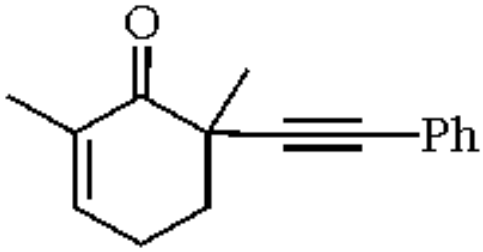

(1)

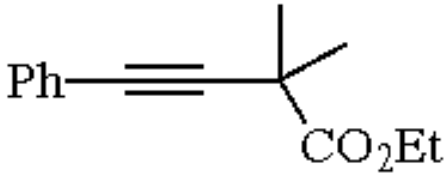

(2)

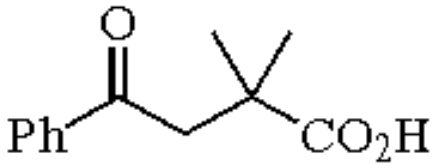

(3)

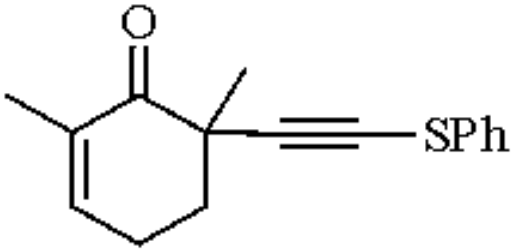

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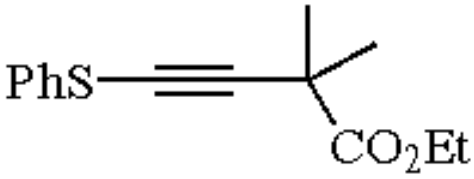

(5)

Preparation of Ynamines and Ynehydrazines.

1-Chloro-2-phenylacetylene reacts with lithium dimethylamide to yield the ynamine (**6**) in 87% yield. Ynamines can also be prepared from the reaction with tertiary amines.[7,8] Similarly, the trimethyl ynehydrazine derivative (**7**) can be prepared from the reaction with lithium trimethylhydrazide.[9]

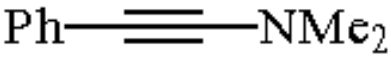

(6)

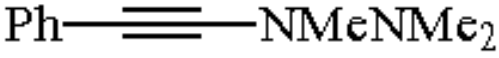

(7)

Reaction with Other Nucleophiles.

1-Chloro-2-phenylacetylene reacts with ***Triethyl Phosphite***, undergoing an Arbuzov reaction to yield the phosphonate (**8**).[10] Similarly, reaction with alkoxides leads to alkoxyacetylenes (**9**).[11]

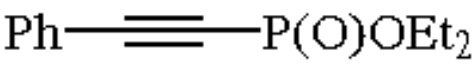

(8)

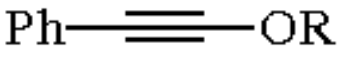

(9)

Related Reagents.

Ethoxyacetylene; ***Phenylthioacetylene***; ***Trichloroethylene***.

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4-Chlorophenyl Chlorothionoformate

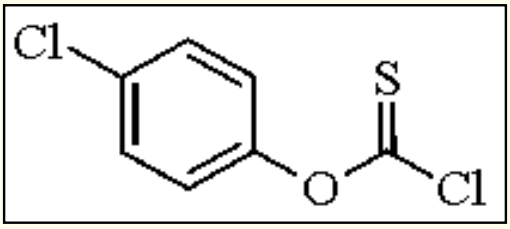

[937-64-4] · $C_7H_4Cl_2OS$ · 4-Chlorophenyl Chlorothionoformate · (MW 207.08) · $C_7H_5BrN_2$ · 3-Bromo-3-phenyldiazirine · $C_7H_5ClN_2$ · 3-Chloro-3-phenyldiazirine

(dehydrating agent;[1] has been used in radical deoxygenation;[2] serves as a building block in the synthesis of penems[3] and heterocycles;[4] used for introduction of the thiocarbonyl group[5])

Alternate Name: O-(4-chlorophenyl) carbonochloridothioate.

Physical Data: bp 82 °C/0.8 mmHg;[6] 114-116 °C/0.8 mmHg.[7]

Form Supplied in: distillable liquid; commercially available.

Preparative Method: from thiophosgene and *p*-chlorophenol in the presence of sodium hydroxide.[2,6]

Handling, Storage, and Precautions: protect from moisture.

Use as Dehydrating Agent.

The reagent converts oximes to nitriles under mild conditions (rt, 1.5 h) (eq 1).[1]

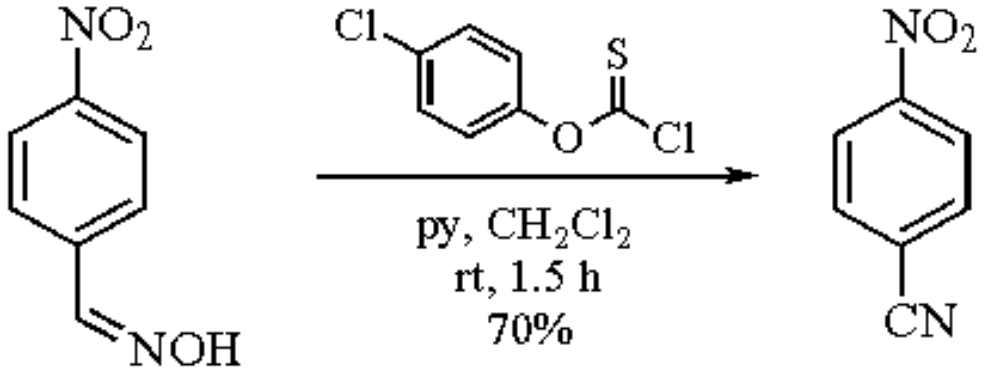

(1)

Use in the Chugaev Reaction.

The closely related reagent, *p*-tolyl chlorothionoformate, has been used for Chugaev eliminations (eq 2);[8] presumably, *p*-chlorophenyl chlorothionoformate could serve the same function.

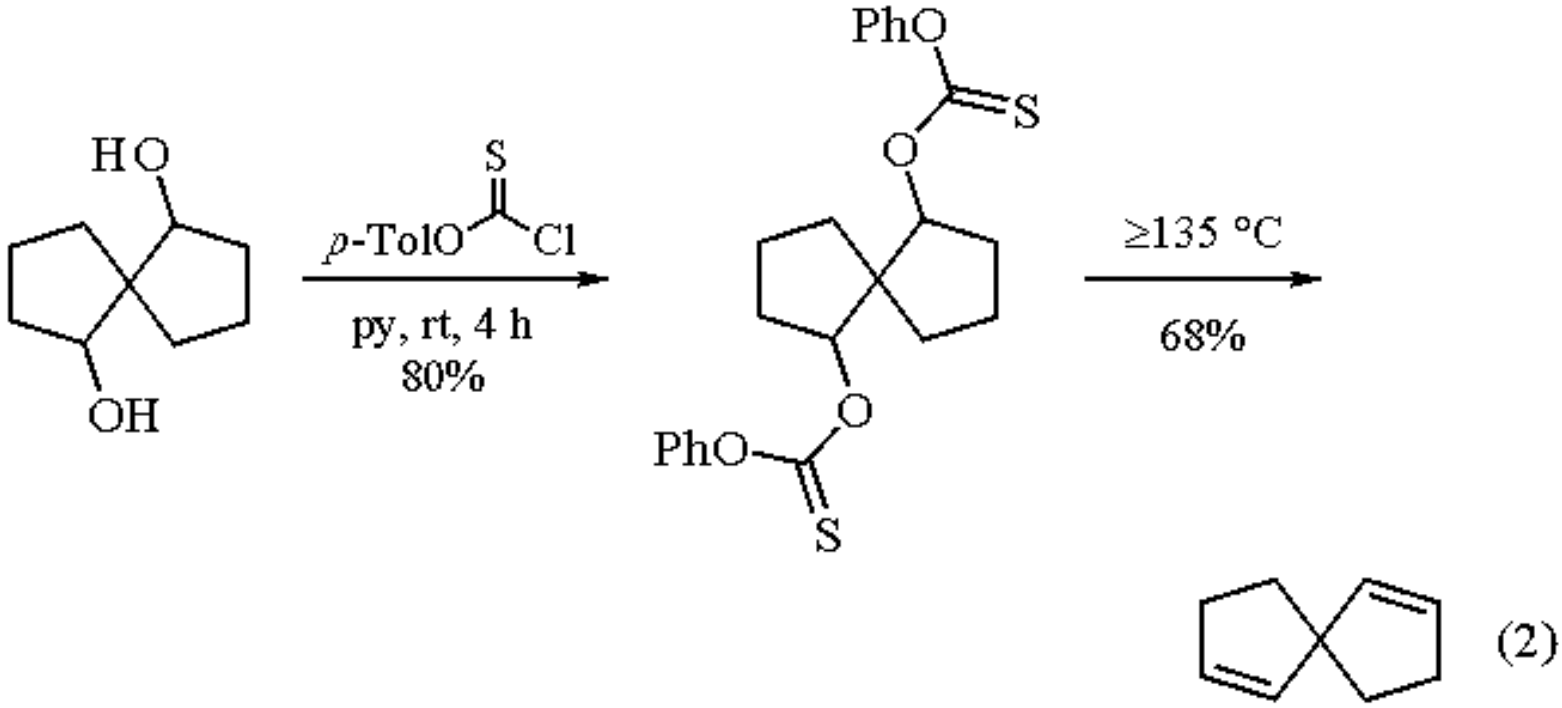

Use in Radical Deoxygenation.

The reagent has been used in radical deoxygenation (eq 3).[2]

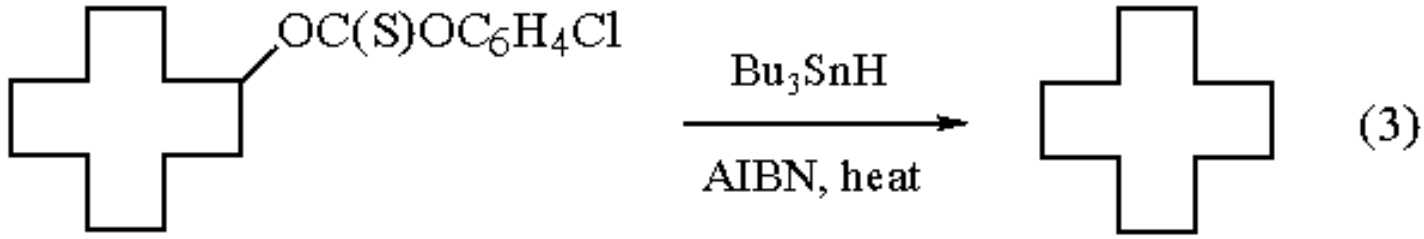

Use as a Building Block.

The reagent has been incorporated into the structure of a thiopenem antibiotic (eq 4).[3]

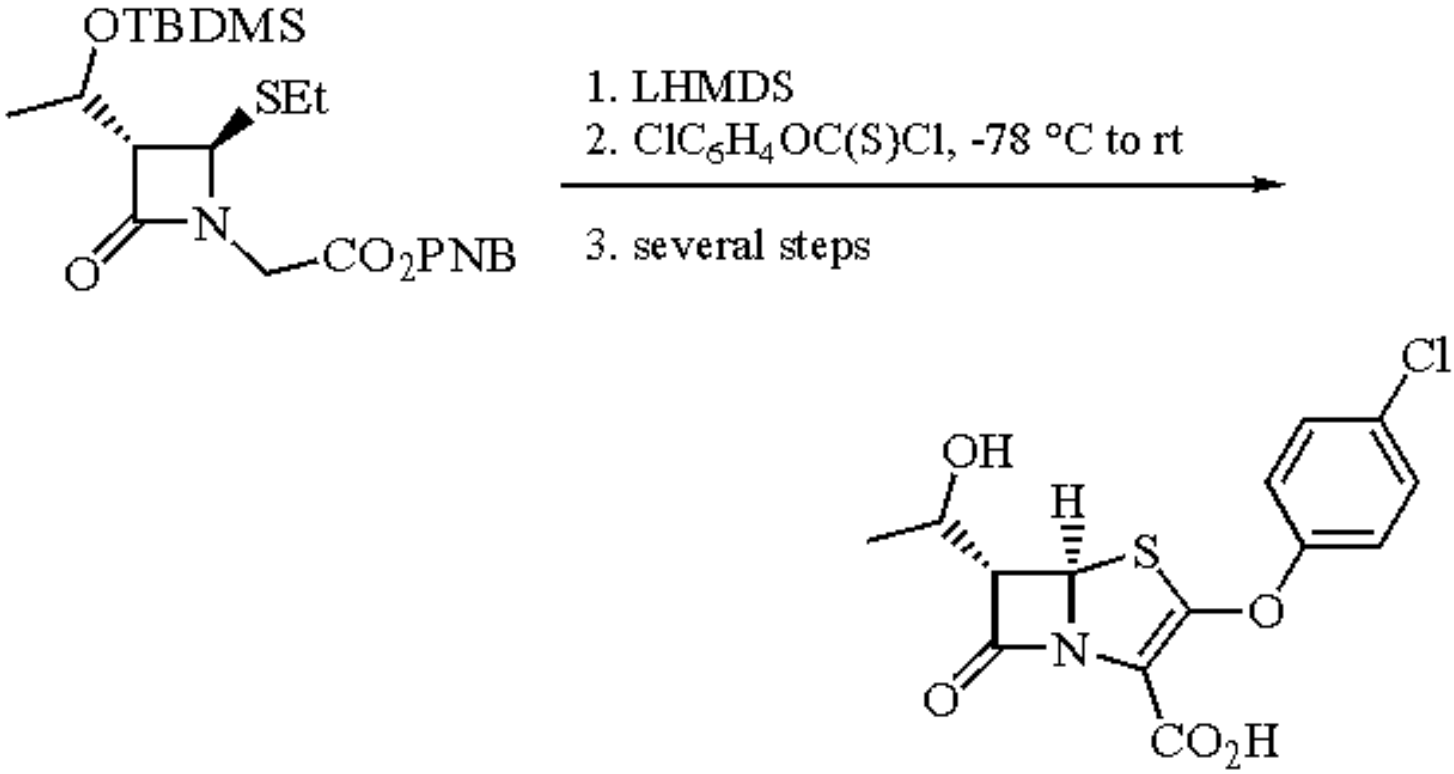

(4)

The reagent is also useful for introducing the thiocarbonyl function, since the chlorine atom and chlorophenol residues can be replaced successively by nucleophiles (eq 5).[4,5]

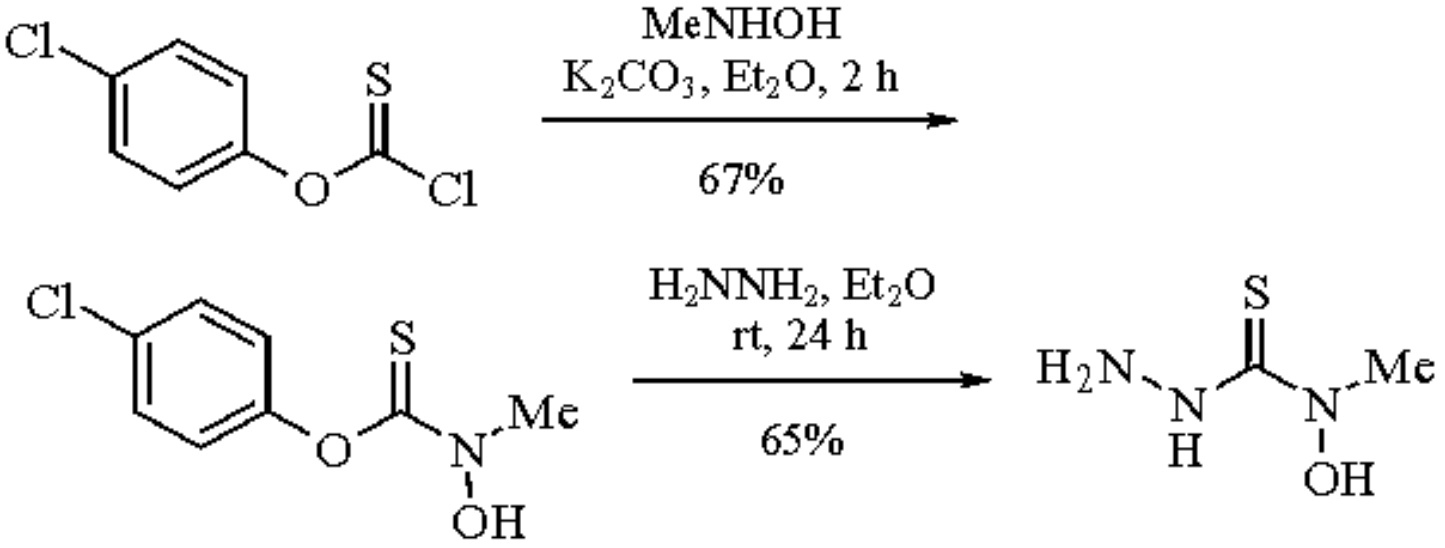

(5)

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3-Chloro-3-phenyldiazirine[1]

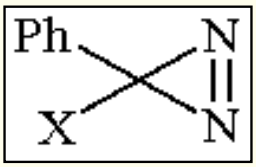

(X = Cl)

[4460-46-2] · $C_7H_5ClN_2$ · 3-Chloro-3-phenyldiazirine · (MW 152.58) (X = Br)

[4222-25-7] · $C_7H_5BrN_2$ · 3-Chloro-3-phenyldiazirine · (MW 191.99)

(stable cyclic isomer of chlorodiazomethane; excellent source of chlorocarbene following thermolysis or photolysis[2])

Physical Data: colorless liquid; bp 33-35 °C/0.5 mmHg; IR N=N stretch 1560 cm^{-1}; UV λ = 388 nm.

Solubility: sol hydrocarbons, diethyl ether, ethyl acetate, and acetonitrile

Preparative Methods: by treatment of benzamidine hydrochloride with NaOCl (eq 1).

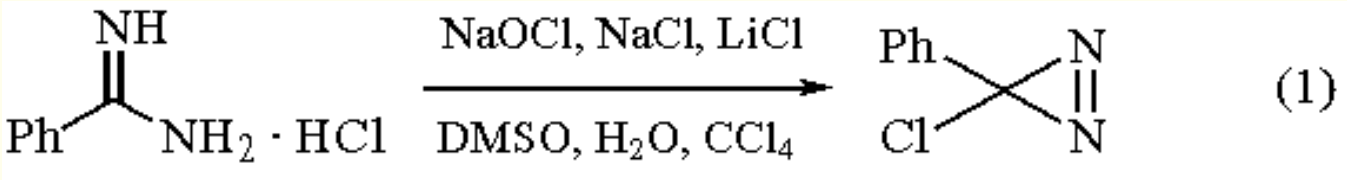

Handling, Storage, and Precautions: can be stored in the dark at 0-10 °C for several weeks under Ar without decomposition; solutions of the reagent have not been known to detonate, although more volatile chlorodiazirines, e.g. methylchlorodiazirine, are prone to explosion[3] and are shock sensitive; explosions have occurred on warming to rt after storage at 77 K. Extreme care is required during cold trap procedures when solid diazirine is present; in GC, diazirine must never be injected neat (the high temperature at the injector block will lead to an explosion). Always take precautions (e.g. safety shields) when working with diazirines.

Diazirines are cyclic isomers of diazoalkanes. The chemistry of diazirines has a relatively short history, dating from the discovery of these compounds in 1960 by Paulsen,[4] and Schmitz and Ohme.[5] The increasing interest and the progress in this field have encouraged continuous reviews.[6] In 1965, Graham's pioneering paper described the synthesis of 3-chloro-3-phenyldiazirine.[1b] The mechanism for hypochlorite oxidation of amidines (with diazirine formation) has been reviewed.[7,8]

Reactions of Diazirines.

The reaction of phenylchlorodiazirine with ***Phenyllithium*** (eq 2) yields diphenylbenzamidine, whereas the reaction with ***Methyllithium*** gives acetophenone.[1d]

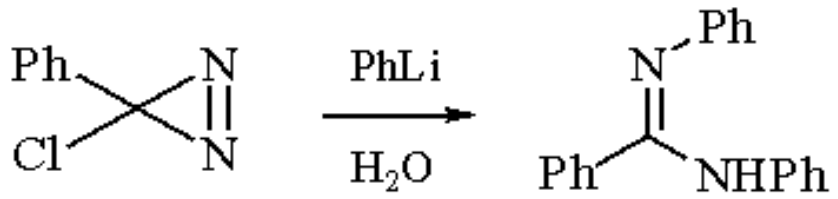

(2)

Another facet of halodiazirine chemistry is the reaction with nucleophiles[7,8] and this is illustrated by the reaction of phenylbromodiazirine with the nucleophiles methoxide, fluoride, and cyanide ions (eq 3).

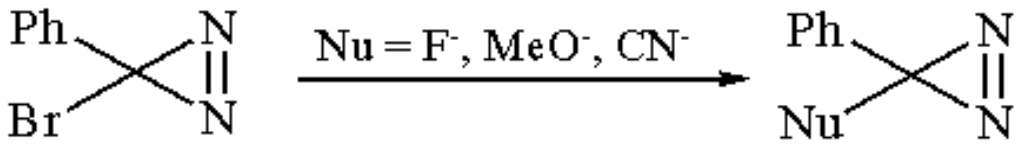

(3)

Synthetically, the exchange reaction has been used to prepare methoxy-substituted methylenecyclopropanes (eq 4).[8]

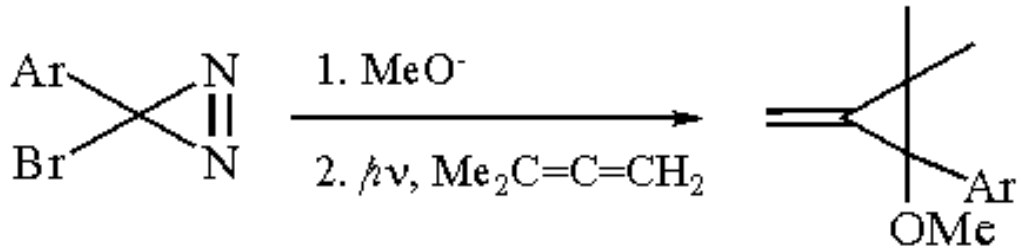

(4)

An exchange reaction of phenylbromodiazirine with *N*-methylethanolamine affords diazirine, which yields the carbene upon loss of nitrogen. The oxazolidine product is formed by the intramolecular O-H insertion of the carbene (eq 5).[9]

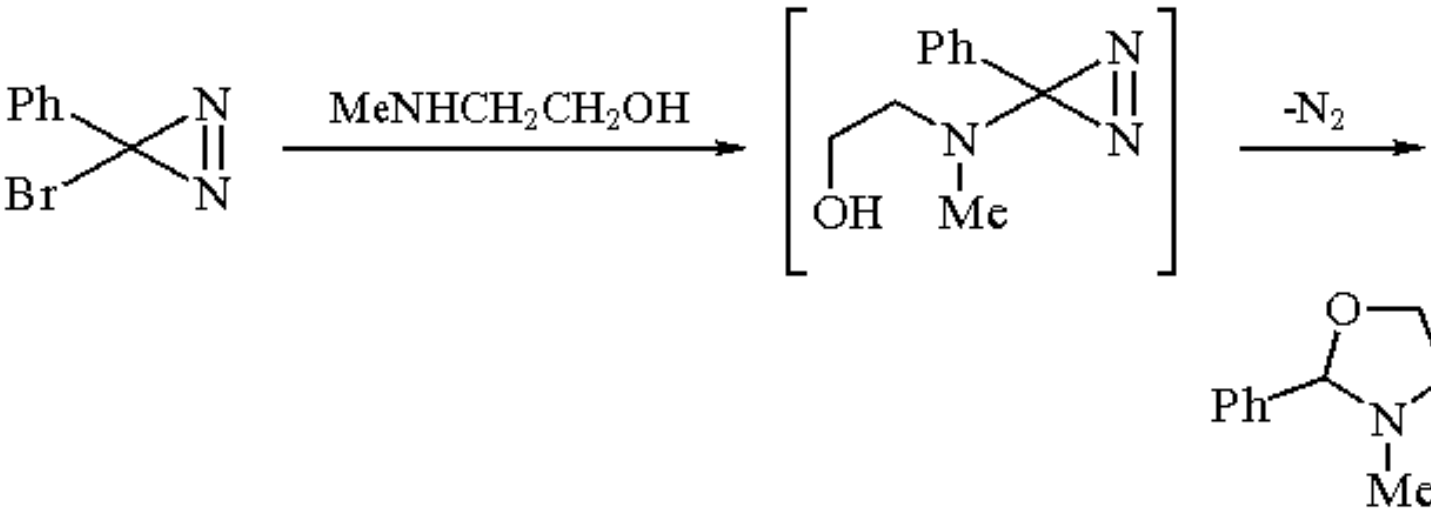

(5)

Reactions of Carbenes.

Chlorodiazirine compounds are remarkably stable in the presence of organic and inorganic reagents, in sharp contrast to the behavior of their linear isomers, which can only be detected by isolation matrix techniques.[10] Because of their stability, chlorodiazirines have been investigated as a source of chlorocarbenes following thermolysis, photolysis,[2] or ultrasound.[11] Thermal decomposition of phenylchlorodiazirine in cyclohexene gives a mixture of *exo*- and *endo*-7-chloronorcaranes.[1b,12] Thus chlorodiazirines have played an essential role in the development of singlet chlorocarbene reactivities toward alkenes. Arylchlorocarbenes can be classified as electrophilic carbenes.[7b,13] Accordingly, selectivity for addition to alkenes is greatest when the alkene possesses electron-donating substituents. Phenylchlorocarbene reacts readily with α,β-unsaturated esters to produce cyclopropane products in high yields (eq 6).[14,15]

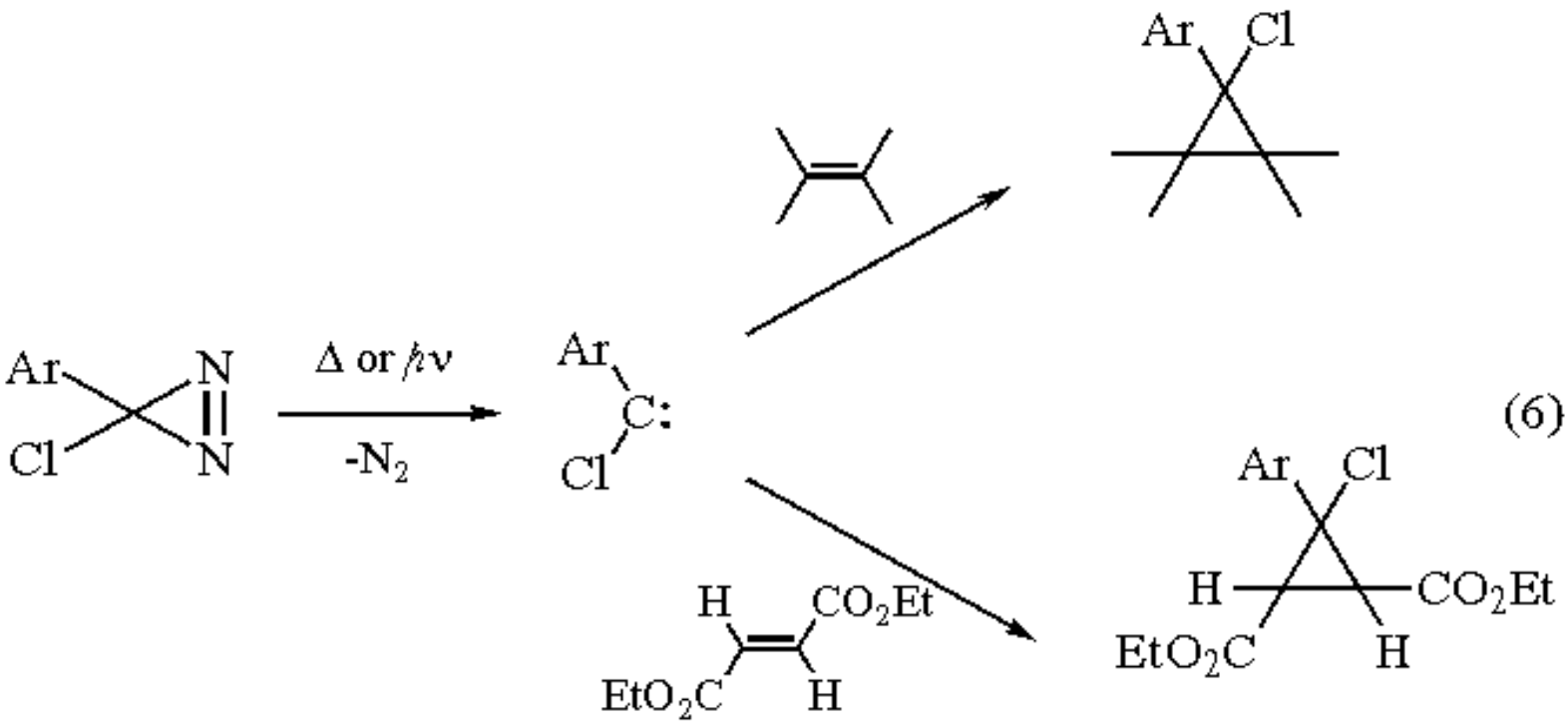

(6)

Phenylchlorocarbene may be trapped with ***Tri-n-butylstannane***,[1d] substituted alkynes,[1d] triethylsilane,[16] or cumene (eq 7).[16]

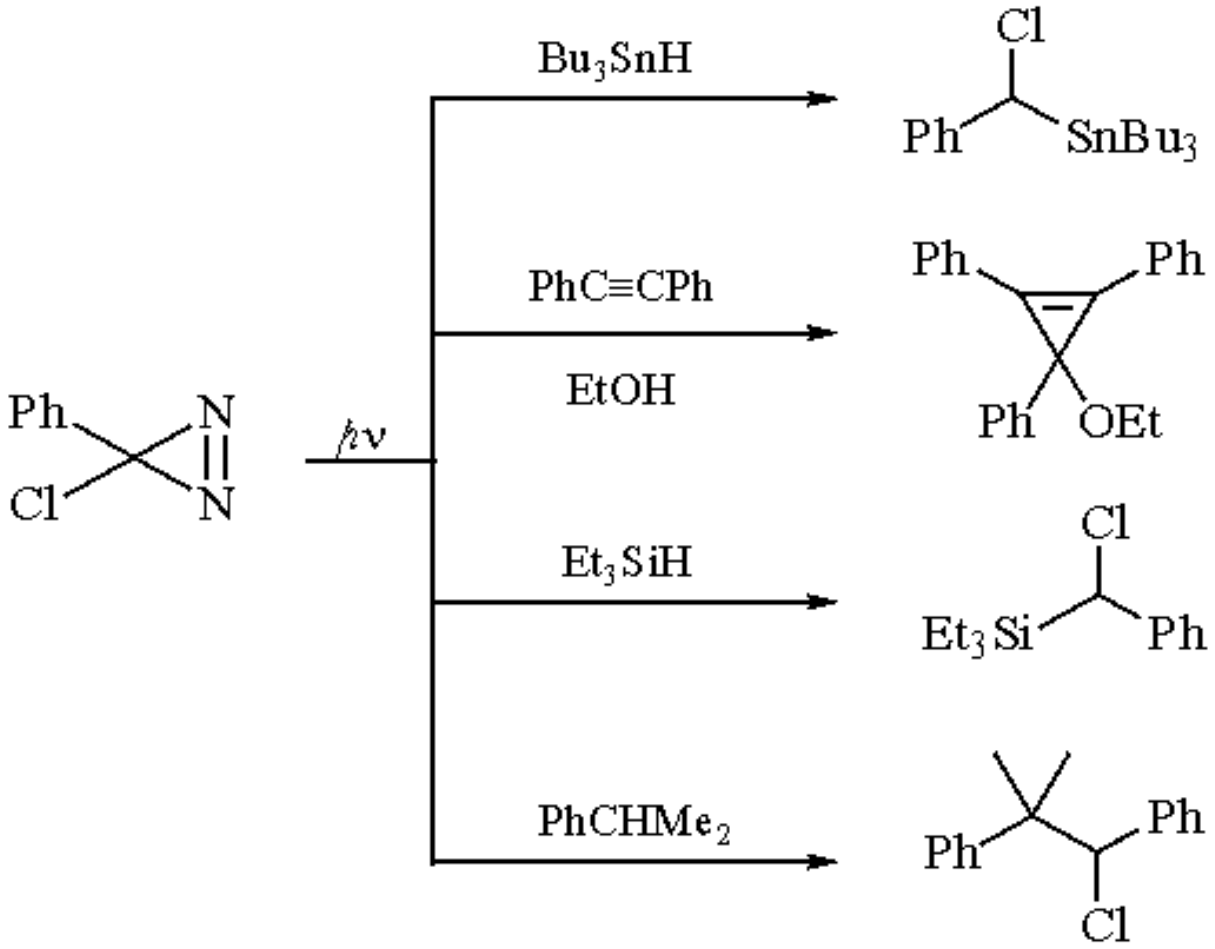

(7)

Transformation of phenylchlorodiazirine to 1,3-dioxolane and 1,3-dithiolane has been demonstrated (eq 8).[17]

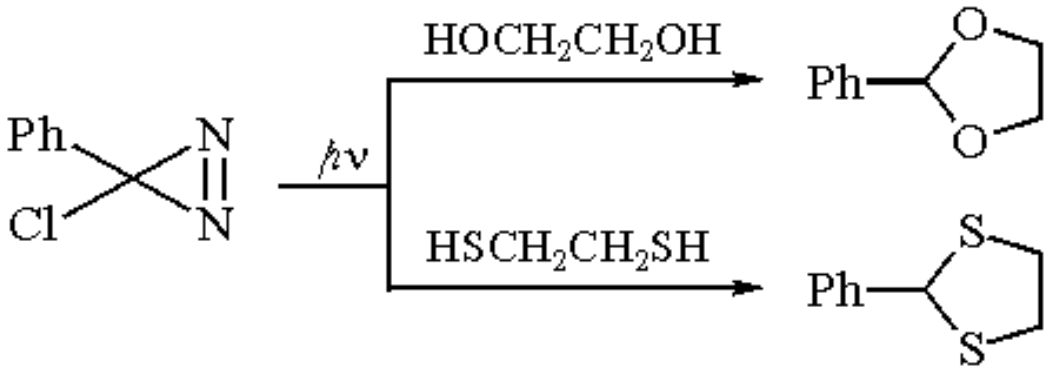

(8)

The carbonyl ylide generated from arylchlorodiazirine and acetone undergoes 1,3-dipolar cycloaddition to either benzaldehyde[18] or diethyl fumarate (eq 9).[19]

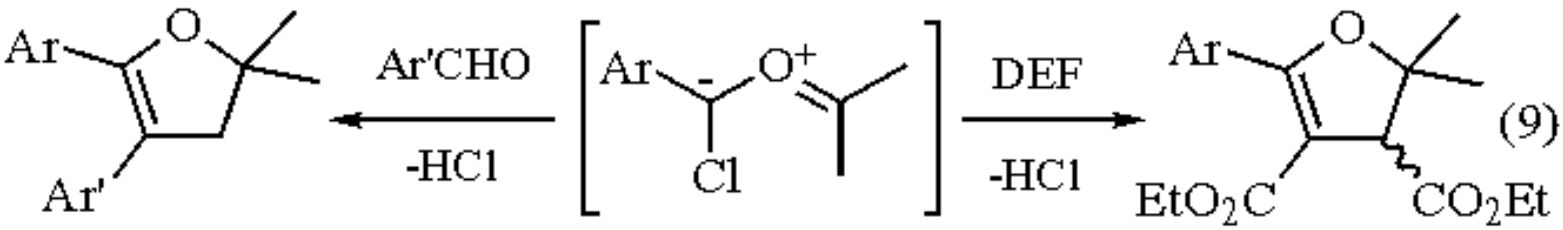

(9)

Photolysis of phenylchlorodiazirine in the presence of pyridine yields a pyridinium ylide (λ = 480 nm). Cycloaddition of the pyridinium ylide to ***2-Chloroacrylonitrile*** yields 1-cyano-3-phenylindolizine regioselectively (eq 10).[20]

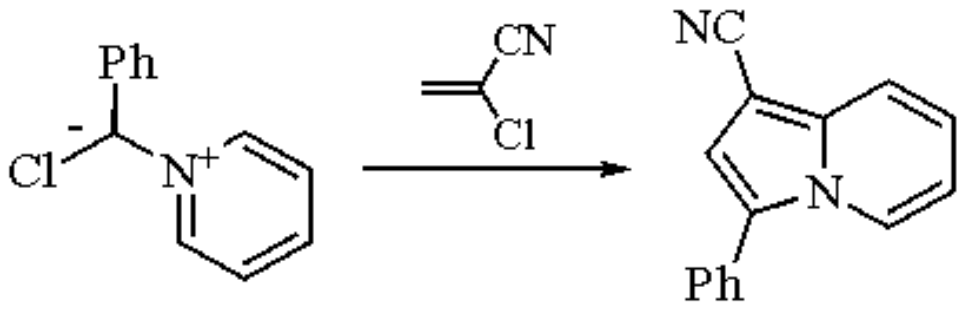

(10)

In the reaction of arylchlorodiazirine with ***Allylamine***, the insertion of the carbene into an N-H bond is followed by HCl elimination to give a Schiff base in good yield (eq 11).[21]

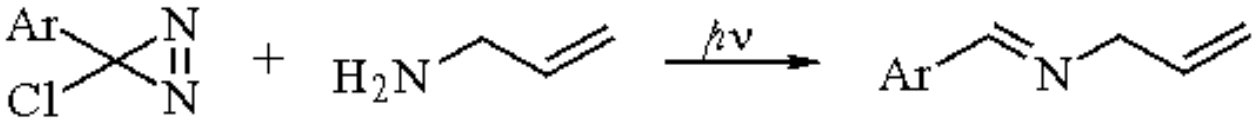

(11)

Related Reagents.

Diazomethane; ***Di-t-butyl Dicarbonate***.

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3-Chloro-1-propynyllithium[1]

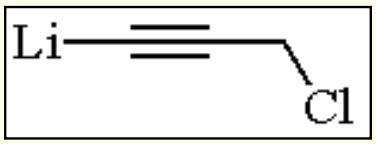

[67811-22-7] · C_3H_2ClLi · 3-Chloro-1-propynyllithium · (MW 80.44)

(undergoes addition/substitution reactions[3-5] with electrophiles; adducts with organoboranes are good sources of allenes,[2] enynes,[7,8] alkenes,[9] and alkynes[2,6])

Alternate Name: lithium chloropropargylide.

Solubility: sol ether, THF.

Form Supplied in: not commercially available; used as a solution prepared prior to reaction.

Preparative Methods: to freshly distilled ***Propargyl Chloride*** (20 mmol) in THF (10 mL) at -70 °C is added 1.6 M ***Methyllithium*** (20 mmol) in ether. The resulting clear solution is ready for use.[2] Use of ***n-Butyllithium*** in place of MeLi is reported to result in lower yields in the subsequent reactions.[3]

Handling, Storage, and Precautions: highly moisture sensitive; use soon after preparation, in a fume hood.

Reaction with Electrophiles.

The carbenoid is used for C-C/C-X bond formation with a number of electrophiles, as shown in eqs 1-5.[3-5]

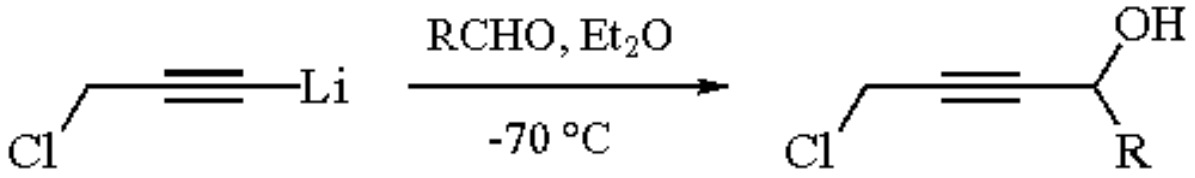

(1)

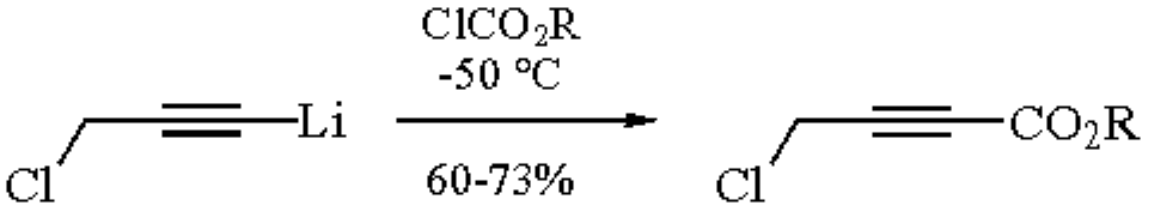

(2)

chlorotetrolic esters

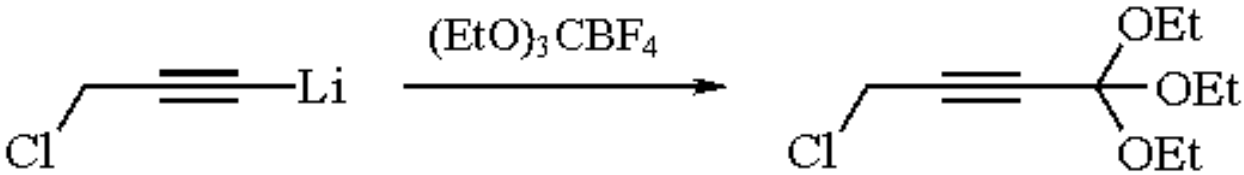

(3)

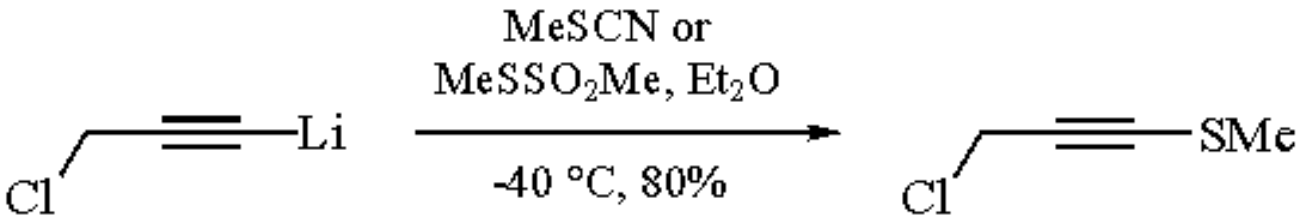

(4)

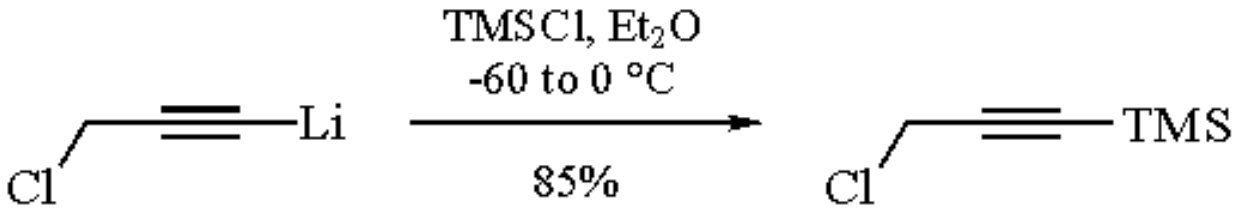

(5)

Synthesis of Alkylallenes.[2]

Trialkylboranes add to 3-chloro-1-propynyllithium in THF at -70 °C to form the adduct (**1**) (eq 6), which after being warmed to 25 °C can be protonated with acetic acid to give terminal alkylallenes (**2**) (eq 7). Where chiral, the migrating alkyl group retains its configuration.

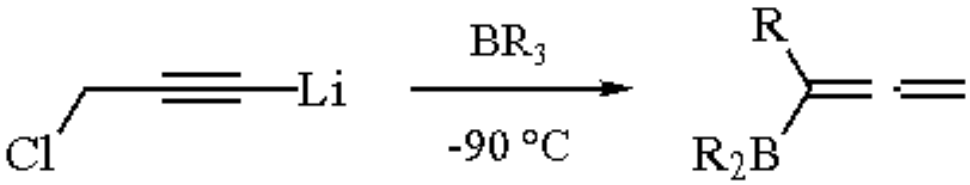

(6)

(1)

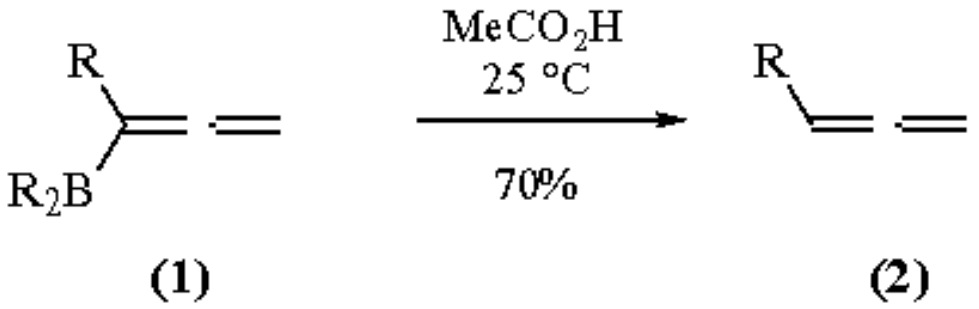

(7)

Synthesis of α-Allenic and Homopropargylic Alcohols.[6]

The intermediate organoborane (**1**) can be treated with an aldehyde to form a C-C bond, resulting in an allenic or alkynic alcohol, depending on the temperature at which the organoborane precursor is maintained. Warming the adduct (**1**) to 25 °C and cooling back to -78 °C before reacting with aldehyde affords α-allenic alcohol (**3**) after oxidative workup (eq 8). On the other hand, if the organoborane is maintained at -78 °C or below throughout and treated with aldehyde, the resulting product, after an oxidative workup, is homopropargylic alcohol (**4**) (eq 9). The reaction conditions permit a wide variety of structural features in both the organoborane and aldehyde.

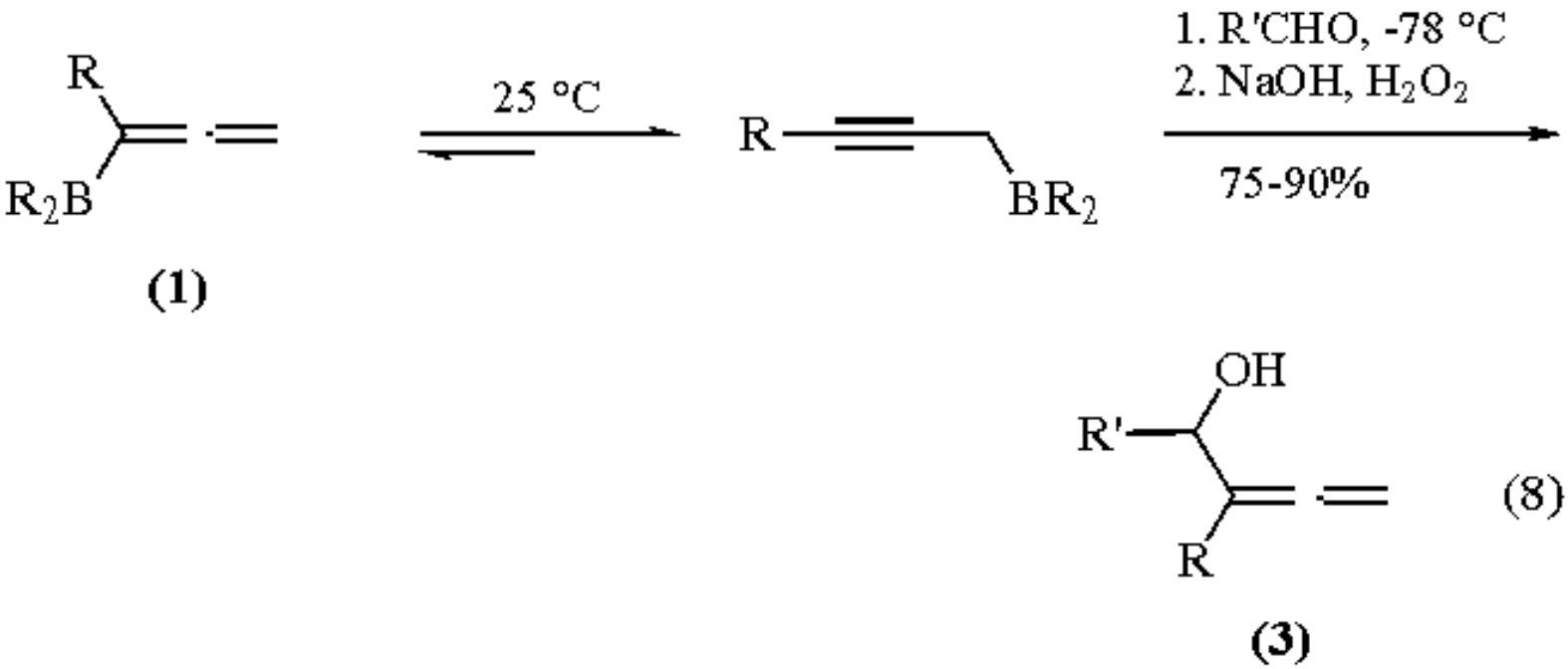

(8)

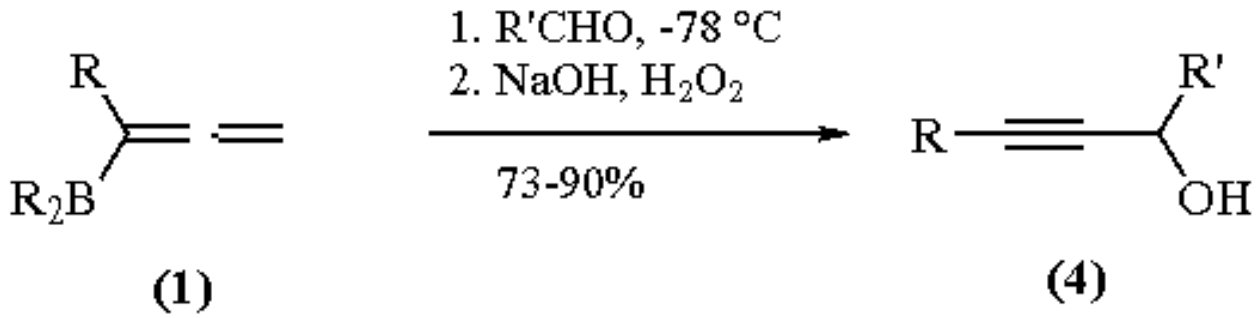

(9)

Synthesis of 1,5-Enynes.[7]

The organoborane (**1**) is converted to a 1,5-enyne by treating it with an allylic bromide in the presence of ***Copper(I) Iodide*** and LiOMe (eq 10).

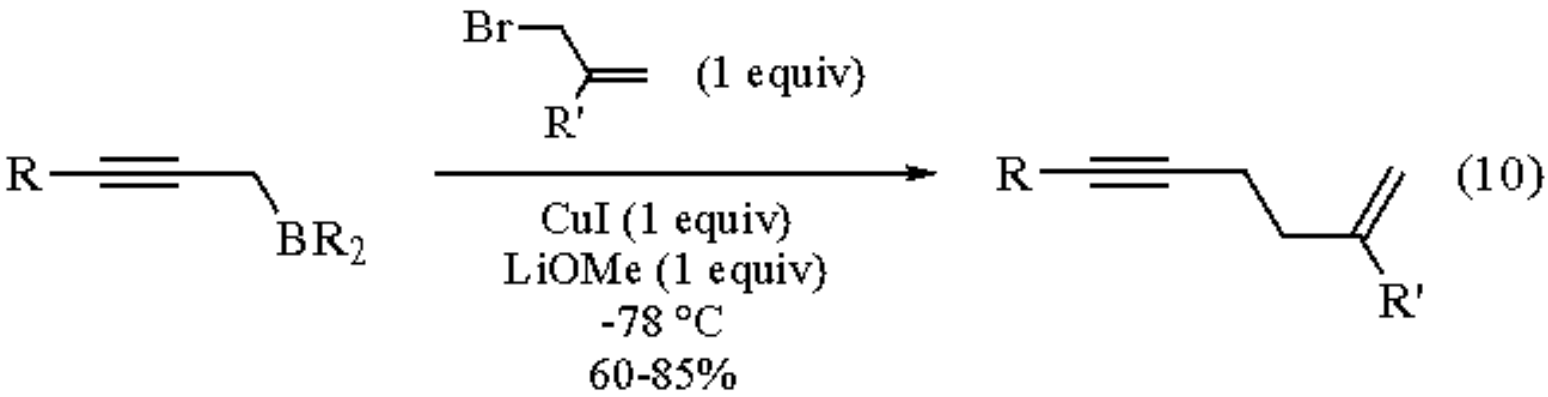

Synthesis of Alkylallenes and 1,3-Enynes.[8]

As a γ-halo organolithium compound, 3-chloro-1-propynyllithium has been used for C-C bond formation with organotransition metals via migratory insertion to give terminal alkylallenes or 1,3-enynes (eqs 11 and 12).

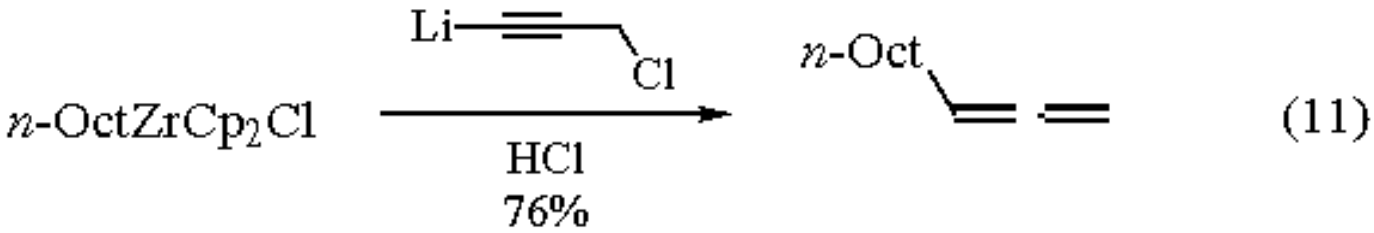

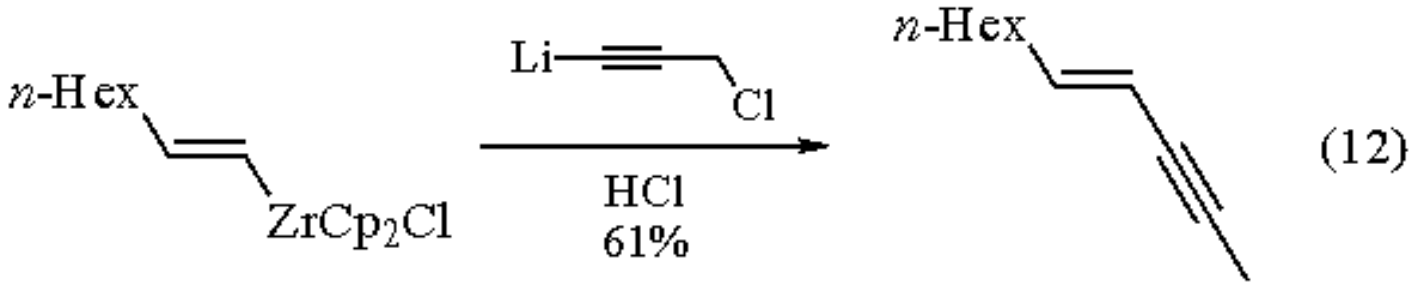

Synthesis of α,β-Unsaturated Aldehydes or Ketones.[9]

1,2-Dienols can be obtained by treating the title reagent with an aldehyde, followed by reduction with ***Lithium Aluminum Hydride***. These allenols can be coupled to aryl or alkenyl halides under palladium catalysis in the presence of a tertiary amine, resulting in a facile synthesis of β-methyl-α,β-unsaturated carbonyls (eq 13).

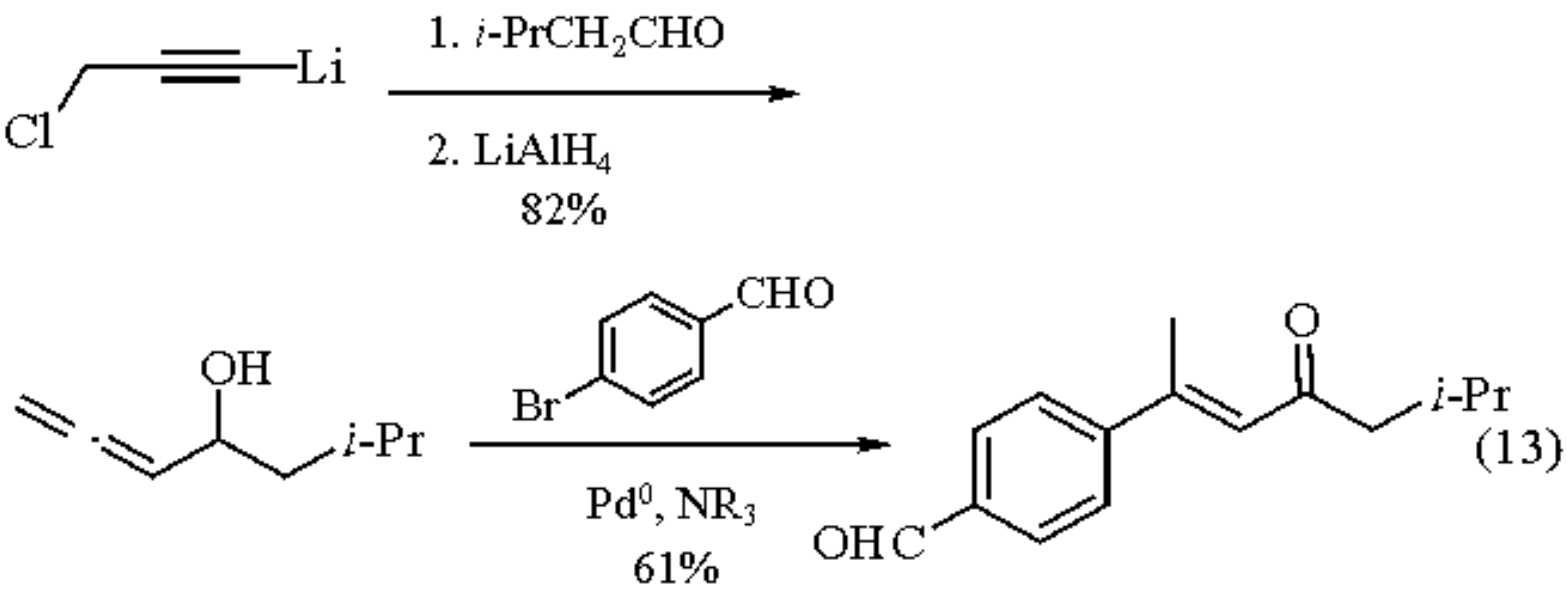

Enones containing other carbonyl groups in the same molecule that are not accessible by the conventional aldol condensation can be synthesized using this approach.

Related Reagents.

Propargyl bromide, 3-chloro-1-butyne, and 3-chloro-3-methyl-1-butyne can also be metalated, and the derived lithium reagents, 3-bromo-1-propynyllithium, 3-chloro-1-butynyllithium, and 3-chloro-3-methyl-1-butynyllithium, can be trapped with electrophiles.[10]

See also ***Lithium Acetylide***; ***Propynyllithium***; and ***3,3-Diethoxy-1-propyne***.

---

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A. V. Rama Rao

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N-Chlorosuccinimide

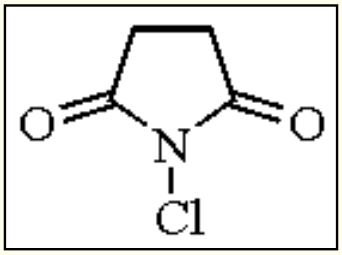

[128-09-6] · $C_4H_4ClNO_2$ · *N*-Chlorosuccinimide · (MW 133.53)

(electrophilic α-chlorination of sulfides, sulfoxides, and ketones; preparation of *N*-chloroamines)

Alternate Name: 1-chloro-2,5-pyrrolidinedione; NCS.

Physical Data: mp 144-146 °C.

Solubility: sol H_2O; sl sol CCl_4, benzene, toluene, AcOH; insol ether.

Form Supplied in: white powder or crystals having a weak odor of chlorine when pure; widely available.

Purification: the commercial reagent acquires a light yellow color and a rather strong odor of chlorine after long storage but is easily recrystallized from acetic acid: rapidly dissolve 200 g of impure sample in 1 L preheated glacial AcOH at 65-70 °C (3-5 min); cool to 15-20 °C to effect crystallization; filter through a Buchner funnel and wash the white crystals once with glacial AcOH and twice with hexane; dry in vacuo (>85% recovery).

Analysis of Reagent Purity: the standard iodide-thiosulfate titration method is suitable.

Handling, Storage, and Precautions: store under refrigeration and protect from moisture; acutely irritating solid, with toxic effects similar to those of the free halogens; avoid inhalation; use an efficient fume hood; perform all operations as rapidly as possible to avoid extensive decomposition of the reagent.

N-Chlorosuccinimide is a convenient reagent for the electrophilic substitution and addition of chlorine to organic compounds. Other chlorinating agents of use include ***Chlorine***, ***Sulfuryl Chloride***, ***Chloramine-T***, ***t-Butyl Hypochlorite***, and ***Trichloroisocyanuric Acid***. The primary advantages of using NCS include the ease in handling, the mild conditions under which chlorination proceeds, and the ease of removal of the inoffensive byproduct succinimide.

α-Chlorination of Carbonyl Derivatives.

Carbonyl compounds can be chlorinated in the α-position by addition of NCS directly to the lithium enolates, enoxyborinates, or more commonly to the silyl enol ether derivatives.[1] In combination with methods for the regiospecific generation of enolates and silyl enol ethers, α-chloroketones of desired structure can be produced. For example, β-ionone can be chlorinated selectively in the α´-position by addition of NCS to the kinetic enolate (eq 1).[2] With the appropriate chiral auxiliary, NCS chlorinates silyl ketene acetals with high levels of diastereoselectivity (eq 2).[3] α-Chloro ketones, α-chloro esters, and α-chloro sulfones may also be prepared by reaction of NCS with the β-keto derivatives and in situ deacylation in the presence of base (eq 3).[4] NCS is also an effective reagent for the α-chlorination of acid chlorides.[5]

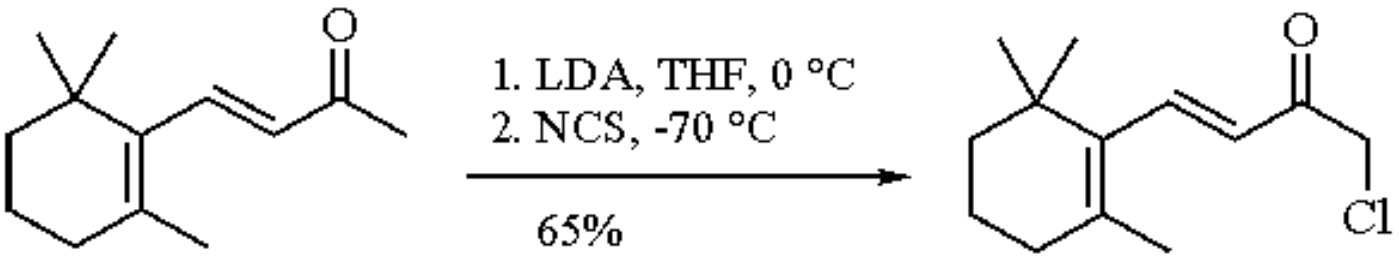

(1)

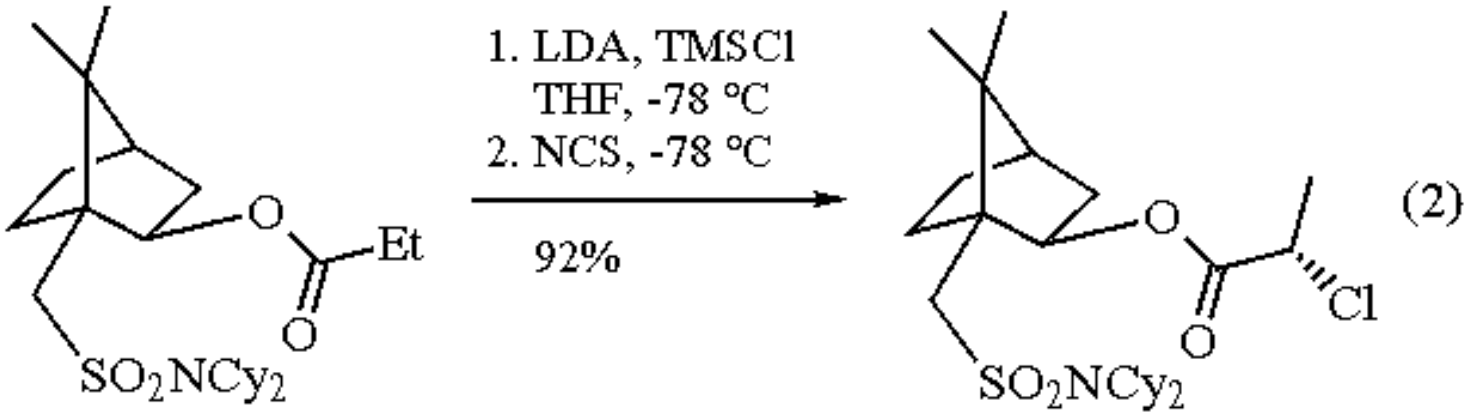

(2)

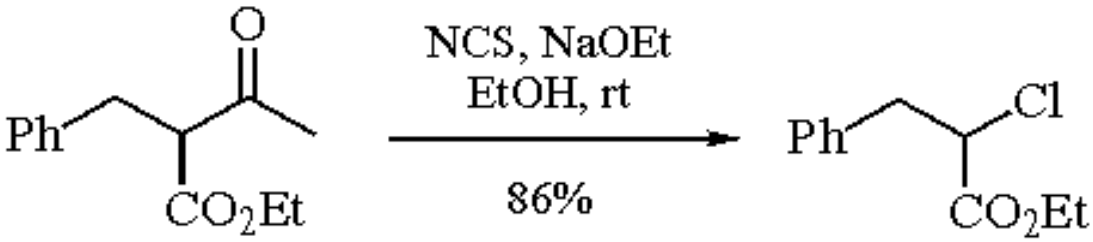

(3)

Chlorination of Sulfides and Sulfoxides.[6]

The reaction of alkyl sulfides with NCS has been used extensively for the preparation of α-chloro sulfides, and NCS is generally regarded as the reagent of choice for the preparation of these useful synthetic intermediates (see also ***Trichloroisocyanuric Acid***). Since the mechanism of chlorination involves initial formation of an *S*-chlorosulfonium salt followed by a Pummerer-like rearrangement, monochlorination proceeds smoothly in CCl_4 or benzene in the absence of added acid or base.[7] The most straightforward procedure involves the addition of NCS to a solution of the sulfide in CCl_4 at rt or reflux, followed by removal of insoluble succinimide by filtration. The resulting α-chloro

sulfides are easily hydrolyzed and, as this is usually undesirable, α-chloro sulfides must be prepared under strictly anhydrous conditions and are often used without further purification. A method has been developed for the conversion of benzylic halides to aromatic aldehydes (eq 4);[8] however, this transformation is more conveniently effected in one operation with other reagents (see ***Hexamethylenetetramine***). Many advantages have led to the preferred use of NCS in the Ramberg-Bäcklund rearrangement sequence (eq 5), which has been recently reviewed.[9]

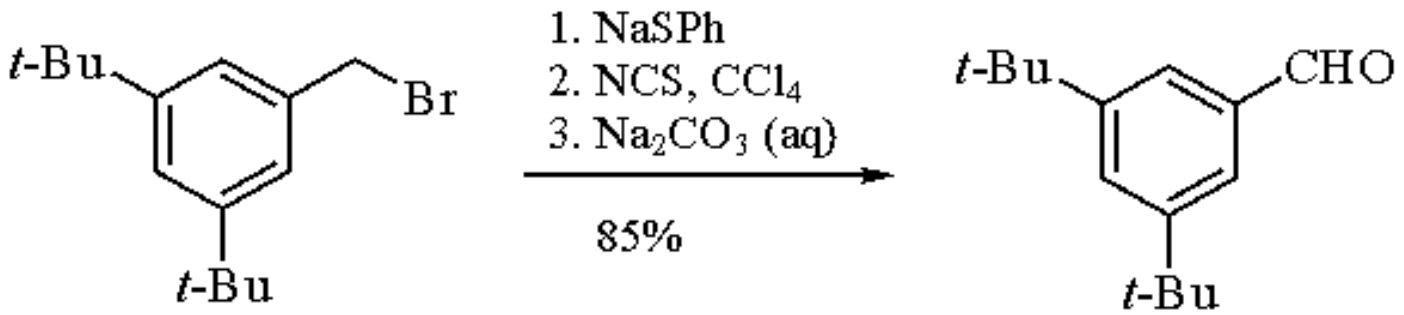

(4)

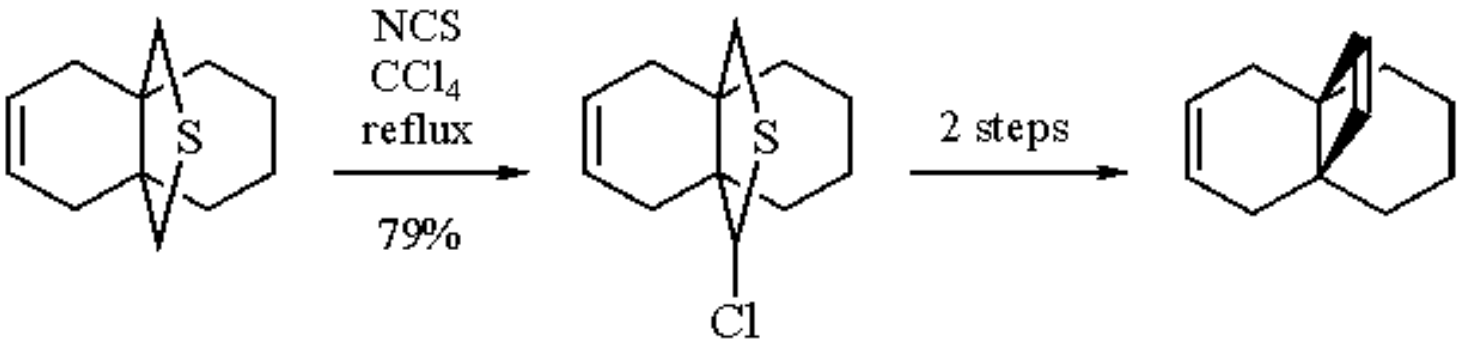

(5)

The chlorination of trimethylsilylmethyl sulfides with NCS and trifluoroacetic acid affords the product of chlorodesilation in high yield.[10] The degradation of carboxylic acids to ketones can be achieved by α-sulfenation followed by reaction with NCS in the presence of $NaHCO_3$ (eq 6).[11] The *S*-chlorosulfonium ion intermediate undergoes a decarboxylative Pummerer-like rearrangement to afford the ketone upon hydrolysis. α-Phenylthio esters and amides can be successfully α-chlorinated using NCS in CCl_4 at 0 °C (eq 7).[12] 1,3-Dithianes are deprotected to afford ketones by reaction with NCS alone or in combination with ***Silver(I) Nitrate*** in aqueous acetonitrile (see also ***N-Bromosuccinimide***, ***Mercury(II) Chloride***, ***1,3-Diiodo-5,5-dimethylhydantoin***).[13]

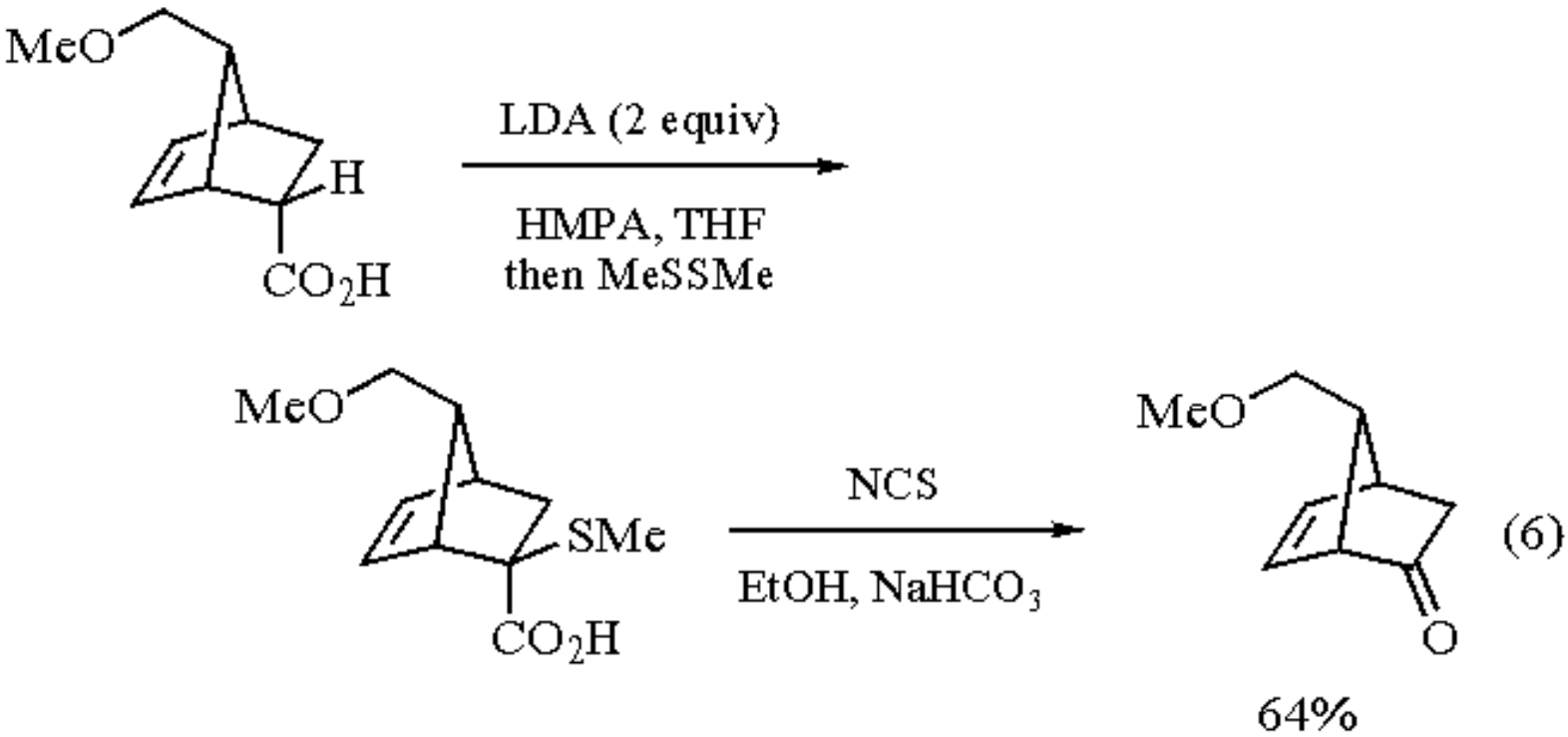

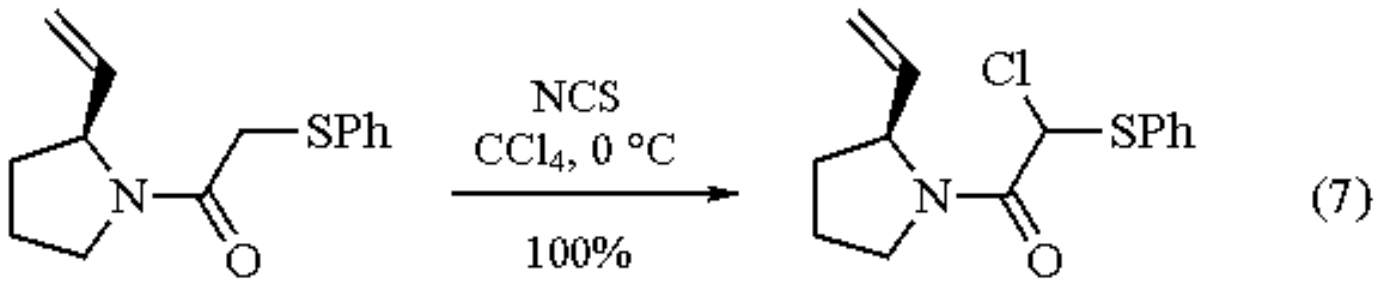

Sulfides can be oxidized to sulfoxides by reaction with NCS in methanol (0 °C, 1 h).[14] Similarly, selenides couple with amines when activated by NCS to form selenimide species. These have been generated from allylic selenides in order to prepare allylic amines and chiral secondary allylic carbamates by [2,3]-sigmatropic rearrangement (eq 8).[15]

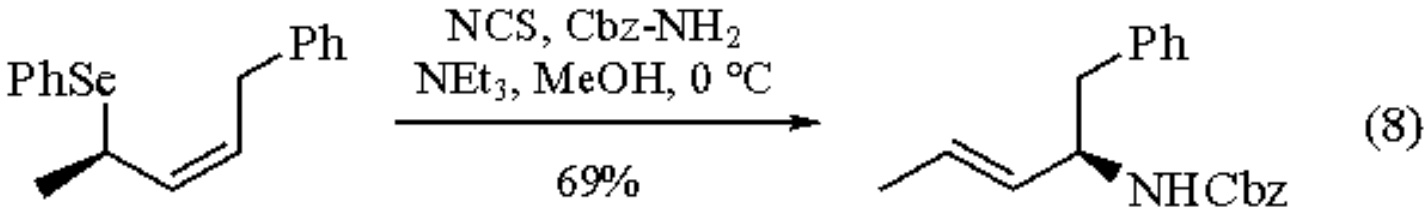

The α-chlorination of sulfoxides is generally performed in dichloromethane in the presence of a base (either K_2CO_3 or pyridine) and proceeds more slowly than the reactions with sulfides.[16] α-Chloro sulfoxides bearing high optical purity at sulfur are especially useful in asymmetric synthesis, but unfortunately the chlorination of optically active sulfoxides is generally accompanied by significant racemization at sulfur. Alternate procedures are available for achieving chlorination with predominant retention or inversion.[17] Using NCS and ***Potassium Carbonate*** the degree of racemization is minimized and chloromethyl *p*-tolyl sulfoxide can be prepared in 87% ee and 91% chemical yield (eq 9).[18]

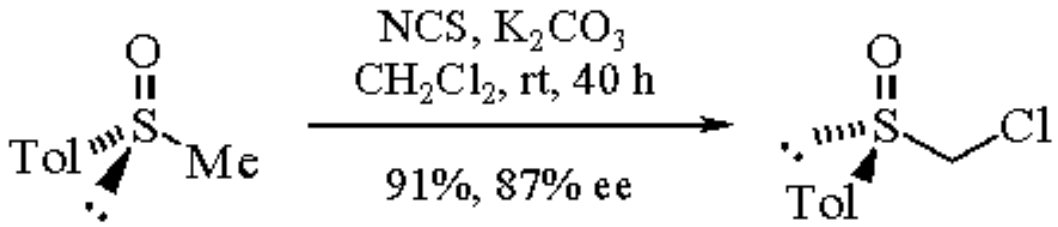

(9)

Reaction with Vinylic and Acetylenic Derivatives.

NCS is a suitable source of chlorine for the conversion of vinylcopper and other organometallic derivatives to the corresponding vinyl chlorides.[19] (*E*)-(1-Chloro-1-alkenyl)silanes are available from the appropriate 1-trimethylsilylalkynes by hydroalumination with ***Diisobutylaluminum Hydride*** followed by direct treatment of the vinylaluminum intermediate with NCS in ether at -20 °C (eq 10) (the corresponding (*Z*)-isomer is obtained by NBS-catalyzed isomerization of the (*E*)-isomer).[20] 1-Chloroalkynes can be prepared by reaction of the corresponding lithium acetylides with NCS in THF.[21]

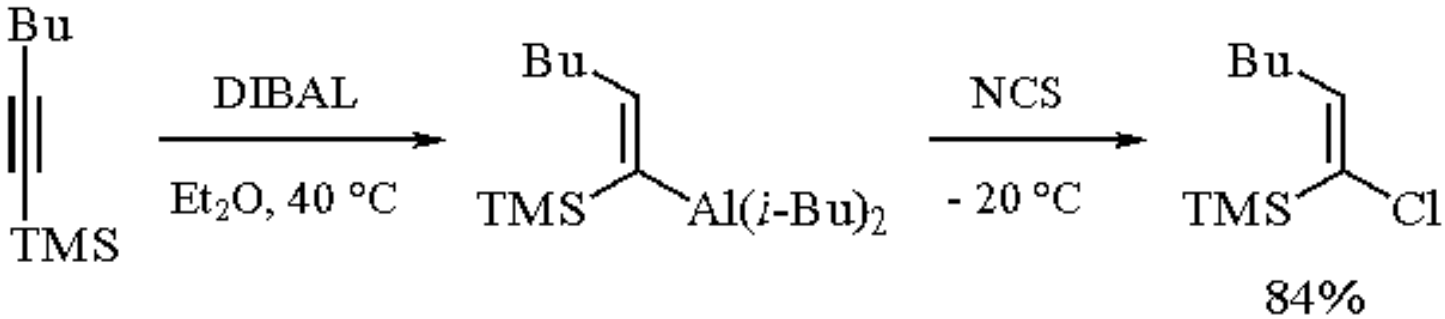

(10)

Chlorination of Aromatic Compounds.

NCS has also been used for the chlorination of pyrroles and indoles; however, the reaction is less straightforward than when NBS and ***N-Iodosuccinimide*** are used.[22] In the chlorination of 1-methylpyrrole, it has been demonstrated that basic conditions ($NaHCO_3$, $CHCl_3$) lead to the formation of 1-methyl-2-succinimidylpyrrole (eq 11).[23] In the presence of catalytic amounts of perchloric acid, thiophenes and other electron-rich aromatic compounds have been chlorinated with NCS.[24] (***N-Chlorosuccinimide-Dimethyl Sulfide*** is used for the selective *o*-substitution of phenols.)

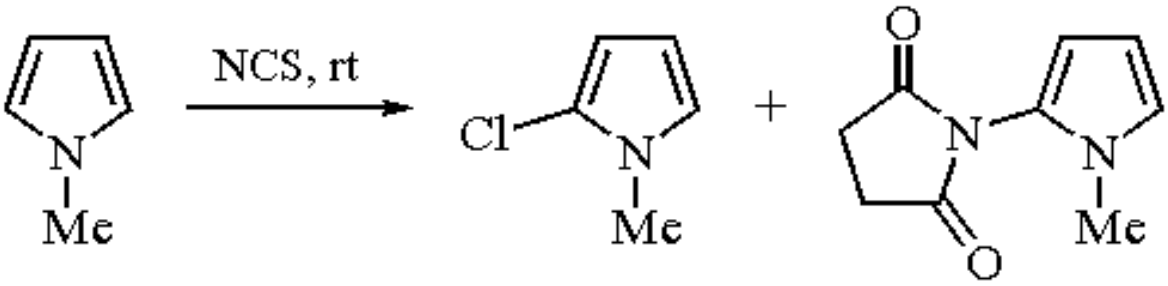

(11)

THF	89%	3%
$CHCl_3$, $NaHCO_3$	-	76%

Synthesis of *N*-Chloroamines.

The conversion of secondary amines to *N*-chloroamines by reaction with NCS in ether or dichloromethane has many advantages over the use of aqueous hypochlorite, including ease of isolation. This method has been used repeatedly in the preparation of *N*-chloroamines for alkene amination (eqs 12 and 13)[25] and other reactions.[26]

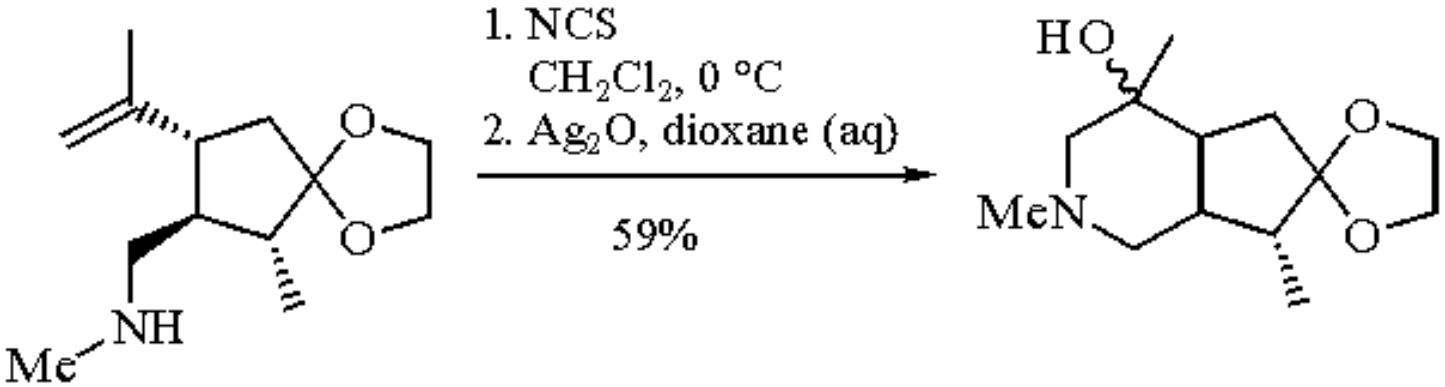

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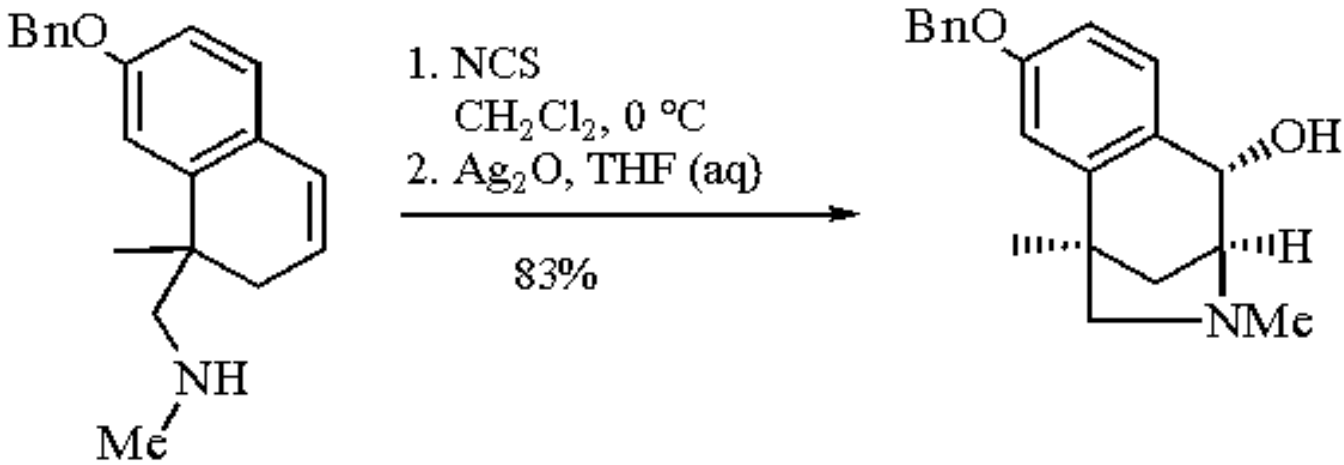

(13)

Other Oxidation and Chlorination Reactions.[27]

gem-Chloronitro compounds are prepared by treating nitronate anions with NCS in aqueous dioxane, or alternatively by reaction of ketoximes with NCS (eq 14).[28] Oxidative decarboxylation of carboxylic acids with ***Lead(IV) Acetate*** and NCS has been used effectively for the synthesis of tertiary alkyl chlorides (eq 15).[29]

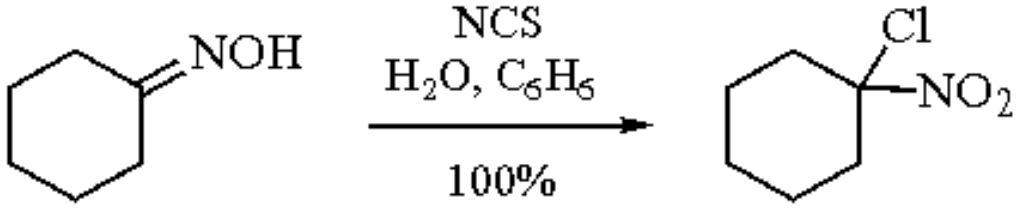

(14)

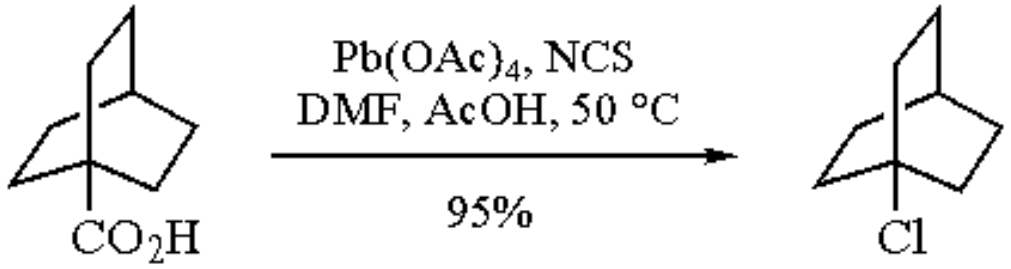

(15)

NCS is also regularly used for the direct oxidation of alcohols to ketones. The presence of ***Triethylamine*** serves to activate the reagent for rapid quantitative oxidation of catechols and hydroquinones to *o*- and *p*-quinones, respectively, and for the oxidation of benzophenone hydrazone to diphenyldiazomethane.[30] ***N-Chlorosuccinimide-Dimethyl Sulfide*** is also used in the mild oxidation of alcohols, as well as in the conversion of allylic alcohols to allylic chlorides.

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N-Chlorosuccinimide-Dimethyl Sulfide[1]

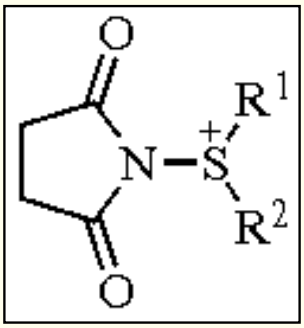

(R^1 = R^2 = Me)

[39095-38-0] · $C_6H_{10}ClNO_2S$ · *N*-Chlorosuccinimide-Dimethyl Sulfide · (MW 195.66) (R^1 = Me, R^2 = Et)

[54959-52-3] · $C_7H_{12}ClNO_2S$ · *N*-Chlorosuccinimide-Ethyl Methyl Sulfide · (MW 209.69) (R^1 = Me, R^2 = *n*-Pr)

[54959-53-4] · $C_8H_{14}ClNO_2S$ · *N*-Chlorosuccinimide-Methyl Propyl Sulfide · (MW 223.72) (R^1 = Et, R^2 = $CH_2CH{=}CH_2$)

[59321-40-3] · $C_9H_{14}ClNO_2S$ · *N*-Chlorosuccinimide-Allyl Ethyl Sulfide · (MW 235.73) (R^1 = Me, R^2 = CH_2CHMe_2)

[54959-54-5] · $C_9H_{16}ClNO_2S$ · *N*-Chlorosuccinimide-Isobutyl Methyl Sulfide · (MW 237.74) (R^1 = R^2 = *n*-Pr)

[59741-19-4] · $C_{10}H_{18}ClNO_2S$ · *N*-Chlorosuccinimide-Dipropyl Sulfide · (MW 251.77) (R^1 = Me, R^2 = Ph)

[82661-92-5] · $C_{11}H_{12}ClNO_2S$ · *N*-Chlorosuccinimide-Methyl Phenyl Sulfide · (MW 257.73) (R^1 = Et, R^2 = $CH_2CH{=}CMe_2$)

[59321-43-6] · $C_{11}H_{18}ClNO_2S$ · *N*-Chlorosuccinimide-3,3-Dimethylallyl Ethyl Sulfide · (MW 263.78) (R^1 = Me, R^2 = CH_2Ph)

[65824-49-9] · $C_{12}H_{14}ClNO_2S$ · *N*-Chlorosuccinimide-Benzyl Methyl Sulfide · (MW 271.76) (R^1 = Et, R^2 = CH_2Ph)

[65824-51-3] · $C_{13}H_{16}ClNO_2S$ · *N*-Chlorosuccinimide-Benzyl Ethyl Sulfide · (MW 285.79) (R^1 = Et,

$R^2 = CH_2C_6H_4$-4-Me)

[65824-52-4] · $C_{14}H_{18}ClNO_2S$ · *N*-Chlorosuccinimide-Ethyl *p*-Tolylmethyl Sulfide · (MW 299.82)
(R^1 = Et, $R^2 = CH_2(1\text{-}C_{10}H_7)$)

[65824-54-6] · $C_{17}H_{18}ClNO_2S$ · *N*-Chlorosuccinimide-Ethyl 1-Naphthylmethyl Sulfide · (MW 335.85)
($R^1 = R^2 = n\text{-}C_7H_{15}$)

[59741-21-8] · $C_{20}H_{38}ClNO_2S$ · *N*-Chlorosuccinimide-Diheptyl Sulfide · (MW 392.04)

(oxidizing agent for alcohols to aldehydes and ketones,[1] catechols and hydroquinones to quinones,[2] aromatic amines to sulfilimines,[3] hydroxamic acids to acylnitroso compounds;[4] chlorination of allylic and benzylic alcohols,[5] *ortho* alkylation and formylation of phenols,[6] preparation of chloromethyl thioethers,[7] thioalkylation of pyrroles, indoles, and enamines;[8] preparation of sulfur ylides of active methylene compounds,[9] preparation of sulfonium salts from enamines and cyclopentadienyl anions,[10] dehydration to form keto enamines from β-diketones and nitriles from aldoximes[11])

Alternate Names: Corey-Kim reagent; dimethyl(succinimido)sulfonuim chloride.

Physical Data: $R^1 = R^2$ = Me: mp 70-72 °C.

Solubility: the reagents are slightly more sol in CH_2Cl_2, toluene, and THF than the NCS from which they are derived.

Form Supplied in: prepared in situ from NCS and dialkyl sulfides.

Handling, Storage, and Precautions: see ***N-Chlorosuccinimide***, ***Dimethyl Sulfide***, and other articles on alkyl sulfides.

N-Chlorosuccinimide-Dialkyl Sulfides.

These reagents are generally prepared in situ in solvents such as toluene, CH_2Cl_2, or THF. The reagents themselves are generally more soluble than the NCS from which they are derived and are often prepared at a temperature of about 0 °C to facilitate reaction with the limitedly soluble NCS, but because of their thermal instability are not prepared at higher temperature. They are often used at temperatures as low as -78 °C.

Oxidations.

N-Chlorosuccinimide-dimethyl sulfide (NCS-DMS) is one of several reagents for converting alcohols to alkoxydimethylsulfonium salts, which in the presence of base convert to the corresponding carbonyl compounds via intramolecular proton transfer and loss of dimethyl sulfoxide.[1,12] These oxidations are among the mildest and most selective for conversions of alcohols to aldehydes and ketones. This reaction does not suffer the overoxidation to acids

or the carbon-carbon bond cleavages which are often encountered in chromium(VI) or manganese(VII) oxidations (eq 1).[1,13]

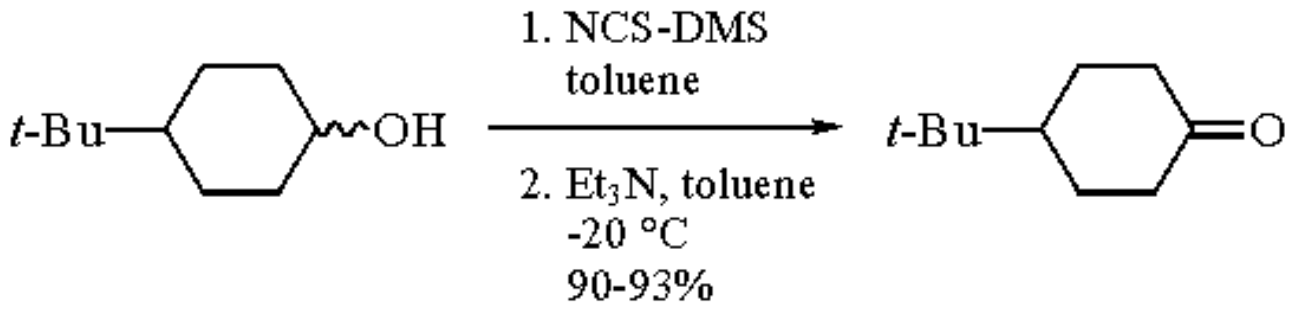

(1)

Several higher members of this class, including the NCS-diisopropyl sulfide reagent, are reported to show unusual selectivity for primary and secondary alcohols. Thus at 0 °C the reagent selectively oxidizes primary alcohols rather than secondary, whereas at -78 °C it selectively oxidizes secondary alcohols rather than primary (eq 2).[14]

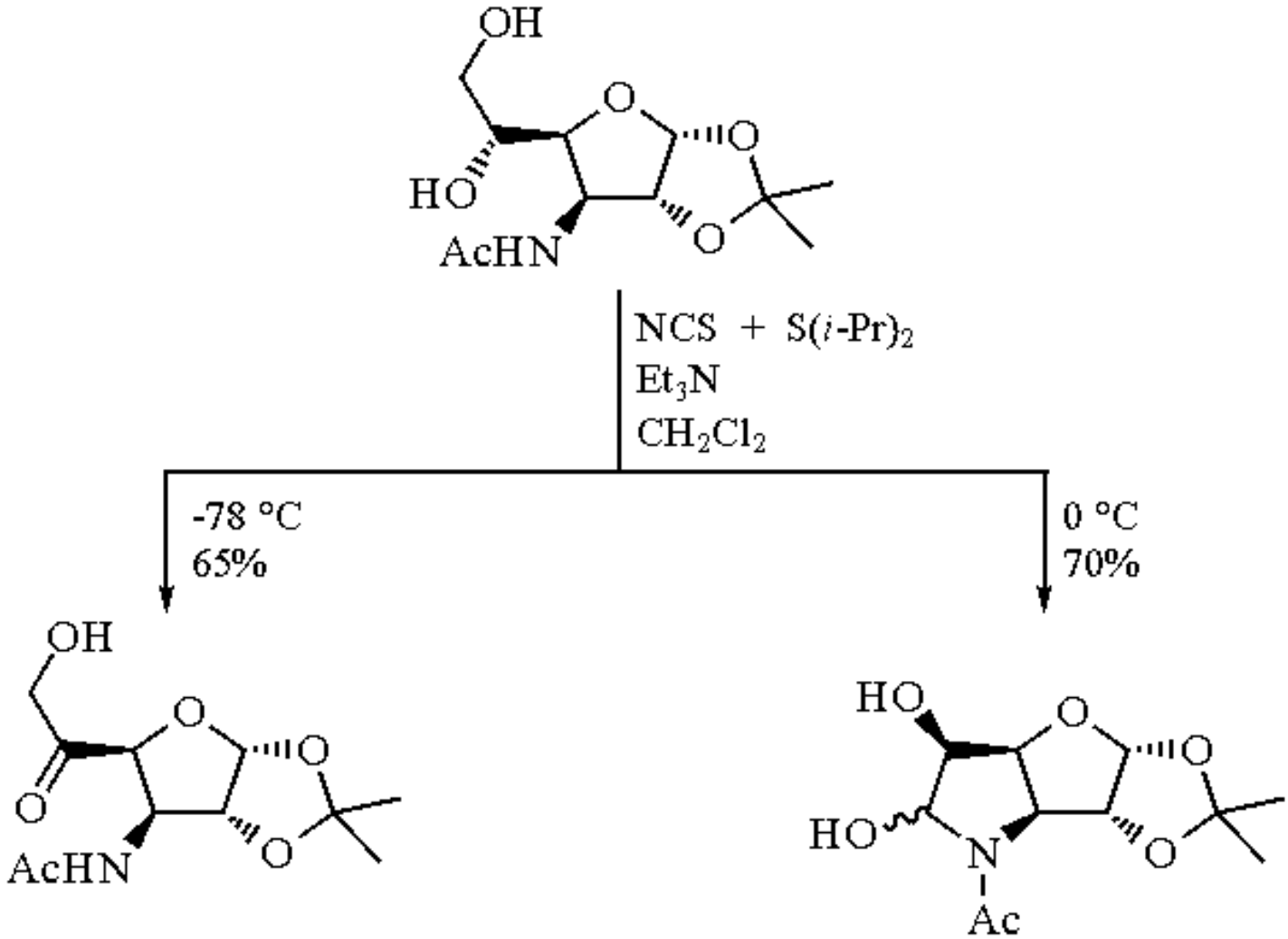

(2)

These reagents are also effective in the oxidation of *s,t*-1,2-diols to α-ketols (eq 3).[13] Metal-based reagents give carbon-carbon bond cleavage with such diols.

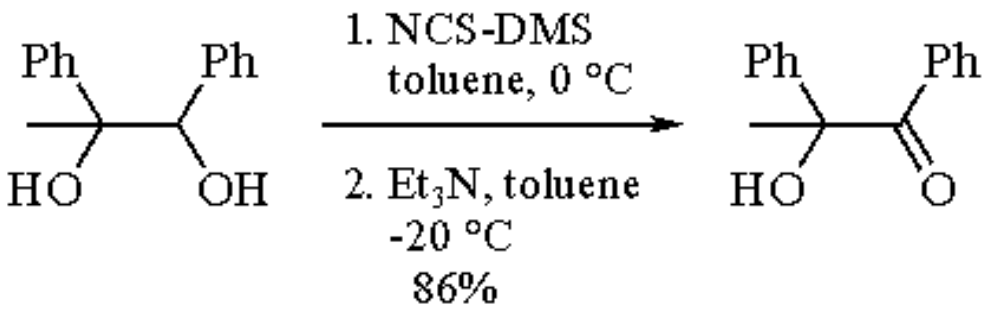

(3)

Oxidation of 1,3-keto alcohols or 1,3-diketones gives 1,3-diketo sulfonium ylides, which may be reduced to the 1,3-diketones (eq 4).[9]

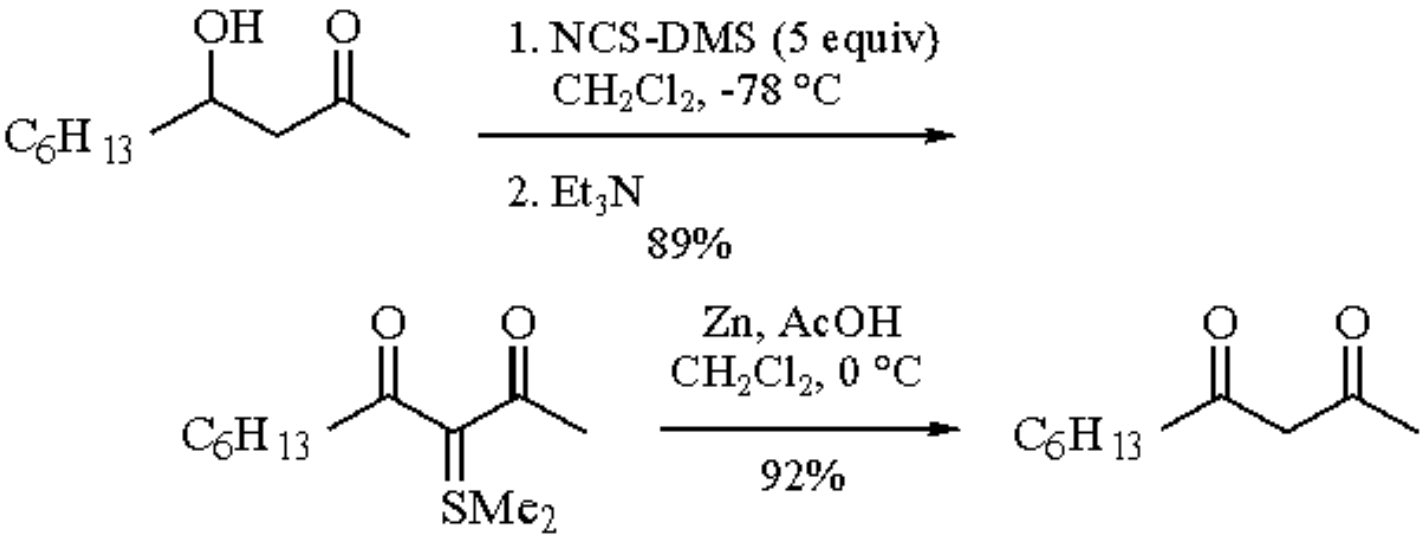

(4)

Catechols and hydroquinones are oxidized to quinones (eq 5),[3] and *N*-hydroxyureas are oxidized to nitroso compounds (eq 6).[4]

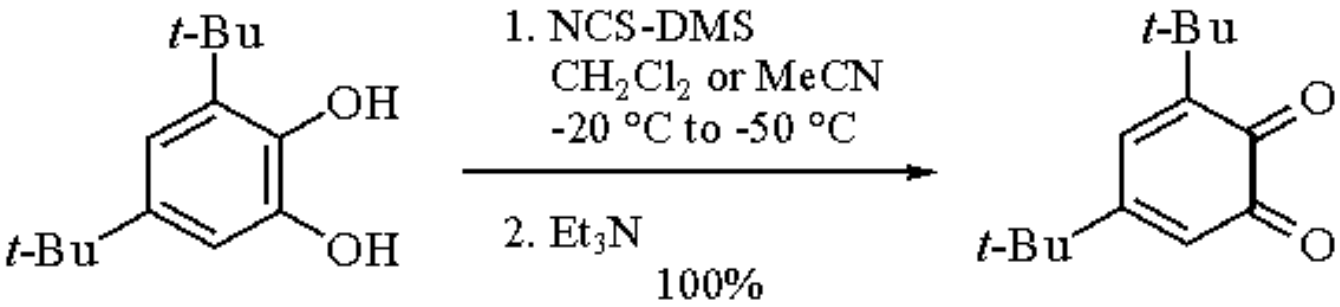

(5)

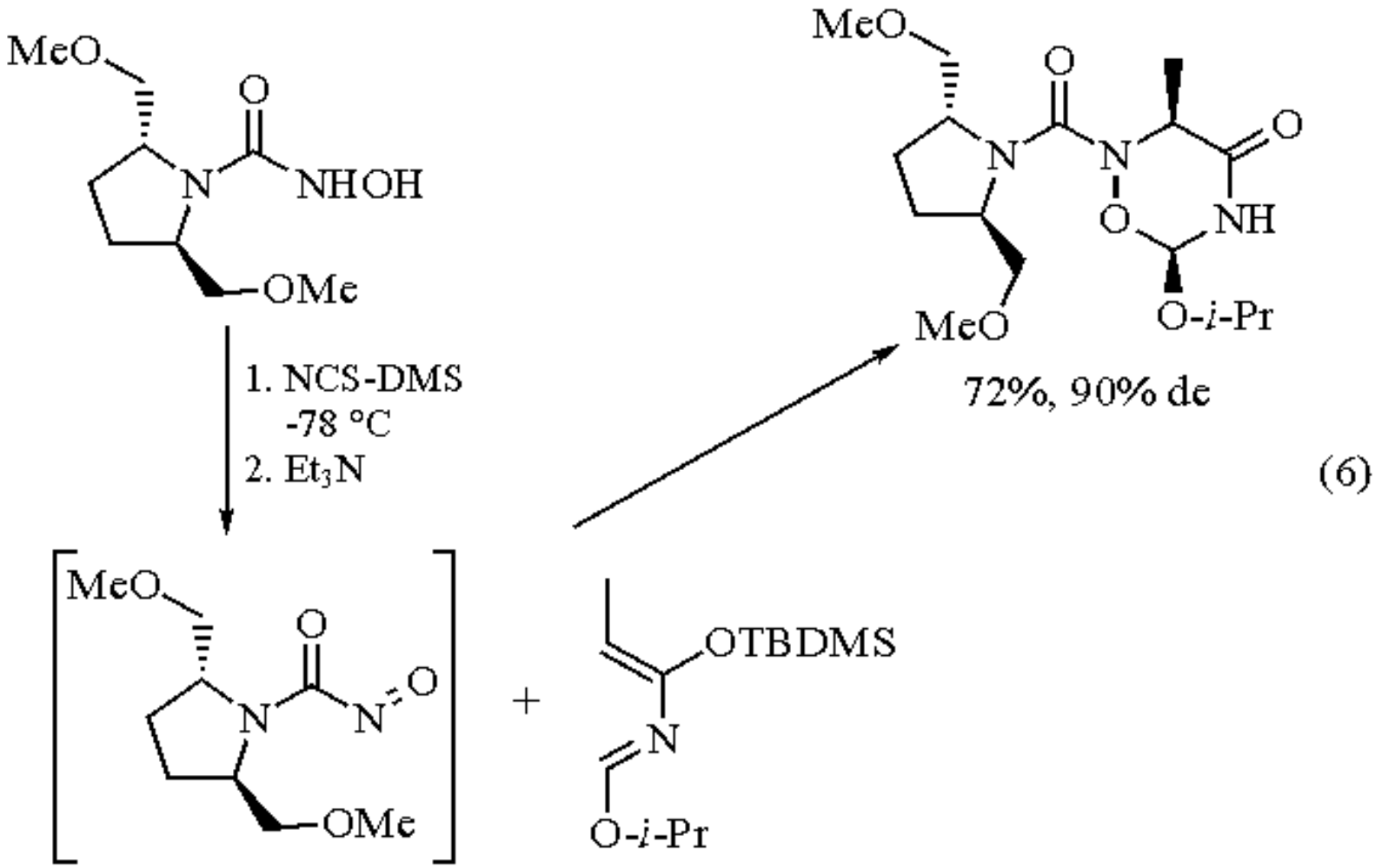

Halogenations.

Allylic, benzylic, and cyclopropyl carbinyl alcohols are reported to undergo chlorination with or without allyl rearrangement, depending upon structure.[15] Thus primary and secondary allylic carbinols generally give the chlorides without rearrangement (eqs 7 and 8), whereas 2-formyl secondary allylic alcohols give the rearranged product (eq 9).[5]

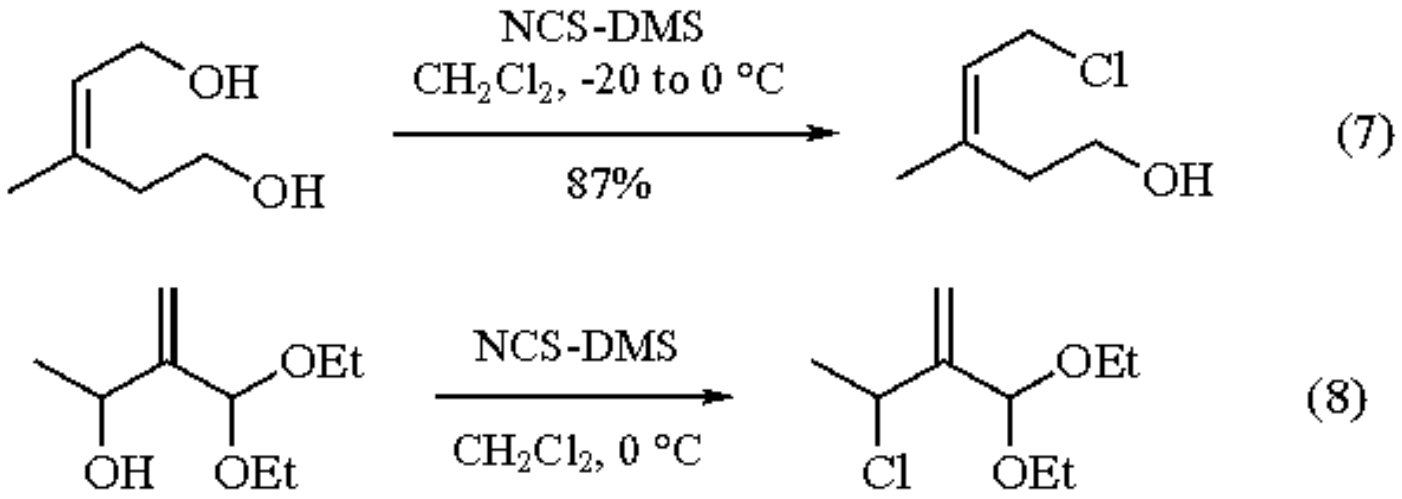

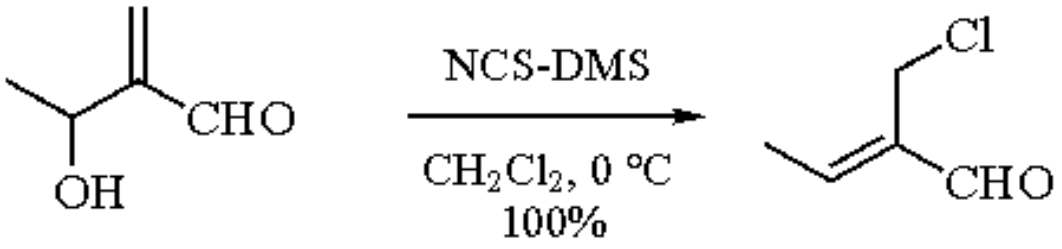

(9)

The NCS-dialkyl sulfide reagents are thermally labile, and depending on structure undergo a variety of transformations leading ultimately to α-chlorination of the sulfide (eq 10).[7]

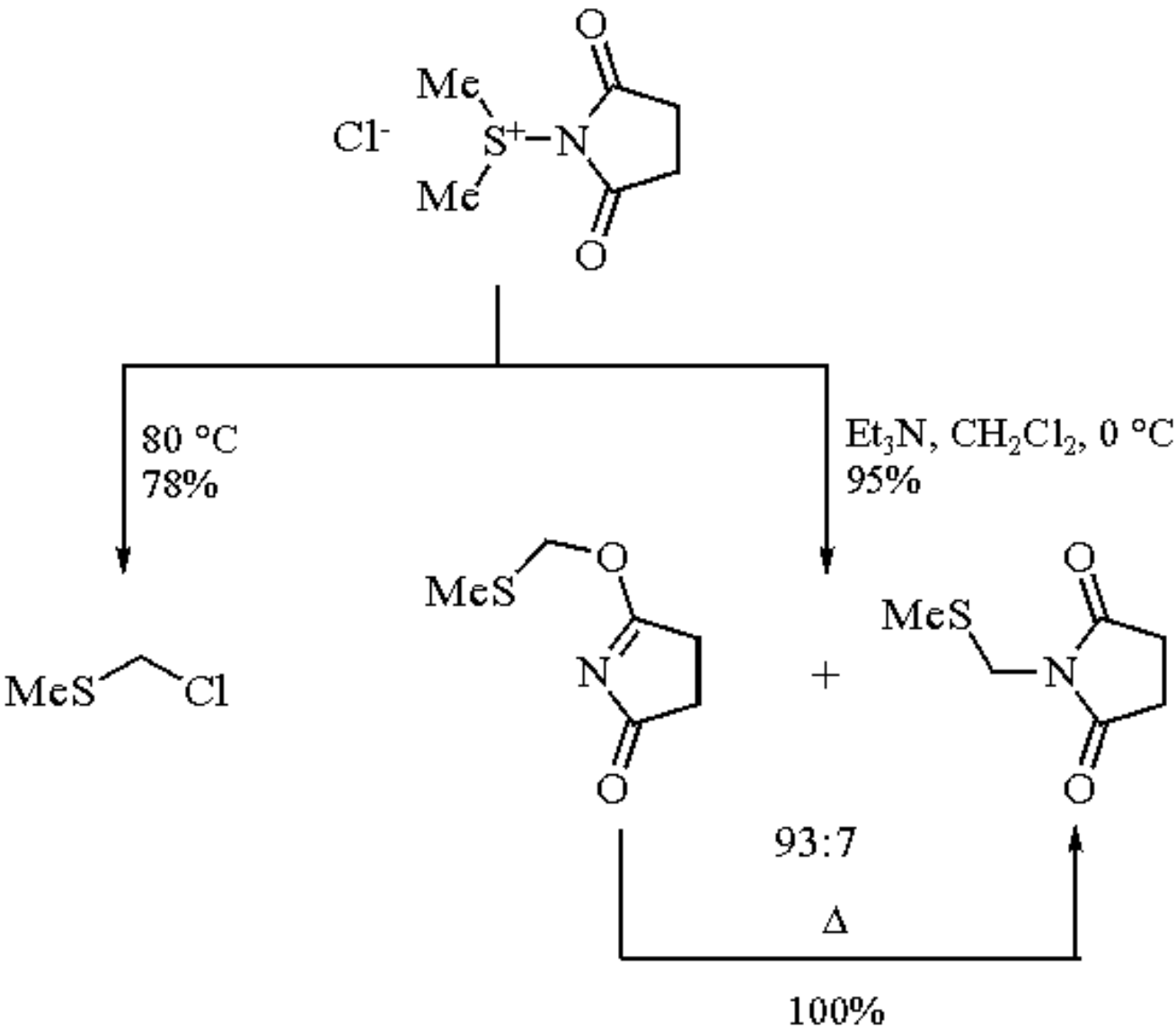

(10)

O-Alkylation of Anilines and Phenols.

Treatment of anilines with NCS-DMS leads to sulfilimines, which may be converted to 2-alkylanilines (eq 11).[3] Similarly, phenols give directly the 2-substituted product (eq 12).[6]

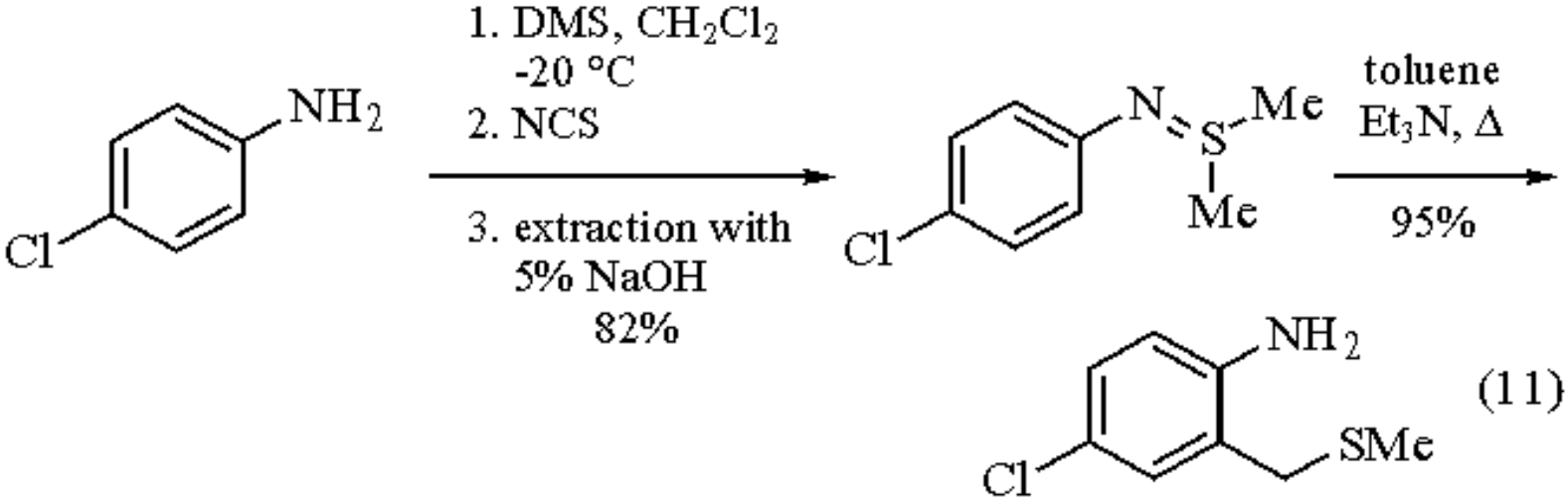

(11)

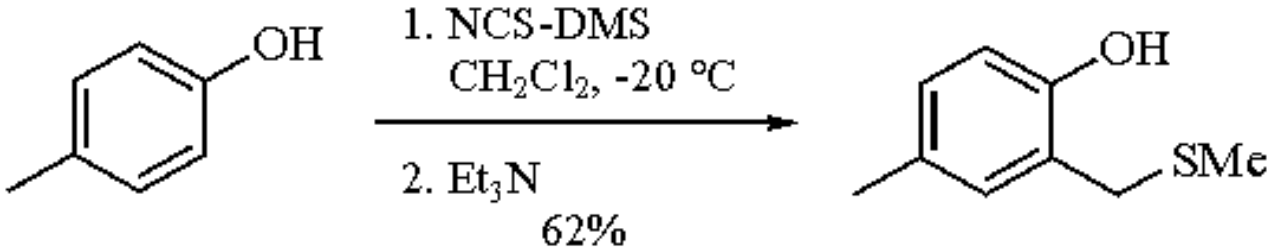

(12)

Other Alkylations.

NCS and allylic sulfides react with 3-unsubstituted indoles at -20 °C to give initially 3-sulfonium salts which on warming to 20 °C rearrange to 2-allyl-3-thiomethylindoles (eq 13). These are readily desulfurized, either with or without concomitant reduction of the allylic double bond, to give 3-allyl or 3-alkyl substituted indoles.[8b,8c]

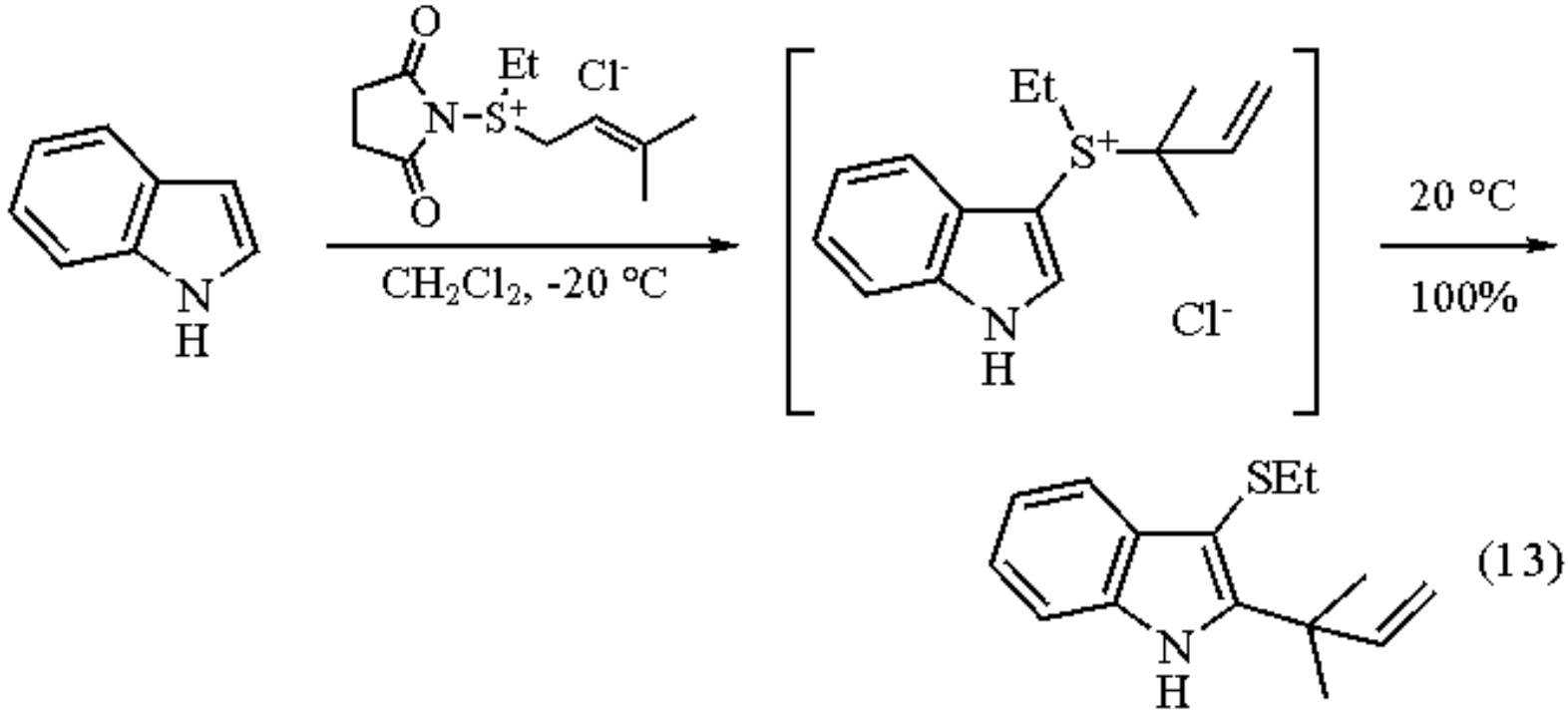

(13)

On the other hand, 3-alkyl-1*H*-indoles react with NCS-dialkyl sulfides in the presence of base to give 3-alkyl-3-alkylthioalkyl-3*H*-indoles (indolinenes, eq 14).[16]

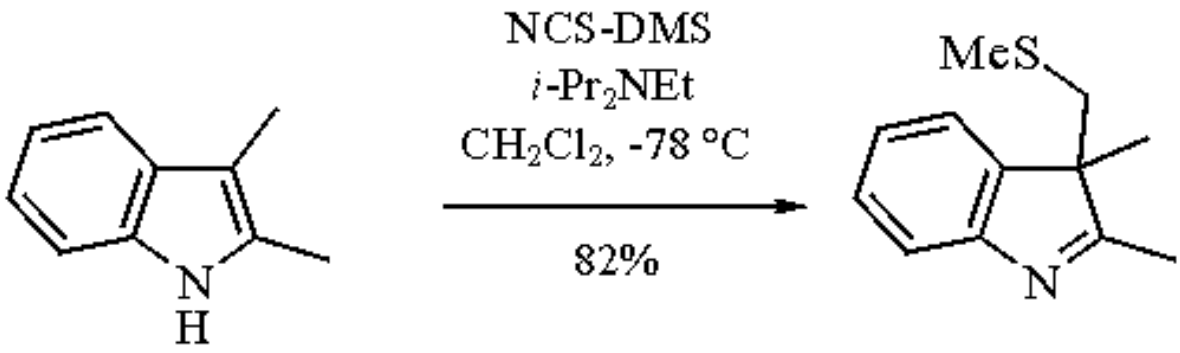

(14)

NCS-DMS reacts with cyanoacetate anions nearly exclusively at nitrogen to give *N*-alkylthiomethylketenimines (eq 15).[17]

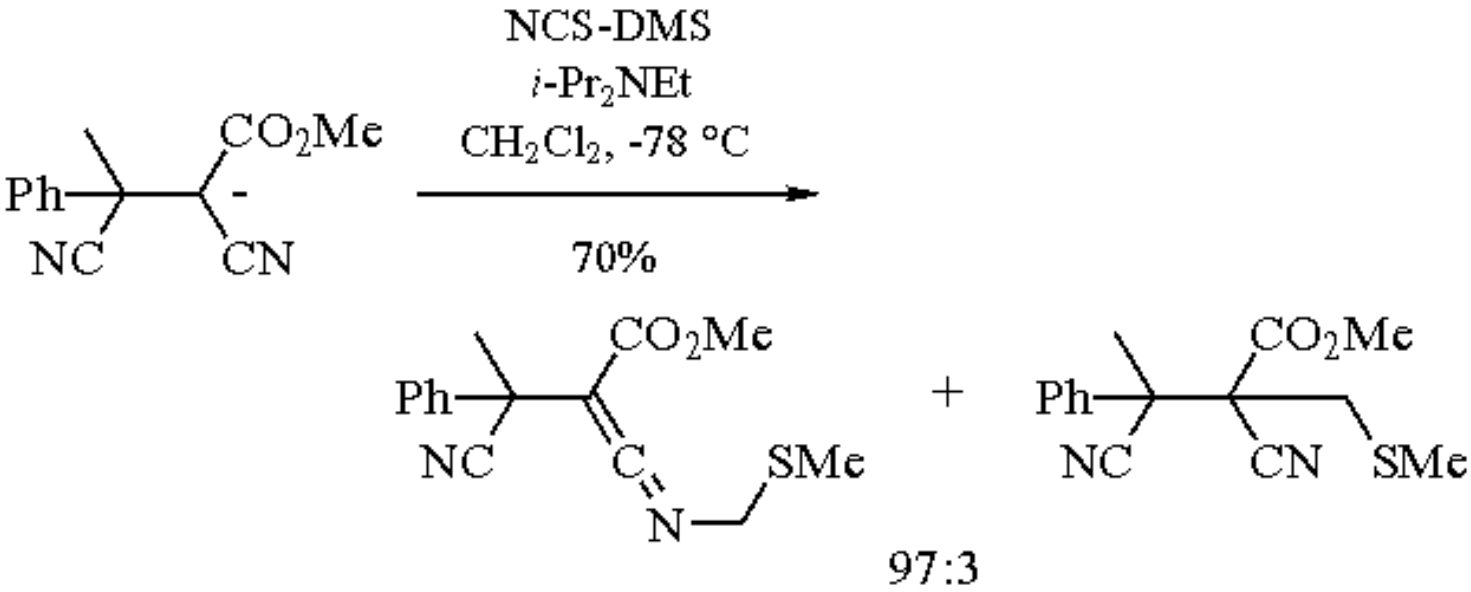

(15)

Thioalkylation.

Treatment of pyrroles with NCS-DMS leads to 2-thiomethylpyrroles (eq 16). Indoles give 3-thioalkylindoles (eq 17).[8a-c]

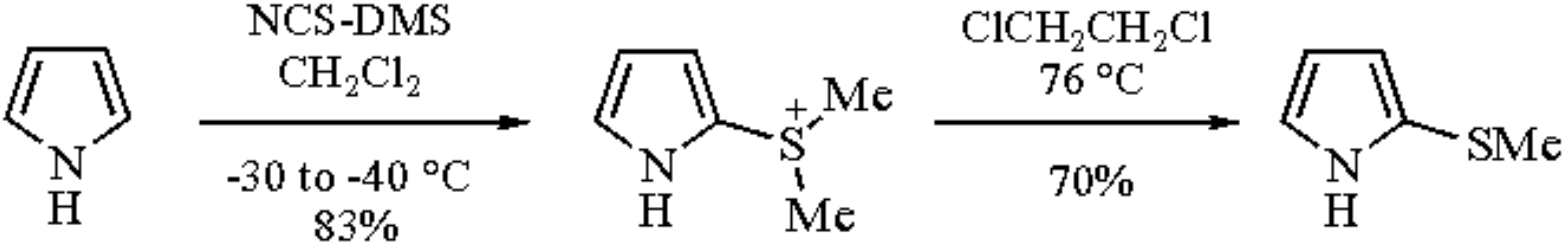

(16)

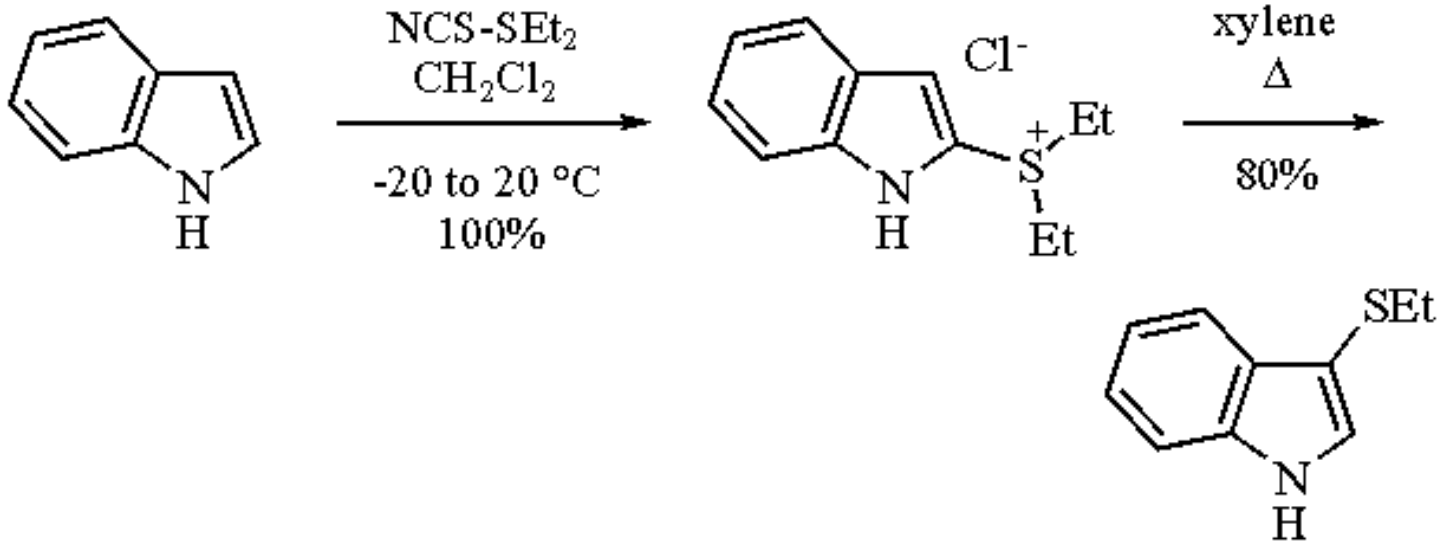

(17)

NCS-DMS reacts with enamines to give sulfonium salts (eq 18),[10a,10b] and with cyclopentadienyl anions to give bis- and tris-substituted sulfonium salts (eq 19).[10c]

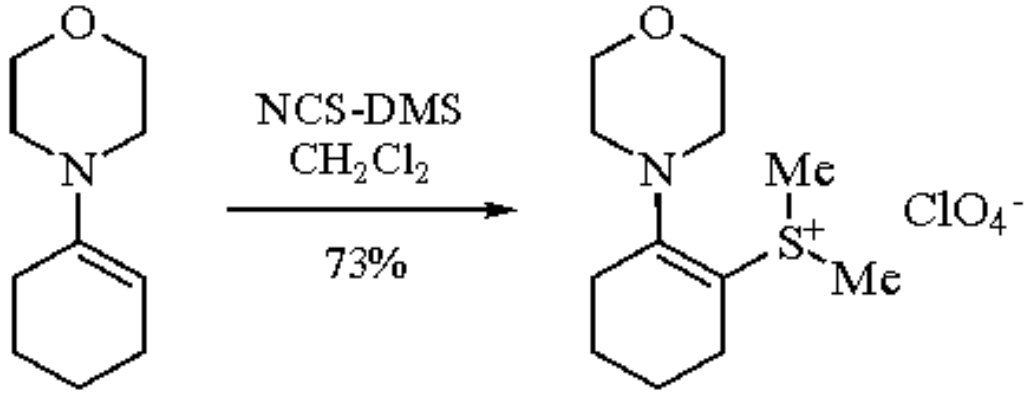

(18)

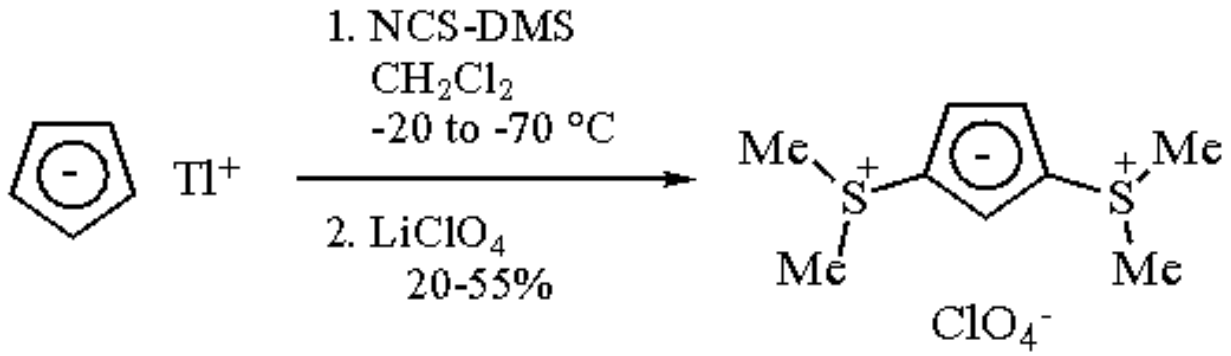

(19)

Dehydrations.

While certain 1,3-diketones produce the sulfonium ylide, the treatment of *N*-acetylpiperidine-3,5-dione first with NCS-DMS and then with an amine in the presence of TFA resulted in the formation of the enaminone. The yields for this conversion were report to be significantly better than in the traditional method of azeotropic water removal (eq 20).[11a]

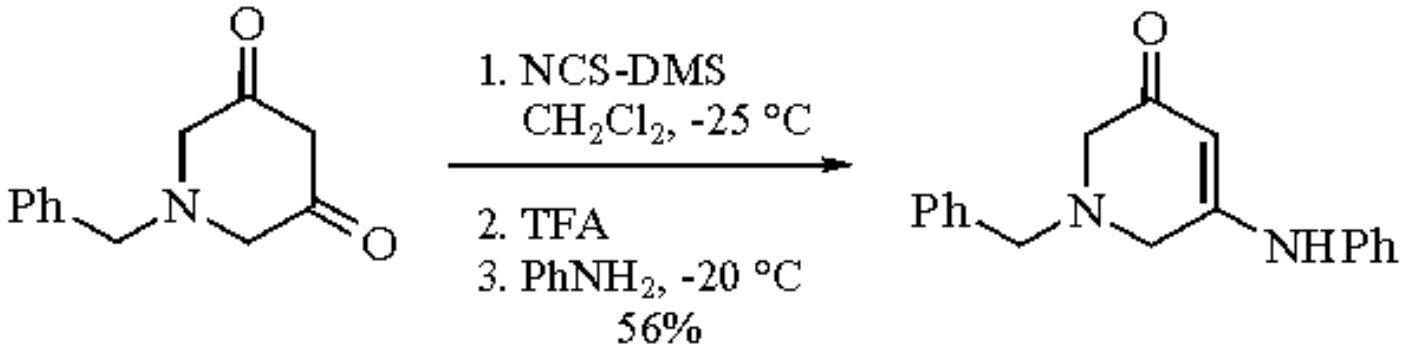

(20)

It was found during an attempt to produce *N*-methylthiomethyl nitrones that treatment of aldoximes with NCS-DMS resulted in high yields of nitriles (eq 21).[11b]

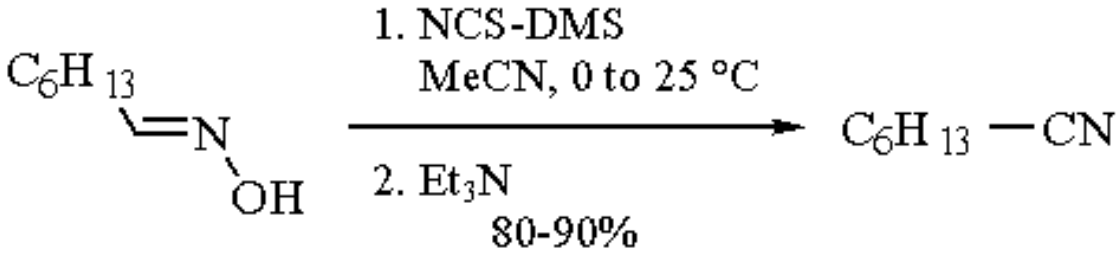

(21)

Related Reagents.

Dimethyl Sulfoxide-Oxalyl Chloride; ***Dimethyl Sulfoxide-Phosgene***; ***Dimethyl Sulfoxide-Triphosgene***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Fisher, L. E.; Muchowski, J. M. *OPP* **1990**, *22*, 399.
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7. (a) Vilsmaier, E.; Sprugel, W. *LA* **1971**, *747*, 151. (b) Vilsmaier, E.; Dittrich, K. H.; Sprugel, W. *TL* **1974**, 3601.
8. (a) Franco, F.; Greenhouse, R.; Muchowski, J. M. *JOC* **1982**, *47*, 1682. (b) Tomita, K.; Terada, A.; Tachikawa, R. *H* **1976**, *4*, 729. (c) Tomita, K.; Terada, A.; Tachikawa, R. *H* **1976**, *4*, 733. (c) Vilsmaier, E.; Sprugel, W.; Gagel, K. *TL* **1974**, 2475. (d) Vilsmaier, E.; Troger, W.; Sprugel, W.; Gagel, K. *CB* **1979**, *112*, 2997.
9. (a) Katayama, S.; Fukuda, K.; Watanabe, T.; Yamauchi, M. *S* **1988**, 178. (b) Katayama, S.; Watanabe, T.; Yamauchi, M. *CL* **1989**, 973. (c) Katayama, S.; Watanabe, T.; Yamauchi, M. *CPB* **1990**, *38*, 3314.
10. (a) Vilsmaier, E.; Sprugel, W.; Gagel, K. *TL* **1974**, 2475. (b) Vilsmaier, E.; Troger, W.; Sprugel, W.; Gagel, K. *CB* **1979**, *112*, 2997. (c) Schlingensief, K. H.; Hartke, K. *TL* **1977**, 1269.
11. (a) Tamura, Y.; Chen, L. C.; Fujita, M.; Kiyokawa, H.; Kita, Y. *CI(L)* **1979**, 668. (b) Dalgard, N. K. A.; Larsen, K. E.; Torssell, K. B. G. *ACS,B* **1984**, *38*, 423.

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Robert C. Kelly

The Upjohn Company, Kalamazoo, MI, USA

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Chlorosulfonic Acid[1]

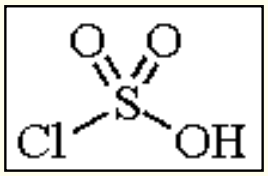

[7790-94-5] · $ClHO_3S$ · Chlorosulfonic Acid · (MW 116.53)

(strong acid with weak sulfur-chlorine bond; a strong sulfating, sulfonating, and dehydrating agent; also a chlorinating agent)

Alternate Name: chlorosulfuric acid.

Physical Data: mp -81 to -80 °C; bp 151-152 °C/755 mmHg; *d* 1.753 g cm^{-3}.

Solubility: sol 1,1,2,2-tetrachloroethylene, chloroform, dichloromethane, nitrobenzene, acetic acid, and acetic anhydride; slightly sol carbon disulfide and carbon tetrachloride; reacts with alcoholic solvents.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: strong acid, causing severe chemical burns if in contact with skin; use in a fume hood, since fumes are hazardous and extremely irritating to eyes, nose, and respiratory tract; reacts violently with moisture, releasing HCl and H_2SO_4; store under nitrogen in a cool dry place.

Aromatic Sulfonation/Chlorosulfonation.

Aromatic compounds react with chlorosulfonic acid to produce the corresponding sulfonated products.[2] The resulting sulfonic acids react with excess chlorosulfonic acid to produce sulfonyl chlorides (eqs 1 and 2).

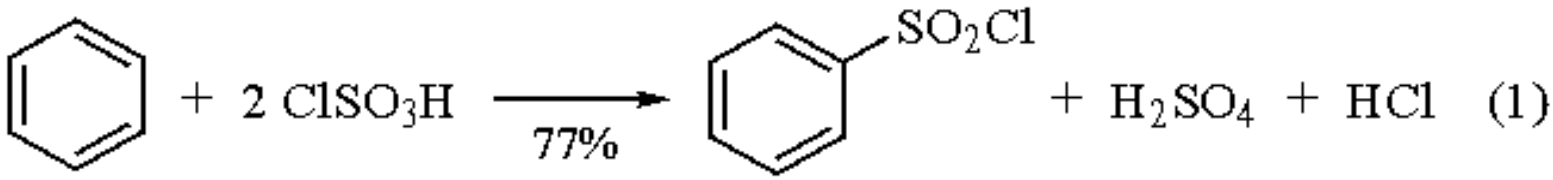

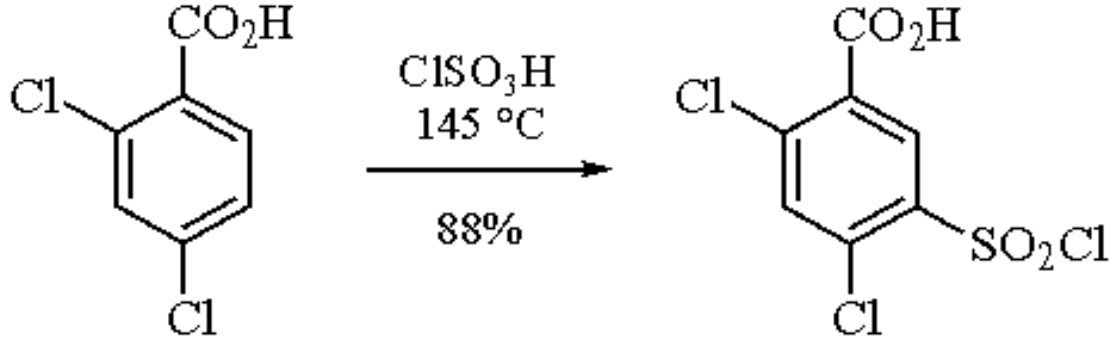

(2)

This method has been used to prepare the sulfonated derivatives of benzene,[2] benzoic acid,[3] acetanilide,[4] naphthalene,[2] and anthracene.[5] Additional examples include chlorosulfonation of biphenyl (eq 3),[6] chlorophenols,[6,7] benzophenone,[8] diphenyl sulfone,[8] and ferrocene.[9]

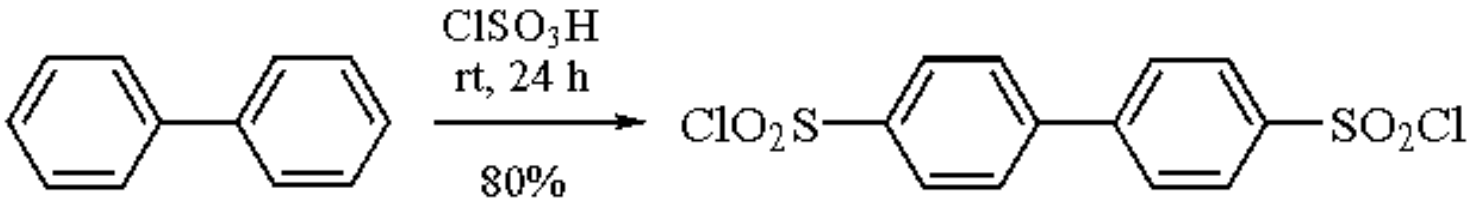

(3)

Arylsulfonamides are obtained by the reaction of aromatic compounds with $ClSO_3H$ followed by ammonia (eqs 4 and 5).[10]

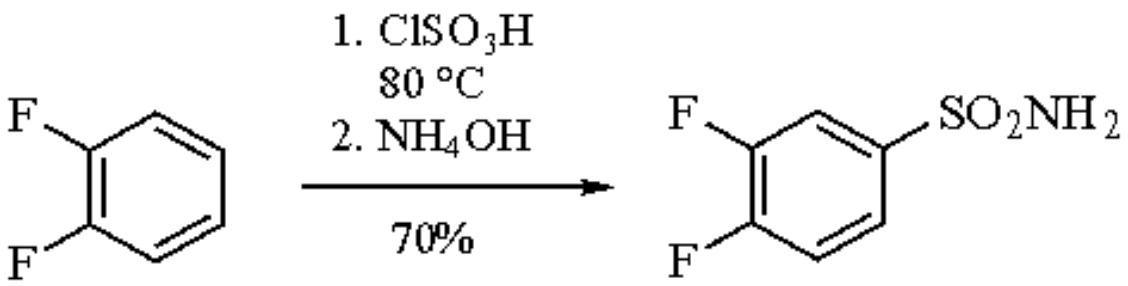

(4)

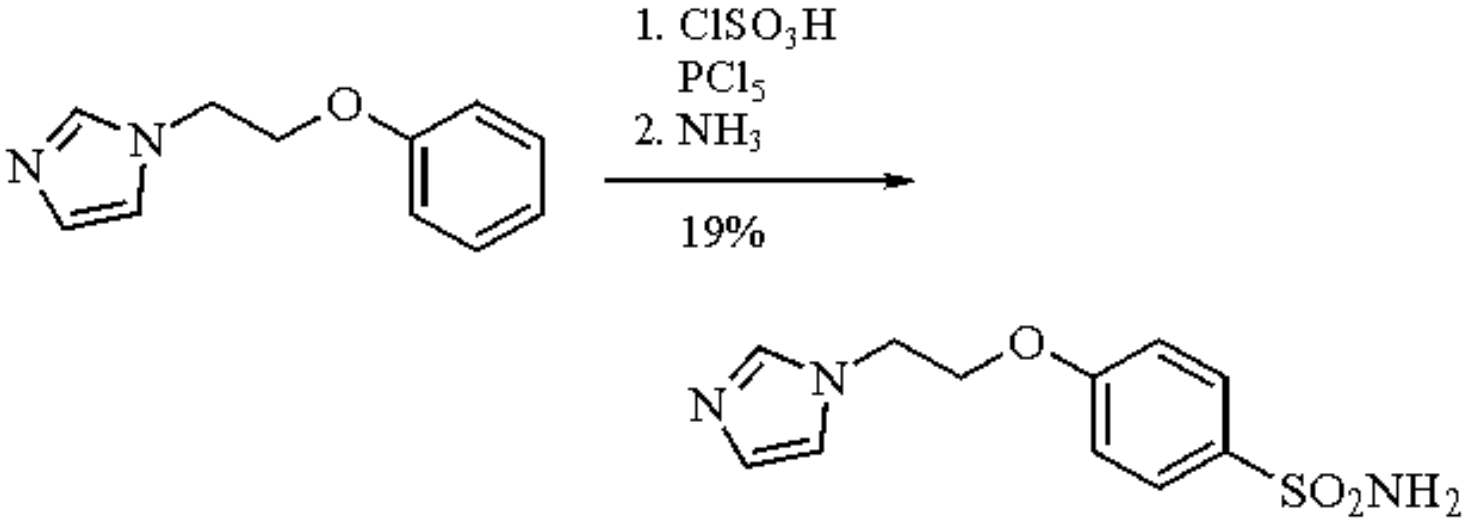

(5)

Treatment of aromatic amino acids such as tyrosine and tryptophan with $ClSO_3H$ leads to the formation of the

corresponding arylsulfonic acids (eq 6). This technique has been used to modify peptides.[11]

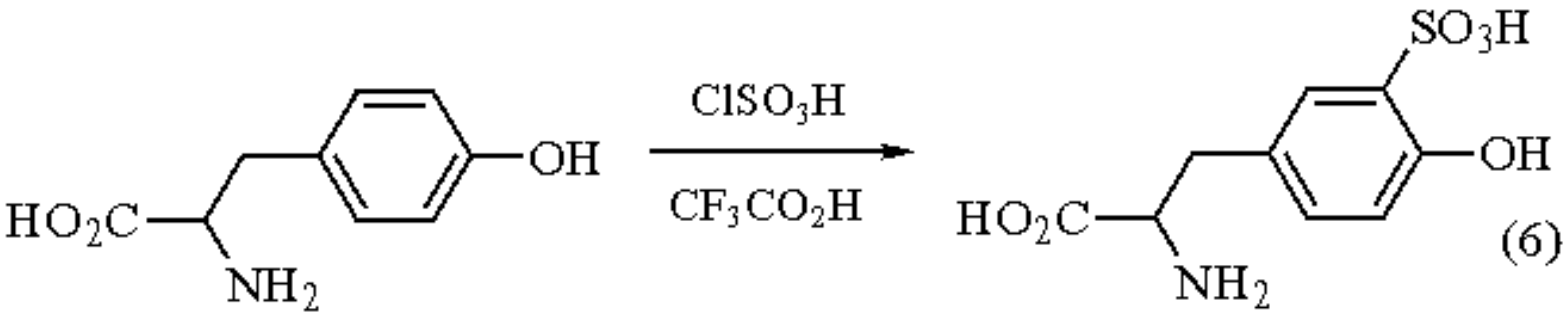

Some abnormal products are obtained when aromatic halides react with $ClSO_3H$. For example, *p*-dichlorobenzene and *p*-dibromobenzene undergo chlorination on reaction with $ClSO_3H$ in the presence of iodine (eq 7).[2a,12] Fluorobenzene, iodobenzene, *o*-dichlorobenzene, and *o*-dibromobenzene yield the corresponding sulfones.[2a,12]

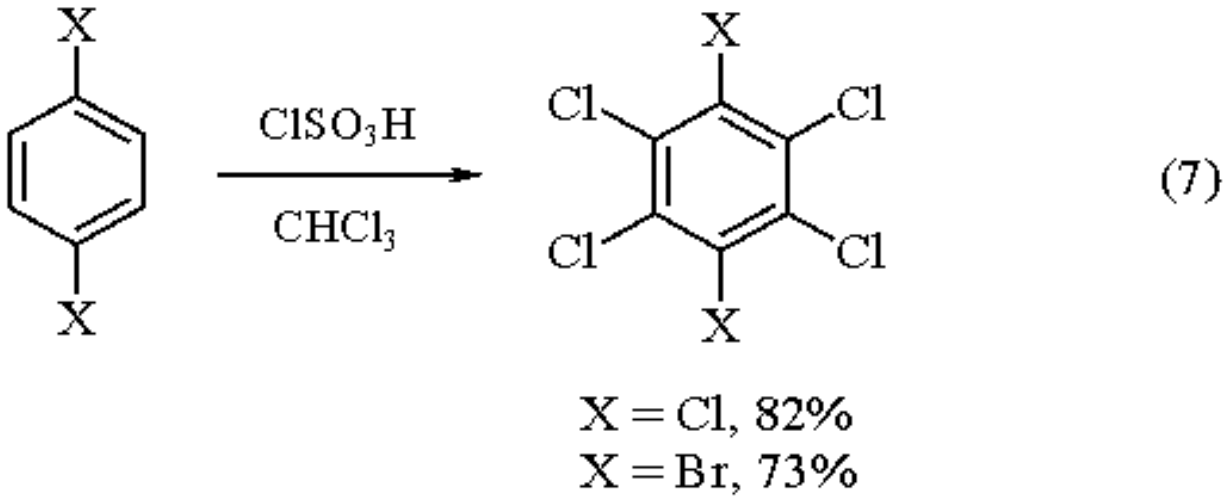

α-Sulfonation of Carboxylic Acids.

Chlorosulfonic acid has been used to prepare α-sulfonated derivatives of carboxylic acids (eqs 8 and 9).[13]

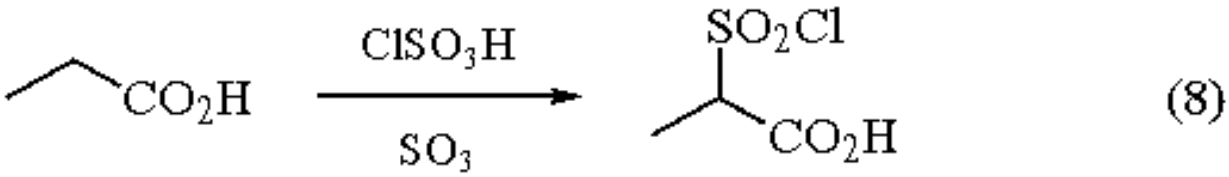

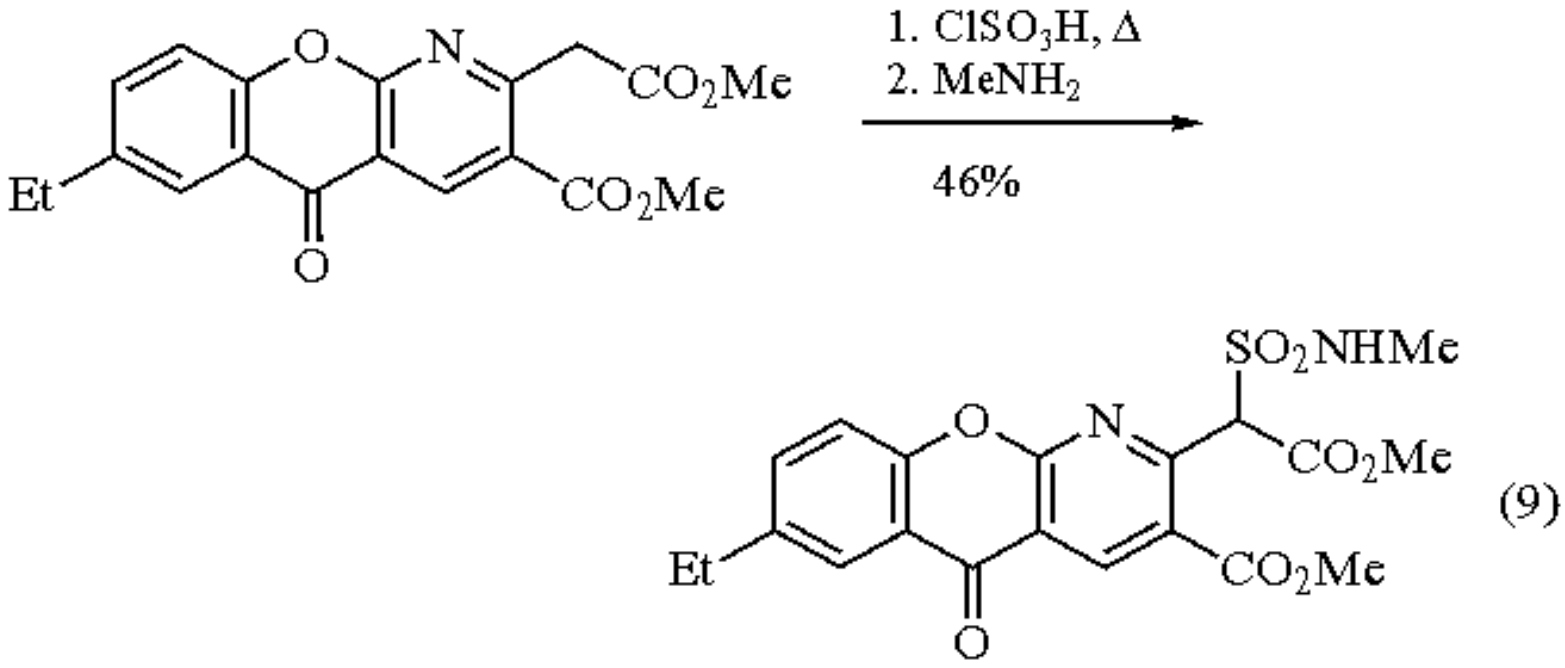

Sulfation.

Treatment of alcohols with $ClSO_3H$ produces the corresponding sulfate esters. By this method the carotenoid alcohols lycoxanthin and zeaxanthin were converted to their sulfate esters (eqs 10 and 11).[14] The hydroxy amino acids serine and threonine are converted to their corresponding sulfate esters by $ClSO_3H$.[11] Carbohydrates[15] and chitin[16] are also sulfated by treatment with $ClSO_3H$.

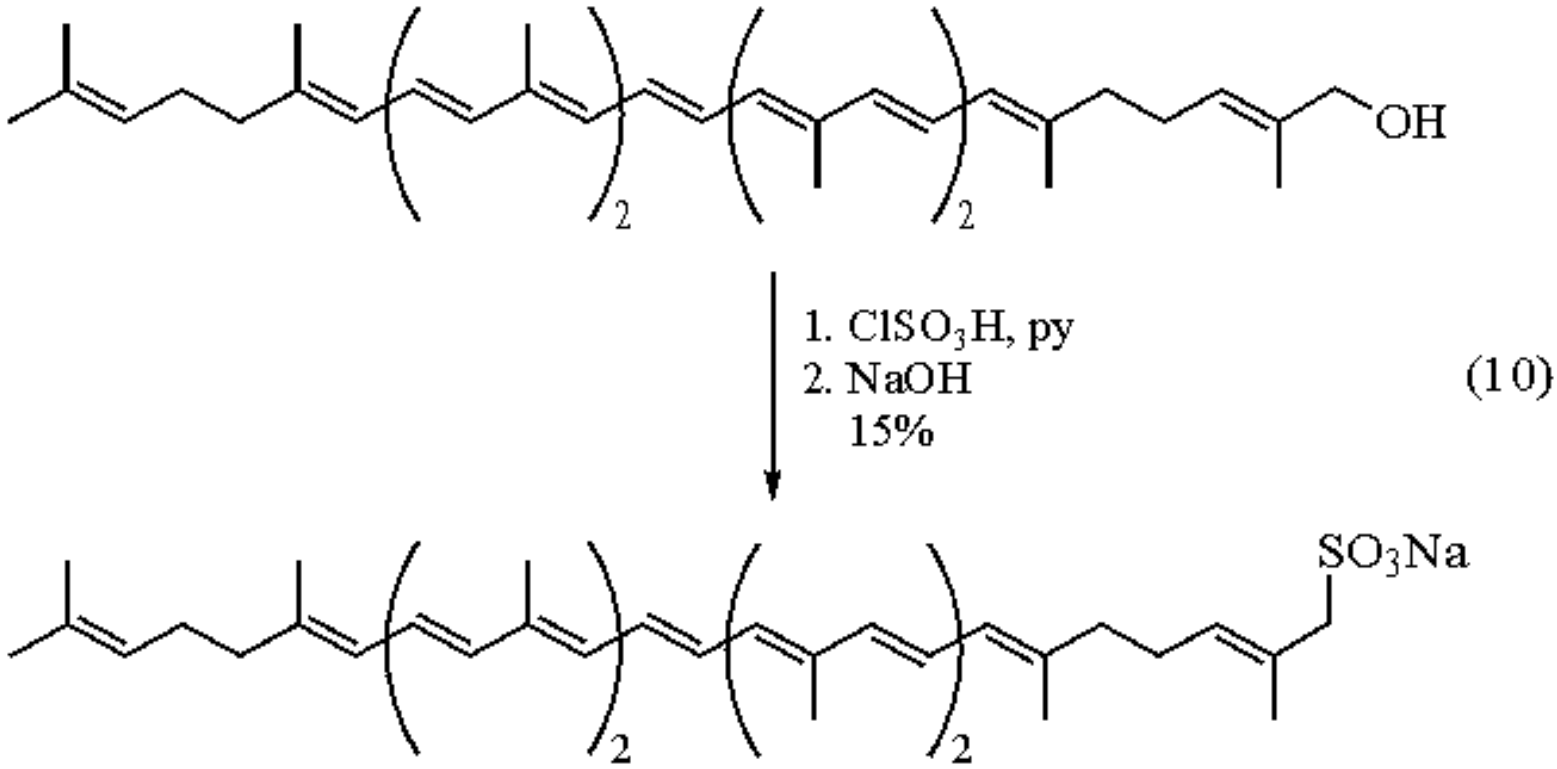

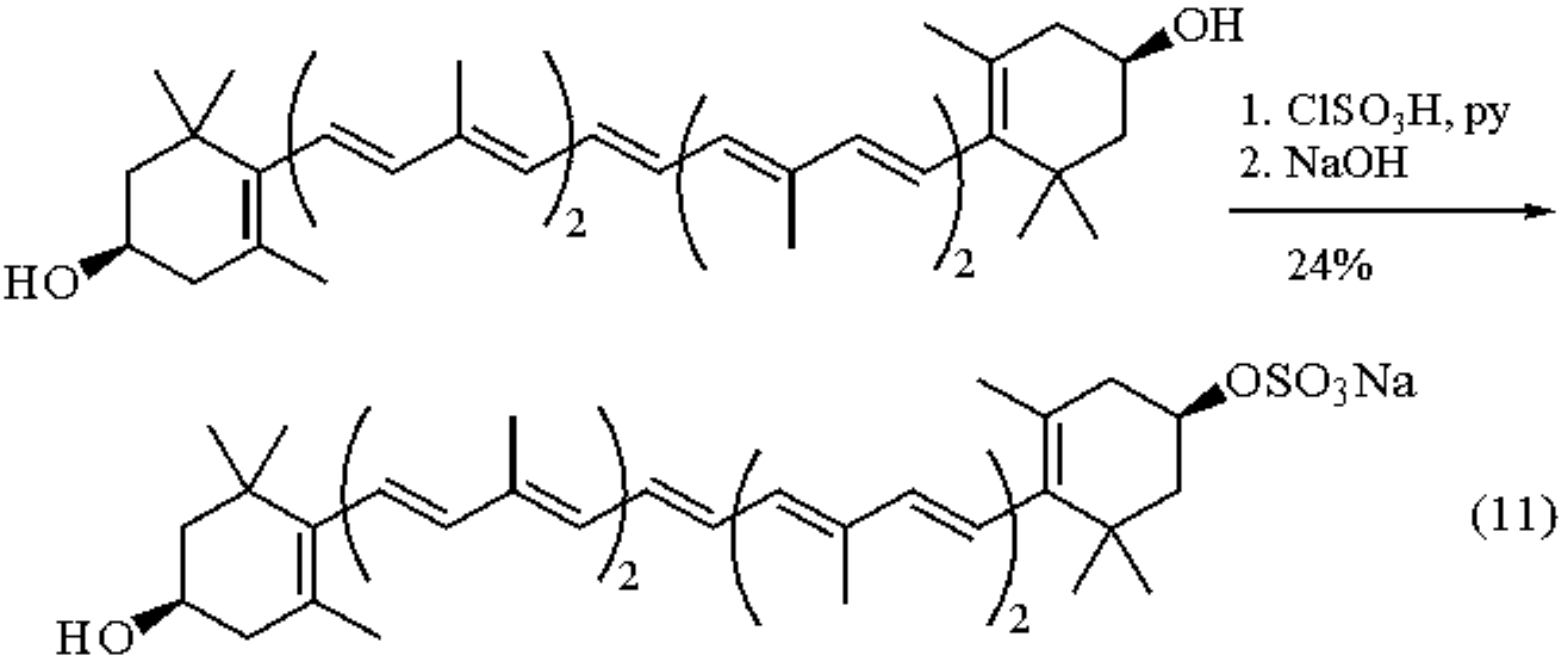

(11)

Sulfamation.

Reaction of amines with $ClSO_3H$ produces sulfamates (eq 12).[17]

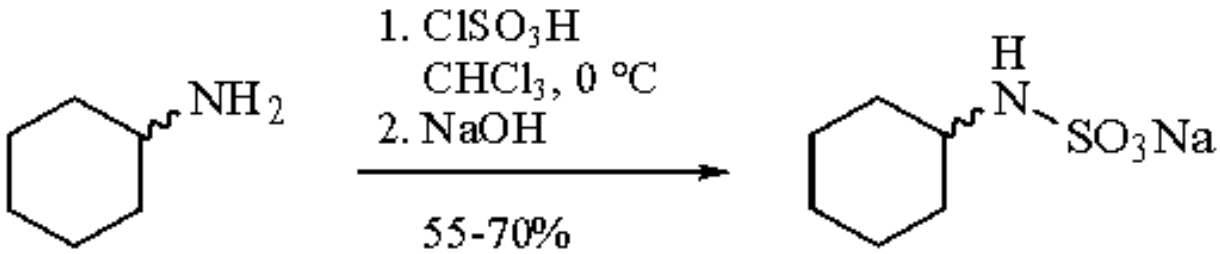

(12)

Chlorination.

$ClSO_3H$ has been used to chlorinate polycyclic alkanes such as adamantane (eq 13).[18,19]

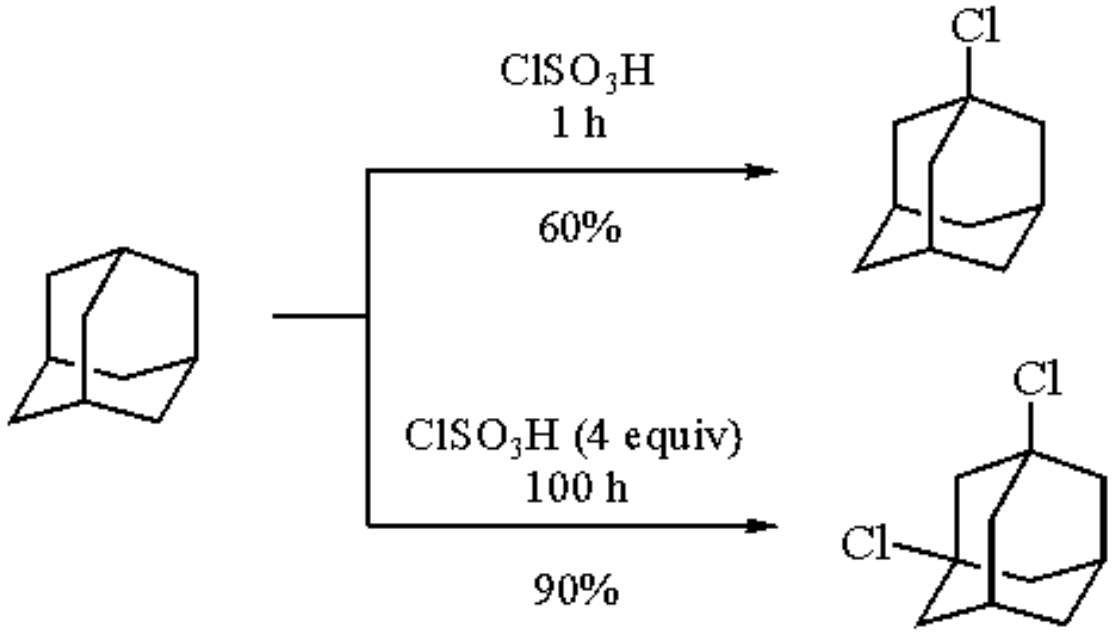

(13)

Aliphatic acids react with $ClSO_3H$ in the presence of chlorine to give corresponding α-chloro acids (eqs 14 and 15).[20]

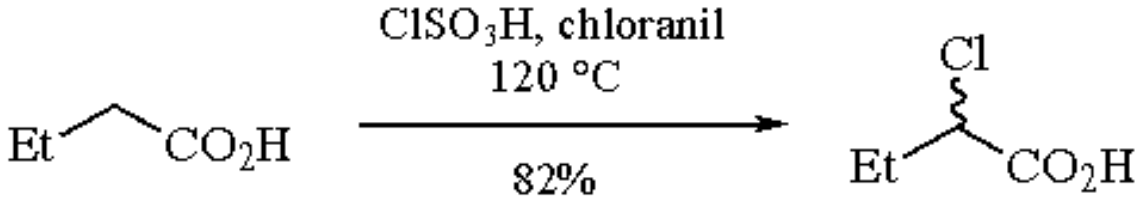

(14)

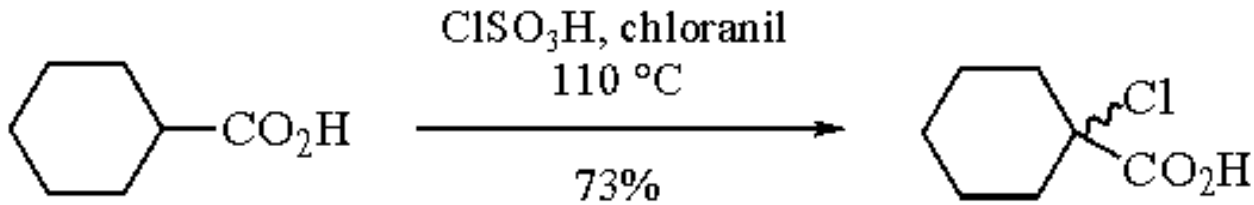

(15)

Rearrangement of Ozonides.

Chlorosulfonic acid catalyzes the rearrangement of 1,2,4-trioxalans (ozonides) to 1,2,4,5-tetraoxans (eq 16).[21]

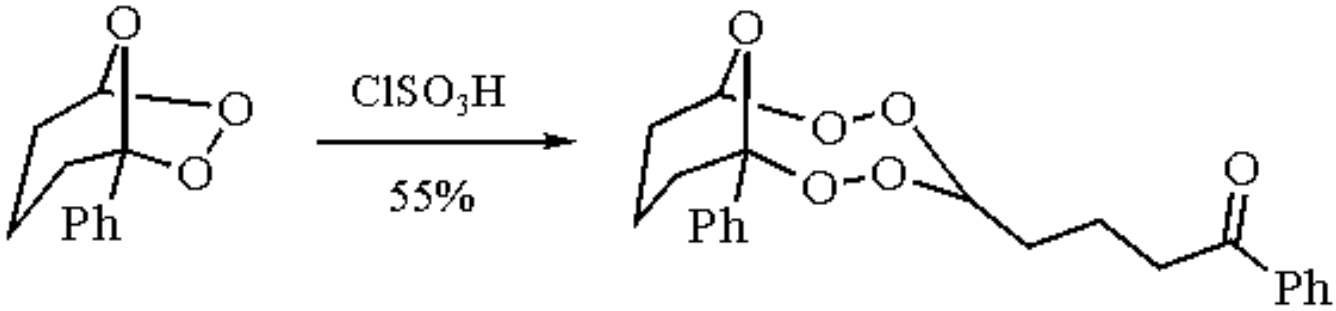

(16)

Decarbonylation.

Cyclopropenyl carboxylic acids and esters have been efficiently decarbonylated using $ClSO_3H$ and this method has been used for the generation of cyclopropenyl carbocations (eqs 17 and 18).[22]

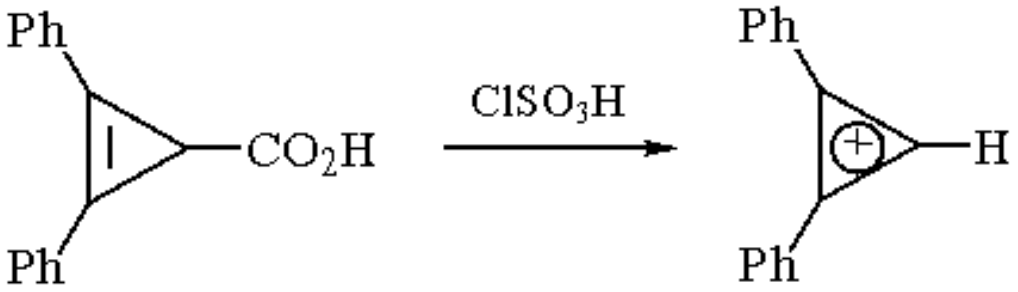

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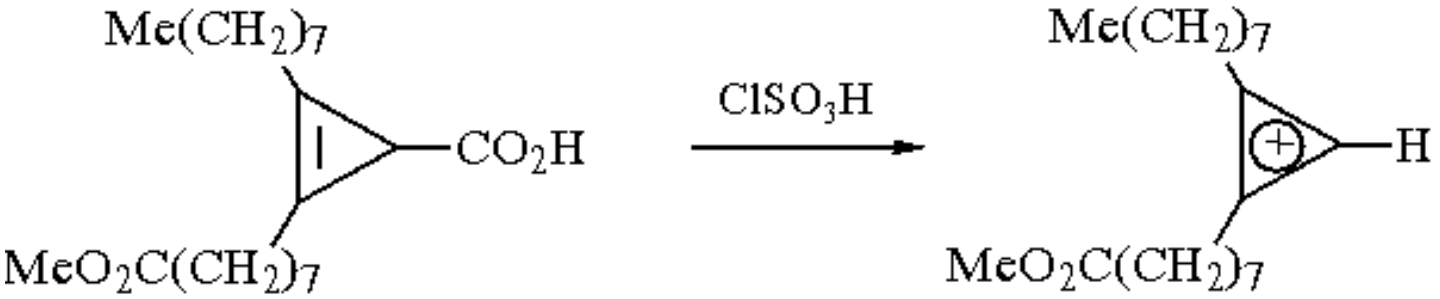

(18)

Cyclization of Benzils.

Treatment of benzils with excess of $ClSO_3H$ leads to the formation of chlorosulfonated phenylbenzofurans (eq 19).[23]

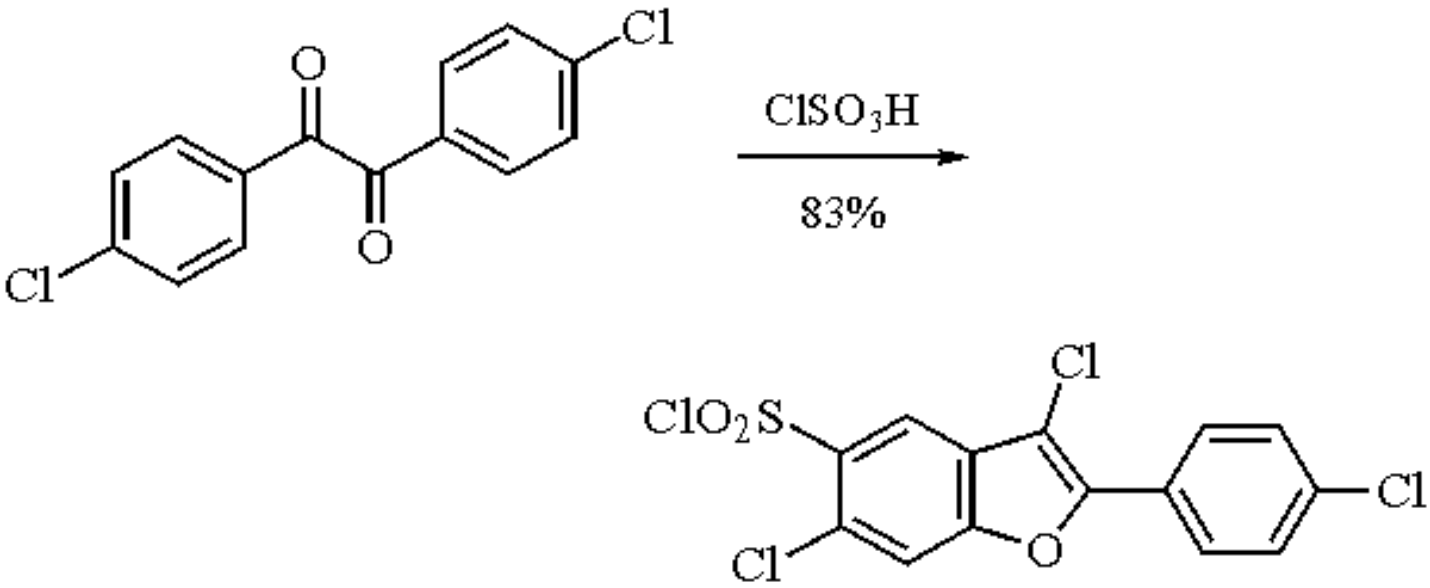

(19)

Related Reagents.

Chlorine-Chlorosulfuric Acid; ***Tungsten(VI) Oxide-Chlorosulfuric Acid***.

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Chlorosulfonyl Isocyanate[1]

$ClSO_2NCO$

[1189-71-5] · $CClNO_3S$ · Chlorosulfonyl Isocyanate · (MW 141.53)

(most chemically reactive isocyanate;[1] CSI can undergo two types of nucleophilic addition, namely to the carbonyl carbon and to the sulfur of the sulfonyl chloride; the isocyanate portion can undergo formal cycloaddition)

Alternate Name: CSI.

Physical Data: mp -44 to -43 °C; bp 107-108 °C/760 mmHg, 38 °C/50 mmHg; *d*204 = 1.626 g cm^{-3}; *n*27D = 1.4435.

Solubility: sol most organic solvents; reacts violently with water.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: reacts explosively with water to form sulfamic acid, hydrogen chloride, and carbon dioxide; fumes slightly in air, has a choking smell, and undergoes thermal decomposition only above about 300 °C. Glass stoppers of bottles used for storage of CSI stick fast after a short time, even when covered with silicone grease, so that polyethylene bottles with screw caps are best for longer storage times (a few weeks); can be kept indefinitely in sealed glass ampules. Suitable solvents include saturated aliphatic hydrocarbons (more or less limited solubility below 0 °C), aromatic hydrocarbons such as benzene and toluene, chlorinated hydrocarbons such as CH_2Cl_2, $CHCl_3$, CCl_4, and chlorobenzene, diethyl ether, diisopropyl ether, and acetonitrile. Liquid sulfur dioxide is particularly favorable, since it increases the reactivity of CSI still further. Solvents such as acetone and ethyl acetate can be used to a limited extent, but only at low temperatures.

Classification of Reactions.

CSI is probably the most chemically reactive isocyanate known, and has been the subject of several reviews.[1] It can be synthesized by reaction of sulfur trioxide with cyanogen chloride.[2]

Reactions with CSI are classified according to the probable site of reaction. The CSI molecule has two electrophilic sites for attack by nucleophilic reagents, namely the carbonyl carbon (Class I) and the sulfur of the sulfonyl chloride group (Class III). The isocyanate portion can also undergo formal cycloaddition reactions (Class II), which makes CSI a very versatile reagent (eq 1).

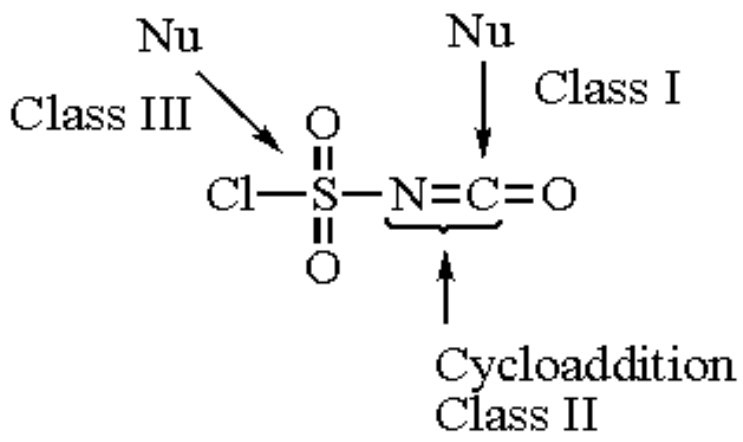

(1)

Class I: Addition Involving Initial Attack on the Isocyanate Carbon.

CSI undergoes nucleophilic additions by alcohols (thiols/phenols) and amines to yield *N*-chlorosulfonyl carbamates and urea derivatives, respectively, which can undergo further transformations with water/alcohol/amine (eq 2; X = OR, SH, or NR_2).[1] Primary alcohols can be selectively derivatized with CSI in the presence of other groups without affecting, in general, other sterocenters in complex molecules (eqs 3 and 4).[3a,3b]

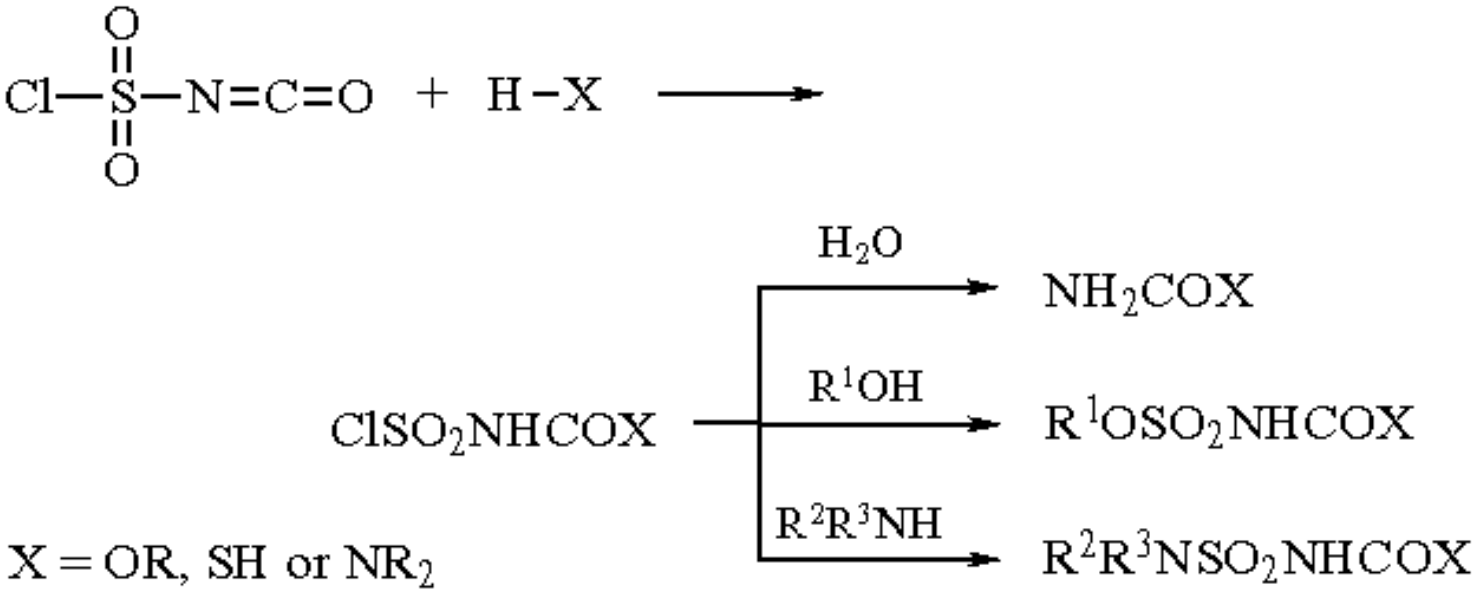

(2)

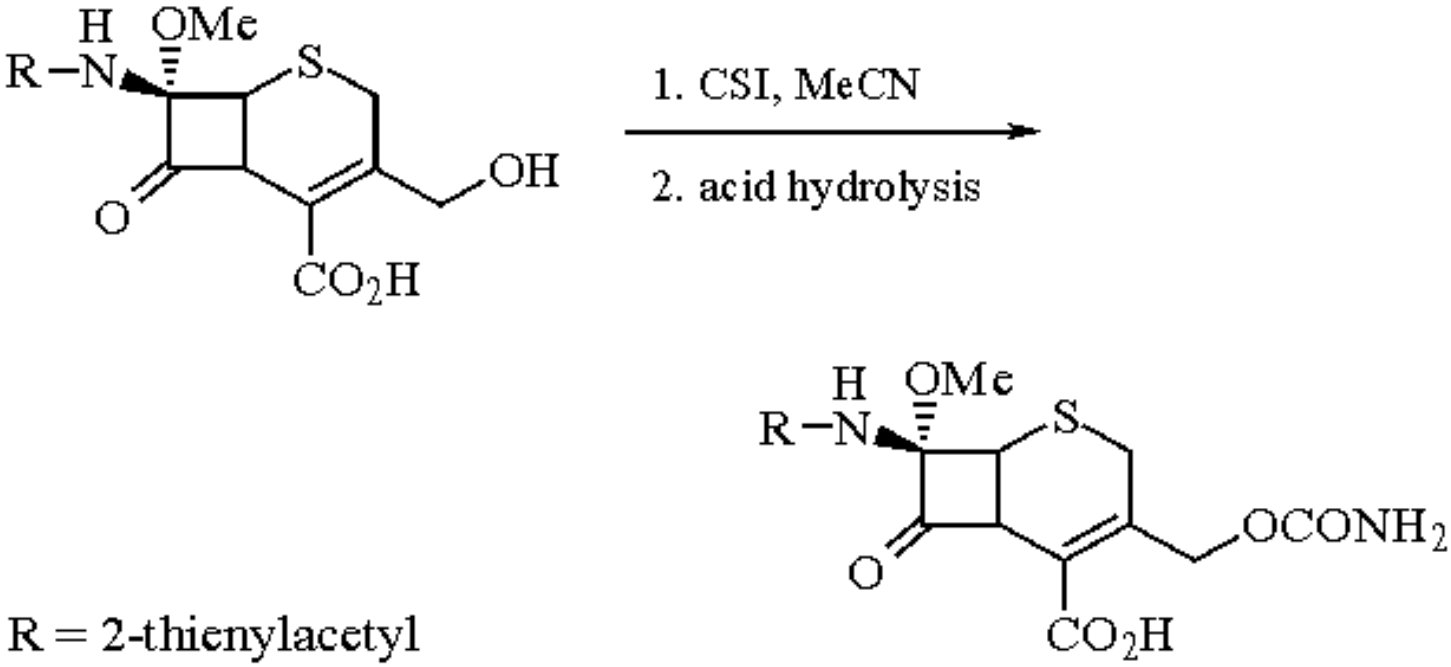

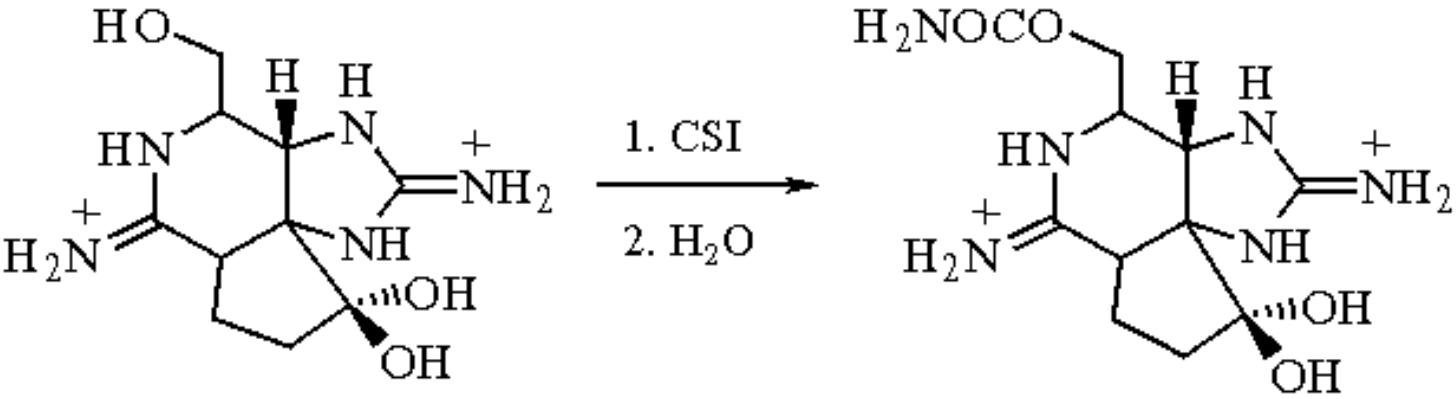

The reagent obtained by reaction of CSI with methanol followed by treatment of the intermediate with ***Triethylamine*** (eq 5) has been used to synthesize carbamates from primary alcohols and to dehydrate secondary alcohols.[4] The above intermediate itself has been used for the synthesis of various heterocycles.[5] Similar intermediates obtained from reaction of CSI and 2,4,6-trichlorophenol are found to be useful bactericides and fungicides,[6] and can be further transformed to the isocyanates by treatment with alcohols followed by pyrolysis of the resultant carbamates (eq 6).[7]

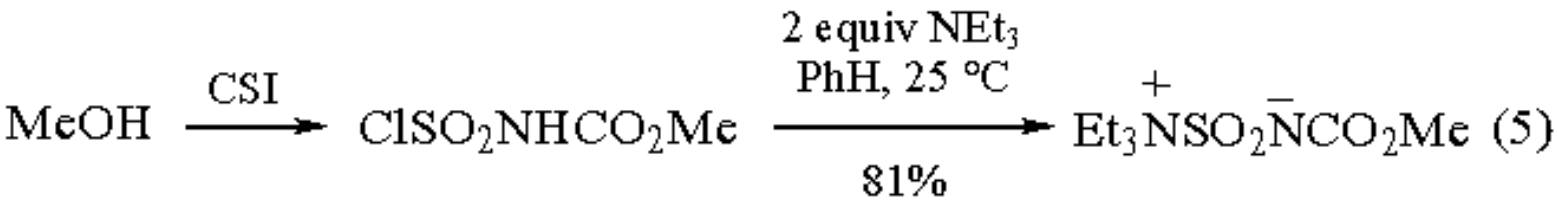

$$ClSO_2NHCO_2Ar \xrightarrow[-\,HCl]{ROH} ROSO_2NHCO_2Ar \xrightarrow[-\,ArOH]{\Delta} ROSO_2NCO \quad (6)$$

$$R = Me,\ Pr,\ MeOCH_2CH_2$$

The reaction of CSI with hydroxy groups of α-hydroxy ketones, followed by thermal ring closure of the intermediate carbamate, results in the formation of oxazolones (eq 7).[8]

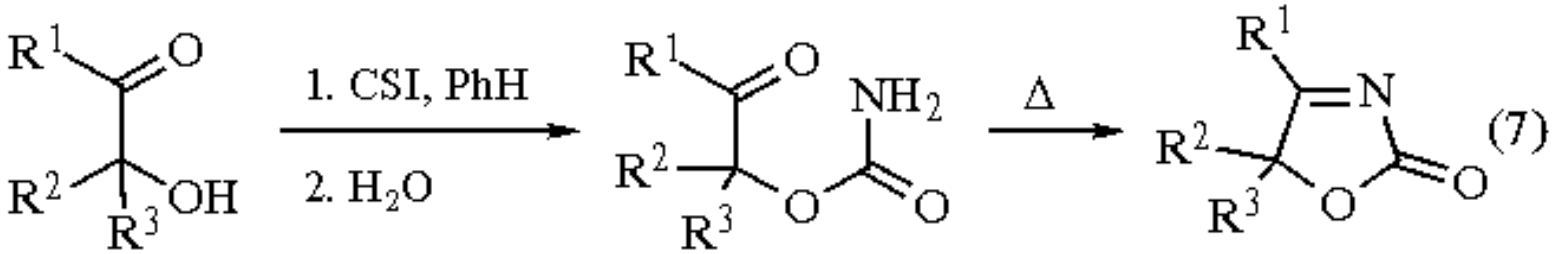

$$R^1 = Ph,\ t\text{-}Bu;\ R^2,\ R^3 = Me,\ Ph$$

Thiocarbamates are obtained from the reaction of CSI with thiols (eq 8), and have been used for the synthesis of potential herbicides.[9]

$$RSH \xrightarrow[PhH]{CSI} ClSO_2NHCOSR \xrightarrow{PhNH_2} PhNHSO_2NHCOSR \quad (8)$$

90%

$$R = C_{12}H_{25}$$

CSI also undergoes reaction with amides, sulfonamides (eq 9), and certain phosphoramides.[10,1b] The addition products can be readily converted to the corresponding isocyanates by pyrolytic elimination of the sulfamoyl chloride. However, the dipolar intermediate postulated for the reaction of *N*,*N*-dialkylamides produces amidines through loss of carbon dioxide (eq 10).[11] The amidines were further derivatized to prepare insecticidal and acaricidal compounds.[12]

$$RSO_2NH_2 \xrightarrow{CSI} RSO_2NHCONHSO_2Cl \xrightarrow[-\,ClSO_2NH_2]{\Delta} RSO_2NCO \quad (9)$$

75-92%

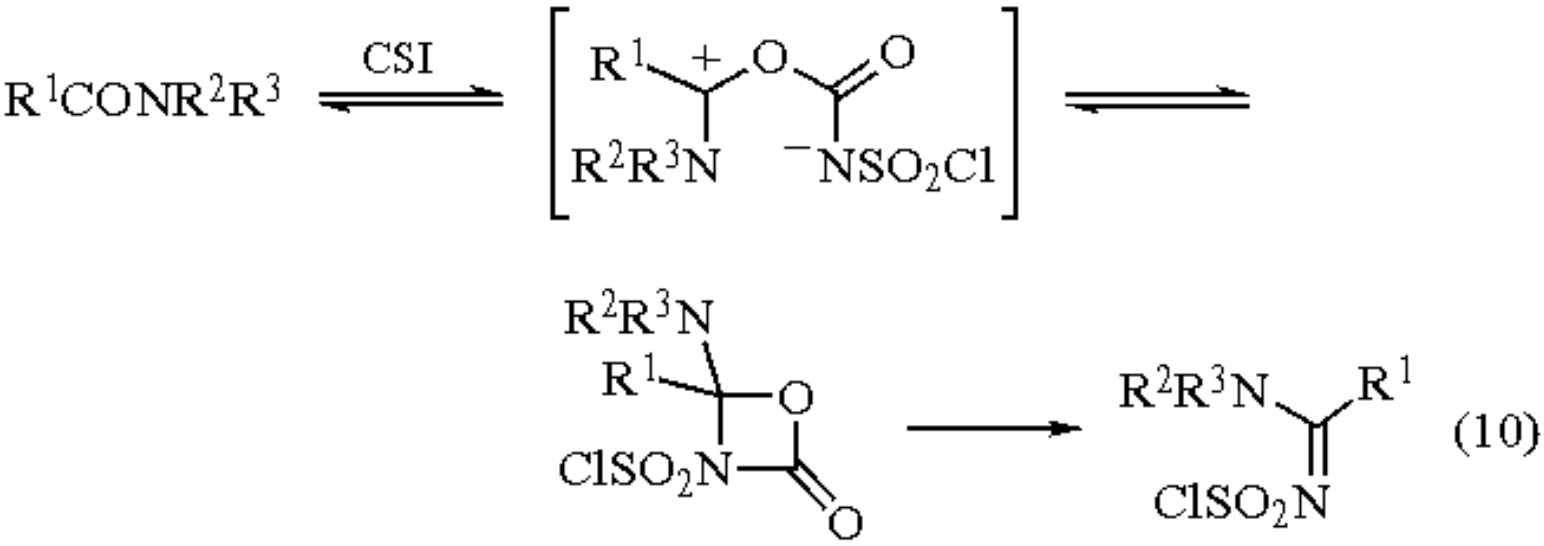

The generality of the reaction of CSI with acetals of aliphatic aldehydes,[13] and similar reactivity of orthoesters,[1b] has been reviewed. The reaction of acetals has been used for the conversion of isopropylidine-protected sugars to the corresponding carbonates (eq 11).[14] A similar reaction sequence with carboxylic acids[15] sometimes provides intermediate *N*-chlorosulfonylcarboxamides which are stable enough to be isolated, or which can be treated with ***N,N-Dimethylformamide*** to provide a one-pot synthesis of nitriles (eq 12). The reported[16] anhydropenicillin rearrangement (eq 13) is believed to proceed by an intermediate similar to that described above. Interestingly, such an intermediate also has been used as a mild reagent for displacement of an *N*-trimethylsilyl group.[17]

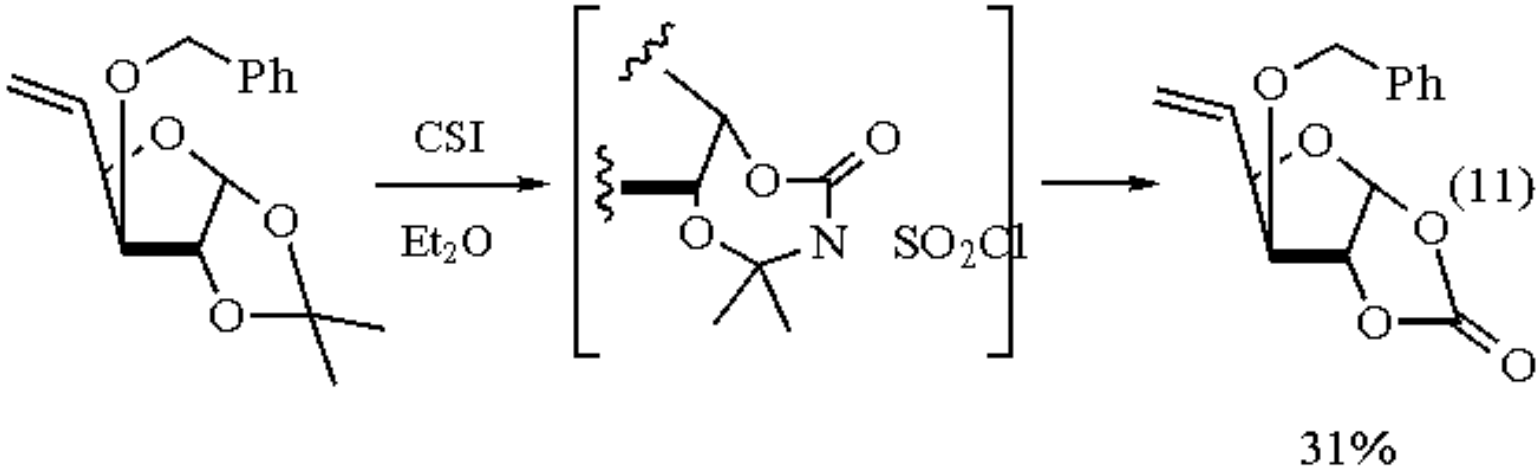

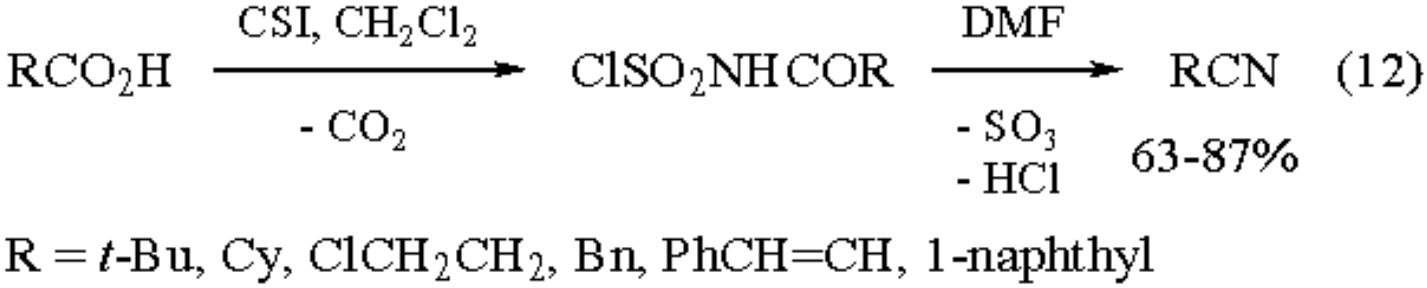

R = *t*-Bu, Cy, $ClCH_2CH_2$, Bn, PhCH=CH, 1-naphthyl

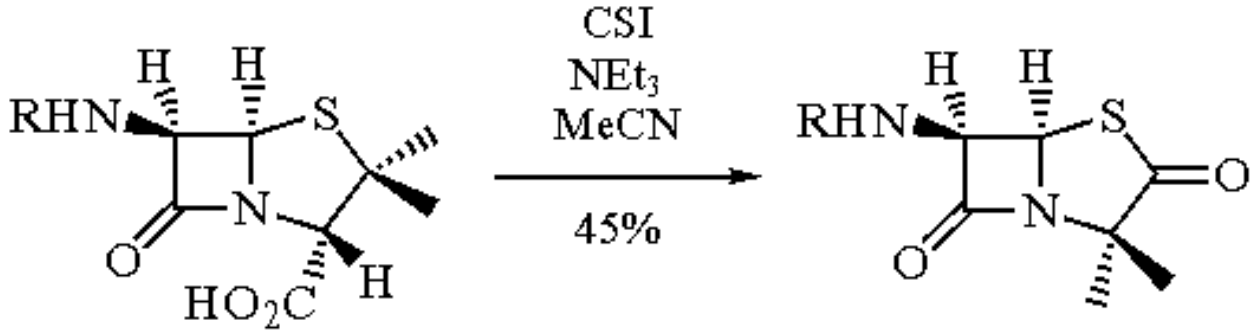

R = Ph_3C

Aromatic compounds undergo facile reaction with CSI. Treatment of the resultant *N*-chlorosulfonylcarboxamides with DMF in situ afforded the corresponding nitriles (eq 14).[18]

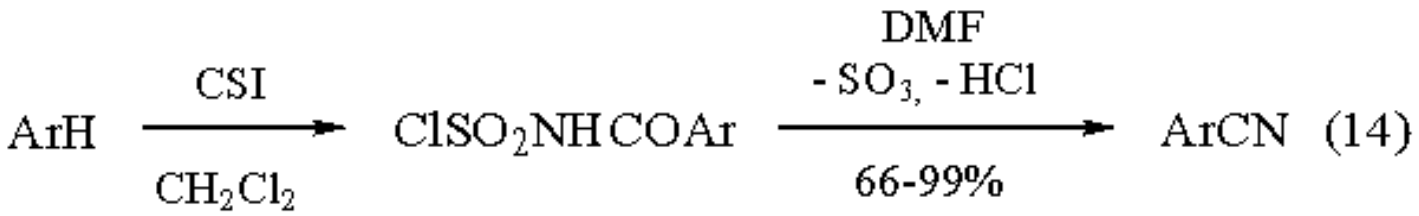

Nucleophilic attack by aldehydic carbonyl groups on the isocyanate carbon atom gives products as shown in eq 15, by way of 1,4-dipolar intermediates.[13] Reaction of arylmethylene malonaldehydes with CSI has provided bicyclic 1,3-oxazin-2-one derivatives (eq 16).[19]

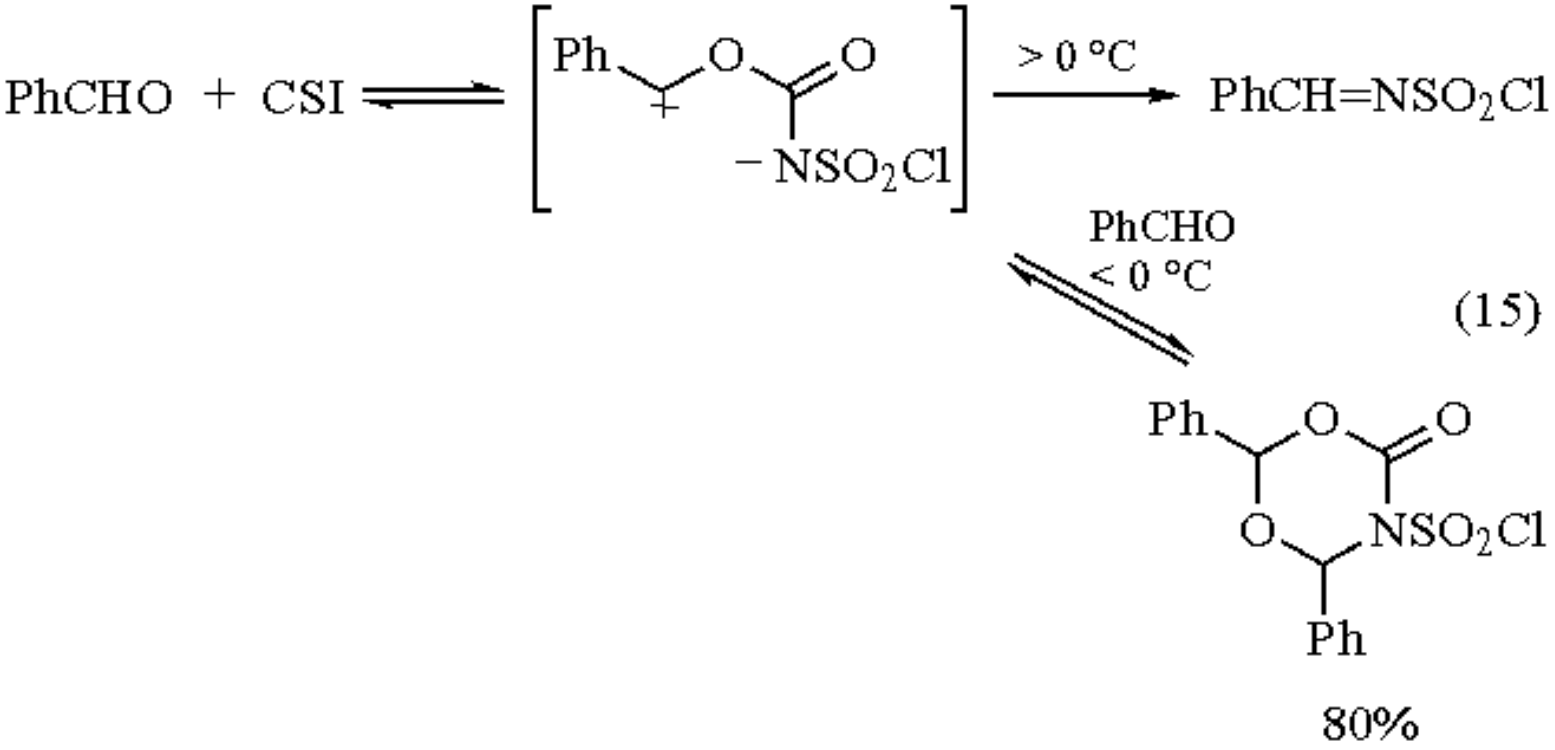

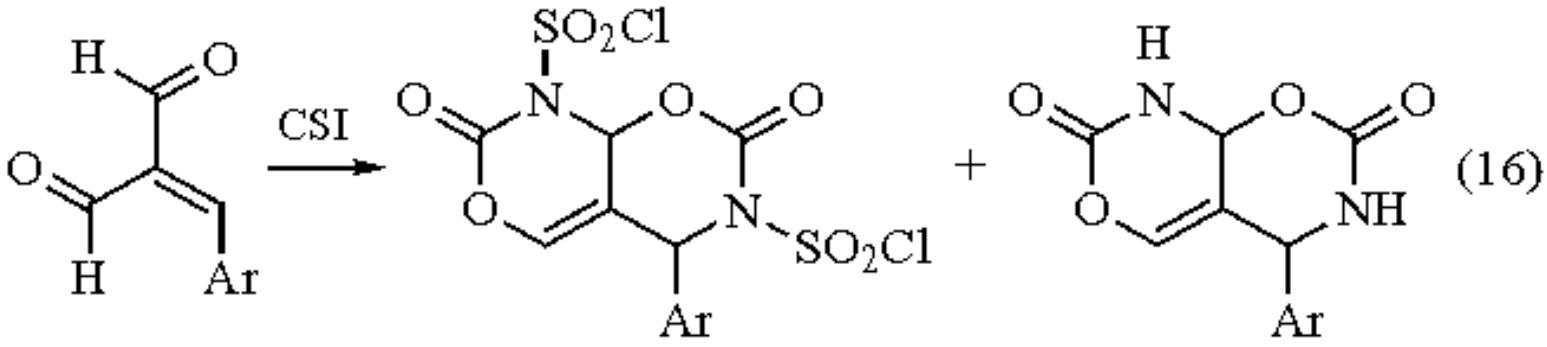

Enolizable ketones upon treatment with CSI produce *N*-chlorosulfonyl-β-ketocarboxamides, which have been used for the synthesis of β-ketonitriles by in situ treatment with DMF (eq 17).[20] However, in the presence of excess CSI, ketones with two α-hydrogens have been observed to undergo further transformations (eq 18).[21] The final product distribution depends on solvent, substituents, and concentration. Nonenolizable ketones, such as benzophenone and γ-pyrones,[22] produce azomethines (eq 19). The azomethine intermediate of benzophenone further cyclizes to provide benzoisothiazole (eq 20).[13] α,β-Unsaturated ketones are converted into 3,4-dihydro-1,3-oxazin-2-ones (eq 21).[13]

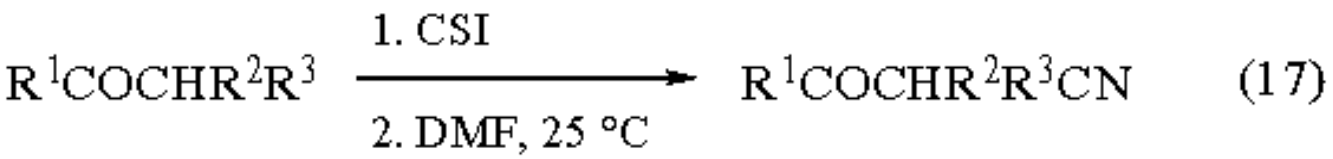

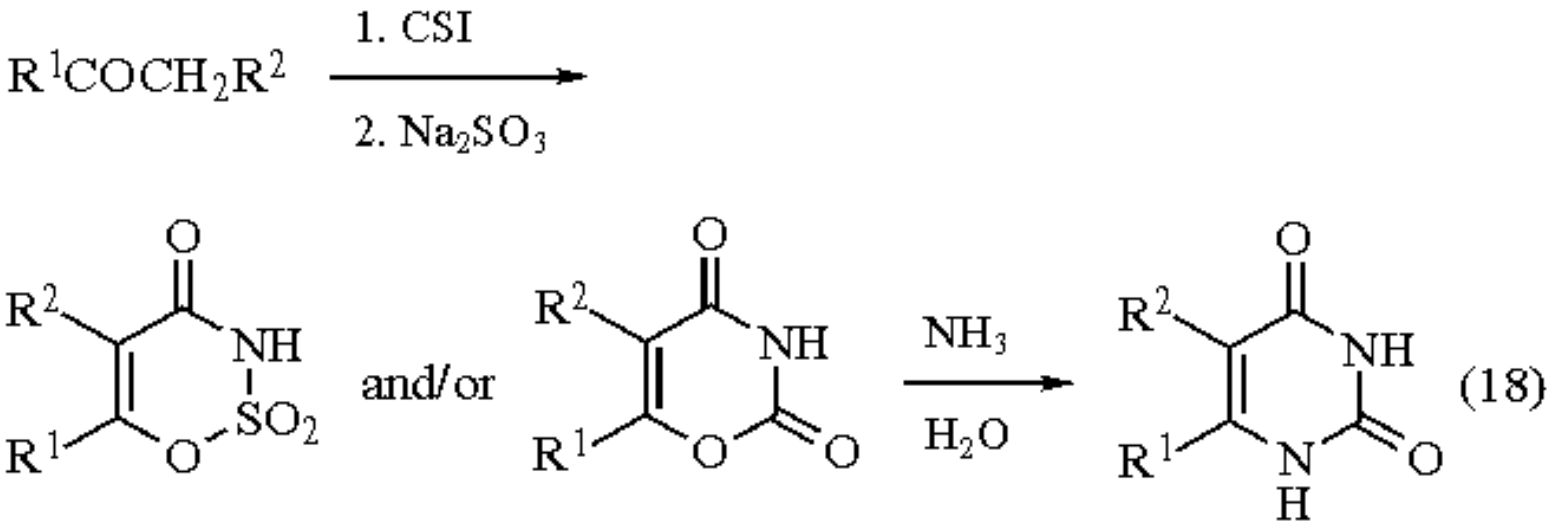

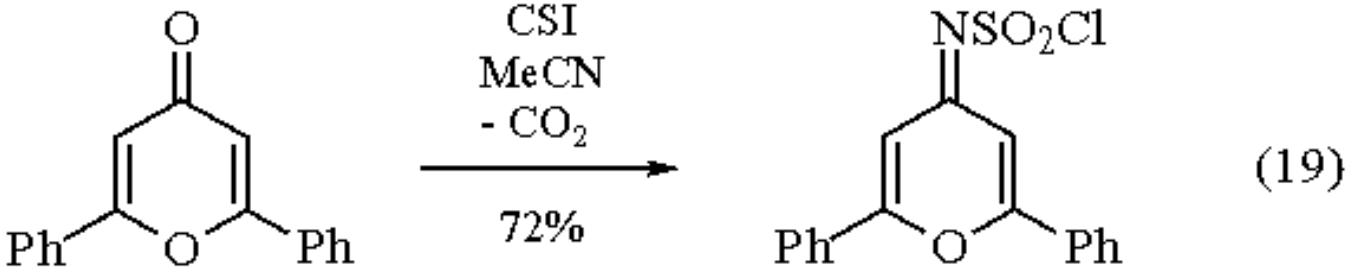

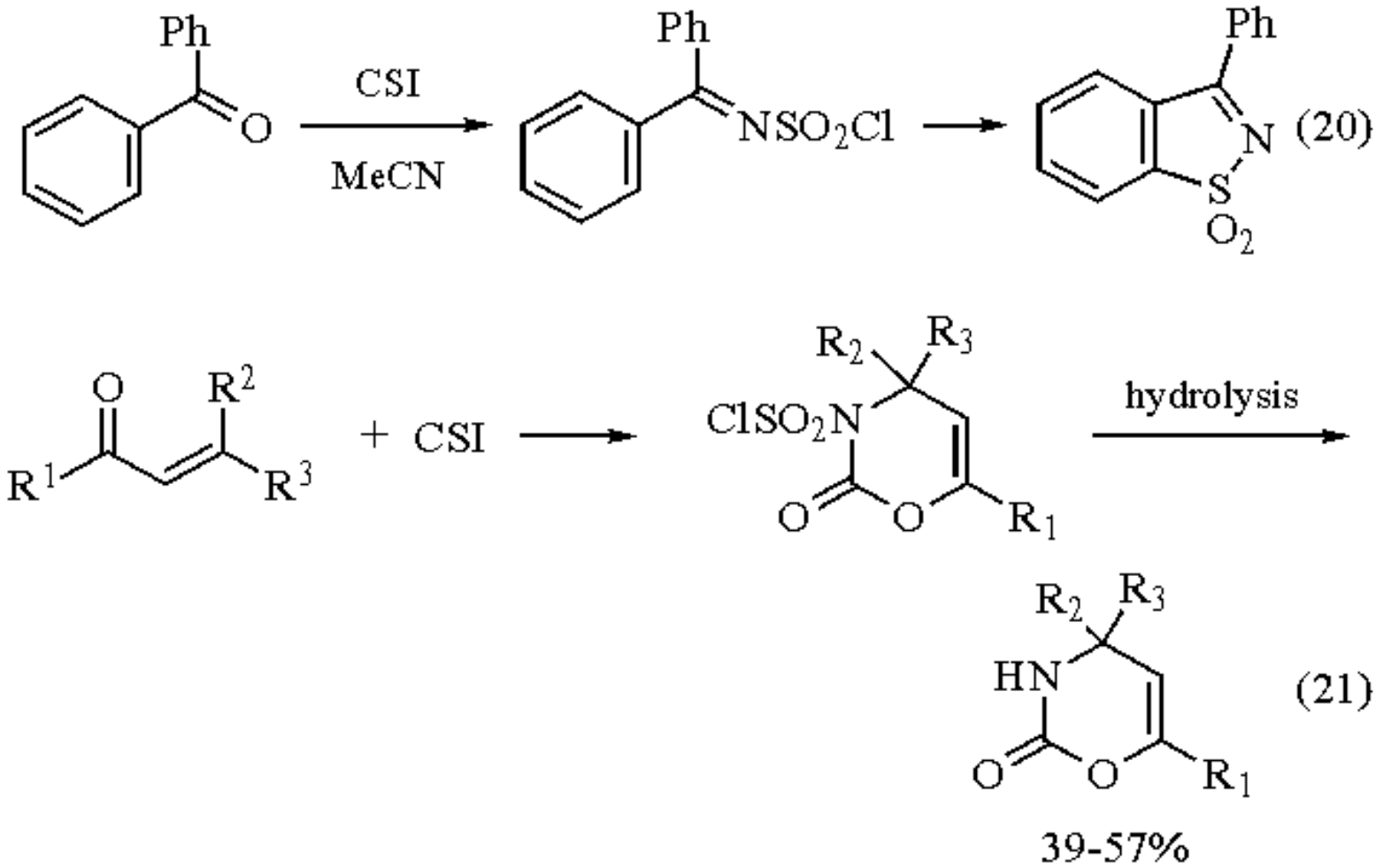

β-Diketones and β-keto esters react with CSI to produce amides (eqs 22 and 23).[13] Heterocycles have been obtained from the reaction of CSI with amino compounds having ester or carbonyl functions.[23] The reaction of CSI with ethyl 3-oxo-2-(arylhydrazono)butanoates gives thiazolotriazinediones (eq 24).[24]

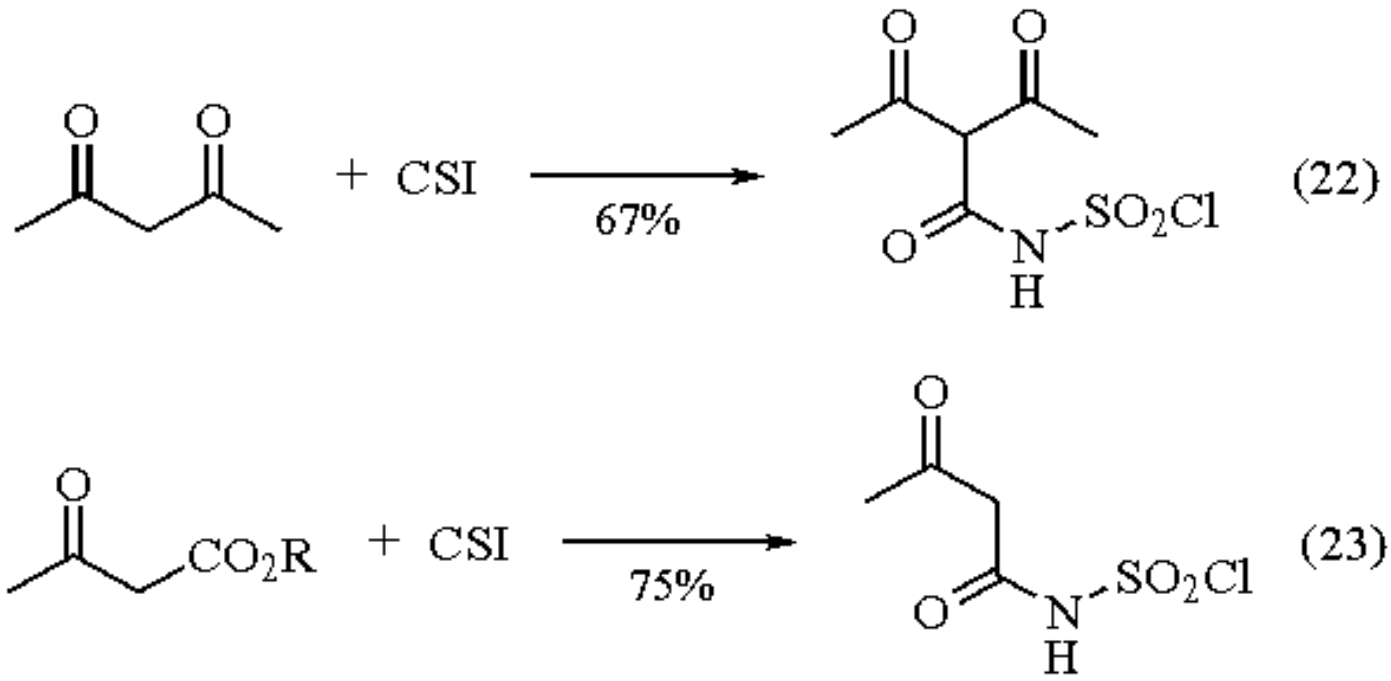

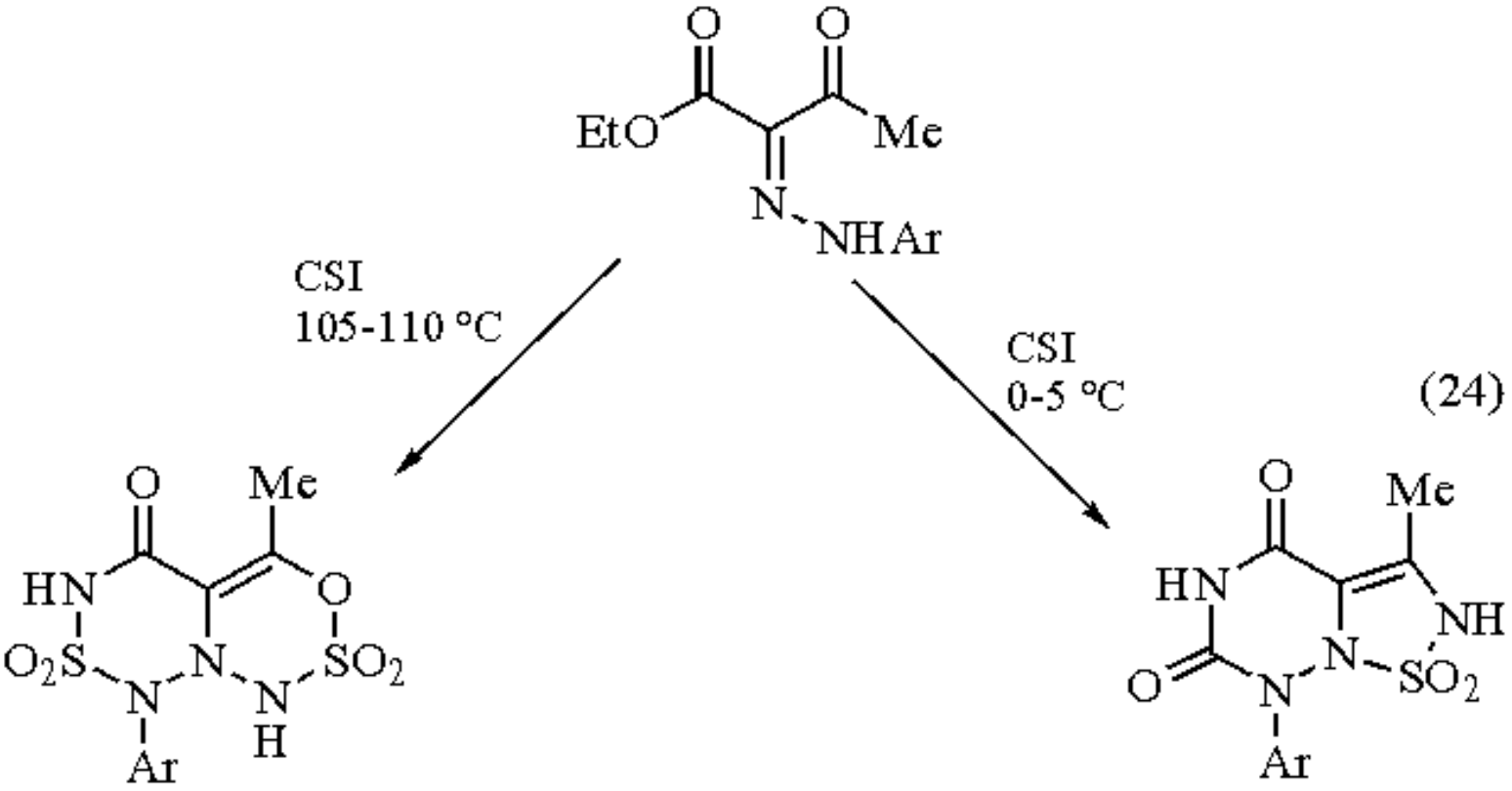

CSI has been used as a dipolar synthon of the type shown in eq 25 in its reaction with cyanohydrins. The final products of this one-pot reaction are 5,5-disubstituted 2,4-oxazolidinediones.[25]

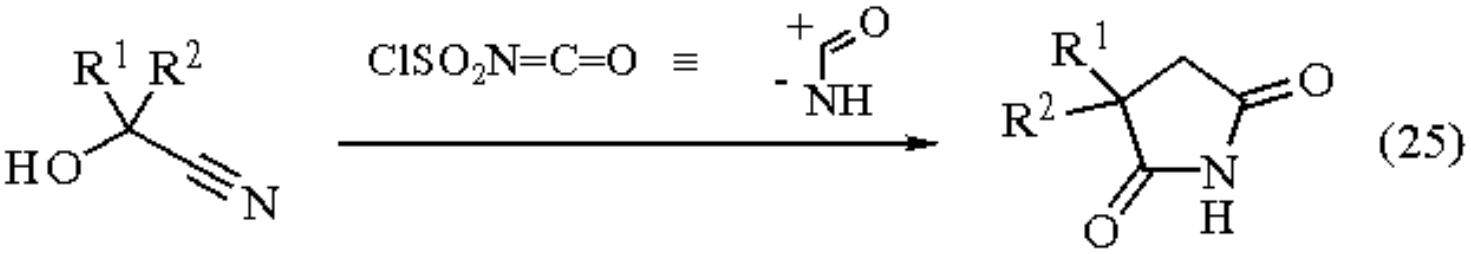

The reagent has been used to introduce the nitrile functionality in cyclic enamides (eq 26)[26] and in some other electron-rich alkenes (eqs 27 and 28).[27,28]

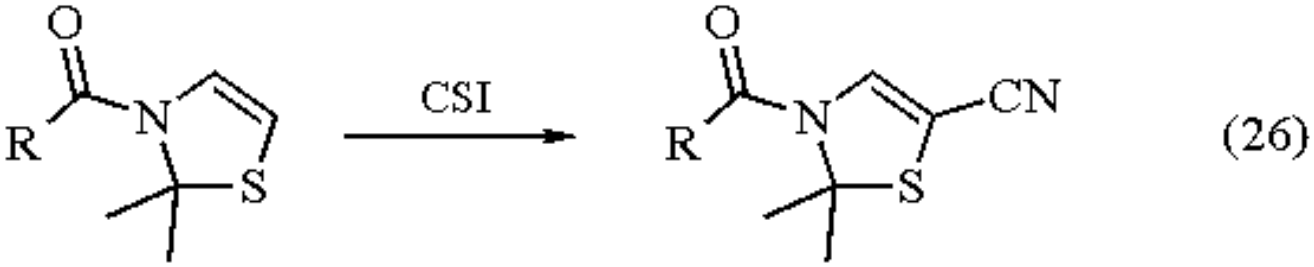

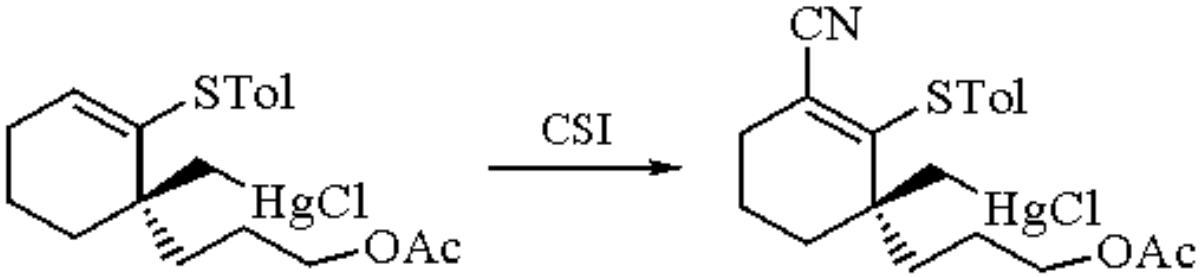

(27)

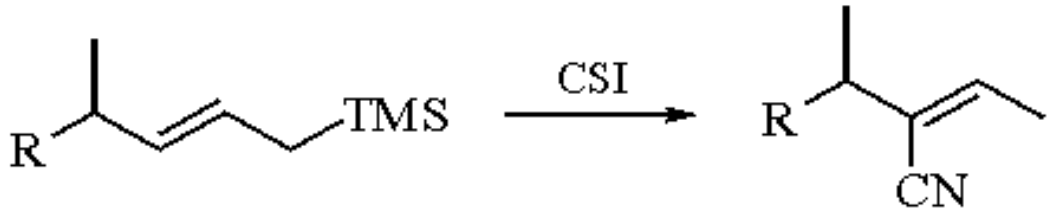

(28)

An attempt to use CSI as a dienophile in its reaction with 2-vinylindole was not successful (eq 29).[29] The product obtained was the indole-3-carboxamide, as reported earlier.[30] Similar electrophilic substitution on pyrroles[31] and thiophene[32] using CSI in the presence of DMF has furnished the respective cyanation products.

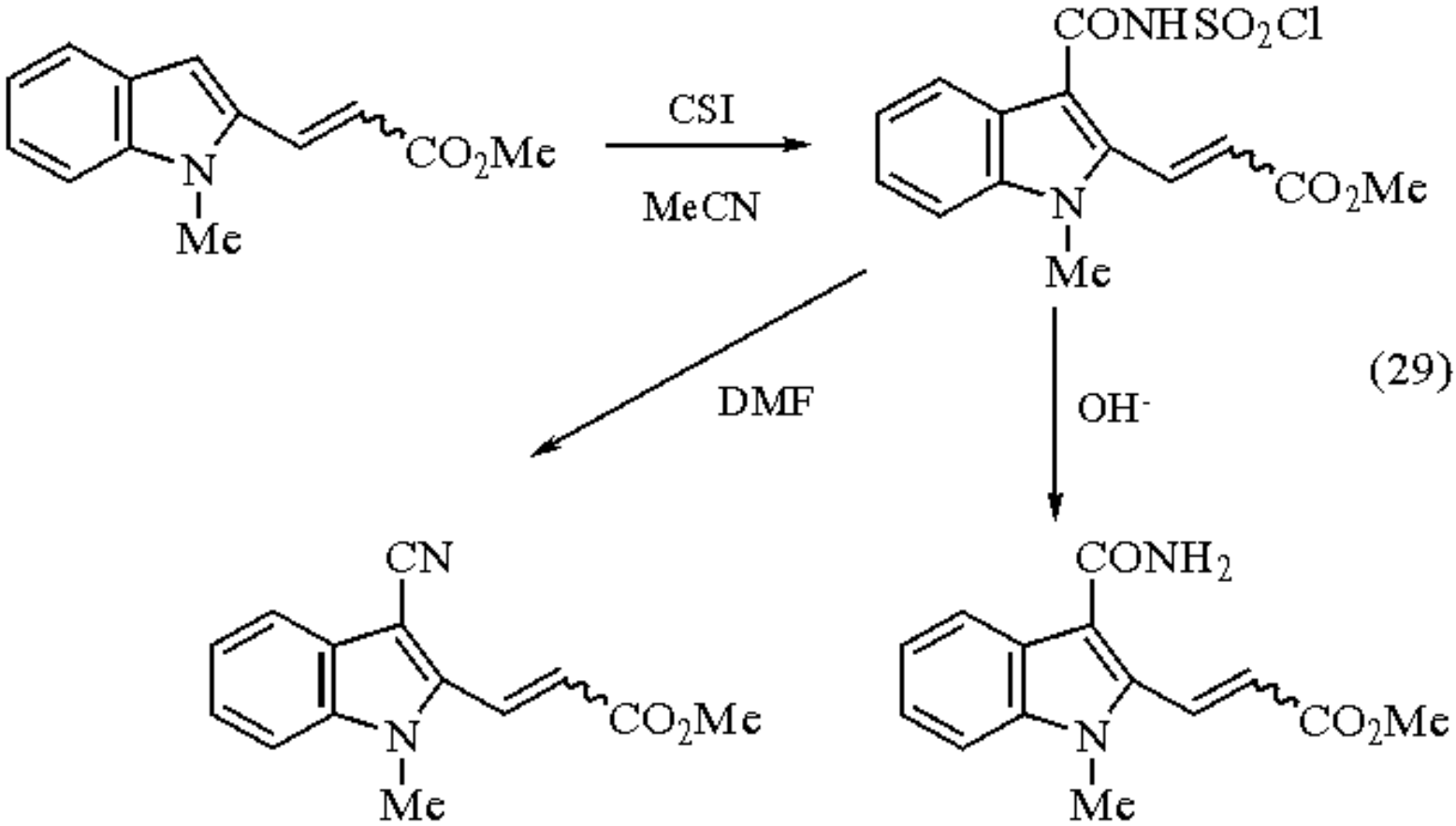

(29)

Brief treatment of CSI with epoxides at low temperature has provided the corresponding 1,3-dioxolan-2-ones (major products) and oxazolidine-2-one derivatives (eq 30).[33] This reaction is both regio- and stereospecific. Aziridines have also provided analogous products from their reaction with CSI.[33a] 1,2-Diols having substituents with good migratory aptitudes gave the rearrangement products, but unsubstituted or alkyl substituted 1,2-diols gave the corresponding carbamates as the major product (eq 31).[34]

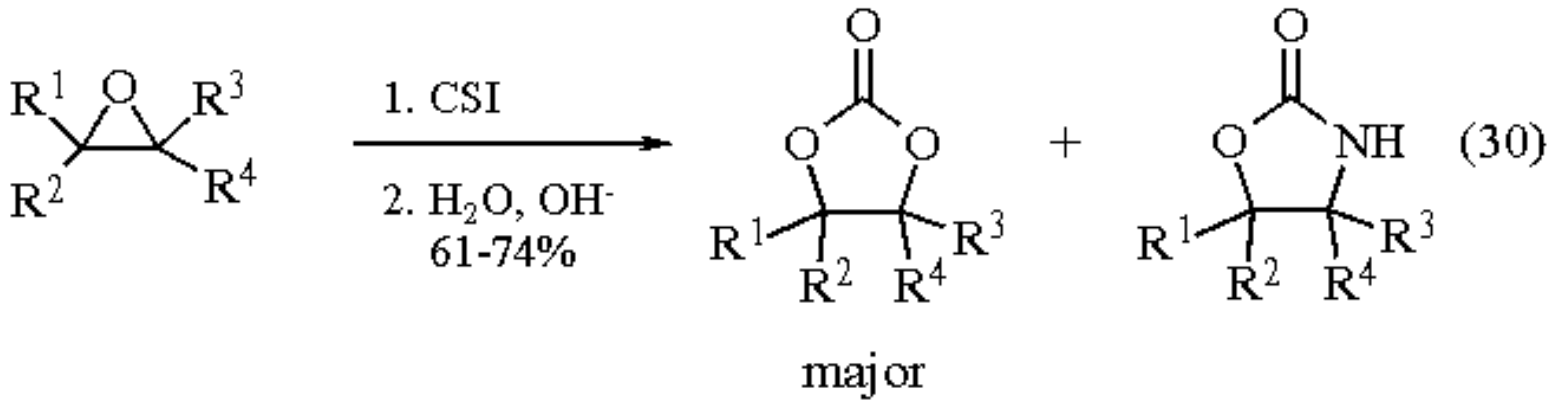

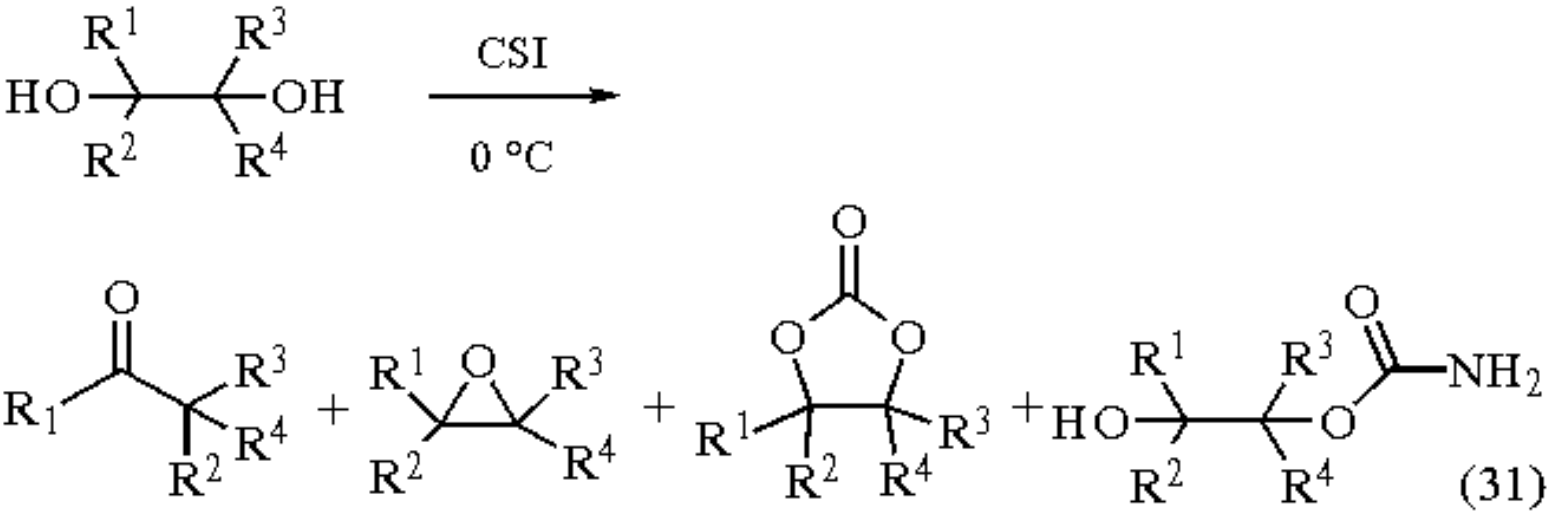

CSI also has been used as a mild chlorinating agent in its reaction with 6-aryl-3(2*H*)-pyridazinones to produce 6-aryl-3-chloropyridazines (eq 32).[35] 1-Trimethylsilylalkynes react with CSI to produce primary 2-alkynamides after hydrolysis (eq 33).[36] CSI reacts with nitrones derived from cyclic conjugated ketones to produce enamides (eq 34),[37] and with substituted nitrones to produce amides (eq 35).[38] Similar reactions with substituted 3,4-dihydro-2*H*-pyrrole 1-oxide produce 2*H*-pyrroles (eq 36).[39]

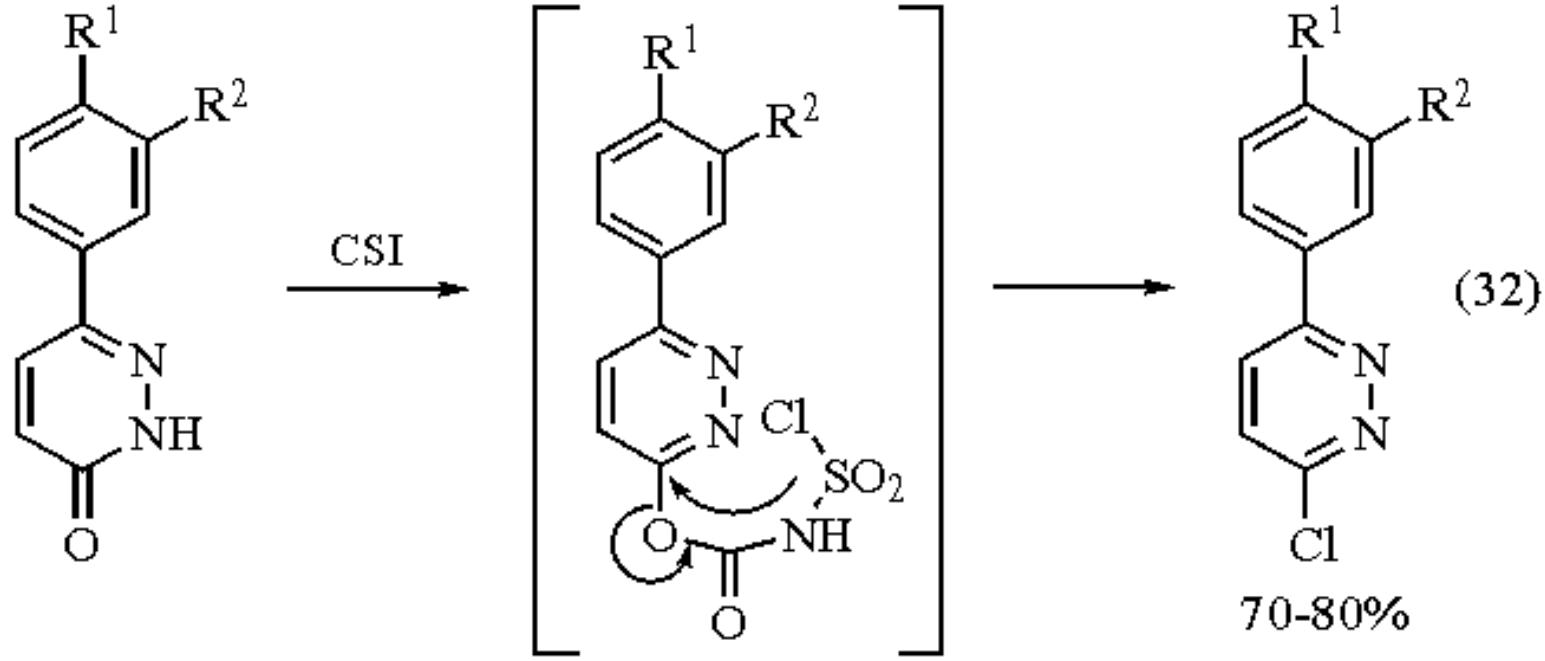
R1
R2
CSI
N
NH
O
N
N
Cl
SO2
O
NH
O
70-80%

(32)

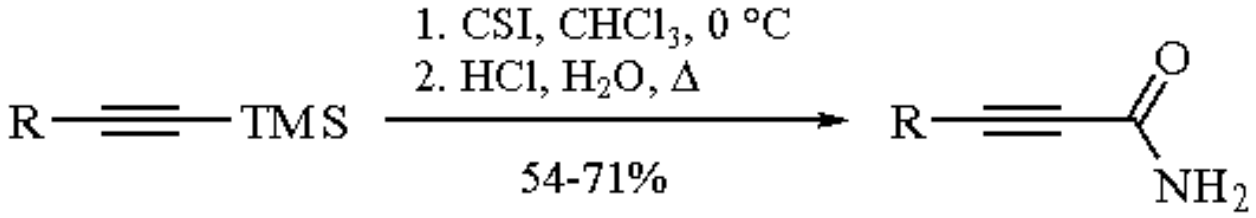
1. CSI, CHCl3, 0 °C
2. HCl, H2O, Δ
R
TMS
54-71%
O
NH2

(33)

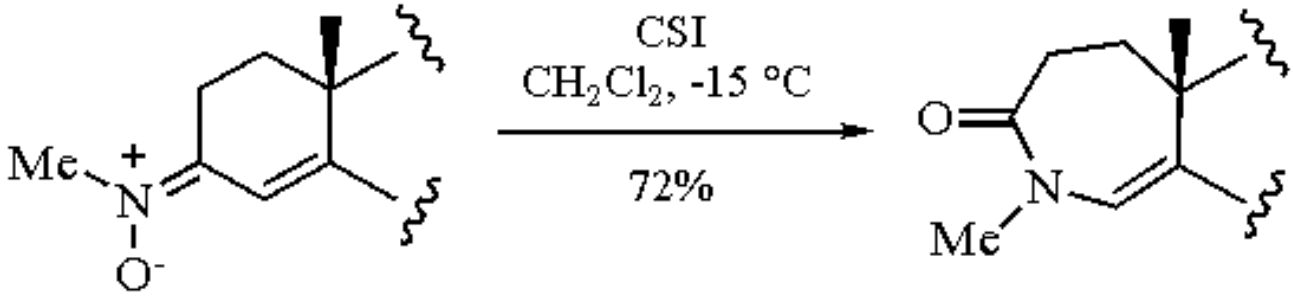
CSI
CH2Cl2, -15 °C
Me
N
O-
72%
O
N
Me

(34)

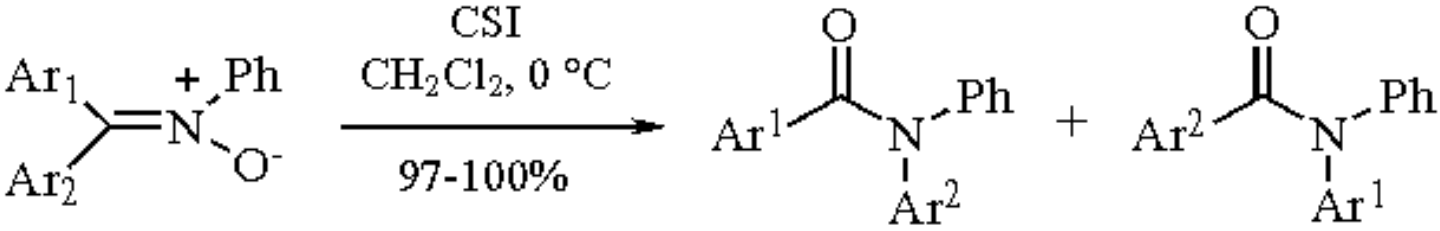
Ar1
Ph
N
O-
Ar2
CSI
CH2Cl2, 0 °C
97-100%
O
Ar1
N
Ph
Ar2
+
O
Ar2
N
Ph
Ar1

(35)

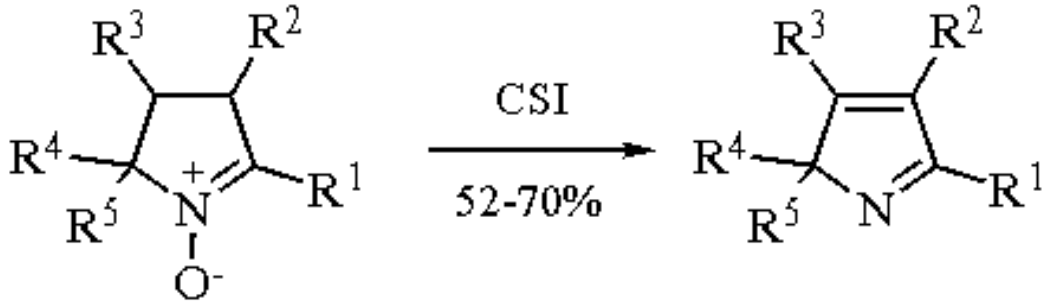

(36)

Recently, a facile denitrosation of *N*-nitrosoamines has been demonstrated by Dhar et al. (eq 37).[40] The reactivity of CSI towards sulfoxides[41] has been used for the reduction of sulfoxides to sulfides in the presence of ***Sodium Iodide*** (eq 38).[41c]

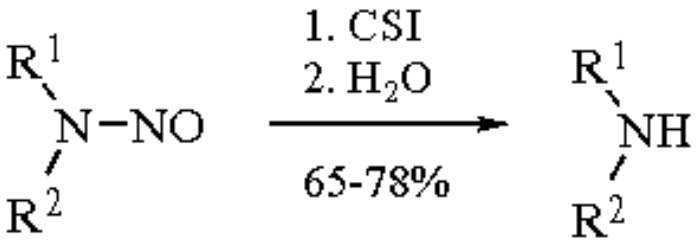

(37)

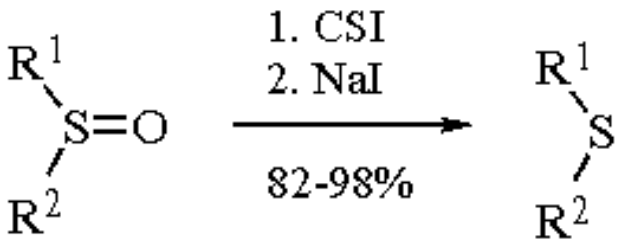

(38)

The new reagent *N*-carbo(trimethylsilyloxy)sulfamoyl chloride, obtained from CSI as a substitute for sulfamoyl chloride, has been used for the synthesis of 3-amino-4-*N*-alkyl-5-aryloxy-1,2,4,6-thiatriazine-1,1-dioxides.[42]

Class II: Cycloaddition to Isocyanate C=N.

The formal [2 + 2] cycloaddition of CSI to a variety of alkenes to produce β-lactams has been the most thoroughly studied reaction (eq 39).[43] A competing elimination reaction (path b) forms an alkene byproduct. The ratio of β-lactam to alkene is determined by the pattern and type of substitution on the alkene. Both concerted and nonconcerted 1,4-dipolar mechanisms have been proposed for these reactions. Regiochemistry is dictated by the formation of the most stable carbocation, and the *cis* adduct is generally formed. Several examples are given in review articles,[1] which show the diversity of β-lactams available from this route. An improved procedure for β-lactam formation from volatile alkenes and CSI has been published.[44]

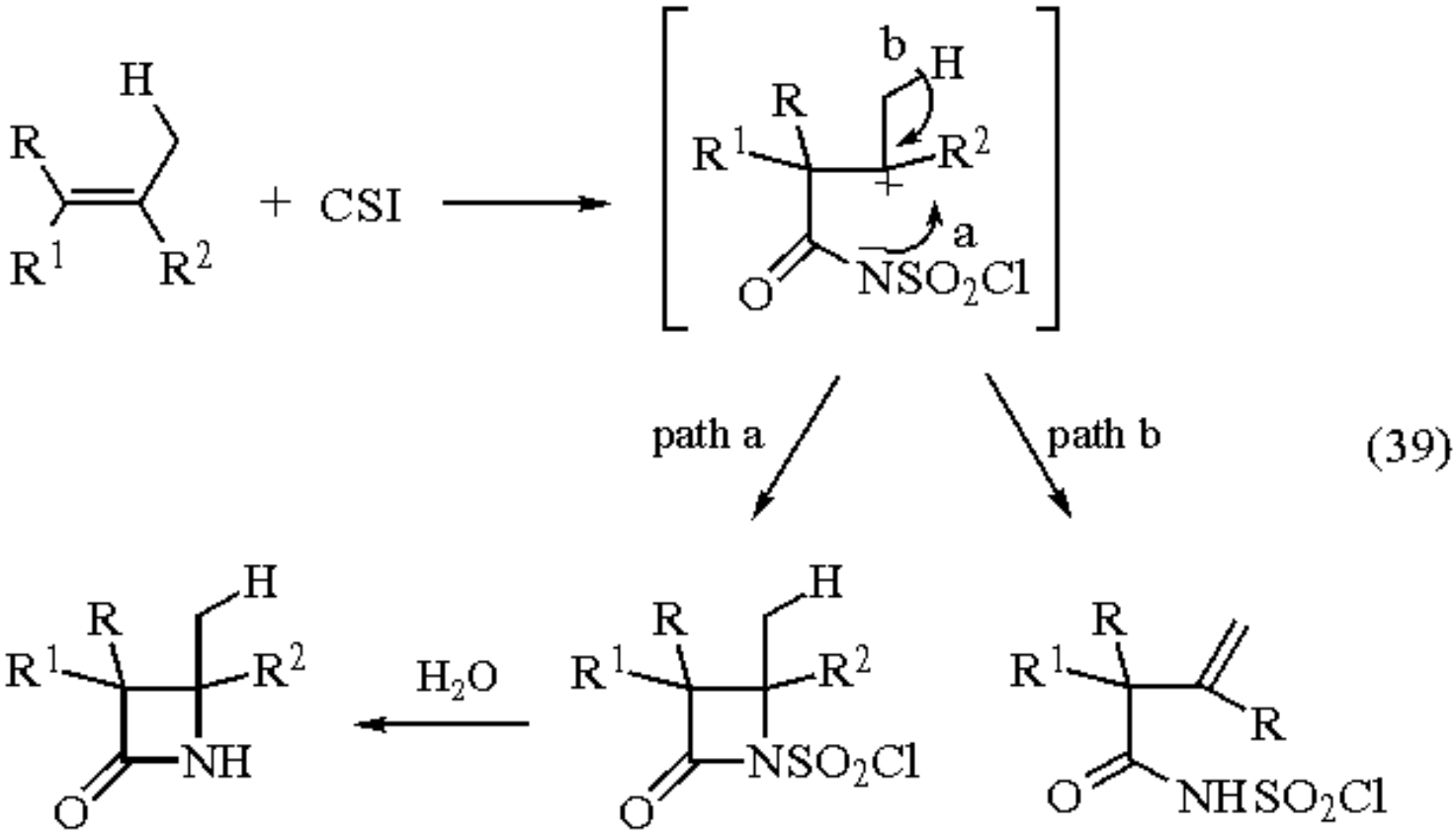

Reaction of CSI with conjugated or nonconjugated dienes also leads to 2-azetidinones after hydrolysis of the *N*-chlorosulfonyl group (eqs 40 and 41).[45]

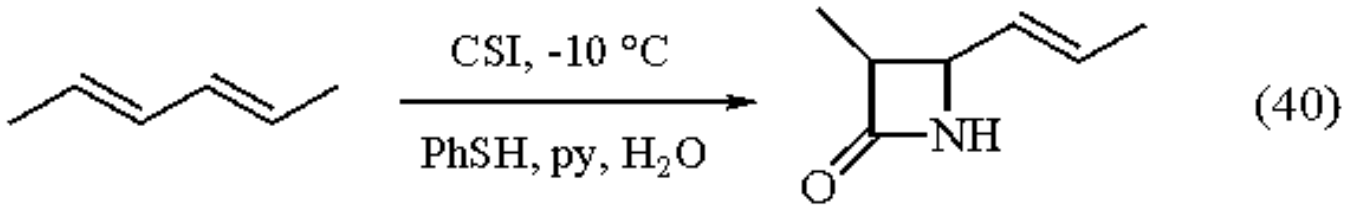

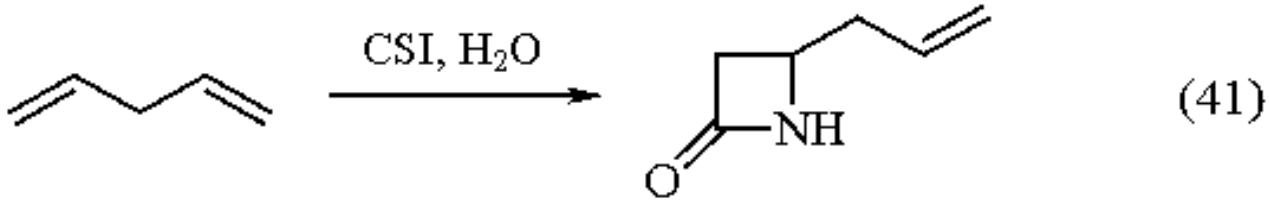

The reaction of CSI with vinyl acetates leads to 4-acetoxy-2-azetidinones upon hydrolysis (eq 42).[46] These β-lactams are ideal building blocks for synthesis of a wide variety of classes of antibiotics. The resulting β-lactams are also convenient precursors to *erythro*- and *threo*-amino acids.[47]

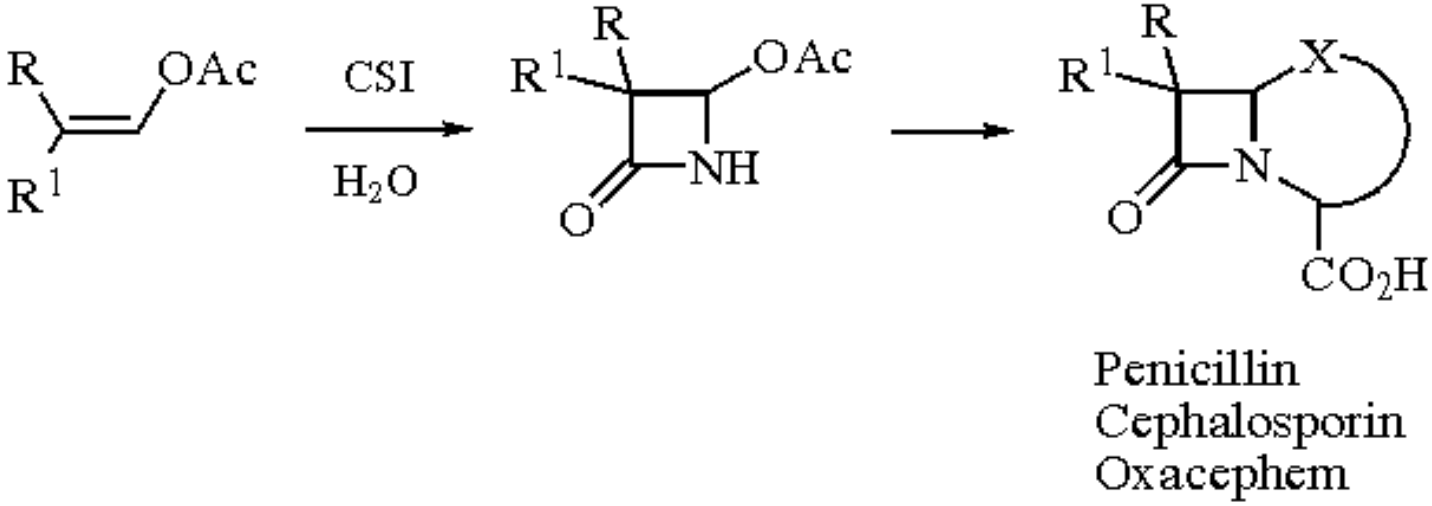

(42)

CSI reacts with functionalized allenes to provide α-alkylidene β-lactams (eq 43).[48]

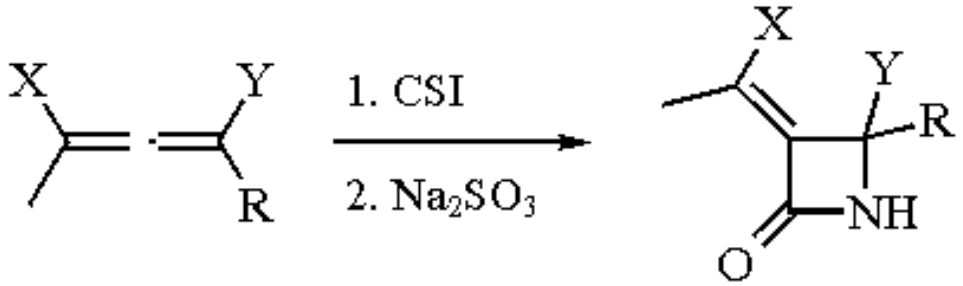

(43)

X	Y	R	Yield (%)
Me	SAr	Me	55[48d]
Me	SAr	TMS	87[48d]
Me	SAr	$(CH_2)OTBDMS$	66[48f]
Me	OAc	H	22[48e]
$Cl_2P(O)$	Me	Me	93[48g]

Alternative acyl and sulfonyl isocyanates that are preparatively useful for β-lactam synthesis include $Cl_3CH_2OSO_2NCO$, $Cl_3CH_2SO_2NCO$, and CF_3CONCO.[49] Methods for deprotection to the core β-lactam are described.

CSI has been useful as a mechanistic probe to study uniparticulate electrophilic addition to a number of fluxional molecules such as bullvalene, barrelene, and homobarrelene.[50]

CSI yields 2:1 adducts with Schiff's bases to form *s*-triazinediones (eq 44).[51]

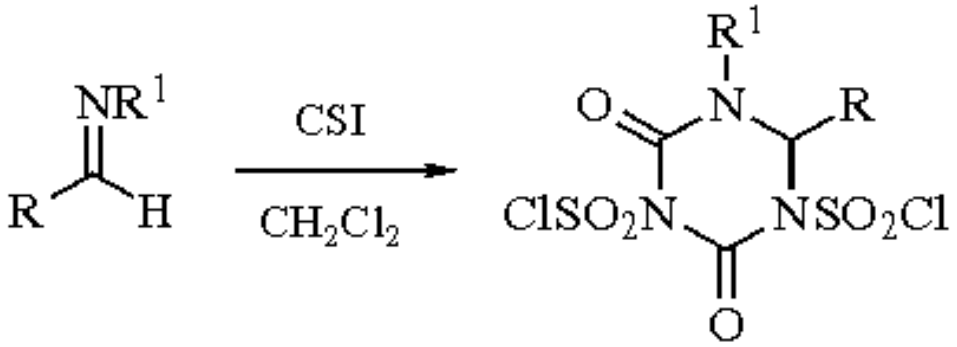

(44)

As a result of their large degree of p character, highly strained carbon-carbon single bonds can undergo formal cycloaddition with CSI (eq 45).[52]

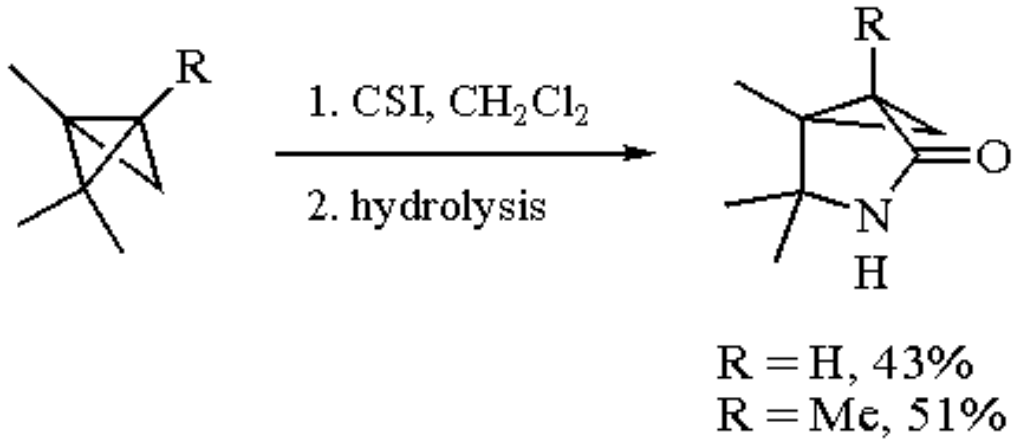

(45)

CSI reacts with most alkynes to give six-membered heterocyclic ring structures. Hydrolysis affords ketones (eq 46), while methanolysis affords β-keto esters. Interestingly, only the alkynic portion of 1-octene-4-yne reacts with CSI.[53]

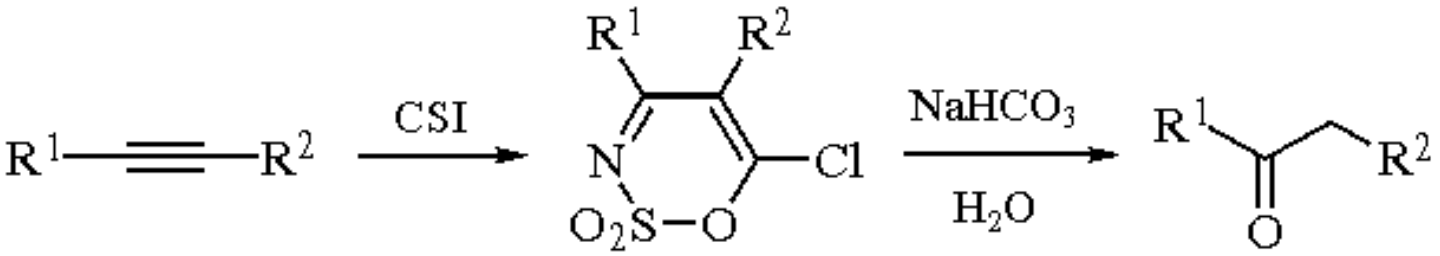

(46)

Azirines react with CSI to give three products derived from [2 + 2 + 2] cycloadducts (eq 47).[54]

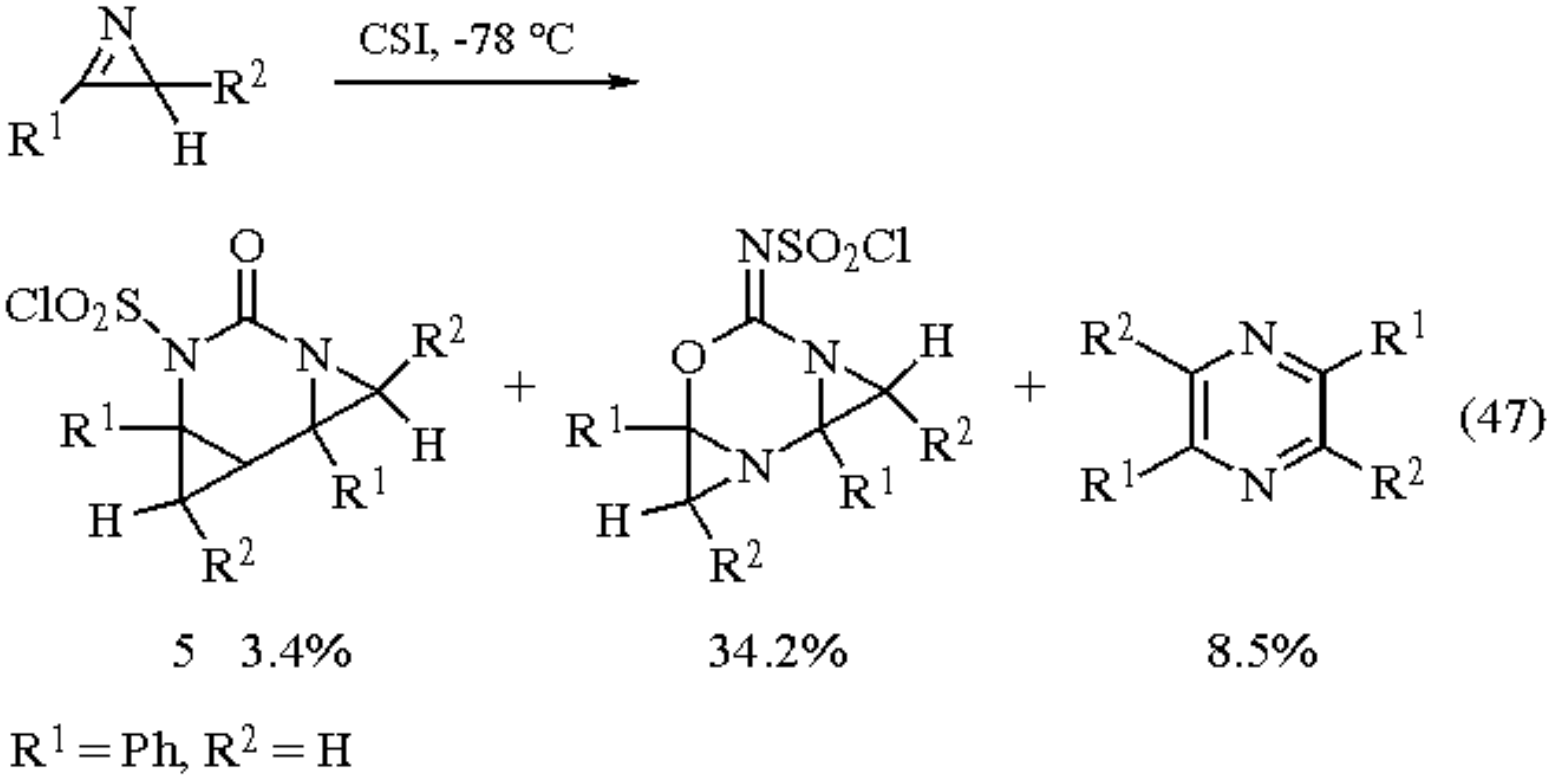

(47)

Amidines react with CSI to form mesionic compounds with an interesting structure (eq 48).[55]

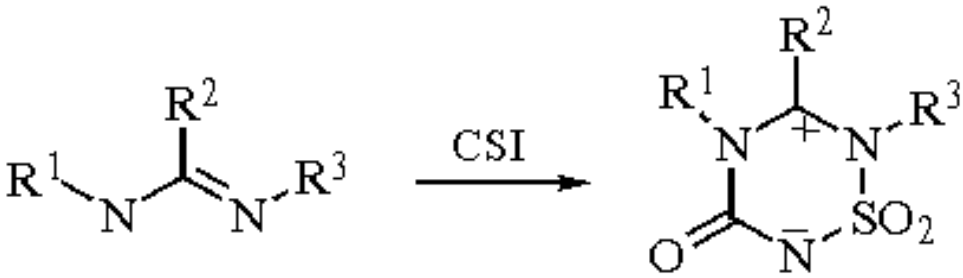

(48)

Regioselective 1,3 dipolar cycloaddition of nitrile oxides with CSI gives 3-aryl-substituted 1,2,4-oxadiazolin-5-ones after hydrolysis (eq 49).[56]

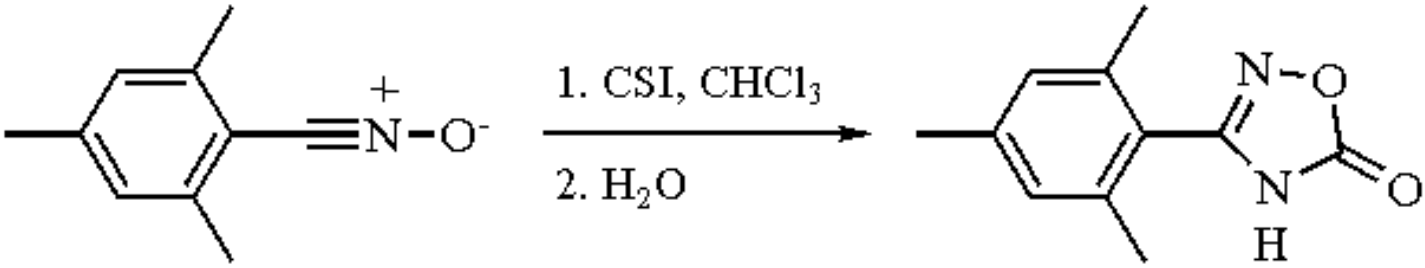

(49)

Transition metal 2-alkenyl and 2-alkynyl complexes undergo [3 + 2] cycloadditions with CSI, which lead to pyrrolidones and pyrrolinones respectively with migration of the metal atom (eqs 50 and 51).[57]

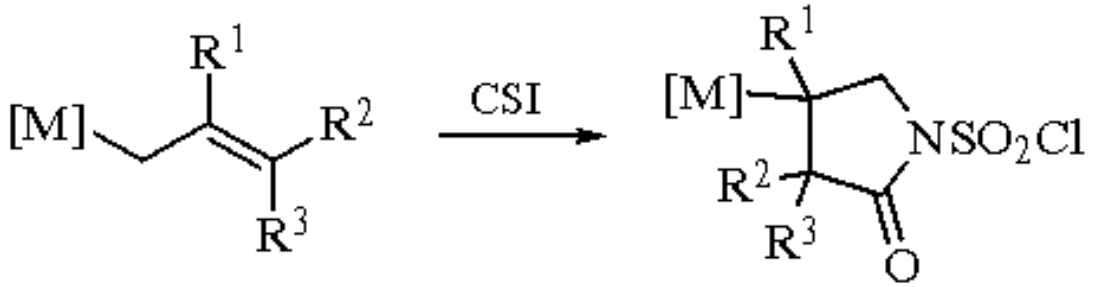

(50)

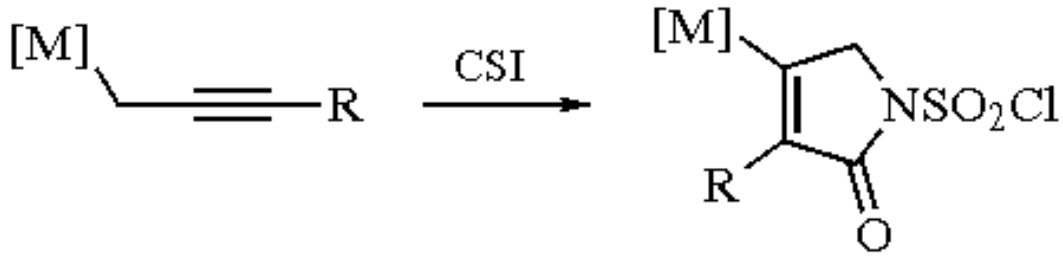

(51)

[M] = $CpFe(CO)_2$, $CpMo(CO)_3$, $Mn(CO)_5$, $Pt(PR_3)_2Cl$

Type III Reactions.

Type III reactions involve compounds which react with the chlorosulfonyl portion of CSI. These include compounds which are unreactive towards the isocyanate group (eqs 52 and 53)[58,59] or which react with the chlorosulfonyl portion under special experimental conditions such as high temperature (eq 54)[60] or radical conditions (eq 55).[61]

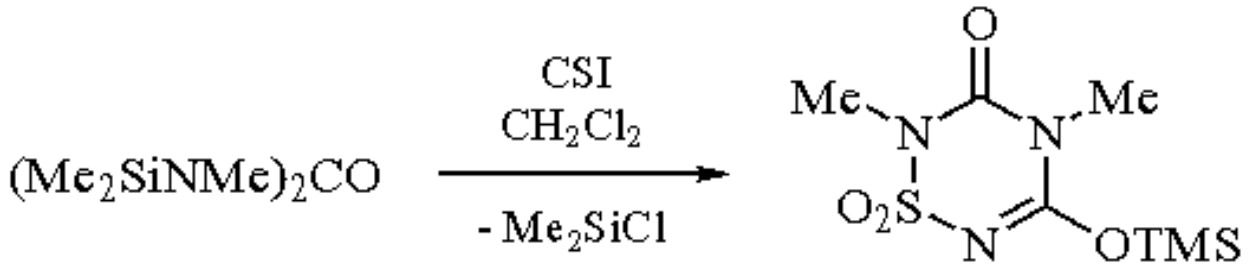

(52)

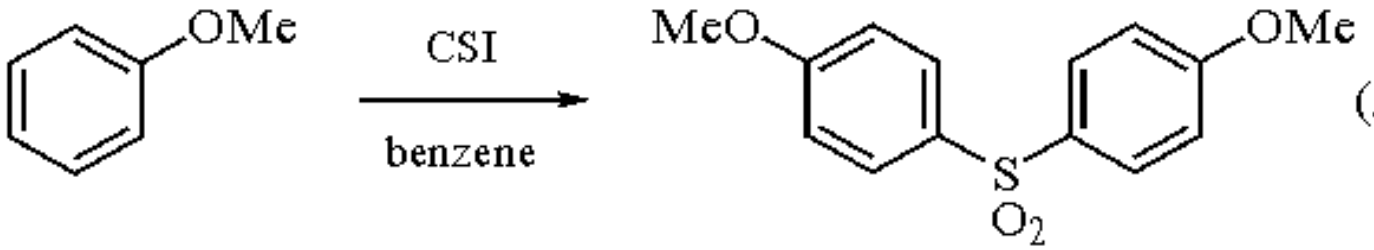

(53)

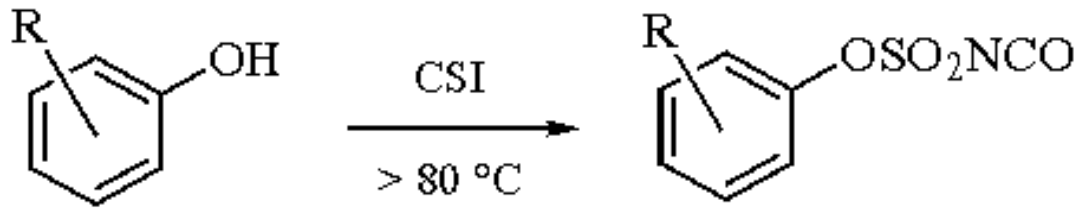

(54)

R = H, 3-Cl, 4-Cl, 4-Me, 4-MeO, 4-CN

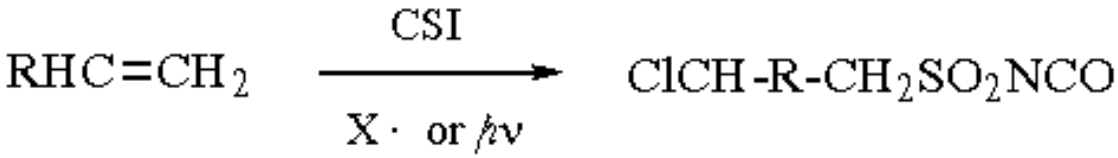

(55)

R = H, Me, Et, Bu, $ClCH_2$, Cl_2CHCH_2

By changing the reaction conditions in eq 55, a dramatically different product is obtained (eq 56).[1a]

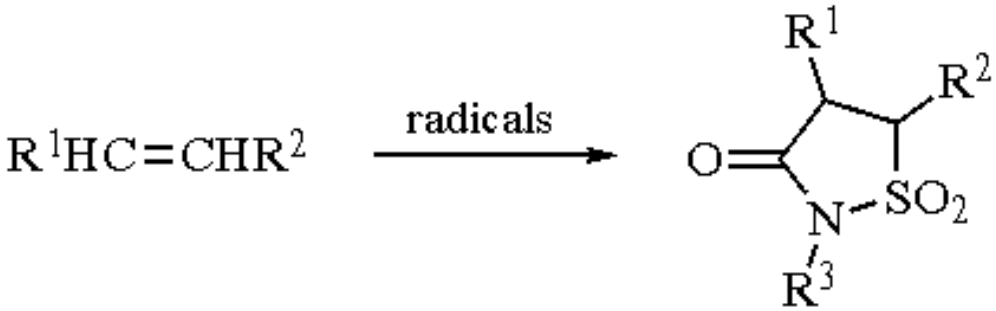

(56)

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Chloro(thexyl)borane

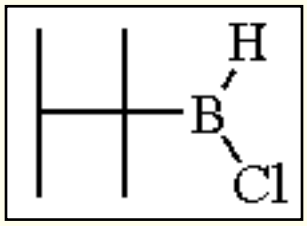

[75030-54-5] · $C_6H_{14}BCl$ · Chloro(thexyl)borane · (MW 132.43)

(hydroboration agent)

Alternate Name: chloro(1,1,2-trimethylpropyl)borane.

This reagent, which was first used in hydroboration reactions by Zweifel and Pearson,[1] has been replaced by ***Chloro(thexyl)borane-Dimethyl Sulfide***. In fact, Zweifel and Pearson prepared their reagent from borane-dimethyl sulfide in THF, so there is reason to believe that they were actually working with the dimethyl sulfide complex of the chloro(thexyl)borane that they prepared. Brown and Sikorski[2] have prepared chloro(thexyl)borane free of dimethyl sulfide in both THF and Et_2O and examined the reactions of the reagents obtained with alkenes in the same solvents. The THF complex of chloro(thexyl)borane could be obtained cleanly by treating BH_2Cl with 2,3-dimethyl-2-butene in THF, but the same reaction in Et_2O gave a complex, equilibrating mixture containing thexylborane, chloro(thexyl)borane, and dichloro(thexyl)borane. Hydroboration of terminal alkenes with the chloro(thexyl)borane reagent in THF (or with the complex mixture obtained in Et_2O) led to mixtures containing trialkylborane, dialkylchloroborane, and alkyldichloroborane species. However, these workers showed that the chloro(thexyl)borane-dimethyl sulfide reagent in CH_2Cl_2 reacts cleanly with alkenes to give the desired alkylchlorothexylborane product.[2]

---

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William S. Mungall

Chloro(thexyl)borane-Dimethyl Sulfide

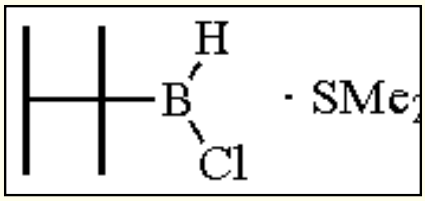

[75067-06-0] · $C_8H_{20}BClS$ · Chloro(thexyl)borane-Dimethyl Sulfide · (MW 194.57)

(highly regioselective, monohydroborating agent for alkenes and alkynes, producing thexylalkylchloroboranes or thexylalkenylchloroboranes, respectively, which are synthetically useful intermediates;[1] reduces carboxylic acids to aldehydes;[2] reduces aldehydes and ketones to alcohols[2b])

Solubility: sol CH_2Cl_2, ether, and THF, but CH_2Cl_2 is the solvent of choice;[3] reacts rapidly with protic solvents.[2b]

Form Supplied in: prepared in situ.

Preparative Method: most conveniently prepared from commercially available monochloroborane-dimethyl sulfide complex and 2,3-dimethyl-2-butene in CH_2Cl_2 (eq 1).[1a,3]

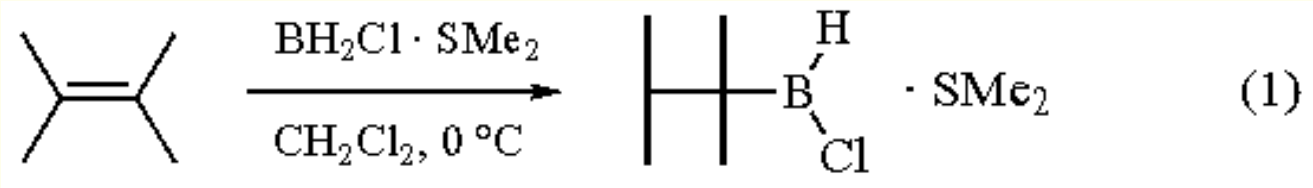

Analysis of Reagent Purity: analyzed by ^{11}B NMR and IR spectroscopy and by hydrogen evolution upon reaction with methanol.[3]

Handling, Storage, and Precautions: very reactive with oxygen and moisture and must be handled using standard techniques for handling air-sensitive materials.[4] Reported to be stable for at least two months when stored at 0 °C in CH_2Cl_2 solution under N_2.[2b]

Hydroboration of Alkenes and Alkynes.

Chloro(thexyl)borane-dimethyl sulfide (ThxBHCl.SMe_2) in CH_2Cl_2 is a monohydroborating agent with exceptionally high regioselectivity.[1] This reagent has also been prepared in THF/Et_2O by the reaction of ***Thexylborane-Dimethyl Sulfide*** with one equivalent of HCl.[5] However, CH_2Cl_2 is superior to Et_2O or THF as a solvent for hydroborations with

this reagent.[3] Like ***Disiamylborane*** (Sia_2BH) and ***9-Borabicyclo[3.3.1]nonane*** (9-BBN), $ThxBHCl.SMe_2$ has large steric requirements and reacts preferentially to add boron at the least hindered carbon atom of the carbon-carbon double or triple bond (eq 2).

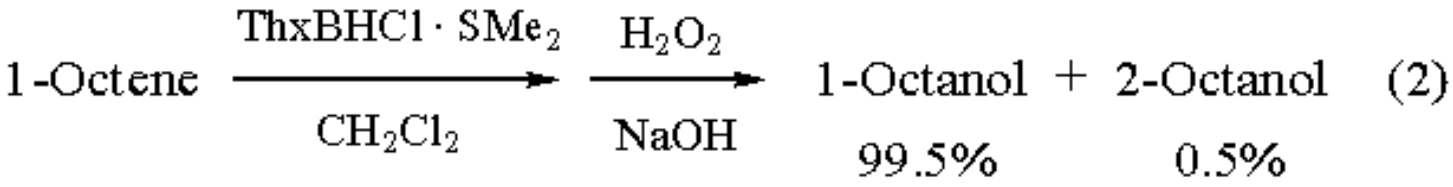

However, $ThxBHCl.SMe_2$ is more sensitive to electronic factors that either Sia_2BH or 9-BBN due to its higher Lewis acidity. Upon reaction with styrene followed by oxidation, $ThxBHCl.SMe_2$ gives a greater than 99:1 ratio of 2-phenylethanol to 1-phenylethanol, which is higher than any of the other common hydroborating agents.[1b] Internal alkenes are much less reactive than terminal alkenes toward hydroboration with $ThxBHCl.SMe_2$, and this reagent shows a much higher rate of reaction with *cis* disubstituted alkenes than with the *trans* isomers.[1c] Cyclohexenes and trisubstituted alkenes react more slowly with $ThxBHCl.SMe_2$ than do terminal or *cis* alkenes, and some redistribution of the reagent to $ThxBH_2.SMe_2$ and $ThxBCl_2.SMe_2$ can be observed with the long reaction times (>10 h) required for the reaction with relatively unreactive alkenes.[1b] $ThxBHCl.SMe_2$ reacts more rapidly with 1-hexyne or 3-hexyne than with 1-hexene.[6] Hydroborations of terminal alkynes with this reagent result in regioselective *syn* addition, affording the alkenylchloro(thexyl)borane in high yield.

Alkylchloro(thexyl)boranes (**1**) are useful intermediates in a variety of organic transformations. Reduction of these intermediates with ***Potassium Triisopropoxyborohydride*** (KPBH) in the presence of another alkene produces the mixed dialkylthexylborane (**2**), which can be converted to the corresponding unsymmetrical ketones (eq 3).[1b,7] Dialkylthexylboranes (**2**) are also produced by reaction of alkylchloro(thexyl)boranes (**1**) with equimolar amounts of organolithium or Grignard reagents.[5] Reduction of alkylchloro(thexyl)boranes at -78 °C with KPBH followed by addition of a 1-halo-1-alkyne and warming to room temperature affords *B*-(*cis*-1-halo-1-alkenyl)alkyl(thexyl)boranes (**3**) (eq 4). Treatment with ***Sodium Methoxide*** induces a selective migration of the alkyl group, resulting in the formation of *B*-(*trans*-1-alkyl-1-alkenyl)thexylborinate (**4**), which can be converted to the (*E*)-alkene (**5**) by protonolysis with isobutyric acid or to the ketone (**6**) by alkaline hydrogen peroxide oxidation.[8] The low migratory aptitude of the thexyl group results in only 2-7% of product where the thexyl group has migrated.

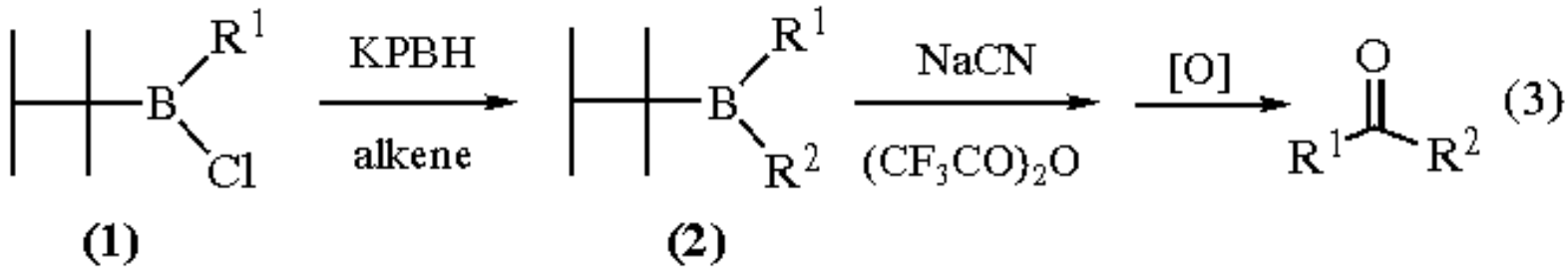

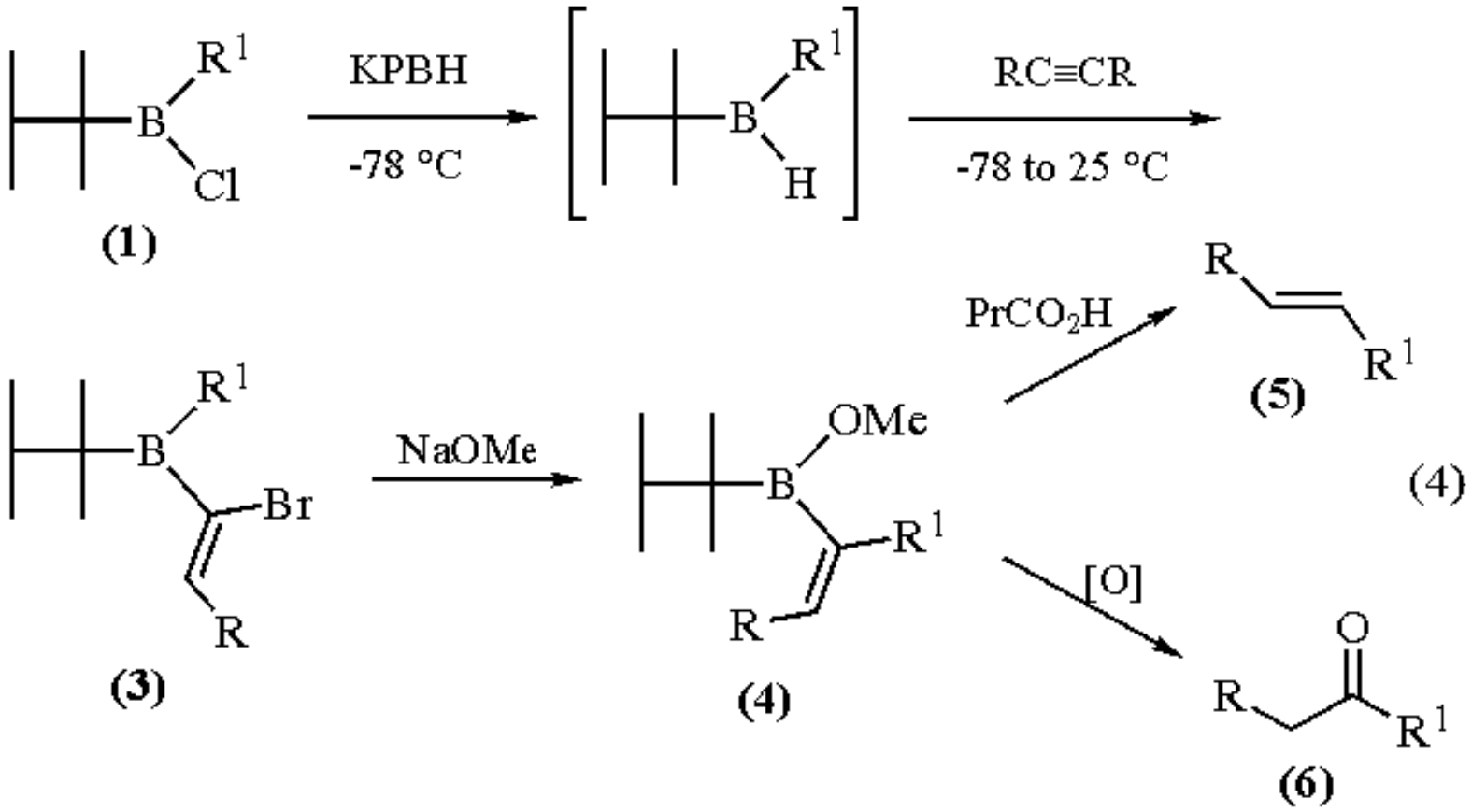

Hydroboration of 1-bromo-1-alkynes with chloro(thexyl)borane leads to the synthesis of alkynyl ketones in 61-63% yields by the sequence of reactions[9] shown in eq 5. Sequential treatment of alkenylchloro(thexyl)boranes, which are formed by the reaction of chloro(thexyl)borane with alkynes, with lithium chloropropargylide and aldehydes affords 1,3-enynols or 1,2,4-trienols depending on the reaction conditions.[10]

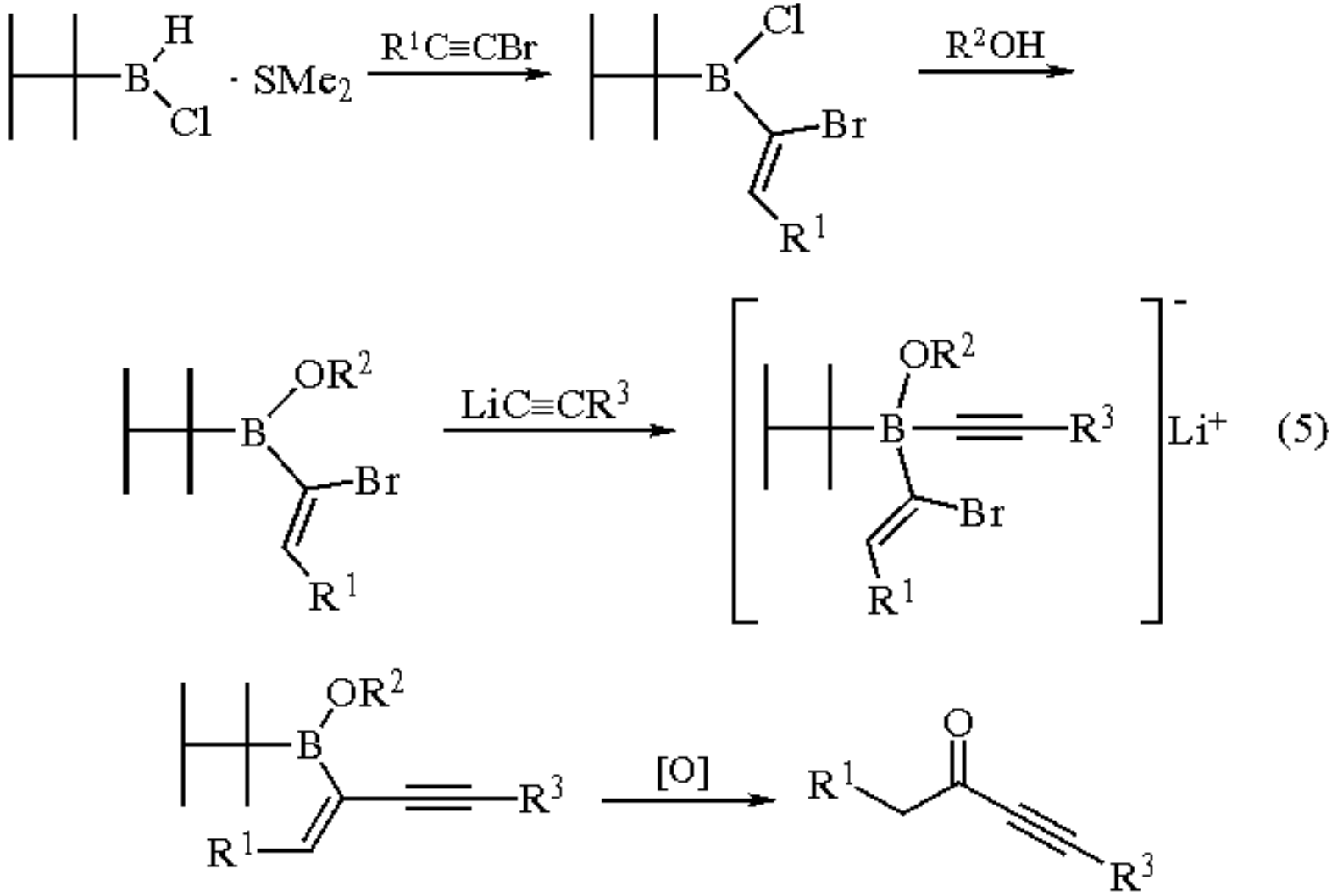

Alkylchloro(thexyl)boranes prepared from terminal alkenes can be hydrolyzed with one equivalent of water and then oxidized with ***Pyridinium Chlorochromate*** (PCC) to the corresponding aldehyde in moderate yields (eq 6).[11]

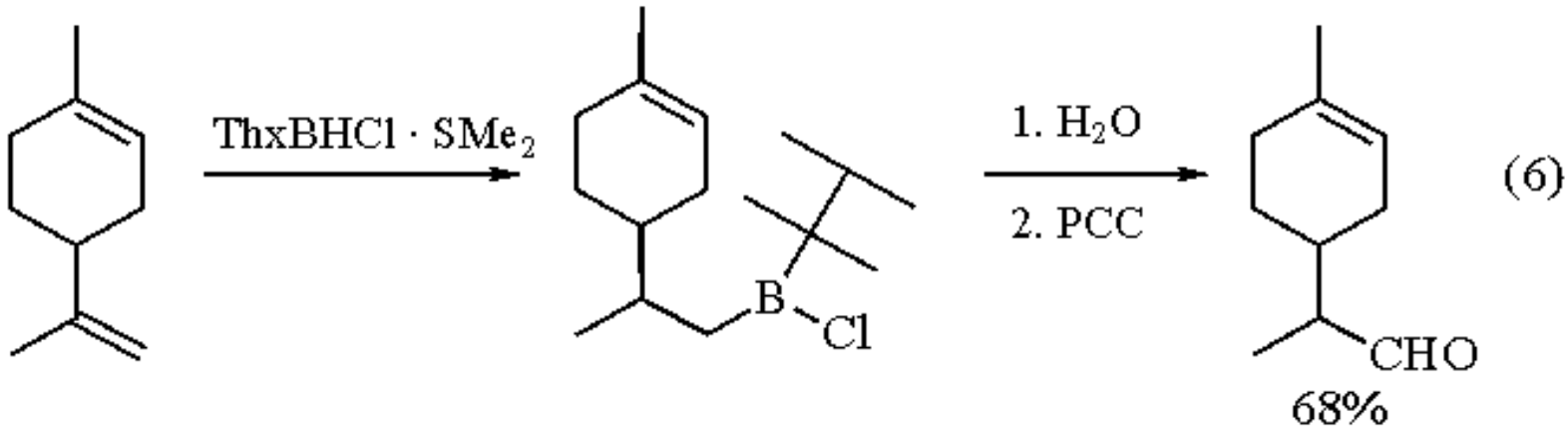

Reduction of Carboxylic Acids to Aldehydes.

Aliphatic carboxylic acids are reduced rapidly (15 min) and aromatic carboxylic acids are reduced slowly (24 h) by chloro(thexyl)borane-dimethyl sulfide to the corresponding aldehydes.[2] Sodium bisulfite adducts were prepared to

purify the aldehydes. Aliphatic aldehydes are isolated in 80-93% yields, and aromatic aldehydes are isolated in 46-78% yields.[2a] Alkoxy, nitro, cyano, halo, and ester functional groups are not reduced under these conditions.

Reductive Cyclization of o-Azidoalkenes.

Hydroboration of o-azidoalkenes with chloro(thexyl)borane followed by hydrolysis affords, via an intramolecular reductive cyclization, the corresponding pyrrolidine (78%) or the piperidine (53%) (eq 7).[12]

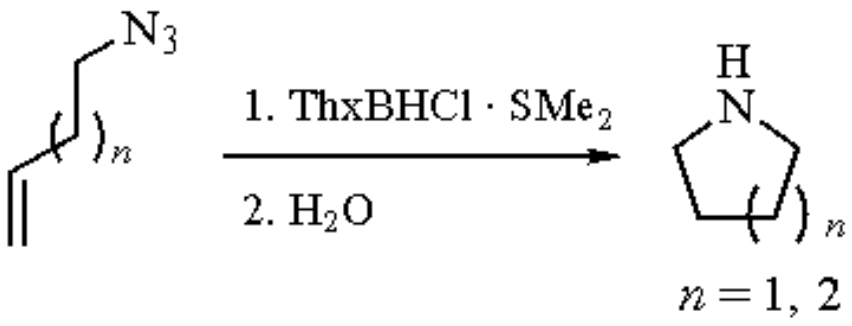

(7)

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Chlorotitanium Triisopropoxide[1]

$ClTi(O\text{-}i\text{-}Pr)_3$

[20717-86-6] · $C_9H_{24}ClO_3Ti$ · Chlorotitanium Triisopropoxide · (MW 260.62)

(mild Lewis acid used for the preparation of organotitanium derivatives[1] and titanium enolates;[1,2] alkyl, [3-5] allyl,[3,4,6] aryl,[3-5] alkenyl,[7] allenyl,[8] and alkynyl[9,10] titanium triisopropoxides exhibit reduced basicity and add to carbonyl compounds with enhanced chemo-, regio-, and stereoselectivity;[1b-f] titanium enolates[2] react with aldehydes and imines[11] with high levels of *syn* selectivity[12] and greatly enhanced diastereofacial selectivity;[13] titanium isopropoxides mediate the regioselective opening of epoxides[14,15] and serve as a titanium source for the preparation of chiral titanium complexes[16])

Alternate Names: chlorotitanium tris(isopropoxide); chlorotriisopropoxytitanium; chlorotris(2-propanolato)titanium.

Physical Data: mp 45-50 °C; bp 61-65 °C/0.1 mmHg; *d* 1.091 g cm^{-3}.

Solubility: sol most nonprotic organic solvents, e.g. Et_2O, THF, CH_2Cl_2, toluene, hexanes.

Form Supplied in: syrupy liquid; 1.0 M solution in CH_2Cl_2 or hexanes.

Preparative Method: available commercially, but can be easily made from a 3:1 mixture of ***Titanium Tetraisopropoxide*** and ***Titanium(IV) Chloride***,[3] which can be distilled to give the pure reagent or used in situ.[17]

Handling, Storage, and Precautions: corrosive; moisture sensitive; flammable liquid; can be stored under nitrogen, in pure form or in solution, for months.

Organotitanium Reagents.

The conversion of a variety of readily available organomagnesium (RMgX, Grignard) or organolithium reagents (RLi) to organotitanium derivatives of the general type $RTiX_3$ (X = Cl, OR´, or NR_2´´) often results in significant improvements in chemo-, regio-, diastereo-, and enantioselectivity.[1] Similar effects are also possible with the titanation of enolates. The synthetic advantages of the organotitanium species are derived not only from the modulation of their nucleophilicity and Lewis basicity, but also through their improved solubility in organic solvents and their increased steric and electronic requirements.

Among the various titanium alkoxides, the isopropoxy derivatives are most synthetically useful because they exist in a monomeric form while retaining adequate titanium reactivity. Although less bulky alkoxide ligands (e.g. MeO, EtO) are expected to form more reactive titanium species, these derivatives are, overall, less reactive because they exist as oligomers.

Titanation of Organomagnesium and Organolithium Reagents.

The widely used 1,2-additions of organometallic reagents to aldehydes and ketones often take place with low stereoselectivity and without significant discrimination among different carbonyl groups. Treatment of these carbon nucleophiles with $ClTi(O\text{-}i\text{-}Pr)_3$ (**1**) can have a dramatic effect in their chemo- and stereoselectivity. The resulting alkyltitanium triisopropoxide reagents are usually employed in carbonyl additions in situ, although some, such as ***Methyltitanium Triisopropoxide***, can also be isolated in a pure form. An important advantage of these reagents is that they generally react much faster with aldehydes than with ketones (eq 1).[1b-f,3,5,9,18] They also tolerate a variety of other electrophilic functional groups, such as halides, esters, cyano, and nitro groups.

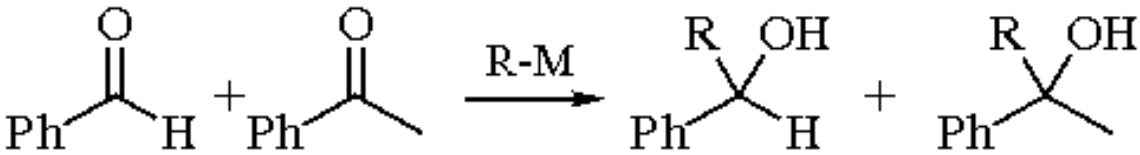

(1)

MeLi	42:58
MeMgBr	79:21
$MeTi(O\text{-}i\text{-}Pr)_3$	>99:<1
$BuTi(O\text{-}i\text{-}Pr)_3$	>99:<1
PhLi	40:60
$PhTi(O\text{-}i\text{-}Pr)_3$	>99:<1
$NCCH_2Li$	64:36
$NCCH_2Ti(O\text{-}i\text{-}Pr)_3$	98:2
PhC≡CLi	80:20
$PhC{\equiv}CTi(O\text{-}i\text{-}Pr)_3$	>99:<1

The addition of the $RTi(O\text{-}i\text{-}Pr)_3$ reagents to aldehydes and ketones often proceeds with significant diastereofacial selectivity, which varies with the R group (eq 2).[4]

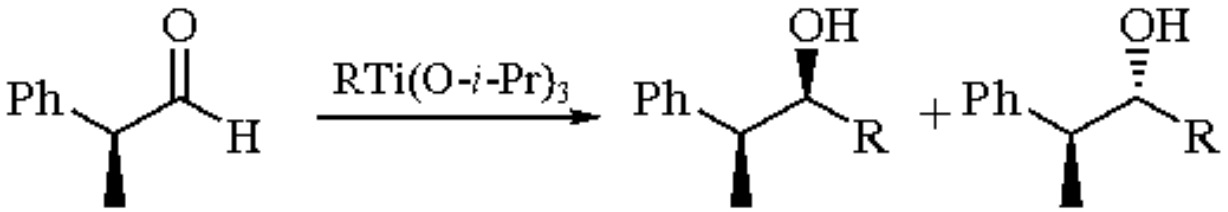

(2)

R	*syn*	*anti*
Me	88:12	
n-Bu	88:12	
Ph	75:25	
$CH_2{=}CHCH_2$	68:32	

Addition of these reagents to α- or β-alkoxy carbonyl compounds proceeds with a variable extent of chelation.[19] Thus while methyltitanium triisopropoxide adds to aldehydes without chelation, it adds to similar ketones with chelation.[4] The nature of the R group can also have a dramatic effect on the outcome of these carbonyl additions (eq 3).[20]

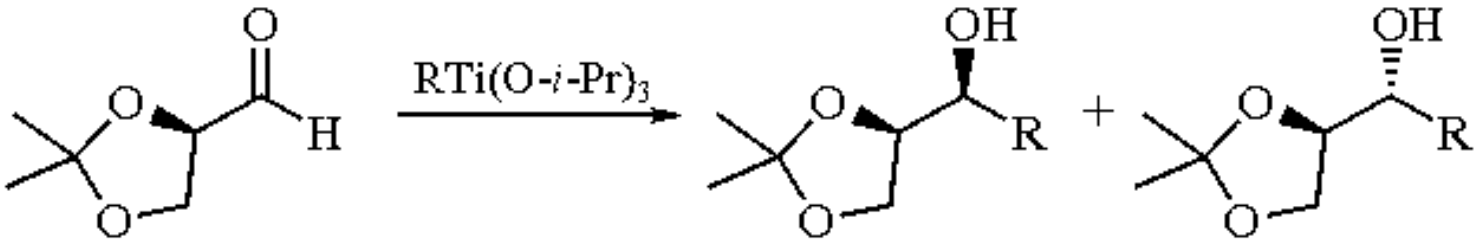

(3)

R	
Me	75:25
n-Bu	90:10
$CH_2{=}CHCH_2$	71:29
Ph	9:91

Titanation of functionalized organozinc nucleophiles[21] results in highly stereocontrolled additions to aldehydes (eq 4).[22]

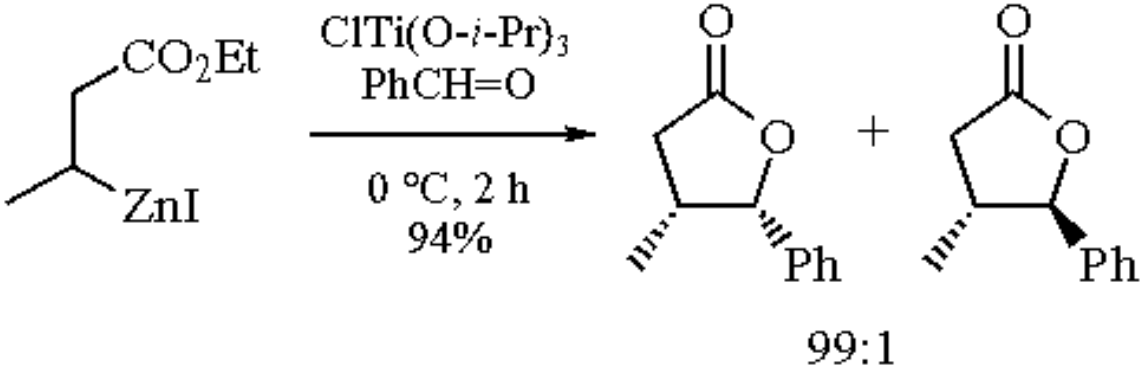

(4)

Titanation of lithiated allyl or crotyl carbamates allows a highly stereoselective homoaldol[6] addition to aldehydes in an S_N2' fashion. Titanation with ***Titanium Tetraisopropoxide*** or ***Chlorotris(diethylamino)titanium***, however, is often a more stereocontrolled process than titanation with (**1**) (eq 5).[23]

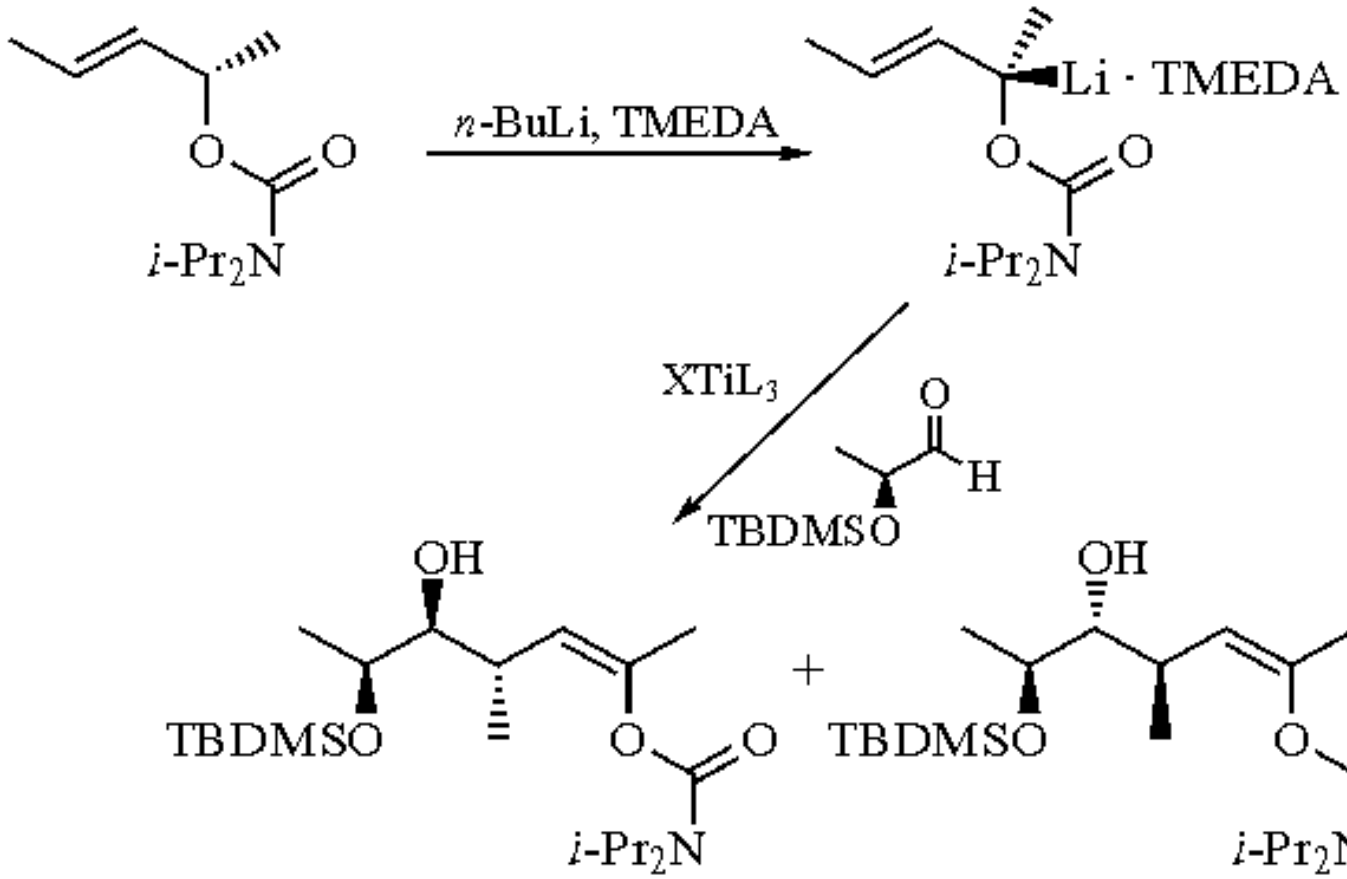

(5)

XTiL$_3$	
ClTi(O-*i*-Pr)$_3$	53:47
Ti(O-*i*-Pr)$_4$	93: 7
ClTi(NEt$_2$)$_3$	2:98

Although vinyltitanium reagents dimerize rapidly (eq 6),[7] they can be efficiently added to aldehydes at low temperatures.[7] The diastereoselectivity of these additions can be opposite to that observed for the lithium reagents (eq 7).[24]

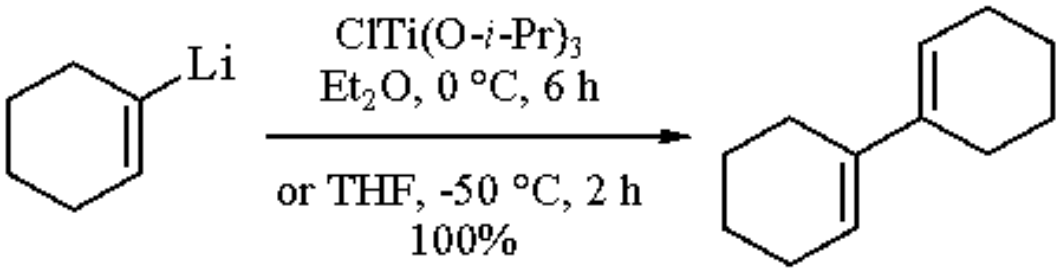

(6)

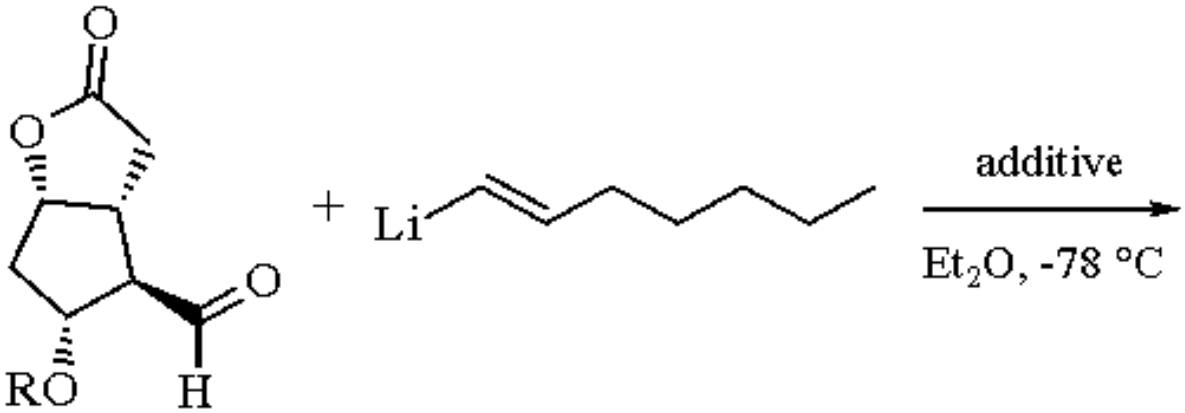

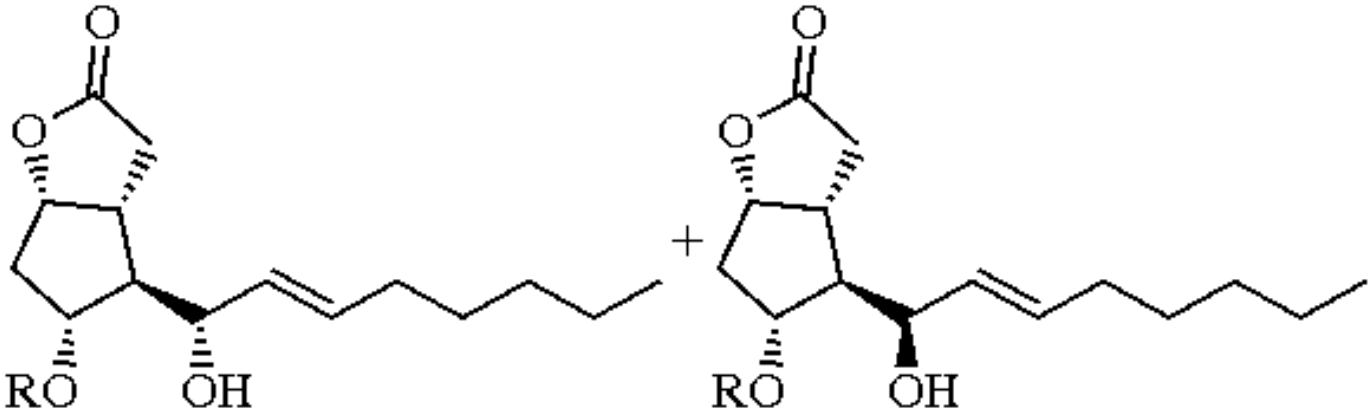

(7)

additive	
none	9:91
ClTi(O-*i*-Pr)$_3$	74:26

Titanated alkynyl and aryl derivatives add regioselectively to pyridinium salts and pyrimidinones (eq 8).[25]

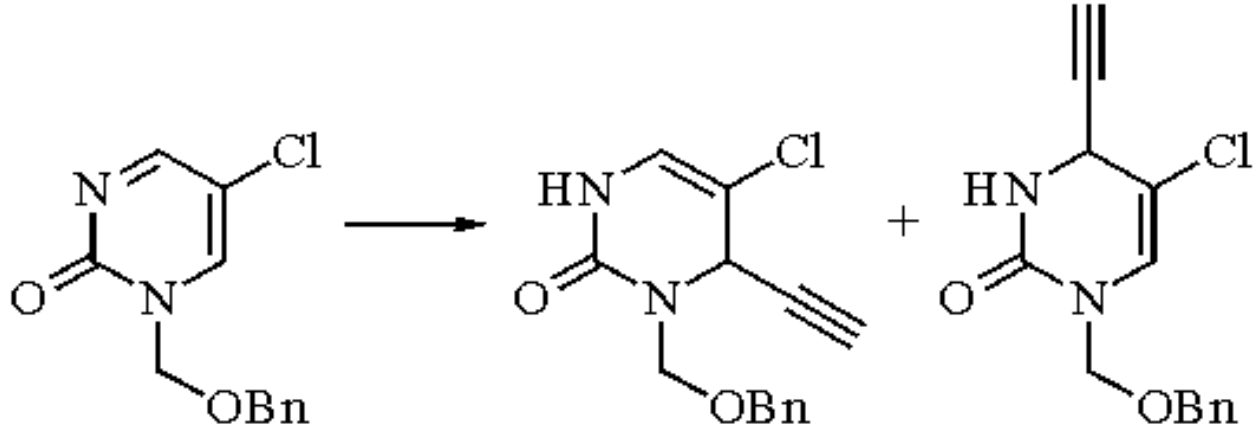

(8)

HC≡CLi, ClTi(O-*i*-Pr)$_3$	1:0
HC≡CLi	4:1
HC≡CMgBr	1:1

Titanation of phosphonate- or phosphinoxide-stabilized carbanions improves their aldehyde selectivity[26] and can affect the stereoselectivity of their additions to aldehydes.[27] With phosphonate acetate, titanation results in a stereoselective Knoevenagel condensation (eq 9).[28]

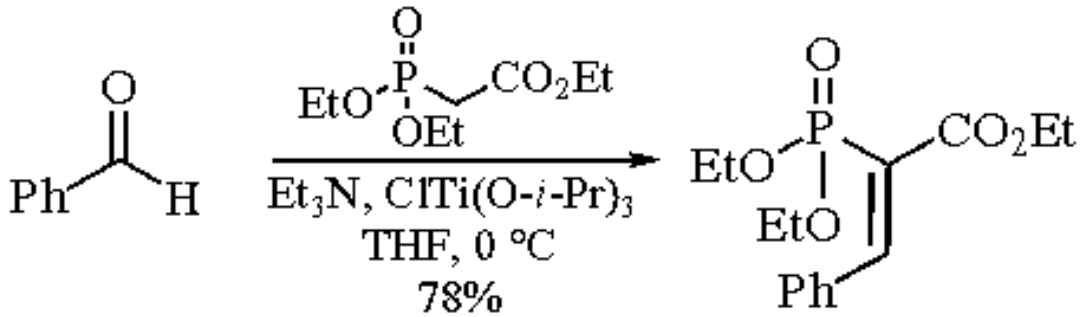

E:*Z* = 90:10

(9)

Titanation of Enolates.[2]

The conversion of lithium enolates to the corresponding titanium derivatives often results in enhanced chemo-, regio-, and stereoselectivities during the aldol reactions with aldehydes. Due to their suppressed Lewis acidity, the titanium enolates add selectively to aldehydes in the presence of ketones, while the reverse selectivity can be achieved via the in situ protection of the aldehyde moiety with ***Titanium Tetrakis(diethylamide)*** (eq 10).[29]

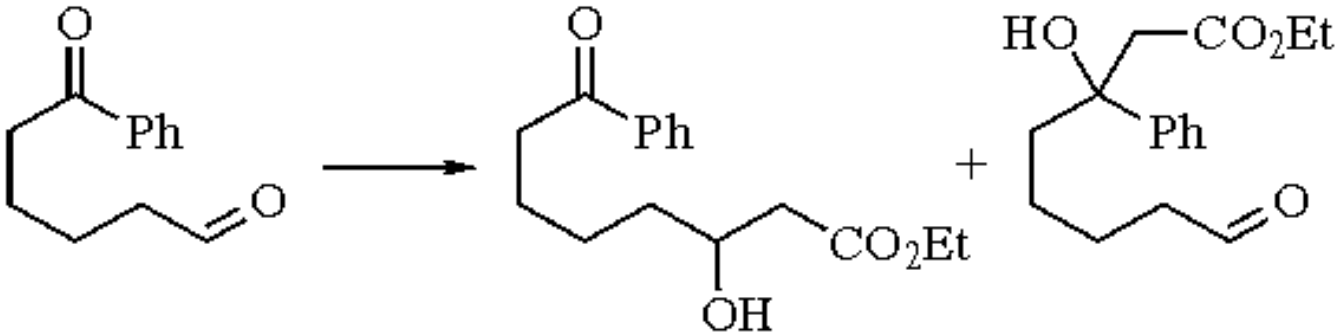

(10)

$CH_2{=}C(OEt)OLi$	50:50
$CH_2{=}C(OEt)OLi$, $ClTi(O\text{-}i\text{-}Pr)_3$	97:3
$Ti(NEt_2)_4$) then $CH_2{=}C(OEt)OLi$	<1:>99

Regardless of their enolate geometry and substitution pattern,[30] titanium enolates undergo aldol reactions with high levels of *syn* selectivity (eq 11).[12]

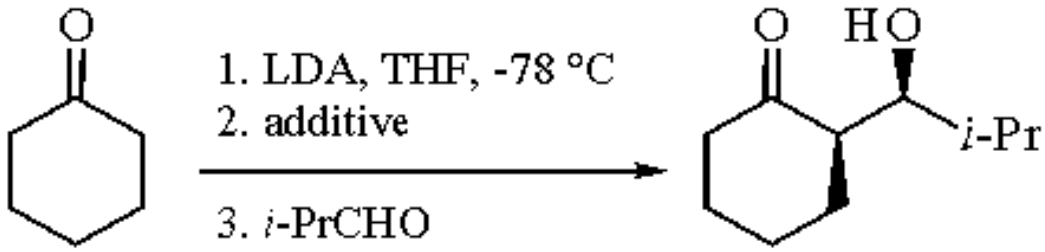

(11)

additive	*syn*:*anti*
none	52:48
$ClTi(O\text{-}i\text{-}Pr)_3$	86:14
$ClTi(OPh)_3$	90:10
$ClTi(NEt_2)_3$	93: 7

Addition of titanium enolates to chiral aldehydes, including α-alkoxy derivatives, takes place with no chelation[19] and with high diastereoselectivity (eq 12).[31]

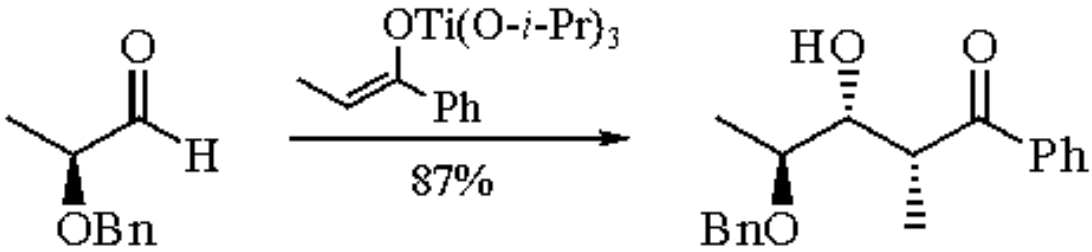

(12)

A complete reversal of diastereoselectivity upon titanation is possible during addition of ester enolates to chiral imines (eq 13).[11]

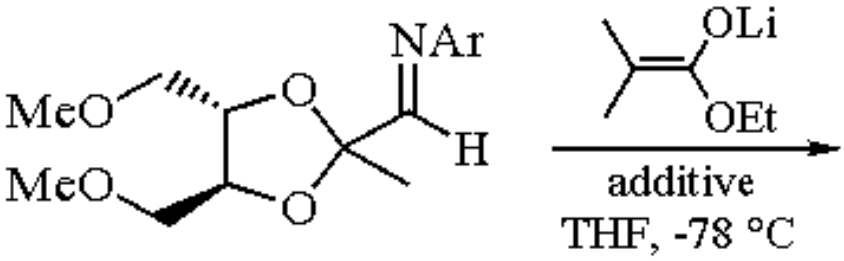

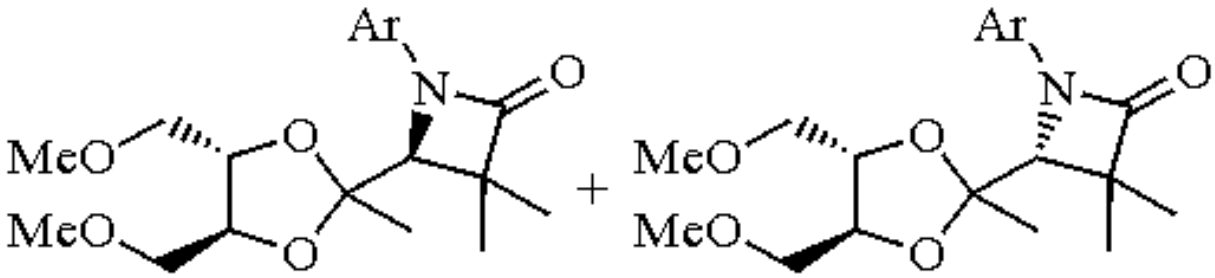

(13)

additive	
none	93: 7
$ClTi(O\text{-}i\text{-}Pr)_3$	8:92

Titanation of chiral enolates often has a dramatic effect on their diastereofacial selectivity; examples include the enolates of chiral amides,[32] chiral imides,[33] chiral α´-silyloxy ketones,[34] and chiral α´-benzoyloxy ketones (eq 14).[13]

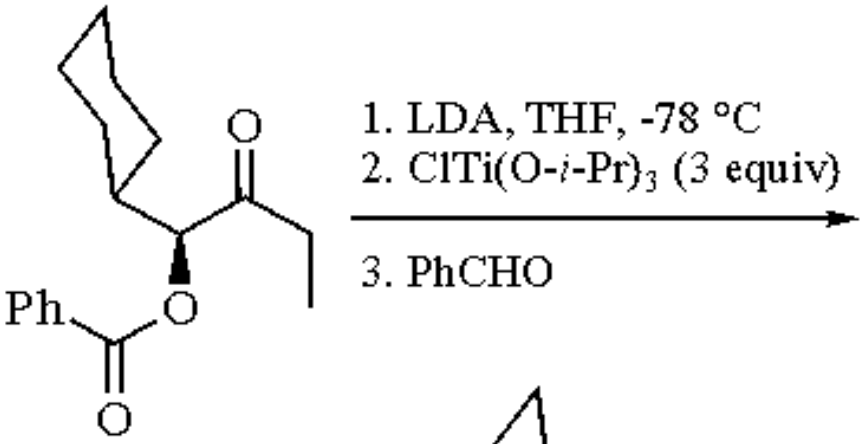

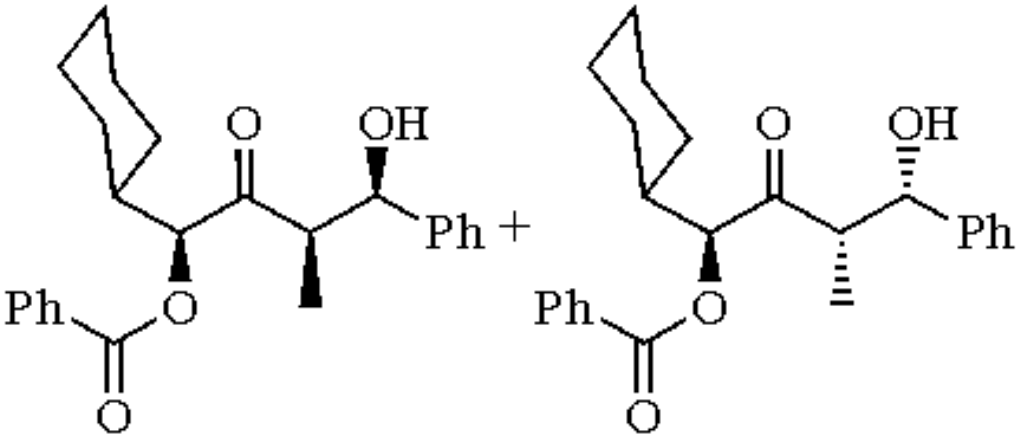

(14)

365:1

A complete reversal of regioselectivity is observed in the reactions of enedithiolates with α,β-unsaturated ketones in the presence of (**1**). Although the lithium enedithiolates react by 1,4-addition, the titanium derivatives afford only 1,2-addition products, while the corresponding aluminum species give 1,4-addition through the sulfur atom (eq 15).[35]

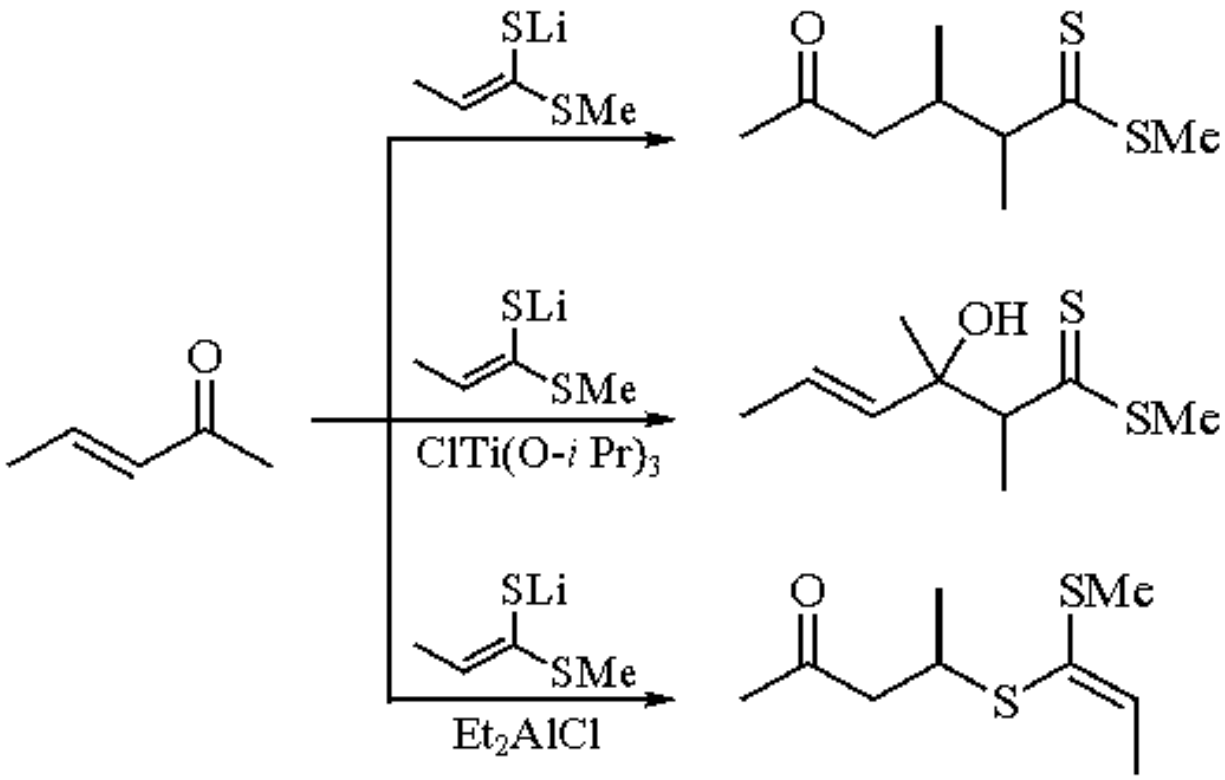

(15)

Enolization of the imines of α-amino esters generates *N*-metalated azomethine ylides, which react with α,β-unsaturated carbonyl compounds to form pyrrolidine derivatives. The use of titanium intermediates,[36,37] formed with a base and (**1**) or ***Dichlorotitanium Diisopropoxide***, results in an increase of the regio- and stereoselectivity of this process (eq 16).[37]

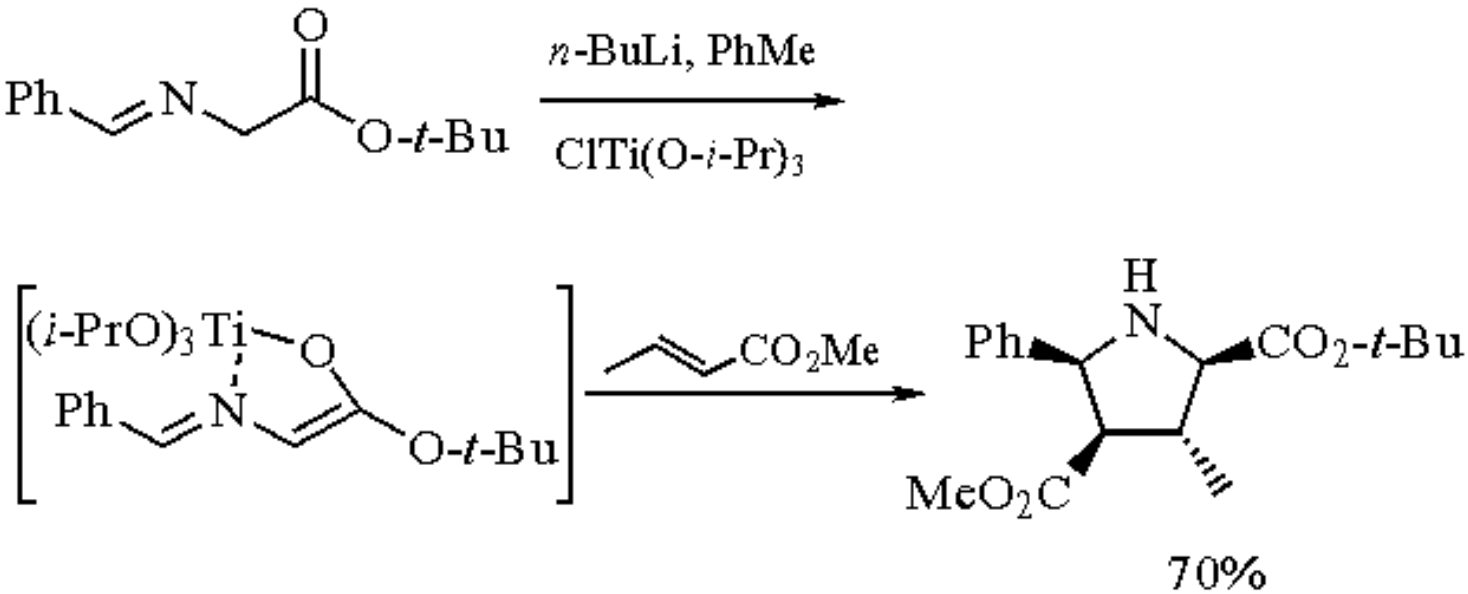

(16)

Regioselective Epoxide Opening.

Titanium alkoxides promote the regioselective opening of asymmetric epoxides and epoxy alcohols with a variety of nucleophiles. Although ***Titanium Tetraisopropoxide*** is used more often for this purpose,[14,15] (**1**) is used in the formation of titanium acetylide nucleophiles,[9] or as a source of the Cl^- nucleophile (eq 17).[15]

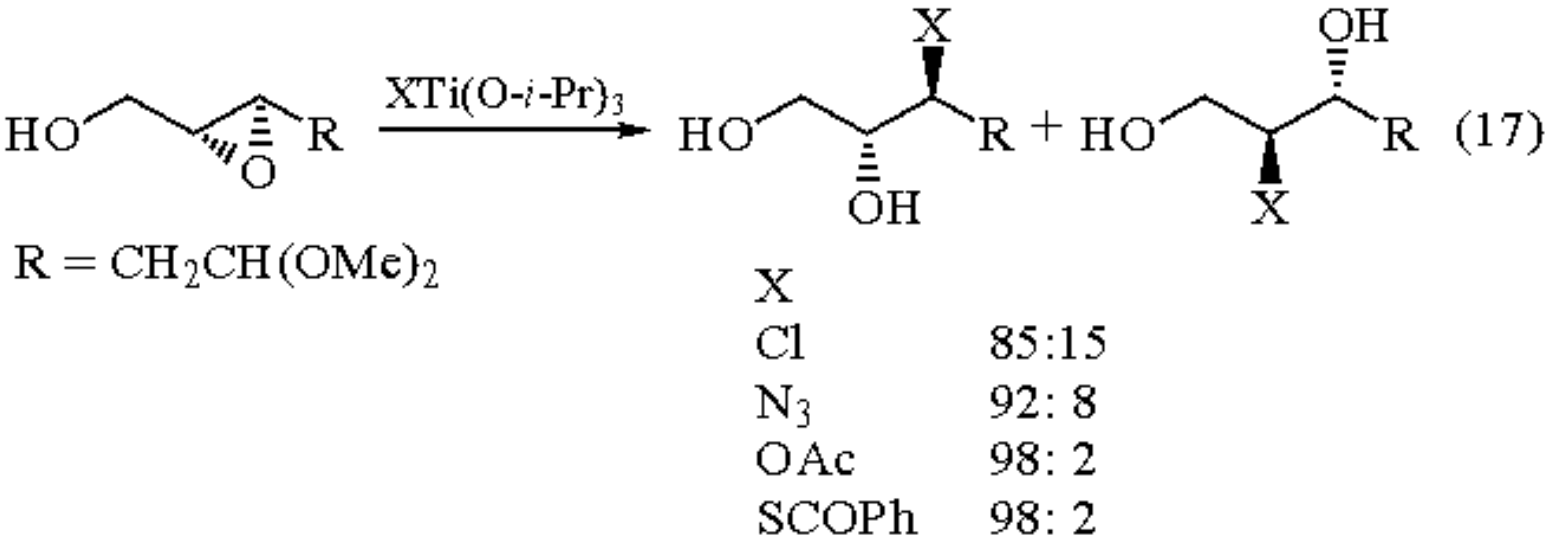

Preparation of Chiral Titanium Complexes.[16]

Chiral ligands on titanium can lead to significant enantioselectivities in various titanium-mediated reactions. For this purpose, numerous chiral alkoxytitanium complexes have been investigated.[16] A common titanium source for many of these derivatives is (**1**), although dichlorotitanium diisopropoxide and titanium(IV) isopropoxide are also often used. One successful application is the enantioselective addition of alkyl groups to aldehydes (eq 18).[38]

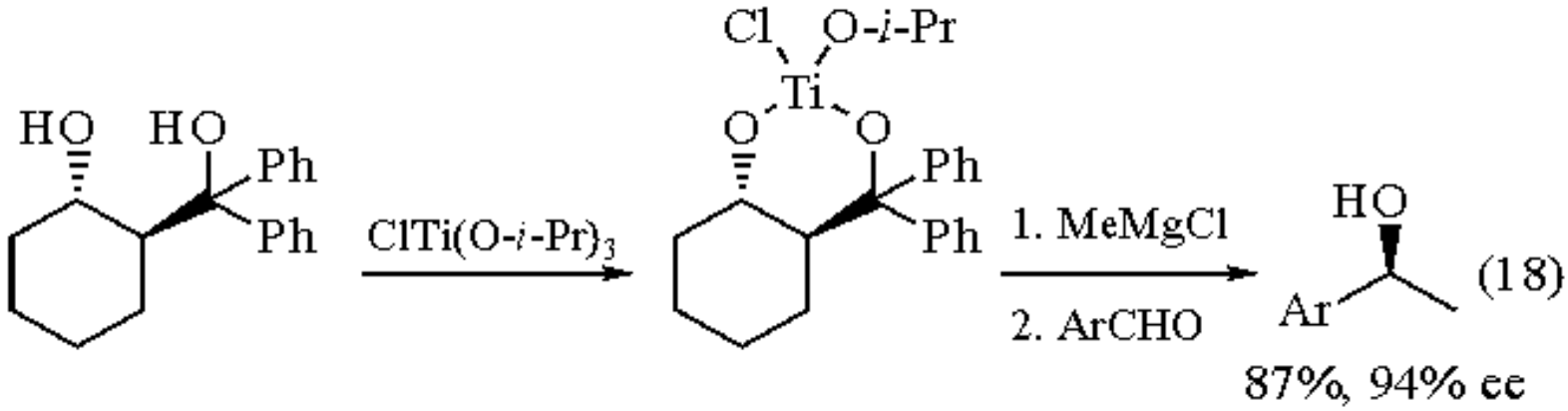

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Chlorotris(diethylamino)titanium[1]

$ClTi(NEt_2)_3$

[6607-37-0] · $C_{12}H_{30}ClN_3Ti$ · Chlorotris(diethylamino)titanium · (MW 299.72)

(efficient transmetalating agent useful in the conversion of reactive and nonselective organolithium or -magnesium compounds into organotitanium reagents for chemo- and stereoselective Grignard-type,[2,3] aldol,[4-6] homoaldol,[7,8] and Michael additions[9])

Alternate Name: chlorotitanium tris(diethylamide).

Physical Data: bp 94-96 °C/0.02 mmHg.

Solubility: sol ether, THF, CH_2Cl_2, toluene.

Form Supplied in: liquid.

Preparative Methods: the reaction of ***Lithium Diethylamide***, prepared by the reaction of $HNEt_2$ with BuLi[10a] or Li/styrene,[10b] with a stoichiometric amount of ***Titanium(IV) Chloride*** affords $ClTi(NEt_2)_3$ (eq 1). The reaction of $TiCl_4$ with ***Titanium Tetrakis(diethylamide)*** also leads to $ClTi(NEt_2)_3$.[10c] $ClTi(NMe_2)_3$ is accessible via similar routes.[10a]

$$LiNEt_2 + TiCl_4 \longrightarrow ClTi(NEt_2)_3 \qquad (1)$$

Handling, Storage, and Precautions: moisture-sensitive; should be handled and stored under an inert gas atmosphere (e.g. N_2). Syringe techniques are adequate.

Traditional carbanions such as alkyllithium reagents, lithium enolates, and other deprotonated CH-acidic compounds, as well as some organomagnesium reagents, are so basic and reactive that carbonyl addition and substitution reactions often show low degrees of chemo- and stereoselectivity. In many of these cases, titanation using $ClTiX_3$ (X = Cl, OR, NR_2) increases carbanion selectivity dramatically.[1,11] Control of chemoselectivity is best achieved by titanating with ***Titanium(IV) Chloride*** or ***Chlorotitanium Triisopropoxide***, the alternative and less readily available $ClTi(NEt_2)_3$ not being necessary. However, in stereoselective reactions the nature of the ligands on titanium play a pivotal role. The transmetalating agents $ClTi(NMe_2)_3$ and $ClTi(NEt_2)_3$ (or their Br analogs) have been used in a number of such cases.[1] All of them involve resonance stabilized ambident carbanions, e.g. enolates, allylic, and heteroallylic species. In contrast, saturated titanium compounds of the type $RTi(NEt_2)_3$ (R = alkyl), although readily available from RLi and

$ClTi(NEt_2)_3$, do not undergo Grignard-type reactions, aminoalkylation being the preferred reaction mode.[1,11]

The aldol addition of titanium enolates generally affords the *syn* configured aldols, irrespective of the geometry of the enolate.[1,4] This property is of particular synthetic interest in the case of cyclic ketones (eq 2),[4] because the boron analogs afford the *anti*-aldols in a complementary manner.[12]

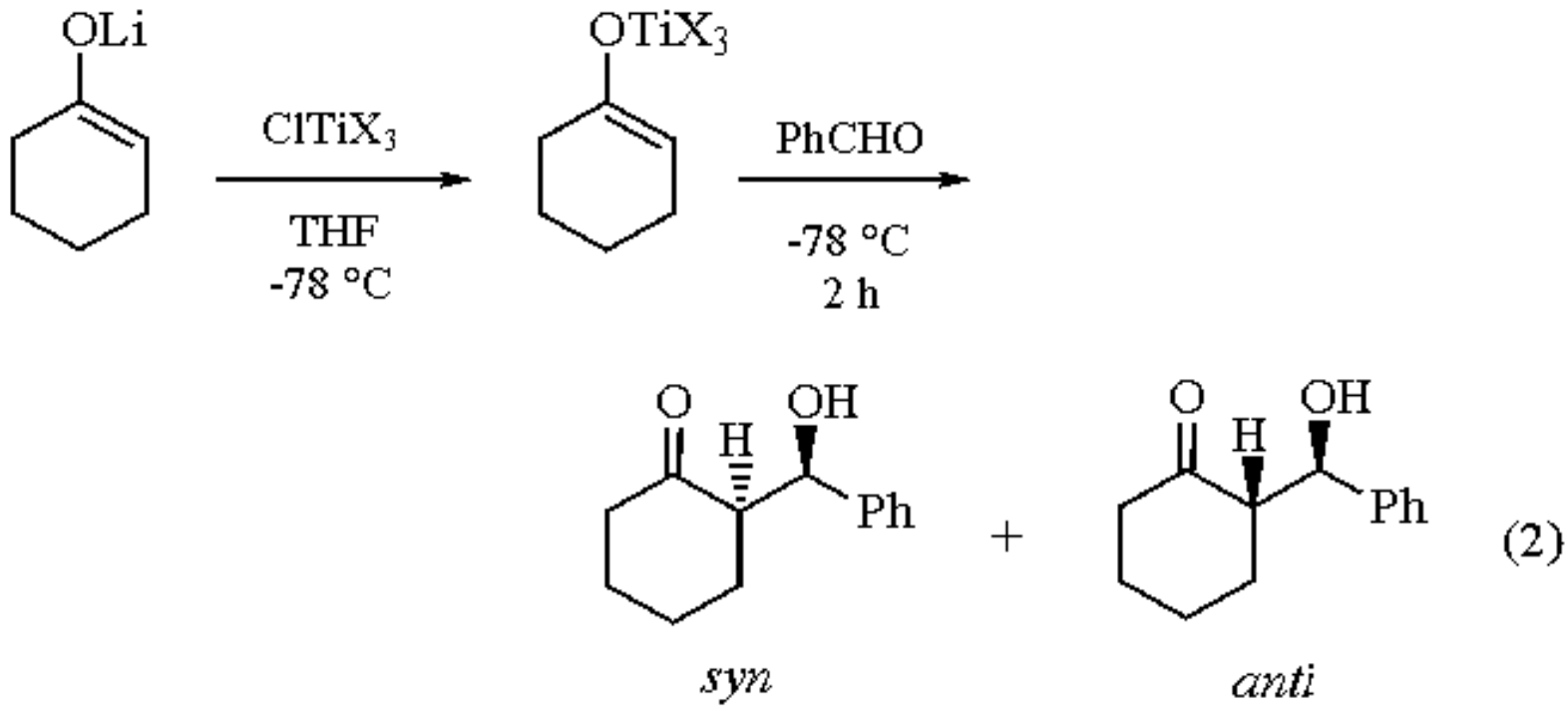

X =	O-*i*-Pr	86:14
	NMe_2	92:8
	NEt_2	97:3

Cram selectivity in the reaction of chiral aldehydes with the very reactive allylmagnesium chloride can also be increased dramatically by prior titanation, $CH_2{=}CHCH_2Ti(NEt_2)_3$ being most selective.[2] This reagent is also useful in axially selective allyl additions to cyclohexanone derivatives.[3]

The tris(diethylamino)titanium enolate of ethyl acetate reacts with chiral α-siloxy ketones to afford the aldol adducts with >99% nonchelation control.[5] Simple diastereoselectivity in the addition of crotyltitanium reagents to ketones is of particular synthetic interest because other metal reagents fail. $MeCH{=}CHCH_2Ti(NEt_2)_3$ is best suited for prochiral aliphatic ketones (ds > 90%),[3] whereas aromatic ketones require reagents with alkoxy ligands at titanium.[3,11]

Racemic aminotitanium homoenolate equivalents react stereoselectively with achiral[7] and chiral aldehydes.[13] For example, of eight possible diastereomers from γ-attack on 2-phenylpropanal, only two are formed in a ratio of 93:7 (eq 3).[13] The results obtained by employing $ClTi(NEt_2)_3$ in related cases are similar or better, as in the synthesis of D- and L-3,6-dideoxy-3-*C*-methylhexofuranosides.[13] Enantiomerically pure analogs react with achiral aldehydes enantio- and diastereoselectively.[14]

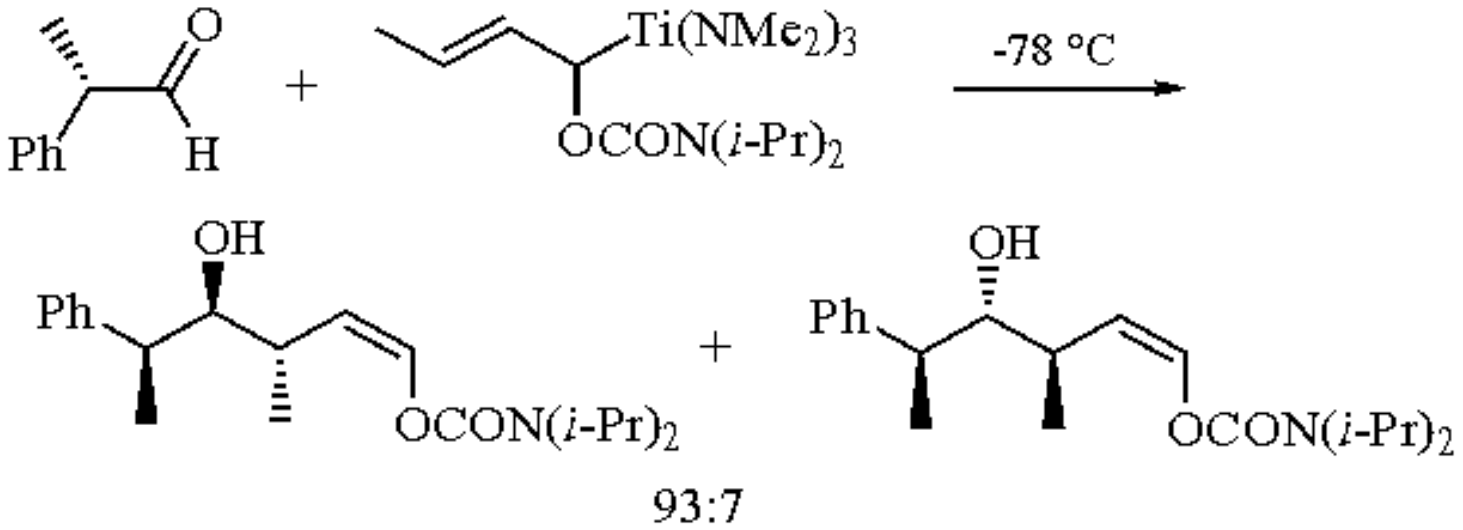

(3)

Several other chiral titanium compounds having amino ligands have been reported,[1] including one of the most stereoselective reagents for homoaldol additions currently available.[8]

Lithiated bis-lactim ethers do not react stereoselectively with aldehydes, but can be titanated with $ClTi(NR_3)_3$ (R = Me, Et) to form highly selective reagents for the synthesis of enantio- and diastereomerically pure α-amino-β-hydroxy acids (eq 4).[6] These reagents also undergo enantioselective Michael additions to nitro alkenes and α,β-unsaturated esters.[9]

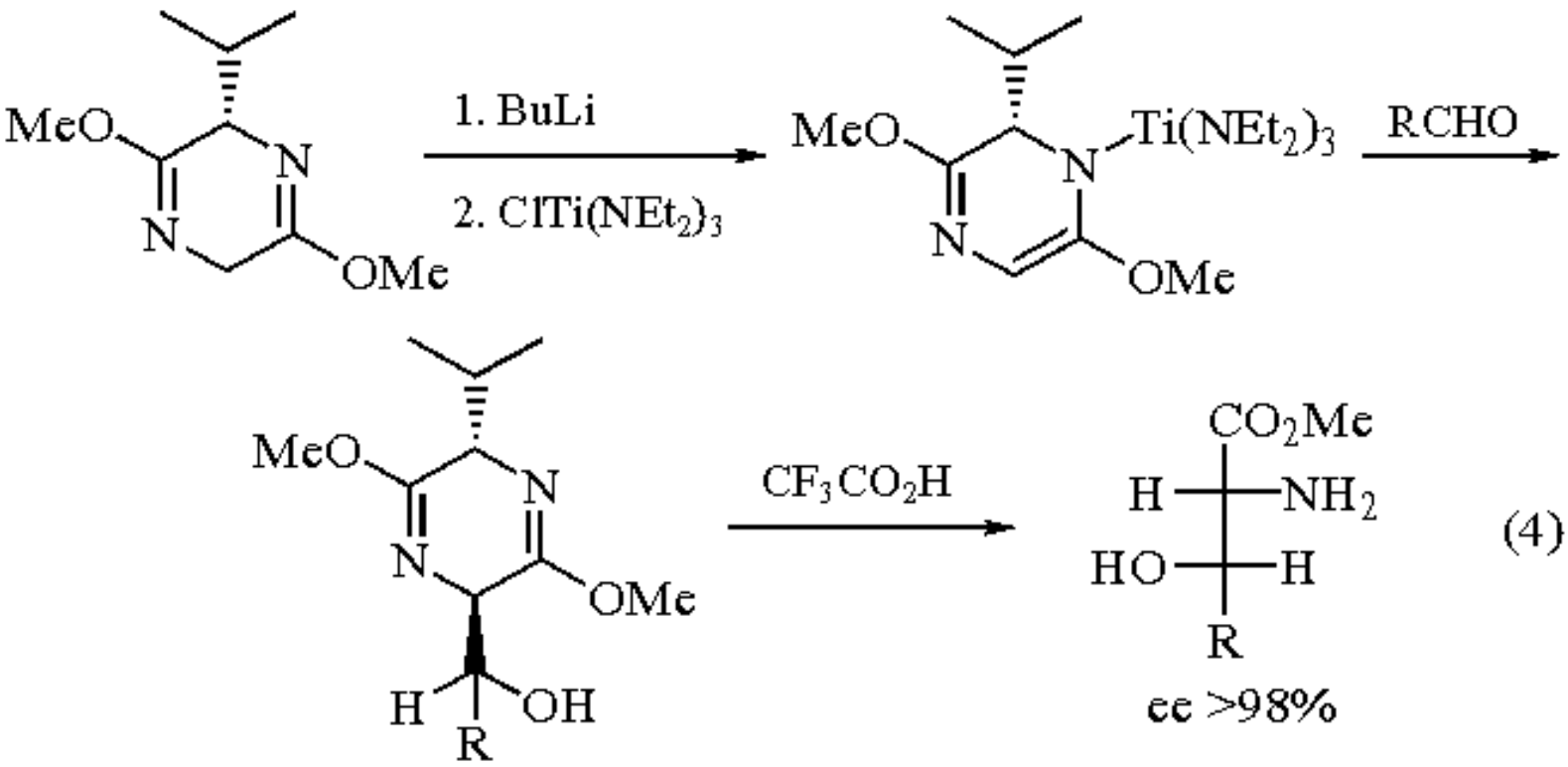

(4)

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Chlorotriethylsilane

Et_3SiCl

[994-30-9] · $C_6H_{15}ClSi$ · Chlorotriethylsilane · (MW 150.75)

(silylating agent, Lewis acid catalyst)

Alternate Name: triethylsilyl chloride.

Physical Data: bp 145-147 °C; *d* 0.898 g cm^{-3}.

Solubility: readily sol most aprotic organic solvents, although CH_2Cl_2 is most commonly used; reacts with H_2O and other protic solvents.

Form Supplied in: colorless liquid, or as a 1.0 M solution in THF.

Handling, Storage, and Precautions: should be handled and stored under an anhydrous, inert atmosphere.

General Considerations.

The triethylsilyl moiety is often used as a protecting group for alcohols because of its greater stability towards hydrolysis than the smaller trimethylsilyl group. Alcohols can normally be silylated with Et_3SiCl using either ***Imidazole*** in DMF or ***Triethylamine/4-Dimethylaminopyridine*** in CH_2Cl_2 (eqs 1 and 2).[1,2] For substrates which are more difficult to derivatize, it may be advantageous to carry out the reaction in neat ***Pyridine*** (eq 3)[3] or to generate the alkoxide salt prior to the addition of Et_3SiCl (eq 4).[4-6]

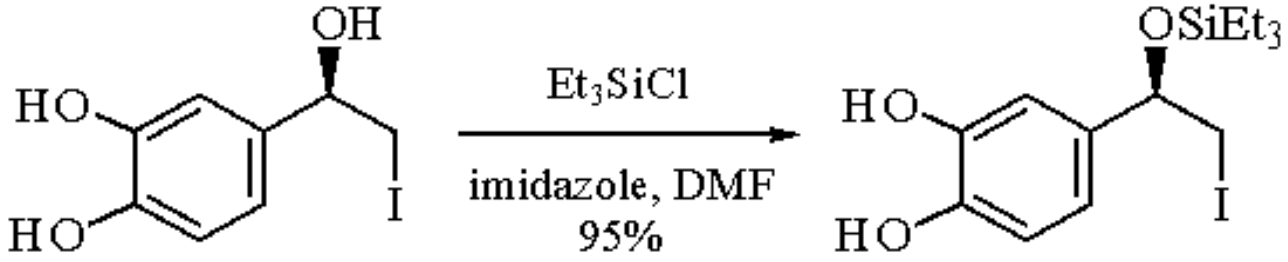

(1)

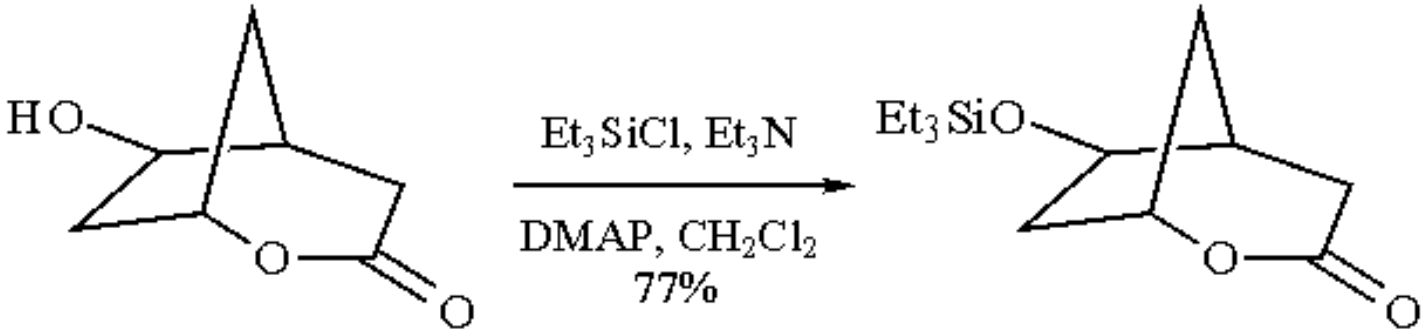

(2)

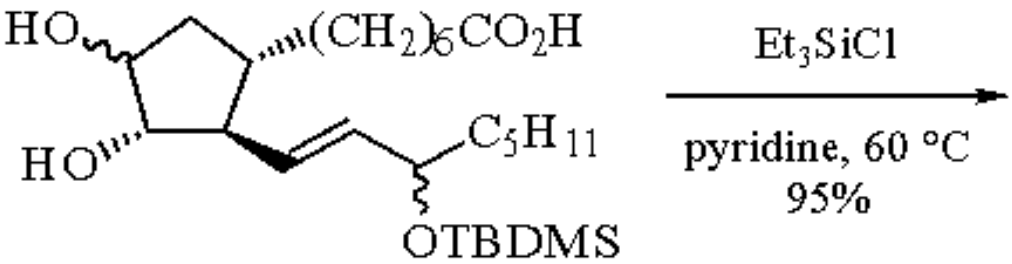

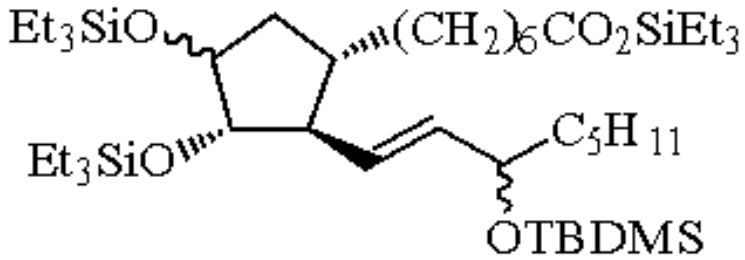

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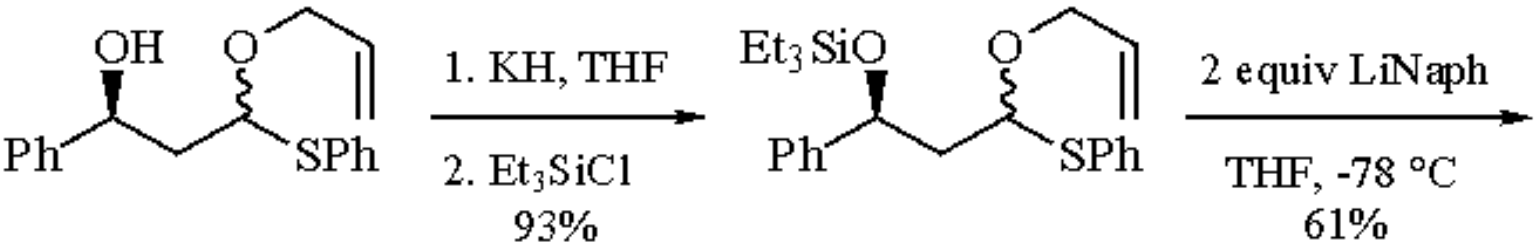

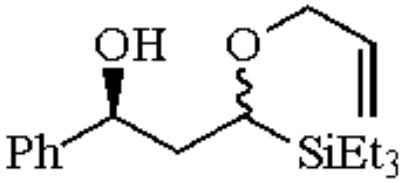

(4)

Silyl ethers have also been obtained by in situ trapping of an intermediate alkoxide that results from a nucleophilic addition onto an ester[7] or epoxide[8] (eqs 5 and 6).

Silyl enol ethers can be prepared from ketones by trapping the kinetically formed lithium enolate with Et_3SiCl (eqs 7 and 8),[9,10] or by the conjugate addition of a dialkylcuprate to an α,β-unsaturated ketone with silylation of the enolate intermediate (eq 9).[11-13] Surprisingly, the addition of ***Lithium Di-n-butylcuprate*** to an α,β-unsaturated lactone in the presence of Et_3SiCl resulted in the 1,4-addition of the triethylsilyl moiety, apparently via the in situ formation of an

intermediate silylcuprate species (eq 10).[14]

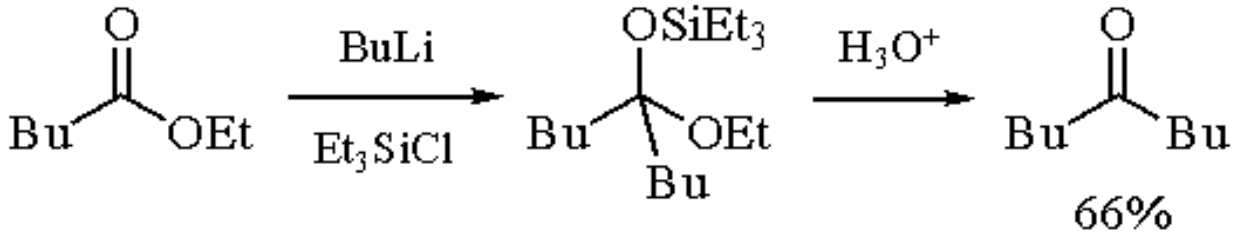

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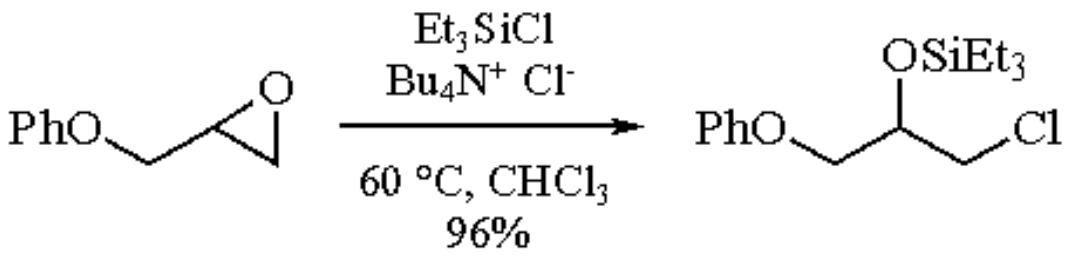

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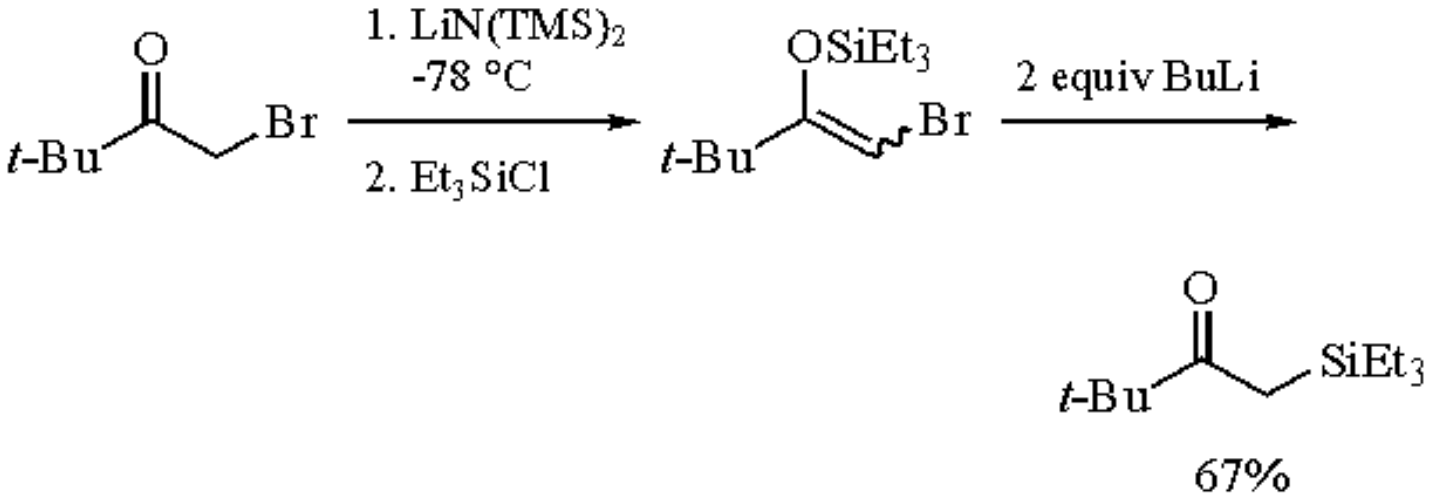

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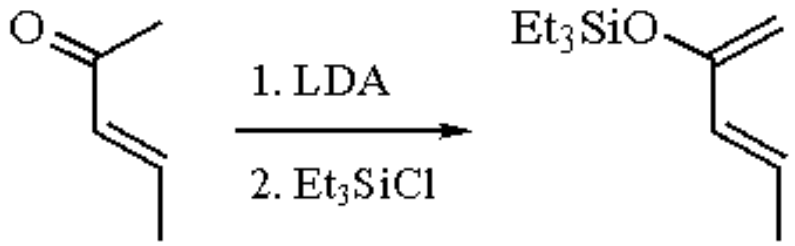

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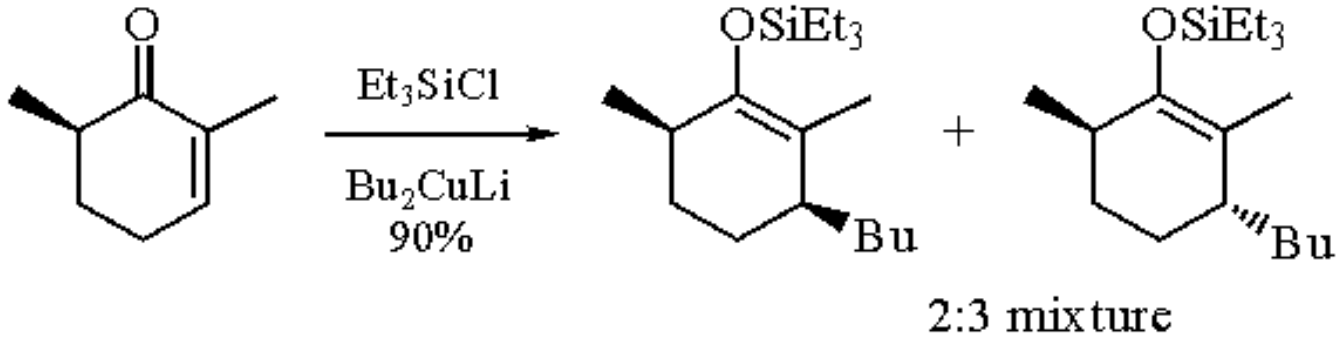

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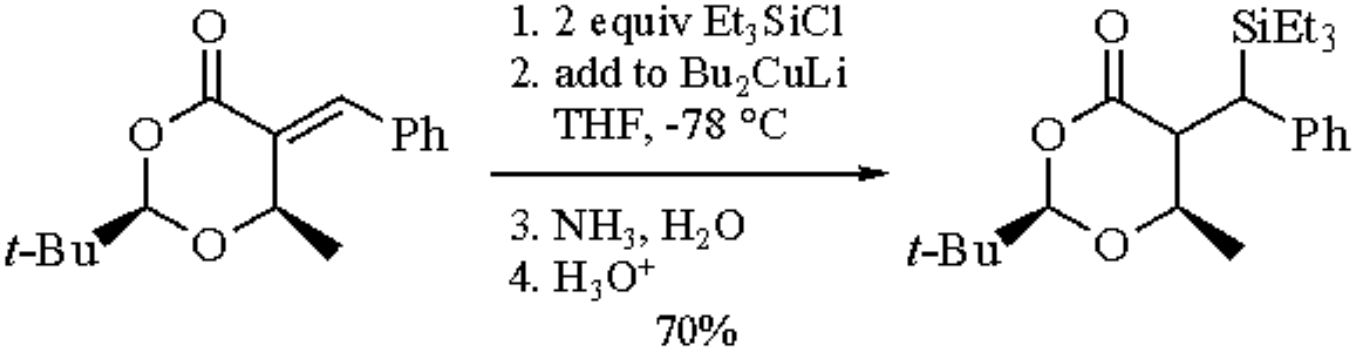

(10)

Organolithium salts generally react with Et_3SiCl to afford organosilanes. Schlessinger used a deprotonation-silylation procedure to introduce a triethylsilyl group at the α-position of an alkylimine (eq 11).[15] A variety of other stabilized carbanions have been reported to react cleanly with Et_3SiCl (eqs 12-15).[16 -19]

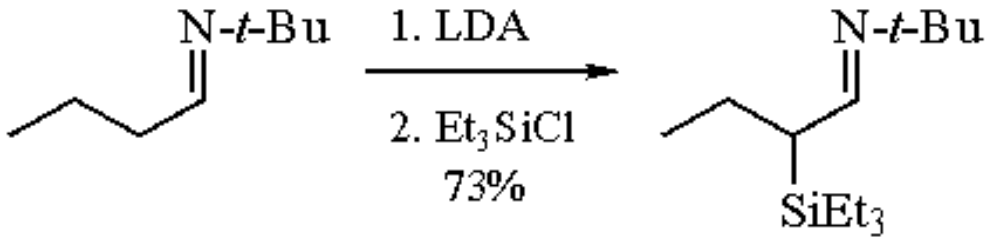

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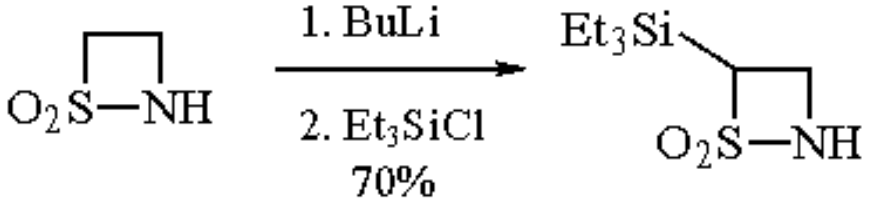

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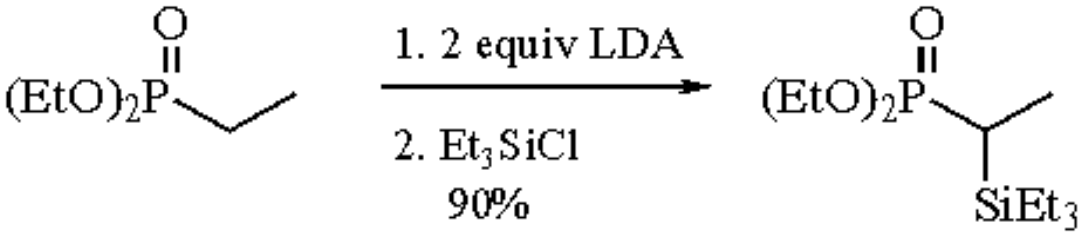

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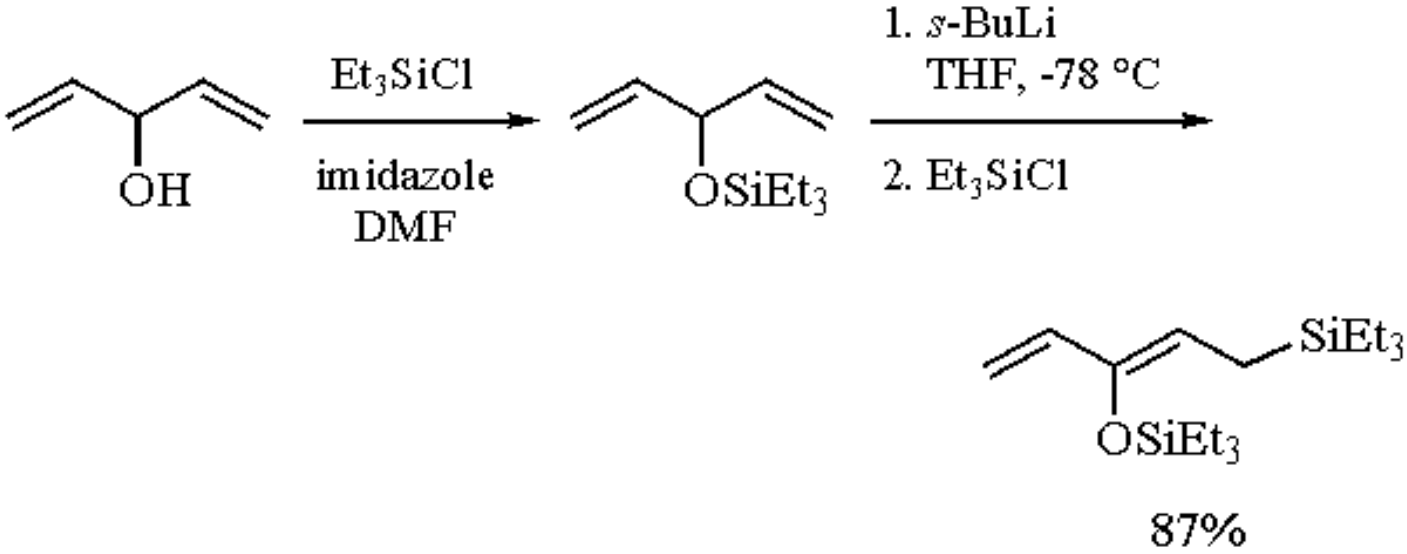

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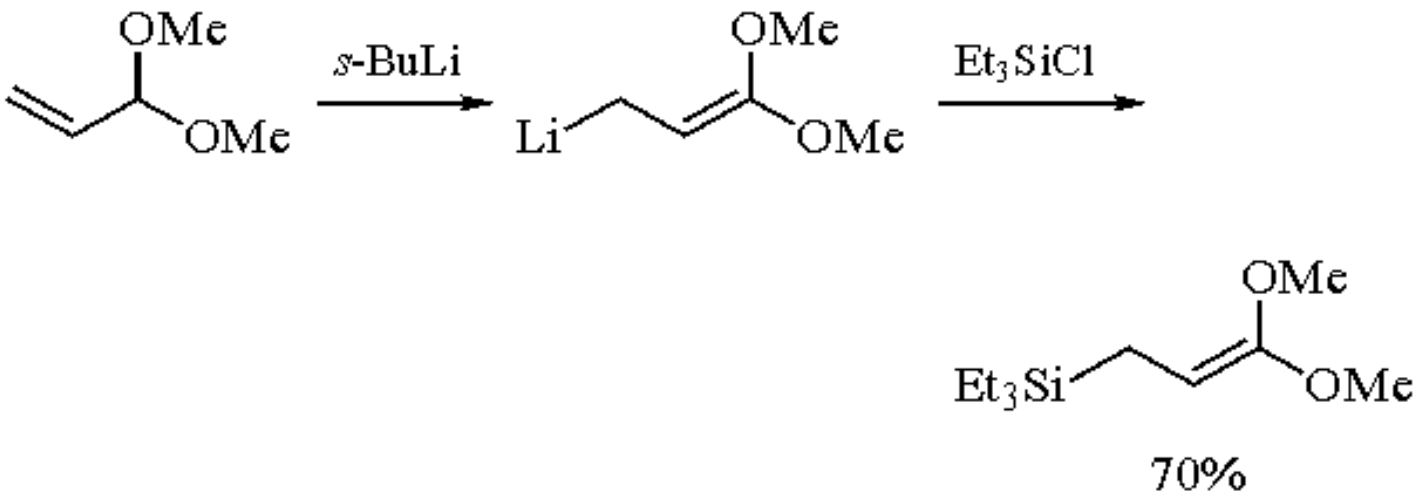

(15)

In a similar manner, aryl, vinyl-, and alkynylsilanes can be prepared by the reaction of the appropriate carbanion with Et_3SiCl (eqs 16-21).[20-25]

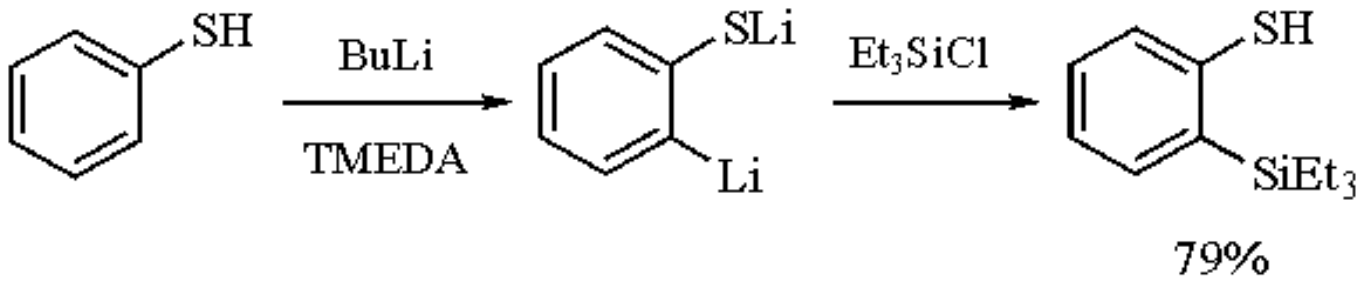

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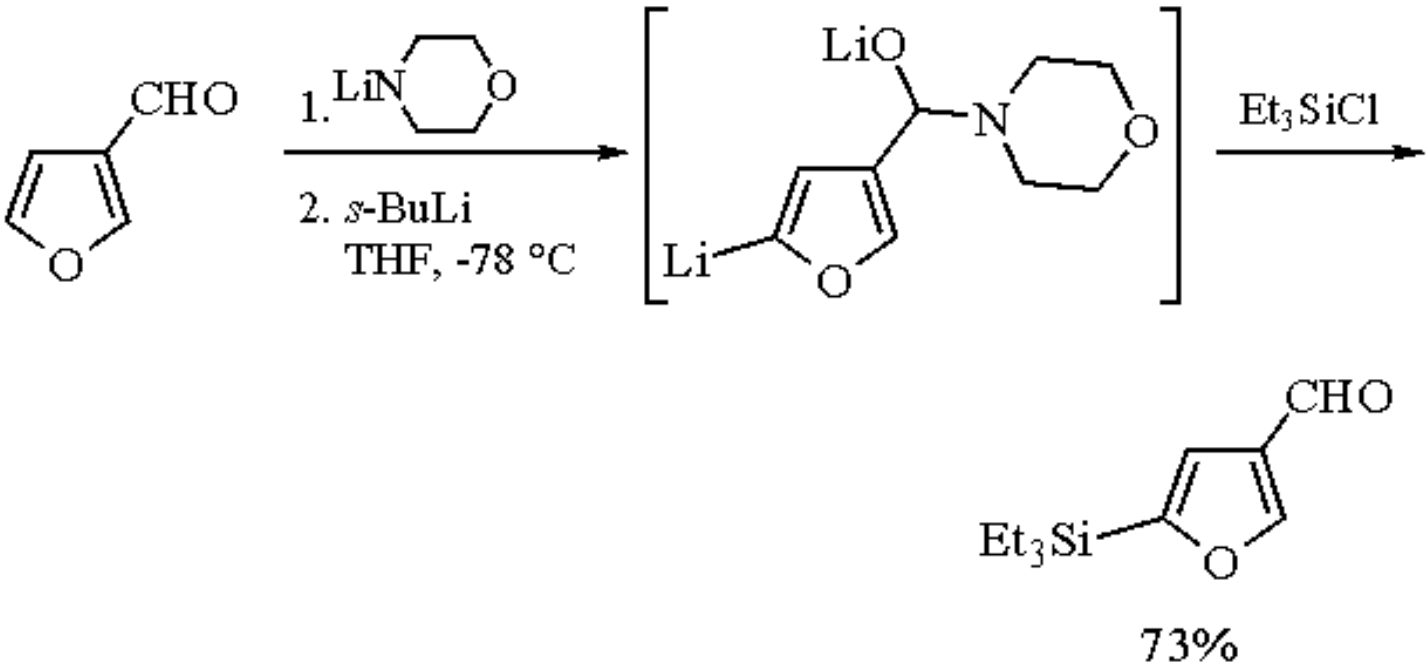

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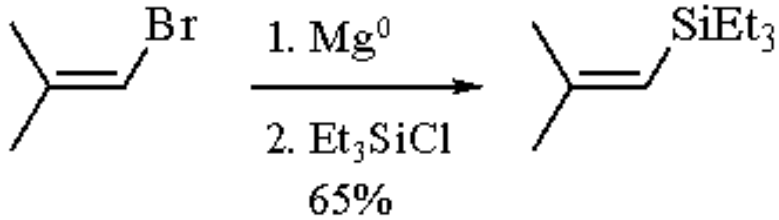

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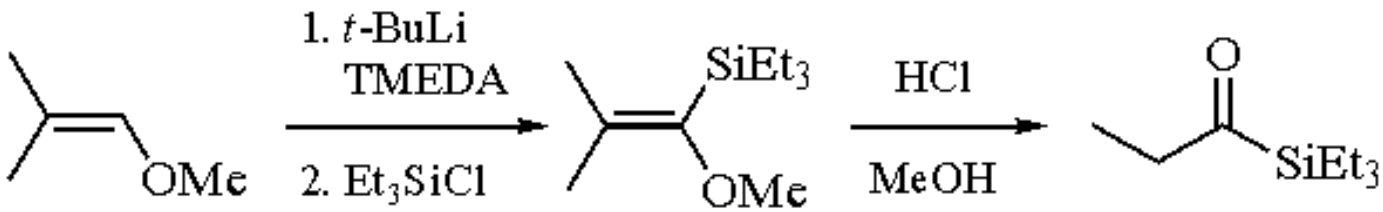

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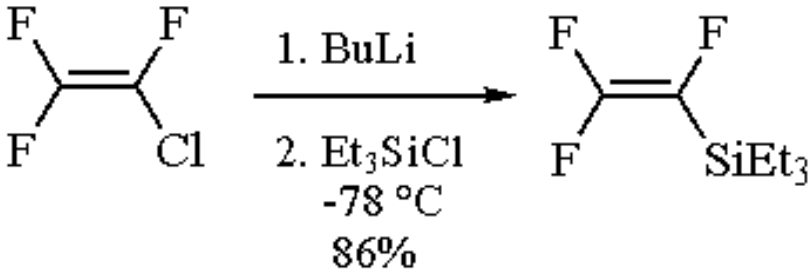

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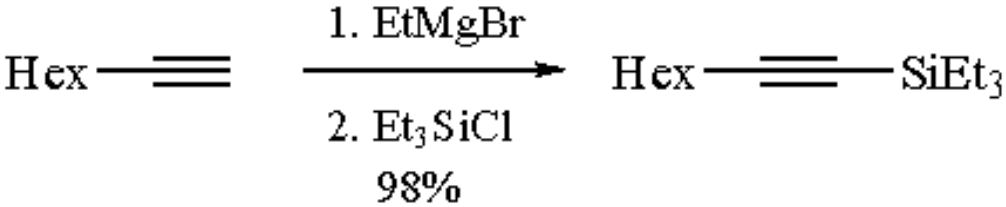

(21)

Related Reagents.

t-Butyldimethylchlorosilane; ***Chlorotrimethylsilane***; ***Chlorotriphenylsilane***.

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(2-Chloro-1,1,2-trifluoroethyl)diethylamine[1]

Et_2NCF_2CHFCl

[357-83-5] · $C_6H_{11}ClF_3N$ · (2-Chloro-1,1,2-trifluoroethyl)diethylamine · (MW 189.61)

(mild electrophilic fluorinating agent capable of nucleophilic substitution of hydroxyl group[1-7] by fluorine)

Alternate Name: Yarovenko reagent.

Physical Data: bp 32-33 °C/6 mmHg;[2] bp 33-34 °C/6 mmHg.[1]

Solubility: sol most aprotic organic solvents.

Preparative Method: from diethylamine and chlorotrifluoroethylene at -5 to -10 °C without solvent.

Purification: by distillation.

Handling, Storage, and Precautions: highly sensitive toward moisture (elimination of HF) and should be stored in tightly closed polyethylene vessels; reactions should be performed in thoroughly predried glass or quartz vessels; use in a fume hood.

Fluorination.

The main application of the reagent (**1**) is in the preparation of alkyl or acyl flourides by the substitution reaction of hydroxyl groups (alcohols, carboxylic acids, and their salts) by fluorine (eqs 1 and 2).[2]

$$\underset{}{ROH} + \underset{\textbf{(1)}}{Et_2NCF_2CHFCl} \longrightarrow RF \qquad (1)$$

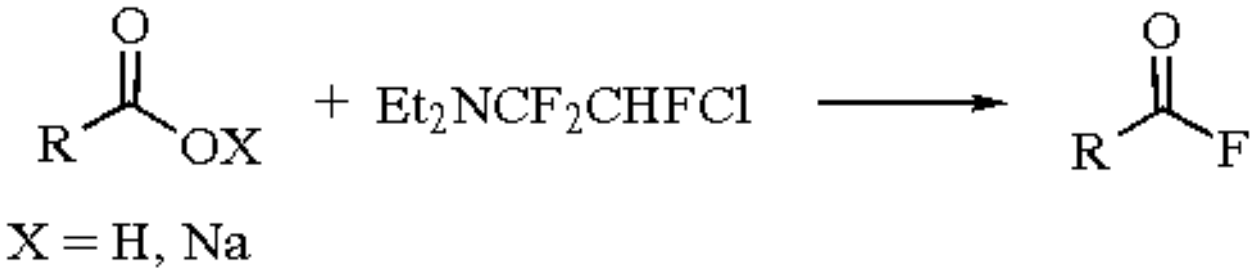

(2)

The fluorination of some cyclic secondary and especially tertiary alcohols may lead to the elimination of HF and alkene formation.[3,4] Thioacids give acyl fluorides, rather than thioacyl fluorides.[2]

The fluorination can be performed using equimolar amounts or a slight excess of the reagent, either without solvent or in a solvent such as CH_2Cl_2, MeCN, Et_2O, or THF. As a rule, the reactions are slightly exothermic or performed at rt. Neither *t*-amino groups nor alkoxycarbonyl groups prevent fluorination (eq 3).[5]

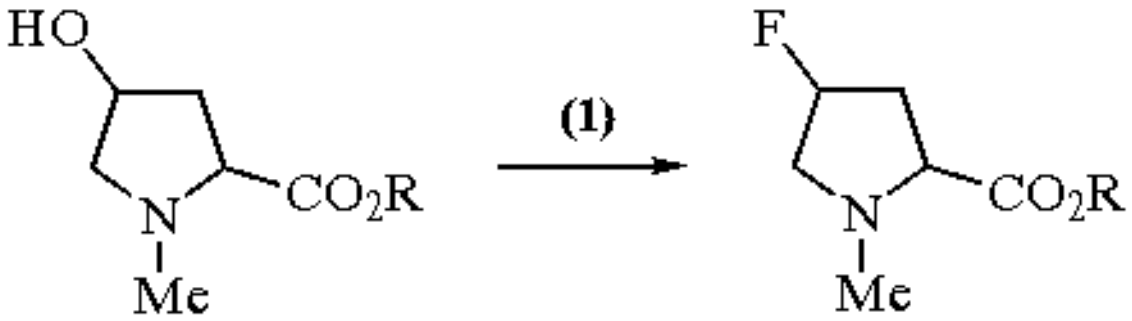

(3)

The reagent has been used extensively for the fluorination of steroids (eq 4).[6-8]

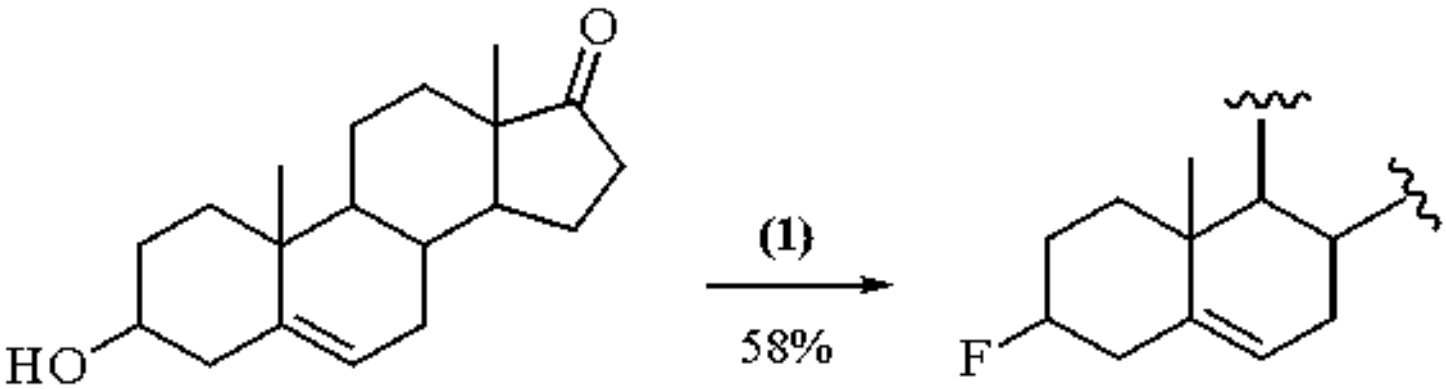

(4)

One paper[9] describes the application of (**1**) to the fluorination of aromatic aldehydes to give difluoromethylene compounds (eq 5).

$$\mathrm{ArCHO} \xrightarrow{(1)} \mathrm{ArCHF_2} \qquad (5)$$

$$\mathrm{Ar} = \mathrm{Ph},\ p\text{-}\mathrm{NO_2C_6H_4},\ m\text{-}\mathrm{NO_2C_6H_4}$$

The mechanism of the fluorination includes nucleophilic substitution of the highly labile fluorine atom in the α-position to nitrogen to give the alkoxyamino intermediate which, in turn, undergoes S_N2 reaction to give the corresponding fluoride and diethylamide of fluorochloroacetic acid (eq 6).

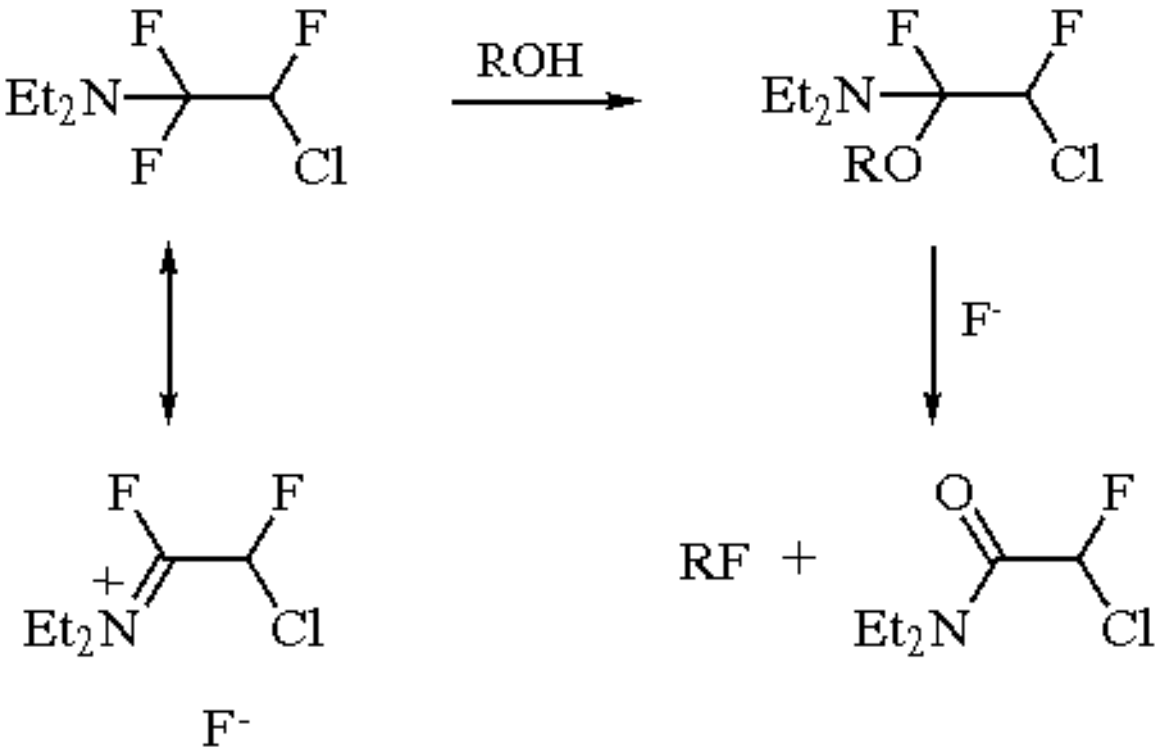

(6)

An analogous reagent ($Et_2NCF_2CHFCF_3$ + $Et_2NCF{=}CFCF_3$; Ishikawa reagent) has been described.[10]

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Chlorotrifluoroethylene

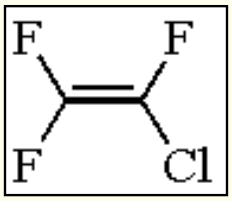

[79-38-9] · C_2ClF_3 · Chlorotrifluoroethylene · (MW 116.47)

(addition reactions; cycloadditions; trifluorovinylations)

Physical Data: mp -158 °C; bp -28.4 °C.

Solubility: sol organic solvents (ether, THF).

Form Supplied in: flammable gas, inhibited with 1% Bu_3N.

Handling, Storage, and Precautions: inhalation toxicity LC_{50}: 1000 ppm; flammable; use in a fume hood.

Addition Reactions.

Chlorotrifluoroethylene is a starting material for the preparation of fluorinated molecules, via addition or addition-elimination reactions, the regioselectivity of which is not always, but can be, excellent. Halogenation according to eq 1 is a good example.[1] Hydrobromination under UV irradiation also gives a unique pentahaloethane (eq 2).[2]

$$CF_2{=}CFCl + ICl \xrightarrow[62\%]{-5\ °C} \underset{98:2}{CF_2Cl\text{-}CFClI + CF_2I\text{-}CFCl_2} \qquad (1)$$

$$CF_2{=}CFCl + HBr \xrightarrow[\substack{20\ °C \\ 92.5\%}]{h\nu} CF_2Br\text{-}CHFCl \qquad (2)$$

Lewis acid catalyzed addition of CCl_4 proceeds via addition-substitution (eq 3).[3]

$$CF_2{=}CFCl + CCl_4 \xrightarrow[\text{75 °C, 70\%}]{AlCl_3} CCl_3\text{-}CF_2\text{-}CCl_3 + \ldots \quad (3)$$

The nucleophilic addition of alcohols,[4] thiols,[5] and primary and secondary amines[6] in the presence of base occurs readily; the regioselectivity corresponds to a better stabilization of the negative charge by -CFCl, than by $-CF_2$ (eqs 4 and 5). With diethanolamine,[7] further substitution occurs (eq 6).

$$CF_2{=}CFCl + PrSH \xrightarrow[\text{50\%}]{B^-} PrSCF_2\text{-}CHFCl \quad (4)$$

$$CF_2{=}CFCl + ROH \xrightarrow{B^-} ROCF_2\text{-}CHFCl \quad (5)$$

$$CF_2{=}CFCl + HN(CH_2\text{-}CH_2OH)_2 \xrightarrow[\text{92\%}]{B^-}$$

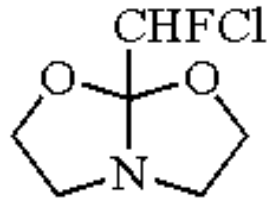

(6)

Various organometallic reagents[8-11] follow the addition-elimination pattern (eqs 7-9), as do lithium amides (eq 10).

$$CF_2{=}CFCl + PhMgBr \xrightarrow[\text{82\%}]{} Ph\text{-}CF{=}CFCl \quad (7)$$

$$CF_2{=}CFCl + PhLi \xrightarrow[\text{55\%}]{} Ph\text{-}CF{=}CFCl \quad (8)$$

$$CF_2{=}CFCl + MeC{\equiv}CLi \xrightarrow[\text{73\%}]{} MeC{\equiv}C\text{-}CF{=}CFCl \quad (9)$$

$$CF_2{=}CFCl + Ph\text{-}N(Me)Li \xrightarrow[\text{71\%}]{} Ph\text{-}N(Me)\text{-}CF{=}CFCl \quad (10)$$

Thiolates and alcoholates follow the same scheme. Allylates represent an interesting case since the initially formed allyl fluorovinyl ether undergoes a fluorine accelerated Claisen rearrangement, even at -35 °C (eq 11).[12]

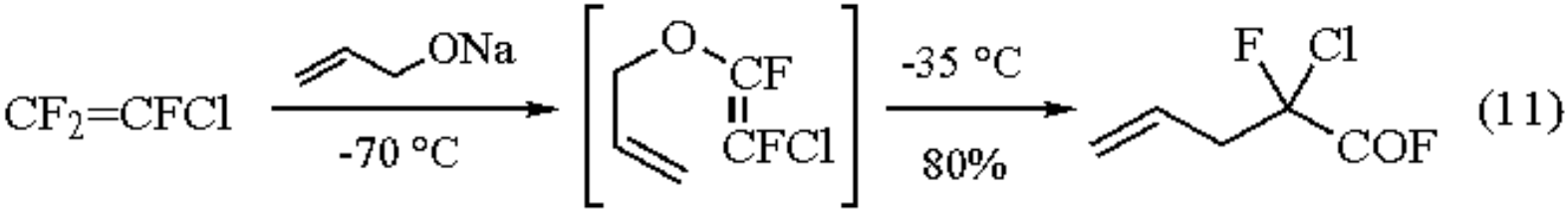

Cycloadditions.

Insertion of difluorocarbene generates chloropentafluorocyclopropane (eq 12).[13]

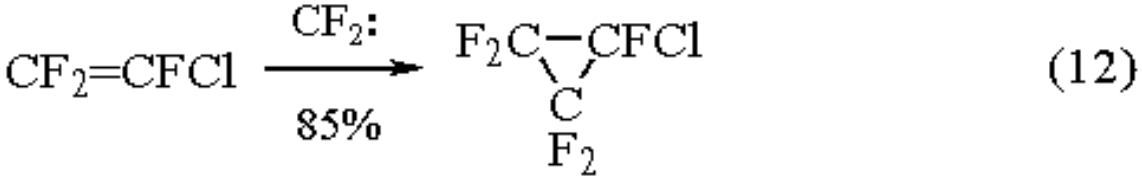

Various cycloadditions are observed at high temperatures (pressure vessel) with alkenes, alkynes, and conjugated dienes ([2 + 2] addition prevails largely over [4 + 2]) (eqs 13-15).[14-16]

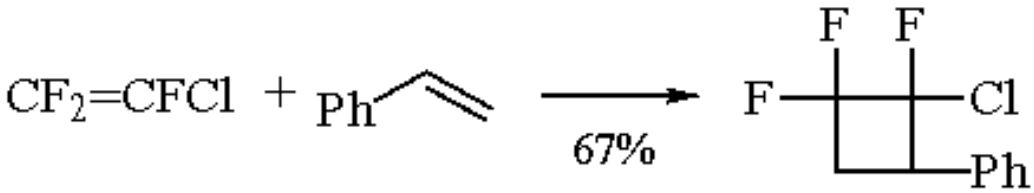

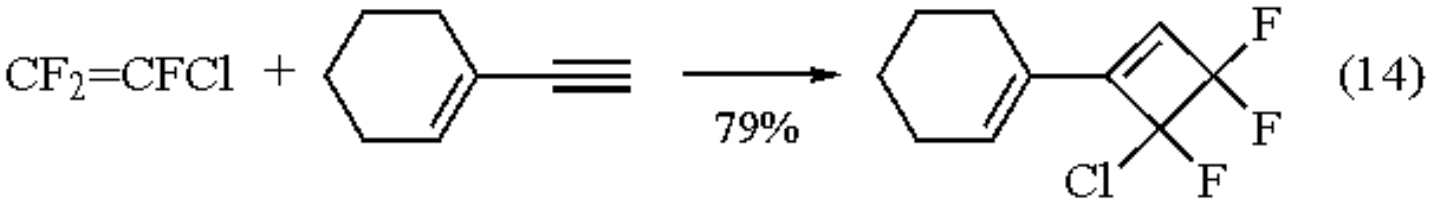

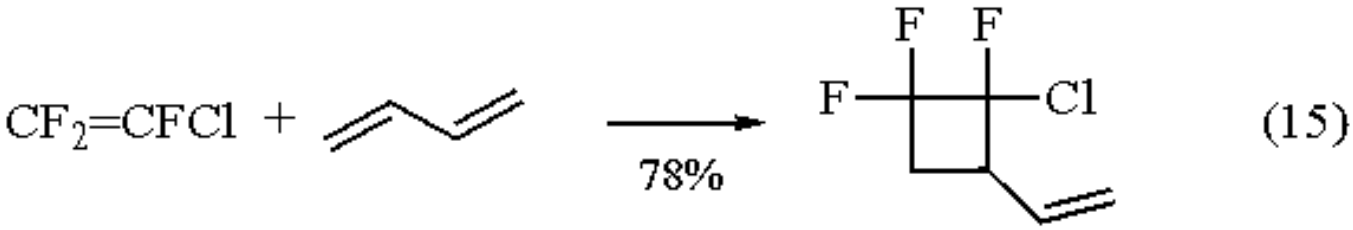

Trifluorovinylations.

A useful synthon for the nucleophilic introduction of the trifluorovinyl moiety is obtained by chlorine/lithium exchange (eq 16).[17]

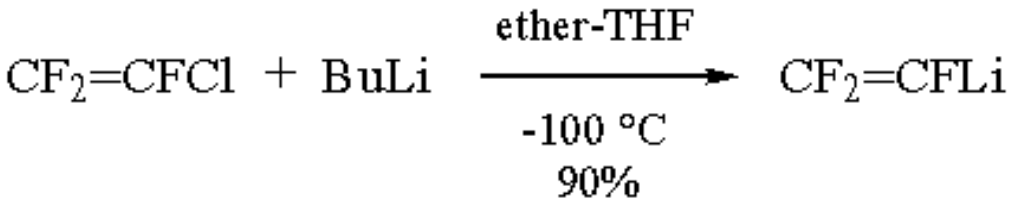

(16)

The vinyllithium species must be handled at low temperatures. It reacts with aldehydes or ketones to give trifluorovinylcarbinols, which are a source of α-fluoro-α-ethylenic acids (by acidic treatment). They are also a source of α,β-difluoro-α-ethylenic alcohols if a lithium reagent is added, in a second step, to the reaction mixture (eq 17).[18]

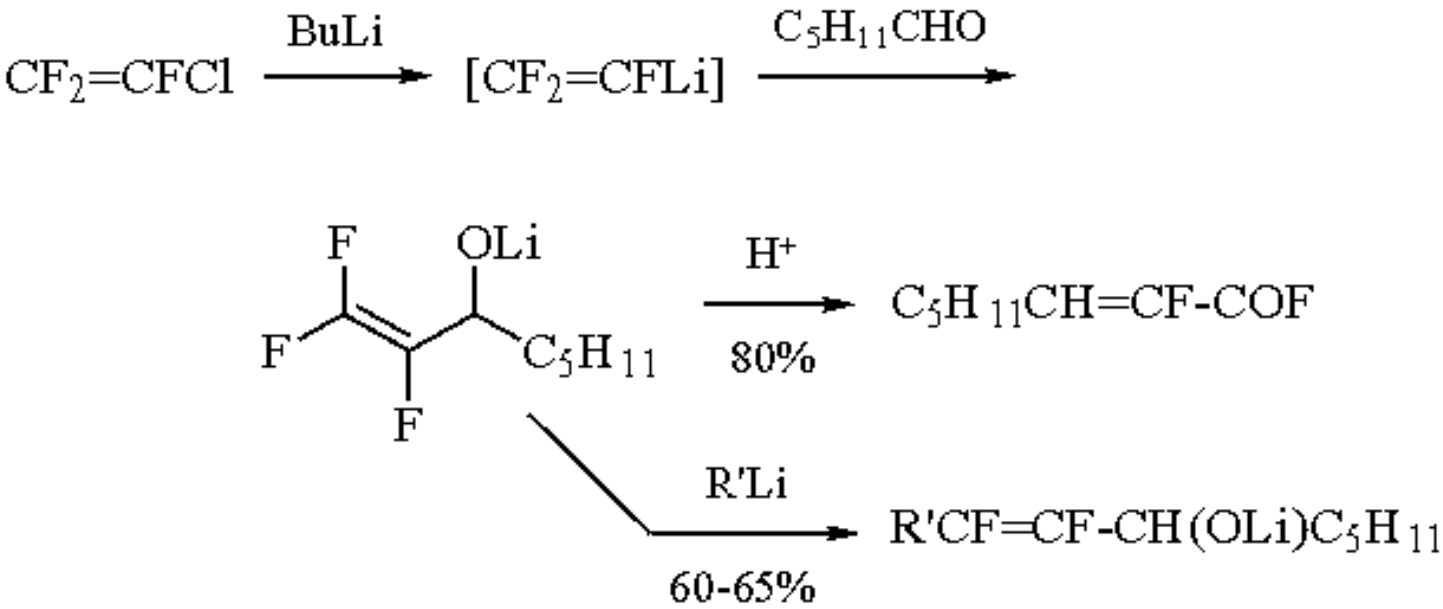

(17)

The analogous zinc derivative[19] is much more thermally stable, and can be vinylated, arylated, or acylated by a palladium catalyzed reaction with vinyl or aryl halides, or with acyl chlorides (eq 18).[18]

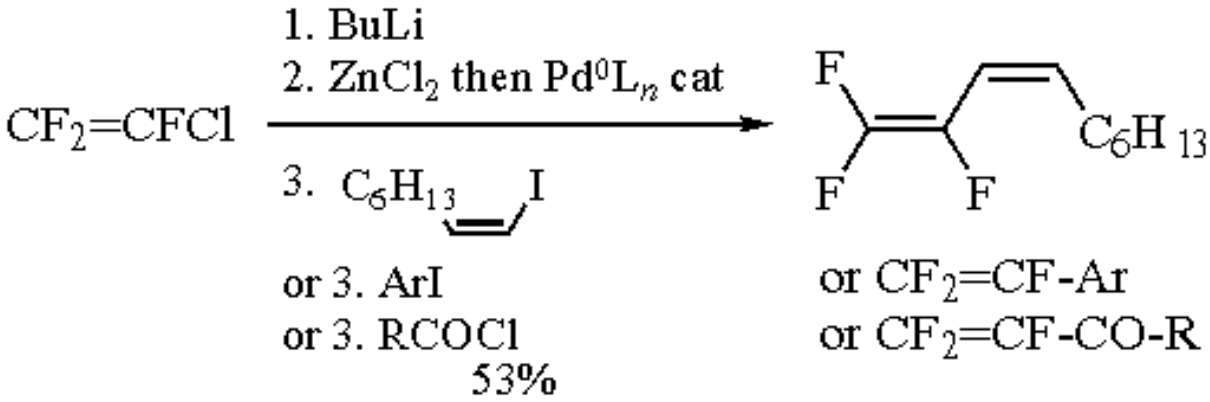

(18)

The analogs CF_2=CFBr and CF_2=CFI have been used in several similar reactions, but they are more expensive. However, when treated with ***Zinc*** powder, they deliver the corresponding zinc derivative.[20]

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1-Chloro-*N*,*N*,2-trimethylpropenylamine[1]

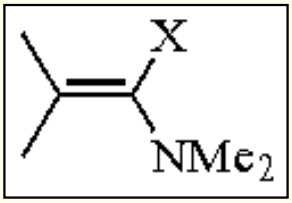

(X = Cl)

[26189-59-3] · $C_6H_{12}ClN$ · 1-Chloro-*N*,*N*,2-trimethylpropenylamine · (MW 133.62) (X = F)

[65560-29-4] · $C_6H_{12}FN$ · 1-Fluoro-*N*,*N*,2-trimethylpropenylamine · (MW 117.17) (X = Br)

[73630-93-0] · $C_6H_{12}BrN$ · 1-Bromo-*N*,*N*,2-trimethylpropenylamine · (MW 178.07) (X = I)

[65560-41-0] · $C_6H_{12}IN$ · 1-Iodo-*N*,*N*,2-trimethylpropenylamine · (MW 225.07)

(mild halogenation of alcohols and acids under neutral conditions;[2] conversion of *N*-protected amino acids into peptides without racemization;[3] coupling of acids and allylic alcohols with organometallics;[9] [2 + 2] cycloaddition synthons, more reactive than dimethylketene[1b,4,5])

Alternate Name: tetramethyl-α-chloroenamine; TMCE

Physical Data: X = Cl: bp 129-130 °C (760 mmHg), *d* 1.01 g cm^{-3}; X = F: bp 89-92 °C (760 mmHg); X = Br: bp 42-45 °C (15 mmHg); X = I: bp 61-63 °C (9 mmHg), *d* 1.55 g cm^{-3}.

Solubility: very sol most organic solvents; reacts instantaneously with H_2O, alcohols, and protic solvents.

Preparative Methods: 1-chloro-*N*,*N*,2-trimethylpropenylamine is conveniently prepared by the reaction of *N*,*N*,2-trimethylpropanamide with ***Phosgene*** followed by dehydrochlorination of the intermediate α-chloroiminium chloride (eq 1).[1a,6] Recent unpublished results of our laboratory have shown that ***Phosphorus Oxychloride*** or di- or triphosgene can also be used for the preparation of TMCE.

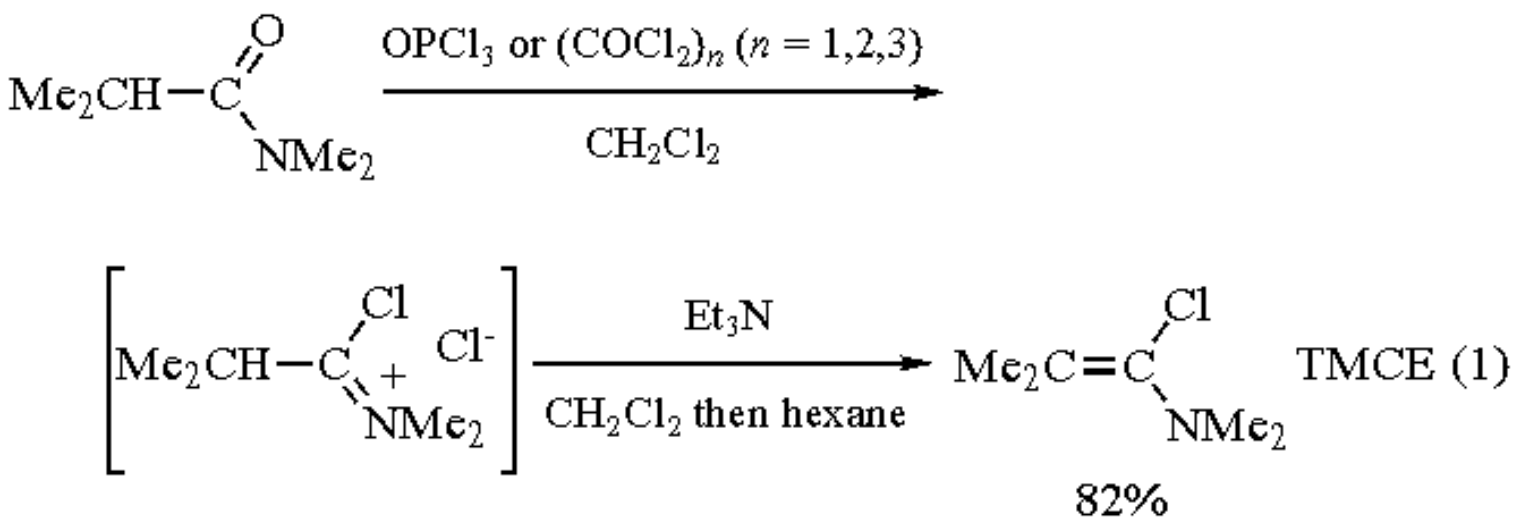

The corresponding 1-fluoro-, 1-bromo- and 1-iodo-*N*,*N*,2-trimethylpropenylamines (tetramethyl-α-fluoro-, -bromo-, and -iodoenamines; TMFE, TMBE, and TMIE) are readily prepared from TMCE by halogen exchange (eq 2).[1a,7]

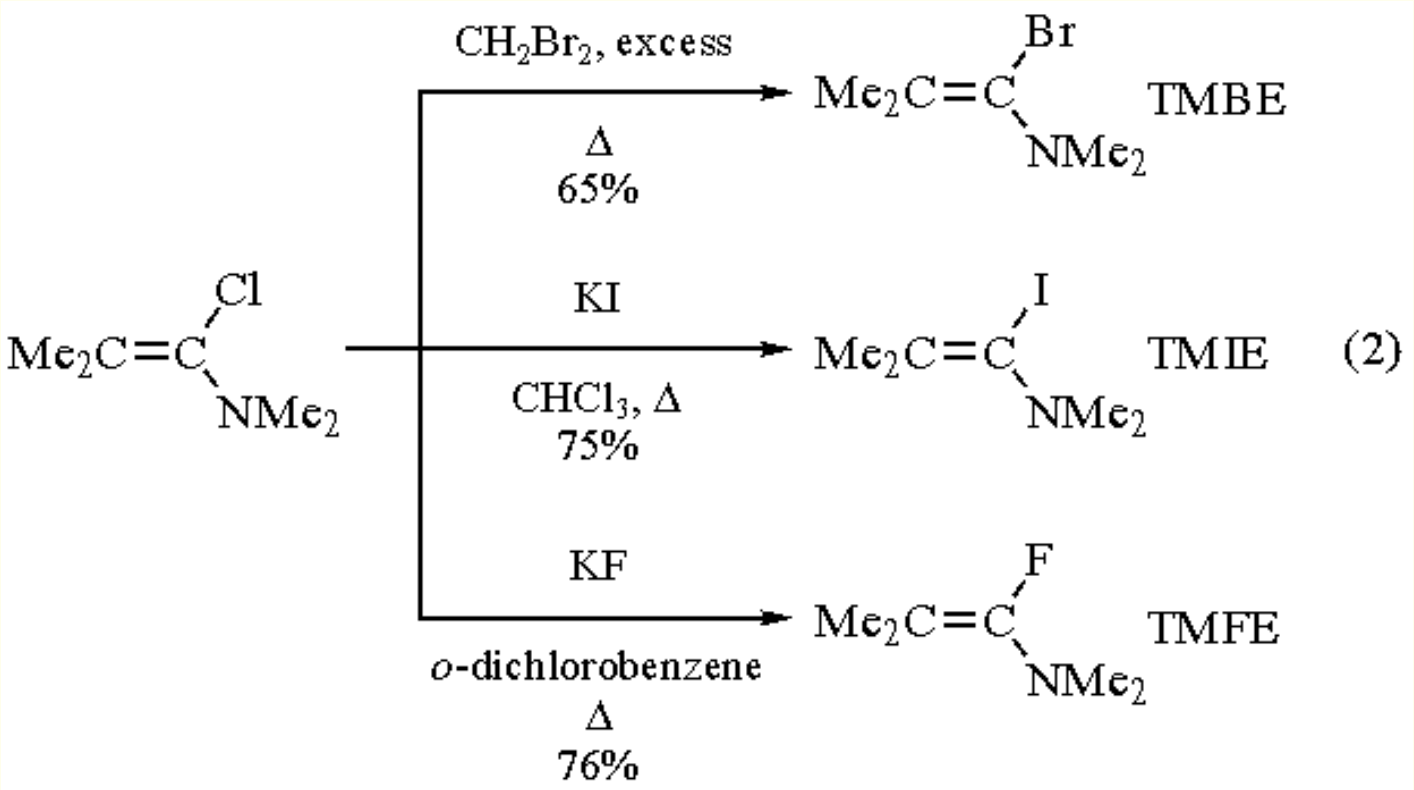

Analysis of Reagent Purity: IR, ^{1}H NMR, elemental analysis.[6]

Handling, Storage, and Precautions: 1-chloro-, 1-fluoro-, and 1-bromo-*N*,*N*,2-propenylamines are thermally stable. They must be transferred in the absence of moisture and stored under nitrogen in sealed tubes. In spite of these precautions, light precipitates sometimes may form. 1-Iodo-*N*,*N*,2-trimethylpropenylamine is less stable and should be used when freshly prepared.

Halogenation Reactions.

1-Chloro-, 1-bromo- and 1-iodo-*N*,*N*,2-trimethylpropenylamines are mild reagents which transform alcohols into the corresponding halides (eqs 3-6).[2b] The reaction proceeds under neutral conditions, thus allowing the presence of acid-sensitive functional groups. The reaction occurs with inversion of configuration (eq 4). Secondary allylic and propargylic alcohols give some rearranged halides (eqs 5 and 6), but their formation seems to occur after the halogenation step.

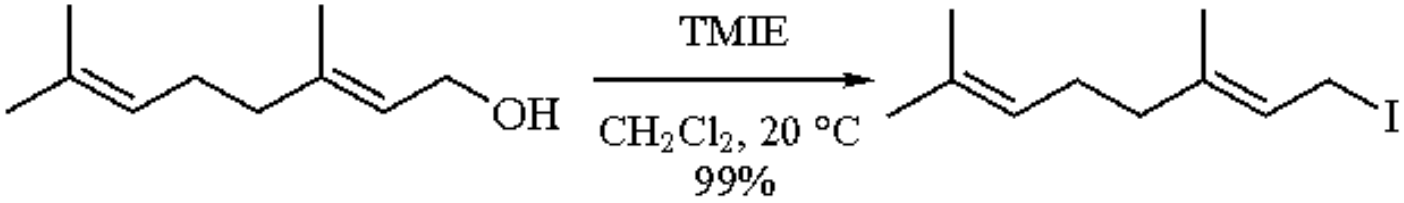

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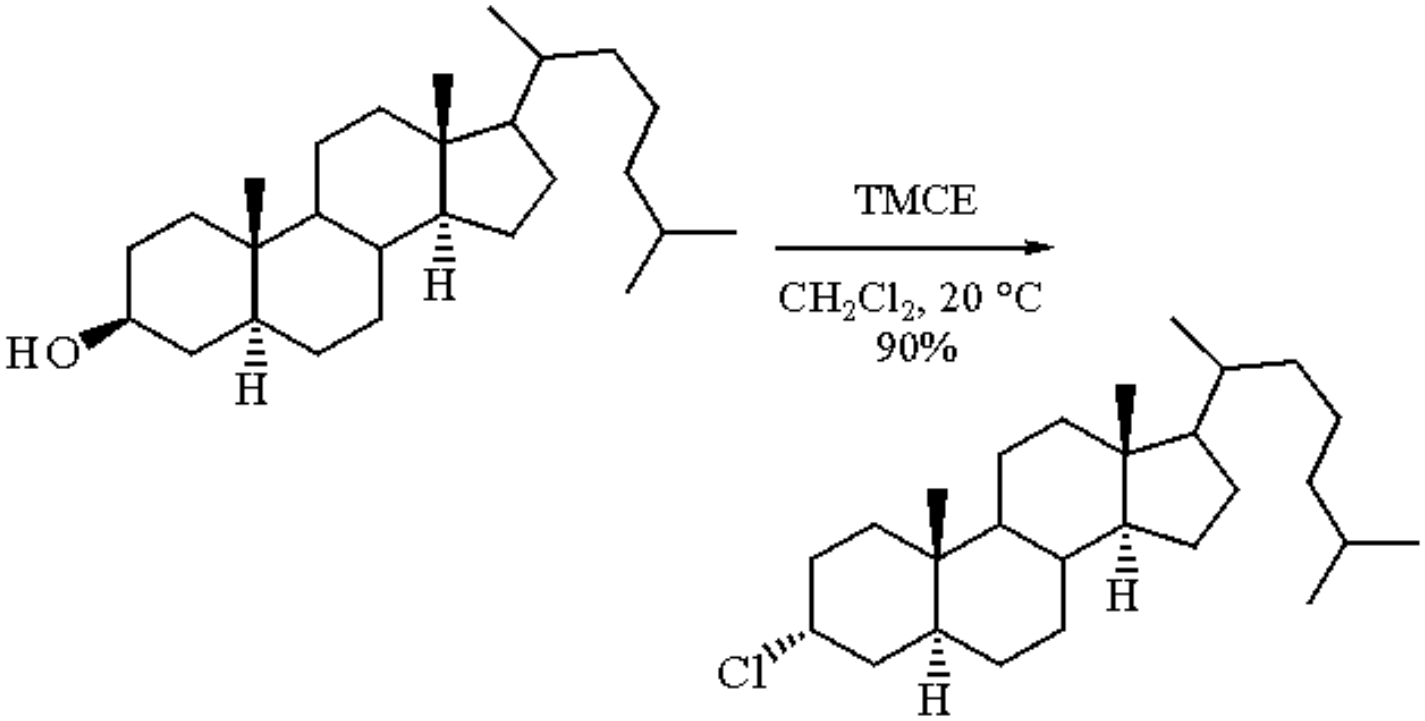

(4)

100% inversion

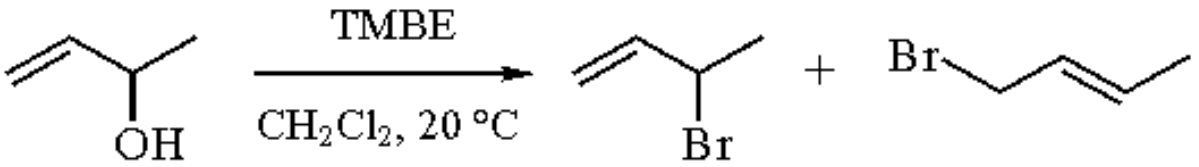

(5)

71% 29%

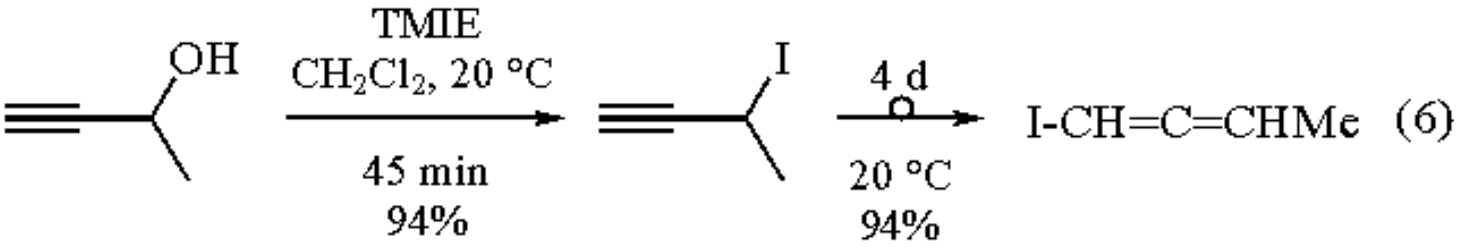

The halogenation reaction has been applied to the modification of various furanose and pyranose hemiacetals (eqs 7 and 8).[8]

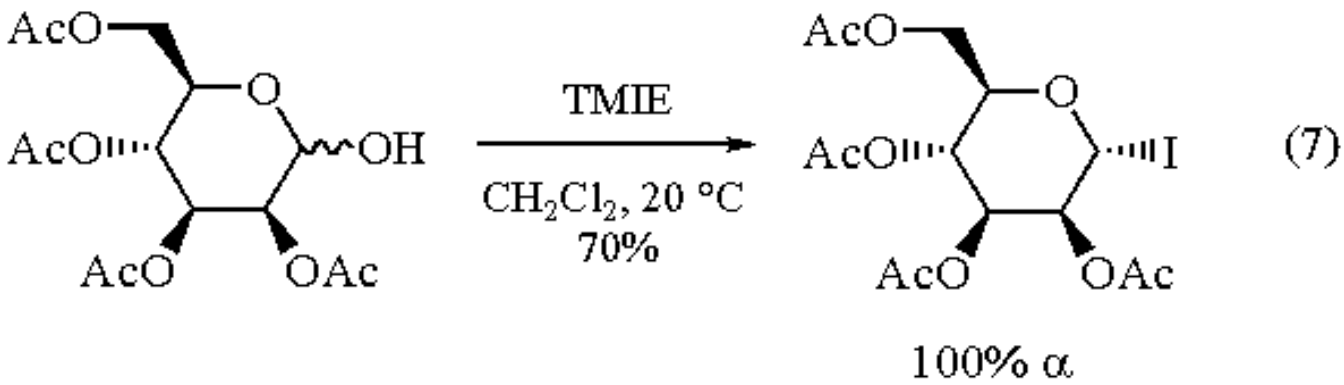

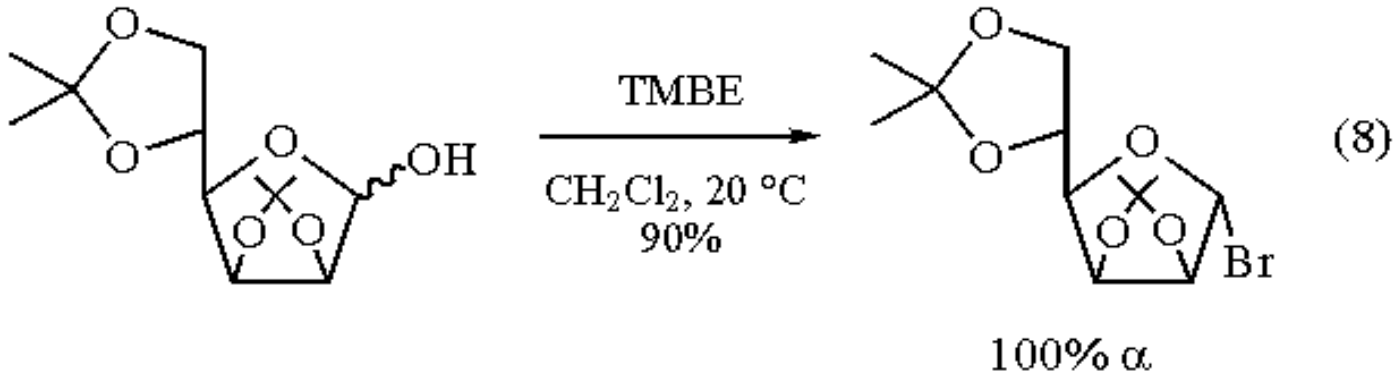

The reaction of 1-fluoro-*N*,*N*,2-trimethylpropenylamine with alcohols usually gives a mixture of products.[2b] In some cases a bulkier derivative has been successfully used to transform alcohols into fluorides (eqs 9 and 10).[2b,8]

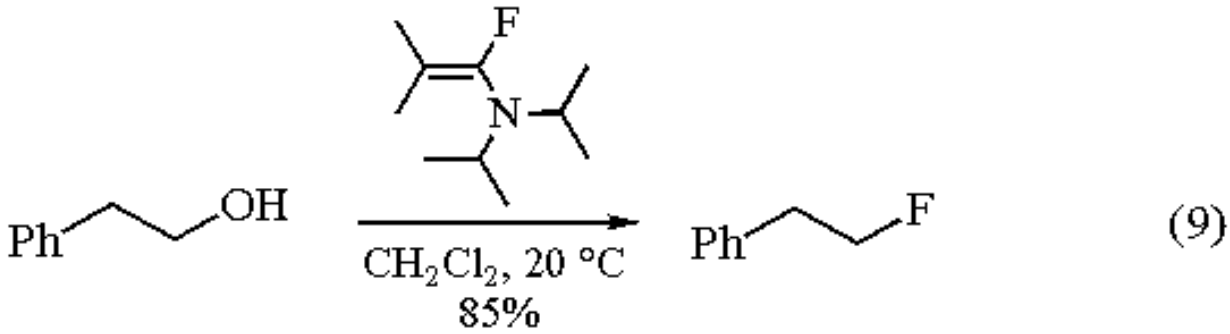

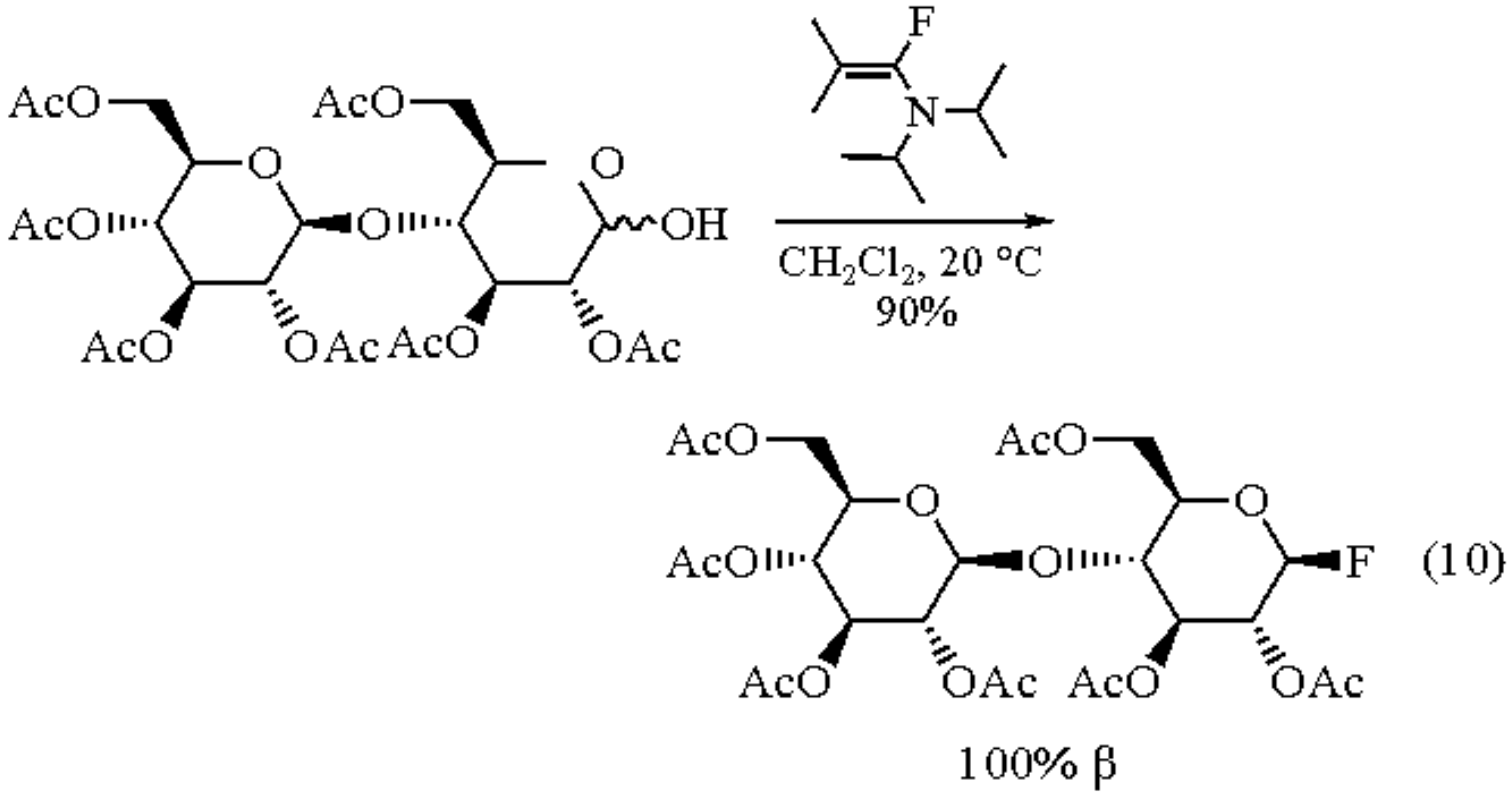

(10)

All the 1-halo-*N*,*N*,2-trimethylpropenylamines rapidly convert acids into acid halides (eqs 11 and 12).[2a] Since the only byproduct is the relatively inert *N*,*N*,2-trimethylpropanamide, the isolation of the acid halide will often be unnecessary. This method has been applied in peptide synthesis; no racemization was observed (eq 13).[3]

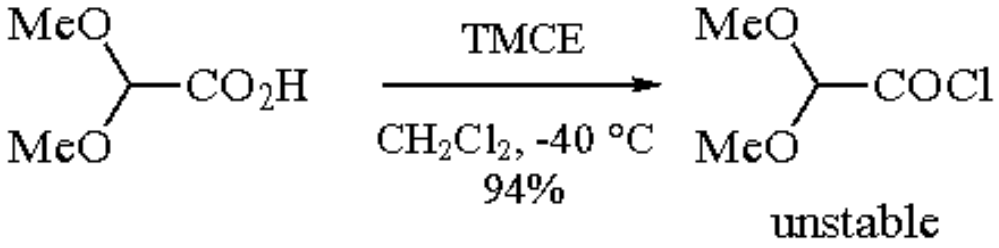

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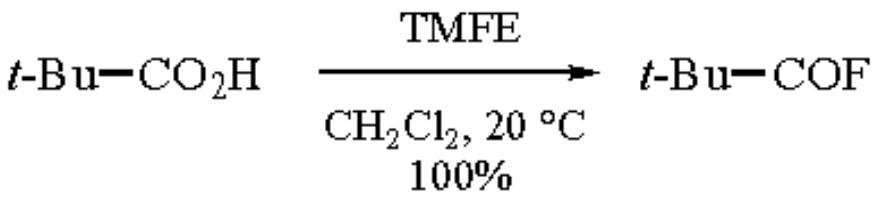

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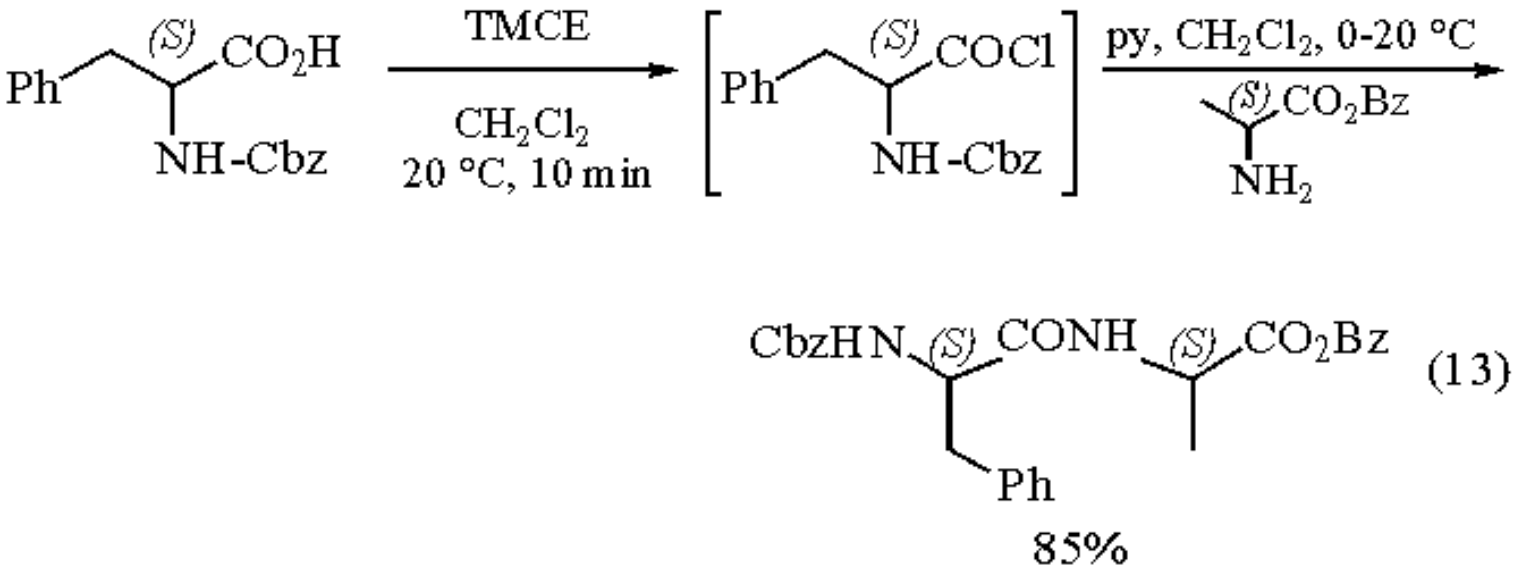

(13)

Coupling Reactions.

1-Chloro-*N*,*N*,2-trimethylpropenylamine is an excellent reagent for the coupling of carboxylic acids (eq 14) or allylic alcohols (eq 15) with organometallic compounds.[9]

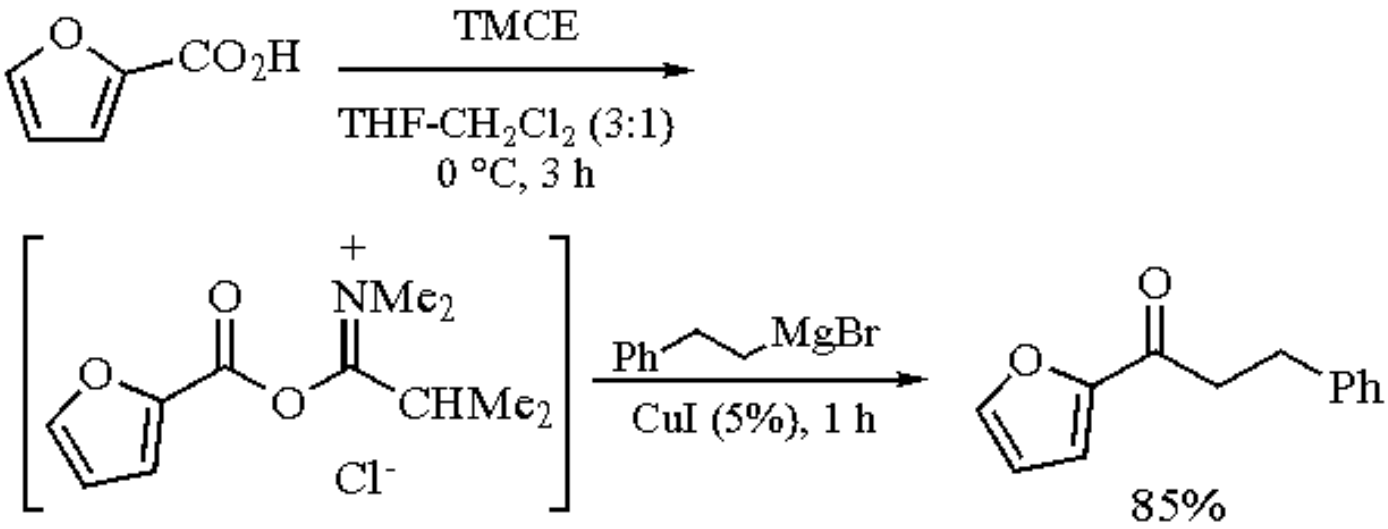

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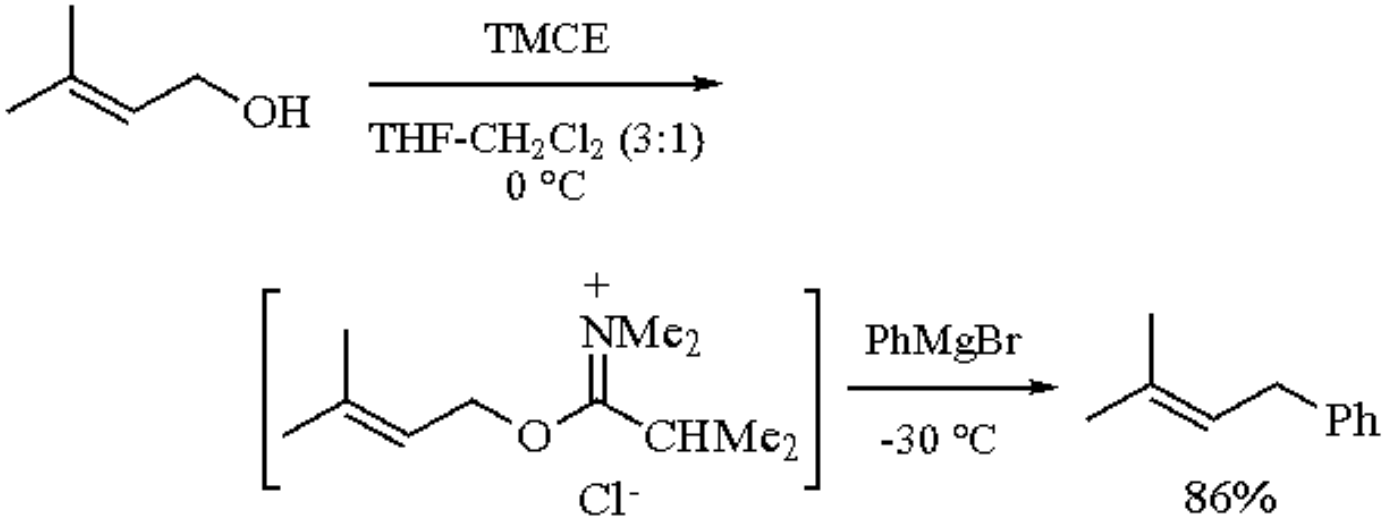

(15)

[2 + 2] Cycloadditions.

TMCE is a source of tetramethylketeniminium chloride.[1a] This highly electrophilic intermediate can be trapped by Schiff bases to generate azetidiniminium salts which readily hydrolyze to β-lactams (eq 16).[1b,5a] This has been developed into a general method to produce β-lactams from tertiary amides (eqs 17 and 18).[5c,5d]

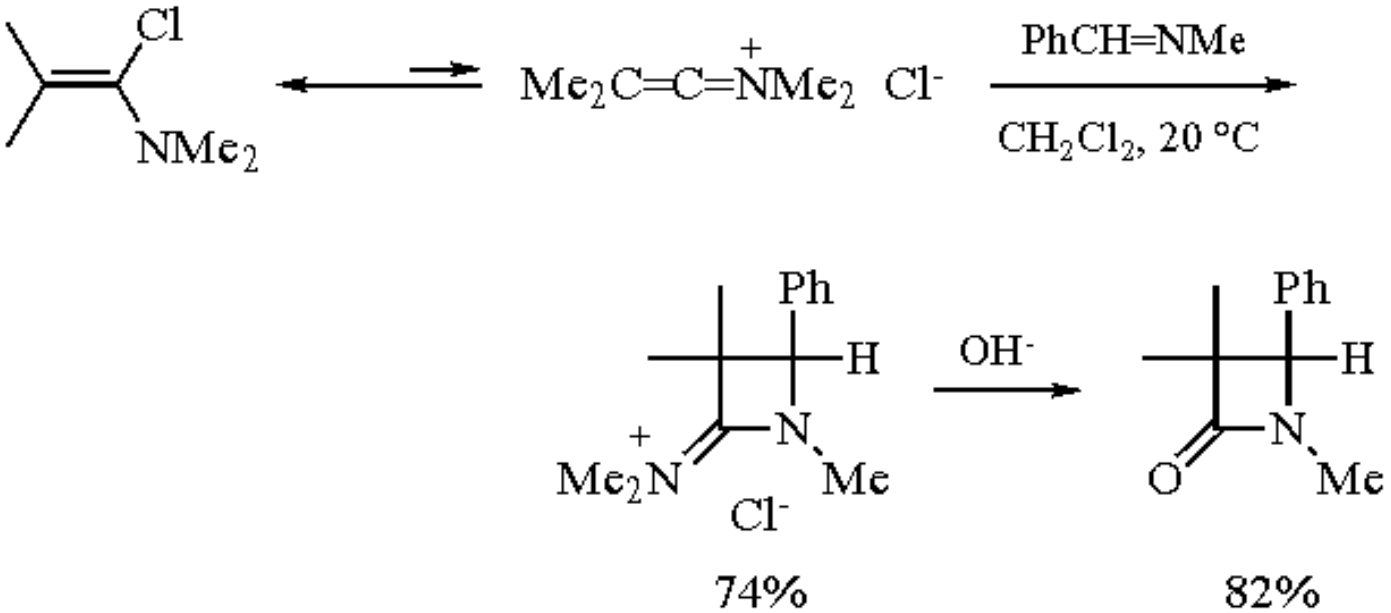

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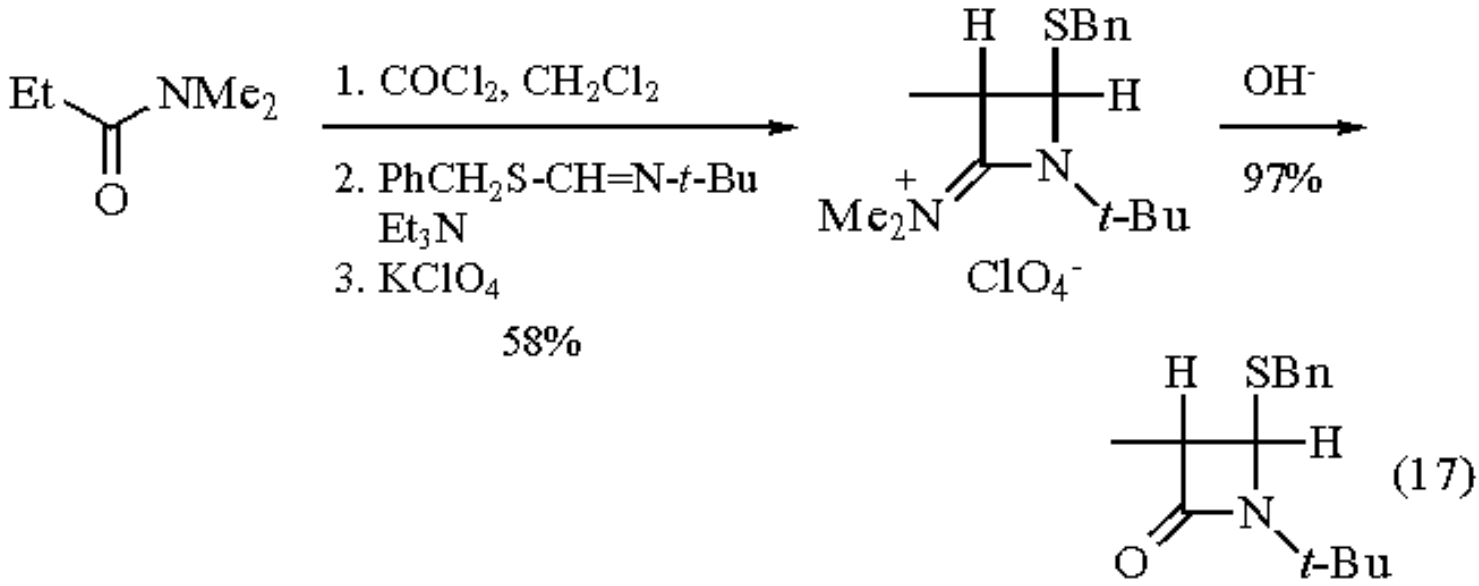

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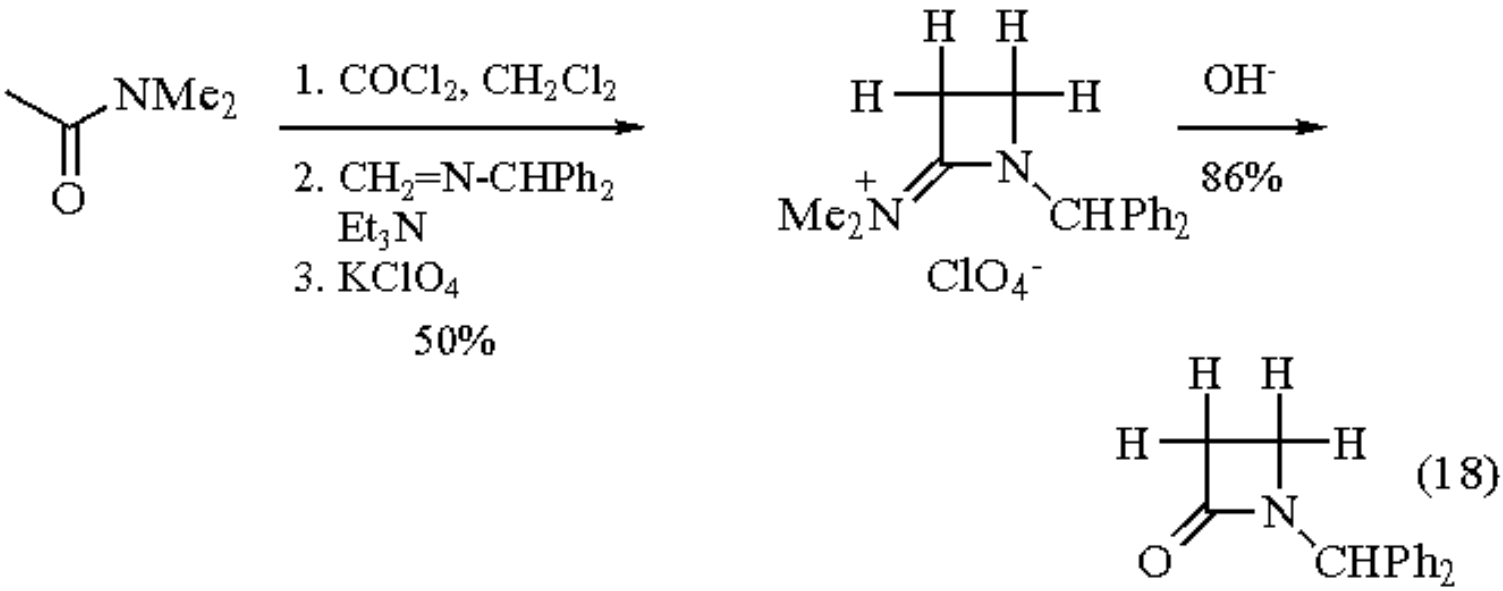

(18)

With the less nucleophilic carbon-carbon multiple bonds, cycloaddition will only occur in the presence of a Lewis acid which displaces the equilibrium toward the cumulene form (eq 19).[1a,4] $AgBF_4$, $ZnCl_2$, $AlCl_3$, and $SnCl_4$ have been successfully used, but the combination of TMCE with ***Zinc Chloride*** is the most convenient in many cases.[4b] Thus tetramethylketeniminium salts, which are most often generated in situ, behave as highly reactive equivalents of dimethylketene for the preparation of cyclobutanones and cyclobutenones. Indeed, the cyclobutane- and cyclobuteneiminium salts intermediates are readily hydrolyzed (eqs 20-23).

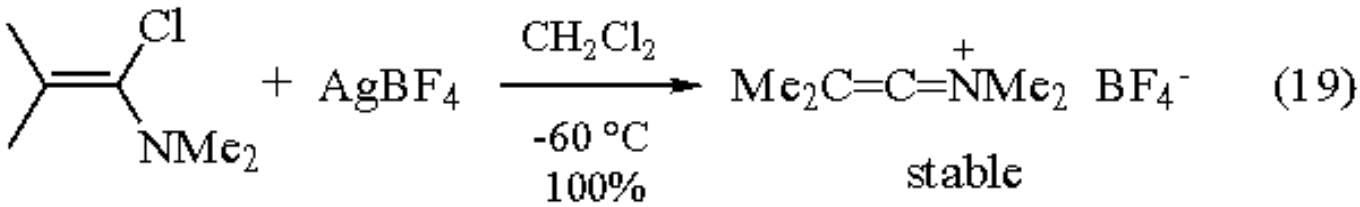

(19)

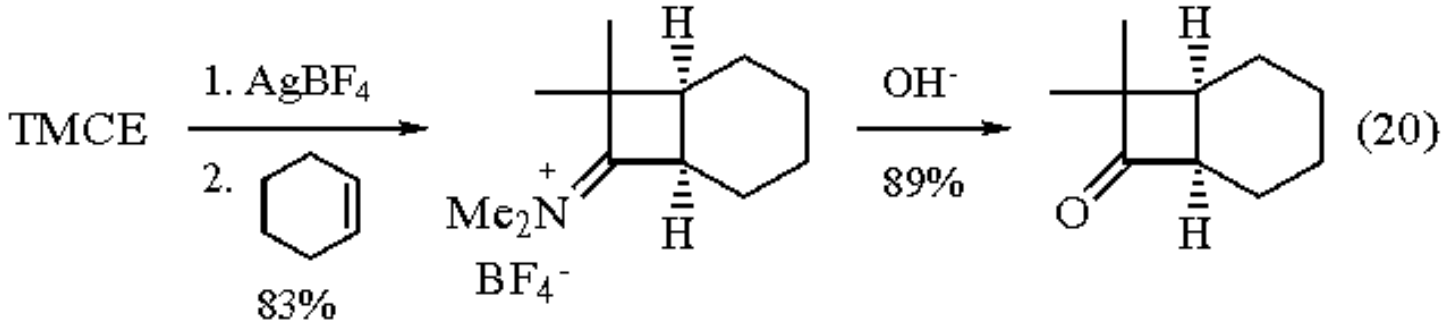

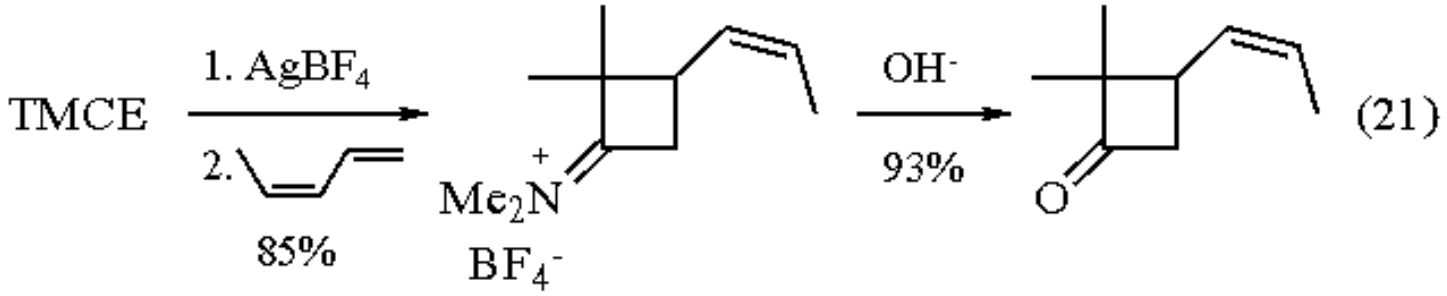

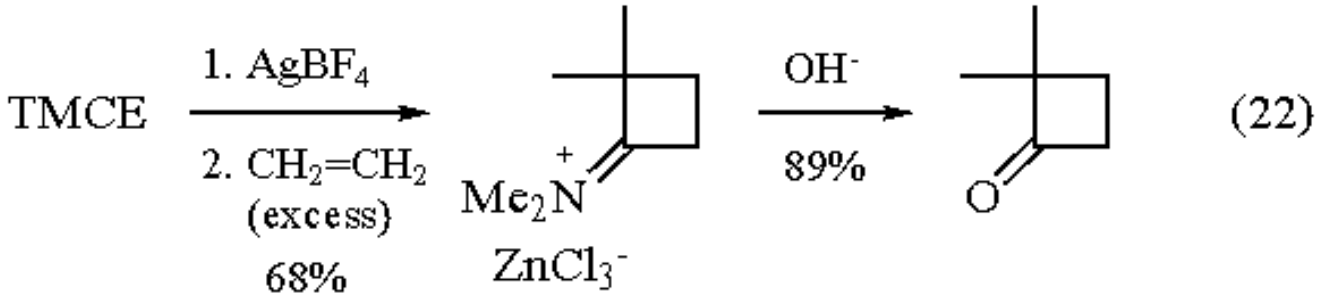

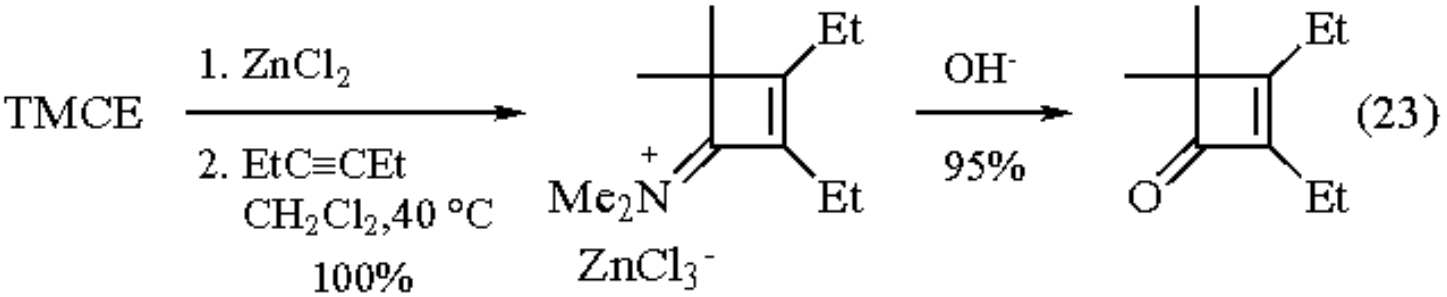

The reaction has been extended to other 2-substituted 1-chloro-*N*,*N*-dialkylvinylamines.[10] An asymmetric version of the cycloaddition has been described (eq 24).[11]

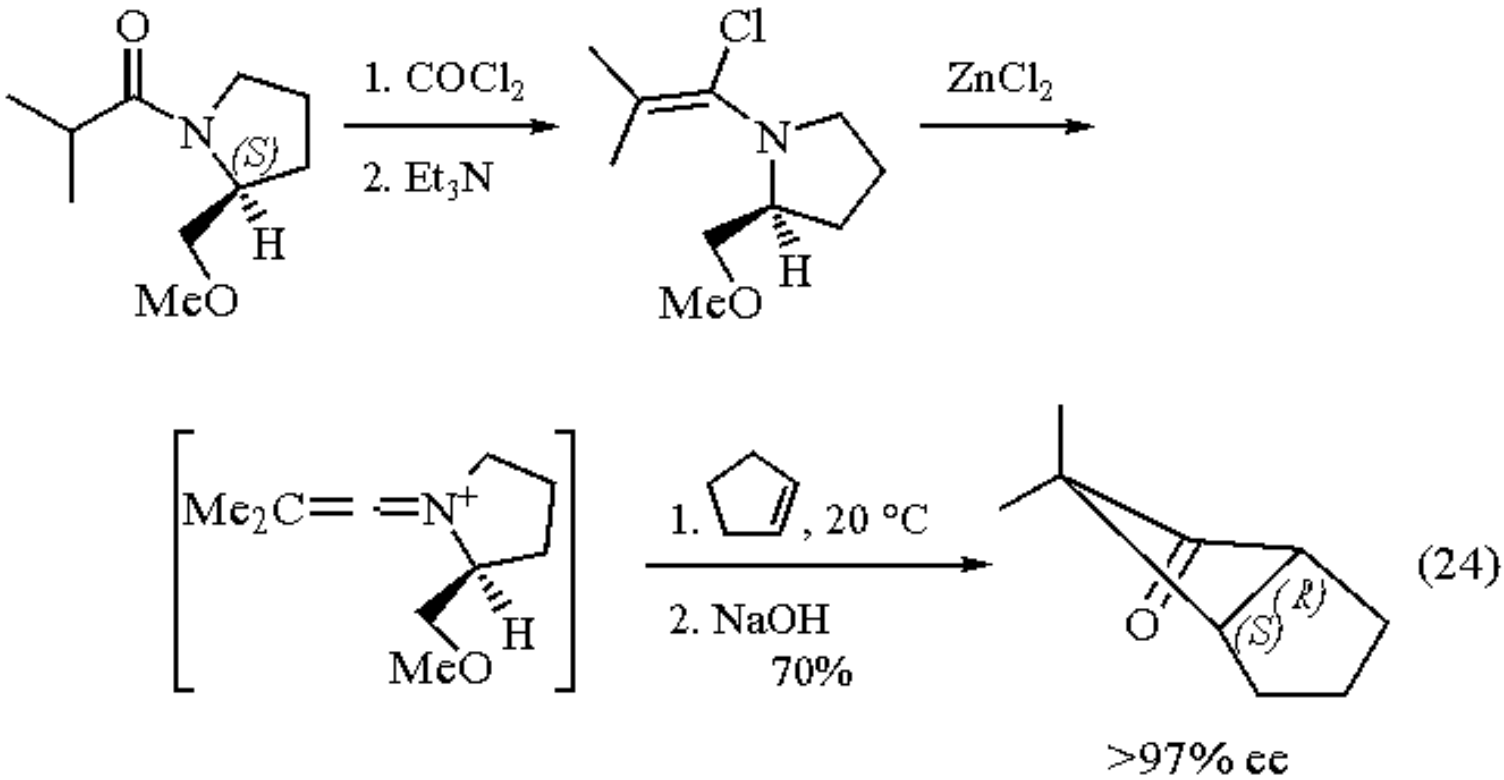

Miscellaneous Reactions.

Reaction of 1-chloro-*N*,*N*,2-trialkylpropenylamines with azide ion gives 2-amino-1-azirines; these three-membered ring amidines are useful intermediates for the synthesis of pyridines.[12] 1-Chloro-*N*,*N*,2-trialkylpropenylamines react readily with electron-rich aromatics in electrophilic substitutions, without the need of an acid catalyst.[13] The corresponding α-metalated vinylamines give nucleophilic aminoalkenylation reactions.[14] TMCE reacts with potassium cyanide to yield 1-cyano-*N*,*N*,2-trimethylpropenylamine, a synthetic intermediate for the preparation of α-diketones.[15] TMCE is smoothly converted to *N*,*N*-dimethylmethacrylamide in the presence of ***Pyridine N-Oxide*** and ***Triethylamine***; this reaction has been applied successfully to the preparation of various α,β-unsaturated amides.[16] 1-Phosphonato enamines have been obtained by treatment of TMCE with trialkyl phosphites.[17] The reaction of metal carbonyl anions with TMCE has been described; this leads to the formation of new transition metal organometallic compounds with novel structural features.[18]

---

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Chlorotrimethylgermane

Me_3GeCl

[1529-47-1] · C_3H_9ClGe · Chlorotrimethylgermane · (MW 153.16)

(precursor of germanium masked dienolate for regioselective C-C bond formation;[1] germanium enolates and α-germyl ester for aldol,[10] Peterson-type reaction,[8] and Claisen rearrangement[11])

Alternate Name: trimethylgermanium chloride.

Physical Data: mp -13 °C; bp 102 °C; *d* 1.240 g cm^{-3}.

Solubility: sol ether, THF, hexane, benzene, CH_2Cl_2, $CHCl_3$.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: is air-stable, but moisture sensitive. Germanium compounds are reputed to be of lower toxicity than stannanes. Use in a fume hood.

Allylgermanes.

The reaction of certain lithium dienolates with trimethylgermanium halides (Me_3GeCl and Me_3GeBr) produces the α-trimethylgermylated β,γ-unsaturated esters (**1**) (eq 1).[1] On the other hand, the reaction of lithium dienolate (**2a**) with tin chlorides Bu_xSnCl_{4-x} (x = 0-3) produces the γ-stannylated α,β-unsaturated esters, and the same reaction with ***Chlorotrimethylsilane*** gives the *O*-silylated dienol ethers (eq 2). The α-germylation of (**2**) is a reflection of kinetic control, as is observed in the alkylation of (**2**) with alkyl halides. The γ-stannylation is due to the thermodynamic stability of the product, and the *O*-silylation is ascribed to the strong affinity of Si for oxygen. In fact, the α-germylated (**1a**) undergoes rearrangement to the γ-isomer upon heating. Further, treatment of (**2a**) with chlorotriphenylgermane gives the γ-germylated product, owing to the steric bulkiness of the triphenylgermyl group.

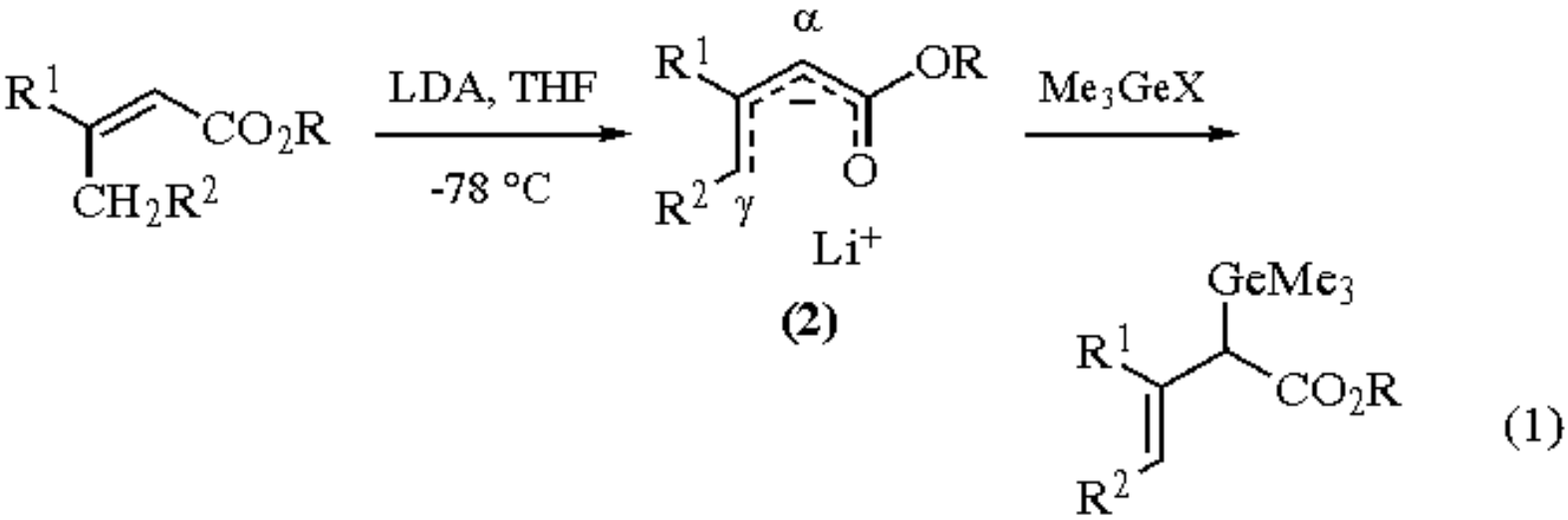

(1a) $R^1 = Me$, $R^2 = H$, $R = Et$
(1b) $R^1 = H$, $R^2 = H$, $R = Me$
(1c) R^1-$R^2 = (CH_2)_3$, $R = Et$
(1d) R^1-$R^2 = (CH_2)_4$, $R = Me$

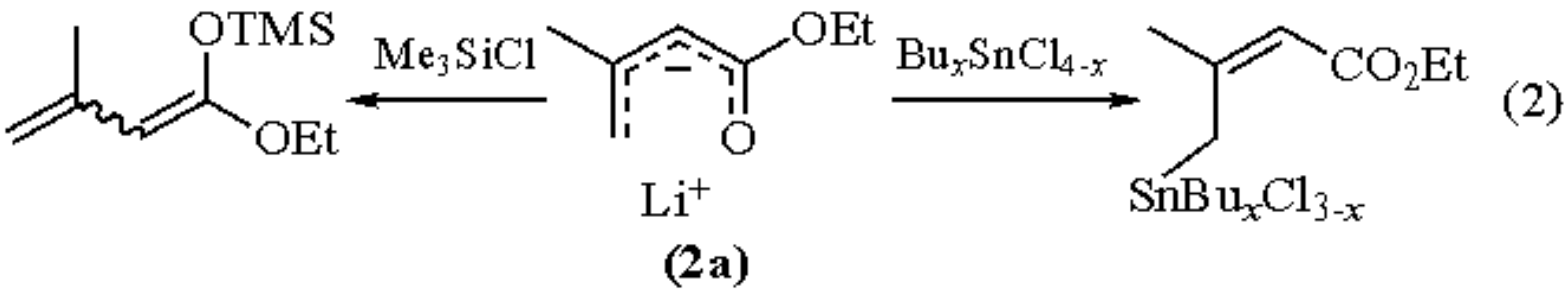

In general, lithium dienolates (for example **2**) react with carbon electrophiles at the α-position and thus the carbon chain elongation at the γ-position is not easy. However, C-C bond formation at the γ-position takes place via the α-germylated compounds (**1**), which are α-alkoxycarbonylallylgermane derivatives. The Lewis acid mediated reactions of (**1**) with acetals, aldehydes, and reactive halides afford the γ-alkylated α,β-unsaturated esters having predominant (*E*) geometry (eq 3). The reaction of allylic halides with (**1a**) in the presence of TMSCl at 10 kbar is highly regioselective and gives the head-to-tail coupling product in high yields (e.g. eq 4). The use of high pressures and TMSCl is essential to this regioselective allylic-allylic coupling. The amination reaction of lithium dienolates often produces a mixture of α- and γ-amino acid derivatives. However, the Lewis acid mediated reaction of α-germyl (Ge-masked dienolates) derivatives (**1**) with DEAD (***Diethyl Azodicarboxylate***) regioselectively provides the γ-adduct (see eq 5).[1,2] On the other hand, the ***Zinc Chloride*** mediated reaction of the γ-stannylated dienolates (shown in eq 2) with DEAD gives the α-adduct.

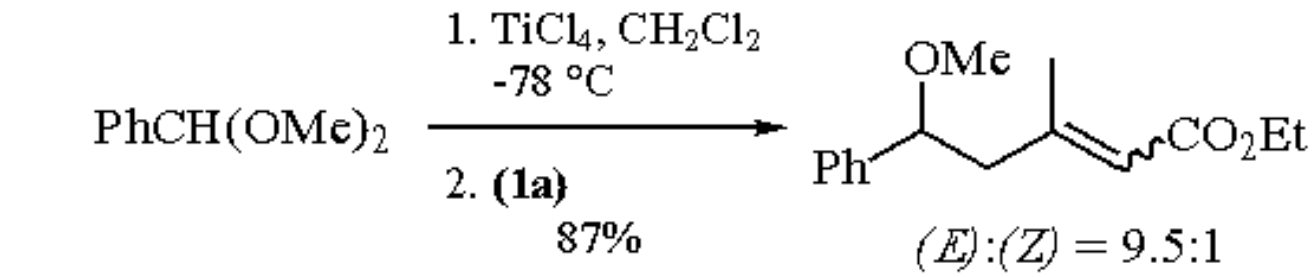

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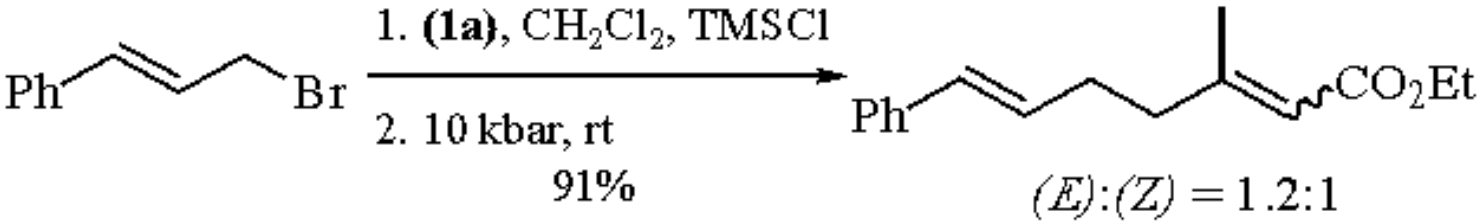

(4)

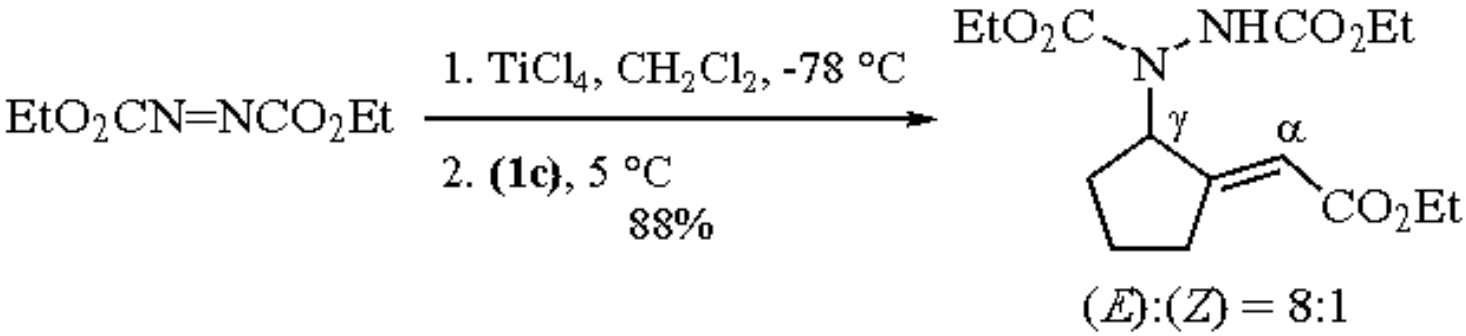

(5)

The reaction of Ge-masked dienolates (**1**) with Michael acceptors in the presence of Lewis acids produces the 1,4-γ-adduct regioselectively, whereas the reaction in the presence of ***Tetra-n-butylammonium Fluoride*** gives the 1,4-α-adduct exclusively (eq 6).[3] The coupling between cyclopentenone and the crotonate lithium dienolate gives a 1,4-α-adduct,[4] and the reaction of some enones with the vinylogous Reformatsky reagent derived from ethyl 4-bromocrotonate to some enones affords a 1,4-α-adduct under the controlled reaction conditions.[5] The 1,2-γ-selectivity is obtained in the reaction of lithium dienolates with certain enones[6] and enols.[7]

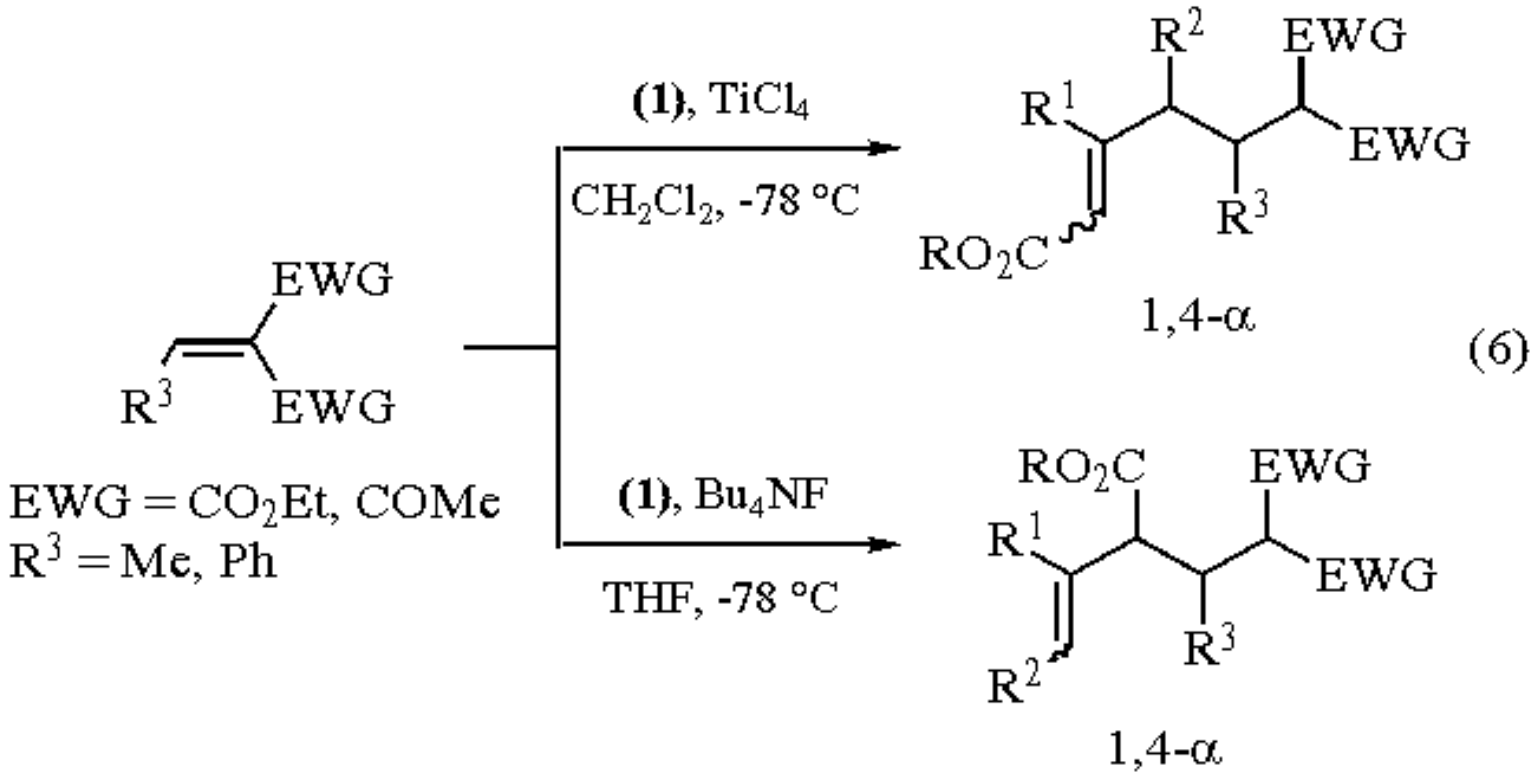

(6)

Germanium Enolates and α-Germyl Esters.

Peterson-type reaction of *t*-butyl (trimethylgermyl)acetate, derived from lithium *t*-butylacetate and Me_3GeCl, with aldehydes and ketones gives stereoselectively (*E*)-2-alkenoic acid esters (eq 7).[8] Normally, high (*E*)-selectivity is obtained: (*E*)/(*Z*) = 93:7 for $R^1 = Me(CH_2)_6$, R^2 = H; (*E*)/(*Z*) = >99:1 for R^1 = Ph, R^2 = Me. The (*E*) selectivity via trimethylgermylacetate is higher than that via trimethylsilylacetates.[9]

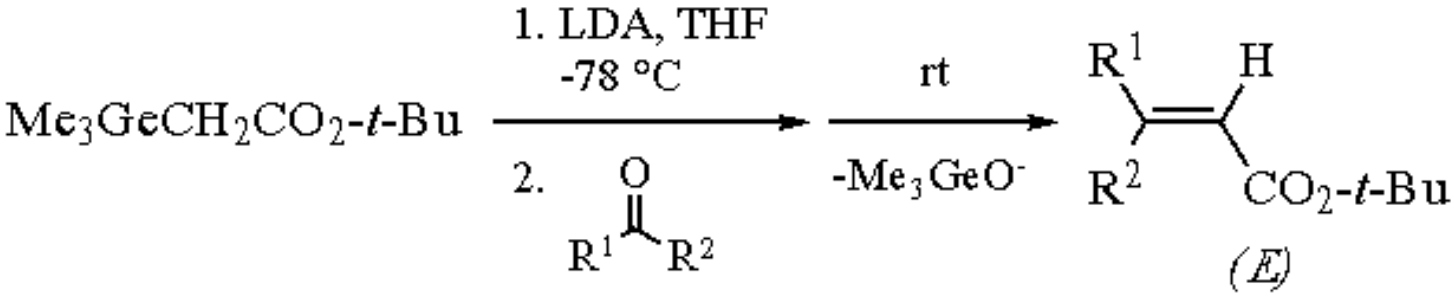

(7)

The germanium enolate of propiophenone, prepared in situ by the reaction with ***Lithium Diisopropylamide*** in ether followed by treatment with Me_3GeCl, reacts with benzaldehyde to give mainly the *syn*-aldol, while the same enolate produces the *anti*-aldol predominantly if the coexisting lithium halides are removed before condensation (eq 8).[10] The chemical yield is low in the absence of LiX, but is increased in the presence of ***Boron Trifluoride Etherate***. The salt effect on the diastereoselectivity is not observed with the germanium enolate prepared with chlorotriphenylgermane.

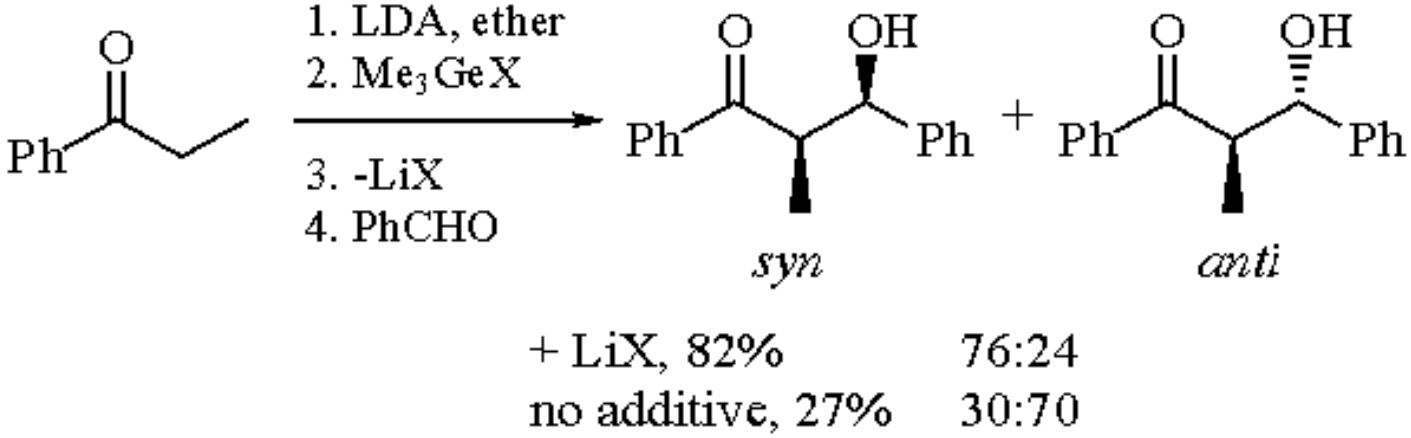

(8)

The asymmetric Claisen rearrangement of allyl vinyl ethers is effected with a chiral organoaluminum reagent, (*R*)-(**3**) or (*S*)-(**3**).[11] This method provides a facile asymmetric synthesis of various acylgermanes (and acylsilanes) with high enantiomeric purity (eq 9). The reactions of the trimethylgermyl derivative proceeds with higher enantioselectivity (91% ee) than that of the trimethylsilyl analog (80% ee).

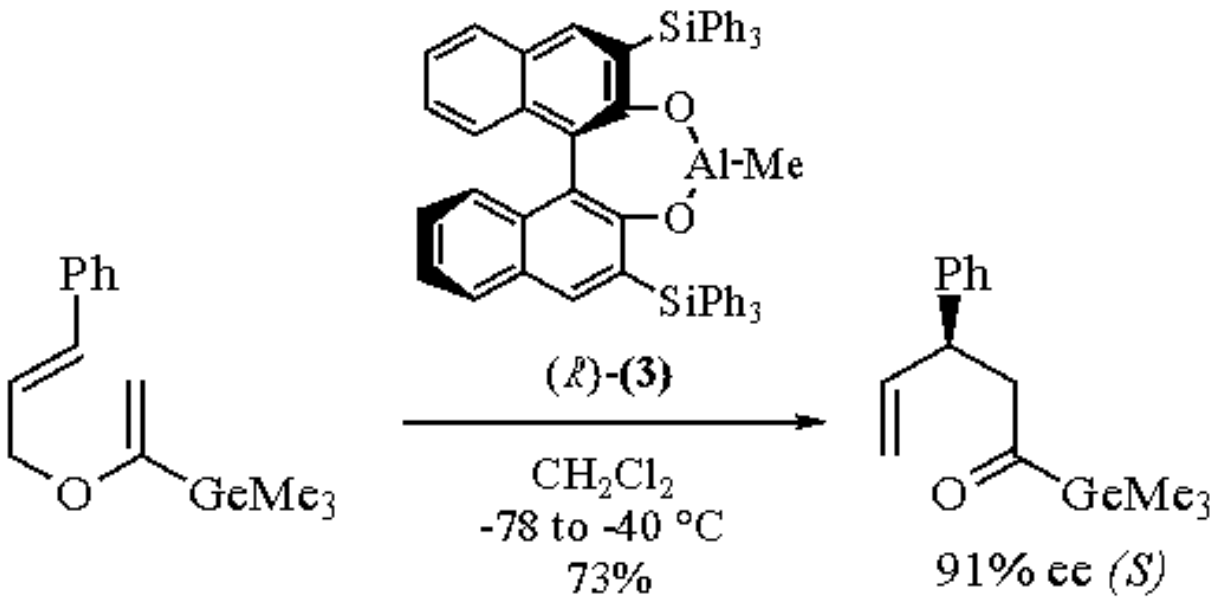

(9)

Other Trimethylgermyl Derivatives.

Reactions of α-stannylvinyllithiums RR´C=C(Li)$SnMe_3$ with Me_3MCl (M = Si, Ge, Pb) give the corresponding mixed bis(trimethylmetal)alkenes, RR´C=C($SnMe_3$)MMe_3.[12] Irradiation of acyltriphenylgermanes in THF gives five- and six-membered cyclic ketones bearing an α-(triphenylgermyl)methyl group (eq 10).[12] Cyanotrimethylgermane, prepared from Me_3GeCl and ***Silver(I) Cyanide***, reacts with terminal alkynes in the presence of ***Palladium(II) Chloride*** catalyst in toluene to produce (*Z*)-3-trimethylgermyl-2-alkenenitriles in good yields.[13] Similar addition reactions take place with ***Cyanotrimethylsilane***, but the reaction is slower than that of Me_3GeCN.

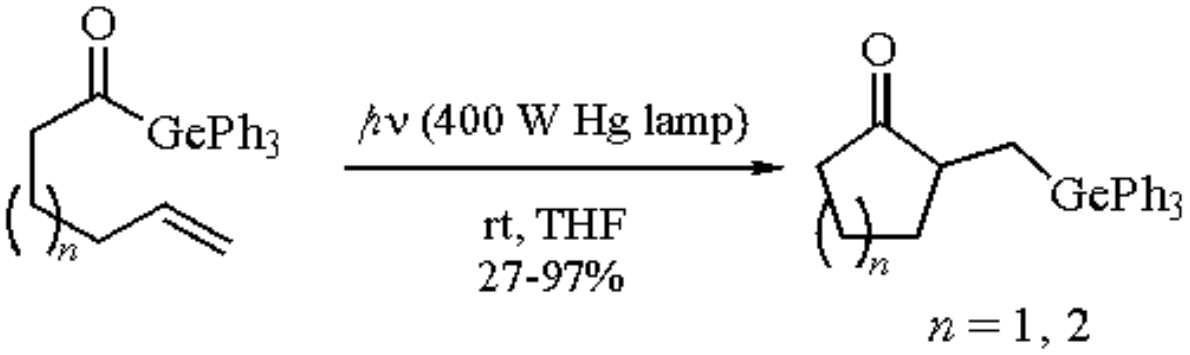

(10)

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Chlorotrimethylsilane[1,2]

$ClSiMe_3$

[75-77-4] · C_3H_9ClSi · Chlorotrimethylsilane · (MW 108.64)

(protection of silyl ethers,[3] transients,[5-7] and silylalkynes;[8] synthesis of silyl esters,[4] silyl enol ethers,[9,10] vinylsilanes,[13] and silylvinylallenes;[15] Boc deprotection;[11] TMSI generation;[12] epoxide cleavage;[14] conjugate addition reactions catalyst[16-18])

Alternate Names: trimethylsilyl chloride; TMSCl.

Physical Data: bp 57 °C; *d* 0.856 g cm^{-3}.

Solubility: sol THF, DMF, CH_2Cl_2, HMPA.

Form Supplied in: clear, colorless liquid; 98% purity; commercially available.

Analysis of Reagent Purity: bp, NMR.

Purification: distillation over calcium hydride with exclusion of moisture.

Handling, Storage, and Precautions: moisture sensitive and corrosive; store under an inert atmosphere; use in a fume hood.

Protection of Alcohols as TMS Ethers.

The most common method of forming a silyl ether involves the use of TMSCl and a base (eqs 1-3).[3,19-22] Mixtures of TMSCl and ***Hexamethyldisilazane*** (HMDS) have also been used to form TMS ethers. Primary, secondary, and tertiary alcohols can be silylated in this manner, depending on the relative amounts of TMS and HMDS (eqs 4-6).[23]

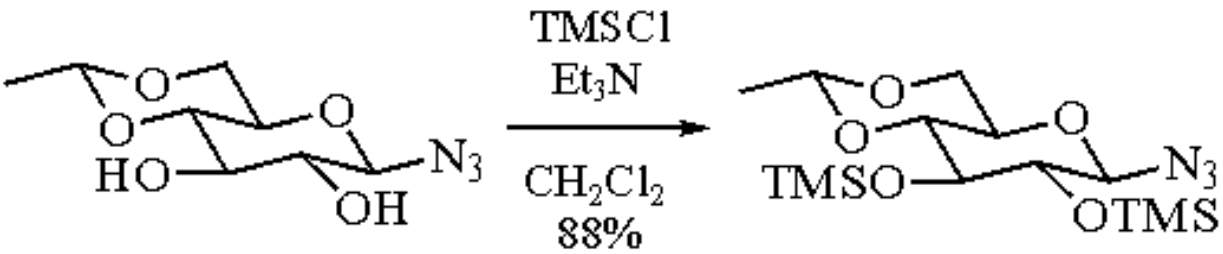

(1)

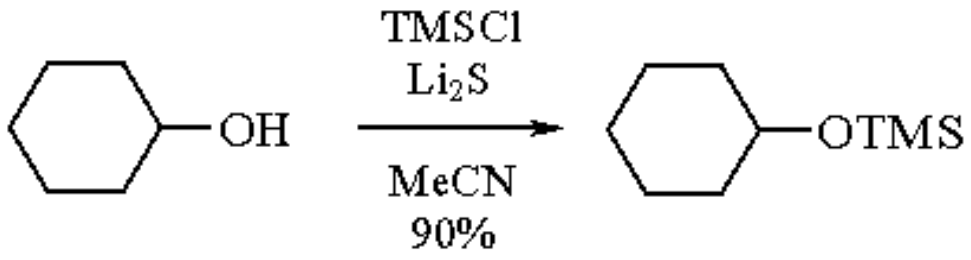
OH
TMSCl
Li_2S
MeCN
90%
OTMS

(2)

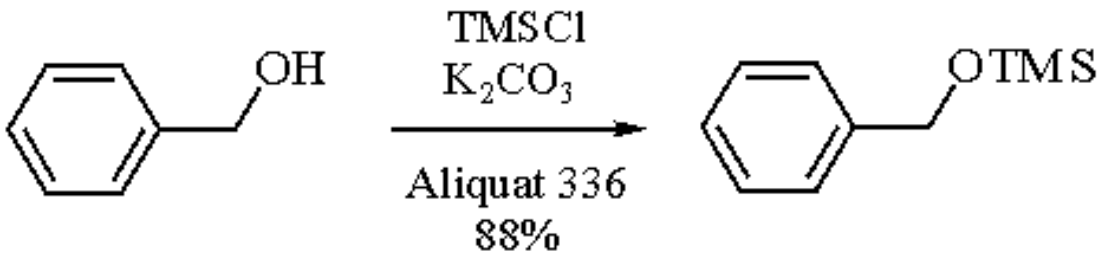
OH
TMSCl
K_2CO_3
Aliquat 336
88%
OTMS

(3)

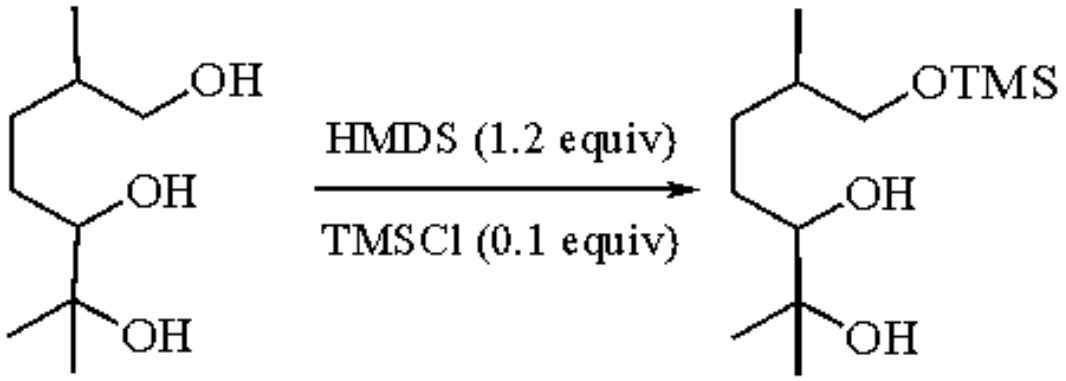
OH
OH
OH
HMDS (1.2 equiv)
TMSCl (0.1 equiv)
OTMS
OH
OH

(4)

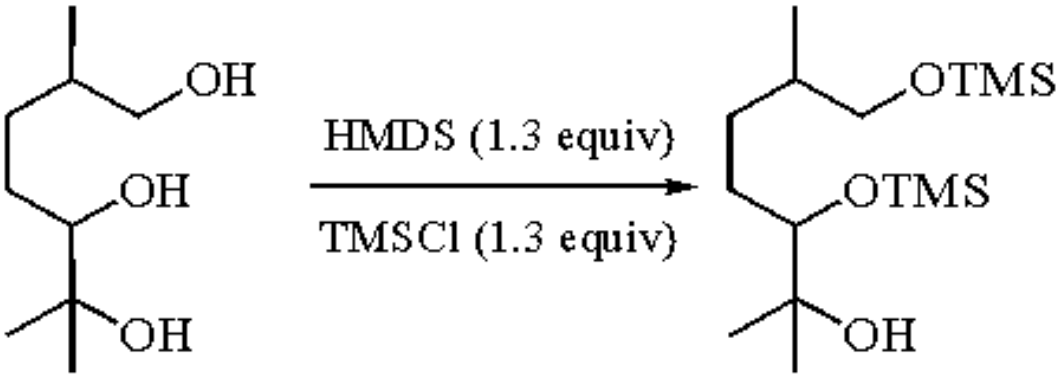
OH
OH
OH
HMDS (1.3 equiv)
TMSCl (1.3 equiv)
OTMS
OTMS
OH

(5)

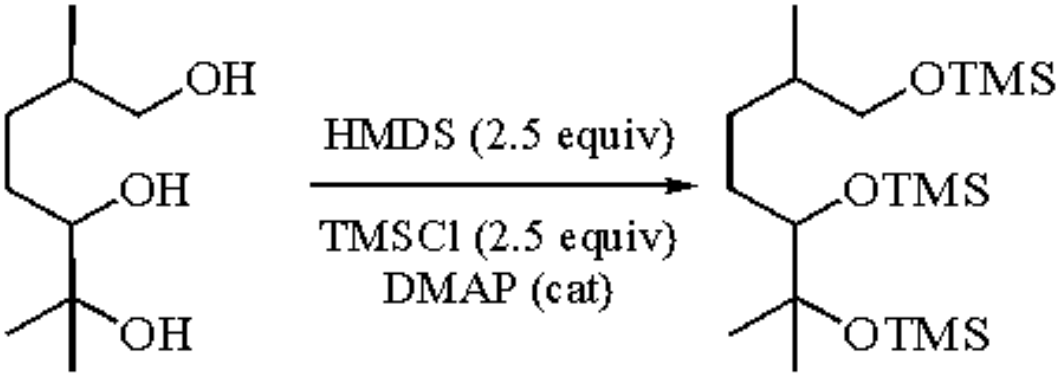
OH
OH
OH
HMDS (2.5 equiv)
TMSCl (2.5 equiv)
DMAP (cat)
OTMS
OTMS
OTMS

(6)

Trimethysilyl ethers can be easily removed under a variety of conditions,[19] including the use of ***Tetra-n-butylammonium Fluoride*** (TBAF) (eq 7),[20] citric acid (eq 8),[24] or ***Potassium Carbonate*** in methanol (eq 9).[25] Recently, resins ($OH^-$and H^+ form) have been used to remove phenolic or alcoholic TMS ethers selectively (eq 10).[26]

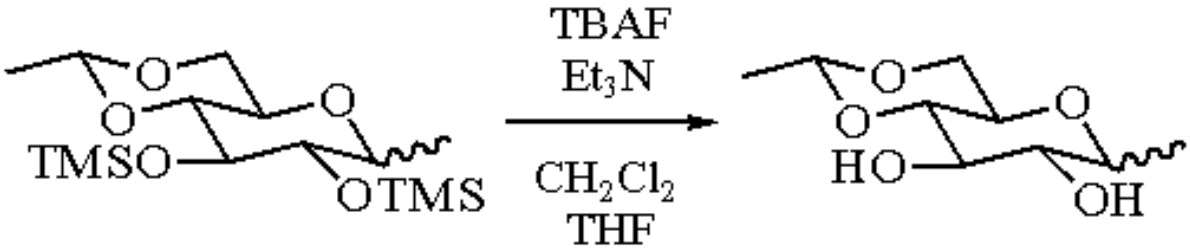

(7)

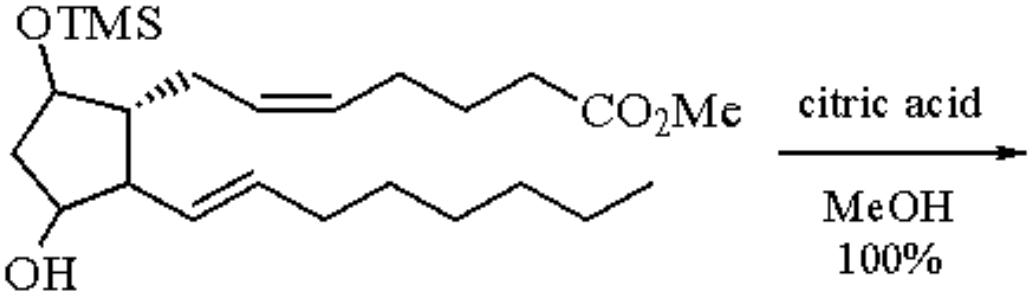

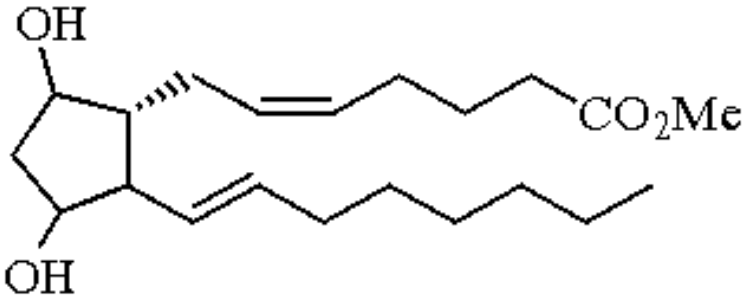

(8)

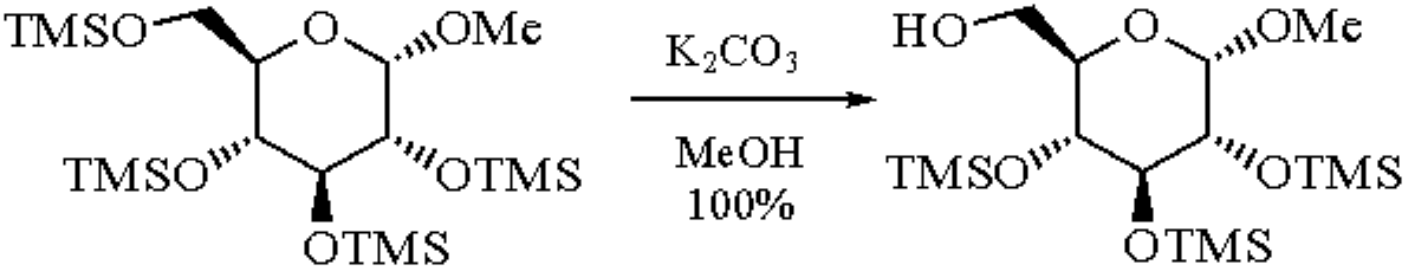

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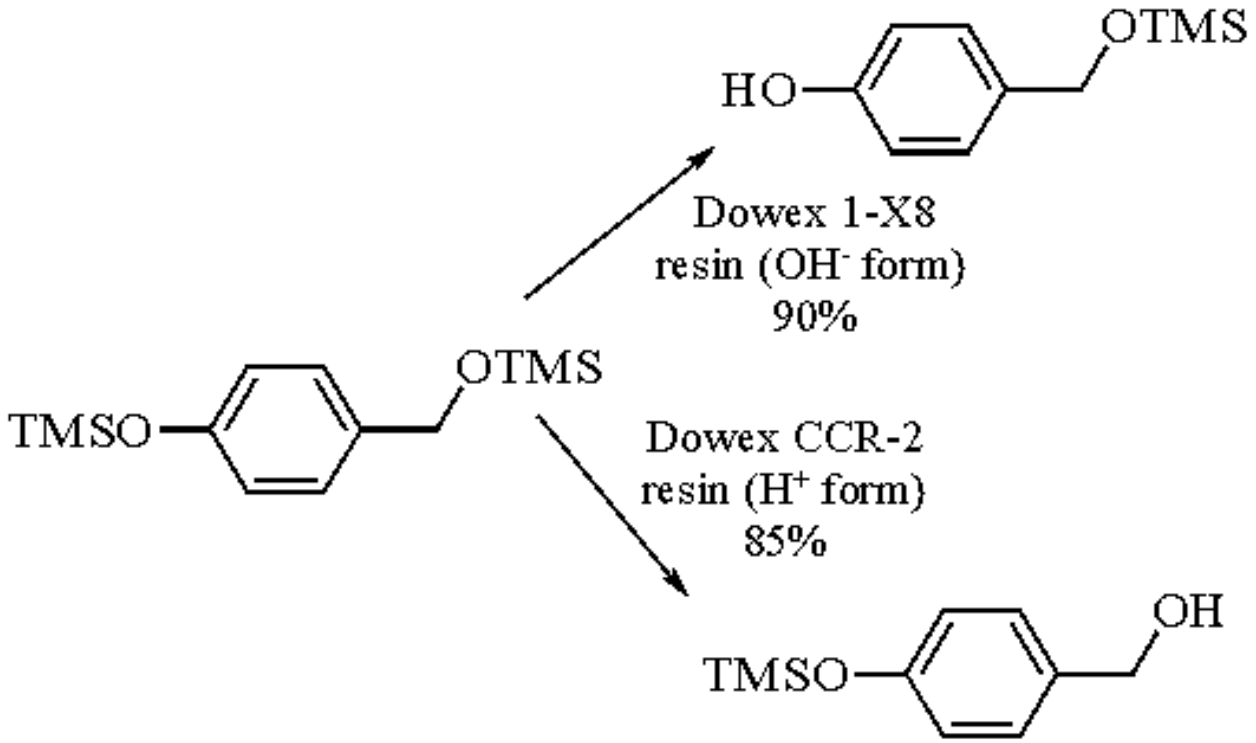

(10)

Transient Protection.

Silyl ethers can be used for the transient protection of alcohols (eq 11).[27] In this example the hydroxyl groups were silylated to allow tritylation with concomitant desilylation during aqueous workup. The ease of introduction and removal of TMS groups make them well suited for temporary protection.

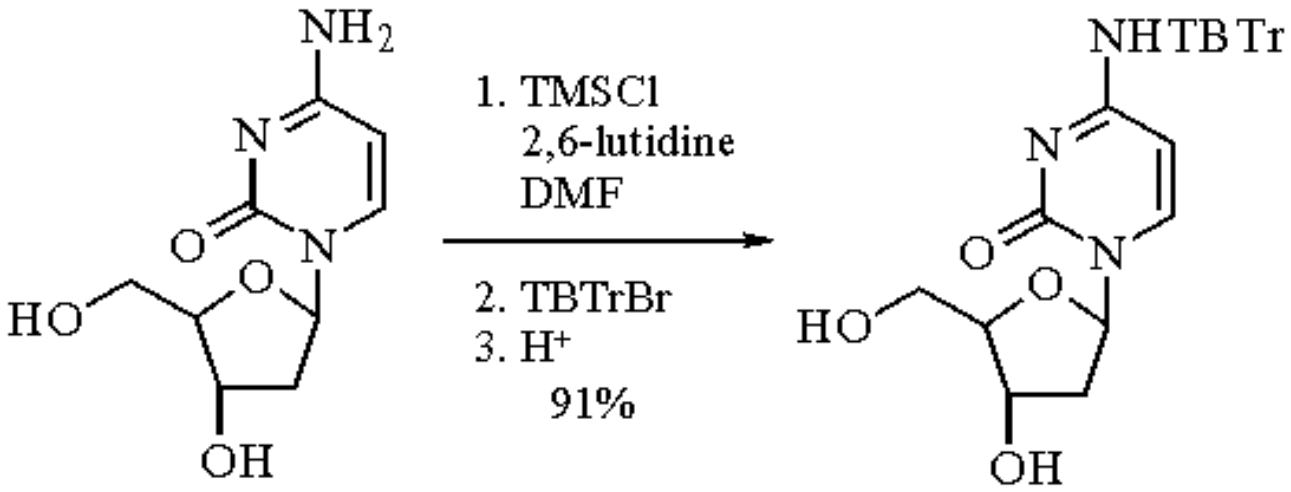

(11)

Trimethylsilyl derivatives of amino acids and peptides have been used to improve solubility, protect carboxyl groups, and improve acylation reactions. TMSCl has been used to prepare protected amino acids by forming the *O*,*N*-bis-trimethylsilylated amino acid, formed in situ, followed by addition of the acylating agent (eq 12).[5] This is a general method which obviates the production of oligomers normally formed using Schotten-Baumann conditions, and which can be applied to a variety of protecting groups.[5]

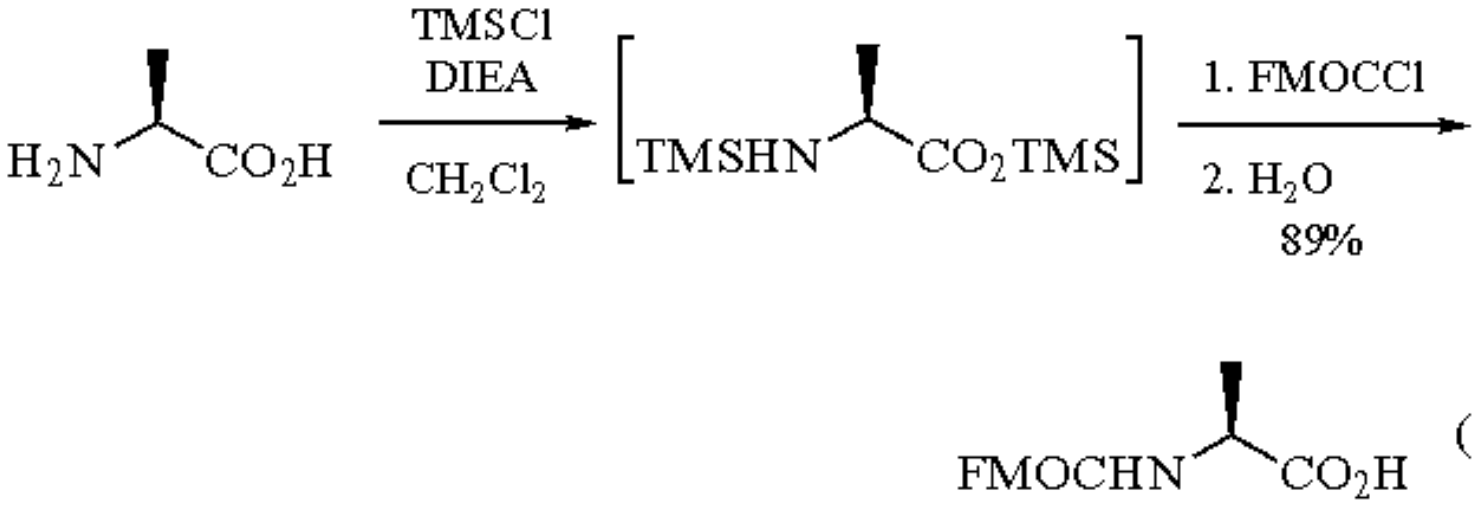

(12)

Transient hydroxylamine oxygen protection has been successfully used for the synthesis of *N*-hydroxamides.[6] Hydroxylamines can be silylated with TMSCl in pyridine to yield the *N*-substituted *O*-TMS derivative. Acylation with a mixed anhydride of a protected amino acid followed by workup affords the *N*-substituted hydroxamide (eq 13).[6]

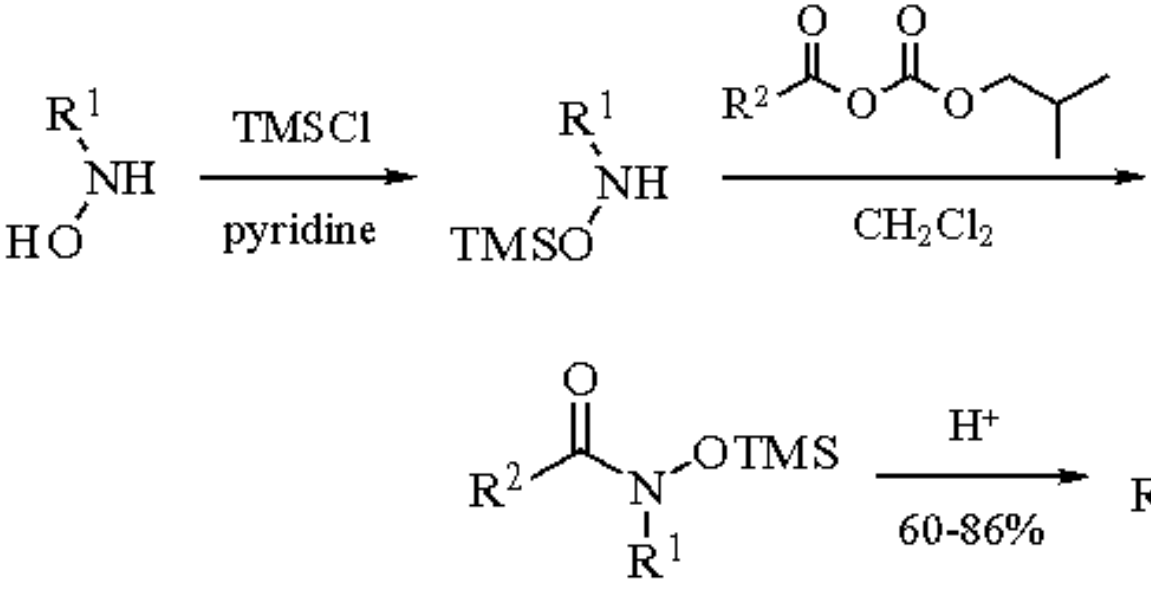

(13)

Formation of Silyl Esters.

TMS esters can be prepared in good yields by reacting the carboxylic acid with TMSCl in 1,2-dichloroethane (eq 14).[4] This method of carboxyl group protection has been used during hydroboration reactions. The organoborane can be transformed into a variety of different carboxylic acid derivatives (eqs 15 and 16).[7] TMS esters can also be reduced with metal hydrides to form alcohols and aldehydes or hydrolyzed to the starting acid, depending on the reducing agent and reaction conditions.[28]

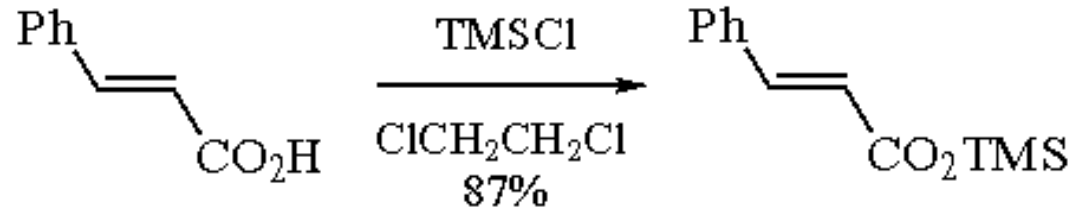

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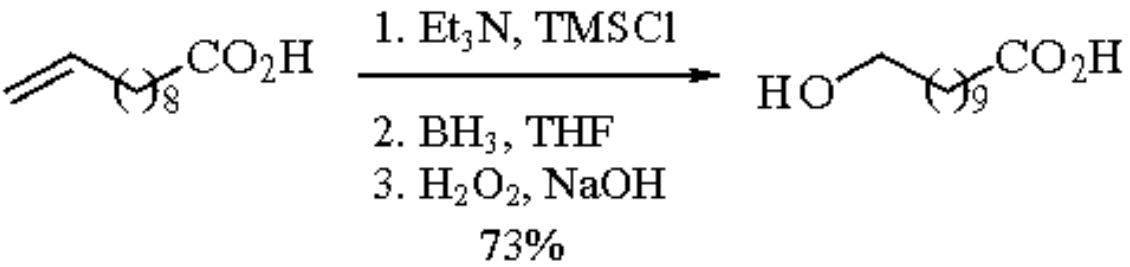

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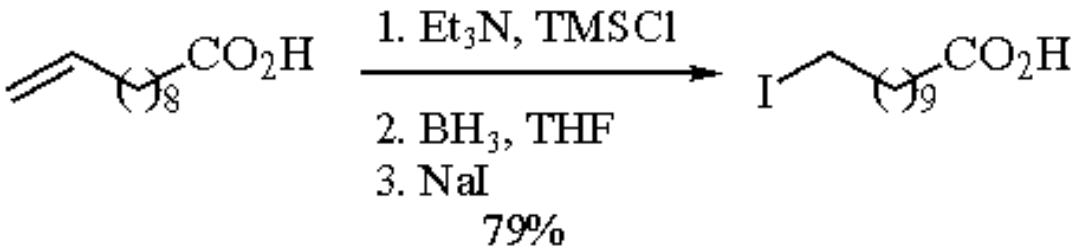

(16)

Protection of Terminal Alkynes.

Terminal alkynes can be protected as TMS alkynes by reaction with ***n-Butyllithium*** in THF followed by TMSCl (eq 17).[8] A one-pot β-elimination-silylation process (eq 18) can also yield the protected alkyne.

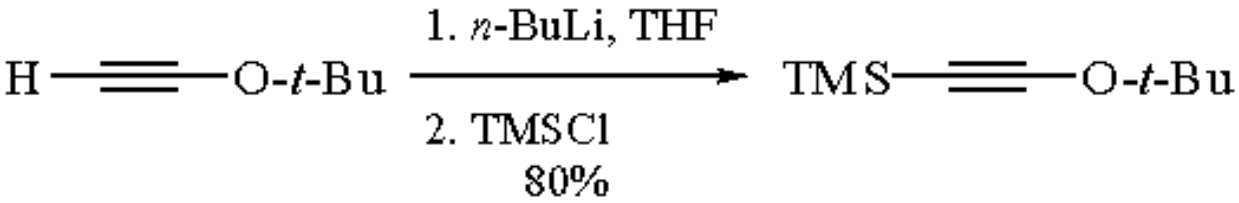

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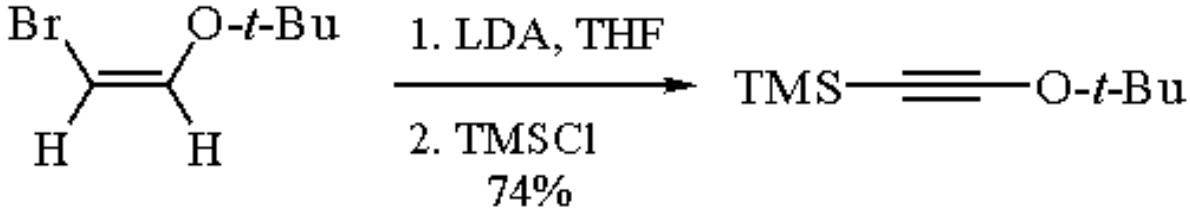

(18)

Silyl Enol Ethers.

TMS enol ethers of aldehydes and symmetrical ketones are usually formed by reaction of the carbonyl compound with ***Triethylamine*** and TMSCl in DMF (eq 19), but other bases have been used, including ***Sodium Hydride***[29] and ***Potassium Hydride***.[30]

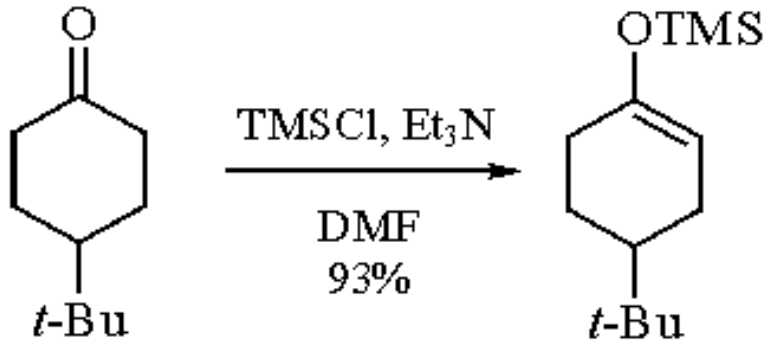

(19)

Under the conditions used for the generation of silyl enol ethers of symmetrical ketones, unsymmetrical ketones give mixtures of structurally isomeric enol ethers, with the predominant product being the more substituted enol ether (eq 20).[10] Highly hindered bases, such as ***Lithium Diisopropylamide*** (LDA),[31] favor formation of the kinetic, less substituted silyl enol ether, whereas ***Bromomagnesium Diisopropylamide*** (BMDA)[10] generates the more substituted, thermodynamic silyl enol ether. A combination of TMSCl/***Sodium Iodide*** has also been used to form silyl enol ethers of simple aldehydes and ketones[32] as well as from α,β-unsaturated aldehydes and ketones.[33] Additionally, treatment of α-halo ketones with ***Zinc***, TMSCl, and TMEDA in ether provides a regiospecific method for the preparation of the more substituted enol ether (eq 21).[34]

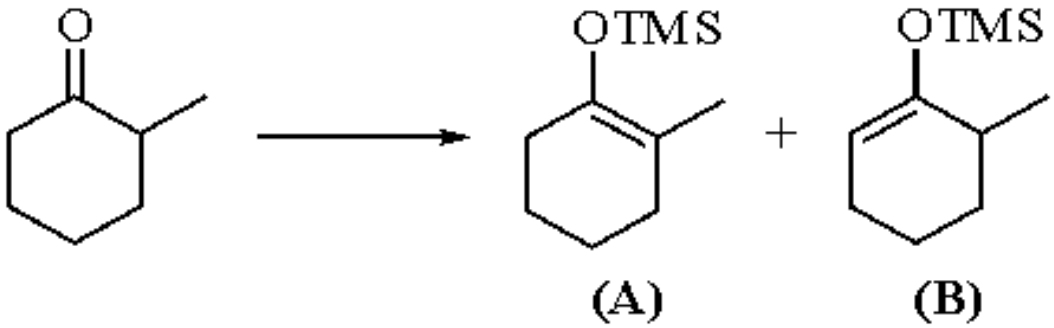

(20)

Reagents	Ratio (A):(B)
LDA, DME; TMSCl	1:99
NaH, DME; TMSCl	73:27
Et_3N, TMSCl, DMF	78:22
KH, THF; TMSCl	67:33
TMSCl, NaI, MeCN, Et_3N	90:10
BMDA, TMSCl, Et_3N	97:3

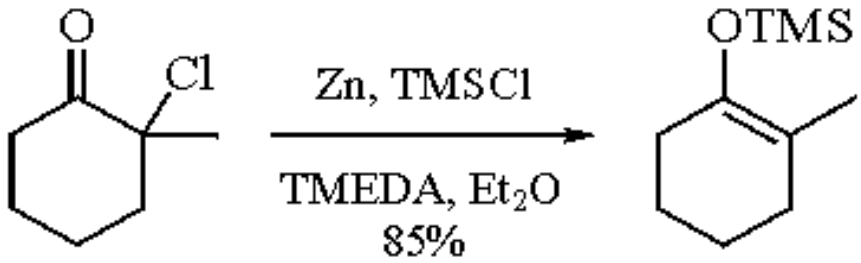

(21)

Mild Deprotection of Boc Protecting Group.

The Boc protecting group is used throughout peptide chemistry. Common ways of removing it include the use of 50% ***Trifluoroacetic Acid*** in CH_2Cl_2, ***Trimethylsilyl Perchlorate***, or ***Iodotrimethylsilane*** (TMSI).[19] A new method has been developed, using TMSCl-phenol, which enables removal of the Boc group in less than one hour (eq 22).[11] The selectivity between Boc and benzyl groups is high enough to allow for selective deprotection.

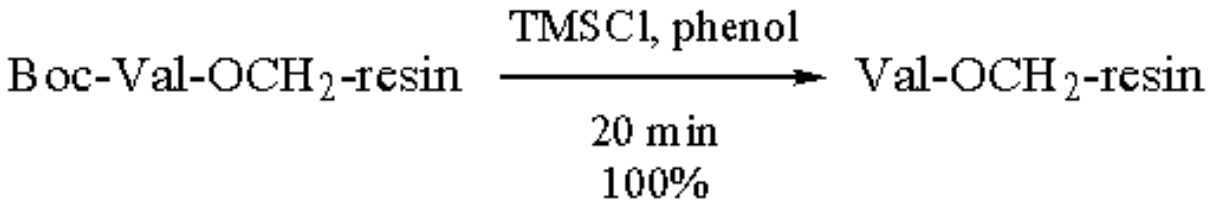

(22)

In Situ Generation of Iodotrimethylsilane.

Of the published methods used to form TMSI in situ, the most convenient involves the use of TMSCl with NaI in acetonitrile.[12] This method has been used for a variety of synthetic transformations, including cleavage of phosphonate esters (eq 23),[35] conversion of vicinal diols to alkenes (eq 24),[36] and reductive removal of epoxides (eq 25).[37]

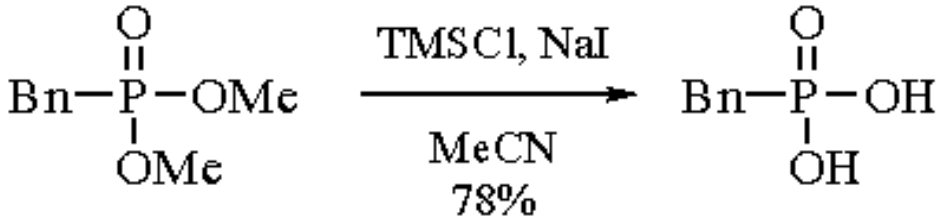

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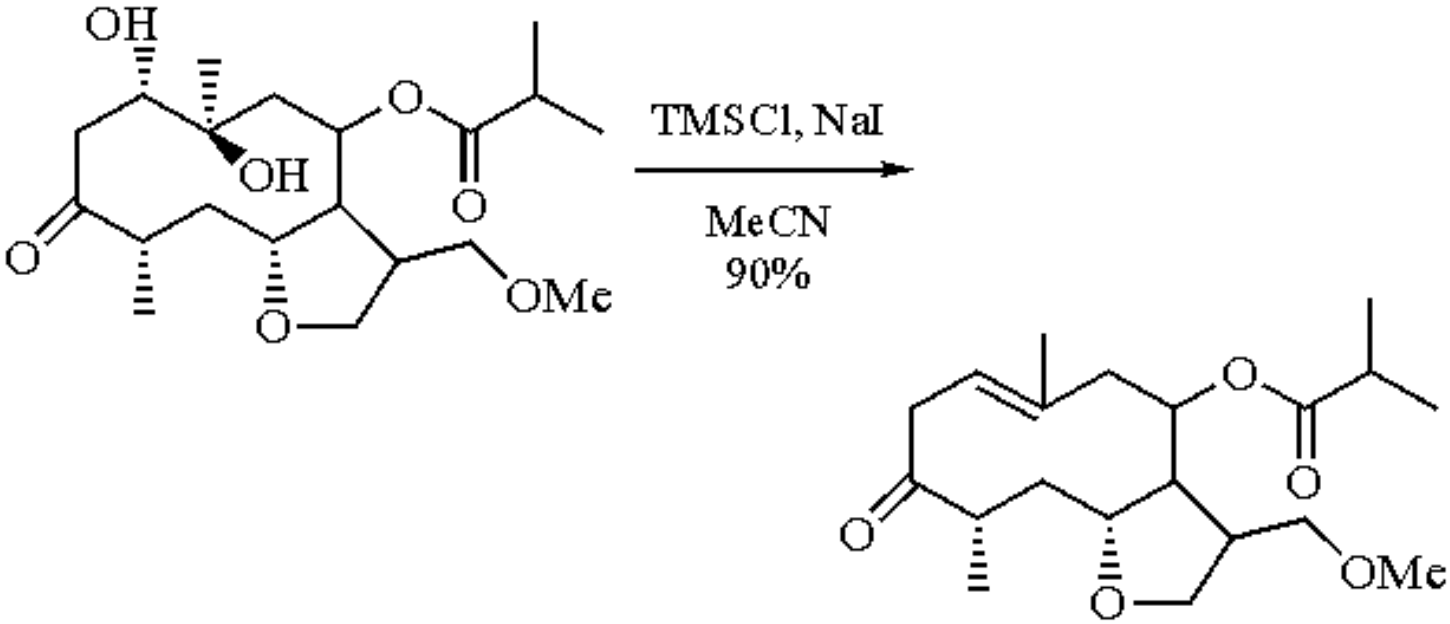

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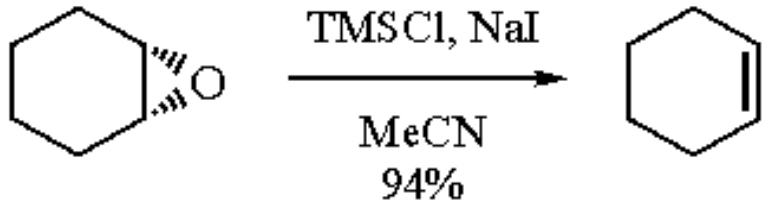

(25)

Conversion of Ketones to Vinylsilanes.

Ketones can be transformed into vinylsilanes via intermediate trapping of the vinyl anion from a Shapiro reaction with TMSCl. Formation of either the tosylhydrazone[38] or benzenesulfonylhydrazone (eq 26)[13,39] followed by reaction with *n*-butyllithium in TMEDA and TMSCl gives the desired product.

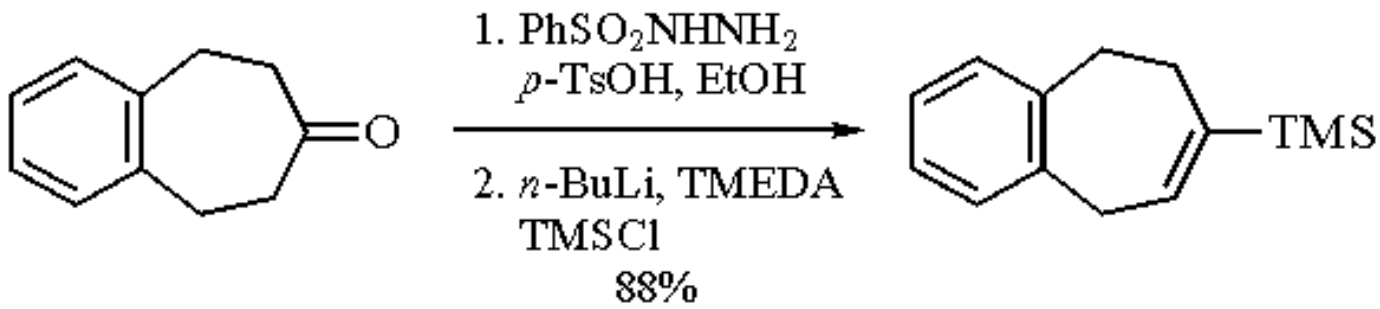

(26)

Epoxide Cleavage.

Epoxides open by reaction with TMSCl in the presence of ***Triphenylphosphine*** or tetra-*n*-butylammonium chloride to afford *O*-protected vicinal chlorohydrins (eq 27).[14]

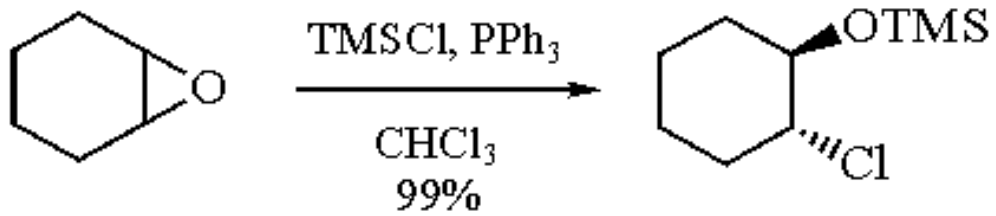

(27)

Formation of Silylvinylallenes.

Enynes couple with TMSCl in the presence of Li/ether or Mg/***Hexamethylphosphoric Triamide*** to afford silyl-substituted vinylallenes. The vinylallene can be subsequently oxidized to give the silylated cyclopentanone (eq 28).[15]

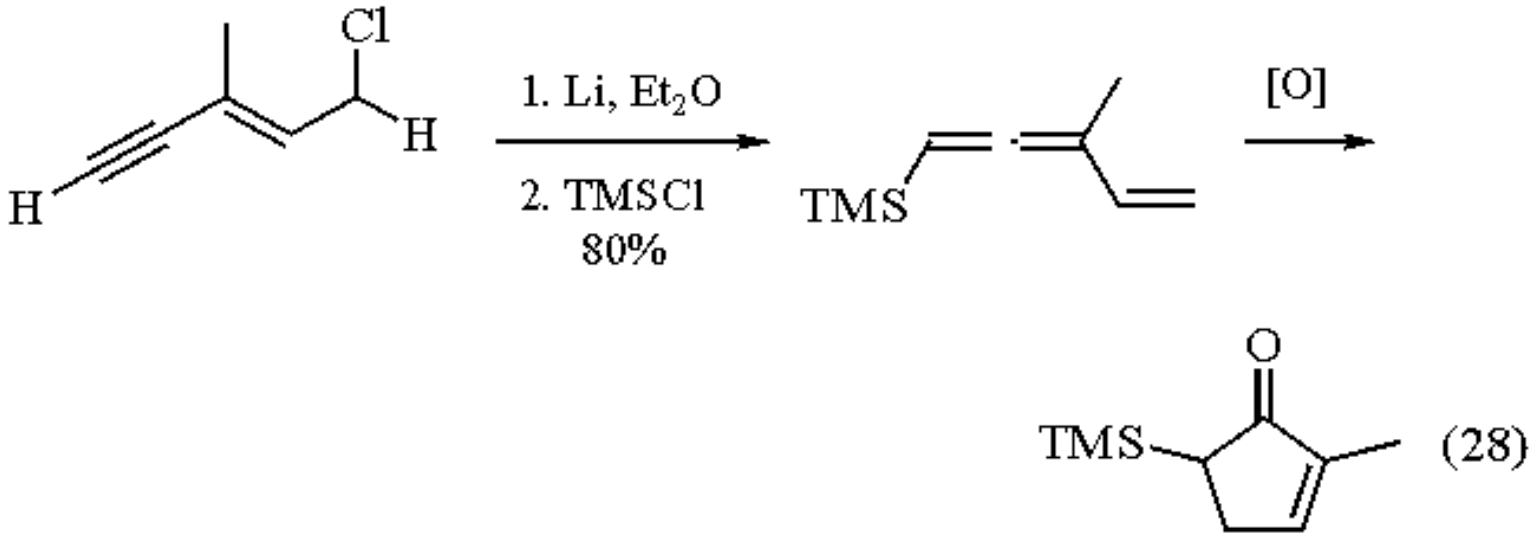

Conjugate Addition Reactions.

In the presence of TMSCl, cuprates undergo 1,2-addition to aldehydes and ketones to afford silyl enol ethers (eq 29).[16] In the case of a chiral aldehyde, addition of TMSCl follows typical Cram diastereofacial selectivity (eq 30).[16,40]

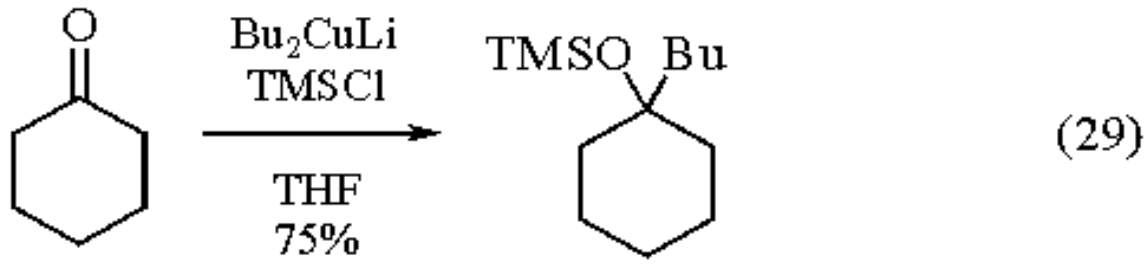

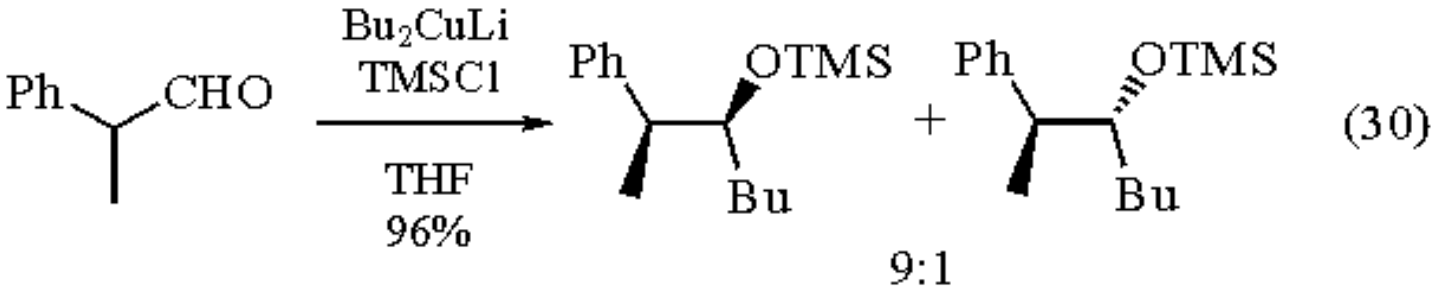

Conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds, including ketones, esters, and amides, are accelerated by addition of TMSCl to provide good yields of the 1,4-addition products (eq 31).[17,41,42] The effect of additives such as HMPA, DMAP, and TMEDA have also been examined.[18,43] The role of the TMSCl on 1,2- and 1,4-addition has been explored by several groups, and a recent report has been published by Lipshutz.[40] His results appear to provide evidence that there is an interaction between the cuprate and TMSCl which influences the stereochemical outcome of these reactions.

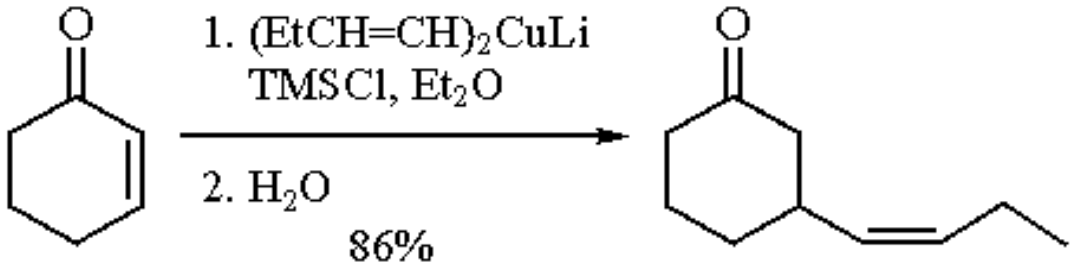

(31)

The addition of TMSCl has made 1,4-conjugate addition reactions to α-(nitroalkyl)enones possible despite the presence of the acidic α-nitro protons (eq 32).[44] Copper-catalyzed conjugate addition of Grignard reagents proceeds in high yield in the presence of TMSCl and HMPA (eq 33).[45] In some instances the reaction gives dramatically improved ratios of 1,4-addition to 1,2-addition.

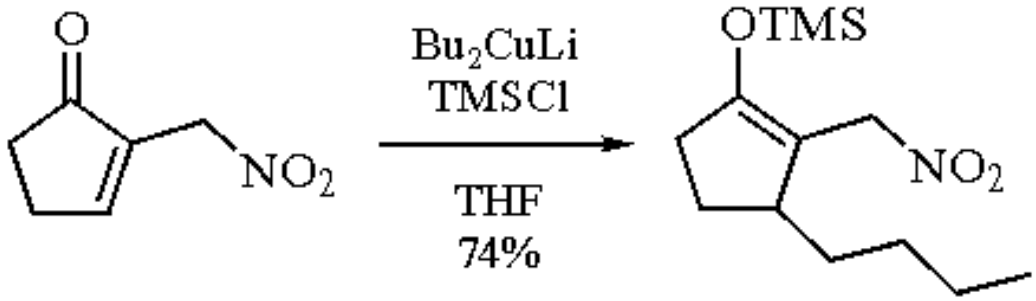

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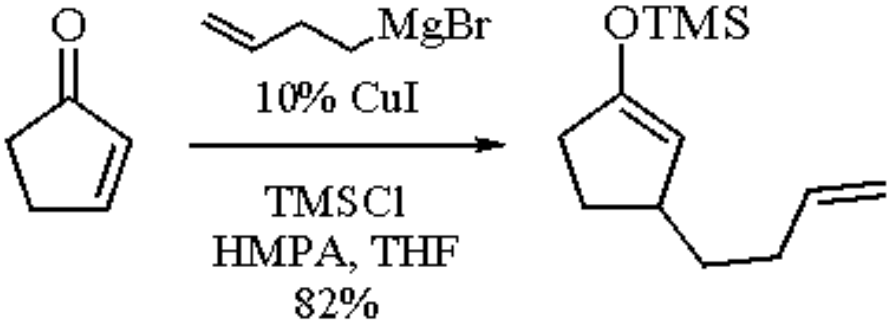

(33)

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Chloro(trimethylsilylmethyl)ketene

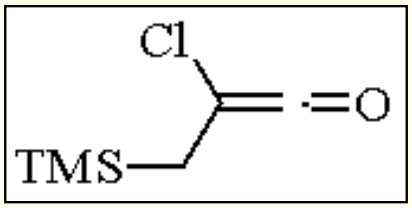

[89121-60-8] · $C_6H_{11}ClOSi$ · Chloro(trimethylsilylmethyl)ketene · (MW 162.67)

(intermediate capable of cycloadding to activated alkenes[1] for direct conversion to α-methylenecyclobutanones and -cyclopentanones[2])

Solubility: sol nonpolar organic solvents usually employed for [2 + 2] cycloadditions.

Form Supplied in: generated in situ by dehydrochlorination of the acid chloride precursor.

Chloro(trimethylsilylmethyl)ketene[2] presently stands as the preferred synthetic equivalent to the very unstable methyleneketene (CH_2=C=C=O)[3] in [2 + 2] cycloaddition reactions. Generation of the title ketene is achieved by conversion of β-(trimethylsilyl)propionic acid[4] to its acyl chloride, subsequent α-chlorination with ***N-Chlorosuccinimide*** in thionyl chloride as solvent at 70 °C,[5] and ultimate dehydrochlorination with ***Triethylamine*** (eq 1).[2] If an adequately reactive acceptor alkene is not present, the ketene is captured by the acid chloride to produce the ester shown.

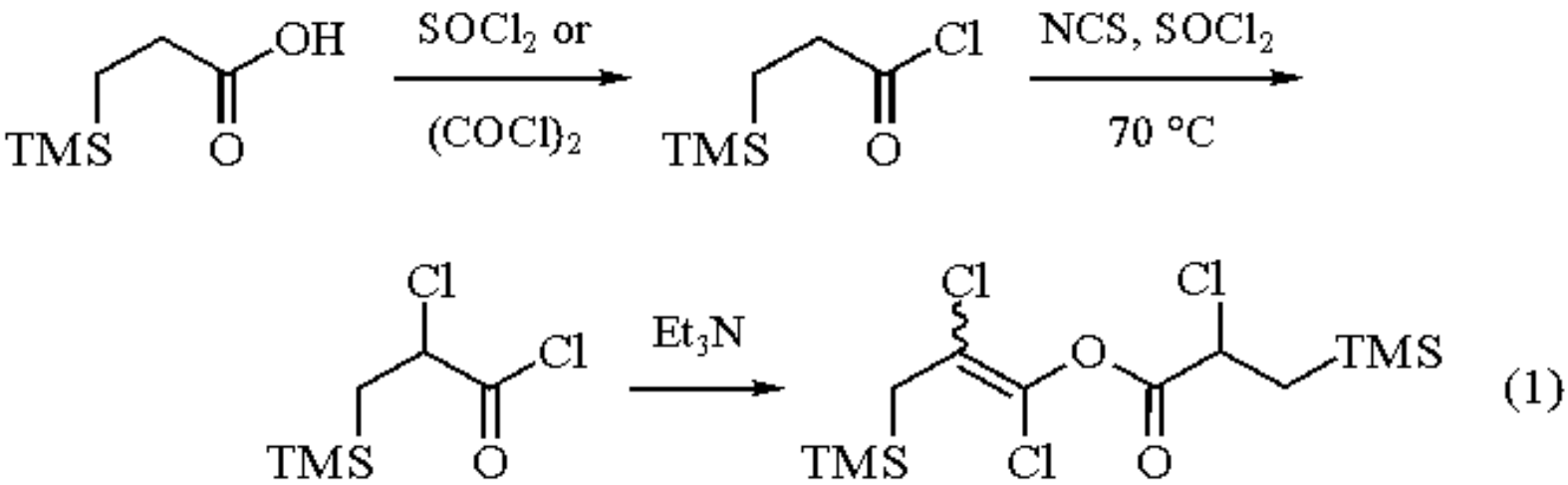

With cyclopentadiene, vinyl ethers, and silyl enol ethers, smooth [2 + 2] cycloaddition takes place in both a regio- and stereocontrolled fashion. In a manner paralleling that observed with alkyl-substituted ketenes,[6] chloro(trimethylsilylmethyl)ketene is captured with the Me_3SiCH_2 group projected into the more sterically crowded

endo environment; the chlorine atom finds itself *exo* oriented (eq 2).[2] Although the silicon atom is sterically congested, elimination in the presence of fluoride ion from ***Tetra-n-butylammonium Fluoride*** proceeds rapidly in DMSO solution at 20 °C to give the annelated 2-methylenecyclobutanone derivative. Treatment of the initial adduct with ethereal ***Diazomethane*** results in ring expansion via 1,2-shift of the nonhalogenated carbon atom.[7] Comparable treatment of this product with F^- leads to the methylenecyclopentanone.

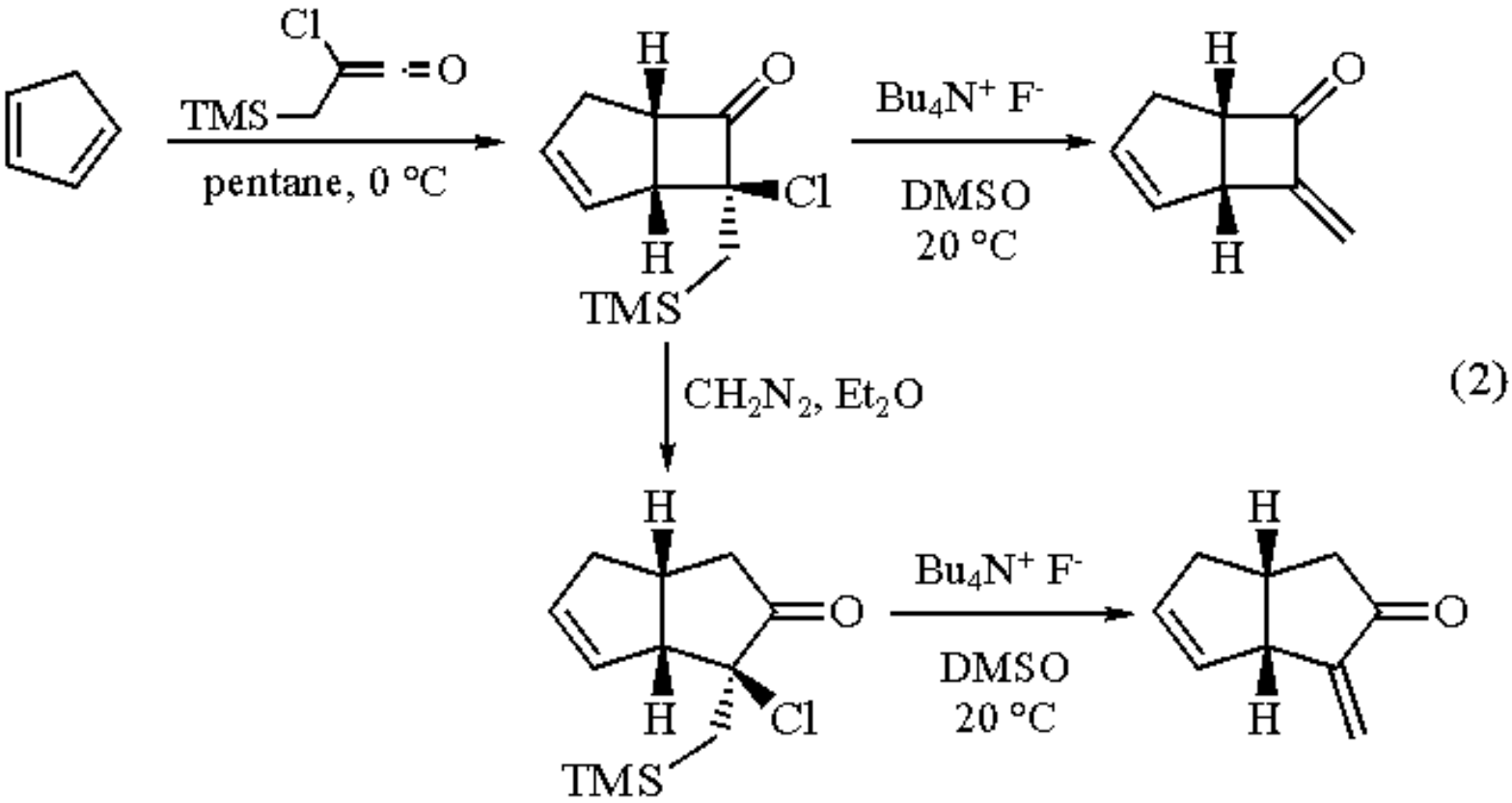

The same chemical behavior is exhibited by vinyl ethers, as illustrated for the dihydropyran adduct in (eq 3).[2] As seen before, the high level of α-substitution does not deter attack by diazomethane. Attempts to accomplish analogous Baeyer-Villiger ring expansions have failed.

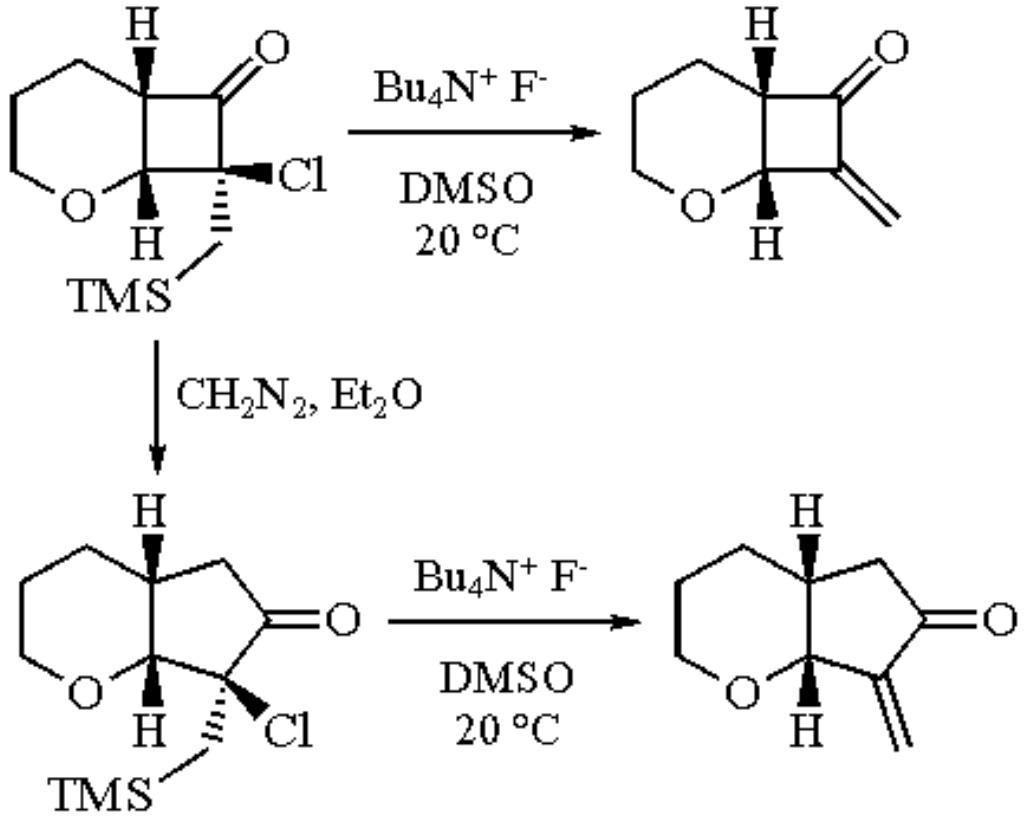

(3)

When silyl ethers are the co-reactants, more highly functionalized, angularly hydroxylated products are obtained following mild acidic hydrolysis (eq 4).

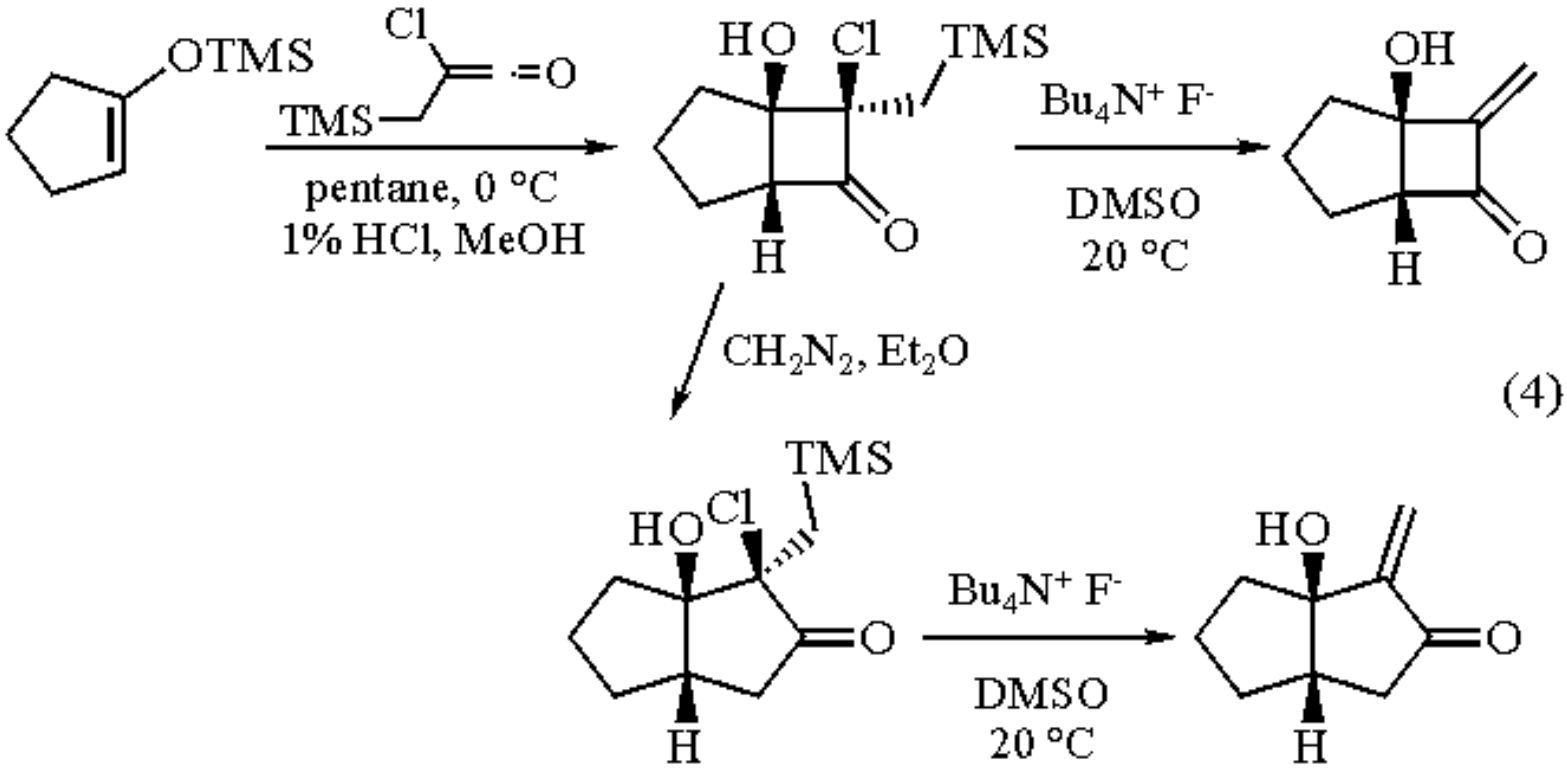

(4)

Although methyl(phenylthiomethyl)ketene enters satisfactorily into analogous [2 + 2] cycloaddition, the conditions required for reductive elimination appear too vigorous for implementation with polyfunctional molecules.[8,9]

Related Reagents.

Dichloroketene; ***Diphenylketene***.

---

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3-Chloro-2-trimethylsilyloxy-1-propene[1]

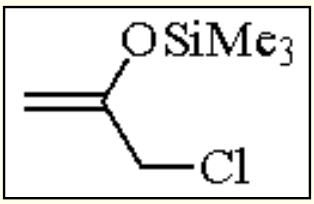

[76634-95-2] · $C_6H_{13}ClOSi$ · 3-Chloro-2-trimethylsilyloxy-1-propene · (MW 164.71)

(used for silyl enol ether synthesis;[2] electrophilic acetonylation reagent[3])

Physical Data: 61-63 °C/35-37 mmHg.

Solubility: sol common organic solvents but avoid hydroxylic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: a mixture of 16.5 g (0.10 mol) of 3-chloro-1-(trimethylsilyl)propan-2-one and 454 mg (1.0 mmol) of mercury(II) iodide was heated at 75-85 °C for 72 h. The mixture was distilled to give 13 g of 3-chloro-2-trimethylsilyloxy-1-propene.[2] Alternatively, isomerization of 3-chloro-1-(trimethylsilyl)propan-2-one with ***Tetrakis(triphenylphosphine)nickel(0)*** gave the product in 90% yield.[3]

Purification: by distillation.

Handling, Storage, and Precautions: can be stored in a glass bottle under nitrogen. The reagent must be protected from moisture. The reagent should be handled in a well-ventilated hood and contact with the skin and eyes should be avoided.

Synthesis of Silyl Enol Ethers via Alkylation Reactions.

Alkylation and arylation of 3-chloro-2-trimethylsilyloxy-1-propene with lithium dialkyl- and diarylcuprate, respectively, gives silyl enol ethers in a regiospecific manner (eq 1).[2]

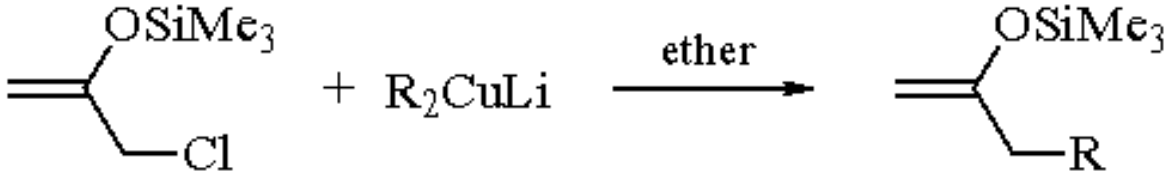

(1)

R = Me, 96%; Bu, 74%; Ph, 79%

Electrophilic Acetonyl Equivalent.[4]

α-Metalated imines, hydrazones, and activated methylene compounds are acetonylated with 3-chloro-2-trimethylsilyloxy-1-propene in high yield (eq 2).

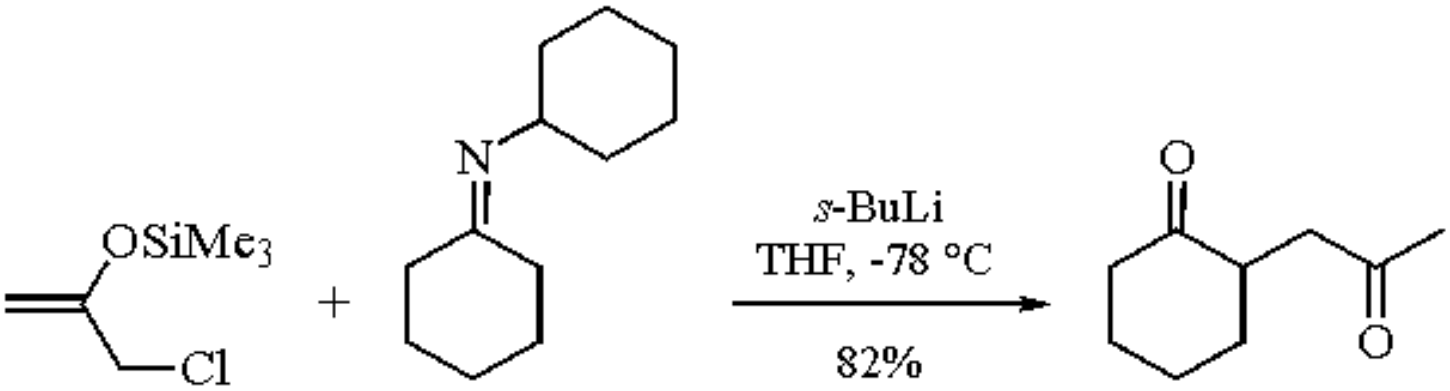

(2)

Highly regioselective acetonylation at either the tertiary or secondary α-carbon of 2-methylcyclohexanone can be achieved by selecting the optimal nitrogen substituent (eqs 3-5).

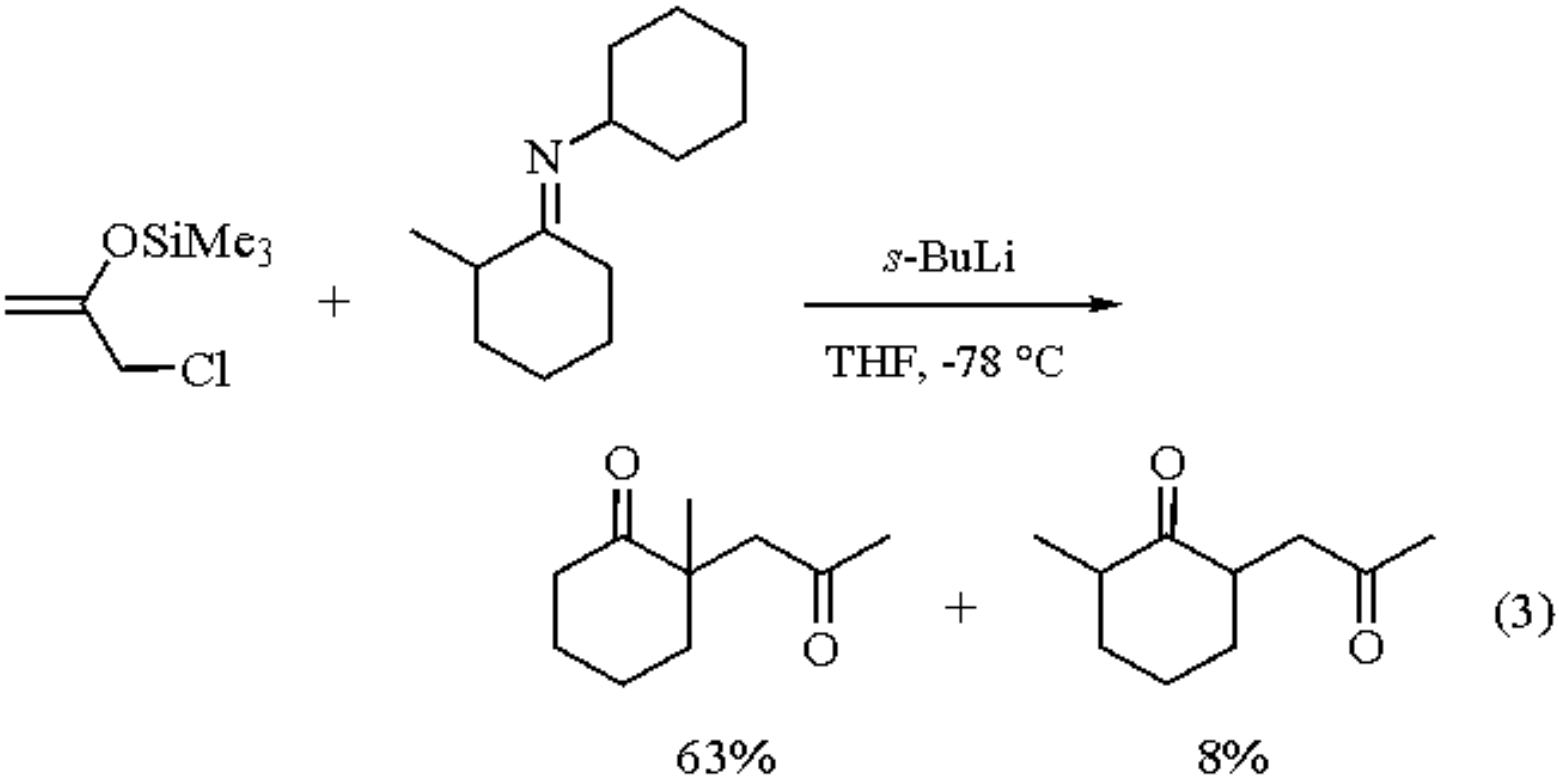

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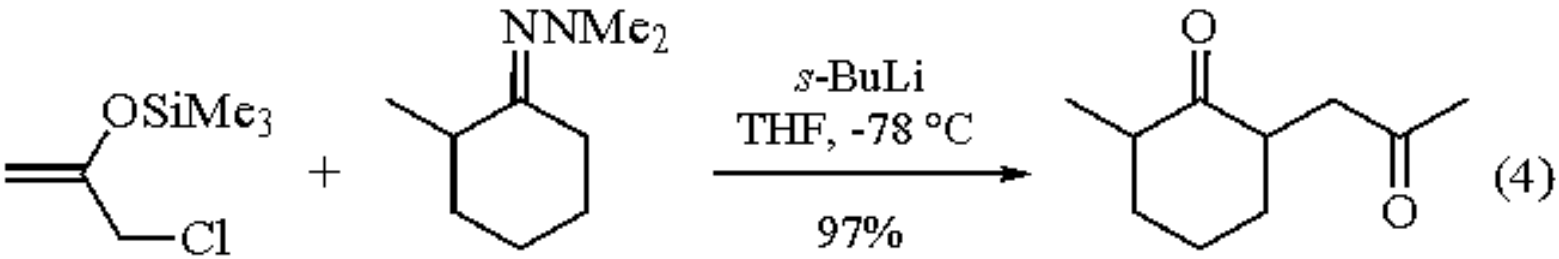

(4)

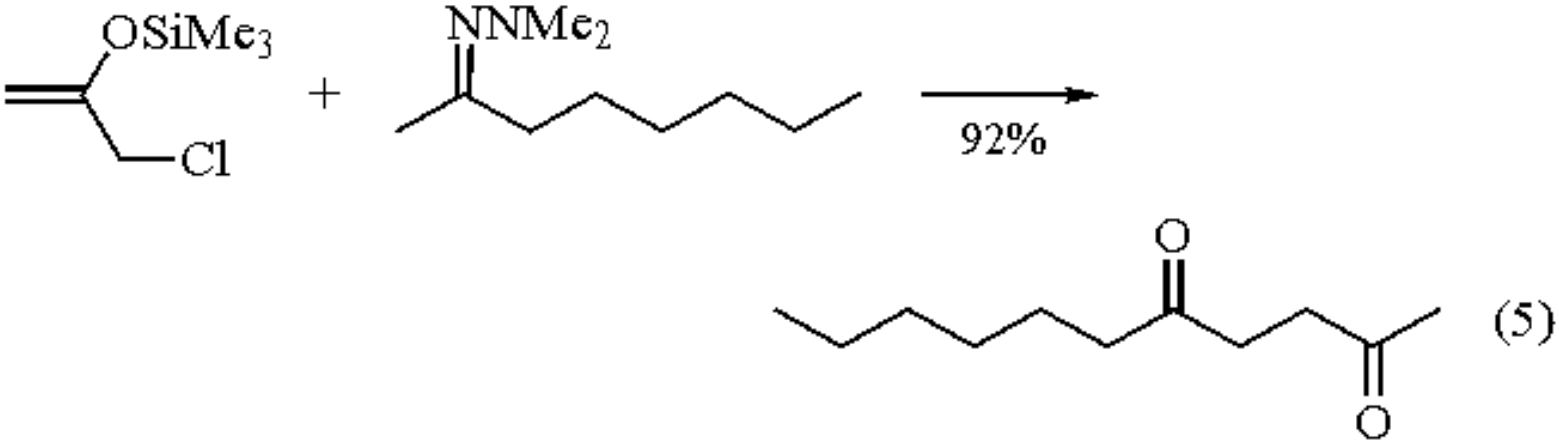

(5)

Formation of Imino Ketones.

Reaction of the title reagent with *N*-acetoxyaminoquinazolone gave the corresponding chloro ketone, which was converted to an imino ketone (eq 6).[5]

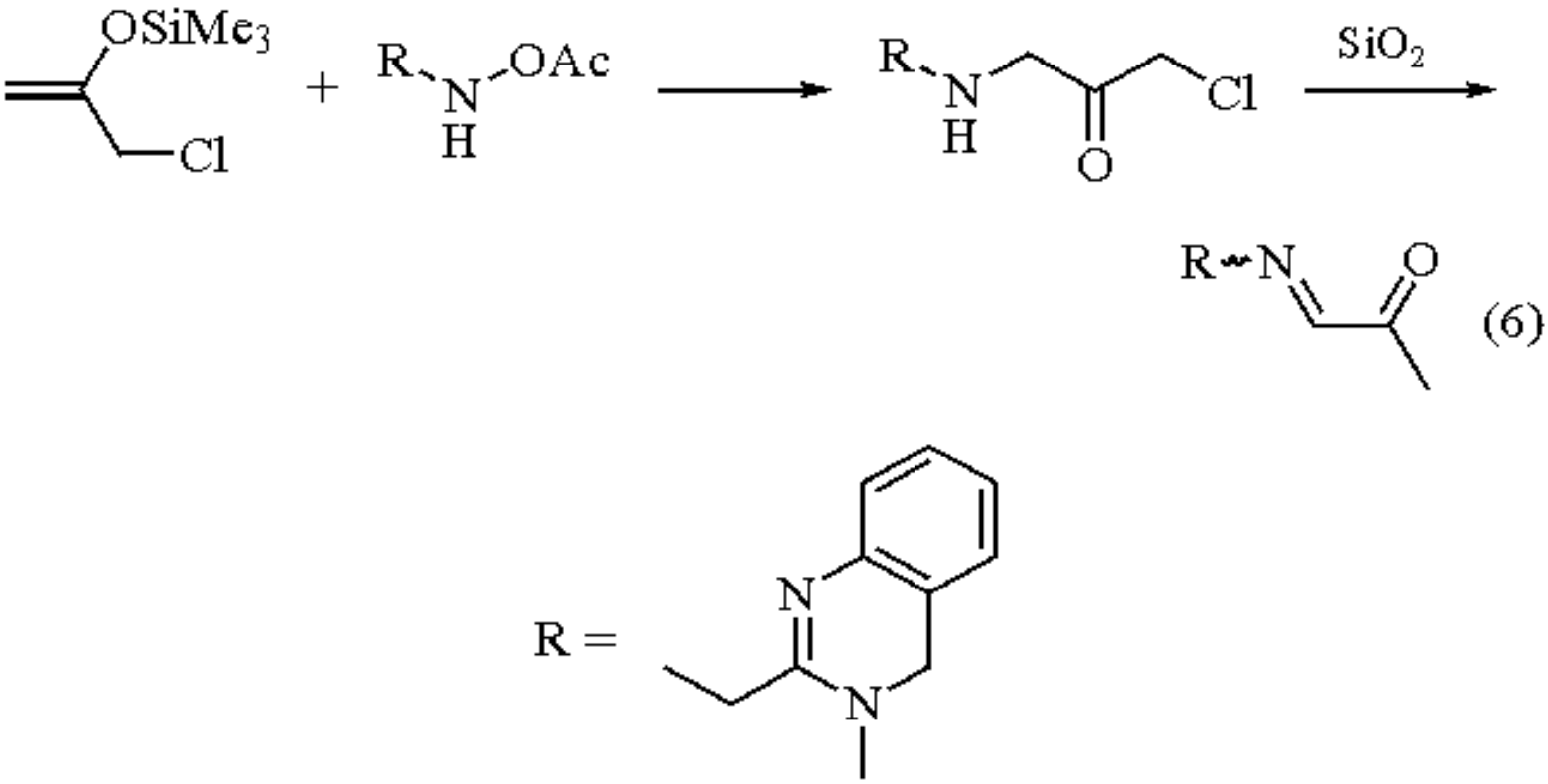

Reaction with Transition Metal Complexes.

3-Chloro-2-trimethylsilyloxy-1-propene can be a precursor of oxyallyl cations or a formal analog of trimethylenemethane. The reaction with ***Nonacarbonyldiiron*** gives the (oxodimethylidenemethane)iron dimer $[(MeCOMe)(CO)_3Fe]_2$.[6] A similar (η^3-2-trimethylsiloxyallyl)$Fe(CO)_2NO$ complex was also prepared.[7] Os, Ir, and Pt carbonyls gave the corresponding metallacyclobutan-3-ones.[2a]

Cycloaddition.

The reaction of an analog, 3-bromo-3-methyl-2-trimethylsiloxy-1-butene, with 1,3-dienes in dichloromethane in the presence of ***Zinc Chloride*** gave cycloheptenones as [3 + 4] cycloaddition products in good to excellent yields (eqs 7 and 8).[8] Styrene derivatives give [3 + 2] cycloadducts as major products. For example, 2-(*p*-methylphenyl)-1-propene affords an aromatic sesquiterpene, α-cupranone, and its regiosomer (eq 9).

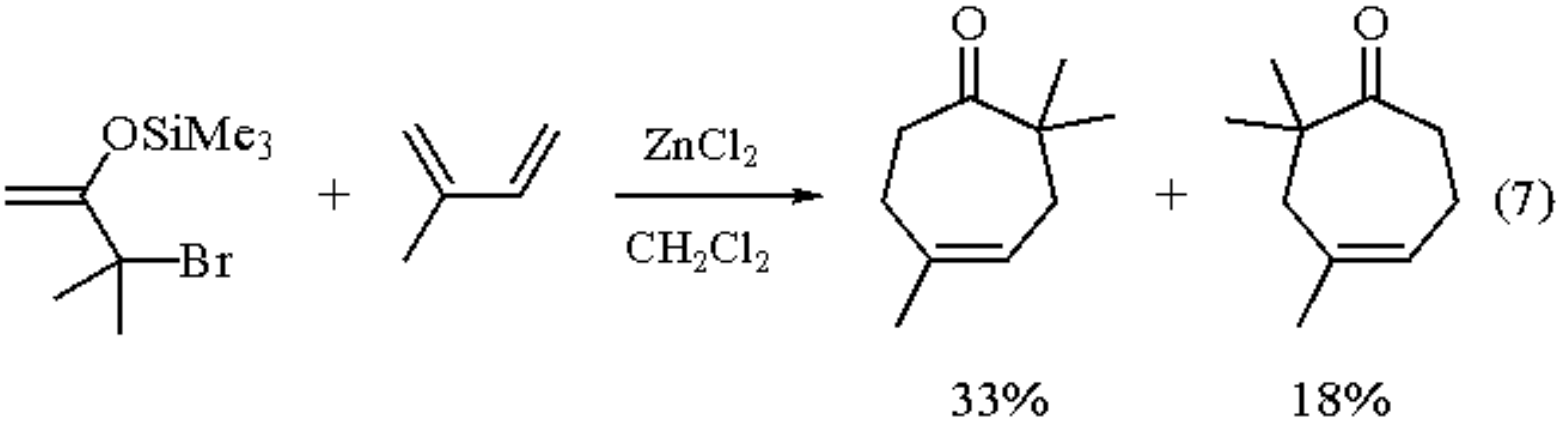

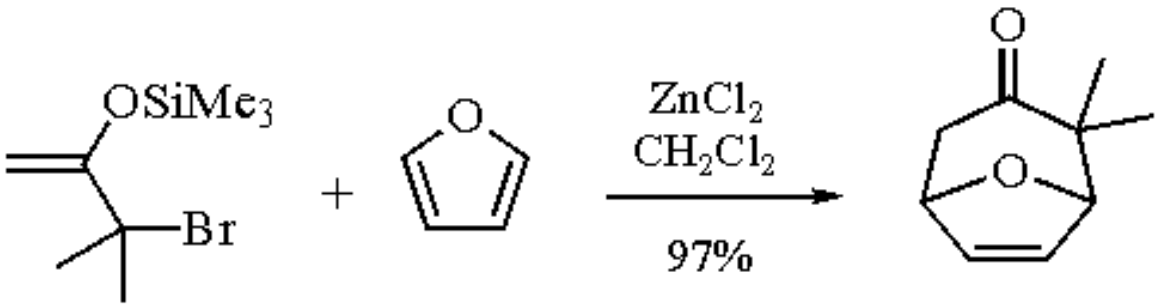

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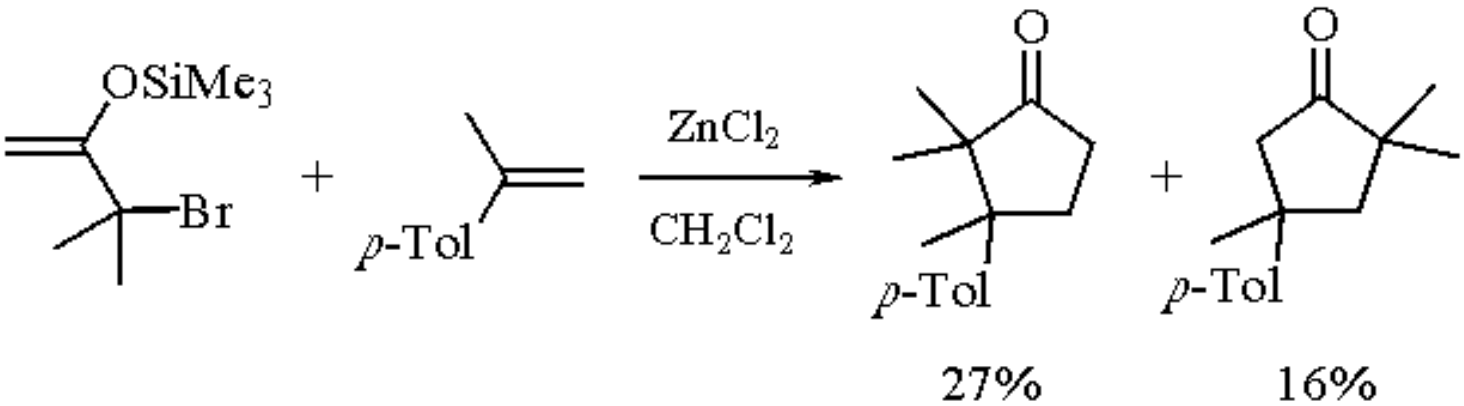

(9)

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Chlorotrimethylstannane

Me_3SnCl

[1066-45-1] · C_3H_9ClSn · Chlorotrimethylstannane · (MW 199.25)

(starting material for the synthesis of alkyl-, allyl-, alkenyl-, and alkynyltrimethylstannanes and trimethyltin enolates; palladium-catalyzed coupling reactions[14])

Alternate Name: trimethyltin chloride.

Physical Data: mp 37-39 °C; bp 153-156 °C.

Solubility: sol ether, THF, hexane, CH_2Cl_2.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: is air stable, but is decomposed by moisture. Commercially available trimethyltin chloride may be used as received. The reagent is very toxic and corrosive, and should be handed with gloves in a fume hood.

Introduction.

Trimethyltin hydride, cyanide, methoxide, azide, and lithium are prepared from trimethyltin chloride by the procedures similar to those given in ***Tri-n-butylchlorostannane***. Similarly, hexamethylditin, bis(trimethyltin) oxide, and diethylaminotrimethyltin are prepared from trimethyltin chloride.

Organotrimethyltins via Transmetalation.

Lithiated 1,3-dithianes react with trialkyltin or triphenyltin chlorides to form the corresponding 1,3-dithian-2-yltin compounds.[1] The organocopper compound, derived from (α-(dialkoxyboryl)alkyl)zinc iodide and CuCN.2LiCl, reacts with trimethyltin chloride to afford the α-boron substituted organotin in 87% yield (eq 1).[2] Accordingly, sulfur- and boron-stabilized anions are readily converted to the corresponding trimethyltin derivatives.

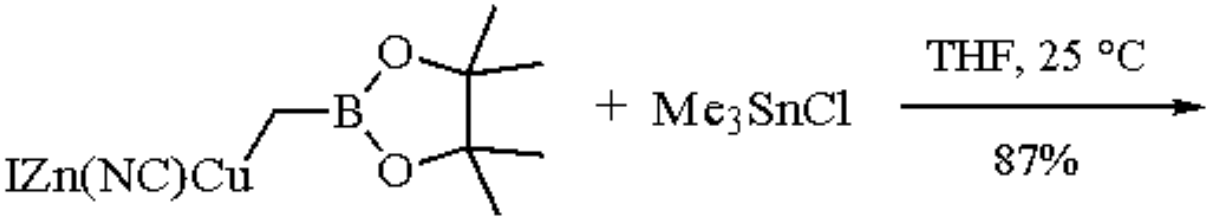

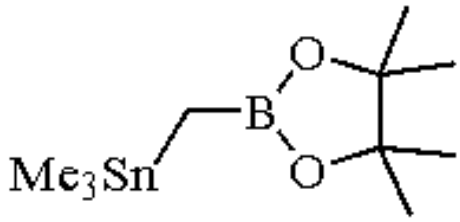

(1)

Allyl anions are also transformed to the corresponding allyltrimethyltin derivatives in high yields. Allyl anions substituted by 9-BBN, generated from ***B-Allyl-9-borabicyclo[3.3.1]nonane*** by treatment with ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LTMP) react with trimethyltin chloride to afford the α-trimethyltin-substituted allyl-9-BBN in good yields (eq 2).[3] Trimethyltin bromide may also be used in this procedure. The resulting allylic borane reacts with aldehydes in the presence of pyridine to produce the *anti*-homoallyl alcohols with a (*Z*)-alkenyltrimethylstannyl group (eq 3)[4] (see also ***9-[1-(Trimethylsilyl)-2(E)-butenyl]-9-borabicyclo[3.3.1]nonane***). γ-Chloro-substituted allyltrimethyltins are prepared by the reaction of trimethyltin chloride with chloro-substituted allyllithiums, which are generated from allyl chlorides and LTMP.[5] 2,4-Pentadienyltrimethylstannane, prepared by the reaction of pentadienyllithium with trimethyltin chloride, reacts with *p*-quinones in the presence of $BF_3.OEt_2$ to afford the corresponding pentadienylated conjugate adducts in fair to good yields without formation of the Diels-Alder adduct (eq 4).[6] On the other hand, the use of 2,4-pentadienyltrimethylsilane produces the Diels-Alder adduct exclusively. The tin reagent produces the conjugate adducts with *p*-quinones, regardless of the substituents and their substitution pattern. With α,β-unsaturated aldehydes, the pentadienyl tin reagent gives the 1,2-adducts (pentadienyl carbinols), whereas the 1,4-adduct is obtained with chalcone.[6] Here also, the reaction of pentadienyltrimethylsilane with crotonaldehyde affords the corresponding Diels-Alder adduct.[7]

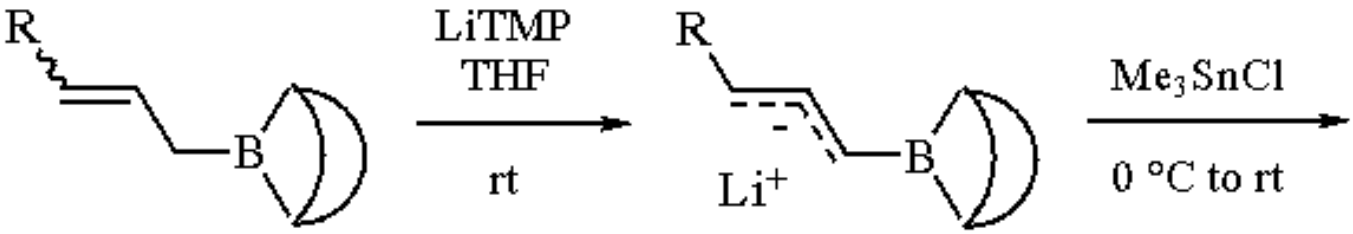

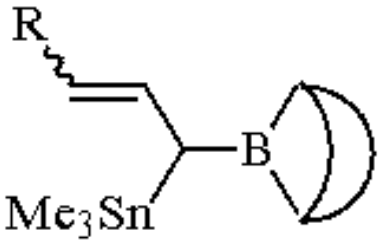

(2)

R = Bu, 70%; Me, 72%

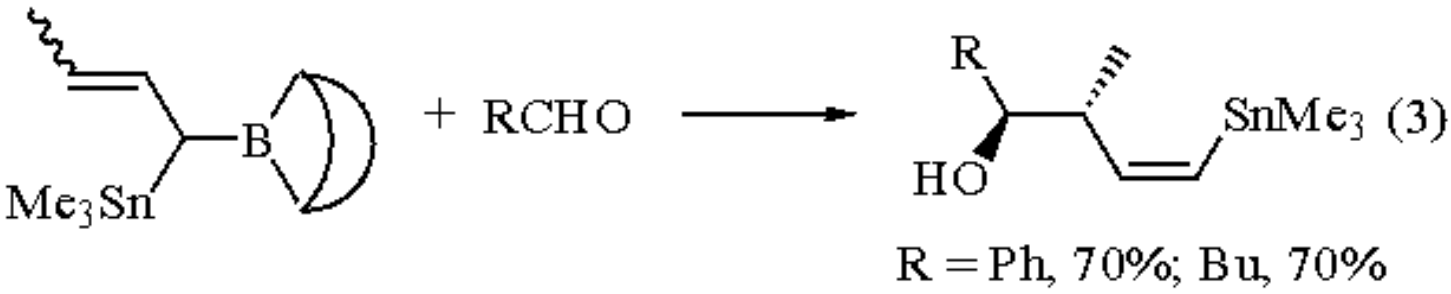

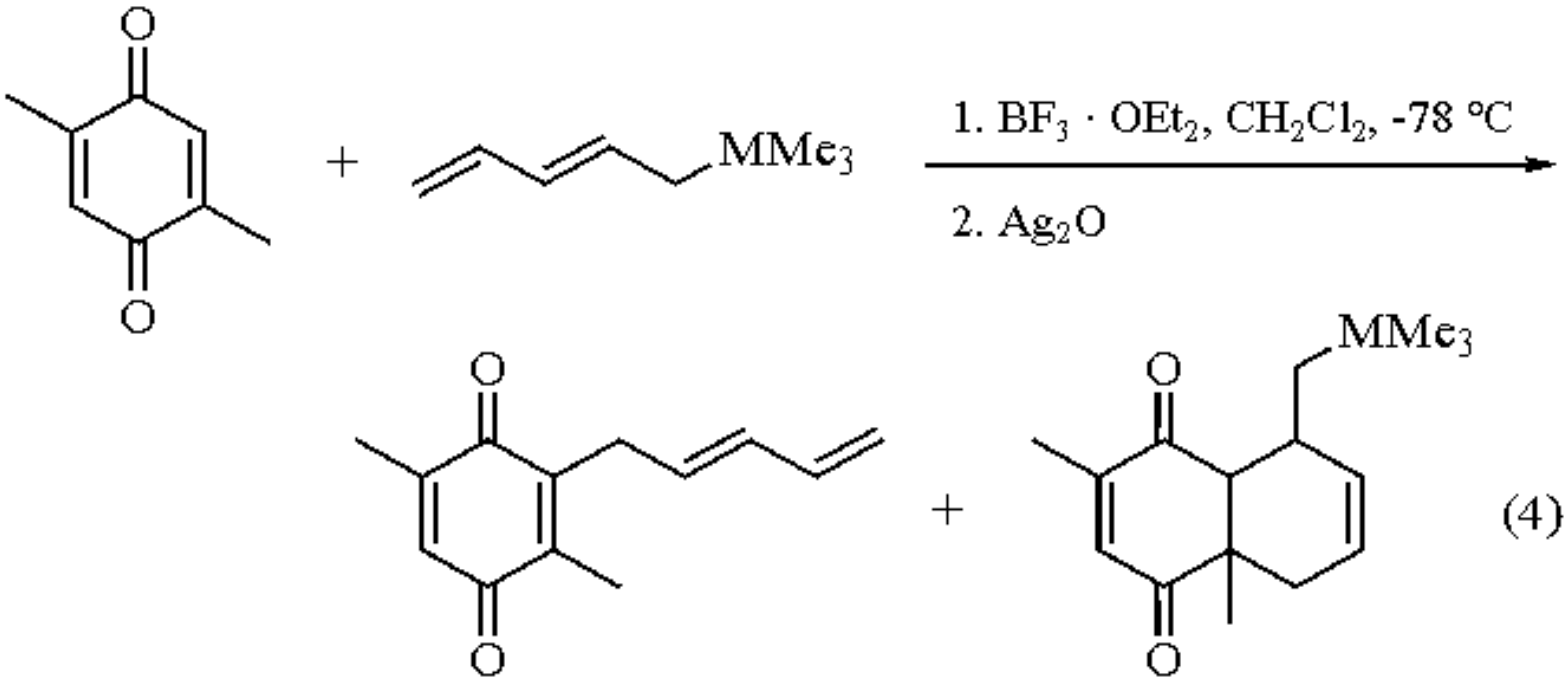

M = Sn	86%	0%
M = Si	0%	91%

The intramolecular transfer reaction of lithium 1-alkynyltrialkylborates, prepared in situ from lithium acetylides and trialkylboranes, induced by trimethyltin chloride is highly stereoselective, with the resultant dialkylboryl-substituted alkenylstannanes having the migrating alkyl group *trans* to the trialkyltin group (eq 5).[8] Conversion of the resulting dialkylboryl group (R = Et) to the alkenylcopper followed by treatment with methanol or alkyl halides produces di- or trisubstituted alkenyltrimethylstannanes, respectively (eq 6).[9] By starting from conjugated terminal enynes, 2-(trimethylstannyl)-1,3-butadienes are similarly synthesized.

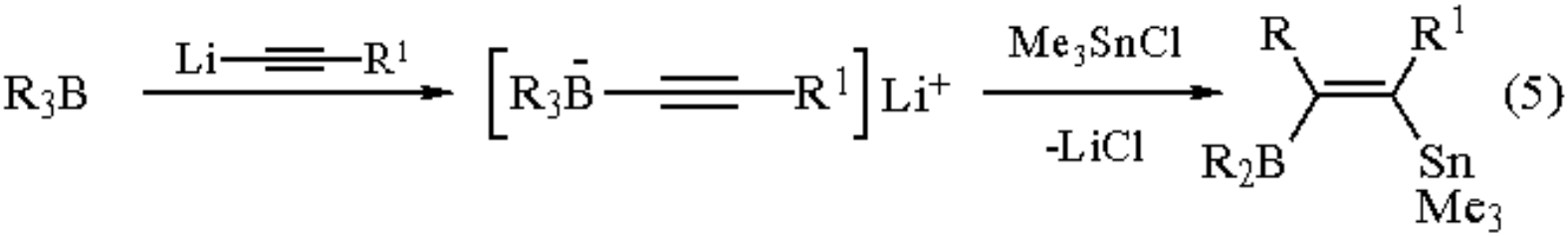

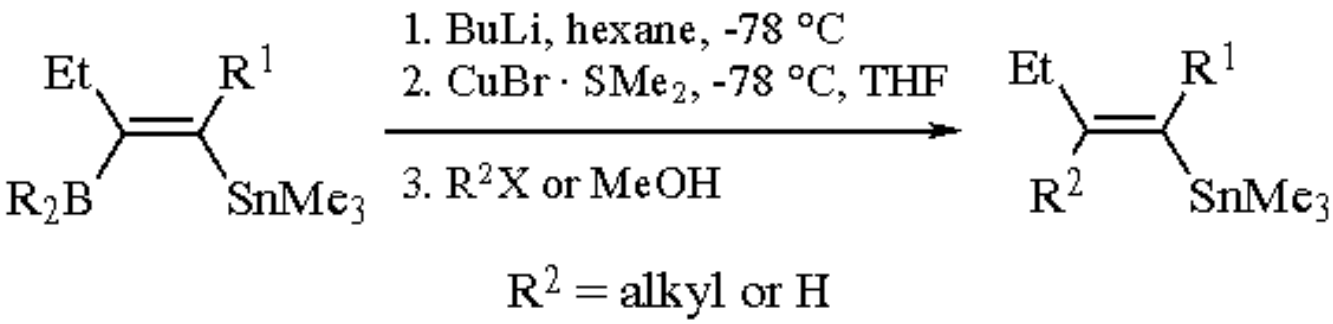

Alkenylstannanes have been utilized for a variety of synthetic applications. The palladium-catalyzed coupling reaction of vinyl triflates and vinyl halides with alkenylstannanes affords 1,3-dienes.[10] The facile transmetalation reaction between alkenylstannanes and alkyllithiums remains as one of the most direct routes to certain alkenyllithium reagents. Treatment of alkenylstannanes with iodine affords the corresponding vinyl iodides with retention of configuration of the vinyl group.

Although the hydrostannylation reaction of alkynes provides a simple route to alkenylstannanes, it is generally not stereoselective. The addition reaction of (trialkylstannyl)copper and related reagents to 1-alkynes and α,β-alkynic esters and amides exhibits high regio- and stereoselectivity.[11] Vinyl triflates and vinyl iodides have also been converted to alkenylstannanes by the reaction with $Me_3SnMgMe$ in the presence of ***Copper(I) Cyanide*** catalyst.[11b] The hydroalumination of alkynes with ***Diisobutylaluminum Hydride*** followed by treatment with ***Methyllithium*** yields alanates, which are converted to alkenyltrimethylstannanes by addition of trimethyltin chloride (see also ***Tri-n-butylchlorostannane***).[12] Generally, conversion of vinylalanes to alanates (ate complexes) is needed to enhance the reactivity toward electrophiles such as Me_3SnCl. The direct transmetalation of vinylalanes to vinylstannanes is accomplished by carrying out the reaction with Me_3SnCl in the presence of LiX (X = Cl, Br, I) in DME.[13]

Palladium-Catalyzed Reactions.

Benzylchlorobis(triphenylphosphine)palladium(II) catalyzes the reaction of acid chlorides with tetraorganotin compounds (Me_4Sn, Ph_4Sn, Ph_3SnMe, Me_3SnCH_2Ph, $(PhCH_2)_4Sn$, Bu_4Sn, $Bu_3SnCH{=}CH_2$, Me_3SnCl) to give ketones in quantitative yields (eq 7).[14] Trimethyltin chloride (1 equiv) also reacts with benzoyl chloride to give acetophenone in quantitative yield, although the reaction takes five times longer to reach completion than the reaction using ***Tetramethylstannane***. By using a trimethyl- or tributylorganotin reagent, the group other than the methyl or butyl groups transfers exclusively in the following order:
RC&tbond;C > RCH=CH > aryl > $RCH{=}CHCH_2$ &AApprox; $arylCH_2$ > $MeOCH_2$.

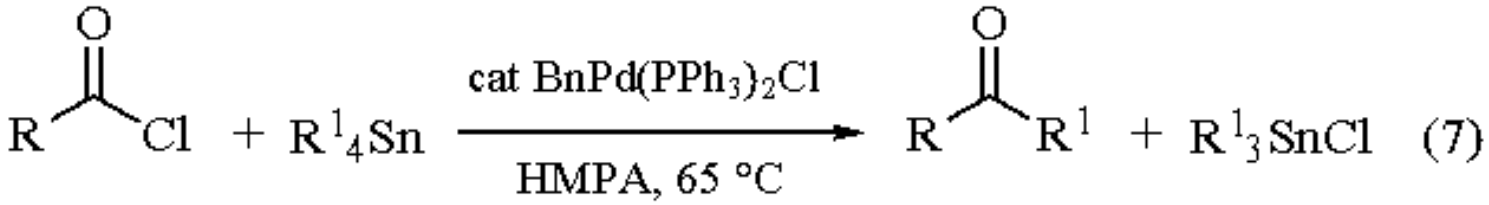

The palladium-catalyzed coupling of alkenyl iodides with alkynyltrimethylstannanes takes place under mild conditions, stereospecifically and chemoselectively, to give high yields of conjugated enynes (eq 8).[15] Organic groups on tin undergo selective transmetalation with palladium, as shown above, and the alkynic group has the fastest transfer rate of all the organic substituents.

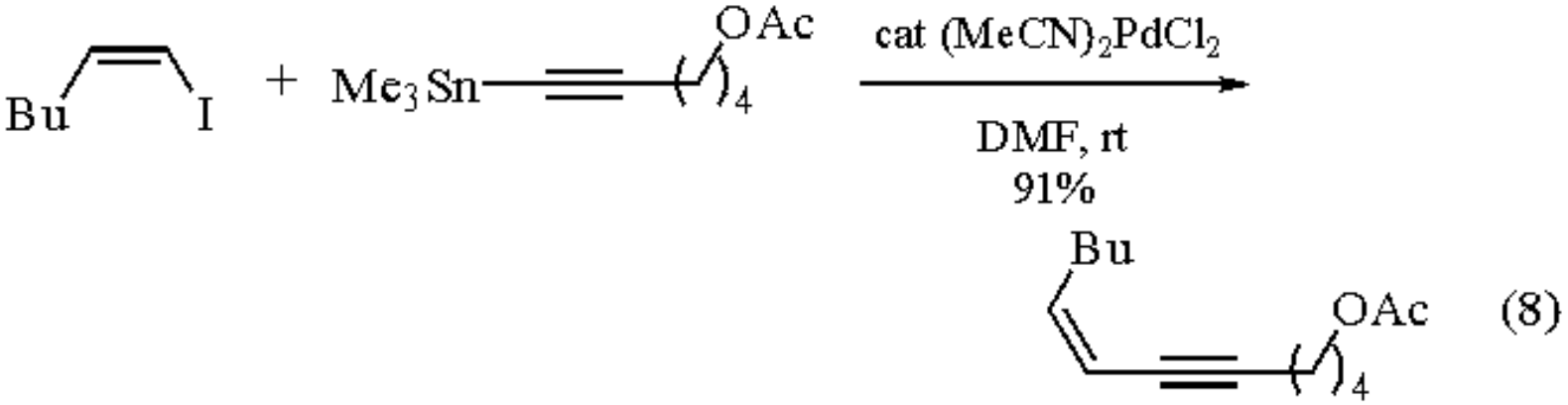

Trimethyltin Enolates.

Trimethyltin enolates, prepared in situ from lithium enolates and trimethyltin chloride, undergo a rapid aldol condensation with aldehydes to give nearly a 1:1 mixture of the *syn* and *anti* aldols in high yields.[16] However, the trimethyltin enolate generated in situ from the lithium enolate of 4-thianone gives the *anti* aldol with very high diastereoselectivity upon treatment with 2-methylpropanal (eq 9).[17] The lithium enolate itself also provides high *anti* diastereoselectivity (95:5) in this case.

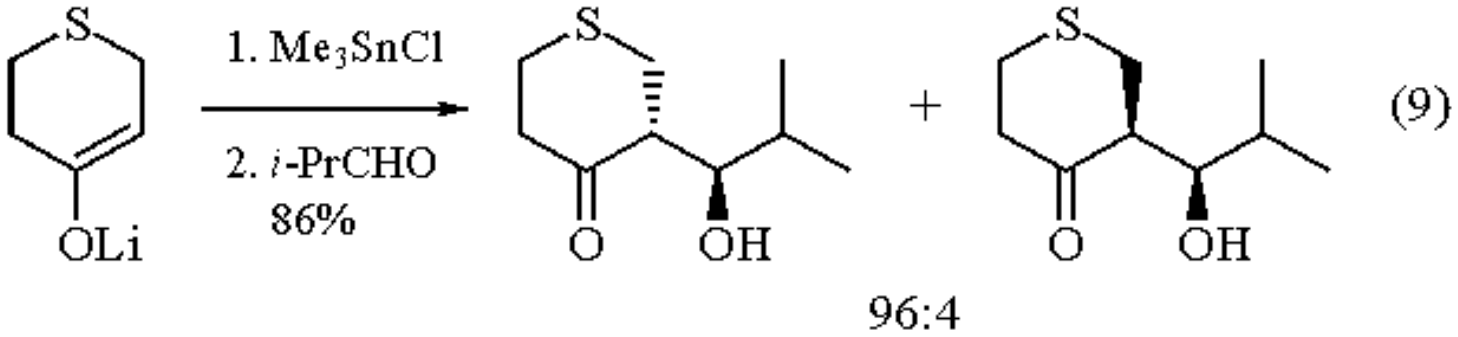

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4-Chloro-2-trimethylstannyl-1-butene

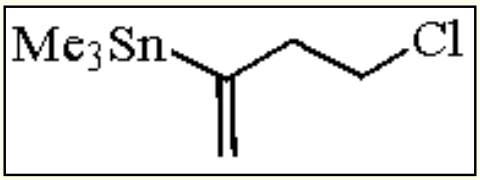

[85370-32-7] · $C_7H_{15}ClSn$ · 4-Chloro-2-trimethylstannyl-1-butene · (MW 253.34)

(precursor of a number of bifunctional reagents,[1,2] which have been employed for effecting synthetically useful methylenecyclopentane annulation sequences[1-4])

Physical Data: colorless liquid, distillation temperature (bulb-to-bulb) 55-60 °C/12 mmHg.

Solubility: insol H_2O; sol THF, Et_2O, $CHCl_3$, and other common organic solvents.

Preparative Methods: 4-chloro-2-trimethylstannyl-1-butene (**3**) is readily prepared from the commercially available butynol (**1**). Regioselective addition of $Me_3SnCu.Me_2S$[5] (see ***Trimethylstannylcopper-Dimethyl Sulfide***) to (**1**) provides[6] 3-trimethylstannyl-3-buten-1-ol (**2**), which upon reaction with Ph_3P-CCl_4 in the presence of Et_3N affords (**3**) (eq 1). This preparative sequence can be carried out on a reasonably large scale (0.2 mol) and produces overall yields of about 50%.

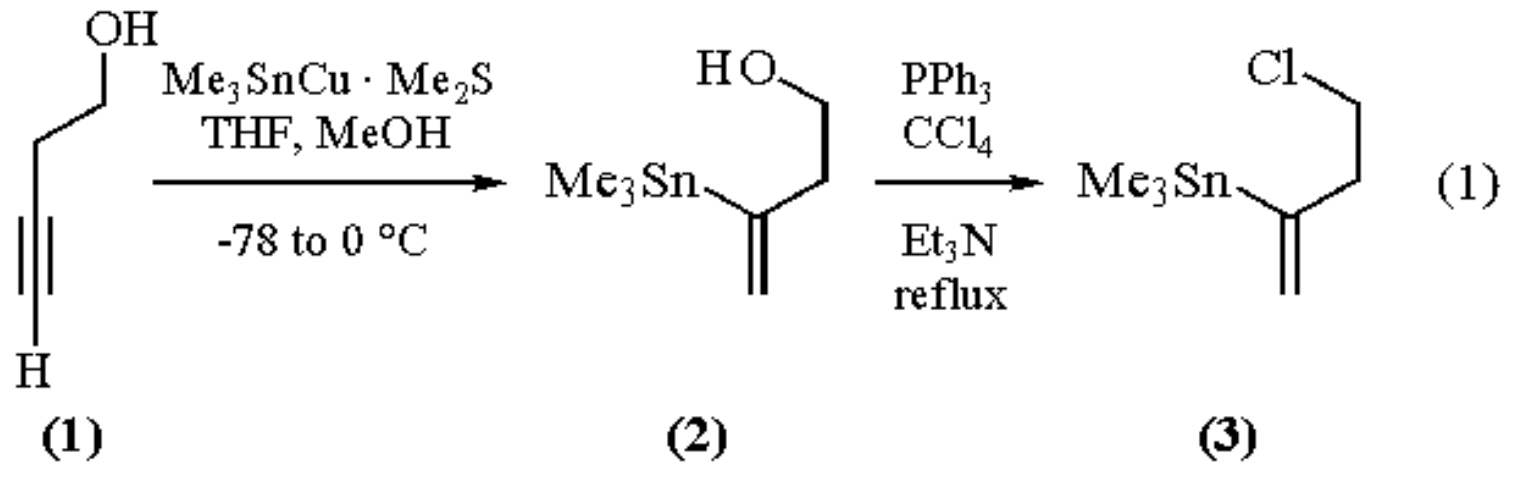

Handling, Storage, and Precautions: when stored in a freezer under an atmosphere of argon the reagent is stable for extended periods of time (years). It should be distilled prior to use and handled only in a well-ventilated fume hood.

Conversion into Bifunctional Reagents.

Reagent (**3**) is an effective precursor to a number of synthetically useful bifunctional reagents. Transmetalation[7] of (**3**) with MeLi in THF at low temperature provides the novel reagent (**4**) (eq 2).[1] The latter species is stable in THF if the temperature of the solution is kept below -50 °C. At higher temperatures, (**4**) self-destructs,[2] presumably[8b] to produce LiCl and methylenecyclopropane. Treatment of (**4**) with $MgBr_2$,[1c] $CuBr.Me_2S$ (0.5 equiv),[2] CuCN,[1b,c] or PhSCu[1b,c] produces, respectively, the Grignard reagent (**5**), the homocuprate (**6**), and the heterocuprates (**7**) and (**8**).

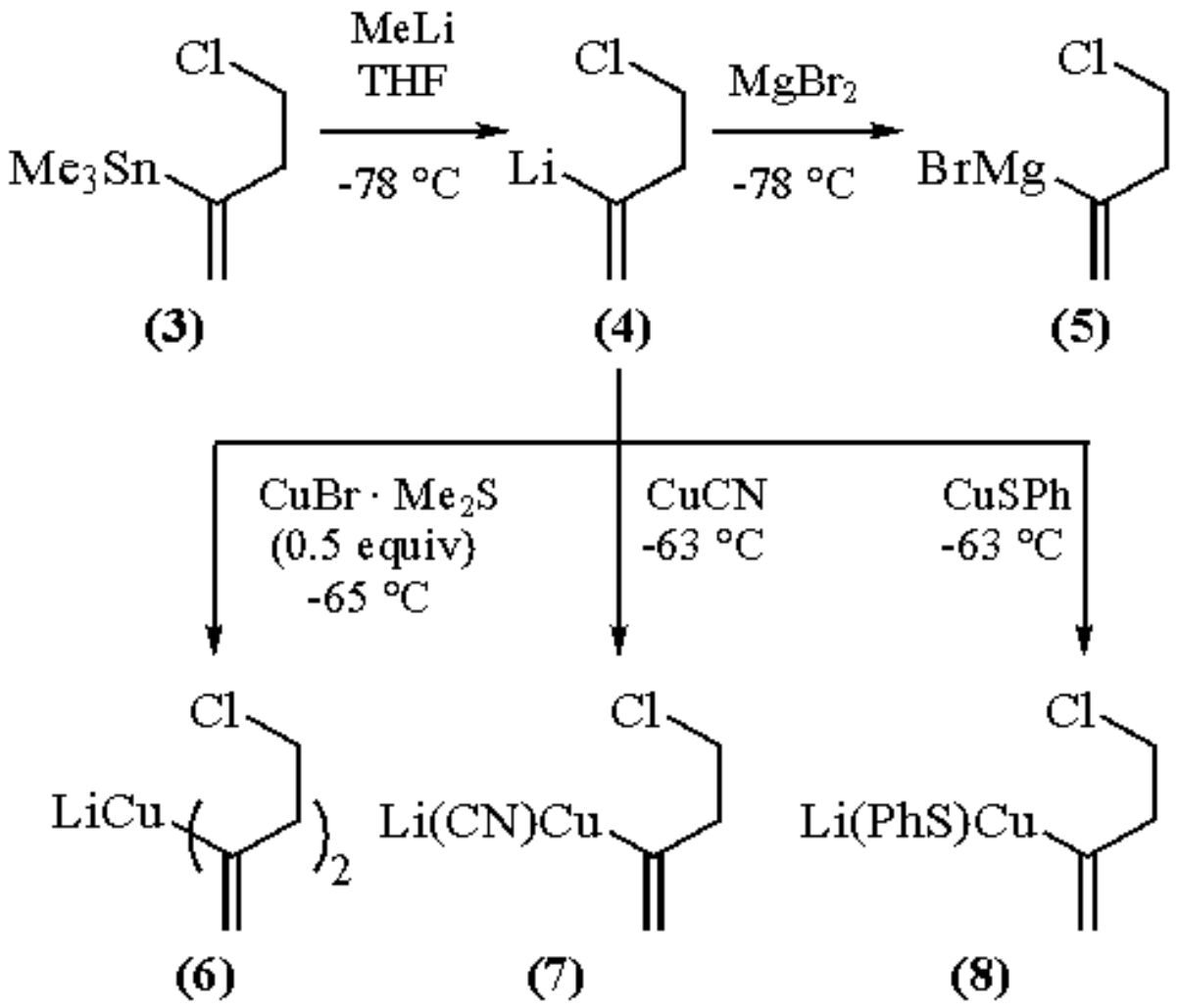

(2)

Methylenecyclopentane Annulations.

Reagents (**4**)-(**8**) serve as useful bifunctional species in a variety of contexts. The lithio reagent (**4**) has been employed for the direct conversion of aldehydes and ketones into substituted 3-methylenetetrahydrofurans (eq 3)[1a,c] and of α,β-unsaturated *N,N′,N′*-trimethylhydrazides into functionalized methylenecyclopentanes (eq 4).[1a,c]

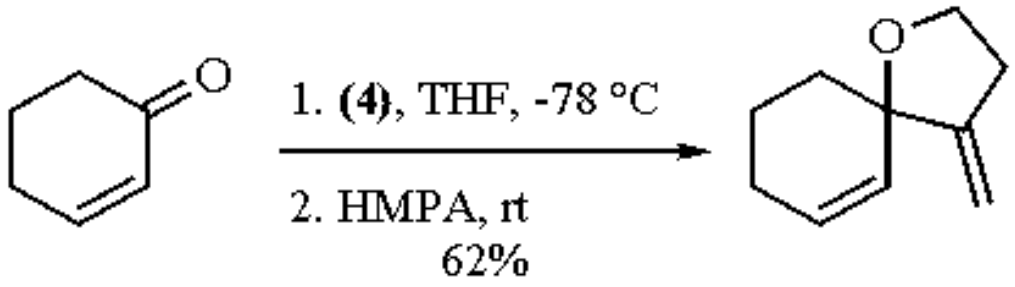

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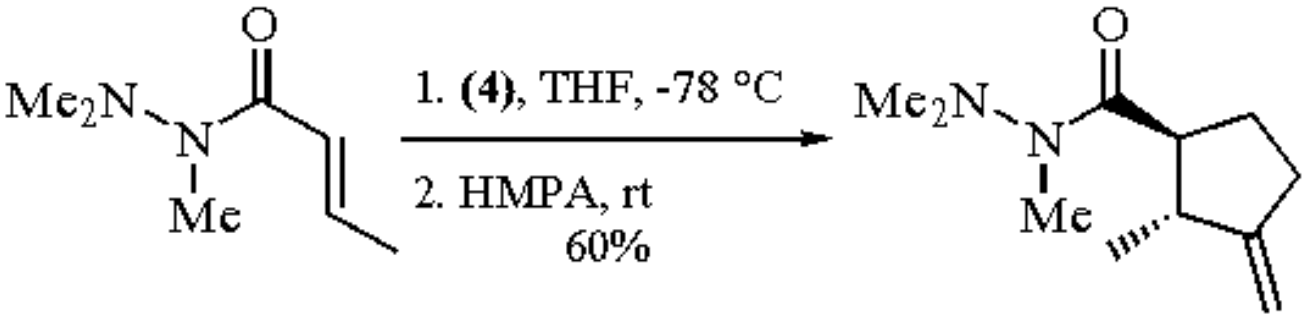

(4)

More importantly, reagents (**5**)-(**8**) have been employed effectively in the development of a synthetically useful methylenecyclopentane annulation method involving α,β-unsaturated ketones as substrates.[9] The two required steps, involving conjugate addition of the 2-(4-chloro-1-butenyl) group to the enone and subsequent intramolecular alkylation, may be carried out separately (eqs 5, 6 and 8)[1-3] or via a one-pot protocol (eq 7).[4] The importance of the one-pot process is particularly illustrated by the conversion of (**11**) into (**12**) (eq 7), since attempted intramolecular alkylation of (**13**) gives very poor yields of (**12**).[4] Although, normally, reagents (**5**)-(**8**) may be successfully interchanged for the conjugate addition step, it has been reported[2] that attempted additions of reagents (**7**) and (**8**) to the enone (**14**) are singularly unsuccessful. It is worth noting that substances (**9**), (**10**), (**12**), and (**15**) have played central roles in the total synthesis of a number of terpenoid natural products: (±)-$\Delta^{9(12)}$-capnellene,[1c,3a] (±)-pentalenene,[3b,c] (±)-methyl cantabrenonate,[4] (±)-methyl epoxycantabronate,[4] and (+)-ceroplastol I.[2]

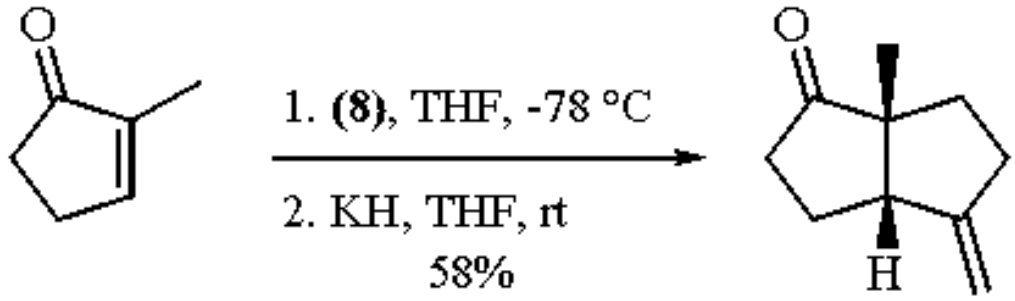

(5)

(9)

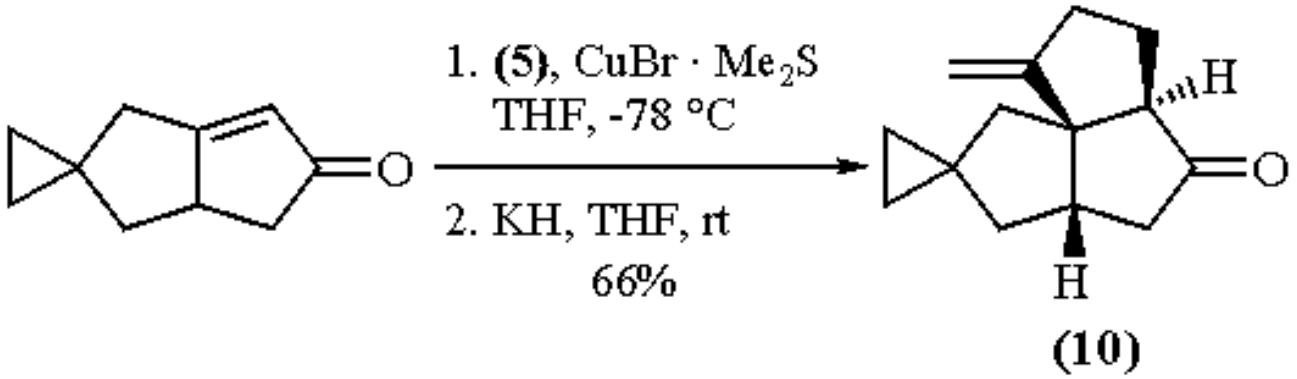

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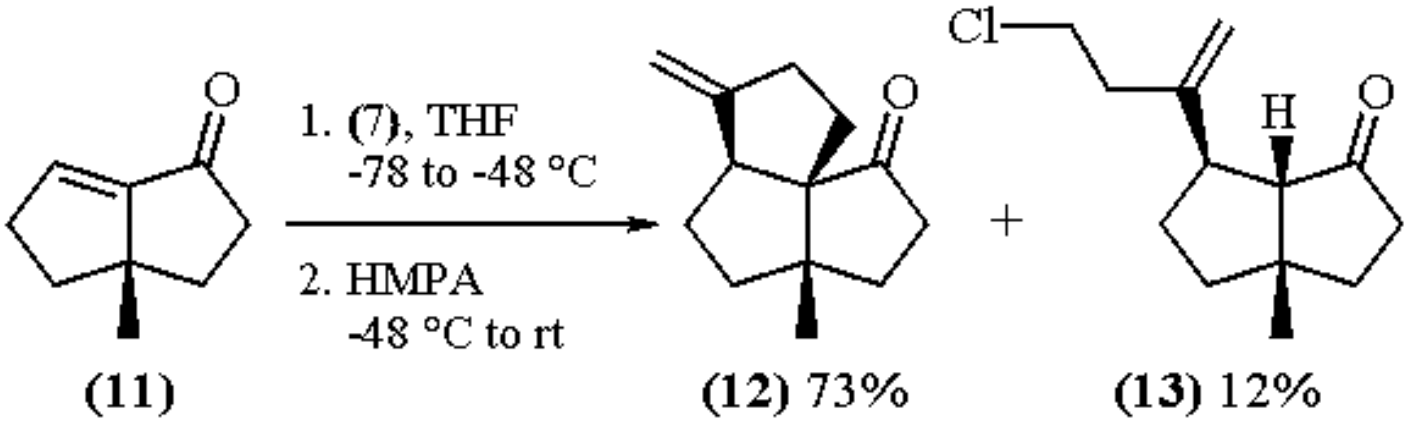

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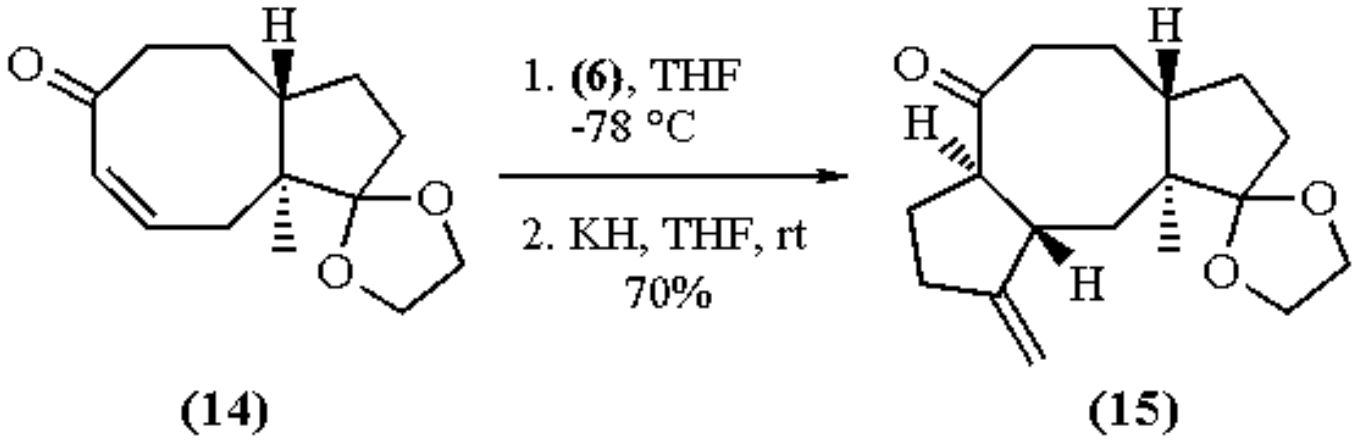

(8)

Related Reagents.

By use of chemistry similar to that outlined above, ***5-Chloro-2-trimethylstannyl-1-pentene*** (**16**)[6] and (*Z*)-5-chloro-3-trimethylstannyl-2-pentene (**20**)[8] have also been employed as precursors of useful bifunctional reagents. The Grignard reagent (**18**) and the cuprate (**19**), both obtained from (**16**) via the lithio species (**17**), can be used to carry out efficient methylenecyclohexane annulation sequences (eq 9).[10,11] Similarly, (*Z*)-ethylidenecyclopentane annulations (eq 10)[8b] can be accomplished by utilizing reagent (**22**), which is derived from (**20**) via (**21**). These annulation methods have found appreciable use in natural product synthesis.[8b,10c,12]

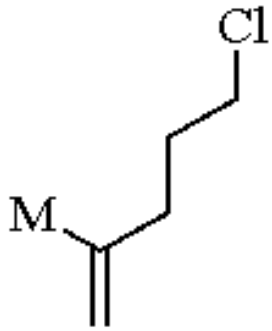

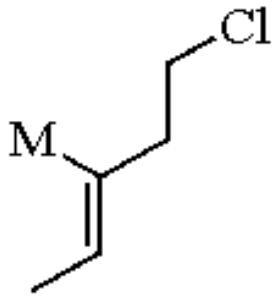

(16) M = Me_3Sn
(17) M = Li
(18) M = BrMg
(19) M = Li(CN)Cu

(20) M = Me_3Sn
(21) M = Li
(22) M = BrMg

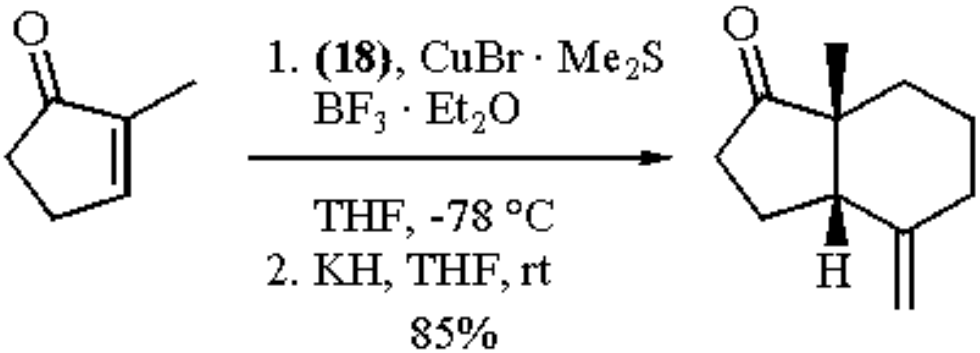

(9)

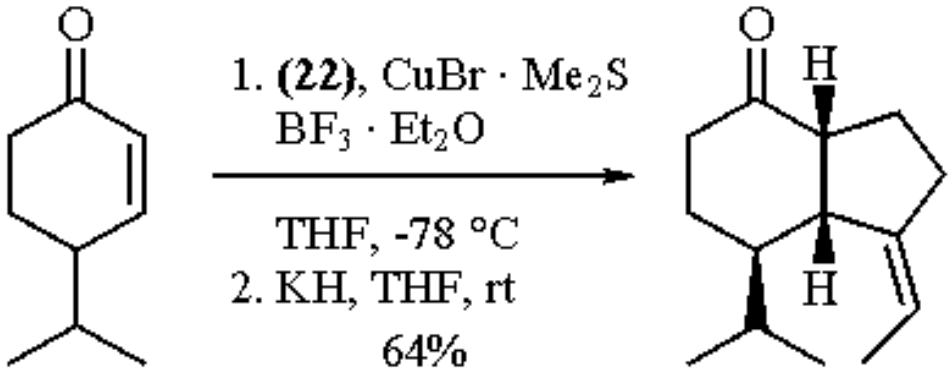

(10)

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1. Piers, E.; Karunaratne, V. (a) *JOC* **1983**, *48*, 1774. (b) *CC* **1983**, 935. (c) *T* **1989**, *45*, 1089.
2. Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *JACS* **1993**, *115*, 1676.
3. Piers, E.; Karunaratne, V. (a) *CJC* **1984**, *62*, 629. (b) *CC* **1984**, 959. (c) *CJC* **1989**, *67*, 160.
4. Piers, E.; Renaud, J. (a) *CC* **1990**, 1324. (b) *S* **1992**, 74.
5. (a) Piers, E.; Chong, J. M.; Morton, H. E. *TL* **1981**, *22*, 4905. (b) Piers, E.; Morton, H. E.; Chong, J. M. *CJC* **1987**, *65*, 78.
6. Piers, E.; Chong, J. M. (a) *CC* **1983**, 934. (b) *CJC* **1988**, *66*, 1425.
7. Reich, H. J.; Borst, J. P.; Coplien, M. B.; Phillips, N. H. *JACS* **1992**, *114*, 6577 and citations therein.
8. Piers, E.; Gavai, A. V. (a) *CC* **1985**, 1241. (b) *JOC* **1990**, *55*, 2380.

9. For annulation sequences involving organocopper(I) reagents related in structure to (**6**)-(**8**), see Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *JACS* **1978**, *100*, 5565 and Magnus, P.; Quagliato, D. *JOC* **1985**, *50*, 1621.
10. (a) Piers, E.; Yeung, B. W. A. *JOC* **1984**, *49*, 4567. (b) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *CJC* **1993**, *71*, 280. (c) Piers, E.; Yeung, B. W. A.; Rettig, S. J. *T* **1987**, *43*, 5521.
11. Piers, E.; Roberge, J. Y. *TL* **1991**, *32*, 5219.
12. (a) Piers, E.; Yeung, B. W. A. *CJC* **1986**, *64*, 2475. (b) Piers, E.; Wai, J. S. M. *CC* **1987**, 1342. (c) Piers, E.; Wai, J. S. M. *CC* **1988**, 1245. (d) Piers, E.; Fleming, F. F. *CC* **1989**, 1665. (e) Piers, E.; Roberge, J. Y. *TL* **1992**, *33*, 6923.

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5-Chloro-2-trimethylstannyl-1-pentene[1]

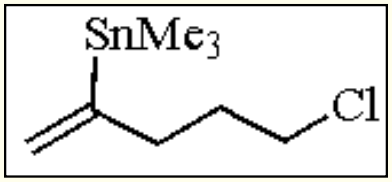

[89045-21-6] · $C_8H_{17}ClSn$ · 5-Chloro-2-trimethylstannyl-1-pentene · (MW 267.38)

(cyclohexane annulation; bifunctional reagent;[2-4] intramolecular Stille coupling[5])

Alternate Name: (4-chloro-1-methylenebutyl)trimethylstannane.

Physical Data: bp 55-60 °C/12 mmHg.[6]

Analysis of Reagent Purity: GLC, ^{1}H NMR.[6]

Preparative Methods: treatment of commercially available 5-chloro-1-pentyne with $Me_3SnCu.Me_2S$ (see ***Trimethylstannylcopper-Dimethyl Sulfide***) in THF at -68 °C in the presence of excess MeOH provides a 9:1 mixture of 5-chloro-2-trimethylstannyl-1-pentene and 5-chloro-1-trimethylstannyl-1-pentene.[6-8] Slow column chromatography removes the minor product.[6]

Purification: silica gel chromatography (pet. ether) followed by distillation.[6]

Handling, Storage, and Precautions: organostannanes should be considered as toxic compounds.[9] This reagent should be handled in a well-ventilated fume hood and gloves should be worn to prevent contact with the skin.

1,2-Additions.

See also ***(Z)-5-Chloro-3-trimethylstannyl-2-pentene*** and ***4-Chloro-2-trimethylstannyl-1-butene***. Addition of 5-chloro-2-lithio-1-pentene, prepared from the title reagent and MeLi at -78 °C, to cyclohexanone affords the chloro alcohol in 84% yield (eq 1). At higher temperatures (-50 °C), decomposition of this product occurs.[10]

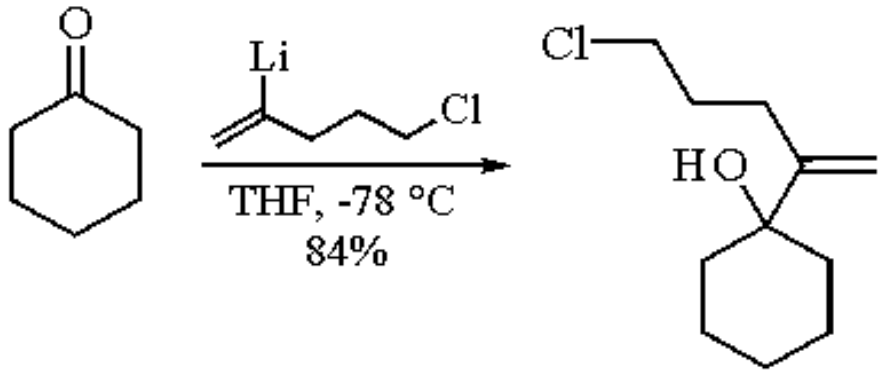

(1)

Methylenecyclohexane Annulations.

Alkylation of the *N,N*-dimethylhydrazone of a cyclohexanone with 5-iodo-2-trimethylstannyl-1-pentene (prepared from the title reagent by treatment with NaI, acetone, 84%) and immediate cleavage of the hydrazone provides a ketovinylstannane. Conversion of the stannane to the iodide and metal-halogen exchange completes the annulation, affording the allylic, angular alcohol (eq 2).[11]

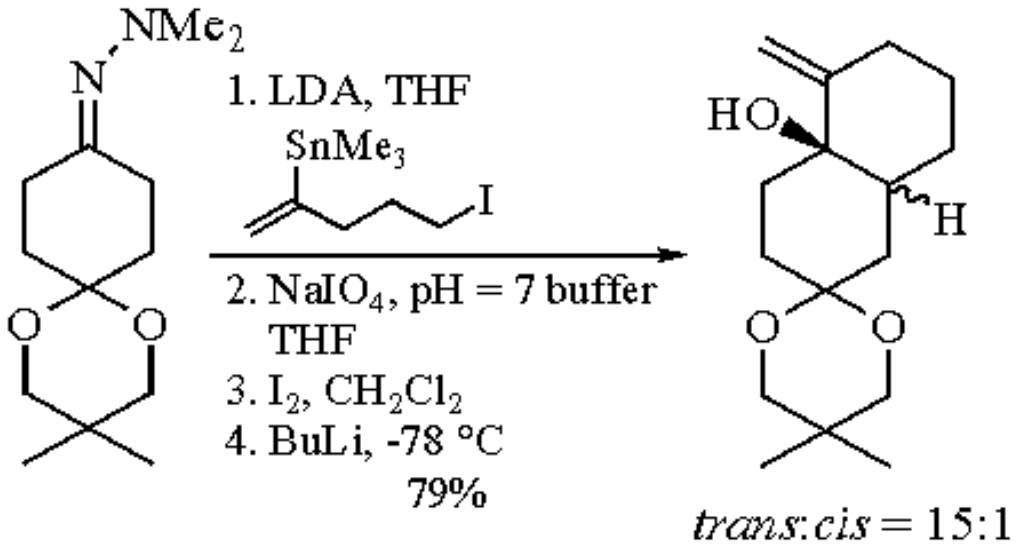

(2)

Methylenecyclohexanes have been prepared from enones in a two-step sequence by means of a cuprate addition followed by an intramolecular alkylation. The cuprate is prepared from 5-chloro-2-lithio-1-pentene (see above) either by treatment with ***Tri-n-butylphosphine*** and copper(I) bromide-dimethyl sulfide in THF or with ***Magnesium Bromide*** (to make the Grignard) followed by $CuBr.Me_2S$.[10] Addition of the cuprate to an enone occurs to give a mixture of diastereomers (R &neq; H). Intramolecular alkylation is effected by ***Potassium Hydride*** in THF to give the kinetic products, which possess a *cis* ring fusion. These may be equilibrated (MeONa, MeOH) to provide the thermodynamically favored product when R = H (Table 1) (eq 3).[10]

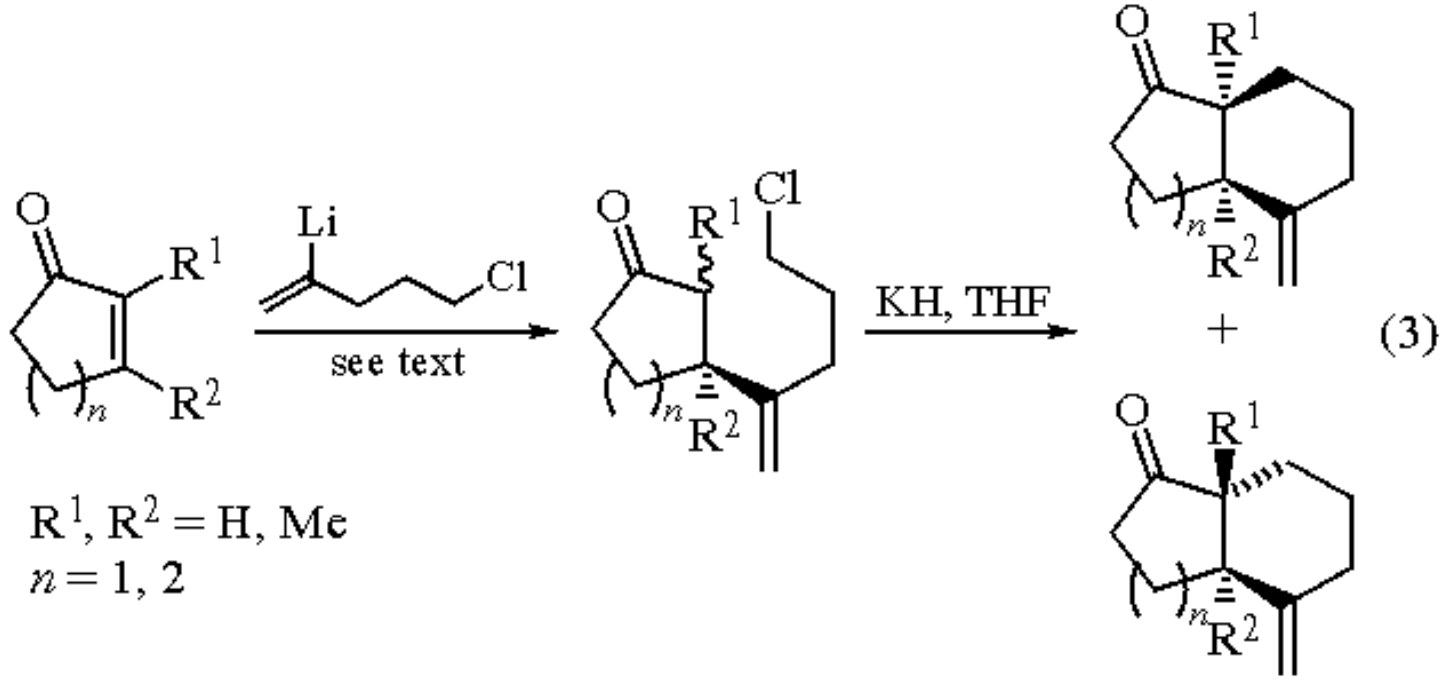

Table 1 Cyclohexane Annulations

n	R^1	R^2	Yield (conjugate addition) (%)	Yield [cyclization (*cis*:*trans*)] (%)
1	H	H	65	84 (4.9:1)
1	H	Me	38	88 (100:0)
1	Me	H	67	90 (100:0)
2	H	H	61	86 (1:2)
2	H	Me	55	82 (3.5:1)
2	Me	H	58	78 (100:0)

This methodology has been used to synthesize the sesquiterpenoids (±)-axamide-1 and (±)-axisonitrile-1,[12,13] and the sesterterpenoid (±)-palauolide (eqs 4 and 5).[14]

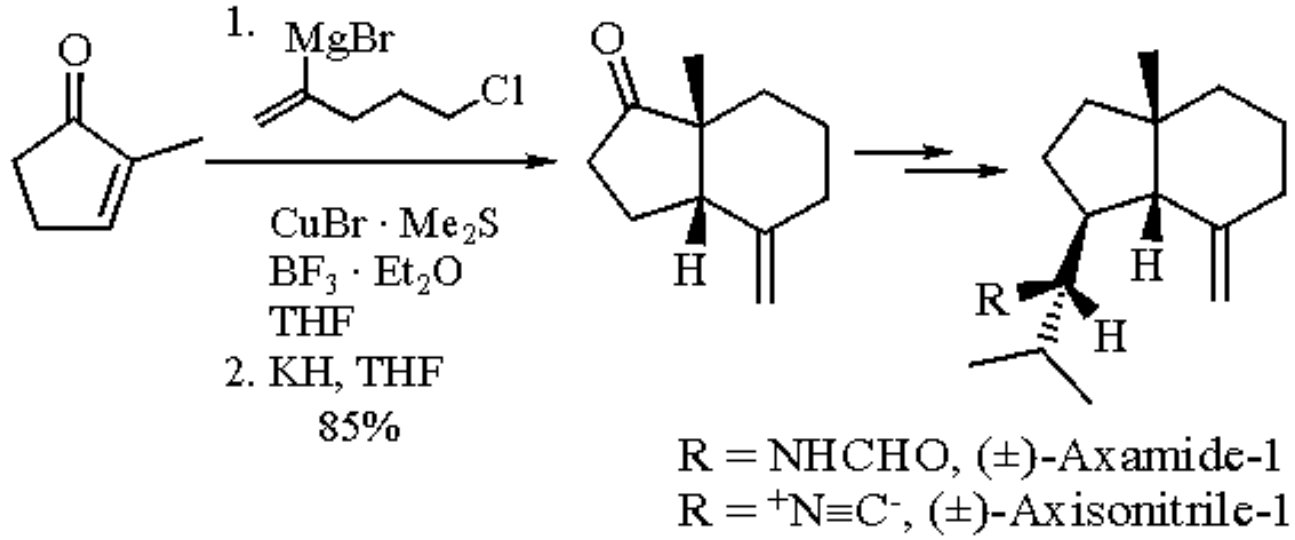

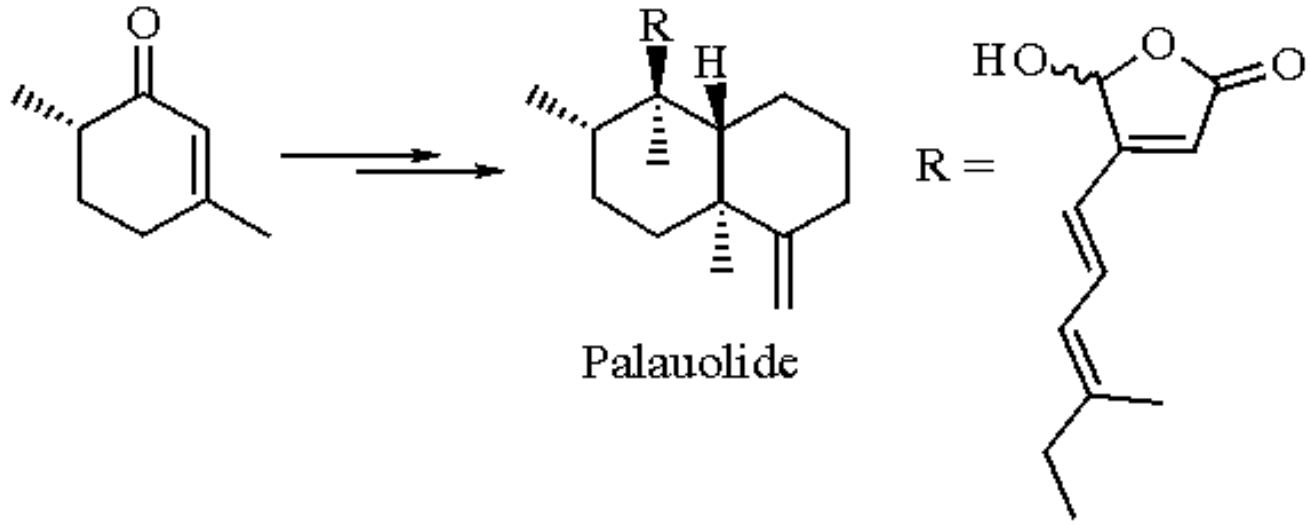

A trimethylstannyl group has been used as a removable anchoring group in an annulation sequence directed towards enantiomerically pure clerodane diterpenoids (eq 6).[15]

5-Chloro-2-trimethylstannyl-1-pentene

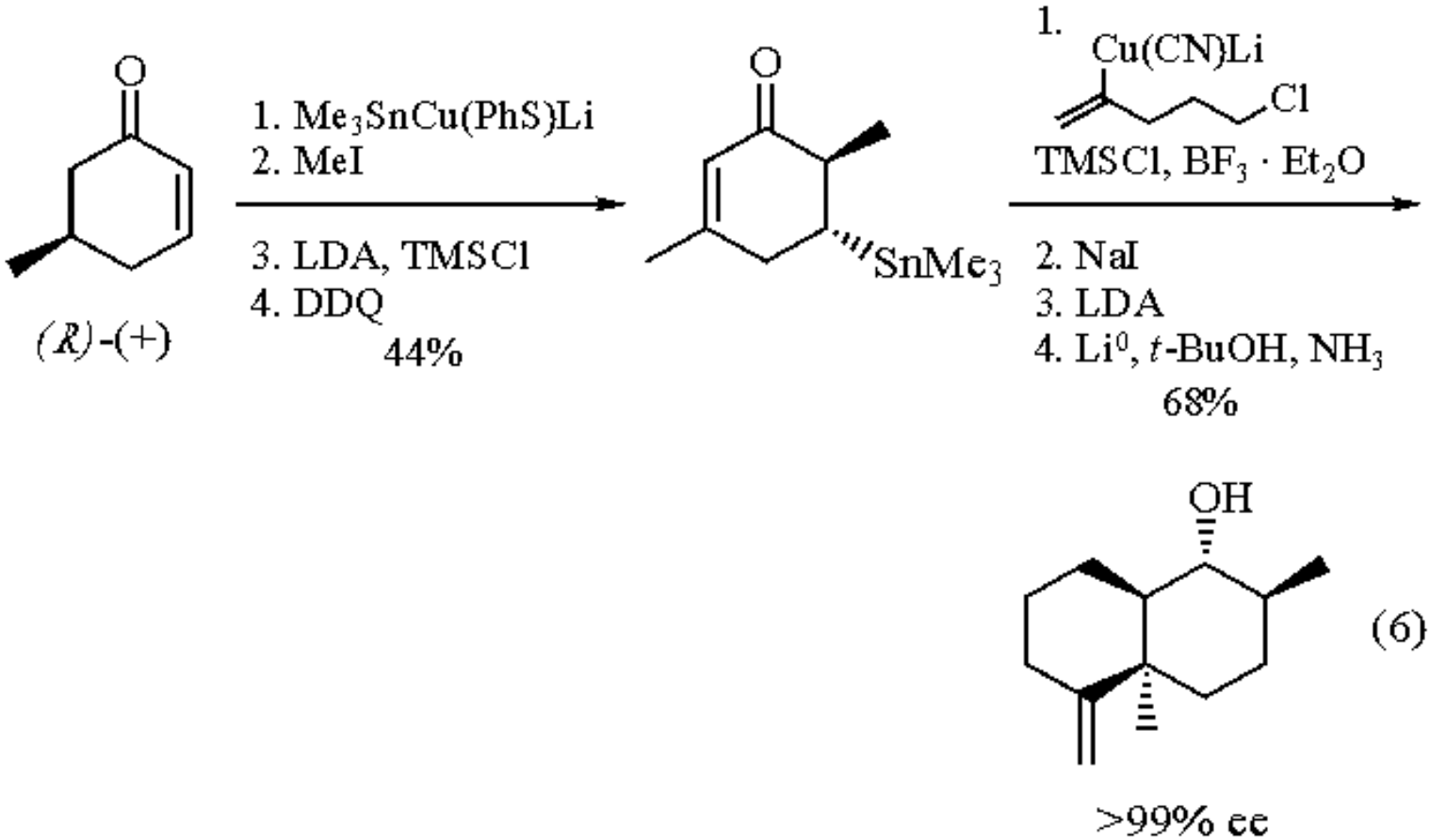

Intramolecular Stille Couplings.

Bicyclic dienes have been prepared from the alkylated keto acetal (see eq 2) by formation of the enol triflate, followed by palladium-catalyzed Stille coupling (eq 7).[7,16]

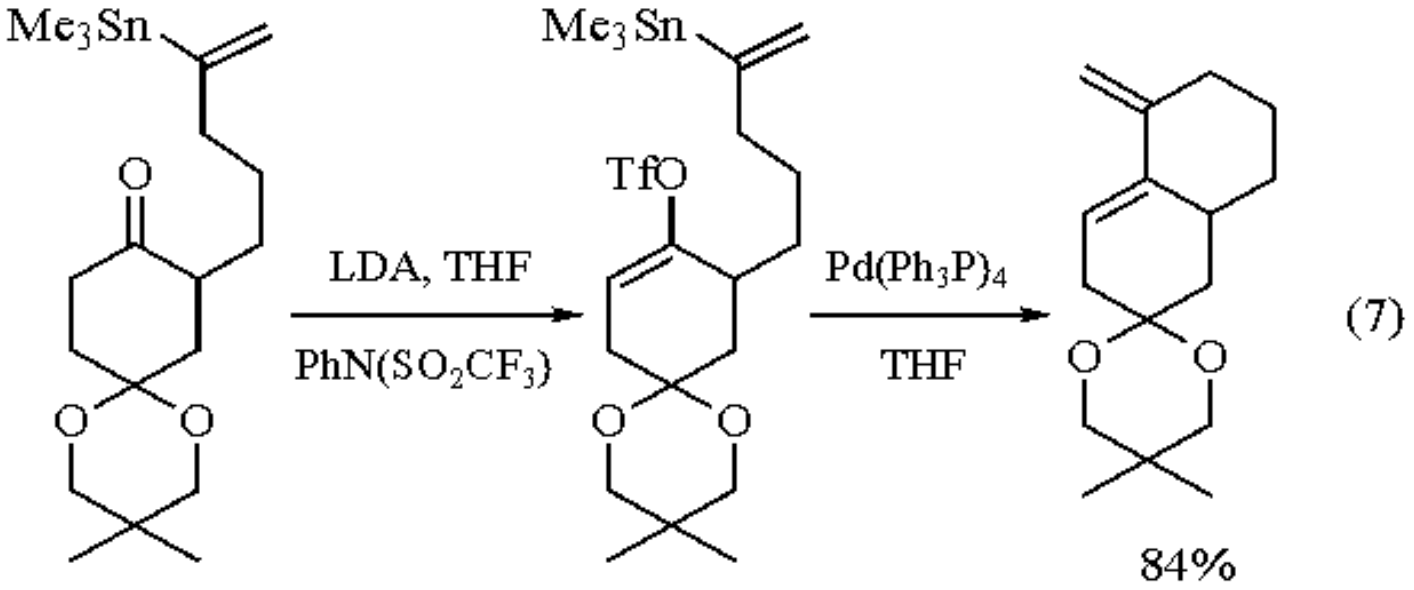

Related Reagents.

4-Chloro-2-trimethylstannyl-1-butene; ***(Z)-5-Chloro-3-trimethylstannyl-2-pentene***.

---

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4. Trost, B. M. *AG(E)* **1986**, *25*, 1.
5. Stille, J. K.; Tanaka, M. *JACS* **1987**, *109*, 3785.
6. Piers, E.; Chong, J. M. *CJC* **1988**, *66*, 1425.
7. Piers, E.; Friesen, R. W.; Keay, B. A. *T* **1991**, *47*, 4555.
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10. Piers, E.; Yeung, B. W. A. *JOC* **1984**, *49*, 4567.
11. Piers, E.; Marais, P. C. *TL* **1988**, *29*, 4053.
12. Piers, E.; Yeung, B. W. A. *CJC* **1986**, *64*, 2475.
13. Piers, E.; Yeung, B. W. A.; Rettig, S. J. *T* **1987**, *43*, 5521.
14. Piers, E.; Wai, J. S. M. *CC* **1987**, 1342.
15. Piers, E.; Roberge, J. Y. *TL* **1991**, *32*, 5219.
16. Piers, E.; Friesen, R. W.; Keay, B. A. *CC* **1985**, 809.

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Chlorotriphenylsilane

Ph_3SiCl

[76-86-8] · $C_{18}H_{15}ClSi$ · Chlorotriphenylsilane · (MW 294.87)

(bulky silylating agent[1-3])

Alternate Name: triphenylsilyl chloride.

Physical Data: mp 92-94 °C; bp 240-243 °C/35 mmHg.

Solubility: readily sol most aprotic organic solvents, although CH_2Cl_2 is most commonly used; reacts with H_2O and other protic solvents.

Form Supplied in: colorless solid.

Handling, Storage, and Precautions: somewhat prone to hydrolysis, and should be handled and stored under an anhydrous, inert atmosphere.

General Considerations.

Like other bulky trialkylsilyl groups, the triphenylsilyl group was introduced to serve as a hydrolytically stable protecting group for alcohols. The hydroxyl functionality can be easily derivatized using Ph_3SiCl in the presence of a tertiary amine or ***Imidazole*** as a base (eqs 1 and 2).[1-3]

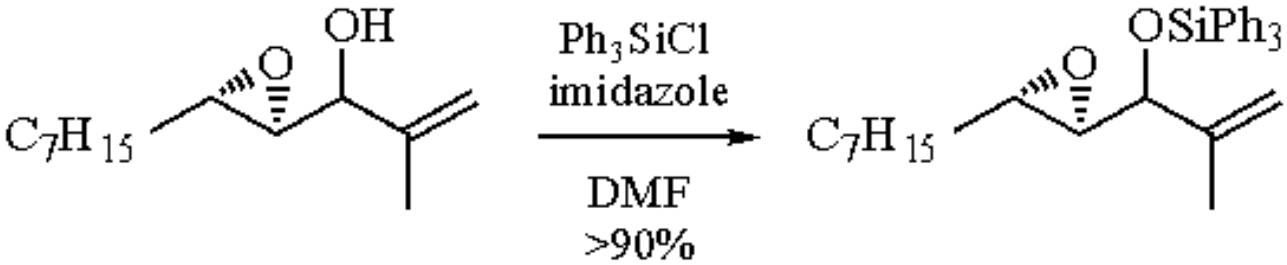

(1)

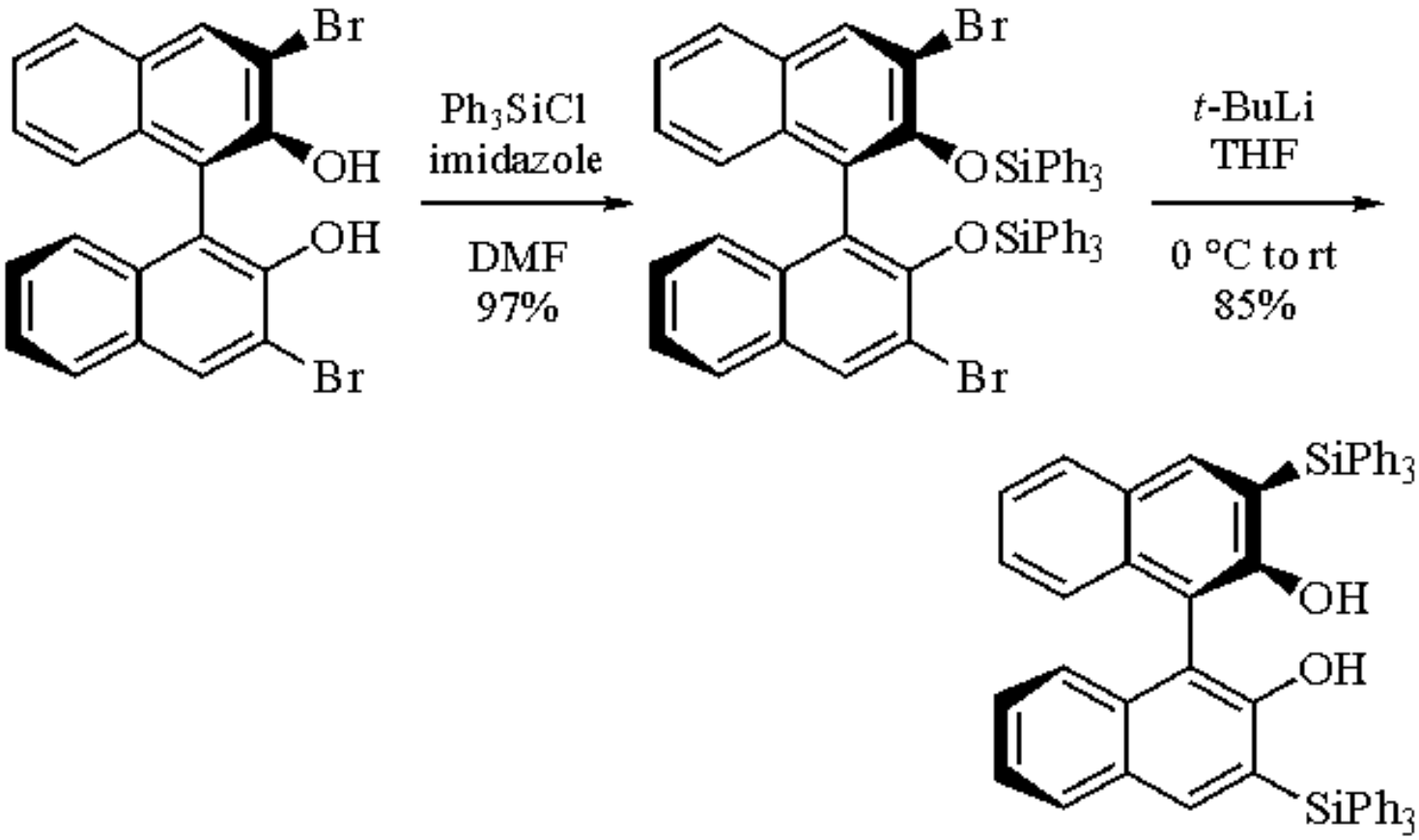

(2)

A wide variety of Grignard reagents and organolithium complexes participate in reactions with Ph_3SiCl to afford organosilanes. Thus the reaction of allylmagnesium chloride with Ph_3SiCl gives the allylsilane in high yield (eq 3).[4] However, when hydrosilyl Grignard reagents are employed, reduction to the silane occurs (eq 4).[5] Azaallyl anion[6] and diazolithium salts[7] can each be silylated to give the anticipated silane adducts (eqs 5 and 6). Similarly, arylsilanes[8] and alkynylsilanes[9-12] are produced upon silylation of the appropriate metalated[13] carbanions with Ph_3SiCl (eqs 7-11).

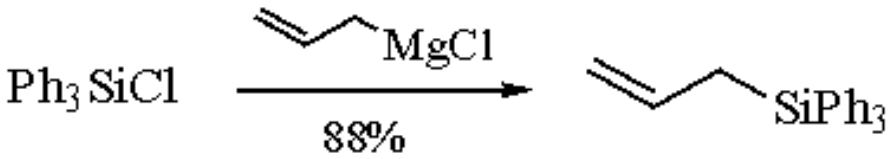

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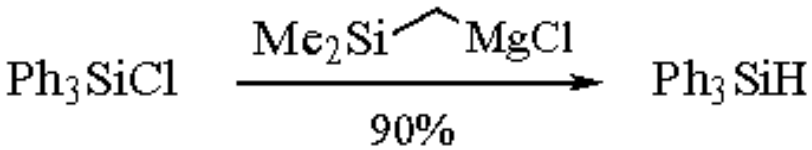

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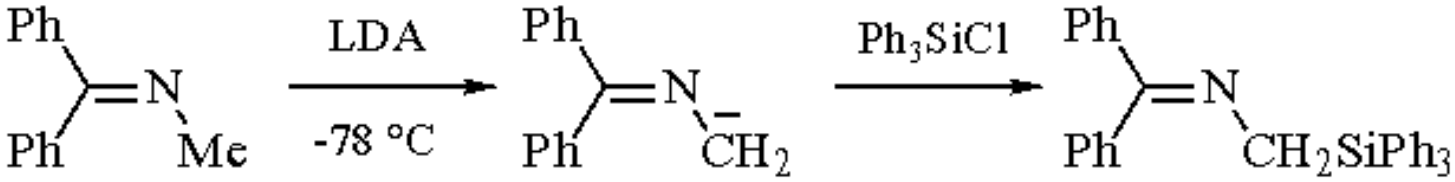

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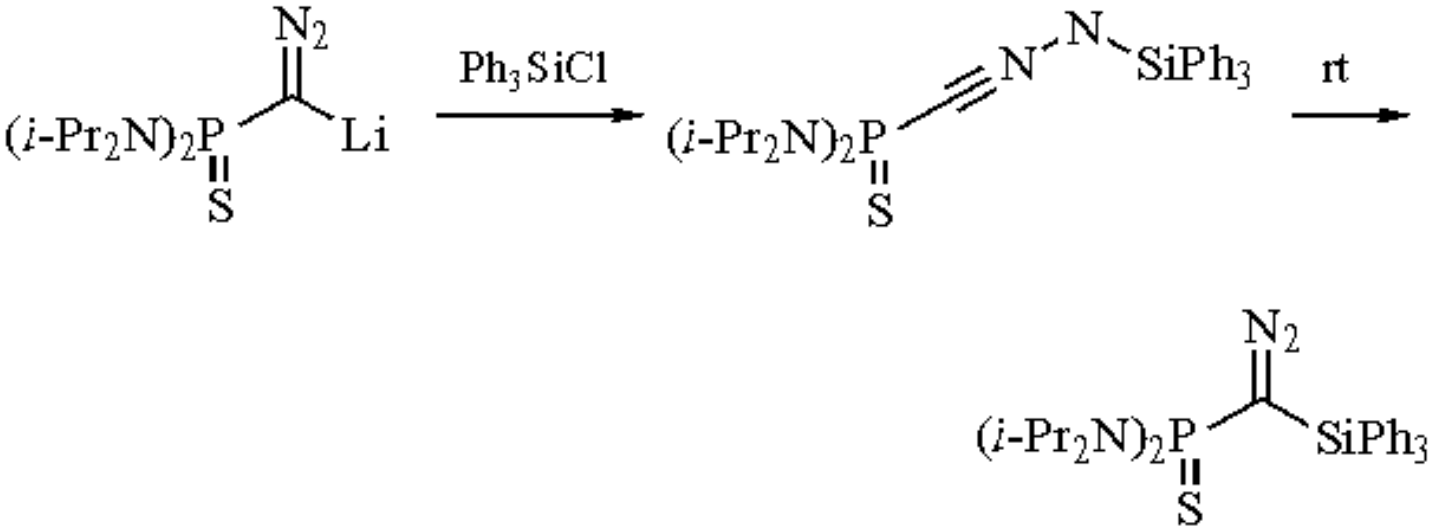
N2
(i-Pr2N)2P
Li
S
Ph3SiCl
N
N
SiPh3
rt
SiPh3

(6)

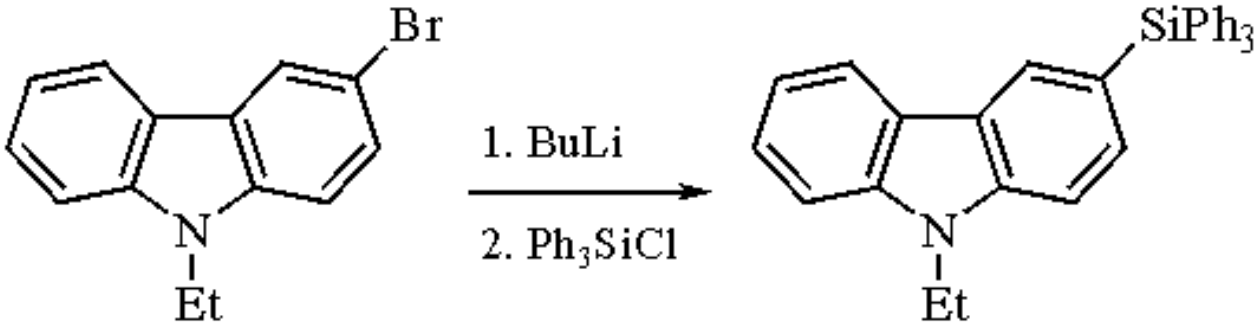
Br
1. BuLi
2. Ph3SiCl
SiPh3
N
Et

(7)

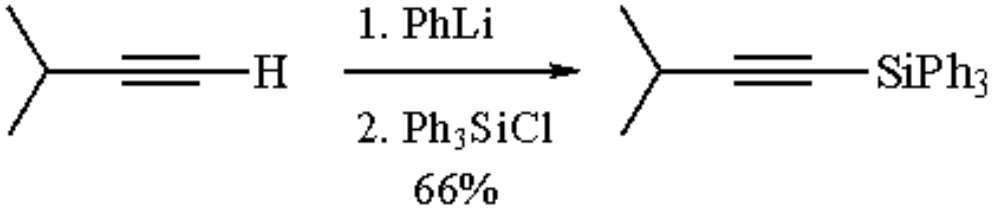
H
1. PhLi
2. Ph3SiCl
66%
SiPh3

(8)

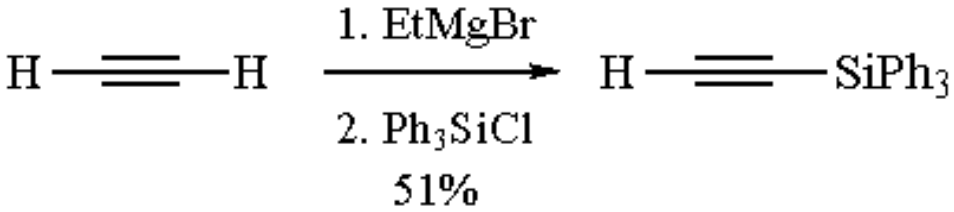
H
H
1. EtMgBr
2. Ph3SiCl
51%
SiPh3

(9)

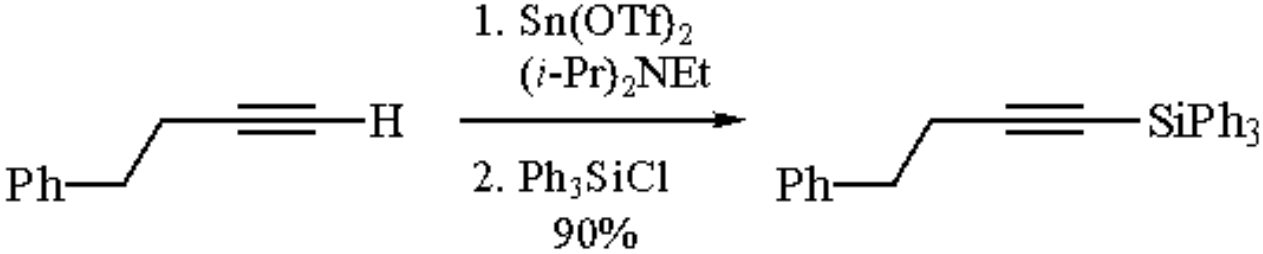
1. Sn(OTf)2
(i-Pr)2NEt
H
Ph
2. Ph3SiCl
90%
SiPh3

(10)

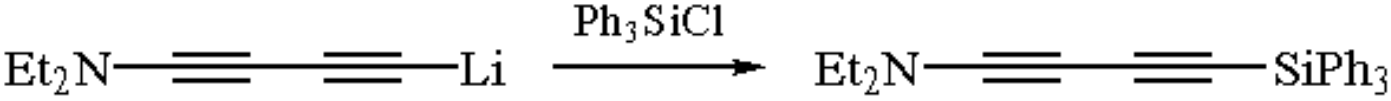
Et2N
Li
Ph3SiCl
SiPh3

(11)

Other types of heteroatomic nucleophiles are capable of reacting with Ph_3SiCl to produce the silyl derivative. For example, ***Sodium Dicarbonylcyclopentadienylferrate*** combines with Ph_3SiCl to give the iron silane (eq 12).[14] Silylcuprates can be prepared by lithiation of Ph_3SiCl followed by treatment with copper(I) ion.[15] Addition of the lithium disilylcuprate to aroyl chlorides produces the acyl silane (eq 13),[16] while conjugate addition of the higher order silyl cyanocuprate to an alkynic morpholinium species was utilized for the synthesis of a heterosubstituted allenylsilane (eq 14).[17]

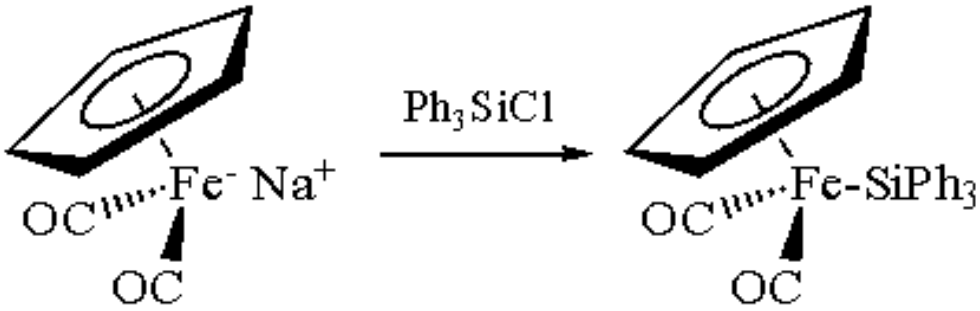

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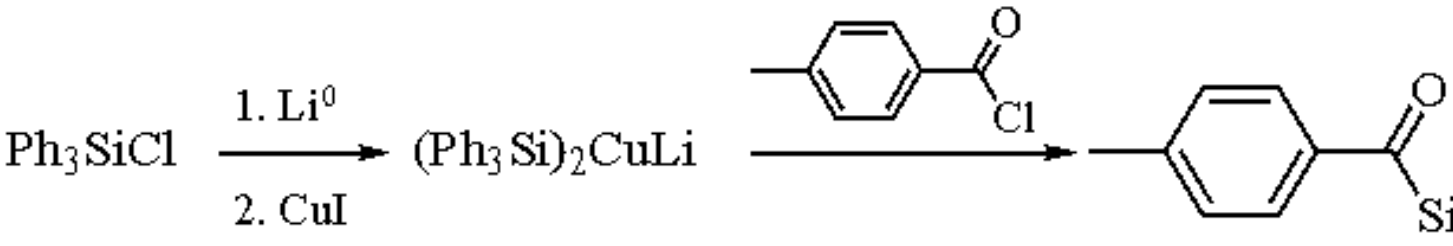

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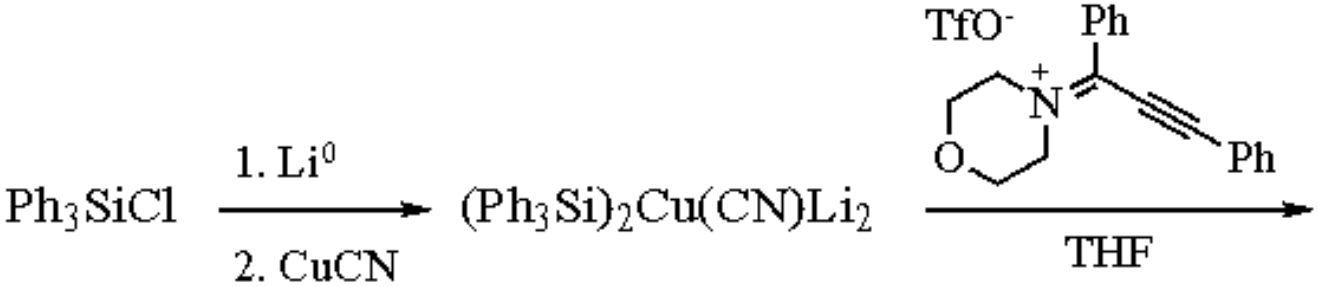

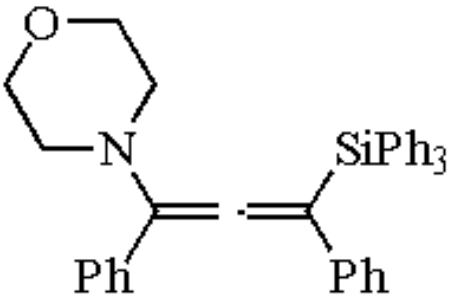

(14)

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Related Reagents.

t-Butyldimethylchlorosilane; ***Chlorotriethylsilane***; ***Chlorotrimethylsilane***.

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Chlorotriphenylstannane

Ph_3SnCl

[639-58-7] · $C_{18}H_{15}ClSn$ · Chlorotriphenylstannane · (MW 385.49)

(precursor of alkyl-, allyl-, and allenyltriphenylstannanes for stereo- and regioselective C-C bond formation;[1,4] triphenyltin enolates for diastereoselective aldol condensation[5,6] and for avoiding polyalkylation[11])

Alternate Name: triphenyltin chloride.

Physical Data: mp 108 °C (dec); bp 240 °C/13.5 mmHg.

Solubility: sol THF, CH_2Cl_2; slightly sol ether.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: normally, commercially available chlorotriphenylstannane may be used as received. The reagent is air stable, but is decomposed by moisture. The reagent is toxic and should be handled with gloves. Use in a fume hood.

Introduction.

As mentioned in the entry for ***Tri-n-butylchlorostannane***, Ph_3SnCl is a useful starting material for the synthesis of other triphenyltin reagents such as ***Triphenylstannane***, cyanotriphenylstannane, triphenyltin methoxide, triphenyltin azide, and triphenylstannyllithium, etc.

Organotriphenyltins via Transmetalation.

The reaction of Ph_3SnCl with allylic anions substituted with heteroatoms such as sulfur and oxygen affords allylic triphenylstannanes having heteroatoms at the γ-position. The subsequent reaction of the allylic tin derivatives with aldehydes in the presence of ***Boron Trifluoride Etherate*** give the *syn*-γ-adduct predominantly (eq 1).[1] In general, the reaction with aldehydes is carried out without isolating the intermediate allylic stannanes; thus treatment of the allylic anion with Ph_3SnCl, followed by addition of aldehydes/$BF_3.OEt_2$, produces the homoallyl alcohols. The γ-regioselectivity is perfect, but the *syn* diastereoselectivity is between 90 and 70% de.

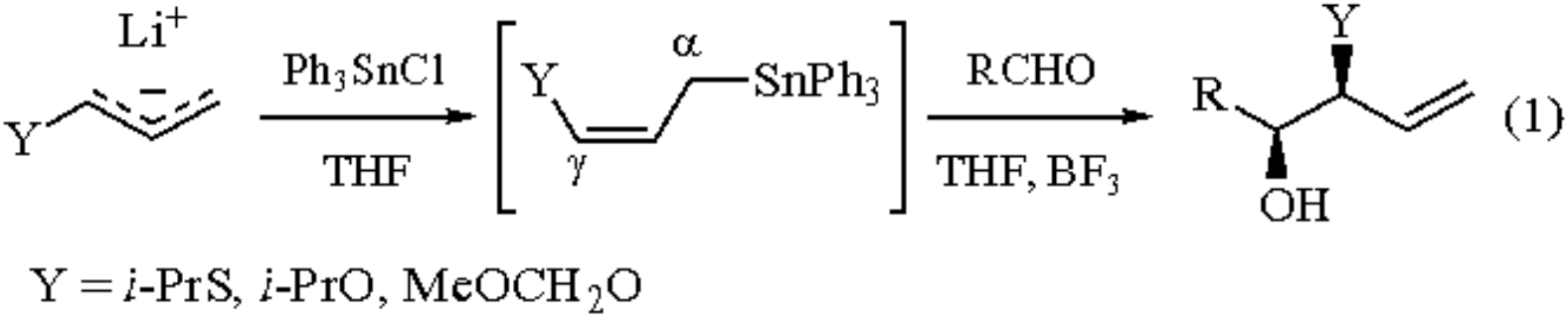

Chlorotributylstannane may be used instead of Ph_3SnCl, and similar levels of diastereoselectivity are obtained. However, the use of triphenylstannane derivatives is recommended due to their lower toxicity and easier separation of the triphenylstannyl residue. Lithiated 1,3-dithianes react with chlorotrialkyl- or chlorotriphenylstannanes to form the corresponding 1,3-dithian-2-ylstannyl compounds.[2] Cyclohexyl- and cyclohexenyltriphenylstannanes are prepared from the corresponding Grignard reagents with Ph_3SnCl.[3] The reaction of allenylmagnesium bromides with Ph_3SnCl and ***Sodium Iodide*** gives allenyltriphenylstannanes, which react regioselectively with α,β-enones in the presence of ***Titanium(IV) Chloride*** to afford the conjugate propargylation products in good yields (eq 2).[4] Propargylation of nitroalkenes takes place with allenyltriphenylstannanes in the presence of $TiCl_4$.[4]

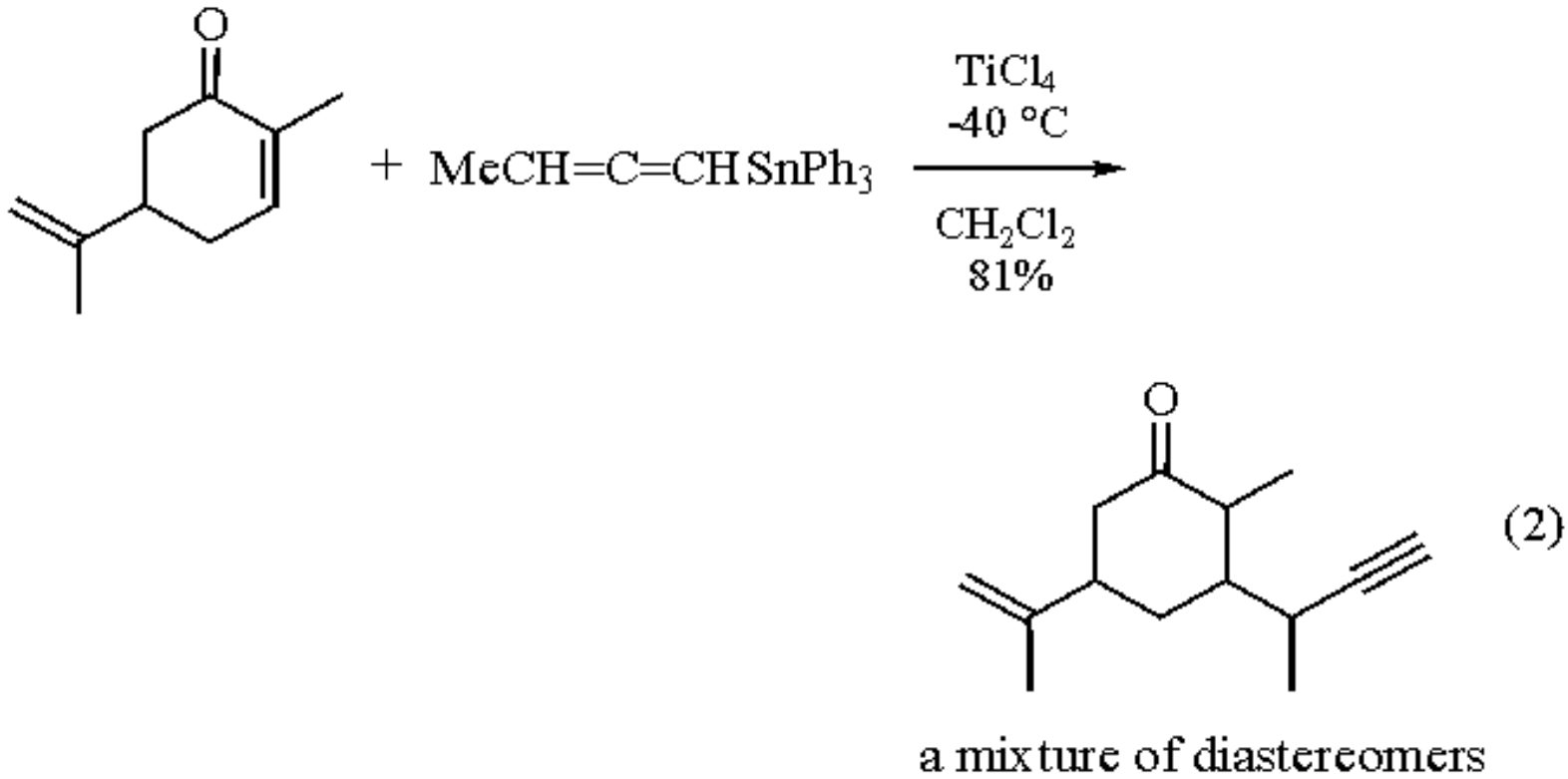

Triphenylstannyl Enolates.

Triphenylstannyl enolates, prepared in situ by reaction of lithium enolates with Ph_3SnCl, react with aldehydes at -78 °C to afford mainly *syn* products, irrespective of the geometry of the enolate (eq 3). Assistance with a Lewis acid is not necessary.[5] The corresponding tributylstannyl and trimethylstannyl enolates, prepared in a similar manner, react with benzaldehyde to give a ca. 1:1 mixture of *syn* and *anti* adducts. On the other hand, the reaction of the enol stannanes of cyclohexanone or propiophenone, prepared from enol acetates and trimethyl- or tributyltin methoxide and isolated by

distillation, with aldehydes under kinetic conditions (-78 °C) give predominantly the *anti* aldols, with diastereoselectivity as high as 95:5 being achieved (eq 4).[6]

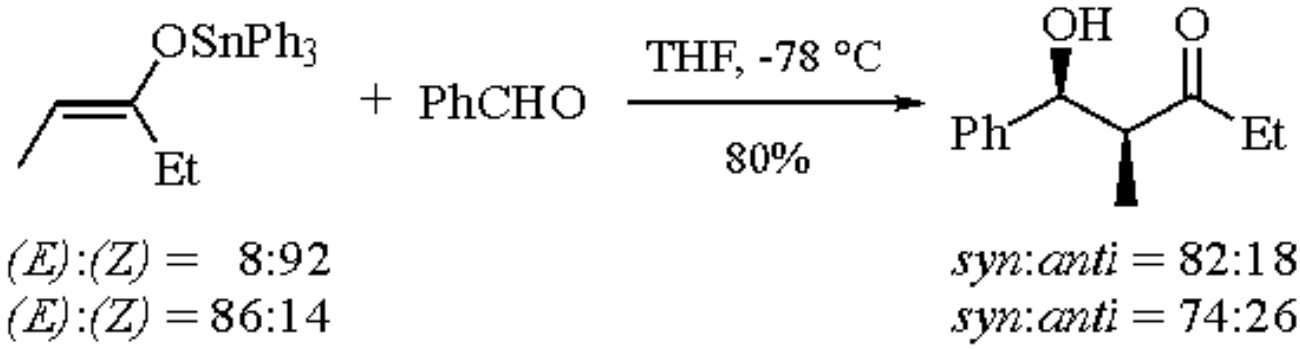

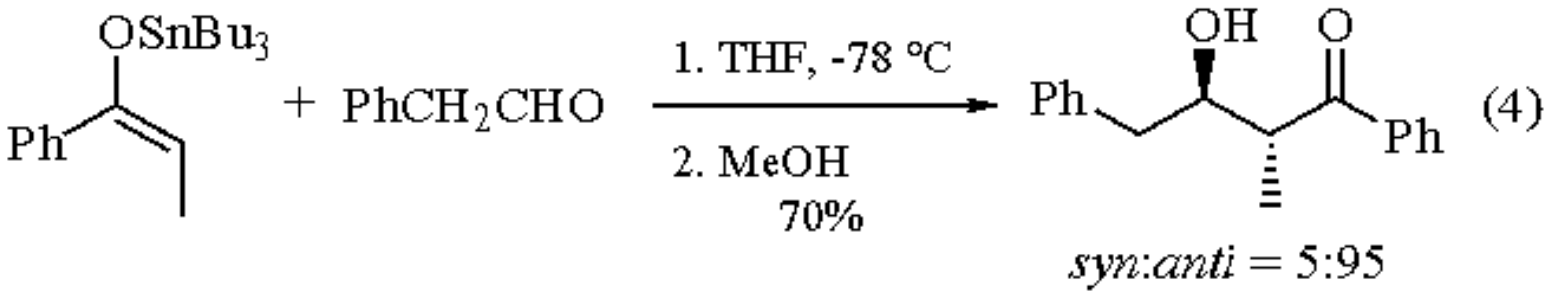

At higher temperatures (45 °C), mainly *syn* selectivity is observed. ***Lithium Chloride***, present in the in situ generated tin enolate, plays an important role in producing the *syn* diastereoselectivity in these reactions, as has been established for the reactions of germanium enolates.[7] However, the triphenylstannyl or trimethylstannyl enolate of 4-thianone, prepared in situ from the corresponding lithium enolate and Ph_3SnCl or Me_3SnCl, reacts with 2-methylpropanal to form the *anti* aldol predominantly.[8]

α-Lithiostannylalkylphosphonates react with aldehydes with the complete elimination of the organotin moiety (eq 5).[9] The stereoselective formation of the (*E*)- or (*Z*)-α-alkenylphosphonates is dependent on the tin substituent; Ph_3Sn derivatives produce the (*Z*)-alkene predominantly (with 60-97% stereoselectivity), whereas Bu_3Sn analogs afford the (*E*)-alkene with 80-97% selectivity.

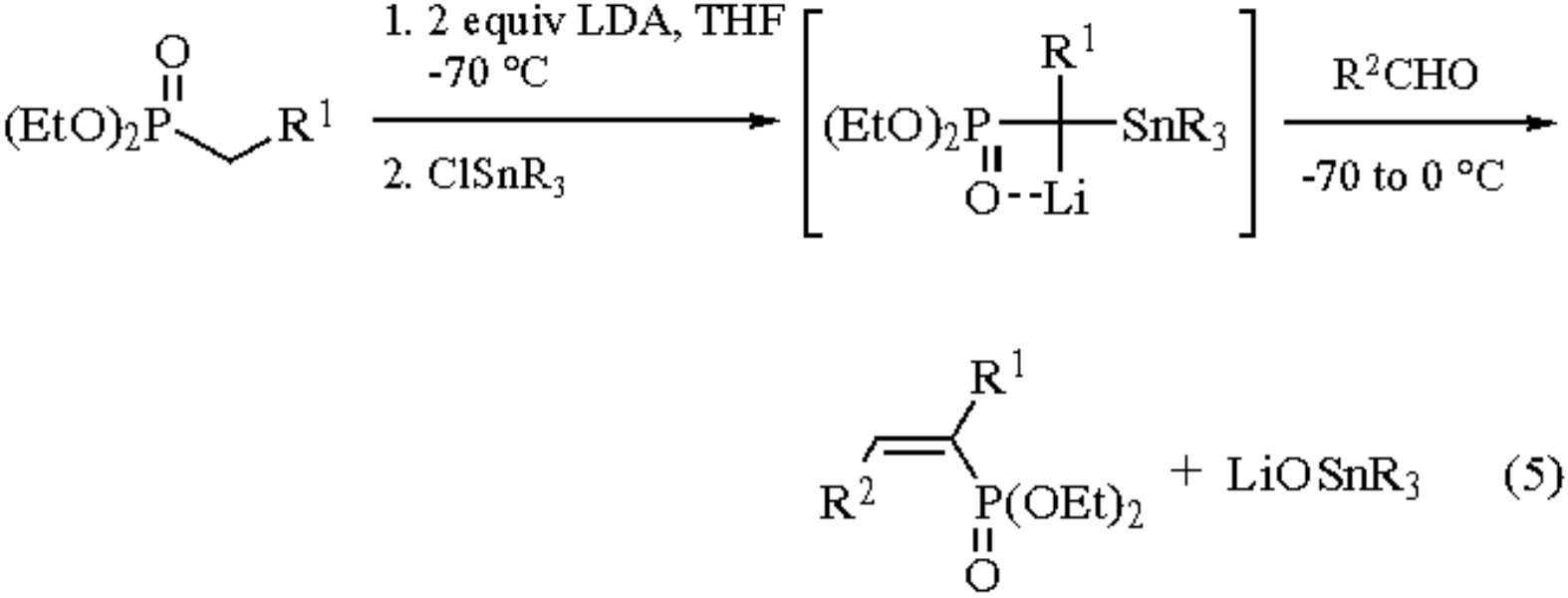

Although the alkylation of lithium enolates is often accompanied by undesired polyalkylation, it is avoided by using tin enolates.[10] The polyalkylation is a major drawback in the alkylation of enolates formed by cuprate conjugate addition to enones, but the use of trialkylstannyl and triphenylstannyl enolates prevents polyalkylation and enhances the yield of the desired monoalkylation product.[11]

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Chlorotris(triphenylphosphine)cobalt

$CoCl(Ph_3P)_3$

[26305-75-9] · $C_{54}H_{45}ClCoP_3$ · Chlorotris(triphenylphosphine)cobalt · (MW 881.28)

(monovalent cobalt complex; homogeneous catalyst for hydrogenation and hydrodimerization of alkenes; strong nucleophile, reacting with alkyl acyl halides to afford coupling products; useful for the preparation of organocobalt complexes)

Physical Data: mp 177 °C (N_2, sealed tube).

Solubility: sol benzene and CH_2Cl_2; insol EtOH.

Preparative Methods: a solution of ***Cobalt(II) Chloride*** hexahydrate (0.6 g, 2.5 mmol) and ***Triphenylphosphine*** (2.0 g, 7.6 mmol) in EtOH (70 mL) was treated under N_2 and stirring with a solution of ***Sodium Borohydride*** (0.08 g, 2.1 mmol) in EtOH at 30-40 °C; the resulting brown-green precipitate was washed several times with EtOH and water and dried (yield 92%);[1] reductions with powdered Zn, and electrolysis, are equally effective methods; corresponding Br and I complexes are prepared similarly from $CoBr_2$ and CoI_2.

Handling, Storage, and Precautions: the solid reagent is fairly stable in air; it has been stored under N_2 atmosphere over several months at rt.

Hydrogenation Catalyst.

Like ***Chlorotris(triphenylphosphine)rhodium(I)***, $CoCl(Ph_3P)_3$ is a homogeneous hydrogenation catalyst that effects the reduction of alkenes and dienes to saturated alkanes; details are available in the patent literature. The Co complex is a less effective hydrogenation catalyst than the corresponding Rh complex, and vigorous reaction conditions are required. However, under mild reaction conditions the complex is a suitable catalyst for the selective reduction of dienes to alkenes, because of its low catalytic activity (eq 1).

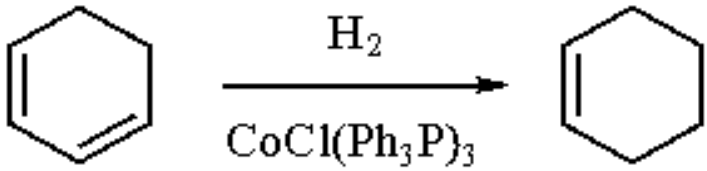

(1)

Dimerization and Hydrodimerization of Alkenes.

$CoCl(Ph_3P)_3$ selectively catalyzes the dimerization of ethylene to butenes in the presence of ***Boron Trifluoride Etherate*** via formation of one-to-one complexes (eq 2).[2]

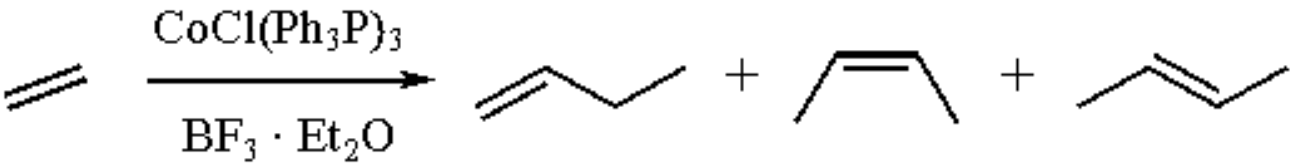

(2)

Terminal alkenes (1-butene, 1-pentene) neither dimerize nor isomerize under these conditions, demonstrating the highly selective behavior of the catalyst. At a higher temperature (60 °C), $CoCl(Ph_3P)_3$ acts as an effective catalyst for the cyclic dimerization of butadiene and mainly affords 1,5-cyclooctadiene (eq 3).[3] A hydridocobalt species is presumed to be an active catalyst in these reactions.

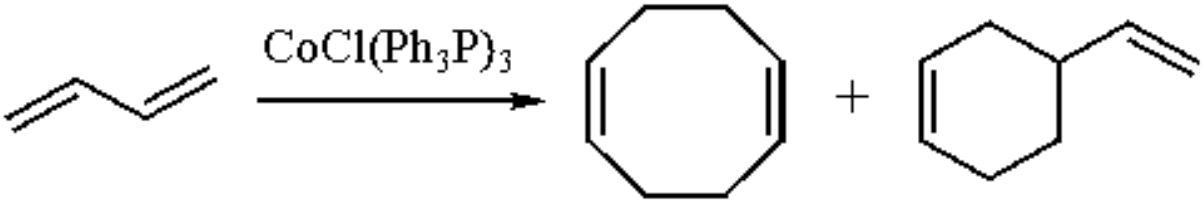

(3)

Hydrodimerization of methyl acrylate is effectively catalyzed by this complex, giving mainly β-to-β coupled dimethyl adipate (eq 4),[4] in contrast to $HCo(dmg)_2P(n\text{-}Bu)_3$, which affords the α-substituted cobaloxime derivative (eq 5).[5]

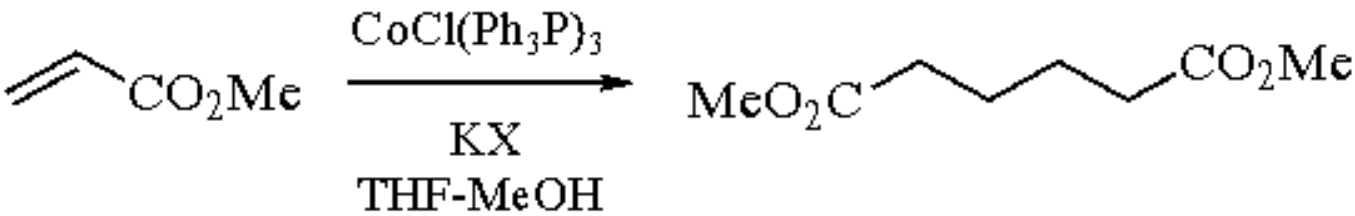

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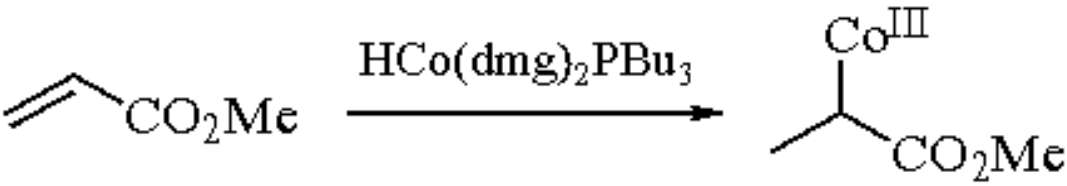

(5)

Reaction with Alkyl Halides.

$CoCl(Ph_3P)_3$ is highly nucleophilic and reacts with alkyl halides to give trivalent alkyl cobalt complexes, followed by cleavage of the resulting Co-C bond which leads to the formation of a new C-C bond. The reaction of benzylic mono-, di-, and trihalides with $CoCl(Ph_3P)_3$ gives coupling products with a single, double, and triple bond, respectively (eq 6).[6]

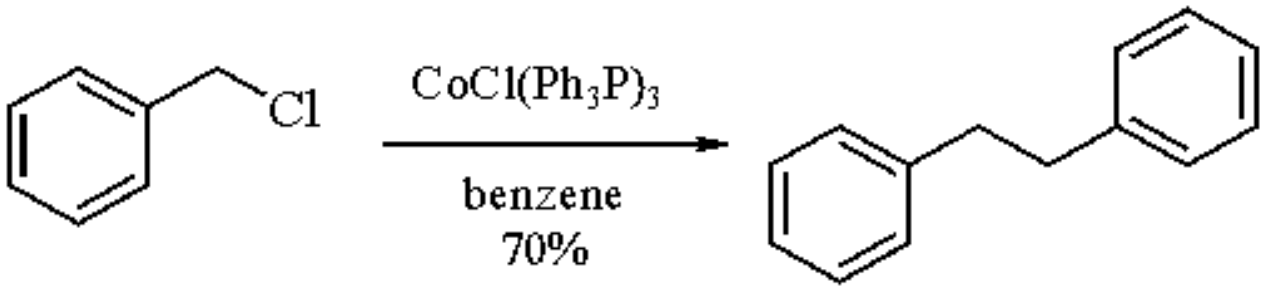

(6)

The coupling of allylic halides affords regioselectively a 1,5-diene with retention of the geometry of the double bond; squalene was synthesized by this method in moderate yields (eq 7).[7]

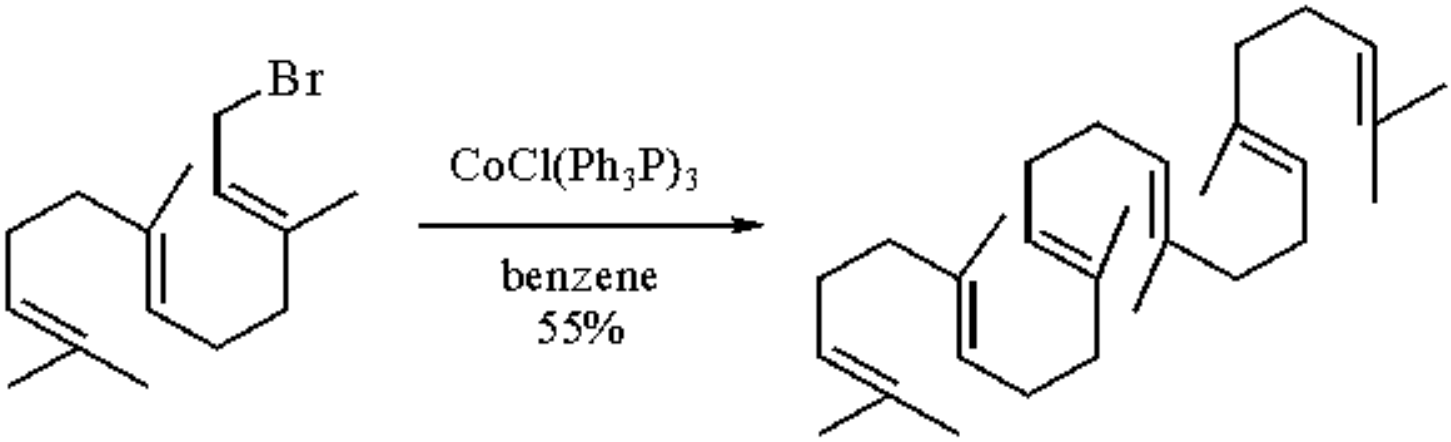

(7)

Biomimetic conversion of bromohydrins to ketones is achieved by $CoCl(Ph_3P)_3$ in good yield (eq 8).[8] This process is analogous to the biological transformation of 1,2-diols to ketones catalyzed by diol dehydrogenase and vitamin B_{12}.

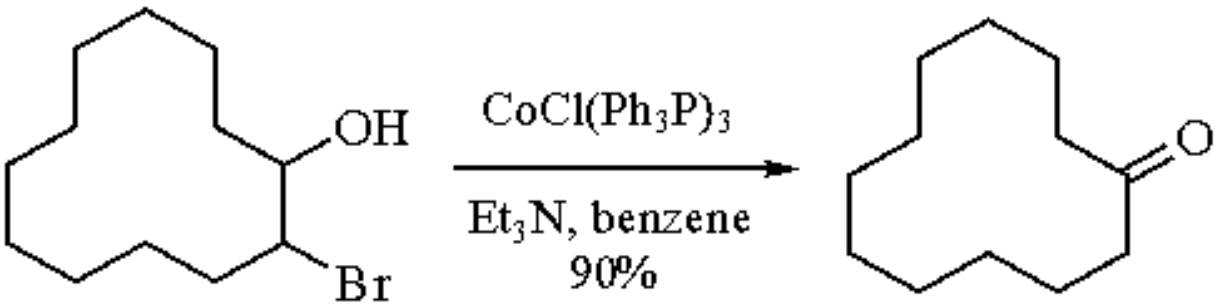

(8)

Organocobalt Reagent.

Air-stable, crystalline phthaloylcobalt and malonylcobalt complexes are conveniently synthesized in high yield by the reaction of cyclobutenediones with $CoCl(Ph_3P)_3$ (eq 9).[9]

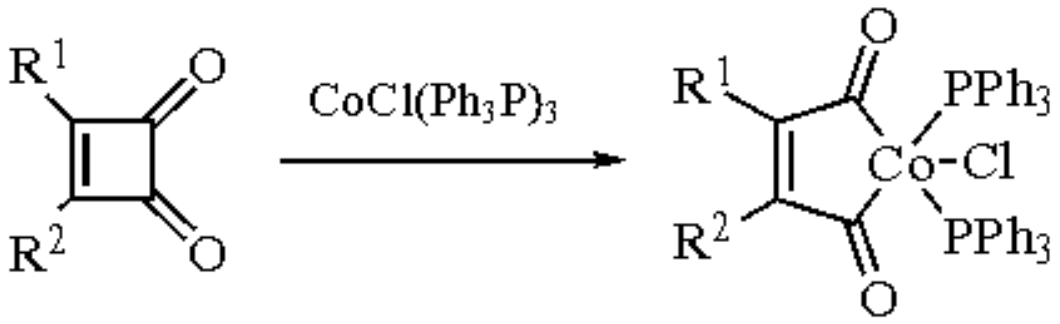

(9)

The addition-elimination reaction of the complex with alkynes provides an efficient and regioselective synthetic method for the preparation of substituted benzoquinones (eq 10).[10]

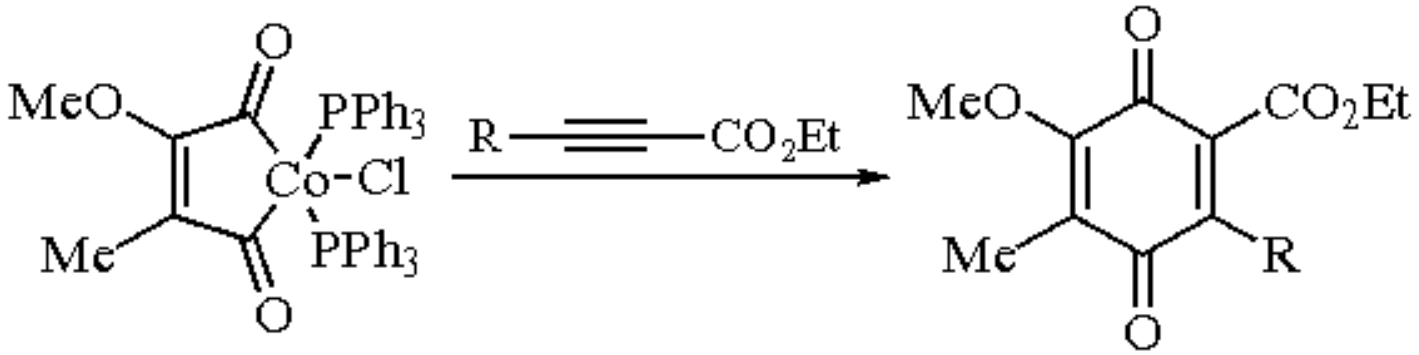

(10)

Related Reagents.

Phthaloylbis(triphenylphosphine)cobalt Chloride; ***Chlorotris(triphenylphosphine)rhodium(I)***.

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Chlorotris(triphenylphosphine)rhodium(I)[1,2]

$RhCl(PPh_3)_3$

[14694-95-2] · $C_{54}H_{45}ClRh$ · Chlorotris(triphenylphosphine)rhodium(I) · (MW 925.24)

(catalyst precursor for many reactions involving alkenes, alkynes, halogenated organics, and organometallic reagents; notably hydrogenations, hydrosilylations, hydroformylations, hydroborations, isomerizations, oxidations, and cross-coupling processes)

Alternate Name: Wilkinson's catalyst.

Physical Data: mp 157 °C. It exists in burgundy-red and orange polymeric forms, which have identical chemical properties (as far as is known).

Solubility: about 20 g L^{-1} in $CHCl_3$ or CH_2Cl_2, about 2 g L^{-1} in benzene or toluene; much less in acetic acid, acetone, methanol, and other aliphatic alcohols. Virtually insol in alkanes and cyclohexane. Reacts with donor solvents like DMSO, pyridine, and acetonitrile.

Form Supplied in: burgundy-red powder, possibly containing excess triphenylphosphine, triphenylphosphine oxide, and traces of rhodium(II) and -(III) complexes.

Analysis of Reagent Purity: ^{31}P NMR displays resonances for the complex in equilibrium with dissociated triphenylphosphine (CH_2Cl_2, approximate δ ppm: 31.5 and 48.0 {*J* values: Rh-P^1 -142 Hz; Rh-P^2 -189 Hz; P^1-P^2 -38 Hz} shifted in the presence of excess PPh_3).[3] Triphenylphosphine oxide contaminant can also be observed (CH_2Cl_2, δ ppm: 29.2) but paramagnetic impurities are generally not evident. In rhodium NMR a signal is observed at -1291 ppm.

Preparative Method: good quality material can be obtained using the latest *Inorganic Syntheses* procedure,[4] with careful exclusion of air. Recrystallization is *not* recommended.

Handling, Storage, and Precautions: the complex should be stored at reduced temperature under dinitrogen or argon. It oxidizes slowly when exposed to air in the solid state, and faster in solution. Such partial oxidation can influence the catalytic efficacy. Consequently, the necessary precautions are governed by the reaction in question. For mechanistic and kinetic studies, reproducible results may only be obtained if the catalyst is freshly prepared and manipulated in an inert atmosphere; even the substrate should be treated to remove peroxides. For hydrogenations of alkenes on a preparative scale, complex that has been handled in the air for very brief periods should be active, but competing isomerization processes may be enhanced as a result of partial oxidation of the catalyst. At the other extreme, exposure to air just before use is clearly acceptable for oxidations in the presence of O_2 and *t*-BuOOH.

Background.[1]

In solution, Wilkinson's catalyst is in equilibrium with the 14e species $RhCl(PPh_3)_2$ (**1**) and triphenylphosphine. The 14e complex is far more reactive than the parent material; consequently it is the reactive entity most likely to coordinate with the substrate and/or the reagents. Generally, the catalytic cycles involving this material then proceed via a cascade of oxidative addition, migratory insertion, and reductive elimination reactions. The postulated mechanism for the hydrogenation of alkenes illustrates these features (Scheme 1), and is typical of the rationales frequently applied to comprehend the reactivity of $RhCl(PPh_3)_3$. Other types of transformations may be important (e.g. transmetalations), and the actual mechanisms are certainly more complicated in many cases; nevertheless, the underlying concepts are similar.

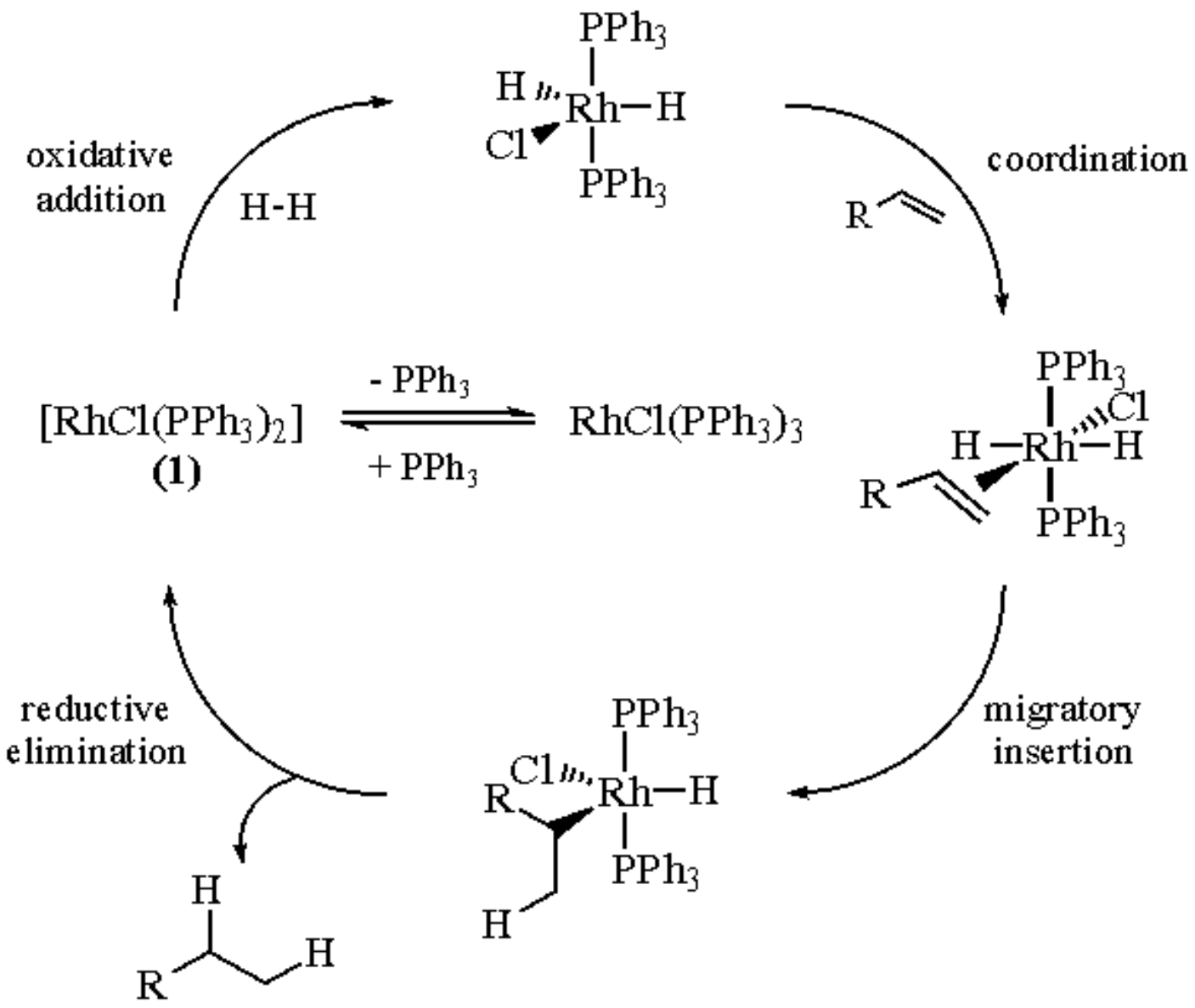

Scheme 1 Simplified mechanism for alkene hydrogenations mediated by $RhCl(PPh_3)_3$

Two important conclusions emerge from these mechanistic considerations. First, $RhCl(PPh_3)_3$ is not a catalyst in the most rigorous sense, but a catalyst precursor. This distinction is critical to the experimentalist because it implies that there are other ways to generate catalytically active rhodium(I) phosphine complexes in solution. Wilkinson's catalyst is a convenient source of homogeneous rhodium(I); it has been extensively investigated because it is easily obtained, and because it was discovered early in the development of homogeneous transition metal catalysts. However, for any transformation there always may be better catalyst precursors than $RhCl(PPh_3)_3$. Secondly, reactions involving a catalytic cycle such as the one shown in Scheme 1 are inherently more complicated than most in organic chemistry. Equilibria and rates for each of the steps involved can be influenced by solvent, temperature, additives, and functional groups on the substrate. Competing reactions are likely to be involved and, if they are, the performance of the catalytic systems therefore is likely to be sensitive to these parameters. Consequently, the purity of the Wilkinson's catalyst used is an important factor. Indeed, less pure catalyst occasionally gives superior results because removal of a fraction of the triphenylphosphine in solution by oxidation to triphenylphosphine oxide gives more of the dissociation product (**1**).

In summary, practitioners of organometallic catalysis should consider the possible mechanistic pathways for the desired transformation, then screen likely catalyst systems and conditions until satisfactory results are obtained. Wilkinson's catalyst is one of the many possible sources of homogeneous rhodium(I).

Hydrogenations.

Wilkinson's catalyst is highly active for hydrogenations of unconjugated alkenes at ambient temperatures and pressures. Steric effects are important insofar as less hindered alkenes react relatively quickly, whereas highly encumbered ones are not reduced (eq 1).[5] Hydrogen in the presence of $RhCl(PPh_3)_3$ under mild conditions does not reduce aromatic compounds, ketones, carboxylic acids, amides, or esters, nitriles, or nitro (eq 2) functionalities. Moreover, hydrogenations mediated by Wilkinson's catalyst are stereospecifically *cis* (eq 1). These characteristics have been successfully exploited to effect chemo-, regio-, and stereoselective alkene reductions in many organic syntheses (eqs 1-3). For instance, steric effects force delivery of dihydrogen to the least hindered face of the alkene in (eq 3).[6] Eq 4 illustrates that 1,4-cyclohexadienes can be reduced with little competing isomerization/aromatization,[7] unlike many other common hydrogenation catalysts.[5]

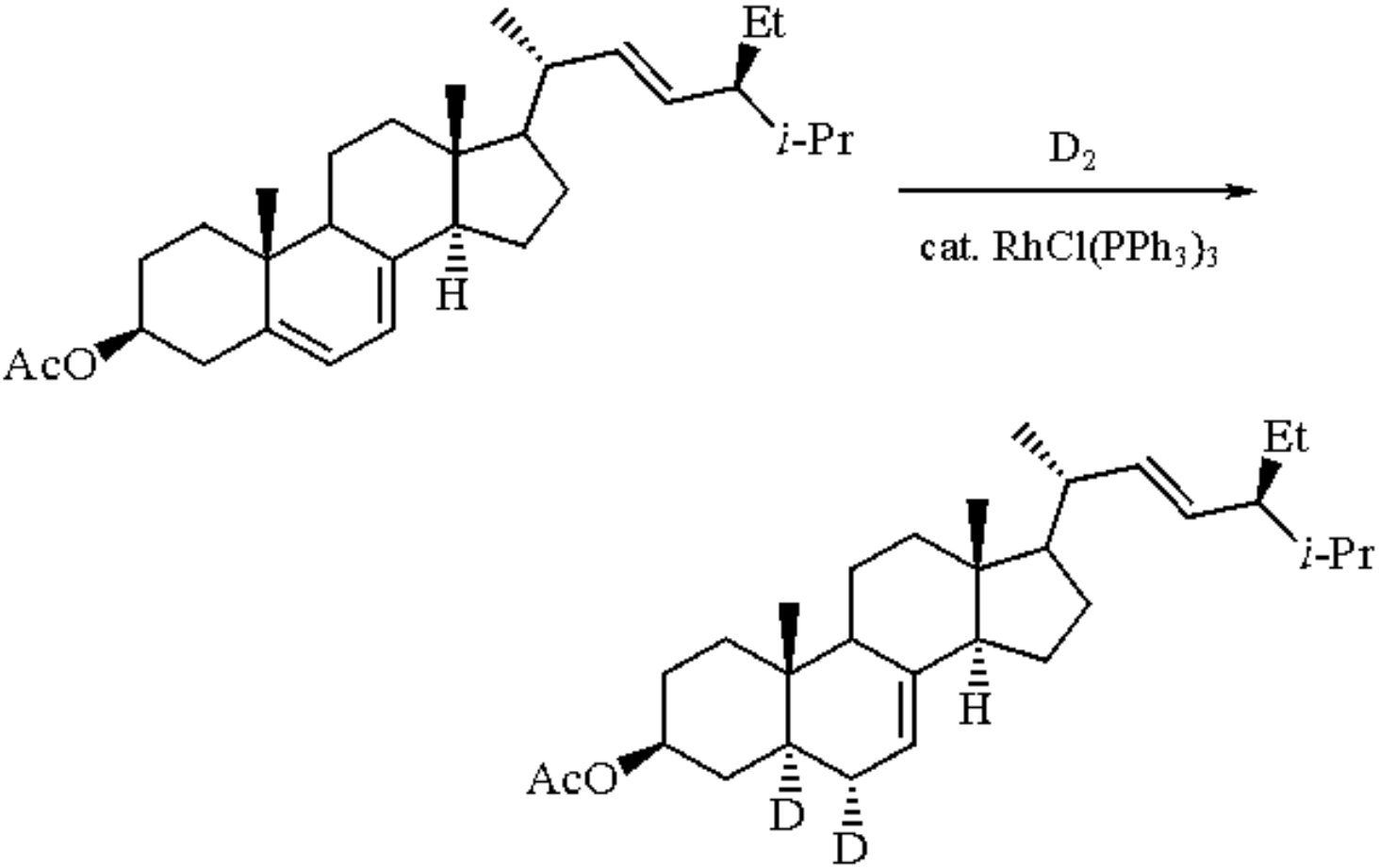
Et
i-Pr
H
AcO
D2
cat. RhCl(PPh3)3
Et
i-Pr
H
AcO
D
D

(1)

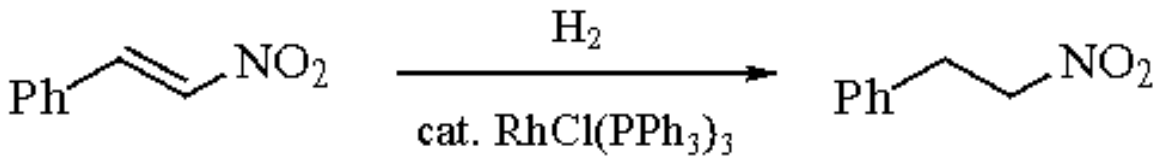
Ph
NO2
H2
cat. RhCl(PPh3)3
Ph
NO2

(2)

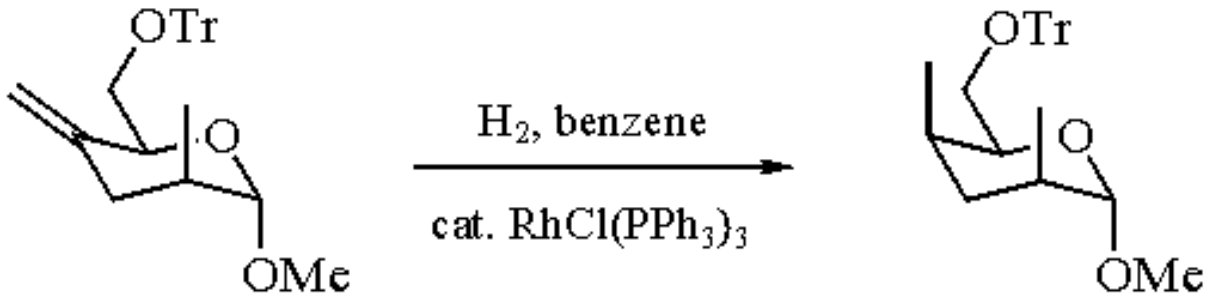
OTr
O
OMe
H2, benzene
cat. RhCl(PPh3)3
OTr
O
OMe

(3)

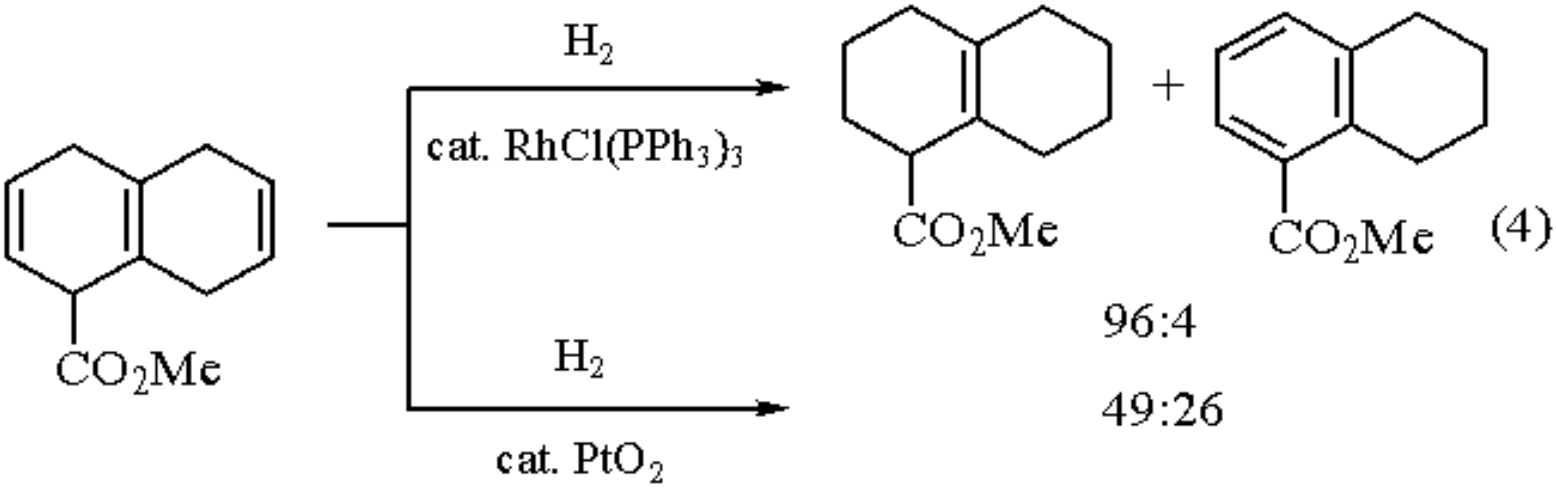

Strongly coordinating ligands can suppress or completely inhibit hydrogenations mediated by Wilkinson's catalyst; examples include 1,3-butadiene, many phosphorus(III) compounds, sulfides, pyridine, and acetonitrile. Similarly, strongly coordinating substrates are not hydrogenated in the presence of Wilkinson's catalyst, presumably because they bind too well. Compounds in this category include maleic anhydride, ethylene, some 1,3-dienes, and some alkynes. Conversely, transient coordination of functional groups on the substrate can be useful with respect to directing $RhCl(PPh_3)_3$ to particular regions of the molecule for stereoselective reactions. However, in directed hydrogenations Wilkinson's catalyst is generally inferior to more Lewis acidic cationic rhodium(I) and iridium(I) complexes.[8] The activity of Wilkinson's catalyst towards hydrogenation of alkenes has been reported to be enhanced by trace quantities of oxygen.[9]

Hydrogenations of alkynes mediated by Wilkinson's catalyst generally give alkanes. *Cis*-alkene intermediates formed in such reactions tend to be more reactive than the alkyne substrate, so this is usually not a viable route to alkenes. Some alkynes suppress the catalytic reactions of $RhCl(PPh_3)_3$ by coordination. Nevertheless, hydrogenation of alkynes mediated by $RhCl(PPh_3)_3$ can be useful in some cases, as in eq 5 in which the catalyst tolerates sulfoxide functionalities and gives significantly higher yields than the corresponding reduction catalyzed by ***Palladium on Barium Sulfate***.[10]

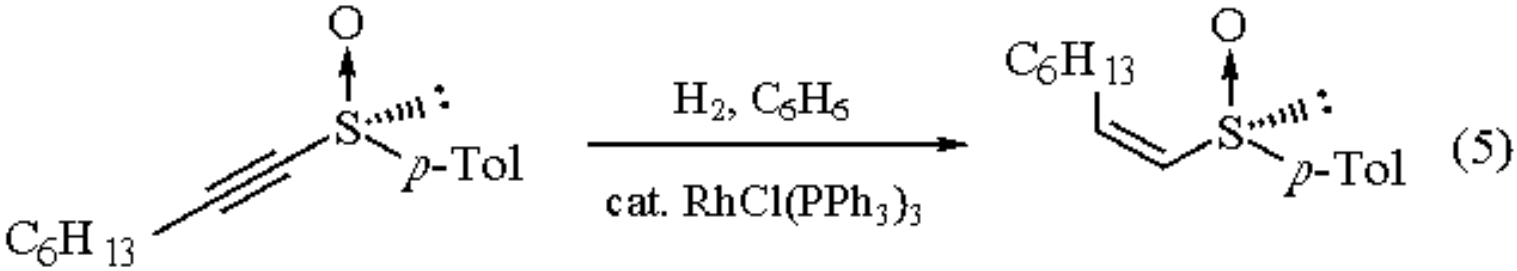

Wilkinson's catalyst can mediate the hydrogenation of allenes to isolated alkenes via reduction of the least hindered bond.[11] Di-*t*-butyl hydroperoxide is hydrogenated to *t*-BuOH in the presence of $RhCl(PPh_3)_3$, though this transformation could occur via a radical process.[12]

Hydrogen Transfer Reactions.

Wilkinson's catalyst should lower the energy barrier for dehydrogenations of alkanes to alkenes since it catalyzes the

reverse process, but no useful transformation of this kind have been discovered. Presumably, the activation energy for this reaction is too great since alkanes have no coordinating groups. Alcohols and amines, however, do have ligating centers, and can dehydrogenate in the presence of Wilkinson's catalyst. These reactions have been used quite often, mostly from the perspective of hydrogen transfer from an alcohol or amine to an alkene substrate, although occasionally to dehydrogenate alcohols or amines.

2-Propanol solvent under basic conditions has been extensively used to transfer hydrogen to alkenes and other substrates. Elevated temperatures are usually required and under these conditions $RhCl(PPh_3)_3$ may be extensively modified prior to the catalysis. Ketones, alkenes (eq 6), aldimines (eq 7),[13] nitrobenzene, and some quinones are reduced in this way.

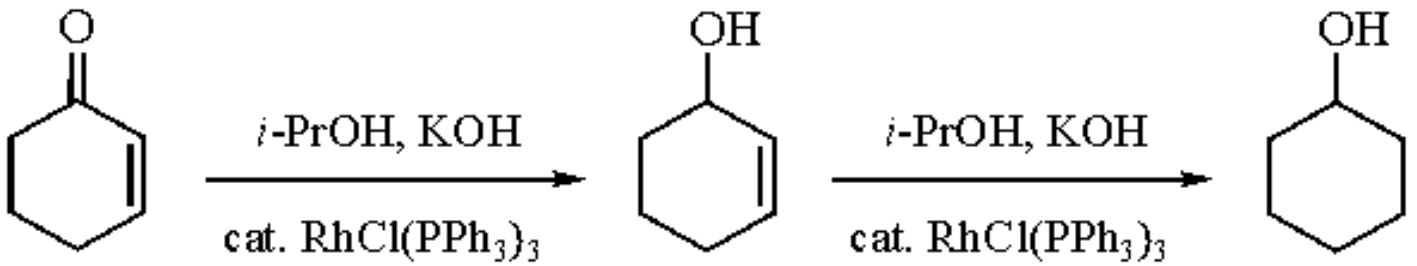

(6)

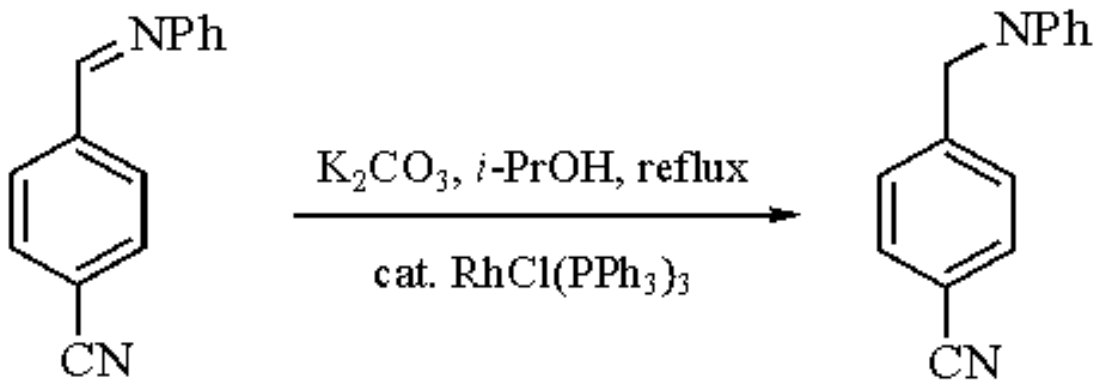

(7)

Wilkinson's catalyst mediates a Cannizzaro-like process with benzaldehyde in ethanol; the aldehyde serves as a dihydrogen source to reduce itself, and the benzoic acid formed is esterified by the solvent (eq 8).[14] Pyrrolidine is *N*-methylated by methanol in the presence of $RhCl(PPh_3)_3$, a reaction that presumably occurs via hydrogen transfer from methanol, condensation of the formaldehyde formed with pyrrolidine, then hydrogen transfer to the iminium intermediate (eq 9).[15]

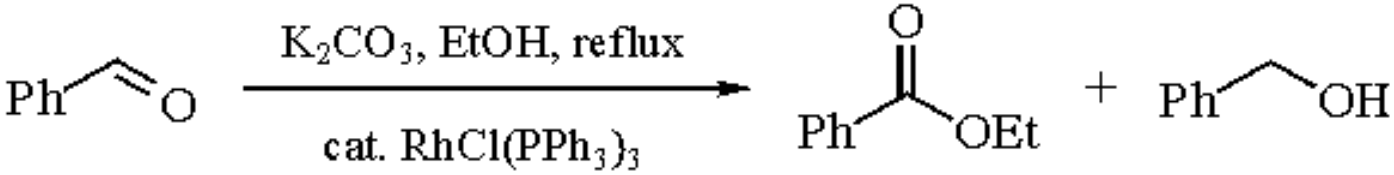

(8)

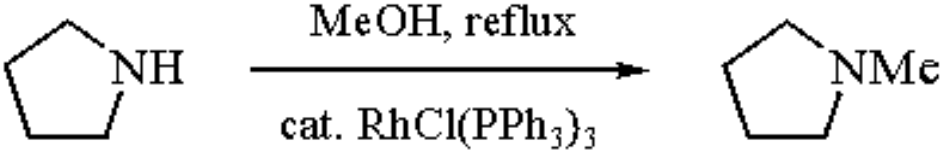

(9)

Hydrosilylations.[16]

Wilkinson's catalyst is one of several complexes which promote hydrosilylation reactions, and it often seems to be among the best identified.[17] However, hydrosilylations with $RhCl(PPh_3)_3$ tend to be slower than those mediated by H_2PtCl_6. Good turnover numbers are observed, the catalyst eventually being inactivated by P-C bond cleavage reactions at the phosphine,[18] and other unidentified processes. Catalysts without phosphine ligands may be even more robust than $RhCl(PPh_3)_3$ because they are unable to decompose via P-C bond cleavage.[19] Wilkinson's catalyst is relatively efficient with respect to converting silanes to disilanes.[20] The latter reaction could be useful in its own right but in the context of hydrosilylation processes it means that the product yields based on the silane are less than quantitative.

For hydrosilylation of alkenes, the reaction rate increases with temperature and hence many of these reactions have been performed at 100 °C. Higher reaction rates are obtained for silanes with very electronegative substituents and low steric requirements (e.g. $HSi(OEt)_3$ > $HSi(i\text{-}Pr)_3$). Terminal alkenes usually are hydrosilylated in an anti-Markovnikov sense to give terminal silanes. Internal alkenes tend not to react (e.g. cyclohexene), or isomerize to the terminal alkene which is then hydrosilylated (eq 10). Conversely, terminal alkenes may be partially isomerized to unreactive internal alkenes before the addition of silane can occur. 1,4-Additions to dienes are frequently observed, and the product distributions are extremely sensitive to the silane used (eq 11).

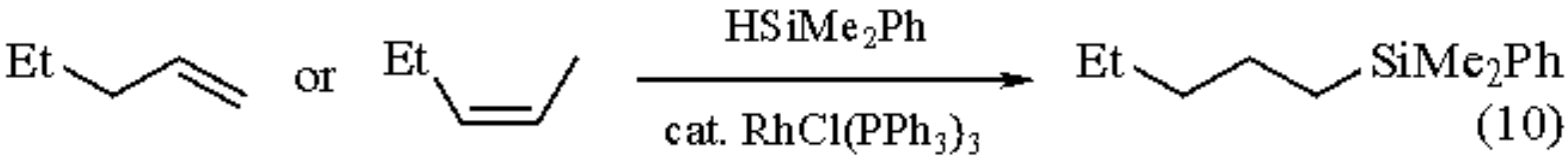

(10)

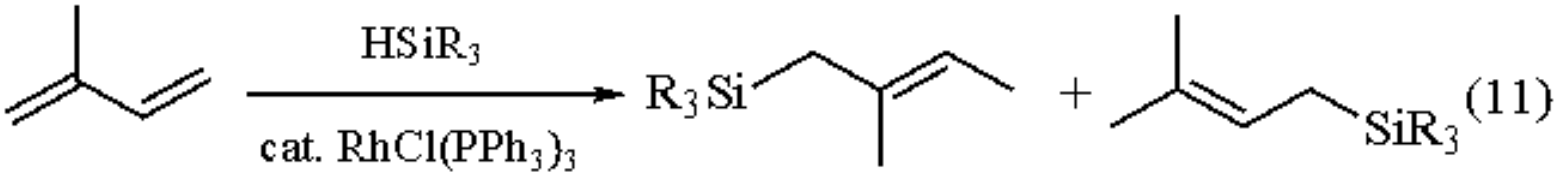

(11)

α,β-Unsaturated nitriles are hydrosilylated, even γ-substituted ones, to give 2-silyl nitriles with good regioselectivity (eq 12).[21] Secondary alkyl silanes are also formed in the hydrosilylation of phenylethylene. In fact, the latter reaction has been studied in some detail, and primary alkyl silanes, hydrogenation product (i.e. ethylbenzene), and *E*-2-silylphenylethylenes are also formed (eq 13).[22] Equimolar amounts of ethylbenzene (**2**) and *E*-2-silylphenylethylene (**4**) are produced, implying these products arise from the same reaction pathway. It has been suggested that this involves dimeric rhodium species because the relative amounts of these products increase with the rhodium:silane ratio; however, competing radical pathways cannot be ruled out. Certainly, product distributions are governed by the proportions of all the components in the reaction (i.e. catalyst, silane, and alkene), and the reaction temperature. Side products in the hydrosilylation of 1-octene include vinylsilanes and allylsilanes (eq 14).[23,24]

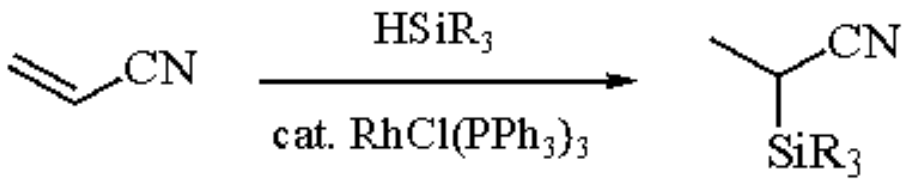

(12)

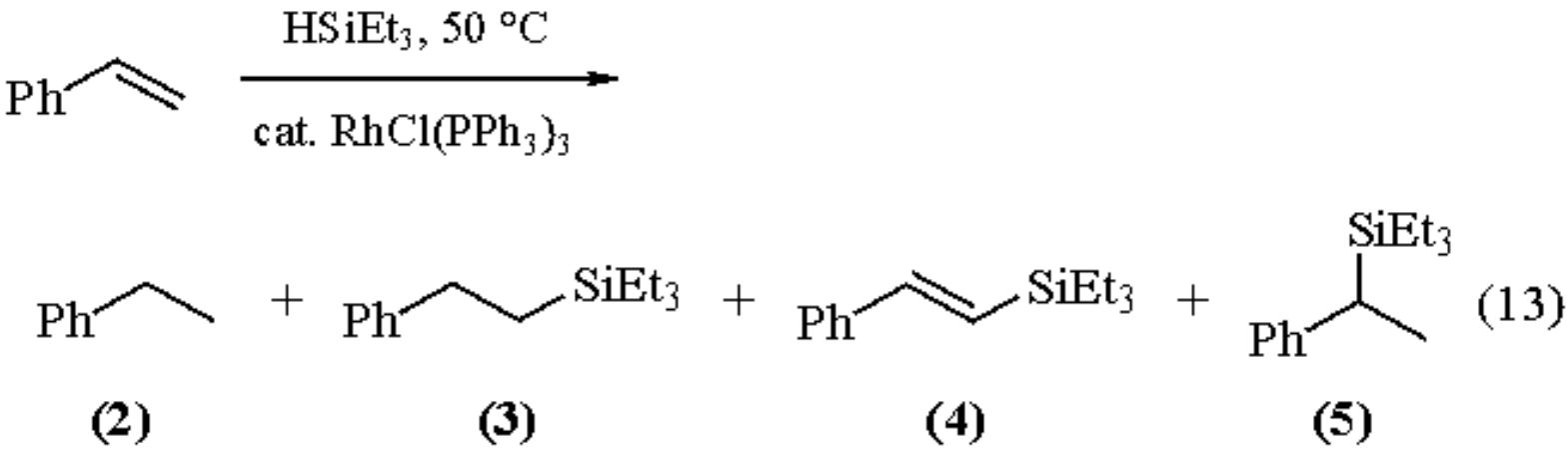

mol % catalyst	(2):(3):(4):(5)
3.1	39: 34: 43: 3
0.12	3: 25: 2: 47

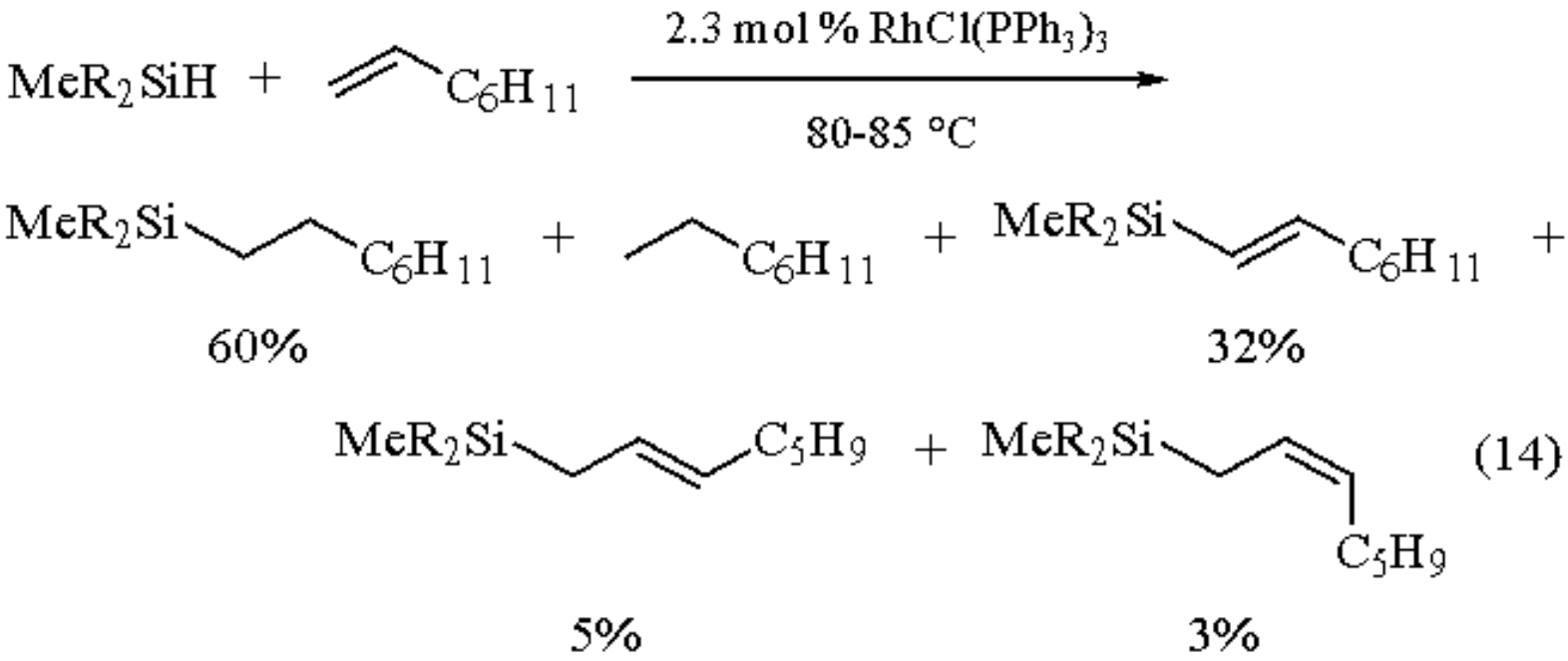

Hydrosilylation of alkynes gives both *trans* products (i.e. formally from *cis* addition), and *cis* products (from either isomerization or *trans* addition); H_2PtCl_6, however, gives almost completely *cis* addition to *trans* products.[25] Moreover, CC-H to CC-SiR_3 exchange processes can occur for terminal alkynes giving (**6**) (eq 15).[25-27] The product distribution in these reactions is temperature dependent, and other factors may be equally important. Nonstereospecific transition metal catalyzed hydrosilylations of alkynes are not confined to Wilkinson's catalyst, and the origin of the *trans* addition product has been investigated in detail for other homogeneous rhodium and iridium complexes.[19]

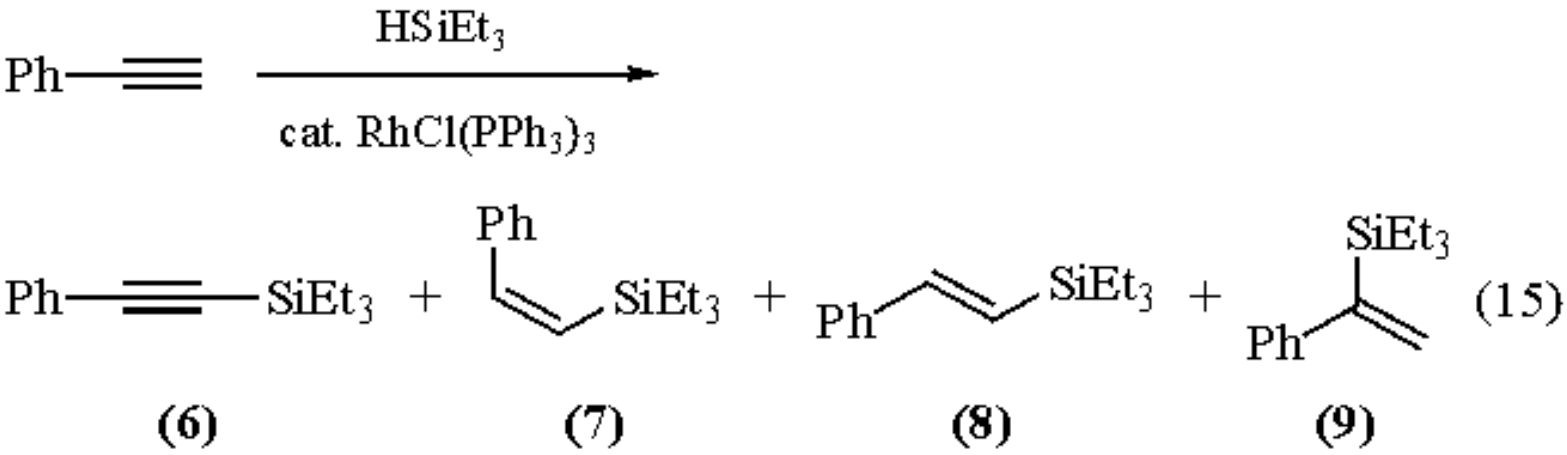

temperature	(6):(7):(8):(9)
65 °C	4: 31: 57: 8
80 °C	3: 55: 35: 7

Hydrosilylation of terminal alkenes has been used in a polymerization process to form new polymeric organic materials.[28]

Hydrosilylation of α,β-unsaturated aldehydes and ketones gives silylenol ethers via 1,4-addition, even when the 4-position is relatively hindered.[29] Hydrolysis of the silyl enol ethers so formed gives saturated aldehydes. Combination of these reduction and hydrolysis steps gives overall reduction of alkenes conjugated to aldehydes, in selectivities which are generally superior to those obtained using hydridic reducing agents (eqs 16 and 17). Dihydrosilanes tend to reduce α,β-unsaturated carbonyl compounds to the corresponding alcohols, also with good regioselectivity (eq 18).

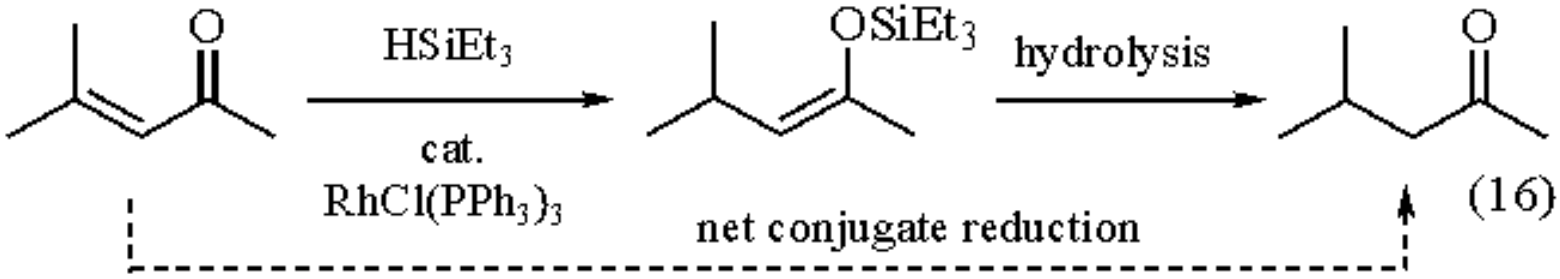

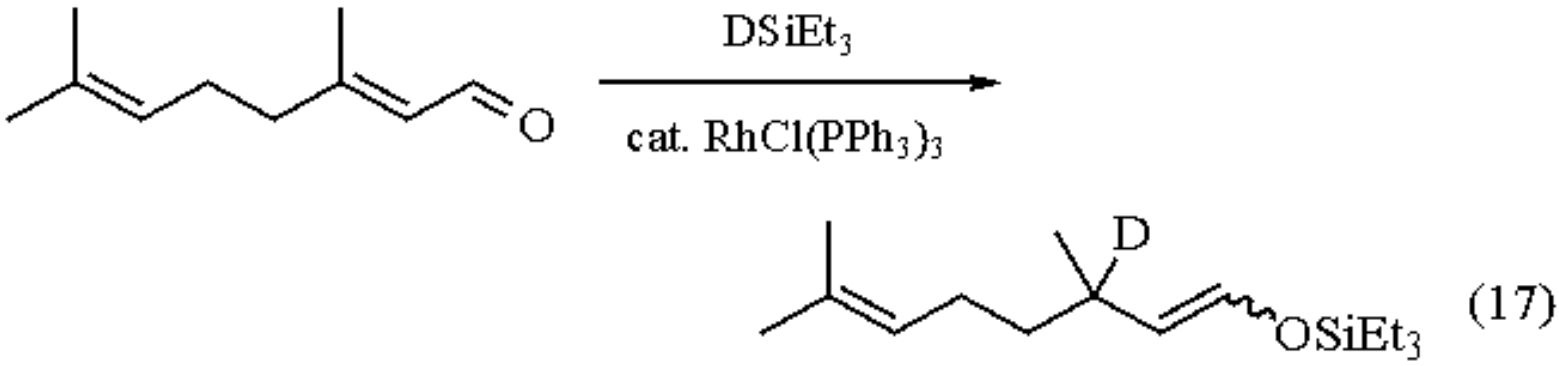

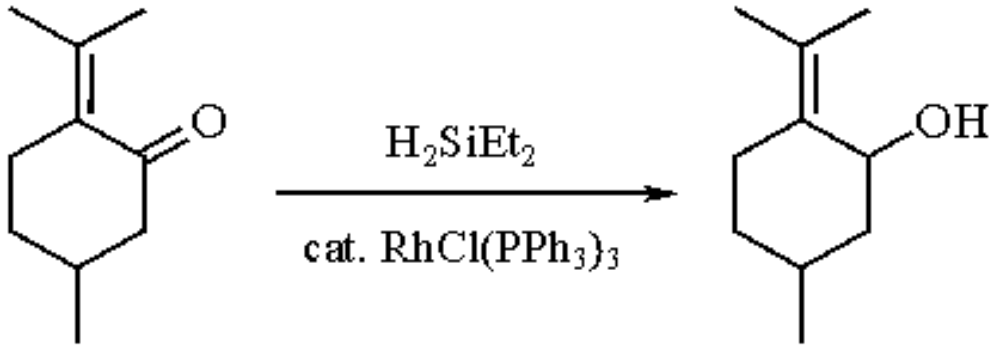

(18)

Similar hydrosilylations of α,β-unsaturated esters are useful for obtaining silyl ketene acetals with over 98:2 (*Z*) selectivity (eq 19);[30] this transformation is complementary to the reaction of α-bromo esters with zinc and chlorotrialkylsilanes, which favors the formation of the corresponding (*E*) products.[30] In cases where (*E*):(*Z*) stereoselectivity is not an issue, ***Rhodium(III) Chloride*** ($RhCl_3.6H_2O$) may be superior to Wilkinson's catalyst.[31] Unconjugated aldehydes and ketones are reduced by silanes in the presence of $RhCl(PPh_3)_3$; trihydrosilanes react quicker than di- than monohydrosilanes.[32,33]

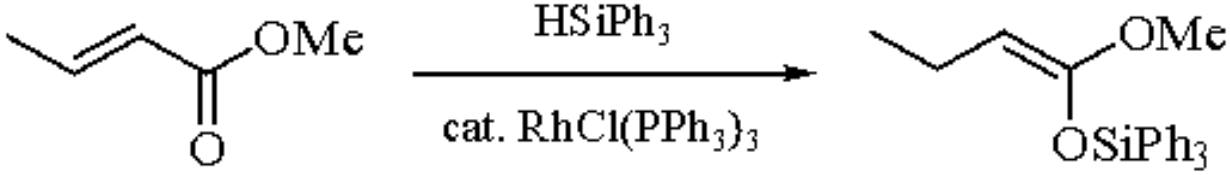

(19)

Alcohols (eq 20)[34] and amines (eq 21)[35] react with silanes in the presence of Wilkinson's catalyst to give the silylated compounds and, presumably, hydrogen. These reactions are useful in protecting group strategies.

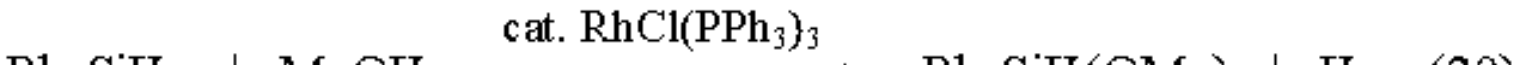

(20)

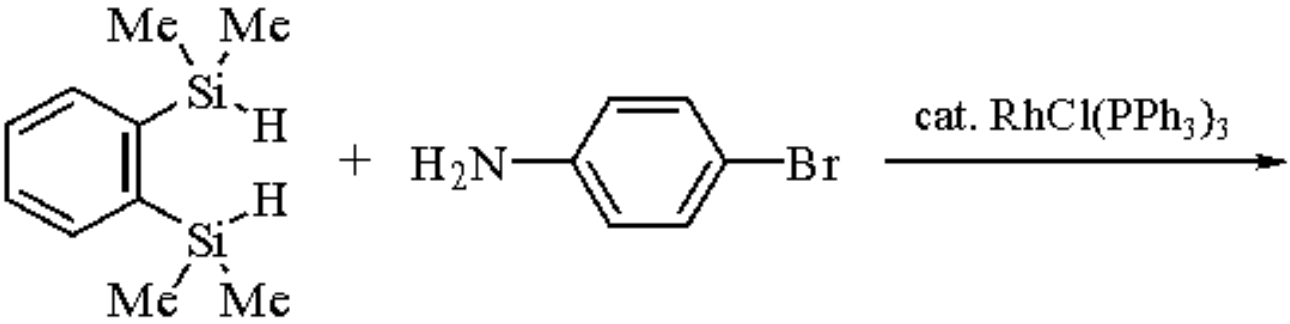

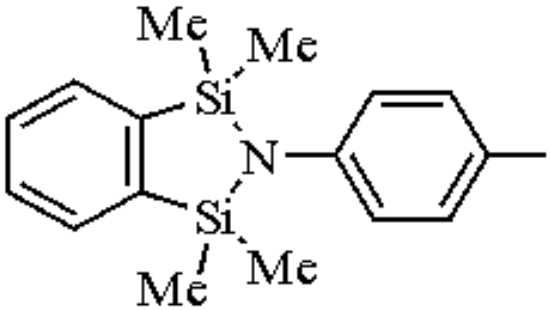

(21)

N,*N*-Dimethylacrylamide and triethylsilane combine in the presence of Wilkinson's catalyst (50 °C) to give a *O*,*N*-silylketene acetal as the pure (*Z*) isomer after distillation; this reaction can be conveniently performed on a gram scale (eq 22). The products have been used in new aldol methodology.[36]

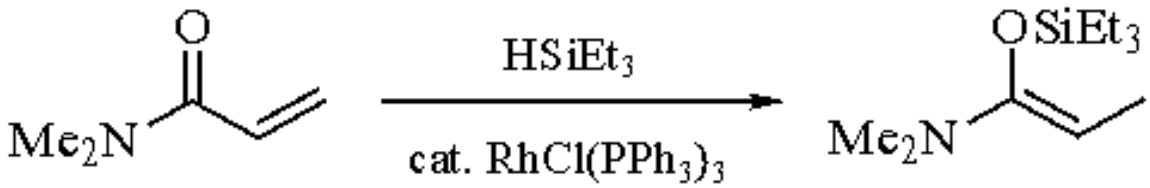

(22)

Hydrostannylations.

Hydrostannanes add to alkynes in uncatalyzed reactions at 60 °C. Phenylacetylene, for instance gives a mixture of (*E*)- and (*Z*)-vinylstannanes, wherein the tin atom has added to the terminal carbons. In the presence of Wilkinson's catalyst, however, the hydrostannylation proceeds at 0 °C to give mostly the regioisomeric vinylstannanes (eq 23).[37] Terminal stannanes in the latter process seem to result from competing free radical additions. This may not be a complication with some other catalysts; the complexes $PdCl_2(PPh_3)_2$ and $Mo(\eta^3\text{-allyl})(CO)_2(NCMe)_2$ also mediate hydrostannylations of alkynes, and they are reported to be 100% *cis* selective.[38] Hydrostannanes and thiols react in a similar way to silanes and alcohols (eq 24).[39]

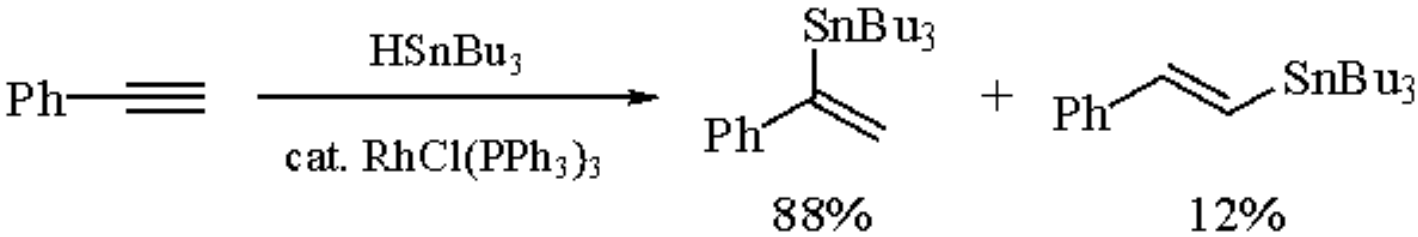

(23)

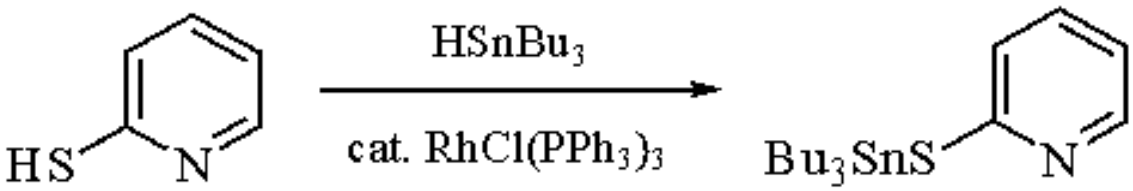

(24)

Hydroacylations.

Alkenes with aldehyde functionality in the same molecule, but displaced by two carbon atoms, can cyclize via intramolecular hydroacylation reactions. Substituent effects can have a profound influence on these transformations. For instance, 3,4-disubstituted 4-pentenals cyclize to cyclopentanones without serious complications,[40] but 2,3-disubstituted 4-pentenals give a cyclopropane as a competing product (eqs 25 and 26).[41] Formation of the latter material illustrates two features which restrict the applicability of this type of reaction. First decarbonylation of the aldehyde can occur, in this case presumably giving a rhodium alkyl complex which then inserts the pendant alkene functionality. Secondly, decarbonylation reactions convert the catalyst into $RhCl(CO)(PPh_3)_2$, which tends to be inactive. Moreover, the reaction is only generally applicable to the formation of five-membered rings, and it is apparently necessary to use quite large amounts of Wilkinson's catalyst to ensure good yields (eq 27).[42] Rhodium(I)

complexes other than $RhCl(PPh_3)_3$ can give better results in some cases.[43]

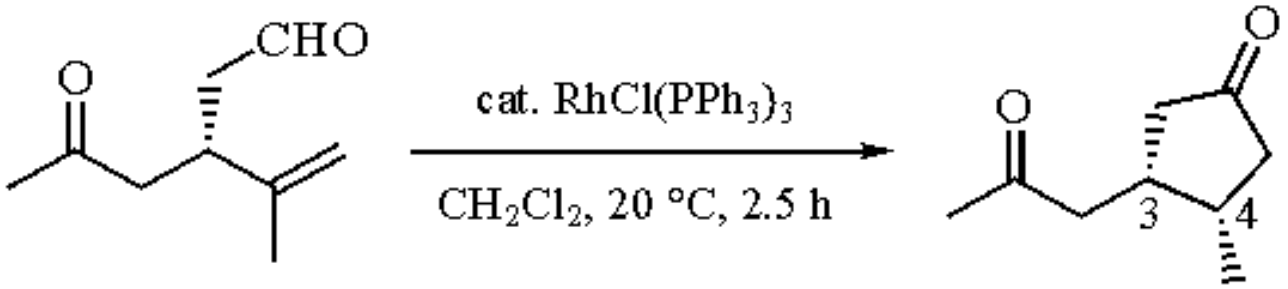

(25)

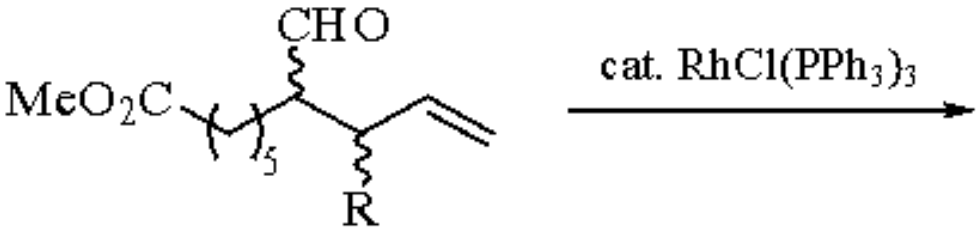

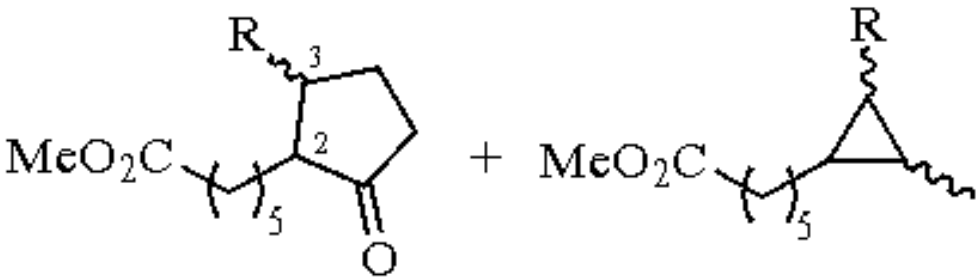

(26)

$R = (CH_2)_7Me$ 1:1

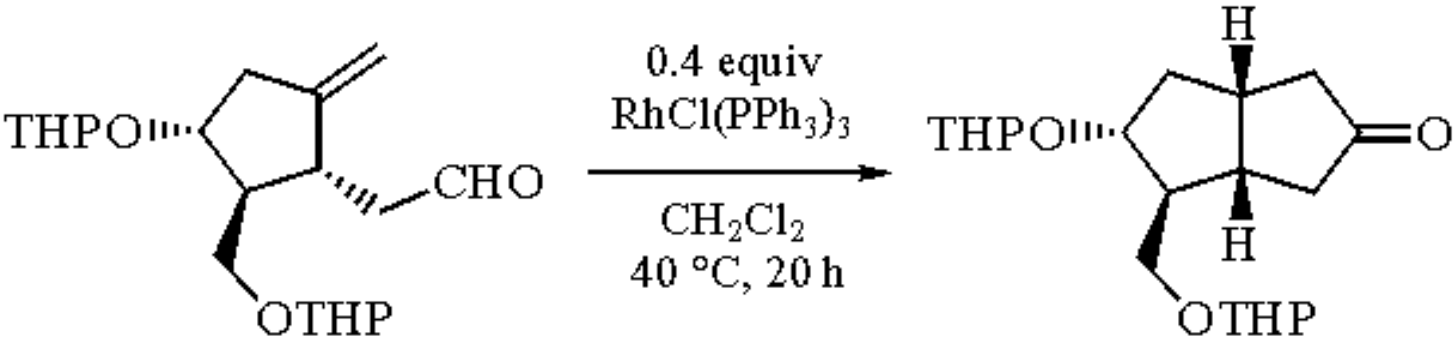

(27)

Lactols can be cyclized under the typical hydroacylation conditions (eq 28), presumably via equilibrium amounts of the corresponding aldehyde.[40] Finally, intermolecular hydroacylation has been formally achieved in the reaction of a pyridyl aldimine with ethylene under pressure at 160 °C; here the pyridine functionality anchors the aldimine to the rhodium, and decarbonylation is impossible (eq 29).

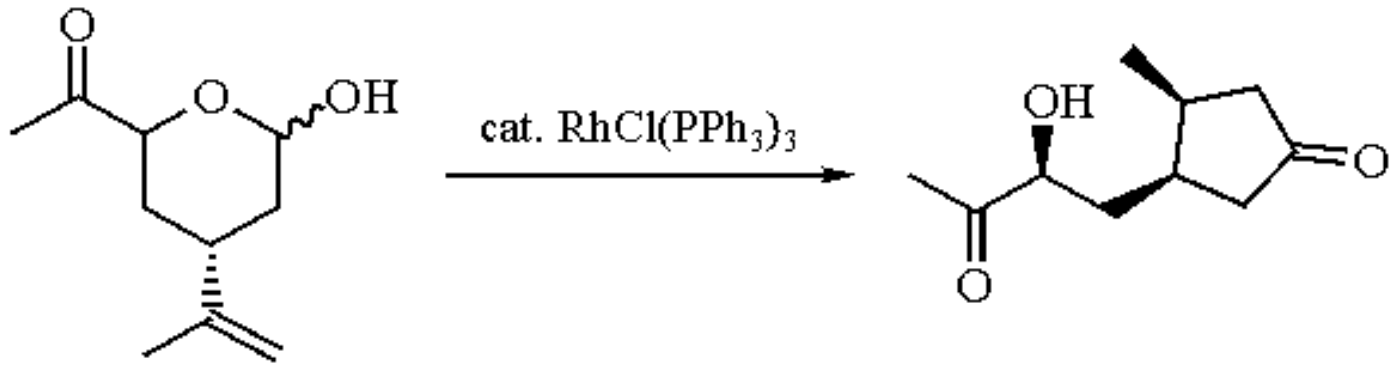

(28)

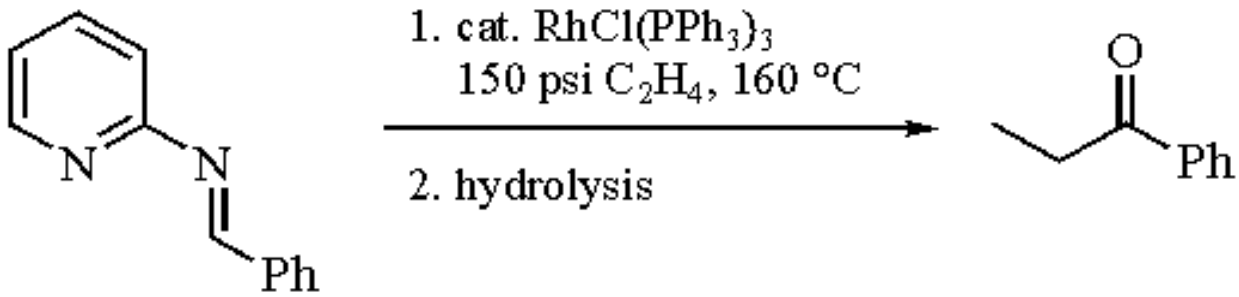

(29)

Decarbonylations.

Wilkinson's catalyst has been known for some time to decarbonylate aldehydes, even heavily functionalized ones, to the corresponding hydrocarbons.[44] Some examples are shown in eqs 30-33, illustrating high stereochemical retention in the decarbonylation of chiral, cyclopropyl, and unsaturated aldehydes.[45,46] Acid chlorides are also decarbonylated by $RhCl(PPh_3)_3$.

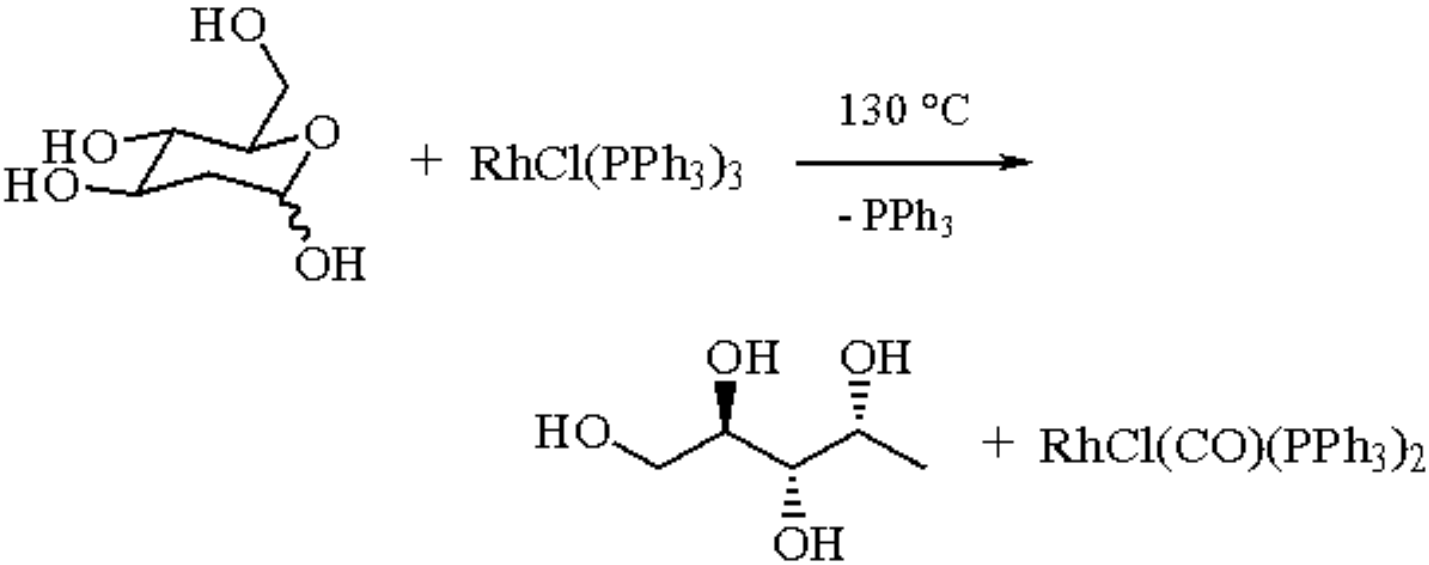

(30)

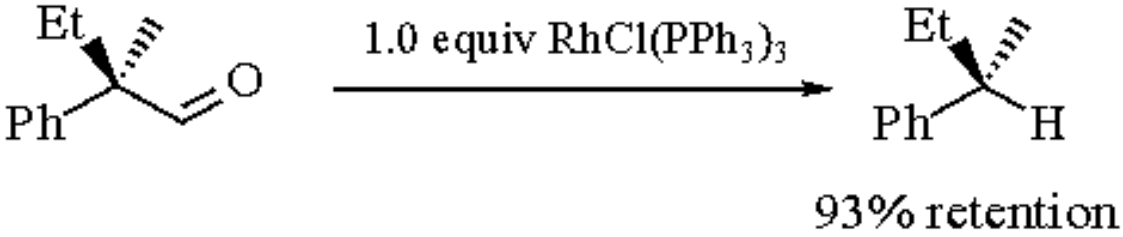

(31)

93% retention

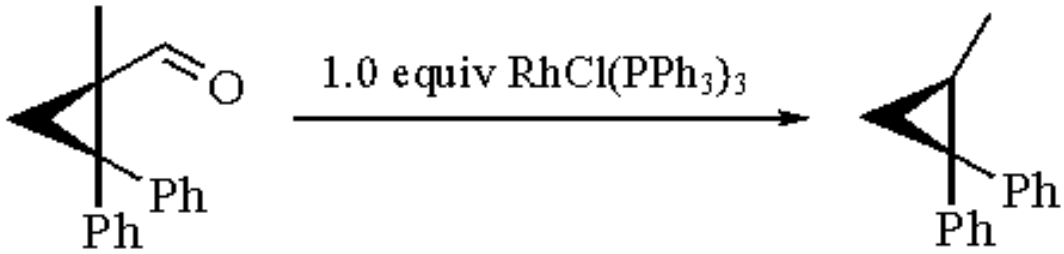

(32)

94% retention

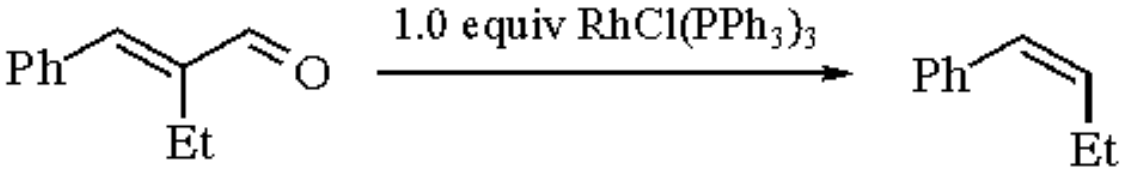

(33)

100% retention

The problem with all these reactions is that stoichiometric amounts of the catalyst are required, and the process is inordinately expensive. Consequently, it has only been used by those wishing to illustrate a decarbonylation occurs for some special reason, or in the closing stages of small scale syntheses of complex organic molecules. Very recently, however, it has been shown that the reaction can be made catalytic by adding ***Diphenyl Phosphorazidate***.[47] The role of the latter is to decarbonylate the catalytically inactive $RhCl(CO)(PPh_3)_2$, regenerating rhodium(I) without carbonyl ligands. Examples of this catalytic process are shown in eqs 34 and 35. The path is now clear for extensive use of $RhCl(PPh_3)_3$ for catalytic decarbonylation reactions in organic synthesis.

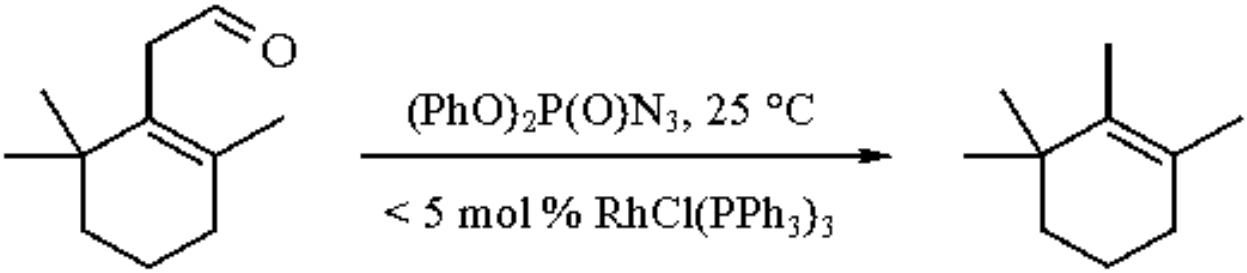

(34)

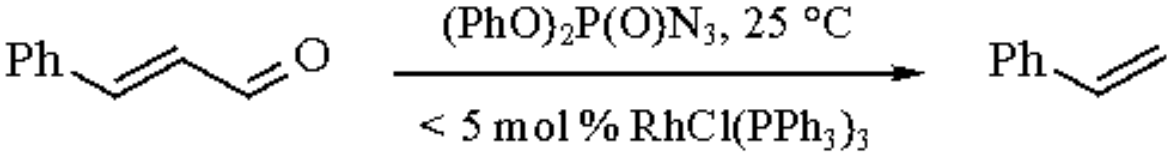

(35)

Catalytic decarbonylations of a few substrates other than aldehydes have been known for some time, e.g. conversion of benzoic anhydrides to fluorenones at high temperatures (ca. 225 °C).[48]

Hydroformylations.[49]

Carbon monoxide reacts rapidly with $RhCl(PPh_3)_3$ to give $RhCl(CO)(PPh_3)_2$. With hydrogen, in the presence of triphenylphosphine, the latter carbonyl complex affords some ***Carbonylhydridotris(triphenylphosphine)rhodium(I)***, and this very actively mediates hydroformylations.[50] Reactions wherein $RhCl(PPh_3)_3$ is used as a hydroformylation catalyst probably proceed via this route. A more direct means of hydroformylation is to use $RhH(CO)(PPh_3)_3$. Nevertheless, Wilkinson's catalyst (an unfortunate term here because Wilkinson also pioneered hydroformylations using $RhH(CO)(PPh_3)_3$) has been used to effect hydroformylations of some substrates. Eq 36 is one example and illustrates that transient coordination of the acyl group with rhodium apparently leads to predominant formation of a branched chain aldehyde, whereas straight chain aldehydes are usually formed in these reactions.[51] Other hydroformylation catalysts that have been studied include cobalt and iridium based systems.[49]

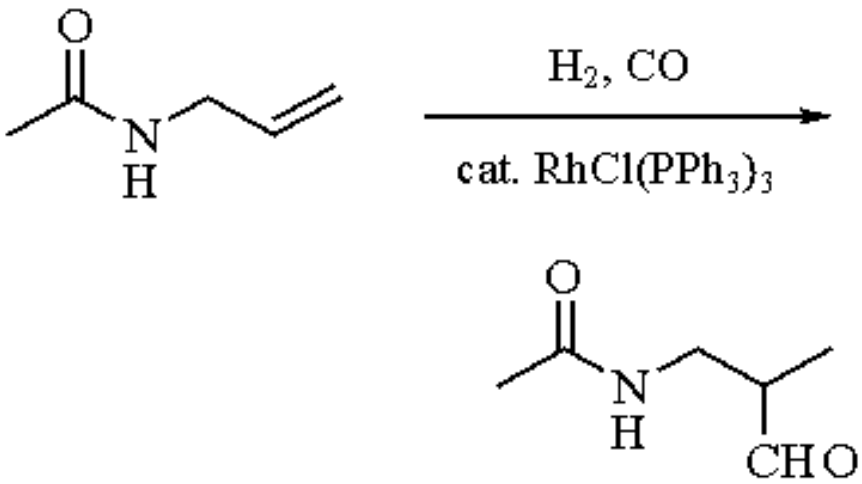

(36)

Hydroborations.[52]

Addition of ***Catecholborane*** to alkenes is accelerated by Wilkinson's catalyst, and other sources of rhodium(I) complexes.[53] Unfortunately, the reaction of Wilkinson's catalyst with catecholborane is complex; hence if the conditions for these reactions are not carefully controlled, competing processes result. In the hydroboration of styrene, for instance, the secondary alcohol is formed almost exclusively (after oxidation of the intermediate boronate ester, eq 37); however, the primary alcohol also is formed if the catalyst is partially oxidized and this can be the major product in extreme cases.[54,55] Conversely, hydroboration of the allylic ether (**12**) catalyzed by pure Wilkinson's catalyst gives the expected alcohol (**13**), hydrogenation product (**14**), and aldehyde (**15**), but alcohol (**13**) is the exclusive (>95%) product if the $RhCl(PPh_3)_3$ is briefly exposed to air before use.[54] The *syn*-alcohol is generally the favored diastereomer in these and related reactions (eq 38), and the catalyzed reaction is therefore stereocomplementary to uncatalyzed hydroborations of allylic ether derivatives.[56-58]

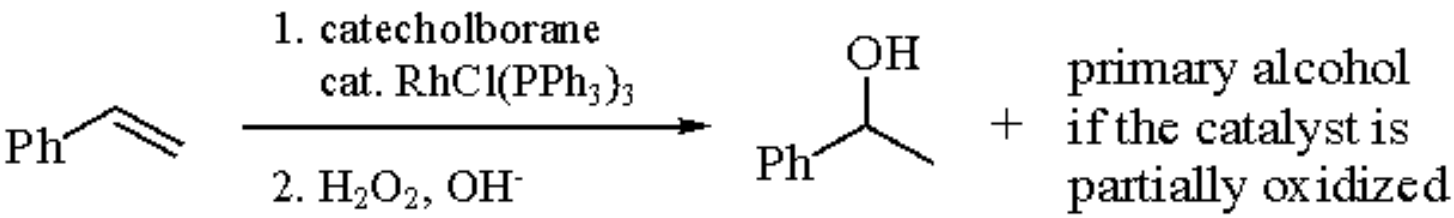

(37)

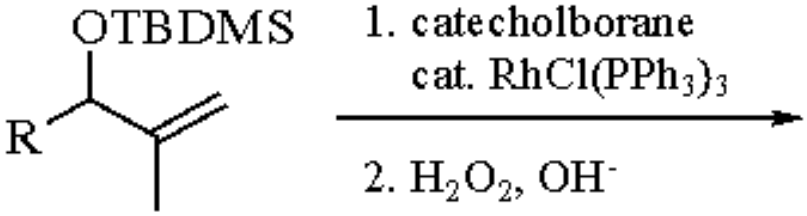

(12)

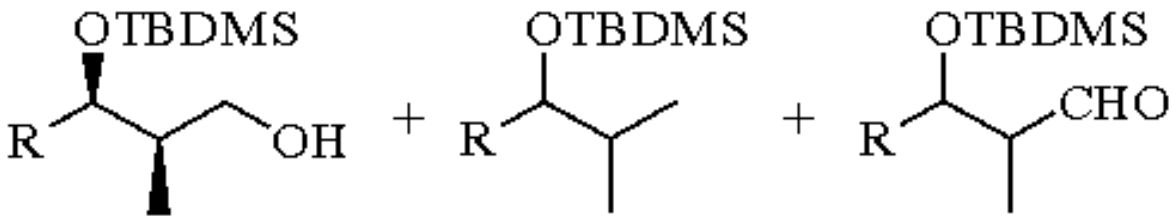

(38)

(13) **(14)** **(15)**

syn product favored

Other sources of rhodium(I) are equally viable catalysts for hydroborations, notably Rh(η^3-CH_2CMeCH_2)(*i*-$Pr_2PCH_2CH_2P$-*i*-Pr_2) which gives a much cleaner reaction with catecholborane than Wilkinson's catalyst.[59] Other catalysts for hydroborations are also emerging.[60-62]

Catecholborane hydroborations of carbonyl and related functionalities are also accelerated by $RhCl(PPh_3)_3$ (eqs 39-41); however, several related reactions proceed with similar selectivities in the absence of rhodium.[63-65]

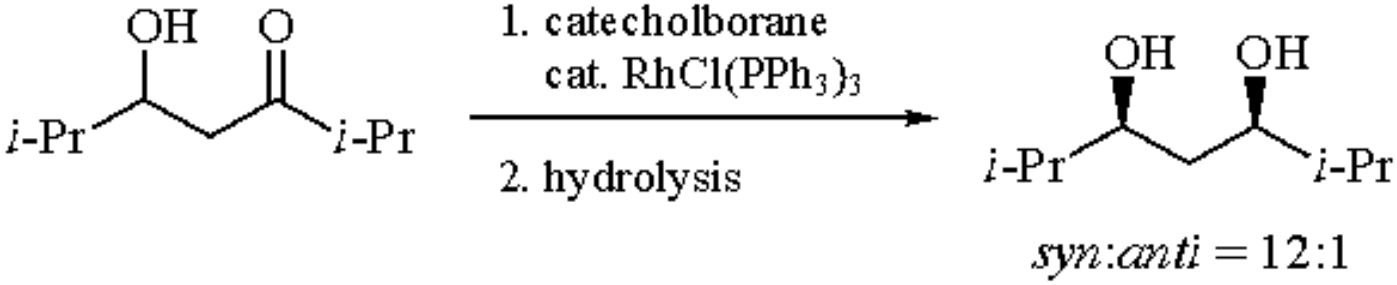

(39)

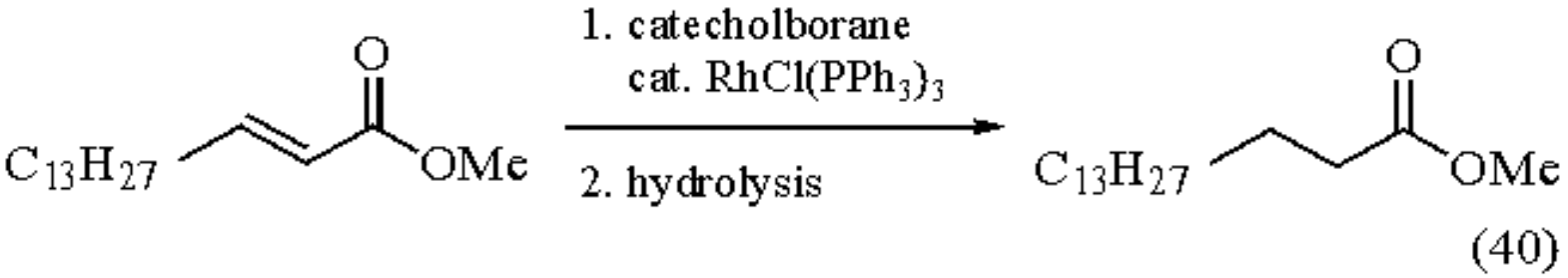

(40)

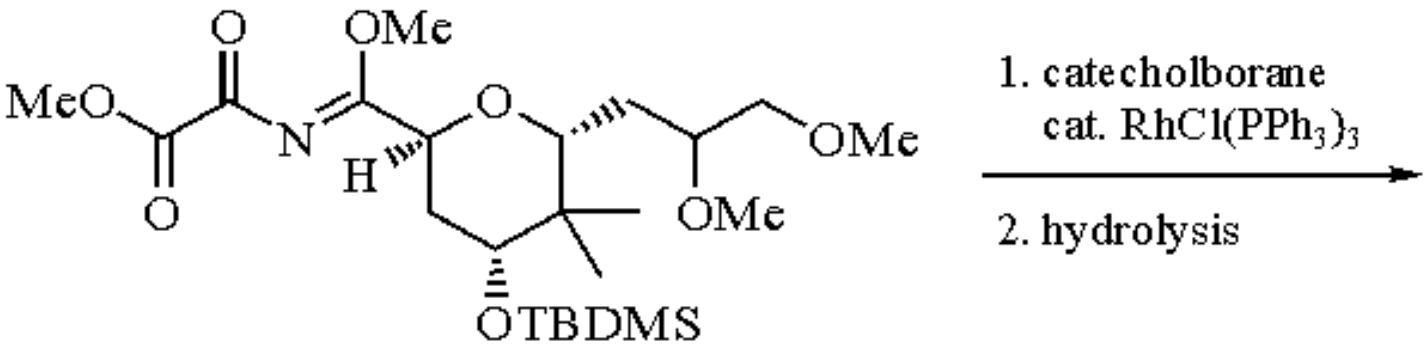

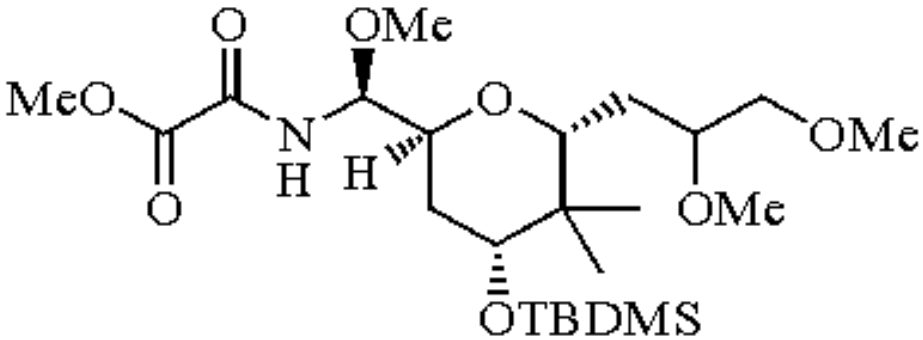

(41

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Cyclization, Isomerization, and Coupling Reactions.

Inter- (eq 42)[66] and intramolecular (eq 43)[67] cyclotrimerizations of alkynes are mediated by Wilkinson's catalyst. This is an extremely efficient route to ring fused systems. Similarly, Diels-Alder-like [4 + 2] cyclization processes are promoted by $RhCl(PPh_3)_3$;[68] dienophile components in these reactions need not be electron deficient, and they can be an alkene or alkyne (eqs 44 and 45). Allenes oligomerize in pathways determined by their substituents. For instance, four molecules of allene combine to give a spirocyclic system (eq 46), but tetraphenylallene isomerizes to give an indene (eq 47).[69]

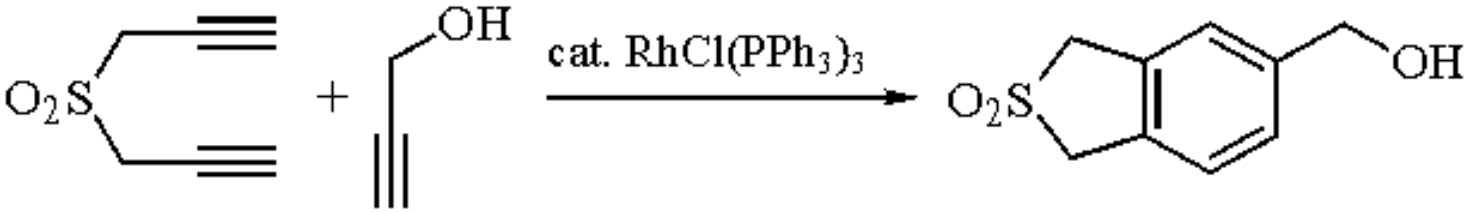

(42)

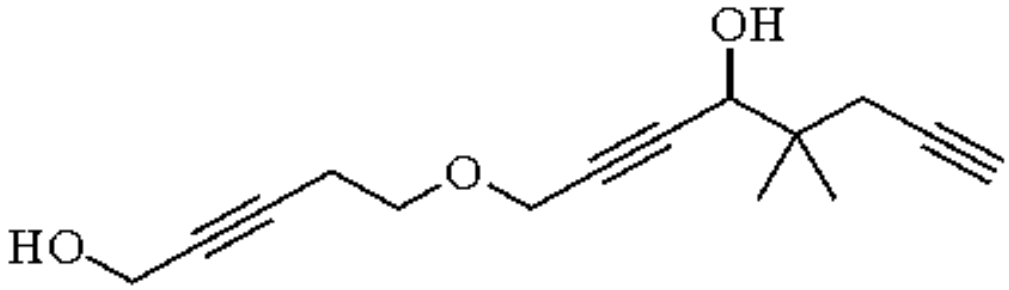
OH
O
HO

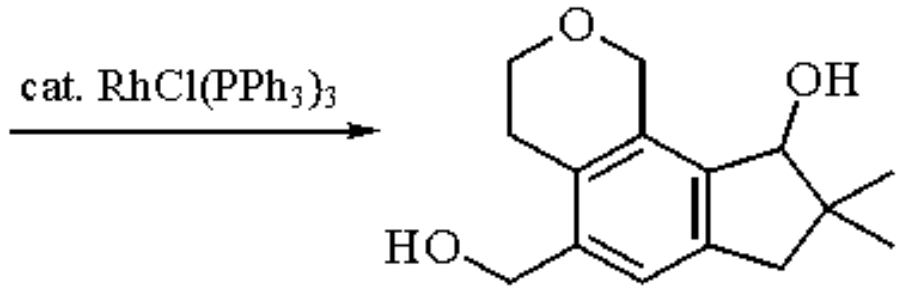
cat. RhCl(PPh3)3
O
OH
HO

(43)

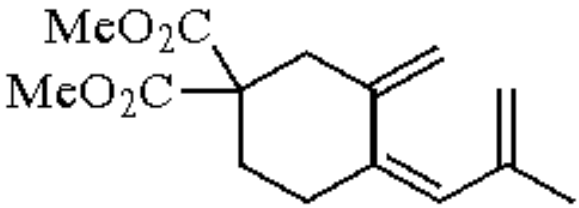
MeO2C
MeO2C

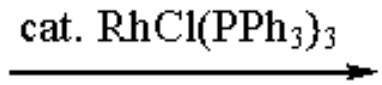
cat. RhCl(PPh3)3

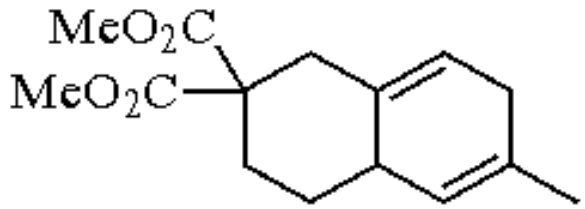
MeO2C
MeO2C

(44)

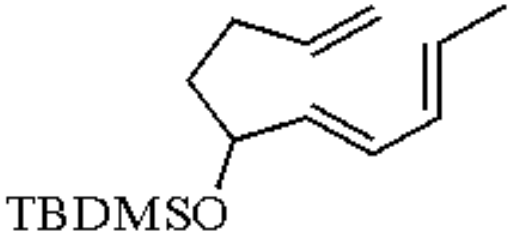
TBDMSO

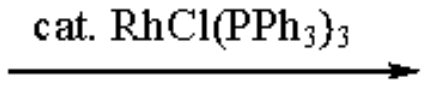
cat. RhCl(PPh3)3

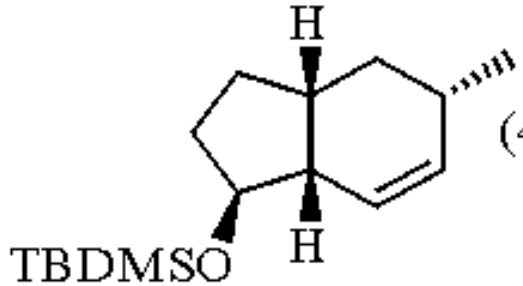
H
H
TBDMSO

(45)

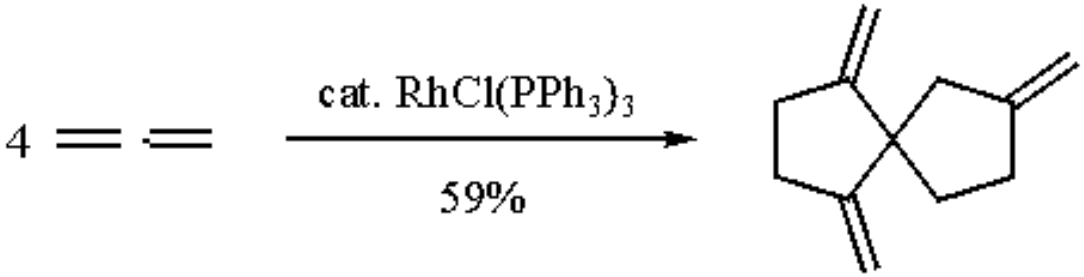
4
cat. RhCl(PPh3)3
59%

(46)

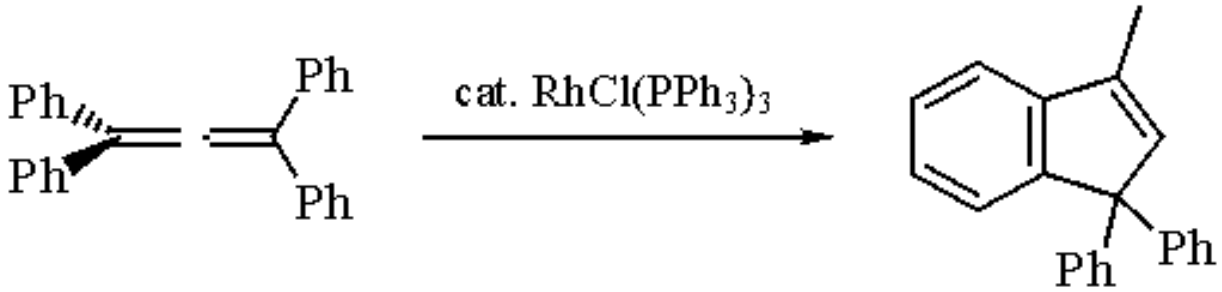

(47)

Wilkinson's catalyst is also capable of mediating the formation of C-C bonds in reactions which apparently proceed via oxidative addition of an unsaturated organohalide across the metal (eq 48),[70] or via transmetalation from an organometallic (eq 49).[71] These two transformation types are very similar to couplings developed by Heck so, predictably, some palladium complexes also mediate these reactions (see ***Tetrakis(triphenylphosphine)palladium(0)*** and ***Palladium(II) Acetate***).

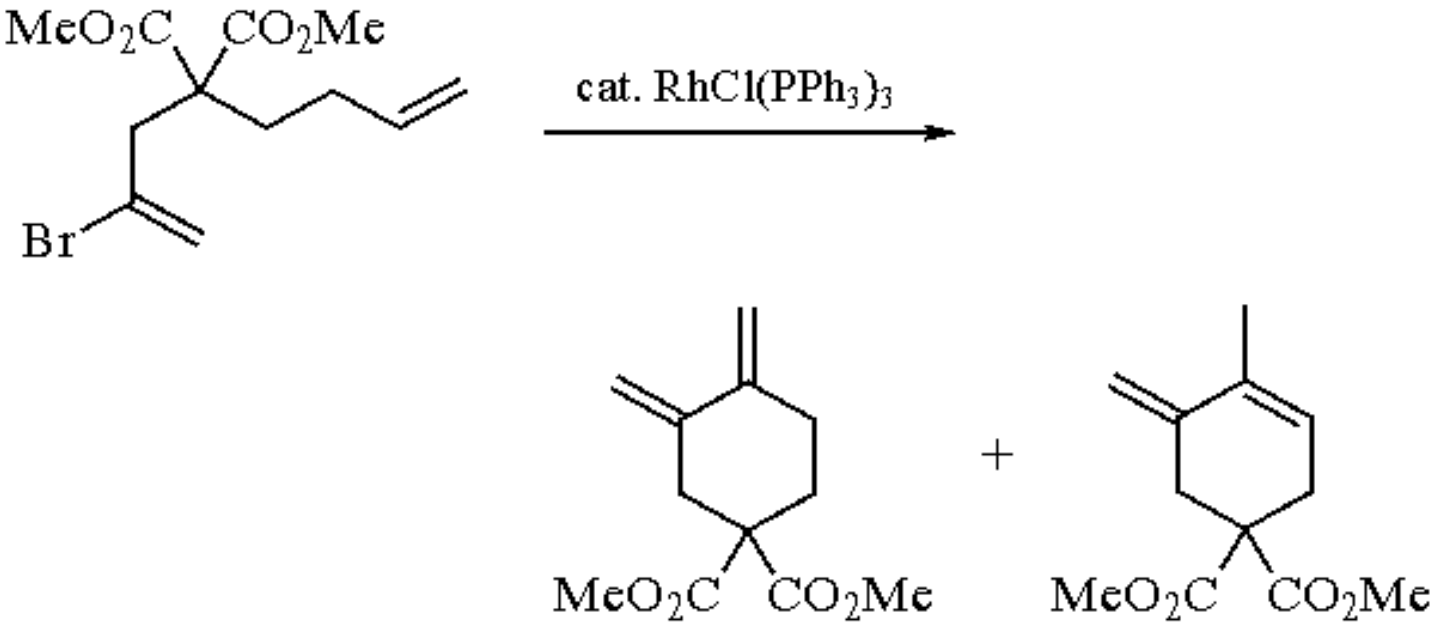

(48)

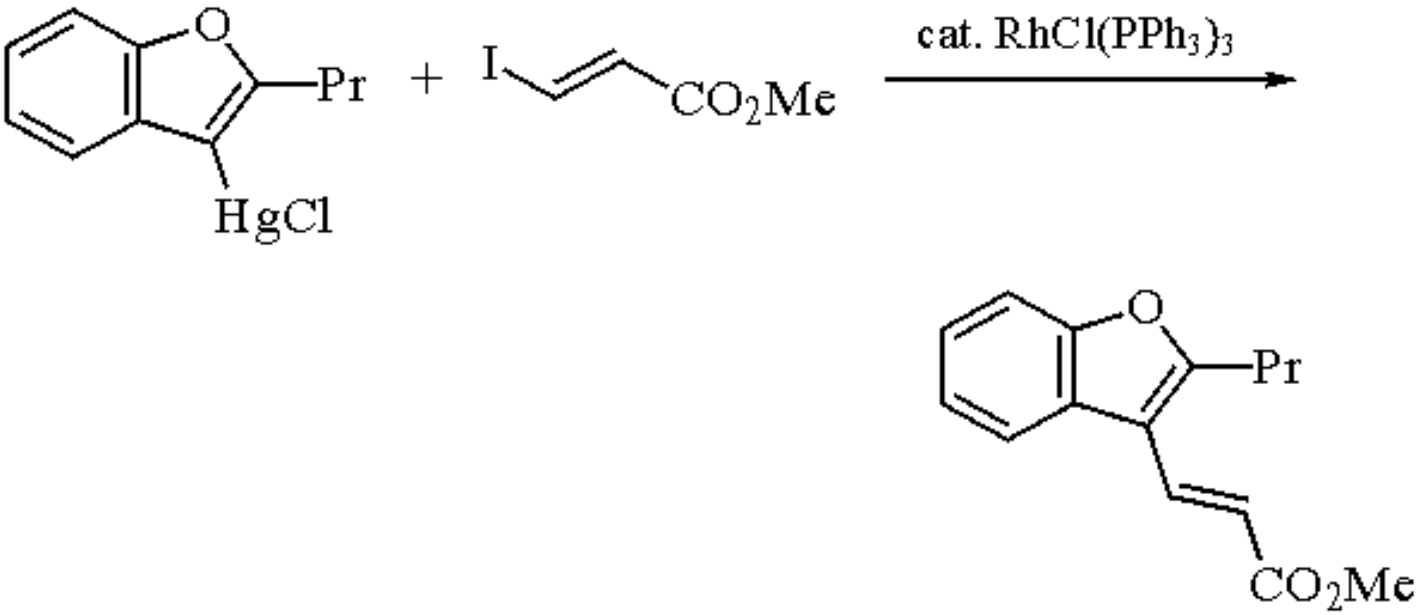

(49)

Intermolecular reactions of dienes, allenes, and methylenecyclopropanes with alkenes are mediated by $RhCl(PPh_3)_3$, although mixtures of products are usually formed (eqs 50, 51).[72-75]

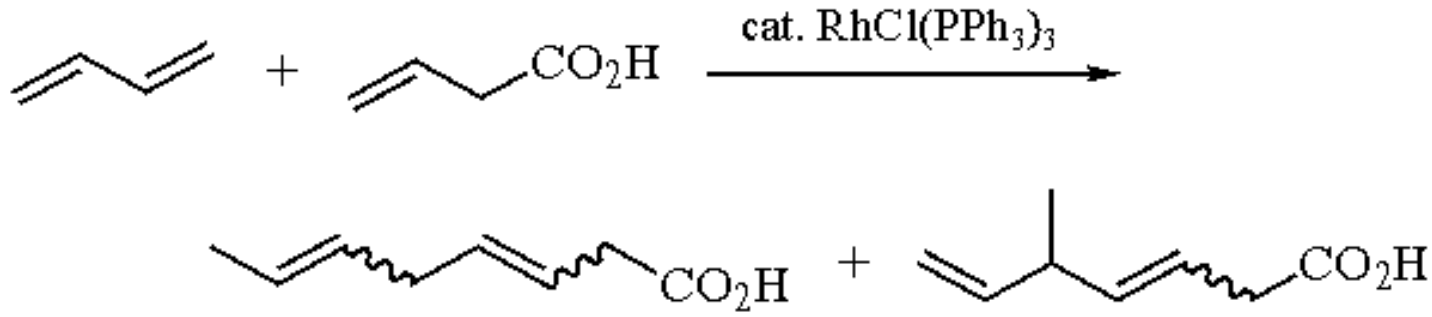

(50)

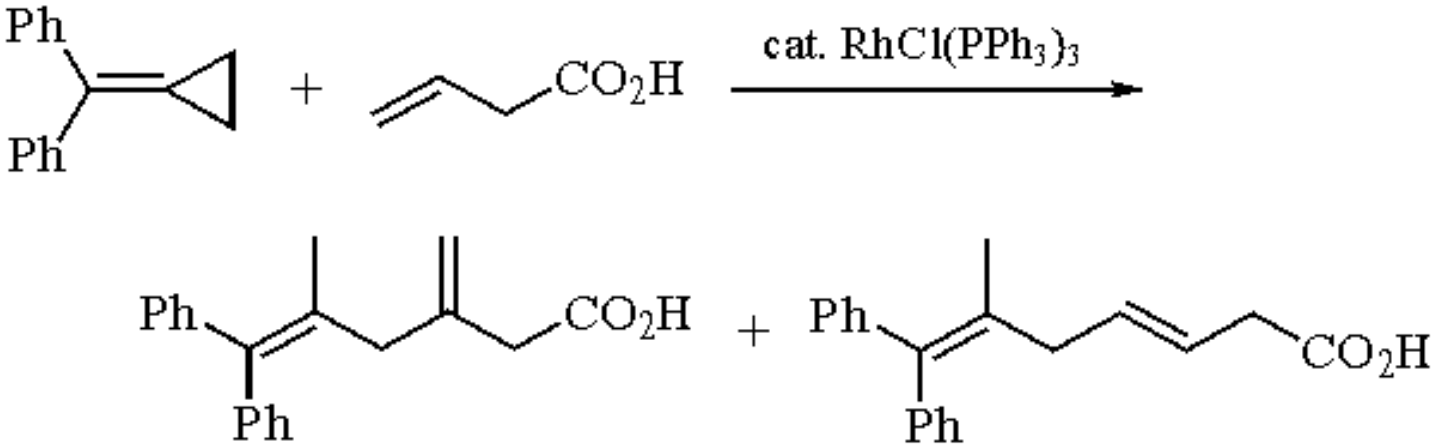

(51)

Wilkinson's catalyst mediates hydrogenation of 1,4-cyclohexadienes without double bond isomerization (see above), but at elevated temperatures in the absence of hydrogen it promotes isomerization to conjugated dienes (eq 52).[76] Isomerization of allylamines to imines followed by hydrolysis has also been performed using $RhCl(PPh_3)_3$ (eq 53),[77] although $RhH(PPh_3)_4$ and other catalysts are more frequently used for this reaction type.[78]

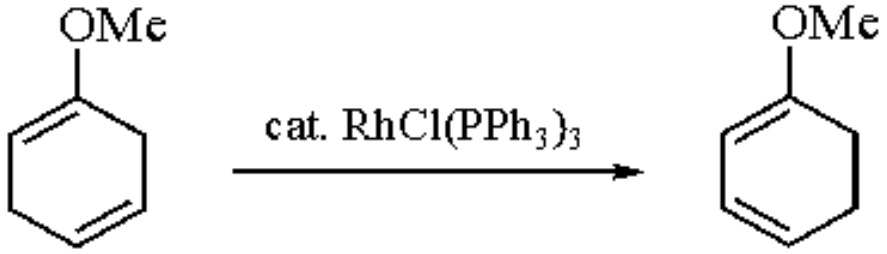

(52)

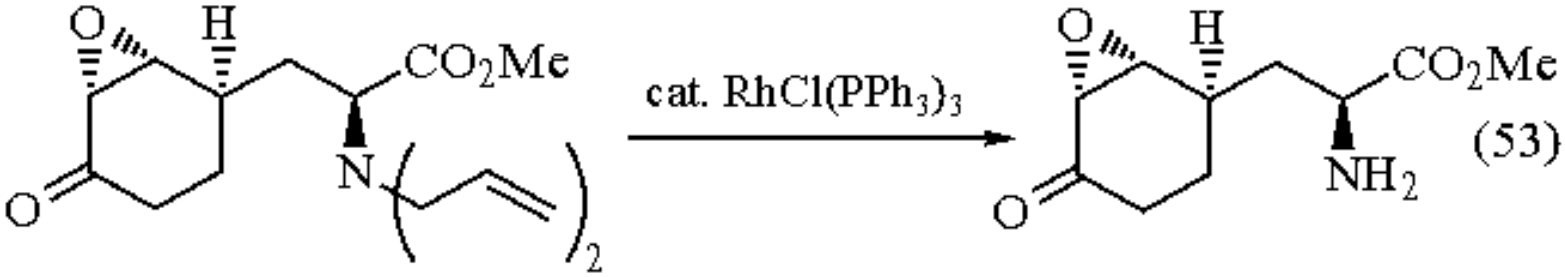

(53)

Oxidations.

Cleavage of alkenes to aldehydes and ketones is promoted by Wilkinson's catalyst under pressures of air or oxygen,[79] but these reactions are inferior to ozonolysis because they tend to form a mixture of products. More useful are the oxidations of anthracene derivatives to anthraquinones in the presence of oxygen/***t-Butyl Hydroperoxide*** and catalytic $RhCl(PPh_3)_3$ (eq 54).[80,81] Wilkinson's catalyst reacts with oxygen to form an adduct so $RhCl(PPh_3)_3$ is clearly quite different from the true catalyst in all the reactions mentioned in this section.

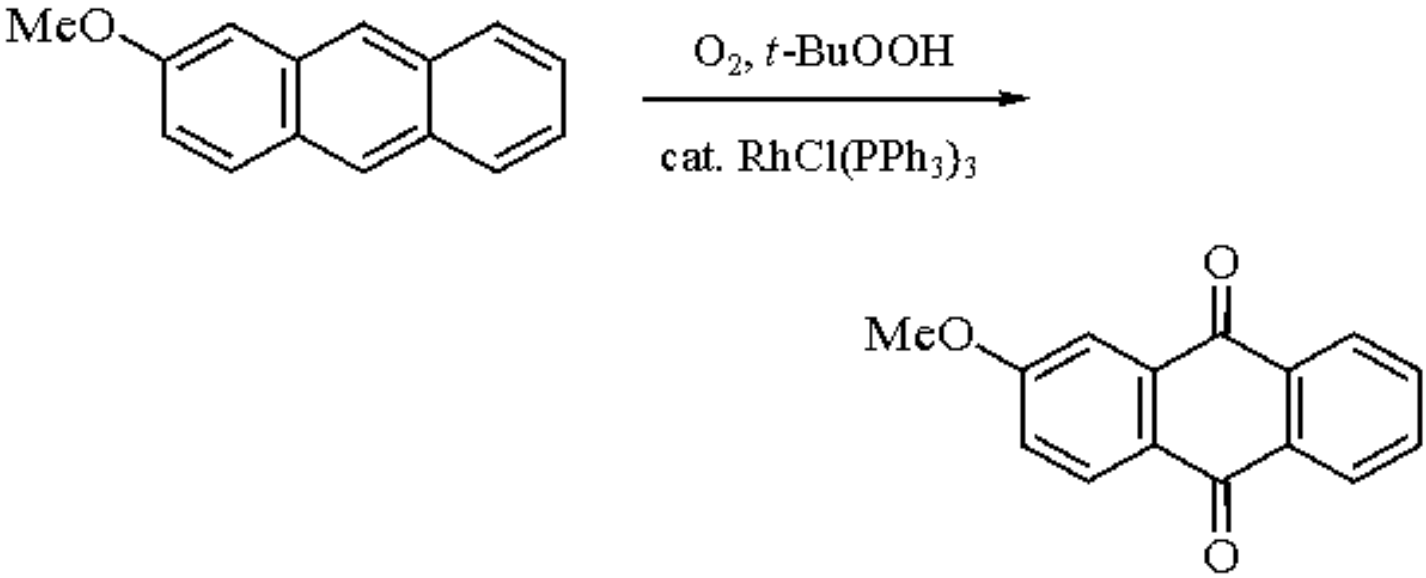

(54)

Other Transformations.

At high temperatures (>200 °C) aromatic sulfonyl chlorides are desulfonated to the corresponding aryl halides in the presence of Wilkinson's catalyst (eq 55).[82] Benzamides and malonamide also decompose under similar conditions, giving benzonitrile and acetamide, respectively.[83]

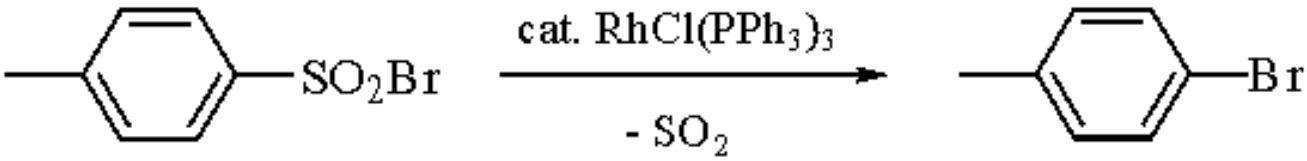

(55)

Diazonium fluoroborates are reduced to the corresponding unsubstituted aryl compounds by Wilkinson's catalyst in DMF; the solvent is apparently the hydride source in this reaction (eq 56).[84]

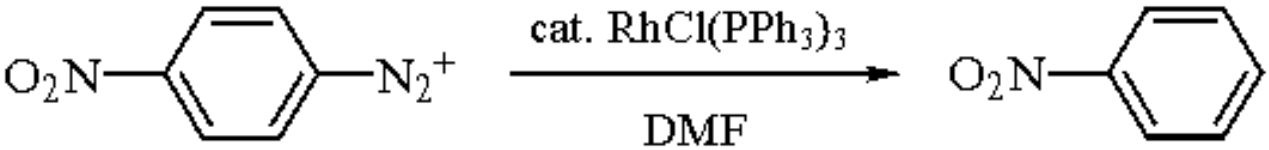

(56)

Finally, aryl group interchange between triarylphosphines is mediated by Wilkinson's catalyst at 120 °C, but a near

statistical mixture of the exchanged materials is formed along with some byproducts.[85]

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate; [1,4-bis(diphenylphosphino)-butane](norboradiene)rhodium tetrafluroborate ***Catecholborane***; ***(1,5-Cyclooctadiene)[1,4-bis(diphenylphosphino)butane]iridium(I) Tetrafluoroborate***; ***(1,5-Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate***; ***Octacarbonyldicobalt***; ***Palladium(II) Chloride***; ***Tetrakis(triphenylphosphine)palladium(0)***.

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(*Z*)-5-Chloro-3-trimethylstannyl-2-pentene[1]

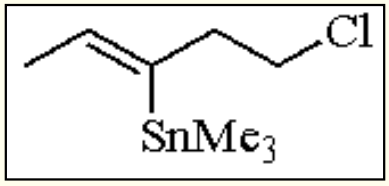

[101849-67-6] · $C_8H_{17}ClSn$ · (*Z*)-5-Chloro-3-trimethylstannyl-2-pentene · (MW 267.36)

(cyclopentane annulations;[2,3] bifunctional reagent;[4-6] spirotetrahydrofuran synthesis[7])

Alternate Name: [1-(2-chloroethyl)-1-propenyl]trimethylstannane.

Physical Data: bp 40-50 °C/0.3 mmHg.[8]

Analysis of Reagent Purity: ^{1}H NMR.[8]

Preparative Methods: by the addition of ***Lithium Phenylthio(trimethylstannyl)cuprate*** to ethyl 2-pentynoate,[9] followed by stereospecific deconjugation (eq 1)[10,11] to afford ethyl (*Z*)-3-trimethylstannyl-3-pentynoate as a single isomer.[10] Reduction and conversion to the chloride provides the title reagent (eq 2).[8]

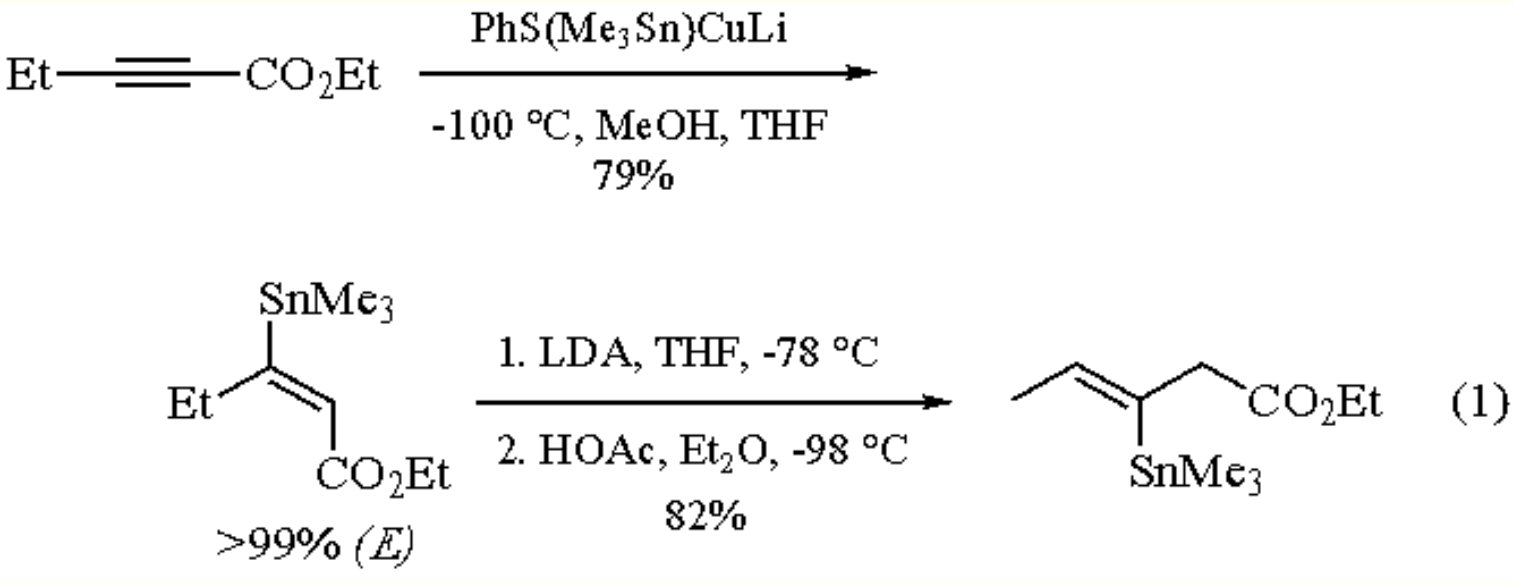

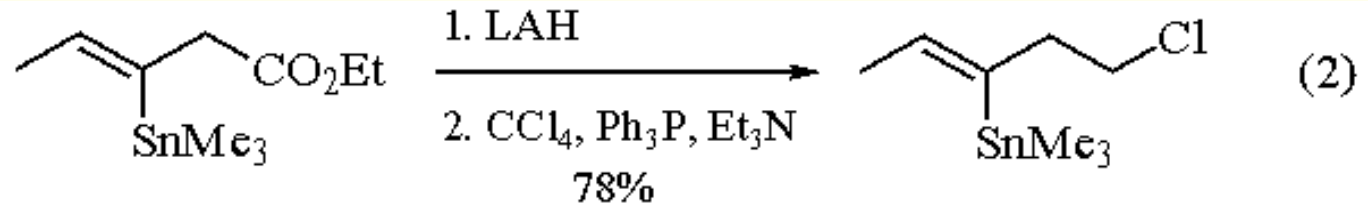

Purification: by distillation.[8]

Handling, Storage, and Precautions: organostannanes should be considered as toxic compounds.[12] This reagent should be handled in a well-ventilated fume hood and gloves should be worn to prevent contact with the skin.

Spirotetrahydrofuran Synthesis.

See also ***4-Chloro-2-trimethylstannyl-1-butene***. Treatment of the title reagent with ***Methyllithium*** results in complete formation of the (*Z*)-vinyllithium reagent. Addition to cyclohexanone affords a mixture of the chloro alcohol (31%) and the spirotetrahydrofuran (40%) (eq 3).[8]

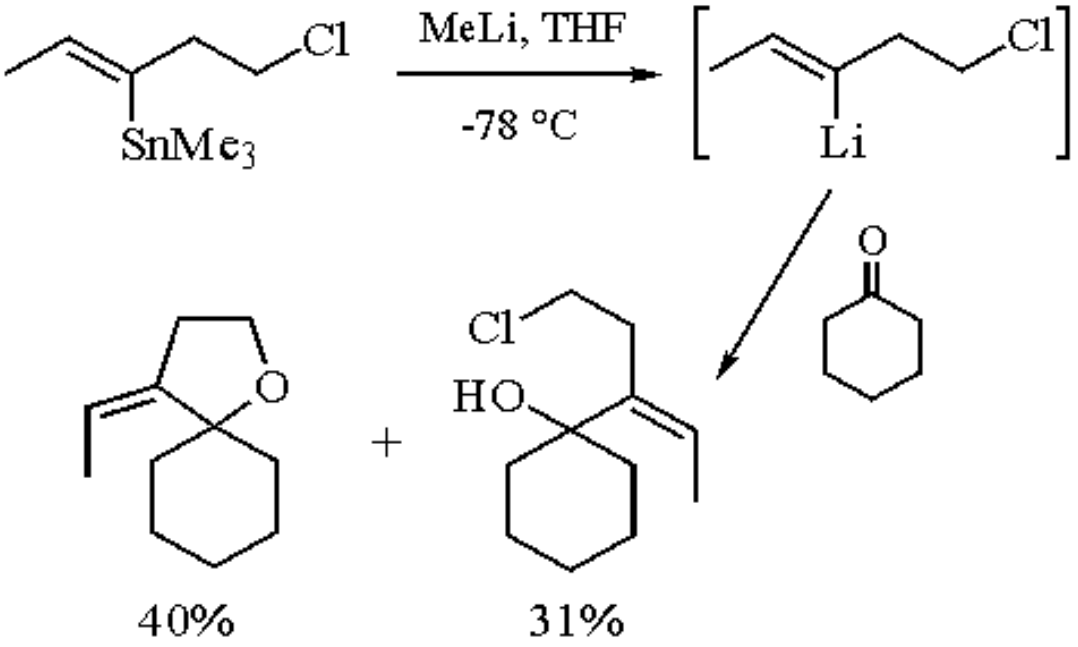

(3)

It is interesting to note that treatment of (*E*)-5-chloro-3-trimethylstannyl-2-pentene under these conditions (MeLi, THF, -78 °C, cyclohexanone or benzaldehyde) provided only the ethylidenecyclopropane (isolated as a chloro sulfide by treatment with ***2,4-Dinitrobenzenesulfenyl Chloride***).[8] A 1,2-addition product was not isolated.

[3 + 2] Annulations.

See also ***4-Chloro-2-trimethylstannyl-1-butene***. (*Z*)-5-Chloro-3-trimethylstannyl-2-pentene has been used in a two-step process as a cyclopentane annulation reagent.[8,13] (*Z*)-5-Chloro-3-lithio-2-pentene (see above) is treated with ***Magnesium Bromide*** in THF to provide the vinyl Grignard. The cuprate derived from this adds in a 1,4-fashion to cycloalkenones to afford the chloro ketone (as a mixture of diastereomers when R &neq; H). Closure to the *cis*-fused bicyclic ketone is accomplished by an intramolecular alkylation (Table 1; eq 4).[8]

(Z)-5-Chloro-3-trimethylstannyl-2-pentene

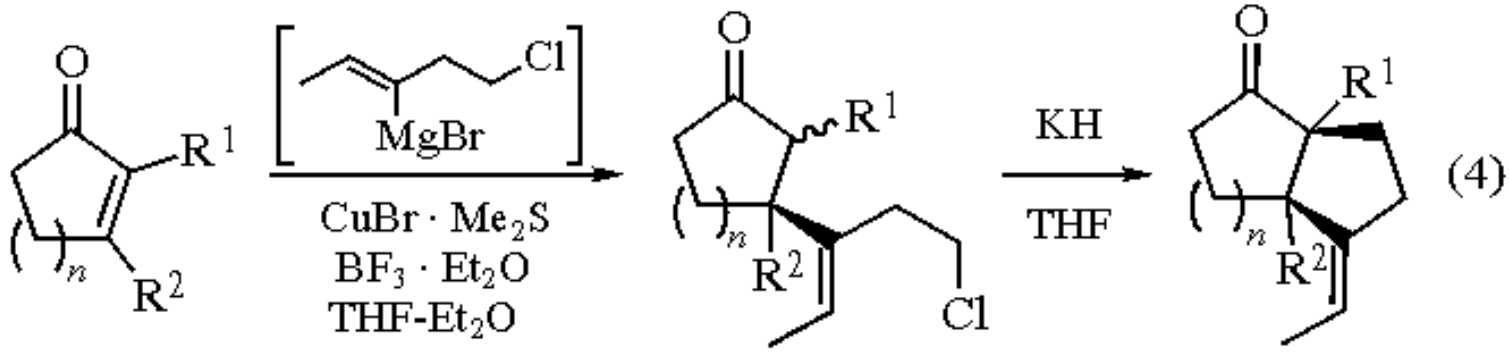

Table 1 (Z)-Ethylidenecyclopentane Annulations

n	R^1	R^2	Yield (conjugate addition)(%)	Yield (annulation product) (%)
1	H	H	69	78
1	H	Me	57	86
1	Me	H	56	79
2	H	H	70	78
2	H	Me	61	79
2	Me	H	64	83

This methodology has been used to accomplish the total synthesis of (±)-oplopanone, (±)-8-epi-oplopanone, and (±)-anhydro-oplopanone (eq 5).[8,13]

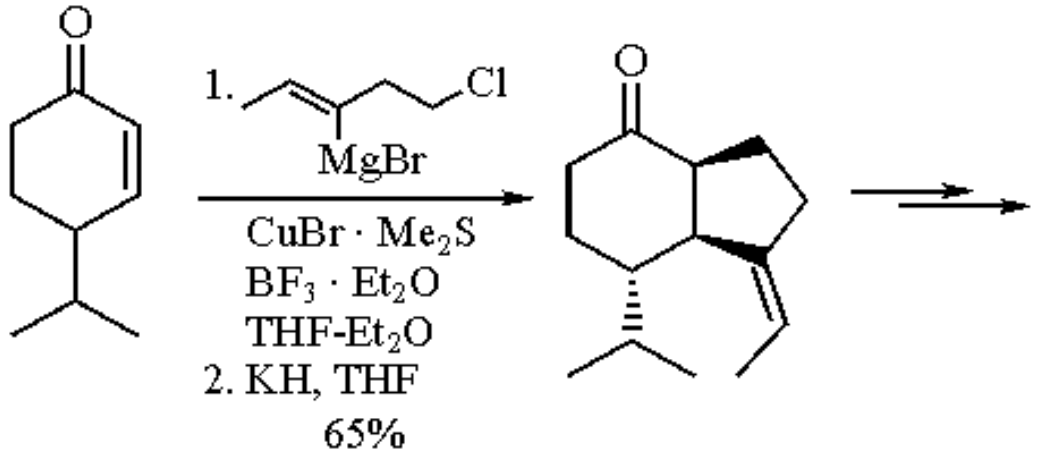

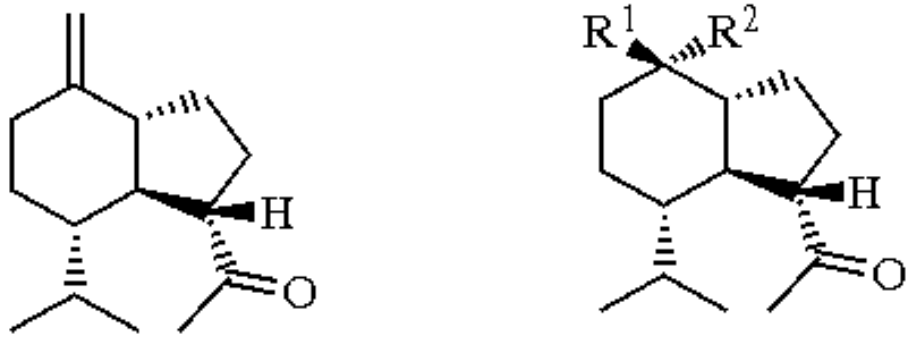

(5)

Anhydro-oplopanone

Oplopanone, $R^1 = OH$, $R^2 = Me$
8-Epi-oplopanone, $R^1 = Me$, $R^2 = OH$

---

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Chromic Acid[1]

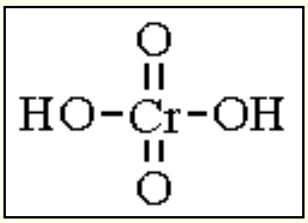

[7738-94-5] · CrH_2O_4 · Chromic Acid · (MW 118)

(reagent for oxidizing secondary alcohols to ketones, primary alcohols to carboxylic acids, and α-hydroxy ketones to α-diketones; for converting tertiary cyclobutanols to 1,4-ketols and 1,4-diketones; for cleaving 1,2-glycols to keto acids)

Alternate Name: Jones reagent.

Solubility: sol acetone and water.

Preparative Methods: the Jones reagent is a solution of chromium(VI) oxide and sulfuric acid in water,[2-4] in a typical procedure,[4a] 67g of CrO_3 is dissolved in 125 mL of H_2O and 58 mL of conc H_2SO_4 is then carefully added; the precipitated salts are dissolved by adding an additional (minimal) quantity of water (the total volume of the resultant solution should not exceed 225 mL); alternatively, 23.5 g of CrO_3 is dissolved in 21 mL of conc H_2sO_4 with cooling and then diluted with distilled water to give a total volume of 175 mL.[2,4b]

Handling, Storage, and Precautions: the mutagenicity of chromium(VI) compounds is well documented;[1f] handle with great care; use in a fume hood.

Oxidation of Secondary Alcohols to Ketones.

The Jones reagent oxidizes cyclooctanol to cyclooctanone (92-96%) on a fairly large scale.[4] Nortricyclanol (**1**) is oxidized to the highly strained and reactive ketone nortricyclanone (**2**) (eq 1).[5] An epimeric mixture of 3,3-dimethyl-*cis*-bicyclo[3.2.0]heptan-2-ols is oxidized by Jones reagent to 3,3-dimethyl-*cis*-bicyclo[3.2.0]heptan-2-one (83-93%).[6] Jones reagent oxidizes alcohols (**3**) and (**5**) to the acid labile ketones (**4**) and (**6**), respectively (eqs 2 and 3).[7] A 90% yield of Δ^5-pregnene-3,20-dione is obtained from the Jones oxidation of pregnenolone.[8] The Jones reagent, in the presence of oxalic acid, oxidizes 1,2-diphenylethanol and *t*-butylphenylmethanol to benzyl phenyl ketone and *t*-butyl phenyl ketone, respectively, in quantitative yield.[9] This procedure is also effective for the oxidation of 7-norbornanol to 7-norbornone. Chromic acid in aqueous acetic acid oxidizes *t*-butylphenylmethanol to *t*-butyl phenyl ketone, with formation of significant amounts of the cleavage products benzaldehyde and *t*-butanol.

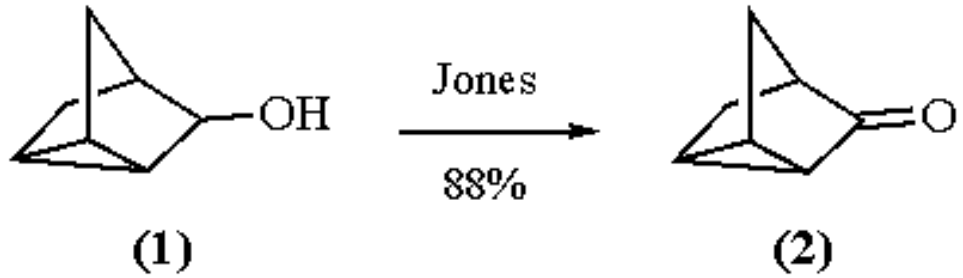

(1)

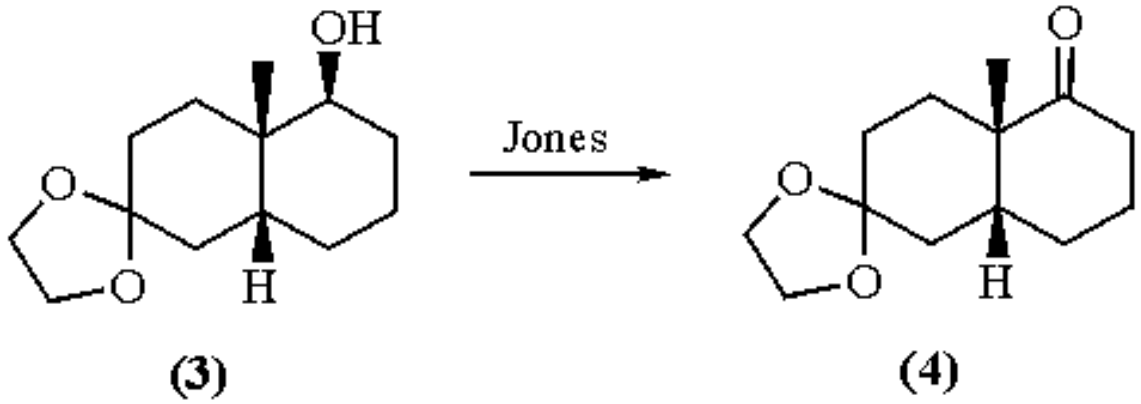

(2)

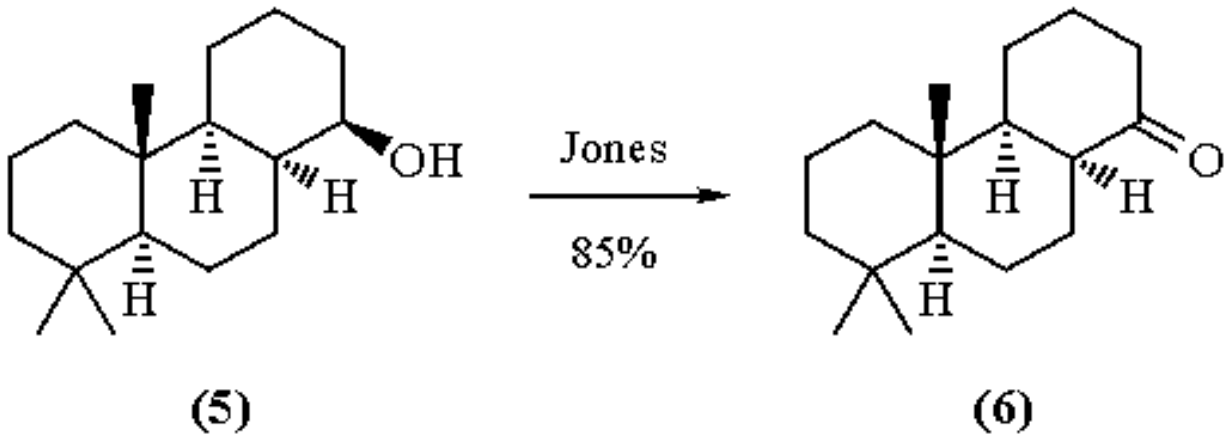

(3)

1,4-Ketols and 1,4-Diketones from tertiary Cyclobutanols.

Jones reagent cleaves tertiary cyclobutanols to 1,4-ketols (eq 4) and 1,4-diketones (eqs 5 and 6).[10]

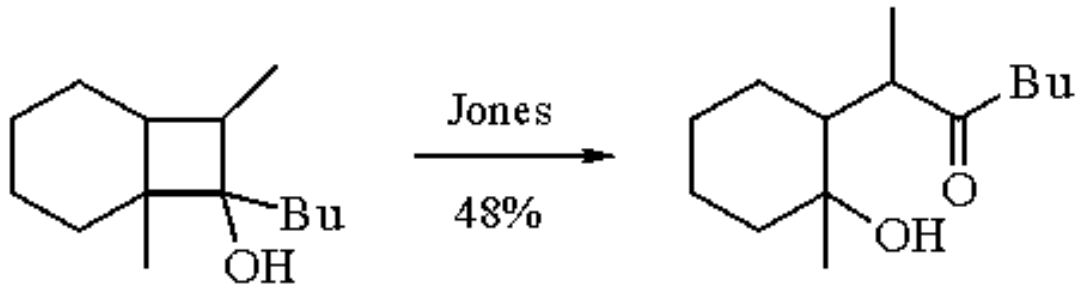

(4)

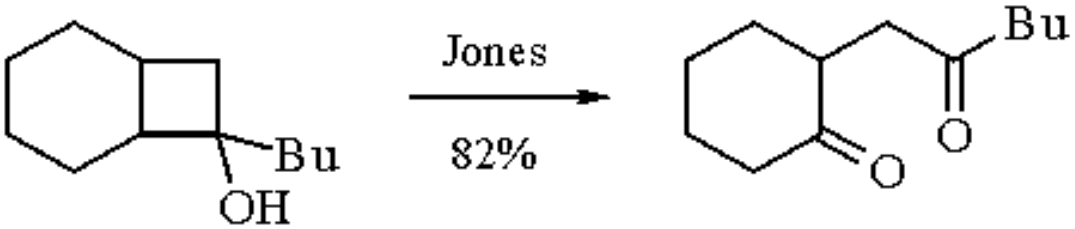

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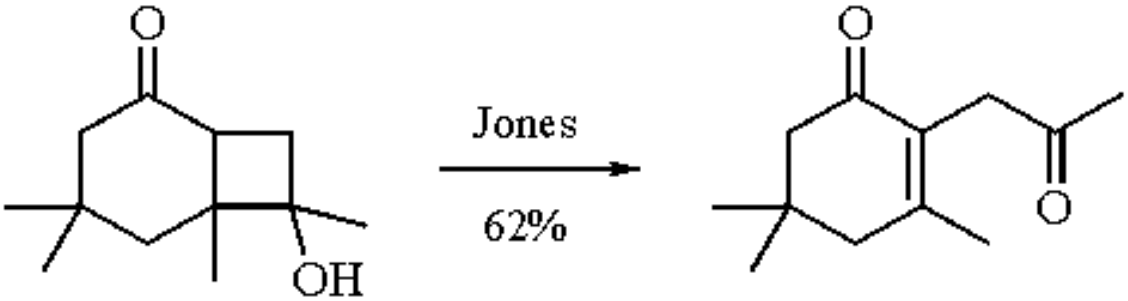

(6)

Oxidation of α,β-Unsaturated Alcohols.

In general, allylic alcohols are easily converted to the corresponding α,β-unsaturated ketones. Ethyl 3-hydroxy-4-pentenoate (**7**) is oxidized to the volatile ketone ethyl 3-oxo-4-pentenoate (**8**) (eq 7),[11] which is an intermediate in the preparation of the Nazarov annulation reagent.[12] The Jones reagent was superior to ***Pyridinium Chlorochromate***, ***Pyridinium Dichromate***, and ***Dimethyl Sulfoxide-Oxalyl Chloride*** (Swern reagent) for the oxidation of this alcohol.

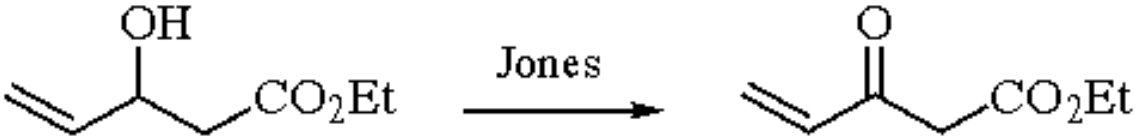

(7) (7) (8)

The steroidal lactone (**9**) and its isomeric allylic alcohol (**10**) are stereospecifically oxidized to the epoxy ketone (**11**) by the Jones reagent (eq 8).[13] Epoxidation occurs only when the hydroxyl group is axial and epoxidation is faster than oxidation of the hydroxyl group.

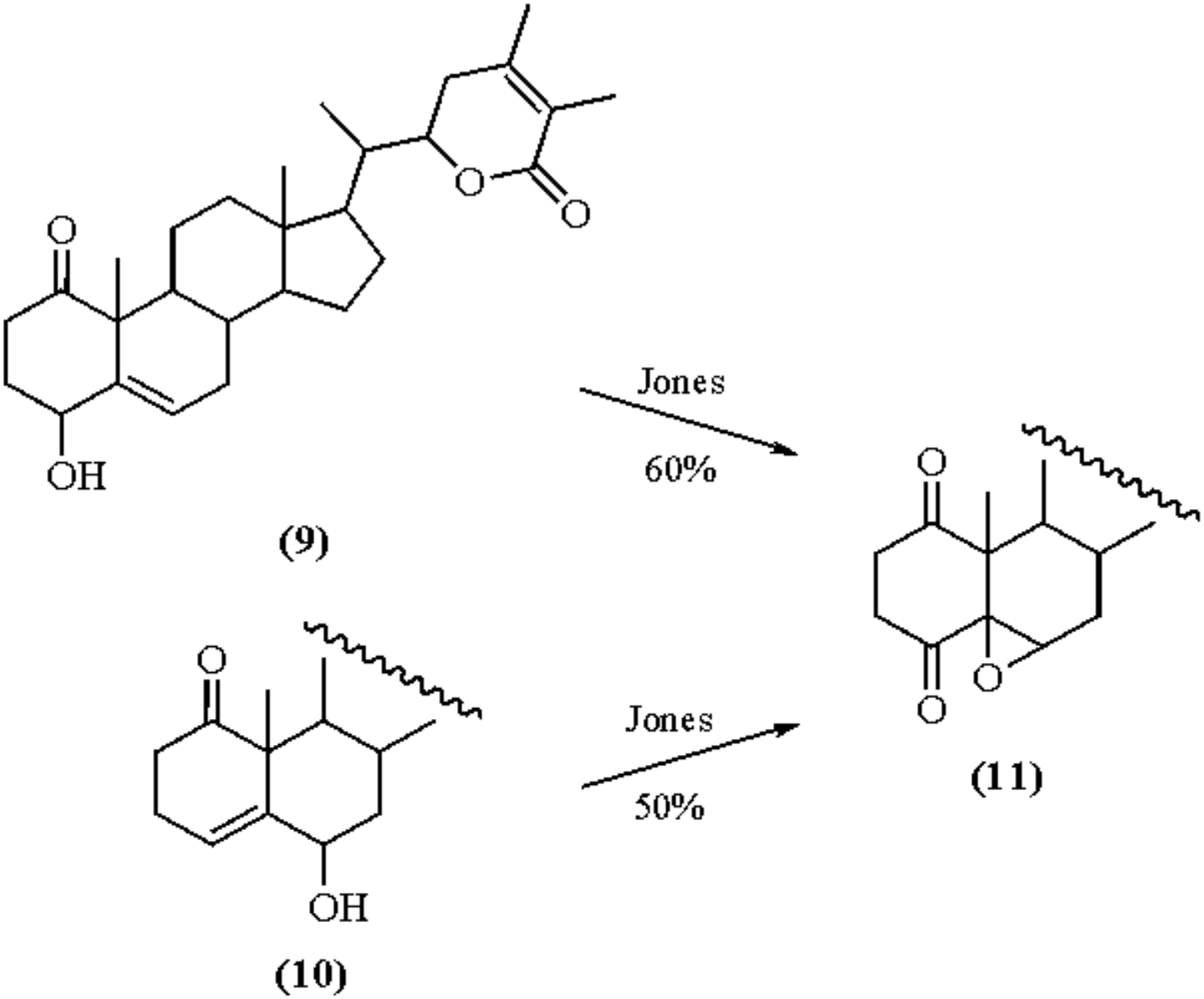

Oxidation of 6-hydroxy-2-(4-methoxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-ones (**12**) (eq 9) with Jones reagent affords diones (**13**), which are intermediates in the synthesis of 5-substituted 2-pyrrolidinones[14] and 1-oxaspiro[5.5]undecane derivatives.[15] The pyrrolidinone (γ-lactam) skeleton is found in molecules with great value in medicinal chemistry, and spiroacetals are subunits in numerous important natural products.

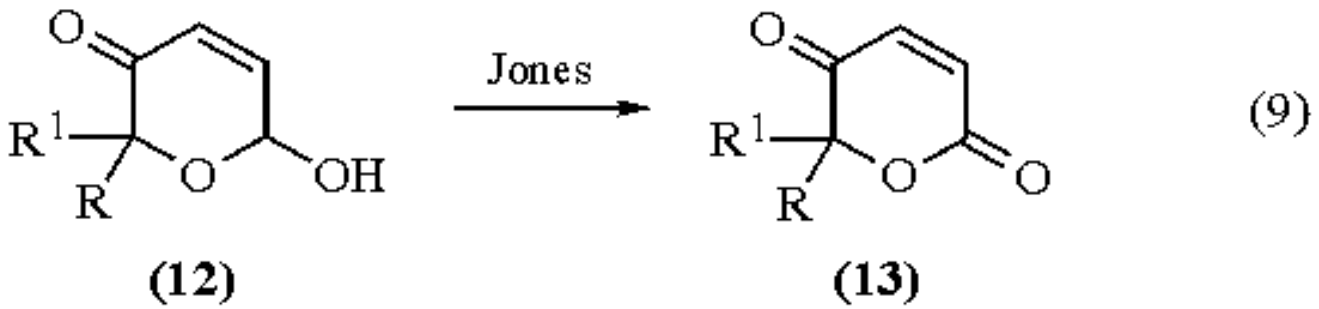

Jones oxidation of phosphorus-containing tertiary allylic alcohols such as (**14**) led to formation of the 1,3-carbonyl transposed β-substituted α,β-unsaturated ketones (**15**) (eq 10), which are useful intermediates for a variety of

phosphorus-substituted and nonphosphorus-bearing heterocyclic systems.[16]

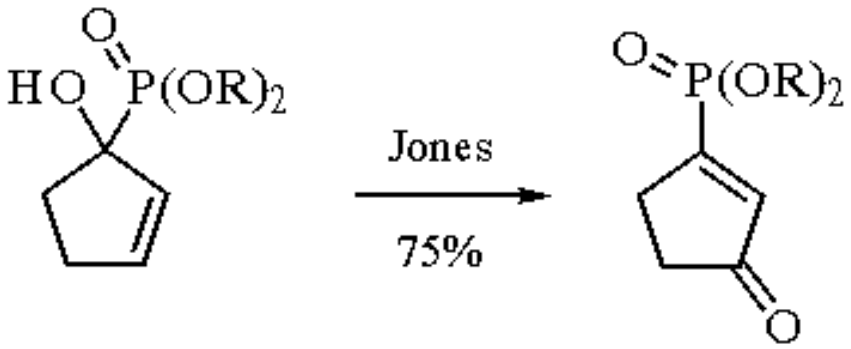

(10)

(14) **(15)**

Alkynic ketones are prepared in 40-80% yield via the Jones oxidation of the corresponding secondary alcohols.[2] Alkynic glycols are oxidized to the diketones with Jones reagent.[2]

Cleavage of *s*,*t*-1,2-Glycols to Keto Acids.

Jones reagent oxidatively cleaves *s*,*t*-1,2-glycol (**16**) to keto acid (**17**) (eq 11), and (**18**) or (**19**) to (**21**) (eq 12).[17]

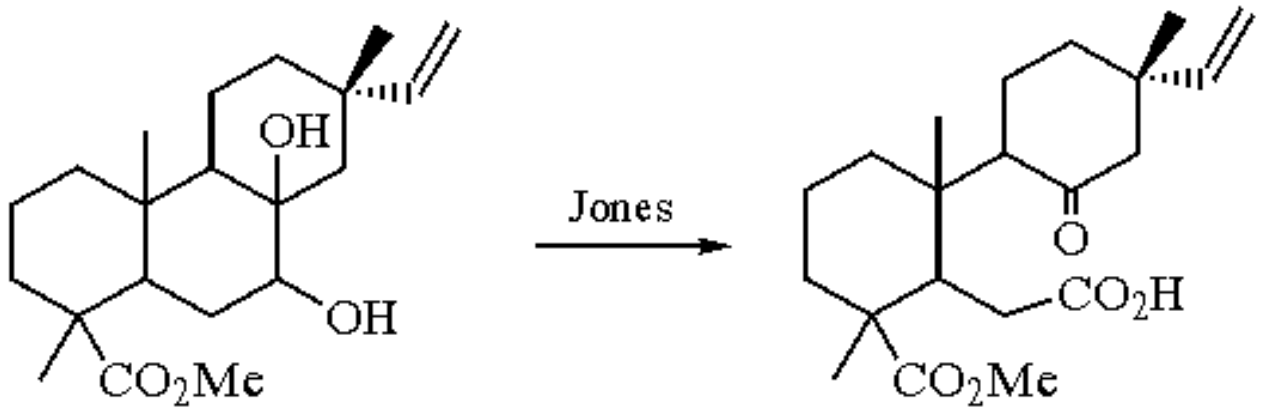

(11)

(16) **(17)**

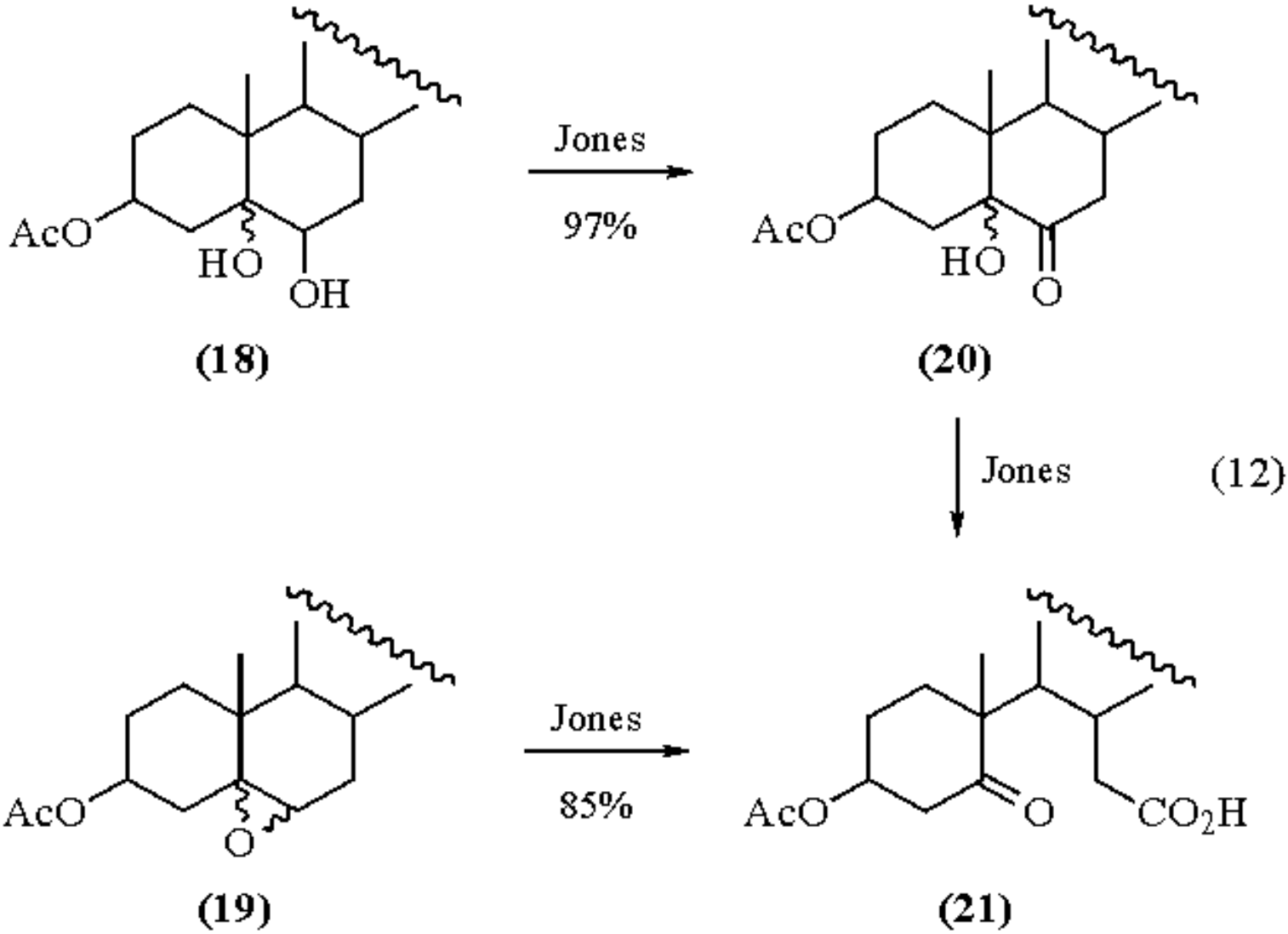

Oxidation of Benzoins to Benzils.

Benzoins are oxidized to benzils (90-95%) with Jones reagent in acetone.[18]

Oxidation of Primary Alcohols.

Primary alcohols are rapidly oxidized by the Jones reagent to carboxylic acids. Double bonds and triple bonds are not oxidized.[19,20] Jones oxidation of alcohol (**22**) affords carboxylic acid (**23**), which is used in the synthesis of the antitumor agent (±)-sarkomycin (eq 13).[21]

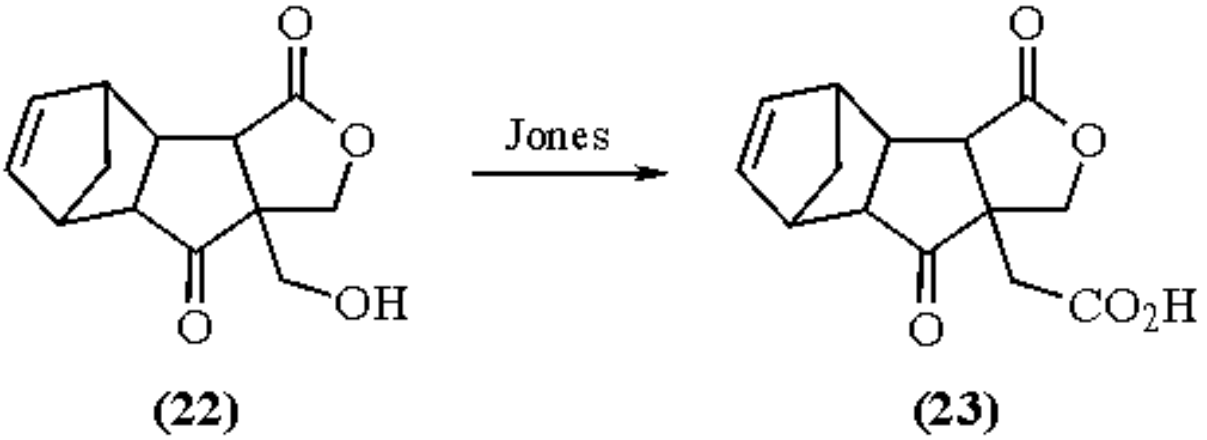

(13)

Other Applications.

Although ethers are generally inert toward chromic acid oxidation, the Jones reagent oxidizes benzyl ethers to the benzoic acid, esters, and ketones (eq 14).[22] The bicyclic acetoxy ether (**24**) is oxidized to the acetoxylactone (**25**) with Jones reagent at room temperature (eq 15).[23]

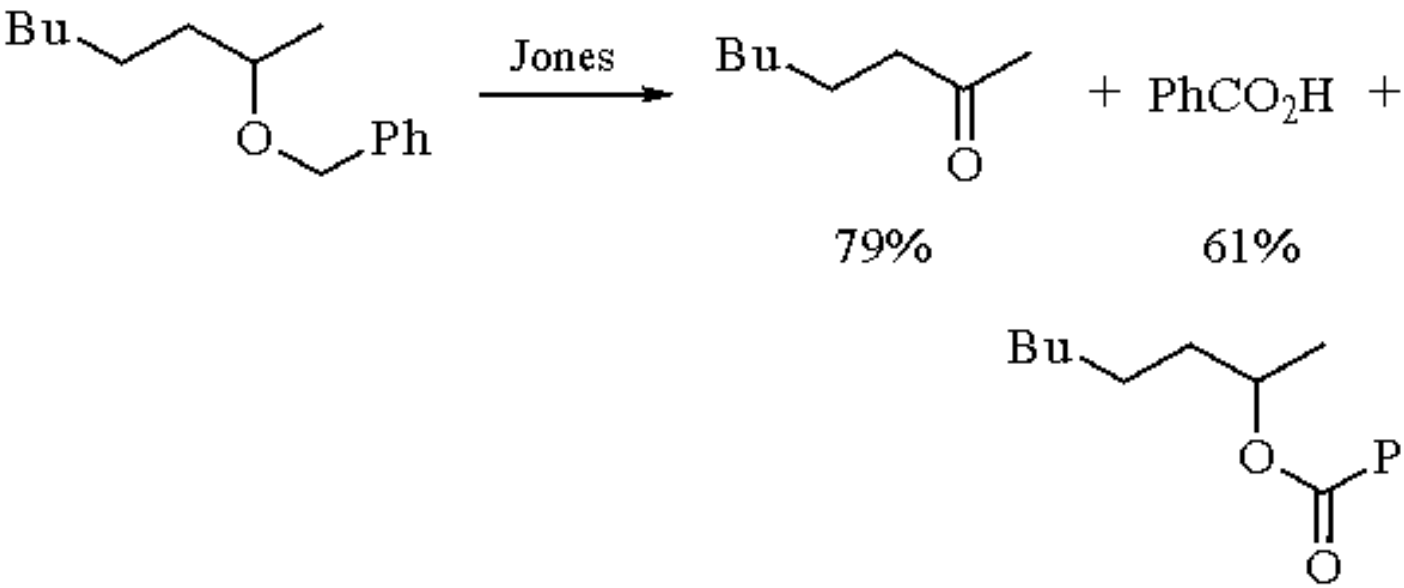

(14)

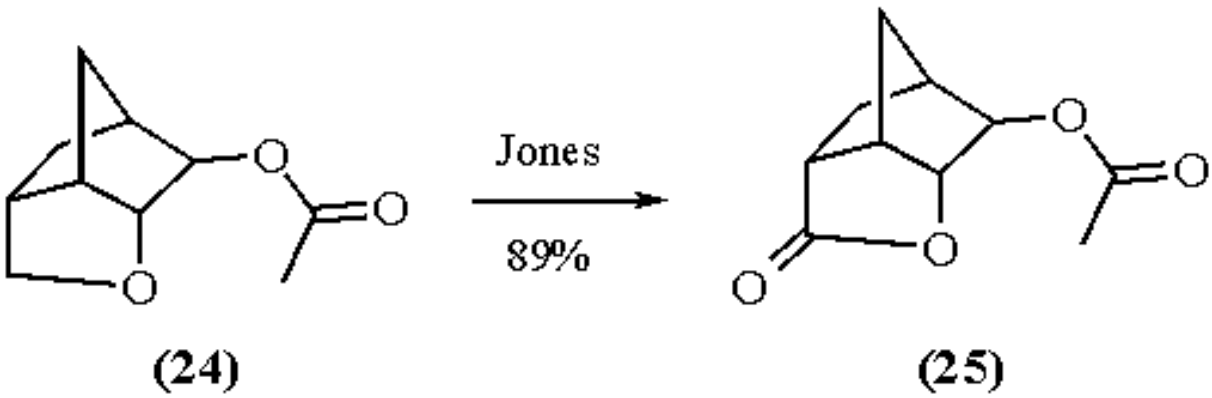

(15)

Oxidation of the alcohol (**26**) with Jones reagent gives the δ-lactone (**27**) instead of the ketone (eq 16).[24] The *p*-

methoxy group is necessary for this oxidation of a methyl group.

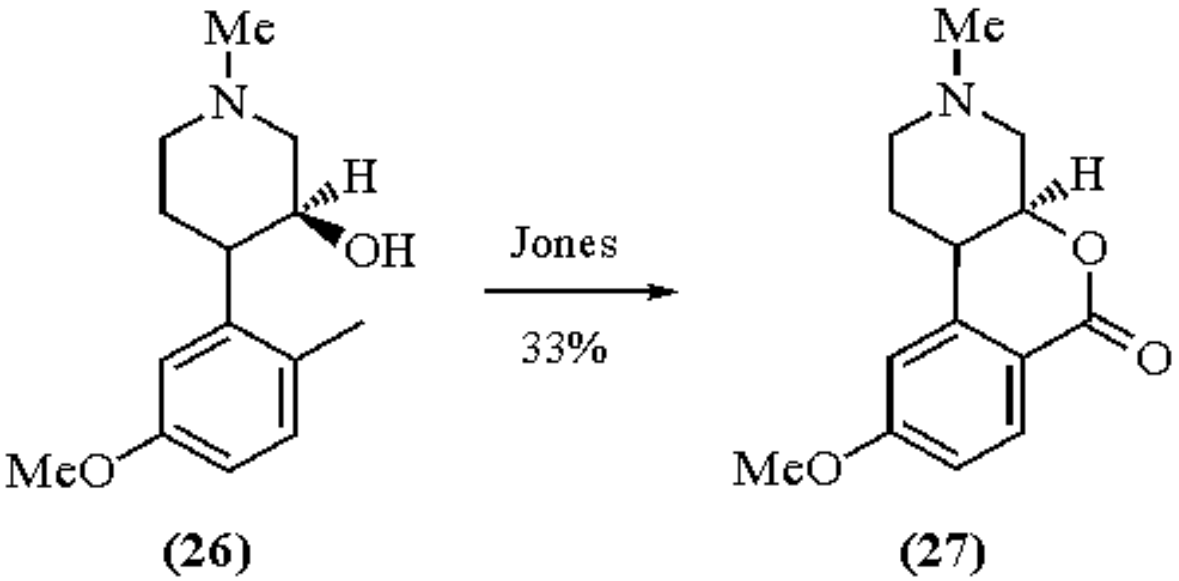

(16)

Phenols substituted by at least one alkyl group in the *ortho* position are oxidized to *p*-quinones by a two-phase (ether/aqueous CrO_3) Jones reagent.[25] Chromic acid in 50% aqueous acetic acid, Collins reagent, and Jones reagent oxidatively deoximate ketoximes to the corresponding carbonyl compounds.[26] Jones reagent oxidizes 3-trimethylsilyl-3-buten-2-ol to the Michael acceptor 3-methylsilyl-3-buten-2-one.[27] A combination of a catalytic amount of ***Osmium Tetroxide*** and stoichiometric Jones reagent in acetone at room temperature oxidizes various types of alkenes into acids and/or ketones.[28]

---

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Chromium(II) Acetate

$Cr(OAc)_2.H_2O$

[14976-80-8] · $C_4H_8CrO_5$ · Chromium(II) Acetate · (MW 188.12)

(capable of reducing reactive carbon-halogen bonds (e.g. allylic, benzylic, α-halo carbonyl);[1] bromohydrins[2] and epoxides;[3] used in the conversion of ketoximes to ketones[4] in the presence of acid- and base-sensitive functional groups)

Physical Data: d 1.79 g cm^{-3}.

Solubility: slightly sol cold water; readily sol hot water; sol in and reacts with most acids; slightly sol alcohol; practically insol ether.

Form Supplied in: deep red powder or monoclinic crystals; composed of dimeric units. *Drying:* loses water when dried over P_2O_5 at 100 °C, changing color to brown.

Handling, Storage, and Precautions: easily oxidized, especially when moist, to chromium(III) acetate. It can be stored for several months in a stoppered vial under carbon dioxide.

Reduction of Carbon-Halogen Bonds.

2α,4α-Dibromocholestan-3-one (**1**) has been reduced to 4α-bromocholestan-3-one (**2**) in 97% yield[5] (recrystallization afforded 78% yield) when treated with a large excess of freshly prepared chromium(II) acetate in acetic acid for 10 min (eq 1). On the other hand, with the theoretical amount of reagent the yield was only 20%.[6]

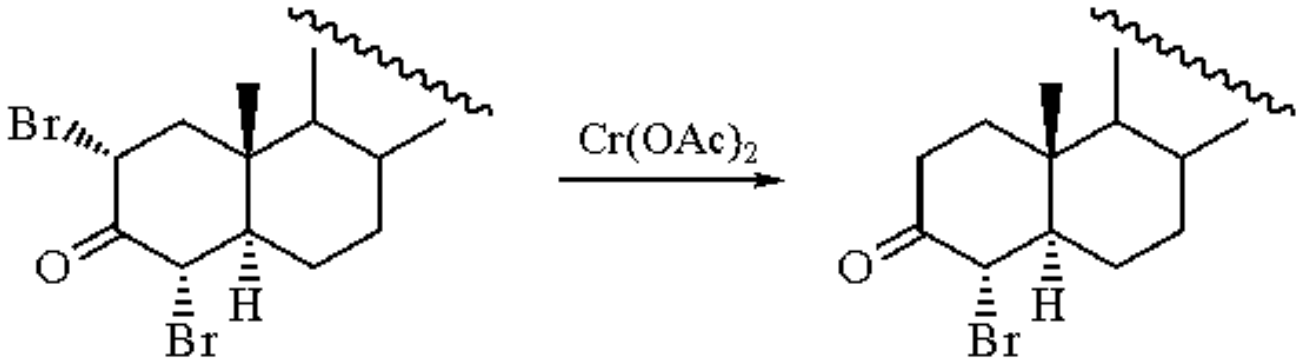

(1)

(1) **(2)**

Reduction of 4-bromoisophorone (**3**) with chromium(II) acetate gives β-phorone (**4**) as the major product;[7] isophorone (**5**) is obtained as a minor product (eq 2). The reagent is freshly prepared by treatment of $CrCl_3.6H_2O$ with amalgamated zinc and then with sodium acetate.

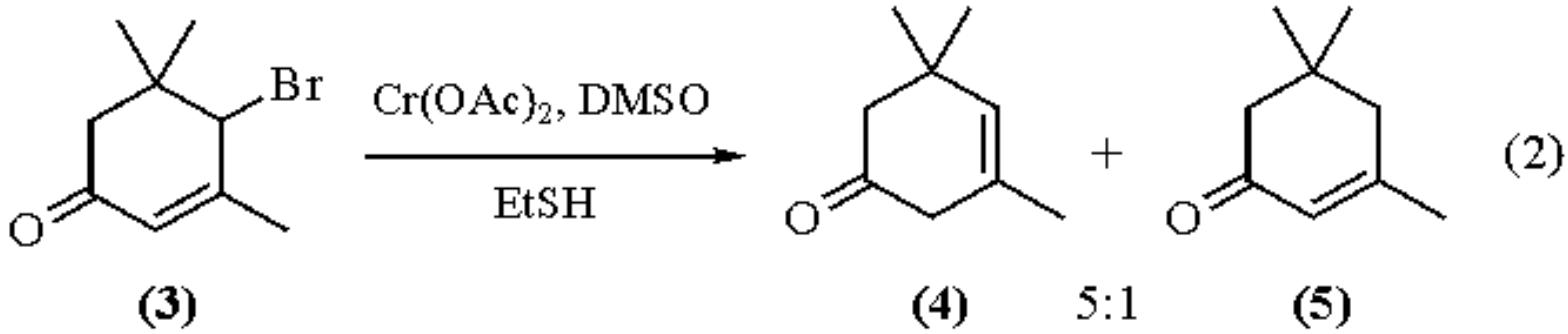

In the construction of the ring A system of some of the giberellins,[8] iodolactone (**6**) has been reduced following the method developed by Barton and co-workers (eq 3).[2,9] Chromium(II) ion in DMSO is used in the presence of ethanethiol. The reaction occurs with inversion to give the *cis*-fused decalin system (**7**) (presumably through a radical mechanism).[8] A variety of conditions (irradiation, catalytic hydrogenation) are useless for the deiodination.

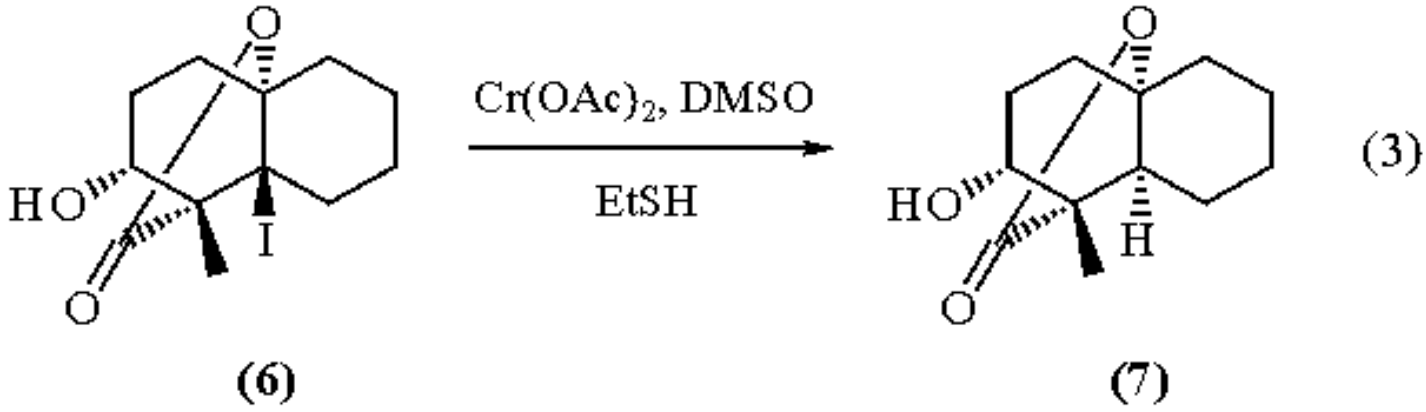

1,2,3,4,7,7-Hexachloro-5-*endo*-acetoxybicyclo[2.2.1]-2-heptene (**8**) is reduced by refluxing with chromium(II) acetate in acetic acid for 16 h to furnish (**9**) in 78% yield in which the chlorine atom *anti* to the double bond is mainly replaced (eq 4).[10] With zinc-acetic acid the reduction is not so clean since four products are formed. Reaction with ***Palladium on Carbon*** leads to reduction and dechlorination of the vinyl system.

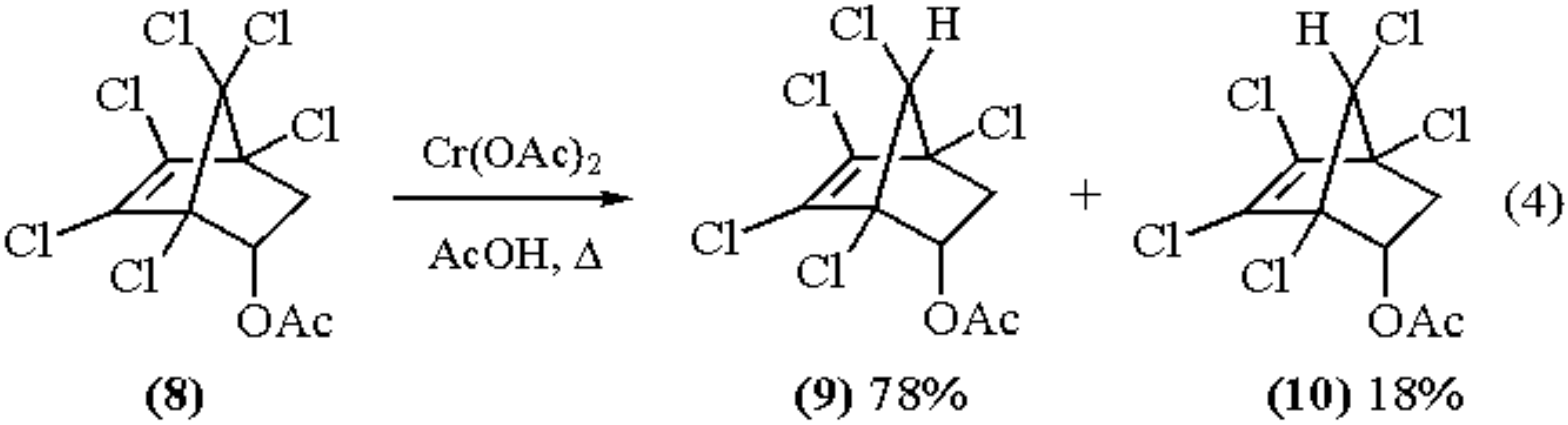

Reduction of Bromohydrins.[2,9]

Treatment of 9α-bromo-11β-hydroxyprogesterone (**11**) with chromium(II) acetate (5 equiv) in DMSO containing butane-1-thiol (7.5 equiv) gives 11β-hydroxyprogesterone (**12**) in 80% yield (eq 5).[11] Similarly, 9α-bromocortisol-21-acetate,[12] 9α-bromoprednisolone-21-acetate,[13] and 17,20:20,21-bismethylenedioxy-9α-bromocortisol[14] afford cortisol-21-acetate (78%), prednisolone-21-acetate (74%) and 17,20:20,21-bismethylenedioxycortisol (80%), respectively. In the absence of butane-1-thiol the reduction proceeds in a different manner. The bromohydrin gives 5,9-cyclo-11β-hydroxypregnane-3,20-dione (**13**) (58%).

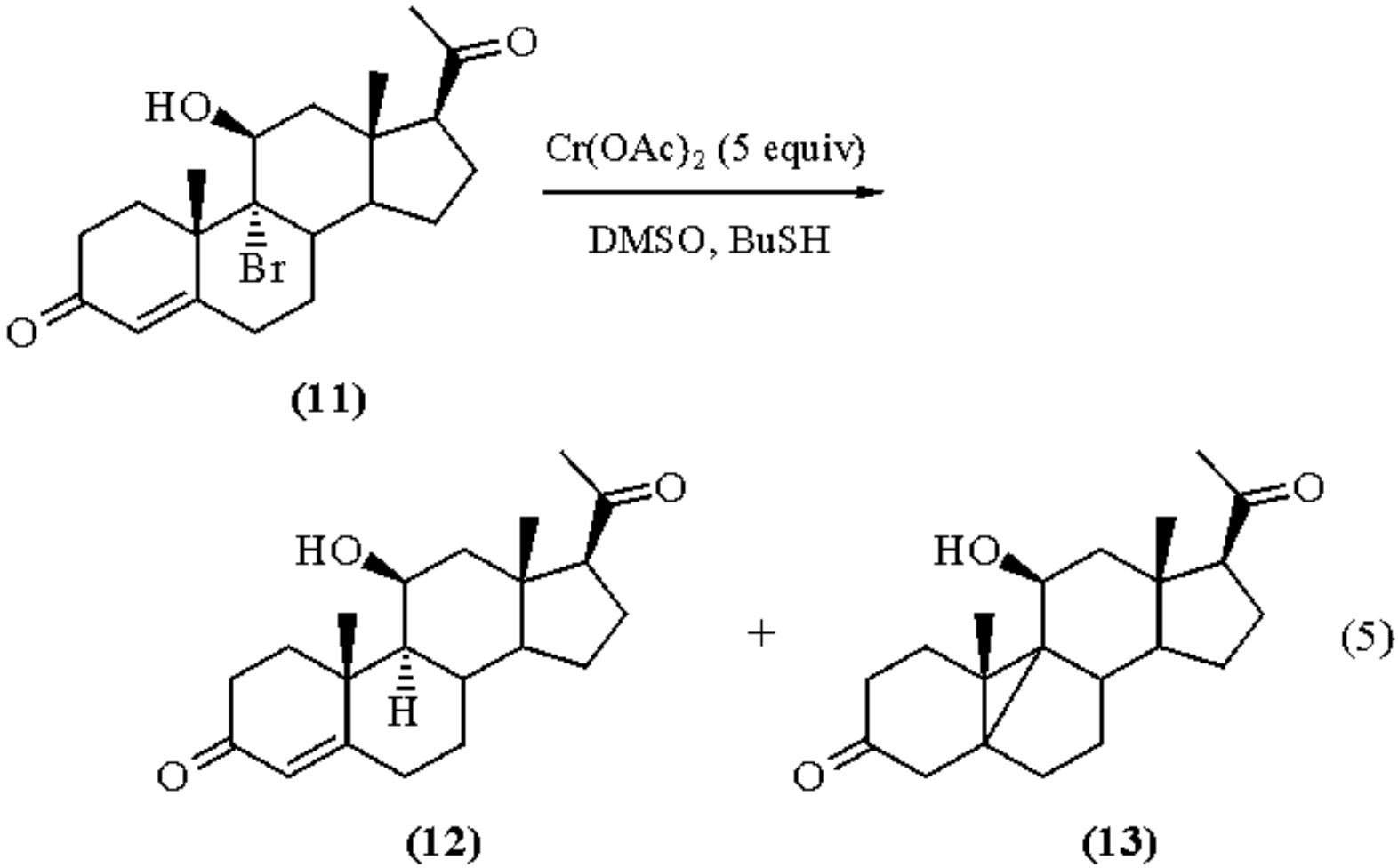

According to Barton et al.[2,9] the chromium(II) ion reduction of a bromohydrin (**14**) would proceed in two stages as shown in (eq 6). Thus a radical intermediate (**15**) would be the first product of reduction. Further reduction of this radical would furnish the anion (**16**), which by elimination would give the normal product (**17**) of bromohydrin reduction. The radical (**15**) could, in principle, be captured by a ready transfer donor of radical hydrogens such as butanethiol with the formation of (**18**). The BuS&bdot; radical will dimerize to $(BuS)_2$ (**19**).

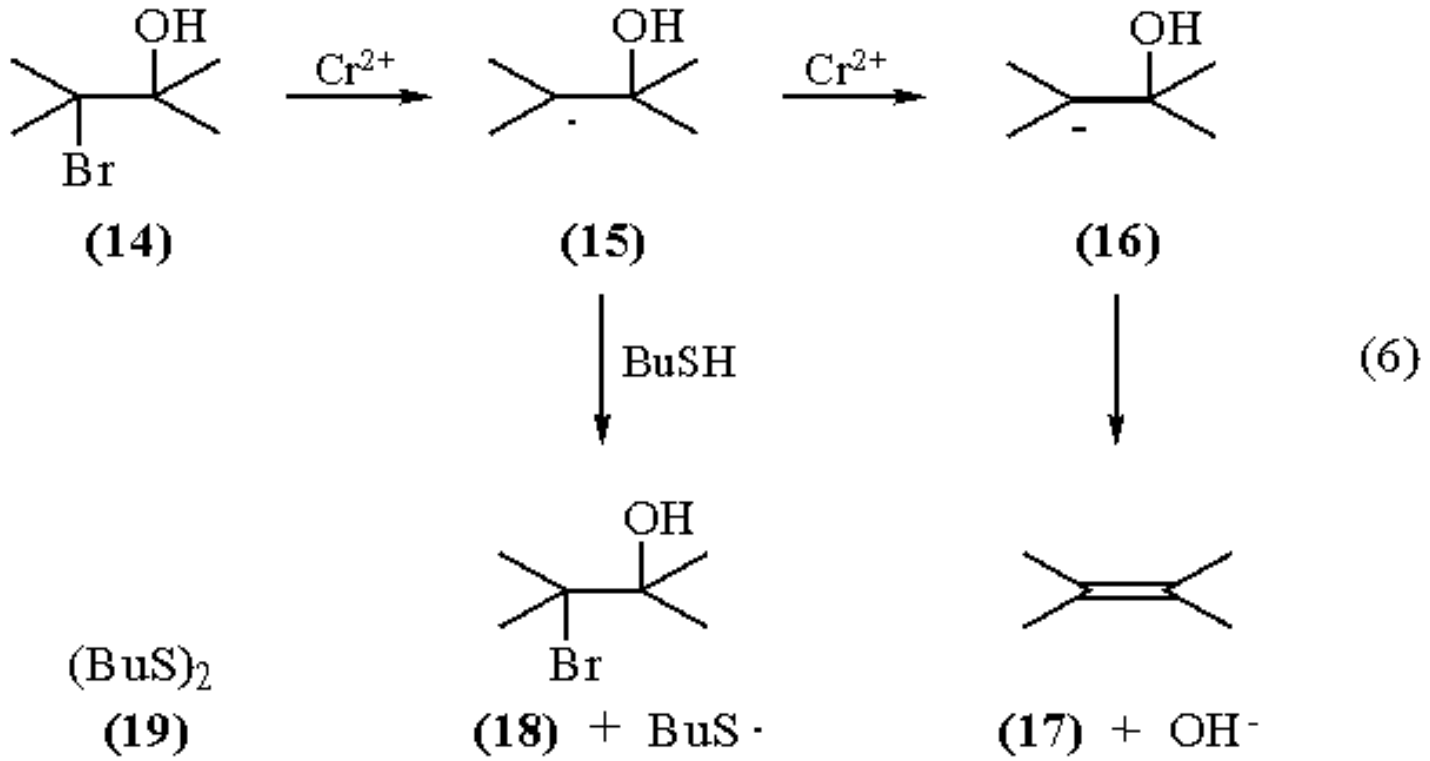

Reductive Cleavage of an Epoxide.

The 16α,17α-epoxy steroid (**20**) is converted by chromium(II) acetate into the β-hydroxy ketone (**21**) and the unsaturated ketone (**22**) (eq 7).[15]

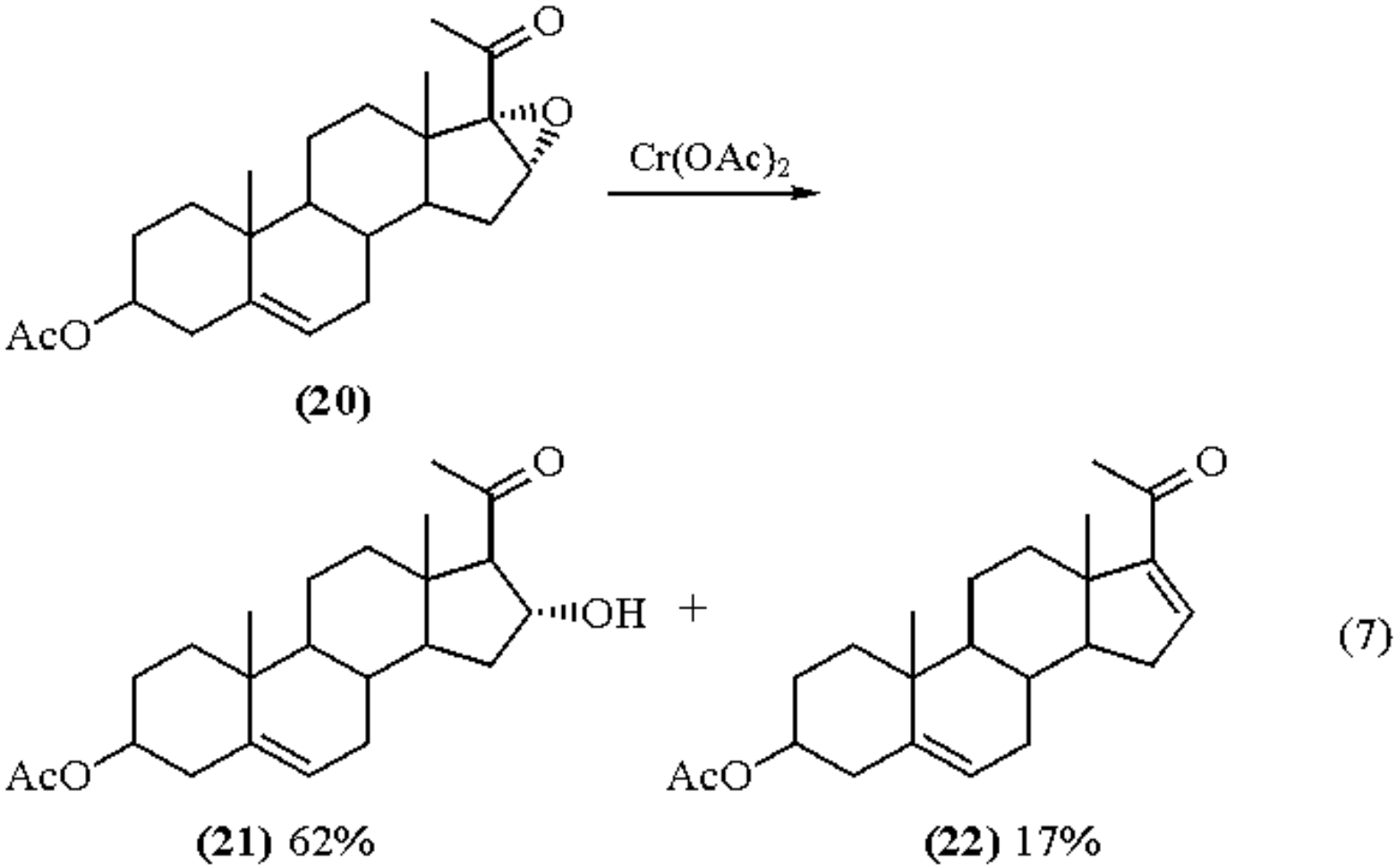

In a study of potential routes to the A/B ring system of cardiac active steroids (periplogenin, strophanthidin) Robinson and Henderson[3] studied the reduction of 4β,5β-oxidocholestan-3-one (**23**) with chromium(II) acetate. The best results were obtained by reduction of (**23**) with a large excess of freshly prepared chromium(II) acetate in aqueous acetone. In this case the desired product (**24**) could be obtained in about 50% yield (eq 8). The minor product (**25**) can be recycled.

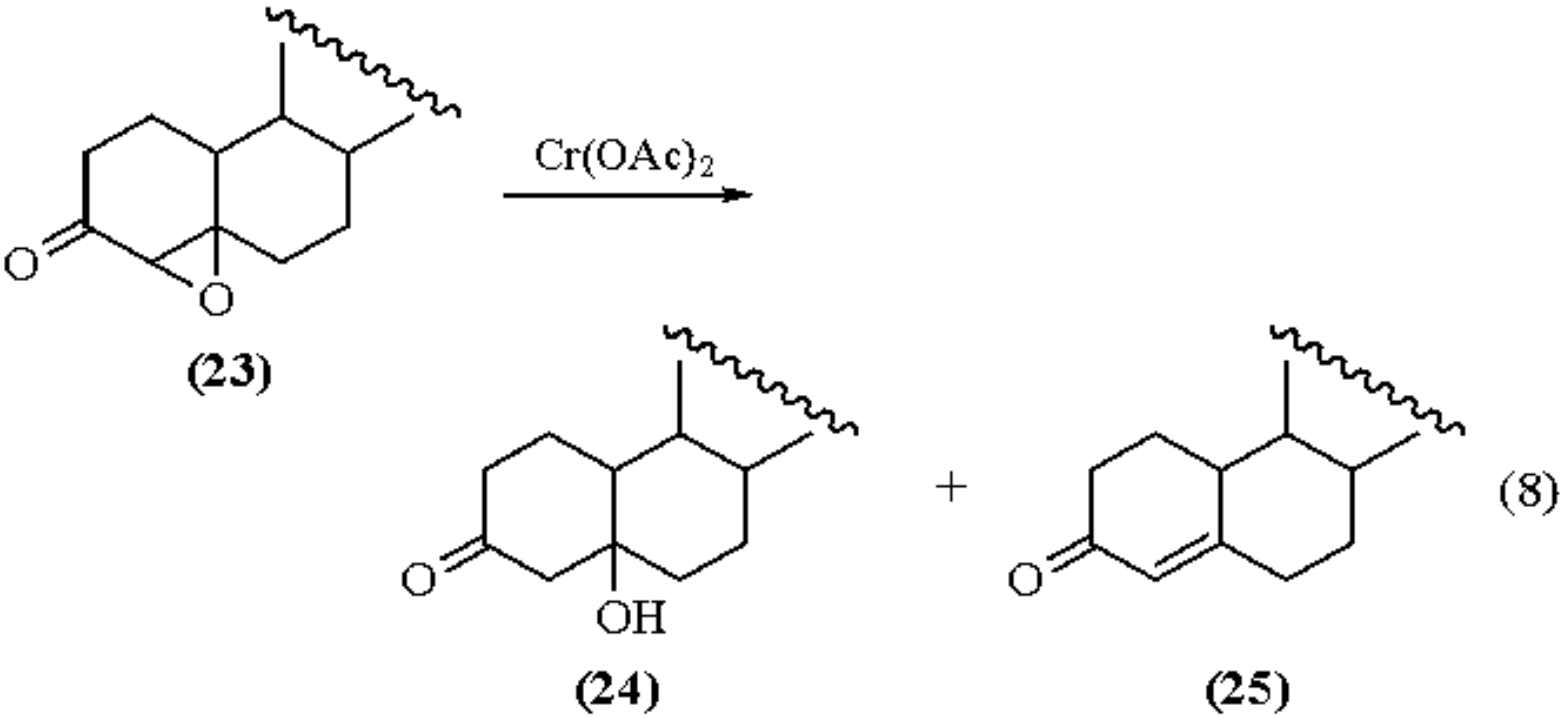

Conversion of Ketoximes to Ketones.

The method involves the conversion of an oxime to the *O*-acetate derivative, followed by reaction with >2 mol equiv of chromium(II) acetate in 9:1 THF-water (by weight) at a temperature between 25 °C and 65 °C. Chromium(II) acetate causes reductive fission of the oxime N-O linkage to give an imine which will rapidly hydrolyze to a ketone. This method is highly effective even in the presence of acid- and base-sensitive functional groups, such as acetals, hemithioacetals, esters, and epoxides. It is noteworthy that the reaction occurs more readily with acetoximes of conjugated ketones than with those of nonconjugated ketones, and that the reaction ocurs readily with acetoximes of hindered ketones such as camphor. The reaction has been used in a three-step conversion of alkenes into ketones. For example, ***Nitrosyl Chloride*** is added to cyclooctene (**26**) and the resulting 2-chlorocyclooctanone oxime (**27**)[16] is then acetylated and treated with chromium(II) acetate at 65 °C for 16 h. Cyclooctanone (**28**) is obtained in 88% yield (eq 9).

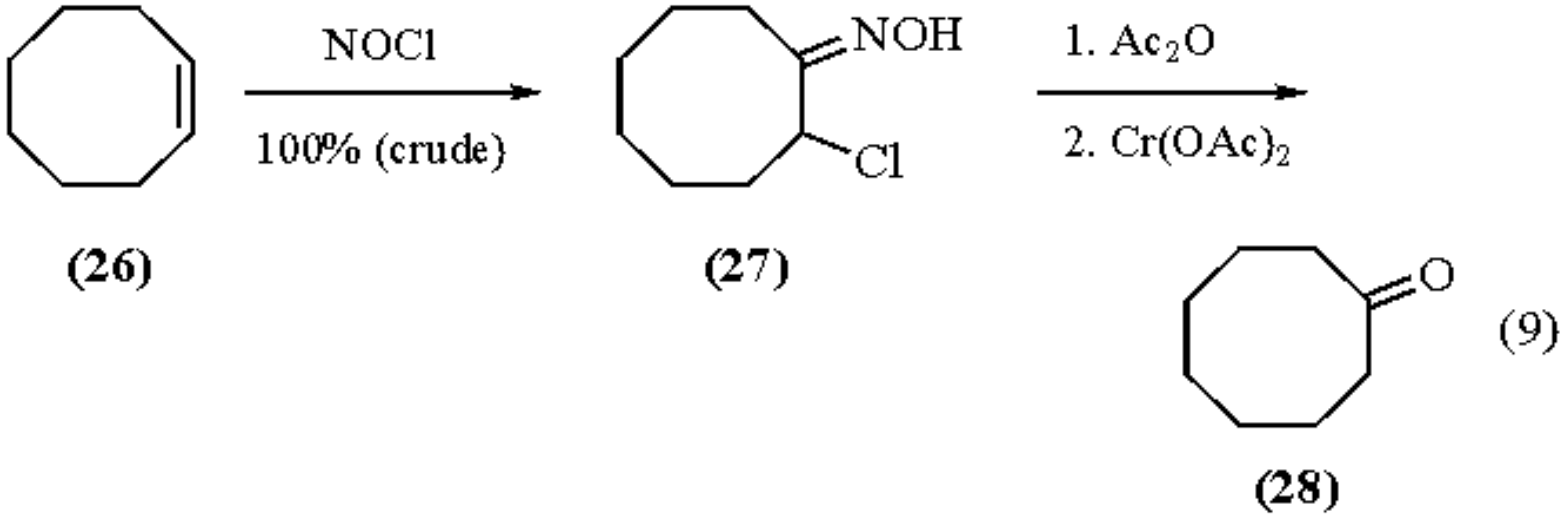

The reaction also has been used for transposition of a carbonyl group. Oxidation of propiophenone (**29**), followed by

reduction with ***Sodium Borohydride*** and acetylation, gives the α-acetoxy acetoxime (**30**) which on treatment with excess chromium(II) acetate affords phenyl acetone (**31**) (eq 10).

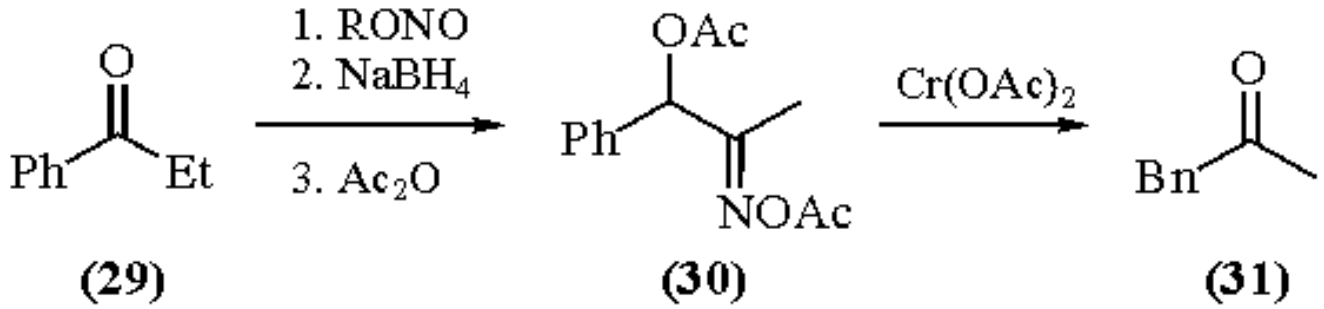

(10)

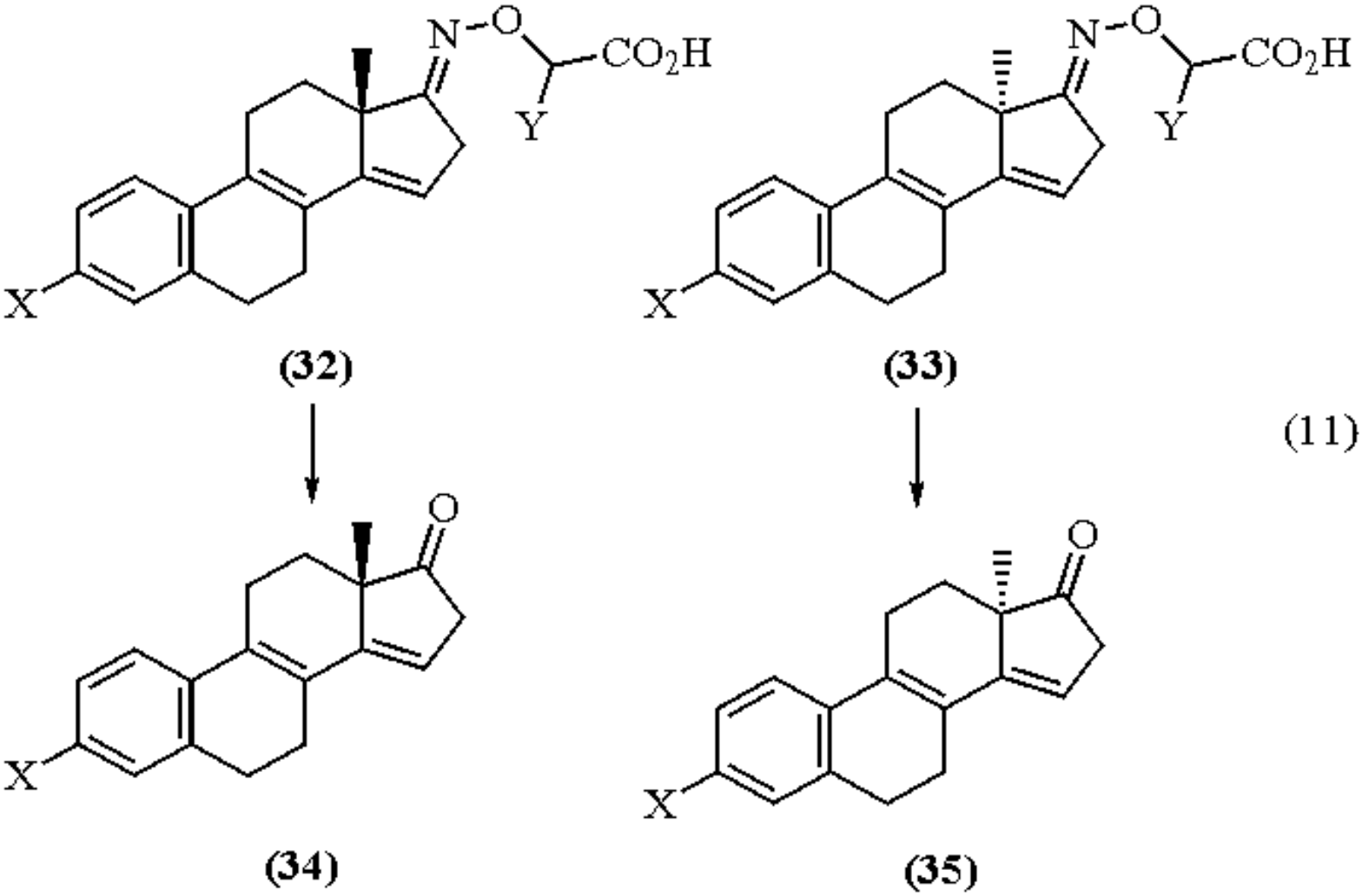

(11)

X = morpholino; Y = Me, *i*-Pr, *t*-Bu

In an asymmetric synthesis of 19-norsteroids, Pappo et al.[17] cleaved (**32**) and (**33**) to (**34**) and (**35**), respectively (eq 11), in high yield using chromium(II) acetate in aqueous THF (16 h, 30-40 °C). The methyl esters of (**32**) and (**33**) were not cleaved. Hence the presence of a carbonyl group in close proximity to the N-O bond is essential for this reaction.

---

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Chromium(II) Chloride

$CrCl_2$

[10049-05-5] · Cl_2Cr · Chromium(II) Chloride · (MW 122.92)

(reducing agent for dehalogenation of organic halides, especially allylic and benzylic halides, and for transformation of carbon-carbon triple bonds leading to (*E*)-alkenes; conversion of dibromocyclopropanes to allenes; preparation and reaction of allylic chromium reagents; reduction of sulfur- or nitrogen-substituted alkyl halides to give hetero-substituted alkylchromium reagents)

Physical Data: mp 824 °C; d_4^{14} 2.751 g cm^{-3}.

Form Supplied in: off-white solid; commercially available.

Solubility: sol water, giving a blue solution; insol alcohol or ether.

Handling, Storage, and Precautions: very hygroscopic; oxidizes rapidly, especially under moist conditions; should be handled in a fume hood under an inert atmosphere (argon or nitrogen).

Reduction of Alkyl Halides.[1,2]

Typically, the chromium(II) ion is prepared by reduction of chromium(III) salts with zinc and hydrochloric acid. Organochromium compounds produced in this way can subsequently be hydrolyzed to yield dehalogenated compounds (eq 1[3] and eq 2[4]). Anhydrous chromium(II) chloride is commercially available and can be used without further purification. The relative reactivities of various types of halide toward chromium(II) salts are shown in Scheme 1.

$$ClCH_2CO_2H \xrightarrow[HCl,\ H_2O]{CrCl_3,\ Zn} MeCO_2H \qquad (1)$$

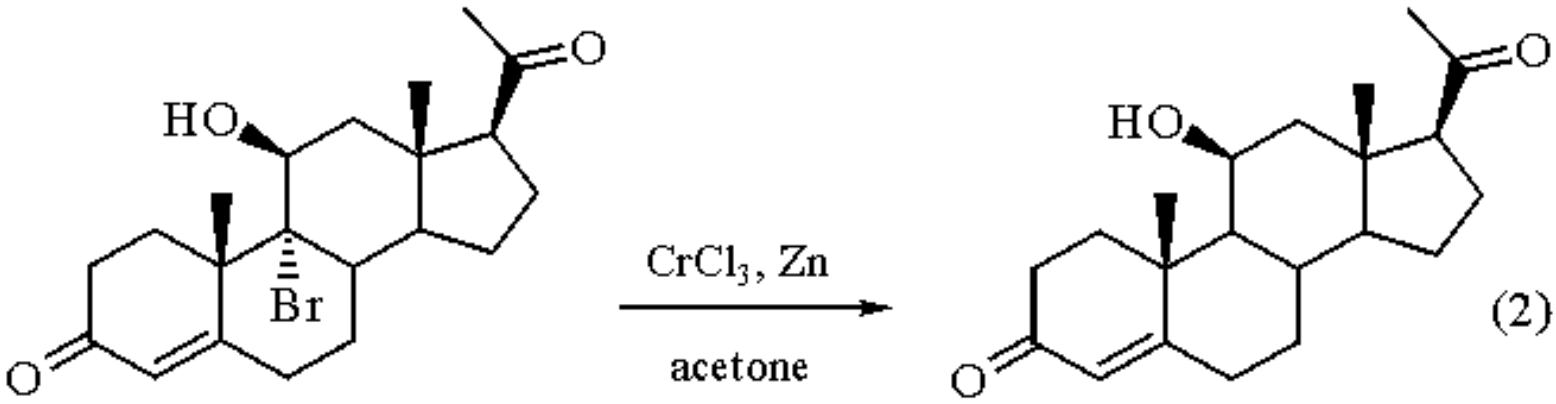

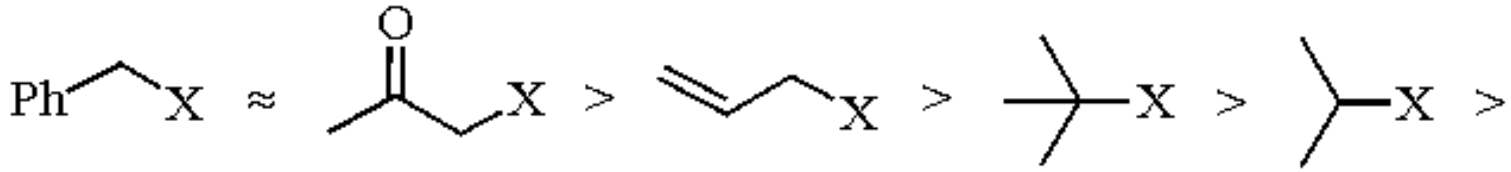

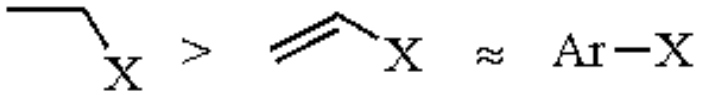

$$X = I > Br > Cl$$

Scheme 1

Conversion of Dihalocyclopropanes to Allenes.

Reduction of geminal dihalides proceeds smoothly to give chromium carbenoids.[5] In the case of 1,1-dibromocyclopropanes, the intermediate carbenoids decompose instantaneously to give allenes (eq 3).[6,7]

(3)

Reductive Coupling of Allylic and Benzylic Halides.

Active halides, such as allyl and benzyl halides, are reduced with $CrCl_2$ smoothly to furnish homocoupling products. Allylic halides undergo coupling, forming mainly the head-to-head dimer (eq 4).[6,8]

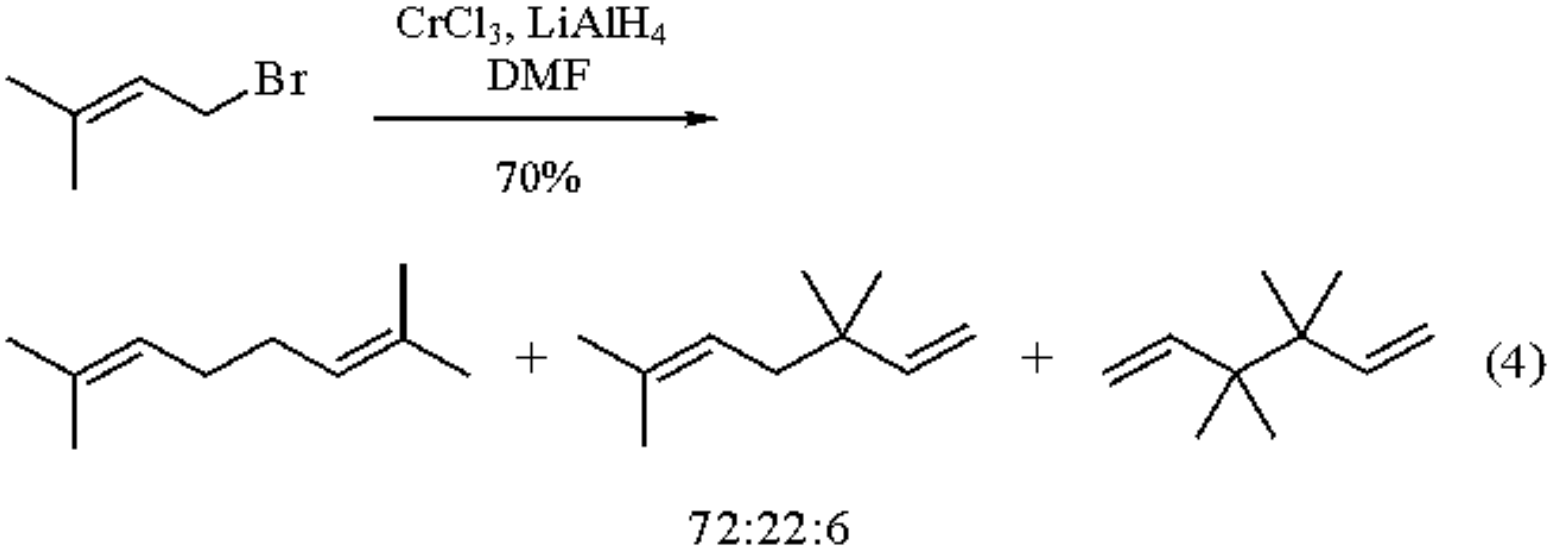

Formation of *o*-Quinodimethanes.

α,α´-Dibromo-*o*-xylenes are reduced with $CrCl_2$ in a mixed solvent of THF and HMPA to an *o*-quinodimethane, which can be trapped by a dienophile. The method has been applied to some anthracycline precursors (eq 5).[9]

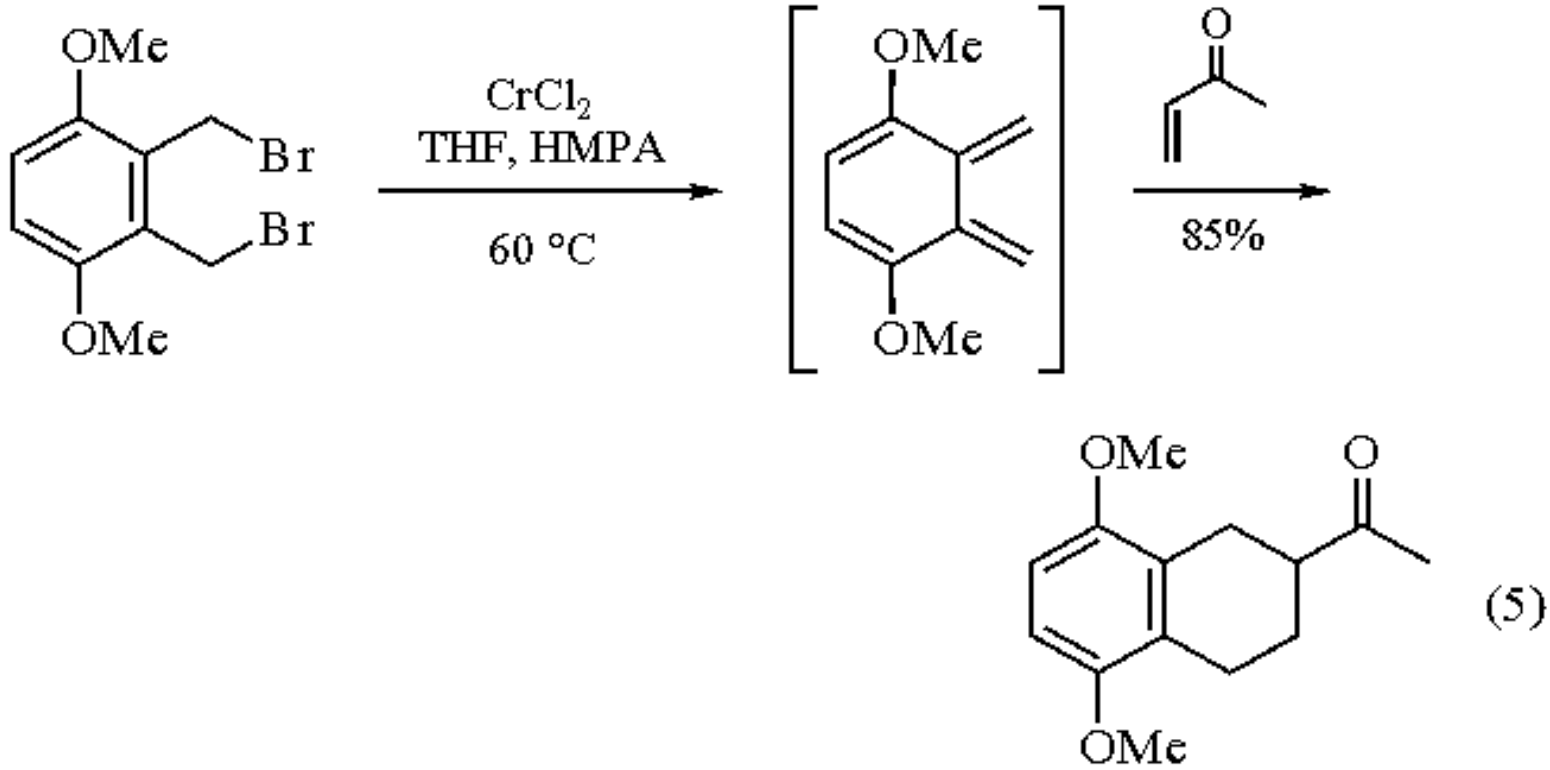

Reduction of Carbon-Carbon Unsaturated Bonds.

The reduction of alkynes with chromium(II) salts in DMF leads to (*E*)-substituted alkenes.[10] The ease of reduction depends on the presence of an accessible coordination site in the molecule (eq 6). Chromium(II) chloride in THF/H_2O (2:1) (or ***Chromium(II) Sulfate*** in DMF/H_2O) is effective at reducing α-alkynic ketones to (*E*)-enones. Less than 2%

of (*Z*)-enones are produced except in the case of highly substituted substrates, which also require longer reaction times.[11]

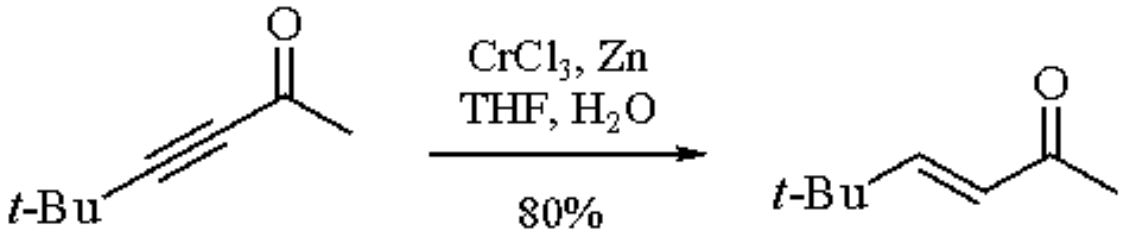

(6)

Reduction of Other Functional Groups.

Deoxygenation of α,β-epoxy ketones proceeds with acidic solutions of $CrCl_2$ to form α,β-unsaturated ketones.[12] Chromium(II) chloride has been regularly used in the deoxygenation of the limonoid group of triterpenes, in which ring D bears an α,β-epoxy-δ-lactone.[13] Treatment of nitrobenzene derivatives with $CrCl_2$ in methanol under reflux gives anilines (eq 7), while aliphatic nitro compounds afford aldehydes under the same reaction conditions.[14] Reduction of a nitroalkene with acidic solutions of $CrCl_2$ resulted in the formation of an α-hydroxy oxime.[15]

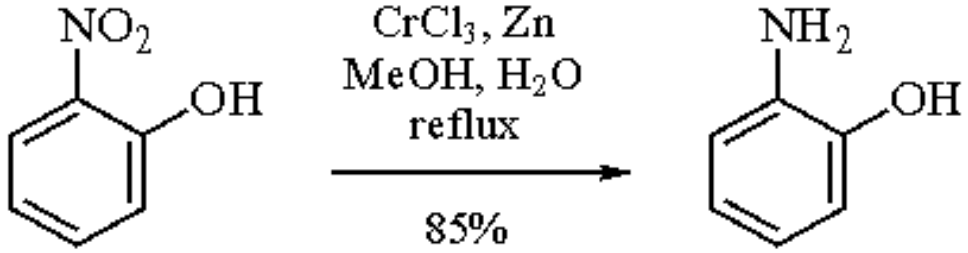

(7)

Preparation of Allylic Chromium Reagents.[16]

Allylic halides are reduced with low-valent chromium ($CrCl_3$-$LiAlH_4$) or $CrCl_2$ to give the corresponding allylic chromium reagents, which add to aldehydes and ketones in good to excellent yields.[17] The electronegativity of chromium is 1.6, almost the same as that of titanium (1.5). Therefore the nucleophilicity of organochromium reagents is not strong compared to the corresponding organolithium or -magnesium compounds. Chemoselective addition of allylic chromium reagents can be accomplished without affecting coexisting ketone and cyano groups (eq 8).[17] The reaction between crotylchromium reagents and aldehydes in THF proceeds with high diastereoselectivity (eq 9).[18,19] The *anti* (or *threo*) selectivity in the addition of acyclic allylic chromium reagents with aldehydes is explained by a chair-form six-membered transition state in which both R^1 and R^2 possess equatorial positions (**1** > **2**).

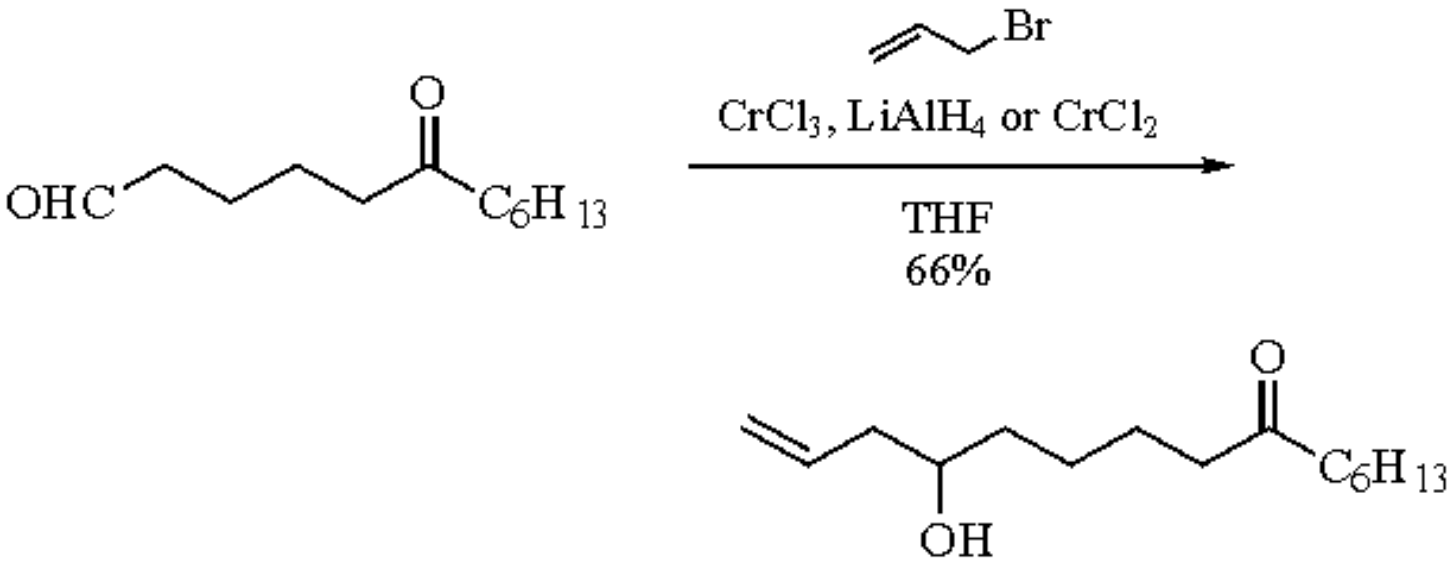

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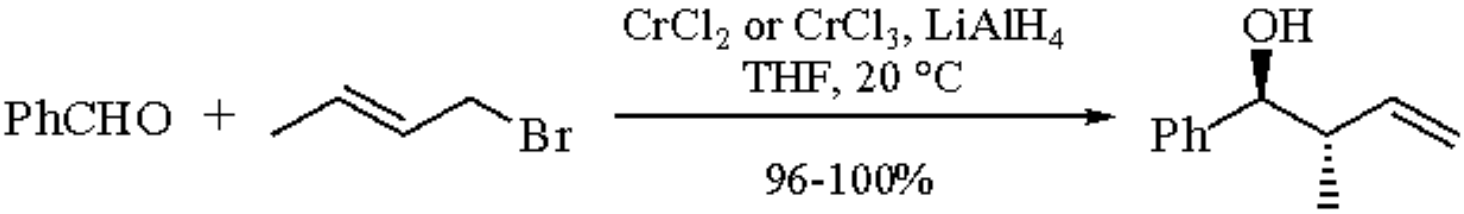

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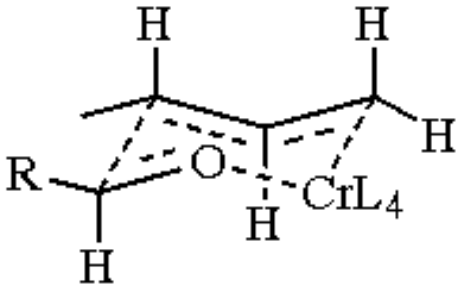

(1)

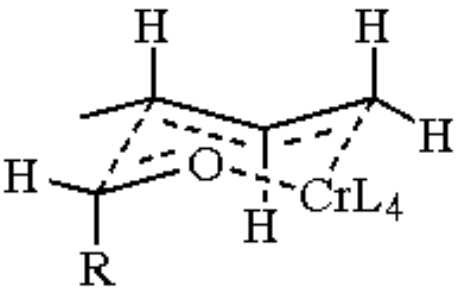

(2)

Addition of crotylchromium reagents to aldehydes bearing a stereogenic center α to the carbonyl provides three of the four diastereomers (eq 10).[19] Excellent *anti* selectivity is observed with respect to the 1,2-positions, but the stereoselectivity with respect to the 2,3-positions (Cram/anti-Cram ratio) is poor.[20-22] High 1,2- and 2,3-diastereoselectivity is obtained with aldehydes having large substituents, especially a cyclic acetal group, on the α-carbon of the aldehyde (eq 11).[20,23] Reaction between chirally substituted acyclic allylic bromides and aldehydes proceeds with high stereocontrol (eq 12).[24]

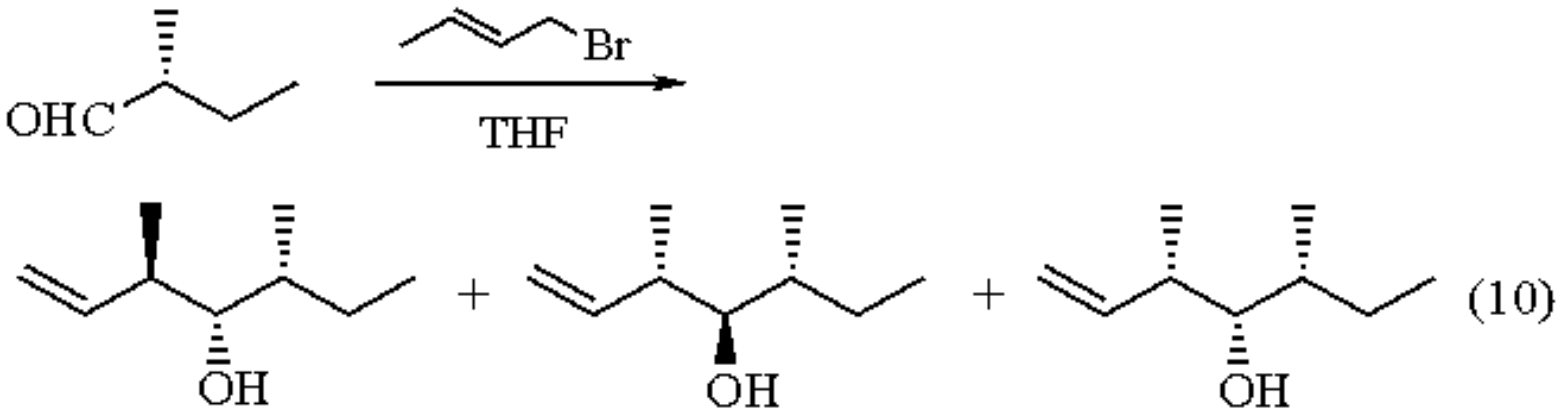

$CrCl_2$ 90%, 62:31:7
$CrCl_3$, $LiAlH_4$ 78%, 64:29:7

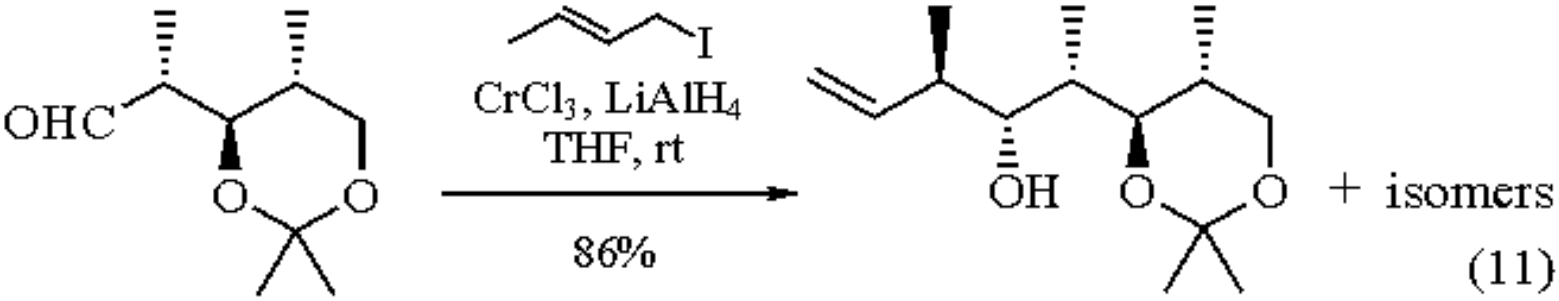

>20:1

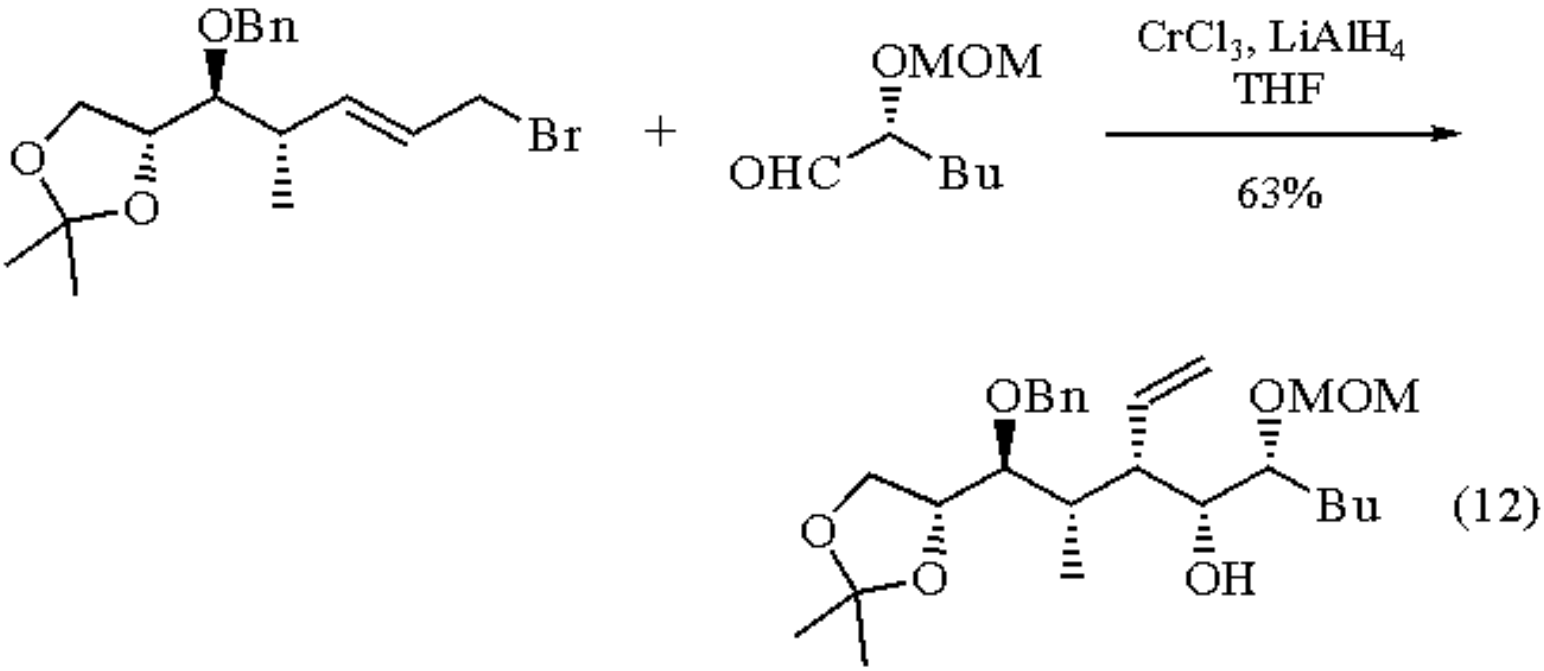

As with allylic halides, allylic diethylphosphates[25] and mesylates[26,27] are reduced with chromium(II) salts to give allylic chromium reagents which add to aldehydes regio- and stereoselectively. This transformation reveals conversion of the electronic nature of allylic phosphates (or mesylates) from electrophilic to nucleophilic by reduction with low-

valent chromium.

The reaction of γ-disubstituted allylic phosphates with aldehydes mediated by $CrCl_2$ and a catalytic amount of LiI in DMPU is not stereoconvergent and proceeds with high stereoselectivity (eqs 13 and 14).[27] The presence of the two substituents at the γ-position slows down the process of equilibration between the intermediate allylic chromium reagents.

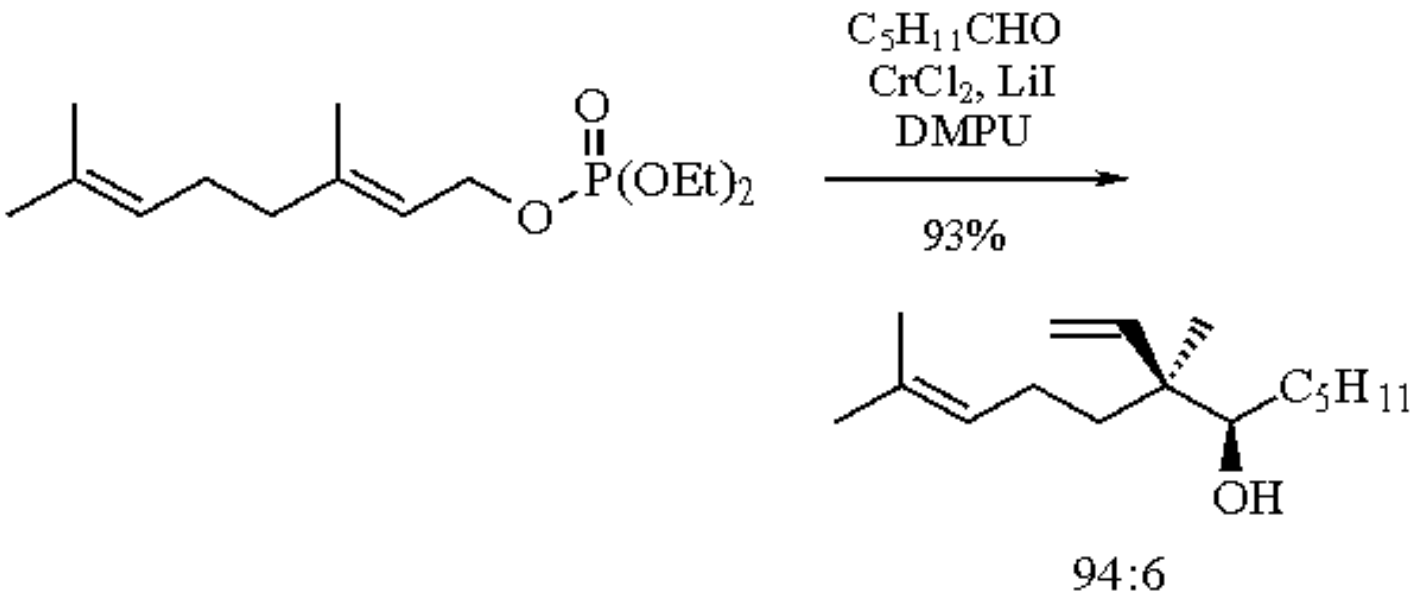

(13)

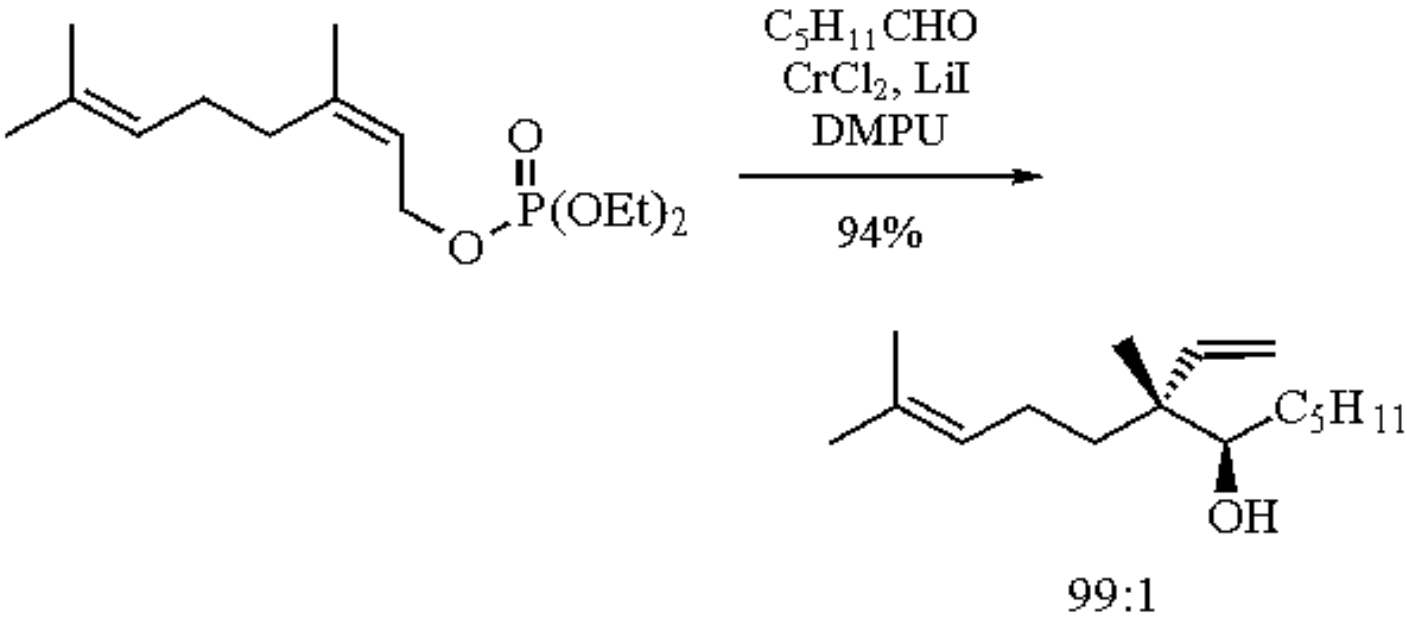

(14)

Because the coupling reaction between allylic halides and aldehydes proceeds under mild conditions, the reaction has been employed, in particular, in intramolecular cyclizations.[28-32] The intramolecular version also proceeds with high *anti* selectivity (eqs 15 and 16).

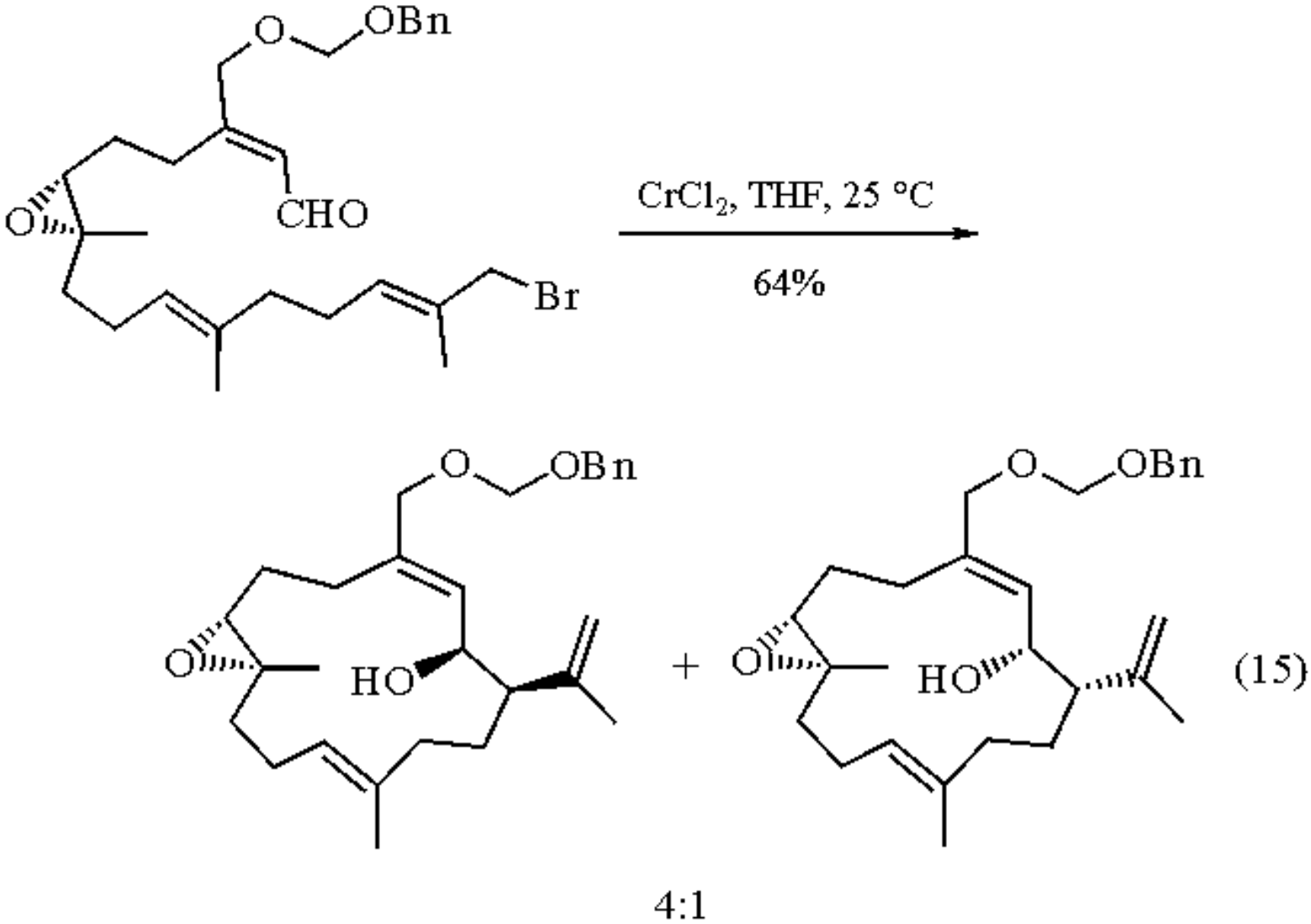

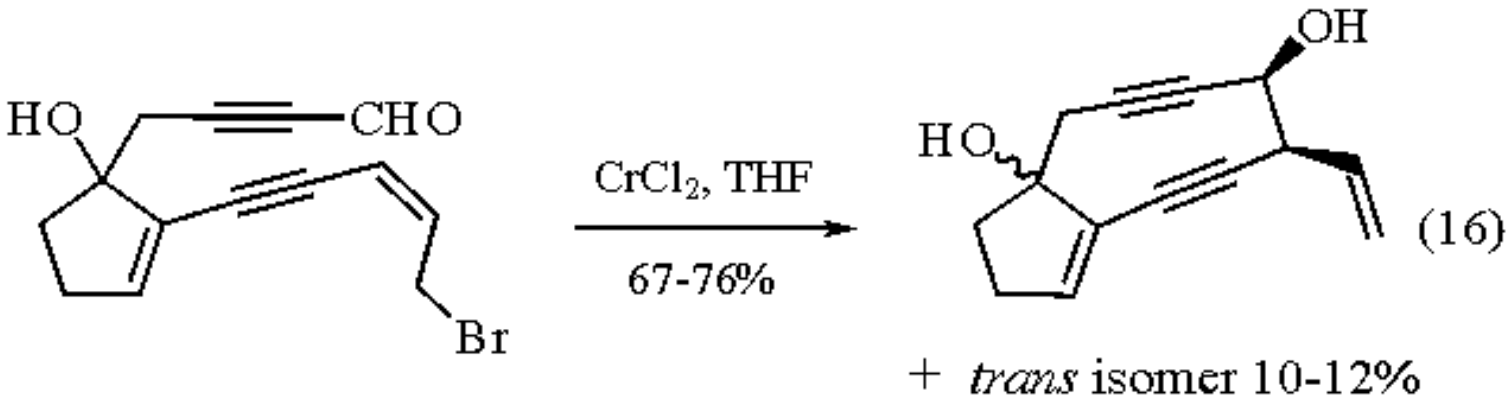

Functionalized and Hetero-Substituted Allylic Chromium Reagents.

When functionalized allylic halides are employed as precursors of allylic chromium reagents, an acyclic skeleton bearing a foothold for further construction is produced. Reaction of α-bromomethyl-α,β-unsaturated esters with aldehydes mediated by $CrCl_2$ (or $CrCl_3$-$LiAlH_4$) affords homoallylic alcohols, which cyclize to yield α-methylene-γ-

lactones in a stereoselective manner (eq 17).[33] Reaction between α-bromomethyl-α,β-unsaturated sulfonates and aldehydes also proceeds with high stereocontrol.[34]

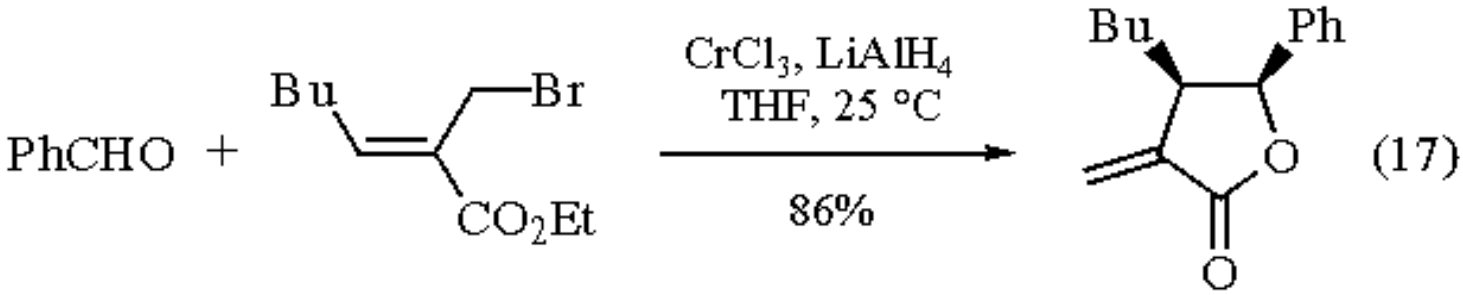

The reaction of 3-alkyl-1,1-dichloro-2-propene with $CrCl_2$ results in α-chloroalkylchromium reagents, which react with aldehydes to produce a 2-substituted *anti*-(*Z*)-4-chloro-3-buten-1-ol in a regio- and stereoselective manner (eq 18).[35] Vinyl-substituted β-hydroxy carbanion synthons are produced by reduction of 1,3-diene monoepoxides with $CrCl_2$ in the presence of LiI, which react stereoselectively with aldehydes to give (*R**,*R**)-1,3-diols having a quaternary center at C-2.[36] Reduction in situ of acrolein dialkyl acetals with $CrCl_2$ in THF provides γ-alkoxy-substituted allylic chromium reagents which add to aldehydes at the same position of the alkoxy group to afford 3,4-butene-1,2-diol derivatives. The reaction rate and stereoselectivity are increased by addition of ***Iodotrimethylsilane*** (eq 19).[37]

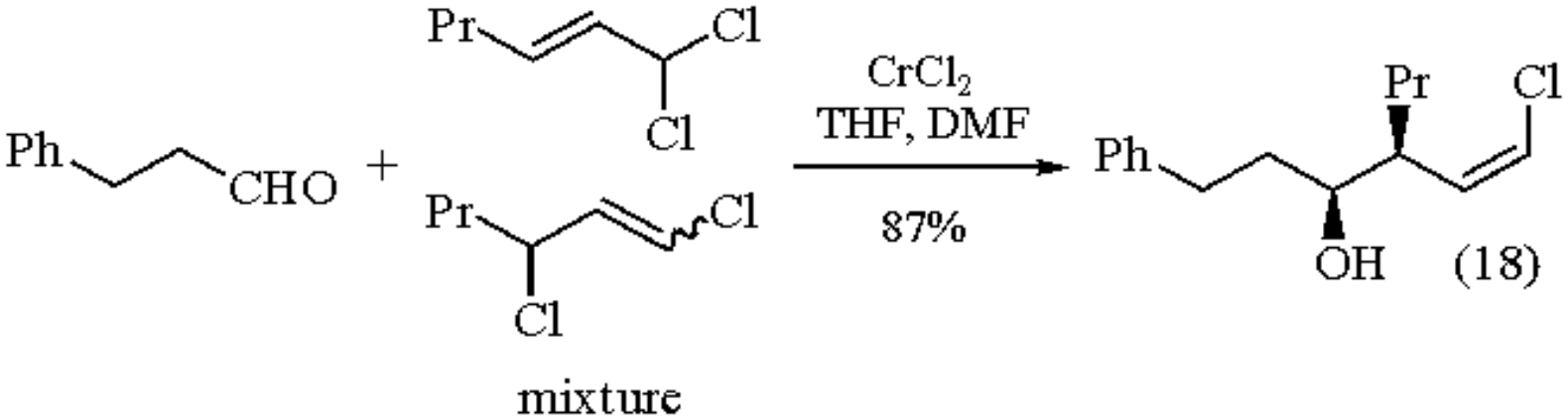

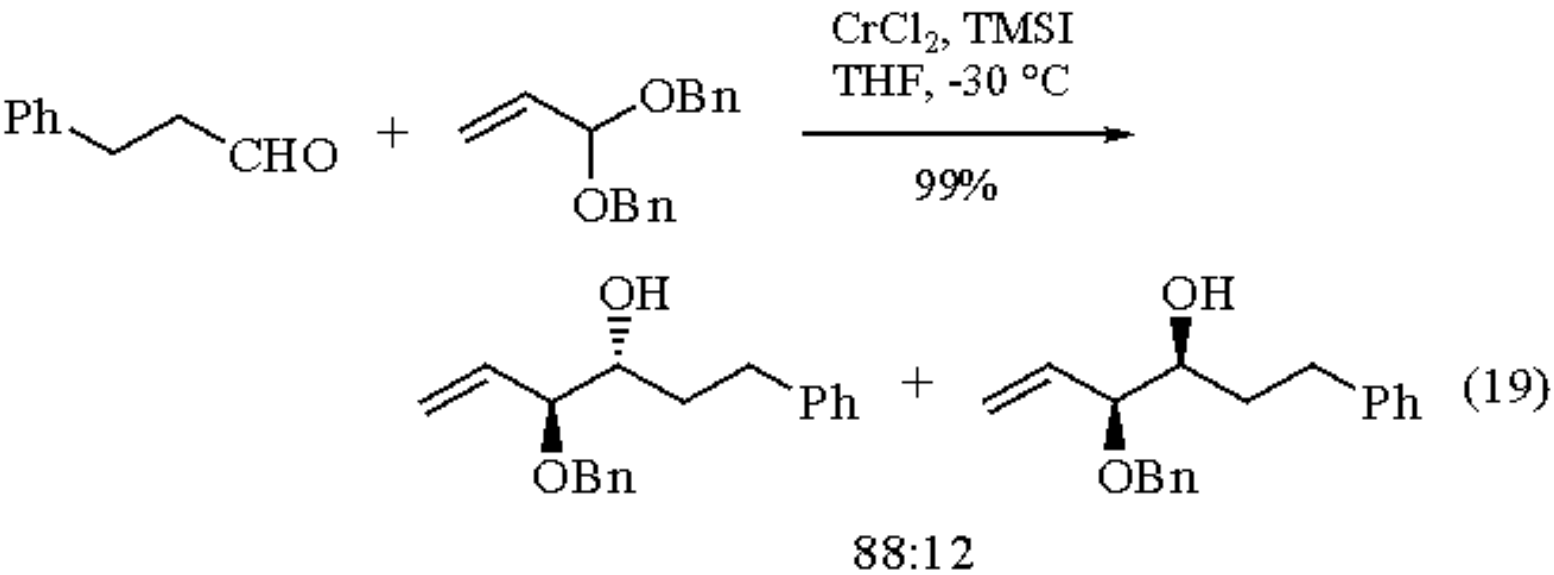

Preparation of Propargylic Chromium Reagents.

Propargyl halides react with aldehydes or ketones in the presence of $CrCl_2$ with HMPA as cosolvent to give allenes stereoselectively (eq 20).[38] The reaction was modified to include polyfunctional propargylic halides by using $CrCl_2$ and ***Lithium Iodide*** in DMA, and allenic alcohols accompanied only by small amounts of homopropargylic alcohols are produced.[39]

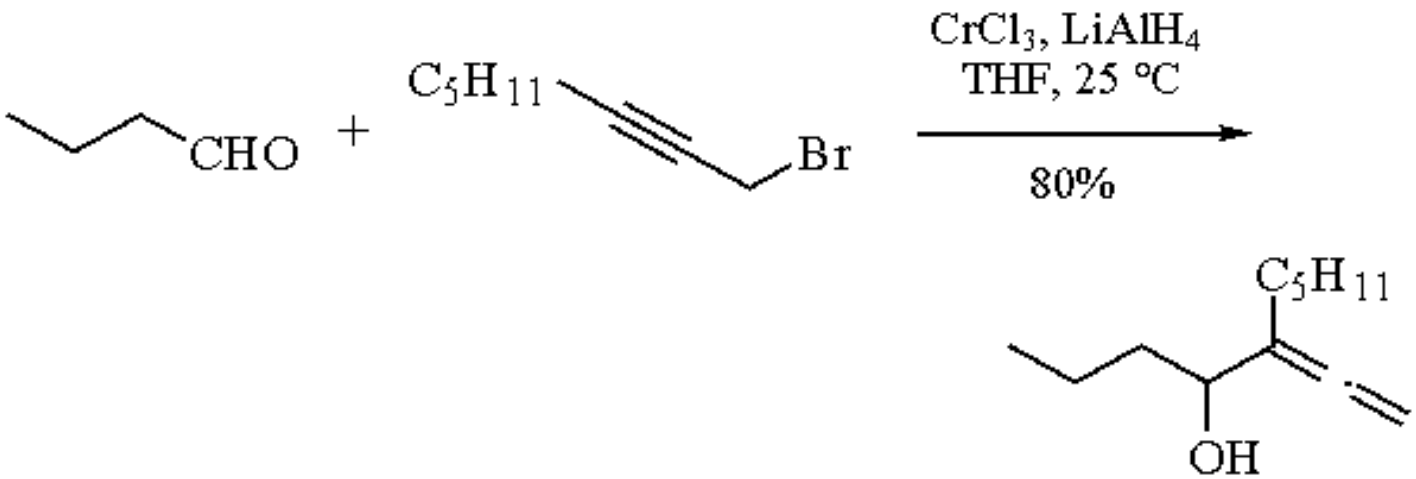

(20)

Sulfur- and Nitrogen-Stabilized Alkylchromium Reagents.

In combination with LiI, $CrCl_2$ reduces α-halo sulfides to (α-alkylthio)chromium compounds, which undergo selective 1,2-addition to aldehydes. Acetophenone is recovered unchanged under the reaction conditions. The (1-phenylthio)ethenylchromium reagents prepared in this way add to aldehydes under high stereocontrol in the presence of suitable ligands like 1,2-diphenylphosphinoethane (dppe) (eq 21).[40] The reaction of *N*-(chloromethyl)succinimide and -phthalimide with $CrCl_2$ provides the corresponding α-nitrogen-substituted organochromium reagents in the presence of LiI. These organochromium reagents react in situ with aldehydes, affording protected amino alcohols (eq 22).[41]

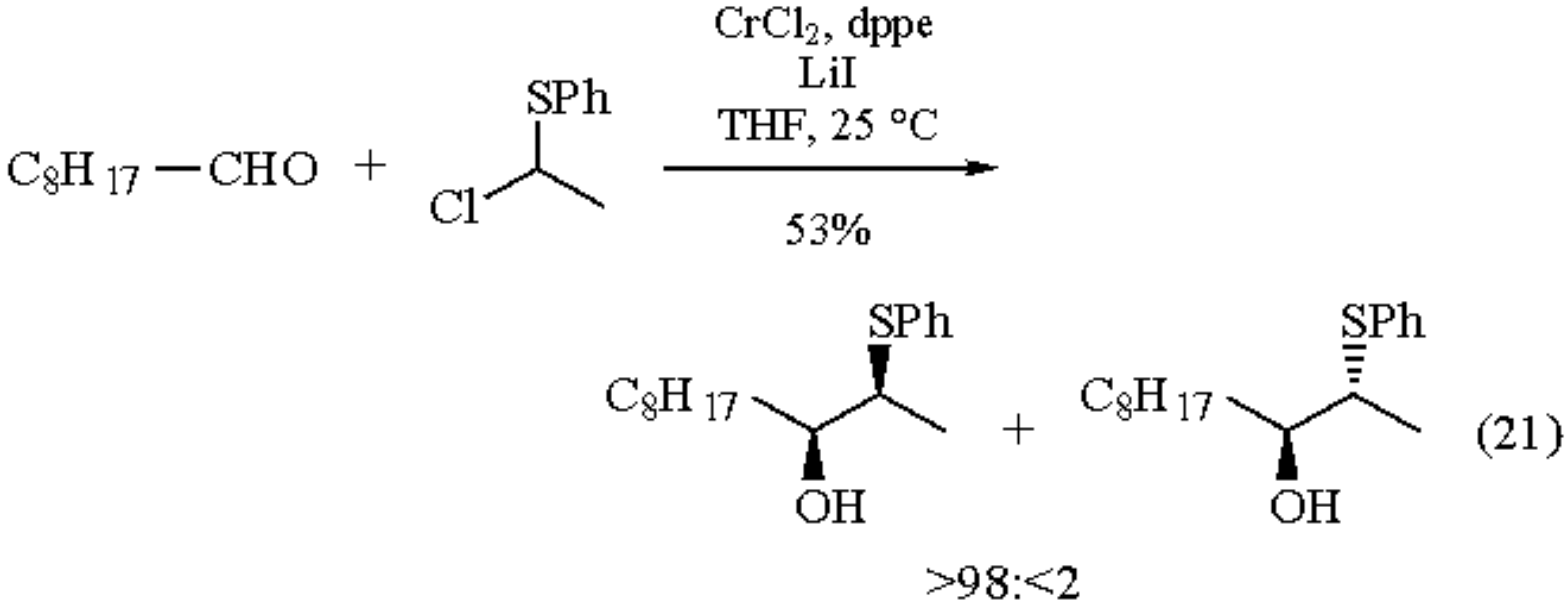

(21)

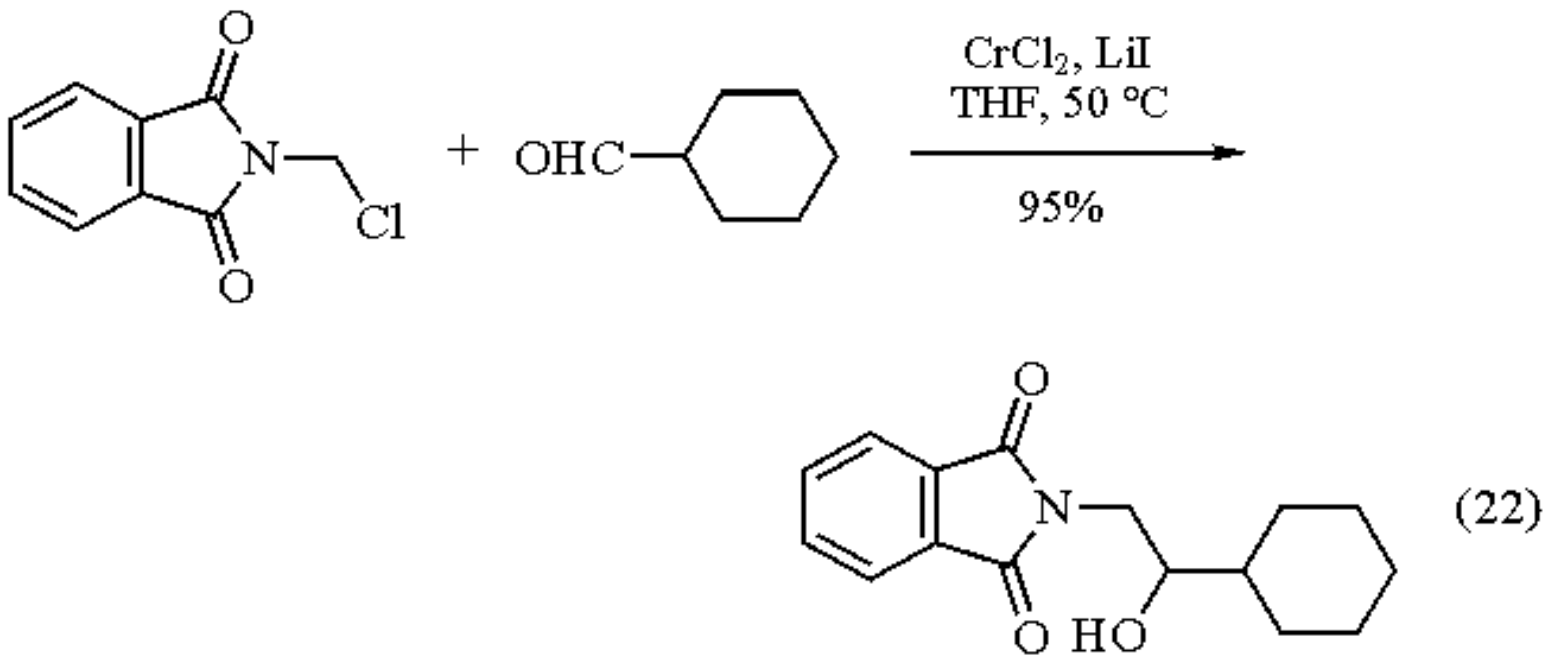

(22)

Preparation of Alkylchromium Reagents.[42]

With the assistance of catalytic amounts of ***Vitamin B_{12}*** or cobalt phthalocyanine (CoPc), $CrCl_2$ reduces alkyl halides, especially 1-iodoalkanes, to form alkylchromium reagents which add to aldehydes without affecting ketone or ester groups. The chemoselective preparation of organochromium reagents can be done by changing either the catalyst or the solvent. Alkenyl and alkyl halides remain unchanged under the conditions of the preparation of allylchromium reagents; on the other hand, alkenyl- and alkylchromium reagents are produced selectively under nickel and cobalt catalysis, respectively (eqs 23 and 24).

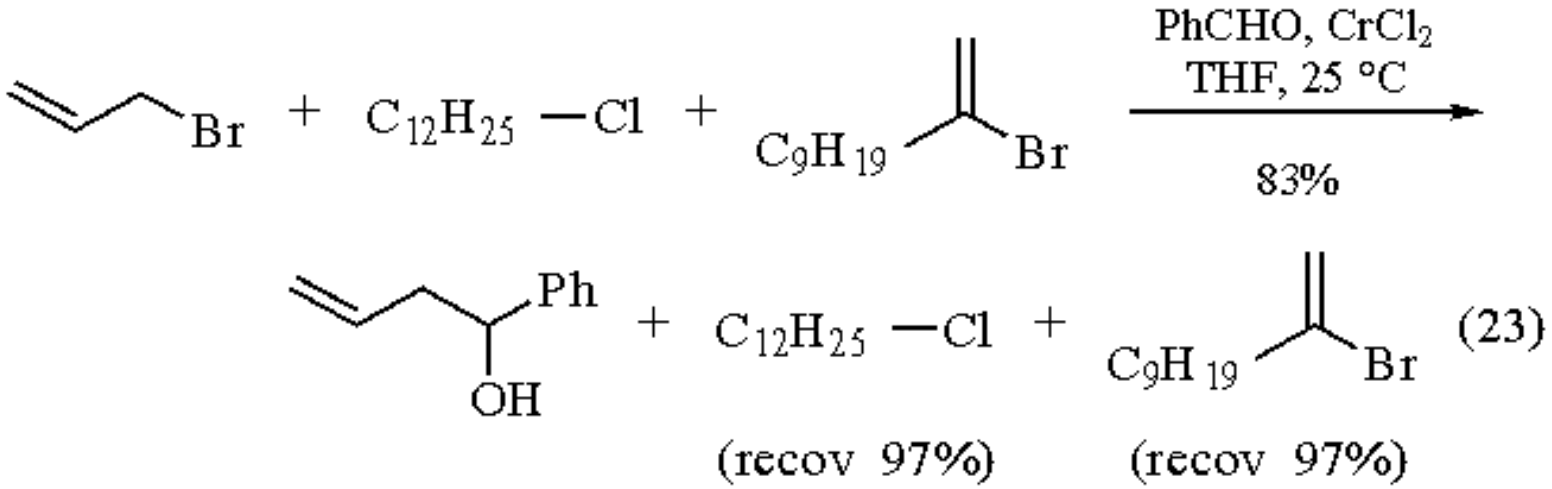

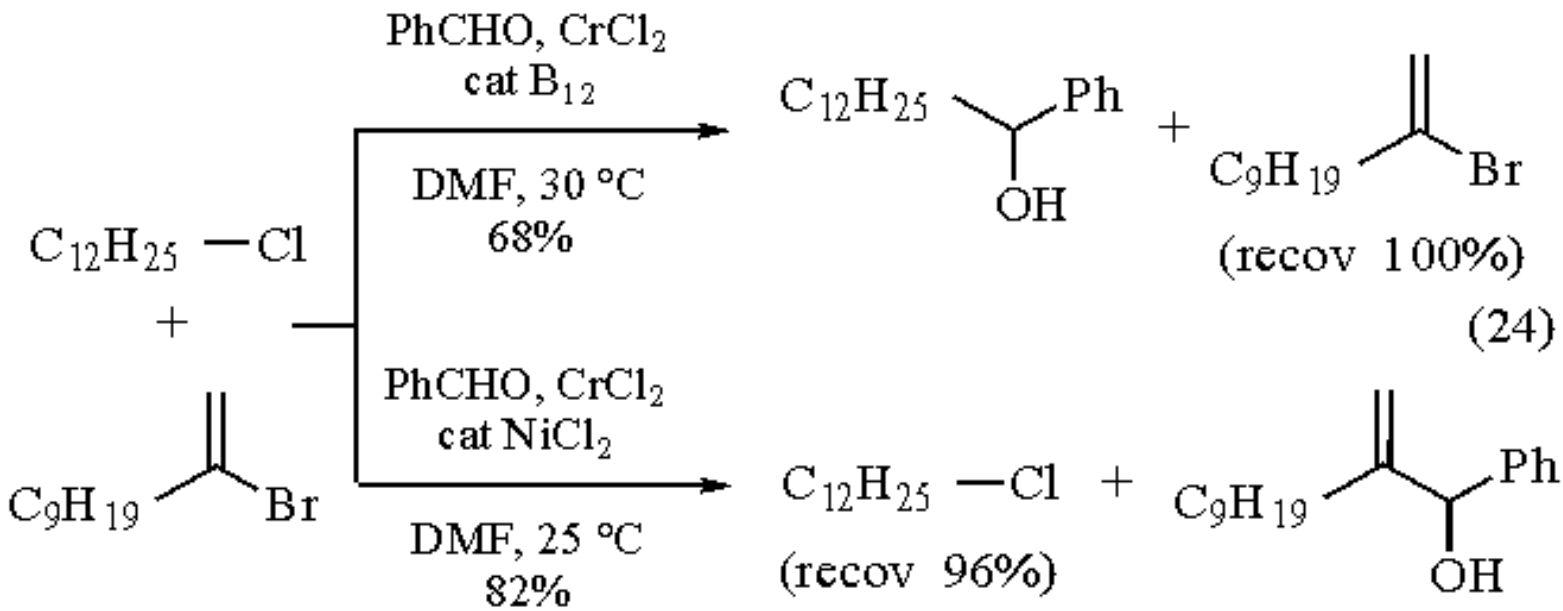

Related Reagents.

Chromium(II) Chloride-Haloform; ***Chromium(II) Chloride-Nickel(II) Chloride***.

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Chromium(II) Chloride-Haloform

$CrCl_2$-CHX_3

($CrCl_2$)

[10049-05-5] · Cl_2Cr · Chromium(II) Chloride-Haloform · (MW 122.92) (CHI_3)

[75-47-8] · CHI_3 · Chromium(II) Chloride-Iodoform · (MW 393.78) ($CHBr_3$)

[75-25-2] · $CHBr_3$ · Chromium(II) Chloride-Bromoform · (MW 252.77) ($CHCl_3$)

[67-66-3] · $CHCl_3$ · Chromium(II) Chloride-Chloroform · (MW 119.39) ($Me_3SiCHBr_2$)

[2612-42-2] · $C_4H_{10}Br_2Si$ · Chromium(II) Chloride-(Dibromomethyl)trimethylsilane · (MW 246.02)

(conversion of aldehydes to (*E*)-alkenyl halides or (*E*)-alkenylsilanes with one-carbon homologation; (*E*)-selective alkylidenation of aldehydes)

Physical Data: see entries for ***Chromium(II) Chloride***, ***Iodoform***, ***Bromoform***, ***Chloroform***, and ***(Dibromomethyl)trimethylsilane***.

Preparative Method: prepared in presence of reactant aldehyde: to a suspension of anhyd $CrCl_2$ (0.74 g, 6.0 mmol) in THF (10 mL) under Ar, add a solution of aldehyde (1.0 mmol) and iodoform (0.79 g, 2.0 mmol) in THF (5 mL) dropwise at 0 °C, at 0 °C for 3 h, pour the reaction mixture into water (25 mL) and extract with ether; dry the combined extracts over Na_2SO_4 and concentrate; purification by column chromatography gives an alkenyl halide. Low-valent chromium derived by reduction of $CrCl_3$ (6.0 mmol) with ***Lithium Aluminum Hydride*** (3.0 mmol) can be used instead of $CrCl_2$.

Handling, Storage, and Precautions: use in a fume hood; chromium(II) chloride should be used under an inert atmosphere (argon or nitrogen).

Preparation of (*E*)-Alkenyl Halides.[1]

The reagent prepared by treatment of CHI_3 or $CHCl_3$ with $CrCl_2$ gives iodo- and chloroalkenes, respectively (eq 1). When bromoform is employed, a mixture of bromo- and chloroalkenes is produced. This side-reaction is overcome by using a combination of $CrBr_3$ and $LiAlH_4$ instead of $CrCl_2$.[1] The rates of reaction of the haloforms are in the sequence I > Br > Cl. Reflux of a mixture of $CHCl_3$ and $CrCl_2$ in THF before addition of an aldehyde and sonication are reported

to accelerate the reaction. An iodoalkene having a terminal ^{13}C can be prepared by using $^{13}CHI_3$ (eq 2).[2] An ene-reaction product is obtained as a byproduct in the case of an aldehyde having a suitable alkenic bond.[1,3]

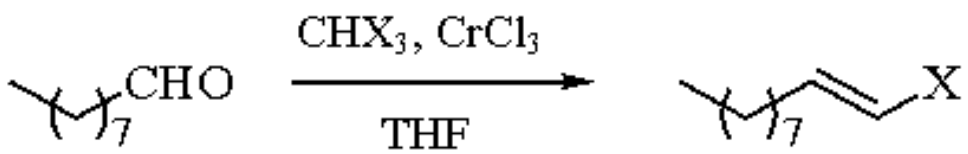

(1)

X = I, 0 °C, 82%, (*E*):(*Z*) = 83:17
X = Cl, 65 °C, 76%, (*E*):(*Z*) = 94:6

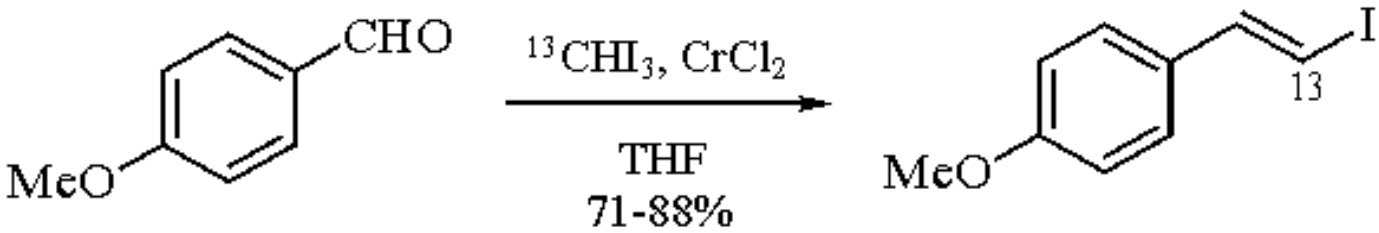

(2)

(*E*)-Isomers of alkenyl halides are produced selectively. The (*E*):(*Z*) ratios of the alkenyl halides increase in the order I < Br < Cl. A mixed solvent of dioxane and THF is employed to improve the (*E*):(*Z*) ratios in certain cases.[4] Isomerization using NaOH in *t*-BuOH is also effective to obtain high (*E*):(*Z*) ratios (eq 3).[5]

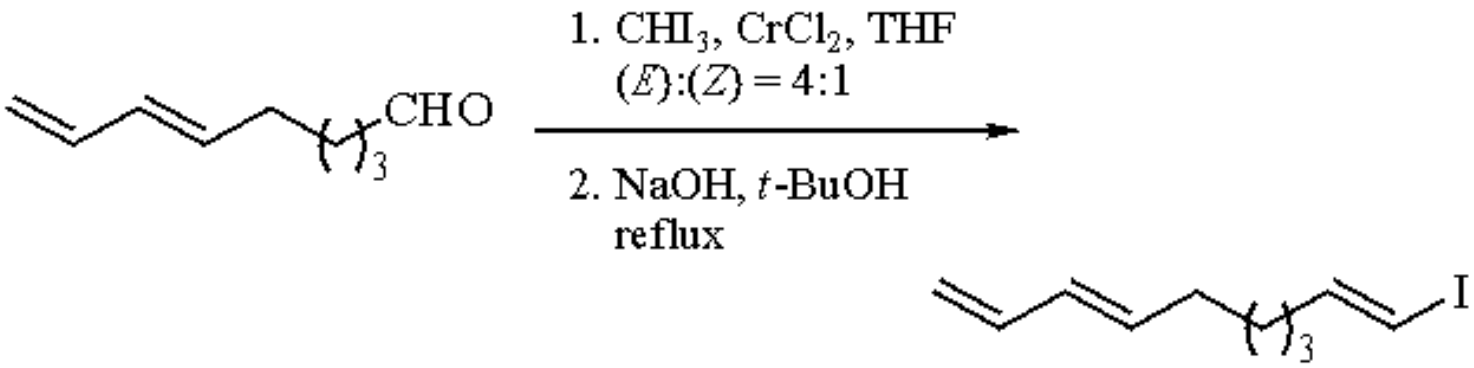

(3)

(*E*):(*Z*) = >40:1

Although ketones are also converted into the corresponding alkenyl halides, they are less reactive than aldehydes. Selective conversion of an aldehyde into an (*E*)-iodoalkene can thus be accomplished without affecting the coexisting ketone group.[1] The following functional groups are also tolerated during the reaction: ester, lactone, amide, nitrile, 1,3-diene, alkyne, alkene, bromide, chloride, and acetal of ethylene glycol. A hydroxyl group can be protected by using the following groups: OMe, OCH_2Ph, $OSiMe_3$(*t*-Bu), OAc, OCOPh, OTHP, and OMPM. Because the basicity of the reagent is not strong, epimerization at the α-position of aldehydes does not generally take place. The alkenyl iodides (RCH=CHI) (**1**),[6] (**2**),[7] (**3**),[8] and (**4**)[9] are prepared from the corresponding aldehydes (RCHO).

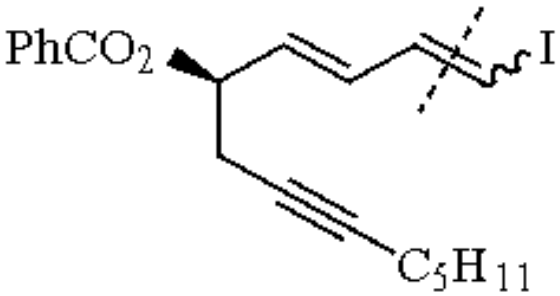

THF, 0 °C, 75%, (*E*):(*Z*) = 4:1

(1)

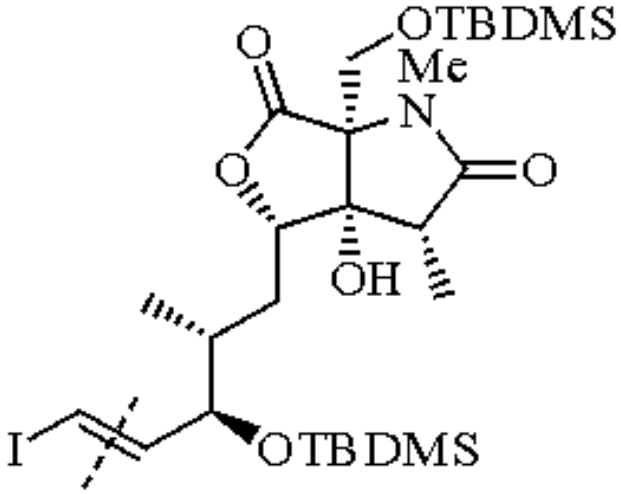

THF, 25 °C, 70%

(2)

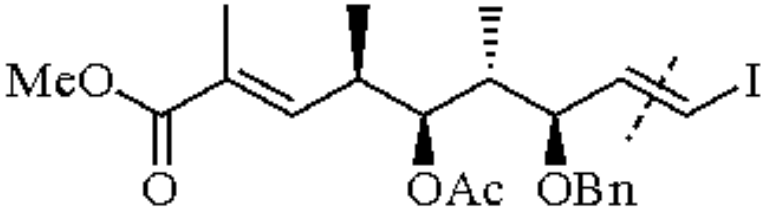

THF, 0 °C, 80%, (*E*):(*Z*) = 98:2

(3)

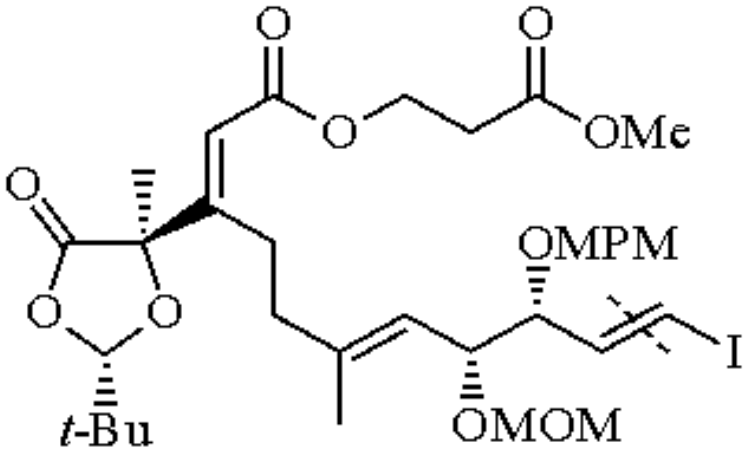

THF, 23 °C, 66%

(4)

Preparation of (*E*)-Alkenylsilanes.[10]

When $Me_3SiCHBr_2$ is used instead of a haloform, (*E*)-alkenylsilanes are produced from aldehydes stereoselectively (eq 4). Because the reaction proceeds under mild conditions, selective transformation of an aldehyde to an (*E*)-alkenylsilane can be performed in the presence of ketone, cyano, ether, acetal, and ester groups (eq 5).[10-12]

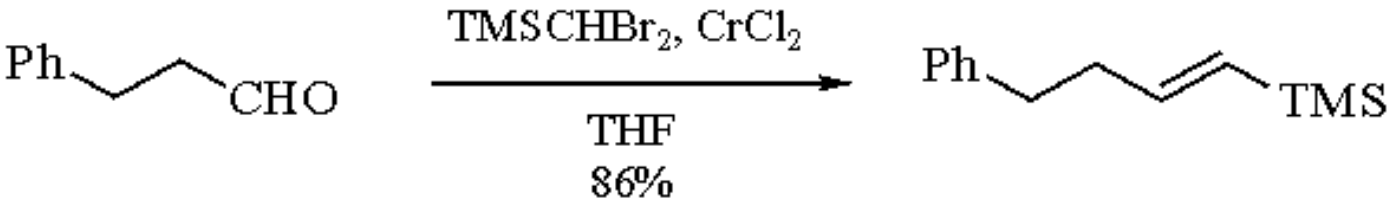

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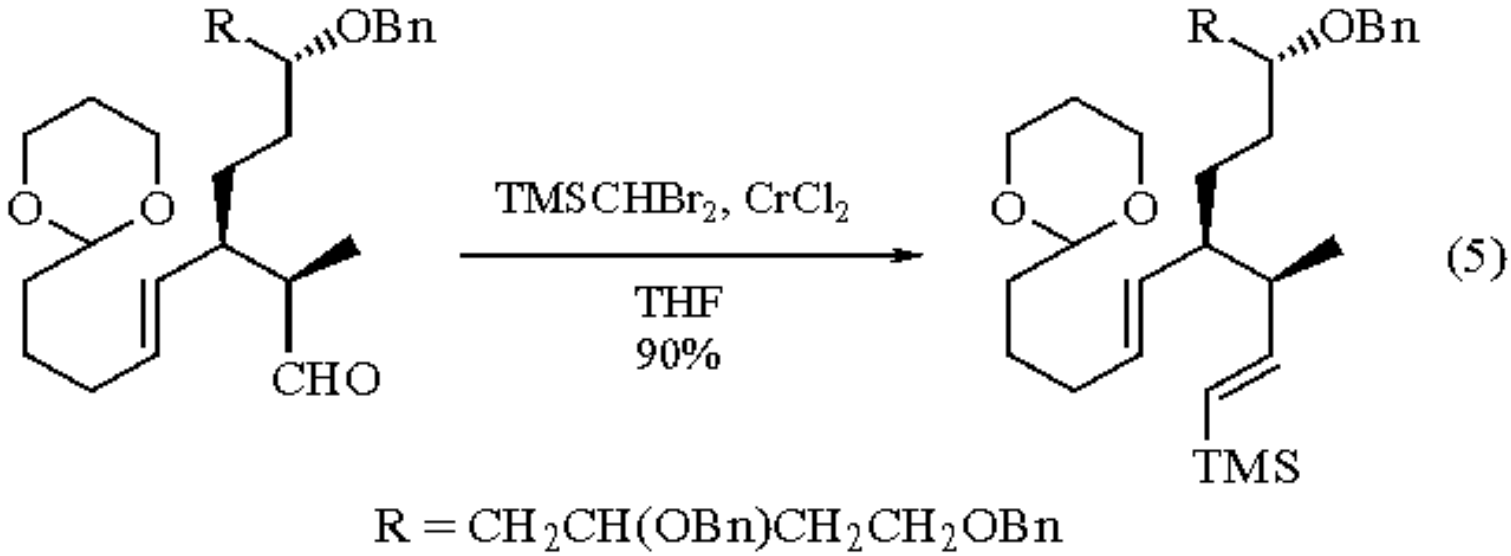

(*E*)-Selective Wittig-Type Alkylidenation of Aldehydes.[13]

Treatment of aldehydes in THF with the reagent derived by reduction of 1,1-diiodoalkane with $CrCl_2$-DMF produces (*E*)-alkenes with high stereocontrol (eq 6).

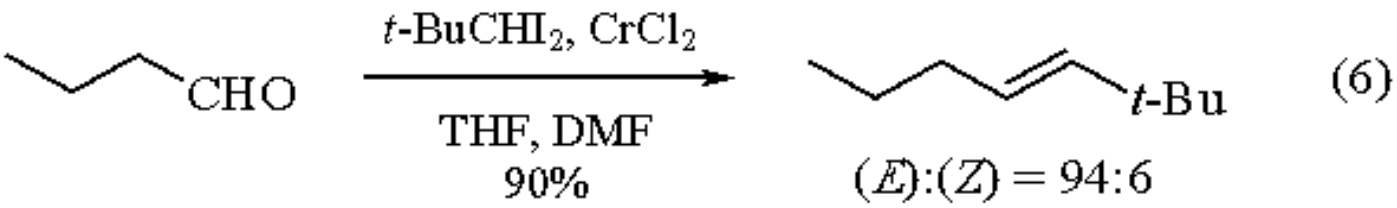

Related Reagents.

Bromoform; ***Chloroform***; ***Chromium(II) Chloride***; ***1,1-Diiodoethane***; ***Diiodomethane***; ***Iodoform***.

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Chromium(II) Chloride-Nickel(II) Chloride

$CrCl_2$-$NiCl_2$

($CrCl_2$)

[10049-05-5] · Cl_2Cr · Chromium(II) Chloride-Nickel(II) Chloride · (MW 122.92) ($NiCl_2$)

[7718-54-9] · Cl_2Ni · Chromium(II) Chloride-Nickel(II) Chloride · (MW 129.61)

(catalyst for coupling reactions between haloalkenes (or alkenyl triflates) and aldehydes; active low-valent nickel catalyst)

Physical Data: see entries for ***Chromium(II) Chloride*** and ***Nickel(II) Chloride***.

Preparative Method: a mixture of anhyd $CrCl_2$ (0.47 g, 4.0 mmol) and a catalytic amount of $NiCl_2$ (2.6 mg, 0.020 mmol) in dry, oxygen-free DMF (10 mL) is stirred at 25 °C for 10 min under Ar; add successively a solution of an aldehyde (1.0 mmol) in DMF (5 mL) and a solution of a haloalkene (or an alkenyl triflate; 2.0 mmol) in DMF (5 mL) and stir at 25 °C for 1 h, dilute the reaction mixture with ether (20 mL), pour into water (20 mL), and extract with ether repeatedly; dry the combined extracts over Na_2SO_4 and concentrate; purification by column chromatography gives an allylic alcohol; DMSO or a DMF/THF mixture may be used as solvent (ether and THF are unsuitable).

Handling, Storage, and Precautions: chromium(II) chloride should be used in a fume hood under an inert atmosphere (argon or nitrogen).

Grignard-Type Carbonyl Addition of Haloalkenes to Aldehydes.[1-3]

The carbonyl addition reaction mediated by $CrCl_2$ was first reported without any catalyst.[4] Later, a catalytic amount of nickel proved to be indispensable to promote the Grignard-type carbonyl addition of haloalkenes to aldehydes with good reproducibility (eq 1).[1,2] It is important to keep the content of $NiCl_2$ in $CrCl_2$ low (about 0.01-1% w/w) to avoid formation of dienes by homocoupling of the haloalkenes.[5] The Grignard-type reaction between alkenyl triflates and aldehydes proceeds under the same conditions.[1] In the case of α,β-unsaturated aldehydes, 1,2-addition products are the major products.

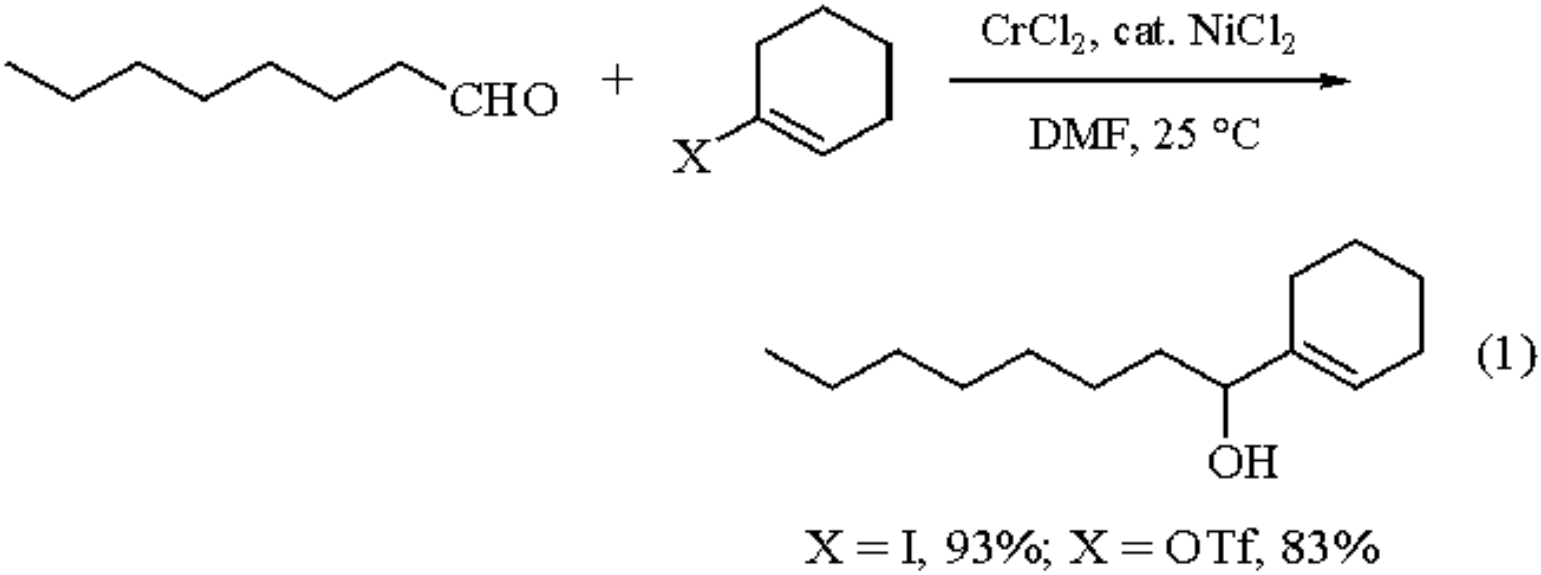

The process has many advantages. The basicity of the formed alkenylchromium reagent is not high, and epimerization at the α-position of aldehydes therefore generally does not take place. The regiochemistry of double bonds is maintained during the coupling reaction (eq 2).[6] Mild nucleophilicity of the alkenylchromium reagents permits addition to aldehydes in good to excellent yields without affecting coexisting ketone, ester, amide, acetal, silyl ether, cyano, and sulfinyl groups.[1-4,6-9] The system is especially effective for coupling reactions of highly oxygenated multifunctional substrates.[2,3,7] The stereochemistry of *trans*- and *cis*-haloalkenes is retained, at least in the case of disubstituted haloalkenes and trisubstituted trans-haloalkenes (eqs 3 and 4).[1,2] Treatment of a trisubstituted *cis*-haloalkene (or an alkenyl triflate) with the $CrCl_2$-$NiCl_2$ system often results in a *cis-trans* isomerization-coupling reaction sequence or in recovery of the starting alkenyl halide. With respect to the newly introduced stereogenic center, the process produces a mixture of two possible diastereomers with a moderate to good preference for one stereoisomer. The major products produced from α-alkoxy- and α,β-bisalkoxyaldehydes have the stereochemistry opposite to cuprate or Grignard products.[2]

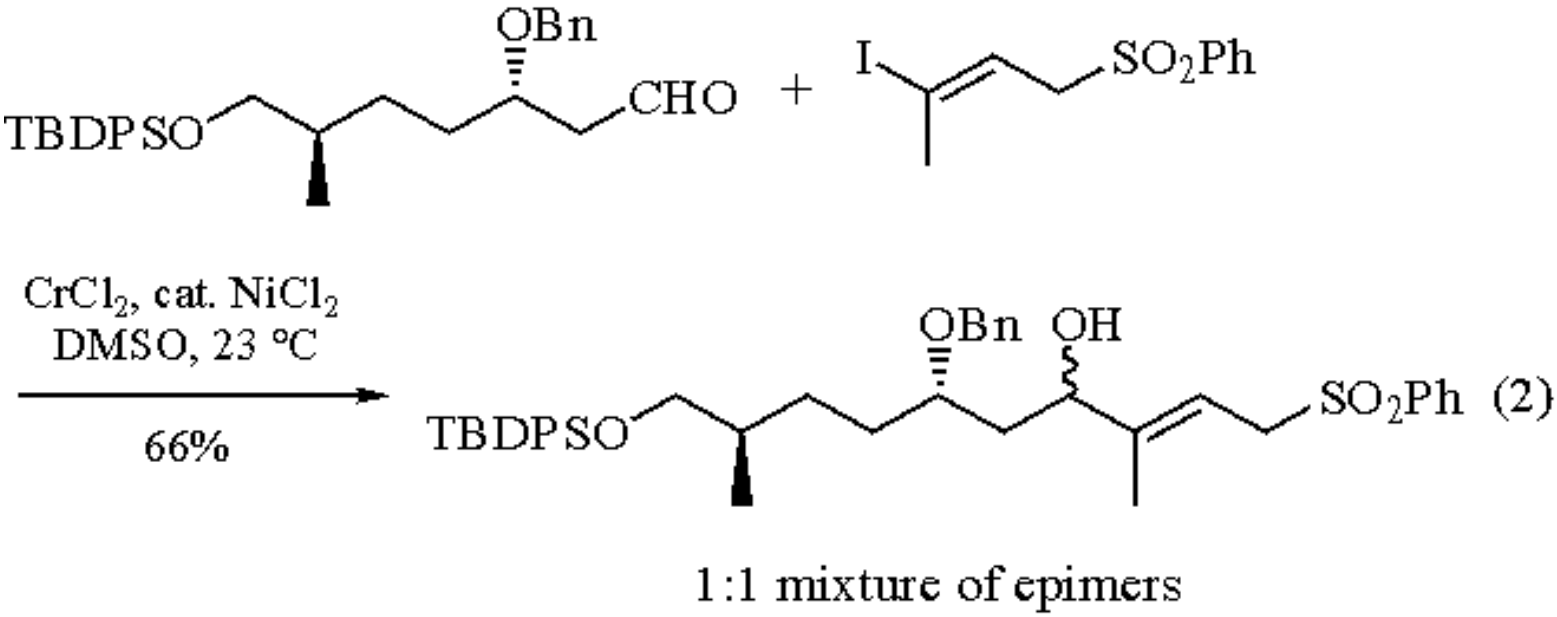

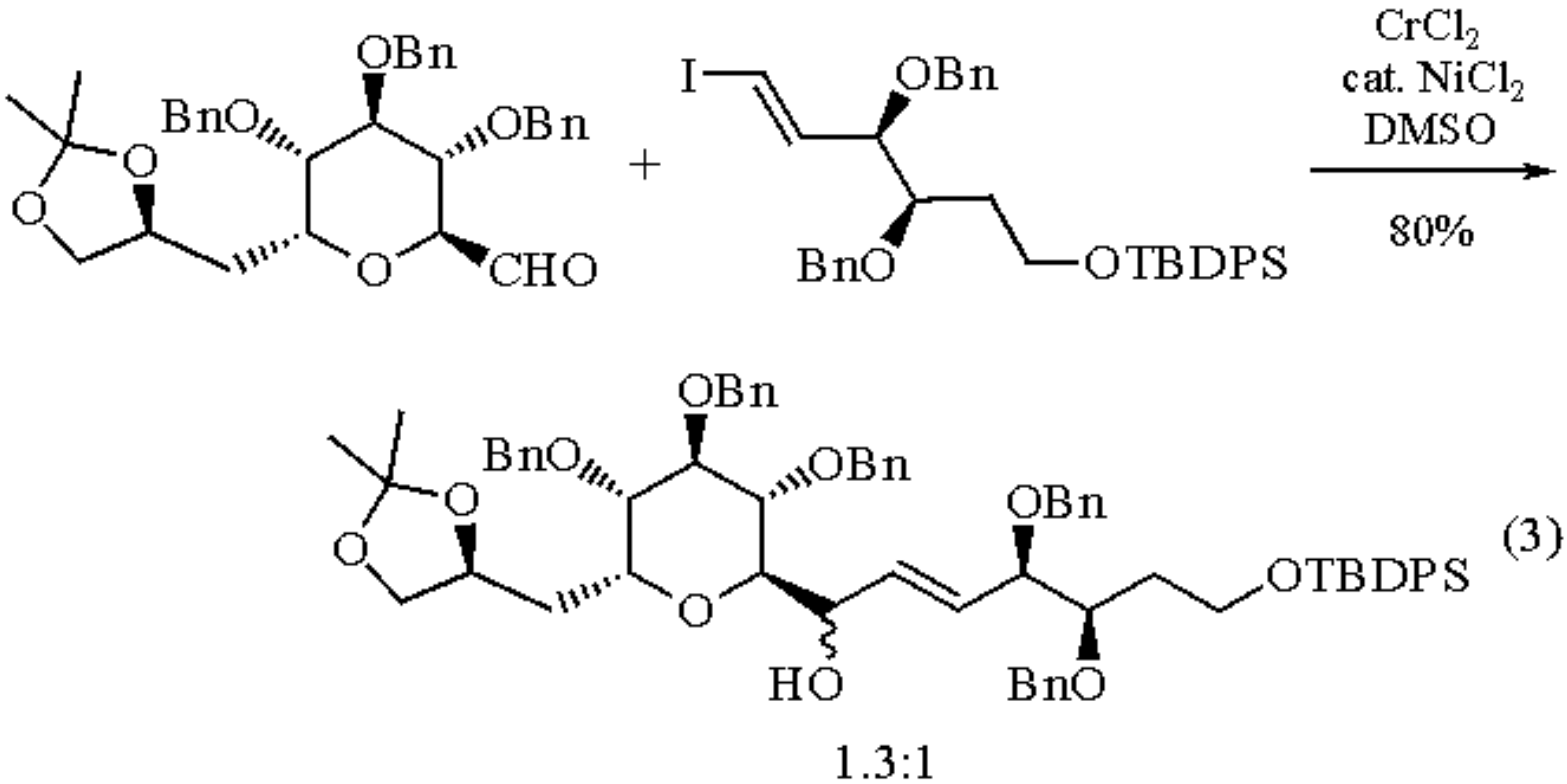

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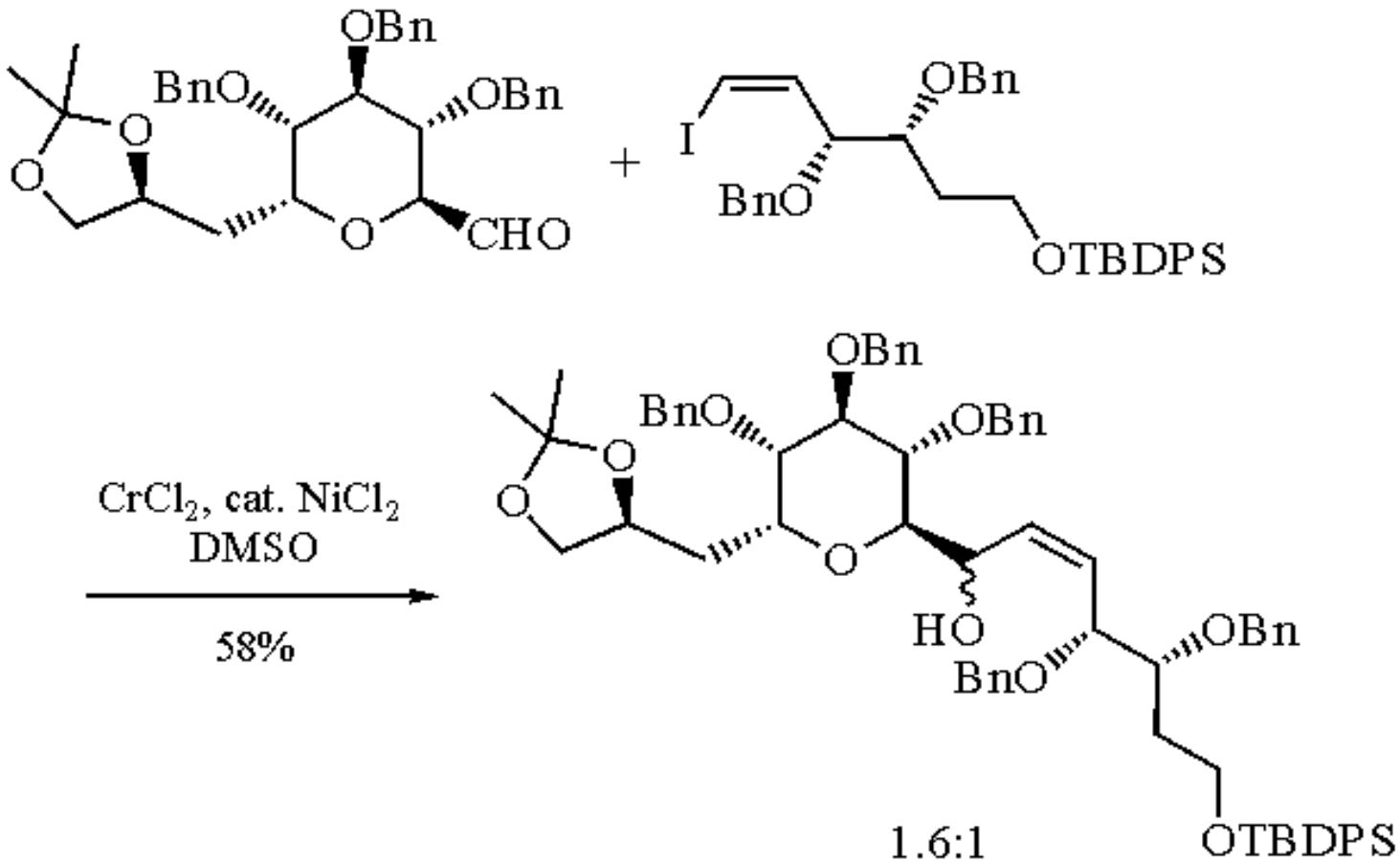

(4)

Intramolecular cyclization using the reagent proceeds under mild conditions (eqs 5 and 6).[8,9]

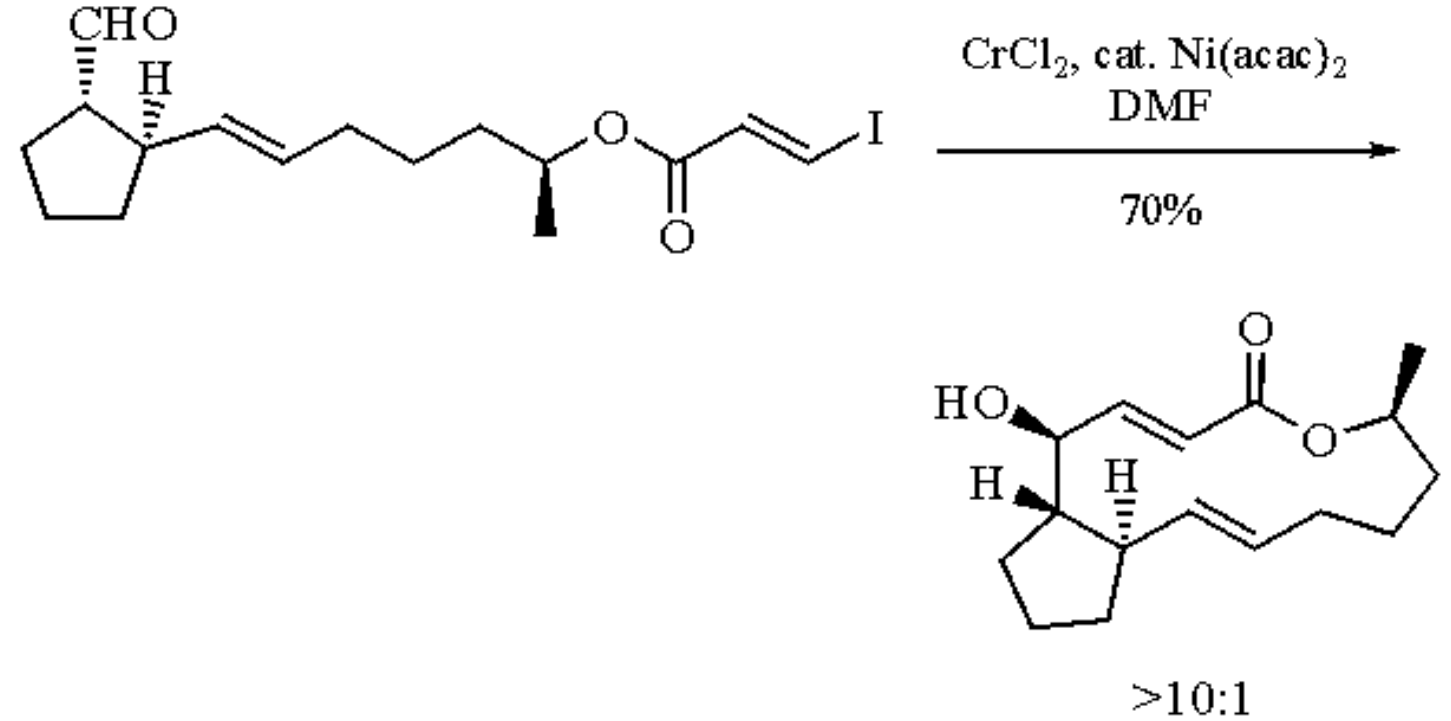

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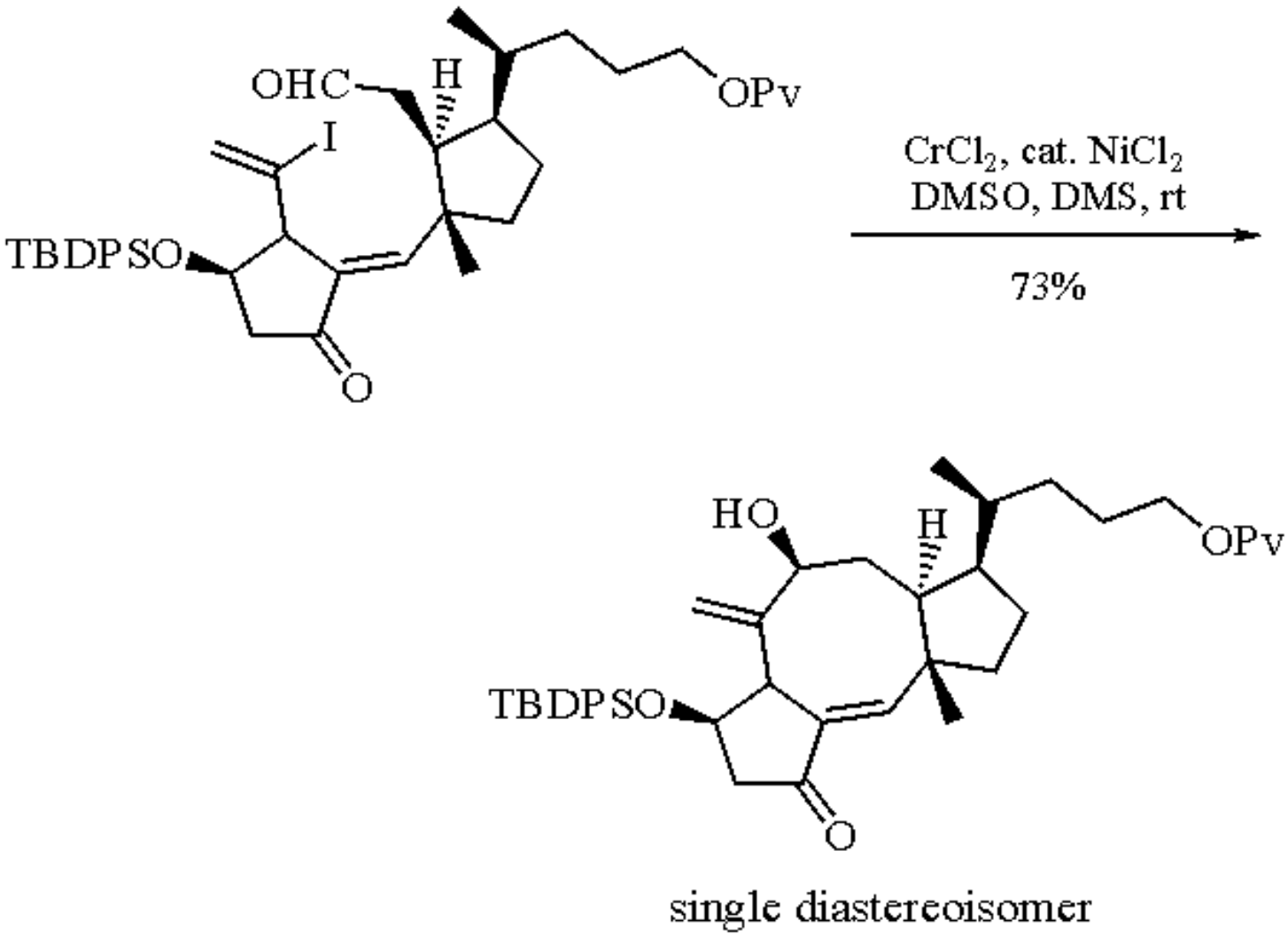

(6)

Grignard-Type Carbonyl Addition of Haloalkynes to

Aldehydes.

Although reactions between simple haloalkynes and aldehydes proceed in the absence of $NiCl_2$, the $CrCl_2$-$NiCl_2$ system is employed in the case of highly-oxygenated substrates (eq 7)[10,11] and for intramolecular cyclizations (eq 8).[12,13] The process is exceptionally well suited for cases where the aldehyde is labile.

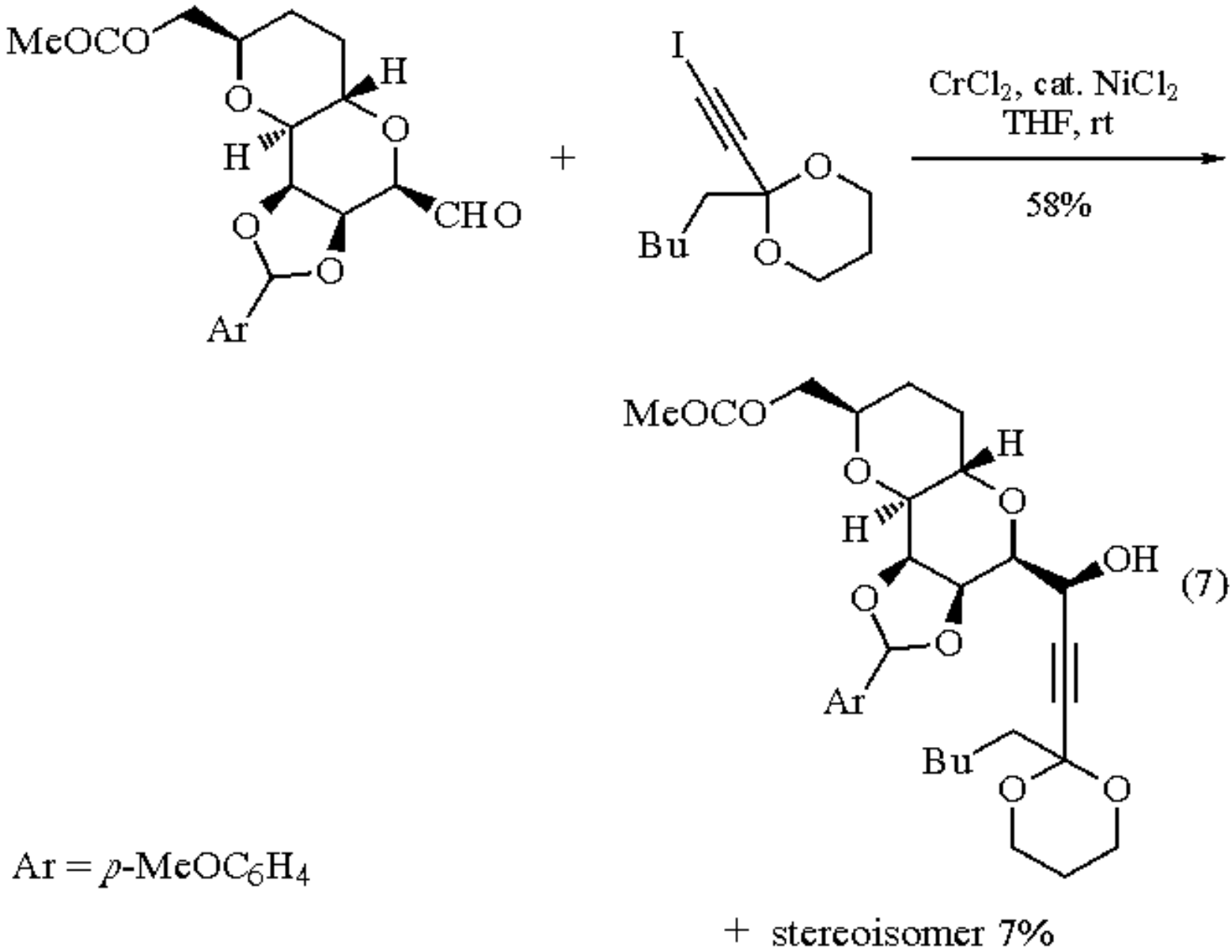

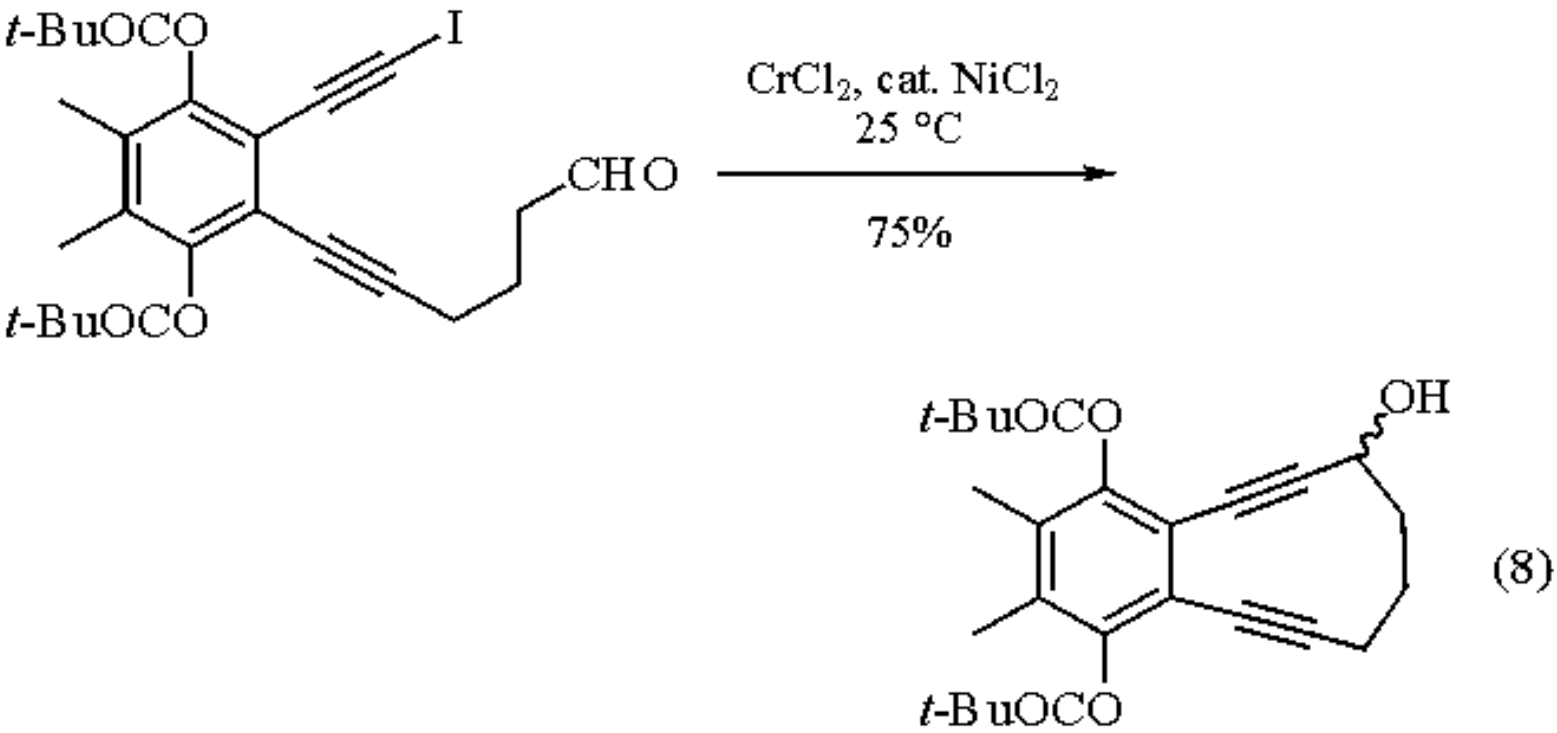

Active Low-Valent Nickel Catalyst.

Intramolecular cyclization of enynes[14] and enallenes[15] proceeds with a catalytic amount of low-valent nickel derived by reduction of $NiCl_2$ with $CrCl_2$ in the presence of triphenylphosphine (eq 9). Decrease of catalytic activity of the nickel is suppressed by using a polymer-supported nickel catalyst.

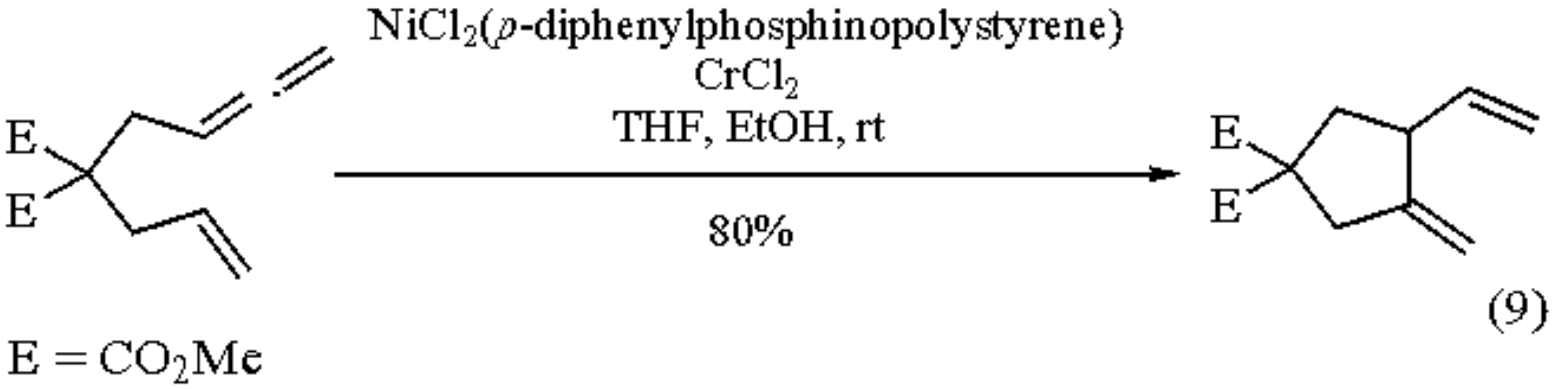

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Chromium(VI) Oxide[1]

CrO_3

[1333-82-0] · CrO_3 · Chromium(VI) Oxide · (MW 99.99)

(reagent for oxidizing carbon-hydrogen bonds to alcohols, oxidizing alkylaromatics to ketones and carboxylic acids, converting alkenes to α,β-unsaturated ketones, oxidizing carbon-carbon double bonds, oxidizing arenes to quinones, oxidizing alcohols to aldehydes, ketones, acids, and keto acids)

Alternate Names: chromic anhydride; ***Chromic Acid*** in aqueous media.

Physical Data: mp 196 °C; *d* 2.70 g cm^{-3}.

Solubility: sol ether, H_2O, HNO_3, H_2SO_4, DMF, HMPA.

Form Supplied in: red crystals.

Handling, Storage, and Precautions: **caution**: chromium(VI) oxide is a highly toxic cancer suspect agent. All chromium(VI) reagents must be handled with care. The mutagenicity of Cr^{VI} compounds is well documented.[7] HMPA is also a highly toxic cancer suspect agent. Special care must always be exercised in adding CrO_3 to organic solvents. Add CrO_3 in small portions to HMPA in order to avoid a violent decomposition. This reagent must be handled in a fume hood.

Each mol of chromium(VI) oxide has 1.5 equivalents of oxygen. The oxidizing power of the reagent increases with decreasing water content of the solvent medium. The oxidizing medium may be aqueous acetic acid,[2,3] anhydrous acetic acid (Fieser reagent),[4] or concentrated[5] or aqueous[6] sulfuric acid.

Oxidation of Carbon-Hydrogen Bonds to Alcohols.

Chromium(VI) oxide in 91% acetic acid oxidizes the methine hydrogen of (+)-3-methylheptane to (+)-3-methyl-3-heptanol with 70-85% retention of configuration.[8] 3β-Acetoxy-14α-hydroxyandrost-5-en-17-one is obtained by direct introduction of an α-hydroxyl group at C-14 in the dibromide of 3β-acetoxyandrost-5-en-17-one (eq 1).[9]

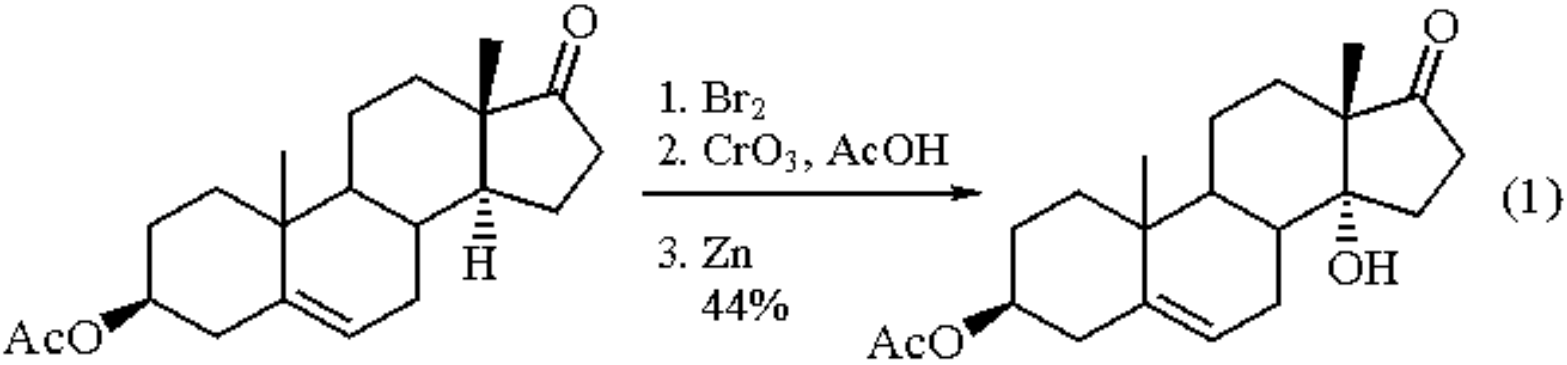

Oxidation of Alkylaromatics to Ketones and Carboxylic Acids.

Chromium(VI) oxide in concentrated sulfuric acid oxidizes 3,4-dinitrotoluene to 3,4-dinitrobenzoic acid (89%).[5] Under milder conditions, with longer alkyl chains, the benzylic position is converted to carbonyl. Chromium(VI) oxide in acetic acid oxidizes ethylbenzene to acetophenone and benzoic acid. More rigorous oxidizing experimental conditions convert longer chain alkyl groups to carboxyl, thus yielding benzoic acid or its derivatives. Methylene groups between two benzene rings are oxidized to carbonyl derivatives in preference to reaction at alkyl side chains.[10] Indans are oxidized to 1-indanones by use of a dilute (10%) solution of chromium(VI) oxide in acetic acid at room temperature (eq 2).[11]

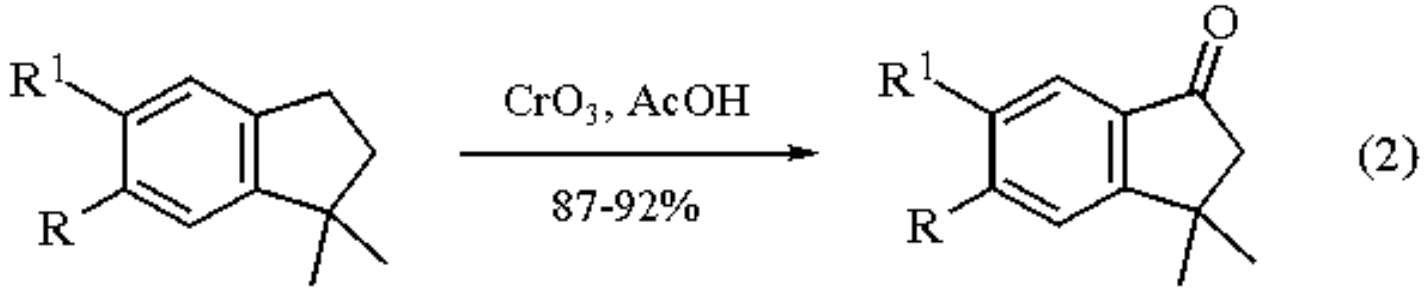

Allylic Oxidations.

Allylic oxidations may be complicated by carbonyl formation at either one or both allylic positions. Although chromium(VI) oxide appears to be useful for allylic oxidation in steroid chemistry, better results may be obtained in other systems with ***Di-t-butyl Chromate*** or ***Dipyridine Chromium(VI) Oxide*** (Collins reagent). However, the ***Chromium(VI) Oxide-3,5-Dimethylpyrazole*** complex (CrO_3.DMP) is useful for allylic oxidations. The complex oxidized the allylic methylene group in (**1**) to the α,β-unsaturated ketone (**2**) which was used in the synthesis of the antibacterial helenanolide (+)-carpesiolin (eq 3).[12] Chromium(VI) oxide in glacial acetic acid oxidizes 3,21-diacetoxy-4,4,14-trimethyl-Δ^8-5-pregnene to the enetrione (eq 4).[13] Complex product mixtures are formed when epoxidation competes with the allylic oxidation.[14]

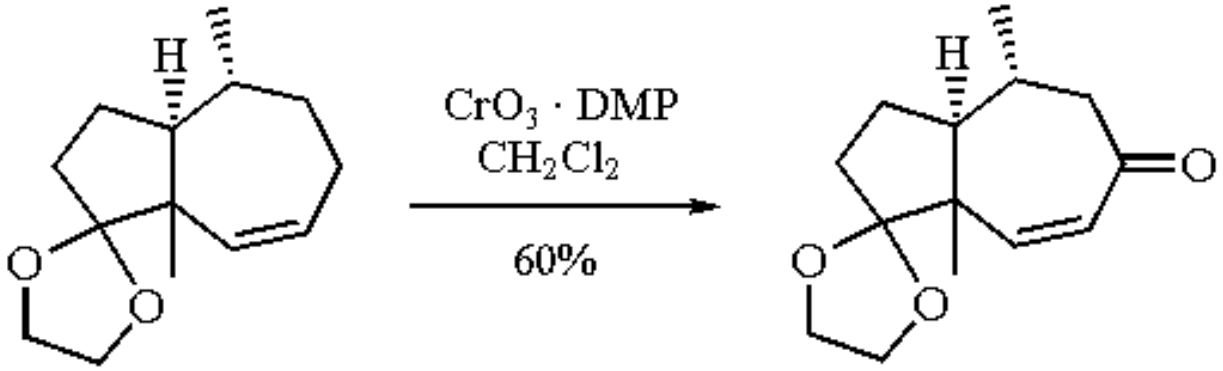

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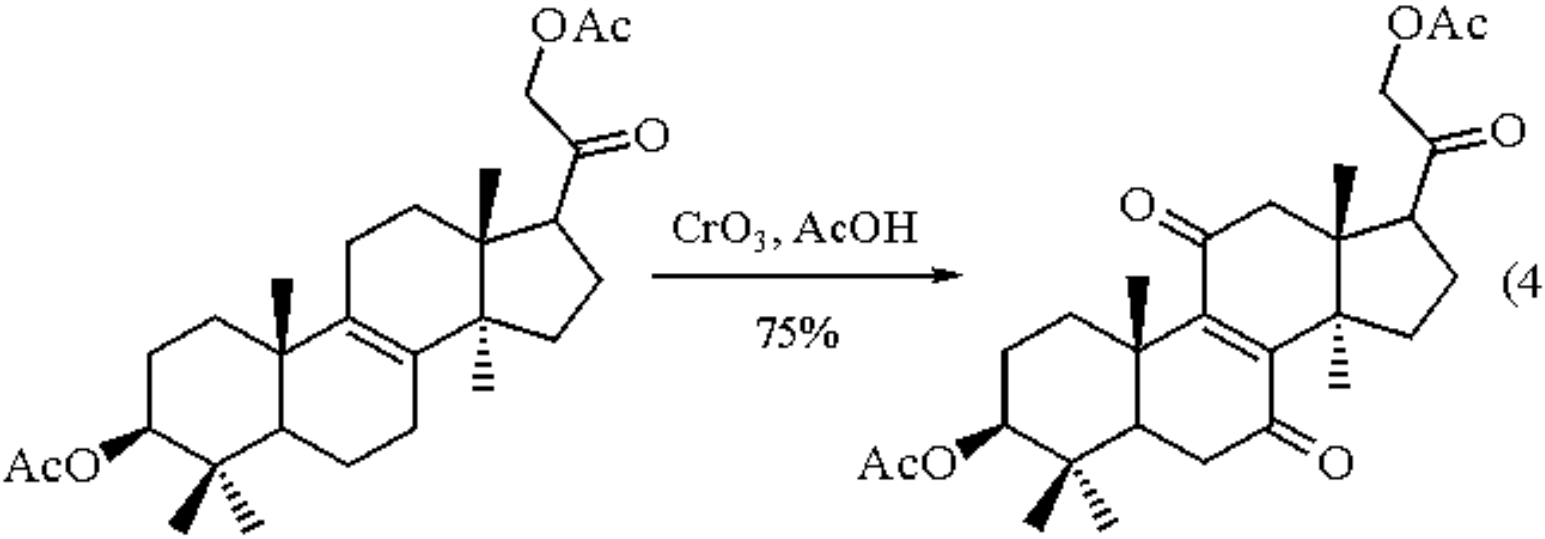

(4)

Oxidation of Carbon-Carbon Double Bonds.

Chromium(VI) oxide in aqueous sulfuric acid generally cleaves carbon-carbon double bonds. Rearrangements may further complicate the oxidation. In anhydrous acetic acid, chromium(VI) oxide oxidizes tetraphenylethylene to the oxirane (70% yield) and benzophenone (11%).[15] The yield is lower and more double bond cleavage occurs in aqueous acetic acid. However, use of acetic anhydride as solvent (see ***Chromyl Acetate***) affords the oxiranes from tri- and tetrasubstituted alkenes in 50-88% yields, along with benzopinacols.[16,17] Many steroidal and terpenic cyclic alkenes react with chromium(VI) oxide in acetic acid to give oxiranes, and saturated, α,β-unsaturated, α-hydroxy, and α,β-epoxy ketones which arise from the initially formed oxirane.[18,19] A synthetically useful cleavage of double bonds involving chromium(VI) oxide is the Meystre-Miescher-Wettstein degradation[20] which shortens the side chain of a carboxylic acid by three atoms at one time. This procedure is a modification of the Barbier-Wieland degradation.[21,22]

Oxidation of Arenes to Quinones.

In contrast to alkylaromatics, which undergo oxidation at the side chain with some chromium(VI) oxidants, polynuclear aromatic arenes undergo ring oxidation to quinones with chromium(VI) oxide. This chemoselectivity is shown in the chromium(VI) oxide in anhydrous acetic acid (Fieser reagent) oxidation of 2,3-dimethylnaphthalene to

2,3-dimethylnaphthoquinone in quantitative yield (eq 5).[23] In some cases, depending on experimental conditions, both benzylic and ring oxidations occur[24] or the alkyl groups may be eliminated (eq 6).[25] The oxidation of anthracene derivatives is important in the total synthesis of anthracycline antibiotics.[26,27]

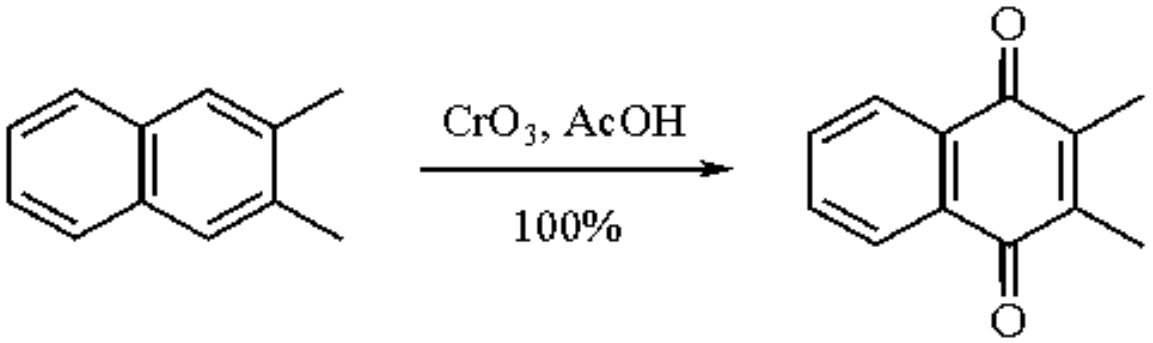

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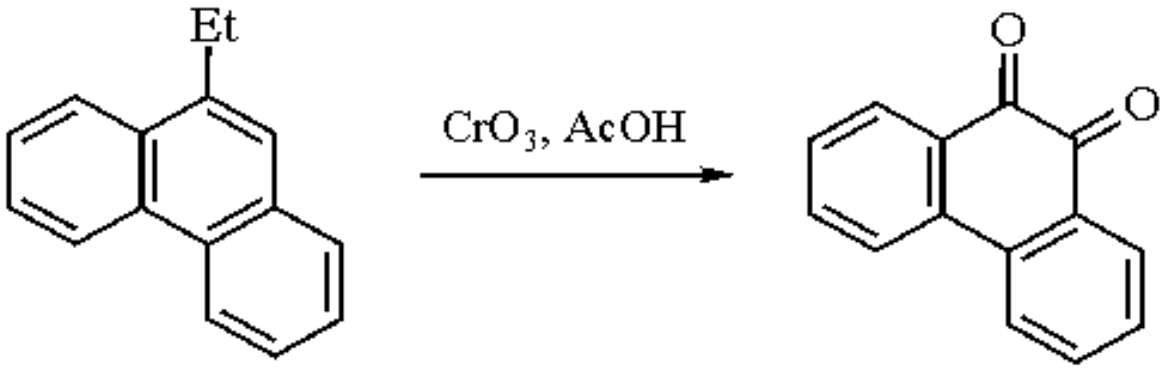

(6)

Oxidation of Alcohols to Aldehydes, Ketones, Acids, and Keto Acids.

Chromium(VI) oxide in acetic acid oxidizes primary alcohols to aldehydes and acids, and secondary alcohols to ketones and keto acids (Fieser reagent) (eq 7).[28] Chromium(VI) oxide in water or aqueous acetic acid oxidizes primary alcohols to carboxylic acids.[29,30] Chromium(VI) oxide-***Hexamethylphosphoric Triamide*** (CrO_3.HMPA) selectively oxidized the primary hydroxyl group of strophanthidol (**3**) to an aldehyde group in the final step in the synthesis of strophanthidin (**4**) (eq 8).[31] The CrO_3.HMPA complex oxidizes saturated primary alcohols to aldehydes in about 80% yield.[32,33] The yields are lower with secondary alcohols and highest with α,β-unsaturated primary and secondary alcohols. It is possible to selectively oxidize certain allylic and benzylic hydroxyl groups in the presence of other unprotected saturated groups (eq 9; cf eq 8). Chromium(VI) oxide in DMF in the presence of catalytic amounts of sulfuric acid oxidizes steroidal alcohols to ketones.[34] Chromium(VI) oxide on graphite selectively oxidizes primary alcohols in the presence of secondary and tertiary alcohols.[35]

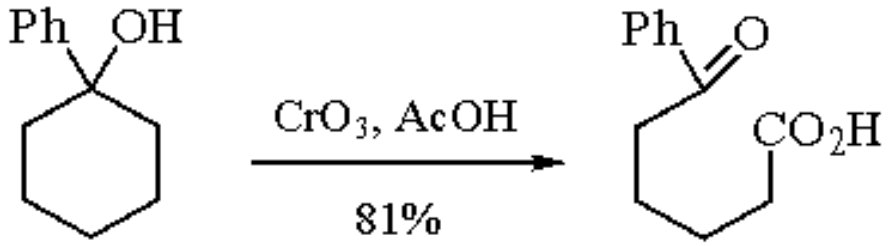

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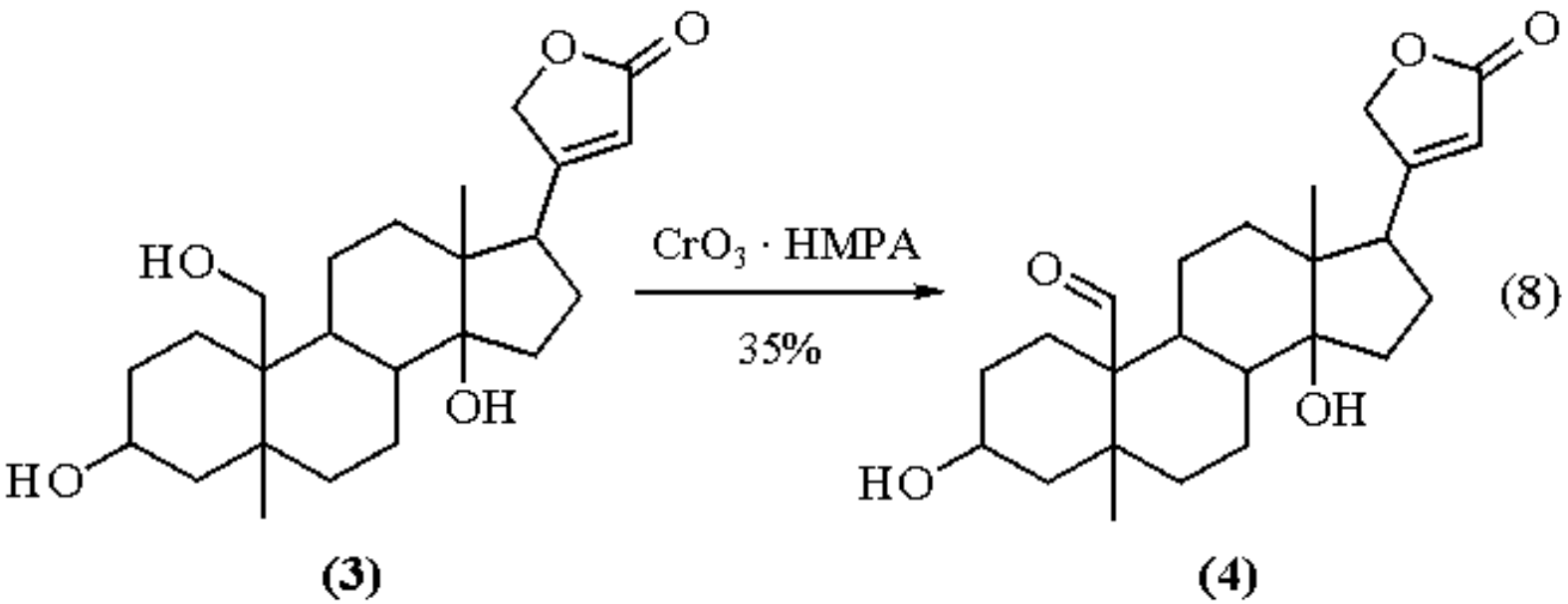

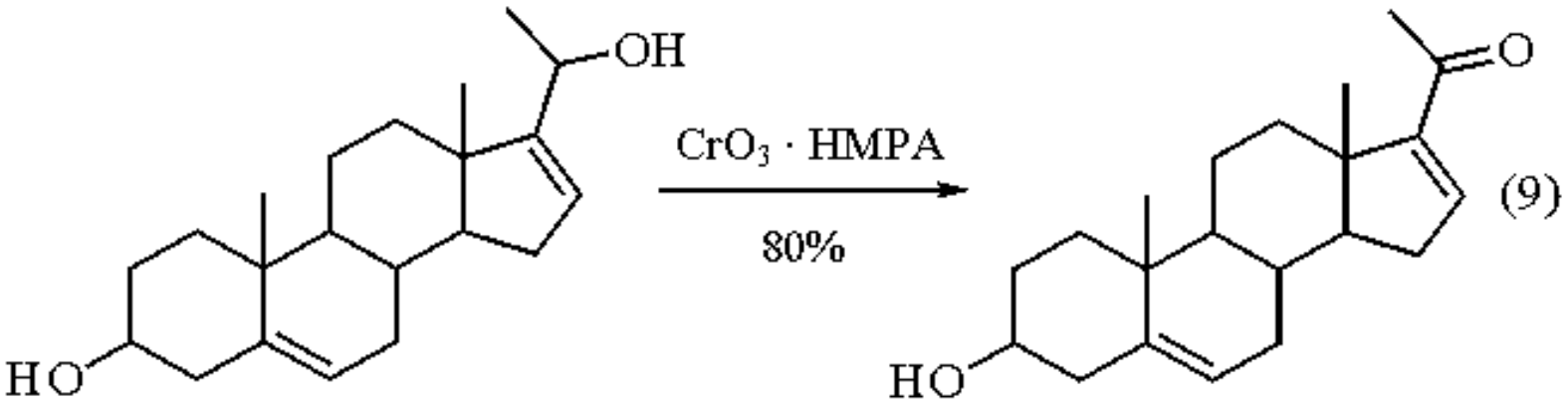

Other Applications.

Chromium(VI) oxide in aqueous acetic acid converts α-chlorohydrindene to α-hydrindanone (50-60%).[36] Suitably protected methylene or benzylidene acetals of alditols are cleaved by chromium(VI) oxide in glacial acetic acid to derivatives of ketoses.[37] Chromium(VI) oxide in anhydrous acetic acid converts methyl ethers into the corresponding formates, which can be hydrolyzed by base to alcohols (demethylation).[38]

Related Reagents.

Chromium(VI) Oxide-3,5-Dimethylpyrazole; ***Chromium(VI) Oxide-Quinoline***; ***Chromium(VI) Oxide-Silica Gel***.

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Chromium(VI) Oxide-3,5-Dimethylpyrazole

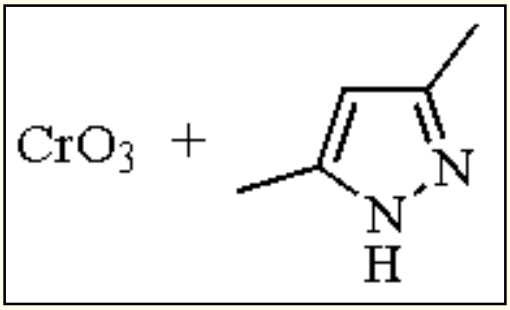

(CrO_3)

[1333-82-0] · CrO_3 · Chromium(VI) Oxide-3,5-Dimethylpyrazole · (MW 99.99) ($C_5H_8N_2$)

[67-51-6] · $C_5H_8N_2$ · Chromium(VI) Oxide-3,5-Dimethylpyrazole · (MW 96.13)

(oxidizing agent for alcohols;[1] oxidant for saturated carbons α to unsaturation[2-5])

Physical Data: see ***Chromium(VI) Oxide***.

Solubility: sol dichloromethane; slightly sol ether and pentane.

Form Supplied in: formed in situ from widely available reagents.

Preparative Method: drying of the CrO_3 over P_2O_5 is recommended; rapid addition of DMP (1 equiv) to a suspension of chromium(VI) oxide (1 equiv) in dry CH_2Cl_2 (-20 °C) results in a dark red homogeneous solution after 10 min; the solution is then treated with the organic substrate (0.05-0.5 equiv).[1,2]

Handling, Storage, and Precautions: chromium salts are carcinogenic; this reagent should be used in a fume hood.

Oxidation of Alcohols.

The oxidation of primary and secondary alcohols is typically effected by treating the alcohol (1 equiv) with CrO_3.DMP (1-10 equiv) at rt (eqs 1-3).[1] Notably similar to ***Pyridinium Chlorochromate*** (PCC), the title reagent system has been shown to oxidize primary alcohols to aldehydes efficiently (eq 2). The ease of oxidation of both equatorial and axial alcohols using this complex has been demonstrated (eq 3); the reactions of both are complete within 40 min when stirred at room temperature. The authors suggest the intermediacy of a cyclic chromate ester species through which rapid intramolecular oxidation may occur.[1]

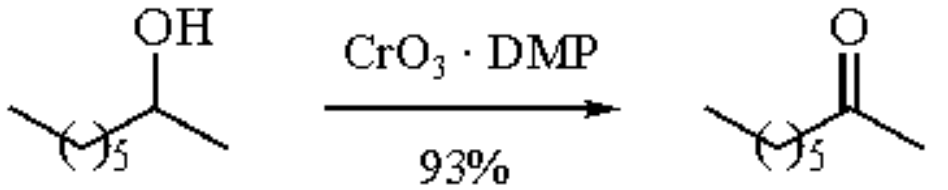

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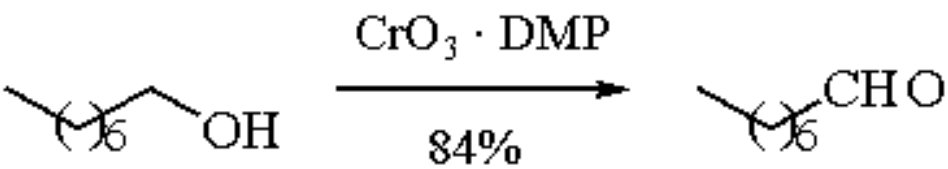

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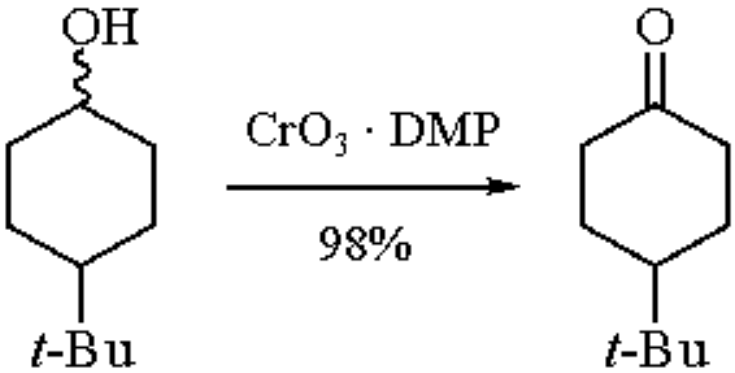

(3)

Oxidation of Unsaturated Alcohols.[1]

Allylic, benzylic, and propargyl alcohols readily interact with CrO_3.DMP to provide the expected carbonyl compounds in good to excellent yield. Allylic alcohols can be oxidized with little or no competing oxidation of allylic methylene positions within the same molecule (eqs 4 and 5).

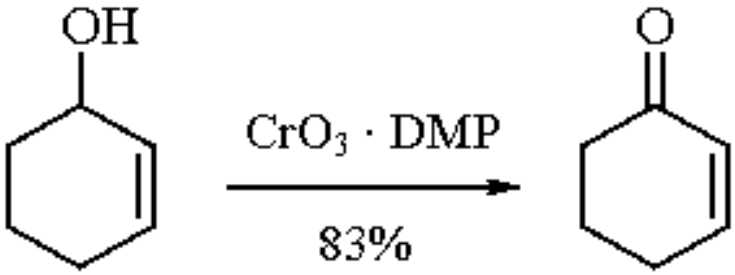

(4)

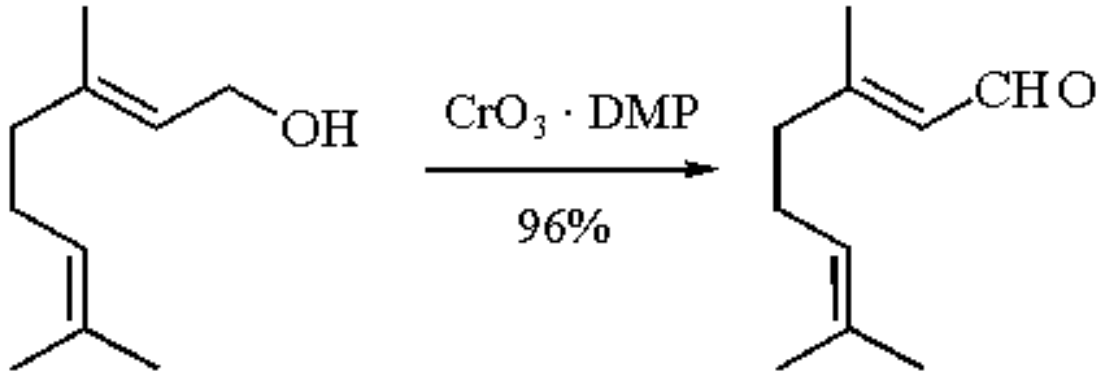

(5)

Benzylic alcohols are oxidized with comparable efficiency and the reaction is not sensitive to the electronic nature of the aromatic ring (eqs 6 and 7). Propargyl alcohols with both internal and terminal triple bonds are oxidized in good yield using CrO_3.DMP (eq 8).

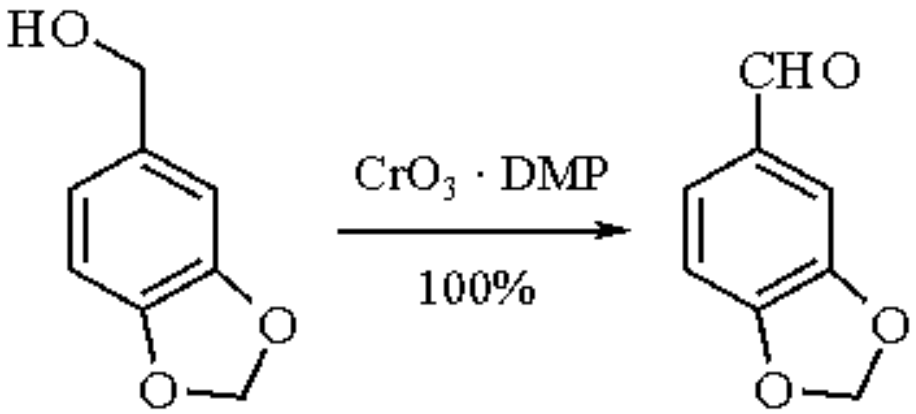

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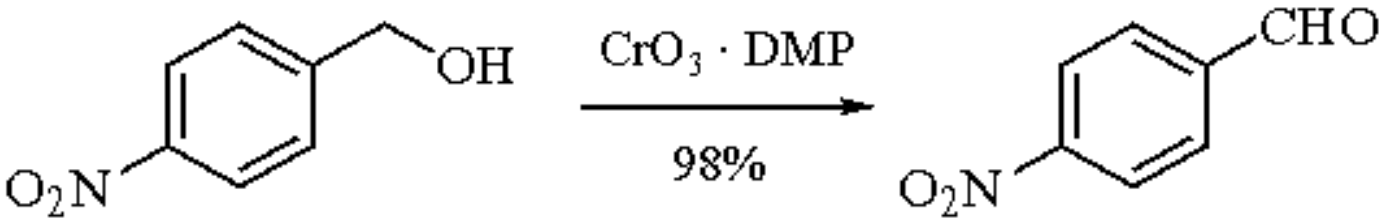

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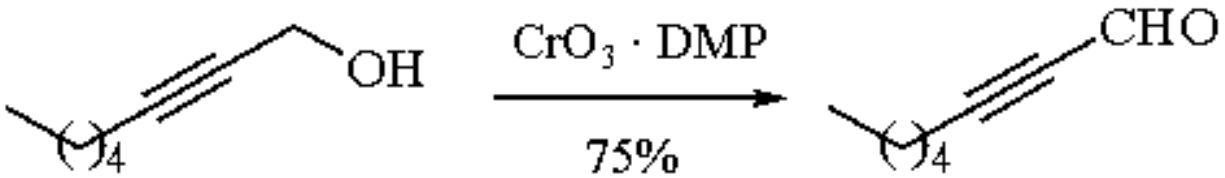

(8)

Oxidation of Saturated Allylic and Benzylic Carbons.

The CrO_3.DMP complex appears to offer two unique advantages over PCC: an empty Lewis acidic coordination site on chromium, and an internal basic nitrogen that may aid in cleavage of a carbon-hydrogen bond.[2] As a result, for allylic and benzylic oxidations, CrO_3.DMP is superior to more conventional chromium oxidants which often suffer from low yields, practical complications, and/or inconvenient and

extended reaction times. In the total synthesis of (±)-carpesiolin, CrO_3.DMP was used to install an enone from an alkene precursor (eq 9).[3] It was used once more for a similar transformation in the total synthesis of (-)-retigeranic A and several of its derivatives, where it was found to be the most efficient reagent for the purpose (eq 10).[4]

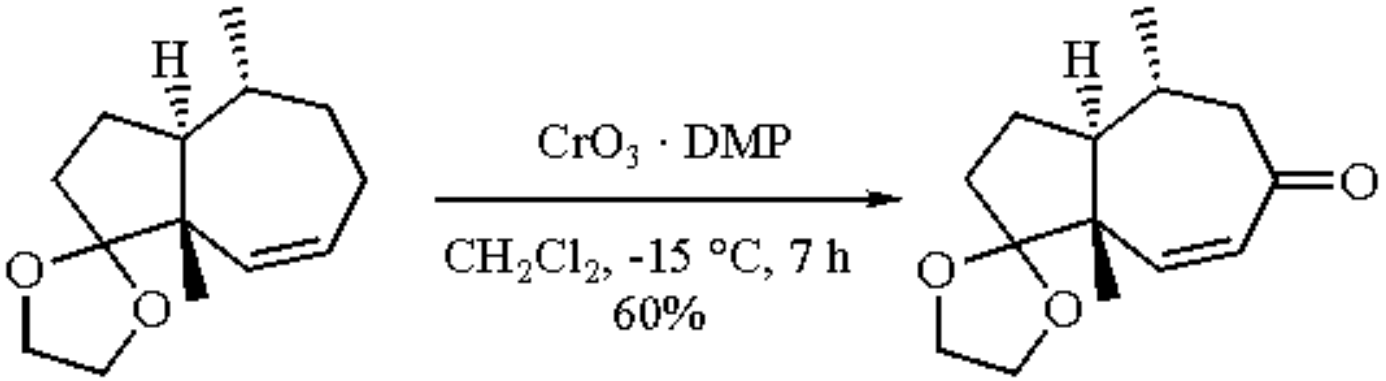

(9)

Observations made in the course of studies toward the synthesis of Δ^5-7-keto steroids provide some insight into the mechanism of CrO_3.DMP-mediated allylic oxidation.[2] Here, axial hydrogens were found to be predisposed to more facile cleavage by this reagent, a common observation with chromium oxidants. The allylic oxidation of cholesteryl benzoate was complete within 30 min when CrO_3.DMP was used in 20-fold excess. Alternatively, use of only a 12-fold excess of CrO_3.DMP provided 74% conversion following stirring for 4 h at 0 °C. Benzylic methylenes are also susceptible to oxidation by this reagent.[5]

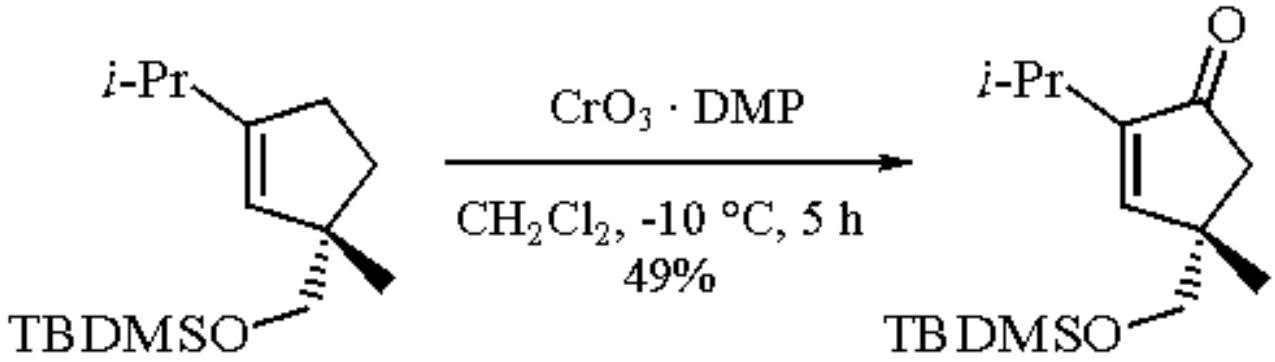

(10)

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Jeffrey N. Johnston

Chromium(VI) Oxide-Quinoline

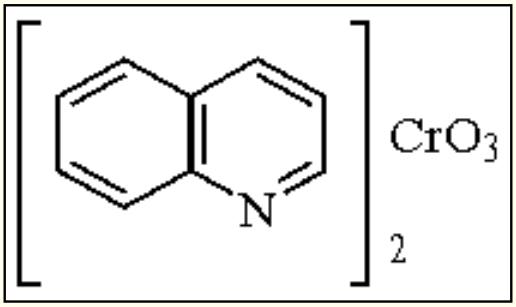

(CrO_3)

[1333-82-0] · CrO_3 · Chromium(VI) Oxide-Quinoline · (MW 99.99) (quinoline)

[91-22-5] · C_9H_7N · Chromium(VI) Oxide-Quinoline · (MW 129.16)

(mild selective reagent for the oxidation of primary and secondary alcohols to the corresponding carbonyl compounds under basic conditions)

Preparative Methods: the reagent is prepared either in solid solid form prior to use or in situ in excess base in the presence of the alcohol.[1]

Handling, Storage, and Precautions: caution all chromium(VI) reagents must be handled with care. The mutagenicity of chromium(VI) compounds is well documented.[2] This reagent should be handled in a fume hood.

General Considerations.

Chromium(VI) oxide reacts with organic bases such as isoquinoline, lutidines, picolines, pyridine, and quinoline to give 1:2 (oxide:base) complexes which are useful for oxidizing primary and secondary alcohols to the corresponding carbonyl compounds.[1,3-5] Other chromium reagents for oxidizing primary and secondary alcohols to carbonyl compounds under basic conditions include ***Dipyridine Chromium(VI) Oxide***,[1,3] chromium(VI) oxide-triethylamine,[1] ***Chromium(VI) Oxide-3,5-Dimethylpyrazole***, Collins' and Ratcliffe's reagents (see ***Dipyridine Chromium(VI) Oxide***), and ***Pyridinium Chlorochromate***.[6,7]

Oxidation of Hydrocortisone Acetate to Cortisone Acetate.

Hydrocortisone acetate (21-acetoxy-11β,17α-dihydroxy-4-pregnene-3,20-dione) reacts with chromium(VI) oxide-quinoline to yield cortisone acetate (eq 1).[1]

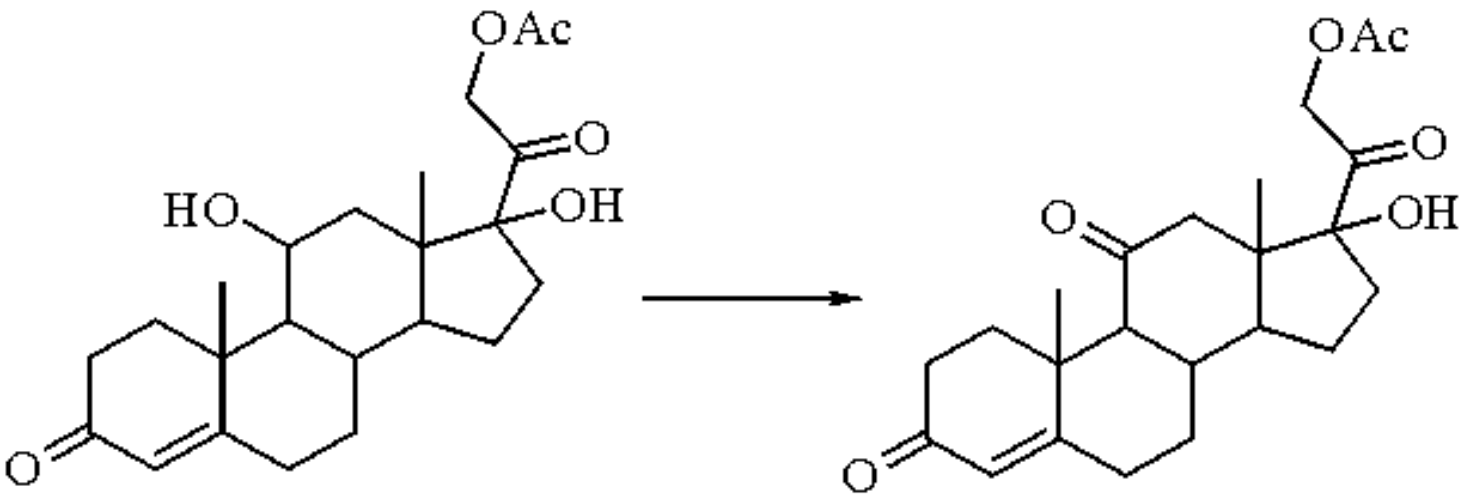

(1)

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Chromium(VI) Oxide-Silica Gel

CrO_3/SiO_2

(CrO_3)

[1333-82-0] · CrO_3 · Chromium(VI) Oxide-Silica Gel · (MW 99.99) (SiO_2)

[60676-86-0] · O_2Si · Chromium(VI) Oxide-Silica Gel · (MW 60.09)

(reagent for oxidizing alcohols to carbonyl compounds)

Physical Data: CrO_3 mp 196 °C; *d* 2.70 g cm^{-3}.

Preparative Methods: the reagent is prepared by addition of silica gel to an aqueous solution of chromium(VI) anhydride.[1]

Handling, Storage, and Precautions: can be stored under vacuum in the dark and must be used within one week. Chromium(VI) anhydride is a highly toxic cancer suspect agent. All chromium(VI) reagents must be handled in a fume hood. The mutagenicity of Cr^{VI} compounds is well documented.[2]

Oxidation of Alcohols to Carbonyl Compounds.

Chromium(VI) anhydride-silica gel oxidizes alcohols to carbonyl compounds in good yields (eqs 1-3).[1] The (*S*)-alcohol (**1**) is oxidized to the aldehyde (**2**) by chromium(VI) anhydride-silica gel with 22% racemization (eq 2).[3] The Collins reagent (***Dipyridine Chromium(VI) Oxide***) gives only 5% racemization. Variations of this reagent include ***Sodium Dichromate*** containing ***Sulfuric Acid*** on silica gel, and pyridinium chromate on silica gel.[4] The former reagent is active after one year's storage under ordinary conditions.

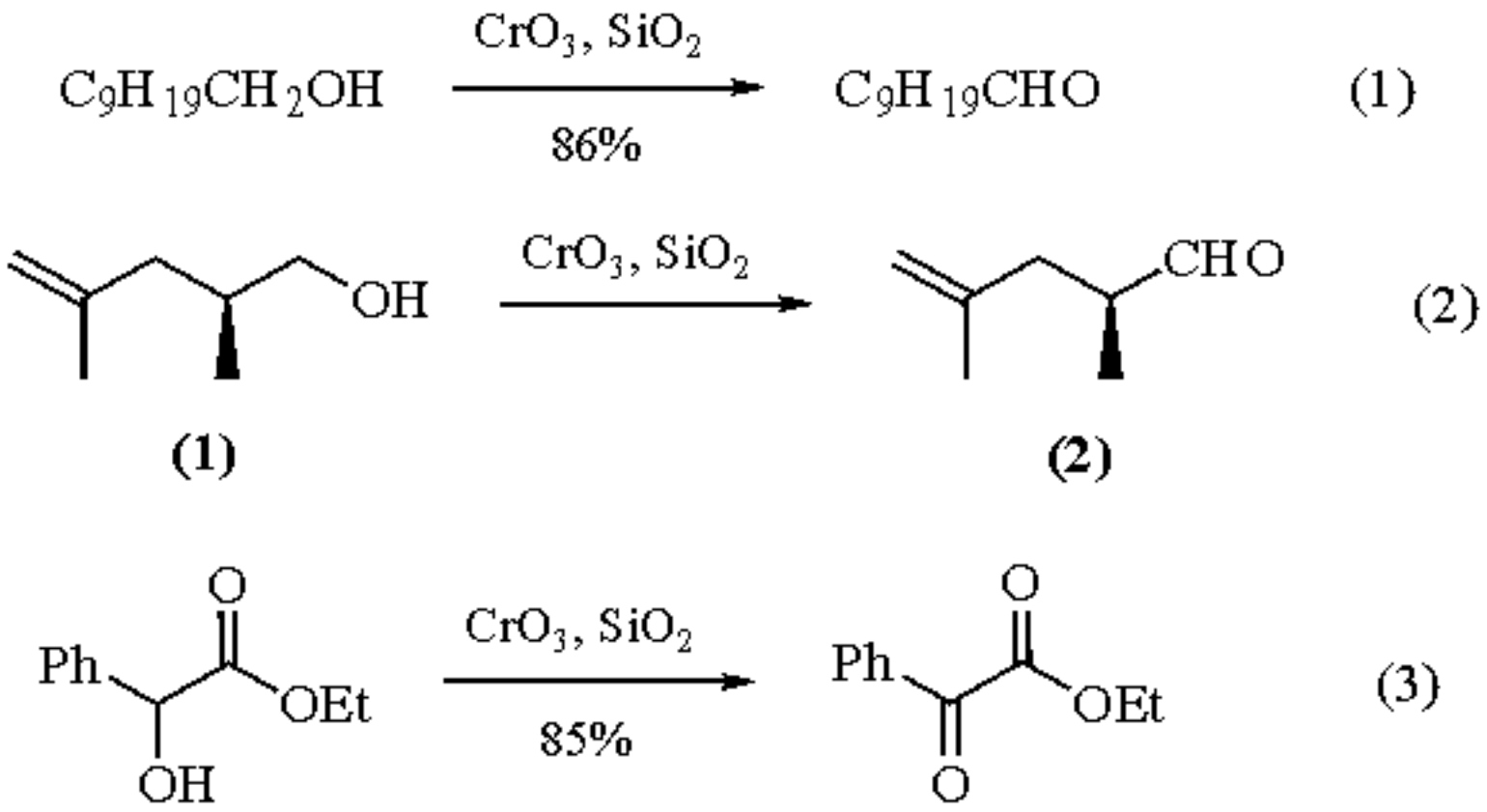

Related Reagents.

In addition to sodium dichromate containing sulfuric acid on silica gel and pyridinium chromate on silica gel,[4] ***Chromyl Chloride*** on silica-alumina,[5] ***Pyridinium Chlorochromate-Alumina***,[6] ***Chromic Acid*** on graphite,[7] chromic acid adsorbed on Kieselguhr,[8] and chromic acid attached to an anion exchange resin[9] are also valuable for oxidizing alcohols to carbonyl compounds. Chromic acid on graphite selectively oxidizes primary alcohols in the presence of secondary and tertiary alcohols.[7]

---

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Chromium(II) Perchlorate[1]

$Cr(ClO_4)_2$

[13931-95-8] · Cl_2CrO_8 · Chromium(II) Perchlorate · (MW 250.91)

(used to reduce aliphatic halides;[2,5,6] reductive dimerization of carbonyl compounds;[8] reduction of cations and peroxides[9,10])

Physical Data: no data available due to instability in pure solid form.

Form Supplied in: not available commercially; must be prepared before use as an aqueous solution.

Preparative Methods: by the reaction of high purity grade chromium powder with dilute $HClO_4$ or by reducing chromium(III) perchlorate with amalgamated Zn in dilute $HClO_4$ under an inert atmosphere.[2] Solutions can be standardized[3a] by quenching an aliquot in standard dilute $FeCl_3$ solution and titrating the Fe^{II} produced to Fe^{III} (1,10-phenanthroline end point) with 0.01 M Ce^{IV}. In kinetic measurements the disappearance of Cr^{II} can be followed spectrometrically at 750 nm.[3b]

Handling, Storage, and Precautions: greater than 1 M solutions of $Cr(ClO_4)_2$ must be prepared at ice-bath temperature, since the reaction mixture decomposes exothermically at room temperature. Dilute solutions may be safely stored at room temperature. Chromium salts are carcinogenic and should be handled with care. Perchlorates are explosive and thus should be handled appropriately behind a safety shield.

Chromium(II) as a Reducing Agent.

Chromium(II) complexes between $Cr(ClO_4)_2$ and ***1,2-Diaminoethane*** react with alkyl halides to give alkanes by the mechanism shown in eqs 1-3.[4]

$$\text{R-X} + \text{Cr}^{\text{II}} \longrightarrow \text{R}\cdot + \text{X-Cr}^{\text{III}} \quad (1)$$

$$\text{R}\cdot + \text{Cr}^{\text{II}} \longrightarrow \text{R-Cr}^{\text{III}} \quad (2)$$

$$\text{R-Cr}^{\text{III}} + \text{H}_2\text{O} \longrightarrow \text{R-H} + \text{Cr}^{\text{III}} \quad (3)$$

If the intermediate radical has an isomerization pathway available, structurally rearranged products can be obtained.[4c] For example, reduction of halides of the types RC&tbond;C$(CH_2)_n$X (n = 4 or 5) with Cr^{II} in aqueous DMF containing ethylenediamine afforded substituted methylenecycloalkanes (eq 4).[5] Geminal, vicinal, and 1,3-dihalides can be reduced by Cr^{II} to generate carbenes, alkenes, and cyclopropanes, respectively.[6]

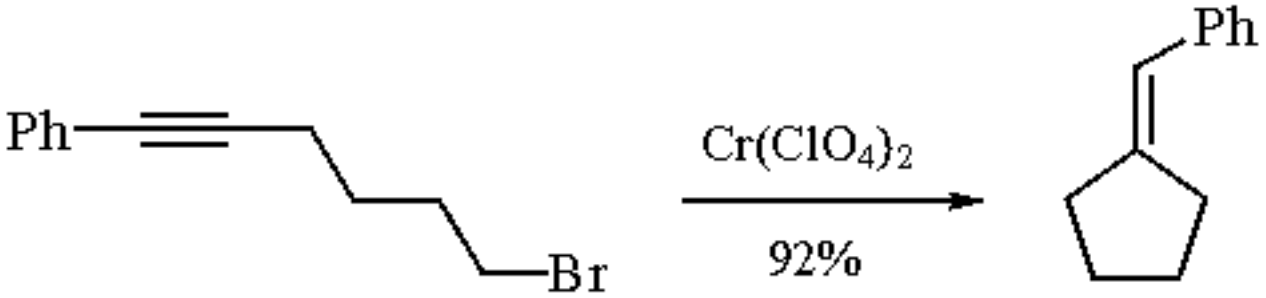

(4)

Reduction of α-haloacetonitriles,[7a] α-haloacetamides,[7b] and α-haloacetic acids[7c,7d] with Cr^{II} gives products derived from intermediate radicals.

Carbonyl Reductions.

Aromatic aldehydes, α,β-unsaturated aldehydes, and some α,β-unsaturated ketones undergo a one-electron reductive coupling to give bimolecular products, whereas aliphatic aldehydes and ketones, aromatic ketones, and esters are unreactive.[8]

Reduction of Organic Cations.

In aqueous or in acidic ethanolic media, organic cations such as tropylium,[9a] cyclopropenium,[9b] *N*-methylacridinium,[9c] 2,4,6-triphenylpyrylium,[9c] and flavylium[9c] are reduced with $Cr(ClO_4)_2$ to the corresponding radicals or dimers.

Reduction of Organic Peroxides.

Organic peroxides, hydroperoxides, peroxy esters, and peroxy acids undergo reduction with Cr^{2+} to generate alkoxy radicals and organochromium(III) species.[6e,10]

Miscellaneous Reduction.

The addition of $Cr(ClO_4)_2$ to aqueous or methanolic solutions of mitomycin C led to efficient reductive activation of the C-1 and C-10 positions, generating nucleophilic substitution products.[11]

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Chromium(II) Sulfate[1]

$CrSO_4$

[13825-86-0] · CrO_4S · Chromium(II) Sulfate · (MW 148.05)

(reducing agent for alkynes, alkenes, organohalides;[1] reductions via amine or ammonia complexes[2])

Alternate Names: chromium sulfate; chromous sulfate.

Solubility: sol water and aqueous DMF; slightly sol ethanol; insol acetone.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: an aqueous solution of $CrSO_4$ can be standardized by a titration against $(CuCl_4)^{2-}$ or $K_2Cr_2O_7$[3] as well as $FeCl_3$.[4]

Preparative Methods: the most common procedure for preparing an aqueous $CrSO_4$ solution employs a reduction of $Cr_2(SO_4)_3$ with mossy Zn and Hg in water and is used as is.[4] Alternate syntheses start with very pure Cr metal[5] or $K_2Cr_2O_7$.[3] A method for preparing crystalline blue $CrSO_4.5H_2O$ has been published.[5,6]

Handling, Storage, and Precautions: aqueous $CrSO_4$ solutions are stable at temperatures between 20 and 60 °C for several days if stored in an oxygen-free environment.[7] The aqueous solution should be stored in a vented container as the powerful reducing agent will reduce water and, over time, liberate hydrogen gas which may lead to an explosion.[8] Rigorously dried $CrSO_4.5H_2O$ can be stored in the presence of air for at least eight months.[5] However, it degrades quickly in the presence of oxygen if it is finely ground.[5]

Comments on Reaction Conditions and Workups.

Most of the described reactions are carried out in deoxygenated solvents and under an oxygen-free nitrogen atmosphere because of the sensitivity of $CrSO_4$ to oxygen. Two common workups for $CrSO_4$ reductions are described in the literature. The aqueous reaction mixture can be saturated with $(NH_4)_2SO_4$ and extracted with

an organic solvent such as ether.[9] A DMF/water reaction mixture can be directly extracted with ether/pentane.[10] Alternate approaches include oxidation of excess reducing agent by aeration[11] and removal of chromium hydroxide by filtration after making the reaction mixture basic.[9]

Alkynes to (*E*)-alkenes.

The homogeneous reduction of alkynes in water or aqueous DMF at room temperature selectively yields (*E*)-alkenes. Substitution by polar functional groups in the propargylic position accelerates the reduction.[9] Bulky substituents on the alkyne impede the reaction and terminal alkynes are more reactive than internal ones.[9] A study of reductions of α-alkynic ketones provides additional examples for the specific formation of (*E*)-alkenes (here (*E*)-alkenones) and for the steric bias of the reaction (increased steric bulk on the alkynes causes longer reaction times and lower yields).[10] An advantage of $CrSO_4$ in this type of reduction is its specificity for alkynes in the presence of other functional groups. Epoxides (eq 1), esters, and α,β-unsaturated esters are unreactive under these reaction conditions.[10] $CrCl_2$ causes the same transformation to take place but is usually less reactive with the mentioned substrates.[10] Certain alkenes can be reduced to alkanes under these conditions as discussed in the next section.

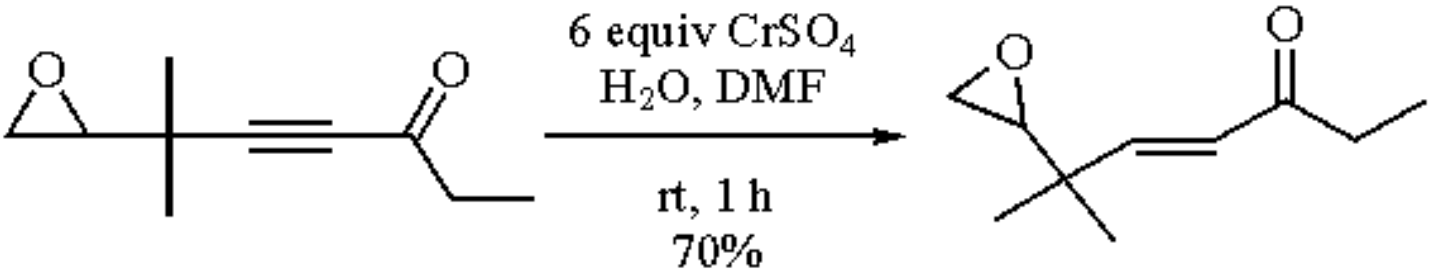

(1)

Alkenes to Alkanes.

Alkenes are reduced to alkanes by $CrSO_4$ in water and in aqueous DMF. In general, (*Z*)-alkenes react more rapidly than the (*E*)-isomers.[12] Conjugated coordination sites (such as hydroxyl groups) and conjugated electron-withdrawing substituents (esters and nitriles, for example) accelerate the rate of reduction.[12] Tetrasubstituted alkenes usually yield an even mixture of *meso*- and (±)-alkanes (eq 2).[12]

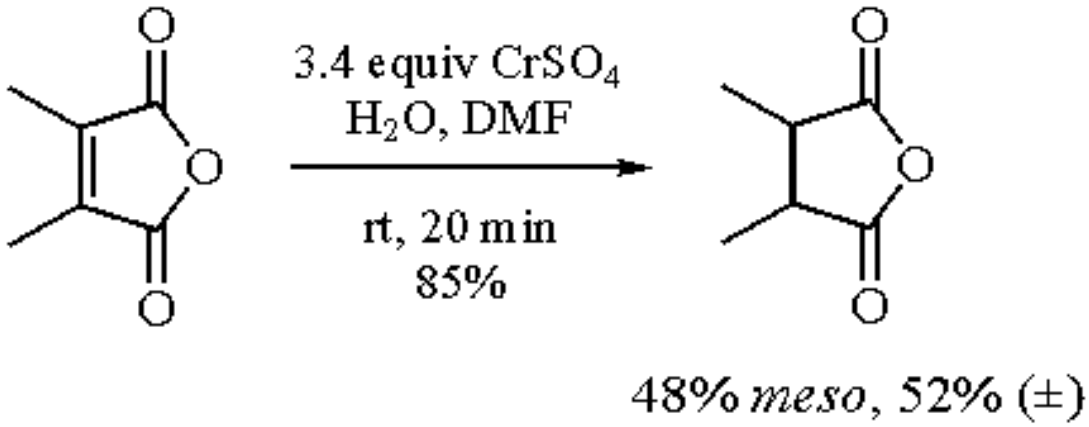

(2)

Reduction of Organic Monohalides.

The reduction of organohalides can yield two different products depending on the substrate and the reaction conditions. Benzylic (arylalkyl) and allylic halides produce the reduced alkane or a coupled product.[13] The amount of coupled product can be increased by slow addition of the $CrSO_4$ to the halide (eq 3) and by use of anhydrous solvents.[13] Aliphatic halides are usually converted to the reduced alkane independent of the reaction conditions (eq 4).[13]

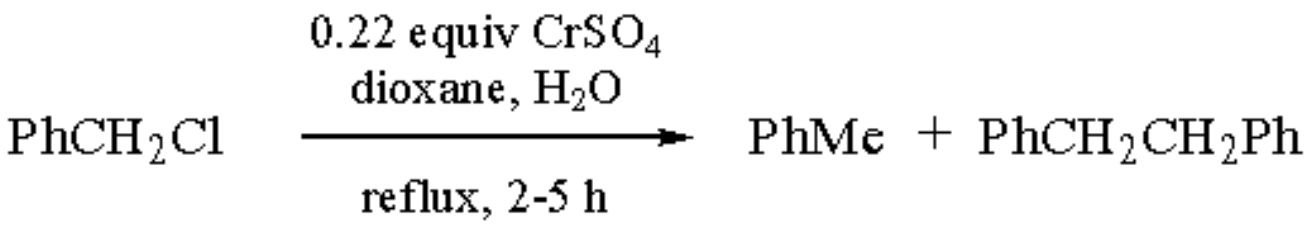

(3)

$CrSO_4$ add'n rate:	1.2 h	82.0%	12.4%
	3.8 h	44.8%	42.6%

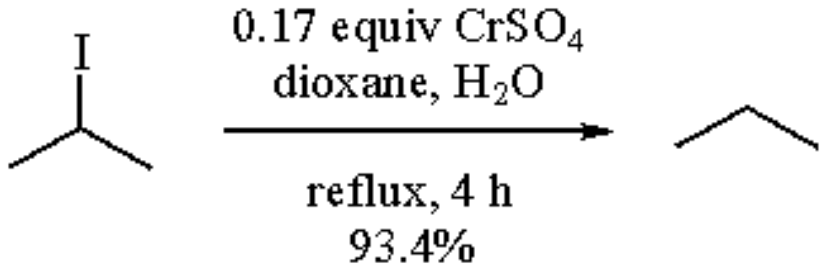

(4)

The nature of the halide affects the rate of this reaction (I > Br > Cl).[13] The presence of a hydrogen donor such as mercaptoacetic acid enhances the yield of reduced alkane.[14] For both sets of halides their reactivity with $CrSO_4$ can be generalized as follows: benzylic, α-halocarbonyl > allylic > tertiary > secondary > primary > vinylic, aromatic.[15]

Reduction of Vicinal Dihalides.

Alkenes which are stable to $CrSO_4$ can be obtained from vicinal dihalides in high yields.[16] Rapid homogeneous reaction takes place in water or aqueous DMF, consuming most of the reducing agent.[16] The stereochemical outcome of the reaction varies as some compounds lead to clean *trans* elimination (eq 5) while others give isomeric mixtures.[16] The reduction of 2,3-dihalopropenes can be influenced by the amount of reducing agent. Excess $CrSO_4$ transforms the initially formed allene into a propene (eq 6).[16] In special instances, alkynes have been prepared from the corresponding vinyl dibromides under these conditions if the alkyne is unreactive toward $CrSO_4$.[16]

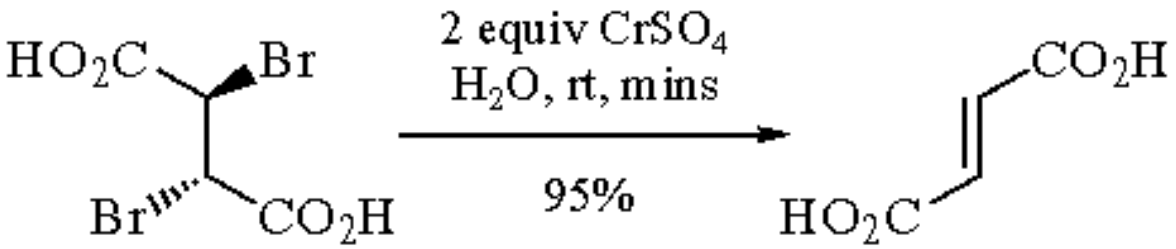

(5)

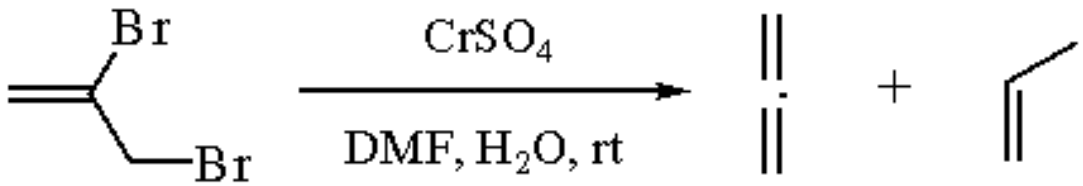

(6)

equiv $CrSO_4$:	5.4	26:74	81%
	2.0	98: 2	65%

Reduction of Geminal Dihalides.

The room temperature reduction of *gem*-dihalides with $CrSO_4$ leads to mixtures of alkanes, alkenes, and alkanols when carried out in aqueous DMF. Alkanes are the predominant product (eq 7).[17] The rate of reaction varies with the halide (I > Br > Cl).[17]

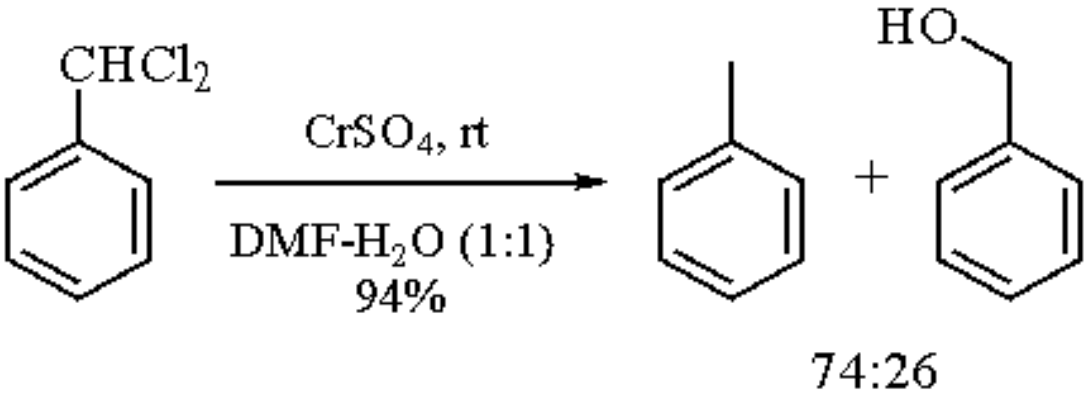

(7)

One report describes the utility of $CrSO_4$ in the reduction of *gem*-dibromocyclopropanes.[11] These cyclopropanes produce mixtures of cyclic allenes, monobromocyclopropanes, cyclopropanes, and allylic alcohols.[11] High yields of cyclic allenes can be obtained with certain substrates (eq 8).[11]

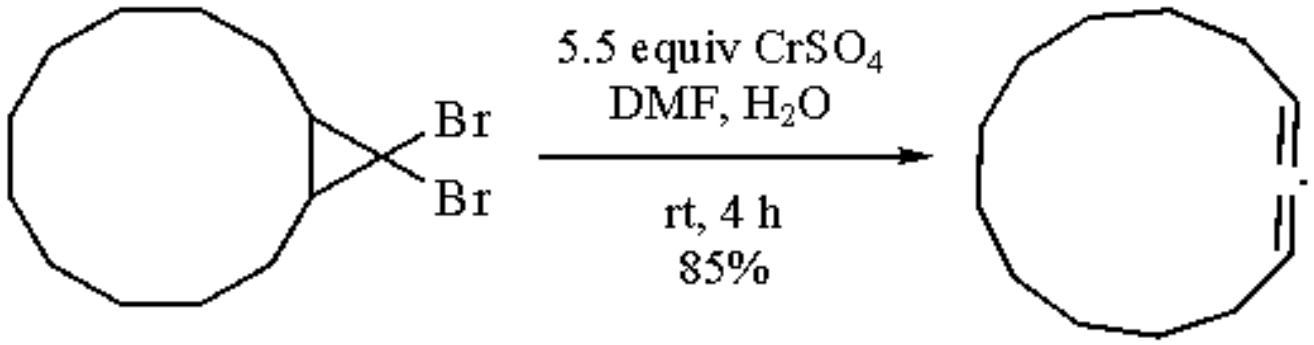

(8)

Miscellaneous Reductions.

$CrSO_4$ is capable of reducing aldehydes.[18] In a special case it has been utilized selectively to hydrogenolize one of the hydroxyl groups in a 3-hexyne-2,5-diol.[19]

Reductions with Chromium(II) Complexes.

Complexation of Cr^{II} with ammonia or amines enhances its reactivity. Ammoniacal Cr^{II} prepared from an aqueous $CrSO_4$ solution readily reduces aldehydes and alkenes.[2a] Complexation with ethylenediamine enables reduction of alkyl halides which are unreactive or only slowly reactive toward $CrSO_4$ itself.[2b]

Related Reagents.

Chromium(II) Acetate; ***Chromium(II) Chloride***; ***Lithium***; ***Lithium Aluminum Hydride***; ***Phenyllithium***; ***Zinc***.

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Chromyl Acetate[1]

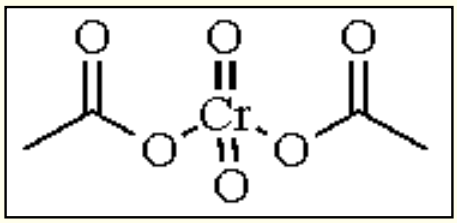

[4112-22-5] · $C_4H_6CrO_6$ · Chromyl Acetate · (MW 202.10)

(oxidizing agent for carbon-hydrogen bonds, carbon-carbon double bonds, macrocyclic lactones, and alcohols)

Physical Data: mp 30.5 °C.

Solubility: sol CCl_4, Ac_2O, HOAc; slowly oxidizes many solvents.

Purification: spectrophotometrically or titrimetrically.[2-5]

Preparative Methods: prepared in situ from CrO_3 and Ac_2O or Ac_2O/HOAc. Slow addition of CrO_3 to a cooled solution of Ac_2O is recommended in order to avoid a highly exothermic reaction.

Handling, Storage, and Precautions: best results are obtained from the freshly prepared oxidant. Chromium compounds are toxic and should be handled with care and disposed of in conformance with established procedures. This reagent should be handled in a fume hood.

This powerful oxidant, which is sometimes called chromium(VI) oxide-acetic anyhdride or chromium(VI)-acetic anhydride-acetic acid, oxidizes carbon-hydrogen bonds in bicycloalkanes and polycycloalkanes to form alcohols and ketones.[6-12] The initially formed alcohol may also be acetylated or oxidized to the ketone in the reaction mixture. Methylbenzenes are oxidized to the corresponding benzoic acids[12] and, in the presence of sulfuric acid (Thiele reagent), benzylidene diacetates (aldehyde precursors) are obtained.[13-15] Alkenes are oxidized to oxiranes[16-18] and diol carbonates.[19] Diarylmethanes and secondary alcohols are oxidized to ketones.[12,20]

Oxidation of Carbon-Hydrogen Bonds to Form Alcohols and Ketones.

Chromyl acetate oxidizes bicyclo[2.2.1]heptane (**1**) to (**2**) and (**3**) (eq 1),[6] bicyclo[2.2.2]octane (**4**) to (**5**) and (**6**) (eq 2),[6] and adamantane (**7**) to (**8**) and (**9**) (eq 3).[6] Tricyclo[3.3.0.0.^{2,6}]octane (**10**) is oxidized to (**11**) and (**12**) in a 9:1

ratio (eq 4).[7] (-)-Isobornyl acetate (**13**) is regioselectively oxidized to (**14**) and (**15**) (4:1; eq 5), which is useful in the synthesis of nojigku acid.[8] Similarly, (-)-bornyl acetate (**16**) is oxidized to (**17**) and (**18**) (eq 6).[9] 3β-Acetoxy-5α,6β-dichloroandrostan-17-one (**19**) is oxidized by chromyl acetate to the corresponding 14α-hydroxy compound (**20**) (eq 7)[10] and 3,5α-cycloandrostane is oxidized to a mixture of three ketones.[11] The latter reaction involves oxidation and carbonyl formation α to a cyclopropane ring.

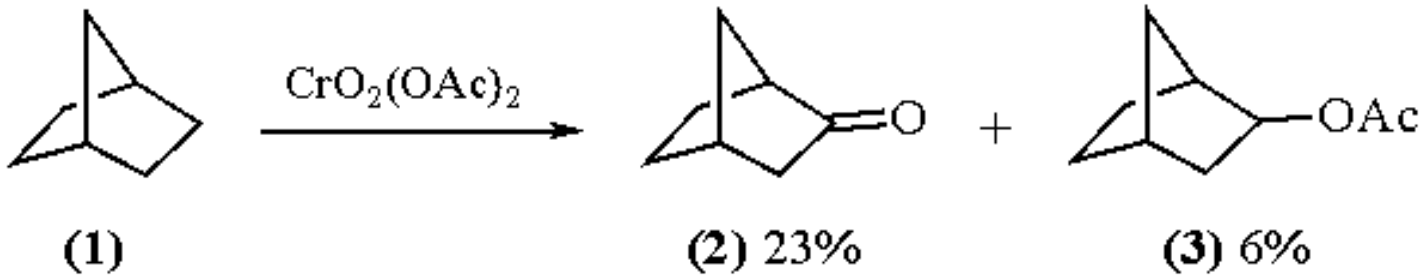

(1) (2) 23% (3) 6% (1)

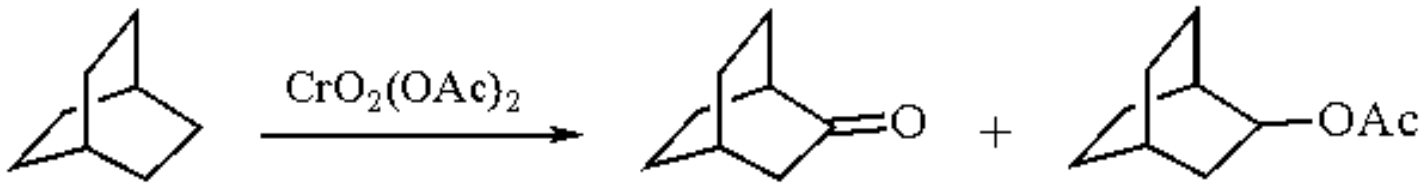

(4) (5) 40% (6) 4% (2)

(7) (8) 71% (9) 9% (3)

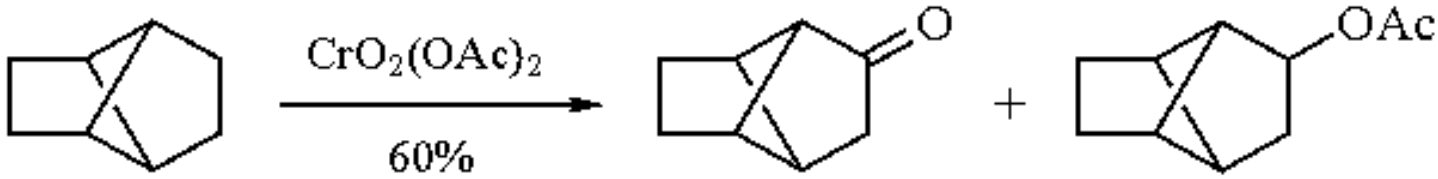

(10) (11) (12) (4)

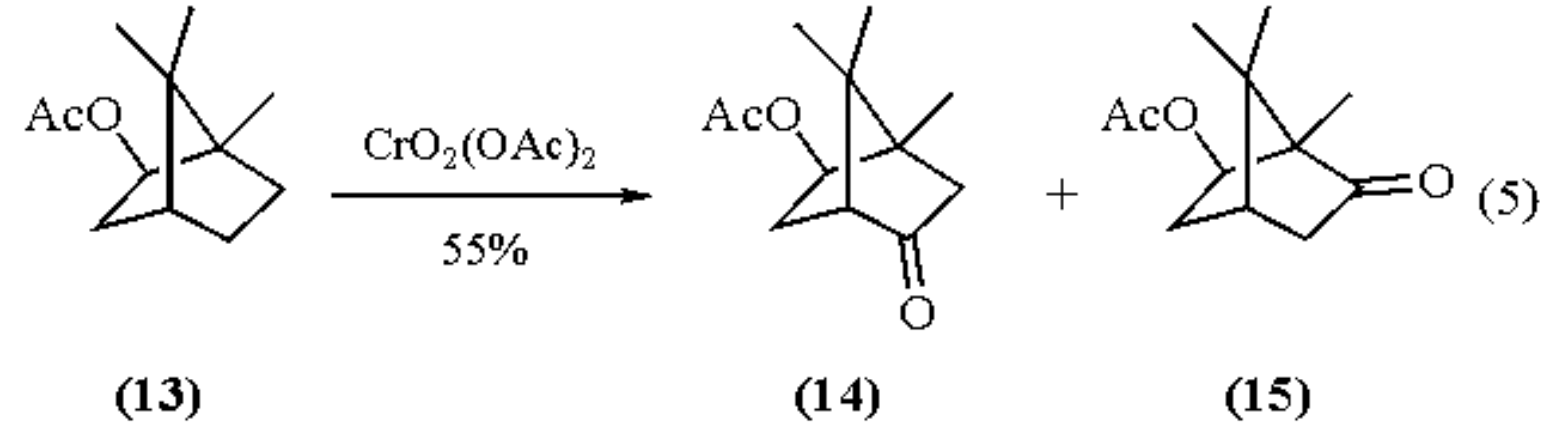

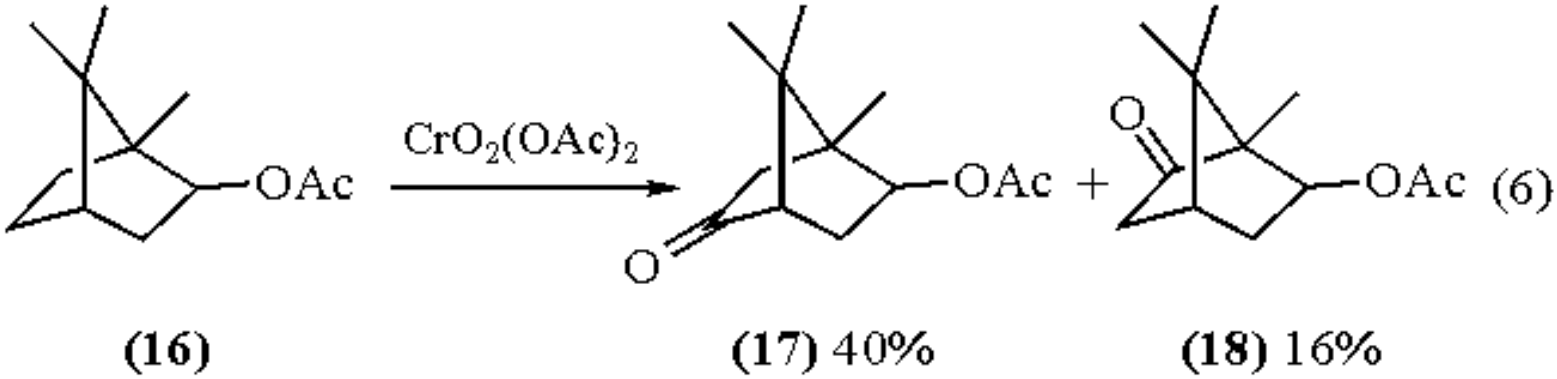

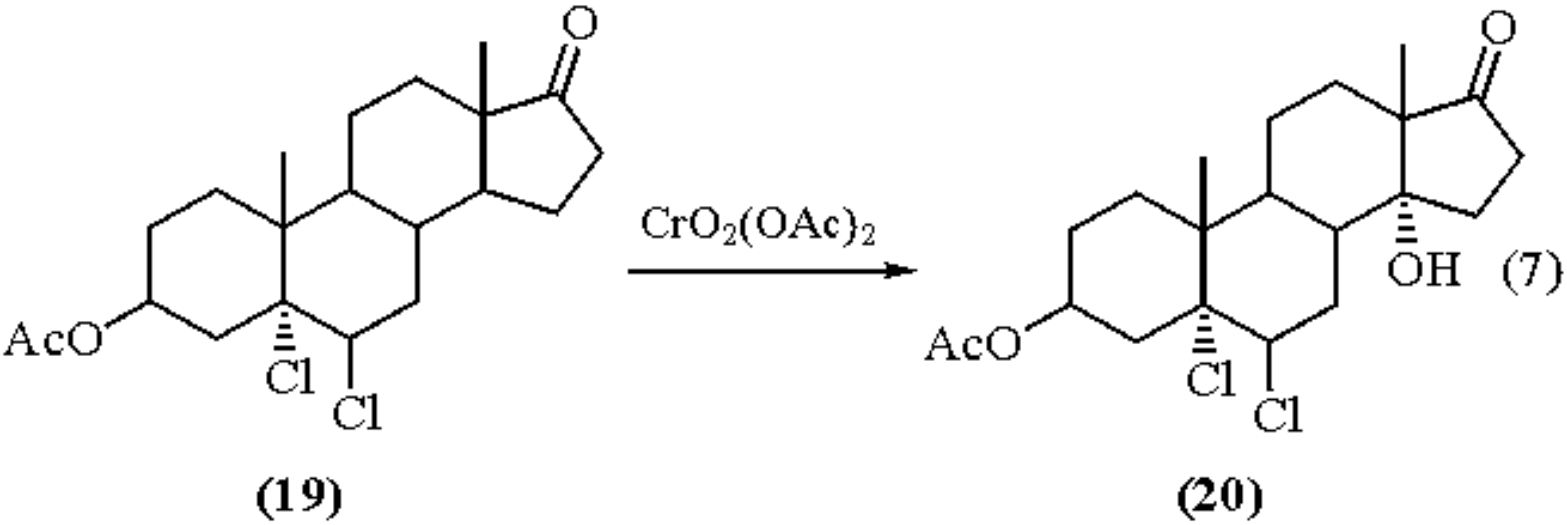

Oxidation of Benzylic Carbon-Hydrogen Bonds to Alcohols, Aldehydes, Carboxylic Acids, and Ketones.

Chromyl acetate in the presence of sulfuric acid converts methyl-substituted aromatic and heteroaromatic compounds to the corresponding benzylidene diacetates in fair to excellent yields (eq 8).[13-15] The benzylidene diacetates are easily hydrolyzed to aldehydes. Diphenylmethane and triphenylmethane are oxidized to benzophenone and triphenylcarbinol, respectively, in near quantitative yields.[12]

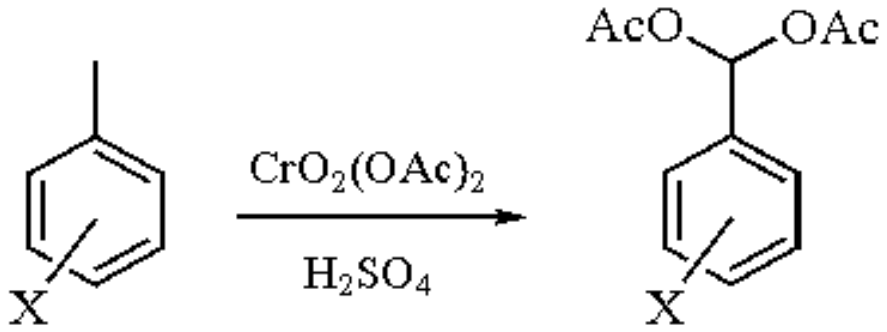

(8)

Oxidation of Carbon-Carbon Double Bonds to Oxiranes.

Chromyl acetate[16-18] and chromyl nitrate[19] stereospecifically oxidize carbon-carbon double bonds to oxiranes (eq 9). Tetraphenylethylene is converted to the oxirane, benzophenone, and benzopinacol (eq 10).[20]

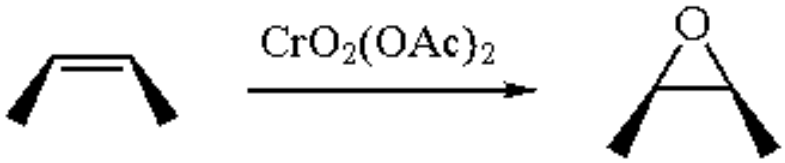

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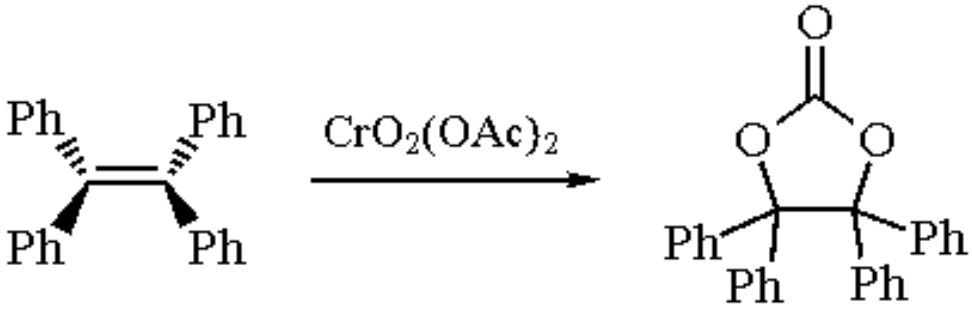

(10)

Other Applications.

Unlike the ***Dipyridine Chromium(VI) Oxide*** complex and ***Pyridinium Chlorochromate*** which gave nearly exclusive α-oxidation of alkynes, chromyl acetate oxidized the α-position and the triple bond.[21] Macrocyclic lactones are oxidized to monoketo lactones with some regioselectivity. The preferred conformation of the lactone probably influences the site of oxidation.[22] New oxygenated derivatives of 1,8-epoxy-*p*-menthane were obtained by the chromyl acetate oxidation of 1,8-cineole.[23]

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Chromyl Chloride[1]

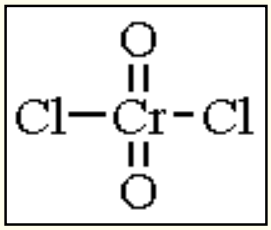

[14977-61-8] · Cl_2CrO_2 · Chromyl Chloride · (MW 154.92)

(reagent for converting alkenes to aldehydes, oxiranes, ketones, chlorohydrins, α-chloro ketones, vicinal chloroacetates, and α-hydroxy ketones, and for oxidizing alkylaromatics to alcohols, aldehydes, and ketones)

Alternate Names: dichlorodioxochromium; Etard reagent.

Physical Data: mp -96.5 °C; bp 117 °C; *d* 1.911 g cm^{-3}.

Solubility: sol CCl_4, CH_2Cl_2, ether.

Form Supplied in: dark red liquid.

Preparative Methods: prepared from ***Chromium(VI) Oxide*** and ***Titanium(IV) Chloride***.[2-4]

Handling, Storage, and Precautions: cancer suspect agent; all chromium(VI) reagents must be handled with care; the mutagenicity of Cr^{VI} compounds is well documented.[5] This reagent should be handled in a fume hood.

Oxidation of Alkenes to Aldehydes, Oxiranes, Ketones, Chlorohydrins, α-Chloro Ketones, Vicinal Chloroacetates, and α-Hydroxy Ketones.

The products from the chromyl chloride oxidation of alkenes depend on the structure of the alkene and the experimental conditions. Oxidation of terminal aliphatic alkenes and alkenylaromatics with chromyl chloride in dichloromethane, followed by reductive workup with ***Zinc*** dust or ***Sulfur Dioxide***, affords the corresponding aldehydes (eqs 1 and 2).[6-9] α-Chloro Ketones are the only products if propanone replaces dichloromethane as the

solvent (eq 3).[10,11] Reductive zinc dust workup affords the corresponding ketones. The initially formed chlorohydrin and oxirane products may also be isolated.[10,12,13] Epoxidation is stereospecific, yielding an oxirane with the same geometry as the starting alkene. Oxiranes are also the intermediates leading to vicinal chloroacetates when the oxidation is performed in 2:1 dichloromethane-acetyl chloride (eq 4).[14] Chromyl chloride reacts regiospecifically with O-silylated enolates in dichloromethane at -78 °C to afford α-hydroxy ketones (eq 5).[15]

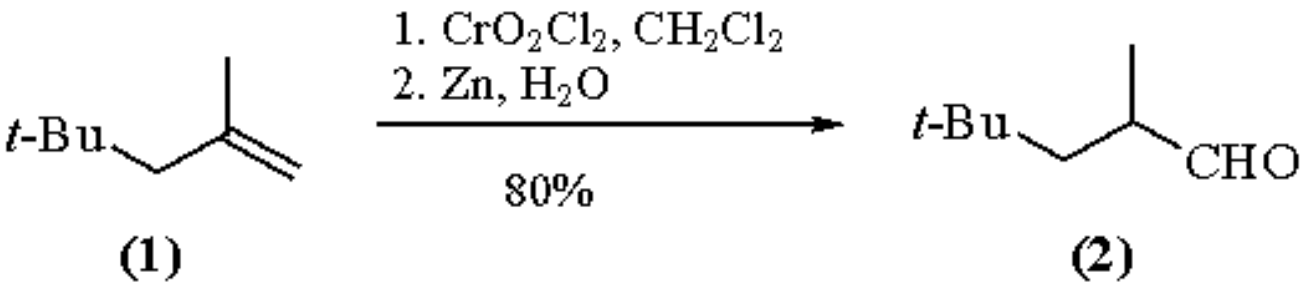

(1) (2) (1)

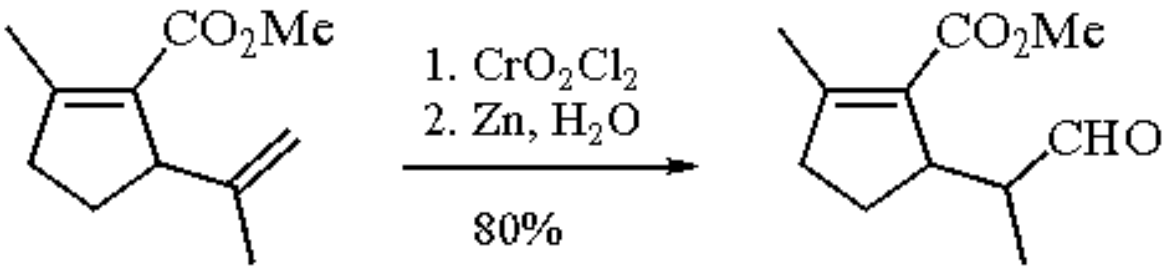

(3) (4) (2)

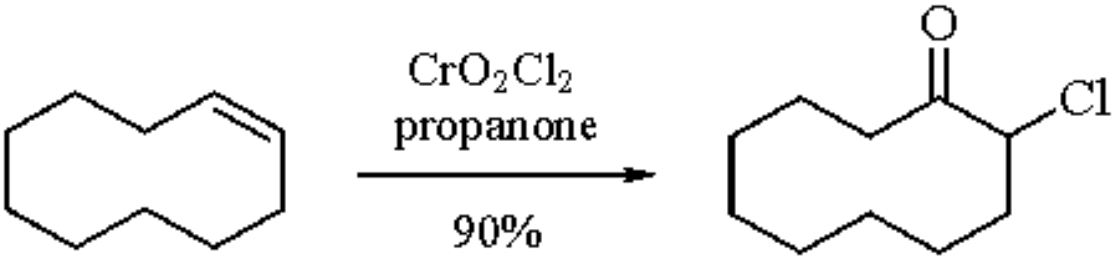

(5) (6) (3)

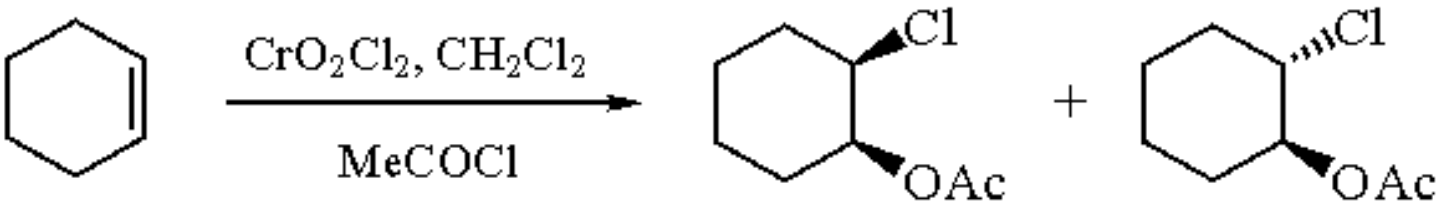

(7) (8) 51% (9) 20% (4)

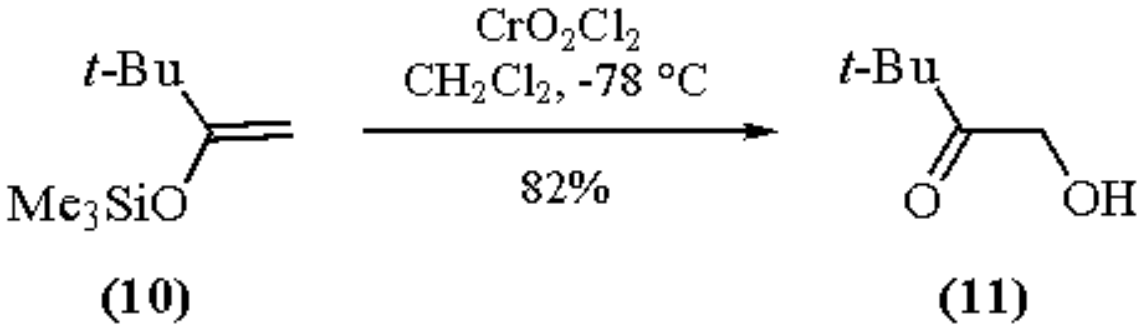

(5)

Oxidation of Alkylaromatics to Aldehydes, Ketones, and Alcohols.

Chromyl chloride oxidizes methylbenzenes to the corresponding aldehydes (Etard reaction).[16,17] The ultrasonic-mediated chromyl chloride oxidation of diphenylmethane, indan, and triphenylmethane affords diphenyl ketone (99%), 1-indanone (80%), and triphenylmethanol (99%), respectively.[2] These yields are higher than those obtained by previous procedures.

Other Applications.

Chromyl chloride oxidizes phenols to quinones and coupling products.[18] Chromyl chloride is used to prepare ***Di-t-butyl Chromate***,[2] *t*-butyl chromate-tripyridine,[19] and 2,4-(2,4-dimethylpentyl) chromate,[2,20] which are useful oxidants.

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trans-Cinnamyltributylstannane[1]

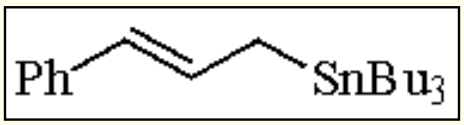

[19752-27-3] · $C_{21}H_{36}Sn$ · *trans*-Cinnamyltributylstannane · (MW 398.15)

(phenylallylating agent as an anion equivalent;[1,2] 3-carbon component in a [3 + 2] cycloaddition reaction with α,β-unsaturated acylirons[3])

Alternate Names: trans-cinnamyltributyltin; *trans*-(3-phenyl-2-propenyl)tributyltin.

Physical Data: bp 163-166 °C/0.4 mmHg;[2] bp 138-142 °C/0.5 mmHg;[4] *n*20D 1.5185.[4]

Solubility: sol THF, methylene chloride, chloroform.

Preparative Methods: by the coupling reaction of *trans*-cinnamylmagnesium bromide with ***Tri-n-butylchlorostannane*** (10-20%)[2,4,5] or trapping of the lithiated derivative of allylbenzene (*s*-BuLi in cyclohexane/TMEDA/THF) with tributylchlorostannane at -78 °C (90%).[6,7]

Analysis of Reagent Purity: CH microanalysis; IR (neat)[2] 2925 (vs), 1637 (s), 1598 (s), 1495 (s), 1463 (s), 1672 (s), 958 (s) cm^{-1};IR (1% CCl_4)[4] 1635, 956 cm^{-1}; UV (MeOH) λ_{max} 267 nm (log ε$_{max}$ 4.036);[4] ^1H NMR (100 MHz, CCl_4) δ 0.89 and 1.5 (m, 27H), 1.93 (d, 2H, *J* = 8 Hz), 5.6-6.4 (m, 2H), 7.09 (m, 5H);[2] ^1H NMR (360 MHz, $CDCl_3$) δ 0.80-0.98 (m, 15H), 1.21-1.31 (m, 6H), 1.39-1.57 (m, 6H), 1.95 (dd, 2H, *J* = 8.7, 1.0 Hz), 6.18 (d, 1H, *J* = 15.6 Hz), 6.40 (dtd, 1H, *J* = 15.6, 8.7, 1.0 Hz), 7.0-7.3 (br s, 5H);[7,8] ^{13}C NMR spectroscopy.

Handling, Storage, and Precautions: although toxicological properties have been virtually unexplored, they may be extrapolated from those observed for ***Allyltributylstannane***.[8] Use in a fume hood.

Lewis Acid-Mediated Phenyallylation Reactions.

Phenylallylation reactions can be realized under Lewis-acid catalysis in a similar manner as those observed using allyltributyl- or ***Allyltriphenylstannane***.[1] However, the regiochemistry of phenylallyl addition depends upon the nature of the reaction and the structure of the electrophile substrate used. For example, treatment of *trans*-cinnamyltributyltin with 2,3-dimethylbenzoquinone in the presence of ***Boron Trifluoride Etherate*** results in the exclusive allylation at the α-carbon (eq 1).[2] In contrast, a similar reaction with 2,6-dimethylbenzoquinone provides a mixture of α- (49%) and γ-adducts (32%) at C-3 of the starting benzoquinone.[2]

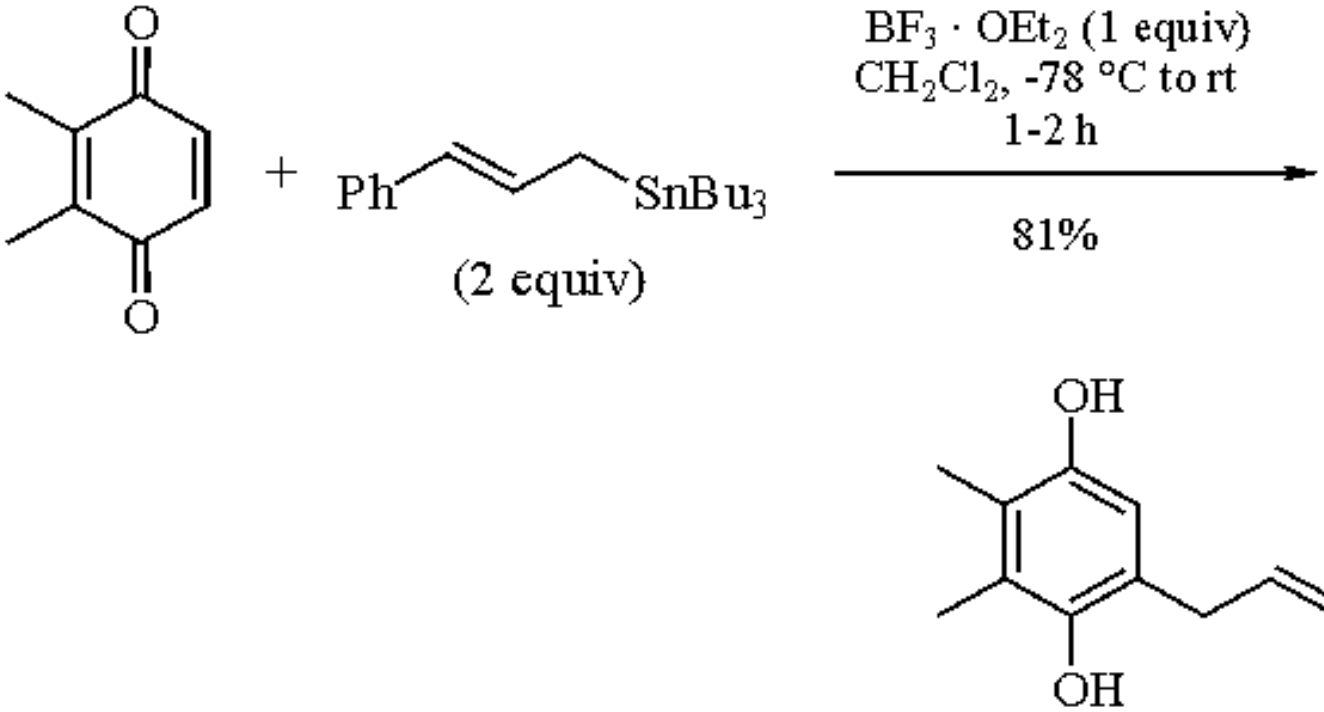

(1)

trans-Cinnamyltributyltin undergoes a $BF_3.OEt_2$-mediated addition reaction with aldehydes (eq 2)[7] as other allyltins (see ***Allyltributylstannane***).[1] Interestingly, however, the stereochemical outcome of this reaction is opposite to the *syn* selectivity encountered for the reactions involving ***Crotyltributylstannane***, where the reactions are postulated to proceed through extended transition states.[1,9] The observed *anti* selectivity of the reaction of *trans*-cinnamyltributyltin has been speculated to proceed through a cyclic transition state, presumably owing to a greater ionic contribution from the C-Sn bond compared with other allyl- or γ-alkylallyltins.[7]

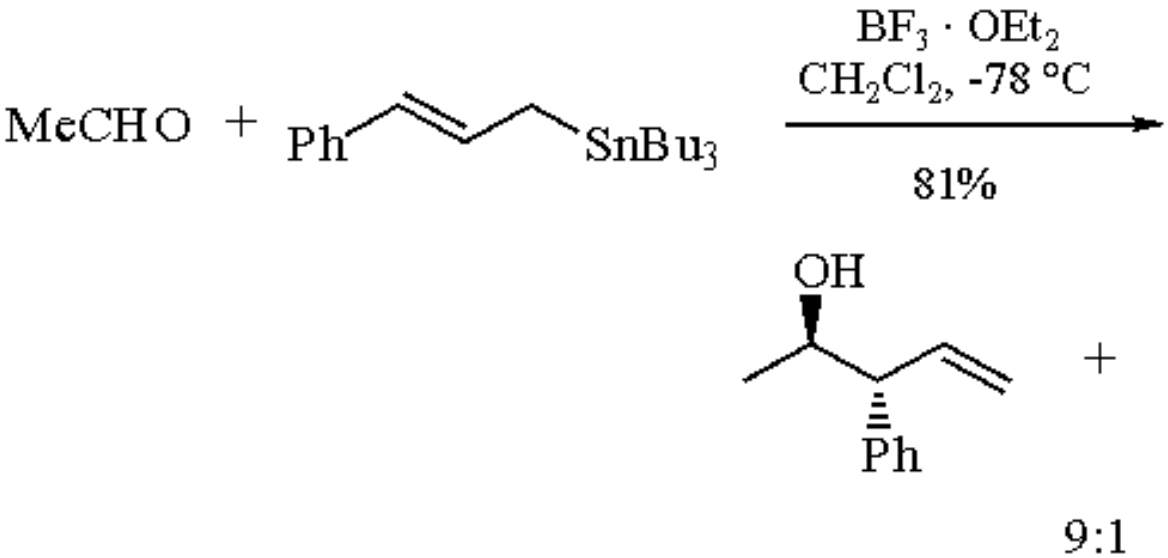

(2)

A novel, highly stereoselective [3 + 2] cycloaddition has been developed between allyltins such as *trans*-cinnamyltributyltin and α,β-unsaturated acyliron complexes (eq 3).[3]

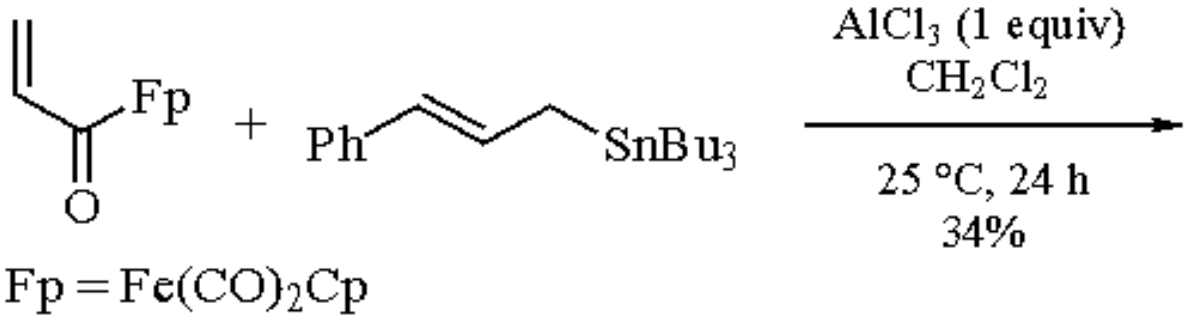

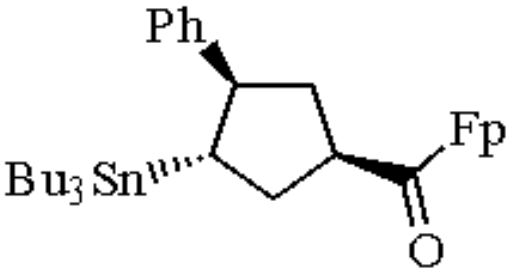

(3)

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Cobalt Boride[1,2]

Co_2B

[12045-01-1] · BCo_2 · Cobalt Boride · (MW 127.8)

(a selective hydrogenation catalyst;[3] reduces nitriles to amines,[4,5] nitroarenes to azobenzenes,[6] sulfoxides to sulfides,[7,8] and, in the presence of CO, carbonylates aryl[9] and benzyl[10] halides)

Physical Data: mp 1265 °C.[11]

Solubility: insol aqueous base and most organic solvents; reacts with aqueous acid.

Form Supplied in: black granules (a mixture of Co_2B and Co_3B).

Preparative Method: a solution of $CoCl_2$ in methanol is treated with five mol equiv of $NaBH_4$ at 0 °C; the black solid which is produced can be isolated after 15 min and is air stable. Drying in vacuo (6 h) produces a pyrophoric solid.

Handling, Storage, and Precautions: while the solid can be easily handled when wet with solvent, most preparations use Co_2B generated in situ. Care must be exercised when handling Co^{II} salts as they are known to be toxic in man (e.g. large amounts of $CoCl_2$ depress erythrocyte production).

Catalyst Composition and Structure.

The composition of the catalyst produced by the reaction of ***Cobalt(II) Chloride*** and ***Sodium Borohydride*** is dependent on the reaction conditions (temperature, solvent, presence of a ligand, etc.). The amount of salts which precipitates onto the surface of the boride during preparation greatly affect their selectivity. Therefore the solubility of the byproduct salt (e.g. NaCl), in the medium in which the boride is prepared is important.[1] Early studies of the action of $NaBH_4$ on transition metal salts[12] (Fe^{II}, Cu^{II}, Pd^{II}, Ni^{II}, Co^{II}, etc.) showed that either the metal is produced (as in the case of $PdCl_2$) or a granular black solid results (as in the case of $CoCl_2$); in either case, hydrogen gas is evolved. Analysis of the black solid formed from $CoCl_2$ suggested, … {the catalyst} to be a cobalt boride….[12,13]

When Co^{II} salts react with $NaBH_4$ in a CO saturated solution, no boride forms (the solution remains green); instead, a cobalt carbonyl complex forms which carbonylates aryl[9] and benzylic[10] halides. Similarly, $CoCl_2/NaBH_4/Ph_3P$ acts as a hydroboration or bond isomerization catalyst.[14]

Hydrogenation of Alkenes and Alkynes.

From early reports[12,15] it was clear that the Co^{II} salt/borohydride catalyst was both a selective reagent for the reduction of alkenes, as well as a convenient source of hydrogen gas. Rhodium, ruthenium, and platinum salts were the most effective in the decomposition of $NaBH_4$ to generate H_2;[16] however, Ni^{II} provided the most active and selective hydrogenation catalyst for simple hydrocarbons. Co^{II} salts/$NaBH_4$ selectively reduces mono- and disubstituted alkenes (trisubstituted alkenes are unaffected) as well as alkynes, as shown in Tables 1 and 2.[3,17]

Table 1 Reduction of Alkenes and Alkynes by Co^{II} Salts and $NaBH_4$ in Ethanol

Substrate	Product (% yield)	Ratio sub:Co^{II}:$NaBH_4$	Reaction time (h)
Styrene	Ethylbenzene (>98)	1:1:2	3.5
cis-Stilbene	1,2-Diphenylethane (98)	1:1:2.5	16
trans-Stilbene	1,2-Diphenylethane (45)	1:1:2.5	16
Octene[a]	Octane (>98)	1:1:2	3
Norbornene	Norbornane (>98)	1:1:2	3
Norbornadiene	Norbornane (>98)	1:1:2	2.5
Cyclohexene	Cyclohexane (>98)	1:1:2	20
1-Methylcyclohexane	No reaction	1:1:3	19
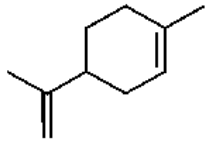	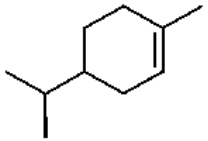 (75)	1:0.5:1	12.5
β-Pinene	Pinane (44)	1:0.5:1	20
α-Pinene	No reaction	1:1:2	24
Cholesterol	No reaction	1:1:2	23
1-Octyne	*n*-Octane (98)	1:0.1:1	3
1-Octyne	*n*-Octene (95) 1-Octyne (trace) *n*-Octane (trace)	1:0.1:0.5	3
1,2-Diphenylacetylene	*cis*-Stilbene (30) *trans*-Stilbene (10) 1,2-Diphenylathane (10) Starting material (50)	1.0:0.1:0.5	11

[a] $CoCl_2 \cdot 6H_2O$ and anhydrous $CoBr_2$ could be used interchangeably.

Table 2 Hydrogenation of Alkenes using $CoCl_2/NaBH_4/MeOH$ in THF[a]

Substrate	Product (% yield)	Reaction time (h)
Styrene	Ethylbenzene (65)	3
trans-Octene	Octane (70)	8
α-Pinene	No reaction	12
Cholesterol	No reaction	12
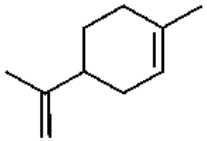	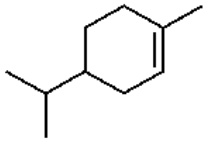 (75)	8

[a] All reactions were carried out with 10 mmol $CoCl_2$, 20 mmol $NaBH_4$, 60 mmol MeOH, and 20 mmol substrate in 40 mL THF.

While there has been a tremendous amount of speculation as to the species responsible for these reactions, it has been shown that use of hydrogen gas over preformed Co_2B works as well as the $Co^{II}/NaBH_4$ reagent and that under conditions which disfavor hydrogen gas evolution (THF-MeOH, 12:1) limonene is not reduced with the $Co^{II}/NaBH_4$ reagent.[5]

Other Co^{II}/boron hydride mixtures which are effective selective reducing agents include *t*-butylamine borane (TAB)/Co_2B (in refluxing methanol)[18] and dimethoxyborane/Co_2B (or Ni_2B)[19] (4-6 equiv hydride, 0.1 equiv boride, 1 equiv alkene).

Several Co^{II}/boron hydride mixtures are effective catalysts for the reduction of α,β-unsaturated systems as shown in Table 3.[18,20-25]

Table 3 Reduction of α,β-Unsaturated Systems using Co^{II}/Boron Hydride Reagents

Substrate	Product	Yield (%)	Reagent	Ref.
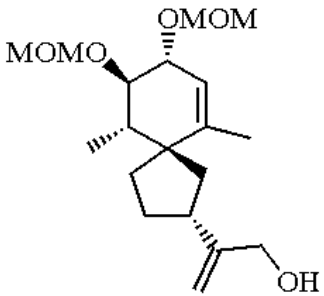	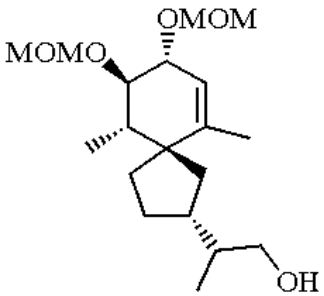	78	$NaBH_4/CoCl_2 \cdot 6H_2O$	20
Methyl cinnamate	Methyl dihydrocinnamate	85	$NaBH_4/Co_2B$ (5:0.1), MeOH, rt, 2 h	18
Methyl cinnamate	Methyl dihydrocinnamate	75	TAB/Co_2B (2:1), MeOH, rt, 3 h	18
Methyl cinnamate	Methyl dihydrocinnamate	85	$NaBH_4/CoCl_2$ (2:0.1), MeOH, rt, 1 h	21
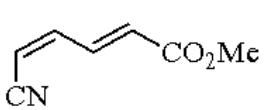	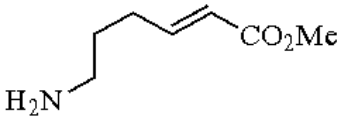	60	$NaBH_4/Co_2B$ (5-10:1), MeOH, 0 °C, 8 h	18

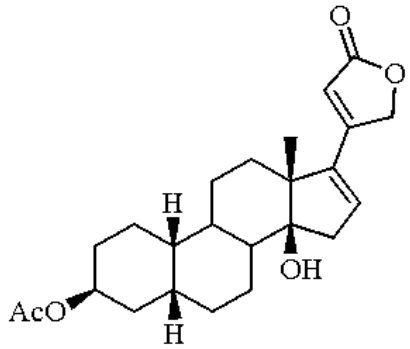	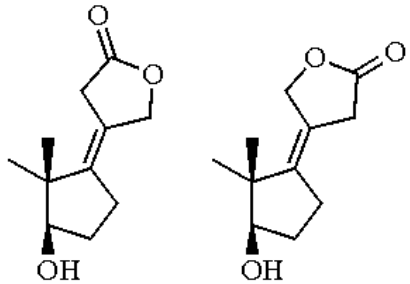	56, 9	$NaBH_4/CoCl_2 \cdot 6H_2O$ (4:0.5)	22
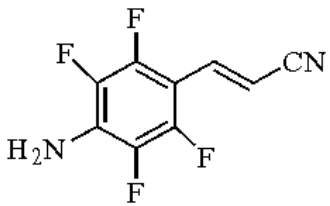	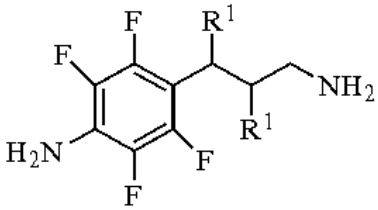	50-90	$NaB(R^1)_4/CoCl_2$ (2:1), MeOH; $R^1 = H, D, T$	23
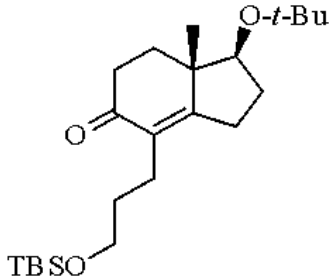	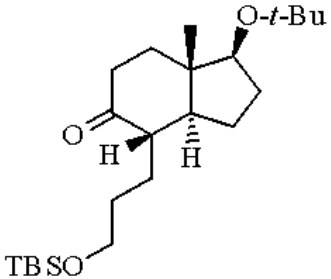	63	$NaBH_4/CoCl_2 \cdot 6H_2O$	24
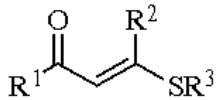	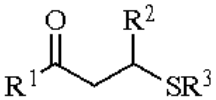			
$R^1 = Ph, R^2 = Me, R^3 = Et$		71	$NaBH_4/CoCl_2$ (2:0.1)	25
$R^1 = Ph, R^2 = Me, R^3 = Ph$		44	$NaBH_4/CoCl_2$ (2:0.1)	25
$R^1 = Ph, R^2 = Ph, R^3 = Et$		84	$NaBH_4/CoCl_2$ (2:0.1)	25
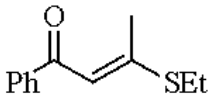	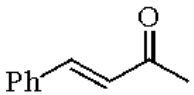	78	$NaBH_4/CeCl_3 \cdot 7H_2O$ (2.0:0.1)	25

The β-thioenone example is noteworthy for several reasons:

- 1)The ketone survives in the presence of an excess of $NaBH_4$; in the absence of $CoCl_2$, an allylic alcohol is formed.
- 2)In general, reactions which use catalytic amounts of $CoCl_2$ are more effective than those which use stochiometric amounts of the chloride.

- 3)$NiCl_2$ is somewhat less effective (10% lower yield). $CeCl_3.7H_2O$ gives the inverted enone as shown in the last entry of Table 3. $FeCl_3$, CuI and $CuCl_2$ had no activity in this system.

Chiral C_2-symmetric semicorrin/Co^{II} complexes (such as **1**), in combination with $NaBH_4$, reduce β-substituted acrylates enantioselectively (eq 1).[26]

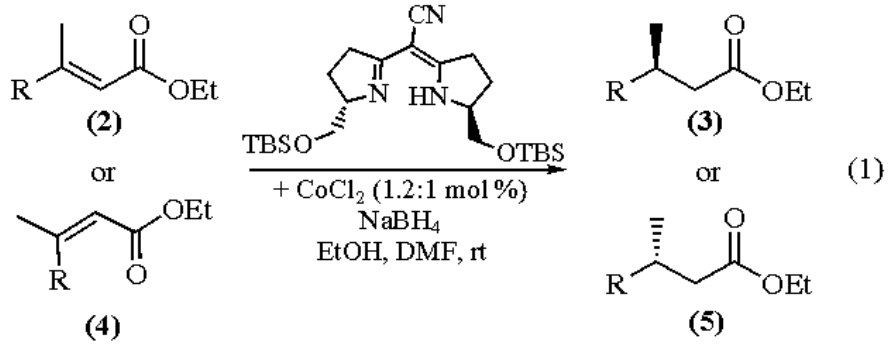

(1)

(a) R = $Ph(CH_2)_2$
(b) R = Ph
(c) R = $Me_2C{=}CH(CH_2)_2$

Substrate	Product	Yield (%)	ee (%)	Configuration
(2a)	**(3a)**	97	94	*(R)*
(4a)	**(5a)**	95	94	*(S)*
(2b)	**(3b)**	95	81	*(S)*
(4b)	**(5b)**	97	73	*(R)*
(2c)	**(3c)**	95	94	*(R)*
(4c)	**(5c)**	95	94	*(S)*

These results are comparable to those obtained with Noyori's Ru^{II}-BINAP[27] but does not require a free alcohol, carboxylate, or amide in the substrate.

Reduction of Nitrogenous Functional Groups.

Nitriles.

One of the most widely used reactions of the $CoCl_2/NaBH_4$ system is the reduction of nitriles to primary amines.[4] This method has been used in the synthesis of ^{11}C[28] and ^{3}H[23] labelled radiodiagnostics. Dimethoxyborane has been substituted for $NaBH_4$ in the reduction of nitriles and aldehydes[19,29] in the presence of transition metals (Ni^{II}, Pd^{II}, and Pt^{II} have also been used).[4]

Studies of the nitrile reduction[5,18] with the $Co^{II}/NaBH_4$ reagent has provided some insight into the mechanism of the reaction:

- 1)Co_2B acts as a heterogenous catalyst (Co_2B/H_2 works as well).
- 2)Co_2B activates the nitrile towards reaction with uncomplexed $NaBH_4$.
- 3)The reaction is pH sensitive (the optimal pH range is 8-9).

This last observation led to the development of the Co_2B/*t*-butylamine/borane system for the reduction of nitriles.[18] Example of the reduction of nitriles to amines are shown in Table 4.[4,28,30-34]

Table 4 Reduction of Nitriles to Amines

Substrate	Product	Yield (%)	Reagent	Ref.
Benzonitrile	Benzylamine	72	$NaBH_4/CoCl_2/MeOH$ (0.5:0.1)	4

Octanenitrile	Octylamine	80	$NaBH_4/CoCl_2/MeOH$ (05:0.1)	4
β-Cyanomethylpyridine	β-Aminoethylpyridine	35	$NaBH_4/CoCl_2/MeOH$ (0.5:0.1)	4
Acrylonitrile	Allylamine	70	$NaBH_4/CoCl_2/MeOH$ (0.5:0.1)	4
4-Chlorophenylacetonitrile	4-Chlorophenylethylamine	85	$BH(MeO)_2/CoCl_2$ (16:5)	28
	Bis(4-chlorophenylethyl)amine	5		
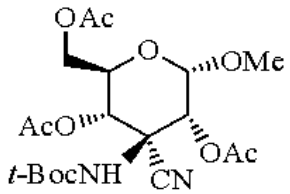	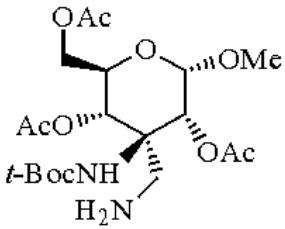	82	$NaBH_4/CoCl_2$	30
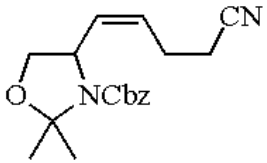	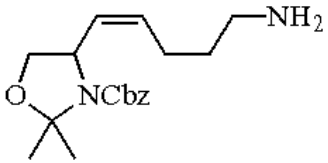	60	$NaNH_4/CoCl_2$ (10:1.2)	31
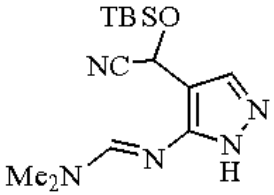	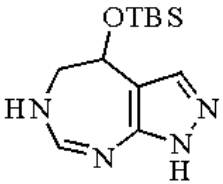	65	Co_2B/H_2	32
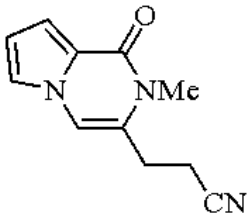	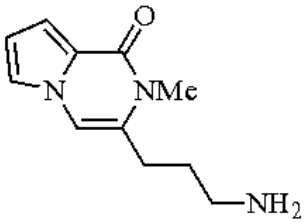	62	$CoCl_2/NaBH_4$ (2:5)	33
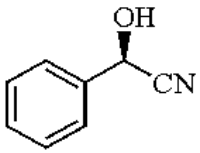	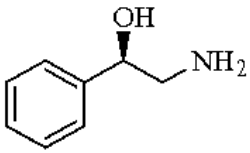	77	$CoCl_2/NaBH_4$	34

Nitro Groups.

While nitroarenes are reduced to anilines in modest yields (30-50%) using the $Co^{II}/NaBH_4$ system,[4] nitroalkanes are reduced slowly in good yields to amines (Ni^{II} [1] and Cu^{II} [35] are preferred reagents for this reduction). Some examples of this reduction are

given in Table 5.[32,34,36,37]

Table 5 Reduction of Nitro Groups with Transition Metal/$NaBH_4$

Substrate	Product	Yield (%)	Reagent	Ref.
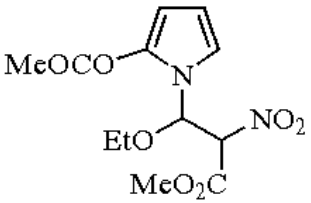	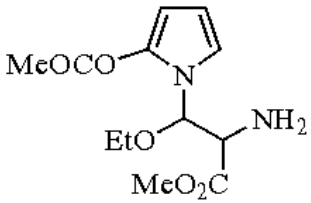	80	$CoCl_2/NaBH_4$ (5:2)	32
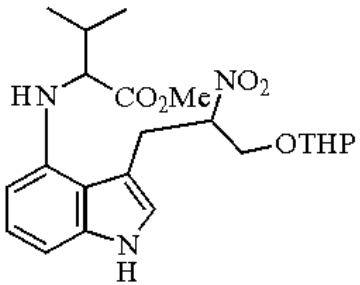	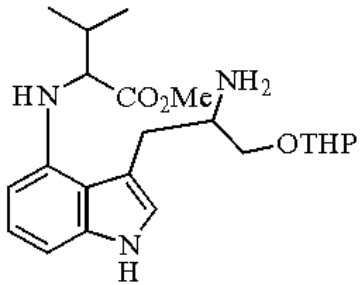	73	$CoCl_2/NaBH_4$	36
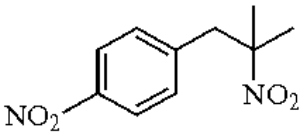	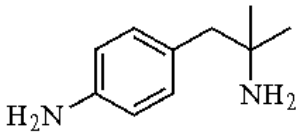	80	$CuCl_2/NaBH_4$	34
Nitrobenzene	Aniline	82.5	$Ni_2B/NaBH_4$ (0.5:4)	37
Nitrobenzene	Azobenzene	41	$Co_2B/NaBH_4$ (0.5:4)	36
	Aniline	33		

Other Nitrogenous Functional Groups.

Satoh[4] has reported the use of $CoCl_2/NaBH_4$ in methanol for the reduction of primary amides to amines: however, others[1,18,38] have reported problems with reproducibility in this reaction. Azobenzenes are reduced to hydrazobenzenes and hydrazobenzenes to anilines by the action of $CoCl_2/NaBH_4$.[39] Similarly, imines (and enamines) can be reduced to secondary amines[40] by $CoCl_2/NaBH_4$. By contrast, oximes are converted into secondary alcohols by $CoCl_2/NaBH_4$.[41]

Miscellaneous Reactions.

As noted above, the course of reaction involving Co^{II} and various borohydrides is sensitive to reaction conditions. When $NaBH_4$ is added to a solution of $CoCl_2$ saturated with CO, no precipitate of Co_2B is observed; in the presence of a base, this mixture carbonylates benzylic halides (eq 2).[10]

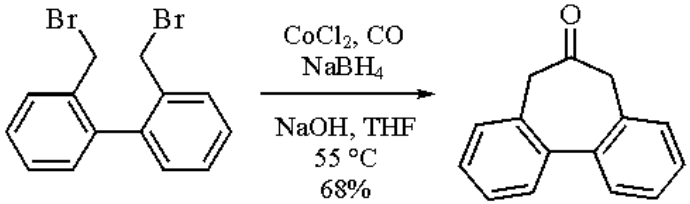

(2)

When an aryl bromide or iodide[9] is used, a mixture of α-keto acid, glycolic acid, and benzoic acid results (the α-keto acid predominates). These reactions are thought to proceed via a $Co(CO)_4$ anion generated in situ (***Sodium Sulfide*** and NaSMe have also been used in the place of the $NaBH_4$).[10] Under phase transfer conditions this reaction has been used to prepare malonates from chloroacetates in high yield.[42]

The $Co^{II}/NaBH_4$ reduction system deoxygenates aromatic and aliphatic sulfoxides in good to excellent yields.[7] This mixture also desulfurizes sulfides, sulfoxides, and disulfides[8] in good to excellent yields (however, ***Nickel Boride*** is a generally superior desulfurizing agent). $NaBH_4$, ***Lithium Triethylborohydride***, and $NaBHEt_3$ have been used in combination with $CoCl_2$ or ***Iron(II) Chloride*** to desulfurize thiols and thioketones[43] ($FeCl_2$ is the preferred reagent for this reaction).

Adams[44] reported the reduction of an aldehyde in the presence of a ketone using the $Co^{II}/NaBH_4$ reagent in DMSO solution (***Cerium(III) Chloride*** also works in this system, a reversal of the Luche reduction protocol).[45] Satyanarayana found $CoCl_2/NaBH_4$ to be an effective hydroboration[17] and alkene isomerization catalyst[14] (in the presence of ***Triphenylphosphine*** as a ligand). The same group also found that the $CoCl_2/Ph_3P/NaBH_4$ system is an effective catalyst for the synthesis of *trans* dienes via reductive dimerization of alkynes.[46]

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1. (a) Ganem, B.; Osby, J. O. *CRV* **1986**, *86*, 763. (b) Wade, R. C. *J. Mol. Catal.* **1983**, *48*, 763.
2. It should be noted that Co_2B represents a nominal stoichiometry of the reagent prepared by the action of $NaBH_4$ on a cobalt(II) salt as described above. Several Co_xB_y species have been described in the literature. Chemical Abstracts uses the registry number *12619-68-0* to designate cobalt boride of unspecified stochiometry. Furthermore, the reagent prepared from a cobalt(II) salt in the presence of a ligand (such as CO, Ph_3P, and glyoximate) does not always involve a boride species.
3. Chung, S.-K. *JOC* **1979**, *44*, 1014.
4. Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *TL* **1969**, 4555.
5. Osby, J. O.; Heinzman, S. W.; Ganem, B. *JACS* **1986**, *108*, 67.
6. Satoh, T.; Suzuki, S.; Kikuchi, T.; Okada, T. *CI(L)* **1970**, 1626.
7. Chung, S.-K.; Han, G. *SC* **1982**, *12*, 903.
8. Back, T. G.; Baron, D. L.; Yang, K. *JOC* **1993**, *58*, 2407.
9. Itoh, K.; Miura, M.; Nomura, M. *BCJ* **1988**, *61*, 4151.
10. Satyanarayana, N.; Periasamy, M. *TL* **1987**, *28*, 2633.
11. This is the melting point of Co_2B prepared by the fusion of the elements (*AC* **1961**, *32*, 53). Material prepared by the reduction of $CoCl_2$ with $NaBH_4$ begins to decompose at 100 °C, when heated in vacuo, with the liberation of hydrogen (Maybury, P. C.; Mitchell, R. W.; Hawthorne, M. F. *CC* **1974**, 534).
12. Schlesinger, H. I.; Brown, H. C.; Finholt, A. E.; Gilbreath, J. R.; Hoekstra, H. R.; Hyde, E. K. *JACS* **1953**, *75*, 215.
13. A boride of the same composition had been previously described (Stock, A.; Kuss, E. *CB* **1914**, *47*, 810; *CA* **1914**, *8*, 2129).
14. Satyanarayana, M.; Periasamy, M. *JOM* **1987**, *319*, 113.
15. Paul, R.; Buisson, P.; Joseph, N. *CR(C)* **1951**, *232*, 627 (*CA* **1951**, *45*, 10 436h).
16. Brown, H. C.; Brown, C. *JACS* **1962**, *84*, 1493.
17. Satyanarayana, M.; Periasamy, M. *TL* **1984**, *25*, 2501.
18. Heinzman, S.; Ganem, B. *JACS* **1982**, *104*, 6801.
19. Nose, A.; Kudo, T. *CPB* **1990**, *38*, 1720.
20. Iwata, C.; Takemoto, Y.; Kubota, T.; Imanishi, T. *TL* **1985**, *26*, 3231.
21. Satoh, T.; Nanba, K.; Suzuki, S. *CPB* **1971**, *19*, 817.
22. Satoh, D.; Hashimoto, T. *CPB* **1976**, *24*, 1950.
23. Bracchini, B.; Adams, E. W.; Eagan, L. A.; Murtiashaw, M. *J. Labelled Comp. Radiopharm.* **1992**, *31*, 384. Note: when $NaBT_4$ was used the chemical yield was 49% with a radiochemical purity of 89%.
24. Ihara, M.; Tokunaga, Y.; Fukumoto, K. *JOC* **1990**, *55*, 4497.
25. Nishio, T.; Omote, Y. *JCS(P1)* **1981**, 934.
26. Leutenegger, U.; Madin, A.; Pfaltz, A. *AG(E)* **1989**, *28*, 60. Note: it is not known whether this reaction involves a boride intermediate or not.
27. (a) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, S.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *JACS* **1987**, *109*, 1596. (b) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *JOC* **1987**, *52*, 3174.
28. (a) Ding, Y. S.; Antoni, G.; Fowler, J. S.; Wolf, A. P.; Langstrom, B.; *J. Labelled Comp. Radiopharm.* **1989**, *27*, 1079. (b) Antoni, G.; Langstrom, B.; *J. Labelled Comp. Radiopharm.* **1989**, *27*, 571.
29. Nose, A.; Kudo, T. *CPB* **1989**, *37*, 808.
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Cobalt(II) Acetate

$Co(OAc)_2.4H_2O$

[6147-53-1] · $C_4H_{14}CoO_8$ · Cobalt(II) Acetate · (MW 249.08)

(mediator of C-C bond formations,[1-5] functional group transformations,[6,7] oxidations,[8-14] reductions and carbonylations[15-17])

Physical Data: loses $4H_2O$ at 140 °C; *d* 1.705 g cm^{-3}.

Solubility: sol acid, alcohol, cold and hot water.

Form Supplied in: red-violet monoclinic crystals; widely available.

Analysis of Reagent Purity: red $Co(OAc)_2.4H_2O$ can be crystallized from solutions of cobalt bases in acetic acid. It can be dehydrated by heating at 100-120 °C for 12-15 h under vacuum.

Handling, Storage, and Precautions: anhydrous $Co(OAc)_2$ can be handled under a N_2 atmosphere for strict anhydrous conditions and must be stored in the absence of moisture; i.e. bottles flushed with N_2 in a desiccator. It is hygroscopic and an irritant. This reagent should be handled in a fume hood.

Introduction.

Cobalt diacetate has been proven to be a useful reagent for several synthetic transformations. It is generally employed with another reagent for applications.

Carbon-Carbon Bond Forming Reactions.

Cobalt(II) acetate-promoted addition of methyl acetoacetate to terminal alkenes gives substituted tetrahydrofurans (eq 1) in a highly stereoselective manner in the presence of atmospheric oxygen in acetic acid.[1] Michael addition reactions have been found to proceed in the presence of a $Co(OAc)_2$-2,2´-bipyridine complex in DMF at room temperature without any dimerization products.[2] α,β-Unsaturated ketones, methyl acrylate, and acrylonitrile react with nitromethane, malononitrile, and aniline at room temperature under neutral

conditions to afford addition products.

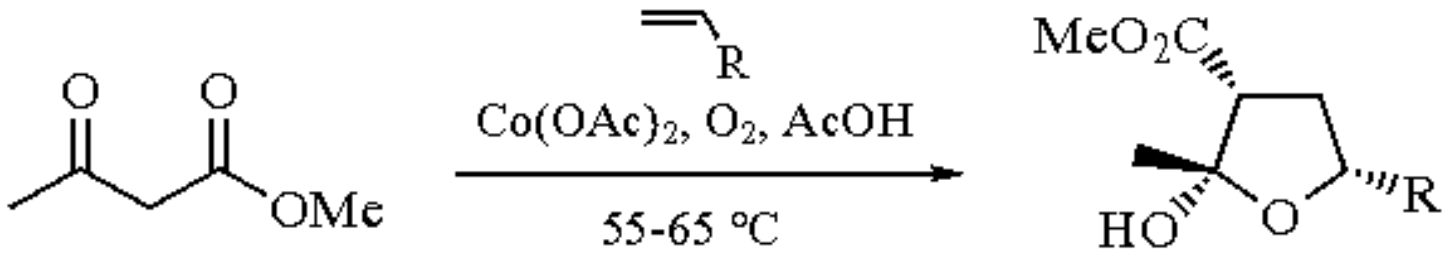

(1)

Cobalt(II) acetate also catalyzes the conversion of methyl formate into acetic acid (eq 2)[3] and aldol condensation of aldehydes and ketones in combination with 4-vinylpyridine-styrene-divinylbenzene copolymer (eq 3).[4]

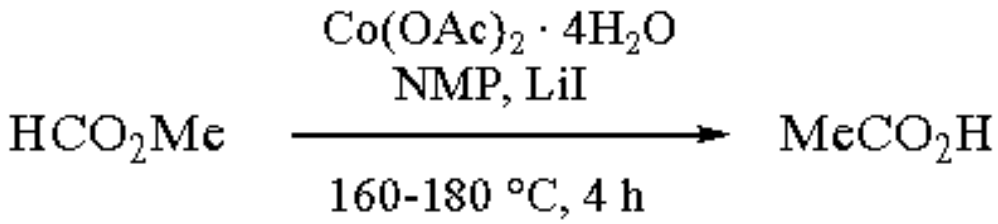

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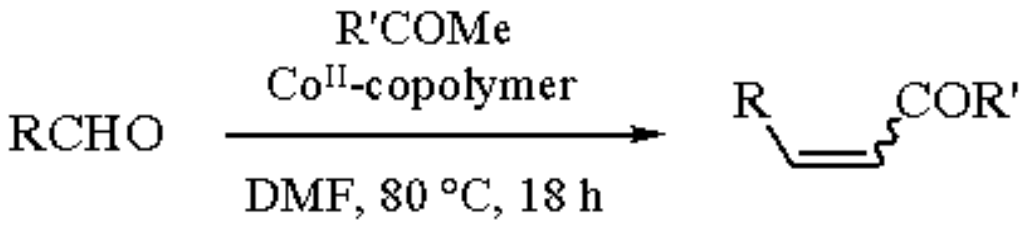

(3)

The reagent generated from $Co(OAc)_2$-***Sodium Hydride***-sodium *t*-pentoxide is useful for the synthesis of biaryls from aryl bromides.[5]

Functional Group Transformations.

Cobalt(II) acetate catalyzes dehydration of carboxamides and aldoximes to nitriles.[6] Under phase transfer conditions, cobalt(II) acetate is a useful catalyst for the preparation of diacetate from dibromo compounds (eq 4).[7]

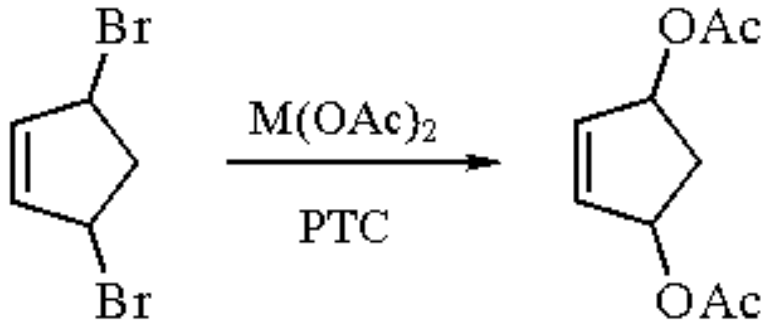

(4)

Oxidations.

Cobalt(II) acetate, in the presence of ***Nickel(II) Acetate***, in MeOH and EtOH oxidizes benzoin to benzil.[8] Under aerobic conditions, cobalt(II) acetate gives dihydrofurans with methyl acetoacetate and terminal alkenes.[9] Cobalt(II) acetate is one among the various metal catalysts useful for the metal catalyzed oxidation of tetralenes to α-tetralones in the presence of *N*,*N*-dialkylamides.[10] In the presence of the $Co(OAc)_2$-$Mn(OAc)_2$-NaBr system and molecular oxygen, dimethylpyrazoles can be oxidized to corresponding acids (eq 5).[11] Cobalt(II) acetate, along with ***t-Butyl Hydroperoxide*** and ***Iodosylbenzene*** as prototypical terminal oxidants, in the presence of certain ligands oxidizes alkenes to epoxides (eq 6).[12]

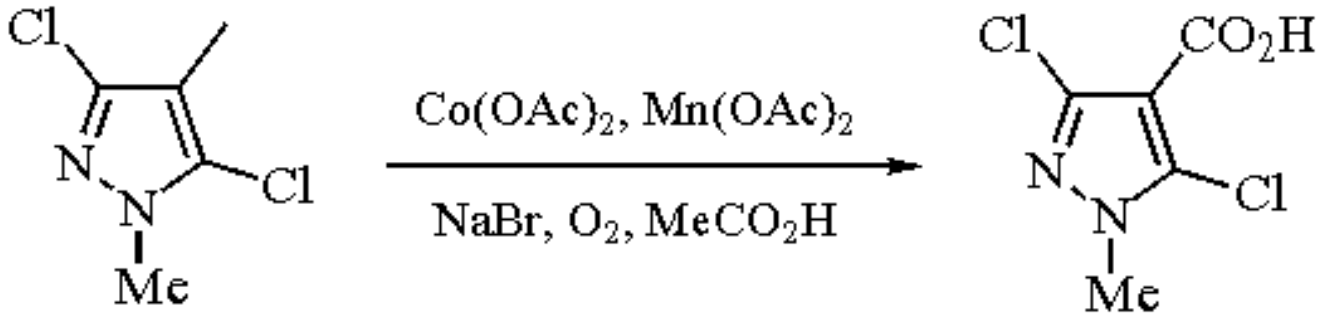

(5)

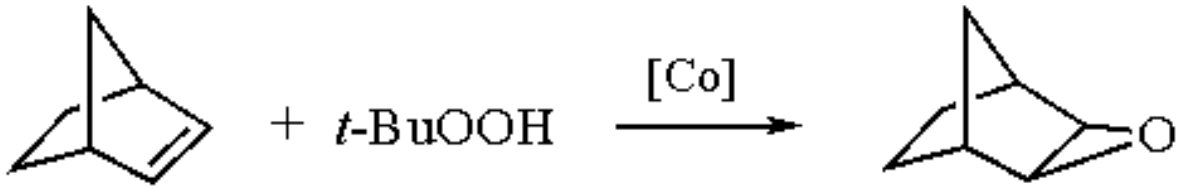

(6)

Cobalt(II) acetate oxidizes alkyltoluenes in the presence of oxygen (eq 7).[13] The reaction involves continuous conversion of Co^{II} to Co^{III} promoted by methyl ethyl ketone. The relative ease of oxidation of alkyl groups is methyl > ethyl > isopropyl > *s*-butyl.

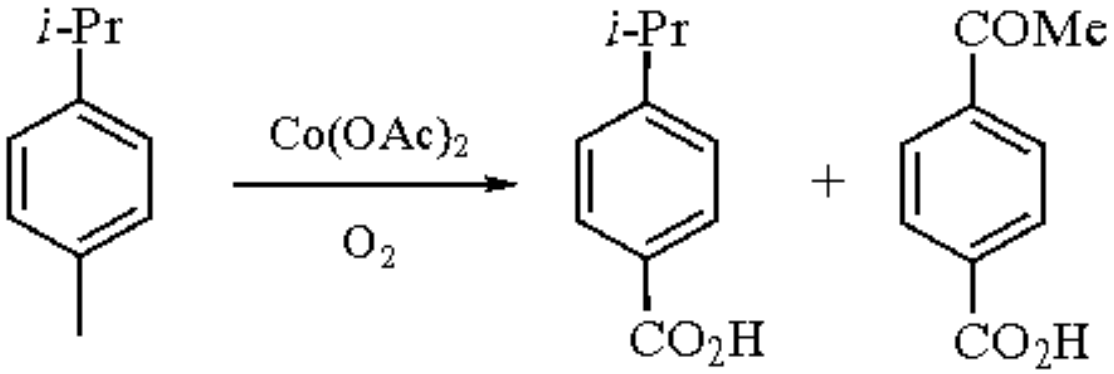

(7)

The oxidation of primary and secondary aromatic alcohols to aldehydes and ketones, respectively, can be achieved with ***Peracetic Acid*** catalyzed by $Co(OAc)_2$ and ***Sodium Bromide***.[14]

Reductions and Carbonylations.

Complex reducing agents prepared from $Co(OAc)_2$/NaH/*t*-$C_5H_{11}ONa$ reduce organic halides,[15] and *gem*-dihalogenocyclopropyl compounds to monohalogeno derivatives.[16] The reagent system is also useful for carbonylations of organic halides (eq 8).[17]

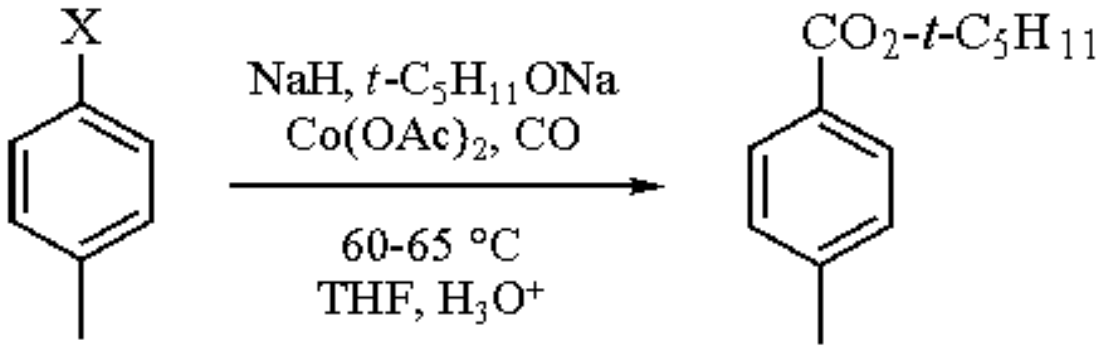

(8)

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Cobalt(II) Chloride

$CoCl_2$

[7646-79-9] · Cl_2Co · Cobalt(II) Chloride · (MW 129.84)

(catalyst for functional group transformations,[1-13] C-C bond formations,[8,12,14-17] oxidations and reductions,[18-27] carbonylations[28,29])

Physical Data: mp 86 °C; loses $6H_2O$ at 110 °C; *d* 3.356 g cm^{-3}.

Solubility: sol alcohol, acetone, ether, cold and hot water.

Form Supplied in: hexahydrate as orange-pink crystals; widely available.

Analysis of Reagent Purity: with alkali, the pink hexaaquacobalt(II) chloride gives a pale blue precipitate of the hydroxide. With excess ammonia this precipitate dissolves and slowly gives a brown solution through oxidation. At room temperature, the orange-pink hexahydrate crystallizes from aq solutions. Anhydrous cobalt chloride is blue in color. It can be prepared by dehydration of the hexahydrate either at 150-160 °C in vacuo or by treatment with thionyl chloride followed by evaporation of the solution and further drying under vacuum at 150 °C for 1 h.

Handling, Storage, and Precautions: anhydrous cobalt chloride should be handled under a N_2 atmosphere for strict anhydrous conditions. It should be stored in the absence of moisture, in bottles flushed with N_2 in a desiccator for a reasonable period of time. It is toxic and is an irritant. This reagent should be handled in a fume hood.

Introduction.

Cobalt chloride is a useful reagent on its own or in combination with other reagents. Several interesting transformations utilizing cobalt chloride have been reported in recent years.

Functional Group Transformations.

Anhydrous $CoCl_2$ in dry acetonitrile catalyzes several interesting transformations such as cleavage of ethers by acyl chlorides to give esters,[1] acylation of alcohols and amines by anhydrides,[2] regioselective cleavage of oxiranes with ***Chlorotrimethylsilane***,[3] acyl chlorides (eq 1),[4] anilines,[5] and benzenethiols.[6] It also catalyzes addition reactions of

alcohols with vinyl ethers to give mixed acetals,[7] and the reaction of trimethylsilyl cyanides and acetals or orthoesters to give α-cyano derivatives.[8]

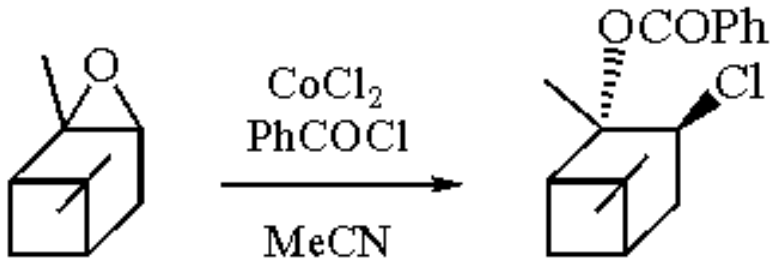

(1)

$CoCl_2$ is also useful for dealkylation of tertiary amines,[9] in the synthesis of acid anhydrides from acid chlorides,[10] and for thionation of carbonyl compounds in the presence of ***Bis(trimethylsilyl) Sulfide***, providing a simple access to thioketones and thioaldehydes.[11]

Cobalt hydrides, generated from $CoCl_2$-***Sodium Borohydride-Triphenylphosphine*** in a 1:1:4 ratio, hydrodimerize terminal alkynes to the corresponding *trans,trans*-1,3-dienes (eq 2).[12] This reagent system is also useful for selective isomerization of certain alkenes.[13]

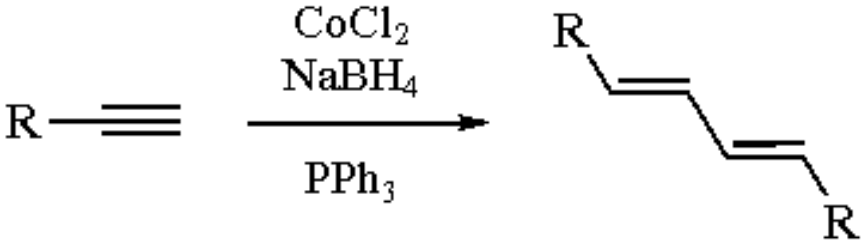

(2)

Carbon-Carbon Bond Forming Reactions.

A catalytic amount of anhydrous $CoCl_2$ in dry acetonitrile is a very useful reagent for condensation reactions involving active methylene compounds (eqs 3 and 4).[14-16]

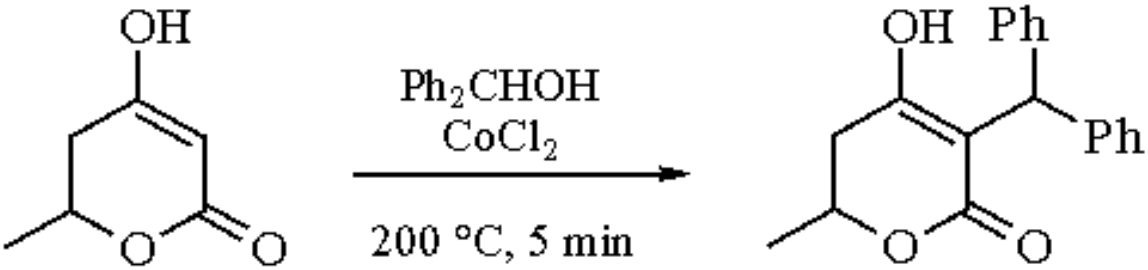

(3)

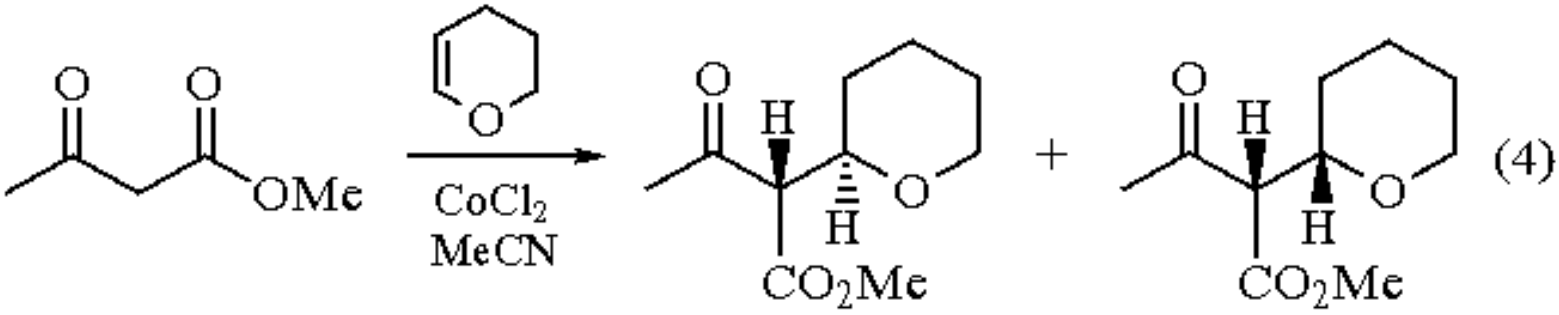

Anhydrous $CoCl_2$ also catalyzes the asymmetric cyclopropanation of fumarates with ***Dibromomethane***.[17]

Oxidations.

Anhydrous $CoCl_2$ catalyzes the oxidation of a variety of aromatic and aliphatic aldehydes to carboxylic acids in the presence of molecular ***Oxygen*** and ***Acetic Anhydride*** at room temperature.[18] The $CoCl_2/O_2$ system in 1,2-dimethoxyethane gives lactones from ethers,[19] and in diglyme it is an effective system for benzylic group oxidation.[20]

Reductions.

The combination of anhydrous $CoCl_2$ and complex metal hydrides gives useful reagent systems for deoxygenation of allylic alcohols to alkenes,[21] hydroboration or hydrogenation of alkenes,[22] and reduction of imines to amines[23] and organic halides.[24] Reduction of β-sulfenylated unsaturated ketones with $NaBH_4$ in the presence of $CoCl_2$ gives saturated ketones.[25] Both aliphatic and aromatic sulfoxides are readily deoxygenated with $CoCl_2.6H_2O/NaBH_4/EtOH$ under a nitrogen atmosphere.[26] The same recipe is also useful for the selective reduction of certain disubstituted alkenes (eq 5).[27]

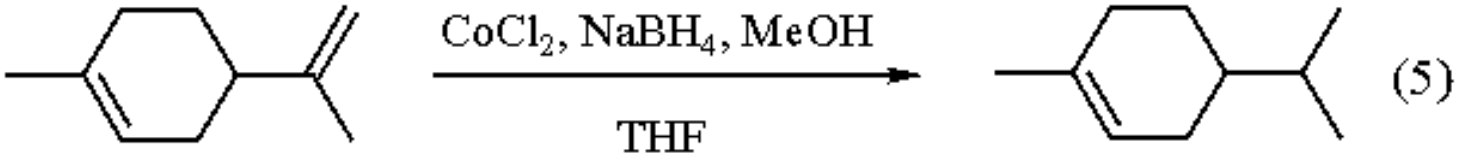

Carbonylations.

Reduction of anhydrous $CoCl_2$ by $NaBH_4$ in THF under a ***Carbon Monoxide*** atmosphere followed by aqueous NaOH treatment gives ***Sodium Tetracarbonylcobaltate***, which is useful for in situ carbonylations of benzyl halides.[22b] Reduction of anhydrous $CoCl_2$ with ***Zinc*** in THF in the presence of alkynes while bubbling CO gives alkyne-$Co_2(CO)_6$ complexes (eq 6) which are useful synthetic intermediates[28] (e.g. Pauson-Khand cyclopentenone synthesis).

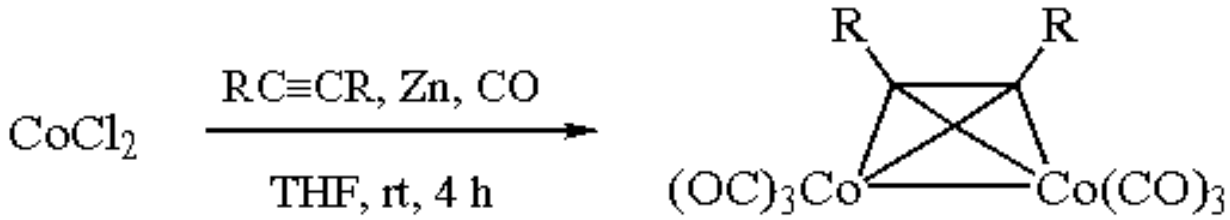

(6)

The $CoCl_2.6H_2O$ reagent, under phase transfer conditions, gives reductive hydroxycarbonylations of *gem*-dibromocyclopropanes.[29]

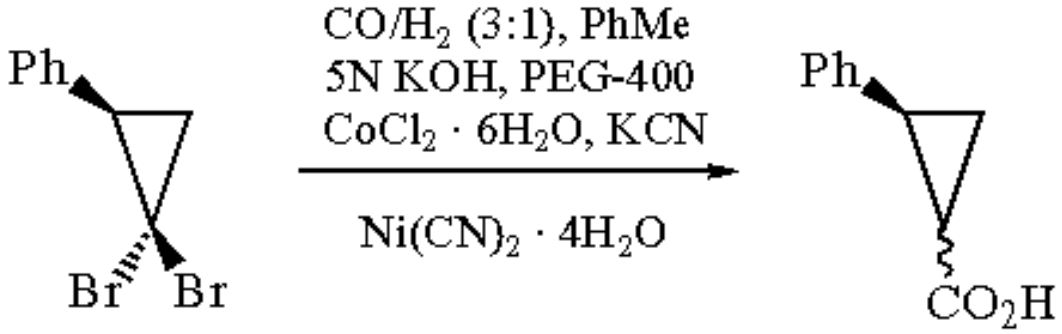

(7)

Related Reagents.

Lithium Aluminum Hydride-Cobalt(II) Chloride; ***Octacarbonyldicobalt***; ***Sodium Tetracarbonylcobaltate***.

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Cobalt(III) Fluoride[1]

CoF_3

[10026-18-3] · CoF_3 · Cobalt(III) Fluoride · (MW 115.94)

(powerful Lewis acid, used almost exclusively for fluorination of organic compounds in a solid-vapour phase reaction)

Physical Data: mp unknown; *d* 3.88 g cm^{-3}.

Solubility: reacts violently with water and hydroxylic solvents; insol almost all solvents at room temperature.

Form Supplied in: buff/brown powder when freshly prepared; rapidly darkens in moist air. Not commercially available.

Preparative Methods: cobalt(III) fluoride is normally prepared by reaction of cobalt(II) fluoride with elemental ***Fluorine*** at 200-300 °C in a stirred reactor usually constructed of copper or nickel and is then reacted with organic substrates at 100-500 °C.[1]

Handling, Storage, and Precautions: normally prepared and used in situ immediately after preparation. Can be stored in sealed vessels under dry nitrogen. Must be handled with caution since it readily releases hydrogen fluoride in contact with air. This reagent should be handled in a fume hood.

General Considerations.

The use of cobalt(III) fluoride as a fluorinating agent was suggested in 1929 by Ruff,[2] but it was not until the work on the so-called Manhattan project concerned with the development of atomic weapons in the 1940s by Fowler[3] that it came to prominence as a powerful reagent for the preparation of highly fluorinated compounds.

Much of the further development of this reagent was carried out at the University of Birmingham by Tatlow and his group over the period between 1950 and 1980 and subsequently on an industrial scale by the RTZ group at Avonmouth, Bristol.

The degree of fluorination obtained with this reagent depends very largely on the reaction temperature and to a lesser extent on the substrate structure. Thus at temperatures in excess of 400 °C, most of the hydrogen is replaced by fluorine, all double bonds including aromatic unsaturation are saturated, and functional groups are destroyed. At lower temperatures, hydrogen atoms are retained and some functional groups remain in the molecules. These general principles are exemplified in the specific reactions discussed below.

Fluorination of Hydrocarbons.

Synthesis of Perfluorocarbons.

Much of the earlier work, particularly that associated with the atomic energy project, was concerned with the preparation of perfluorocarbons used as oils and greases in the diffusion process for the separation of uranium isotopes. A wide range of open chain aliphatic compounds ranging from butane to dodecane have thus been perfluorinated.[4,5] Much of this work was carried out before the advent of modern analytical techniques and it was assumed that there was no isomerization of the hydrocarbon chain. Recent results[6] indicate that this is not so and the degree of isomerization increases with increasing chain length. After a period of inactivity, there was a resurgence of interest in this area with the identification of perfluoro compounds as blood substitutes, evaporative coolants, and as potential chlorofluorocarbon replacements. This work was largely pioneered by the RTZ (now Rhône-Poulenc) group. Two kinds of reactors have been used: for small scale work, horizontal stirred reactors of the type described by Tatlow[7] are employed, but the industrial scale reactors are largely of a fluidized-bed type. By this kind of fluorination a large number of alicyclic perfluorocarbons have been produced and have been marketed for the range of uses indicated above. The types of material produced are exemplified in Scheme 1.

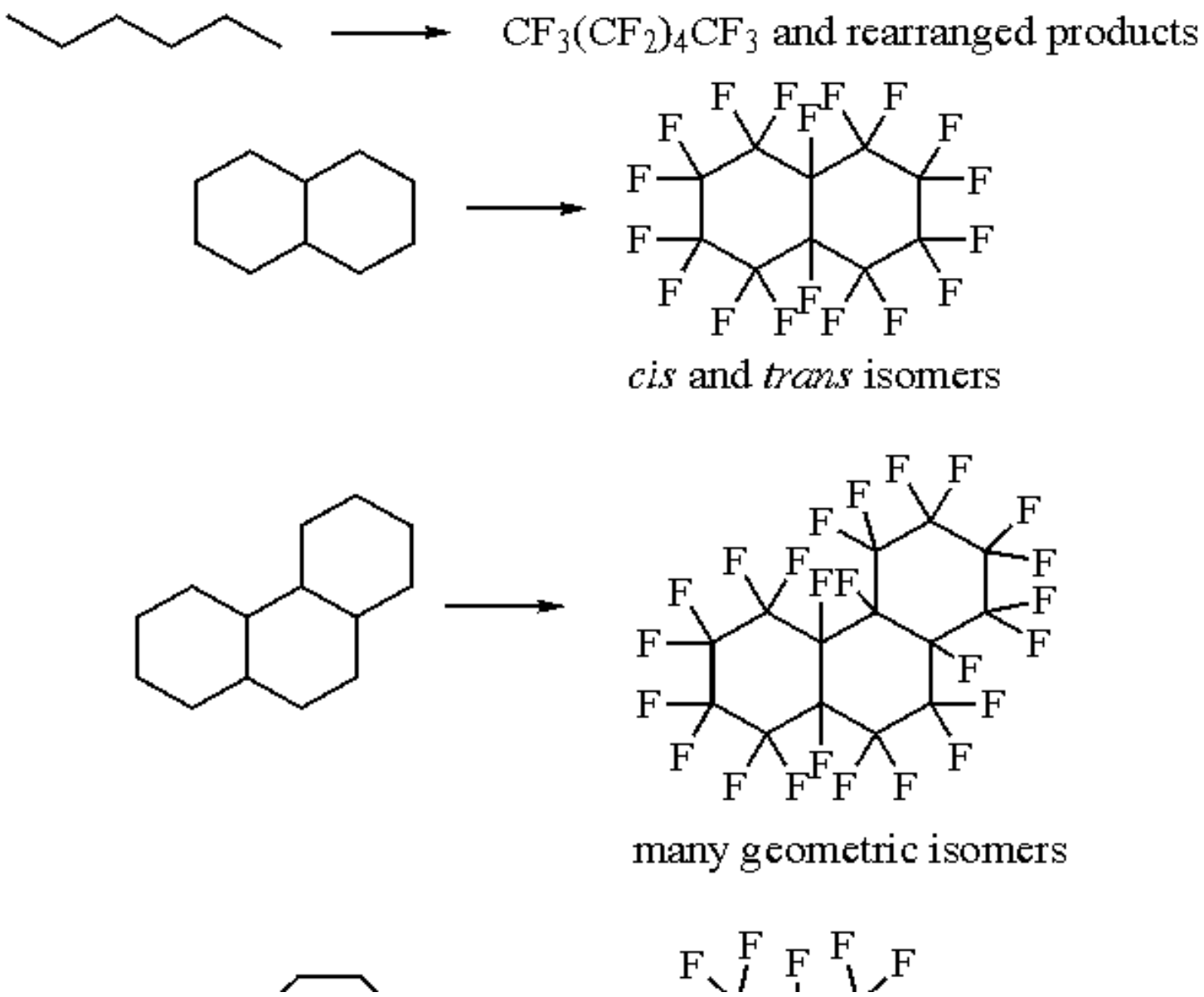

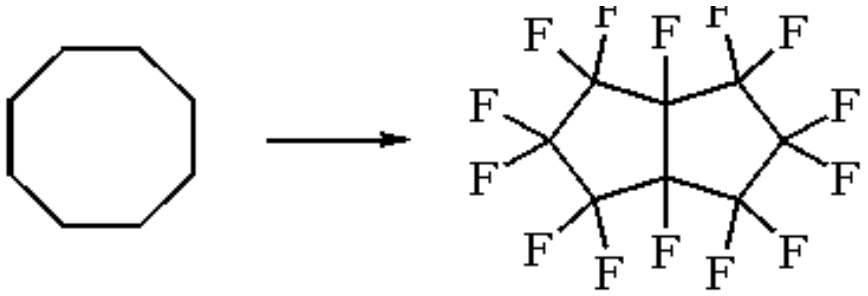

Scheme 1 Examples of the fluorination of hydrocarbons with CoF_3 between 150 and 300 °C

Synthesis of Fluorohydrocarbons.

An important aspect of cobalt trifluoride chemistry has been the partial fluorination of a considerable number of substrates of varying structure, ranging from hydrocarbons through to heterocycles and ethers. In all of these fluorinations, mixtures of different levels of complexity, depending on the substrate, are obtained. As well as regioisomers, the products may also be stereoisomers. This pattern is exemplified in Scheme 2 for the fluorination of benzene at temperatures between 150 and 200 °C, much lower than those used for complete fluorination.

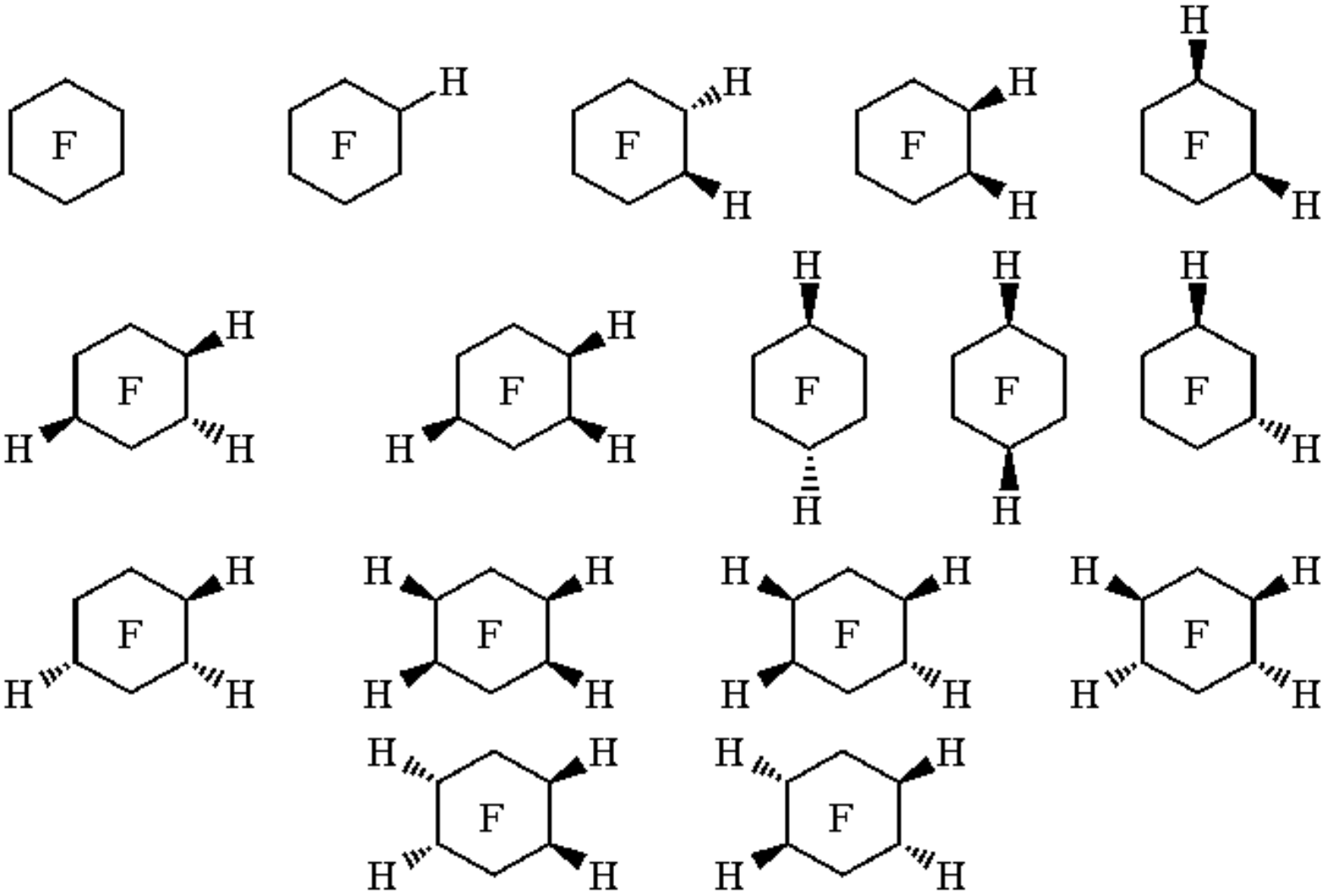

Scheme 2 Major (>1%) compounds formed in the cobalt trifluoride fluorination of benzene; unmarked bonds are joined to fluorine

Scheme 2 Major (> 1%) compounds formed in the cobalt trifluoride fluorination of benzene; unmarked bonds are joined to fluorine

This kind of pattern is repeated for other cyclic systems including cyclopentane,[8] cycloheptane,[9] norbornane,[10] and decalin[11]. Attempts at fluorination of cyclooctane and higher homologs result in very complex mixtures, including rearrangement products containing bicyclic systems.[12] The fluorination of bicyclo[2.2.2]octane or adamantane[13] result, somewhat surprisingly, in largely rearranged products. These rearrangements can readily be diminished or even prevented by the fluorination of analogs containing relatively small amounts of fluorine.[12]

Fluorination of Heterocycles.

A large range of heterocycles have been fluorinated including tetrahydrofuran and its alkyl and fluoroalkyl derivatives,[14] thiophene,[15] pyrrole and *N*-methylpyrrole,[16] and a number of quinoline and isoquinoline derivatives.[17] Attempts to fluorinate pyridine (unless there is already fluorine present) result in substantial degradation of the molecule.[18] These reactions lead to products which may be further elaborated to the corresponding aromatic compounds in some cases. The kinds of products which may be obtained are shown in Scheme 3.

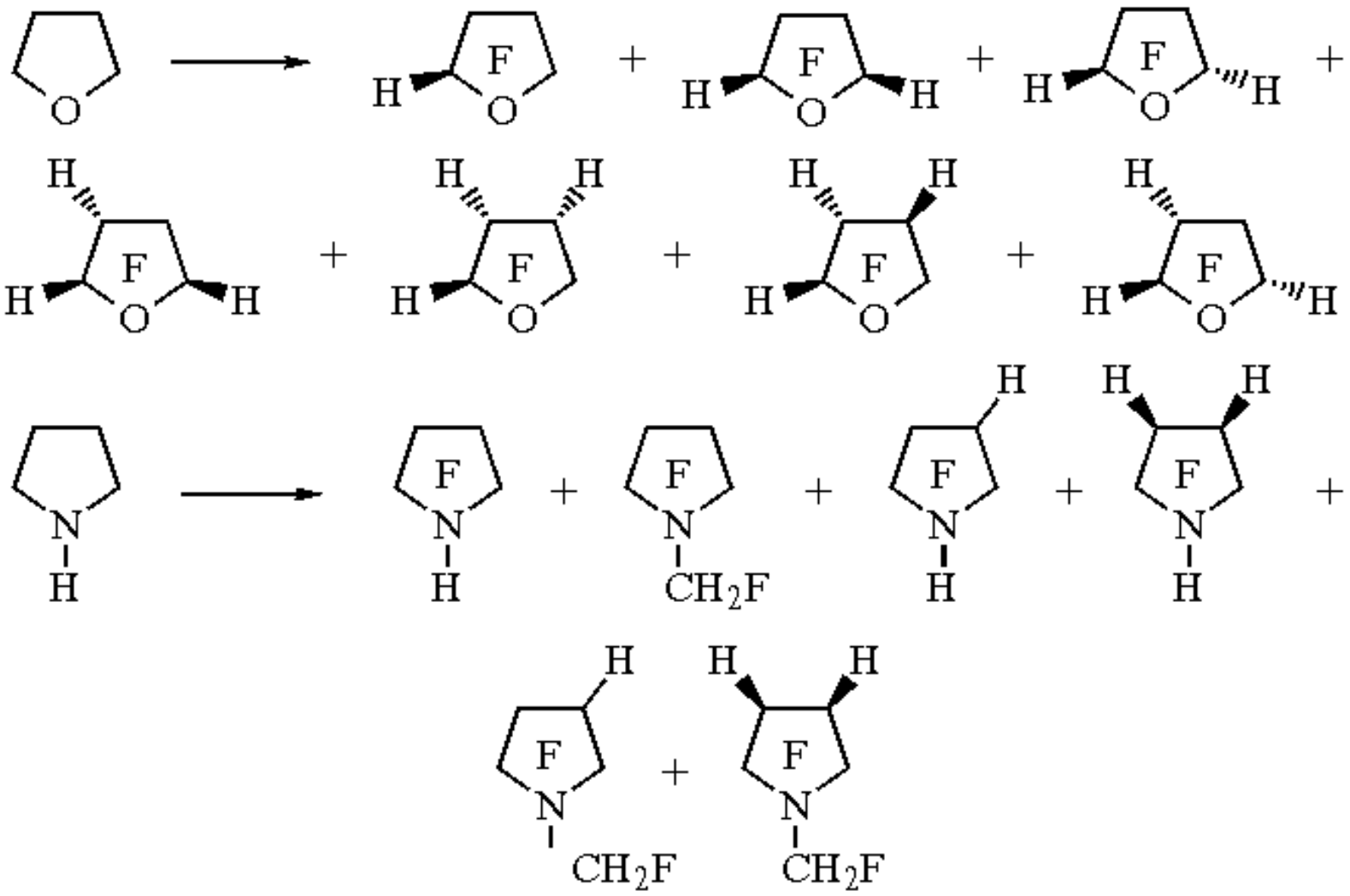

Scheme 3 Examples of the fluorination of heterocycles with cobalt trifluoride; all unmarked bonds in products are joined to fluorine

Fluorination of Ethers.

The fluorination of ethers has been of considerable interest in the anesthetic field and a number of ethers have been fluorinated to obtain products which have shown interesting activity as well as some interesting chemistry.[19] More recently, fluorination of partly fluorinated ethers has been studied as a potential route to CFC alternatives (Scheme 4).[20]

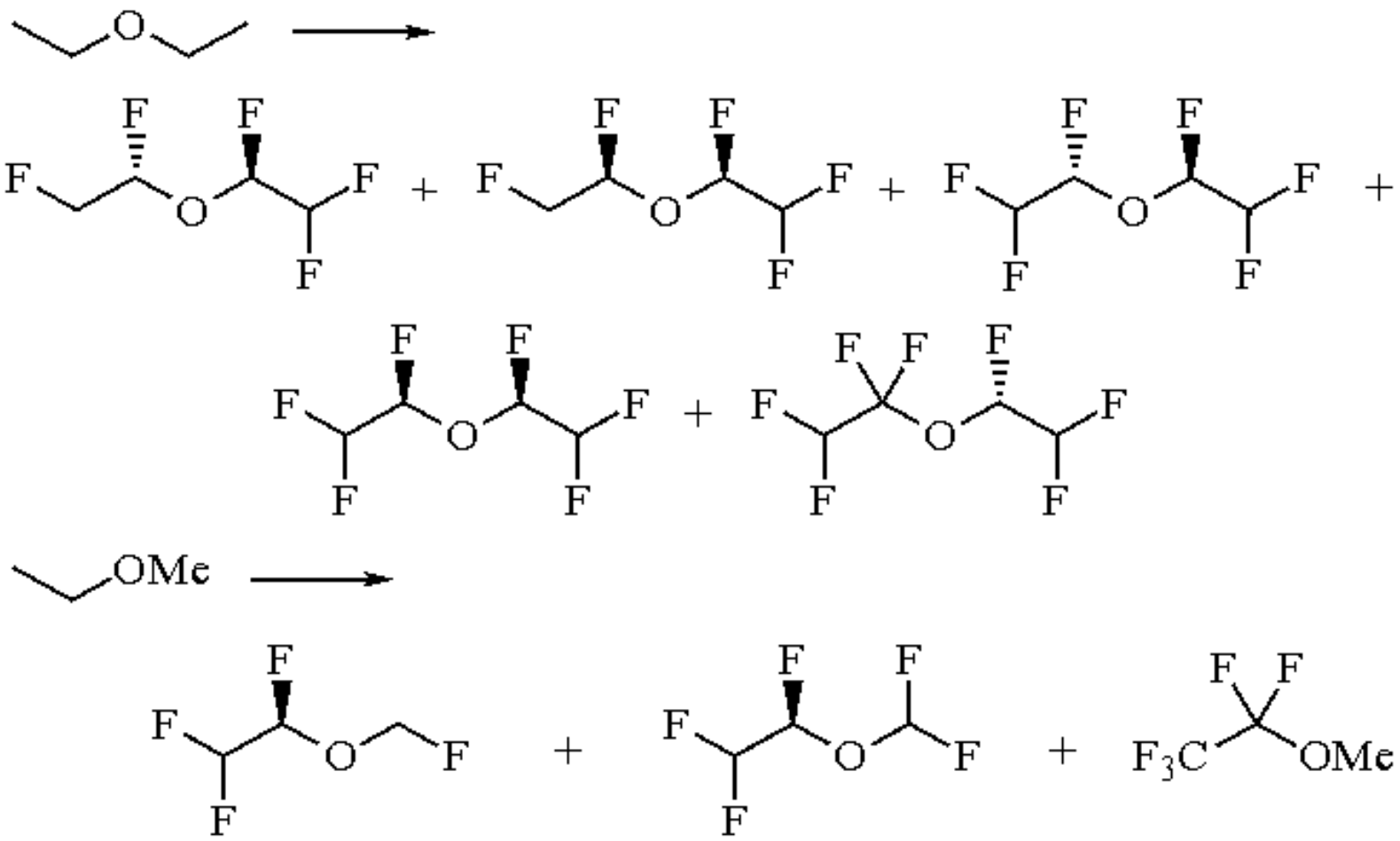

Scheme 4 Fluorination of ethers with cobalt trifluoride

Mechanistic Features.

An unusual feature of cobalt trifluoride fluorinations which produce partially fluorinated materials is that the fluorinations are not random and for any given substrate there is a distinct pattern as to the position of the residual hydrogen atoms; this can be seen from the benzene fluorination products and also from the ether fluorinations. These results have been elegantly explained by Burdon and Parsons in terms of oxidative processes[20] and so far their postulates have stood the test of time.

Conclusions.

It must be concluded that cobalt trifluoride, although being a very useful reagent for producing highly fluorinated

substances, is rather specialized and needs nonstandard equipment for its use. In particular it needs a source of elemental fluorine and to work efficiently needs to be run on a moderately large scale (5-25 kg of fluorinating agent).

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Cobalt Salen Complexes[1]

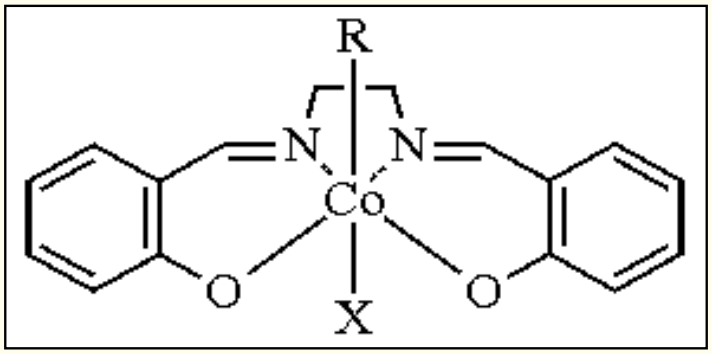

(X = Br, R = PPh_3)

[15603-80-2] · $C_{34}H_{29}BrCoN_2O_2P$ · Cobalt Salen Complexes · (MW 587.53)

(reagents for the generation of carbon centered radicals and vitamin B_{12} mimics)

Physical Data: dark brown-black solids; usually stable up to 200 °C.

Solubility: sol most organic solvents, e.g. benzene, THF, dichloromethane; also partially sol H_2O.

Preparative Methods: RCo^{III}(salen) complexes have been prepared in the same manner as the corresponding RCo^{III}(salophen) and $RCo^{III}(dmgH)_2$ complexes, and they undergo similar reactions (see also ***Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)*** and ***Cobalt Salophen Complexes***). The formation of RCo^{III}(salen) complexes can be accomplished by reacting Co^{I}(salen) complexes, Co^{II}(salen) complexes, or Co^{III}(salen) complexes with electrophiles, radicals, and nucleophiles, respectively.[1] $NaCo^{I}$(salen) can be prepared by reduction of the $BrCo^{III}$(salen)PPh_3 complex[2] using sodium, metal amalgams,[3] $NaBH_4$/cat $Pd^{II}Cl_2$,[4] or electrochemically.[5] The supernucleophilic $NaCo^{I}$(salen) complex reacts with a variety of alkyl halides, vinyl halides, acyl halides,[3,5] and alkyl tosylates to form RCo^{III}(salen) species. Alkyl and vinyl RCo^{III}(salen) complexes can be prepared by the addition of $NaCo^{I}$(salen) to alkenes and alkynes, respectively.[1,3]

Handling, Storage, and Precautions: often light- and air-sensitive and should be stored in tinted bottles.

Reactions of $NaCo^{I}$(salen) with Aryl Halides.

$NaCo^{I}$(salen) complex has the advantage that it is more nucleophilic than $NaCo^{I}(dmgH)_2$, particularly in reactions with aryl iodides. Reactions of $NaCo^{I}$(salen) with aryl halides initially give the corresponding aryl radical via a single-

electron transfer process (see ***Cobalt Salophen Complexes***). These radicals can add either intramolecularly or intermolecularly to alkenes and alkynes (eq 1).[5b,6] The new carbon radical formed from these additions is then trapped by the Co^{II}(salen) formed in situ to form either alkyl or vinyl RCo^{III}(salen) complexes, respectively.

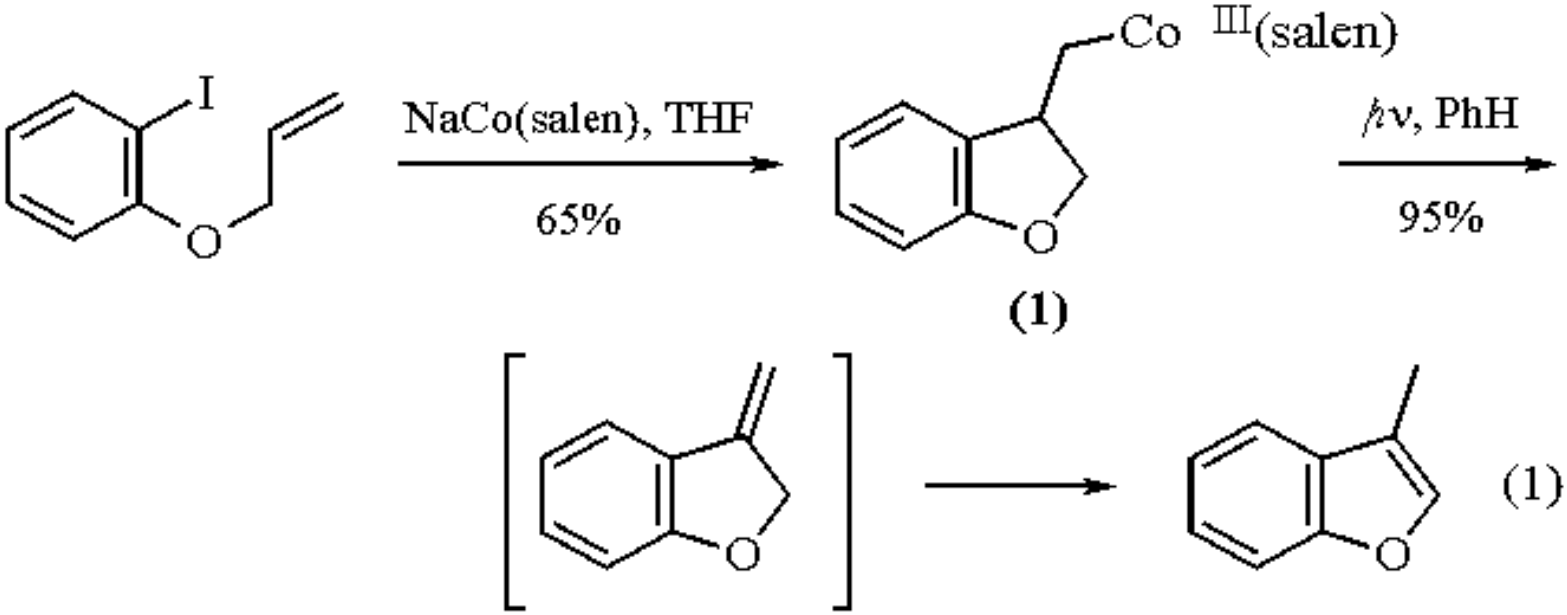

Reactions of RCo^{III}(salen) Complexes.

Owing to the weak nature of the Co^{III}-carbon bond (18-25 kcal mol^{-1}),[7] photolysis or thermolysis leads to homolytic cleavage and the formation of carbon-centered radicals. In practice, RCo^{III}(salen) complexes often undergo β-elimination to give alkenes unless the initially formed radical is allowed to react with an added radical trap (eq 1) (see also ***Cobalt Salophen Complexes***).[5b,6] In the presence of oxygen, alkylperoxy Co^{III}(salen) complexes ($ROOCo^{III}$(salen)) result, which can then be reduced with ***Sodium Borohydride*** to give alcohols (eq 2),[5b] while thermolysis in the presence of $(PhS)_2$, SO_2, $(PhSe)_2$, NO, $MeSO_2Cl$, $BrCCl_3$, or I_2 gives the corresponding sulfur, selenium, nitrogen, or halogen functionalized products, respectively (eq 2).[1f] The combination of the reaction of $NaCo^{I}$(salen) with an aryl halide followed by radical cyclization and β-elimination of the resulting intermediate Co^{III}(salen) complex has been used in an approach to physovenine (eq 3).[8]

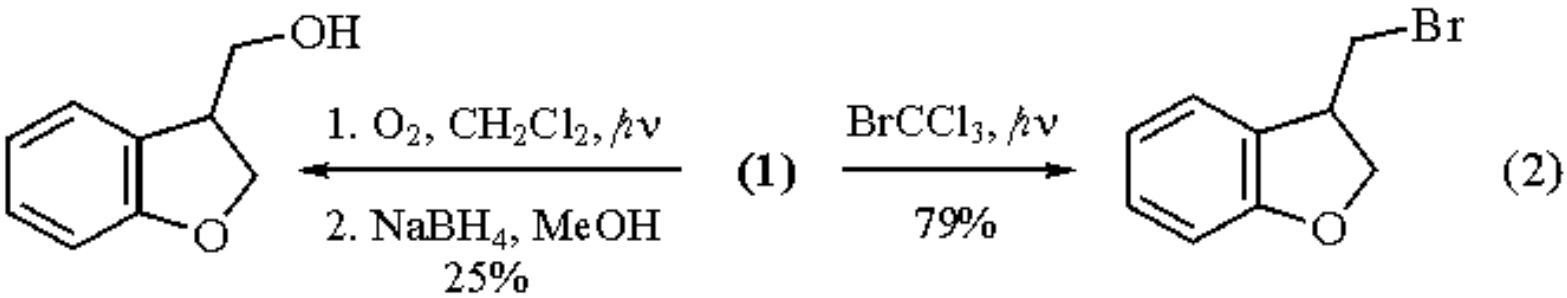

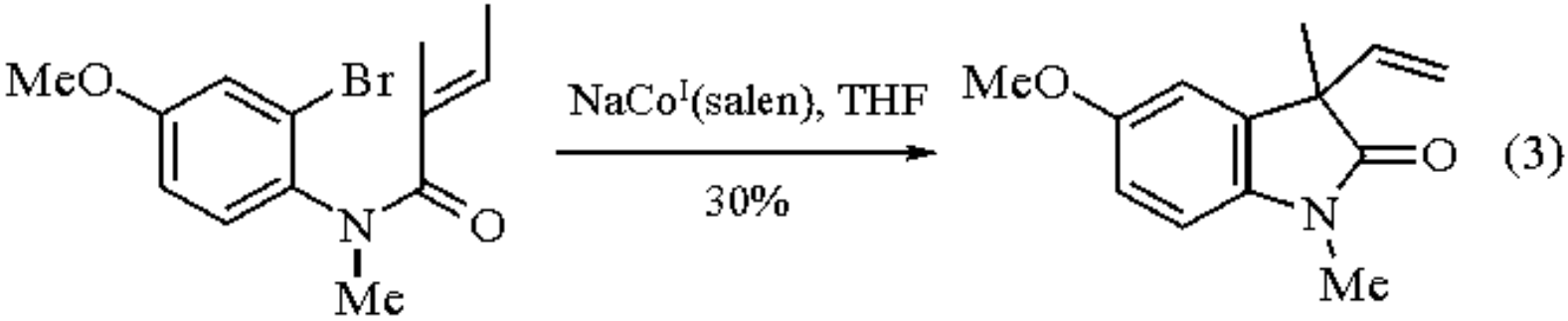

The oxidative radical cyclization process has the advantage over conventional reductive cyclization processes (see also ***Tri-n-butylstannane*** and ***Tris(trimethylsilyl)silane***) in that functionality is retained in the products.

Reactions of Co^{II}(salen).

Co^{II}(salen) catalyzes the oxidation of phenols to the corresponding *p*-benzoquinones or *p*-diphenoquinones in high yield (eq 4).[9] Oxidation in the presence of ***t-Butyl Hydroperoxide*** leads to *t*-butylhydroperoxyquinol ethers, and the reagent catalyzes the oxidation of 2,4,6-trisubstituted anilines to give either 4-*t*-butylperoxy-2,5-cyclohexadiene-1-imine or nitrobenzene derivatives, depending upon the nature of the substituents in the substrate.[10] Co^{II}(salen) also catalyzes the oxidation of alcohols and amines.[11]

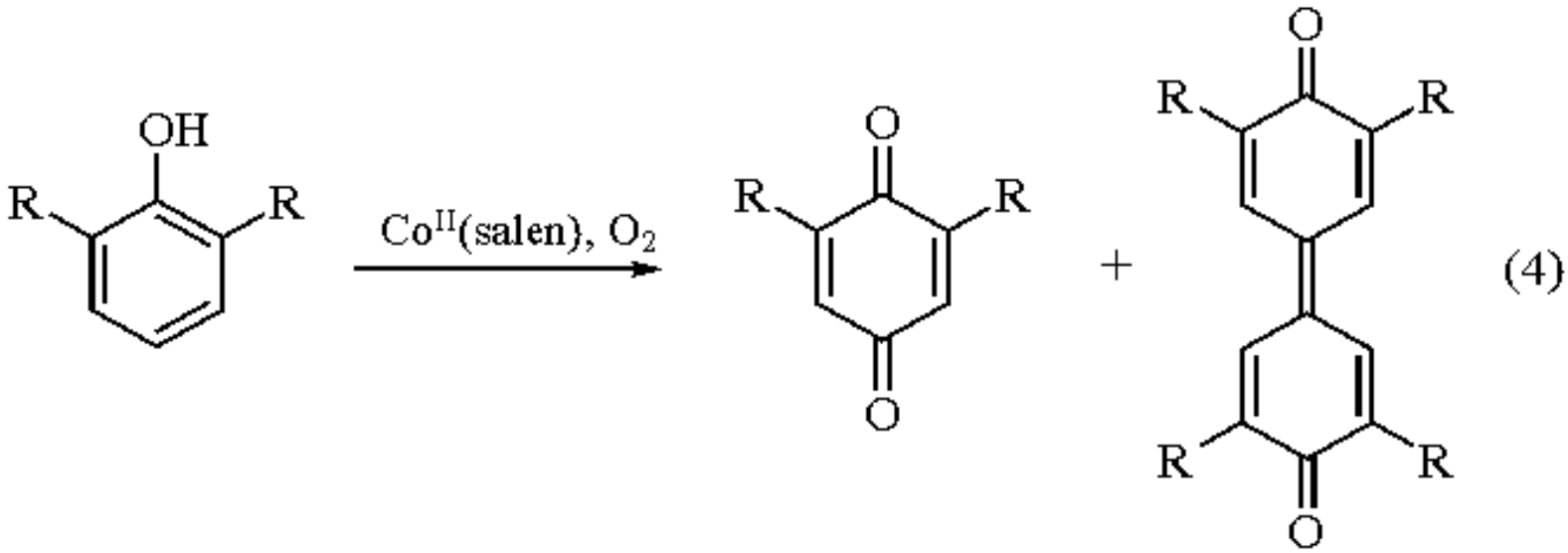

Related Reagents.

Salcomine.

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Cobalt Salophen Complexes[1]

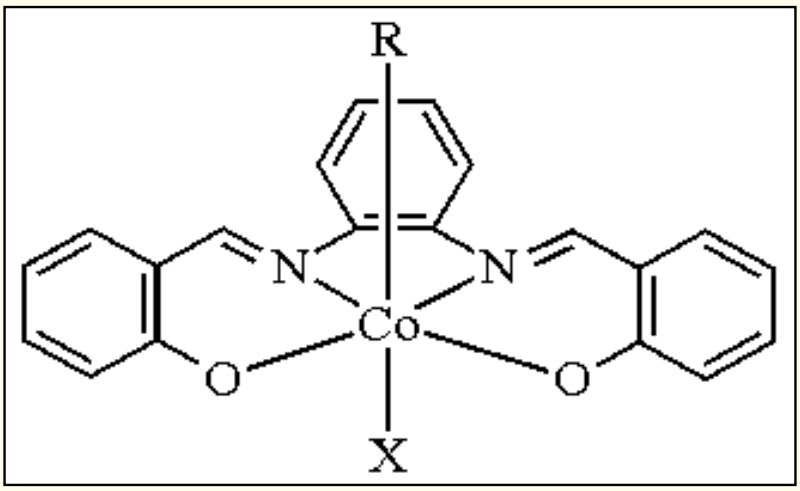

(R, X absent)

[17457-14-6] · $C_{20}H_{14}CoN_2O_2$ · Cobalt Salophen Complexes · (MW 373.29)

(reagents for the generation of carbon-centered radicals; vitamin B_{12} mimics[2])

Physical Data: dark brown-black solids; usually stable up to 200 °C.

Solubility: sol most organic solvents, e.g. benzene, methanol, THF, dichloromethane.

Preparative Methods: RCo^{III}(salophen) complexes have been prepared in the same manner as for the corresponding Co^{III}(salen) and $Co^{III}(dmgH)_2$ complexes, and they undergo similar reactions (see ***Bis(dimethylglyoximato)(methyl)(pyridine)cobalt(III)*** and ***Cobalt Salen Complexes***). The formation of organoCo^{III}(salophen) complexes can be accomplished by reacting Co^{I}(salophen) or Co^{II}(salophen) with electrophiles or radicals, respectively.[1] The supernucleophilic $NaCo^{I}$(salophen) complex reacts with a variety of alkyl halides[2] and acyl halides[3] to form RCo^{III}(salophen) species.

Handling, Storage, and Precautions: often light- and air-sensitive and should be stored in tinted bottles.

Reactions of Co^{I}(salophen) Complexes with Aryl Halides.

$NaCo^{I}$(salophen) has the advantage that it is generally more nucleophilic than $Co^{I}(dmgH)_2$ and Co^{I}(salen) complexes, particularly in reactions with aryl iodides. Reactions of Co^{I}(salophen) complexes with aryl halides do not lead to isolable $ArCo^{III}$(salophen) complexes. Instead, $NaCo^{I}$(salophen) initially gives the corresponding aryl radical via a

single-electron transfer process. For example, (**1**) reacts with Co^{I}(salophen) to give the corresponding aryl radical which then undergoes a smooth 5-*exo*-trig radical cyclization, followed by trapping with Co^{II}(salophen), to give the RCo^{III}(salophen) complex (**2**); photolysis of (**2**) in C_6H_6 leads to β-elimination of HCo^{III}(salophen) (eq 1).[4] Photolytic homolysis of (**2**) in the presence of styrene leads to a new alkene product resulting from radical addition to the C-C double bond in styrene, followed by β-elimination of HCo^{III}(salophen) (eq 2).[5] Radicals produced from photolysis of (**2**) have also been trapped with O_2, TEMPO, NO, SO_2, $(PhS)_2$, $(PhSe)_2$, $MeSO_2Cl$, $BrCl_3C$, and I_2, to give oxygen, nitrogen, sulfur, selenium, and halogen functionalized products, respectively (eq 2).[6]

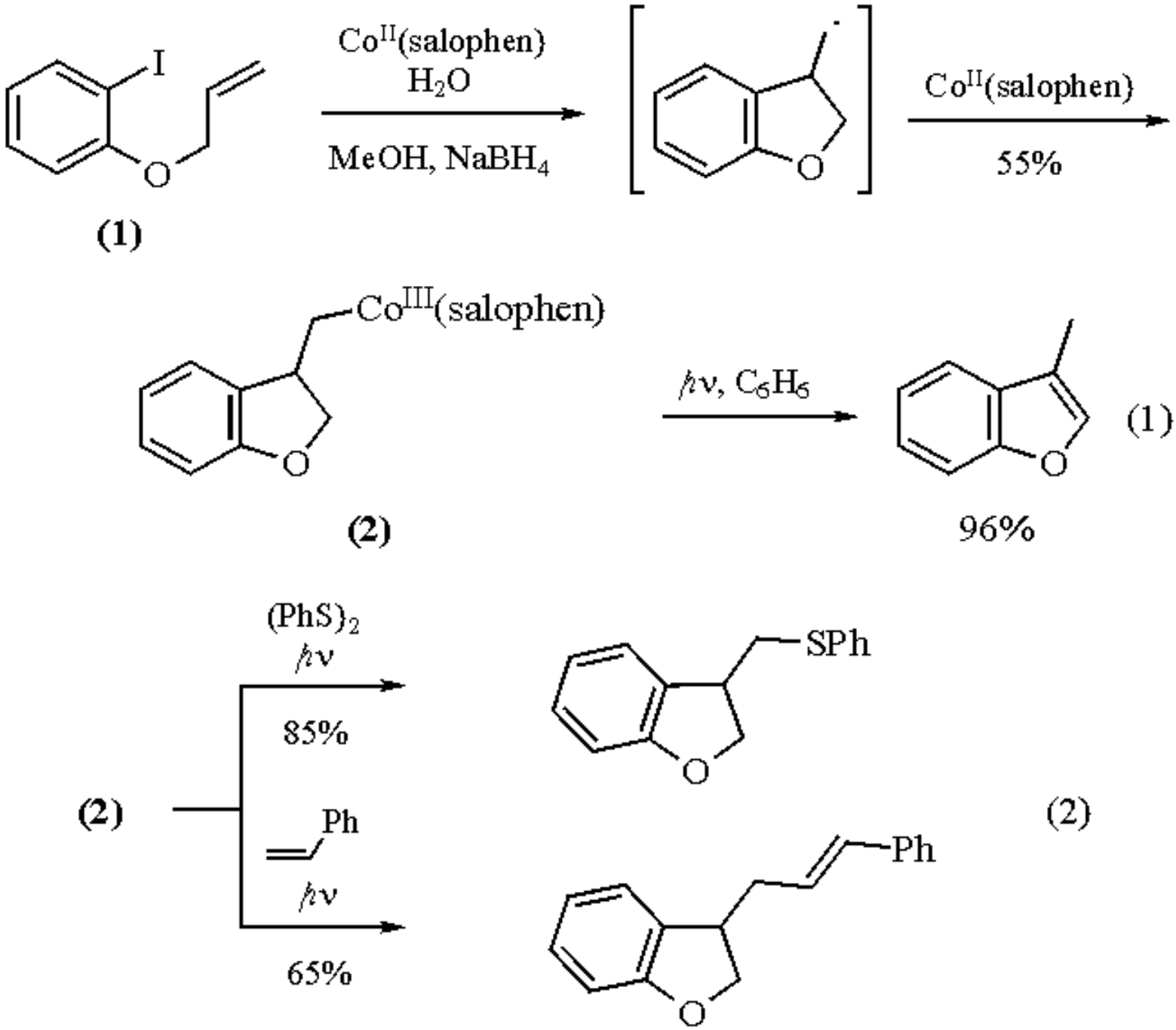

Reactions of AcylCo^{III}(salophen) Complexes.

AcylCo^{III}(salophen) species are conveniently prepared from acid chlorides, or the mixed acid anhydrides with 2,6-

dichlorobenzoic acid, following treatment with $NaCo^{I}$(salophen).[3] In this manner a range of primary, secondary, tertiary, vinyl, aryl, arylmethyl, oxy, and aminylacyl salophens, all of which are brightly colored, stable crystalline solids, have been prepared. Irradiation of deaerated, refluxing solutions of acylCo^{III}(salophen) complexes in methylene dichloride results in acyl carbon-cobalt bond homolysis to produce acyl radicals. These acyl radicals may add to activated alkenes intermolecularly in a Michael fashion (eq 3), or in an intramolecular manner leading to ring synthesis (eq 4).[7] The resulting product radicals are trapped by Co^{II}(salophen) to give RCo^{III}(salophen) complexes which undergo dehydrocobaltation leading to conjugated enones.[8] This method of generating acyl radicals has the advantage over conventional reductive methods for their preparation in that functionality is retained in the products (see ***Tri-n-butylstannane***). ArylmethylCo^{III}(salophen) and allylacylCo^{III}(salophen) complexes undergo carbon-cobalt bond homolysis and in situ decarbonylation, producing new alkyl radical centers which can be intercepted with oxygen, nitrogen, halogen, sulfur, and selenium containing radical trapping agents, leading to functionalized nor-alkanes (eq 5).[3] The sequence constitutes a useful, and in some cases more flexible, variant of the classical Hundsdiecker reaction, and amounts to the cobalt equivalent of the Barton radical decarboxylation reaction of carboxylic acids via their corresponding thiohydroxamic acids.[9] *N*-AllylcarbamoylCo^{III}(salophen) complexes undergo efficient 4-*exo*-trig oxidative cyclization giving rise to β-lactams; this procedure has provided a new approach to the antibiotic substance thienamycin.[10] A range of γ- and δ-lactams is available by this chemistry (eq 6).[11]

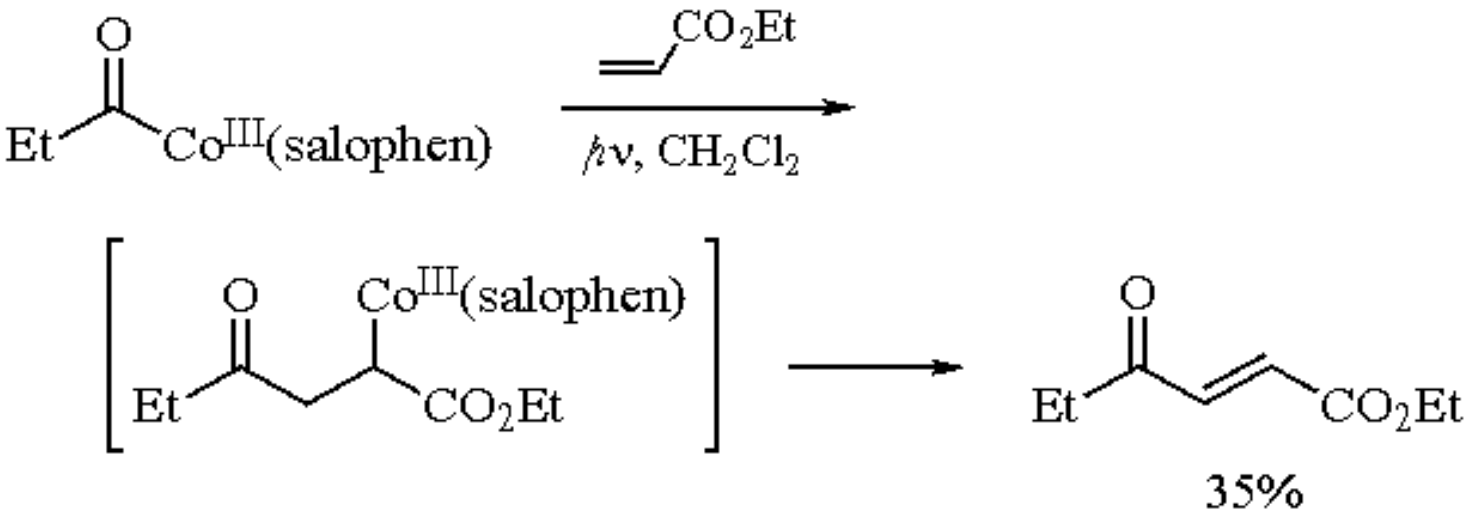

(3)

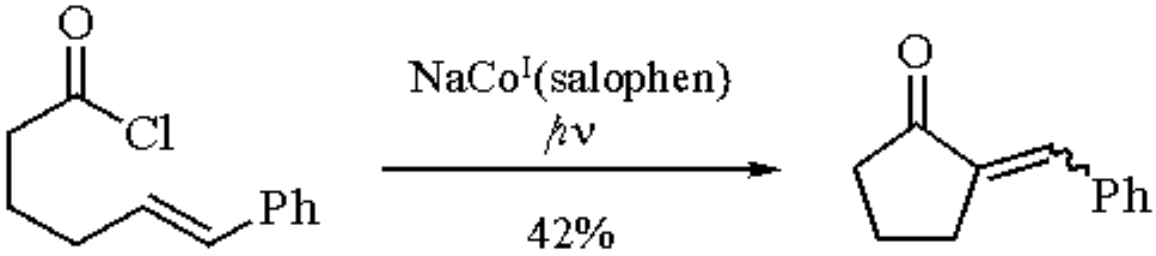

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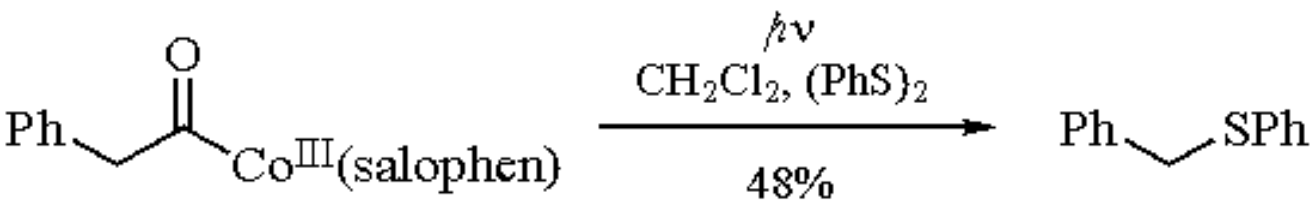

(5)

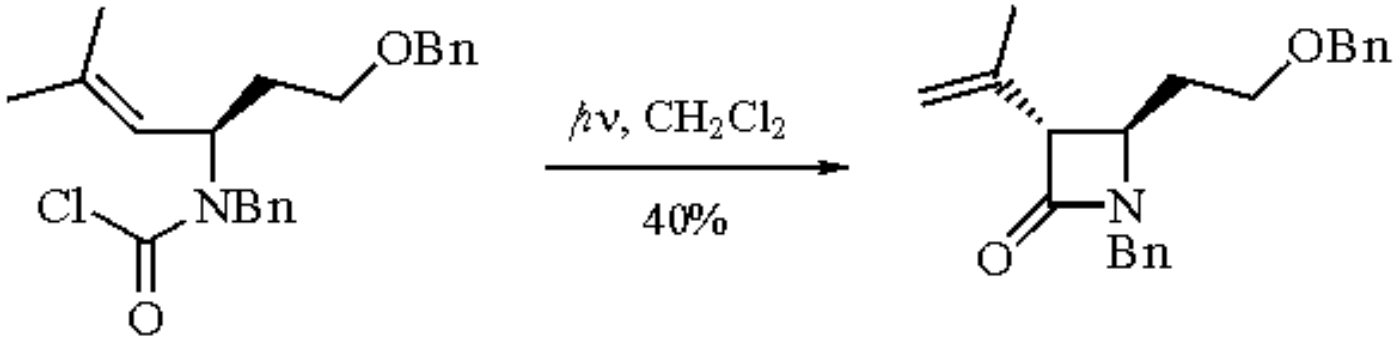

(6)

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Cobalt(III) Acetate[1]

$Co(OAc)_3$

[917-69-1] · $C_6H_9CoO_6$ · Cobalt(III) Acetate · (MW 236.07)

(one-electron oxidizing agent for aromatic[4] and aliphatic hydrocarbons,[10] for oxidative halogenation,[15] oxidation of alcohols[23] and acids[26])

Physical Data: dec 100 °C.

Solubility: hydrolyzed in water; sol acetic acid, ethanol, DMSO, DMF, and MeCN; slightly sol THF, diethyl ether, $CHCl_3$, and acetone.

Form Supplied in: dark green solid, widely available.

Analysis of Reagent Purity: cobalt(III) can be determined by treating it with excess iron(II) ammonium sulfate and titration with cerium(IV) sulfate or dichromate.[2]

Preparative Methods: involves oxidation of ***Cobalt(II) Acetate*** in acetic acid solution. The various oxidants used for this purpose are ozone,[2] peracid,[3a] peroxide,[3b] and oxygen.[4] An electrochemical procedure for the generation of $Co(OAc)_3$ in solution is also available.[3c]

Handling, Storage, and Precautions: the dark green solid or solution in acetic acid is reputed to be stable at rt for three months.

Introduction.

Cobalt triacetate is a powerful one-electron oxidant in acidic media. This reagent has been successfully used in the oxidation of a variety of organic substrates.

Oxidation of Hydrocarbons.

The cobalt(III) acetate oxidation of 2-methylnaphthalene at 70 °C in acetic acid gives mainly 2-acetoxynaphthalene (eq 1).[4]

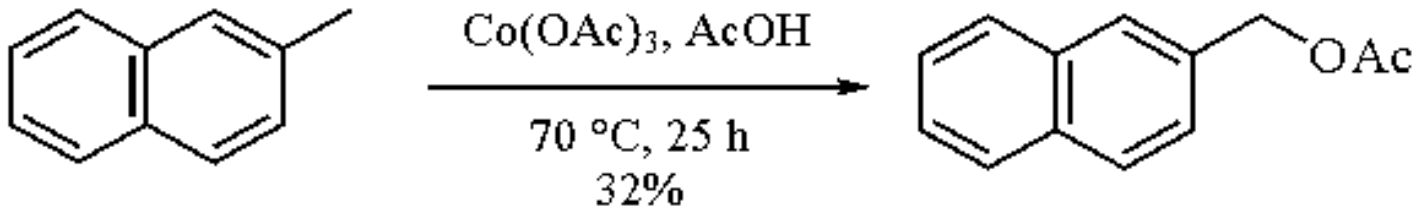

(1)

The reaction of toluene,[4] 2-methylindan,[6] isodurene,[7] hemimellitene,[8] *p*-cymene,[9] heptane,[10] adamantane,[11] and cyclohexane[12] proceeds analogously under a N_2 atmosphere to give the corresponding acetates as the main products; in the presence of ***Oxygen***, oxidation furnishes aldehydes,[5] ketones,[10] and acids.[5,12] The rate of oxidation of alkylarenes[5] and alkanes[10] is enhanced in the presence of strong acids.

Halogenation.

Treatment of representative substrates of alkylbenzene with $Co(OAc)_3$ in the presence of ***Hydrogen Fluoride***,[13] ***Lithium Chloride***,[4] ***Sodium Bromide***,[15] or ***Potassium Iodide***[14] results in corresponding halogenated derivatives.

Oxidation of Alkenes and Dienes.

Treatment of styrene,[16] 1-phenylbutadiene,[17] phenylcyclohexene,[18] α-methylstyrene,[19] or β-methylstyrene substituted with an electron donating group[20] with $Co(OAc)_3$ gives the corresponding 1,2-diol monoacetates as major products. However, oxidation of *cis*- and *trans*-β-methylstyrene at higher temperature affords the corresponding allylic acetate.[19] Reaction of 1,5-hexadienes with $Co(OAc)_3$ in the presence of 3-oxobutanoate under reflux conditions gives bis(dihydrofuran) and mono(dihydrofuran) (eq 2).[21]

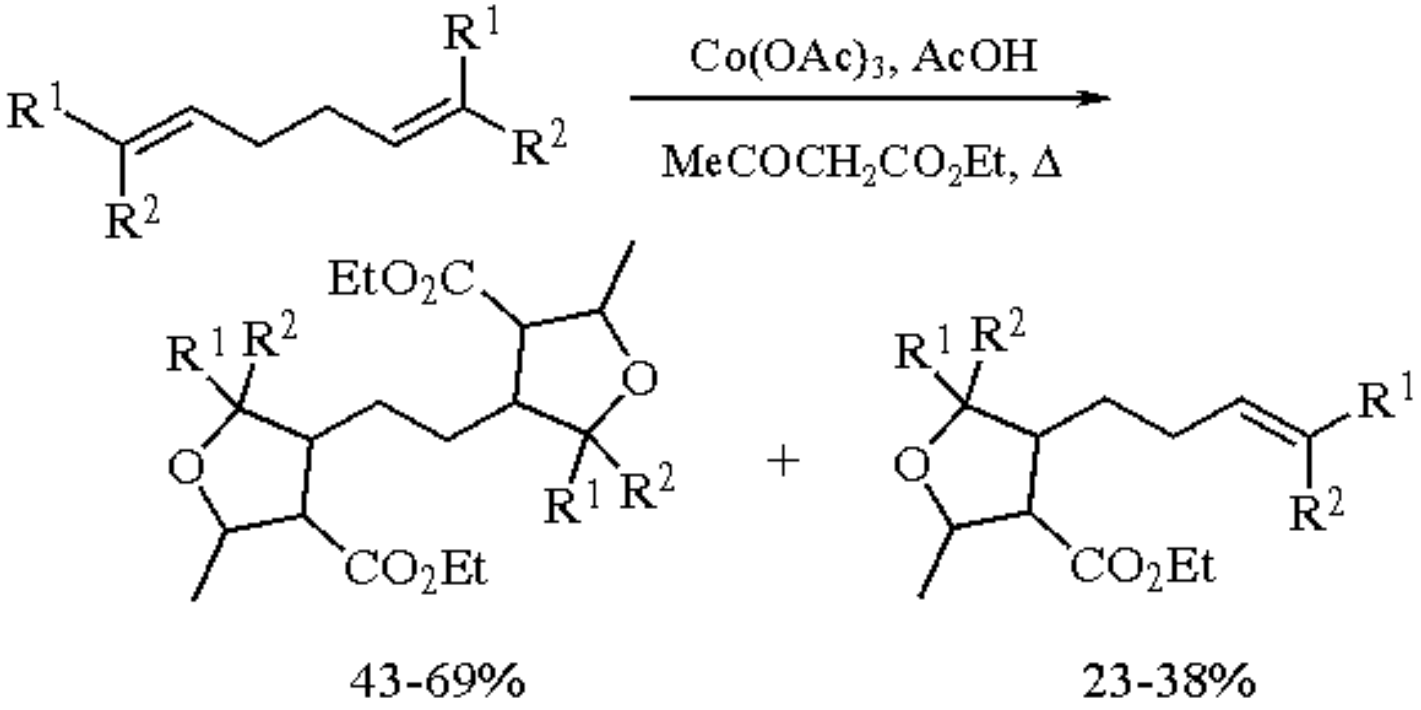

(2)

Oxidation of Functionalized Substrates.

The *o*-, *m*-, and *p*-substituted benzyl alcohols[22] and aromatic secondary alcohols[23,24] are readily oxidized by $Co(OAc)_3/Br^-$ to aldehydes and ketones, respectively. The reaction of 2,6-dimethylphenol with $Co(OAc)_3$ results in the formation of 3,3´,5,5´-tetramethyl-4,4´-diphenoquinone.[25]

In the presence of $Co(OAc)_3$ along with ***Copper(II) Acetate***, phenylacetic acids are decarboxylated to benzyl acetates.[26] Aryl substituted aliphatic acids are oxidized by $Co(OAc)_3$ to γ-phenylbutyrolactone (eq 3).[26,27]

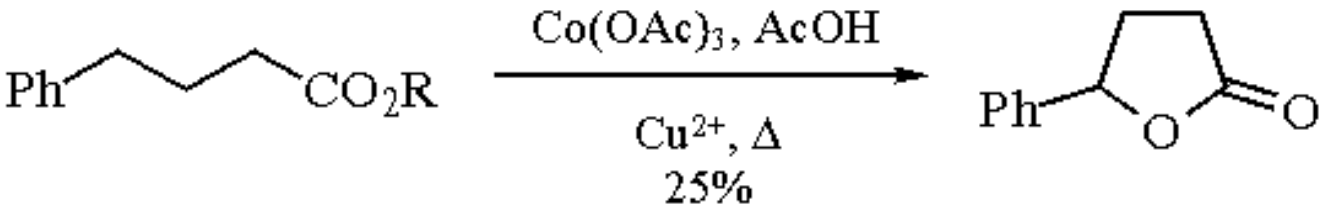

(3)

$Co(OAc)_3$ can be used in an interesting dealkylation of arylalkylamines in a mixture of chloroform and acetic anhydride.[28] Dihydroanisoin (DHA) and 1,2-bis(4-methoxyphenyl)propane-1,3-diol can be cleaved cleanly to *p*-anisaldehyde by $Co(OAc)_3$.[29]

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2,4,6-Collidine

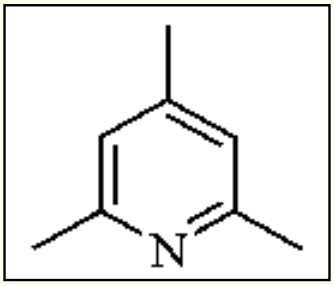

[108-75-8] · $C_8H_{11}N$ · 2,4,6-Collidine · (MW 121.18)

(most useful in dehydrohalogenation reactions;[1] used for basic properties as reaction solvent or additive)

Alternate Name: 2,4,6-trimethylpyridine.

Physical Data: bp 170 °C; mp -44.5 °C; *d* 0.913 g cm^{-3} at 20 °C. Isomers of the title reagent include 2,3,4-collidine (*[2233-29-6]*; bp 192-193 °C), 2,3,5-collidine (*[695-98-7]*; bp 182-183 °C/739 mmHg), 2,3,6-collidine (*[1462-84-6]*; bp 176-178 °C), 2,4,5-collidine (*[1122-39-0]*; bp 165-168 °C), and 3,4,5-collidine (*[20579-43-5]*; bp 205-207 °C).[2-4]

Solubility: sol 3.5 g/100 mL H_2O (20 °C) and 20.8 g/100 mL H_2O (6 °C); miscible with ether; sol methanol, ethanol, chloroform, benzene, toluene, dilute acids.[3]

Form Supplied in: liquid.

Analysis of Reagent Purity: GLC.

Purification: by distillation.

Handling, Storage, and Precautions: protect from light; moisture sensitive; incompatible with strong oxidizing agents.[5]

Dehydrohalogenation Reactions.

Numerous examples in the literature describe the utility of collidines to aid in dehydrohalogenation reactions. One example (eq 1) is the synthesis of 2-methyl-2-cyclohexenone (**2**) from 2-chloro-2-methylcyclohexanone (**1**).[6] Another example involves the dehydrobromination of tetrahydrofuran (**3**) to diene (**4**) en route from linalool to karahanaenone (62%, overall, eq 2).[7] Similarly, dehydrobromination of stigmasteryl acetate (**5**) affords 7-dehydrostigmasteryl acetate

(**6**) in a refluxing mixture of collidine and mesitylene (eq 3).[1]

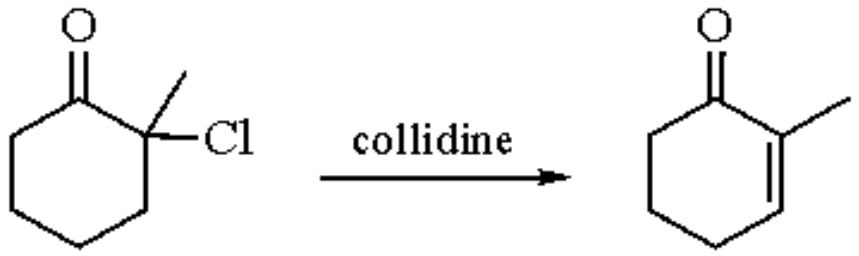

(1)

(1) **(2)**
(45-49% from
2-methylcyclohexanone)

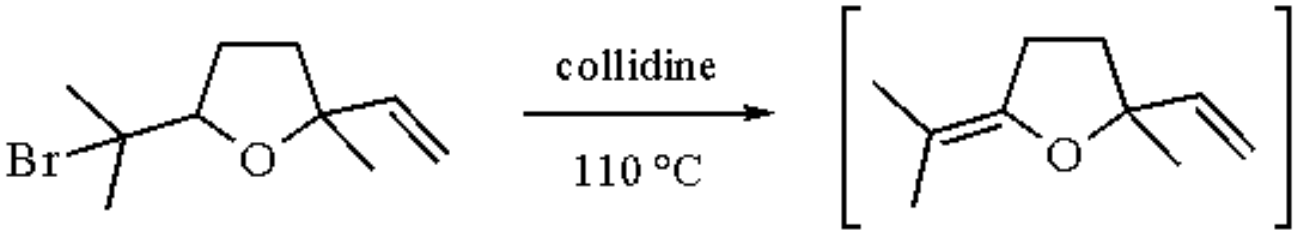

(2)

(3) **(4)**

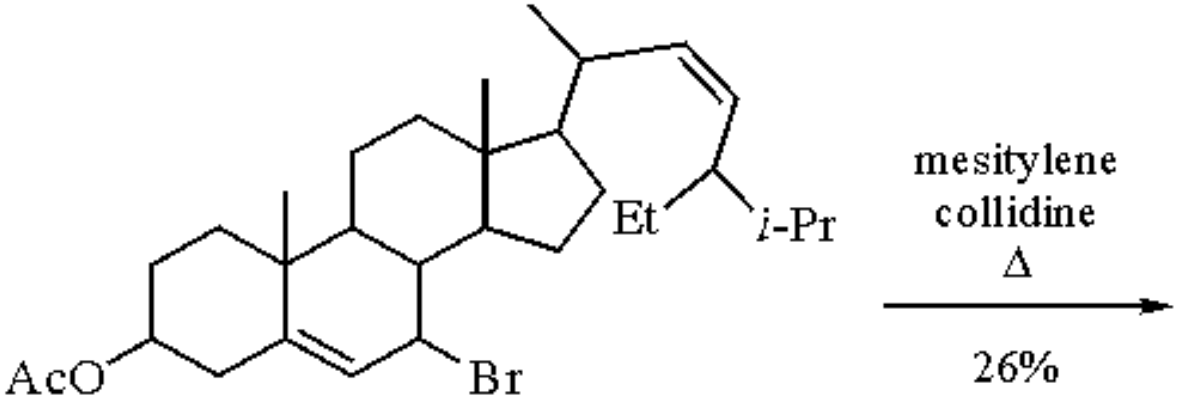

(5)

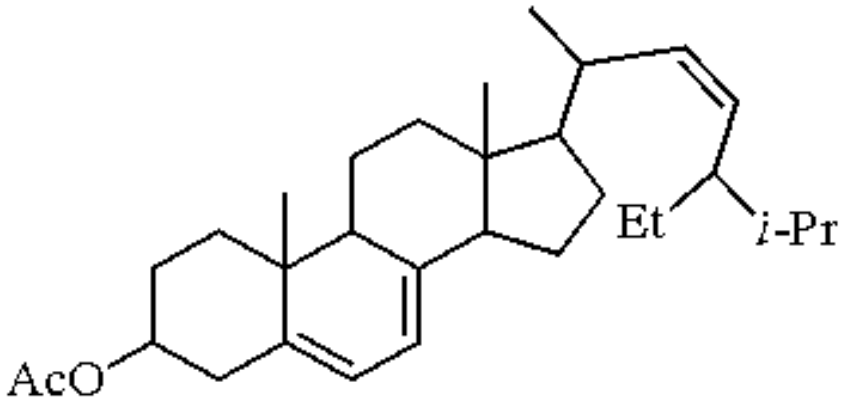

(6) (3)

A key step in a synthesis of pyridocarbazoles used collidine in THF for a dehydrochlorination. A hindered base such as collidine was required to avoid cleavage of the lactone ring, the preferred reaction using a base such as *N*,*N*-dimethylaniline (eq 4).[8]

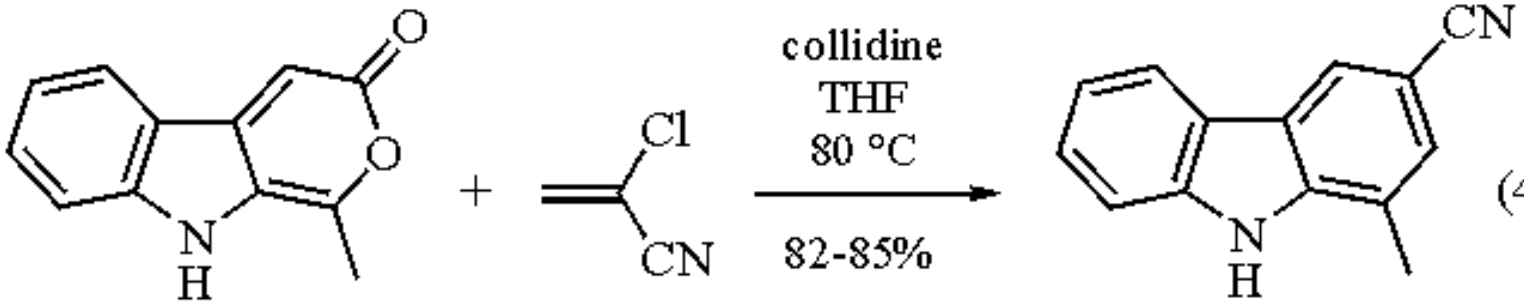

(4)

2,4,6-Collidine is used as solvent in the preparation of 2-benzylcyclopentanone (**8**) from 2-benzyl-2-methoxycarbonylcyclopentane (**7**) (eq 5).[9]

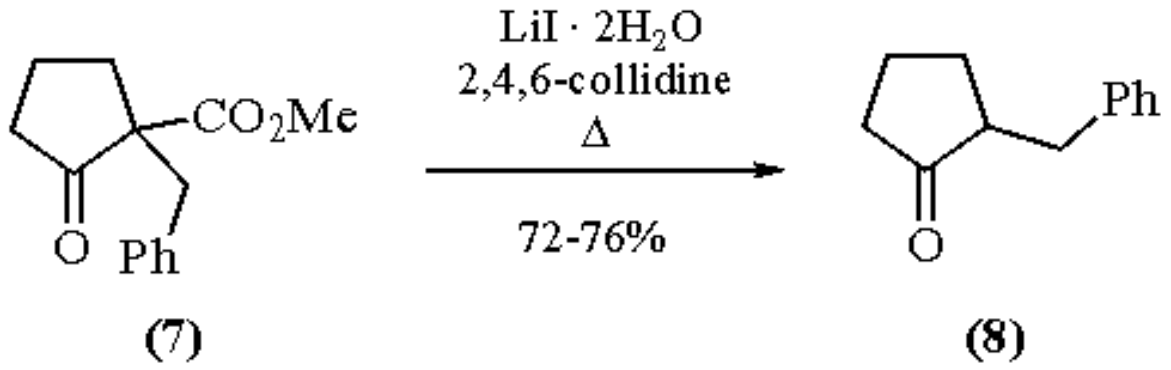

(5)

Cleavage of alkyl aryl ethers (72-76%) occurs in high yield with ***Lithium Iodide*** with 2,4,6-collidine as solvent.[10] In the absence of a solvent, high reaction temperatures are required.

Collidine as a Base Catalyst.

Collidine is useful as a base in a variety of reactions. Sometimes it doubles as reaction base and solvent. A mixture of monobromo isomers is obtained in very high yield when 1-methylcyclopropyl-3-methyl-3-butenylcarbinol (**9**) is treated with ***Phosphorus(III) Bromide*** and collidine (eq 6).[11] The bromo compounds shown underwent further reaction with ***Zinc Bromide*** to form *trans*-1-bromo-3,7-dimethylocta-3,7-diene in 85-90% yield.

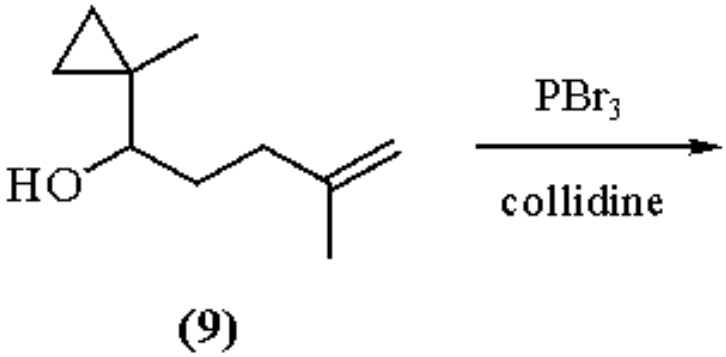

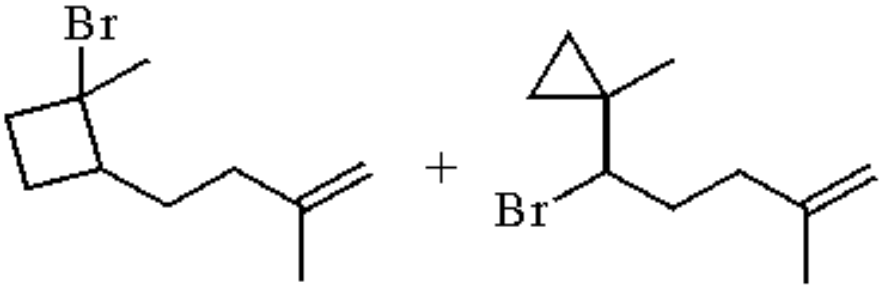

(6)

Collidine is effective as a proton scavenger in the Koenigs-Knorr synthesis of disaccharide glycosides. ***Silver(I) Trifluoromethanesulfonate*** and collidine are paired as a useful promoter of glycosylation reactions of alcohols with glycosyl halides. For example, the reaction of hepta-*O*-acetyl-α-D-cellobiosyl bromide (**10**) with 8-ethoxycarbonyloctanol (**11**) in the presence of silver triflate and collidine afforded a 78% yield of the corresponding 1,2-orthoacetate derivative (**12**) (eq 7).[12] When a similar reaction was carried out with *N*,*N*,*N*´,*N*´-tetramethylurea in place of collidine, a different reaction path was followed to give isomeric 1,2-*trans*-glycosides.

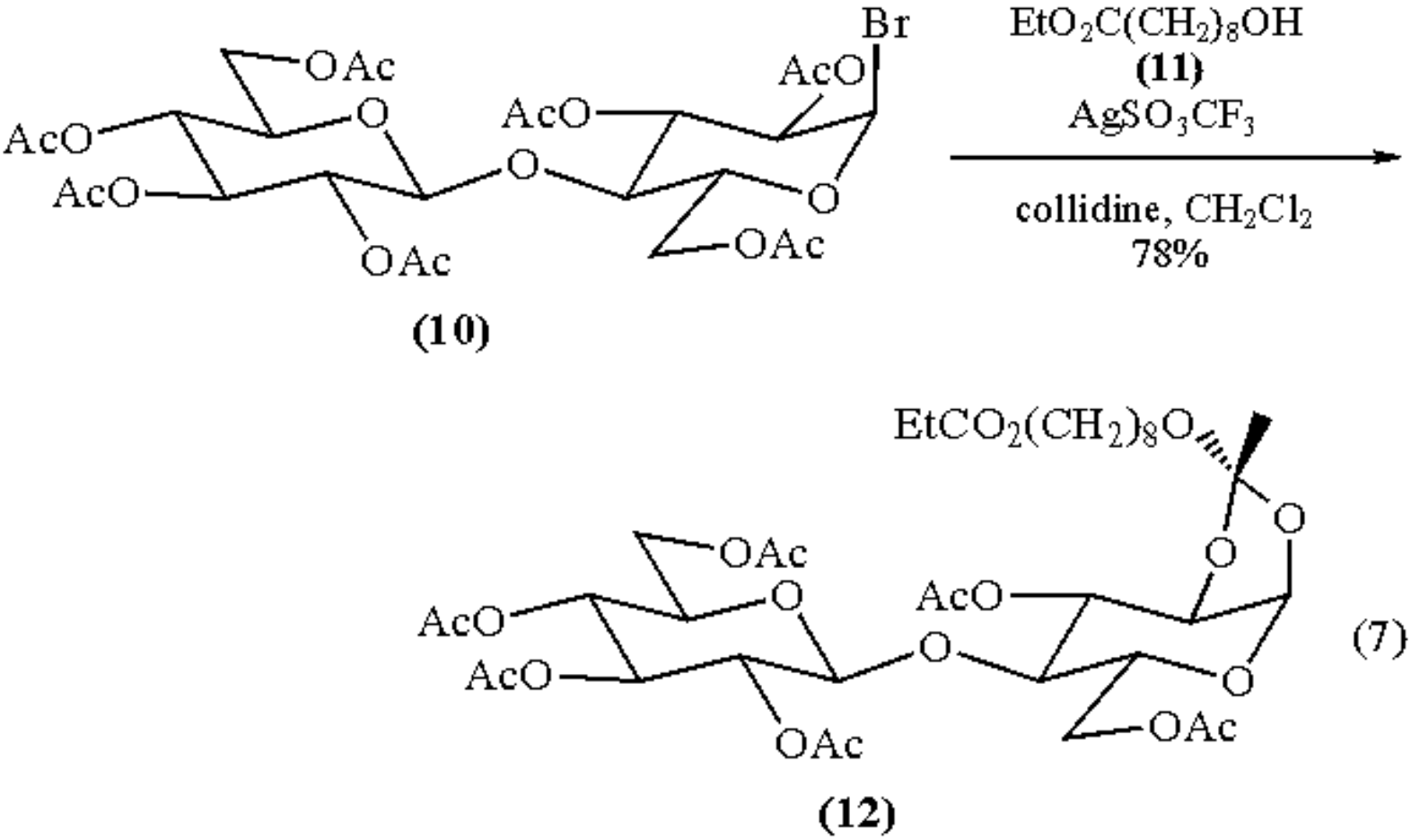

Collidine is also used as the base for glycosidation reactions promoted by ***Tin(II) Trifluoromethanesulfonate***. Starting with glucose derivative (**13**) and protected sugar derivatives, 1,2-*trans*-β-D-disaccharides have been prepared by this method (eq 8)[13]

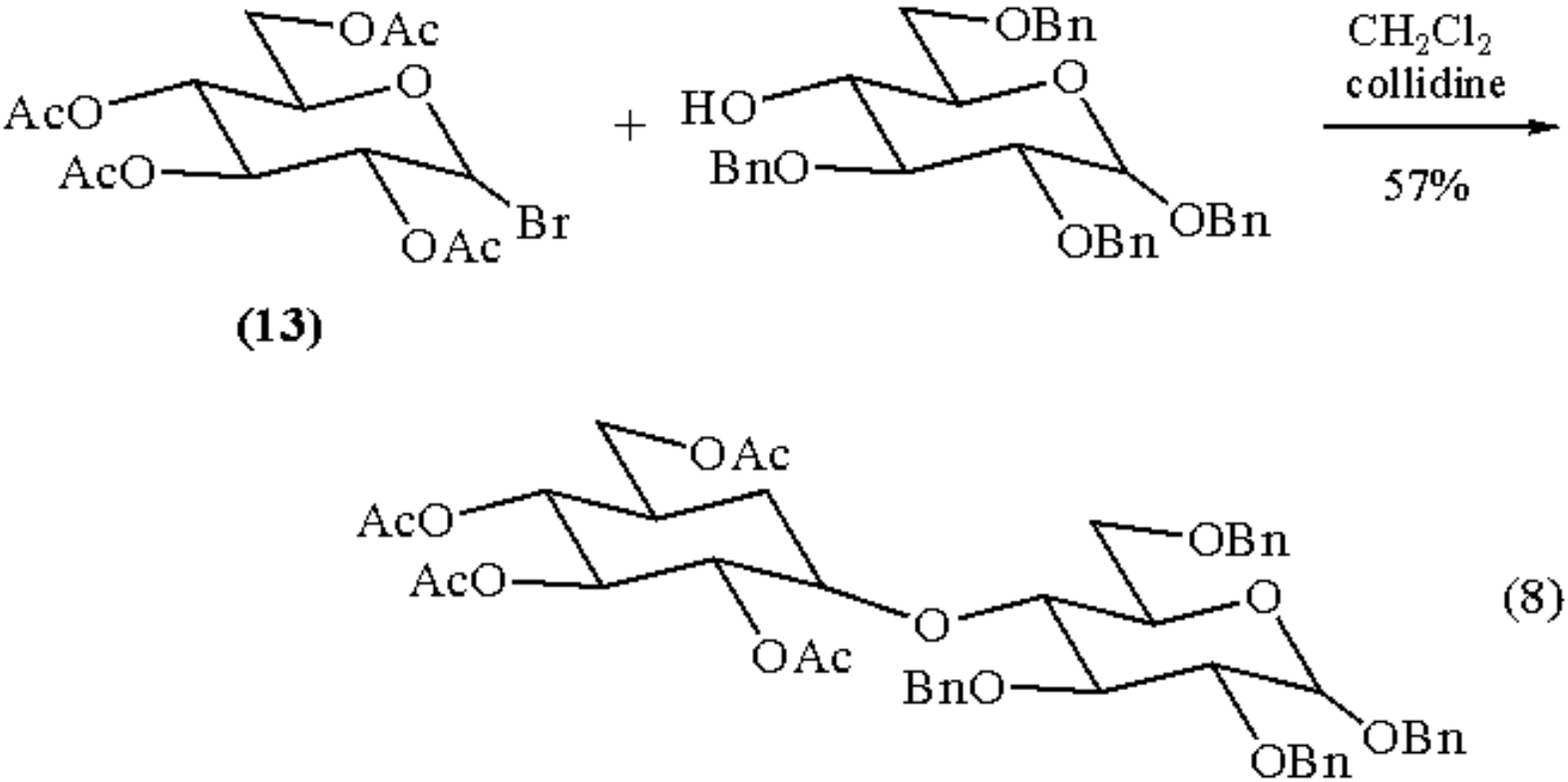

Collidine behaves as a nucleophilic catalyst in reactions such as the hydrolysis of picryl chloride. The reaction proceeds by formation of intermediate *N*-picryl-2,4,6-trimethylpyridinium ion (**14**) (eq 9).[14]

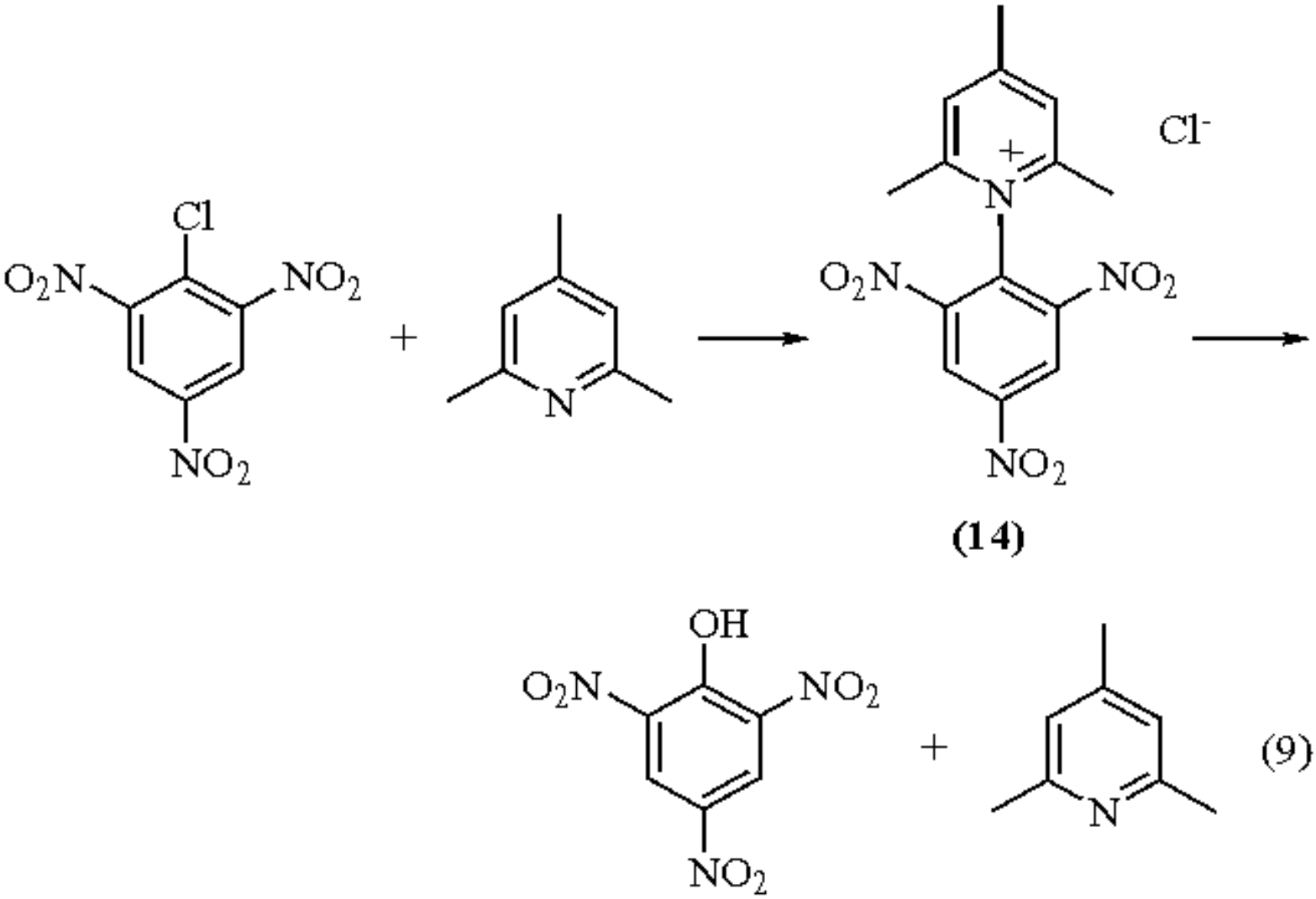

Collidine acts as a sterically hindered base in tritylation reactions of very weakly acidic compounds. The tritylation reaction proceeds in high yield for both acetone and acetonitrile, which serve as both reactant and solvent in the syntheses of 1,1,1-triphenyl-3-butanone (**15**) and 1,1,1-triphenylpropionitrile (**16**), respectively (eqs 10 and 11).[15] This tritylation is a general reaction, applicable to more strongly acidic compounds such as diethyl malonate and nitromethane. In the nitromethane reaction, a low yield of the desired product is obtained due to side reactions.

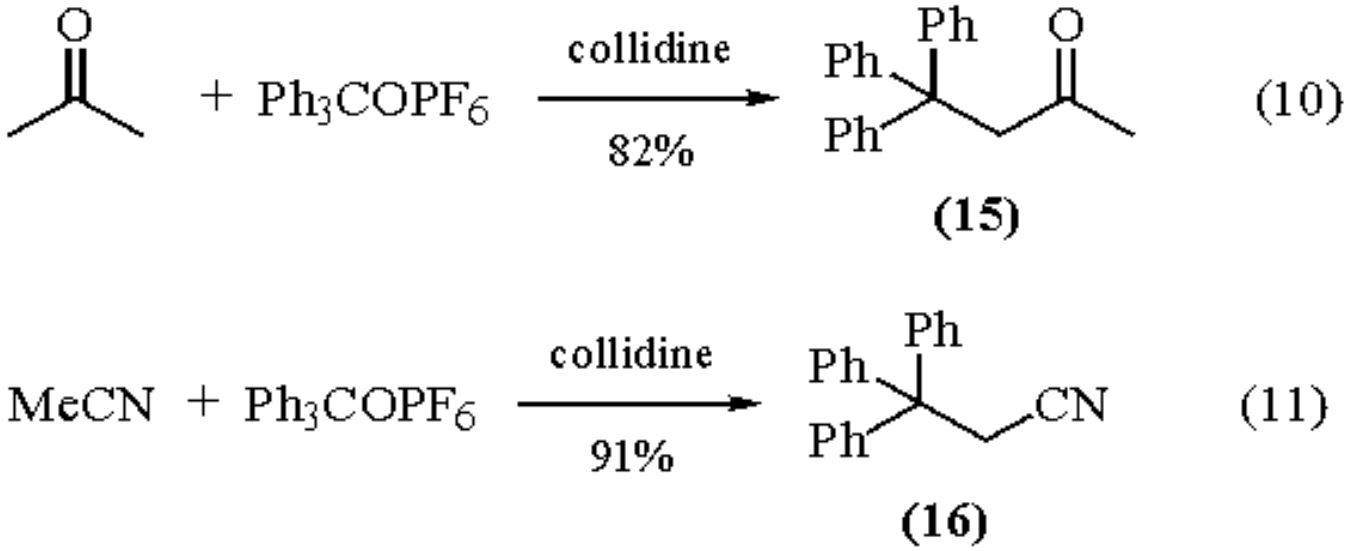

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2,4,6-Collidinium *p*-Toluenesulfonate

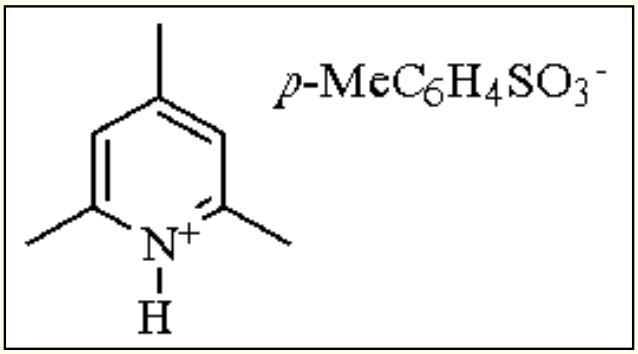

[59229-09-3] · $C_{15}H_{19}NO_3S$ · 2,4,6-Collidinium *p*-Toluenesulfonate · (MW 293.39)

(acid catalyst in acetalization,[1,2] transacetalization,[7] macrolactonization,[8] and conversion of enynones to phenols[9])

Physical Data: mp 130-132 °C.

Solubility: sol benzene, toluene, dichloromethane, chloroform, ethanol, acetone.

Form Supplied in: white, moisture-sensitive, crystalline solid. Commercially available.

Preparative Method: can be prepared by the slow addition of ***p-Toluenesulfonic Acid*** in methanol to a rapidly stirred solution of ***2,4,6-Collidine*** in diethyl ether, at 20 °C. Cooling to 0 °C results in crystallization of the title reagent.

Purification: recrystallization from acetone.

Handling, Storage, and Precautions: store in desiccator under nitrogen. Very good shelf life at room temperature when kept dry. Irritant; handle with gloves.

Acid-Catalyzed Selective Acetalization.

Collidinium *p*-toluenesulfonate (**1**) is a weakly acidic salt that catalyzes selective acetalization of α,β-unsaturated ketones in the presence of saturated ketones (eq 1). Using ***Ethylene Glycol*** in the presence of (**1**) results in the isomerization of the enone double bond and acetalization of the carbonyl.[1]

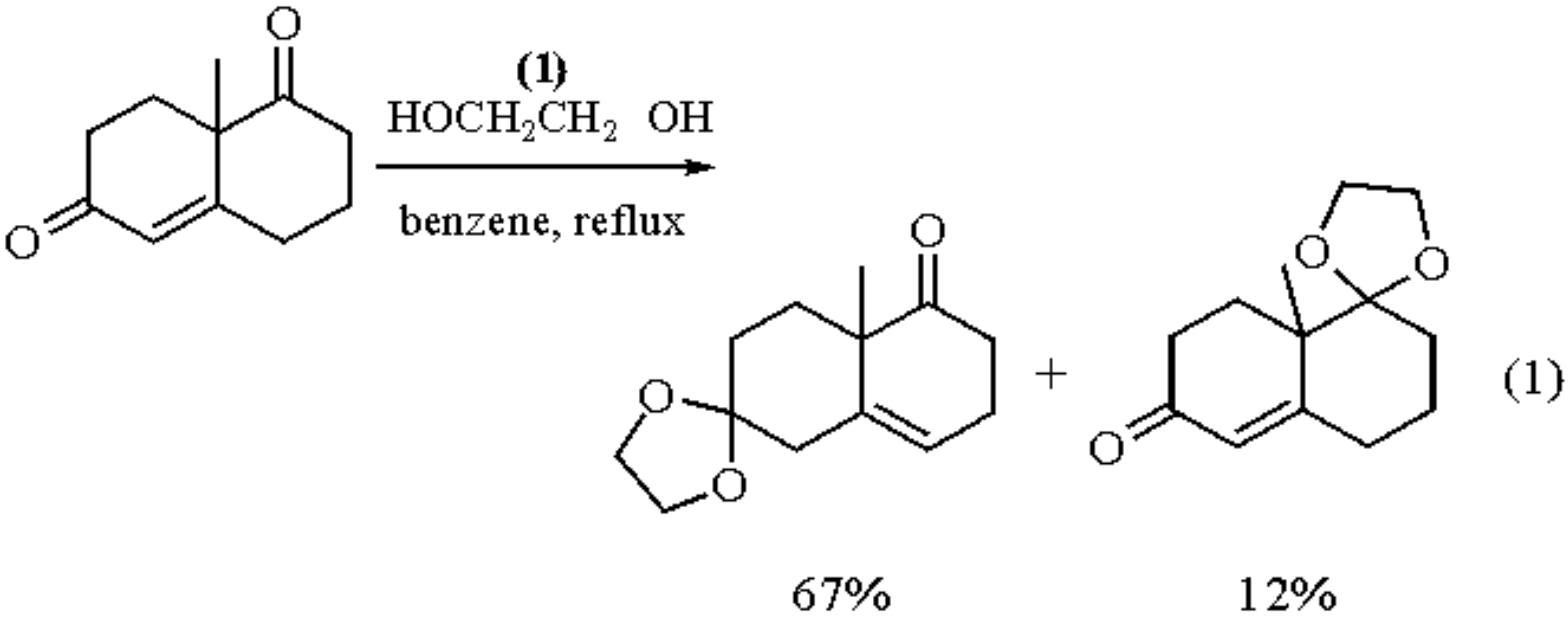

A recent improvement uses (**1**) to form a mixture of acetal isomers (eq 2) which undergo isomerization in the presence of (**1**) to give the thermodynamically more stable acetal (eq 3).[2]

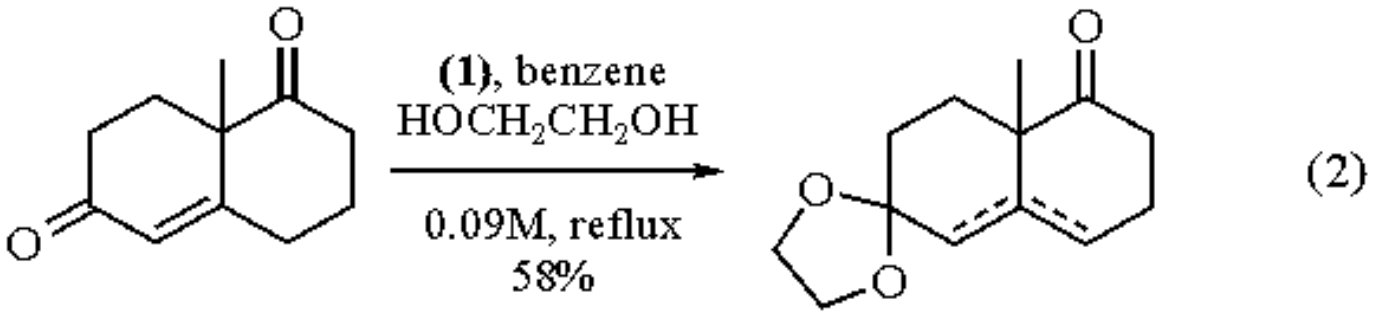

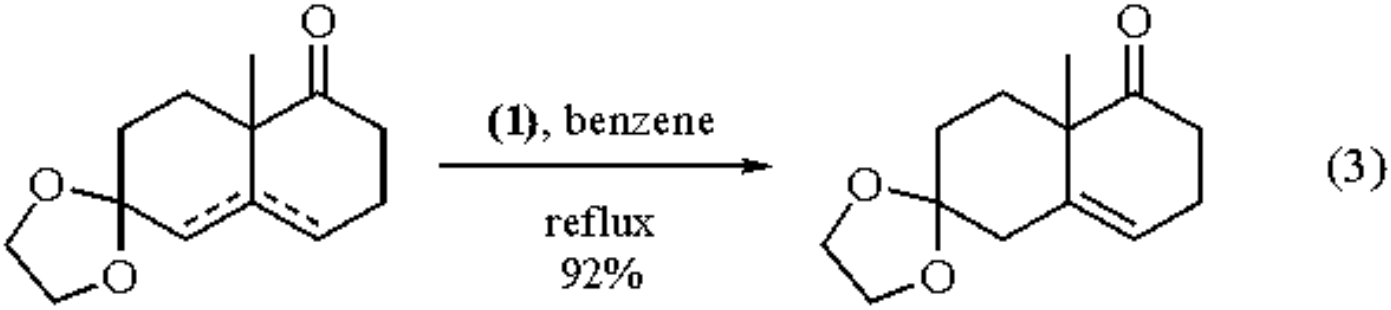

The title reagent has been used in the acetalization of a steroidal ketone with ethylene glycol in the presence of an acid sensitive epoxide functionality (eq 4).[3]

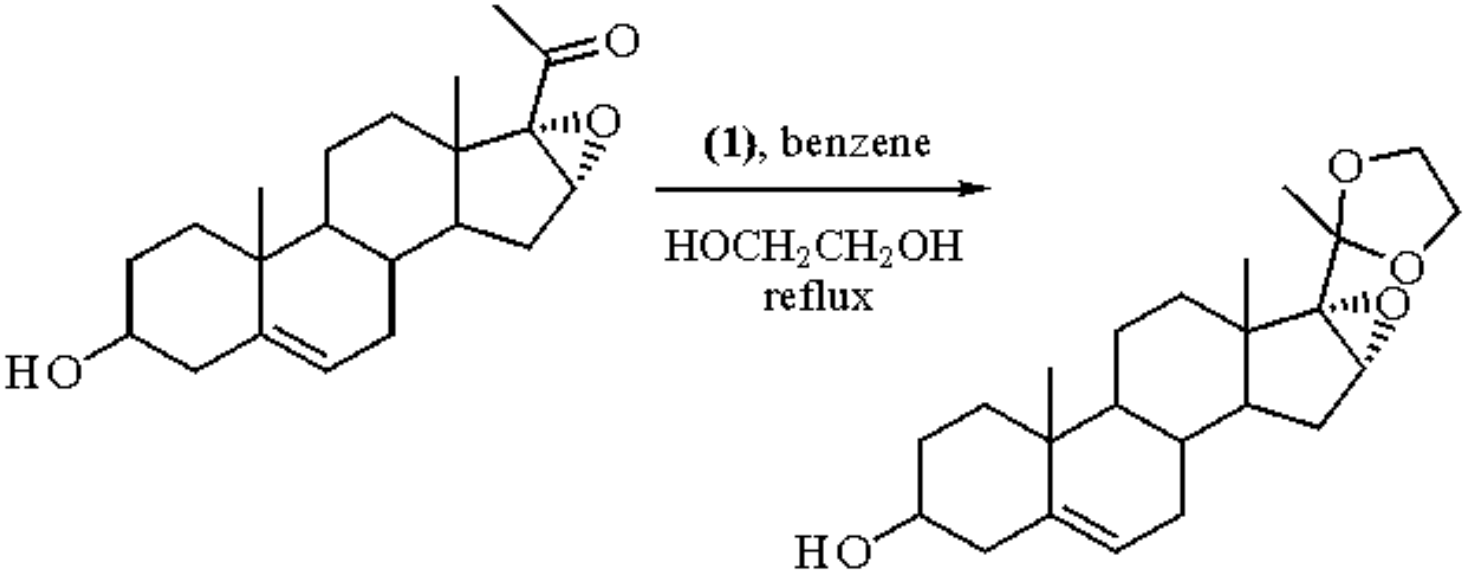

(4)

Acetalization of ketones (e.g. cyclohexanone) with the optically active diols (**2**) (eq 5)[4] and (**3**) (eq 6)[5] has been achieved using (**1**) in refluxing benzene, accompanied by the azeotropic removal of water. Use of toluene reduces the reaction time with no loss of yield.[6]

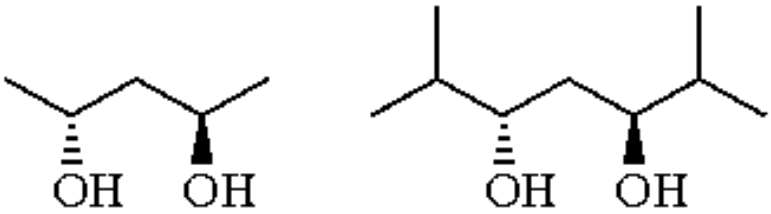

(2) **(3)**

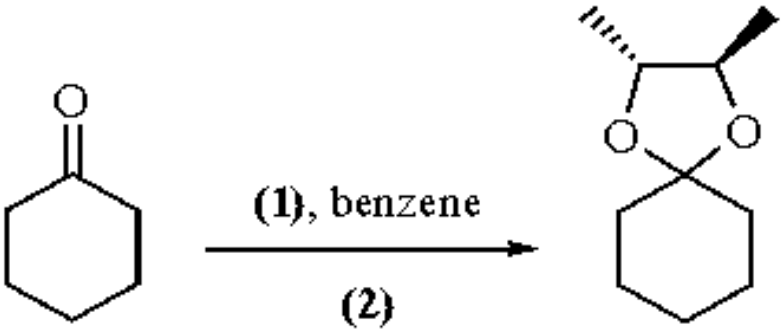

(5)

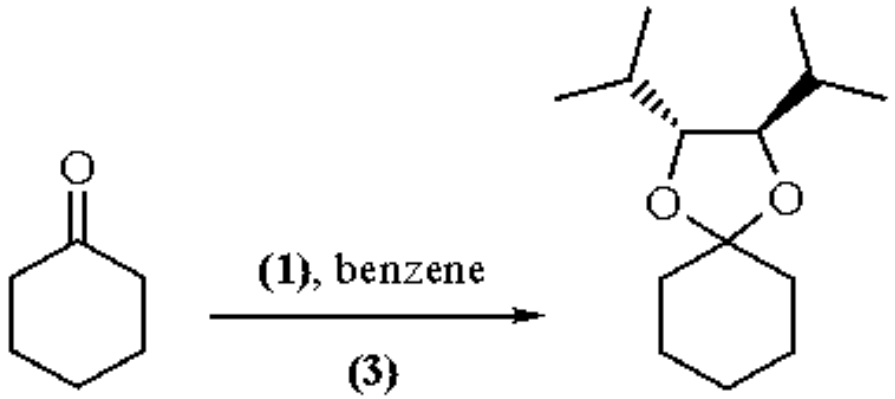

(6)

Transacetalization of Dioxolane Protecting Groups.

A stoichiometric amount of (**1**) in refluxing acetone-water (120 h) leads to the deprotection of an acetal (eq 7), maintaining the integrity of an acid-sensitive TBS ether and the oxetane ring (84% yield).[7]

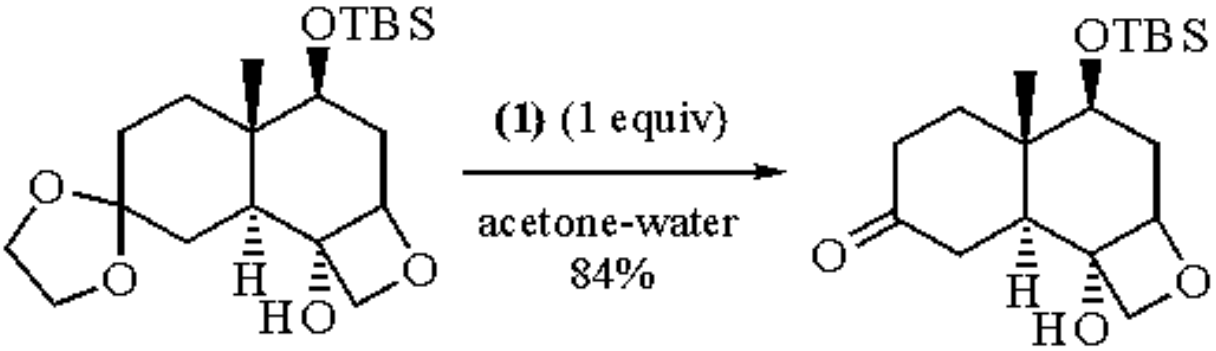

(7)

Acid-Catalyzed Macrolactonization.

The title reagent effects the intramolecular macrolactonization of hydroxy triamides, resulting in 8- and 10-membered lactones (eq 8).[8] The reaction is achieved by the syringe pump addition of a triamide solution in benzene to a refluxing solution of (**1**) under high dilution.

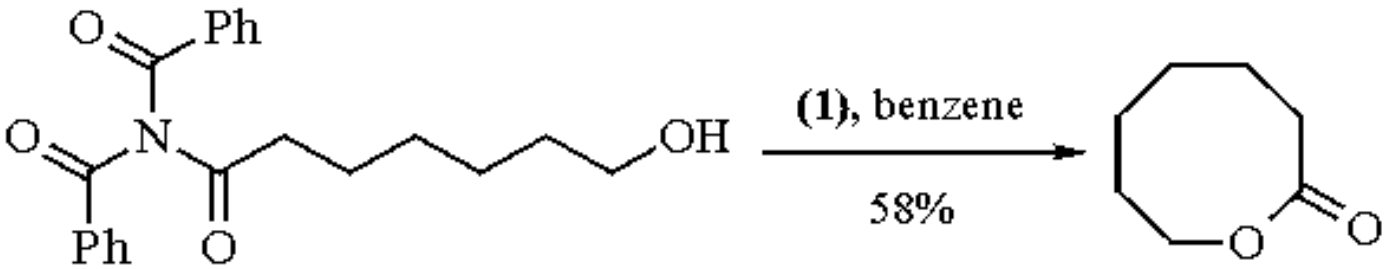

(8)

Acid-Catalyzed Cyclization of Enynones to Phenols.

The title reagent catalyzes the cyclization of enynones to phenols (eq 9).[9] The reaction is carried out at 250 °C to give yields of 30-89%.

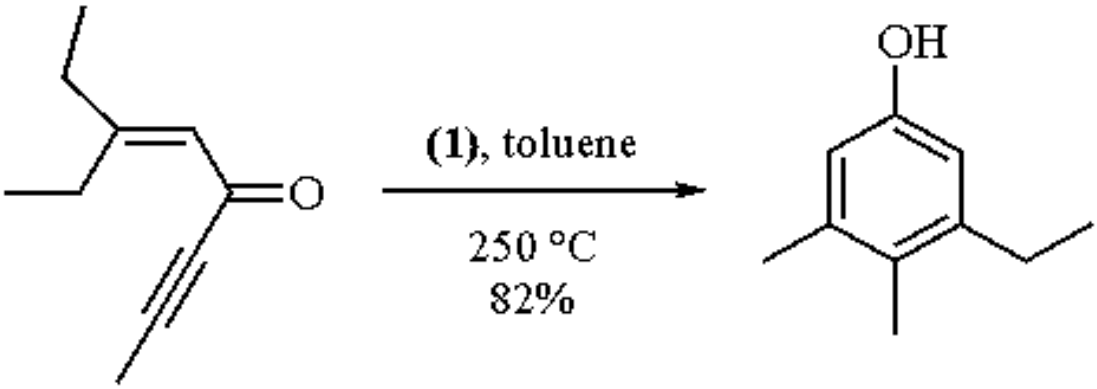

(9)

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Copper[1]

Cu

[7440-50-8] · Cu · Copper · (MW 63.54)

(reagent for the cyclization and/or coupling of various functional groups;[1] decarboxylation;[10] preparation of α-alkynic alcohols;[12] cyclopropanes,[13] nitriles,[15] ketones by benzylic oxidation[10])

Physical Data: mp 1083 °C; *d* 8.94 g cm^{-3}.

Solubility: slowly sol aq NH_3.

Form Supplied in: reddish, lustrous solid; ingots, sheets, wire, or powder (most synthetic reactions require the use of the powder form); widely available.

Analysis of Reagent Purity: by electrolytic assay,[21] or EDTA/iodometric titration.[1d]

Handling, Storage, and Precautions: should be stored in the absence of moisture; in moist air it gradually becomes coated with copper carbonate. The powder may be flammable when exposed to excessive heat or flame.

Ullmann Reaction.

Alkyl halides containing electron-attracting substituents may be coupled in the presence of copper in good yields.[1] The reaction is believed to proceed through organocopper intermediates, in an oxidant addition, rather than radicals.[2] Details for the activation of the copper catalyst by iodine in acetone are described along with the Ullmann coupling of 2-chloronitrobenzene to yield 2,2´-dinitrobiphenyl.[3]

Procedures for the preparation of unsymmetrical biaryls from a mixture of halides have been described.[4] Similarly, the coupling of vinyl bromides by copper in a stereospecific synthesis of conjugated dienes has also been reported.[5] A highly reactive copper powder has been developed that is particularly effective for Ullmann reactions.[6]

Other Ullmann-type coupling reactions include the reaction of phenols with aryl halides to yield diaryl ethers,[7] the synthesis of triarylamines through the coupling of diarylamines with aryl halides,[8] the cross coupling of allylic and benzylic bromides with acid chlorides,[6b] and the cyclization of epoxyalkyl halides.[9]

Decarboxylation.

Commercial copper powder in quinoline solution is a standard reagent for decarboxylation reactions.[10] In some instances, decarboxylation and dehydration occur to produce an exocyclic alkene.[11]

α-Acetylenic Alcohols.

Heating 1,4-diformyloxy-2-butyne with copper and adipic acid followed by treatment with acid and methanol gives 2-butyn-1-ol.[12]

Cyclopropanes.

In the presence of copper, α-diazo ketones decompose and react with alkenes to yield cyclopropyl ketones by intermolecular or intramolecular cyclization.[13] Also, copper assists the reaction of alkenes with *gem*-dihalides to produce cyclopropanes.[14]

Nitriles.

Nitriles may be prepared from aromatic aldehydes by reaction with copper powder and ammonium chloride (in situ preparation of $CuCl_2$ and NH_3).[15]

Ketones.

The formation of ketones has been reported to result from benzylic oxidation using a copper powder catalyst (eq 1).[16] The initial oxidized product (**2**) may further cyclize to (**3**) by continued use of the same reagent. The latter reaction is similar to tetramethoxydibenzofuran formation resulting from heating 4-bromo-5-iodoveratrole with copper in nitrobenzene.[17]

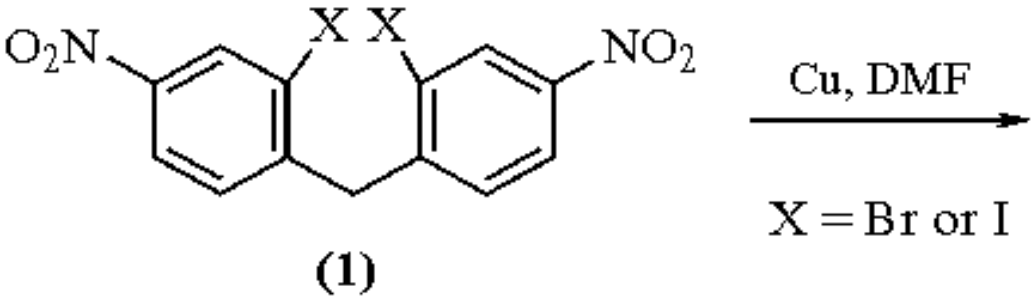

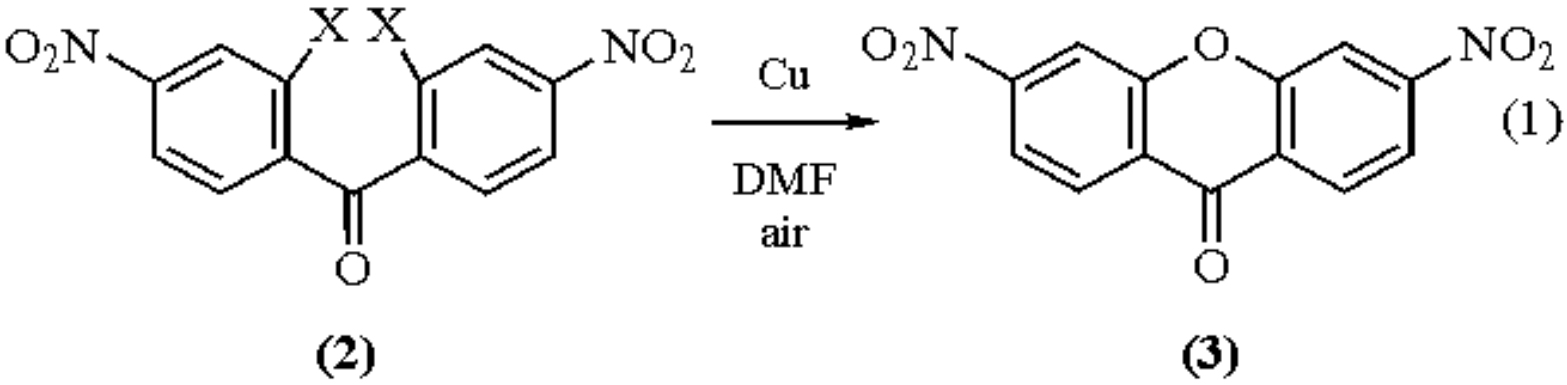

Other minor reactions of copper include its use as a catalyst in the synthesis of azo compounds from diazonium tetrafluoroborates,[18] rearrangements of bicyclic hydrocarbons,[19] and in the classic Gattermann version of the Sandmeyer reaction for the conversion of arenediazonium salts to halides.[20]

Related Reagents.

Copper Bronze; ***Sodium Iodide-Copper***.

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Copper(I) Acetate[1]

CuOAc

[598-54-9] · $C_2H_3CuO_2$ · Copper(I) Acetate · (MW 122.58)

(acetoxylation;[4] oxidation of phenols;[6] hydrogenation[3])

Alternate Name: cuprous acetate.

Physical Data: dec 285 °C.

Solubility: sol water (hydrolyzes to form Cu_2O), pyridine, HOAc; dissolves slowly in ether.

Form Supplied in: tan or white powder; commercially available.

Preparative Methods: obtained as a sublimate by heating copper(II) acetate in vacuo to temperatures above 220 °C.[2] Prepared from ***Copper(I) Oxide*** and ***Acetic Acid-Acetic Anhydride***;[3] also, from a reaction involving ***Copper(II) Acetate*** and ***Copper*** foil in anhydrous acetonitrile with acetic acid-acetic anhydride. The mixture is stirred under nitrogen for 48 h after excess copper is removed, and precipitation of copper(I) acetate in ether occurs.[4,5] Obtained by slow addition of a solution of hydroxylamine hydrogen sulfate to a hot mixture of ammoniacal copper(II) acetate solution buffered with a large amount of ammonium acetate; addition of excess acetic acid precipitates the copper(I) acetate.[1]

Handling, Storage, and Precautions: stable when dry, but decomposes with moisture or strong heating.

Acetoxylation.

Vinyl acetates are often very hard to prepare from vinyl halides. They can be synthesized either by reacting cyclic vinylic bromides with excess copper(I) acetate in acetonitrile at 80-110 °C for 2-10 h (eq 1),[4,6] or by reacting acyclic vinyl iodides with copper(I) acetate in refluxing pyridine. However, the latter

method produces poor yields of vinyl acetates (eq 2). When copper(II) acetate in refluxing *N*-methylpyrrolidone (NMP) is utilized instead, vinyl acetates are obtained in higher yields (eq 2).[7]

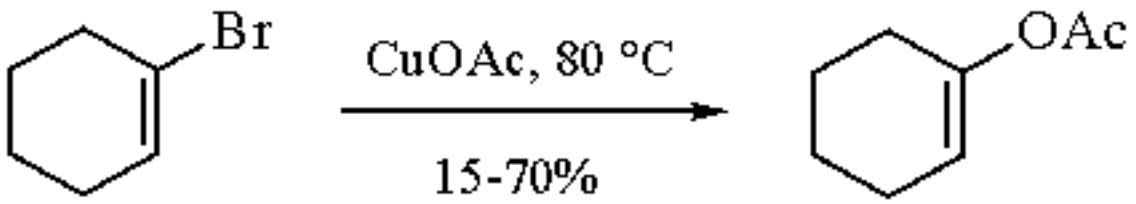

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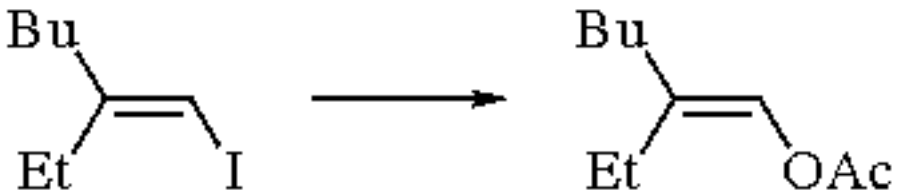

(2)

CuOAc, py	26%
$Cu(OAc)_2$, NMP	70%

Oxidation of Phenols.

Copper(I) acetate functions as a catalyst in the oxidation of phenols to the corresponding poly(phenylene) ethers and diphenoquinones in the presence of tertiary amines.[8]

Hydrogenation.

A dimer of the copper(I) acetate-***Quinoline*** complex activates molecular hydrogen in the homogeneous catalytic hydrogenation of quinone in solution.[3]

Related Reagents.

Copper(II) Acetate, ***Sodium Tetracarbonylcobaltate***.

---

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Copper(II) Acetate[1]

$Cu(OAc)_2$

[142-71-2] · $C_4H_6CuO_4$ · Copper(II) Acetate · (MW 181.64)

(oxidizes carbanions,[2] radicals[3] and hydrocarbons;[4] for oxidative coupling and solvolytic cleavage of Si-C,[5] Bi-C, Pb-C, and Sb-C bonds; rapid radical scavenger; catalyst for cyclopropanation of alkenes with diazo esters;[6] Lewis acid catalyst)

Alternate Name: cupric acetate.

Physical Data: blue crystals, mp 130-140 °C (dec); *d* 1.92-1.94 g cm^{-3}.[7]

Solubility: sol H_2O (6.79 g/100 mL, 25 °C); sol AcOH, pyridine; insol ether.

Form Supplied in: widely available; the anhydrous salt can be prepared from the usually available monohydrate $Cu(OAc)_2.H_2O$ *[6046-93-1]* by heating to 90 °C until constant weight[7,8] or by refluxing $Cu(OAc)_2.H_2O$ in acetic anhydride and washing the insoluble product with Et_2O.[9]

Analysis of Reagent Purity: iodometric titration;[10] atomic absorption spectroscopy.[11]

Purification: recrystallize (as monohydrate) from warm dil HOAc.[57]

Handling, Storage, and Precautions: must be stored in the absence of moisture; is decomposed on heating to hydrogen and $Cu^{I}OAc$.[7] Irritating to skin, eyes, and respiratory system. May be dissolved in a combustible solvent for incineration.

Oxidation of Carbanions.

Oxidative coupling of terminal alkynes to diynes (eq 1) with $Cu(OAc)_2$ and ***Pyridine*** can be carried out in MeOH or in benzene/ether.[2] The reaction requires the presence of copper(I) salt; the rate-determining step corresponds to the formation of the Cu^{I} acetylide.[12]

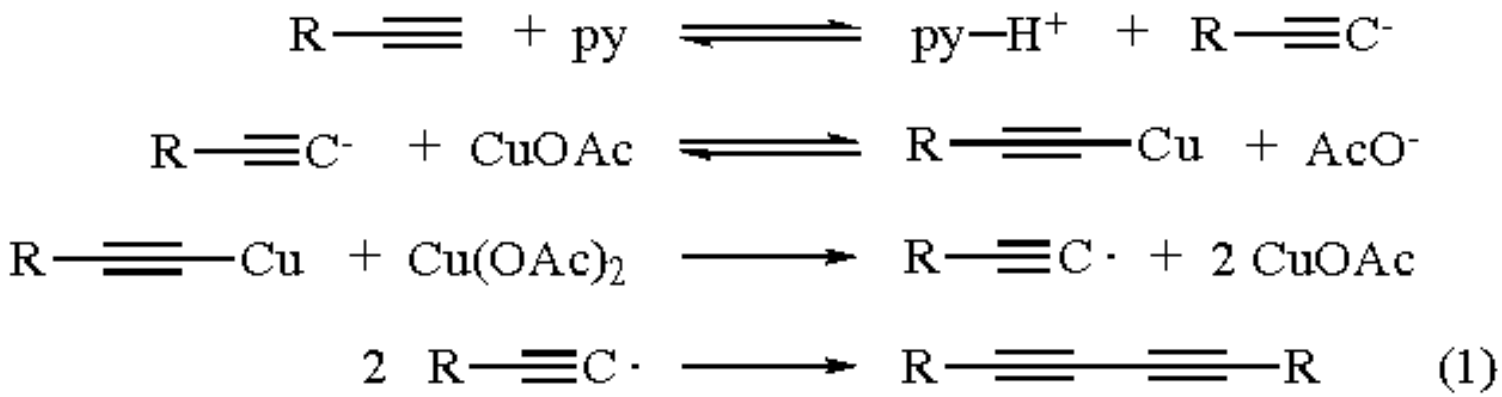

While α-sulfonyl lithiated carbanions are oxidatively coupled with ***Copper(II) Trifluoromethanesulfonate*** (eq 2), $Cu(OAc)_2$ oxidizes them to the corresponding (*E*)-α,β-unsaturated sulfones (eq 3).[13]

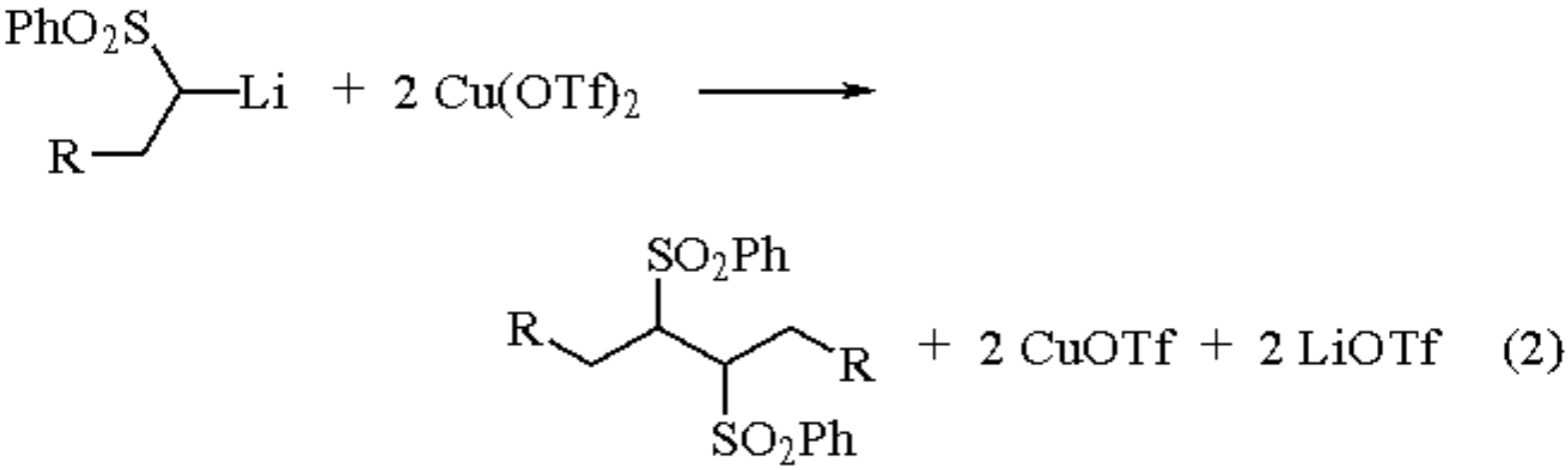

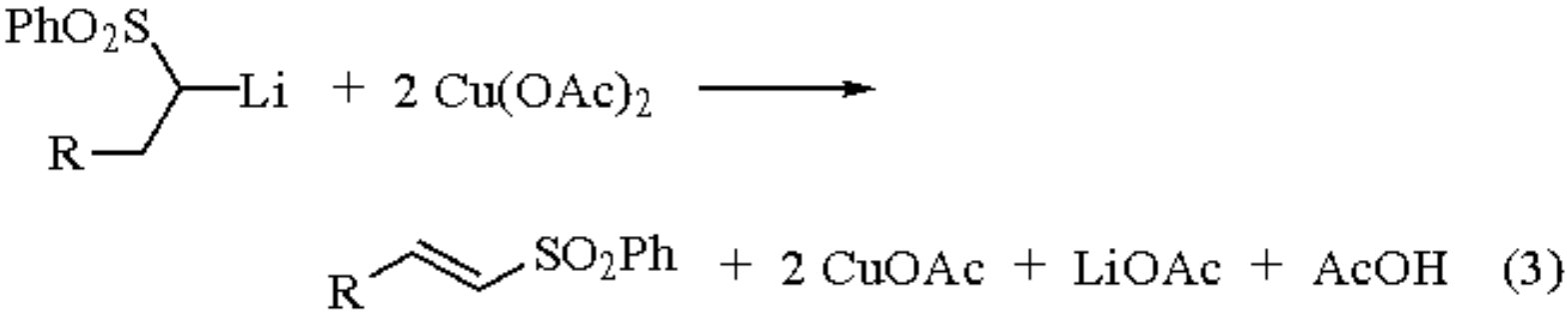

Other carbanions can be coupled oxidatively by $Cu(OAc)_2$, as shown in the synthesis of β-lactams (eq 4).[14]

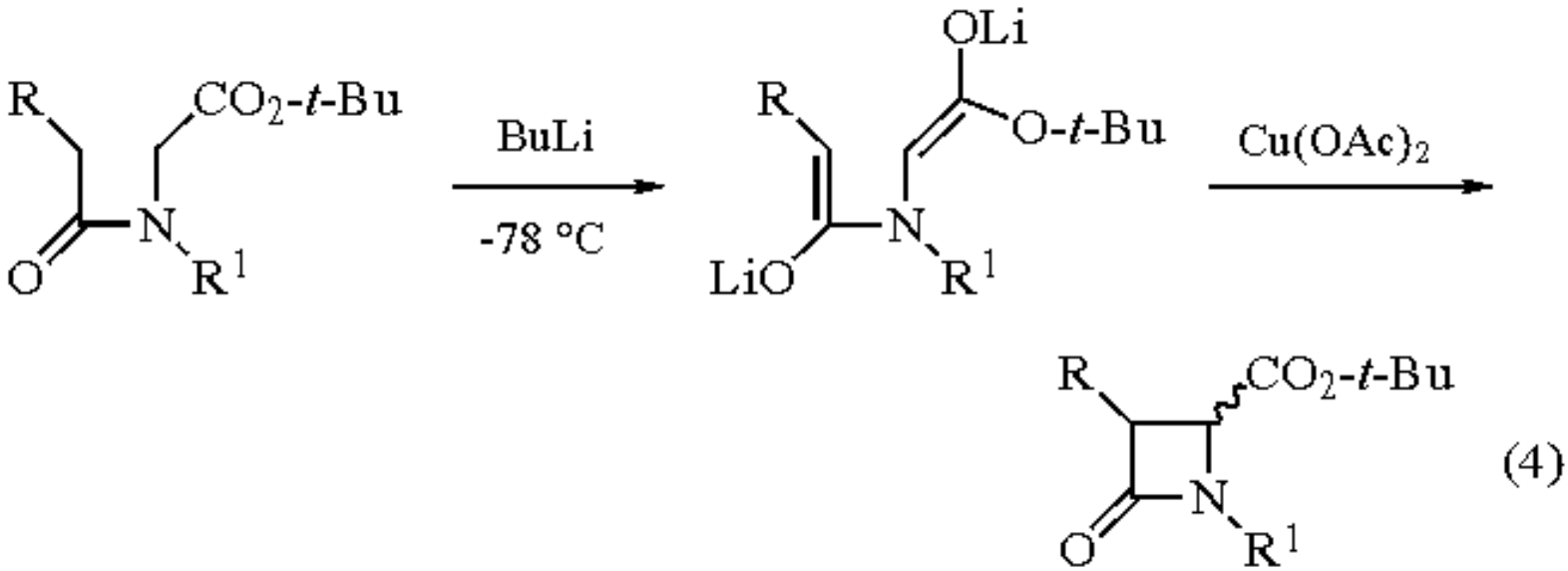

In the presence of ***1,4-Diazabicyclo[2.2.2]octane*** in DMF, the complex of $Cu(OAc)_2$ and 2,2´-bipyridyl catalyzes the oxygenation of α-branched aldehydes with O_2 to ketones.[15]

Carbon-Hydrogen Bond Oxidations.

Ortho hydroxylation of phenols with O_2 is catalyzed by a complex of $Cu(OAc)_2$ and ***Morpholine*** (soluble in EtOH).[16] In the absence of O_2, *ortho* acetoxylation of phenols can be induced with equimolar amounts of $Cu(OAc)_2$ in AcOH (eq 5).[17]

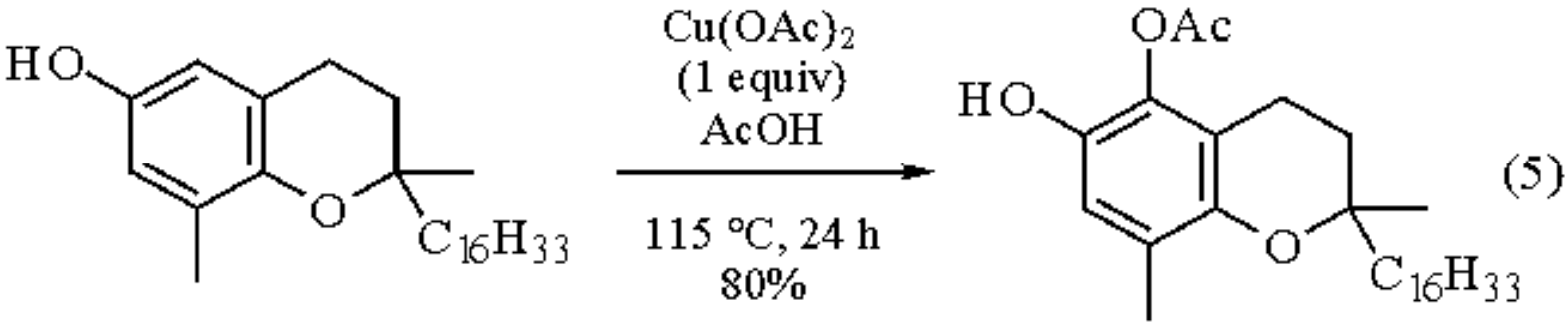

Allylic hydrogens are replaced by acyloxy groups by reaction of peroxy esters in the presence of catalytic amounts of copper salts, including $Cu(OAc)_2$.[18] The reaction probably proceeds via the formation of an allylic radical, which reacts quickly with Cu^{II} to form a Cu^{III} intermediate that generates the most substituted alkene, probably via a pericyclic transition state (eq 6).[19] Allylic oxidation can be enantioselective when performed in AcOH and ***Pivalic Acid*** in the presence of $Cu(OAc)_2$ and an L-amino acid.[20]

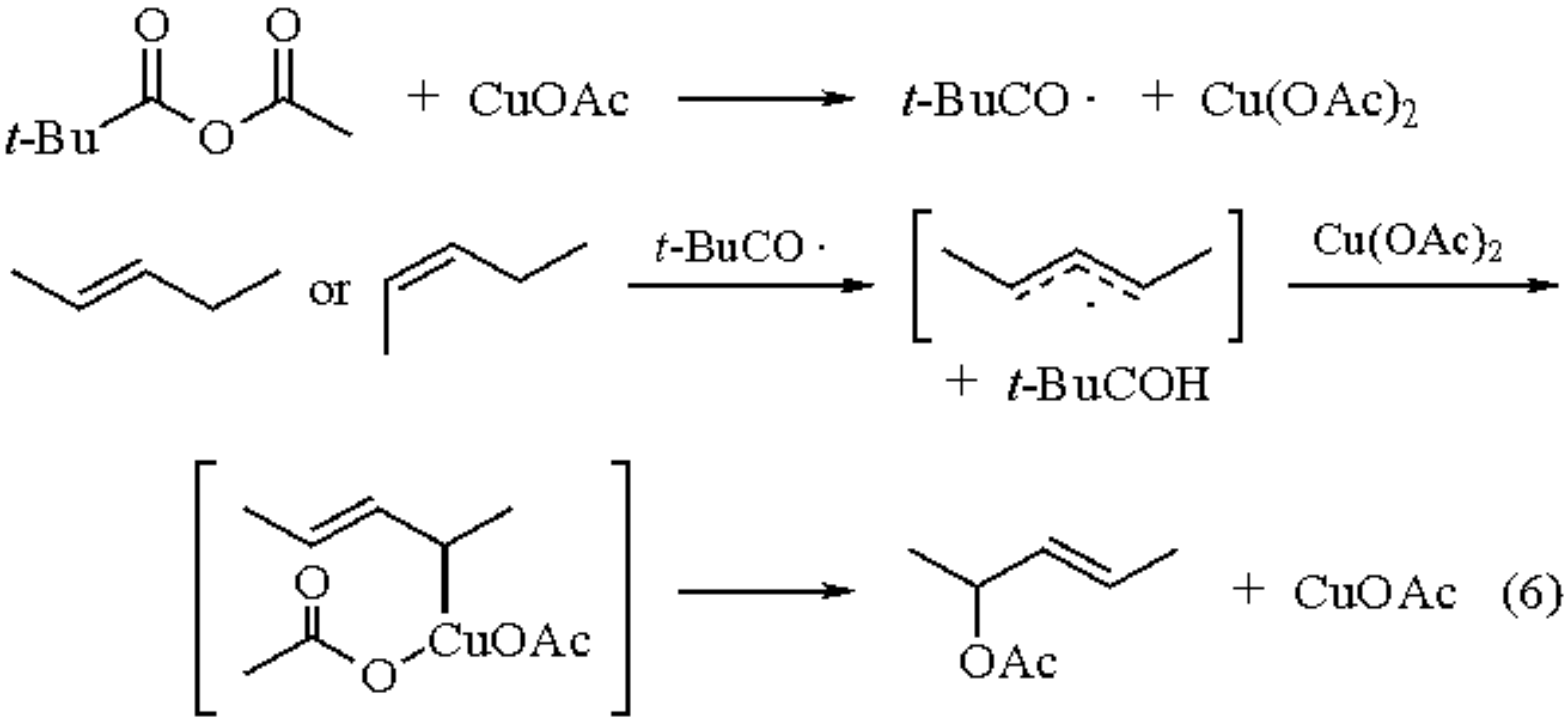

Allylic oxidation of cyclohexene and related alkenes can be achieved with catalytic amounts of ***Palladium(II) Acetate***, $Cu(OAc)_2$, hydroquinone, and O_2 as oxidant in AcOH, leading to allylic acetates.[21] Methyl glyoxylate adducts of *N*-Boc-protected allylic amines cyclize, in the presence of catalytic $Pd(OAc)_2$ and an excess of $Cu(OAc)_2$ in DMSO at 70 °C, to 5-(1-alkenyl)-2-(methoxycarbonyl)oxazolidines (eq 7).[22]

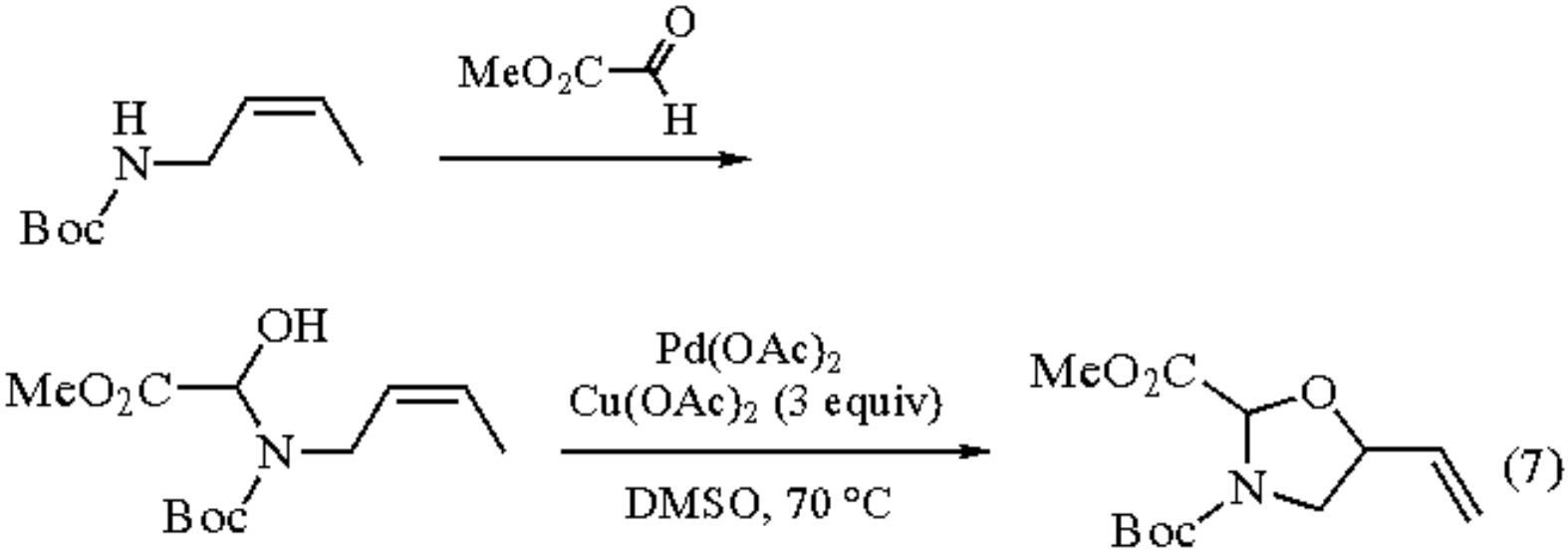

Methyl substituted benzene derivatives are oxidized in boiling AcOH to the corresponding benzyl acetates (eq 8) with sodium, potassium, or ***Ammonium Peroxydisulfate***, $Cu(OAc)_2.H_2O$, and NaOAc.[4] The peroxydisulfate radical is responsible for the primary oxidation, whereas $Cu(OAc)_2$ prevents dimerization of the intermediate benzylic radical by oxidizing it to benzyl acetate. The benzylic acetoxylation of alkyl aromatics can also be carried out with O_2 using $Pd(OAc)_2$ and $Cu(OAc)_2$ as catalysts.[23]

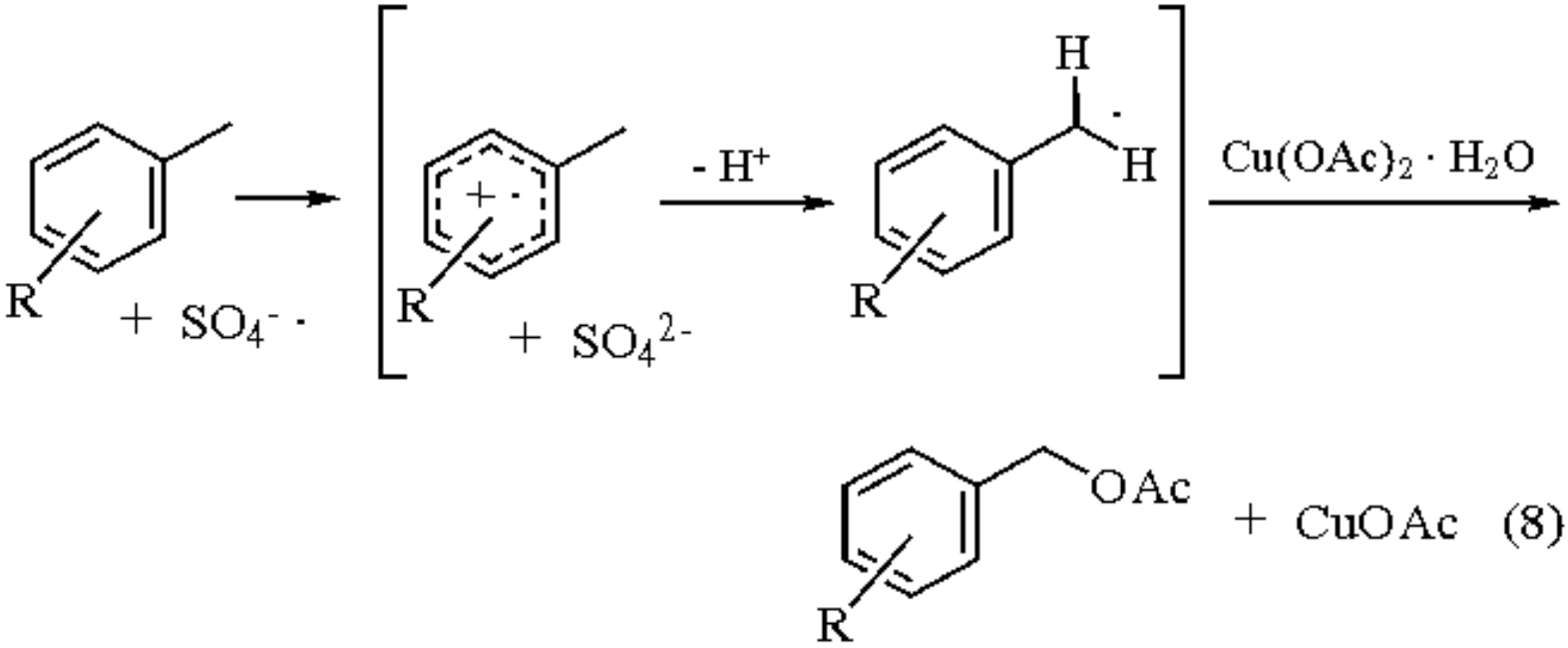

Cycloalkanes are transformed into the corresponding cycloalkenes by treatment with ***t-Butyl Hydroperoxide*** in pyridine/AcOH solution containing $Cu(OAc)_2.H_2O$. When Fe^{III} salts are used instead of $Cu(OAc)_2.H_2O$, the major product is the corresponding cycloalkanone.[24] Cyclohexanone is the main product of cyclohexane oxidation with H_2O_2, $Cu(OAc)_2.H_2O$ in pyridine, and AcOH (GoCHAgg system).[25] $Cu(OAc)_2$ also catalyzes the oxidation of secondary alcohols by ***Lead(IV) Acetate***.[26]

Carbon-Metal Bond Oxidations.

In MeOH and under O_2 atmosphere, a catalytic amount of $Cu(OAc)_2$ promotes the cleavage of the Si-C bond of (*E*)-alkenylpentafluorosilicates to give alkenyl ethers (eq 9). The reaction is highly stereoselective and leads to the (*E*)-enol ethers. In the presence of H_2O the corresponding aldehydes are obtained.[5]

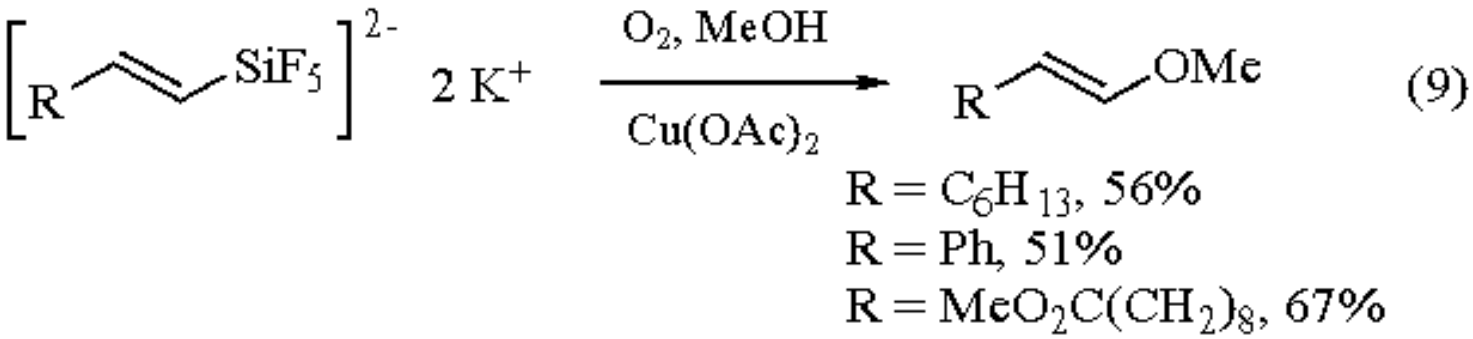

In the presence of $Cu(OAc)_2$, 1,4-additions of alkylpentafluorosilicates to α,β-unsaturated ketones take place on heating (eq 10).[5] This reaction proceeds probably by initial one-electron oxidation with formation of an alkyl radical (eq 11), which then adds to the enone.

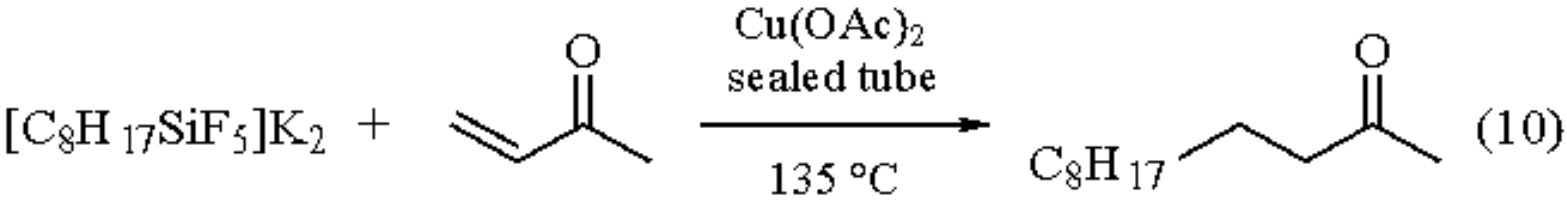

$$RSiF_5^{2-} + CuX_2 \longrightarrow R\cdot + [XSiF_5]^{2-} + CuX \quad (11)$$

The monophenylation of 1,*n*-diols with ***Triphenylbismuth Diacetate***[27] is greatly accelerated by catalytic amounts of $Cu(OAc)_2$.[28] This reaction can be enantioselective in the presence of optically active pyridinyloxazoline ligands as cocatalysts (eq 12).[29] Reaction of alcohols (ROH) with ***Triphenylbismuthine*** and $Cu(OAc)_2$ gives the corresponding phenyl ethers (PhOR) and benzene.[30] The treatment of Ph_5Sb with a catalytic amount of $Cu(OAc)_2$ in toluene at 20 °C gave 100% yields of Ph_3Sb, Ph-Ph, and PhH.[31] $Cu(OAc)_2$ catalyzes the arylation of amines by diaryliodonium salts,[32] aryl halides,[33] $Ph_3Bi(OCOCF_3)_2$,[34] and aryllead triacetates.[35]

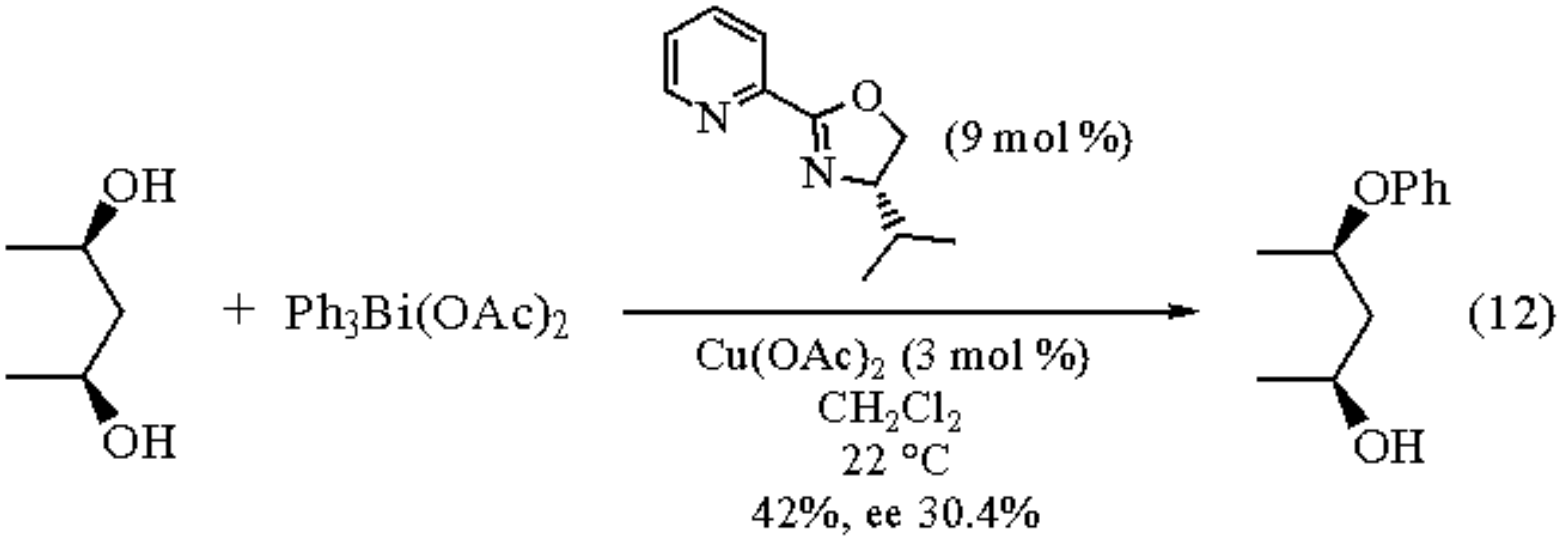

Fast Radical Scavenging and Oxidation.

Rates of oxidative decarboxylation by $Pb(OAc)_4$ of primary and secondary carboxylic acids to alkenes[36] are enhanced in the presence of catalytic amounts of $Cu(OAc)_2$ or $Cu(OAc)_2.H_2O$. This effect is attributed to the fact that the rate of one-electron-transfer oxidation of alkyl radicals by Cu^{II} salts (eq 13) approaches a diffusion-controlled rate.[3] Oxidative decarboxylation of carboxylic acids can also be carried out with ***(Diacetoxyiodo)benzene*** in the presence of a catalytic amount of anhydrous $Cu(OAc)_2$.[37]

$$RCO_2Pb(OAc)_3 \longrightarrow R\cdot + CO_2 + Pb(OAc)_3$$

$$R\cdot + Cu(OAc)_2 \longrightarrow \text{alkene} + CuOAc + AcOH$$

$$CuOAc + RCO_2Pb(OAc)_3 \longrightarrow Cu(OAc)_2 + RCO_2Pb(OAc)_2$$

$$RCO_2Pb(OAc)_2 \longrightarrow R\cdot + CO_2 + Pb(OAc)_2 \quad (13)$$

The case of radical oxidation with $Cu(OAc)_2$ has been exploited by Schreiber[38] in the fragmentation of α-alkoxyhydroperoxides, as in eq 14.[38b]

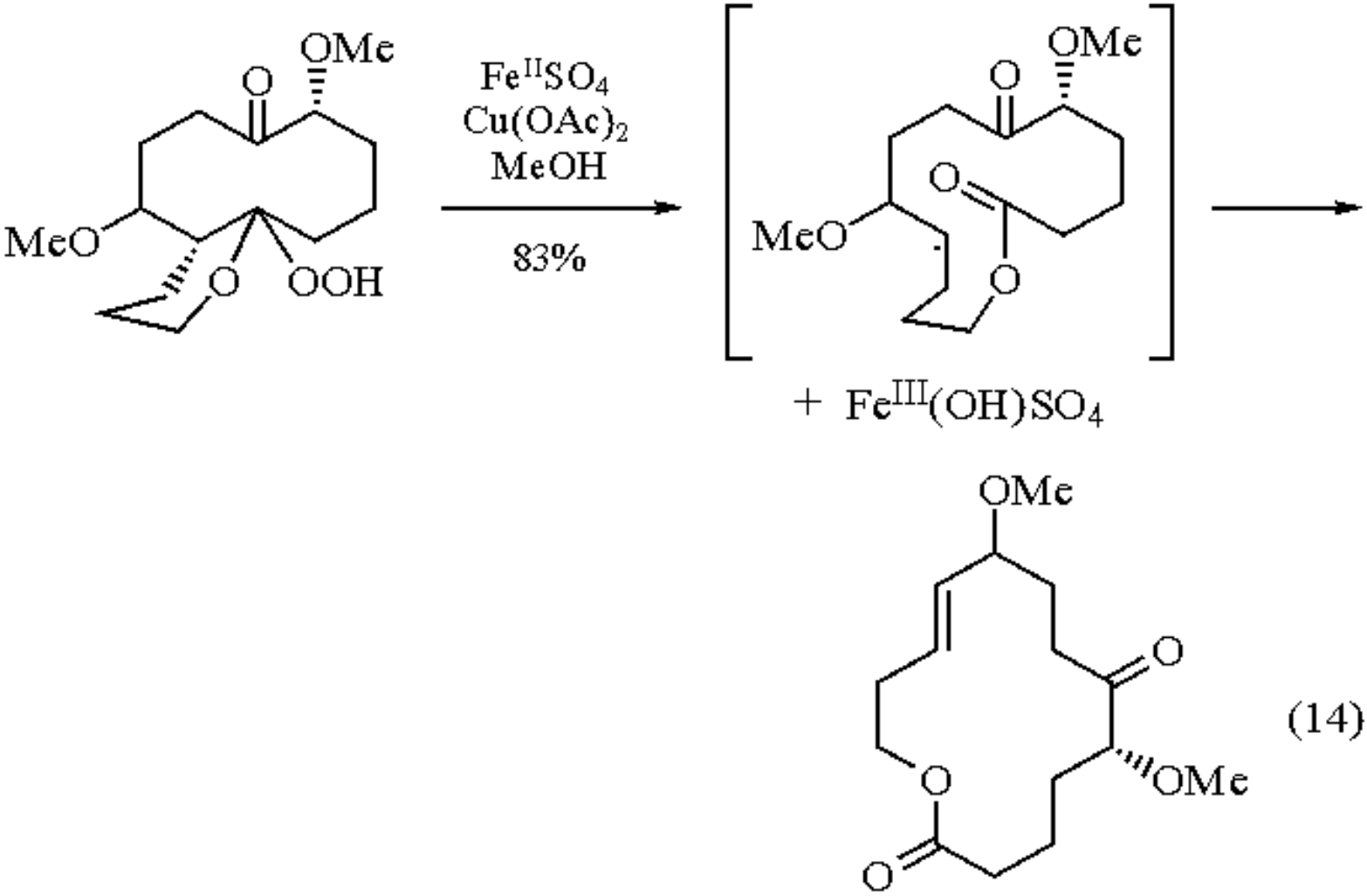

(14)

In an electrochemical system containing ***Manganese(III) Acetate***, acetic acid is added to butadiene to generate an allylic radical intermediate that is oxidized with $Cu(OAc)_2.H_2O$ to the corresponding allylic cation, leading to γ-vinyl-γ-butyrolactone (eq 15),[39] a precursor in the industrial synthesis of sorbic acid.

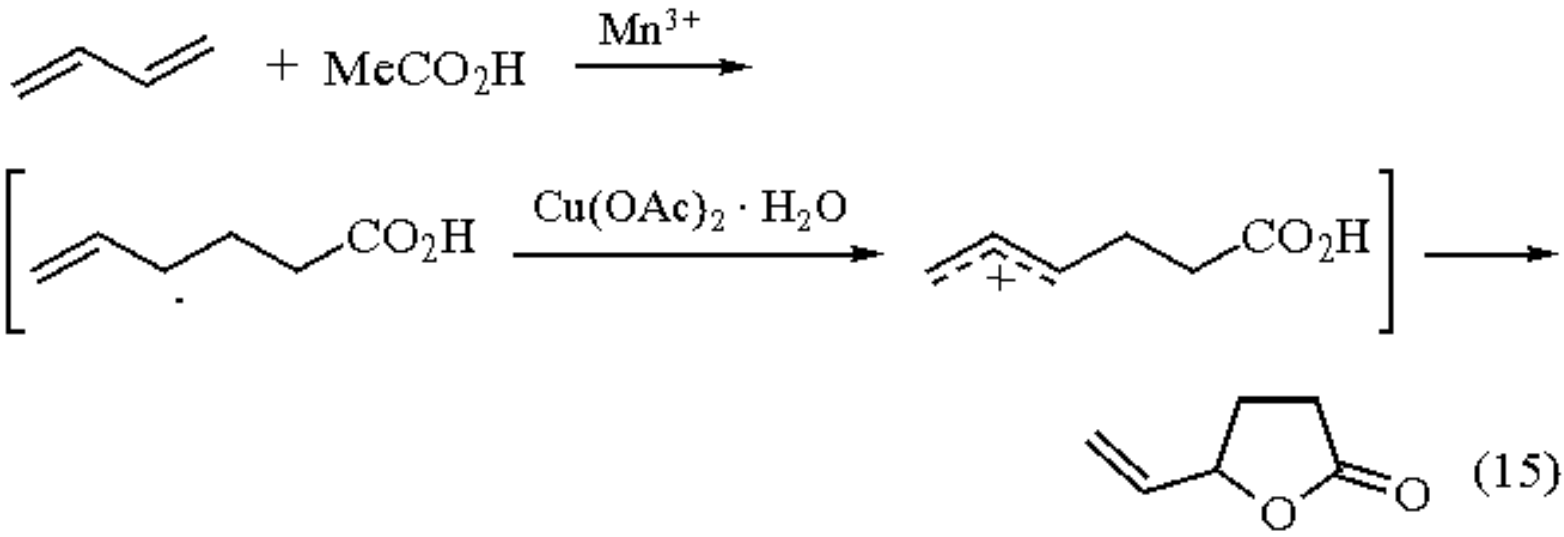

(15)

β-Oxoesters are oxidized with $Mn(OAc)_3$ to the corresponding radicals that can add intermolecularly[40] or intramolecularly (eq 16)[41] to generate alkyl radicals. In the presence of $Cu(OAc)_2$ the latter are rapidly quenched and oxidized to give alkenes. Radical arylation with alkyl iodides can be induced with ***Dibenzoyl Peroxide***; the yield of the reaction can be improved using a catalytic amount of $Cu(OAc)_2.H_2O$,[42] which minimizes hydrogen abstraction by the intermediate radical but introduces a competitive electron-transfer oxidation of the intermediate radical. The oxidative addition of disulfides to alkenes (Trost hydroxysulfenylation[43]) can be promoted by catalytic amounts of $Cu(OAc)_2$.[44]

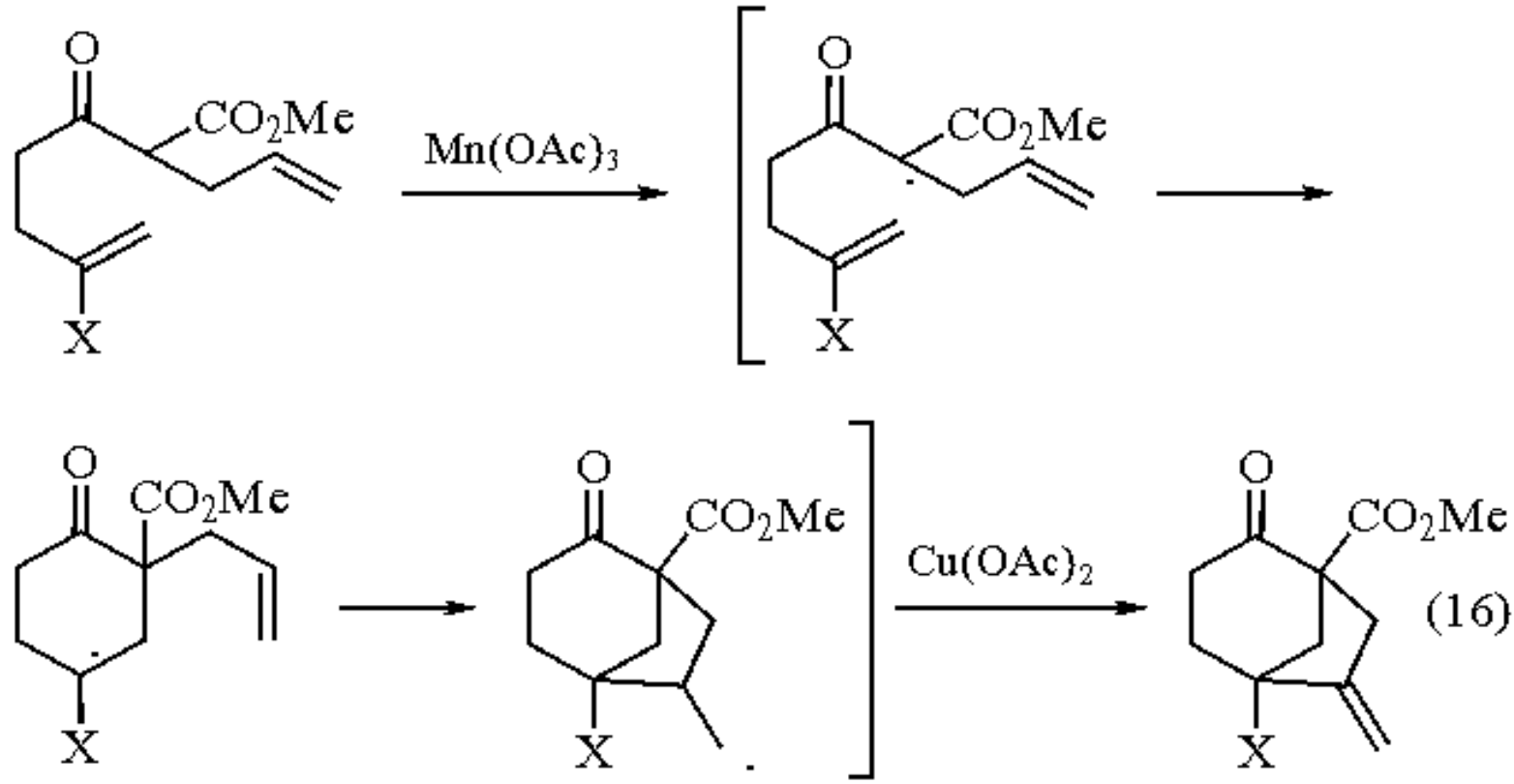

(16)

Reoxidant in Palladium-Catalyzed Reactions.

$Cu(OAc)_2$ has been used as a reoxidant in the Wacker oxidation ($CH_2{=}CH_2 + O_2 \rightarrow CH_3CHO$)[45] and in the $Pd(OAc)_2$-catalyzed alkenylation of aromatic compounds with alkenes[46] (eq 17).[47] $Pd(OAc)_2$ and $Cu(OAc)_2$ are effective catalysts for the reactions of nitrosobenzenes with carbon monoxide, dioxygen, and alcohols that give the corresponding *N*-alkylcarbamates.[48]

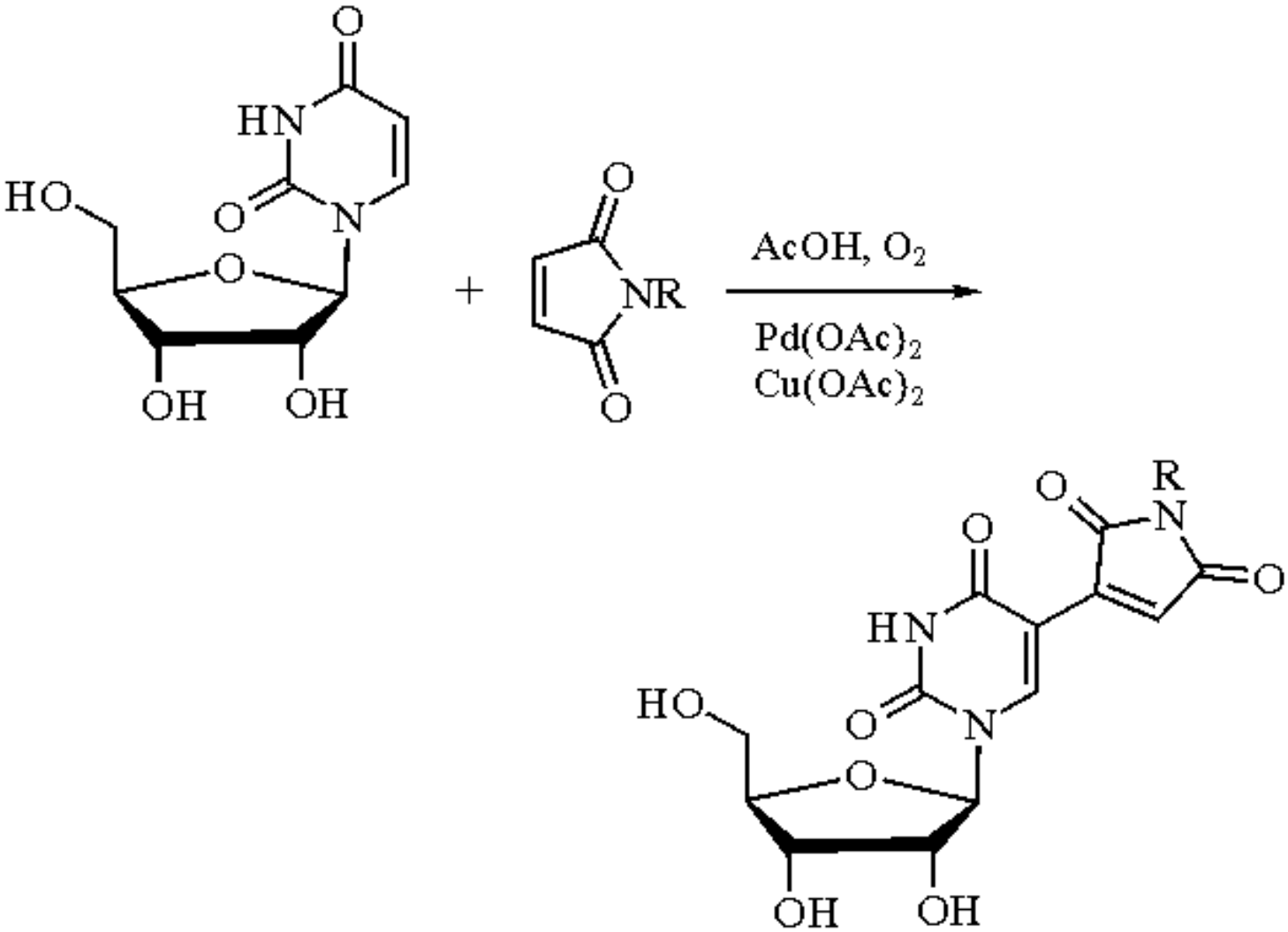

(17)

Enantioselective Cyclopropanation.

$Cu(OAc)_2$ has been used as procatalyst in the asymmetric cyclopropanation[49] of alkenes with alkyl diazoacetates with optically pure imines as cocatalyst (eq 18).[6]

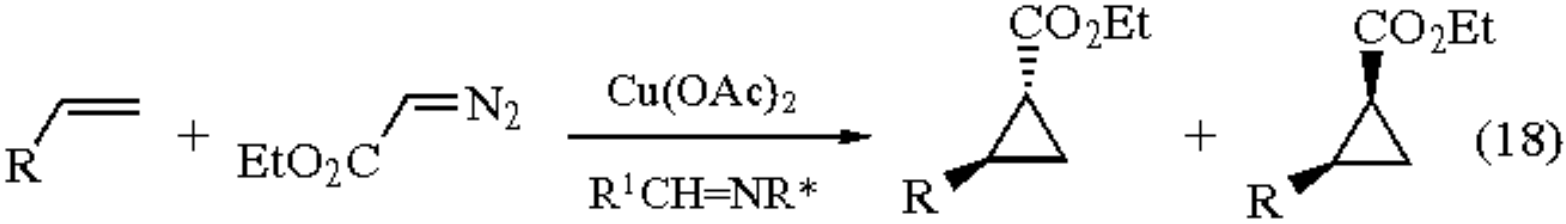

$Cu(OAc)_2$ as Lewis Acid.

Decarboxylation of L-tryptophan into L-tryptamine proved most effective in HMPA in the presence of $Cu(OAc)_2$.[50] In boiling MeCN and under $Cu(OAc)_2.H_2O$ catalysis, aldoximes are converted smoothly into nitriles.[51] In the presence of various Lewis acids including $Cu(OAc)_2$, cyclodeca-1,2,5,8-tetraene is rearranged to *cis,syn*-tricyclo[4.4.0.$0^{2,4}$]deca-5,8-diene (eq 19).[52]

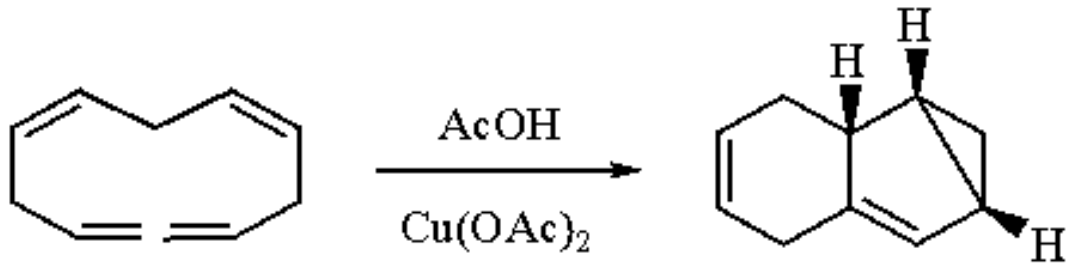

(19)

The Michael reaction of $O_2NCH_2CO_2R$ (R = Me, Bn) with $R^1COCH{=}CHR^2$ (R^1 = Me, Et, R^2 = H; R^1 = R^2 = Me) is catalyzed by $Cu(OAc)_2$ and gives $R^1COCH_2CHR^2CH(NO_2)CO_2R$ in dioxane at 100 °C.[53] Knoevenagel condensation of *t*-butyl malonate with ***Paraformaldehyde*** to give di-*t*-butyl methylidenemalonate can be achieved in the presence of KOH and $Cu(OAc)_2$.[54] Lithium imine anions of α-amino esters undergo $Cu(OAc)_2$-catalyzed reactions with α,o-dihalogenoalkanes to give the corresponding o-halogenoalkylimines.[55] $Cu(OAc)_2$ catalyzes the coupling of PhYbI with *n*-BuI, giving *n*-BuPh and Ph-Ph.[56]

Acyl hydrazides are converted to the corresponding carboxylic acids by bubbling oxygen through a THF or MeOH solution containing the hydrazide and a catalytic amount of $Cu(OAc)_2$ (eq 20).[58]

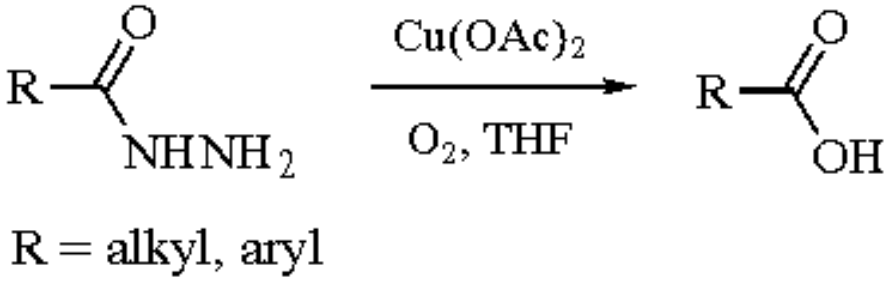

(20)

Synthesis of Ynamines.

Phenylacetylene reacts with dimethylamine under $Cu(OAc)_2$ catalysis to produce *N*,*N*-dimethyl-2-phenylethynylamine (eq 21).[59] The reaction is effected by bubbling oxygen through a benzene solution of the reagents and $Cu(OAc)_2$; in the absence of oxygen, 1,4-diphenylbutadiyne is the sole product. This may be suppressed by adding a reducing agent, such as hydrazine, to the reaction mixture.

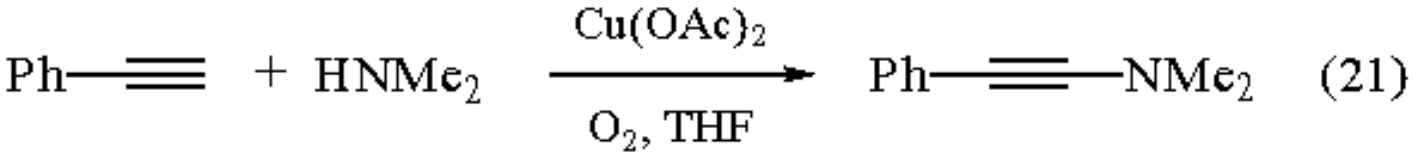

Related Reagents.

Copper(I) Acetate; ***Copper(II) Acetate-Iron(II) Sulfate***; ***Iodine-Copper(II) Acetate***; ***Lead(IV) Acetate-Copper(II) Acetate***; ***Manganese(III) Acetate-Copper(II) Acetate***; ***Sodium Hydride-Copper(II) Acetate-Sodium t-Pentoxide***; ***Zinc-Copper(II) Acetate-Silver Nitrate***.

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Copper(II) Acetate-Iron(II) Sulfate

$Cu(OAc)_2$-$FeSO_4$

($Cu(OAc)_2$)

[142-71-2] · $C_4H_6CuO_4$ · Copper(II) Acetate-Iron(II) Sulfate · (MW 181.64) ($Cu(OAc)_2.H_2O$)

[6046-93-1] · $C_4H_8CuO_5$ · Copper(II) Acetate-Iron(II) Sulfate · (MW 199.65) ($FeSO_4.7H_2O$)

[7782-63-0] · FeO_4S · Copper(II) Acetate-Iron(II) Sulfate · (MW 278.02)

(hydroperoxide reduction; alkoxy radical formation and β-fragmentation; carbon radical oxidation and alkene formation; stereocontrolled macrolide synthesis)

Alternate Name: cupric acetate-ferrous sulfate.

Physical Data: $Cu(OAc)_2.H_2O$: mp 115 °C (dec 240 °C); *d* 1.882 g cm^{-3}. $FeSO_4.7H_2O$: forms tetrahydrate at 56.6 °C, monohydrate at 65 °C, loses last H_2O at about 300 °C and dec at higher temperatures; *d* 1.897 g cm^{-3}.

Solubility: $Cu(OAc)_2.H_2O$: sol H_2O and alcohol; slightly sol ether and glycerol. $FeSO_4.7H_2O$: sol H_2O; very slightly sol alcohol.

Form Supplied in: $Cu(OAc)_2.H_2O$: dark green solid; widely available. $FeSO_4.7H_2O$: blue-green solid; widely available.

Preparative Methods: the reagents are prepared individually as saturated solutions in methanol and used directly. Generally, the substrate is mixed with methanolic copper acetate and to this is added a methanolic solution of iron sulfate.

Handling, Storage, and Precautions: aqueous solutions of $FeSO_4$ are oxidized by air. Use in a fume hood.

Alkoxy Radical Generation by Iron(II) Sulfate.

One-electron reduction of peroxide bonds by $FeSO_4$ generates alkoxy radicals[1-4] which are valuable intermediates in organic synthesis.[5] Alkoxy radicals rearrange to more stable alkyl radicals via δ-hydrogen abstraction,[6-8] β-fragmentation[9-17] or, in the presence of a suitably disposed pendant alkene, cyclization[18] pathways. In most cases the

generated alkyl radical is oxidatively trapped giving, for example, alkene or alkyl halide products; copper(II) acetate plays the role of alkyl radical oxidant in the reagent pair.

Alkyl Radical Oxidation by Copper(II) Acetate.

One-electron oxidation of secondary carbon radicals by $Cu(OAc)_2$ efficiently generates alkene products. Oxidation of simple alkyl radicals, such as 3-pentyl and 2-butyl, gives a mixture of alkene isomers.[2,19] In more complex systems, however, alkene formation often proceeds regio- and stereoselectively.[1,20-23] In some cases, heteroatom coordination to a Cu^{III} alkyl intermediate has been invoked to explain product selectivity.[1,22,24]

Macrolide Synthesis from α-Alkoxy Hydroperoxides.

Schreiber has used the fragmentation of α-alkoxy hydroperoxides with copper(II) acetate-iron(II) sulfate to prepare macrolides (eqs 1-3).[20-22] Requisite α-alkoxy hydroperoxides can be prepared by direct peroxyacetalization of carbonyl precursors or by trapping carbonyl oxide intermediates generated by ozonolysis. In eq 1 an alkoxy radical is produced from the hydroperoxide by the transfer of an electron from Fe^{2+}; the alkoxy radical then spontaneously transforms into a carbon-centered radical which is then oxidized by the Cu^{2+} ion to give an alkylcopper intermediate which undergoes a β-elimination to furnish the product recifeiolide.[2] The exclusive *trans* geometry observed in the product is explained by means of internal coordination of the intermediate alkylcopper with transannular oxygen lone pairs.[22]

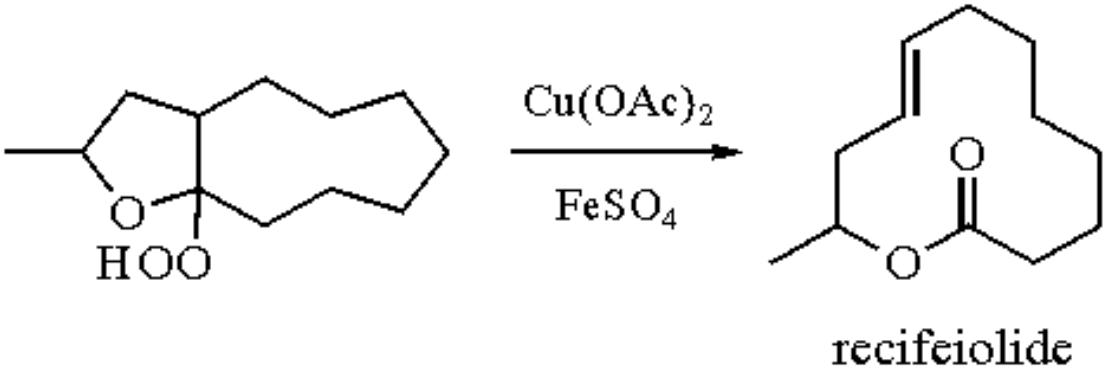

(1)

This method has been used to prepare substrates for use in studies directed towards preparation of ionophore subunits (eq 2)[27] and for the preparation of 14-membered macrocycles from octalins (eq 3).[21] Ozonolysis of (**1**) (eq 3) selectively gives hydroperoxide (**2**) with the allylic methoxy group of (**1**) directing breakdown of the primary ozonide.[25] The sequence of hydroperoxide reduction, followed by β-fragmentation and alkene oxidation, results in overall dehydration of the molecule. Similar fragmentations have been achieved by treatment of α-alkoxy hydroperoxides with ***Methanesulfonyl Chloride/Sulfur Dioxide***.[26]

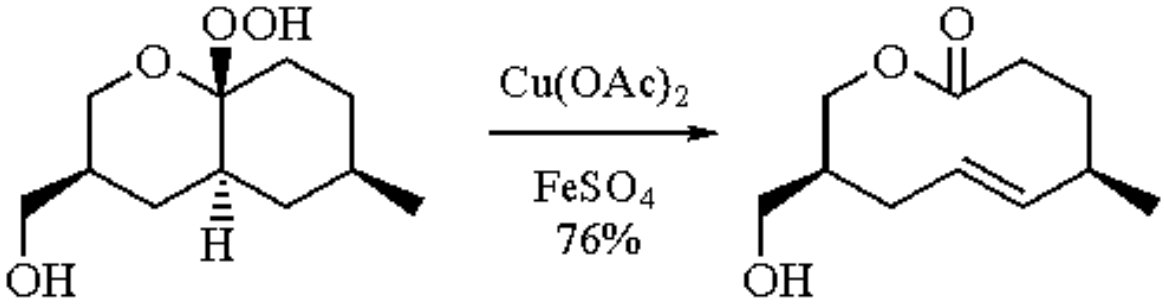

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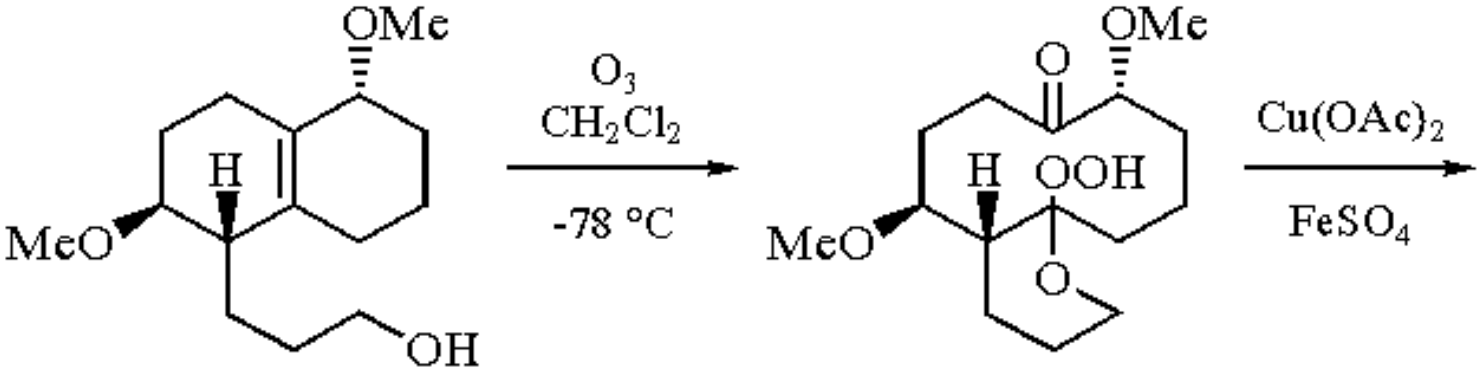

(1) (2)

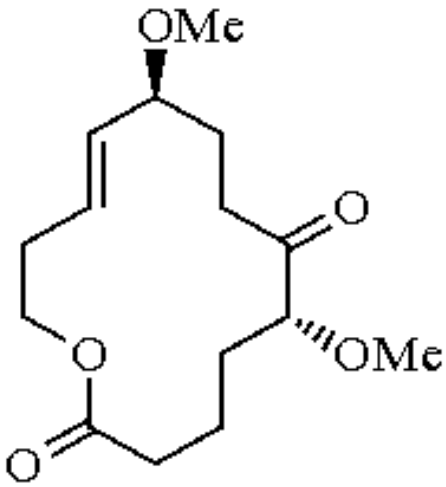

(3)

(3)

The redox reagents were also used in a new synthesis of racemic *syn*-4,8-dimethyldecanal, the aggregation pheromone of the confused and red flour beetles, respectively.[32]

Other β-Fragmentation Reactions.

The isopropenyl group of carvone derivatives can be removed by ozonolysis in methanol, followed by treatment of the intermediate α-methoxy hydroperoxide with the reagents (eqs 5 and 6).[13,22] The (+)-6-methylcyclohex-2-enone produced in eq 5 is a useful synthetic intermediate.[22] A similar reaction occurs with ozonolysis products from cycloalkenes (eqs 4 and 7).[28,32]

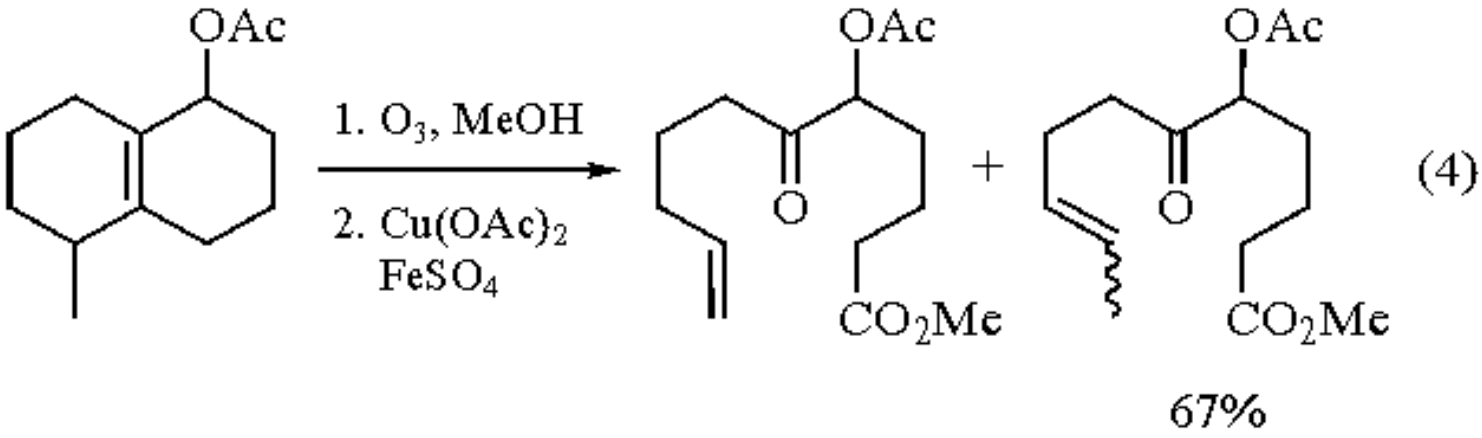

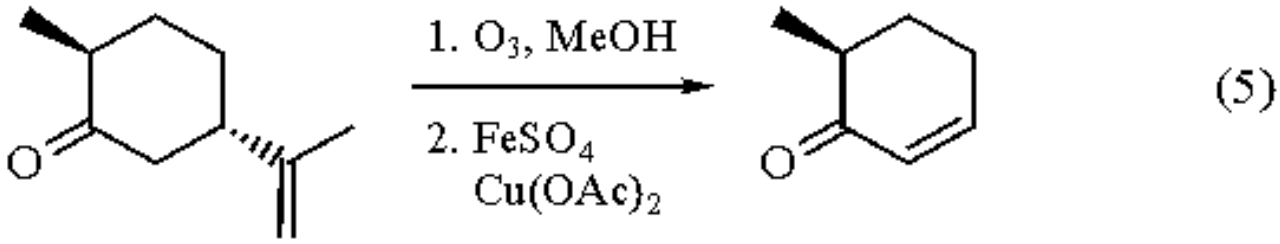

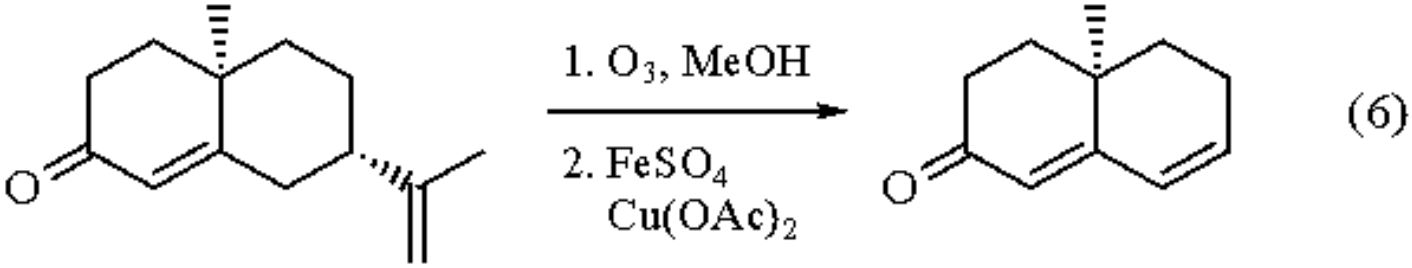

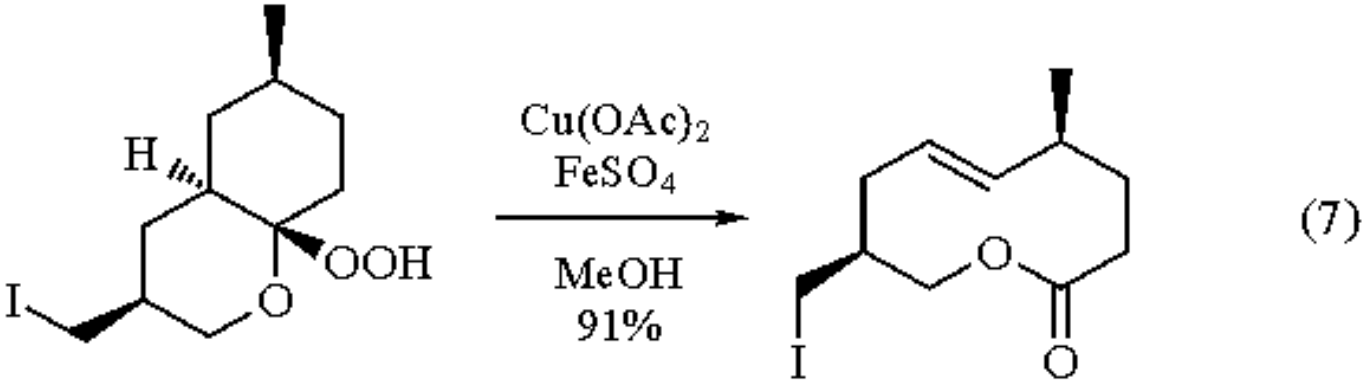

Copper(II) acetate-iron(II) sulfate was used to convert allyl hydroperoxide (**4**) to cyclic ether (**5**) (eq 8), which is an important fragrance chemical.[12] Here the oxidized alkyl radical is trapped by an internal nucleophile before it can form the normal alkene product. Other methods to reduce the hydroperoxide (**4**) were ineffective.

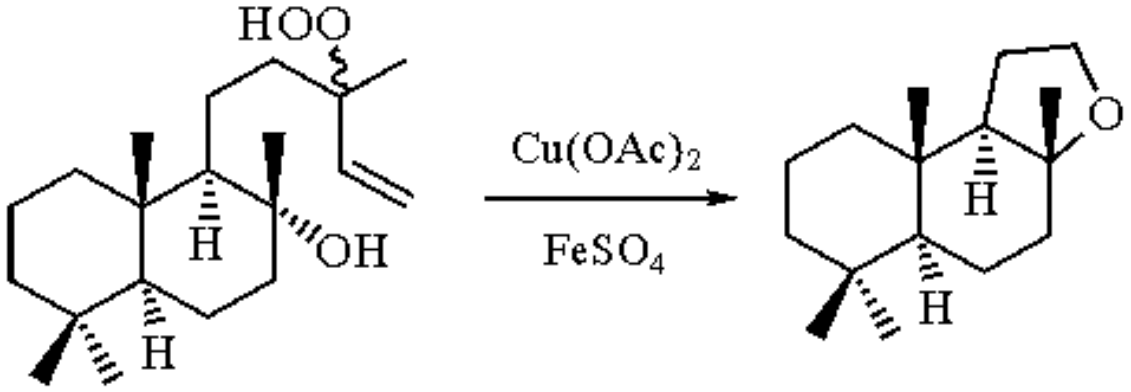

(8)

(4) (5)

Iron(II) will promote homolysis of the O-O bond in cyclic peroxides.[29,30] Treatment of tetracyclic secondary ozonide (**6**) with the reagents gives cyclopentene derivative (**7**) (eq 9).[31]

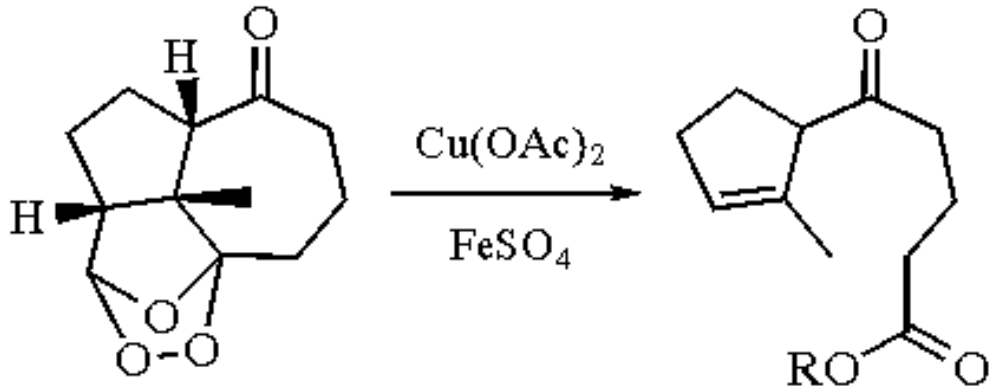

(9)

(6) (7)

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Copper(I) Acetylacetonate

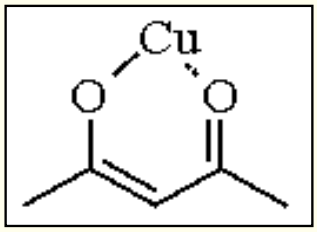

[14220-26-9] · $C_5H_7CuO_2$ · Copper(I) Acetylacetonate · (MW 162.65)

(catalyst for the decomposition of diazo compounds[2] and for Michael addition[3,4])

Alternate Names: cuprous acetylacetonate; (2,4-pentanedionato)copper.

Physical Data: prepared in situ.[1]

Solubility: sol dioxane, $MeNO_2$, MeCN, acetic acid.[3]

Preparative Method: can be prepared by reacting acetylacetone (***2,4-Pentanedione***) with an ammoniacal solution of CuOH (copper(I) hydroxide).[1]

Handling, Storage, and Precautions: air-sensitive; irritant.

Catalysis of the Decomposition of Diazo Compounds.

Copper(I) acetylacetonate is an effective catalyst for the decomposition of α-diazo ketones to copper carbenoids, which can undergo carbene insertion reactions (eq 1). This strategy was used in a synthesis of *cis*-jasmone (eqs 2 and 3).[2] However, the catalyst more commonly used in the decomposition of diazo compounds is ***Copper(II) Acetylacetonate***, which is commercially available.[2]

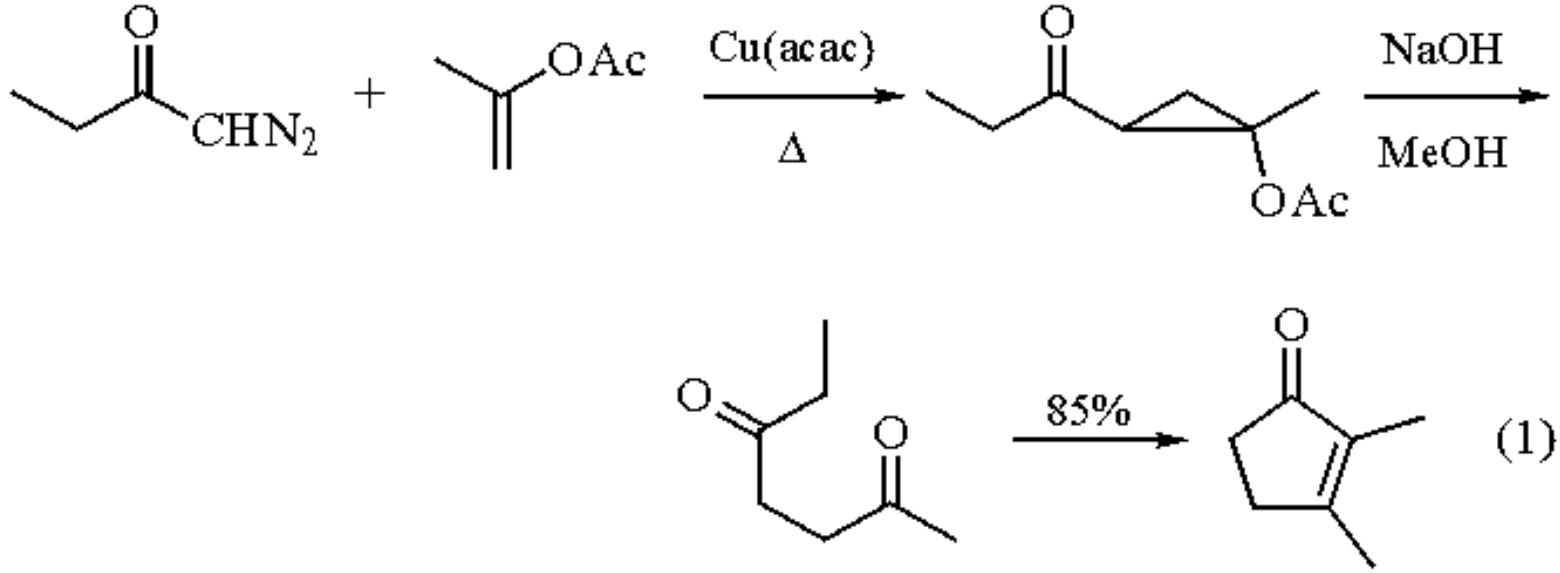
O
CHN2
+
OAc
Cu(acac)
Δ
O
OAc
NaOH
MeOH
O
O
85%
O
(1)

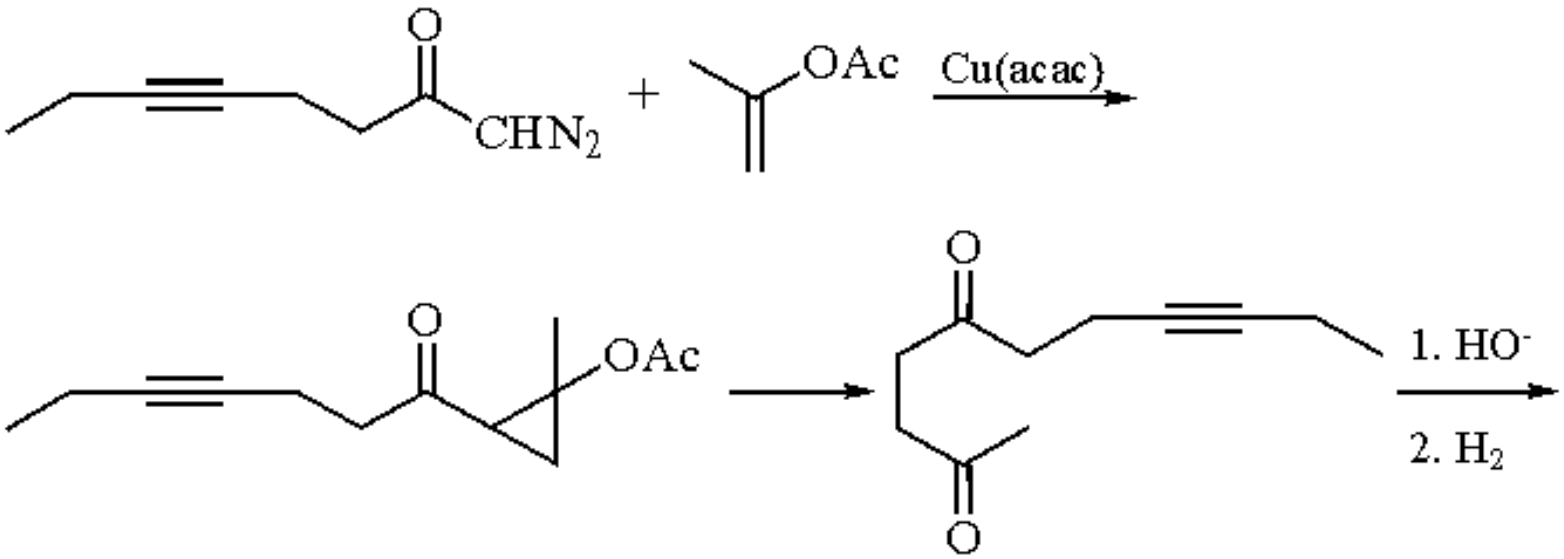
O
CHN2
+
OAc
Cu(acac)
O
OAc
O
O
1. HO-
2. H2

(1)

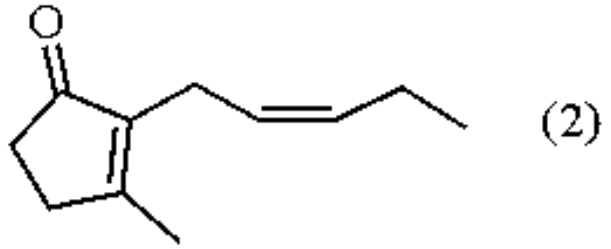
O
(2)

(2)

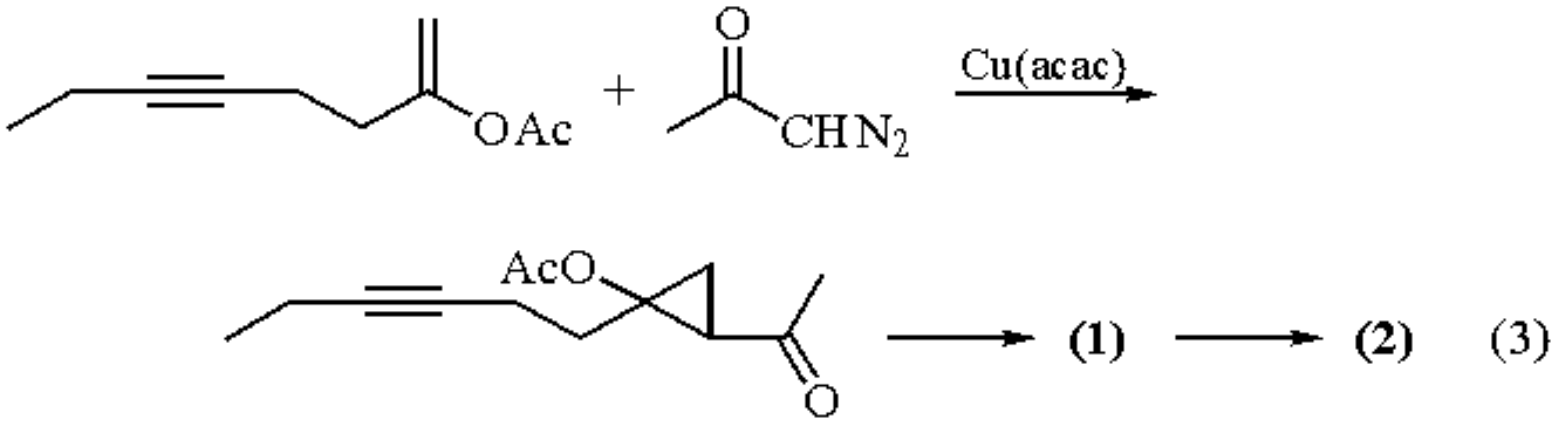

Hou reported an intramolecular carbene insertion reaction catalyzed by this reagent and also by ***Palladium(II) Acetate***.[5] The reaction of α-*O*-allyl- or α-*N*-allyl-α´-diazopropanone derivatives, such as $CH_2{=}CHCH_2OCH(Ph)COCHN_2$, give high yields of the corresponding pyranones in CH_2Cl_2 at room temperature under the catalysis of copper(I) acetylacetonate.[5]

Catalysis of Michael Additions.[3]

Cu(acac) catalyzes the Michael addition of β-dicarbonyls to 2-cyclohexenones and 2-cyclopentenones in the presence of ***Boron Trifluoride Etherate*** (eqs 4-6).[3,4]

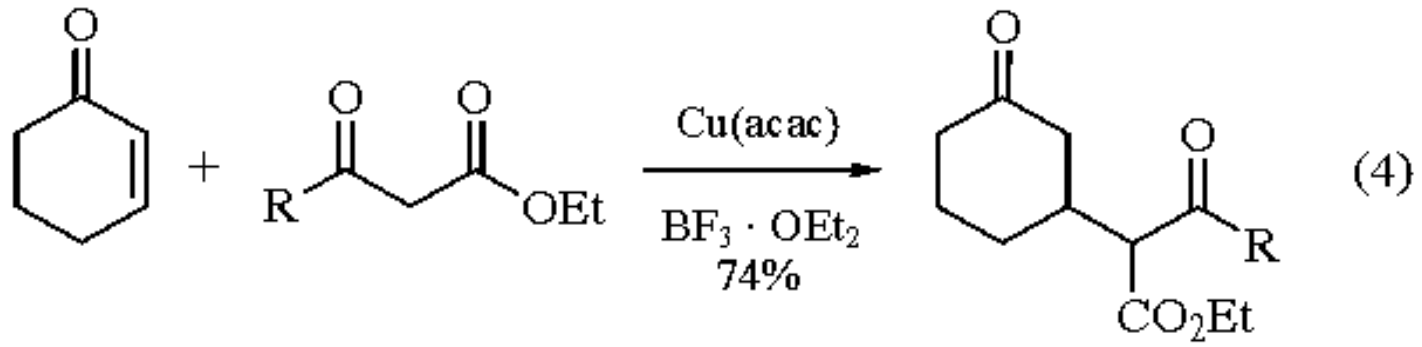

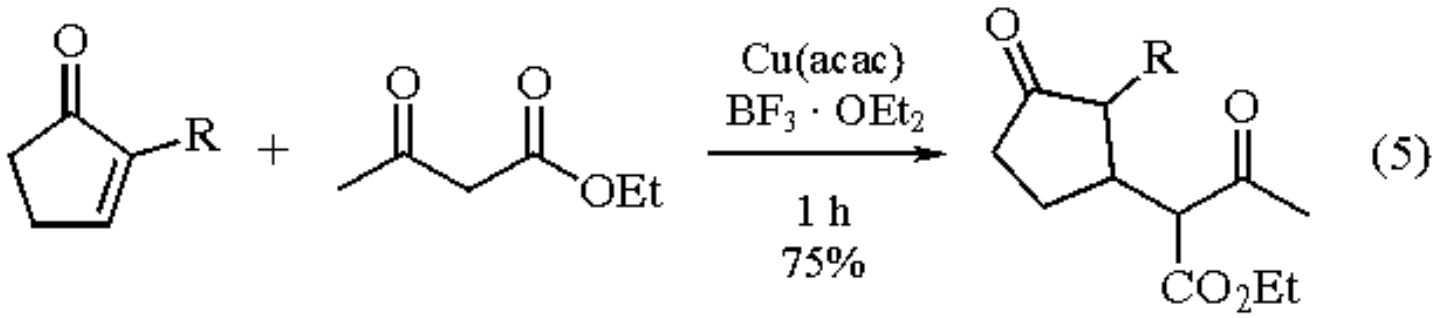

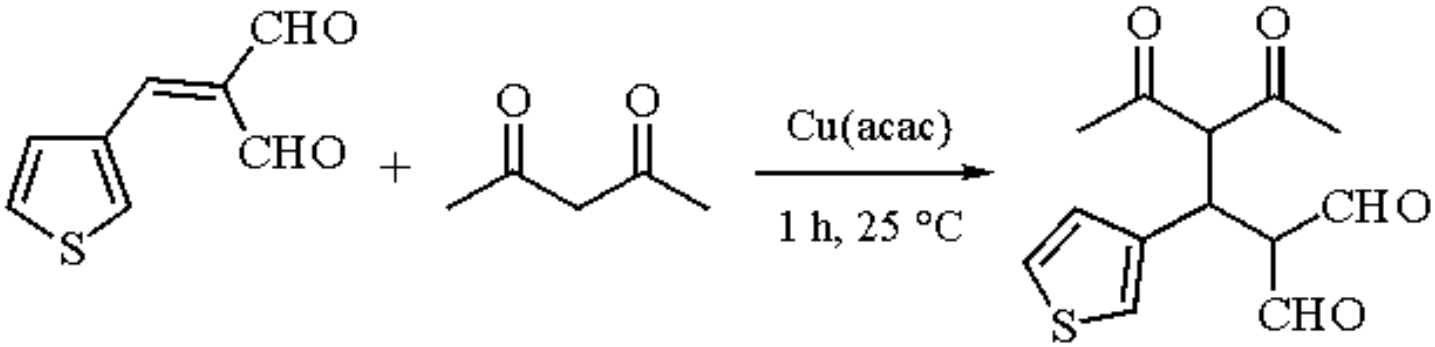

(6)

It is believed that the catalyzed Michael addition has the mechanism shown in eq 7. Because the metal chelate is very stable, this catalytic method is irreversible, which explains the high yield of the method compared to the base-catalyzed Michael addition.[3,4]

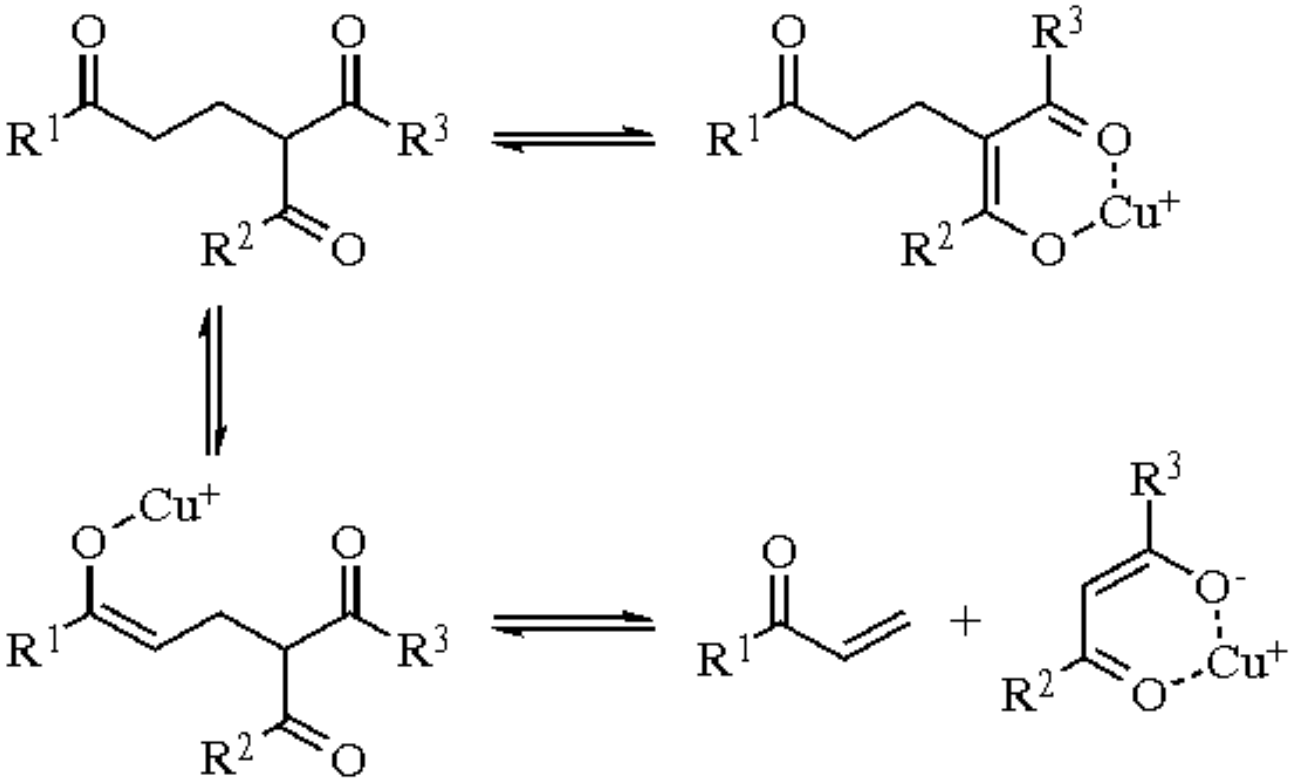

(7)

Under a variety of conditions with this catalyst, the substituted α,β-unsaturated ketones and esters (**3-6**) are inert to Michael addition.

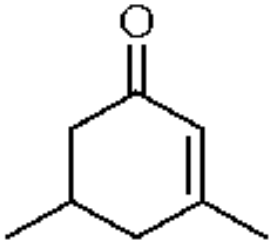

(3)

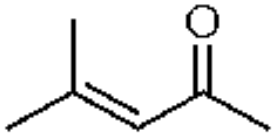

(4)

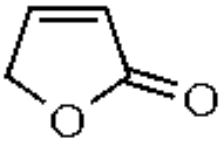

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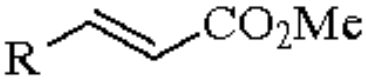

(6)

R = Me, Ph

Related Reagents.

Bis(acetylacetonato)zinc(II); ***Copper(II) Acetylacetonate***; ***Tris(acetylacetonato)indium***; ***Manganese(III) Acetylacetonate***; ***Nickel(II) Acetylacetonate***; ***Palladium(II) Acetylacetonate***; ***2,4-Pentanedione***; ***Tris(acetylacetonato)iron(III)***; ***Vanadyl Bis(acetylacetonate)***.

---

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Copper(II) Acetylacetonate

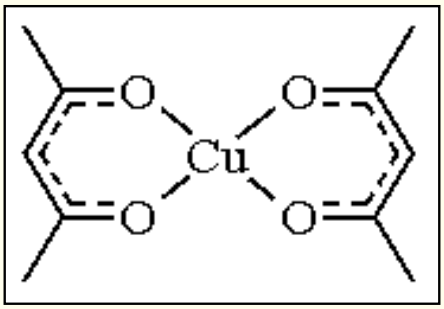

[13395-16-9; 46369-53-3] · $C_{10}H_{14}CuO_4$ · Copper(II) Acetylacetonate · (MW 261.76)

(catalyst for decomposition of diazo compounds[1-4] and for coupling reactions of organometallics with organic halides and sulfones[9-11,13])

Alternate Names: cupric acetylacetonate; bis(2,4-pentanedionato-*O,O´*)copper.

Physical Data: crystalline solid, mp 284-288 °C (dec); structural studies have been reported.[14]

Solubility: sol $CHCl_3$; sl sol alcohols.

Form Supplied in: commercially available solid.

Preparative Methods: several available, e.g. addition of acetylacetone (***2,4-Pentanedione***) to an aq soln of $Cu(NH_3)_4^{2+}$ prepared from copper(II) nitrate trihydrate and conc aq NH_3.[15]

Purification: recrystallization from $CHCl_3$.[15a]

Handling, Storage, and Precautions: irritant.

Decomposition of Diazo Compounds.

Copper(II) acetylacetonate has been used to catalyze the decomposition of diazo compounds in preparations of carbenoids. The influence of copper chelates on carbene reactions is due to coordination with the diazoalkane as a fifth ligand to give a complex which decomposes to a copper-carbene complex. ***Copper(I) Acetylacetonate*** was also reported to have similar functionality. The reaction mechanism has been studied, based on the decomposition of ***Diphenyldiazomethane*** (eqs 1 and 2).[1]

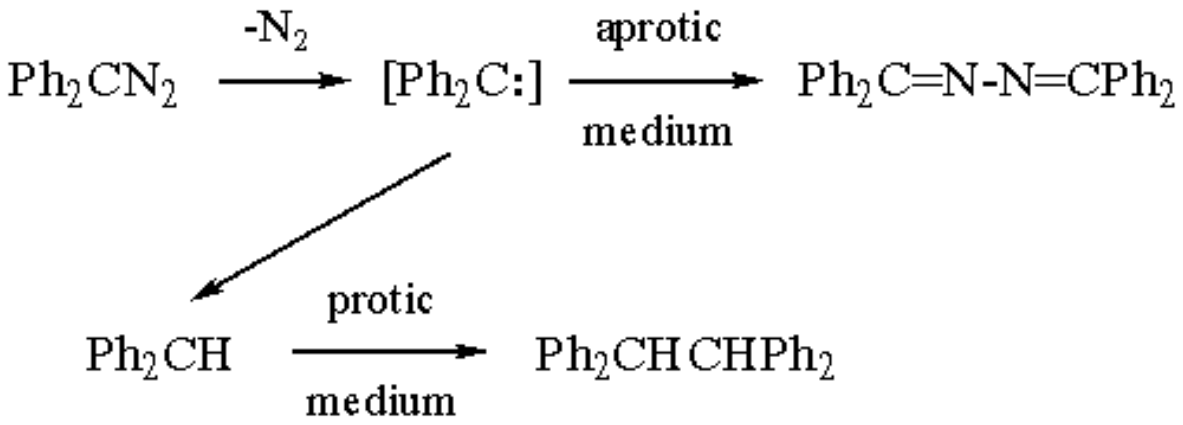

(1)

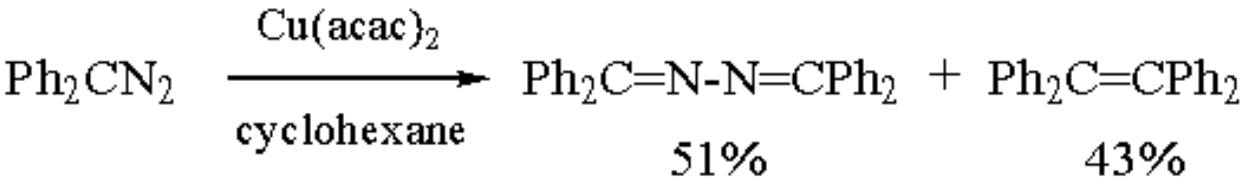

(2)

A variety of thermal cyclizations utilize copper(II) acetylacetonate-catalyzed carbene reactions (eqs 3-5).[2-6]

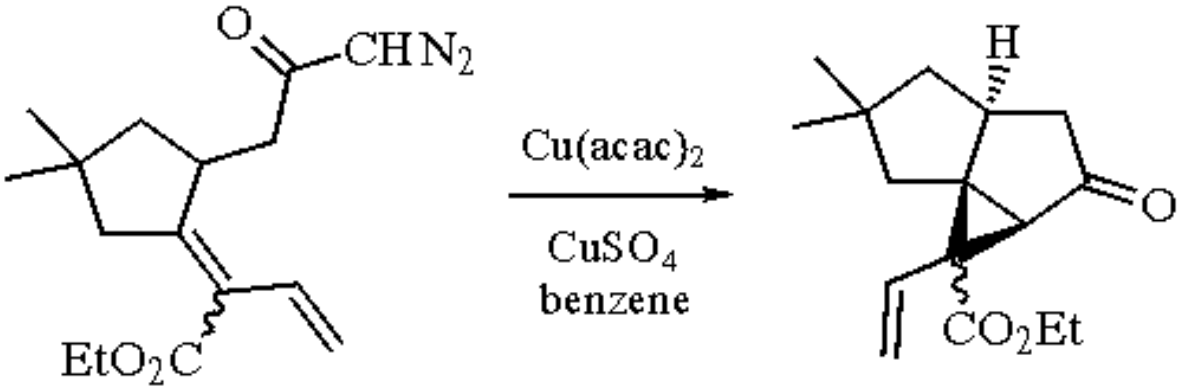

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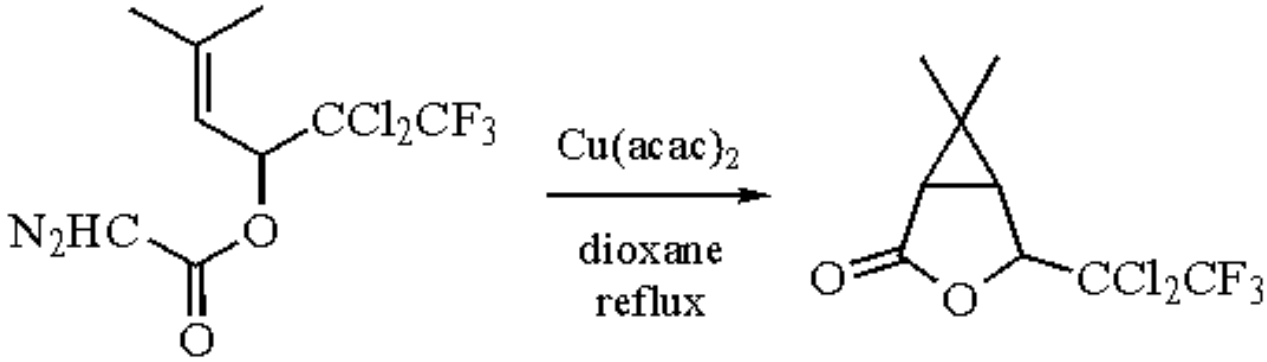

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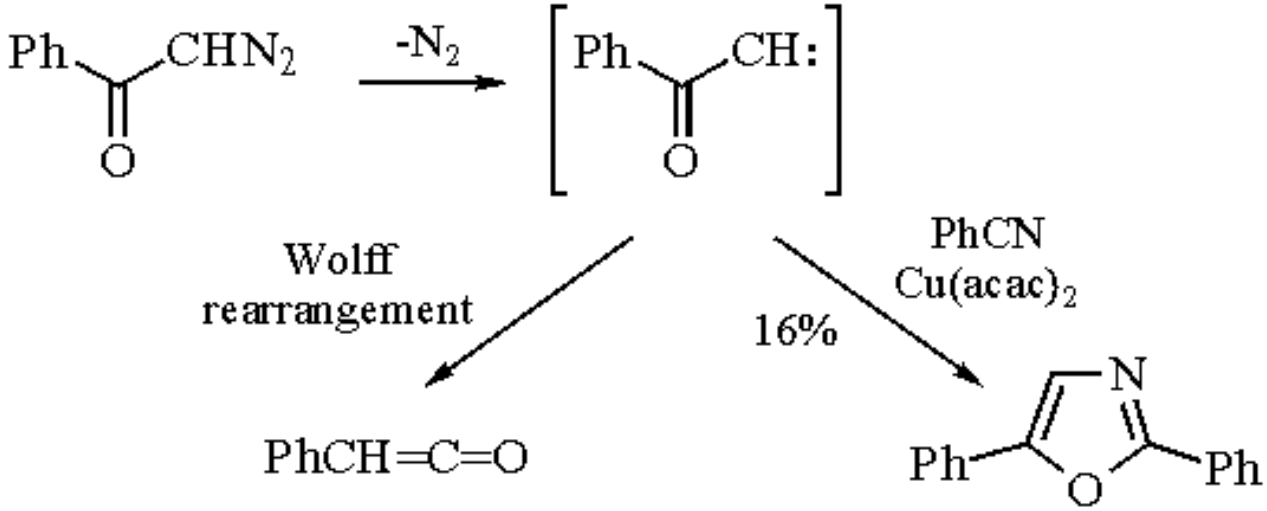

(5)

Copper(II) acetylacetonate catalyzes the reaction of 2-azido-1,4-quinones with conjugated alkadienyl side chains, giving dihydropyrroloindoloquinones or dihydropyrroloquinolinoquinones, which are not produced by uncatalyzed pyrolysis or photochemical reactions (eq 6).[7] In this example, $Cu(acac)_2$ showed greater activity then many other acetylacetonate complexes or copper powder.

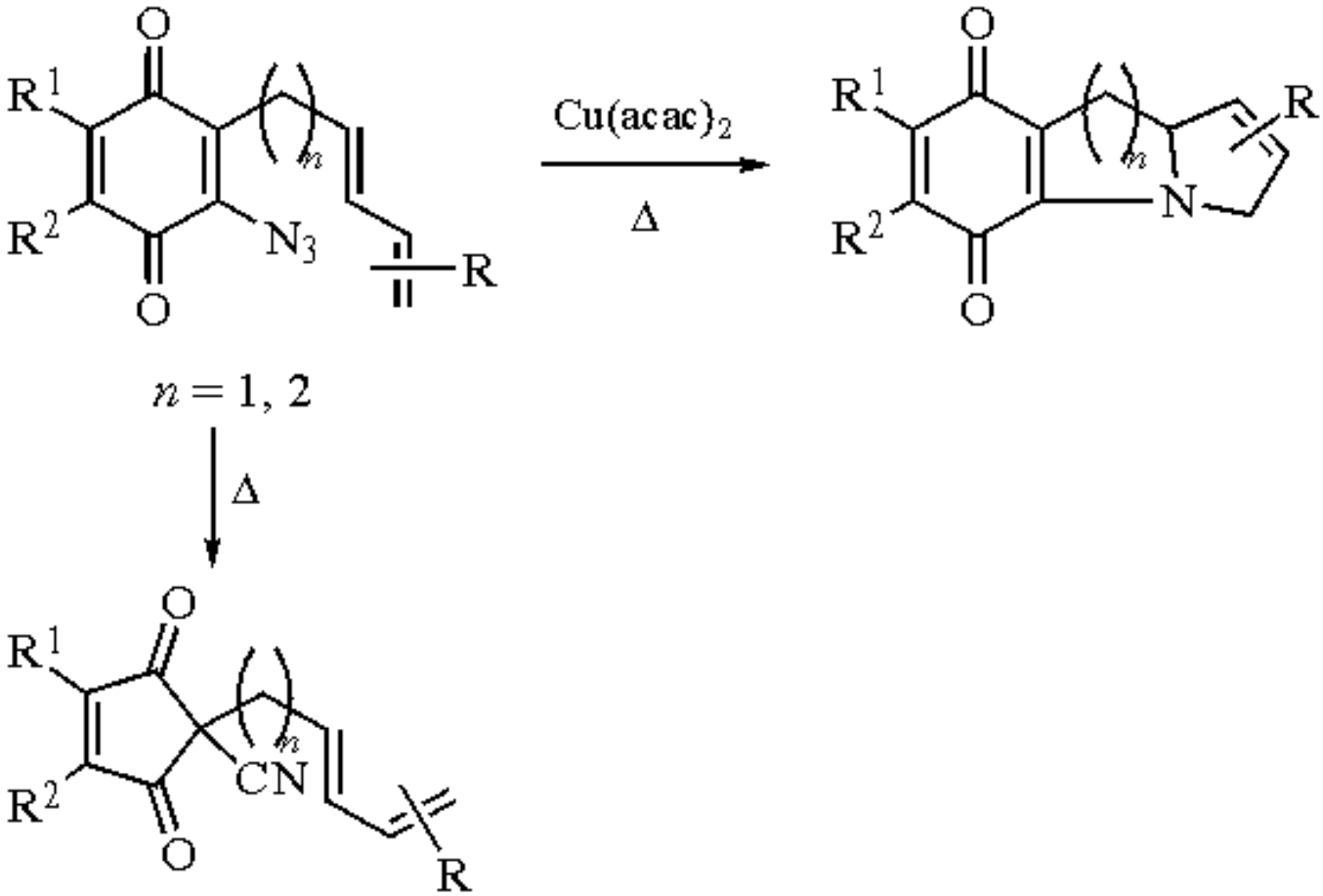

(6)

Copper(II) acetylacetonate has been used as a catalyst for the coupling of bis-diazo ketones to enediones (eq 7).[8]

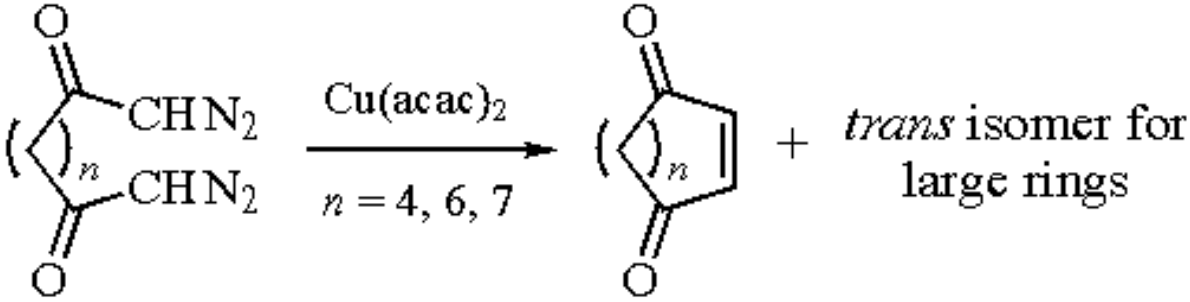

(7)

Coupling Reactions.

The reactions of allylic sulfones and Grignard reagents take place readily under $Cu(acac)_2$ catalysis (eq 8).[9,10] The carbon-carbon bond-forming method is useful for introducing medium-length alkyl groups, e.g. butyl, hexyl, and octyl, and also succeeds with allylic chloride and acetate substrates at or below 20 °C.

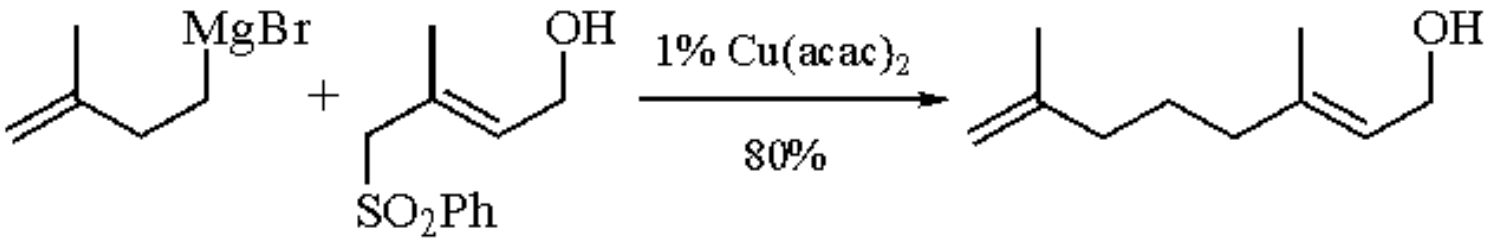

(8)

The reagent also catalyzes the stereospecific cross coupling of alkenyldicyclohexylboranes with allylic or alkynic halides (eq 9).[11] (*E*)-Enynes and 1,4-dienes are produced in good yields and high isomeric purity; ***Tetrakis(triphenylphosphine)palladium(0)*** gives comparative results in similar or better yields.[11]

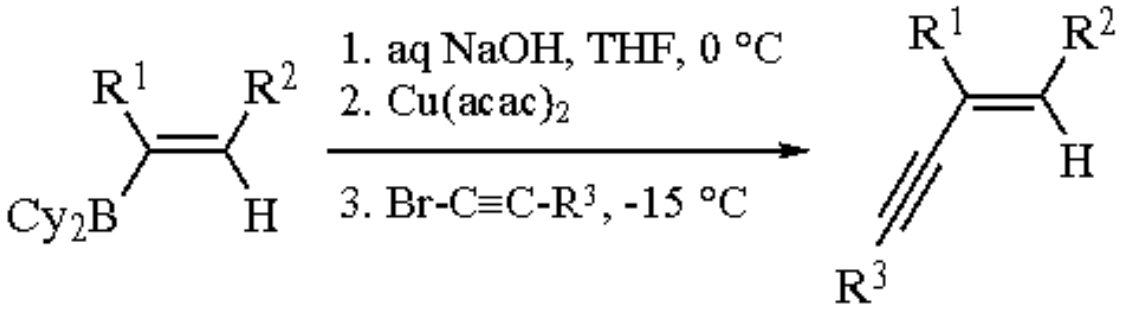

(9)

The coupling reaction of Reformatsky reagents with allylic halides can also be accomplished in high yield under the catalysis of copper(II) acetylacetonate.[13]

Reductive Reactions.

It was reported that aromatic nitro compounds can be reduced to the corresponding amines by ***Sodium Borohydride***-$Cu(acac)_2$ in high yield.[12]

Related Reagents.

Bis(acetylacetonato)zinc(II); ***Copper(I) Acetylacetonate***; ***Tris(acetylacetonato)indium***; ***Manganese(III) Acetylacetonate***; ***Nickel(II) Acetylacetonate***; ***Palladium(II) Acetylacetonate***; ***2,4-Pentanedione***; ***Tris(acetylacetonato)iron(III)***; ***Vanadyl Bis(acetylacetonate)***.

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Copper(I) Bis(trimethylsilyl)amide

$(Me_3Si)_2NCu$

[65225-97-0] · $C_6H_{18}CuNSi_2$ · Copper(I) Bis(trimethylsilyl)amide · (MW 223.93)

(reagent for the conversion of aryl and vinyl iodides into the corresponding amines)

Alternate Name: copper(I) hexamethyldisilazide.

Physical Data: colorless crystals, subl. 180 °C/0.2 mmHg.[1]

Preparative Methods: prepared in situ from ***Lithium Hexamethyldisilazide*** and ***Copper(I) Iodide***.

Handling, Storage, and Precautions: moisture and oxygen sensitive.

Aminating Agent.

The title reagent couples with aryl iodides in boiling pyridine (18 h) to give the corresponding silyl-protected primary aromatic amine, $ArN(SiMe_3)_2$ (**1**), in approximately 50% yield.[2] Methanolysis of (**1**) quantitatively liberates the free amine, $ArNH_2$. Aryl bromides also couple with $(Me_3Si)_2NLi$ to give (**1**), but higher temperatures (160 °C in quinoline, 18 h) are necessary. 1-Iodo-6-alkylcycloheptatrienes can be converted into their 1-amino counterparts using this reagent.[3] Finally, this reagent deoxygenates carbon dioxide in the presence of added ligand to produce a copper(I) isocyanate complex which can be further transformed into an alkyl isocyanate by treatment with an alkyl iodide.[4]

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3. Okazaki, R.; O-oka, M.; Tokitoh, N.; Shishido, Y.; Inamoto, N. *AG(E)* **1981**, *20*, 799.
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Copper(II) Bromide

$CuBr_2$

[7789-45-9] · Br_2Cu · Copper(II) Bromide · (MW 223.36)

(brominating agent; oxidizing agent; Lewis acid)

Alternate Name: cupric bromide.

Physical Data: mp 498 °C; *d* 4.770 g cm^{-3}.

Solubility: very sol water; sol acetone, ammonia, alcohol; practically insol benzene, Et_2O, conc H_2SO_4.

Form Supplied in: almost black solid crystals or crystalline powder; also supplied as reagent adsorbed on alumina (approx. 30 wt % $CuBr_2$ on alumina).

Purification: recryst from H_2O and dried in vacuo.[35]

Handling, Storage, and Precautions: anhydrous reagent is hygroscopic and should therefore be stored in the absence of moisture.

α-Bromination of Carbonyls.

Copper(II) bromide is an efficient reagent for the selective bromination of methylenes adjacent to carbonyl functional groups.[1] Thus 2´-hydroxyacetophenone treated with a heterogeneous mixture of $CuBr_2$ in $CHCl_3$-EtOAc gives complete conversion to 2-bromo-2´-hydroxyacetophenone with no aromatic ring bromination (eq 1).[2]

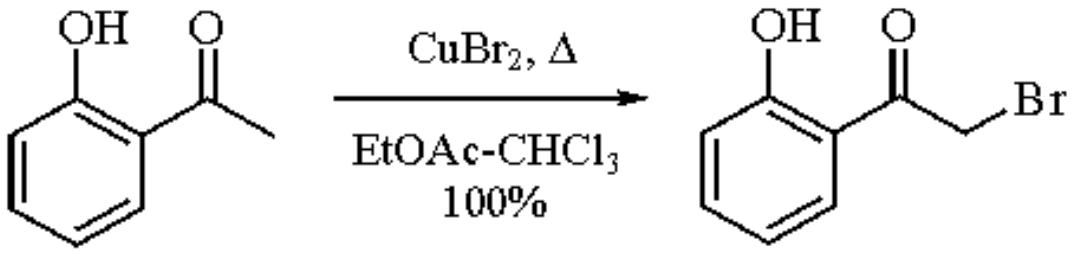

(1)

Similar selectivity is obtained with a homogeneous solution of the reagent in dioxane.[3] A limitation of the reaction is observed with 2´-hydroxy-4´,6´-dimethoxyacetophenone, which undergoes aromatic nuclear bromination with $CuBr_2$.[4]

Steroidal ketones have been selectively α-brominated with $CuBr_2$ in the presence of a double bond without bromination of the alkene (eq 2),[5] while γ-bromination occurs in other steroidal enones.[1]

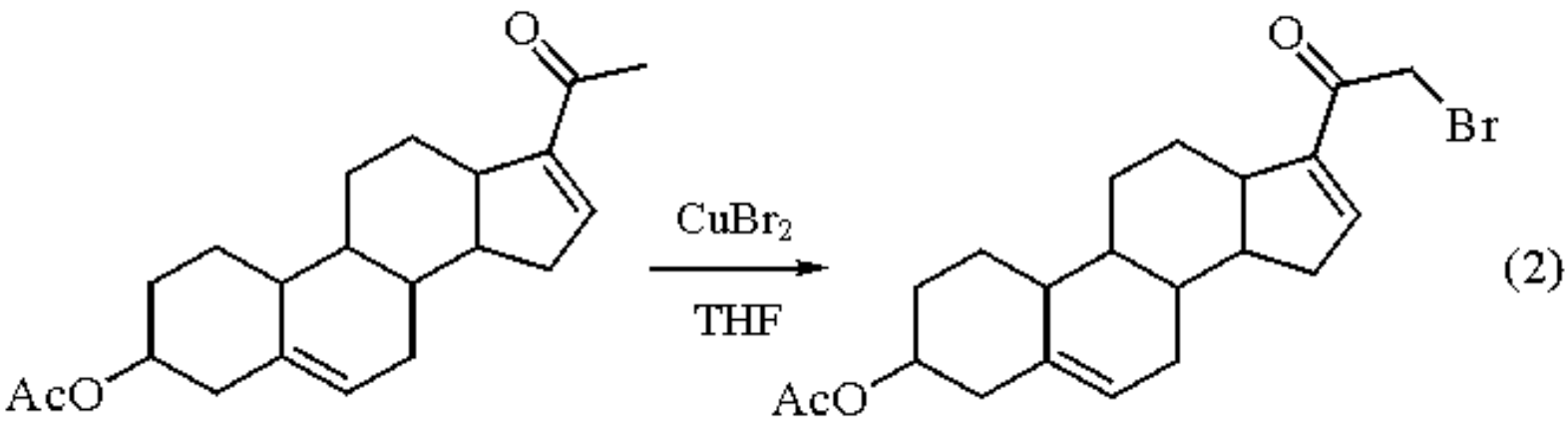

(2)

Copper(II) bromide has been used to α-brominate diketotetraquinanes[6] and to introduce a double bond into a prostanoid nucleus in a one-pot bromination-elimination procedure (eq 3).[7] 3,7-Dibromo-2*H*,6*H*-benzodithiophene-2,6-diones (eq 4)[8] and 5-bromo-4-oxo-4,5,6,7-tetrahydroindoles (eq 5)[9] are prepared by the selective α-bromination of their respective ketone starting materials without bromination of the aromatic or heterocyclic rings. 4-Carboxyoxazolines are converted to the corresponding oxazoles using a mixture of $CuBr_2$ and ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (eq 6).[10]

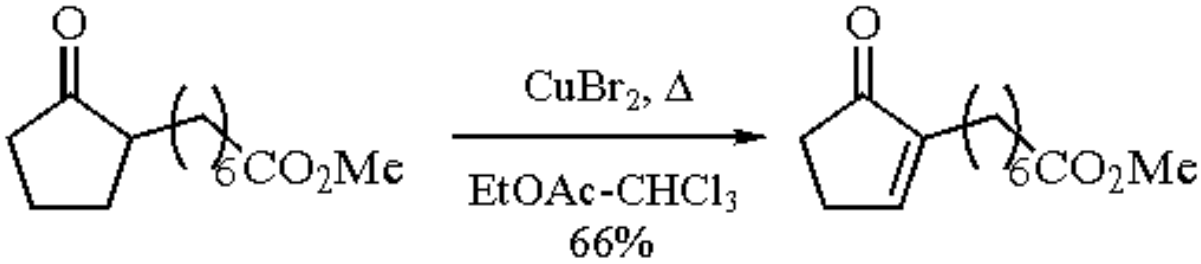

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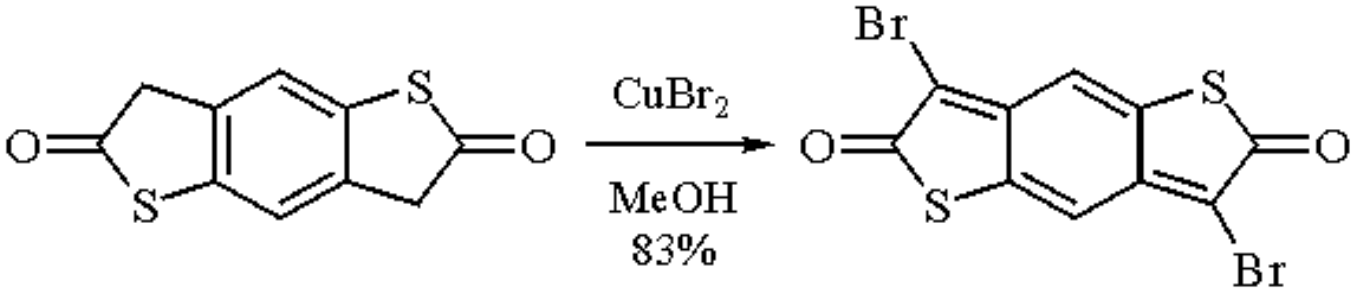

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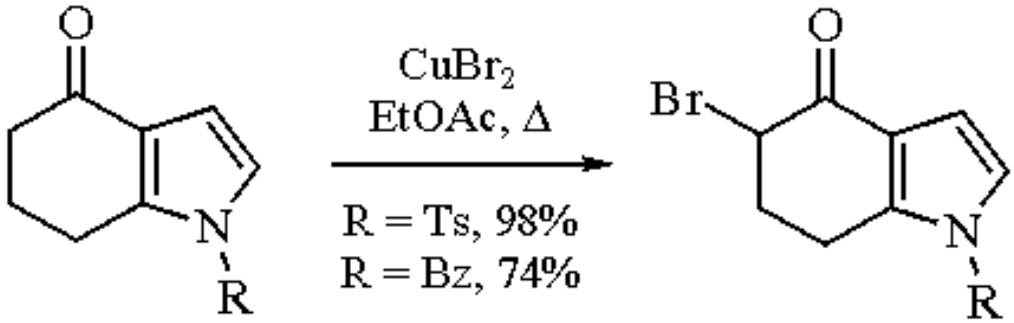

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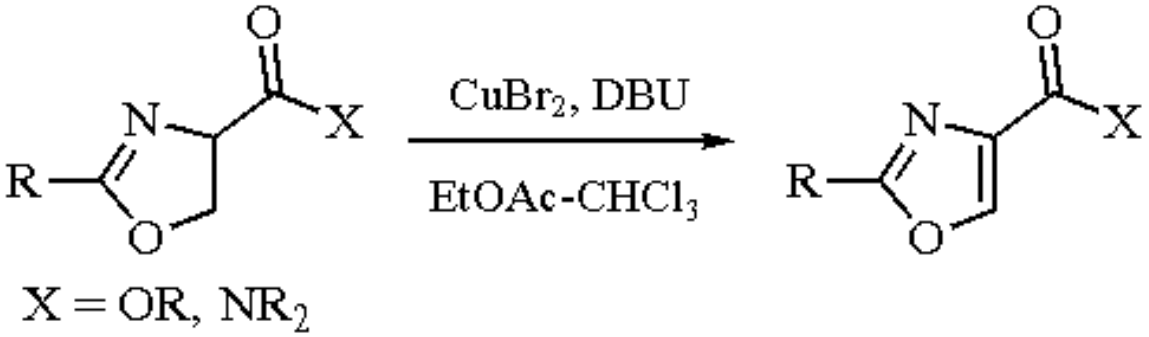

(6)

Bromination of Alkenes and Alkynes.

Heating copper(II) bromide in methanol with compounds containing nonaromatic carbon-carbon multiple bonds leads to di- or tribromination.[11] For example, under these conditions allyl alcohol is converted to 1,2-dibromo-3-hydroxypropane in 99% yield (eq 7), while propargyl alcohol produces a mixture of *trans* di- and tribromoallyl alcohols (eq 8). 2´-Hydroxy-5´-methyl-4-methoxychalcone undergoes a bromination-ring-closure reaction, affording 3-bromo-6-methyl-5´-methoxyflavanone when heated with $CuBr_2$ in refluxing dioxane (eq 9).[12] The mechanism of the bromination of cyclohexene to 1,2-dibromocyclohexane with $CuBr_2$ has been studied.[13]

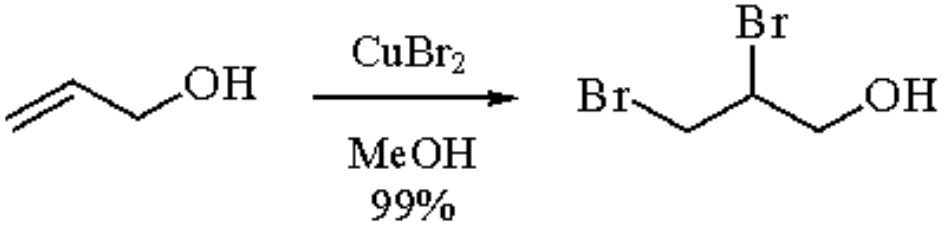

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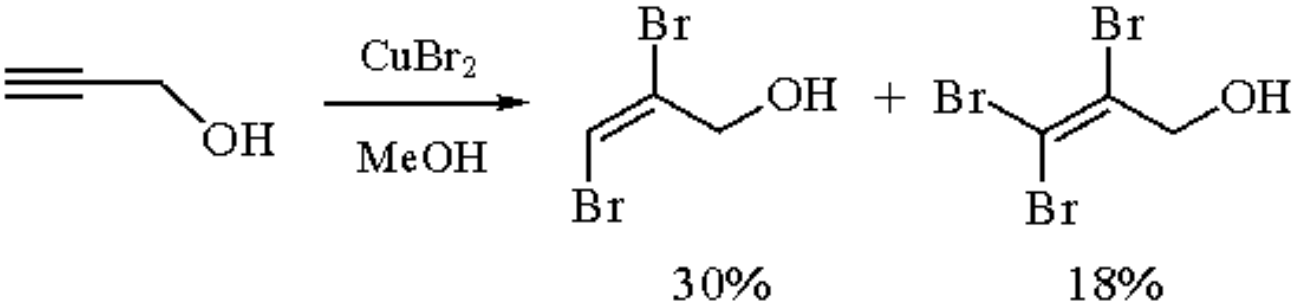

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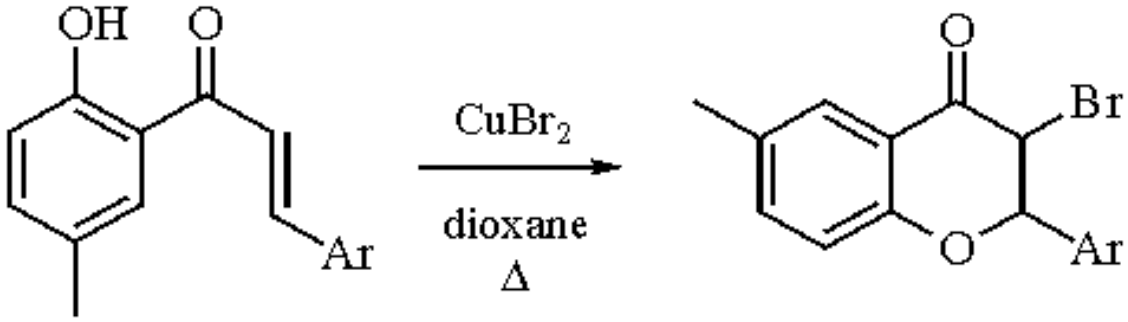

(9)

Bromination of Aromatics.

Aromatic systems are brominated by copper(II) bromide. For example, 9-bromoanthracene is prepared in high yield by heating anthracene and the reagent in carbon tetrachloride (eq 10).[14] When the 9-position is blocked by a halogen, alkyl, or aryl group, the corresponding 10-bromoanthracene is formed.[15] Under similar conditions, 9-acylanthracenes give 9-acyl-10-bromoanthracenes as the predominant products.[16] The aromatic nuclear bromination of monoalkylbenzenes has been shown to proceed cleanly under strictly anhydrous conditions (eq 11).[17a] Polymethylbenzenes are efficiently and selectively converted to the nuclear brominated derivatives by $CuBr_2$/***Alumina***.[17b] In the absence of alumina, a mixture of products resulting from benzylic halogenation is isolated. 3-Acetylpyrroles are nuclear monobrominated at the 4-position in high yield by $CuBr_2$ in acetonitrile at ambient temperature (eq 12).[18] The reaction also proceeds with ethyl 3-pyrrolecarboxylates to give 4-bromopyrrole derivatives,[19] while an excess of brominating agent at 60 °C affords 4,5-dibromopyrroles.[20]

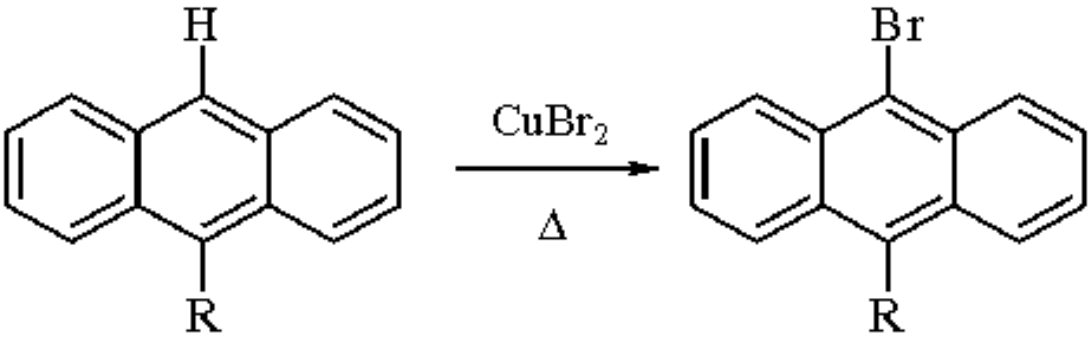

(10)

R = H, Me, Ph, Ac

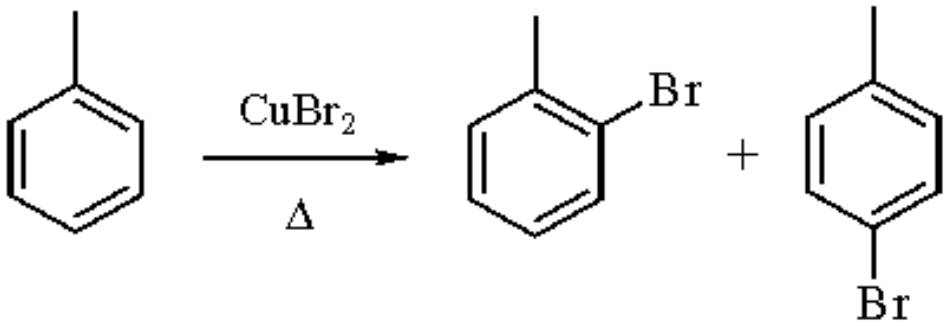

(11)

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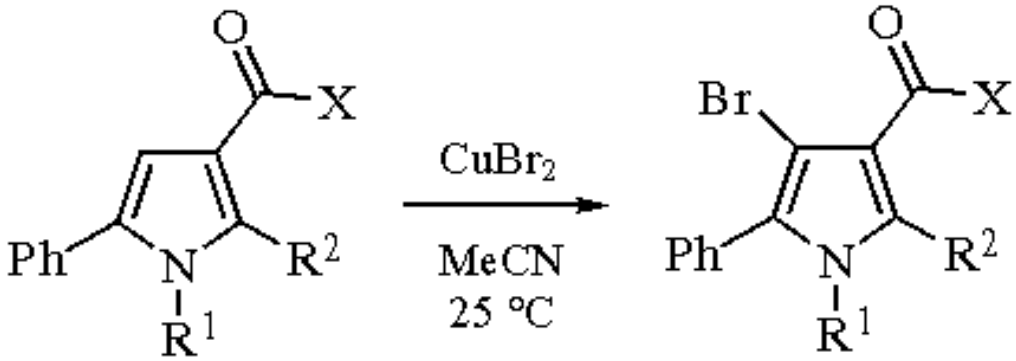

(12)

R^1 = H, Me, Ph, Bn; R^2 = Me, Ph; X = Me, OH, OEt

Bromination of Allylic Alcohols.

Silica gel-supported copper(II) bromide has been used for the regioselective bromination of methyl 3-hydroxy-2-methylenepropanoates and 3-hydroxy-2-methylenepropanenitriles (eq 13).[21a] In the absence of silica gel, no reaction occurs between $CuBr_2$ and these substrates, while adsorption onto Al_2O_3, MgO, or TiO_2 leads to side reactions rather than the clean allylic bromination observed with $CuBr_2/SiO_2$. The reaction is stereoselective with respect to formation of the (*Z*) isomer.

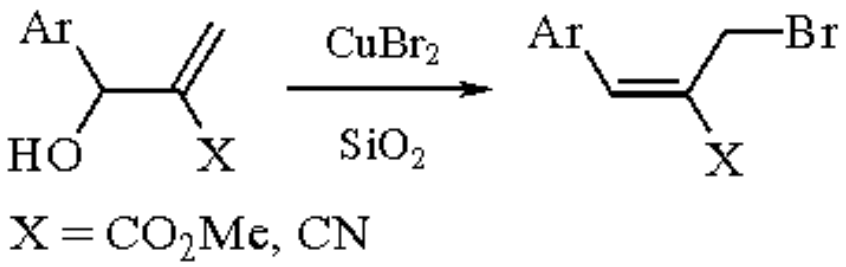

(13)

Benzylic Bromination.

Toluene and substituted methylbenzenes undergo benzylic bromination using $CuBr_2$ and ***t-Butyl Hydroperoxide*** in acetic acid or anhydride (eq 14).[21b] While the yields (43-95%) are not quite as high as those obtained using ***N-Bromosuccinimide***, the copper(II) bromide procedure allows the benzylic bromination of compounds which are insoluble in nonpolar solvents.

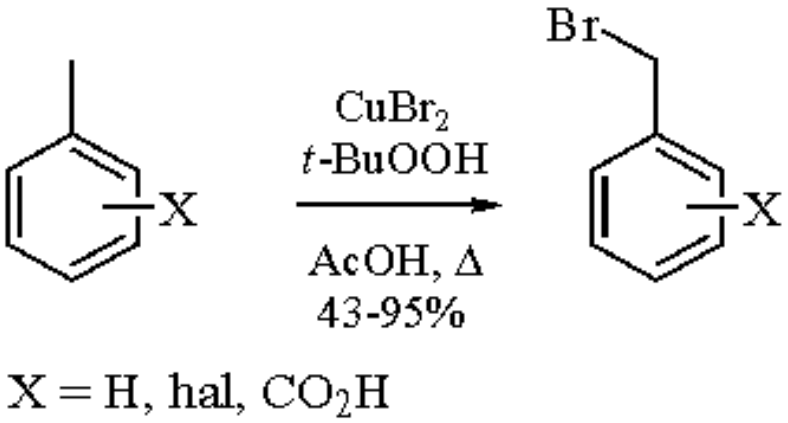

(14)

Esterification Catalyst.

Highly sterically hindered esters are prepared by the reaction of *S*-2-pyridyl thioates and alcohols in acetonitrile with copper(II) bromide as the catalyst.[22] The reaction proceeds at ambient temperature under mild conditions and affords high yields of a range of sterically crowded esters such as *t*-butyl 1-adamantanecarboxylate (eq 15).

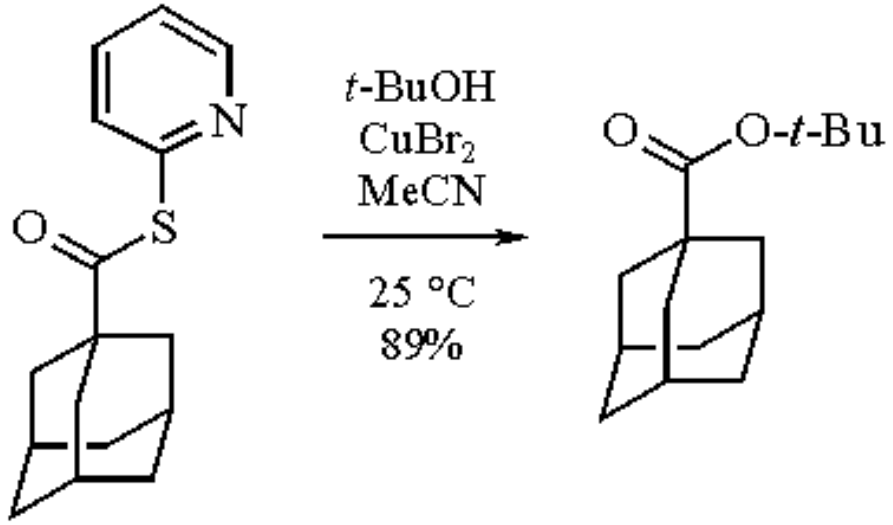

(15)

Conjugate Addition Catalyst.

The 1,4-addition of Grignard reagents to α,β-unsaturated esters is promoted by catalytic $CuBr_2$ (1-5 mol%) with ***Chlorotrimethylsilane***/HMPA (eq 16).[23] Under these conditions the copper(II) species is not reduced by the Grignard reagent, resulting in high yields of the conjugate addition products.

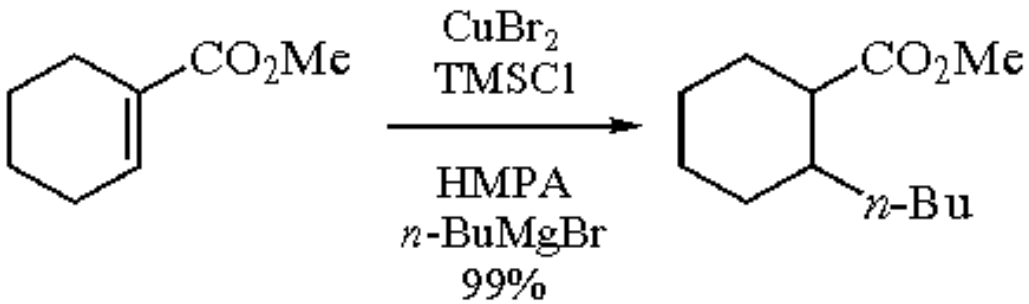

(16)

Oxidation of Stannanes and Alcohols.

Allylstannanes have been oxidized with copper(II) bromide in the presence of various nucleophilic reagents (H_2O, ROH, AcONa, RNH_2) to afford the corresponding allylic alcohols, ethers, acetates, and amines.[24] This chemistry has been extended to trimethylsilyl enol ethers, which undergo a $CuBr_2$-induced carbon-carbon bond forming process with allylstannanes (eq 17).[25] Alkoxytributylstannanes may be converted to the corresponding aldehyde or ketone with two equivalents of $CuBr_2$/***Lithium Bromide*** in THF at ambient temperature (path a, eq 18).[26] A combination of copper(II) bromide/***Lithium t-Butoxide*** oxidizes alcohols to carbonyl compounds quite rapidly and in high yield (path b, eq 18).[27]

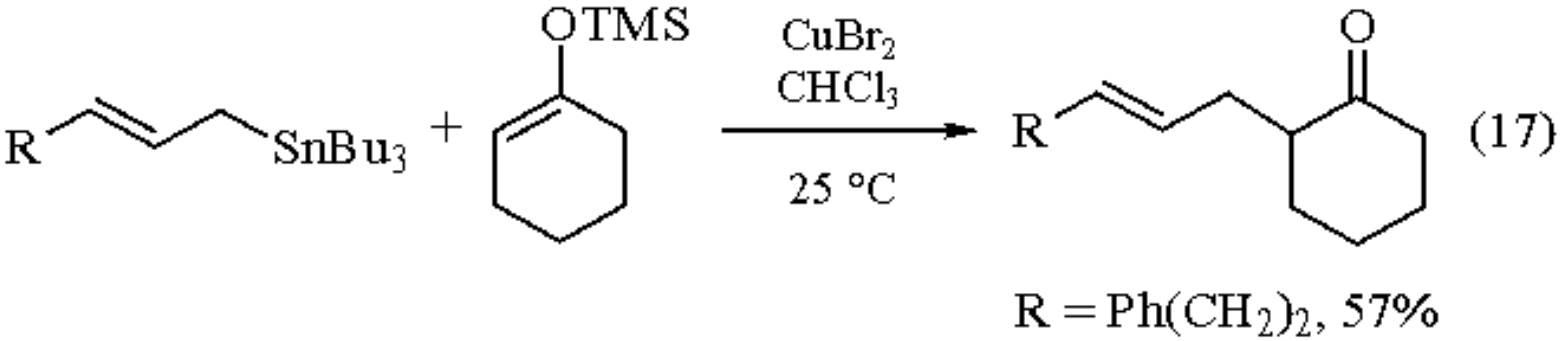

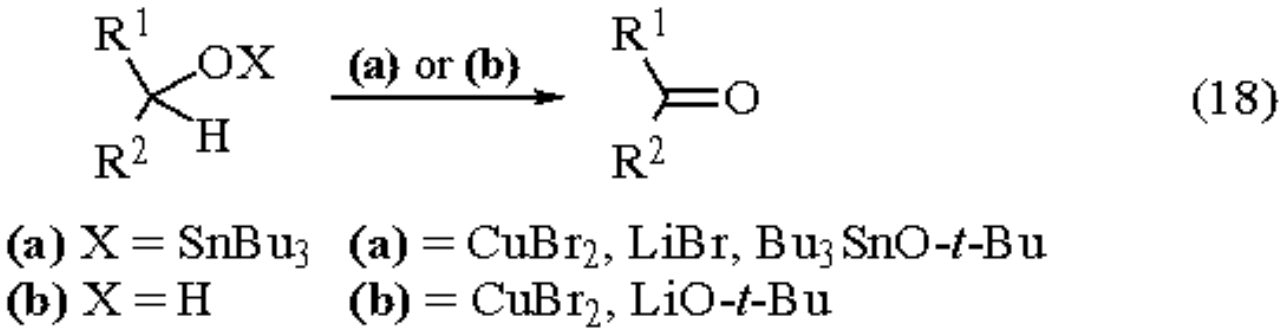

Desilylbromination.

β-Silyl ketones are desilylbrominated to α,β-unsaturated ketones with $CuBr_2$ in DMF.[28] This occurs spontaneously in cyclic ketones, while with open-chain ketones sodium bicarbonate is required to eliminate HBr from the β-bromo ketone thus formed. The carbon-silicon bond in organopentafluorosilicates prepared from alkenes and alkynes is cleaved with copper(II) bromide to give the corresponding alkyl and alkenyl bromides (eq 19).[29] The reaction is stereoselective; thus (*E*)-alkenyl bromides are obtained from (*E*)-alkenylsilicates.

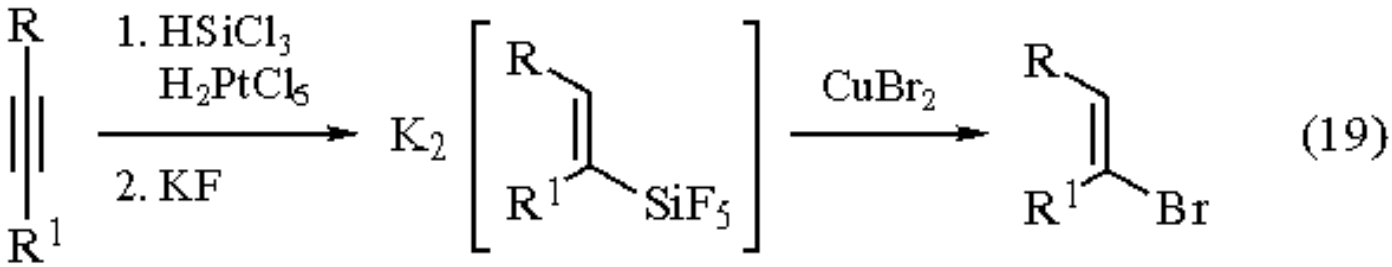

Reagent in the Sandmeyer and Meerwein Reactions.

Diazonium salts of arylamines are converted to aryl halides (Sandmeyer reaction)[30] in the presence of copper(II) halides. Recent procedures have utilized *t*-butyl nitrite/$CuBr_2$[31] or *t*-butyl thionitrite/$CuBr_2$[32] combinations to afford aryl bromides from the corresponding arylamines in high yields (eq 20). The copper salt-catalyzed haloarylation of alkenes with arenediazonium salts (Meerwein reaction) also proceeds with copper(II) halides. For example, treatment of *p*-aminoacetophenone with *t*-butyl nitrite/$CuBr_2$ in the presence of excess acrylic acid gives *p*-acetyl-α-bromohydrocinnamic acid (59% yield, eq 21).[33] The intramolecular version of this reaction, which affords halogenated dihydrobenzofurans, has been accomplished by reacting arenediazonium tetrafluoroborates with $CuBr_2$ in DMSO (eq 22).[34]

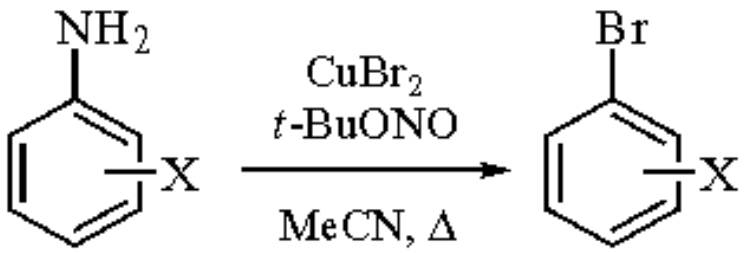

(20)

X = H, hal, CO_2R, NO_2, OMe, etc.

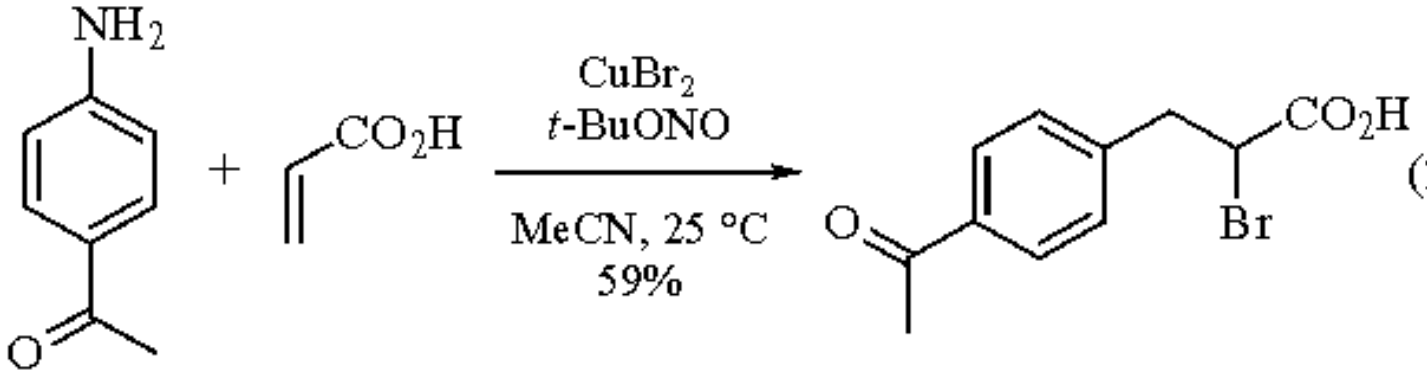

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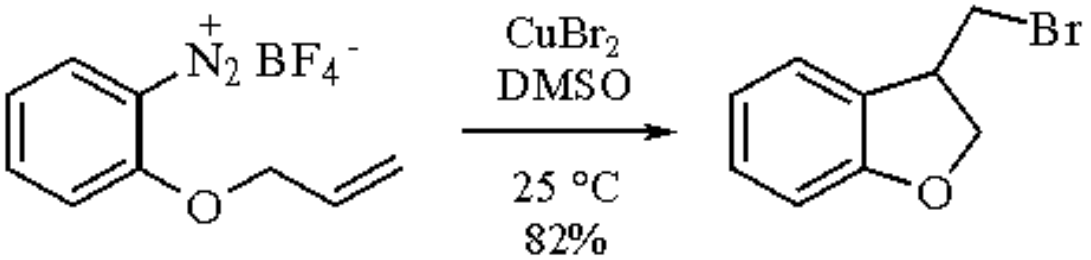

(22)

Related Reagents.

Bromine; ***N-Bromosuccinimide***; ***Copper(I) Bromide***.

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Copper(I) Bromide[1]

CuBr

[7787-70-4] · BrCu · Copper(I) Bromide · (MW 143.45) ($CuBr.SMe_2$)

[54678-23-8] · C_2H_6BrCuS · Copper(I) Bromide-Dimethyl Sulfide · (MW 205.59)

(precursor for organocopper(I) reagents and organocuprates;[1a-f] catalyst for diazo chemistry)

Alternate Name: cuprous bromide.

Physical Data: mp 504 °C; the complex with dimethyl sulfide (DMS) decomposes at ca. 130 °C; *d* 4.720 g cm^{-3}.

Solubility: insol H_2O and most organic solvents; partially sol dimethyl sulfide.

Form Supplied in: light green or blue-tinged white solid. 99.999% grade available. The DMS complex is a white solid.

Handling, Storage, and Precautions: maintenance of a dry N_2 or Ar atmosphere is recommended. The DMS complex must be tightly sealed to prevent loss of DMS. Storage of this complex in a cold place is recommended.

Precursor for Organocopper(I) Reagents and Organocuprates.

Although ***Phenylcopper*** was prepared from ***Copper(I) Iodide*** by Reich in 1923[2] and Gilman in 1936,[3] the material used for the modern characterization of this archetypal arylcopper(I) is prepared from CuBr,[4] which continues to be a favored precursor for new organocopper(I) compounds.[5-9] For example, Bertz discovered that halide-free organocopper compounds can be prepared from CuBr in ***Dimethyl Sulfide*** (DMS), owing to the precipitation of LiBr from this solvent.[5] Thus it was possible to prepare and structurally characterize the first bona fide higher order cuprate.[5a,6] Weiss recently reported the second example, a higher order alkynyl cuprate,[9] prepared from CuBr.DMS. The chemistry of organocopper reagents in DMS has now become a flourishing subfield of organometallic chemistry.[5-9]

For the first decade of the modern era of organocopper reagents, CuI was used almost exclusively as the precursor to

organocopper(I) and organocuprate reagents.[1f] In 1975, House introduced the DMS complex of CuBr, symbolized $CuBr.SMe_2$ or CuBr.DMS, as a convenient precursor for the generation of lithium organocuprates.[10] Unlike the commercial CuBr, which is invariably contaminated with traces of colored Cu^{II} impurities, CuBr.DMS is a microcrystalline white solid. This material should be stored under a dry, inert atmosphere in a refrigerator in order to minimize the loss of DMS, which is quite volatile (bp 38 °C). It is not surprising that Lipshutz found that low quality material gave poor results.[11] This author has found that for ultraprecision work, where stoichiometry is of paramount importance, the ultrapure (99.999%) grade of CuBr is preferable.[5]

Nevertheless, in a side-by-side comparison of seven Cu^{I} salts (CuCN, CuI, CuBr, CuBr.DMS, CuCl, CuOTf, and CuSCN) as precursors of a typical alkyl and a typical aryl cuprate (***Lithium Di-n-butylcuprate*** and ***Lithium Diphenylcuprate***, respectively), CuBr.DMS and ***Copper(I) Cyanide*** were found to give the best results.[12] The comparison between ultrapure CuBr and CuBr.DMS is especially interesting, as it demonstrates a dramatic effect for just 1 equiv of DMS in THF and especially in ether. Another example of a significant difference between CuBr and CuBr.DMS is provided by Davis's study of 1,6 vs. 1,4 and 1,2-addition (eq 1).[13]

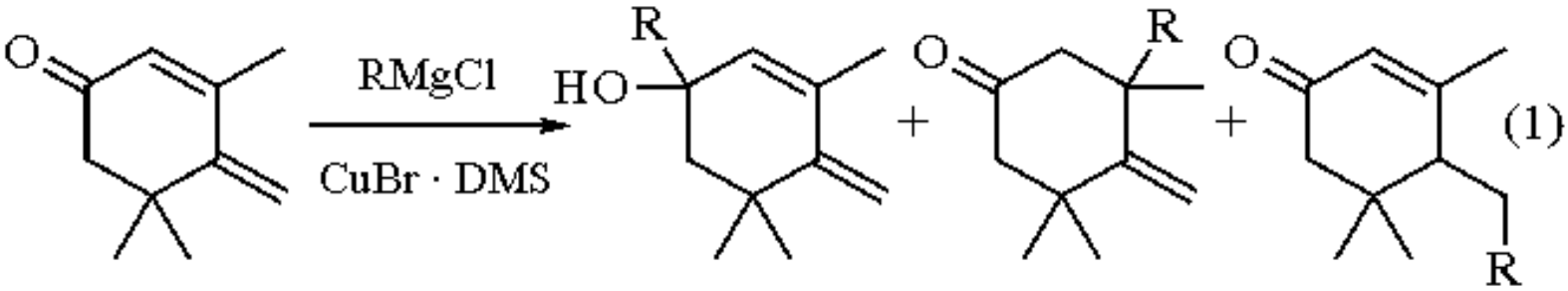

No Cu	4	1	3
CuBr	4	1	15
CuBr · DMS	3	1	30

Some of the most fundamental studies in organocopper chemistry have been carried out using CuBr or CuBr.DMS as starting materials. House showed that the chemoselectivity of ***Lithium Dimethylcuprate-Lithium Bromide*** could be completely controlled by the choice of solvent.[14] Thus a molecule with remote bromoalkane and α-enone functional groups gave only conjugate addition in ether-DMS and only displacement of the Br when HMPA (***Hexamethylphosphoric Triamide***) was present (eq 2). In a recent ^{13}C NMR study it was shown that phenylcuprates are dimeric in nonpolar solvents and monomeric in polar solvents.[15] It was further conjectured that the dimer is responsible for the conjugate addition reaction, and the monomer is responsible for the (much slower) S_N2-like displacement reaction.

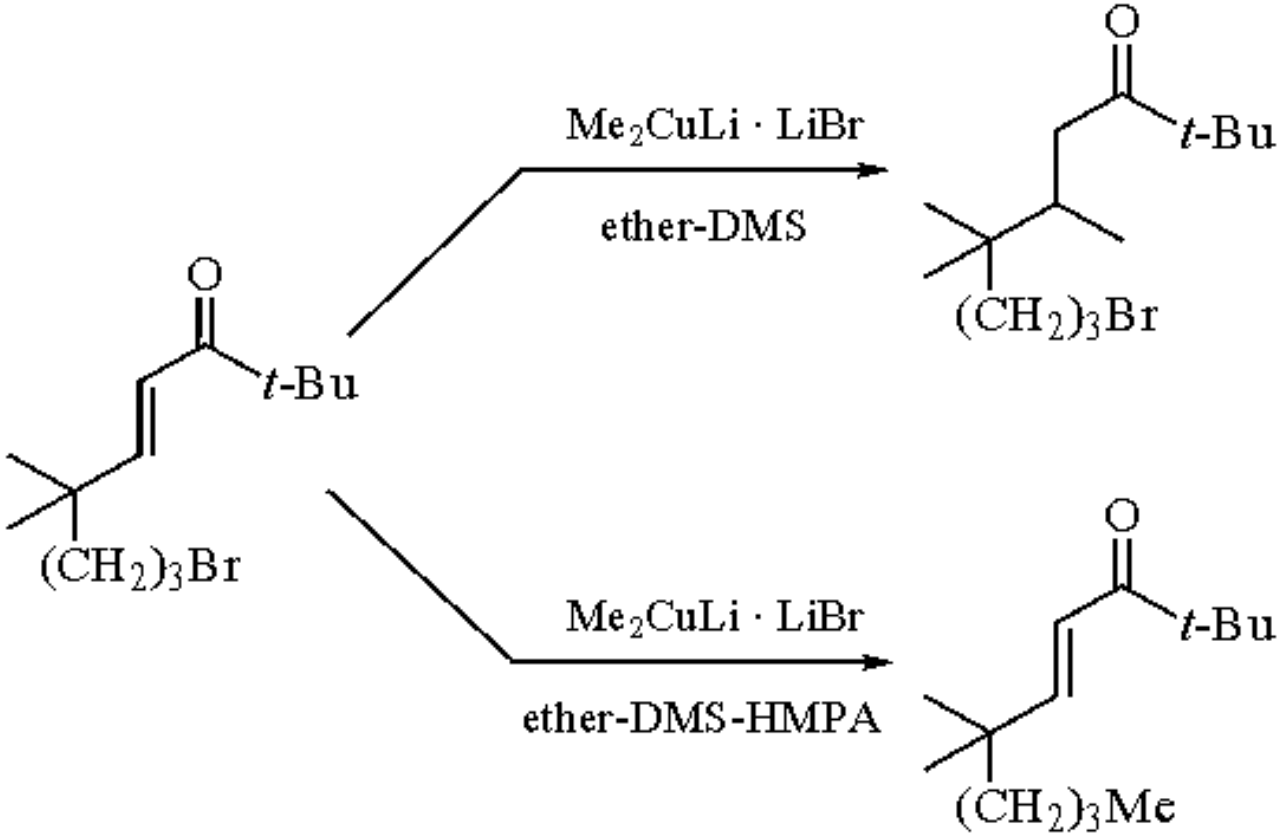

(2)

The preparation of the first higher order cuprate, $Ph_5Cu_2Li_3$ = $[Ph_3CuLi_3][Ph_2Cu]$ or Ph_3CuLi_2 + Ph_2CuLi, from CuBr/DMS was mentioned above.[5] House first proposed higher order Ph_3CuLi_2 in solutions prepared from 3 equiv of PhLi and CuBr in ether to account for the higher reactivity observed for this mixture in certain coupling reactions.[16] However, ^{13}C NMR and ^{6}Li NMR studies did not detect any higher order phenylcuprate in ether or THF, only in DMS.[5] While the presence of a small amount of higher order cuprate acting as a catalytic intermediate cannot be ruled out, a more plausible explanation involves the attack of PhLi on a cuprate-complexed intermediate.

The first thermally stable phosphido- and amidocuprates were prepared from $CuBr.SMe_2$.[17] (It was also shown that LiBr has a beneficial effect on the reactions of organocuprates with typical substrates.[17c]) Chiral amidocuprates have been extensively studied because of their potential for asymmetric induction.[18-20] The chiral auxiliary has also been put on the substrate, e.g. cuprates have been added to chiral unsaturated imides.[21] A good recent review provides many more examples.[1b]

Whereas Grignard reagents and lithium reagents generally give thiophilic addition to dithioesters, the corresponding organocopper reagents give carbophilic addition.[22] The best yields were obtained with CuBr.DMS and ***Copper(I) Trifluoromethanesulfonate***; good results were also obtained with CuCN and CuI. This carbophilic addition has been applied to 1,3-thiazole-5(4*H*)-thiones.[23] It is interesting to note that CuBr has also been used in the preparation of the dithioesters (eq 3).[24]

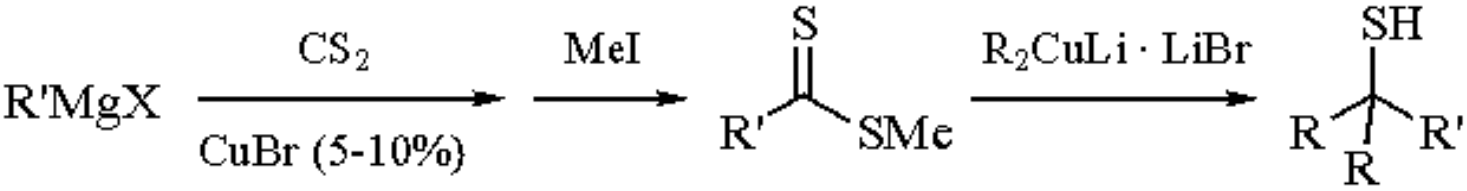

(3)

Nakamura and Kuwajima have reported the CuBr.DMS catalyzed acylation and conjugate addition reactions of the Zn homoenolate from 1-alkoxy-1-siloxycyclopropanes and ***Zinc Chloride***.[25a] They have also reported the ***Chlorotrimethylsilane***/HMPA accelerated conjugate addition of stoichiometric organocopper reagents prepared from CuBr.DMS,[25b] and of catalytic copper reagents,[25c] to α,β-unsaturated ketones and aldehydes. This procedure appears to be more general than that based on putative cuprates of intermediate stoichiometry (see ***Copper(I) Iodide***). In a very significant observation, they report that reagents derived from cuprous iodide consistently gave lower yields.[25b]

Wipf has used CuBr.DMS to catalyze the addition of alkyl and alkenylzirconocenes to acid chlorides to yield ketones,[26a] and also the 1,4-addition of alkylzirconocenes to α-enones.[26b] The hydrozirconation of alkynes followed by transmetalation to Cu^I was devised by Schwartz et al.,[27] who used CuI and ***Copper(I) Chloride***. Transmetalation from Al, B, Pb, Mn, Hg, Sm, Sn, Te, Ti, Zn, and Zr to Cu has been reviewed recently.[1h]

Carbocupration of alkynes by organocopper reagents is a very important area, as judged by the number of citations.[1a,i] An interesting example involves the use of organocopper reagents bearing protected α-hydroxy or α-thio functions.[28a] The preparation of γ-silylvinylcopper reagents via the addition of α-silylated organocopper reagents to alkynes has also been described.[28b] The carbocupration of alkynes is the key step in the synthesis of γ,γ-disubstituted allylboronates.[29] The stannylalumination of 1-alkynes is catalyzed by Cu^I and involves stannylcupration by an intermediate stannylcopper(I) reagent.[30]

The use of Grignard reagents in conjunction with Cu^I salts has been thoroughly reviewed.[1a,d] A very edifying example of the difference between organocopper reagents prepared from lithium reagents vs. Grignard reagents has been provided by Curran (eq 4).[31]

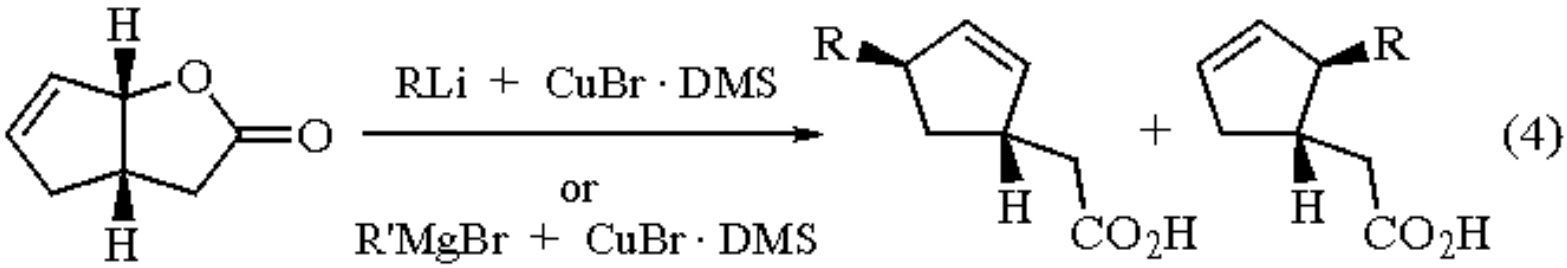

$Me_2CuLi \cdot LiBr$, THF	62	38
$Me_2CuLi \cdot LiBr$, ether	54	46
$MeCu \cdot MgBr_2$	98	2
$MeCu \cdot LiBr$	86	14
$MeCu \cdot LiI$	76	24
$MeCu(CN)Li$	75	25

Yields were 90-97%, except for the cuprate from CuCN: 60%

In chemistry that is clearly related to that of organocopper reagents, aryl bromides and aryl iodides undergo a Gabriel reaction with potassium phthalimide in the presence of CuBr (or CuI).[32] They also undergo coupling reactions with the sodium salts of active methylene compounds catalyzed by CuBr.[33] Copper-assisted nucleophilic substitution of aryl halogen has been reviewed.[1g] In a potentially far-reaching development, thermally stable, yet reactive formulations of

organocuprates suitable for commercialization have been patented.[34]

Catalysts for Diazo Chemistry.

CuBr has been used in other reactions besides those involving organocuprates. It is a popular catalyst for the activation of ***Diazomethane***, e.g. tropylium perchlorate is isolated in 85% yield starting from benzene.[35] CuBr has been used for the activation of diazoacetic esters,[1j] but not as often as CuCN, and especially CuCl. CuBr is the preferred catalyst for the Sandmeyer reaction of arenediazonium salts to afford bromoarenes,[36] and for the Meerwein reaction, the arylation of alkenes by diazonium salts.[37]

Related Reagents.

Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride; ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***; ***Copper(I) Chloride***; ***Copper(I) Chloride-Oxygen***; copper(I) chloride-tetrabutylammonium chloride ***Copper(I) Chloride-Sulfur Dioxide***; ***Copper(I) Cyanide***; ***Copper(I) Iodide***; ***Copper(I) Trifluoromethanesulfonate***.

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Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride[1,2]

$LiCuHBr.Al(OMe)_3$

(CuBr)

[7787-70-4] · BrCu · Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride · (MW 143.45) ($LiAlH(OMe)_3$)

[12076-93-6] · $C_3H_{10}AlLiO_3$ · Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride · (MW 128.05)

(in situ prepared hydridocopper reagent; reduces 1-alkynyl sulfides to *cis*-1-alkenyl sulfides;[3] 1,4-reduction of enones[2,4])

Preparative Methods: [4] an anhydrous THF solution of lithium trimethoxyaluminum hydride (1.9 mmol) is added dropwise to a suspension of dry[5] ***Copper(I) Bromide*** (1 mmol) in THF maintained at -5 to 0 °C under an inert atmosphere. After 30 min, the resulting dark brown suspension is cooled to -78 °C and treated with the substrate (1.1 mmol) via syringe. After a 50 min stirring time at -20 °C, methanol is added and the mixture is poured into a saturated aqueous ammonium chloride solution. The organic layer is removed from the blue (copper) layer and dried. A modification of this procedure has been reported where $CuBr.Me_2S$ was used as the copper source and HMPA was used as a cosolvent.[6] In another procedure, $CuBr.Me_2S$-lithium dimethoxyaluminum hydride-boron tribromide was used to prepare 2,6-dialkyl-2,3-dihydro-4-pyridones.[7] ***Lithium Tri-t-butoxyaluminum Hydride***-copper(I) bromide was used to regiospecifically reduce 1-acylpyridinium salts to the desired 1-acyl-1,4-dihydropyridines.[8]

Alkynes.

The use of this reagent was first reported for the reduction of 1-alkynyl sulfides to *cis*-1-alkenyl sulfides (eq 1).[3] Reduction of these compounds with ***Lithium Aluminum Hydride*** in THF produced the

corresponding *trans*-1-alkenyl sulfides (eq 2). The reduction of 1-alkynyl phenyl sulfones also proceeds to give the *cis*-alkene.[9] However, the reduction of alkynic esters showed a great tendency to oligomerize.[4]

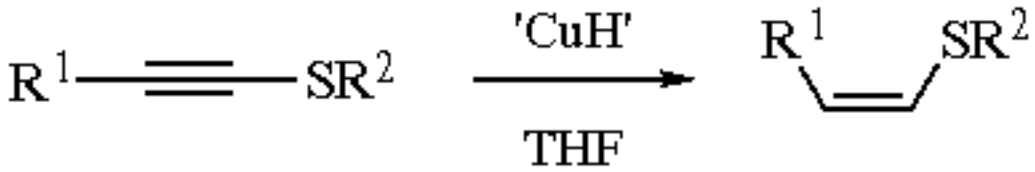

(1)

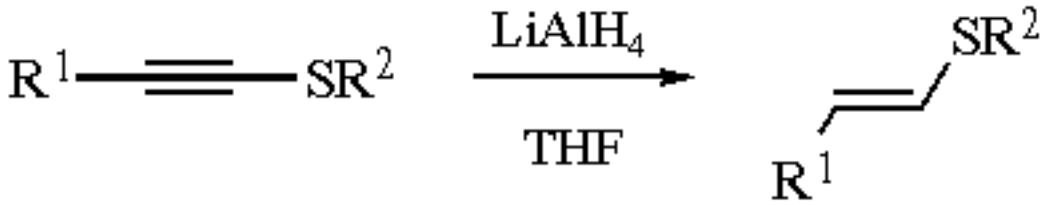

(2)

Enones.

This reagent reduces acyclic[2,4,10] and bicyclic[11,12] α,β-unsaturated ketones to ketones and 2-cyclohexenones to cyclohexanones.[2,4] This reagent reduces cyclohexenones better than ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***.[4] The deuterated copper reagent (copper(I) bromide-lithium trimethoxyaluminum deuteride) reacts with (**1**) to afford the deuterium label at the β-position (eq 3). The reduction of α,β-unsaturated esters tends to give high molecular weight materials.[4]

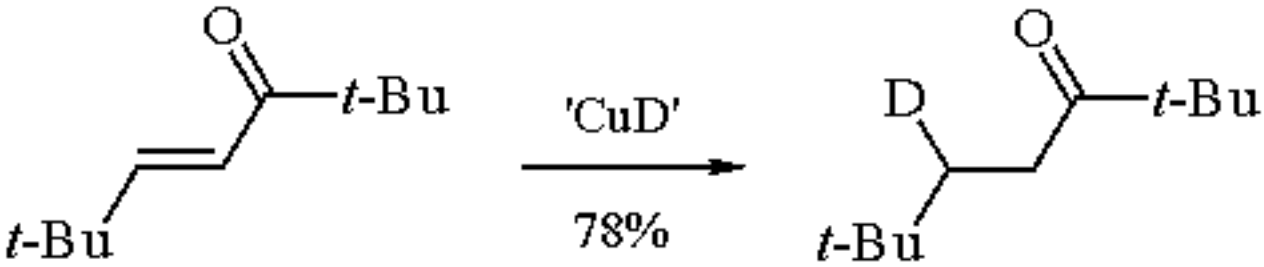

(3)

(**1**)

Limitations.

Although the exact structure of this reagent has not been determined, it is clearly different from other hydridocopper reagents[4] and has been shown to be superior to the ***Lithium Aluminum Hydride-Copper(I) Iodide*** reagent[13] for the preparation of (**2**) (eq 4).[10] Substitution of ***Copper(I) Iodide*** for copper(I) bromide affords a much less selective reagent (***Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride***).[4] Additional limitations are discussed for the ***Copper(I) Bromide-***

Sodium Bis(2-methoxyethoxy)aluminum Hydride reagent.

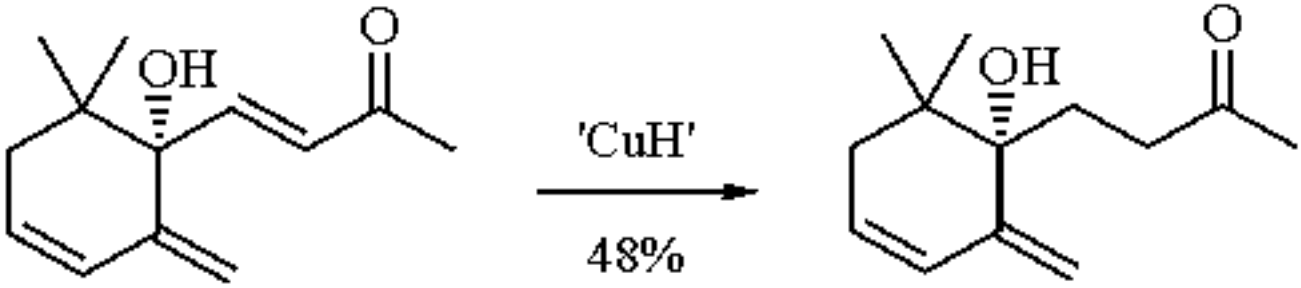

(4)

(2)

Alternative Methods.

For a discussion on alternative methods of alkyne reduction to *cis*-alkenes, see ***Magnesium Hydride-Copper(I) Iodide***. For a discussion on alternative methods of 1,4-reduction of enones, see ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***. See also ***Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride***.

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Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride[1,2]

$NaCuHBr.AlH(OCH_2CH_2OMe)_2$

(CuBr)

[7787-70-4] · BrCu · Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride · (MW 143.45) ($NaAlH_2(OCH_2CH_2OMe)_2$)

[22722-98-1] · $C_6H_{16}AlNaO_4$ · Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride · (MW 202.19)

(in situ prepared hydridocopper reagent; 1,4-reduction of α,β-unsaturated ketones,[2] esters,[2] lactones,[3] nitriles[4] and selected alkynes[5])

Preparative Method: [2] a benzene (toluene) solution of ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (16 mmol of hydride) is added dropwise to a suspension of dry[6] ***Copper(I) Bromide*** (8 mmol) in anhydrous THF at 0 °C under an inert atmosphere. After 30 min, the black mixture is cooled to -78 °C and anhydrous 2-butanol (18 mmol) is added, followed by a THF solution of substrate (1 mmol). The mixture is stirred at -20 °C for 2 h, quenched with water and poured into saturated aqueous ammonium chloride solution. After ether addition, the organic layer is washed with water and aqueous ammonium chloride solution and dried.

Handling, Storage, and Precautions: use in a fume hood.

Modifications.

Copper(I) Iodide has been used as the copper source for the reduction of α,β-unsaturated esters[7] and butenolides.[8]

α,β-Unsaturated Ketones.

The reagent is used for the 1,4-reduction of α,β-unsaturated ketones (eq 1).[2,9-12] This reagent is reported to reduce acyclic enones and enoates (in the presence of 2-butanol) better than the ***Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride*** reagent.[9] The reagent has been used to reduce 2-cyclopentenone,[13] cyclohexenones,[9,14,15] and macrocyclic enones.[16]

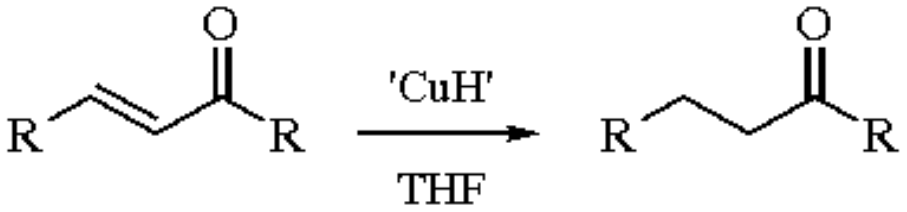

(1)

R = *t*-Bu, 98%; Ph, 54%

Other Enones.

The reagent reduces α,β-unsaturated esters (eq 2),[9,17-22] lactones (eqs 3 and 4),[3,23-25] and nitriles (eq 5).[4]

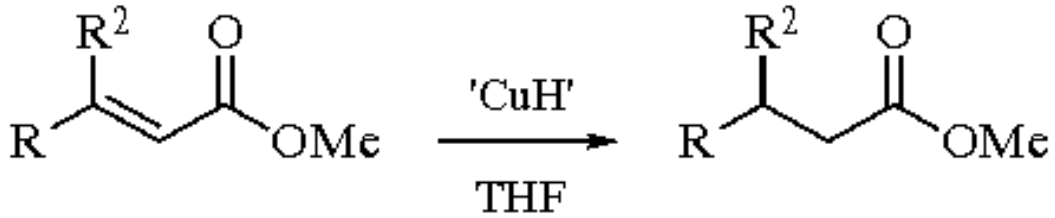

(2)

R = H, R^2 = Me, 84%; R = R^2 = Me, 92%; R = R^2 = Ph, 82%

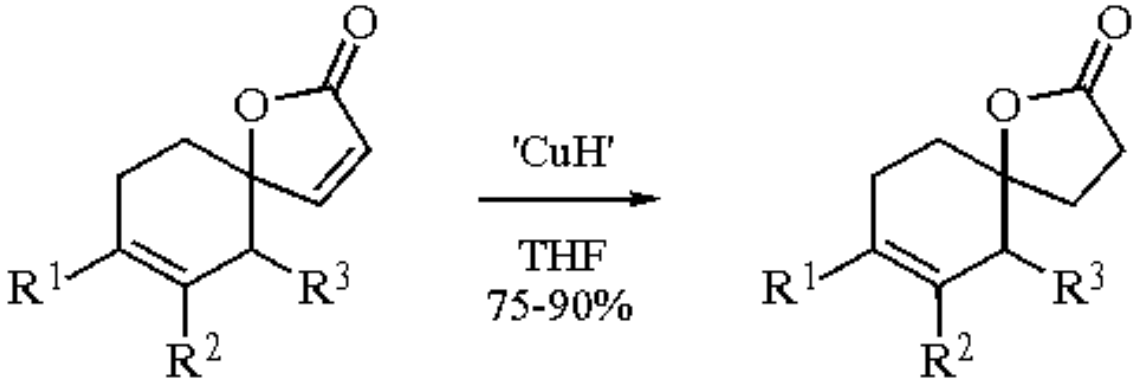

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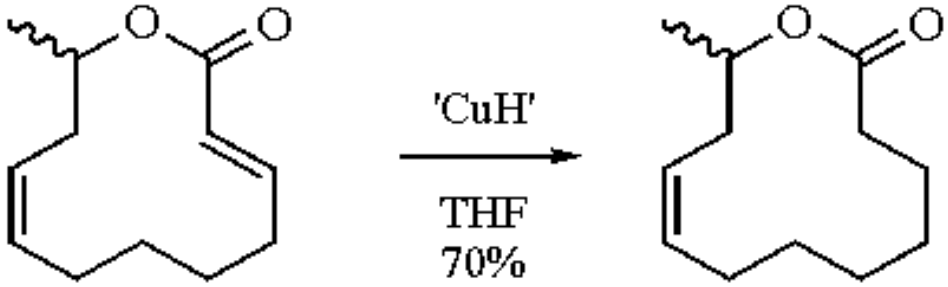

(4)

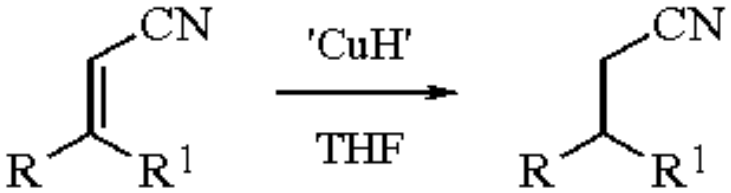

(5)

R = Ph, R^1 = H, 99%; R = cyclopropyl, R^1 = Me, 70%; R = 2-furyl, R^1 = H, 51%; R = R^1 = Pr, 83%

Alkynes.

The reduction of alkynic esters affords unsaturated esters, albeit in poor yield and as a *cis*/*trans* mixture (eq 6).[9] In contrast to this, the reduction of 1-alkyl-3-(trifluoromethyl)propargyl alcohols affords only the *cis* alkene (eq 7).[5] Deuterium trapping experiments (AcOD) resulted in deuterium incorporation at the CF_3 sp^2 carbon.

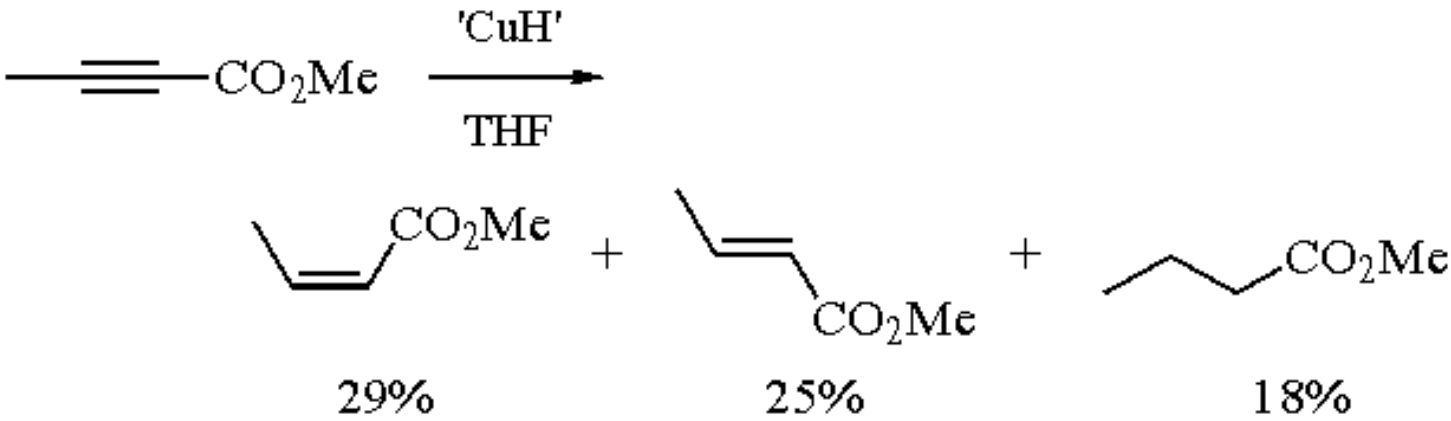

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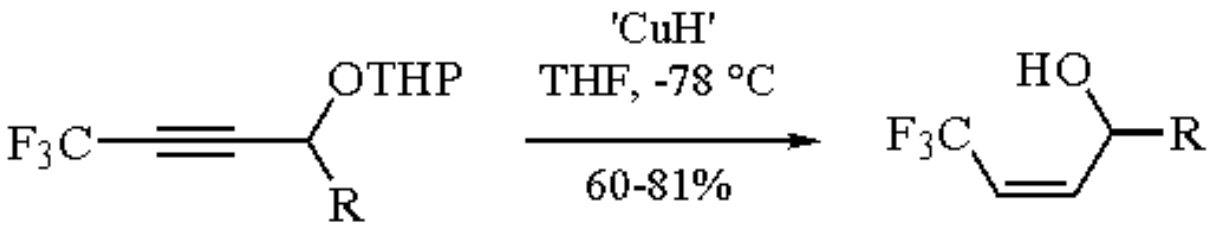

(7)

Limitations.

Although the exact structure of this reagent has not been determined, it is clearly different from other hydridocopper reagents.[9] The title reagent fails to reduce sterically hindered enones (e.g. **1** and **2**).[26-29] This reagent also lacks chemoselectivity, such that it will reduce saturated ketones to alcohols and alkyl (aryl) bromides to their corresponding hydrocarbons.[30] The reagent $[(Ph_3P)CuH]_6$ is reported to reduce α,β-unsaturated carbonyl compounds in the presence of alkyl halides or sulfonates.[31]

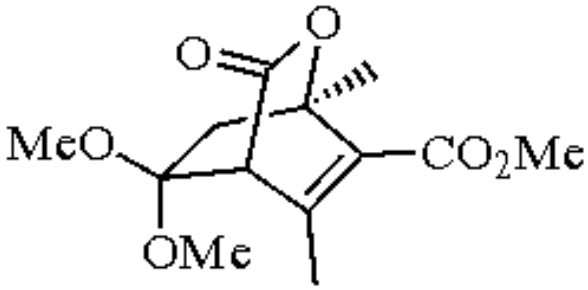

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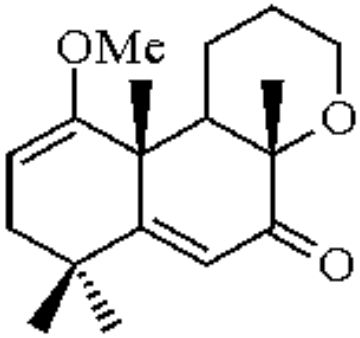

(2)

Alternative Methods.

The 1,4-reduction of enones can be accomplished by many other methods, such as catalytic hydrogenation,[32,33] dissolving metal reduction,[34,35] benzylamine/potassium *t*-butoxide,[36] ***Pentacarbonyliron***/base,[37,38] lithium or potassium trialkyl(aryl)borohydrides,[39,40] $NaHFe_2(CO)_8$,[41] ***Tri-n-butylstannane***,[42] ***Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride***,[30,43] ***Selenium***/CO/H_2O,[44] and ***Sodium Borohydride***/CuCl.[45] See ***Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride***, ***Lithium Aluminum Hydride-Copper(I) Iodide***, ***Lithium n-Butyl(hydrido)cuprate***. For a discussion on alternative methods of alkyne reduction to *cis*-alkenes, see ***Magnesium Hydride-Copper(I) Iodide***.

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Copper Bronze[1]

Cu

[7440-50-8] · Cu · Copper Bronze · (MW 63.54)

(Ullmann coupling;[6] thermal decomposition of diazo compounds;[9] vinyl ether synthesis;[10] Guerbet reaction[3])

Physical Data: mp 1083 °C; bp 2595 °C; *d* 8.95 g cm^{-3}.

Solubility: slowly sol in ammonia water.

Form Supplied in: copper-colored, finely ground powder; commercially available.

Preparative Methods: copper bronze can be activated either by the method of Vogel[1a] or by addition of a 2% solution of iodine in acetone.[2]

Handling, Storage, and Precautions: may lose its activity due to aging. Flammable when exposed to heat, sparks, and open flame. Irritant. May discolor on exposure to air and moisture. Incompatible with strong acids, strong oxidizing agents, acid chlorides, and halogens. Use of safety goggles and chemical-resistant gloves is strongly recommended. Avoid breathing the dust. Avoid contact in eyes, on skin, on clothing.

Guerbet Reaction.

Preparation of ethylhexanol from butanol occurs within an autoclave at autogenous pressures of 50-60 atm and temperatures of about 300 °C in the presence of the hydrogenation-dehydrogenation catalyst, copper bronze. Butanol is first dehydrogenated to an aldehyde in the presence of sodium and copper bronze before undergoing aldol condensation and subsequent dehydration. The resulting α,β-unsaturated aldehyde is then hydrogenated, yielding 2-ethylhexanol.[3]

Ullmann Coupling.

Under Ullmann conditions,[6] halogen-substituted aromatic compounds react with organic halides in the presence of activated copper bronze[1b,2,4] to give the corresponding coupled products in moderate yields. A recent example is the synthesis of perfluoroalkyl-substituted aromatic aldehydes via the coupling of two different substrates (i.e. perfluorooctyl iodide and *p*-iodobenzaldehyde) (eq 1).[5]

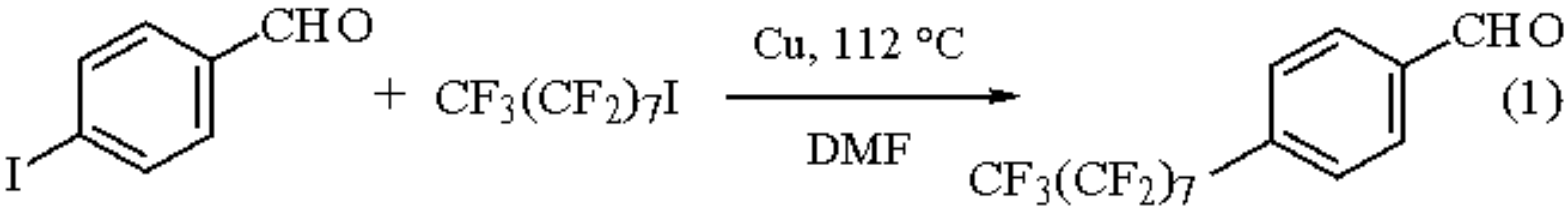

Thermal Decomposition of Diazo Compounds.

Copper bronze can promote the intramolecular cyclization of diazo ketones in boiling cyclohexane (eq 2); anhydrous ***Copper(II) Sulfate*** in boiling THF can also be used.[7] Other diazo compounds that have been shown to undergo copper-catalyzed thermal decomposition include ethyl diazopyruvates in the presence of enol ethers or alkynes[8] and diazoacetates (eq 3).[9]

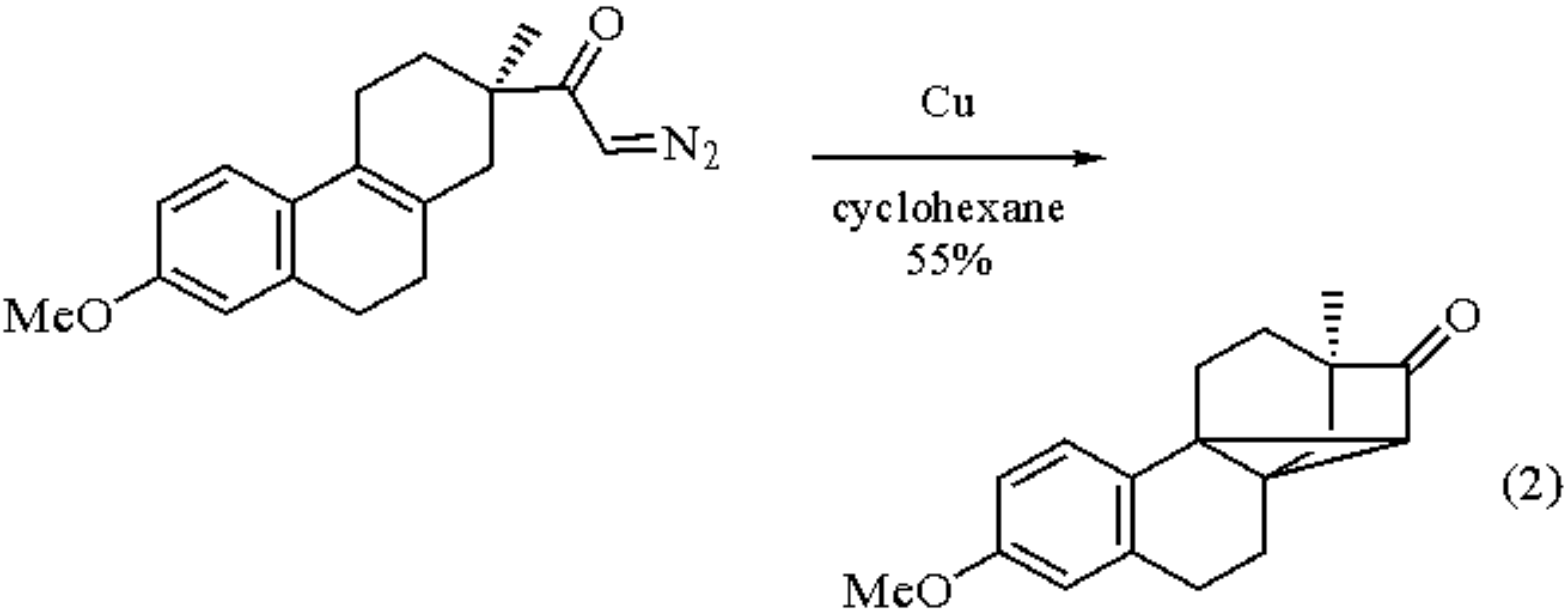

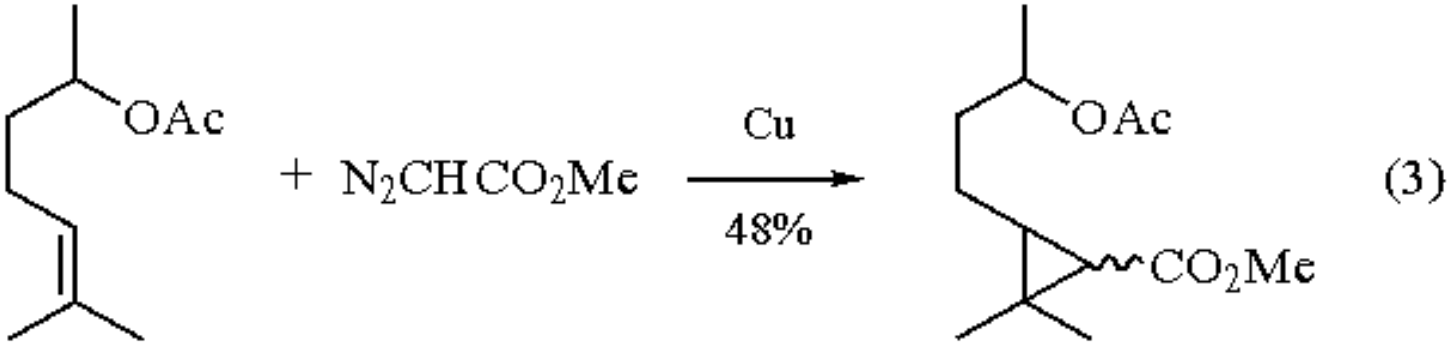

Vinyl Ether Synthesis.

Rearrangement of β-alkoxycyclopropanecarboxylates in the presence of copper bronze catalyst produces vinyl ethers (eq 4). Vicinal alkoxy and ethoxycarbonyl groups activate the substrate as the reaction proceeds.[10]

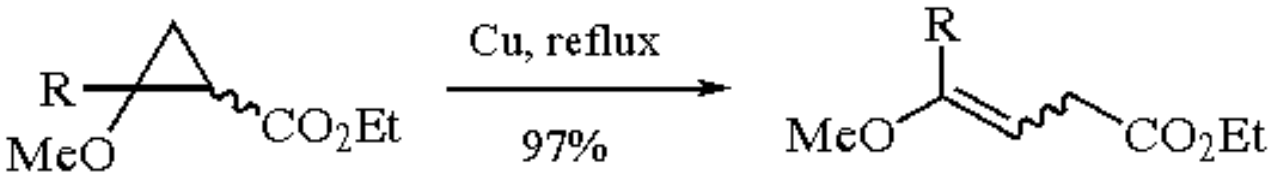

(4)

Related Reagents.

Copper.

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Copper(I) *t*-Butoxide

***t*-BuOCu**

[35342-67-7] · C_4H_9CuO · Copper(I) *t*-Butoxide · (MW 136.66)

(metalation agent for active hydrogen compounds;[1] cross-coupling agent of 1,3-dinitrobenzenes and aryl iodides;[2] nontransferable group of mixed organocuprates;[3] volatile copper precursor for MOCVD[4])

Physical Data: sublimation temp 160 °C (0.1 mmHg), 110 °C (10^{-4} mmHg); mp 260 °C (dec).

Solubility: slightly sol THF, benzene, cyclohexane, and hexane.

Preparative Methods: Cu^I *t*-butoxide prepared in situ by the metathesis reaction between ***Copper(I) Chloride*** and alkali metal *t*-butoxide in appropriate organic solvents can be used for synthetic purposes. Cu^I *t*-butoxide can be isolated by sublimation under vacuum.

Handling, Storage, and Precautions: extremely oxygen- and moisture-sensitive. Preparation and reaction should be conducted under rigorously oxygen-free and anhydrous conditions.

Metalation.

Cu^I *t*-butoxide metalates a variety of active hydrogen compounds under mild conditions, with concomitant quantitative liberation of *t*-butyl alcohol, in the presence or absence of added ligands to generate corresponding organic Cu^I compounds, which generally can be easily isolated by evaporation or filtration of *t*-butyl alcohol and the solvent (eqs 1 - 11).[1,5 -11] This preparative method is characterized by the absence of alkali metal salts that usually accompany Cu^I compounds prepared by the metathesis reaction between Cu^I halides and organoalkali metal compounds. Acylation of ***(Trimethylsilyl)ethynylcopper(I)*** (eq 2) with acid chlorides gives trimethylsilylethynyl ketones.[5] The Cu^I bicarbonate complex (eq 6) acts as a reversible CO_2 carrier to transfer its CO_2 moiety to cyclohexanone.[8] Cu^I carbamate (eq 7) reacts with MeI in the presence of a *t*-butyl isocyanide ligand to produce methyl carbamate.[9] Cu^I cyclohexanone-2-carboxylate (eq 8) undergoes a specific two-step decarboxylation in DMF to afford Cu^I enolate.[10] Hydrogenolysis of Cu^I *t*-butoxide occurs in the presence of ***Triphenylphosphine*** to afford hexameric $HCuPPh_3$ (eq 11), which is a useful reducing agent.[11] For the synthetic use of Cu^I acetylides, ***Copper(I) Phenoxide***, and ***Copper(I) Cyanoacetate***, see the corresponding entries.

$$t\text{-BuOCu} \xrightarrow[\text{rt}]{\text{PhC}\equiv\text{CH}} \text{PhC}\equiv\text{CCu} \qquad (1)$$

$$t\text{-BuOCu} \xrightarrow[\text{THF, 0 °C}]{\text{Me}_3\text{SiC}\equiv\text{CH}} \text{Me}_3\text{SiC}\equiv\text{CCu} \qquad (2)$$

$$t\text{-BuOCu} \xrightarrow[\text{C}_6\text{H}_6\text{, rt}]{(\text{Ph}_2\text{P})_2\text{CH}_2} (\text{Ph}_2\text{PCHPPh}_2)\text{Cu} \qquad (3)$$

$$t\text{-BuOCu} \xrightarrow[\text{THF, rt}]{\text{H}_2\text{O}} \text{CuOH} \qquad (4)$$

$$t\text{-BuOCu} \xrightarrow[\text{py, rt}]{\text{PhOH}} \text{PhOCu} \qquad (5)$$

$$t\text{-BuOCu} \xrightarrow[\text{DMF, 0 °C}]{\text{H}_2\text{O, CO}_2\text{, PEt}_3} \text{HOCO}_2\text{Cu(PEt}_3)_3 \qquad (6)$$

$$t\text{-BuOCu} \xrightarrow[\text{C}_6\text{H}_6\text{, rt}]{\text{Et}_2\text{NH, CO}_2} \text{Et}_2\text{NCO}_2\text{Cu} \qquad (7)$$

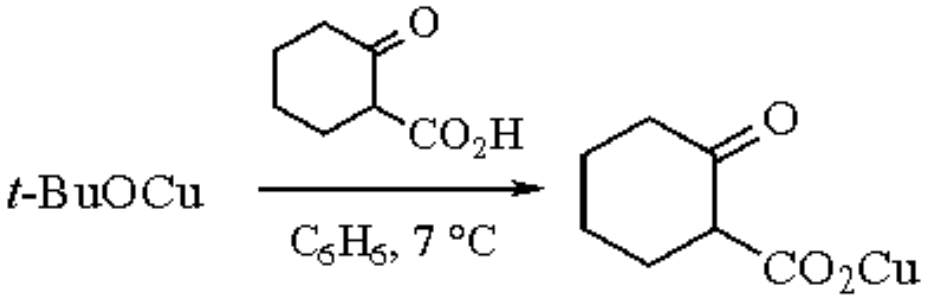

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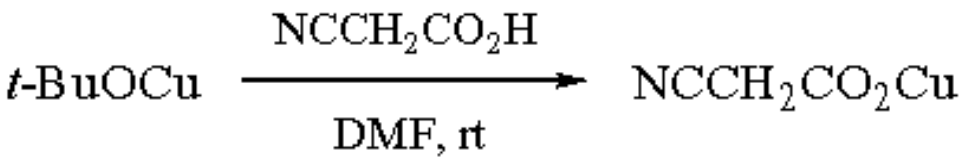

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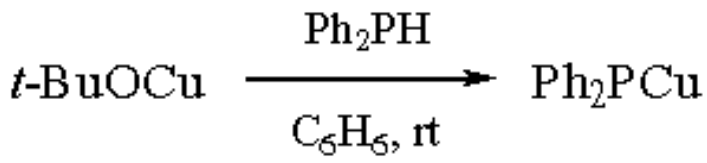

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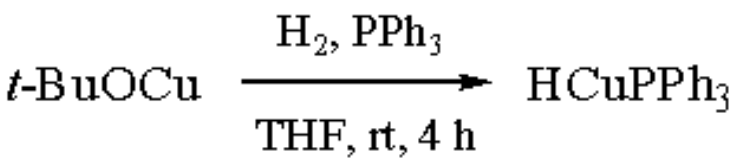

(11)

Cross-Coupling of 1,3-Dinitrobenzenes and Aryl Iodides to 2,6-Dinitrobiphenyls.

Cu^I *t*-butoxide with ***Pyridine*** mediates cross-coupling of 1,3-dinitrobenzenes with aryl iodides to give 2,6-dinitrobiphenyls under mild conditions (eq 12).[2] This 2,6-dinitrobiphenyl synthesis is superior to the Ullmann condensation of aryl iodides with 2,6-dinitrochlorobenzene or ***Copper(I) Oxide***-promoted reaction of 1,3-dinitrobenzenes with aryl iodides in quinoline. Aryl iodides with Me, MeO, Cl, Br, CO_2Me, and NO_2 substituents and with at least one free *ortho* position can be used to give substituted 2,6-dinitrobiphenyls in 30-95% yield. Aryl iodides substituted in both *ortho* positions react sluggishly and without positional preference. Aryl bromides react less effectively. (*E*)-β-Iodostyrene reacts but alkyl iodides and allyl bromide fail to give arylated products. The incorporation of extra substituents such as Me, CO_2Bu-*t*, and CN in the dinitrobenzene unit is successful. The presence of two nitro groups is an essential requirement, the alternative use of electron-withdrawing substituents such as CO_2Me and CN instead of one nitro group of 1,3-dinitrobenzene proving ineffective.

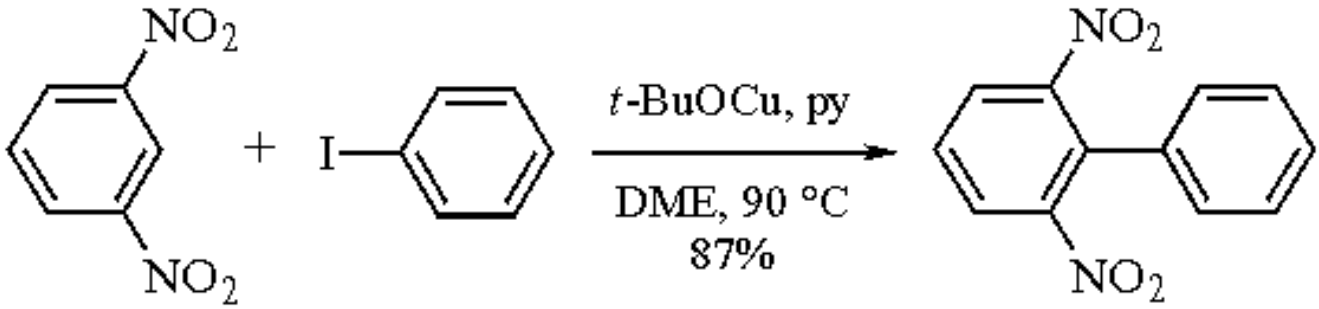

(12)

1,3-Dinitrobenzene reacts with 4- and 2-iodophenols in the presence of Cu^I *t*-butoxide, ***Potassium t-Butoxide***, and pyridine to give 2´,6´-dinitrobiphenyl-4-ol (eq 13) and 1-nitrodibenzofuran (eq 14), respectively.[12] A similar reaction occurs by using iodomethyl phenyl sulfone and sulfoxide (eq 15). The reaction mechanism of copper-mediated vicarious nucleophilic substitution has been proposed.

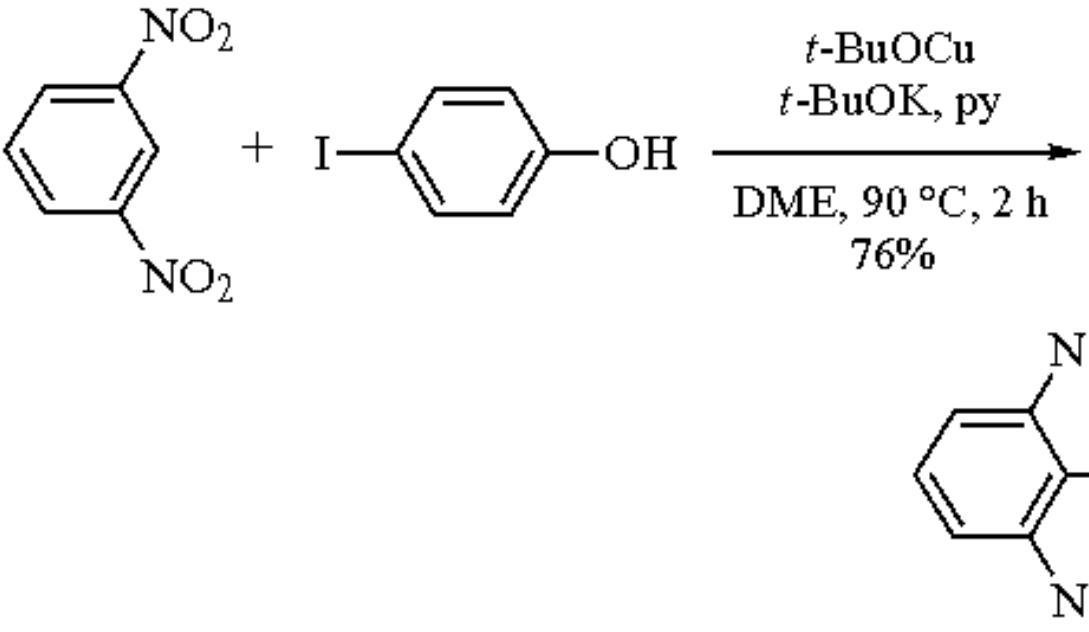

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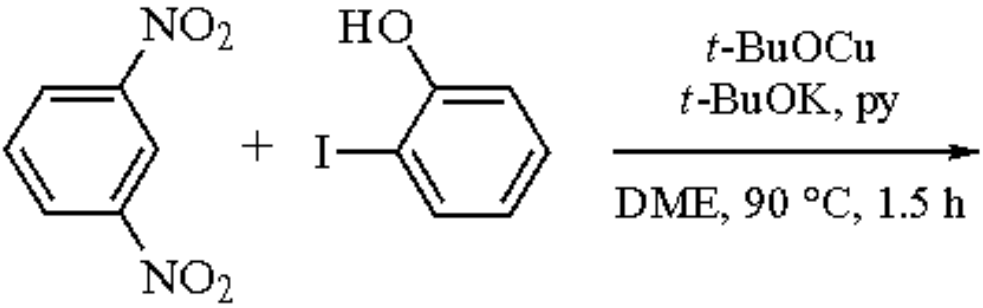

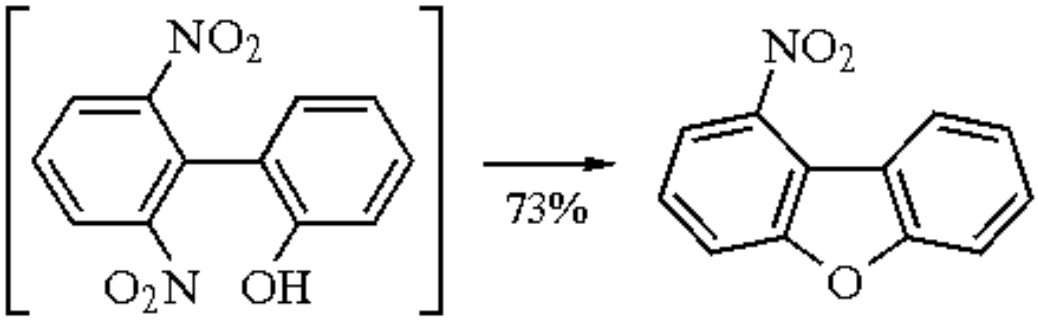

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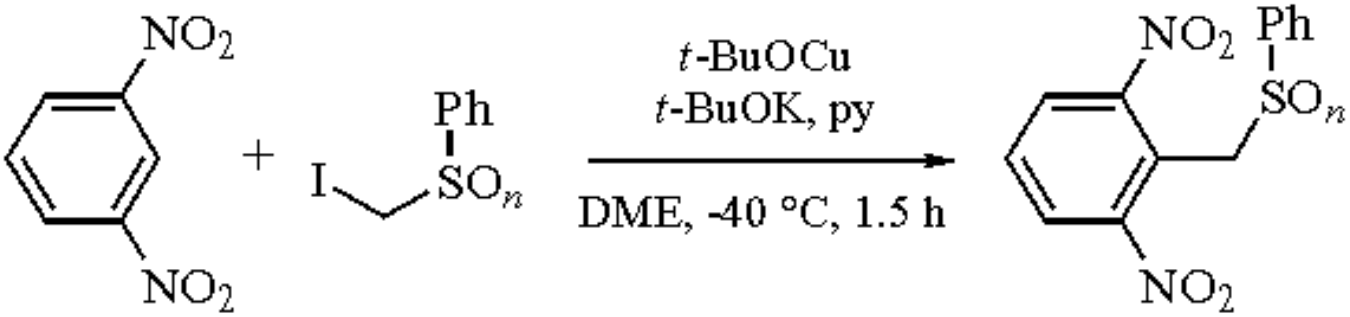

(15)

$n = 1$, 68%; $n = 2$, 76%

In a similar fashion, Cu^{I} *t*-butoxide effects one-pot formation of isocoumestans in the presence of pyridine by cross-coupling of 2-iodophenols with ethyl acetylenecarboxylate via alkenylcopper intermediates (eq 16).[13]

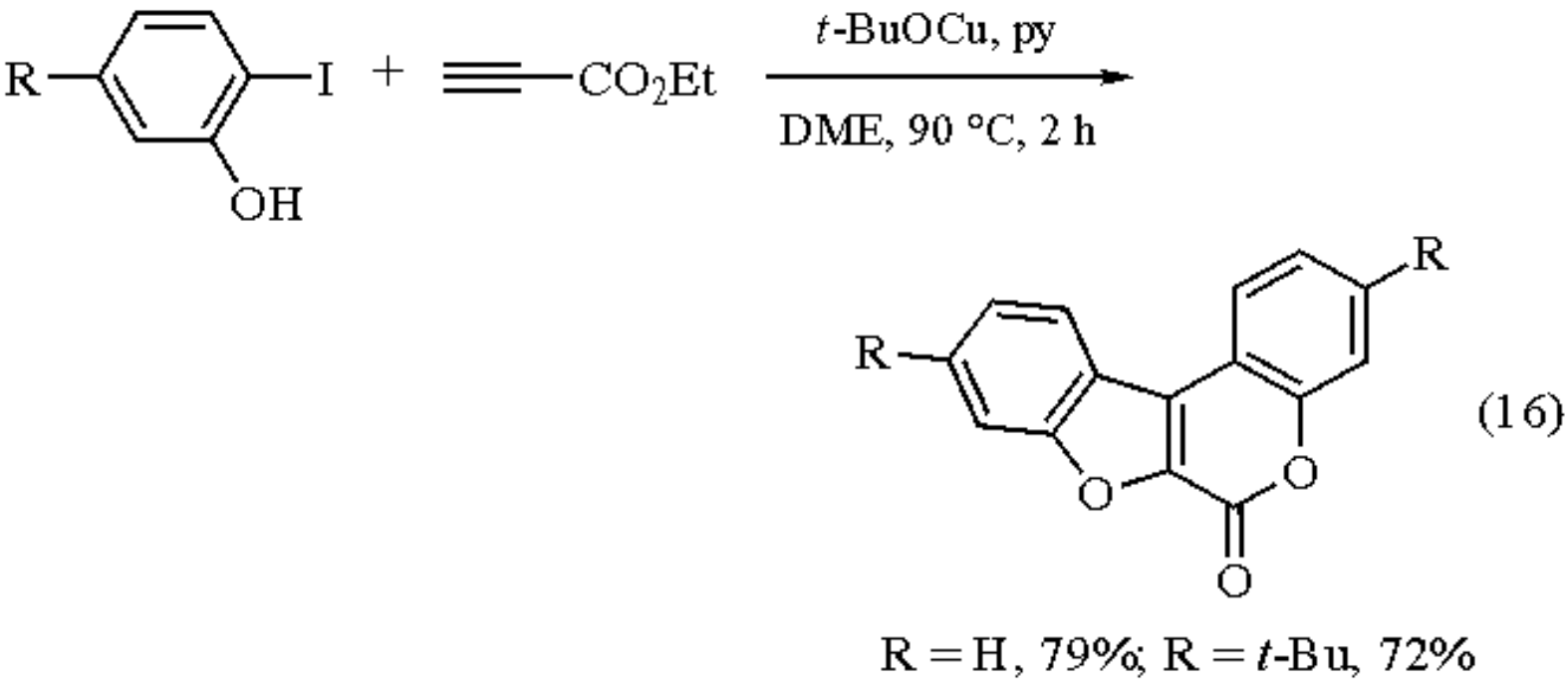

Nontransferable Group of Mixed Organocuprates.

A nontransferable group of mixed organocuprates has been developed for stabilizing organocuprate reagents and for saving one organic group of diorganocuprates. Cu^I *t*-butoxide can be used for a nontransferable group of mixed organocuprates (eq 17).[3] The nontransferable thiophenoxy group from Cu^I thiophenoxide has been reported to be the most useful compared to *t*-BuO, PhO, *t*-BuS, and Et_2N in the reaction of lithium mixed organocuprates, but Cu^I *t*-butoxide has the advantage of easier handling. A variety of reactions of lithium and magnesium organocuprates utilizing Cu^I *t*-butoxide for the nontransferable group have been reported: *syn* carbocupration ((*t*-BuOCuR)Li/HC&tbond;CH, HC&tbond;CCH$(OEt)_2$, and MeC&tbond;CCH$(OEt)_2$);[14,15] acylation with acid chlorides ((*t*-BuOCuCH_2OBu-*t*)Li);[16] and asymmetric conjugate addition of (*t*-BuOCuBu-*n*)MgCl to 3-alkyl- and aryl-substituted cyclopentenone 2-sulfoxide enantiomers.[17]

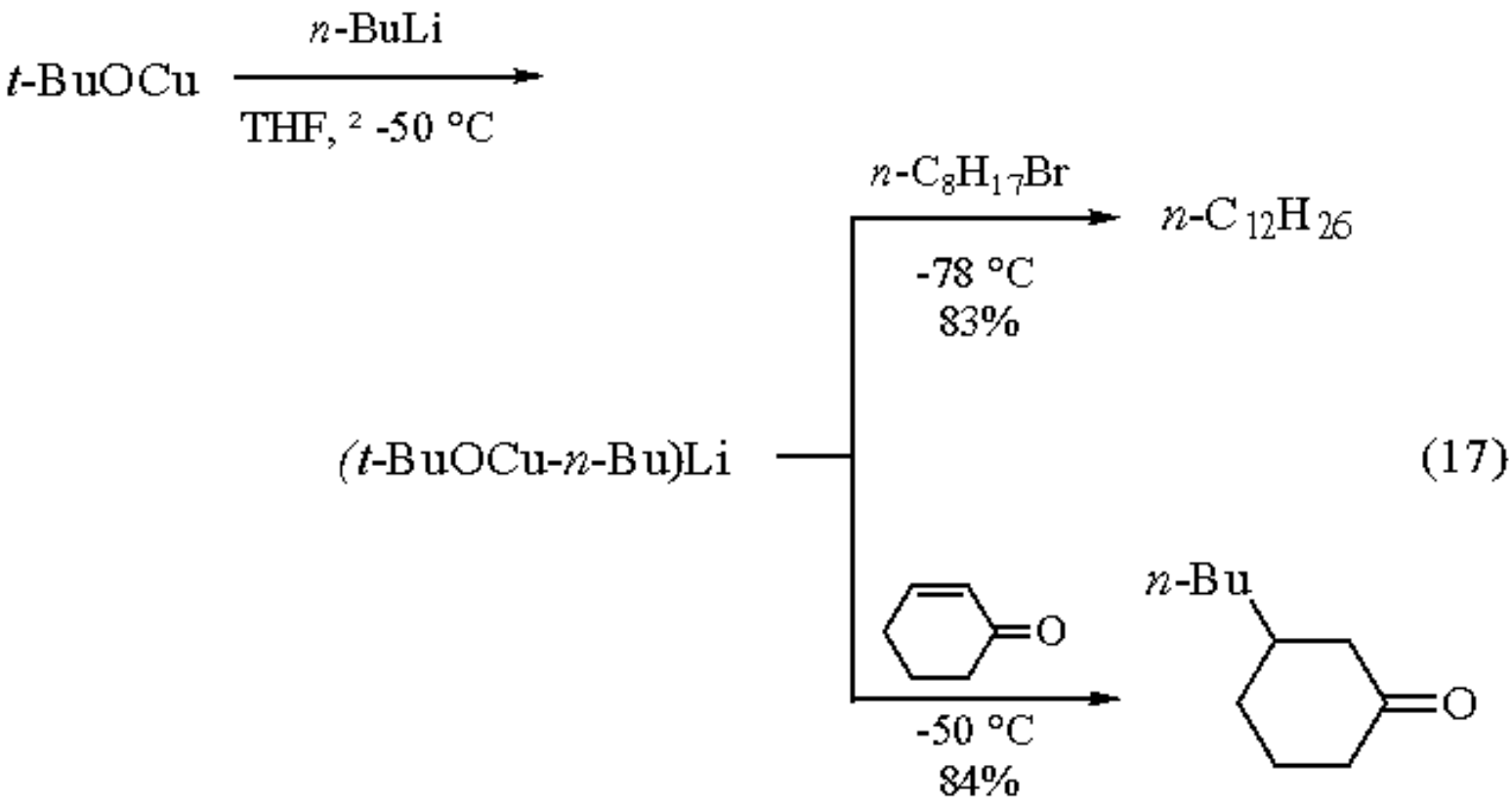

t-BuOCuL (L = CO, *t*-BuNC, and PEt_3) Complexes.

Cu^I *t*-butoxide forms sublimable copper complexes *t*-BuOCuL (L = CO,[18] *t*-BuNC,[18] and PEt_3[1]). These complexes metalate cyclopentadiene to afford η^5-C_5H_5CuL complexes.[1,18] *t*-BuOCu(*t*-BuNC) effects metalation of, and subsequent ligand insertion with, fluorene (eq 18).[18] Cu^I *t*-butoxide-trialkylphosphine complexes effect hydride transfer to a carbonyl group (Tishchenko reaction and Meerwein-Ponndorf reduction)[19] and cyclopropane formation from methyl α-chloropropionate and methacrylonitrile.[20] *t*-BuOCu(*t*-BuNC) absorbs CO_2 reversibly (eq 19).[21] At an elevated reaction temperature, *t*-BuOCu(*t*-BuNC) effects deoxygenation of CO_2 to produce CO and *t*-butyl isocyanate, which is converted to carbamate by addition of alcohol (eq 20).[22]

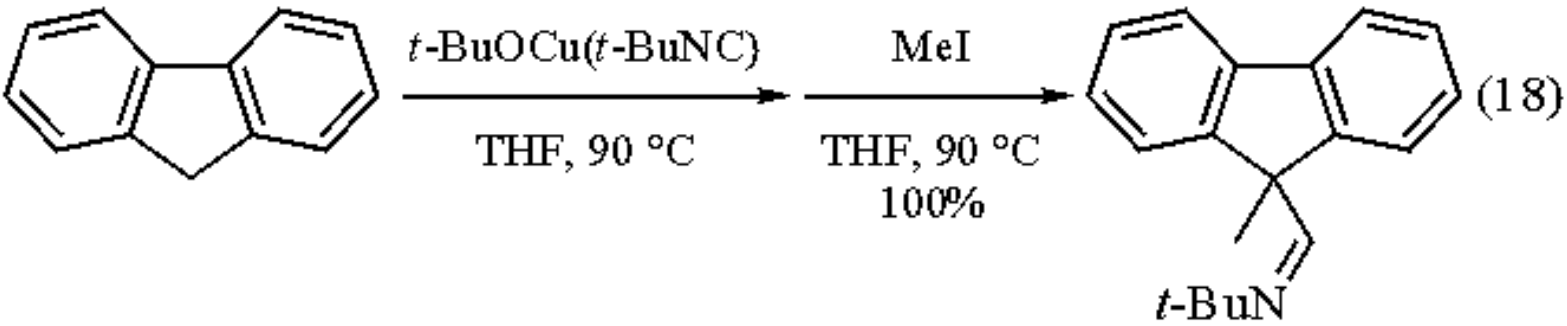

$$t\text{-BuOCu}(t\text{-BuNC}) + 2\ t\text{-BuNC} + CO_2 \underset{C_6H_6,\ \text{reflux}}{\overset{C_6H_6,\ \text{rt}}{\rightleftharpoons}} t\text{-BuOCO}_2\text{Cu}(t\text{-BuNC})_3 \quad (19)$$

$$CO_2 + t\text{-BuNC} \xrightarrow[\text{tetralin, 120 °C}]{t\text{-BuOCu}} CO + t\text{-BuNCO} \xrightarrow[\text{rt}]{n\text{-BuOH}} \underset{119\%}{CO} + \underset{116\%}{t\text{-BuNHCO}_2\text{-}n\text{-Bu}} \quad (20)$$

(based on Cu)

Volatile Copper Precursor for Metallic Copper and Cu^{I} Oxide Films by MOCVD.

Metal-organic chemical vapor deposition with Cu^{I} *t*-butoxide results in the deposition of pure Cu^{I} oxide whiskers at 237 °C and of metallic copper films at 397 °C (eq 21).[4a] An elimination mechanism has been proposed for the formation of Cu^{I} oxide: elimination of isobutene from *t*-butoxide groups yields Cu^{I} hydroxide intermediates, which subsequently engage in proton transfer processes to produce Cu^{I} oxide, *t*-butyl alcohol, and water. η^5-$C_5H_5CuPEt_3$[1] and *t*-BuOCuCO[18] also act as the volatile copper precursor for MOCVD.[4b]

$$[CuOCMe_3]_4 \longrightarrow 2\ Cu_2O + xH_2O + (2\text{-}x)HOCMe_3 + (2+x)CH_2{=}CMe_2 \quad (21)$$

$$2\ Cu_2O \longrightarrow 4\ Cu + O_2$$

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Copper(II) Chloride

$CuCl_2$

[7447-39-4] · Cl_2Cu · Copper(II) Chloride · (MW 134.45) (.$2H_2O$)

[10125-13-0] · $Cl_2CuH_4O_2$ · Copper(II) Chloride · (MW 170.48)

(chlorinating agent; oxidizing agent; Lewis acid)

Physical Data: anhydrous: *d* 3.386 g cm^{-3}; mp 620 °C (reported mp of 498 °C actually describes a mixture of $CuCl_2$ and CuCl); partially decomposes above 300 °C to CuCl and Cl_2; dihydrate *d* 2.51 g cm^{-3}; mp 100 °C.

Solubility: anhydrous: sol water, alcohol, and acetone; dihydrate: sol water, methanol, ethanol; mod sol acetone, ethyl acetate; sl sol Et_2O.

Form Supplied in: anhydrous: hygroscopic yellow to brown microcrystalline powder; dihydrate: green to blue powder or crystals; also supplied as reagent adsorbed on alumina (approx. 30 wt % $CuCl_2$ on alumina).

Analysis of Reagent Purity: by iodometric titration.[70]

Purification: cryst from hot dil aq HCl (0.6 mL g^{-1}) by cooling in a $CaCl_2$-ice bath.[71]

Handling, Storage, and Precautions: the anhydrous solid should be stored in the absence of moisture, since the dihydrate is formed in moist air. Irritating to skin and mucous membranes.

Chlorination of Carbonyls.

Copper(II) chloride effects the α-chlorination of various carbonyl functional groups.[1] The reaction is usually performed in hot, polar solvents containing ***Lithium Chloride***, which enhances the reaction rate. For example, butyraldehyde is α-chlorinated in DMF (97% conversion, eq 1) while the same reaction in methanol leads to an 80% yield of the corresponding α-chloro dimethyl acetal (eq 2).[2]

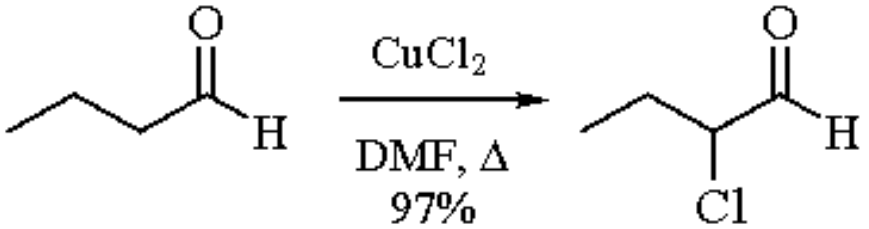

(1)

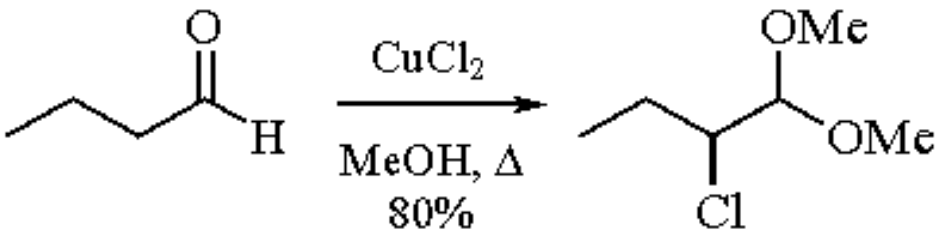

(2)

The process has been extended to carboxylic acids, anhydrides, and acid chlorides by using an inert solvent such as sulfolane.[3] 4-Oxo-4,5,6,7-tetrahydroindoles are selectively α-chlorinated, allowing facile transformation to 4-hydroxyindoles (eq 3).[4] The ability of the reaction to form α-chloro ketones selectively has been further improved by the use of trimethylsilyl enol ethers as substrates.[5] Recently, phase-transfer conditions have been employed in a particularly difficult synthesis of RCH(Cl)C(O)Me selectively from the parent ketones (eq 4).[6]

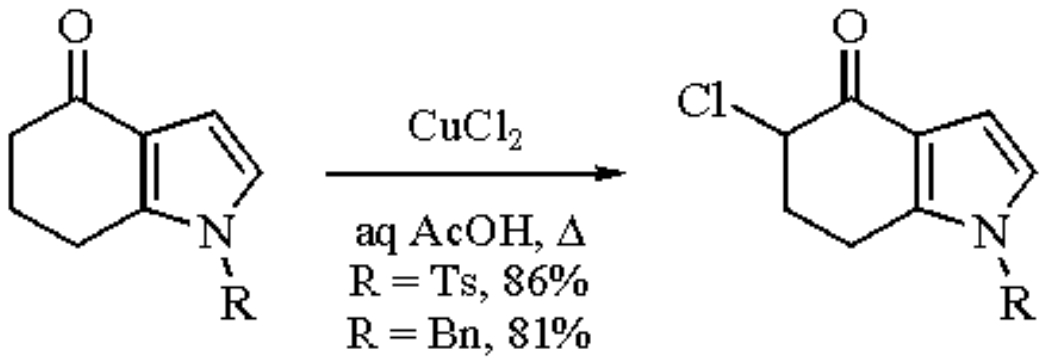

(3)

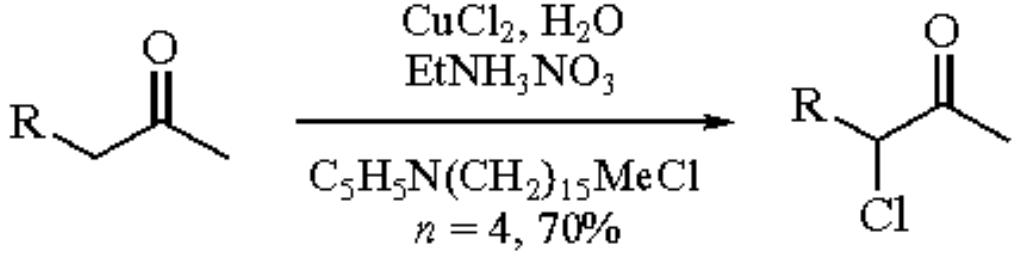

(4)

$R = Me(CH_2)_n$, $n = 2\text{-}5, 8$

Chlorination of Aromatics.

Aromatic systems may be chlorinated by the reagent. For example, 9-chloroanthracene is prepared in high yield by heating anthracene and $CuCl_2$ in carbon tetrachloride (eq 5).[7] When the 9-position is blocked by a halogen, alkyl, or aryl group, the corresponding 10-chloroanthracenes are formed by heating the reactants in chlorobenzene.[8,9] Under similar conditions, 9-acylanthracenes give 9-acyl-10-chloroanthracenes as the predominant products.[10]

Polymethylbenzenes are efficiently and selectively converted to the nuclear chlorinated derivatives by $CuCl_2$/***Alumina*** (eq 6).[11]

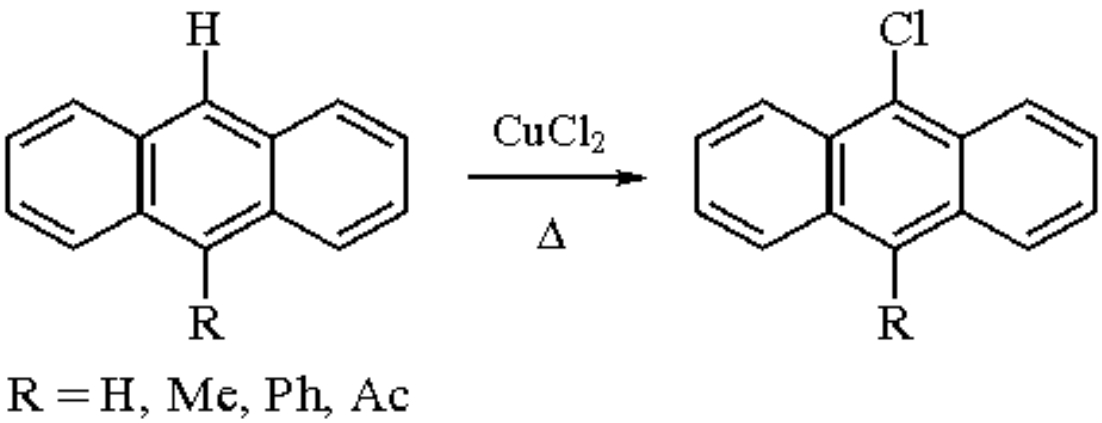

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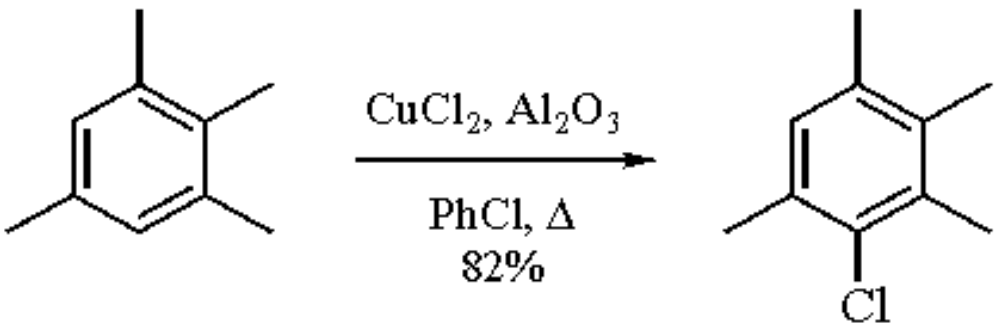

(6)

Reactions with Alkoxy and Hydroxy Aromatics.

Hydroxy aromatics such as phenols and flavanones undergo aromatic nuclear chlorination with copper(II) chloride.[12] Thus heating 3,5-xylenol with a slight excess of the reagent in toluene at 90 °C gave a 93% yield of 4-chloro-3,5-xylenol (eq 7).[13] 2-Alkoxynaphthalenes are similarly halogenated at the 1-position.[14] Attempted reaction of $CuCl_2$ with anisole at 100 °C for 5 h gave no products; in contrast, it was found that alkoxybenzenes were almost exclusively *para*-chlorinated (92-95% *para*:0.5-3% *ortho*) using $CuCl_2/Al_2O_3$ (eq 8).[15] Anisole reacts with benzyl sulfides in the presence of equimolar $CuCl_2$ and ***Zinc Chloride*** to give anisyl(phenyl)methanes (*para:ortho* = 2:1, eq 9).[16,17]

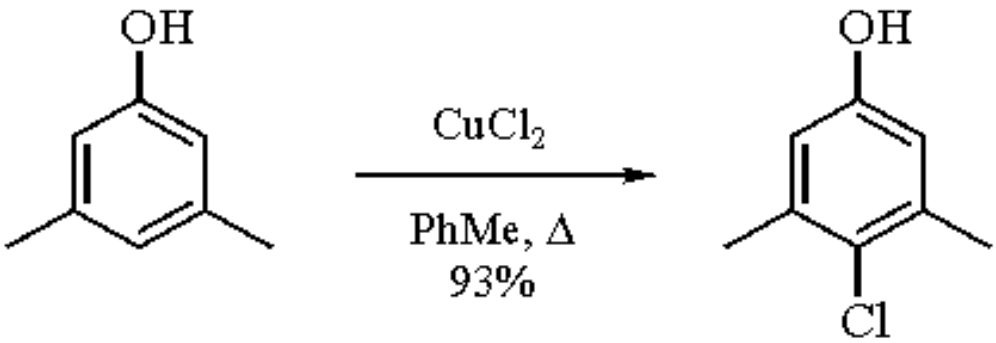

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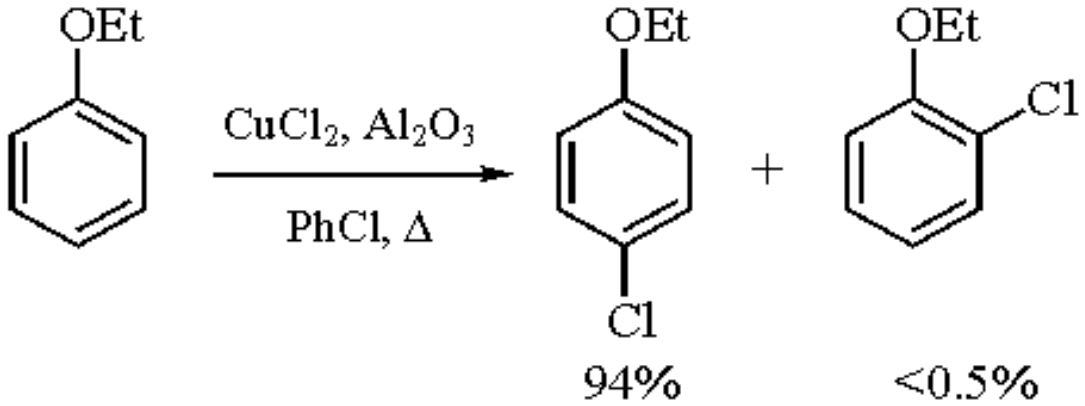

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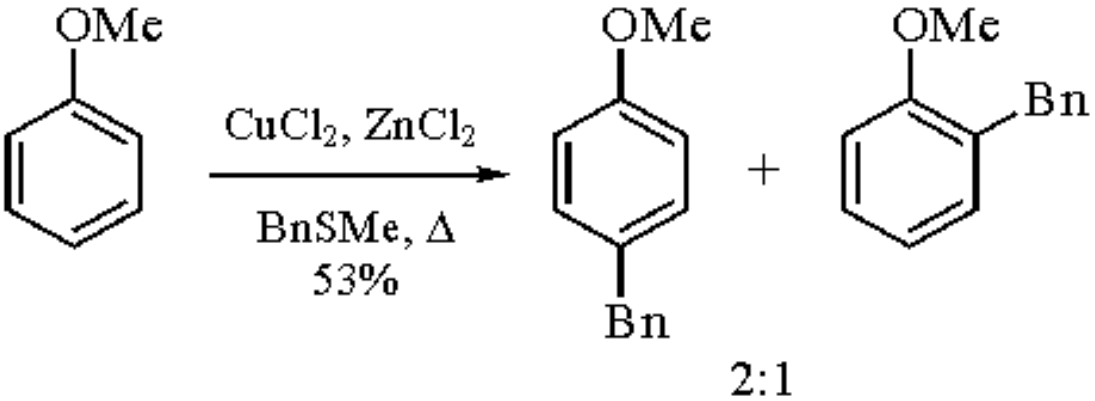

(9)

Reactions with Active Methylene-Containing Compounds.

9-Alkoxy(or acyloxy)-10-methylanthracenes react with $CuCl_2$ to give coupled products (eq 10), while the analogous 9-alkoxy(or acyloxy)-10-benzyl(or ethyl)anthracenes react at the alkoxy or acyloxy group to afford 10-benzylidene(or ethylidene)anthrones (eq 11).[18] The reactions are believed to proceed via a radical mechanism.

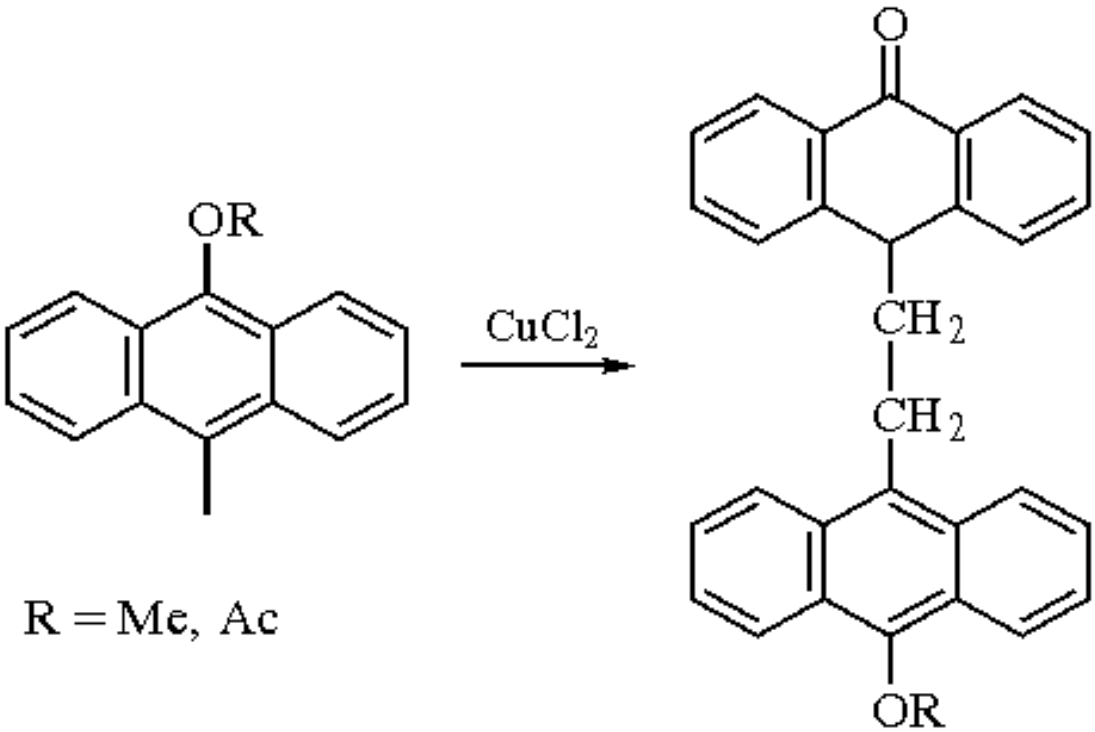

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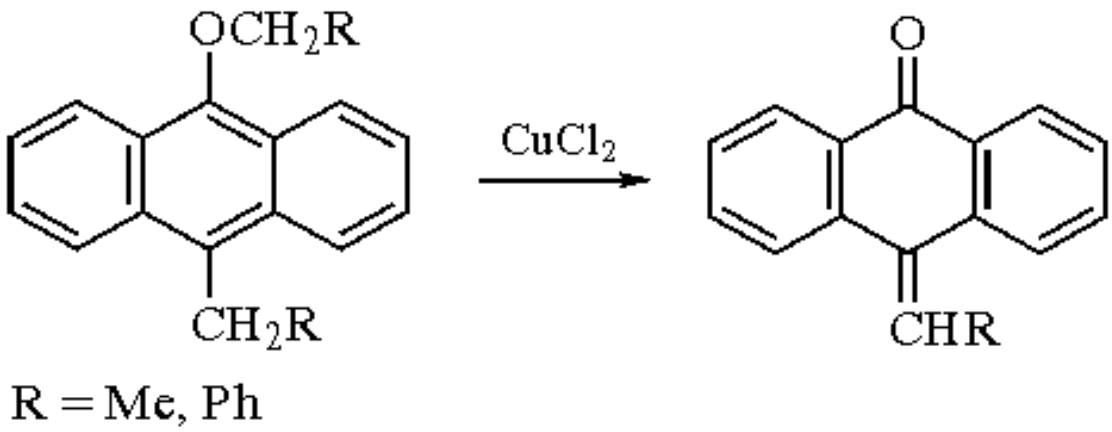

(11)

Under similar conditions, 9-alkyl(and aryl)-10-halogenoanthracenes give products resulting from replacement of the halogen, alkyl, or aryl groups with halogen from the $CuCl_2$.[19] Boiling toluene reacts with $CuCl_2$ to yield a mixture of phenyltolylmethanes.[20]

Lithium enolates of ketones[21] and esters[22] undergo a coupling reaction with copper(II) halides to afford the corresponding 1,4-dicarbonyl compounds. Thus treating a 3:1 mixture of *t*-butyl methyl ketone and acetophenone with ***Lithium Diisopropylamide*** and $CuCl_2$ gives a 60% yield of the cross-coupled product (eq 12).

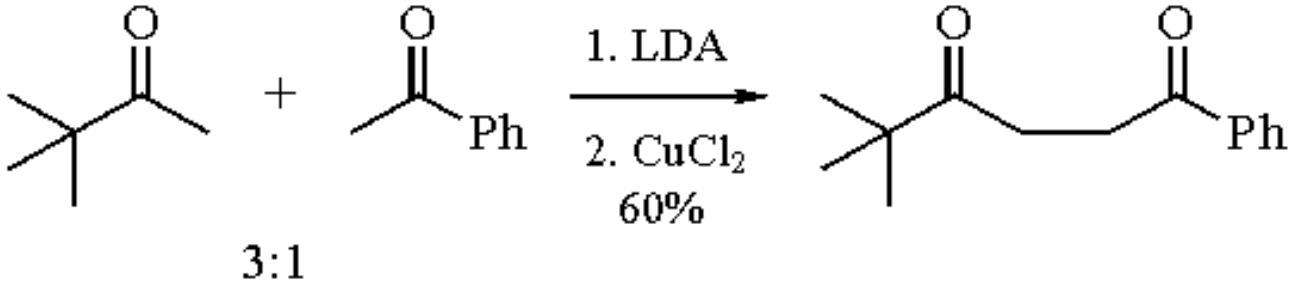

(12)

The intramolecular variant of this reaction producing carbocyclic derivatives has been reported.[23] Copper(II) chloride catalyzes the Knoevenagel condensation of 2,4-pentanedione with aldehydes and tosylhydrazones (eq 13).[24] The reagent also catalyzes the reaction of various 1,3-dicarbonyls with dithianes such as benzaldehyde diethyl dithioacetal to give the corresponding condensation products (eq 14).[25]

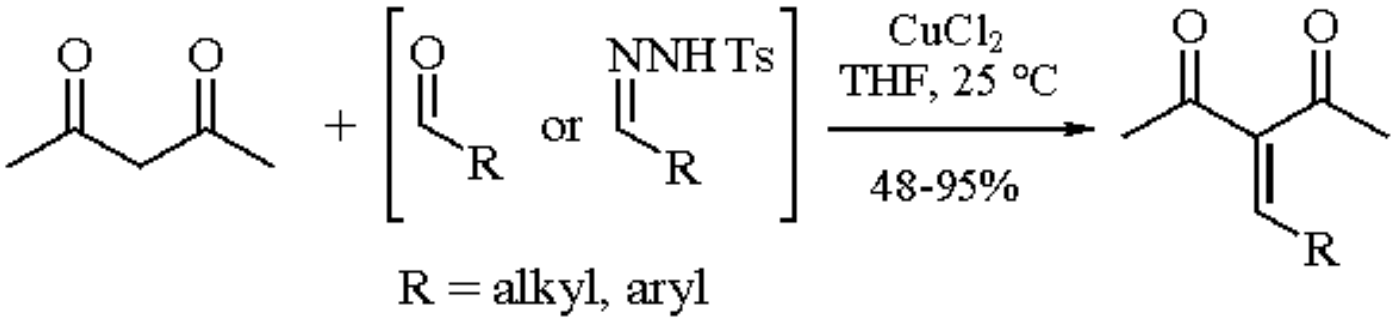

(13)

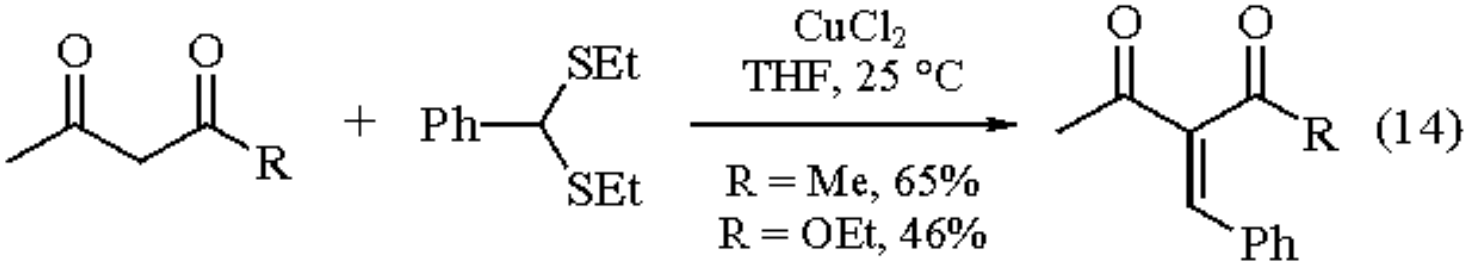

Catalyst for Conjugate Additions.

The catalytic effect of copper(II) chloride on the 1,4-addition of β-dicarbonyl compounds to (arylazo)alkenes[26,27] and aminocarbonylazoalkenes[28,29] has been studied in some detail. The reactions proceed at ambient temperature in THF and afford the corresponding pyrrole derivatives (eq 15). This mild method requires no other catalyst and succeeds with β-diketones, β-ketoesters, and β-ketoamides. Copper(II) chloride also catalyzes the addition of water, alcohols, phenol, and aromatic amines to arylazoalkenes (eq 16).[30]

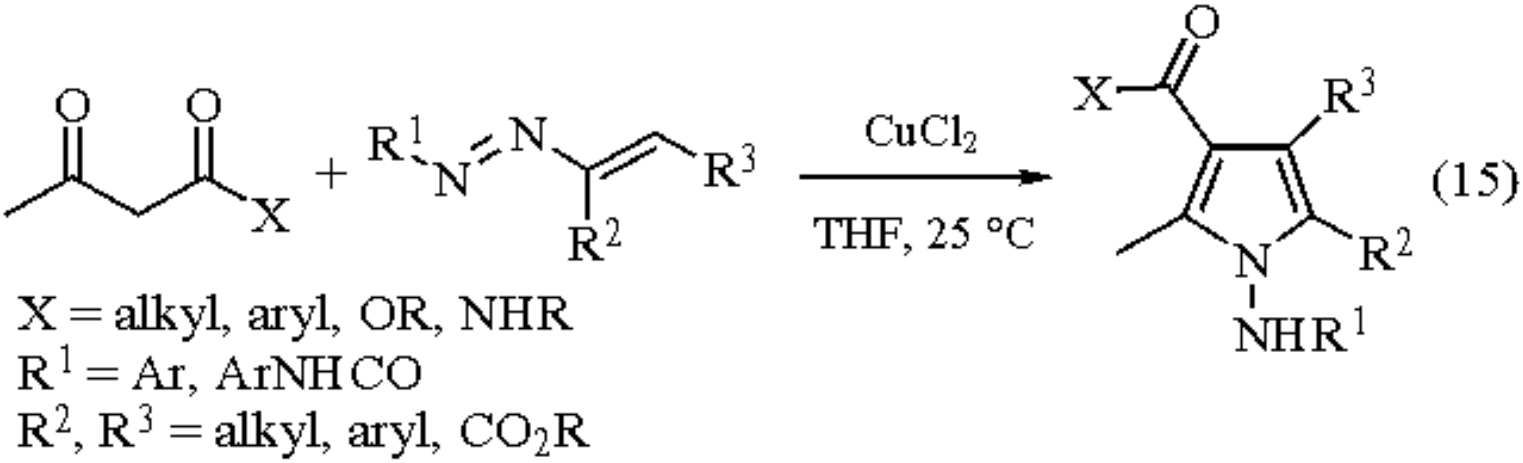

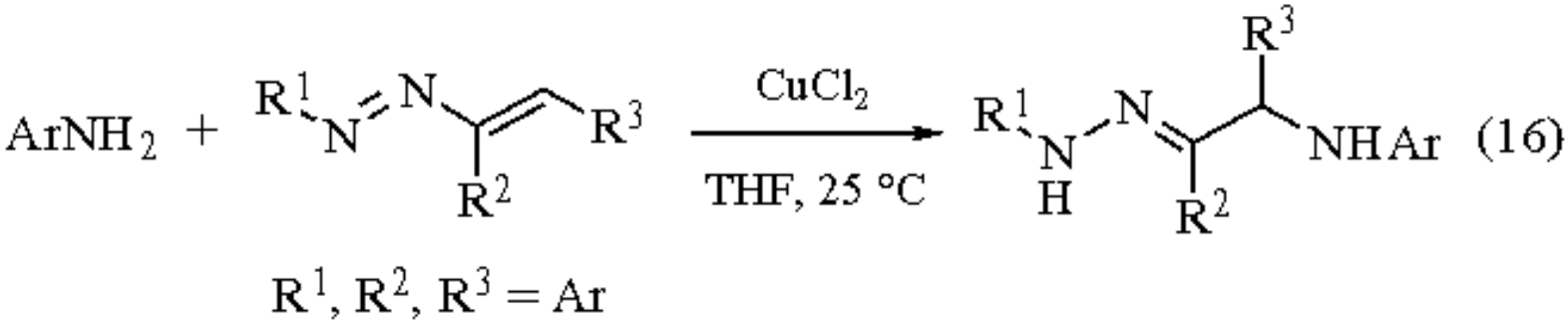

Oxidation and Coupling of Phenolic Derivatives.

In the presence of oxygen, copper(II) chloride converts phenol derivatives to various oxidation products. Depending on the reaction conditions, quinones and/or coupled compounds are formed.[31] Several groups have examined different sets of conditions employing $CuCl_2$ to favor either of these products. Thus 2,3,6-trimethylphenol was selectively oxidized to trimethyl-*p*-benzoquinone with $CuCl_2$/amine/O_2 as the catalyst (eq 17),[32] while 2,4,6-trimethylphenol was converted to 3,5-dimethyl-4-hydroxybenzaldehyde using a catalytic system employing either acetone oxime or amine

(eq 18).[33,34]

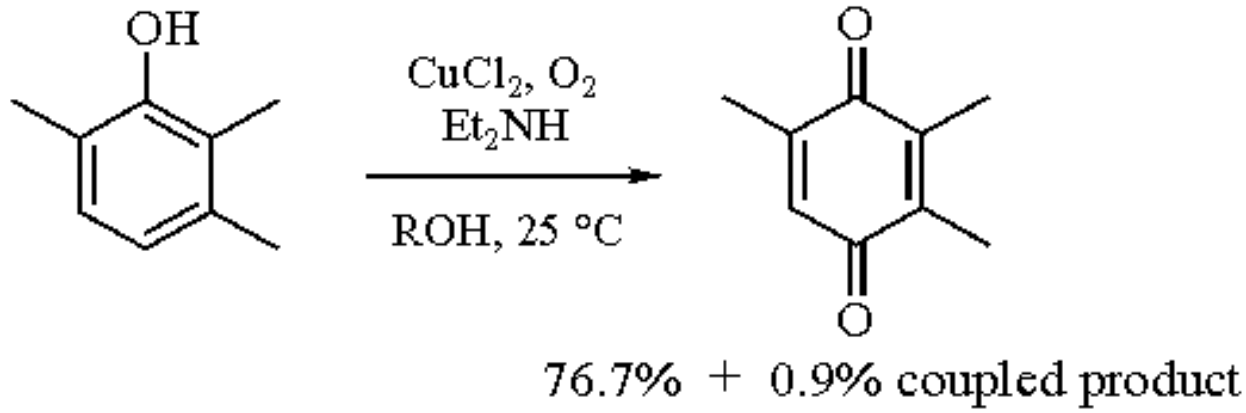

(17)

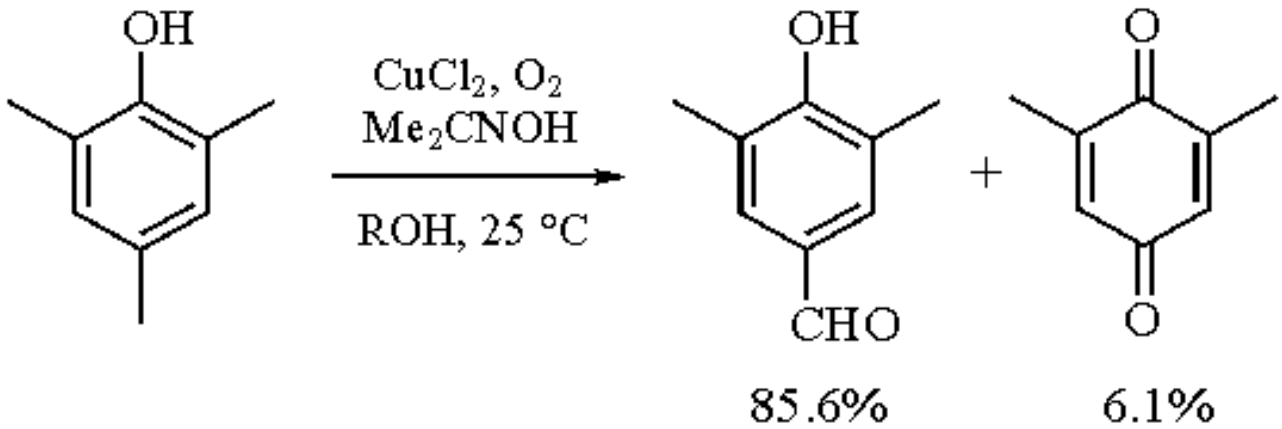

(18)

The oxidation of alkoxyphenols to the corresponding quinones has been studied,[35] and even benzoxazole derivatives are oxidized by a mixture of copper(II) chloride and ***Iron(III) Chloride*** (eq 19).[36] A $CuCl_2/O_2$/alcohol catalytic system has been used for the oxidative coupling of monophenols.[37]

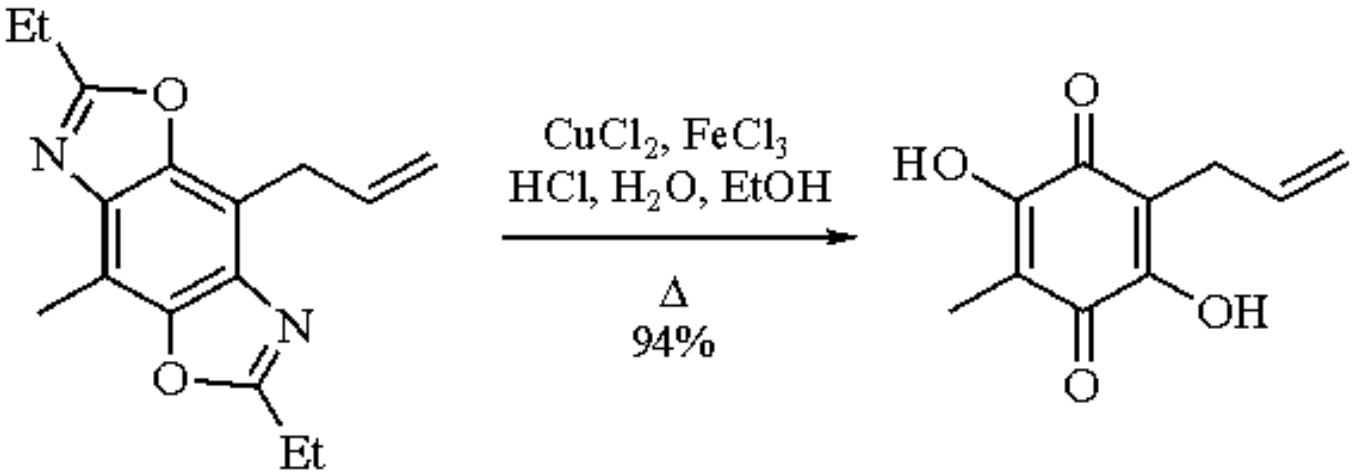

(19)

Copper(II) amine complexes are very effective catalysts for the oxidative coupling of 2-naphthols to give symmetrical 1,1´-binaphthalene-2,2´-diols.[38] Recent work has extended this methodology to the cross-coupling of various substituted 2-naphthols.[39,40] For example, 2-naphthol and 3-methoxycarbonyl-2-naphthol are coupled under strictly anaerobic conditions using $CuCl_2$/***t-Butylamine*** in methanol to give the unsymmetrical binaphthol in 86% yield (eq 20).

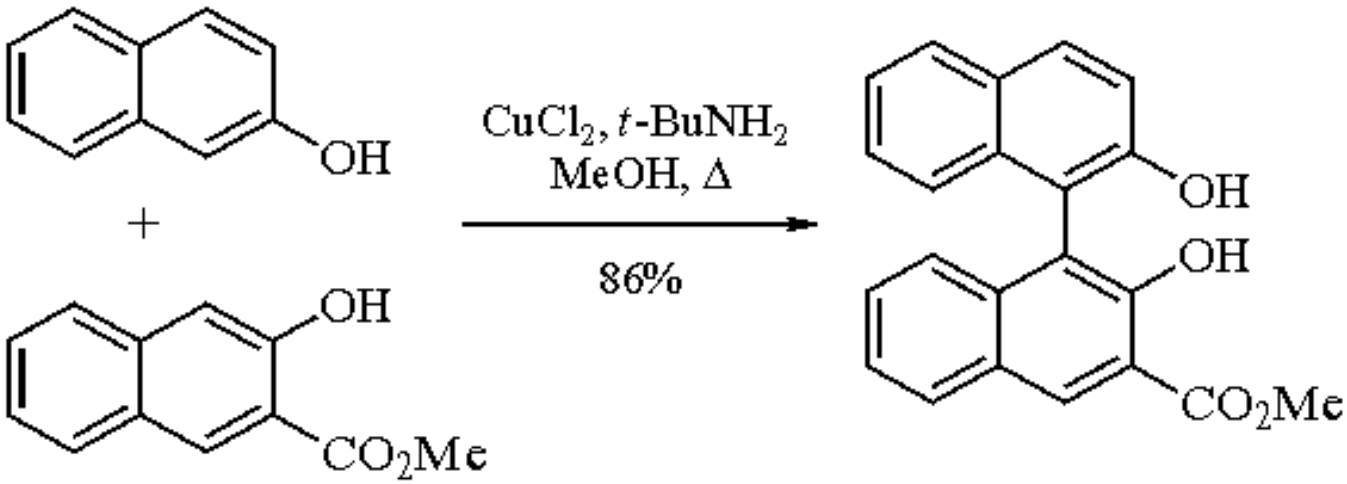

(20)

Other ligands such as methoxide are also effective; a mechanistic study indicates that the selectivity for cross- rather than homo-coupling is dependent upon the copper:ligand ratio.[41] A 1:1 mixture of 2-naphthol and 2-naphthylamine is cross-coupled with $CuCl_2$/benzylamine to give 2-amino-2´-hydroxy-1,1´-binaphthyl (68% yield, eq 21).[42] The cross-coupled products from these reactions are important in view of their use as chiral ligands for asymmetric synthesis.

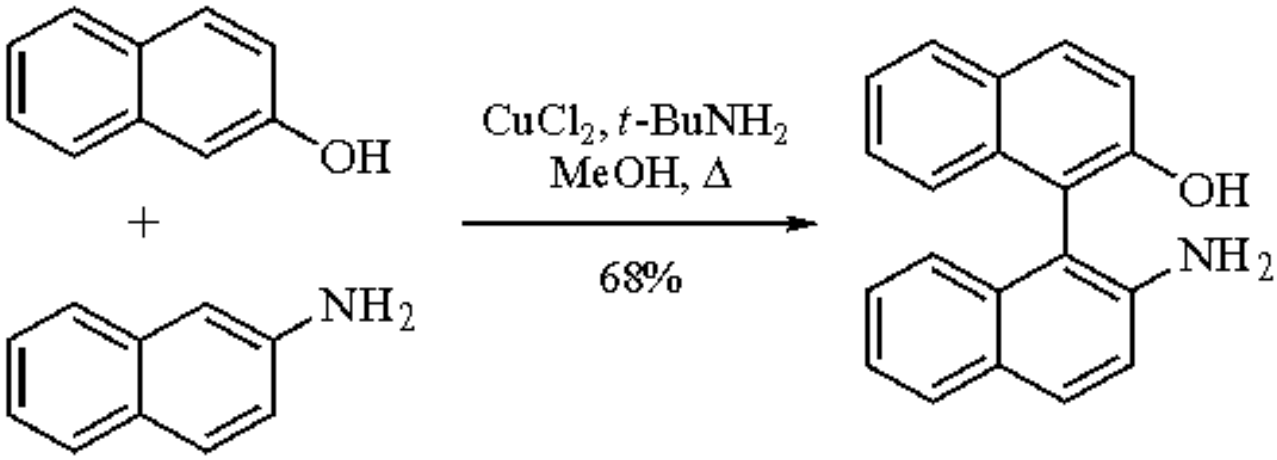

(21)

Dioxygenation of 1,2-Diones.

1,2-Cyclohexanedione derivatives have been converted to the corresponding 1,5-dicarbonyl compounds by oxidation with O_2 employing copper(II) chloride as the catalyst.[43] More recently, $CuCl_2$-***Hydrogen Peroxide*** has been used to prepare terminal dicarboxylic acids in high yield.[44] While 1,2-cyclohexanedione afforded α-chloroadipic acid in 85% yield, 1,2-cyclododecanedione was converted to 1,12-dodecanedioic acid in 47% yield under identical conditions (eq 22).

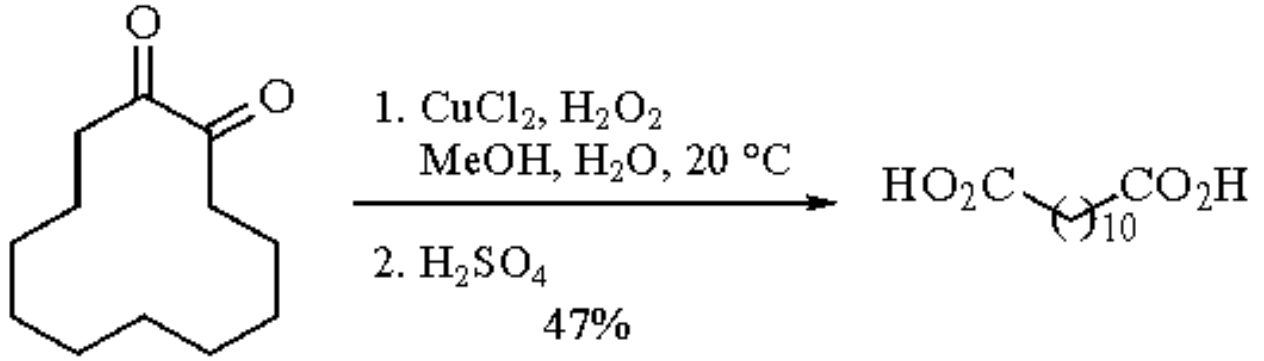

(22)

Addition of Sulfonyl Chlorides to Unsaturated Bonds.

The addition of alkyl and aryl sulfonyl chlorides across double and triple bonds is catalyzed by copper(II) chloride.[45-51] The reaction appears to be quite general and proceeds via a radical chain mechanism. The 2-chloroethyl sulfones produced in the reaction with alkenes undergo base-induced elimination to give vinyl sulfones (eq 23).[45-48] 1,3-Dienes similarly react, yielding 1,4-addition products (eq 24) which may be dehydrohalogenated to 1,3-unsaturated sulfones.[45,49]

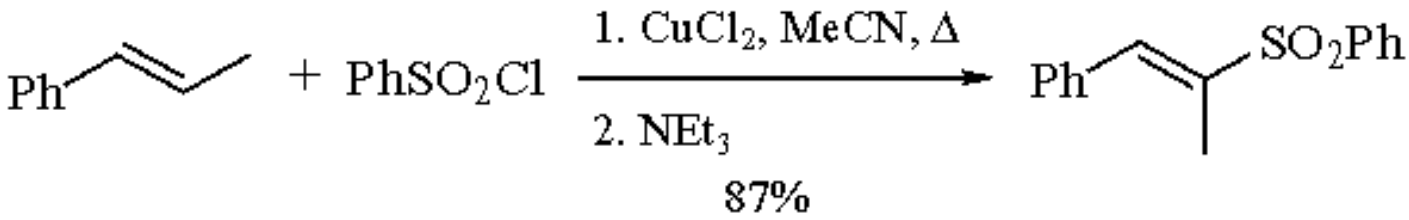

(23)

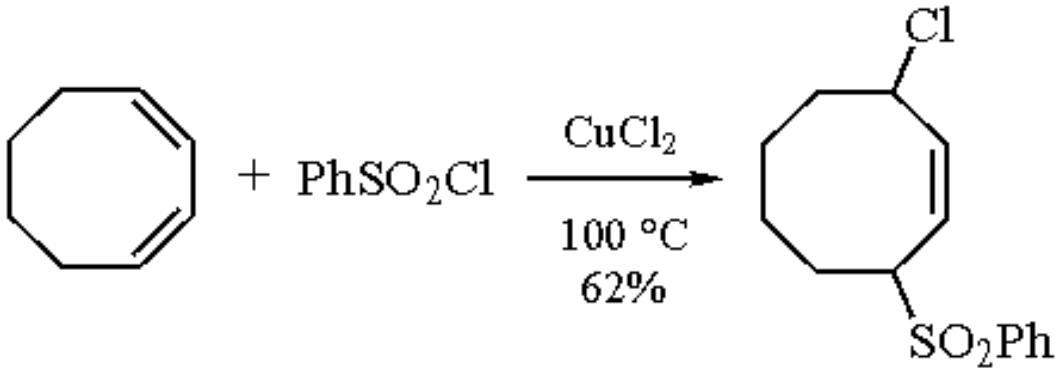

(24)

The stereoselectivity of the addition to alkynes can be controlled by varying the solvent or additive, and thus favoring either the *cis* or *trans* β-chlorovinyl sulfone.[50,51] For example (eq 25), when benzenesulfonyl chloride is reacted with phenylacetylene in acetonitrile with added triethylamine hydrochloride, the *trans*:*cis* ratio is 92:8, while the same reaction performed in CS_2 without additive favors the *cis* isomer (16:84).

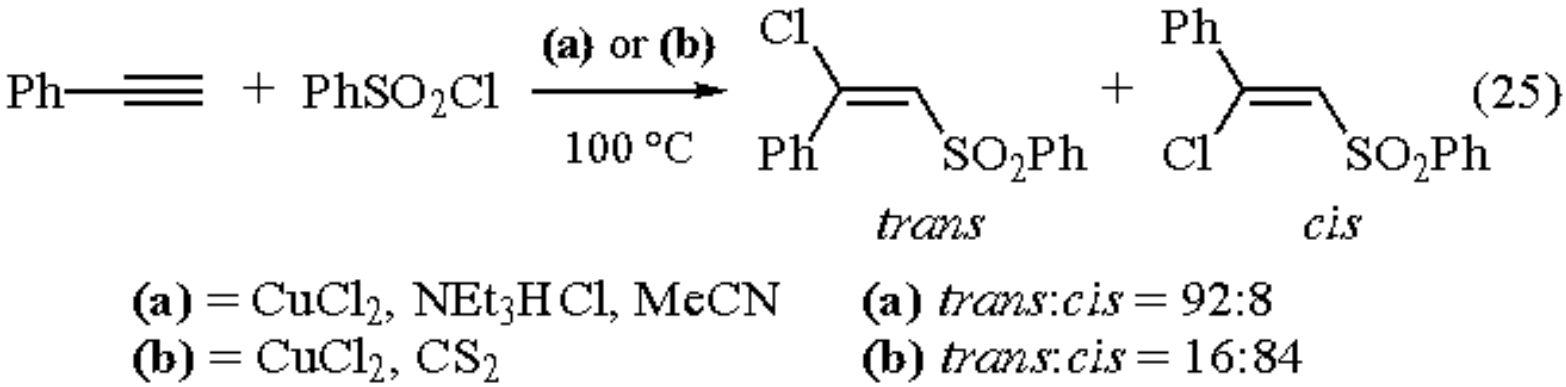

Acylation Catalyst.

N-Trimethylsilyl derivatives of (+)-bornane-2,10-sultam (Oppolzer's chiral sultam) and chiral 2-oxazolidinones (the Evans chiral auxiliaries) are *N*-acylated with a number of acyl chlorides including acryloyl chloride in refluxing benzene in the presence of $CuCl_2$.[52] The *N*-acylated products were prepared in high yields; the method does not require an aqueous workup, making it advantageous for large-scale preparations.

Racemization Suppression in Peptide Couplings.

A mixture of copper(II) chloride and ***Triethylamine*** catalyzes the formation of peptide bonds.[53] Furthermore, when used as an additive, $CuCl_2$ suppresses racemization in both the carbodiimide[54] and mixed anhydride[55] peptide coupling methods. Recently it was shown that a combination of ***1-Hydroxybenzotriazole*** and $CuCl_2$ gives improved yields of peptides while eliminating racemization.[56,57]

Reaction with Palladium Complexes.

π-Allylpalladium complexes undergo oxidative cleavage with copper(II) chloride to form allyl chlorides with the concomitant release of $PdCl_2$ (eq 26).[58]

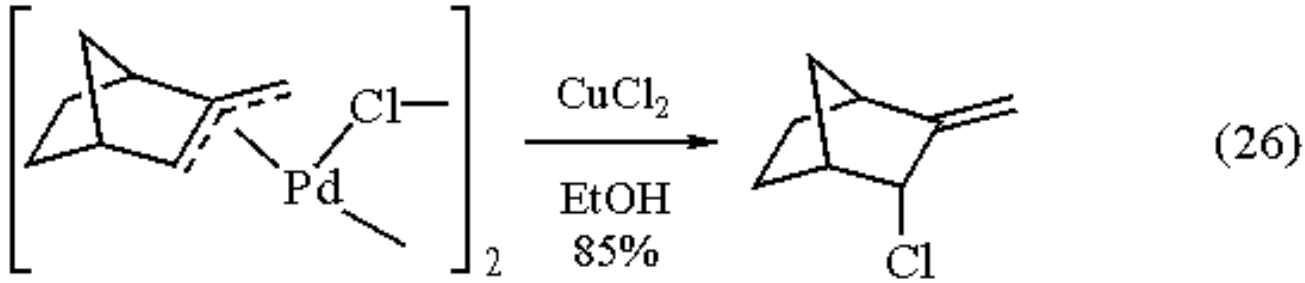

This methodology has been used in the dimerization of allenes to 2,3-bis(chloromethyl)butadienes.[59] 1,5-Bismethylenecyclooctane was transformed into the bridgehead-substituted bicyclo[3.3.1]nonane system using $CuCl_2$/HOAc/NaOAc, while the same substrate produced bicyclo[4.3.1]decane derivatives (eq 27) with a ***Palladium(II) Chloride***/$CuCl_2$ catalytic system.[60]

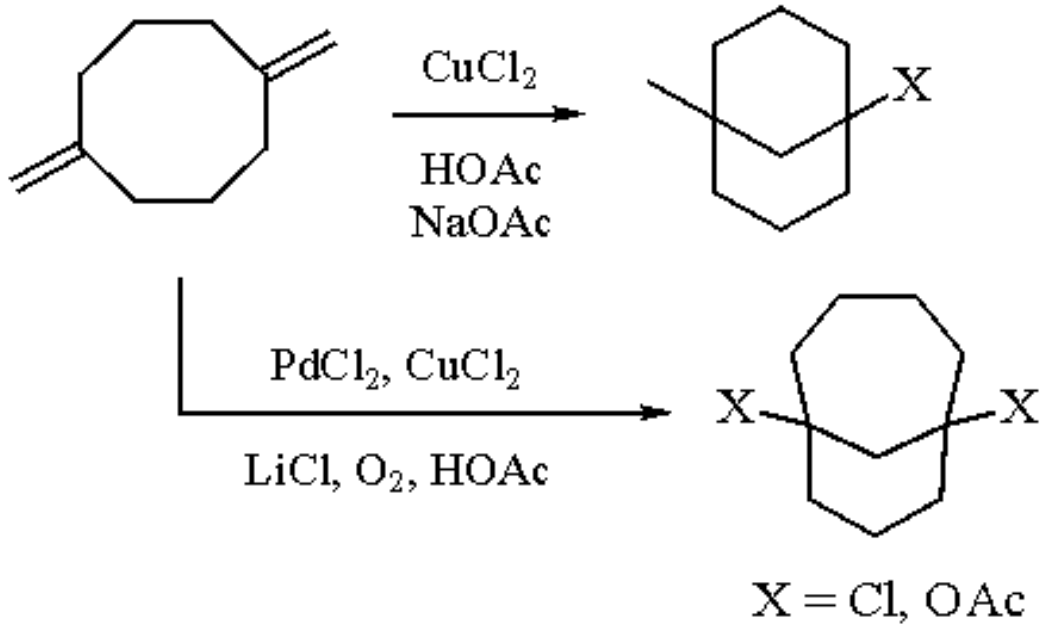

(27)

While reaction of a steroidal π-allylpalladium complex with AcOK yields the allyl acetate arising from *trans* attack, treatment of a steroidal alkene with $PdCl_2/CuCl_2$/AcOK/AcOH gave the allyl acetate arising from *cis* attack.[61]

Reoxidant in Catalytic Palladium Reactions.

Copper(II) chloride has been used extensively in catalytic palladium chemistry for the regeneration of Pd^{II} in the catalytic cycle. In particular, the reagent has found widespread use in the carbonylation of alkenes,[62-64] alkynes,[65] and allenes[66,67] to give carboxylic acids and esters using $PdCl_2/CuCl_2$/CO/HCl/ROH, and in the oxidation of alkenes to ketones with a catalytic $PdCl_2/CuCl_2/O_2$ system (the Wacker reaction).[68] The $PdCl_2/CuCl_2$/CO/NaOAc catalytic system has been used in a mild method for the carbonylation of β-aminoethanols, diols, and diol amines (eq 28).[69]

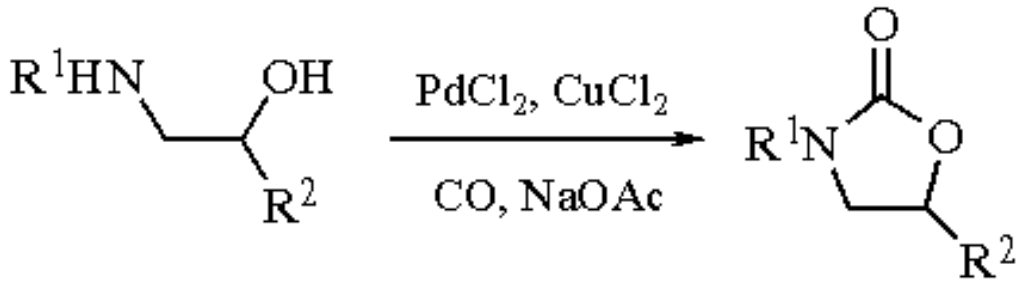

(28)

Cyclopropanation with $CuCl_2$-$Cu(OAc)_2$ Catalyst.

Ethyl Cyanoacetate reacts with alkenes under $CuCl_2$-***Copper(II) Acetate*** catalysis to give cyclopropanes.[72] Thus heating cyclohexene in DMF (110 °C, 5 h) with this reagent combination gives a 53% yield of the isomeric cyclopropanes. The reaction also proceeds with styrene, 1-decene, and isobutene. Byproducts formed from the addition to the alkene are removed with ***Potassium Permanganate***.

Related Reagents.

Chlorine; ***N-Chlorosuccinimide***; ***Copper(I) Chloride***; ***Copper(II) Chloride-Copper(II) Oxide***; ***Iodine-Copper(II) Chloride***; ***Copper(I) Chloride-Oxygen***; copper(I) chloride-tetrabutylammonium chloride ***Copper(I) Chloride-Sulfur Dioxide***; ***Iodine-Aluminum(III) Chloride-Copper(II) Chloride***; ***Iodine-Copper(I) Chloride-Copper(II) Chloride***; ***Methylmagnesium Iodide-Copper(I) Chloride***; ***Palladium(II) Chloride-Copper(I) Chloride***; ***Palladium(II) Chloride-Copper(II) Chloride***; ***Phenyl Selenocyanate-Copper(II) Chloride***; ***Vinylmagnesium Chloride-Copper(I) Chloride***; ***Zinc-Copper(I) Chloride***.

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Copper(I) Chloride[1]

CuCl

[7758-89-6] · ClCu · Copper(I) Chloride · (MW 99.00)

(catalyst for diazo and diazonium chemistry; for use with Grignard reagents[1])

Alternate Name: cuprous chloride.

Physical Data: mp 430 °C; *d* 4.140 g cm^{-3}.

Solubility: insol H_2O and most organic solvents; partially sol dimethyl sulfide (DMS).

Form Supplied in: light green-tinged white solid; 99.99% grade available commercially.

Handling, Storage, and Precautions: maintenance of a dry N_2 or Ar atmosphere is recommended.

General Discussion.

Copper(I) chloride is the most popular Cu^I salt for use in many of the classic name reactions of organic chemistry.[1a] Examples include the Sandmeyer reaction,[1b] the CuCl induced decomposition of arenediazonium salts to afford aryl chlorides,[2] and the related Bart reaction[1c] of arenediazonium salts with sodium metaarsenite to yield arylarsonic acids,[3] which is also catalyzed by CuCl. Kochi has elucidated the mechanisms of the Sandmeyer reaction and the Meerwein reaction[1d] of arenediazonium salts with alkenes and established that they proceed via a common radical intermediate which could be generated from other precursors.[4] Nagashima et al. took advantage of this fact when they cyclized an *N*-allyltrichloroacetamide derivative with CuCl,[5] in what is a significant extension and generalization of the Meerwein reaction (eq 1).

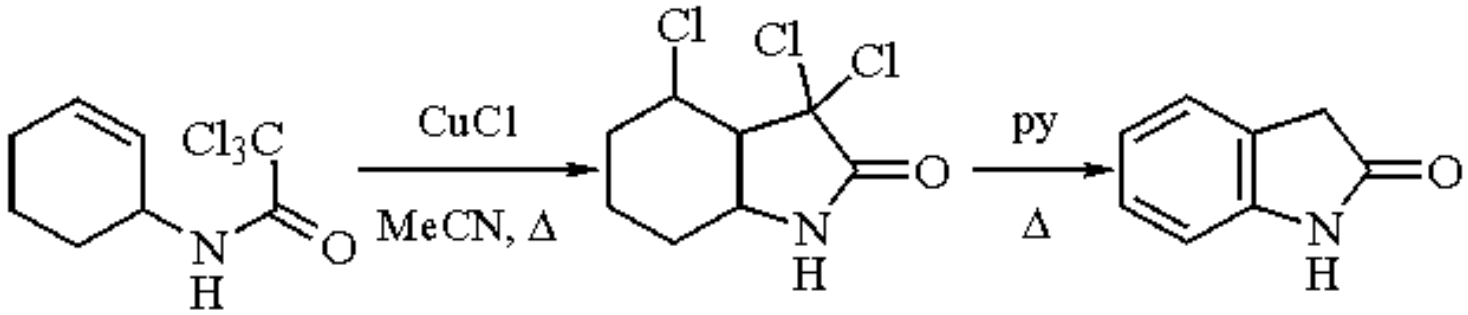

(1)

α-Diazo ketones with aryl substituents in the β´- or γ´-positions are decomposed by CuCl to give cyclized products. For example, Scott has reported an azulene synthesis starting from 3-phenylpropanoic acid,[6] and Iwata et al. have developed a spiroannulation method for phenolic α-diazo ketones,[7,8] as illustrated in eq 2 by the synthesis of α-chamigrene.[7] Many other examples[1e] of intramolecular reactions of diazo carbonyl compounds are known in an area that was pioneered by Stork,[9] who used ***Copper Bronze***. CuCl has also been used to catalyze cyclopropanations with ***Diazomethane***,[10] and with diazoacetic esters.[1f] It should be noted that CuI, CuBr, and CuCN have also been used to catalyze the reactions of diazo compounds, as have Cu^0 and Cu^{II}.[1e,f,9]

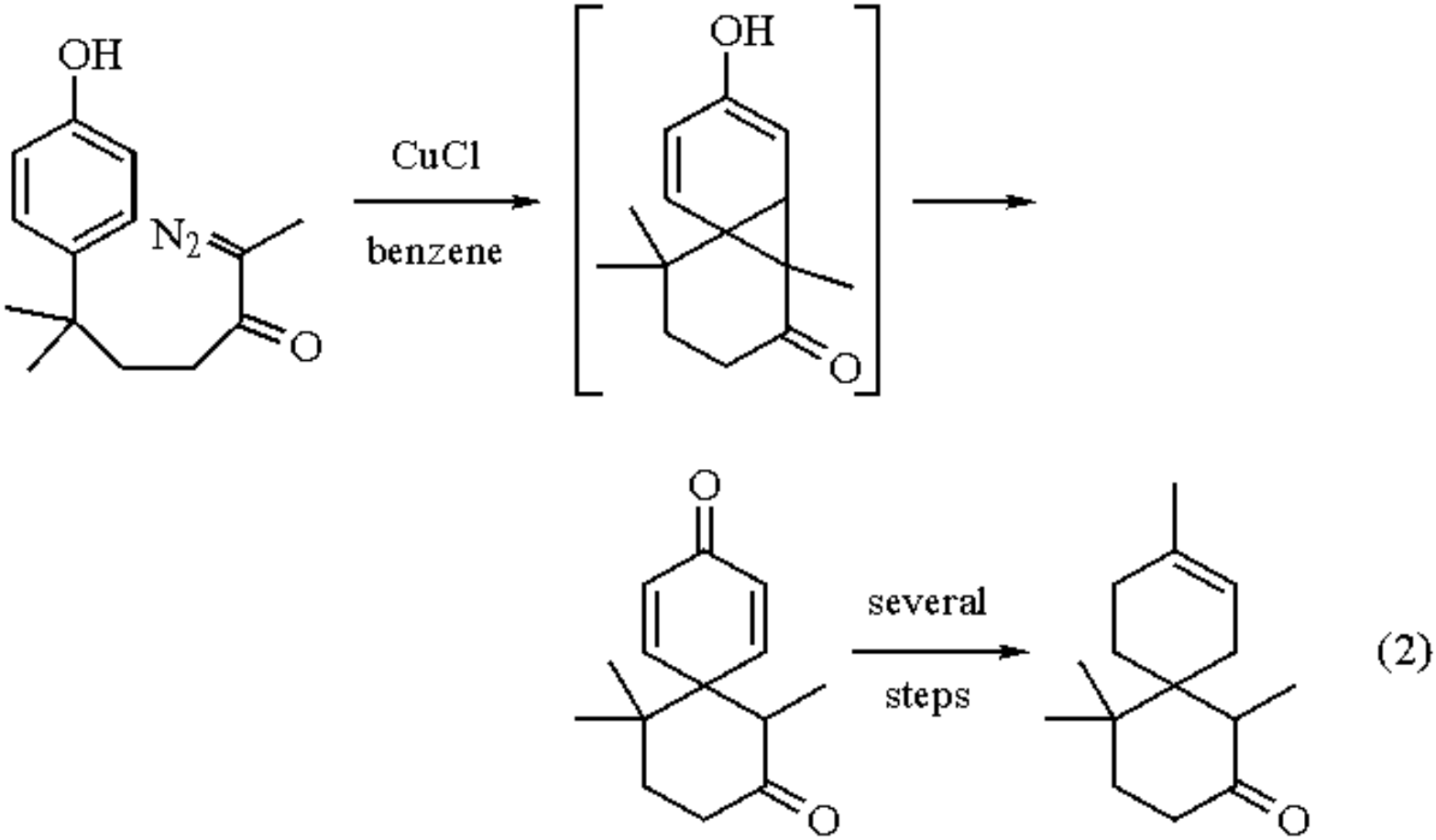

(2)

The Gattermann-Koch synthesis of aromatic aldehydes involves a Friedel-Crafts formylation by ClCHO in the presence of ***Aluminum Chloride*** and CuCl catalysts.[1g,11] The reaction proceeds without Cu, but at much higher pressures.[1g]

The Glazer reaction couples terminal alkynes by using dioxygen and CuCl, usually in the presence of ammonia or another amine (pyridine, $EtNH_2$).[1h] Many examples are known; eq 3 shows an example in the overlapping areas of medium-sized ring formation and annulene chemistry.[12] A related reaction mixture which uses pyridine instead of ammonia oxidatively cleaves 1,2-diaminobenzene to *cis,cis*-muconononitrile,[13a] and phenanthrenequinone to 2,2´-biphenyldicarboxylic acid.[14a] It also oxidizes the bishydrazones of α-diketones to alkynes and the monohydrazones to α-diazo ketones.[13b] 1,10-Phenanthroline has been used in conjunction with CuCl and dioxygen to oxidize alcohols to ketones or aldehydes.[14b]

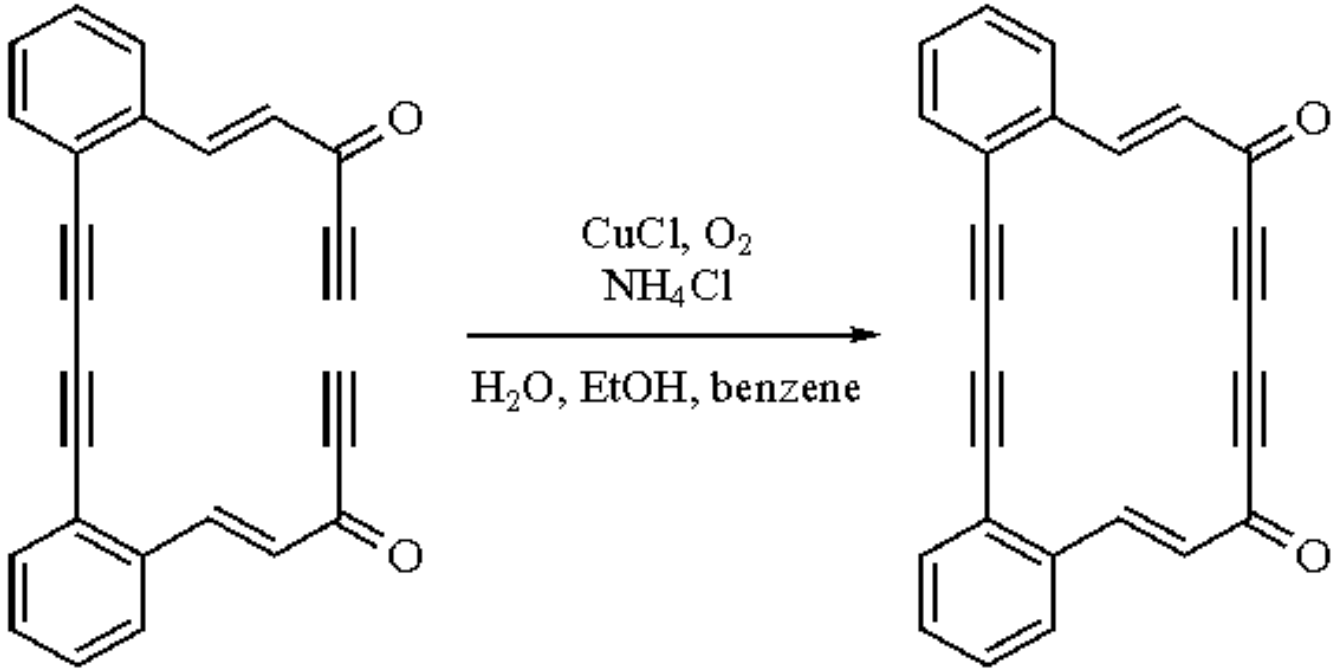

(3)

Marino has reported that cyclic α,β-unsaturated epoxides react with Cu carboxylates, generated in situ from Na carboxylates and CuCl, to give *syn*-1,4-diol derivatives.[15a] Goering has shown that allyl pivalates give α-alkylation with inversion of configuration with Grignard reagents catalyzed by CuCl, but (*anti*) γ-alkylation with ***Copper(I) Cyanide*** as catalyst.[15b]

Kharasch discovered that CuCl catalyzes the coupling of aryl Grignard reagents with aryl halides,[16a] and also the 1,4-addition of Grignard reagents to α,β-unsaturated ketones.[16b] While the former has been called the Kharasch reaction,[1i] today the latter is much more important synthetically,[1i-k] and it should be named for its inventor, who was one of the true pioneers in the synthetic applications of transition metals. One way to avoid confusion would be to call the reagent prepared from a Grignard reagent and a Cu^I salt a (catalytic or stoichiometric) Kharasch Reagent by analogy with the commonly used Gilman Reagent, which is synonymous with cuprate prepared from 2 equiv of lithium reagent and a Cu^I salt.

While ***Copper(I) Iodide***, CuBr.DMS (see ***Copper(I) Bromide***), and CuCN are now used more commonly than CuCl in the preparation of organocopper reagents, there are still interesting examples which utilize CuCl. For example, the addition of BuMgBr to sorbate esters gives a mixture of 1,2- and 1,4-addition products; however, upon the addition of CuCl, 1,6-addition predominates.[17] This example also illustrates one of the problems commonly encountered when trying to interpret the results of experiments using the Kharasch reagent. Experimenters frequently mix a Grignard reagent containing one halide with a Cu^I salt containing another. CuBr.DMS has also been shown to dramatically favor 1,6-addition of Grignard reagents (see ***Copper(I) Bromide***).

Tandem organocuprate β-addition to α,β-unsaturated carbonyl compounds followed by α-alkylation, acylation or other functionalization of the regiospecifically generated α-enolate has become an important methodology.[1j,k] In what has been described as the first one-pot, three-component tandem vicinal difunctionalization reaction,[1j] Stork used CuCl to catalyze the 1,4-addition of *m*-methoxyphenylmagnesium bromide to 5,5-dimethylcyclohex-2-en-1-one, followed by α-alkylation with allyl bromide,[18] which was the seminal step in the synthesis of lycopodine. Bunce and Harris have recently combined β-addition with *intramolecular* α-acylation in a tandem conjugate addition-Dieckmann condensation reaction, which was used to prepare six-membered rings (eq 4).[19] It is interesting to note that the Stork

conditions (RMgBr/CuCl) gave better results than the Gilman reagents prepared from 2 equiv of the corresponding Li reagent and either CuI or CuCN.[19]

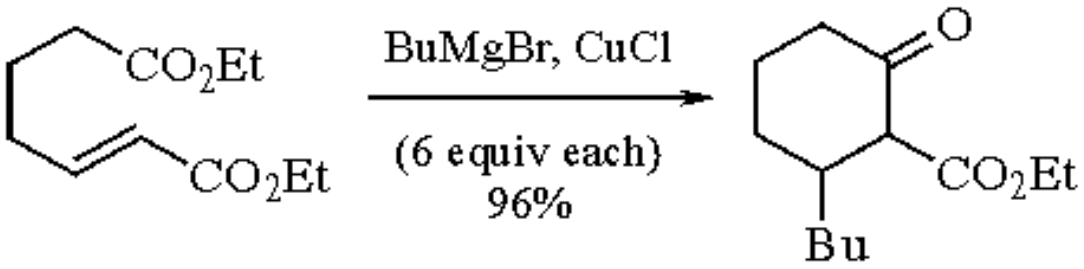

(4)

CuCl has been directly compared with CuBr, CuBr.DMS, CuI, CuCN, and ***Copper(I) Trifluoromethanesulfonate*** as a precursor for Gilman reagents,[20] and it appears to be inferior to the usual Cu^{I} salts for this important class of compounds. It was found early on that Cu^{II} salts catalyze many of the same organic reactions as the corresponding Cu^{I} salts,[1] e.g. a popular catalyst for coupling reactions with Grignard reagents is ***Dilithium Tetrachlorocuprate(II)*** = $CuCl_2$ + 2LiCl.[1i-l] It is generally assumed that the Cu^{II} salt is reduced to Cu^{I} under the reaction conditions; however, in most cases this has not been proven.

Along with CuBr and CuBr.DMS, CuCl continues to be a favored precursor for structural work and the preparation of new organocopper derivatives. For example, π-complexes between nonconjugated dienes and CuCl or CuBr have been characterized by X-ray crystallography.[21] Chaudret et al. have shown that $(C_5Me_5)Ru(PCy_3)H_3$ reacts smoothly with CuCl to give $(C_5Me_5)Ru(PCy_3)H_3CuCl$,[22] which was of interest in relation to the proposal that trihydrogen ligands might exist. In these two cases the product still contains the Cl atom. Many interesting examples exist where it does not (see below). A study illustrating both Cl-containing and Cl-free products is provided by Zybill and Müller, who reacted hexaphenylcarbodiphosphorane with CuCl to form a 1:1 adduct, which they reacted further with $[C_5Me_5]^-$ to yield $(C_5Me_5)CuC(PPh_3)_2$.[23]

Both dinuclear and tetranuclear Cu alkyl complexes have been prepared from CuCl and 2-substituted pyridines containing bis(trimethylsilyl)methyl and trimethylsilylmethyl substituents, respectively.[24] $MeCu(PPh_3)_3$ has been prepared and studied by NMR and X-ray crystallography;[25] such phosphine-complexed organocopper reagents have proven useful for organic synthesis. Several copper(I) cupracarboranes have been synthesized, including an interesting trimer.[26] (Trimers are much less common than tetramers in Cu^{I} chemistry.[27]) In a most incredible communication, Fenske et al. characterize the brobdingnagian product of the reaction 146 CuCl + 73 $Se(SiMe_3)_2$ + 30 PPh_3 -> $Cu_{146}Se_{73}(PPh_3)_{30}$ + 146 $ClSiMe_3$.[28]

One of the most interesting arylcopper(I) compounds is mesitylcopper(I),[29] which is a pentamer in the solid state and a tetramer in the presence of S-ligands.[30] It has recently been shown to split dioxygen,[31] and is highlighted here because it is prepared from CuCl. Hexafluoroacetylacetonatocopper(I)-alkyne complexes (prepared from CuCl) have been shown to be useful in the chemical vapor deposition of Cu metal.[32] (*E*)-1-Trimethylsilyl-1-alkenes have been prepared in high yields by the CuCl-catalyzed decomposition of α-trimethylsilyldiazoalkanes.[33] Finally, Indian chemists have shown that 1,2-diketones are produced in good yield when $Na(RCO)Fe(CO)_4$ is treated with CuCl.[34]

Related Reagents.

Copper(II) Chloride; ***Copper(II) Chloride-Copper(II) Oxide***; ***Iodine-Copper(II) Chloride***; ***Copper(I) Chloride-***

Oxygen; copper(I) chloride-tetrabutylammonium chloride ***Copper(I) Chloride-Sulfur Dioxide***; ***Iodine-Aluminum(III) Chloride-Copper(II) Chloride***; ***Iodine-Copper(I) Chloride-Copper(II) Chloride***; ***Methylmagnesium Iodide-Copper(I) Chloride***; ***Palladium(II) Chloride-Copper(I) Chloride***; ***Palladium(II) Chloride-Copper(II) Chloride***; ***Phenyl Selenocyanate-Copper(II) Chloride***; ***Vinylmagnesium Chloride-Copper(I) Chloride***; ***Zinc-Copper(I) Chloride***.

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Copper(II) Chloride-Copper(II) Oxide[1,2]

$CuCl_2$-CuO

($CuCl_2$)

[7447-39-4] · Cl_2Cu · Copper(II) Chloride-Copper(II) Oxide · (MW 134.45) (CuO)

[1317-38-0] · CuO · Copper(II) Chloride-Copper(II) Oxide · (MW 79.54)

(carbonyl deprotection reagent; allows transformation of thioacetals, α-heterosubstituted sulfides, and selenoacetals to aldehydes or ketones)

Solubility: sol aq acetone, alcohols, THF, MeCN.

Form Supplied in: both components are commercially available solids.

Introduction.

The combination reagent $CuCl_2$-CuO, originally introduced by Mukaiyama for the hydrolysis of 1,3-dithiane derivatives to carbonyl compounds,[3] also proved to be valuable for the hydrolysis of α-heterosubstituted sulfides and vinyl sulfides to carbonyl compounds.[1] It provides an interesting alternative to other methods.[1,2,4] The reaction occurs under mild conditions; the presence of copper oxide prevents the medium from becoming too acidic.[1] It delivers disulfides[5,6] as byproducts besides the desired carbonyl compounds.

The reactions are usually carried out in wet acetone (1%) or in aqueous or anhydrous alcohols (usually MeOH or EtOH)[3] at 20 °C or at reflux temperature. In the latter case, the alcohol can be involved in the transformation[6,7] (see eq 10). A higher percentage (10%) of water proved, in one specific case, important in order to avoid side reactions (eq 2).[8] Acetonitrile, as well as THF, can be used as solvent but proved, at least in one case, less efficient.[3]

Transformation of Thioacetals and Selenoacetals to Aldehydes or Ketones.

The reaction has been successfully achieved with cyclic thioacetals such as 1,3-dithiolanes,[9] 1,3-dithianes (eq 1),[3,10-12] α,α-bis(alkylthio)alkanes,[13] α,α-bis(phenylthio)alkanes,[14] and 1,5-dihydro-2,4-benzodithiepins (eq 2).[8] The nature of the protecting group does not seem to affect the rate of the reaction, which is usually fast (20 °C or reflux, 0.5-2 h). It has been performed on several functionalized thioacetals including β,γ-unsaturated,[13] γ-keto,[15] and α-hydroxy derivatives.[15]

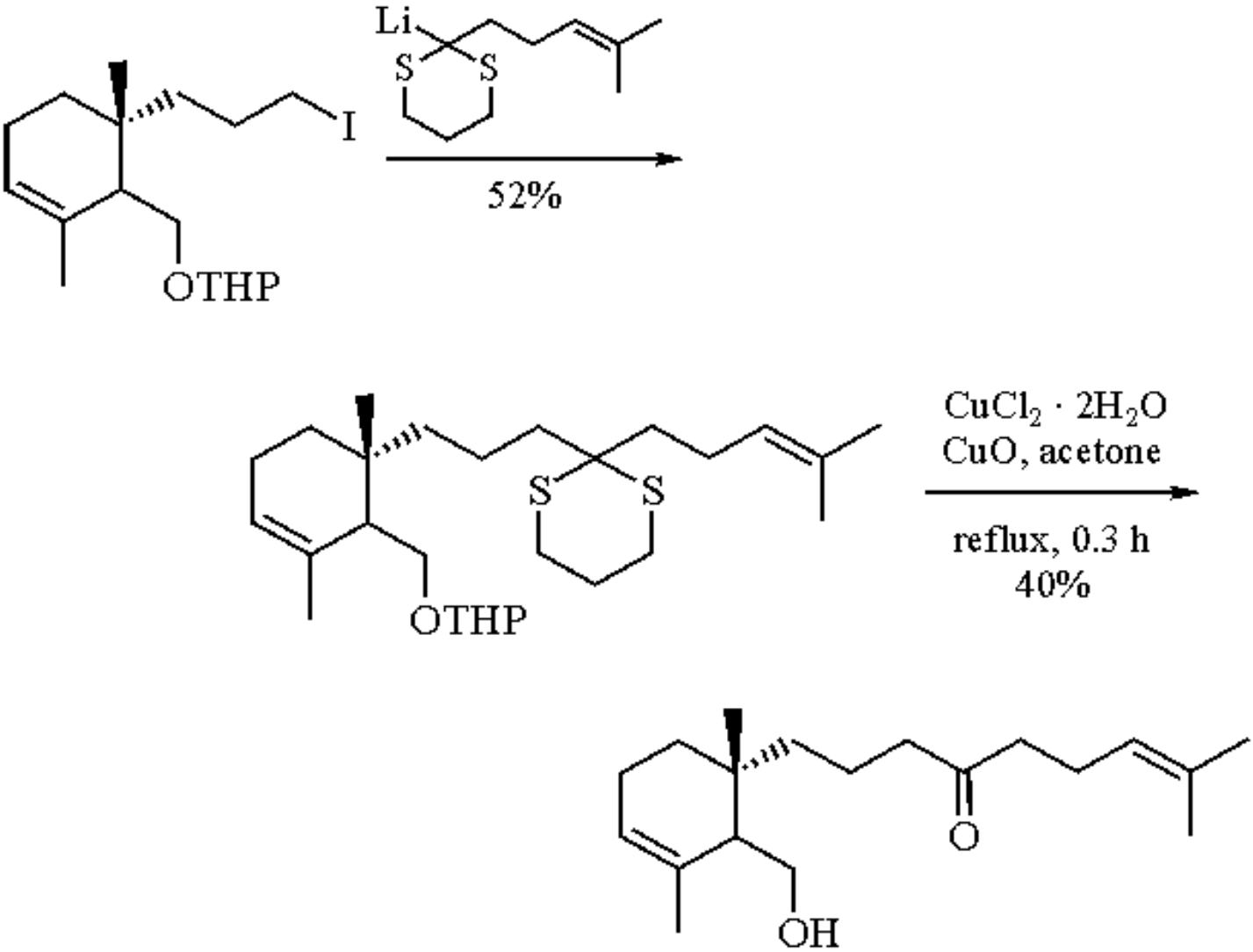
Li
S
S
I
OTHP
52%
S
S
OTHP
$CuCl_2 \cdot 2H_2O$
CuO, acetone
reflux, 0.3 h
40%
O
OH

(1)

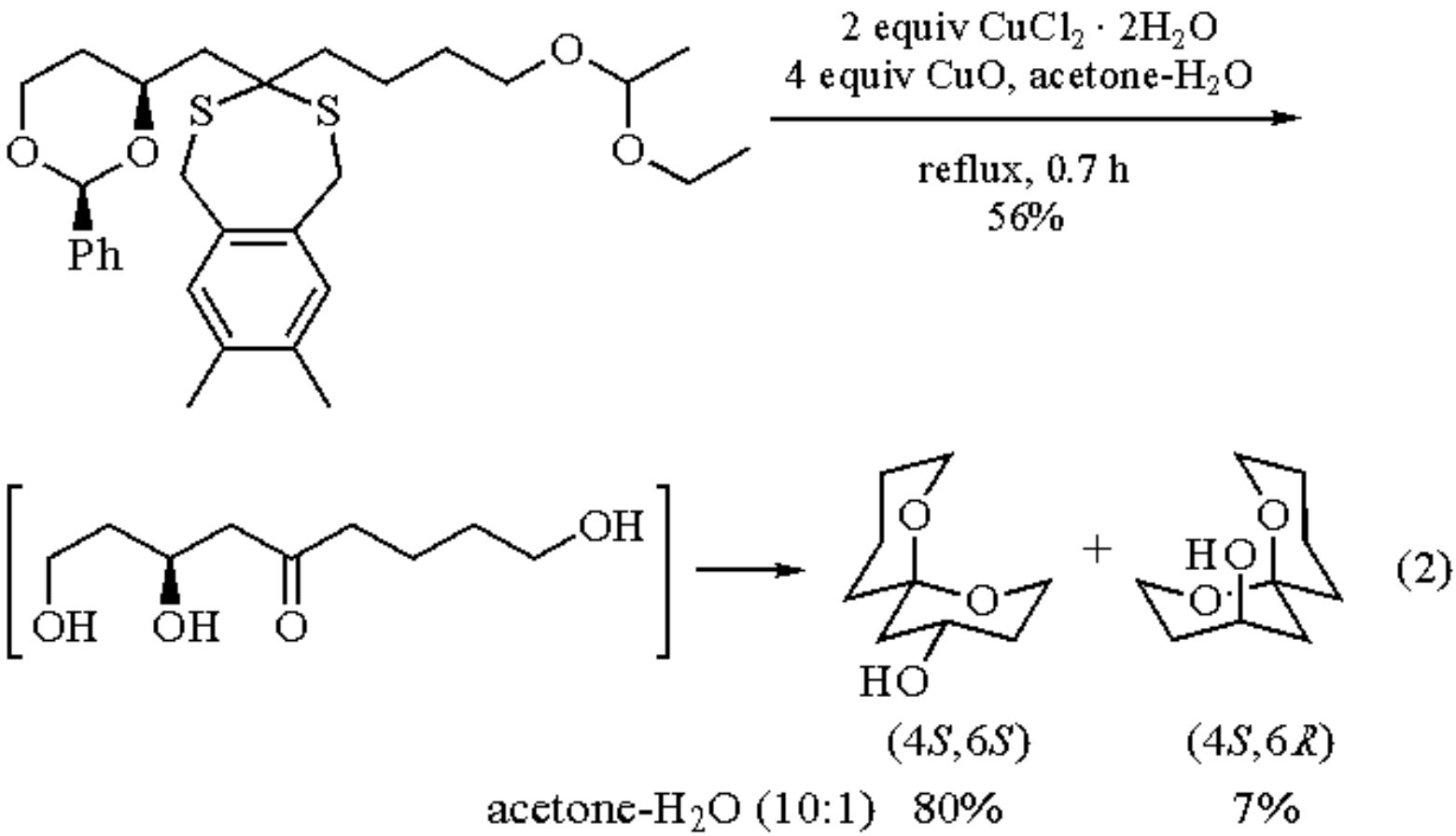

This reaction, coupled with the transformation of cyclic *O,O*-acetals to the corresponding 1,3-dithianes (***1,3-Propanedithiol***, ***Boron Trifluoride Etherate***, CH_2Cl_2, 0 °C), has been used to deprotect cleanly δ-keto acetals to δ-keto aldehydes without affecting the chiral center α to the aldehyde group (eq 3).[12]

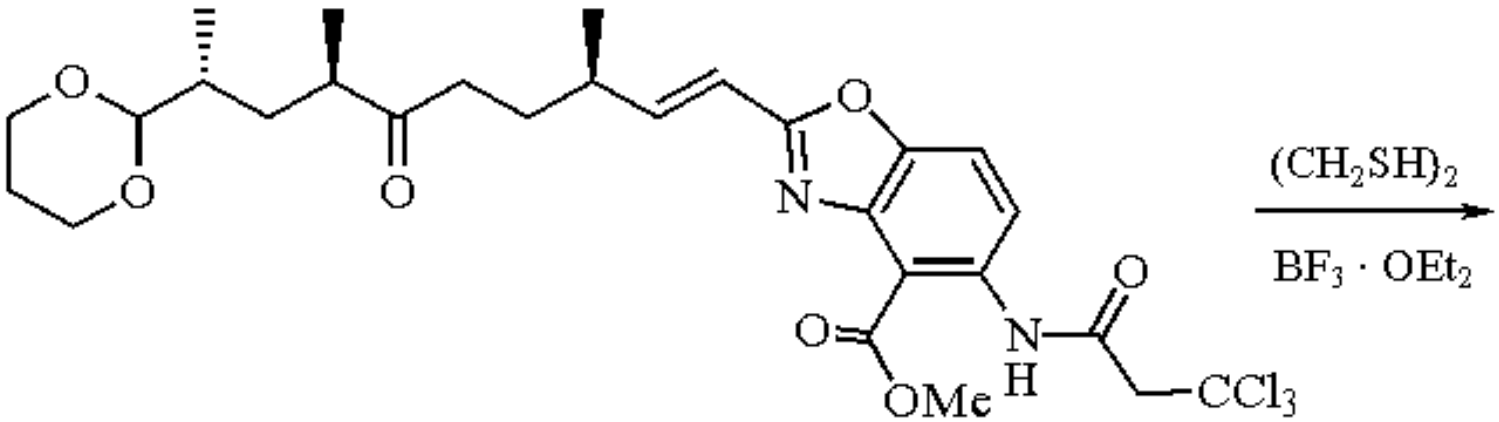

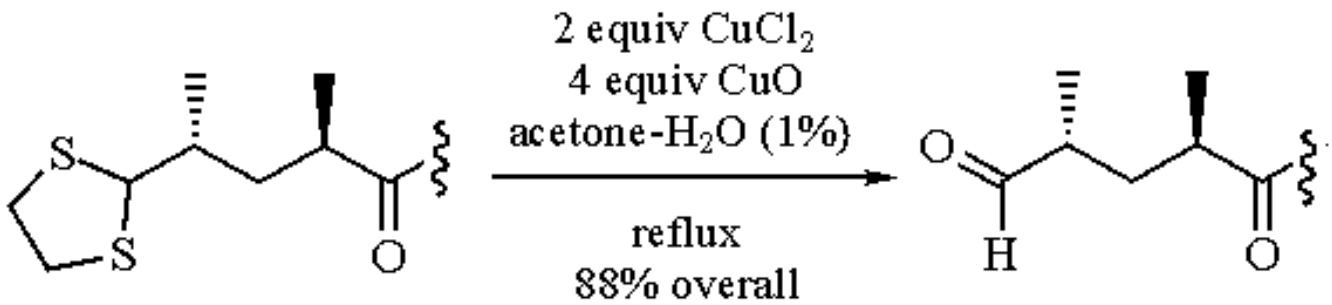

(3)

Selenoacetals derived from both the methylseleno and phenylseleno series,[16] including functionalized examples,[15,17,18] have been readily transformed to the corresponding aldehydes or ketones with $CuCl_2$-CuO (eq 4). These conditions proved as effective as those involving seleninic acid.[16]

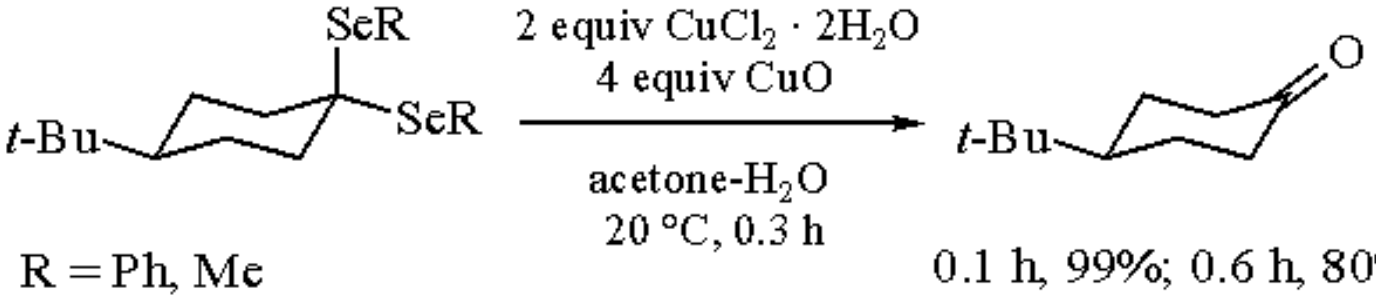

(4)

Transformation of Other α-Heterosubstituted Sulfides to Carbonyl Compounds.

α-Chloro sulfides are efficiently transformed to aldehydes[19-21] and ketones[22-24] on reaction with $CuCl_2$-CuO (eq 5). This includes the synthesis of polyfunctionalized carbonyl compounds such as α-diketones,[23,25] α-keto aldehydes,[20] and β-keto esters.[26] Particularly interesting is the one-pot transformation of ketones to α-diketones (eq 5),[23,25] which takes advantage of the in situ oxidation of intermediate α-thioketones to α-thio-α-chloro ketones by $CuCl_2$.[25]

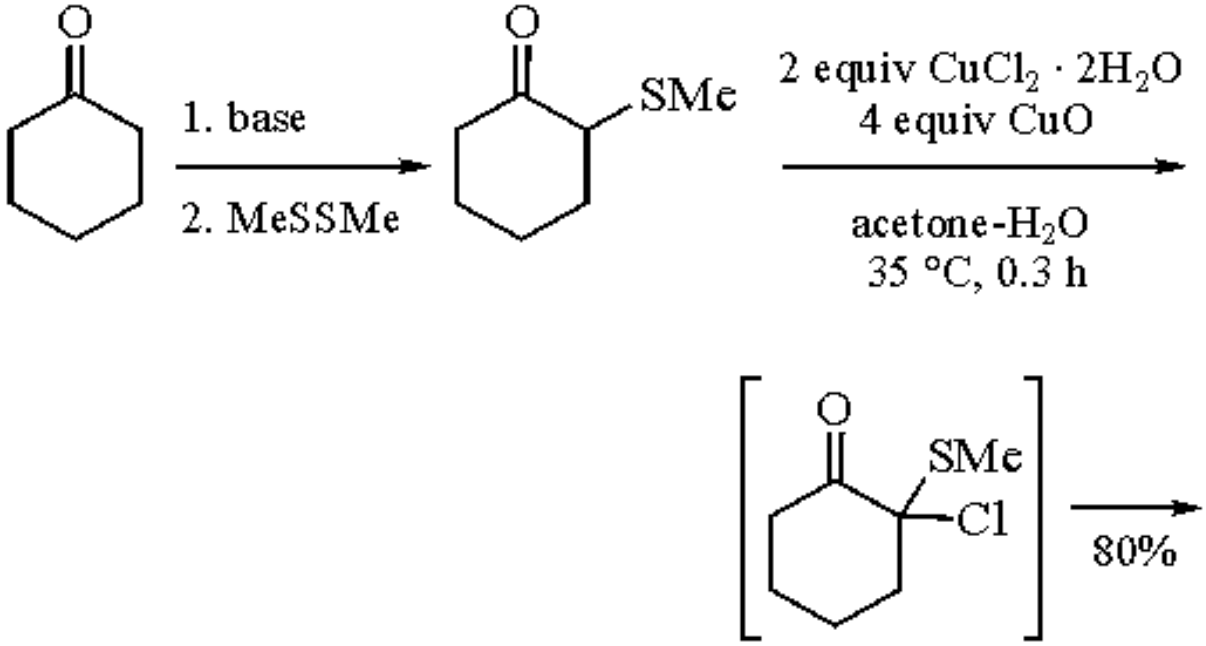

(5)

2-Phenylthiotetrahydropyrans and 2,2-bis(alkylthio)tetrahydropyrans have been transformed, on reaction with $CuCl_2$-CuO, to 2-hydroxytetrahydropyrans[27] and to the corresponding six-membered lactones,[28] respectively (eqs 6 and 7). The latter strategy proved better by far in producing the six-membered lactones than the one implying oxidation of initially formed 2-hydroxytetrahydropyrans with Jones' reagent.

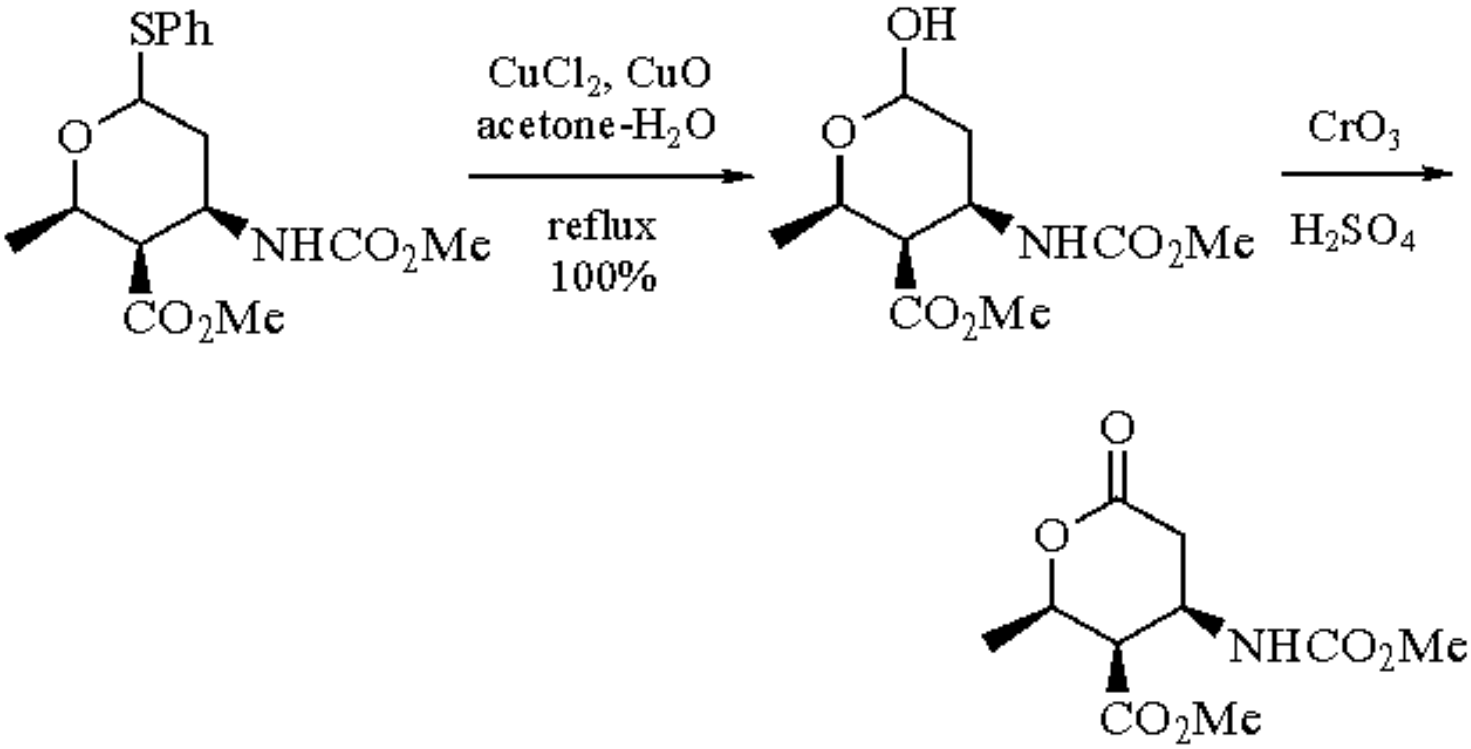

(6)

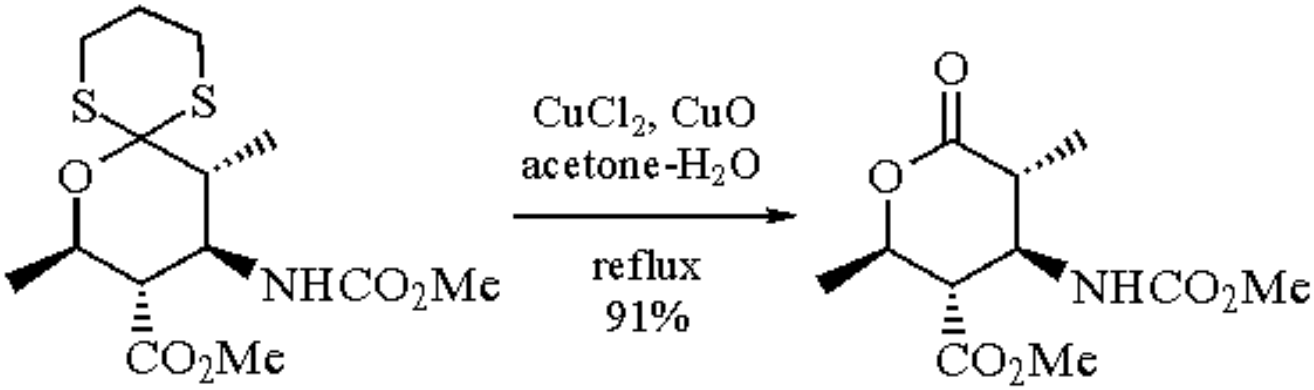

(7)

Transformation of Vinyl Sulfides and Related Derivatives.

$CuCl_2$-CuO also promotes the transformation of vinyl sulfides and related derivatives to aldehydes or ketones.[1] The reaction takes another course with 3-methylthio-[29] and 3-hydroxy-1-thio-1-alkenes,[5,30] which lead instead to α,β-unsaturated aldehydes and ketones (eq 8). The intermediate formation of a β-hydroxycarbonyl compound is not observed, and the entire conjugated system is involved in the transformation.

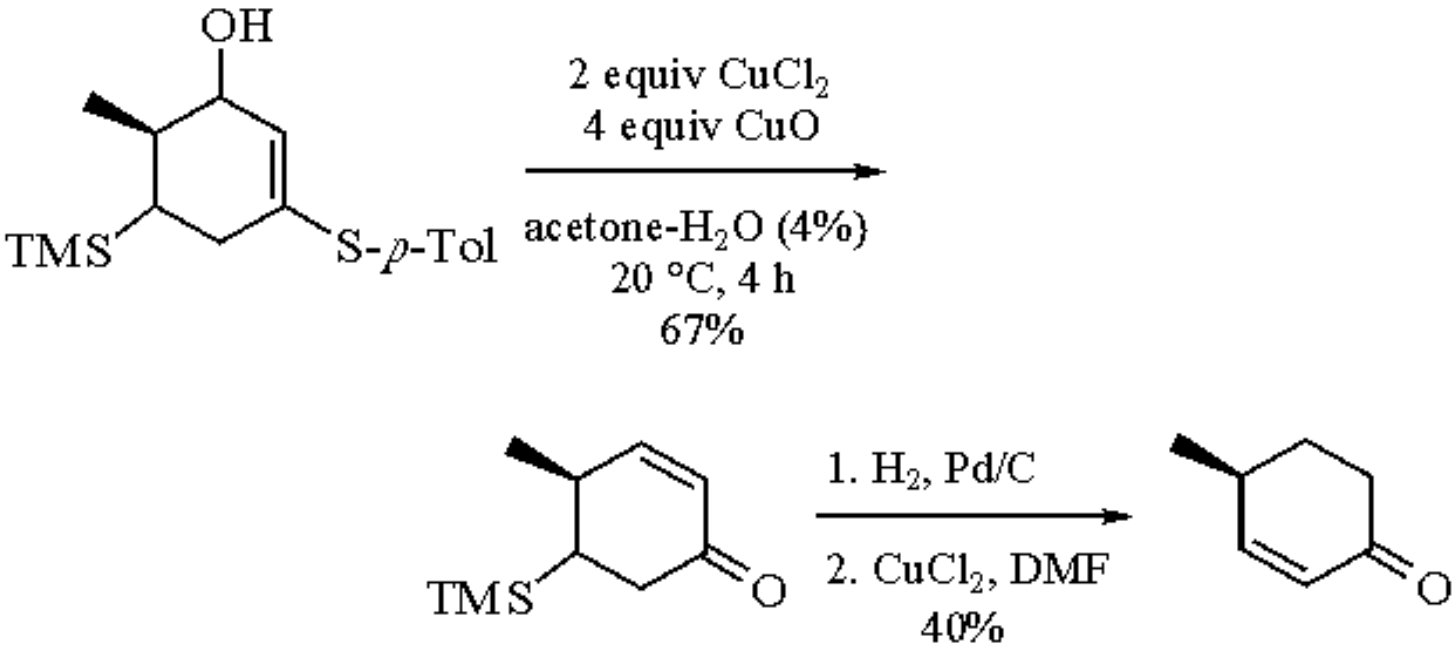

(8)

1-Alkoxy-3-thioalkyl-1-alkenes, which bear the thio substituent at the allylic position, have also been successfully transformed to α,β-unsaturated aldehydes and ketones using the same reagent (eq 9).[31] The reaction is easier with those derivatives that produce aldehydes rather than ketones, as in these cases the reaction mixture does not require heating.[31]

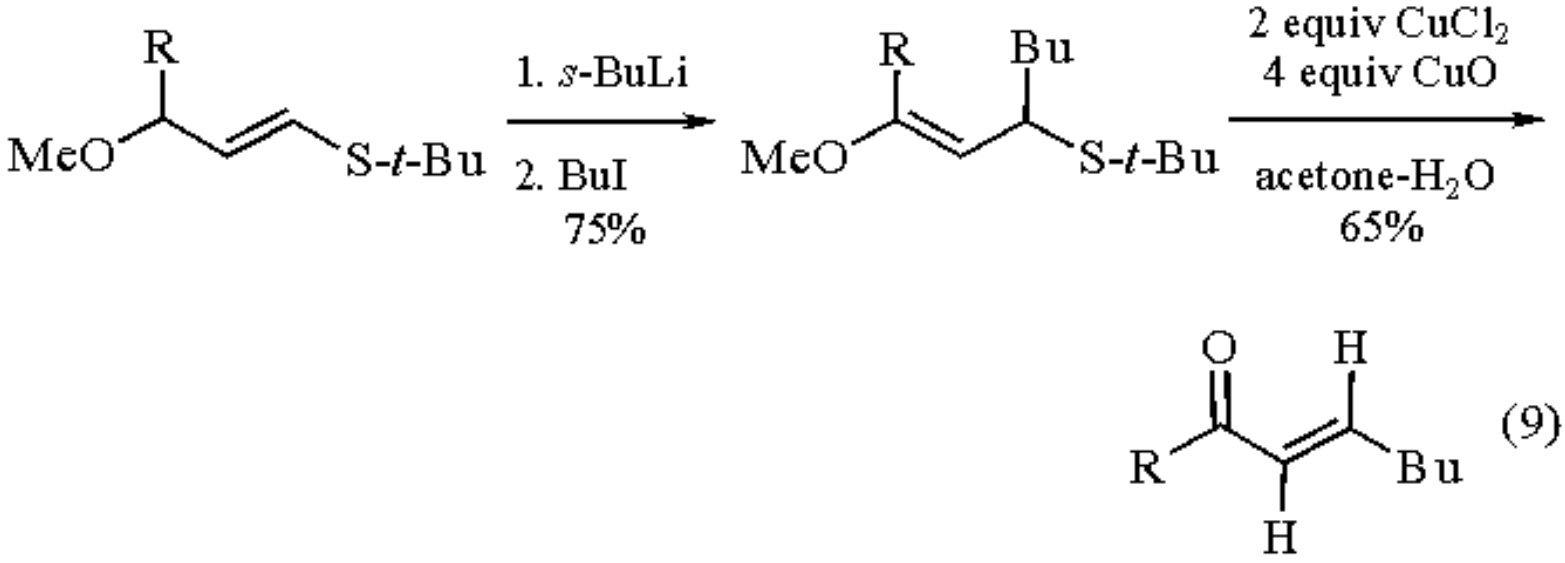

(9)

Ketene thioacetals are usually transformed into esters, provided that the reaction is performed in alcohols, and 1,1-bis(methylthio)allenes are converted to α,β-unsaturated esters (eq 10).[6]

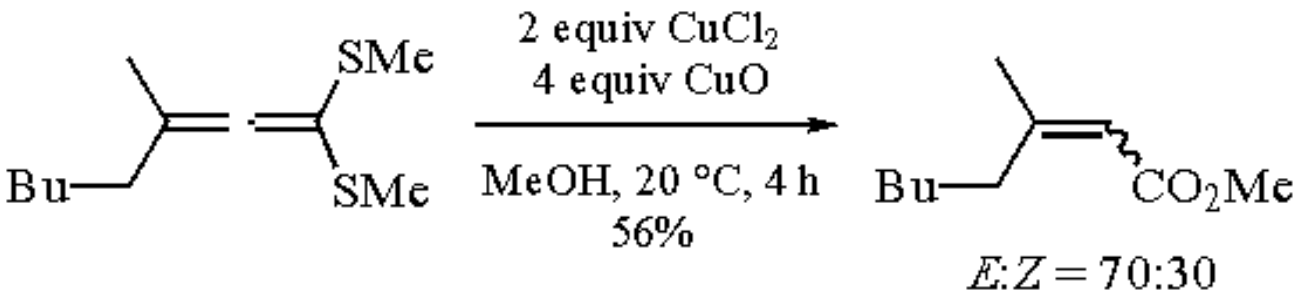

(10)

Finally, $CuCl_2$-CuO in alcohol promotes the transformation of thioisoxazoles to aldehydes[32] and of alkyl dithioesters to methyl or ethyl esters.[7,14,33] The former reaction requires an additional reduction step (1. Al/Hg; 2. $CuCl_2$-CuO). Remarkably, this reagent allows the synthesis of β-hydroxy esters bearing a chiral α-carbon without affecting the α-chiral center and without the loss of water, which would have produced the corresponding α,β-unsaturated ester.[7]

Synthetic Uses.

The transformation of thioacetals to their corresponding carbonyl compounds is valuable in synthesis. It allows the formation of carbonyl compounds via acyl anion equivalents using 1-metallo-1,1-dithioalkanes (eqs 1 and 2).[1] Other important examples include the aldol condensation involving metallo-dithioesters,[7] which exhibits very high facial stereoselectivity (>99:1) and high simple diastereoselectivity (95:5), and the version of the thio-Claisen rearrangement which allows the very stereoselective synthesis of (*E*)-trisubstituted double bonds (eq 11).[14] It is therefore important that the conditions involved for the transformation of the thio moiety to the carbonyl compound do not interfere with the other functional groups present in the molecule.

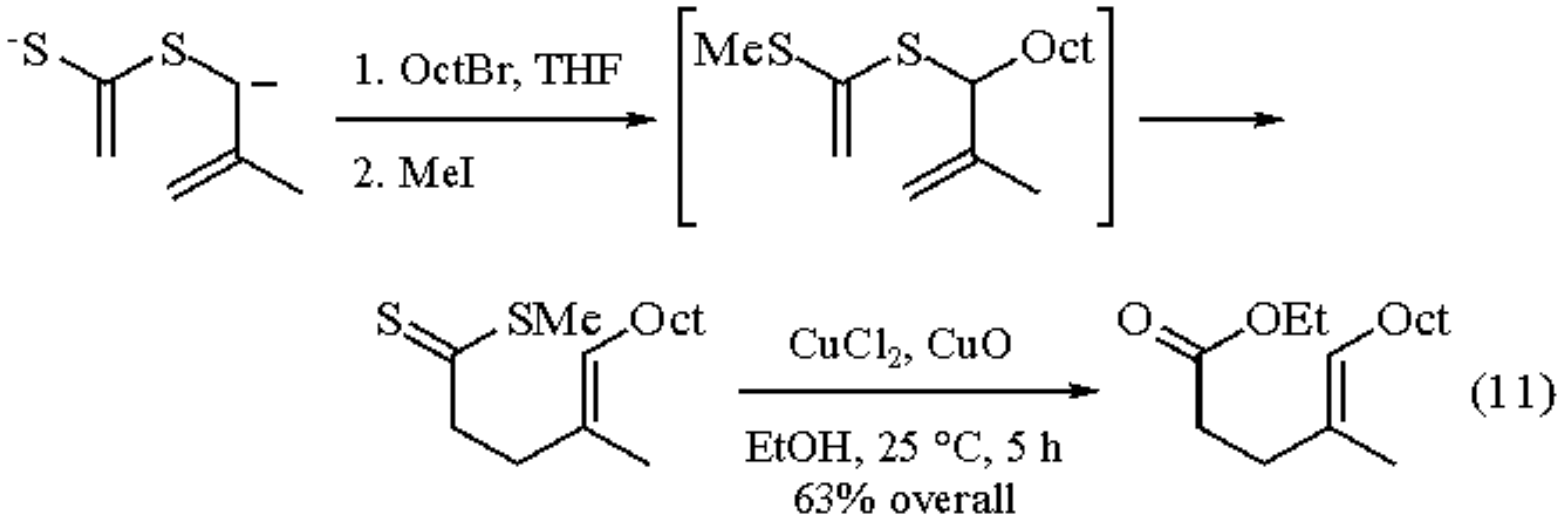

Chemoselectivity.

Even under the mild conditions used in carbonyl group generation, $CuCl_2$-CuO deprotects THP (eq 1)[11] and ethoxyethyl (eq 2)[34] ether-protected alcohols and leads to diols from benzylidenedioxy compounds (eq 2).[34] This feature has been successfully applied to the direct synthesis of the dioxaspiro[5.5]undecanes shown in eq 2. It allows, under suitable conditions, the concomitant acetalization of ketones.[33] However, this reagent does not promote (a) cyclization of 1,4-diketones to α-enones from γ-keto-α,α-bis(thio)alkanes;[14] (b) the retro-aldol reaction of the intermediate β-hydroxy ketone shown in eq 2 (provided that 10% water is used instead of 1%), which would have produced the (4*S*,6*R*) rather than the expected (4*S*,6*S*) stereoisomer;[8,34] (c) epimerization at the α-position of an aldehyde,[12] a ketone,[12] an ester,[7] or a dithio ester;[7] (d) the (*Z*) to (*E*) or (*E*) to (*Z*) isomerization of C=C double bonds (eq 11);[14] or (e) conjugation of the C=C double bond in β,γ-unsaturated aldehydes[21] and ketones.[35]

Related Reagents.

Copper(II) Chloride.

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Copper(I) Chloride-Oxygen[1]

$CuCl\text{-}O_2$

(CuCl)

[7758-89-6] · ClCu · Copper(I) Chloride-Oxygen · (MW 99.00) (O_2)

[7782-44-7] · O_2 · Copper(I) Chloride-Oxygen · (MW 32.00)

(oxidation of alcohols,[2] amines,[6] alkenes;[7] oxidative coupling;[1] allylic oxidation;[9] oxidative cleavage;[1] oxidative dealkylation;[22] Ullmann reaction[23])

Physical Data: see ***Copper(I) Chloride***.

Solubility: sol ether, HCl, TMEDA, and NH_4OH; sl sol cold water; insol alcohol and nonpolar solvents.

Form Supplied in: O_2 is widely available as cylinders of compressed gas. CuCl is also commercially available.

Handling, Storage, and Precautions: strong oxidant. Appropriate precautions for handling of combustible compressed gases should be taken. Use in a fume hood.

Oxidation of Alcohols.

Various oxidation systems have been used to synthesize aldehydes from alcohols. In the presence of ***Copper(I) Chloride*** in pyridine, alcohols can be oxidized by molecular ***Oxygen*** to give aldehydes or ketones.[2] High yields of aldehydes or ketones are obtained when 1,10-phenanthroline is used instead of pyridine (eq 1). Under this CuCl/amine/O_2 system, 1,10-phenanthroline is more effective and allows benzylic and allylic alcohols to be oxidized much faster than aliphatic alcohols.[3]

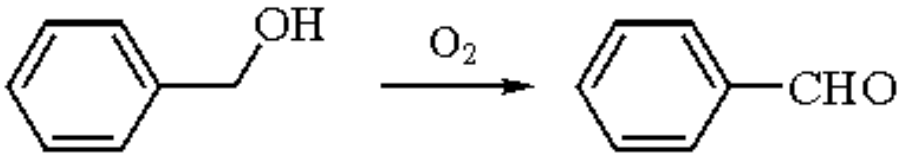

(1)

CuCl, pyridine	36%
CuCl, 1,10-phenanthroline	86%

In the presence of a catalytic mixture of copper(I) chloride and the radical reagent ***2,2,6,6-Tetramethylpiperidin-1-oxyl*** (TEMPO), secondary alcohols are preferred over primary alcohols in their oxidation by oxygen to yield the corresponding ketones. Overoxidation is not observed, as benzylic and allylic alcohols yield aldehydes (eqs 2 and 3). However, electron-withdrawing groups attached to the aryl ring in benzylic alcohols tend to retard the reaction.[4]

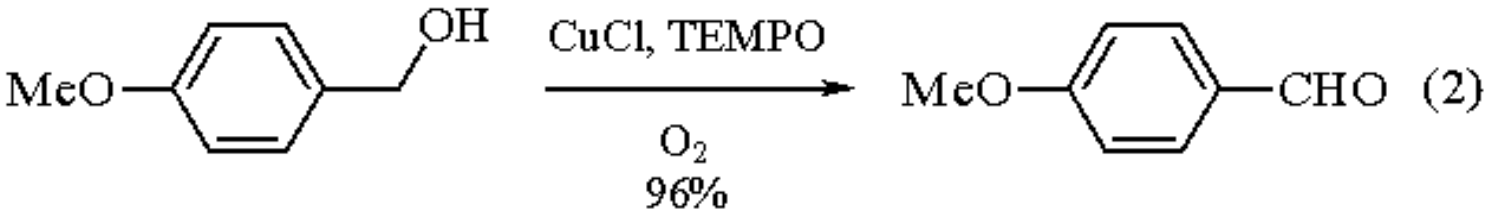

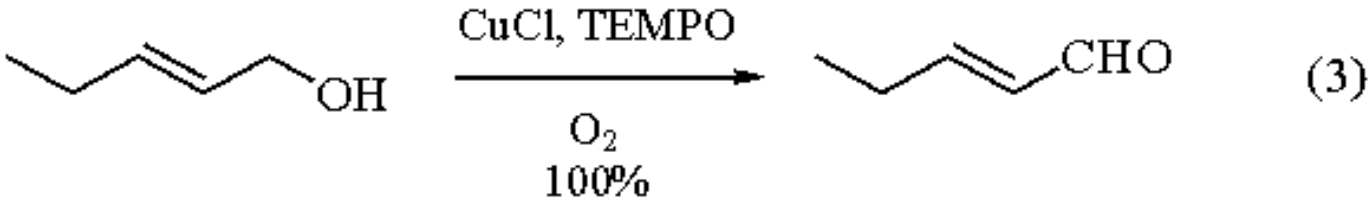

An oxidation system composed of a transition metal ($M^0 = Fe^0$ or Cu^0), a transition metal ion ($M^{n+}Cl_n = FeCl_2$ or CuCl) in catalytic amounts, and molecular oxygen oxidizes (hydroxymethyl)phenols to give the corresponding salicylaldehydes (eq 4).[5]

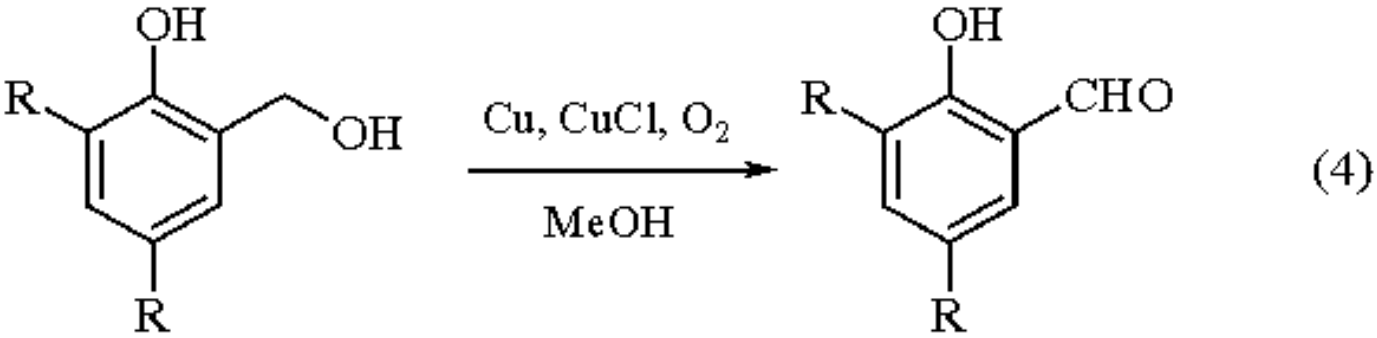

Oxidation of Phenols.

Selectivity in copper-amine catalyzed phenol oxidations is controlled by a number of factors: substituent effects, solvent effects, and stability of phenoxy radicals. Oxidative coupling of 2,6-disubstituted phenols occurs in two ways, depending on the size of the substituent group on the benzene ring. When the substituent groups are small, carbon-oxygen coupling occurs and poly-2,6-disubstituted 1,4-phenylene ethers (**2**) are obtained. However, the presence of bulky groups allows the synthesis of 3,3,5,5-tetrasubstituted diphenoquinones (**3**) to occur through carbon-carbon coupling (eq 5).[6]

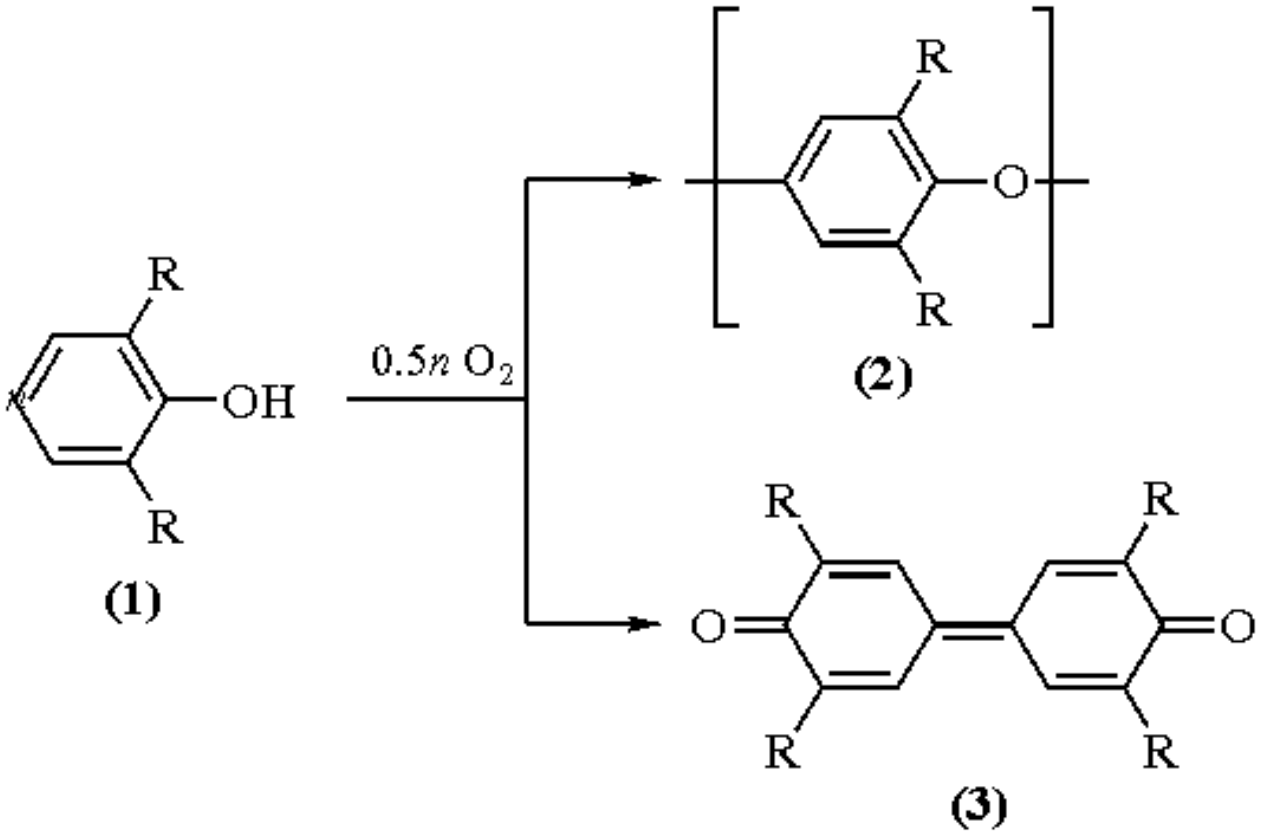

(5)

Selective phenol oxidation by oxygen may occur, depending on the type of solvent used. Synthesis of *t*-butyl-*p*-benzoquinone from *t*-butyl hydroquinones (eq 6) occurs in the presence of copper(I) chloride in pyridine, whereas 2-*t*-butyl-6-hydroxy-*p*-benzoquinone is synthesized in the presence of copper(I) chloride in a secondary amine such as piperidine, morpholine, dipropylamine, or 2,6-dimethylpiperidine (eq 7).[7]

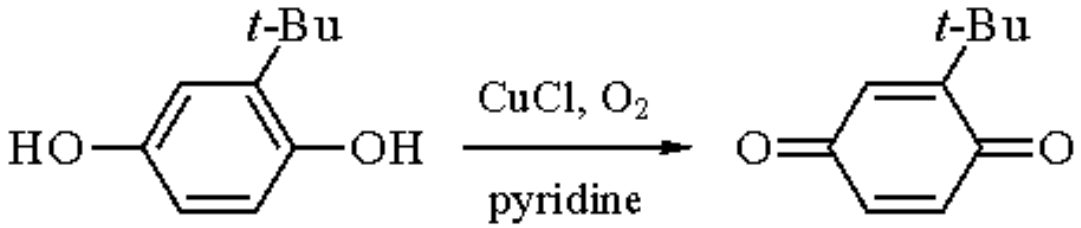

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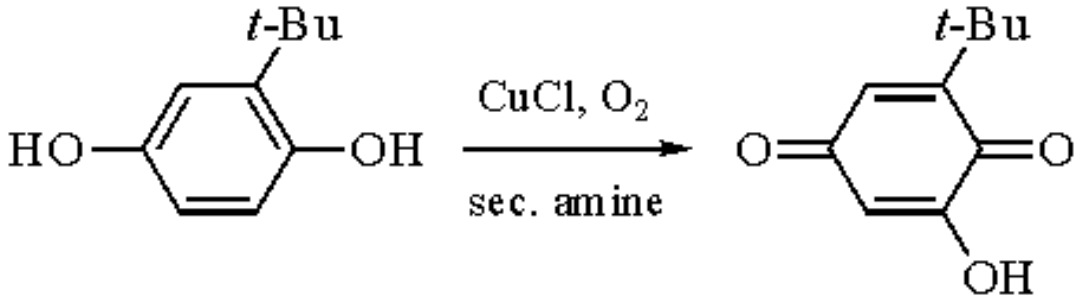

(7)

Regarding stability of the phenoxy radical, selectivity can be achieved in the oxidation of 2,6-diphenyl-4-methoxyphenol by oxygen in the presence of copper(I) chloride (eq 8). The resulting product would be a dimeric quinone acetal (or 4-methoxy-2,6-diphenylphenoxyl) in high yield, obtained through an oxygen-stable radical.[8]

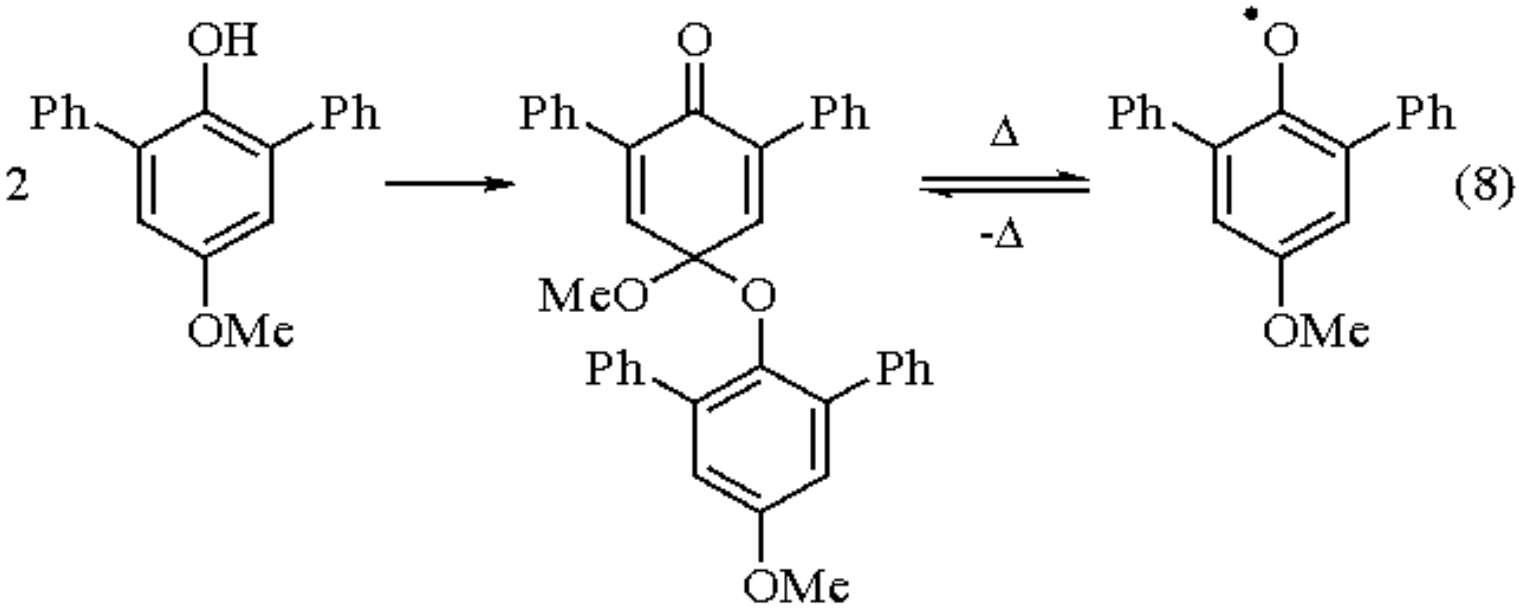

Oxidation of Amines.

Under an oxygen atmosphere, copper(I) chloride in pyridine converts amines to the corresponding nitriles (eq 9) or aldehydes (eq 10).[9] However, low yields prompted the modification of this reaction system by (a) increasing the reaction temperature (from rt to 60 °C), (b) adding molecular sieves, and (c) changing the order of addition of the reactants. This improved, extended method gives high yields of aliphatic or aromatic nitriles (eq 11).[10]

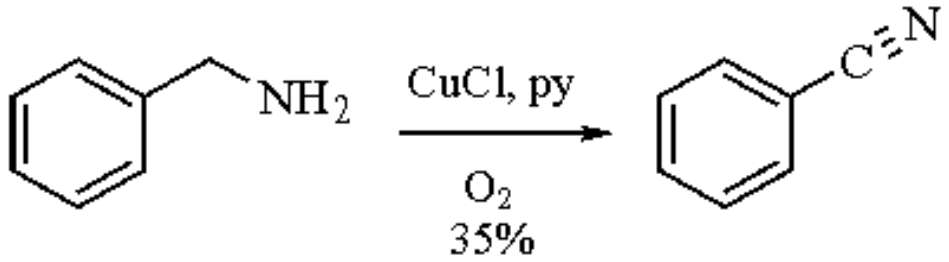

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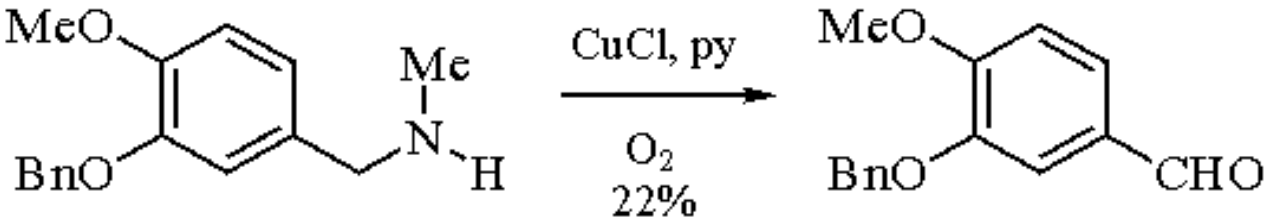

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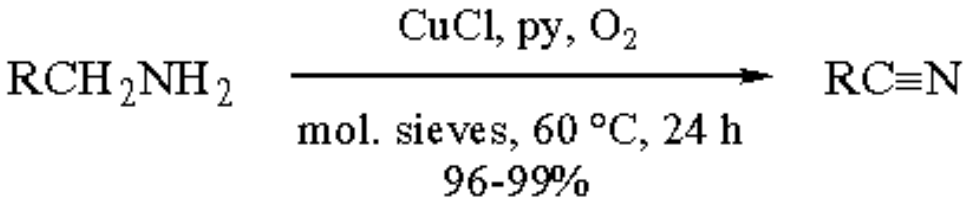

(11)

R = aliphatic or aromatic

Oxidation of Alkenes.

In the presence of a catalyst, copper(I) chloride, and ***Palladium(II) Chloride*** in aqueous DMF, terminal alkenes are oxidized by oxygen to methyl ketones (eq 12).[11]

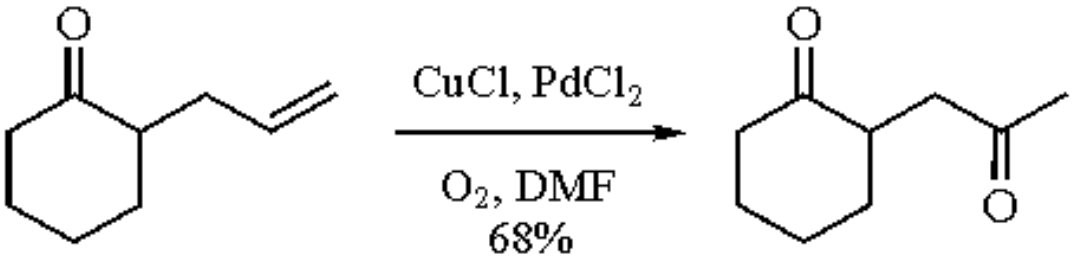

(12)

Allylic Oxidation.

Synthesis of α,β-unsaturated ketones via copper-catalyzed allylic oxidation is possible. In the presence of copper(I) chloride, valencene was oxidized by molecular oxygen in the dark to nootkatone (eq 13). ***Iron(II) Sulfate***, $NiSO_4$, $ZnSO_4$, ***Copper(II) Sulfate*** and $MnSO_4$ are among other catalysts that have been used in allylic oxidation under an oxygen atmosphere.[12]

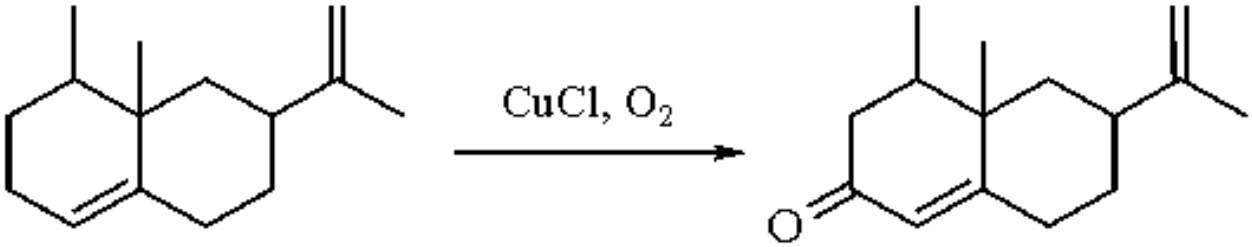

(13)

Oxidative Cleavage of Diols.

A copper-catalyzed oxidation system involving oxygen/copper(I) chloride in a mixture of pyridine and alcohol is able to cleave catechols to monoesters of *cis,cis*-muconic acid (eq 14).[13]

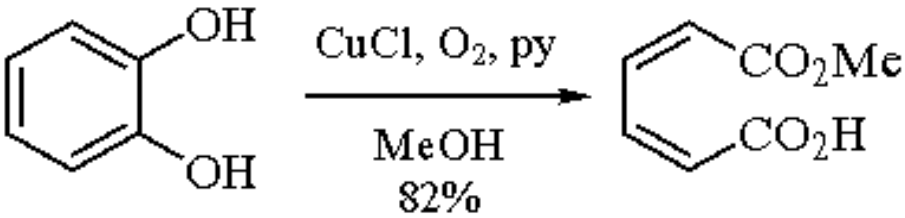

(14)

Oxidative Cleavage of Hydrazones.

Alkynes can be synthesized in high yields from dihydrazones of α-diketones via oxidation under an oxygen atmosphere in the presence of copper(I) chloride in pyridine at room temperature (eq 15). The monohydrazone of benzil can be dehydrogenated to produce azibenzil in high yield (eq 16).[14]

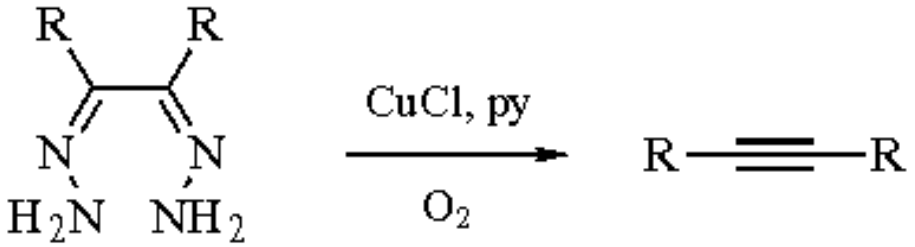

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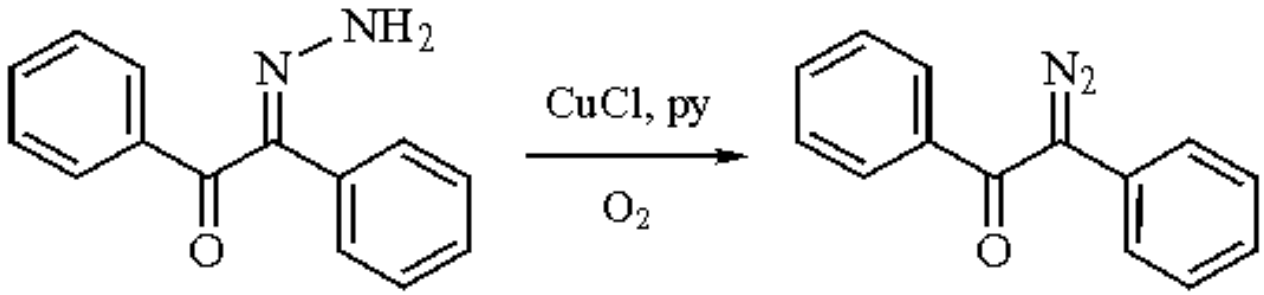

(16)

Oxidative Cleavage of Diamines and Diketones.

Various oxidizing reagents, for example ***Nickel(II) Peroxide***, ***Lead(IV) Acetate***, and ***Silver(I) Oxide*** in stoichiometric quantities, have limited effectiveness in the oxidation of these substrates, producing less than 50% yields of the projected oxygenation products. However, under an oxygen atmosphere, *o*-phenylenediamine undergoes oxidative cleavage in the presence of copper(I) chloride in pyridine to yield *cis,cis*-muconononitrile (eq 17).[15]

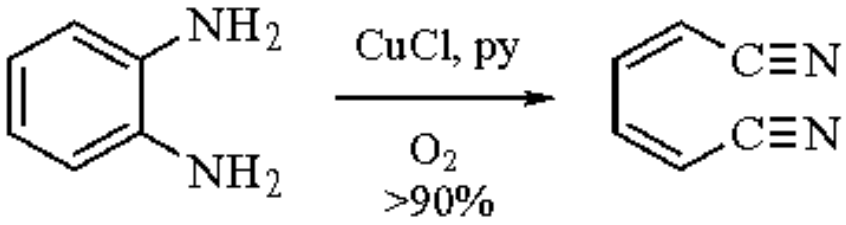

(17)

Diketones can also be oxidatively cleaved to dicarboxylic acids, as in the oxidation of phenanthrenequinone to 2,2´-biphenyldicarboxylic acid in high yield (eq 18).[16]

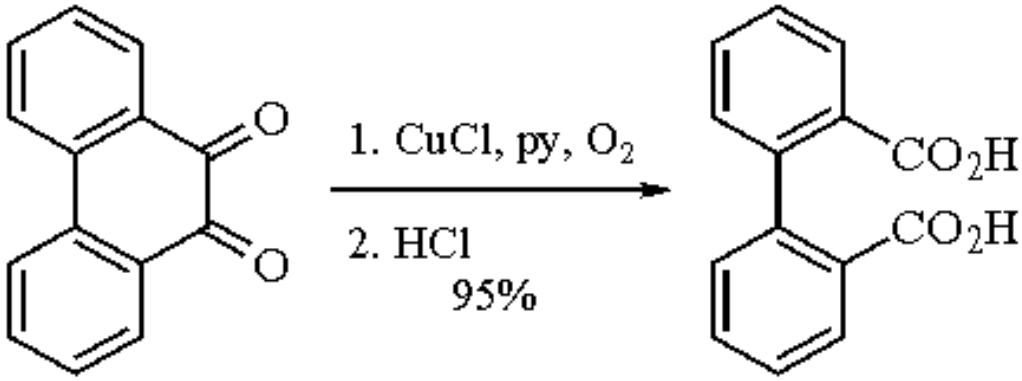

(18)

Oxidative Coupling of Ethynyl Compounds.

Under Glaser conditions, ethynyl compounds dissolved in polar, protic solvents are oxidatively coupled by oxygen (or air) in the presence of a catalytic mixture of copper(I) chloride and ammonium chloride in water (eq 19).[17a] This coupling reaction has been applied to ethynyl-bearing carbinols,[18] aliphatic[17b] and aromatic hydrocarbons,[17c] thiophenes,[17d] esters,[17e] acids,[17f] ethers,[17g] nitriles,[17h] enynes,[17i] alleneynes,[17j] α-diynes,[17k] triynes,[17l] and tetraynes.[17m]

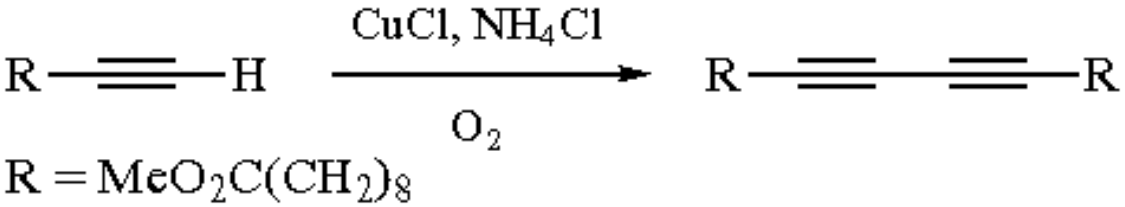

(19)

Under Hay conditions, tertiary amines complexed with copper(I) chloride are effective catalysts in the oxidative polymerization of 2,6-disubstituted phenols with molecular oxygen to produce high molecular weight polyarylene ethers (eq 20). Tertiary amines such as ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) are preferred due to their ability to solubilize copper salts in nonpolar solvents such as benzene.[18]

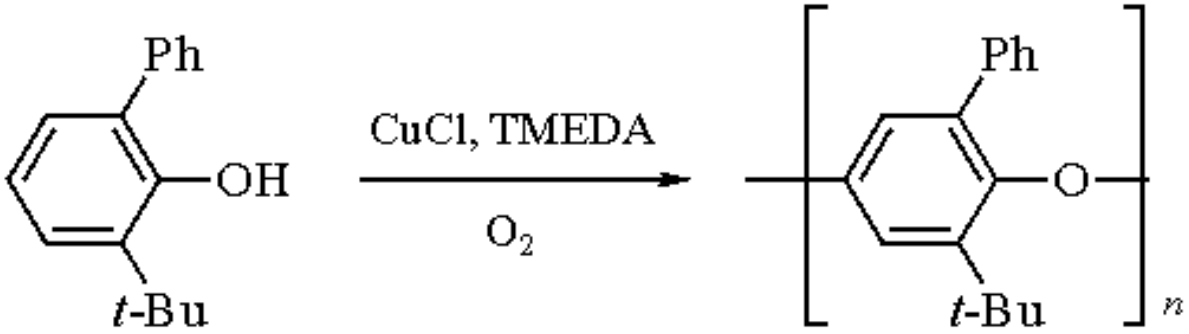

(20)

Even though Glaser conditions are applicable to a wide range of substrates, limitations exist when comparisons to Hay conditions are made. For example, unsymmetrical coupling[19b] and oxidative cleavage of heterocyclic alkynes[20] will work under Hay conditions, but not under Glaser conditions. Yet, symmetrical coupling[19a] is possible under both conditions.[1]

Oxidative Coupling of Activated Methine Compounds.

In the presence of copper(I) chloride in TMEDA, there occurs oxidative carbon-carbon coupling of compounds containing activated CH, CH_2, or CH_3 groups that can complex with the copper catalyst. An example is the oxidation of methyl *p*-tolylcyanoacetate to 1,2-bis(methoxycarbonyl)-1,2-dicyano-1,2-di-*p*-tolylethane (eq 21).[21]

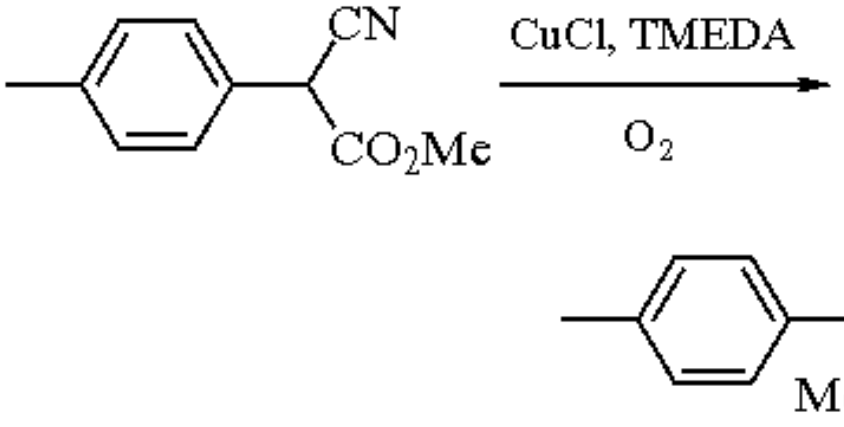

(21)

Oxidative Dealkylation.

4-Substituted *N*,*N*-dimethylanilines undergo oxidative dealkylation in the presence of the catalyst copper(I) chloride and acetic anhydride under an oxygen atmosphere to give the corresponding *N*-methylacetanilides and *N*-methylformanilides (eq 22).[22]

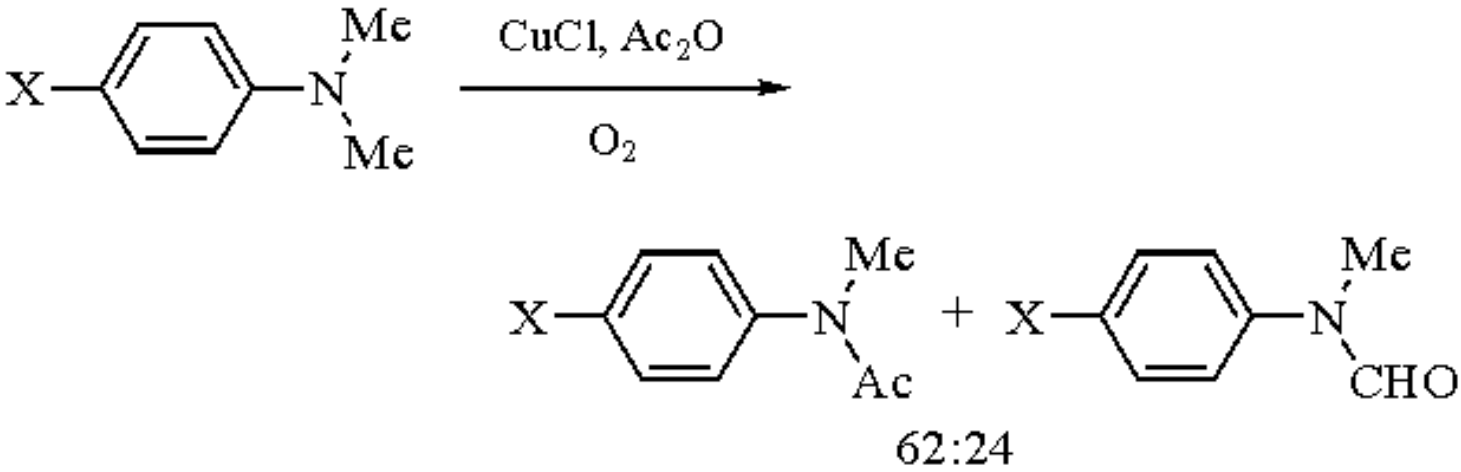

(22)

Ullmann Reaction.

Haloanthraquinones undergo Ullmann condensation reactions in the presence of amines in aprotic solvents under an oxygen atmosphere to form other derivatives (eq 23). In this particular reaction, chloromethoxycopper(II) (prepared in situ from the partial oxidation of copper(I) chloride with oxygen in methanol (eq 24)) increases the rate of reaction by increasing the catalytic activity of copper(I) chloride.[23]

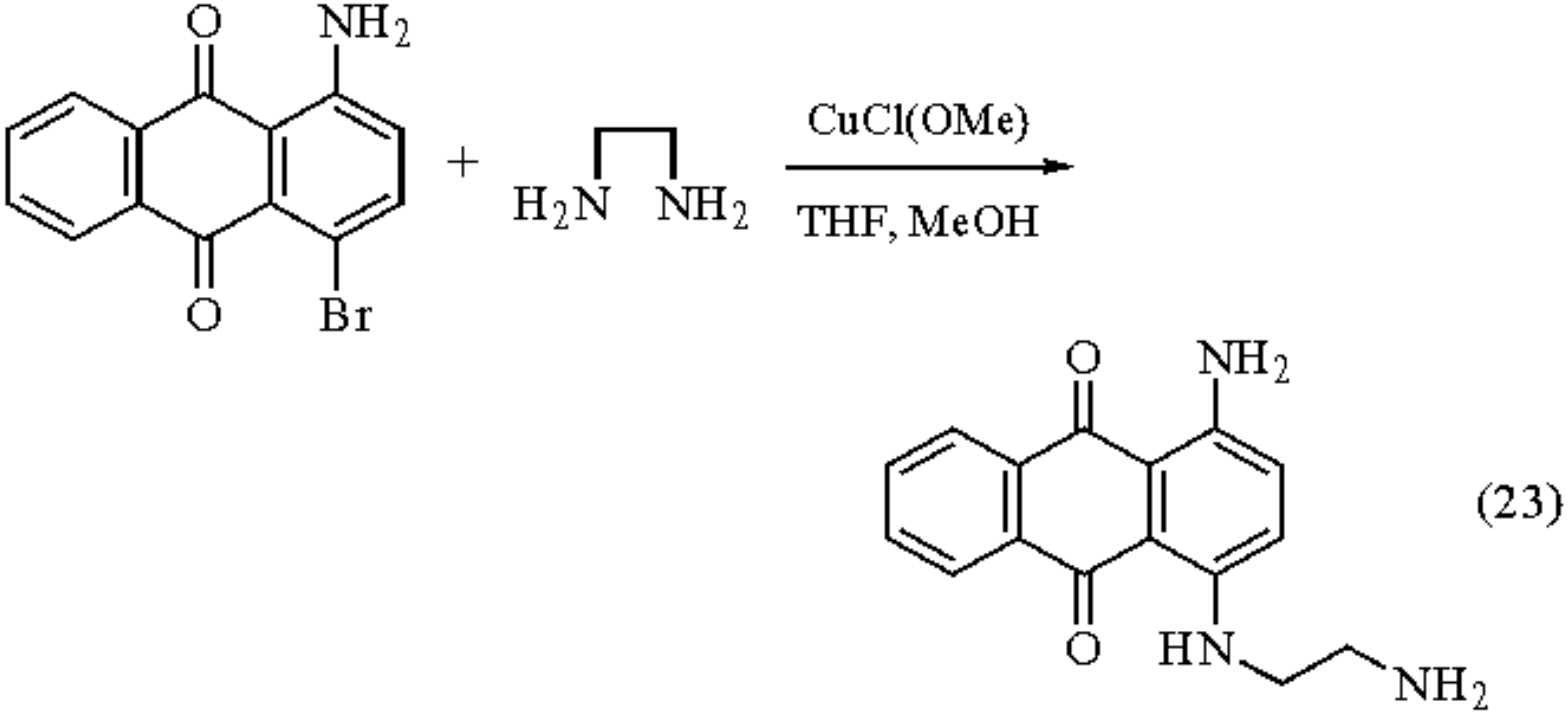

$$4\ CuCl + O_2 \xrightarrow{MeOH} 4\ CuCl(OMe) + 2H_2O \qquad (24)$$

Related Reagents.

Copper(I) Chloride; ***Palladium(II) Chloride-Copper(I) Chloride***.

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Copper(I) Chloride-Sulfur Dioxide

$CuCl.SO_2$

(CuCl)

[7758-89-6] · ClCu · Copper(I) Chloride-Sulfur Dioxide · (MW 99.00) (SO_2)

[7446-09-5] · O_2S · Copper(I) Chloride-Sulfur Dioxide · (MW 64.06)

(reagent for the preparation of arenesulfonyl chlorides from arenediazonium ions[1])

Physical Data: see entries for ***Copper(I) Chloride*** and ***Sulfur Dioxide***.

Form Supplied in: individual reagents commercially available; mixture is normally prepared in glacial acetic acid.

Preparative Methods: for a reaction of typical scale, glacial acetic acid (600 mL) is placed in a 4000 mL beaker and stirred magnetically. Sulfur dioxide is delivered from a cylinder through a bubbler tube with a fritted glass end immersed beneath the surface of the acetic acid. Introduction is continued for 15-30 min until saturation is evidenced by the fact that most of the SO_2 bubbles reach the surface of the acetic acid. Copper(I) chloride (15 g) is added to the solution, and the introduction of sulfur dioxide is continued until the yellow-green suspension becomes blue-green and most of the solids dissolve (20-30 min). The mixture is placed in an ice bath until use.

Handling, Storage, and Precautions: mixtures of copper(I) chloride and sulfur dioxide should be prepared immediately before use. The saturated SO_2 solution is noxious and must be prepared and used in a fume hood. Sulfur dioxide is intensely irritating to the eyes and respiratory tract.

Arenesulfonyl Chlorides.

A mixture of copper(I) chloride and sulfur dioxide is very effective in converting arenediazonium ions to arenesulfonyl chlorides (eq 1).[1] The diazonium solution is added slowly to the cooled copper(I) chloride-sulfur dioxide mixture and a normally vigorous evolution of nitrogen occurs with formation of the sulfonyl chloride. The original literature[2] recommends copper(II) chloride as the copper source which is reduced in situ to copper(I) chloride, the active catalyst. More recently, it has been found that the use of copper(I) chloride in the above procedure is superior in reproducibly providing active catalytic mixtures.[1,3]

$$ArN_2^+Cl^- \xrightarrow[MeCO_2H]{CuCl,\ SO_2} ArSO_2Cl + N_2 \qquad (1)$$

A wide variety of aromatic amines can be converted to aromatic sulfonyl chlorides via their diazonium salts by this method. Some examples are collected in Table 1. In addition, a group of fluorinated arenesulfonyl chlorides have been prepared by the same method.[4] In general, aromatic amines with electron-withdrawing substituents give the best results. For aromatic amines with electron-donating substituents, yields can be improved by the addition of magnesium chloride, which serves to raise the chloride concentration.[2] This method for the preparation of arenesulfonyl chlorides is simple and straightforward compared to alternate methods such as aromatic substitution by ***Chlorosulfonic Acid*** or oxidation of aromatic thiols with ***Chlorine*** water.

Table 1 The Conversion of Aromatic Amines to Arenesulfonyl Chlorides

Amine, $XC_6H_4NH_2$	Yield of $XC_6H_4SO_2Cl$ (%)
X = *m*-CF_3	72
p-NO_2	68
m-NO_2	86
p-Cl	90
p-CO_2Me	90
3,5-di-NO_2	81
m-Me	71
H	53
p-OMe	27
3,5-di-CF_3	81

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Copper Chromite[1]

$$2CuO \cdot Cr_2O_3$$

[12053-18-8] · $Cr_2Cu_2O_5$ · Copper Chromite · (MW 311.10)

(hydrogenation catalyst for many functional groups;[3] decarboxylation;[4] dehydrogenation[5])

Alternate Name: Adkins or Lazier catalyst.[2]

Solubility: insol organic solvents; practically insol water and dilute acids; reactions are typically carried out in ethanol, dioxane, ether, methylcyclohexane or without solvent.

Form Supplied in: fine black powder; the best catalysts contain ca. 10% barium oxide.

Preparative Methods: although commercially available, the original preparations are often referenced in the literature.[6]

Handling, Storage, and Precautions: stable to air and moisture; care should be taken to avoid skin contact and inhalation since chromium and barium compounds are highly toxic.

Hydrogenation.[1]

The main use of copper chromite is as a hydrogenation catalyst, especially in the reduction of oxygen-containing functionality. The reactions are generally carried out at high temperatures (100-300 °C) and high pressures (40-375 atm compressed at rt), limiting the catalyst's use to robust and/or lightly functionalized molecules. Many of the possible functional group reductions may be easier to carry out using metal hydrides such as ***Lithium Aluminum Hydride*** or ***Sodium Borohydride*** under milder conditions. However, the yields of copper chromite-catalyzed hydrogenations are often high and may be well suited to large scale preparations of simple intermediates.

At the high temperatures involved in the hydrogenations, side reactions with solvent need to be considered; ethanol, for example, can behave as an alkylating agent of amines, amides may undergo alcoholysis, and esters transesterification. Consequently it may be advantageous to perform some reactions neat.

Carbonyl Compounds.

Aldehydes and ketones are amongst the easiest functional groups to hydrogenate, giving primary and secondary alcohols, respectively. However, at higher temperatures further reduction to the hydrocarbons may occur if the

alcoholic product is activated in some way (eq 1).[7] Alkenes in the molecule may also be reduced under the reaction conditions.[8] A study of the competitive hydrogenation of aldehydes, ketones, and alkenes has been published[9] and alkene reduction in the presence of cyclopropyl rings has also been reported.[10] The *cis* and *trans* stereoisomers from the reduction of 2-hydroxycyclodecanone have been separated by fractional crystallization (eq 2).[11]

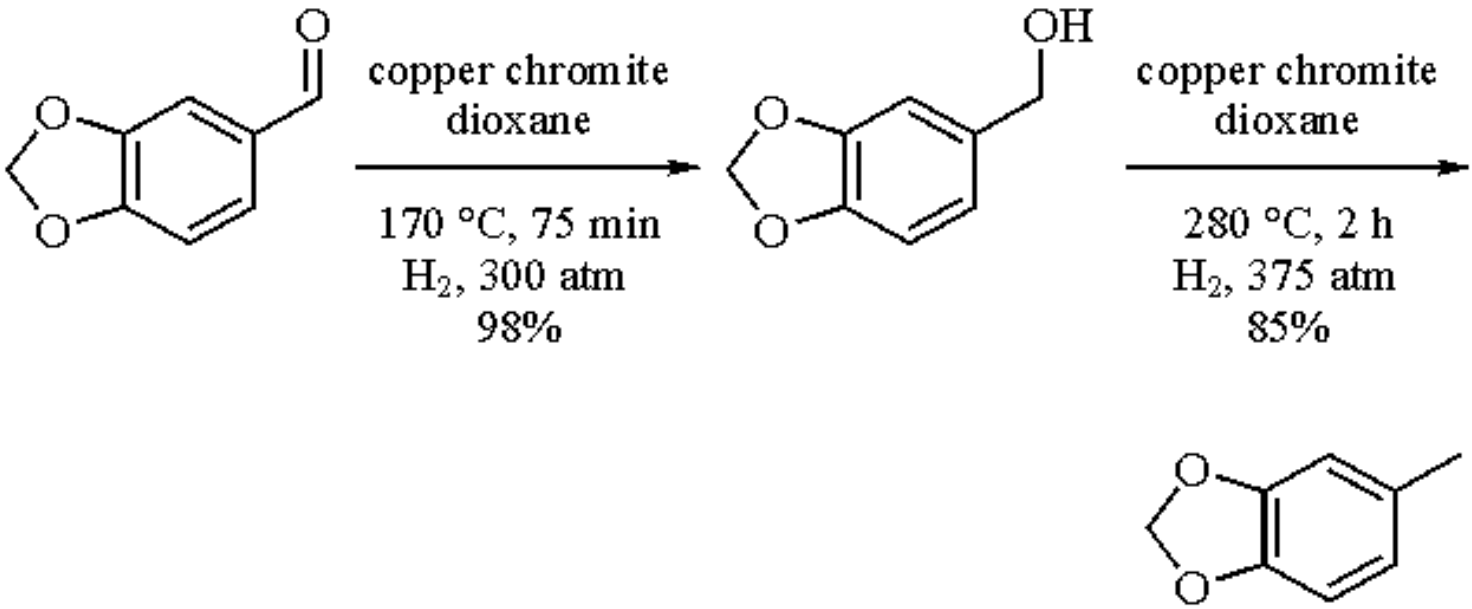

(1)

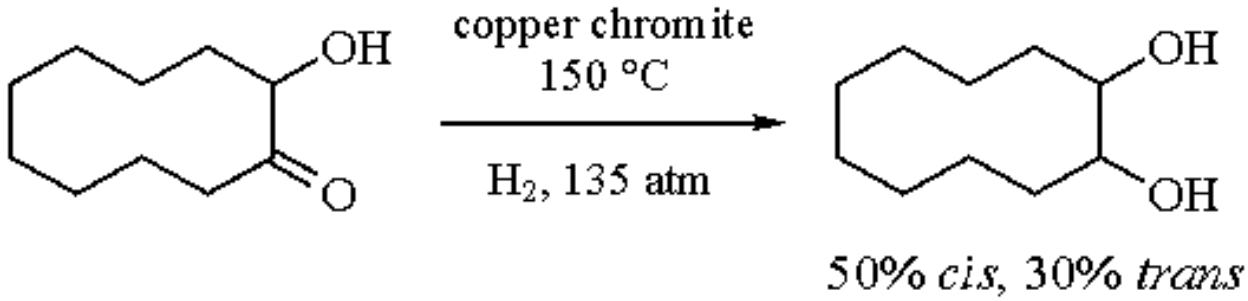

(2)

The hydrogenation of esters yields the expected primary alcohols and this reaction has been reviewed.[12] Lactones give the corresponding diols (eq 3).[13] Alkenes in the molecule will also be reduced[14] but amides may be left intact since they generally require much higher temperatures before reduction takes place (eq 4).[15]

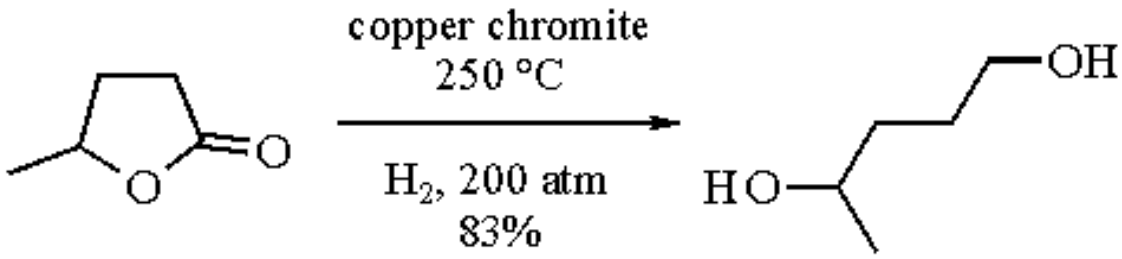

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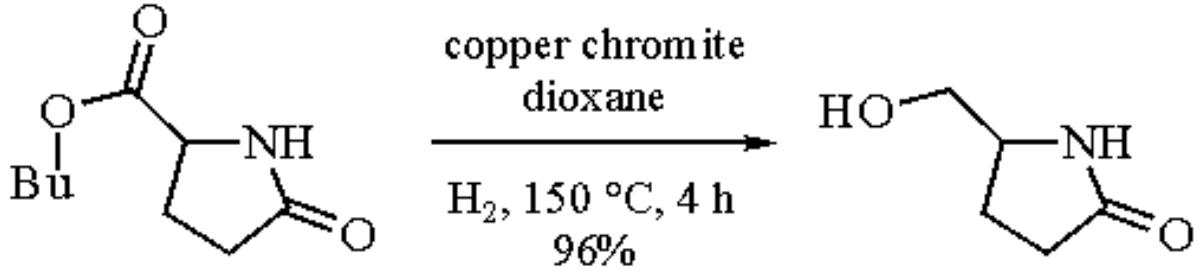

(4)

Amides[16] will react at high temperature (usually above 200 °C) and pressure to give amines (eq 5).[17] Nitro groups also give amines.[3] Glutaramides have been shown to cyclize to piperidines upon reduction[18] and indolizidines have been prepared in a similar way (eq 6).[19] Nitriles react when carbonyl groups are present in the same molecule to give cyclic amines[20] and lactams (eq 7).[21]

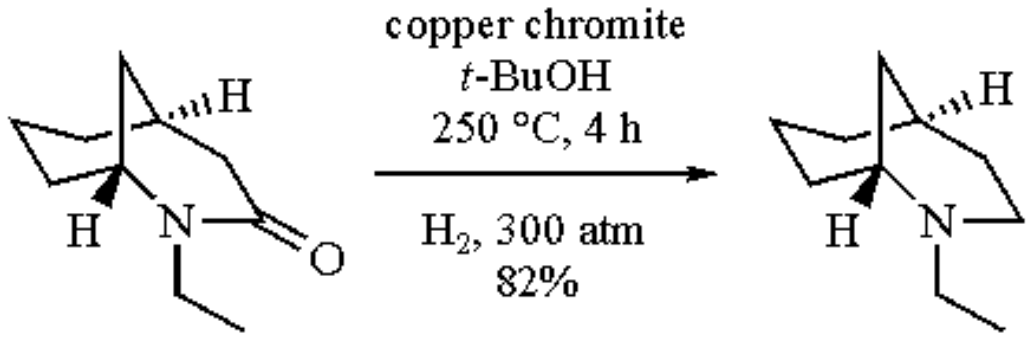

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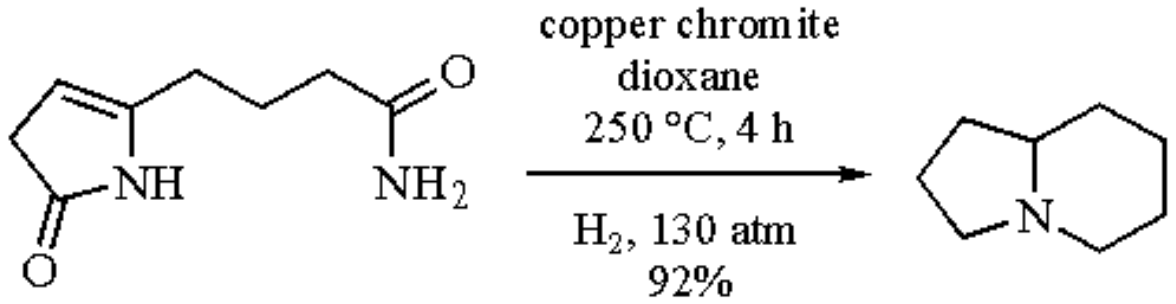

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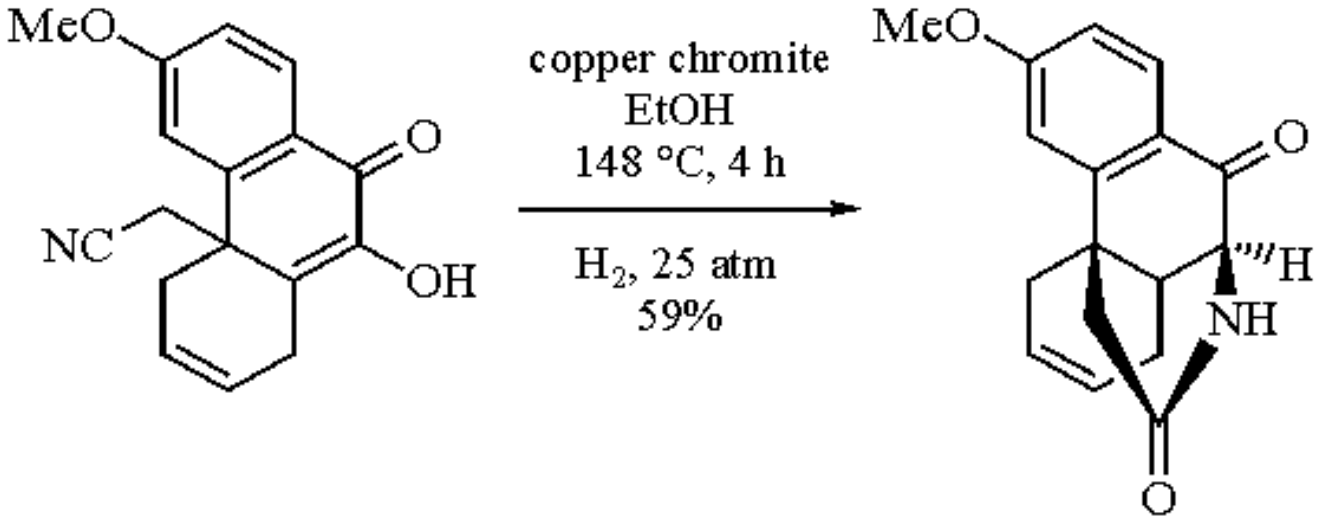

(7)

Aromatic Compounds.

In some cases, selective hydrogenation of aromatic nuclei can be achieved. Saturation of the 9,10-double bond of phenanthrene is possible with careful monitoring of the hydrogen uptake to prevent over-reduction.[22] Heteroaromatics are also partially reduced over copper chromite, where ***Raney Nickel*** is unselective (eq 8).[23] At 300 °C, total reduction of 2-methyl-2,3-dihydrobenzofuran to propylcyclohexane was observed in 96% yield.[24]

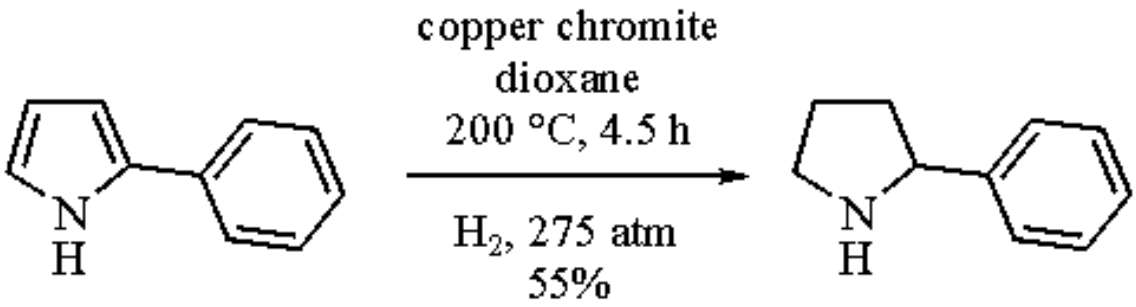

(8)

Hydrogenolysis.

Amines can be hydrogenolyzed to the corresponding methyl compounds (eq 9),[25] as can the benzyl alcohols.[26] Some cyclic ethers also show carbon-oxygen bond cleavage (eq 10).[27]

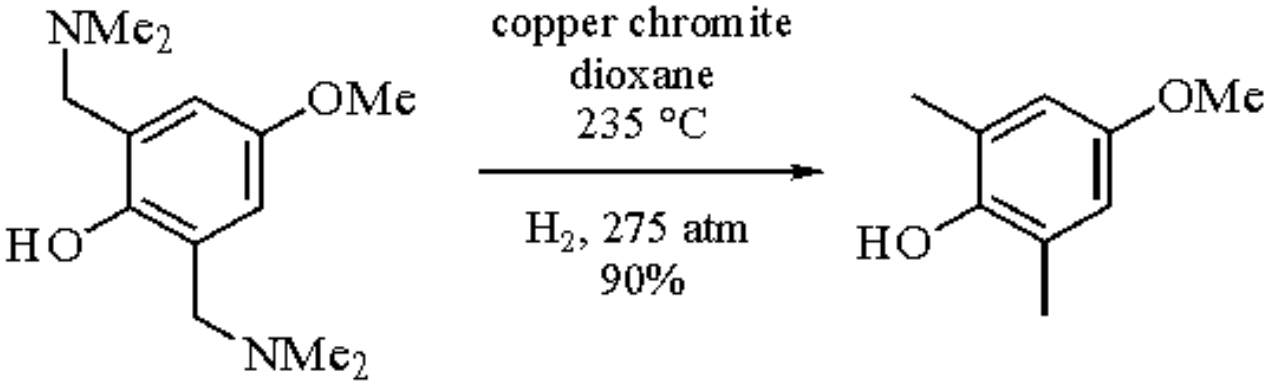

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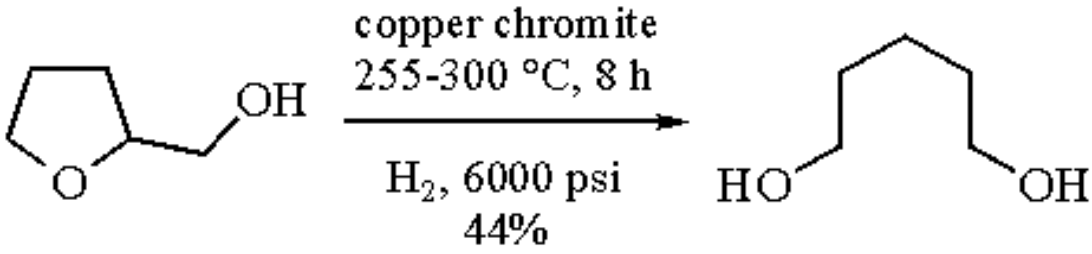

(10)

Decarboxylation of Aromatic Compounds.

Copper chromite has been used, usually in the presence of ***Quinoline***, as a decarboxylating reagent for aromatic compounds. Yields can be high for simple substrates[4] and a decarboxylation-aromatization has been reported (eq 11).[28] Some fairly sensitive molecules can survive the reaction conditions, including nitrile pyrroles[29] and isothiazoles (eq 12).[30] Copper chromite-catalyzed hydrogenation of *o*-acylbenzoic acid to *o*-ethylbenzoic acid was accomplished by first forming the sodium salt.[31] See also ***Copper Chromite-Quinoline***.

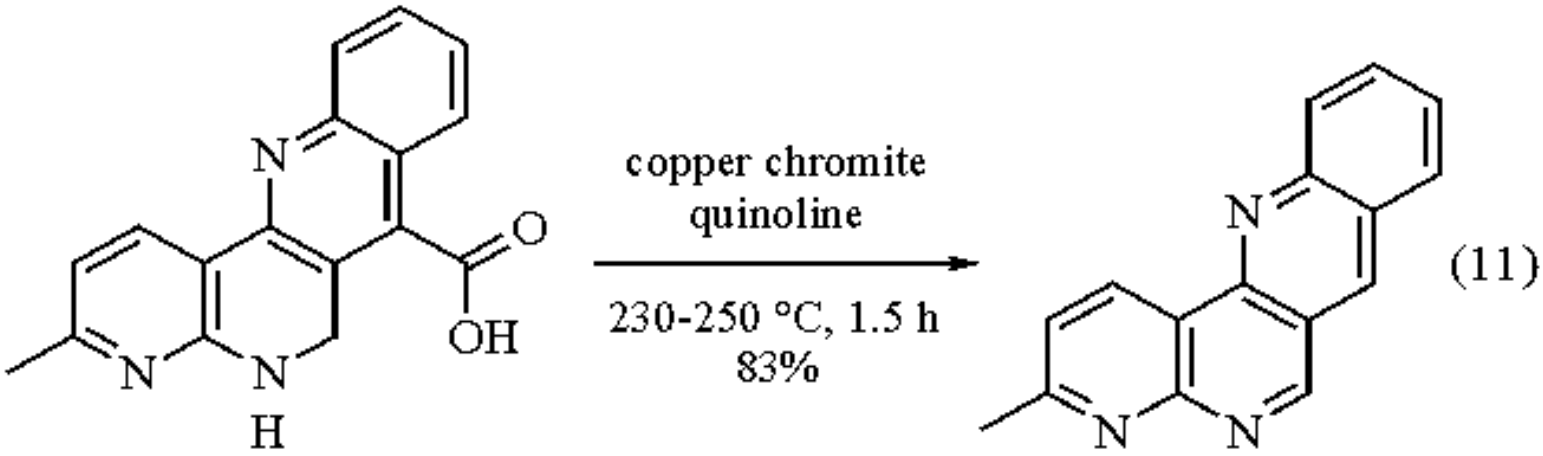

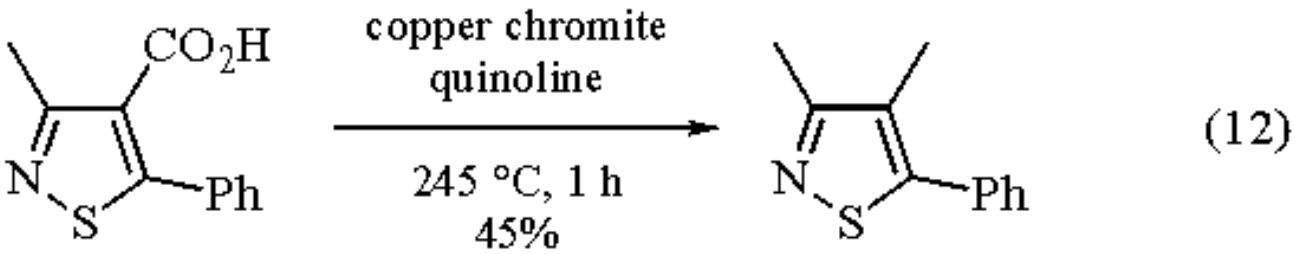

Dehydrogenation of Alcohols.

A few examples of copper chromite acting as a dehydrogenating agent are known.[32] Alcohols can be oxidized to ketones (eq 13)[5] and diols to lactones, presumably via the lactols (eq 14).[33] Dehydration following dehydrogenation has also been observed (eq 15).[34] Copper chromite can be activated prior to use in hydrogenation reactions by heating at reflux in cyclohexanol for 4 h, during which time cyclohexanone is formed.[5]

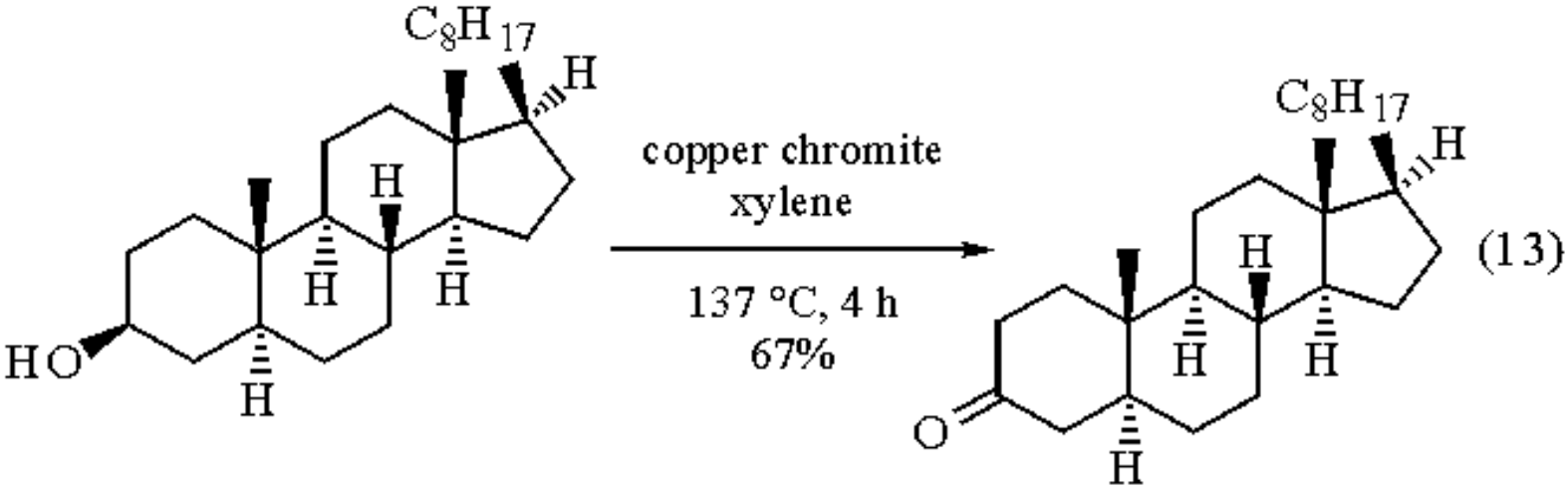

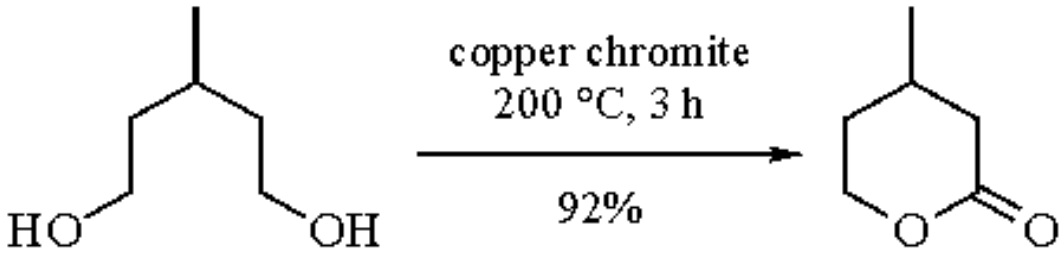

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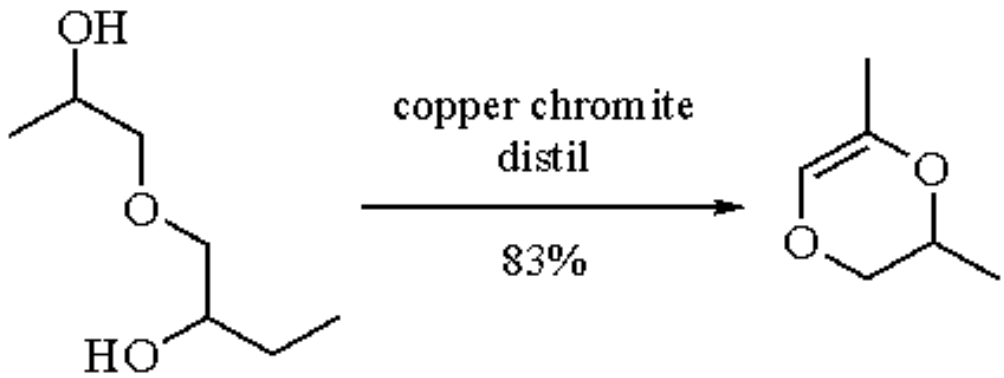

(15)

Other Reactions.

More unusual reactions mediated by copper chromite include carbon-carbon bond hydrogenolysis (eq 16);[35] oxidation of a carbon-hydrogen bond α to a ketone;[36] a ring contraction to give thiophenes (eq 17);[37] and a one pot conversion of β-amino alcohols to α-methyl ketones (eq 18),[38] a reaction which proceeds mechanistically via alcohol dehydrogenation, amine elimination, and resultant double bond hydrogenation.

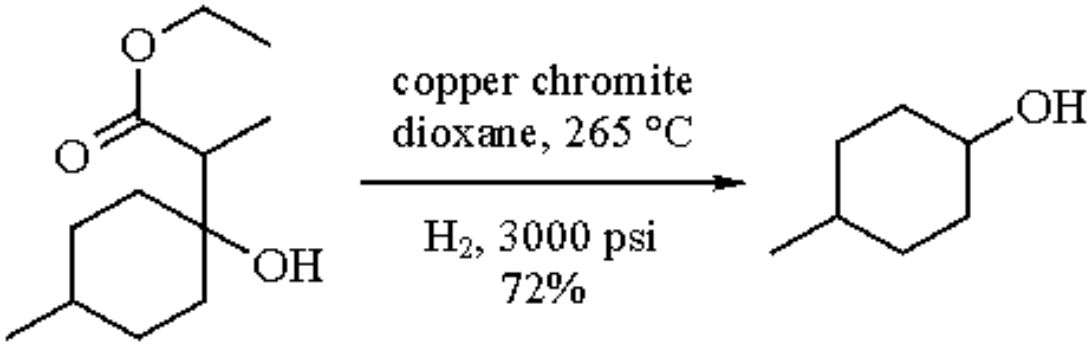

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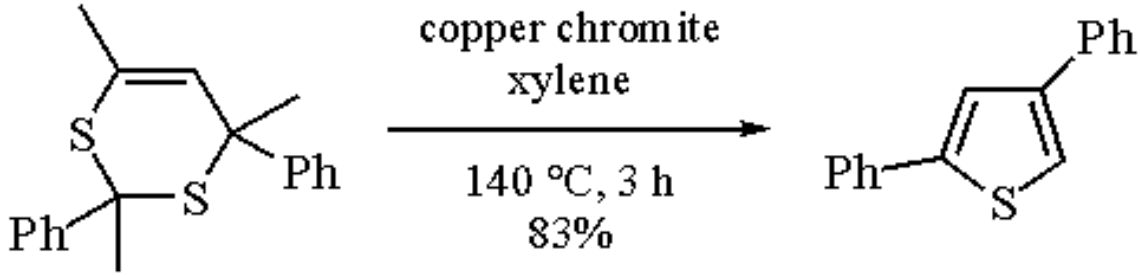

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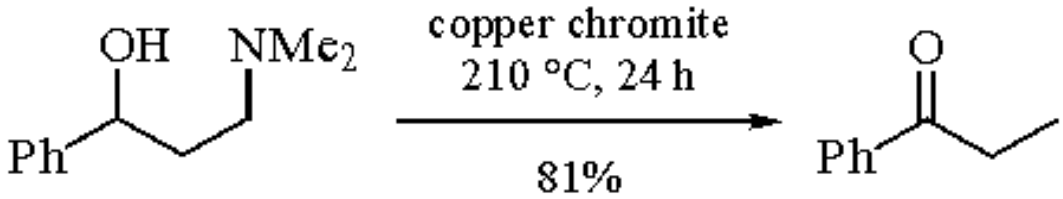

(18)

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Copper Chromite-Quinoline

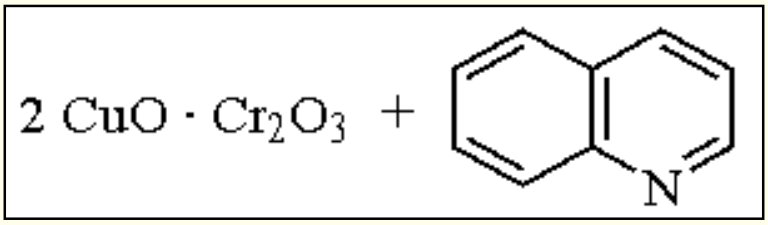

[12053-18-8] · $Cr_2Cu_2O_5$ · Copper Chromite-Quinoline · (MW 311.07)

[91-22-5] · C_9H_7N · Copper Chromite-Quinoline · (MW 129.16)

(decarboxylation catalyst)

Physical Data: see the entries for ***Copper Chromite*** and ***Quinoline***.

Form Supplied in: both components are widely available. The frequently-used barium-promoted copper chromite contains varying amounts (ca. 10%) of BaO.

Preparative Methods: see the entries for the individual components.

Handling, Storage, and Precautions: the copper chromite catalyst is air- and moisture-stable; however, it should be kept as dry as possible to avoid spattering at elevated temperatures. Both reagents are toxic irritants and should be handled in a well-ventilated fume hood.

Copper Chromite (chromium copper oxide) has long been used, both industrially and in the academic laboratory, as a catalyst for hydrogenation and other reductions, but has been supplanted in recent years by the development of hydrides and other reducing agents.

Decarboxylation.

Quinoline is a favorable solvent for the decarboxylation of unsaturated carboxylic acids with ***Copper*** powder, $Cu_2Cr_2O_5$, and similar catalysts, as it forms the requisite carboxylate anion while providing a relatively low-boiling reaction medium;[1a-b] most reactions are performed at reflux between 170-200 °C. Both anhydrous $Cu_2Cr_2O_5$ and its barium-promoted forms effect decarboxylations, although metal oxide (e.g. BaO) content tends to increase reaction rates. Thus (*E*)-α-phenylcinnamic acid is decarboxylated in high yield to *cis*-stilbene in 10 min (eq 1).[1b]

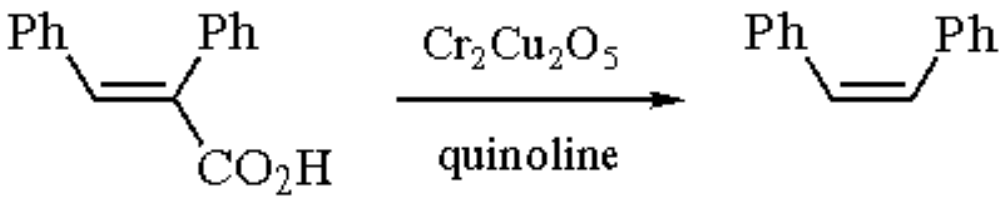

(1)

Decarboxylation of 4-acyl-2-pyrrolecarboxylic acids, which gives low yields of 3-acylpyrrole products when ethanolamine and 2,6-lutidine are employed as solvents, is effected at 180-200 °C in much improved (76-85%) yields, with minimal tarring, when quinoline is used (eq 2).[2]

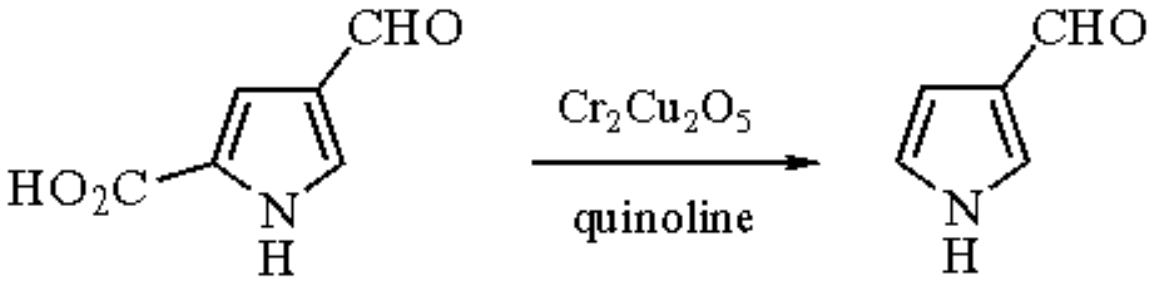

(2)

In a synthesis of benzo[*a*]cycl[3.2.2]azine, decarboxylation of the intermediate diacid (eq 3) gave the desired product in 49% yield.[3] Similar reactions with benzoic acid (eq 4) and acylfuran (eq 5) derivatives have been reported.[4,5]

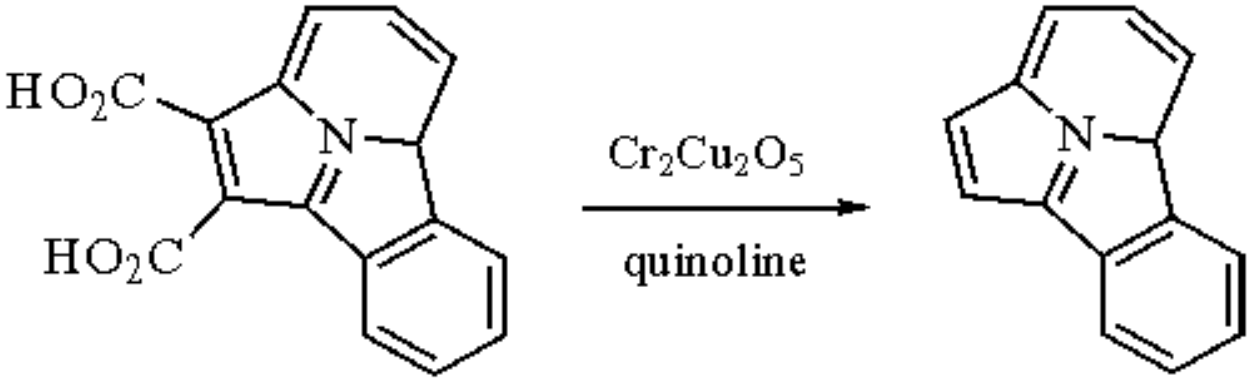

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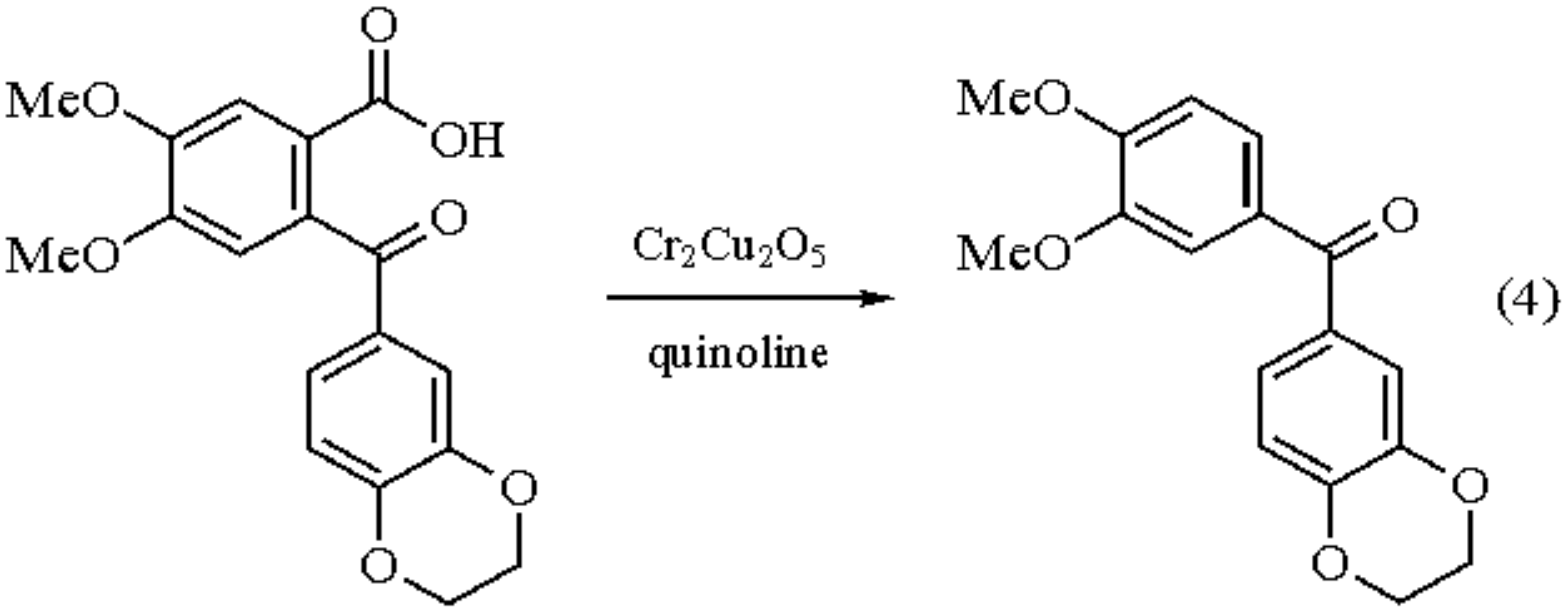

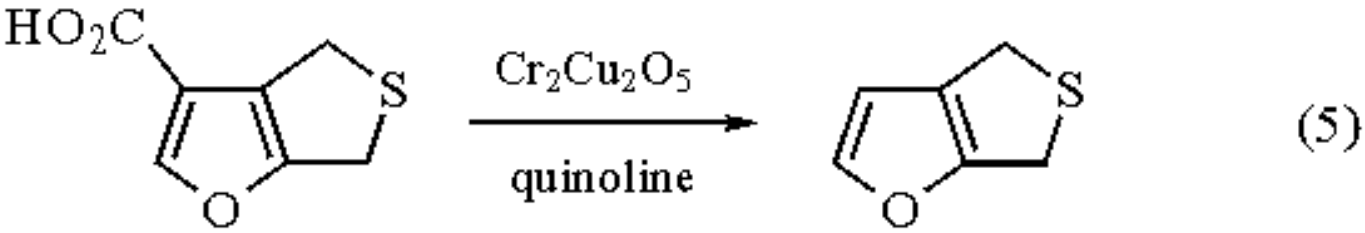

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Copper(I) Cyanide[1]

CuCN

[544-92-3] · CCuN · Copper(I) Cyanide · (MW 89.57) (.NaCN)

[13715-19-0] · C_2CuN_2Na · Copper(I) Cyanide-Sodium Cyanide · (MW 138.58) (.LiCl)

[59219-07-7] · CClCuLiN · Copper(I) Cyanide-Lithium Chloride · (MW 131.96) (.2LiCl)

[121340-53-2] · CCl_2CuLi_2N · Copper(I) Cyanide-Lithium Chloride · (MW 174.35) (.2LiBr)

[129126-28-9] · CBr_2CuLi_2N · Copper(I) Cyanide-Lithium Bromide · (MW 263.25)

(useful precursor for organocopper(I) and organocuprate(I) reagents[1])

Alternate Name: cuprous cyanide.

Physical Data: mp 474 °C; *d* 2.920 g cm^{-3}.

Solubility: insol H_2O and most organic solvents. The lithium halide complexes are sol THF.

Form Supplied in: off-white solid.

Handling, Storage, and Precautions: highly toxic; must be handled with care.

General Discussion.

The first investigation of organocopper chemistry was carried out by Kondyreva and Fomin,[2] who in 1915 studied the effect of heavy metal salts on organomagnesium compounds. They found that organocopper compounds, prepared from CuCl, CuBr, CuI, CuSCN, and CuCN, decomposed to give equimolar amounts of alkane and alkene when the organic group was *n*-alkyl, and biaryl when it was aryl. These observations were confirmed by Whitesides et al. a half century later.[3] The Russian authors also noted that the solutions prepared from Grignard reagents and copper salts no longer reacted with acetone to give *t*-butanol. While they did not find a synthetic application for their solutions, it should be noted that Gilman did not investigate the reaction chemistry of the solutions he prepared from 2 equiv of MeLi and copper(I) salts, either.[4] Nevertheless, organocuprates are now commonly called Gilman reagents.

The pioneering work on synthetic applications of organocopper reagents was done almost exclusively with ***Copper(I)***

Iodide. Unfortunately, nearly two decades were to pass before it was found that Gilman reagents prepared from CuCN and 2 equiv of RLi were purer, more thermally stable,[5] and often gave higher yields of the desired product than Gilman reagents prepared from CuI.[1,7] Gilman reagents such as $Bu_2CuLi.LiI$ appear to be more prone to electron transfer and radical reactions than the corresponding reagents prepared from CuCN.[6]

Based upon their apparent higher reactivity, it was originally claimed that the reagents prepared from 2 equiv of RLi and CuCN were higher order cyanocuprates, $R_2Cu(CN)Li_2$;[1a-c,7] however, NMR studies,[9-11] EXAFS investigations,[12] and theoretical calculations[13] have recently converged on the conclusion that the CN is not bonded to Cu. Lipshutz has recently conceded that the CN is not σ-bonded to Cu.[8] Thus these reagents should be represented as $R_2CuLi.LiCN$ by analogy with $R_2CuLi.LiI$ and $R_2CuLi.LiBr$ for the cuprates prepared from CuI and ***Copper(I) Bromide***, respectively. It has been demonstrated by ^{13}C NMR and ^{6}Li NMR that LiI is not free in the Gilman reagent prepared from CuI and 2PhLi in DMS,[14] and that LiI and LiCN are not part of the cuprate bonding in THF.[9-11] It has recently been shown how the aggregation states of organocopper reagents in solution may be assigned by using ^{13}C NMR spectroscopy.[11]

In contrast, both NMR and EXAFS studies confirm that CN is bonded to Cu in the so-called lower order cyanocuprates, RCu(CN)Li,[10,12] prepared from 1 equiv of RLi and CuCN. While they are relatively unreactive towards α-enones and alkyl halides,[15] they have been used successfully with more reactive substrates such as allylic carboxylates[16] and vinyloxiranes.[17] The introduction of additives such as ***Boron Trifluoride***[18,19] should give these reagents broader applicability. Trost used lower order cyanocuprates when he introduced the concept of chirality transfer in acyclic systems,[20] which has been applied brilliantly by Ibuka and Yamamoto.[18]

Recently, several novel lower order cyanocuprates have found application. For example, Piers has converted 2-alkynoates into either (*Z*)- or (*E*)-3-trimethylstannyl-2-alkenoates by treatment with $Me_3SnCu(CN)Li$ under the appropriate conditions (eq 1).[21a] He also compared lower order phenyl cyano- and thiocuprates in developing an efficient methylenecyclopentane annulation (eq 2).[21b]

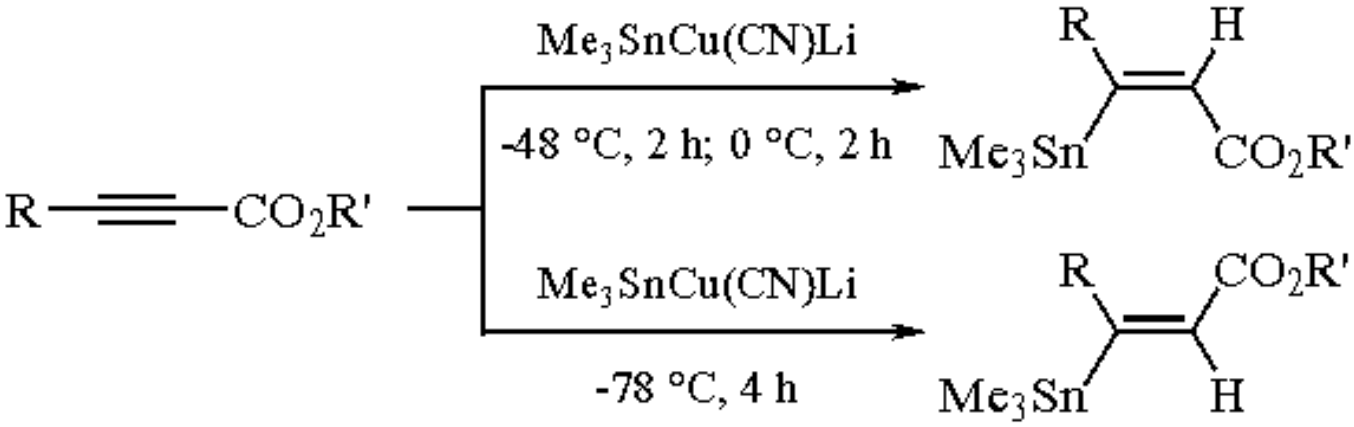

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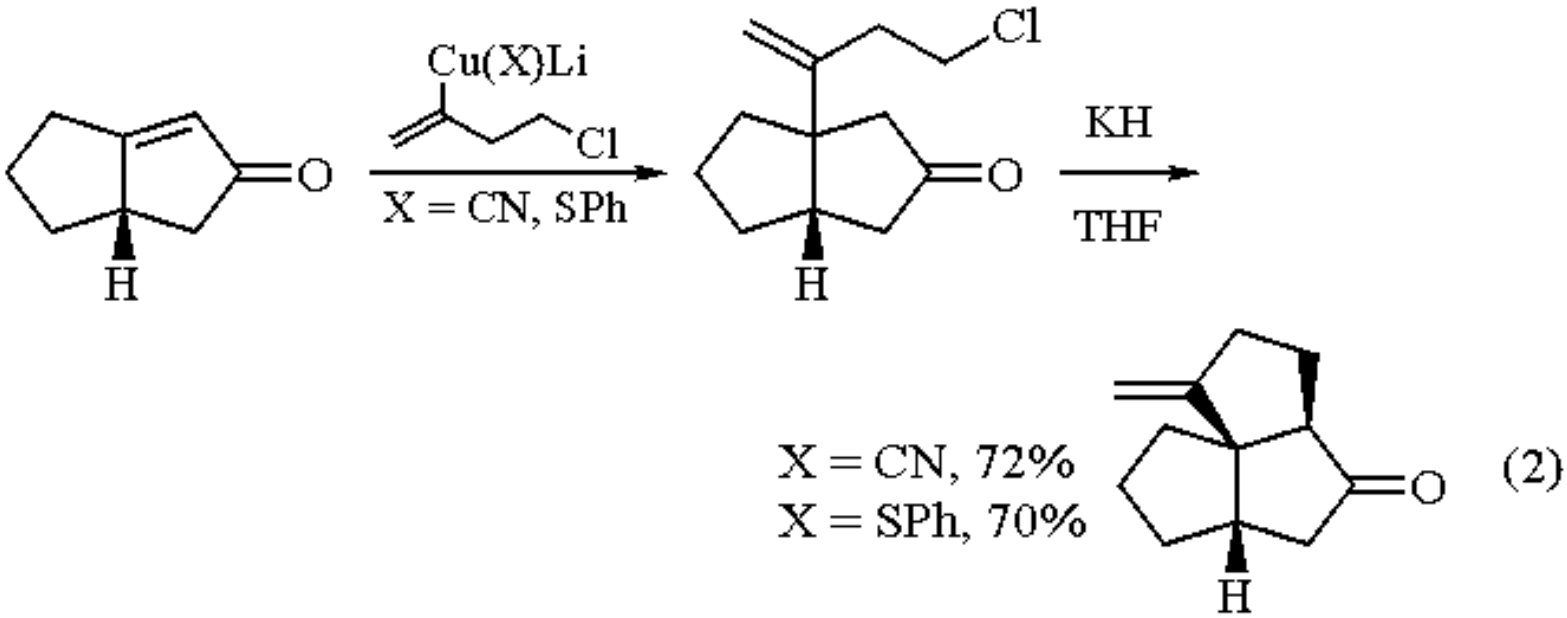

In a most exciting development from the viewpoint of molecular complexity, Knochel has prepared highly functionalized cyanocuprates RCu(CN)ZnX, where X = I, Br, Cl, OMs, OTs, or $OP(O)(OR)_2$, from the corresponding alkylzinc reagents.[22] In a related development, Rieke has reported the direct formation of highly functionalized allylic organocopper reagents via the reduction of CuCN.2LiBr, CuCN.LiCl, or CuCN.2LiCl with ***Lithium Naphthalenide*** to give a highly reactive form of Cu metal.[23] Linderman has prepared α-alkoxyorganocuprate reagents from the corresponding organotin compounds and reacted them with α,β-unsaturated carbonyl compounds (eq 3).[24]

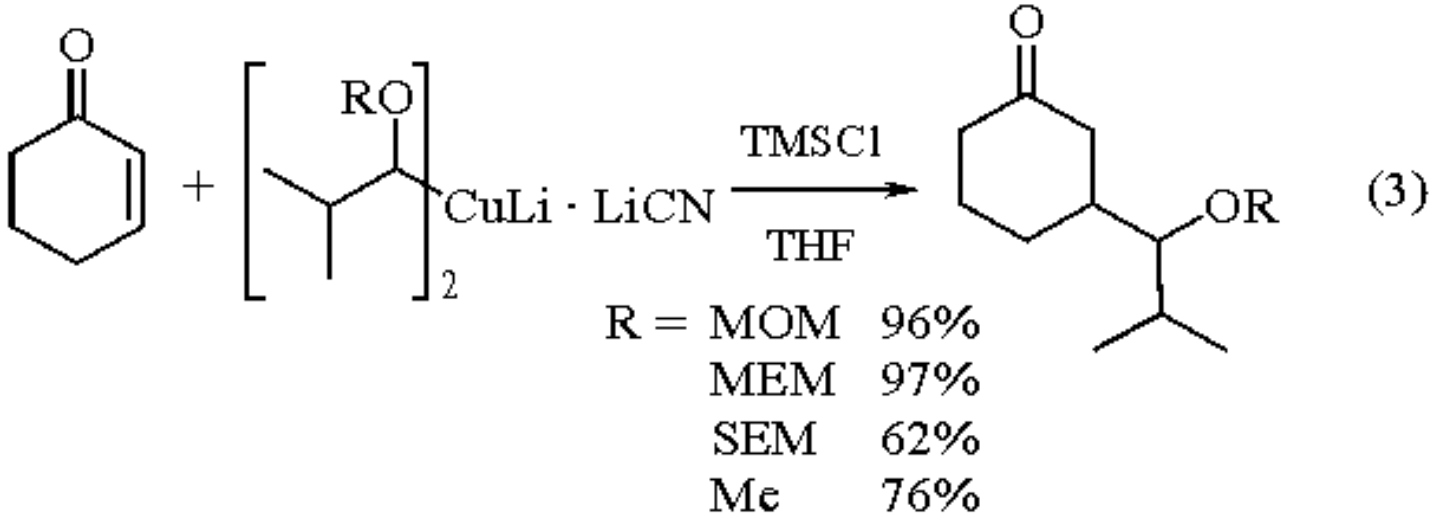

Corey has used $Bu_4NCu(CN)_2$ as a precursor to a new class of cuprate reagents, which he symbolizes as $RCu(CN)_2(NBu_4)Li$,[25] implying that they are higher order cuprates with two CN ligands bonded to Cu, although this remains to be proven. The ^{13}C NMR spectroscopy of organocopper reagents has now been developed to the point where conjectures concerning the structures of new organocopper species should not be made without making sure that they are consistent with the NMR data.[11] At the time of this writing there is still a backlog of structures that need to be checked. Theory is also being developed to the point where it can shed considerable light on whether structures are feasible or not.[13]

As discussed above, when the Gilman reagents prepared from CuI were introduced, side-by-side comparisons were not

made with the corresponding cuprates prepared from other Cu^I salts. (Or, if comparisons were made, they were not reported.) In other words, a depth-first search was done, rather than a breadth-first one.[26] Unfortunately, the same pattern was repeated when the cuprates prepared from CuCN were introduced: papers with tables of yields for typical substrates were published, but very few direct comparisons with other cuprates were made.[1b,c,7a] Thus the best advice we can give the synthetic chemist is to try several of the most successful versions of the Gilman reagent, viz, those prepared from CuI, $CuBr.SMe_2$ (see ***Copper(I) Bromide***), and CuCN.[1a-c] It is also useful to compare organocopper reagents prepared from lithium reagents with those prepared from the corresponding Grignard reagents (See ***Copper(I) Chloride***).

In one of the few direct comparisons, Fleming has shown that the silylcupration of alkynes with $(Me_2PhSi)_2CuLi.LiCN$ gives the opposite regiochemistry to $(Me_2PhSi)_2CuLi.LiBr$, prepared from CuBr.DMS.[27] It is interesting to note that Fleming's work predates Lipshutz's, and that he uses the correct (lower order) formulation. Bertz has compared CuCN with CuI, CuBr, CuBr.DMS, CuCl, CuSCN and CuOTf as far as the formation of alkyl and aryl Gilman reagents is concerned,[28a] and also reacted a number of them, including those made from CuCN, with dithioesters, where they give carbophilic addition.[28b] For the preparation of stoichiometric cuprates from Grignard reagents, ***Copper(I) Trifluoromethanesulfonate*** (copper(I) triflate) was demonstrated to be superior to the other Cu^I salts, including CuCN.[28b]

While CuCN has been used in catalytic amounts with Grignard reagents (where the ate complex may be presumed to be the active species),[16b,29,30] CuCN has not been shown to be superior to the other Cu^I salts, and even some Cu^{II} salts appear to be equally effective.[1a] For example, in the addition of Grignard reagents to nitriles, CuCN, CuI, CuBr, CuBr.DMS, and CuCl all gave the same yield of product to within ±3%. Thus the yields of ketimine product from *t*-BuMgCl and 4-methoxybenzonitrile were 87-93% (i.e. 90 ± 3%) after 2 h in refluxing THF in the presence of 2 mol % of the Cu^I salt.[30] This is a very useful extension and generalization of Bertz's work on the activation of the carbon-nitrogen double bond by Cu^I.[31]

Lipshutz has described stoichiometric higher order, mixed lithio magnesio organocuprates prepared from CuCN, 2-lithiothiophene, and Grignard reagent (1:1:1), although no evidence that a higher order species is present in such solutions has been adduced.[32a] In fact, the authors admit that these reagents are not discrete.[32a] The corresponding organocuprates prepared from CuCN, 2-lithiothiophene, and a lithium reagent (or lithium 2-thienyl(cyano)cuprate(I) and a lithium reagent) have been assigned a higher order structure,[1b] but are probably lower order R(2-thienyl)CuLi.LiCN reagents.[9-11] The 2-thienyl group was introduced as a nontransferred ligand for mixed cuprates by the Swedish group of Malmberg, Nilsson, and Ullenius.[32b] Whatever their structure may be, they have been applied to some interesting synthetic problems, such as the prostaglandin synthesis shown in eq 4.[33]

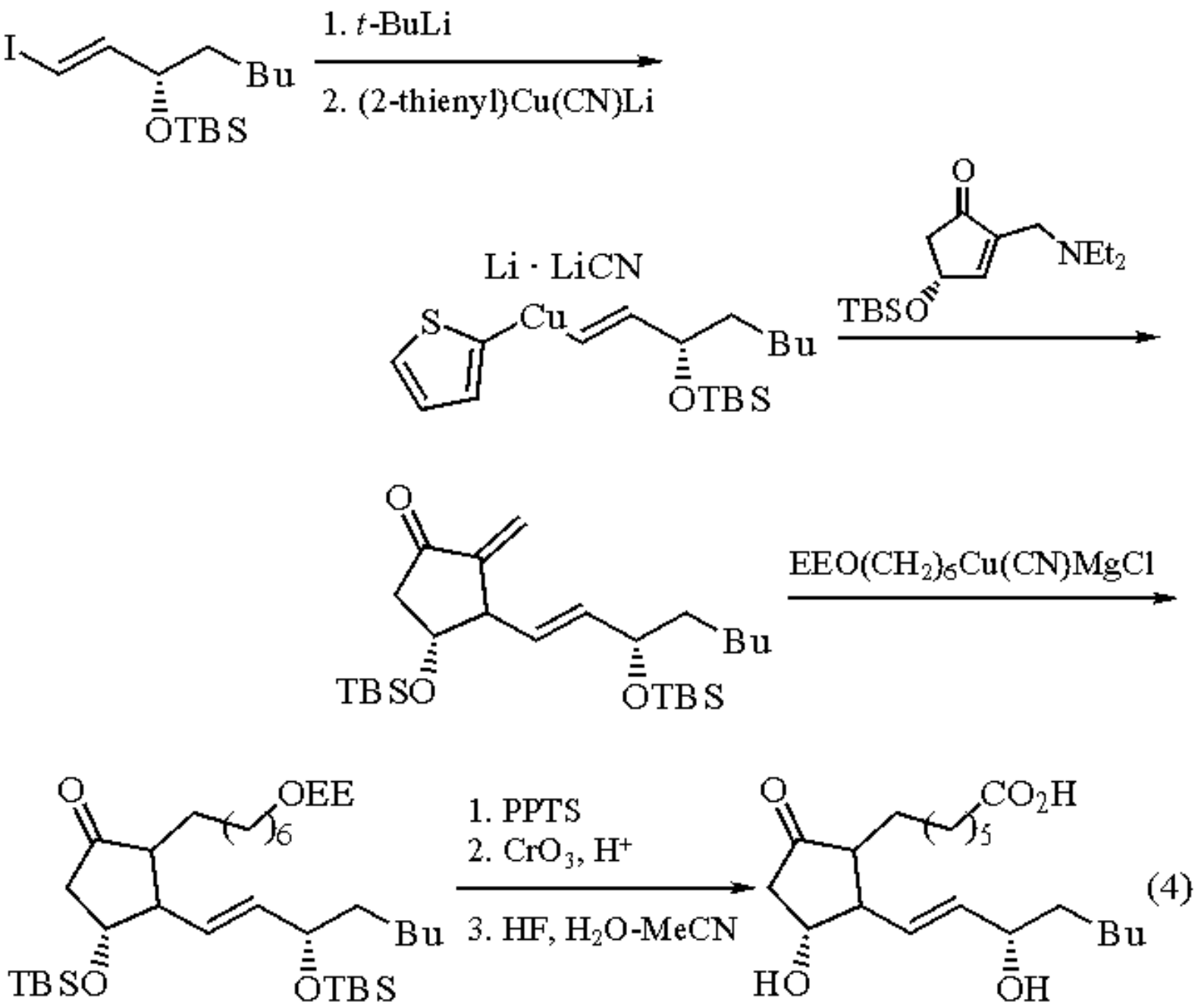

As mentioned above, $Bu_4NCu(CN)_2$ has been used as a cuprate precursor. The related alkali metal dicyanocuprates, especially $NaCu(CN)_2$, have been used in typical cuprate coupling reactions with aryl and vinyl halides.[34,35] In other typical organocopper reactions, CuCN itself reacts with acid chlorides to yield α-ketonitriles,[36] and with aryl iodides to afford aryl cyanides.[37]

It is noteworthy that the first sodium organocuprate, $Bu_2CuNa.NaCN$, was prepared from BuNa and CuCN,[38] and Seyferth prepared the first acyl cuprates from $R_2CuLi.LiCN$ and CO.[39] The latter development enables the synthesis of 1,4-diketones directly from α-enones via conjugate addition.

Whitesides et al. introduced the oxidative coupling of Cu^I ate complexes, which they prepared from CuI.[40] Bertz and Gibson demonstrated that the oxidation of organocuprates from CuCN gave significantly different results,[41] which Lipshutz et al. developed into a synthesis of unsymmetrical biaryls.[42] Oxidative couplings of heterocuprates usually proceed in poor yields;[1e,43] however, Snieckus et al. have developed useful synthetic methodology for the *N*-arylation

of amines based upon the oxidation of aryl amidocuprates.[44]

In one of his many pioneering studies, House showed that the enolates formed upon the addition of $Me_2CuLi.LiBr$ to α-enones were basically lithium enolates.[45] Nevertheless, Posner showed that the addition of 1 equiv of CuCN to a lithium enolate could dramatically decrease polyalkylation in cyclopentanone derivatives.[46]

Finally, CuCN has been used to catalyze the reactions of diazoacetic esters;[1f] however, ***Copper(I) Chloride*** is the Cu^I salt most frequently used for this purpose.

Related Reagents.

See ***Copper(I) Bromide***, ***Copper(I) Chloride***, ***Copper(I) Iodide*** (and their combination reagents); also ***Copper(I) Trifluoromethanesulfonate***. For examples of cyanocuprates, see ***Lithium Butyl(cyano)cuprate***, ***Lithium Cyano(methyl)cuprate***, etc.

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Copper(I) Cyanoacetate

$NCCH_2CO_2Cu$

[51249-59-3] · $C_3H_2CuNO_2$ · Copper(I) Cyanoacetate · (MW 147.60)

(agent generating cyanomethylcopper(I);[1] transcarboxylating agent for epoxides[2] and ketones[5])

Solubility: insol ordinary organic solvents; sol organic solvents in the presence of tertiary phosphine ligands.

Preparative Methods: acidolysis of ***Copper(I) t-Butoxide***;[1] carboxylate exchange reaction between Cu^I *n*-butyrate and ***Cyanoacetic Acid***.[3]

Handling, Storage, and Precautions: oxygen- and moisture-sensitive; preparation and reaction should be conducted under rigorously oxygen-free and anhydrous conditions.

Generation of Cyanomethylcopper(I).

Cu^I cyanoacetate decarboxylates in DMF at 50 °C to generate cyanomethylcopper(I) (eq 1).[1] Preparation of cyanomethylcopper(I) using decarboxylation of Cu^I cyanoacetate is characterized by the absence of lithium halide, in contrast to its preparation using the metathesis reaction between Cu^I halide and ***Isocyanomethyllithium***. Cyanomethylcopper(I) acts as a cyanomethylating agent of organic halides (eq 1). Cu^{II} cyanoacetate decarboxylates similarly to produce cyanomethylcopper(I) with concomitant formation of succinonitrile (eq 2).[1] Synthetic use of ***Cyanomethylcopper*** is described in the corresponding entry.

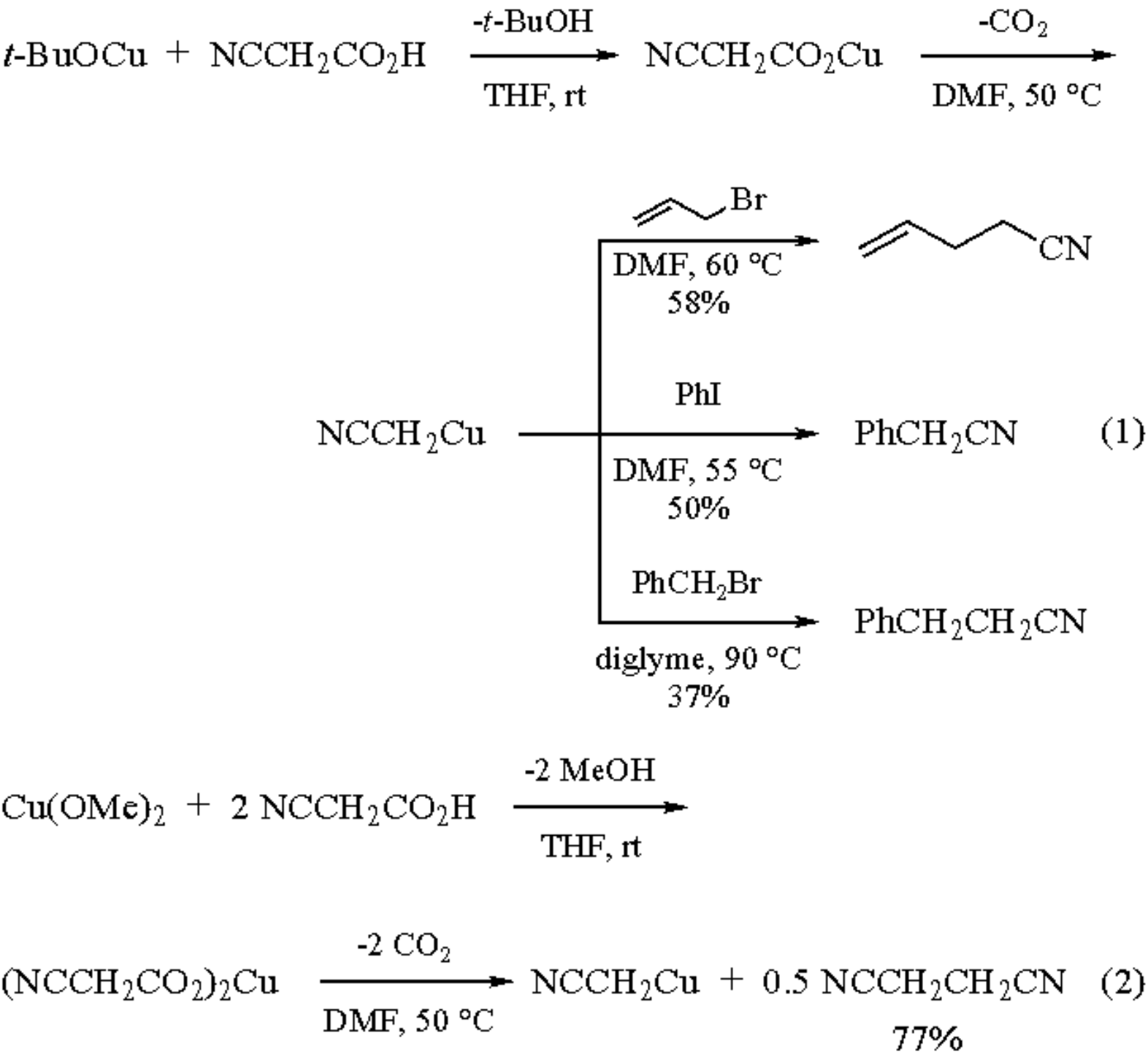

Transcarboxylation of Epoxides and Ketones.

Cu^I cyanoacetate acts as a CO_2 carrier, transferring its CO_2 moiety to propene oxide to afford propene carbonate in high yield (eq 3).[2] Cu^I cyanoacetate and cyanomethylcopper(I) catalyze the reaction of propene oxide with CO_2 to give propene carbonate.

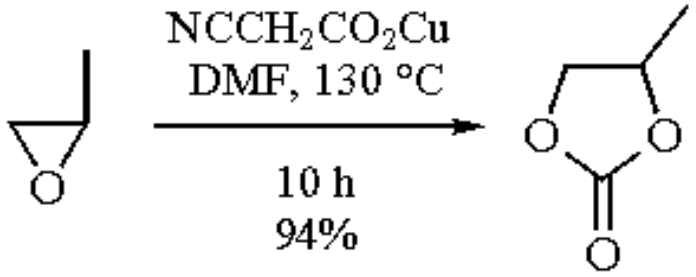

(3)

Cu^I cyanoacetate-catalyzed carboxylation of *trans*-1,2-dideuteroethylene oxide proceeds stereospecifically with retention of configuration, while the nickel(0) catalyst effects nonstereospecific reaction (eq 4).[4]

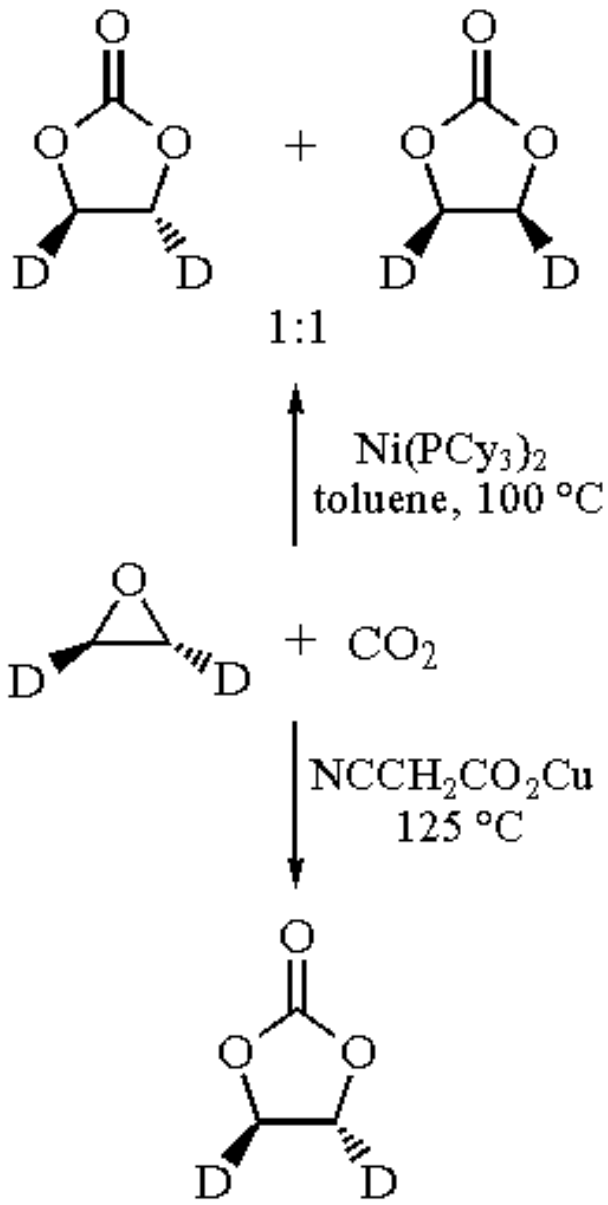

(4)

In the presence of ***Tri-n-butylphosphine*** ligand, the decarboxylation of Cu^I cyanoacetate in DMF is highly suppressed, resulting in reversible decarboxylation (eq 5).[5] The Cu^I cyanoacetate-tri-*n*-butylphosphine complex acts as a reversible CO_2 carrier to transfer its CO_2 component to cyclohexanone in good yield (eq 6).[5]

$$NCCH_2CO_2Cu(Bu_3P)_3 \overset{DMF}{\rightleftharpoons} NCCH_2Cu(Bu_3P)_3 + CO_2 \quad (5)$$

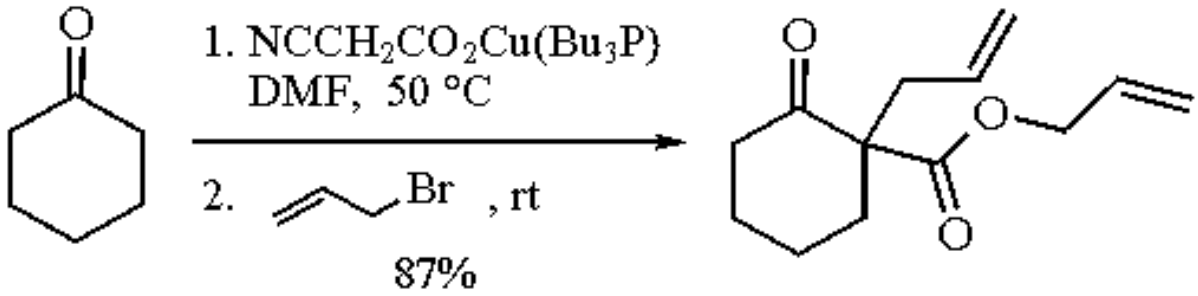

(6)

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Copper(II) Hexafluoroacetylacetonate

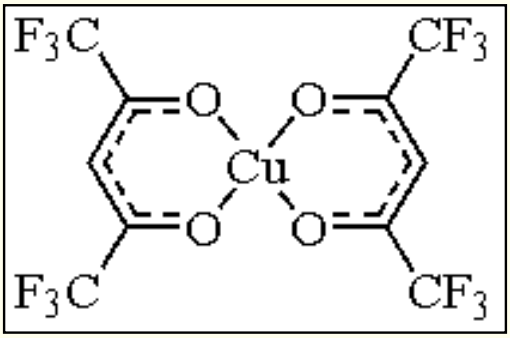

[14781-45-4] · $C_{10}H_{12}CuF_{12}O_4$ · Copper(II) Hexafluoroacetylacetonate · (MW 477.66)

(catalyzes diazo compound decomposition and ylide formation;[3] carbene additions[4])

Alternate Names: cupric hexafluoroacetylacetonate; bis(1,1,1,5,5,5-hexafluoro-2,4-pentanedionato-*O,O´*)copper.

Physical Data: green solid, mp 130-135 °C (hydrated forms),[2] 114-116 °C (anhyd).[1]

Solubility: sol EtOH, dioxane, CCl_4, polar solvents; insol H_2O.[2]

Form Supplied in: commercially available as a hydrated solid.

Preparative Methods: the dihydrate can be prepared from reaction of ***Copper(II) Acetate*** and hexafluoroacetylacetone dihydrate in aq NaOH, or by directly heating $Cu(OAc)_2.H_2O$ and anhydrous hexafluoroacetylacetone.[2]

Purification: recryst from 50% EtOH or CCl_4.[2]

Handling, Storage, and Precautions: irritant.

Unusual Heteroatomic Ylides.

Copper(II) hexafluoroacetylacetonate is an effective catalyst for the preparation of ylides from diazo compounds under mild conditions. This reagent is more effective than ***Copper(I) Acetylacetonate*** and ***Copper(II) Acetylacetonate***, two examples of many transition metal chelates available for decomposition of diazo compounds. Lower reaction temperatures result in a purer product, but reaction times are greatly increased. The heat-sensitive arsonium, stibonium, bismuthonium, sulfonium, telluronium, and thiouronium ylides have been prepared in 20-78%

yield under the catalysis of this reagent (eqs 1-3).[3] ***Copper Bronze*** and other copper salts are effective, but give lower yields.

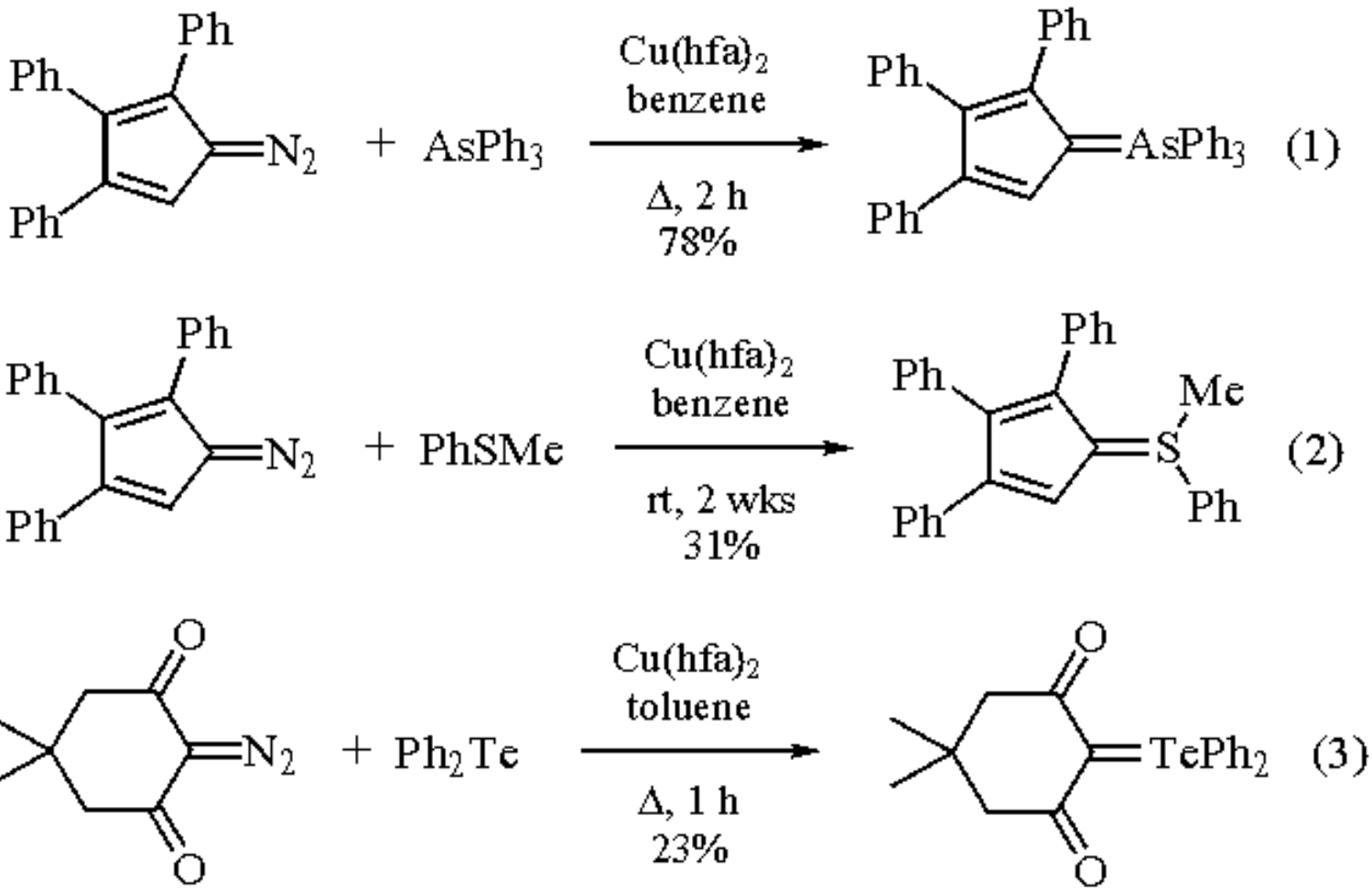

Carbene Additions to Vinyl Ethers.

The addition of ***Dimethyl Diazomalonate*** to the cyclic vinyl ether (**1**) was studied using several transition metal catalysts (eq 4).[4] The intermediate zwitterionic species (**2**) was rationalized from the formation of rearrangement products (**4a**) and (**4b**). Although $Cu(hfa)_2$ significantly reduces reaction times, as does the widely used catalyst $Rh_2(OAc)_4$, both result in significant skeletal fragmentation of the carbenium ion. However, ***Copper(II) Trifluoromethanesulfonate***, $Cu(acac)_2$, and other copper(II) acetonato chelates give little or no rearranged product while providing (**3**) in 74-80% yield.

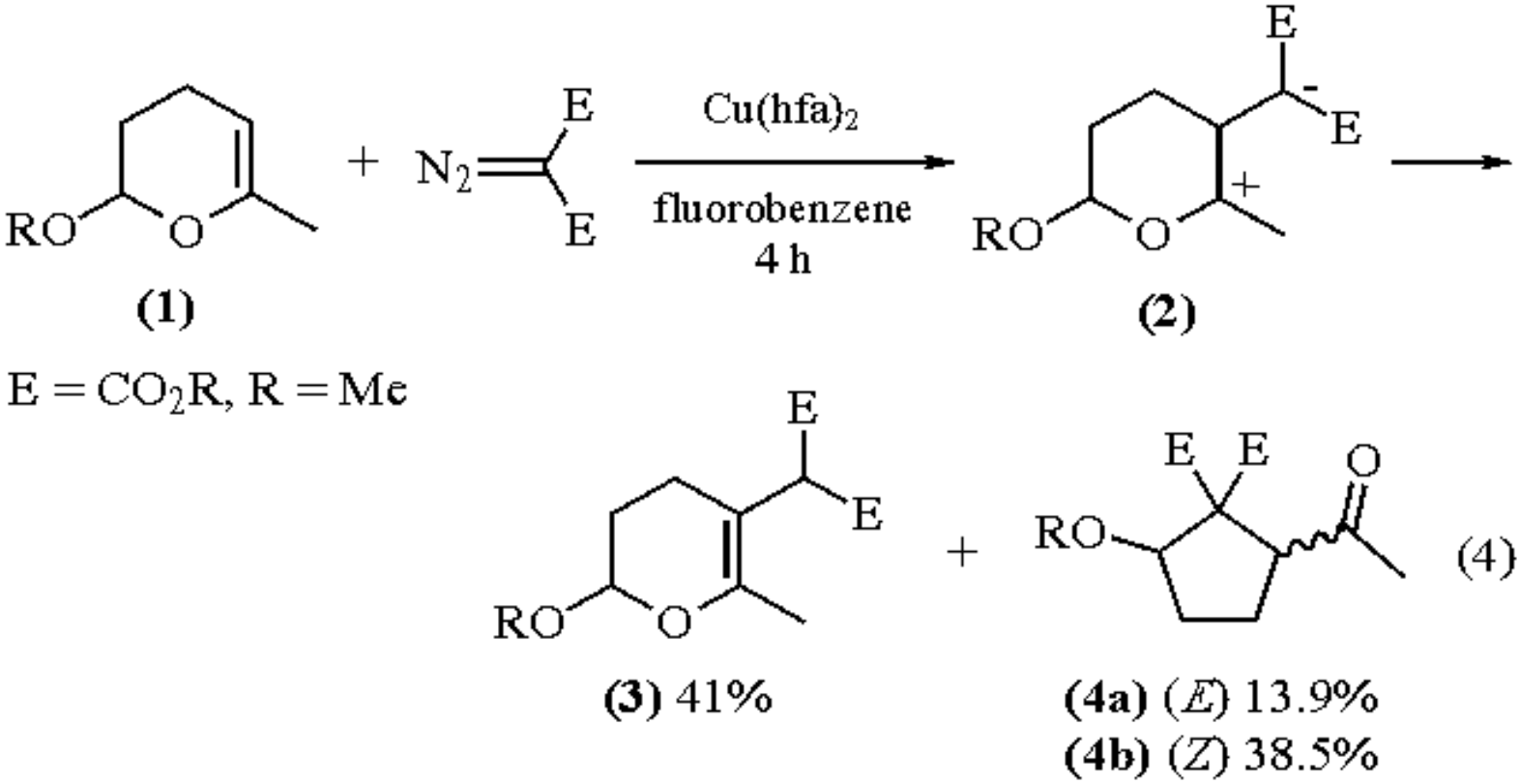

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Copper(II) Hydroxide

$Cu(OH)_2$

[20427-59-2] · CuH_2O_2 · Copper(II) Hydroxide · (MW 97.56)

(catalyst for the Ullmann condensation;[1] mediates conversion of acid hydrazides to carboxylic acids[2])

Physical Data: d 3.37 g cm^{-3}.

Solubility: sol acids, conc alkali, NH_4OH, and ethylenediamine; insol water.

Form Supplied in: blue to blue-green gel or light blue crystalline powder.

Handling, Storage, and Precautions: may decompose to Cu^{II} oxide at 60-80 °C, although the stability is dependent on the method of preparation. Hygroscopic.

Aryl Amine Synthesis.

Cu^{II} hydroxide catalyzes the Ullmann condensation reaction of 1-bromoanthraquinone or 1-amino-4-bromoanthraquinone with a large excess of ethylenediamine (eq 1).[1] The hydroxo-bridged Cu^{I}-Cu^{II} mixed valence complex formed by the reduction of Cu^{II} hydroxide has been proposed as an active species. ***Copper(II) Chloride*** and ***Copper(II) Bromide*** are ineffective. The combination catalyst of ***Copper(I) Chloride***/$Cu(OH)_2$ (2:1) shows a higher activity in the reaction of 1-amino-4-bromoanthraquinone than with $CuCl_2$ alone, but still lower than with $Cu(OH)_2$ alone.

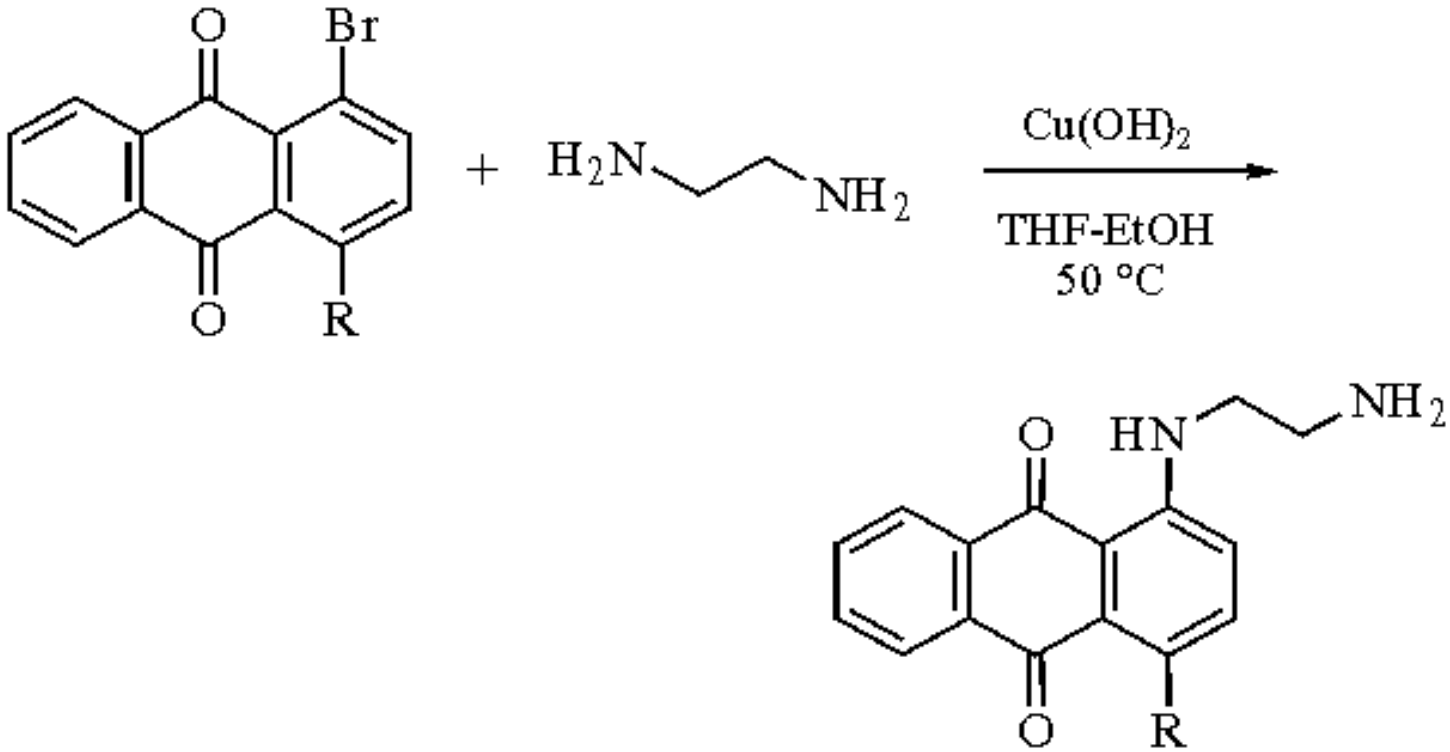

(1)

R = H, 62%; R = NH_2, 53%

Conversion of Acid Hydrazides to Carboxylic Acids.

A stoichiometric amount of Cu^{II} hydroxide, prepared in situ from $CuCl_2$ and ***Potassium Hydroxide***, effects conversion of acid hydrazides to carboxylic acids at room temperature (eq 2).[2] Under similar reaction conditions, $Cu(OAc)_2.H_2O$ and $CuCO_3$ react slowly and $CuCl_2$, $Cu(NO_3)_2$, $CuSO_4$, and CuO are ineffective. $Cu(OAc)_2.H_2O$ and $CuCO_3$ are effective at 70 °C. In the presence of oxygen, ***Copper(II) Acetate*** acts as a catalyst at room temperature to afford carboxylic acids in excellent yields. An acyl cation intermediate generated by the oxidation of acid hydrazides with Cu^{II} hydroxide has been proposed. The copper-promoted conversion of acid hydrazides to carboxylic acids may provide a convenient method of protecting carboxylic acids bearing labile functional groups.

$$RCONHNH_2 + 4\,Cu(OH)_2 \xrightarrow{\text{THF, rt}} RCO_2H + N_2 + 3\,H_2O + 4\,CuOH \quad (2)$$

R = C_7H_{15}, 90%; R = Ph, 92%

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Copper(I) Iodide[1]

CuI

[7681-65-4] · CuI · Copper(I) Iodide · (MW 190.45) (.PBu_3)

[21591-31-1] · $C_{12}H_{27}CuIP$ · Copper(I) Iodide-Tributylphosphine · (MW 392.81) (.$(SBu_2)_2$)

[35907-81-4] · $C_{16}H_{36}CuIS_2$ · Copper(I) Iodide-Bis(dibutyl sulfide) · (MW 483.11)

(the classical precursor for organocopper(I) and organocuprate reagents[1])

Alternate Name: cuprous iodide.

Physical Data: mp 605 °C; *d* 5.620 g cm^{-3}.

Solubility: insol H_2O and most organic solvents; partially sol dimethyl sulfide (DMS).

Form Supplied in: off-white to grayish solid; 99.999% grade available.

Handling, Storage, and Precautions: maintenance of a dry N_2 or Ar atmosphere is recommended.

General Discussion.

The first organocopper compound to be isolated, ***Phenylcopper***, was prepared in 1923 by Rene Reich from ***Phenylmagnesium Bromide*** and CuI.[2] In 1936, Gilman repeated the preparation of PhCu from CuI,[3a] and in 1952 he prepared ***Methylcopper*** and ***Lithium Dimethylcuprate*** from CuI and 1 and 2 equiv of ***Methyllithium***, respectively.[3b] An improved preparation of halide-free MeCu and Me_2CuLi from CuI has recently been reported,[4] and an appreciation of the role of the lithium salt from the preparation in the structure and reactivity of the reagent has developed in recent years.[5-10] Therefore it has been proposed that any salt from the metathesis reaction used to prepare the organocopper reagent should be explicitly shown in the formula, e.g. $Ph_2CuLi.LiI$,[5] PhCu/LiI,[6] $Bu_2CuLi.LiBr$,[7] $Bu_2CuNa.NaCN$,[8a] etc. Unfortunately, many of the tables in the latest *Organic Reactions* chapter on organocopper reagents do not list the Cu^I salt from which the reagents were prepared.[1a]

Interest in organocopper reagents was rekindled in 1966 when House and Whitesides[9] showed that organocuprates were intermediates in what we propose to call the Kharasch reaction, the Cu-catalyzed 1,4-addition of Grignard reagents to enones.[11] They also reported the development of two organocopper reagents which have the stoichiometry

$Li^+Me_2Cu^-$ and $MeCuP(n\text{-}Bu)_3$.[9] Both of these classes of reagents are important today (see below). Corey and Posner also used CuI to prepare $Me_2CuLi.LiI$[12] and $Bu_2CuLi.LiI$,[13] which were coupled with alkyl halides and iodobenzene. These initial reports of the synthetic value of organocopper reagents for selective C-C bond formation led to an explosion of applications,[1a-g] which like the big bang is still expanding today. The principal applications of organocopper reagents to C-C bond formation in the areas of conjugate addition to α,β-unsaturated carbonyl compounds, carbocupration of alkynes, and coupling reactions with oxiranes and alkyl, alkenyl, and aryl halides have been well reviewed.[1a -h] While CuI has been supplanted by CuBr.DMS (see ***Copper(I) Bromide***) and ***Copper(I) Cyanide*** for many purposes, it is still one of the main precursors that should be tried when optimizing an organocopper synthesis.[7]

In addition to the ate complexes prepared from 2 equiv of RLi, the organocopper(I) compounds RCu, prepared from 1 equiv of RLi and CuI, have found synthetic application in the presence of additives, which enhance the reactivity of these otherwise relatively unreactive compounds. Both Lewis bases and Lewis acids[1d] have been used for this purpose, and their utility has been extended to the organocuprates as well. Examples of the former are phosphines, such as ***Tri-n-butylphosphine***,[14] and sulfides, such as dibutyl sulfide[15] and ***Dimethyl Sulfide***;[6,16a] examples of the latter are ***Boron Trifluoride***[17,18] and ***Aluminum Chloride***.[17a,19] ***Chlorotrimethylsilane*** (TMSCl) is a useful additive,[20,21] especially in conjunction with HMPA.[6,22] In analogy with these major additives, triethylphosphine,[23a] triphenylphosphine,[23b,24] tricyclohexylphosphine,[24] dppe,[24,25] triethyl phosphite,[26] diisopropyl sulfide,[16b] triethylboron,[27] trimethylaluminum,[28] titanium tetrachloride,[17b,18a] TMSCl-DMAP,[22] TMSCl-TMEDA,[29] TMSI,[30,31] and TMSCN[31] have been used. One unique phosphine is polymer-supported $RPPh_2$,[32] where R is the polymer backbone.

The addition of BF_3 improves some of the usual organocopper reactions,[17] and it enables some unprecedented ones, e.g. the direct alkylation of allylic alcohols.[17c] It also favors 1,4- over 1,6-addition to methyl sorbate: 1,6-addition predominates with $Bu_2CuLi.LiI$,[17b] and also with BuMgBr/CuCl,[11a] but 1,4-addition is observed for $BuCu.BF_3$.[17b] One particularly interesting application of the BF_3 procedure is the conjugate addition of Cu^I aldimines to α,β-unsaturated carbonyl compounds (eq 1), which after hydrolysis gives 1,4-diketones.[18b]

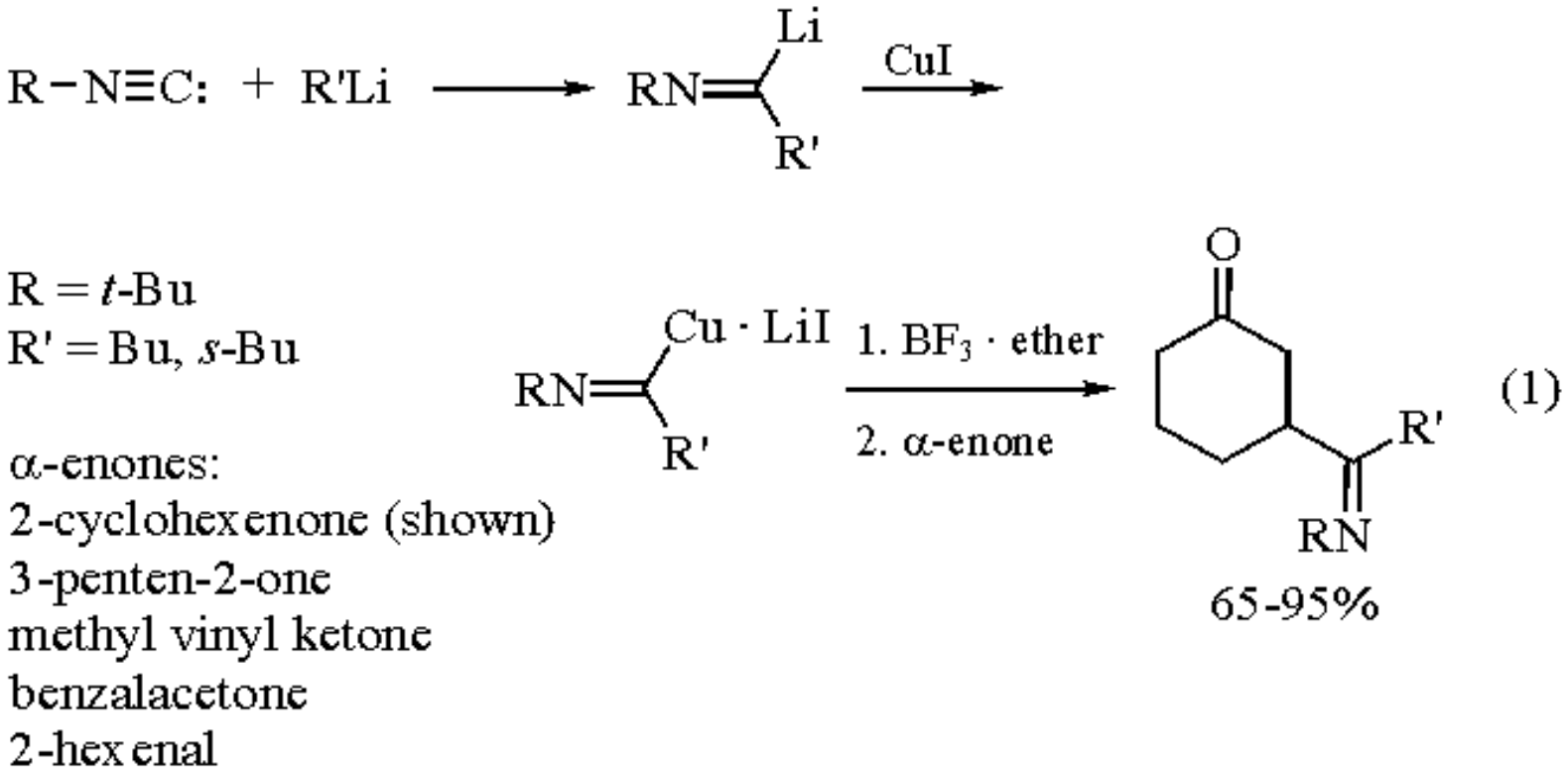

In some cases the additives improve solubility; in other cases, entirely new reagents result. For example, PhCu is insoluble in ether, but it is soluble in DMS, where it has been shown to be an equilibrium mixture of $(PhCu)_4$ and $(PhCu)_3$.[25] When prepared from CuBr or CuCN in DMS, the product is Li-free, due to the precipitation of LiBr or LiCN from DMS.[6] This Li-free PhCu is relatively unreactive compared to the reagent prepared from CuI, PhCu/LiI, which still contains the LiI.[6] This LiI may be considered an activating additive. The LiI present in $Me_2CuLi.LiI$ also has an important effect in conjugate addition reactions, as the percentage of 1,2-addition can be significant for halide-free organocuprates.[4]

The LiI in PhCu/LiI is not incorporated into the organocopper(I) clusters;[6] however, in the case of $Ph_2CuLi.LiI$, ^{13}C NMR shows that both I-containing (major) and I-free (minor) clusters are present.[5] House found that although the conjugate addition of lithium dimethylcuprate to α,β-unsaturated ketones appears to require no other species in the reaction solution, ***Trimethyl Phosphite*** and ***Tri-n-butylphosphine*** complexes of methylcopper will undergo conjugate addition only if various salts such as ***Lithium Iodide***, ***Lithium Bromide***, ***Magnesium Bromide***, or ***Lithium Cyanide*** are present in the reaction medium.[10]

Organocopper reagents are assuming an increasing role in asymmetric synthesis and many of the procedures involve complex mixtures containing one or more of the additives discussed above.[15,17a,18a,c] This area has been reviewed recently,[1b] so we highlight one especially interesting example here, the enantiocontrolled synthesis of quaternary carbon centers via the asymmetric conjugate addition of organometallic reagents to enantiomerically pure 2-(arylsulfinyl)cycloalkenones.[33] Posner has noted that although $Me_2CuLi.LiI$ and $Me_5Cu_3Li_2$ work well, $Me_2CuLi.LiCN$ and $MeCu.BF_3$ do not. He concludes that no one type of organocopper reagent will be universally preferred over others for all different kinds of carbon-carbon bond-forming reactions.[33]

Tandem β-addition-α-functionalization reactions are an important strategy for rapidly building molecular complexity.[1c] A particularly impressive example (eq 2) is the three component coupling used by Suzuki and Noyori to prepare

prostaglandins,[14c,d] which owes its success to the use of derivatives of House's $RCu(PBu_3)$.[9,10,14a,b] An interesting intramolecular version involving conjugate addition-cycloacylation of alkynic diesters to give highly functionalized cyclopentenones has been developed by Crimmins.[34] Tandem organocopper addition-electrophilic functionalization of alkynes is well established,[1a,f] and Meyers has even performed such a sequence on a benzyne.[35]

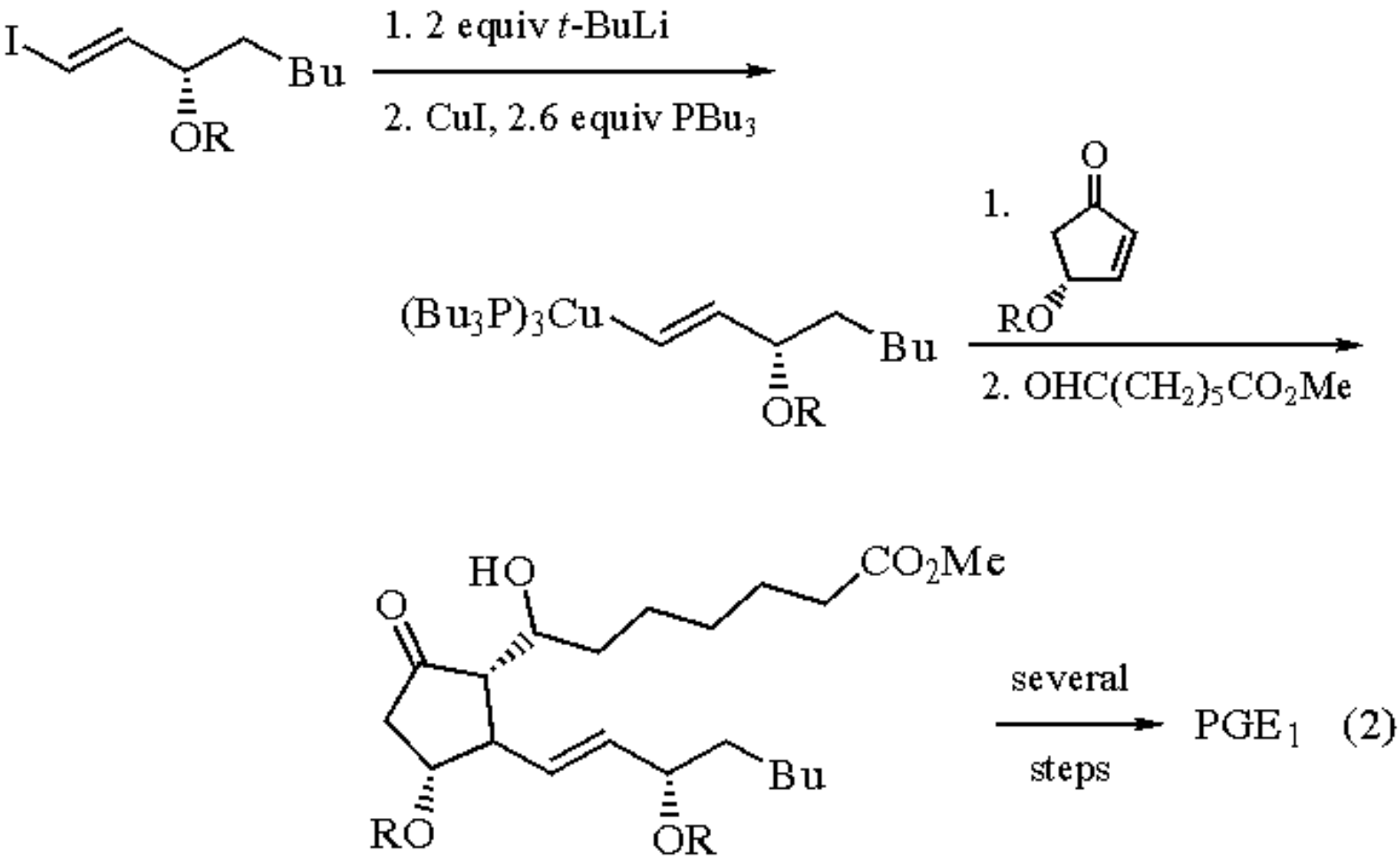

Useful applications of organocopper reagents to carbohydrate chemistry have been made by the Kocienski and Fraser-Reid groups. In the former case, an oxirane ring was opened regio- and stereoselectively.[36] In a contraintuitive finding, the latter group reported that the homogeneous system using the soluble $CuI.PBu_3$ complex was less satisfactory than the heterogeneous system based upon CuI for the conjugate addition-alkylation of hex-2-enopyrano-4-ulosides.[37]

Some exciting recent developments extending the scope of organocopper chemistry involve CuI. Rieke has reported the preparation of $RCu.PBu_3$ from a highly reactive copper intermediate prepared via the reduction of $CuI.PBu_3$.[23,38] Ebert has used a similar procedure to prepare remote ester and ketone functionalized organocopper reagents.[39]

Alkenes with perfluoroalkyl substituents have been prepared by the reaction of perfluoroalkyl iodides with terminal alkynes in the presence of ultrasonically dispersed ***Zinc*** and CuI.[40a] A general procedure for the formation of organocopper reagents from alkyl and aryl halides and ***Lithium*** metal in the presence of CuI or ***1-Pentynylcopper(I)*** under ultrasonic irradiation has also been described.[40b]

One of the extraordinary things about displacement reactions mediated by Cu^I is the fact that they occur with both facility at sp^3 and sp^2 centers, as eqs 3 and 4 illustrate. Eq 3 involves a classic S_N2-like reaction, but is noteworthy

because of the complexity of the other functionality in the substrate, an α-amino acid derivative.[15a] Eq 4, the alkylation of alkenyl triflates,[41] adds a versatile alternative to the alkylation of alkenyl halides.[1a,g]

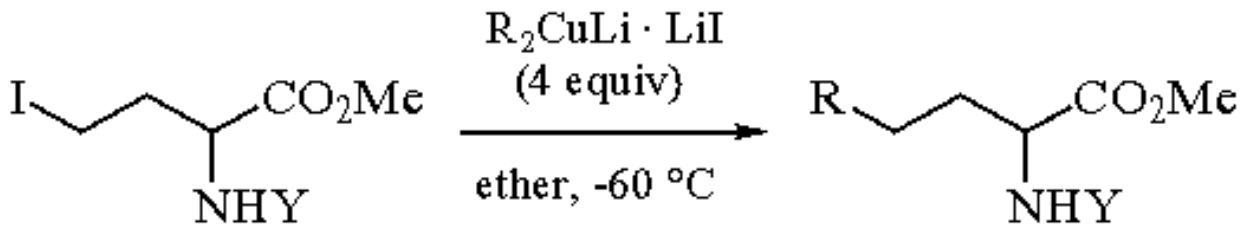

(3)

Y =		Bz	Z	Boc
R =	Me	52	65	82
	Et	70	82	87
	Pr	75	84	87
	Bu	74	85	90
	vinyl	69	-	79
	allyl	61	-	-
	Ph	60	-	81

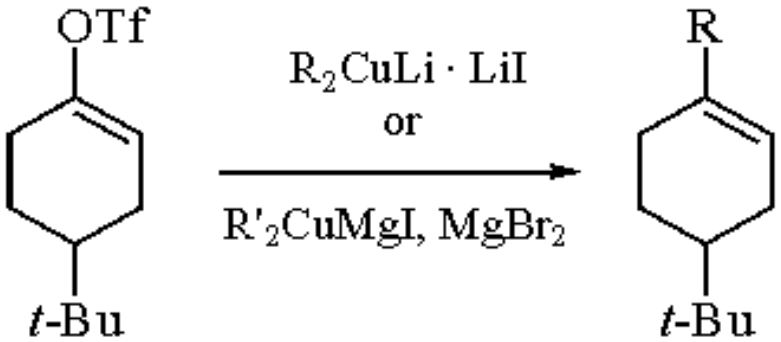

R =	Me	75%
	Bu	100%
	Ph	75%
R' =	vinyl	62%
	cyclopropyl	86%
other substrates		

(4)

Good reviews are available of stoichiometric cuprates prepared from lithium reagents,[1a] stoichiometric cuprates prepared from Grignard reagents,[1a] and the use of Grignard reagents with catalytic amounts of Cu^I salts.[1a,e] Sadly, direct comparisons have not been made among all the variations. When one adds further variables such as which Cu^I salt is used, what halide is present in the Grignard reagent, and whether the stoichiometry is 2:1 or 1:1, it is easy to see that the choice of conditions is a complex problem, even before all the possible additives are considered. The best advice we can give the synthetic chemist is to try several sets of conditions based upon similar examples in the literature. Fortunately, an exhaustive compilation has been published recently.[1a]

A species of intermediate stoichiometry between organocopper(I) and organocuprate(I) (RCu and R_2CuLi, respectively) has been described as $Me_5Cu_3Li_2$ = MeCu + $(Me_2CuLi)_2$. While the structure of the reagent has yet to be determined, it has proved to be useful for the conjugate addition of Me to α,β-unsaturated aldehydes.[42]

In recent work that is related to the organocuprate chemistry discussed above, Miura et al. have reported the CuI-catalyzed reaction of aryl and vinyl iodides with terminal alkynes,[43a] and of aryl iodides with active methylene compounds.[43b]

Finally, not all applications of CuI involve organocuprates or related reagents. For example, Corey used CuI to catalyze intramolecular diazoalkene cyclization reactions,[44] and Yates used CuI to catalyze the Wolff rearrangement of diazo ketones.[45] House recommended $CuI.(SBu_2)_2$ for the intermolecular cyclopropanation of alkenes with α-diazo ketones. The intermediates are undoubtedly organocopper species of some kind, perhaps Cu-carbene complexes; however, it should be noted that Cu^0 and Cu^{II} are more commonly used as catalysts in conjunction with diazo compounds.[1i]

Related Reagents.

See the copper(I) iodide combination reagents following this entry; also ***Copper(I) Bromide*** and ***Copper(I) Chloride*** (and their combination reagents), ***Copper(I) Cyanide***, and ***Copper(I) Trifluoromethanesulfonate***.

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Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride[1]

$LiCuHI.Al(OCH_3)_3$

[7681-65-4] · CuI · Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride · (MW 190.45)

[12076-93-6] · $C_3H_{10}AlLiO_3$ · Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride · (MW 128.05)

(in situ prepared hydridocopper reagent; reductive removal of halogen or mesyloxy groups; reduction of epoxides to alcohols[2])

Preparative Method: [2] an anhydrous THF solution of lithium trimethoxyaluminum hydride (2.0 mmol) is added dropwise to an ice-cold suspension of ***Copper(I) Iodide*** (dried at 100 °C in vacuo prior to use; 1 mmol) in THF under an inert atmosphere. After 30 min, the resulting brown mixture is treated with substrate (1 mmol). The cooling bath is removed after 15 min and the mixture is stirred vigorously for 2 h at room temperature. Additional THF may be added to effect efficient stirring. The reaction mixture is quenched with methanol, diluted with ether, and filtered through Celite. This filtrate is washed with saturated aqueous ammonium chloride and dried.

Handling, Storage, and Precautions: use in a fume hood.

General Discussion.

This reagent was first reported for the reductive removal of primary, secondary, tertiary, allyl, vinyl, aryl, and neopentyl bromides. In all cases the halide was removed in excellent yield (85-100%) (Table 1). Simple primary and secondary mesylates and cyclohexene oxide were reductively cleaved by the conditions stated. However, the use of additional reagent and a longer reaction time (15 h) was required for the reduction of 1-chlorooctane to *n*-octane (96% yield).[2] This reagent was used to prepare allocyathin B_3 methyl acetal from a vinyl bromide (eq 1)[4] and (+)-cyclohex-2-en-1-ol from its corresponding vinyl iodide (**1**).[5] The reduction of either *exo*- or *endo*-2-bromonorbornane with CuD (prepared from $LiAlD(OMe)_3$ and CuI) proceeds with 100% retention, whereas the corresponding mesylates are reduced with complete inversion of stereochemistry.[2] This retention of stereochemistry is also observed for an adamantane ring system.[6]

Table 1 Reductions Using Copper(I) Iodide Lithium Trimethoxyaluminum Hydride

Substrate	Product	Yield (%)
1-Bromooctane	*n*-Octane	98
2-Bromononane	*n*-Nonane	100
1-Bromocyclooctene	Cyclooctene	99
1-Bromonaphthalene	Naphthalene	100
1-Octanol mesylate	*n*-Octane	95
Cyclohexene oxide	Cyclohexanol	100

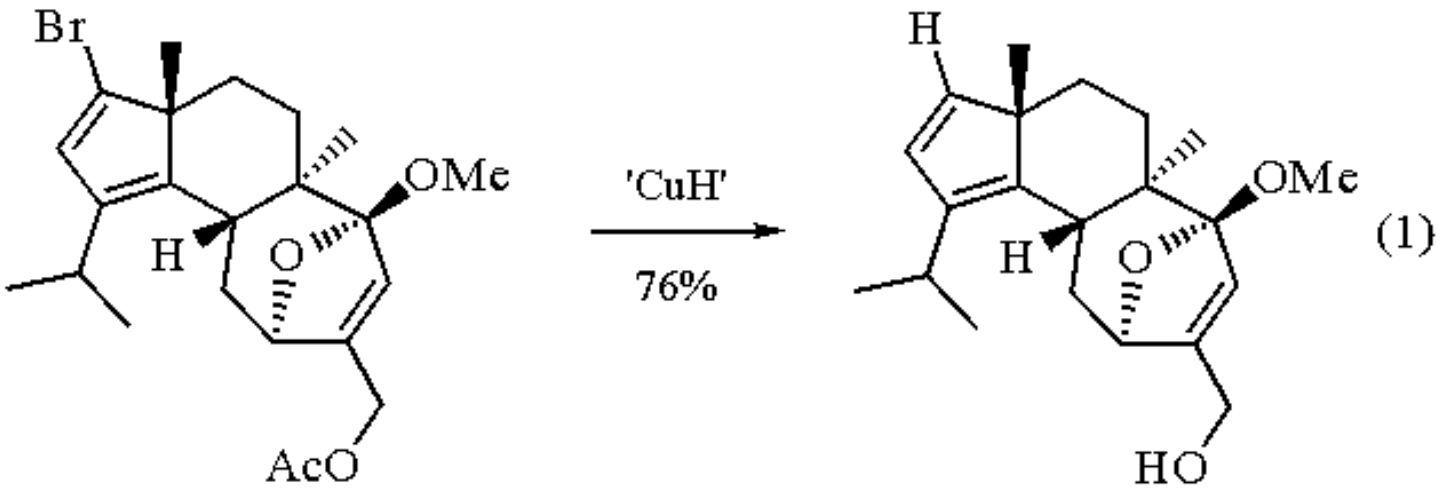

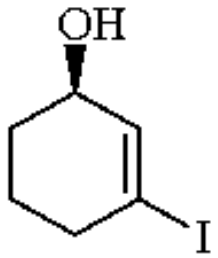

(1)

Limitations.

There are examples where mesylate reductions have produced only recovered starting material (e.g. **2** and **3**),[7,8] a mixture of reduced product and the corresponding alkene,[9] or alcohols from O-S cleavage (e.g. **4**).[10]

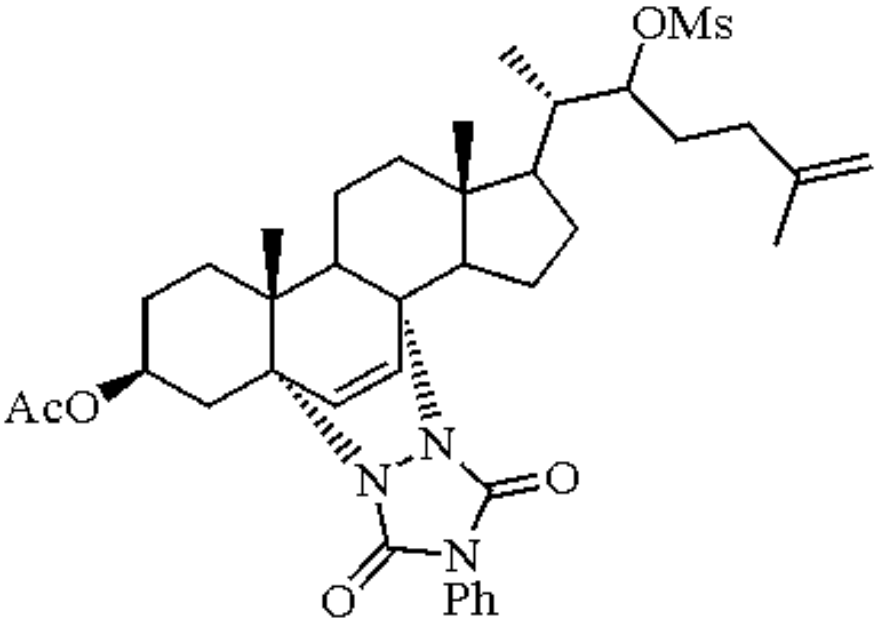

(2)

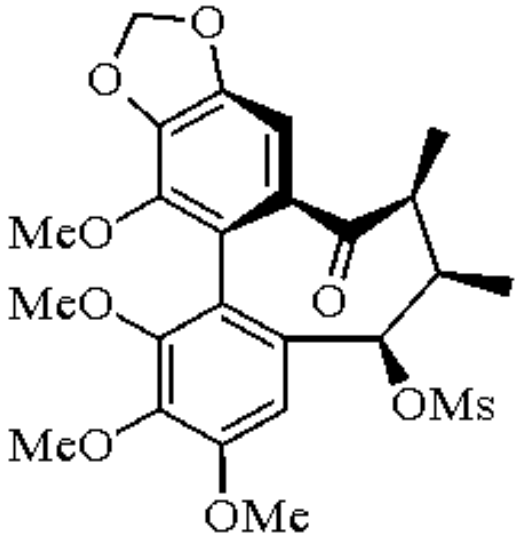

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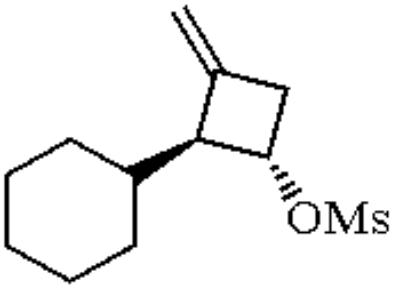

(4)

Alternative Methods.

Potassium Tri-s-butylborohydride has been used as the hydride source.[3] The reductive removal of halogen, hydroxy, or mesyloxy groups can be accomplished by a number of different methods, such as hydrogenolysis,[11] $TiCl_3$.3THF-Mg,[12] Bu_3SnH-thiocarbonate,[13,14] NaI-Zn,[15] trialkylSiH-$AlCl_3$,[16] $LiAlH_4$-transition metal,[17-19] $LiEt_3BH$,[20,21] $NaBH_4$,[22] $NaBH_4$-Ni^0, [23] and *i*-PrMgBr-titanocene dichloride.[24] See also ***Lithium n-Butyl(hydrido)cuprate*** and ***Lithium Tri-t-butoxyaluminum Hydride***. Other hydridocopper reagents include ***Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride*** and ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***.

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Copper(I) Iodide-Potassium Naphthalenide[1]

$CuI.K(C_{10}H_8)$

[7681-65-4] · CuI · Copper(I) Iodide-Potassium Naphthalenide · (MW 190.45)

[4216-48-2] · $C_{10}H_8K$ · Copper(I) Iodide-Potassium Naphthalenide · (MW 167.27)

(used to prepare a zerovalent copper species which is particularly effective in promoting the Ullmann condensation, in the production of organocopper compounds, and in cross-coupling of aryl and allylic halides)

Solubility: copper species generated in dimethoxyethane under Ar.

Preparative Methods: by the reduction of ***Copper(I) Iodide*** with a stoichiometric concentration of ***Potassium*** and ca. 10% naphthalene in DME under Ar, resulting in a gray-black granular solid.

Handling, Storage, and Precautions: the reagent is generated in situ in an inert atmosphere as needed; reactions are usually carried out under argon; use in a fume hood.

Reactions of Organocopper Reagents.

The reagent reacts with pentafluorophenyl iodide in DME to yield a solid, presumed to be pentafluorophenylcopper, which subsequently produces decafluorobiphenyl either thermally or by oxidation (eq 1).[1] Alternatively, aryl-alkyl coupling (eq 2) can also be effected.[1]

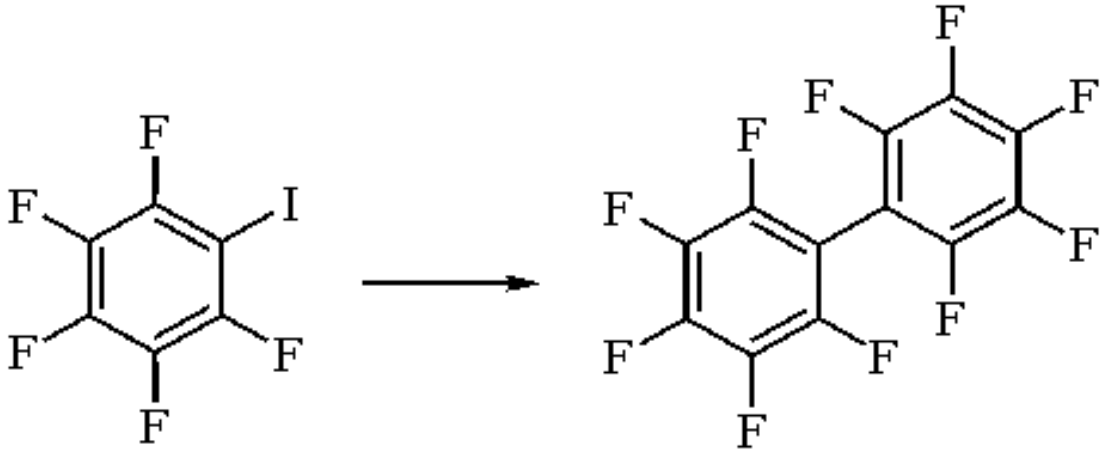

(1)

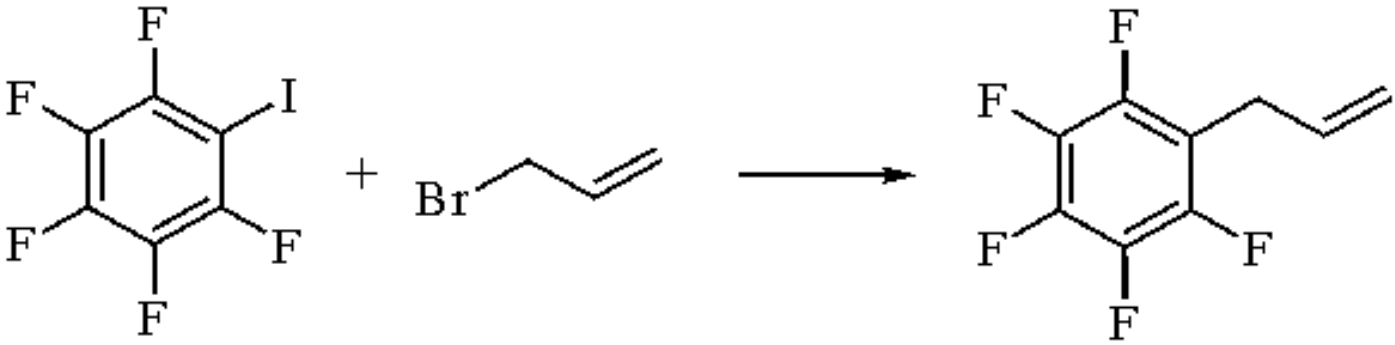

(2)

Aside from this early report, the number of instances in which this method has been used successfully for the purposes intended is limited. Thus, while the substituted biaryl was formed in over 50% yield in the presence of CuI.K($C_{10}H_8$) (eq 3),[2] the corresponding reaction at nitrogen (eq 4) failed.[3] Coupling at nitrogen has, however, been reported to be successful in a different system (eq 5).[4]

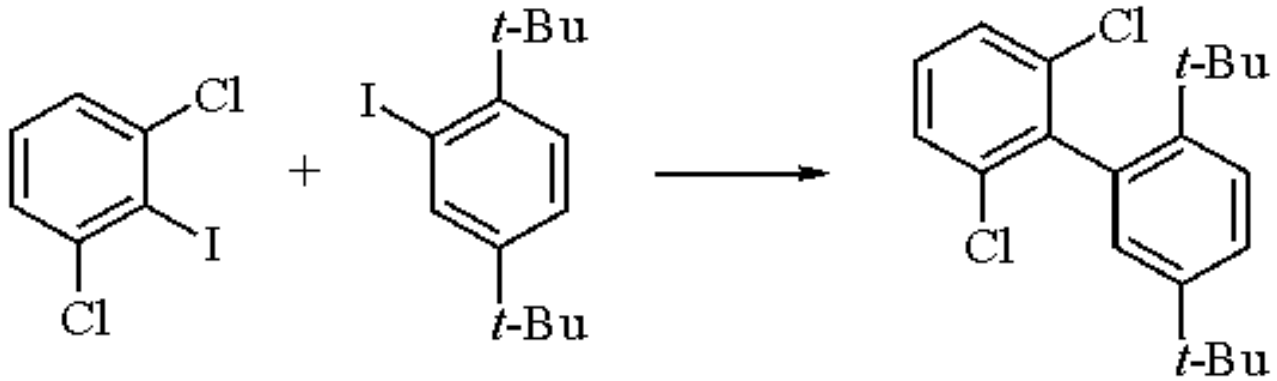

(3)

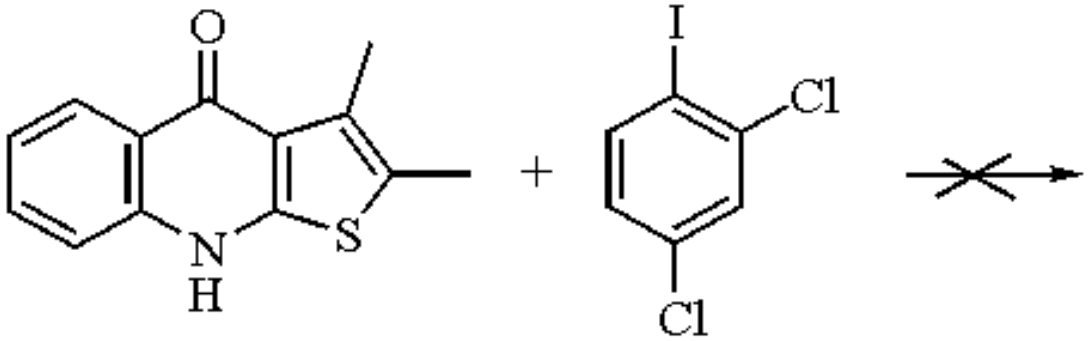

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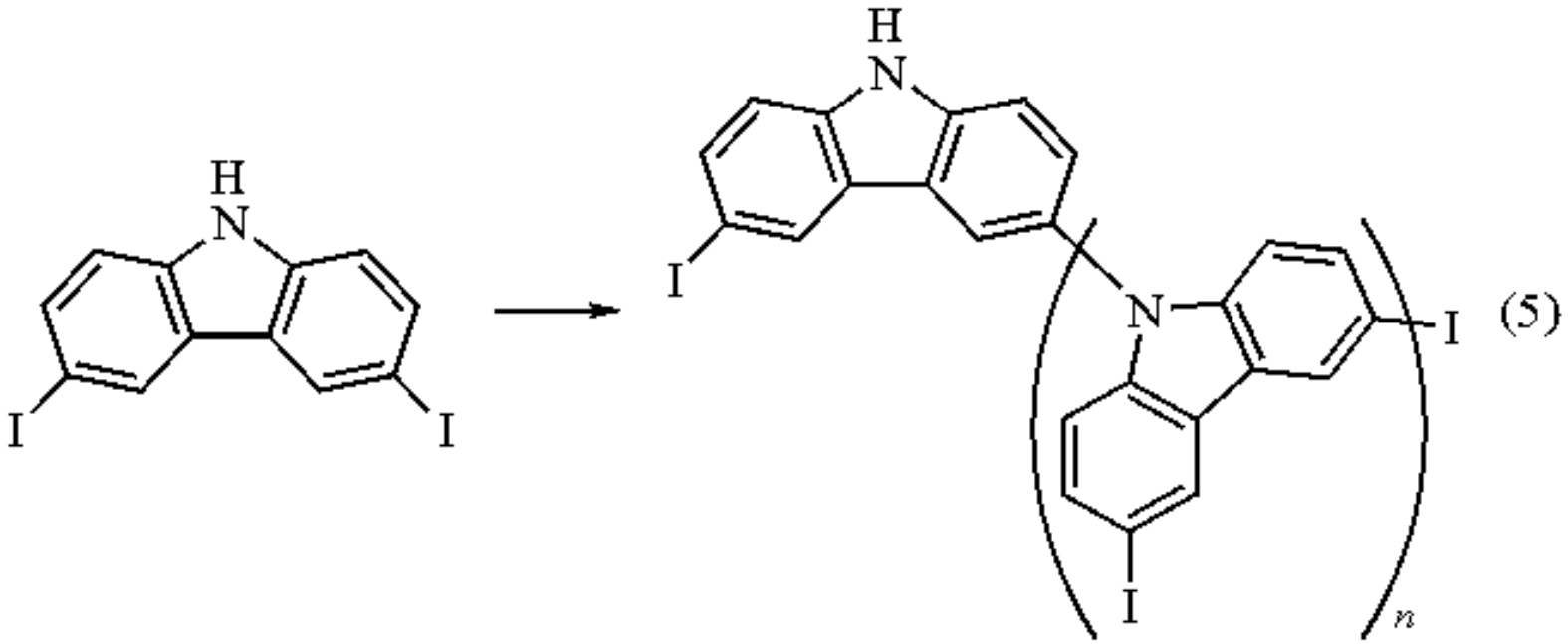

Finally, there are suggestions that the procedure described to produce active copper from CuI.K($C_{10}H_8$) may prove useful in the preparation of cluster compounds[5] and in coupling reactions in metallocenes.[6]

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Copper(I) Iodide-Tributylphosphine[1]

$[CuI\{(n\text{-}Bu)_3P\}]_4$

[28132-72-1] · $C_{48}H_{108}Cu_4I_4P_4$ · Copper(I) Iodide-Tributylphosphine · (MW 1571.08)

(promoter for conjugate addition of alkyl (vinyl, etc.) lithium reagents to α,β-unsaturated ketones and related compounds; preformed copper-phosphorus compound (occasionally generated in situ) to stabilize and solubilize organocoppers whose conjugate addition is facilitated by the use of a phosphorus auxiliary;[1] also used to effect oxidative coupling[2])

Alternate Name: tetrakis[iodo(tri-*n*-butylphosphine)copper(I)].

Physical Data: mp 75 °C; *d* (at 78 °C) 1.390 g cm^{-3}; decomposition to CuI and tributylphosphine at 200-210 °C/0.01 mmHg.

Solubility: sol chloroform, benzene, toluene, and ethyl ether; moderately sol ethanol, 2-propanol, and water.

Preparative Methods: generated in situ or prepared either via the reaction of ***Copper(I) Iodide*** with freshly distilled ***Tri-n-butylphosphine***[3a] or with copper(I) iodide dissolved in saturated aqueous ***Potassium Iodide*** and stirred with tri-*n*-butylphosphine.[3b]

Purification: may be recrystallized from ethanol-2-propanol and air dried.[3]

Analysis of Reagent Purity: decomposed by heating with Na_2CO_3 and residue treated with HNO_3; dissolved in water, sulfuric acid added, and Cu determined by electrolytic reduction;[3] ^1H NMR spectra[4] and electronic absorption and emission spectra have been studied.[5]

Handling, Storage, and Precautions: toxicity data unavailable. Unless refrigerated it decomposes in several days at rt to a viscous syrup;[3] use in a fume hood.

Conjugate Addition.

Early in the study of the reactions of organometallic reagents with α,β-unsaturated ketones it became clear that the reaction of organomagnesium compounds could be diverted from the normal path of 1,2-addition to favor the abnormal path of 1,4-addition by the presence of a small amount of a copper compound.[6,7] Thus *trans*-3-penten-2-one

in ether (in a flowing stream reactor) gave, in >99% conversion, <1% conjugate addition on reaction with ***Methyllithium*** to yield 2-methyl-3-hexen-2-ol. However, under the same conditions, when an organocopper reagent was preformed by adding 1 mole of *n*-Bu_3PCuI to 1 mole of MeLi, again in >99% conversion, there was >99% conjugate addition in the product to form 4-methyl-2-pentanone (eq 1).[7]

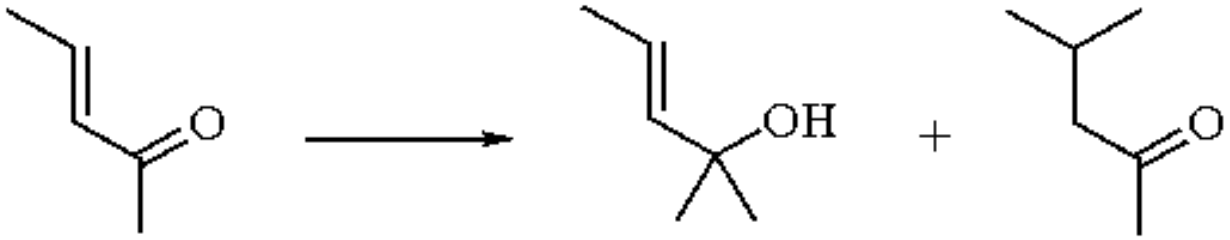

(1)

In a continuation of this work[8] the tri-*n*-butylphosphine complex of copper(I) iodide and ***Lithium Dimethylcuprate*** were compared to the corresponding trimethyl phosphite complex (see ***Copper(I) Iodide-Trimethyl Phosphite***) in the addition reactions to 5-methyl-2-cyclohexenone (eq 2), 3-methyl-2-cyclohexenone (eq 3), and 5,5-dimethyl-2-cyclohexenone (eq 4).

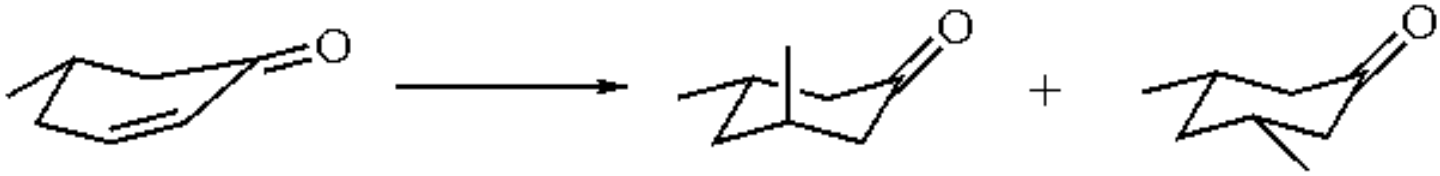

(2)

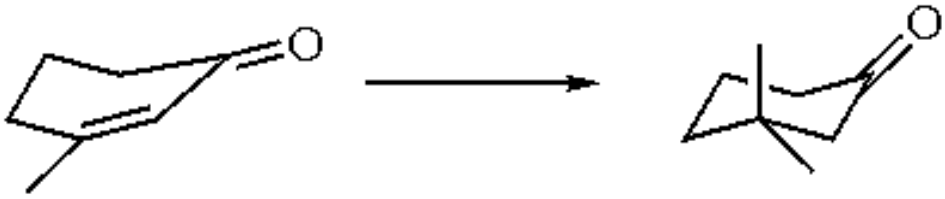

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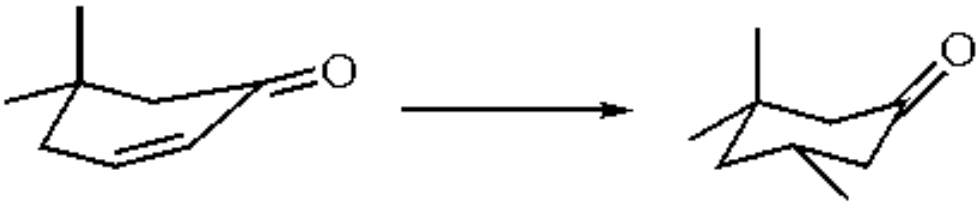

(4)

For the first case (eq 2), both reagents gave predominately *trans* product (*trans*:*cis* = 98:2), but the reaction with the tri-*n*-butylphosphine complex produced a 34% yield of products while the trimethyl phosphite complex yielded product in 73-87% yield (as a function of the amount of ***Lithium Iodide*** added or of tertiary phosphine ligand present).[9] In both the second and third cases (eqs 3 and 4) the two complexes gave approximately the same yields.[8] Shortly thereafter, conjugate addition of the corresponding vinyl reagent to yield γ,δ-unsaturated ketones was reported.[10]

Conjugate addition reactions of both lithium[11-15] and magnesium[16] alkyls to substituted[11-14] and unsubstituted[15,16] cyclopentenones followed by aldol type condensations[11,14] or alkylations[15,16] (if α-substitution was not present initially) have served as entries into prostaglandin synthesis. Additionally, the same process has served as a key step

in the syntheses of terpenes,[17] carbohydrates,[18] pyridine derivatives,[19] *N*-enoylsultams (producing β-silylcarboxyl derivatives[20] or alkyl substituted derivatives with good stereoface differentiation),[21] macrolides,[22] acetals,[23] and silyl enol ethers.[24]

Oxidative Coupling.

It was early reported[2] that the dialkylcuprate (e.g. ***Lithium Di-n-butylcuprate***) prepared by reaction of one equivalent of tetrakis[iodo(tri-*n*-butylphosphine)copper] in THF at -78 °C with ***n-Butyllithium*** on oxygenation produced ca. 84% octane. Subsequently, vinyl,[25-28] aryl,[29,30] and other alkyl[31,32] couplings have been effected, some with polymer supported cuprate[33] and one to a thioester to facilitate an otherwise difficult Grignard reaction.[34] Alkyl coupling to phosphorus in cyclophosphazines $(NPX_2)_{3\&b;or\&b;4}$ (X = Cl, F) can also be brought about in the presence of the title reagent.[35]

Rearrangements and Unusual Reactions.

Regioselective ring opening of β-propiolactones to yield β-substituted propanoic acids has been observed,[36] as has an unusually gentle cyclization of an azetidinone derivative to a penem (eq 5).[37] In the presence of a strained carbocycle the reagent has been found to behave much like a Lewis acid, yielding rearranged alkene (eq 6).[38]

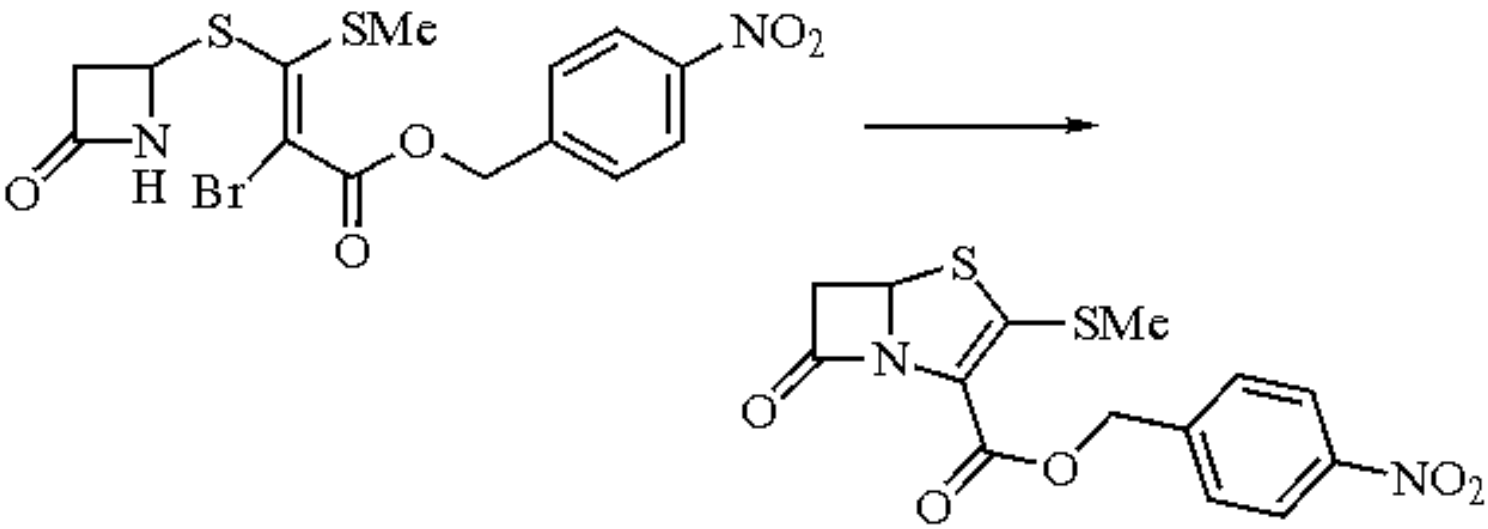

(5)

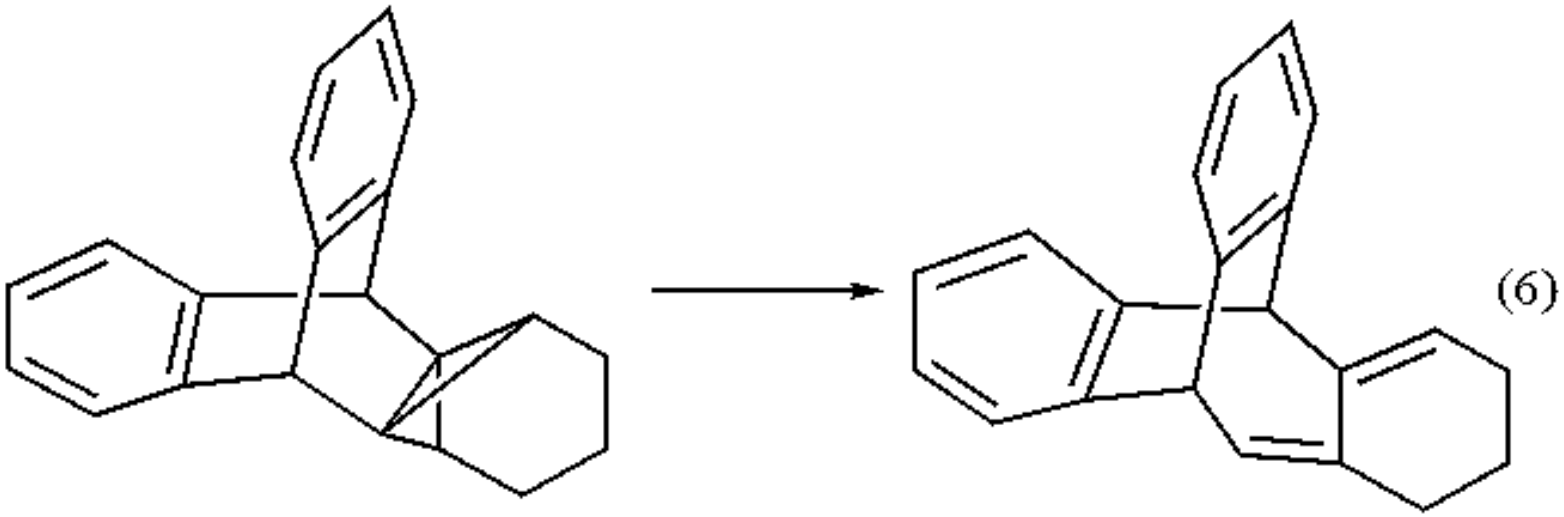

Other Transformations and Limitations.

Organosamarium species have been generated by in situ transmetalation with the reagent.[39] It is claimed that solutions of highly reactive zerovalent copper, useful for oxidative addition to alkyl, vinyl, and aryl halides, are easily prepared by ***Lithium Naphthalenide*** reduction of the title reagent and similar species.[40] Superior results in prostaglandin synthesis have recently been obtained by substituting higher order cuprates.[41] Unlike other organometallic reagents, tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] fails to react with arenesulfonyl fluorides to produce sulfones.[42]

Related Reagents.

Copper(I) Iodide-Tributyl Phosphite; ***Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide***; ***Copper(I) Iodide-Triethyl Phosphite***; ***Copper(I) Iodide-Trimethyl Phosphite***; ***Lithium Diethylcuprate-Tributylphosphine***.

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Copper(I) Iodide-Tributyl Phosphite

$CuI[(n\text{-}BuO)_3P]$

(CuI)

[7681-65-4] · CuI · Copper(I) Iodide-Tributyl Phosphite · (MW 190.45) ($P(OBu)_3$)

[102-85-2] · $C_{12}H_{27}O_3P$ · Copper(I) Iodide-Tributyl Phosphite · (MW 250.36)

(seldom used promoter of conjugate addition of alkyllithium reagents to α,β-unsaturated ketones)

Solubility: sol ether and THF.

Form Supplied in: reported to be generated in situ; not isolated in either case where use is reported; not commercially available.

Conjugate Addition.

A comparison of the ***Lithium Dimethylcuprate*** addition reaction to 5-methyl-2-cyclohexenone in the presence of copper(I) iodide-tributyl phosphite, ***Copper(I) Iodide-Trimethyl Phosphite***, and ***Copper(I) Iodide-Tributylphosphine*** complexes, respectively, has been reported (eq 1).[1] For the particular case in which the copper(I) iodide-tributyl phosphite was used, the reagent was generated in situ, the ratio of products in the mixture was not determined (although the overall yield was reported as 88%), and the authors point out that the trimethyl phosphite ester has proved to be a more satisfactory complexing agent … because of its volatility and partial water solubility.[1] In the only other report,[2] an *n*-butylcopper complex was added to 2-cyclopentenone, again in the presence of a variety of phosphine and phosphite complexing agents; in this case, miniscule yields of adduct were obtained when copper(I) iodide-tributyl phosphite was used.

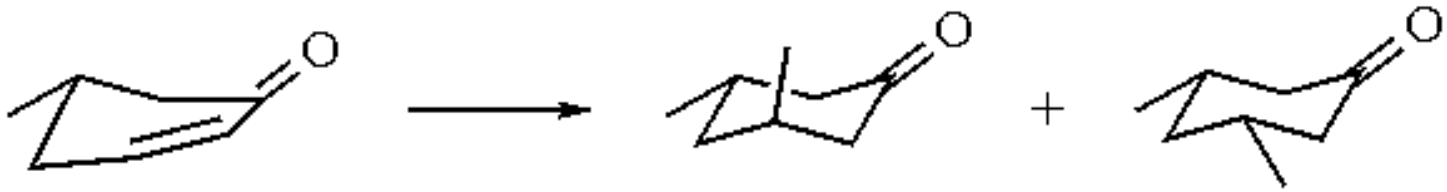

(1)

Related Reagents.

Copper(I) Iodide-Tributylphosphine; ***Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide***; ***Copper(I) Iodide-Triethyl Phosphite***; ***Copper(I) Iodide-Trimethyl Phosphite***; ***Lithium Diethylcuprate-Tributylphosphine***.

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Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide[1]

$CuI.Et_3P.Li(C_{10}H_8)$

(LiNaph)

[7308-67-0] · $C_{10}H_8Li$ · Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide · (MW 135.12) ($CuI.PEt_3$)

[56667-47-1] · $C_6H_{15}CuIP$ · Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide · (MW 308.63)

(a zerovalent copper species which adds to organic halides to produce organocopper compounds; used to cross-couple aryl, alkynyl, and vinyl halides with acid chlorides and reactive alkyl halides; to effect conjugate additions to α,β-unsaturated ketones; to promote intramolecular cyclization with epoxide cleavage or of α,o-dihaloalkanes; to remotely functionalize esters)

Solubility: copper species generated in THF, dioxane, glyme, etc.

Form Supplied in: not commercially available; generated in situ.[2]

Analysis of Reagent Purity: not reported; reactions usually carried out under argon or dry nitrogen.

Handling, Storage, and Precautions: the reagent is generated in an inert atmosphere as needed.

Reactions of Organocopper Reagents.

It is suggested that treatment of ***Lithium Naphthalenide*** in THF or glyme under an argon atmosphere with the copper(I) iodide-triethylphosphine complex in THF (or glyme) produces a highly reactive form of zerovalent copper which is subsequently allowed to react with allyl, aryl, and alkyl halides (in the same solvent) to yield homocoupled products (eq 1).[2] Alternatively, if two alkyl, aryl, etc. halides are mixed prior to addition to the active copper species, cross-coupling occurs (eq 2).[2] A variety of functional groups (e.g. cyano, nitro) is tolerated during the coupling.[2]

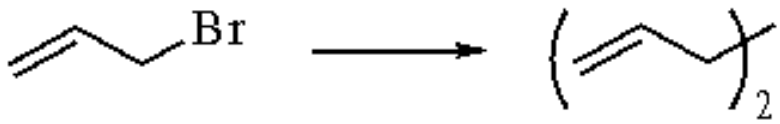

(1)

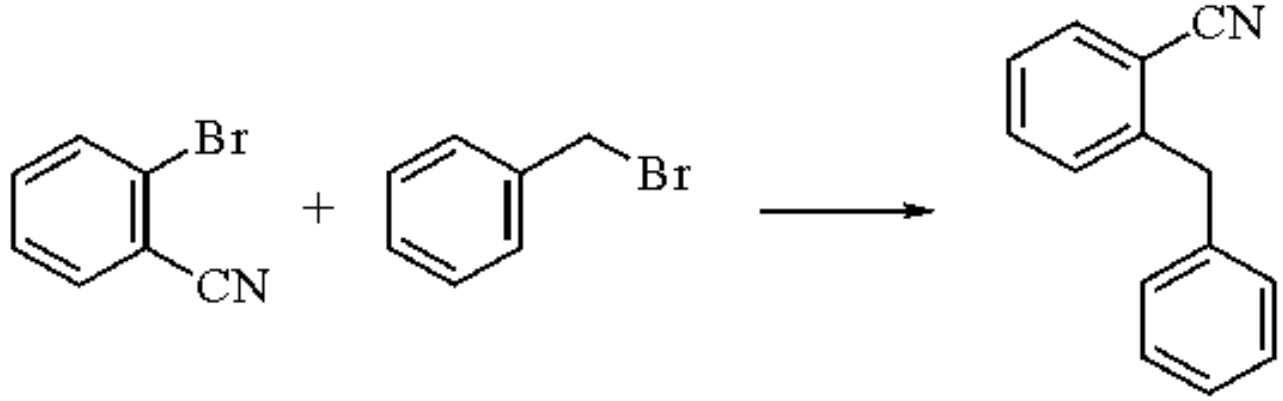

(2)

The conjugate addition to 2-cyclohexenone of a variety of alkyl halides, some bearing additional functionality, has also been effected in the presence of $CuI.Et_3P.Li(C_{10}H_8)$ (eq 3).[1]

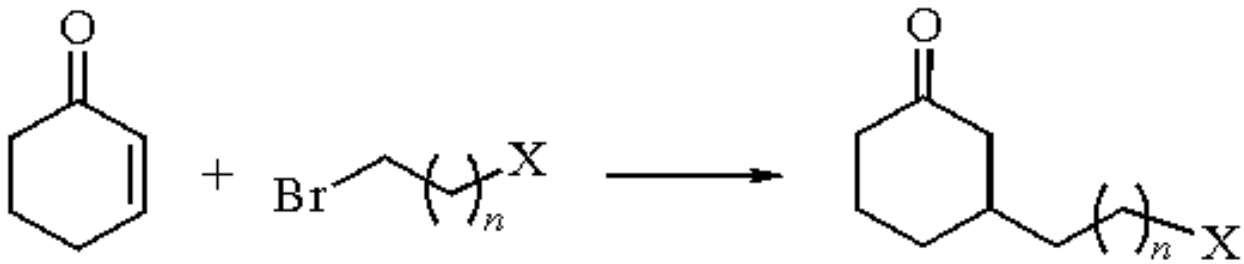

(3)

n	X	Yield (%)
6	Me	94
2	CO_2Et	90
2	CN	71
5	Cl	51

Additionally, a number of epoxides (terminal and otherwise) have been opened both intermolecularly and intramolecularly in the presence of $CuI.Et_3P.Li(C_{10}H_8)$ (eq 4). The solvent has been shown to play an important role in determining whether an *exo-tet* or *endo-tet* process occurs.[1,3] Thus for the products shown in eq (4), the ratio of cyclopentylmethanol to cyclohexanol is 1:6 in THF but 1:0 in toluene![1]

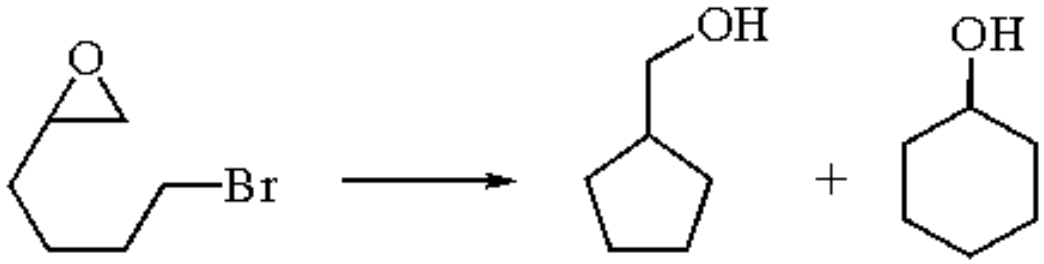

(4)

In the presence of $CuI.Et_3P.Li(C_{10}H_8)$, dihalides have been induced to undergo intramolecular cyclization (eq 5)[4] and

esters have been functionalized at remote positions (eq 6).[5]

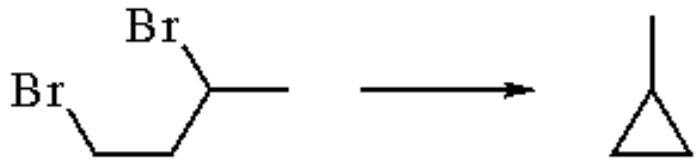

(5)

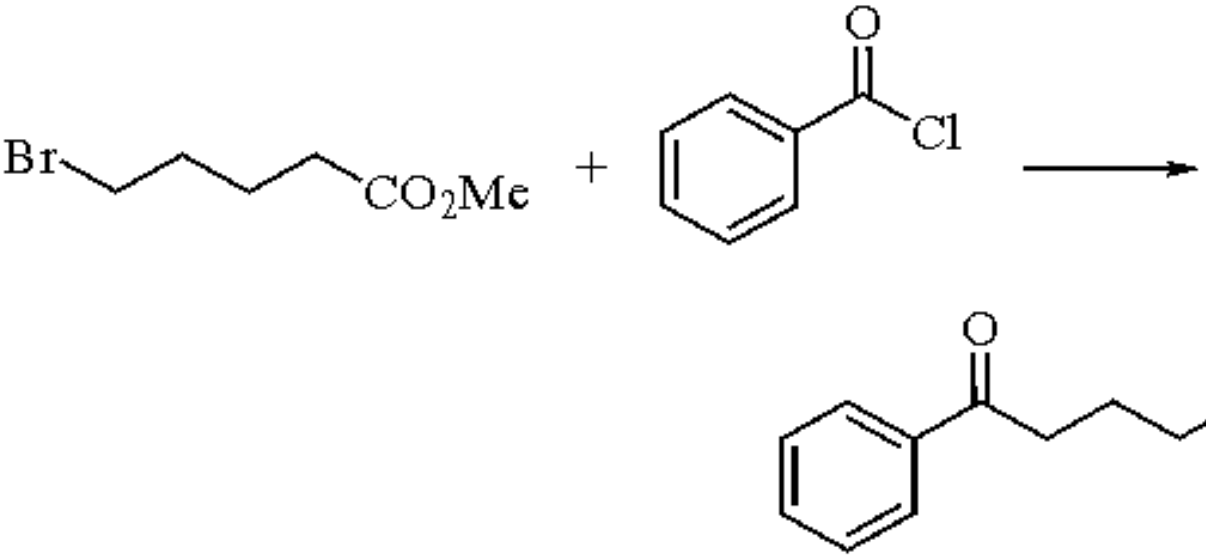

(6)

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2. (a) Ebert, G. W.; Rieke, R. D. *JOC* **1984**, *49*, 5282. (b) Ebert, G. W.; Rieke, R. D. *JOC* **1988**, *53*, 4482.
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Copper(I) Iodide-Triethyl Phosphite

$CuI[(OEt)_3P]$

[51717-23-8] · $C_6H_{15}CuIO_3P$ · Copper(I) Iodide-Triethyl Phosphite · (MW 356.60)

(promoter for the conjugate addition of alkyllithium and other reagents to α,β-unsaturated ketones and related compounds, regiospecific Ullmann reactions, alkylation of aluminates, and stereoselective synthesis of vinylsilanes)

Physical Data: mp 107-109 °C.[1,2]

Solubility: sol benzene, cyclohexane, bromoform, acetone, ether, and THF; also sol warm petroleum ether.

Form Supplied in: white crystals (97%).

Preparative Method: the complex is obtained in 88.6% yield by addition of ***Copper(I) Iodide*** to a solution of ***Triethyl Phosphite*** in benzene; the mixture is stirred and heated until the CuI dissolves; the complex is obtained upon evaporation of the solvent under reduced pressure.[2]

Purification: recrystallized from petroleum ether.[2]

Analysis of Reagent Purity: recrystallization and elemental analysis; IR spectrum provided.[2]

Handling, Storage, and Precautions: irritant; use in a fume hood; mechanical exhaust required; harmful by inhalation, ingestion, or skin absorption; incompatible with strong oxidizing agents; sensitive to air, moisture, and light; store under N_2 in a cool dry place.

Copper(I) iodide-triethyl phosphite reacts with acid chlorides in an Arbuzov-type process.[2] This complex also promotes alkylation of 1-trimethylsilylvinylaluminates with primary alkyl iodides to produce trisubstituted alkenes (eq 1),[3] as well as with 1-trimethylsilylvinylboranes and other alkyl halides.[4]

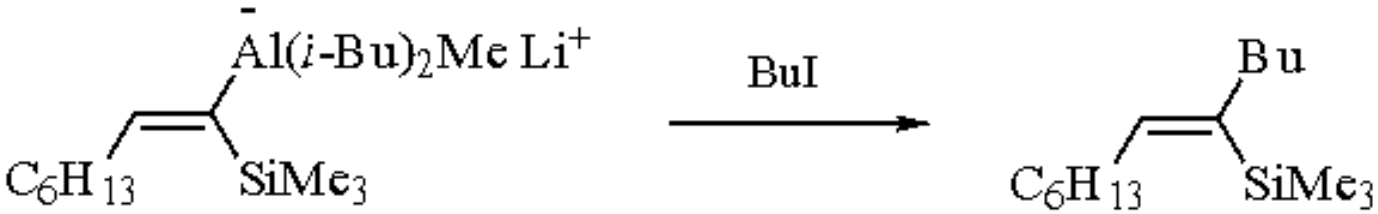

(1)

Organosamarium species have been generated by in situ transmetalation with copper(I) iodide-triethyl phosphite.[5] Although primary alkyl halides are reported to be relatively inert to copper solutions prepared from CuI and triethyl phosphite,[6] the complex was found to be effective for the transmetalation of an aryl organolithium which was subsequently utilized in an Ullmann type condensation (eq 2).[7]

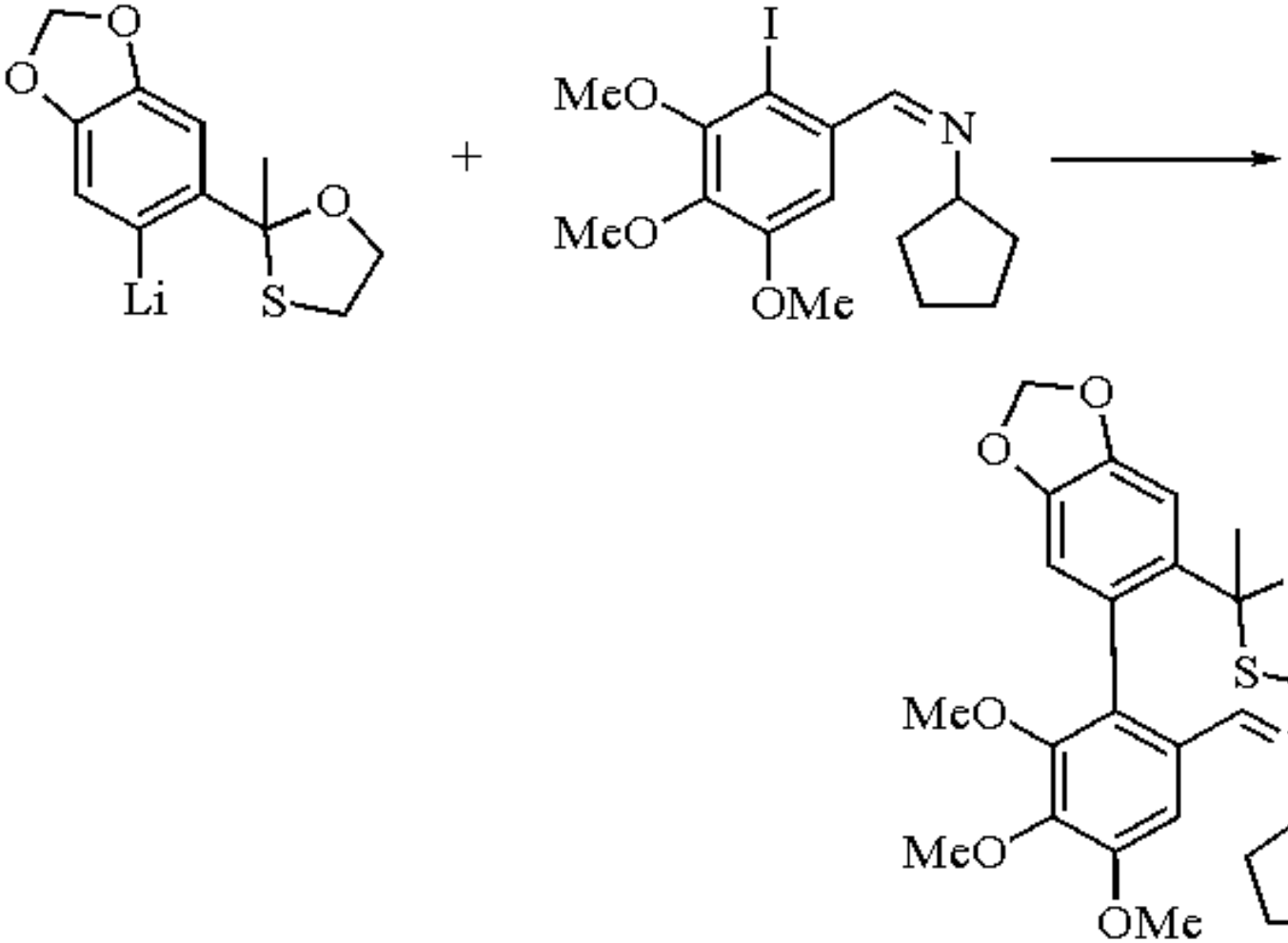

(2)

Related Reagents.

Copper(I) Iodide-Tributylphosphine; ***Copper(I) Iodide-Tributyl Phosphite***; ***Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide***; ***Copper(I) Iodide-Trimethyl Phosphite***.

---

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Copper(I) Iodide-Trimethyl Phosphite

$CuI[(OMe)_3P]$

[34836-53-8] · $C_3H_9CuIO_3P$ · Copper(I) Iodide-Trimethyl Phosphite · (MW 314.52)

(promoter for the decomposition of diazo ketones and esters and for conjugate addition of alkyl (vinyl, etc.) lithium reagents to α,β-unsaturated ketones and related compounds)

Physical Data: mp 192-193 °C.[1]

Solubility: sol warm methanol, ethyl acetate, acetone, aniline, and dimethylaniline; also sol aq ammonia.

Form Supplied in: white crystalline powder (98%). *Drying:* dried at 60 °C (1 mmHg) for 12 h.

Purification: recrystallized from acetone or chloroform.

Analysis of Reagent Purity: recrystallization to constant mp and elemental analysis.

Handling, Storage, and Precautions: irritant; use in a fume hood; mechanical exhaust required; harmful by inhalation, ingestion or skin absorption; incompatible with strong oxidizing agents; sensitive to air, moisture, and light; store under N_2 in a cool dry place.

Decomposition of Diazo Ketones and Diazo Esters.

Along with other copper(I) salts, copper(I) iodide-trimethyl phosphite has been utilized to promote the decomposition of α-diazoacetophenone in cyclohexene to the mixture of insertion products shown in eq 1, with overall yields less than 50% and with the cyclopropane derivative produced in amounts at least six times that of the others.[1]

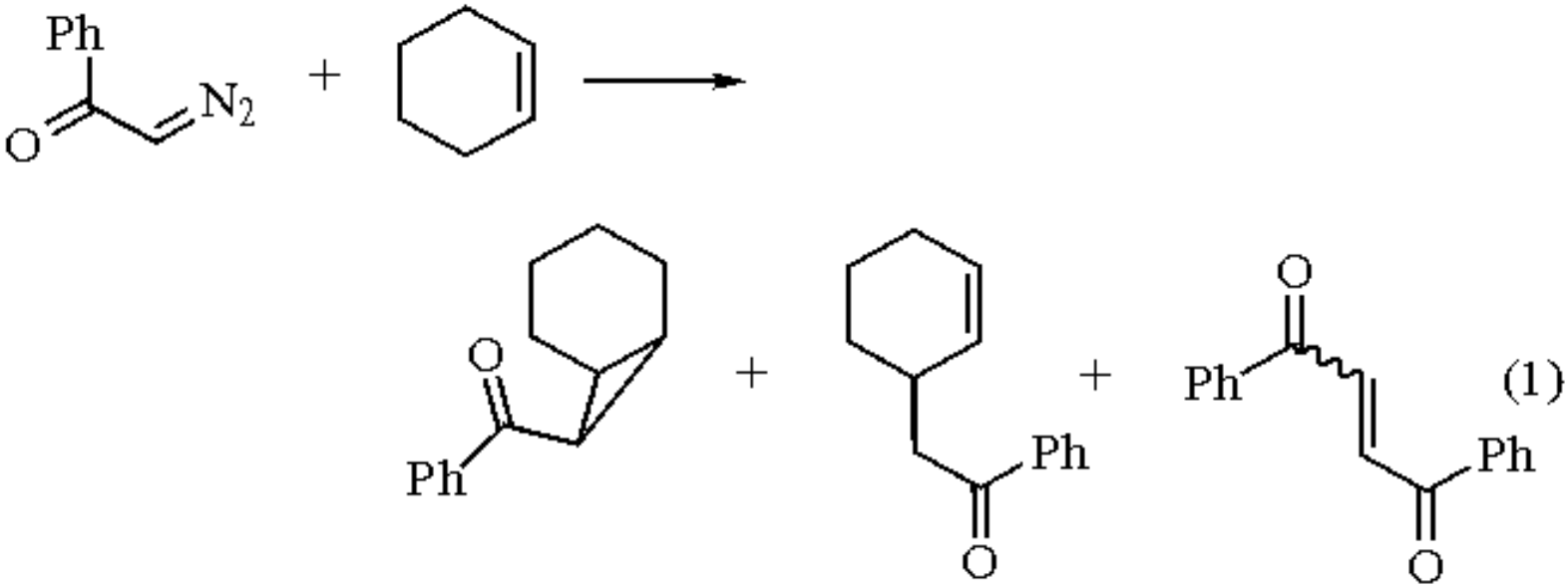

Indeed, decomposition of diazoacetic and diazomalonic esters in the presence of copper(I) iodide-trimethyl phosphite appears to be the method of choice.[2] The decomposition of diazomalonates in the presence of 1,2-ethylenedithiolato metallocene complexes is reported to be accelerated by CuI-P(OMe)$_3$.[3,4] It has also been reported that the intramolecular cyclization of the presumed carbonyl ylides derived from diazoacetates produces furanones directly (eq 2),[5,6] or the corresponding reaction products with alkenes.[7,8] Diethyl diazomalonate, in ethanol and in the presence of the copper(I) iodide-trimethyl phosphite reagent, permitted insertion into the hydroxyl group of the solvent to produce diethyl ethoxymalonate (82%) and a small amount (12%) of tetraethyl ethylenetetracarboxylate.[9]

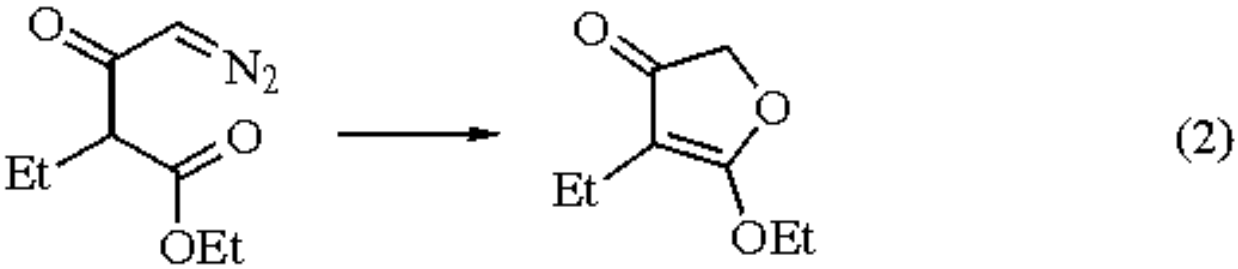

Conjugate Addition.

The copper(I) iodide-trimethyl phosphite/lithium dimethylcuprate complex has been compared with the corresponding ***Tri-n-butylphosphine*** complex of ***Copper(I) Iodide*** and ***Lithium Dimethylcuprate*** in the addition reactions to 5-methyl-2-cyclohexenone (eq 3), 3-methyl-2-cyclohexenone (eq 4), and 5,5-dimethyl-2-cyclohexenone (eq 5).[10]

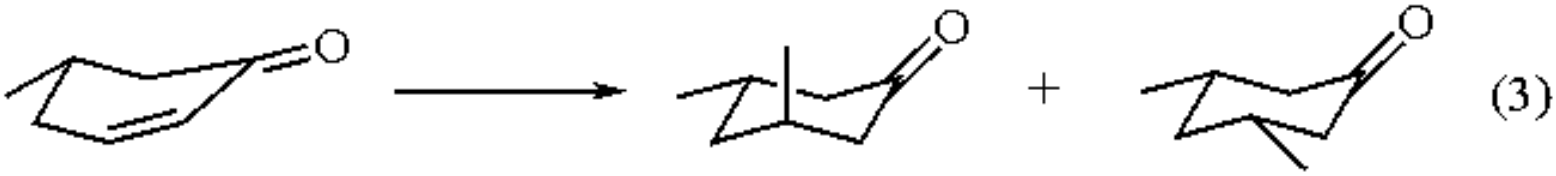

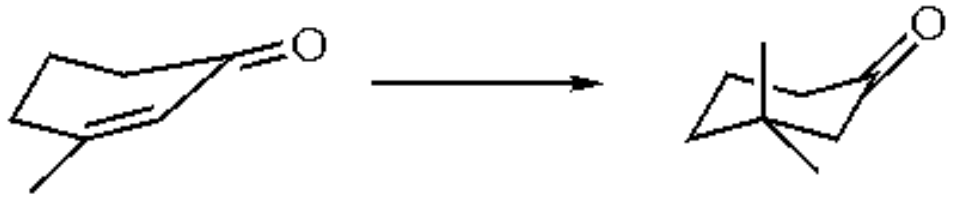

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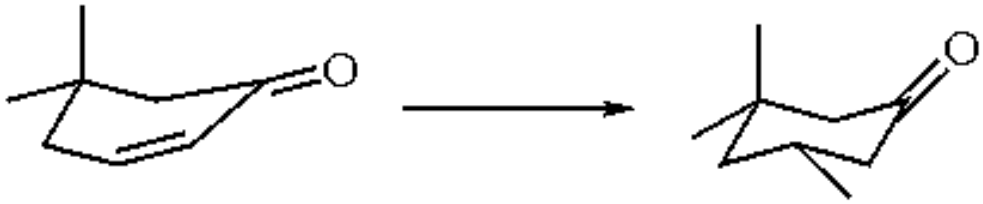

(5)

For the first case (eq 3), both reagents gave predominately *trans* product (*trans*:*cis* = 98:2), but the reaction with the tri-*n*-butylphosphine complex produced a 34% yield of products while the trimethyl phosphite complex yielded product in 73-87% (as a function of the amount of ***Lithium Iodide*** added or of tertiary phosphine ligand present). In both the second and third cases (eqs 4 and 5) the two complexes gave approximately the same yields.[10] Under other circumstances (where the complexes were not isolated but rather generated and used in situ), the relative yields for conjugate addition reactions have been reported to be much diminished for the copper(I) iodide-trimethyl phosphite reagent.[11] The same observation was also made with regard to the ring opening reaction of β-propiolactones with various copper reagents.[12] Additionally, an early investigation of the attempted preparation of dialkenylcuprates [$(CH_2{=}CH)_2CuLi$] suggested that the use of copper(I) iodide-trimethyl phosphite as the source of copper was only partially successful (as were many others) in avoiding decomposition of the vinyl cuprate.[13] Nonetheless, in the presence of ***Boron Trifluoride Etherate***, copper(I) iodide-trimethyl phosphite clearly has a salutary effect on the conjugate addition of the copper reagent derived from lithium *N*-*t*-butylvaleraldimine to 2-cyclohexenone.[14]

Related Reagents.

Copper(I) Iodide-Tributylphosphine; ***Copper(I) Iodide-Tributyl Phosphite***; ***Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide***; ***Copper(I) Iodide-Triethyl Phosphite***; ***Lithium Diethylcuprate***; ***Lithium Diethylcuprate-Tributylphosphine***.

---

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Copper(II) Nitrate-K10 Bentonite Clay[1]

$Cu(NO_3)_2$-K10

($Cu(NO_3)_2$)

[3251-23-8] · CuN_2O_6 · Copper(II) Nitrate-K10 Bentonite Clay · (MW 187.55)

(mild dethioacetalization agent;[2] oxidizing agent for 1,4-dihydropyridines;[3] highly selective nitrating reagent of halobenzenes[4] and aromatic hydrocarbons[5])

Alternate Name: claycop.

Solubility: insol water and organic solvents.

Form Supplied in: light blue, free-flowing powder prepared from K10 clay (30 g) and $Cu(NO_3)_2.3H_2O$ (20 g) in acetone (375 mL). After elimination of the solvent it retains about 10% H_2O.[1a,b]

Handling, Storage, and Precautions: no loss of activity is observed on standing for several weeks.[1a] Nitrates are potentially dangerous compounds. Scaling-up should be attempted only after appropriate safety tests. Avoid breathing dust; use in a fume hood. Store below 50 °C.

Oxidative Coupling of Thiols.

Claycop as a source of NO^+ ion effects the coupling of thiophenol into diphenyl disulfide (eq 1).[1a] This quantitative reaction serves as a reactivity test (see also ***Iron(III) Nitrate-K10 Montmorillonite Clay*** (clayfen)).[6]

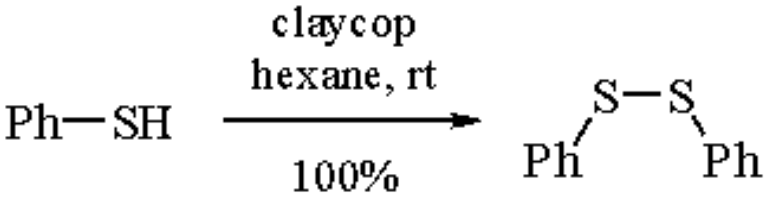

(1)

Carbonyl Group Deprotections.

Thioacetals are used in organic syntheses for protection or umpolung of the reactivity of a carbonyl group.[7] *S,S*-Diethyl acetals, 1,3-dithianes, and 1,3-dithiolanes (eq 2) are cleaved into aldehydes and ketones by claycop under very mild conditions.[2] No external source of water is needed; it is provided by the internal structure of the clay. Although a wide

variety of reagents (e.g. *t*-BuSNO, Ph_3+PPMe Br_3^-, $Ph_2Se_2O_3$, $Fe(bipy)_3(ClO_4)_3.3H_2O$)[8a-d] are known to be equally effective for dethioacetalization, use of claycop shows advantages over existing methods. The reaction product is isolated simply by filtration of the spent reagent and evaporation of the filtrate.

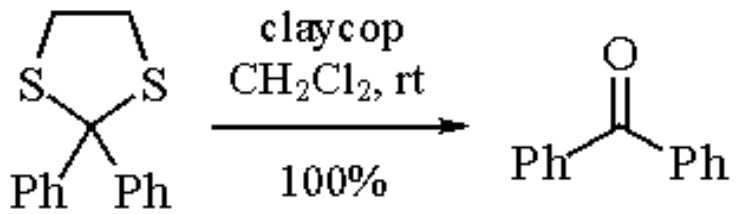

(2)

Claycop has been utilized for the cleavage of selenoacetals (eq 3),[9] but higher yields can be obtained by the use of clayfen (97%)[9] or ***Copper(II) Chloride-Copper(II) Oxide*** (99%).[10]

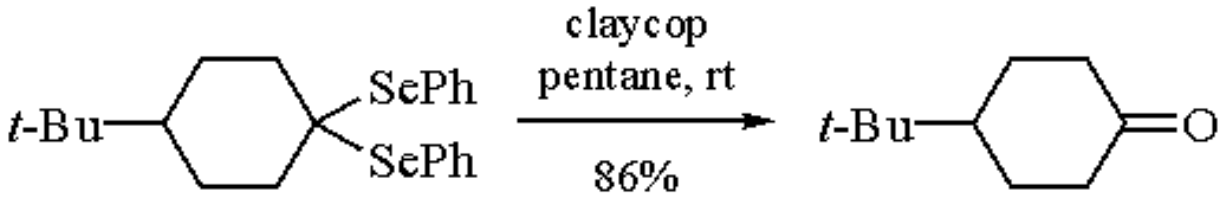

(3)

Thiocarbonyl to carbonyl transformation is promoted by NO^+ ion (see also ***Nitrosonium Tetrafluoroborate***).[11] Clayfen gives excellent results with aromatic substrates while claycop is less reactive and is limited in use to aliphatics (eq 4).[12]

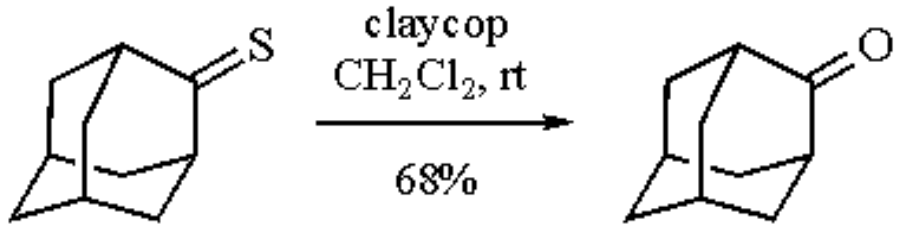

(4)

Aromatization of 1,4-Dihydropyridines.

1,4-Dihydropyridinedicarboxylates are aromatized smoothly at ambient temperature by claycop (eq 5).[3] 4-Arylpyridines are formed in 80-93% yields. Sonication greatly reduces the reaction time (from hours to 5-10 min).[13a] ***Pyridinium Chlorochromate*** adsorbed on ***Montmorillonite K10*** exhibits similar activity.[13b]

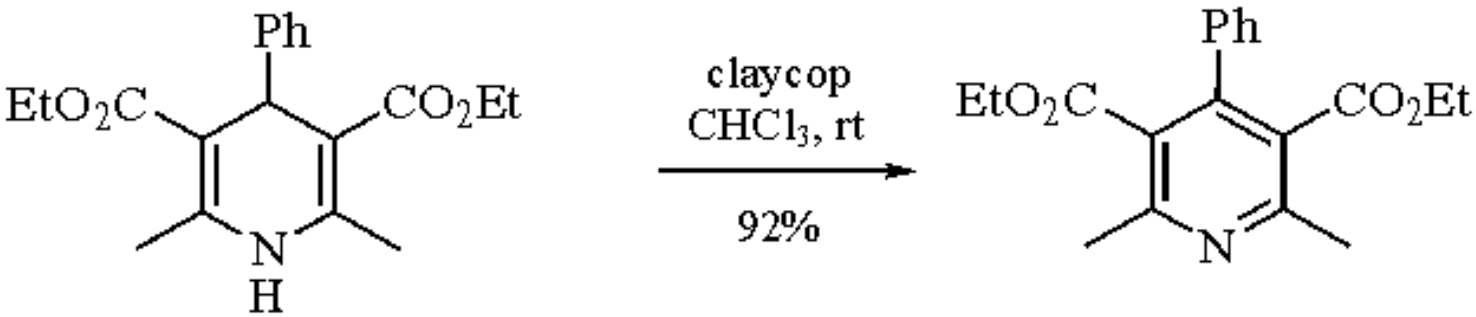

(5)

Nitration by Claycop Under Menke Conditions.

Halobenzenes, deactivated for electrophilic aromatic substitution, are mononitrated by means of claycop in the presence of Ac_2O.[4] The proportion of *para* product is the largest for fluorobenzene (eq 6) and the smallest for iodobenzene. The *para* preference can be further improved: lowering the temperature to 0 °C increases the *para*:*ortho* ratio to 35:1. The *para* preference is modest under classical nitration procedures (e.g. 10.8:1 by ***Nitronium Tetrafluoroborate***/sulfolane).[14]

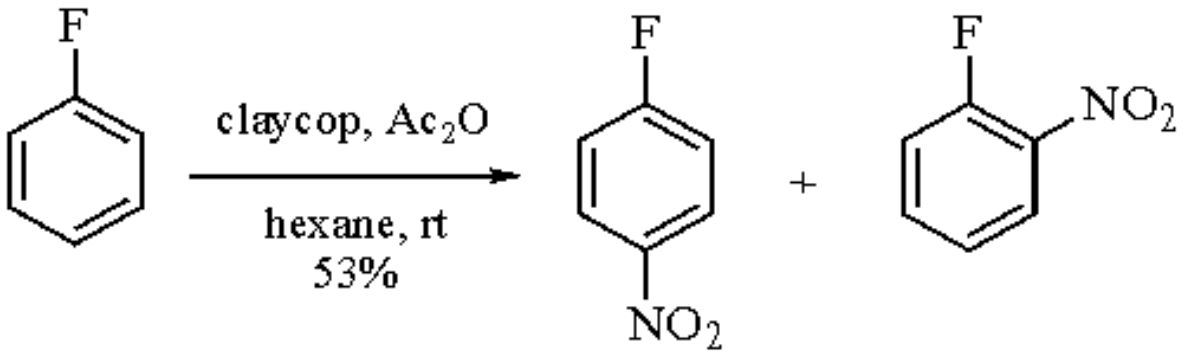

(6)

25:1

Quantitative mononitration of toluene can be performed by claycop under Menke conditions with high *para* selectivity (eq 7).[5] Acetyl nitrate is the likely nitrating species. The process is catalytic using ***Nitric Acid*** as reagent.[5c] Similar results are achieved by ***Benzoyl Nitrate***-zeolite catalyst.[15] Highly selective nitrating agents are obtained by complexation of NO_2BF_4 or Bu_4NNO_3 with crown ethers.[16a,b]

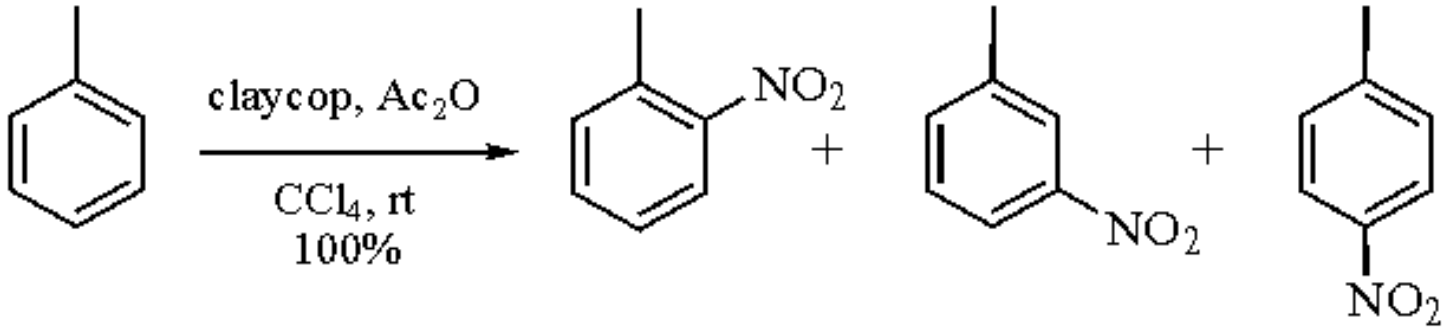

(7)

20:1:79

Related Reagents.

For further discussion on the use of clays in synthesis, see ***Montmorillonite K10***.

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1. (a) Cornelis, A.; Laszlo, P. *S* **1985**, 909. (b) Cornelis, A.; Laszlo, P. *Aldrichim. Acta* **1988**, *21*, 97. (c) *Preparative Chemistry Using Supported Reagents*; Laszlo, P., Ed.; Academic: San Diego, 1987. (d) Balogh, M.; Laszlo, P. In *Organic Chemistry Using Clays*; Springer: Berlin, 1993.

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Copper(II) Nitrate-(±)-1-Phenylethylamine[1]

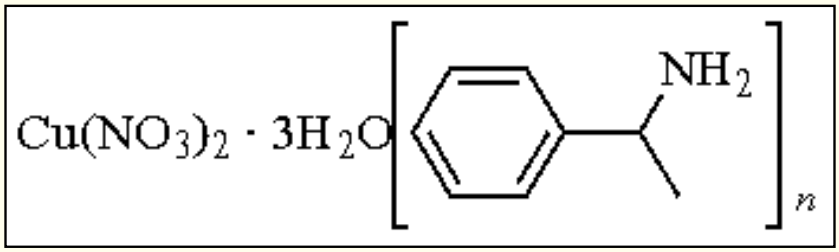

($Cu(NO_3)_2.3H_2O$)

[10031-43-3] · CuN_2O_6 · Copper(II) Nitrate-(±)-1-Phenylethylamine · (MW 241.60) ((±)-PhCH(Me)NH_2)

[618-36-0] · $C_8H_{11}N$ · Copper(II) Nitrate-(±)-1-Phenylethylamine · (MW 121.18)

(reagent for the oxidative coupling of phenols[2])

Physical Data: $Cu(NO_3)_2.3H_2O$: mp 114 °C. (±)-1-Phenylethylamine: bp 185 °C/756 mmHg; *d* 0.95 g cm^{-3}. The exact structure of the copper(II) complex is unknown; the number of phenylethylamine ligands is preferentially 4 (*n* = 4).

Form Supplied in: the reagent is prepared in situ; both compounds are commercially available. (±)-1-Phenylethylamine is a colorless oil; copper(II) nitrate trihydrate is a blue crystalline deliquescent material.

Analysis of Reagent Purity: $Cu(NO_3)_2.3H_2O$: > 99%. (±)-1-Phenylethylamine: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.37 (d, *J* = 6.4 Hz, 3H), 4.07 (q, *J* = 6.7 Hz, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.29 MHz) δ 25.2 (q), 50.8 (d), 125.2 (d), 126.3 (d), 127.9 (d), 147.3 (s).

Preparative Methods: prepared in situ by complexation of copper(II) nitrate with 4 equiv of (±)-1-phenylethylamine in methanol under inert atmosphere.[1,2]

Handling, Storage, and Precautions: (±)-1-phenylethylamine is stable when stored in a sealed container under nitrogen.

General Considerations.

The copper(II) nitrate-(±)-1-phenylethylamine reagent (**1**) is a typical example of a number of copper(II) amine oxidizing agents.[1-3] Reagent (**1**) can effect the oxidative coupling of phenols under anaerobic conditions. Both C-C and C-O coupled products can be obtained. Characteristic examples are given.

Synthesis of Dehydrogriseofulvin.

Reaction of (**1**) with bisphenols leads to intramolecular C-O coupled products (eq 1).[1]

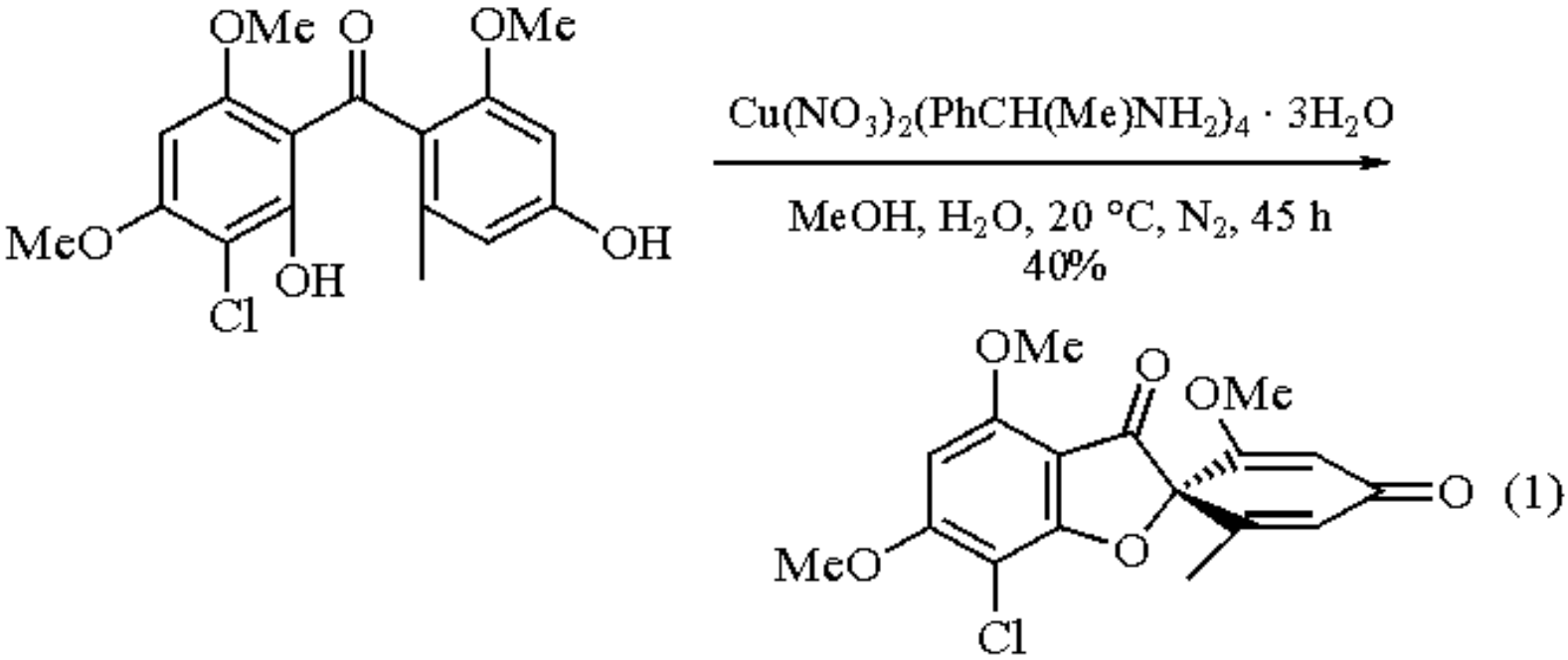

Synthesis of 1,1´-binaphthalene-2,2´-diols.

The oxidative dimerization of 2-naphthols with (**1**) provides 1,1´-binaphthols (eq 2).[2]

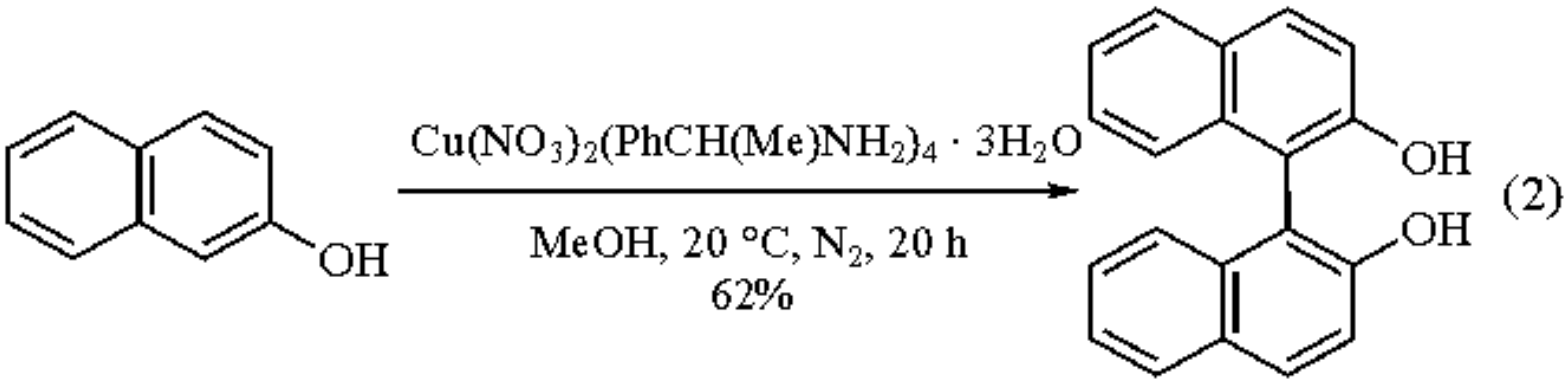

Unsymmetrical 1,1´-binaphthalene-2,2´-diols are formed in 80-97% yield by oxidative cross-coupling of differently substituted 2-naphthols mediated by related Cu^{II}-primary amine complexes.[3b] (*S*)-(-)-1,1´-Binaphthalene-2,2´-diol and (*S*)-(-)-10,10´-dihydroxy-9,9´-biphenanthryl have been prepared with optical purities up to 98% by a similar oxidative coupling using chiral nonracemic primary amines.[1,3a,3d]

---

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Copper(I) Oxide

Cu_2O

[1317-39-1] · Cu_2O · Copper(I) Oxide · (MW 143.08)

(weak base; activates halides towards nucleophilic substitution;[1] forms carbenoid intermediates from diazo compounds[2] and radicals from arenediazonium salts;[3] activates isocyanides towards 1,1-addition[4])

Physical Data: mp 1235 °C; *d* ~6 g cm^{-3}.

Solubility: insol most organic solvents; slightly sol quinoline and benzonitrile;[1a] variously sol acids (salt formation, in some cases disproportionation to Cu^0 and Cu^{II}).

Form Supplied in: red to brown powder; widely available. Typical impurities: Cu, CuO,[5] NaCl,[5] stabilizers (e.g. gelatine,[5] oil, zinc stearate), moisture.[5] For reactions in anhydrous media the reagent is vacuum-dried before use.

Preparative Methods: since reactions involving Cu_2O are heterogeneous, they may critically depend on the particle size.[6b] An active preparation is obtained by reduction of Cu^{II} solutions[7] but may suffer deactivation at high reaction temperatures.[1a]

Handling, Storage, and Precautions: Cu_2O is incompatible with alkynes, diazonium salts, and diazo compounds. Copper compounds are moderately toxic.

Activation of Halides Towards Nucleophilic Substitution.

Aryl halides react in the presence of Cu_2O with a variety of nucleophiles such as thiols and thiolates (eq 1),[6] phenols and phenoxides (eq 1),[1a,8,9] ammonia and amines,[9,10] lactams (eq 2),[11] cyclic imides,[11,12] ***Sodium Borohydride***,[5] and alkynes (eq 3).[13] Copper thiolates have been prepared from Cu_2O and subsequently used in a separate step.[6a,b] ***Lithium Bromide*** or ***Tetra-n-butylammonium Bromide*** transforms iodides into bromides.[1a] Typical solvents include pyridine, 2,4,6-collidine, quinoline, DMF, and DMA; elevated temperatures are required. DMSO has been used but methylthiolation occurs as a side reaction.[1a] The order of reactivity is chlorides < bromides < iodides. Besides aryl halides, vinyl halides and also 1-bromododecane react with CuSPh in good yields.[6a] An allylic iodide has been hydrolyzed by warming with Cu_2O in DMSO/water.[14] Fluorides are obtained from secondary and tertiary aliphatic chlorides or bromides with ***Hydrogen Fluoride*** and Cu_2O in ether or THF.[15]

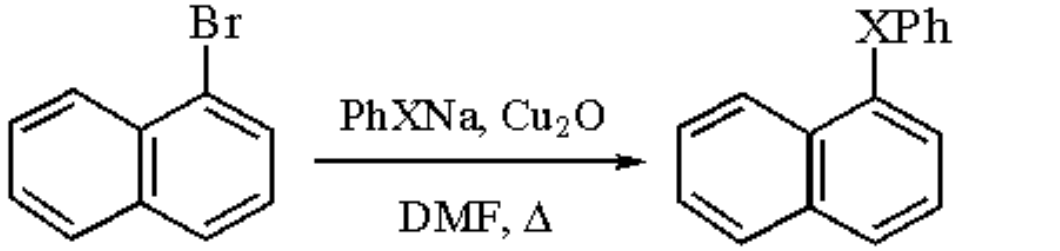

(1)

X = O, 84%; S, 99%

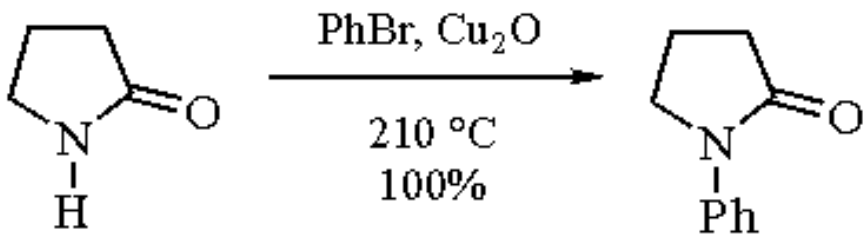

(2)

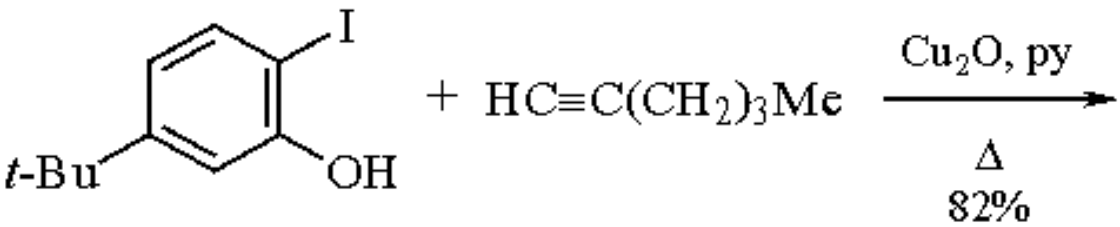

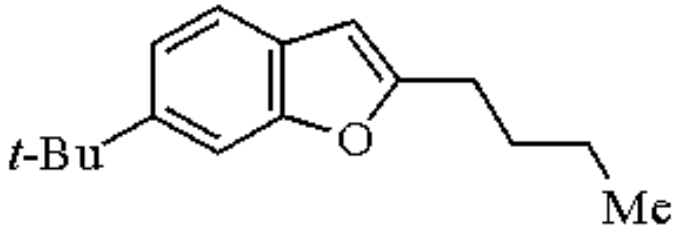

(3)

Reduction is a common side reaction for aryl halides,[1,5,9,10e] especially with alkoxides and with phenols bearing electron-withdrawing substituents. With ***Sodium Ethoxide*** in refluxing 2,4,6-collidine, reduction can be the main pathway.[5] The same reagent system reduces α-bromo ketones to ketones.[5,10e] Replacement of Cu_2O by ***Copper(I) Iodide*** gives largely substitution for sodium derivatives of *n*-alkanols and cyclohexanol.[16] Reduction of 1-bromonaphthalene also predominates with carboxylic acids,[17] whereas haloferrocenes give acyloxyferrocenes.[18] Ullmann coupling to form biaryls is occasionally observed.[1,19]

Thiophenes,[20] benzothiazole,[21] pentafluorobenzene (eq 4),[20] and di- and trinitrobenzenes[22] are arylated by aryl iodides/Cu_2O. Carboxylic acids may also serve as starting materials, the reaction then proceeding with concomitant decarboxylation (see below).[23]

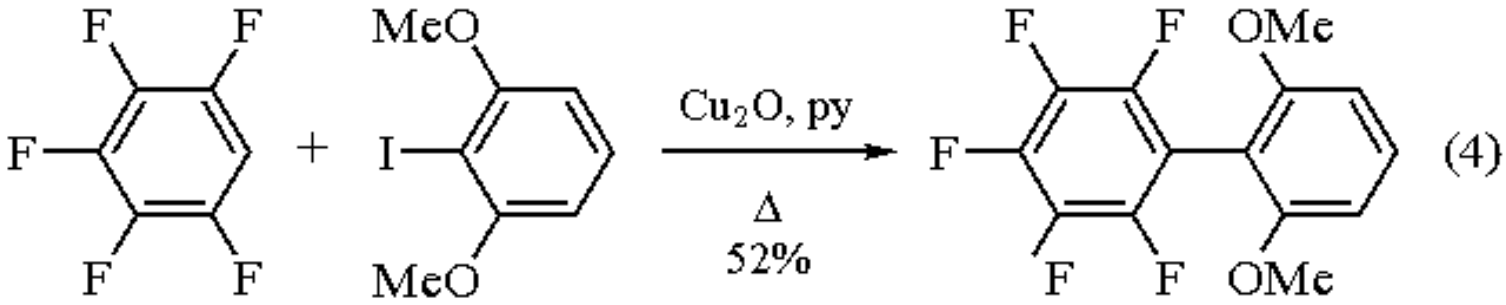

Decarboxylations.

Aromatic and vinylic carboxylic acids are decarboxylated by heating with Cu_2O (alone or with addition of 2,2´-bipyridyl)[24] in high-boiling solvents such as DMF, NMP, or quinoline. The Cu_2O-bipyridyl protocol has been applied to a homocubanecarboxylic acid which decarboxylates with skeletal rearrangement.[25] On dry heating with Cu_2O, α-cyanoacrylic acids furnish predominantly *cis*-α,β-unsaturated nitriles (eq 5).[26] Malonic acids (eq 6)[27] as well as some arylacetic acids capable of forming stabilized benzylic anions[28] decarboxylate with Cu_2O in acetonitrile.

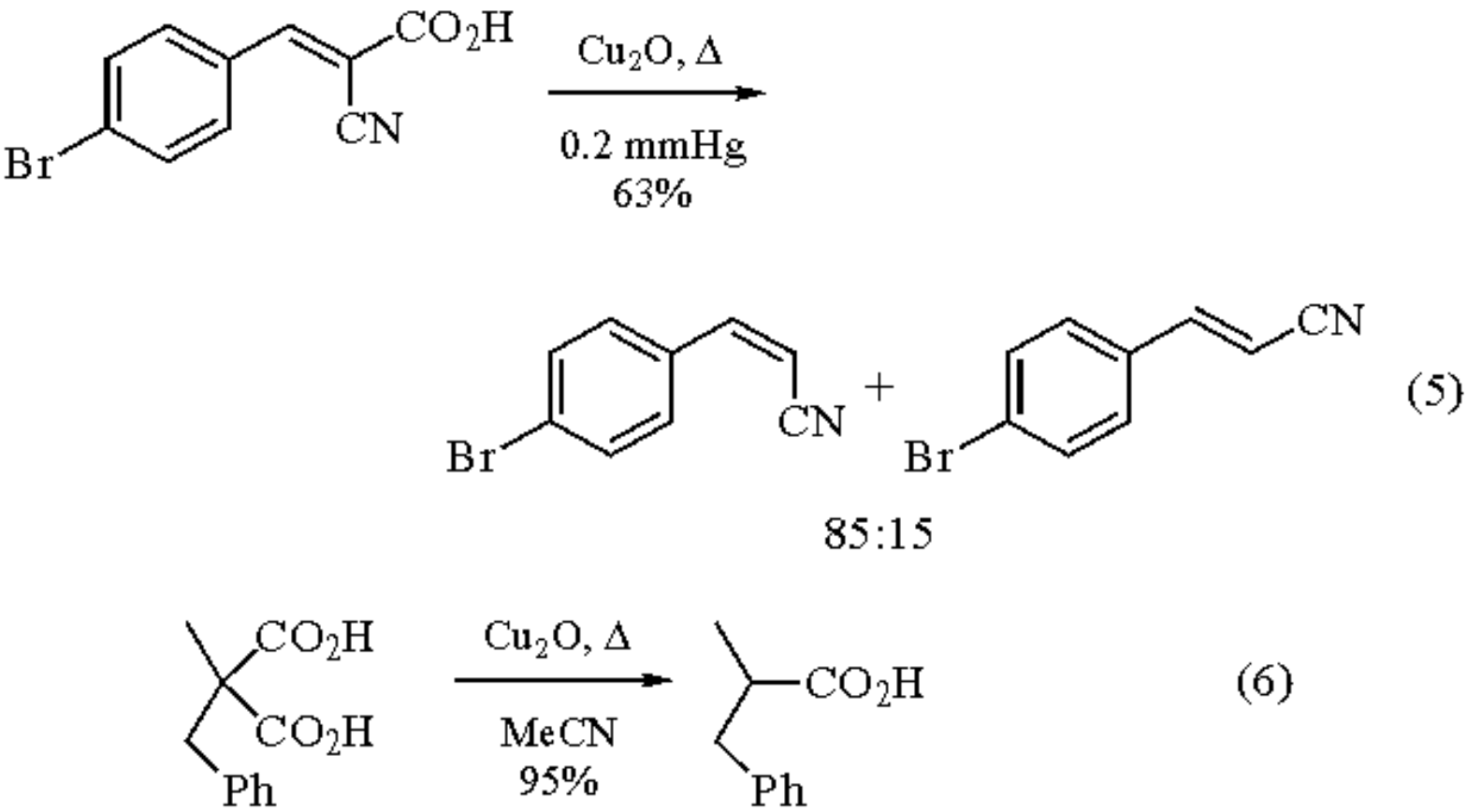

Vicinal dicarboxylic acids undergo oxidative bisdecarboxylation to form alkenes when treated with Cu_2O and 2,2´-bipyridyl (eq 7).[29] Yields are usually higher than those obtained by electrolysis or with ***Lead(IV) Acetate*** but aromatization may interfere. Under 1 bar of oxygen at 50 °C, diphenylacetic acid and α-hydroxy carboxylic acids are oxidatively decarboxylated to ketones by Cu_2O in acetonitrile.[30]

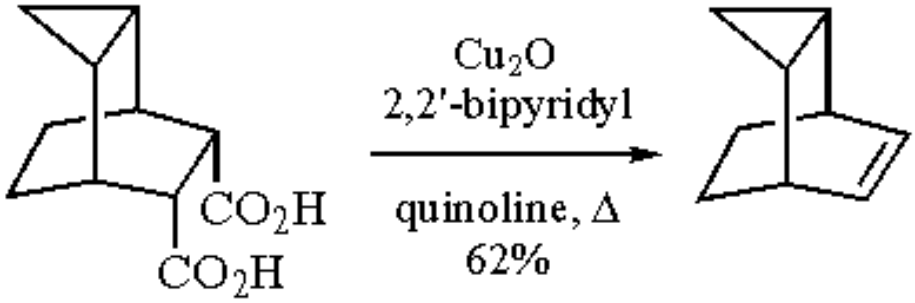

(7)

Reactions of Diazo Compounds.

Cu_2O acts as a catalyst for the decomposition of α-diazo carbonyl compounds (more often used are ***Copper*** powder or ***Copper(II) Sulfate***) to give rise, via carbenoid intermediates, to cyclopropanation (eq 8) and C-H insertion (eq 9) products.[2] Most examples are intramolecular, but the reaction of *N*-methylpyrrole with ethyl diazoacetate giving predominantly insertion into the α-C-H bond has been described.[31] The performance of Cu_2O vs. other catalysts is variable.[2] In the intramolecular cyclopropanation of a 4-diazoindol-7-one derivative, a copper(I) triflate carbonyl complex prepared in situ from Cu_2O gave best results.[32]

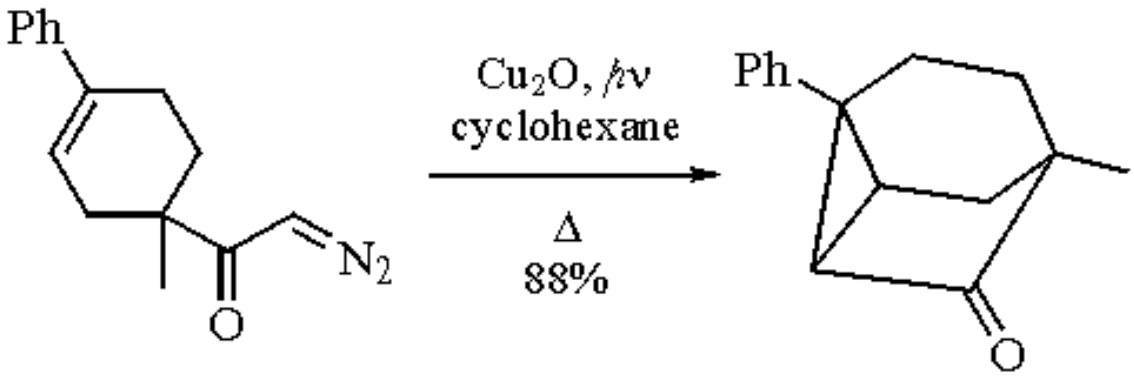

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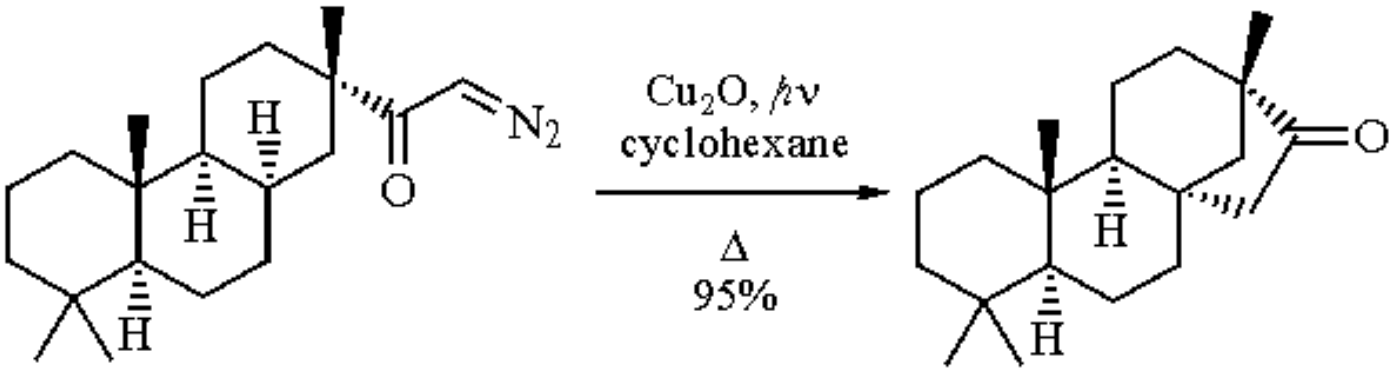

(9)

Reactions of Diazonium Salts.

Copper(I) oxide forms radicals from arenediazonium salts which may undergo subsequent transformations like reduction (eq 10),[33] coupling to form biaryls,[34] oxidation to phenols by copper(II) nitrate (eq 11),[3] Meerwein arylation of acrylic acid derivatives,[35] homolytic aromatic substitution (eq 12),[3,36] or substitution by nitrite.[37] The oxidation reaction offers the advantage to uncatalyzed thermolysis in that it proceeds without heating or a large excess of strong

acid and usually gives phenols, even in cases where cyclization onto an *ortho* substituent normally predominates.

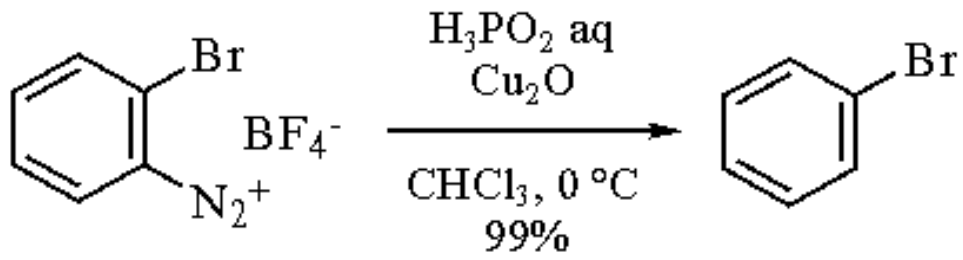

(10)

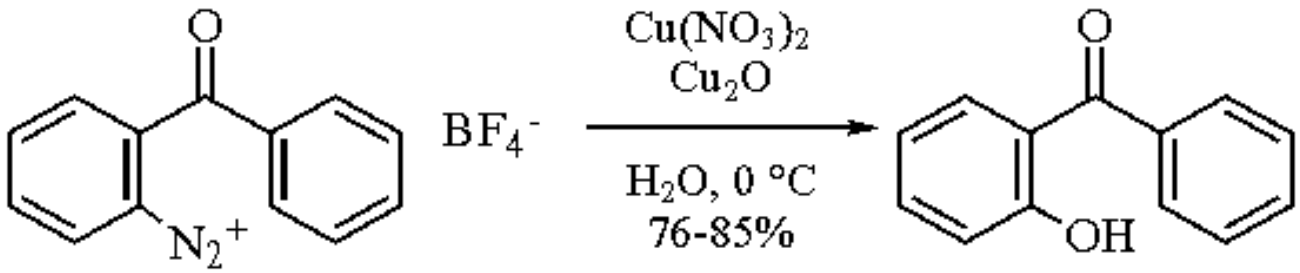

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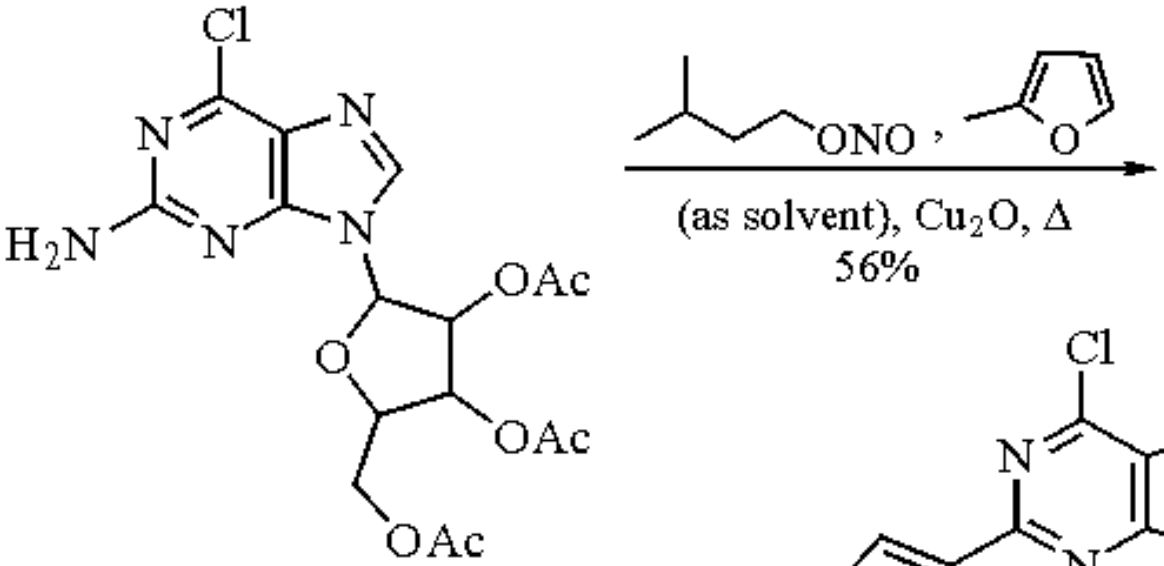

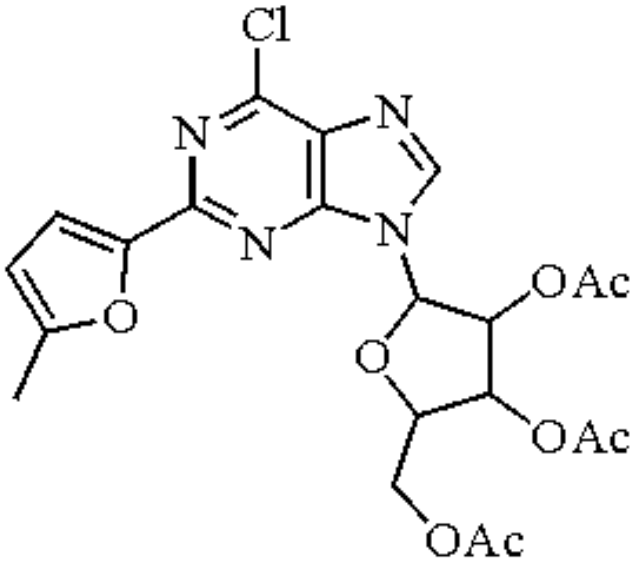

(12)

1,1-Addition to Isocyanides.

Substituted formimidates are obtained from isocyanides and alcohols, thiols, amines (eq 13), or amides in the presence of Cu_2O.[4] The intramolecular version of this reaction, combined in one pot with the hydroxyalkylation of an activated (allyl, benzyl, α-alkoxycarbonyl) isocyanide by an aldehyde or ketone, results in Δ^2-oxazolines.[38] Selenol esters as electrophiles yield oxazoles (eq 14),[39] and α,β-unsaturated esters or nitriles produce Δ^1-pyrrolines.[38] Analogous

schemes involving aromatic side chain metalation have been utilized in the synthesis of indoles (eq 15),[40] 3,1-benzoxazepines,[41] 3,1-benzoxazocines,[41] and 1,3-benzodiazepin-4-ones.[40a]

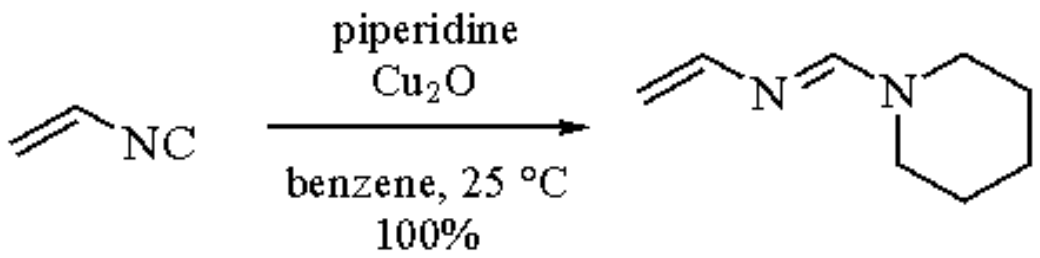

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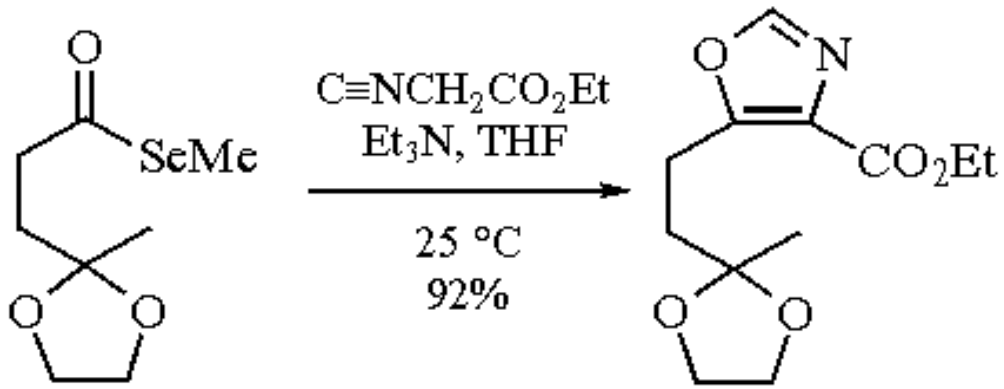

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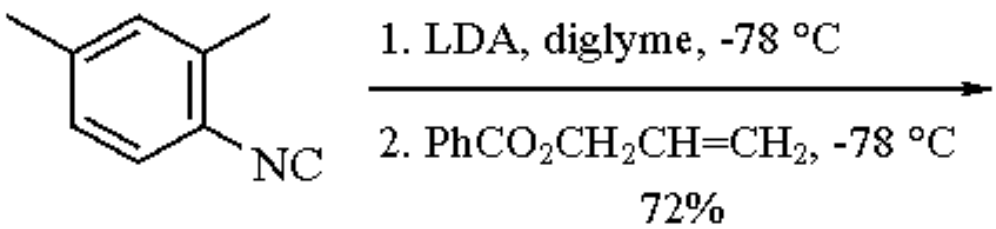

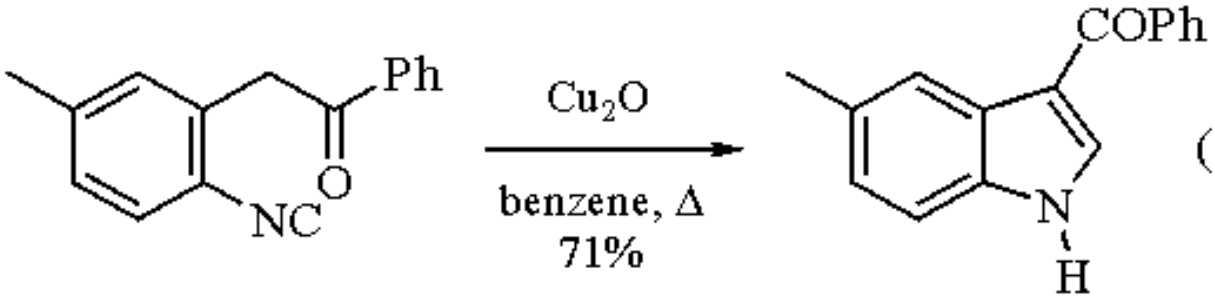

(15)

Miscellaneous Reactions.

Cu_2O catalyzes a variety of other transformations such as the Koch carboxylation of alkenes and alcohols by CO in strong acids. The reaction proceeds via carbenium ions, and skeletal rearrangements are the rule.[42] Polyhalomethanes and di- and trichloroacetic acid esters add to 1,3-butadiene and styrene.[43] Terminal alkynes form dimeric vinyl alkynes in boiling AcOH (eq 16).[44] Michael additions are catalyzed by Cu_2O in the presence of isocyanides,[45] as is the esterification of carboxylic acids with alkyl halides[46] and the cyclopropanation of electron-poor alkenes with α-halo carbonyl and trichloromethyl compounds.[38c,47] Exclusive β-hydrosilylation of acrylonitrile occurs with Cu_2O and TMEDA under sonication.[48] Cyclohexene is acetoxylated in up to 30% enantiomeric excess by ***t-Butyl Hydroperoxide***

and AcOH in acetonitrile with Cu_2O/proline as catalyst.[49] Autoxidation of furfural to furoic acid takes place in the presence of a Cu_2O-Ag_2O catalyst.[50] Allylic alcohols are transformed into acetates with oxygen attached to the less substituted terminus by Cu_2O in AcOH/Ac_2O (eq 17).[51] ***Copper(II) Trifluoromethanesulfonate*** in the presence of Cu_2O in nitrile solvents oxidatively couples enol silyl ethers to 1,4-diketones[52] and oxidatively cyclizes δ,ε- and ε,ζ-unsaturated enol silyl ethers (eq 18).[53]

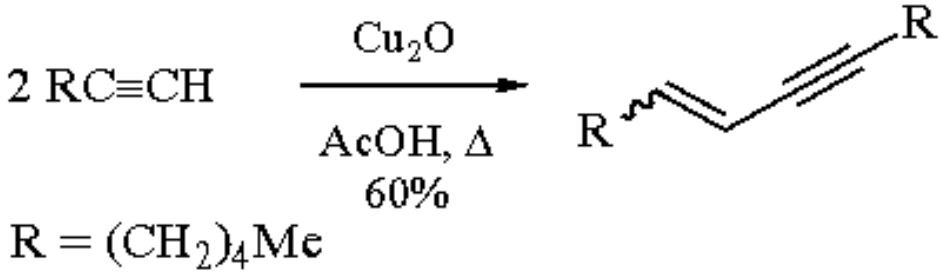

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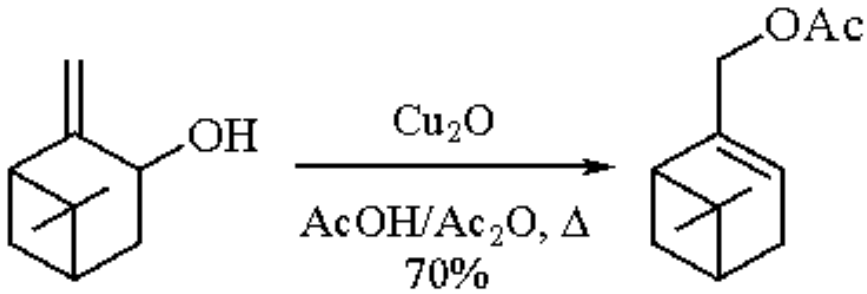

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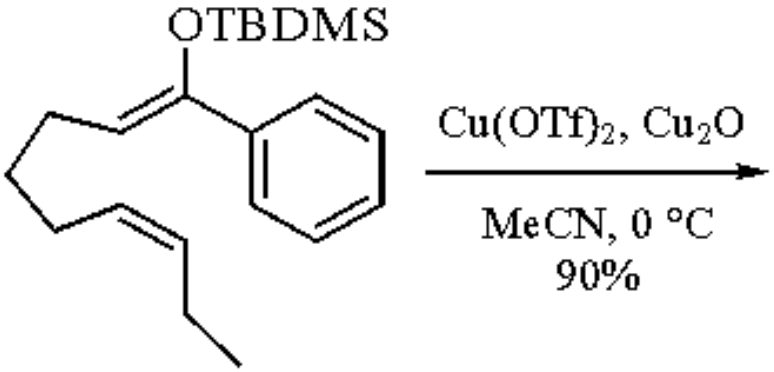

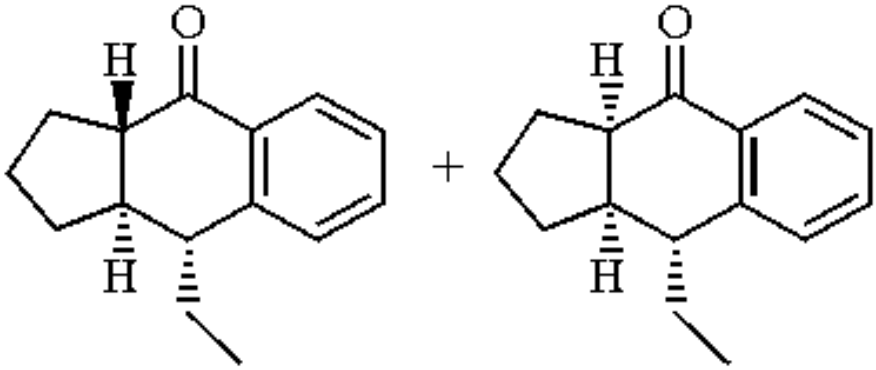

20:1

(18)

Related Reagents.

For related chemistry, see the entries dealing with other copper(I) and copper(II) reagents.

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Copper(I) Oxide-*t*-Butyl Isocyanide

$Cu_2O.[t\text{-}BuNC]_m$

(Cu_2O)

[1317-39-1] · Cu_2O · Copper(I) Oxide-*t*-Butyl Isocyanide · (MW 143.08) (*t*-BuNC)

[7188-38-7] · C_5H_9N · Copper(I) Oxide-*t*-Butyl Isocyanide · (MW 83.13)

(precursor to organocopper compounds reacting in aldol- and Michael-type fashion; cyclopropanation reagent; used in heterocycle synthesis)

Physical Data: reagent prepared in situ; see entries for ***Copper(I) Oxide*** and ***t-Butyl Isocyanide***.

Solubility: sl sol H_2O; sol common organic solvents.

Form Supplied in: *t*-BuNC: liquid; purified by distillation.

Preparative Methods: *t*-butyl isocyanide may be prepared by dehydration of the corresponding *N*-*t*-butylformamide.[1] The reagent is generated in situ by mixing *t*-butyl isocyanide with copper(I) oxide (or copper powder) under nitrogen prior to use. Reactions with copper(0) are described below.

Handling, Storage, and Precautions: *t*-BuNC is flammable and highly toxic. All reactions should be conducted in a well-ventilated fume hood.

Aldol and Michael Reactions: Heterocycle Synthesis.

Copper(I) oxide-*t*-butyl isocyanide and copper(0)-*t*-butyl isocyanide react with active methylene compounds to form the corresponding organocopper(I) complexes with the accompanying formation of H_2O and H_2, respectively.[2] The reaction mixture thus obtained reacts with ketones and aldehydes in the manner of the aldol condensation[2] and with α,β-unsaturated carbonyl and nitrile compounds in the manner of the Michael addition.[2]

Alkyl isocyanides having an active α-hydrogen react, in the presence of a catalytic amount of copper(I) oxide, with α,β-unsaturated carbonyl or nitrile compounds and with ketones or aldehydes, producing 1-pyrroline and 2-oxazoline derivatives, respectively (eqs 1 and 2).[3]

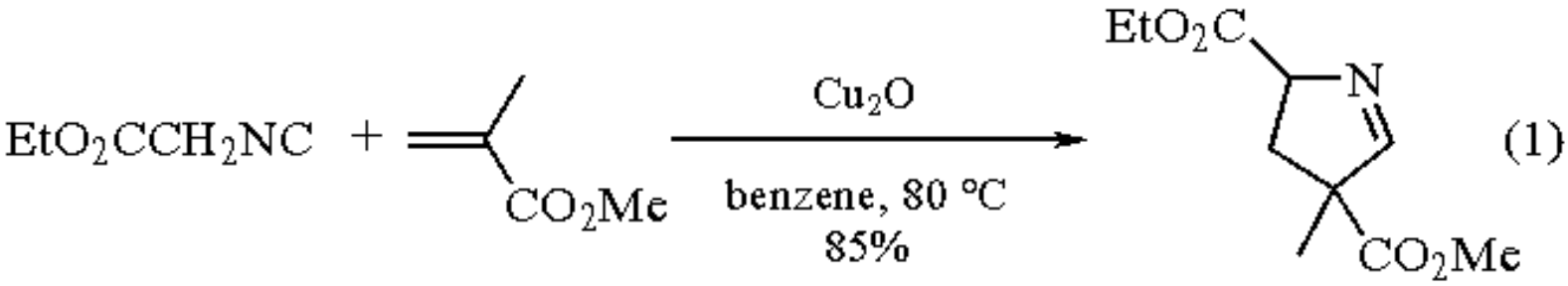

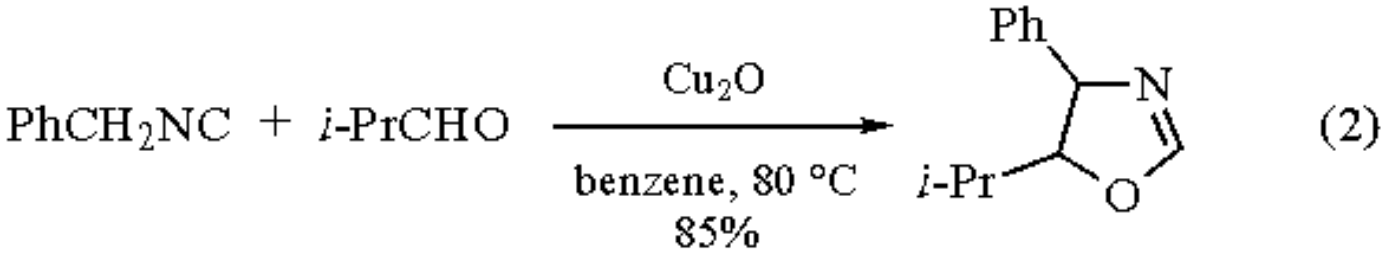

Copper(I) oxide-*t*-butyl isocyanide induces dimerization of α,β-unsaturated carbonyl and nitrile compounds (eq 3).[4]

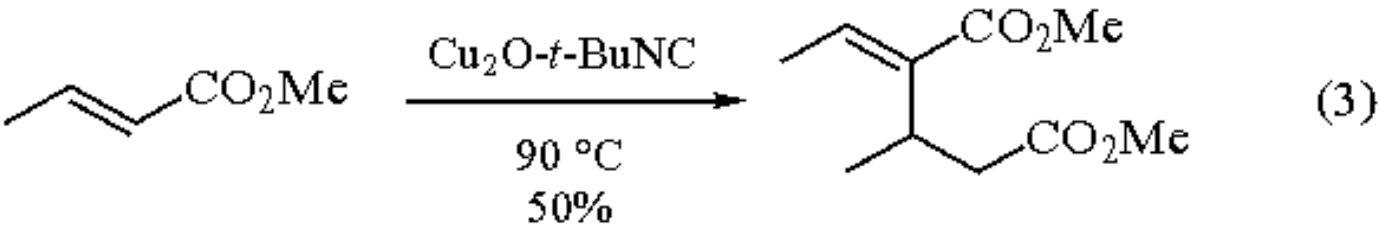

Cyclopropanations: Use of Copper(0).

Copper(I) carbenoid intermediates, which may be generated in situ by the reactions of α-halo carboxylic acid esters and nitriles with copper(I) oxide-*t*-butyl isocyanide complexes, are used for cyclopropanation of electron-deficient alkenes (eq 4).[5]

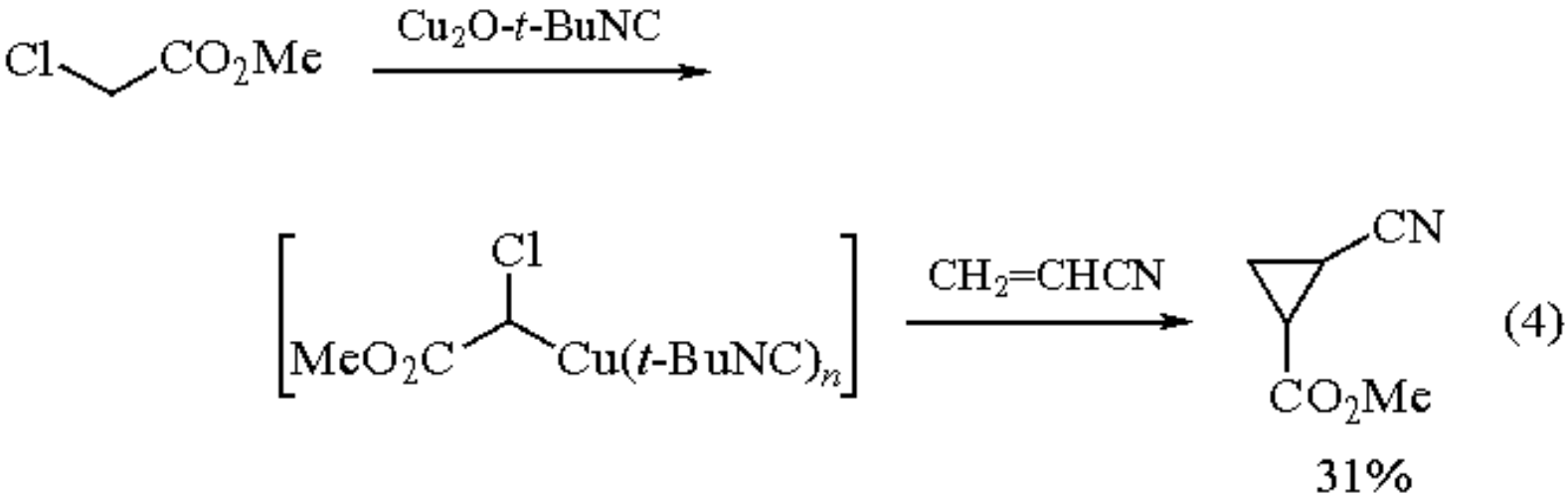

When ***Copper*** powder is substituted for Cu_2O, the resulting mixed reagent reacts with active halogen compounds, probably through an oxidative addition of the carbon-halogen bond, to generate organocopper compounds. Copper(0)-*t*-

butyl isocyanide promotes cyclopropanation of α,β-unsaturated esters and nitriles with trichloromethyl compounds such as trichloroacetonitrile and trichloroacetate (eq 5).[6]

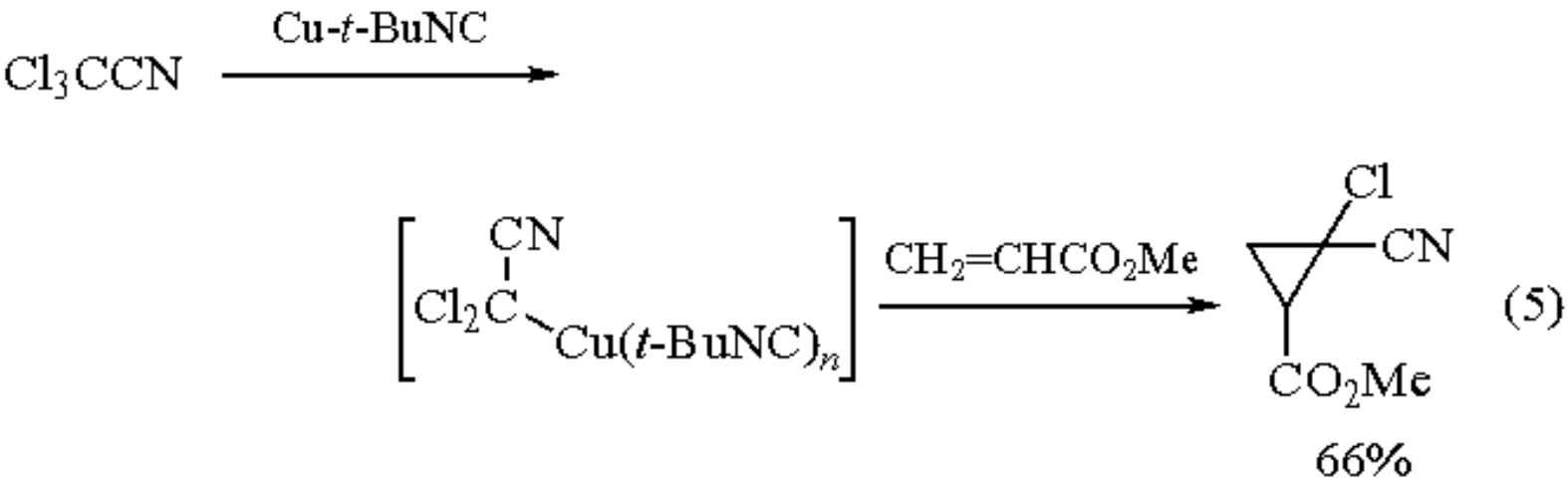

Similarly, as shown in eq 6, vinylcyclopropanes can be prepared in moderate yields by the reaction of 1,3- or 3,3-dichloropropenes with α,β-unsaturated esters.[7]

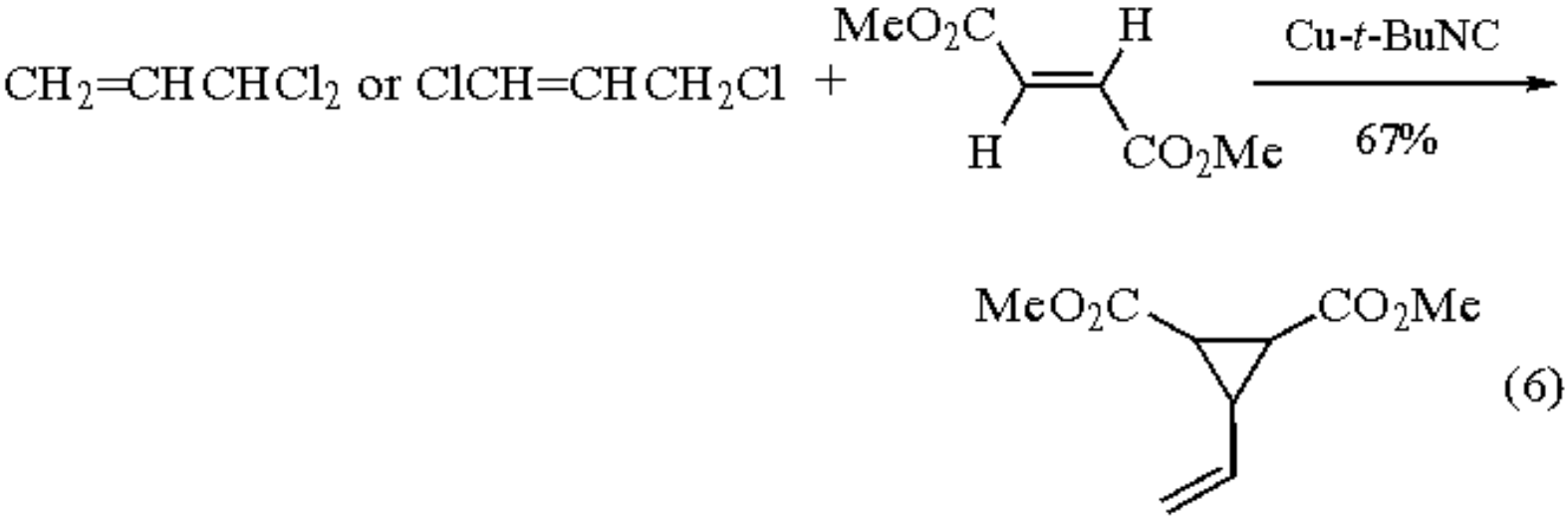

Allenes.

The reagent employing copper powder reductively transforms *gem*-dibromocyclopropanes to allenes (eqs 7 and 8).[8]

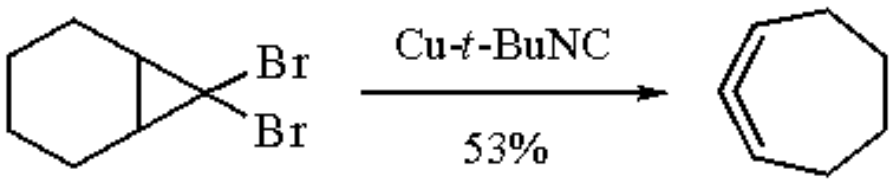

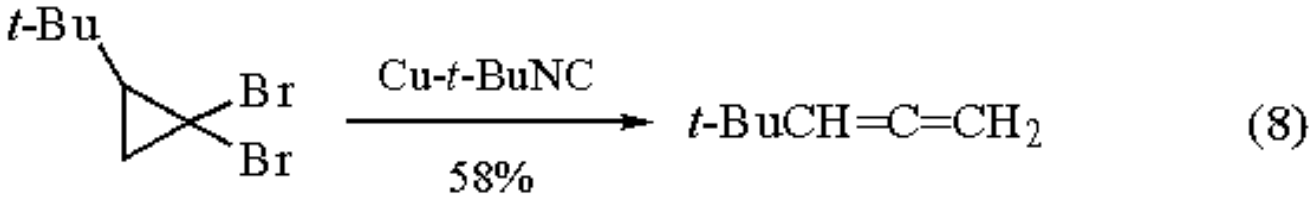

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Copper(II) Permanganate

$$Cu(MnO_4)_2.7H_2O$$

[82002-29-5] · $CuMn_2O_8$ · Copper(II) Permanganate · (MW 427.52)

(oxidant capable of converting saturated and α,β-unsaturated secondary alcohols into the corresponding ketones, primary alcohols and aldehydes into carboxylic acids, and sulfides into sulfones)

Physical Data: high-melting solid.

Solubility: sol water; insol methylene chloride.

Form Supplied in: red solid, commercially available.

Handling, Storage, and Precautions: oxidant, store in glass vessel at rt.

Oxidation.

Hydrated copper permanganate is an excellent oxidant for alcohols and sulfides when used heterogeneously in methylene chloride.[1,2] For secondary alcohols, the reaction is complete in a few minutes when alcohol (2.5 mmol in 2 mL of methylene chloride) is added to the oxidant (1.2 g, 2.7 mmol). For primary alcohols, aldehydes, and sulfides the reaction time is on the order of 24 h.[2,3] In all cases the products are easily isolated in good yields by filtration followed by flash evaporation of the solvent. The anhydrous reagent is much less effective. Examples of typical reactions are given in eqs 1-7.

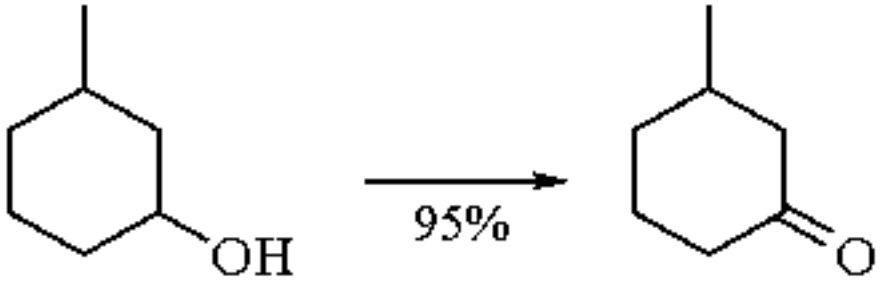

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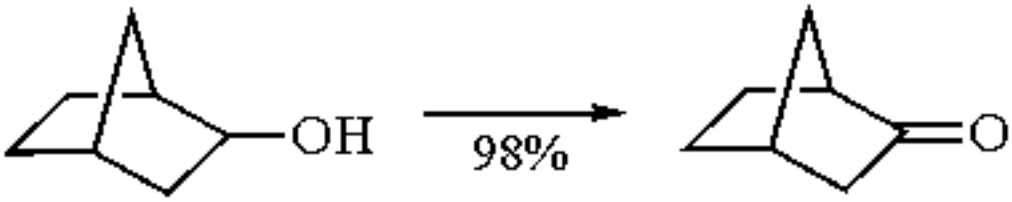

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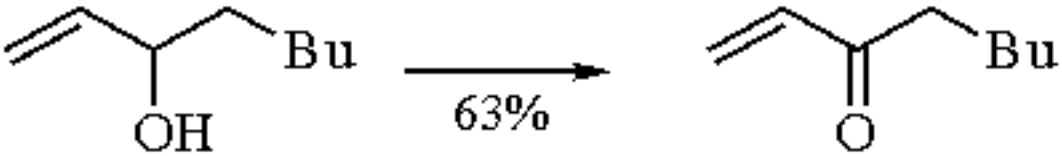

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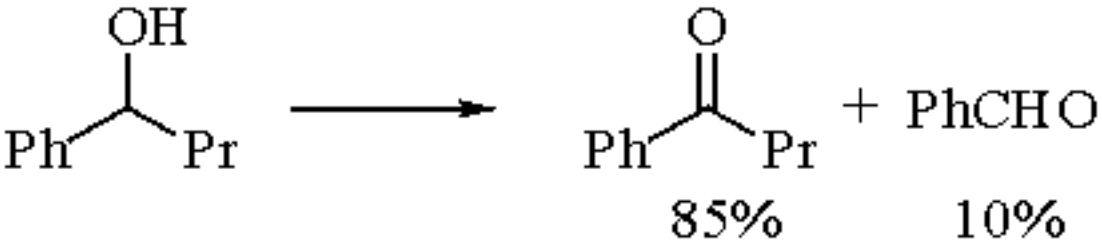

(4)

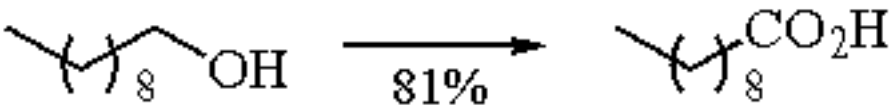

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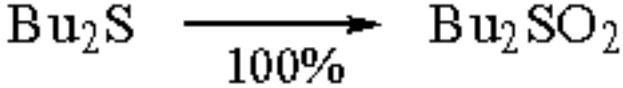

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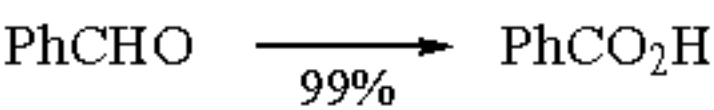

(7)

The presence of alkenes inhibits the oxidation of alcohols[4] and sulfides,[3] presumably by formation of π-complexes at the active site of the homogeneous reagent, thereby preventing direct contact between the alcohol and the oxidant. Interestingly, although alkenes inhibit the oxidation of other reductants, their presence does not result in reduction of the reagent to an observable extent. It has been suggested that the failure of the reagent to oxidize non-allylic unsaturated alcohols, such as cholesterol, may also be due to formation of a π-complex with the remote double bond.[4]

A reagent prepared from a finely ground mixture of $KMnO_4$ and $CuSO_4.5H_2O$ has properties similar to copper(II) permanganate heptahydrate; however, its reactions are in general less vigorous and require longer times to reach completion (see ***Potassium Permanganate-Copper(II) Sulfate***).

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Copper(I) Phenoxide

PhOCu

[34046-55-4] · C_6H_5CuO · Copper(I) Phenoxide · (MW 156.65)

(phenoxylating agent for organic halides,[1] organosulfur compounds,[2] and carbon tetrachloride;[3] undergoes carbon-carbon bond cleavage by oxygen[4])

Solubility: sol DMF, diglyme; insol ether and benzene.

Preparative Methods: metathesis reaction between ***Copper(I) Chloride*** and alkali metal phenoxide in MeCN or THF produces a solution of Cu^I phenoxide complexed with alkali metal chloride,[1,2] which can be used for synthetic purposes. Cu^I phenoxide without alkali metal chloride can be prepared by phenolysis of ***Methylcopper***,[1] ***Phenylcopper***,[5] and ***Copper(I) t-Butoxide***[4] or by metathesis between $[Cu(MeCN)_4]PF_6$ and sodium phenoxide.[6]

Handling, Storage, and Precautions: oxygen- and moisture-sensitive; preparation and reaction should be conducted under rigorously oxygen-free and anhydrous conditions.

Aryl Ether Synthesis.

Alkyl phenyl ethers (eq 1) and diphenyl ether (eq 2) are prepared in good yield using Cu^I phenoxide.[1] Phenyl ether synthesis proceeds under milder reaction conditions than the Williamson ether synthesis. Cu^I phenoxide has been proposed to be an intermediate of the Ullmann ether synthesis.

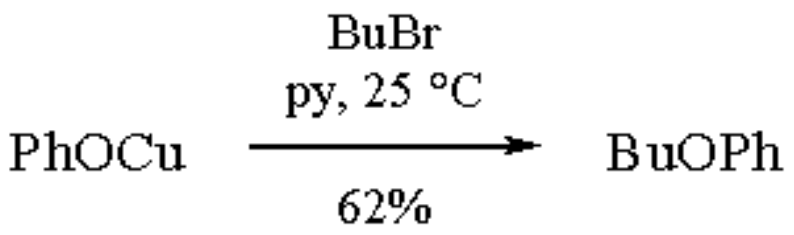

(1)

$$\text{PhOCu} \xrightarrow[\text{94\%}]{\text{PhI, py, 115 °C}} \text{PhOPh} \qquad (2)$$

Sulfur Substitution.

Cu^I phenoxide reacts with carbon disulfide at room temperature to afford phenyl orthocarbonate (eq 3).[2] Substituted Cu^I phenoxides can also be used. This reaction has been called the thiophilic reaction of Cu^I and provides a synthetic method for phenyl orthocarbonate without using phosgene. Nucleophilic addition and substitution in a tetrameric Cu^I phenoxide cluster has been proposed. The reaction in the presence of a tri-*n*-butylphosphine ligand produces thiocarbonate $(PhO)_2C{=}S$ in excellent yield. At the elevated reaction temperature of 65 °C, the reaction of Cu^I phenoxide with thiocarbonates takes place to give mixed orthocarbonates $(ArO)_2(PhO)_2C$. Substitution of the sulfur atom of sodium xanthates ROCSSNa, dithioesters RCSSR, and trithiocarbonates $(RS)_2CS$ by the phenoxide anion occurs to afford mixed thiocarbonates (PhO)(RO)C=S, phenyl thioesters R(PhO)C=S, and phenyl thiocarbonate $(PhO)_2C{=}S$, respectively.

$$4\ \text{PhOCu} + CS_2 \xrightarrow[\text{92\%}]{\text{MeCN, rt}} C(OPh)_4 + 2\ Cu_2S \qquad (3)$$

Chlorine Substitution of CCl_4.

Cu^I phenoxide reacts with CCl_4 via a radical mechanism to afford phenyl orthocarbonate (eq 4),[3] while nucleophilic reaction of sodium phenoxide with CCl_4 does not give phenyl orthocarbonate. The reaction depends upon the substitution pattern at the *ortho* positions of the phenyl group. Two examples are shown in eqs 5 and 6.

$$\text{PhOCu} \xrightarrow[\text{50\%}]{CCl_4,\ \text{MeCN, rt}} C(OPh)_4 \qquad (4)$$

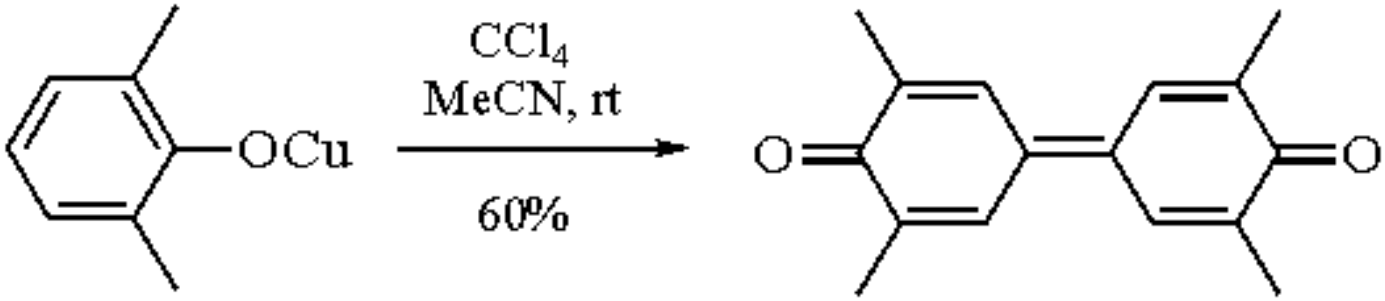

(5)

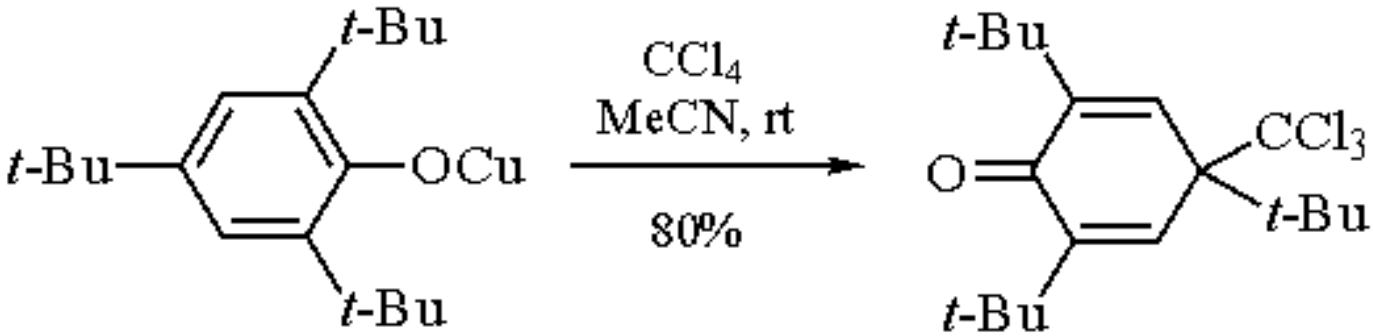

(6)

Oxygenolysis.

Cleavage of the carbon-carbon bond of Cu^I phenoxide takes place upon exposure to oxygen to afford *cis,cis*-muconic acid monophenyl ester (eq 7).[4] Cu^I phenoxide has been proposed to be an active reaction intermediate in the copper-promoted oxygenolysis of phenol.

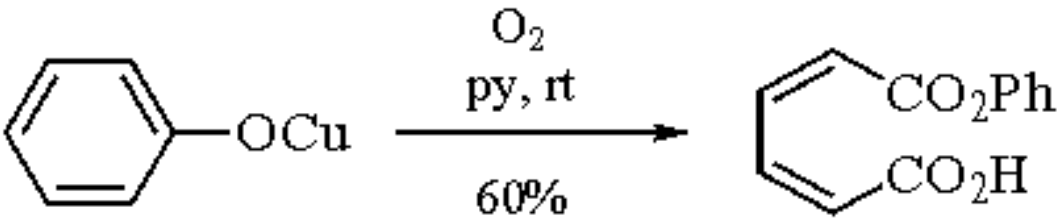

(7)

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Tetsuo Tsuda

Kyoto University, Japan

Copper(II) Sulfate

$CuSO_4.5H_2O$

[7758-99-8] · CuO_4S · Copper(II) Sulfate · (MW 249.68)

(Lewis acid catalyst for alcohol dehydration,[1] acetonide formation,[6] acetal exchange;[9] reagent for formation of copper carbenoids,[15] intramolecular cyclopropanations;[21] redox catalyst with potassium permanganate for oxidation of alcohols[25] and alkenes[28])

Physical Data: 110 °C, -4H_2O; 150 °C, -5H_2O; heating above 560 °C causes decomposition to CuO; *d* 2.28 g cm^{-3}.

Solubility: sol H_2O and methanol; slightly sol ethanol; insol acetone and ether; anhyd form sol H_2O, practically insol methanol and ethanol.

Form Supplied in: blue solid, widely available. *Drying:* for certain applications, copper(II) sulfate must be used as an anhyd reagent; dehydration of $CuSO_4.5H_2O$ can be accomplished by heating in an open porcelain dish at 275 °C for two days in a drying oven, stirring the sample several times during the drying period to break up any lumps; during this time the deep blue crystals are converted to an off-white powder.

Handling, Storage, and Precautions: $CuSO_4.5H_2O$ can be stored and handled in the laboratory using normal laboratory methods; anhyd $CuSO_4$ is a powerful desiccant and must be stored out of contact with moisture, but can be weighed and transferred in the laboratory if atmospheric exposure is minimized; copper(II) sulfate is a strong irritant to the skin and mucous membranes.

Introduction.

The principal uses of $CuSO_4$ in organic synthesis stem from the chemical properties of Cu^{2+}. Firstly Cu^{2+} functions as a Lewis acid towards electron donor functions and can thus promote a variety of acid-catalyzed processes. Secondly Cu^{2+} reacts readily with diazo compounds to give carbenoid intermediates useful in subsequent addition reactions. Thirdly Cu^{2+} functions as an effective redox catalyst in several mixed oxidizing systems.

Lewis Acid Catalysis.

Complexation of oxygen by Cu^{2+} makes an oxygen-containing functional group a much better leaving group. As

such, the Cu^{2+} functions as a typical Lewis acid; however, anhyd $CuSO_4$ can be used effectively to promote a variety of reactions that would be adversely affected by significant amounts of water. The dehydration of alcohols by anhyd $CuSO_4$ is an excellent general method for the preparation of alkenes.[1] The alcohol (neat or in an inert solvent) is heated with 0.75-1.0 equiv of $CuSO_4$.[1-3] The copper sulfate can be used alone or supported on silica gel.[4] The method works well for benzylic, allylic, tertiary, and secondary alcohols, but is unsuitable for primary alcohols, which give the bis-ether rather than the alkene. The product mixtures are similar to those obtained in proton-catalyzed eliminations and suggest that carbocation intermediates are involved in the reaction. The method is mild and suitable for the formation of sensitive alkenes (eq 1).[5] See also ***Copper(II) Trifluoromethanesulfonate***, ***Phosphoric Acid***, ***Potassium Hydrogen Sulfate***, and ***Sulfuric Acid***.

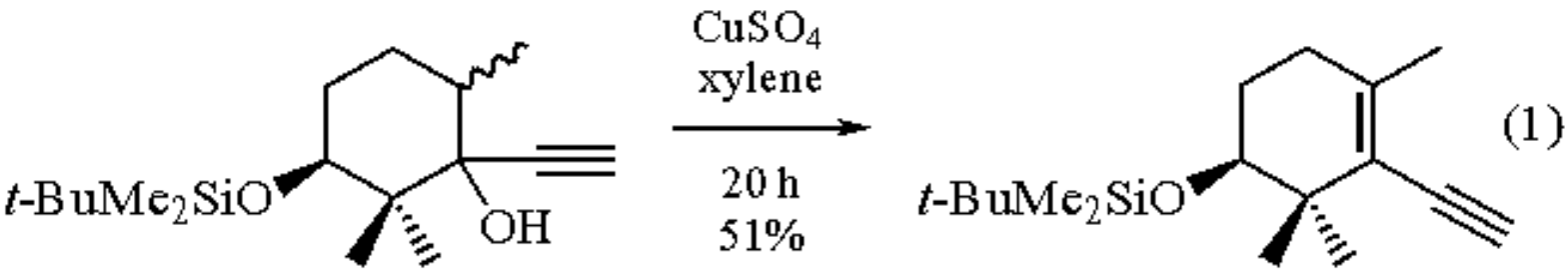

Anhyd copper sulfate is also an excellent catalyst for the formation of acetonides from glycols and acetone (eq 2).[6,7] Either ***2,2-Dimethoxypropane*** or ***2-Methoxypropene*** can sometimes improve the efficiency. The regiochemistry of the copper-catalyzed process is different from that found in the proton-catalyzed reaction.

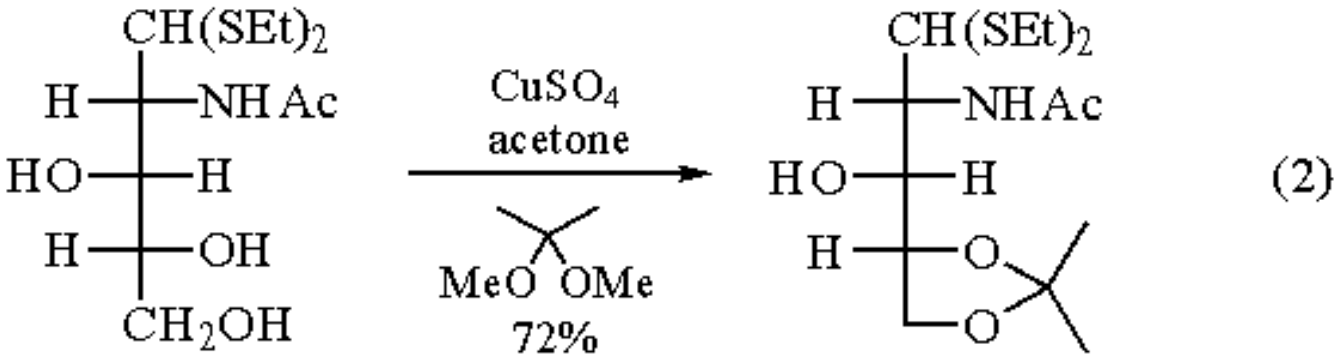

Acetonides can also be produced directly from epoxides and acetone using anhyd $CuSO_4$,[8] and acetal exchange can be used to deprotect ethylene glycol acetals under very mild conditions (eq 3).[9] Anhyd $CuSO_4$ has also been used as a Lewis acid catalyst for the removal of trityl protecting groups[10] and for Friedel-Crafts acylation of alkenes.[11]

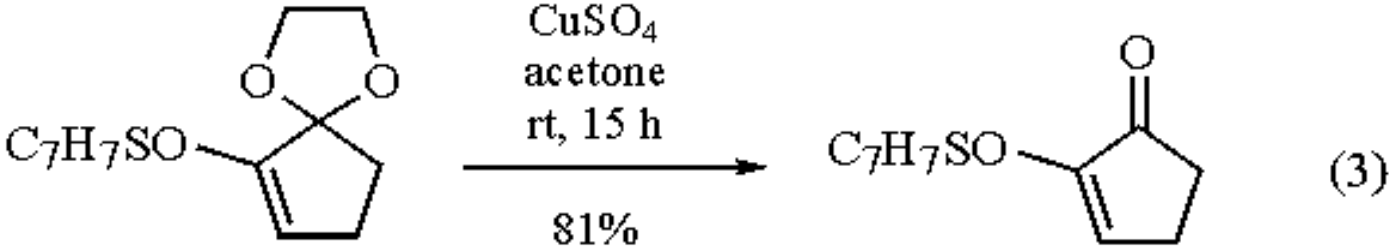

Complexation of nitrogen by Cu^{2+} has been used to advantage in several cases. The selective hydrolysis of α-

aminodiesters is guided by chelation to nitrogen and activation of the vicinal ester group (eq 4).[12] Cycloreversions of 2-azanorbornenes to give primary amines are catalyzed efficiently by copper sulfate (eq 5).[13] Copper sulfate (or other Cu^{2+} sources) facilitates the preparation of ***Diimide*** from ***Hydrazine*** by complexation with nitrogen.[14] See also ***Copper(II) Acetate***.

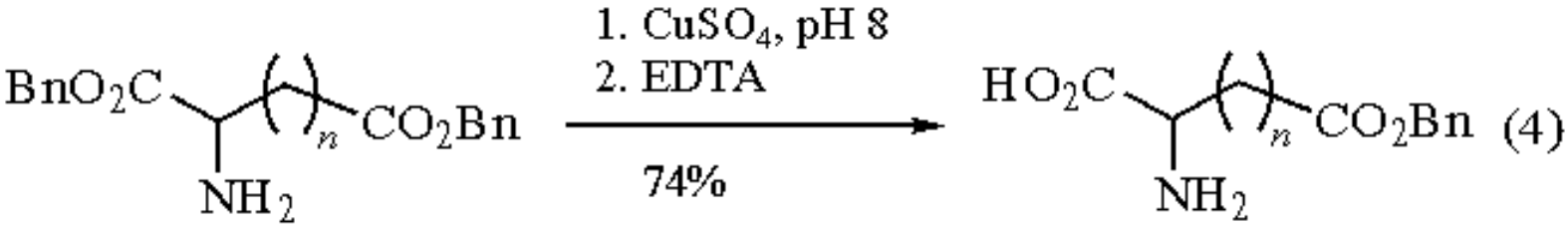

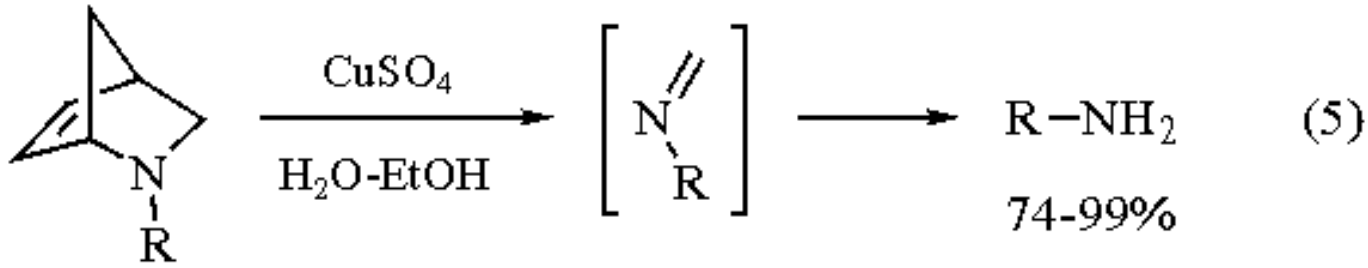

Copper Carbenoids.

Copper(II) catalysts (as well as other copper species) promote the decomposition of diazo compounds and produce copper carbenoids as reactive intermediates. This is particularly useful for α-diazo carbonyl compounds, which then can add to unsaturated systems to give cyclopropanes.[15] In addition, chiral ligands can be attached to the copper, yielding cyclopropanes in high optical purities.[16,17]

Because intramolecular alkene additions are particularly favored with copper catalysts,[18] and because the low coordinating ability of the sulfate counterion is thought to contribute to an increased electrophilicity of the copper carbenoid when copper sulfate is used as the catalyst,[19] anhyd $CuSO_4$ has been used in a variety of intramolecular cyclopropanations (eqs 6 and 7, for example).[20,21]

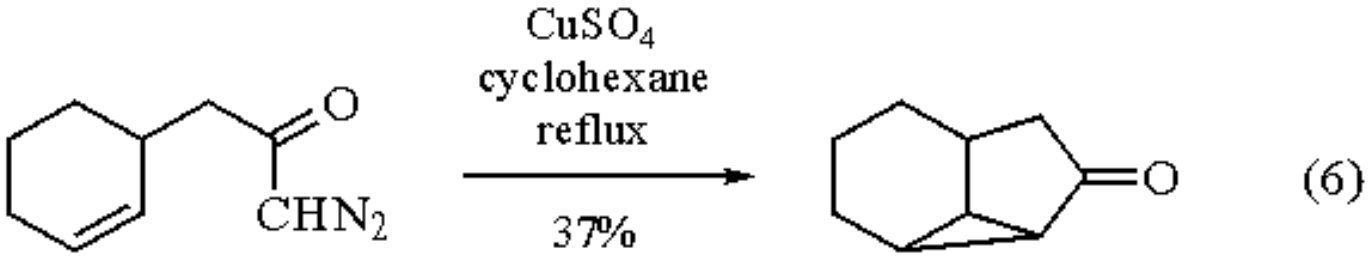

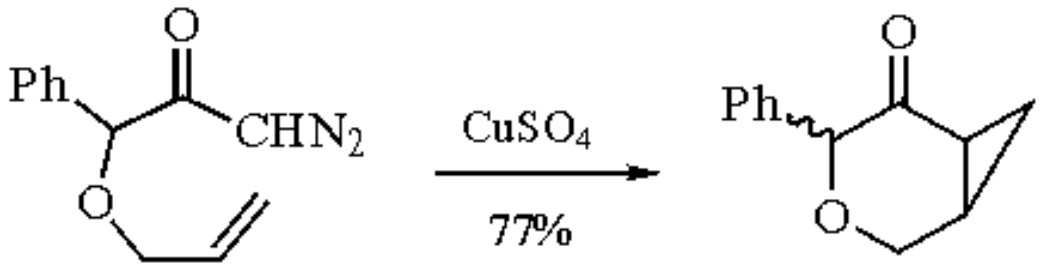

(7)

In the absence of double bonds, intramolecular insertion reactions into C-H bonds are observed (eq 8).[22] Recently, intramolecular insertion into the B-H bond of a carborane has been found to occur readily.[23] Anhyd $CuSO_4$ has also been used effectively to promote the formation of sulfur ylides in the reactions of diazo compounds and sulfides.[24] See also ***Copper(I) Acetylacetonate***.

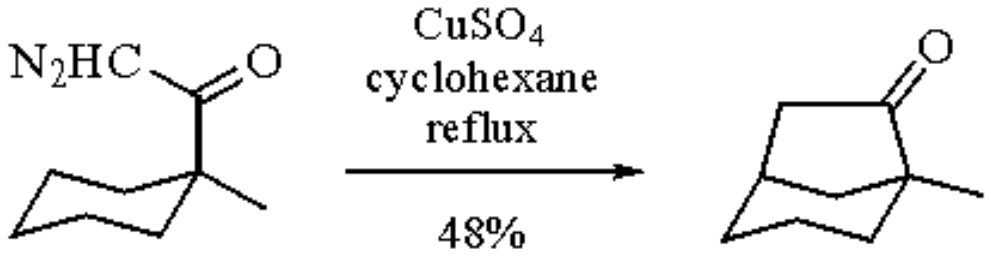

(8)

Redox Catalyst.

Solid mixtures of $CuSO_4$ and oxidizing agents are useful for the oxidation of alcohols. For example, it was found that a solid mixture of ***Potassium Permanganate*** and copper sulfate pentahydrate oxidized secondary alcohols to ketones in high yields; however, primary alcohols were not oxidized under the same conditions.[25] This selectivity is quite unusual since under homogeneous conditions potassium permanganate vigorously oxidizes both primary and secondary alcohols. This selectivity is reversed by admixture of a solid base (either $CuCO_3$, ***Copper(II) Hydroxide***, or ***Potassium Hydroxide***) to the $KMnO_4$-$CuSO_4.5H_2O$ oxidant (eq 9).[26]

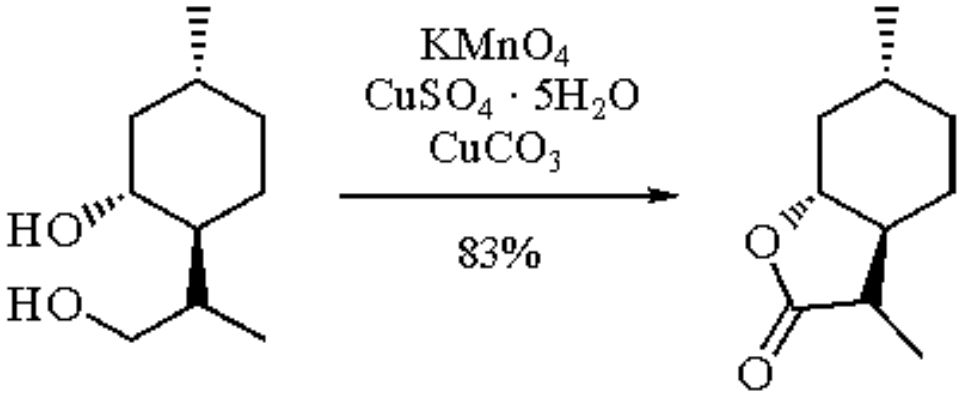

(9)

These results are rationalized on the basis of the heterogeneous oxidation which takes place on the surface of the solid oxidant. In the absence of an admixed base, secondary alcohols produce ketones which diffuse away from the oxidant surface. Primary alcohols produce carboxylic acids which are bound to the oxidizing surface, effectively blocking further reaction. Inclusion of the heterogeneous base results in neutralization of the acid product and reexposure of the oxidant surface; thus the normal selectivity is restored.

In these oxidations the use of hydrated $CuSO_4$ is mandatory. In fact, it was found that addition of catalytic amounts of water to the solid oxidant creates a more reactive oxidant for the synthesis of lactones from hydroxyaldehydes (eq 10).[27] Small quantities of aqueous *t*-butanol added to the solid oxidant permit the direct conversion of alkenes to α-hydroxy ketones and α-diketones (eq 11).[28] Normally, alkenes are inert to the solid oxidant. These differences are attributed to the formation of a thin aqueous phase on the surface of the oxidant (&OOmega; phase) which facilitates phase transfer between the bulk liquid and the surface.

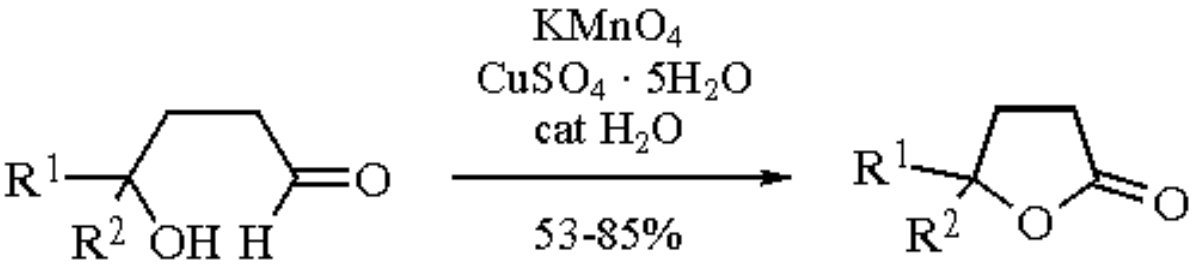

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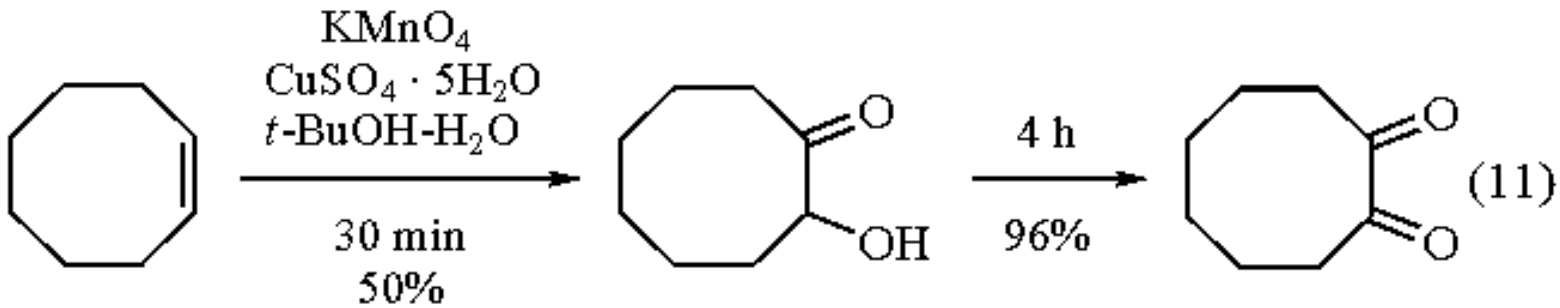

(11)

Copper sulfate in combination with ascorbic acid and oxygen has been used as a source of hydroxyl radicals to study the oxidation of dopamine.[29] Furthermore, copper sulfate has been used as a catalyst in the Ullmann reaction.[30] In both these cases, however, the copper sulfate merely serves as a source of Cu^{2+} which is reduced to a copper(I) species that is thought to be the key player in the process.

Related Reagents.

Potassium Permanganate-Copper(II) Sulfate.

---

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Copper(II) Sulfate-Pyridine

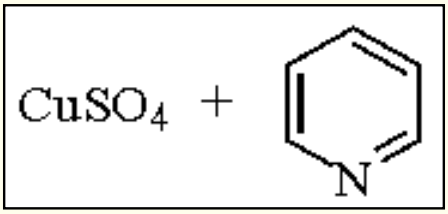

($CuSO_4.5H_2O$)

[7758-99-8] · CuO_4S · Copper(II) Sulfate-Pyridine · (MW 249.68) (py)

[110-86-1] · C_5H_5N · Copper(II) Sulfate-Pyridine · (MW 79.10)

(hydration of aryl-substituted oxiranes;[1] oxidation of hydroxy ketones[2])

Physical Data: see ***Copper(II) Sulfate*** and ***Pyridine***.

Hydration of Aryl-Substituted Epoxides.

Aryl-substituted oxiranes undergo stereospecific *cis* ring opening in the presence of copper(II) sulfate and pyridine in an aqueous phosphate buffer (pH 7), producing *cis*-diols. Hydration occurs at the benzylic position of the aryl-substituted epoxide. *Trans* cleavage products are also obtained in less than 15% yield (eq 1).[1]

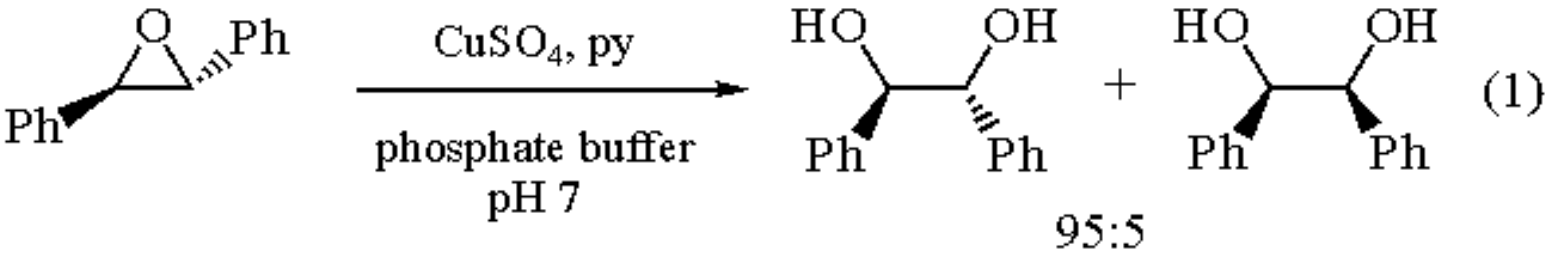

It was also shown that *cis*-chlorohydrins could be prepared from aryl-substituted epoxides in a reaction involving copper sulfate, pyridine, and ***Lithium Chloride*** in THF (eq 2). Lithium chloride increases the catalytic activity of copper(II) sulfate in this reaction. However, when methanol is used as a solvent, *cis*-glycol monomethyl ethers are obtained (eq 3). Under such conditions, a reaction with alkyl-substituted epoxides does not take place. Substitution occurs at the benzylic position.[1]

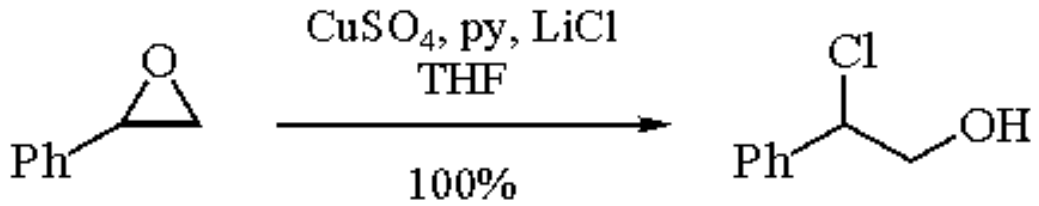

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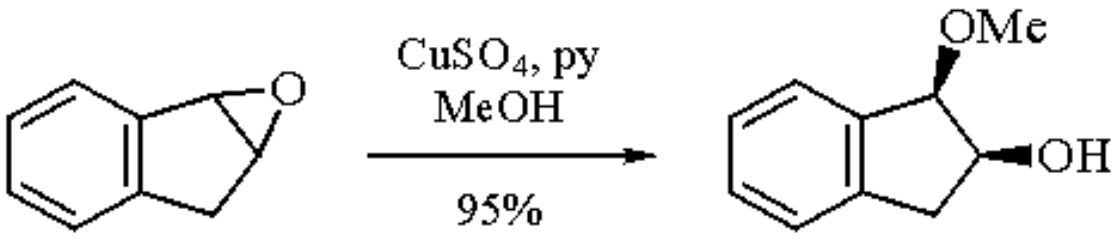

(3)

Oxidation of Hydroxy Ketones.

Oxidation of benzoin by oxygen (or air) in the presence of stoichiometric amounts of copper(II) sulfate in aqueous pyridine gives benzil in 80% yield (eq 4).[2] Similarly, furil was obtained from furoin in 63% yield (eq 5)[3] and α-hydroxybenzyl 2-pyrrolyl ketone was oxidized to phenyl-2-pyrrolylglyoxal in 95% yield (eq 6).[4]

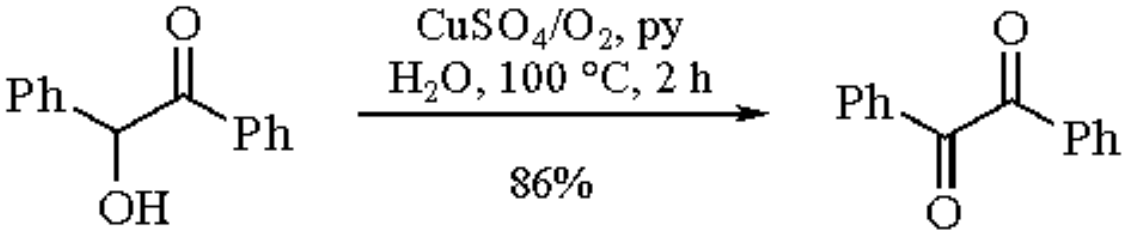

(4)

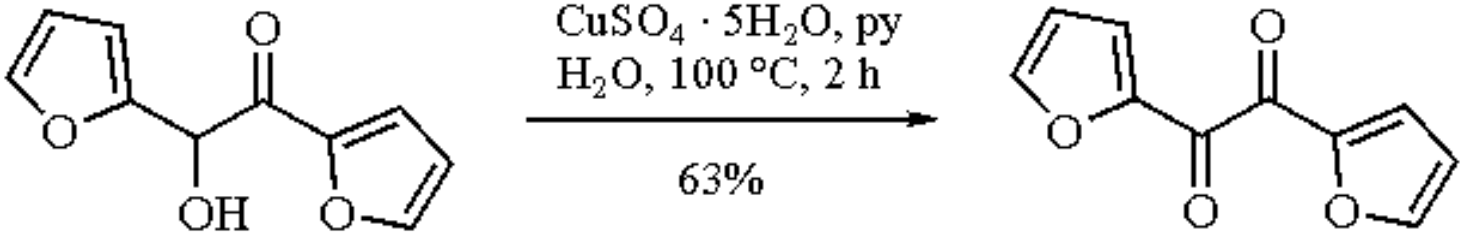

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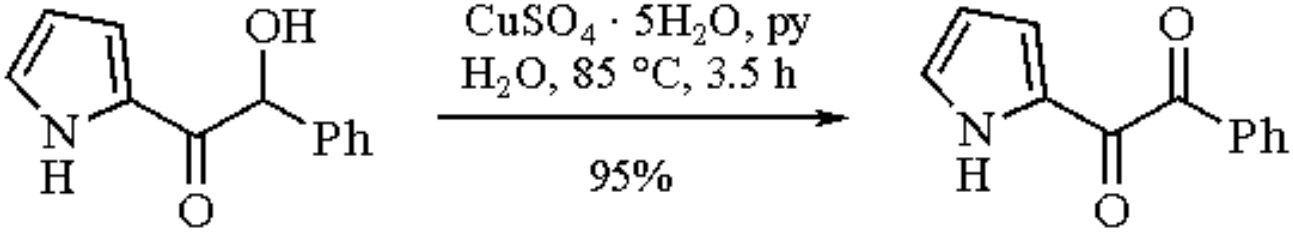

(6)

Related Reagents.

Copper(II) Sulfate; ***Potassium Permanganate-Copper(II) Sulfate***.

1. Imuta, M.; Ziffer, H. *JACS* **1979**, *101*, 3990.
2. Clarke, H. T.; Dreger, E. E. *OSC* **1941**, *1*, 87.
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4. Gardner, T. S.; Wenis, E.; Lee, J. *JOC* **1958**, *23*, 823.

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Copper(II) Tetrafluoroborate

$Cu(BF_4)_2$

[38465-60-0] · B_2CuF_8 · Copper(II) Tetrafluoroborate · (MW 237.15)

(Lewis acid capable of promoting Diels-Alder reactions;[1] promotes decomposition of diazo compounds;[2] functions as an oxidizing agent;[3] reacts with siloxycyclopropanes to generate β-acylalkylcopper(II) species;[4] in combination with hydrosilanes is a *syn*-selective reducing agent of alkynic sulfones[5])

Physical Data: d 2.175 g cm^{-3} for the hexahydrate.[6]

Solubility: sol water, THF, MeOH, EtOH; insol ether.

Form Supplied in: blue powder. *Drying:* copper(II) tetrafluoroborate ($Cu(BF_4)_2.xH_2O$), irrespective of the number of crystalline water, has a highly hygroscopic nature. Therefore, prior to use, it should be dried and stored in a dry nitrogen atmosphere (e.g. over KOH at 25 °C for 5 d;[1] P_2O_5 at 50 °C/1 mmHg overnight;[4,5] at 100 °C, under high vacuum for 5 h[7]). Previous work has suggested that dehydration of the hexahydrate to give a tetrahydrate[8] takes place easily at reduced pressure at rt, while the anhydrous salt appears to be unknown. Accordingly, note that the procedures so far examined for drying are unlikely to give a pure anhydrous salt.

Handling, Storage, and Precautions: because of its highly hygroscopic nature, copper(II) tetrafluoroborate should be stored so as to preclude contact with moisture. Lumps should be crushed only in a glove bag or dry box filled with N_2. Use in a fume hood.

Catalyst of Diels-Alder Reactions.

Copper(II) tetrafluoroborate has been found to promote Diels-Alder reaction of 5-methoxymethyl-1,3-cyclopentadiene and α-chloroacrylonitrile (eq 1).[1] This dienophile serves as a ketene synthon; thus, when subjected to alkaline hydrolysis, the product gives the bicyclic ketone. A similar acceleration of Diels-Alder reactions by copper tetrafluoroborate is recognized in the reaction of α-methylthioacrylonitrile and cyclopentadiene (eq 2).[9] The thermal process requires heating to 140 °C without solvent, whereas the copper-catalyzed reaction can be conducted at 20 °C in benzene solution. With furan as a dienophile, copper tetrafluoroborate in combination with hydroquinone catalyzes the [4 + 2] cycloaddition (eqs 3 and 4).[10,11] In this reaction system, a copper(I) tetrafluoroborate complex, formed through the reduction of copper(II) by hydroquinone, is believed to play a key role.[10]

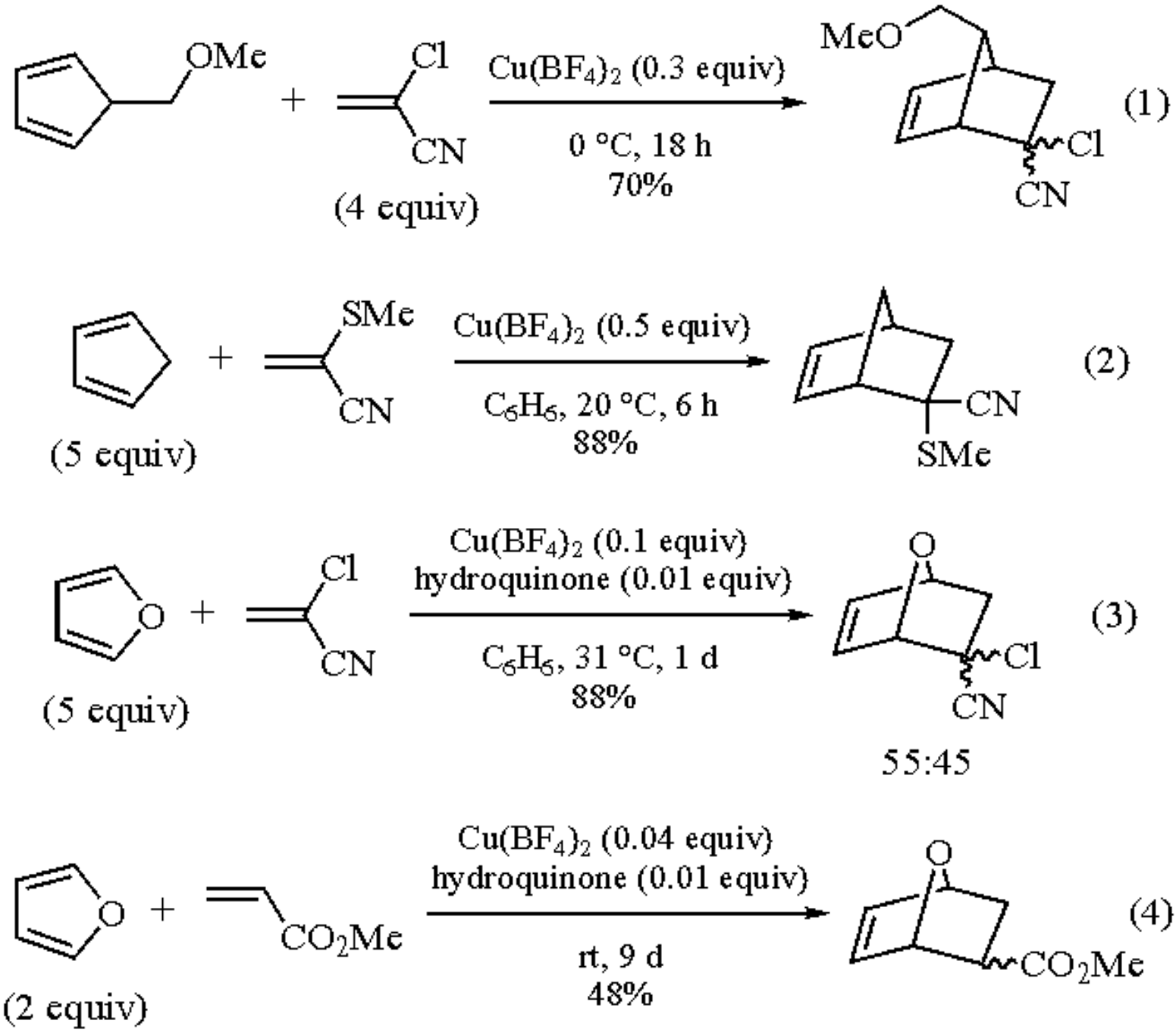

Decomposition of Diazo Compounds.

Like other copper salts, copper(II) tetrafluoroborate can serve as the catalyst for the decomposition of diazo compounds to generate copper carbenoids.[2] The preference of cyclopropanation by ***Ethyl Diazoacetate*** (EDA) for less-substituted alkenes has been observed specifically with copper(II) tetrafluoroborate (also with ***Copper(II) Trifluoromethanesulfonate***), showing different selectivity with other copper catalysts (***Copper(II) Acetylacetonate***, ***Copper(I) Iodide-Trimethyl Phosphite***, $(MeO)_3P.CuCl$, ***Copper(II) Sulfate***, etc.) (eq 5). The active catalyst may be alkene coordinated copper(I) tetrafluoroborate,[12] which might be generated by the reduction of copper(II) tetrafluoroborate by diazo compounds.

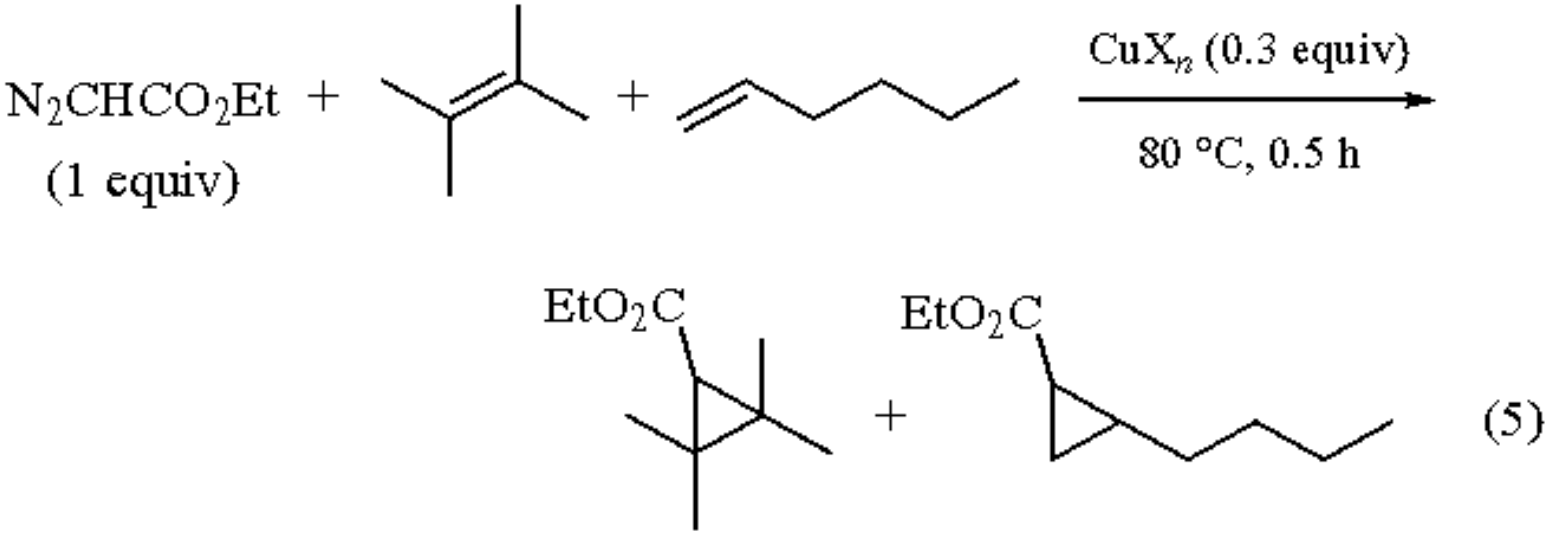

$Cu(BF_4)_2$	98% (19:81)
$Cu(OTf)_2$	96% (21:79)
$Cu(acac)_2$	96% (64:36)

The copper(II) tetrafluoroborate-catalyzed reaction of EDA with *N*-methylpyrrole gives a mixture of 2- and 3-acetate adducts (eq 6).[13] Thermal decomposition of a pyrazoline to give a cyclopropane ring can be performed efficiently with a catalytic amount of copper tetrafluoroborate in refluxing benzene (eq 7).[14]

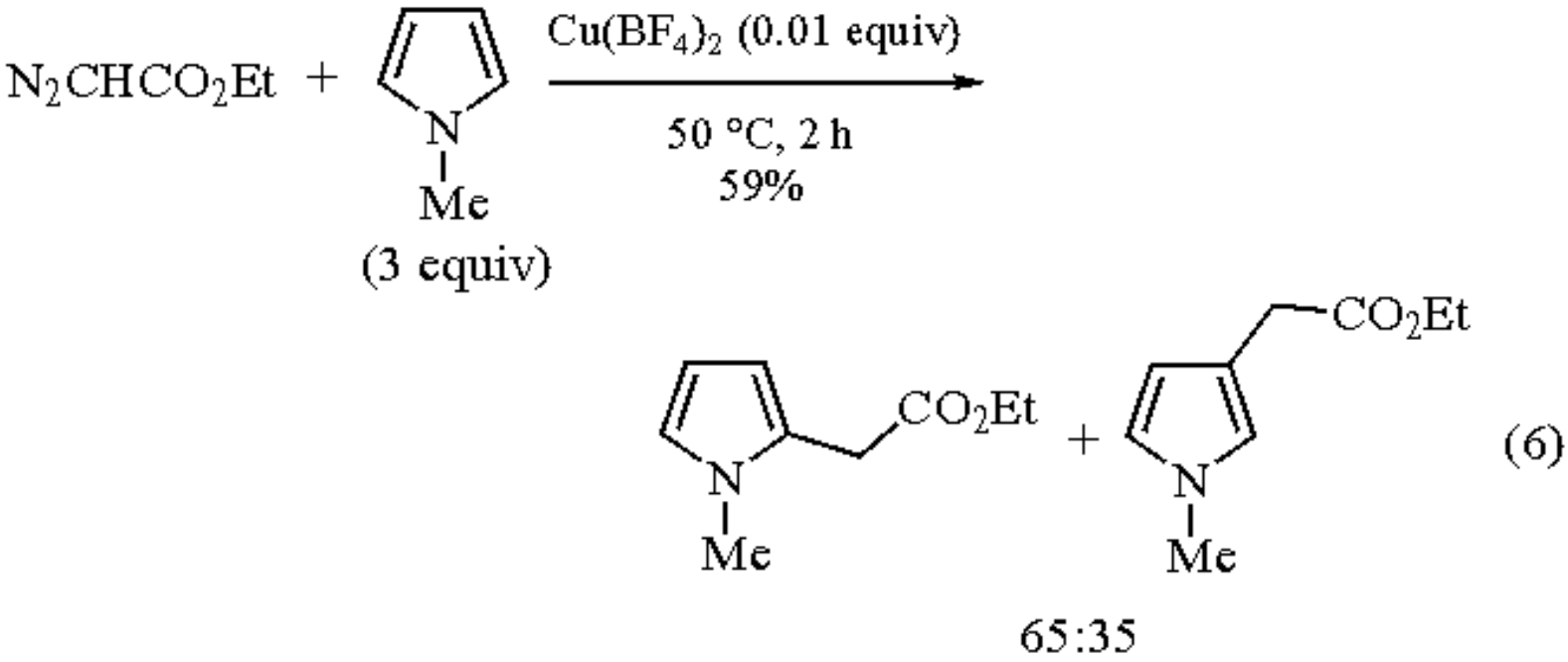

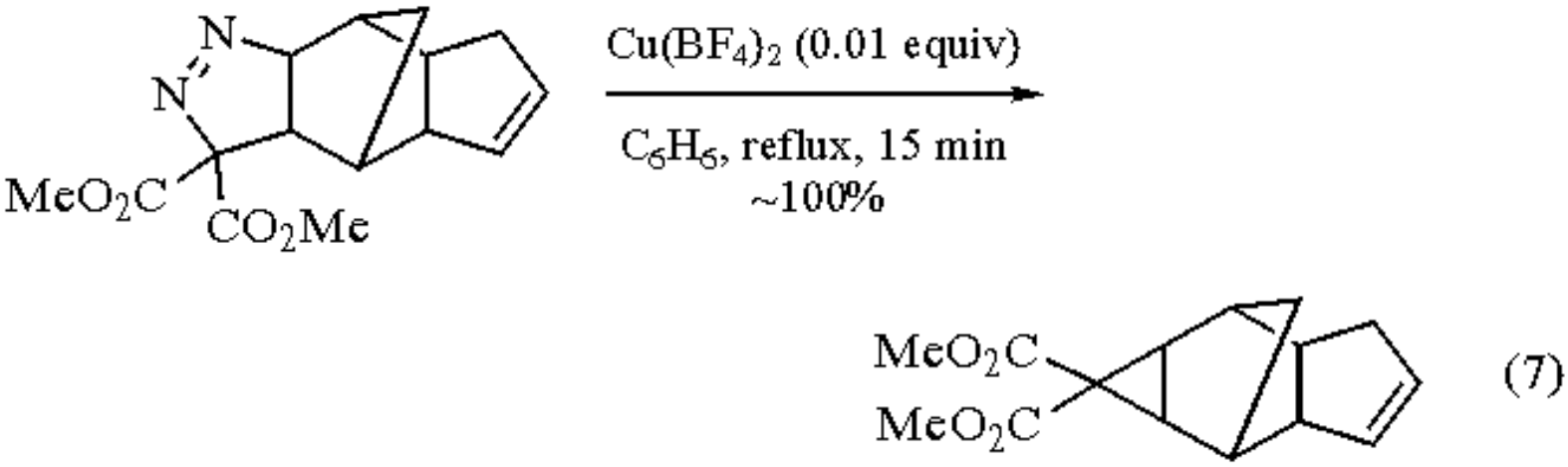

Oxidations.

Irradiation of a solution of benzyltrimethylsilane and 2 equiv of copper tetrafluoroborate in acetonitrile-methanol (3:1) with a 300 W high-pressure mercury lamp through a quartz filter gives benzyl methyl ether in 70% yield. Tetrakis(acetonitrile)copper(I) tetrafluoroborate is formed as a byproduct (eq 8).[3] The oxidation sequence can be applied to benzylgermanes and benzylstannanes. The reaction mechanism may involve (i) one-electron transfer from photoexcited singlet organometallic compounds to Cu^{II} to form the cation radical and Cu^{I}, (ii) dissociation of the cation radical to an arylmethyl radical, and (iii) the second oxidation of the radical by Cu^{II} to give the benzyl cation and Cu^{I}. It has also been reported that copper(II) tetrafluoroborate can be used for the effective oxidation of 5-*exo*-alkyl-5*H*-phlorin derivatives to give the corresponding 5-alkylporphyrins.[15] The oxidation ability of copper tetrafluoroborate has been utilized for the iodofunctionalization of alkenes, where Cu^{2+} ion oxidizes iodine to form iodonium cation.[16] In this reaction, water, alcohol, carboxylic acid, lithium chloride, sodium iodide, etc. can be used as the nucleophile.

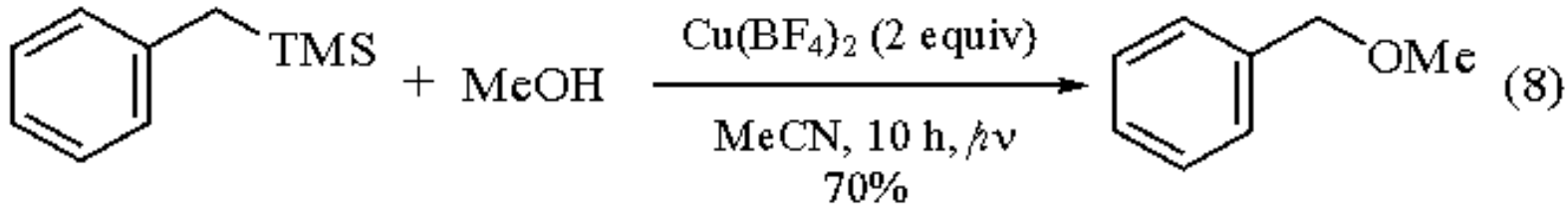

Reaction with Siloxycyclopropanes.

Copper tetrafluoroborate causes ring-opening of siloxycyclopropanes to provide useful synthetic reactions.[4] Treatment of a siloxycyclopropane with $Cu(BF_4)_2$ results in desilylative dimerization to give a 1,6-diketone in good yield (eq 9).[17] The ring-opening takes place regioselectively across the bond between the methylene and siloxy carbons. The reaction is reasonably interpreted by assuming electrophilic ring-opening by Cu^{2+} ion to form the β-copper(II) ketone, followed by dimerization.

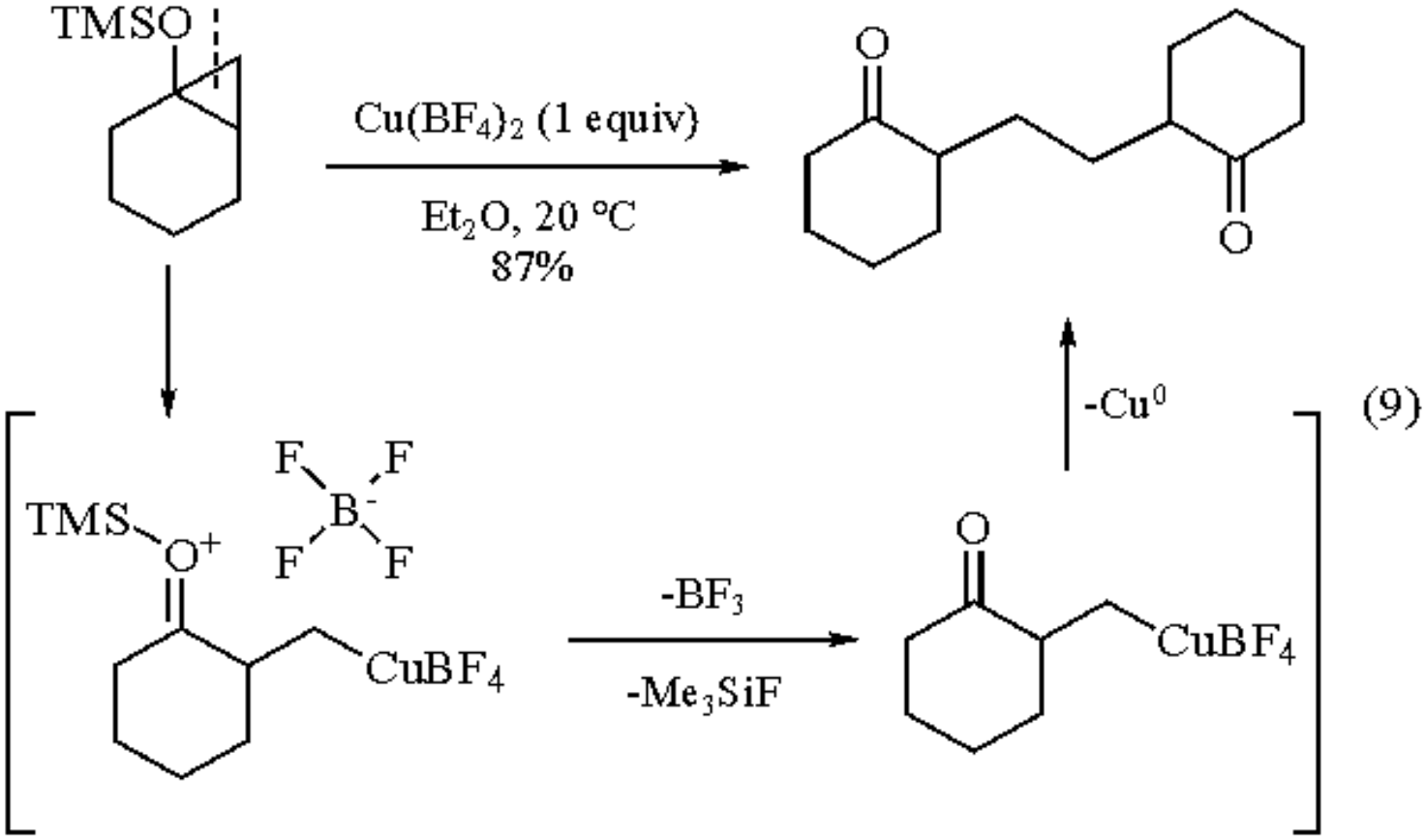

(9)

With ***Dimethyl Acetylenedicarboxylate*** and water, β-(acyl)alkyls can be trapped to give dimethyl 2-(3-oxoalkyl)maleates with a high degree of stereoselectivity (eq 10).[17] The selectivity arises from *syn* addition of β-copper(II) ketone across the triple bond followed by in situ protonation of the resulting vinylcopper species with retention of configuration. The stereoselective transfer of β-(acyl)alkyls to alkynic sulfones, which gives β-(acyl)alkylated vinylic sulfones, is also successful (eq 11). Intramolecular cyclization with 1-phenyl-2-trimethylsilyloxy-2-(3-hexenyl)cyclopropane results in modest amounts of the 5-*exo* cyclization product.[18]

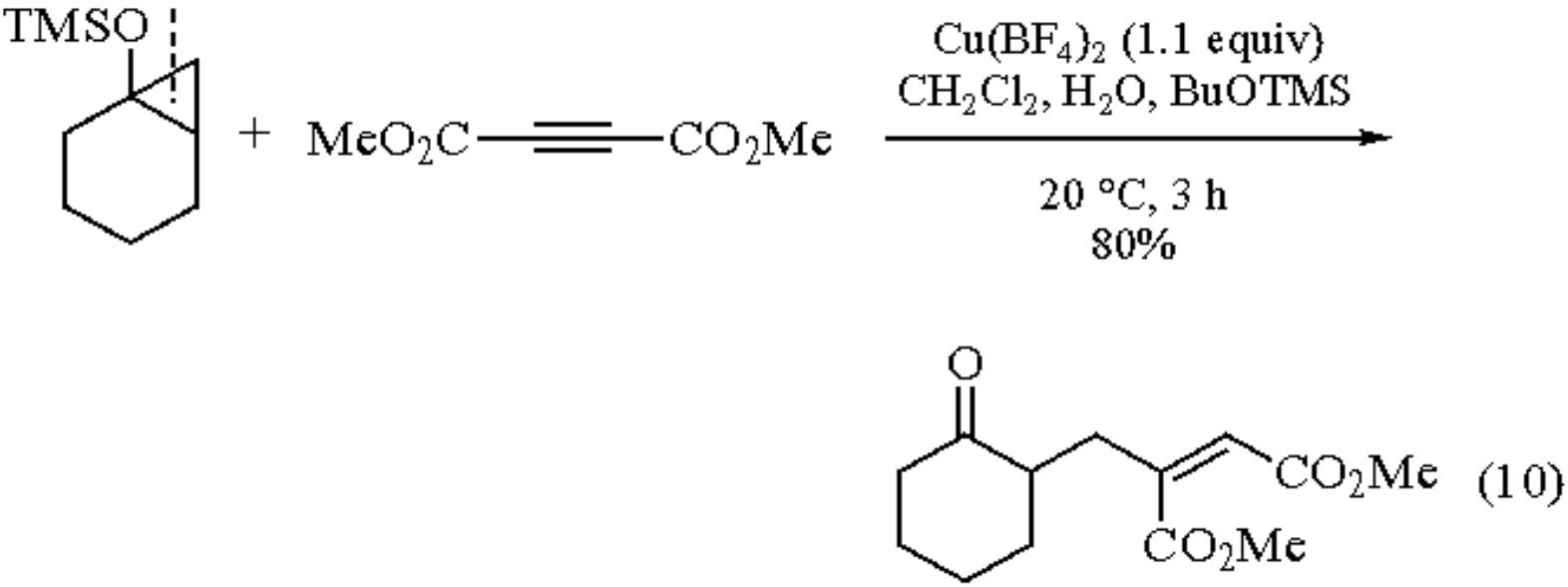

(10)

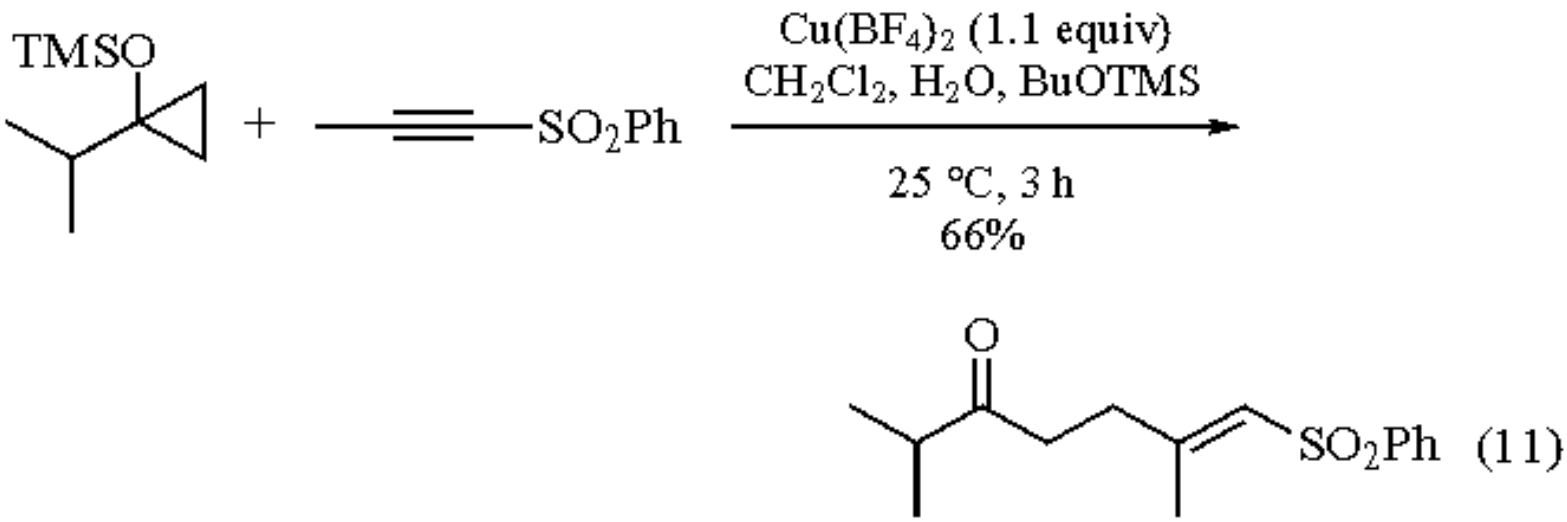

Reaction with Hydrosilanes.

Copper(II) tetrafluoroborate reacts readily with hydrosilanes to give hydrogen and trialkylfluorosilanes (eq 12). When an alkynic sulfone is present in this system, highly stereoselective *syn* reduction takes place to give a vinylic sulfone (eq 13).[5] The mechanism involving the *syn* addition of HCu^{II} seems likely.

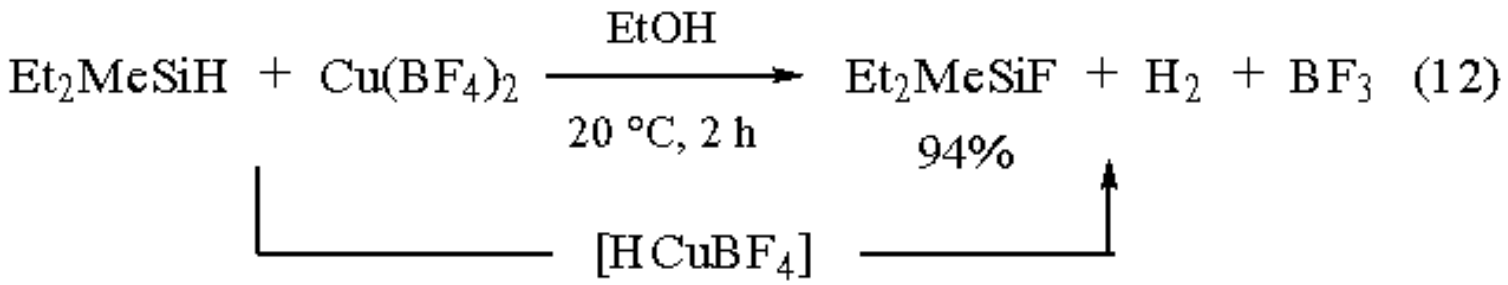

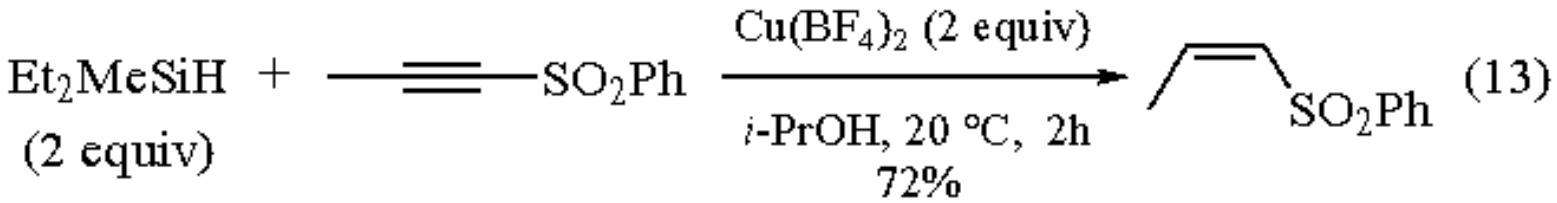

Related Reagents.

Silver(I) Tetrafluoroborate; ***Tetrafluoroboric Acid***.

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Copper(II) Trifluoromethanesulfonate

$Cu(OSO_2CF_3)_2$

[34946-82-2] · $C_2CuF_6O_6S_2$ · Copper(II) Trifluoromethanesulfonate · (MW 361.68)

(dimerization of ketone enolates and TMS enol ethers;[2a,2b] cyclization of dienolates[2c] and unsaturated silyl enol ethers;[4] allylation of ketones;[3] reactions of diazo compounds;[5-10] dehydration of alcohols[11])

Alternate Name: copper(II) triflate.

Physical Data: dec at 530 °C (no definite mp).

Solubility: sol MeOH, EtOH, DMF, MeCN, and formamide; also sol *i*-PrCN and acetone.

Form Supplied in: white powder, commercially available. Blue powder when freshly prepared (see below).

Preparative Methods: most conveniently prepared from copper(II) carbonate and triflic acid (***Trifluoromethanesulfonic Acid***) in MeCN.[1] The freshly prepared salt precipitated from Et_2O is pale blue.

Handling, Storage, and Precautions: moisture sensitive; can be handled in air for quick transfers; pure samples are only mildly corrosive. Appears to be indefinitely stable in the absence of air, moisture, and light.

Oxidative Coupling.

Both intermolecular and intramolecular oxidative coupling reactions can be effected using $Cu(OTf)_2$. Examples of dimerization include one-pot syntheses of 1,4-diketones from ketone enolates or from silyl enol ethers (eqs 1 and 2),[2a,2b] and coupling of allylstannanes with TMS-enol ethers to give γ,δ-unsaturated ketones in good to moderate yields (eq 3). Other copper(II) or tin(IV) catalysts can also be used with allylstannanes. The regiochemistry depends on both the substrate and the catalyst.

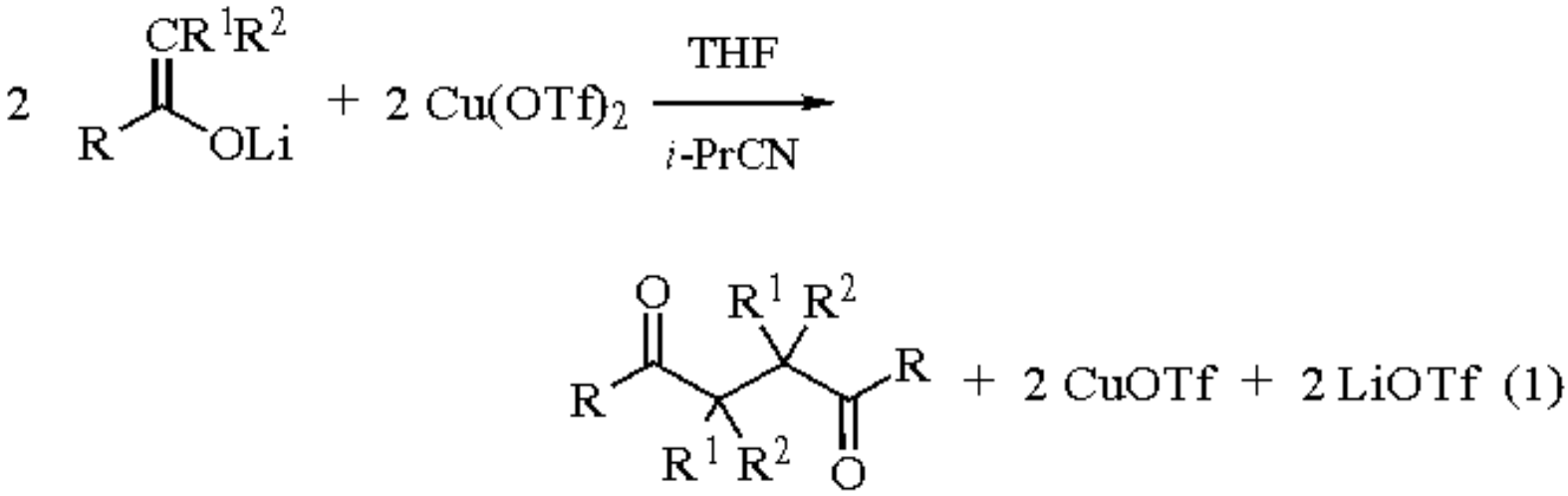

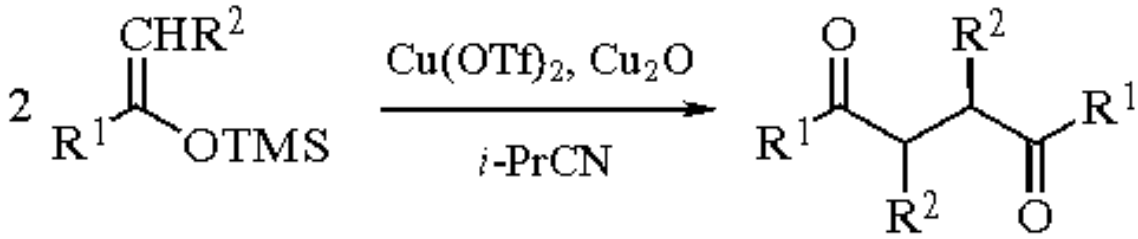

$R^1 = Ph,\ R^2 = H$ 55%
$R^1 = Ph,\ R^2 = Me$ 27%

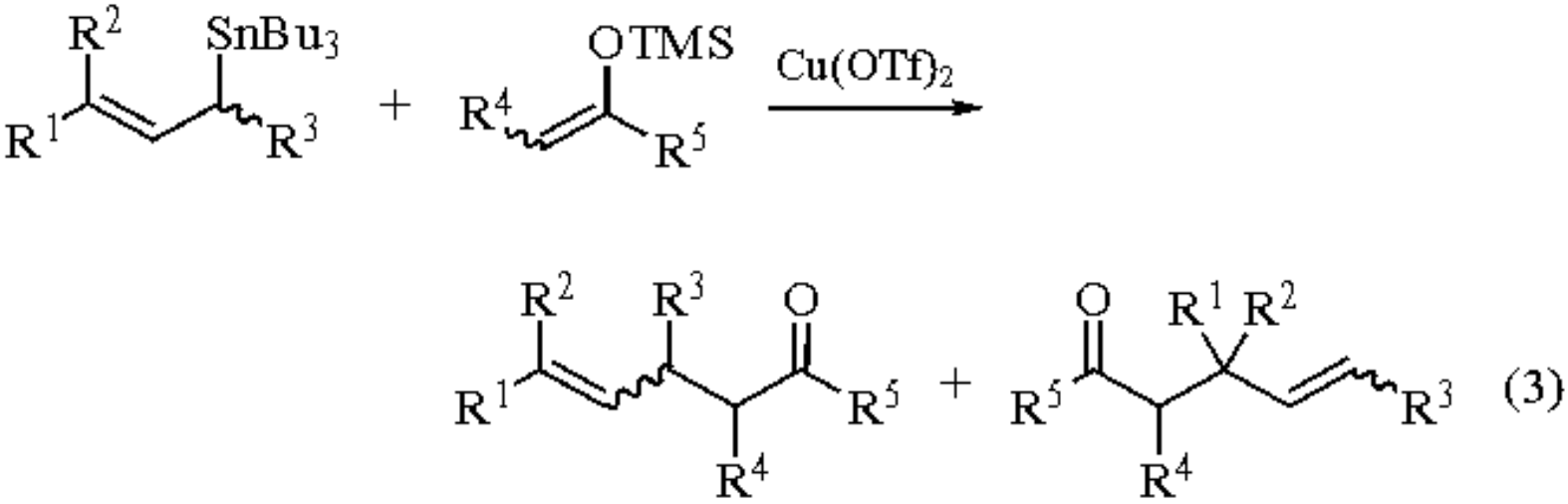

Examples of intramolecular oxidative cyclizations promoted by $Cu(OTf)_2$ include cyclization of enolates of diketones and diesters (eq 4)[2c] and oxidative cyclization of hydrolytically resistant δ,ε- and ε,ζ-unsaturated silyl enol ethers.[4] For instance, (**1**) reacts with excess $Cu_2O/Cu(OTf)_2$ in MeCN to give a 90% yield of a 20:1 mixture of the *trans*-fused and *cis*-fused tricyclic ketones (**2**) and (**3**) (eq 5).[4]

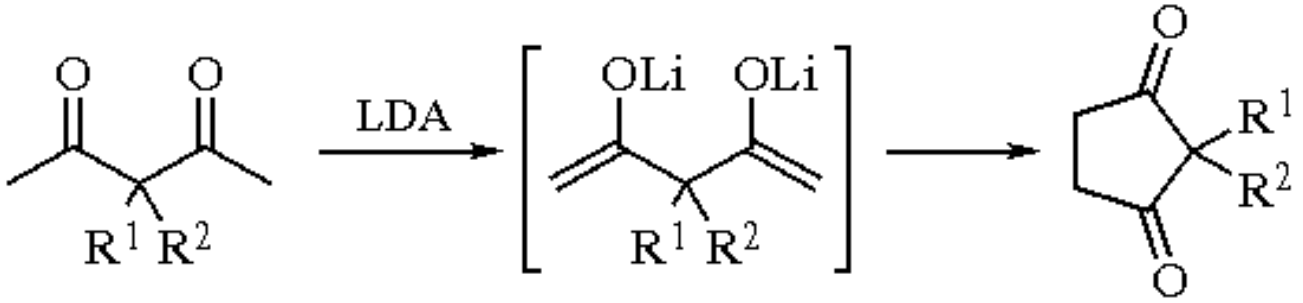

(4)

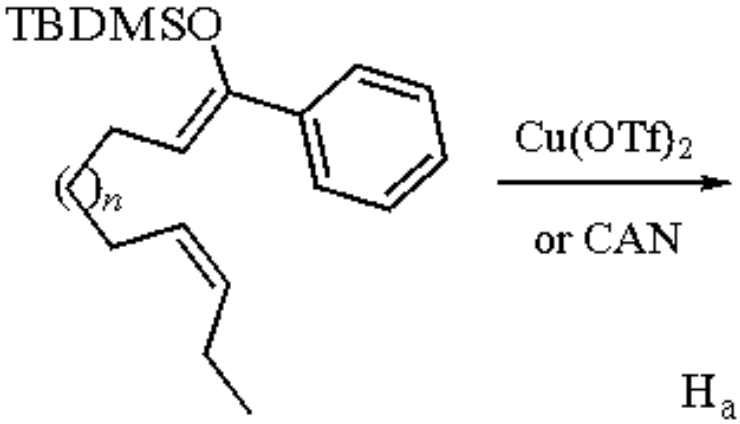

(1)

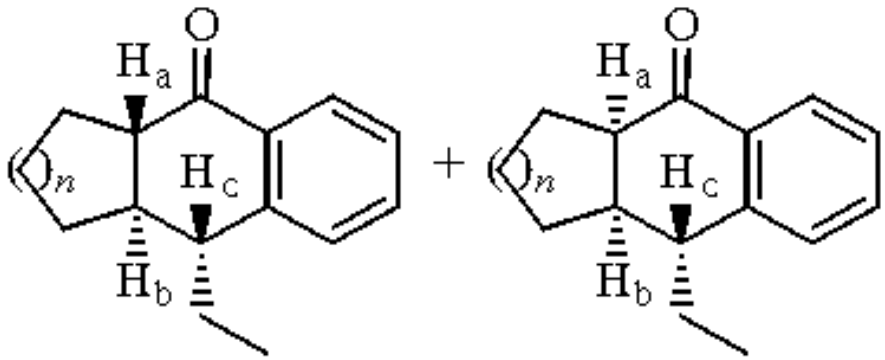

(2) (3)

(5)

Reactions of Diazo Compounds.

These include various cyclopropanations where the metal carbenoid generated from the diazoacetic acid esters/$Cu(OTf)_2$ system reacts with alkenes (eq 6) or carbodiimides (eq 7).[5,6]

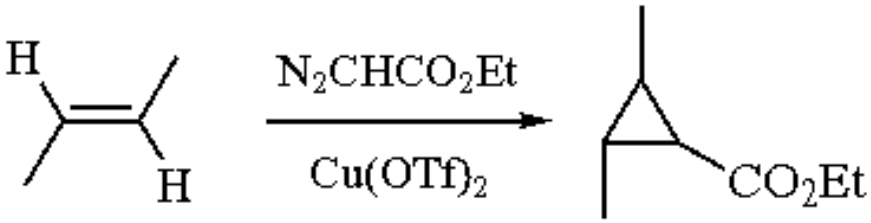

(6)

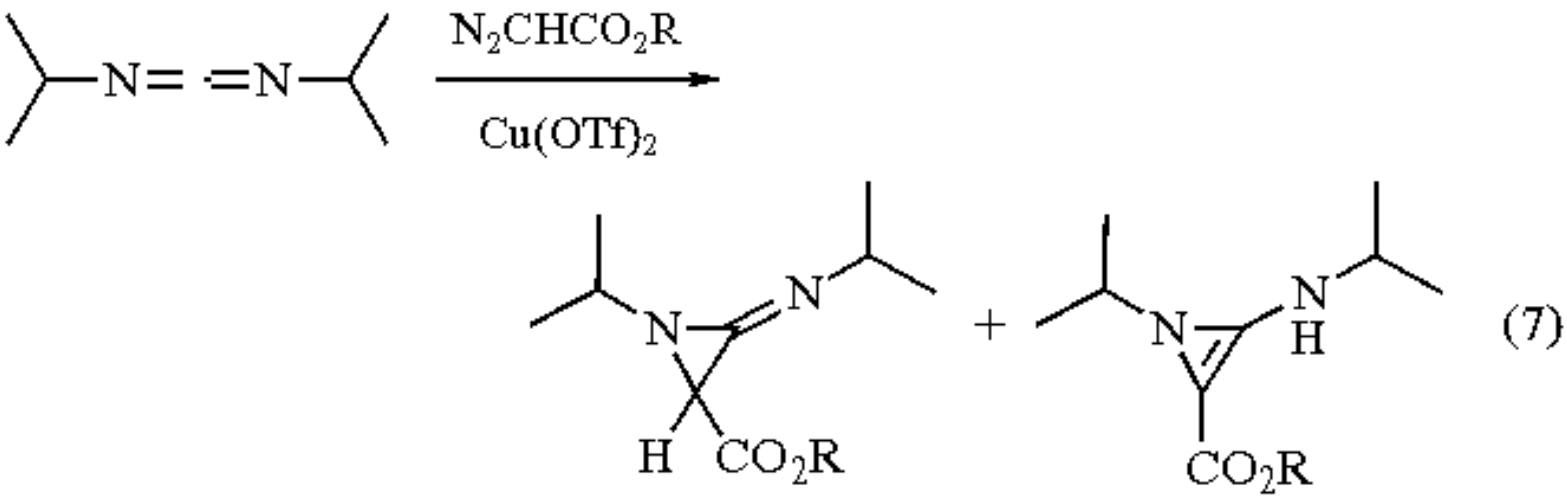

$Cu(OTf)_2$ is the reagent of choice for intramolecular cyclization of β,γ-unsaturated diazo ketones to cyclopentenones (eq 8) and for intramolecular cyclopropanation of γ,δ-unsaturated diazo ketones (eq 9).[7]

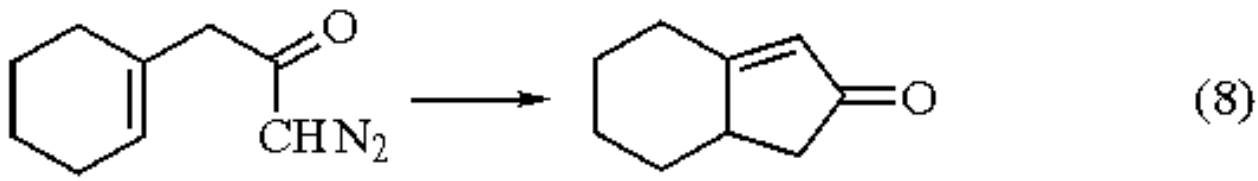

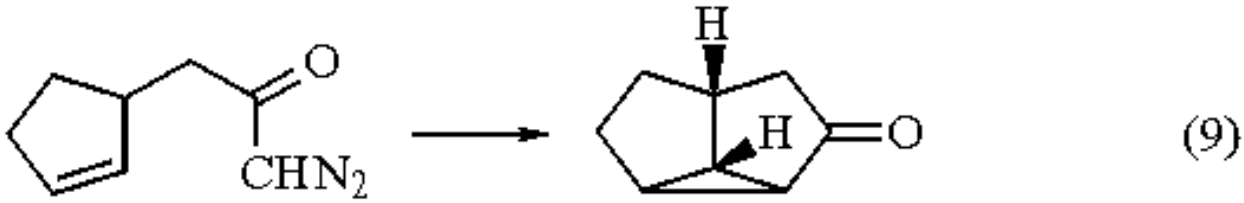

It is a useful reagent for orthoester homologation via dialkoxycarbenium ions and for oxazole formation by reaction of ketocarbenes (via diazo esters/$Cu(OTf)_2$) with nitriles (eq 10).[8] With unsaturated nitriles, the nitrile group is selectively attacked. Kinetic and ESR evidence shows that Cu^{II} -> Cu^{I} reduction is the key step.[9]

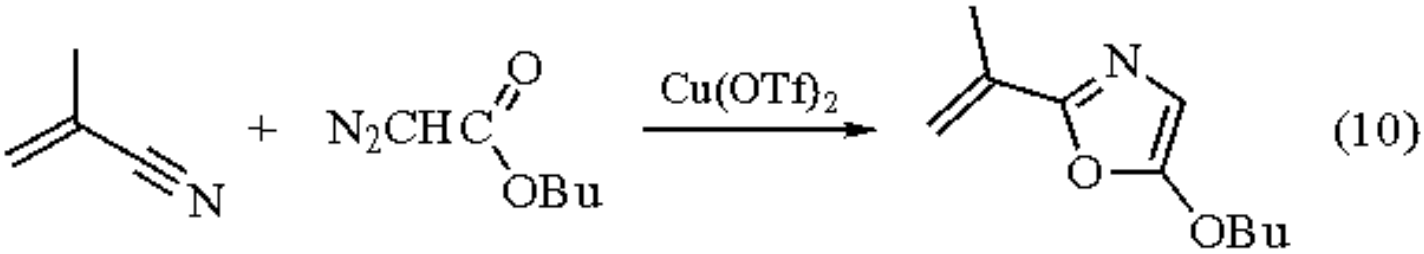

The regiochemistry of the monoacetate adducts formed from *N*-methylpyrrole with the carbenoid derived from $N_2CHCO_2Et/Cu(OTf)_2$ is indicative of a reactive and less discriminating intermediate compared to carbenoids generated from N_2CHCO_2Et with other Cu^{II} reagents (eq 11).[10]

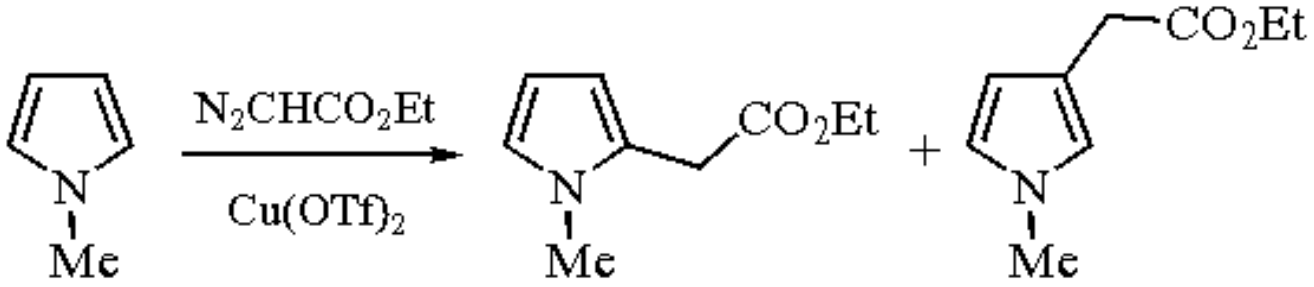

(11)

Angularly functionalized polycyclic systems may be prepared from β,γ-unsaturated diazo ketones by a vinylogous Wolff rearrangement in the presence of copper(II) triflate. Dry ***Copper(II) Acetylacetonate*** is equally suitable.[10]

Dehydration of Alcohols.

Various tertiary, secondary, and primary alcohols are dehydrated with $Cu(OTf)_2$ to alkenes.[11] Preferred formation of Zaitsev orientation products and (*E*)-alkenes are indicative of a carbocationic mechanism. $Zn(OTf)_2$ and $Mg(OTf)_2$ are ineffective. In selected examples, yields are superior to those of H_2SO_4 and $POCl_3$/pyridine dehydrations.[11] See also ***Copper(II) Sulfate***.

Elimination Reactions.

A $Cu(OTf)_2$/Hünig base combination provides a useful method for converting 1,1-bis(phenylthio)cyclobutanes to 1-(phenylthio)cyclobutenes (eq 12).[12]

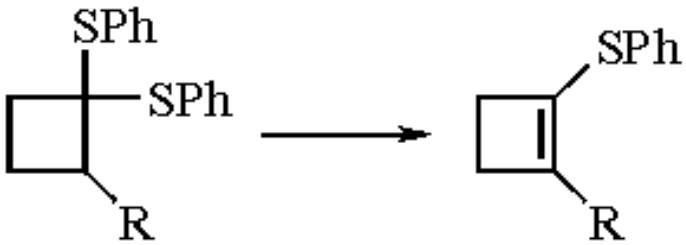

(12)

Reduction of Alkynyl Sulfones.

The $HSiEt_2Me/Cu(OTf)_2$ system reduces alkynyl sulfones to *cis* vinylic sulfones (eq 13).[13] The yields with ***Copper(II) Tetrafluoroborate*** are higher than those with $Cu(OTf)_2$. Dimeric side products are formed in some cases.

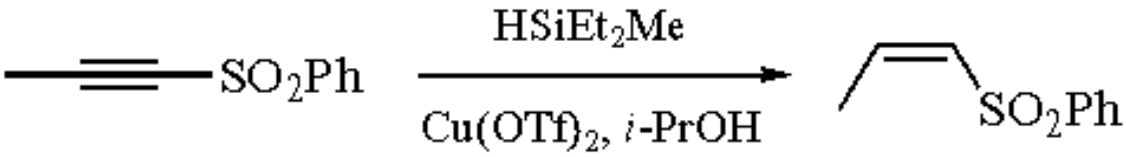

(13)

Oxazoles from Ketones.

Aliphatic ketones react with nitriles in the presence of $Cu(OTf)_2$ and catalytic amounts of ***p-Toluenesulfonic Acid*** in refluxing MeCN to give oxazoles.[14] The oxazole produced in this way is isomeric with that formed from a ketone and an amide (eq 14).

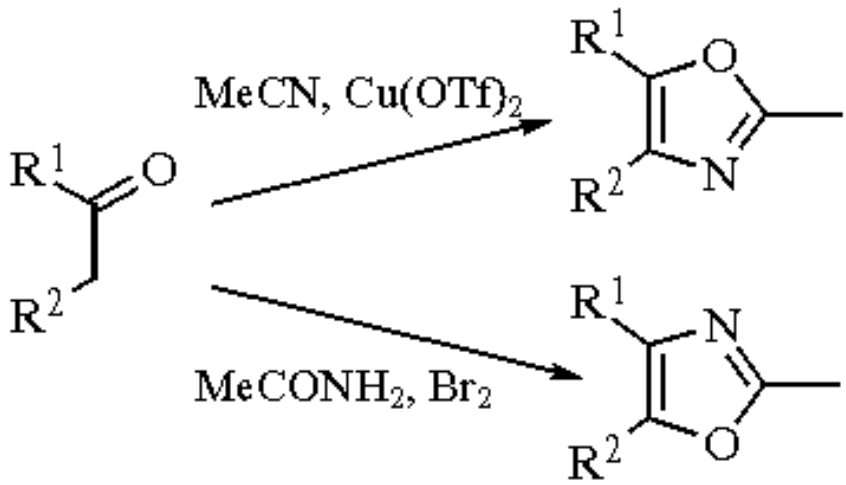

(14)

Oxidation of Alkyl Radicals.

Various alkyl radicals are oxidized with Cu^{II} triflate or perchlorate to carbenium ions whose reactivities are similar to solvolytically formed cations (eq 15).[1] The synthetic utility of such $Cu(OTf)_2$-catalyzed oxidations remains to be explored.

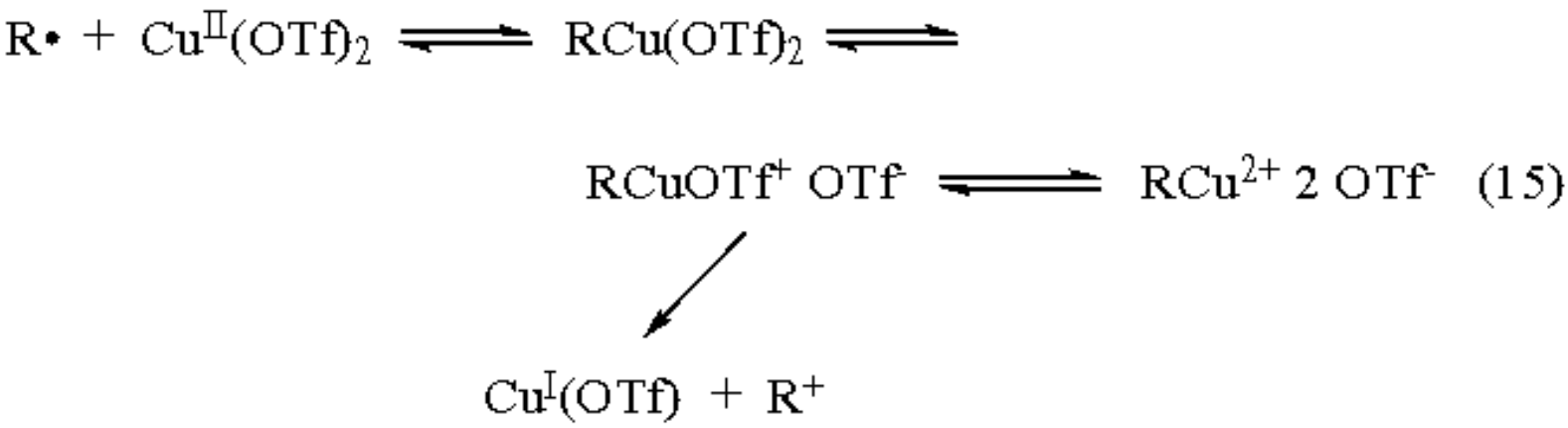

(15)

Related Reagents.

Copper(II) Sulfate; ***Copper(I) Trifluoromethanesulfonate***.

---

1. Jenkins, C. L.; Kochi, J. K. *JACS* **1972**, *94*, 843.
2. (a) Kobayashi, Y.; Taguchi, T.; Tokuno, E. *TL* **1977**, 3741. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *CPB* **1980**, *28*, 262. (c) Kobayashi, Y.; Taguchi, T.; Morikawa, T. *TL* **1978**, 3555.
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Copper(I) Trifluoromethanesulfonate

$CuOSO_2CF_3$

[42152-44-3] · $CCuF_3O_3S$ · Copper(I) Trifluoromethanesulfonate · (MW 212.62) (2:1 benzene complex)

[37234-97-2; 42152-46-5] · $C_8H_6Cu_2F_6O_6S_2$ · Copper(I) Trifluoromethanesulfonate · (MW 503.34)

(efficient catalyst for 2π + 2π photocycloadditions and other photoreactions of alkenes,[1] and for alkene cyclopropanation and other reactions of diazo compounds; also a selenophilic and thiophilic Lewis acid that enhances the nucleofugacity of selenide and sulfide leaving groups)

Alternate Name: copper(I) triflate.

Physical Data: moisture-sensitive white crystalline solid.

Solubility: sol MeCN, $MeCO_2H$, 2-butanone, alkenes; slightly sol benzene.

Form Supplied in: must be freshly prepared.

Preparative Methods: copper(I) trifluoromethanesulfonate (CuOTf) was first prepared as a solution in acetonitrile by synproportionation of ***Copper(II) Trifluoromethanesulfonate*** with copper(0).[2] The Cu^I in these solutions is strongly coordinated with acetonitrile, forming complexes analogous to ***Tetrakis(acetonitrile)copper(I) Perchlorate***.[3] A white crystalline solid benzene complex, $(CuOTf)_2.C_6H_6$, is prepared by the reaction of a suspension of ***Copper(I) Oxide*** in benzene with ***Trifluoromethanesulfonic Anhydride***.[4] Traces of ***Trifluoromethanesulfonic Acid*** apparently catalyze the reaction.[5] CuOTf is generated in situ by the reduction of $Cu(OTf)_2$ with diazo compounds.[6]

Handling, Storage, and Precautions: moisture sensitive.

Cyclopropanation with Diazo Compounds.

Copper(I) triflate is a highly active catalyst for the cyclopropanation of alkenes with diazo compounds.[6] In contrast to other more extensively ligated copper catalysts, e.g. ***Copper(II) Acetylacetonate***, that favor cyclopropanation of the most highly substituted C=C bond, cyclopropanations catalyzed by CuOTf show a unique selectivity for cyclopropanation of the least alkylated C=C bond in both intermolecular (eq 1) and intramolecular (eq 2) competitions. The same selectivity is found with $Cu(OTf)_2$ as *nominal* catalyst. This is because $Cu(OTf)_2$ is reduced by the diazo compound to CuOTf, and CuOTf is the *actual* cyclopropanation catalyst in both cases.[6] Selective cyclopropanation of

the least substituted C=C bond is a consequence of the alkene coordinating with the catalyst prior to interaction with the diazo compound, and the increase in stability of Cu^I-alkene complexes with decreasing alkyl substitution on the C=C bond. For catalysts with more strongly ligated Cu^I, an electrophilic carbene or carbenoid intermediate reacts with the free alkene, and the preference for cyclopropanation of the more highly substituted C=C bond arises from the enhancement of alkene nucleophilicity with increasing alkyl substitution (see ***Copper(II) Trifluoromethanesulfonate***).

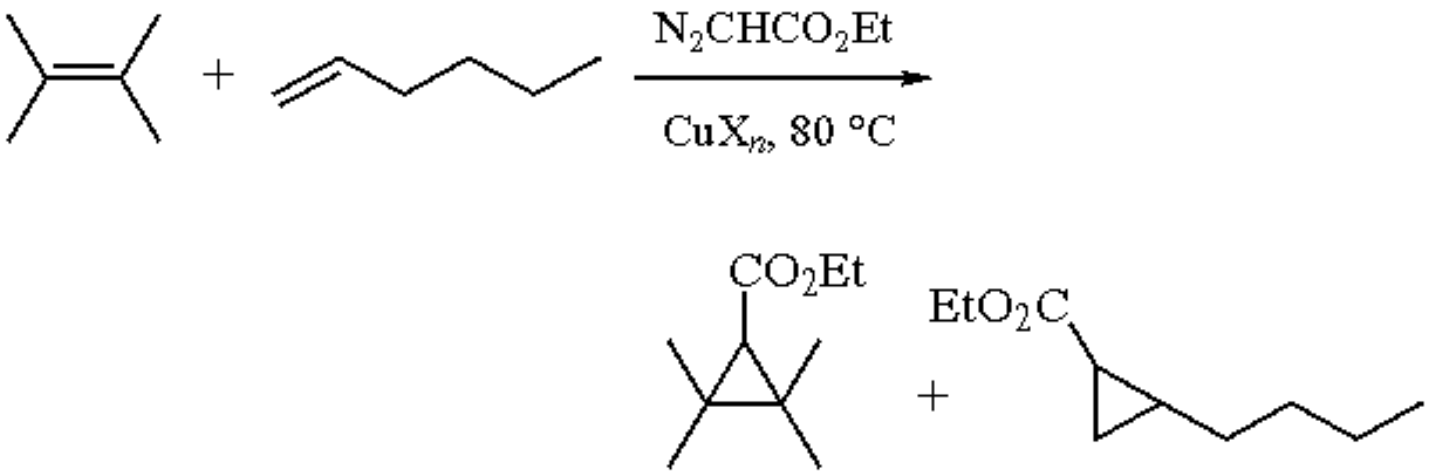

(1)

CuX_n	Ratio		
CuOTf	17%	0.25:1	67%
$Cu(OTf)_2$	21%	0.27:1	77%
$Cu(acac)_2$	61%	1.78:1	35%

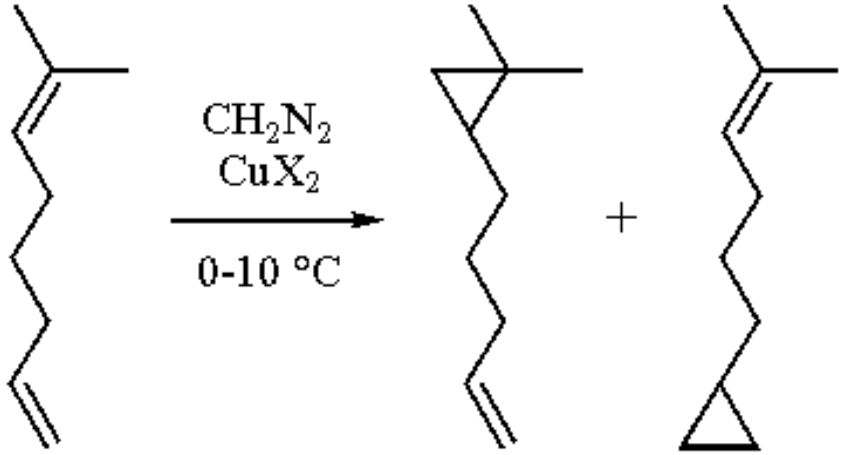

(2)

X = acetylacetonate	86%	14%
X = triflate	33%	66%

Cyclopropanecarboxylic esters are conveniently available, even from volatile alkenes, because CuOTf promotes cyclopropanations in good yields at low temperatures. Thus *trans*- and *cis*-2-butenes, boiling under reflux, react stereospecifically with ***Ethyl Diazoacetate*** to produce the corresponding ethyl 2,3-dimethylcyclopropanecarboxylates (eqs 3 and 4),[6] and cyclobutene reacts with ethyl diazoacetate at 0 °C to deliver a mixture of *exo*- and *endo*-5-ethoxycarbonylbicyclo[2.1.0]pentanes (eq 5).[7]

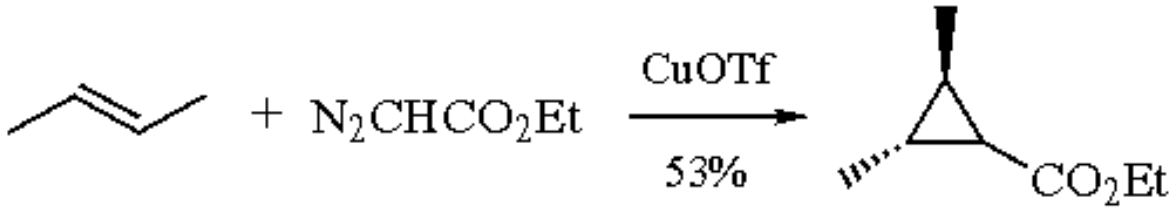

(3)

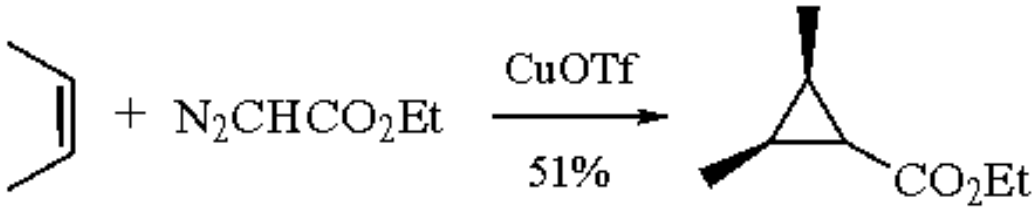

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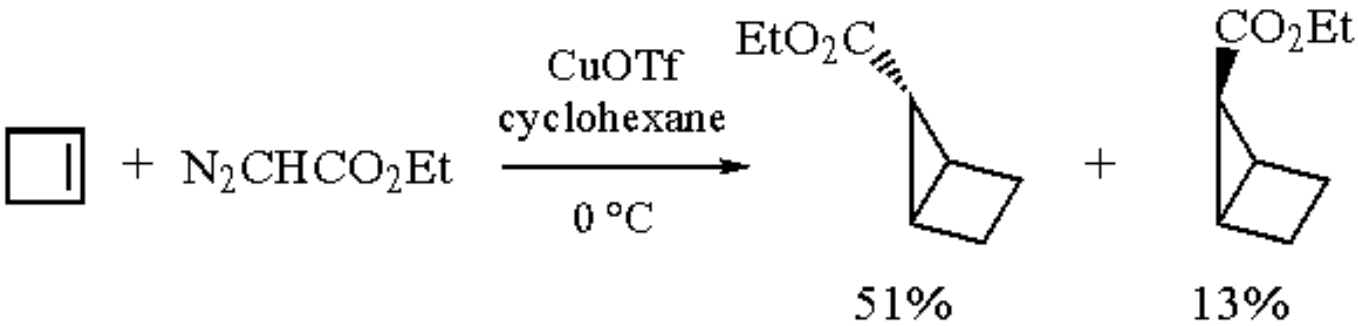

(5)

CuOTf is an outstandingly effective catalyst for the synthesis of cyclopropyl phosphonates by the reaction of ***Diethyl Diazomethylphosphonate*** with alkenes (eq 6).[8] The resulting cyclopropylphosphonates are useful intermediates for the synthesis of alkylidenecyclopropanes by Wadsworth-Emmons alkenation with aromatic carbonyl compounds (eq 7).[8]

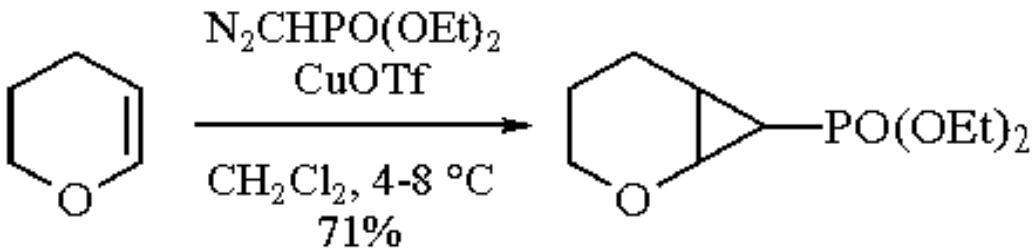

(6)

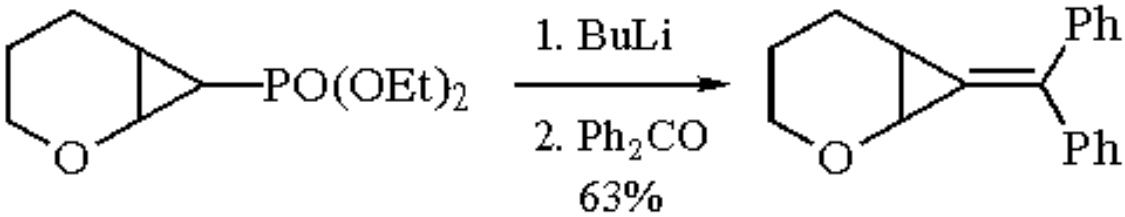

(7)

A complex of a chiral, nonracemic bis(oxazoline) with CuOTf is a highly effective catalyst for asymmetric cyclopropanation of alkenes.[9] Copper(II) triflate complexes do not catalyze the reaction unless they are first converted to Cu^{I} by reduction with a diazo compound or with phenylhydrazine. CuOTf complexes are uniquely effective. Thus the observed enantioselectivity and catalytic activity, if any, are much lower with other Cu^{I} or Cu^{II} salts including halide, cyanide, acetate, and even perchlorate. Both enantiomers of the bis(oxazoline) ligand are readily available. Spectacularly high levels of asymmetric induction are achieved with both mono- (eq 8) and 1,1-disubstituted alkenes (eq

9).

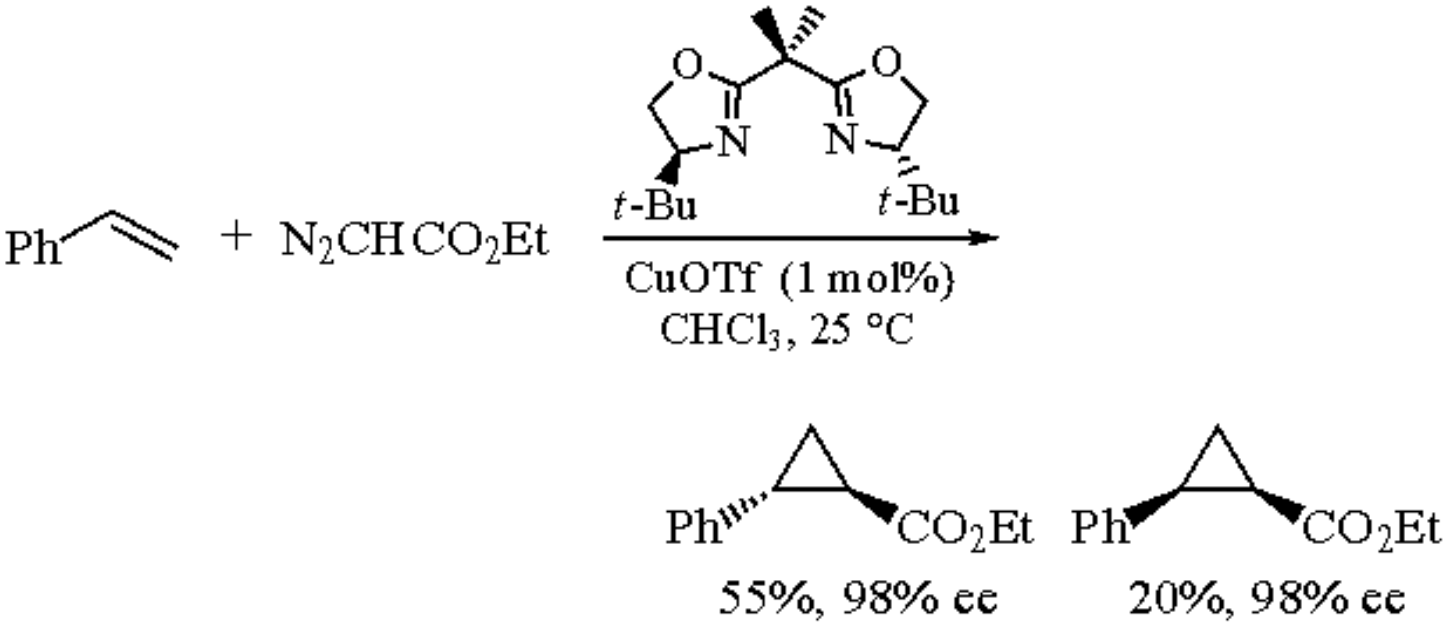

(8)

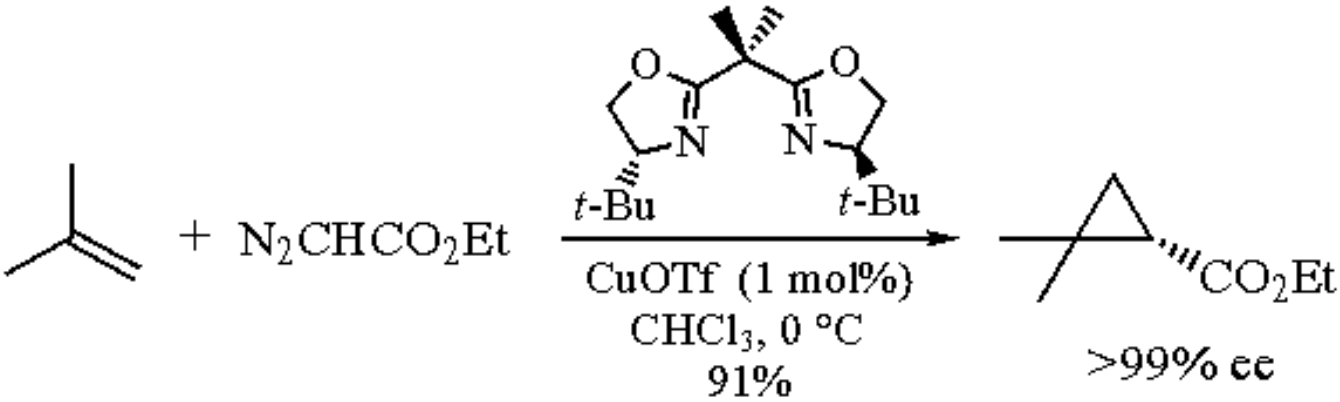

(9)

Asymmetric Aziridination.

A chiral, nonracemic bis(oxazoline) complex of copper(I) triflate catalyzes asymmetric aziridination of styrene in good yield (eq 10).[9] However, enantioselectivity is not as high as the corresponding cyclopropanation (eq 8).

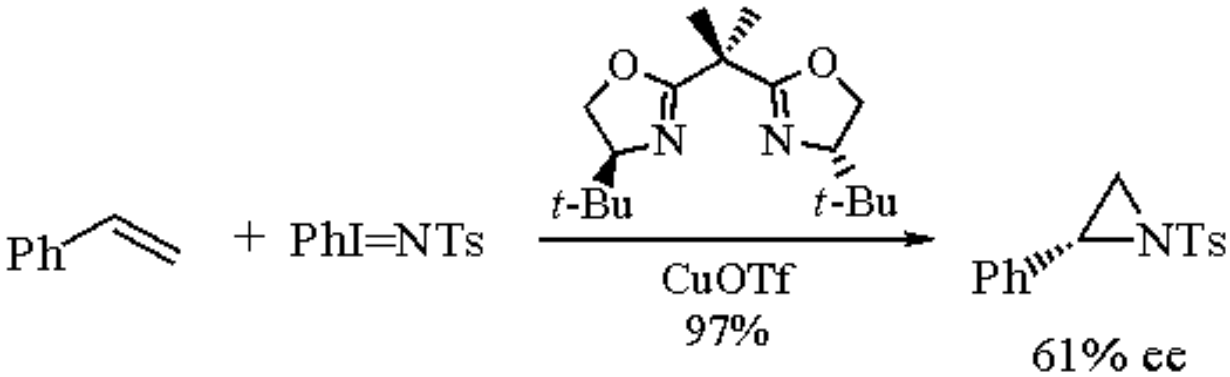

(10)

Photocycloadditions.

CuOTf is an exceptionally effective catalyst for 2π + 2π photocycloadditions of alkenes.[1] Thus while CuBr promotes photodimerization of norbornene in only 38% yield,[10] the same reaction affords dimer in 88% yield with CuOTf as catalyst (eq 11).[11] A mechanistic study of this reaction revealed that although both 1:1 and 2:1 alkene Cu^I complexes are in equilibrium with free alkene and both the 1:1 and 2:1 complexes absorb UV light, only light absorbed by the 2:1 complex results in photodimerization. In other words, photodimerization requires precoordination of both C=C bonds with the Cu^I catalyst. Thus the exceptional ability of CuOTf, with its weakly coordinating triflate counter anion, to form π-complexes with as many as four C=C bonds[12] is of paramount importance for its effectiveness as a photodimerization catalyst.

The importance of precoordination is also evident in the CuOTf-promoted 2π + 2π photocycloaddition of *endo*-dicyclopentadiene. This diene forms an isolable 2:1 complex with CuOTf involving *exo*-monodentate coordination with the 8,9-C=C bond of two molecules of diene. Consequently, intermolecular 2π + 2π photocycloaddition involving *exo* addition to the 8,9-C=C bond is strongly favored over intramolecular reaction between the 8,9- and 3,4-C=C bonds (eq 11).[11] This contrasts with the intramolecular photocycloaddition that is promoted by high energy triplet sensitizers.[12]

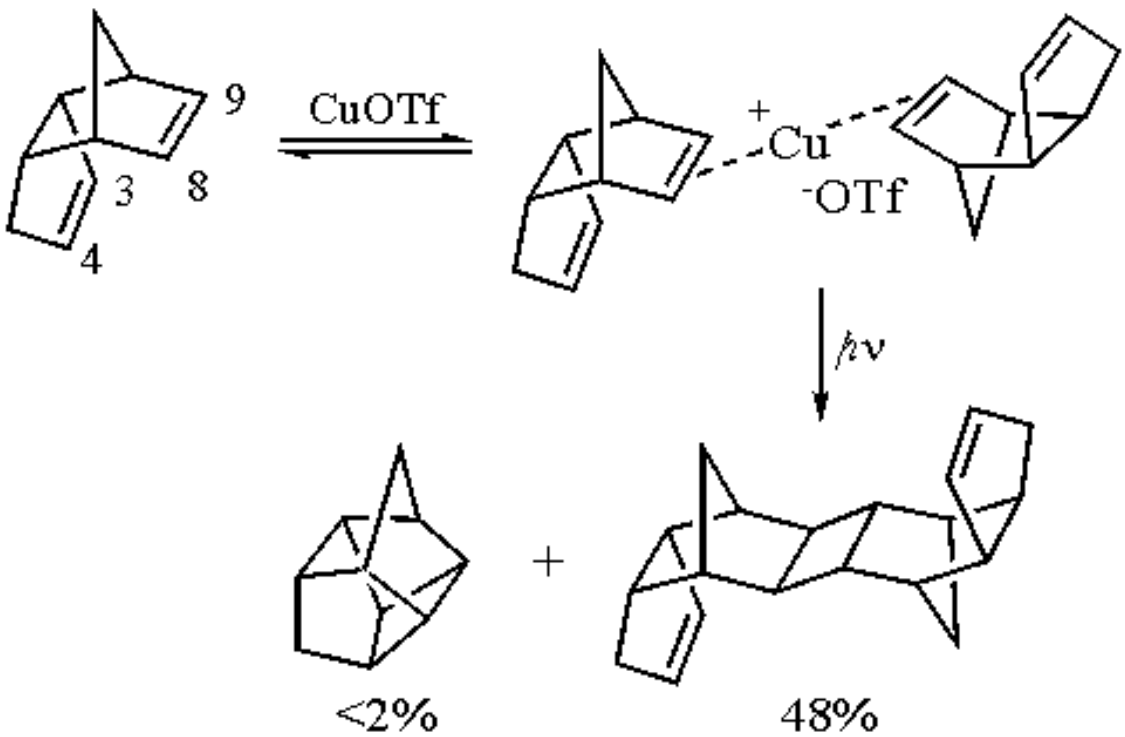

(11)

Especially interesting is the *trans,anti,trans* stereochemistry of the major cyclobutane product generated in the photodimerization of cyclohexene (eq 12).[13] It was noted that the formation of this product may be the result of a preliminary CuOTf promoted *cis-trans* photoisomerization that generates a *trans*-cyclohexene intermediate (eq 13).[13] Since one face of the *trans* C=C bond is shielded by a polymethylene chain, the *trans*-cyclohexene is restricted to suprafacial additions. Although a highly strained *trans*-cyclohexene intermediate could be stabilized by coordination with Cu^I, such a complex has not been isolated.

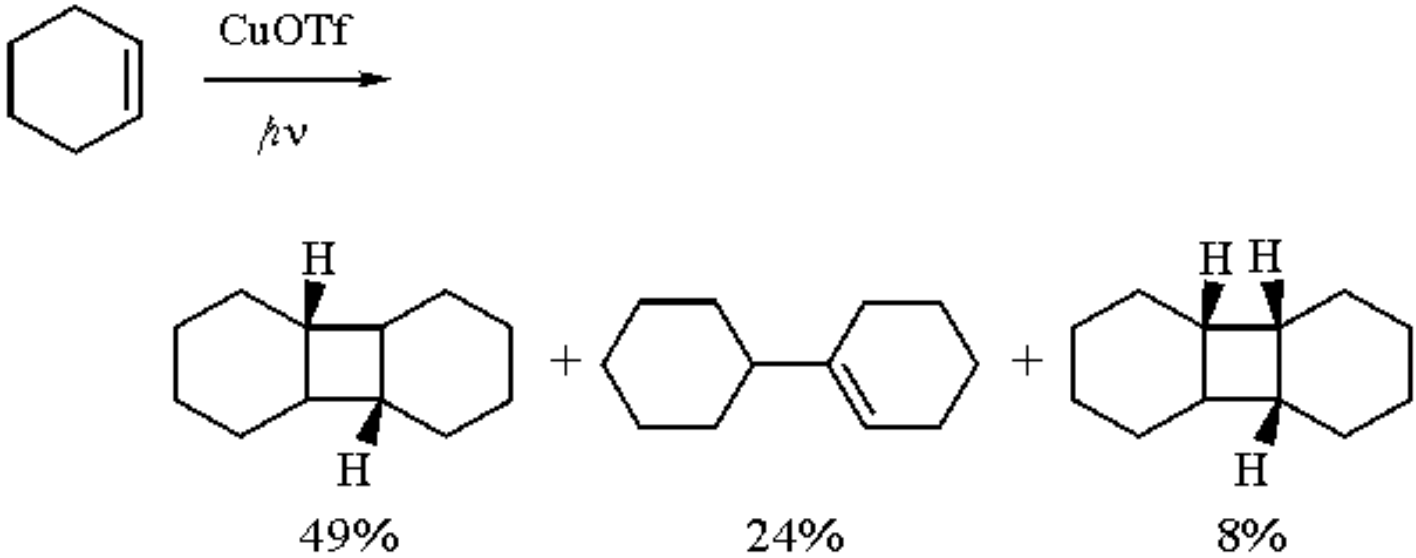

(12)

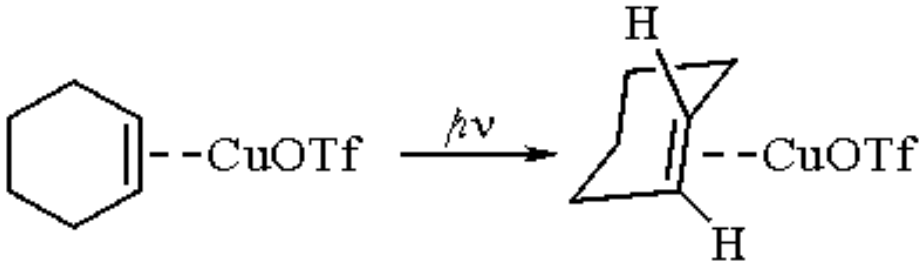

(13)

An isolable CuOTf complex of a highly strained alkene, *trans*-cycloheptene, is produced by UV irradiation of a hexane solution of *cis*-cycloheptene in the presence of CuOTf (eq 14).[14] Photocycloaddition of cycloheptene is also catalyzed by CuOTf. Surprisingly, the major product is not a *trans,anti,trans* dimer analogous to that formed from cyclohexene (eq 12) but rather a *trans,anti,trans,anti,trans* trimer (eq 15).[15]

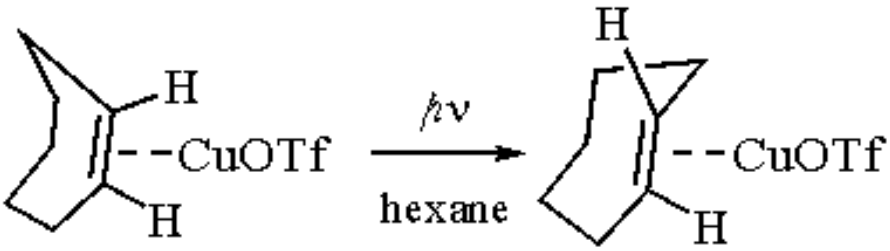

(14)

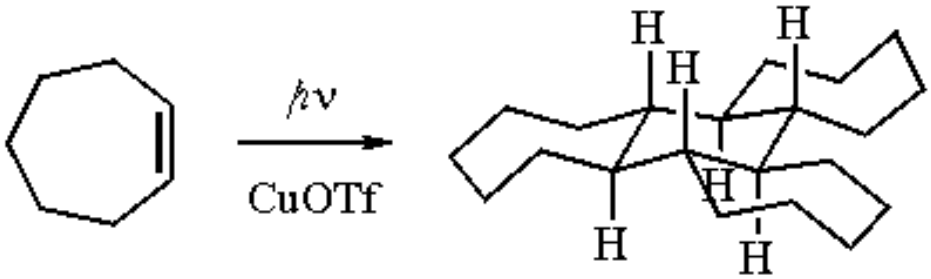

(15)

Dissolution of the *trans*-cycloheptene-CuOTf complex in cycloheptene and evaporation of the solvent delivers a tris alkene complex of CuOTf containing one *trans*-cycloheptene and two *cis*-cycloheptene ligands. Heating *trans*-cycloheptene-CuOTf in neat *cis*-cycloheptene delivers the *trans,anti,trans,anti,trans* trimer (eq 16). Experiments with

cis-cycloheptene-d_4 show that the cyclotrimerization involves only *trans*-cycloheptene molecules, although the reaction is accelerated by the presence of *cis*-cycloheptene.[16] A likely explanation for these observations is concerted "template" cyclotrimerization of a tris-*trans*-cycloheptene-CuOTf complex formed by ligand redistribution (eq 16).[16]

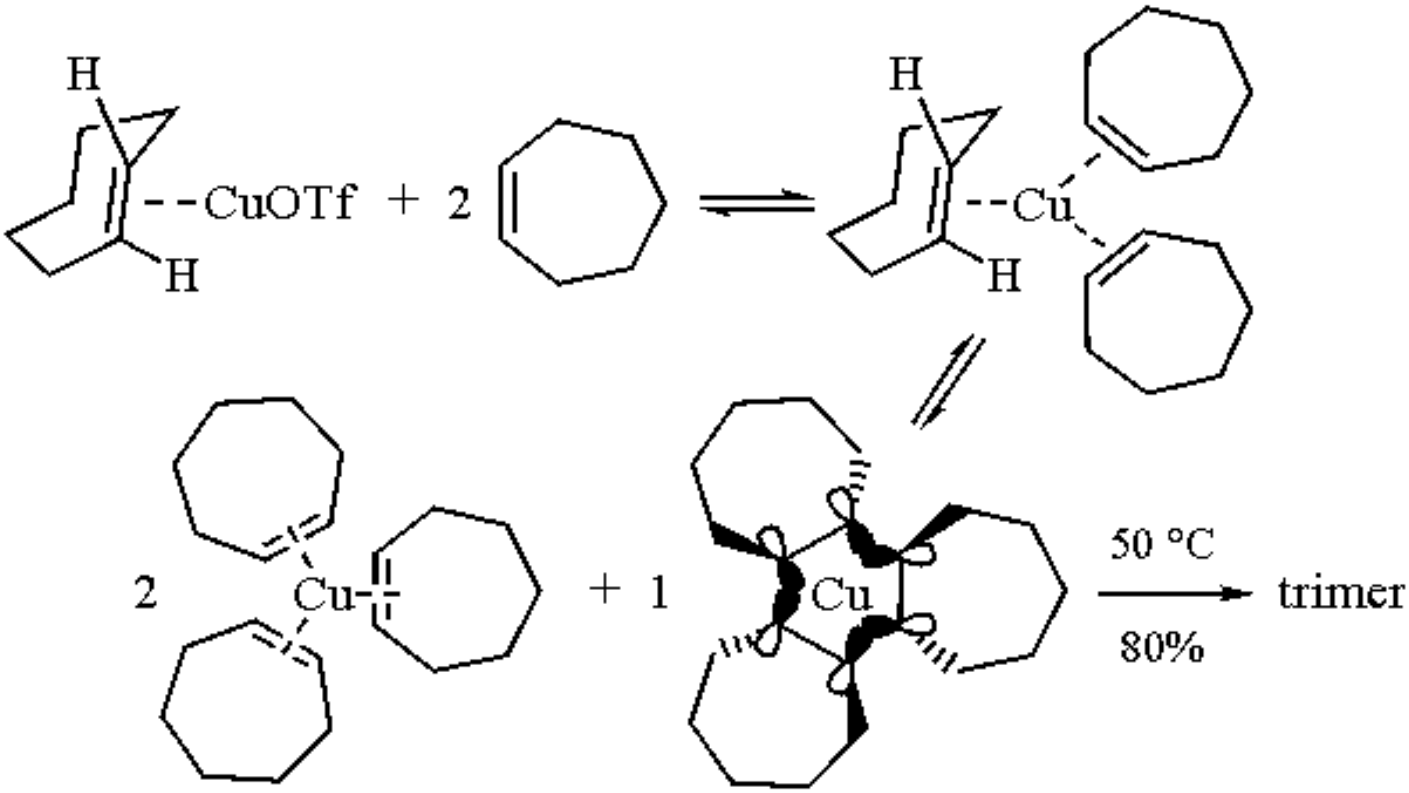

(16)

The involvement of a transient photogenerated *trans*-cyclohexene-CuOTf intermediate was also adduced to explain CuOTf catalysis of photoinduced 2π + 4π cycloaddition between *cis*-cyclohexene and 1,3-butadiene (eq 17).[17] In contrast to thermal Diels-Alder reactions, this reaction generates *trans*-Δ^2-octalin rather than the *cis* cycloadduct expected for a $2\pi_s + 4\pi_s$ cycloaddition. A mechanism was proposed that involves the $2\pi_s + 4\pi_s$ cycloaddition of a *trans*-cyclohexene with 1,3-butadiene in the coordination sphere of Cu^I (eq 18).[17]

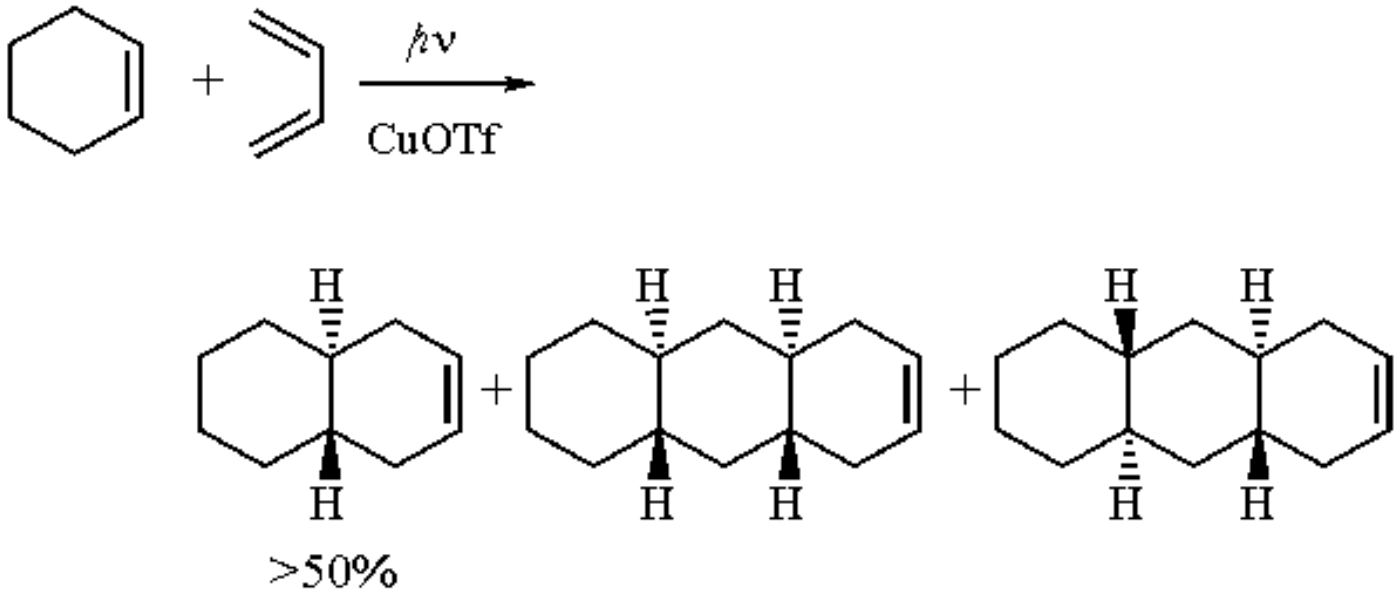

(17)

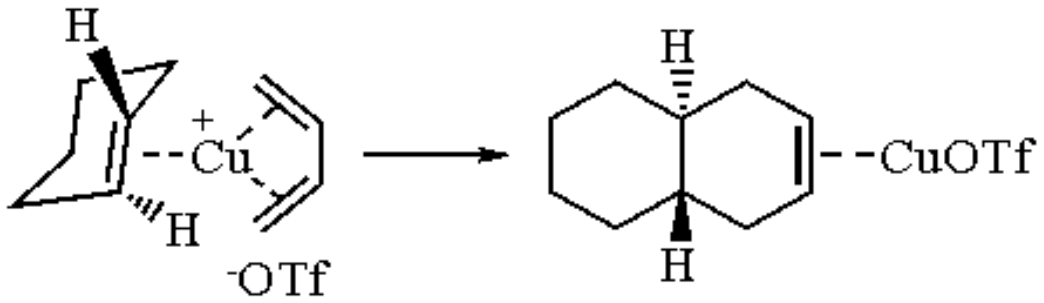

(18)

That CuOTf-catalyzed 2π + 2π photocycloadditions are not restricted to cyclic alkenes was first demonstrated in mixed cycloadditions involving allyl alcohol. To suppress homodimerization of *endo*-dicyclopentadiene (i.e. eq 11) the diene to Cu^{I} ratio is maintained at <=1:1 and allyl alcohol is used as solvent. Under these conditions, a high yield of mixed cycloadduct is generated (eq 19).[18]

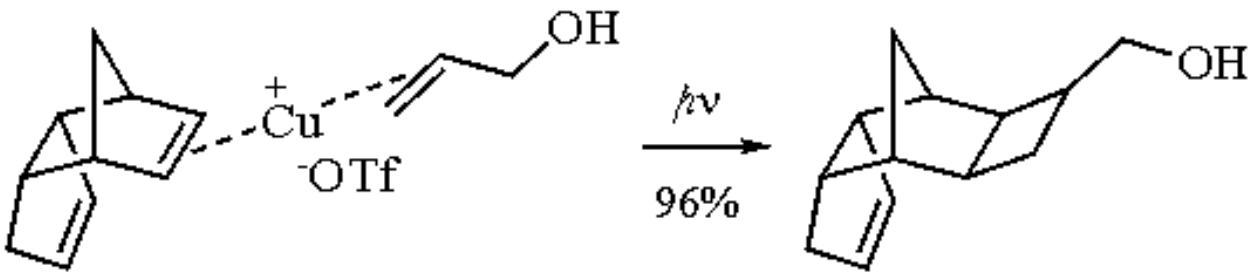

(19)

That both C=C bonds participating in 2π + 2π photocycloadditions can be acyclic is evident from the photobicyclization reactions of simple diallyl ethers that deliver bicyclic tetrahydrofurans (eq 20).[19,20] In conjunction with ***Ruthenium(VIII) Oxide***-catalyzed oxidation by ***Sodium Periodate***, these CuOTf-catalyzed photobicyclizations provide a synthetic route to butyrolactones from diallyl ethers (eq 20).[20] The synthetic method is applicable to the construction of multicyclic tetrahydrofurans and butyrolactones from diallyl ethers (eqs 21 and 22) as well as from homoallyl vinyl ethers (eq 23).[20]

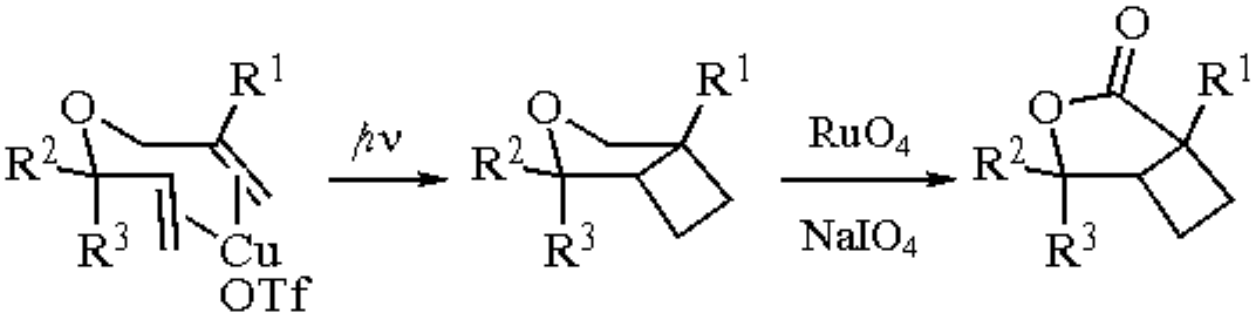

(20)

R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	H	52	91
Me	Me	H	56	94
Me	Me	Me	54	44
Me	H	H	54	56
n-Bu	H	Me	83	83

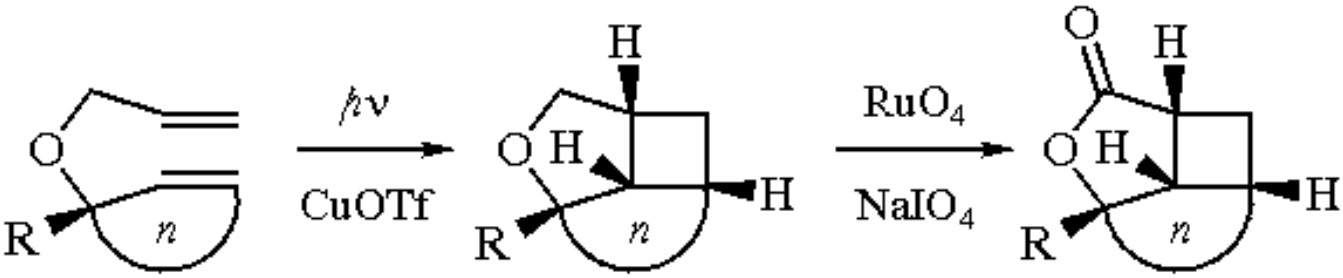

(21)

R	*n*	Yield (%)	Yield (%)
H	5	47	73
H	8	56	56
Me	5	28	87
Me	6	35	82

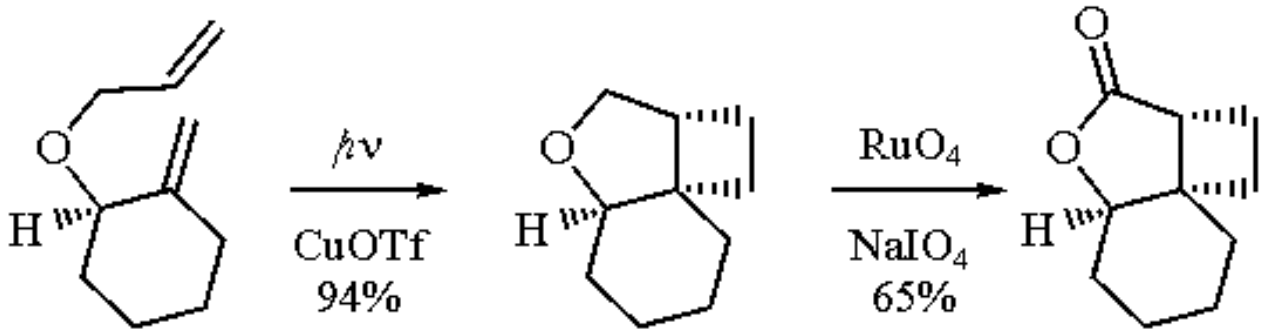

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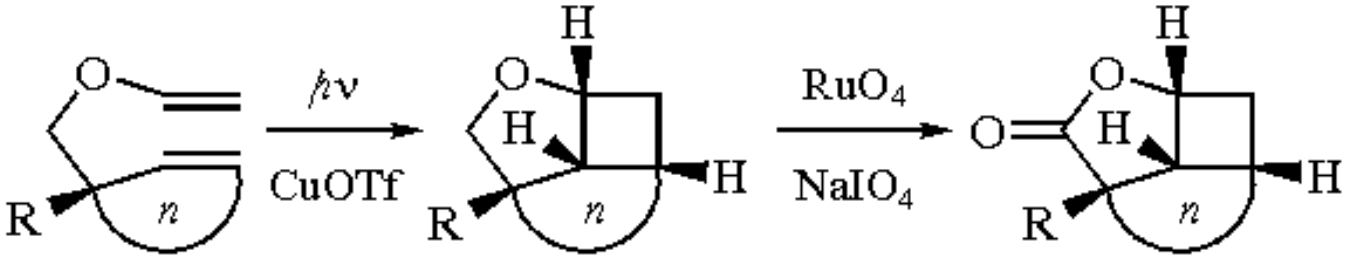

(23)

R	*n*	Yield (%)	Yield (%)
H	5	92	78
Me	5	50	71
H	6	48	85

3-Oxabicyclo[3.2.0]heptanes are also produced in the CuOTf-catalyzed photocycloadditions of allyl 2,4-hexadienyl ethers (eq 24).[21] The CuOTf-catalyzed photocycloadditions of bis-2,4-hexadienyl ethers are more complex. Thus UV irradiation of 5,5´-oxybis[(*E*)-1,3-pentadiene] in THF for 120 h produces vinylcyclohexene and tricyclo[3.3.0.0^{2,6}]octane derivatives (eq 25).[22] However, shorter irradiations reveal that these products arise by secondary CuOTf-catalyzed rearrangements of 6,7-divinyl-3-oxabicyclo[3.2.0]heptanes that are the primary photoproducts (eq 26). UV irradiation of the divinylcyclobutane intermediates in the presence of CuOTf promotes formal [1,3]- and [3,3]-sigmatropic rearrangements to produce a vinylcyclohexene and a 1,5-cyclooctadiene that is the immediate precursor of the tricyclo[3.3.0.0^{2,6}]octane.

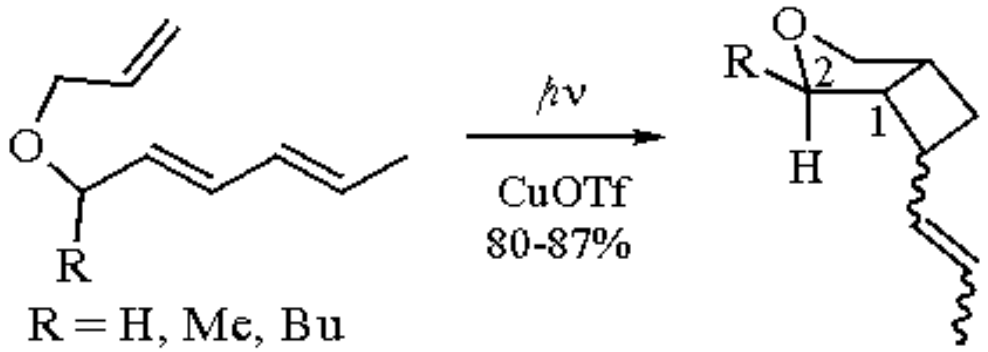

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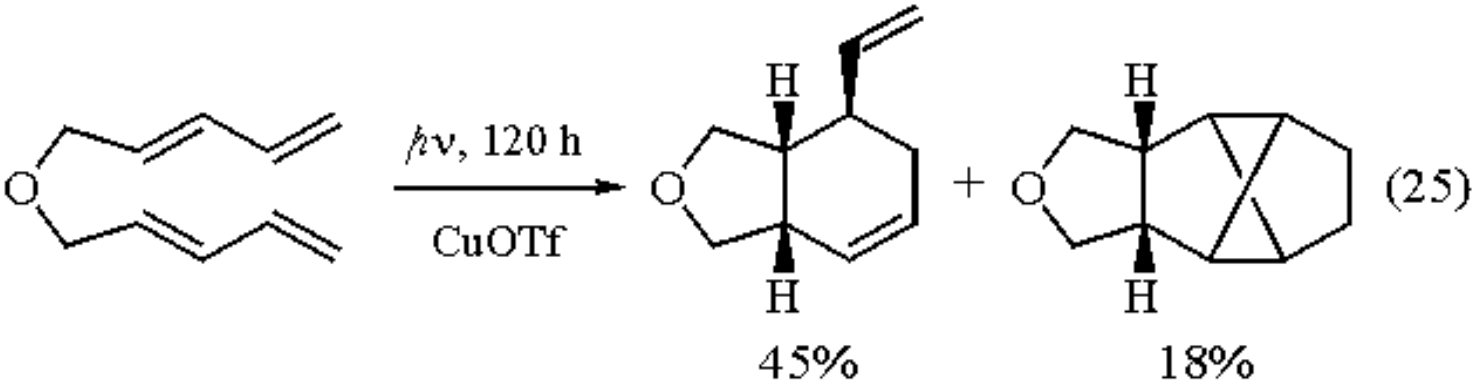

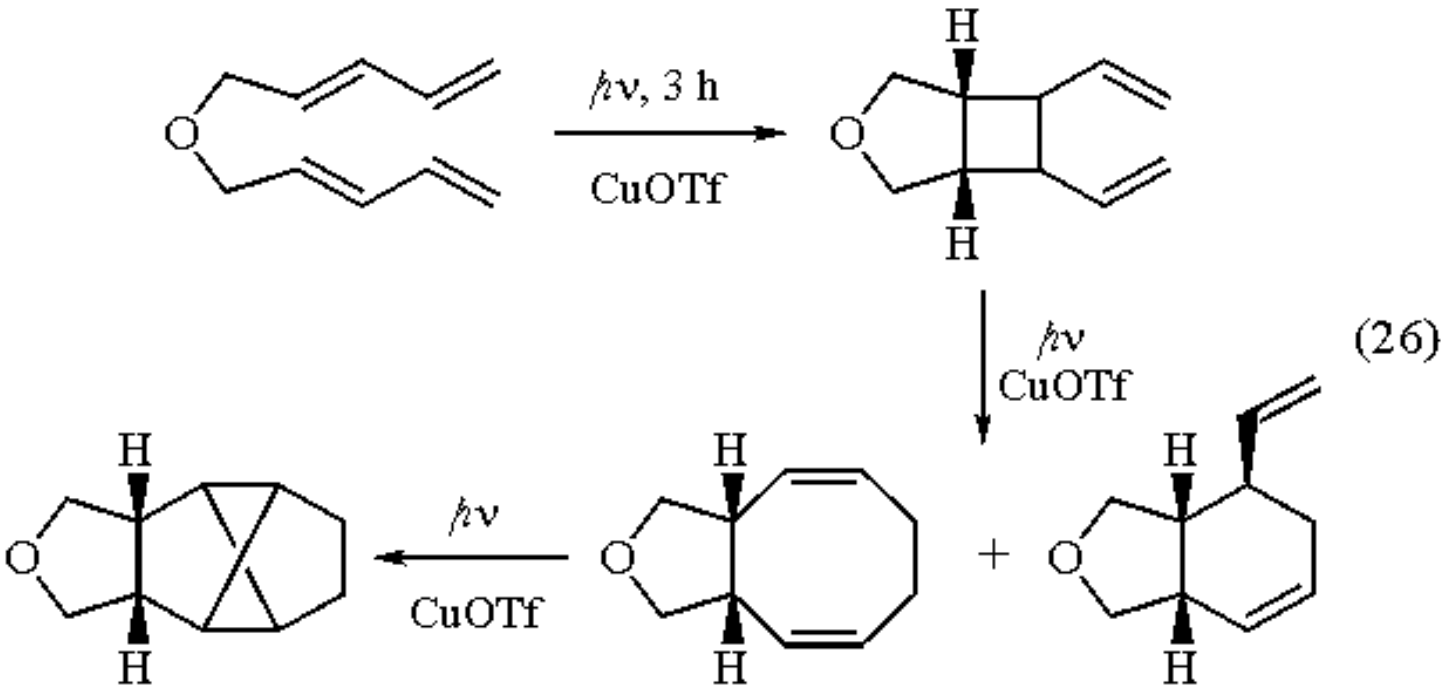

CuOTf-catalyzed photobicyclization of 1,6-heptadien-3-ols produces bicyclo[3.2.0]heptan-2-ols (eq 27).[23] In conjunction with pyrolytic fragmentation of the derived ketones, these CuOTf-catalyzed photobicyclizations provide a synthetic route to 2-cyclopenten-1-ones from 1,6-heptadien-3-ols (eq 28).[23] The derived ketones can also be converted into lactones by Baeyer-Villiger oxidation and, in conjunction with pyrolytic fragmentation, CuOTf-catalyzed photobicyclizations provide a synthetic route to enol lactones of glutaraldehydic acid from 1,6-heptadien-3-ols (eq 28).[23]

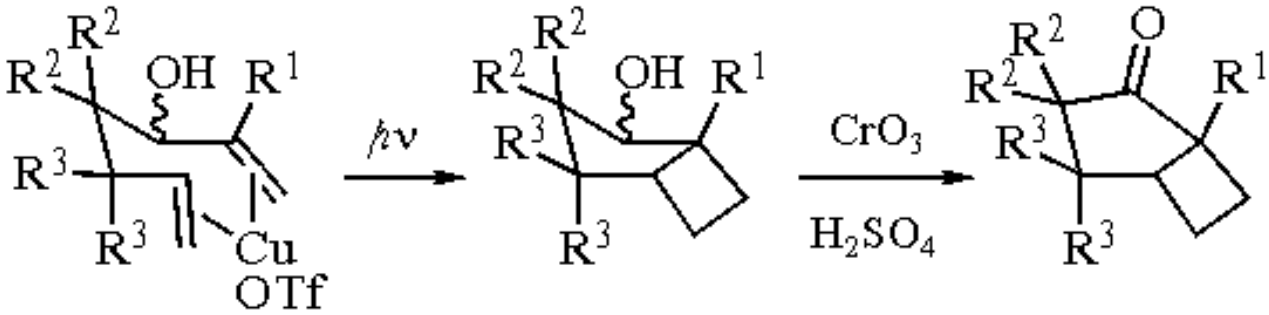

(27)

R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	H	86	78
Me	H	H	81	67
H	Me	H	91	92
H	H	Me	84	92
Me	Me	H	83	93

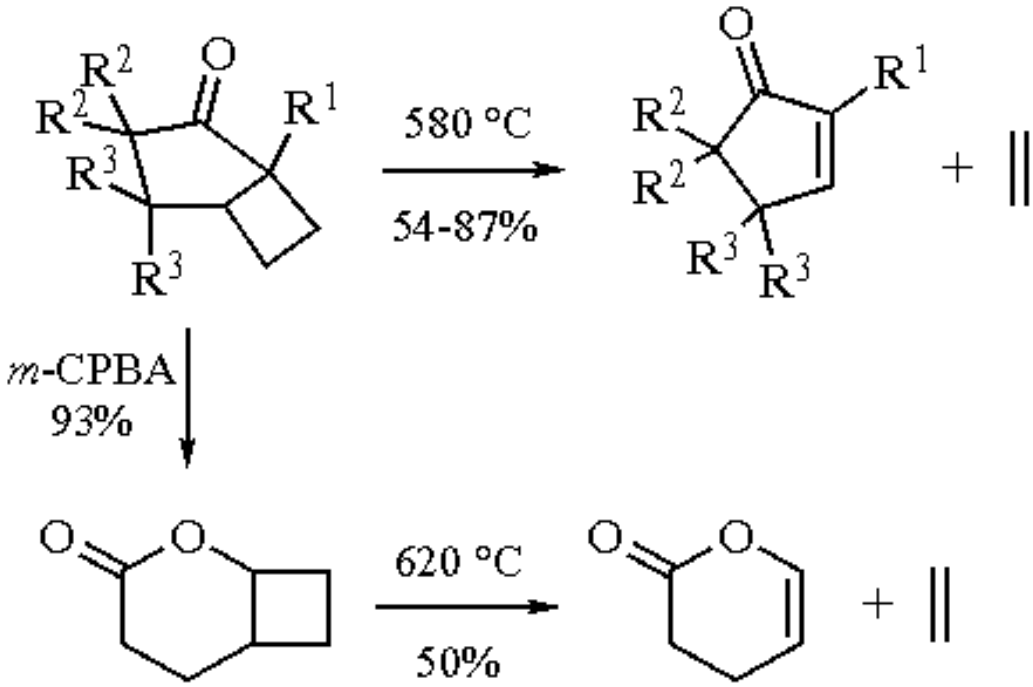

(28)

Copper(I) triflate-catalyzed photobicyclization of β- and γ-(4-pentenyl)allyl alcohols provides a synthetic route to various multicyclic carbon networks in excellent yields (eqs 29-31).[24] The reaction was exploited in a total synthesis of the panasinsene sesquiterpenes (eq 32).[25] It is especially noteworthy in this regard that attempted synthesis of a key tricyclic ketone intermediate for the panasinsenes by the well-known photocycloaddition of ***Isobutene*** to an enone failed to provide any of the requisite cyclobutyl ketone (eq 33).[25]

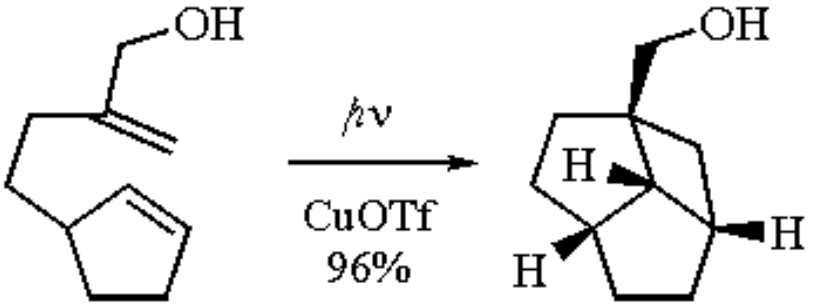
OH
hν
CuOTf
96%
OH
H
H
H

(29)

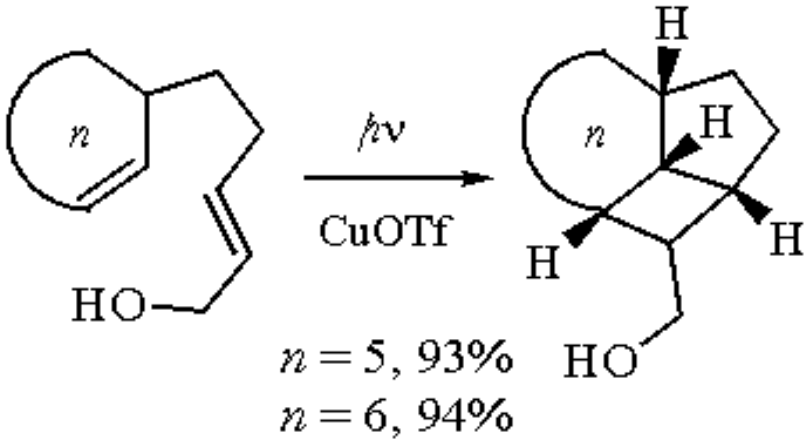
n
HO
hν
CuOTf
H
n
H
H
H
HO
n = 5, 93%
n = 6, 94%

(30)

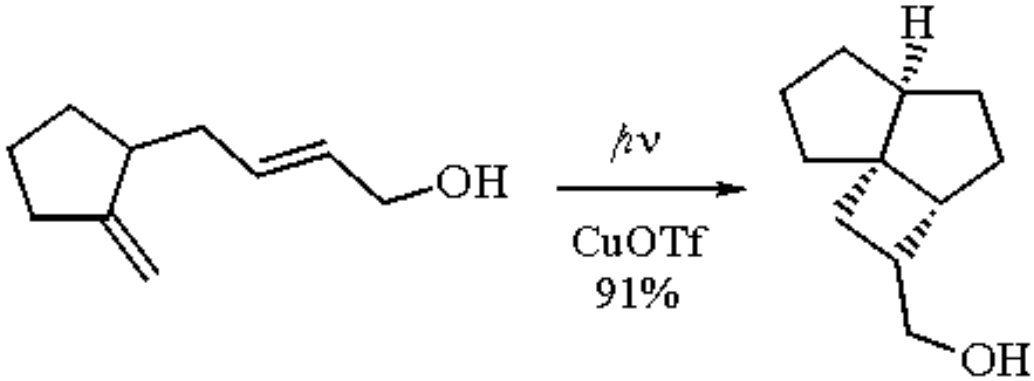
OH
hν
CuOTf
91%
H
OH

(31)

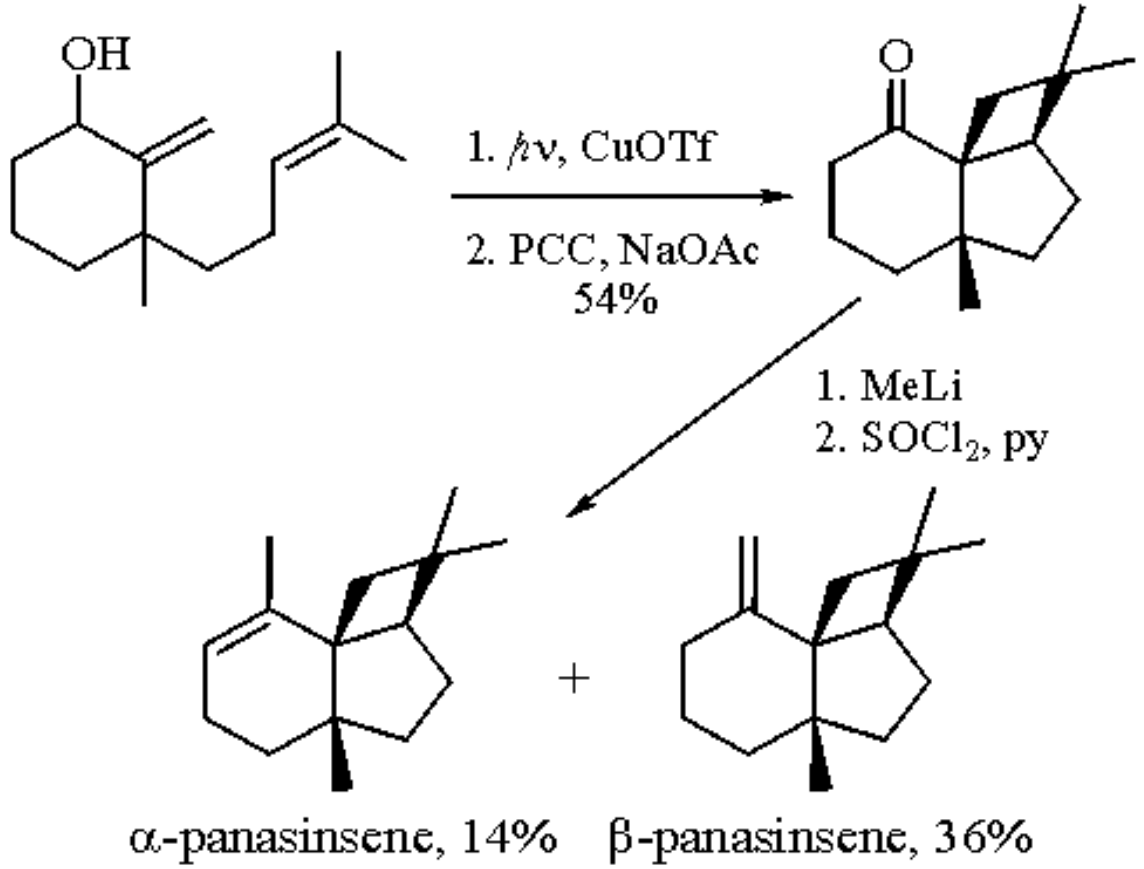

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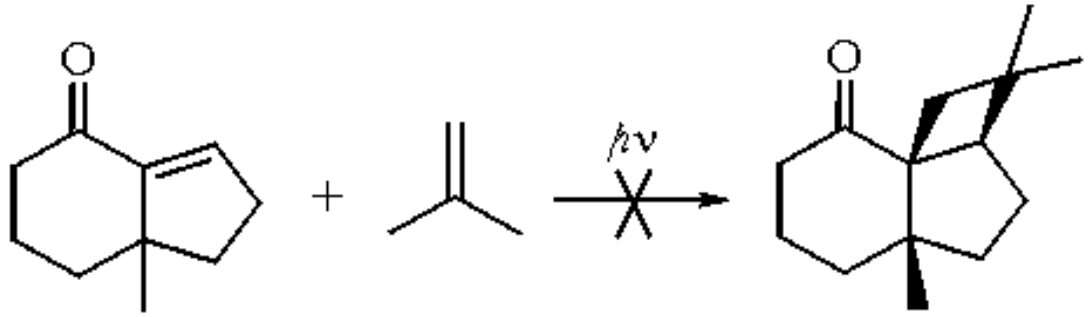

(33)

In conjunction with carbocationic skeletal rearrangement, photobicyclization of 1,6-heptadien-3-ols provides a synthetic route to 7-hydroxynorbornanes (eq 34).[26] Noteworthy is the stereoselective generation of *exo*-1,2-polymethylenenorbornanes from either the *exo* or *endo* epimer of 2,3-polymethylenebicyclo[3.2.0]heptan-3-ol.

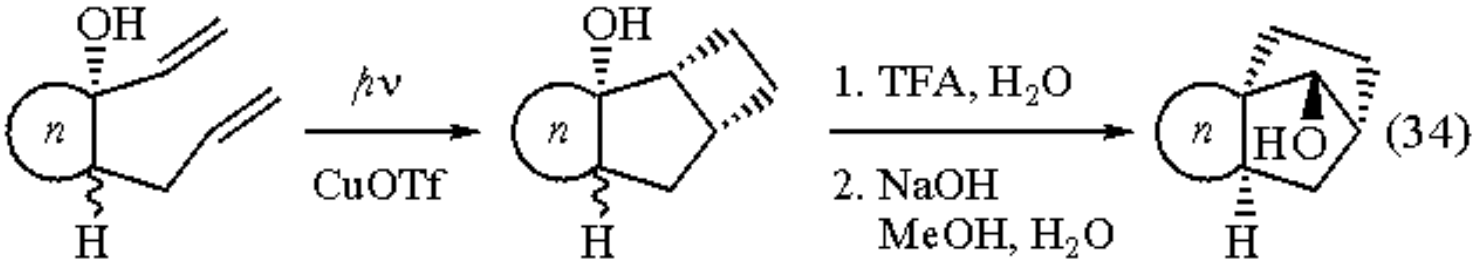

n	Yield (%)	Yield (%)
5	70-75	64-85
6	51-84	76-77
7	73	73
8	74	66

N,*N*-Diallylamides are recovered unchanged when irradiated in the presence of CuOTf.[27] This is because the amide chromophore interferes with photoactivation of the Cu^{I}-alkene complex. Thus CuOTf-alkene complexes containing one, two, three, or even four coordinated C=C bonds exhibit UV absorption at 235 ± 5 nm (ε$_{max}$ 2950 ± 450).[12] The CuOTf complex of ethyl *N*,*N*-diallylcarbamate exhibits λ_{max} = 233.4 nm (ε$_{max}$ 2676) but the free ligand is virtually transparent at this wavelength. Consequently, UV irradiation of ethyl *N*,*N*-diallylcarbamates in the presence of CuOTf delivers bicyclic (eq 35) or tricyclic (eq 36) pyrrolidines incorporating the 3-azabicyclo[3.2.0]heptane ring system.[27]

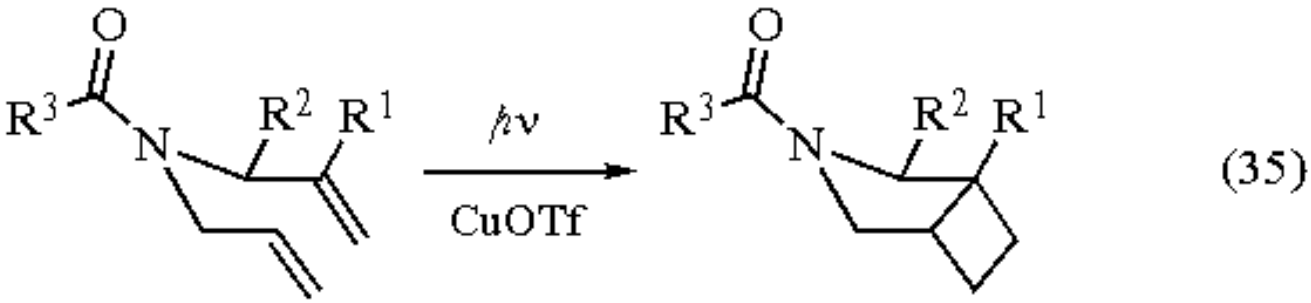

R^1	R^2	R^3	$\varepsilon_{233\ nm}$	Yield (%)
H	H	Me	192	0
H	H	H	231	0
H	H	OEt	15	74
H	Me	OEt	-	60
Me	H	OEt	-	76

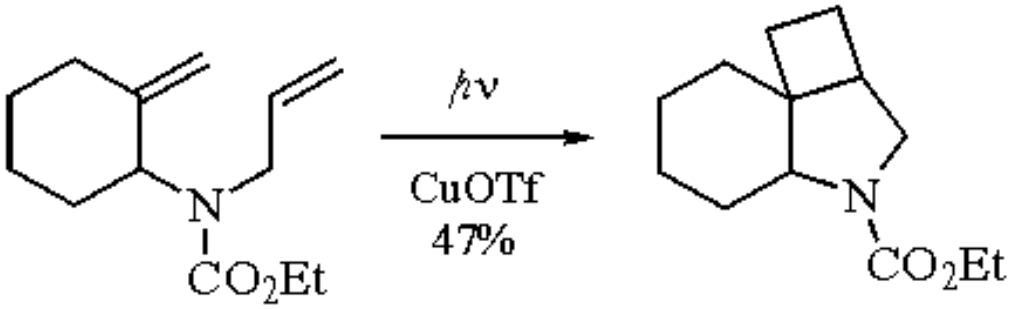

(36)

Catalyzed Diels-Alder Reactions.

The uncatalyzed thermal intramolecular Diels-Alder reaction of 5,5´-oxybis[(*E*)-1,3-pentadiene] nonstereoselectively generates four isomeric 4-vinylcyclohexenes (eq 37). The major product has a *trans* ring fusion, in contrast to the single *cis* ring-fused isomer generated in the copper(I) triflate-catalyzed photoreaction of the same tetraene (eq 25). Copper(I) triflate also catalyzes a thermal Diels-Alder reaction of 5,5´-oxybis[(*E*)-1,3-pentadiene] that proceeds under milder conditions than the uncatalyzed reaction. The stereoselectivity is remarkably enhanced, generating mainly the major isomer of the uncatalyzed thermal reaction and a single *cis*-fused isomer (eq 37) that is different than the one favored in the photochemical reaction (eq 25).

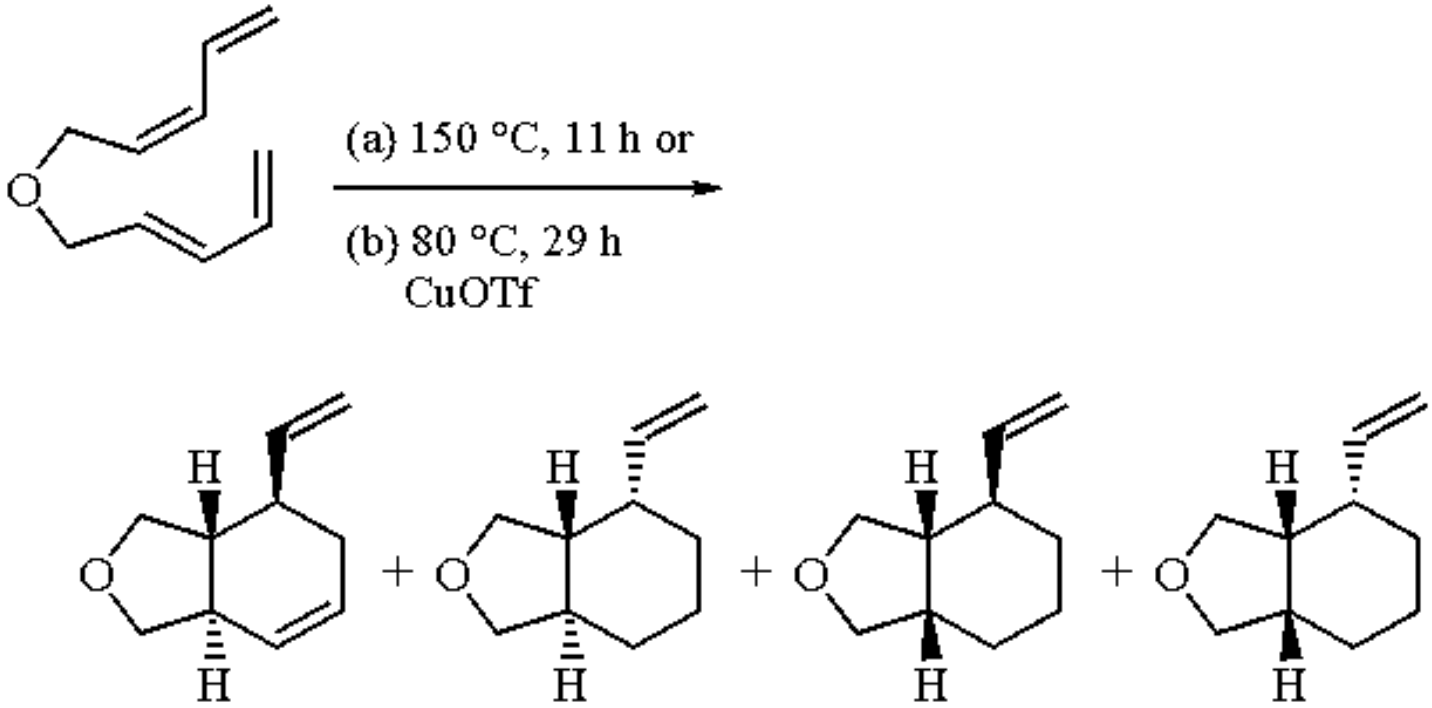

(37)

(a)	46%	10%	21%	3%
(b)	76%	<1%	<1%	11%

C_{sp}-H Bond Activation.

Hydrogen-deuterium exchange between terminal alkynes and CD_3CO_2D is catalyzed by CuOTf (eq 38).[28] Proton NMR studies revealed that CuOTf and alkynes form π-complexes that rapidly exchange coordinated with free alkyne. A complex of CuOTf with 1,7-octadiene was isolated (eq 39). The complex rapidly exchanges terminal alkynic hydrogen

with deuterium from CD_3CO_2D and undergoes a much slower conversion to a copper alkynide (eq 39).[28] Exchange of alkynic hydrogen and deuterium is also catalyzed by CuOTf (eq 40).[28]

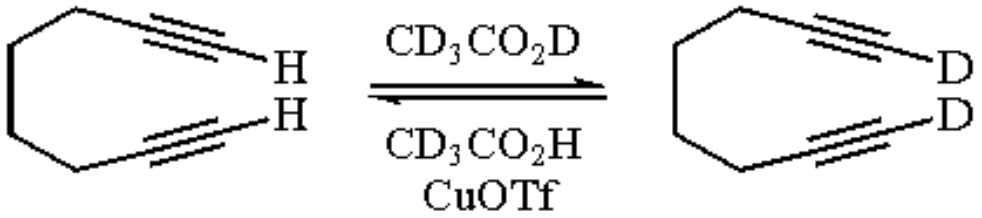

(38)

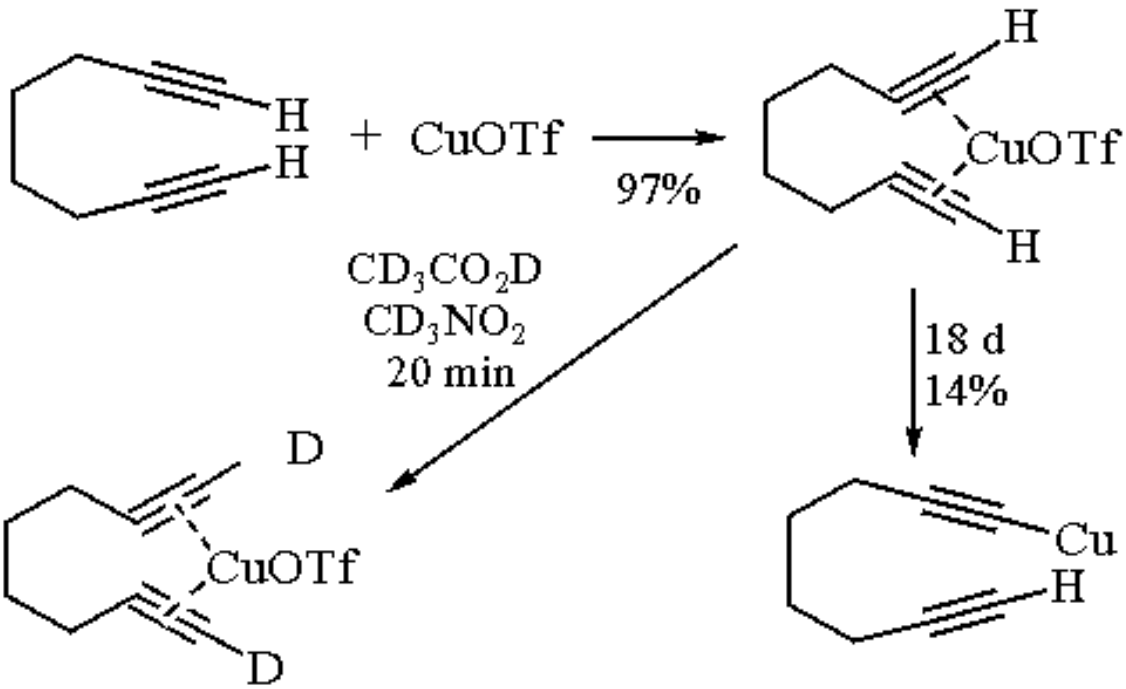

(39)

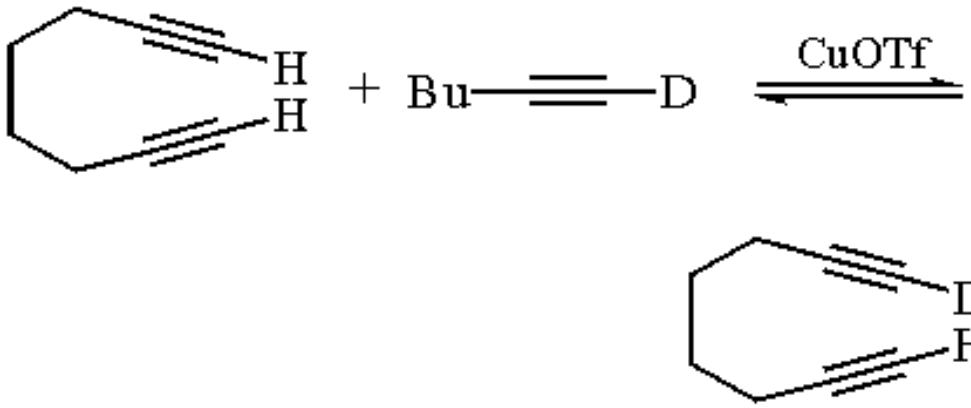

(40)

Activation of Aryl Halides.

Ullmann coupling of *o*-bromonitrobenzene is accomplished under exceptionally mild conditions and in homogeneous solution by reaction with copper(I) triflate in the presence of aqueous NH_3 (eq 41).[29] Yields are enhanced by the presence of a small quantity of copper(II) triflate. That the reaction is diverted to reductive dehalogenation by ***Ammonium Tetrafluoroborate*** is presumptive evidence for an organocopper intermediate that can be captured by protonation.

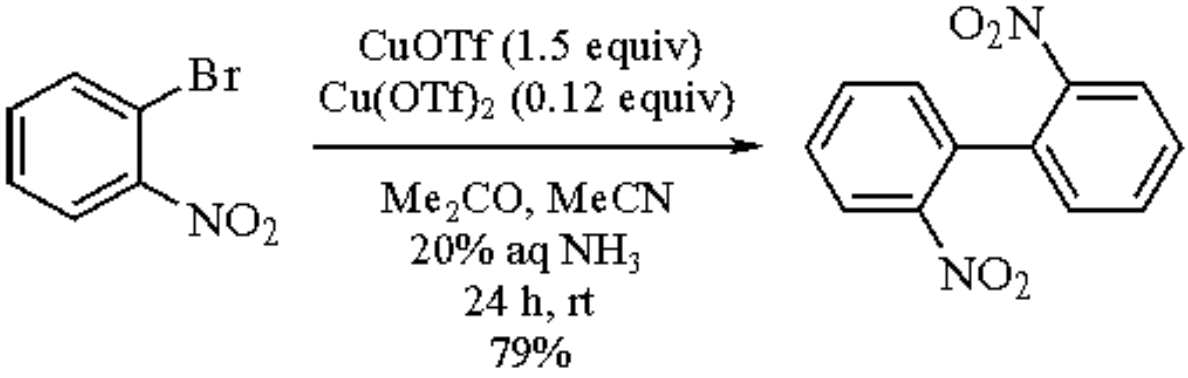

(41)

Biaryl is only a minor product from the reaction of methyl *o*-bromobenzoate with CuOTf (eq 42). The major product can result from replacement of the halide by NH_2, H, or OH, depending on reaction conditions. In the presence of 5% aqueous NH_3, methyl anthranilate is the major product.[30] More concentrated aqueous NH_3 (20%) favors the generation of methyl salicylate, and the yield of this product is enhanced by the presence of a substantial quantity of Cu^{II} ion.[29] Reductive dehalogenation is favored by the presence of ammonium ions, presumably owing to protonolysis of an arylcopper(III) intermediate.[29]

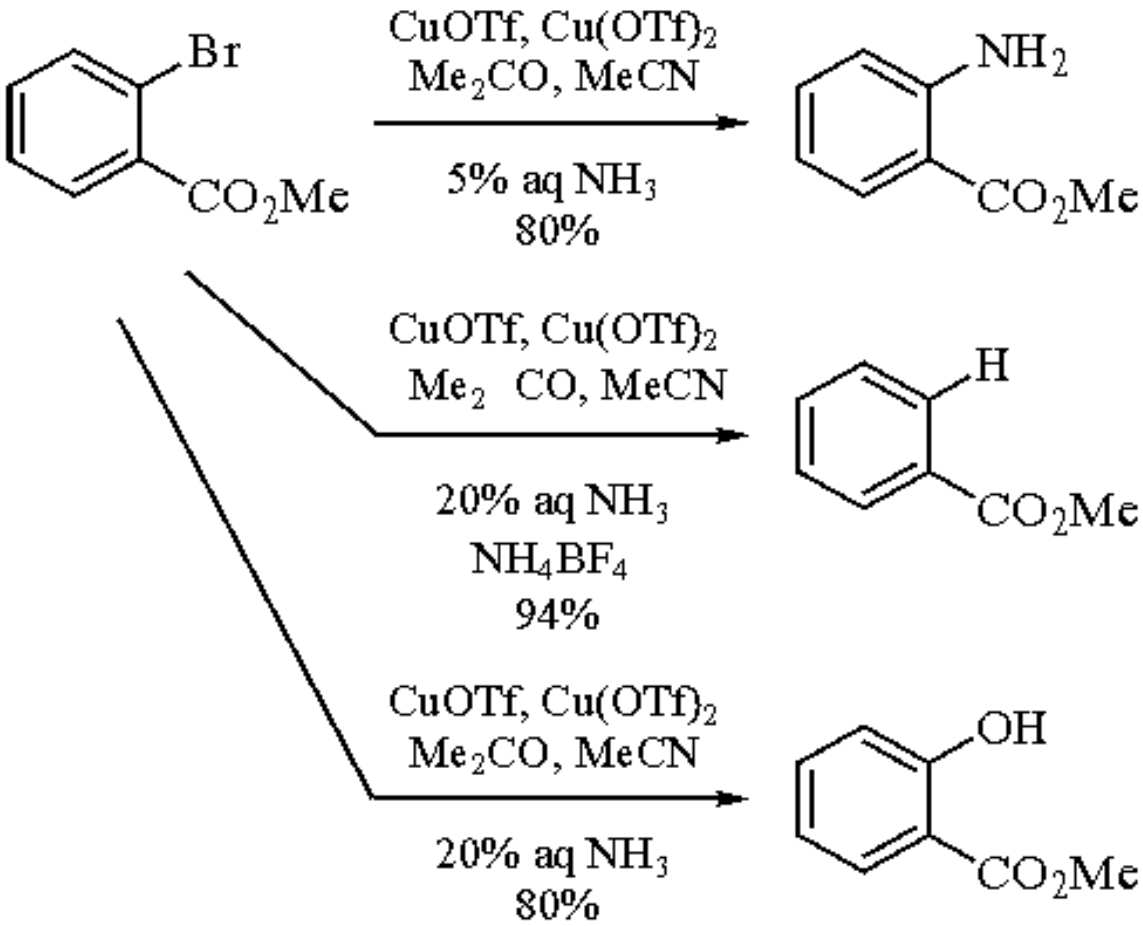

(42)

Activation of Vinyl Halides.

Under the optimum conditions for reductive coupling of *o*-bromonitrobenzene (eq 41), diethyl iodofumarate gives very little coupling product; the overwhelming product was diethyl fumarate generated by hydrodehalogenation (eq 43).[29]

Reductive coupling delivers *trans,trans*-1,2,3,4-tetraethoxycarbonyl-1,3-butadiene in 95% yield (GLC, or 80% of pure crystalline product) in 2 h if aqueous NH_3 is replaced by anhydrous NH_3.[29] Under the same conditions, diethyl iodomaleate undergoes 45% conversion in 20 h to deliver diethyl maleate, as well as minor amounts of *cis,cis*- and *trans,trans*-tetraethoxycarbonyl-1,3-butadiene (eq 44).[29] The stereospecificity of the reductive dehalogenations in eqs 43 and 44 is presumptive evidence for the noninvolvement of radicals in these reactions.

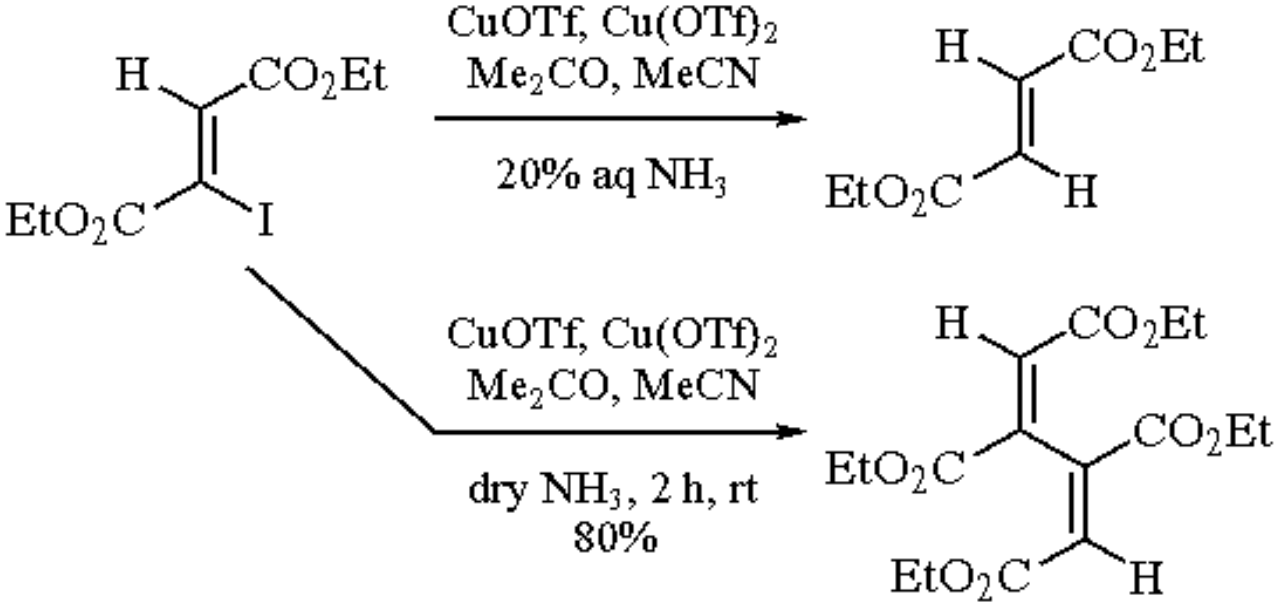

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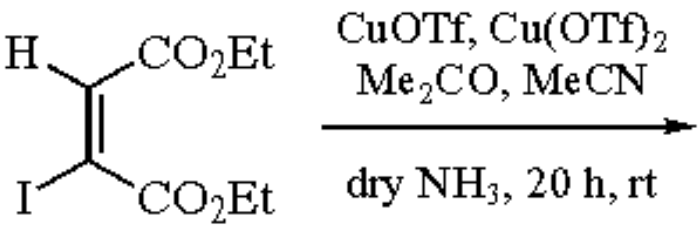

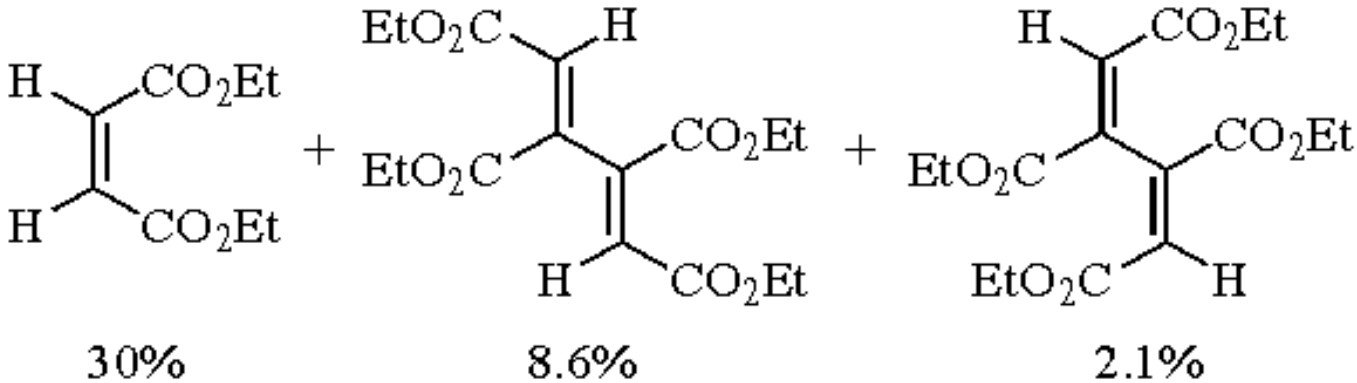

(44)

Elimination of Thiophenol from Thioacetals.

Conversion of thioacetals to vinyl sulfides is accomplished under exceptionally mild conditions by treatment with $(CuOTf)_2.C_6H_6$ (eq 45).[31] The reaction involves an α-phenylthio carbocation intermediate. Three factors contribute to the effectiveness of this synthetic method: the Lewis acidity of a copper(I) cation that is unencumbered by a strongly coordinated counter anion, the solubility of the copper(I) triflate-benzene complex, and the insolubility of CuSPh in the

reaction mixture. An analogous elimination reaction provides an effective route to phenylthio enol ethers from ketones (eq 46).[31]

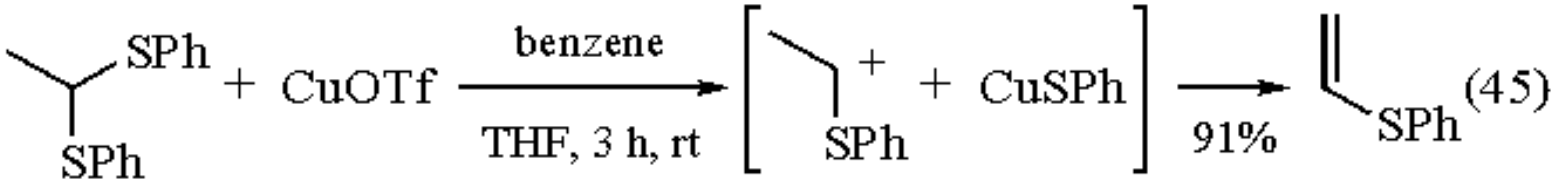

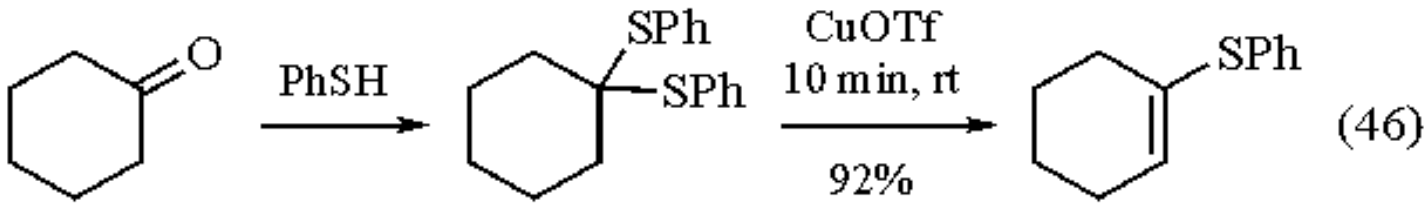

This conversion of thioacetals into vinyl sulfides was applied to a C-C connective synthesis of 2-phenylthio-1,3-butadienes from aldehydes (eq 47).[32] The key elimination step converts cyclobutanone thioacetal intermediates into 1-phenylthiocyclobutenes that undergo electrocyclic ring opening to deliver dienes.

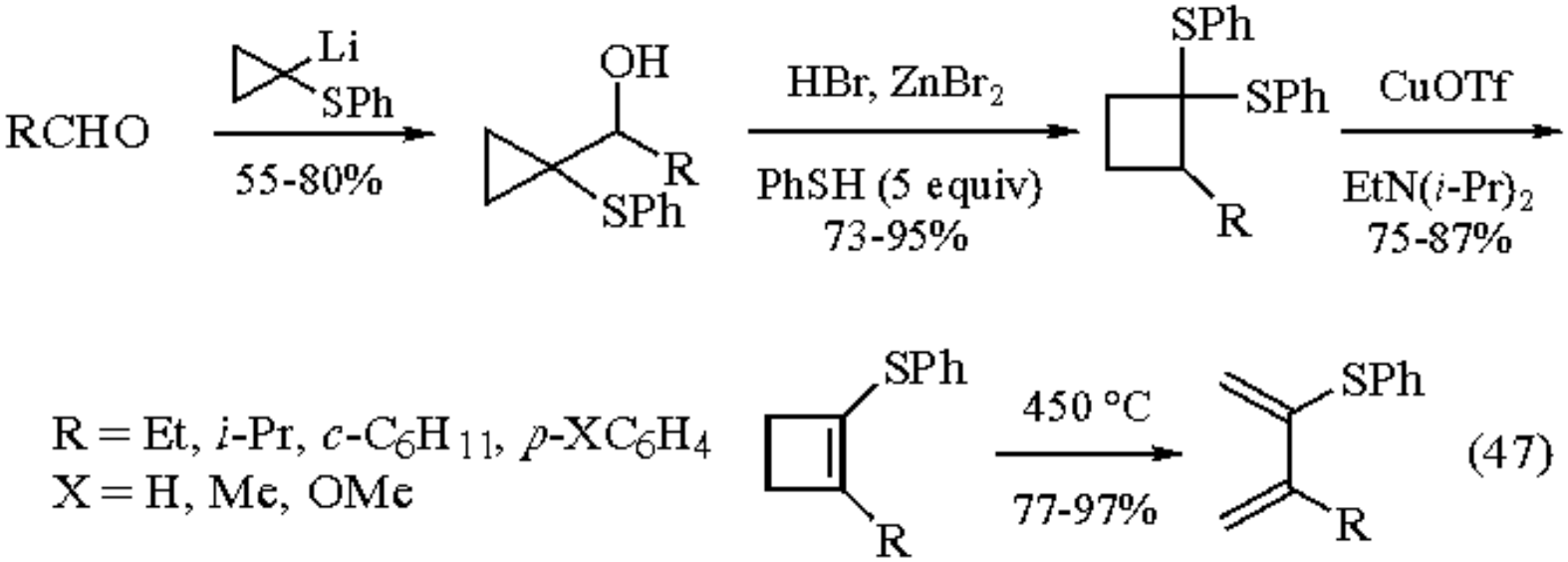

A different synthesis generates 2-phenylthio-1,3-butadienes directly by elimination of two molecules of thiophenol from β-phenylthio thioacetals that are readily available from the corresponding α,β-unsaturated ketones (eq 48).[33]

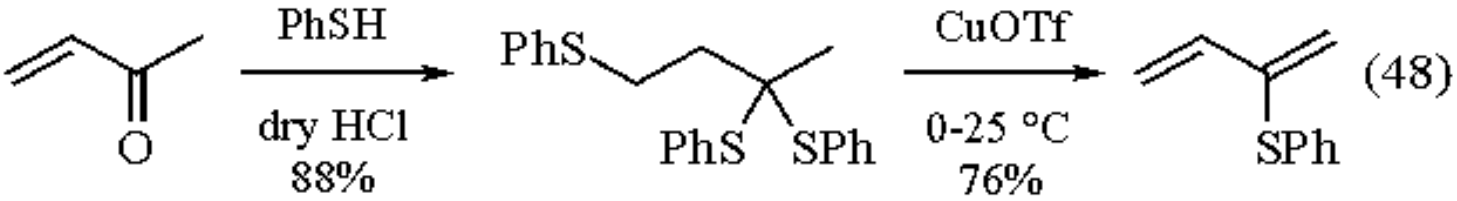

CuOTf-promoted elimination of thiophenol was exploited in two syntheses of 1-phenylthio-1,3-butadiene, one a C-C connective route from allyl bromide[31] and bis(phenylthio)methyllithium,[34] and another from ***Crotonaldehyde*** (eq 49).[33] A topologically analogous C-C connective strategy provides 2-methoxy-1-phenylthio-1,3-butadiene from acrolein (eq

50).[5,33] That the phenylthio rather than the methoxy substituent in 2-methoxy-1-phenylthio-1,3-butadiene controls the orientation of its Diels-Alder cycloadditions is noteworthy (eq 50).

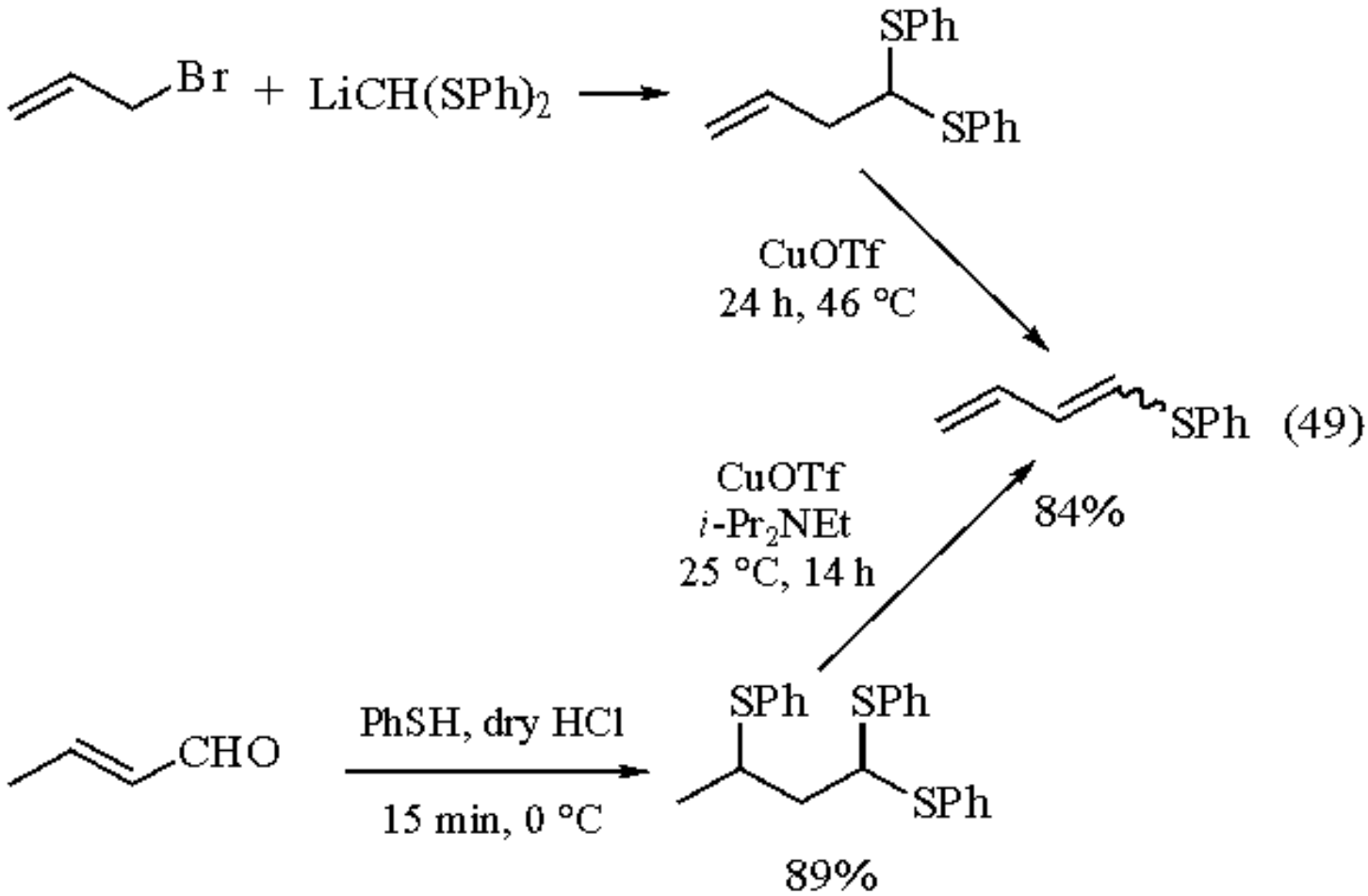

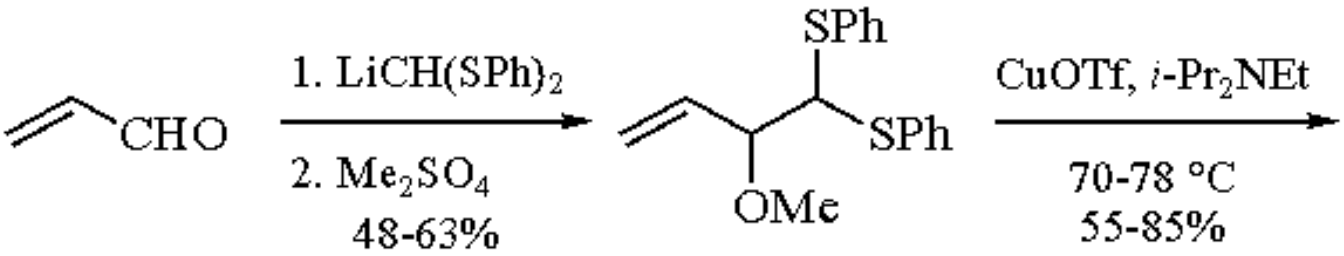

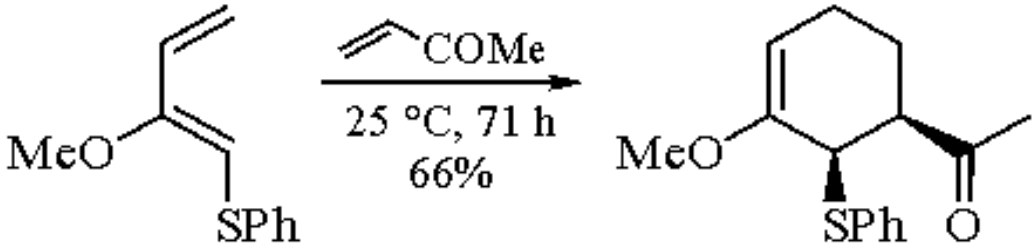

(50)

A synthesis of 4-alkyl-2-methoxy-1-phenylthio-1,3-butadienes by a simple β-elimination of thiophenol from a thioacetal is not possible owing to skeletal rearrangement that is fostered by stabilization of a cyclopropylcarbinyl carbocation intermediate by the alkyl substituent (eq 51).[35] Interconversion of an initial α-phenylthio carbocation to a more stable α-methoxy carbocation intermediate leads to the generation of a 4-alkyl-1-methoxy-2-phenylthio-1,3-butadiene instead.

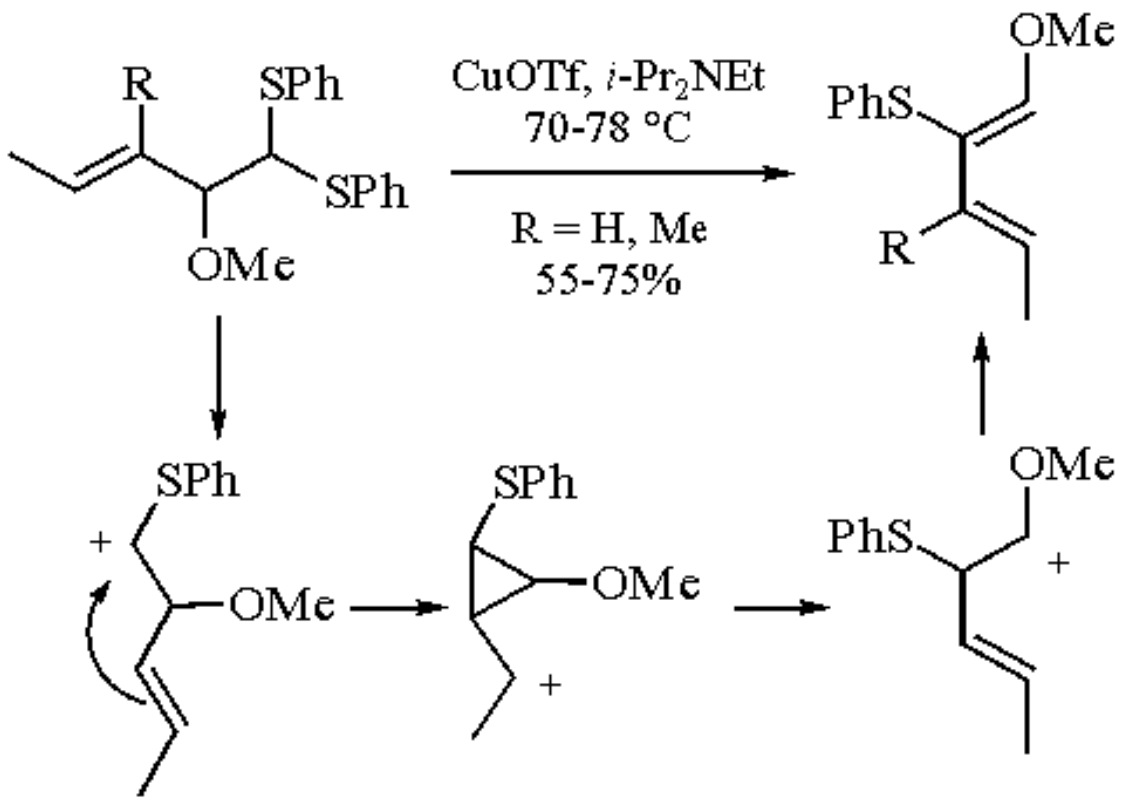

(51)

Syntheses of 1-phenylthio-1,3-butadienes from carboxylic esters (eq 52) and carboxylic acids (eq 53) are achieved by CuOTf-promoted elimination of thiophenol from intermediate thioacetals.[36]

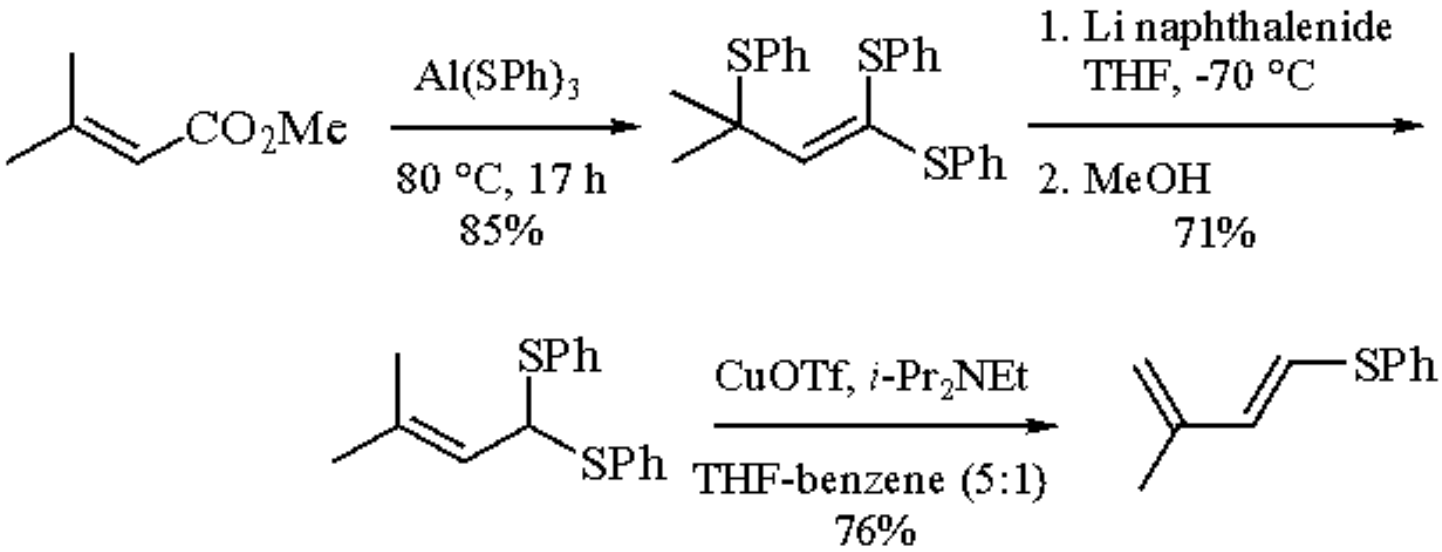

(52)

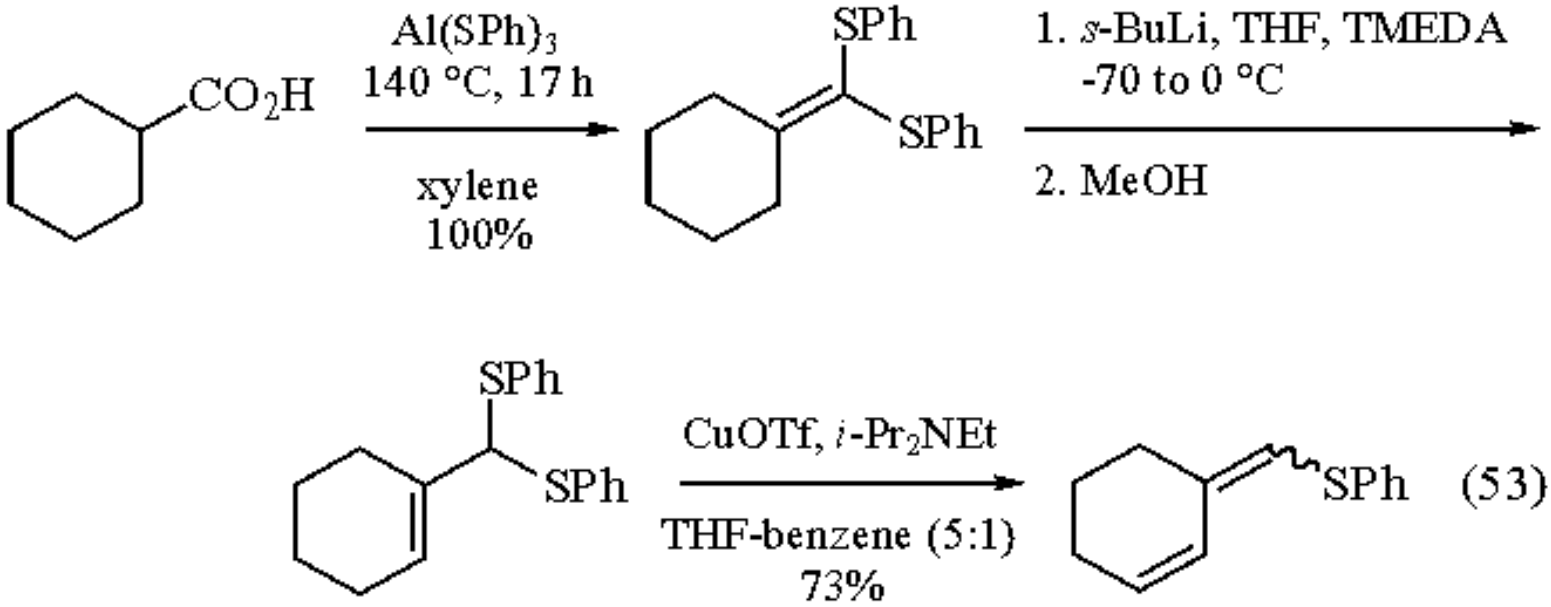

Heterocyclization of γ-Keto Dithioacetals.

A C-C connective synthesis of furans is completed by a CuOTf-promoted heterocyclization of γ-keto thioacetals (eq 54).[31] Rather than simple β-elimination to generate a vinyl sulfide (eq 46), a presumed γ-keto carbocation intermediate is captured intramolecularly by an intimately juxtaposed carbonyl oxygen nucleophile.

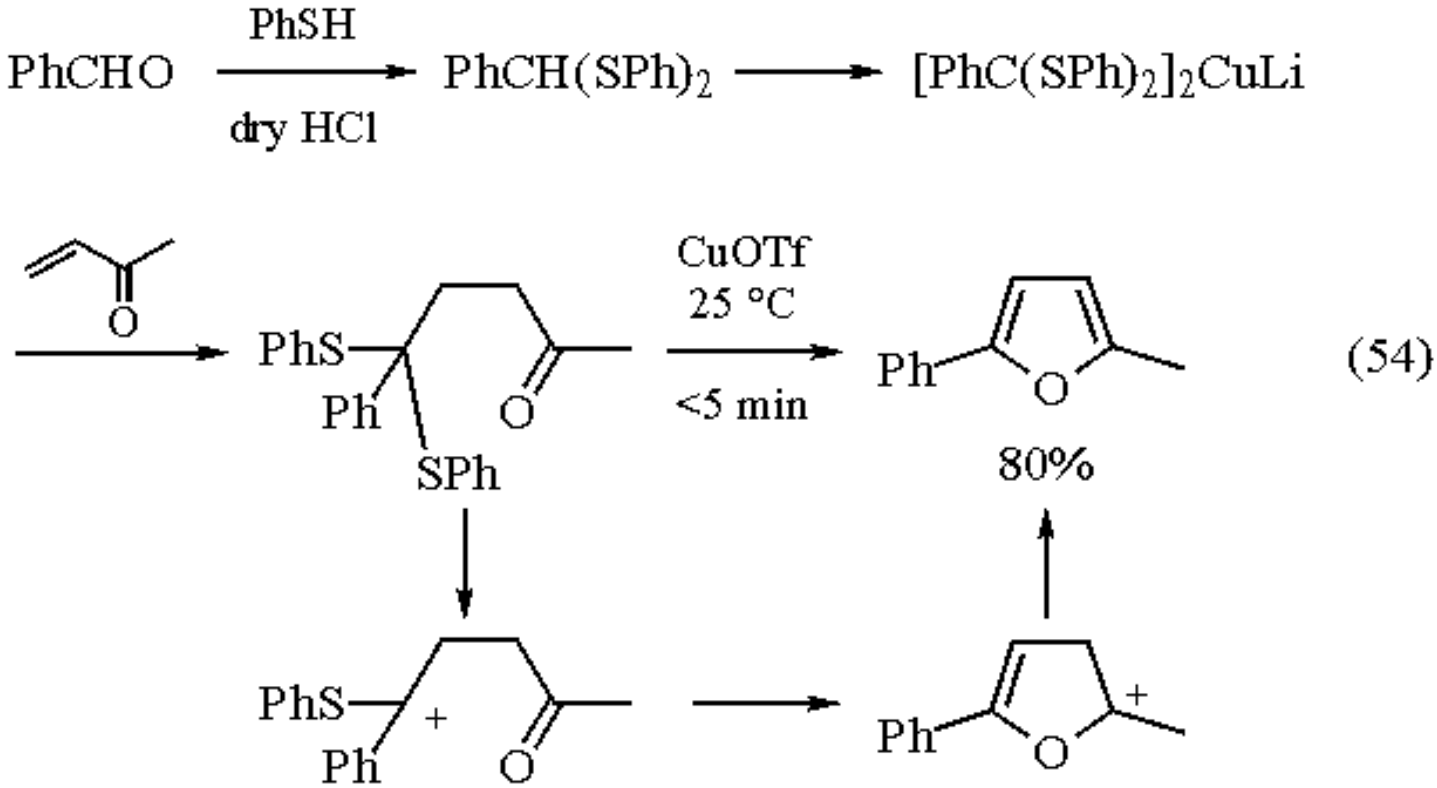

Friedel-Crafts Alkylation of Arenes with Thioacetals.

$(CuOTf)_2.C_6H_6$ promotes α-thioalkylation of anisole by a dithioacetal under mild conditions (eq 55).[37]

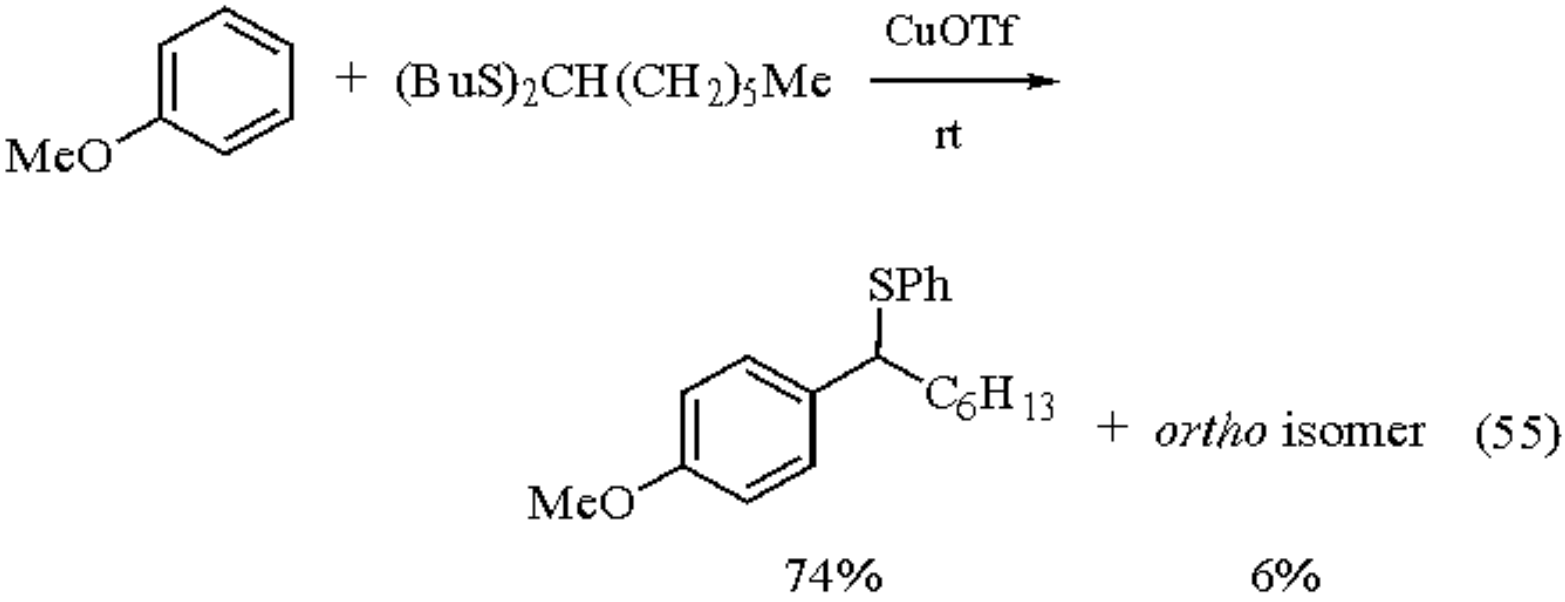

Elimination of Benzylic Phenyl Thioethers.

That C-S bond activation by CuOTf is not limited to substrates that can generate sulfur-stabilized carbocation intermediates is illustrated by a C-C connective synthesis of *trans*-stilbene (eq 56).[31] The elimination of thiophenol under mild conditions is favored by benzylic stabilization of a carbocation intermediate or an E2 transition state with substantial carbocationic character.

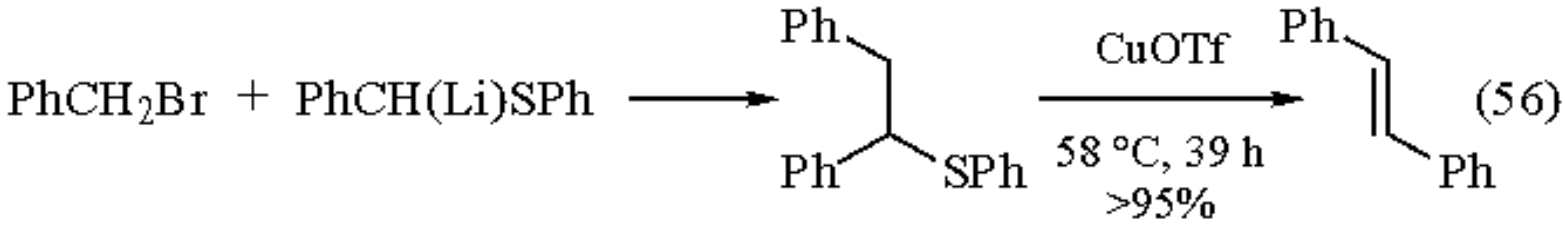

Hydrolysis of Vinylogous Thioacetals.

Carbanions prepared by lithiation of γ-phenylthioallyl phenyl thioethers can serve as synthetic equivalents of β-acyl vinyl anions.[38] Umpölung of the usual electrophilic reactivity of 2-cyclohexenone is achieved by a sequence exploiting electrophilic capture of a lithiated vinylogous thioacetal and subsequent CuOTf-assisted hydrolysis (eq 57).[39] Otherwise unfunctionalized vinylogous thioacetals can be hydrolyzed to enones by ***Mercury(II) Chloride*** in wet acetonitrile.[38] However, the keto-substituted derivative in eq 57 gave only a 25% yield of enone by this method. A superior yield was obtained by CuOTf-assisted hydrolysis.[39]

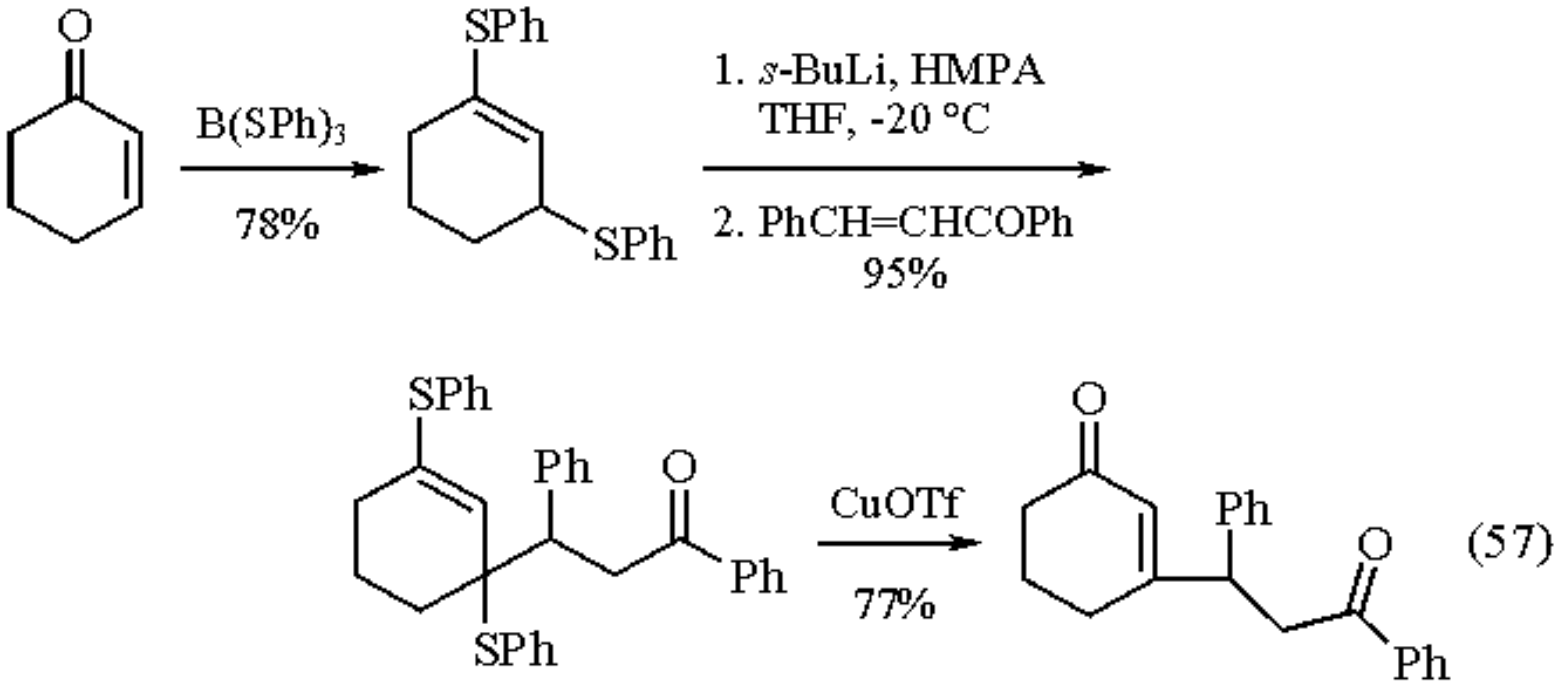

Grob Fragmentation of β-[Bis(phenylthio)methyl]alkoxides.

A method for achieving Grob-type fragmentation of five- and six-membered rings depends upon the ability of a thiophenyl group to both stabilize a carbanion and serve as an anionic leaving group. For example, reaction of cyclohexene oxide with lithium bis(phenylthio)methide[34] produces a β-[bis(phenylthio)methyl]alkanol that undergoes fragmentation in excellent yield upon treatment with ***n-Butyllithium*** followed by CuOTf (eq 58).[40] Copper(I) trifluoroacetate is equally effective but salts of other thiophilic metals, e.g. mercury or silver, were ineffective. Treatment of the intermediate β-[bis(phenylthio)methyl]alkanol with CuOTf in the absence of added strong base leads primarily to elimination of thiophenol as expected (see eq 45). Fragmentation does not occur with only one equivalent of CuOTf. This suggests a key intermediate with at least one Cu^{I} ion to coordinate with the alkoxide and another to activate the phenylthio leaving group (eq 58).

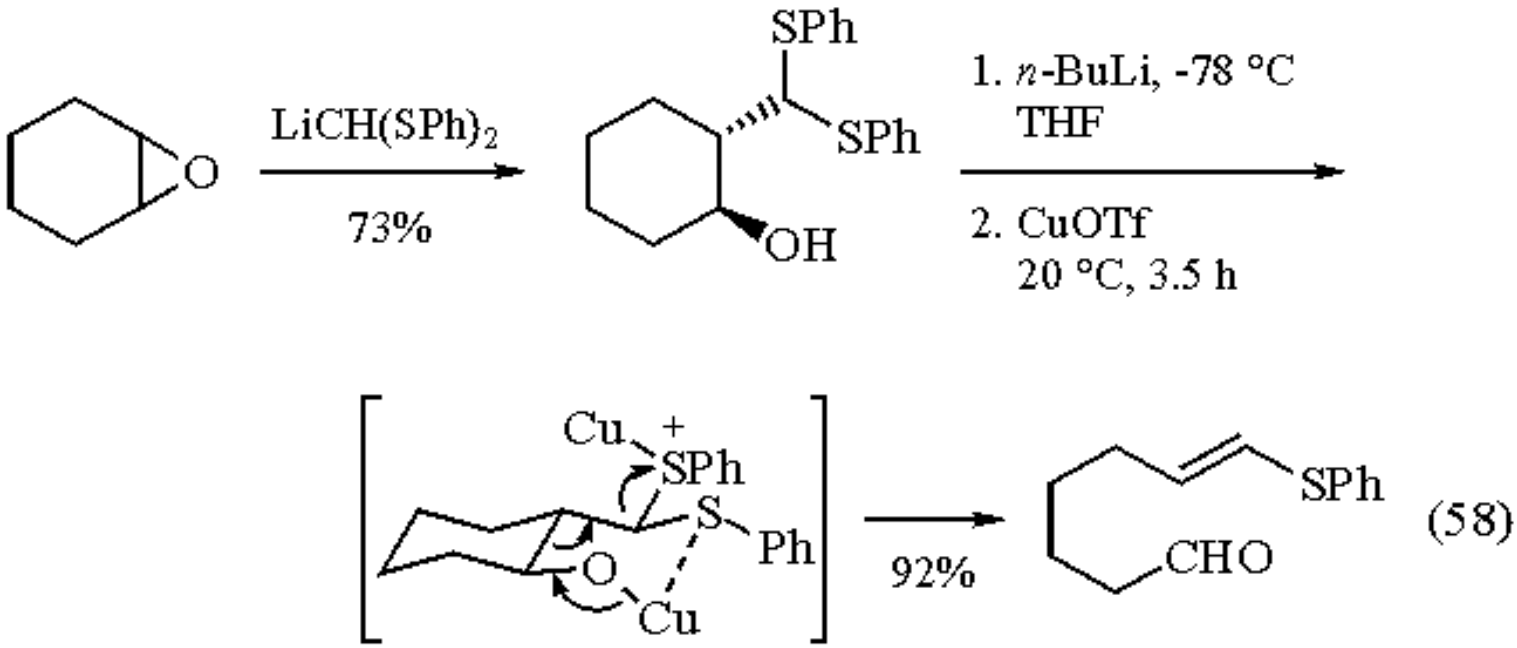

Ring-Expanding Rearrangements of α-[Bis(phenylthio)methyl]alkanols.

A one-carbon ring-expanding synthesis of α-phenylsulfenyl ketones from homologous ketones depends upon the ability of a thiophenyl group to both stabilize a carbanion and serve as an anionic leaving group. For example, reaction of cyclopentanone with lithium bis(phenylthio)methide[34] produces an α-[bis(phenylthio)methyl]alkanol that rearranges to a ring-expanded α-phenylsulfenyl ketone in good yield upon treatment with CuOTf in the presence of ***Diisopropylethylamine*** (eq 59).[41] Epoxy thioether intermediates are generated from the α-[bis(phenylthio)methyl]alkanols by intramolecular nucleophilic displacement of thiophenoxide.

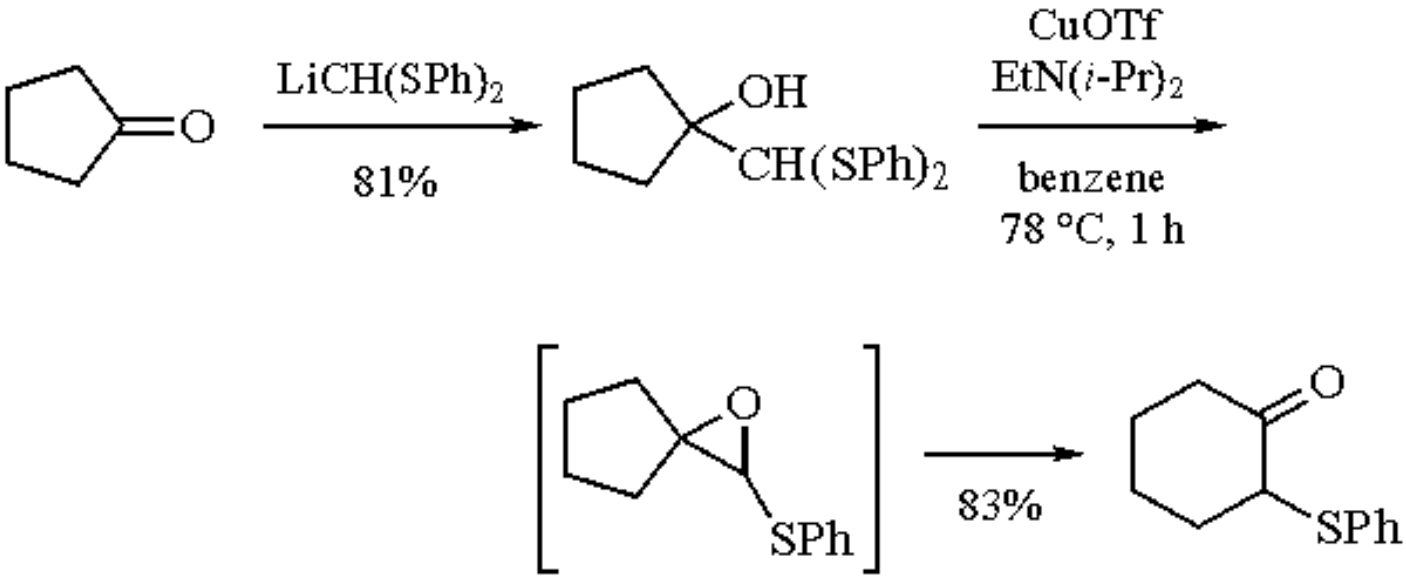

(59)

An analogous synthesis of α,α-bis(methylsulfenyl) ketones from homologous ketones by one-carbon ring expansion depends on copper(I)-promoted rearrangement of an α-tris(methylthio)methyl alkoxide intermediate (eq 60). Both ***Tetrakis(acetonitrile)copper(I) Perchlorate***[42] and ***Tetrakis(acetonitrile)copper(I) Tetrafluoroborate***[43] are effective in promoting the rearrangement but $(CuOTf)_2.C_6H_6$, $HgCl_2$, or $Hg(TFA)_2$ are not. Apparently, the MeCN ligand is crucial. Furthermore, treatment of the intermediate α-[tris(methylthio)methyl] alcohol with CuOTf and $EtN(i\text{-}Pr)_2$ in toluene followed by aqueous workup delivers an α-hydroxy methylthio ester (eq 61),[43] in contrast to the ring-expanding rearrangement of the analogous α-[bis(phenylthio)methyl]alkanol (eq 59).[41]

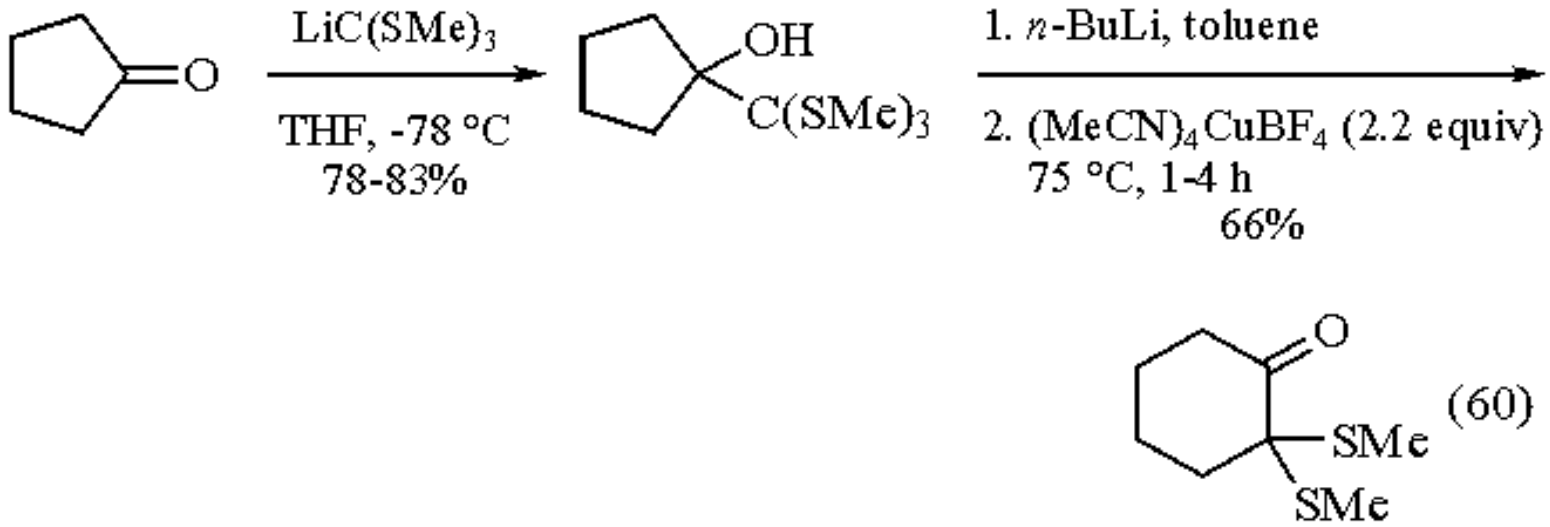

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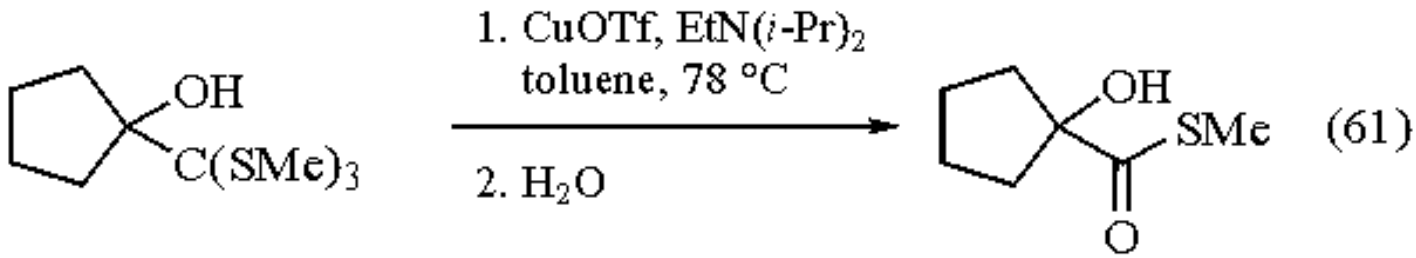

(61)

The α-[bis(phenylthio)methyl]alkanol derived from cycloheptanone does not undergo ring expansion upon treatment with CuOTf and EtN(*i*-Pr)$_2$ in benzene. Instead, 1,3-elimination of thiophenol delivers an epoxy thioether intermediate that undergoes a rearrangement involving 1,2-shift of a phenylsulfenyl group to produce an α-phenylsulfenyl aldehyde (eq 62).[41]

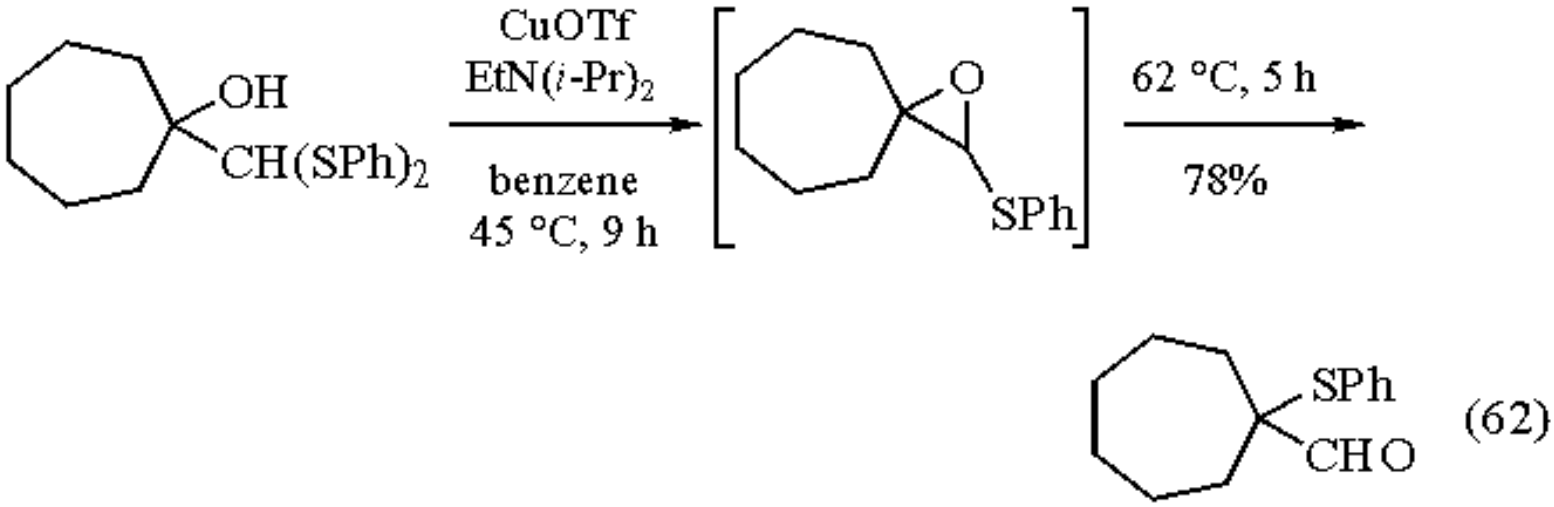

(62)

The α-[bis(phenylthio)methyl]alkanol derived from cyclohexanone, upon treatment with CuOTf and EtN(*i*-Pr)$_2$ in benzene, undergoes both ring-expanding rearrangement to deliver α-phenylsulfenylcycloheptanone as the major product, as well as rearrangement involving 1,2-shift of a phenylsulfenyl group to produce an α-phenylsulfenylcyclohexanecarbaldehyde (eq 63).[41] In contrast, neither ring expansion nor 1,2-shift of a methylsulfenyl group occurs upon treatment of α-[tris(methylthio)methyl]cyclohexanol with *n*-butyllithium followed by (MeCN)$_4$CuBF$_4$. Rather, after aqueous workup, an α-hydroxy methylthio ester is obtained (eq 64).[43]

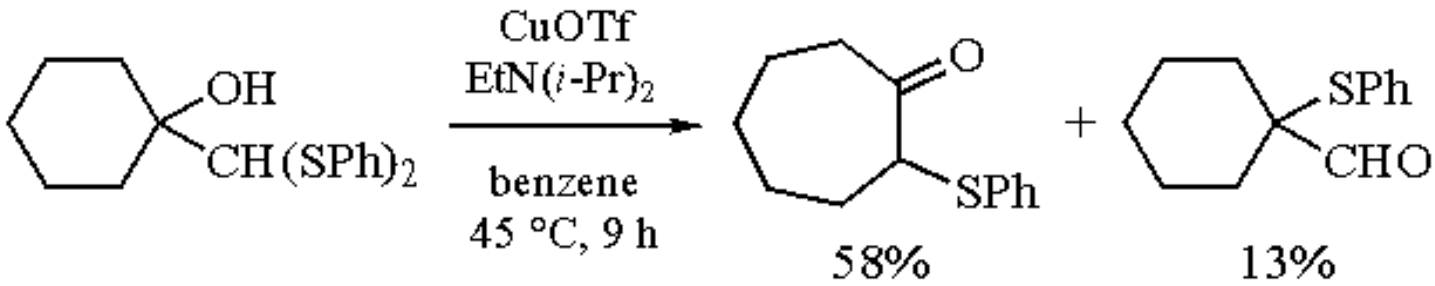

(63)

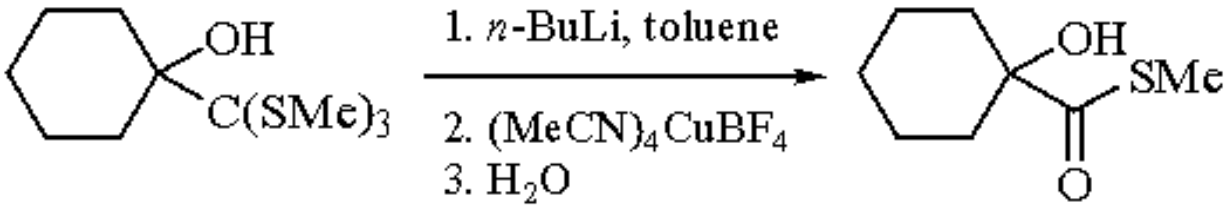

(64)

Chain-Extending Syntheses of α-Phenylsulfenyl Ketones.

A C-C connective, chain-extending synthesis of α-phenylsulfenyl ketones from aldehydes (eq 65) or acyclic ketones (eq 66)[41] can be accomplished by a CuOTf-promoted activation of the α-[bis(phenylthio)methyl]alkanols generated by addition of lithium bis(phenylthio)methide.[34] Preferential migration of hydride generates phenylsulfenylmethyl ketones from aldehydes (eq 65). Regioselective insertion of a phenylsulfenylmethylene unit occurs owing to a preference for migration of the more highly substituted alkyl group of dialkyl ketones (eq 66).

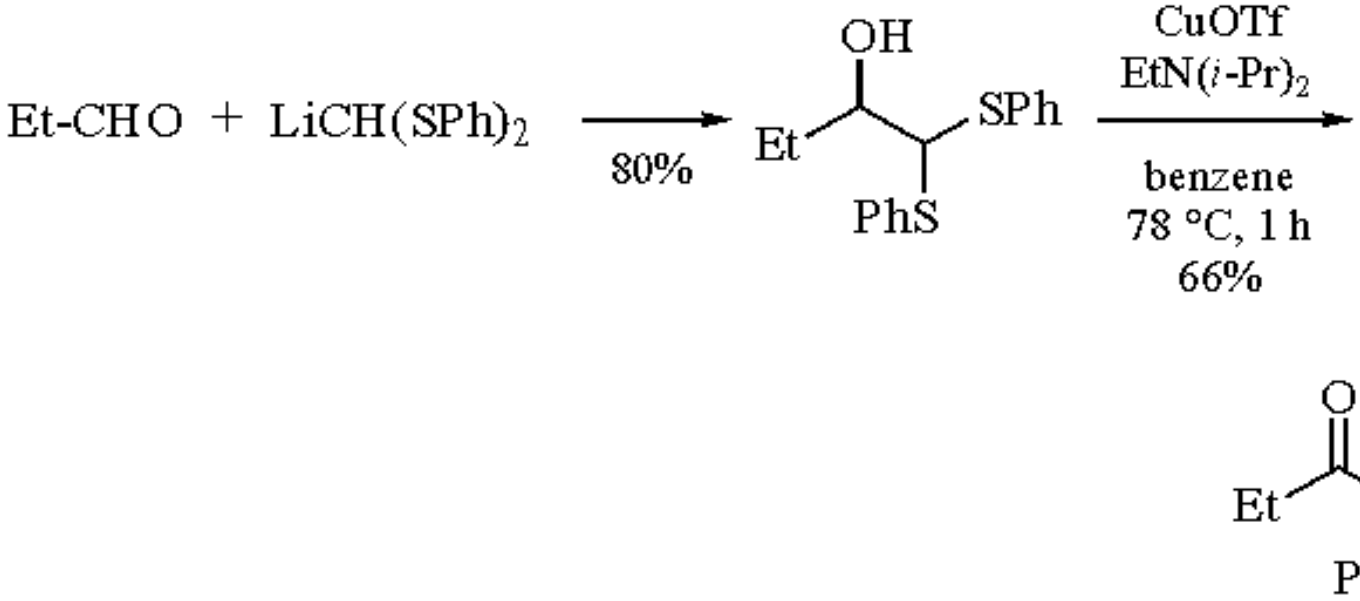

(65)

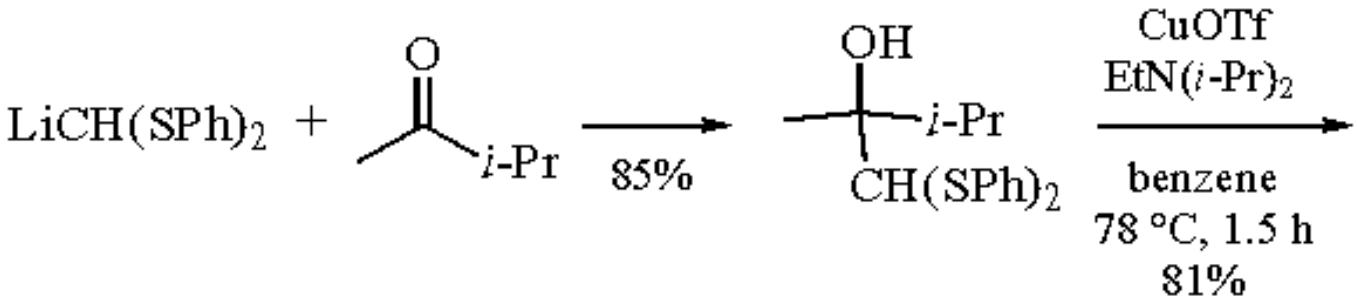

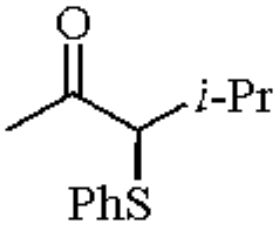

(66)

Cyclopropanation of Enones.

Conjugate addition of lithium tris(phenylthio)methide[44] to α,β-unsaturated ketones produces enolates that cyclize to bis(phenylthio)cyclopropyl ketones at -78 °C upon treatment with nearly one equivalent of $(CuOTf)_2.C_6H_6$, i.e. 1.9 equivalents of Cu^I (eq 67).[45] The mild conditions that suffice to bring about nucleophilic displacement of thiophenoxide in the presence of CuOTf are especially noteworthy. In view of the requirement for more than one equivalent of Cu^I to achieve Grob-type fragmentation of β-[bis(phenylthio)methyl]alkoxides (see eq 58), it seems likely, although as yet unproven, that one equivalent of Cu^I coordinates strongly with the enolate oxygen and that a second equivalent of Cu^I is required to activate the thiophenoxide leaving group.

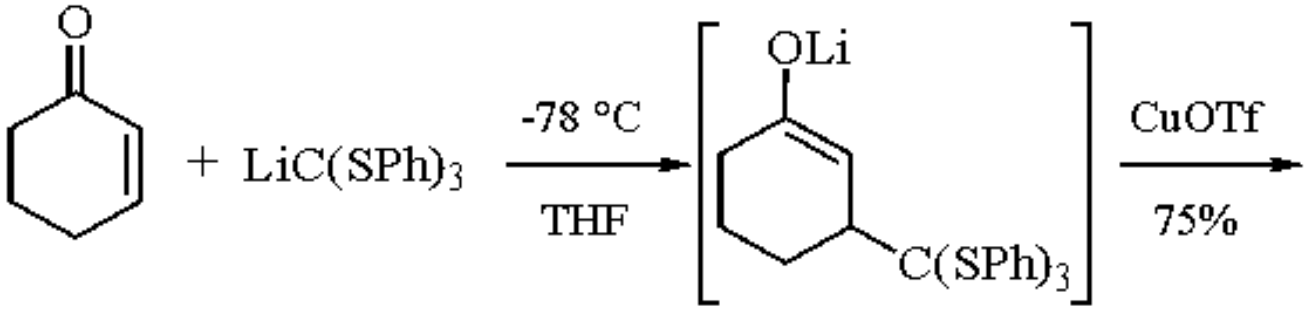

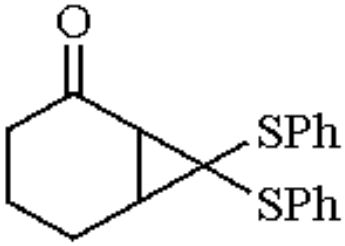

(67)

Vinylcyclopropanation of Enones.

Conjugate addition of sulfur-stabilized allyl carbanions to α,β-unsaturated ketones produces enolates that cyclize to vinylcyclopropyl ketones upon treatment with nearly one equivalent of $(CuOTf)_2.C_6H_6$, i.e. 1.9 equivalents of Cu^I (eq 68).[45]

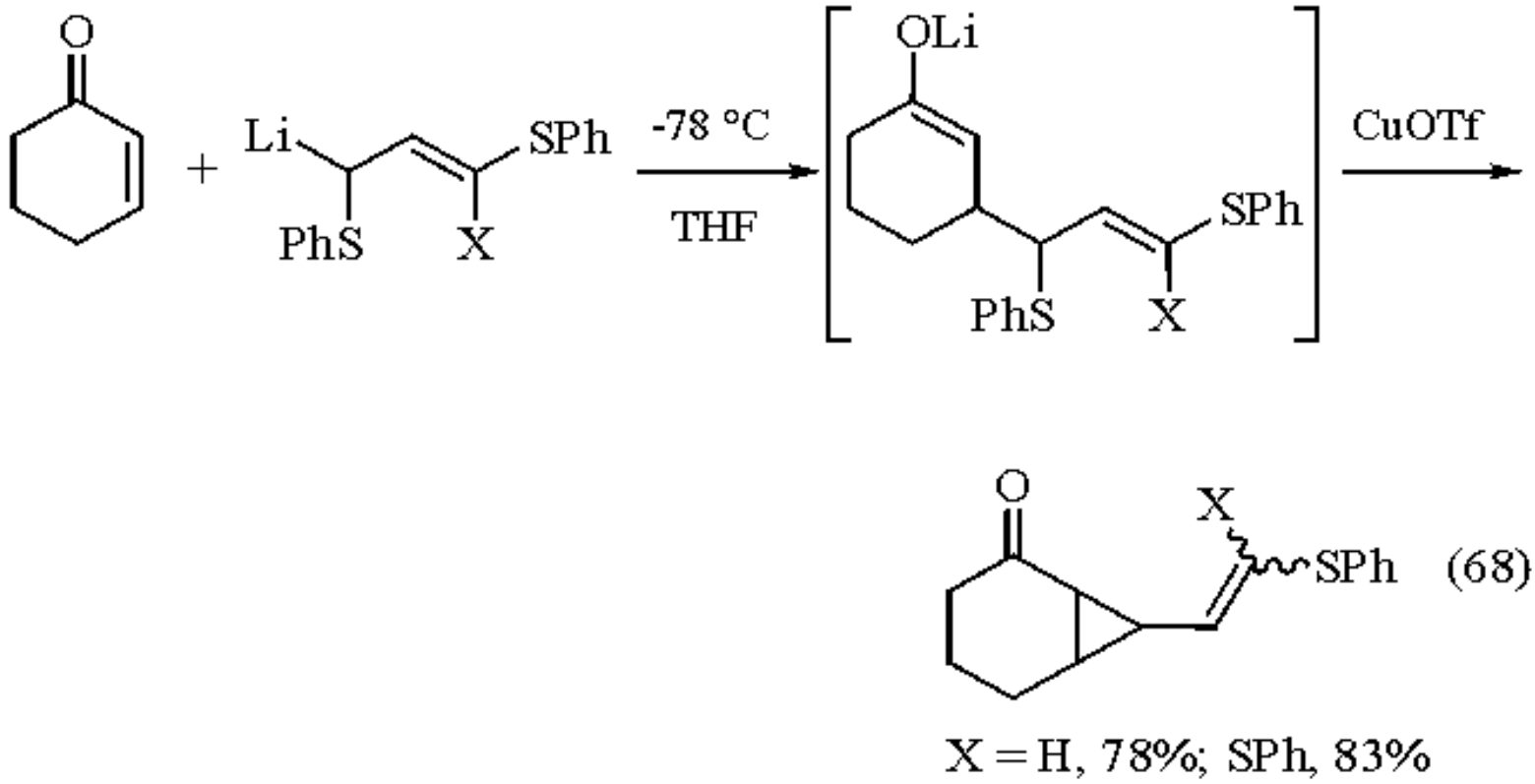

Friedel-Crafts Acylation with Thio- or Selenoesters.

Methylseleno esters are readily available in excellent yields by the reaction of ***Dimethylaluminum Methylselenolate*** with *O*-alkyl esters.[37] These selenoesters will acylate reactive arenes (eq 69) and heterocyclic compounds (eq 70) when activated by CuOTf, a selenophilic Lewis acid.[37] Of the potential activating metal salts tested, $(CuOTf)_2.C_6H_6$ is uniquely effective. Mercury(II) or copper(I) trifluoroacetates that are partially organic-soluble, as well as the corresponding chlorides, silver nitrate, and copper(I) oxide that are not organic-soluble, all failed to promote any acylation. The highly reactive CuOTf-benzene complex, in dramatic contrast, was found to readily promote the acylations in benzene solution within minutes at room temperature. The presence of vinyl and keto groups is tolerated by the reaction, and while the alkyl- and vinyl-substituted derivatives afford *para* substitution only, a 2:1 mixture of *para* and *ortho* substitution occurs with the methylseleno ester of levulinic acid. Acylation of toluene is sluggish. Excellent yields of 2-acylfurans, -thiophenes, and -pyrroles are generated by this new variant of the Friedel-Crafts acylation reaction (eq 70). An intramolecular version of this reaction was shown to generate 1-tetralone from the methylseleno ester of γ-phenylbutyric acid (eq 71).[37]

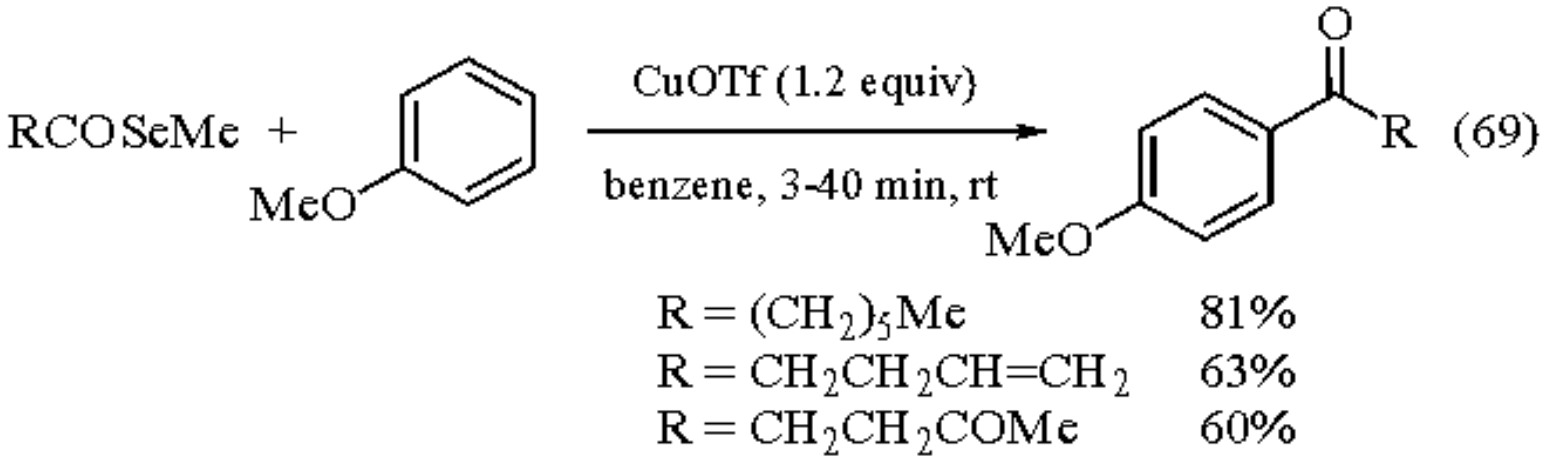

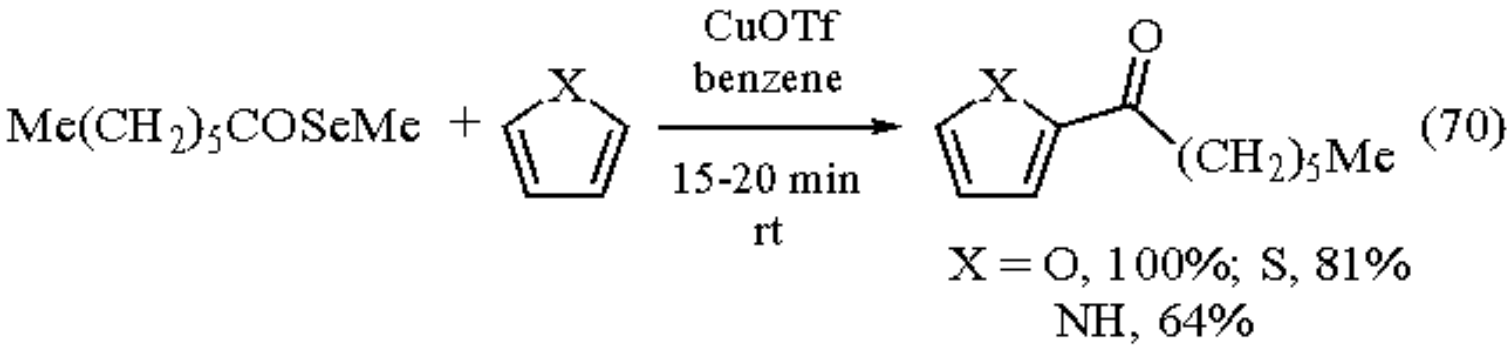

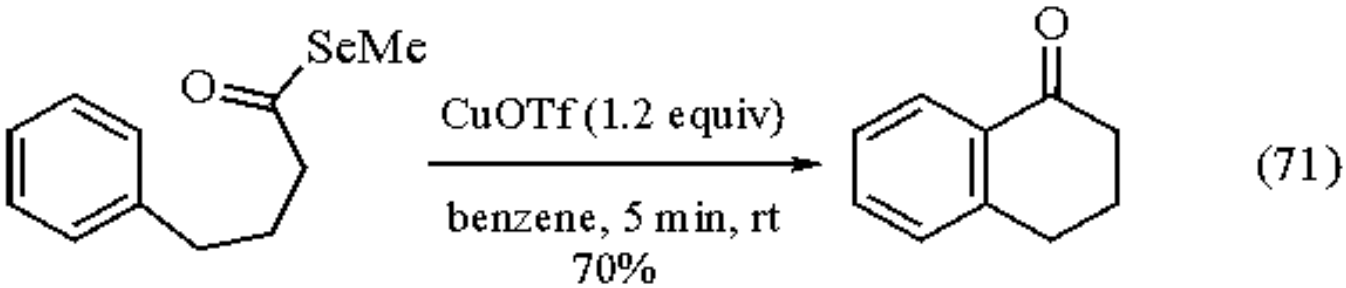

Notwithstanding a prior claim that methylthio esters react only sluggishly under these conditions,[37] such a variant proved effective for a short synthesis of the 4-demethoxy-11-deoxyanthracycline skeleton (eq 72).[46] This is especially significant because methylthio esters are available by an efficient C-C connective process involving *C*-acylation of ketone lithium enolates with ***Carbon Oxysulfide*** (COS) followed by *S*-methylation with ***Iodomethane***.[46] For the deoxyanthracycline synthesis, the requisite enolate was generated by 1,4-addition of a silyl-stabilized benzyllithium derivative to 2-cyclohexenone. Treatment of the methylseleno ester with $(CuOTf)_2.C_6H_6$ in benzene, according to the method employed with analogous seleno esters,[37] results in efficient cyclization to deliver a tetracyclic diketone in good yield.

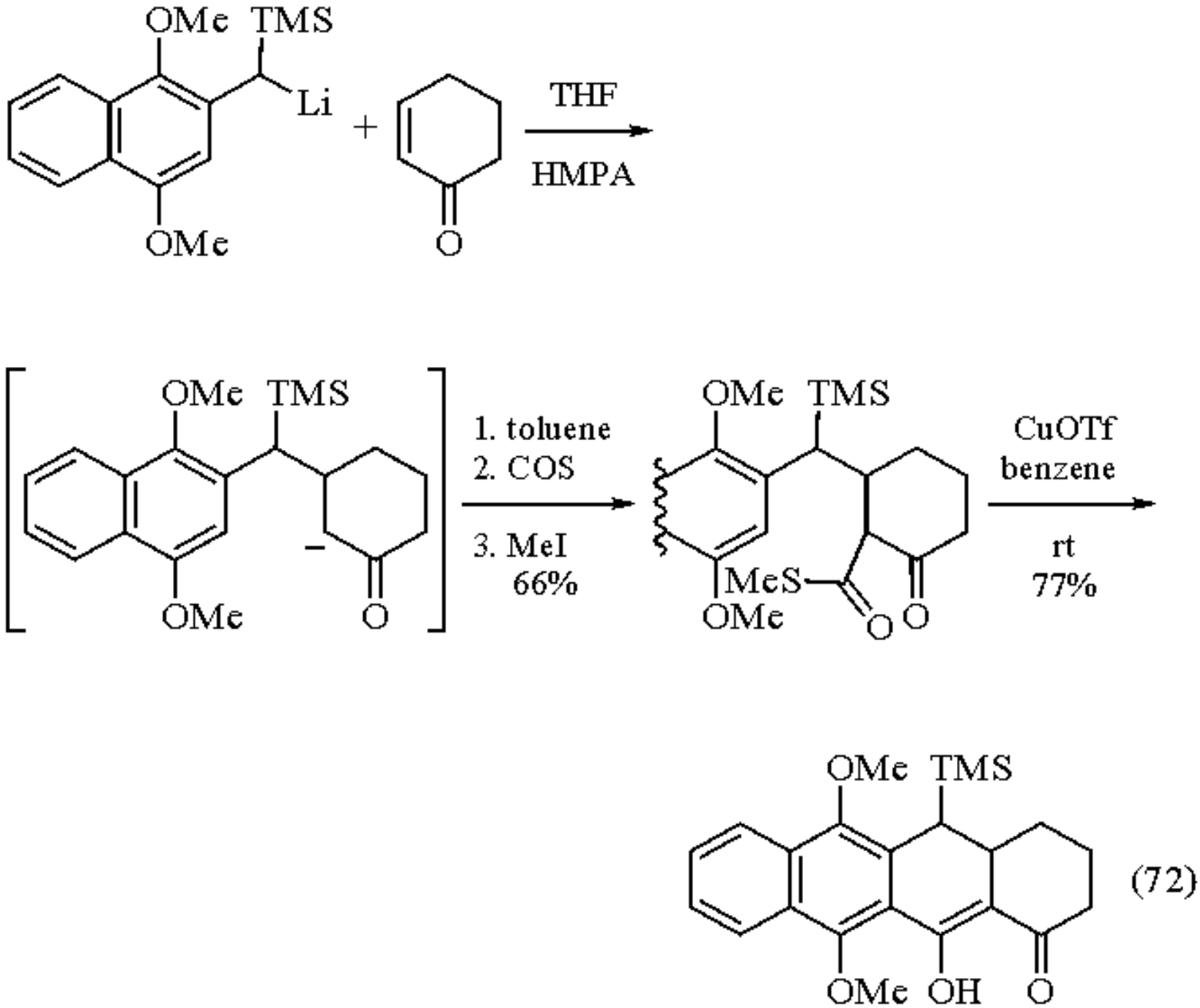

O-Acylation with Thioesters.

Activation of a thioester with $(CuOTf)_2.C_6H_6$ was exploited as a key step in the synthesis of a macrocyclic pyrrolizidine alkaloid ester (eq 73).[47] Since thioesters are relatively unreactive acylating agents, a highly functionalized imidazolide containing acetate and *t*-butyl thioester groups selectively acylated only the primary hydroxyl in the presence of the secondary hydroxyl group in (+)-retronecine. Completion of the synthesis required activation of the *t*-butylthio ester. ***Mercury(II) Trifluoroacetate***, that had proven effective for the synthesis of several natural products by lactonization,[48,49] failed to promote any lactonization in the present case.[47] Similarly, ***Mercury(II) Chloride*** and ***Cadmium Chloride***, that have proven effective for promoting lactonizations,[49] had no effect in the present case. Even copper(I) trifluoroacetate failed to induce the crucial lactonization. In contrast, CuOTf was uniquely effective for inducing the requisite macrolactonization by activating the thioester.

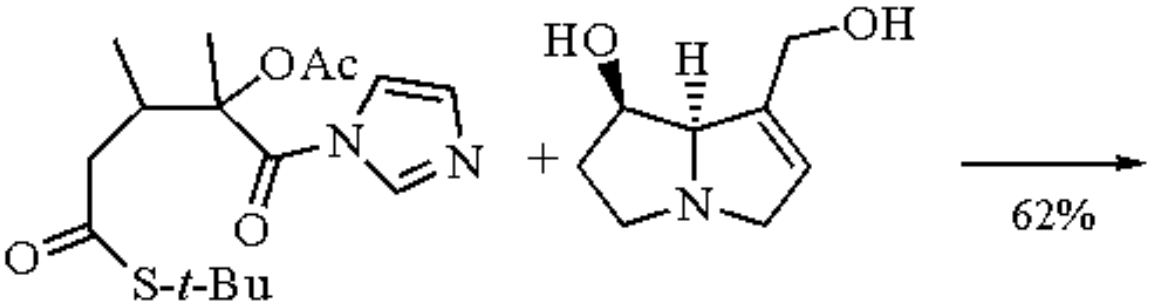

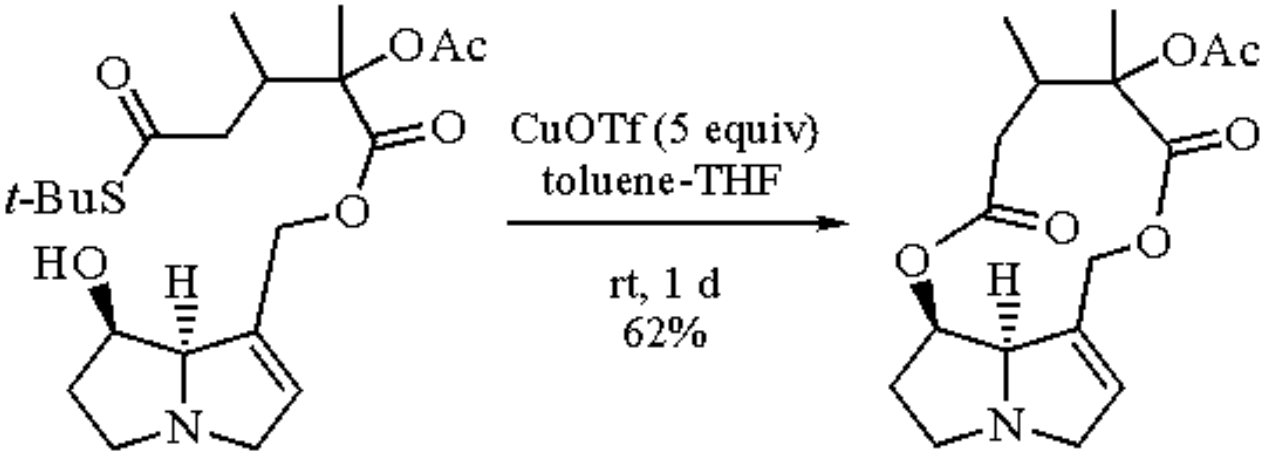

(73)

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Crotonaldehyde[1]

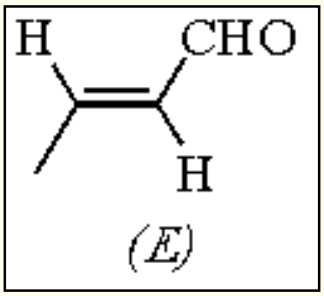

(*E*)

[123-73-9] · C_4H_6O · Crotonaldehyde · (MW 70.09) (*Z*)

[15798-64-8]

(key electrophilic component in a wide variety of reactions[1])

Alternate Names: 2-butenal; crotonic aldehyde.

Physical Data: (*E*) isomer: mp -76.5 °C; bp 104.0 °C *d* 0.846 g cm^{-3}.

Solubility: sol H_2O (19.2 g/100 mL); sol alcohol, ether, and most organic solvents.

Form Supplied in: commercial crotonaldehyde is predominately the (*E*) isomer containing 4-6% of the (*Z*) isomer; also available as a 90% solution stabilized with 8-10% water.

Preparative Methods: pure (*E*) isomer and highly enriched (*Z*) isomer have been prepared by oxidation of (*E*)- and (*Z*)-crotyl alcohols.[2] Pure (*Z*) isomer has been prepared via a retro-Diels-Alder reaction at high temperature.[3]

Purification: fractionally distilled through a short Vigreux column.

Handling, Storage, and Precautions: to prevent polymerization and autooxidation, store under nitrogen atmosphere and refrigerate. Crotonaldehyde is readily absorbed through the skin and should be handled with gloves and protective clothing in a well ventilated fume hood. Toxicity: oral-rat LD_{50}: 300 mg kg^{-1}. Incompatible with strong acids, strong bases, oxidizing and reducing agents. Decomposes on prolonged exposure to air.

1,2-Additions.

Crotonaldehyde serves as an electrophilic target for a vast array of nucleophilic reagents. Grignard and organolithium reagents react to afford, after hydrolysis, good yields of secondary allyl alcohols.[1,4] 1,3-Dienes can be prepared by elimination of the resulting secondary allyl alcohols,[5] or via Wittig[6] and Wittig-type reactions.[7] Allyl[8] and alkynyl[9] organometallic reagents afford good yields of the allyl alcohols from crotonaldehyde, some with a good stereocontrol.[8c,d] Allylation in aqueous solvent is also possible.[10] Reformatsky reaction of difluorochloromethyl ketones utilizing a copper(I) or silver(I) catalyst with crotonaldehyde generates α,α-difluoro-β-hydroxy ketones in high yields,[11] while the corresponding dichlorofluoroacetates afford the (*Z*)-α-fluoro-α,β-unsaturated carboxylates.[12] Substituted lactones and butenolides are produced from 1,2-additions with nucleophilic reagents that possess latent carboxylate functionalities.[13] 1,3-Asymmetric induction has been achieved on addition of 2-lithio-2-(1-methyl-2-alkenyl)-1,3-dithianes to crotonaldehyde to produce predominately 1,3-*syn* adducts (eq 1).[14] Enantioselective 1,2-addition has been demonstrated using chiral allenic boranes to produce the propargyl carbinol in 97-98% ee.[15] The silylated cyanohydrin of crotonaldehyde is conveniently prepared using ***Sodium Cyanide*** impregnated on Amberlite XAD resin in the presence of ***Chlorotrimethylsilane***.[16] The enzyme mandelonitrile lyase catalyzes the enantioselective cyanohydrin formation from crotonaldehyde in as high as 95% ee.[17]

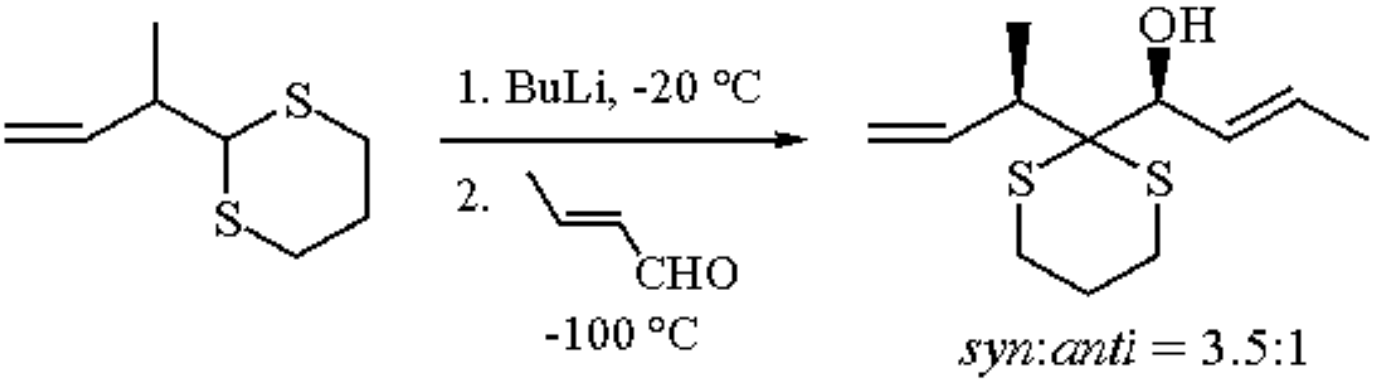

(1)

1,4-Additions.

In comparison, nucleophilic agents that preferentially add to the alkenic terminus of crotonaldehyde are few in number. Thiols,[1] sodium nitrite,[18] or imides,[1] malonate esters,[19] and nitromalonic or nitroacetic esters[1] in the presence of base generally add with good 1,4-selectivity. Methanetricarboxylic esters under phase transfer catalysis afford a 90% yield of the two-carbon elongated Michael adduct.[20] Surprisingly, the lithium dienolate of a chiral dioxinone adds in a Michael addition to give the four-carbon chain extended aldehyde with high diastereoselectivity (eq 2).[21] Cyclopropylacylsilanes are formed from initial Michael addition of an acylsilylsulfur ylide.[22] Examples of ring formation from crotonaldehyde involve an initial Michael addition followed by closure on the aldehyde carbonyl.[23] The Skraup synthesis of 2-methylquinolines utilizes this mode of cyclization.[24] Cyclization of crotonaldehyde on certain anthraquinones occurs through a Michael reaction followed by an intramolecular Marschalk reaction.[25] Organocopper reagents react predominately with 1,4-addition to produce the substituted aldehydes.[26]

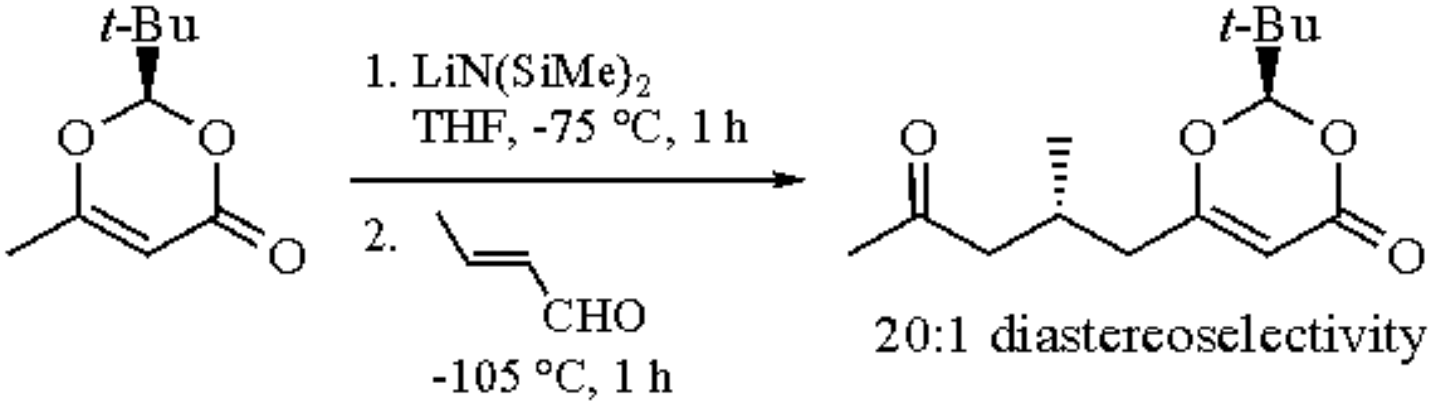

(2)

Acetal Formation.

Crotonaldehyde reacts with a variety of alcohols or orthoformates, usually under acid catalysis, to form acetals.[1,27] Chiral C_2-symmetric acetals, for use as chiral auxiliaries, have been prepared (eq 3).[28] Cyclic dithioacetals of crotonaldehyde can easily be prepared from the dithiol using SiO_2-$SOCl_2$ as catalyst.[29]

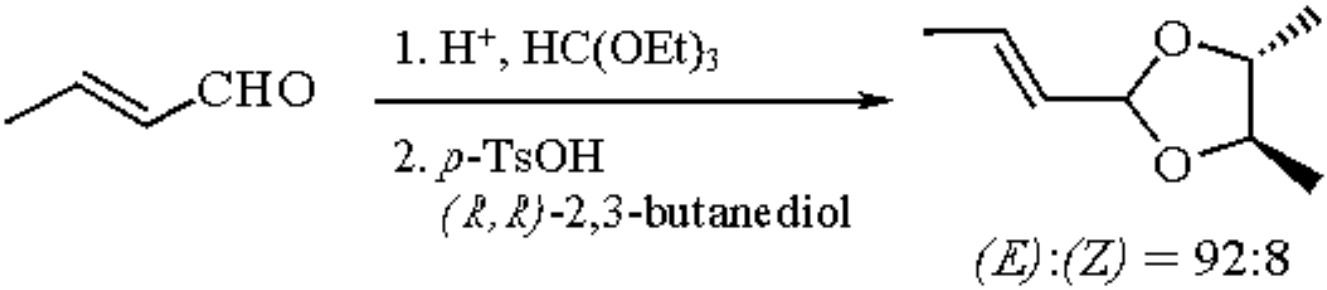

(3)

Reduction.

Crotonaldehyde can be selectively reduced at either the carbonyl or the double bond to afford good yields of crotyl alcohol or butyraldehyde. Hydride transfer reagents, Meerwein-Pondorf-Verley reduction, or catalytic hydrogenation using Os on charcoal, all give crotyl alcohol.[30] Hydrogenation over Pd catalysts gives varying amounts of butyraldehyde.[1,30] Nickel catalysts at elevated temperatures fully hydrogenate crotonaldehyde to butanol.[1,30]

Aldol Condensations.

Crotonaldehyde readily participates in a wide variety of aldol condensations. Classic Knoevenagel condensation as well as Co^{II}-catalyzed Knoevenagel condensations lead to dienone products.[31] Dienones and dienoates may also be produced by reaction with the lithium enolates of ketones and esters in the presence of TMSCl at low temperature.[32] Stereoselective aldol additions to crotonaldehyde have been numerous. Many highly *anti*-[33] and *syn*-selective[34] additions to crotonaldehyde have been demonstrated, one a catalytic asymmetric *syn*-selective

aldol (eq 4).[35] An asymmetric aldol between crotonaldehyde and ***p-Tolylsulfonylmethyl Isocyanide*** catalyzed by a chiral silver(I) catalyst affords the *trans*-4-tosyl-2-oxazoline in 85% ee.[36] Diastereoselective aldols can also be achieved using chiral (η^6-arene)chromium complexes.[37]

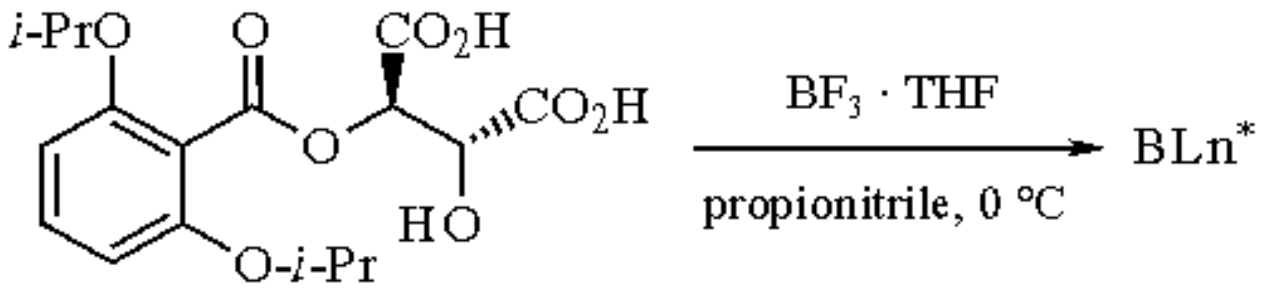

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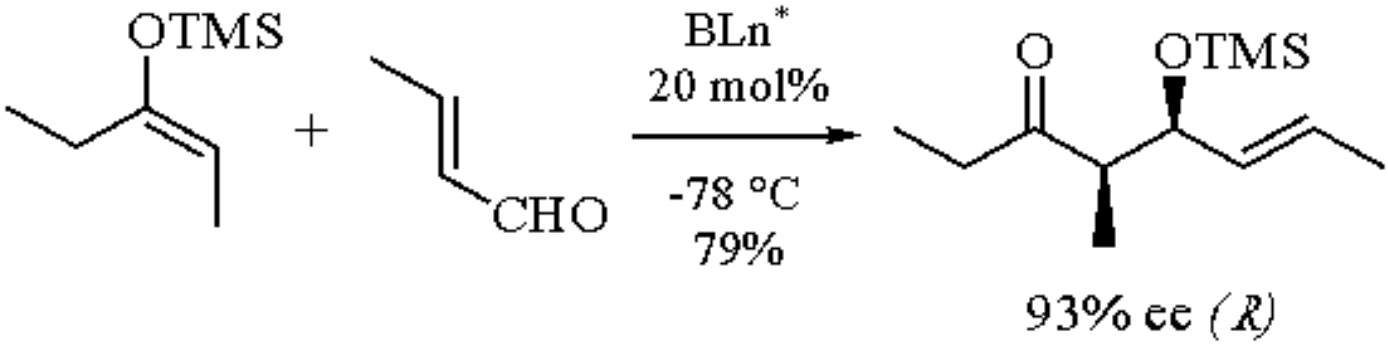

Pericyclic Reactions.

Crotonaldehyde is a versatile participant in pericyclic reactions. In Diels-Alder reactions it may either function as a diene or dienophile. As a diene, crotonaldehyde reacts at elevated temperatures with alkenes to afford a wide variety of substituted dihydropyrans.[1,38] The addition of a lanthanide catalyst allows the cyclization to occur at significantly lower temperature.[39] Additionally, enolized forms of crotonaldehyde also function as dienes.[40] The double bond of crotonaldehyde acts as dienophile towards an array of 1,3-dienes.[1] The temperature required for these cyclizations may be reduced by the addition of Lewis acid catalysts.[41] Asymmetric catalysts have been developed for the reaction of crotonaldehyde with cyclopentadiene.[42] The *endo* isomer predominates and ee's range from 2-96%. An asymmetric catalyst that promotes the hetero-Diels-Alder reaction of crotonaldehyde with Danishefsky diene, affording product dihydropyrone in 92% ee (eq 5), has also been described.[43] Lewis-acid complexes of crotonaldehyde are normally unreactive towards ordinary alkenes in ene processes. However, a Lewis acid assisted ene-reaction of crotonaldehyde with achiral[44] and chiral[45] 2-(alkylthio)allyl silyl ethers has been reported. The achiral ene-reaction is highly *trans* selective and the chiral ene-reaction occurs with almost complete chirality transfer.

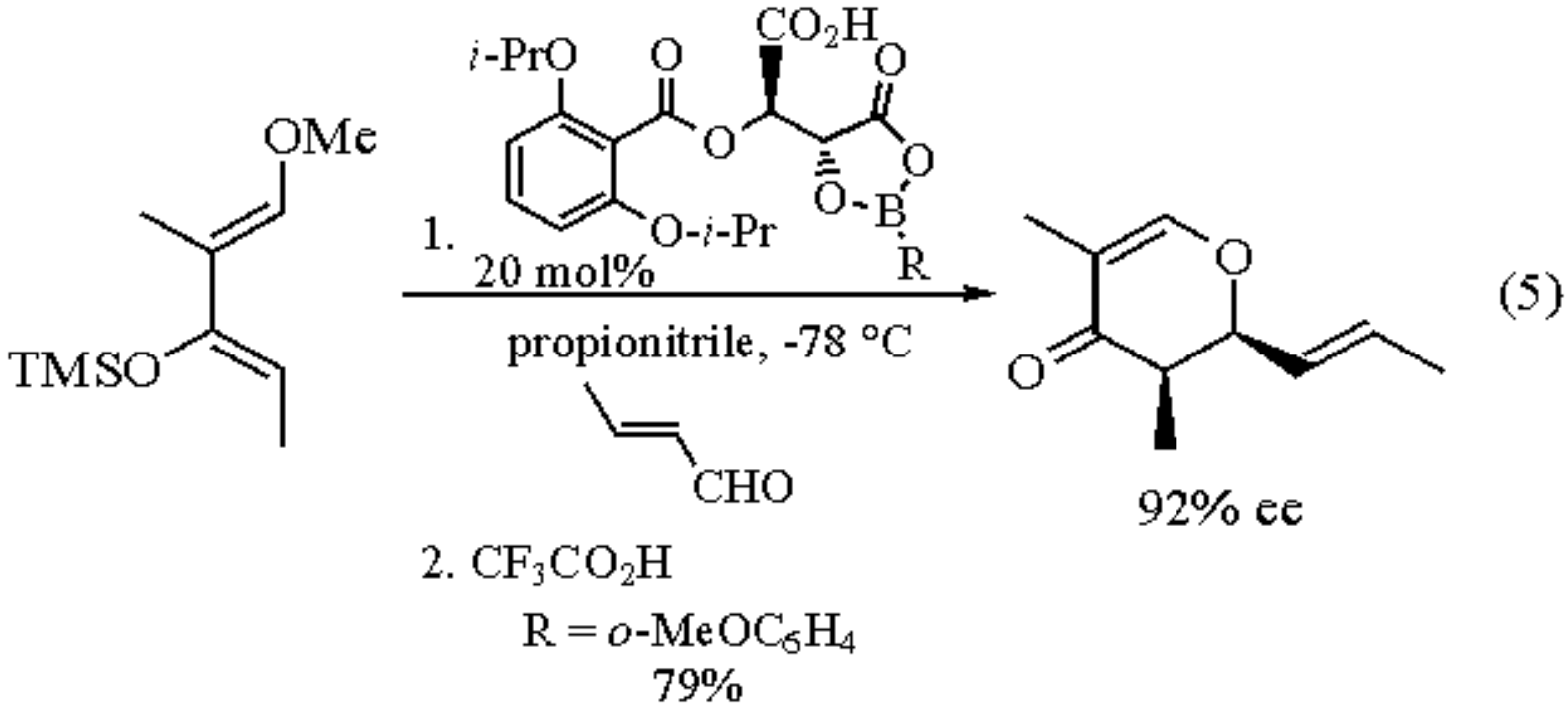

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Crotyl Chloride

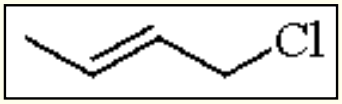

[591-97-9] · C_4H_7Cl · Crotyl Chloride · (MW 90.55)

(butenylating agent via Grignard and other organometallic reagents,[1,2] organoborane compounds,[3] other nucleophiles,[4] and organosilane compounds[5])

Alternate Name: 1-chloro-2-butene.

Physical Data: (*E*) isomer: bp 84.8 °C/752 mmHg; n_D^{20} 1.4350; d_4^{20} 0.9295 g cm^{-3}; (*Z*) isomer: bp 84.1 °C/758 mmHg; n_D^{20} 1.4390; d_4^{20} 0.9426 g cm^{-3}.

Solubility: (*Z*) isomer: insol H_2O; sol alcohol, acetone, and chloroform; (*E*) isomer: insol H_2O; sol acetone and chloroform.

Form Supplied in: clear liquid; widely available in 70% purity, predominantly (*E*) isomer. Main impurity: 3-chloro-1-butene.

Preparative Methods: pure isomers can be prepared by chloride displacement of corresponding alcohols via Ph_3P in various solvents,[7] and other chlorinating agents.[8]

Handling, Storage, and Precautions: flammable and corrosive; incompatible with strong oxidizing agents and strong bases; store in a cool dry place. Use in a fume hood.

Electrophilic Reactions.

Crotyl chloride, like other allylic chlorides, acts as an electrophile to undergo nucleophilic substitution with organometallic agents[1,9] which include Grignard reagents,[1,10] organolithium[11] and organocuprate reagents.[12] Extensive mechanistic studies suggest that these transformations proceed via concerted S_N2 (which gives α-substituted product) and S_N2' (which gives γ-substituted product) reactions.

In reactions with a given nucleophile, (*E*) and (*Z*) isomers often afford different ratios of α- and γ-substituted products. In the case of phenyllithium,[11] (*E*)-crotyl chloride gives an α/γ ratio of 75/25, whereas the (*Z*) isomer gives an α/γ ratio of 25/75.

The regioselectivity of α- vs. γ-substitution is enhanced in reaction with alkyl cuprates, e.g. ***Lithium Di-n-butylcuprate*** gives an α/γ ratio of 96/4. When combined with an alkylcopper in the presence of a Lewis acid, e.g. with *n*-BuCu/BF_3, regioselectivity is reversed to afford an α/γ ratio of 2/98.[9b] However, the Lewis acid does not significantly increase the regioselectivity with PhCu (the α/γ ratio remains the same at 16/84 in presence of ***Boron Trifluoride Etherate***).[9b] Higher regioselectivity for α-phenyl substitution can be achieved by converting crotyl chloride to crotyl triethylsilyloxy ether, then combining it with ***Phenylmagnesium Bromide*** in the presence of a catalytic amount of ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)*** ($PdCl_2$(dppf)). This gives a α/γ ratio of 96/4.[2,10] When $NiCl_2$(dppf) is used as the catalyst, γ-substitution is the major pathway with α/γ of 12/88. High γ-substitution (95-100%) regioselectivity is observed when crotyl chloride reacts with alkyl(aryl)zinc chlorides mediated by CuCN.2LiBr (see ***Copper(I) Cyanide***).[12]

In addition to reaction with organometallic reagents, crotyl chloride also undergoes substitution with other nucleophiles. For example, when reacted with sodium benzenethiosulfonate in ethanol at 50 °C, it gives crotyl thiosulfonates. This can then be followed by reaction with vinylalanates to generate crotyl vinyl sulfides (eq 1),[4a] which readily undergo thio-Claisen rearrangement when heated in a mixture of dimethoxyethane and water.

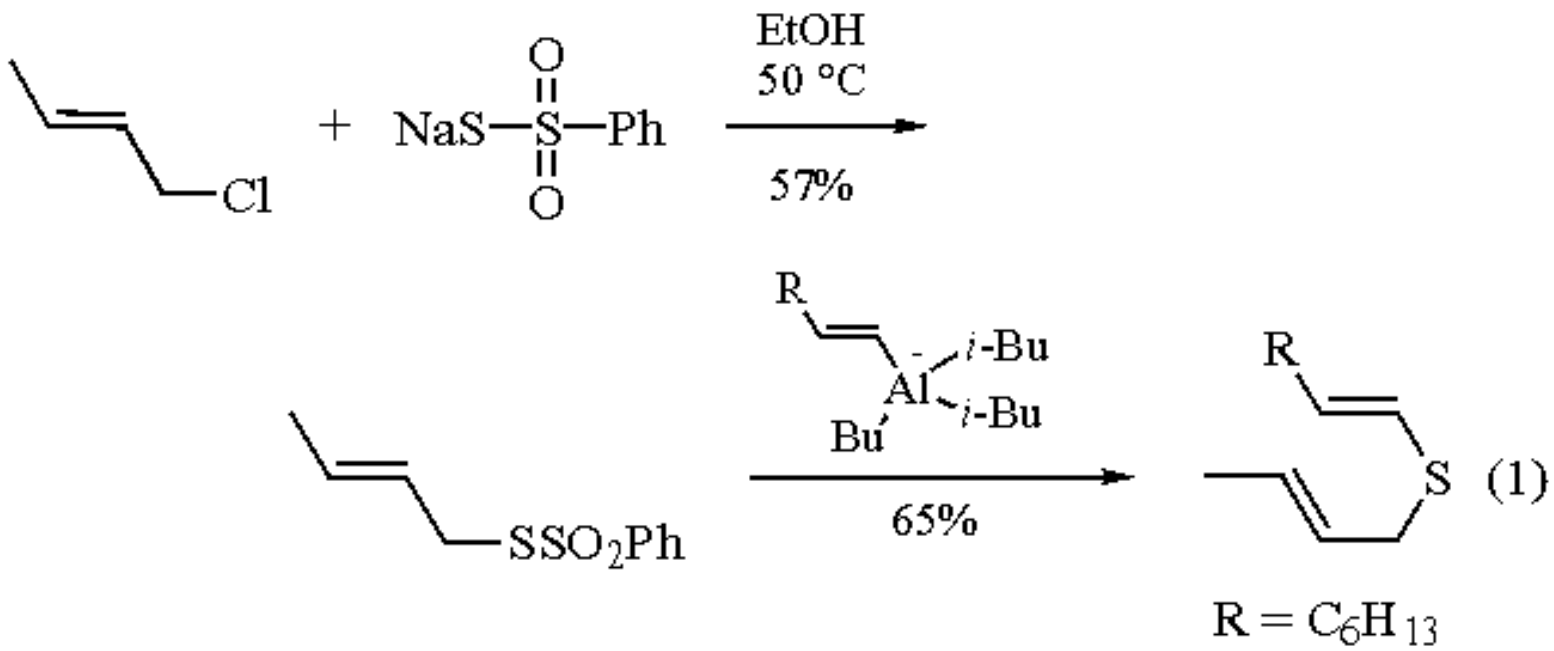

Another example of such nucleophilic substitution is the regioselective cross-coupling with organoboranes. Crotyl chloride can be cross-coupled with alkyl-9-BBN mediated by ***Methylcopper*** to give mainly the 1,4-diene γ-substitution products (eq 2).[3,13] The 1,5-diene α-substitution products can be obtained by reacting crotyl chloride with lithium alkylthioallyl borates.[14]

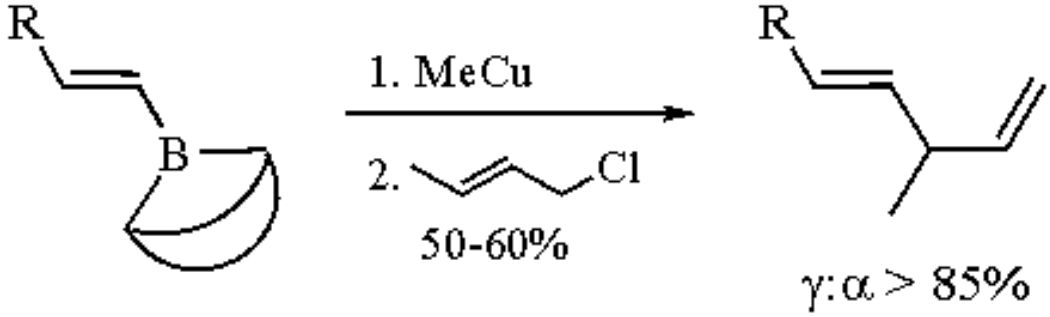

(2)

Upon deprotonation with a strong base (e.g. ***Lithium Diisopropylamide***) at -78 °C, a crotyl chloride carbanion is formed.[6] This carbanion then reacts with ***Chlorotrimethylsilane*** to generate α-chlorocrotyltrimethylsilane. Like other substituted allylsilanes, it reacts with a variety of electrophiles when activated by Lewis acids (e.g. $BF_3.OEt_2$, ***Titanium(IV) Chloride***) to afford vinyl chlorides with (*Z*) selectivity (eq 3).

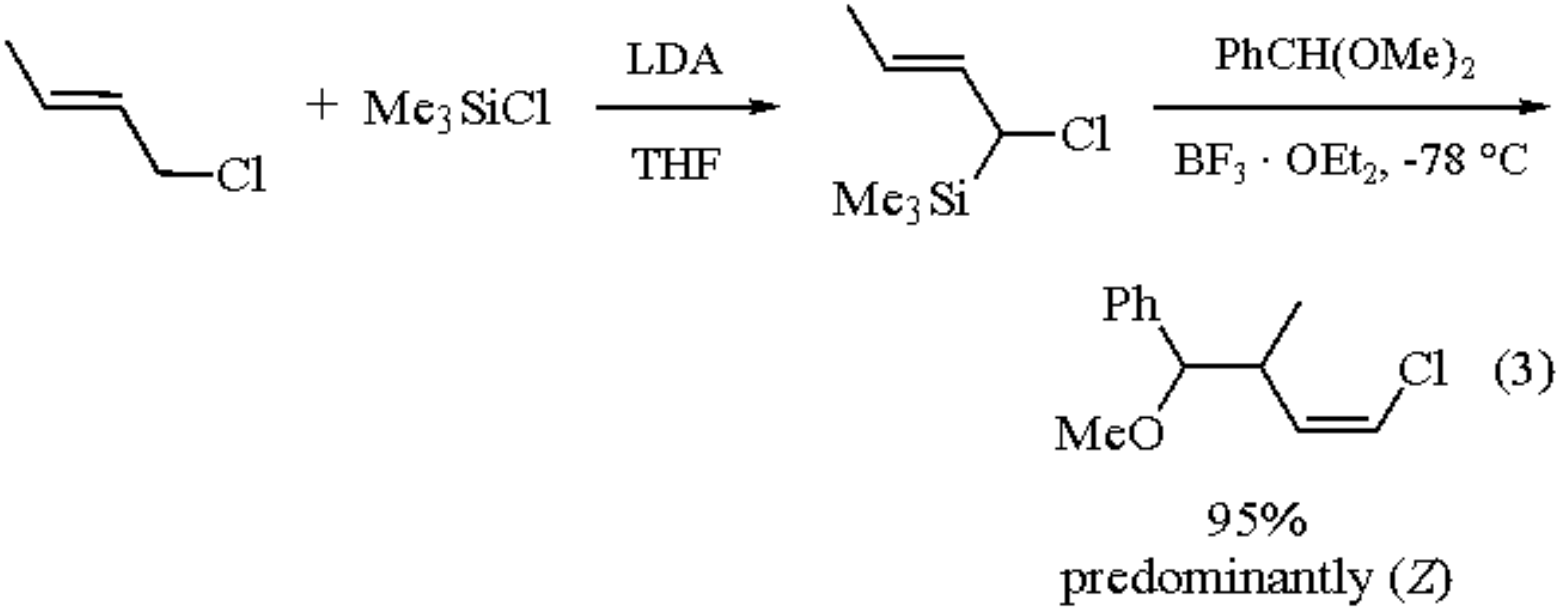

(3)

Nucleophilic Reactions.

As an allylic chloride, crotyl chloride can be easily converted into a wide variety of crotyl organometallic reagents[5b] and crotylsilane compounds.[15] The reagents serve as nucleophiles for addition to various carbonyl compounds, imines, oxime silyl ethers, and other electrophiles to generate homoallylic alcohols, amines, and hydroxylamines. Crotyl chloride forms organometallic reagents with a wide range of metals including lithium, potassium, magnesium, barium, tin, zinc, copper, boron, aluminum, titanium, zirconium, chromium, etc. An extensive review on the use of crotyl organometallic and other allylic organometallic compounds has appeared.[5b]

Crotylmagnesium chloride (see ***Crotylmagnesium Bromide***), easily prepared by stirring crotyl chloride with excess magnesium in ether at rt,[15a] has recently been used to generate nitrones or *N*,*N*-disubstituted hydroxylamines by reaction with aliphatic nitro compounds.[16] More commonly, however, crotylmagnesium chloride is used for nucleophilic addition to carbonyl groups to yield homoallylic alcohols. The regioselectivity and yields of these reactions are often enhanced by addition of other metals and/or metal salts, e.g. Mn, ***Cerium(III) Chloride***, $TiCl_4$, etc.[16,17]

Related Reagents.

Allyl Chloride; ***3-Chloro-1-butene***; ***Methallyl Chloride***.

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B-Crotyldiisopinocampheylborane[1]

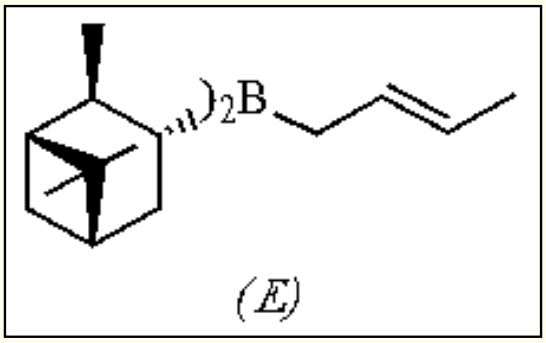

(+)-(*Z*)

[99397-92-9] · $C_{24}H_{41}B$ · *B*-Crotyldiisopinocampheylborane · (MW 340.40) (+)-(*E*)

[99438-29-6] (-)-(*Z*)

[99438-30-9] (-)-(*E*)

[99493-12-6]

(reagent for the asymmetric crotylboration of aldehydes to produce either *syn*- or *anti*-β-methylhomoallylic alcohols[2])

Solubility: reagent is prepared and used in situ at -78 °C in THF.

Preparative Methods: prepared from ***B-Methoxydiisopinocampheylborane*** and either (*Z*)- or (*E*)-crotylpotassium (eq 1).

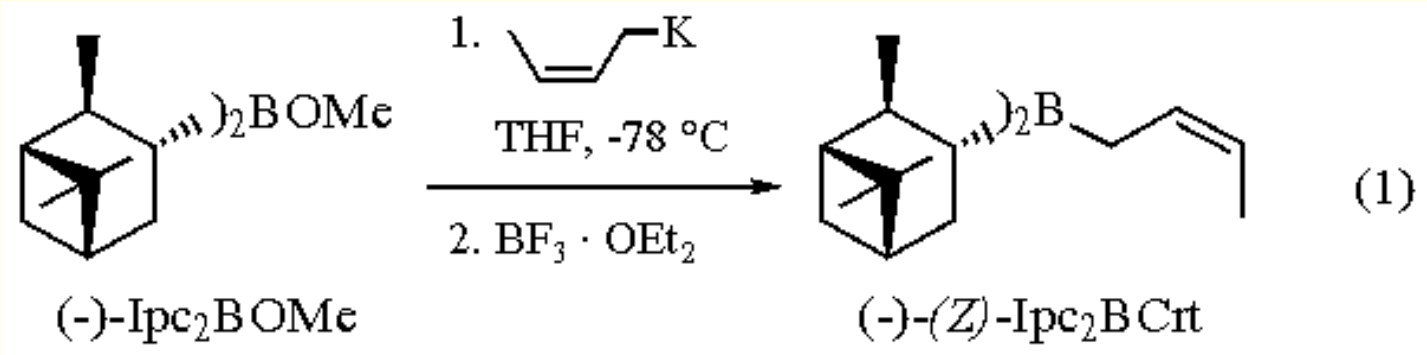

Handling, Storage, and Precautions: because of the facile isomerization of allylic boranes, crotylborane reagents should be generated and reacted at -78 °C.

Addition to Aldehydes.

B-Crotyldiisopinocampheylboranes (Ipc_2BCrt) condense with aldehydes at low temperatures (-78 °C) to provide β-methylhomoallylic alcohols in 60-80% yield and with excellent enantio- (90-94% ee) and diastereoselection (&egt;99% de).[2] Several workup procedures have been employed to decompose the initial borinate adduct and facilitate recovery of the product from the chiral auxiliary (see ***B-Allyldiisopinocampheylborane***).[3] This reaction is stereospecific, with (*Z*)-crotylboranes giving *syn* products, and (*E*)-crotylboranes providing the *anti* isomers. By varying the configuration of Ipc_2BOMe (+ or -) and the crotylpotassium alkene isomer (*Z* or *E*) used in the reagent preparation, all four isomers of the product β-methylhomoallylic alcohols can be obtained (eqs 2 and 3).

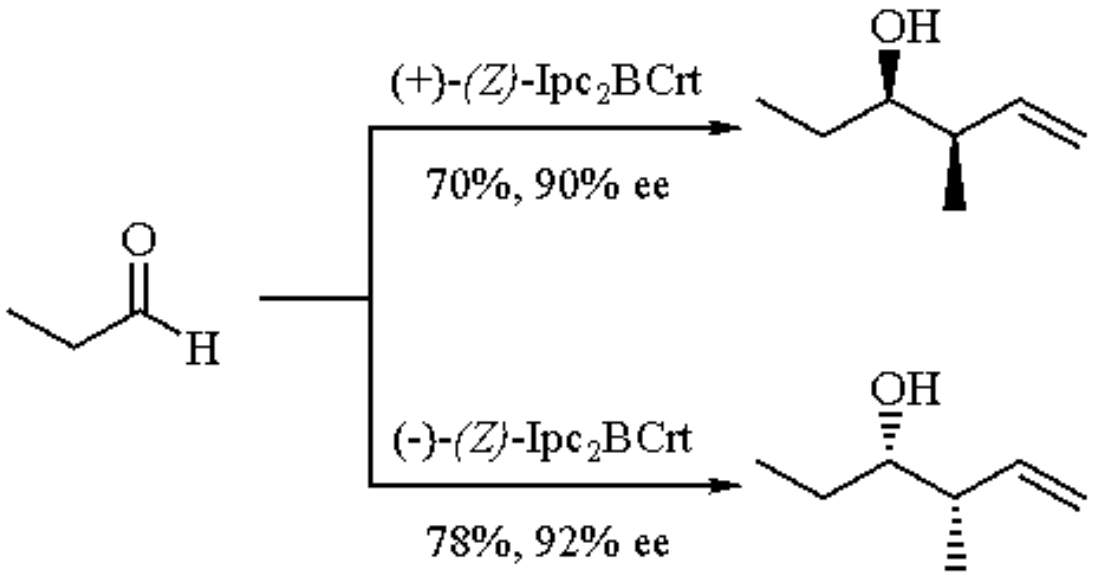

(2)

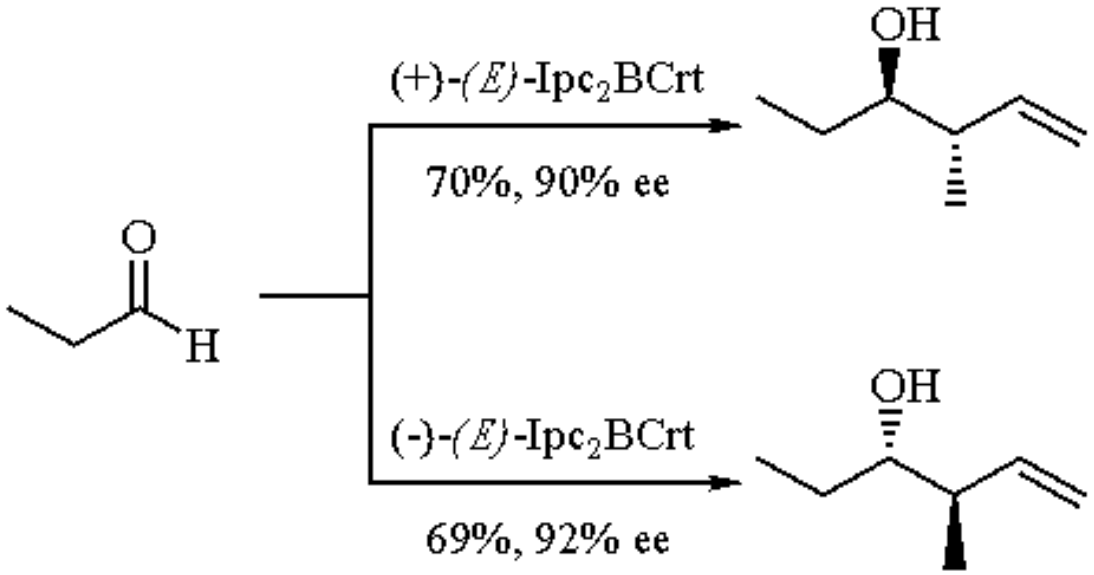

(3)

Ipc_2BCrt has been used with a variety of aldehyde structures in the synthesis of natural products containing polypropionate-derived units (eq 4).[4,5]

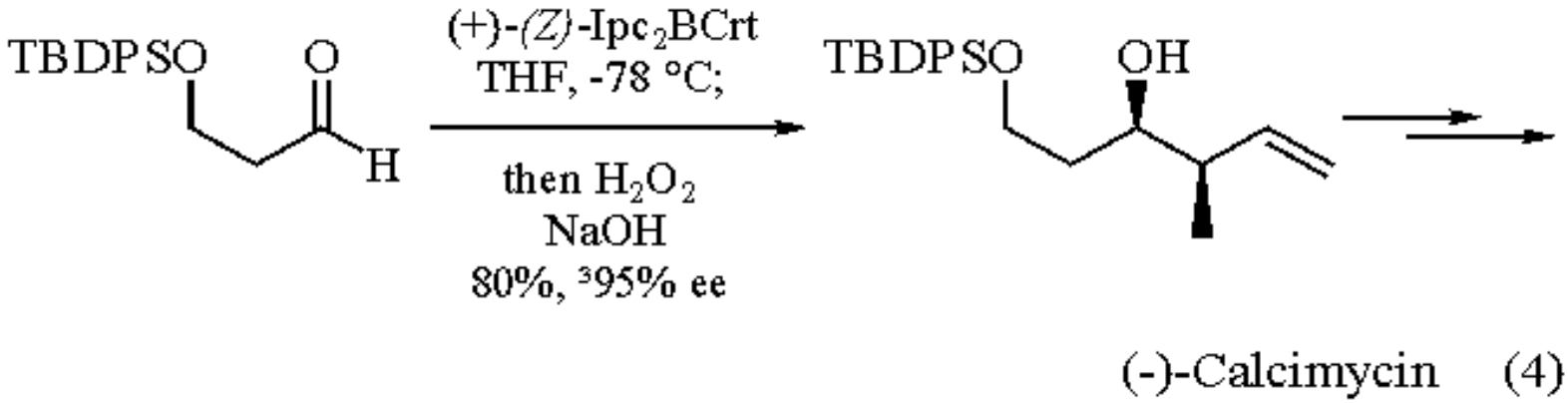

Addition to α-Substituted Aldehydes.

Addition of Ipc_2BCrt to α-substituted aldehydes allows the preparation of extended polypropionate arrays. In this reaction the diastereofacial selectivity is good, even in the case of mismatched double asymmetric reactions (eqs 5 and 6).[6]

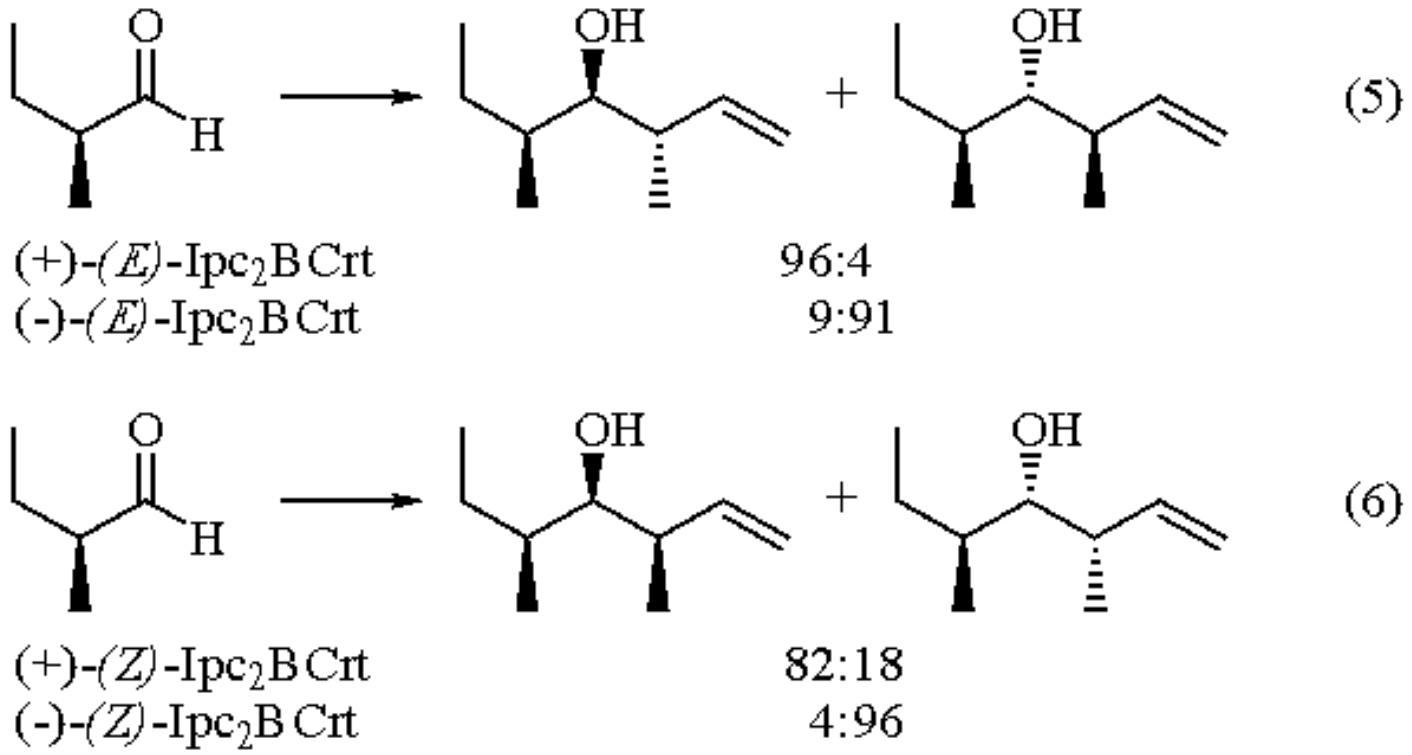

As with simple allylboration (see ***B-Allyldiisopinocampheylborane***), the Ipc_2BCrt reagents provide comparable or, in many cases, superior levels of enantioselection compared to alternative methods of crotylboration[6b] (see also ***B-Allyldiisocaranylborane***, ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate*** and ***(R,R)-2,5-Dimethylborolane***).

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Crotyldimethoxyborane[1]

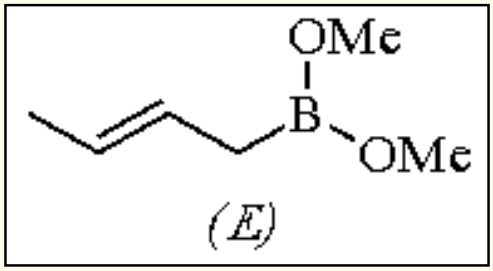

(*E*)

[76347-09-6] · $C_6H_{13}BO_2$ · Crotyldimethoxyborane · (MW 127.98) (*Z*)

[76347-11-0]

(stereoselective aldehyde crotylborating agents;[1] precursors of other crotylboronic esters via hydrolysis and esterification with diols[2])

Alternate Name: dimethyl crotylboronate.

Physical Data: the title reagents are generated and used in situ.[3] The analogous diisopropyl (*E*)- and (*Z*)-crotylboronates have been isolated and characterized:[4] diisopropyl (*E*)-crotylboronate, bp 49-60 °C/3-4 mmHg; diisopropyl (*Z*)-crotylboronate, bp 40-50 °C/2-4 mmHg.[5]

Solubility: crotylboronic esters are soluble in common organic solvents (Et_2O, CH_2Cl_2, toluene, etc.). The title reagents are moisture sensitive and hydrolyze to the crotylboronic acids when exposed to water; they undergo transesterification reactions with alcohols.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: in general, allylboronic esters may be purified by distillation and characterized by ^1H, ^{13}C, or ^{11}B NMR.[3a,6,7] Chemical and isomeric purity has been determined in many cases by capillary GC analysis.[3a,7]

Preparative Methods: the title reagents have been generated and used in situ (see below).

Handling, Storage, and Precautions: allylboronates that are purified by distillation may be stored, often for months, in a refrigerator either neat or as a solution in an inert solvent such as CH_2Cl_2 or toluene.[7] Allylboronic esters are moisture sensitive and are readily hydrolyzed by water to the

allylboronic acids (which readily undergo aerial oxidation). The most stable allylboronic esters are the pinacol esters; however, these are also the least reactive members of the group.[1,8] In general, the reactions of allylboronic esters with carbonyl compounds should be performed in a well ventilated hood in a dry solvent under an inert atmosphere.

Reagent Preparation.

The title reagents are prepared in situ by metalation of (*E*)- or (*Z*)-2-butene with ***n-Butyllithium-Potassium t-Butoxide*** followed by treatment of the resulting (*E*)- or (*Z*)-crotylpotassiums with ***Fluorodimethoxyborane Diethyl Etherate*** diethyl etherate ($(MeO)_2BF.Et_2O$; typically two equiv; (eqs 1 and 2)).[3] Erratic yields and stereoselectivity are reported for reactions of the dimethyl (*E*)- or (*Z*)-crotylboronates (**1**) and (**2**) with aldehydes if two equiv of $(MeO)_2BF.Et_2O$ are not used; the second equiv is added to trap *t*-BuOLi which is generated in the metalation step.[3c] Related procedures have been used to synthesize a range of substituted allylboronic esters, including γ-alkoxyallylboronates (**3**) and (**4**).[9]

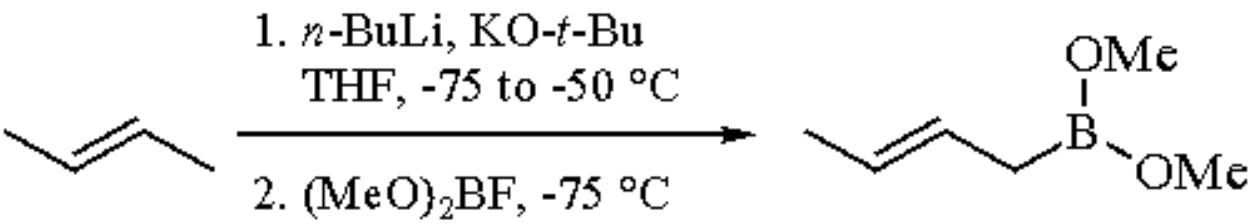

(1)

(1)

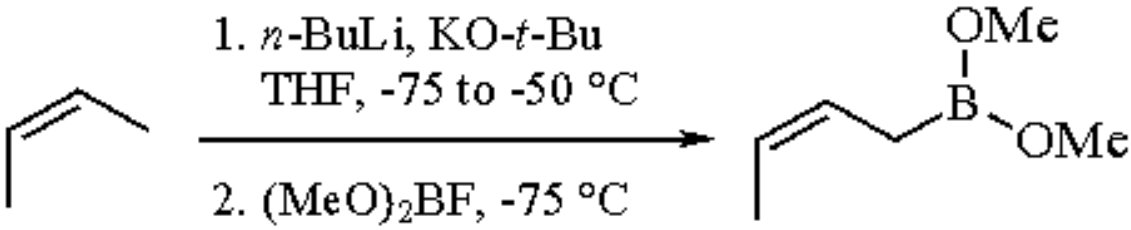

(2)

(2)

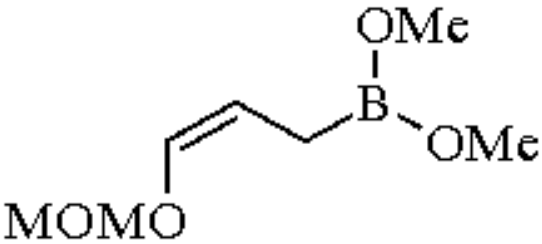

(3)

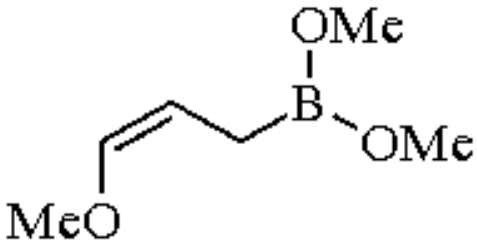

(4)

Acid hydrolysis of THF solutions of (**1**) and (**2**) provides the corresponding (*E*)- and (*Z*)-crotylboronic acids (note: air sensitive) that are readily esterified when treated with diols in the presence of a drying agent (typically

$MgSO_4$). Eqs 3 and 4 illustrate the application of this procedure for the synthesis of pinacol crotylboronates (**5**) and (**6**).[2a] The procedure was fully optimized for the synthesis of the tartrate ester modified crotylboronates (**7**) and (**8**) (eqs 5 and 6).[7] It was found that the yield and isomeric purity of the crotylboronates decreased as the scale increased when $(MeO)_2BF$ was used to functionalize the crotylpotassium intermediates. For example, on scales up to 100 mmol using $(MeO)_2BF$ as the borylating agent, (**7**) and (**8**) were obtained in 70-88% yield following distillation with isomeric purities of 96-97% for (**7**) and 97-98% for (**8**). However, the yields of (**7**) and (**8**) fell to 14-35% on scales larger than 200 mmol with isomeric purity of 94-96% and 92-95% for (**7**) and (**8**), respectively. It is believed that these problems result from competitive formation of tricrotylborane.[7] A far superior procedure involves use of ***Triisopropyl Borate*** as the electrophilic borylating agent.[10] The $(i\text{-PrO})_3B$ procedure has been performed on 100-400 mmol scales with excellent results: 70-75% yields of (**7**) (&egt;98% *E*) and (**8**) (&egt;99% *Z*) have been obtained consistently.[7] Kabalka has adopted this procedure for the preparation of the diisopropyl crotylboronates (**9**) and (**10**) (43-46% yield following distillation).[4,5]

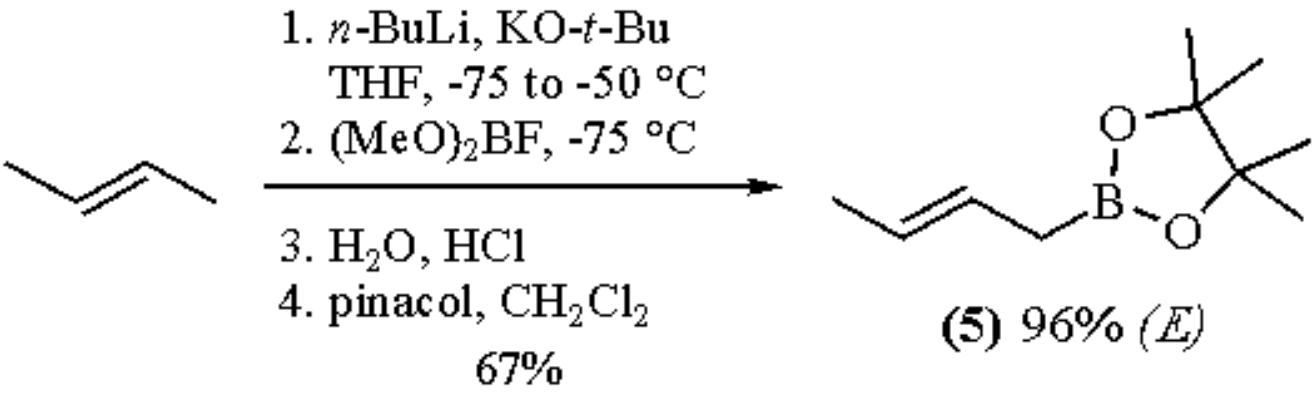

(3)

(5) 96% *(E)*

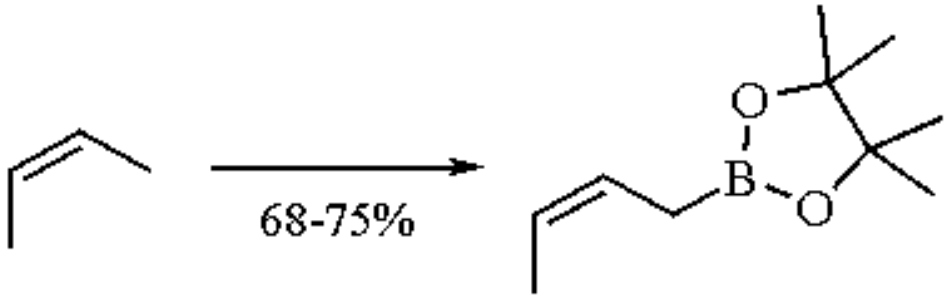

(4)

(6) 97% *(Z)*

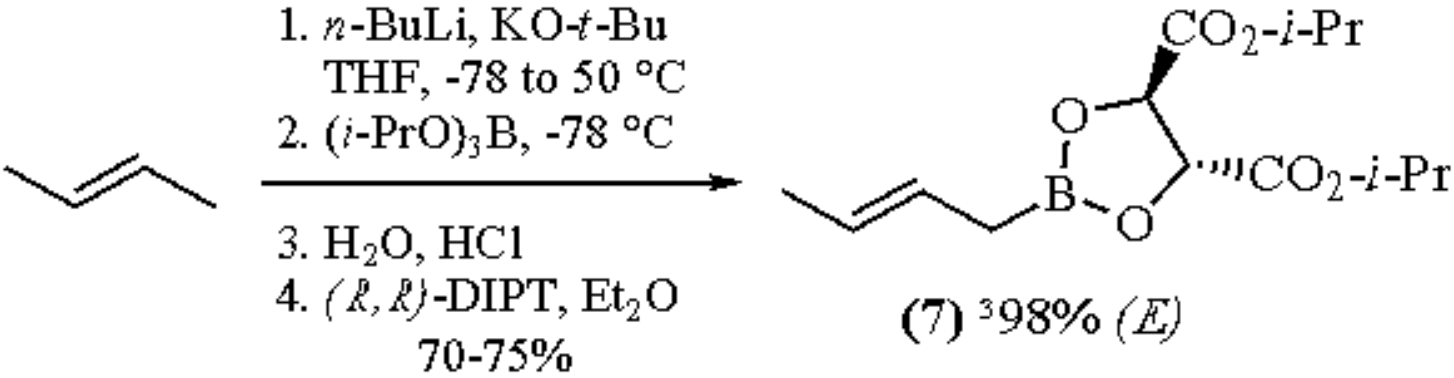

(5)

(7) [3]98% *(E)*

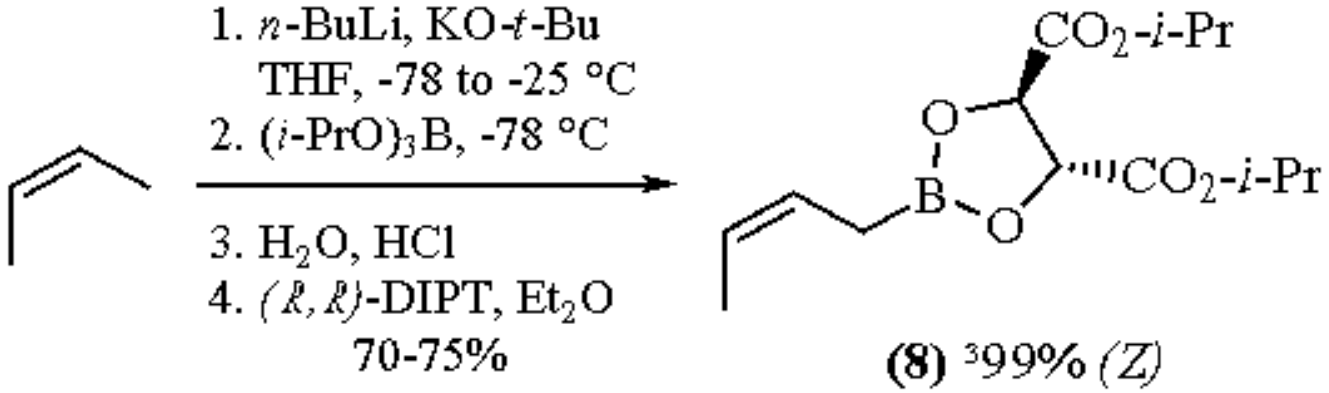

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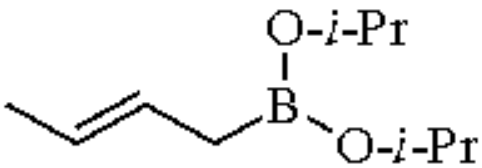

(9) *(E)*

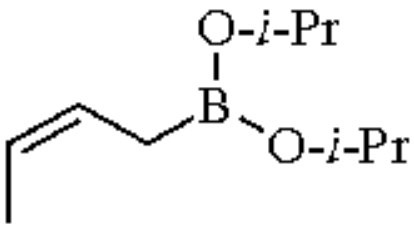

(10) *(Z)*

Diastereoselective Reactions with Aldehydes.

(*E*)- and (*Z*)-crotylboronates react with aldehydes generally with excellent diastereoselectivity.[1,6] As shown in eqs 7 and 8, the reaction of propanal and (*E*)-crotylboronate (**1**) provides the *anti* homoallyl alcohol with 96:4 selectivity, while the reaction with the (*Z*)-crotylboronate (**2**) gives the *syn* diastereomer with 97% selectivity.[3c] The stereochemical outcome of the reactions of allylboronates and aldehydes is best rationalized by way of cyclic, chair-like transition states (**11**).[1a] Numerous examples of reactions of substituted allylboronates and aldehydes have been documented in the literature, and in most cases the diastereoselectivity parallels the isomeric purity of the reagent.[1a] Chiral reagents (**7**) and (**8**) can be used to perform these reactions enantioselectively (65-90% ee for most aldehydes).[7]

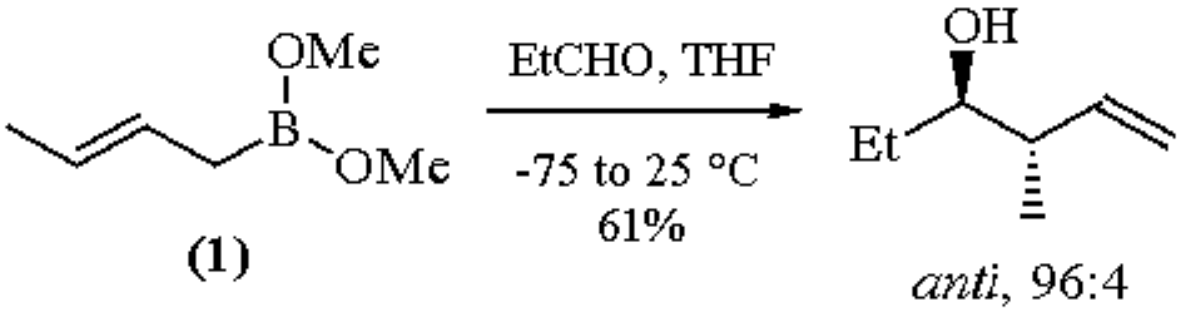

(1)

(7)

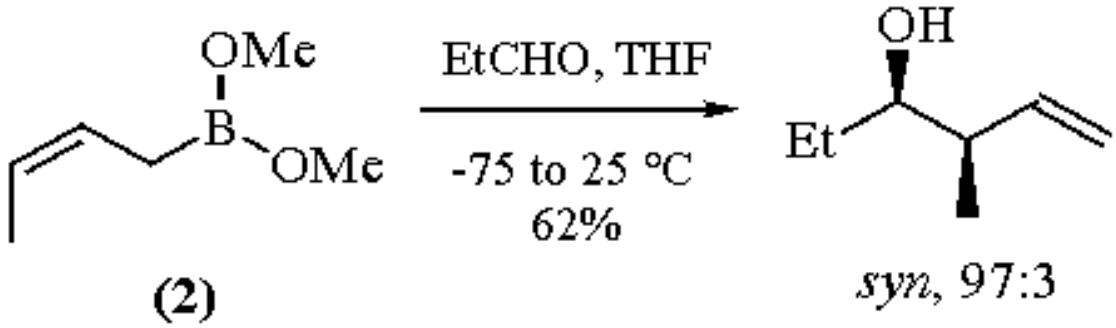

(2) (8)

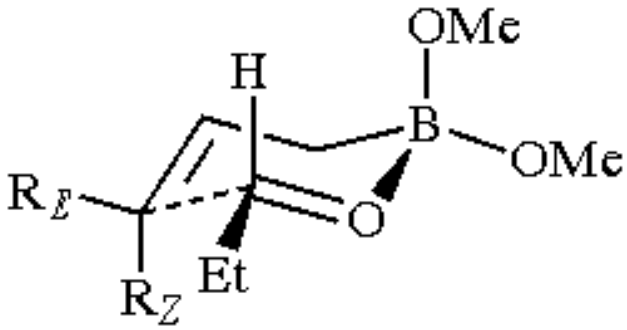

(11)

Diastereoselective Reactions with α-Hydroxy Ketones and α-Oxocarboxylic Acids.

The addition reaction of allylboronates to ketones is very slow; for example, the reactions of ketones of (*E*)- and (*Z*)-pentenylboronates requires 4-5 day reaction times at elevated pressure.[11] However, Kabalka has demonstrated that the diisopropyl crotylboronates (**9**) and (**10**) react readily with α-hydroxy ketones (eq 9).[4] The reaction presumably involves transesterification of the α-hydroxy ketone with the reagent and then crotyl transfer by way of the chair-like transition state (**12**). Allylboronates also react with α-oxocarboxylic acids, presumably by way of a similar transition state.[12]

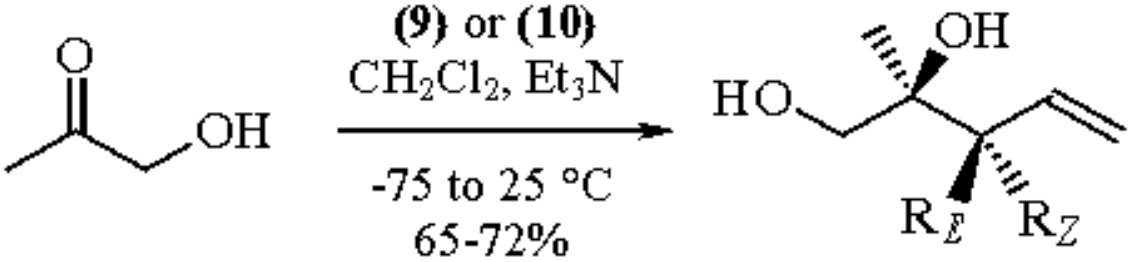

(9)

(9) $R_E = Me$, $R_Z = H$	97: 3
(10) $R_E = H$, $R_Z = Me$	6:94

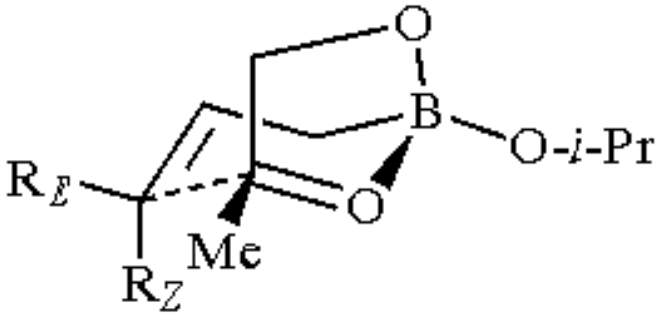

(12)

Related Reagents.

B-Allyldiisocaranylborane; ***B-Crotyldiisopinocampheylborane***; ***Crotyltrichlorosilane***; ***Crotyltrifluorosilane***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***Triethylammonium Bis(catecholato)allylsiliconate***.

---

1. (a) Roush, W. R. *COS* **1991**, *2*, 1. (b) Yamamoto, Y.; Asao, N. *CR* **1993**, *93*, 2207.
2. (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *JACS* **1986**, *108*, 3422. (b) Roush, W. R.; Halterman, R. L. *JACS* **1986**, *108*, 294.
3. (a) Rauchschwalbe, G.; Schlosser, M. *HCA* **1975**, *58*, 1094. (b) Schlosser, M.; Fujita, K. *AG(E)* **1982**, *21*, 309. (c) Fujita, K.; Schlosser, M. *HCA* **1982**, *65*, 1258.
4. Wang, Z.; Meng, X.-J.; Kabalka, G. W. *TL* **1991**, *32*, 1945.
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6. Hoffmann, R. W.; Zeiss, H.-J. *JOC* **1981**, *46*, 1309.
7. Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *JACS* **1990**, *112*, 6339.
8. (a) Roush, W. R.; Banfi, L.; Park, J.-C.; Hoong, L. K. *TL* **1989**, *30*, 6457. (b) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *JOC* **1990**, *55*, 1868.
9. (a) Wuts, P. G.; Bigelow, S. S. *JOC* **1982**, *47*, 2498. (b) Roush, W. R.; Michaelides, M. R. *TL* **1986**, *27*, 3353. (c) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *JACS* **1989**, *111*, 2984.
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12. Wang, Z.; Meng, X.-J.; Kabalka, G. W. *TL* **1991**, *32*, 4619.

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Crotyllithium

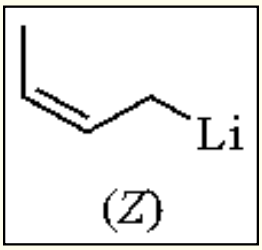

[16327-44-9] · C_4H_7Li · Crotyllithium · (MW 62.03) (*E*)

[13950-06-6] (*Z*)

[51760-91-9]

(crotylating agent in substitutions and additions; used to attach crotyl groups to other metals and nonmetals)

Physical Data: (*E*) and (*Z*) forms equilibrate rapidly in solution, with typical equilibrium composition 85% (*Z*)-15% (*E*) as shown by ^{1}H and ^{13}C NMR.[1,2]

Solubility: sol ethers; sparingly sol hydrocarbons.

Preparative Methods: by metallating 1-butene or (*E*)- and/or (*Z*)-2-butene with ***n-Butyllithium*/*N,N,N´,N´-Tetramethylethylenediamine***;[1b] from organotin[1a] or organoselenium[3] compounds by exchange with ***Methyllithium*** or butyllithium.

Form Supplied in: prepared in situ and used directly.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas to exclude oxygen and moisture.

Reactions.

Crotyllithium alkylates mainly at the less hindered end to give mixtures of (*E*) and (*Z*) products with the latter predominating due to the greater stability of (*Z*)-crotyllithium.[1b,4] Additions to aldehydes and ketones[5] can sometimes be made more stereo- and regioselective by adding boron,[6] zirconium,[7] or chromium[8] compounds. Crotyllithium has been used to make crotylpalladium reagents.[9]

When stereospecificity is desired, crotylpotassiums are preferable to crotyllithiums since they can be made and reacted at low temperatures with preservation of configuration,[10] e.g. to make crotyldiisopinocampheylboranes (eqs 1 and 2; Ipc = isopinocampheyl) for asymmetric syntheses (see ***B-Crotyldiisopinocampheylborane***).[11]

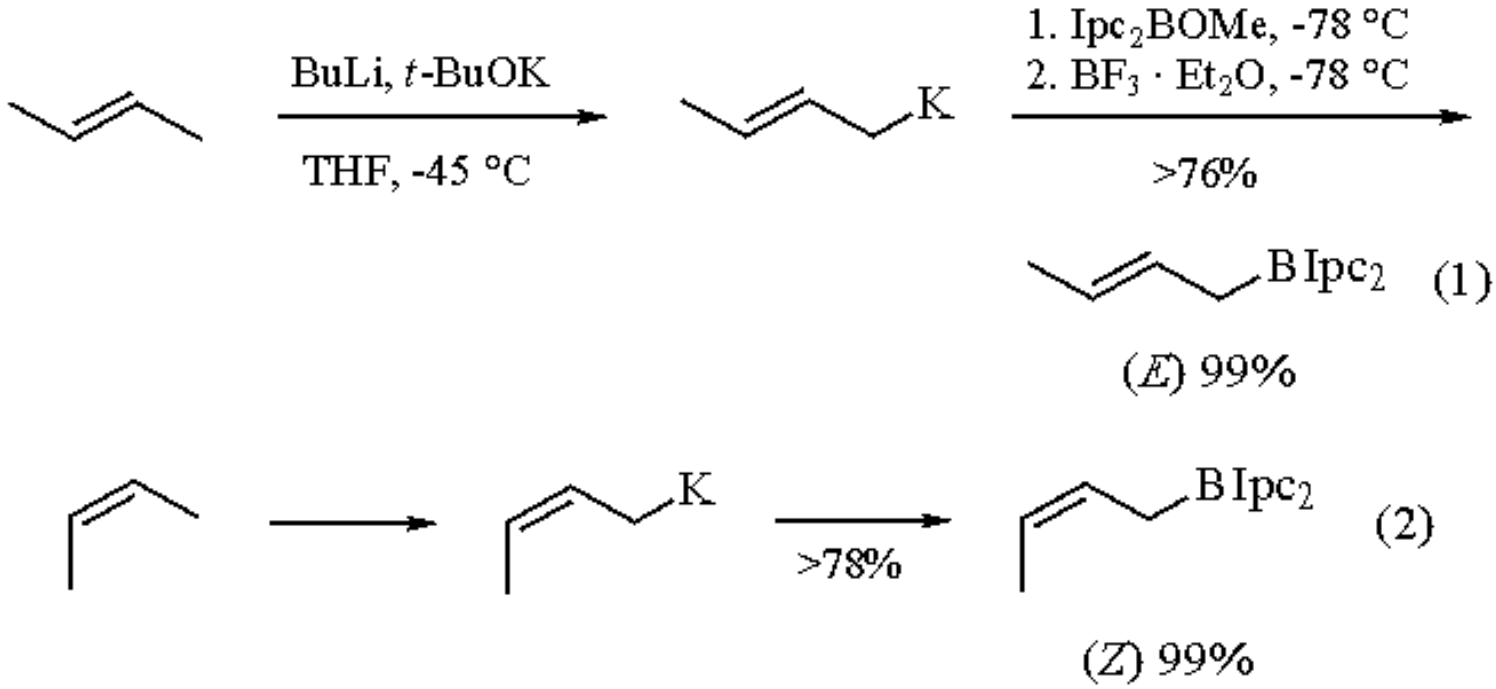

Related Reagents.

Table 1 lists some useful crotyllithium derivatives. The first five entries all strongly prefer the (*Z*) geometry.[12,13] The last, with no stereochemical complications, provides isoprene units in coupling reactions with alkyl bromides.[4] See also ***Allyllithium*** and ***Allylmagnesium Bromide***.

Table 1 Crotyllithium Derivatives

Structure	Molecular formula
$LiCH_2CH{=}CHEt$ [12]	C_5H_9Li
$LiCH_2CH{=}CHC_6H_{13}$ [3,13]	$C_9H_{17}Li$
$LiCH_2CH{=}CH\text{-}i\text{-}Pr$ [12]	$C_6H_{11}Li$
$LiCH_2CH{=}CHCH(Me)CONMe_2$ [14]	$C_8H_{14}NOLi$
$LiCH_2CH{=}CH\text{-}t\text{-}Bu$ [12]	$C_7H_{13}Li$
$LiCH_2CH{=}CMe_2$ [3,5,15]	C_5H_9Li

1. (a) Seyferth, D.; Jula, T. F. *JOM* **1974**, *66*, 195. (b) Bates, R. B.; Beavers, W. A. *JACS* **1974**, *96*, 5001.
2. van Dongen, J. P. C. M.; van Dijkman, H. W. D.; de Bie, M. J. A. *RTC* **1974**, *93*, 29.
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4. Korte, W. D.; Cripe, K.; Cooke, R. *JOC* **1974**, *39*, 1168.
5. (a) Rautenstrauch, V. *HCA* **1974**, *57*, 496. (b) Yamamoto, Y. *ACR* **1987**, *20*, 243.
6. Yamamoto, Y.; Yatagai, H.; Maruyama, K. *CC* **1980**, 1072.
7. Yamamoto, Y.; Maruyama, K. *TL* **1981**, *22*, 2895.
8. Uemura, M.; Minami, T.; Isobe, K.; Kobayashi, T.; Hayashi, Y. *TL* **1986**, *27*, 967.
9. Goliaszewski, A.; Schwartz, J. *T* **1985**, *41*, 5779.
10. Schlosser, M.; Hartmann, J.; David, V. *HCA* **1974**, *57*, 1567.
11. Brown, H. C.; Bhat, K. S. *JACS* **1986**, *108*, 293.
12. Schlosser, M.; Hartmann, J. *JACS* **1976**, *98*, 4674.
13. Seyferth, D.; Mammarella, R. E. *JOM* **1979**, *177*, 53.
14. Beak, P.; Hunter, J. E.; Jun, Y. M. *JACS* **1983**, *105*, 6350.
15. Cazes, B.; Julia, S. *TL* **1978**, 4065.

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Crotylmagnesium Bromide

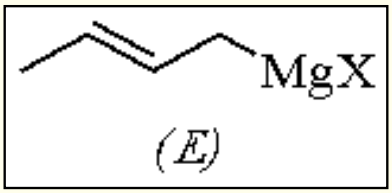

(X = Br)

[6088-87-5] · C_4H_7BrMg · Crotylmagnesium Bromide · (MW 159.32) (X = Cl)

[6088-88-6] · C_4H_7ClMg · Crotylmagnesium Chloride · (MW 114.86)

(agent capable of regioselective addition to carbonyl compounds[1,23-27] and derivatives,[28,34] unactivated C-C double bonds,[43] nitro compounds,[30-32] nitriles,[34] imines,[34] and aza aromatics,[35-39] and of displacement of halogens from halo compounds.[1,29,40,41])

Alternate Name: 2-butenylmagnesium bromide.

Solubility: bromide: sol diethyl ether, dibutyl ether;[3] chloride: sol diethyl ether, THF.

Form Supplied in: the precursor crotyl bromide and chloride (the latter 95% predominantly (*E*)) are commercially available.

Analysis of Reagent Purity: titration of crotylmagnesium bromide can be carried out with *s*-BuOH in xylene using 1,10-phenanthroline[12] or *N*-phenyl-1-naphthylamine[14] as indicators or with a double titration method using dibromoethane.[13] Other procedures are available.[10,15-17]

Preparative Methods: crotylmagnesium bromide and chloride can be prepared from commercial crotyl halides and ***Magnesium*** in diethyl or dibutyl ether.[2,18,19] The undesired homocoupling reaction[3] can be minimized by increasing the time of addition of the halide, the solvent/halide ratio, and by using 20-30 mesh magnesium turnings prepared just prior to use.[1] CrotylMgBr can be prepared from commercial crotyl bromide which usually contains 13% of α-methylallyl bromide as an impurity owing to an equilibration between the two isomers (eq 1). These two isomers can be separated by low-temperature distillation,[4] although this is not needed since both the bromo isomers produce the same Grignard reagent. Similarly, crotylMgCl is prepared from commercial ***Crotyl Chloride*** which is frequently[5,6] a mixture of α-methylallyl chloride and *cis*- and *trans*-crotyl chlorides separable from the former by simple fractional distillation. *cis*-Crotyl chloride can be prepared from *cis*-crotyl alcohol.[11]

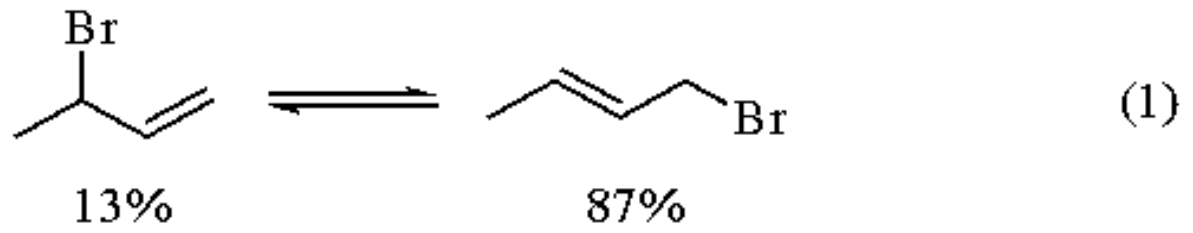

(1)

Handling, Storage, and Precautions: the precursor isomeric butenyl chlorides are much more stable than the bromides and can be stored without rearrangement for long periods of time in sealed Teflon bottles over anydrous $MgSO_4$.[18] Crotylmagnesium halides are moisture sensitive reagents, inflammable, reacting violently with water.

Structure.

Crotylmagnesium halides exist as a rapidly equilibrating mixture of two forms, the less branched being the more abundant (eq 2).[7]

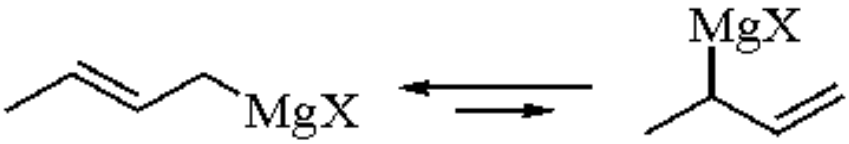

(2)

The isotopic perturbation technique[8] has been used to distinguish between the σ- and π-bond structures of allyl- and crotylmagnesium reagents.[9] The ^{13}C NMR spectra of the deuterated crotyl reagents have demonstrated that crotylmagnesium halides are σ-structures in which the metal is attached to the primary carbon. Alkyl-substituted allylic Grignard reagents in diethyl ether solution exist as a rapidly equilibrating mixture of (*Z*) and (*E*) primary isomers.[18] Protonation and coupling constant studies have shown that the percentage of (*Z*) isomer decreases as the size of the alkyl substituent (R) on the carbon of the Grignard reagent increases (eq 3).

(3)

Reactions.

With few exceptions, crotylmagnesium halides react with electrophiles at the internal C atom. Treatment of crotylmagnesium halides with a wide variety of protonating agents[20-22] gives rise to a mixture of 1- and 2-butene with the former usually predominating.

The reaction of unhindered carbonyl compounds with crotyl Grignards gives the γ-adduct (eq 4).[23] This regioselectivity can be reversed by addition of ***Aluminum Chloride***, which results in a predominant formation of the α-adduct.[24] With a hindered ketone,[2] such as di-*t*-butyl ketone, the α-adduct is sometimes obtained because of the reversible addition of

the allylic organometallic reagent.[25,26] CrotylMgCl gives 1,2-addition to α,β-ethylenic ketones; the relevant stereochemistry has been studied.[27]

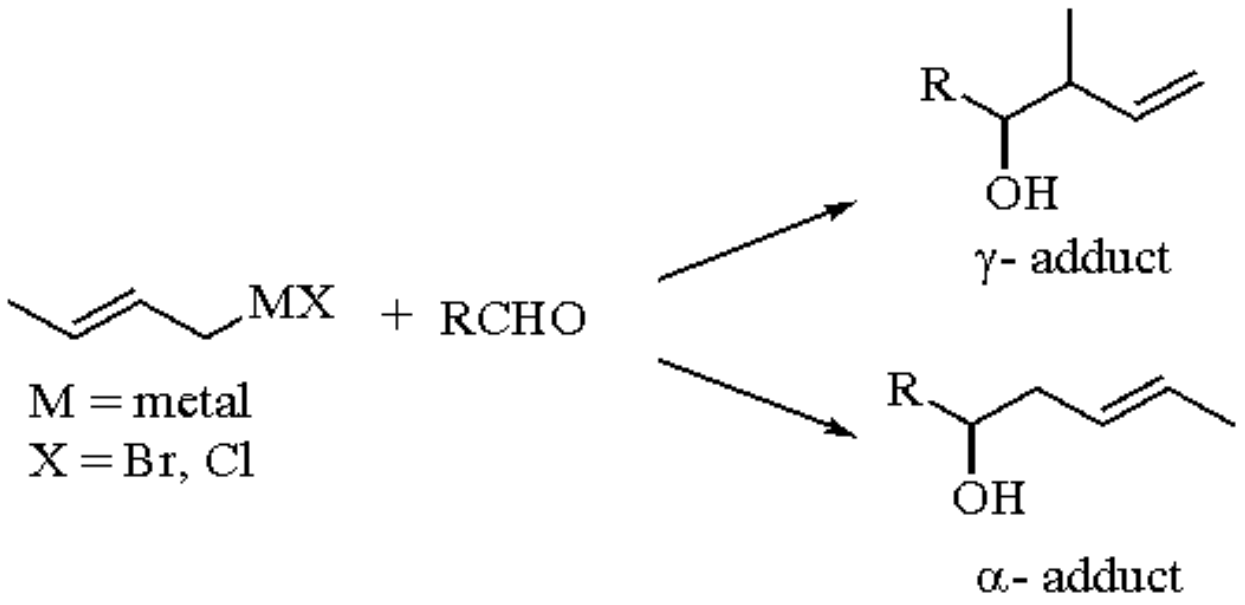

(4)

Other typical reactions with epoxides, acid chlorides, amides, and many other classes of compounds have been extensively treated;[1,28d] the formation of tetrahydropyridines from aryl nitriles has also been reported.[34]

Alkylation of crotyl Grignard reagents in the presence of ***Copper(I) Iodide*** results in almost exclusive substitution at the α-position; the reaction is very slow in the absence of CuI.[29]

Butenylmagnesium chloride adds to nitro compounds, leading to allylic nitrones (eq 5).[30] The chemo-, regio- and stereoselectivity of this reaction,[31] as well as a possible enantioselective synthesis of nitrogen derivatives (hydroxylamines and amines) by allyl Grignard addition to optically active nitroalkanes, have been reported.[32]

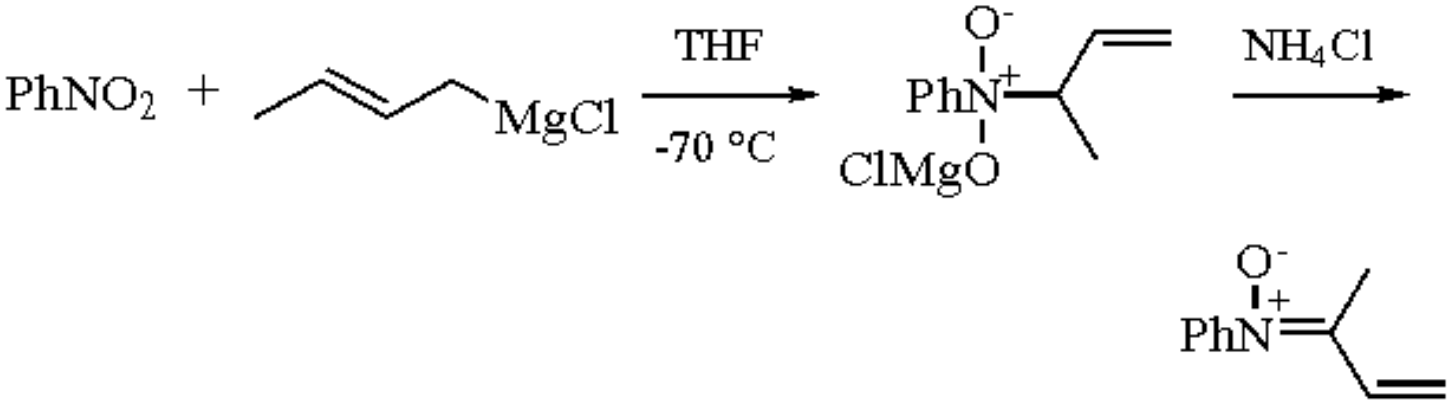

(5)

In the presence of ***Dichlorobis(cyclopentadienyl)titanium***, Cp_2TiCl_2, isoprene undergoes a regioselective insertion into the allyl-magnesium bond (eq 6). This insertion has been applied to the synthesis of various natural terpenoids and related products.[33]

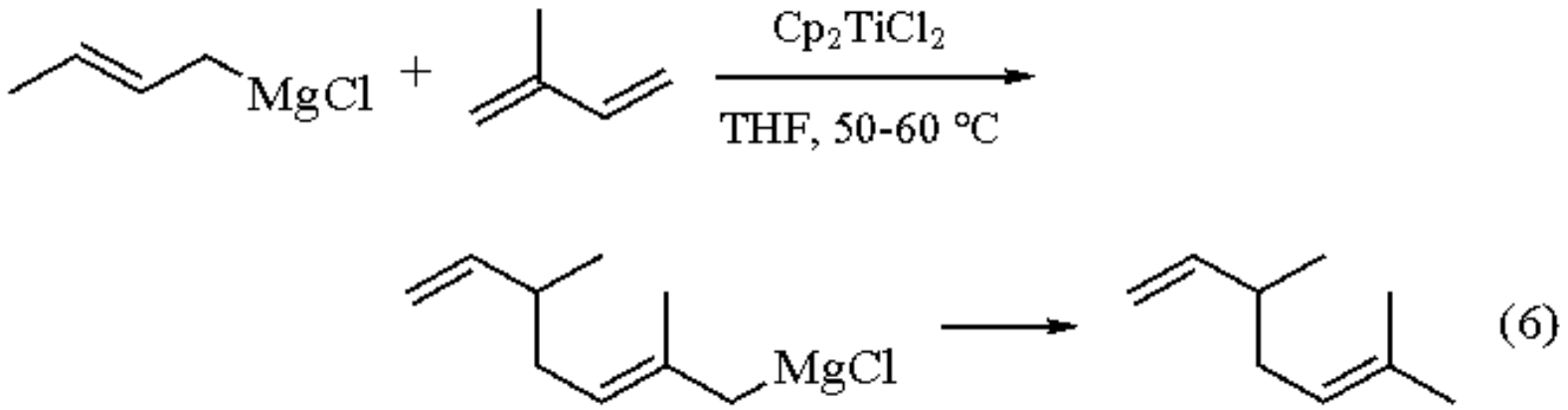

Crotylmagnesium halides add promptly to the C=N moiety of 2-alkylthiazolines, leading to 2-alkyl-2-α-methylallylthiazolidines,[35] and to 2-alkylbenzothiazoles, leading to 2-alkyl-2-α-methylallylbenzothiazolines or *N*-alkyl-bis(α-methylallyl)methyl-*o*-aminobenzenethiol depending upon the experimental conditions.[36] 2-Heterosubstituted benzothiazoles react with crotylmagnesium halides, regioselectively producing 2-α-methylallylbenzothiazole, 2,2-bis(α-methylallyl)benzothiazoline, or *N*-tris(α-methylallyl)methyl-*o*-aminobenzenethiol depending upon the experimental conditions.[37] Comparable results were obtained in the reaction of benzoxazole derivatives.[38,39] Cross-coupling of crotylmagnesium halides with halogenoquinoxalines,[40] -pyrimidines,[41] and -pyridines[42] provides a regioselective synthesis of the corresponding α-methylallyl derivatives.

CrotylMgCl adds regioselectively to the unactivated C-C double bond of some aza aromatics.[43]

Related Reagents.

Prenylmagnesium chloride (**1**),[44] cyclohexenylmethylmagnesium bromide (**2**),[44b] cinnamylmagnesium bromide (**3**),[45] and 2-pentenylmagnesium bromide (**4**)[46] have been prepared by reacting the appropriate halide with magnesium and their reactivity is comparable with that of crotylmagnesium halides.

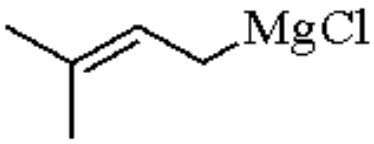

(1)

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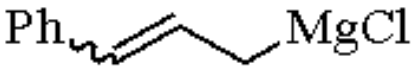

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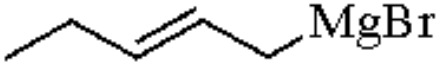

(4)

See also ***Allyllithium***, ***Allylmagnesium Bromide***, ***B-Crotyldiisopinocampheylborane***, ***Crotyllithium***, ***Crotyltrimethylsilane***, ***Methallyllithium***, and ***Methallylmagnesium Chloride***.

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Crotyltributylstannane[1]

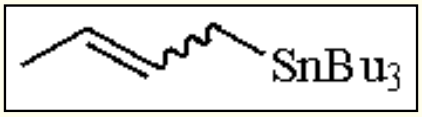

(*E*)

[35998-93-7] · $C_{16}H_{34}Sn$ · Crotyltributylstannane · (MW 345.13) (*Z*)

[35998-94-8]

(allylating reagent for many compounds, including alkyl halides, carbonyl compounds, imines, acetals, thioacetals, and sulfoximides)

Alternate Name: 2-butenyltributyltin.

Physical Data: bp 100-110 °C/1 mmHg;[2f] ^{1}H NMR (*E*) isomer δ 5.95-5.10 (m, 2 H), 2.00-0.70 (m, 32 H); ^{13}C NMR (*E*) isomer δ 130.5, 120.3, 29.3, 27.5, 27.4, 17.9, 13.8, 9.2;[2f] ^{1}H NMR (*Z*) isomer δ 6.84-5.96 (m, 2 H), 3.30-1.43 (m, 32 H); ^{13}C NMR (*Z*) isomer δ 129.6, 118.2, 29.3, 27.5, 27.4, 13.8, 12.5, 9.4.[2f]

Solubility: sol methylene chloride, diethyl ether, tetrahydrofuran, toluene, and benzene.

Form Supplied in: not commercially available.

Preparative Methods: several methods have been described.[2]

Purification: by distillation.

Handling, Storage, and Precautions: all organotin compounds are highly toxic. This reagent therefore must be used in a well-ventilated fume hood. Contact with the eyes, skin, and respiratory system should be avoided.

Introduction.

Allylstannanes are widely used storable allyl anion equivalents.[1] Since the chemistry associated with allystannanes and crotylstannanes is, in most cases, very similar, this section will focus on the reactions of crotyltrialkylstannane and crotyl derivatives (methallyltributylstannane, β-methylcrotylstannane, pent-3-en-2-yltrialkylstannanes, and cinnamylstannane. A more comprehensive review of allylation reactions employing allylic stannanes is presented in the article on ***Allyltributylstannane***. Related allylic stannane chemistry is also found under articles on α-

alkoxyallylstannanes and ***Allyltriphenylstannane*** derivatives.

Additions to Aldehydes and Ketones.

The addition of allylic reagents to carbonyl compounds has become a very attractive synthetic strategy in carbon-carbon bond formations. γ-Substituted allylmetal reagents are especially attractive in natural product synthesis since additions can provide two new adjacent stereocenters. Thus methods to control the stereochemical outcome of both diastereofacial and bond construction selectivity have received a lot of attention.

Crotyltrialkyltin reagents can undergo transmetalation reactions in the presence of Lewis acids.[3] Competing transmetalation process can affect the mechanistic pathway and product distribution (eq 1).[4] 1,3-Isomerization results in linear (α) adducts, while branched (γ) adducts occur through the Lewis acid-carbonyl complex or the transmetalated intermediate, a crotyltin halide. The course of the reaction depends upon the Lewis acid, temperature, substrate, stoichiometry, and order of addition.

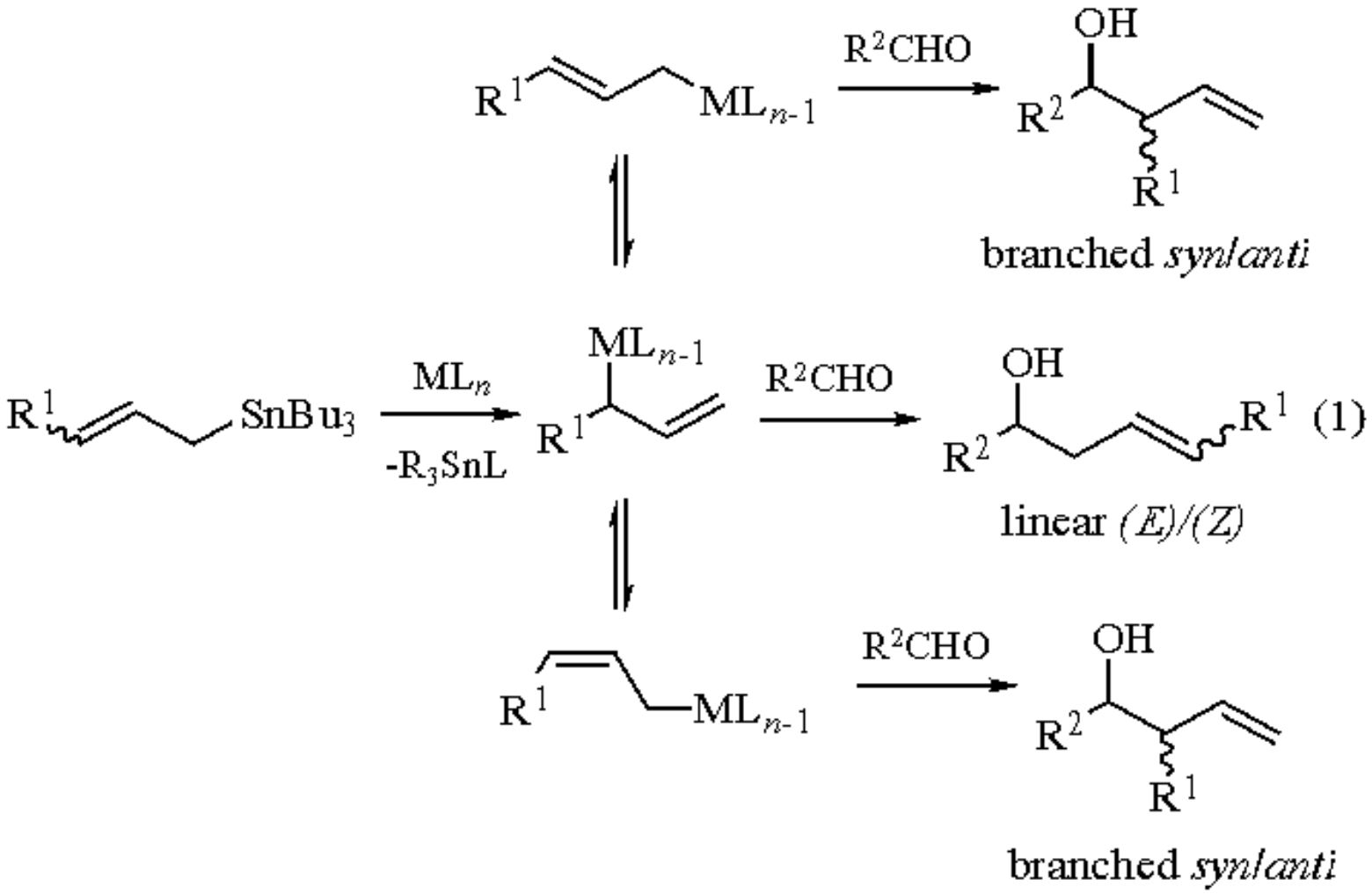

In thermal reactions, the stereochemical outcome of crotyltin additions to aldehydes is dependent upon the geometry of the but-2-enyl unit. Thus the (*E*) isomer produces *anti* alcohols while the (*Z*) isomer produces the *syn* alcohols.[5] The allylic coupling to aldehydes also occurs at rt under high pressure.[6]

The Lewis acid-mediated reactions of crotylstannanes and -silanes produces *syn* homoallylic alcohols predominantly,

regardless of the geometry of the but-2-enyl unit (eq 2). The selectivity was rationalized with an extended acyclic transition state geometry. This is in contrast to other crotyl organometallic reagents in which the crotyl geometry is linked to the observed stereoselectivity.[7]

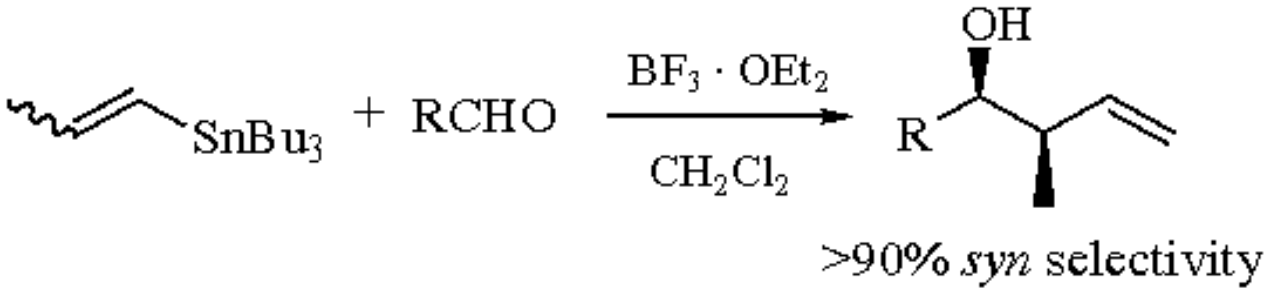

(2)

(*E*)-Crotyltributylstannane has been shown to react faster with aldehyde-Lewis acid complexes than the corresponding (*Z*) isomer.[8] Thus even higher levels of *syn* selectivity (25:1; 94% yield) can be achieved when 2 equiv of crotylstannane, which consists of a mixture of the (*E*) and (*Z*) isomers, is employed in the ***Boron Trifluoride Etherate***-mediated addition to aldehydes (eq 3). A decrease in selectivity to 9:1 is observed when only 1 equiv of stannane is used. ***Titanium(IV) Chloride***-mediated reactions show *syn* or *anti* selectivity depending upon the order of addition. For example normal addition (crotyltin added last) shows high *syn* selectivity (93:7) and only minor amounts of the linear alcohols (<3%). Under reverse addition (stannane addition to $TiCl_4$, followed by aldehyde addition) *anti* selectivity is observed, again with only minor amounts of the linear alcohols (<5%). The use of chiral Lewis acid catalyst, as opposed to Lewis acid promoters, has also been successfully employed in the stereoselective allylations of aldehydes.[9]

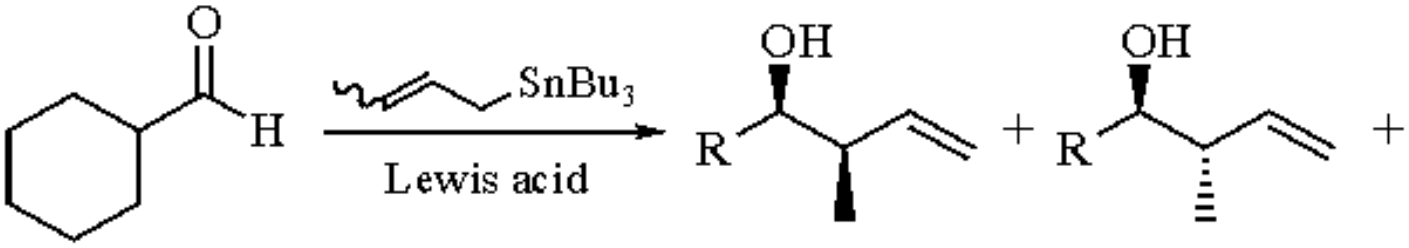

Lewis acid	crotyltin equiv		
$BF_3 \cdot OEt_2$	2.1	96.1	3.9
$TiCl_4$ normal	1.05	90.5	7.0
$TiCl_4$ reverse	2.0	4.4	90.8

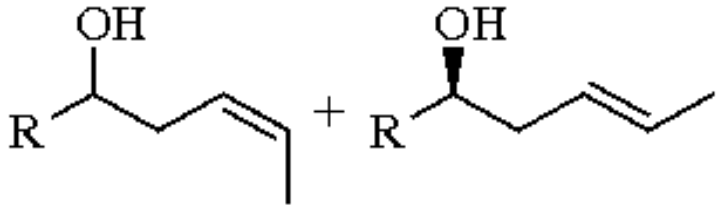

(3)

-	-
2.1	0.5
-	4.9

The effect of addition modes upon product distributions for (*E*)- and (*Z*)-crotyltributyltins with various Lewis acids and aldehydes has been investigated.[4d,10] The linear (α) homoallylic alcohol adduct with (*Z*) double bond geometry can be obtained selectively when (*Z*)-crotyltributylstannane is combined with an aldehyde followed by the addition of ***n-Butyltrichlorostannane*** (eq 4).[11] The reaction is believed to proceed through transmetallation to form the methallylbutyldichlorotin. The selectivity for the linear homoallylic products is reduced or lost when the order of addition of the aldehyde and $BuSnCl_3$ is reversed or when an (*E/Z*) mixture of crotylin is used. Similarly, the transmetalation of (*E*)-γ-(phenyl)allyltributyltin with $BuSnCl_3$ in the presence of an aldehyde produces the corresponding linear homoallylic alcohol adduct with (*Z*) double bond geometry.[12]

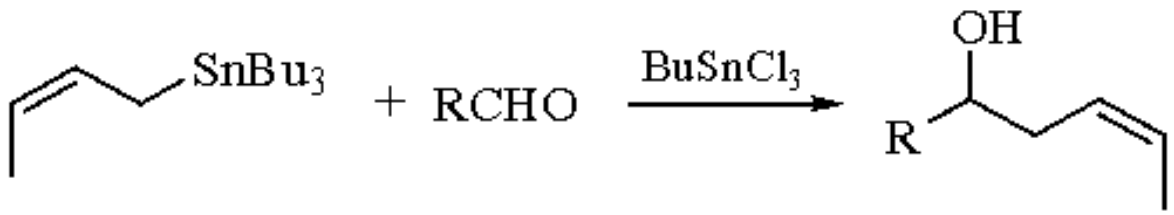

(4)

	(*Z*) Linear:branched	yield (%)
R = Ph	96:4	96
R = *n*-Hex	95:5	94

The addition of crotyltributylstannane to aldehydes in the presence of ***Cobalt(II) Chloride*** also affords the linear homoallylic alcohols exclusively (yields: 54-74%) (eq 5).[13] The regiochemistry is not affected by the steric hinderance of the aldehyde or the order of addition.

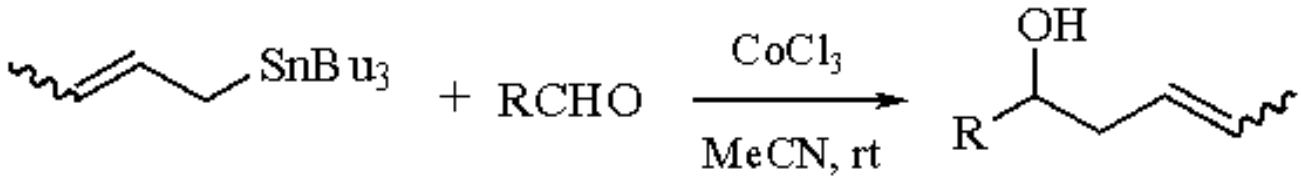

(5)

In the Lewis acid-mediated additions of crotyltributylstannane to α-alkoxyaldehydes, $MgBr_2$ and $TiCl_4$ provide chelation control diastereofacial selectivity (&egt;99:1) (eq 6). The diastereofacial selectivity for all crotylin additions is higher than the corresponding allyl additions. Both diastereofacial and bond construction selectivity increase with the size of R^1 (cyclohexyl > *n*-butyl > Me). Within the chelation control manifold, *syn* selectivity for bond construction is &egt;90:10; $MgBr_2$ is the Lewis acid of choice.[14]

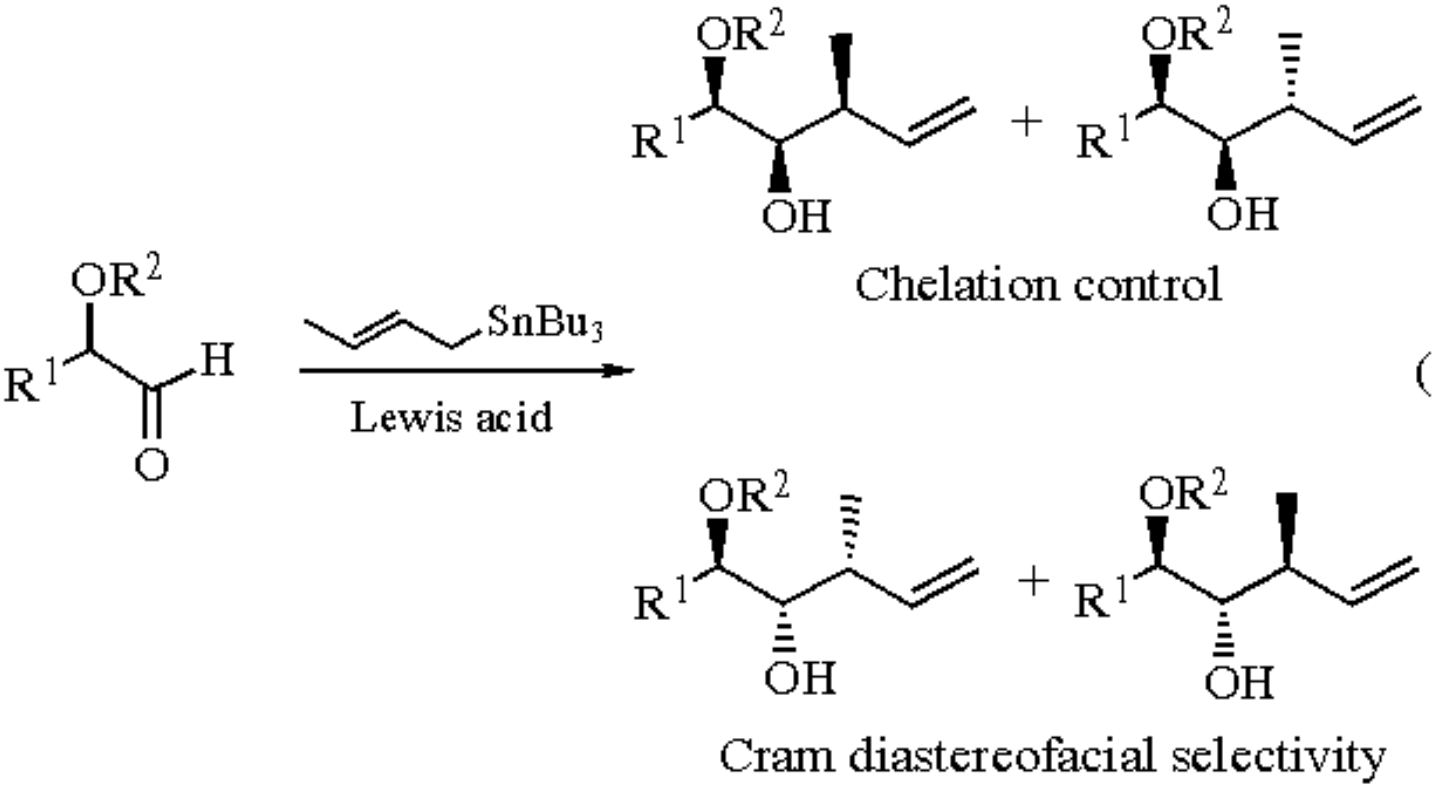

The Lewis acid and hydroxy-protecting group also strongly influence stereoselectivity in the crotylstannane additions to 2-methyl-3-hydroxypropanal derivatives (β-alkoxyaldehydes). The promoter $BF_3.OEt_2$ shows high *syn* diastereofacial selectivity (Cram) with the characteristic *syn* bond construction selectivity. The *syn,syn* isomer is formed in 92% yield with high diastereofacial selectivity (18:1) and essentially complete bond construction selectivity when the *t*-butyldimethylsilyl protecting group is present. Chelation control diastereofacial selectivity (*anti*) is high for all Lewis acids capable of chelation; however, bond construction selectivity is low. $MgBr_2$ provides the *anti,syn* isomer with 91:9 *anti* facial selectivity and 89:11 *syn* bond construction selectivity.[8] Using chelation control conditions, the protected β-alkoxyaldehyde (**1**) was selectively allylated with crotyltriphenylstannane (as a 1:1 *cis*/*trans* mixture) to provide the desired stereoisomer in 60% yield and a 20% yield of a regiomeric crotyl addition product (eq 7).[15]

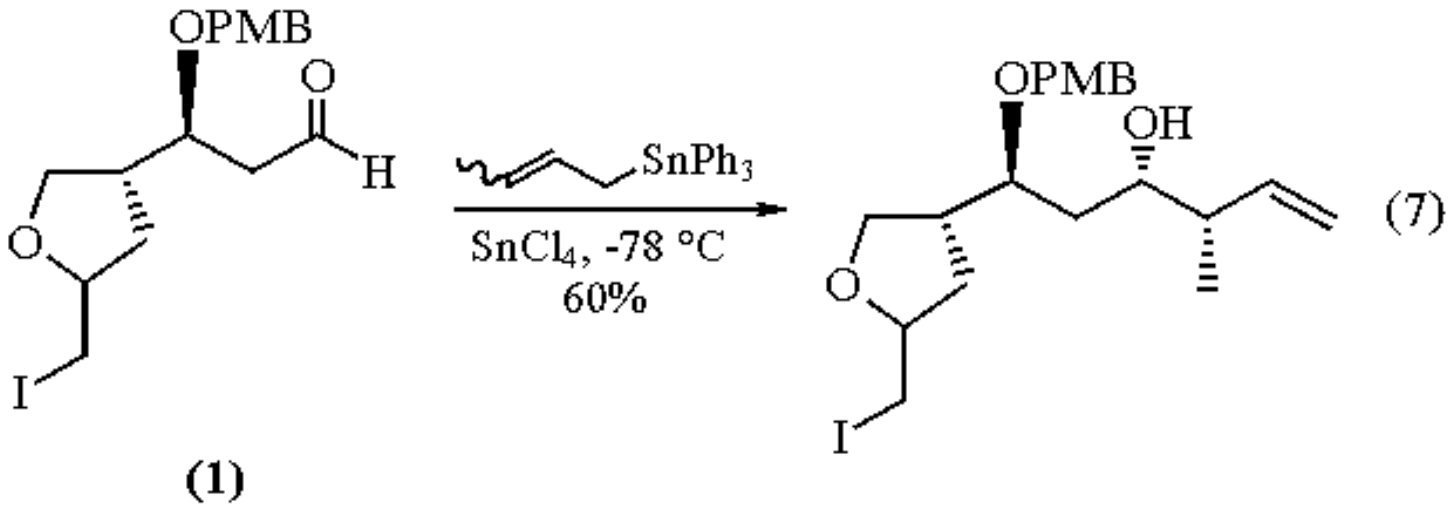

High *syn* diastereofacial control and *anti* bond construction selectivity is observed, under chelation control conditions, for the additions of β-methylcrotylstannanes to 2-(benzyloxy)-propanal (eq 8).[16]

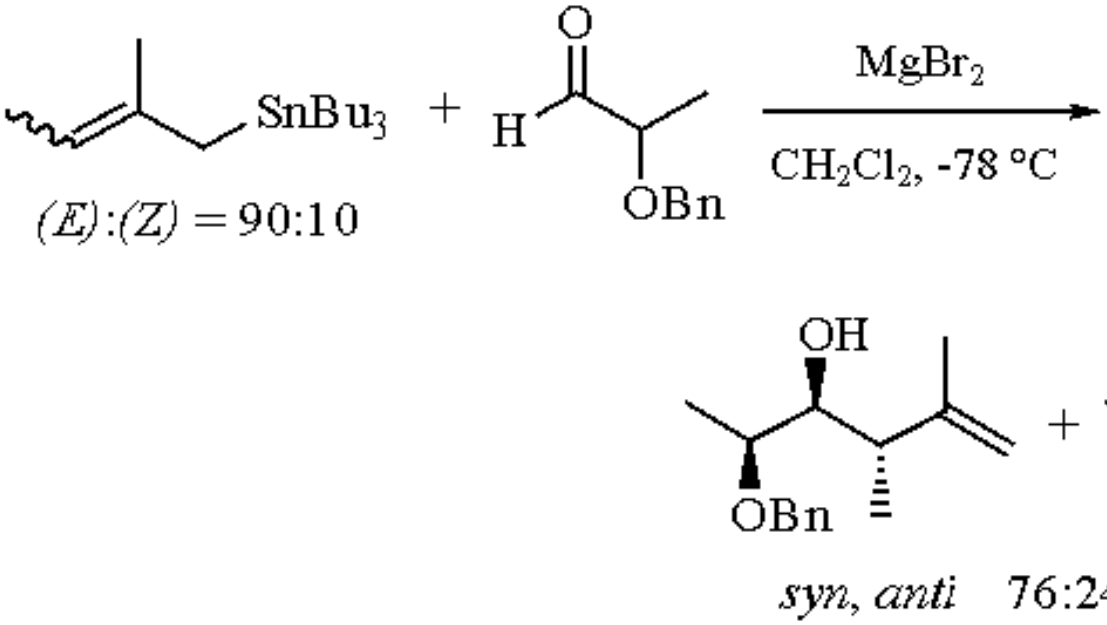

(8)

The Lewis acid-mediated addition of crotyltributylstannane to pyruvates slightly favors the *anti* products when the ester group is small; however, *syn* products dominate as the size of the ester group is increased (eq 9).[17] The BF_3 etherate-mediated addition to glyoxylate esters is also influenced by the size of the ester group, providing a *syn*:*anti* ratio of 90:10 for the isopropyl ester and decreasing to 75:25 for the methyl ester.[18] Crotyltin addition to *meso*-dimethylglutaric hemialdehyde, also mediated by BF_3 etherate, shows chelation control *syn* selectivity. The selectivity is based upon the conformationally rigid substrate, which prefers a chelate-like conformation.[19]

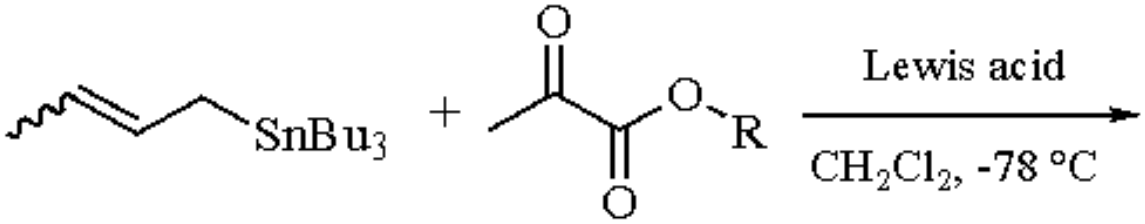

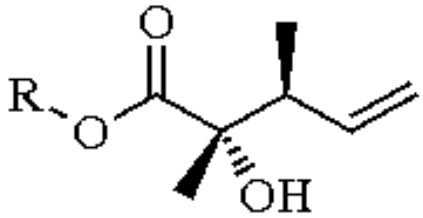

(9)

	yield (%)	*anti*:*syn*
R = Me	84	60:40
R = 2,6-dimethylphenyl	84	35:65

Iminines and Iminium Ions.

Crotyltributylstannane additions to aliphatic and furyl imines (R^1 = *i*-Pr, Cy, furyl; R^2 = Bn) provide addition products with very high *syn* selectivity (*syn*:*anti* > 20:1) (eq 10).[20] This high selectivity requires extended Lewis acid-imine complexation at -78 °C (2.5 h) prior to crotylstannane addition, otherwise a modest 4:1 *syn* selectivity is attained.

Crotyltributylstannane additions to aromatic imines (R^1 = Ph; R^2 = Ph, *p*-tolyl) occur with much lower diastereoselectivity (*syn*:*anti* > 75:25).[21]

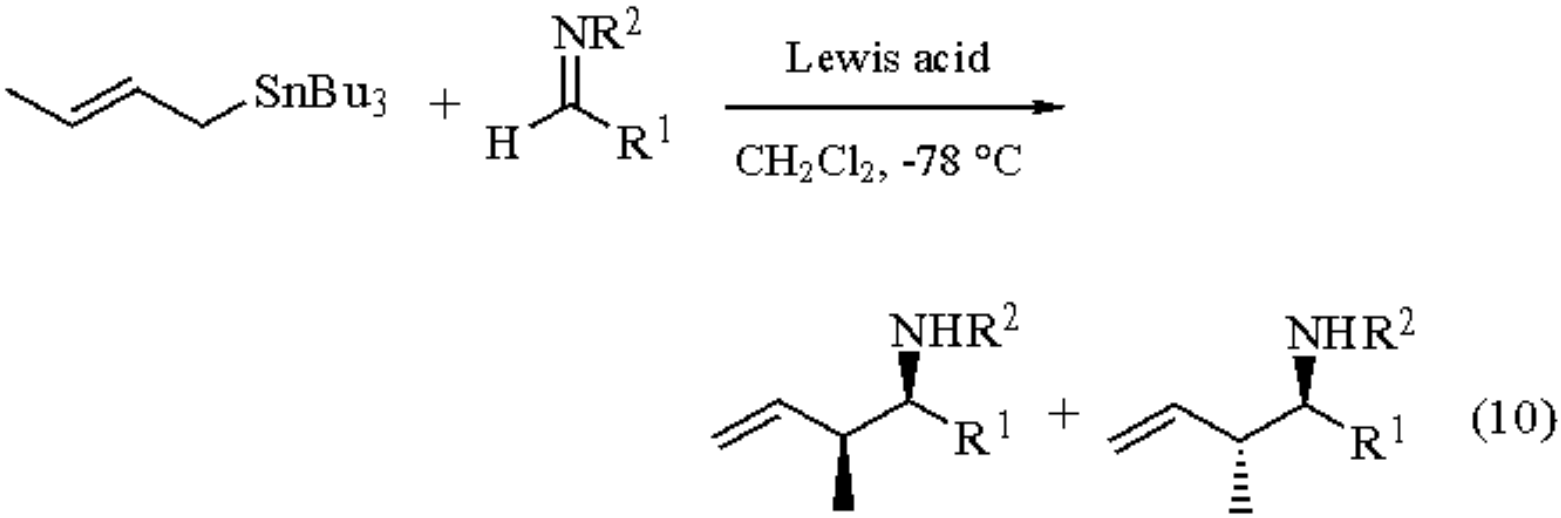

Methallyl- and crotyltin reagents add to pyridine activated by ***Methyl Chloroformate*** (i.e. prior iminium salt formation) with poor regioselectivity (α:γ = 48:52 to 36:64) (eq 11).[22] Allylstannanes add in a highly α-selective fashion (86-99%) while prenyltributylstannane additions occur exclusively at the γ-carbon of pyridine. Crotyltin reagents add to larger aromatic N-heterocycles with excellent regioselectivity (>95%) (eq 12).

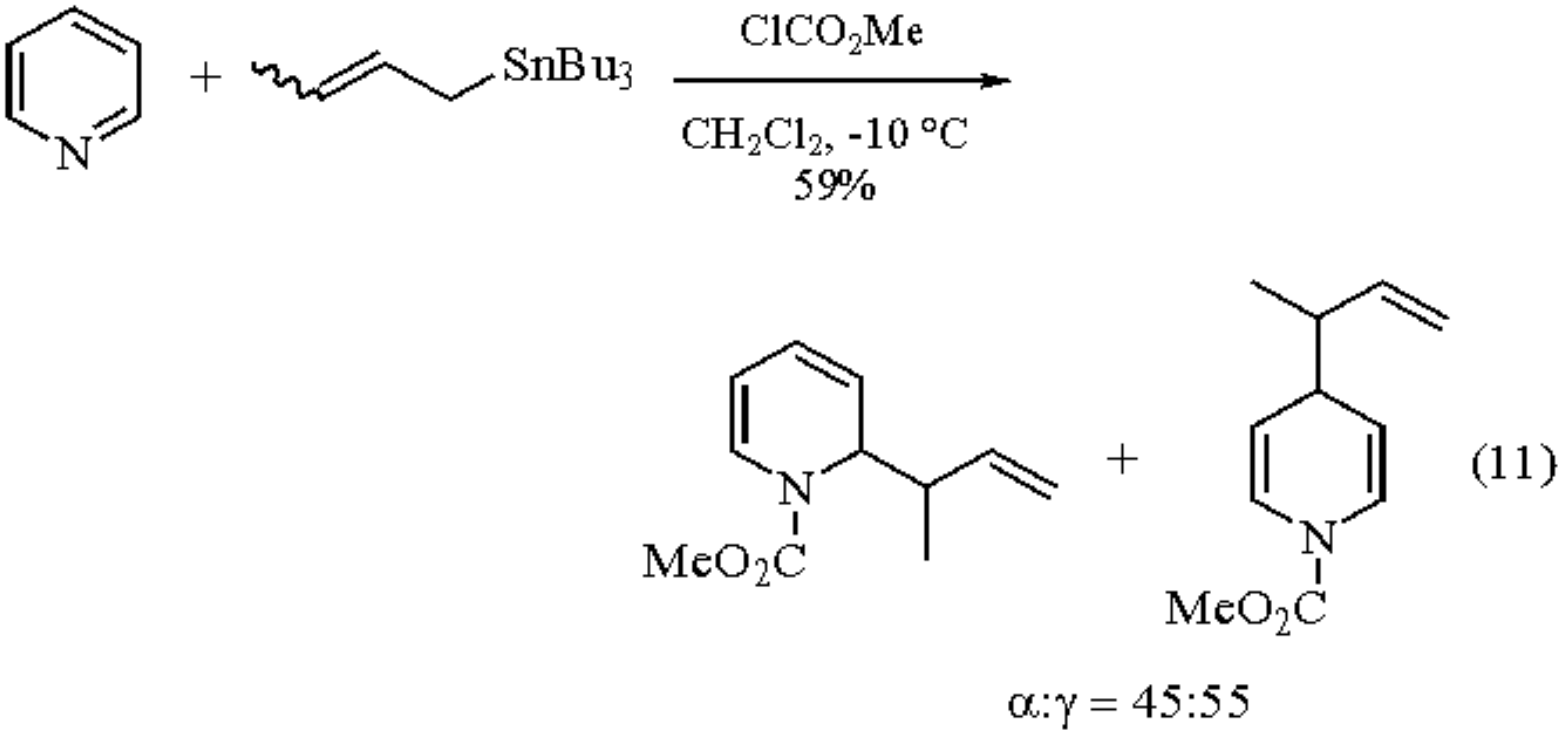

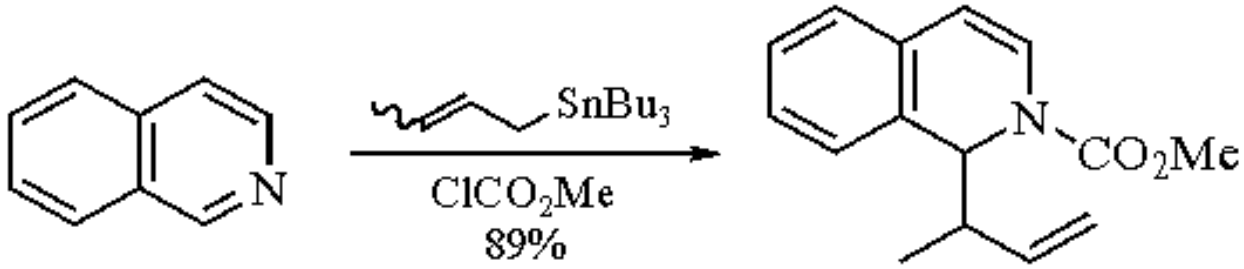

(12)

Conjugate Addition.

Conjugate additions of crotyltributylstannanes to Michael acceptors occur with poor to modest *anti* selectivity in variable yields (eq 13).[23] ***Tin(IV) Chloride*** promotion provides the highest selectivity for the crotyltributylstannane addition to an enoate (90:10; 52%). Other Lewis acids provide slightly lower selectivities (>80:20) in higher yields (>94%). Conjugate additions to nitroalkenes occur with very low selectivity (*anti*:*syn* = 45:55 to 70:30). Yields are higher for the phenyl-substituted nitroalkene (53-92%) than for the methyl derivative (29-42%). The trialkylsilyl triflate-promoted conjugate addition of allylstannes to α,β-enones affords the corresponding β-alkylated silyl enol ethers in high yields (85-95%).[24]

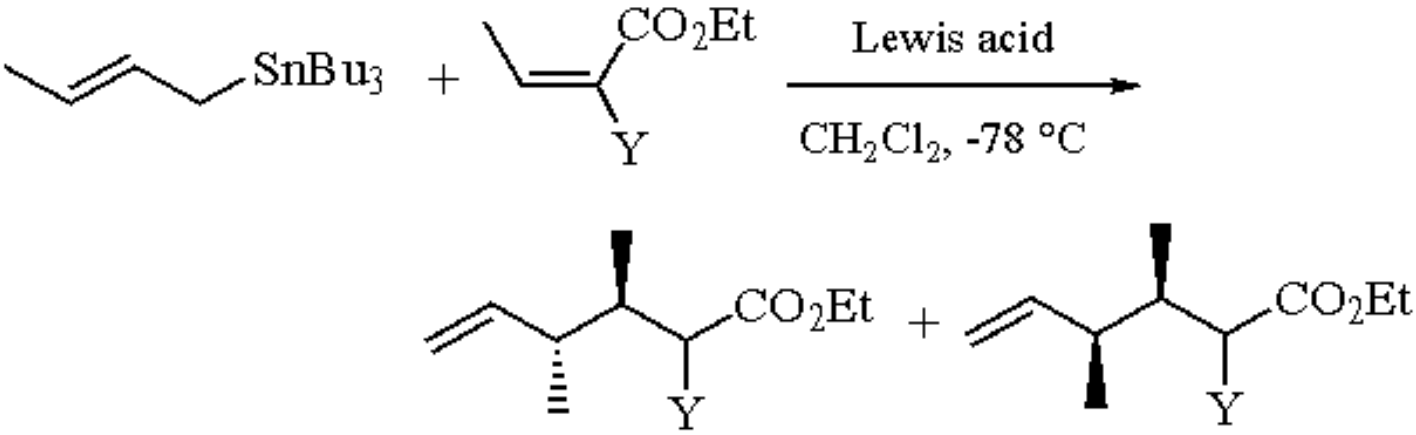

(13)

Y = CO_2Et, CN

Reactions with Orthoamides.

The $BF_3.OEt_2$ promoted addition of crotyltributylstannane to orthoamides occurs with complete stereoselectivity (eq 14).[25] Interestingly, the $TiCl_4$-promoted reaction provides the other diastereomer exclusively.

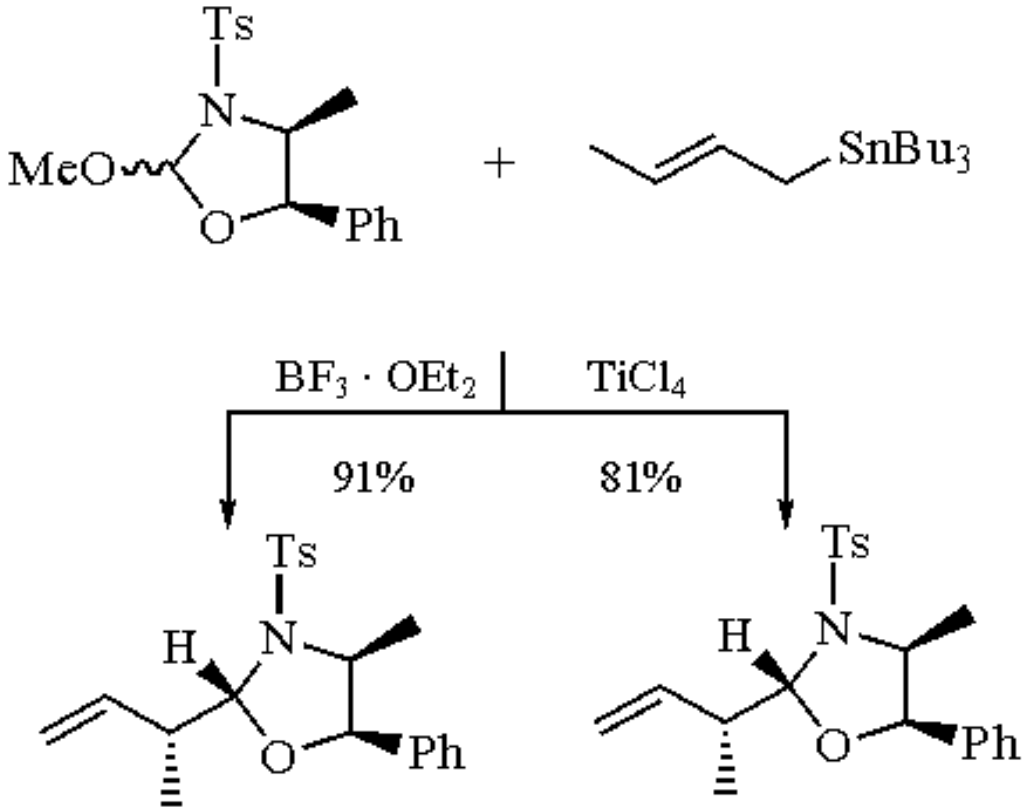

(14)

Intramolecular Cyclizations.

Intramolecular condensation reactions between allylstannanes and a carbonyl group joined by a one-carbon tether afford silyloxyvinylcyclopropanes.[26] A variety of 1-butenyl- and 5-hexenyltributylstannanes undergo intramolecular cyclization in the presence of ***N-Phenylselenophthalimide*** and $SnCl_4$.[27]

Radical Reactions.[28]

The radical allyl transfer reactions from allyl- or methallyltributylstannane to a variety of substrates under various initiation conditions have been demonstrated to be synthetically useful.[29] For example, thiophenyl glycosides are converted into C-gylcosides by reaction with methallyltributylstannane. The stereoselectivity is dependent on the reaction conditions. Using photochemical initiation, the reaction of (**2**) with methallylbutylstannane gives an 87% yield of the C-glycoside with a 92:8 ratio of α:β anomers (eq 15). In contrast, the reaction in the presence of catalytic (0.2 equiv) tributylstannyl triflate provides a 95% yield preferentially of the β-isomer (99:1).[30]

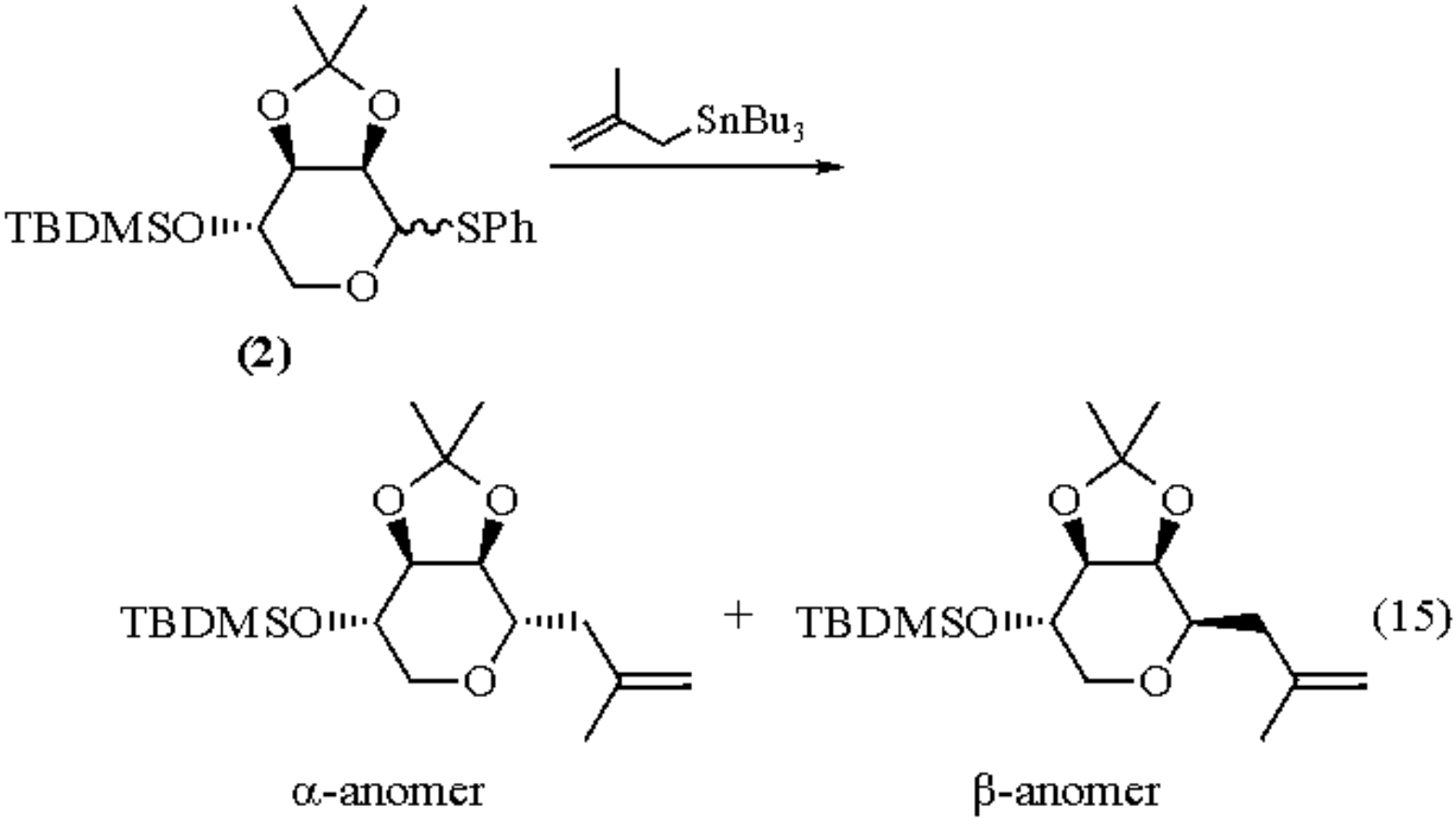

Crotylstannanes are less reactive than allyltributylstannane towards carbon-centered radicals. In contrast to allylstannanes, which readily react by radical pathways with alkyl halides, the use of crotylstannane affords only reduction products under a variety of initiation processes.[31] However, the successful allyl transfer reaction of crotylstannane has been reported for a bromine-substituted glycine (eq 16).[32] Thus a mixture of (*E*) and (*Z*) isomers (ca. 1:1) of crotyltributyltin reacted with (**3**) to produce a 57% yield of the allylated product as a 1:1 mixture of diastereomers. The reduction product and 5-methylallylglycine were not observed in the reaction mixture. Radical S_H2' substitution reaction using hetero-centered radicals (RS&bdot;, RSO_2&bdot;, and PhSe&bdot;) and crotylstannane has also been demonstrated.[33]

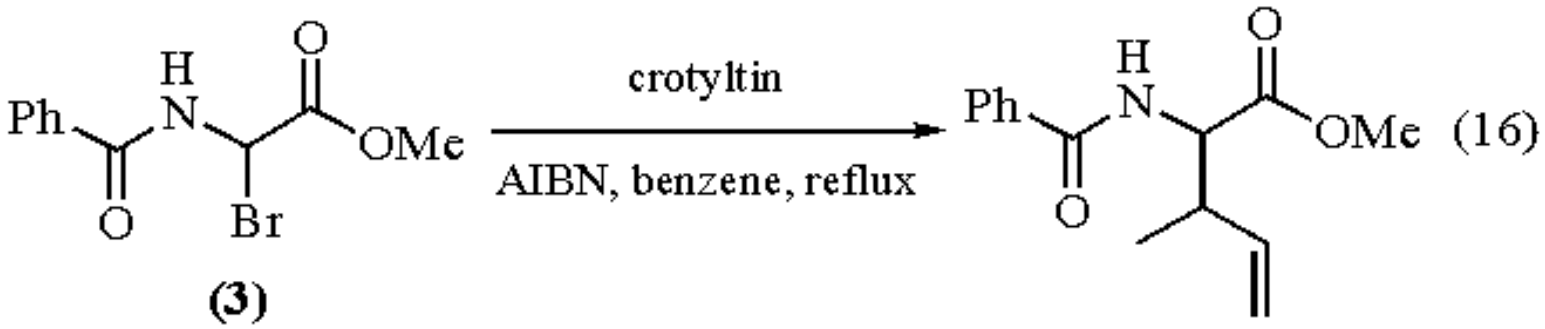

Irradiation of benzil in the presence of (*E*)- and (*Z*)-crotyl, -pent-2-enyl-, or -hex-2-enyltributylstannane affords predominantly the linear homoallylic alcohols in good yields with retention of the double bond configuration.[34]

Related Reagents.

Allyltributylstannane; ***Allyltrimethylsilane***; ***Allyltriphenylstannane***; ***trans-Cinnamyltributylstannane***; ***Crotyltrimethylsilane***; ***Tri-n-butyl(1-methoxymethoxy-2-butenyl)stannane***; ***Trimethyl(3-methyl-2-butenyl)stannane***.

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Crotyltrichlorosilane[1]

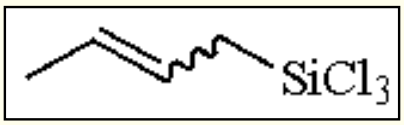

(*Z*)

[49749-84-0] · $C_4H_7Cl_3Si$ · Crotyltrichlorosilane · (MW 189.54) (*E*)

[52885-13-9]

(regio- and stereospecific crotylation of aldehydes through pentacoordinate silicate intermediates[2])

Physical Data: bp (*Z*) 140-142 °C, (*E*) 142-144 °C.

Solubility: sol hydrocarbons, halogenated hydrocarbons, and ethers. Protic solvents, especially alcohols, should not be used due to chemical reactivity.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: the reaction of isomerically pure (*E*) ***Crotyl Chloride*** and ***Trichlorosilane*** in the presence of ***Copper(I) Chloride*** and ***Triethylamine*** in ether at rt produces (*E*)-crotyltrichlorosilane in 76% yield with isomeric purity higher than 99%.[3] Purification of (*E*)-crotyl alcohol[4] is critical for preparation of the isomerically pure compound.[2] The ***Tetrakis(triphenylphosphine)palladium(0)***-catalyzed hydrosilation of ***1,3-Butadiene***[5] with trichlorosilane at -78 °C gives (*Z*)-crotyltrichlorosilane in 84% yield with isomeric purity of 99.1%.[2] The reaction temperature is of key importance for the preparation of stereohomogeneous crotyltrichlorosilane. Higher temperatures give unsatisfactory results.[2]

Purification: by distillation.

Handling, Storage, and Precautions: the reagents can be stored in a glass bottle but should be rigorously protected from moisture. The reagents should be handled in a well-ventilated hood and contact with the skin and eyes should be avoided.

Allylation Through Pentacoordinate Silicate Intermediates.

The reaction of crotyltrichlorosilane with dihydroxy compounds such as catechol gives pentacoordinate crotylsilicon

bis(catecholate). The catecholate, isolated and purified, reacts with benzaldehyde without activators to afford homoallyl alcohols with complete regioselectivity. The reaction can be performed without isolation of the intermediate catecholate (eq 1).[2,6]

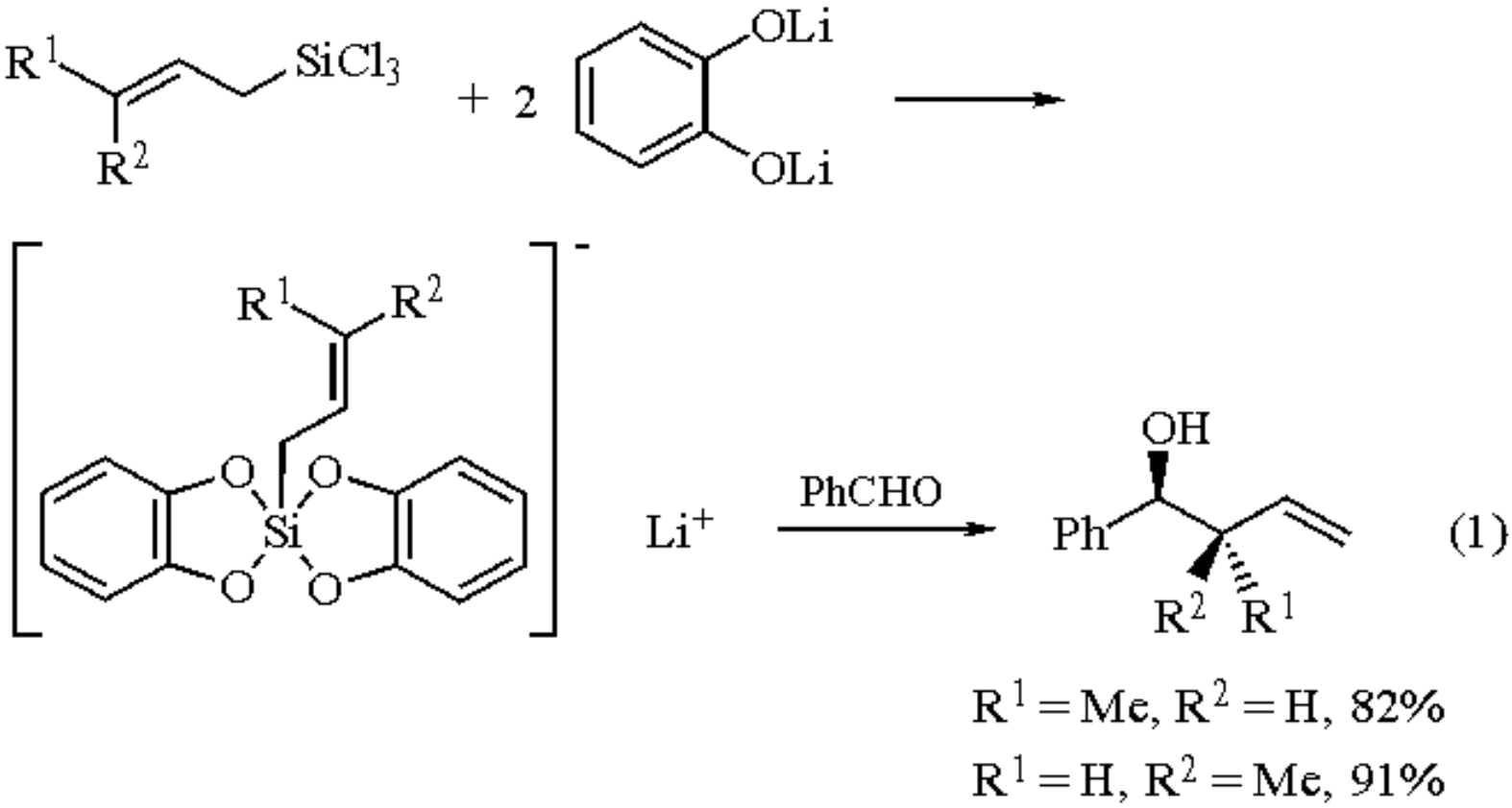

Friedel-Crafts Reaction.

Like other allyltrichlorosilanes, crotyltrichlorosilane undergoes Friedel-Crafts reaction with benzene.[7] The reaction of crotyltrichlorosilane with benzene in the presence of ***Aluminum Chloride*** gives a mixture of two positional isomers, (2- and (3-phenylbutyl)trichlorosilane (eq 2). The former is the initial product, but thermally isomerizes to the latter. The equilibrium mixture of the 2-phenyl and 3-phenyl isomers is 9:91.

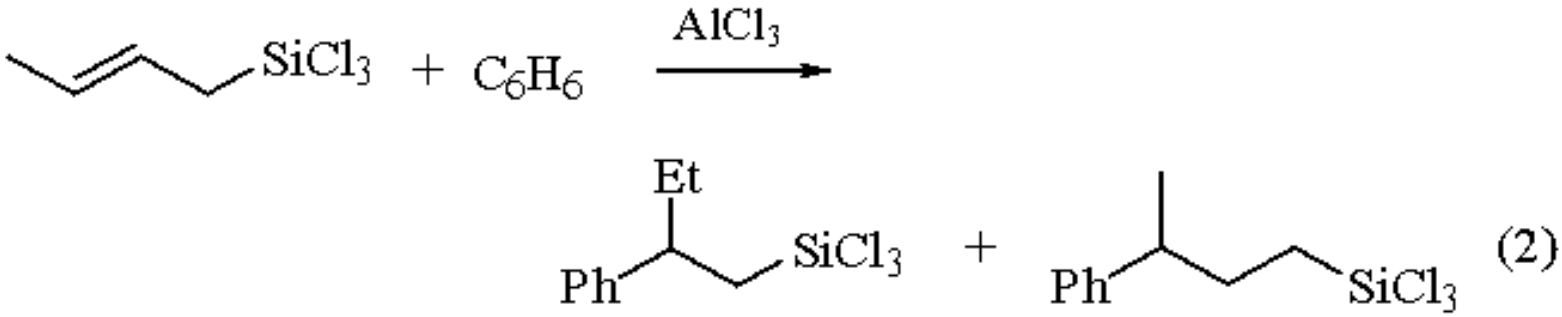

Conversion to Crotyltrifluorosilane.

Crotyltrichlorosilanes are readily converted to the corresponding crotyltrifluorosilanes, which are useful for regio- and stereospecific crotylation.[2]

Related Reagents.

B-Allyldiisocaranylborane; ***B-Crotyldiisopinocampheylborane***; ***Crotyldimethoxyborane***; ***Crotyltrifluorosilane***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***Triethylammonium Bis(catecholato)allylsiliconate***.

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Crotyltrifluorosilane[1]

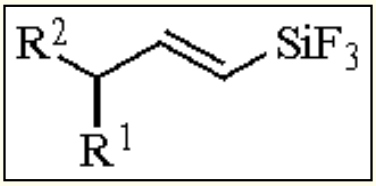

($R^1 = R^2 = H$) (allyl)

[690-19-7] · $C_3H_5F_3Si$ · Allyltrifluorosilane · (MW 126.15) (R^1 = Me, R^2 = H) (*Z*-crotyl)

[51676-18-74] · $C_4H_7F_3Si$ · Crotyltrifluorosilane · (MW 140.18) (R^2 = Me, R^2 = H) (*E*-crotyl)

[114067-35-5] ($R^1 = R^2$ = Me) (Me-crotyl)

[114067-34-4] · $C_5H_9F_3Si$ · (Methylcrotyl)trifluorosilane · (MW 154.21)

(highly regioselective and stereoselective allylation and crotylation reagent, usually activated by fluoride ions or hydroxy compounds[1a])

Physical Data: (*Z*)-crotyl: bp 52 °C; Me-crotyl: bp 71 °C.

Solubility: sol common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Purification: by distillation.

Preparative Methods: allyltrifluorosilanes are most conveniently prepared by the reaction of the corresponding trichlorosilanes with SbF_3[2] or $ZnF_2.4H_2O$.[3] Stereohomogeneous (*E*)- and (*Z*)-crotyltrifluorosilanes are prepared as shown in eqs 1 and 2.[4]

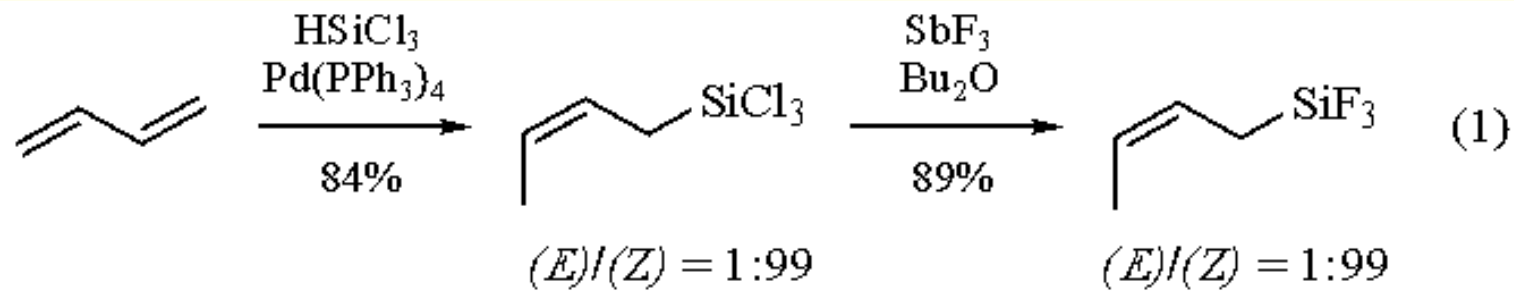

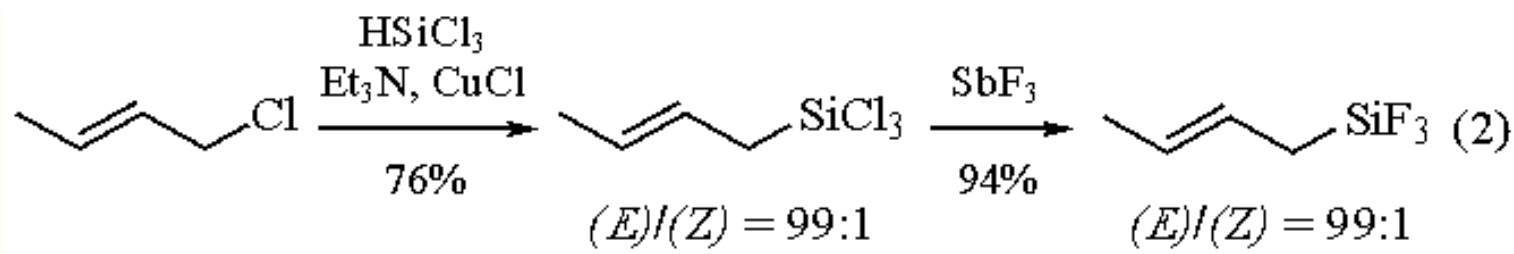

Handling, Storage, and Precautions: the reagents can be stored in a glass bottle but must be protected from moisture. Use in a fume hood.

Fluoride Ion-Mediated Allylation of Aldehydes.

Allyltrifluorosilanes undergo regiospecific and stereospecific allylation reactions with a variety of aldehydes. Thus in the presence of an excess amount of ***Cesium Fluoride***, allyltrifluorosilanes form pentacoordinate tetrafluorosilicates which undergo the allylation reaction with aldehydes, presumably through a six-membered transition state. The regio- and stereochemistry of the products are consistent with this postulate (eq 3).

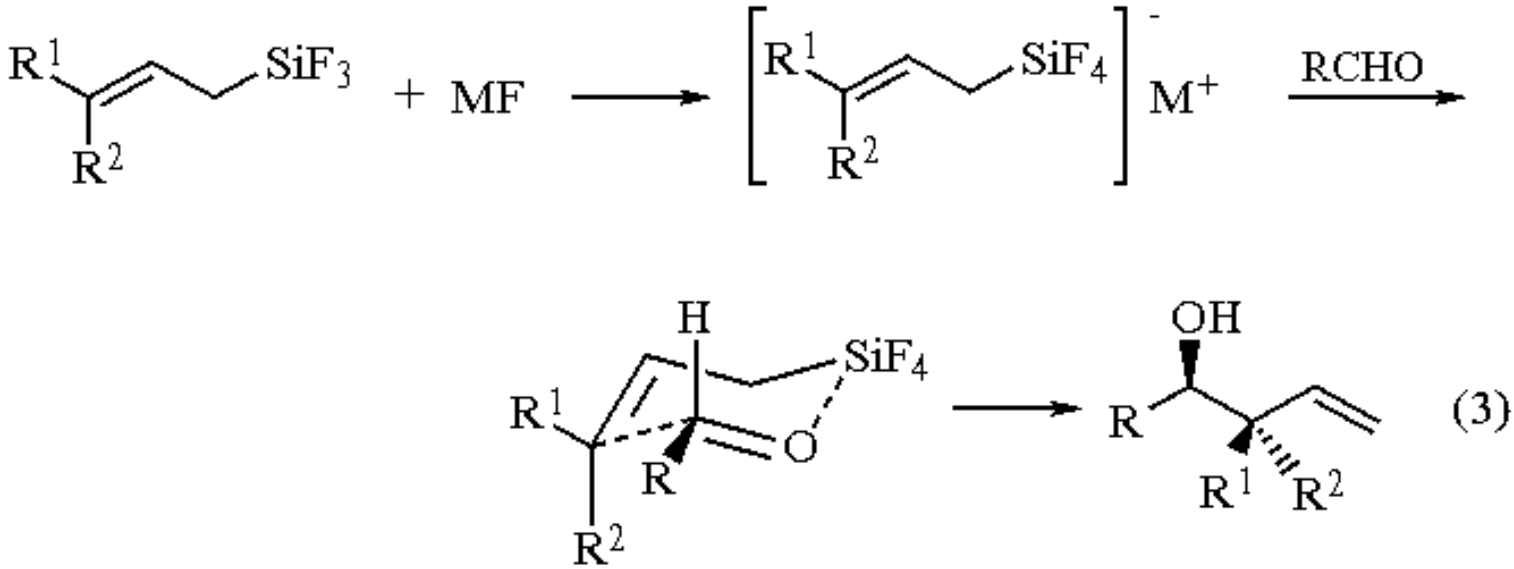

$R^1 = R^2 = Me$, $R = Ph$	96%
$R^1 = H$, $R^2 = Me$, $R = C_8H_{17}$	89%
$R^1 = Me$, $R^2 = H$, $R = {}^{\backprime}Et_2CH$	88%

Hydroxy Compound-Mediated Allylation.

Allylation reactions of aldehydes with allyltrifluorosilanes can also be effected in the presence of a wide variety of hydroxy compounds and ***Triethylamine*** to give the corresponding homoallyl alcohols in a regio- and stereospecific manner.[5] Typically in the case with catechol, allyldifluorosilicon catecholate is proposed to be the intermediate (eqs 4 and 5). No rigorous drying of the reaction system is necessary. Interestingly, this reagent system can discriminate linear from α-branched alkanals. The structure-reactivity relationships in pentacoordinate allylsilicates are explained in terms of the Lewis

acidity of the silicon centers.

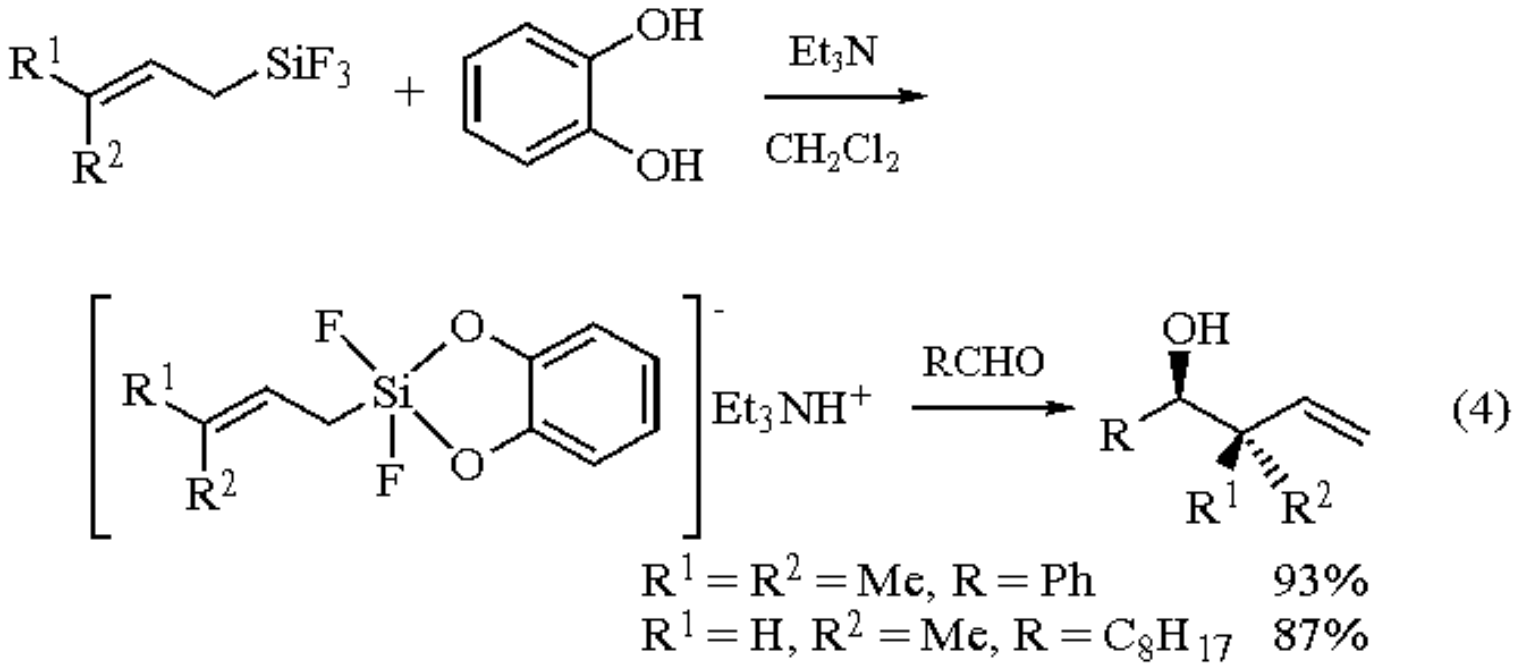

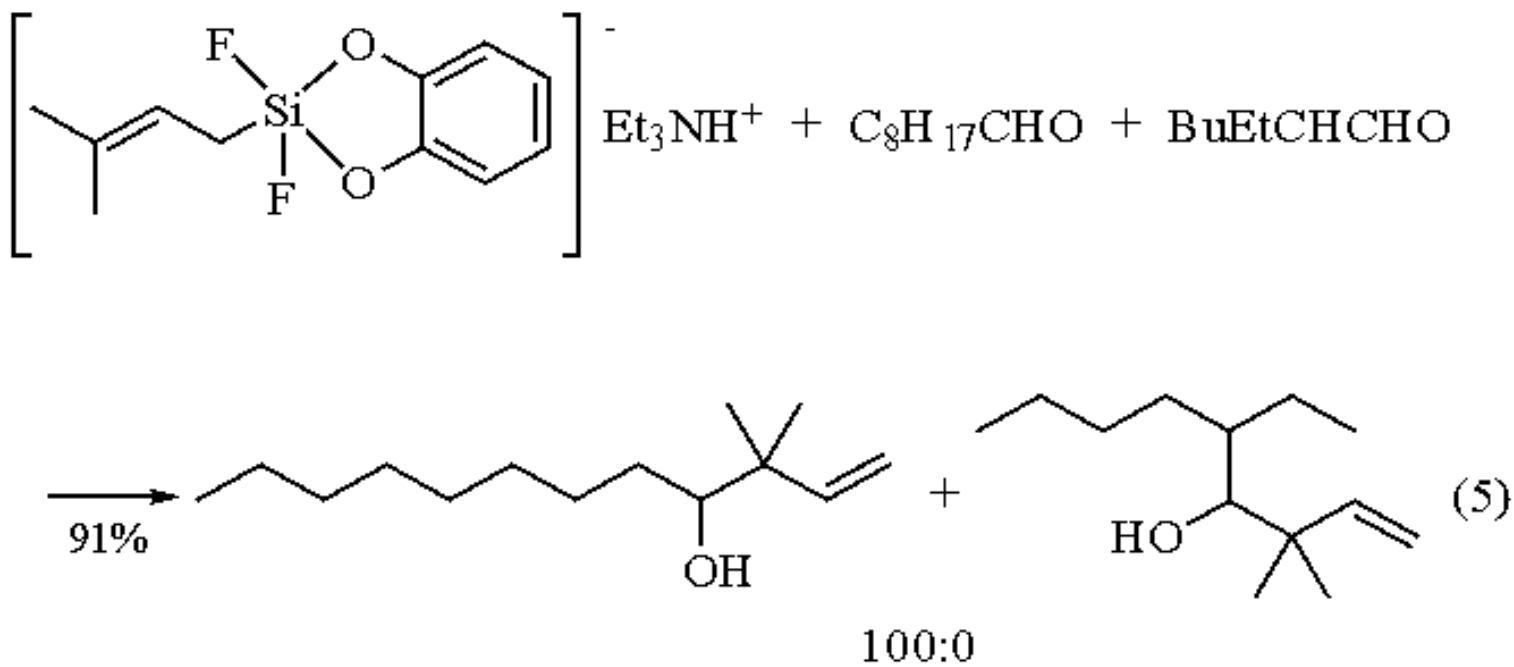

Allylation of α-Hydroxy Ketones.

Allyltrifluorosilanes react with α-hydroxy ketones, without protection of the hydroxy group, in the presence of triethylamine to yield tertiary homoallyl alcohols with extremely high regio- and diastereospecificity (eqs 6 and 7).[6]

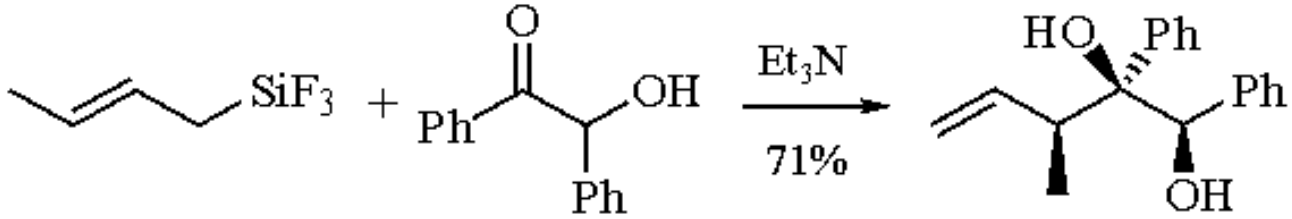

(6)

(*E*):(*Z*) = 97:3

2,3-*syn*:2,3-*anti* = 97:3
1,2-*syn*:1,2-*anti* = 100:0

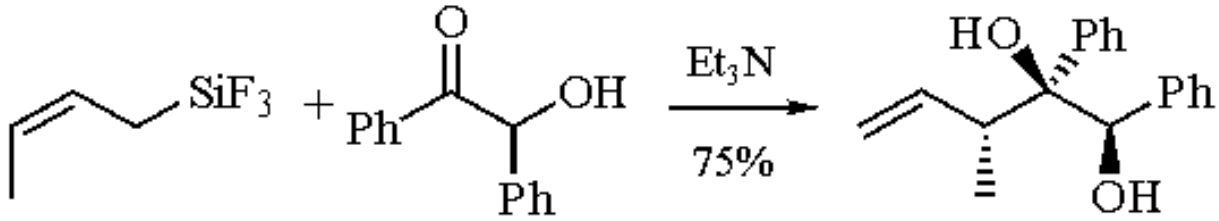

(7)

(*E*):(*Z*) = 5:95

2,3-*syn*:2,3-*anti* = 5:95
1,2-*syn*:1,2-*anti* = 100:0

Crotylation of Aldimines.

Aliphatic and aromatic aldimines are crotylated in a selective manner by the reaction with (*E*)- and (*Z*)-crotyltrifluorosilanes in the presence of CsF (eq 8).

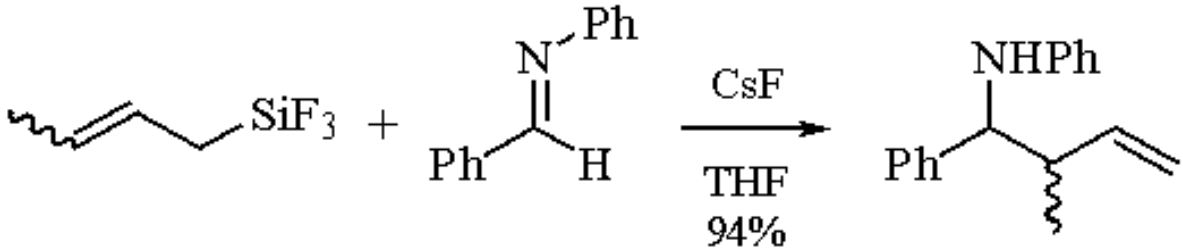

(8)

Related Reagents.

B-Allyldiisocaranylborane; ***B-Crotyldiisopinocampheylborane***; ***Crotyldimethoxyborane***; ***Crotyltrichlorosilane***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***.

---

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Crotyltrimethylsilane[1]

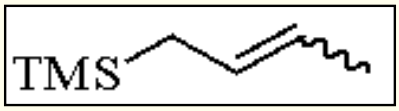

[18292-28-9] · $C_7H_{16}Si$ · Crotyltrimethylsilane · (MW 128.29) (*E*)

[17486-12-3] (*Z*)

[17486-13-4]

(carbon nucleophile for the introduction of 1-methylallyl groups by Lewis acid-catalyzed reaction with aldehydes, iminium ions, enones, and similar carbon electrophiles, with some heteroatom electrophiles, and as a starting material for synthesis of α-branched allylsilanes)

Physical Data: bp 110-115 °C; (*E*) isomer: *n*25D 1.4159; (*Z*) isomer: *n*25D 1.4208.[2]

Solubility: freely sol all organic solvents.

Analysis of Reagent Purity: $\delta_H(CCl_4)$ (*E*) isomer: 5.4-5.1 (2H, m), 1.55 (3H, d, *J* = 4), 1.26 (2H, d, *J* = 5), and 0.11 (9H, s); (*Z*) isomer: 5.36 (2H, m), 1.9-1.2 (5H, br m), and 0.05 (9H, s).[2]

Preparative Methods: both (*E*)- and (*Z*)-crotyltrimethylsilane can be prepared separately from the *exo*- and *endo*-crotylpotassium compounds[3] and ***Chlorotrimethylsilane***,[4] by nickel(II)-catalyzed coupling of (*E*)- or (*Z*)-1-bromopropene with ***(Chloromethyl)trimethylsilane***,[5] and by reaction of methylmagnesium iodide on 1,3-bis(trimethylsilyl)propene oxide followed by acid- or base-catalyzed (Peterson) desilylative elimination.[6] A mixture of the (*E*) and (*Z*) isomers in a 9:1 ratio can be prepared by the reaction of ***Trichlorosilane*** and ***Triethylamine*** with ***Crotyl Chloride***, followed by treatment with methylmagnesium iodide.[7] Coupling of the crotyl Grignard reagent with chlorotrimethylsilane similarly gives mixtures of both stereoisomers, but also some of the regioisomer.[8] The three components may be separated by GC. The pure (*Z*) isomer can be prepared by hydrosilylation of ***1,3-Butadiene*** with trimethylsilane using ***Hexacarbonylchromium***.[9] The regio- and stereoisomers can be equilibrated by ***Tetra-n-butylammonium Fluoride*** (TBAF) in refluxing THF.[10] Methods for the synthesis of allylsilanes in general have been reviewed.[11]

Handling, Storage, and Precautions: crotyltrimethylsilane is inflammable.

As a Carbon Nucleophile in Uncatalyzed and in Lewis Acid-Catalyzed Reactions with Carbon Electrophiles.

Crotyltrimethylsilane is an alkene some 10^5 times more nucleophilic than propene and some 20 times more nucleophilic than ***Allyltrimethylsilane***, as judged by its reactions with diarylmethyl cations.[7,12] It reacts with cationic carbon electrophiles at the alkenic carbon remote from the silyl group to give an intermediate cation, and the silyl group is lost to create a double bond at the terminus, i.e. with allylic inversion, as illustrated for the tropylium cation (eq 1).[13]

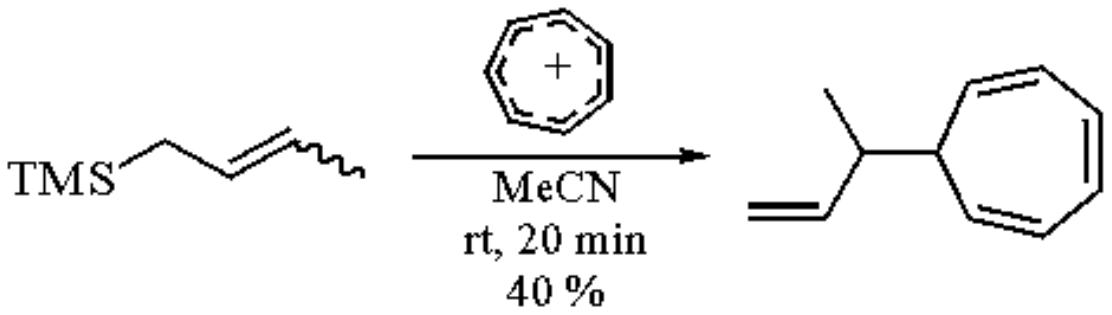

(1)

More usually the electrophile is created by coordination of a Lewis acid to a functional group. Among the stereochemically straightforward electrophiles are ***Trichloroacetonitrile*** (eq 2),[14] ketones (eq 3),[15] linear methoxyethoxymethyl mixed acetals and monothioacetals,[16] and alkoxyalkyl halides.[18]

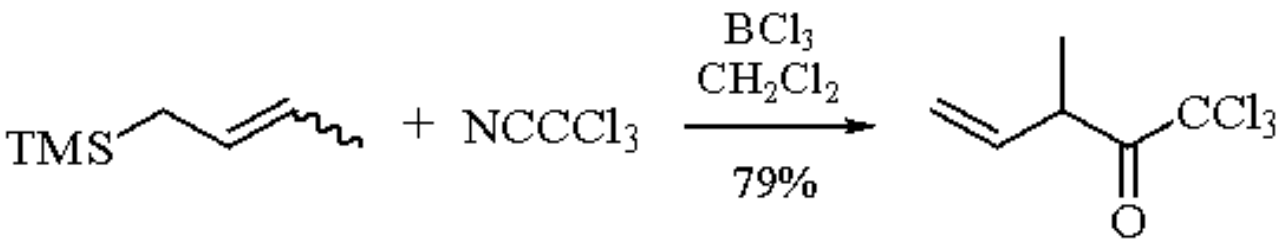

(2)

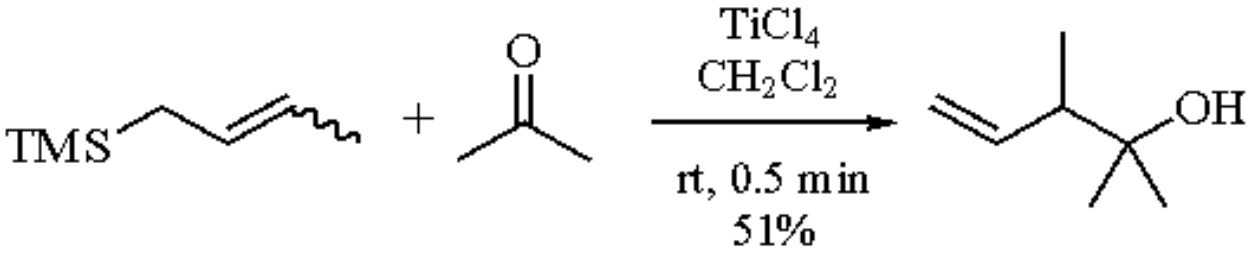

(3)

Somewhat more complicated are those reactions where two adjacent stereogenic centers are set up simultaneously, as in the reactions with aldehydes (eq 4),[5] acetals (eq 5),[17] the corresponding alkoxymethyl halides,[18] and α,β-unsaturated ketones and esters (eq 6).[19]

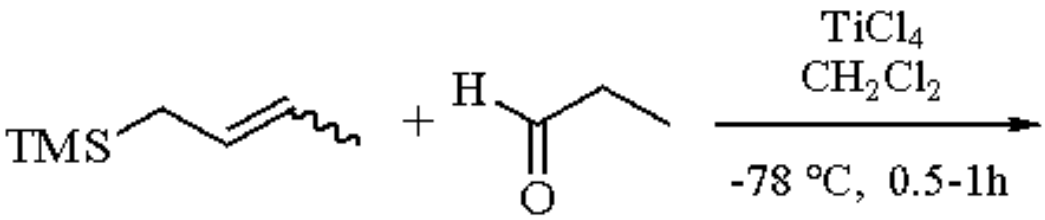

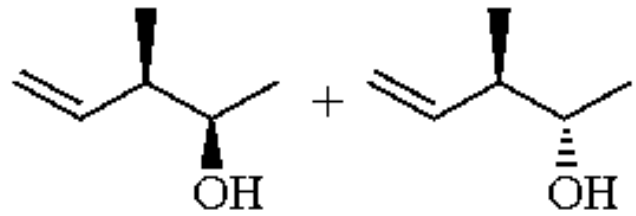

(4)

from *(E)* isomer, 91% 95:5
from *(Z)* isomer, 98% 69:31

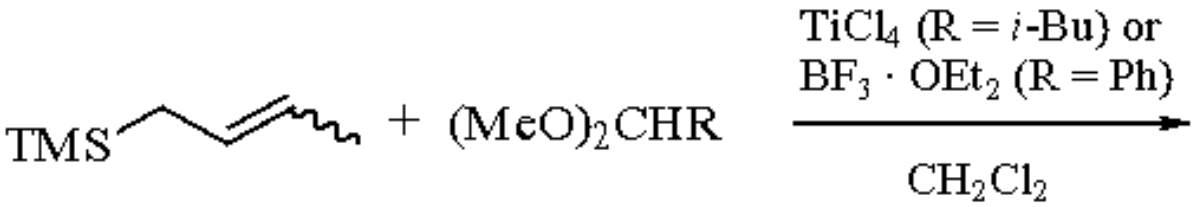

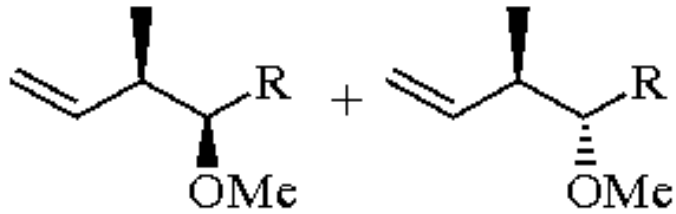

(5)

R = *i*-Bu

from *(E)* isomer, 90% 91:9
from *(Z)* isomer, 99% 91:9

R = Ph

from *(E)* isomer, 94% 75:25
from *(Z)* isomer, 78% 28:72

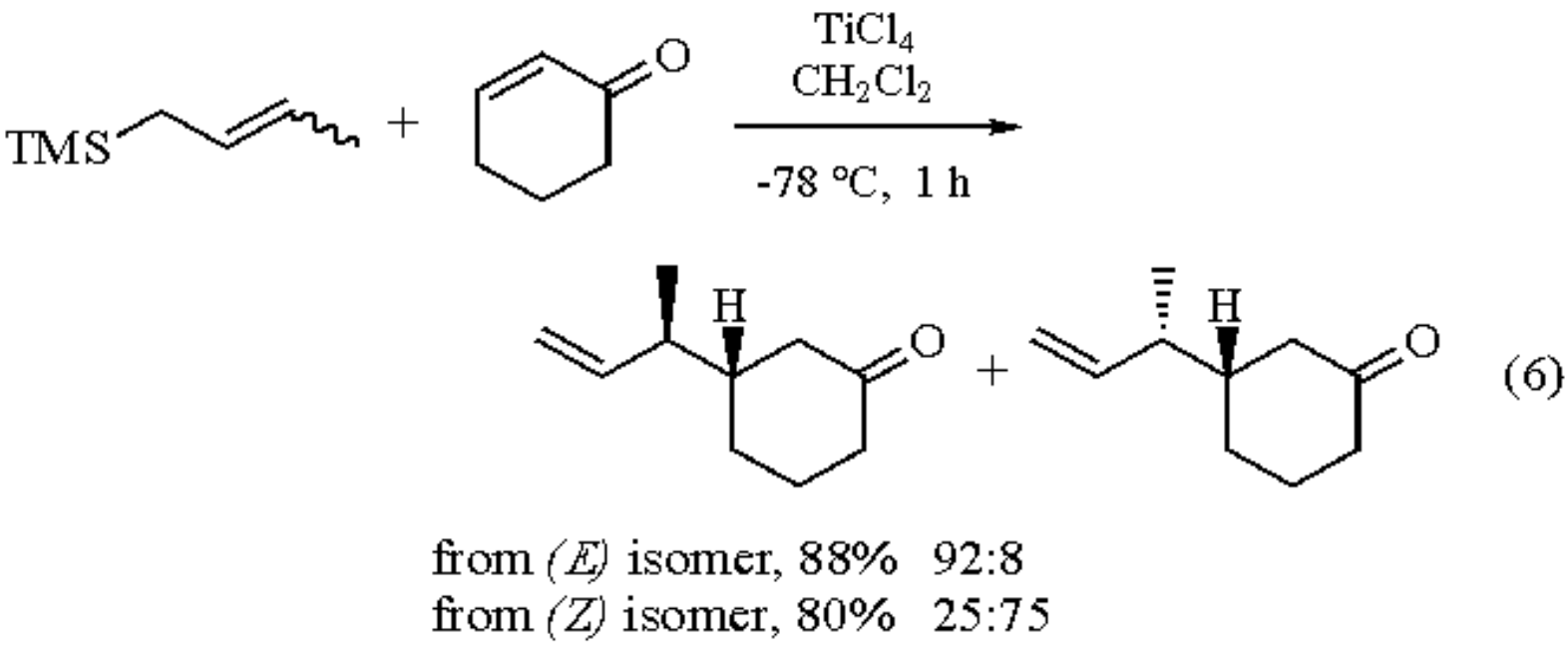

There is a trend for the (*E*)-crotylsilane to produce the *syn* and the (*Z*)-crotylsilane to produce the *anti* arrangement of substituents along the backbone, but in several reactions (for example, eq 5, R = *i*-Bu) the stereochemistry of the starting material appears to make no difference. The (*E*)-crotylsilane is more diastereoselective than the (*Z*)-crotylsilane. In the reaction with acetals (eq 5, R = Ph), substituents on the phenyl ring affect the diastereoselectivity.[17]

Suitable chiral electrophiles allow enantiocontrol as well as diastereocontrol. There are examples with aldehydes (eq 7),[20] glycal 3-acetates (eq 8),[21] acyliminium ions (eq 9),[22] and α,β-unsaturated sulfoxides.[23] Some tailoring of the substituents on the silicon atom can be helpful in achieving higher levels of diastereo- and enantiocontrol.[19,21]

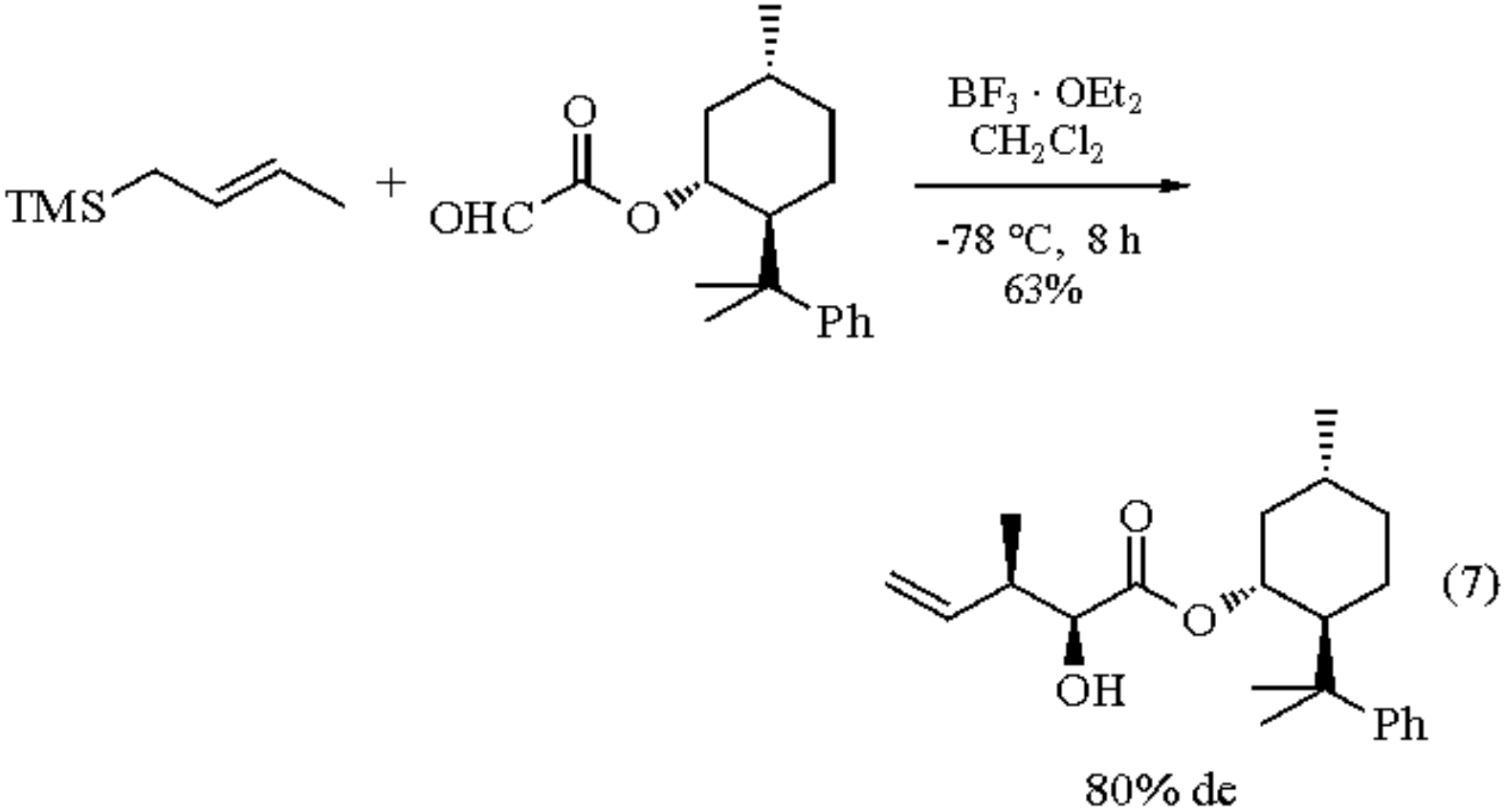

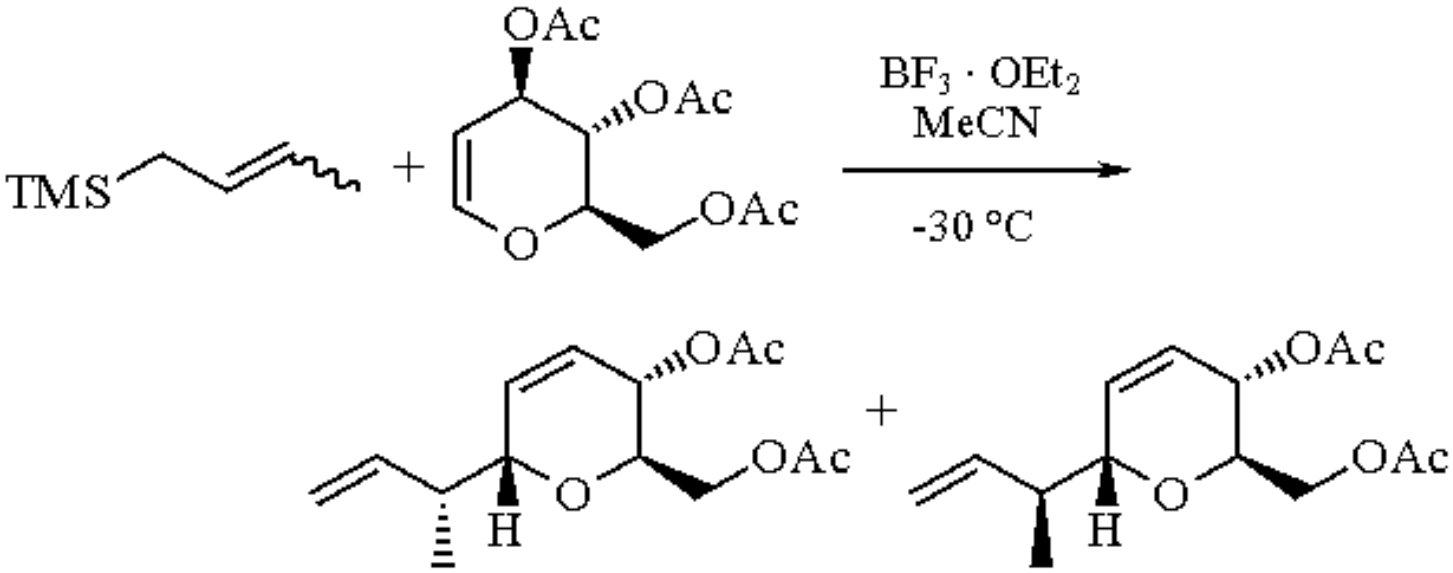

(8)

from *(E)* isomer, 58% 75:25
from *(Z)* isomer, 80% 25:75

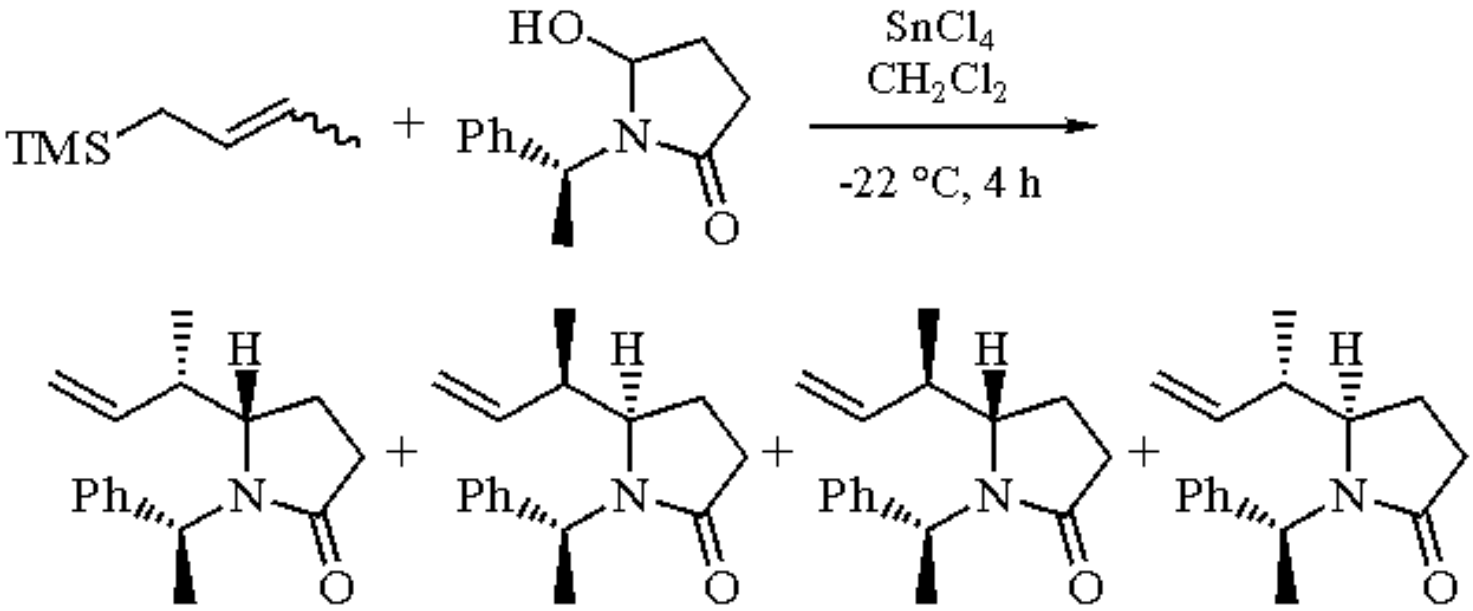

(9)

from *(E)*, 94% 79:11:7:3
from *(Z)*, 90% 20:62:5:13

Fluoride ion-catalyzed reactions of crotylsilanes are not regiospecific (eq 10), the ratio of the two products (**3**) and (**4**) being much the same whether crotyltrimethylsilane (**1**) or its regioisomer (**2**) is used.[24]

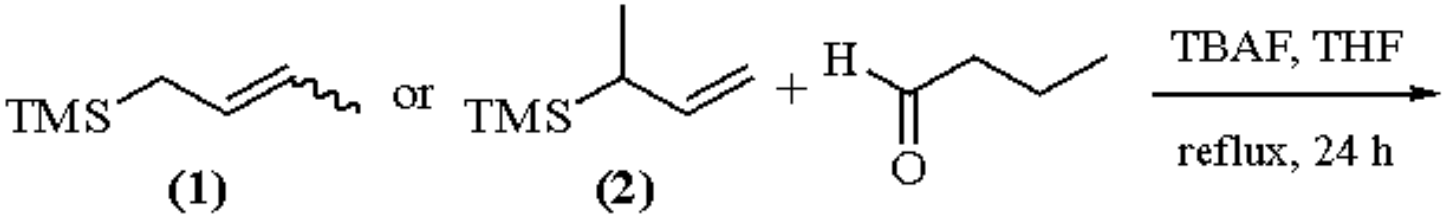

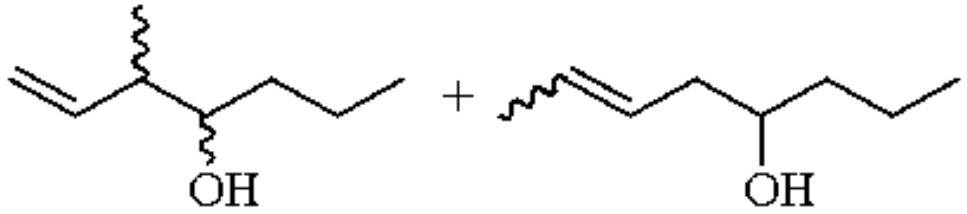

(10)

	(3)	(4)
from (1)	23%	37%
from (2)	30%	41%

As a Carbon Nucleophile in Reactions with Heteroatom Electrophiles.

Crotyltrimethylsilane reacts with nitrogen[25] and sulfur electrophiles with the usual allylic shift (eq 11). In the corresponding reactions with selenium,[26] tellurium,[27] and thallium[28] electrophiles the products are themselves allylically unstable, giving overall the products that appear simply to have replaced the silyl group with the electrophile.

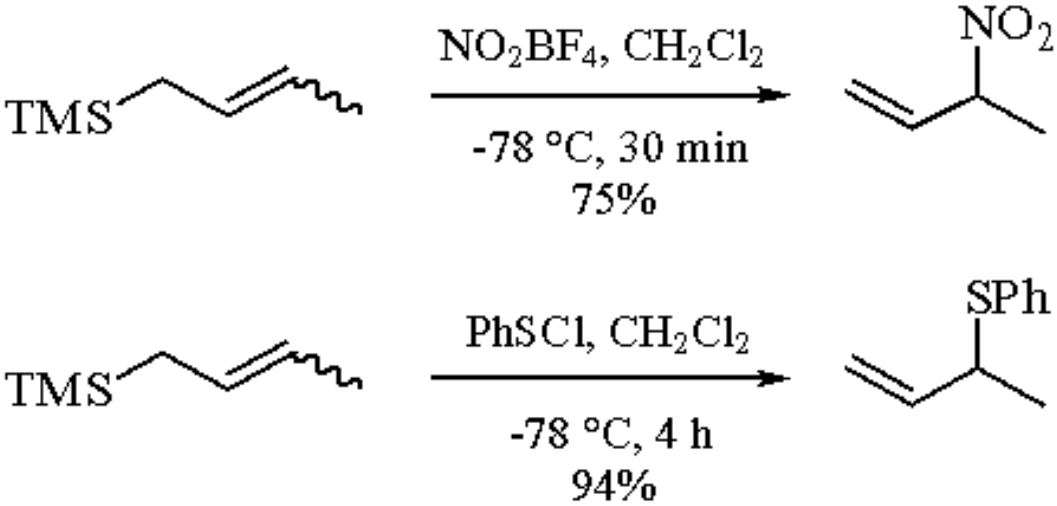

(11)

As a Source of the 1-Methyl-3-trimethylsilylallyl Anion.

The (*E*)- or (*Z*)-crotylsilanes react with ***n-Butyllithium*** and ***Potassium t-Butoxide*** (Schlosser's base) to give the corresponding allyl anions (**5**) and (**6**). Left for a few hours, these anions equilibrate to give largely the isomer (**6**).

Alkylation of either anion takes place α to the silyl group, to give new (*E*) or (*Z*) α-branched allylsilanes (eq 12).[4]

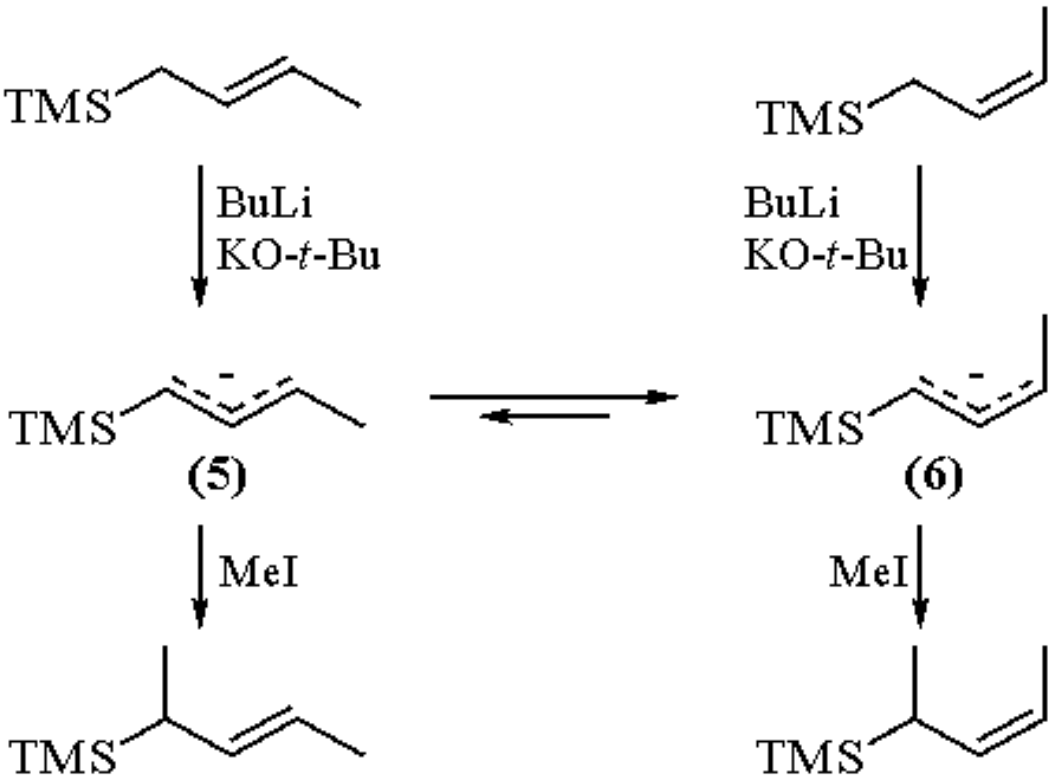

(12)

Related Reagents.

Allyltrimethylsilane; ***Crotyltributylstannane***.

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18-Crown-6

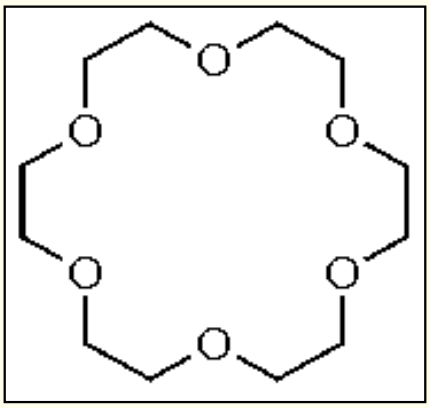

[17455-13-9] · $C_{12}H_{24}O_6$ · 18-Crown-6 · (MW 264.32)

(solubilization of a variety of metal salts, particularly potassium salts, in nonpolar solvents; activating agent for many nucleophilic substitutions and eliminations)

Physical Data: colorless, mp 36.5-38.0 °C; IR (neat) 2875, 1450, 1350, and 1120 cm^{-1}; ^1H NMR (60 MHz, CCl_4) 3.56 ppm (singlet).

Preparative Methods: commercially available. 18-Crown-6 has been synthesized by a variety of methods involving modified Williamson ether procedures.[1-6] Crude 18-crown-6 forms a crystalline complex with ***Acetonitrile*** from which the pure crown can be isolated.[4,5] 18-Crown-6 may also be isolated from the cyclic oligomerization of ***Ethylene Oxide*** in the presence of gaseous ***Boron Trifluoride*** and alkali metal cation templates such as $CsBF_4$.[7-10]

Handling, Storage, and Precautions: use in a fume hood.

Complexation with Metal Salts: Solubilities and Reactivities.

18-Crown-6 provides a simple and efficient means of solubilizing simple metal salts in nonpolar and dipolar aprotic solvents where solvation of the anionic portion of the salt should be minimal.[11] Indeed, this ligand is an effective catalyst in liquid-liquid and solid-liquid phase transfer catalysis.[12-14] Since 18-crown-6 has cavity dimensions (2.6-3.2 Å) of the same magnitude as the ionic diameter of the potassium cation (2.66 Å), it is usually more specific for potassium salts than other alkali metal salts. Nevertheless, 18-crown-6 is reasonably effective in complexing sodium and cesium salts as well. The solubilities of potassium salts in acetonitrile at 25 °C in the presence and absence of 18-crown-6 (0.15 M) are summarized in Table 1.[11]

Table 1 Solubilities of Potassium Salts in Acetonitrile at 25 °C in the Presence and Absence of 18-Crown-6

Salt	Sol. in 0.15 M 18-C-6 in MeCN	Sol. in MeCN
KF	0.0043	0.000318
KCl	0.0555	0.000243
KBr	0.135	0.00208
KI	0.202	0.105
KCN	0.129	0.00119
KOAc	0.102	0.00050
KN_3	0.138	0.00241
KSCN	0.850	0.755

The differences between the solubilities in the presence and the absence of crown are indications of the solubility enhancements due to the presence of 18-crown-6. The solubilities of ***Potassium Fluoride*** in benzene containing 18-crown-6 at concentrations of 1.01 M and 0.34 M are reported to be 0.052 M and 0.014 M, respectively, while the solubilities of potassium acetate in benzene containing 18-crown-6 at concentrations of 0.55 M and 1.0 M are reported to be 0.4 M and 0.8 M, respectively.[11] The solubilities of ***Lithium Fluoride***, ***Sodium Fluoride***, KF, RbF, and ***Cesium Fluoride*** in acetonitrile, ***Acetone***, THF, ***N,N-Dimethylformamide***, benzene, and cyclohexane have been determined in the presence and absence of 18-crown-6.[15]

The complexation and solubilization of metal salts by 18-crown-6 produces highly reactive anions. There are at least two factors that contribute the this enhanced reactivity. Since a nonpolar aprotic solvent such as benzene or a dipolar aprotic solvent such as acetonitrile should not have a great affinity for the anion, as compared to polar, protic media, the anion is not expected to be highly solvated. In addition, the increased physical separation of the cation from the anion as a result of the complexation should decrease the coulombic interaction between these oppositely charged species.[13] This latter effect is translated directly into a decrease in activation energy. As a consequence, the anion is a potent nucleophile as well as a potent base. These anionic species have been termed naked anions. Studies related to the relative nucleophilicities of naked anions toward benzyl tosylate in acetonitrile at 30 °C are summarized in Table 2.[11,13,16] Compared to polar, protic media, there seems to be a general leveling of nucleophilicities in acetonitrile. Several reversals of the usual order of nucleophilicities may be noted.

Table 2 Second-Order Rate Constants at 30 °C in Acetonitrile for the Reaction with Benzyl Tosylate

Nucleophile	k (M^{-1} s^{-1})	Relative rates
N_3^-	1.02	10.0
OAc^-	0.95	9.6
CN^-	0.23	2.4
Br^-	0.12	1.3
Cl^-	0.12	1.3
I^-	0.09	1.0
F^-	0.14	1.4
SCN^-	0.02	0.3

Reactions.

Halides.

Potassium fluoride reacts with a variety of organic substrates under solid-liquid phase transfer catalytic conditions[17] to give both substitution and elimination products (eq 1).

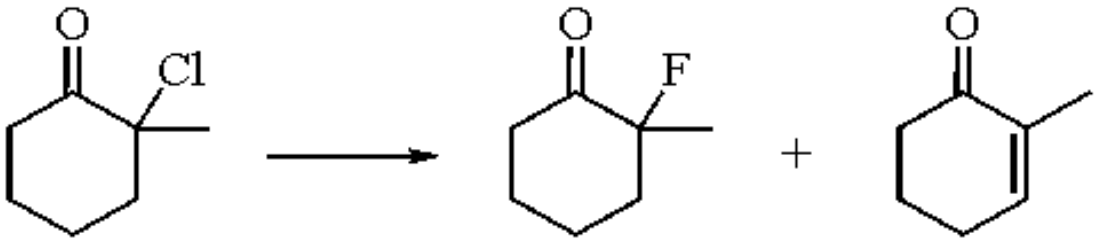

(1)

The σ-anionic complex (Meisenheimer complex) resulting from the reaction of fluoride with 2,4,6-trinitrofluorobenzene (**1**) in acetonitrile has been observed using ^1H and ^{19}F NMR spectroscopy.[18]

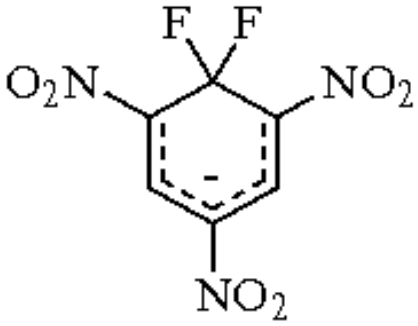

(1)

Potassium fluoride or cesium fluoride solubilized in toluene with 18-crown-6 induces alkyl- and aryl-group rearrangement on chloromethyl-substituted silanes.[19]

Oxygen Anions.

Acetate solubilized as the potassium salt in acetonitrile or benzene containing 18-crown-6 becomes sufficiently nucleophilic to react smoothly and quantitatively, even at room temperature, with a wide variety of organic substrates.[20,21] Substitution reactions at primary, secondary, tertiary, and benzylic positions have been demonstrated.[18] In certain cases, competing elimination processes are observed. Mixed anhydrides are formed in the reaction of the potassium or sodium salts of carboxylic acids with ***Ethyl Chloroformate***, cyanuric chloride, or ***Benzyl Chloroformate*** in acetonitrile in the presence of 18-crown-6.[22] Potassium phenylacetate has been reacted with a series of 2-bromo-substituted carbonyl compounds in the presence of 18-crown-6 to form aldehydo or keto esters which were subsequently cyclized to five-membered unsaturated lactones on further heating (eq 2).[23]

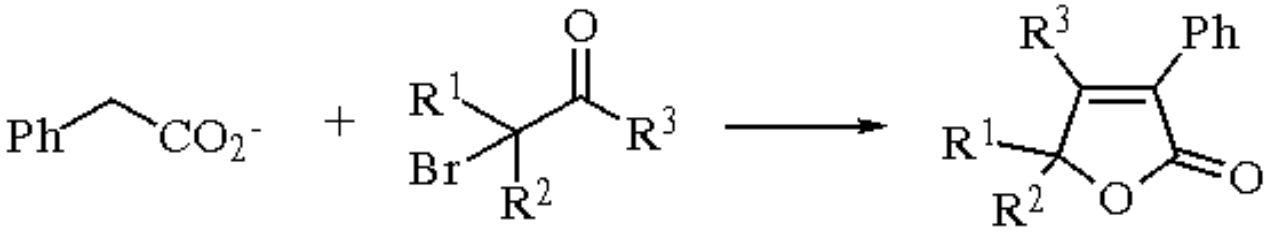

(2)

3-Bromoacetyl-7-methoxycoumarin is readily coupled with a wide variety of carboxylic acids in the presence of potassium bicarbonate and 18-crown-6[24] to form fluorescent derivatives. Reaction of alcohol mesylate with cesium acetate and 18-crown-6 in benzene is an effective method for the inversion of cyclopentyl and cyclohexyl alcohols.[25]

Reaction of 3-(bromomethyl)thiophene with the potassium salt of 4-cyano-4´-hydroxybiphenyl in THF, in the presence of 18-crown-6, produces high yields of the substitution product.[26]

Potassium Superoxide, dissolved in benzene, THF, or DMF using 18-crown-6, reacts with stoichiometric quantities of primary and secondary alkyl bromides to produce dialkyl peroxides.[27] The nucleophilic displacements by the superoxide radical anion and the intermediate alkyl peroxyanion on a chiral alkyl bromide ((*R*)-2-bromooctane) proceeds with inversion of configuration.[26] The nucleophilic reaction of alkyl halides, methanesulfonates, and tosylates in ***Dimethyl Sulfoxide***, DMF, or DME with 4 equiv of potassium superoxide in the presence of 18-crown-6 produces excellent yields of the corresponding alcohols (eq 3).[28,29]

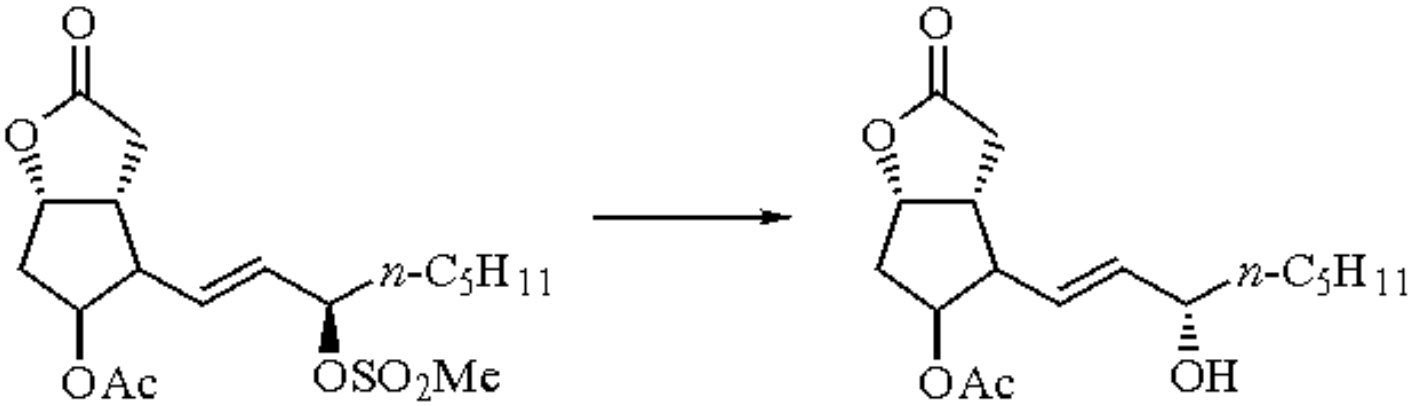

(3)

When secondary halides were used, some elimination products accompanied the formation of the alcohol product. In general, substrate reactivity varied as follows: benzyl > primary > secondary > tertiary > aryl and I > Br > OTs > Cl. Reaction of the tosylate of (+)-(*S*)-2-octanol with superoxide produced (-)-(*R*)-2-octanol.[28] The reaction of esters of carboxylic acids with approximately a threefold excess of potassium superoxide solubilized in benzene with 18-crown-6 produces, after acidic workup, the corresponding alcohols and carboxylic acids.[30] Reaction of superoxide with the acetate ester of (-)-(*R*)-2-octanol gave only (-)-(*R*)-2-octanol, indicating that the reaction proceeds by means of an acyl-oxygen cleavage.[29] Potassium superoxide dissolved in benzene with 18-crown-6 is an effective reagent for promoting the oxidative cleavage of α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids to carboxylic acids.[31]

18-Crown-6 enhances the rate of anionic oxy-Cope rearrangement by ion-pair dissociation.[32]

The reaction of ethyl tosylate and ***Ethyl Iodide*** with the sodium salt of ***Ethyl Acetoacetate*** in THF has been studied in the absence and presence of 18-crown-6. In the reaction with ethyl tosylate the presence of the crown increases the amount of oxygen alkylation. In contrast, the crown has little effect on the ratio of oxygen to carbon alkylation when ethyl iodide is used.[33]

An addition reaction of 3-benzyloxymethyl-3-methyloxetane with *S*-phenyl thioacetate in the presence of 18-crown-6/potassium phenoxide gave 3-benzyloxy-2-methyl-2-phenylthiomethylpropyl acetate in excellent yields.[34]

The dibenzyl ether of optically active diethyl tartrate has been prepared on a large scale using ***Sodium Hydride***, ***Benzyl Bromide***, ***Tetra-n-butylammonium Iodide***, and a catalytic quantity of 18-crown-6.[35]

Carbon Anions.

Potassium Cyanide dissolved in acetonitrile using 18-crown-6 reacts with a variety of alkyl halides to produce the corresponding alkyl cyanides.[36] As in the cases involving fluoride and acetate, some elimination processes accompanied substitution in certain cases. Under solid-liquid phase transfer catalytic conditions, primary alkyl chlorides react faster than bromides whereas the opposite is true for the corresponding secondary halides. ***Cyanotrimethylsilane*** has been synthesized from ***Chlorotrimethylsilane***.[37] *cis*-2-Chloro-4-methylcyclohexanone reacts with naked cyanide to exclusively produce the substitution product.[11] Hydrocyanation of α,β-unsaturated nitriles and ketones with naked cyanide in the presence of ***Acetone Cyanohydrin*** has been reported (eq 4).[38]

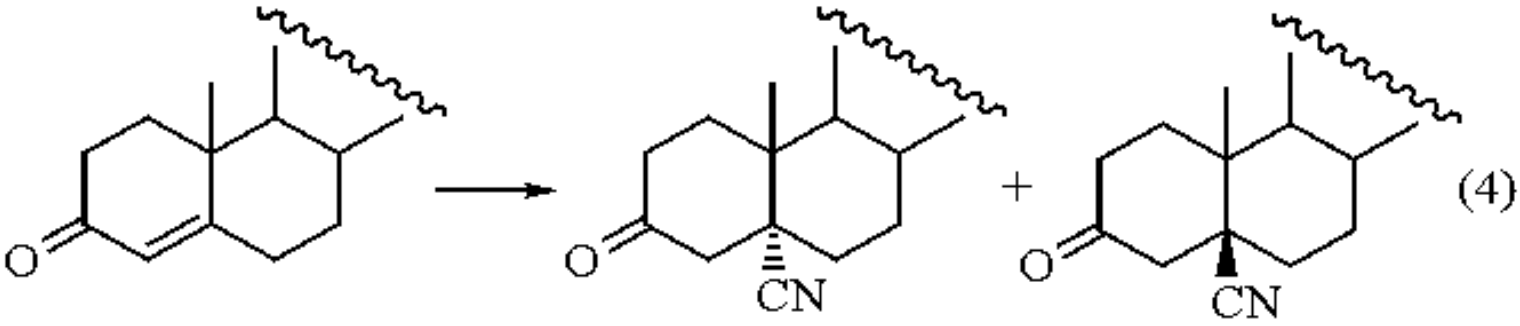

Either 1,4-, 2,4-, or 1,5-hexadiene has been deprotonated with Cs 18-crown-6 solutions to produce hexadienyl anions.[39]

The isomerization of 2-methylbicyclo[2.2.1]hepta-2,5-diene to 5-methylenebicyclo[2.2.1]hept-2-ene using excess ***Potassium t-Butoxide*** in DMSO in the presence and in the absence of an equivalent concentration of 18-crown-6 has been investigated (eq 5).[40] In the absence of crown, the order with respect to the base changed from zero order at high concentrations to first order at more dilute concentrations. In the presence of crown, the order with respect to base remained first order at all reported concentrations.

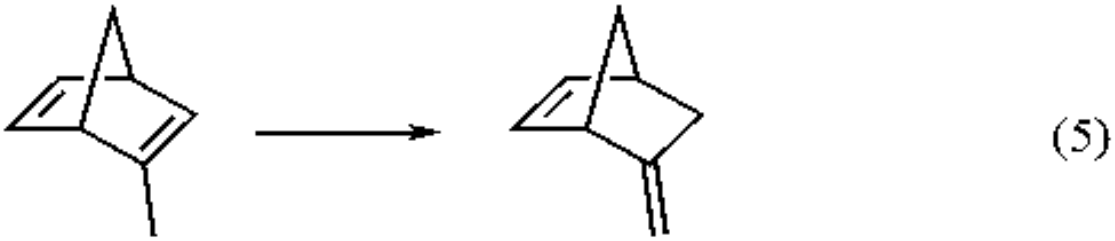

2,2,3-Triphenylpropylcesium rearranges in THF at 65 °C with 96% 1,2-migration of phenyl, whereas the corresponding lithium salt rearranges with at least 98% 1,2-migration of benzyl at 0 °C. The addition of 18-crown-6 as a ligand for the potassium and cesium salts significantly increases the extent of 1,2-benzyl migration.[41]

Treatment of trimethylsilyl trichloroacetate with α,α,α-trifluoroacetophenone in the presence of catalytic quantities of 18-crown-6 and ***Potassium Carbonate*** at 150 °C, followed by treatment with methanolic ***Potassium Hydroxide*** at 50 °C, produced excellent yields of Mosher's acid (α-methoxy-α-(trifluoromethyl)phenylacetic acid).[42]

18-Crown-6 is an effective catalyst in the dialkylation of *o*-nitrophenacyl derivatives.[43]

Nitrogen Anions.

N-Propargylpyrrole was prepared by the reaction of pyrrole with powdered potassium hydroxide in toluene, catalyzed by 18-crown-6.[44]

The reaction of naked nitrite with primary alkyl halides forms nitro compounds as the major product; the major byproducts are nitrite esters.[23]

Excellent yields of *N*-alkylation products were obtained in the reaction of dry alkali metal salts of 2-nitroimidazoles and methyl bromoacetate under homogeneous conditions at room temperature in the presence of 18-crown-6 in acetonitrile.[45]

Organic carbamates have been prepared in good yields from the reaction of primary amines, carbon dioxide, and an alkyl

halide in the presence of 18-crown-6.[46]

Nitrogen Cations.

Photolysis of 1-aminopyridinium salts, 2-aminoisoquinolinium salts, and 1-aminoquinolinium salts is reported to give aniline or a mixture of 2-, 3-, and 4-toluidines in benzene-trifluoroacetic acid or in toluene-trifluoroacetic acid.[47] An intermediate nitrenium ion is postulated. The presence of 18-crown-6 increases the yields of the above products.

Indazoles are produced in good yields from the reaction of *o*-methyl- and *o*-ethylbenzenediazonium tetrafluoroborates with two equivalents of potassium acetate in the presence of catalytic quantities of 18-crown-6 in ethanol-free chloroform.[48]

Other Anions.

Reaction of potassium dihydrogenphosphide with aromatic esters in the presence of 18-crown-6 produces potassium benzoylphosphide.[49] Reaction of potassium dihydrogenphosphide with diethyl phthalate produces the potassium 18-crown-6 complex salt of the 2*H*-isophosphindoline-1,3-dione ion (**2**).[50]

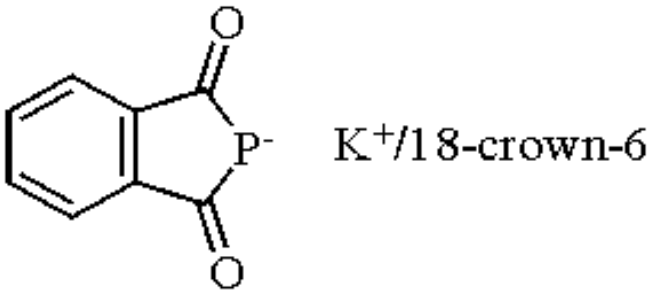

(2)

Reductions.

Alkoxysulfonium salts dissolved in methylene chloride are smoothly reduced with ***Sodium Cyanoborohydride*** dissolved in methanol or ethanol in the presence of 18-crown-6.[51] Even in the presence of aldehydes or ketones, only reduction of alkoxysulfonium salt was observed.

The titanium complex generated by the reaction of ***Dichlorobis(cyclopentadienyl)titanium*** with ***Sodium Borohydride*** promotes hydroboration of alkenes and alkynes in the presence of 18-crown-6.[52,53]

Radical anions of mesitylene, toluene, and benzene are formed in the reaction with alkali metals and 18-crown-6.[54] The alkyl-oxygen bond of oxetane is cleaved with K^-/K^+ and Na^-/K^+ complexes in which the potassium cation has been complexed with 18-crown-6 to form an organometallic alkoxide.[55]

Hydrosilylation of carbonyl groups with ***Dimethyl(phenyl)silane*** proceeds in methylene chloride, benzene, or THF, in the presence of catalytic quantities of cesium, rubidium, or potassium fluoride/18-crown-6.[56]

Oxidations.

The homogeneous photosensitization of oxygen by solubilizing the anionic dyes Rose Bengal and Eosin Y in methylene chloride and ***Carbon Disulfide*** using 18-crown-6 has been reported. The presence of singlet ***Oxygen*** was demonstrated by trapping with anthracene and tetramethylethylene.[57]

The carbanions from tri- and diarylmethanes are generated and oxidized to triaryl carbinols and diaryl ketones, respectively, using potassium hydroxide/DME/18-crown-6 in the presence of oxygen.[58]

Chromium(VI) Oxide, in the presence of 18-crown-6 catalyst in methylene chloride, is an efficient oxidizing system for the chemoselective oxidation of thiols to disulfides.[59]

Eliminations.

The generation of free carbenes was demonstrated in the reaction of ***Potassium t-Butoxide*** with ***Chloroform***, α-bromo-α-fluorotoluene, and α,α-dichlorodimethyl sulfide in the presence of 18-crown-6 from competitive reactivities toward alkenes.[60,61] ***Diazomethane*** was synthesized in 48% yield from the reaction of ***Hydrazine*** hydrate, chloroform, and potassium hydroxide in ether in the presence of catalytic quantities of 18-crown-6.[62]

Reaction of *exo*-2-norbornyl-*exo*-3*d* tosylate with the sodium salt of 2-cyclohexylcyclohexanol in triglyme produces norbornene containing no deuterium. This represents an exclusive *syn* elimination process.[63] In the presence of 18-crown-6, 27% of the product contains deuterium, thus indicating some *anti* elimination.[63] The results were interperted in terms of the effects of crown on base association and ion-pairing.

Polymerization.

In the polymerization of methacrylic esters and hindered alkyl acrylates, the presence of 18-crown-6 produces living polymers in apolar solvents, such as toluene, and at temperatures as high as 0 °C.[64] The polymerization of β-lactones proceeds smoothly in the presence of ***Potassium Naphthalenide*** only after the addition of a cation complexing ligand such as 18-crown-6.[65] The anionic polymerization of ***Propylene Oxide*** and ethylene oxide is catalyzed by the potassium salt of methoxypropanol in the presence of 18-crown-6.[66] The monomer 5-(bromomethyl)-1,3-dihydroxybenzene undergoes self-condensation in the presence of potassium carbonate and 18-crown-6 to give hyperbranched polyethers.[67] The synthesis of soluble, substituted silane high polymers by Wurtz coupling techniques is facilitated by the presence of 18-crown-6.[68] Interfacial polycondensation to produce poly(arylcarboxylate)s,[69] polyphosphates,[70] and polyphosphonates[46] has been studied in the presence of 18-crown-6. Polycondensations of 4-bromomethylbenzyl bromide were carried out with 4,4´-oxydibenzenesulfinate in the presence of 18-crown-6.[71]

Reactions on Polymers.

18-Crown-6 facilitates the alkaline hydrolysis of nitrile groups in acrylonitrile-divinylbenzene copolymer.[72] Starting from linear polycarbonate, carbonate-formal copolymers were prepared by reaction with ***Dibromomethane***, potassium hydroxide, and 18-crown-6.[73] Polystyrene has been successfully grafted onto carbon whiskers by anionic graft polymerization of styrene in which OLi groups on the surface of the carbon whiskers are activated by 18-crown-6.[74] The reaction of chloromethylated poly(styrene-*co*-divinylbenzene) with potassium superoxide in the presence of 18-crown-6 has been reported.[75]

Related Reagents.

Dibenzo-18-crown-6; ***Dicyclohexano-18-crown-6***; ***Potassium t-Butoxide-18-Crown-6***; ***Potassium Carbonate-18-Crown-6***; ***Potassium Hydroxide-18-Crown-6***.

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12-Crown-4

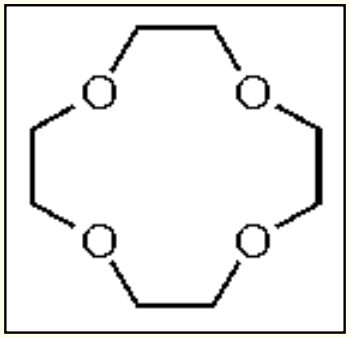

[294-93-9] · $C_8H_{16}O_4$ · 12-Crown-4 · (MW 176.21)

(lithium-selective complexing agent, useful for activation and solubilization of lithium salts such as cyanide, diisopropylamide, and aluminium hydride, as well as organolithium reagents and lithium enolates)

Physical Data: bp 67-70 °C/0.5 mmHg, 118-119 °C/15 mmHg; IR (neat, NaCl plates) 2925, 1465, 1365, 1280, 1250, 1130, 1100, 1095, and 920 cm^{-1}; ^1H NMR 3.65 ppm (sharp singlet); ^{13}C NMR ($CDCl_3$) 70.621 ppm.

Preparative Methods: 12-crown-4 has been synthesized by a variety of modified Williamson ether procedures;[1,2] 12-crown-4 is also formed in the cyclic oligomerization of ***Ethylene Oxide*** using gaseous ***Boron Trifluoride***;[3] commercially available.

Handling, Storage, and Precautions: hygroscopic; use in a fume hood.

Complexation With Metal Salts.

The cavity diameter of 12-crown-4 is estimated to be 1.2-1.5 Å, which is ideal for complexing with a lithium cation which has an ionic diameter of 1.36 Å. While the selectivity of 12-crown-4 for lithium salts is well documented, this macrocyclic multidentate ligand will also effectively complex with other alkali metal cations.[4,6] The selectivities of 12-crown-4 for a wide variety of metal cations have been estimated from solvent extraction studies of metal picrates.[5]

Reactions.

The cycloaddition of 2-phenylallylmagnesium phenoxide and *trans*-stilbene in THF is better catalyzed by ***15-Crown-5*** than 12-crown-4.[6] No reaction takes place in the absence of a ligand or in the presence of 18-crown-6.

12-Crown-4 dissolves the alkali metals ***Sodium***, ***Potassium***, rubidium, and cesium to produce blue solutions

containing metal cations, metal anions, electrons, and cation-electron pairs.[7]

The reaction of ***Lithium Cyanide*** with enol trifluoromethanesulfonates in benzene solvent at rt in the presence of 12-crown-4 and ***Tetrakis(triphenylphosphine)palladium(0)*** gives good to excellent yields of the corresponding unsaturated nitrile (eq 1).[8]

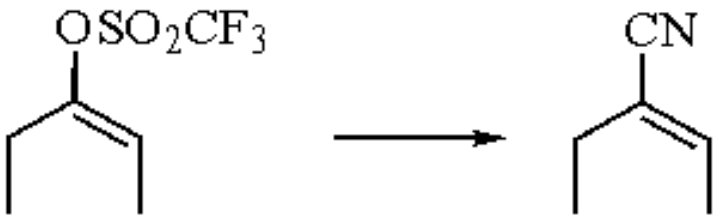

(1)

Deprotonation of tropinone with ***Lithium Diisopropylamide*** followed by reaction with ***Methyl Cyanoformate*** in the presence of 12-crown-4 resulted in ring opening with the formation of a pyrrolidine derivative (eq 2).[9]

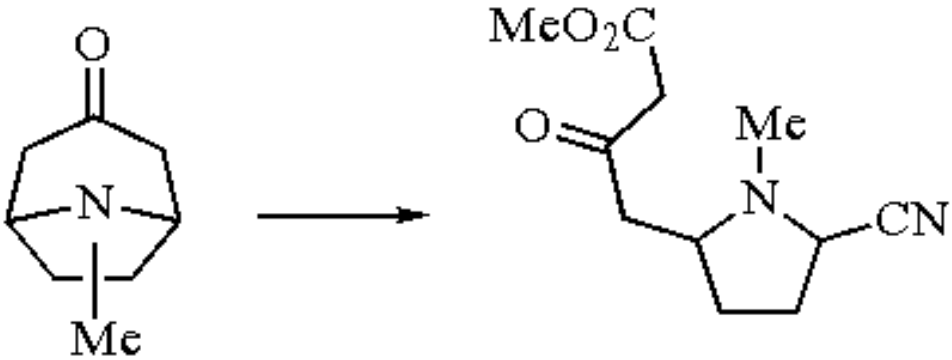

(2)

1,1-Dichloroallyllithium preferentially reacts at the γ-position with substituted benzaldehydes and acetophenone. In the presence of 12-crown-4 the selectivity toward the α-position is significantly increased.[10]

The regiochemistry of ring opening of 1,2-epoxides can be controlled by the presence of a chelating species. *cis*-4-(Benzyloxy)-1,2-epoxycyclohexane reacts with ***Lithium Aluminum Hydride*** to produce 3-benzyloxycyclohexanol almost exclusively. In the presence of premixed LAH and 12-crown-4 the major product was 4-benzyloxycyclohexanol (eq 3).[11]

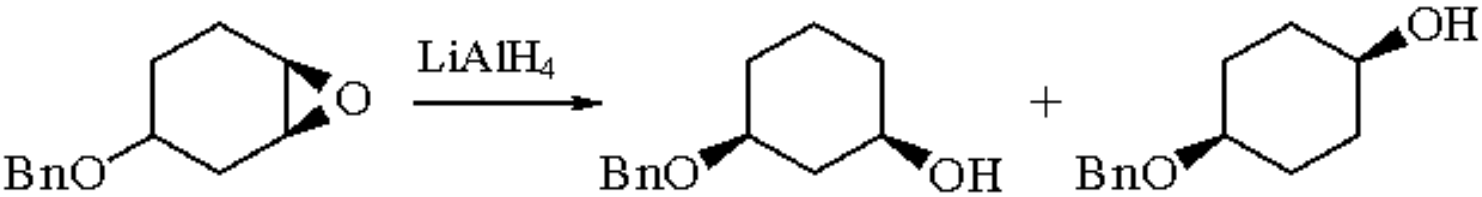

(3)

ether	98:2
ether/12-crown-4	18:82

12-Crown-4 enhances the rate of the α-chymotrypsin-catalyzed transesterification of *N*-acetyl-L-phenylalanine ethyl ester with propan-1-ol in octane. Studies with subtilisin indicate that the catalytic effects of crown are much less pronounced.[12]

The lithium enolate of the acetonide of (*S*,*S*)-dimethyl tartrate was prepared by treatment with LDA in the presence of 12-crown-4. Addition of this enolate to acetonylacetone followed by treatment of the product with acid gave a mixture of cyclized adducts from which a single diastereoisomer was isolated (eq 4).[13] The reaction failed in the absence of 12-crown-4.

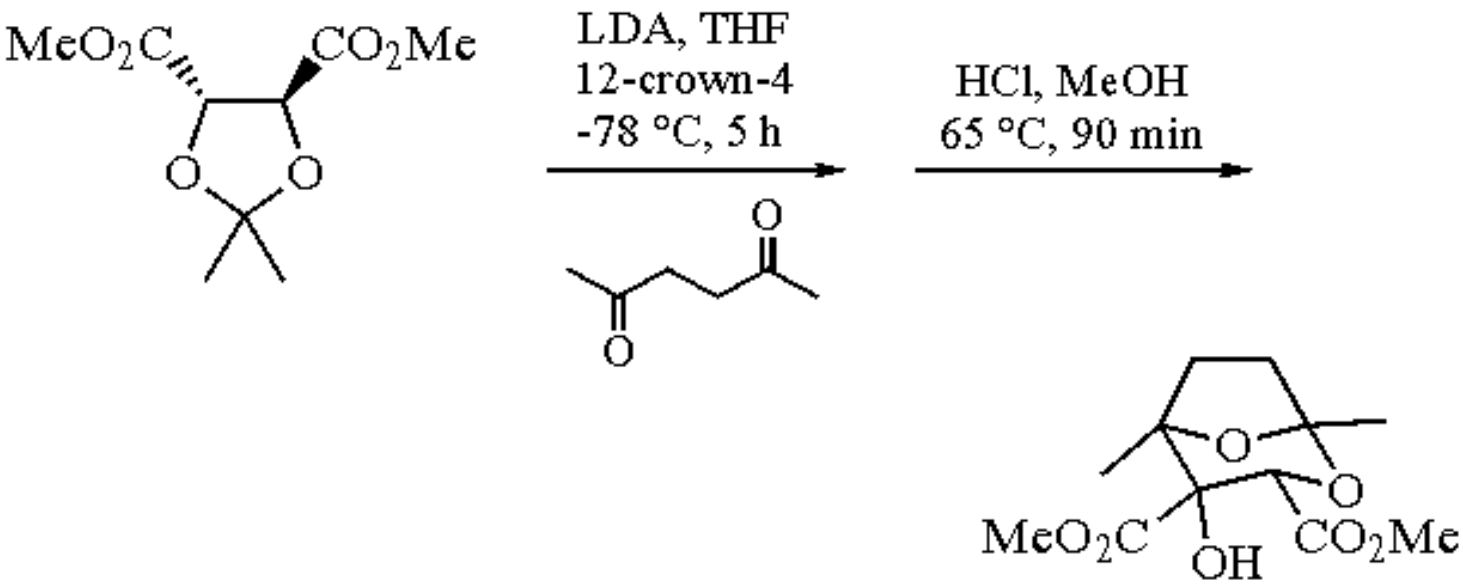

(4)

Related Reagents.

15-Crown-5; ***Hexamethylphosphoric Triamide***; ***N,N´-Dimethylpropyleneurea***; ***N,N,N´,N´-Tetramethylethylenediamine***.

---

1. Cook, F. L.; Caruso, T. C.; Byrne, M. P.; Bowers, C. W.; Speck, D. H.; Liotta, C. L. *TL* **1974**, 4029.
2. Johns, G.; Ransom, C. J.; Reese, C. B. *S* **1976**, 515.
3. Dale, J.; Daasvatn, K. *CC* **1976**, 295.
4. Pacey, G. E., Wu, Y. P. *Talanta* **1984**, *31*, 165.
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13. Aggarwal, V. K.; Wang, M. F.; Zaparucha, A. *CC* **1994**, 87.

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15-Crown-5

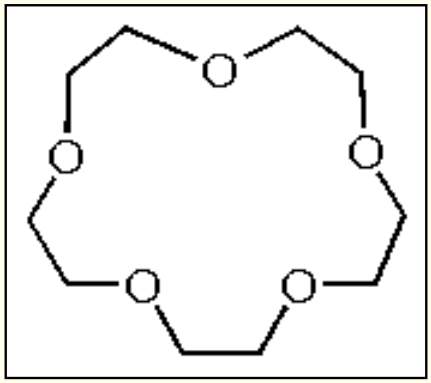

[33100-27-5] · $C_{10}H_{20}O_5$ · 15-Crown-5 · (MW 220.27)

(sodium-selective complexing agent used for the activation of various sodium salts such as the hypochlorite, sulfide, hydroxide, and imidazolide; phase transfer catalyst; activation of potassium and magnesium reagents)

Physical Data: bp 78 °C/0.05 mmHg; IR (CCl_4, 0.1 mm NaCl cell) 2875, 1445, 1350, 1280, 1250, 1185, 975, and 925 cm^{-1}; ^1H NMR (CCl_4) 3.58 ppm (sharp singlet); ^{13}C NMR ($CDCl_3$) 70.621 ppm.

Preparative Methods: 15-crown-5 has been synthesized by a variety of methods involving modified Williamson ether procedures;[1,2] in addition, 15-crown-5 is formed from the cyclic oligomerization of ***Ethylene Oxide*** in the presence of gaseous ***Boron Trifluoride***;[3] commercially available.

Handling, Storage, and Precautions: use in a fume hood.

Complexation With Metal Salts.

The cavity diameter of 15-crown-5 is estimated to be 1.7-2.2 Å, which is ideal for complexing with a sodium cation (ionic diameter of 1.94 Å). While the selectivity of 15-crown-5 for sodium salts is well documented, this macrocyclic multidentate ligand will also effectively complex with other alkali metal cations.[4]

Reactions.

The cycloaddition of 2-phenylallylmagnesium phenoxide and *trans*-stilbene in THF is better catalyzed by 15-crown-5 than 12-crown-4.[4] No reaction takes place in the absence of a ligand or in the presence of 18-crown-6 (eq 1).

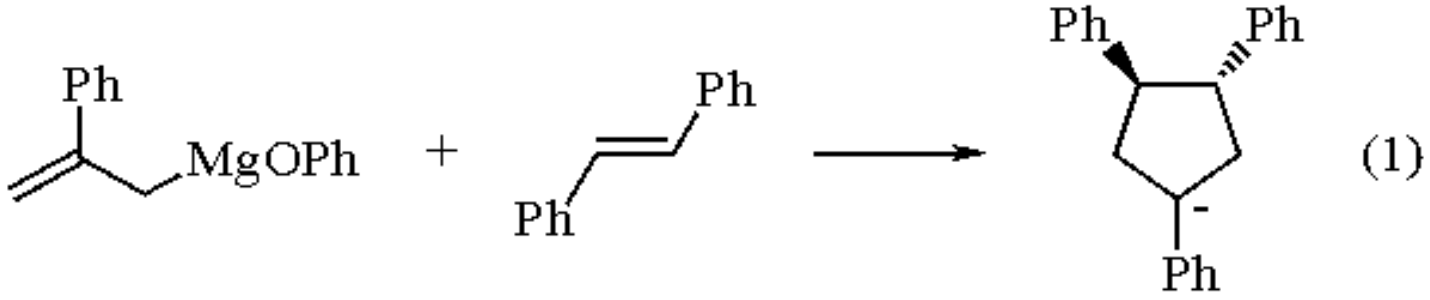

The benzylation of ***Potassium Thiocyanate*** yields benzyl thiocyanate as the kinetic product and benzyl isothiocyanate as the thermodynamic product. Solid-liquid phase-transfer catalytic reaction of ***Benzyl Chloride*** with potassium thiocyanate produces approximately a 50/50 mixture of the two products in the presence of 15-crown-5.[5] ***Dibenzo-18-crown-6*** produces substantially more of the isothiocyanate (eq 2).

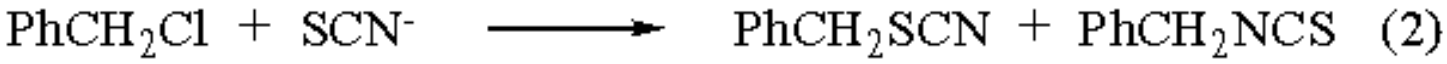

The preparation of *N*-(arylsulfonyl)sulfoximines by oxidation of the sulfilimines with ***Sodium Hypochlorite*** in an aqueous methylene chloride-ethyl acetate two-phase system in the presence of 15-crown-5 has been reported (eq 3).[6]

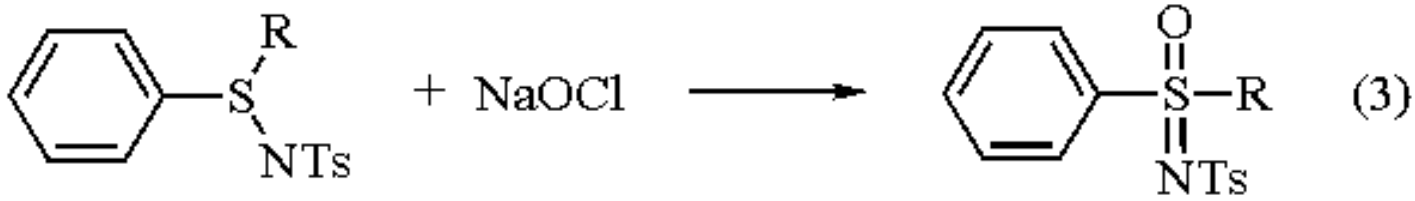

4,4´-Dicyanodiphenyl thioether was prepared in excellent yield from the reaction of 4-cyanochlorobenzene and ***Sodium Sulfide*** in dipolar, aprotic solvents (DMF, *o*-dichlorobenzene) at 200 °C in the presence of 15-crown-5 (eq 4).[7]

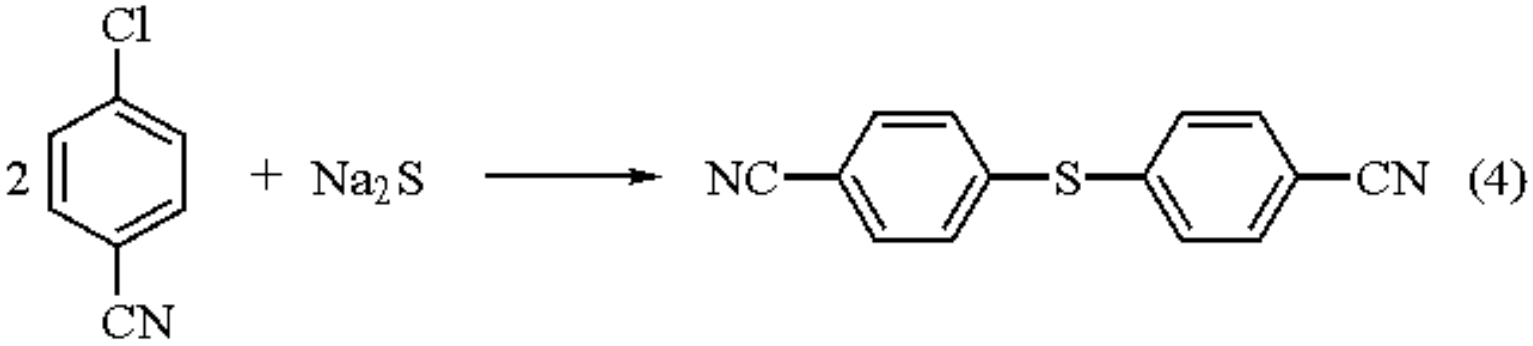

The Wittig rearrangement of the phenyl ether of 9-fluorenol was investigated under solid-liquid phase transfer catalytic conditions using solid, powdered base and an organic phase in the presence of crown ethers (eq 5). In the presence of ***Potassium Hydroxide*** the order of effectiveness is: dibenzo-18-crown-6 < ***Dicyclohexano-18-crown-6*** < 15-crown-5 < ***18-Crown-6***. In the presence of ***Sodium Hydroxide*** the order of effectiveness is: ***12-Crown-4*** < 18-crown-6 < 15-crown-5.[8]

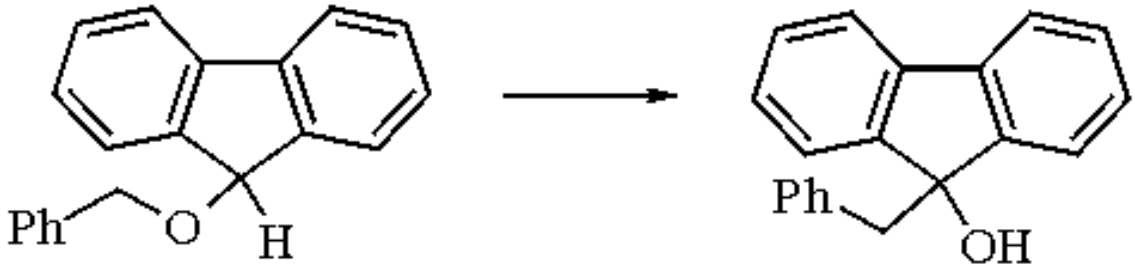

(5)

The sodium salt of theophylline undergoes *N*-alkylation with 1-chloro-4-iodobutane in acetonitrile in the presence of 15-crown-5. The resulting chloride reacts smoothly with the potassium salt of 2-nitroimidazole, again in the presence of 15-crown-5, to give the second *N*-alkylation (eq 6).[9]

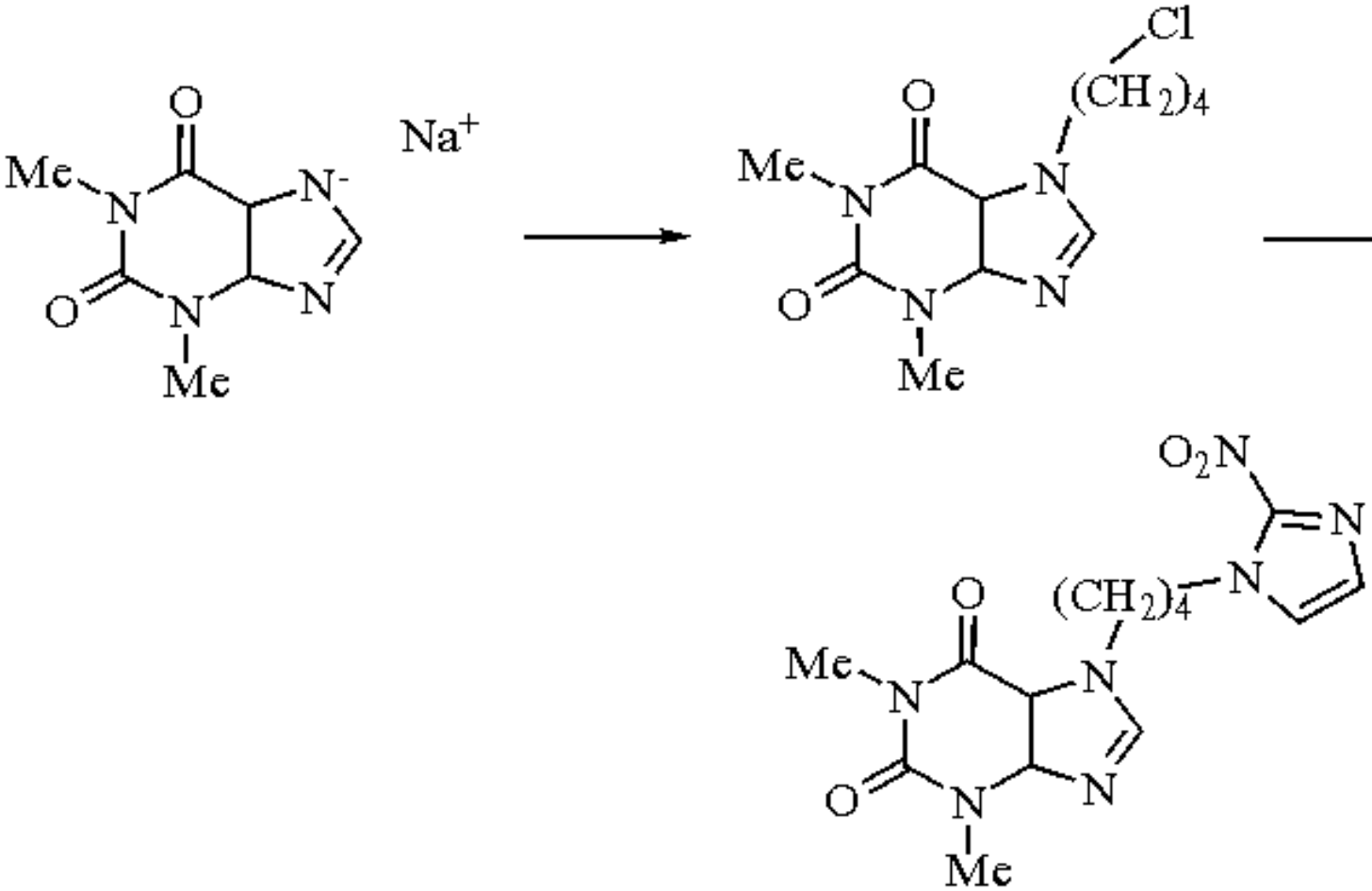

(6)

The polymerization of phenylmethyldichlorosilane with sodium metal (Wurtz Coupling) in toluene/heptane solvent has been found to be catalyzed by 15-crown-5.[10]

Related Reagents.

12-Crown-4; ***18-Crown-6***; ***Hexamethylphosphoric Triamide***.

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1. Cook, F. L.; Caruso, T. C.; Byrne, M. P.; Bowers, C. W.; Speck, D. H.; Liotta, C. L. *Tl* **1974**, 4029.
2. Johns, G.; Ransom, C. J.; Reese, C. B. *S* **1976**, 515.
3. Dale, J.; Daasvatn, K. *CC* **1976**, 295.
4. Liotta, C. L. In *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M.; Christensen, J. J., Eds.; Academic: New York; pp. 111-205.
5. Dehmlow, E. V.; Torossian, G. O. *ZN(B)* **1990**, *45b*, 1091.
6. Akutagawa, K.; Furukawa, N. *JOC* **1984**, *49*, 2282.
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Cumyl Hydroperoxide[1]

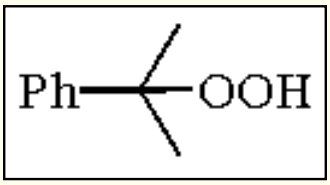

[80-15-9] · $C_9H_{12}O_2$ · Cumyl Hydroperoxide · (MW 152.19)

(oxidant useful for metal-catalyzed enantioselective epoxidation of allylic alcohols[2] and enantioselective oxidation of sulfides to sulfoxides[3])

Alternate Name: cumene hydroperoxide.

Physical Data: mp 44-45 °C; bp 100-101 °C/8 mmHg; *d* 1.030 g cm^{-3}; flash point 56 °C.

Solubility: sol most organic solvents; slightly sol H_2O (15 g L^{-1}).

Form Supplied in: a colorless to light yellow solution consisting of 80% cumene hydroperoxide in cumene; widely available.

Analysis of Reagent Purity: iodometric titration.[4,5]

Handling, Storage, and Precautions: cumyl hydroperoxide (CHP) is an unusually stable hydroperoxide which is resistant but still susceptible to induced explosive decomposition.[6] Like most alkyl hydroperoxides, CHP should be stored cold (ca. 0 °C) in the absence of light in a container, such as a polyethylene bottle, that is unlikely to shatter if there is pressure build up. Exposing pure or concentrated solutions of CHP to heat, acid, reducing materials, and transition metal salts should be avoided. Upon completion of reactions involving CHP, steps should be taken to destroy any remaining reagent safely. This can usually be done by exposing the reaction mixture to a mild reducing agent such as aqueous sodium sulfite, methyl sulfide, or triphenylphosphine.

Enantioselective Epoxidation of Allylic Alcohols.

While ***t-Butyl Hydroperoxide*** (TBHP) is most often used in the Sharpless-Katsuki asymmetric epoxidation of allylic alcohols to give scalemic epoxy alcohols, CHP is sometimes used to advantage.[4] For example, CHP is reported to epoxidize allyl alcohol and methallyl alcohol enantioselectively, with yields higher than TBHP (eq 1). Epoxidation with CHP is also apparently faster than with TBHP. In general, CHP can substitute for TBHP without loss of enantioselectivity.

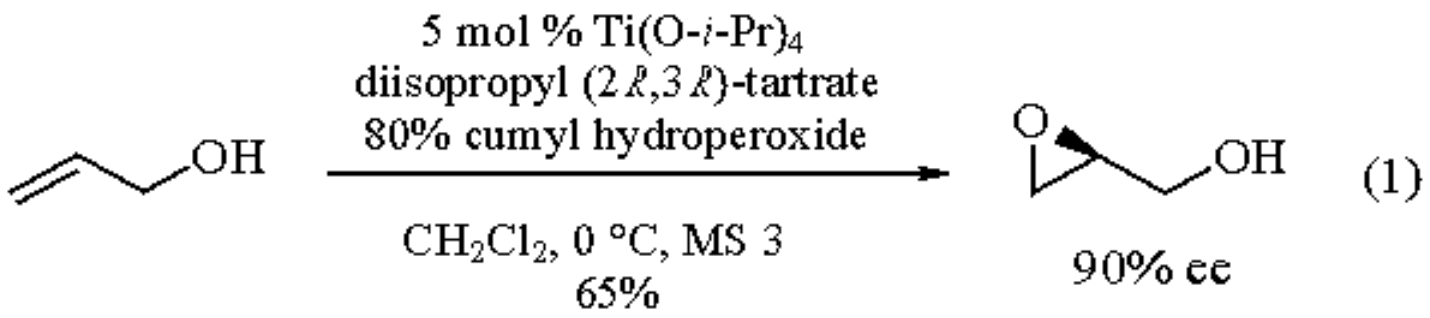

Enantioselective Oxidation of Sulfides to Sulfoxides.

CHP[3] has been shown to be superior to TBHP[7] as the oxidant for the enantioselective oxidation of prostereogenic sulfides to scalemic sulfoxides using ***Titanium Tetraisopropoxide***, diethyl tartrate, and water (eq 2).[8]

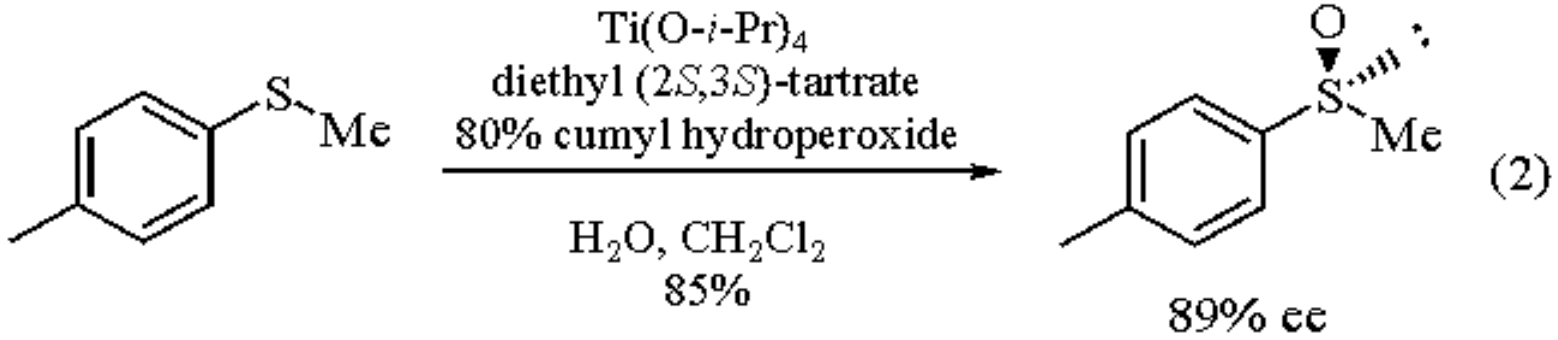

Related Reagents.

t-Butyl Hydroperoxide; ***Triphenylmethyl Hydroperoxide***.

---

1. (a) Patai, S. *The Chemistry of Hydroxy, Ether and Peroxide Groups*; Wiley: New York, 1993. (b) Patai, S. *The Chemistry of Peroxides*; Wiley: New York, 1983. (c) Swern, D. *Organic Peroxides*; Wiley: New York, 1970; Vol. 1. (d) Swern, D. *Organic Peroxides*; Wiley: New York, 1970; Vol. 2. (e) Swern, D. *Organic Peroxides*; Wiley: New York, 1972; Vol. 3. (f) *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley: New York, 1982; Vol. 17, pp 27-90. (g) Davies, A. G. *Organic Peroxides*; Butterworths: London, 1961. (h) Hawkins, E. G. E. *Organic Peroxides*; Spon: London, 1961. (i) Tobolsky, A. V.; Mesrobian, R. B. *Organic Peroxides*; Interscience: New York, 1954.
2. Woodward, S. S.; Finn, M. G.; Sharpless, K. B. *JACS* **1991**, *113*, 106.
3. Zhao, S. H.; Samuel, O.; Kagan, H. B. *T* **1987**, *43*, 5135.
4. (a) Mair, R. D.; Graupner, A. J. *Anal. Chem.* **1964**, *36*, 194. (b) Banerjee, D. K.; Budke, C. C. *Anal. Chem.* **1964**, *36*, 2367.
5. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *JACS* **1987**, *109*, 5765.
6. The explosion of a cumyl hydroperoxide manufacturing facility was recently reported. See *Chem. Eng. News* **1993**, *71* (22), 4; **1993**, *71* (42), 4.
7. (a) Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *JACS* **1984**, *106*, 8188. (b) Duñach, E.; Kagan, H. B.

NJC **1985**, *9*, 1. (c) Kagan, H. B.; Duñach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S. H. *PAC* **1985**, *57*, 1911.
8. Zhao, S. H.; Samuel, O.; Kagan, H. B. *OS* **1990**, *68*, 49.

Bryant E. Rossiter&dead;

Brigham Young University, Provo, UT, USA

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Cyanamide

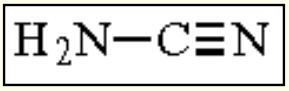

[420-04-2] · CH_2N_2 · Cyanamide · (MW 42.04)

(ammonia equivalent, urea equivalent, guanidine equivalent; sulfur bioequivalent)

Alternate Names: cyanoamine; carbodiimide.

Physical Data: mp 45-46 °C; bp 83 °C/380 mmHg; moist white crystals.[1]

Solubility: sol 100 g/100 g H_2O at 43 °C; also sol alcohols, amines, ethers, ketones, ethyl acetate; sparingly sol benzene and halogenated hydrocarbons; insol cyclohexane.

Form Supplied in: pure hygroscopic solid; 50% aq. solution; salts: sodium, calcium, lead, etc.

Preparative Method: widely available. A checked literature preparation is available.[2] Calcium salt is prepared from calcium carbide and nitrogen.

Handling, Storage, and Precautions: hygroscopic, caustic, highly toxic (LD_{50} rats 125 mg/kg), readily absorbed through the skin, produces dermatitis; polymerizes violently above melting point; should be stored in a cool, dry place. Incompatibilities are: various metals, acids, bases, strong oxidizing and reducing agents[1]. Use in a fume hood.

Because of its amphoteric nature, cyanamide displays both nucleophilic and electrophilic characteristics. This property makes it a useful reagent for the preparation of a variety of heterocycles.

Condensation Reactions.

Cyanamide will undergo cyclization reactions with ketols, thioketones, amino ketones, and related functionalities to yield the respective amino azoles (eqs 1-4).[3-6]

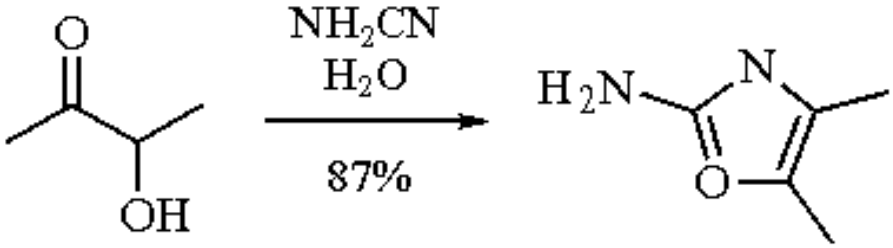

(1)

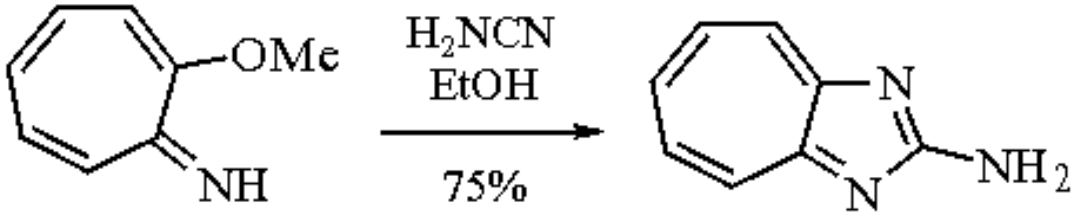

(2)

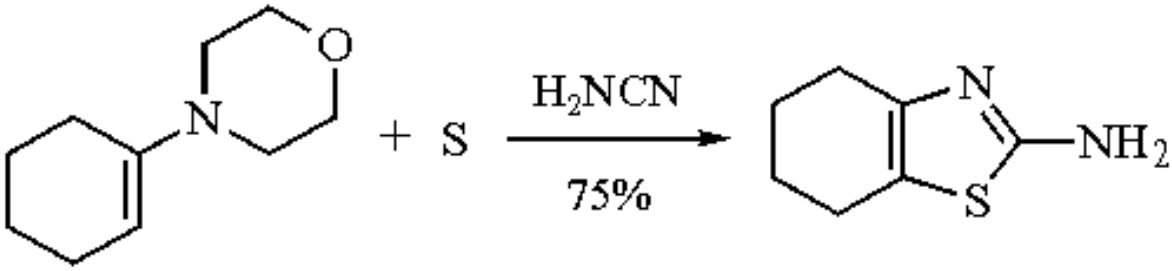

(3)

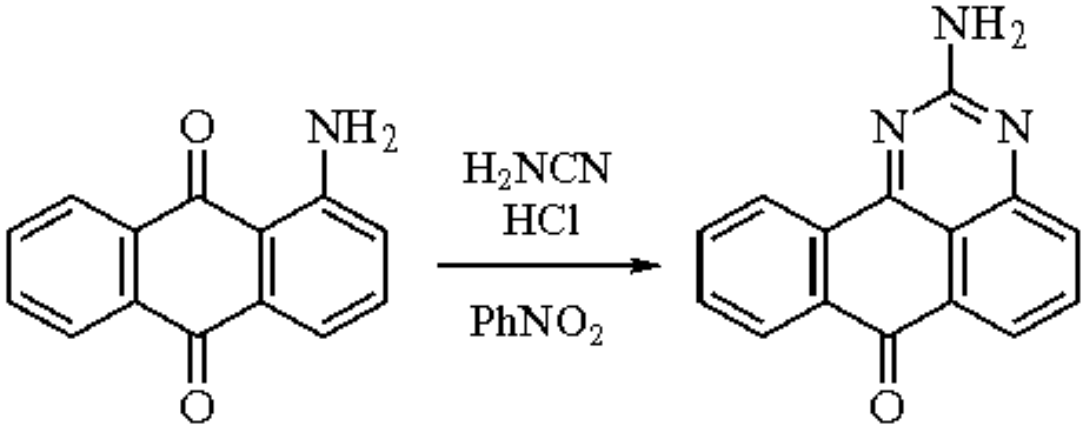

(4)

Nucleophilic Additions.

Cyanamide efficiently adds to a variety of electrophilic functionalities. Thiocyanates react with silver cyanamide to give unusual cyanocarbodiimides, albeit in low yield (eq 5).[7]

$$\text{R-NCS} + \text{Ag}_2\text{NCN} \longrightarrow \text{RNCNCN} + \text{Ag}_2\text{S} \qquad (5)$$

Xanthates and thiono esters undergo addition displacement reactions with potassium cyanamide (eqs 6 and 7).[8]

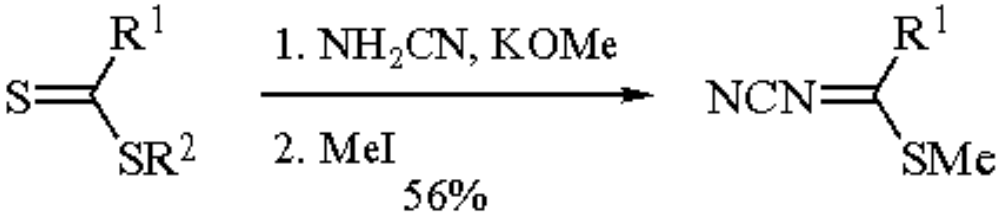

(6)

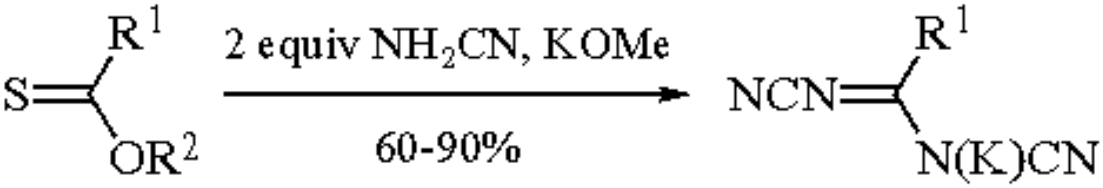

(7)

Thioureas react with lead cyanamide to give the *N*-cyanoguanidines. This technique was utilized in the preparation of the first H_2 blocker, cimetidine (eq 8).[9]

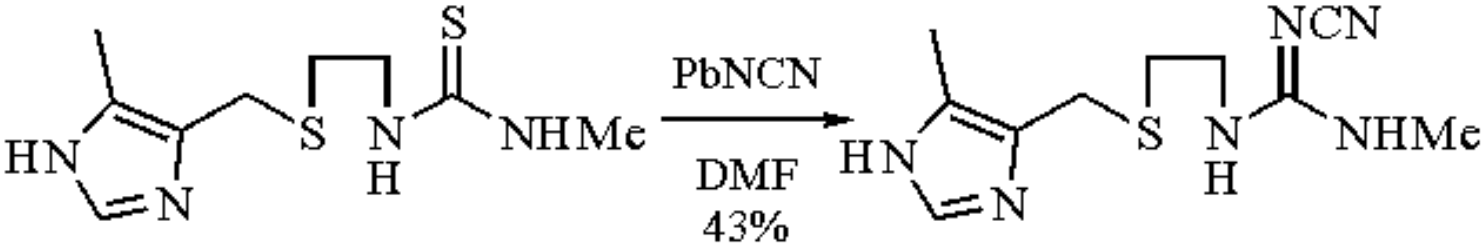

(8)

Carbodiimides bearing electron-withdrawing aryl groups can be converted to the respective cyanoguanidines with cyanamide (eq 9).[10]

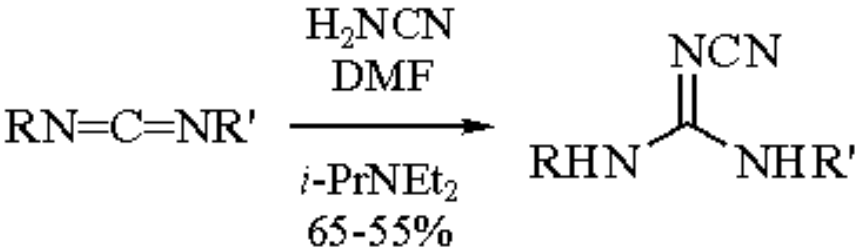

(9)

Orthoesters add cyanamide in the presence of acetic anhydride to give *N*-cyanoimino esters (eq 10).[11]

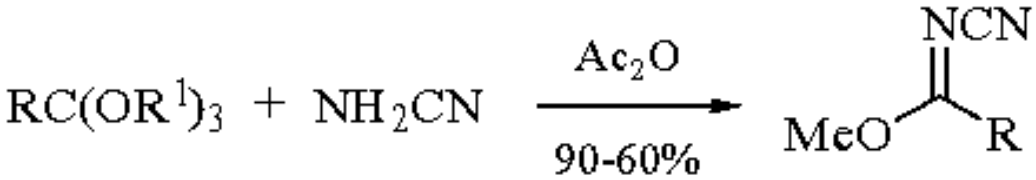

(10)

N-Cyanoimino esters and related thioesters are useful intermediates for the preparation of a variety of heterocycles, as shown in (eq 11).[12]

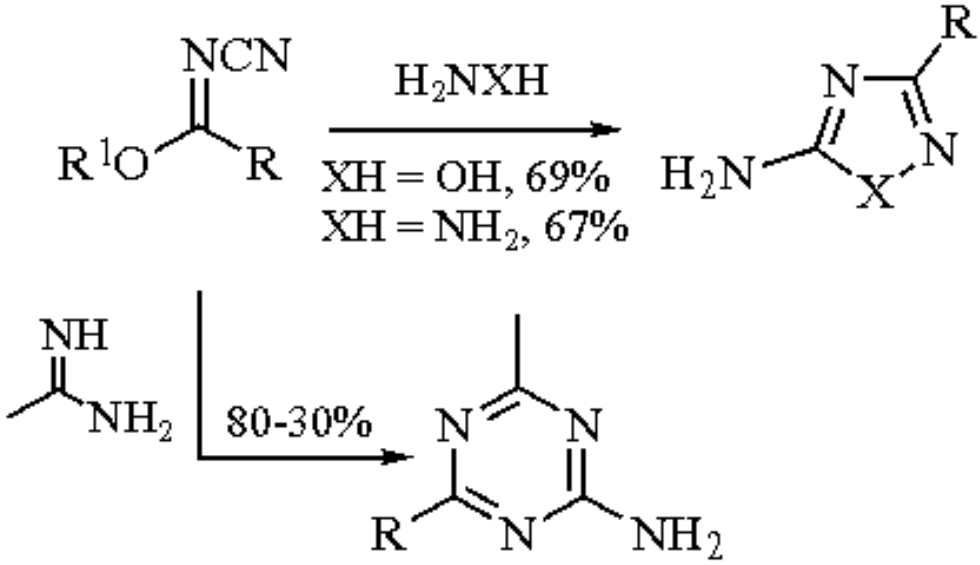

(11)

Cyanamide and the respective sodium salts have been found to add to β-keto esters and 4-pyranones (eqs 12 and 13).[13-15]

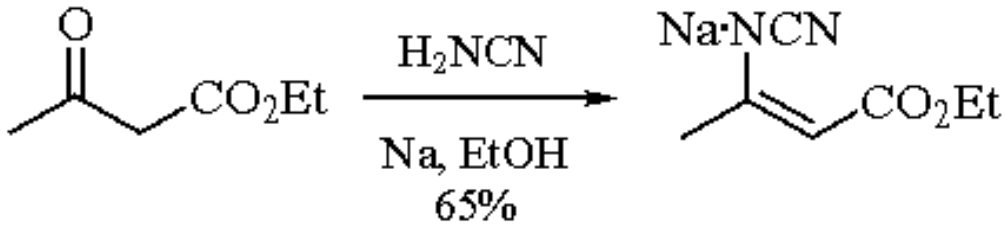

(12)

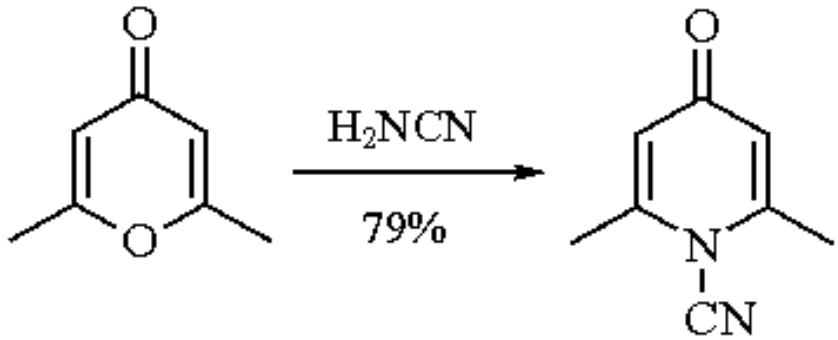

(13)

Disubstituted cyanamides are synthesized by direct alkylation of sodium cyanamide (eqs 14-16)[14,15] (also see von Braun reaction as an alternative).[15c]

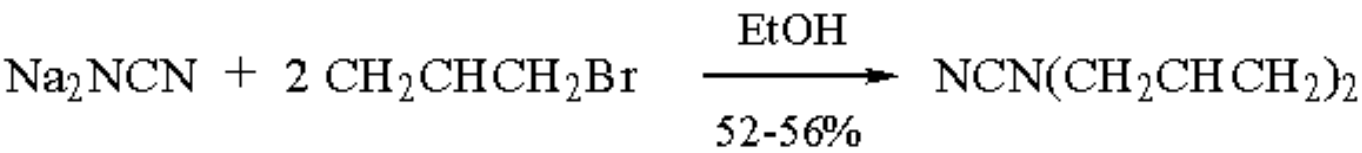

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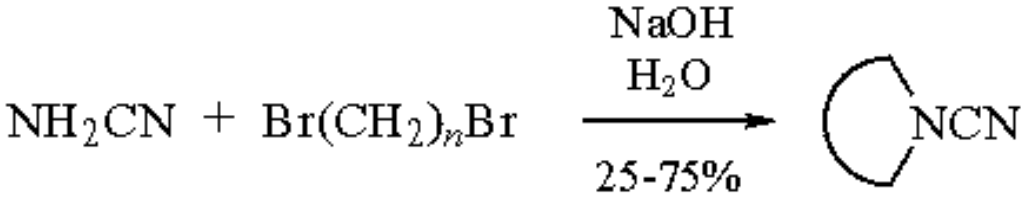

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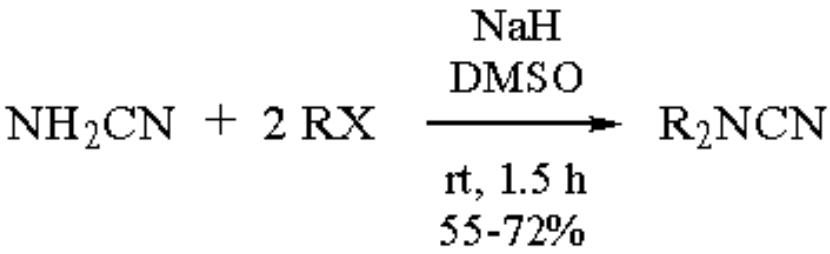

(16)

These cyanamides can be readily hydrolyzed to the respective amines (eq 17).[14,15]

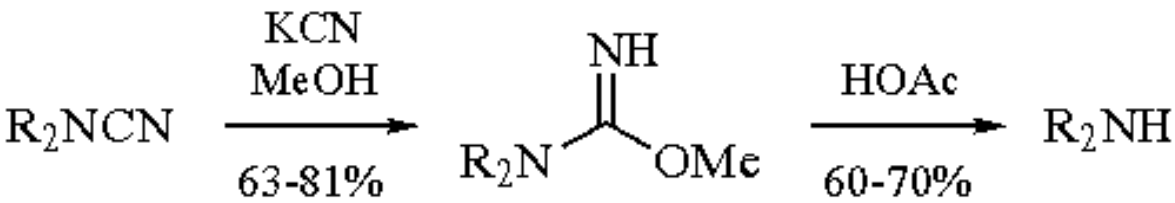

(17)

Calcium cyanamide can be acylated with ***Benzoyl Chloride*** to give the *N*-cyanoamide (eq 18).[16]

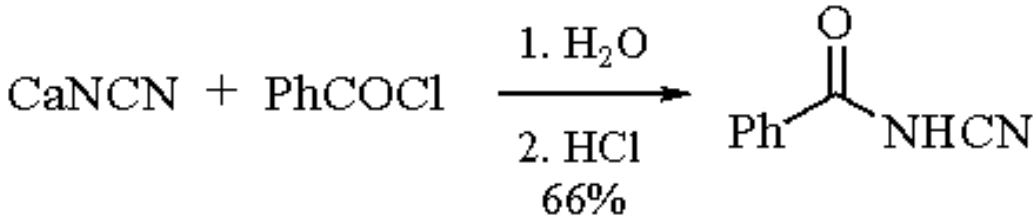

(18)

Cyanamide readily adds to alkenes in the presence of ***N-Bromosuccinimide*** to give the 1,2-*trans*-bromocyanamides.[17] These bromocyanamides can be converted to 1,2-*cis*-diamines in one of two similar three-step procedures, or the bromide may be reductively removed to yield the amines (eqs 19 and 20).[17] The above reactions are reported for a number of alkenes with yields ranging from 35-70%.

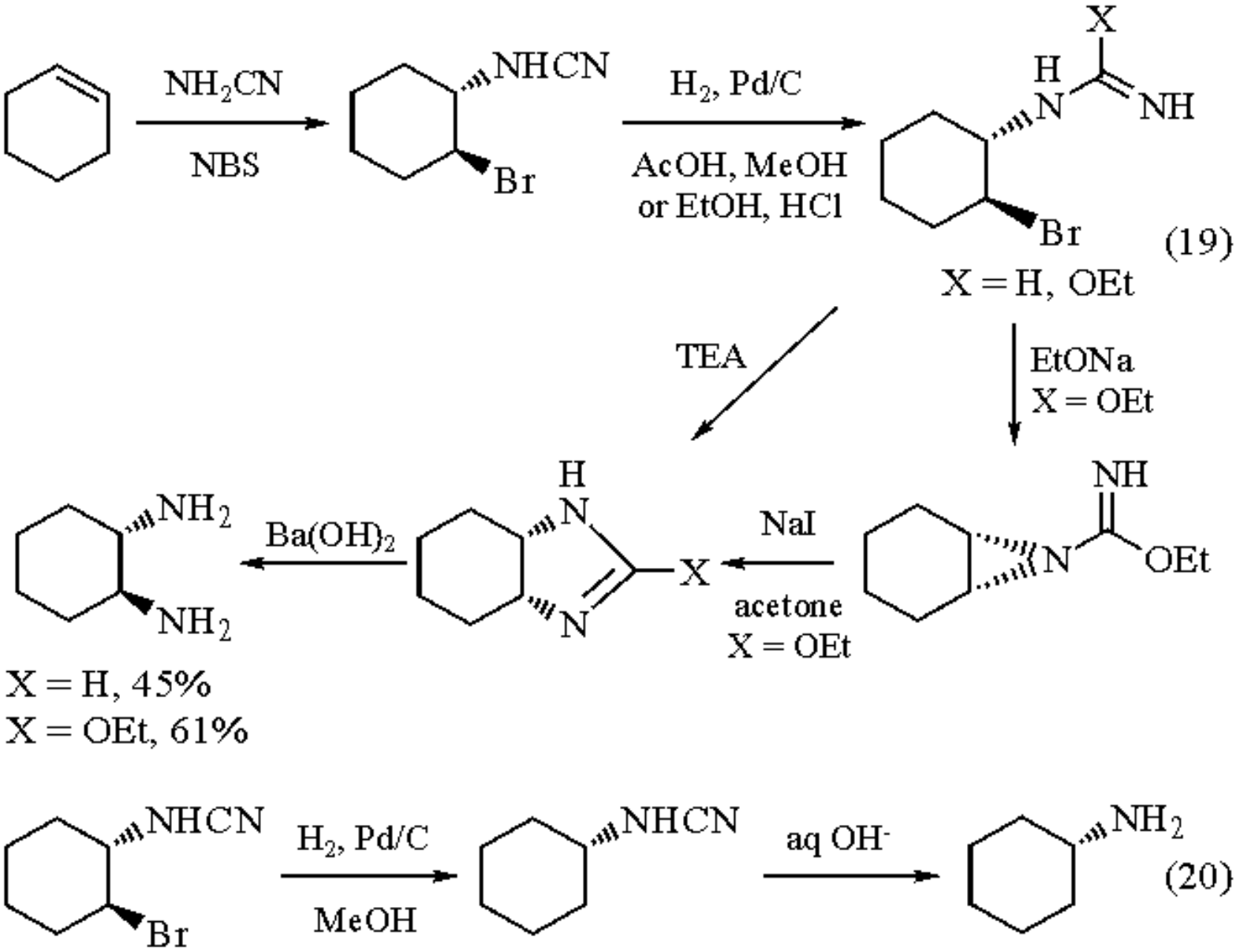

Electrophilic Additions.

Amines, hydrazines, thiols, and alcohols add to cyanamide to give guanidines and pseudourea ethers (eqs 21-23).[18-20]

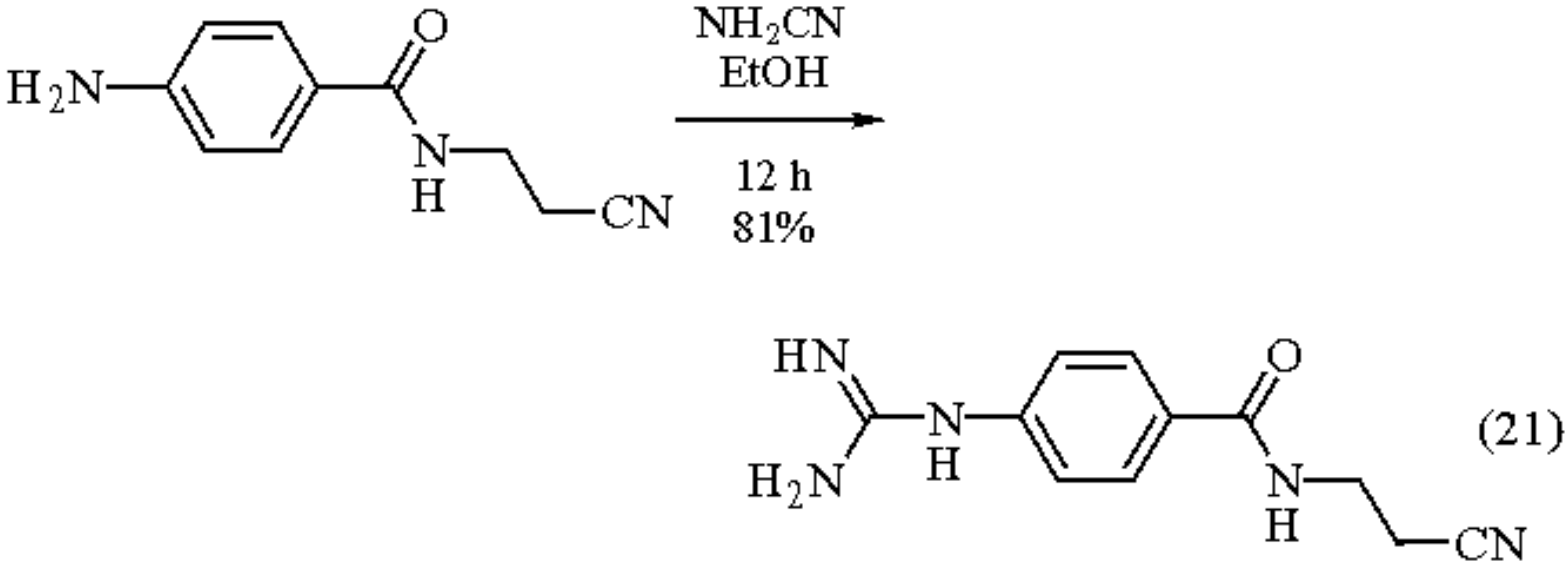

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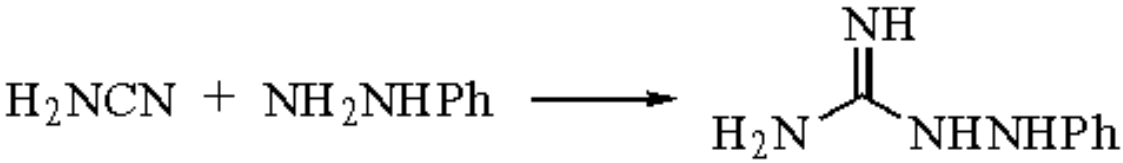

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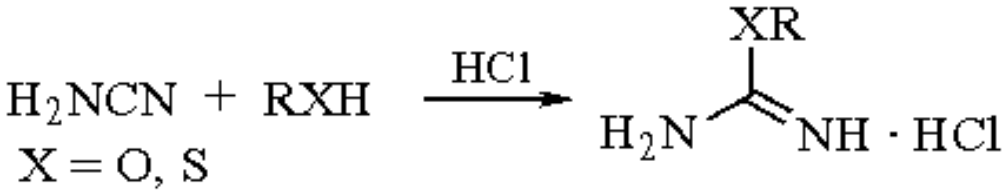

(23)

Cyanamide can also undergo bis addition with diamines to yield amino heterocycles (eqs 24 and 25).[21,22]

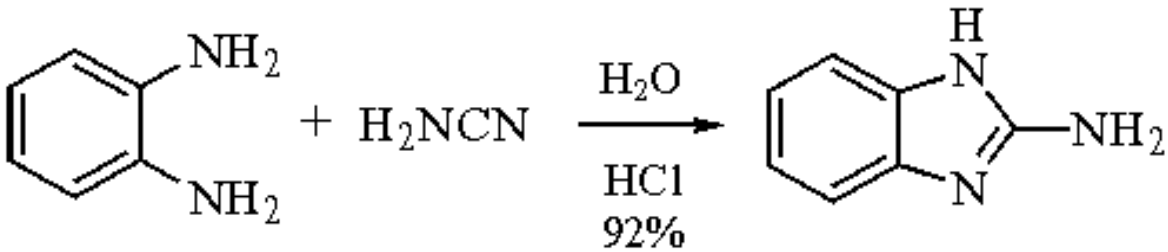

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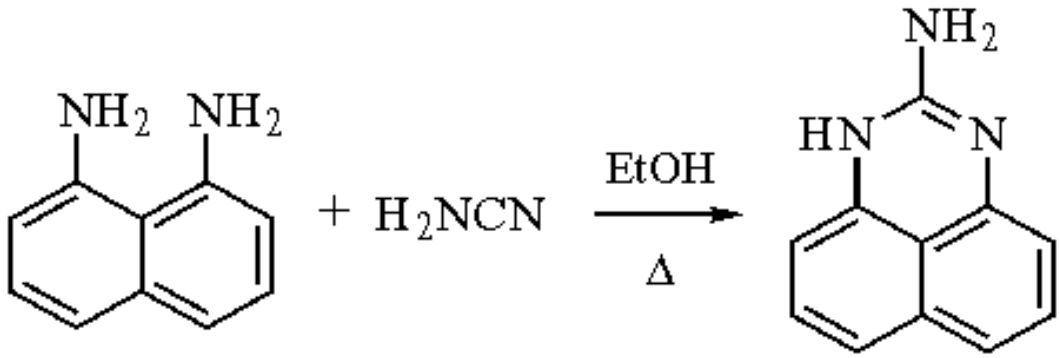

(25)

Related Reagents.

Aminoiminomethanesulfonic Acid; ***Cyanogen Bromide***; ***Guanidine***; ***O-Methylisourea***; ***S-Methylisothiourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

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Steven Schow

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Cyanoacetic Acid

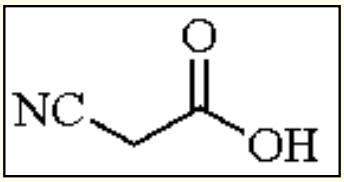

[372-09-8] · $C_3H_3NO_2$ · Cyanoacetic Acid · (MW 85.06)

(active methylene compound for preparing α,β-unsaturated nitriles and esters, for carbolactonization of alkenes to α-cyano γ-lactones, and for converting *trans*-1,2-bromohydrins to *cis*-1,2-diols)

Physical Data: mp 70-71 °C.

Solubility: sol H_2O, ethanol, ether.

Form Supplied in: hygroscopic crystals; widely available.

Analysis of Reagent Purity: gas chromatography; titration.

Handling, Storage, and Precautions: keep container well closed. Inhalation or skin contact should be avoided. Hydrogen cyanide may be liberated in the event of overheating. This reagent should be handled in a fume hood.

Condensation with Carbonyl Compounds.

Ammonium acetate,[1] IR-4B,[2] Dowex-3,[2] pyridine,[3] and potassium hydroxide[4] are effective catalysts for the condensation of cyanoacetic acid with aldehydes and ketones to form α,β-unsaturated nitriles. Cyclohexanone reacts with cyanoacetic acid to yield cyclohexylidenecyanoacetic acid, which can be hydrolyzed to 1-cyclohexenylacetonitrile.[1] Furfural reacts with cyanoacetic acid to afford 3-(2-furyl)acrylonitrile in good yield (eq 1).[3] 2,5-Dihydroxy-3,4,6-trimethylbenzaldehyde condenses with cyanoacetic acid to form a coumarin derivative (eq 2).[4]

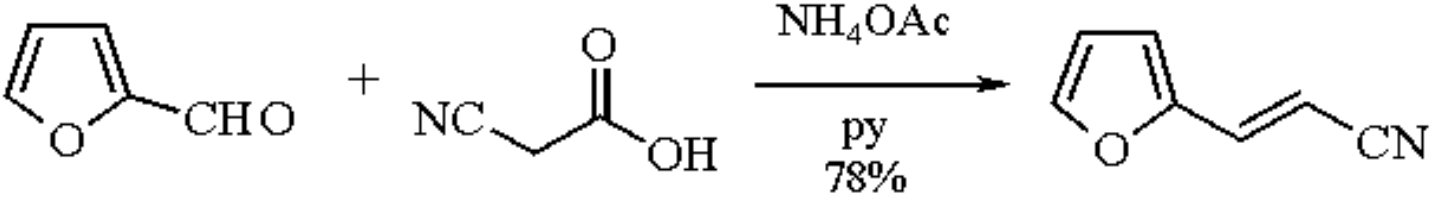

(1)

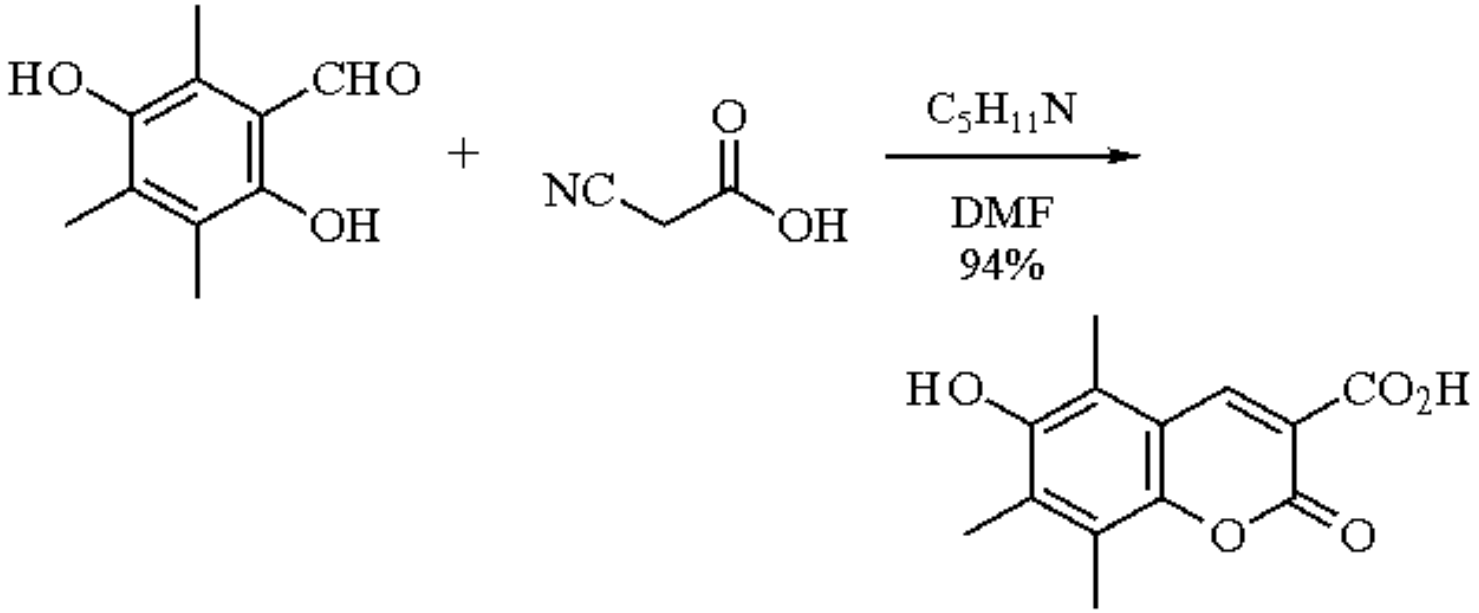

(2)

Carbolactonization of Alkenes to α-Substituted γ-Lactones.

Cyanoacetic acid and malonic acid react with alkenes in the presence of ***Manganese(III) Acetate*** to form α-substituted γ-lactones.[5] In this procedure, cyclohexene is converted to the α-cyano-γ-lactone (**2**) (eq 3).

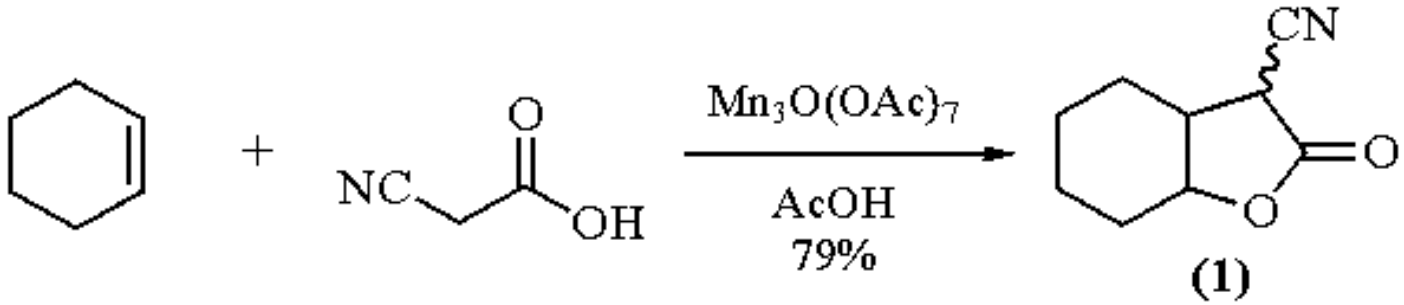

(3)

Conversion of *trans*-1,2-Bromohydrins into *cis*-1,2-Diols.

Esterification of cyanoacetic acid with *trans*-2-bromocyclohexanol forms the cyanoacetate ester (**2**). The ester (**2**) is converted into the ketene acetal (**3**), which is hydrolyzed to the monocyanoacetate of *cis*-cyclohexane-1,2-diol (**4**) (eq 4).[6] Hydrolysis of (**4**) with ***Potassium Carbonate*** in methanol affords the *cis*-cyclohexane-1,2-diol (95%). Similarly, the *trans*-1,2-bromohydrin (**5**) is converted to the *cis*-1,2-diol (**6**) through the cyano ester (eq 5). Attempted dihydroxylation of the alkene precursor to (**5**) with ***Osmium Tetroxide*** led to a 1:1 mixture of the 2α,3α-diol and the 2β,3β-diol.

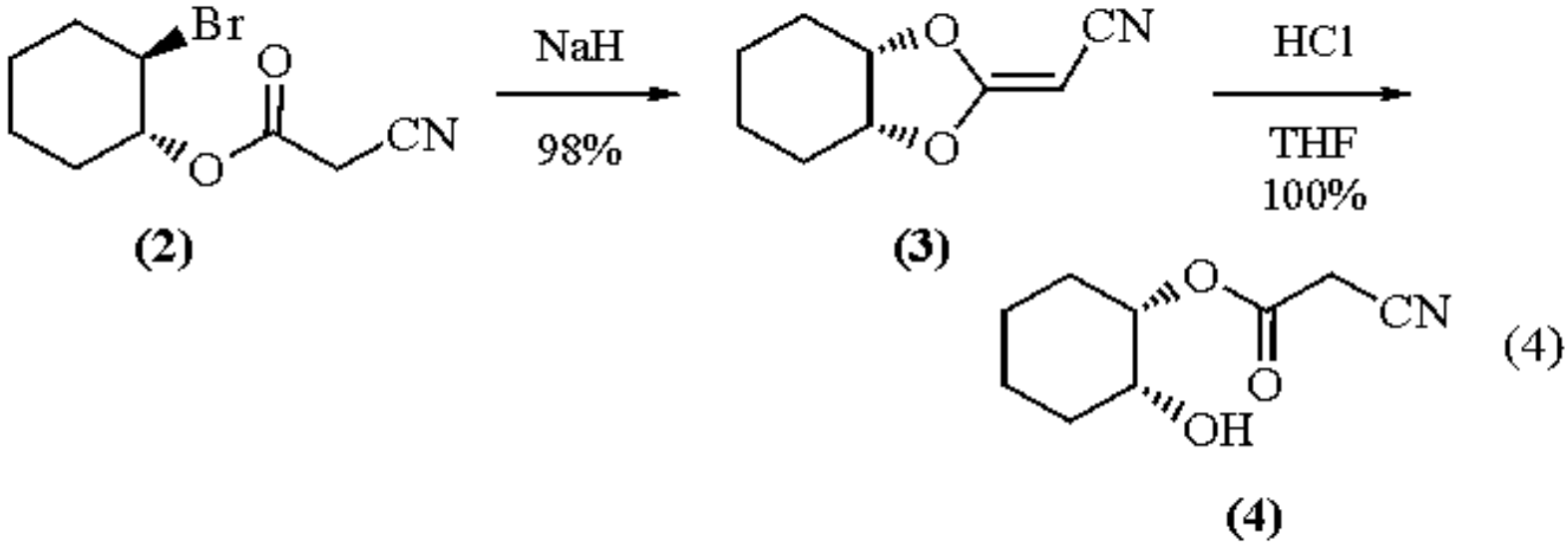

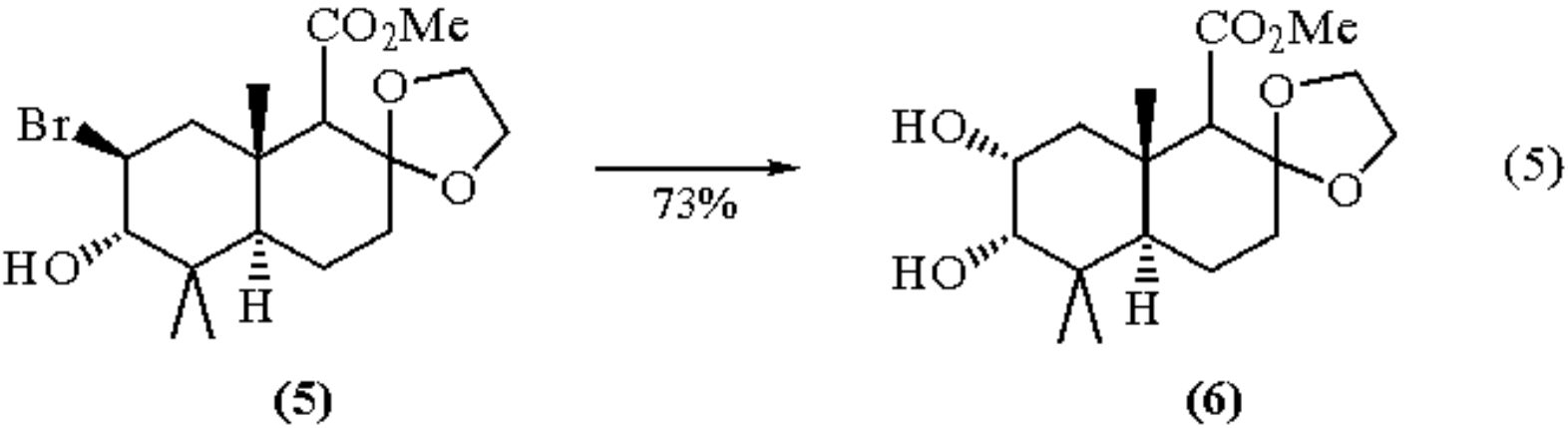

Other Applications.

Cyanoacetic acid is converted to cyanoacetyl chloride which is esterified with *t*-butanol to afford *t*-butyl cyanoacetate,[7] ***N-Bromosuccinimide*** converts cyanoacetic acid to dibromoacetonitrile.[8] A key step in the synthesis of 3-vinylbenzofuran was the alkylation of 3-(pyrrolidin-1-yl)benzofuran to (3-benzofuranyl)cyanoacetic acid with cyanoacetic acid.[9] Cyanoacetic acid serves as an α-ketoacetyl anion equivalent in the diastereoselective synthesis of a highly functionalized decalin fragment of the natural product insecticide azadirachtein.[10]

Related Reagents.

Acetonitrile; ***(Diethoxyphosphoryl)acetonitrile Oxide***; ***Ethyl Cyanoacetate***; ***Lithioacetonitrile***; ***Malononitrile***; ***Trimethylsilylacetonitrile***.

---

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Cyanogen Azide[1]

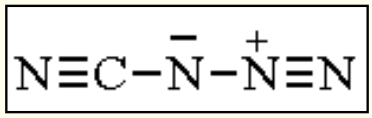

[764-05-6] · CN_4 · Cyanogen Azide · (MW 68.04)

(1,3-dipolar reagent that undergoes cycloaddition and insertion reactions with alkenes[2])

Physical Data: bp 90 °C (est).[1,3]

Solubility: sol most organic solvents including acetonitrile, ethyl acetate, methylene chloride, benzene, toluene, and cyclohexane.[1,3]

Preparative Methods: by the addition of cyanogen chloride or ***Cyanogen Bromide*** to an acetonitrile solution of ***Sodium Azide*** in the temperature range of 10-25 °C. The reagent is used in solution after filtration or decantation of the inorganic salts.[1,3]

Purification: made and used in situ without further purification.[1,3]

Handling, Storage, and Precautions: should be used in solution. In acetonitrile a 27% by weight solution of cyanogen azide has a half-life of 15 days at 25 °C. The pure material is highly explosive and detonates violently when exposed to mild thermal, mechanical, or electrical shock.[1,3] This reagent should be handled in a fume hood.

Dipolar Cycloaddition.

Cycloaddition of cyanogen azide to alkenes affords both aziridines and alkylidenecyanamides. The ratio of the two products depends on the structure of the starting alkene. Isobutene, for example, yields a 1.4:1 mixture of 2-butylidenecyanamide and *N*-cyano-2,2-dimethylaziridine (eq 1).[3,4] The alkylidenecyanamide is formed by a Demjanoff-like rearrangement of a dipolar intermediate resulting from cleavage of the initially formed triazoline.

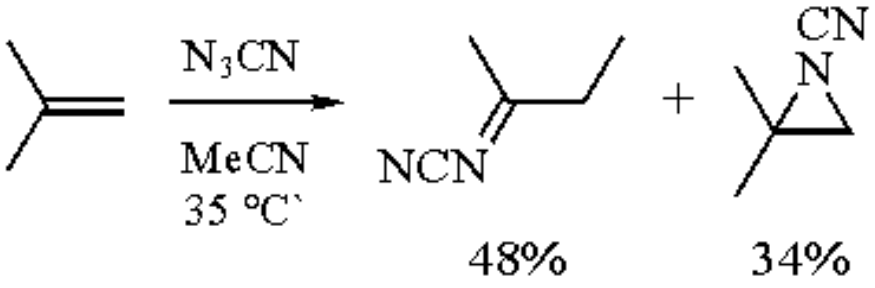

(1)

In contrast to the acyclic case, with cyclopentene the only product is the cyanamide, hydrolysis of which affords cyclopentanone in high yield (eq 2). Strained bicyclic alkenes, however, lead to the opposite result. Norbornene upon treatment with cyanogen azide affords a mixture of aziridine and cyanamide in a ratio of 4:1 (eq 3).[4]

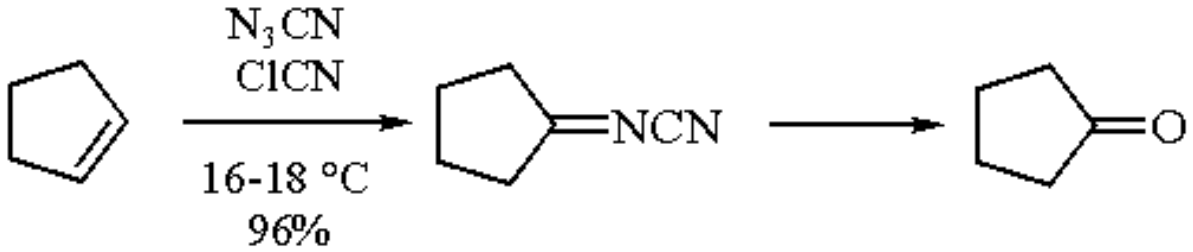

(2)

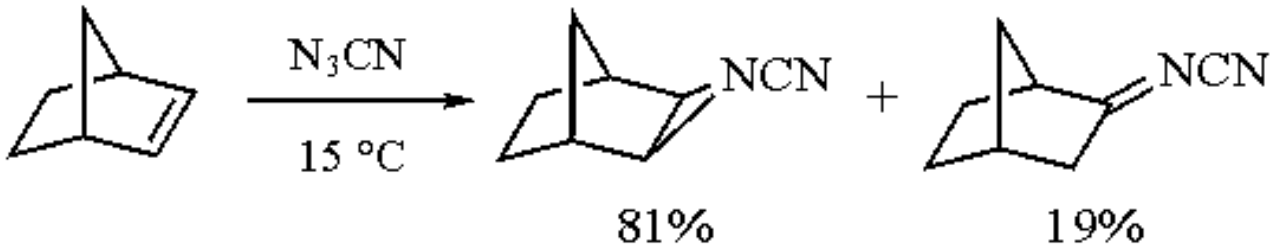

(3)

Ring contraction is also observed for cycloalkenes with trisubstituted double bonds (eq 4).[4]

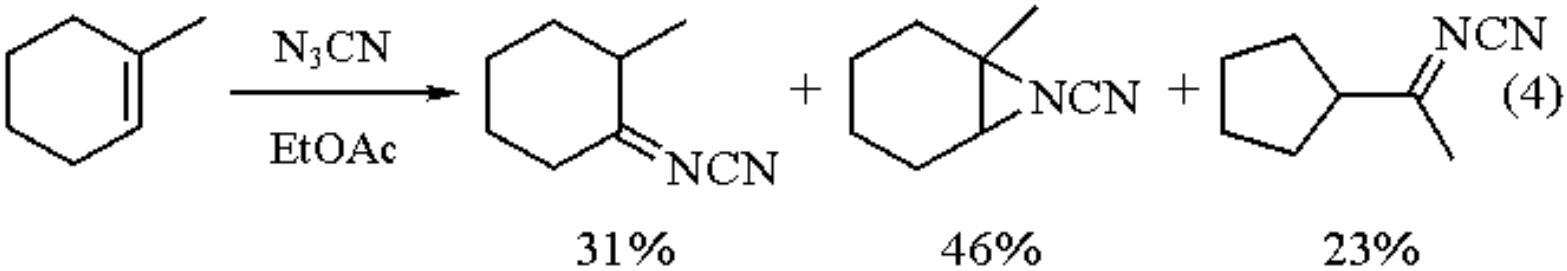

(4)

In the presence of ***Lithium Perchlorate***, methylenecyclohexanes and -cyclohexenes undergo ring enlargement to yield cyclic ketones when treated first with cyanogen azide and then with methanolic HCl (eqs 5 and 6).[5,6]

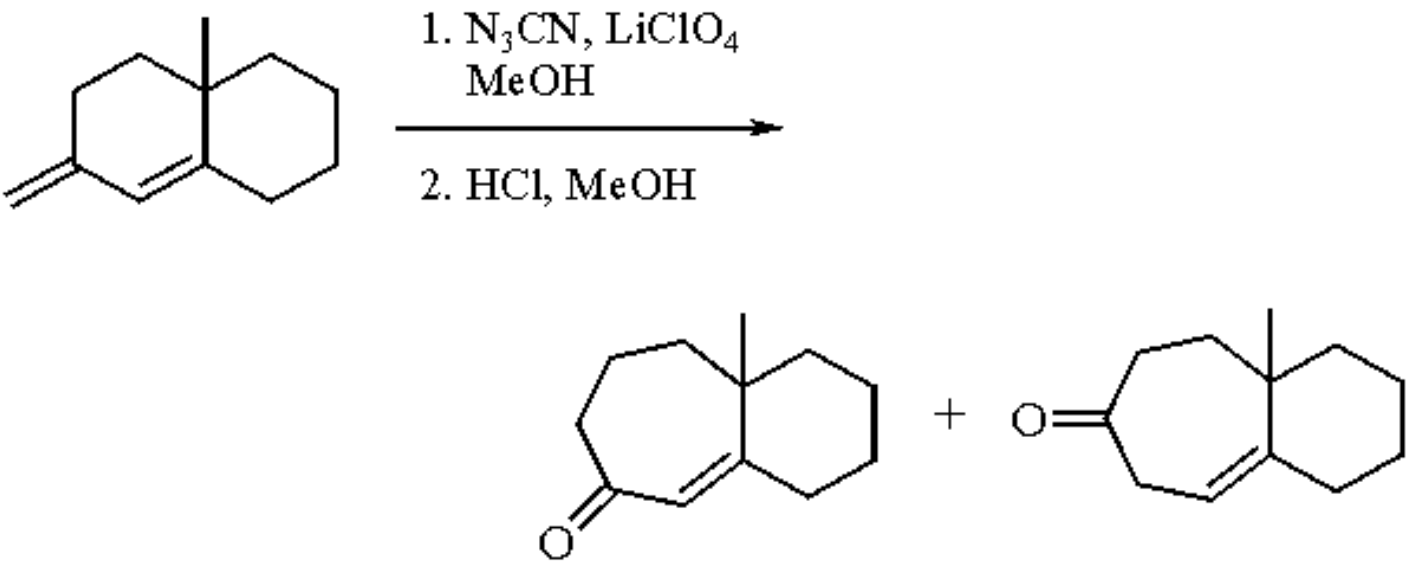

(5)

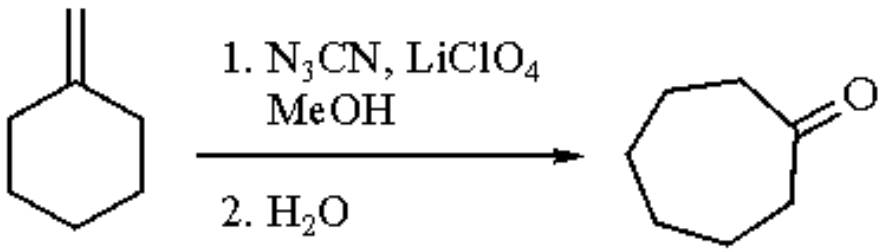

(6)

Ring enlargement is also observed in the absence of the perchlorate salt (eq 7).[7]

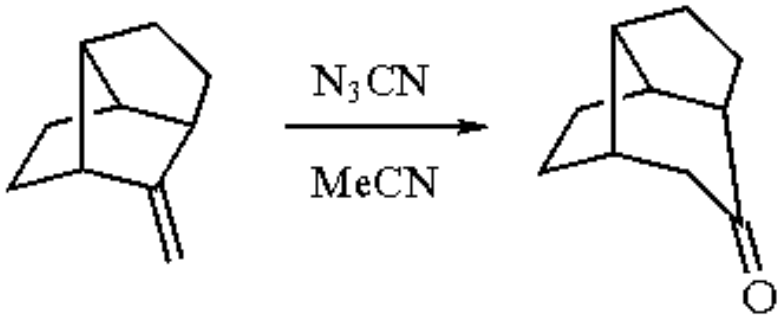

(7)

Dihydro-[8-10] and tetrahydropyridines[11,12] afford cyanoaziridines when treated with cyanogen azide (eqs 8 and 9).

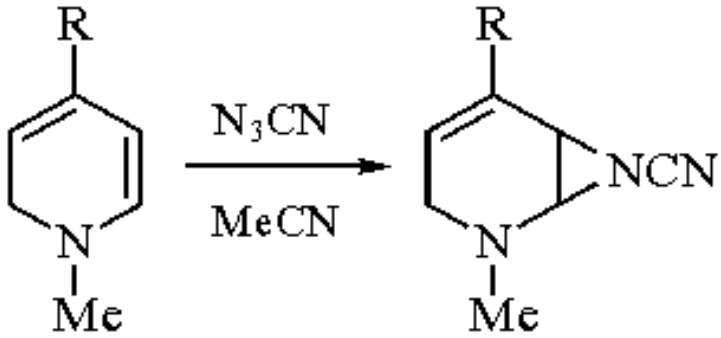

(8)

R = H, 81%; Me, 76%

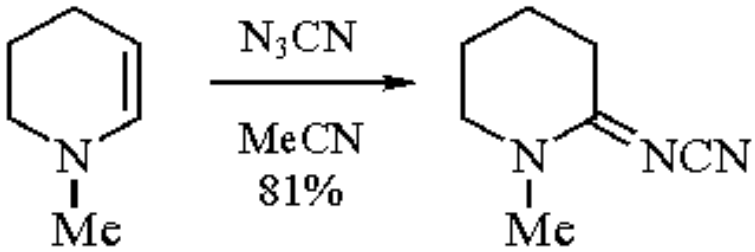

(9)

Nitrene Formation and Insertion.

Thermal decomposition of cyanogen azide leads to a nitrene intermediate which may insert into C-H bonds (eq 10); a nitrene is also proposed for the reaction of cyanogen azide with benzene to give cyanoazepine (eq 11).

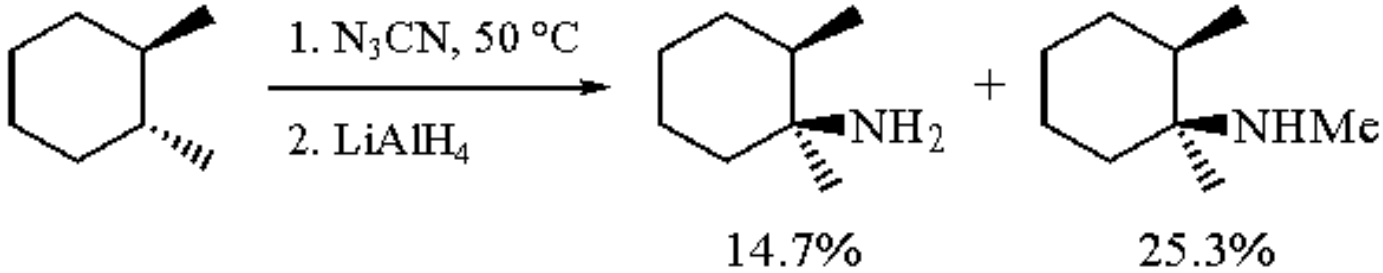

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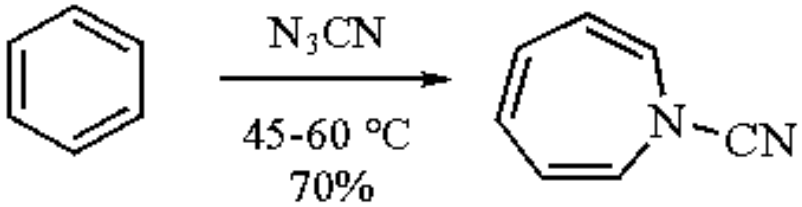

(11)

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Cyanogen Bromide

X-C&tbond;N

(**1**; X = Br)

[506-68-3] · CBrN · Cyanogen Bromide · (MW 105.92) (**2**; X = Cl)

[506-77-4] · CClN · Cyanogen Chloride · (MW 61.47) (**3**; X = I)

[506-78-5] · CIN · Cyanogen Iodide · (MW 152.92) (**4**; X = Ts)

[19158-51-1] · $C_8H_7NO_2S$ · *p*-Toluenesulfonyl Cyanide · (MW 181.21) (**5**; X = OPh)

[1122-85-6] · C_7H_5NO · Phenyl Cyanate · (MW 119.12)

(counter-attack reagent useful for the cleavage of carbon-heteroatom bonds,[1] cyanation,[2] and synthesis of heterocycles[3])

Physical Data: (**1**) bp 61.4 °C; mp 52 °C; *d* 2.015 g cm^{-3}; (**2**) bp 12.7 °C; mp -6 °C; *d* 1.186 g cm^{-3}; (**3**) sublimes at 45 °C; mp 146.7 °C; *d* 2.84 g cm^{-3}; (**4**) mp 49 °C; (**5**) bp 77 °C/13 mmHg; *d* 1.096 g cm^{-3}.

Preparative Methods: *p*-toluenesulfonyl cyanide (TsCN) is prepared from the reaction of sodium *p*-toluenesulfinate with ClCN.[4] Phenyl cyanate (PhOCN) is available from the reaction of phenol with BrCN.[5a,b]

Handling, Storage, and Precautions: BrCN and its analogs are highly toxic. These reagents should be handled in a fume hood.

Counter-Attack Reagent.

Cyanogen halides are representative of a class of counter-attack reagents[6] which are useful for the cleavage of carbon-heteroatom bonds. The classic Von Braun reaction[1] with BrCN provides a convenient method for the demethylation of tertiary methyl amines (eq 1).[7] The products of this reaction are a dialkyl-substituted

cyanamide and an alkyl bromide, with bromide attack occurring at the more electrophilic[8a] or sterically accessible site. Similar methodology with BrCN has been utilized to induce ring opening[8b] as well as ring expansion[8c,d] of N-heterocycles (eq 2).

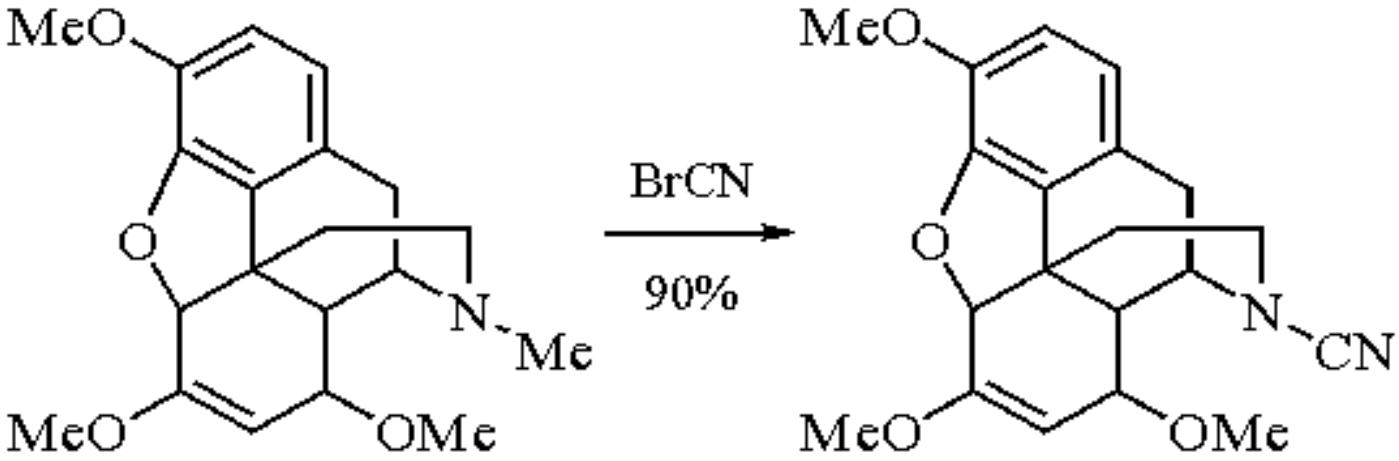

(1)

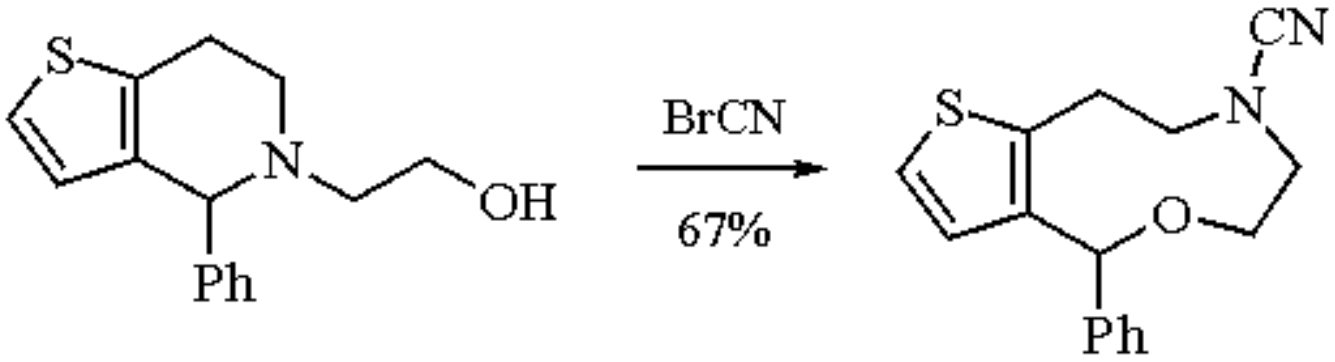

(2)

Cleavage of thioethers is also accomplished with cyanogen halides. The selective reaction of BrCN with methionine in peptide chains (eq 3)[9a] has been applied to the removal of peptide chains from the resin after solid phase synthesis.[9b] In a related sequence, treatment of dithioacetals with ICN affords the α-thionitrile.[10] The synthesis of symmetrical[11a] and mixed[11b] disulfides and the intramolecular formation of disulfide bonds in peptides[11c] have been accomplished with BrCN and ICN, respectively. Another example of the counter-attack properties of BrCN and ICN is shown by their reaction with dialkylvinylboranes to produce *trans*-alkenes (eq 4).[12] In addition, vinyl bromides are available from the treatment of disubstituted vinylsilanes with BrCN and ***Aluminum Chloride***.[13]

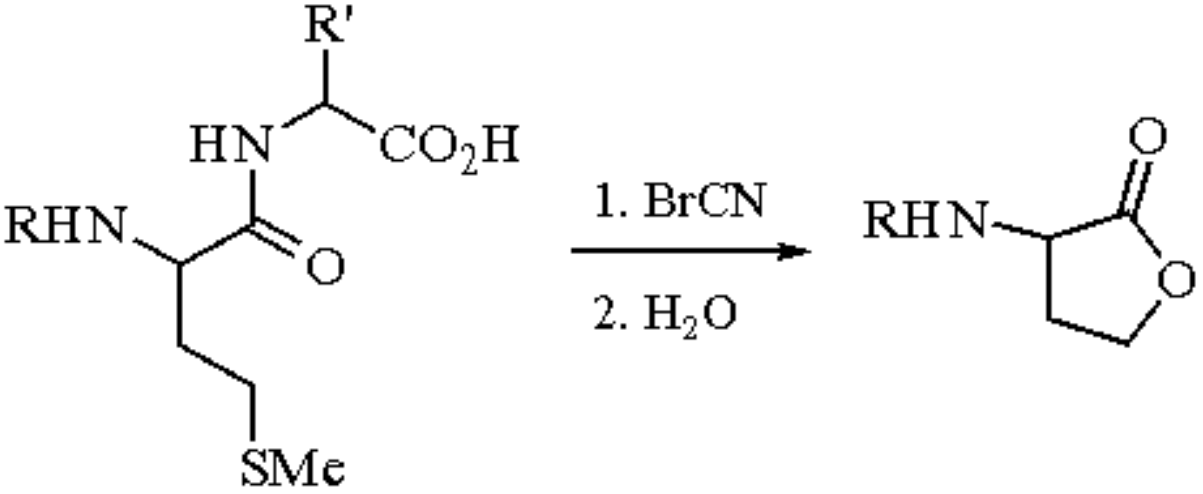

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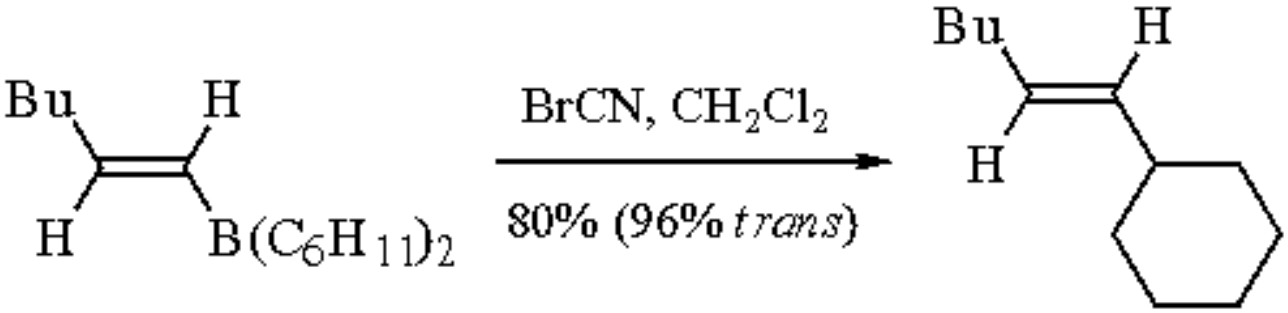

(4)

Cyanation.

The synthesis of unsaturated nitriles is accomplished by treatment of vinyl cuprates with ClCN or TsCN[14] or more conveniently from the reaction of vinyllithium reagents with PhOCN (eq 5).[5a] Cyanation of lithium ketone enolates with TsCN proceeds in good yield (eq 6).[2] In addition, enamines react readily with ClCN to provide the α-cyanoketone.[15a] The use of BrCN in the latter reaction affords the corresponding α-bromo ketone.[15b] Alkylation of an *N*-alkylimidazole to its 2-cyano derivative proceeds through an intermediate imidazolium ylide (eq 7).[16]

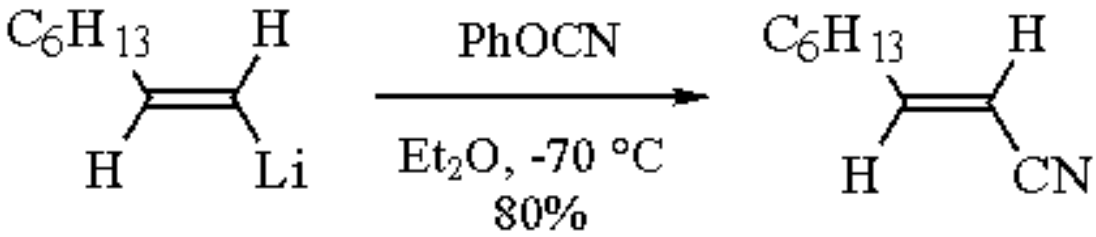

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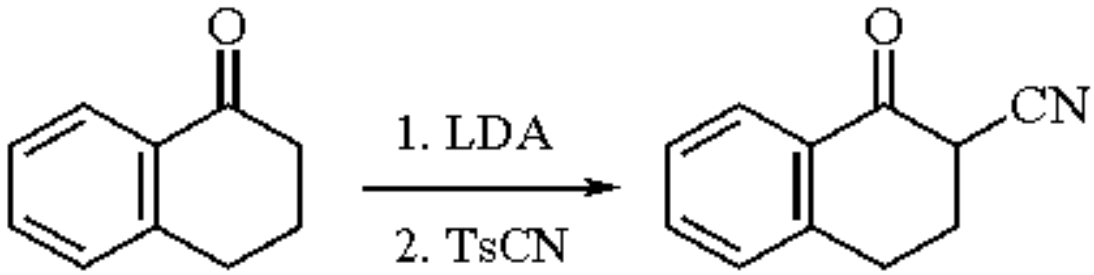

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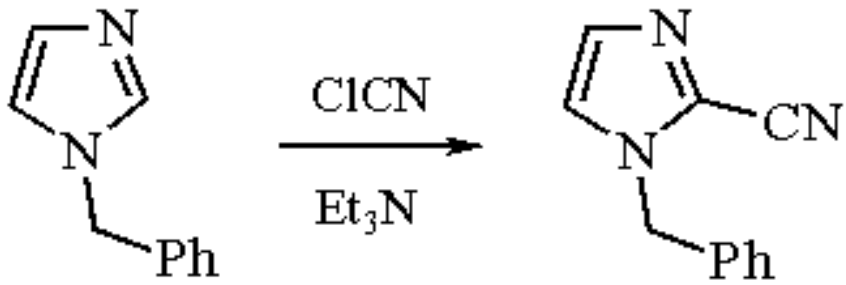

(7)

Heterocycle Synthesis.

Cyanogen halides are useful for the synthesis of N-heterocycles via double attack by nitrogen and/or sulfur nucleophiles.[3] In addition, the cyano group of TsCN participates in a Diels-Alder reaction with selected dienophiles (eq 8).[17]

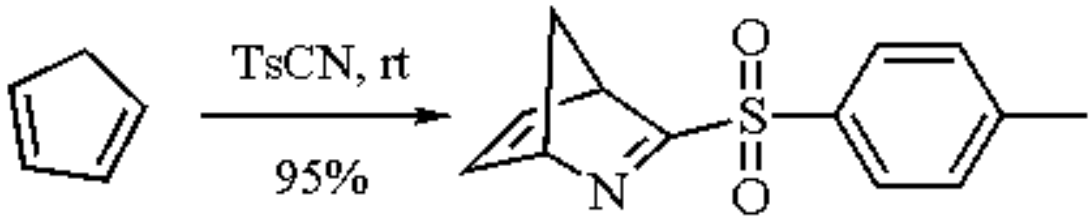

(8)

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Cyanomethylcopper[1]

$CuCH_2CN$

[35219-76-2] · C_2H_2CuN · Cyanomethylcopper · (MW 89.58)

(reagent for the cyanomethylation of allyl halides[2])

Preparative Methods: by the reaction of cyanomethyllithium (***Lithioacetonitrile***) and ***Copper(I) Iodide*** in THF at -25 °C,[2] or by the thermal decarboxylation of ***Copper(I) Cyanoacetate***.[3]

Handling, Storage, and Precautions: can be prepared in two forms, a red solution in THF or an insoluble dark yellow solid. The solid form is stable in the absence of air to 100 °C, but both forms are air- and moisture-sensitive. Use in a fume hood.

General Discussion.

Although both the above preparations produce cyanomethylcopper, the physical characteristics of the specific reagent produced by each method are markedly different, as is the reactivity. The cyanomethylcopper obtained by transmetalation of the lithio precursor in THF is a brick-red solution which gives a negative Gilman test. The soluble reagent is reactive toward allylic electrophiles, but does not react with benzyl bromide, esters, vinyl bromides, or vinyl iodides (eqs 1-3).

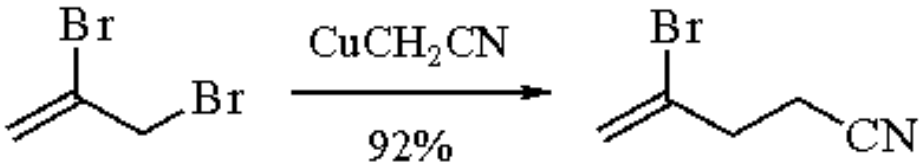

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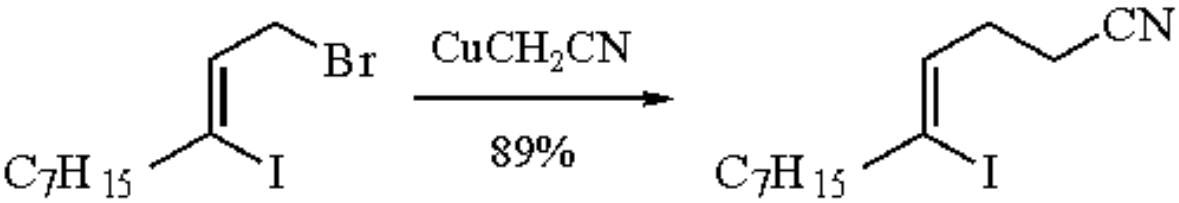

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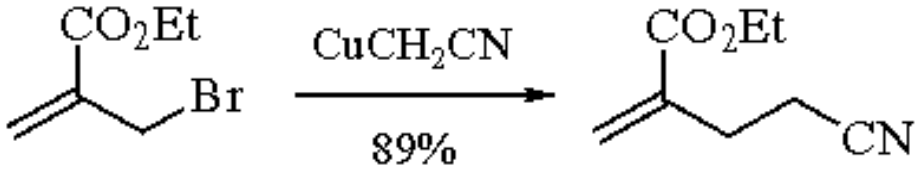

(3)

Cyanomethylcopper produced by the decarboxylation route is a dark yellow solid which is insoluble in most organic solvents. Addition of 1 equiv of ***Lithium t-Butoxide*** to a suspension of the solid reagent in DMF results in a homogeneous solution which does react with benzyl bromide and iodobenzene (no yields are given). The isolated solid cyanomethylcopper is stable under nitrogen to approximately 100 °C, but is rapidly decomposed when exposed to air. The addition of acetic acid results in formation of acetonitrile and copper(I) acetate. Cyanomethylcopper can also be obtained by the reaction of copper(II) methoxide and 2 equiv of cyanoacetate. The initial copper acetate salt decomposes upon heating in DMF to generate cyanomethylcopper, succinonitrile, and carbon dioxide.[3] Decomposition of copper cyanoacetate in the presence of propene oxide produces cyanomethylcopper and propylene carbonate; therefore, copper cyanoacetate also functions as a source of activated carbon dioxide (eq 4).[4] Control reactions revealed that cyanomethylcopper was required for the transcarboxylation reaction. Cyanomethylcopper formed independently (by the decarboxylation route described above) served as a catalyst for the reaction of propene oxide with carbon dioxide gas. Other sources of copper(I) examined, such as CuCN and CuCl, were ineffective as catalysts and did not produce any propylene carbonate.

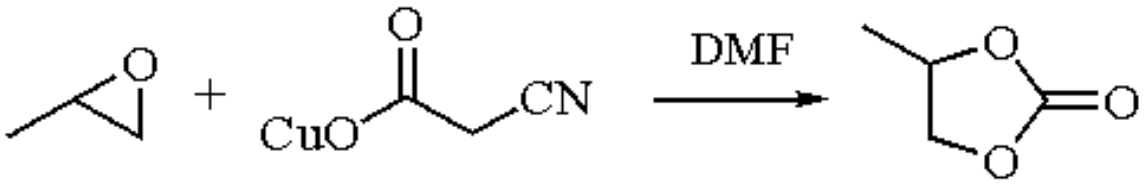

(4)

Cyanomethylation.

Cyanomethylcopper is a relatively unreactive organocopper reagent, similar to other stabilized alkylcopper species such as ***Ethoxycarbonylmethylcopper***. The reagent is ideally suited for cyanomethylation of allylic halides. Reaction occurs cleanly by direct substitution (S_N2) without significant competing allylic transposition (S_N2' alkylation). In a key step in the synthesis of cembrane lactones, Marshall and co-workers reported that cyanomethylcopper gave only the product arising from direct displacement of an allyl bromide, while other approaches to the nitrile product resulted in considerable amounts of the S_N2' alkylation product (eq 5).[5] The synthesis of the alkaloid peramine, the principal insect feeding deterrent isolated from perennial ryegrass, was achieved by an allylic displacement reaction on a 2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system using cyanomethylcopper (eq 6).[6]

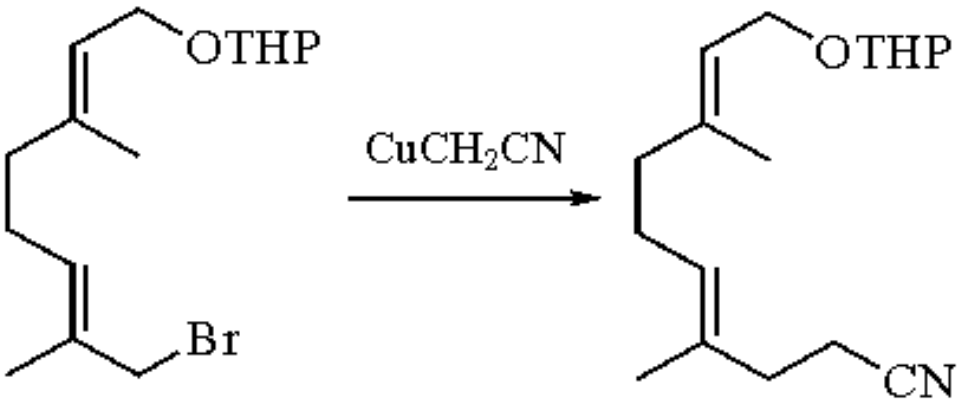

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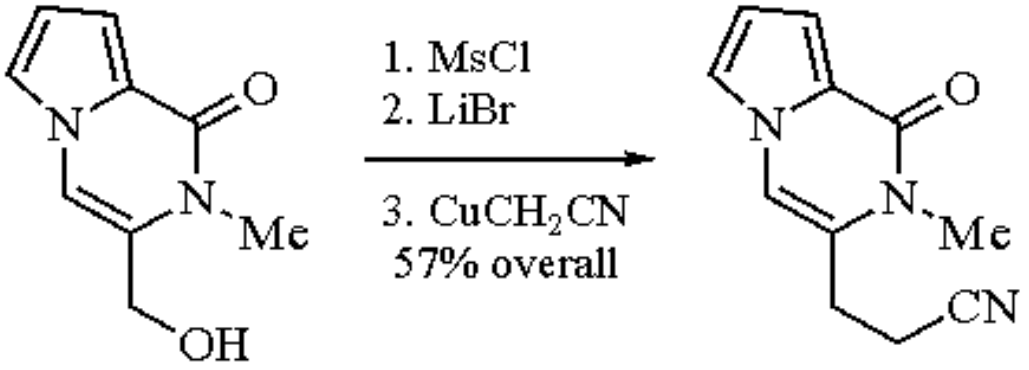

(6)

Cyanomethylcopper does not react with carbonyl groups; however, an iron derivative has been shown to be selective for addition to aldehydic carbonyl groups in the presence of ketones.[7] Knochel and co-workers have achieved the preparation of chain-extended nitriles by the reaction of cyanomethylcopper with ***Iodomethylzinc Iodide***.[8] Subsequent reaction with a variety of electrophiles results in very good yields of products formally derived from 2-cyanoethylcopper. This reagent is more reactive than the parent cyanomethylcopper and undergoes conjugate addition reactions (eq 7) as well as alkylation reactions with allyl halides (eq 8). Reaction of copper cyanide solubilized with ***Lithium Chloride*** and iodomethylzinc iodide generates the parent cyanomethylcopper reagent in situ, thereby avoiding the need to prepare cyanomethyllithium.

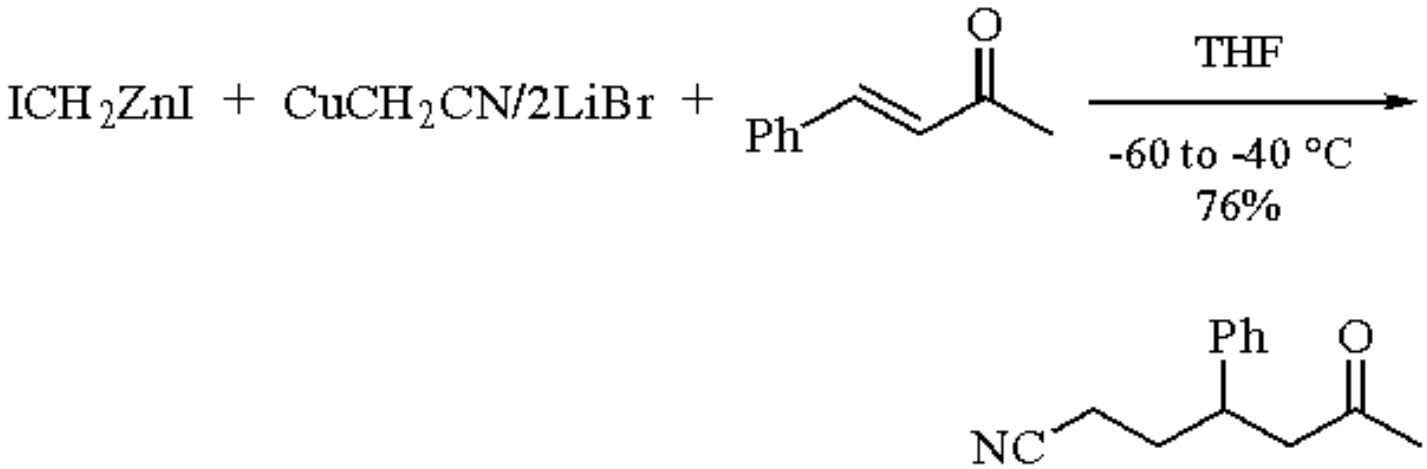

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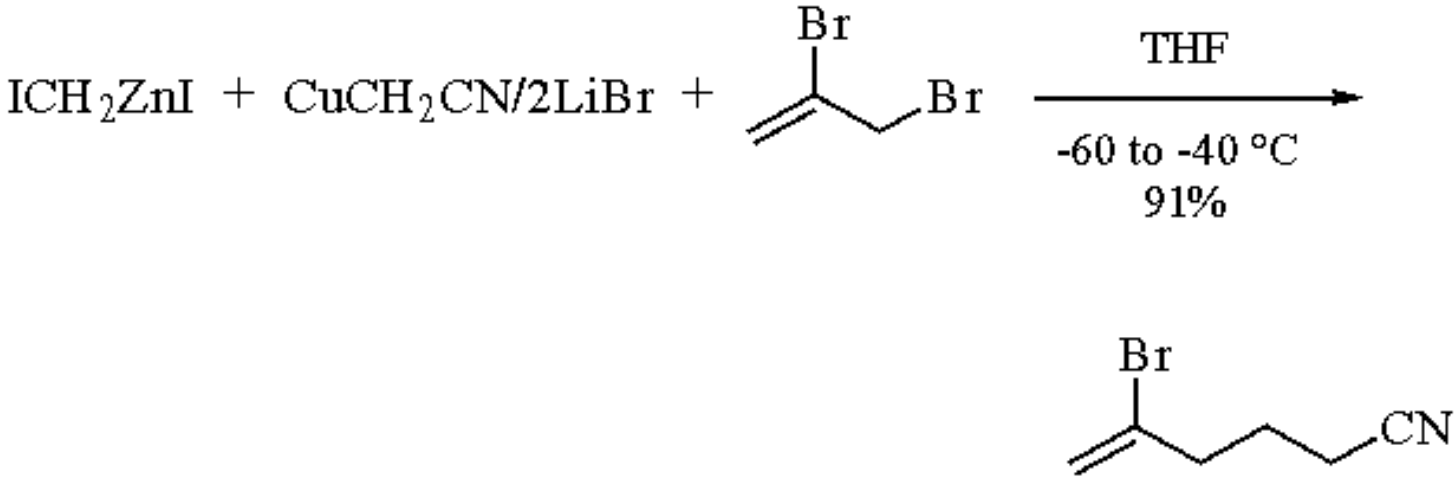

(8)

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Cyanomethyldiphenylphosphine Oxide

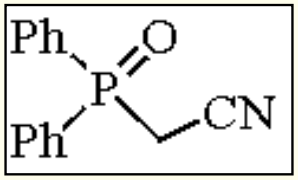

[23040-22-4] · $C_{14}H_{12}NOP$ · Cyanomethyldiphenylphosphine Oxide · (MW 243.23)

(Horner-Wittig reagent for formation of α,β-unsaturated nitriles[1]; reaction with nitrones to form aziridines or enamines[2])

Solubility: sol THF and DMF.

Preparative Methods: reaction of ***Ethyl Diphenylphosphinite***[3] with ***Chloroacetonitrile***;[4] reaction of $Ph_2P(O)CH_2CO_2H$ with urea in acetic anhydride.[5]

Handling, Storage, and Precautions: hazards unknown.

α,β-Unsaturated Nitriles.

Use of cyanomethyldiphenylphosphine oxide (**1**) in a Horner-Wittig reaction for the formation of α,β-unsaturated nitriles provides, stereoselectively, the (*E*) isomer (&egt;90%) with aromatic aldehydes and ca. 75% *(E)* with isobutanal in very good chemical yields (eq 1). The reactions are run in either THF or DMF with ***Potassium t-Butoxide*** as the base at rt. Use of THF provides greater chemical yields and improved stereoselectivity over DMF or ***Lithium t-Butoxide*** in THF. The potassium diphenylphosphinate byproduct is water soluble and easily removed from the reaction mixture.

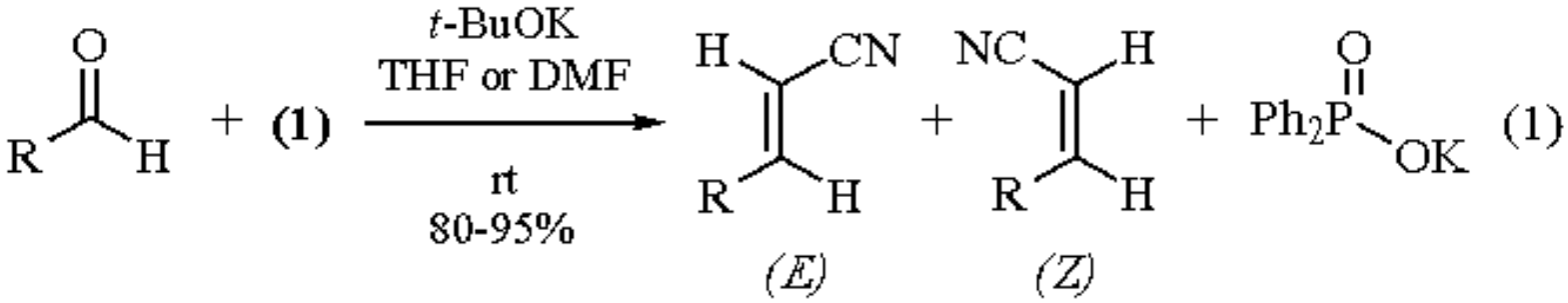

Reaction of the anion of (**1**) with acetophenone provides the (*E*) isomer in a 94:6 ratio in 82% yield. Condensation with cinnamaldehyde provides a 90:10 ratio (*E*:*Z*) (70:30 *E*:*Z* with analogous phosphonate). Use of (**1**) generally provides greater stereoselectivity for the (*E*) isomer than other methods for the formation of α,β-unsaturated nitriles.[1]

Of the other methods available, the Doebner condensation[6] of aldehydes with cyanoacetic acid leads to mixtures of (*E*) and (*Z*) isomers.[7] The Wittig alkenation with ***Cyanomethylenetriphenylphosphorane***,[8] usually in refluxing benzene, yields a predominance of the (*E*) isomer and triphenylphosphine oxide as a byproduct. In alkenation employing the Horner-Emmons reagents, ***Diethyl Cyanomethylphosphonate***,[9] in THF at rt, the (*E*) isomer predominates (&egt;70%) with aromatic aldehydes and little or no selectivity is seen with aliphatic aldehydes.

Reaction with Nitrones.[2]

Reaction of the anion of (**1**) with 3,4-dihydroisoquinoline *N*-oxide (**2**) (eq 2) and 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**5**) (eq 3) can result in the formation of either aziridine or enamine products. The product distribution is markedly different employing (**1**) as opposed to diethyl cyanomethylphosphonate. This is thought to be due to the ability of the phenyl groups of (**1**) to better stabilize the build up of negative charge on phosphorus in the putative oxazaphospholidine intermediate, thereby decreasing the amount of fragmentation to the aziridine.

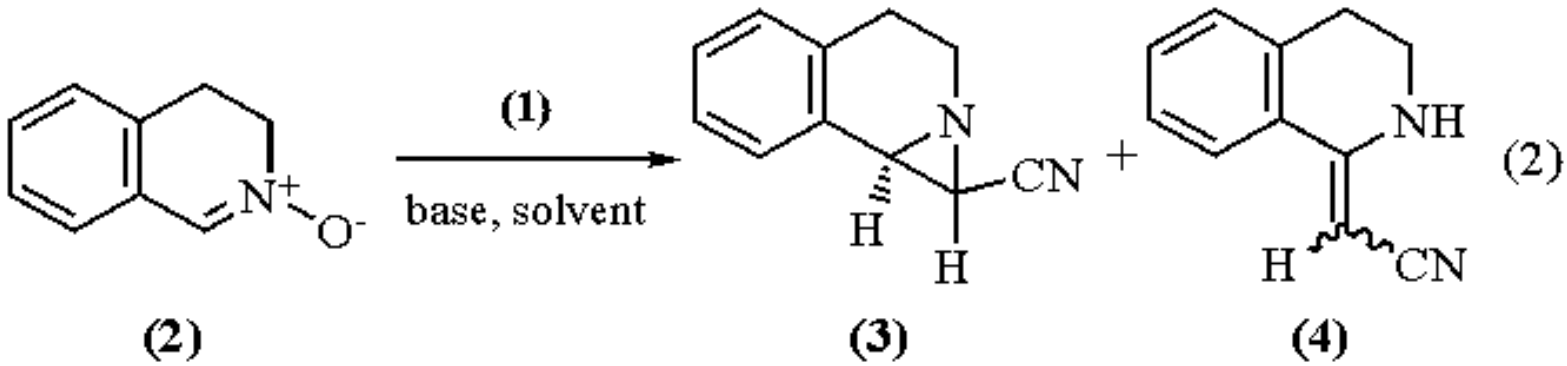

(2)

Base/solvent	Temp (°C)	Time (h)	Ratio **(3)**:**(4)**
NaH/DME	25	3	0:90
t-BuONa/*t*-BuOH	40	3.5	0:95
MeONa/MeOH	Reflux	24	No reaction

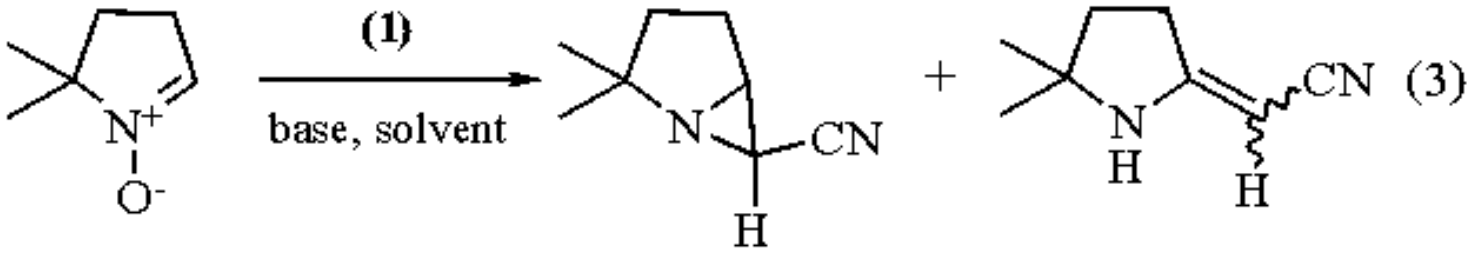

(5) (6) (7)

Base/solvent	Temp (°C)	Time (h)	Ratio **(6)**:**(7)**
NaH/DME	Reflux	1	33:33
NaH/DME	25	3.5	33:33
NaH (2 equiv)/DME	25	3	0:58
t-BuONa/*t*-BuOH	25	3	95:0
MeONa/MeOH	Reflux	72	No reaction

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Cyanomethylenetriphenylphosphorane

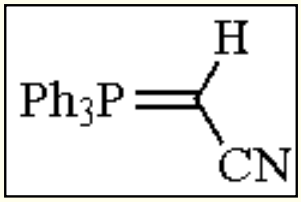

[16640-68-9] · $C_{20}H_{16}NP$ · Cyanomethylenetriphenylphosphorane · (MW 301.33)

(phosphonium ylide, Wittig reagent)

Physical Data: mp 196-197 °C;[1] IR;[1] UV;[2] ^{1}H NMR;[3] ^{31}P NMR;[4] pK_a;[4] rate of hydrolysis.[2]

Preparative Methods: may be generated by deprotonation of the corresponding phosphonium salt,[5,6] by cyanation of ***Methylenetriphenylphosphorane*** with *p*-tolyl cyanate,[1] or by the reaction of ***Acrylonitrile*** with ***(Methoxycarbonylmethylene)triphenylphosphorane*** (eq 1).[7]

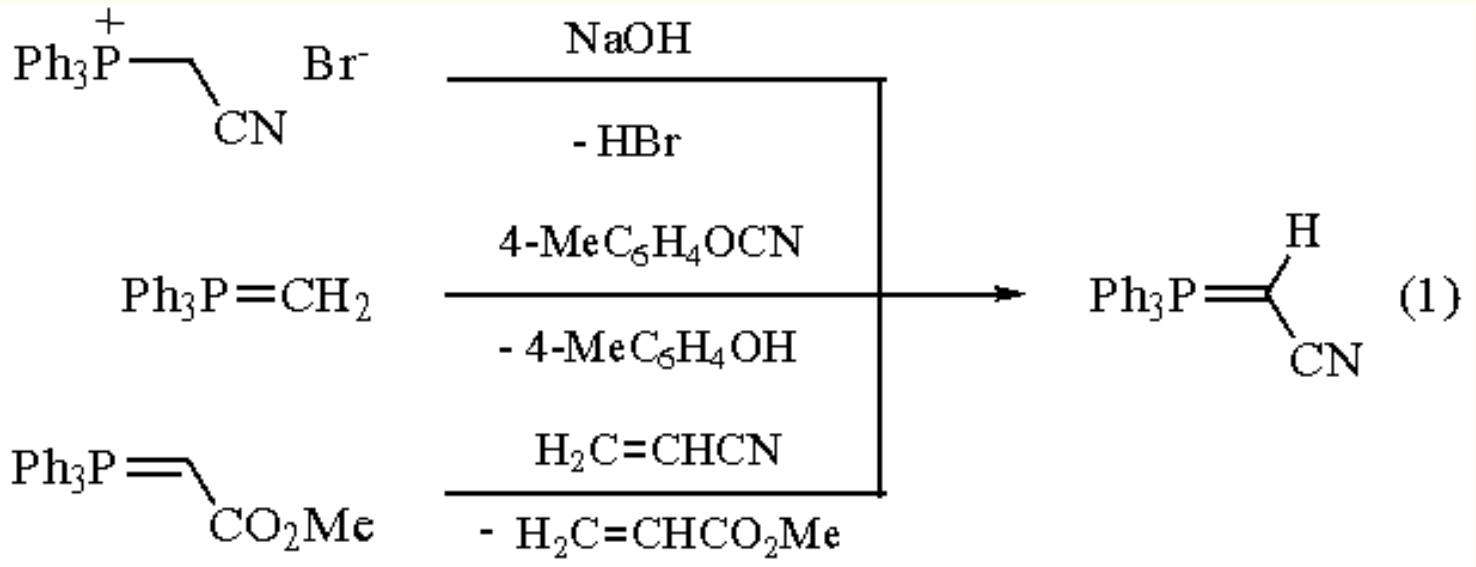

Wittig Reactions.

Cyanomethylenetriphenylphosphorane, as a stabilized phosphonium ylide, has been reacted in Wittig reactions with a great variety of carbonyl compounds to give α,β-unsaturated nitriles with predominantly or exclusively (*E*) configuration at the newly formed alkenic bond (eq 2) (examples,[1,8-15] special application to carbohydrates[16-20]). Besides aldehydes and ketones, activated esters,[21,22] anhydrides,[23,24] and imides[25] have been used as carbonyl reactants.

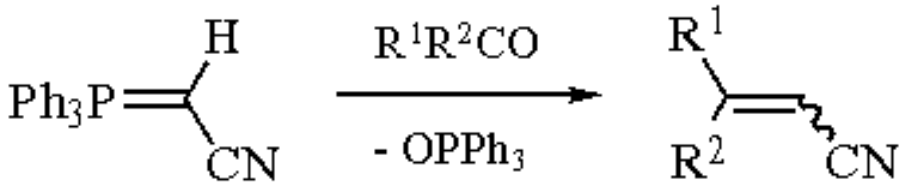

(2)

A Wittig-type reaction is also involved if cyanomethylenetriphenylphosphorane is cleaved with elemental sulfur[26] or selenium.[27,28] The thio- or selenoaldehyde intermediate reacts with a second molecule of ylide to give 1,2-dicyanoethylene (eq 3).

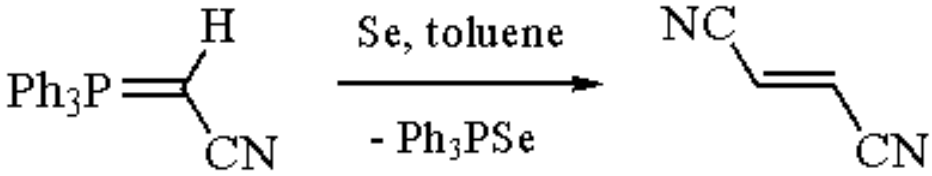

(3)

Reactions with Other Electrophiles.

Various electrophilic compounds have been reacted with cyanomethylenetriphenylphosphorane, affording (in most cases) substituted derivatives of the original ylide, which can then be used in typical ylide reactions (eqs 4-11).

Borane is added with formation of an alkylidenetriphenylphosphorane-borane which, in contrast to analogous compounds, does not rearrange to the triphenylphosphane-monoalkylborane adduct (eq 4).[29] Halogenation may be achieved by using ***t-Butyl Hypochlorite*** or elemental ***Bromine*** or ***Iodine***, respectively (eq 5).[30] The attack of alkylating reagents can occur at the ylide C-atom as well as at the N-atom (eq 6).[1] The reaction with acylaziridines yields 3-pyrrolines, which result from intramolecular Wittig reaction of an initially formed cyano ylide (eq 7).[31,32] The reaction with acid chlorides leads to the formation of 1-acyl-1-cyano ylides,[33-35] which can be pyrolyzed to give 1-cyanoalkynes (eq 8). In the presence of both an aldehyde and an acid chloride, the cyano ylide reacts preferentially at the acid chloride.[35] Isocyanates yield 1-cyano-1-carbamoylmethylenetriphenylphosphoranes (eq 9)[5,36] and the reaction with ***Carbon Disulfide*** followed by an *S*-alkylation leads to the formation of 1-cyano-1-dithio carboxylic derivatives (eq 10).[37] Addition of alkyne carboxylic esters to cyanomethylenetriphenylphosphorane yields 1-alkoxycarbonyl-1-(2-cyanoalkenyl) ylides, presumably via electrocyclic ring opening of an intermediate phosphacyclobutene (eq 11).[38]

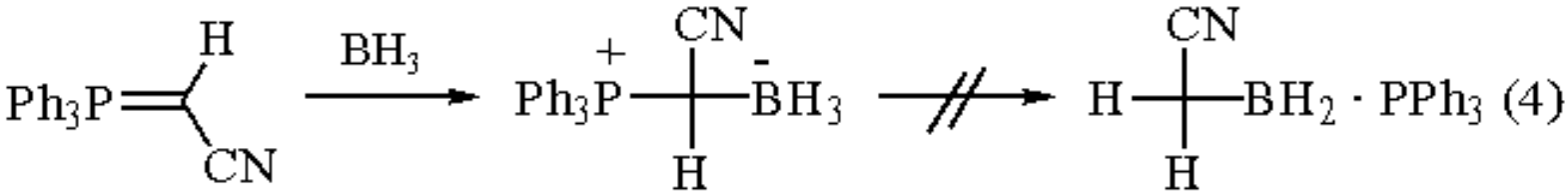

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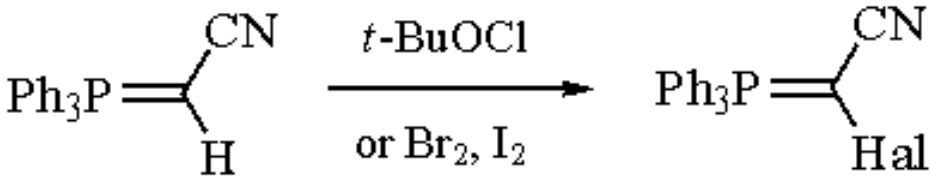

(5)

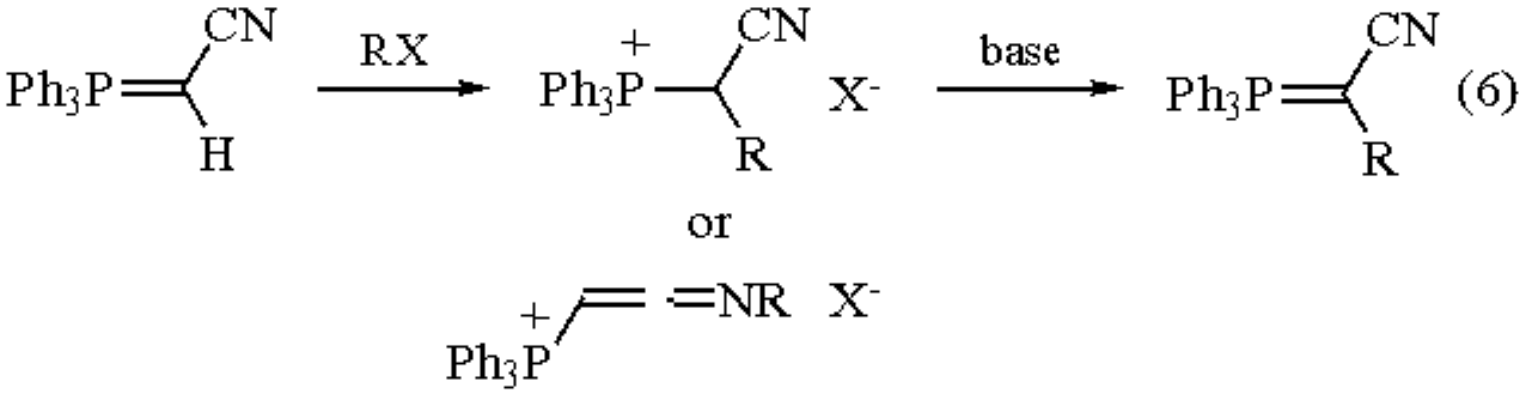
Ph3P
CN
H
RX
+
Ph3P
CN
R
X-
base
Ph3P
CN
R
(6)
or
+
Ph3P
NR
X-

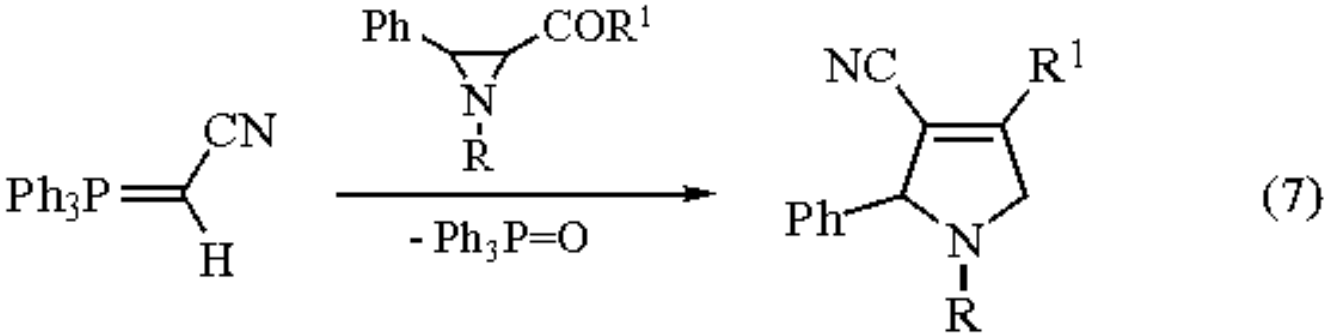
Ph3P
CN
H
Ph
COR1
N
R
- Ph3P=O
NC
R1
Ph
N
R
(7)

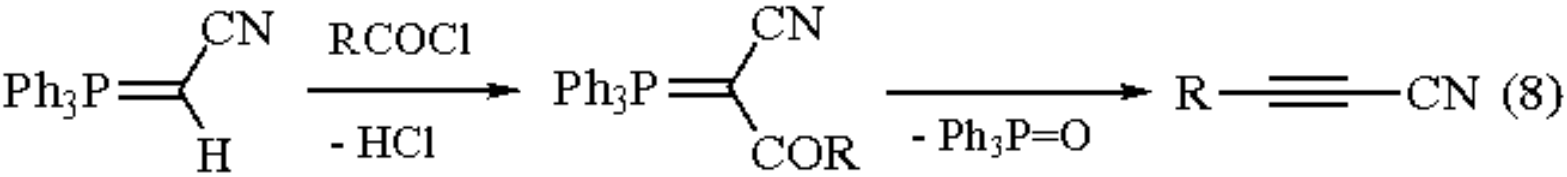
Ph3P
CN
H
RCOCl
- HCl
Ph3P
CN
COR
- Ph3P=O
R
CN
(8)

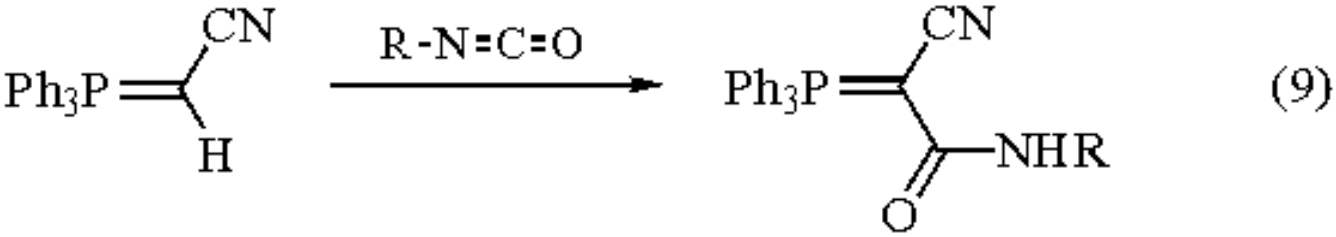
Ph3P
CN
H
R-N=C=O
Ph3P
CN
NHR
O
(9)

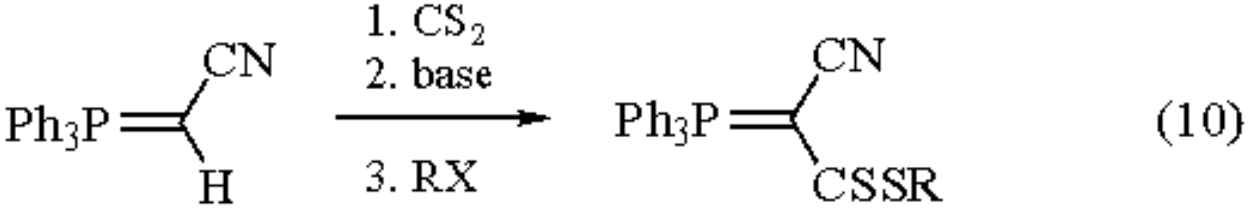
Ph3P
CN
H
1. CS2
2. base
3. RX
Ph3P
CN
CSSR
(10)

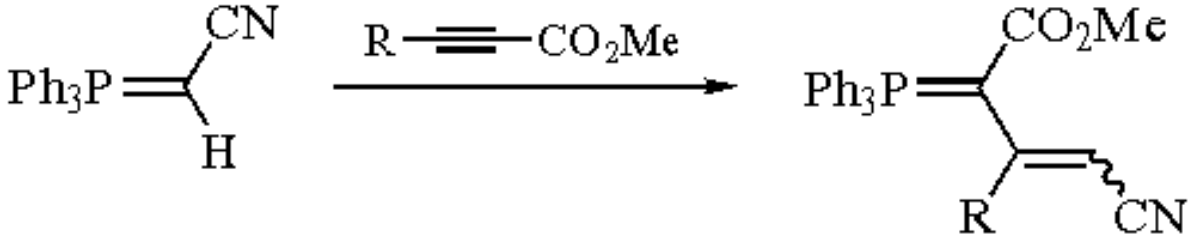

(11)

Cyanomethylenetriphenylphosphorane may be deprotonated to give the corresponding ylide anion.[39-41] This reacts with electrophiles to give a wide variety of 1-substituted cyano ylides, from which various nitriles are available via Wittig reaction or thermolysis (eq 12).[39,40] Reaction with aliphatic aldehydes followed by addition of ***Chlorotrimethylsilane*** leads to the formation of 1-cyano-1-alkenyl ylides (eq 13), which are useful synthons for 2-cyano-1,3-dienes. Ring opening of epoxides by the ylide anion provides a route to γ-hydroxynitriles, γ-butyrolactones, or α-methylene-γ-butyrolactones, depending on the subsequent treatment of the initially formed adduct (eq 13).[40]

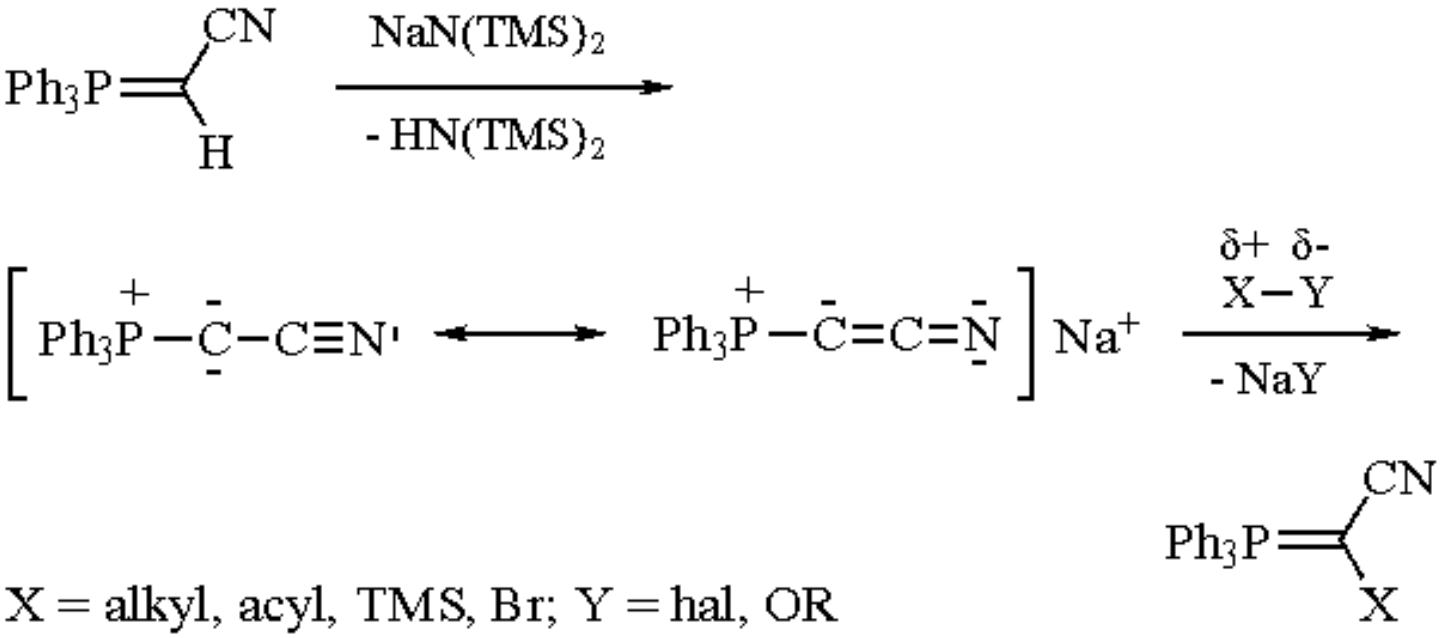

(12)

X = alkyl, acyl, TMS, Br; Y = hal, OR

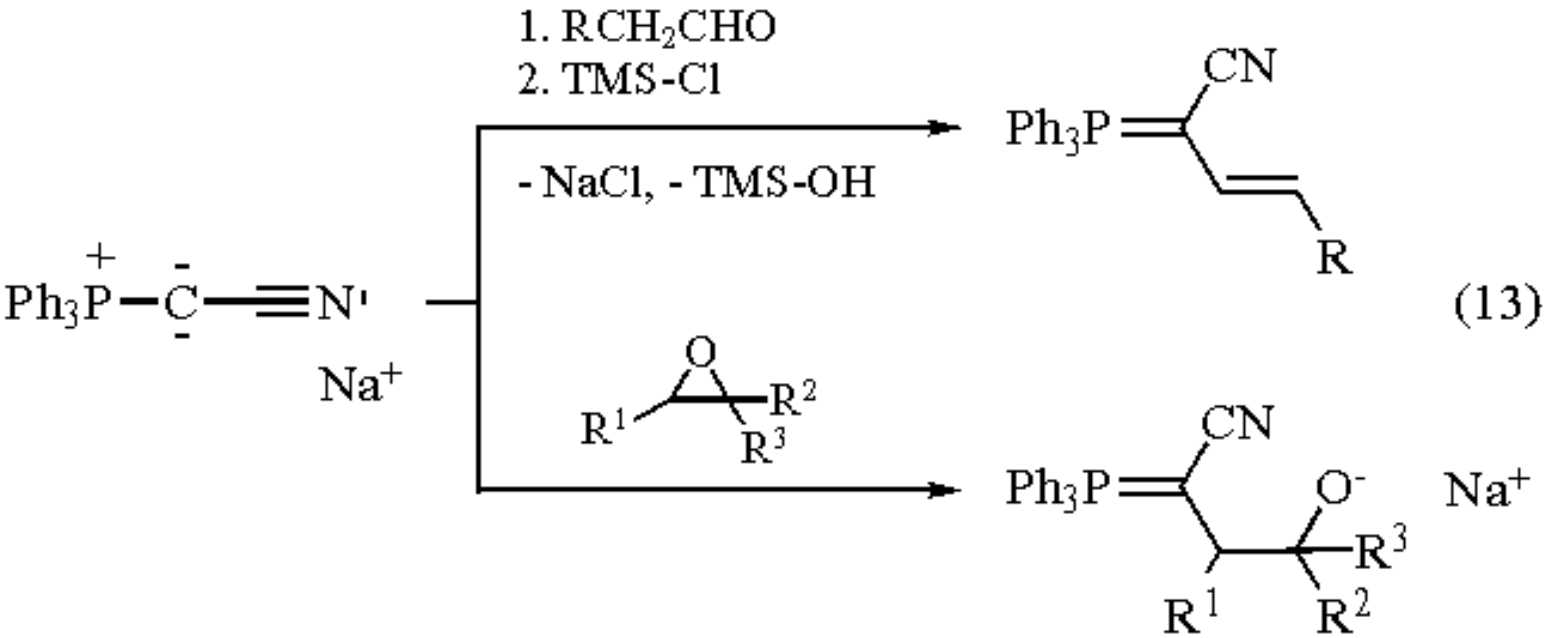

(13)

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Hans Jürgen Bestmann & Reiner Zimmermann

Cyano(methylthio)methyltrimethylsilane[1]

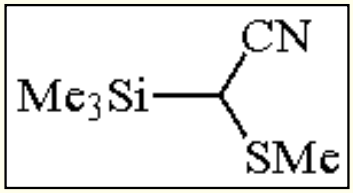

[121221-45-2] · $C_6H_{13}NSSi$ · Cyano(methylthio)methyltrimethylsilane · (MW 159.32)

(reagent for the synthesis of α-cyano-substituted vinyl sulfides[1])

Physical Data: bp 72-74 °C/4 mmHg.[1]

Solubility: sol ether, THF, and $CHCl_3$.

Analysis of Reagent Purity: ^{1}H NMR, IR.[1]

Preparative Method: prepared in 80-85% yield by the treatment of methylthioacetonitrile with ***Trimethylsilyl Trifluoromethanesulfonate*** and ***Triethylamine*** in ether at 0-5 °C for 3 h.[1]

Purification: distillation.

Handling, Storage, and Precautions: use in a fume hood.

Preparation of α-Cyano-Substituted Vinyl Sulfides.

Cyano(methylthio)methyltrimethylsilane is a Peterson alkenation reagent that was developed for the explicit purpose of preparing α-cyano-substituted vinyl sulfides in a one-step operation. Vinyl sulfides are versatile intermediates that participate in a variety of synthetically useful transformations.[2]

The lithiated anion of cyano(methylthio)methyltrimethylsilane reacts with aldehydes and ketones to give α-cyano-substituted vinyl sulfides directly (eq 1).[1]

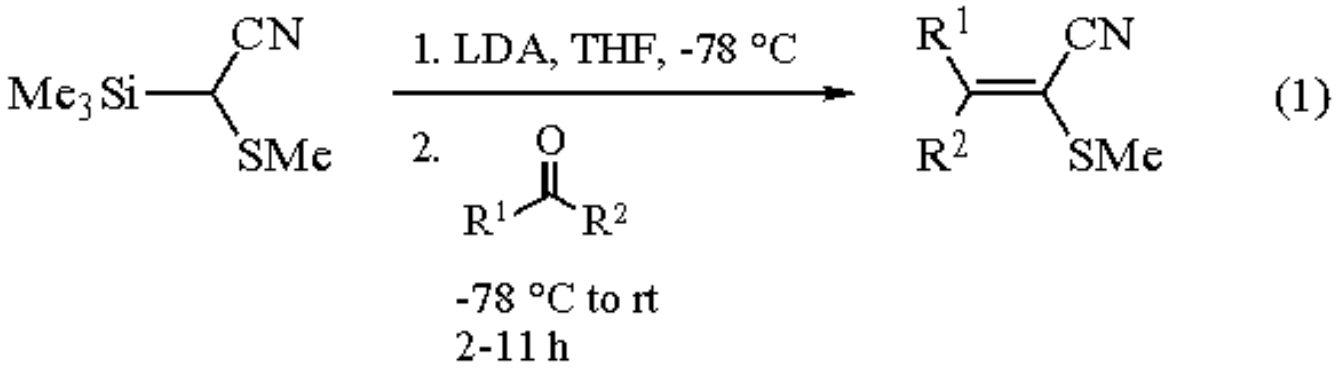

Shown in Table 1 are representative examples that define the scope of this process. In general, cyano(methylthio)methyltrimethylsilane undergoes reaction with aromatic and nonaromatic aldehydes and ketones, and is thus useful for preparing a variety of tri- and tetrasubstituted alkenes. Longer reaction times are required in cases where steric hindrance and competitive enolization impede (entries 4-8). One limitation of the reaction is that there is a lack of stereochemical control. Reaction products are isolated as mixtures of (*E*) and (*Z*) isomers. This nonselectivity is attributed to mechanistic factors associated with the Peterson reaction.

Table 1 Reaction of Aldehydes and Ketones (R^1COR^2) with Cyano(methylthio)methyltrimethylsilane

Entry	R^1	R^2	Reaction time (h)	Yield (%)	(*E*)/(*Z*) ratio
1	Ph	H	3	85	3:4
2	PhCH=CH	H	4	78	1:1
3	Furan	H	3	82	3:2
4	$Me(CH_2)_5$	H	6	67	1:1
5	Ph	Me	12	61	5:1
6	$Me(CH_2)_4$	Me	6	78	1:1
7	$(CH_2)_5$		10	42	
8	$(CH_2)_4CHMe$		12	41	1:1

Alternate Methods for the Preparation of α-Cyano-Substituted Vinyl Sulfides.

Numerous methods have been described for the preparation of α-cyano-substituted vinyl sulfides that vary in complexity and scope. Three approaches that require multi-step substrate modifications include the addition of methylsulfenyl chloride

to acrylonitrile followed by dehydrochlorination (eq 2),[3] potassium bromide induced rearrangement of α-chloro-β-alkylthionitriles (eq 3),[4] and dehydrobromination of α-bromo-α-cyano thioethers (eq 4).[5]

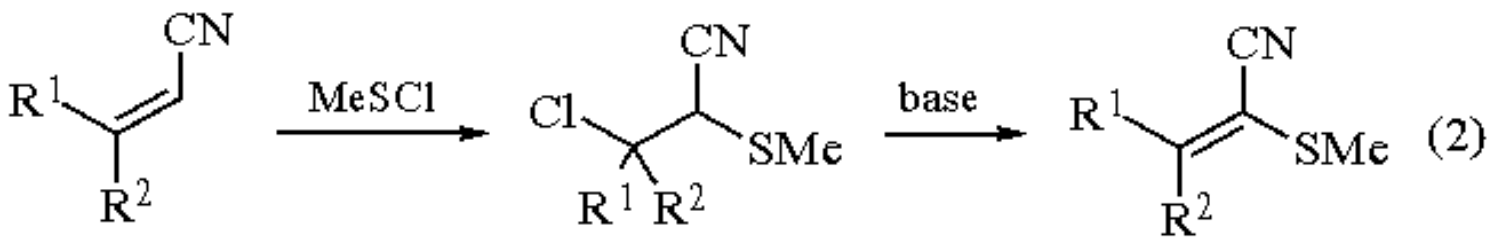

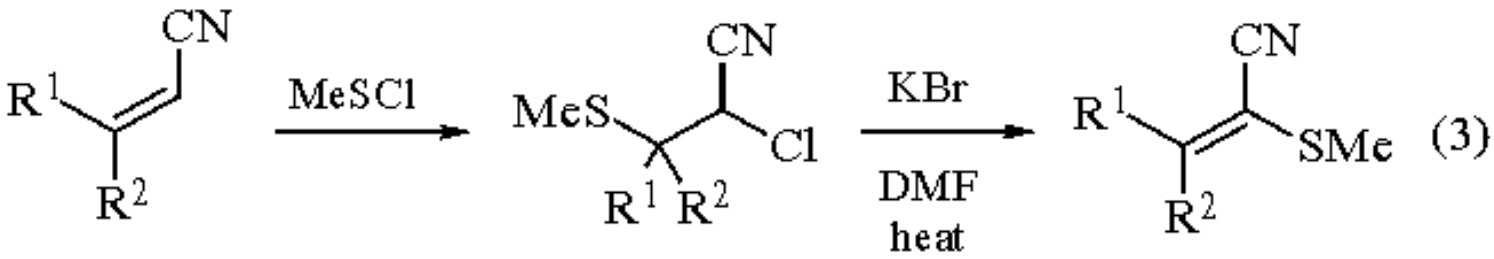

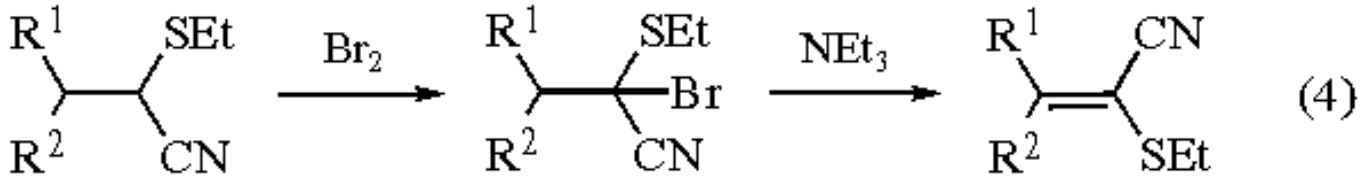

In addition to cyano(methylthio)methyltrimethylsilane, two distinct reagent-based approaches to the synthesis of α-cyano-substituted vinyl sulfides have been reported. The first method involves the Horner-Emmons reaction of an aldehyde or ketone with a thiophenoxy-modified cyanomethylphosphonate (eq 5).[6] This method is not of general utility since the phosphonate reagent is prepared in low yield, and its reactivity is limited by steric and electronic factors. The second method involves the condensation of ethylthioacetonitrile with an aldehyde or ketone (eq 6).[5] This reaction is applicable to a variety of substrates with some limitation due to the strongly basic conditions. Products are isolated as mixtures of (*E*) and (*Z*) isomers.

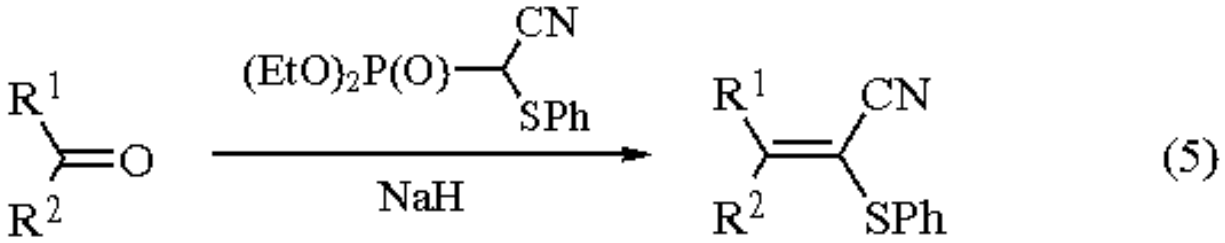

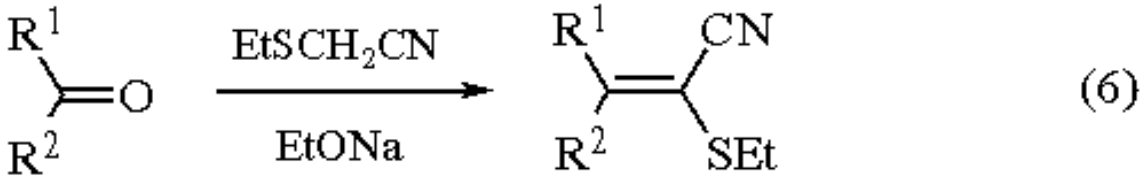

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Lilly Research Laboratories, Indianapolis, IN, USA

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4-Cyanothiolan-3-one

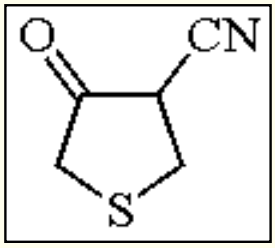

[16563-14-7] · C_5H_5NOS · 4-Cyanothiolan-3-one · (MW 127.11)

(precursor for α-substituted acrylonitriles,[1] 2-cyano-1,3-butadiene,[2] and substituted thiophenes;[3,4] building block for thienobenzodiazepines[5])

Alternate Name: 4-oxothiolane-3-carbonitrile.

Physical Data: mp 71-72 °C (from diethyl ether);[1,4] IR and ^{1}H NMR spectra.[1]

Form Supplied in: commercially available.

Preparative Method: [1,6] can be conveniently prepared in 50% yield by cyclization of the Michael adduct of methyl thioglycolate and acrylonitrile.

Synthetic Equivalent for the α-Acrylonitrile Anion.[1]

Alkylation of 4-cyanothiolan-3-one with a variety of alkyl halides in the presence of ***Potassium Carbonate*** provides *C*-alkylated products in excellent yields. Their treatment with aqueous ***Sodium Hydroxide*** affords α-substituted acrylonitriles through tandem Dieckmann-Michael retrograde reactions (eq 1).

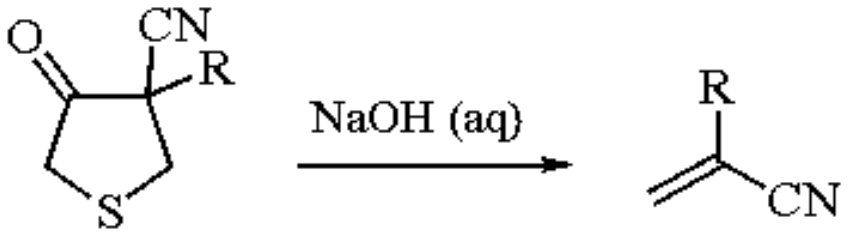

(1)

Synthetic Precursor for 2-Cyano-1,3-butadiene.[2]

This rather unstable conjugated diene can be generated and trapped in situ by dienophiles using the nicely crystalline 3-cyano-2,5-dihydrothiophene 1,1-dioxide as a suitable precursor. This precursor is derived from 4-cyanothiolan-3-one in a three-step sequence involving reduction of the carbonyl group followed by dehydration and *S*,*S*-oxidation. On heating a toluene solution of the diene in the absence of dienophiles, self-condensation takes place to afford the dimer, which has been hydrolyzed to mikanecic acid (eq 2).

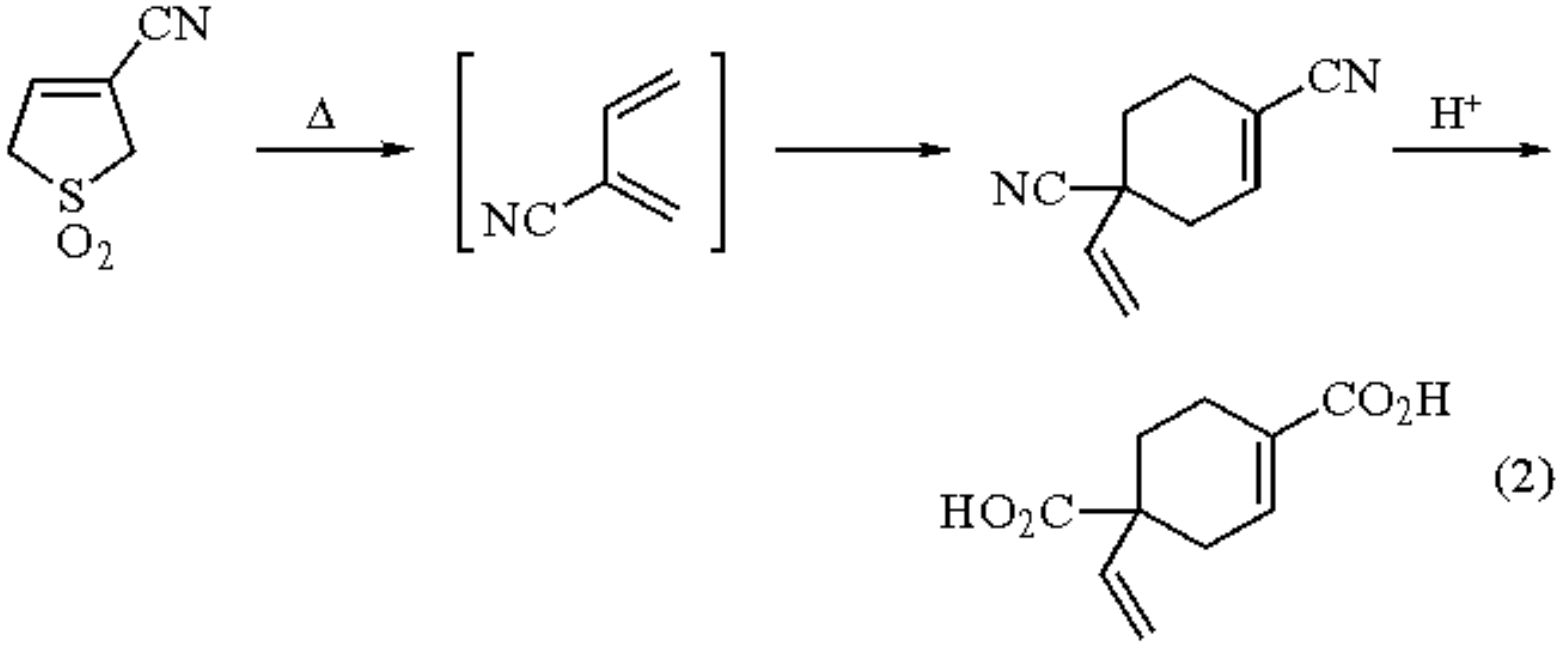

(2)

3,4-Disubstituted Thiophenes.

2,5-Dihydrothiophenes, derived from enamines or enol ethers of 4-cyanothiolan-3-one, can be efficiently aromatized to the corresponding thiophene derivatives by treatment with ***Chloranil***[3,5] or ***Sulfuryl Chloride*** (eq 3).[4]

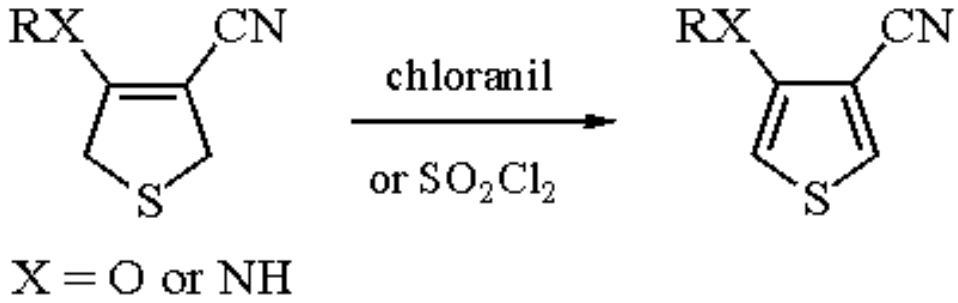

(3)

Building Block for Polycondensed Heterocycles.

The cyclocondensation of 4-cyanothiolan-3-one with 1,2-diaminobenzenes followed by chloranil aromatization affords biologically interesting substituted 10-amino-4*H*-thieno[3,4-*b*][1,5]benzodiazepines (**1**).[5]

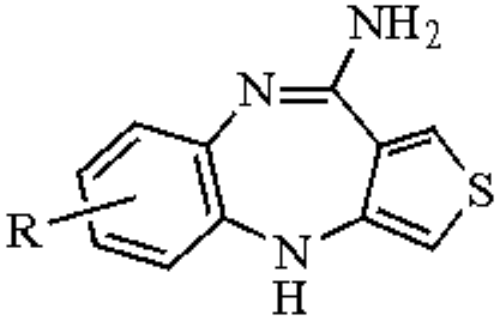

(1)

Related Reagents.

Acrylonitrile; ***2-(Dimethylamino)-3-butenenitrile***; ***Lithioacetonitrile***; ***4-Methoxycarbonylthiolan-3-one***; ***Methyl 3-(Dimethylamino)propionate***; ***Methyl 3-Hydroxypropionate***.

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Achille Barco, Simonetta Benetti, & Gian P. Pollini

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Cyanotributylstannane

Bu_3SnCN

[2179-92-2] · $C_{13}H_{27}NSn$ · Cyanotributylstannane · (MW 316.07)

(reagent for cyanation of halides; can add to aldehydes; catalyst for halosilane substitution)

Alternate Name: tributyltin cyanide.

Physical Data: mp 90-93 °C (from petroleum ether);[1] 93-96.5 °C (from acetonitrile).[2]

Solubility: sol common org solvents.

Form Supplied in: colorless solid.

Preparative Methods: originally from ***Tri-n-butylchlorostannane*** and ***Potassium Cyanide***.[1] Modified procedures using ***18-Crown-6***[2] or ***Lithium Cyanide***[3] give better yields.

Handling, Storage, and Precautions: hygroscopic, but stable under a dry atmosphere. Both cyano and alkyltin compounds are highly toxic.

Coupling with Halides.

Cyanation of vinyl or aryl halides is effectively catalyzed by palladium(0) complexes. The reaction can be applied to the synthesis of cyano homologs of nucleosides (eq 1),[4] nucleoside bases,[5] and *cis*-dihydrodiols derived from arenes.[6]

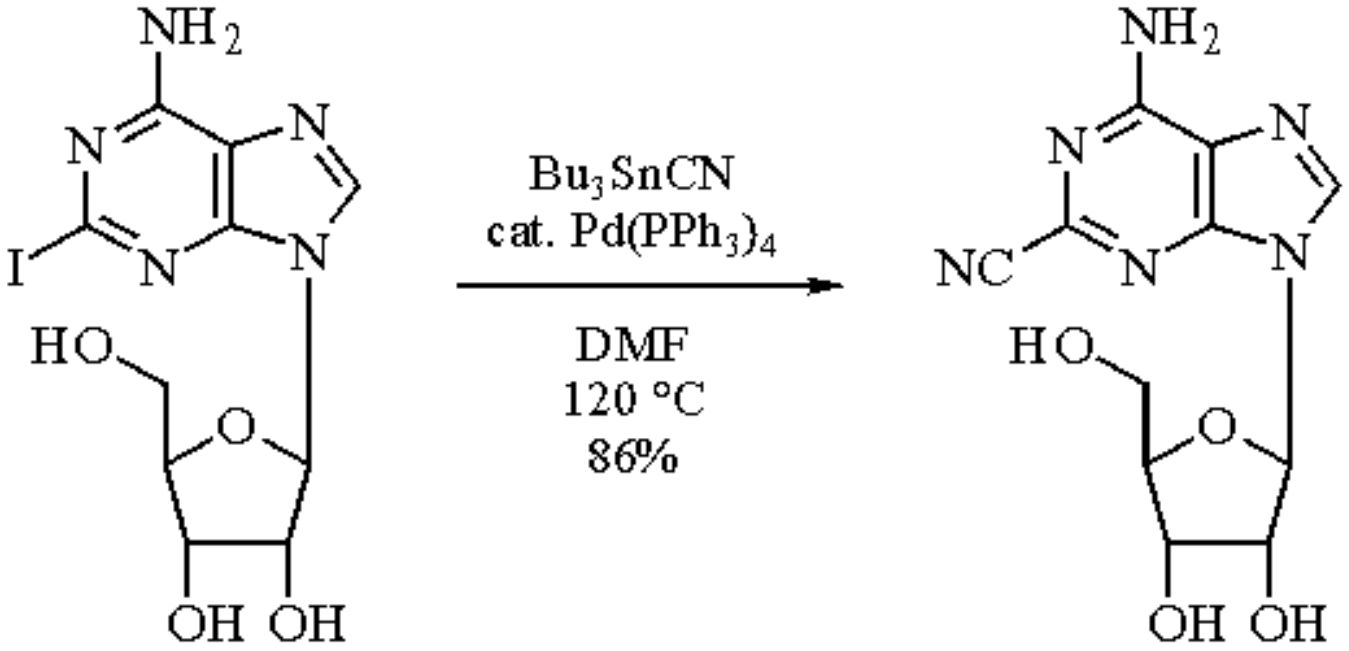

(1)

Aryl, vinyl, and tertiary alkyl acid halides can be cyanated by the reagent to give acyl cyanides in good yields (eq 2).[2] Primary or secondary alkyl acid halides react further to afford acyl cyanide dimers.

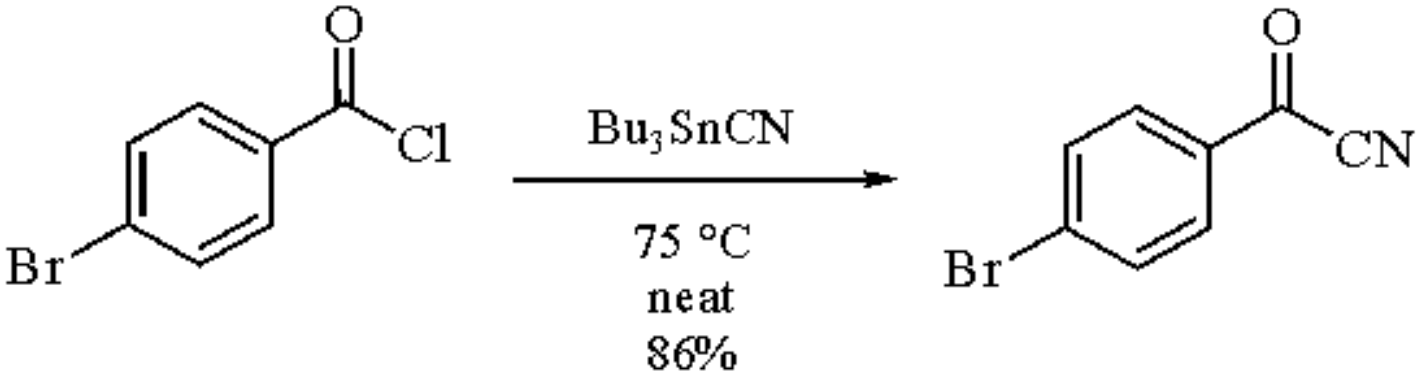

(2)

The three-component coupling of aryl halides, cyanotributylstannane, and isocyanides takes place in the presence of palladium(0) to yield iminoacyl cyanides in moderate yields.[7]

Addition to Aldehydes.

Cyanohydrins are obtained by the reaction of cyanotributylstannane with aldehydes. Although a chiral titanium catalyst did not effect any asymmetric induction,[8a] good 1,2-diastereoselectivity was achieved in the reaction with α-amino aldehydes.[8b]

Catalysis of Halosilane Substitution Reactions.

A catalytic amount of cyanotributylstannane facilitates the substitution of silyl chlorides by Grignard

reagents.[9]

Related Reagents.

Acetyl Cyanide; ***Cyanotrimethylsilane***; ***Hydrogen Cyanide***; ***Diethylaluminum Cyanide***; ***Potassium Cyanide***; ***Sodium Cyanide***; ***Tri-n-butylchlorostannane***; ***Zinc Cyanide***.

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Cyanotrimethylsilane[1]

Me_3SiCN

[7677-24-9] · C_4H_9NSi · Cyanotrimethylsilane · (MW 99.21)

(agent for the cyanosilylation of saturated and unsaturated aldehydes and ketones;[2] powerful silylating agent;[3] reagent for carbonyl umpolung[4])

Alternate Name: trimethylsilyl cyanide.

Physical Data: mp 11-12 °C; bp 118-119 °C; *d* 0.744 g cm^{-3}.

Solubility: sol organic solvents (CH_2Cl_2, $CHCl_3$); reacts rapidly with water and protic solvents.

Form Supplied in: colorless liquid; available commercially. Can also be prepared.[1e]

Handling, Storage, and Precautions: flammable liquid which must be stored in the absence of moisture and used in an inert atmosphere. Reagent is highly toxic: contact with water produces hydrogen cyanide.

Introduction.

Cyanotrimethylsilane is a highly versatile reagent that reacts with a multitude of functional groups to yield an array of products and/or highly valuable synthetic intermediates.

Cyanohydrin Trimethylsilyl Ethers and Derivatives.

Aldehydes and ketones are readily transformed into the corresponding cyanohydrin trimethylsilyl ethers when treated with cyanotrimethylsilane in the presence of Lewis acids (eq 1),[5,6] triethylamine,[7] or solid bases such as CaF_2 or hydroxyapatite.[8] The products can be readily hydrolyzed to the corresponding cyanohydrins. The cyanosilylation of aromatic aldehydes can be achieved with high enantioselectivity in the presence of catalytic amounts of a modified Sharpless catalyst consisting of ***Titanium Tetraisopropoxide*** and L-(+)-diisopropyl tartrate (eq 2).[9] Catalysis with chiral titanium reagents yields aliphatic and aromatic cyanohydrins in high chemical and optical yields (eq 3).[10] Cyanohydrins can be subsequently transformed into a variety of useful synthetic intermediates (eq 4).[11,12]

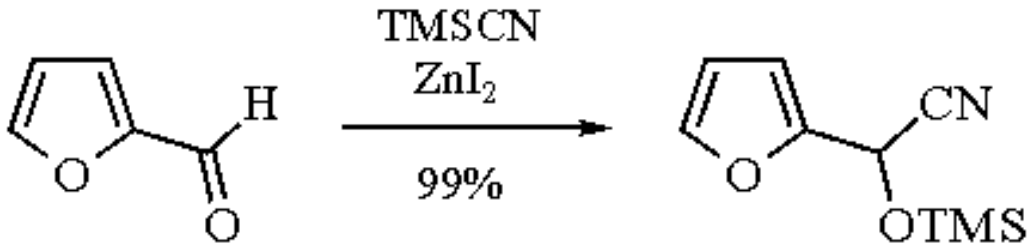

(1)

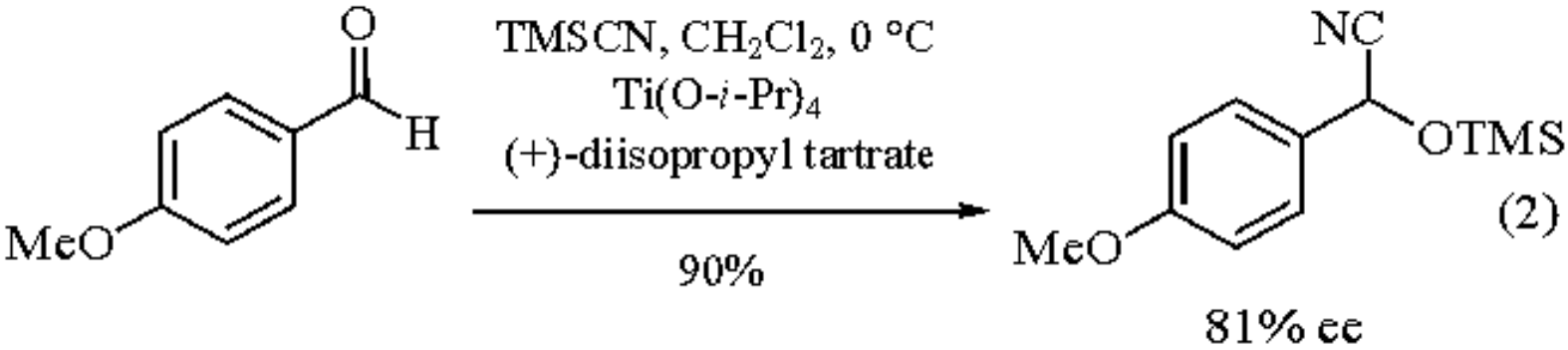

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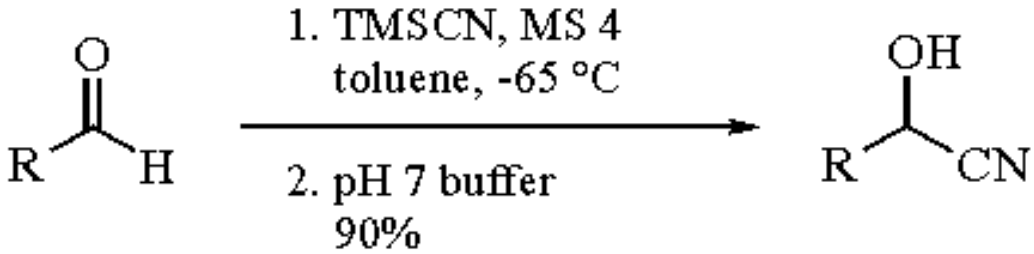

(3)

R = Ph, 79%, 96% ee
R = Bn, 66%, 77% ee
R = phenylethyl, 89%, 89% ee

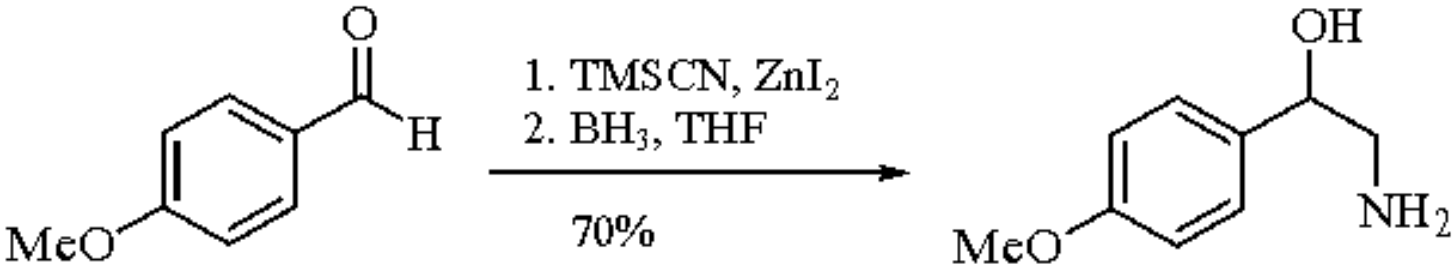

(4)

Conjugate Additions.

Cyanotrimethylsilane reacts with α,β-unsaturated ketones in the presence of Lewis acids (***Aluminum Chloride***, ***Tin(II) Chloride***, ***Triethylaluminum***) to yield, upon hydrolysis, the corresponding 1,4-addition products (eqs 5 and 6).[13] This methodology is superior to other procedures.[14] By controlling the reaction conditions and the stoichiometry of the reaction, the kinetically controlled 1,2-addition products can also be obtained in high yields (eq 7).[13,15]

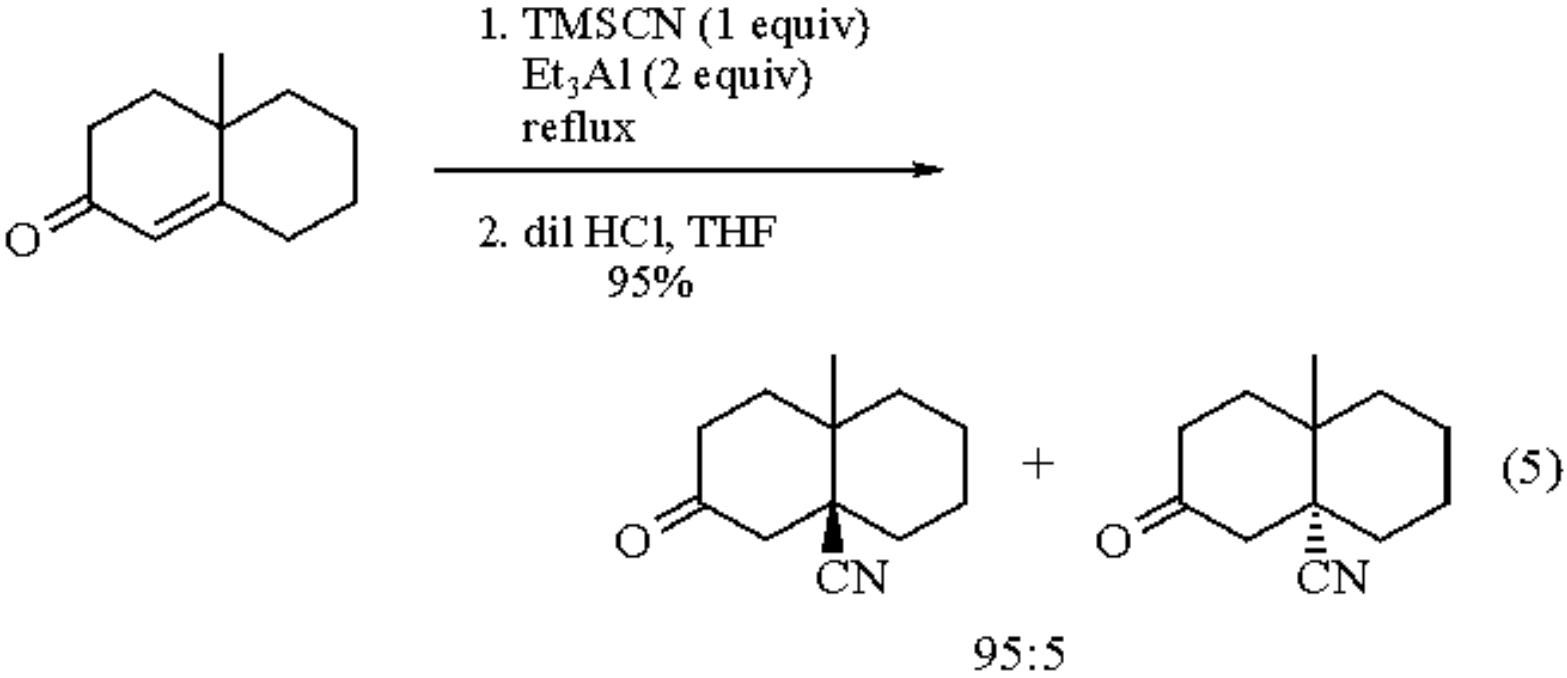

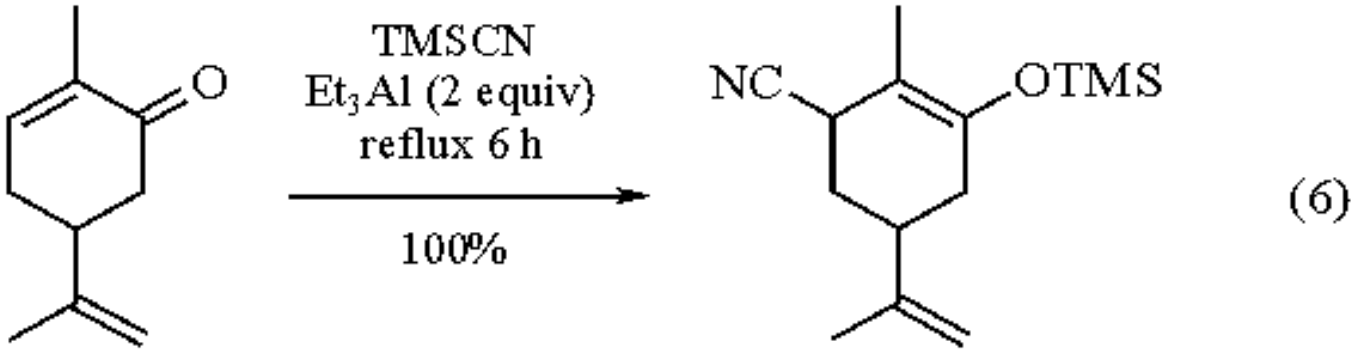

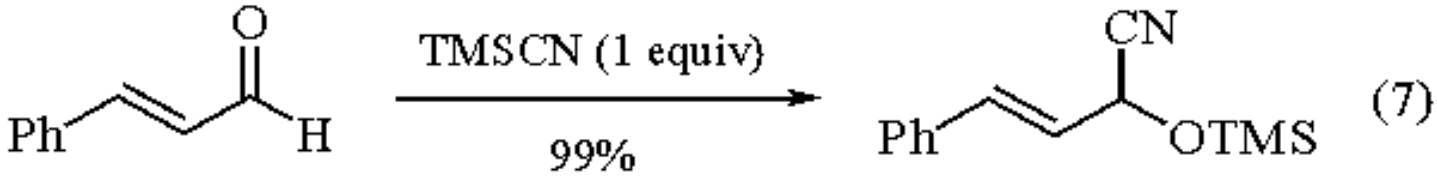

Regioselective cyanosilylation of unsaturated ketones can also be effected efficiently using a solid acid or solid base support.[16] 1,4-Adducts are obtained when a strong solid acid such as Fe^{3+}- or Sn^{4+}-montmorillonite is used (see ***Iron(III) Nitrate-K10 Montmorillonite Clay***), while 1,2-adducts are obtained in the presence of solid bases such as CaO and MgO.

Reactions with Oxiranes, Oxetanes, and Aziridines.

Lewis acids, lanthanide salts, and titanium tetraisopropoxide or ***Aluminum Isopropoxide*** catalyze the reactions of cyanotrimethylsilane with oxiranes, oxetanes, and aziridines, yielding ring-opened products. The nature of the products and the regioselectivity of the reaction are primarily dependent on the nature of the Lewis acid, the substitution pattern in the substrate, and the reaction conditions. Monosubstituted oxiranes undergo regiospecific cleavage to form 3-(trimethylsiloxy)nitriles when refluxed with a slight excess of cyanotrimethylsilane in the

presence of a catalytic amount of ***Potassium Cyanide-18-Crown-6*** complex (eqs 8-10).[17] The addition of cyanide occurs exclusively at the least-substituted carbon.

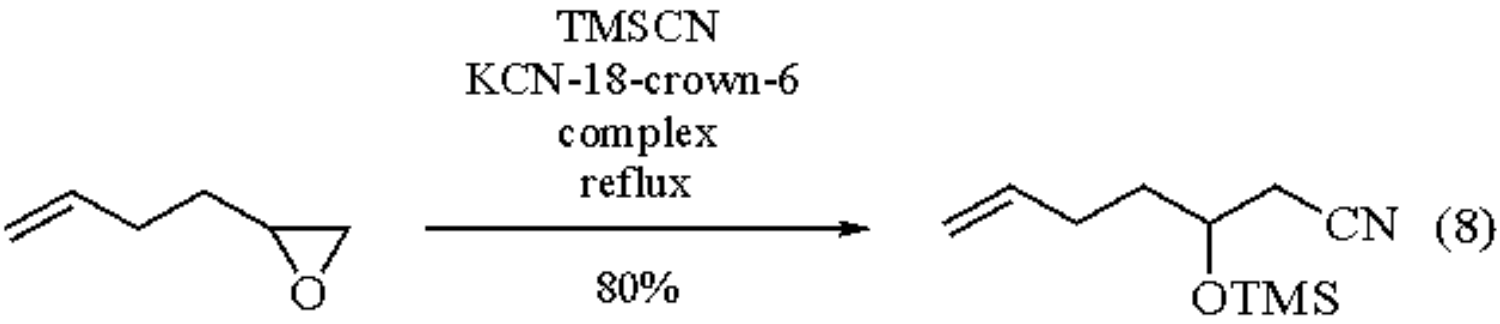

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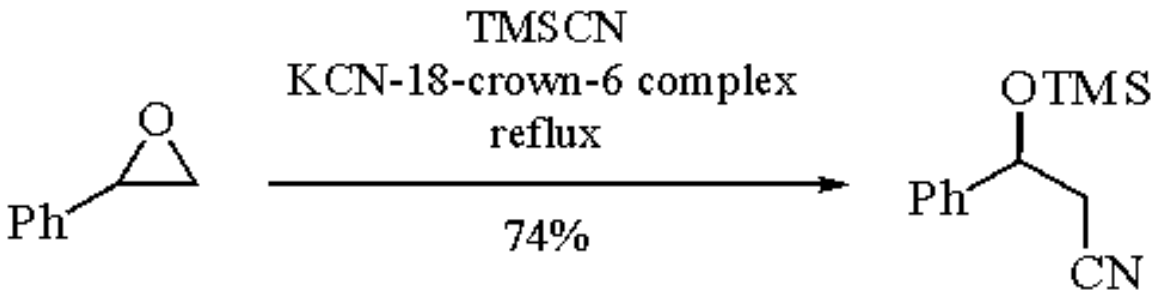

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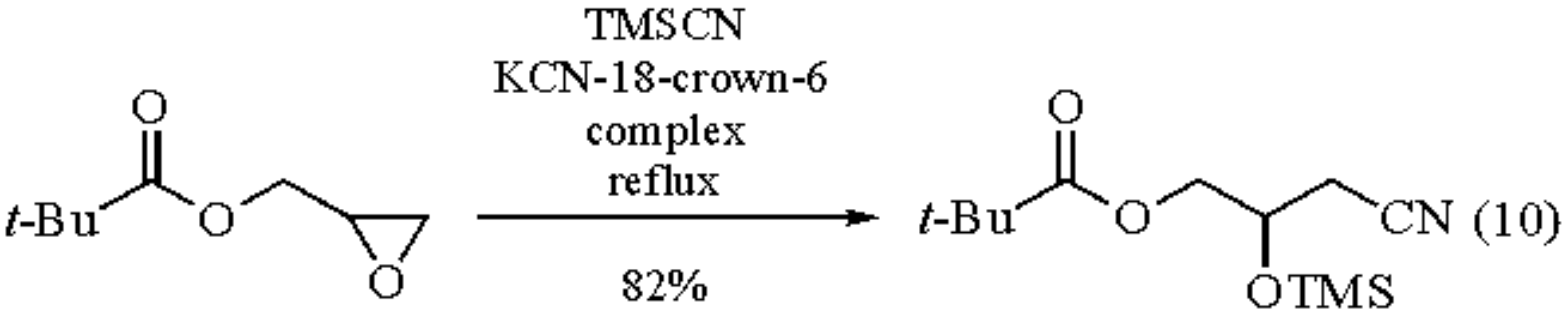

(10)

Good yields of 3-(trimethylsiloxy)nitriles are also obtained from the reactions of oxiranes with cyanotrimethylsilane in the presence of lanthanide salts,[18] or when the reaction is catalyzed by $AlCl_3$ or ***Diethylaluminum Chloride*** (eq 11).[19] Ring opening of chiral glycidyl derivatives by Me_3SiCN catalyzed by $Ti(O\text{-}i\text{-}Pr)_4$ or $Al(O\text{-}i\text{-}Pr)_3$ occurs in a regiospecific and highly stereoselective manner (eq 12).[20]

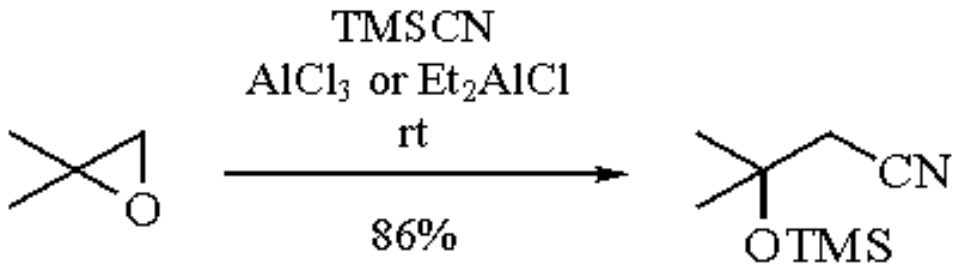

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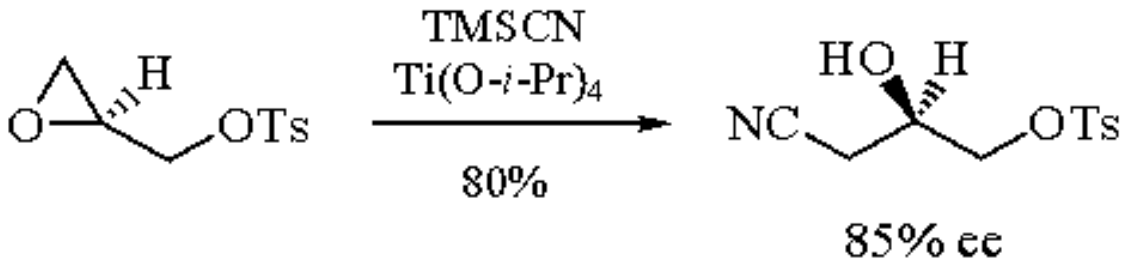

(12)

Oxetanes give rise to 4-(trimethylsiloxy)propionitriles (eq 13).[19] Similar observations have been made in the reactions of *N*-tosylaziridines and cyanotrimethylsilane catalyzed by lanthanum salts (eq 14).[21]

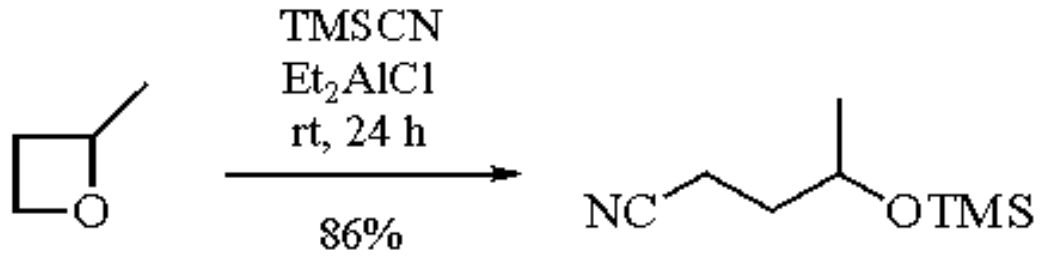

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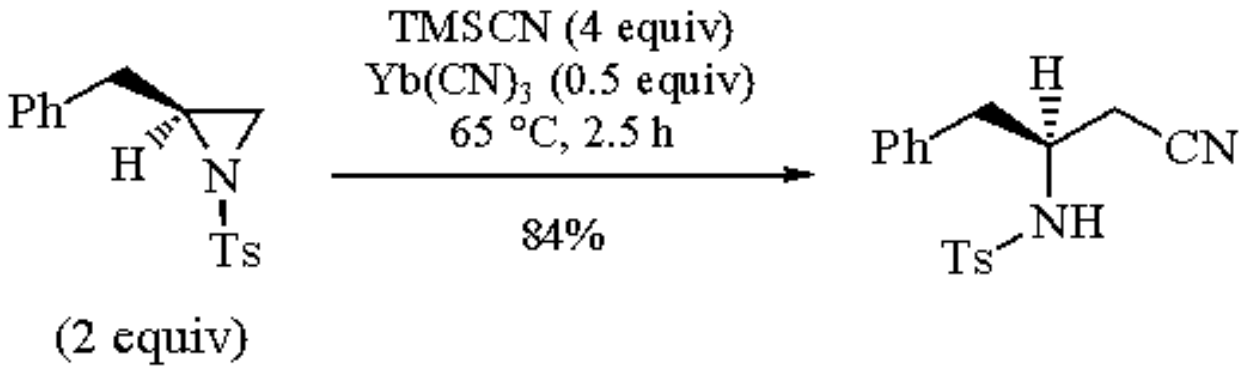

(14)

The ambident nature of cyanotrimethylsilane[22] can lead to the formation of nitriles or isocyanides, depending on the nature of the catalyst. For example, cyanotrimethylsilane reactions with epoxides and oxetanes catalyzed by soft Lewis acids give rise to 2-(trimethylsiloxy) isocyanides arising by attack on the more substituted carbon (eqs 15 and 16).[23-25] Milder reaction conditions and better yields of isocyanides can be realized when the reaction of cyanotrimethylsilane with oxiranes is carried out in the presence of $Pd(CN)_2$, $SnCl_2$, or Me_3Ga (eq 17).[26] Isocyanides are useful precursors for the synthesis of β-amino alcohols and oxazolines.

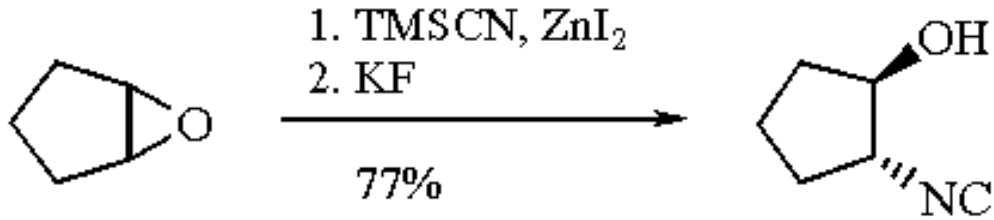

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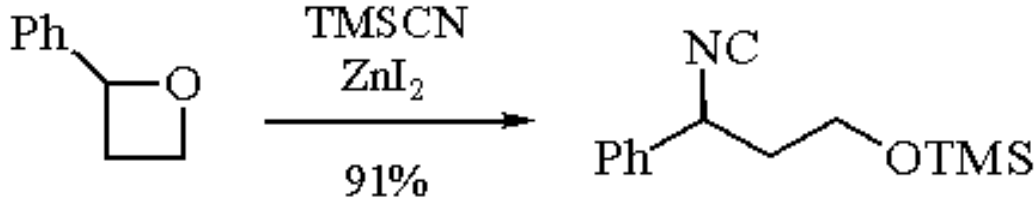

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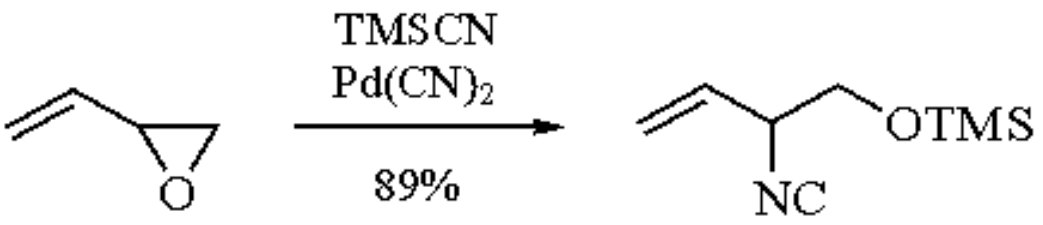

(17)

Carbonyl Umpolung.

When deprotonated with a strong base, *O*-(trimethylsilyl) cyanohydrins can function as effective acyl anion equivalents that can be used to convert aldehydes to ketones,[27] and in the synthesis of 1,4-diketones,[28] tricyclic ketones,[29] and the highly sensitive α,β-epoxy ketone functionality (eq 18).[30]

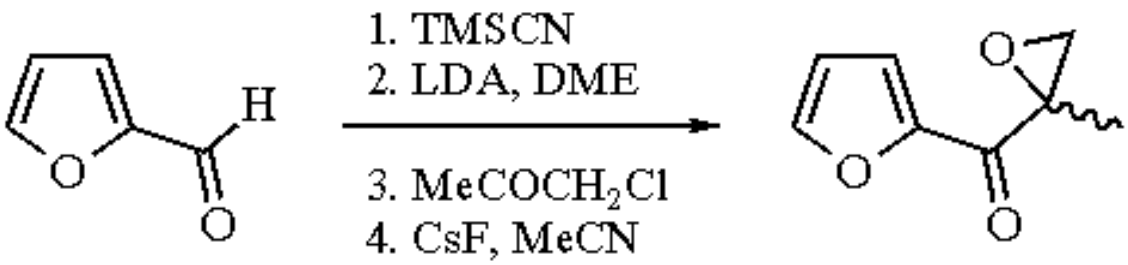

(18)

Miscellaneous Transformations.

Cyanotrimethylsilane effects the transformation of acyl chlorides to acyl cyanides,[31] α-chloro ethers and α-chloro thioethers to α-cyano ethers[32] and α-cyano thioethers (eq 19),[33] *t*-butyl chlorides to nitriles (eqs 20 and 21),[34] 1,3,5-trisubstituted hexahydro-1,3,5-triazines to aminoacetonitriles,[35] the cyanation of allylic carbonates and acetates (eqs 22 and 23),[36] and the formation of aryl thiocyanates from aryl sulfonyl chlorides and sulfinates.[37] The reagent has been used effectively in peptide synthesis[38] and in a range of other synthetic applications.[39-46]

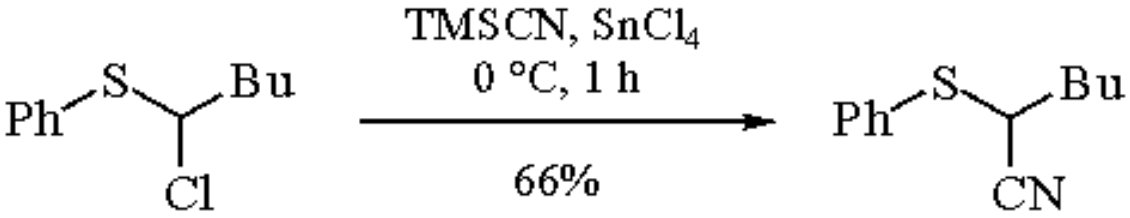

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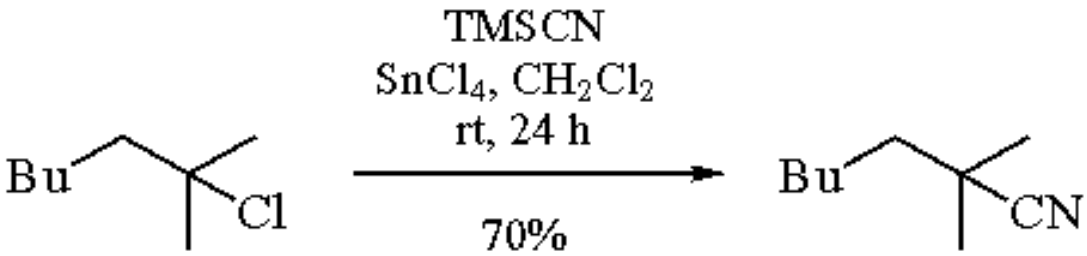

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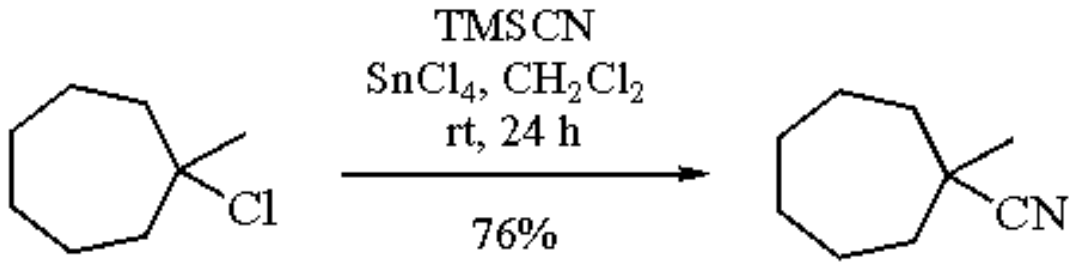

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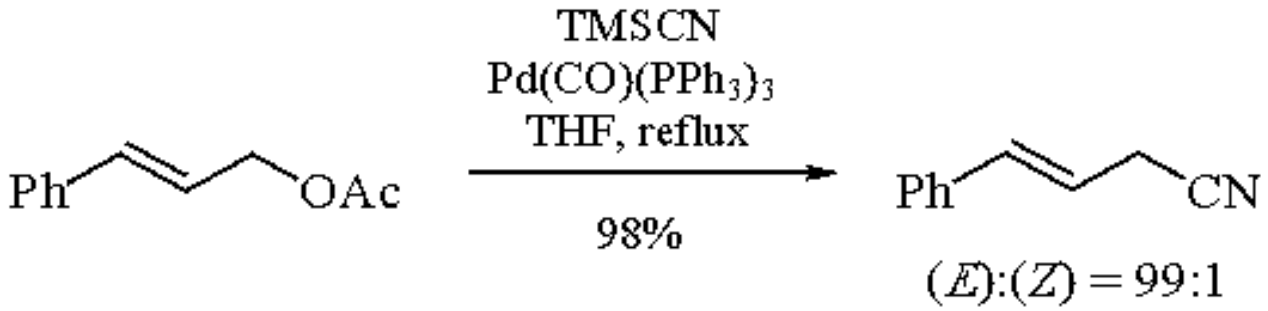

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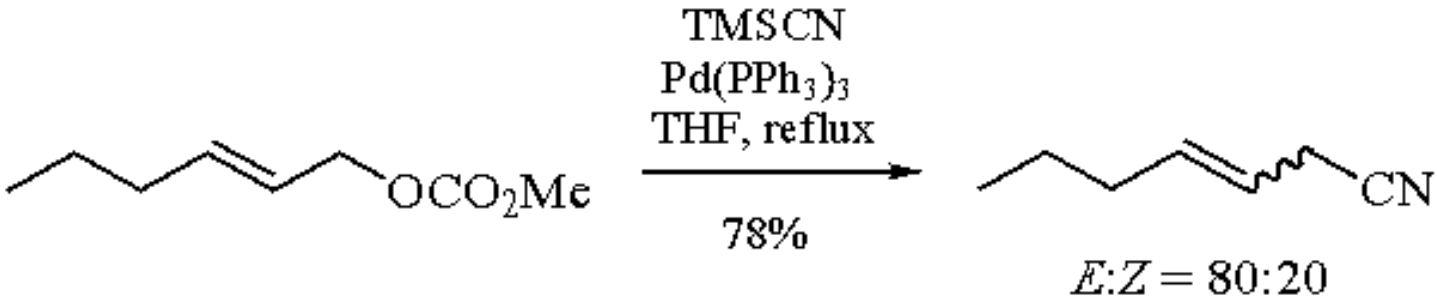

(23)

Related Reagents.

t-Butyldimethylsilyl Cyanide; ***Hydrogen Cyanide***.

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Cyclobutanone[1]

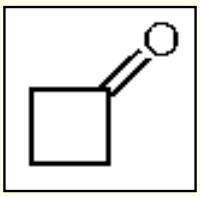

[1191-95-3] · C_4H_6O · Cyclobutanone · (MW 70.09)

(strained cyclic ketone capable of undergoing ring-expansion, ring-contraction and ring-opening reactions to give functionalized cyclopentanones,[2] tetrahydrofurans,[3] cyclopropanes, and terminally functionalized butyric acid derivatives[1d])

Physical Data: mp -51.1 to -52.5 °C; bp 97-100 °C; *d* 0.931 g cm^{-3}; n_D^{20} 1.421.

Solubility: slightly sol H_2O; sol most organic solvents.

Form Supplied in: colorless liquid, >99% pure, limited availability; relatively expensive.

Preparative Methods: over 30 preparative methods have been reported. The most convenient methods include the ketene-diazomethane condensation[4] and the selective di-Grignard reaction using 1,3-dibromopropane with carbon dioxide.[5]

Purification: distillation by spinning band column or preparative GC.

Handling, Storage, and Precautions: flammable liquid (flash point 27 °C). Contact with skin and eyes should be avoided.

Introduction.

The strain associated with the cyclobutanone ring system permits ring-expansion reactions to occur more readily than with larger cycloalkanones.

Ring Expansion to Cyclopentanones.

The one-carbon ring expansion of cyclobutanone and its derivatives represents a convenient method for the preparation of cyclopentanones. The general scheme is represented by eq 1, in which a one-carbon nucleophile bearing a potential leaving group is added to the carbonyl function, followed by an α-carbon migration. The one-

carbon homologation of cyclobutanone with ***Diazomethane*** gives cyclopentanone as the major product (58%), along with small amounts of cycloheptanone (17%) and cyclooctanone (25%).[6] α-Functionalized cyclopentanones are readily prepared by alkylation of cyclobutanone with dithio- or trithiomethide ions followed by rearrangement of the intermediate cyclobutanols. The yields of the cyclopentanones are satisfactory for this two-step sequence (eqs 2 and 3).[2,7] α-(Phenylthio)cyclopentanone may also be obtained by addition of LiCHIS(O)Ph (88%), followed by reductive rearrangement of the β-hydroxy sulfoxide adduct with $TiCl_4$ and Zn (62%).[8]

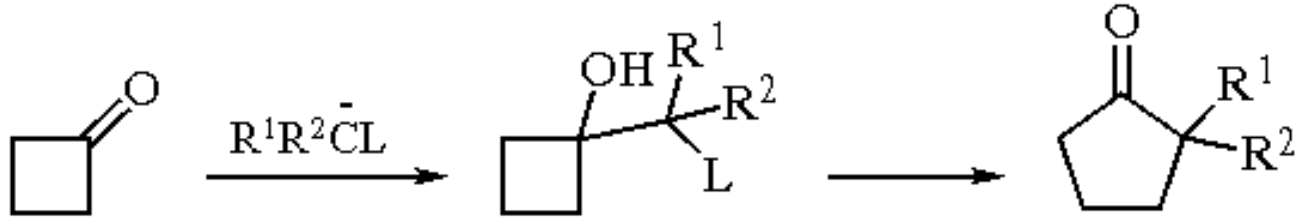

(1)

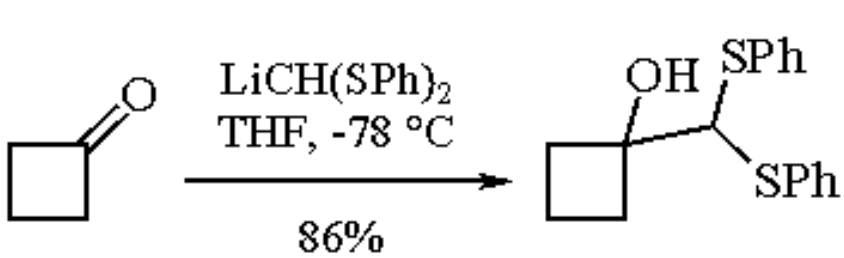

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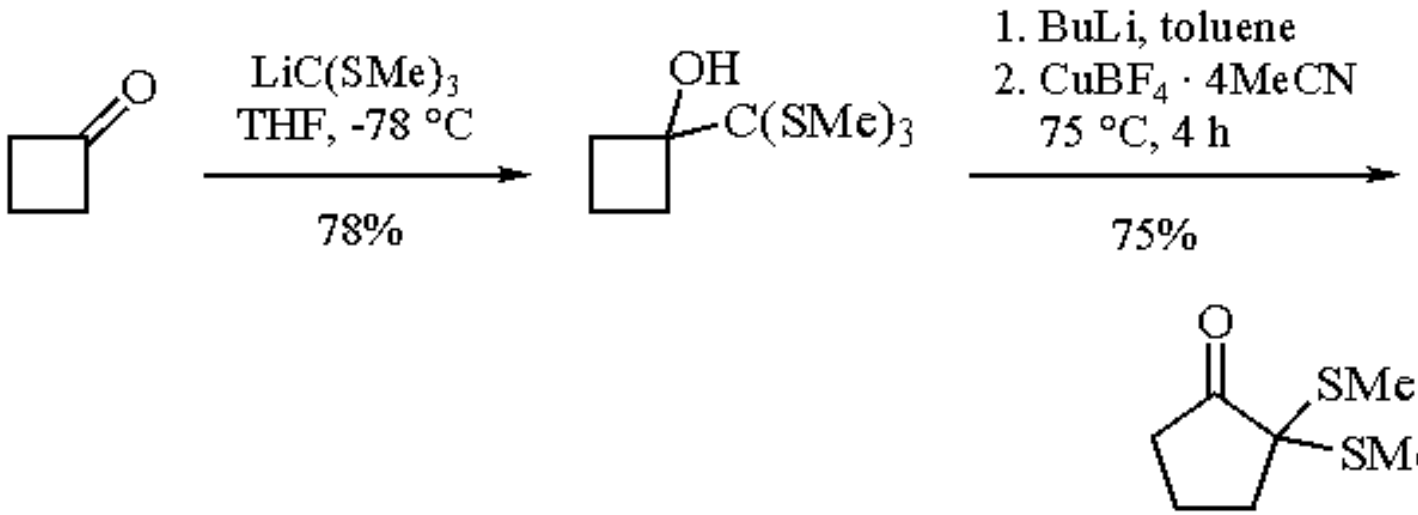

(3)

The electrochemical condensation of ***Ethyl Trichloroacetate*** with cyclobutanone gives the five-carbon α-chloro-β-keto ester (eq 4).[9]

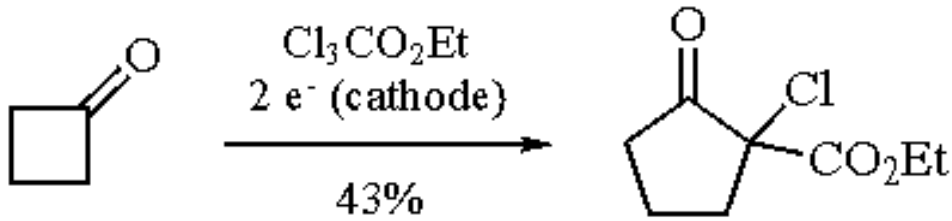

(4)

1-Alkenylcyclobutanols, which are readily prepared by metal alkenyl additions to cyclobutanone, undergo Lewis acid-

catalyzed ring expansion to cyclopentanones. For example, the spirocyclic cyclopentanone is readily prepared in high yields from the acid-catalyzed rearrangement of the 5-lithio-2,3-dihydrofuran condensation product (eq 5).[10]

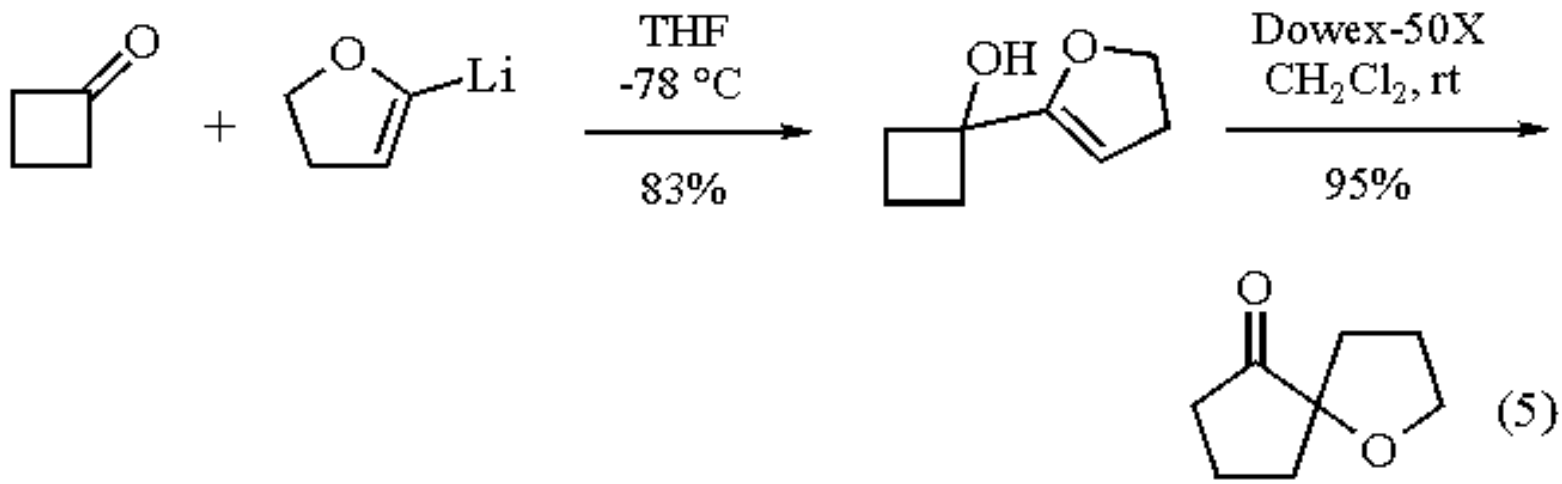

(5)

In similar fashion, 2-chloromethyl-2-methylcyclopentanone can be prepared from 1-isopropenylcyclobutanol (eq 6); this rearrangement may involve a radical mechanism.[11] Acid-catalyzed rearrangement of this cyclobutanol in a sulfuric acid-ethanol mixture gives 2,2-dimethylcyclopentanone, isolated as the DNP in 51% yield.

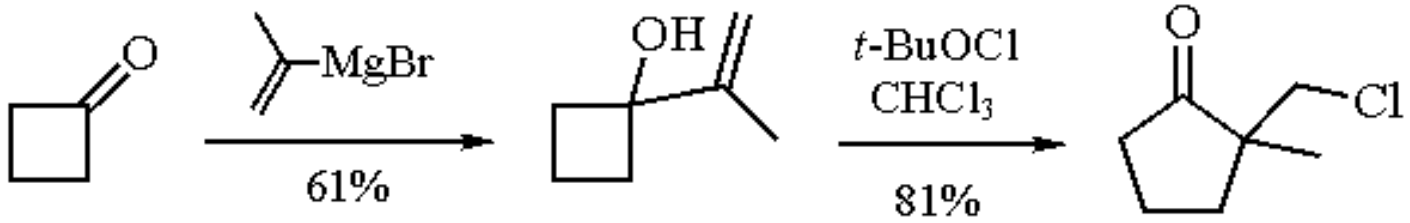

(6)

2-Methylcyclopent-2-enones are readily prepared from the Pd^{II}-assisted rearrangement of 1-vinylcyclobutanols (eq 7). However, this scheme has not been applied to the unsubstituted cyclobutyl ring.[12]

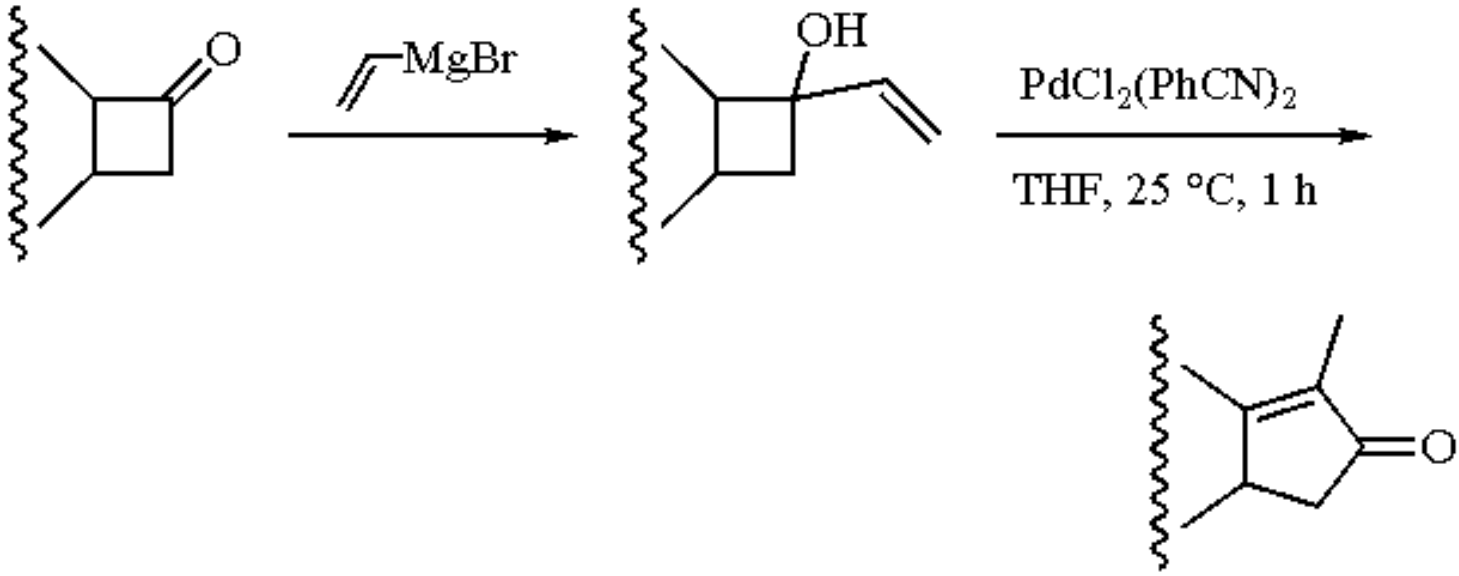

(7)

The pinacol rearrangement of the reductive coupling product of cyclobutanone gives the spirooctanone (eq 8).[13] More recently, the same pinacol has been obtained in higher yields with cerium(II) iodide.[14] The same spirooctanone is obtained by the thermal rearrangement of dicyclobutylidene epoxide (eq 9).[15] Dicyclobutylidene may be obtained by thiadiazoline elimination or, in lower yield, by a direct Wittig reaction with cyclobutylphosphonium ylide.

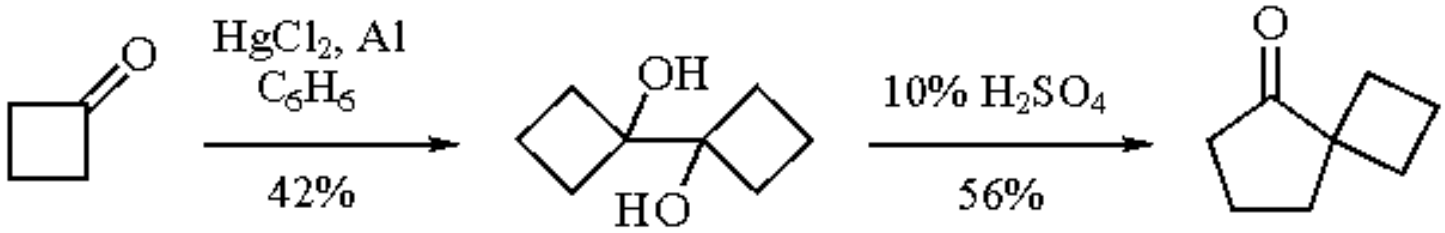

(8)

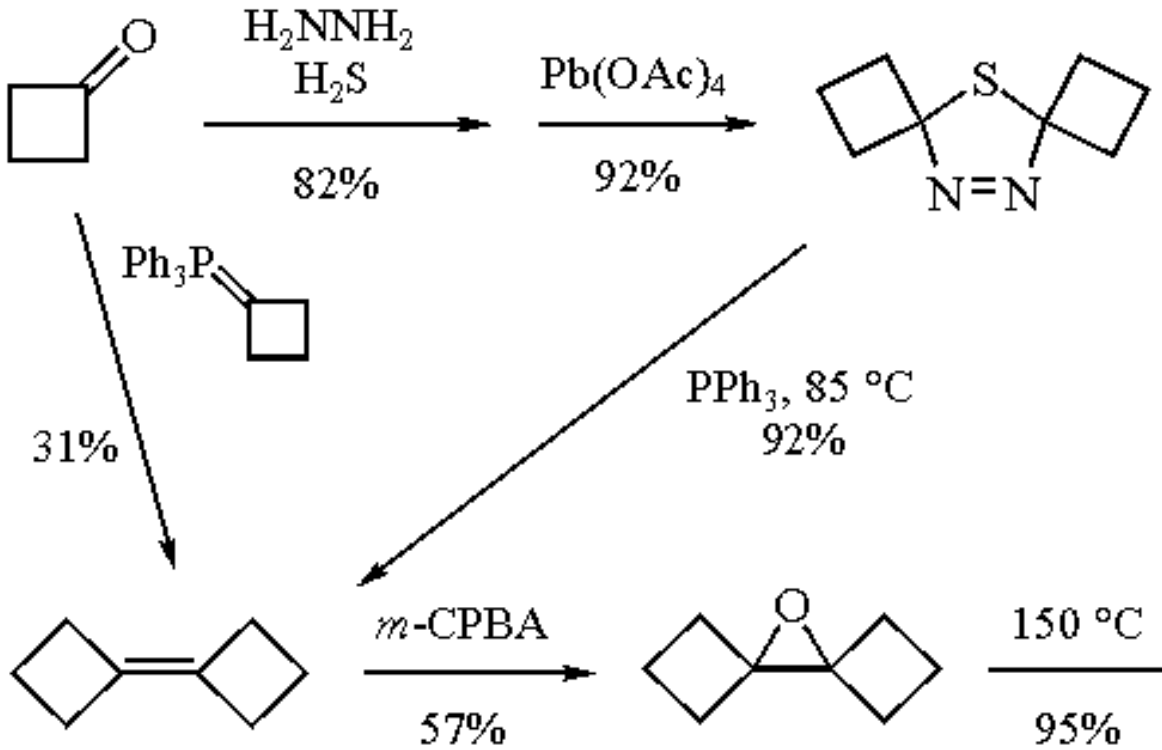

(9)

Ring Expansions to Cyclohexenones and Cyclohexanones.

α-Alkylidene- and α,α´-dialkylidenecyclobutanones, obtained from cross-aldol condensations of cyclobutanone, rearrange readily with ***Polyphosphoric Acid*** (PPA) at elevated temperatures to the corresponding cyclohexenones (eq 10).[16]

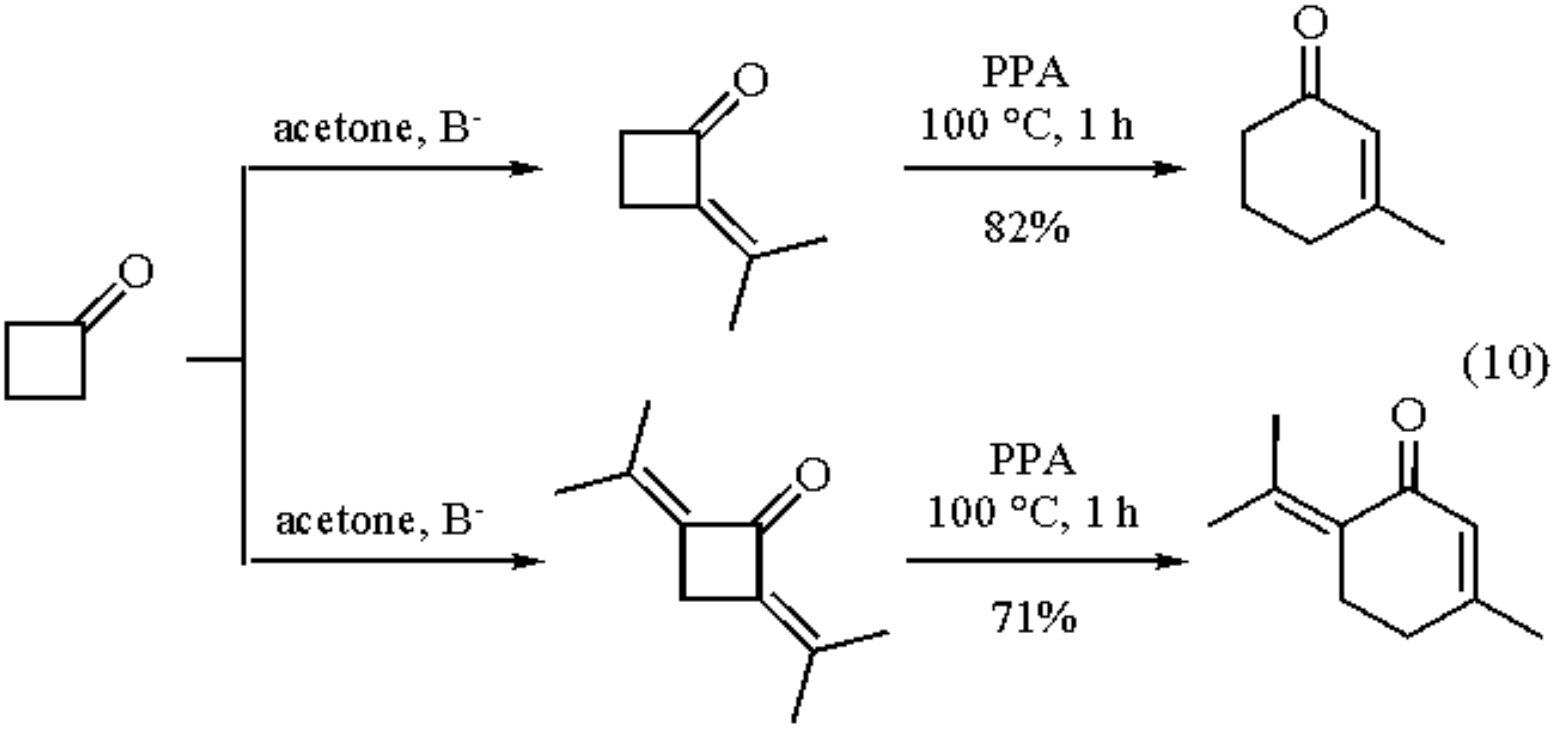

(10)

Cyclohexanones can also be readily prepared by the base-catalyzed 1,3-sigmatropic rearrangement of 1-alkenyl-2-thiophenoxycyclobutanols which are accessible from 2-phenylthiocyclobutanone (eqs 11 and 12).[17] The latter can be obtained from nucleophilic substitution of thiophenoxy ion on 2-bromocyclobutanone,[18] the major bromination product (95%) of cyclobutanone.[19] This substituted cyclobutanone can be used as a cyclobutanone equivalent since the phenylthio group can be reductively cleaved with ***Lithium 1-(Dimethylamino)naphthalenide***.[17]

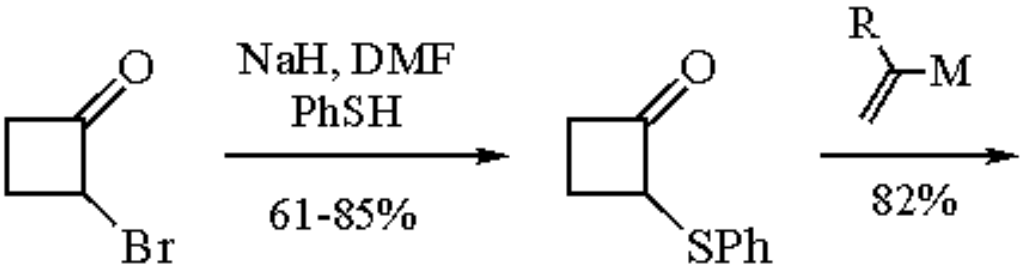

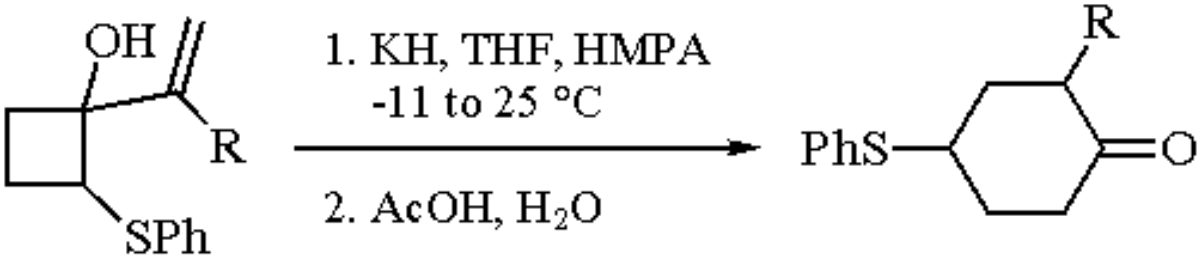

(11)

R = H, 60%; R = Me, 69%

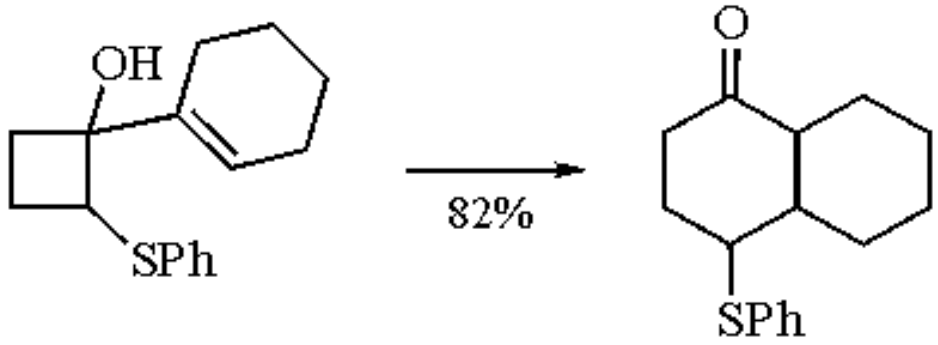

(12)

Ring Expansions to Five-Membered Heterocycles.

Baeyer-Villiger oxidation of cyclobutanone to γ-butyrolactone is best accomplished with ***Hydrogen Peroxide*** in trifluoroethanol (eq 13).[20,21] Some regioselectivity is observed with α-substituted cyclobutanones.[1b] The photochemical ring expansion of cyclobutanones to give 2-alkoxytetrahydrofurans is a general reaction (eq 14); however, for the parent cyclobutanone, the yield is only 8%.[22]

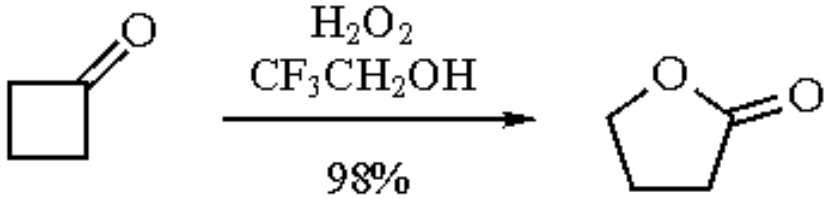

(13)

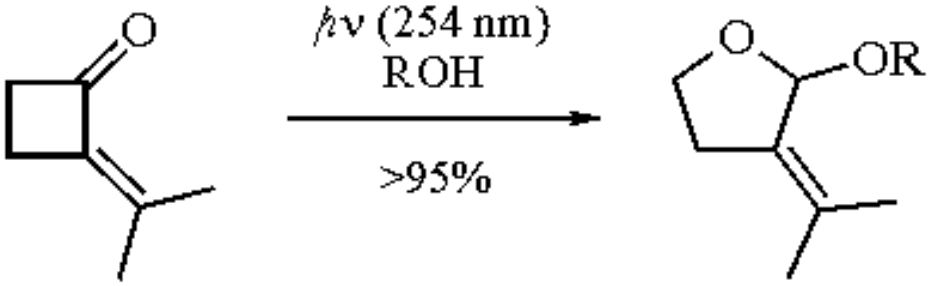

(14)

One example of the ring expansion of a cyclobutanol derivative to a pyrrolidine has been reported in the total synthesis of nor-nicotine. This rearrangement is effected by treatment of the cyclobutanol with ***Hydrazoic Acid*** (eq 15).[23]

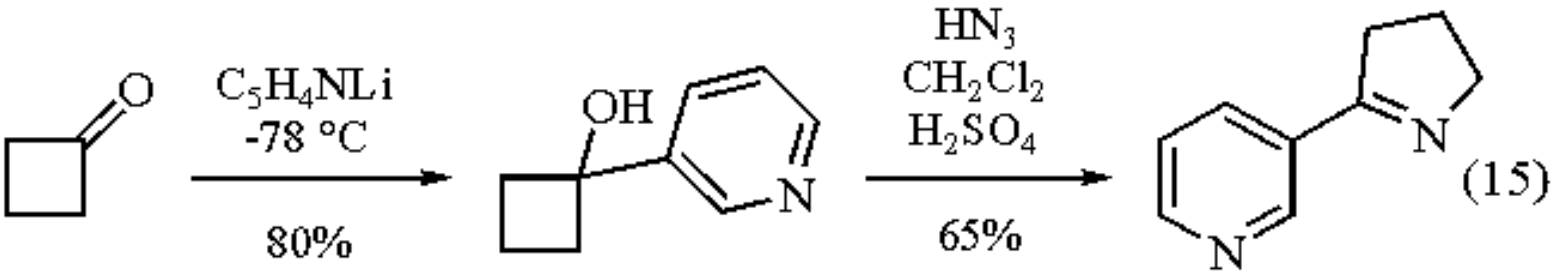

(15)

Ring Contraction to Cyclopropanes.

The nucleophile-assisted Favorskii rearrangement of α-halocyclobutanones gives cyclopropylcarbonyl derivatives (eq 16).[1a]

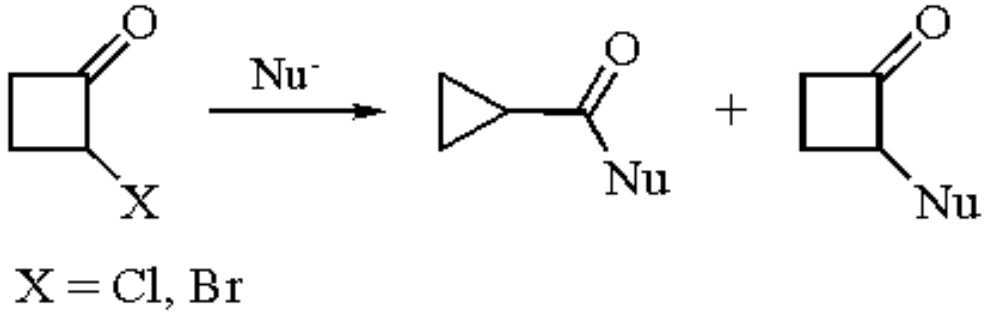

(16)

Nucleophilic substitution may accompany the rearrangement with soft nucleophiles. This transformation is best accomplished with 2-bromocyclobutanone and hard nucleophiles, although 2-chlorocyclobutanone, obtained from the ***Sulfuryl Chloride*** chlorination of cyclobutanone,[24] or 2-tosyloxycyclobutanone can be used (eq 17).

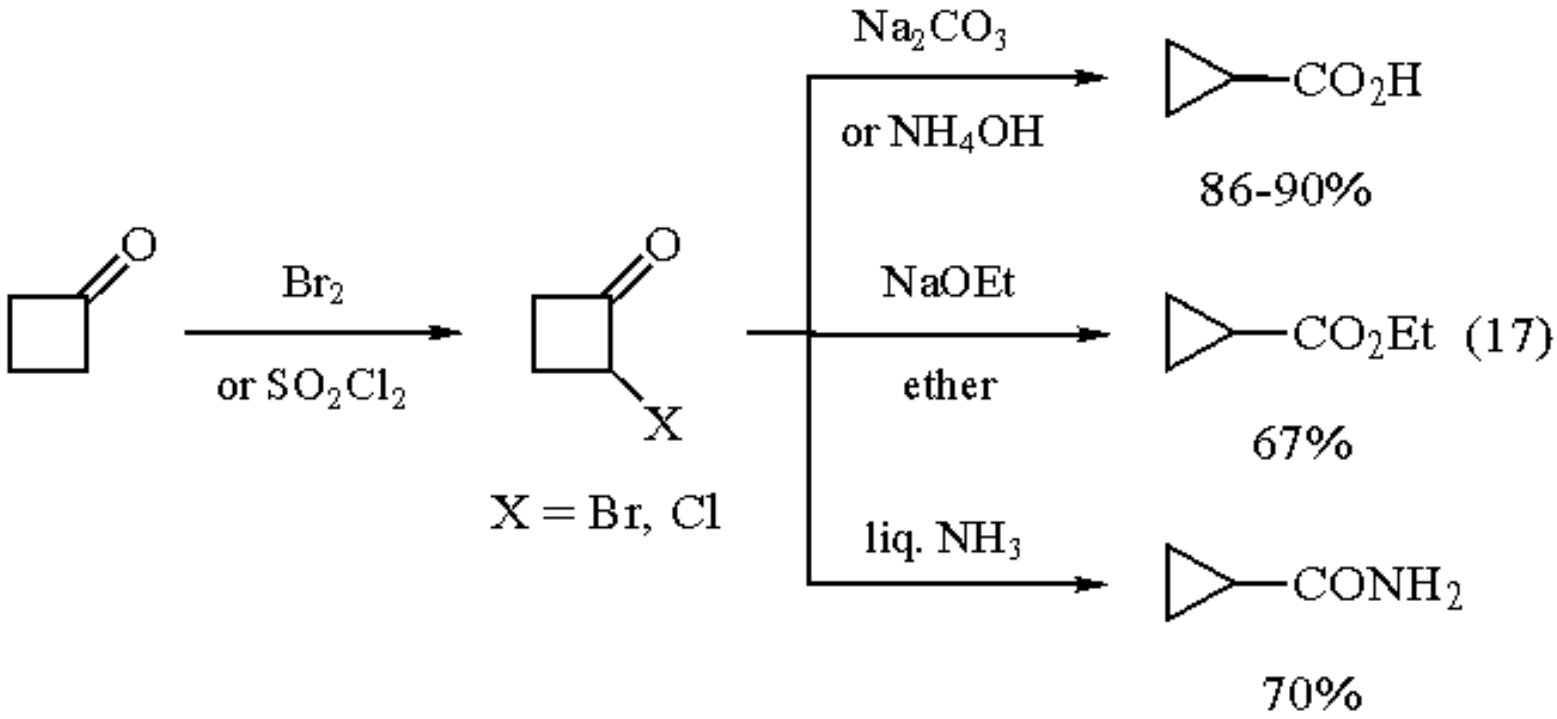

(17)

Whereas 2,2-dibromocyclobutanone undergoes ring-opening reactions (see section on ring-opening reactions), 2,4-dibromocyclobutanone, an overbromination product of cyclobutanone, gives ring-contracted products (eq 18).[24] The stereochemistry of the starting 2,4-dibromocyclobutanone and the ring-contracted products have not been assigned. An interesting thermal reaction of the ethylene acetal derivative of 2-bromocyclobutanone has been reported (eq 19).[25] The pyrolysis of cyclobutanone tosylhydrazone gives methylenecyclopropane (eq 20).[26]

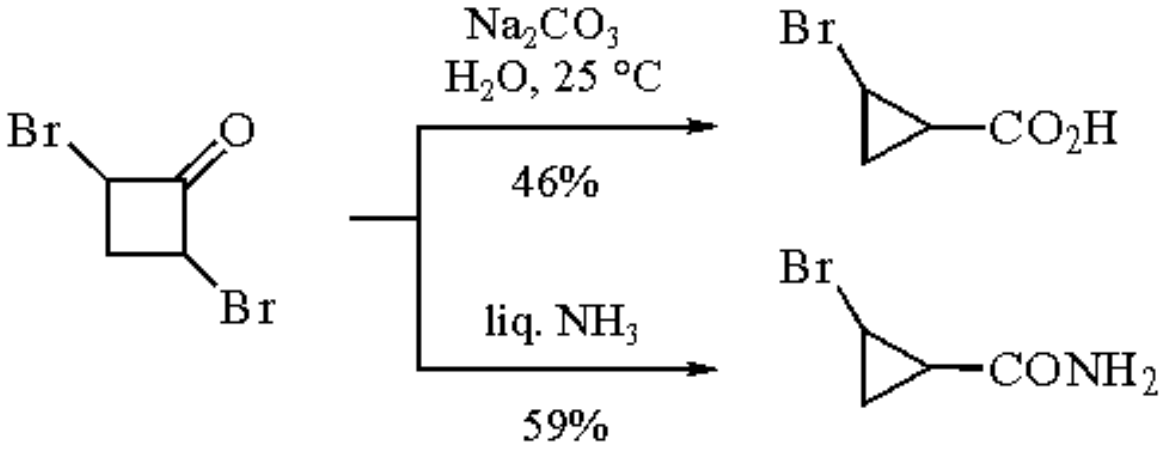

(18)

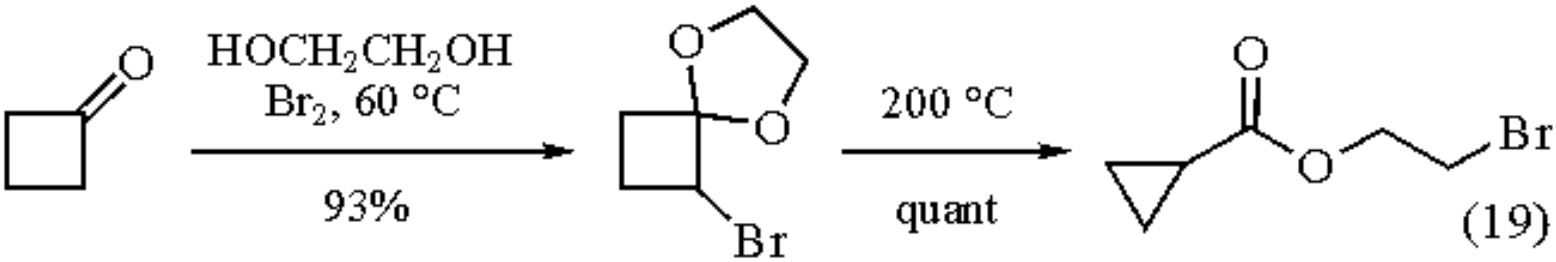

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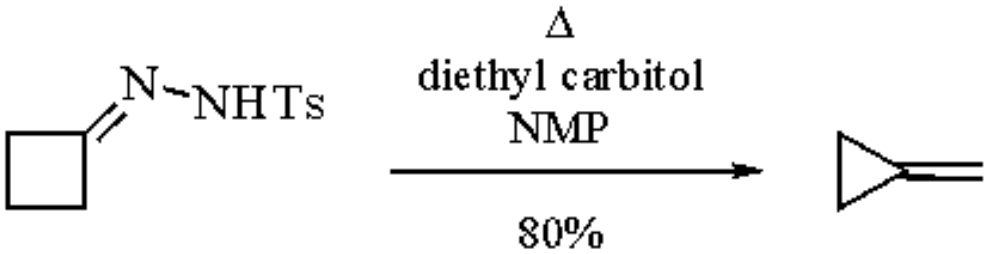

(20)

Condensation and Annulation Reactions.

The carbonyl group in cyclobutanone is more reactive than that of larger ring ketones towards nucleophilic additions and condensations. For example, Wittig-type reactions occur readily with cyclobutanone (see eq 9).[15] Other examples are illustrated in eq 21. Reactions with cyclopentadiene (pyrrolidine, MeOH),[26] $PhSO_2CHLiCH_2TMS$ followed by $MeSO_2Cl$,[27] 2-pentylcyclopropyllithium,[28] 2-lithio-2-trimethylsilyl-1,3-dithiane,[29] and $CNCHLiPO_3Et_2$[30] afforded the addition or alkenation products shown.

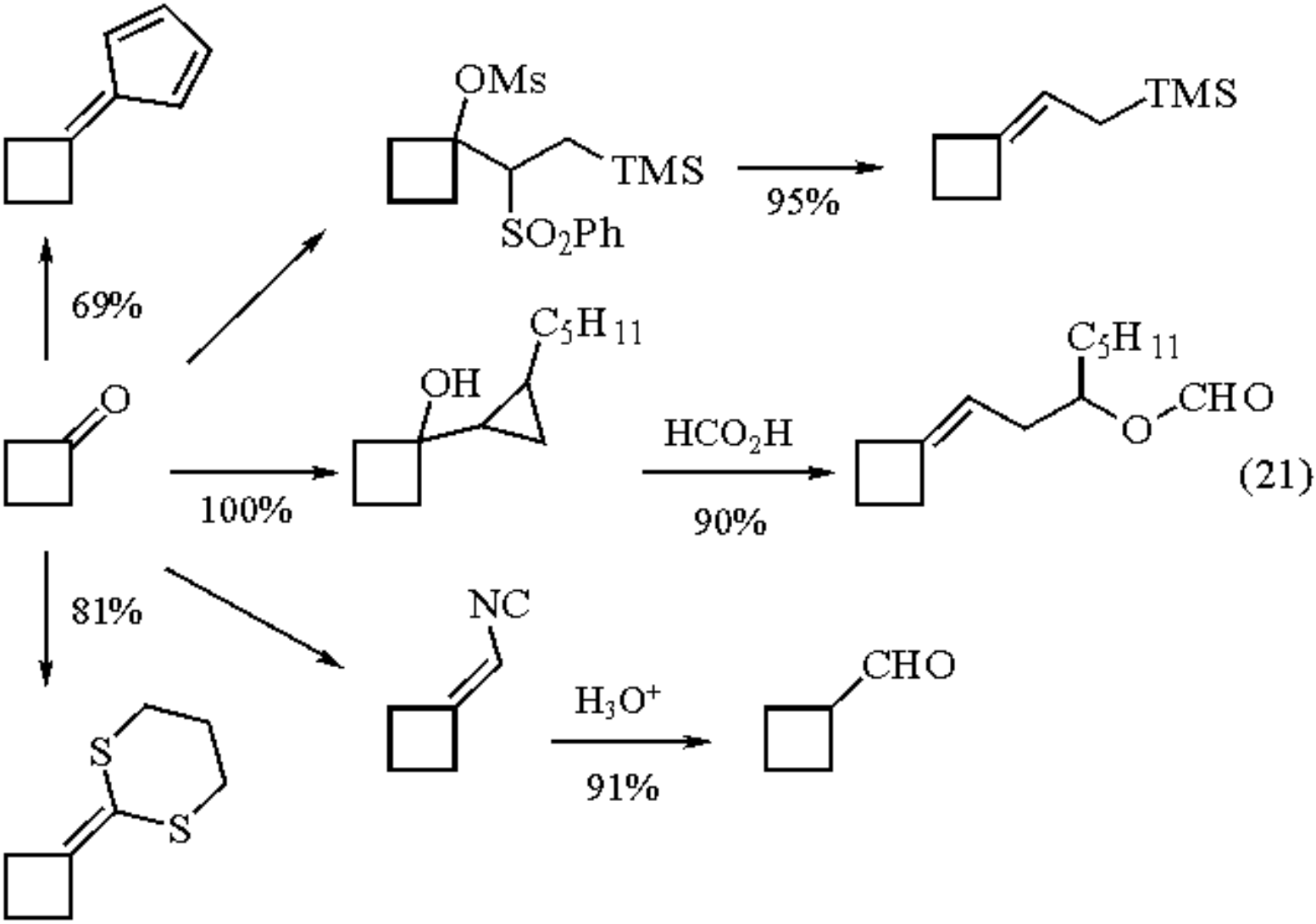

1-Cyclobutenyl ketones and 1-cyclobutenecarbaldehyde are accessible from cyclobutanone in three steps, as shown in eqs 22 and 23.[31,32] The starting α-sulfonylvinyl isocyanide and α-chloro sulfoxide were prepared in one step using ***p-Tolylsulfonylmethyl Isocyanide*** and LiCHClS(O)Ph (93%), respectively.

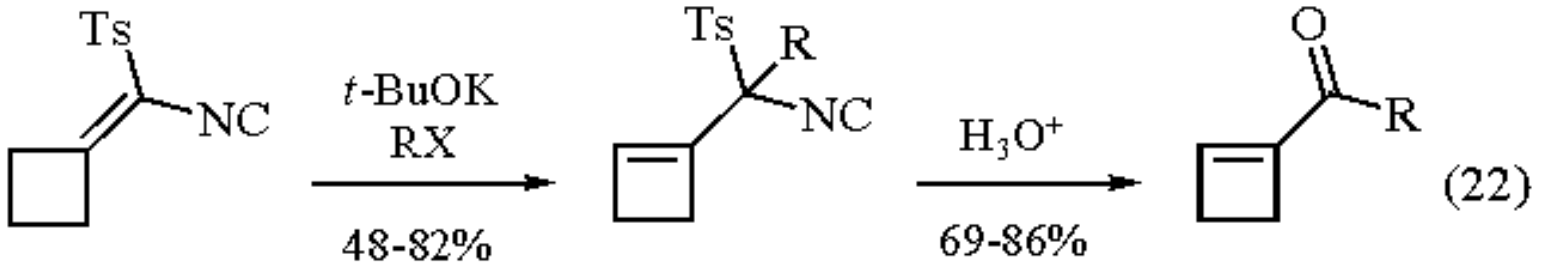

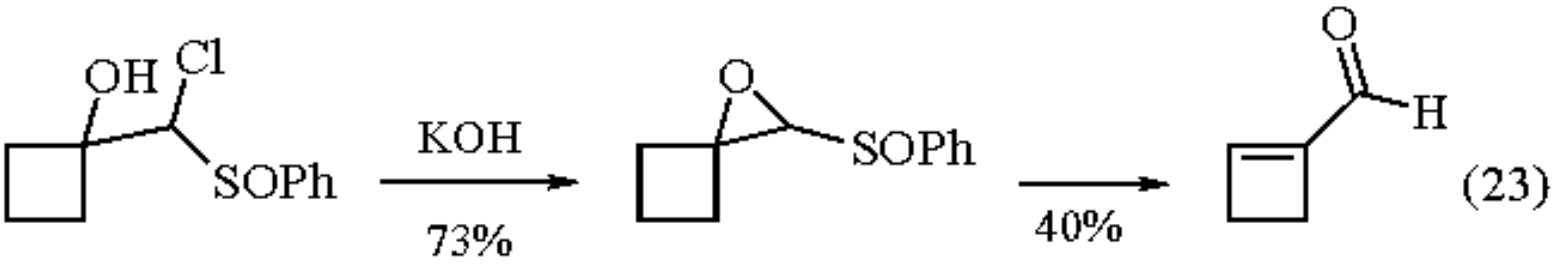

The ring annulation of cyclobutanes is achieved in a Diels-Alder reaction using cyclobutenes as dienophiles or 1-alkenylcyclobutenes as dienes. The piperidine enamine of cyclobutanone readily cycloadds to conjugated ketones to give cyclobutapyrones (eq 24).[33]

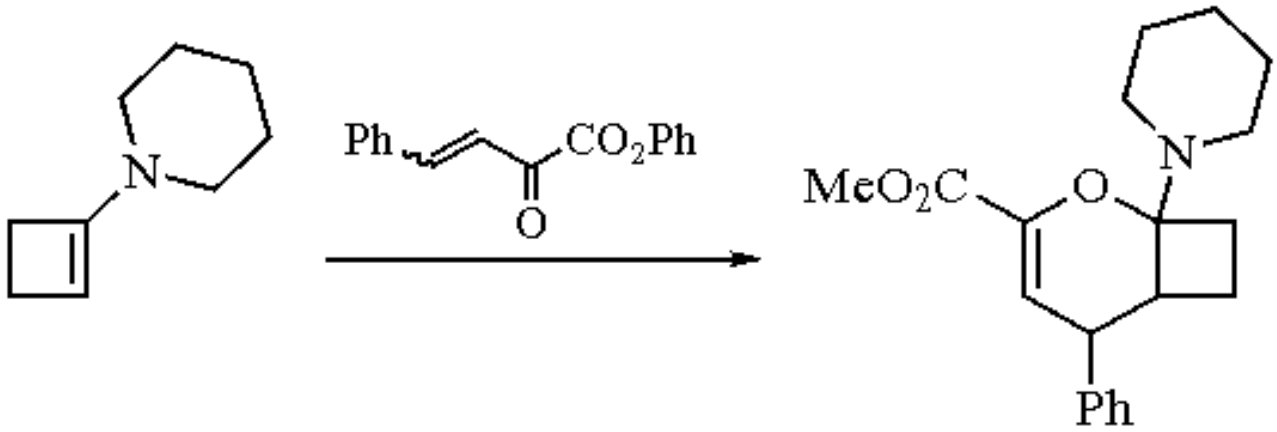

(24)

1-Vinylcyclobutene, available by vinyl Grignard addition (66%) and I_2-induced elimination (72%), undergoes a [4 + 2] cycloaddition with 1,2-cyclobutenedicarboxylic acid dimethyl ester to give a key intermediate in the synthesis of the biscyclobutabenzene (eq 25).[34] The addition of methyl propiolate to 1-vinylcyclobutene gives a mixture of regioisomers in about equal amounts.[35]

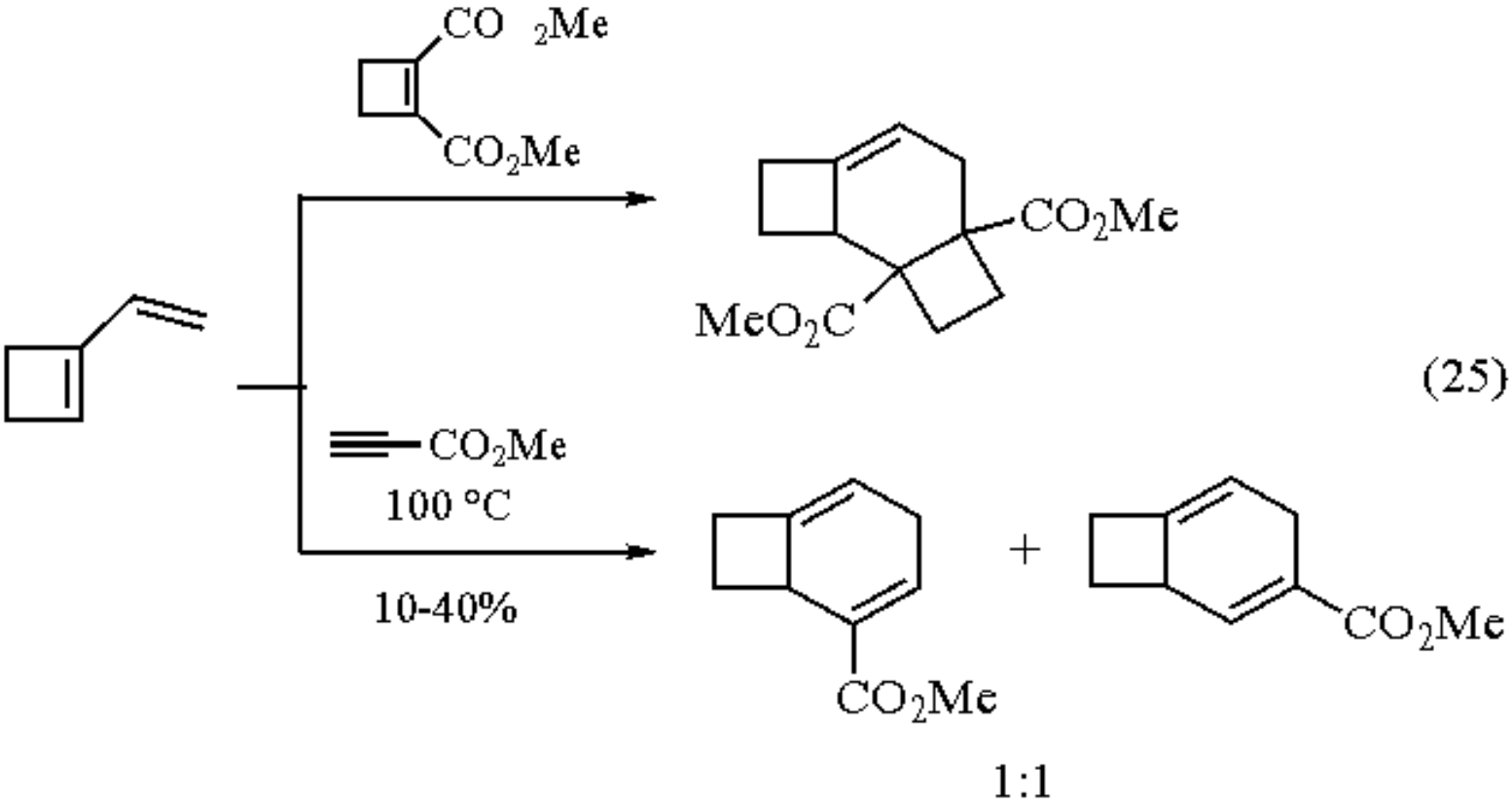

(25)

Ring-Opening Reactions.

The strain associated with cyclobutanones allows ring-opening reactions to occur with ease. Cyclobutenes and

cyclobutenol derivatives are readily available from cyclobutanone, and their thermolytic ring-opening reactions give synthetically useful 1,3-butadienes.[36,37] Two examples are given (eqs 26 and 27).

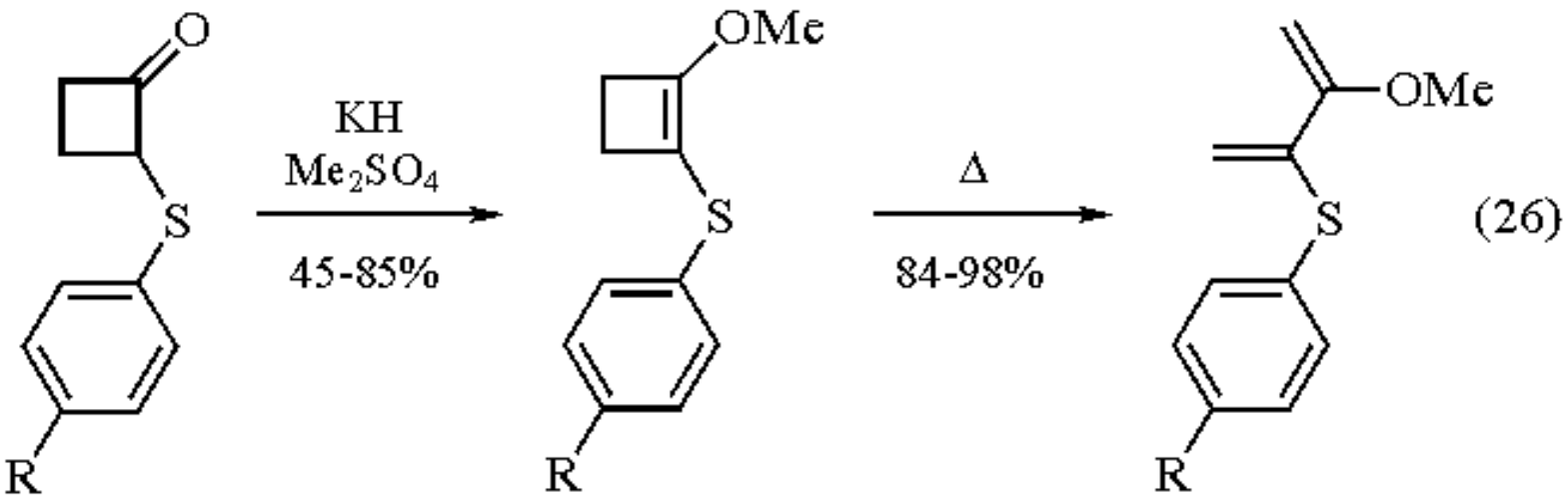

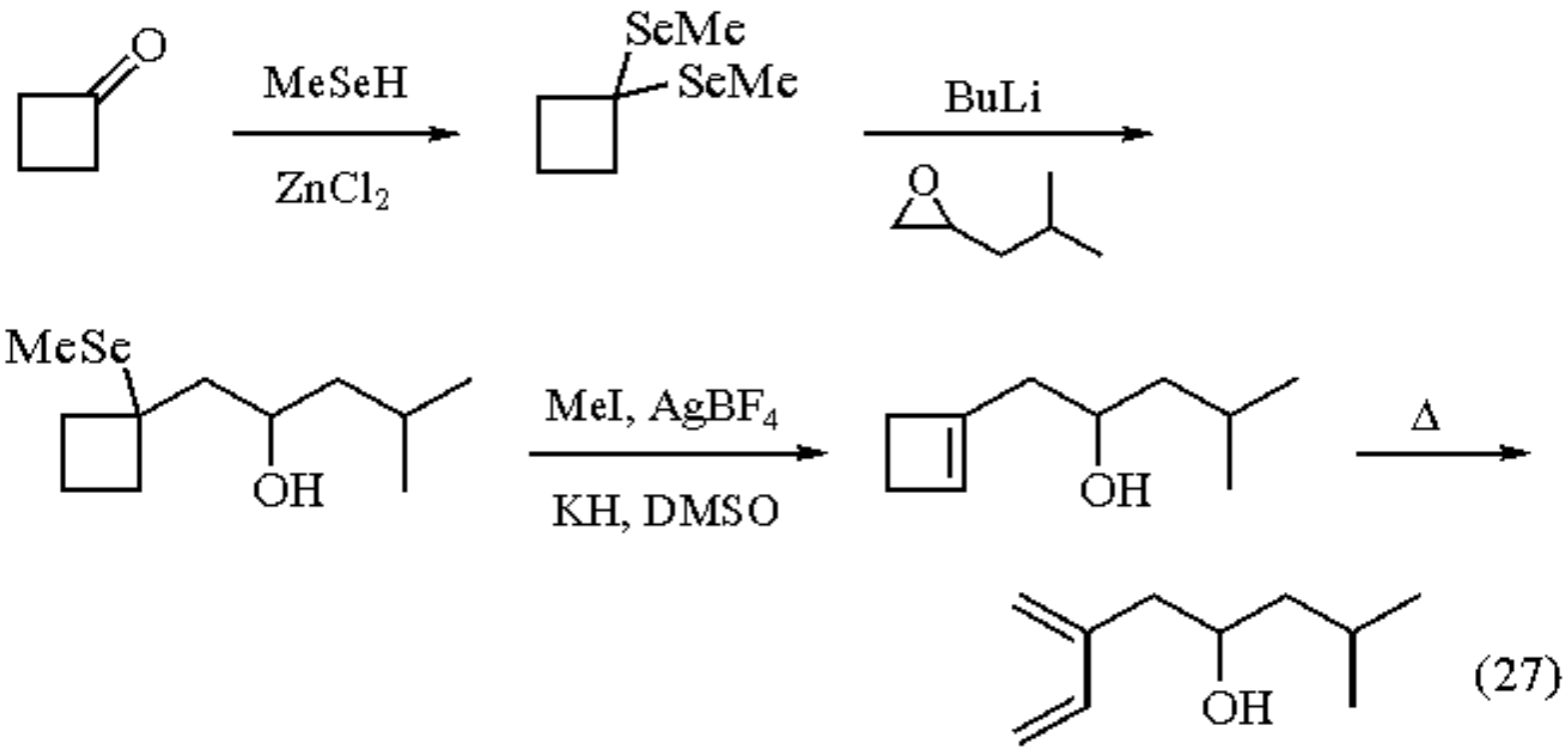

Although 2-halocyclobutanones give ring-contracted products upon treatment with nucleophiles, 2,2-dihalocyclobutanones undergo ring-opening reactions. This is the result of the stabilization of the anion brought about by *gem*-dihalogen substitution (eq 28).[24]

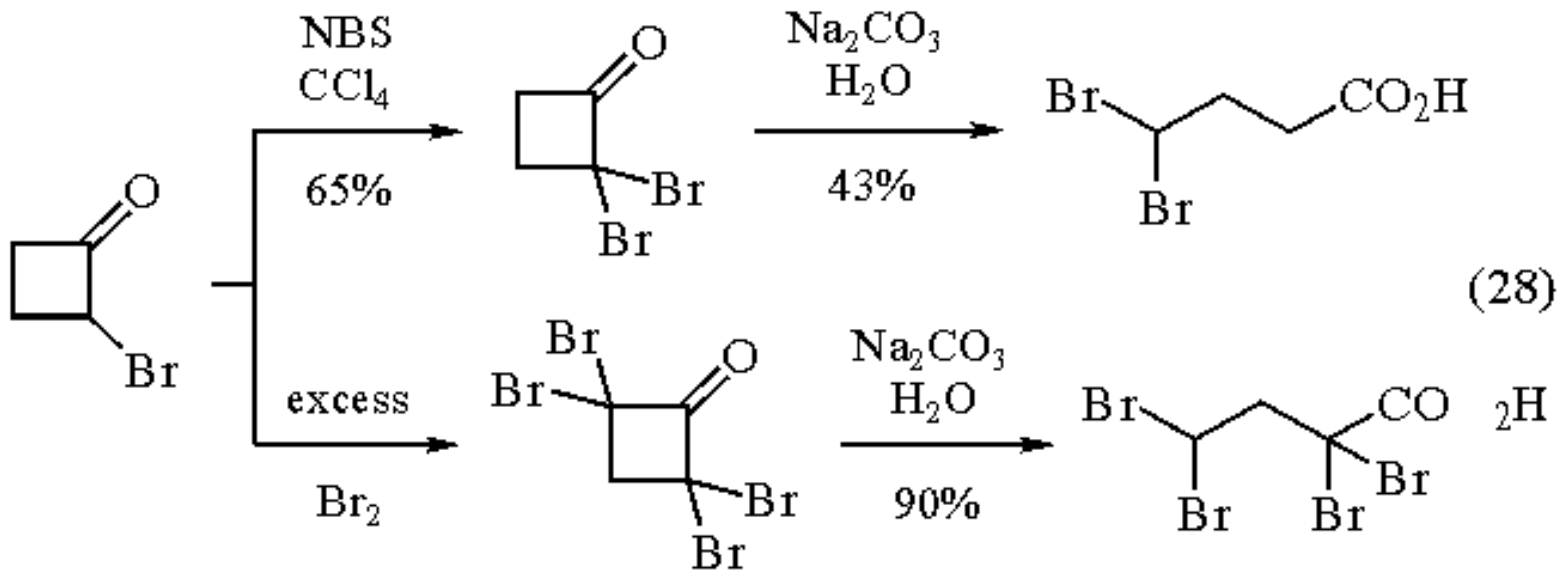

α-Alkylations of Cyclobutanone.

α-Alkylation of cyclobutanone via its enolate anion is not an efficient method for monoalkylation. The reaction usually results in polyalkylations, accompanied by resin formation.[38] Although the trimethylsilyl enol ether[39] and the pyrolidine enamine[40] are known, alkylations of these intermediates cannot be achieved because of the acid and thermal labilities of these intermediates. Monoalkylated cyclobutanones can be prepared from base-assisted alkylation of the cyclobutanone equivalent, 2-phenylthiocyclobutanone, and subsequent reductive cleavage of the thiophenoxy group with lithium 1-dimethylaminonaphthalenide.[17]

Related Reagents.

1,2-Bis(trimethylsilyloxy)cyclobutene; ***Cyclopropanone***; ***Dichloro(ethoxy)oxovanadium(V)***; ***1,2-Dicyanocyclobutene***; ***1-Ethoxycyclopropanol***; ***2-Methoxy-3-phenylthio-1,3-butadiene***; ***Methylenecyclobutane***; ***Squaric Acid***; ***1-(Tetrahydropyranyloxy)cyclopropanecarbaldehyde***; ***p-Tolylsulfonylmethyl Isocyanide***; ***Tricarbonyl(cyclobutadiene)iron***.

---

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1,3,5-Cycloheptatriene[1]

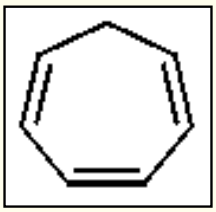

[544-25-2] · C_7H_8 · 1,3,5-Cycloheptatriene · (MW 92.14)

(precursor in the synthesis of troponoids,[1a,b] polycyclic compounds,[1b,c] tropylium salts[1a,b])

Physical Data: mp -79.5 °C; bp 117 °C/749 mmHg; d_4^{22} 0.888 g cm^{-3}.

Solubility: sol EtOH, Et_2O, C_6H_6, $CHCl_3$.

Form Supplied in: slightly colored liquid, purity about 90% (usually contains toluene).

Preparative Methods: 1,3,5-cycloheptatriene (tropylidene) (**1**) is synthesized through benzene ring expansion,[2a] or pyrolysis of 7,7-dibromobicyclo[4.1.0]heptane.[2b,c] These reactions represent general synthetic methods to produce derivatives of (**1**).[2c] Reaction of thiophene *S*,*S*-dioxides with cyclopropenes is extremely advantageous for the synthesis of highly substituted cycloheptatrienes.[2d]

Purification: via transformation into tropylium tetrafluoroborate.

Analysis of Reagent Purity: ^1H NMR, GLC.

Handling, Storage, and Precautions: resinifies in air; flammable liquid; toxic. This reagent should be handled in a fume hood.

Synthesis of Cycloheptatriene Derivatives and Other Monocyclic Compounds.

Several one-step methods for the transformation of (**1**) into potentially more useful functionalized monocyclics have been developed. 1,4-Addition of ***Bromine*** to (**1**) (CCl_4, 0 °C) quantitatively affords 1,4-dibromo-2,5-cycloheptadiene,[3] while reduction of (**1**) with alkali metals (***Lithium***, ***Sodium***) in ether or NH_3 proceeds with 1,6-addition to the conjugated system and produces 1,3-cycloheptadiene after quenching with *N*-methylaniline.[4] Intermediate C(5)-metalated 1,3-cycloheptadienes react with alkyl halides to give 5-alkyl-1,3-cycloheptadienes.[4] These dienes can also be prepared by electrochemical reductive alkylation of (**1**) on a Pt cathode.[5]

Friedel-Crafts acylation of (**1**) is very sensitive to the reaction temperature and nature of Lewis acid. In ***Aluminum Chloride***-catalyzed reactions, the chloro ketones initially formed via 1,6-addition of acyl chlorides are transformed into 1-acyl-1,3,5-cycloheptatrienes or are ring-contracted into benzylic ketones, depending on the workup procedure (eq 1).[6a] With ***Tin(IV) Chloride*** as a catalyst, only benzylic ketones are produced.[6b]

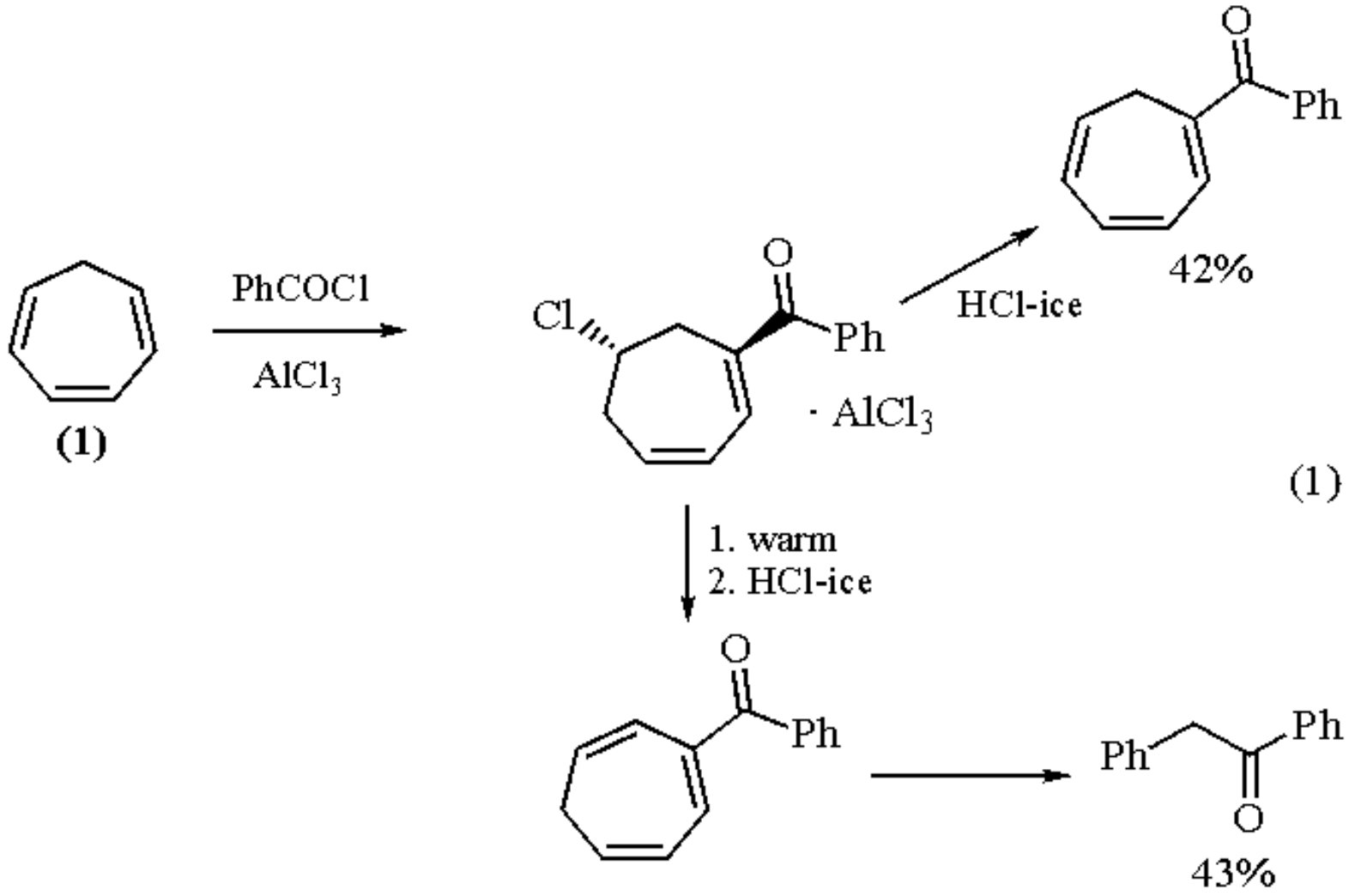

(1)

Stepwise anodic oxidation of (**1**) in MeOH delivers 7-methoxy-1,3,5-cycloheptatriene and then tropone,[7a] which can also be prepared by direct oxidation of (**1**) with ***Selenium(IV) Oxide***-KH_2PO_4.[7b]

Synthesis of Bicyclic Compounds.

Monocyclopropanation of (**1**) with carbenes affords bicyclo[5.1.0]octa-2,4-dienes[8,9] and can be accompanied by seven-membered ring contraction, yielding benzocyclobutenes.[9]

Cycloheptatriene reacts in [4 +2] and [6 + 4] cycloadditions.[10a] An interesting cycloaddition which is an anionic analog of [6 + 4] cycloadditions has been described (eq 2).[10b]

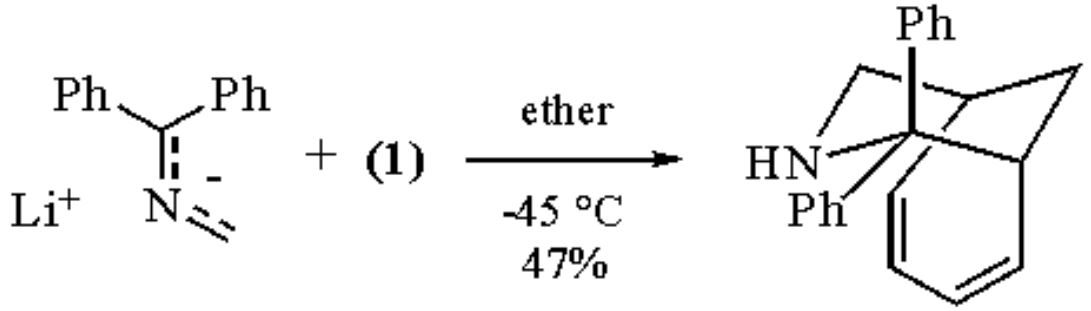

(2)

Synthesis with Complexed 1,3,5-Cycloheptatrienes.

The reactivity of (**1**) in complexes with various transition metals[1c,11] is usually considerably higher than that of noncomplexed (**1**). Tricarbonyl(η^4-cycloheptatriene)iron[1c] is acylated (1. KH; 2. RCOCl) at C(7) with very high diastereoselectivity (*exo*/*endo* = 35-70).[12] Cycloaddition of this complex with tetrazine affords a novel pyridazino[2,3-*d*]cycloheptatriene heterocyclic system.[13] Regiocontrolled and stereocontrolled functionalization of Mn complexes in reactions with sodium enolates has been used in the synthesis of 6-substituted cyclohepta-2,4-dien-1-ols.[14] Either thermally[15a] or photochemically[15b] induced stereospecific [$6_\pi + 4_\pi$] and [$6_\pi + 2_\pi$] cycloaddition reactions have been performed with the chromium(0) complex (**2**) (eq 3).[15b] The same transformations can also be accomplished directly for (**1**) employing only a catalytic quantity of (**2**) as a source of Cr^0.[15a]

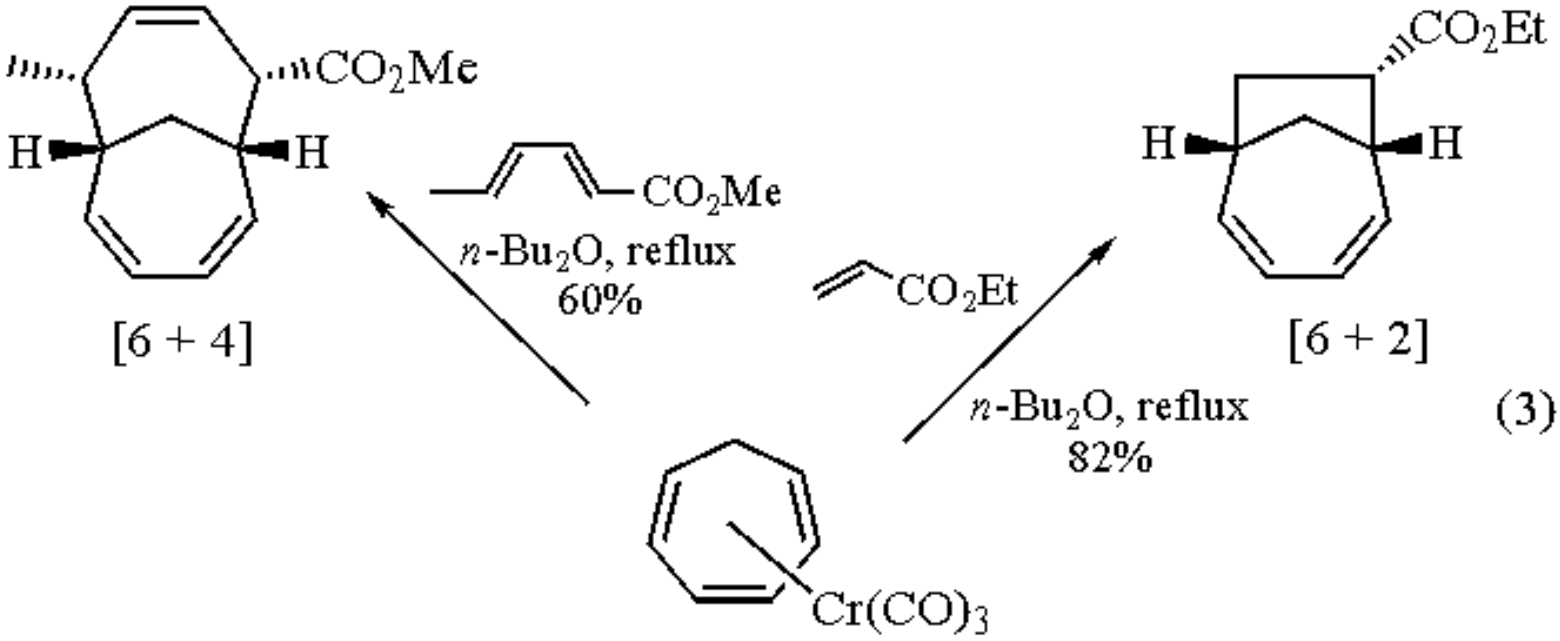

(3)

(**2**)

Tropylium Salts.

Stable carbenium ions abstract hydride ion from C(7) of (**1**), yielding the 6π-electron aromatic system of tropylium salts (**3**).[16] Tropylium salts are also formed by mild pyrolysis of the adduct of (**1**) with Br_2[17] or by heating norcaradienecarboxylic acid azide in C_6H_6.[18] Salts of type (**3**) have been involved in several redox transformations,

such as reductive dimerization into bitropyl,[19a] oxidative ring contraction producing aromatics,[19b] and disproportionation on heating in MeCN or DMSO with formation of (**1**) and tropone.[19c]

Undoubtedly the salts (**3**) are the most powerful synthons to incorporate the cycloheptatrienyl moiety into organic substrates even with moderate reactivity. They effectively alkylate amides,[17] tosylureas,[20] H_2S,[17] and react with RLi to produce 7-alkyl- or 7-arylcycloheptatrienes.[3,21] Aldehydes are α-alkylated by (**3**; X = Br) directly[22] or after preliminary transformation into enamines.[23] The latter approach is especially successful for ketones.[23] The salts (**3**) readily react with carbanions[8,24] to provide a route to heptafulvenes (eq 4).[24b]

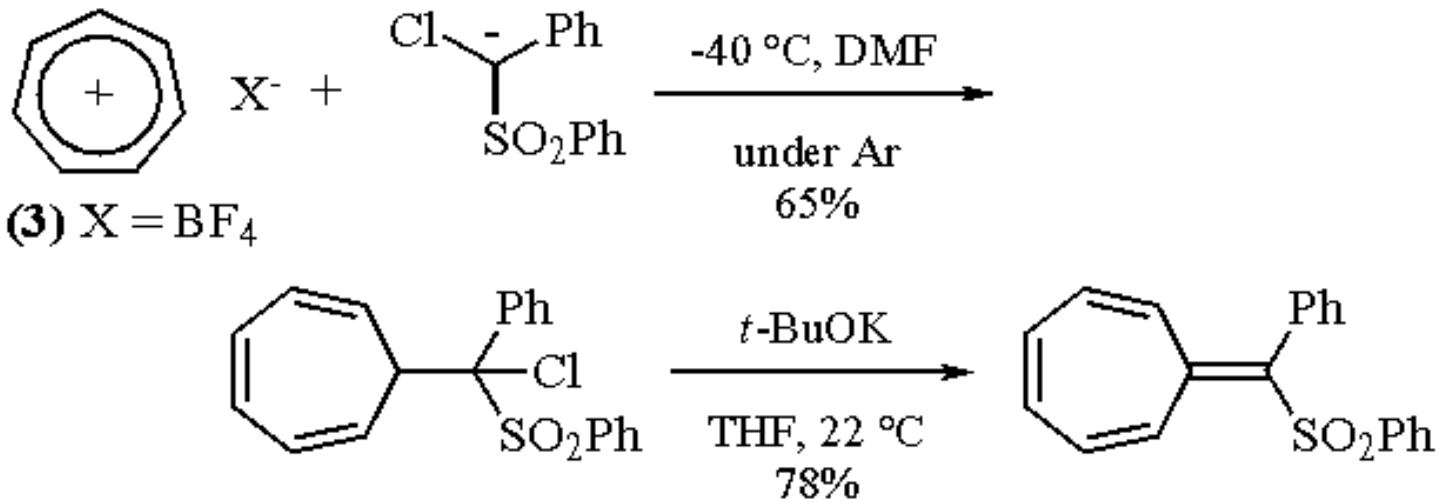

(4)

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2,4,6-Cycloheptatrien-1-one[1]

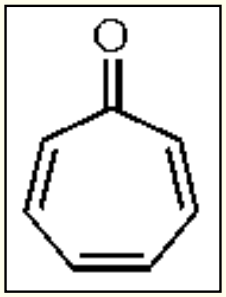

[539-80-0] · C_7H_6O · 2,4,6-Cycloheptatrien-1-one · (MW 106.13)

(synthon for preparation of cycloheptadien-1-ones; building block in the synthesis of troponoids, azulenes,[1a,b] polycyclic compounds,[1c,d] natural products[1d,e])

Alternate Name: tropone.

Physical Data: mp -8 °C to -5 °C; bp 113 °C/15 mmHg; d_4^{22} 1.10 g cm^{-3}; *n*22D 1.6172.

Solubility: sol ether, dioxane, acetone, benzene, toluene, xylene, MeCN, CCl_4; miscible with water.

Preparative Methods: 2,4,6-cycloheptatrien-1-one (**1**) is a functionalized conjugated carbocyclic compound with diversified reactivity. The most popular and simple method of preparation involves oxidation of ***1,3,5-Cycloheptatriene*** with ***Selenium(IV) Oxide***-KH_2PO_4.[2a] Several other procedures have also been developed,[2b-f] among which electrooxidation of cycloheptatrienes[2e] and α-pyrone ring expansion via high-pressure cycloaddition of cyclopropenone acetals[2f] can be considered general methods of synthesis of tropones.

Purification: by distillation.

Analysis of Reagent Purity: ^{1}H NMR, GLC.

Handling, Storage, and Precautions: light- and oxidant-sensitive.

1,8-Additions to Tropone: Synthesis of Cycloheptadien-1-ones.

Reactions of (**1**) with various nucleophiles proceed through 1,8-addition to the troponoid system and offer an approach to conjugated cycloheptadienes.[3] Tropone (**1**) is readily reduced to 3,5-cycloheptadien-1-one through 1,8-addition of

hydride ion from ***Lithium Aluminum Hydride***[4] or adds alkylmagnesium compounds to form 2-alkyl-3,5-cycloheptadien-1-ones.[3,5] Reaction with lithium enolates provides a very efficient route for appending functionalized substituents onto the troponoid nucleus (eq 1).[6]

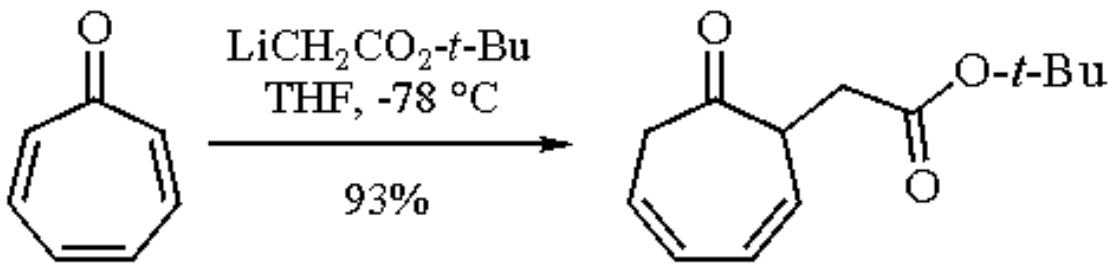

(1)

(1)

Annulation of Tropone: Preparation of Azulenes and Other Polyunsaturated Bicyclo[5.3.0]decane Systems.

Condensation of (**1**) with malonodinitrile in the presence of piperidine gives 2-amino-3-cyano-8*H*-cyclohepta[*b*]furan.[7] This type of reaction is widely used in a general azulene synthesis from tropone that initially involves condensation of 2-substituted tropones (**2**; X = OMe, Cl, OTs) with active methylene compounds (AMC) to give cyclohepta[*b*]furan-2-ones or -2-imines (**3**). Subsequent cycloadditions of (**3**), for example with vinyl ethers, leads to di- and trisubstituted azulenes (**4**) (eq 2).[8]

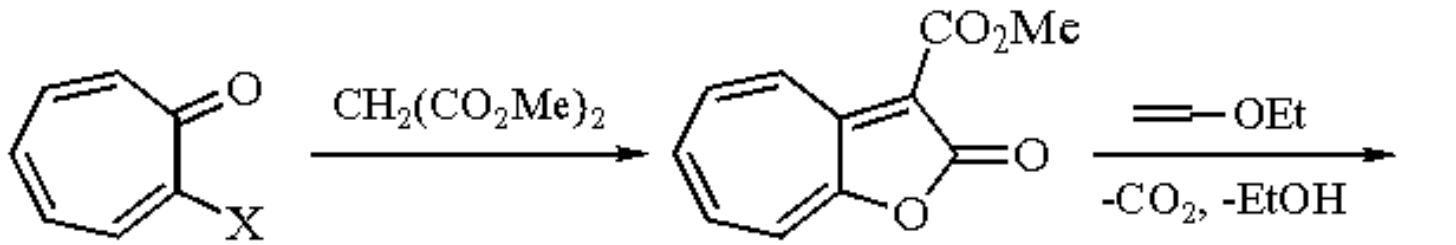

(2)
X = Cl

(3)

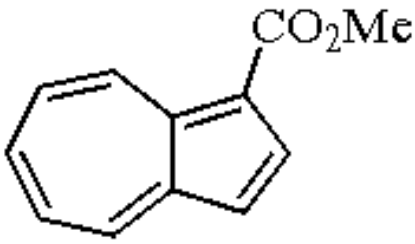

(2)

(4) 74%

An approach to 4-ketohydroazulenes is based on [3 + 2] cyclopentane annulation reactions of tricarbonyl(tropone)iron with η^5-$C_5H_5Fe(CO)_2R$ synthons (where R = alkenyl, alkynyl, allenyl).[9]

On refluxing in C_6H_6 with benzamidine, (**1**) undergoes amination via hydride replacement producing 1,3-diazaazulene.[10] Aza-Wittig reactions between *N*-(1-phenylvinyl)iminophosphoranes and (**1**) or 2-alkyltropones deliver 2-phenyl-8*H*-cycloheptapyrroles which can be oxidized further (***Nickel(II) Peroxide***) to afford 1-azaazulenes.[11]

Photochemical [8 + 2] cycloaddition of alkenes to (**1**) affords 8-oxabicyclo[5.3.0]deca-2,4,6-trienes.[12] Analogously, stereospecific thermally allowed [8 + 2] cycloadditions with sulfenes give bicyclic sultones, which on heating lose SO_2 with stereospecific formation of 2-(*cis*-1-alkenyl)phenols in almost quantitative yields.[13a] An efficient procedure for the synthesis of indoles is based on transformation of bicyclic sultams produced via the same cycloaddition of tropone *N*-methylimine with sulfenes.[13b]

Reactions of (**1**) with enamines derived from cycloalkanones also proceed via [8 + 2] cycloaddition. The primary adduct (**5**) is readily hydrolyzed to give a substituted 3,5-cycloheptadien-1-one (eq 3).[14] This example demonstrates the close relation between 1,8-addition and [8 + 2] cycloaddition in the tropone series.

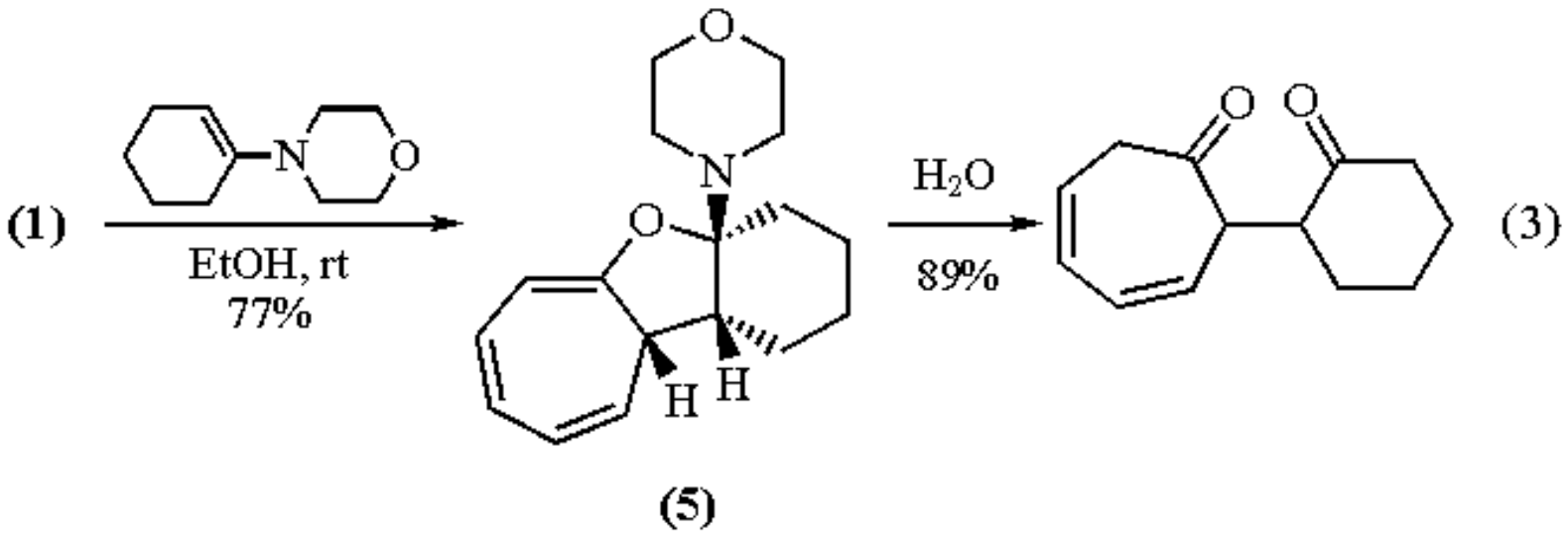

In a similar way, the 2-oxyallyl cation generated from 2,4-dibromo-2,4-dimethylpentan-3-one and ***Nonacarbonyldiiron*** exhibits high periselectivity toward (**1**) to give the formal $[2_\pi(3C) + 8_\pi]$ adduct 9,9,11,11-tetramethyl-8-oxabicyclo[5.4.0]undeca-2,4,6-trien-10-one.[15]

In the reaction of (**1**) with $HS(CH_2)_nSH$ (n = 2,3), 1,2-annulation of the dithiols takes place instead of the expected dithioacetalization.[16]

[4 + 2] and [6 + 4] Cycloadditions: An Approach to Bicyclo[3.2.2]nona-3,6-dien-2-one and Bicyclo[4.4.1]undeca-2,4,8-trien-11-one Systems.

Two cycloaddition modes common for (**1**) involve [4 + 2] cycloaddition across C(2)-C(5) or C(2)-C(3) and [6 + 4] cycloaddition across C(2)-C(7). Tropone undergoes thermal [4 + 2] cycloadditions with both electron-deficient[17] and electron-rich[18] dienophiles and *endo* products usually predominate. With unsymmetrical electron-rich dienophiles, cycloaddition proceeds regiospecifically and only 9-substituted bicyclo[3.2.2]nona-3,6-dien-2-ones are formed[18a,b]

while, for example, electron-deficient acrylonitrile produces both regioisomeric cycloadducts (eq 4).[17e]

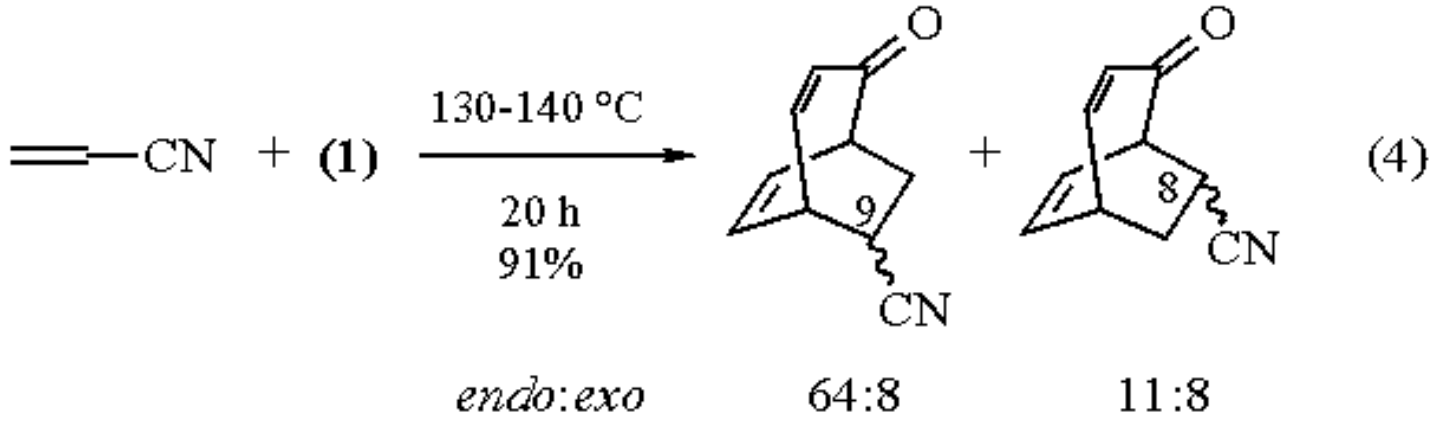

Tropone (**1**) also enters into thermally induced [6 + 4] cycloadditions with nonfunctionalized open-chain dienes (eq 5),[19] cyclopentadiene,[20] and functionalized dienes.[21]

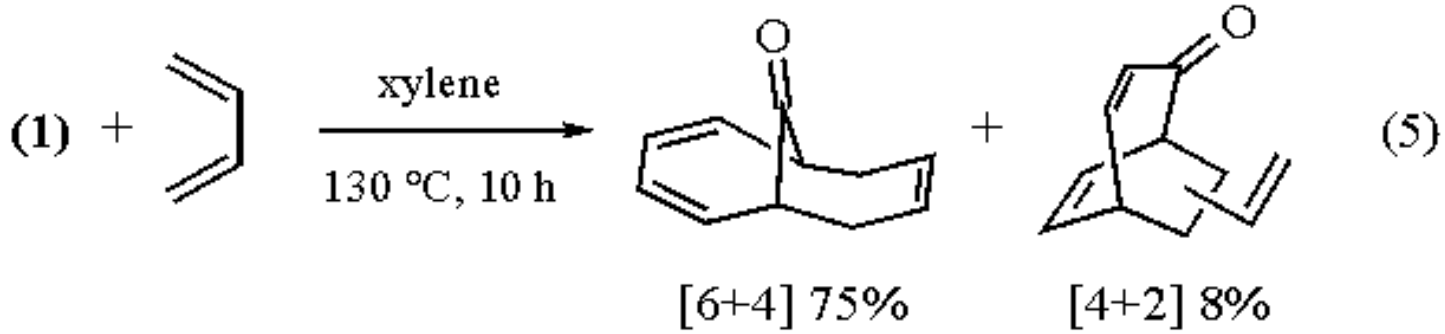

The rearrangement of [6 + 4] cycloadducts into thermodynamically more stable [4 + 2] products via sigmatropic isomerization or by stepwise cycloreversion-readdition has also been reported.[22] Lower temperatures favor the [6 + 4] mode of cycloaddition. Generally, electron-rich dienes give [6 + 4] adducts kinetically, but these cycloadducts are thermodynamically less stable than the adducts derived from electron-deficient dienes.[21] [6 + 4] Adducts are always formed via an *exo* transition state whereas alternative [4 + 2] adducts often originate via an *endo* transition state.[21,22c] However, the photoinduced reaction of tricarbonyl(7,7-dimethoxy-1,3,5-cycloheptatriene)iron, as a masked version of (**1**), with (*E*)-1,3-pentadiene affords the *exo* [6 + 4] cycloadduct.[23] Therefore transition metal-mediated [6 + 4] cycloaddition extends the scope of the thermal reaction. Besides these reactions, (**1**) is also known to react with 1,3-dipoles in [6 + 4] cycloadditions.[22c]

Intramolecular [6 + 4] and [4 + 2] tropone-alkene cycloaddition reactions of 2-alkenyltropones have been used to prepare polycyclic troponoids.[24]

[6 + 3] Cycloaddition: A Route to the Bicyclo[4.3.1]decadien-9-one System.

In the presence of Pd^0 catalysts, 2-[(trimethylsilyl)methyl]allyl carboxylates undergo regioselective addition to C(2) and C(7) of (**1**) (eq 6).[25a] The stereochemistry of the reaction widely varies, depending on the nature of substituents in the trimethylenemethane (TMM) precursors. A phenylthio substituent in the TMM precursor behaves as an effective

selectivity control element.[26b]

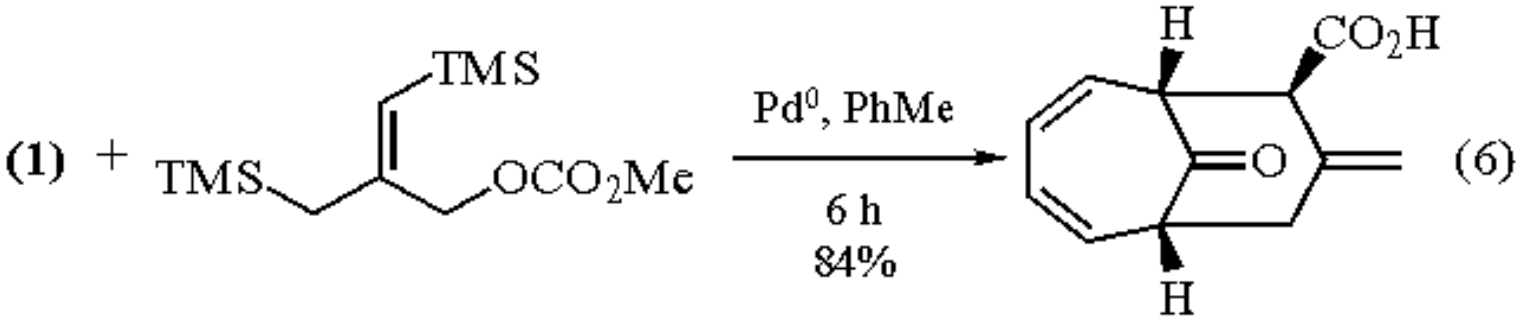

[6 + 2] Cycloaddition.

In contrast to the low periselectivity observed in intermolecular photoinduced [6 + 2] cycloaddition reactions of (**1**),[26] intramolecular [6 + 2] reactions of 2-(4-alkenyl)- or 2-(4-alkynyl)tropones on irradiation in acidic MeOH proceed with high regioselectivity and stereoselectivity (eq 7). These reactions offer an elegant approach to bridged bicyclo[6.3.0]undecanes.[27]

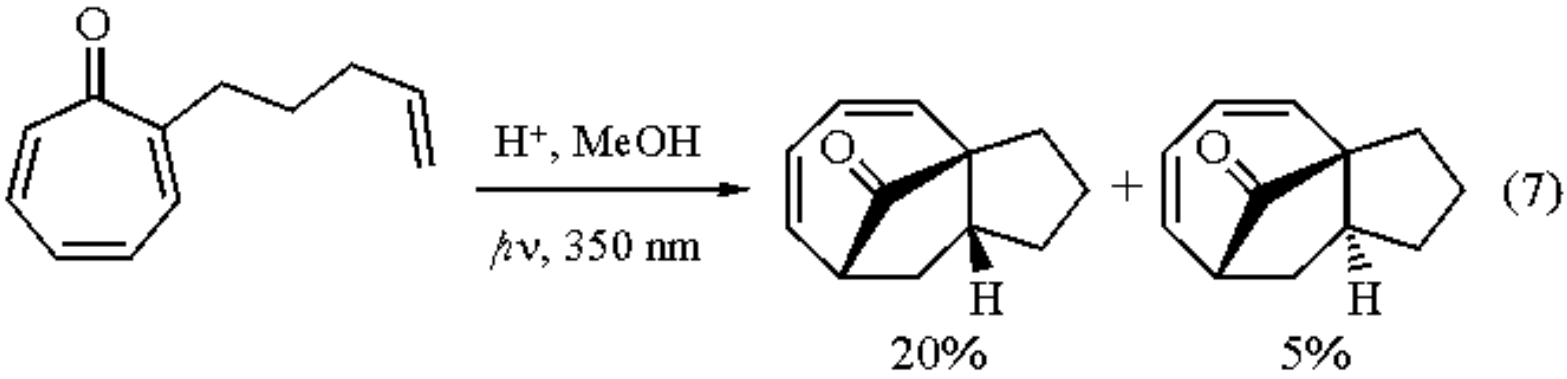

Tricarbonyl[(2,3,4,5-η)-2,4,6-cycloheptatrien-1-one]iron (6).

In most instances the uncomplexed double bond of (**6**)[28] reacts as an electron-rich partner that results in nucleophilic addition to C(3),[9] periselective inverse electron demand cycloaddition across the free C(6)-C(7) double bond,[29] or acylation at C(2) under standard Friedel-Crafts conditions.[30] At the same time, in a number of reactions (**6**) exhibits reactivity which is characteristic of an electron-deficient enone. For example, (**6**) behaves like a cycloheptenone in Diels-Alder [4 + 2] cycloaddition with dienes. Stereoselective conjugate addition of nucleophiles proceeds at the C(6)-C(7) bond to give bicyclo[5.4.0]undeca-3,5,8-trien-2-ones[32,22b] or C(6)-alkylated complex (**7**) (eq 8).[31] With simple nucleophiles (***Vinylmagnesium Bromide***, ***Sodium Borohydride***/***Cerium(III) Chloride***), 1,2-addition is observed.[32] Because (**6**) serves as an equivalent of (**1**) that exhibits electron-deficient enone reactivity, it has been used as a building block in natural product synthesis. Syntheses of *cis*-hydroazulenes,[4a,9a] guaianolides,[4b] grosshemin,[5a] barbarolones,[28b] ingenane and cedrane ring systems,[24a,b] prostaglandins,[32] colchicine and its analogs,[1e,33] sesquicarene,[34] and heptitol derivatives[35] have been based on reactions of (**1**) and its derivatives.

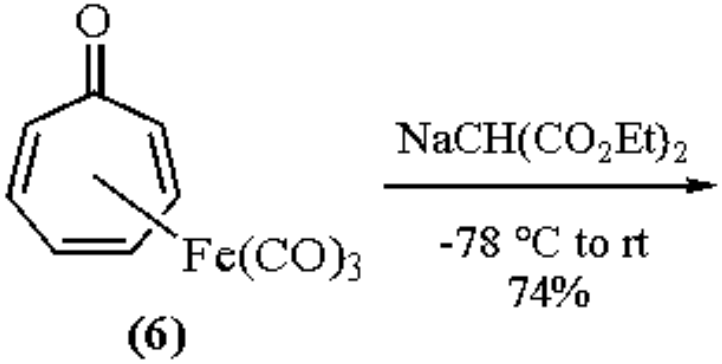

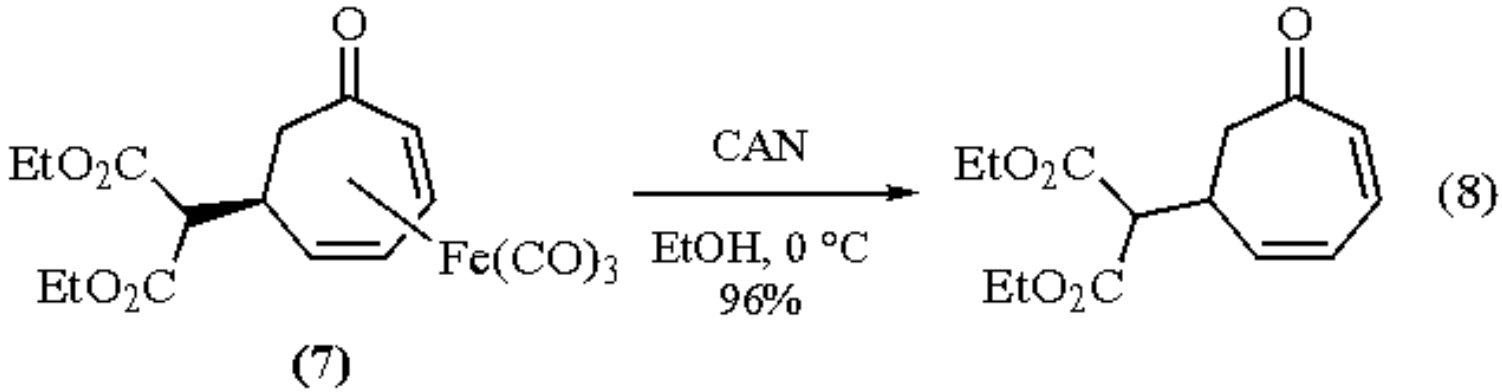

Miscellaneous Reactions.

A unique and extremely simple route to 4-alkyltropones involves homolytic alkylation of (**1**) in the presence of a Lewis acid with alkyl radicals generated from *N*-acyloxy-2-thiopyridones.[36] Tropone oxime tosylate undergoes a stereospecific ring opening reaction with secondary amines and alkoxides to give 6-substituted (1*Z*,3*Z*,5*Z*)-hexa-1,3,5-trienecarbonitriles in almost quantitative yield.[37]

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1,3-Cyclohexanedione[1]

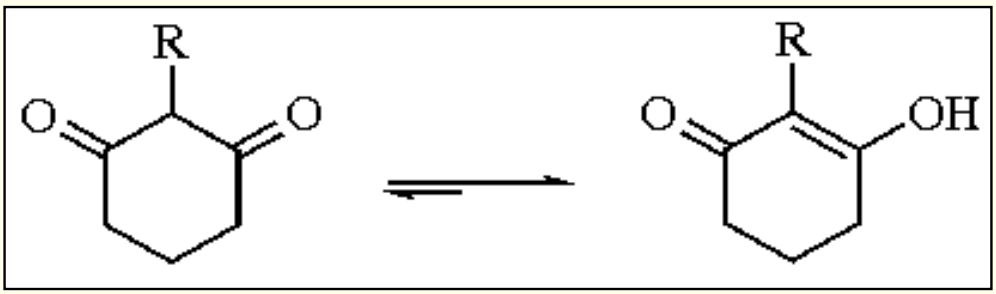

(R = H)

[504-02-9] · $C_6H_8O_2$ · 1,3-Cyclohexanedione · (MW 112.13) (R = Me)

[1193-55-1] · $C_7H_{10}O_2$ · 2-Methyl-1,3-cyclohexanedione · (MW 126.16)

(building block for substituted cyclohexane derivatives[2] and condensed carbo- and heterocycles[3])

Physical Data: 1,3-cyclohexanedione (CHD): mp 103-105 °C; 2-methyl-1,3-cyclohexanedione (MCHD): mp 206-209 °C.

Solubility: CHD easily sol H_2O, EtOH, $CHCl_3$, acetone, and boiling benzene; MCHD sol MeOH and sparingly sol H_2O and EtOH.

Form Supplied in: CHD and MCHD are colorless solids; both reagents are commercially available.

Preparative Methods: Raney nickel-catalyzed hydrogenation of resorcinol for CHD;[4] methylation of CHD[5] with MeI or base-promoted cyclization of ethyl 5-oxoheptanoate for MCHD.[6]

Handling, Storage, and Precautions: CHD is recommended to be stored at 0-5 °C. MCHD can be kept at rt. Both reagents are stable only in pure form. They are reputed to be of low toxicity.

CHD and its 2-monoalkyl homologs are almost completely enolized.[1] Many of their reactions are very similar.

Reactions with Nucleophiles at the Carbonyl Group.

The acid-catalyzed reaction of CHD with alcohols affords β-alkoxy enones (**1**) (eq 1).[2] These compounds can be reduced with ***Lithium Aluminum Hydride*** to the corresponding 2-cyclohexen-1-ones,[7] whereas addition of organometallics affords 3-alkyl-2-cyclohexen-1-ones.[2] With *N*,*N*-disubstituted hydrazines, CHD forms

monohydrazones, which exist as tautomeric enhydrazinones (**2**) (eq 1).[8]

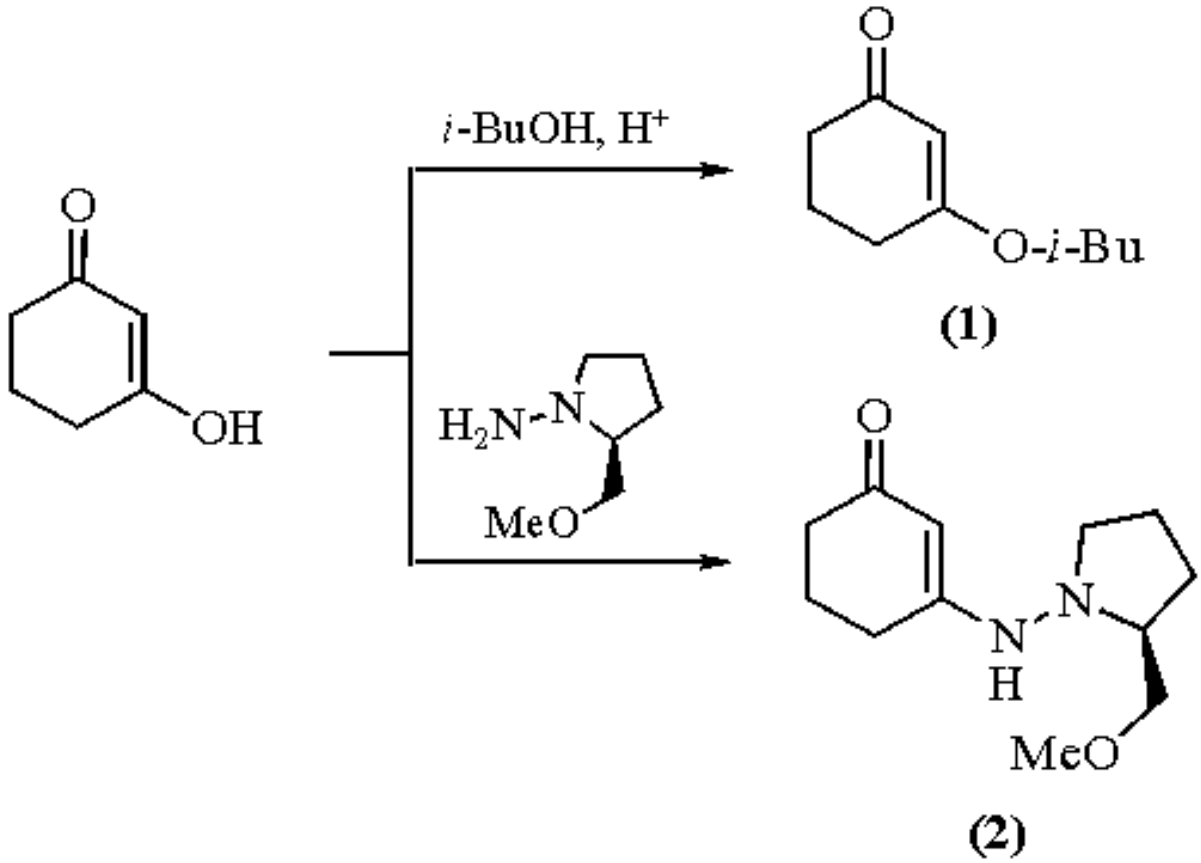

(1)

Reactions with Electrophiles at the Enolic Hydroxy Group.

Acylation of CHD with alkanoyl chlorides in pyridine gives rise to the enol esters (**3**), which can be isomerized to the triketones (**4**) (eq 2).[9] Alkyl tosylates[1] convert the dione into the corresponding β-alkoxy enones of type (**1**).

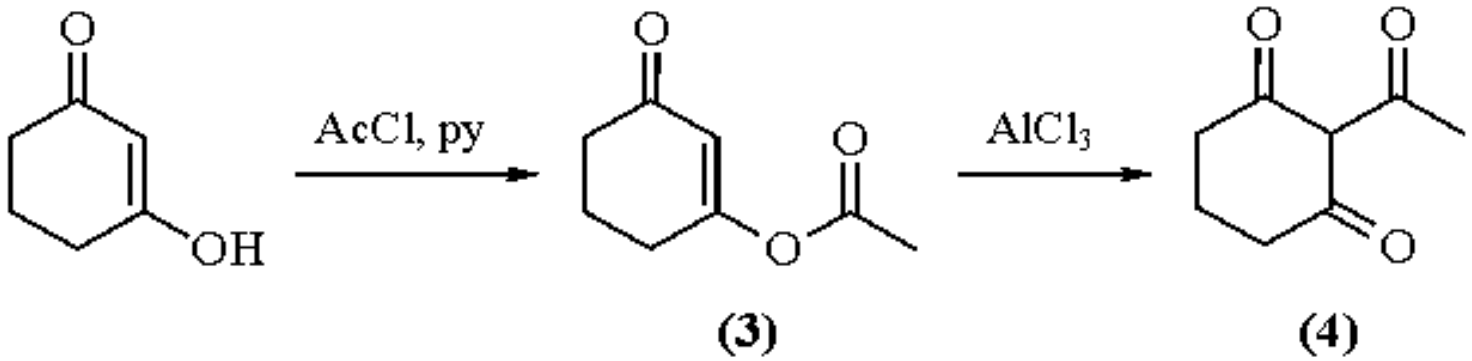

(2)

Reactions with Electrophiles at C-2.

The palladium(0)-catalyzed reaction of MCHD with the substituted allyl acetate (**5**) results in a clean *C*-alkylation (eq 3).[10]

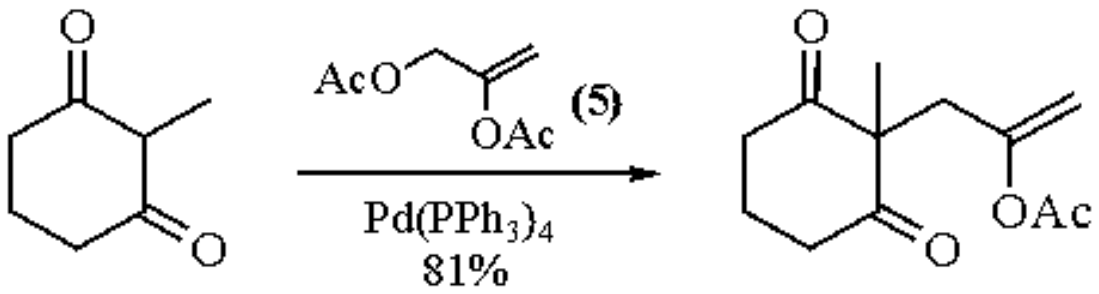

(3)

The alkylation of CHD with alkyl halides affords mixtures of 3-alkoxy-2-cyclohexen-1-ones (*O*-alkylation) and 2-mono- and 2,2-dialkylated 1,3-cyclohexanediones (*C*-alkylation). ***Allyl Bromide*** and ***Benzyl Bromide*** as well as alkyl bromoacetates give *C*-alkylation products in better yields.[1] In Michael reactions, α,β-unsaturated carbonyl compounds (eq 4),[1,11] acetals of α,β-enals,[12] nitroalkenes,[13] and Mannich bases[14] add to C-2 of MCHD. Aldol cyclization of the methyl vinyl ketone adduct affords the octalindione shown (eq 4) in racemic[11a] or optically active form.[11b]

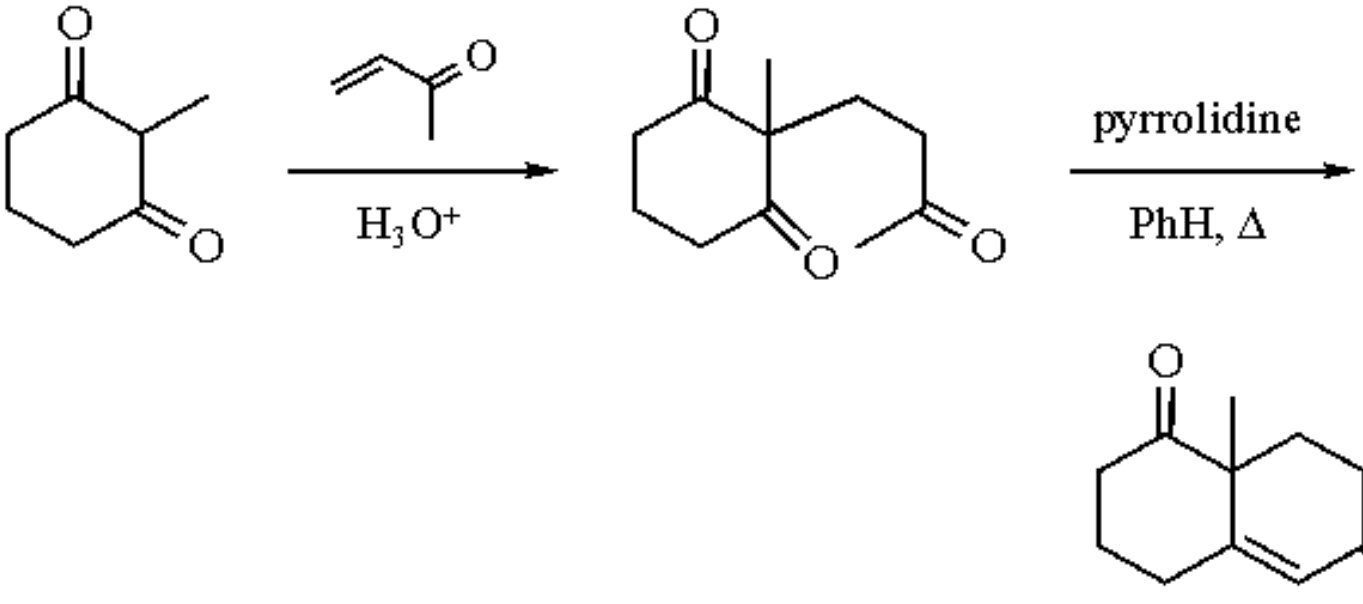

(4)

In the presence of ***Boron Trifluoride Etherate***, 2 equiv of ***Formaldehyde*** condense with CHD forming the 1,3-dioxin (**7**). With 2 equiv of CHD, formaldehyde leads to the adduct (**6**) (eq 5).[1,15]

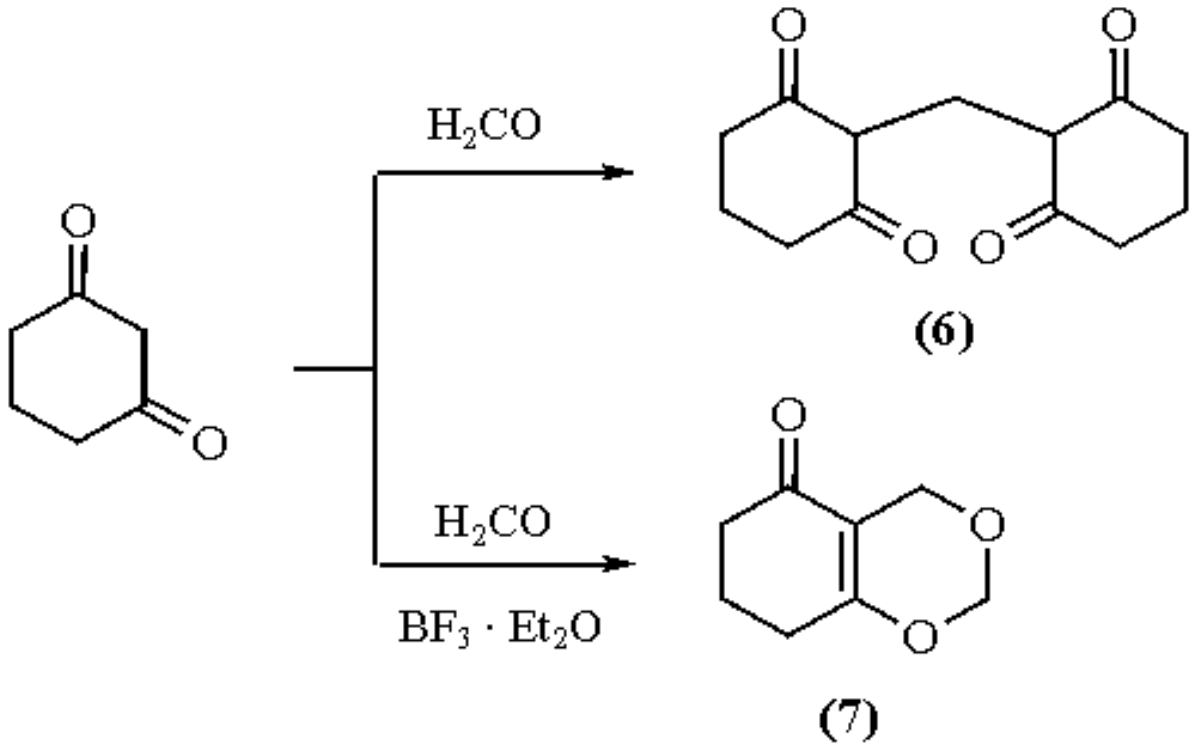

(5)

With DMF dimethyl acetal (see ***N,N-Dimethylformamide Diethyl Acetal***), an α-aminomethylenation takes place at C-2.[16] In the presence of BF_3, carboxylic anhydrides acylate CHD at C-2.[17]

Reactions with Electrophiles at C-4 or at C-6.

The enaminone (**8**) obtained from CHD and ***Pyrrolidine*** is alkylated at C-4 by treatment with ***n-Butyllithium*** and ***Iodomethane*** (eq 6).[18]

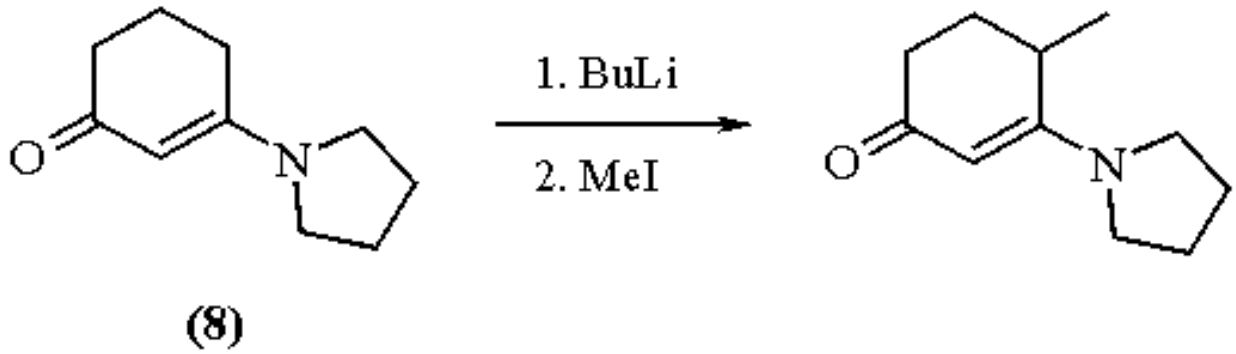

(6)

In contrast, the enol ethers derived from CHD or MCHD can be alkylated at C-6 after deprotonation with ***Lithium Diisopropylamide*** (eq 7).[19]

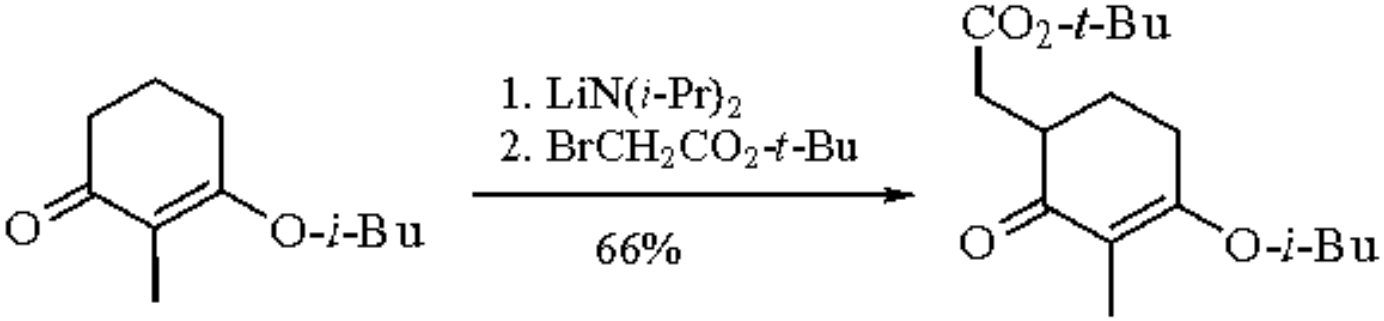

(7)

Annulation Reactions.

Many examples are known for the formation of condensed carbo- and heterocycles by reactions of bifunctional compounds with two of the reactive sites of CHD or MCHD.[3,19]

Ring Cleavage and Contraction.

Hydroxide- or alkoxide-induced retro-Claisen reactions of 2-alkyl- and 2,2-dialkyl-1,3-cyclohexanediones give rise to δ-keto acids or esters (eq 8).[20] Chlorination of 2-pentynyl-1,3-cyclohexanedione at C-2 followed by heating in the presence of sodium carbonate effects a Favorskii-type ring contraction with decarbonylation to 2-pentynyl-2-cyclopentenone (eq 9), a useful intermediate for the synthesis of jasmone.[21]

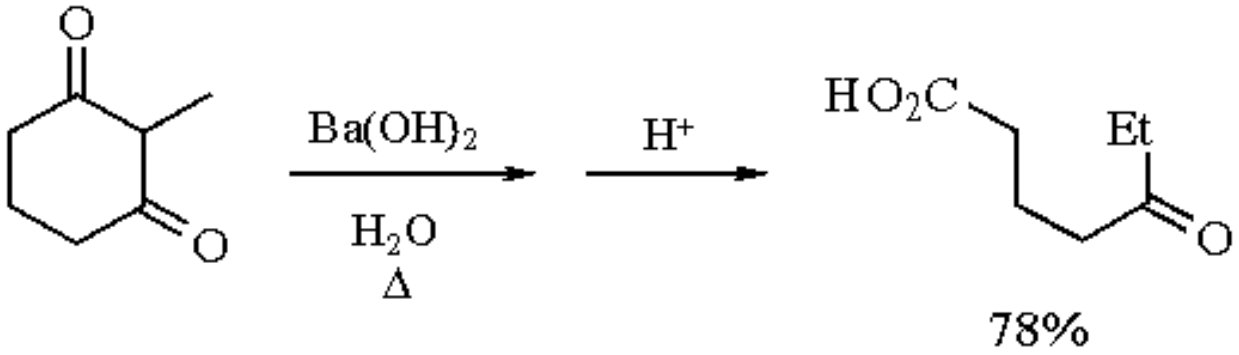

(8)

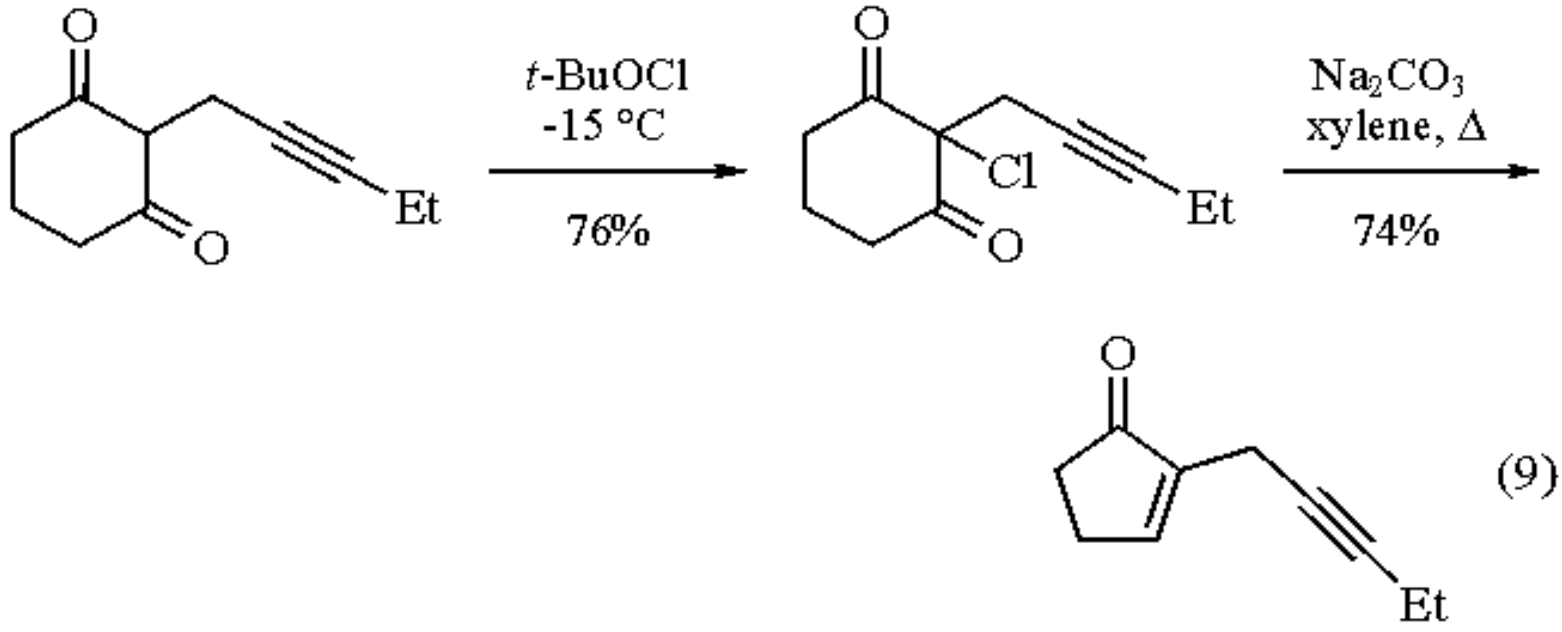

Related Reagents.

1,3-Cyclopentanedione; ***2-Methyl-1,3-cyclopentanedione***; ***Methyl Vinyl Ketone***; ***2,4-Pentanedione***; ***(S)-Proline***.

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N-Cyclohexylhydroxylamine[1]

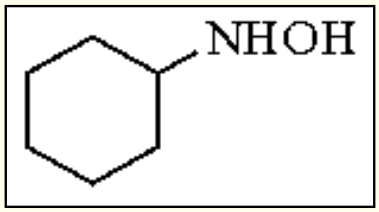

[2211-64-5] · $C_6H_{15}NO$ · *N*-Cyclohexylhydroxylamine · (MW 115.18) (.HCl)

[25100-12-3] · $C_6H_{16}ClO$ · *N*-Cyclohexylhydroxylamine Hydrochloride · (MW 151.64)

(condenses with a wide variety of aldehydes to afford *N*-cyclohexyl nitrones;[2] condenses with alkynes to afford *N*-cyclohexyl nitrones;[3] reagent in the conversion of 1,2-dicarboxylic acids to α,β-unsaturated carboxylic acids;[4] hydroxylamination reagent for allyl esters under palladium(0) catalysis[5])

Alternate Name: hydroxyaminocyclohexane.

Physical Data: mp 140-141 °C; hydrochloride salt, mp 166-171 °C.

Form Supplied in: available commercially as the free hydroxylamine and as the hydrochloride salt.

Preparative Methods: oxime reduction;[6-13] nitroalkene reduction;[14-16] nitro reduction;[17-19] amine oxidation.[20,21]

Purification: by sublimation.

Handling, Storage, and Precautions: hygroscopic; use in a fume hood.

Introduction.

Because of the similarity and overlap of their uses, ***N-Benzylhydroxylamine*** and ***N-t-Butylhydroxylamine***, as well as *N*-cyclohexylhydroxylamine, are all discussed here. Indeed, most of their chemistry is that of any of the *N*-monosubstituted hydroxylamines. They undergo a wealth of condensation reactions analogous to those of amines as well as ones unique to the hydroxylamine group, affording an array of nitrogen-containing compounds too numerous to list. In terms of their use as synthetic reagents, however, they function primarily in the conversion of carbonyl compounds into nitrones. While *N*-benzyl-, *N*-*t*-butyl-, and *N*-cyclohexylhydroxylamine all participate in a few specialized reactions, it is their role in the preparation of nitrone intermediates which has led to their general usage.

Synthesis and Reactions of Nitrones.

N-Benzyl-, *N*-*t*-butyl-, and *N*-cyclohexylhydroxylamine condense with carbonyl compounds under a variety of dehydrating conditions to afford nitrones (eq 1).[2] These reactions proceed smoothly with aldehydes, but poorly or not at all with ketones, especially when the hydroxylamine has a bulky substituent, as in the compounds under consideration. Nitrones are also produced in some cases by the condensation of *N*-cyclohexylhydroxylamine[3] and *N*-*t*-butylhydroxylamine[3,22] with alkynes (eq 2). The nitrones thus formed undergo a number of reactions,[23] the most studied of which are 1,3-dipolar cycloadditions.[24,25] This chemistry encompasses a large number of unsaturated dipolarophiles, providing many different types of heterocyclic product, and is beyond the scope of this discussion.

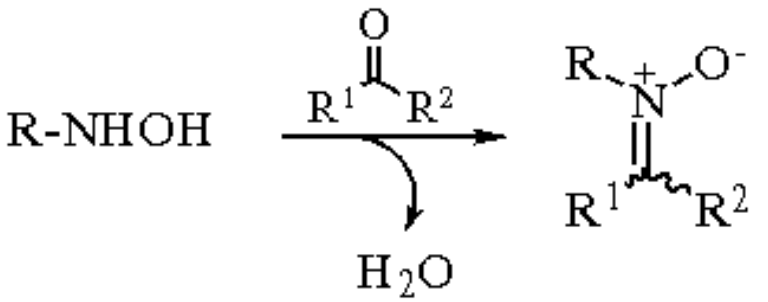

(1)

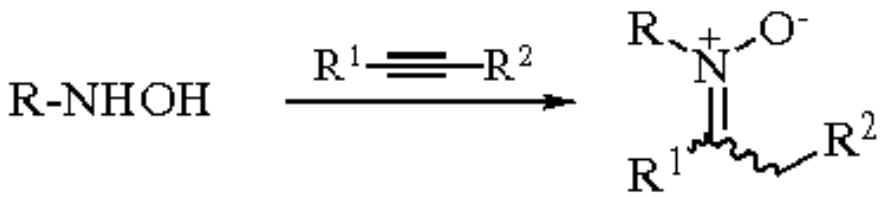

(2)

There are, however, other reactions of nitrones which can be more clearly considered as functional group transformations. In particular, *N*-cyclohexyl-α-chloro nitrones are converted by silver ion to *N*-vinylnitrosonium ions, which readily undergo cycloaddition to unactivated alkenes (eq 3).[26] Formation of the cyanide adduct, followed by base induced rearrangement and hydrolysis, provides γ-lactones (eq 4).[27] In the case of α,β-dichloro nitrones, the same sequence affords α-methylene-γ-butyrolactones (eq 4).[28] Alternatively, treatment with base leads to an enamine-like structure, which undergoes thermal cycloreversion to yield, after hydrolysis, a product in which the original alkene has been oxidatively cleaved (eq 4).[29] Alkynes undergo analogous chemistry with the *N*-cyclohexyl-α-chloro nitrones, ultimately providing α,β-enones (eq 5).[30] Interestingly, in a polar solvent the α-chloro nitrone undergoes substitution reactions with alkenes and arenes, resulting in β,γ-unsaturated aldehydes (eq 6).[31] Similar chemistry is observed for the related *N*-cyclohexyl-α-epoxy nitrones (eq 7).[32,33]

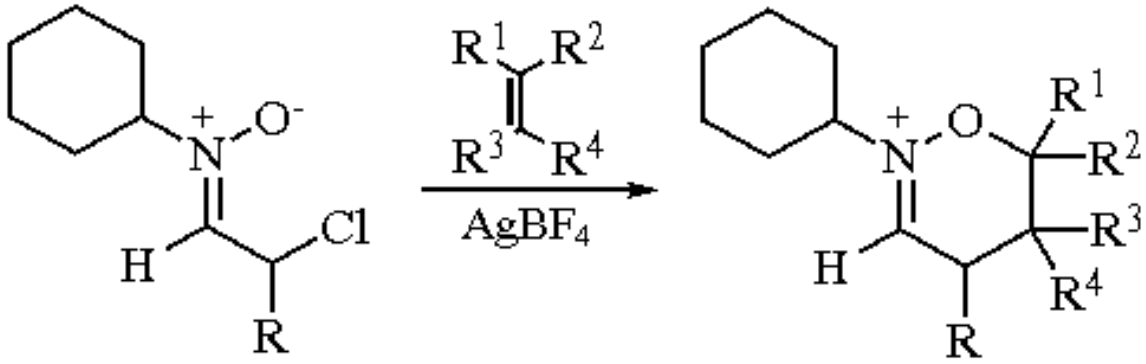

(3)

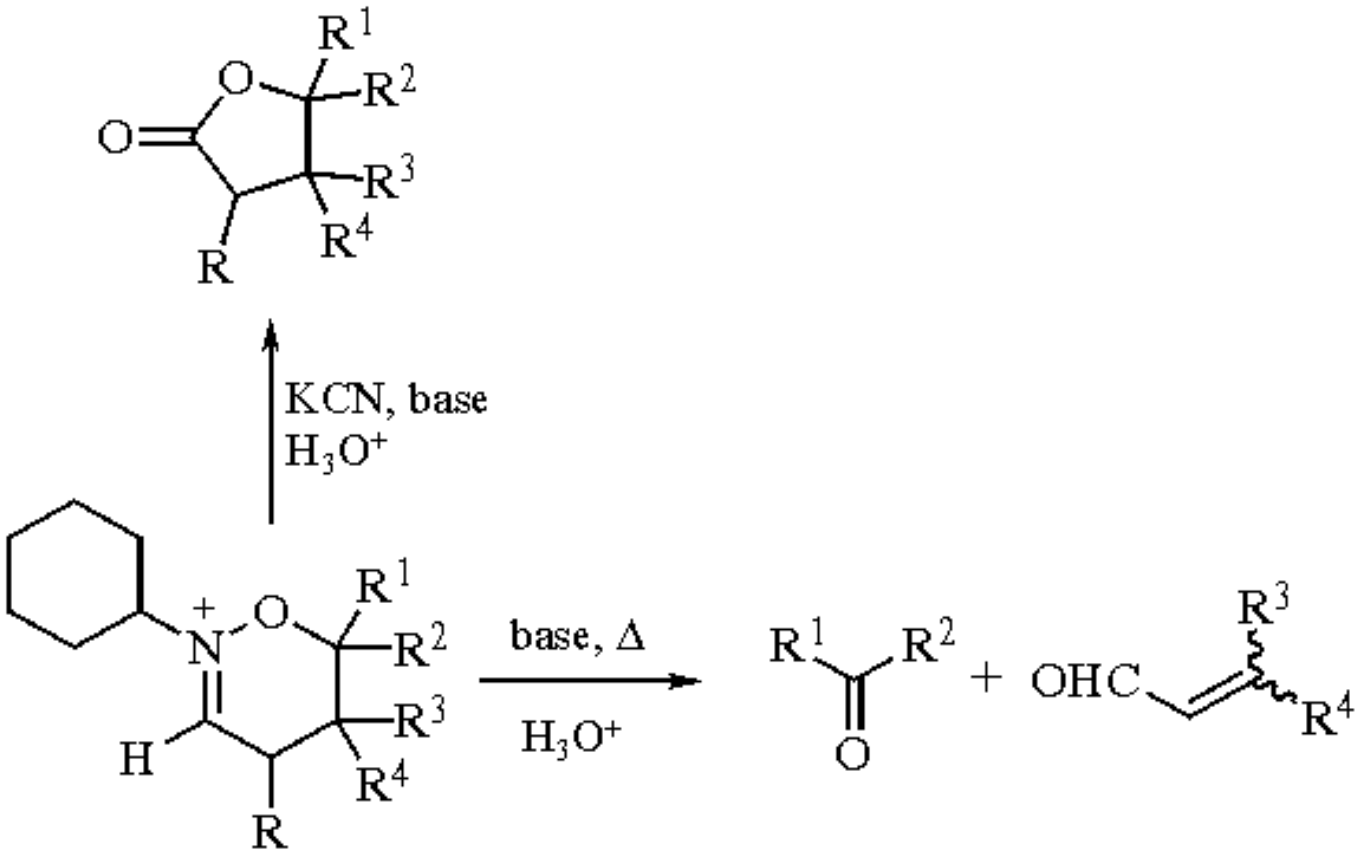
KCN, base
H_3O^+
base, Δ
H_3O^+
R = CH_2Cl
KCN, base
H_3O^+

(4)

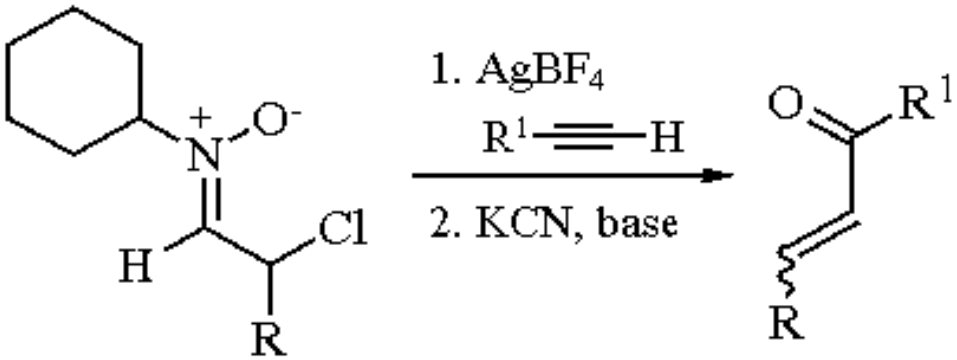
1. $AgBF_4$
R^1—≡—H
2. KCN, base

(5)

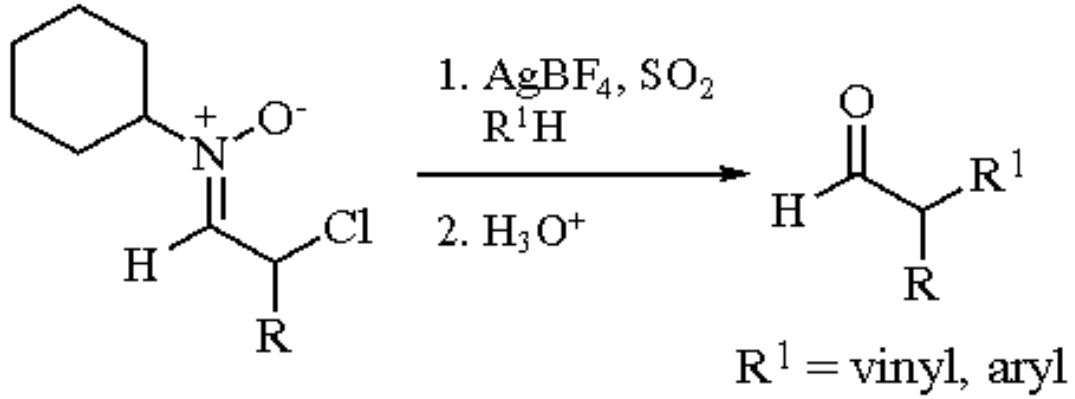

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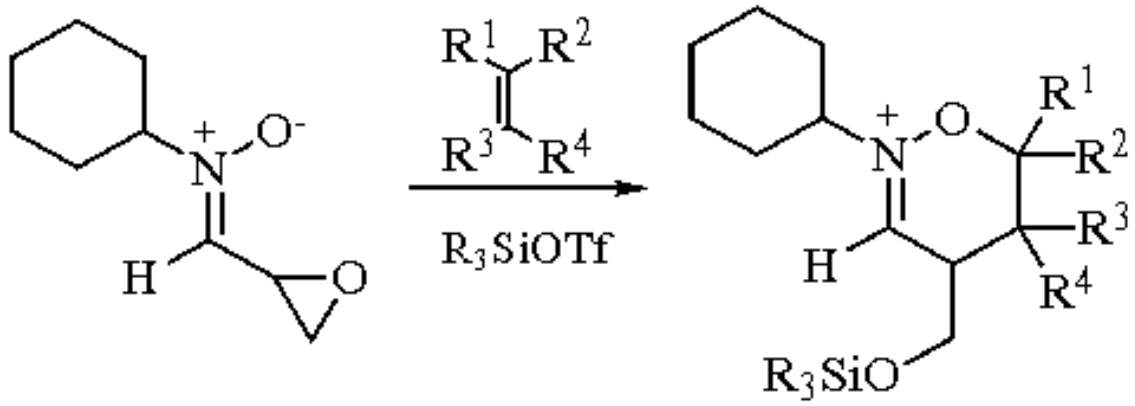

(7)

N-*t*-Butyl and *N*-cyclohexyl nitrones undergo acylation-rearrangement when treated with an acid chloride and triethylamine, affording α-acyloxy imines. These intermediates can be hydrolyzed to α-acyloxy aldehydes (eq 8), corresponding to an overall α-oxygenation of the aldehyde from which the nitrone was prepared.[34] Alternatively, reduction of the imines affords vicinal *N*-alkylamino alcohols (eq 8), corresponding to overall α-oxygenation and reductive amination.[35]

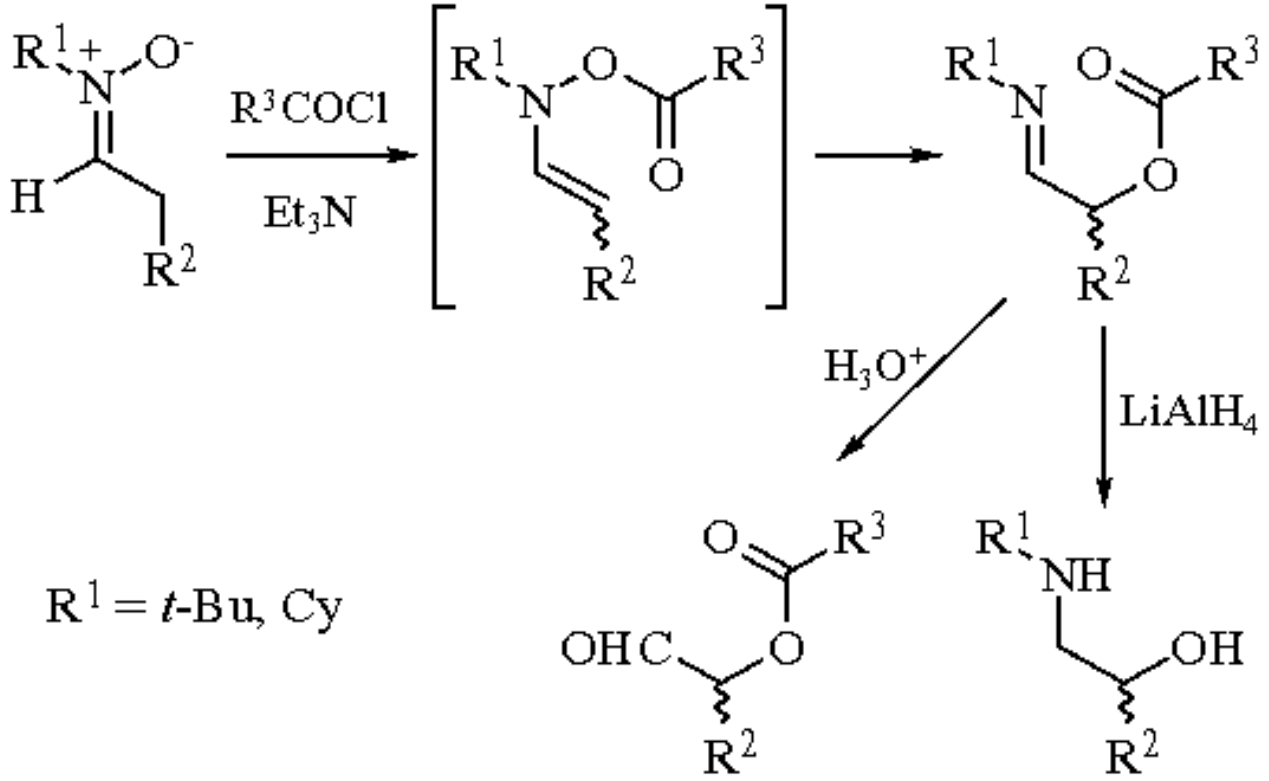

(8)

Alkene Aminations.

Hydroxyamination of allyl esters under palladium(0) catalysis can be accomplished with both *N*-benzyl- and *N*-cyclohexylhydroxylamine (eq 9).[5] The reaction proceeds with retention of configuration and allylic transposition. Amination of unactivated alkenes, again via allylic transposition, has been accomplished using molybdenum-based metallooxaziridines, prepared from *N*-*t*-butylhydroxylamine and a dioxomolybdenum(VI) complex (eq 10).[36]

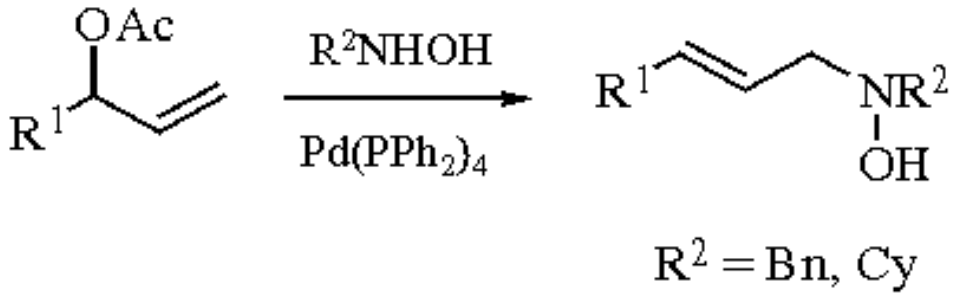

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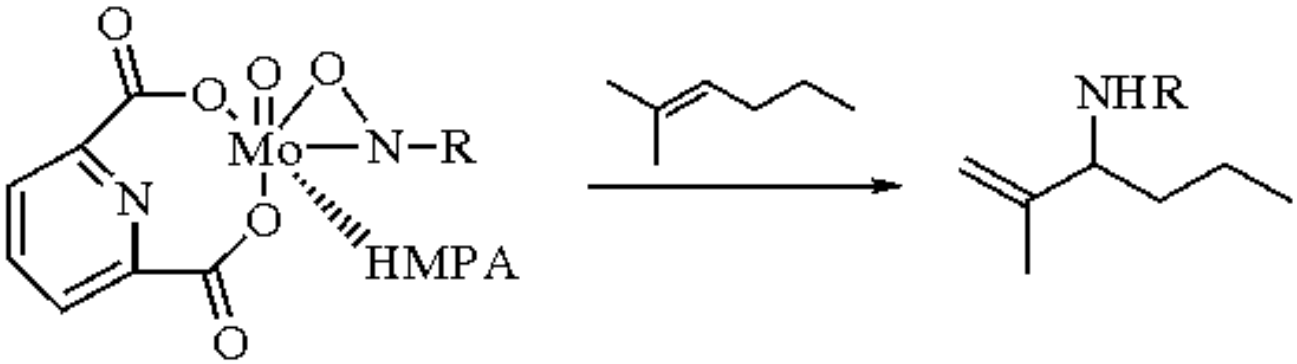

(10)

Decarboxylation and Cyclization Reactions.

The oxidative decarboxylation of 1,4-dicarboxylic acids to α,β-unsaturated acids can be accomplished regiospecifically using *N*-cyclohexylhydroxylamine.[4] The initially formed tetrahydro-1,2-oxazine-3,6-dione can be fragmented in either of two complementary fashions to afford α,β-unsaturated carboxylic acids (eq 11).

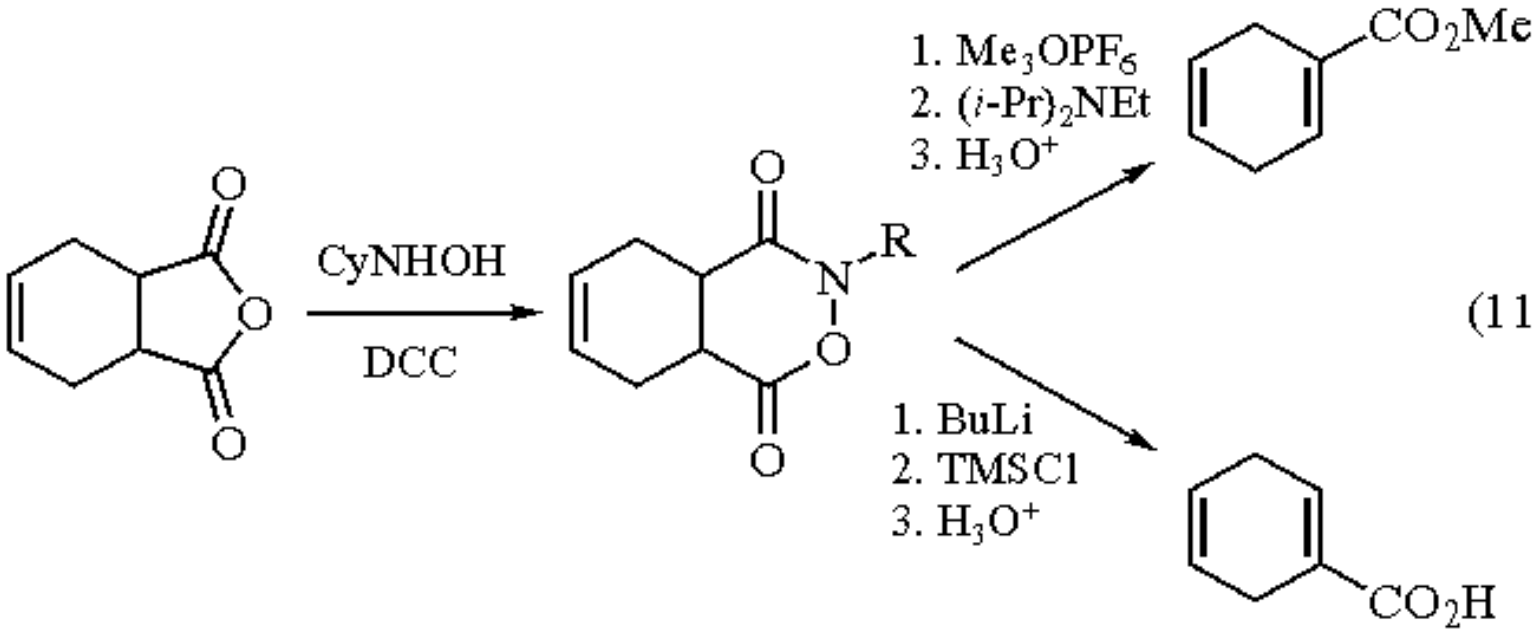

N-*t*-Butylaziridinones can be prepared from *N*-*t*-butylhydroxylamine and phenylacetyl chloride, by way of intermediate hydroxamic acids (eq 12).[37] The use of ***Trifluoromethanesulfonic Anhydride*** is critical; if a sulfonyl chloride is employed, the aziridinone is observed transiently, but it undergoes rapid ring opening by chloride.

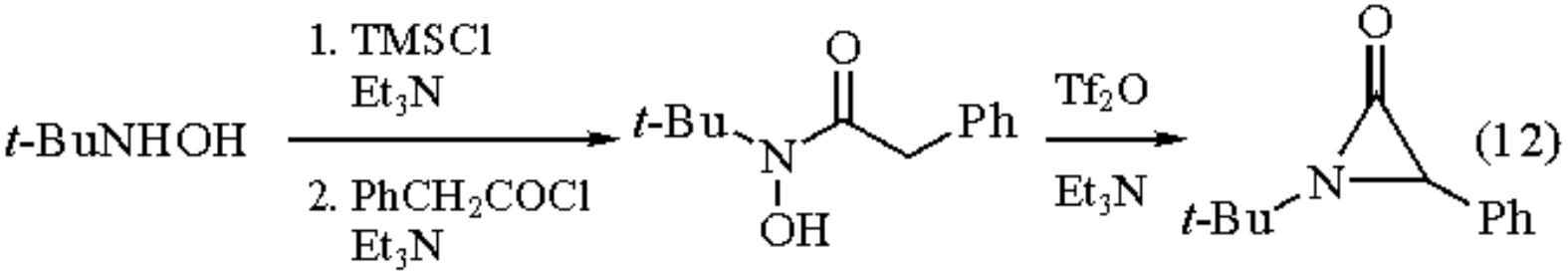

Related Reagents.

N-Benzylhydroxylamine; ***N,O-Bis(trimethylsilyl)hydroxylamine***; ***O-(t-Butyldimethylsilyl)hydroxylamine***; ***N-t-Butylhydroxylamine***; ***C-(1-Chloroethyl) N-Cyclohexyl Nitrone***; ***N,O-Dimethylhydroxylamine***; ***Hydroxylamine***; ***N-Methyl-N,O-bis(trimethylsilyl)hydroxylamine***; ***N-Methylhydroxylamine***.

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Clark H. Cummins

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Cyclohexyl Isocyanide[1]

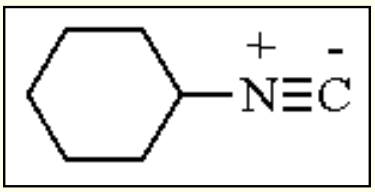

[931-53-3] · $C_7H_{11}N$ · Cyclohexyl Isocyanide · (MW 109.17)

(reagent for phosphorylation of phosphomonoesters;[2] formylation of secondary anilines[4])

Physical Data: bp 173-176 °C; *d* 0.878 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: toxic. Use in a fume hood.

Phosphorylation.

Cyclohexyl isocyanide has been utilized[2] in the activation of phosphates, in a mode similar to ***1,3-Dicyclohexylcarbodiimide***.[3] The method enables the generation of phosphodiesters from phosphomonoesters by selective use of the alcoholic medium (eq 1). An extension of this procedure permits the preparation of 2´,3´-cyclic phosphates of nucleosides from nucleoside 2´ (or 3´) phosphates (eq 2).

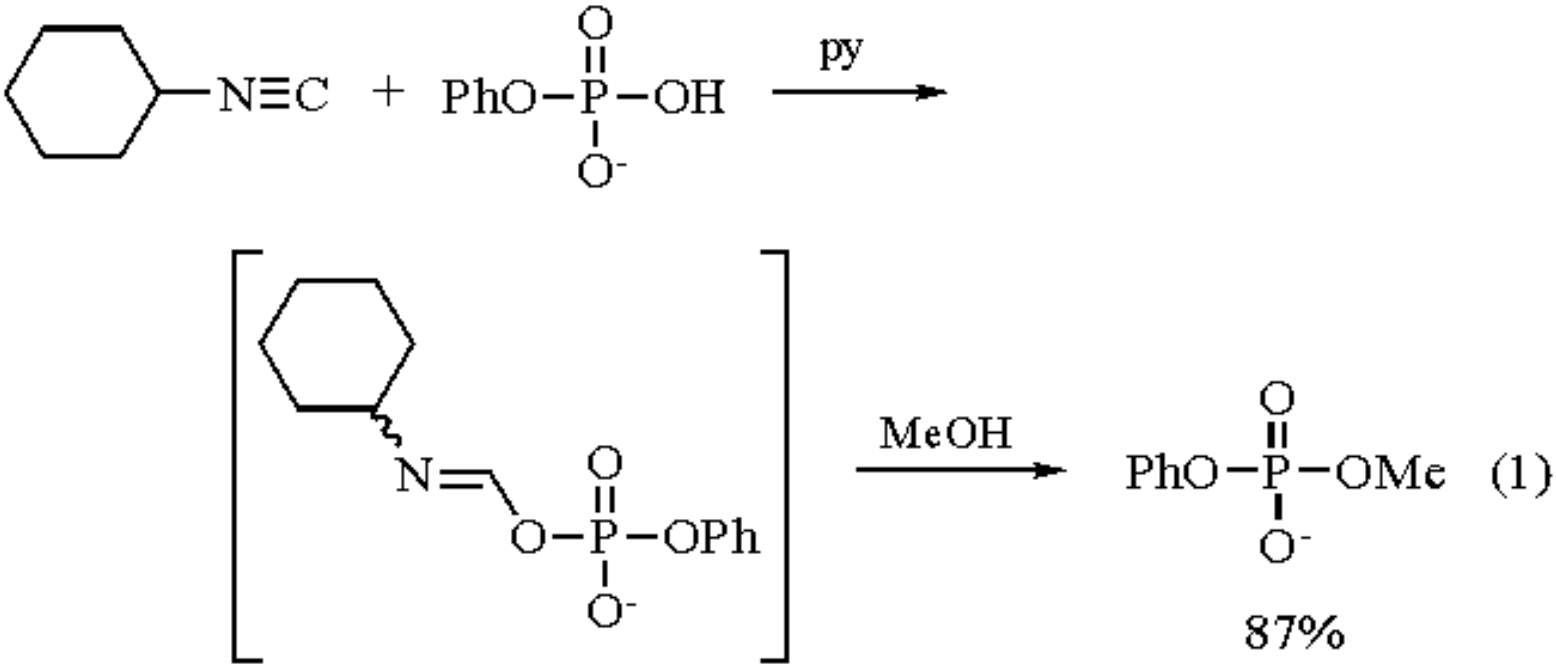

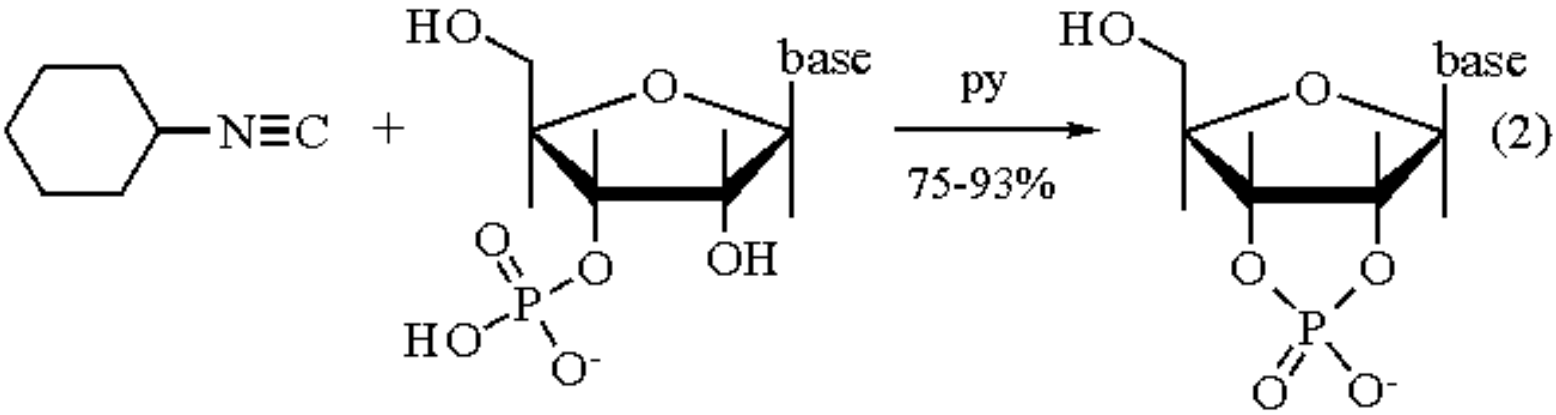

Formylation.

Employment of cyclohexyl isocyanide in the *ortho* formylation of secondary anilines, which are synthetically versatile in heteroannulation reactions, has been demonstrated.[4] In a typical sequence, the secondary aniline is treated with ***Boron Trichloride*** to generate an anilinoborane which may be isolated. Further reaction of the borane with cyclohexyl isocyanide, in the presence of ***Triethylamine***, yields the *o*-alkylaminobenzaldehyde upon acid hydrolysis (eq 3).

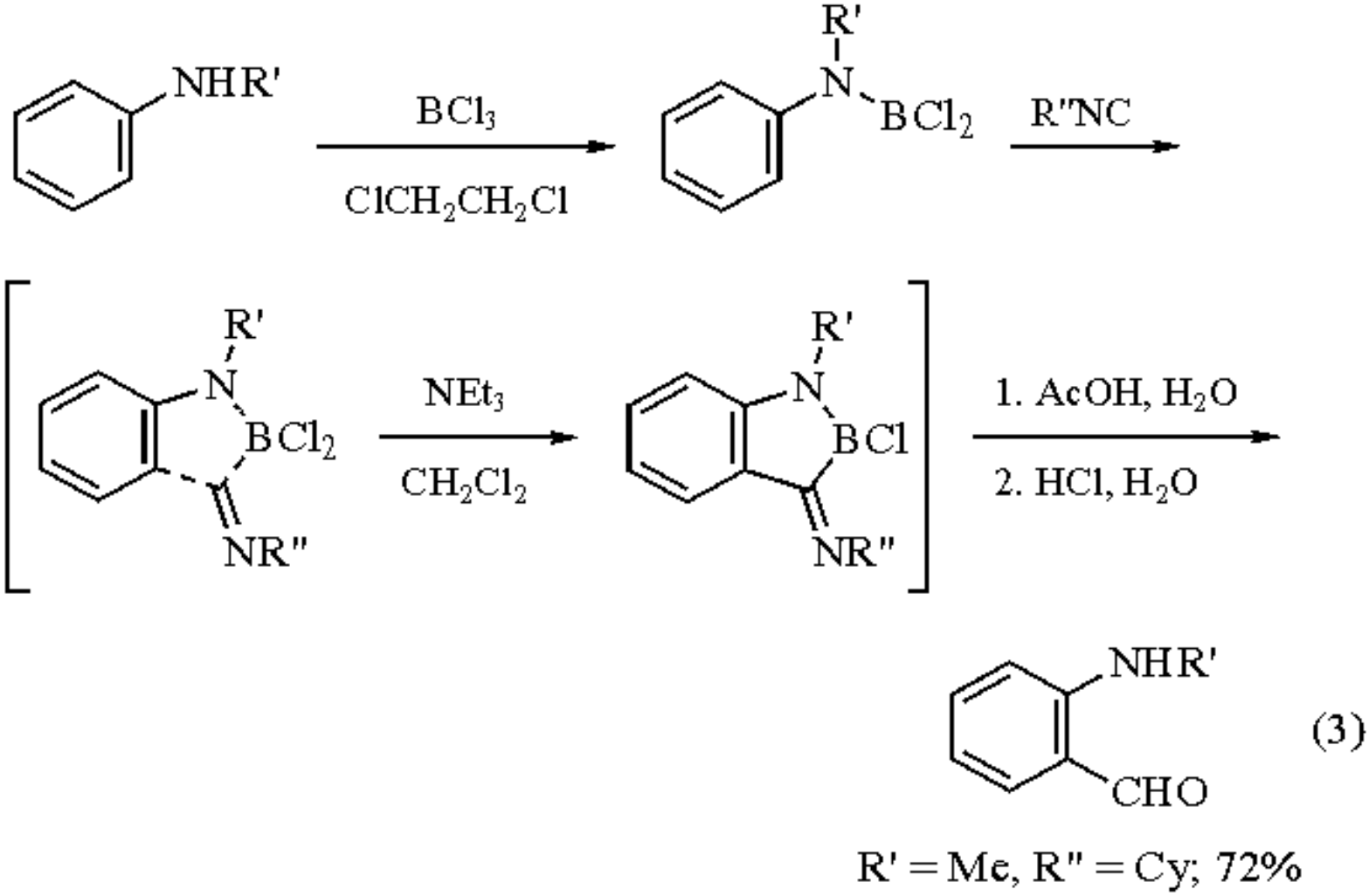

In this investigation, cyclohexyl isocyanide offered the highest yield and shortest reaction time for the isocyanides and secondary anilines studied. Although the method claims a practical advantage over a previous *o*-formylation approach,[5] it was found to be unsuitable for primary anilines.

Copper-Isocyanide Complexes.

The availability of a nonbonding pair of electrons in an sp-hybridized orbital on the terminal carbon atom enables isocyanides to behave as strong carbon ligands for transition metals, for which many complexes have been synthesized. Within the chemical literature, the synthetic value of copper-isocyanide complexes has been amply demonstrated. Cyclopentane- and cyclohexanecarboxylates have been prepared[6] from the stepwise cycloaddition of 1,o-diiodopropanes and -butanes, respectively, with dialkyl fumarate and maleate in the presence of cyclohexyl isocyanide and metallic ***Copper*** (eq 4).

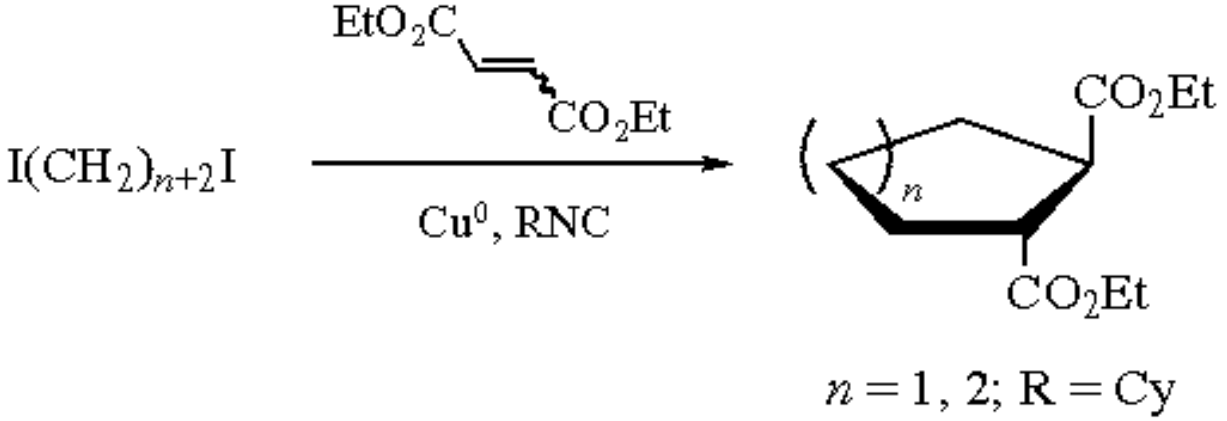

(4)

The reported yields are greater for cyclopentane formation (90% *trans*, 89% *cis*), than for the cyclohexane cycloadduct (37% *trans*, 55% *cis*), where the occurrence of a single stereoisomer for each homolog is a consequence of maleate isomerization by the isocyanide complex prior to cyclization.

Other synthetic uses of copper (or ***Copper(I) Oxide***)-cyclohexyl isocyanide complexes include conjugate additions[7] of activated methylene species, cyclopropanations,[8] allene synthesis[9] from *gem*-dibromocyclopropanes (eq 5), dimerization of alkyl halides,[10] and hydrosilylations of acrylonitriles.[11]

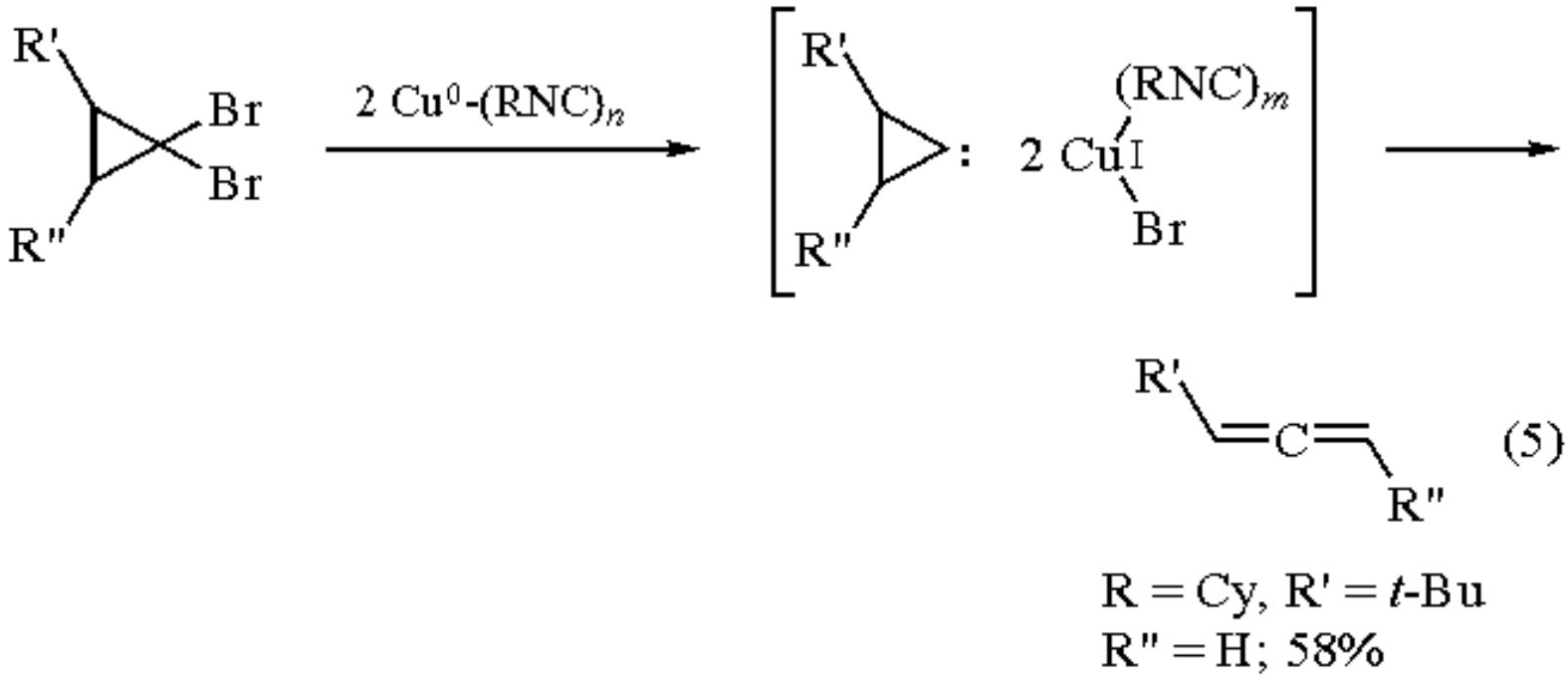

(5)

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(*R*)-(+)-Cyclohexyl(2-anisyl)methylphosphine[1]

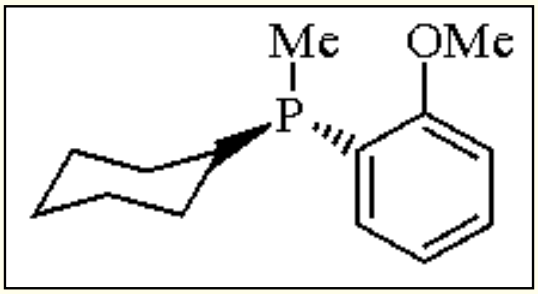

(*R*)

[52885-02-6] · $C_{14}H_{21}OP$ · (*R*)-(+)-Cyclohexyl(2-anisyl)methylphosphine · (MW 236.29) (*S*)

[35144-03-7] (±)

[36293-81-9]

(ligand for transition metal catalyzed asymmetric hydrogenation of alkenes;[2] reagent for asymmetric Wittig[3] and Baylis-Hillman reactions[4])

Alternate Name: (+)-CAMP.

Preparative Method: by hydrogenation (5% Rh/C) of optically pure (2-anisyl)phenylmethylphosphine oxide[5] followed by reduction of the phosphine oxide with ***Trichlorosilane***.[2]

Handling, Storage, and Precautions: readily oxidized to the phosphine oxide and should be handled under N_2 or Ar. This reagent should be handled in a fume hood.

Asymmetric Hydrogenation.

The synthesis of L-Dopa via asymmetric rhodium-catalyzed hydrogenation was reported using a catalyst prepared from rhodium(I) complexes and (+)-CAMP.[2,6] Activation of the catalyst by pretreatment with 1 atm H_2 was necessary. Hydrogenation at lower pressures (10 psi H_2) gave the dihydrocinnamic acid in 90% yield and 88% ee (eq 1). Similar yields and enantioselectivities have been reported with related cinnamic acid derivatives which are capable of bifunctional binding to the rhodium catalyst.[2] Bidentate diphosphine ligands generally lead to higher enantioselectivities in such reactions and are, therefore, employed in the commercial synthesis of L-Dopa.[1]

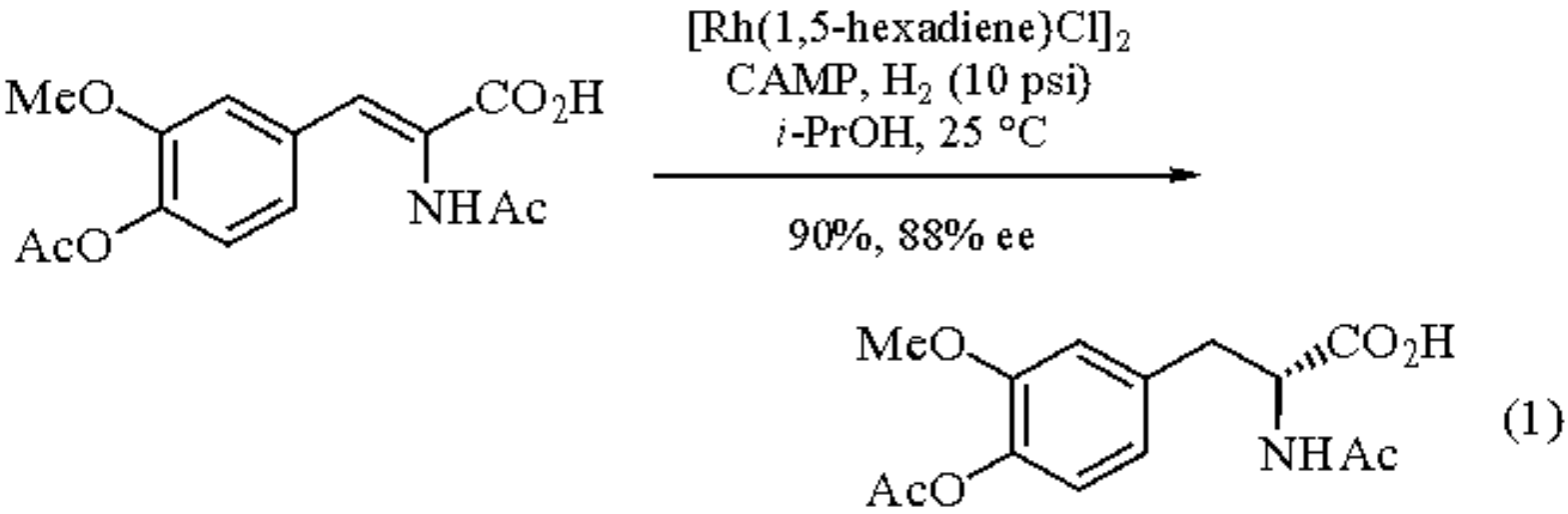

Wittig Reaction.

The intramolecular Wittig reaction of an ylide obtained from (+)-CAMP occurred with 77% ee to give the (*S*)-bicyclic diketone.[3] Although a stoichiometric amount of the optically pure phosphine was required, the phosphine oxide (+)-CAMPO could be recycled. Enantiomeric excesses using CAMP were much higher than similar reactions which employed other chiral phosphines.

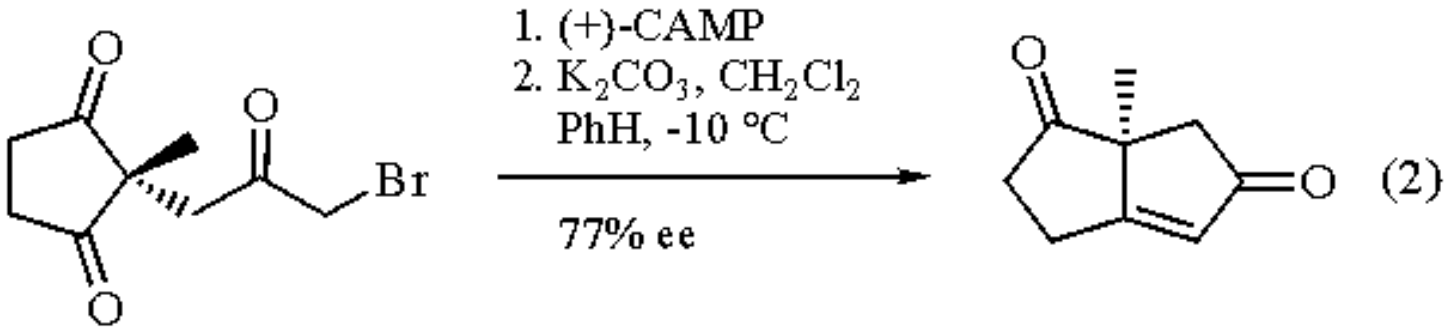

Baylis-Hillman Reaction.

Intramolecular cyclization of $MeCO(CH_2)_2CH{=}CHCO_2Et$ using (+)-CAMP produced the cyclopentene in 40% isolated yield.[4] A 3:1 equilibrium mixture which favored the product cyclopentene was formed after 10 days at 25 °C. CAMP was found to be superior to other phosphines, such as PBu_3. DABCO and other nitrogen bases were ineffective for the cyclization reaction. However, the enantioselectivity of the product using CAMP was only 14%.

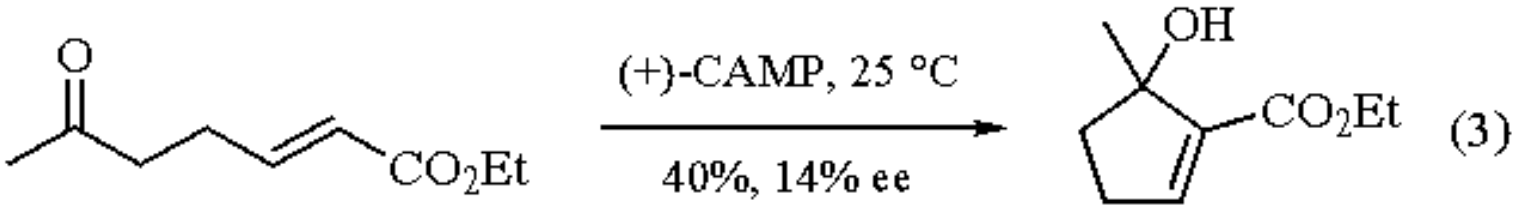

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1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide[1]

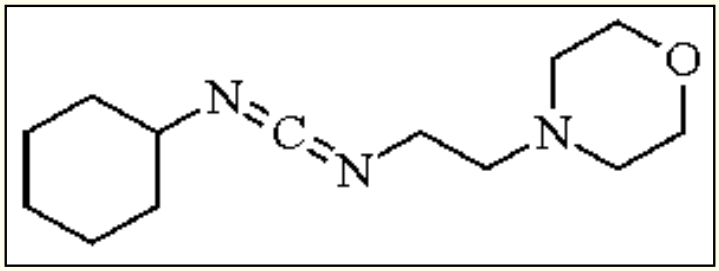

[15580-20-8] · $C_{13}H_{23}N_3O$ · 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide · (MW 237.34)

(coupling agent for peptide synthesis; used to make sulfate esters from alcohols)

Physical Data: bp 145 °C/0.2 mmHg.

Solubility: sol DMF, CH_2Cl_2, dioxane, xylene.

Preparative Methods: from cyclohexyl isothiocyanate and *N*-(2-aminoethyl)morpholine (67% yield);[2] by dehydration of the corresponding urea with ***p-Toluenesulfonyl Chloride***, ***Potassium Carbonate***, and ***Benzyltriethylammonium Chloride*** (91% yield);[3] or by the reaction of cyclohexyl isocyanate, 2-(4-morpholinyl)ethyl diethylphosphoramidate, and potassium carbonate (82% yield).[4] The corresponding *N*-metho-*p*-toluenesulfonate salt is commercially available (see ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-p-toluenesulfonate***).

Peptide Synthesis.

Amide bonds may be formed using carbodiimides but workup procedures are sometimes complicated by the presence of the urea byproduct. 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide (**1**) carries a tertiary amine and has a urea derivative that is soluble in dilute acid, making product separation far easier. It has been used to couple glycine ethyl ester hydrochloride and phthaloyl-L-phenylalanine to give phthaloyl-L-phenylalanylglycine ethyl ester in 81% yield (eq 1).[2]

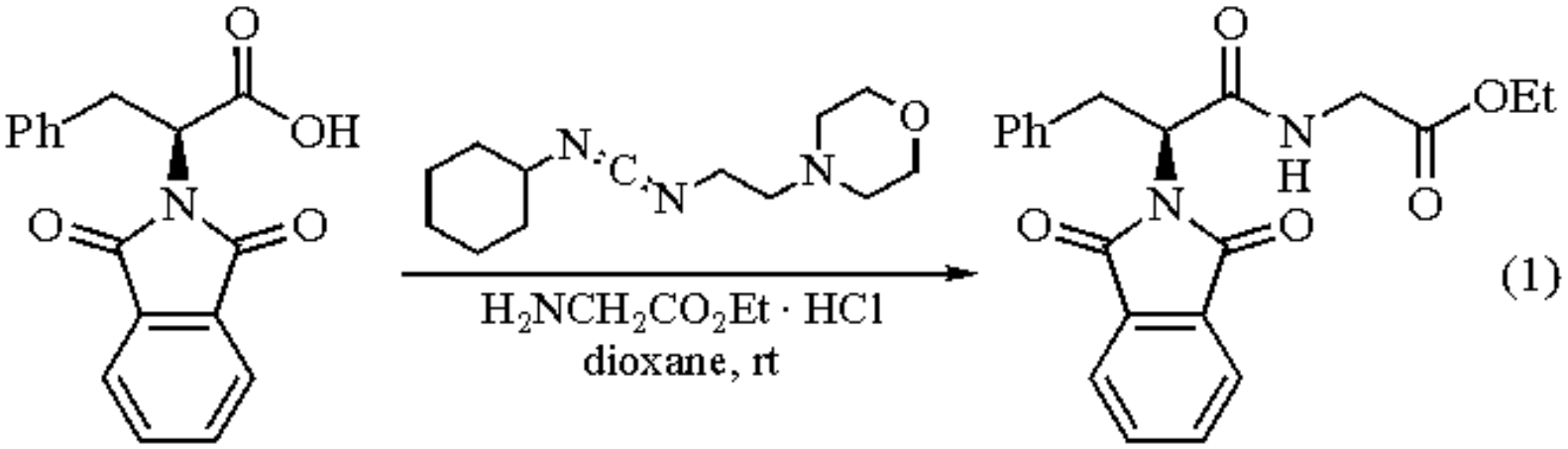

(**1**) has been found to be superior to ***1,3-Dicyclohexylcarbodiimide*** (DCC) for the final cyclization step in the synthesis of a large-ring peptide lactone related to the antibiotic vernamycin B_{α}, with methylene chloride being the solvent of choice.[5] Of all the other coupling reagents examined, only ***N,N´-Carbonyldiimidazole*** gave any cyclization product, although in lower yields.

Preparation of Sulfate Esters.

1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide has been used to mediate the sulfation of 1-hexadecanol to give the corresponding monoalkyl sulfate in 56% yield (eq 2).[6] DCC is superior in this reaction, giving the monoalkyl sulfate in 92% yield.

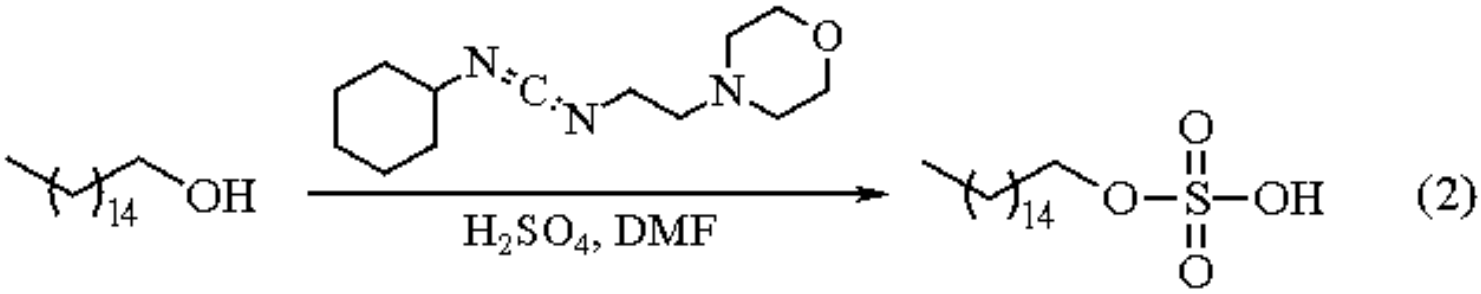

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1. For general reviews on the use of carbodiimides, see (a) Kurzer, F.; Douraghi-Zadeh, K. *CRV* **1967**, *67*, 107. (b) Williams, A.; Ibrahim, I. T. *CRV* **1981**, *81*, 589. (c) Mikolajczyk, M.; Kielbasinski, P. *T* **1981**, *37*, 233.
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1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-*p*-toluenesulfonate[1]

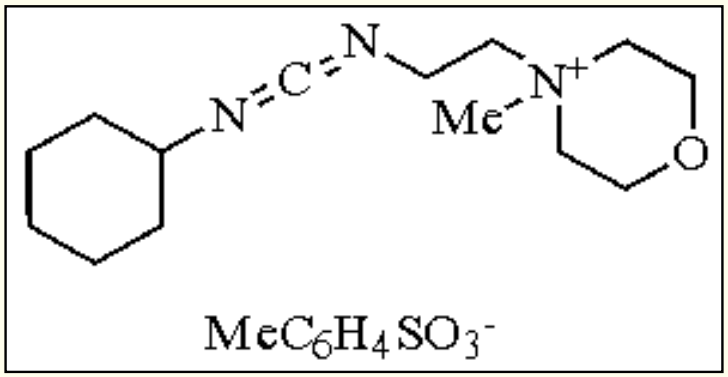

[2491-17-0] · $C_{21}H_{33}N_3O_4S$ · 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-*p*-toluenesulfonate · (MW 423.58)

(used extensively in the activation of alcohols and carboxylic acids)

Alternate Name: morpho-CDI.

Physical Data: mp 113-115 °C.

Solubility: sol DMF, MeCN.

Form Supplied in: commercially available as a colorless solid.

Preparative Methods: prepared by quaternization of the corresponding carbodiimide (see ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide***) with methyl *p*-toluenesulfonate. The carbodiimide is obtained by dehydration of the thiourea.[2]

Handling, Storage, and Precautions: assumed to be harmful by ingestion and skin contact.

Peptide Synthesis.[2]

Phthaloyl-L-phenylalanyl-L-leucine ethyl ester has been prepared in 80% yield by the 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (**1**) mediated coupling of L-leucine ethyl ester hydrochloride

to phthaloyl-L-phenylalanine (eq 1). Any excess of reagent and the corresponding urea were easily separated from the product by washing with aqueous solutions. The ease of separation of byproduct is the main advantage of this reagent over ***1,3-Dicyclohexylcarbodiimide*** (DCC).

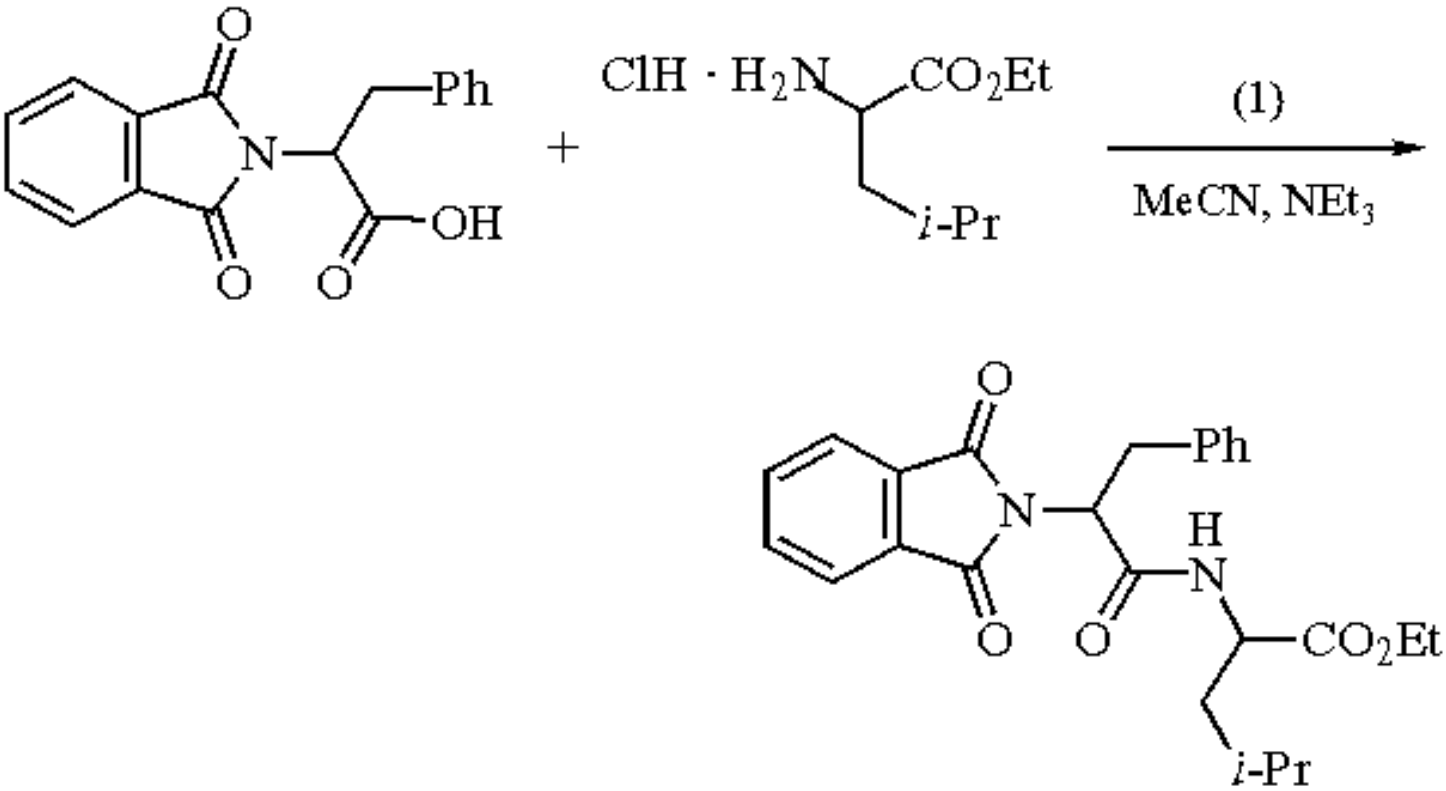

(1)

Macrocyclic Lactonization.[3]

Lactonization of secoacid (**2**) was effected with (**1**), and subsequent cleavage of the methoxymethyl ether results in the antibiotic milbemycin β_3 (**3**) in 85% overall yield (eq 2).

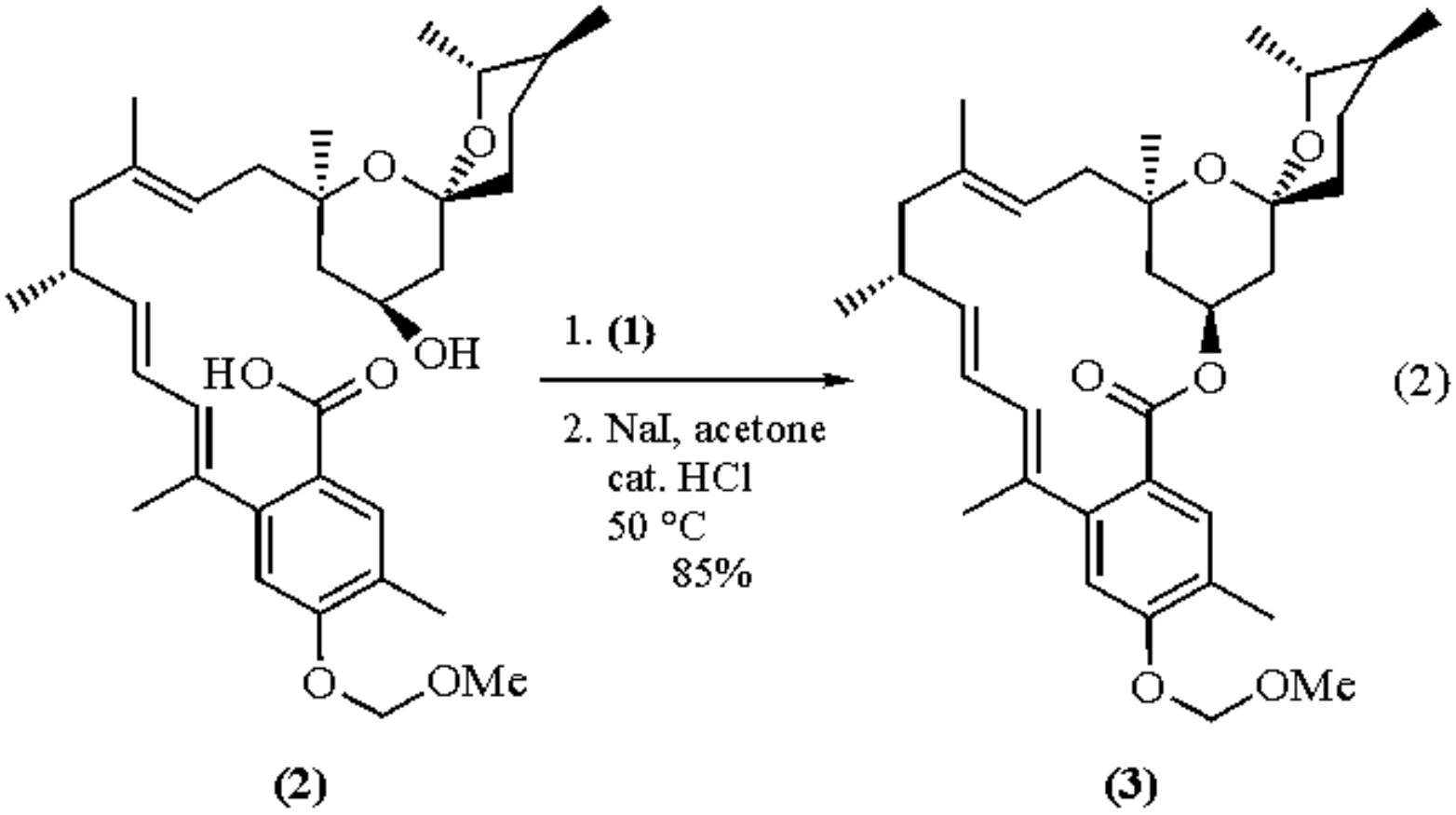

Cyclodehydrations of *N*-Acyl-α-amino Acids.[4]

2-Oxazolin-5-ones are conveniently prepared by dehydration of *N*-acyl-α-amino acids with (**1**) (e.g. eq 3).

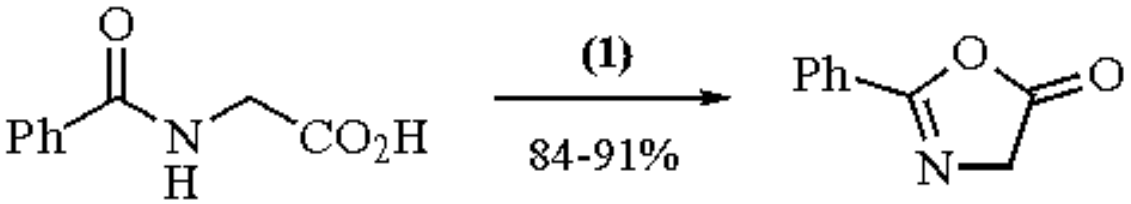

(3)

Modified Moffat-Type Oxidations.[5]

(**1**) used in conjunction with DMSO has been used to oxidize alcohols to ketones, as exemplified in the total synthesis of kopsanone (eq 4). This is another example where the advantage of the water solubility of (**1**) and the corresponding urea makes the use of this reagent more attractive than DCC as the diimide component.

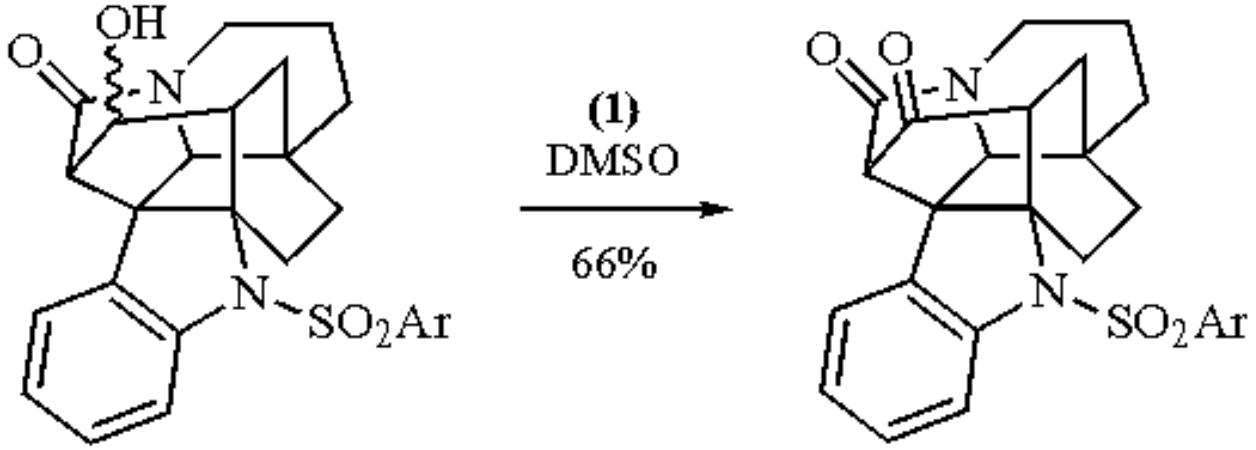

(4)

Dehydration of α-Hydroxymethyl Lactones.[6]

α-Hydroxymethyl lactones can be dehydrated to the corresponding α-methylene lactone with the use of (**1**) in the presence of ***Copper(II) Chloride*** (eq 5). This procedure has been successfully demonstrated in the total synthesis of isolobophytolide.

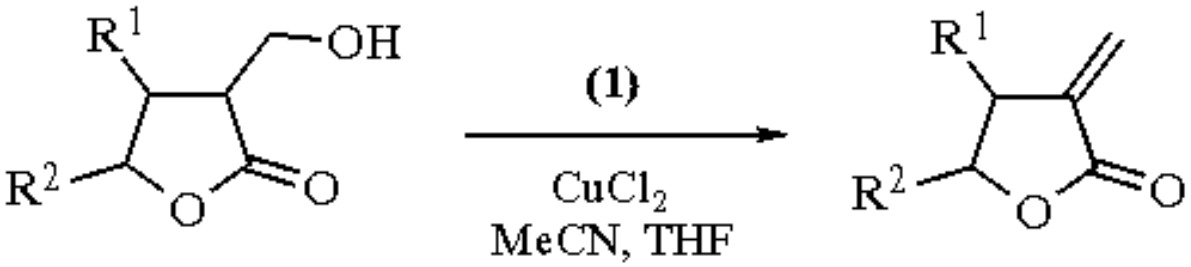

(5)

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(1,5-Cyclooctadiene)[1,4-bis(diphenylphosphino)butane]iridium(I) Tetrafluoroborate

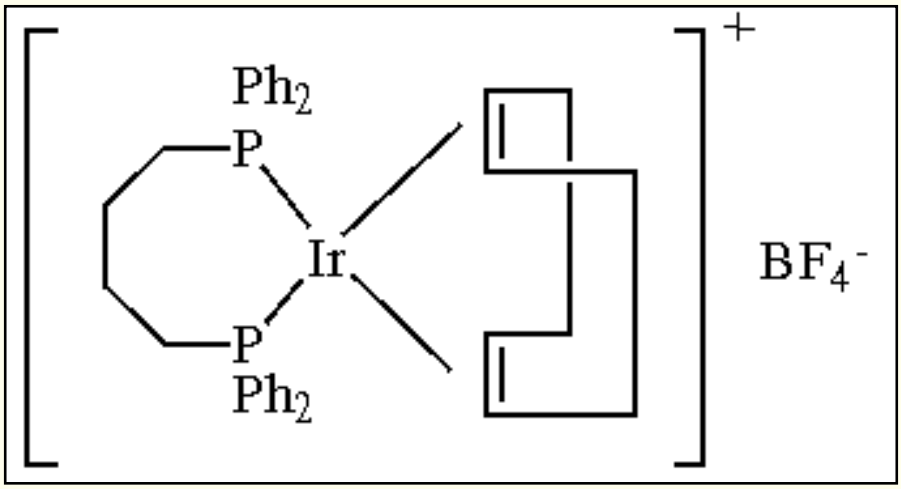

[78036-20-1] · $C_{36}H_{40}BF_4IrP_2$ · (1,5-Cyclooctadiene)[1,4-bis(diphenylphosphino)butane]iridium(I) Tetrafluoroborate · (MW 813.685)

(reagent for hydrogenation;[1] isomerization of butenyl- to allylsilanes[2])

Physical Data: dec. on attempted melting.

Solubility: insol Et_2O, pentane; sol CH_2Cl_2, MeOH, etc.

Form Supplied in: orange powder. *Drying:* used as supplied in anhydrous solvent.

Analysis of Reagent Purity: ^{31}P NMR indicates presence of free phosphine ligand and phosphine oxides.

Handling, Storage, and Precautions: store under argon in freezer; stable as solid; solutions are air sensitive. This compound should be handled in a fume hood.

The complex has enjoyed relatively little use in organic synthesis. For iridium-catalyzed homogeneous hydrogenation of alkenes, Crabtree's iridium complex (***(1,5-***

Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate) is generally preferred, although this readily prepared Ir complex is active.[1] It is more reactive than its rhodium counterpart in the catalytic isomerization of butenyl- to allylsilanes.[2]

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(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) Hexafluorophosphate

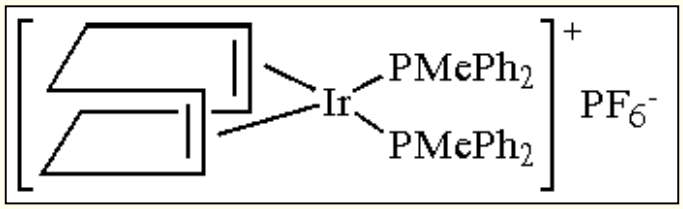

[38465-86-0] · $C_{34}H_{38}F_6IrP_3$ · (1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) Hexafluorophosphate · (MW 845.81)

(reagent for isomerization of allylic alcohols and ethers;[1] hydrogenation catalyst[2])

Physical Data: mp 236 °C (dec); ^{1}H NMR (CD_2Cl_2) δ 1.78 (d, J_{HP} = 8 Hz, P*Me*Ph$_2$), 2.19 (m, C*H*$_2$ of cod), 4.36 (=C*H* of cod), 7.3-7.9 (ov m, PMe*Ph*$_2$); conductivity 135 &OOmega;$^{-1}$ cm^2 mol^{-1}.

Solubility: sol CH_2Cl_2; insol diethyl ether and hexanes.

Form Supplied in: red crystalline solid; commercially available.

Preparative Methods: to a suspension of [Ir(μ-Cl)(1,5-cod)]$_2$ (0.2 g) in 10 mL of ethanol is added methyldiphenylphosphine (0.2 g) in ethanol. The mixture is stirred for ca. 10 min until the original suspension has dissolved. To this is added excess NH_4PF_6 in ethanol. After cooling to 0 °C the precipitate is filtered, washed with ethanol and then ether to give the title reagent (0.36 g) as red prisms.[3]

Handling, Storage, and Precautions: the dry solid is moderately air-stable.

Hydrogenation.

Cationic iridium complexes such as [Ir(1,5-cod)(PR$_3$)$_2$]$^+$ catalyze the homogeneous hydrogenation of cyclooctadiene to give predominant formation of cyclooctene along with minor amounts of cyclooctane and 1,3-cyclooctadiene (formed by isomerization of the starting material). Slower rates of hydrogenation are observed in comparison to reactions employing complexes of the type [Ir(1,5-cod)(PR$_3$)py]$^+$ as catalyst precursor.[4] A number of iridium complexes, including [Ir(1,5-cod)(PMePh$_2$)$_2$]PF$_6$ (**1**), are also active catalysts for the hydrogenation of soybean and other vegetable oils.[5]

Isomerizations.

Addition of dihydrogen to (**1**) produces a very active catalyst for the isomerization of allyl ethers to the corresponding *trans*-propenyl ethers (eq 1). This reaction proceeds with high stereoselectivity (*trans*/*cis* > 30) and under mild conditions.

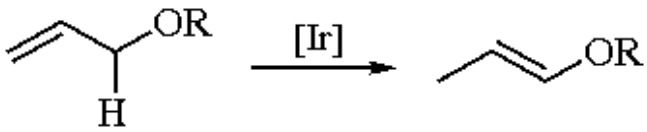

(1)

While substituted allylic ethers can be isomerized (eq 2), the reaction appears to be limited to primary allyl ethers. Complex (**1**) also catalyzes the

isomerization of allyl ethers of glycerol or glucose having various protecting groups.[6] The corresponding propenyl ethers thus formed are converted into free hydroxy compounds by treatment with ***Mercury(II) Chloride/Mercury(II) Oxide***.[7] In a related study, (**1**) is used to catalyze the isomerization of allylic alcohols to aldehydes and ketones.[8]

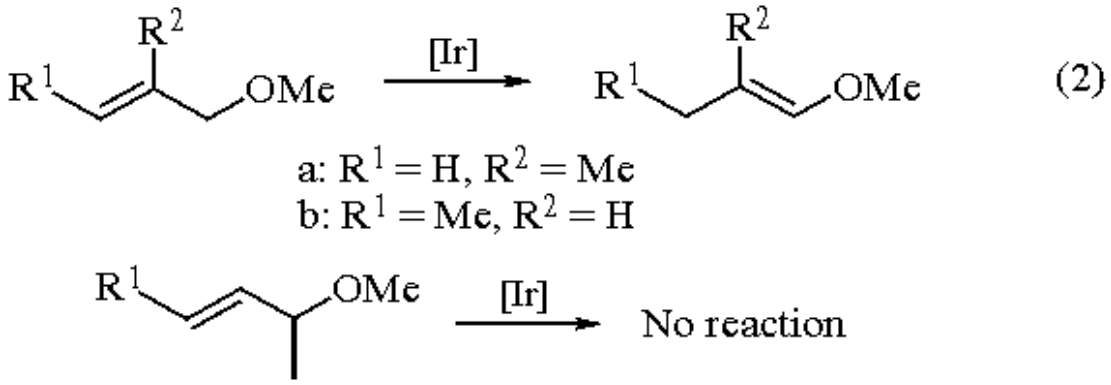

Hydrogen-activated (**1**) is used to isomerize the allyl group in carbohydrates as part of a two-step deallylation procedure.[9] Initial isomerization is followed by treatment with catalytic amounts of ***Osmium Tetroxide*** and ***Trimethylamine N-Oxide*** to cleave the *trans*-1-propenyl group in the presence of an azide group at C-2 (eq 3).[10] This method avoids the formation of intramolecular 1,3-dipolar cycloaddition products which are formed using other deallylation procedures. Unlike many other metal catalysts, cationic iridium complexes are able to perform this isomerization in the absence of elevated temperatures.

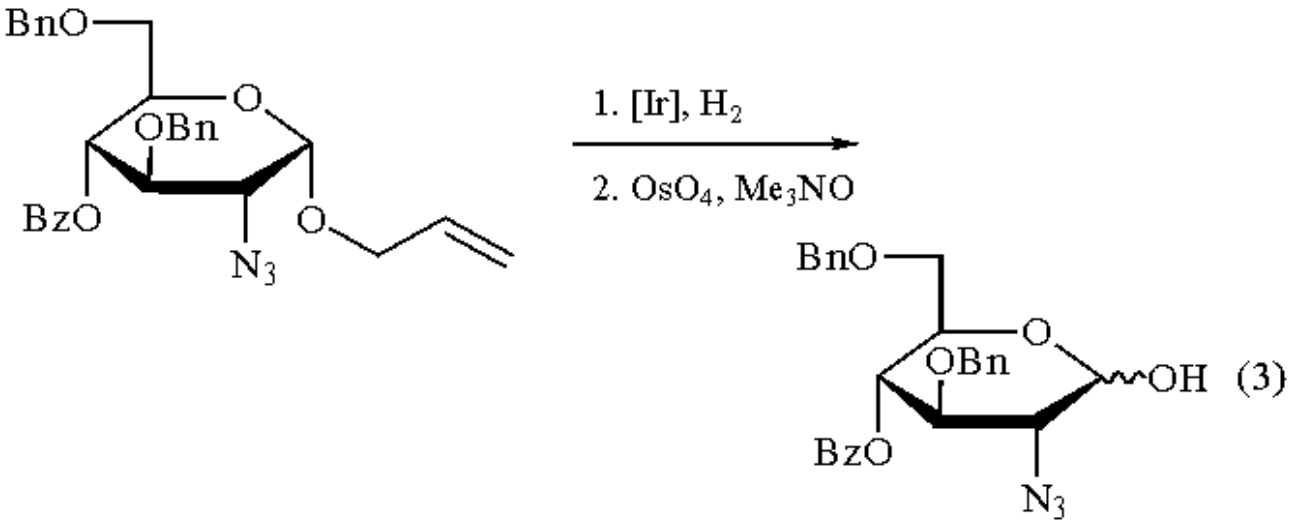

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(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium

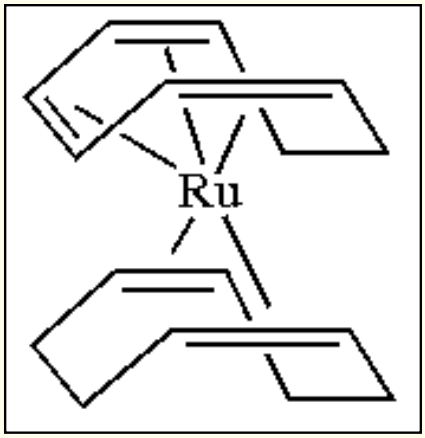

[42516-72-3] · $C_{16}H_{22}Ru$ · (1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium · (MW 315.42)

(catalyst precursor for dehydrogenative silylation of alkenes,[4,5] hydroacylations,[7] carbonylation of amines,[9] and various carbon-carbon bond forming reactions[12-17])

Physical Data: mp 92-94 °C (dec); ^{1}H NMR (C_6D_6) δ 0.9 (m, 2H), 1.64 (m, 2H), 2.22 (m, 8H), 2.92 (m, 4H), 3.79 (m, 2H), 4.78 (m, 2H), 5.22 (dd, 2H).

Solubility: sol toluene and chloroform; insol alcohols.

Form Supplied in: yellow crystalline solid.

Preparative Method: to a solution of $RuCl_3.3H_2O$ (0.34 g, 1.3 mmol) in 10 mL of ethanol is added 1,5-cyclooctadiene (8.8 g, 81 mmol) and zinc dust (3.5 g); the mixture is heated under reflux with stirring for 3 h and then filtered; the resulting brown-yellow solution is evaporated in vacuo, extracted with 20 mL of pentane and filtered through a plug of alumina (20 cm); the volume is reduced to ca. 5 mL and the yellow solution cooled to -78 °C to give yellow crystals of (1,5-cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium (0.2 g, 50%).[1]

Handling, Storage, and Precautions: the compound rapidly decomposes when exposed to air.

Introduction.

While little is known about the chemistry of bis(η^5-cyclooctadienyl)ruthenium, the catalytic activities of (1,5-

cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium, Ru(cod)(cot), and its derivatives in organic synthesis are well established. This article will attempt to cover the chemistry of all these low valent ruthenium compounds.[2]

Dehydrogenative Silylations.

Allylsilanes are highly versatile synthetic intermediates[3] which can be prepared selectively by the Ru(cod)(cot) catalyzed dehydrogenative silylation of alkenes (eq 1).[4] In all reactions reported, only minor amounts of vinylsilanes and alkanes (derived from hydrogenation of the starting alkene)[5] were detected. Conversely, reactions employing $Ru_3(CO)_{12}$ as the catalyst source afforded vinylsilanes as the major product.

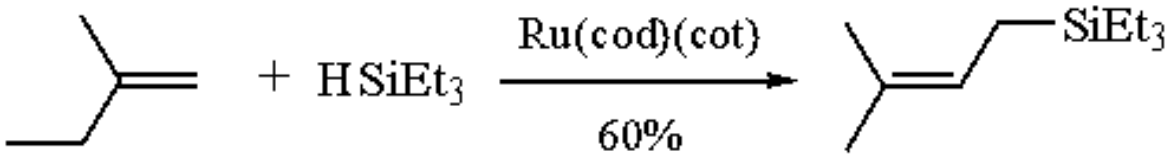

(1)

In a related study, (benzene)(1,3-cyclohexadiene)ruthenium was found to be a moderately active and selective catalyst precursor for the hydrosilation of allyl chlorides with trimethoxysilane.[6]

Hydroacylation.

A number of low valent ruthenium complexes catalyze the intermolecular hydroacylation of alkenes with various aromatic and heteroaromatic aldehydes.[7] Unsymmetrical ketones are produced in moderate to high yields in reactions run at 180-200 °C for 24-48 h under 20 kg cm^{-2} of carbon monoxide. For example, the reaction of 2-thiophenecarbaldehyde with cyclohexene affords the corresponding cyclohexyl 2-thienyl ketone in 62% yield (eq 2). Treatment of cyclohexene with aliphatic aldehydes gives products arising from a transhydroformylation reaction, where the formyl group of the aldehyde has transferred to the alkene with concomitant formation of Tishchenko-type reaction products.[8]

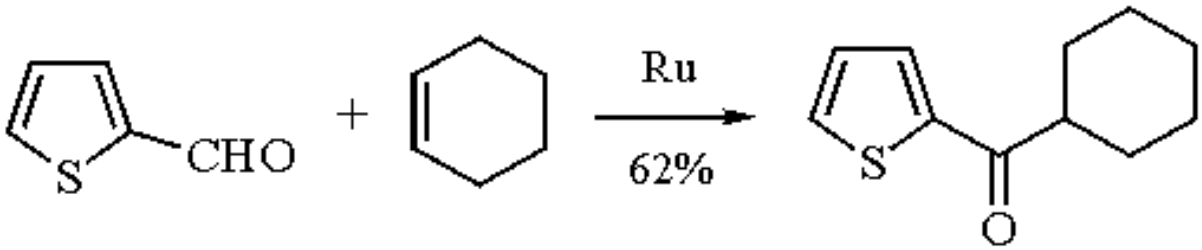

(2)

Carbonylation of Amines.

Ru(cod)(cot) is a moderately effective catalyst precursor for the carbonylation of amines, affording *N*-substituted formamides. In the presence of alkenes, hydroamidation affords *N*-substituted alkanamides (eq 3).[9] In both reactions, addition of phosphine reduces catalytic activity. Indeed, $Ru_3(CO)_{12}$ was found to be the most active and selective catalyst precursor for these transformations.

(1,5-Cyclooctadiene)(1,3,5-cyclooctatriene)ruthenium

$$RNH_2 + R'CH{=}CH_2 + CO \xrightarrow{[Ru]} RNHCOCH_2CH_2R' + RNHCOCH(Me)R' + RNHCHO \quad (3)$$

Secondary amines react with carbon dioxide and terminal alkynes in the presence of a catalytic amount of Ru(cod)(cot)/tertiary phosphine to give enol carbamates with high regio- and stereoselectivity (*Z/E* ca. 9:1).[10] 2-Acetoxyallyl derivatives are produced with high selectivity and in high yield by reaction of acetic acid with propargyl alcohol derivatives at 80 °C using a bis(η^5-cyclooctadienyl)ruthenium/PCy_3/maleic anhydride catalyst system.[11]

Carbon-Carbon Bond Formation.

A number of C-C bond forming reactions catalyzed by low valent ruthenium complexes have been developed, including the oligomerization of alkenes and alkynes,[12] [2 + 2] cross addition of norbornenes with alkynes[13] and allylamines with acrylic compounds (eq 4),[14] aldol condensations, and Michael addition reactions.[15]

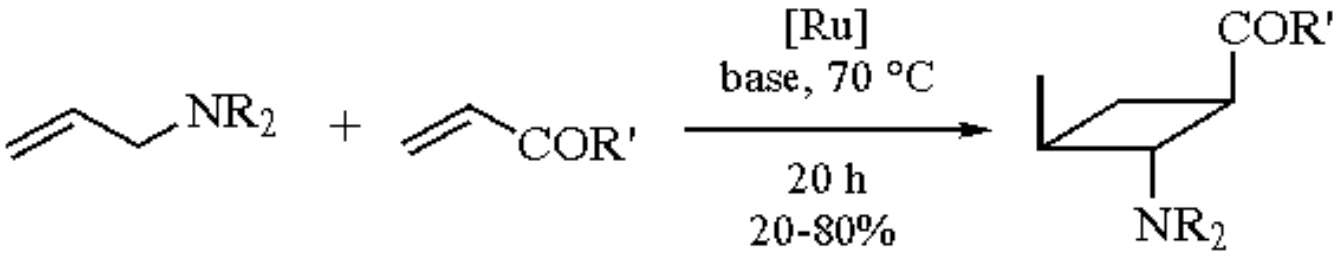

(4)

More recently, ruthenium complexes such as Ru(cod)(cot) were found to catalyze the dehydrohalogenative coupling of vinyl halides with electron deficient alkenes to give substituted dienes (eq 5). In some cases, ruthenium complexes were more active than the well established palladium catalysts. For instance, even the sp^2 carbon-chlorine bond in β-chlorostyrene is activated by Ru(cod)(cot).[16] Monoallylated carbonucleophiles are produced in high yields and with high regioselectivity in the presence of a catalytic amount of Ru(cod)(cot). Regioselectivities are quite different from products obtained from palladium catalyzed reactions. Furthermore, allylations using allyl methyl carbonate give diallylated carbonucleophiles selectively and in high yields. Diallylations are not easily accomplished using other metal catalysts.[17]

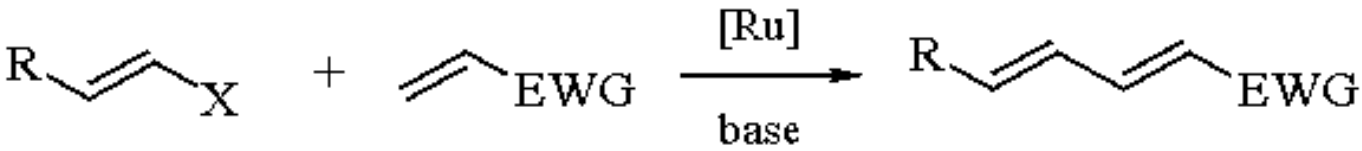

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(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)

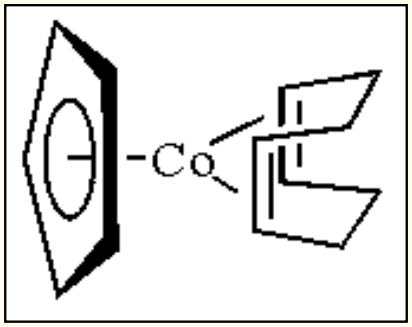

[12184-35-9] · $C_{13}H_{17}Co$ · (1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I) · (MW 232.11)

(catalyst for cyclotrimerization of alkynes and cotrimerization with nitriles to yield pyridine derivatives;[1,2] source of other cobalt complexes and of substituted cyclooctadienes[15-17])

Physical Data: mp 102-104 °C; subl 70 °C/0.1 mmHg.

Solubility: readily sol common org solvents; insol H_2O.

Form Supplied in: golden-yellow cryst.

Preparative Methods: of several effective synthetic routes the most efficient is the direct reaction of cobalt salts [conveniently $Co(acac)_3$] with cyclopentadiene + cycloocta-1,5-diene + anthracene-activated magnesium metal.[1]

Handling, Storage, and Precautions: air sensitive; best stored at low temp (<0 °C) under inert gas (N_2, Ar). Use in a fume hood.

General Remarks.

This compound is representative and is the most commonly used of the class of (dialkene)CoCp complexes which share similar reactivity and can be used more or less interchangeably in reactions which involve replacement of the (di)alkene moiety. The entry therefore also makes reference to derivatives with substituted cyclopentadienyl ring and to analogs, notably CpCo(cyclopentadiene) and $CpCo(C_2H_4)_2$ of which the latter is probably the most reactive, while the C_5H_6 complex is arguably the most readily accessible. $(C_5H_5)Co(C_5H_6)$ *[3302-03-0]*, MW 190.13, mp 98-99 °C, is the product of hydride addition to ***Bis(cyclopentadienyl)cobalt Hexafluorophosphate***; it forms air-sensitive, wine-red crystals, sol in hydrocarbons and sublimable in vacuo. $(C_5H_5)Co(C_2H_4)_2$ *[69393-67-5]*, MW 180.14, is efficiently

(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)

synthesized from ***Bis(cyclopentadienyl)cobalt*** and forms hydrocarbon soluble, air-sensitive, red-brown needles.

Catalysis of Alkyne Cyclotrimerization and Related Reactions.

Cyclotrimerization of alkynes and cotrimerization of two molecules of alkyne with one of a nitrile to give 2-substituted pyridines and related reactions (see below) are efficiently catalyzed by cobaltocene and by a range of cobalt complexes of the type $CpCoL_2$. Of the latter, the carbonyl (L = CO), ***Dicarbonyl(cyclopentadienyl)cobalt(I)***, and the cyclooctadiene (cod, $L_2 = C_8H_{12}$) complex are the most commonly used, but many derivatives and analogs are comparable in efficiency, consistent with the evidence suggesting that the key steps are eqs 1 and 2. Ring closure to a cobaltacyclopentadiene system is probably induced by addition of the third alkyne (eq 3) or nitrile molecule (eq 4). Further reaction with alkyne then continues a chain in which the ligands L or L_2 play no further part. They therefore influence only the conditions necessary to start the process.

$$CpCoL_2 \longrightarrow [CpCo] + 2\,L \qquad (1)$$

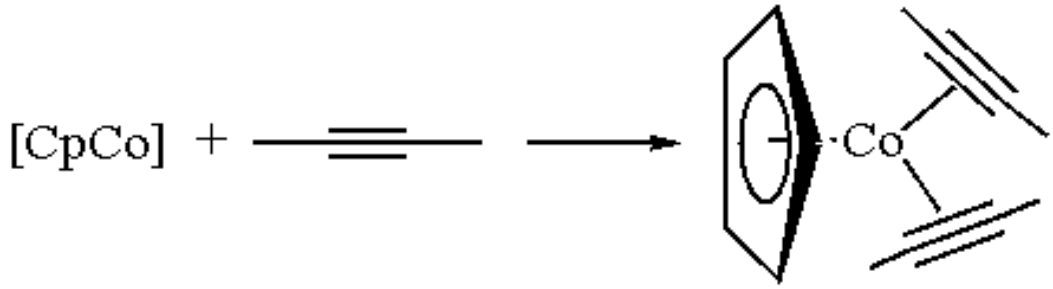

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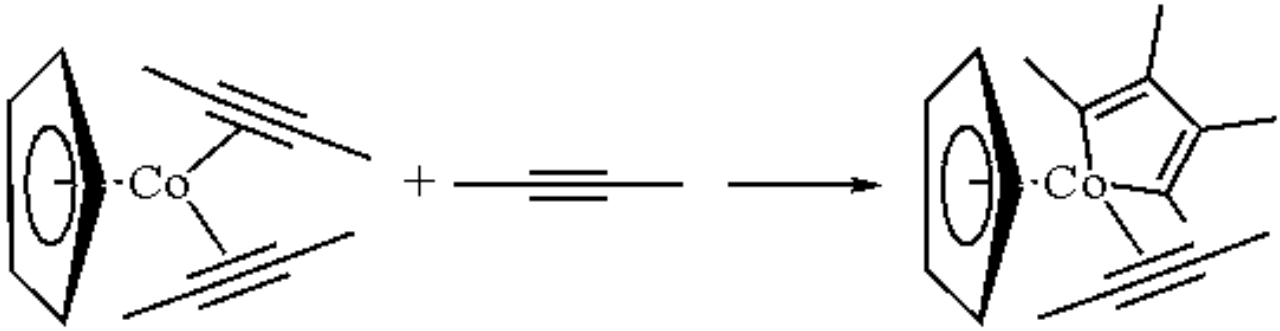

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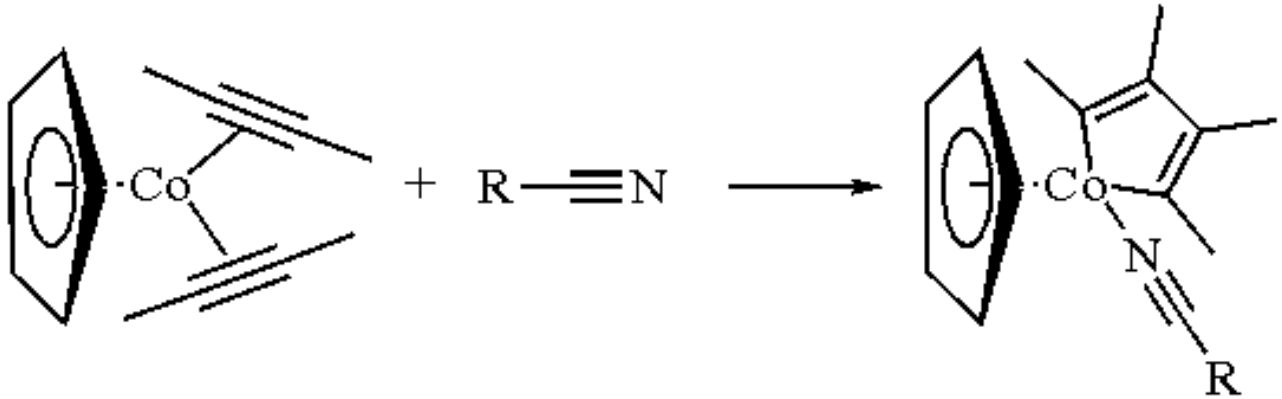

(4)

The complex CpCo(cod) has been most widely used for the pyridine synthesis and the effect of varying catalyst structure on the reaction temperature and selectivity has been extensively studied.[1,2] The choice of propyne reacting with propionitrile (eq 5) allowed the effect on chemo- and regioselectivity to be evaluated at the same time.

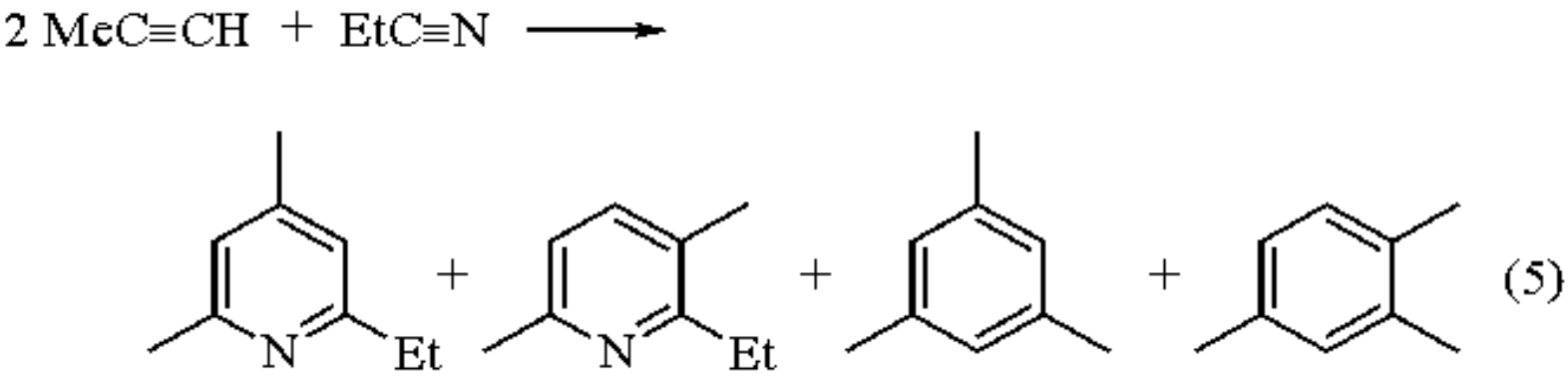

In a flow system, the temperature required for 65% conversion of propyne was 147-150 °C independent of L, although the initiation temperature varied widely, being <30 °C for L = C_2H_4, 75-85 °C for L_2 = C_5H_6, and 120-125 °C for L_2 = cod, but $CpCo(CO)_2$ was unsuitable as catalyst under these conditions, giving only 5% conversion at 150 °C. The reaction temperature was dropped to 125 °C for both the indenyl analog, $(C_9H_7)Co(cod)$, and for the tetraphenyl-substituted complex, $(C_5Ph_4H)Co(cod)$, and the latter gave the highest chemoselectivity (ratio of pyridines to arenes) of 6.9, compared to 1.8 for CpCo(cod). Moreover, the tetraphenyl derivative also gave one of the highest regioselectivities (2,4,6-:2,3,6-trisubstituted pyridine) of 2.70, compared to 1.71 for CpCo(cod). In ethylpyridine synthesis (from acetylene + propionitrile), the complex $(C_5Ph_4H)Co(cod)$ was again the outstanding catalyst with a turnover number of 6946 and 91.8% yield. It also gives relatively good results (TON 1625, 73.7% yield) in the vinylpyridine synthesis (eq 6), which must be conducted at moderate temperature to avoid polymerization.

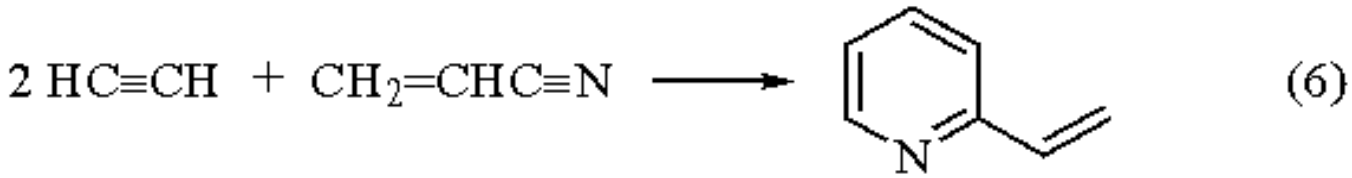

High temperatures can be avoided by employing photolysis[3a] to effect the initiation step (eq 1). Thus an alternative route to 2-vinylpyridine[3b] employs this method to obtain intermediate 2-ethoxy- (or 2-methoxy)ethylpyridine (eq 7) with 99% selectivity (50% conversion); irradiation of acetylene and propionitrile with CpCo(cod) at 15 °C for 1.5 h gave 43% conversion to 2-ethylpyridine.[3a]

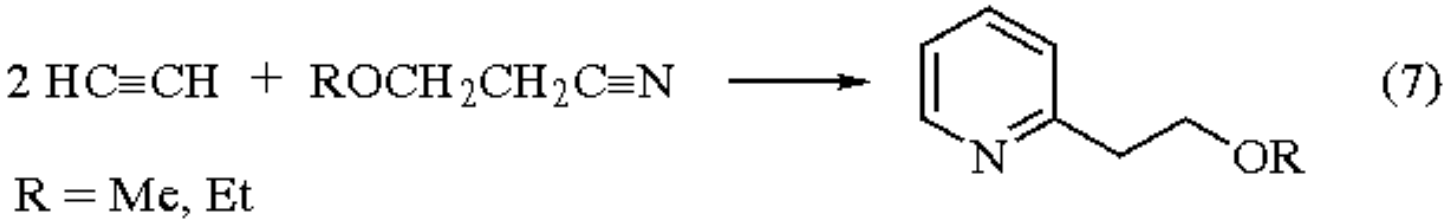

The reaction has been used in approaches to natural products, as illustrated by syntheses of (*N*-benzyloxycarbonylpyrrolidinyl)pyridine (eq 8)[4] and by a route to vitamin B_6.[5] One version of this utilizes the regioselective $CpCo(CO)_2$, Cp_2Co, or CpCo(cod) catalyzed step (eq 9).[5a] The possibility of using homochiral

substrates in such reactions without loss of optical purity has been demonstrated in the examples shown in eq 10[6a] and eq 11.[6b]

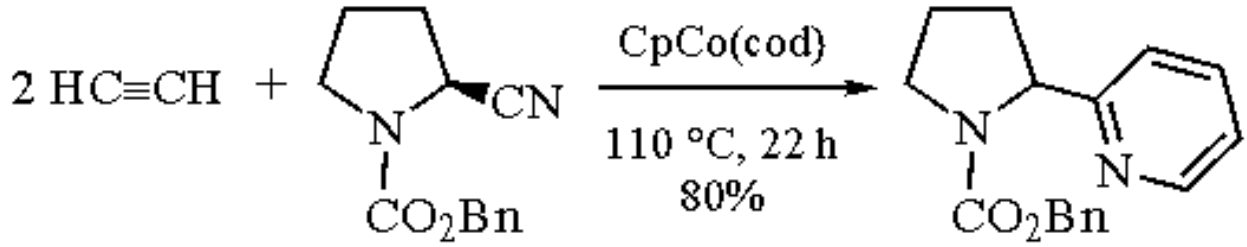

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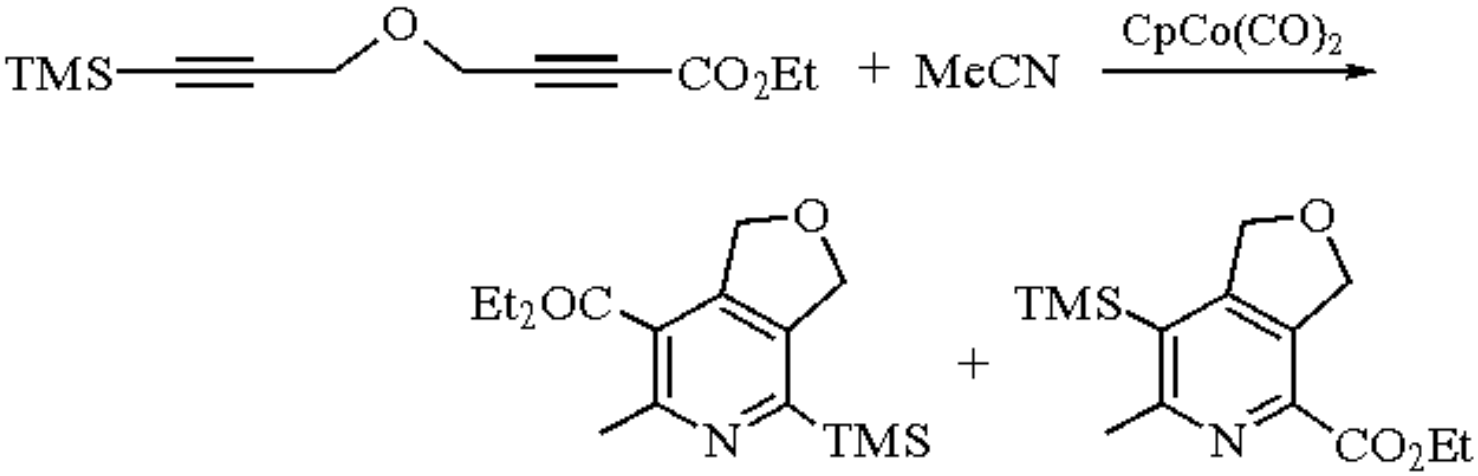

(9)

yield 68% after desilylation with CsF 16:1

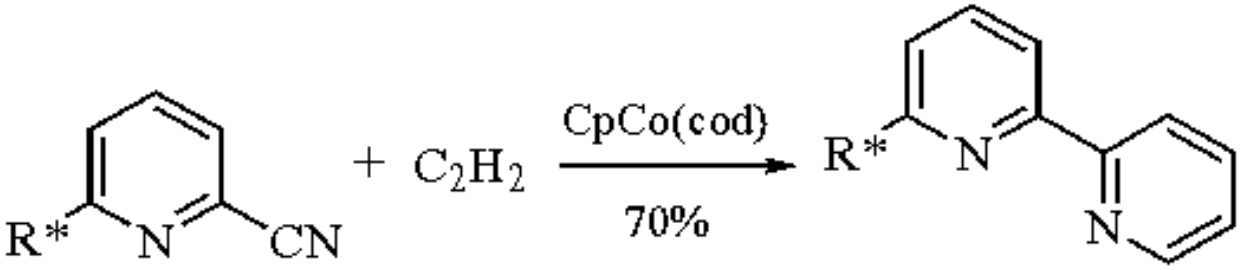

(10)

R* =

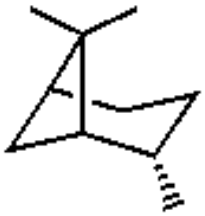

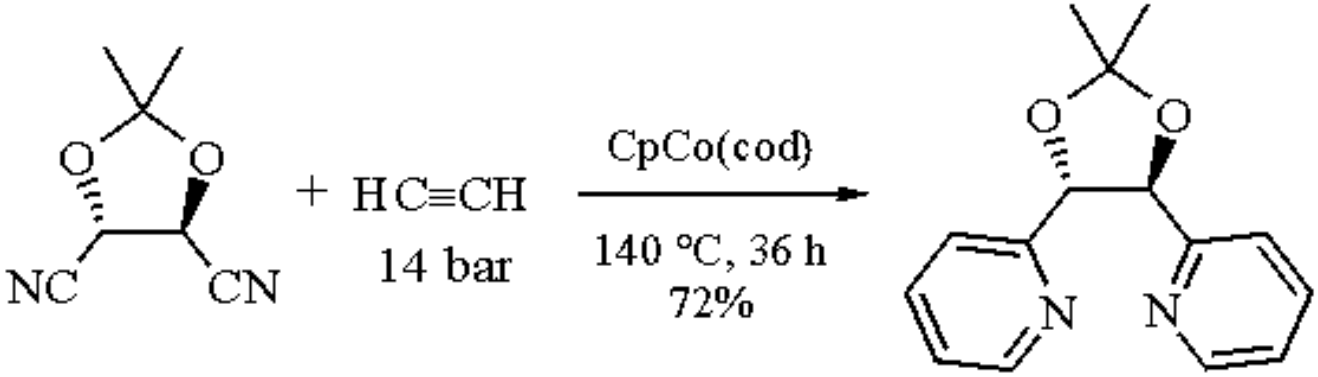

(11)

The ethylene complex was used as catalyst[7] in a study of the dependence of regioselectivity on substrate structure; the same catalyst was employed in a study of the cyclooligomerization of propargyl alcohol, which yielded approximately equal amounts of the aromatic trimerization products and the cyclooctatetraene derivatives (eq 12).[8]

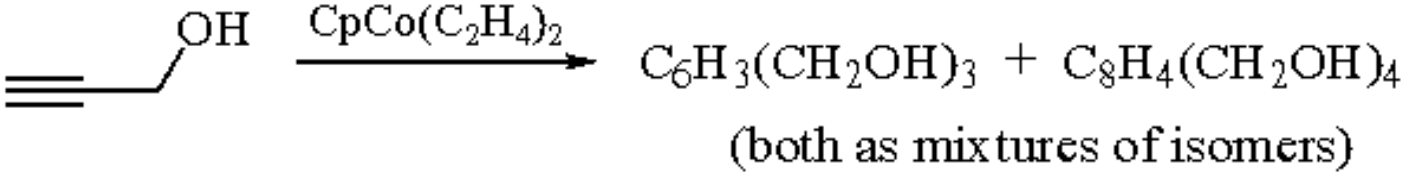

(12)

The use of isocyanates or carbodiimides in cotrimerization with alkynes leads to *N*-substituted pyridones (eq 13) or the corresponding imines (eq 14).[9]

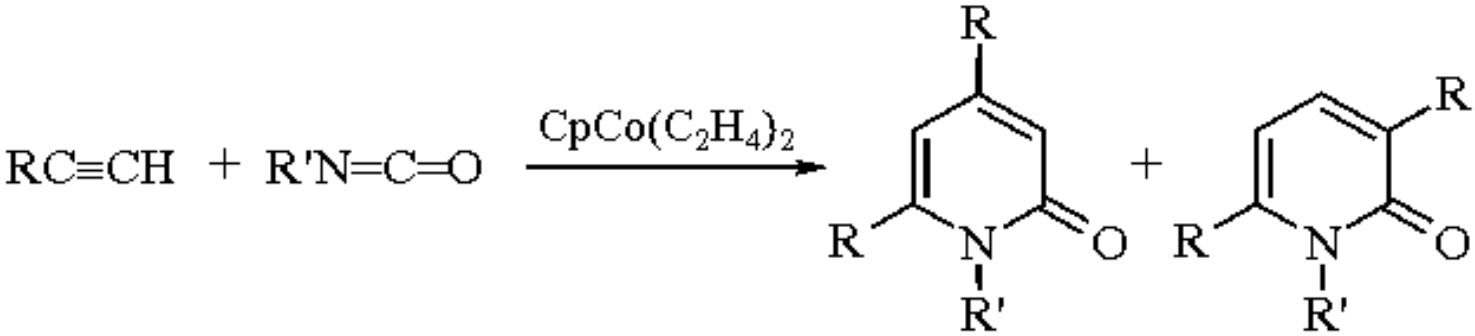

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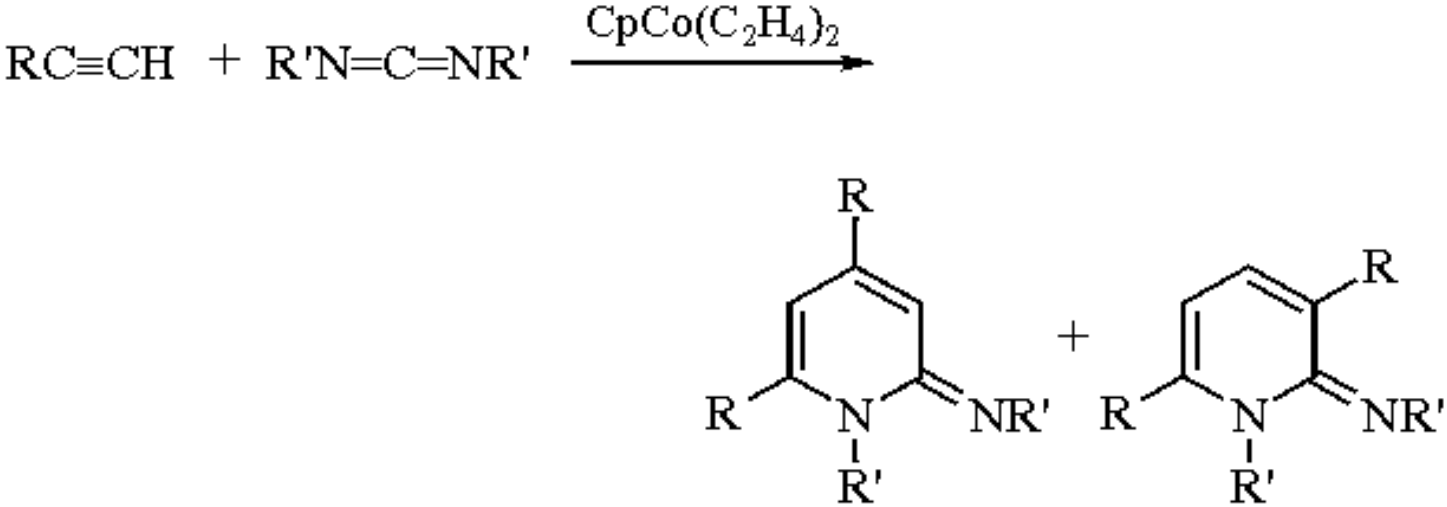

(14)

Other Catalytic Reactions.

The ethylene complex $CpCo(C_2H_4)_2$ catalyzes the ring enlargement and hydrogen shifts which convert octamethyl[4]radialene to an arene (eq 15).[10] Ethylene is also added to 2,5-dimethyl-2,3,4-hexatriene, initially yielding a complexed conjugated triene; under ethylene pressure this is displaced and its formation (eq 16)[10] becomes catalytic.

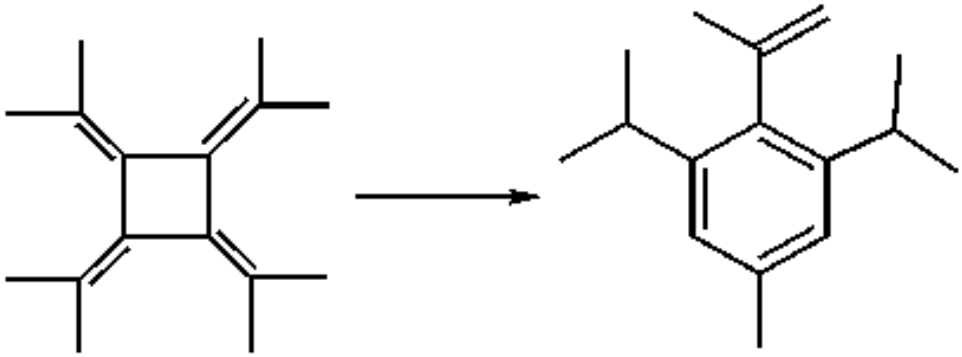

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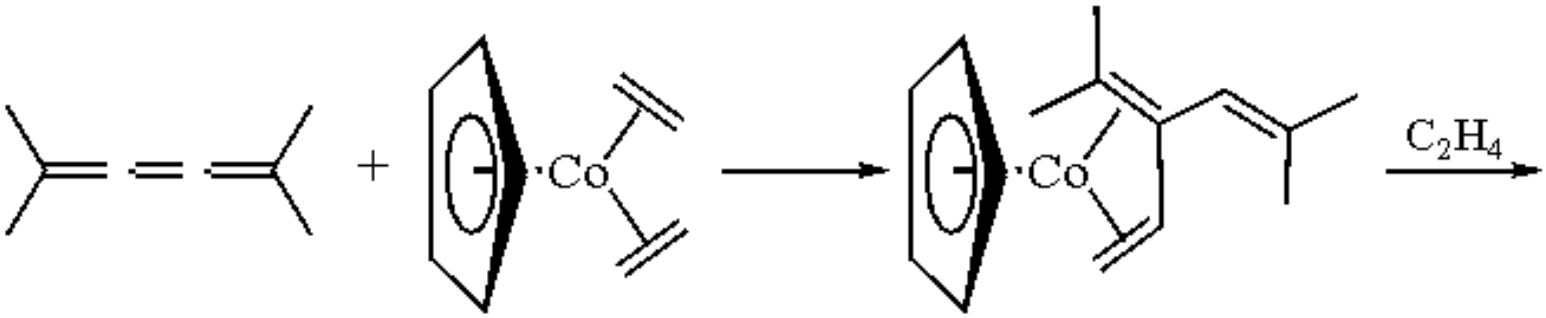

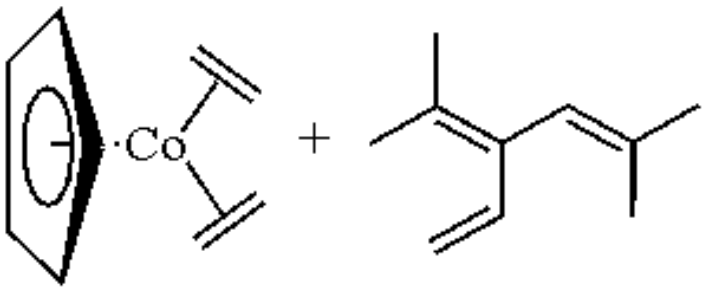

(16)

Stoichiometric Reactions.

Reaction of carbodiimides with stoichiometric amounts of the ethylene complex $CpCo(C_2H_4)_2$ yields a dinuclear and a tetranuclear complex with incorporation of an ethylene ligand into the latter (eq 17).[11] Further use of these products has not been explored. An ethylene fragment is also incorporated in the reaction with diphenylketene (eq 18),[12] whereas reaction with thiocyanates involves coupling of two molecules thereof and both cleavage and formation of C-S bonds (eq 19).[13]

(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)

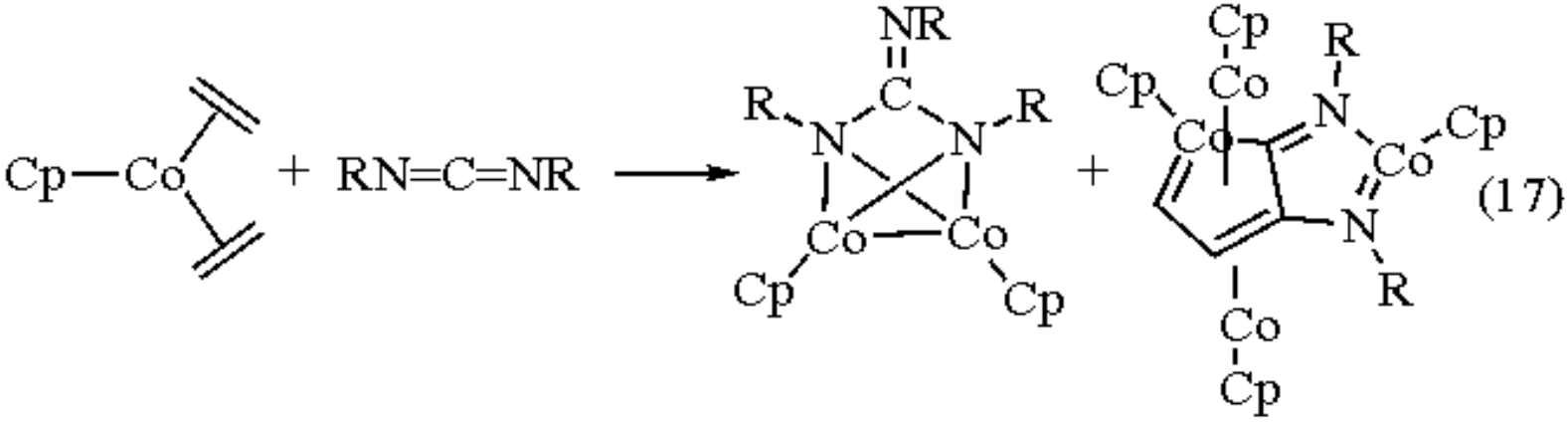

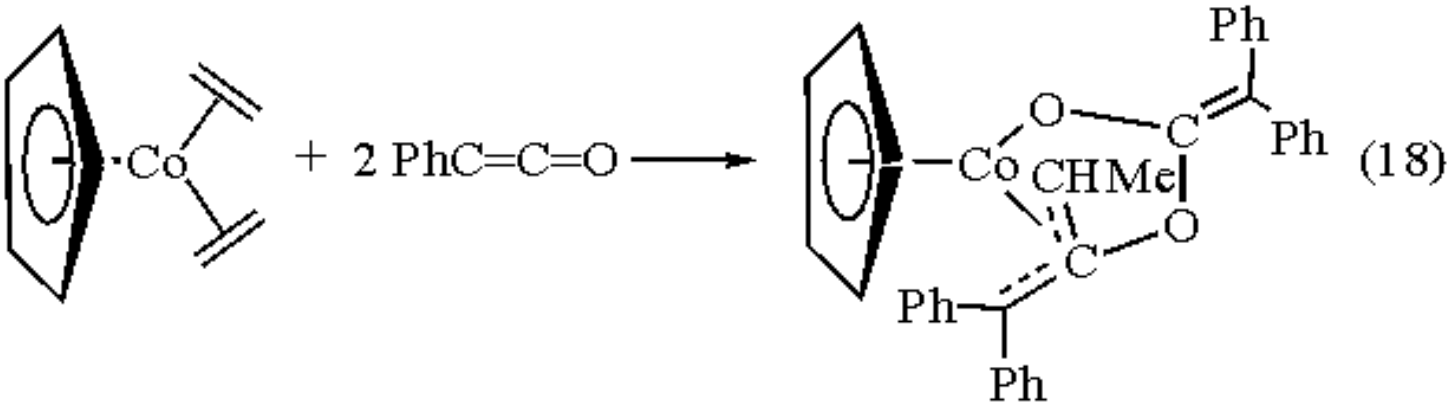

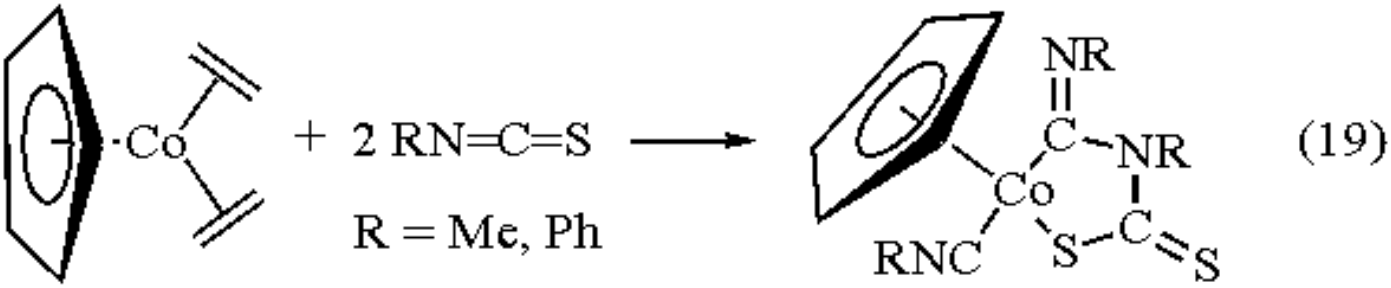

That complexation of alkenes or dienes as CpCo(dialkene) can serve for their protection appears to have been demonstrated only for cyclooctatetraene; its 1,2,5,6-η complex has been converted to the bis(cyclopropane) derivative, leaving the metal-bound double bonds intact, by the reaction shown in eq 20;[14] the free organic ligand was liberated by cerium(IV) oxidation in unspecified yield.

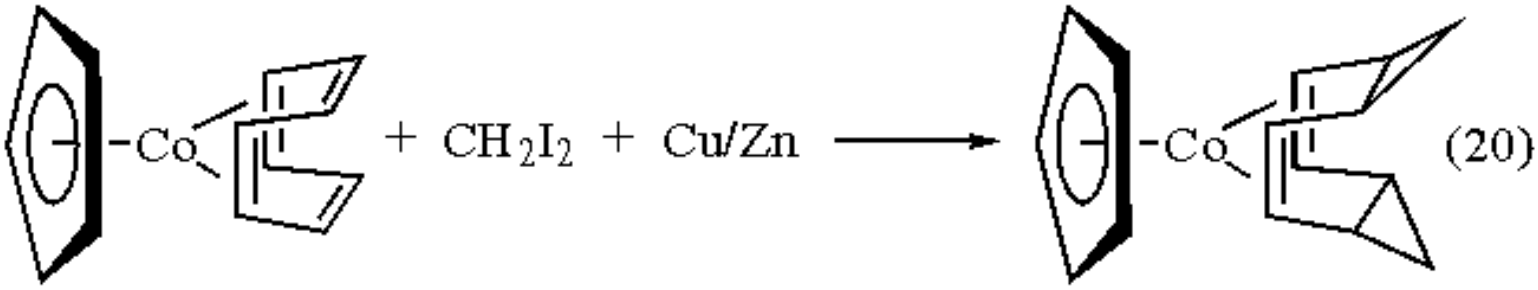

Reaction of CpCo(cod) with trityl cations leads to hydride abstraction from the 3-position of the cod ligand.[15] The

resultant cationic complex readily adds nucleophiles to give complexed 3-substituted cycloocta-1,5-dienes (eq 21).[16] A more profound change of the cod ligand involving ring closure and alkylation occurred when the complex was treated with a cationic allyliron complex (eq 22); $(C_5Me_5)Co(cod)$ reacted similarly.[17]

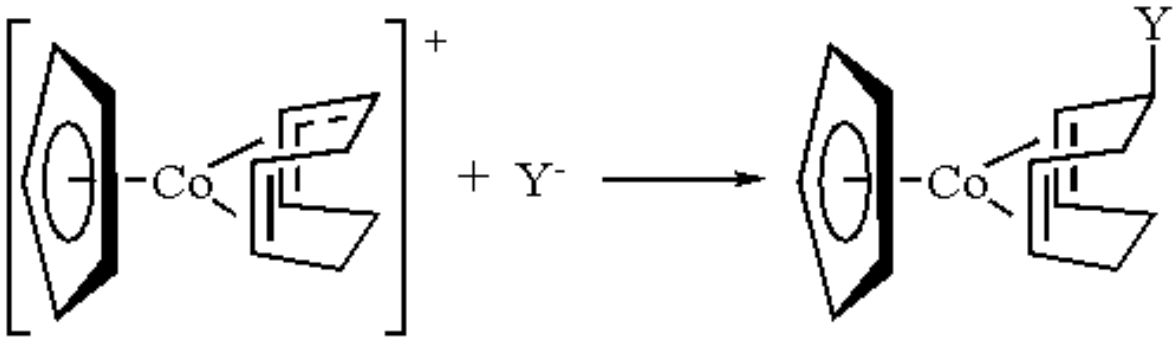

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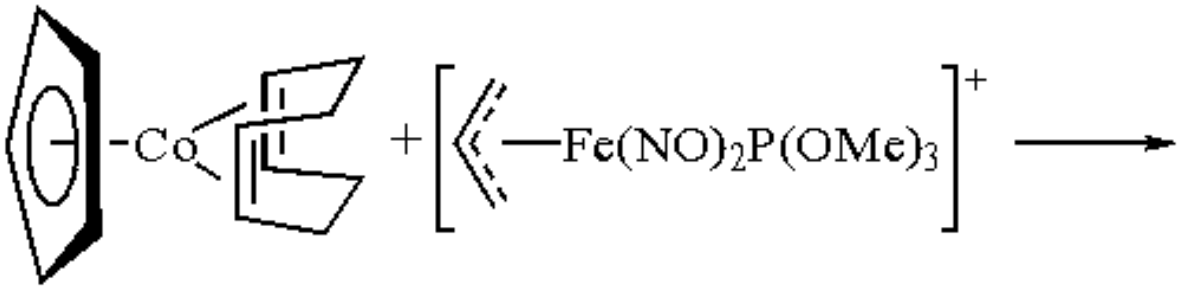

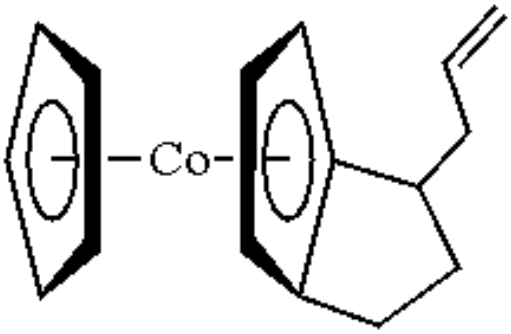

(22)

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(1,5-Cyclooctadiene)[(3*R*,4*R*)-3,4-bis(diphenylphosphino)-1-methylpyrrolidine]rhodium Tetrafluoroborate[1]

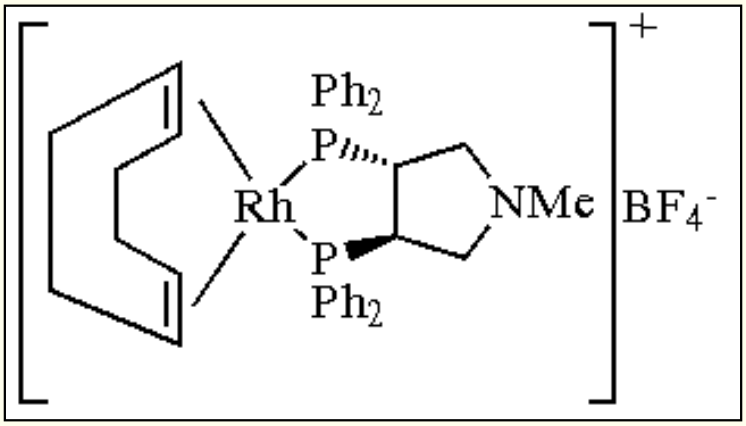

[100366-06-1] · $C_{37}H_{41}BF_4NP_2Rh$ · (1,5-Cyclooctadiene)[(3*R*,4*R*)-3,4-bis(diphenylphosphino)-1-methylpyrrolidine]rhodium Tetrafluoroborate · (MW 737.39)

(catalyst for asymmetric hydrogenation of α-acylaminoacrylic acid derivatives[2])

Solubility: insol ether; sol CH_2Cl_2, MeOH

Analysis of Reagent Purity: ^{31}P NMR (CD_2Cl_2): δ 33.17 (d, $^2J_{Rh,P}$ = 148.2 Hz).

Preparative Methods: the ligand (3*R*,4*R*)-3,4-bis(diphenylphosphino)-1-methylpyrrolidine (**1a**) is prepared from L-tartaric acid via (3*R*,4*R*)-3,4-bis(diphenylphosphino)-1-benzylpyrrolidine (**1b**) as shown in eq 1. The title cationic rhodium complex is made by mixing bis(1,5-cyclopentadiene)rhodium tetrafluoroborate and (**1a**) in CH_2Cl_2 under nitrogen.

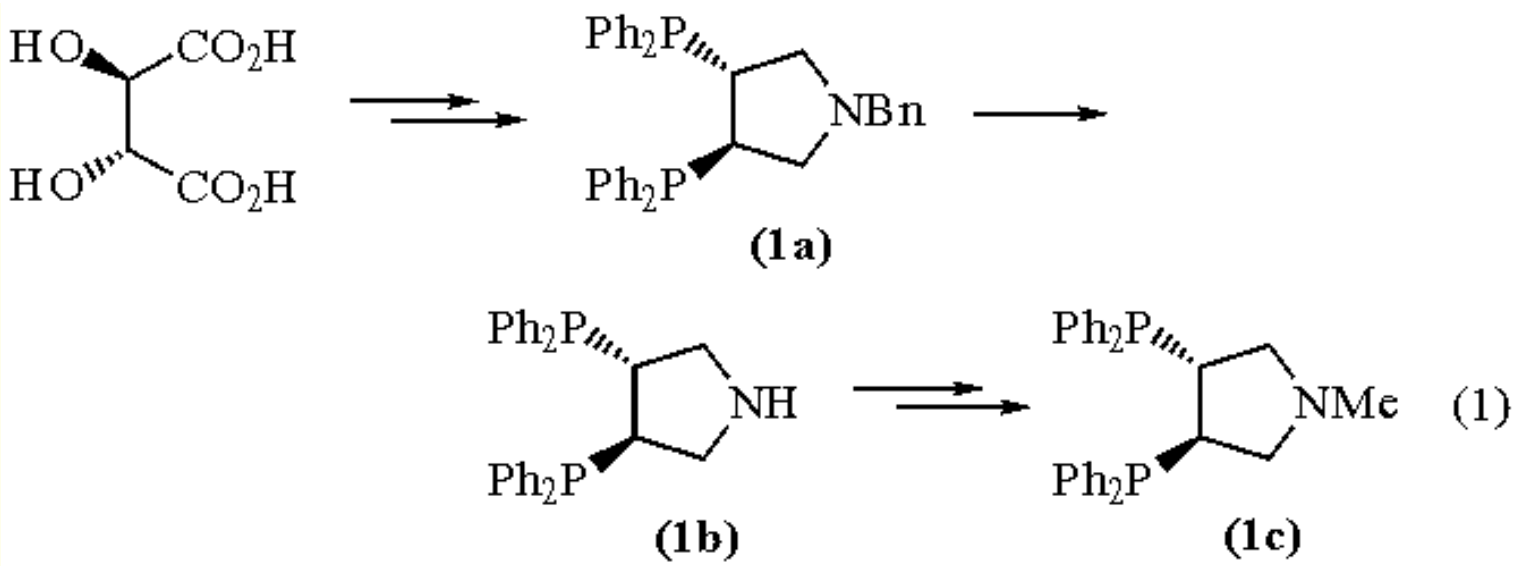

Asymmetric Hydrogenation Catalyst.

Since catalytic asymmetric hydrogenation of α-acylaminoacrylic acid derivatives is an important process to afford α-amino acid derivatives, many rhodium complexes possessing optically active phosphine ligands have been developed in last two decades.[3-7] [Rh{(*R*)-(**1a**)}(cod)]BF_4 (**2a**) is one of the most efficient catalysts for this purpose with respect to activity and enantioselectivity. Besides (**2a**), several derivatives, which have various substituents on the nitrogen atom of the pyrrolidine ring, will be mentioned below.

α-(Acetylamino)cinnamic acid derivatives (**3**) are hydrogenated in the presence of (**2**), which are derived from natural L-tartaric acid, to afford natural (*S*)-*N*-acetylphenylalanine derivatives with high enantioselectivity (eq 1).[8] Some examples are shown in Table 1. Less than 0.01 mol % of catalyst is needed to complete the reaction under mild conditions with high enantioselectivity. The substituents on the nitrogen atom of (**2**) have no marked influence on the catalytic activity or the selectivity. This reaction is also insensitive to the variation of substituents on the phenyl ring of (**3**).

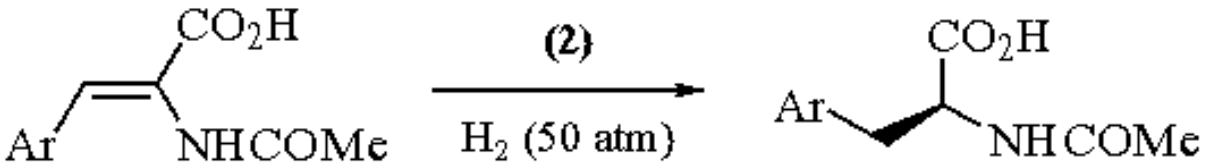

(2)

(3a) Ar = Ph
(3b) Ar = 4-MeOC$_6$H$_4$
(3c) Ar = 3-MeO-4-HOC$_6$H$_3$
(3d) Ar = 3,4-(OCH$_2$O)C$_6$H$_3$
(3e) Ar = 3-indolyl

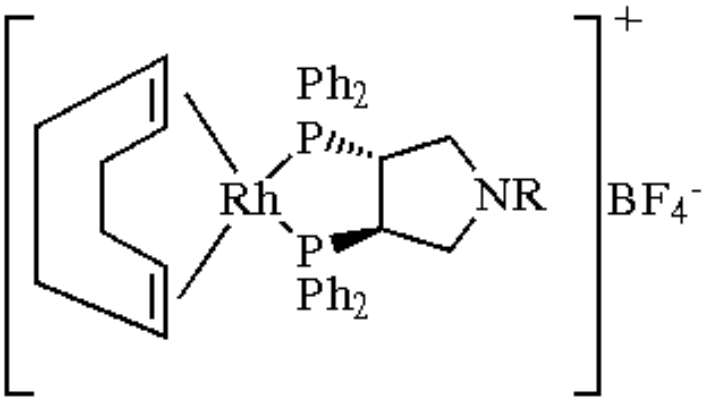

(2a) R = Me
(2b) R = Bn
(2c) R = H
(2d) R = COPh

Table 1 Asymmetric Hydrogenation of Dehydro Amino Acids

Catalyst (2)	Dehydro amino acid (3)	Substrate catalyst	Temp. (°C)	ee (%)
a	**a**	880	22	93
b	**a**	8000	20	98
c	**a**	8000	50	96
d	**a**	15500	22 60	96.5
d	**b**	850	22	98
d	**c**	850	22	100
d	**d**	800	22	93
d	**e**	1500	22	82.5

Water-soluble (1,5-cyclooctadiene)[(3*R*,4*R*)-3,4-bis(diphenylphosphino)-1,1-dimethylpyrrolidinium]rhodium

bis(tetrafluoroborate) (**4**) catalyzes the hydrogenation of the sodium salt of α-(acetylamino)cinnamic acid to afford the (*S*)-acetylphenylalanine sodium salt in 90% ee at 22 °C.[9]

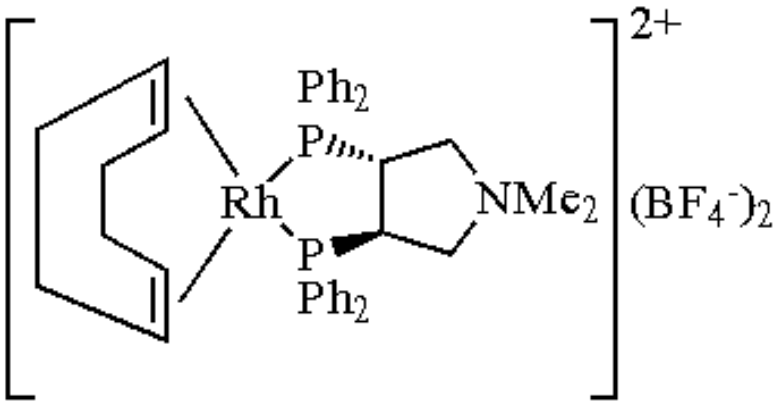

(4)

A silica-supported rhodium complex of (3*R*,4*R*)-3,4-bis(diphenylphosphino)pyrrolidine (**5**) is also an effective catalyst.[10] This heterogeneous catalyst mediates asymmetric hydrogenation of (**3a**) as well as its methyl ester in comparable selectivities to the homogeneous one shown above.

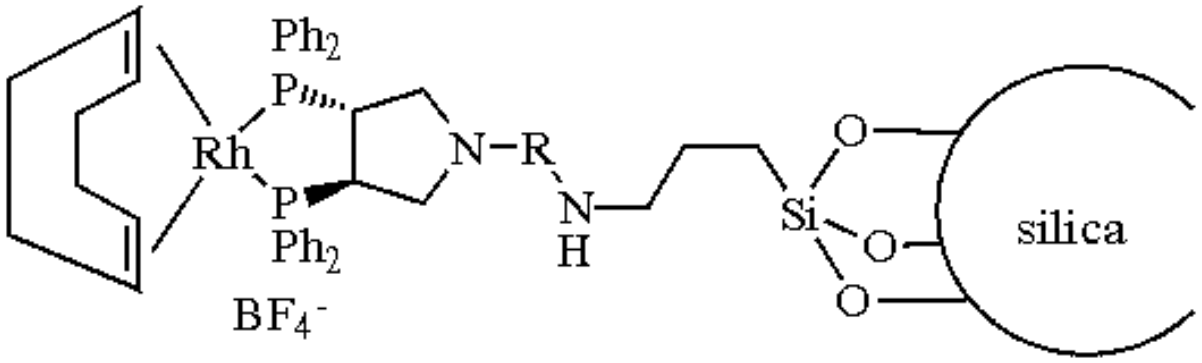

(5)

Related Reagents.

Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate; ***Bis(bicyclo[2.2.1]hepta-2,5-diene)rhodium Perchlorate-(R)-1-(S)-1´,2-Bis(diphenylphosphino)ferrocenylethanol***; ***Bis(1,5-cyclooctadiene)rhodium Tetrafluoroborate-(R)-2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***.

---

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(1,5-Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate

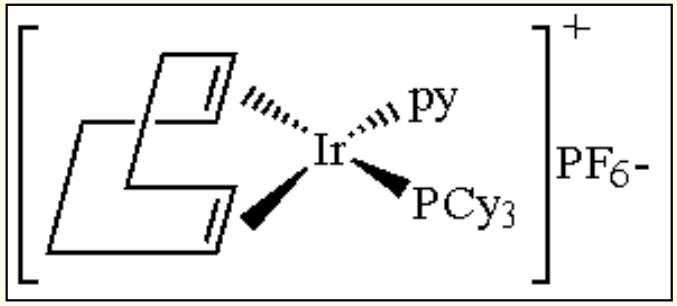

[64536-78-3] · $C_{31}H_{50}F_6IrNP_2$ · (1,5-Cyclooctadiene)(tricyclohexylphosphine)(pyridine)iridium(I) Hexafluorophosphate · (MW 804.5)

(homogeneous catalyst for hydrogenation, especially of hindered and highly substituted alkenes;[5,6] catalyst for directed hydrogenation;[6] catalyst for alkene isomerization and hydroboration[9])

Physical Data: mp 150 °C (dec).

Solubility: sol CH_2Cl_2, acetone, and THF; insol water.

Form Supplied in: yellow microcrystals; not commercially available.

Purification: recrystallization from CH_2Cl_2/Et_2O.

Handling, Storage, and Precautions: air stable for days, but long term storage under N_2 and in the dark recommended.

General Aspects.

$[Ir(cod)(PCy_3)(py)]PF_6$, a readily prepared[1] complex, is one of the standard catalysts for hydrogenation and has also been used for the addition of Si-H and B-H bonds across C=C or C&tbond;C bonds. Room temperature should be employed in all stages of the preparation and use of the catalyst. Although the hexafluorophosphate salt has been used most often, the exact nature of the anion is not important as long as it is noncoordinating. The catalyst deactivates rapidly if exposed to H_2 in the absence of substrate and deactivates slowly in any event; lower concentrations of catalyst (e.g. 2.5 mol %) are often most useful to give adequate catalytic rates without excessive deactivation. The catalyst also deactivates slowly in the presence of substrate, so the catalyst should be added to the substrate solution and hydrogen added promptly. It is not necessary that the solvents be specially dried or that the hydrogen be scrupulously air-free.

The cationic charge gives the catalyst special advantages over neutral catalysts such as ***Chlorotris(triphenylphosphine)rhodium(I)***: better stability to air and to oxidizing solvents, such as halocarbons, and good functional group tolerance. Its unusually high activity, even for hindered substrates, is in part a result of the noncoordinating solvent used, usually CH_2Cl_2, and the low ligand-to-metal (L:M) ratio. A special feature is the very high stereospecificity that can be seen when a functional group such as OH, CO_2Me, or $CONH_2$ binds to the catalyst and directs the attack to one face of the substrate. This has only been seen for catalysts with very low L:M ratios, which allow the functional group, the C=C bond, and H_2 all to bind to the metal at the same time. The catalyst has so far proved most useful for alkene hydrogenation, isomerization, and hydroboration. Other applications have not yet been investigated. The closely related species ***(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) Hexafluorophosphate*** and $[Rh(cod)(Ph_2P\{CH_2\}_4PPh_2)]PF_6$ are sometimes useful for the same types of catalytic reactions, but it is not yet possible to predict which will be best in a given situation. Ideally, all three should be tried.

Isomerization of Allylic Alcohols and Ethers.

$[Ir(cod)(PMePh_2)_2]PF_6$ in THF is activated by hydrogen at room temperature to give $[IrH_2(THF)_2(PMePh_2)_2]PF_6$ which is an active isomerization catalyst, e.g. for the conversion of allylic alcohols to aldehydes or ketones; in eq 1 the reaction takes 30 min at room temperature.[2]

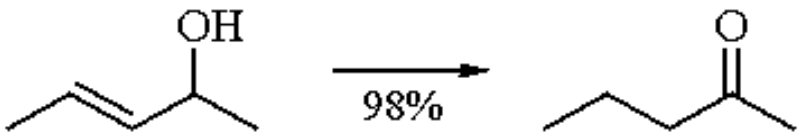

(1)

The conversion of allyl ethers to enol ethers[3] can sometimes be accompanied by hydrolysis, especially on treatment with $HgCl_2$-HgO.[4] This constitutes a useful deprotection sequence for $-OCH_2CH{=}CH_2$ groups (eq 2).

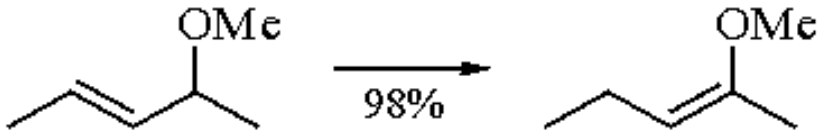

(2)

Directed Hydrogenation of Alkenes.

$[Ir(cod)(PCy_3)(py)]PF_6$ is active for the reduction of hindered alkenes, even tri- and tetrasubstituted ones,[5] while ketone, ester, nitro, amide, and aryl groups remain unaffected. The stereochemistry of the reduction product can be dominated by directing effects[6] in suitable cases. This happens when neighboring carboxamide, hydroxyl, keto, methoxy, or ester groups (in approximate decreasing order of efficiency) bind to the catalyst and ensure addition of H_2 from the face containing the directing group. Directivities of 0.92-1.0 are common, as shown in eq 3 where OH is the directing group. The catalyst seems to work best at low loadings, such as 2.5%. Conversions are high and isomerization is usually a minor pathway. In many cases ***Palladium on Carbon*** in EtOH gave the opposite isomer preferentially, although not exclusively.

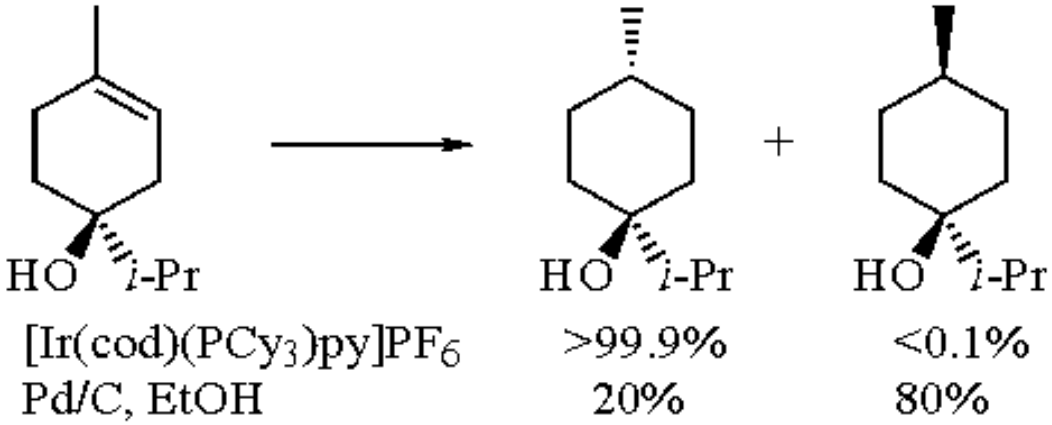

(3)

Terpinen-4-ol is a particularly effective substrate, probably because of the favorable conformation of the OH and C=C groups shown in (**1**), which facilitates chelation of the Ir by simultaneous binding to both groups.

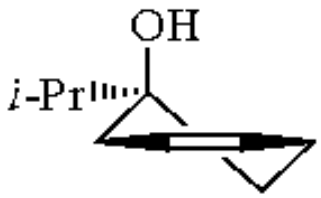

(1)

In the case of the methyl ketone shown, the catalyst shows both its directing effect and ability to reduce highly hindered alkenes (eq 4).

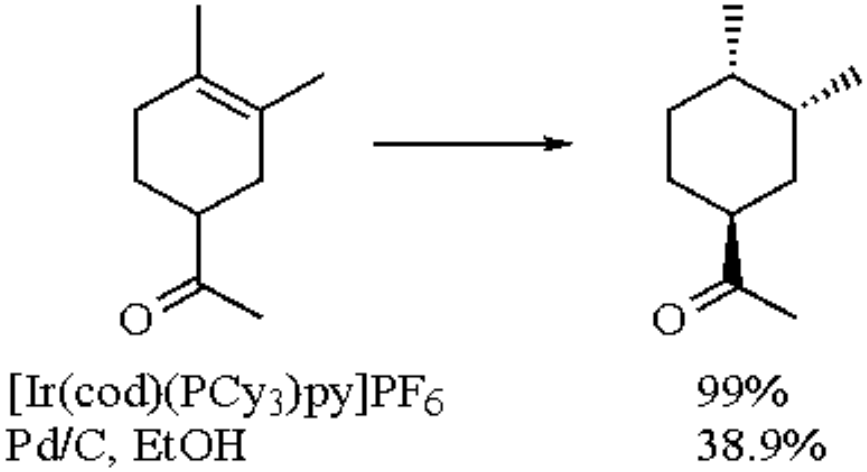

(4)

In indenones, the presence of a suitable hydroxyl group can even completely override the normal tendency to give a *cis* ring junction in the indanone product formed on hydrogenation (eq 5).[6c]

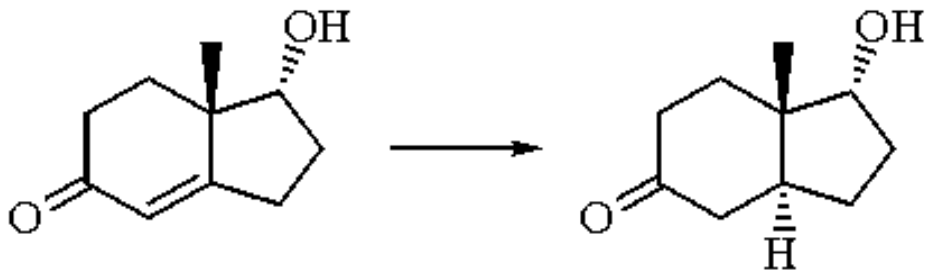

(5)

The directing effect of the catalyst has been useful in key steps of a number of total syntheses, such as of daunomycin[7] and the pumilitoxins.[8]

Directed Hydroboration of Alkenes.

$[Ir(cod)(PCy_3)(py)]PF_6$ can be used at 4-5 mol % catalyst loading in the hydroboration of alkenes, a reaction which shows the same sort of directing effects as noted above for hydroboration.[9]

---

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Cyclopentadiene[1]

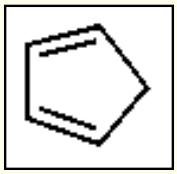

[542-92-7] · C_5H_6 · Cyclopentadiene · (MW 66.10)

(undergoes a variety of cycloaddition reactions;[5] can be deprotonated to form the anion which reacts with electrophiles[27] and forms stable transition metal complexes;[3] can be used to generate polymers[31])

Physical Data: bp 41-42 °C; *d* 0.805 g cm^{-3}.

Solubility: misc. EtOH, benzene.

Form Supplied in: obtained from dicyclopentadiene

Preparative Method: the volatile diene dimerizes readily and is prepared as required by depolymerization of technical dicyclopentadiene (widely available, bp 171-173 °C). The depolymerization is done by heating the dimer carefully under a fractionating column.[2-4]

Handling, Storage, and Precautions: toxic vapor; stench; highly flammable (flash point <25 °C); can dimerize explosively; forms unstable peroxides with oxygen; avoid skin contact. This reagent should be handled only in a fume hood.

Cycloadditions.

Diels-Alder reactions of cyclopentadiene with dienophiles leads predominantly to the *endo* products. In the presence of Lewis acids the *endo* selectivity is greatly increased (eq 1).[5] The use of water as the reaction solvent,[6] or the presence of modified clays[7,8] or zeolites[9] in organic solvents, also leads to a pronounced increase in *endo* selectivity together with increases in reaction rates.

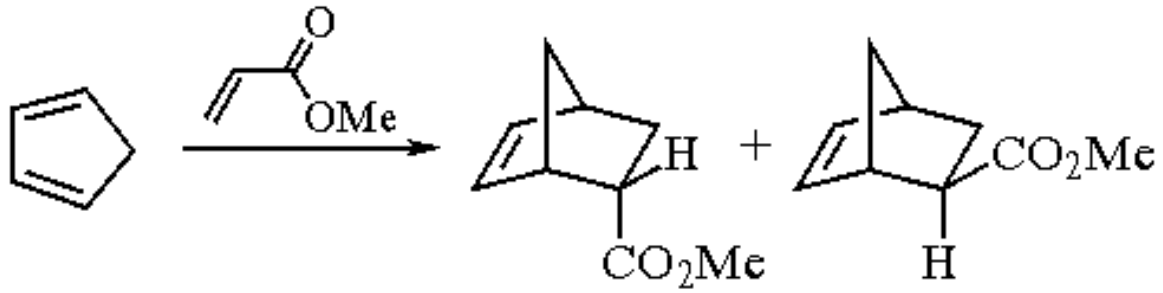

(1)

0 °C	82:18
0.1 equiv $AlCl_3 \cdot OEt_2$, 0 °C	96:4

Cyclopentadiene has also been widely used in asymmetric Diels-Alder reactions (eq 2).[10] Chromium carbene complexes form cycloadducts with cyclopentadiene at increased reaction rates compared to the organic ester analogs (eq 3).[11-13]

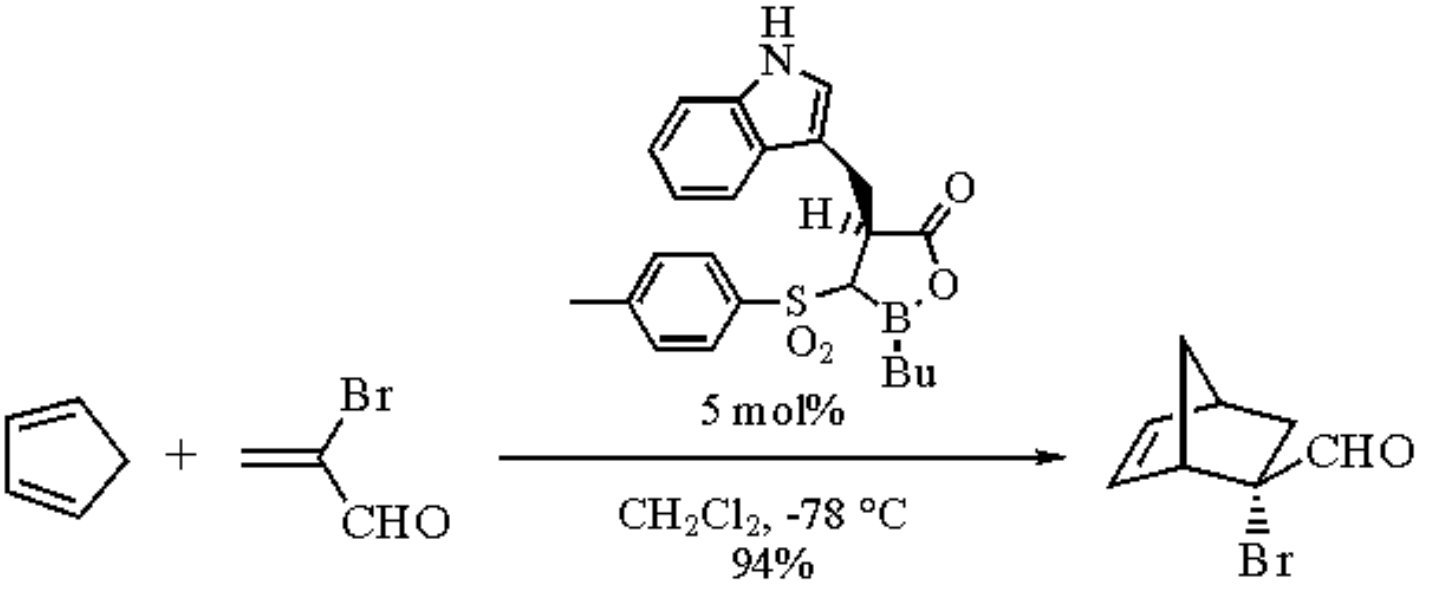

(2)

$(R):(S) = 200:1$
$exo:endo = 96:4$

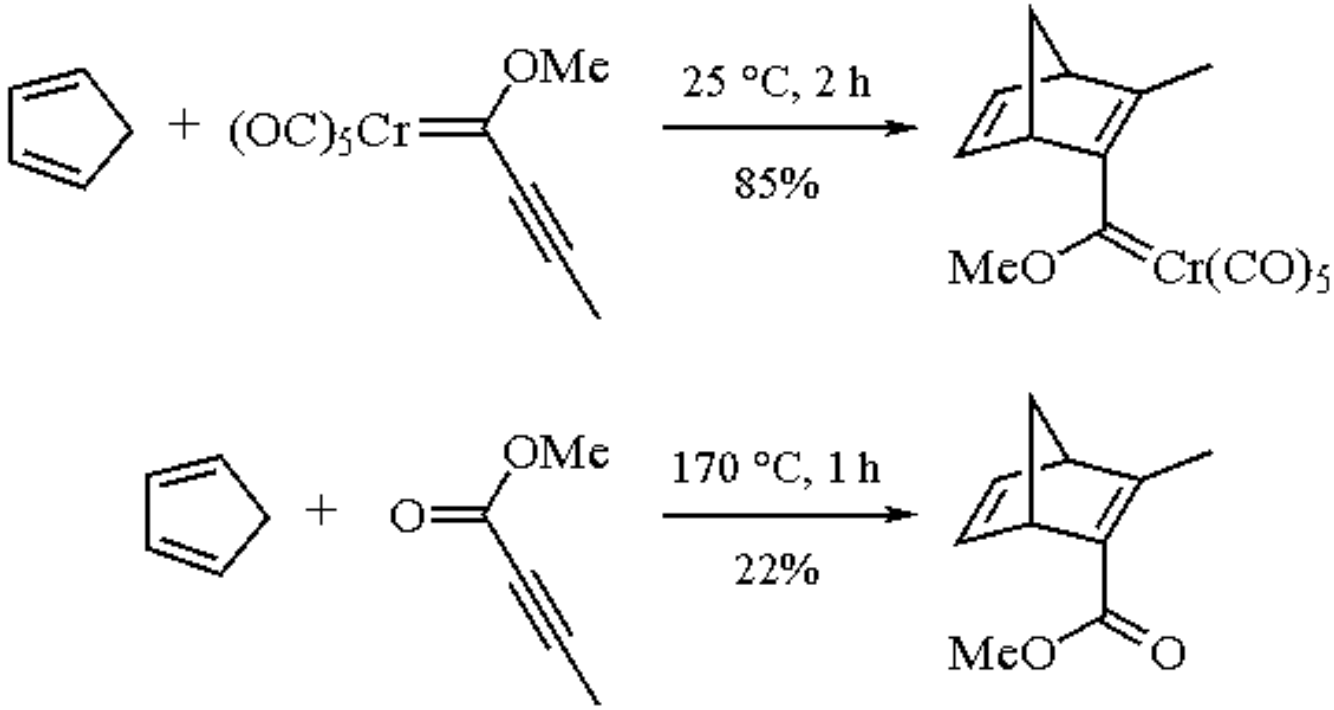

(3)

Cyclopentadiene reacts with benzyne to afford Diels-Alder adducts in high yields (eq 4).[14] This reaction is so efficient that it has been used as a diagnostic test for the formation of benzyne. Heteroatomic dienophiles such as imines,[15,16] thioaldehydes,[17] selenoaldehydes,[18] and sulfenes (eq 5)[19] also react with cyclopentadiene in a [4 + 2] manner.

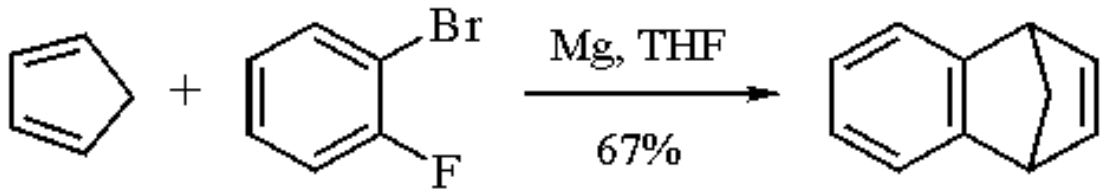

(4)

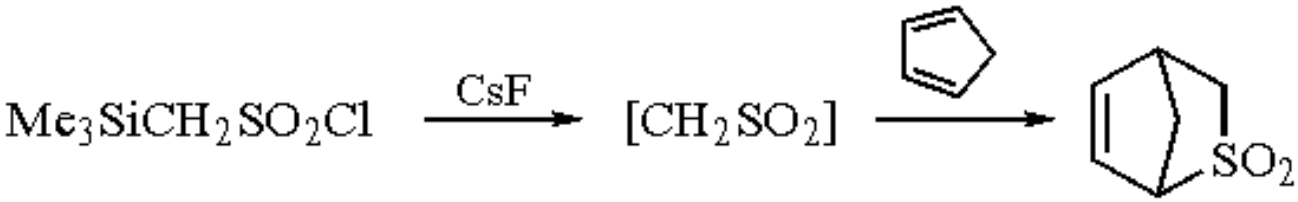

(5)

Cycloaddition with cyclopentadiene has been used for protection of double bonds, which can be subsequently revealed upon pyrolysis (eq 6).[20a] This type of retrograde Diels-Alder reaction has been reviewed.[20b,c]

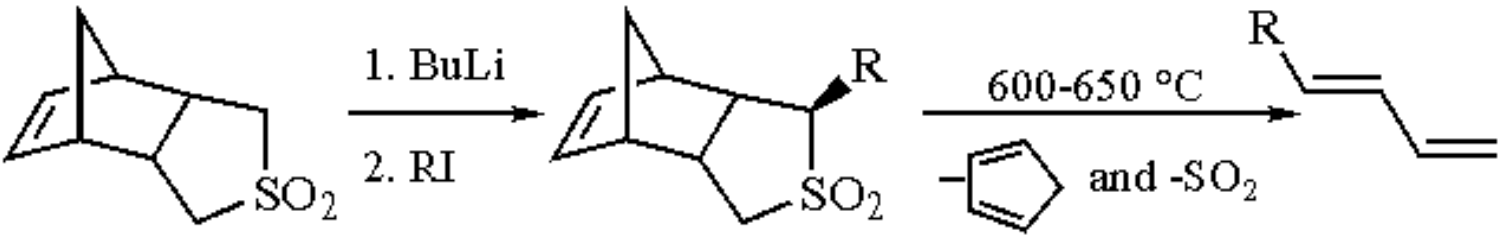

(6)

Cyclopentadiene undergoes a [4 + 3] cycloaddition upon reaction with 2-oxyallyl cations, providing bicyclo[3.2.1]oct-

6-en-3-ones (eq 7).[21] These types of products have been employed as important precursors to natural products.[21]

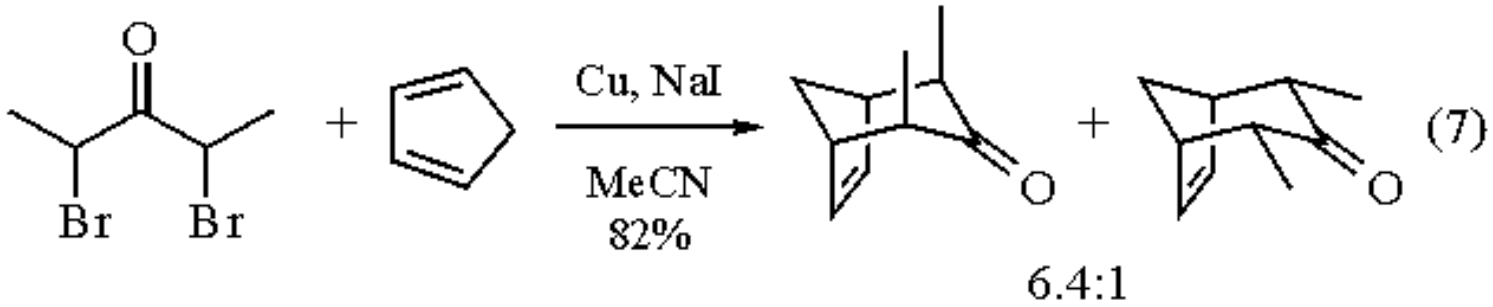

Cyclopentadiene reacts as a simple alkene with ketenes such as 2-carbonyl-1,3-dithiane (eq 8).[22] Likewise, cyclopentadiene reacts chemoselectively with alkynes in the Pauson-Khand cycloaddition. The chemical yields are generally excellent, but the regioselectivity is only moderate (eq 9).[23]

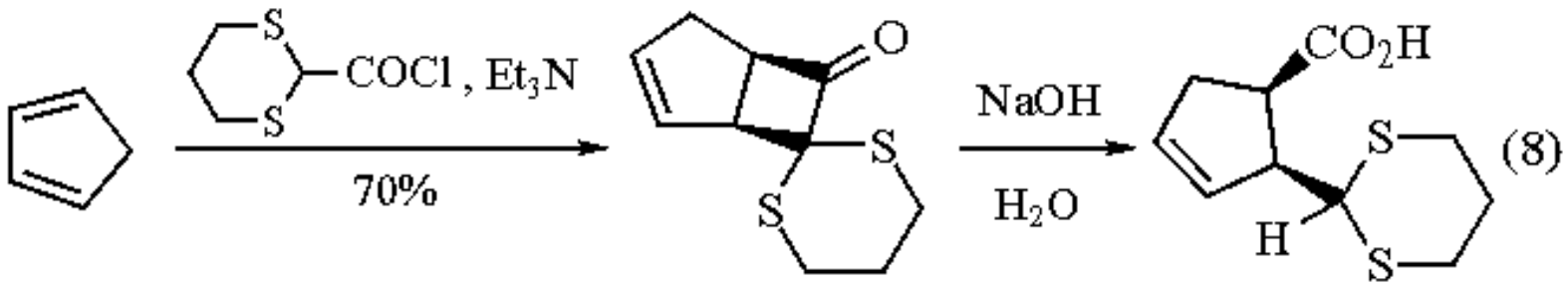

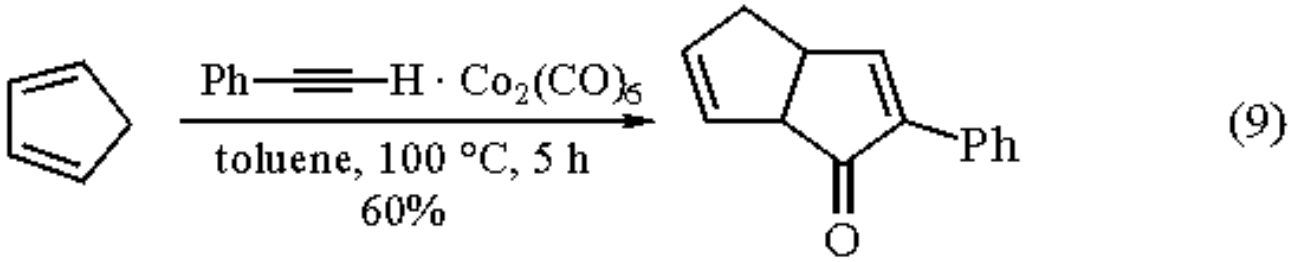

Deprotonation.

Cyclopentadiene can be readily deprotonated by strong bases to give the stabilized (6π-electron) cyclopentadienyl anion. This anion is a ubiquitous ligand for transition metal complexes; examples are ruthenocene[24] and ferrocene (eq 10).[3]

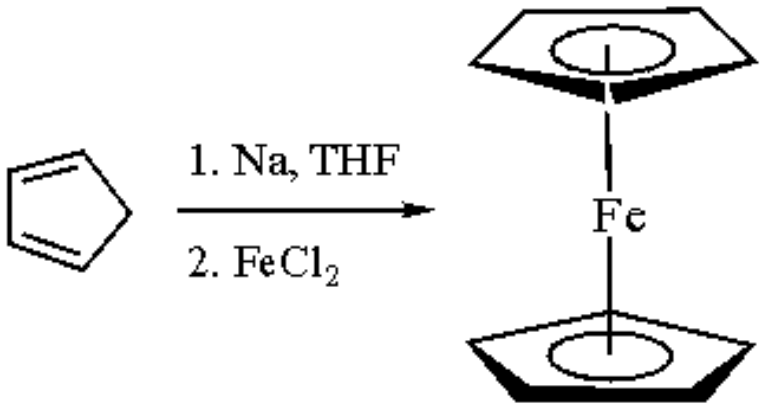

(10)

The cyclopentadienyl anion also reacts with ketones to generate fulvenes (eq 11).[25] Aldehydes only polymerize under these conditions; however, they may be used to form the corresponding fulvenes by employing a modified method.[26] Reaction of the anion with electrophiles often leads to mixtures of regioisomers due to facile ambient temperature 1,5-hydrogen shifts (eq 12).[27a] To circumvent these hydrogen shifts, the use of cyclopentadienylthallium at low temperature has been employed.[27b]

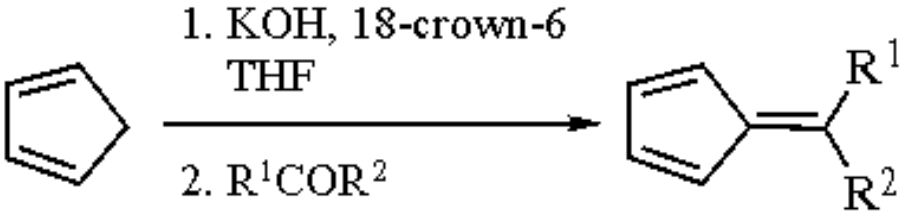

(11)

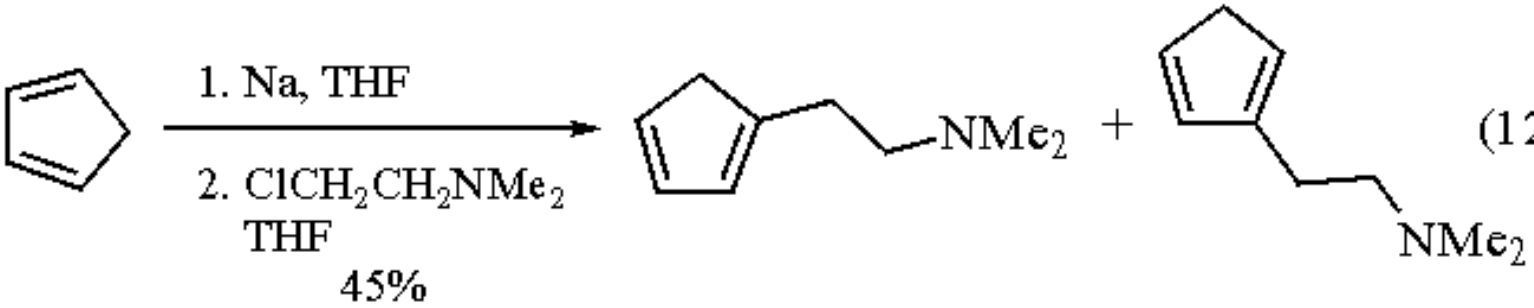

(12)

1,4-Addition Reactions.

Cyclopentadiene reacts with ***Bromine*** to afford the *cis*-1,4-adduct in high yield (eq 13).[28] The *cis*-1,4-diol may be obtained by reaction with singlet oxygen and ***Thiourea*** (eq 14).[29] The diacetate of this diol can be desymmetrized with enzymes to afford the enantiomerically enriched alcohol, which is an important chiral building block (eq 15).[30]

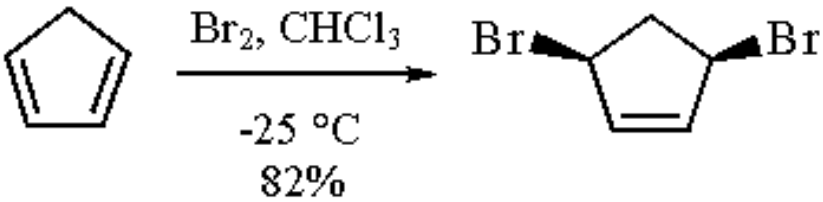

(13)

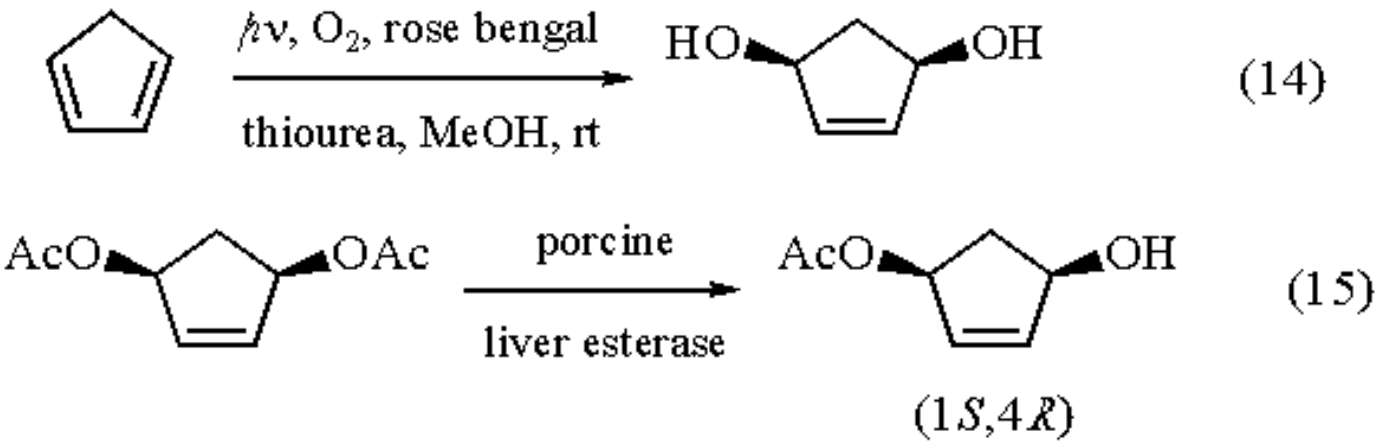

Polymerization.

Cyclopentadiene undergoes polymerization in the presence of 0.1 mol % of a tungsten nitrosyl Lewis acid catalyst (eq 16).[31] The polymer is a mixture of 1,4- and 1,2-polycyclopentadiene.

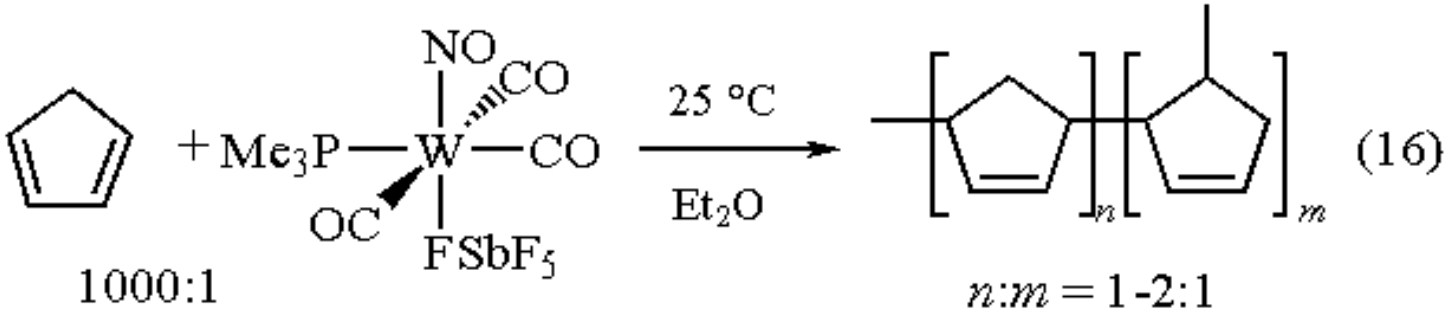

Related Reagents.

5-Bromo-1,3-cyclopentadiene; ***5-(Methoxymethyl)-1,3-cyclopentadiene***.

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Cyclopentadienone Diethyl Acetal[1]

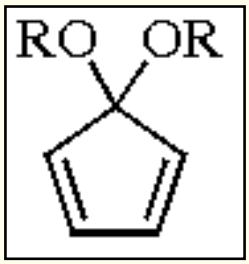

(R = Et)

[2931-32-0] · $C_9H_{14}O_2$ · Cyclopentadienone Diethyl Acetal · (MW 154.21) (R = Me)

[2931-31-9] · $C_7H_{10}O_2$ · Cyclopentadienone Diethyl Acetal · (MW 126.16)

(isolable cyclopentadienone synthon(s) for use in Diels-Alder and related cycloadditions[2])

Physical Data: thermally unstable liquid which rapidly dimerizes in solution.

Solubility: sol pentane, pyridine, hexanes, ether, ethyl acetate; insol water.

Preparative Methods: cyclopentanone acetal (ethyl or methyl) is brominated with ***Pyridinium Hydrobromide Perbromide***. The 2,5-dibromo acetal is double dehydrobrominated using ***Potassium t-Butoxide-Dimethyl Sulfoxide***, the product extracted into cold pentane and used immediately.[2]

Analysis of Reagent Purity: analysis of the dimeric product.

Handling, Storage, and Precautions: pentane solutions should be used immediately.

Diels-Alder Cycloadditions.

Early attempts to utilize cyclopentadienone in Diels-Alder cycloadditions proved fruitless because spontaneous dimerization occurs.[3-5] The same was true of cyclopentadienone ethylene acetal;[3-5] thus attention turned to *n*-alkyl acetals. The diethyl acetal can be prepared in good yield from

dehydrobromination of 2,5-dibromocyclopentanone diethyl acetal, but care must be exercised during isolation.[2] A solution in pentane left to stand for 24 h produces the dimeric Diels-Alder adduct in 70-95% yield.[2] Immediate utilization of the diene allows a versatile range of cycloaddition products to be accessed. A number of phthalimide derivatives have been studied, giving good yields of cycloadducts (eq 1).[2,6-9] Elaboration of this strategy involves unmasking of the ketone function, best achieved using ***Boron Trifluoride Etherate*** (eq 2),[6] allowing full realization of the diene's potential as a cyclopentadienone equivalent. A range of electron deficient dienophiles have been examined in cycloaddition reactions with this diene (eq 3).[2,10,11] Cycloaddition with diethyl maleate has been used to prepare an important intermediate en route to norborna-2,5-dien-7-one.[10] In the cycloaddition with nitroethylene the [4 + 2] adduct is obtained with an *endo*:*exo* ratio of 2.5:1.[11] A similar ratio was observed for the product of cycloaddition with acrolein.[2]

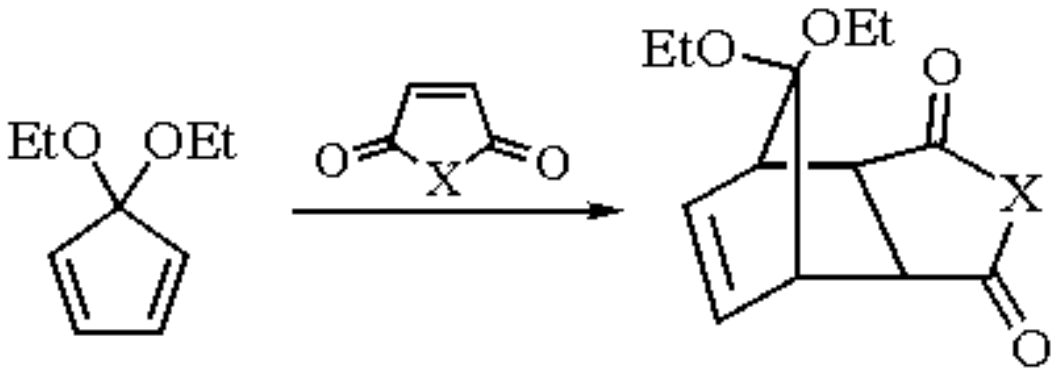

(1)

X = O, HC=CH, S, NPh, NEt, NH

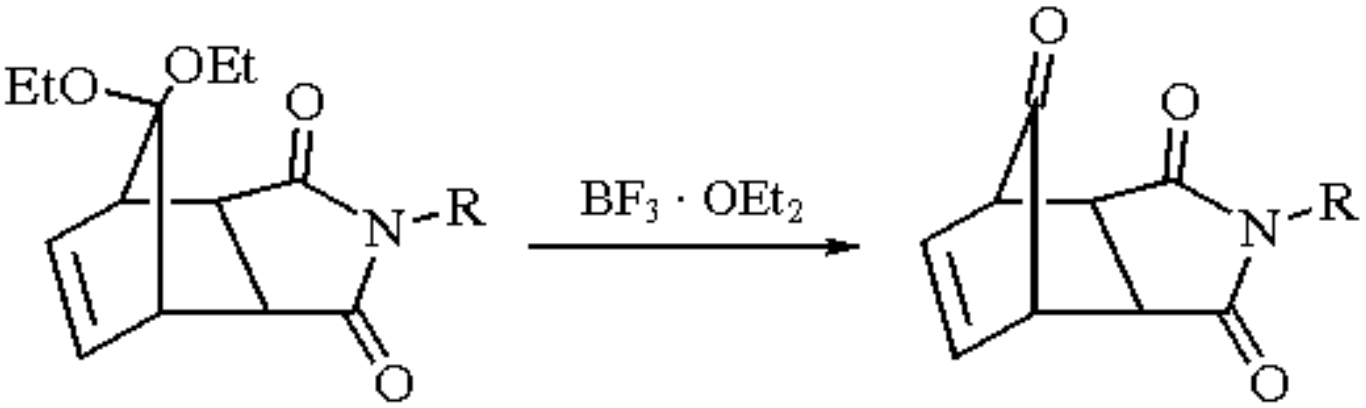

(2)

R = H, Et, Ph

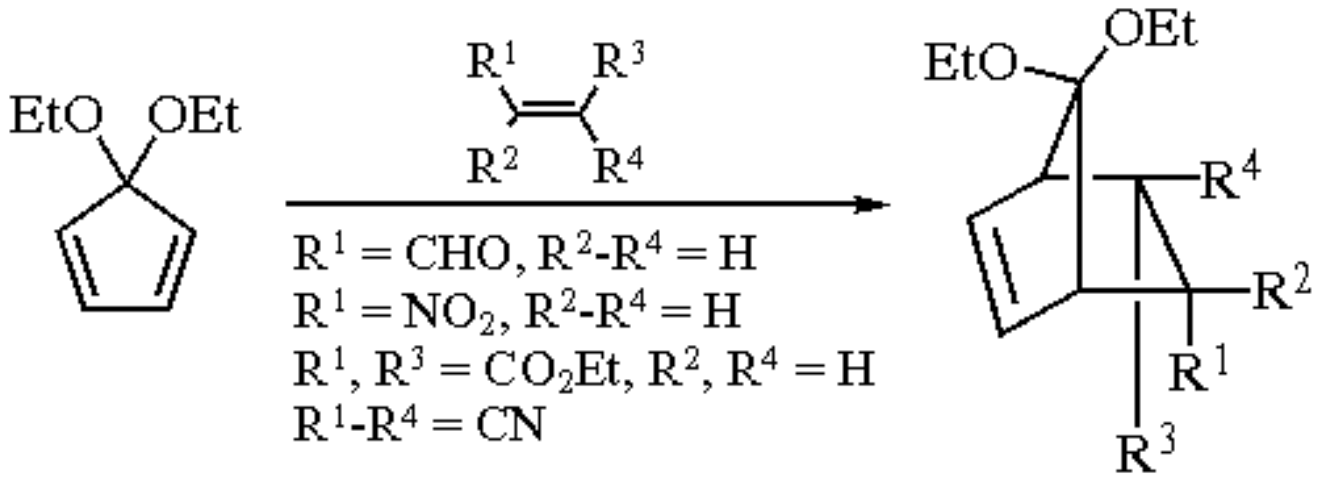

(3)

Cycloaddition to the cyclobutadiene iron carbonyl complex has been accomplished; the structurally interesting adduct was used to prepare a homocubyl species (eq 4).[12] A [4 + 3] cycloaddition to cyclopentadienone diethyl acetal has been reported, the reactive dienophile involved being generated in situ using a ***Zinc/Copper Couple*** (eq 5).[13] The cycloaddition mechanism to this allyl cation was elucidated, and determined to proceed firstly by an electrophilic and then by a nucleophilic step.

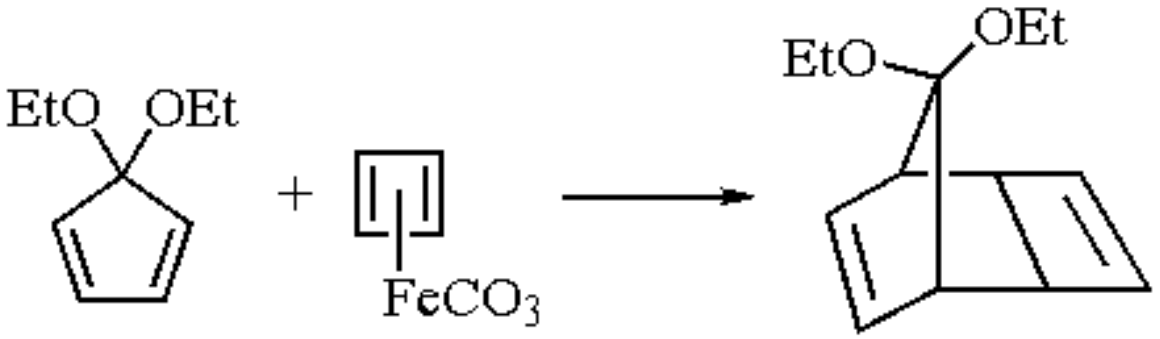

(4)

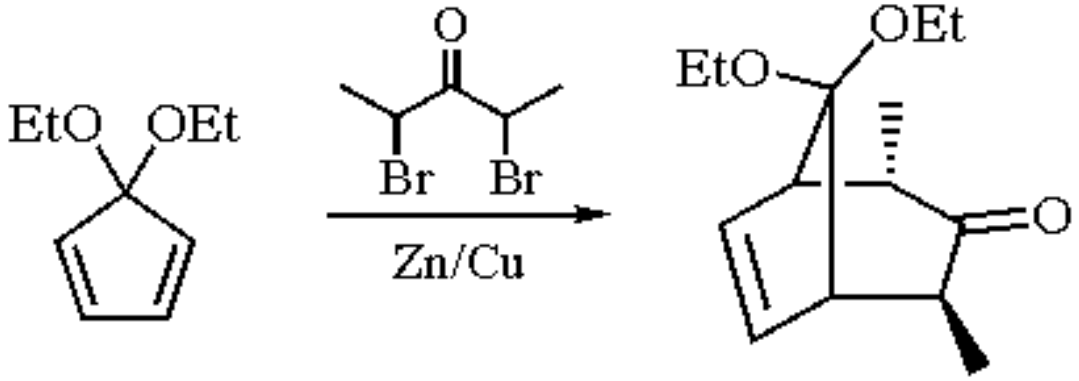

(5)

Reaction of the cyclopentadieneone diethyl acetal with ***4-Phenyl-1,2,4-triazoline-3,5-dione*** (PTAD), followed by hydrogenation of the alkenic bond and liberation of the azo moiety, resulted in isolation of a novel and potentially versatile cycloadduct (eq 6).[14]

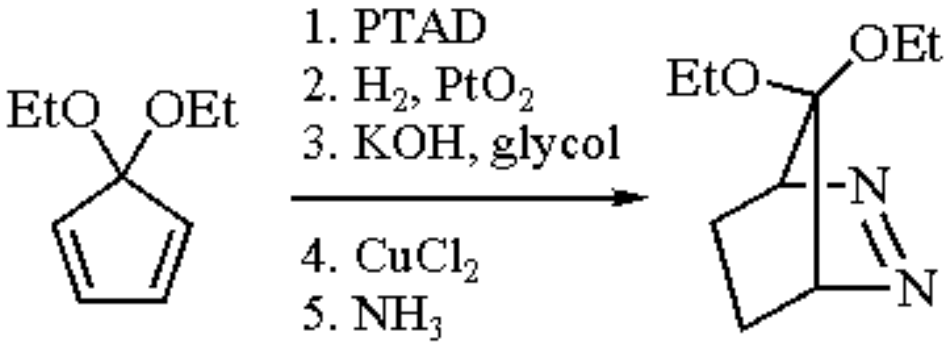

(6)

Cyclopentadienone dimethyl acetal, produced by an identical process, undergoes much of the chemistry as the analogous diethyl acetal.[2] The rates of dimerization of these acetals have been studied in depth. From these studies it emerged that at 25 °C the dimethyl acetal dimerizes 1.7 times faster than the diethyl acetal (eq 7),[2,15] but much slower than the ethylene acetal which proceeds approximately 1070 times faster. This translates into a 500-fold more rapid dimerization for the cyclopentadienone dimethyl acetal than cyclopentadiene, the short half-life explaining the lack of general utility of these dienones.[16] Using electron deficient dienes, however, reasonable yields of cycloadducts can be obtained, a pertinent example being addition to an azo-maleimide (eq 8).[11]

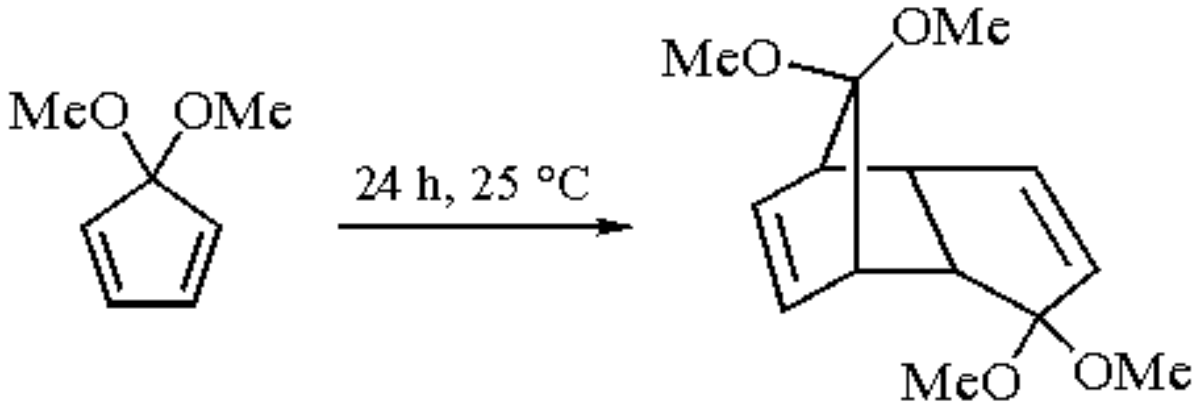

(7)

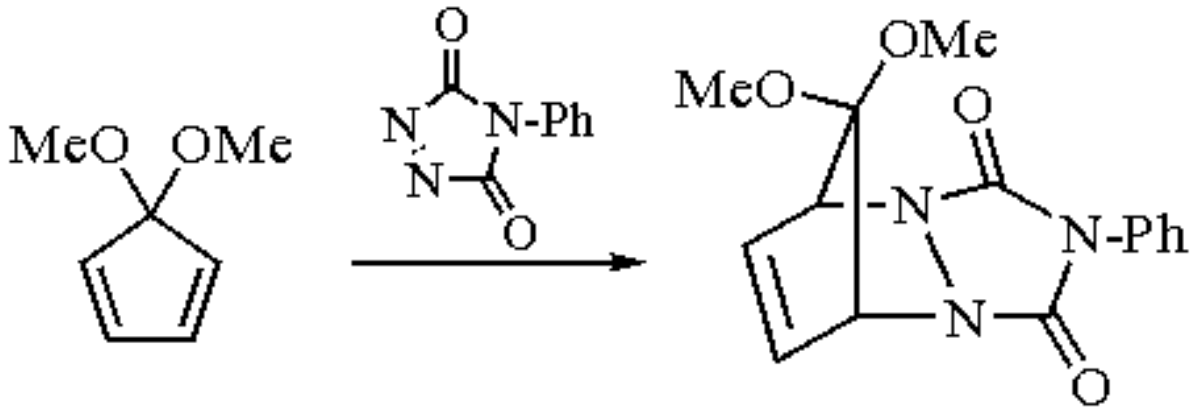

(8)

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Chloro(cyclopentadienyl)bis[3-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)]titanium

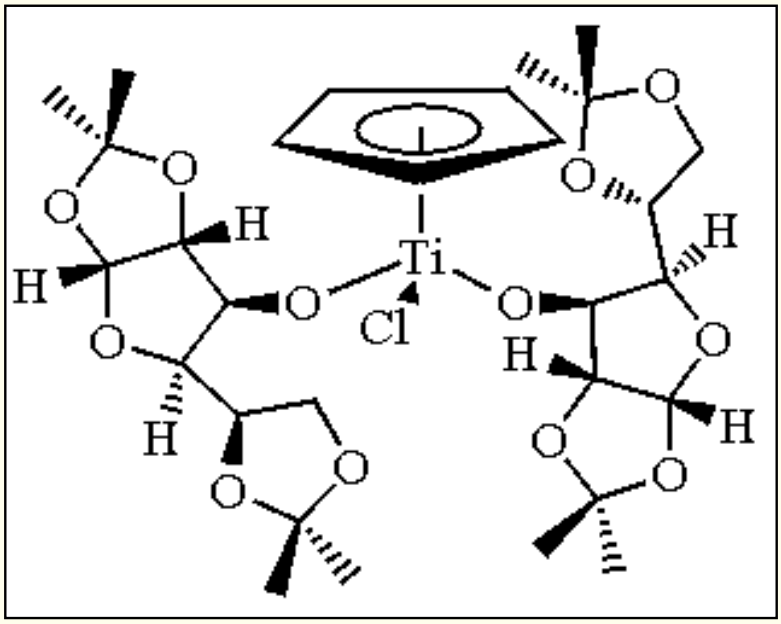

[119528-80-2] · $C_{29}H_{43}ClO_{12}Ti$ · Chloro(cyclopentadienyl)bis[3-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)]titanium · (MW 667.05)

(highly enantio- and diastereoselective aldol reactions of acetic acid,[1] propionic acid,[2] and glycine[3] ester enolates with various aldehydes; stereoselective addition of allyl groups to aldehydes[4])

Physical Data: crystal structure; ^{1}H and ^{13}C NMR.[5]

Solubility: toluene (not determined, 0.155 M possible); Et_2O (not determined, 0.09 M possible).[4]

Analysis of Reagent Purity: ^{1}H NMR; test reaction.

Preparative Methods: see ***Trichloro(cyclopentadienyl)titanium***.

Handling, Storage, and Precautions: best handled as stock solution either in Et_2O (ca. 0.1 M) or toluene (ca. 1.5 M), which must be protected from moisture and UV light. If handled under an inert atmosphere (argon), such solutions can be stored in a refrigerator (8 °C) for several months (possibly much longer) without deterioration. Reactions should be carried out in dry equipment and with absolute solvents under Ar or N_2.

Aldol Reactions.

The titanium enolate (**2**) is obtained by addition of ca. 1.3 equiv of the title reagent (**1**) as a 0.1-0.15 M solution in toluene to the Li enolate of *t*-butyl acetate (**3**) generated at -78 °C with lithium dicyclohexylamide in Et_2O. This transmetalation takes about 24 h at -78 °C but is completed within 1 h at -30 °C (eq 1).[1a,b] The medium might also be important, as it has recently been reported that ***12-Crown-4*** has to be added for reproducible results in THF-Et_2O.[1c] The solution of (**2**) usually is recooled to -78 °C for the reaction with aldehydes, affording β-hydroxy esters (**4**) of high optical purity (90-96% ee) upon hydrolytic workup. Byproducts are insoluble cyclopentadienyltitanium oxides (**5**) and the ligand diacetone-glucose (DAGOH, **6**). The oxides (**5**) can be separated by filtration and may be recycled to $CpTiCl_3$. Ligand (**6**) and product are either separated by conventional methods (crystallization, distillation, chromatography), or glucose is extracted into the aqueous phase after acetonide cleavage in 0.1 N HCl (1.5 h at rt).[1a,b] In the case of isovaleraldehyde (R = *i*-Bu) it could be shown that the enantioselectivity (92-96% ee) is retained up to rt (27 °C).[1a,b]

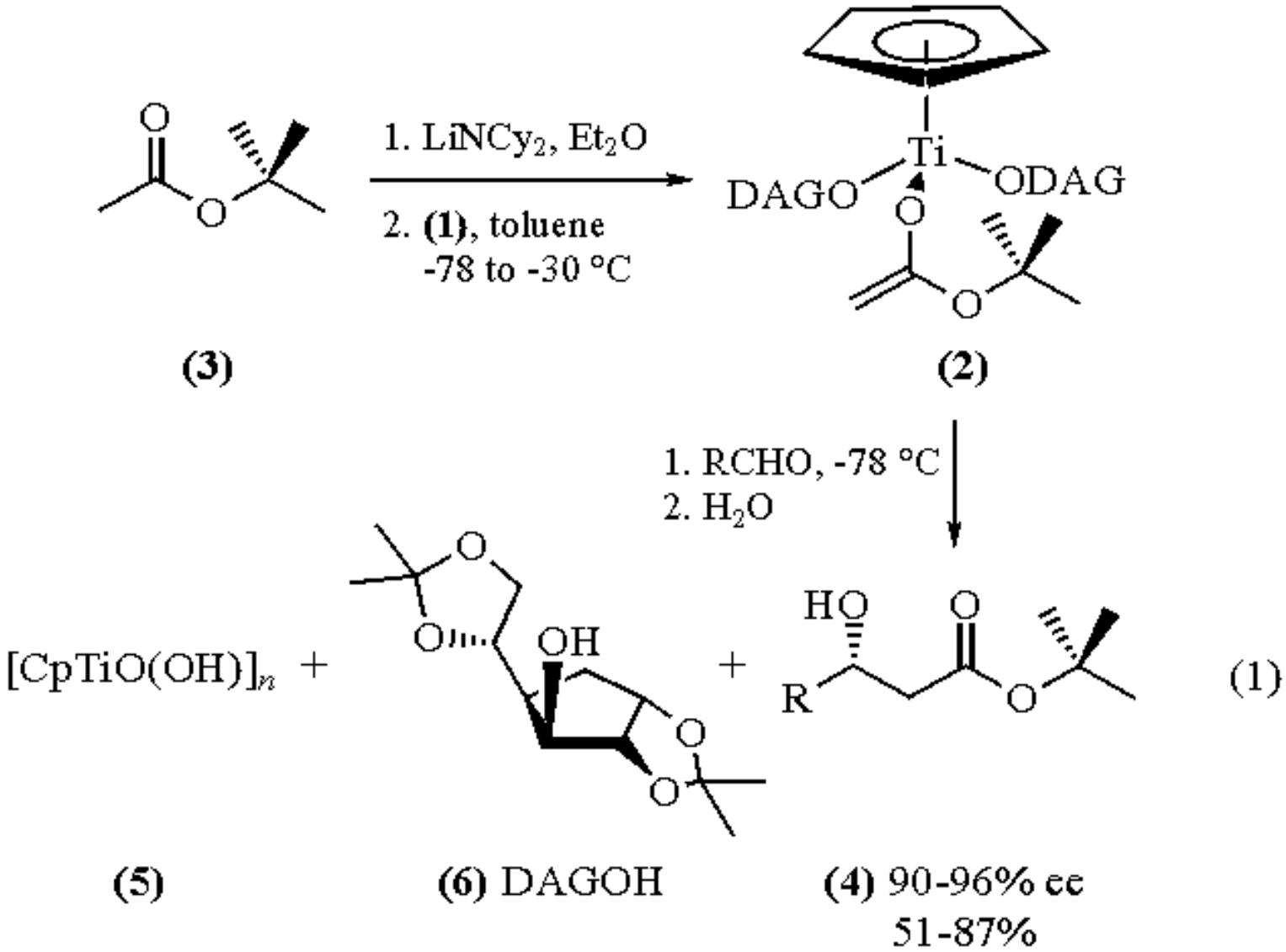

A clear drawback of this reagent is the availability of only one enantiomer, the one favoring the *re* attack to the

aldehyde carbonyl, as only D-glucose is readily available. *si* Attack is observed with the analogous enolate prepared from ***Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O^{α},O$^{α´}$]titanium***, but only with moderate enantioselectivity (78% ee).[1c,6] The reagent (**2**) is probably the most versatile chirally modified acetate enolate. Good results have also been obtained with the Mg enolate of 2-acetoxy-1,1,2-triphenylethanol[7] and with boron enolates derived from 2,4-dialkylborolanes.[8] Chiral Fe-acetyl complexes, which can be considered as acetate equivalents, give impressive stereocontrol upon enolization and aldol reaction.[9] Except for unsaturated residues R, β-hydroxy esters (**4**) of excellent optical purity can also be obtained by enantioselective hydrogenation of the corresponding β-keto esters catalyzed by $RuCl_2$(BINAP).[10]

For the propionate aldol reaction the Li enolate (**7**), generated by deprotonation of 2,6-dimethylphenyl propionate with ***Lithium Diisopropylamide*** in Et_2O,[11] was chosen.[2] Transmetalation with 1.25 equiv of an ethereal solution of (**1**) takes 24 h at -78 °C. The completion of this step is evident by the disappearance of racemic *anti*-aldol (**9**) in favor of optically active *syn*-isomer (**10**) (91-98% ee) upon reaction with an aldehyde (RCHO) and aqueous workup. At this point, 3-11% of *anti*-aldol (**9**) remaining in the reaction mixture is optically active as well (eq 2). This *anti*-isomer (**9**) (94-98% ee) becomes the major product if the reaction mixture, containing the putative (*E*)-titanium enolate derived from (**7**), is warmed for 4-5 h to -30 °C before reaction with an aldehyde (RCHO) again at -78 °C. Isomerization to the (*Z*)-titanium enolate is a possible explanation of this behavior. Some substrates, aromatic and unsaturated aldehydes, behave exceptionally, as a high proportion of *syn*-isomer (**10**) (19-77%) of lower optical purity (47-66% ee) is formed in addition to (**9**) (94-98% ee). After hydrolysis of the acetonide (**6**) the products (**9**/**10**) are isolated and separated by chromatography in 50-87% yield. The reactions of pivalaldehyde (R = *t*-Bu) are sluggish at -78 °C and have therefore been carried out at -50 to -30 °C.

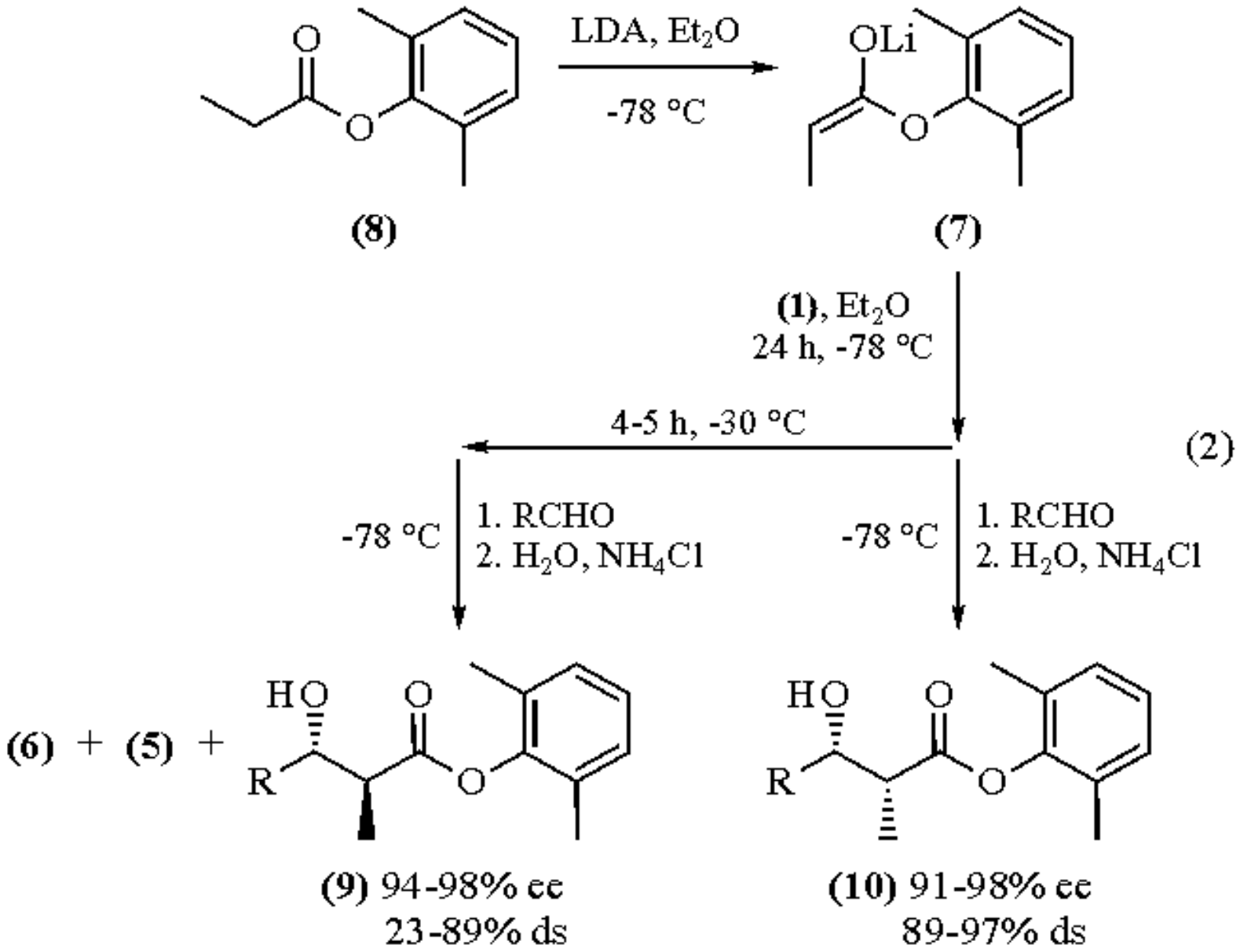

As above (eq 1), a major drawback of this reagent is the lack of a readily available enantiomer. There are many alternative methods for the enantioselective propionate aldol reaction. The most versatile chirally modified propionate enolates or equivalents are *N*-propionyl-2-oxazolidinones,[12] α-siloxy ketones,[13] boron enolates with chiral ligands,[14] as well as tin enolates.[15] Especially rewarding are new chiral Lewis acids for the asymmetric Mukaiyama reaction of *O*-silyl ketene acetals.[16] Most of these reactions afford *syn*-aldols; good methods for the *anti*-isomers have only become available recently.[8,17]

Transmetalation of the (*E*)-*O*-Li-enolate derived from the stabase-protected glycine ethyl ester (**11**) with 1.1 equiv of (**1**) affords the chiral Ti enolate (**12**), which adds with high *re* selectivity to various aldehydes.[3,18] By mild acidic cleavage of the silyl protecting group, the primary product (**13**) can be transformed to various *N*-derivatives (**14**) of D-*threo*-α-amino-β-hydroxy acids in 45-66% yield and with excellent enantio- and *syn*(*threo*) selectivity (97-99%) (eq 3). An exception with lower enantioselectivity is glyoxylic ester (ethyl ester 78% ee; *t*-butyl ester 87% ee).

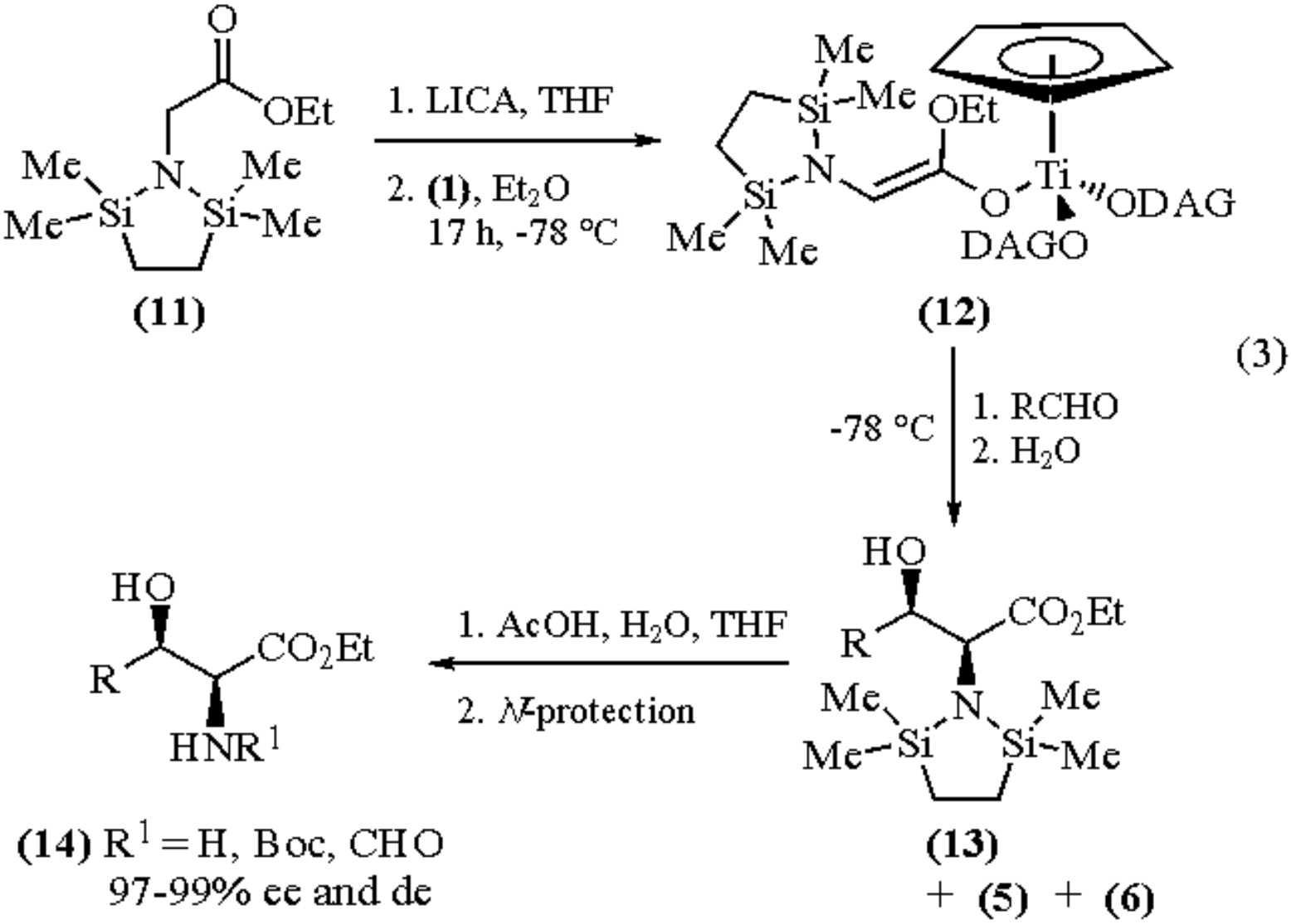

(3)

In this case the enantiomers are available by the analogous conversion of glycine *t*-butyl ester using ***Chloro(*η^5*-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-*$\alpha,\alpha,\alpha',\alpha'$*-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O*$^{\alpha}$*,O*$^{\alpha'}$*]titanium***. An elegant alternative is the enantioselective addition of isocyanoacetate to aldehydes under the catalysis of a chiral Au^I complex.[19] Further methods, also for the *anti*(*erythro*) epimers, can be found in recent reviews of enantioselective α-amino acid synthesis.[20]

Allyltitanation of Aldehydes.

The allyltitanium complex (**15**) is obtained by reaction of chloride (**1**) (1.1 equiv) with allylmagnesium chloride in Et_2O for 1 h at 0 °C.[4] The compound (**15**) has been characterized by ^{13}C NMR.[5] Reaction with various aldehydes (RCHO) at -78 °C and hydrolysis affords the homoallyl alcohols (**16**) (55-88%) of high optical purity (85-94% ee) (eq 4).[4] The isolation of the product is analogous to the aldol reactions (cf. eq 1).

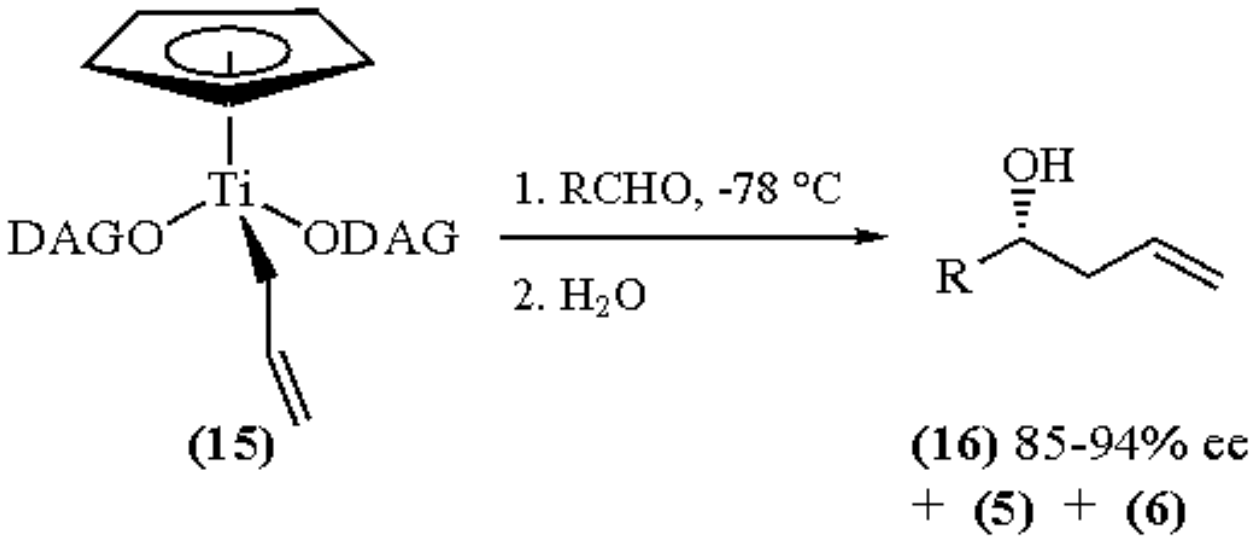

(4)

The enantiomers of (**16**) are obtained analogously by using ***Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O$^{\alpha}$,O$^{\alpha'}$]titanium***.[21] The stereoselectivity of this cyclic Ti complex in allyltitanations is better than the diacetone-glucose system (**1**). It is therefore advisable to use the (4*S*,*trans*) enantiomer instead of (**1**) for controlling the *re* addition to problematic substrates. For further examples of this method and for analogous reagents see the discussion provided in ***Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O$^{\alpha}$,O$^{\alpha'}$]titanium***.

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Cyclopentadienylbis(triphenylphosphine)cobalt(I)[1]

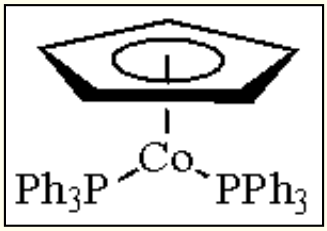

[32993-07-0] · $C_{41}H_{35}CoP_2$ · Cyclopentadienylbis(triphenylphosphine)cobalt(I) · (MW 648.62)

(alkyne cyclotrimerization catalyst; co-cyclotrimerization catalyst for alkynes and nitriles, alkenes and heterocumulenes; reagent for synthesis of substituted thiophenes, selenophenes, and pyrroles)

Physical Data: mp 140-143 °C (benzene adduct).[2a]

Solubility: sol benzene, THF, toluene; insol hexane.

Form Supplied in: dark red, air-sensitive crystalline solid.

Analysis of Reagent Purity: ^{1}HMR and IR.[2a,2b]

Preparative Method: can be prepared by addition of NaCp to ***Chlorotris(triphenylphosphine)cobalt*** in THF.[2c]

Purification: recrystallization from benzene/hexane.[2c]

Handling, Storage, and Precautions: store under an inert atmosphere.

Synthesis of Cyclopentadienyl(triphenylphosphine)cobaltacyclopentadiene Complexes.

The cyclotrimerization of alkynes and co-cyclotrimerization of alkynes with alkenes, nitriles, and heterocumulenes discussed in this section employ cyclopentadienyl(triphenylphosphine)cobaltacyclopentadiene complexes (**2**), either as stoichiometric reagents or as catalysts. They are obtained from the reaction of cyclopentadienylbis(triphenylphosphine)cobalt(I) (**1**) with 2 equiv of an alkyne (eq 1; Table 1). Either symmetrical or unsymmetrical alkynes may be employed but unsymmetrical alkynes often give modest regioselectivity.[2c,2d] The regioisomers are readily separated by chromatography.

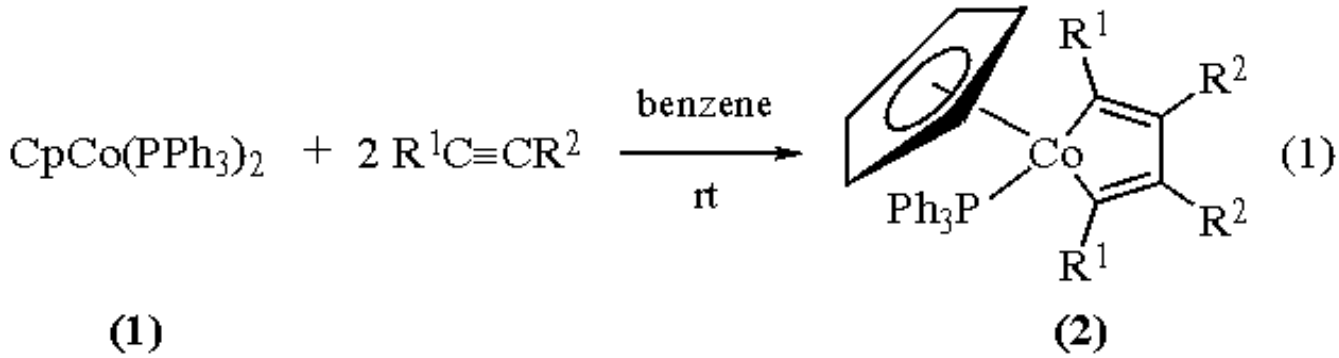

Table 1 Formation of Cobaltacyclopentadiene Complexes from 2 Equiv of Alkyne

Cpd	R^1	R^2	R^1	R^2	Yield
(2a)	Ph	Ph	Ph	Ph	88%
(2b)	CO_2Me	CO_2Me	CO_2Me	CO_2Me	14%
(2c)	CH_2OMe	CH_2OMe	CH_2OMe	CH_2OMe	36%
(2d)	Ph	CO_2Me	Ph	CO_2Me	29%
(2dϕ)	Ph	CO_2Me	CO_2Me	Ph	26%

Significantly, two different alkynes may be incorporated into the metallacycle by employing a stepwise addition of alkyne to the cobalt complex (eq 2; Table 2).[2d] Here too, regioselectivity is often modest with unsymmetrical alkynes.

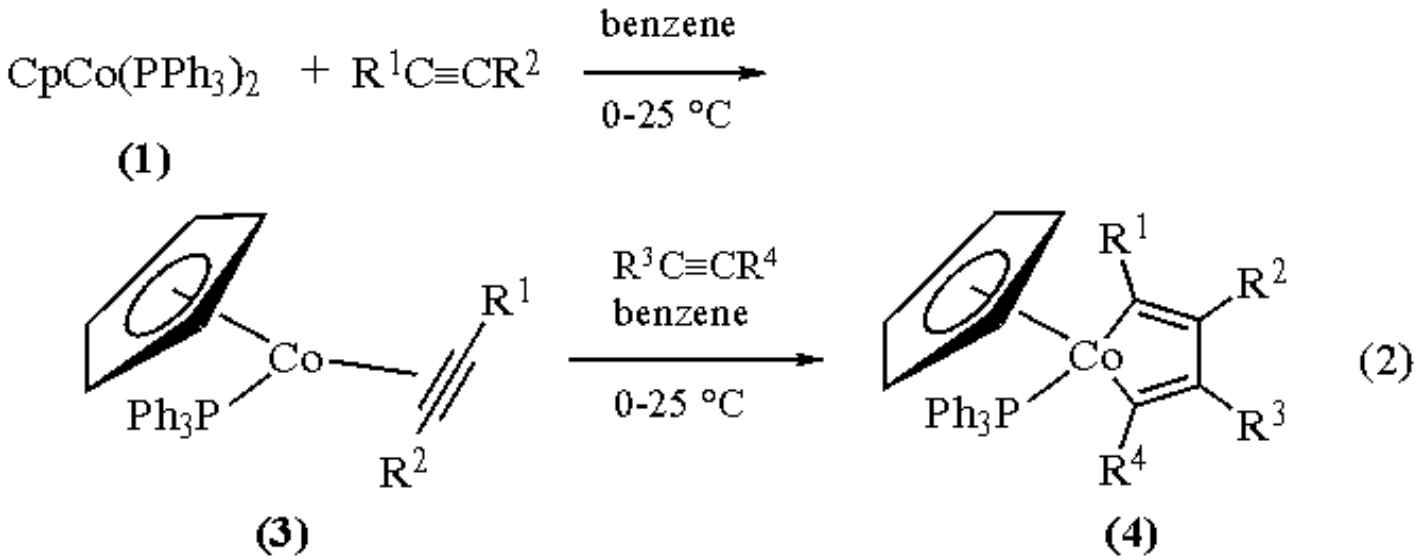

Table 2 Formation of Cobaltacyclopentadiene Complexes by Sequential Addition of Two Different Alkynes

Cpd	R^1	R^2	R^3	R^4	Yield
(4a)	Ph	Ph	Me	Ph	67%
(4b)	Ph	Ph	Me	CO_2Me	48%
(4c)	Ph	Ph	Ph	CO_2Me	5%
(4cϕ)	Ph	Ph	CO_2Me	Ph	43%
(4d)	CO_2Me	Me	Ph	CO_2Me	9%
(4dϕ)	CO_2Me	Me	CO_2Me	Ph	39%

The reaction will tolerate a variety of alkyne substituents including alkyl, aryl, alkoxycarbonyl, and chloro groups, but the presence of cyano or 2-pyridyl substituents leads to the formation of byproducts.[2e,2f] The use of diynes in this reaction in place of monoalkynes gives bicyclic cobaltacyclopentadiene complexes. The yields of the latter reaction depend upon the tether length as well as the presence of substituents on the alkyne or on the tether.[2g,2h] The cobaltacyclopentadiene complexes are generally air-stable materials which will react with a variety of unsaturated organic substrates in stoichiometric or catalytic reactions.

Synthesis of Polysubstituted Unsymmetrical Benzenes, 1,3-Cyclohexadienes, and Heterocycles.

Substituted benzenes such as hexamethylbenzene can be prepared catalytically by treating an excess of the alkyne with the appropriate cobaltacyclopentadiene complex.[3a] The stoichiometric reaction of cobaltacyclopentadiene complexes with alkynes gives polysubstituted benzenes (eq 3; Table 3).[2c,2g,3b,3c]

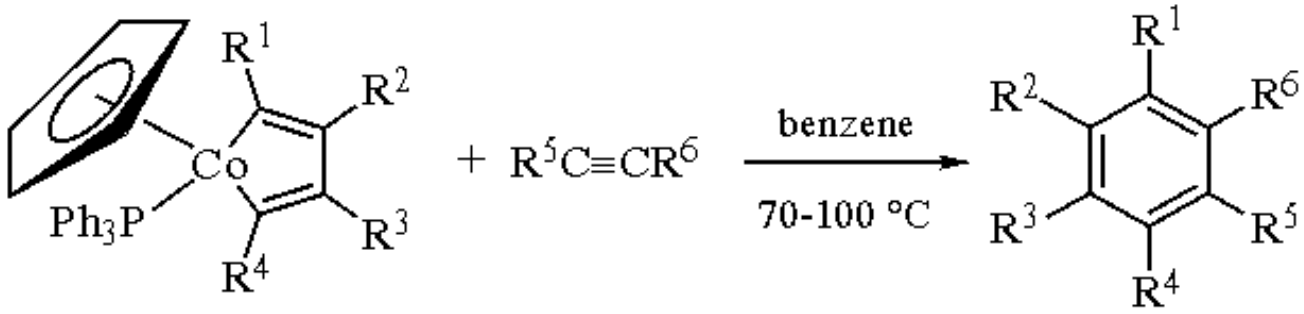

(3)

(4) (5)

Table 3 Formation of Polysubstituted Benzenes from Cobaltacyclopentadiene Complexes

Cpd	R^1	R^2	R^3	R^4	R^5	R^6	Yield
(5a)	Ph	Ph	Me	Ph	CO_2Me	CO_2Me	13%
(5b)	Ph	Me	Me	Ph	Ph	CO_2Me	59%
(5c)	CO_2Me	Me	CO_2Me	Ph	CO_2Me	CO_2Me	36%

Substituted pyridines have been prepared in similar manner by the stoichiometric reaction of cobaltacyclopentadiene complexes with nitriles.[2h,4a] More importantly, cobaltacyclopentadiene complexes will catalytically form pyridines from 2 equiv of an alkyne and 1 equiv of a nitrile.[4b] For example, acrylonitrile reacts with acetylene in the presence of cyclopentadienyl(triphenylphosphine)cobalta(tetraphenylcyclopentadiene) to form 2-vinylpyridine (eq 4). This catalyst may also be used to prepare substituted pyridines from substituted alkynes in good yield, but the use of unsymmetrical alkynes leads to mixtures of isomeric pyridines. Use of this catalyst, however, has been supplanted by more conveniently prepared catalysts.[4c,4d]

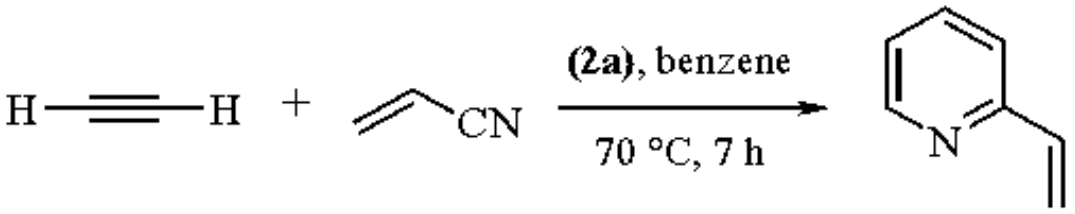

2.3 g 1.2 g (4)

Likewise, the reaction of cobaltacyclopentadienes with heterocumulenes gives heterocycles (eq 5; Table 4).[4a,5a,5b] The reaction of alkynes with carbon disulfide, isothiocyanates, isocyanates, or carbodiimides using cobaltacyclopentadiene complexes affords dithiopyrones, thiopyridones, pyridones, or iminopyridones, respectively, in good yield. Pyridones and iminopyridones could also be prepared with catalytic cyclopentadienyl(triphenylphosphine)cobalta(tetraphenylcyclopentadiene), but unsymmetrical alkynes give mixtures of isomeric heterocycles.[5b]

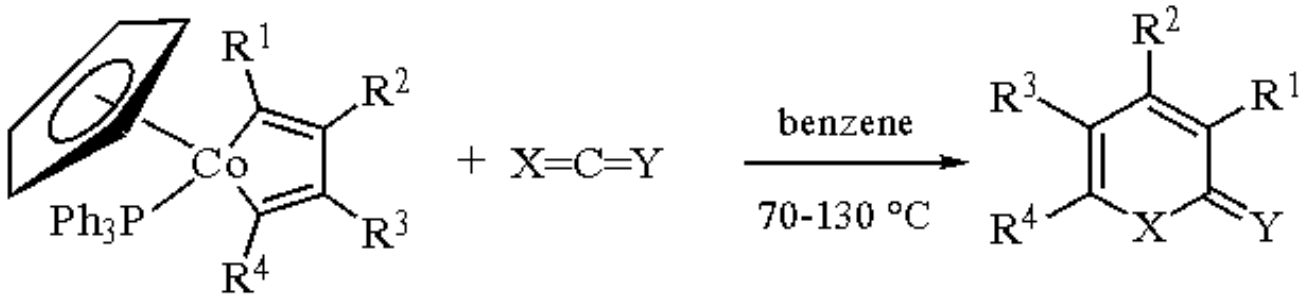

(4) (6) (5)

Table 4 Formation of Heterocycles from Cobaltacyclopentadiene Complexes

Cpd	R^1	R^2	R^3	R^4	X	Y	Yield
(6a)	Ph	Ph	Ph	Ph	S	S	50%
(6b)	Ph	Ph	Ph	Ph	NPh	S	10%
(6c)	Ph	CO_2Me	CO_2Me	Ph	NPh	O	66%
(6d)	Ph	CO_2Me	CO_2Me	Ph	NMe	O	70%
(6e)	Ph	Me	Me	Ph	NPh	O	81%

Thiophenes and selenophenes have also been prepared by replacing the cobalt atom of the metallacycle with either sulfur or selenium.[2c,3b] Pyrroles may also be prepared using nitroso compounds, but the yields are low.[3b]

1,3-Cyclohexadienes or 1,3-cyclohexadiene-cobalt complexes (which render cyclohexadienes in good yield upon treatment with Ce^{IV}) are obtained in fair to good yield by reaction of the cobaltacyclopentadiene complexes with alkenes.[2h,3b,6a] *Cis*-alkenes give mainly the *endo* isomers similar to the Diels-Alder reaction. The catalytic cooligomerization of alkynes and alkenes gives either cyclic or linear products incorporating varying proportions of alkyne and alkene.[6b,6c]

Related Reagents.

(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I); ***Dicarbonyl(cyclopentadienyl)cobalt(I)***.

---

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Cyclopentadienyl(3,5-dimethoxybenzyl)(nitrosyl)(triphenylphosphine)rhenium[1]

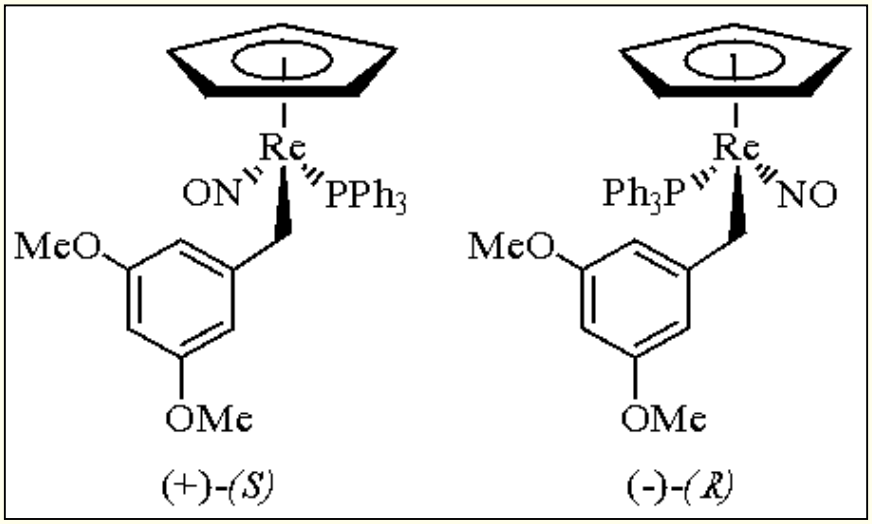

(+)-(*S*)

[109283-17-2] · $C_{32}H_{31}NO_3PRe$ · Cyclopentadienyl(3,5-dimethoxybenzyl)(nitrosyl)(triphenylphosphine)rhenium · (MW 694.78) (-)-(*R*)

[109362-39-2]

(reagents for enantioselective synthesis of organic compounds with chiral methyl groups[1])

Physical Data: mp 204-205 °C; [α]21589 ±116° (CH_2Cl_2, *c* 0.3-0.6 mg cm^{-3}).

Solubility: sol CH_2Cl_2, benzene, ether, and THF; slightly sol hexane.

Form Supplied in: bright orange crystals.

Analysis of Reagent Purity: IR, and ^1H, ^{13}C, and ^{31}P NMR spectroscopies, microanalysis, and polarimetry.[1]

Preparative Methods: reaction of the methyl ester (+)-(*S*)-(Cp)Re(NO)(PPh_3)(CO_2Me) (*S*-**1**)[2] with 3,5-dimethoxyphenylmagnesium iodide in toluene at -24 °C gives 3,5-dimethoxybenzoyl complex (+)-(*S*)-(Cp)Re(NO)(PPh_3)(CO(3,5-$(MeO)_2C_6H_3$)) (*S*-**2**; 85%). Refluxing (+)-(*S*)-(**2**) with BH_3.THF or BD_3.THF in THF gives the title reagents (+)-(*S*)-(**3**) or (+)-(*S*)-(**3**)-α-d_2 (95-84%). The opposite enantiomers (-)-(*R*)-(**3**) or (-)-(*R*)-(**3**)-α-d_2 can be similarly made from (-)-(*R*)-(**1**).[1]

Purification: crystallization from benzene/hexane.

Handling, Storage, and Precautions: the solid reagent is stable for days in air. However, it should be prepared, stored, and reacted under a dry nitrogen atmosphere.

Compounds with chiral methyl groups (RCHDT) play important roles in the elucidation of biological and abiological reaction mechanisms.[3] The title compound can be utilized to prepare chiral 3,5-dimethoxytoluene, which can in turn be degraded to $CHDTCO_2H$. The enantiomeric purity of the latter can be assayed enzymatically.[1] Analogs (Cp)Re(NO)(PPh_3)(CH_2R), which can be similarly synthesized, can usually be converted to the corresponding RCHDT compounds.

Cyclopentadienyl(3,5-dimethoxybenzyl)(nitrosyl)(triphenylphosphine)rhenium

In practice, (+)-(*S*)-(**3**)-α-d_2 and $Ph_3C^+PF_6^-$ are allowed to react to give the alkylidene complex (+)-(*S*)-[(Cp)Re(NO)(PPh_3)(=CD(3,5-$(MeO)_2C_6H_3$)]$^+PF_6^-$ ((+)-(*S*)-(**4t**)-α-d_1; 91%) (eq 1). Addition of $NaBT_4$ gives (+)-(*S,S*)-(**3**)-α-d_1t_1 (87%). Subsequent reaction with HBr gives (+)-(*R*)-(Cp)Re(NO)(PPh_3)(Br) ((+)-(*R*)-(**5**); 93%) and (*R*)-dimethoxytoluene-α-d_1t_1 ((*R*)-(**6**); 85%) with retention of configuration at carbon and rhenium. The latter is treated with O_3 to give, after addition of NaOH, the chiral acetate salt (*S*)-CHDT$CO_2^-Na^+$ in 93% ee. The opposite enantiomer, (*R*)-CHDT$CO_2^-Na^+$, is made from (-)-(*R*)-(**3**)-α-d_2 in 86% ee.[1]

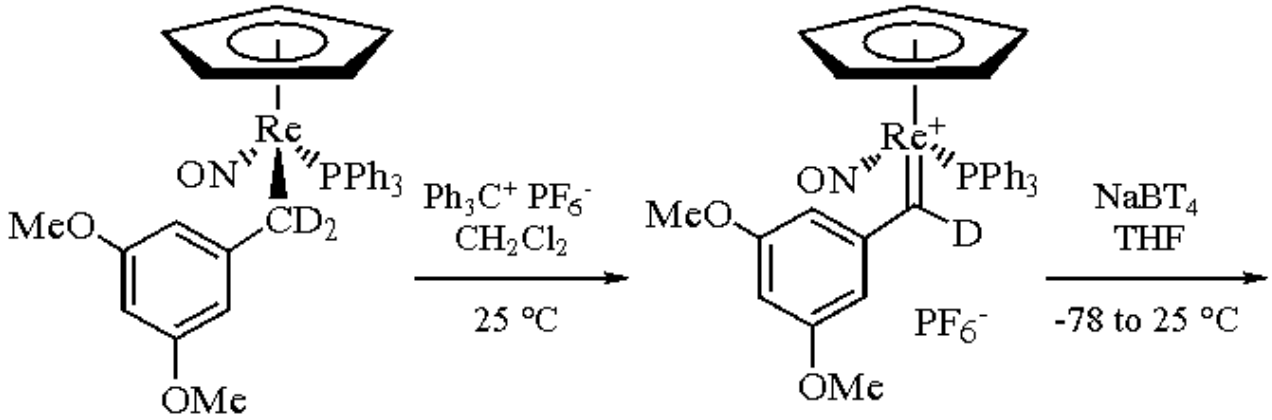

(+)-(*S*)-(**3**)-α-d_2 (+)-(*S*)-(**4t**)-α-d_1

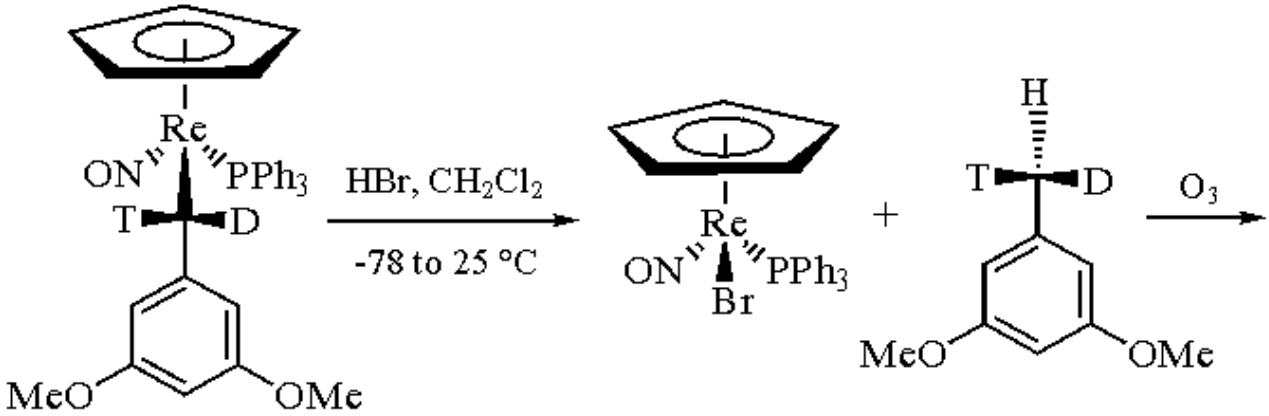

(+)-(*S,S*)-(**3**)-α-d_1t_1 (+)-(*R*)-(**5**) (*R*)-(**6**)

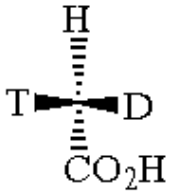

(*R*) (1)

Thus the chiral rhenium auxiliary allows the highly stereoselective introduction of all hydrogen isotopes. The generalization of this methodology to other substrates is shown in eq 2. No complications are encountered for cases where R = *n*-alkyl or aryl. The method fails when R is a secondary alkyl group, as the reaction of (Cp)Re(NO)(PPh_3)($CH_2CHR^1R^2$) and $Ph_3C^+PF_6^-$ gives an alkene complex (β-hydride abstraction).[4]

There are several elements of synthetic flexibility. In most cases, both enantiomers of the target can be generated from the *same* enantiomer of the precursor alkyl complex. For example, the hydrogen isotopes can be introduced in different orders. Alternatively, depending upon reaction temperature, either of the two alkylidene complex Re=C geometric isomers (**7k**) and (**7t**) (eq 2) can be generated in >90% isomeric purity. The hydrogen isotope nucleophile attacks from a direction *anti* to the bulky PPh_3 ligand in each case, giving different diastereomers.[3] These in turn give

different product enantiomers. Finally, if a benzylic rhenium complex is treated with a deuterated or tritiated acid in the rhenium-carbon bond-cleavage step, some aryl C-H bonds are also labeled. The optically active bromide complex (+)-(*R*)-(**5**) can be recycled to the methyl complex (+)-(*S*)-(Cp)Re(NO)(PPh_3)(Me) without racemization.[5] The latter is easily converted to the methyl ester (+)-(*S*)-(**1**),[2] or directly to alkyl complexes.[4]

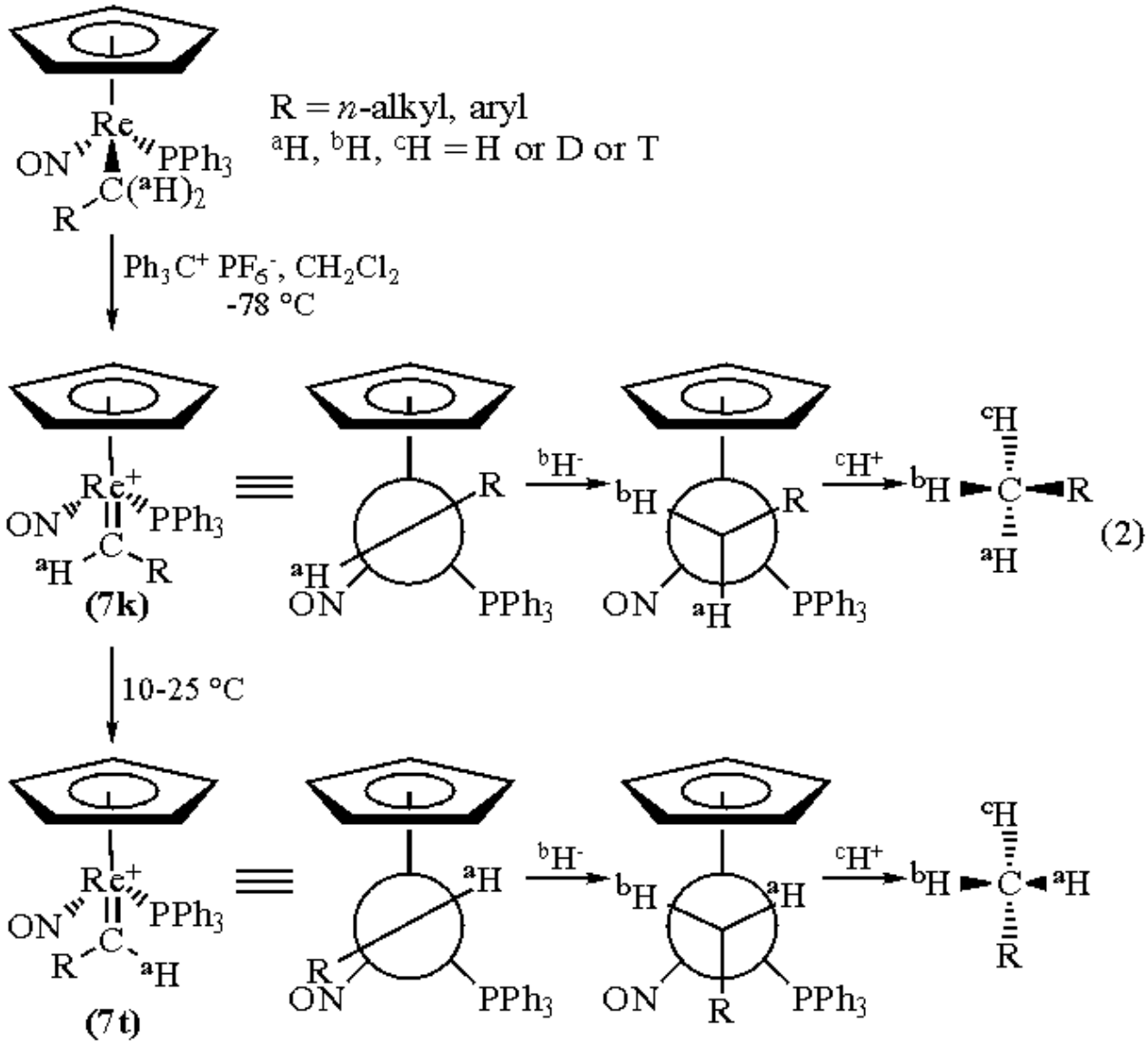

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2. Agbossou, F.; O'Connor, E. J.; Garner, C. M.; Quirós Méndez, N.; Fernández, J. M.; Patton, A. T.; Ramsden, J. A.; Gladysz, J. A. *Inorg. Synth.* **1992**, *29*, 211.
3. Floss, H. G. In *Mechanisms of Enzymatic Reactions: Stereochemistry*; Frey, P. A., Ed.; Elsevier: New York, 1986; pp 71-88.
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5. Ramsden, J. A.; Peng, T.-S.; Gladysz, J. A. *BSF* **1992**, *129*, 625.

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University of Utah, Salt Lake City, UT, USA

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Chloro(cyclopentadienyl)dimethyltitanium[1]

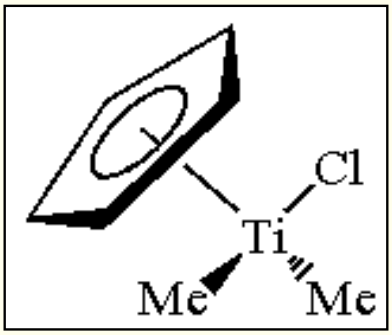

[99279-72-8] · $C_7H_{11}ClTi$ · Chloro(cyclopentadienyl)dimethyltitanium · (MW 178.52)

(heteroannulation agent of alkynylamines;[2] catalyst for metathetic ring-opening of cyclic alkene;[3] thermally stable methylating agent[4])

Physical Data: orange crystals; generally prepared in situ.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 6.48 (Cp) and 1.39 (Me).

Preparative Methods: to a solution of ***Trichloro(cyclopentadienyl)titanium*** (13.7 mmol) in toluene (50 mL) is added slowly (about 10 min) a 2.6M solution of methylmagnesium chloride (1.7 equiv, 23.9 mmol) in THF at rt. The resulting mixture is stirred for 10 min and the precipitate allowed to settle for 1 h. After the solvent is removed in vacuo at 0 °C, the remaining $CpTiMe_2Cl$ is distilled out to a cold trap at -78 °C by warming the flask to room temperature. Yield of $CpTiMe_2Cl$ as orange crystals is 42% based on $CpTiCl_3$. The product is sometimes contaminated with a trace amount of $CpTiMe_3$. This contaminant can be converted to $CpTiMe_2Cl$ by adding the appropriate amount of $CpTiCl_3$ in solution and stirring until equilibration.[4] For the sake of convenience, it is highly recommended that $CpTiMe_2Cl$ be generated in situ by treating $CpTiCl_3$ with 2 equiv of ***Methyllithium*** in THF at -50 °C and stirring the mixture at -50 °C to 0 °C for 1 h.[3]

Handling, Storage, and Precautions: the isolated solid is moisture sensitive and should be stored under an inert atmosphere in a refrigerator.

Heteroannulation.

This reagent generated in situ can be used for the heteroannulation of alkynylamine derivatives through formation of metal-imido complexes (CpTiCl=NR) to give heterocyclic compounds. These reactions are the first examples of intramolecular [2 + 2] cycloaddition involving Group 4 metal-imido complexes (eq 1).[2] It is worth noting that the generation of CpMX=NR complexes from the precursors $CpTiMe_2X$ and H_2NR proceeds rapidly at <=25 °C.

Treatment of the alkynylamine with $CpTiMe_2Cl$ gives the putative azametalletine intermediate with concomitant evolution of methane. Similar intramolecular [2 + 2] reaction can be effected by using catalytic amounts of $CpTiCl_3$[2a,b] and has been applied to the synthesis of an alkaloid.[2b] The intermediate azametalletines can serve as conventional organometallics in electrophilic substitution reactions leading to selective carbon or nitrogen functionalization. Thus the direct trapping of the intermediate with isobutyronitrile followed by protonation with aqueous HCl gives the vinylogous amidine (eq 1).

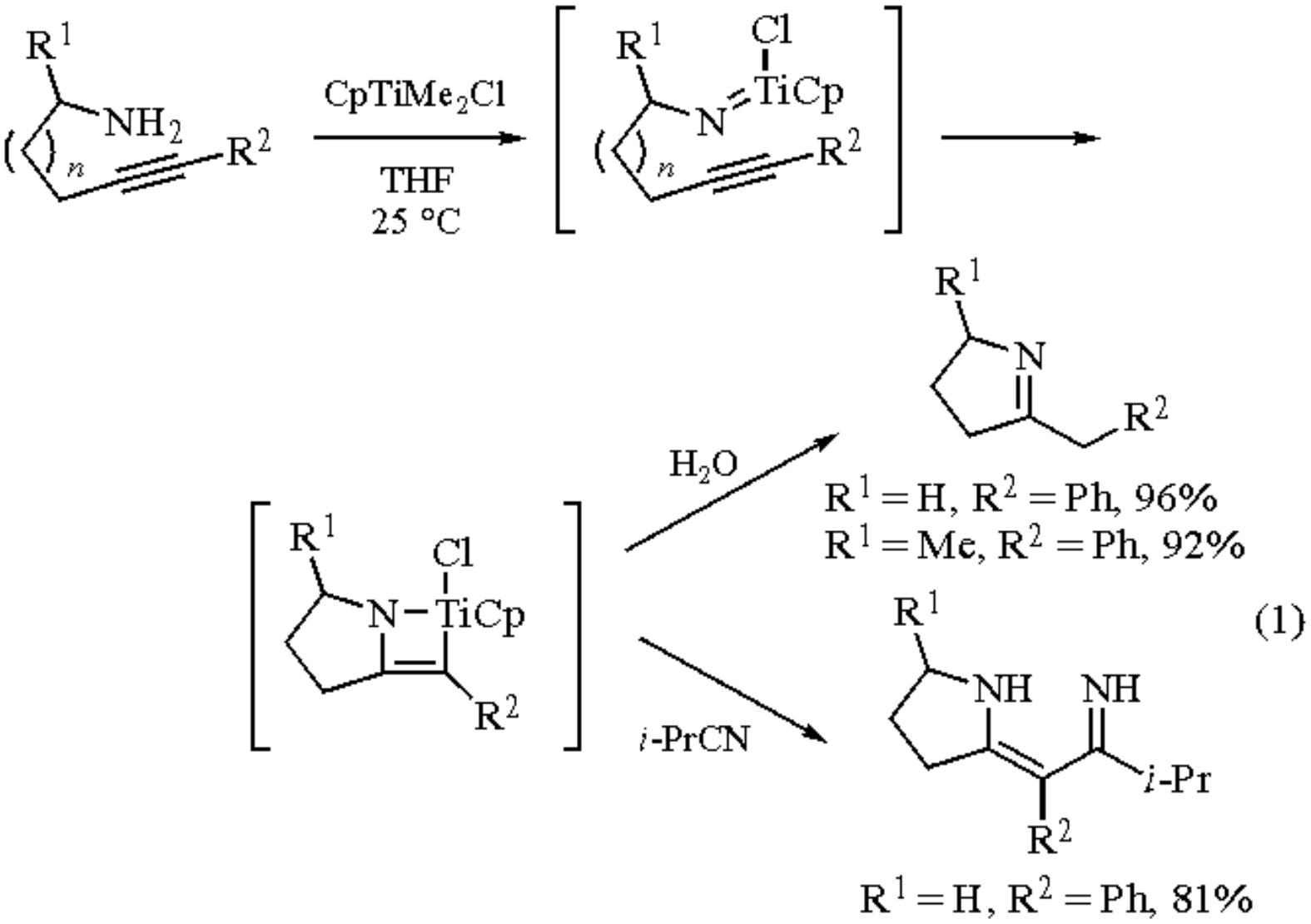

Metathesis Catalyst.

For the ring-opening metathesis polymerization (ROMP) of cyclic alkenes, $CpTiMe_2Cl$ is an effective initiator (eq 2).[3b] It is also found that $CpTiMe_2Cl$ initiates the polymerization at a lower concentration and lower temperature compared to ***Bis(cyclopentadienyl)dimethyltitanium*** (dimethyltitanocene). Furthermore, the use of THF as solvent has no effect on this polymerization initiator while with other zirconium catalysts (Cp_2ZrMe_2, etc.) initiation activities are inhibited by THF. This substituent-dependent solvent effect is attributed to changes in the relative contributions of nucleophilic and neutral resonance structures. For this polymerization it is presumed to involve the in situ generation of free or complexed titanium alkylidene species.

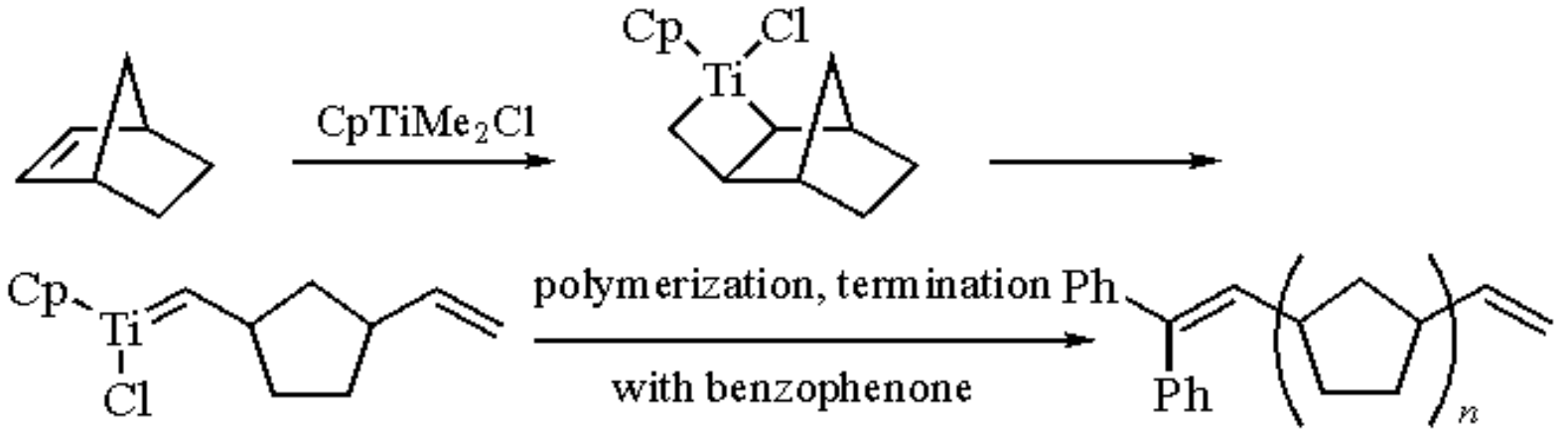

(2)

Alkylation.

Reactions of $CpTiMe_2Cl$ (which possesses significantly greater thermal stability) with carbonyl compounds proceed similarly to other alkyltitanium reagents (eq 3). That is, in the reaction of a 1:1 ratio of $CpTiMe_2Cl$ and acetophenone, the methyl addition product along with a small amount of the *gem*-dimethylated product, *t*-butylbenzene, is obtained.[4]

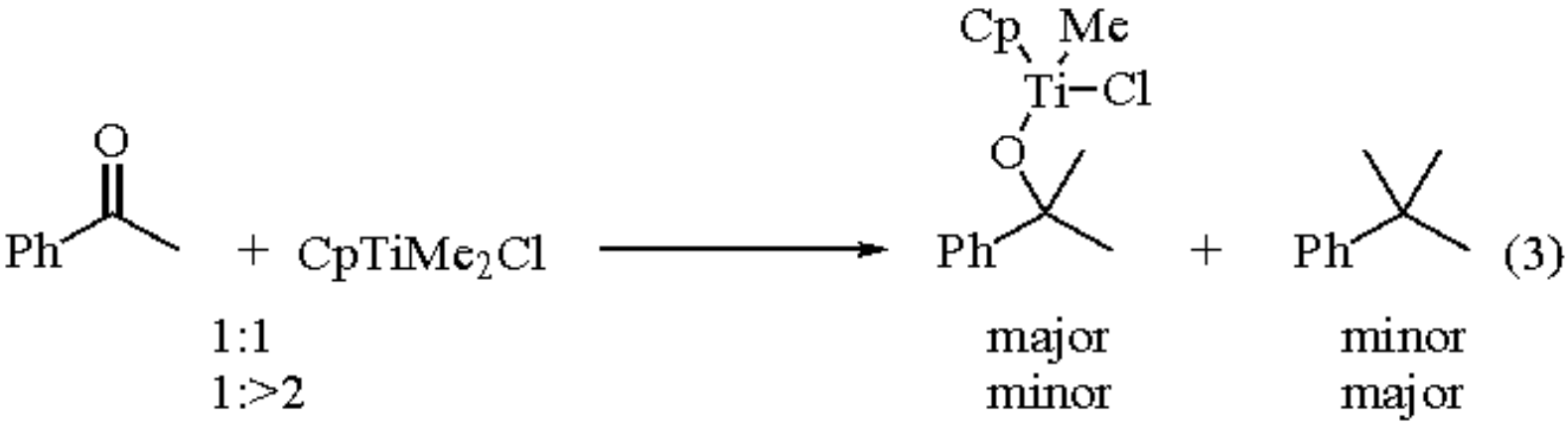

(3)

Related Reagents.

Bis(cyclopentadienyl)bis(2,6-dimethylphenylamino)zirconium; ***Bis(cyclopentadienyl)dimethyltitanium***; ***Trichloro(cyclopentadienyl)titanium***.

---

1. For a review of related titanium complexes, see Bottrill, M.; Gavens, P. D.; McMeeking, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 3, pp 281-329.
2. (a) McGrane, P. L.; Jensen, M.; Livinghouse, T. *JACS* **1992**, *114*, 5459. (b) McGrane, P. L.; Livinghouse, T. *JOC* **1992**, *57*, 1323.
3. (a) Giannini, U.; Cesca, S. *TL* **1960**, 19. (b) Petasis, N. A.; Fu, D.-K. *JACS* **1993**, *115*, 7208.
4. Erskine, G. J.; Hunter, B. K.; McCowan, J. D. *TL* **1985**, *26*, 1371.

1,3-Cyclopentanedione

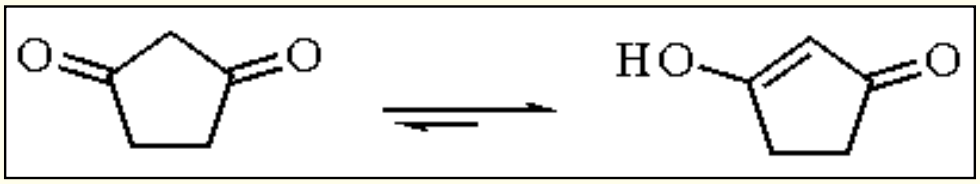

[3859-41-4] · $C_5H_6O_2$ · 1,3-Cyclopentanedione · (MW 98.01)

(building block for the syntheses of cyclic and polycyclic compounds containing the cyclopentane ring)

Physical Data: mp 149-151 °C.

Solubility: sol H_2O (5.5 g/100 g), DMF (20 g/100 g).

Form Supplied in: yellow solid.

Analysis of Reagent Purity: HPLC.

Preparative Methods: the industrial production of 1,3-cyclopentanedione is based on methyl (*E*)-4-chloro-3-methoxy-2-butenoate.[1] Other syntheses are based on norborn-2-ene[2] or D-glucono-1,5-lactone.[3] Further methods for the laboratory preparation have been reviewed.[4]

Handling, Storage, and Precautions: stable; this compound should be handled in a fume hood.

1,3-Cyclopentanedione has found widespread synthetic applications. These include syntheses of prostaglandins,[5] antibiotics,[6] herbicides,[9] and other biologically active compounds.[7,8,10,11] The synthesis of these compounds required controlled alkylation and selective functionalization of 1,3-cyclopentanediones.

There are three possible alkylation sites of the cyclopentanedione enolate, C-2, C-4, and O. Control of the alkylation site can be achieved by proper selection of reaction conditions, in particular the counter-ion (eq 1).[12-14]

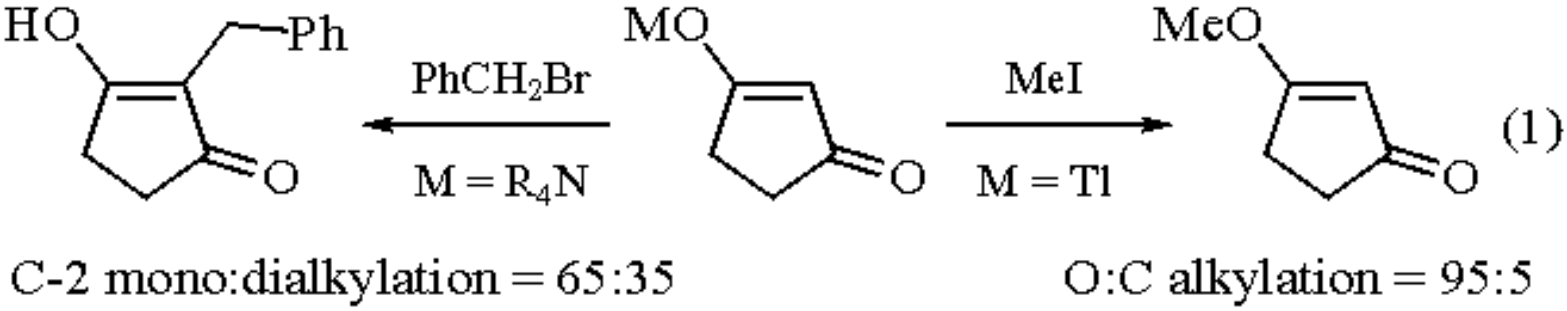

C-2 alkylation is also favored when the *O*-alkylation is reversible, e.g. with Michael acceptors[15] or in the Mannich reaction. In the Pd-catalyzed allylation with allyl acetate, the reaction proceeds further to give 2,2-diallylated product.[16]

Selective alkylation in the C-4 position is achieved by forming the dianion using a strong base,[17] ***n-Butyllithium*** (eq 2).[18]

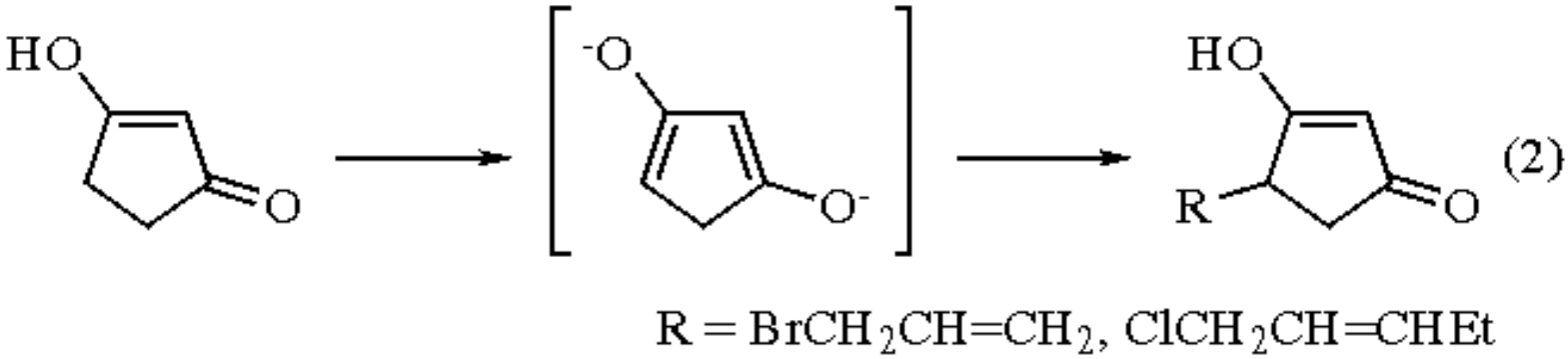

Most common halogenating agents (***Phosphorus(III) Chloride***, ***Oxalyl Chloride***, ***Phosphorus(III) Bromide***)[19-22] give the 3-halo derivative, but the use of ***N-Bromosuccinimide*** in MeOH allows selective 2-bromination (eq 3).[23]

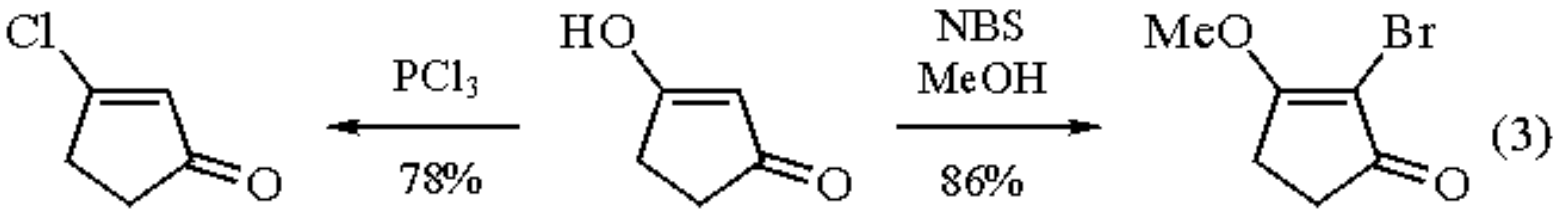

Condensation with amines allows access to key intermediates in 8-aza steroid syntheses (eq 4).[24]

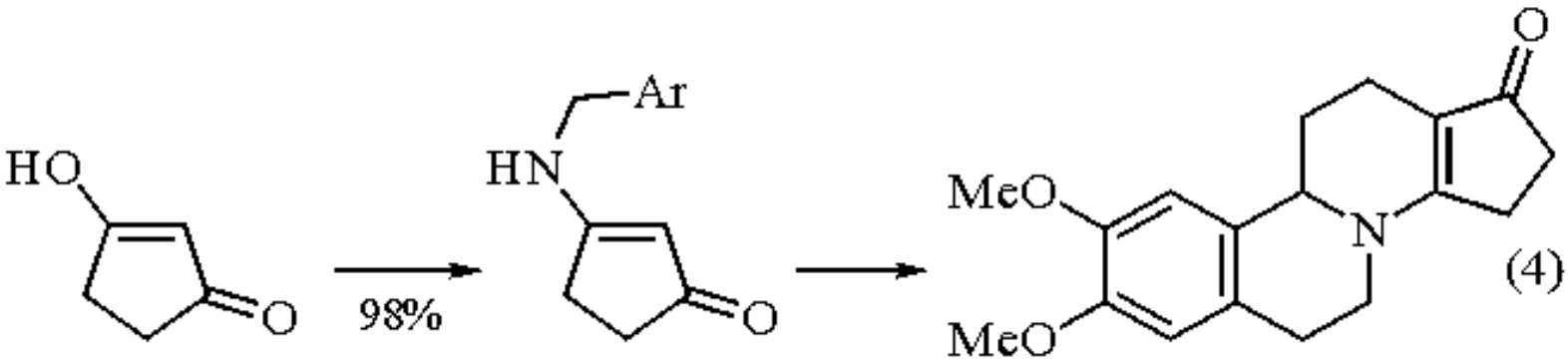

Related Reagents.

1,3-Cyclohexanedione; ***2-Methyl-1,3-cyclopentanedione***; ***2,4-Pentanedione***.

1. Fuchs, R.; McGarrity, J. F. *S* **1992**, 373.
2. Lick, C.; Schank, K. *CB* **1978**, *111*, 2461.
3. Tajima, K. *CL* **1987**, 1319.
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Rudolf Fuchs

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Cyclopropanone[1]

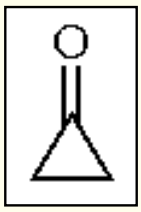

[5009-27-8] · C_3H_4O · Cyclopropanone · (MW 56.06)

(very reactive three-carbon building block;[1] synthesis of geminally functionalized cyclopropanes[1] and methylenecyclopropanes; ring expansion to β-lactams;[2,3] ring opening to propionic acid derivatives)

Solubility: sol ether, dichloromethane; nucleophilic solvents, e.g. alcohols and water, afford the corresponding adducts (e.g. hemiacetals, hydrates).

Form Supplied in: not commercially available; prepared at low temperature (-50 to -78 °C) in solution (see below) and preferably used directly for further elaboration.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: special apparatus is required to perform the reaction of ketene with diazomethane (eq 1).[4] A solution of ***Diazomethane*** in diethyl ether is added to a solution of ***Ketene*** in dichloromethane at -78 °C at such a rate that the temperature does not rise above -60 °C. The reaction mixture is kept at -50 °C for 35 min. The reaction mixture thus obtained is a solution of cyclopropanone in dichloromethane/diethyl ether (yield 75%). This solution is suitable for further elaboration, viz. addition of nucleophiles. As an example, the addition of glacial acetic acid (1.04 equiv) in dichloromethane, at -50 °C, to the solution of cyclopropanone affords, after evaporation of the solvents at 0 °C, a residual liquid which is distilled in vacuo to give 1-acetoxycyclopropanol (bp 26-28 °C/0.5 mmHg) (eq 2) as a storable source of cyclopropanone.[2]

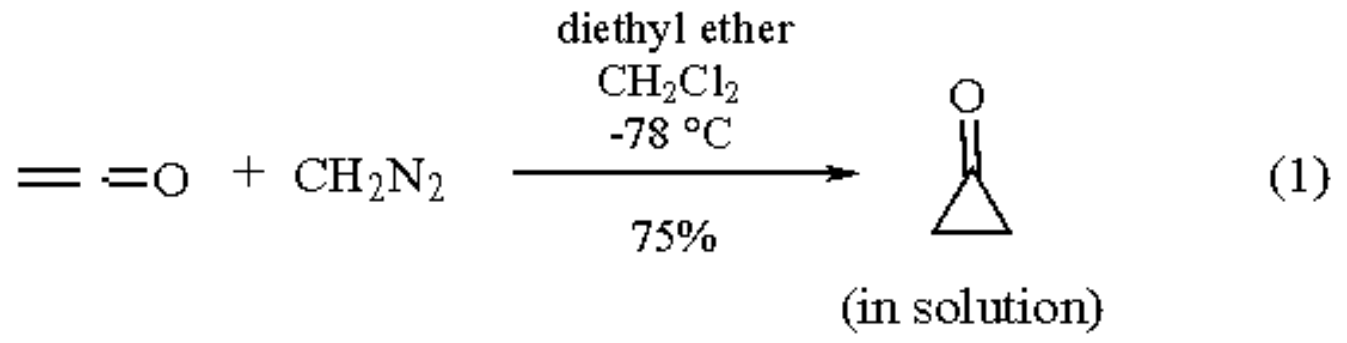

(1)

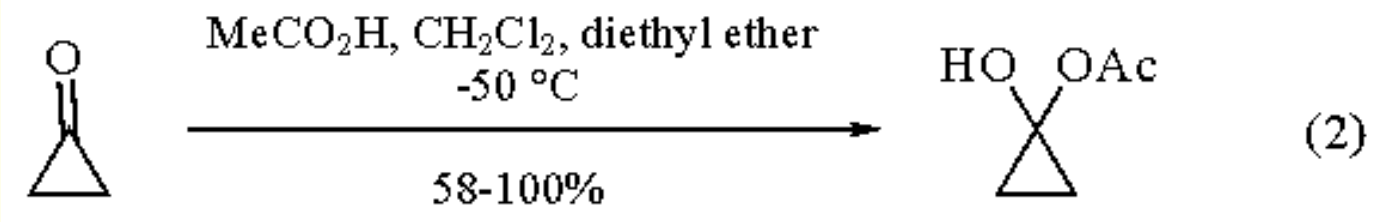

Handling, Storage, and Precautions: in situ preparation in solution at -78 °C as above, using dry solvents (inert atmosphere); the presence of any nucleophilic reagent is incompatible with this preparation; the storage lifetime of the solution of cyclopropanone at -78 °C is very limited as polymerization occurs under the influence of traces of water;[5] inhibition of polymerization occurs with moisture scavengers.[6] This reagent should be handled in a fume hood.

Adduct Formation.

The majority of reactions performed with cyclopropanones originate from the use of cyclopropanone adducts which are in equilibrium with cyclopropanone (eq 3). Such adducts include ***1-Ethoxycyclopropanol*** (**1**)[7] and 1-acetoxycyclopropanol (**2**)[8] (eq 4). Also the magnesium salt of (**1**), i.e. adduct (**3**),[9] and 1-piperidino-1-trimethylsilyloxycyclopropane (**4**) and its free alcohol (**5**)[10,11] have been reported as cyclopropanone sources.

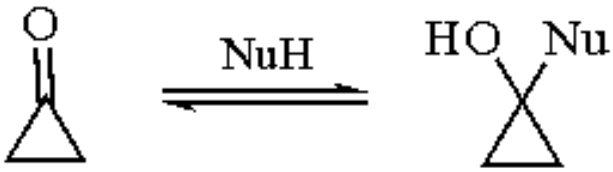

(3)

Nu = nucleophile

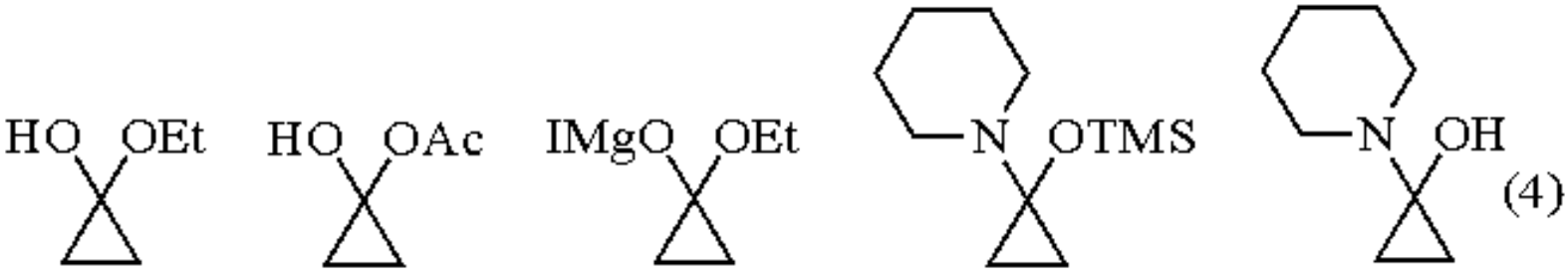

(4)

(1) **(2)** **(3)** **(4)** **(5)**

Addition of water,[1] methanol,[1] ethanol,[1] acetic acid,[4,6,8] hydrogen chloride,[6] and hydrogen cyanide[12] to in situ prepared cyclopropanone affords the corresponding hydrate (eq 5), hemiacetal (eq 6), hemiacylal (eq 2), chlorohydrate (eq 7), and cyanohydrin (eq 8), respectively.

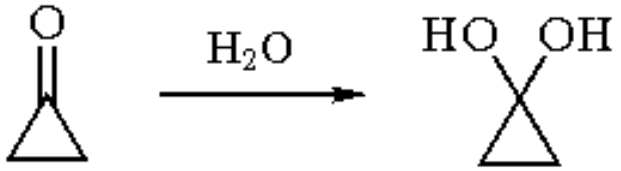

(5)

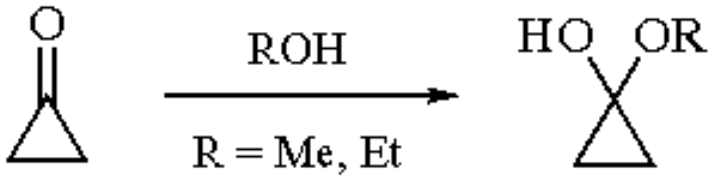

(6)

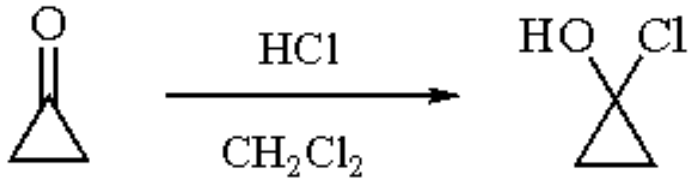

(7)

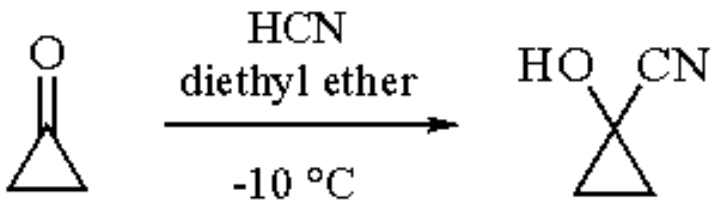

(8)

The addition of amines to cyclopropanone is more complex and is dependent upon the type of amine and the number of molar equivalents of the amine used. The reaction of cyclopropanone with 0.5 equiv ammonia afforded the bis(cyclopropyl)amine derivative as the major product, in addition to the tris(cyclopropyl)amine derivative as a minor product (eq 9).[4] Monoadducts with primary amines were obtained at -78 °C (eq 10),[13] while the same reaction at -30 °C with methylamine produced the bis(cyclopropyl) derivative, which cyclocondensed with cyclopropanone hydrate to form tris-spiro adducts (eq 11).[13] Aniline reacted with cyclopropanone to give mono- and bisadducts,[13] while ***N,N-Dimethylhydrazine*** at elevated temperature afforded the monoadduct which could be dehydrated to cyclopropanone *N*,*N*-dimethylhydrazone (eq 12).[14] Secondary amines,[15,16] such as dimethylamine, produced cyclopropanone monoadducts provided that an inverse addition of cyclopropanone was performed (eq 13).[4] Further addition of the secondary amine produced the corresponding aminals.[15,16]

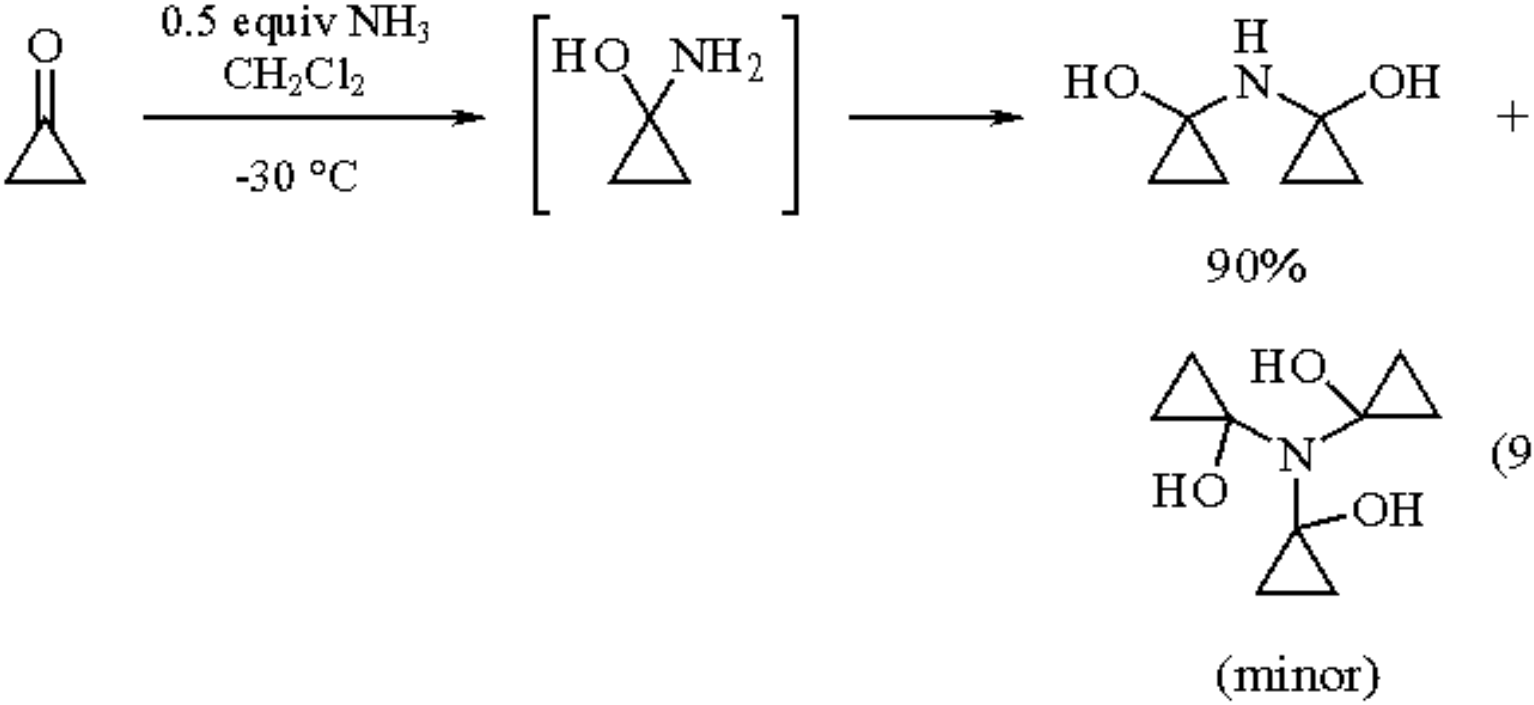
0.5 equiv NH3
CH2Cl2
-30 °C
HO NH2
H
HO N OH
+
90%
HO
N
HO
OH
(minor)

(9)

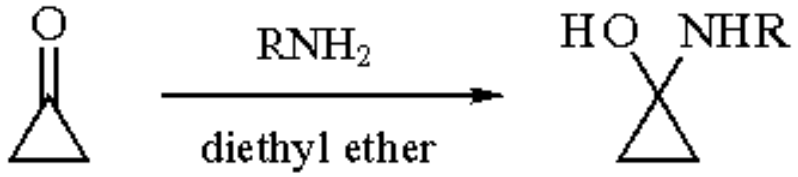
RNH2
diethyl ether
HO NHR

(10)

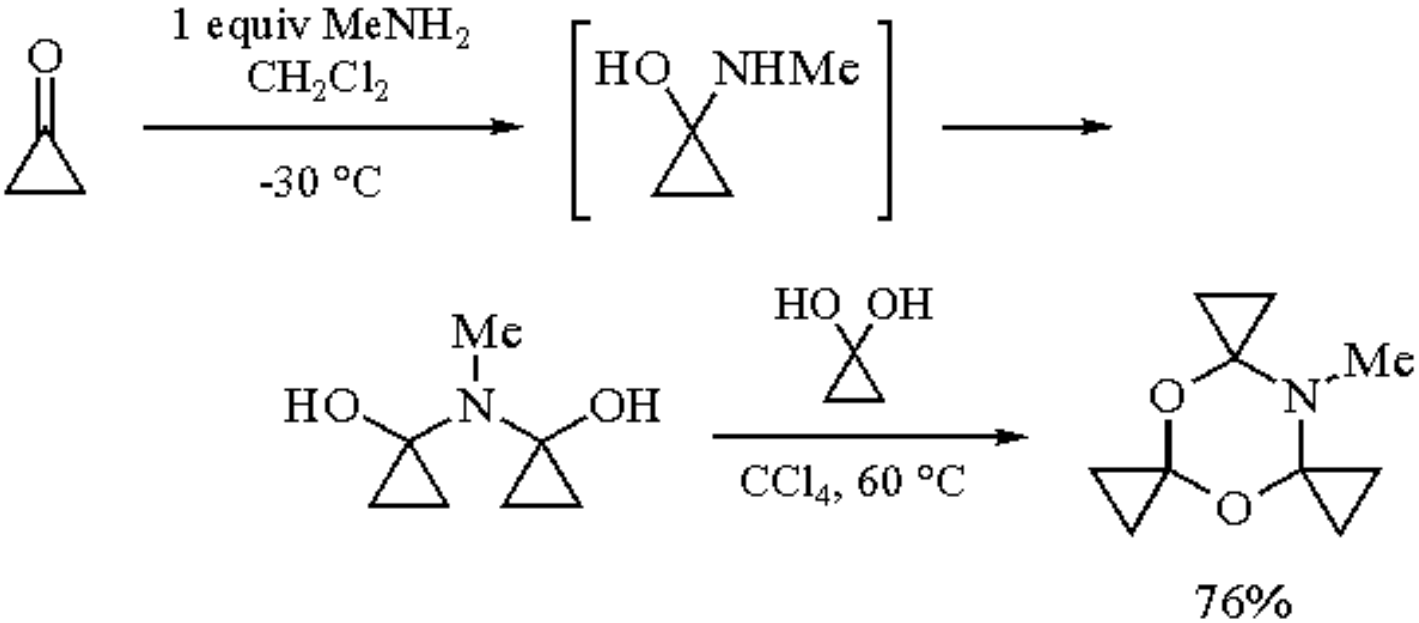
1 equiv MeNH2
CH2Cl2
-30 °C
HO NHMe
Me
HO N OH
HO OH
CCl4, 60 °C
O
N Me
O
76%

(11)

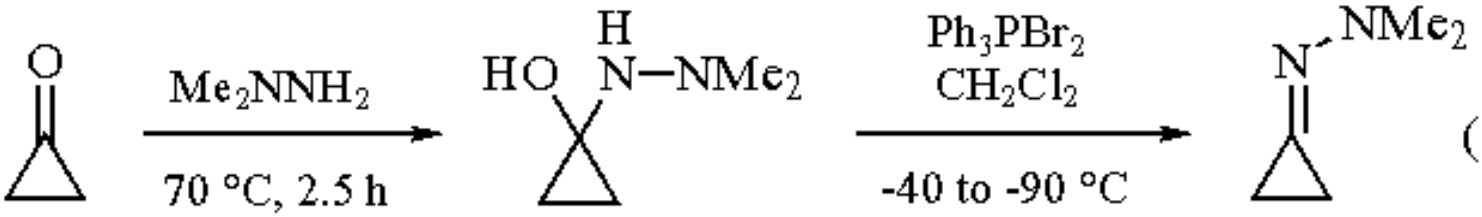
Me2NNH2
70 °C, 2.5 h
H
HO N—NMe2
Ph3PBr2
CH2Cl2
-40 to -90 °C
N NMe2

(12)

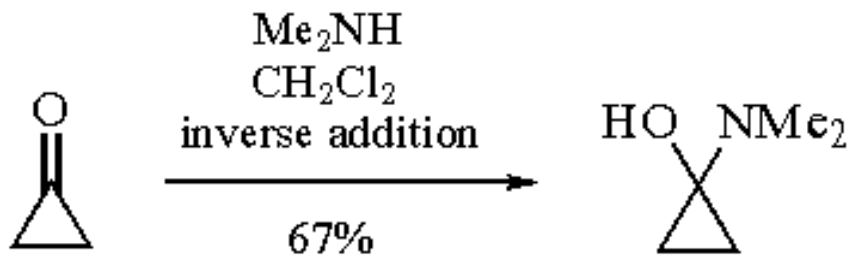

(13)

Sulfur nucleophiles, such as hydrogen sulfide, behave like amines in that they afford bis(cyclopropyl) sulfides which serve as a source of methylenethiirane via flash pyrolysis of a bis-spiro carbonate (eq 14).[17] Thiols added smoothly to cyclopropanone to give the monoadducts (eq 15).[18]

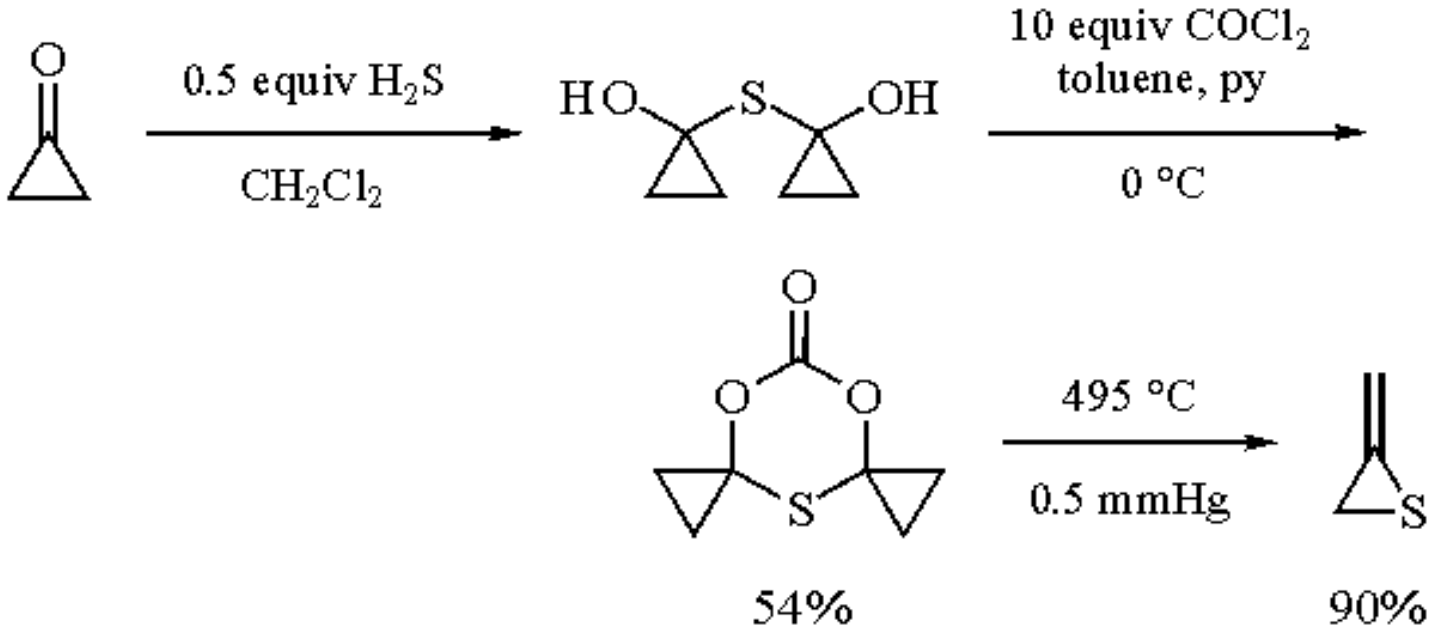

(14)

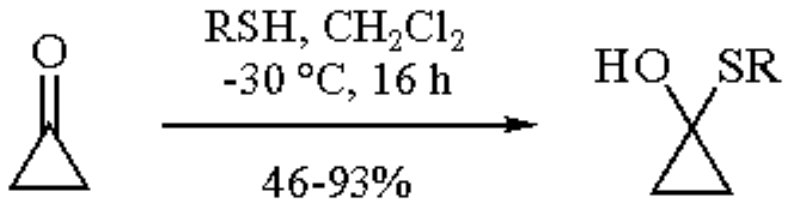

(15)

R = Me, *t*-Bu, CH_2Ph, CH_2CH_2Ph, Ph

Synthesis of β-Lactams.

Sodium Azide in acetone converted cyclopropanone into 1-azidocyclopropanol, which suffered spontaneous rearrangement to azetidin-2-one in variable yields (eq 16).[19,20] A similar rearrangement is observed with the cyclopropanone adduct of *N*-*t*-butyl-*O*-benzoylhydroxylamine to form 1-*t*-butylazetidin-2-one (eq 17).[2] A more general approach to 1-substituted azetidin-2-ones consisted of the addition of primary amines to cyclopropanone at -78 °C, resulting in the monoadducts which were *N*-chlorinated using ***t-Butyl Hypochlorite*** and subsequently rearranged under the influence of ***Silver(I) Nitrate*** to give the ring expanded azetidine derivatives (eq 18).[2] Aliphatic

as well as α-amino carboxylic esters have been converted in this way into a wide range of azetidin-2-ones.[2,21-23]

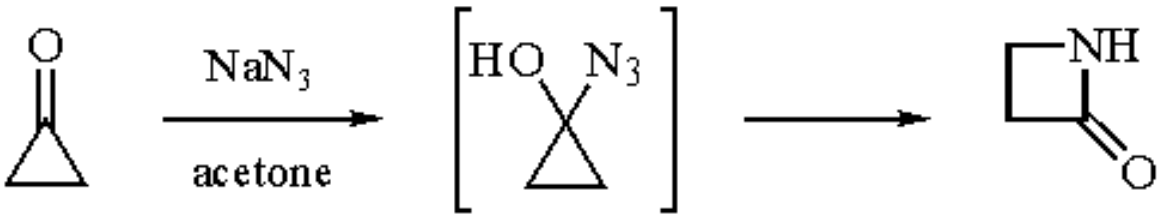

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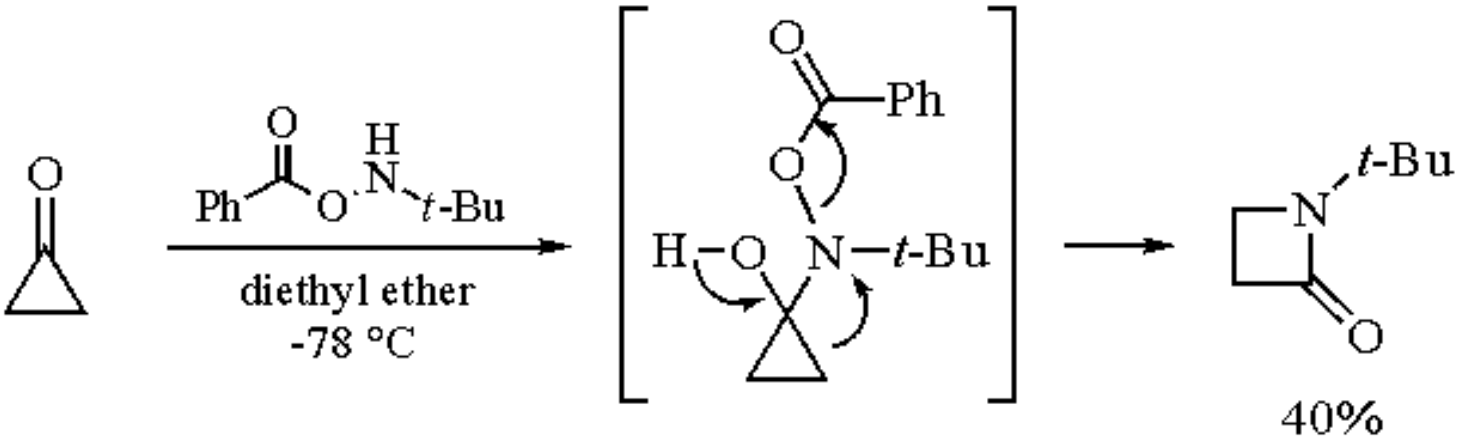

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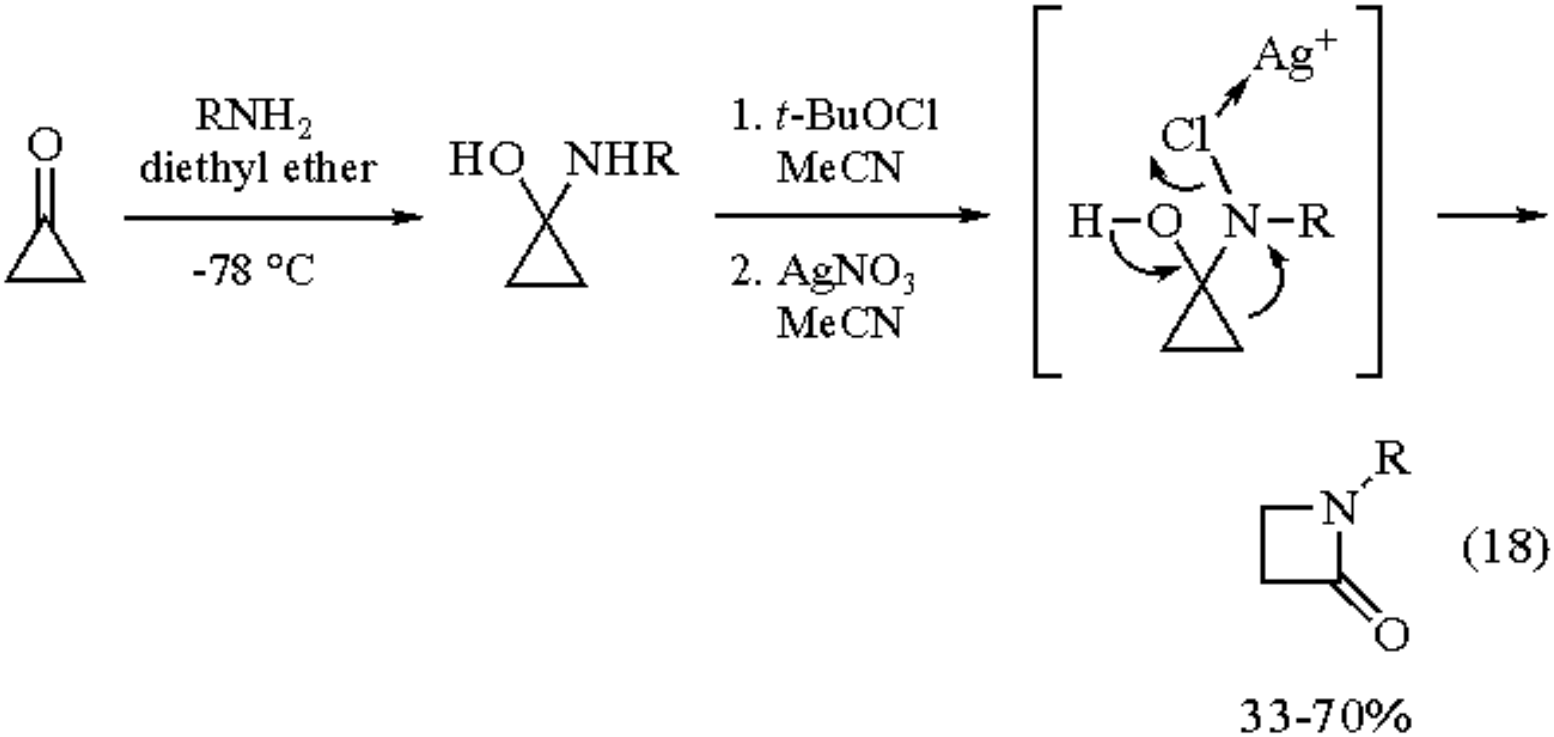

(18)

Addition of Carbon Nucleophiles.

The addition of carbon nucleophiles to cyclopropanone may be accomplished by reactions with 1-ethoxycyclopropanol (**1**)[7,19,20,24-26] or its magnesium salt (**3**).[27] Organolithium[9,27-29] as well as organomagnesium reagents[7,19,20,24-26] add across the carbonyl function of cyclopropanone to afford the corresponding cyclopropanols (eq 19). Moderate yields of alkylidenecyclopropanes are obtained by condensation of the cyclopropanone precursors

with alkylidenephosphoranes (eqs 20,21).[27,30]

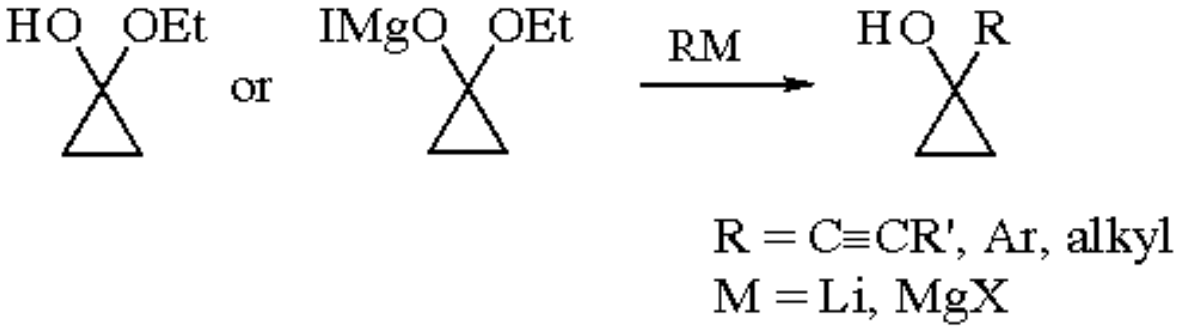

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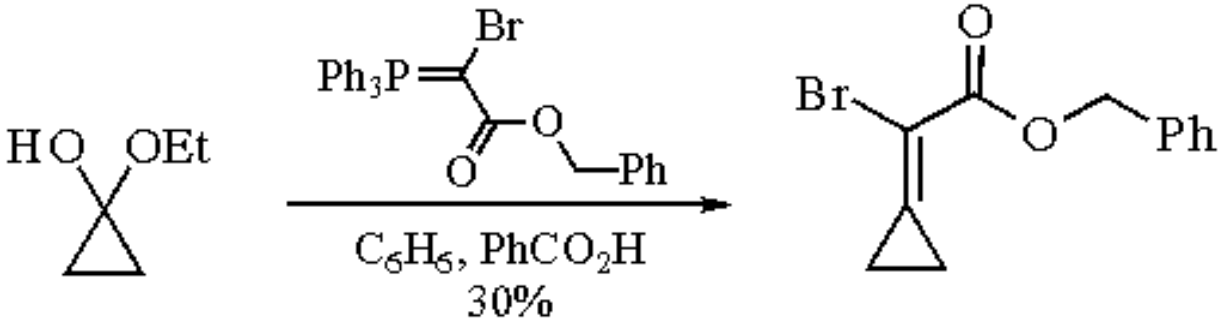

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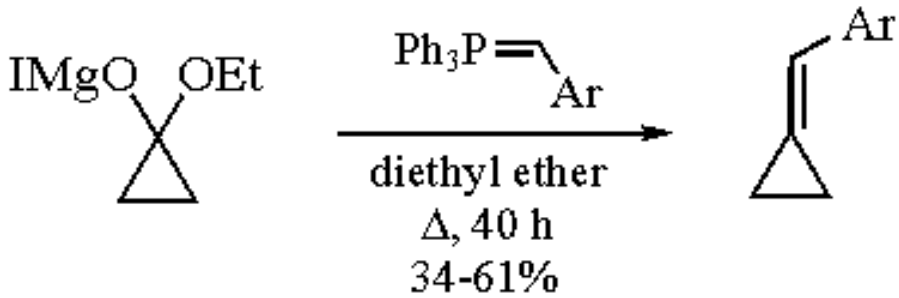

(21)

Ring Opening.

Addition of alcohols to cyclopropanone gives hemiacetals which are opened in a Favorskii-like way to afford propionates (eq 22).[27]

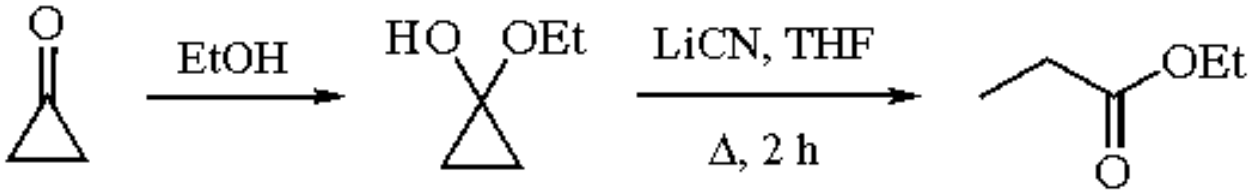

(22)

Polymerization.

Polymerization of a solution of cyclopropanone takes place at temperatures above 0 °C and is initiated by traces of water (eq 23).[1,5,34] The same polymers are obtained by thermolysis.[35]

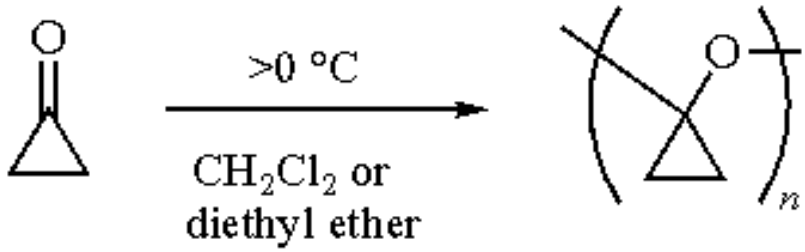

(23)

Natural Product Synthesis.

The cyanohydrin of cyclopropanone was converted into cleonine (**6**) by a sequence of reactions involving protection of the alcohol, aldehyde formation, and Strecker reaction of the latter to give the α-amino acid cleonine (eq 24).[31] The ammonia monoadduct of cyclopropanone is stable as its hydrochloride salt, which is further elaborated to coprine (**7**) (eq 25).[32,33]

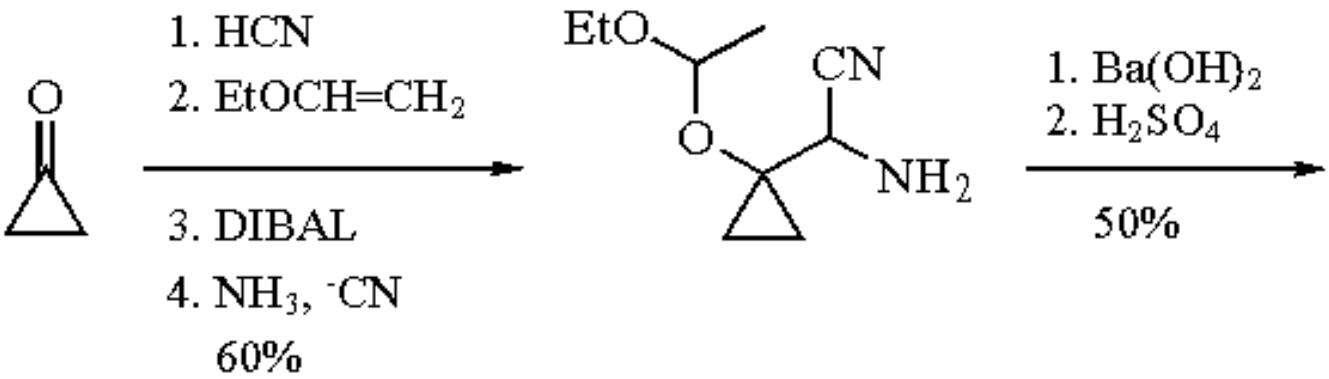

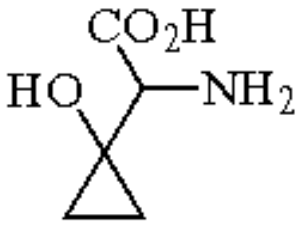

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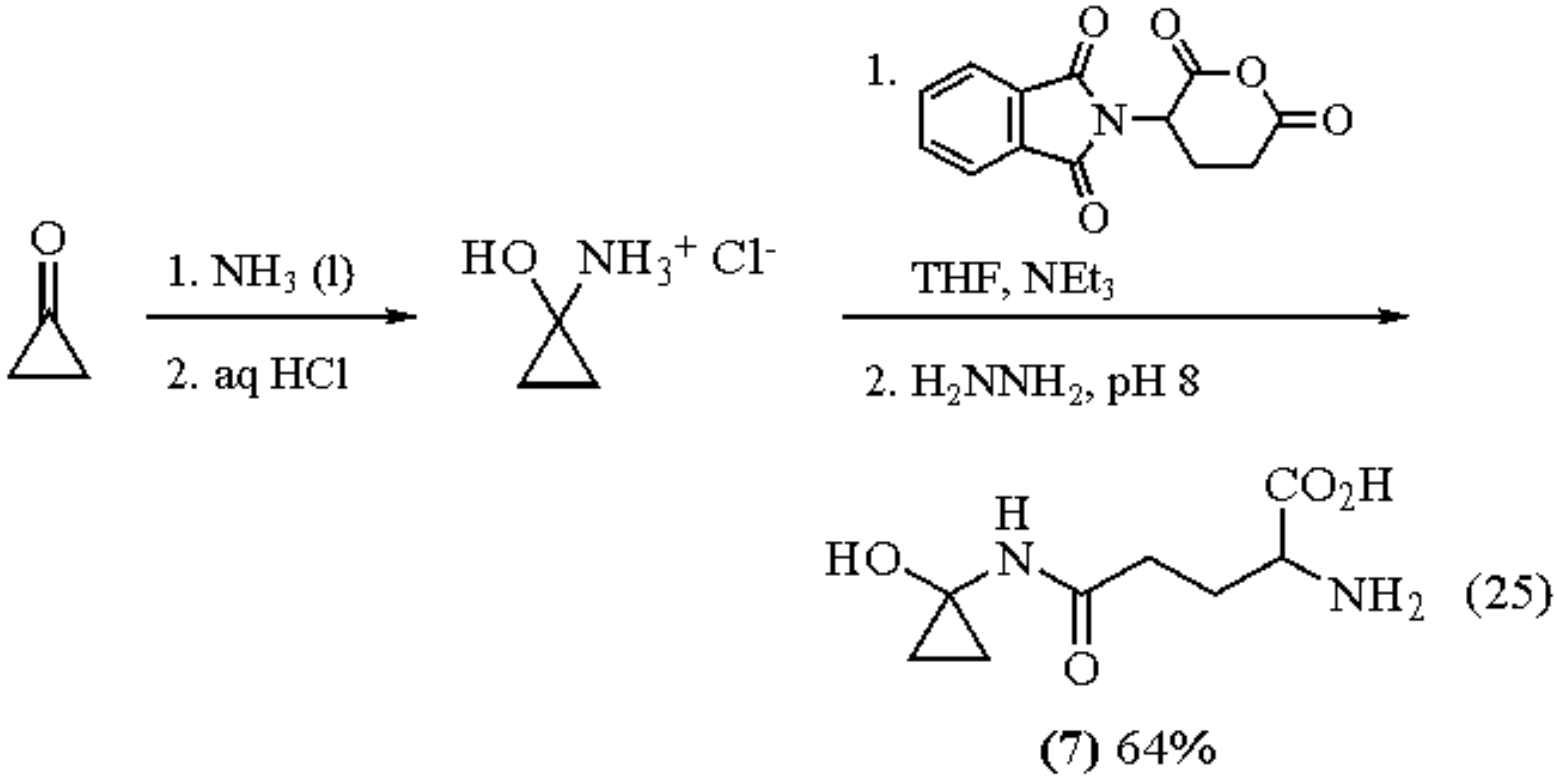

Related Reagents.

Cyclobutanone; ***Cyclopropenone 1,3-Propanediyl Acetal***; ***6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione***; ***1-Ethoxycyclopropanol***; ***Methylenecyclopropane***; ***1-(Tetrahydropyranyloxy)cyclopropanecarbaldehyde***.

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Norbert De Kimpe

University of Gent, Belgium

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Cyclopropenone 1,3-Propanediyl Acetal[1]

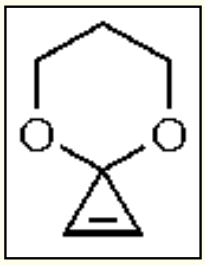

[60935-21-9] · $C_6H_8O_2$ · Cyclopropenone 1,3-Propanediyl Acetal · (MW 112.12)

(cyclopropenone synthesis;[4] vinylcarbene formation;[1] acceptor of organometallic reagents;[13] dienophile[15])

Physical Data: bp 30-35 °C/1.25 mmHg.

Solubility: insol H_2O.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: GLC, NMR.

Preparative Methods: the best current preparation of cyclopropenone acetals involves the reaction of 1,3-dichloroacetone 1,3-propanediyl acetal with ***Sodium Amide*** in a liq. NH_3/Et_2O mixture.[2] The latter acetal can be prepared in high yield from commercially available 1,3-dichloroacetone and 1,3-propanediol. This method is superior to the previous method which employs the less convenient reagents KNH_2 and 1-chloro-3-bromoacetone 1,3-propanediyl acetal.[3]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: cyclopropenone acetals may be stored in a refrigerator.

Cyclopropenone Synthesis.

Alkyl-, aryl-, and vinyl-substituted cyclopropenones have been prepared by the reaction of a metalated cyclopropenone acetal with an electrophile followed by acid hydrolysis of the acetal.[4] Deprotonation of the vinylic proton of the cyclopropenone acetal with ***n-Butyllithium*** or ***Sodium Amide*** afforded the lithium or sodium salt of the cyclopropenone acetals. The lithium salt is treated with 0.5 equiv of ***Zinc Chloride*** to obtain the corresponding zinc salt. The sodium and lithium salts are useful for the synthesis of alkyl- and hydroxymethyl-substituted cyclopropenone acetals by their reaction with an alkyl halide or a carbonyl compound, respectively. Acid hydrolysis of the acetal affords the corresponding cyclopropenone in good yield (eq 1). This reaction is effective for the synthesis of biologically active

cyclopropenones, e.g. penitricin (R^1, R^2 = H) and its congeners.[5]

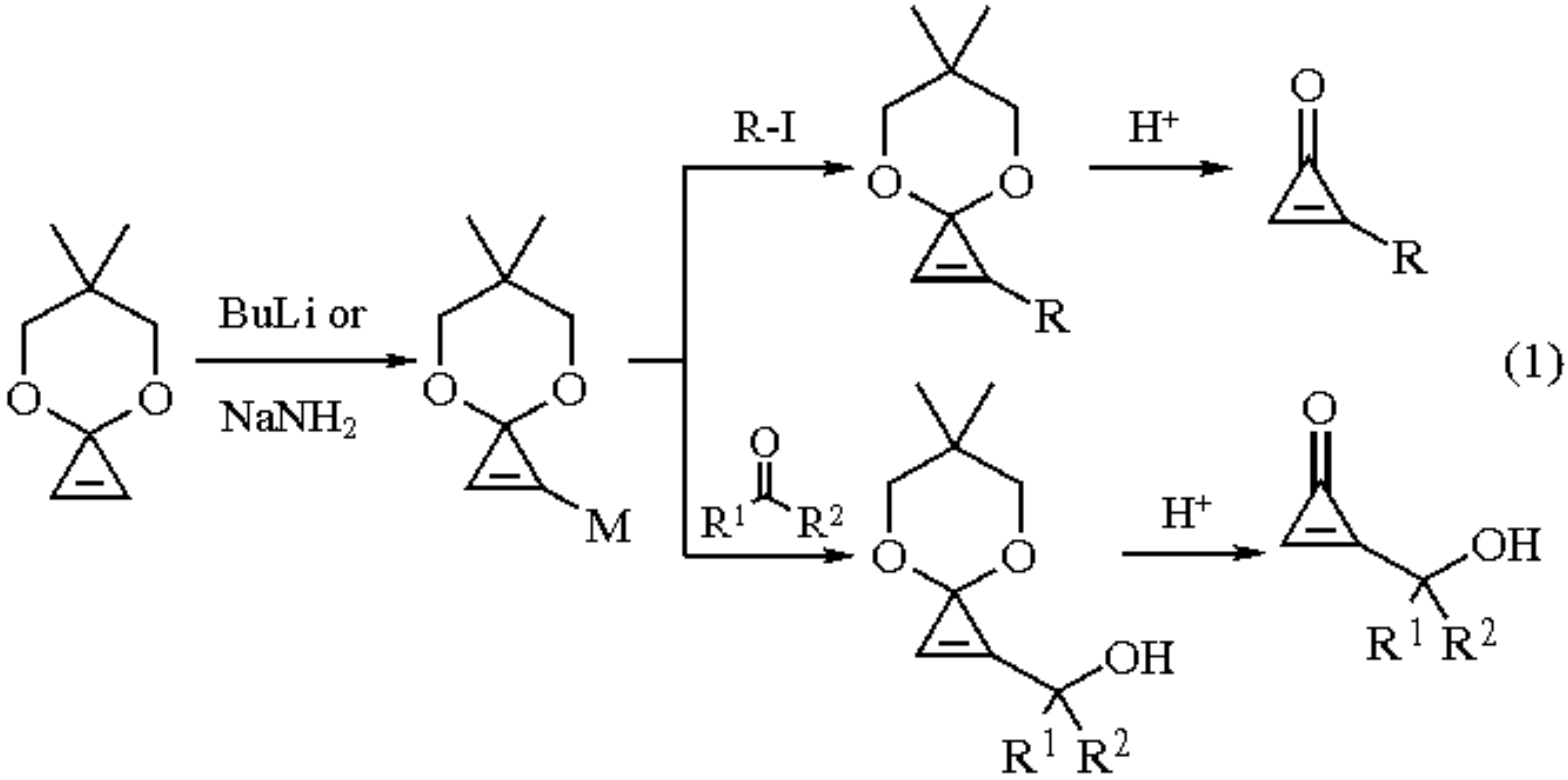

(1)

The zinc salt of cyclopropenone acetal is useful for the synthesis of vinyl- and aryl-substituted cyclopropenones. Thus the reaction of the zinc salt with vinyl iodide, vinyl triflate, and aryl iodide in the presence of a catalytic amount of ***Tetrakis(triphenylphosphine)palladium(0)*** affords vinyl- and aryl-substituted cyclopropenones after acid hydrolysis (eq 2).

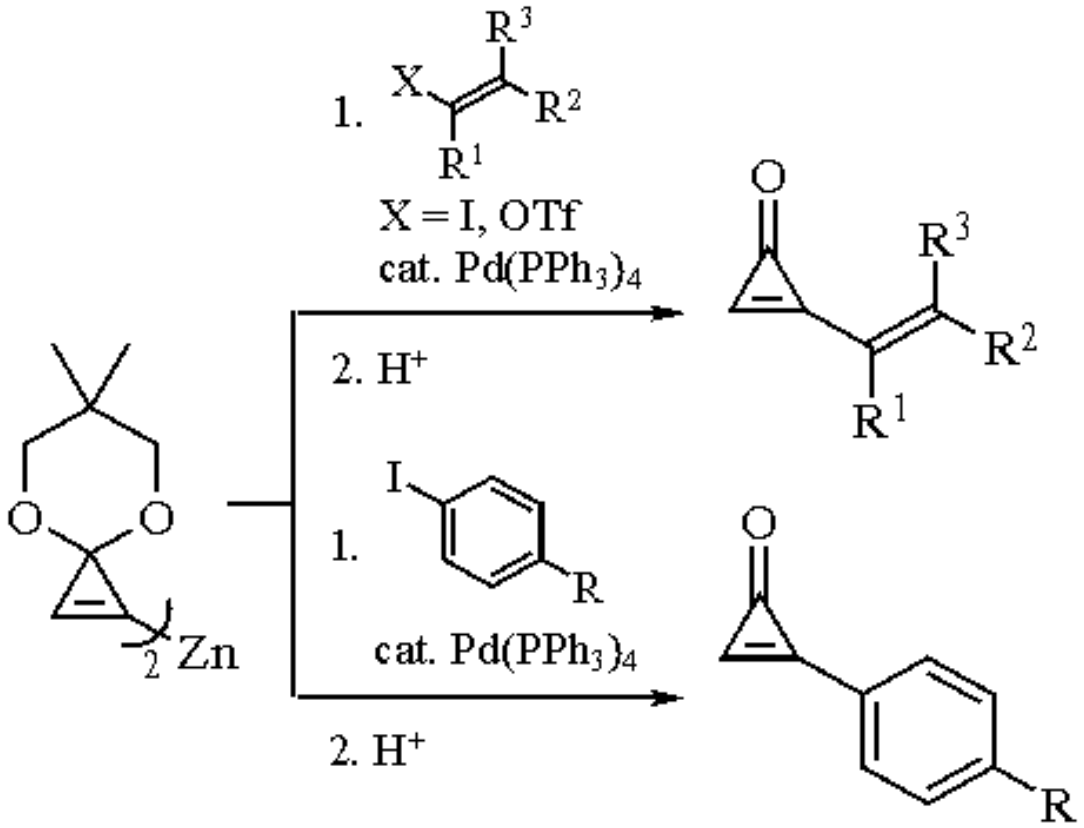

(2)

Disubstituted cyclopropenone acetals are synthesized by repetition of the metalation/alkylation sequence on a monosubstituted cyclopropenone acetal.

Vinylcarbene Precursors.

Thermolysis of cyclopropenone acetal generates a singlet vinylcarbene, which undergoes [2 + 1] and [3 + 2] cycloaddition reactions with electron deficient alkenes. The vinylcarbene, which is generated from the cyclopropenone acetal at 70-120 °C, reacts with an alkene bearing a single electron-withdrawing group in a [2 + 1] manner to afford the cyclopropane derivative.[6] The reaction takes place through an *endo* transition state, and gives predominantly 1,2-*cis*-substituted cyclopropanes (eq 3). The ketene acetal of the product can be easily hydrolyzed to the corresponding ester with aqueous acid. On the contrary, the reaction of cyclopropenone acetal with an alkene bearing geminal electron-withdrawing groups affords exclusively the cyclopentenone acetal derivative by a single-electron transfer pathway (eq 3).[7]

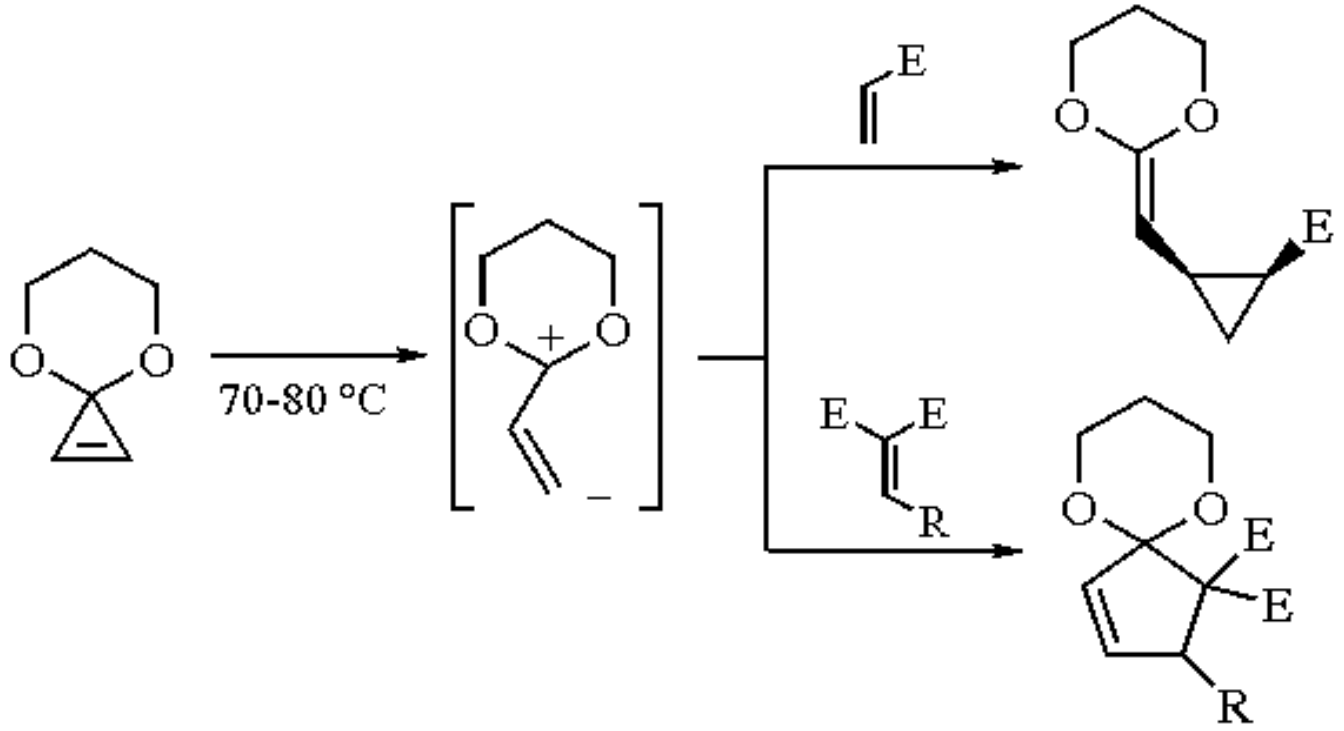

(3)

In contrast to the thermal reaction, Ni^0-catalyzed [1 + 2] cycloaddition of the cyclopropenone dimethyl acetal with methyl acrylate mainly gives thermodynamically stable 1,2-*trans*-disubstituted cyclopropane derivatives.[8] The reaction of the cyclopropenone dimethyl acetal with dimethyl fumarate or maleate in the presence of a catalytic amount of ***Bis(1,5-cyclooctadiene)nickel(0)*** affords *trans*-cyclopropane derivatives with respect to the ester groups (eq 4). The loss of the stereospecificity of this reaction is due to a stepwise cycloaddition of a nickel vinylcarbene complex with an alkane.

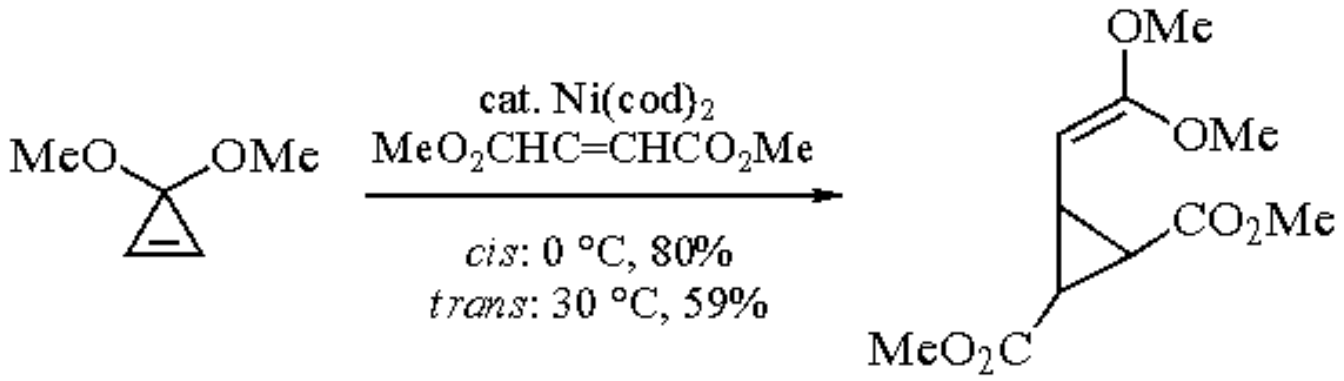

(4)

Treatment of Eschenmoser's α-pyrone with the cyclopropenone acetal at 75 °C afforded the [4 + 3] cycloaddition compound as a single product, which is an important synthetic precursor of colchicine (eq 5).[9] Participation of the cyclopropenone acetal in a competing [4 + 2] Diels-Alder reaction with the α-pyrone is decelerated by unfavorable steric interactions of the acetal group that hinder the *exo* as well as the *endo* transition state required for the [4 + 2] cycloaddition reaction (see below).

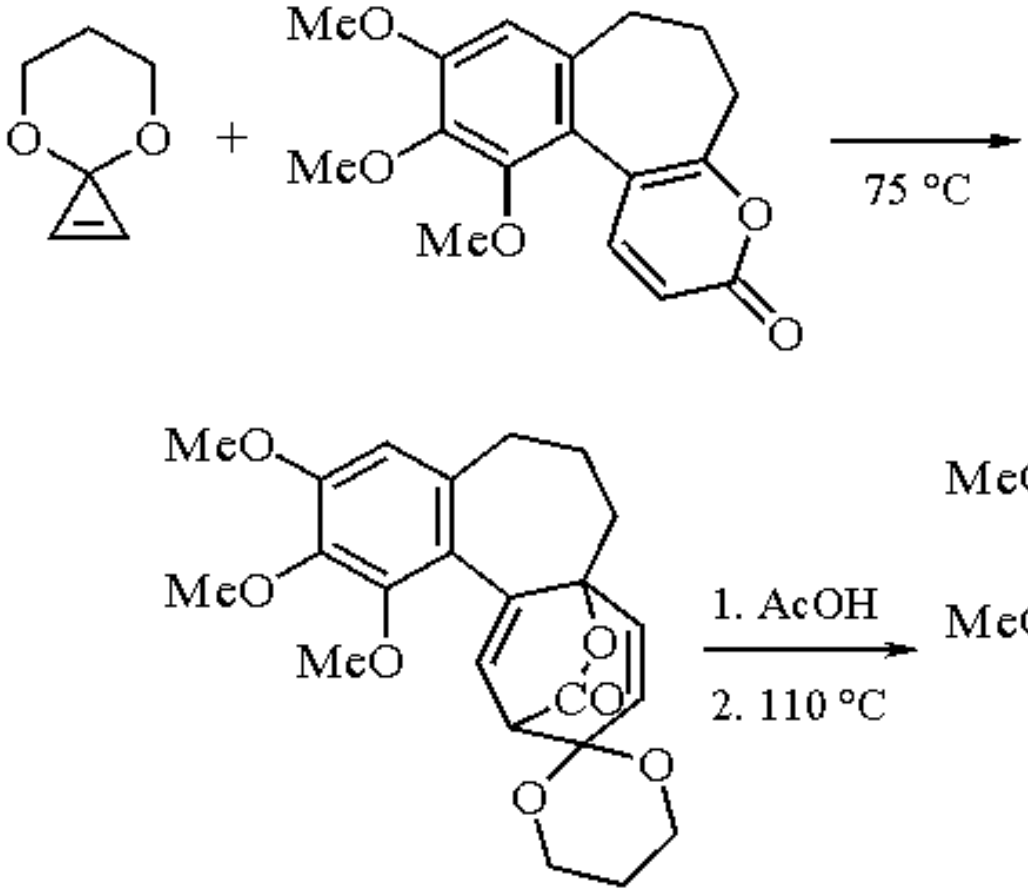

(5)

The vinylcarbene also reacts with carbonyl compounds to give γ-lactone acetals, which hydrolyze to the corresponding γ-lactone or furan depending on the substituents (eq 6).[10]

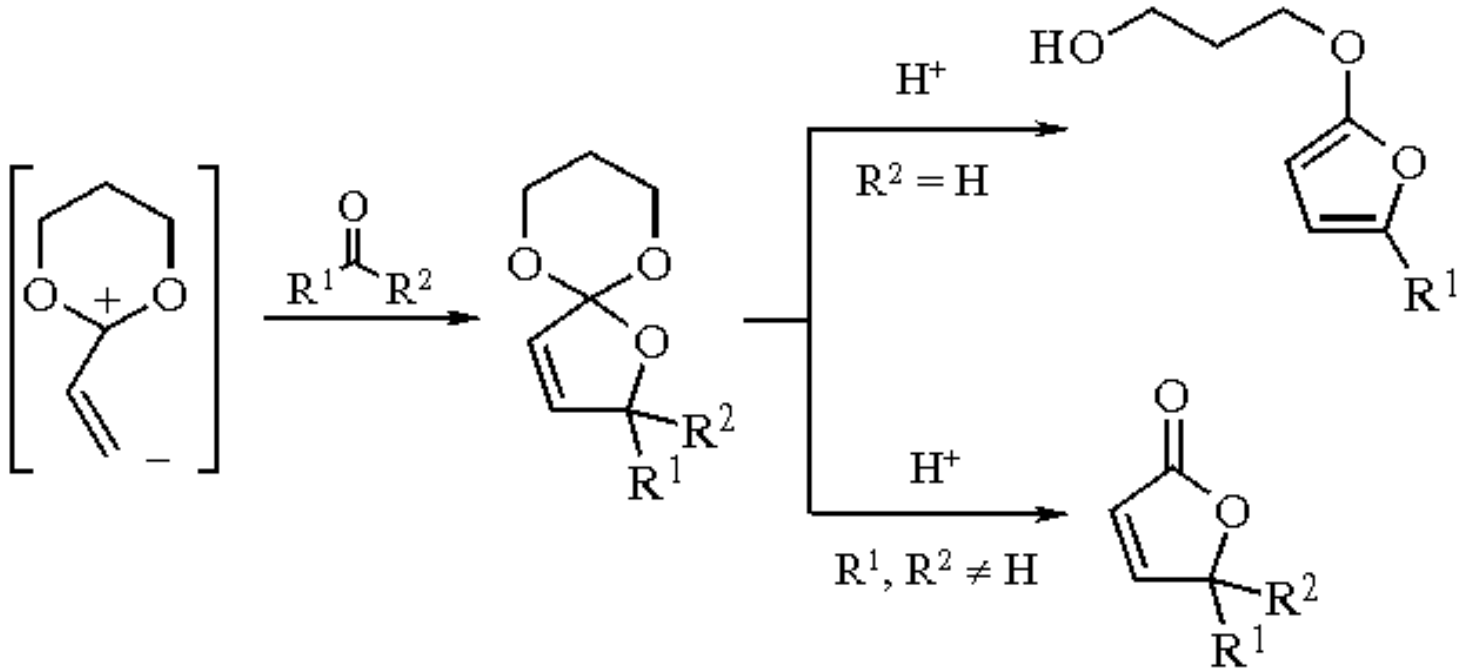

(6)

Substituted cyclopropenone acetals are a good precursor of substituted singlet vinylcarbenes. The substituted vinylcarbenes are formed regio- and stereoselectively, and undergo regioselective [3 + 2] cycloaddition to electron deficient alkanes to give a variety of cyclopentenone acetals.[11] Phenylthio and ester groups connected to the alkenic

carbon effect highly regioselective vinylcarbene formation below rt, permitting the [3 + 2] cycloaddition to take place under extremely mild conditions (eq 7).

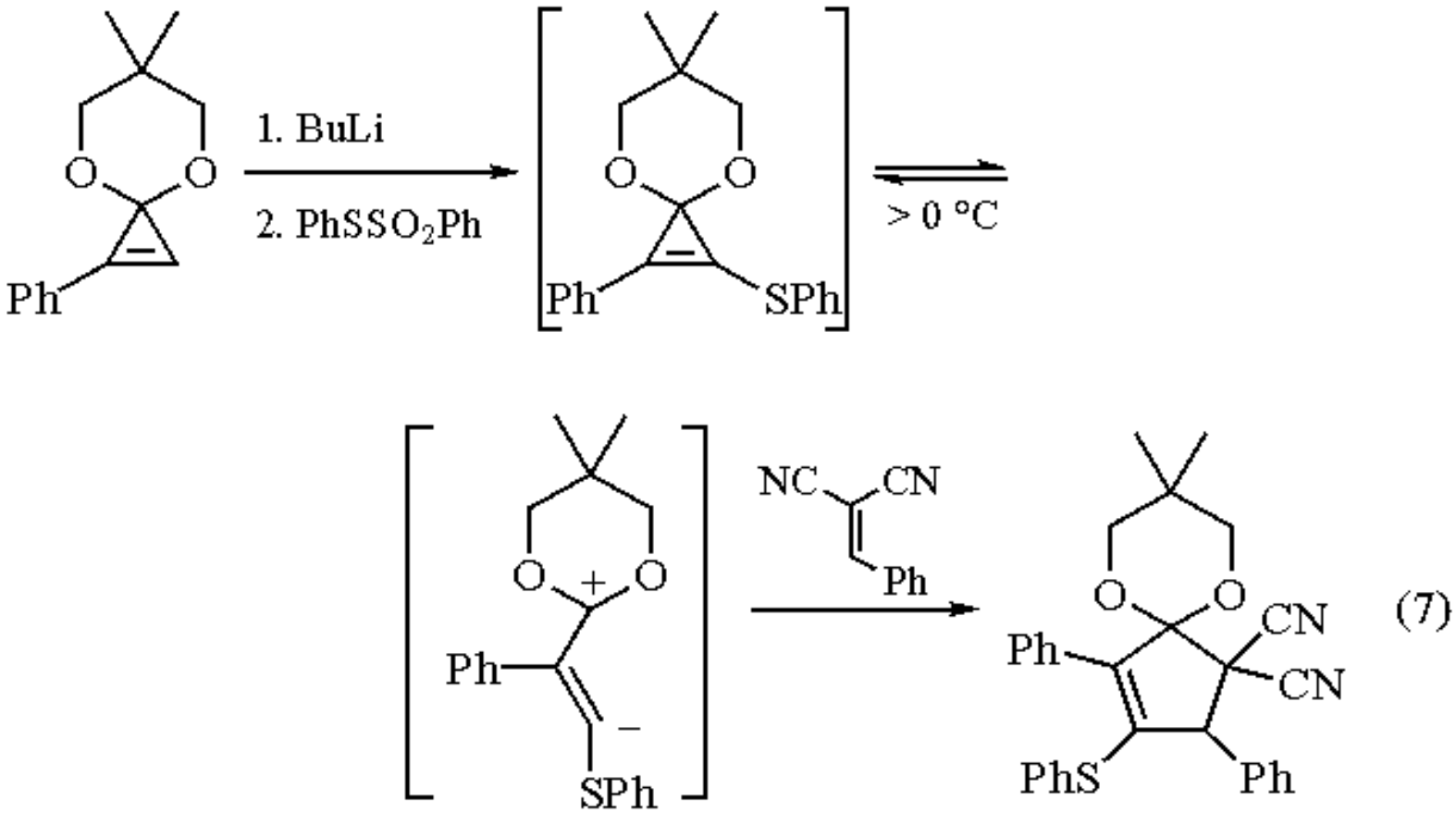

In addition to cycloaddition chemistry, the vinylcarbene undergoes C-H and O-H bond insertion reactions with acidic hydrogens. Thus ***Methyl Propiolate*** and methanol react with the vinylcarbene to afford an acetal of a vinyl ethynyl ketone and an orthoester of an α,β-unsaturated ester (eq 8).[12]

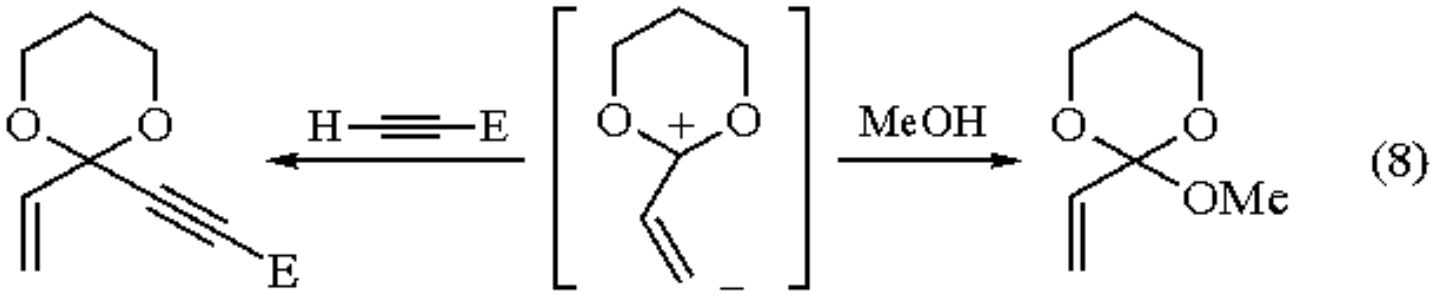

Acceptor of Organometallic Reagents.

Cyclopropenone acetals react with organocopper reagents to produce the copper salt of the cyclopropanone acetal, which serves as a synthetic equivalent of the inaccessible cyclopropanone enolate and reacts with a variety of electrophiles to afford substituted cyclopropanone acetals.[13] Addition of vinylcuprate to the cyclopropenone acetal followed by trapping with water, alkyl halide, and vinyl iodide in the presence of Pd^0 catalyst affords the corresponding vinyl-substituted cyclopropanone acetals (eq 9). These cyclopropane derivatives can be thermally transformed to cyclopentenone acetal, divinyl ketone acetal, and cycloheptadienone acetal by vinylcyclopropane rearrangement, 1,3-

sigmatropic rearrangement, and divinylcyclopropane rearrangement, respectively (eq 9).

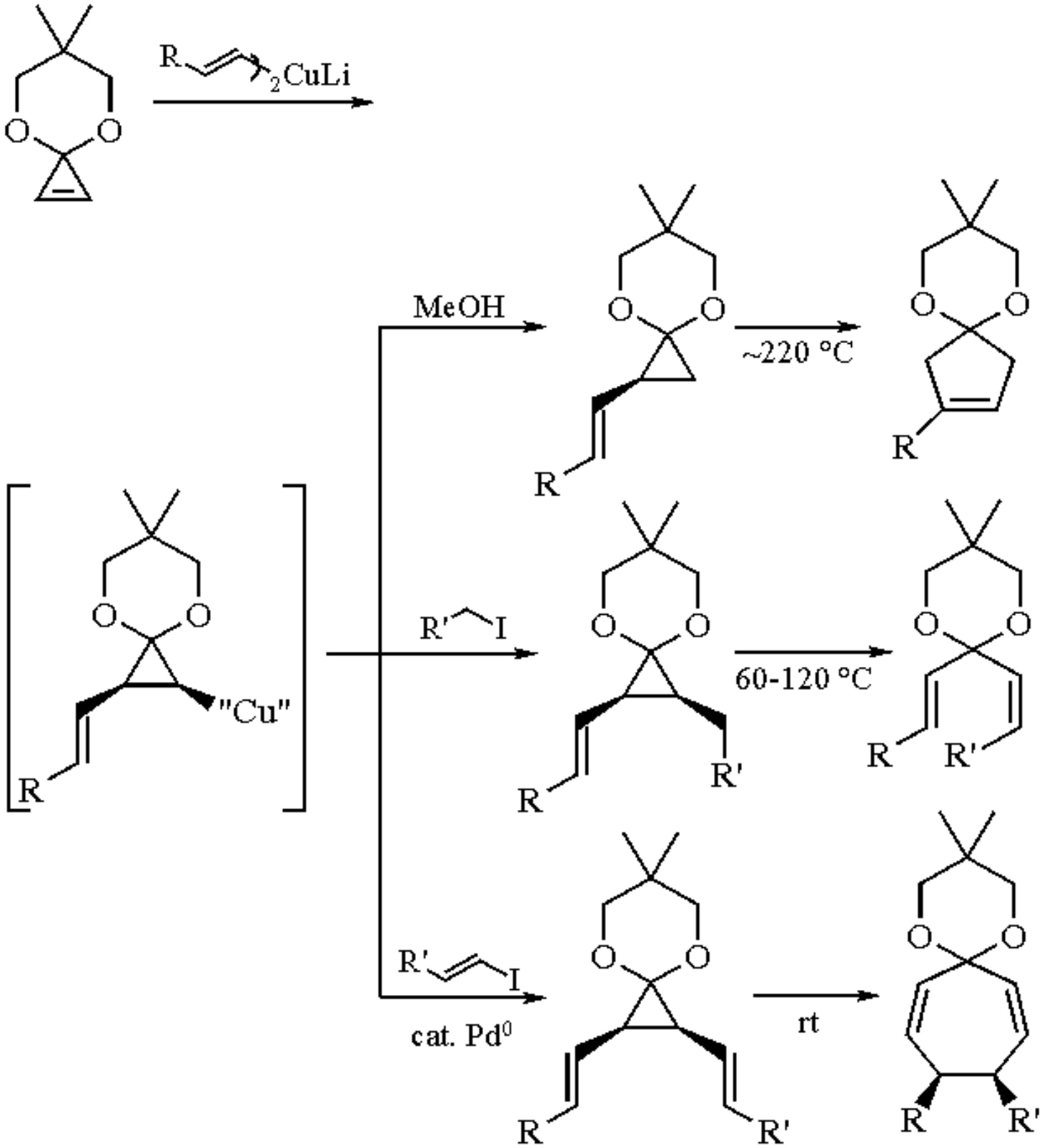

Regio- and stereoselective carbocupration of a 2-substituted cyclopropenone acetal derived from a chiral 2,4-pentandiol can be used for the stereoselective synthesis of a quaternary carbon center.[14] Thus the addition of dimethylcuprate to the ethyl substituted cyclopropenone acetal followed by trapping of the resulting cyclopropylcuprate with benzoyl chloride in the presence of a Pd^0 catalyst affords the cyclopropyl ketone derivative as a single isomer. The ketone is transformed into the γ-keto acid by successive treatment with aqueous HCl, PCC, and K_2CO_3 (eq 10).

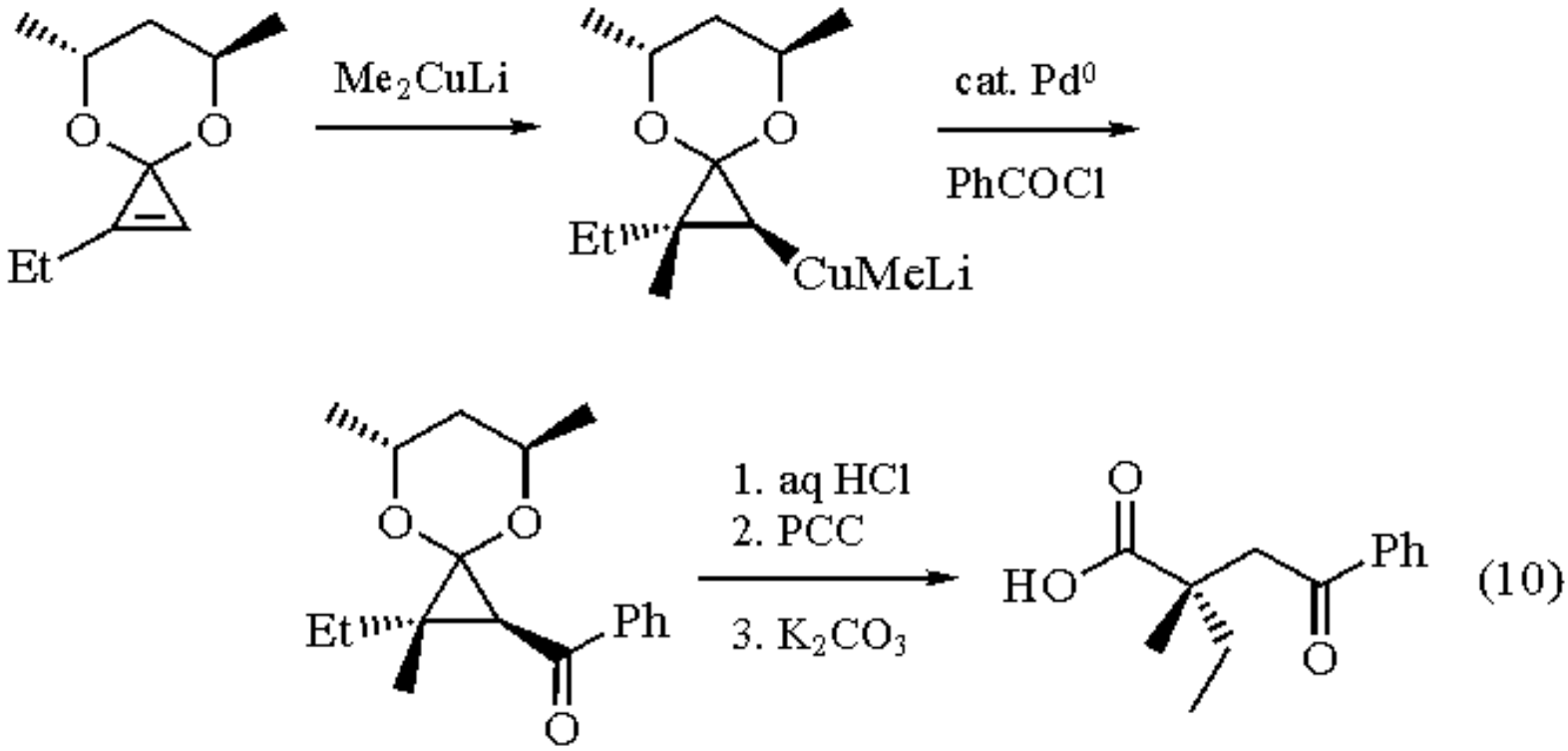

Dienophiles.

A variety of dienes, including electron rich, neutral, and electron deficient ones, react with cyclopropenone acetals under thermal or high pressure conditions.[15] The reaction proceeds through a sterically less hindered *exo* transition state. The utility of this reaction is exemplified by the synthesis of tropone derivatives. The reaction of a cyclopropenone acetal with methyl 4-methoxy-1,3-butadiene-1-carboxylate at rt affords the [4 + 2] cycloaddition adduct as a single stereoisomer that possesses the *trans* relative configuration. Treatment of the cycloadduct with a strong base (***Potassium t-Butoxide***, 25 °C) affords the 3-methoxycarbonyltroponone acetal through an elimination of methanol followed by a rearrangement of the norcaradiene intermediate. Hydrolysis of the troponone acetal provides 3-methoxycarbonylcycloheptatrienone in a good overall yield (eq 11).

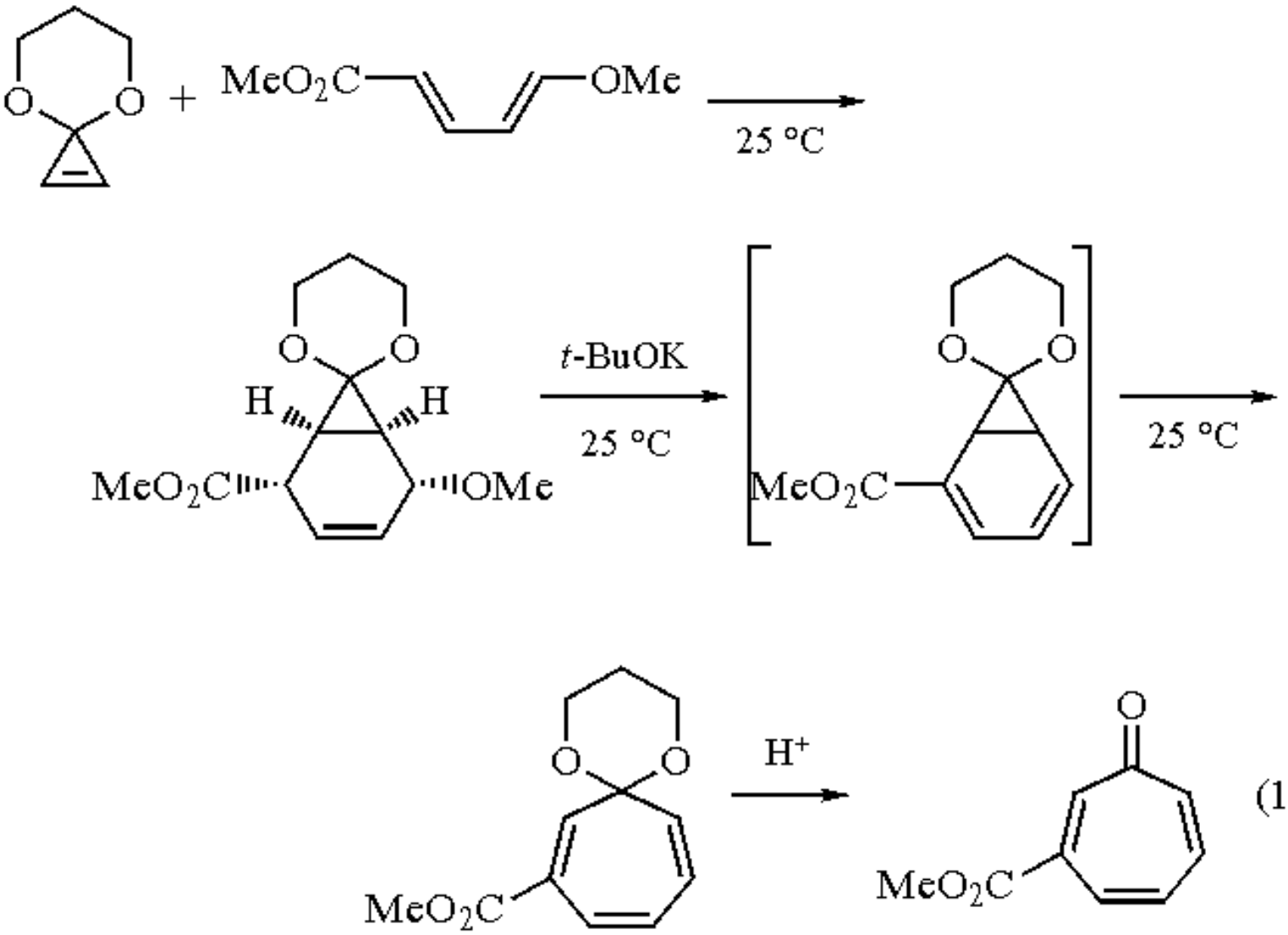

Oligomerization and Polymerization.

Thermal or Pd^0 catalyzed reaction of a cyclopropenone acetal affords a dimer, which is thermally converted to a quinone diacetal derivative (eq 12).

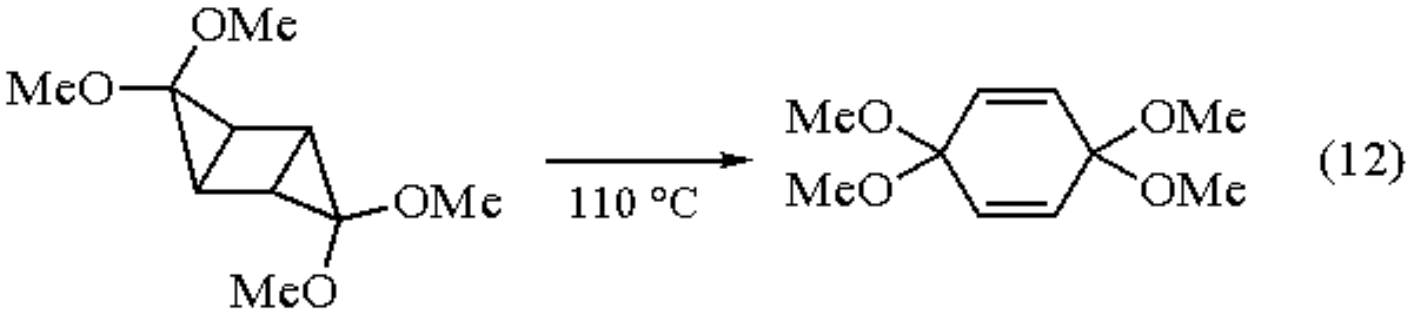

Cyclopropenone acetals undergo ring-opening polymerization under cationic conditions.[16] Among a variety of initiators examined, ***Bromine*** is found to be a good initiator and gives polymers whose M_n values are in the region of 10 000.

Methylenecyclopropane Formation and [3 + 2] Cycloadditions via Trimethylenemethane.

Base-catalyzed isomerization of an alkyl-substituted cyclopropenone acetal gives the alkylidenecyclopropanone acetal, which is utilized for [3 + 2] cycloaddition reactions through a trimethylenemethane intermediate.[17] Upon thermolysis, the alkylidenecyclopropanone acetal generates a dipolar trimethylenemethane, which reacts with an electron-deficient alkene or a carbonyl compound to afford five-membered carbo- and heterocycles (eq 13). This reaction is also useful for the preparation of functionalized buckminsterfullerenes (C_{60}).[18]

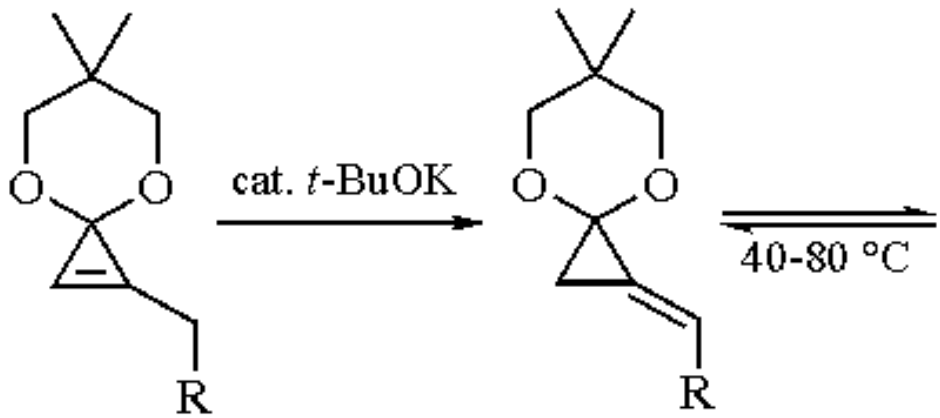

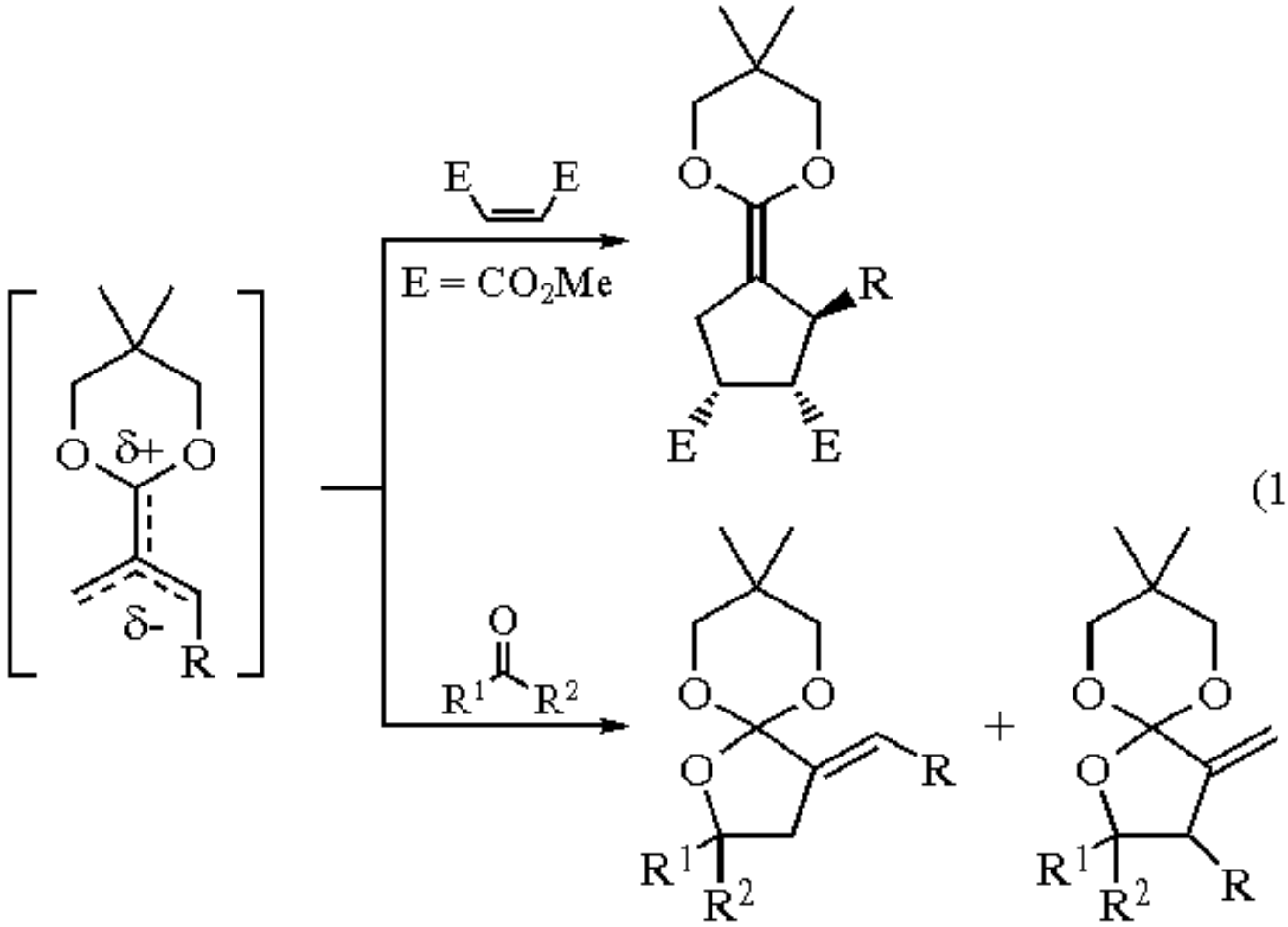

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Cyclopropyldiphenylsulfonium Tetrafluoroborate[1]

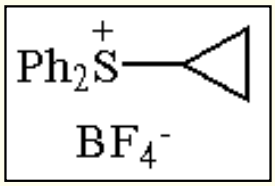

[33462-81-6] · $C_{15}H_{15}BF_4S$ · Cyclopropyldiphenylsulfonium Tetrafluoroborate · (MW 314.15)

(versatile C_3 building block; reagent for the spiroannulation of carbonyl compounds)

Physical Data: mp 136-138 °C.

Solubility: used as a suspension in THF, DME, DMSO, MeCN.

Form Supplied in: white solid; commercially available.

Preparative Methods: see eq 1.[2]

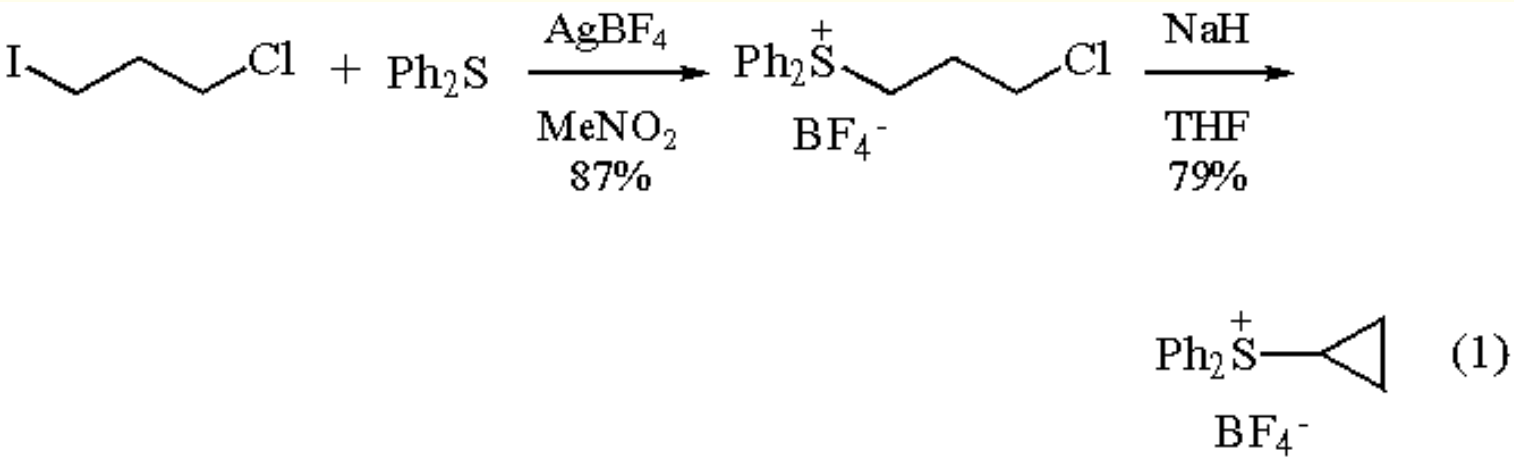

Introduction.

Cyclopropyldiphenylsulfonium tetrafluoroborate is primarily used for the generation of the corresponding ylide which is synthetically useful. The ylide can be used in a variety of transformations including synthesis of cyclobutanones, γ-butyrolactones, cyclopentanones, and spiropentanes.

Generation of Diphenylsulfonium Cyclopropylide.

The ylide can be formed by deprotonation of the sulfonium salt under reversible or irreversible conditions. Treatment with dimsylsodium in DME at -40 °C irreversibly generates the ylide.[3] Low temperatures are required in order to avoid decomposition of the ylide to cyclopropyl phenyl sulfide and benzyne. Generation of the ylide under reversible conditions with powdered ***Potassium Hydroxide*** in DMSO at room temperature[2b] minimizes thermal decomposition because the equilibrium between the sulfonium salt and ylide favors the salt.

Formation of Spiropentanes and Oxaspiropentanes.

Conjugate addition of diphenylsulfonium cyclopropylide to α,β-unsaturated esters and ketones affords spiropentanes (eq 2).[4]

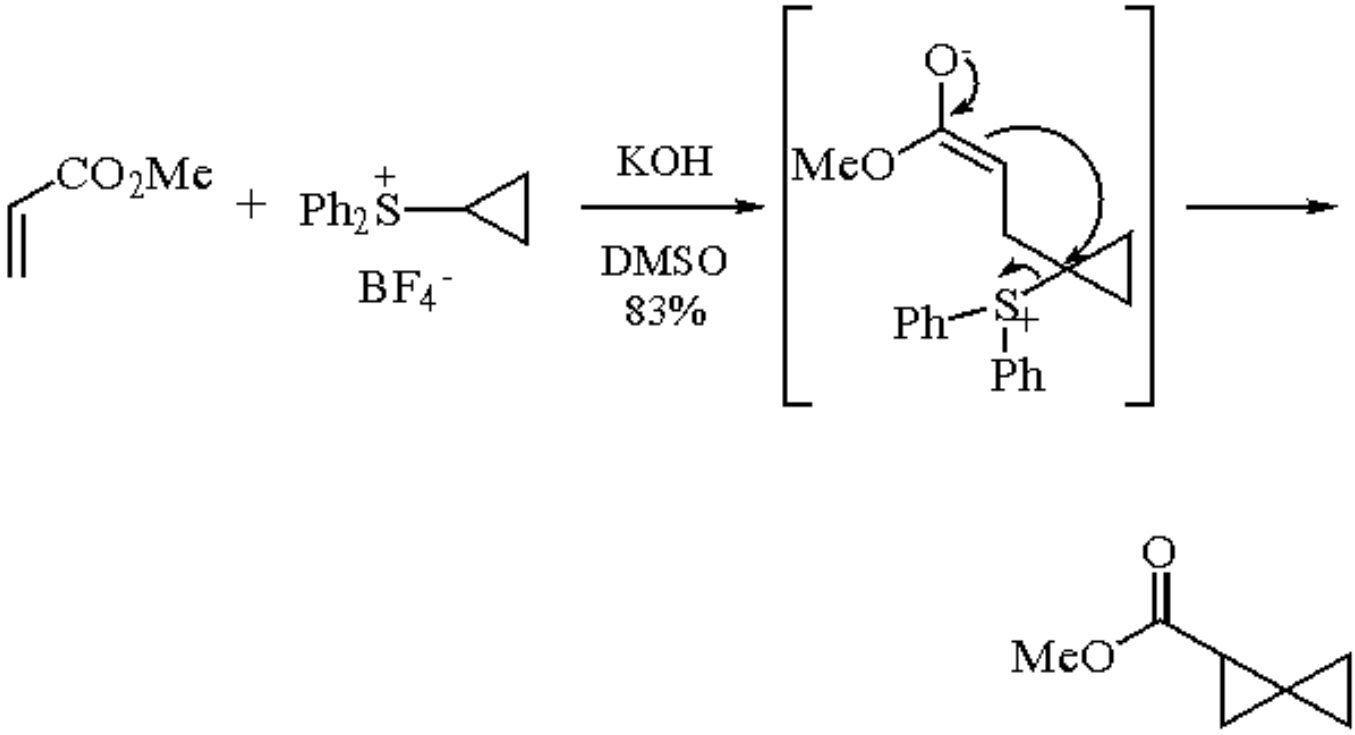

(2)

Analogous to other sulfur ylides (see ***Dimethylsulfonium Methylide***), diphenylsulfonium cyclopropylide reacts with saturated aldehydes and ketones to provide epoxide-type products known as oxaspiropentanes (eq 3).[5] The reaction is general in scope and works well even for readily enolizable ketones, though exceptions are known.[5,6] The good stereoselectivity in reactions with cyclic ketone partners, such as cyclohexanone, results from attack of the ylide from the less hindered equatorial direction. When epimerization of a diastereomeric mixture of ketones occurs under the reaction conditions, formation of one oxaspiropentane can result. This results because epimerization α to the ketone occurs faster than addition of the ylide to the ketone, and because one of the epimers reacts at a faster rate than the other.[1e] Isolated alkenes, esters, alcohols, ethers, and epoxides are some of the functional groups that can be tolerated under the reaction conditions. The ylide is chemoselective for saturated ketones over conjugated enones.[1e]

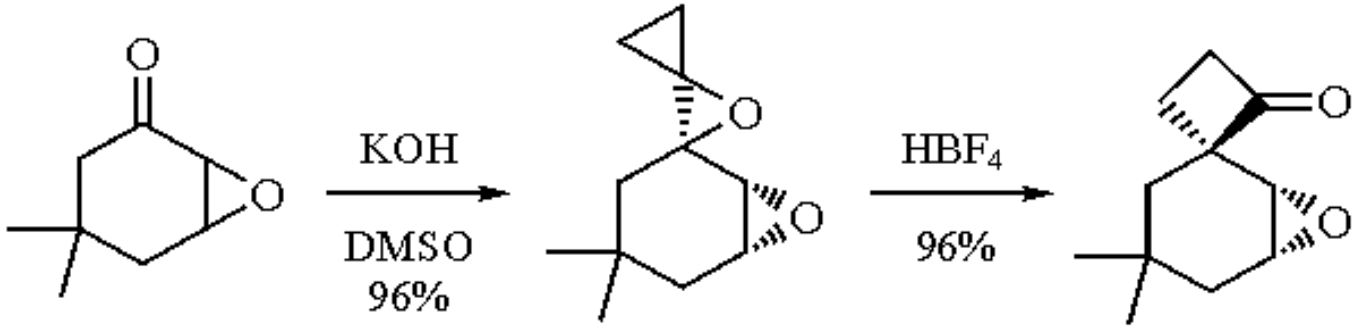

(3)

The chemical versatility of these highly reactive oxaspiropentanes makes them useful building blocks. For example, such highly strained epoxides are very labile towards acid catalyzed rearrangements. This reactivity can be exploited to produce cyclobutanones (eq 3) or vinylcyclopropanol products (see below). In cases where the oxaspiropentanes possess substituents capable of stabilizing a carbonium ion, rearrangement to the cyclobutanone usually occurs under the reaction conditions.[5] In other cases the cyclobutanone can be obtained directly by acidic work-up of the ylide reaction. In general, the major diastereomer arises from inversion of configuration at the migration terminus, which is consistent with a concerted mechanism.[1e,7] If the cyclobutanone of opposite configuration is desired, an alternate procedure can be adopted. Opening of the oxaspiropentane with phenylselenide anion gives the hydroxyselenide, which is directly subjected to oxidation with ***m-Chloroperbenzoic Acid***. Under the reaction conditions, ionization of the selenoxide occurs, leading to rearrangement. The overall process involves two inversions, leading to the stereoreversed cyclobutanone.[8] Such stereoreversed cyclobutanones can be more efficiently prepared from the starting ketones using the alternative reagent 1-lithiocyclopropyl phenyl sulfide.[9] The ring strained spirocyclobutanones are useful for further structural elaborations.[10] Treatment with basic ***Hydrogen Peroxide*** affords γ-butyrolactones (via ring expansion with migration of the more substituted carbon),[11] and fused cyclopentenones by treatment of such γ-butyrolactones with acid (eq 4).[12] Direct transformation of vinylcyclobutanones to fused cyclopentenones can be effected by treatment with acid.[13] Cyclic enol esters can be formed via α-formylation and acid promoted fragmentation.[14] Synthetic elaboration of cyclobutanones via alkylation and subsequent cleavage to release ring strain results in the selective transformation of the original carbonyl group into a variety of substitution patterns. These include geminal dialkylation and reductive alkylation of the carbonyl group.[15-17]

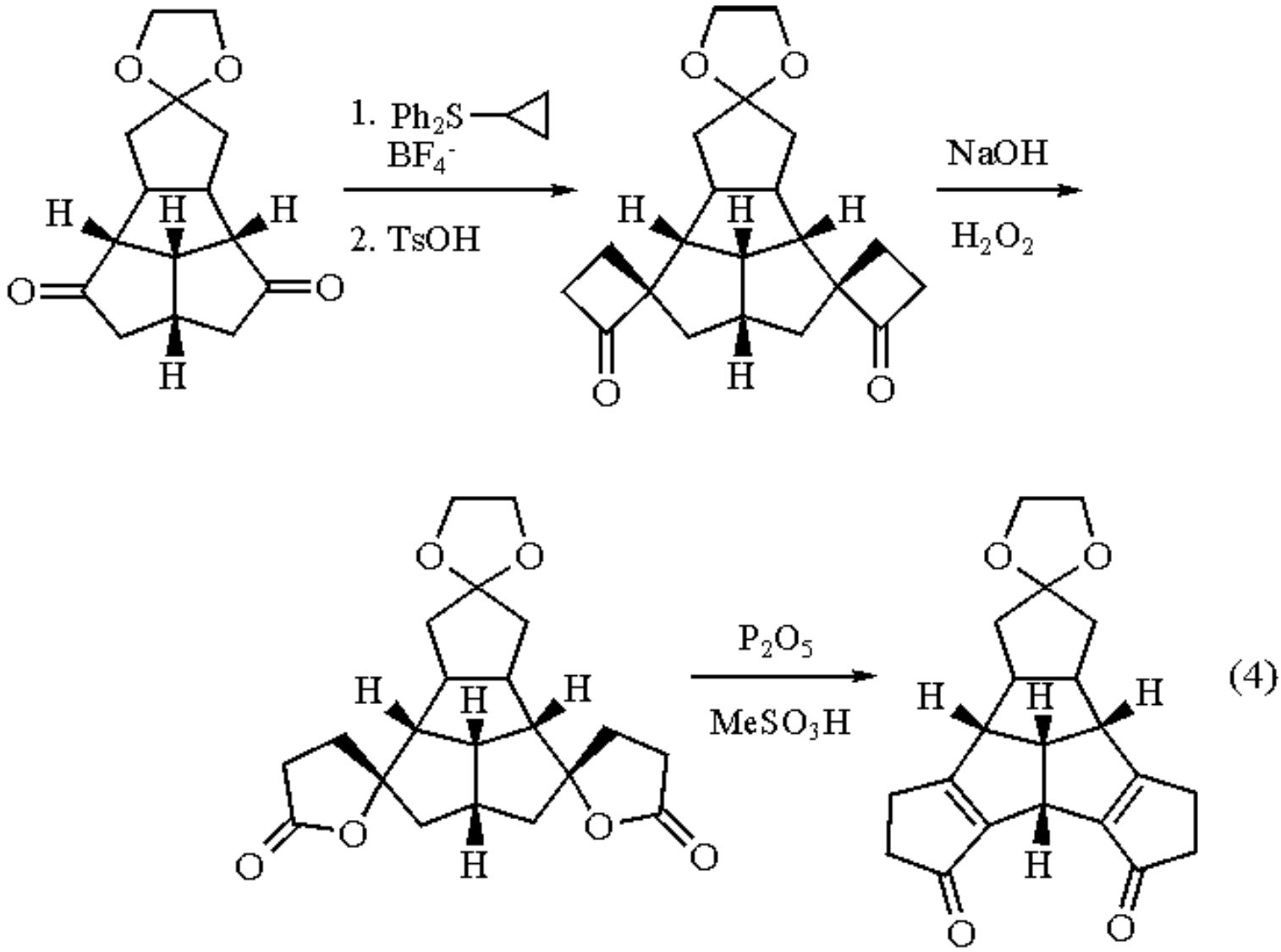

Transformation of Oxaspiropentanes to Vinylcyclopropanol Derivatives.

Treatment of oxaspiropentanes with strong base affords vinylcyclopropanols via a *cis,syn* elimination (eq 5). The regiochemistry of ring opening is dependent on the nature of the base, solvent, and factors determining whether the reaction is under thermodynamic or kinetic control.[18] If the oxaspiropentane does not possess a suitably placed hydrogen for base abstraction, treatment with sodium phenylselenide in a nonprotic solvent at rt can afford the β-hydroxy selenide which eliminates to the vinylcyclopropanol in situ (eq 6).[19] Thus the mechanism has switched from a *cis,syn* to a *trans,anti* elimination. Solvent plays an important role in this reaction; switching the solvent to ethanol affords the hydroxy selenide, an intermediate in the formation of stereoreversed cyclobutanones (see above). Attempts to effect a selenoxide elimination (oxidation of the selenide) often affords the cyclobutanone product.[8]

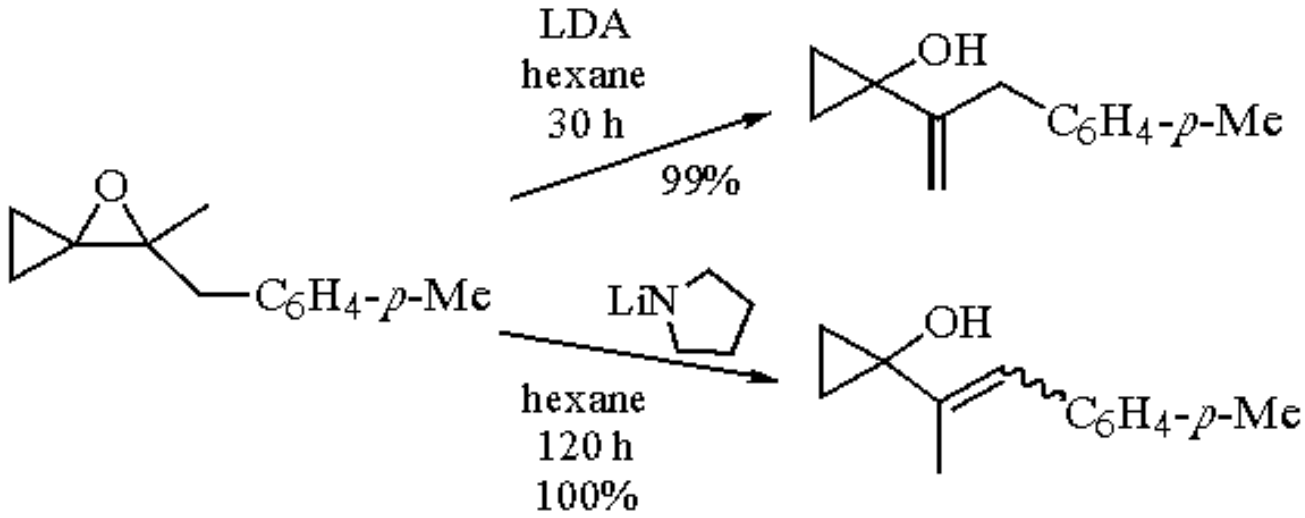

(5)

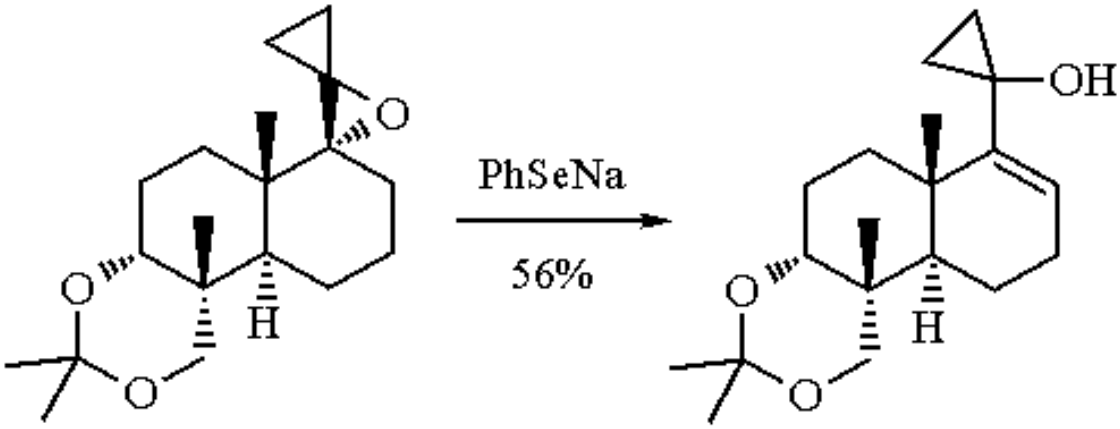

(6)

Vinylcyclopropanol silyl ethers are obtained by quenching the alkoxide formed under strong base conditions with ***Chlorotrimethylsilane***. This composite functional group can undergo thermal rearrangements to cyclopentane trimethylsilyl enol ethers.[5,20] This rearrangement is accelerated by the presence of the siloxy group. The enol silyl ether produced can be further alkylated to provide substituted cyclopentanones. This sequence results in the regiospecific annulation of a cyclopentanone ring to a carbonyl group. In addition, vinylcyclopropanol silyl ethers can undergo ring expansion to cyclobutanones upon treatment with electrophiles.[17b,17c,21] Use of vinylcyclopropanol silyl ethers as cyclization terminators can result in good yields of six- to eight-membered rings (eq 7).[22] The cyclopropyl ring mediates the delocalization of the lone pair on the oxygen into the alkene, enhancing the alkene nucleophilicity, and the reaction is terminated effectively by rearrangement to the cyclobutanone.

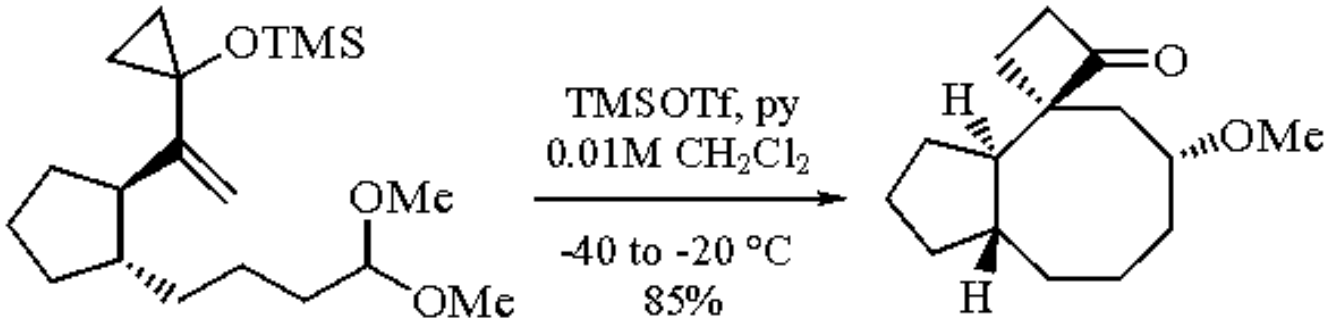

(7)

Homologs of Cyclopropyldiphenylsulfonium

Tetrafluoroborate.

2-Methylcyclopropyldiphenylsulfonium tetrafluoroborate has also been prepared and is formed as a mixture of *trans* (major) and *cis* isomers (eq 8). The stereochemical integrity of the ylide derived from this mixture of sulfonium salts is variable, depending on the conditions under which it is generated. The reactivity profile of the ylide is the same as the parent, but the presence of an additional chiral center often leads to a mixture of stereoisomers.[23]

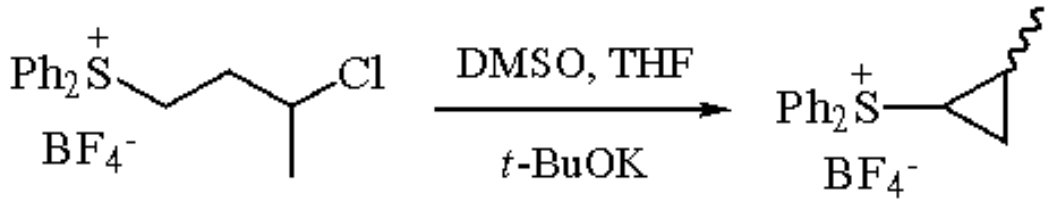

(8)

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Cyclopropylidenetriphenylphosphorane

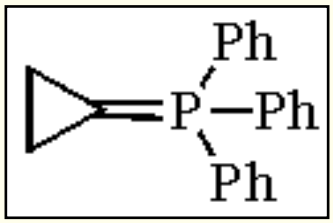

[14633-95-5] · $C_{21}H_{19}P$ · Cyclopropylidenetriphenylphosphorane · (MW 302.36)

(phosphorane for cyclopropylidenation of aldehydes and ketones;[1] utilized in cyclobutanone synthesis;[2] reagent applied to polyspirane synthesis[3])

Physical Data: mp 103 °C (dec); *d* 1.21 g cm^{-3}.

Solubility: sol THF, DME, DMSO.

Analysis of Reagent Purity: proton and heteronuclear NMR and X-ray data have been reported.[4]

Preparative Methods: see ***Cyclopropyltriphenylphosphonium Bromide***.

Handling, Storage, and Precautions: cyclopropylidenetriphenylphosphorane is a fairly stable ylide, capable of withstanding elevated reaction temperatures of approximately 60-65 °C. The ylide is sensitive to moisture and air and should be freshly prepared under anhydrous conditions under an inert atmosphere.

Cyclopropylidenation.

The most frequent application of cyclopropylidenetriphenylphosphorane involves the cyclopropylidenation of aldehydes and ketones. The references cited in the Ylide Generation: Cyclopropylidenetriphenylphosphorane section under the reagent ***Cyclopropyltriphenylphosphonium Bromide*** provide examples of alkene formation. In addition, further examples of alkenation are available,[5] including an application to propellane synthesis,[1a] generation of tetrasubstituted alkenes (reaction with ketones),[6] and synthesis of α,β-unsaturated aldehydes and ketones incorporating a cyclopropylidene unit (eq 1).[7]

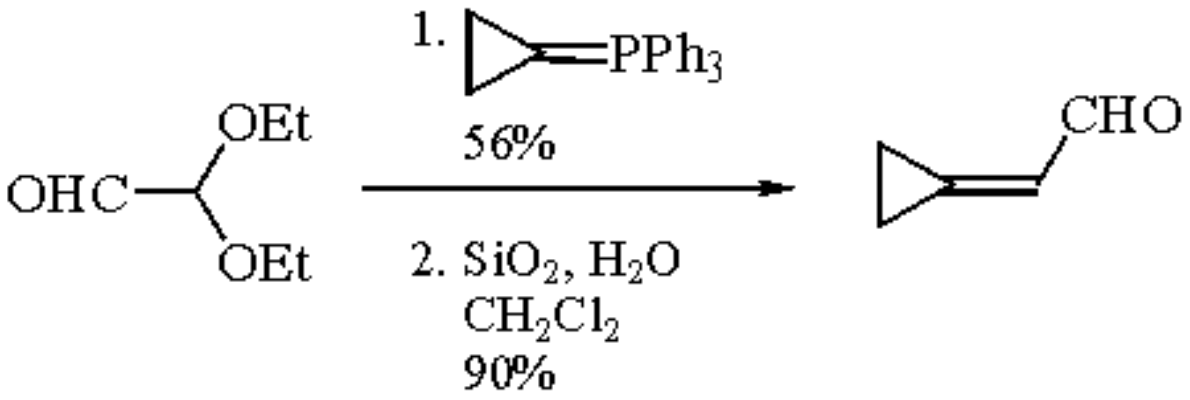

(1)

Cyclobutanone Synthesis.

Coupling cyclopropylidenetriphenylphosphorane with an aldehyde and subsequent oxidation with ***m-Chloroperbenzoic Acid*** produces a spiro epoxycyclopropane which rearranges to a cyclobutanone (eq 2).[2,8]

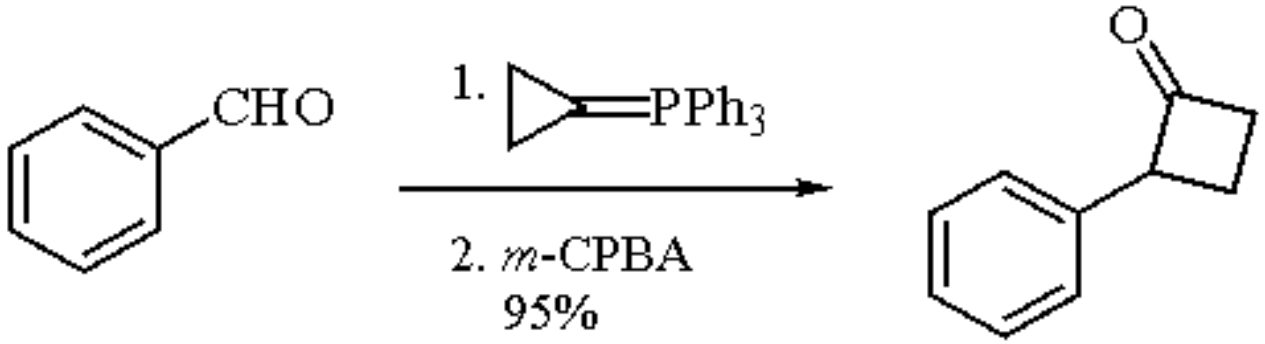

(2)

Cyclopropylidenetriphenylphosphorane as a Nucleophile.

Cyclopropylidenetriphenylphosphorane adds to polarized alkenes to generate spiro compounds incorporating two cyclopropyl rings.[9] In addition, the ylide reacts with epoxides to yield 1-substituted cyclopropylphosphonium salts and with nitrile oxides to yield oxime substituted phosphonium salts (MeI workup) or spiro compounds incorporating a cyclopropyl ring on an azirine ring (thermal workup).[10] Cyclopropylidenetriphenylphosphorane reacts with CO_2 to generate the carboxylate phosphonium salt which decomposes under aqueous base and acid workup to cyclopropanecarboxylic acid.[11]

Cope Rearrangement.

Cyclopropylidenetriphenylphosphorane provides a unique substrate for studying the Cope rearrangement

(eq 3).[12]

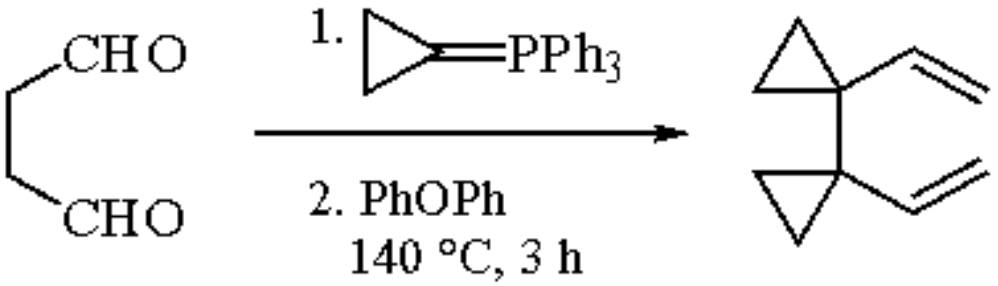

(3)

Diels-Alder Reaction.

Cyclopropylidenetriphenylphosphorane reacts with α,β-unsaturated aldehydes to generate dienes incorporating a cyclopropylidene unit. Subsequent reaction of these unstable dienes with dienophiles results in cyclopropyl substituted cyclohexenes (eq 4).[13]

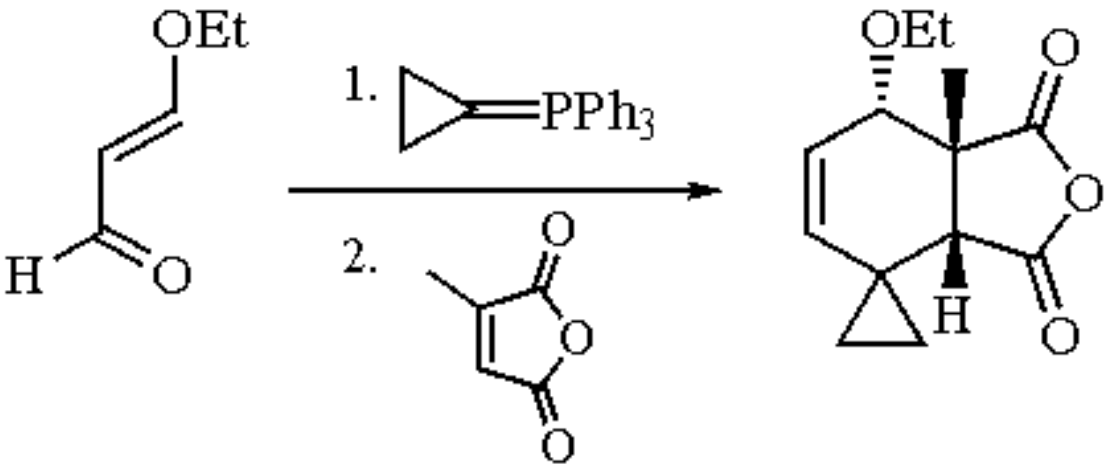

(4)

Polyspiranes.

Research in the synthesis of polyspirane systems has applied cyclopropylidenetriphenylphosphorane to the construction of these complex molecules.[3]

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Edward J. Adams

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Cyclopropyllithium[1]

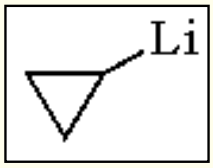

[3002-94-6] · C_3H_5Li · Cyclopropyllithium · (MW 48.02)

(organolithium reagent used in the synthesis of a variety of cyclopropyl derivatives,[2] five-membered ring nitrogen heterocycles via cyclopropylimine rearrangement,[3] and cyclopentenes via vinylcyclopropane rearrangement[4])

Alternate Name: lithiocyclopropane.

Solubility: sol pentane and ether.

Form Supplied in: solution in pentane or ether.

Analysis of Reagent Purity: cyclopropyllithium solutions should be titrated before use by one of the standard titration methods,[5] e.g. Gilman's double titration.[6]

Preparative Methods: cyclopropyllithium is usually prepared as a solution in ether by reacting highly dispersed ***Lithium*** with cyclopropyl chloride[7] or bromide.[8] The reaction can also be conducted in pentane.[2] Transmetalation methods have also been described.[7b,9]

Handling, Storage, and Precautions: solutions of organolithium reagents are highly flammable and moisture sensitive. Appropriate precautions are recommended. Use in a fume hood. Stability of cyclopropyllithium in ether is similar to that of ***n-Butyllithium***, whereas in THF its stability is greater.[8a]

Synthesis of Cyclopropyl Derivatives.

Cyclopropyllithium reacts readily with common electrophiles to form a variety of compounds containing a cyclopropyl group. Thus reaction with aldehydes[10] and ketones[2,11] leads to secondary and tertiary alcohols respectively (eqs 1 and 2).[11a]

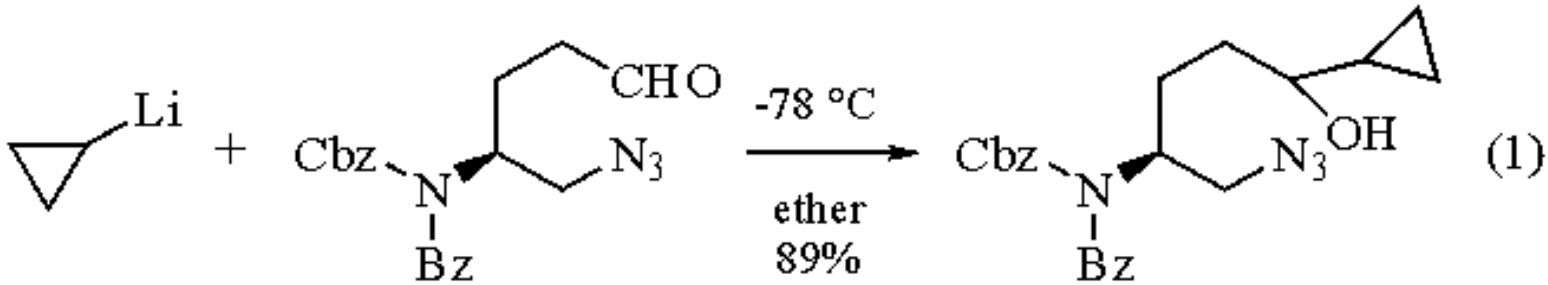

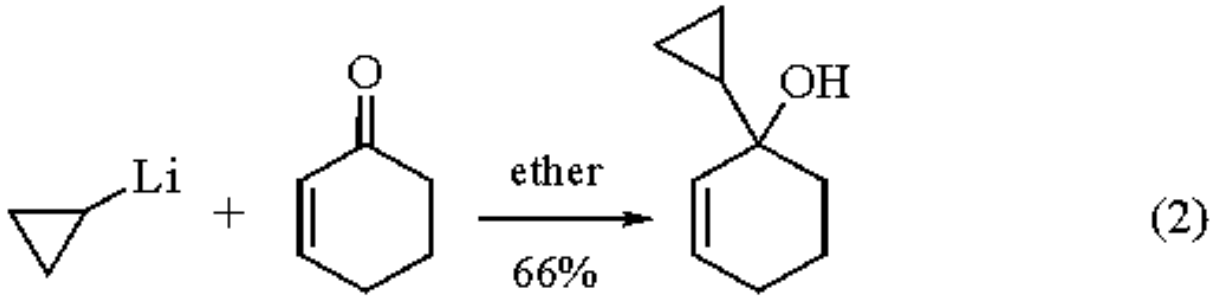

Two- and three-carbon homologations have been realized by using ethylene oxide[7a] and oxetane[8b] as electrophiles. Reaction with vinyl-substituted epoxides (eq 3) constitutes an example of four-carbon homologation.[12]

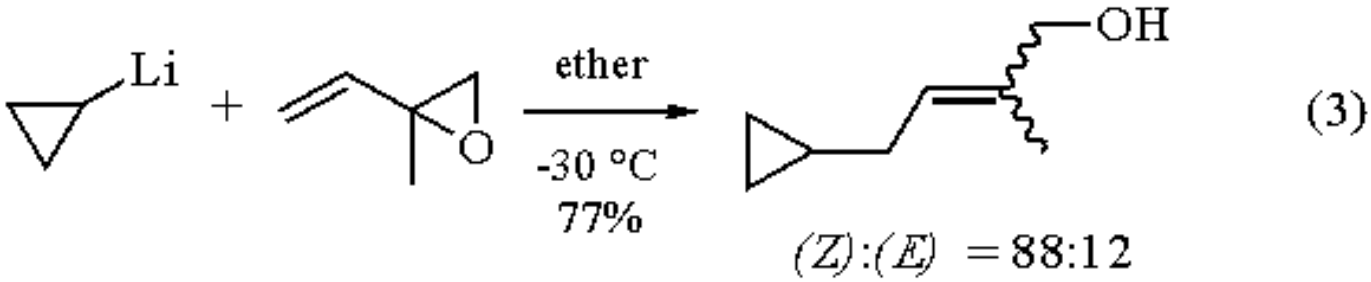

Cyclopropyllithium condenses in a typical fashion with carboxylic acids to give cyclopropyl ketones,[13] and a controlled reaction with ***N-Formylpiperidine*** leads to cyclopropylcarbaldehyde in 75% yield.[14] Cyclopropyllithium also adds to carbon-nitrogen multiple bonds. Thus addition to imines leads to amines[15] while reaction with cyanopyridines yields ketones in good yields (eq 4).[16]

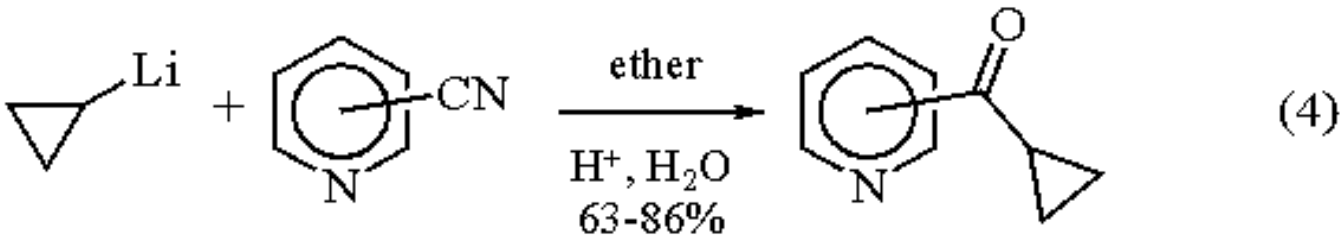

Cyclopropyllithium has also been used in the synthesis of cyclopropylpyridines,[12] ***Cyclopropyltriphenylphosphonium Bromide***,[18] cyclopropyl phosphines,[19] silanes[19,20] and organogermanium compounds.[21]

Synthesis of Five-Membered Ring Nitrogen Heterocycles.

Addition of cyclopropyllithium to α-piperidinocyclopropanenitriles leads to the intermediate imines which subsequently undergo acid catalyzed rearrangement to form nitrogen heterocycles in moderate yields. Different products can be obtained depending on the kind of acid used (eq 5).[3,22]

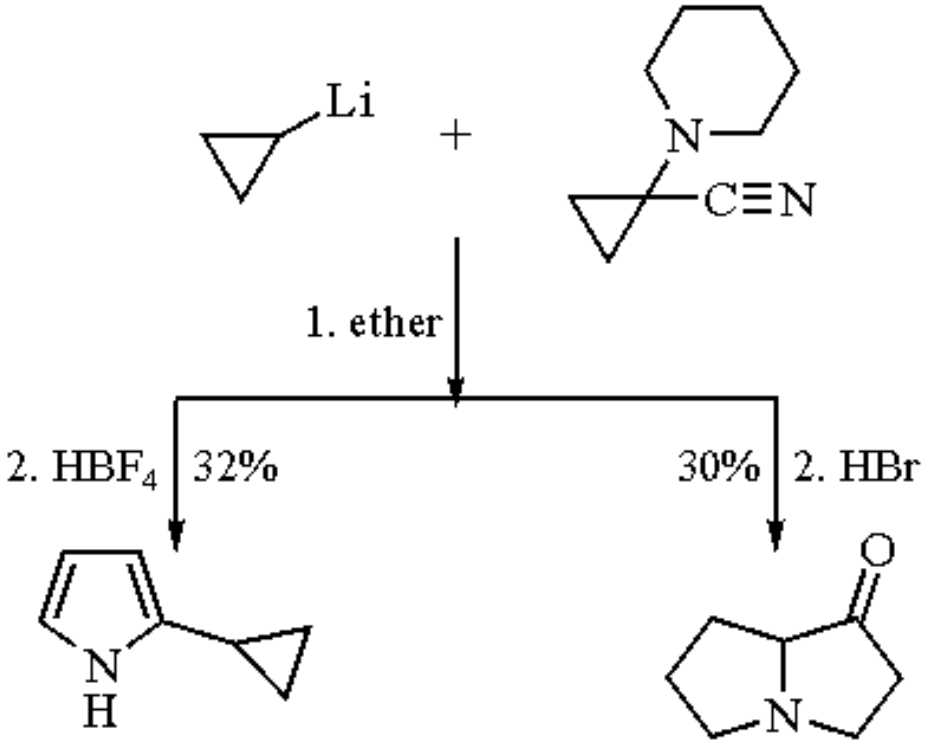

(5)

Synthesis of Cyclopentenes via Thermal Rearrangement of Vinylcyclopropanes.

A mixed cuprate prepared in situ from cyclopropyllithium and PhSCu readily displaces iodide in β-iodocyclopentenones to give the substitution products in high yields. The latter undergo thermal ring expansion, providing an interesting method for cyclopentene annulation (eq 6).[4]

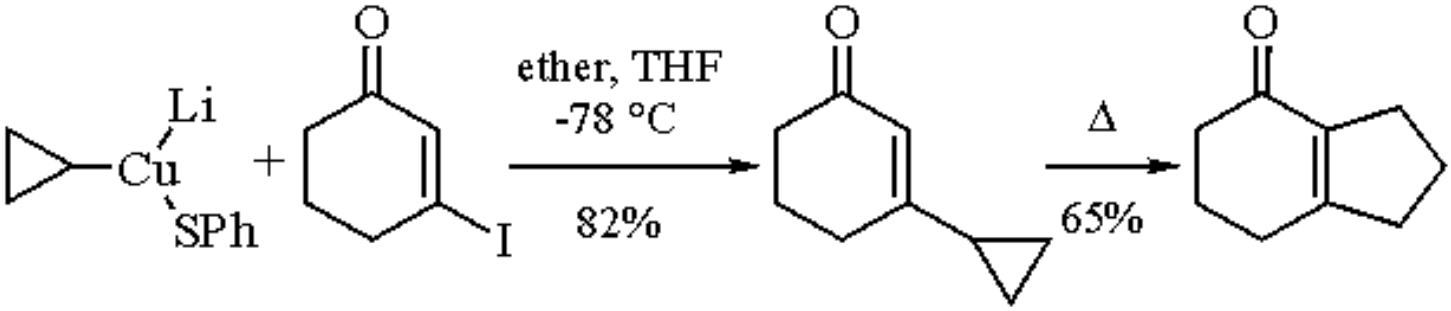

(6)

Related Reagents.

Cis and *trans* 1-lithio-2-methoxycyclopropanes (**1**) were prepared by lithium-halogen exchange reaction from corresponding bromides and condensed with aldehydes to give the addition products which readily undergo acid-catalyzed rearrangement to β,γ-unsaturated aldehydes.[23]

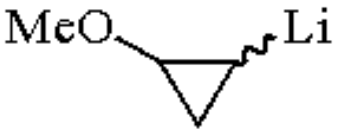

(1)

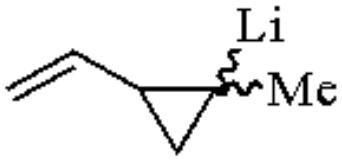

(2)

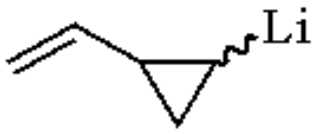

(3)

Both 1-lithio-1-methyl-2-vinylcyclopropanes (**2**) and 1-lithio-2-vinylcyclopropanes (**3**) (*cis* and *trans*) were prepared in similar fashion and subsequently applied to cycloheptane annulations.[24,25] These and other substituted cyclopropyllithium reagents are configurationally stable.[26]

See also ***1-Bromo-1-lithio-2-phenylcyclopropane***; ***Cyclopropylmagnesium Bromide***; ***1-Lithio-1-methoxycyclopropane***; ***Lithium Cyclopropyl(phenylthio)cuprate***.

---

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Cyclopropylmagnesium Bromide[1]

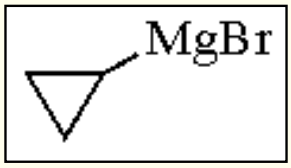

[23179-80-4] · C_3H_5BrMg · Cyclopropylmagnesium Bromide · (MW 145.30)

(cyclopropyl Grignard reagent used in the synthesis of a variety of cyclopropyl derivatives,[2] homoallylic bromides,[3] and dienes[4])

Solubility: sol ethereal solvents.

Form Supplied in: solution in ether or THF.

Analysis of Reagent Purity: it is highly recommended to analyze every batch of cyclopropylmagnesium bromide by using one of the standard titration methods.[5]

Preparative Methods: cyclopropylmagnesium bromide is best prepared by treating magnesium turnings with commercially available cyclopropyl bromide in THF.[6a] Yields usually range from 23 to 43%. Reaction in ether gives even lower yields,[6] mainly due to the extensive disproportionation of cyclopropyl radicals on the magnesium surface.[6a]

Handling, Storage, and Precautions: Grignard reagent solutions are highly flammable and moisture sensitive.

Synthesis of Cyclopropyl Derivatives.

Cyclopropylmagnesium bromide reacts smoothly with aldehydes and ketones to give secondary[2] and tertiary[7] alcohols, respectively (eqs 1 and 2). Controlled reaction with ***N,N-Dimethylformamide*** gives rise to the formation of cyclopropanecarbaldehyde in good yield (eq 3).[8]

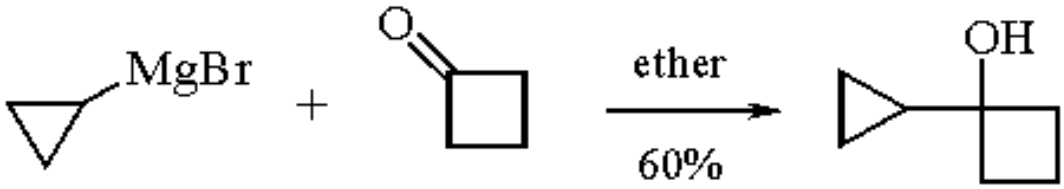

(1)

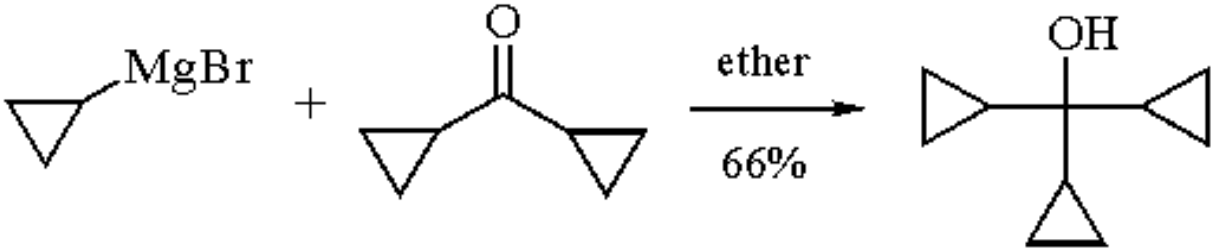

(2)

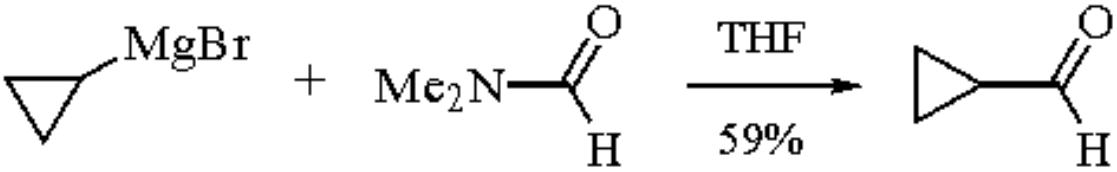

(3)

Direct oxidation of cyclopropylmagnesium bromide with molecular oxygen affords the ellusive cyclopropanol, albeit in low yield (eq 4).[2] Conversion to cyclopropylmercury(II) bromide followed by reaction with aqueous KI-I_2 leads to cyclopropyl iodide (eq 5).[2]

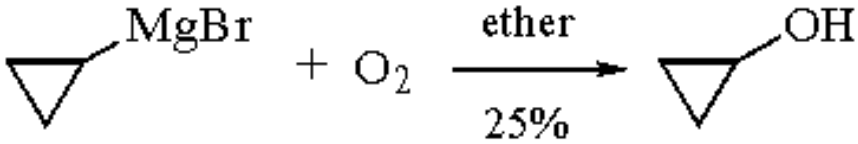

(4)

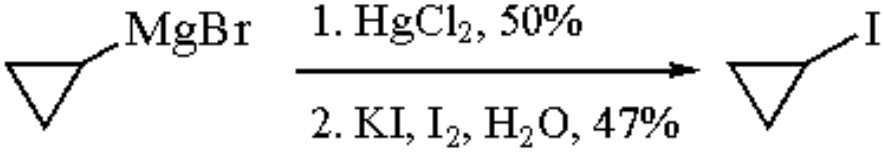

(5)

Cyclopropylmagnesium bromide couples, in the presence of a nickel catalyst, with aryl and vinyl bromides to give the corresponding aryl- and vinylcyclopropanes (eqs 6 and 7).[9]

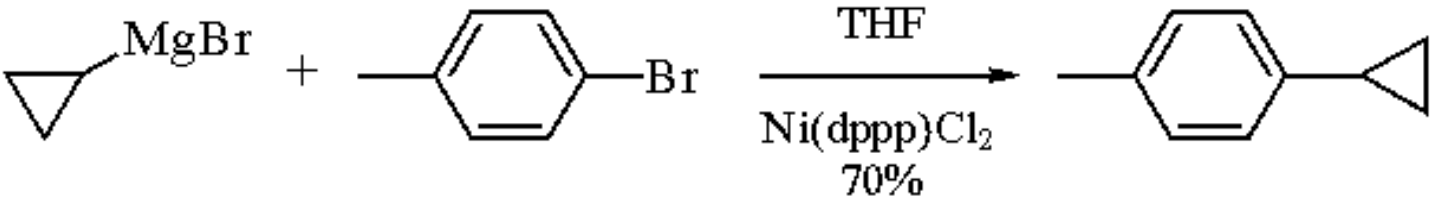

(6)

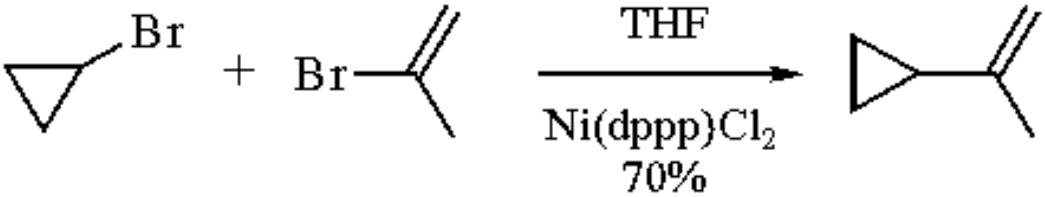

(7)

dppp = 1,3-bis(diphenylphosphino)propane

Other interesting synthetic applications of cyclopropylmagnesium bromide include formation of cyclopropyl ketones

from acyl halides (via dicyclopropylcadmium),[10] conversion of optically pure *p*-tolylsulfinate to cyclopropyl tolyl sulfoxide with virtually complete inversion of configuration at sulfur,[11] and coupling with methyl α-chloro-*N*-benzyloxycarbonylglycinate.[12]

Synthesis of Homoallylic Bromides.

Cyclopropylalkyl alcohols, prepared from cyclopropylmagnesium bromide and appropriate carbonyl compounds, readily rearrange to homoallylic bromides[3,13] upon treatment with ***Hydrobromic Acid***. The entire conversion can be conducted without isolation of the intermediate carbinol (eq 8).[14]

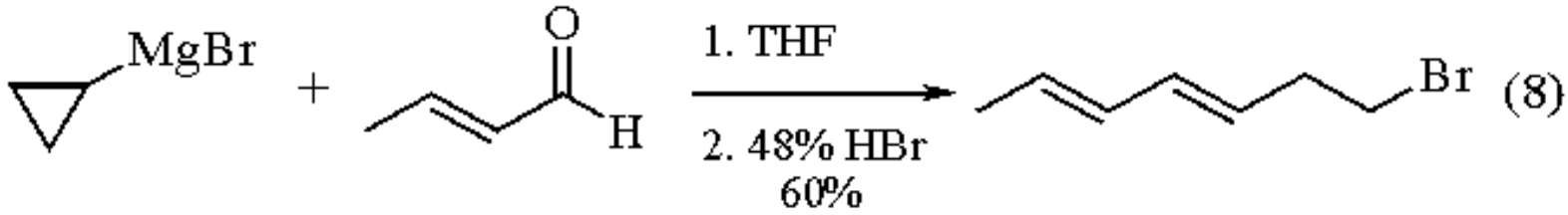

Synthesis of Dienes from Aromatic Dithioacetals.

Cyclopropylmagnesium bromide reacts with aromatic dithioacetals in boiling benzene or toluene, in the presence of a nickel catalyst, to give aryl-substituted dienes in good yields (eq 9).[4]

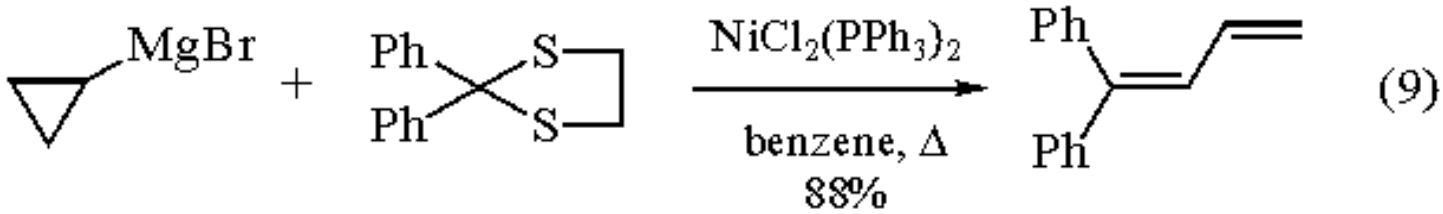

Related Reagents.

Cyclopropyllithium.

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Cyclopropyltriphenylphosphonium Bromide

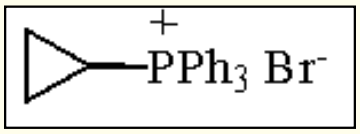

[14114-05-7] · $C_{21}H_{20}BrP$ · Cyclopropyltriphenylphosphonium Bromide · (MW 383.27)

(phosphonium salt used to generate phosphorane;[1] behaves as an electrophile and generates an ylide by ring opening if reacted with a nucleophile;[2] starting material for other functionalized phosphonium salts[3])

Physical Data: mp 183-185 °C (commercial suppliers), mp 189-190 °C when recrystallized from EtOAc.[4]

Solubility: normally used in THF, DME, or DMF, although solubility is reported to be poor.[1b]

Form Supplied in: cream-colored or white powder or crystalline solid, available from various suppliers.

Analysis of Reagent Purity: proton and heteronuclear NMR and IR data have been reported.[5]

Handling, Storage, and Precautions: cyclopropyltriphenylphosphonium bromide exhibits long-term stability and should be protected from moisture in a well-sealed vial. Present data suggest potential skin irritation if contacted and inhalation of the dust may be irritating to the respiratory system.

Ylide Generation: Cyclopropylidenetriphenylphosphorane.

A significant application of cyclopropyltriphenylphosphonium bromide involves the generation of cyclopropylidenetriphenylphosphorane[1a] (for reactions involving this ylide, see ***Cyclopropylidenetriphenylphosphorane***). Ylide generation generally involves an aprotic solvent like THF[6] or DME[7] and ***n-Butyllithium*** as a base. Alkene generation under these reaction conditions often results in poor yields. Subsequent investigations have suggested that the use of a phase transfer catalyst in cooperation with ***Sodium Hydride*** in THF results in a substantial improvement in yield (Table 1 and eq 1).[1b] NaH in DMSO and ***Sodium Hexamethyldisilazide*** in Et_2O have also been utilized in ylide formation.[8] Additional work suggests that an alternate synthetic approach involving 3-bromopropyltriphenylphosphonium bromide and 2 equiv of base (NaH in DME) generates cyclopropyltriphenylphosphonium bromide in situ and results in equivalent or better yields of alkene product.[9]

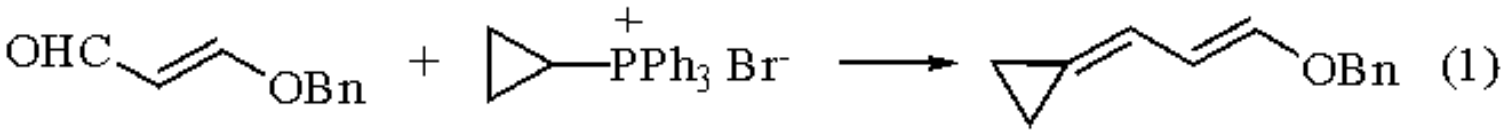

Table 1

Base	Solvent	Additive	Yield
NaH	DMF	None	Nr, dec.
NaH	DMF	18-Crown-6	13 17%
NaH	THF	18-Crown-6	Nr, dec.
NaH	THF	10 mol % TDA-1	83%
NaH	THF	None	Nr, dec.

Cyclopropyltriphenylphosphonium Bromide as an Electrophile.

The phosphonium moiety can stabilize a negative charge on the adjacent carbon atom as an ylide. This stabilization manifests itself as an intrinsic electrophilicity at the remaining two carbon atoms of the cyclopropyl ring. The anion of salicylaldehyde reacts with cyclopropyltriphenylphosphonium bromide at 160 °C to yield a mixture of two products and 75% recovered starting material (eq 2),[4] presumably through a nucleophilic opening of the cyclopropyl ring.

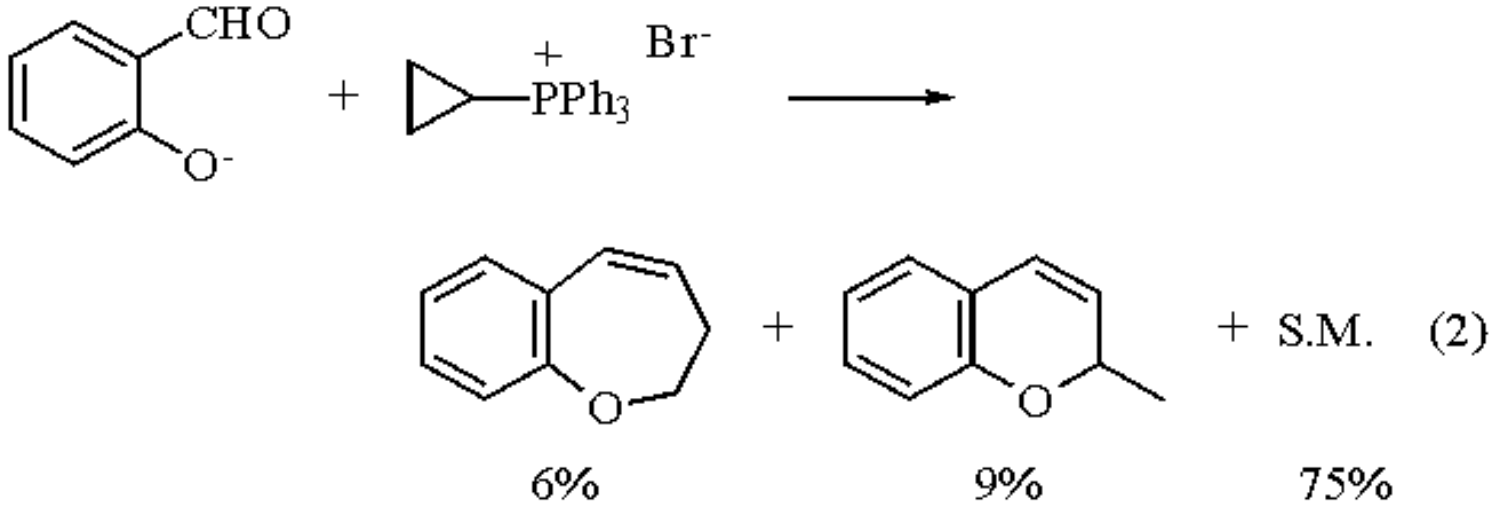

A synthesis of pyrrolizidines provides another application of cyclopropyltriphenylphosphonium bromide as an electrophile. Succinimide anion opens the cyclopropyl ring and the ylide generated cyclizes to yield the bicyclic product after hydrolysis (eq 3).[2] Cyclopropyltriphenylphosphonium bromide can be reduced by ***Lithium Aluminum Hydride*** to yield cyclopropyldiphenylphosphine.[4]

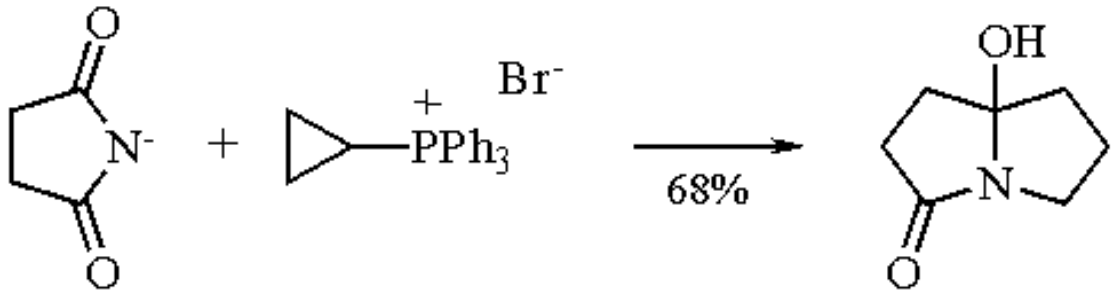

(3)

Investigations have generated two analogs of cyclopropyltriphenylphosphonium bromide designed to improve the yield of cyclopropyl ring opening by nucleophiles. 1-(Ethoxycarbonyl)cyclopropyltriphenylphosphonium tetrafluoroborate (**1**) undergoes facile cyclopropyl ring opening by β-keto ester carbanions (eq 4), salicylaldehyde anion (eq 5), and pyrrole-2-carbaldehyde anion (eq 6).[3a]

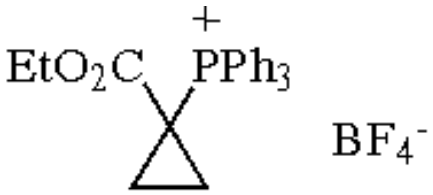

(1)

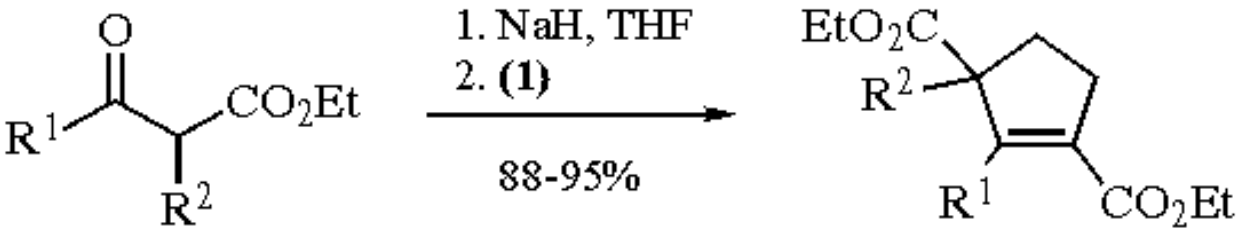

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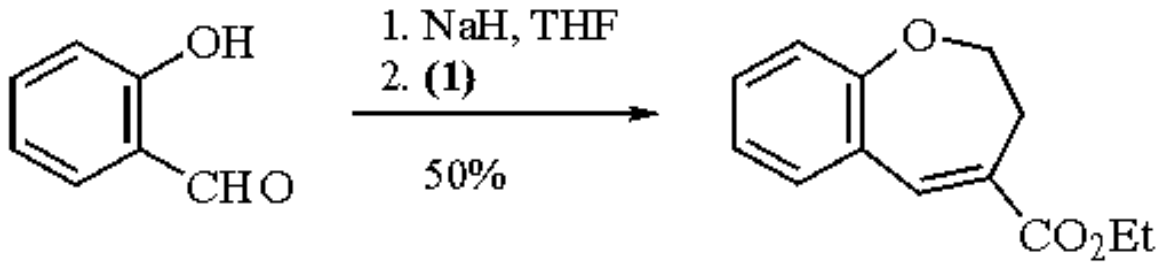

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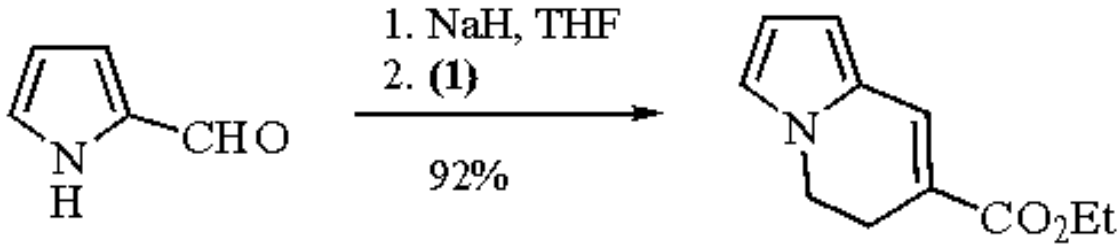

(6)

1-(Phenylthio)cyclopropyltriphenylphosphonium tetrafluoroborate experiences facile cyclopropyl ring opening by β-keto ester carbanions and the subsequent ylide is sufficiently reactive to generate a vinyl sulfide with the ketone moiety.[3b] Acid-catalyzed hydrolysis results in cyclopentanone products in 75-80% yield.

1. (a) Schweizer, E. E.; Thompson, J. G. *CC* **1966**, 666. (b) Stafford, J. A.; McMurry, J. E. *TL* **1988**, *29*, 2531.
2. Flitsch, W.; Hampel, K. *LA* **1988**, 387.
3. (a) Fuchs, P. L. *JACS* **1974**, *96*, 1607. (b) Marino, J. P.; Landick, R. C. *TL* **1975**, 4531.
4. Schweizer, E. E.; Berninger, C. J.; Thompson, J. G. *JOC* **1968**, *33*, 336.
5. (a) Albright, T. A.; Freeman, W. J.; Schweizer, E. E. *JACS* **1975**, *97*, 2942. (b) Baldwin, J. E.; Peavy, R. E. *JOC* **1971**, *36*, 1441.
6. Norden, W.; Sander, V.; Weyerstahl, P. *CB* **1983**, *116*, 3097.
7. Eitel, M.; Pindur, U. *S* **1989**, 364.
8. Zefirov, N. S.; Averina, N. V.; Boganov, A. M.; Laryukova, M. V.; Rashchupkina, Z. A.; Terent'ev, P. B.; Sharbatyan, P. A. *ZOR* **1981**, *17*, 1450. (*JOU* **1981**, *17*, 1291).
9. (a) Sisido, K.; Utimoto, K. *TL* **1966**, 3267. (b) Utimoto, K.; Tamura, M.; Sisido, K. *T* **1973**, *29*, 1169. For additional examples of 3-bromopropyltriphenylphosphonium bromide as the ylide source, see: (c) Salaün, J.; Bennani, F.; Compain, J.-C.; Fadel, A.; Ollivier, J. *JOC* **1980**, *21*, 4129. (d) Bertrand, M.; Leandri, G.; Meou, A. *T* **1981**, *37*, 1703. (e) Schmidbaur, H.; Schier, A.; Milewski-Mahrla, B.; Schubert, U. *CB* **1982**, *115*, 722. (f) Lasne, M.-C.; Ripoll, J.-L. *BSF(2)* **1981**, *2*, 340. For an example utilizing the less hydroscopic cyclopropyltriphenylphosphonium tetrafluoroborate, see: (g) Marino, J. P.; Ferro, M. P. *JOC* **1981**, *46*, 1828.

Edward J. Adams

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Decacarbonyldimanganese

$Mn_2(CO)_{10}$

[10170-69-2] · $C_{10}Mn_2O_{10}$ · Decacarbonyldimanganese · (MW 389.98)

(source of a wide range of manganese complexes; catalyst or cocatalyst for isomerization, oligomerization, radical coupling, etc.)

Alternate Names: dimanganese decacarbonyl; manganese carbonyl.

Physical Data: mp 154 °C; sublimes 80 °C/0.1 mmHg, 70 °C/0.05 mmHg.

Solubility: insol H_2O; mod sol common org solvents.

Form Supplied in: yellow crystalline solid; widely available but expensive.

Preparative Method: the most convenient laboratory synthesis is from tricarbonyl(η^5-methylcyclopentadienyl)manganese by reduction with sodium/naphthalene under carbon monoxide to yield ***Sodium Pentacarbonylmanganate***, acidification, and oxidation;[1] highly efficient stirring is essential in the first stage for good yields, and incomplete oxidation or the loss of the volatile (toxic) intermediate $HMn(CO)_5$ in the final stages must be carefully avoided.

Handling, Storage, and Precautions: use in a fume hood; toxic, but not sufficiently volatile to present handling problems. May be stored indefinitely in a well-stoppered bottle at rt.

Introduction.

The molecule consists of two $Mn(CO)_5$ fragments linked by an Mn-Mn bond such that each Mn atom has octahedral coordination.[2] Many uses of $Mn_2(CO)_{10}$ involve its initial reduction to the anion $[Mn(CO)_5]^-$ or oxidation by halogens to $XMn(CO)_5$ (X = Cl, Br) and their use in turn to produce hydrido, alkyl, acyl, η^3-allyl, η^5-cyclopentadienyl, and η^6-arene complexes, amongst others.

Catalytic Uses.

Most catalytic systems utilizing $Mn_2(CO)_{10}$ require temperatures of approximately 140 °C, sufficient for cleavage of the relatively weak Mn-Mn bond (eq 1). In contrast to such thermolysis, photolysis involves two competitive

processes: the same cleavage (eq 1), as well as loss of CO (eq 2).

$$(OC)_5Mn\text{-}Mn(CO)_5 \longrightarrow 2 \cdot Mn(CO)_5 \qquad (1)$$

$$(OC)_5Mn\text{-}Mn(CO)_5 \longrightarrow (OC)_5Mn\text{-}Mn(CO)_4 + CO \qquad (2)$$

The radicals formed by thermolysis are efficient abstractors of halide from $RCCl_3$ (eq 3),[3] for example, and hence serve to initiate selective hydrogenolysis of such halides in the presence of good hydrogen donors (eq 4)[4] or addition to activated alkenes (eq 5).[5]

$$RCCl_3 + \bullet Mn(CO)_5 \longrightarrow R\dot{C}Cl_2 + ClMn(CO)_5 \qquad (3)$$

$$2\,RCCl_3 + i\text{-}PrOH \longrightarrow 2\,RCHCl_2 + Me_2CO \qquad (4)$$

$$Cl_3CCO_2Me + CH_2{=}CH\,TMS \longrightarrow$$

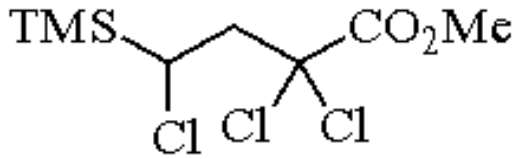

(5)

Addition to unactivated alkenes (except C_2H_4) is generally less efficient[4b,5b] and, whereas $Mn_2(CO)_{10}$ is more efficient and more selective than ***Pentacarbonyliron*** for reductions of the type shown by eq 4, the opposite is true for the additions (eq 5). In such reactions, 1:1 adducts tend to predominate and even in the addition of trichloroacetate to ethylene (eq 6), which gives a significant proportion of the telomers (n = 2-4), the use of DMF as solvent largely suppresses formation of all but the 1:1 adduct (n = 1).[6]

$$Cl_3CCO_2Me + CH_2{=}CH_2 \longrightarrow Cl(CH_2CH_2)_nCCl_2CO_2Me \qquad (6)$$

Similar selective hydrogenolysis and addition reactions involving hydrogen rather than halogen abstraction as the initiating step are involved when such reactive hydrogen sources as silanes, thiols, or phosphites are used with $Mn_2(CO)_{10}$ (eqs 7-9). Detailed study of such reductions as that of 1,3,3,5-tetrachloropentane by Et_3SiH (eq 10)[7] shows clearly that &bdot;$Mn(CO)_5$ acts only as initiator with the silane (not $HMn(CO)_5$) providing the hydrogen in the propagation step and Et_3Si&bdot; abstracting the chlorine atom.

$$Et_3SiH + \bullet Mn(CO)_5 \longrightarrow Et_3Si\bullet + HMn(CO)_5 \qquad (7)$$

$$BuSH + \bullet Mn(CO)_5 \longrightarrow BuS\bullet + HMn(CO)_5 \qquad (8)$$

$$(EtO)_2P(O)H + \bullet Mn(CO)_5 \longrightarrow (EtO)P(O)\bullet + HMn(CO)_5 \qquad (9)$$

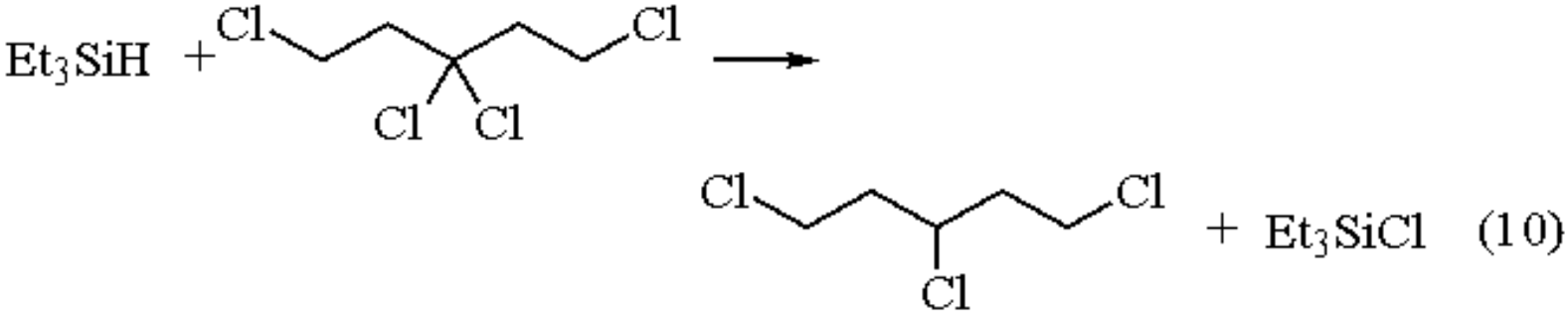

The efficiency and especially the high selectivity of $Mn_2(CO)_{10}$ in this and related reductions, both by silanes[8] and thiols (e.g. eq 11)[9] is only rarely matched or exceeded by other metal carbonyls (including $Re_2(CO)_{10}$, $Fe(CO)_5$, and $Mo(CO)_6$).

$$\mathrm{BuSH} + \mathrm{Cl_3C(CH_2)}_n\mathrm{Cl} \longrightarrow \mathrm{Cl_2CH(CH_2)}_n\mathrm{Cl} \qquad (11)$$
$$n = 4, 6, 8$$

Particularly striking is the selectivity in additions to alkenes of the radicals formed according to eqs 7-9. Here, only the 1:1 adducts are significant products in the additions, exemplified in eqs 12-14,[10-12] when $Mn_2(CO)_{10}$ is used as initiator, whereas substantial amounts of higher telomers result when peroxides or other classical initiators are employed. In a typical comparative study,[11] the addition (eq 15) using $Mn_2(CO)_{10}$ catalysis provided the products (n = 1) and (n = 2) in 99 and 0.5% yields, ***Hexacarbonylmolybdenum*** was almost as selective (but required a long reaction time), ***Decacarbonyldirhenium*** was inactive, while ***1,1-Di-t-butyl Peroxide*** catalysis gave 50% (n = 1) and 20% (n = 2).

$$\mathrm{Et_3SiH} + \mathrm{C_2H_4} \longrightarrow \mathrm{Et_4Si} \qquad (12)$$

$$\mathrm{BuSH} + \mathrm{CH_2{=}CHOAc} \longrightarrow \mathrm{BuSCH_2CH_2OAc} \qquad (13)$$

$$\mathrm{(EtO)_2P(O)H} + \mathrm{CH_2{=}CHBu} \longrightarrow \mathrm{(EtO)_2P(O)CH_2CH_2Bu} \qquad (14)$$

$$\mathrm{BuSH} + \mathrm{CH_2{=}CHCN} \longrightarrow \mathrm{BuS(CH_2CHCN)}_n\mathrm{H} \qquad (15)$$

Stoichiometric Reactions with Unsaturated Hydrocarbons.

Much of the synthetically interesting chemistry involving reactions of $Mn_2(CO)_{10}$ with alkenes and alkynes has been obscured by the fact that few of the metal complexes initially obtained have been subjected to further reactions or even to cleavage of the organic ligand from the metal. Nevertheless, the potential for specific transformations of such unsaturated hydrocarbons is clear from the reactions outlined below.

Enyl and Dienyl Complexes.

Many different dienes are known to react with $Mn_2(CO)_{10}$ to give complexes. In the case of open-chain dienes, η^3-enyl complexes are isolated as initial products of irradiation (eq 16),[13] but these may be smoothly converted to η^5-dienyl complexes (eq 17).

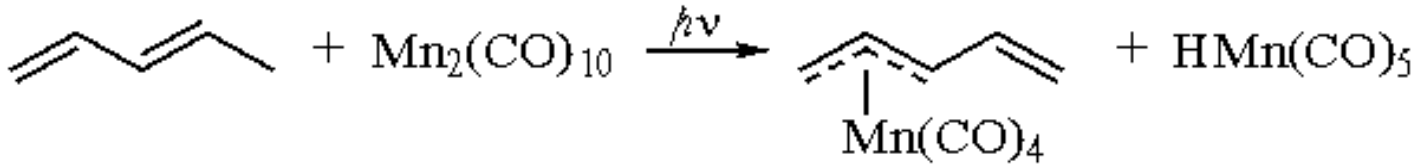

(16)

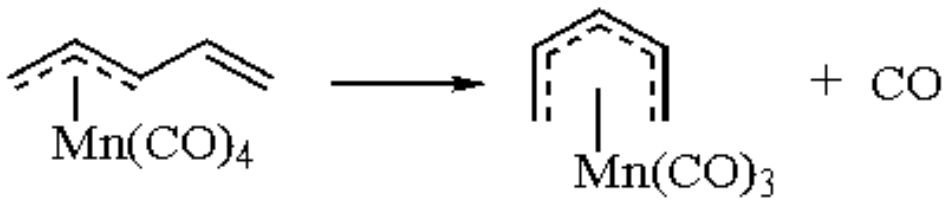

(17)

For cyclopentadiene[14a] (or its pentamethyl derivative[14b]), cyclohexadiene,[15] and cycloheptadiene,[16] thermal conditions have been used that lead to dienyl complexes (eq 18). These reactions occur at temperatures which enable cleavage of the Mn-Mn bond, but it is not established whether the mechanism involves initial H abstraction by &bdot;$Mn(CO)_5$ or a concerted process. Since the temperatures also suffice for decomposition of $HMn(CO)_5$ to dihydrogen and $Mn_2(CO)_{10}$, all of the manganese can be utilized in complex formation.

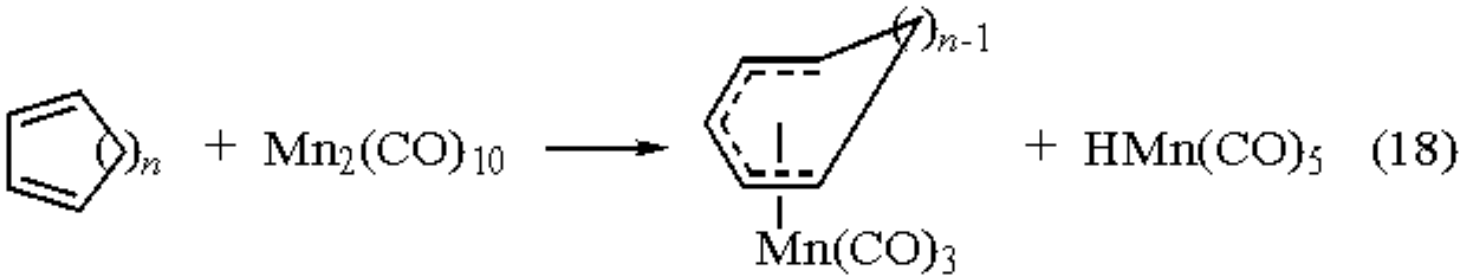

(18)

The synthetic potential of such dienyl complexes is perhaps most strikingly illustrated by the diene photoaddition to the open-chain complexes leading to nine-membered rings (still attached to the metal), as in eq 19.[17] Cyclohexadiene adds in a different manner, involving formation of one C-C bond and H-migration (eq 20); incorporation of a second diene unit occurs in some cases.[13a]

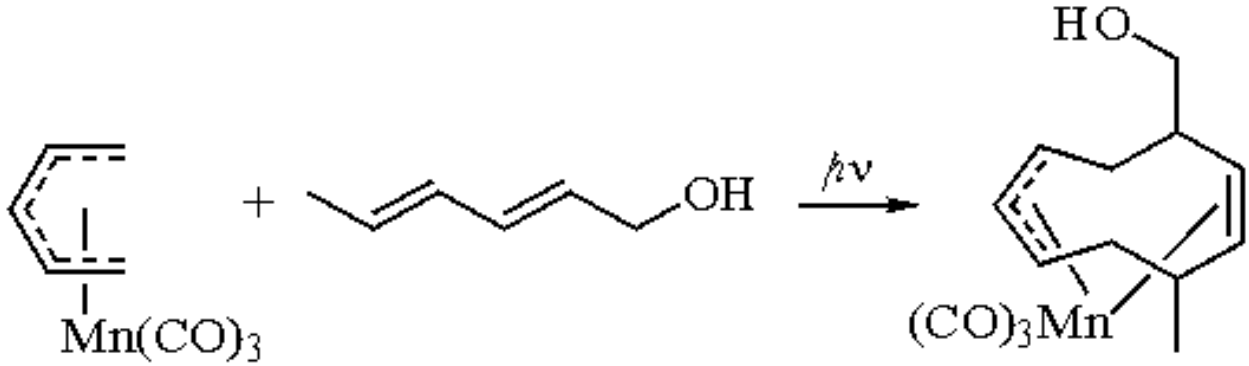

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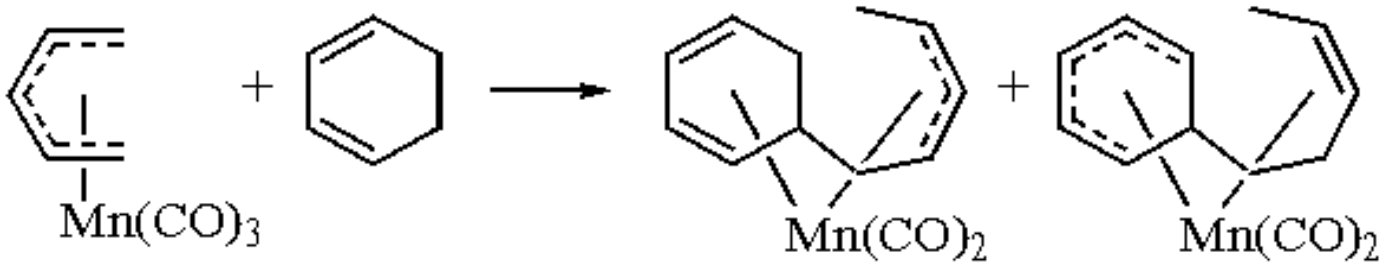

(20)

As open-chain dienyl and cyclohexadienyl tricarbonylmanganese complexes are more usually prepared from halopentacarbonylmanganese, $XMn(CO)_5$ (X = Cl, Br), and (alkyl)cyclopentadienyltricarbonylmanganese from $MnCl_2$ (via $(RC_5H_4)_2Mn$), only the useful reactions of the cycloheptadienyl complex are discussed further here.

Tricarbonylcycloheptadienylmanganese (formed according to eq 18, *n* = 3) is smoothly converted[16] to the cationic triene complex by hydride abstraction (eq 21) and the latter adds a wide range of nucleophiles to give *exo*-substituted cycloheptadienyl complexes (eq 22; Y = OR, NMe_2, CN, $CH(CO_2Me)_2$, Me, Ph, etc.).[16,18] If an *exo*-hydrogen could be specifically abstracted as hydride (eq 23), the product should undergo further nucleophilic addition to give vicinally (i.e. 6,7-) disubstituted cycloheptadienyl complexes. However, trityl either abstracts Y (e.g. when Y = OR, NMe_2, or CN) or fails to react (R = Me), apparently for steric reasons, and other reagents tried also fail to react or cause complete disruption (e.g. NBS to give $[Mn(CO)_4Br]_2$).

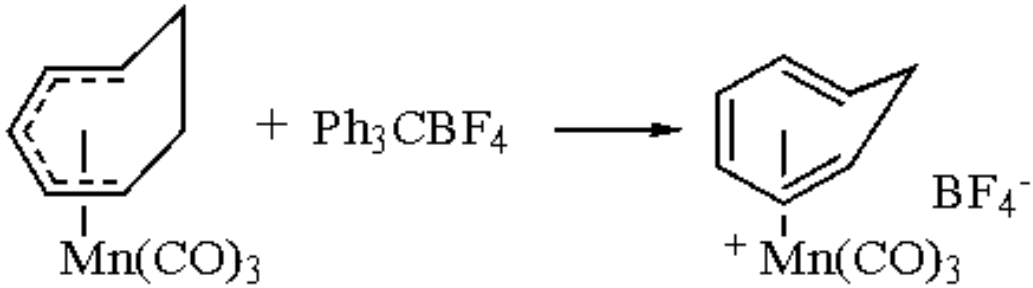

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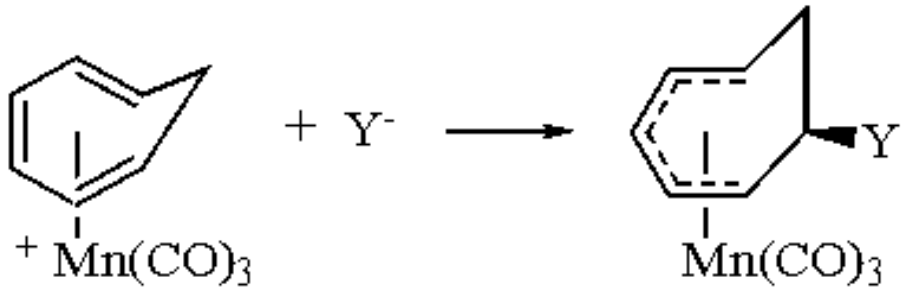

(22)

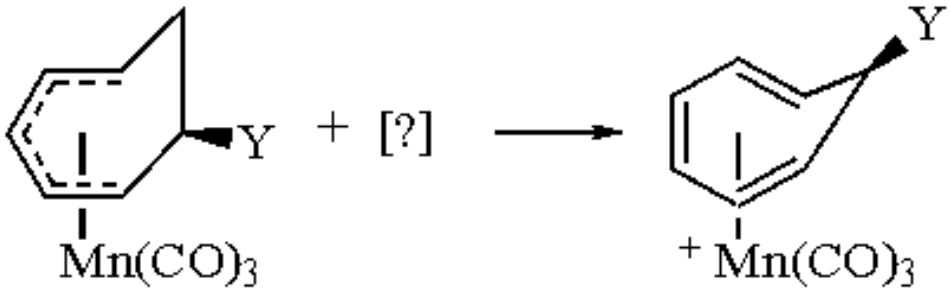

(23)

Regeneration of a cationic system, but at the dienyl level, has been accomplished using nitrosonium

hexafluorophosphate (eq 24) and the products then add nucleophiles specifically to give 5,7-disubstituted cycloheptadiene complexes (eq 25).[18,19] Analogous methods have been used to convert *exo*-substituted cyclohexadienyl complexes to vicinally (i.e. 5,6-) disubstituted cyclohexadienemanganese complexes.[19a,b]

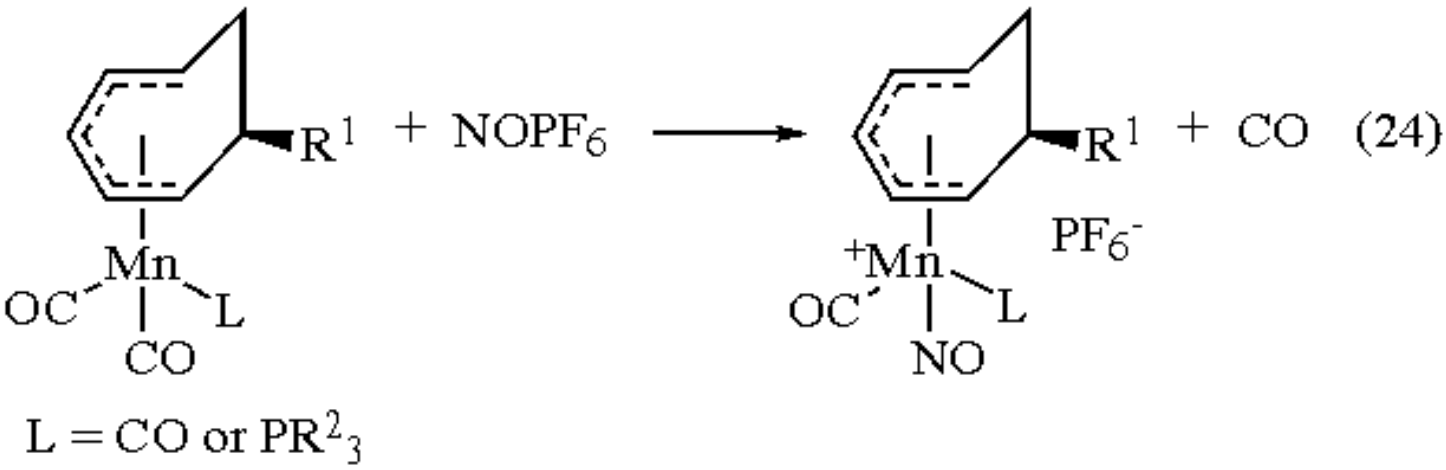

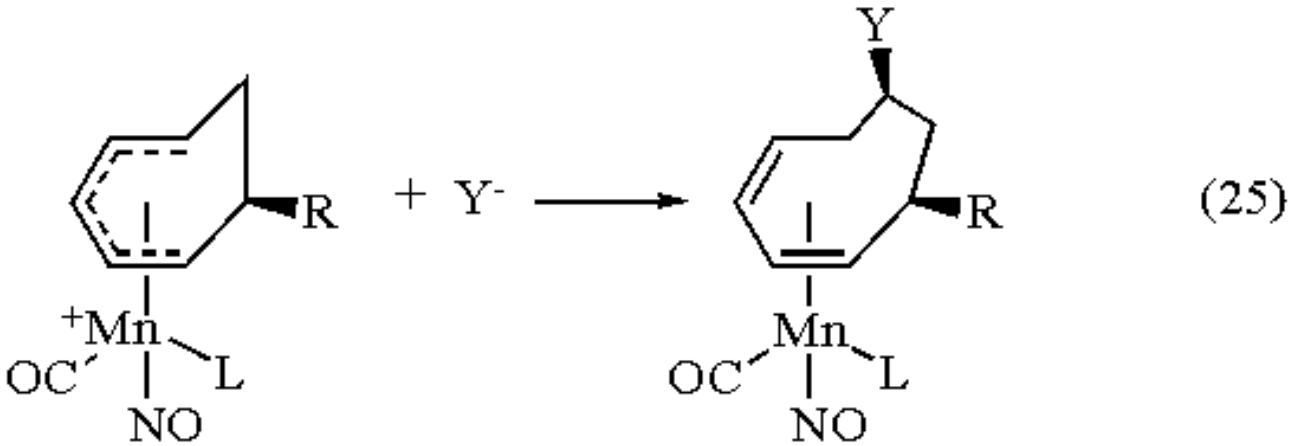

Photolysis of $Mn_2(CO)_{10}$ with allenes leads chiefly to (μ-allene)$Mn_2(CO)_8$ complexes, but is accompanied by allene di- and even trimerization in apparently regioselective fashion (eqs 26 and 27).[13b,20]

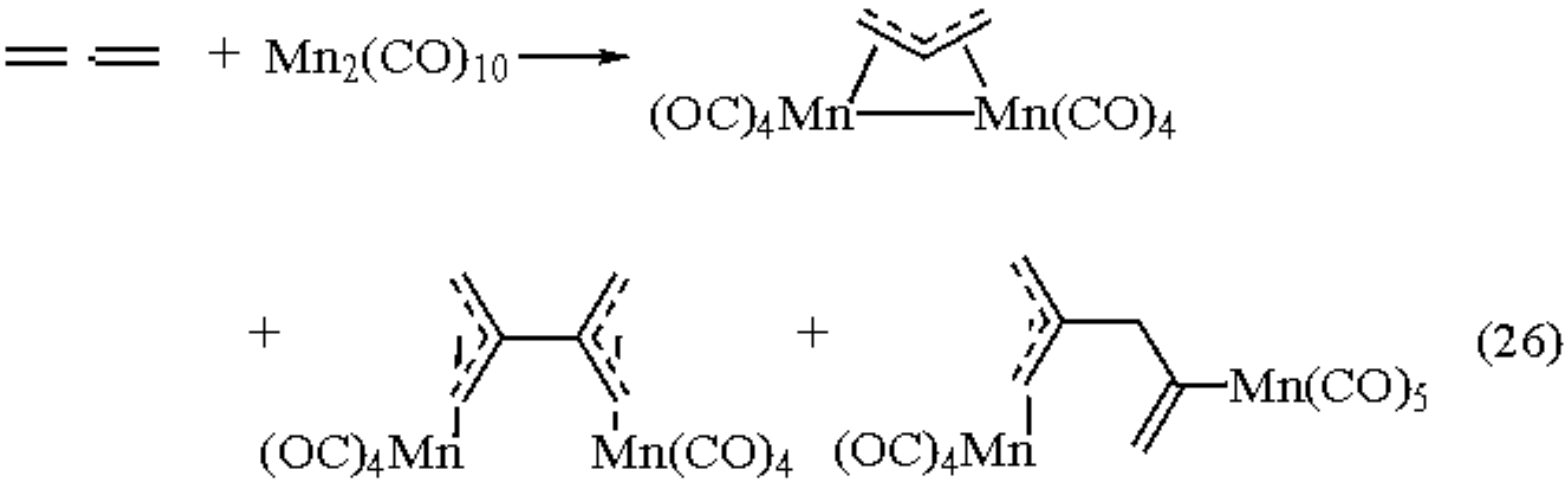

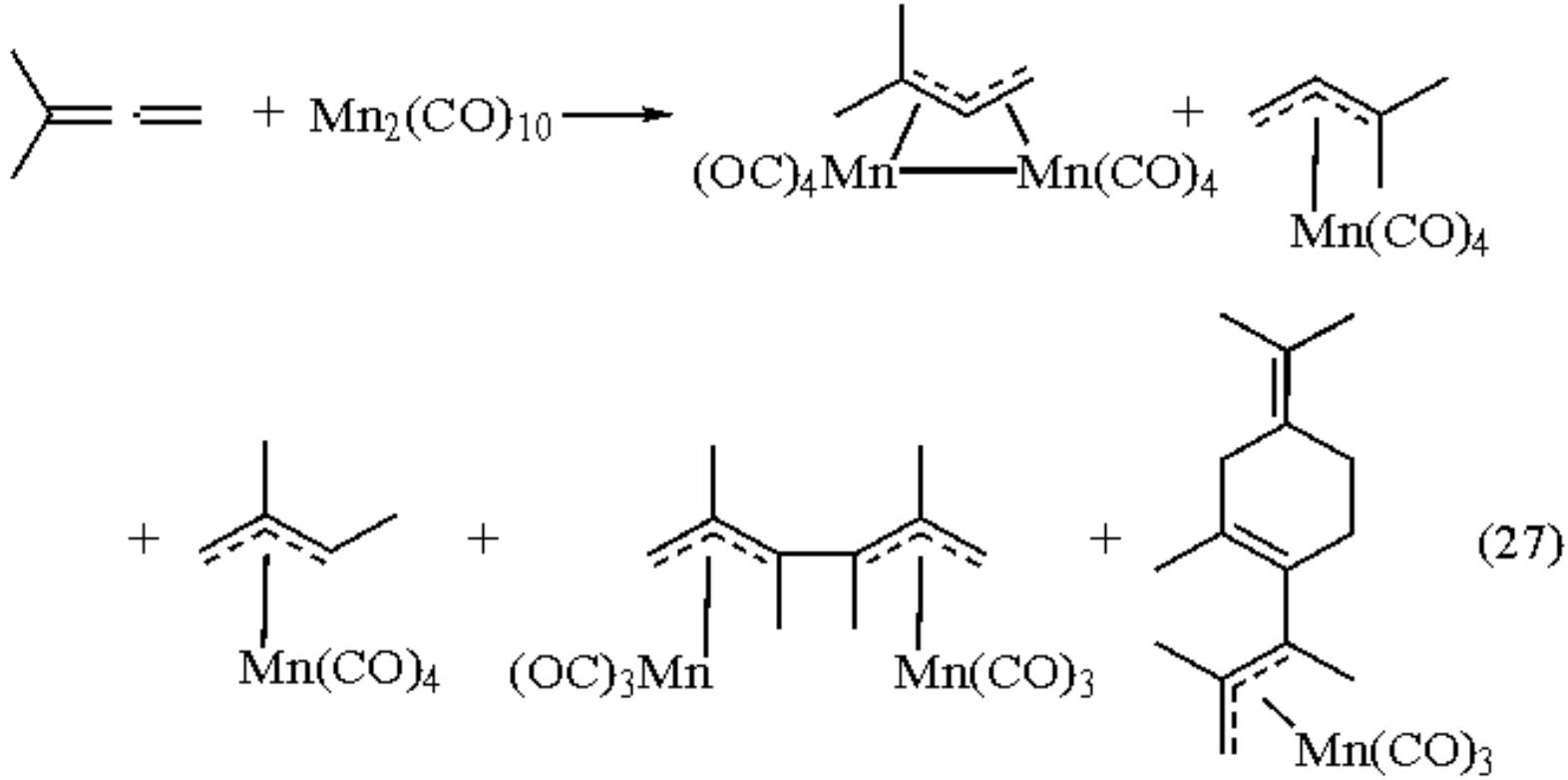

A unique ligand dimerization and ring-opening process occurs in the reaction of $Mn_2(CO)_{10}$ with tropone (eq 28).[21]

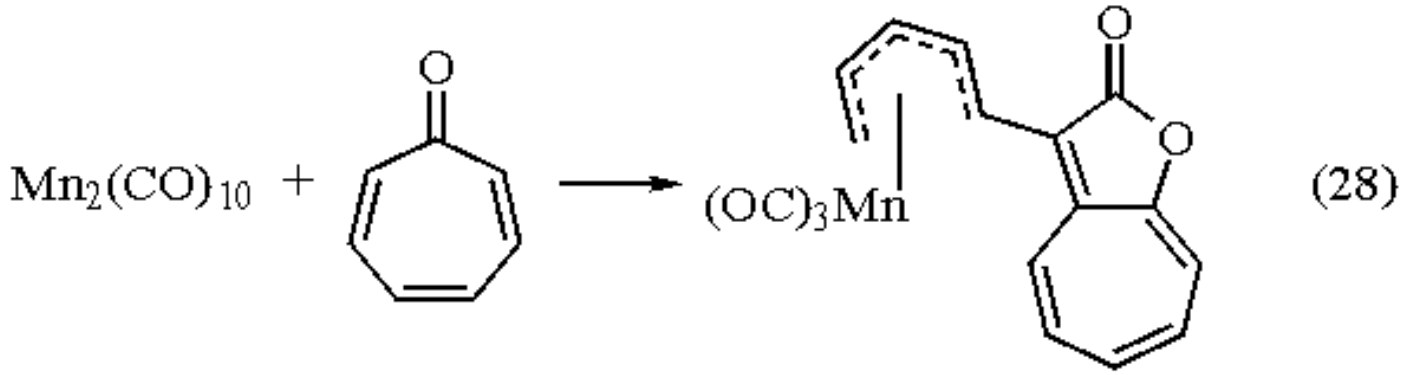

Alkyne Complexes.

Reactions of alkynes with manganese carbonyl do not appear to have been studied systematically, but have yielded synthetically interesting products in several cases. None more so than the formation of a dihydropentalenyl complex from acetylene itself (eq 29).[22]

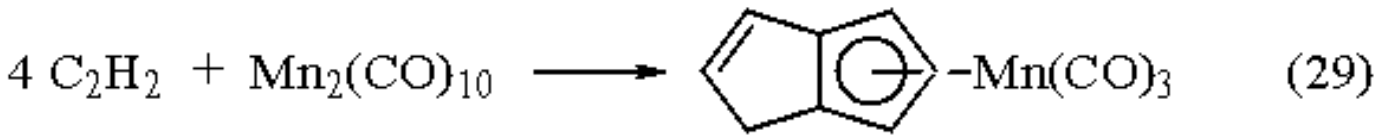

The reaction of diethylaminopropyne (eq 30) yields four complexes whose sequential formation involves two proton migrations, the first of which converts the alkyne to an allene ligand.[23] More obvious synthetic potential can be seen in

the reaction of ethoxy- and dimethylamino-alkynes (with $Mn_2(CO)_{10}$ activated by prior displacement of one CO); thus ethoxyacetylene itself gives a product with a divinyl ketone ligand (eq 31).[24a,b] Similar reactions with diethyl acetylenedicarboxylate have been described.[24c]

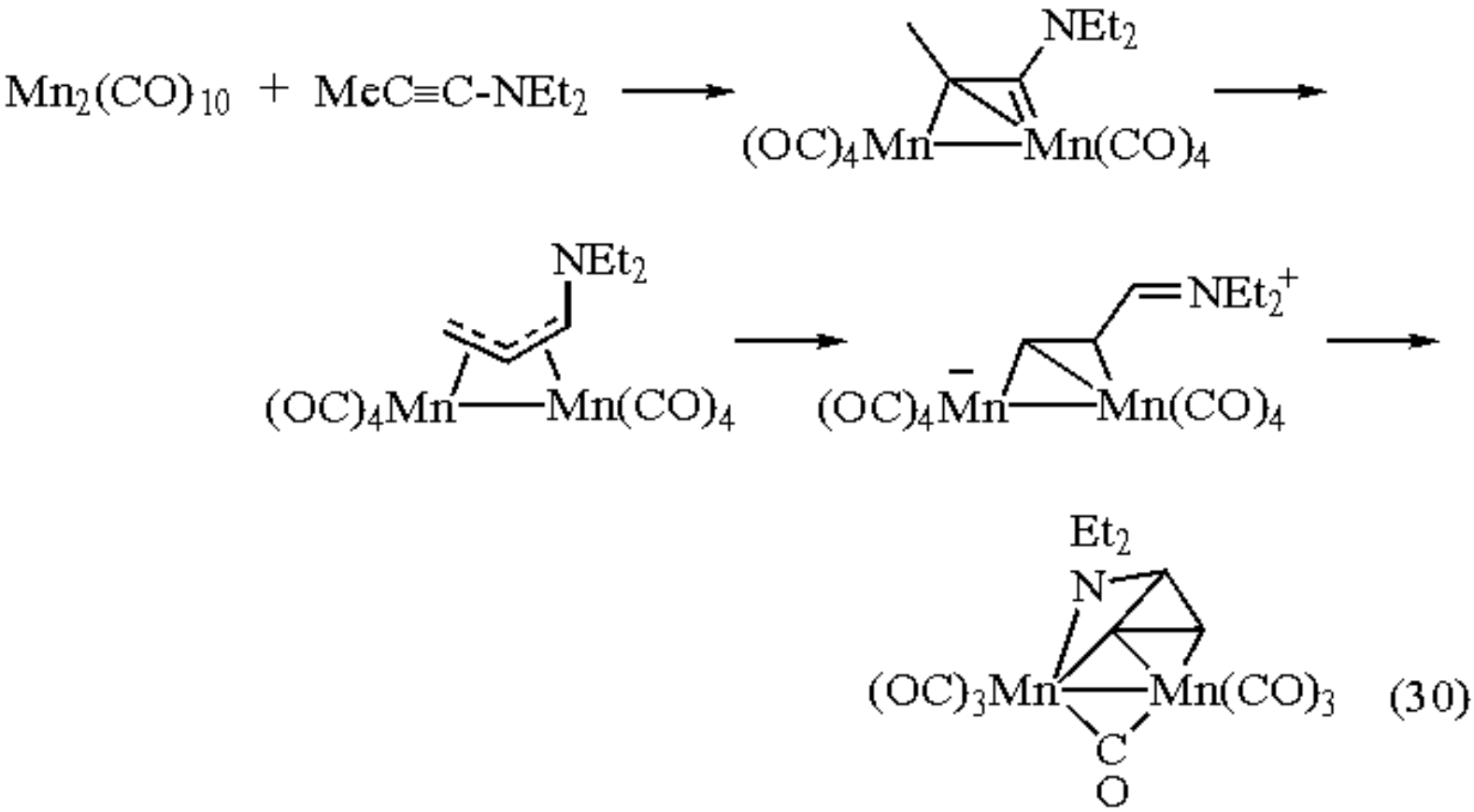

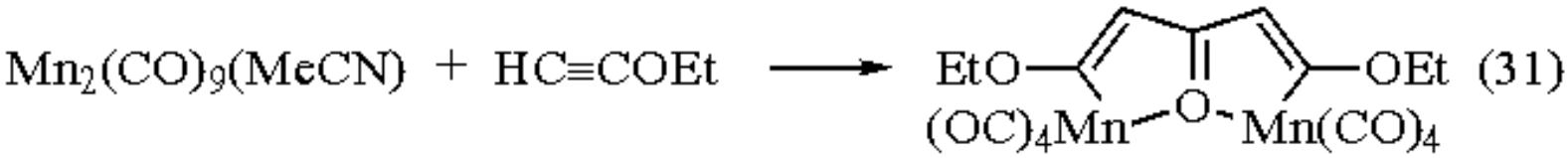

Finally, the lactone synthesis from $Mn_2(CO)_{10}$, a terminal alkyne, and iodomethane (eq 32) probably involves reaction of the alkyne with initially formed acetyl(pentacarbonyl)manganese rather than directly with the decacarbonyl.[25]

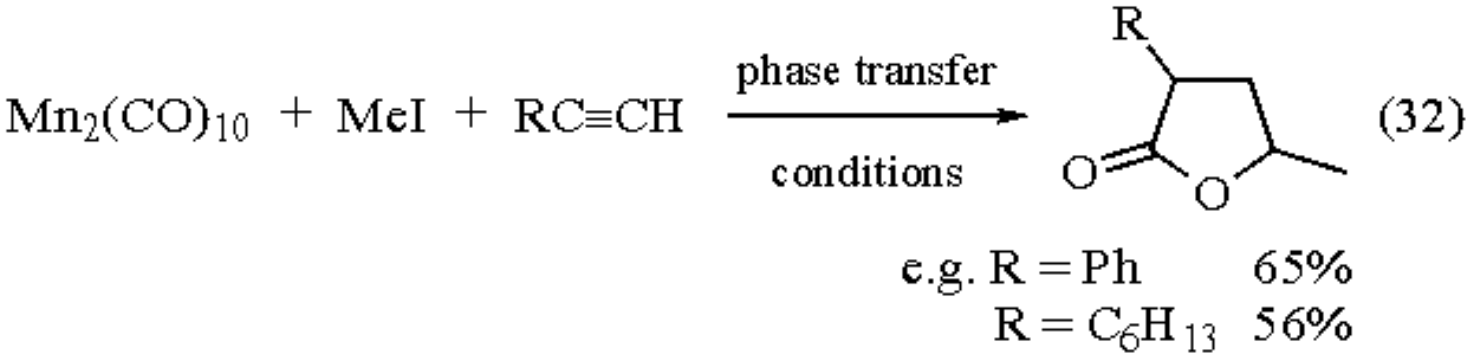

Related Reagents.

Pentacarbonylmethylmanganese; ***Pentacarbonylchloromanganese***; ***Pentacarbonylphenylmanganese***; ***Sodium Pentacarbonylmanganate***; ***Pentacarbonyl(trimethylsilyl)manganese***.

---

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Decacarbonyldirhenium

$Re_2(CO)_{10}$

[14285-68-8] · $C_{10}O_{10}Re_2$ · Decacarbonyldirhenium · (MW 652.52)

(oligomerization catalyst)

Alternate Name: rhenium carbonyl.

Physical Data: mp 177 °C, 170 °C; sublimes 70 °C/0.1 mmHg.

Solubility: sparingly sol common org solvents; insol water.

Form Supplied in: colorless crystals; commercially available.

Handling, Storage, and Precautions: stable to air and to strong acids; may be stored indefinitely at ambient temperature; ignites in air above 140 °C.

Conversion to Other Rhenium Carbonyl Derivatives.

Decacarbonyldirhenium is the starting material for the synthesis of a wide range of organorhenium compounds. Many of these conversions depend on three key initial steps: oxidation by halogens to the halopentacarbonyls, $XRe(CO)_5$[1] (very efficient chlorination occurs with ***Sulfuryl Chloride***);[2] reduction by sodium amalgam to $Na^+[Re(CO)_5]^-$;[3] and substitution of one or more carbonyl groups by other donor ligands, e.g. PPh_3 to give $Re_2(CO)_8(PPh_3)_2$. Thus whereas tricarbonylcyclopentadienylrhenium is readily obtained directly from $Re_2(CO)_{10}$ and cyclopentadiene dimer,[4] and the cyclohexa- and -heptadienyl analogs are prepared similarly from the corresponding dienes (eq 1),[5] a wider range of substituted cyclopentadienyl complexes as well as the open-chain dienyls are available by methods employing the bromocarbonyl (eqs 2 and 3).[6]

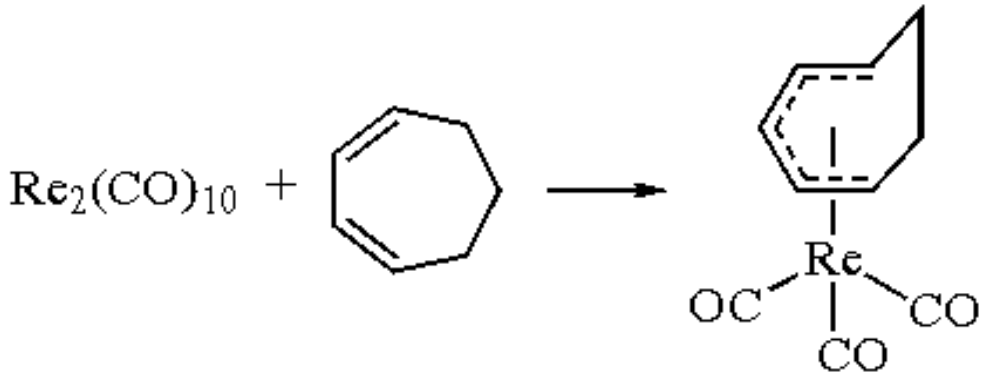

(1)

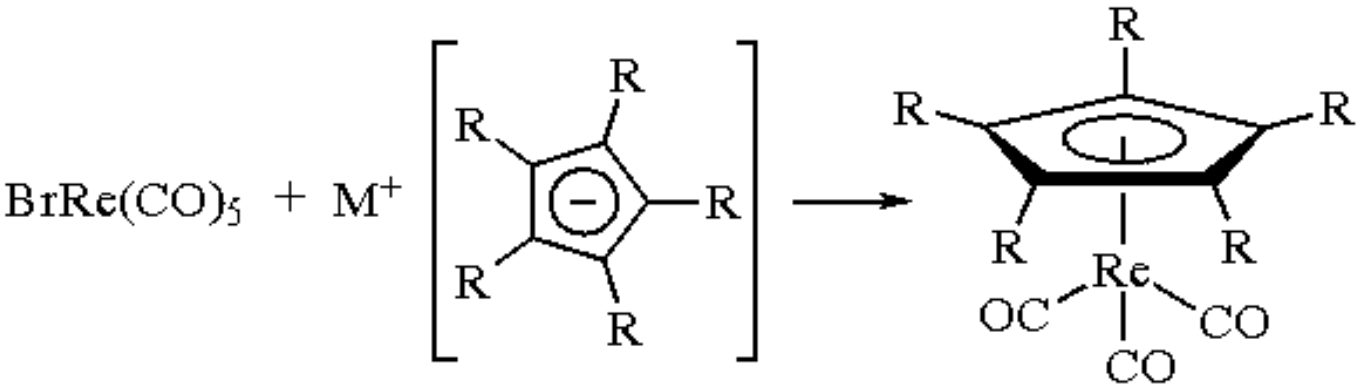

(2)

R = H, Me; M = Li, Na, K or Tl

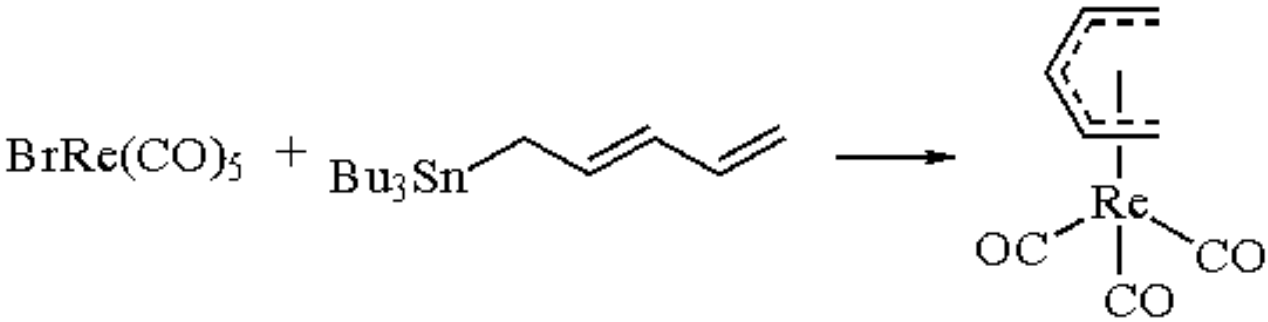

(3)

The chloride or bromide is also used together with ***Aluminum Chloride*** or bromide and alkenes, dienes, and arenes to generate the cationic complexes $[(alkene)Re(CO)_5]^+$, $[(diene)Re(CO)_4]^+$, or $[(arene)Re(CO)_3]^+$ (eq 4).[7]

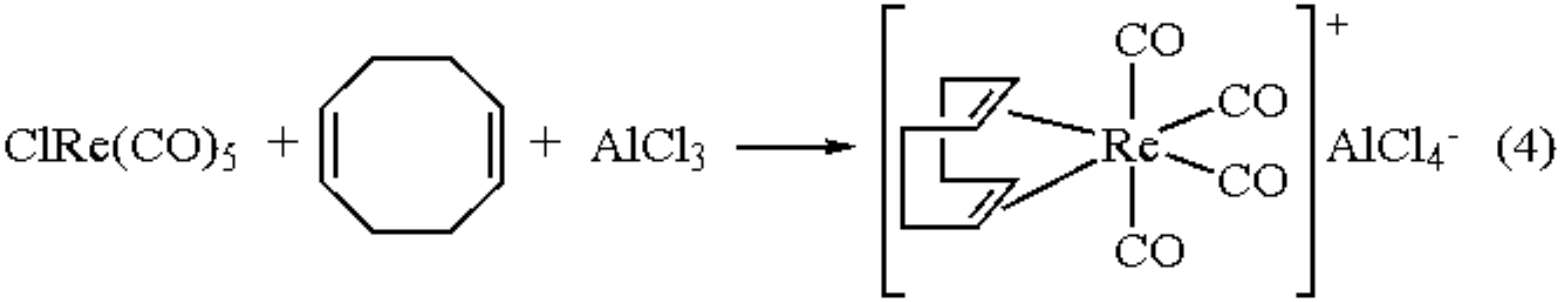

(4)

Catalytic Uses.

Both $Re_2(CO)_{10}$ and $ClRe(CO)_5$ can catalyze chlorination of hydrocarbons. Catalysis of the reaction of cyclohexane with carbon tetrachloride (eq 5)[8] undoubtedly involves initiation by thermal dissociation of the dinuclear carbonyl to give two &bdot;$Re(CO)_5$ radicals followed by chlorine atom abstraction from CCl_4. Surprisingly, the $Re_2(CO)_{10}$ or $ClRe(CO)_5$ catalyzed reaction of toluene with SO_2Cl_2 yields the products of ionic chlorination, 2- and 4-chlorotoluene, and only traces of benzyl chloride.[2]

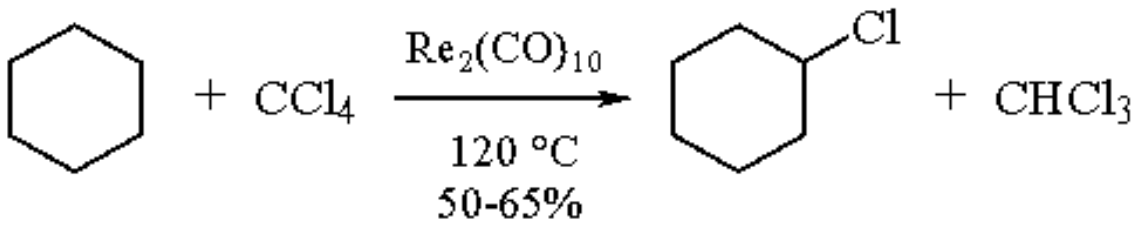

(5)

Decacarbonyldirhenium is more efficient than ***Decacarbonyldimanganese*** in catalyzing the selective hydrogenolysis of 1,3,3,5-tetrachloropentane (eq 6), but the reverse is true of some similar examples.[9] At 230 °C it catalyzes the quantitative hydrogenation of cyclohexene or benzene to cyclohexane.[10] $Re_2(CO)_{10}$ is also marginally better than $Mn_2(CO)_{10}$ (but both are inferior to ***Pentacarbonyliron***/HMPA) as a catalyst for addition of methyl trichloroacetate to vinyltrimethylsilane (eq 7).[11] The rhenium compound is substantially better than manganese carbonyl as catalyst for the addition of butanethiol to acrylonitrile (eq 8).[12] A conflicting picture emerges from comparison of these catalysts for the addition of triethylsilane to alkenes. With 1-hexene, $Re_2(CO)_{10}$ at 145 °C causes fairly smooth addition to yield 1-hexyltriethylsilane (60-81%),[13] whereas $Mn_2(CO)_{10}$ yields unsaturated products. $Re_2(CO)_{10}$ is also the more efficient catalyst in addition to methyl methacrylate, but the opposite is true in the case of methyl acrylate.[14] In the presence of ***Lithium Chloride***, rhenium carbonyl catalyzes the conversion of CO and H_2 to glycol.[15]

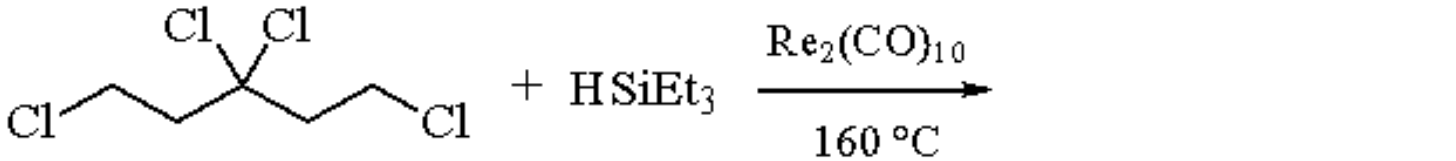

(6)

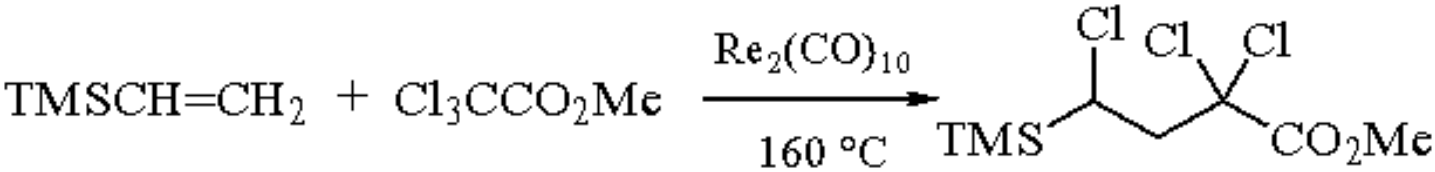

(7)

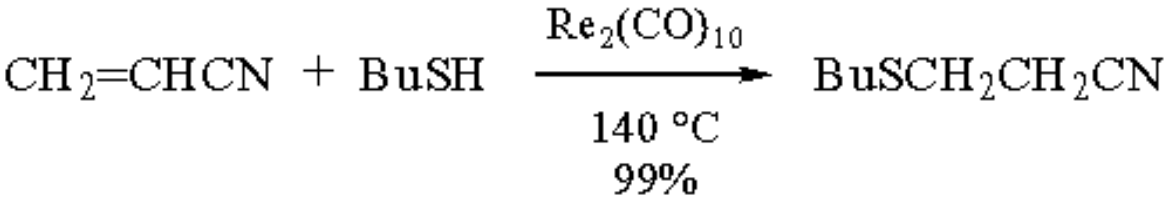

(8)

Stoichiometric Reactions.

Much of the potentially synthetically useful chemistry of rhenium carbonyl consists of transformations which leave the organic fragments bound to the metal so that further reactions have to be explored before the utility of these compounds in the synthesis of metal-free organic molecules can be properly assessed. $Re_2(CO)_{10}$, activated by photolysis with 1-hexene, reacts stepwise with two molecules of dimethylaminopropyne, leading to their combination as shown in eq 9.[16] Reaction of $NaRe(CO)_5$ with alkynyl esters involves linkage of a CO ligand to the alkyne system (eq 10).[17]

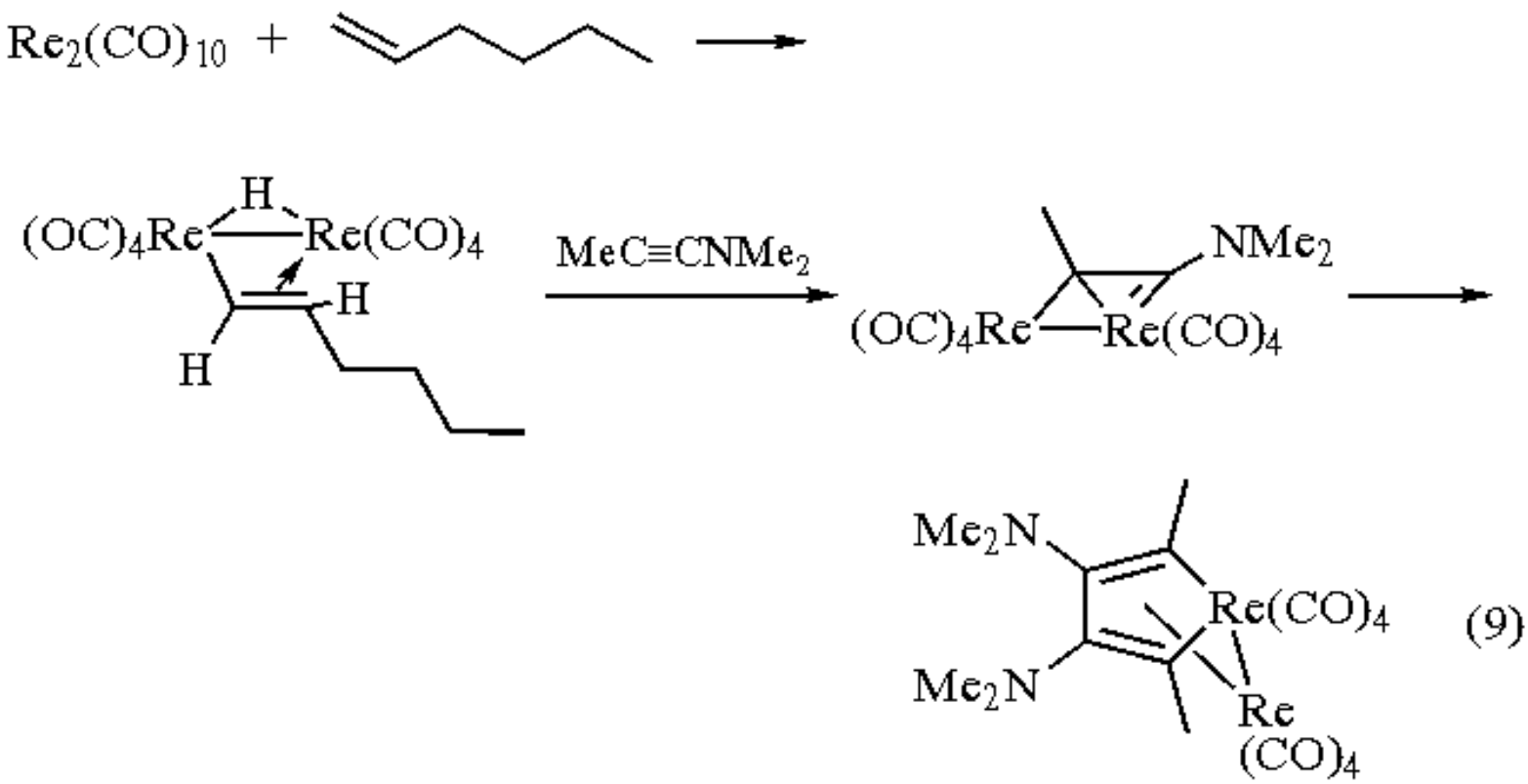

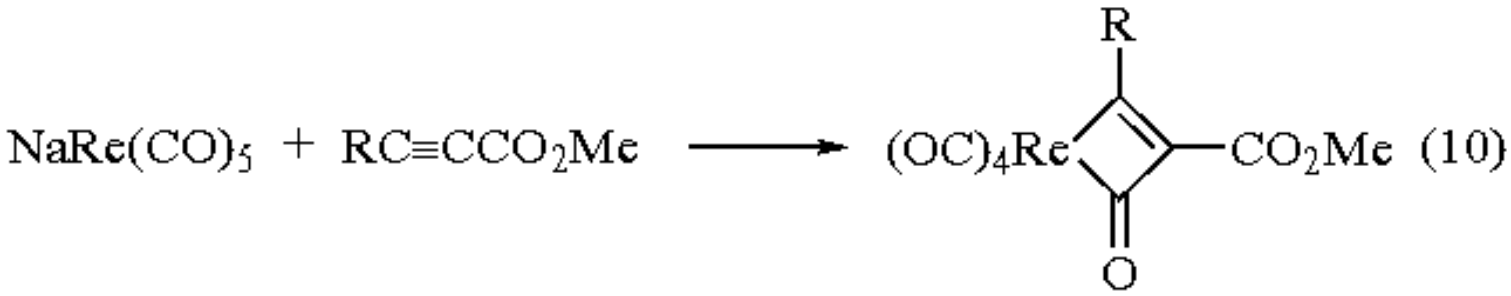

Halocarbene complexes can be obtained, e.g. by the reaction of eq 11,[18] and neutral carbenedicarbonylcyclopentadienylrhenium derivatives are prepared by the Fischer method (eq 12).[19]

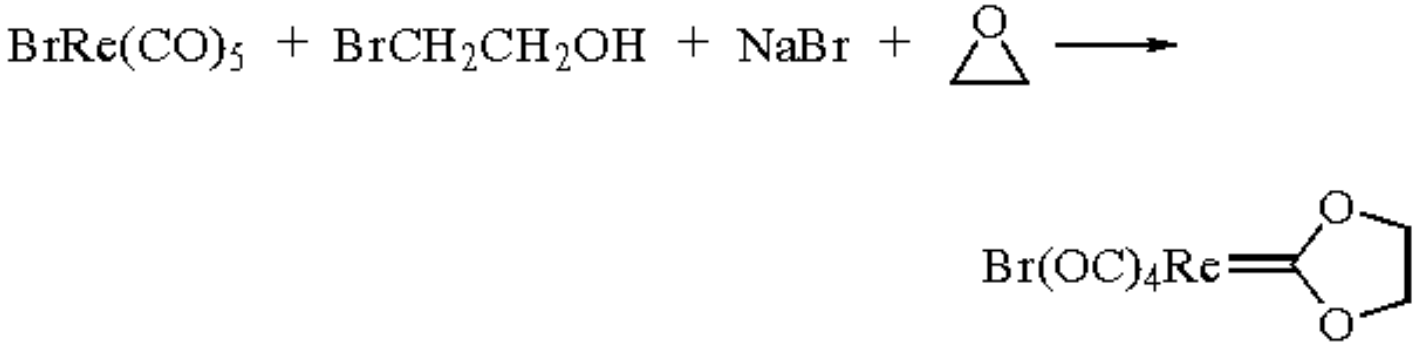

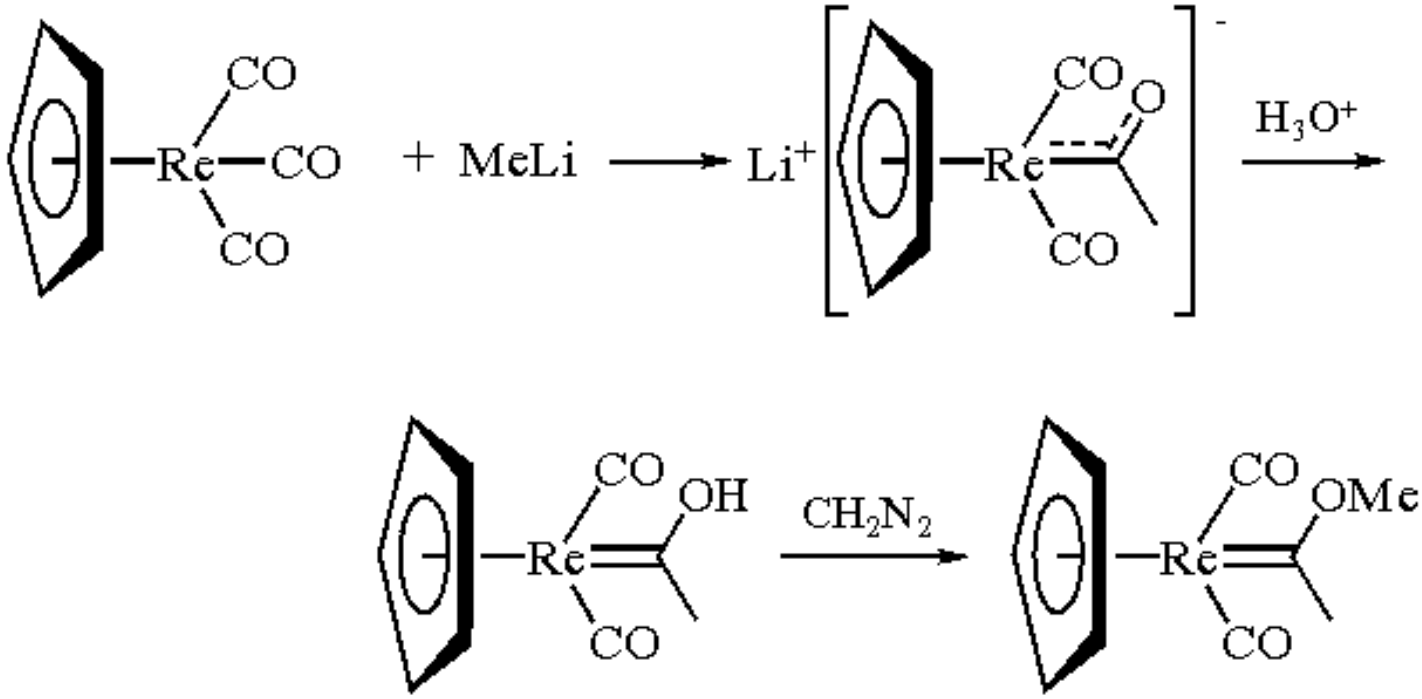

With softer alkylating agents the intermediate of this reaction yields an alkyl-acyl derivative (eq 13) which, on photolysis, eliminates butane-2,3-dione.[20]

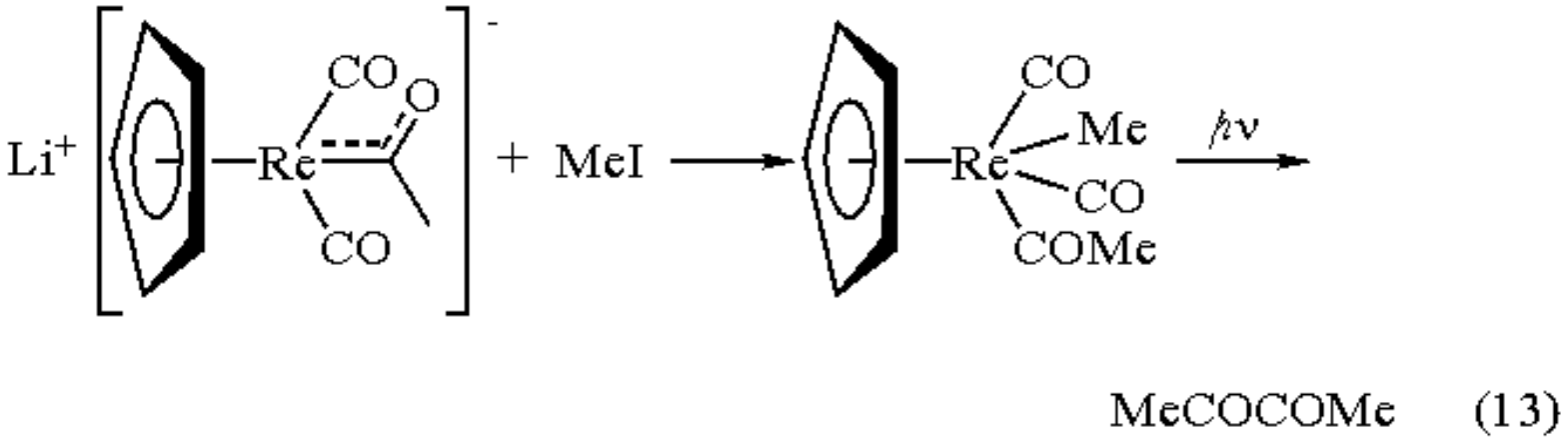

A neutral carbene complex, $CpRe(CO)_2$=C=CHPh, has also been obtained by irradiation of tricarbonylcyclopentadienylrhenium with phenylacetylene.[21] Cationic carbene complexes have been prepared from the NO-substituted cation $[CpRe(CO)_2NO]^+$, itself obtained from $CpRe(CO)_3$ with $NO[HSO_4]$.[22] Replacement of one CO in

this cation by triphenylphosphine gives the chiral cation $[CpRe(CO)(PPh_3)NO]^+$, which has been resolved into its enantiomers.[23] Replacement of the second CO by an alkene, followed by base treatment and protonation e.g. as in eq 14,[24,25] yields a carbene complex isomeric with the precursor cationic alkene complex. Alkylation of the intermediate alkenylrhenium complexes also leads to carbene derivatives in some cases.[25] The alternative route to these involves reaction of the cation $[CpRe(CO)(PPh_3)NO]^+$ with alkyllithium followed by hydride abstraction, as illustrated for the preparation of the parent methylene complex (eq 15). Some other alkyls (CH_2R) behave analogously on hydride abstraction, but alkyls with a tertiary β-H (i.e. CH_2CHR_2) lose this H to give the more stable cationic alkene complexes.[26] Vinylcarbene analogs are also readily available by two routes (eq 16).[27]

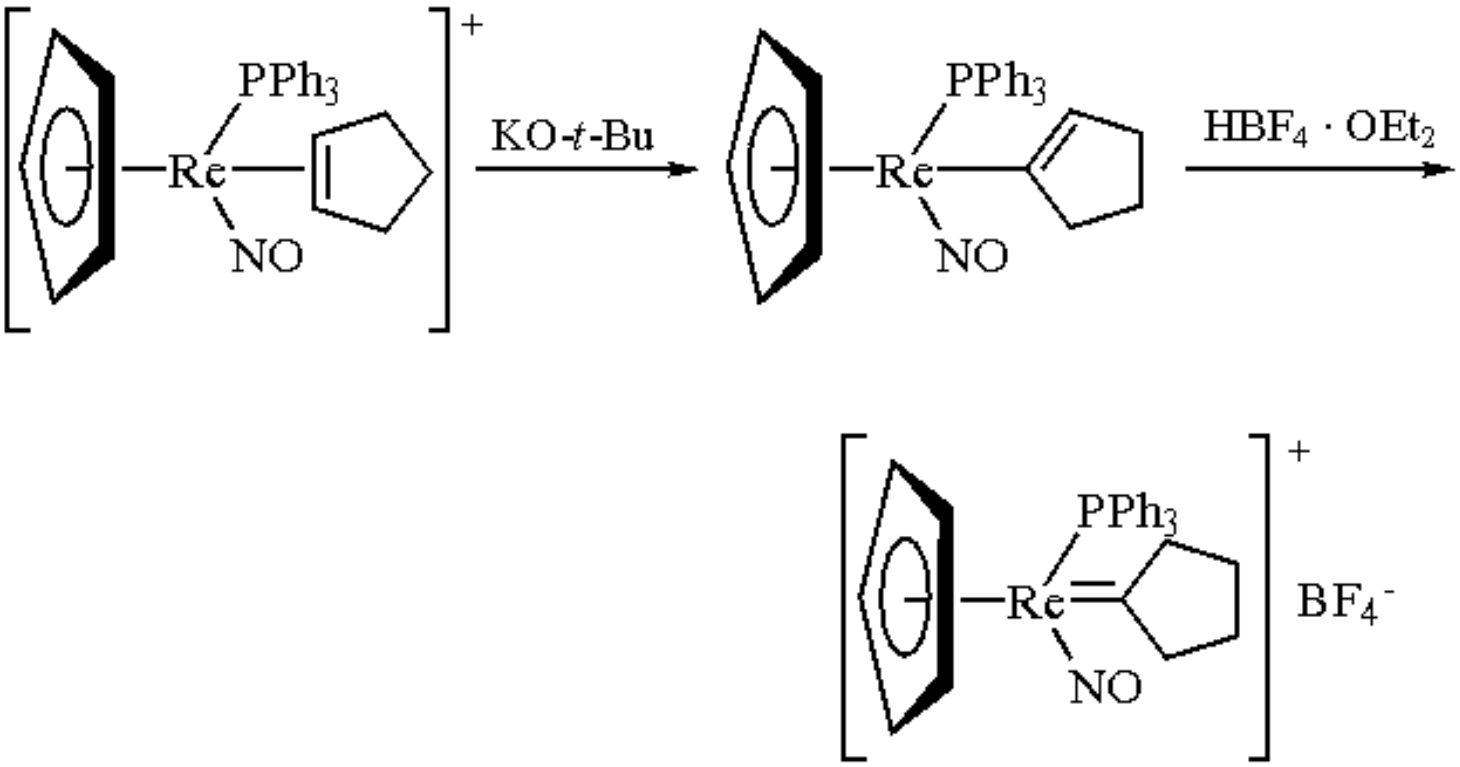

(14)

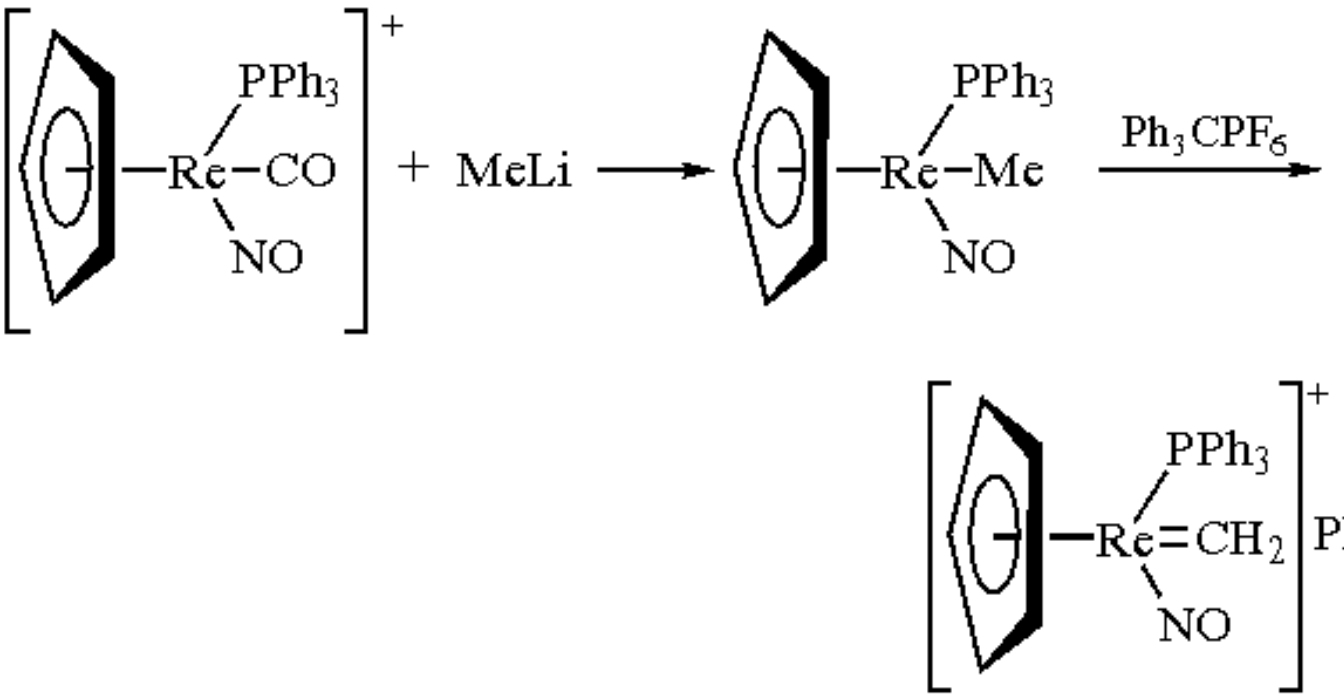

(15)

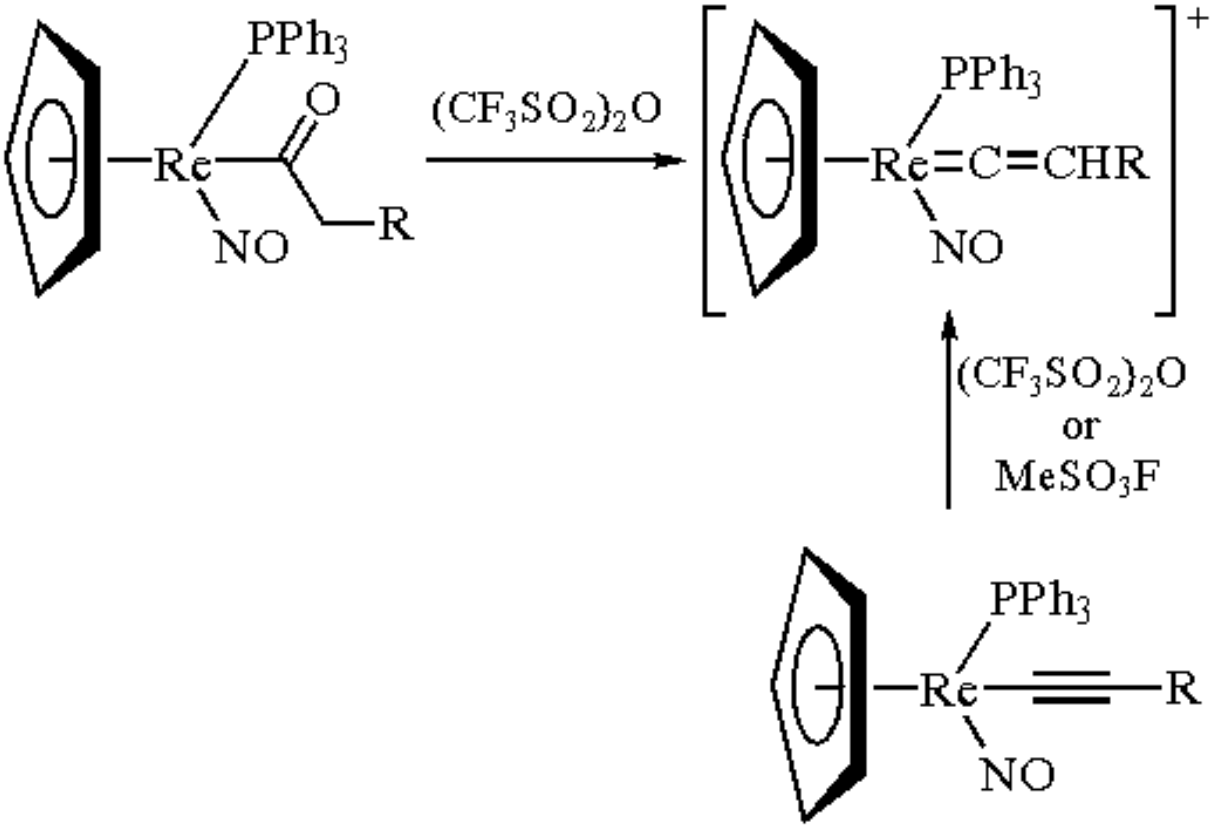

(16)

Cationic solvent complexes are formed from the neutral alkyls (or aryls) on protonation (eq 17),[28] and the use of weak donor solvents (e.g. CH_2Cl_2 or PhCl) then allows replacement of these molecules by alkenes to give $[CpRe(\eta^2\text{-}CH_2{=}CHR)(PPh_3)NO]^+$ or ketones to give $[CpRe(O{=}CR^1R^2)(PPh_3)NO]^+$ salts. Reduction of homochiral salts of the latter type has yielded alkoxides with efficient asymmetric induction (eq 18).[29]

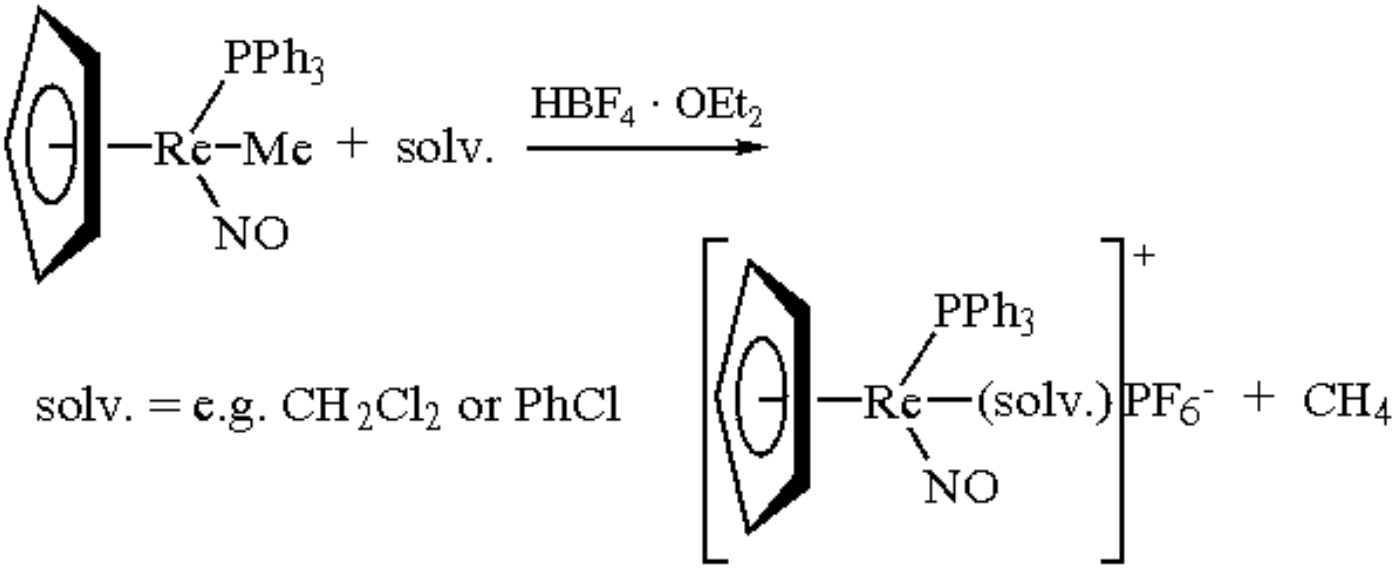

(17)

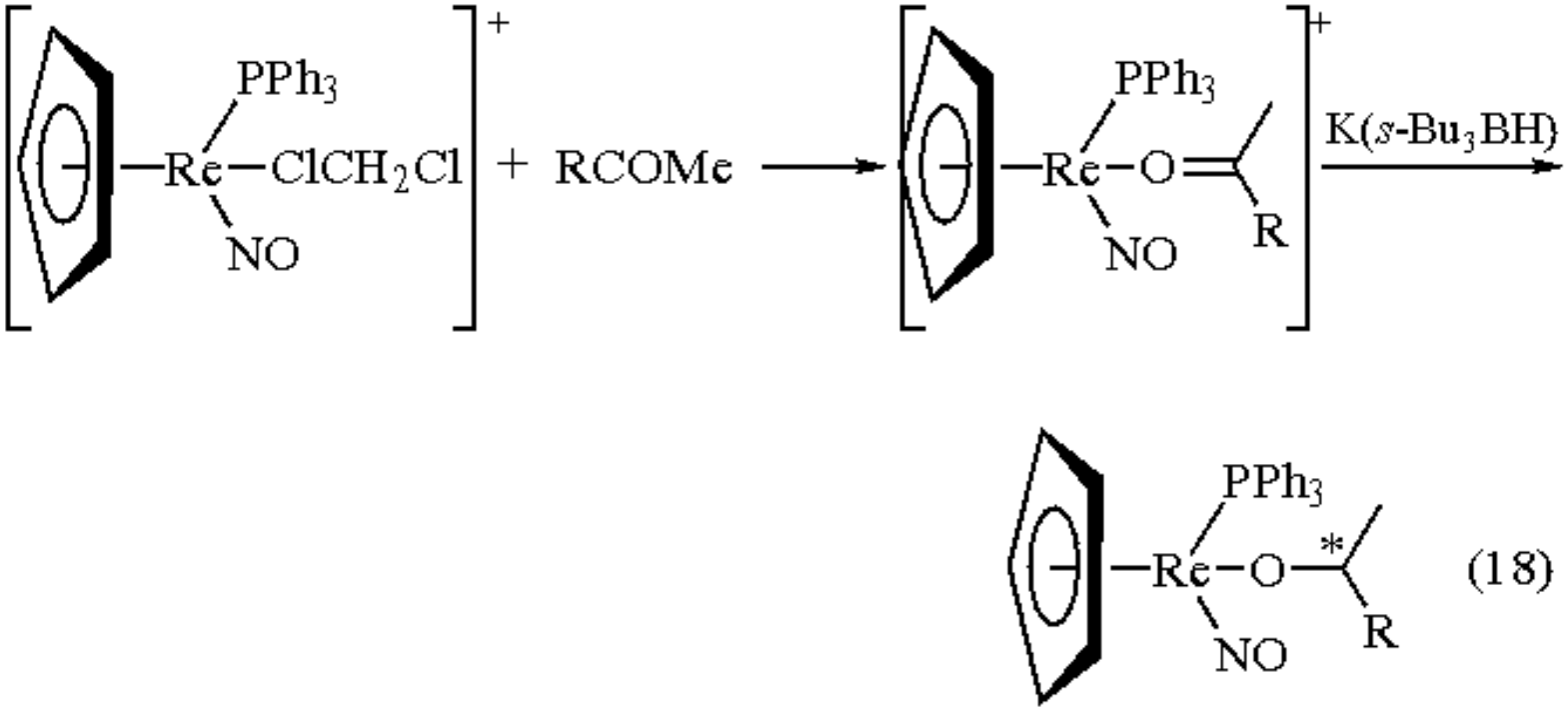

(18)

(Pentamethylcyclopentadienyl)tricarbonylrhenium has been converted to η^2-alkene derivatives as illustrated for the propene complex (eq 19).[30] Hydride abstraction followed by alkylation of the resultant η^3-allyl complex with ***Lithium Dimethylcuprate*** (eq 20)[31] achieves homologation of the propene ligand; other carbanions (e.g. $^-CH(CO_2Et)_2$) add in similar fashion.[31b]

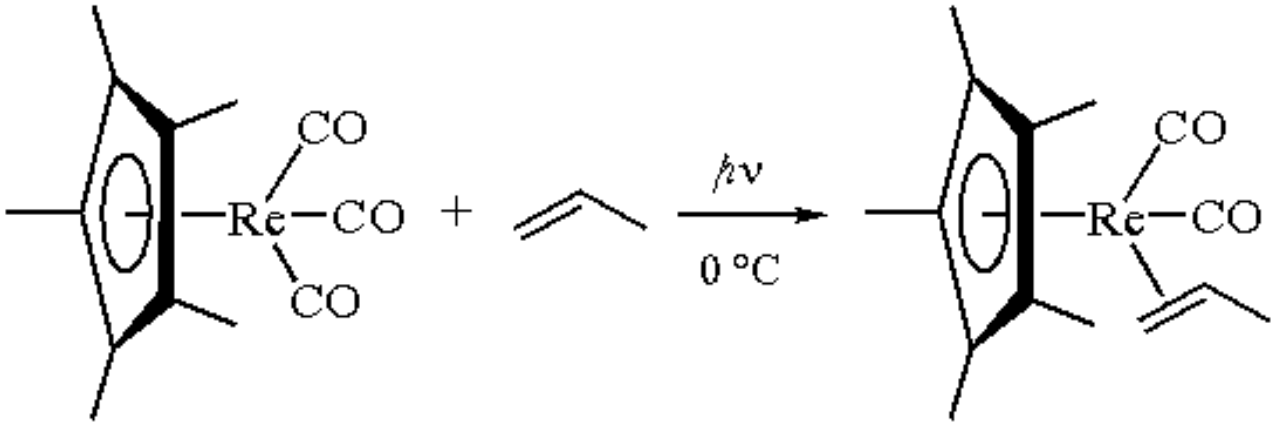

(19)

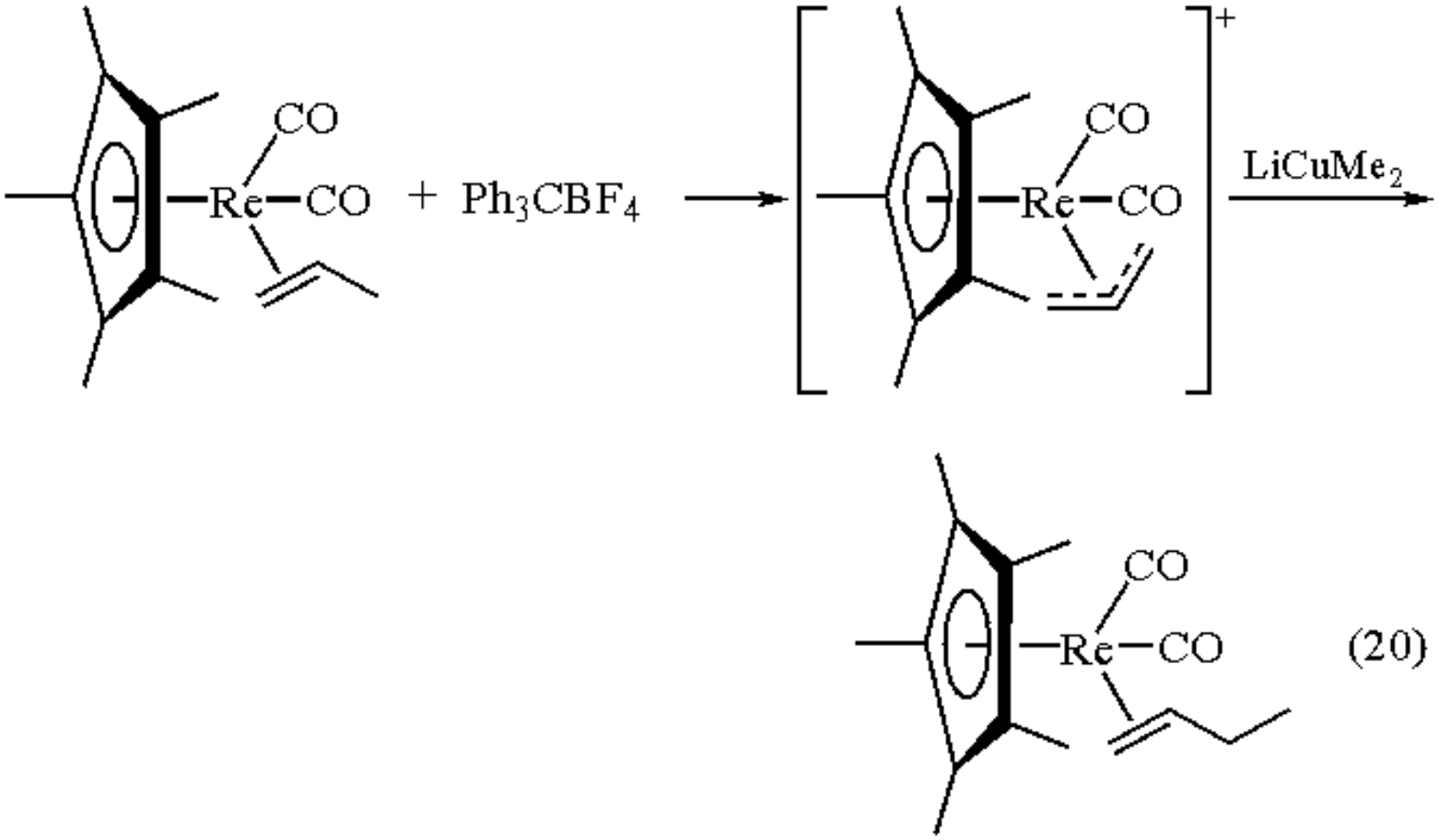

(20)

Acid-catalyzed ***Hydrogen Peroxide*** oxidation smoothly converts the tricarbonyl complex $(C_5Me_5)Re(CO)_3$ to the trioxide complex $(C_5Me_5)ReO_3$. This product lacks the useful alkene-hydroxylating activity of $MeReO_3$, but has served as a source of many organorhenium(III and V) complexes.[32] Reaction of the trioxide with alkynes in the presence of triphenylphosphine yields complexes which give furans on treatment with iodine (eq 21).[33]

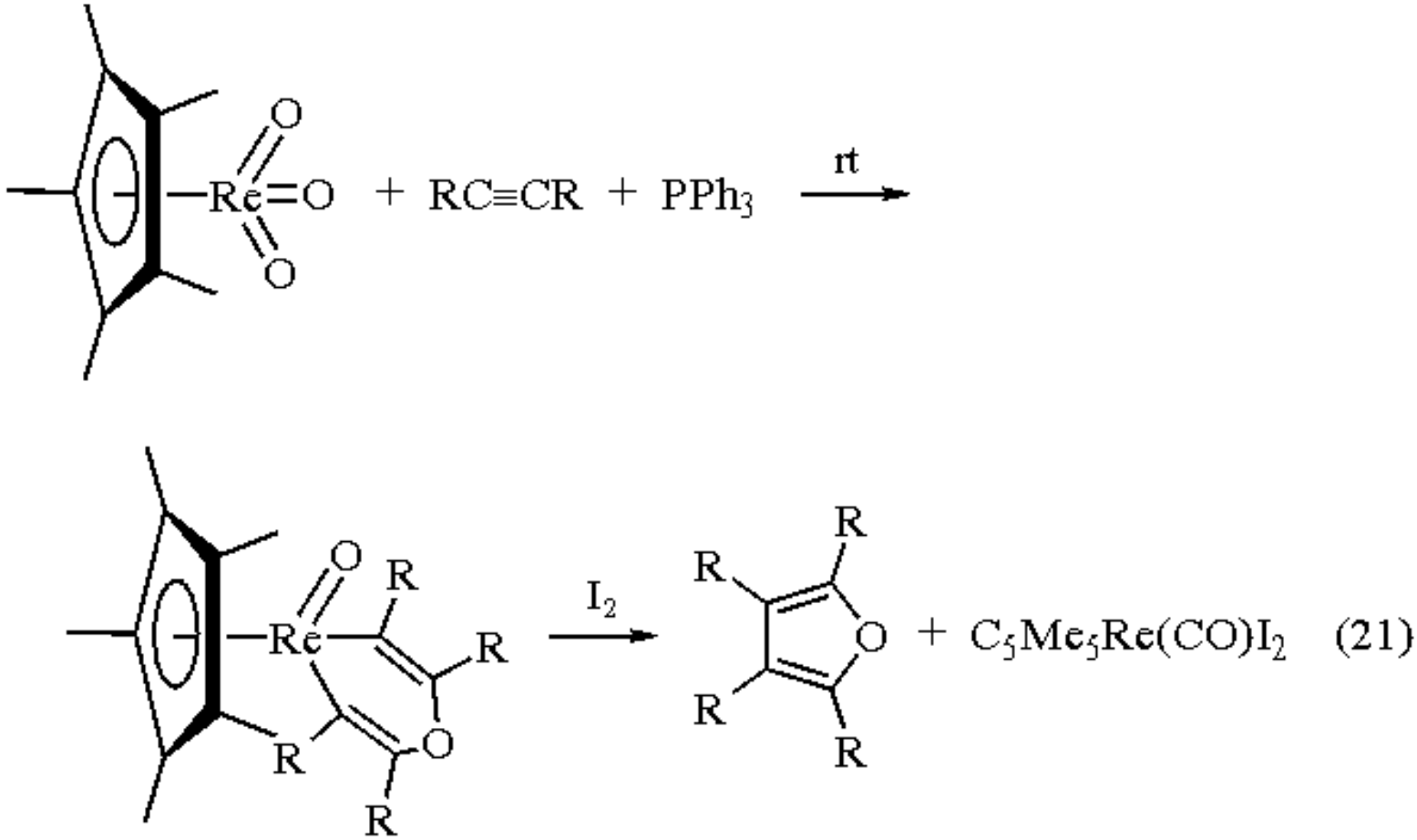

Remarkably smooth formation of a hydroxycyclopentadienyl ligand has been reported to proceed according to eq 22, giving the product as a yellow oil in 84% yield.[34]

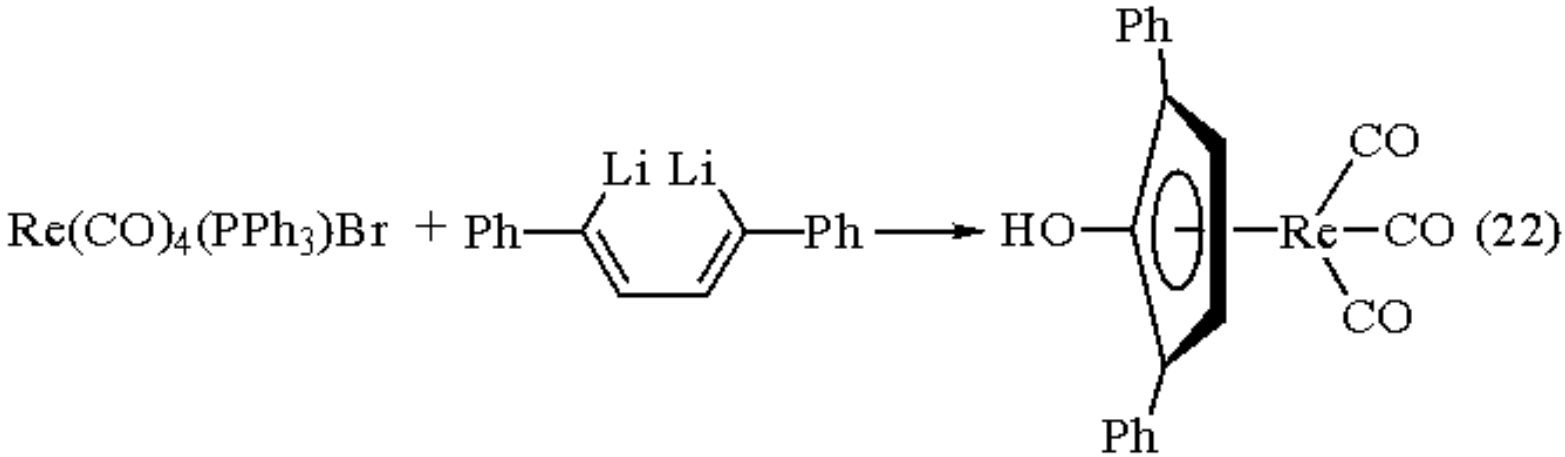

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Decynyl(phenyl)iodonium Tetrafluoroborate[1]

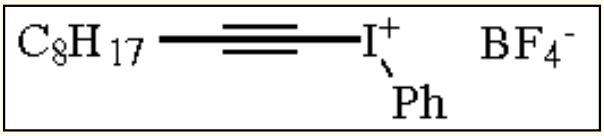

[102987-32-6] · $C_{16}H_{22}BF_4I$ · Decynyl(phenyl)iodonium Tetrafluoroborate · (MW 428.06)

(used in cyclopentene annulation;[3,4] can function as alkynyl equivalent[5] and vinyl cation equivalent[6])

Physical Data: mp 59.5-65 °C.

Preparative Methods: best achieved in 85% yield by reaction of (1-decynyl)trimethylsilane with excess ***Iodosylbenzene*** and ***Boron Trifluoride Etherate***, and subsequent treatment with excess aqueous $NaBF_4$ solution (eq 1).[2] This method provides a general route for the synthesis of alkynyl(phenyl)iodonium tetrafluoroborate salts from alkynyltrimethylsilanes.

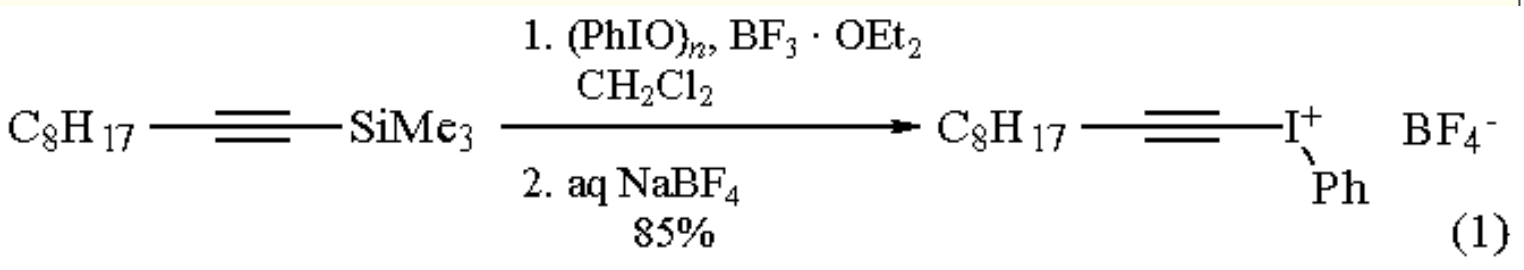

Introduction.

Alkynyl(phenyl)iodonium salts are highly electron-deficient species of formal tetraphilic nature (C_α, $C_{\alpha'}$, C_β, and I) towards nucleophilic attack.

Nucleophilic Attack At C_β.

Despite the wide scope for nucleophilic attack on alkynyl(phenyl)iodonium tetrafluoroborates, only reports of C_β attack have been detailed to date for 1-decynyl(phenyl)iodonium tetrafluoroborate.

The reagent has been employed[3] in cyclopentene annulations, by a process referred to as tandem Michael-carbene insertion, through reaction of the stabilized anion of 1,3-diketones and 1,3-diesters (eq 2). The reaction proceeds, with concomitant reductive elimination of iodobenzene, via an alkylidenecarbene intermediate which subsequently undergoes an intramolecular 1,5 C-H insertion reaction.

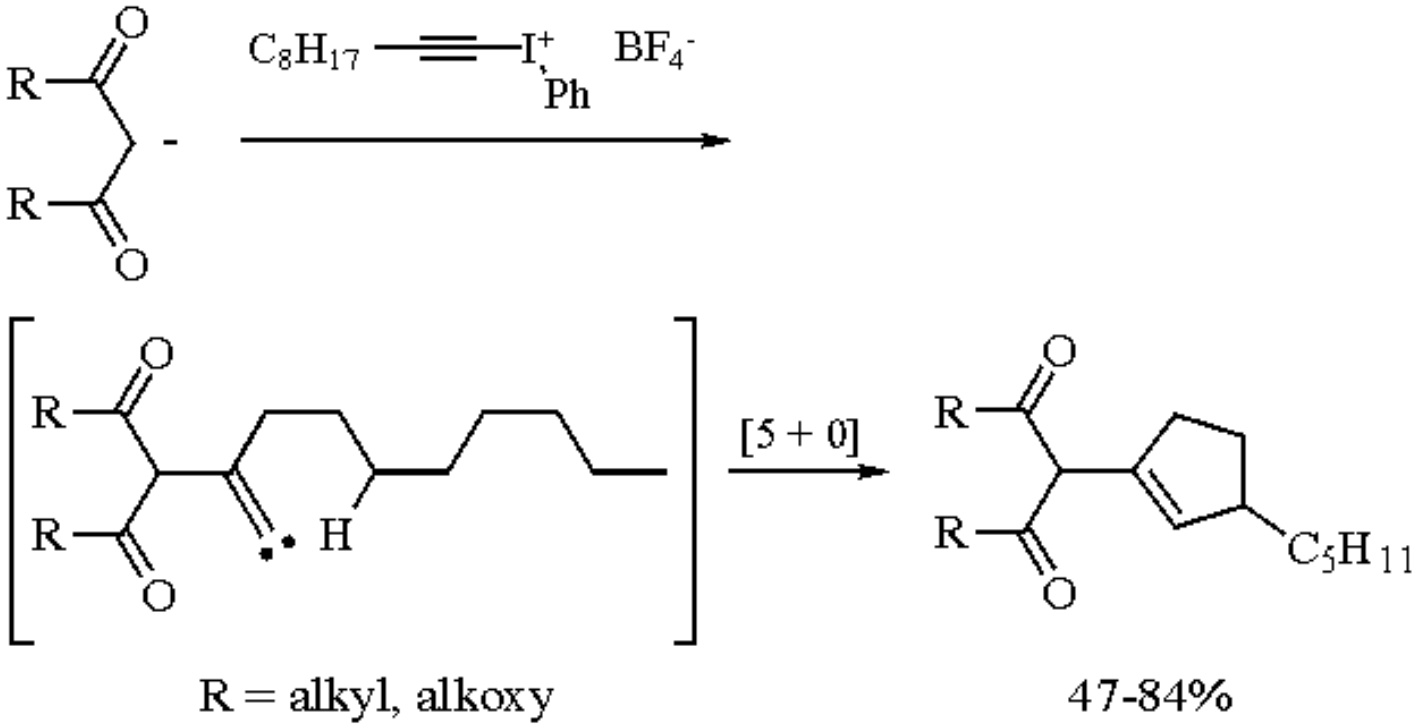

(2)

Similar transformations have been studied[4] with heteronucleophiles to give functionalized cyclopentenes (eq 3).

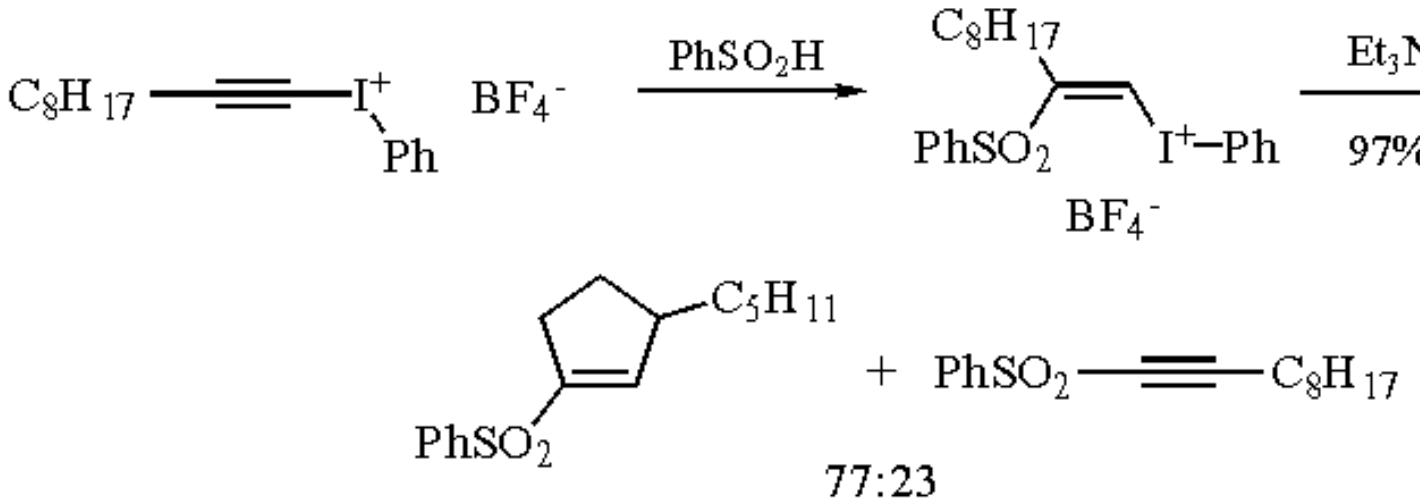

(3)

The use of alkynyl(phenyl)iodonium salts as alkynyl cation synthetic equivalents has been amply demonstrated.[5] In addition, treatment of 1-decynyl(phenyl)iodonium tetrafluoroborate with ***Azidotrimethylsilane*** generates[6] the β-azidovinyliodonium salt (eq 4). Salts of this type behave as vinyl cation equivalents in nucleophilic substitutions owing to the high leaving group potential of the hypervalent iodine(III) substituent, the use of which has been reported[7] in the synthesis of a variety of alkenes including α-cyano, α-nitro, vinyl sulfides, and α,β-unsaturated esters.

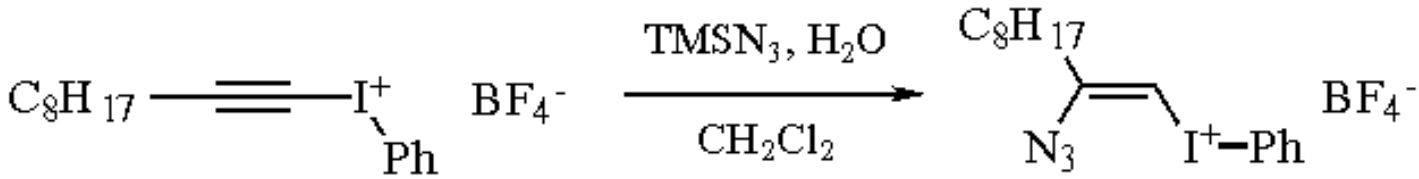

(4)

α-Acyloxy ketones have been synthesized[8] from 1-decynyl(phenyl)iodonium tetrafluoroborate under both basic and acidic

conditions. Treatment of the reagent with excess sodium acetate in THF/H_2O gave 1-acetoxy-2-decanone in 78% yield (eq 5). The use of water is reported as essential for the reaction to proceed effectively.

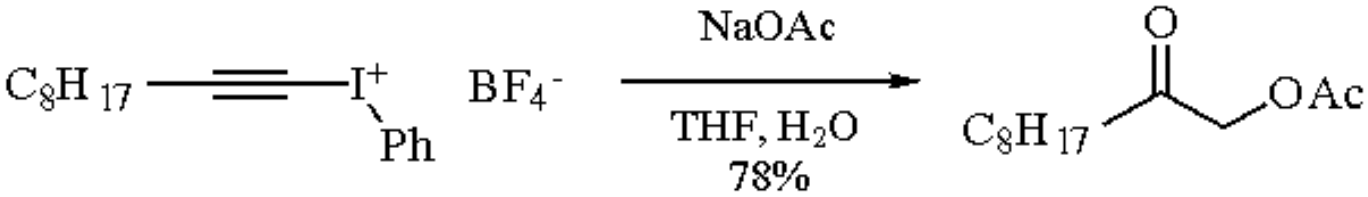

(5)

1-Acetoxy-2-decanone is also produced in 86% yield by refluxing the reagent in acetic acid for 15 h. Syntheses and uses of α-acyloxy ketones have been previously demonstrated.[9]

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Diacetatobis(tri-*o*-tolylphosphine)palladium(II)[1]

$Pd\{P(o\text{-}Tol)_3\}_2(OAc)_2$

[69073-98-9] · $C_{46}H_{48}O_4P_2Pd$ · Diacetatobis(tri-*o*-tolylphosphine)palladium(II) · (MW 833.25)

(catalyst for coupling of aromatic halides and alkenes;[1-3] cycloisomerization reactions of enynes[4])

Alternate Name: bis(tri-*o*-tolylphosphine)palladium(II) diacetate.

Solubility: sol acetonitrile, DMF, halogenated solvents.

Preparative Method: usually generated in situ from ***Palladium(II) Acetate*** and tri-*o*-tolylphosphine and used directly.

Handling, Storage, and Precautions: air sensitive in solution.

Coupling of Aryl Halides with Alkenes.

The title reagent (**1**) has been used to make aromatic alkenes in good yield under mild conditions, tolerating a variety of functionality (eq 1). Aromatic bromides[2] and iodides[3] are coupled with alkenes in the presence of base (typically NEt_3) in refluxing acetonitrile or DMF.

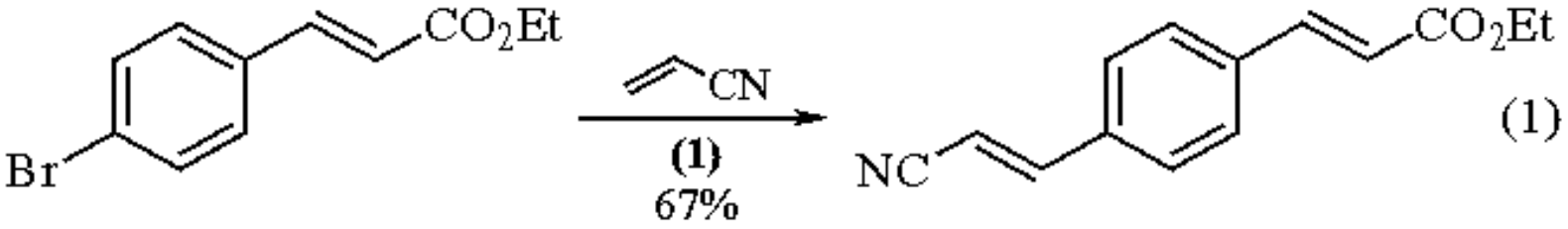

This reaction can be used to produce aromatic polymers.[5] In many cases, (**1**) is superior to the triphenylphosphine analog[1] (see ***Bis(triphenylphosphine)palladium(II) Acetate***).

Cycloisomerization.

$Pd\{P(o\text{-}Tol)_3\}_2(OAc)_2$ will readily effect cycloisomerization of 1,6-enyne substrates to 1,3-dienes,[4,6] and has been used in the synthesis of sterepolide (eq 2).[7]

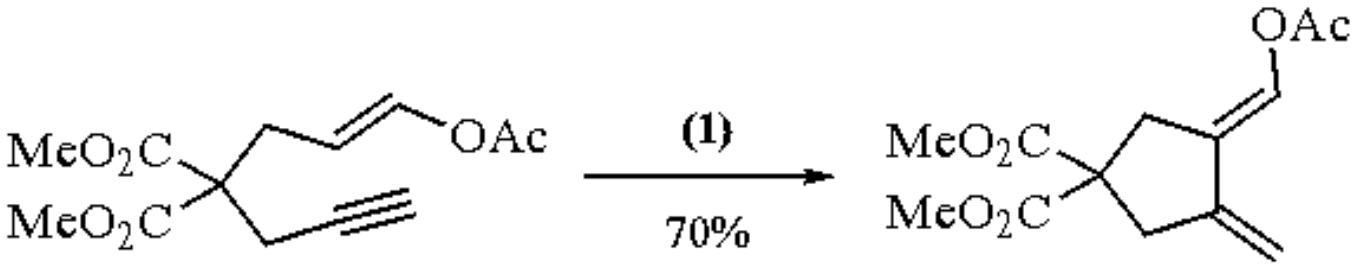

(2)

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(Diacetoxyiodo)benzene[1-3]

$PhI(OAc)_2$

[3240-34-4] · $C_{10}H_{11}IO_4$ · (Diacetoxyiodo)benzene · (MW 322.10)

(transannular carbocyclization,[6] *vic*-diazide formation,[7] α-hydroxy dimethyl acetal formation,[8,10,11,13] oxetane formation,[9] chromone, flavone, chalcone oxidation,[11,12] arene-$Cr(CO)_3$ functionalization,[14] phenolic oxidation[16] and coupling,[17,18] lactol fragmentation,[19] iodonium ylides and intramolecular cyclopropanation,[20] oxidation of amines[24-28] and indoles,[30,31] hydrazine derivatives (diimide[32] and azodicarbonyls[33]) and radical type intramolecular oxide formation[44-46]).

Alternate Names: phenyliodine(III) diacetate; DIB; iodobenzene diacetate; IBD.

Physical Data: mp 163-165 °C.

Solubility: sol AcOH, MeCN, CH_2Cl_2; in KOH or $NaHCO_3$/MeOH it is equivalent to $PhI(OH)_2$.

Form Supplied in: commercially available as a white solid.

Preparative Method: by reaction of iodobenzene with ***Peracetic Acid***.[4,5]

Purification: recrystallization from 5 M acetic acid.[4]

Handling, Storage, and Precautions: a stable compound which can be stored indefinitely.

Reactions with Alkenes.

Reactions of simple alkenes with $PhI(OAc)_2$ are not synthetically useful because of formation of multiple products.

Transannular carbocyclization in the reaction of *cis,cis*-1,5-cyclooctadiene yields a mixture of three diastereomers of 2,6-diacetoxy-*cis*-bicyclo[3.3.0]octane, a useful precursor of *cis*-bicyclo[3.3.0]octane-2,6-dione (eq 1).[6]

(Diacetoxyiodo)benzene

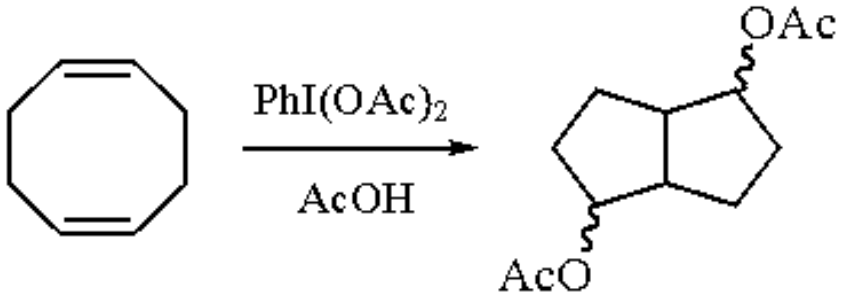

(1)

$PhI(OAc)_2/NaN_3/AcOH$ yields vicinal diazides (eq 2).[7]

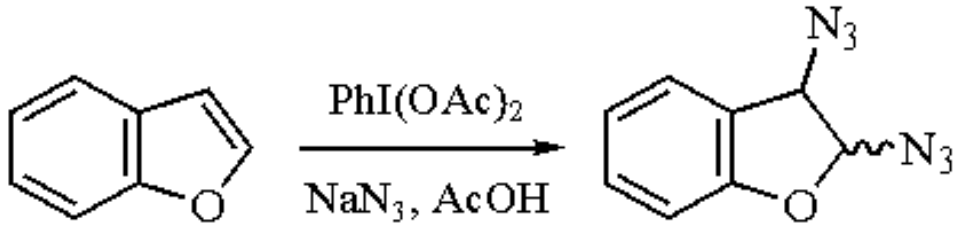

(2)

Oxidation of Ketones to α-Hydroxyl Dimethyl Acetals.

Ketones are converted to the α-hydroxy dimethyl acetal upon reaction with $PhI(OAc)_2$ in methanolic potassium hydroxide (eqs 3-5).[8]

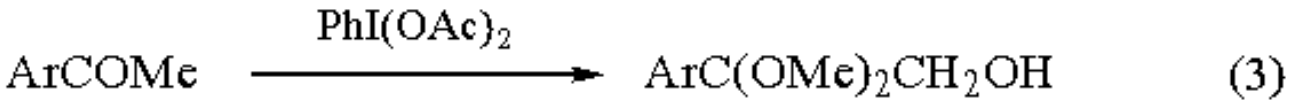

(3)

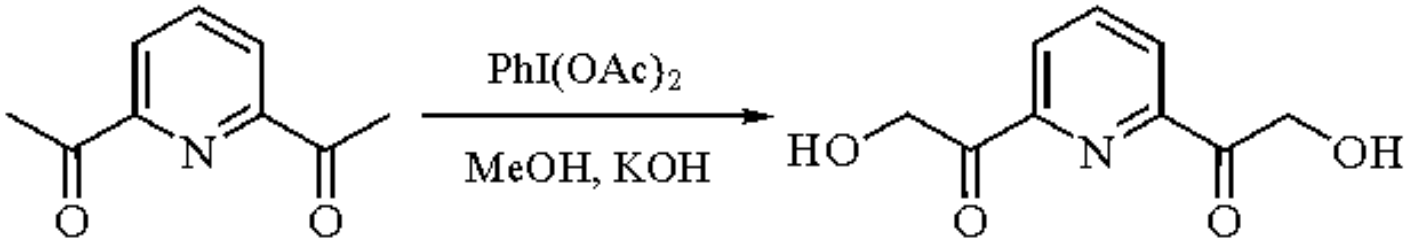

(4)

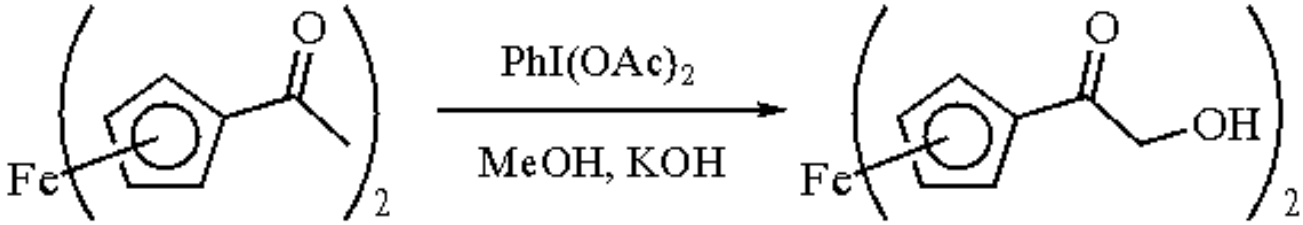

(5)

Several potentially oxidizable groups are unaffected in this reaction (eq 6).[13]

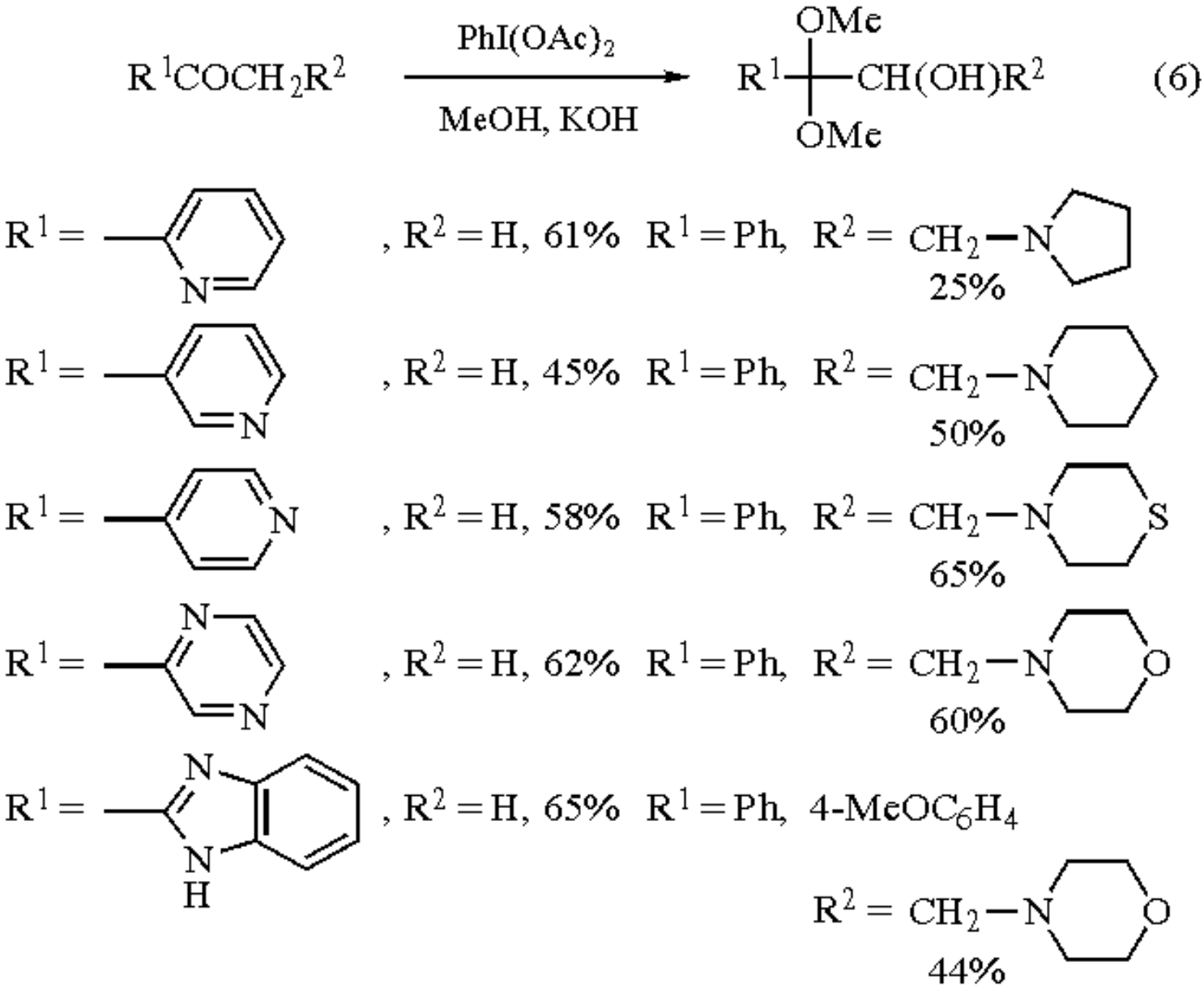

In the case of a 17α-hydroxy steroid the hydroxy group acts as an intramolecular nucleophile to yield the 17-spirooxetan-20-one. It is noteworthy that the 3β-hydroxy-Δ^5-system is unaffected (eq 7).[9]

(Diacetoxyiodo)benzene

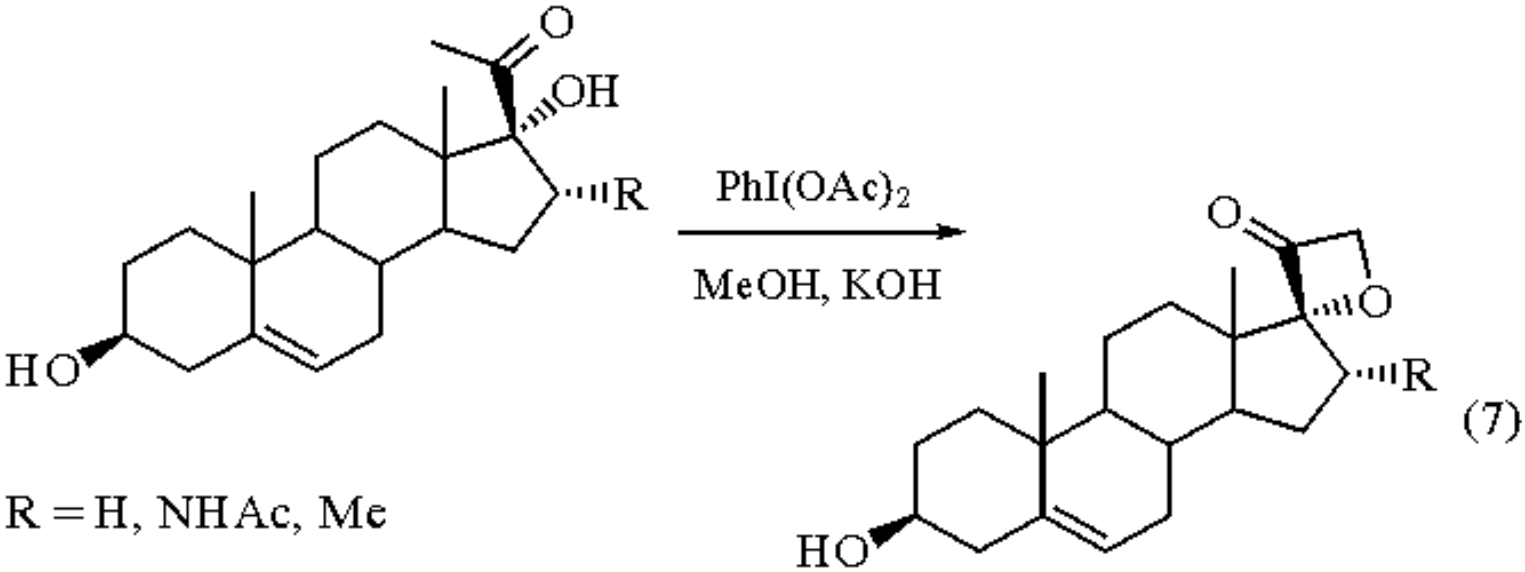

(7)

cis-3-Hydroxyflavonone is obtained via acid-catalyzed hydrolysis of *cis*-3-hydroxyflavone dimethyl acetal, which is formed upon treatment of flavanone with $PhI(OAc)_2$ (eq 8).[10,11]

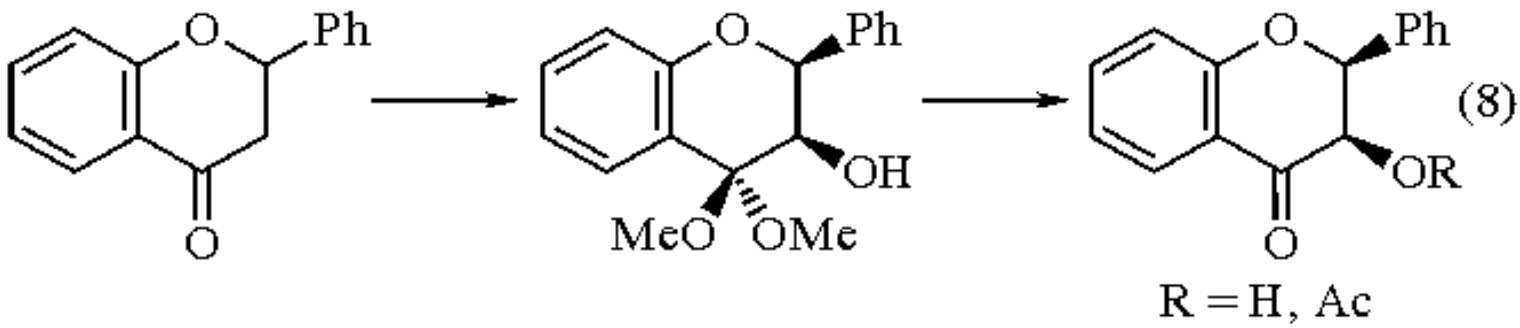

(8)

α,β-Unsaturated ketones, such as chromone, flavone, chalcone, and flavanone, yield α-hydroxy-β-methoxy dimethyl acetal products (eqs 9-11).[12a]

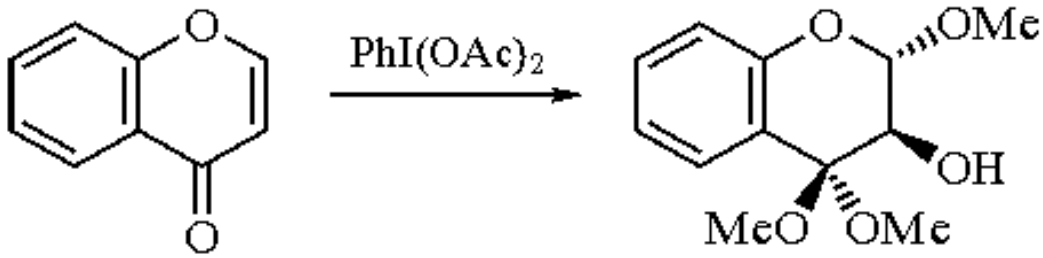

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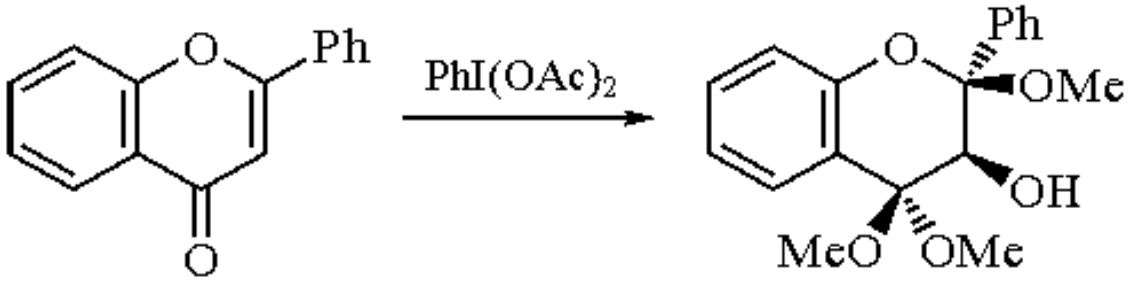

(10)

(Diacetoxyiodo)benzene

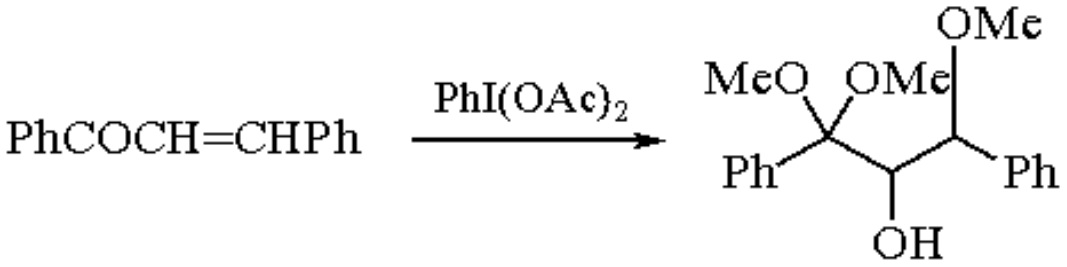

(11)

Intramolecular participation by the *ortho* hydroxy group occurs in the reaction of substituted *o*-hydroxyacetophenones, yielding the corresponding coumaran-3-ones (eq 12).[12b]

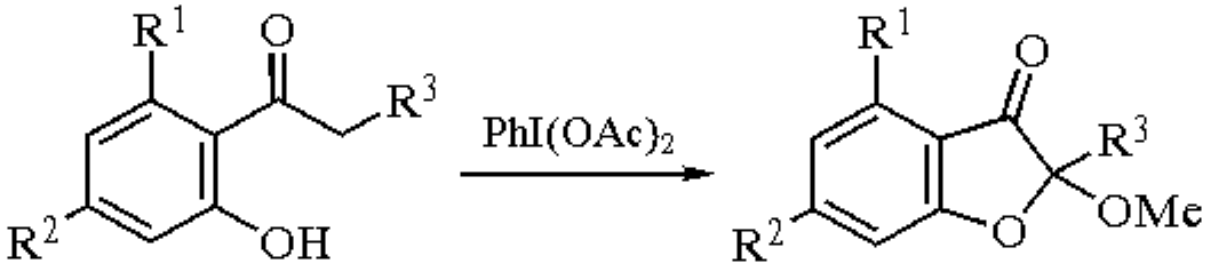

(12)

$R^1 = R^2 = R^3 = H$ $\quad$ $R^3 = OMe$

$R^1 = R^2 = H;\ R^3 = Me$ $\quad$ $R^3 = Me$

$R^1 = R^2 = Me;\ R^3 = H$ $\quad$ $R^3 = OMe$

$R^1 = R^2 = H;\ R^3 = Bn$ $\quad$ $R^3 = Bn$

Formation of the α-hydroxy dimethyl acetal occurs without reaction of the $Cr(CO)_3$ complex of η^6-benzo-cycloalkanones (eqs 13-15).[14]

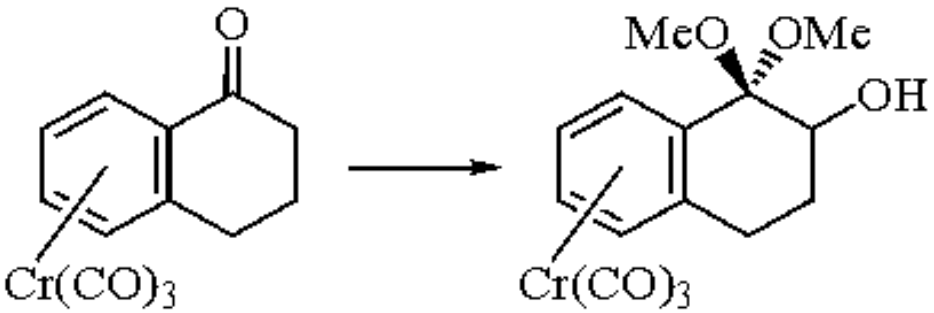

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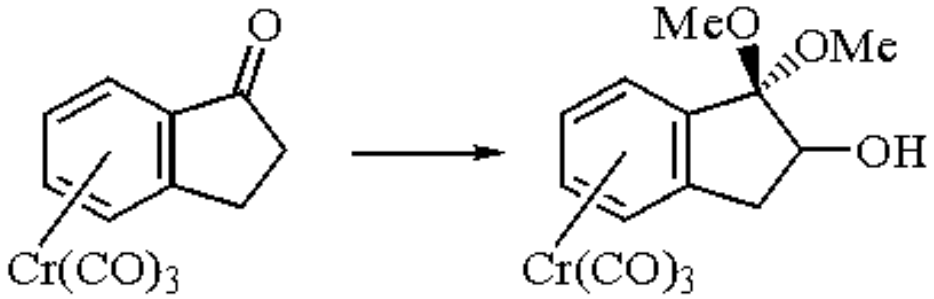

(14)

(Diacetoxyiodo)benzene

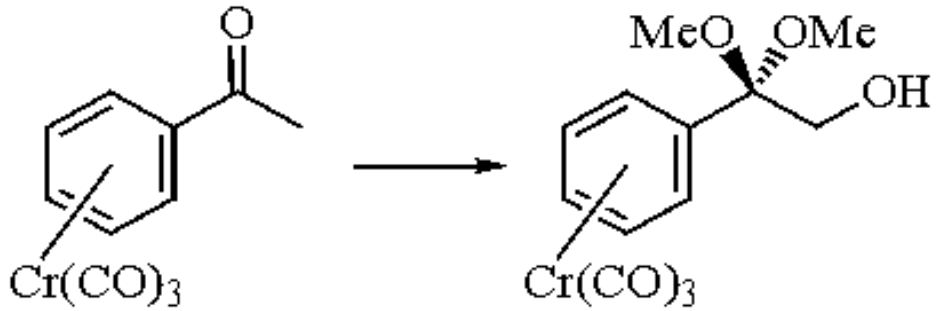

(15)

Carbon-Carbon Bond Cleavage with $PhI(OAc)_2/TMSN_3$.

$PhI(OAc)_2$/***Azidotrimethylsilane*** reacts with unsaturated compounds even at -53 °C to yield keto nitriles (eq 16).[15]

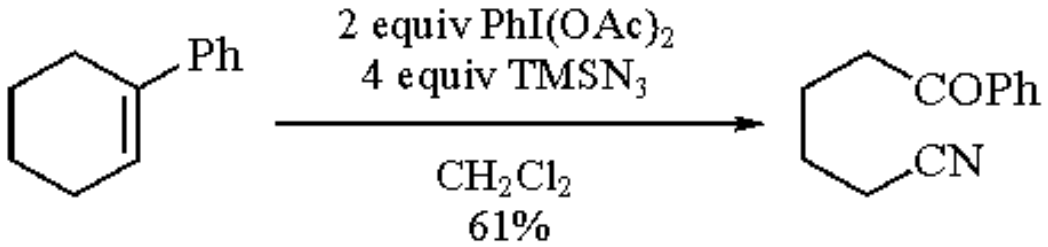

(16)

Oxidation of Phenols.

Phenols are oxidized using $PhI(OAc)_2$ with nucleophilic attack by solvent (eqs 17 and 18),[16] or with intramolecular nucleophilic addition amounting to an overall oxidative coupling as with the bisnaphthol (eq 19)[17] and also with the conversion of reticuline to salutaridine (eq 20).[18]

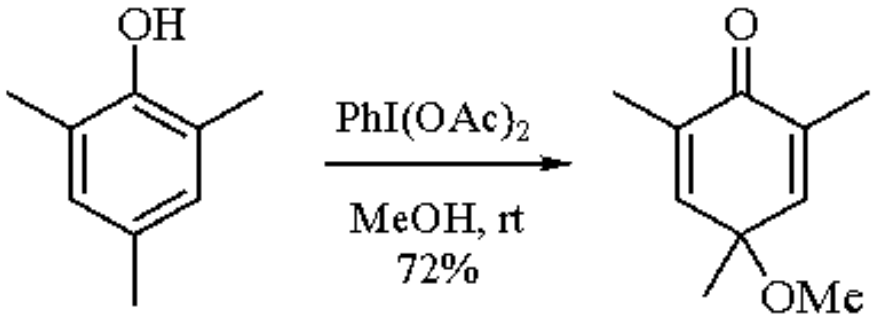

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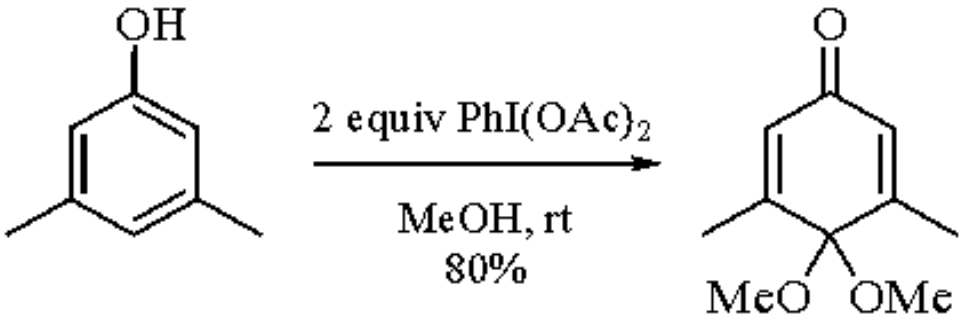

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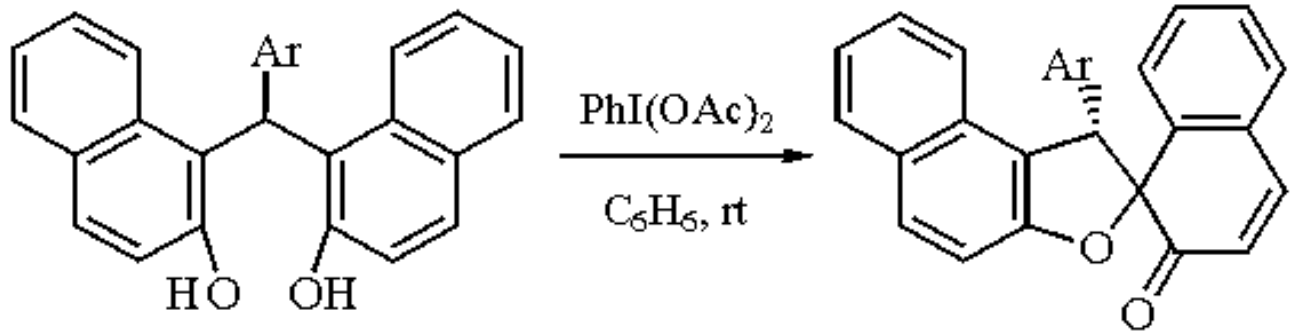

(19)

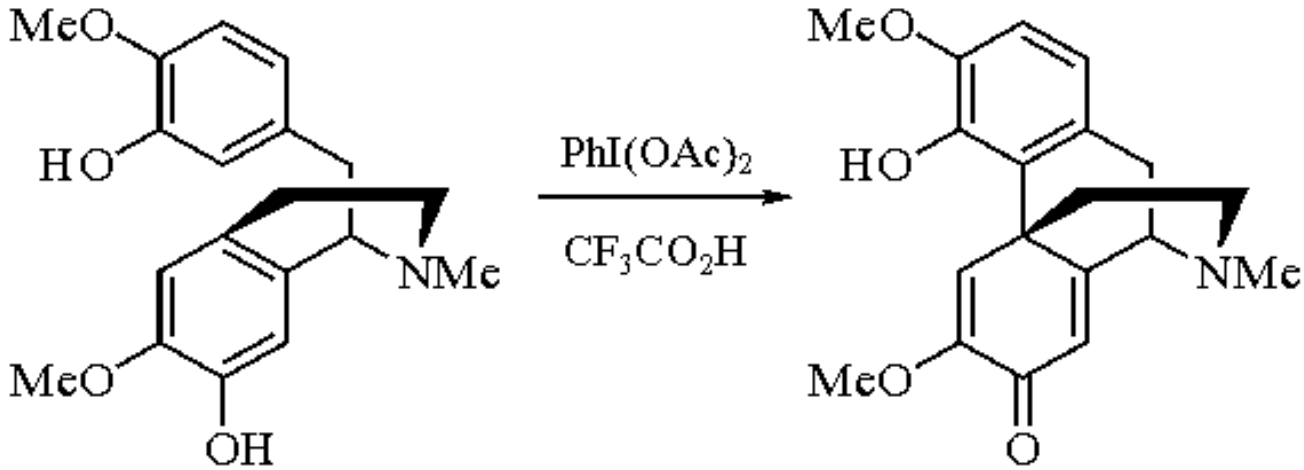

(20)

Fragmentation of Lactols to Unsaturated Medium-Ring Lactones.

Ring cleavage to form a medium-sized ring lactone with a transannular double bond has been observed (eq 21).[19]

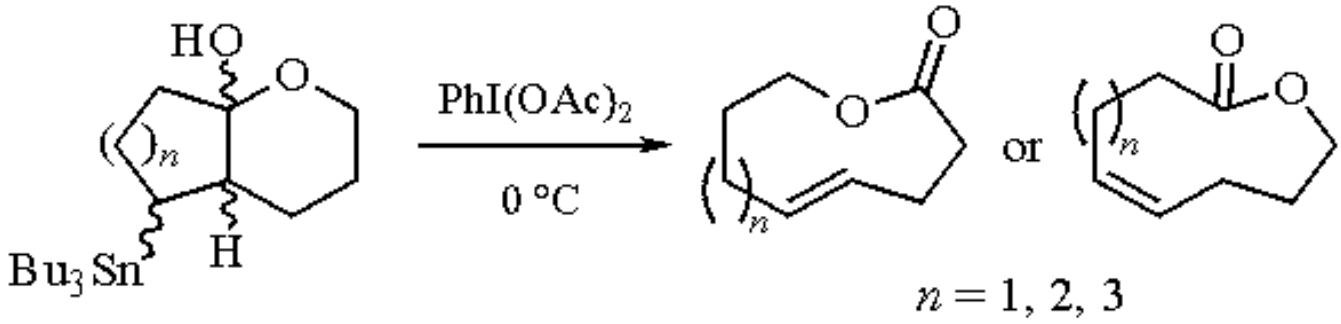

(21)

Reactions with β-Dicarbonyl Systems; Formation of Iodonium Ylides; Intramolecular Cyclopropanation.

β-Dicarbonyl compounds upon reaction with $PhI(OAc)_2$ and KOH/MeOH at 0 °C yield isolable iodonium ylides (eq 22).[20] This is a general reaction which requires two stabilizing groups flanking the carbon of the C=I group, such as NO_2 and SO_2Ph.[21] Decomposition of unsaturated analogs in the presence of ***Copper(I) Chloride*** proceeds with intramolecular cyclopropanation (Table 1).[20]

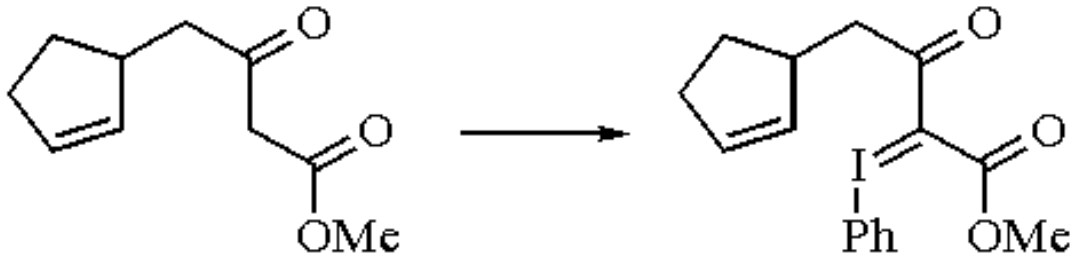

(22)

Table 1 Intramolecular Cyclopropanation of Iodonium Ylides

Reactants	Iodonium ylide	Product	Yield (%)
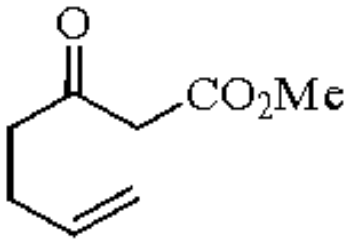	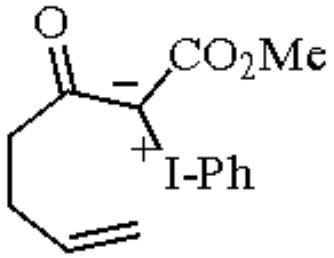	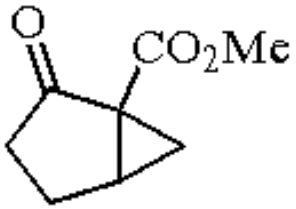	76
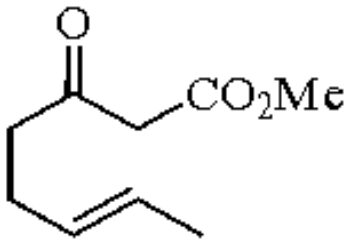	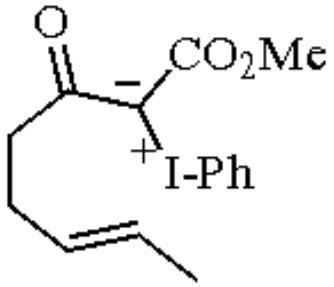	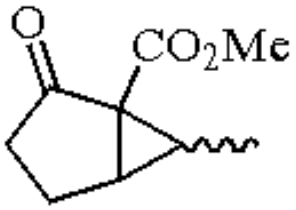	81
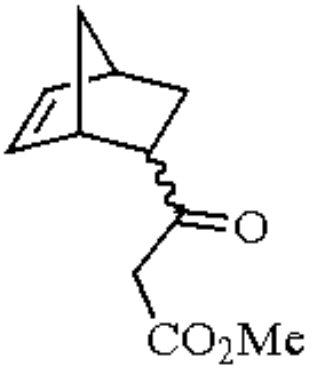	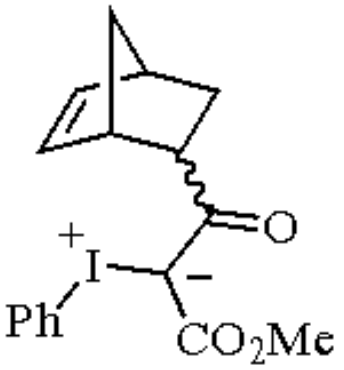	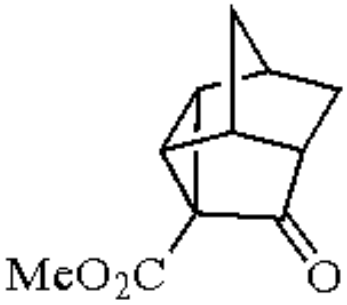	85
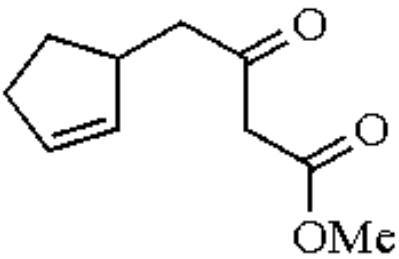	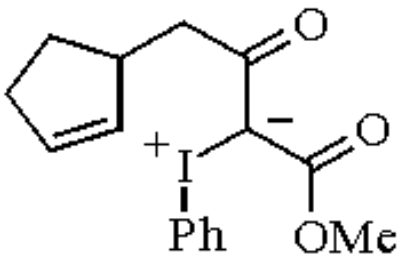	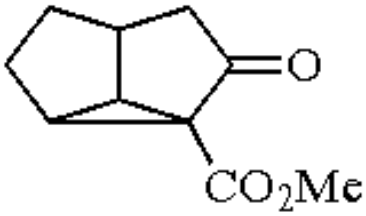	82

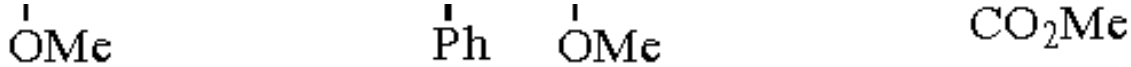

An asymmetric synthesis of a vitamin D ring A synthon employed this intramolecular cyclopropanation reaction (eq 23).[22]

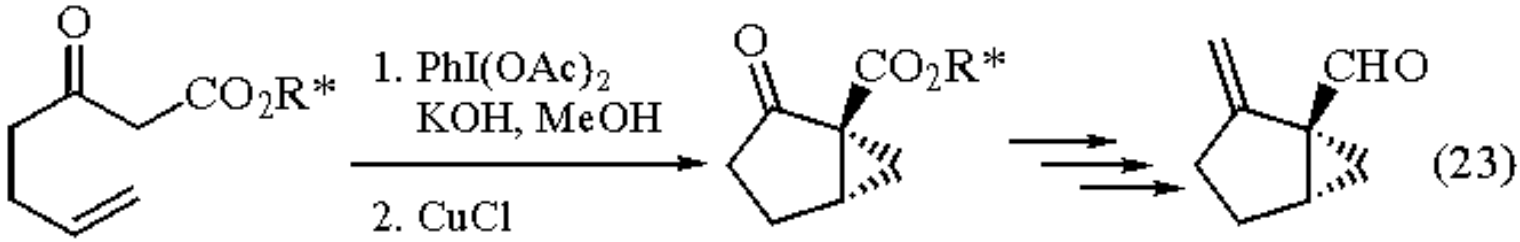

Oxidation of Amines.

Aromatic amines are oxidized with $PhI(OAc)_2$ to azo compounds in variable yield. $PhI(OAc)_2$ in benzene oxidizes aniline in excellent yield (eq 24);[23] however, substituted anilines give substantially lower yields.

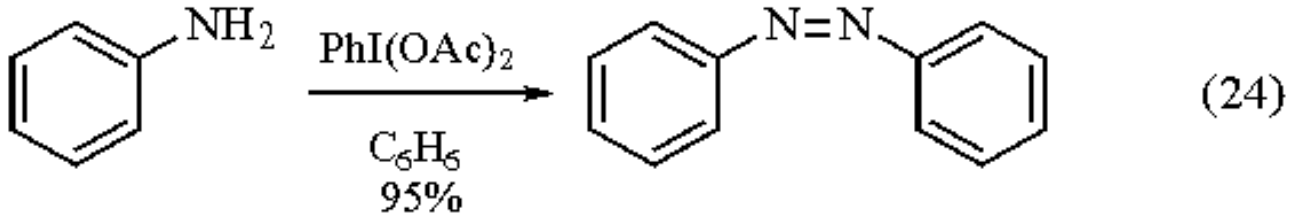

Intramolecular azo group formation is a useful reaction for the formation of dibenzo[*c*,*f*]diazepine (eq 25).[24,25] Other *ortho* groups may react intramolecularly to yield the benzotriazole (eq 26), benzofuroxan (eq 27), or anthranil (eq 28) derivatives.[24-28]

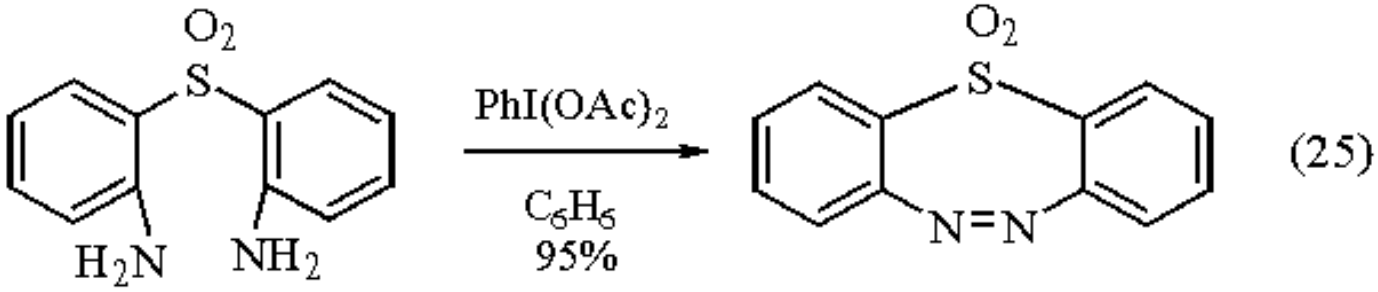

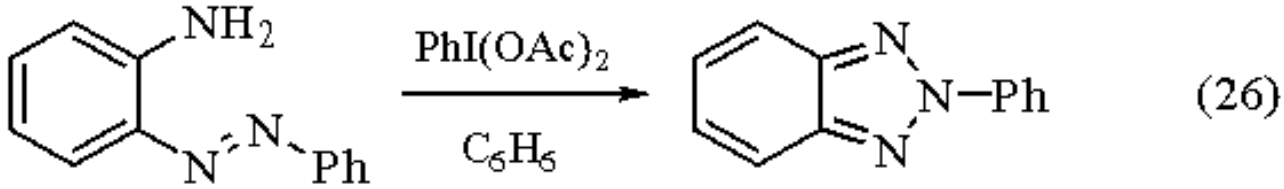

(Diacetoxyiodo)benzene

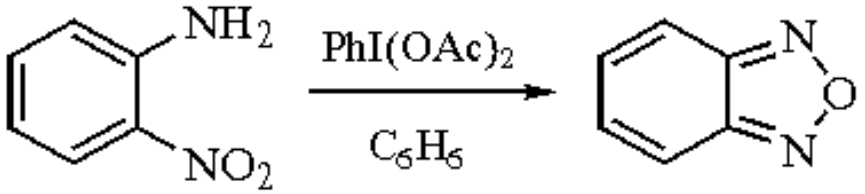

(27)

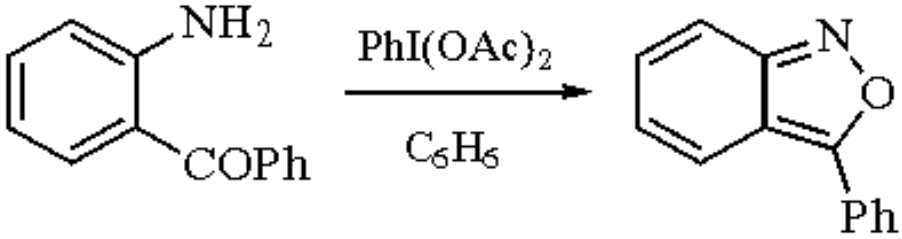

(28)

A number of examples of oxidative cyclization of 2-(2´-pyridylamino)imidazole[1,2-*a*]pyridines to dipyrido[1,2-*a*:2´,1´-*f*]-1,3,4,6-tetraazapentalenes with $PhI(OAc)_2/CF_3CH_2OH$ have been reported (eq 29).[29]

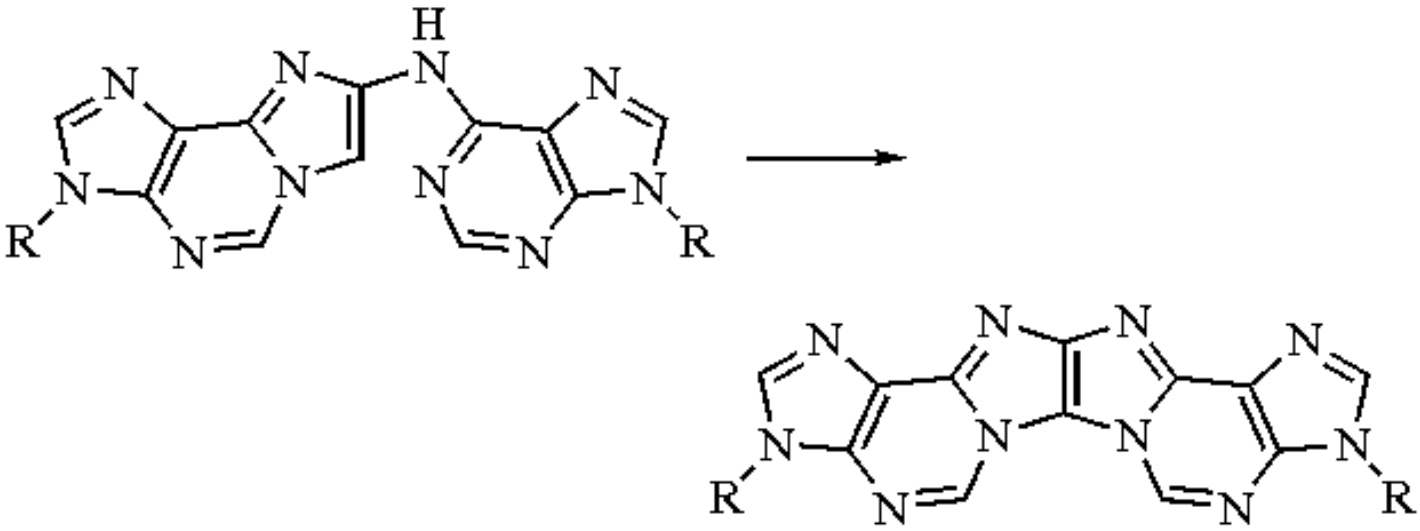

(29)

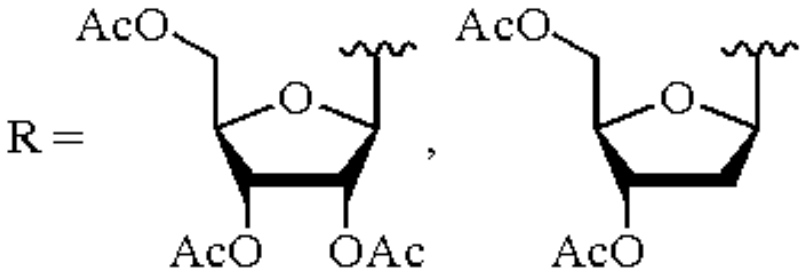

In the case of the oxidation of indole derivatives, nucleophilic attack by solvent may occur (eq 30).[30] Reserpine undergoes an analogous alkoxylation.[30] In the absence of a nucleophilic solvent, intramolecular cyclization occurs, an example of which is illustrated in the total synthesis of sporidesmin A (eq 31).[31]

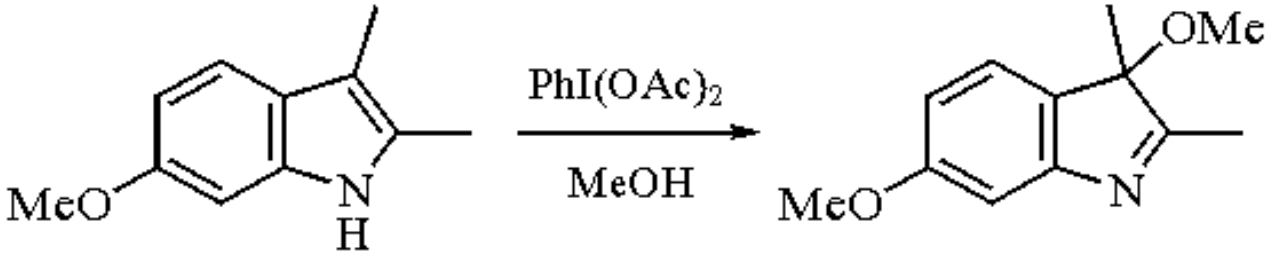

(30)

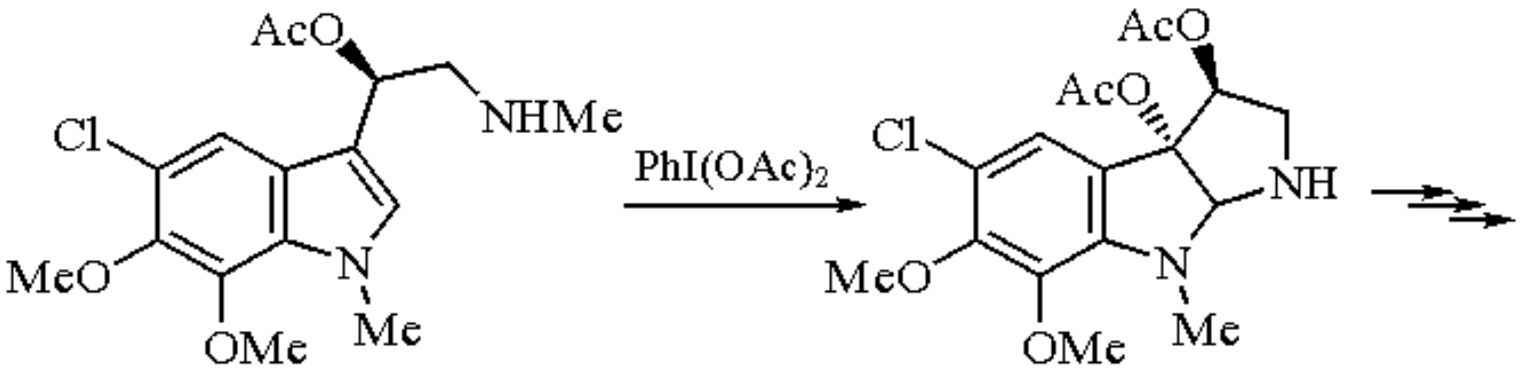

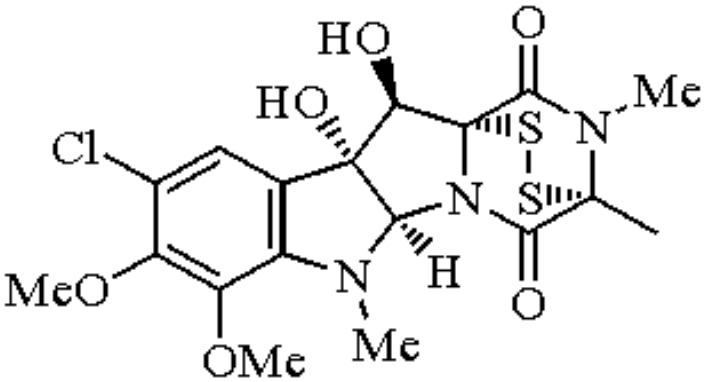

(31)

Hydrazine is oxidized by $PhI(OAc)_2$ to diimide, which may be used to reduce alkenes and alkynes under mild conditions (Table 2).[32]

Table 2 Diimide Reduction of Various Compounds

Compound	Product	Yield (%)
$PhSCH{=}CH_2$	$PhSCH_2Me$	85
cis-$EtO_2CCH{=}CHCO_2Et$	$EtO_2CCH_2CH_2CO_2Et$	94
$EtO_2C\ N{=}N\ CO_2Et$	$EtO_2CNH\ NHCO_2Et$	90
Maleic anhydride	$(MeCO)_2O$	83
$PhC^{o}\ CPh$	*cis*-$PhCH{=}CHPh$	80
$PhCH{=}CHCO_2Et$	$PhCH_2CH_2CO_2Et$	96
$CH_2{=}CHCN$	$MeCH_2CN$	97

The hydrazodicarbonyl group is smoothly oxidized by $PhI(OAc)_2$ to the azodicarbonyl group (eqs 32 and 33).[33]

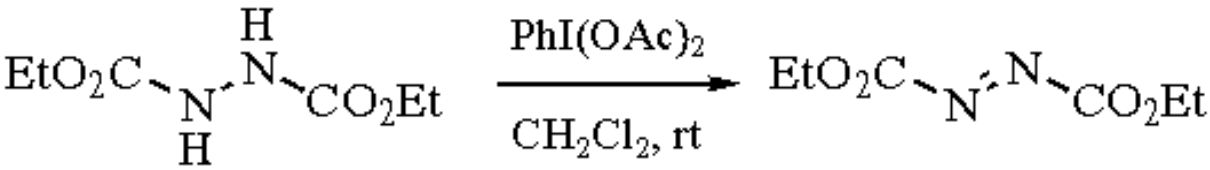

(32)

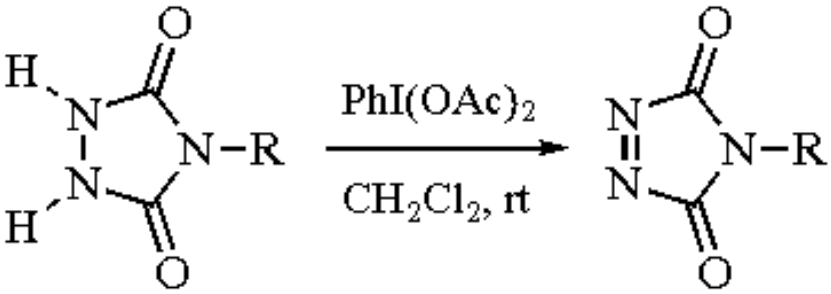

(33)

An intramolecular application of this reaction was used in a tandem sequence with $PhI(OAc)_2$ oxidation and a Diels-Alder reaction in the synthesis of nonpeptide β-turn mimetics (eq 34).[34,35]

(Diacetoxyiodo)benzene

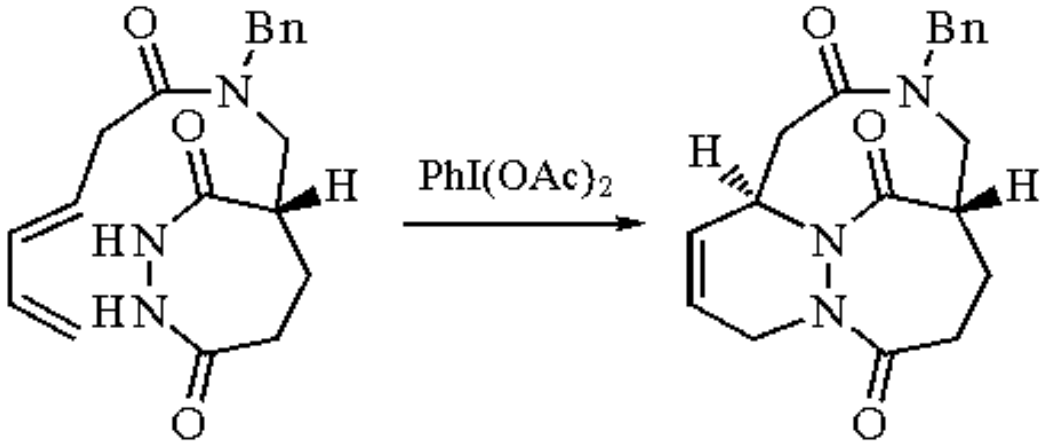

(34)

Oxidation of 5-Substituted Pyrazol-3(2*H*)-ones; Formation of Alkynyl Esters.

Oxidation of various 5-substituted pyrazol-3(2*H*)-ones proceeded with fragmentative loss of molecular nitrogen to yield methyl-2-alkynoates (eq 35).[36] An analogous fragmentation process with pyrazol-3(2*H*)-ones occurs with ***Thallium(III) Nitrate***[37,38] and ***Lead(IV) Acetate***.[39]

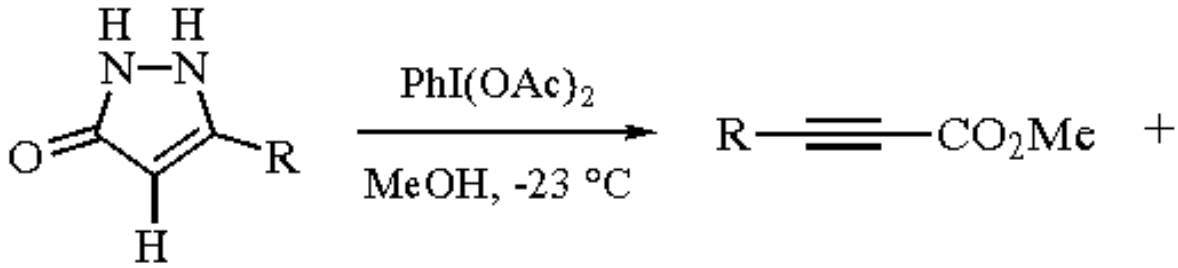

(35)

R = Me, 60%	R = Ph, 59%
R = Et, 63%	R = *p*-ClC_6H_4, 61%
R = CO_2Me, 59%	R = *p*-MeC_6H_4, 59%
R = CH_2CO_2Me, 62%	R = *p*-$MeOC_6H_4$, 64%

Oxidation of Hydrazones, Alkylhydrazones, *N*-Amino Heterocycles, *N*-Aminophthalimidates, and Aldazines.

The oxidation of hydrazones to diazo compounds is not a generally useful reaction but it was uniquely effective in the oxidation of a triazole derivative (eq 36).[40]

(Diacetoxyiodo)benzene

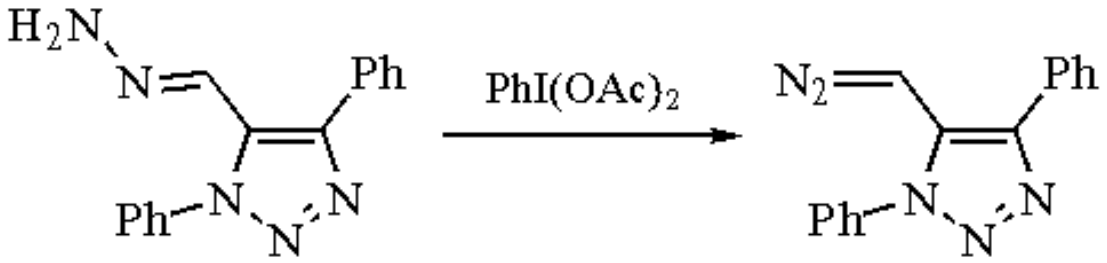

(36)

Oxidation of arylhydrazones proceeds with intramolecular cyclizations (eqs 37 and 38)[41] and aziridines may be formed via nitrene additions (eq 39).[42]

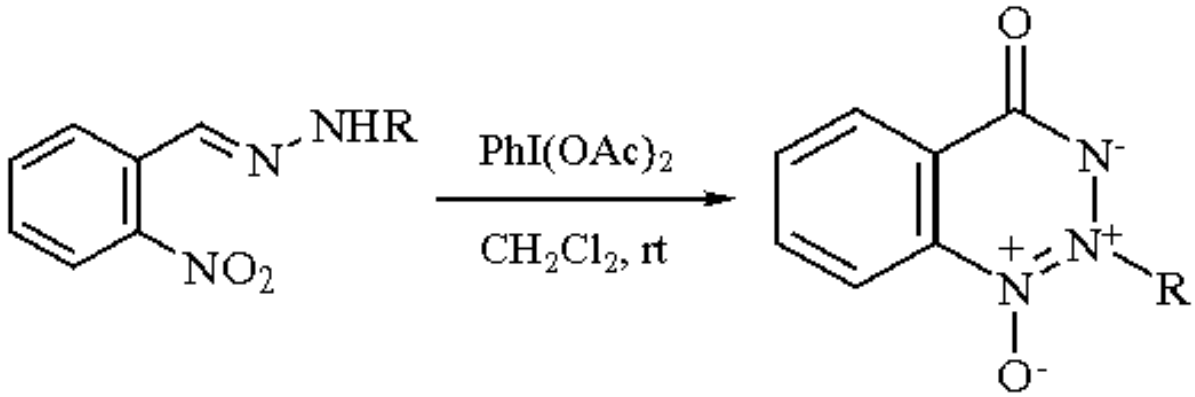

(37)

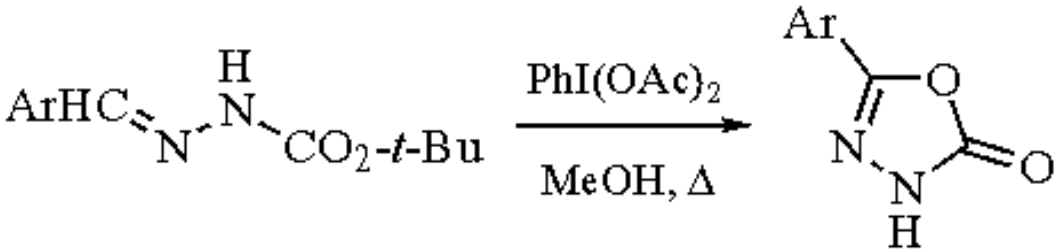

(38)

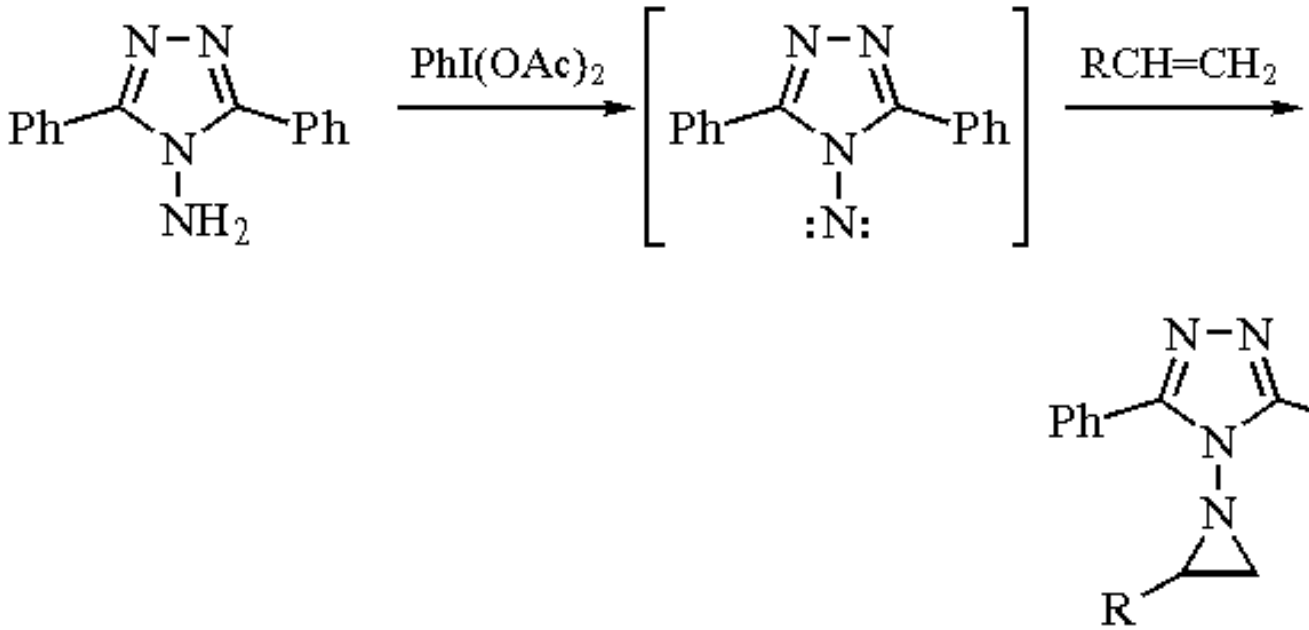

(39)

A linear tetrazane is formed in the oxidation of *N*-aminophthalimide (eq 40).[43]

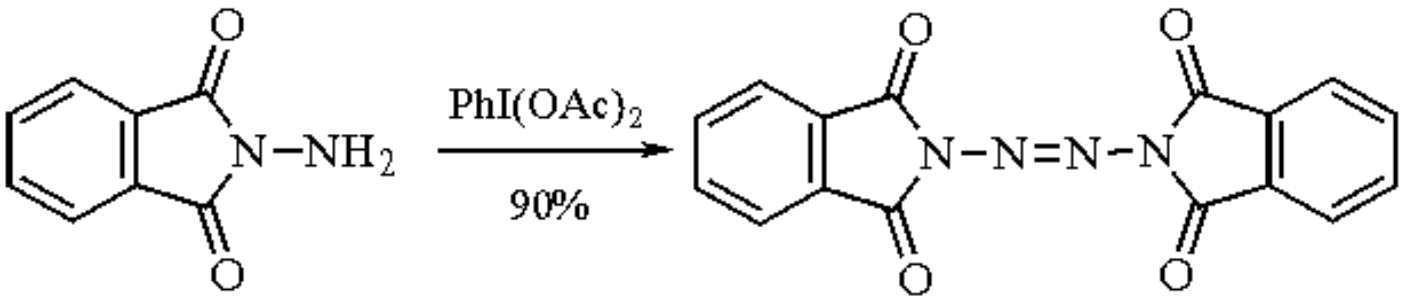

(Diacetoxyiodo)benzene/***Iodine*** is reported to be a more efficient and convenient reagent for the generation of alkoxyl radicals than Pb^{IV}, Hg^{II}, or Ag^{I}, and this system is useful for intramolecular oxide formation (eqs 41 and 42).[44]

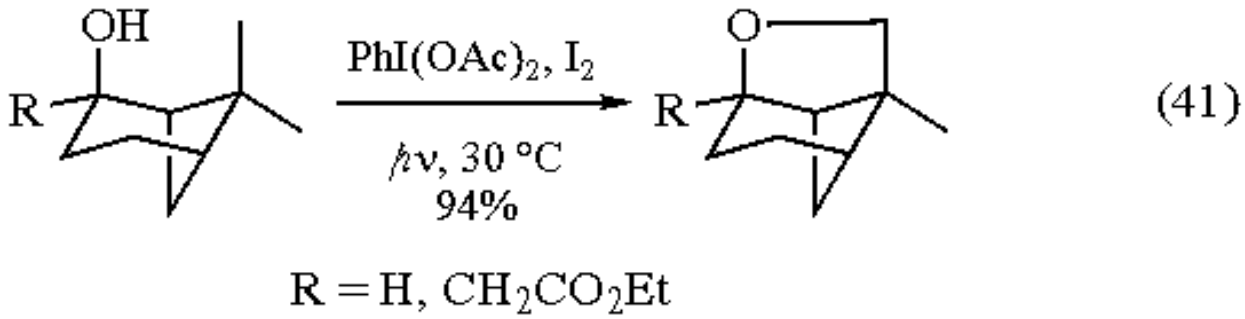

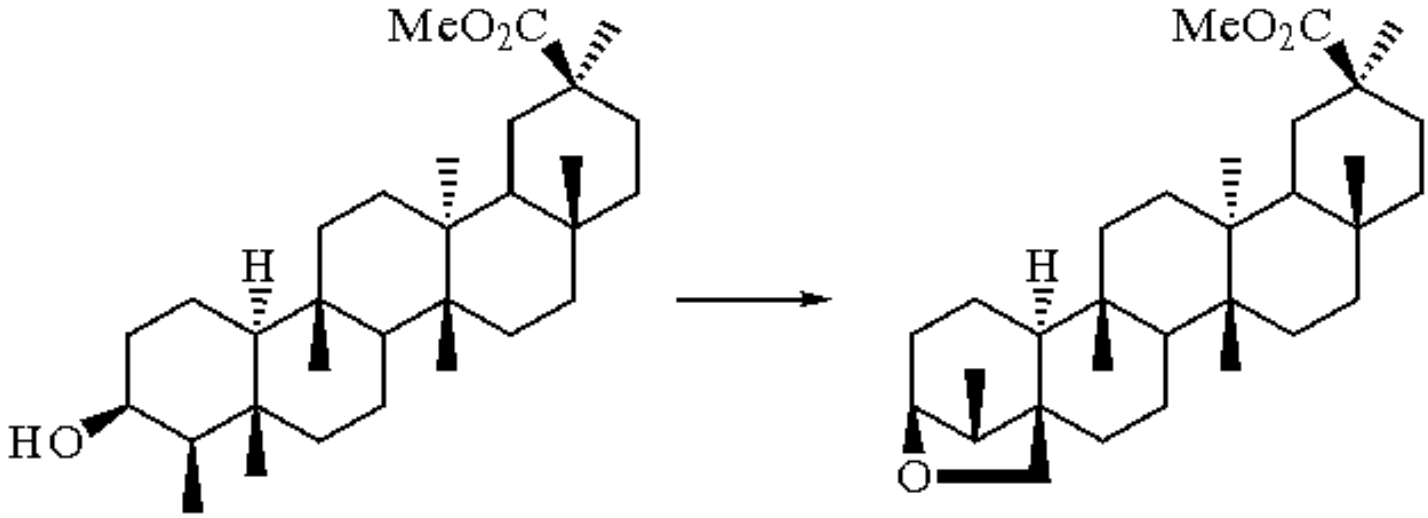

Fragmentation processes of carbohydrate anomeric alkoxyl radicals[45] and steroidal lactols[46] using $PhI(OAc)_2/I_2$ have been reported.

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Diallyl Sulfoxide

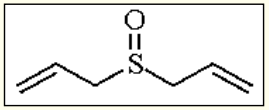

[14180-63-3] · $C_6H_{10}OS$ · Diallyl Sulfoxide · (MW 130.20)

(source of thioacrolein in solution[1])

Physical Data: colorless oil solidifying at 5 °C.

Solubility: sol most organic solvents.

Preparative Method: conveniently prepared in 91% yield from commercially available diallyl sulfide by oxidation with 30% H_2O_2 in acetone at rt followed by recrystallization at -20 °C from pentane/ether.[1]

In Situ Generation and Trapping of Thioacrolein: Synthesis of 3,4-Dihydro-2*H*-thiopyrans.

When an excess of diallyl sulfoxide (or a homolog such as bis(2-methyl-2-propenyl) sulfoxide) is heated with dienophiles, thioacrolein Diels-Alder adducts, 3,4-dihydro-2*H*-thiopyrans, are formed in good to excellent yield (eq 1 and Table 1).[1]

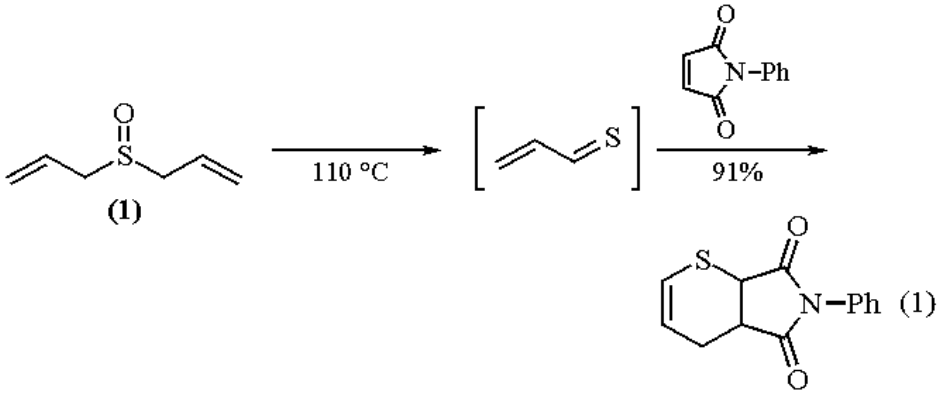

Table 1 3,4-Dihydro-2*H*-thiopyrans from Allyl Sulfoxides

Sulfoxide	Reagent	Conditions	Product	Yield (%)
(1)	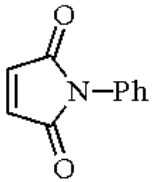	110 °C, 4.5 h	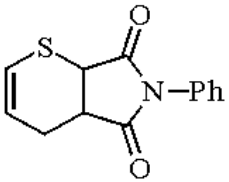	91
$(H_2C{=}CMeCH_2)_2SO$	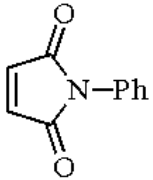	127 °C, 12 h	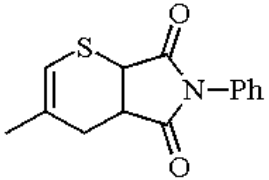	85
(1)	(*E*)-$MeO_2CCH{=}CHCO_2Me$	107 °C, 4.5 h	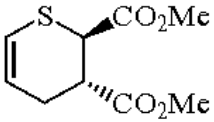	95
(1)	(*E*)-PhCH=CHPh	150 °C, 3 h	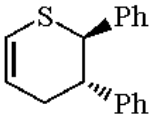	28
(1)	Norbornene	87 °C, 3 d	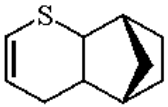	40
(1)	$H_2C{=}CHCO_2Et$	103 °C, 5 d	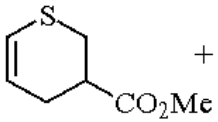 + 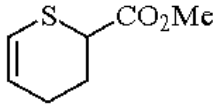	50

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1,2-Diaminoethane

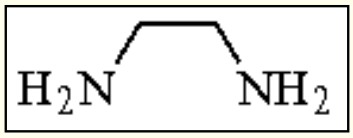

[107-15-3] · $C_2H_8N_2$ · 1,2-Diaminoethane · (MW 60.10) (.H_2O)

[6780-13-8] · $C_2H_{10}N_2O$ · 1,2-Diaminoethane · (MW 78.11)

(base and reducing agent;[1] used to complex metal ions;[2] used as building block for linking chains;[3] used to prepare imidazolines,[4] pyrazines,[5] 1,4-diazepine derivatives,[6] N_{2n}-containing macrocycles,[7] and fused heterocycles[8])

Alternate Names: DAE; ethylenediamine; EDA.

Physical Data: mp 8.5 °C; bp 117 °C; *d*204 0.8977 g cm^{-3}; *n*20D 1.4568.

Solubility: sol H_2O and alcohol; slightly sol Et_2O (1:300).

Form Supplied in: colorless liquid, widely available.

Purification: for some applications, 1,2-diaminoethane must be dried by standard methods used for amines.[9,11]

Handling, Storage, and Precautions: the reagent has low toxic, genotoxic, and oncogenic activity and should be handled with caution.[10a-c]

Complexation of Metal Ions.

1,2-Diaminoethane forms stable complexes with heavy metal ions: Ag, Au, Cd, Co, Cr, Cu, Fe, Hg, Ni, Zn, and others. Complexes of DAE with Cd^{II}, Co^{II}, Cu^{II}, or Hg^{II} are used in quantitative analysis of this metal or, conversely, of DAE. Ten- to 18-membered macrocycles with 2*n* nitrogen atoms, which can be prepared from the reagent, selectively form polydentate complexes with metal ions.[2] These complexes have been used for specific goals in catalytic reactions. For example, Cu^{II} complexed with the Shiff base prepared from DAE and chiral aldehydes shows high enantioselectivity in catalytic cyclopropanations of styrene with ethyl diazoacetate.[12] Copper(II) complexes of chiral diaminodiamides [$HXNHCH_2CH_2XH$ (X = Ala, Phe, Val)] have been used for enantioselective recognition of amino acids.[13] Addition of DAE after reactions of aryl halides with CuCN facilitates isolation of the nitrile from the reaction mixture by removing the Cu^{II} as a complex.[14]

Chromium(II) salts, with DAE as a ligand added in situ, are easily prepared reducing agents. The DAE greatly enhances the ability of Cr^{II} to reduce primary alkyl halides to alkanes,[15a] and aryl bromides or iodides to arenes (100%).[15b] This complex in aqueous DMF will selectively reduce a bridgehead chloride (eq 1),[15c] and convert β-substituted alkyl halides and epoxides to alkenes at rt in high yields.[15b] 4´-R-$\Delta^{1,8'}$-β-Octalones (R = CH_2OH, CO_2H) have been reduced by a ***Chromium(II) Sulfate***-DAE complex with *cis* stereospecificity, to the saturated ketones in 90% yield.[16]

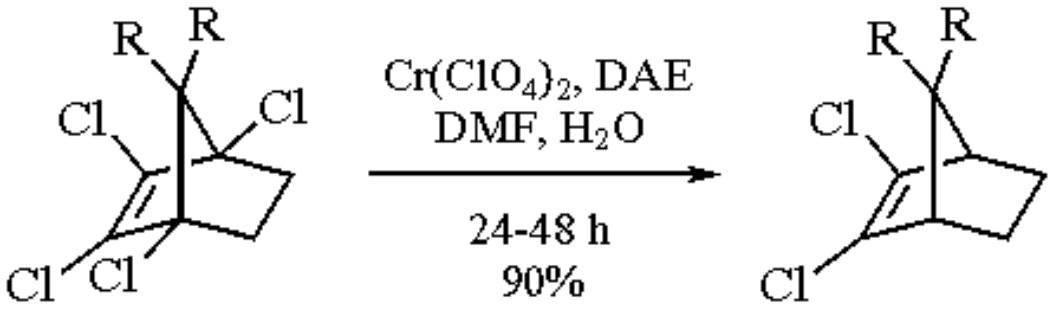

(1)

Complex with Borane.

The 1:1 complex of B_2H_6 with DAE in THF is a highly selective reducing agent, exhibiting reactivity comparable to ***Sodium Borohydride***. For example, it will transform cinnamaldehyde to cinnamyl alcohol.[17]

Solutions of KI_3 in DAE will iodinate phenols, anilines, tyrosines, pyrrole, and hydroxybenzoic acids.[18]

With Lithium in Reductions.

Lithium in DAE is a powerful reducing system. Reduction of alkenes, aromatic hydrocarbons, phenols, and alcohols have been reported. An example, the reduction of tetralin to octalin, is shown in eq 2.[1a] The 16,17 double bond and 20-keto group in pregnadienone were reduced to give the (20*R*)-alcohol in 95% yield.[19] Reduction of the 3α,4α- and 3β,4β-epoxides of friedel-3-ene,[20a] or the epoxides of pinene,[20b] gave the corresponding alcohols.

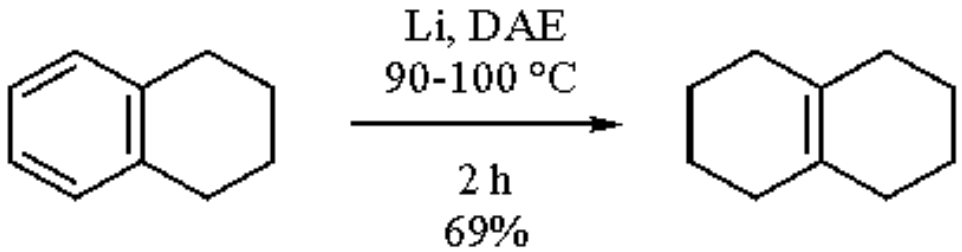

(2)

Isomerizations.

The lithium salt of DAE ($LiNHCH_2CH_2$-NH_2) is a very strong base. It has been used in the dehydrogenation and aromatization of vinylcyclohexene derivatives (4-vinylcyclohexene, limonene; 75-91%).[1b] Rapid and quantitative isomerization of terminal alkenes to internal alkenes has also been described (eq 3).[1b] Migration of triple bonds to terminal positions can also be accomplished. Internal alkynic hydrocarbons or alcohols are easily (40-50 °C, 20 min)

transformed to terminal isomers in yields of 74-87%.[21a] The yield of the terminal isomer can be raised by increasing base concentration and using nonpolar solvents.[21b] This reagent even rapidly shifts two triple bonds to terminal positions in 70-75% yields (eq 4).[22a,b] Similar migration of triple bonds is observed with ***Sodium Amide*** in DAE.[23]

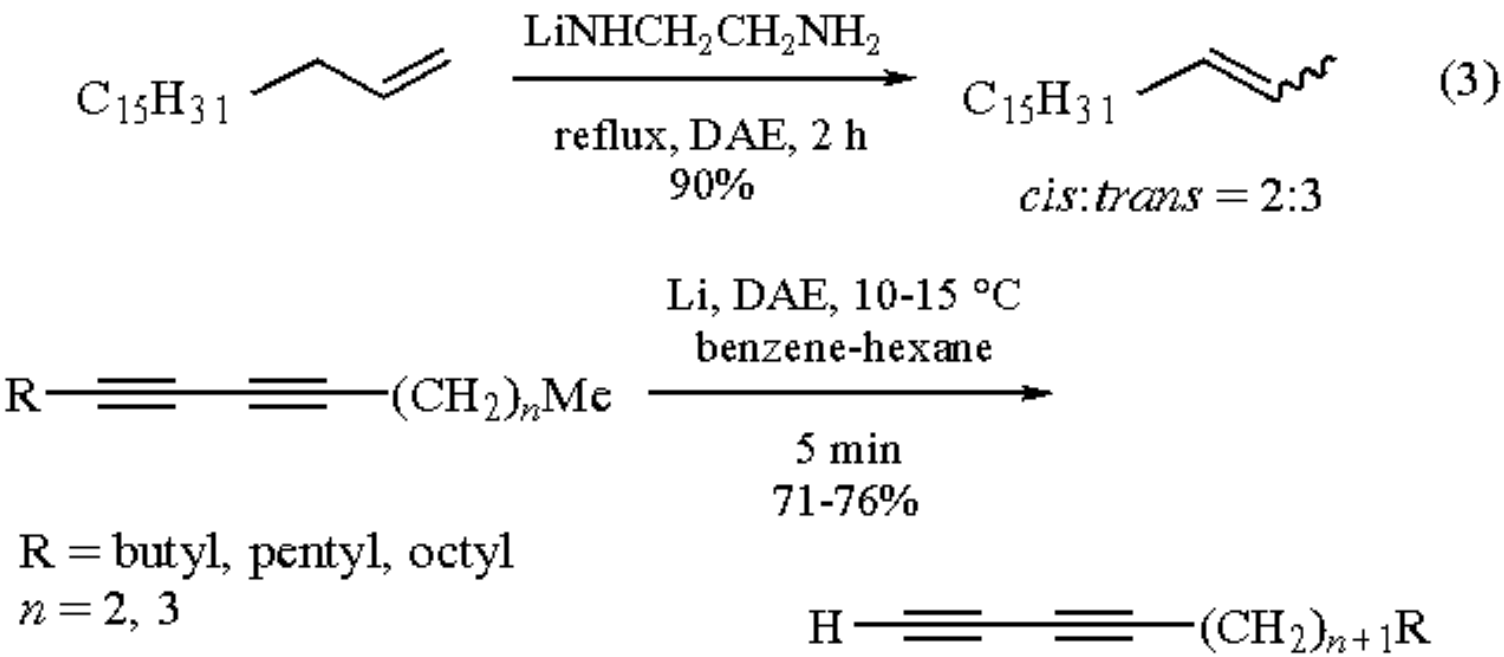

Building Block for Synthesis.

The synthetic significance of DAE is based on specific features of its structure. The reagent reacts with electrophiles to give mono or bis derivatives. For example, DAE has been monoacylated to give 2-(*t*-butoxycarbonylamino)ethylamine.[24] Reaction of the amino group and subsequent removal of the protecting group reveals a new amine which can be used in the next stage of a synthesis.

DAE has been used as a symmetric building block for the linking of molecular fragments by 1,2-bisamino,[3a,b] 1,2-bisimino,[3c] 1,2-bisamido,[3d] 1,2-bisimido,[25] or dimethylene chains (eqs 5 and 6).[26]

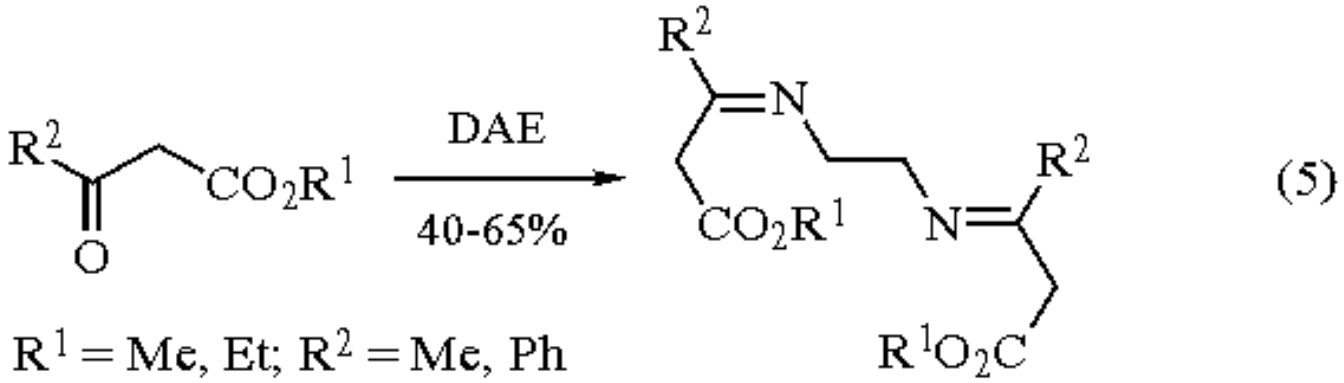

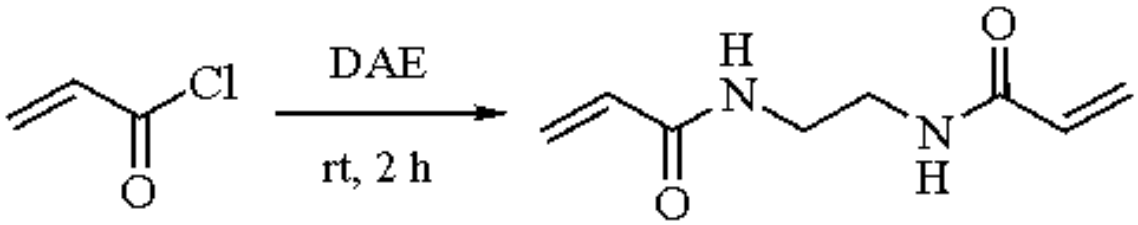

(6)

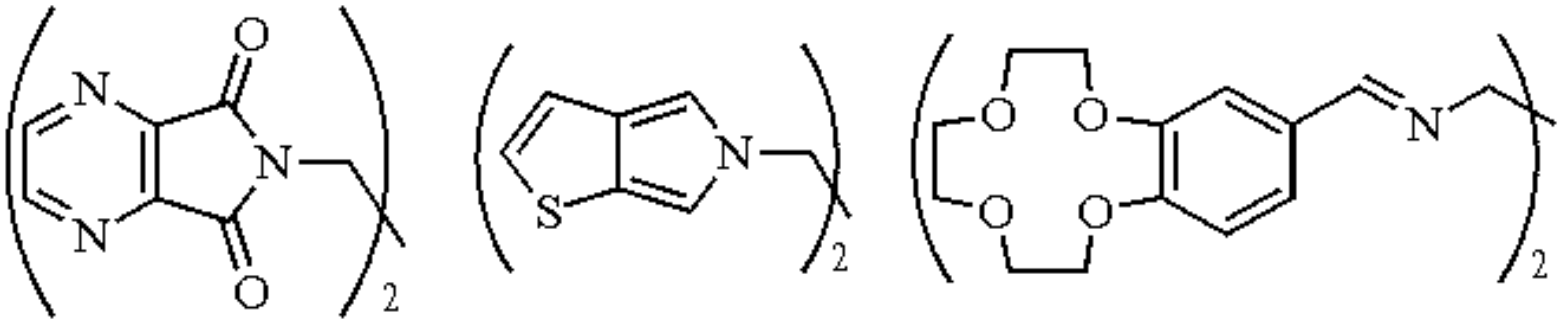

DAE is an excellent synthon for the synthesis of heterocycles with two nitrogen atoms. Condensation of DAE with 4-dialkylamino-3-butyn-2-ones led to 2-acetonylimidazoline (70%).[27a] Similar reactions with 1-haloalkynes give 2-alkylideneimidazolidines[27b] or 2-alkylimidazolines.[27c] Substituted 2-methyleneimidazolines can be prepared from DAE and compounds of the type R(W)C=CX_2, as outlined in eq 7.[28]

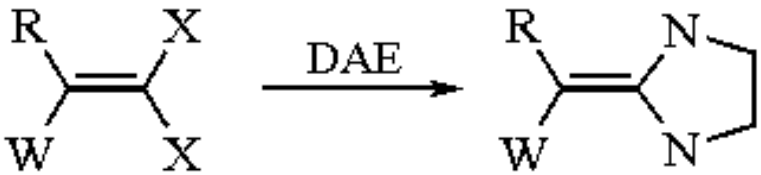

(7)

X = Br, SMe; R = H, alkyl, aryl
W = NO_2, acyl

Reaction of DAE with acids,[4a] esters,[4b] amides,[4c] dithioesters,[4d] imidoesters,[4e] nitriles,[4d,f] 2-aryloxazolines,[4g] or 2-phenylthiazolium salts[4h] gives 2-substituted imidazolines (eqs 8-10).

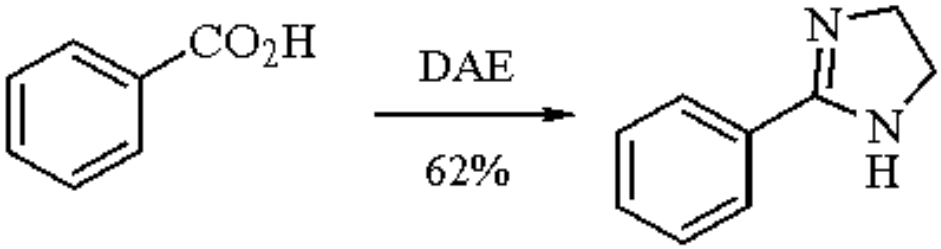

(8)

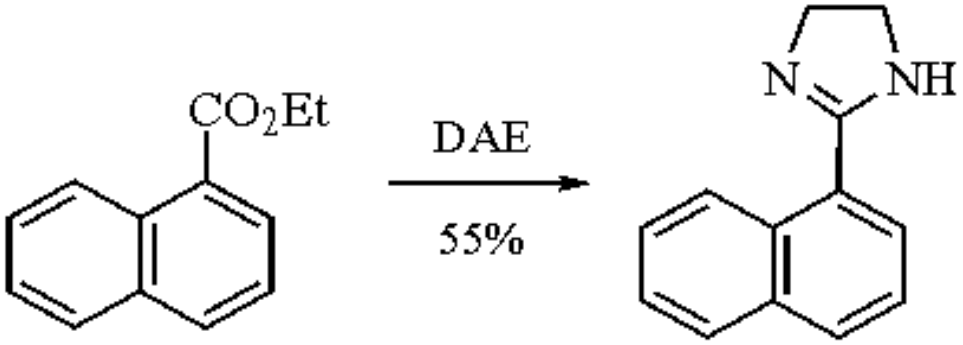

(9)

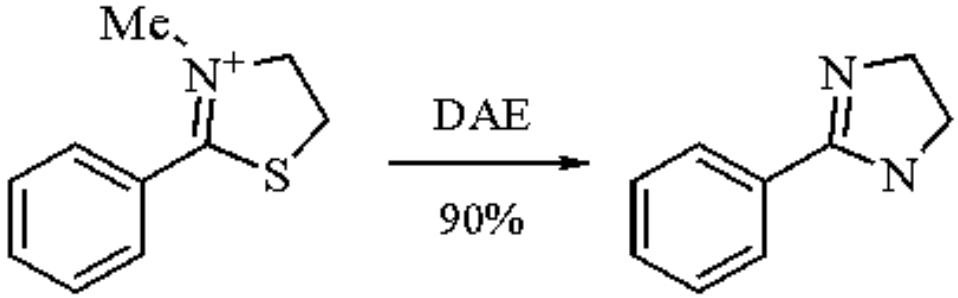

(10)

Imidazoline-2-thiol has been prepared in 60% yield by condensation of DAE with CS_2.[29] 2-Methylimidazole has been prepared in three steps from DAE and acetic acid in an overall yield of 80%.[30]

Cyclic guanidines have been prepared from DAE and *O*-alkyl thiocarbamates[31a] or *N*-aryldithiocarbamates.[31b] Similarly, these compounds have been obtained from DAE and imidoyl chlorides[32a,b] or dialkyl thioacetals of isothiocyanates (eq 11).[32c]

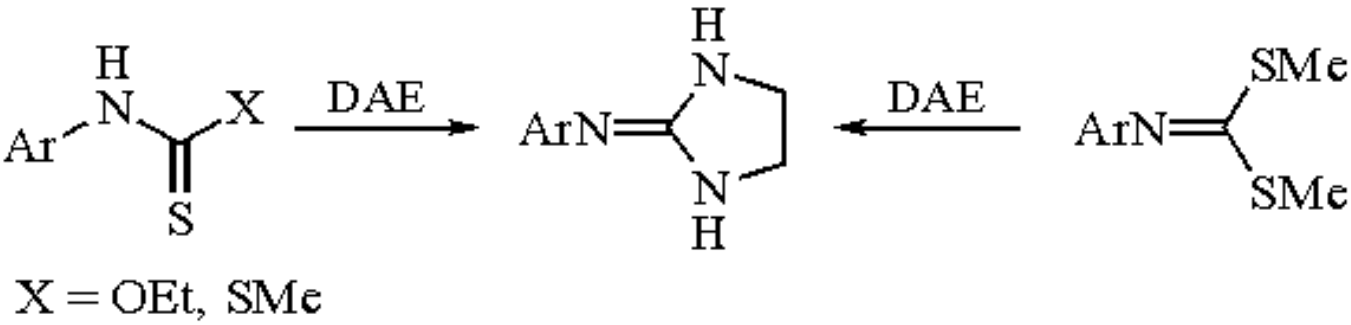

(11)

Reactions of DAE with dialdehydes, diketones, dicarboxylic acids, and their derivatives lead to cyclic products, containing $(N\text{-}C\text{-}C\text{-}N)_n$ fragments (eq 12). Thus 1,2-dicarbonyl compounds (α-diketones, *o*-quinones, alkyl oxalates) gave dihydropyrazines and, after subsequent oxidation, pyrazines.[5] Tetrahydropyrazines were obtained from α-halo carbonyl compounds.[33a] Piperazines were formed from *vic*-diols and DAE in the presence of a ruthenium catalyst.[33b] 1,4-Diazepines were prepared from the reaction of DAE with 1,3-diketones,[6a] vinyl ketones,[6b] or enynes.[6c] Twelve- to 20-membered macro N_4-heterocycles have been synthesized by the reaction α,o-dicarbonyl compounds with two molecules of DAE.[7] This method has been used to prepare some macrocycles with unique abilities for complexation of ions.[2]

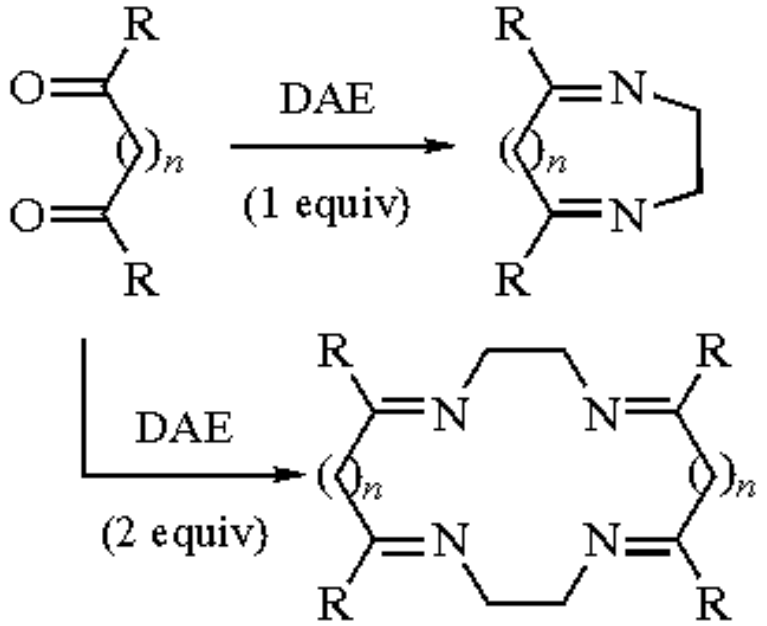

(12)

Molecules with two reaction sites react with DAE to give bicyclic products. Heterocycles prepared in this manner include pyrrolo[1,2-*a*]imidazoles,[8a] imidazo[3,4-*a*]imidazoles,[8b] imidazo[1,2-*b*]isoquinolines,[8c] and imidazo[1,2-*c*]pyrimidines.[8d] Polycyclic condensed systems with pyrazine[34a,b] and 1,4-diazepine[34c] substructures have been synthesized by means of DAE. An example is shown in eq 13.[35]

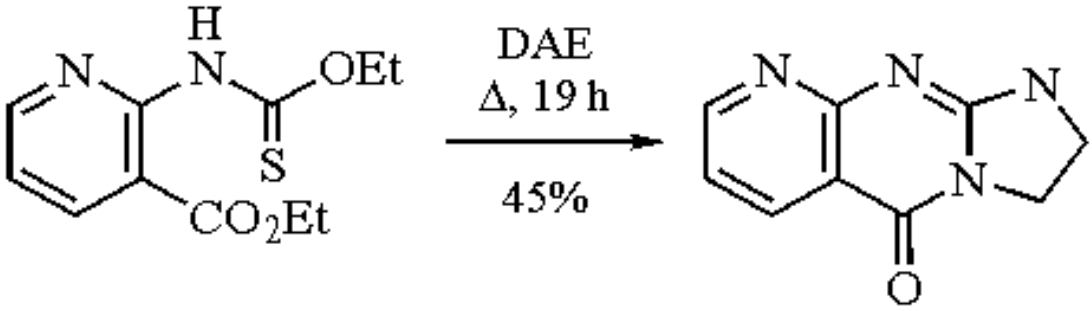

(13)

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Diaminomaleonitrile[1]

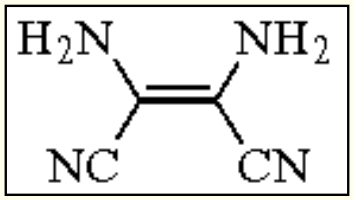

[1187-42-4] · $C_4H_4N_4$ · Diaminomaleonitrile · (MW 108.10)

(useful for a preparation of substituted imidazoles,[2,4-6] pyrazines,[9-13] and nucleosides[14])

Alternate Name: DAMN.

Physical Data: mp 184 °C (dec); sublimes at 120 °C/0.1 mmHg; dipole moment 7.9 D; pK_b 2.18; heat of combustion 5230 cal g^{-1}; *d* 1.29 g cm^{-3}.

Solubility: 25 °C (g/100 mL): acetone (15), DMA (39), water (0.5), THF (14), MeCN (7), EtOAc (3.6), ether (0.4), MeOH (6.1), EtOH (3.6), isopropanol (2.6), dioxane (9.6).

Preparative Methods: can be prepared from HCN by oligomerization[1d] or by hydrogenation of diiminosuccinonitrile.[1a]

Handling, Storage, and Precautions: the title reagent has an ALD of 450 mg/kg in rats; use in a fume hood.

Heterocycle Synthesis.

Diaminomaleonitrile is a weakly basic diamine with similar reactivity to *o*-phenylenediamine. DAMN has been used to prepare a variety of heterocyclic compounds. 4,5-Dicyanoimidazole was synthesized by refluxing DAMN and ***Triethyl Orthoformate*** in anisole (eq 1).[2] One possible intermediate can also be isolated under different reaction conditions (eq 2).[3] Cyanogen chloride or *N*-dichloromethylenephenylsulfonamide reacts with DAMN to give aminodicyanoimidazole or 4,5-dicyano-2-phenylsulfonylaminoimidazole, respectively (eqs 3 and 4).[4,5]

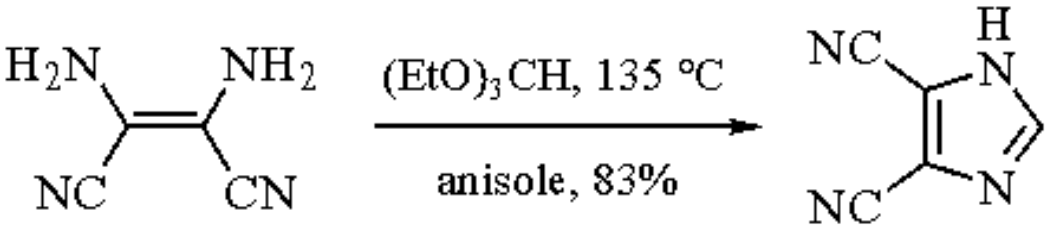

(1)

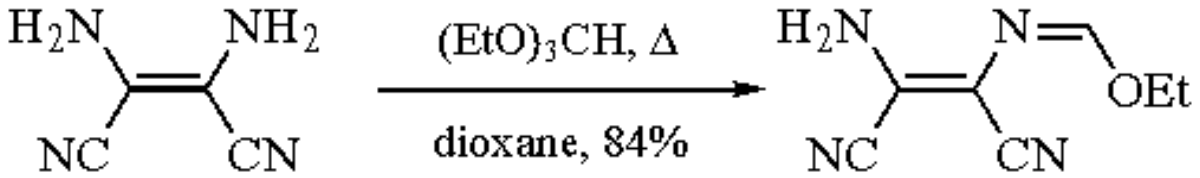

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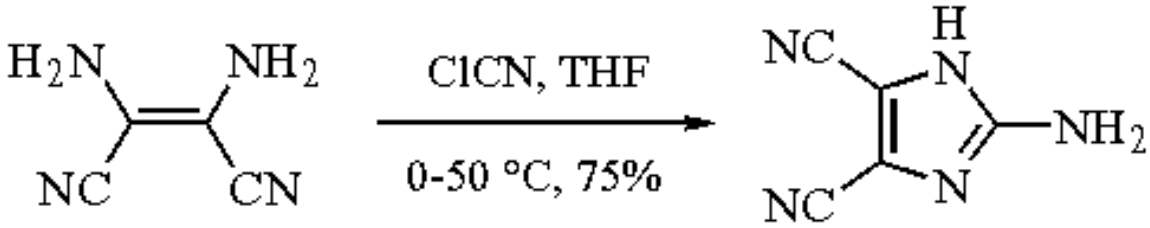

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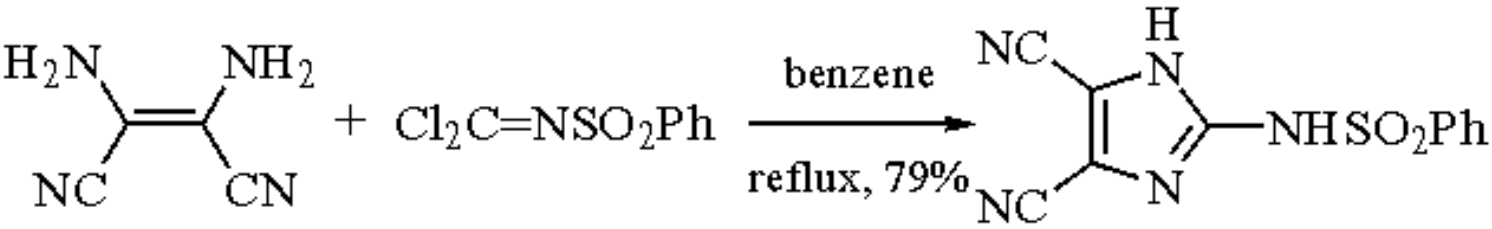

(4)

5-Amino-4-(*C*-cyanoformimidoyl)-1,2-dimethylimidazole was made by controlled basification of the salt which was formed from DAMN and nitrilium triflate (eq 5).[6]

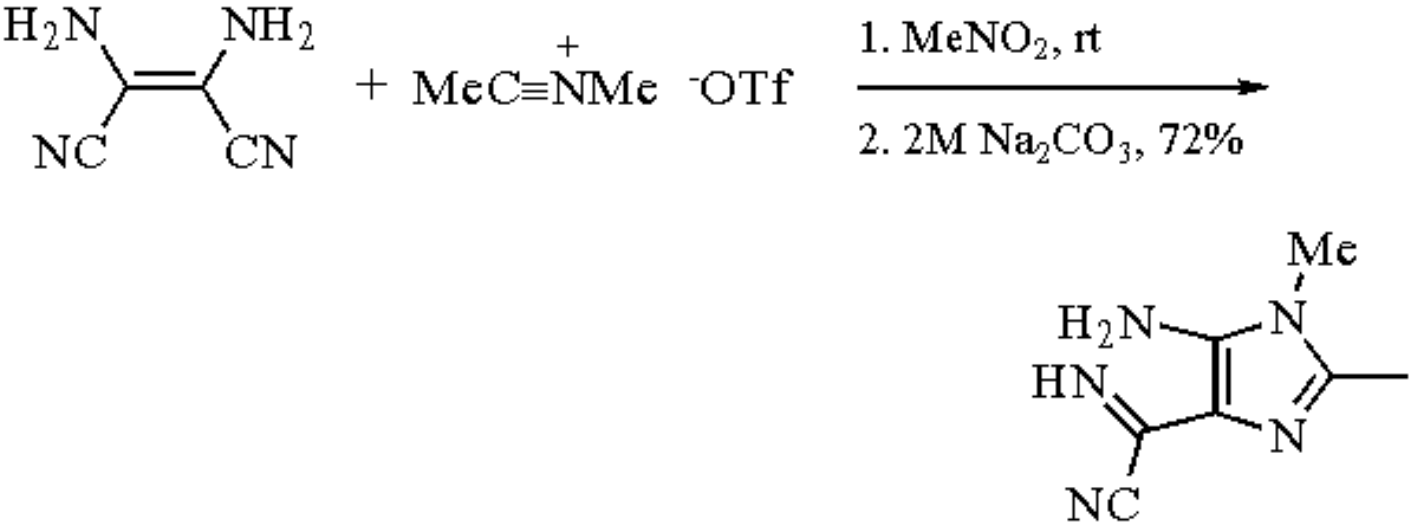

(5)

An efficient synthesis of 3,4-dicyano-1,2,5-thiadiazole was accomplished by reaction of DAMN with ***Thionyl Chloride*** (eq 6).[7]

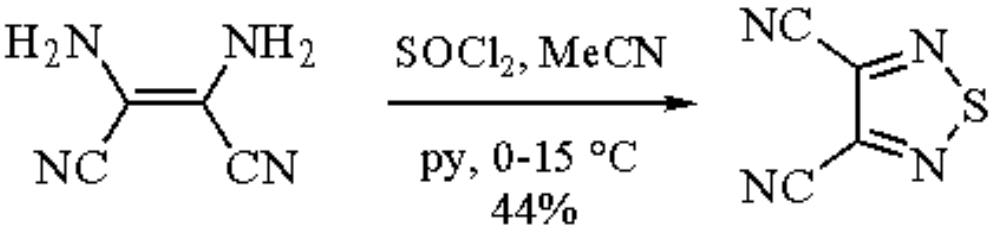

(6)

Phosphorus(III) Chloride reacts with DAMN to yield 2-chloro-2,3-dihydro-1*H*-1,3,2-diazaphosphole-4,5-dinitrile (eq 7).[8]

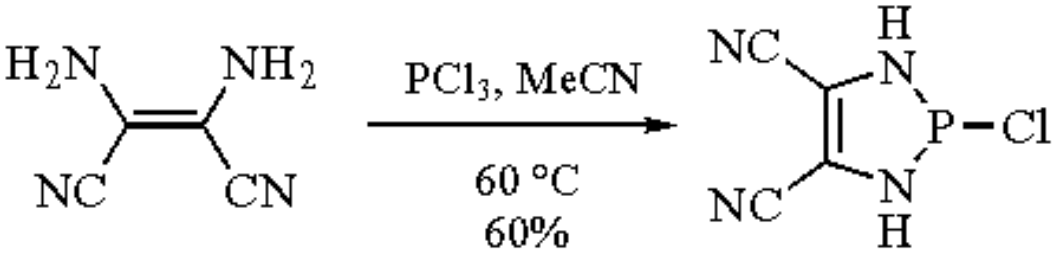

(7)

Substituted pyrazines can be prepared by condensation of DAMN with either 1,2-diketones or β-keto sulfoxides or acylsulfonium halides (eqs 8-10).[9-11]

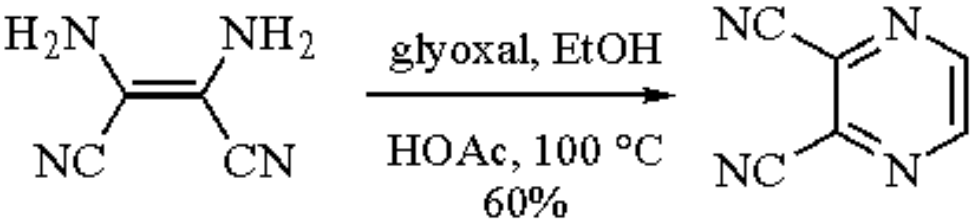

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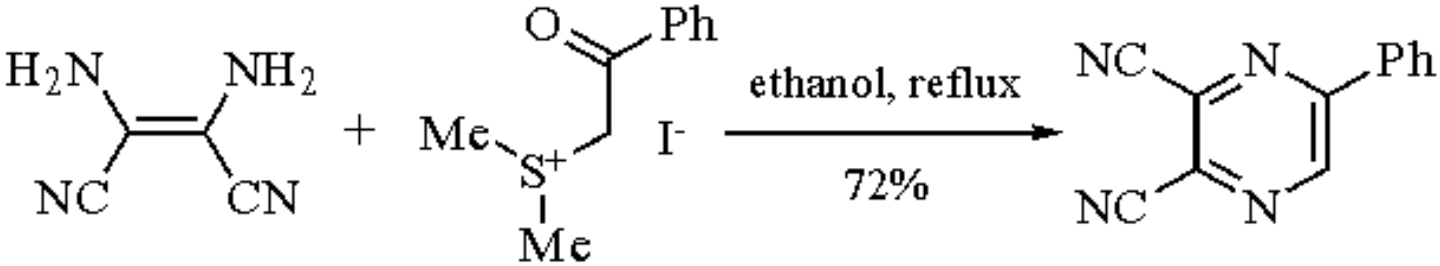

(9)

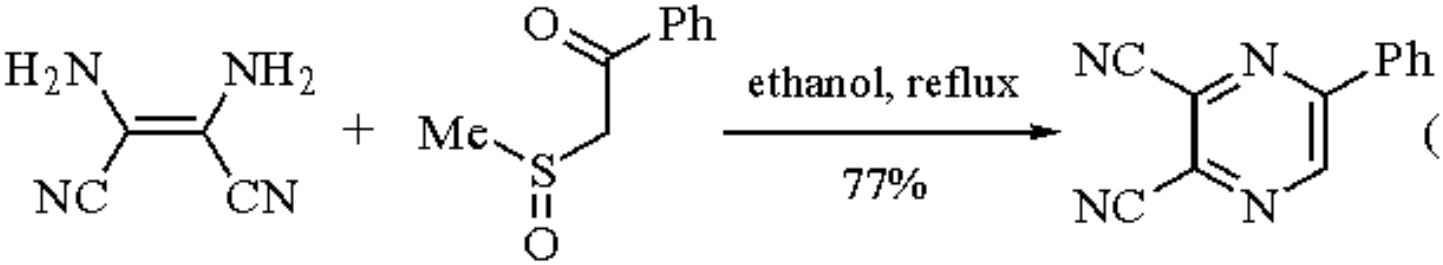

(10)

Oxalyl Chloride or ethyl ethoxycarbonylformimidate reacts with DAMN to afford pyrazine derivatives (eqs 11 and 12).[12,13]

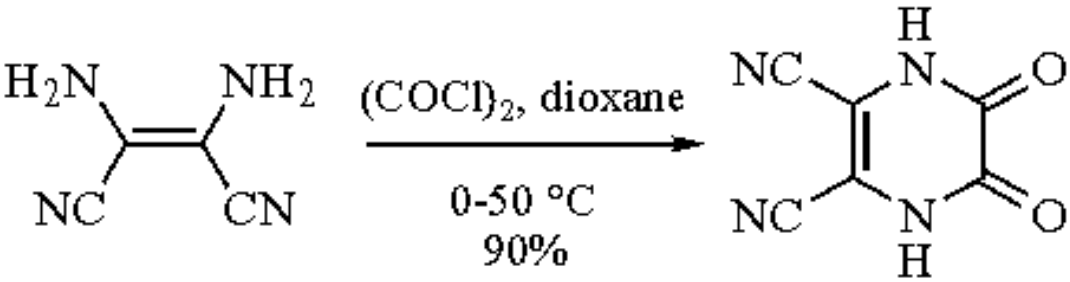

(11)

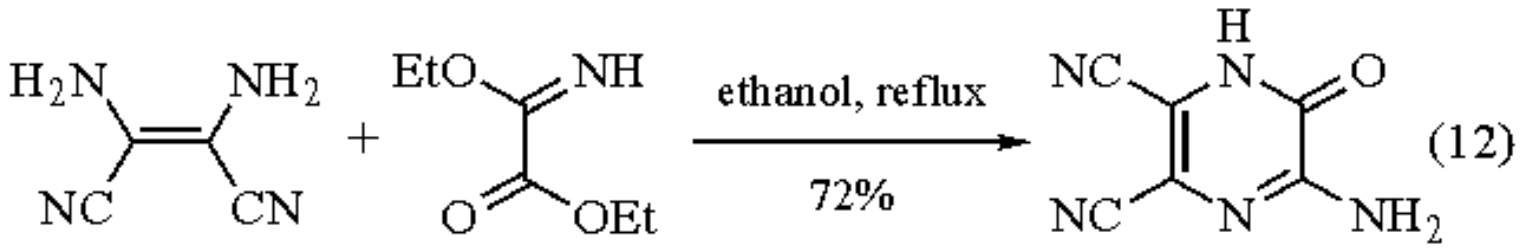

DAMN has been proposed to be an essential intermediate to purines in prebiotic origins of life and it has been used to prepare some nucleosides (eq 13).[14]

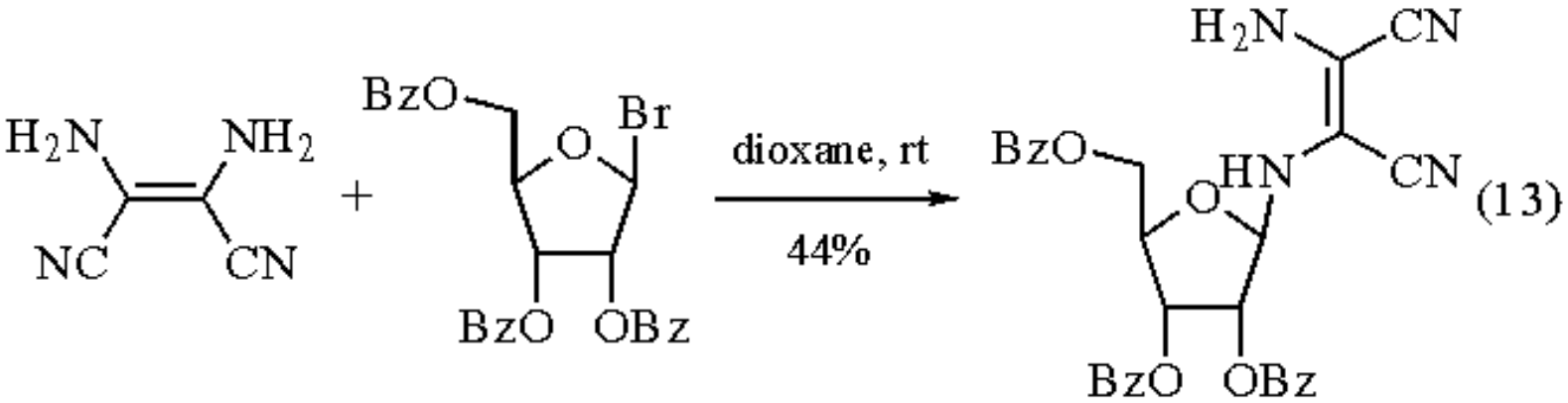

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2,4-Diamino-1,3-thiazole Hydrotribromide[1]

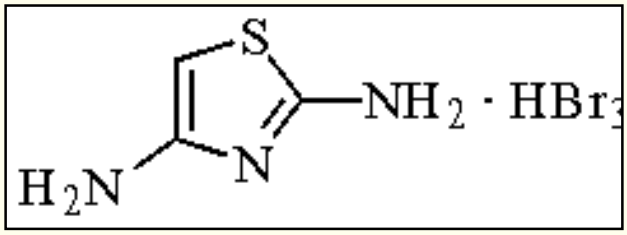

[75117-14-5] · $C_3H_6Br_3N_3S$ · 2,4-Diamino-1,3-thiazole Hydrotribromide · (MW 355.87)

(solid brominating agent[1])

Physical Data: mp 198-200 °C (dec).

Solubility: sol methanol, ethanol; slightly sol acetic acid; insol H_2O, ether, chloroform; sol but reacts with DMSO, acetone.

Preparative Methods: to a solution of 11.7 g of 2,4-diamino-1,3-thiazole *[67355-26-4]* in acetic acid or in water, 12 mL of 48% hydrobromic acid is added. Slightly less than 1 equiv of bromine is then slowly added at 0 °C. After 1-2 h, the solid hydrotribromide precipitates and is collected by filtration and washed with ether or chloroform. The solid is recrystallized from methanol (without heating) to yield 13 g (60%) of the desired reagent.[2] 4-Amino-2-dimethylamino-1,3-thiazole hydrotribromide (mp 150-153 °C) is prepared in the same way from 4-amino-2-dimethylamino-1,3-thiazole and is slightly more stable than the corresponding 2,4-diamino derivative.

Analysis of Reagent Purity: usual KJ titration indicates the amount of free bromine.

Handling, Storage, and Precautions: the dry solid is stable in the dark for several weeks.

Bromination of Aryl Ketones.[1]

α-Bromo ketones are obtained by reaction of the reagent (**1**) with aryl ketones in acetic acid at 25 °C (eq 1).

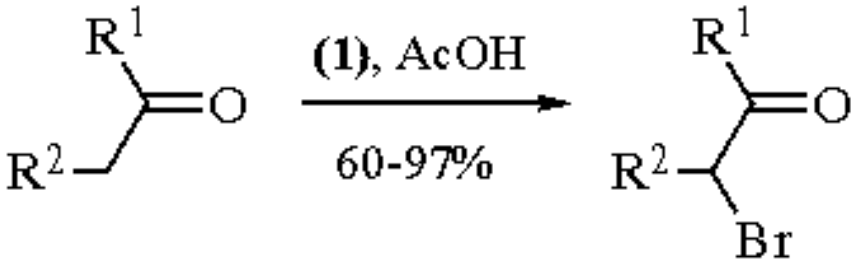

(1)

Bromination of Phenols.[1]

Bromination of phenol with this reagent produces the *para* and *ortho* monobromides in a 4:1 ratio (eq 2).

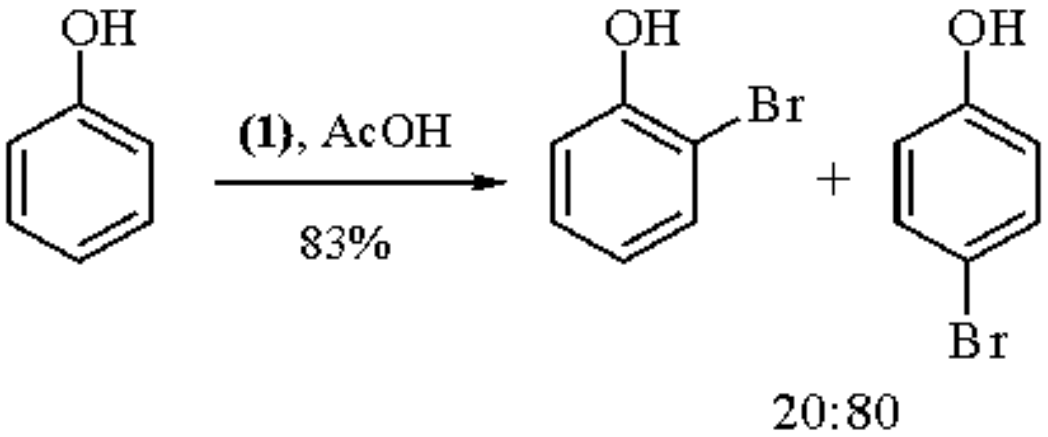

(2)

Both α- and β-naphthols are monobrominated to bromonaphthols (eq 3). β-Naphthol affords 1-bromo-2-naphthol in 82% yield.

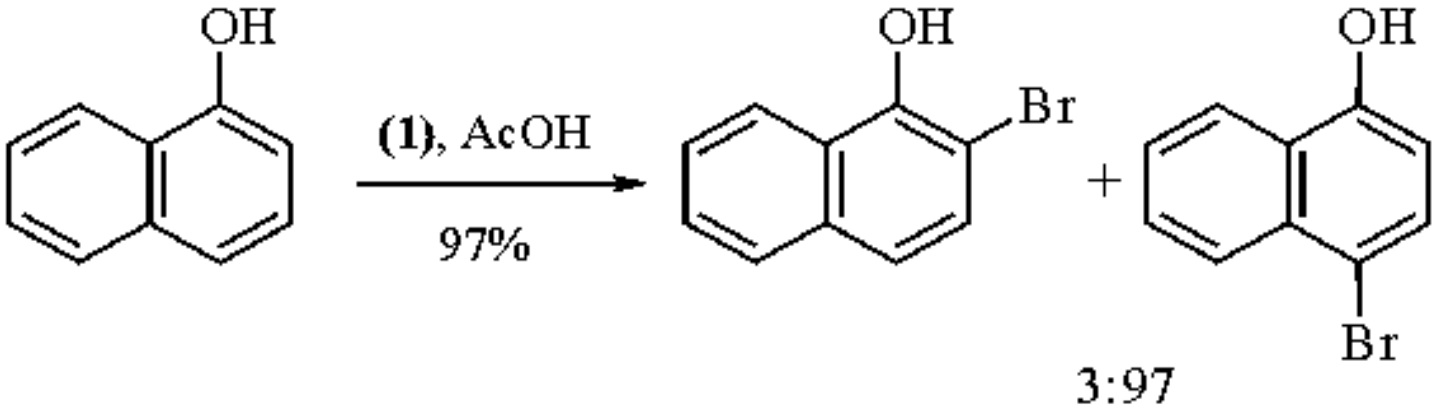

(3)

2,4-Diaminothiazole (and 4-amino-2-dimethylaminothiazole) are slightly soluble in acetic acid and may be recovered and collected by simple filtration after each bromination run.

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1. Forlani, L. *S* **1980**, 487.

Dianisyl Telluroxide[1]

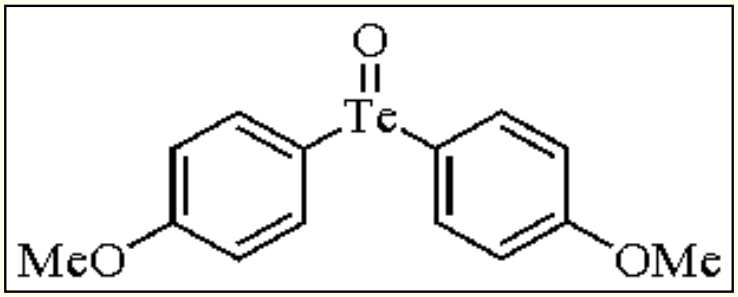

[57857-70-2] · $C_{14}H_{14}O_3Te$ · Dianisyl Telluroxide · (MW 357.88)

(mild oxidant for diphenols, thiols, and thio compounds;[2] aldol catalyst[11])

Alternate Name: bis(4-methoxyphenyl) telluroxide.

Physical Data: mp 190-191 °C.[2]

Solubility: poorly sol most organic solvents; sol acetic acid.

Preparative Method: by base-catalyzed hydrolysis (2N NaOH, 95 °C, 1 h) of dianisyltellurium dichloride,[2] which is itself prepared by reaction of anisole with tellurium tetrachloride.[3]

Handling, Storage, and Precautions: stable white powder; dried in vacuo over P_2O_5. All manipulations must be carried out in a well ventilated hood.

Oxidation Reactions.

Ortho and *para* diphenols are easily oxidized by dianisyl telluroxide to quinones, and 1,2-glycols are cleaved with this reagent, whereas simple phenols and alcohols are not affected.[2] Aryloxyl radicals have been observed during the reaction of 2,6-di-*t*-butylphenol derivatives with the telluroxide and these radicals were further oxidized, when possible, to the diphenoquinone.[4] Thiols are rapidly oxidized to disulfides in high yields, even in the presence of sensitive functional groups such as aromatic amines or amino acids. A number of thio or seleno compounds have been transformed into their oxo derivatives with this reagent (eqs 1 and 2), including thionoesters, selenoesters, dithioesters, thionocarbonates, trithionocarbonates, thioketones, and xanthates. In the case of thiocamphor, a more complex sequence led to a poor yield of the ketone (10%) and to the formation of the disulfide, which was slowly converted to the dimeric thioketone. The behavior of thiourea and thioamides is dependent on the nature of the substrate and the reaction conditions. Thus thiourea and *N*,*N*´-diphenylthiourea gave the corresponding ureas but *N*-phenylthiourea gave the dimeric 1,2,4-thiadiazole in 97% yield (eqs 3 and 4).[5,6]

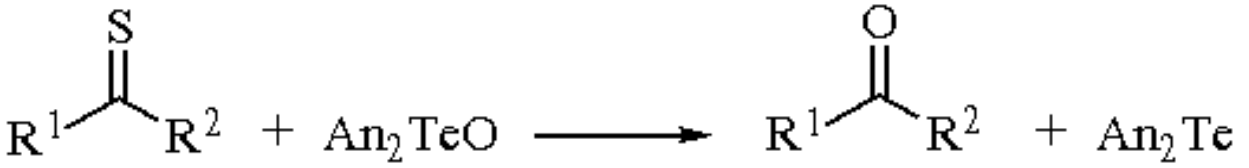

(1)

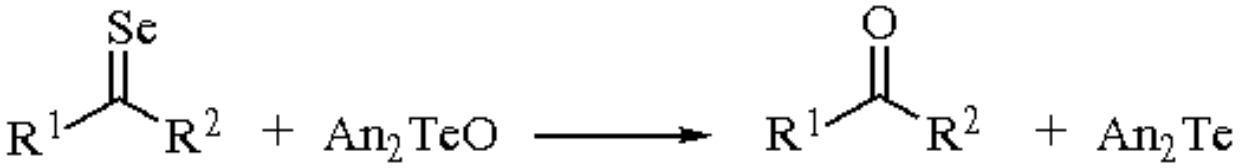

(2)

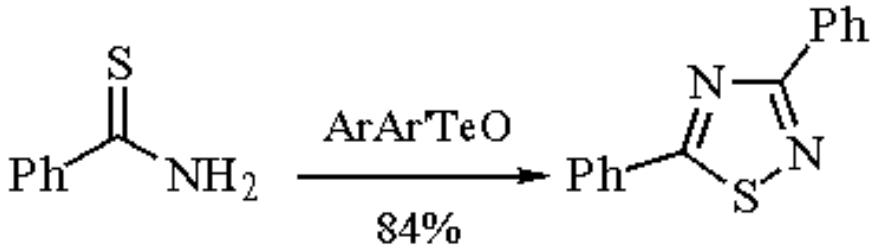

(3)

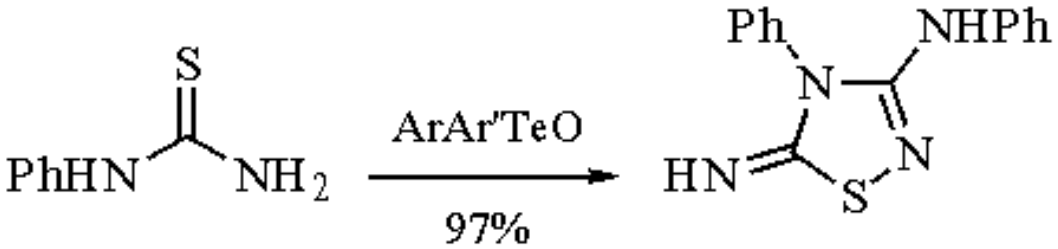

(4)

Pyrrolidinethione gave the corresponding pyrrolidinone, but primary thiobenzamides gave either benzonitrile or underwent oxidative dimerization to 1,2,4-thiadiazoles. Thiobenzoylurea and thiobenzoylguanidine afforded only the 1,2,4-thiadiazole derivatives. Phosphines are easily oxidized to the corresponding phosphine oxides, although this method does not offer any specific advantage over classical methods.

Acylhydrazines are converted to acylhydrazides, in a reaction similar to the oxidation with diphenyl selenoxide. Arylhydrazines furnish a mixture of the corresponding arenes, of anisole, and diaryl tellurides. Benzophenone hydrazone was oxidized to diphenyldiazomethane, which was trapped with *p*-anisic acid. Phenylhydroxylamine afforded nitrosobenzene in 90% yield in 5 min without overoxidation.

A large number of functional groups are inert toward this telluroxide, including aldehydes, ketones, hydroxybenzoic acid esters, enamines, pyrrole, indole, amino acids, aromatic amines, isocyanides, hindered thionocarbonates, oximes, arylhydrazones, dithiolanes, sulfides, and selenides.

A polystyrene-bound diaryl telluroxide was reported to present the same spectrum of oxidizing properties as the monomeric reagent.[7] The reduced reagent can be easily recovered and then reused after reoxidation. However, in the case of primary thiobenzamide, the thiadiazole was formed with the polymeric reagent in acetic acid, as well as with the monomeric dianisyl telluroxide ditosylate, whereas benzonitrile was obtained with dianisyl telluroxide.

A related reagent, bis(4-methoxyphenyl) tellurone *[82342-66-3]*, is prepared by oxidation of the telluroxide with ***Sodium Periodate***. It is also a mild oxidant of thiophenols to disulfides and of hydroquinones to quinones, but slightly

more powerful than the telluroxide as it oxidized benzylic alcohols to benzaldehydes and benzoin to benzil. Glycols were also oxidatively cleaved.[8]

Catalytic Version of the Reagent.

The oxidation of thiocarbonyl compounds to their oxo analogs can also be performed with dianisyl telluride in a catalytic system with 1,2-dibromotetrachloroethane acting as a brominating agent. In the presence of aqueous base, the dibromo telluride is hydrolyzed to the telluroxide which reacts in a two-phase system.[2,9] In the course of the synthesis of 1α,25-dihydroxyvitamin D_3, oxidation of a cyclic hydrazine derivative was performed under these conditions to afford directly the very sensitive *trans*-trienic system of the vitamin (eq 5).[10]

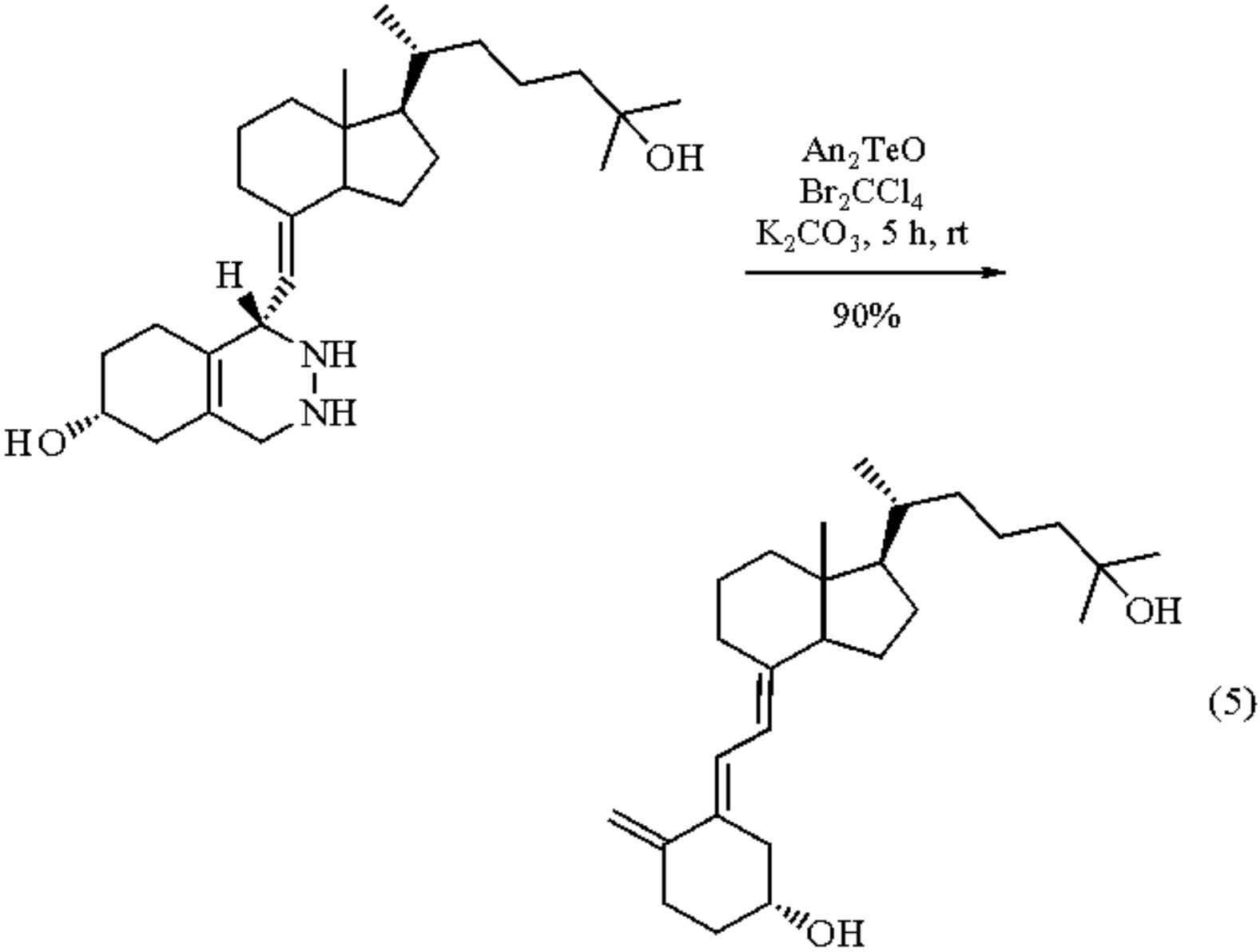

Electrochemically generated telluroxide also reacts with thiobenzamide. The outcome of the reaction is directly related to the nature of the supporting electrolyte: with Bu_4NOAc, benzonitrile is the only product, whereas with Et_4NOTs the thiadiazole was the major or only product.[7]

Aldol Condensation Catalyst.

Dianisyl telluroxide acts efficiently as a mild catalyst for aldol condensations under aprotic conditions (toluene, reflux for 2 h, 0.1 equiv of the catalyst). Dibenzotropone, which cannot be obtained by using classical basic catalysis, was prepared in 96% yield with this catalyst (eq 6).[11,12]

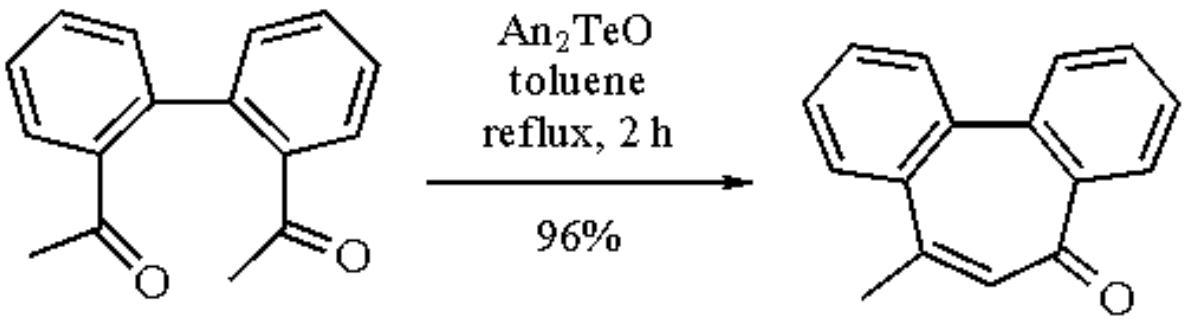

(6)

However, aldol condensations with very acidic methylene compounds gave only moderate yields. This reagent also catalyzed the condensation of cinnamaldehydes with ketones and activated nitriles in high yield.[13]

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1,5-Diazabicyclo[4.3.0]non-5-ene[1]

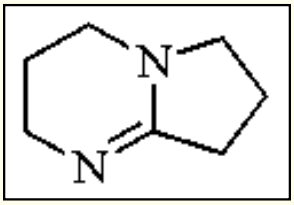

[3001-72-7] · $C_7H_{12}N_2$ · 1,5-Diazabicyclo[4.3.0]non-5-ene · (MW 124.19)

(organic soluble base for elimination reactions,[2-11] isomerizations,[12-19] esterifications,[26-31] and condensations[20-25])

Alternate Name: DBN.

Physical Data: bp 95-98 °C/7.5 mmHg; *d* 1.005 g cm^{-3}.

Solubility: sol polar solvents such as water, ethanol, benzene, methylene chloride, chloroform, THF, and DMSO.

Form Supplied in: clear, colorless or light yellow liquid.

Handling, Storage, and Precautions: stable at ambient temperatures, but is hygroscopic; contact with undiluted product may cause skin irritation or burns.

Introduction.

1,5-Diazabicyclo[4.3.0]non-5-ene is an organic soluble amidine base which has been used effectively, under relatively mild conditions, for a variety of base-mediated organic transformations including eliminations, isomerizations, esterifications, and condensations. A related reagent, ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU), is used for similar reactions.

Elimination Reactions.

DBN has been used for dehydrohalogenations as well as for the introduction of unsaturation by elimination of sulfonic acids. Typical reactions are conducted with equimolar or excess base in solvents such as DMF, DMSO, benzene, methylene chloride, and chloroform. Products may be distilled directly from the reaction mixture or separated from the DBN salt byproduct by extraction with a nonpolar solvent. Terminal as well as internal double bonds have been introduced in this manner. Additionally, DBN has been used to prepare functionalized alkenes such as vinyl thioethers.

Oediger and Möller compared DBN with DBU in the dehydrohalogenation of bromoalkanes. Conditions were equimolar base and 80-90 °C. DBN was found to be only moderately effective, affording heptenes from bromoheptanes in 36-60% yield. Corresponding yields using DBU were 78-91%.

DBN was effective, however, for the conversion of β-substituted primary alkyl iodides into terminal alkenes.[2] Thus treatment of iodide (**1**) with 1.5 equiv of DBN in benzene at 80-90 °C for 3-4 h afforded alkene (**2**) in 91% yield (eq 1).

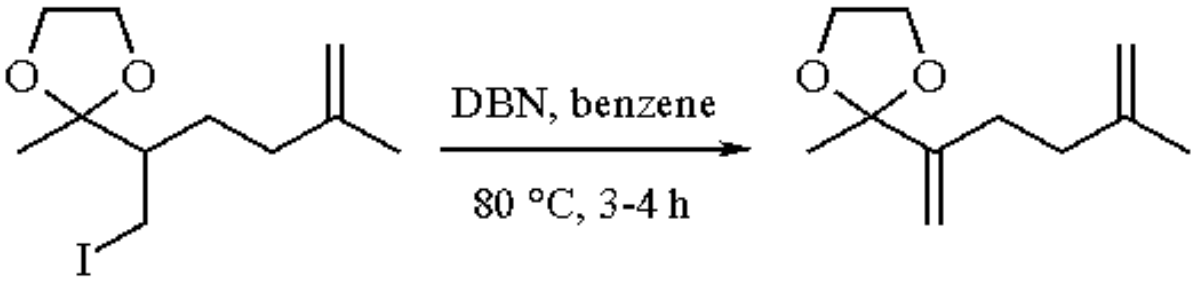

(1)

(1) **(2)**

Both DBN and DBU have been employed in aprotic solvents for the dehydrobromination of substrates containing acetate functionality.[3-5] DBN was used in the preparation of chrysene derivative (**4**) (eq 2).[5] Diacetate (**3**) was brominated with NBS in methylene chloride, then dehydrobrominated using DBN in THF. Acetate functionality was preserved (note that DBU has been used for rt deacetylations in methanol[6]) and (**4**) was isolated in 51% yield after 16 h at -20 °C.

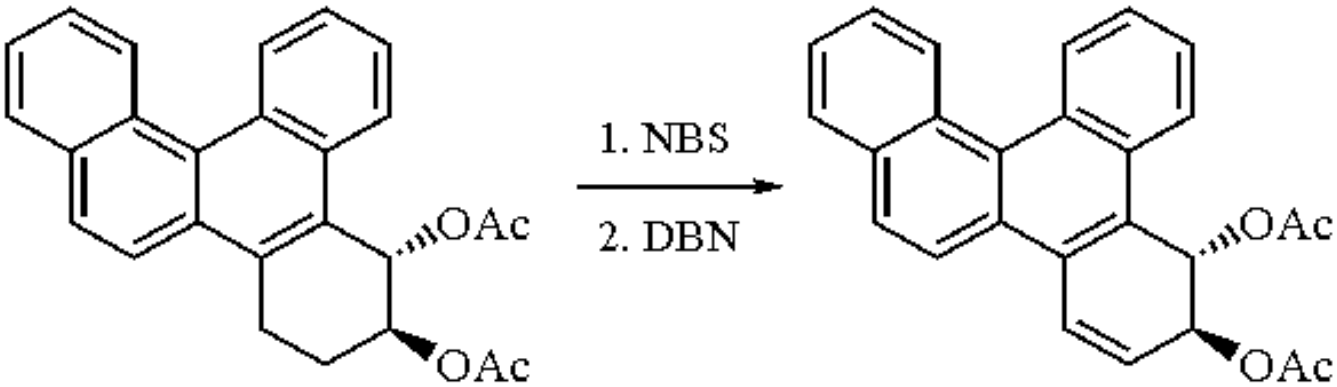

(2)

(3) **(4)**

DBN promoted the elimination of methanesulfonic acid in the preparation of pyranoside (**5**) (eq 3).[7] Use of $NaHCO_3$ in place of DBN also afforded the desired pyranoside; however, the yield was low (15%) and the reaction time was longer. With NaH in refluxing DME, a mixture of regioisomeric elimination products resulted.

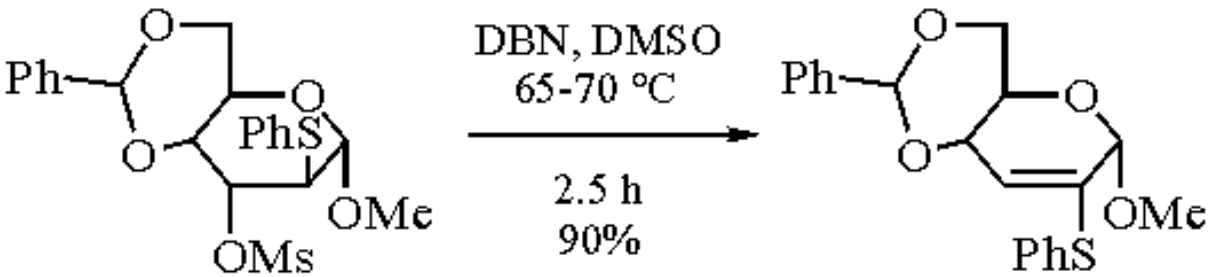

(3)

(5)

DBN was used for the elimination of methanesulfonic acid from ester (**6**) to give *trans* α,β-unsaturated ester (**7**) in 86% yield after 4 h at rt (eq 4).[8] Interestingly, the nitrile analog of (**6**) (i.e. side chain cyano group rather than the methyl ester)

afforded a 6:5 *cis*:*trans* mixture of α,β-unsaturated nitriles, probably due to the smaller steric requirements of the cyano group.

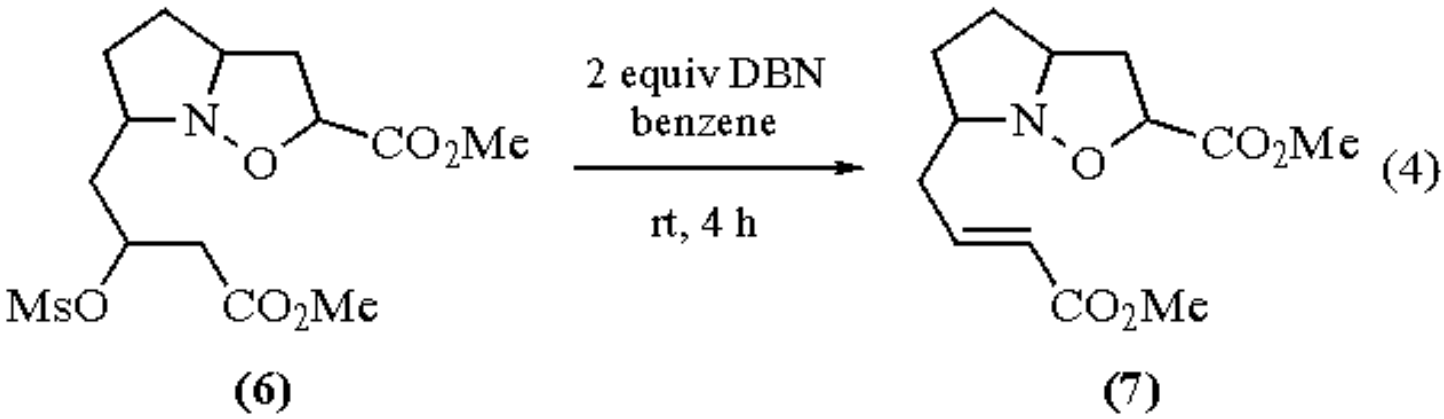

Elimination of an intermediate thiolate in the presence of DBN was postulated to occur in a thiazolidine ring enlargement of penams (eq 5).[9,10]

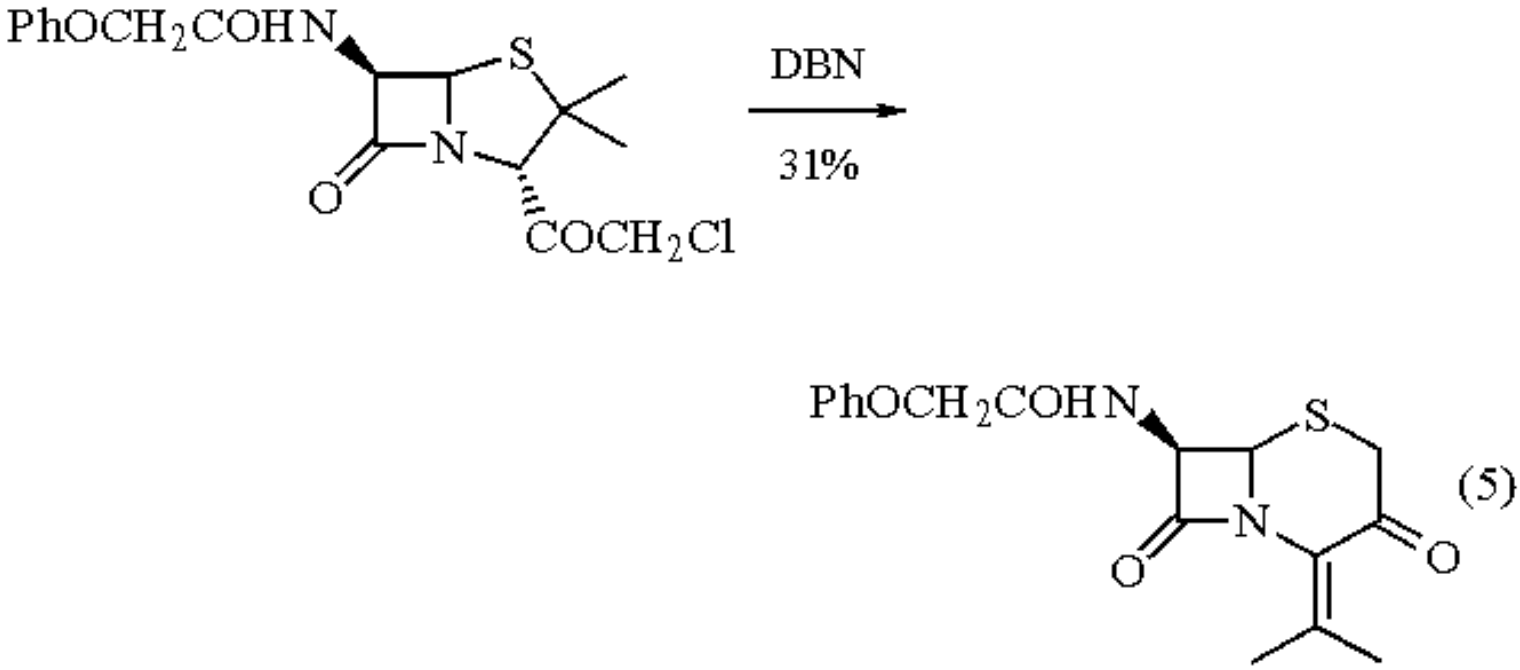

Another rearrangement which has been postulated to occur via a DBU-mediated elimination is the conversion of 2-amino-5-imino-4,5-dihydrothiazoles (e.g. **8**) to imidazoline thiones (e.g. **9**) and diazolidines (e.g. **10**).[11] The rearrangement is thought to proceed through a ring-opened carbodiimide intermediate which subsequently cyclizes to (**9**) or (**10**). The relative amounts of (**9**) and (**10**) formed vary with substrate structure. A representative reaction is shown in eq 6.

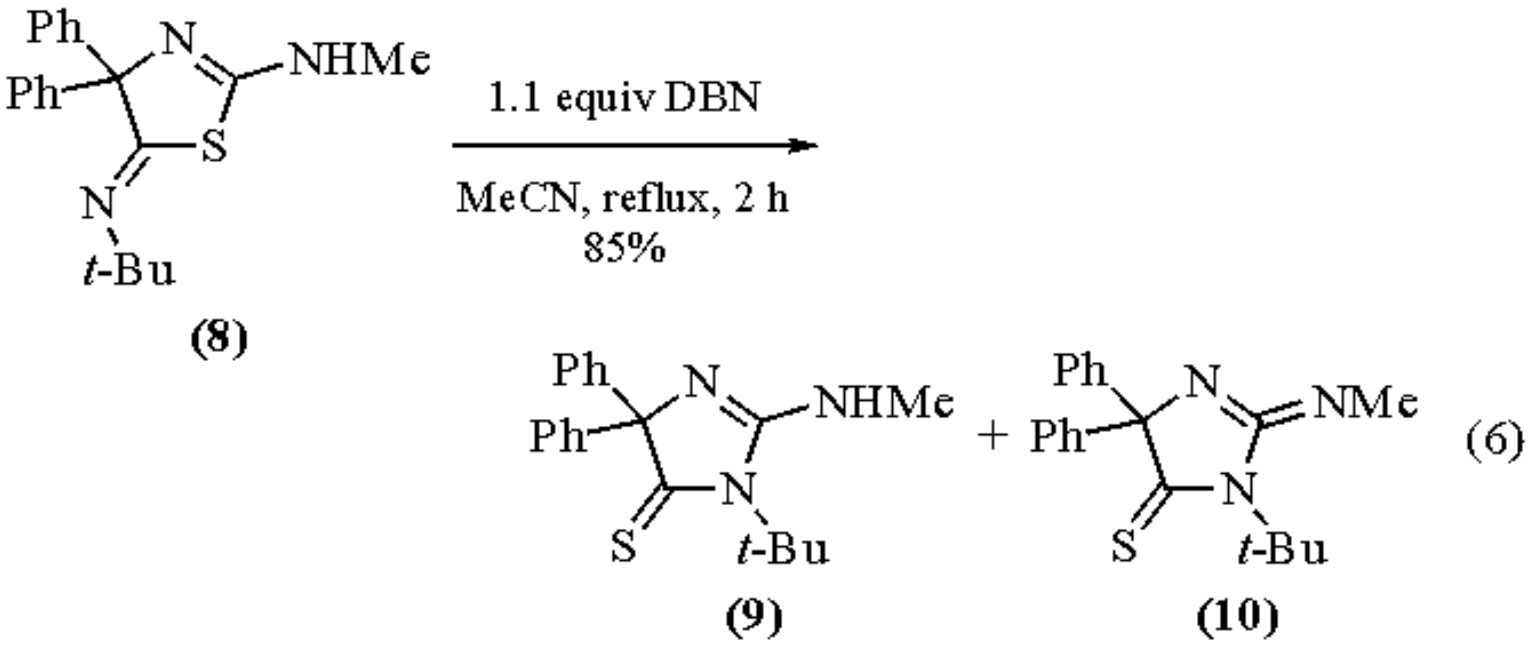

Isomerizations.

DBN has been used for base-mediated epimerizations and double bond migrations. Isomerizations generally require proton abstraction at a carbon α to a carbonyl group (or related functionality) and are thermodynamically controlled.

DBN is widely used for epimerizations of 6β-substituted penicillins to the corresponding 6α-isomers.[12-17] Epimerization of penicillins occurs rapidly and without competitive formation of 1,4-thiazepines (e.g. **12**). Methylene chloride is the most frequently used solvent. Various bases were compared in the epimerization of (**11**) (eq 7).[14] DBN and ***1,1,3,3-Tetramethylguanidine*** were equally effective. Other tertiary amine bases, including *N*-methylmorpholine, *N,N*-dimethylbenzylamine, *N*-alkylpiperidines, and ***Triethylamine***, afforded considerable amounts of thiazepine (**12**).

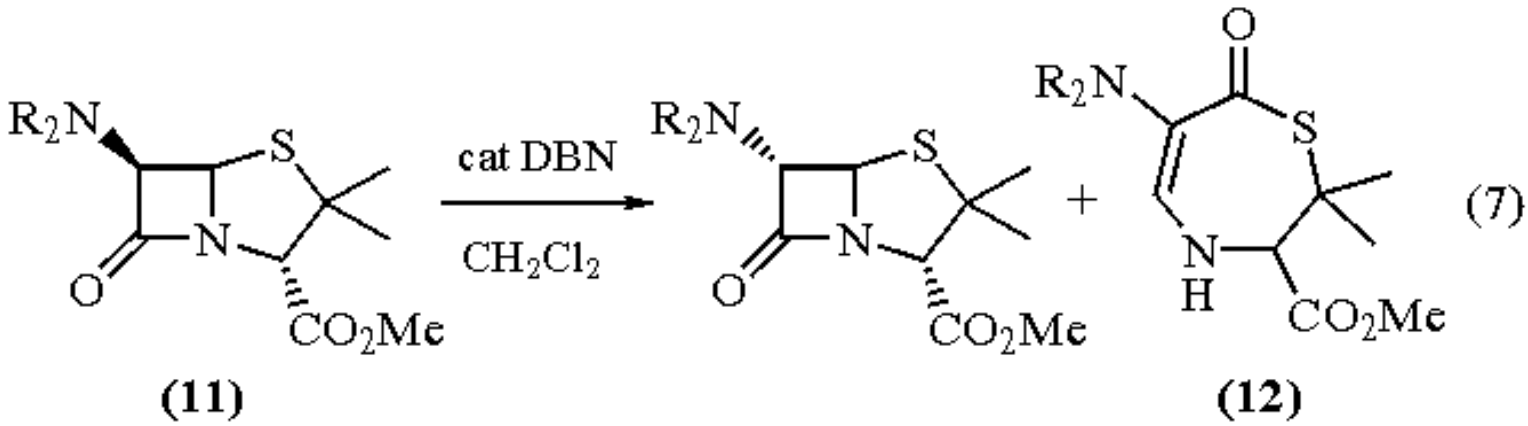

DBN was used to achieve the equilibration of medium-ring cycloalkenones in a study of the effect of substituents on the 3-cycloalkenone/2-cycloalkenone product distribution.[18] Isomerizations were conducted in toluene or benzene from 25 to 100 °C in the presence of a catalytic amount of DBN. Generally, electron-withdrawing substituents at C-3 favored 3-cycloalkenones. Table 1 shows equilibration results for various 3-substituted cycloheptenones after treatment with a catalytic amount of DBN in toluene at 80 °C.

Table 1 Isomerization of 3-Substituted Cycloheptenones

3-Substituent	2-Cycloheptenone (%)	3-Cycloheptenone (%)
H	76.8	23.2
CO_2Me	16.8	83.2
CN	15.1	84.9
COMe	20.7	79.3

Several biomimetic methods for the conversion of amines to carbonyl compounds have used amidine bases to effect equilibration of the intermediate imine.[19-21] Corey used DBN in the oxidation of amines with mesitylglyoxal (**13**).[19] Thus cyclohexylamine and (**13**) were combined in benzene to form a Schiff base which was subsequently treated with DBN in THF/DMSO to afford cyclohexanone in 87% yield after hydrolysis (eq 8).

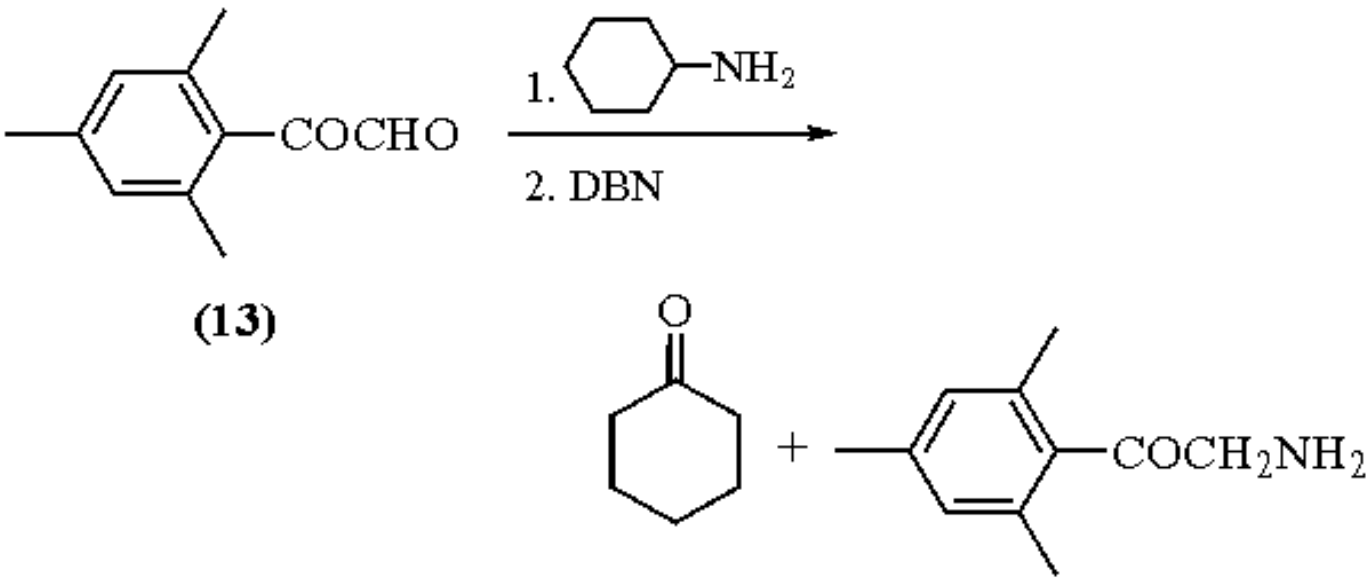

(8)

Condensations.

DBN has been used to effect the reaction of active methylene compounds and other substrates containing active hydrogen. Corey used a catalytic amount of DBN to effect ring closure of the ketoaldehyde (**14**) in a prostaglandin synthesis (eq 9).[22] The cyclopentanol derivative (**15**) was obtained in 45% yield upon treatment of (**14**) with 0.1 equiv of DBU in methylene chloride at 0 °C for 24 h followed by deacetylation.

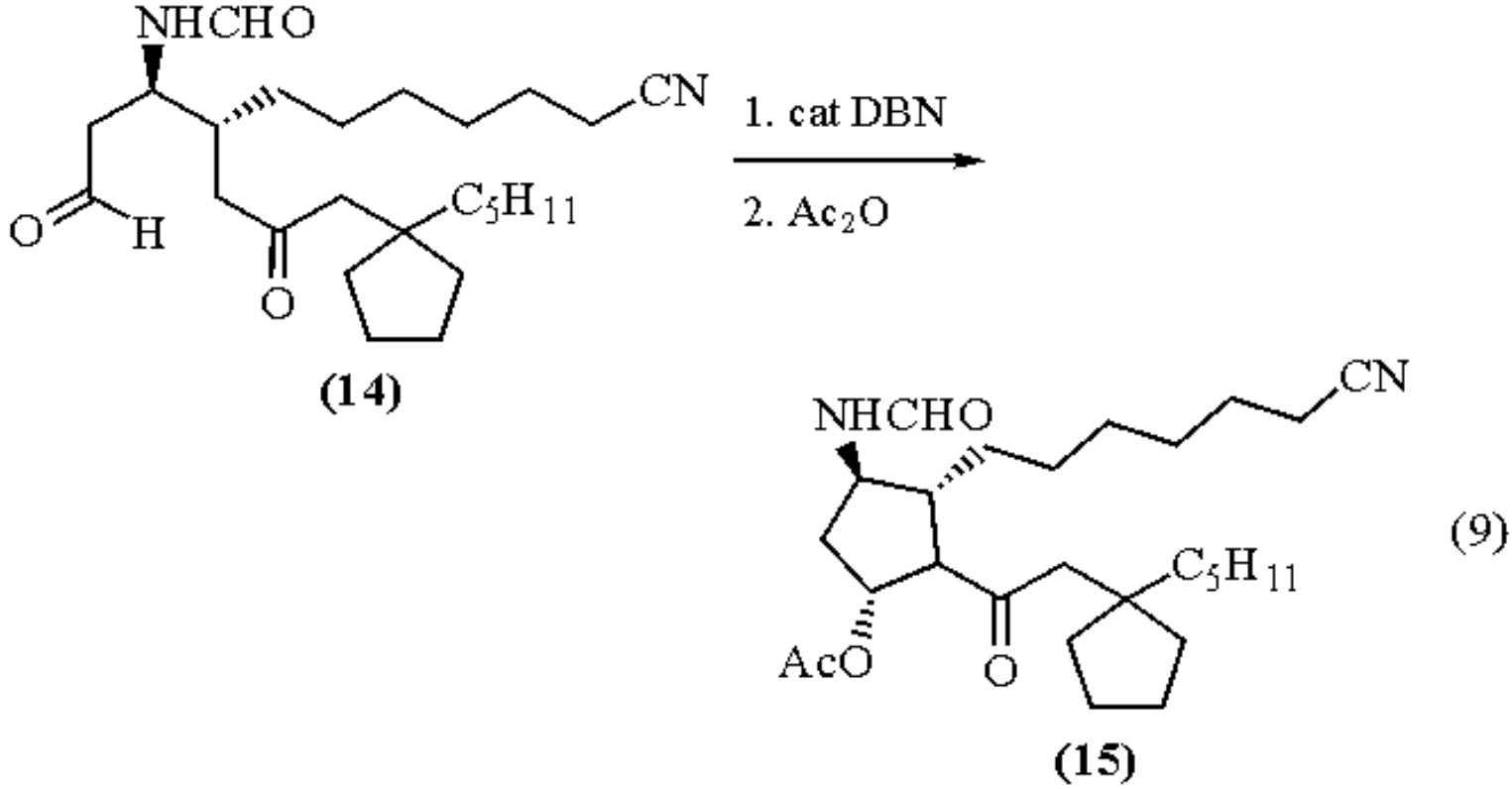

(9)

An insecticide intermediate, 1-(*p*-ethoxyphenyl)-2-nitro-1-propanol, resulted from the DBN catalyzed reaction of nitroethane and *p*-ethoxybenzaldehyde (eq 10).[23]

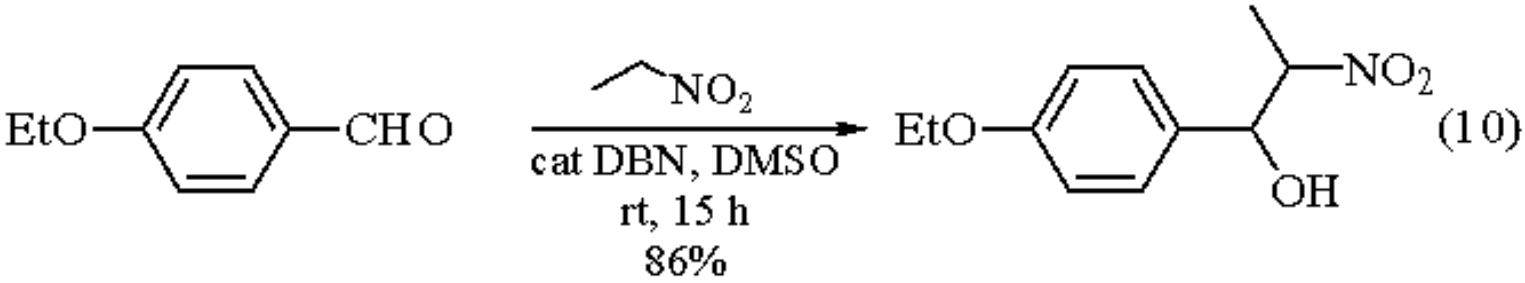

(10)

DBN has been used to generate resonance stabilized ylides in Wittig reactions.[24,25] The synthesis of dienoate (**17**) from benzaldehyde and phosphonium salt (**16**) is representative (eq 11).

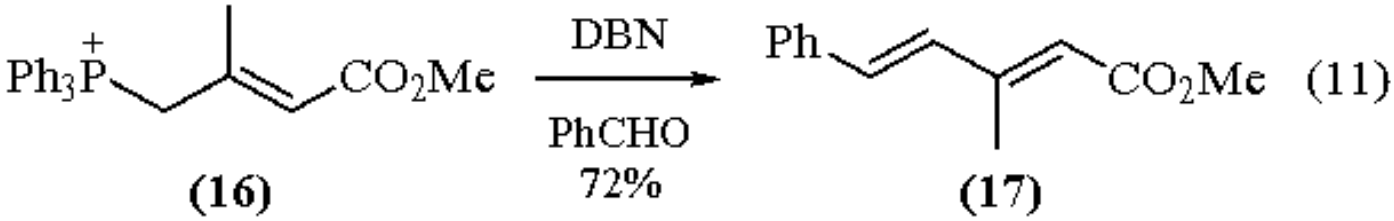

(11)

Esterifications.

There are few examples of the use of DBN in esterification reactions, although the related amidine, DBU, is widely used for this purpose.[26-30] Colvin reported a DBN mediated esterification in one of the final steps of the synthesis of the

macrolide antibiotic pyrenophorin.[31] Thus treatment of bisimidazol-1-yl ketone (**18**) with a catalytic amount of DBN afforded bis-lactone (**19**) in 60% yield (eq 12). In the same study, Colvin and Raphael also used DBN for the quantitative selective removal of a *p*-toluenesulfonylethyl protecting group (eq 13). Stronger bases cleaved the central ester.

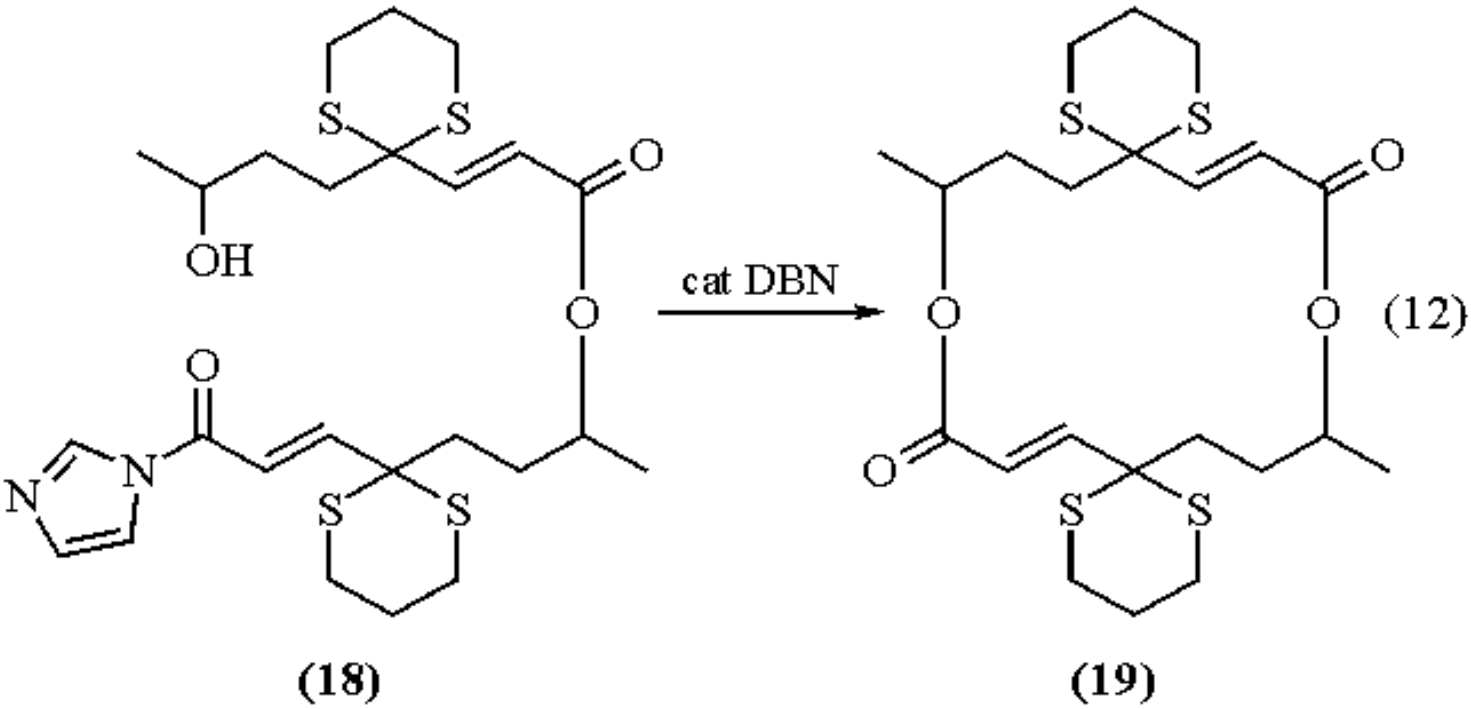

1,5-Diazabicyclo[4.3.0]non-5-ene

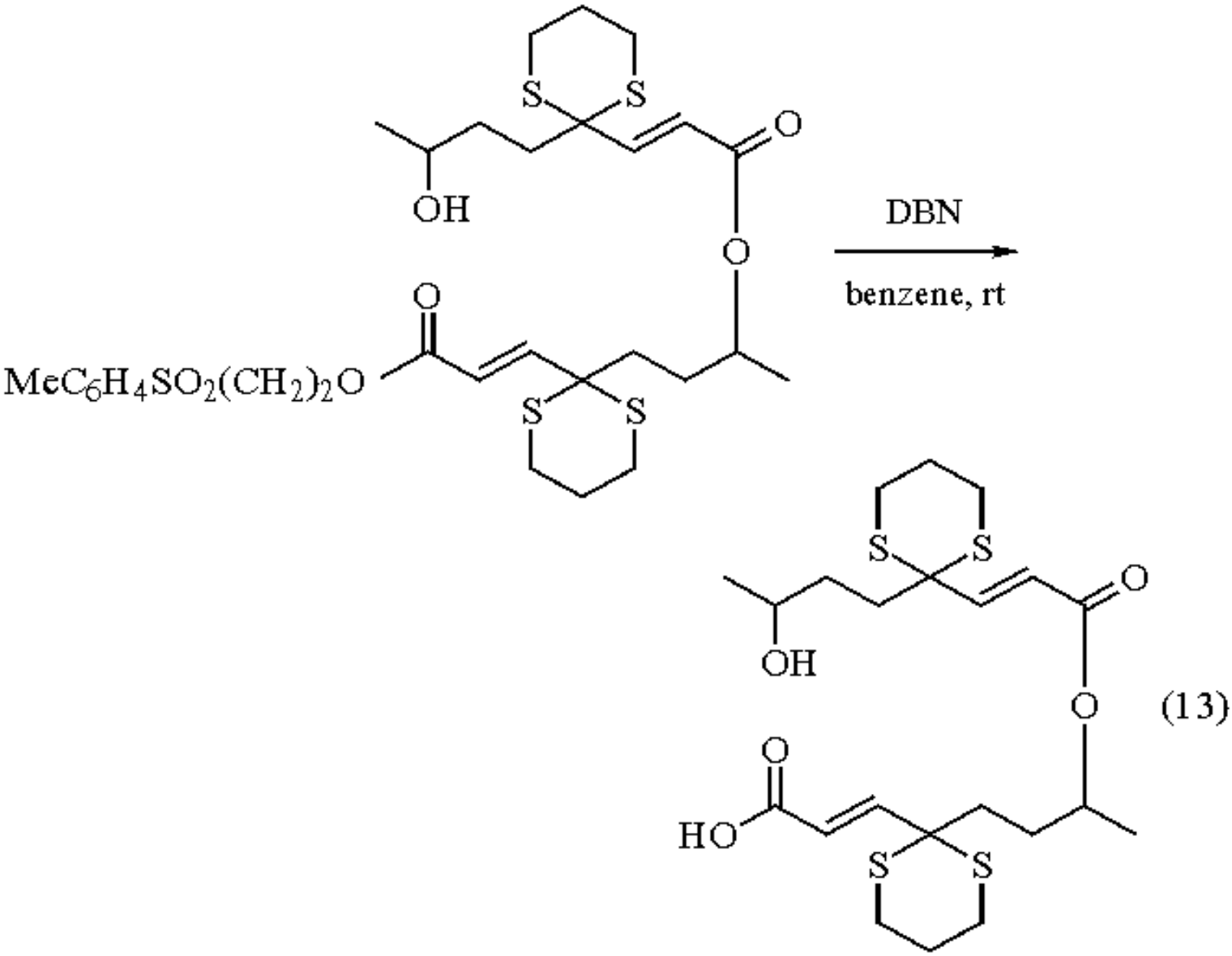

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1,4-Diazabicyclo[2.2.2]octane[1]

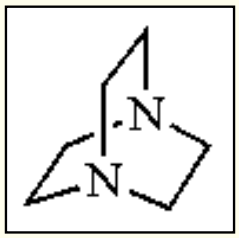

[280-57-9] · $C_6H_{12}N_2$ · 1,4-Diazabicyclo[2.2.2]octane · (MW 112.20)

(forms crystalline organometallic complexes;[2] selective base catalyst for Baylis-Hillman reaction;[3] can activate sodamide;[4] cleaves esters selectively;[5] transalkylating agent;[6] dehydrohalogenating agent;[7] pyrolysis catalyst;[8] nucleophilic acylating agent;[9] additive for trialkyl borohydrides;[10] reagent in miscellaneous reactions[11-13])

Alternate Names: DABCO; triethylenediamine; TED.

Physical Data: mp 161 °C (subl. sample); bp 174 °C; fp 62 °C; *d* 1.14 g cm^{-3}.

Solubility: (g/100g of the solvent at 25 °C): water 45, ethanol 77, benzene 51, acetone 13, ethyl methyl ketone 26.

Form Supplied in: colorless crystalline compound; commercially available.

Analysis of Reagent Purity: HCl titration.

Purification: purified by either vacuum sublimation or azeotropic distillation with benzene followed by recrystallization from petroleum ether or methanol-ethyl ether (1:1).

Handling, Storage, and Precautions: is extremely hygroscopic, corrosive, and readily sublimes at room temperature. This reagent should be stored at 0-5 °C under nitrogen. Moderately toxic by ingestion or inhalation; skin and eye irritant. Use in a fume hood.

Crystalline Organometallic Complexes.

DABCO forms stable and crystalline complexes with organometallic compounds of Li, Zn, and Mg in hydrocarbon solvents.[2] The organolithium complexes are particularly useful in promoting inert metalations of aromatic hydrocarbons.[14] An interesting application of the DABCO-BuLi complex is the quantitative lithiation of thioanisole to phenylthiomethyllithium and its subsequent use in homologation of primary alkyl bromides and iodides (eq 1).[15,16]

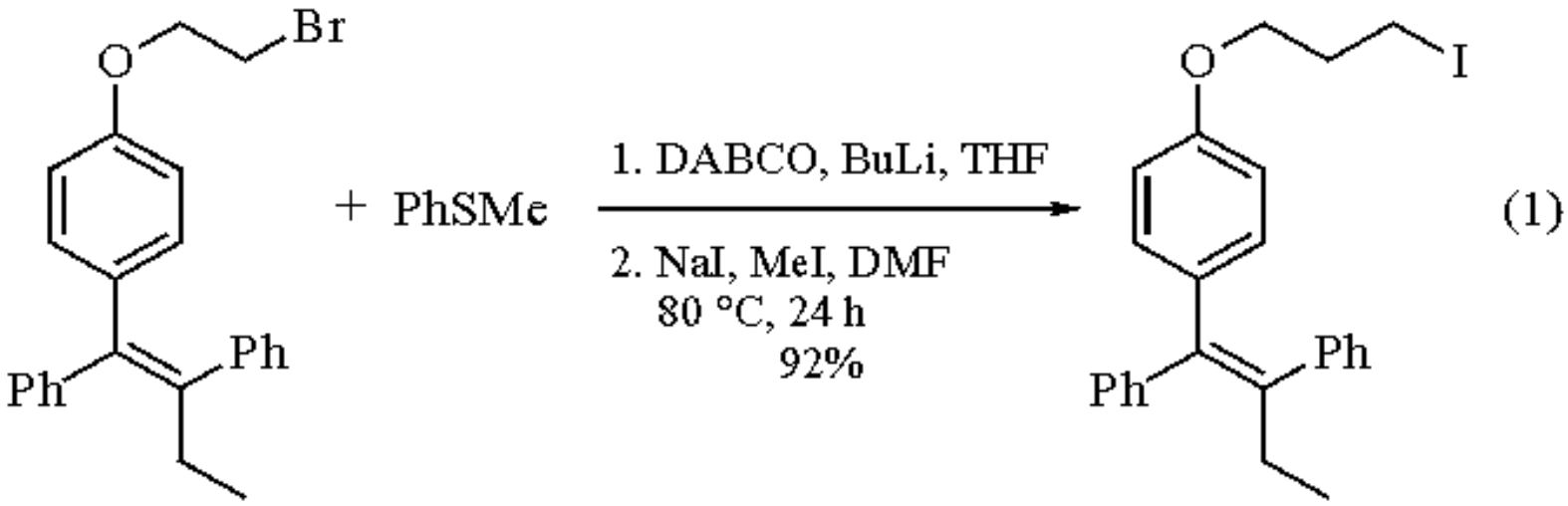

Catalyst for Baylis-Hillman Reaction.

DABCO is a very effective catalyst for the Baylis-Hillman reaction[17] of α,β-unsaturated vinylic systems with electrophiles (e.g. aldehydes) to produce α-substituted acrylates (eq 2).[3,18,19]

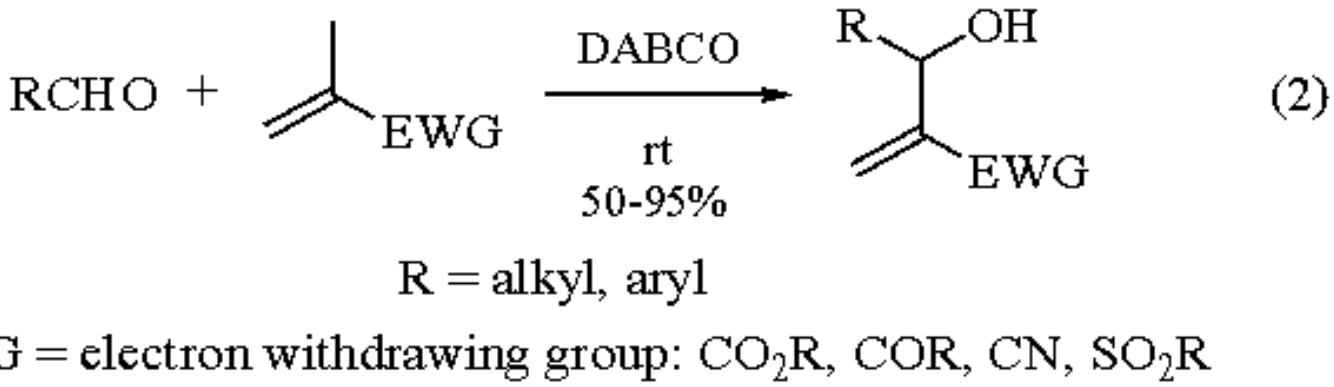

These typically slow reactions can be accelerated by increasing the molar proportions of DABCO or by varying experimental conditions, or even by use of microwave energy.[19-21] The asymmetric Baylis-Hillman reaction with a variety of chiral auxiliaries is also effectively catalyzed by DABCO (eqs 3-5).[22 -24] The use of DABCO with chiral (arylaldehydeimine)tricarbonylchromium complexes significantly enhances the yields and diastereoselectivity (eq 6).[25]

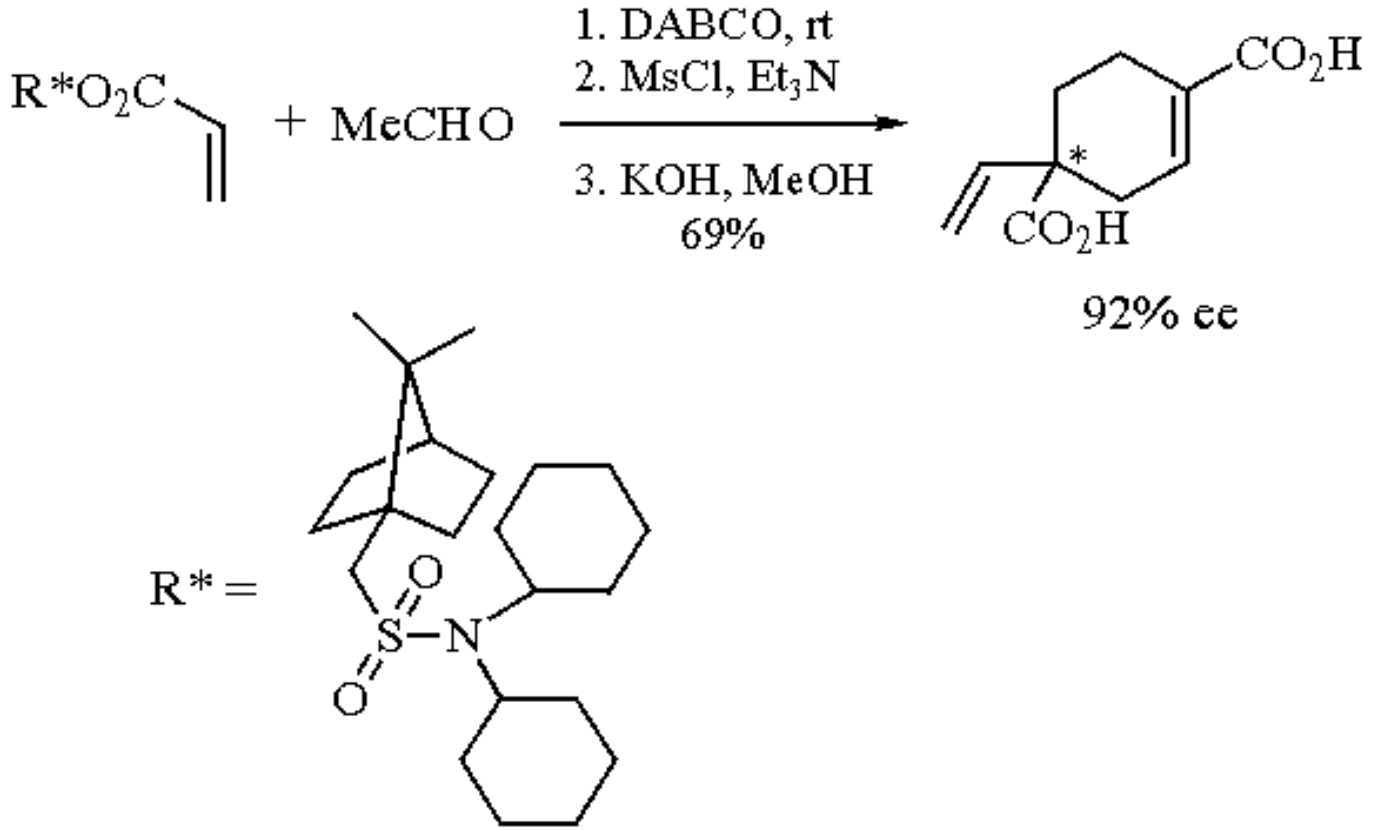
R*O2C
+ MeCHO
1. DABCO, rt
2. MsCl, Et3N
3. KOH, MeOH
69%
CO2H
CO2H
*
92% ee
R* =
O
S
N
O

(3)

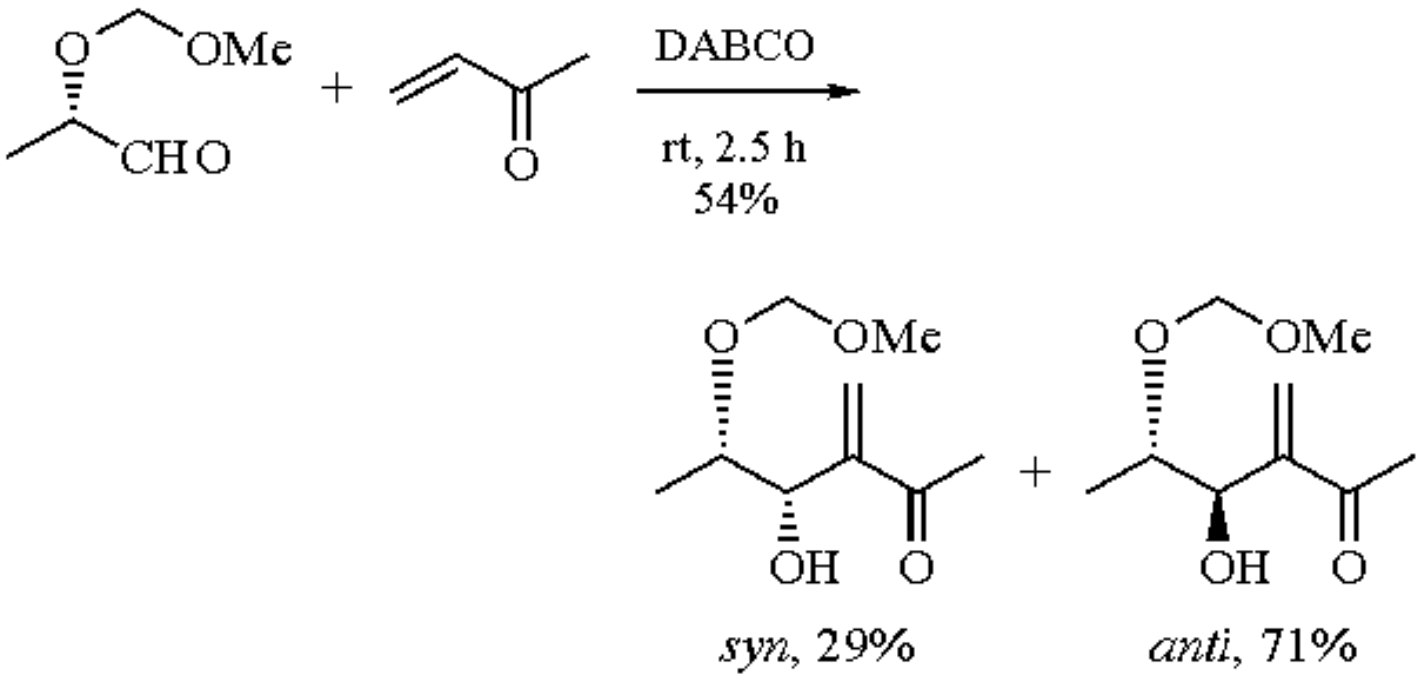
O
OMe
CHO
+
O
DABCO
rt, 2.5 h
54%
O
OMe
OH
O
+
O
OMe
OH
O
syn, 29%
anti, 71%

(4)

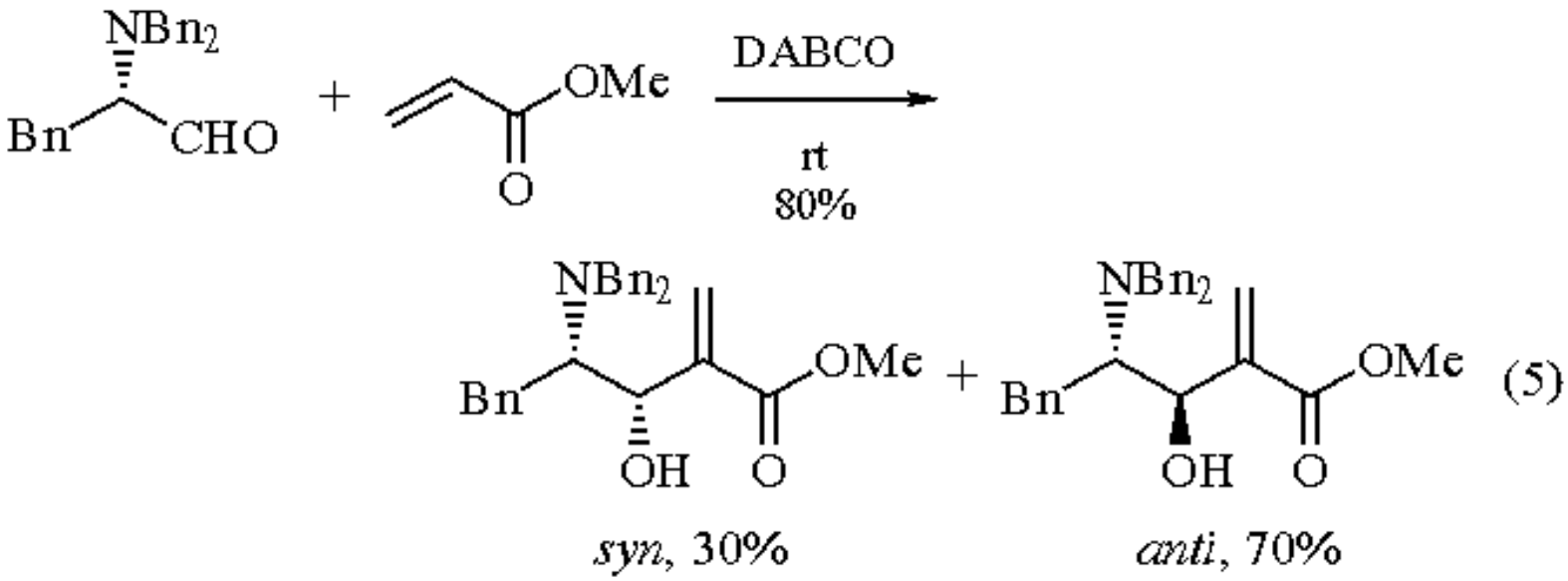

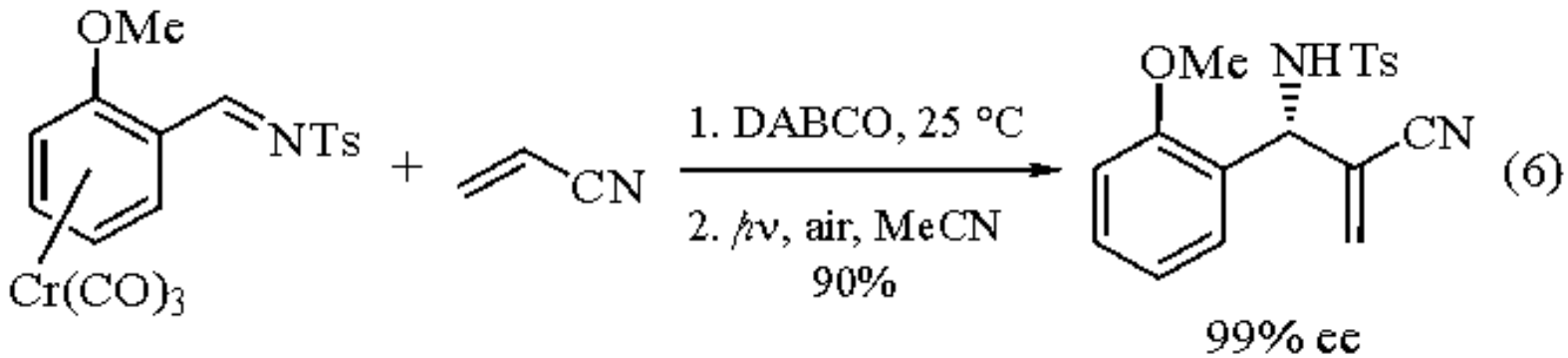

Activation of Sodamide.

DABCO remarkably enhances the reactivity of sodamide in the Haller-Bauer cleavage of nonenolizable ketones to the corresponding carboxamides (eq 7).[4,26]

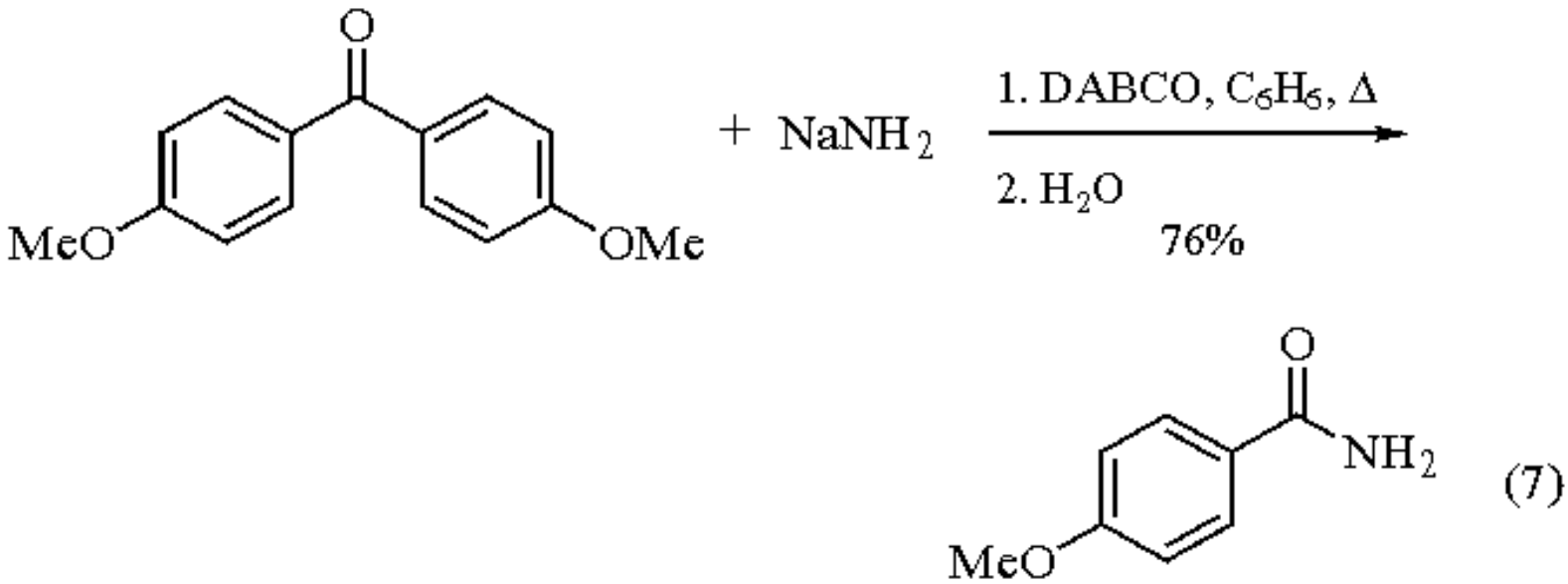

Selective Cleavage of Esters.

DABCO is a selective reagent for the single-pot dealkoxycarbonylation of β-keto esters, geminal diesters, and α-sulfonyl(alkyl)malonic esters.[5,27,28] Good selectivity was noticed with β-keto esters (eq 8) and geminal diesters (eq 9), which gave ketones and monoesters, respectively. The deethoxycarbonylation of α-sulfonyl(alkyl)malonic esters in presence of DABCO is a competitive reaction with desulfonylation and is dependent on the size of alkyl groups (eqs 10, 11).[28] As the alkyl group changes from methyl to benzyl to phenyl, more desulfonation than deethoxycarbonylation is observed. This method is very effective for the cleavage of esters over conventional methods, which are essentially multi-step.

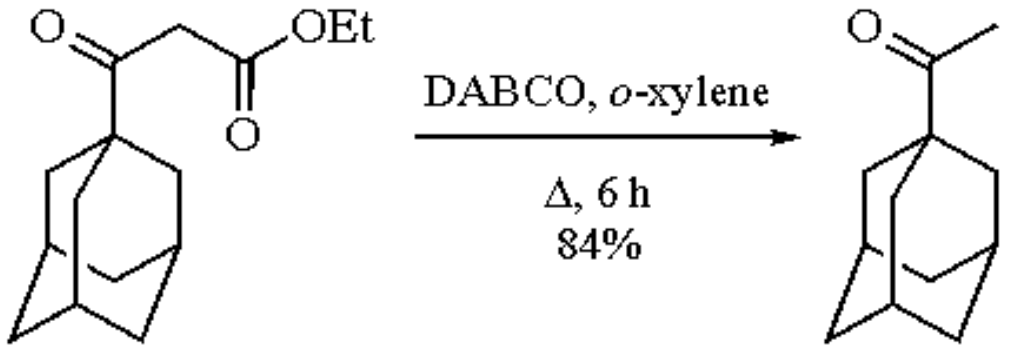

(8)

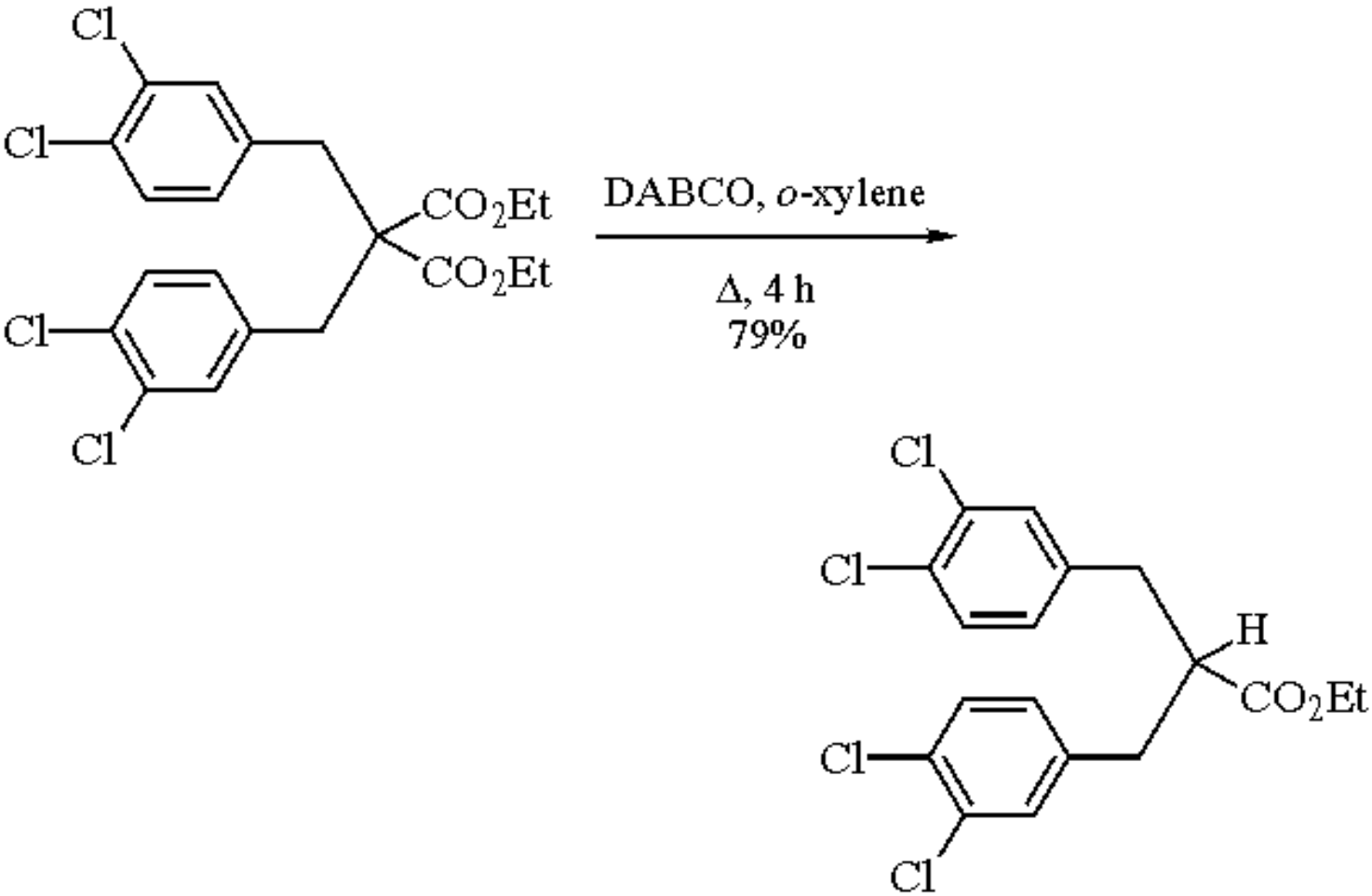

(9)

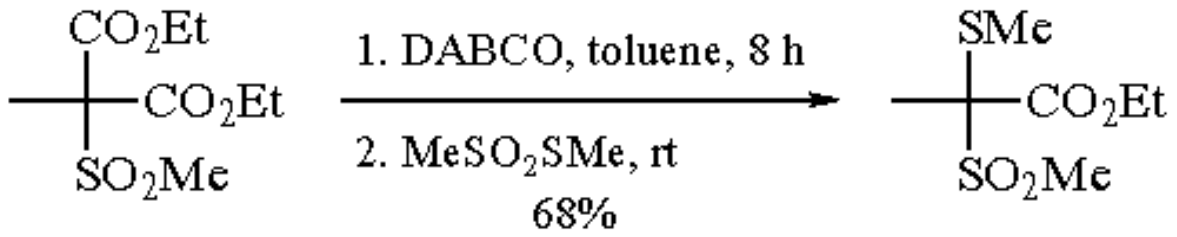

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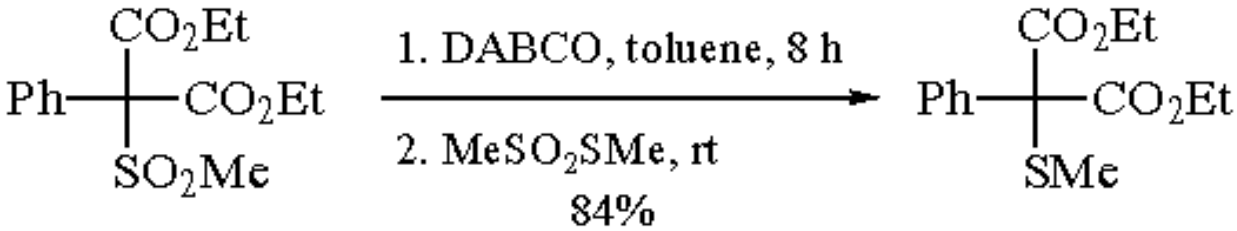

(11)

Transalkylating Agent.

The exposed lone pair of electrons and interactions between the nitrogen atoms of DABCO, which are separated by only 2.5 Å, are the key factors in the transalkylation reactions with quaternary ammonium salts (eq 12).[6]

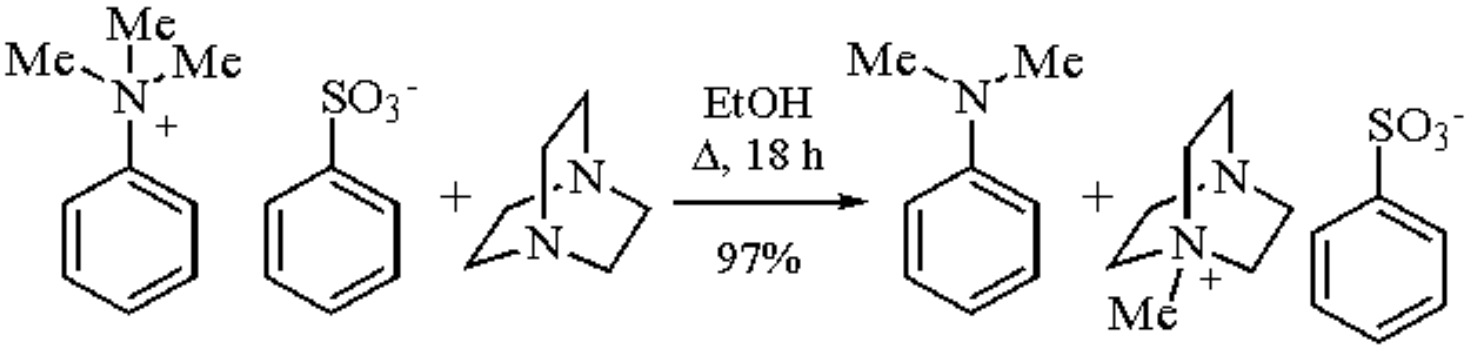

(12)

Dehydrohalogenating Agent.

The Ramberg-Bäcklund rearrangement of α,α-dichlorobisbenzyl sulfones to the corresponding 2,3-diphenylthiirene 1,1-dioxides involves dehydrohalogenation and can be achieved very effectively by stirring with DABCO in DMSO at rt (eq 13).[7]

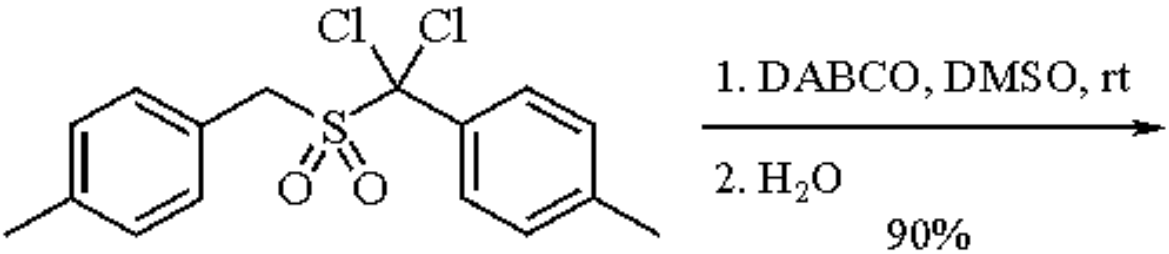

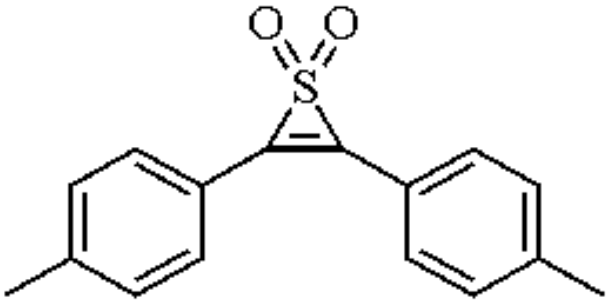

(13)

DABCO is also effective in the dehydrobromination of substituted dibromocyclohexanones to the corresponding cyclohexadienes (eq 14).[29]

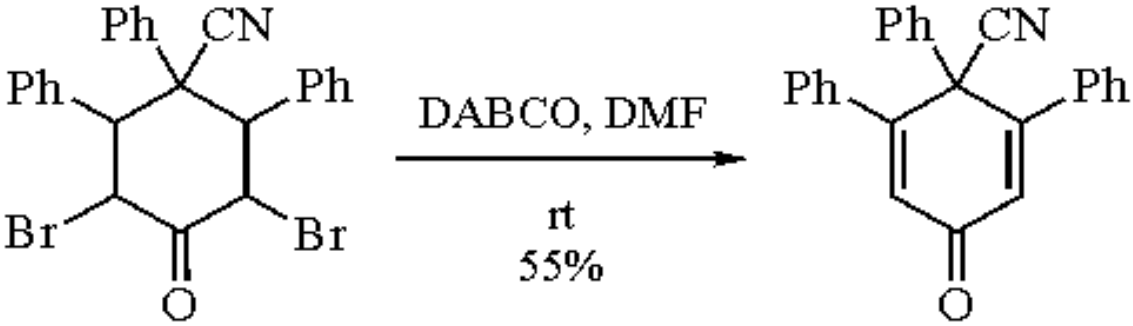

(14)

As a Pyrolysis Catalyst.

DABCO is very effective among the tertiary amines studied for the pyrolysis of vinyl azides.[8] The products are 1-azirines and are obtained in 44-95% yields (eq 15). Use of aprotic solvents with DABCO decreases the yields.

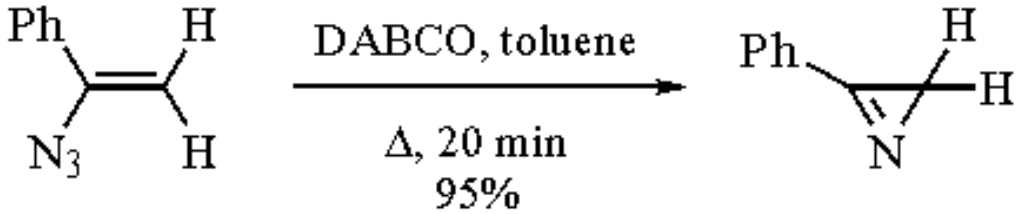

(15)

As a Nucleophilic Acylating Agent.

Its action as a nucleophilic acylation catalyst is significant in the formation of a large number of cyanohydrin esters from α-keto nitriles and aldehydes (eqs 16, 17).[9] The homogeneous, mild, and safe experimental conditions make this method very attractive over the two-phase PTC methods with use of excess cyanide ion.[30] Commercially useful 6´-*O*-

acylsucroses were synthesized by the DABCO-catalyzed regioselective acylation of sucrose with 3-acyl-5-methyl-1,3,4-thiadiazole-2(3*H*)-thiones (eq 18).[31]

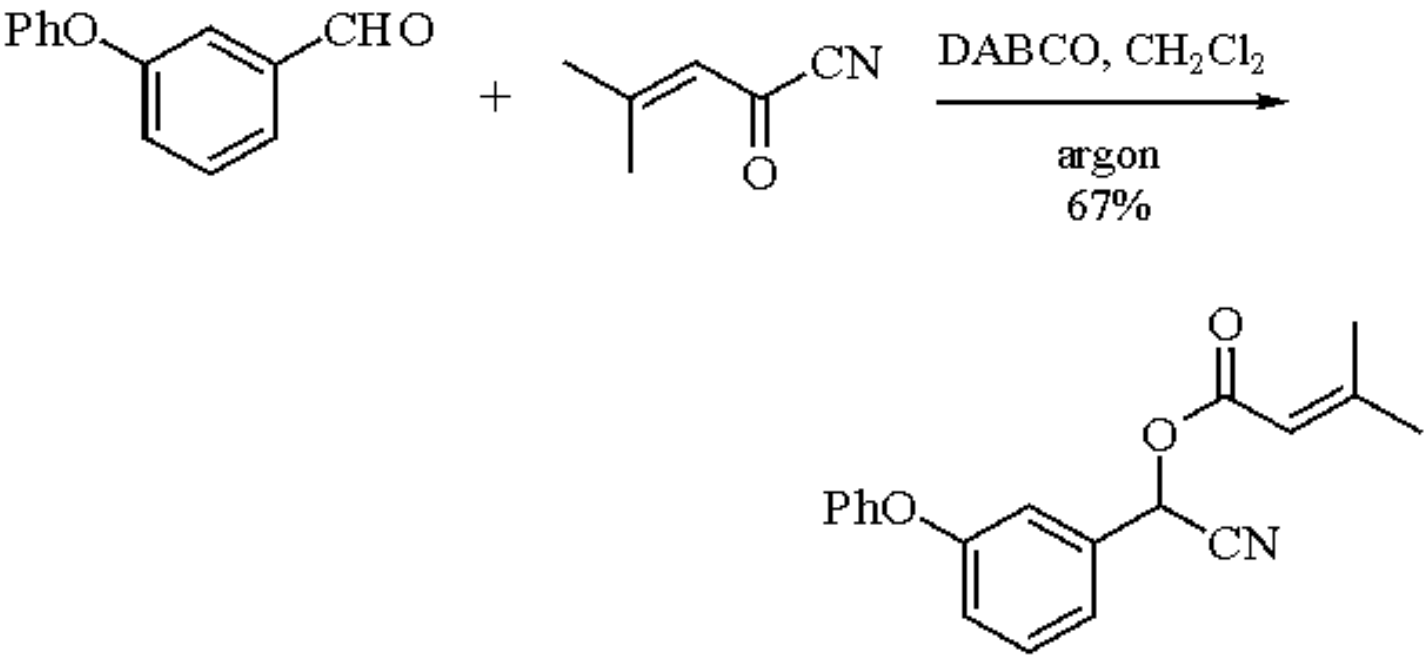

(16)

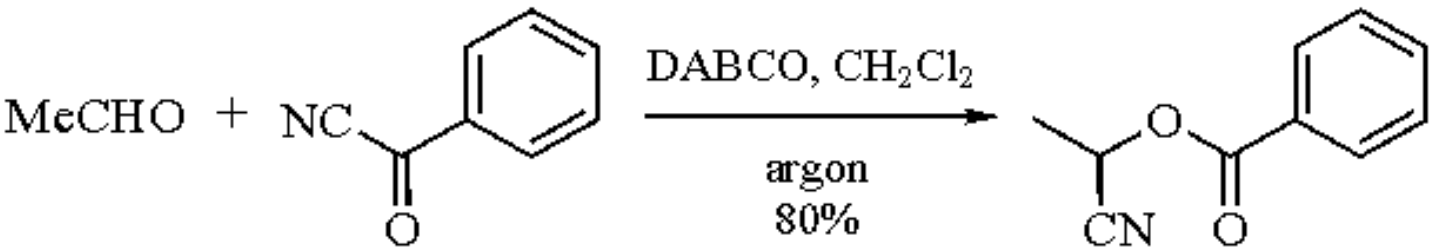

(17)

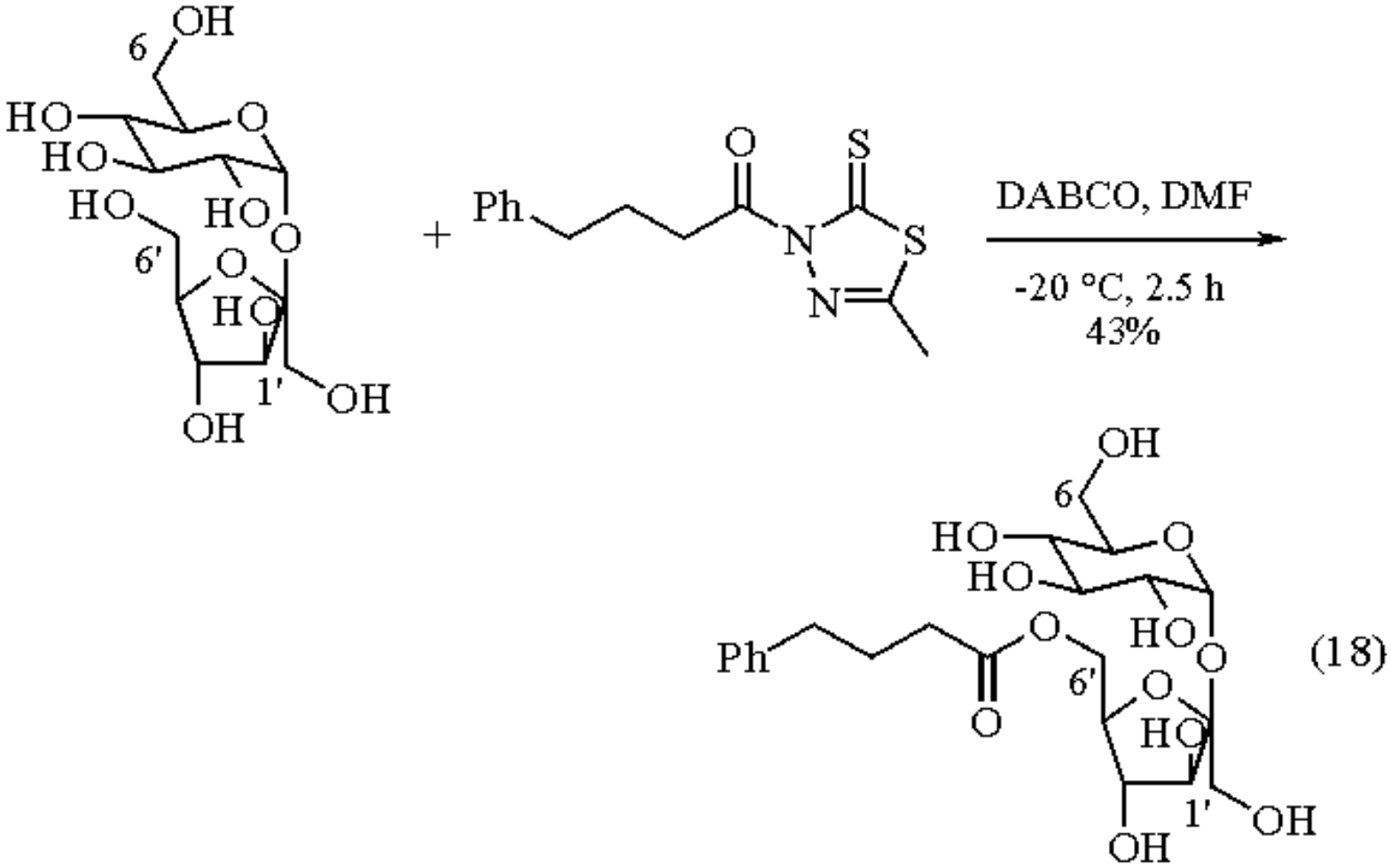

As an Additive for Trialkylborohydrides.

Alkali metal trialkylborohydrides (Li and Na) with bulky alkyl groups are useful chiral reducing agents for carbonyl compounds. These hydrides can be prepared in high yield by the reaction of trialkylboranes with ***Lithium Aluminum Hydride*** or with $NaEt_2AlH_2$ in presence of DABCO (eqs 19, 20). The role of DABCO is to precipitate AlH_3 and Et_2AlH from the reaction medium.[10,32]

$$LiAlH_4 + R_3B \xrightarrow[\text{0-25 °C, 90\%}]{\text{DABCO, ether}} LiR_3BH + DABCO \cdot AlH_3 \quad (19)$$

$$NaEt_2AlH_2 + R_3B \xrightarrow[\text{0-25 °C, 96\%}]{\text{DABCO, ether}} NaR_3BH + DABCO \cdot Et_2AlH \quad (20)$$

As a Catalyst in Miscellaneous Reactions.

DABCO effects singlet oxygen quenching very efficiently without undergoing any chemical change.[11] It is a selective basic catalyst for the reaction of phenyl isocyanate with polyhydric alcohols to form polyurethanes.[12] DABCO is particularly effective as a base catalyst in the Michael addition reactions of α,β-unsaturated ketones with β-keto thiolesters and *S,S´*-diethyl dithiomalonate (eqs 21, 22).[13] The reaction is so specific to the base catalyst that the use of strong bases did not result in any product formation. Recently its use as a base in the phospha-Witting reaction to form C-P double bonds was also reported (eq 23).[33]

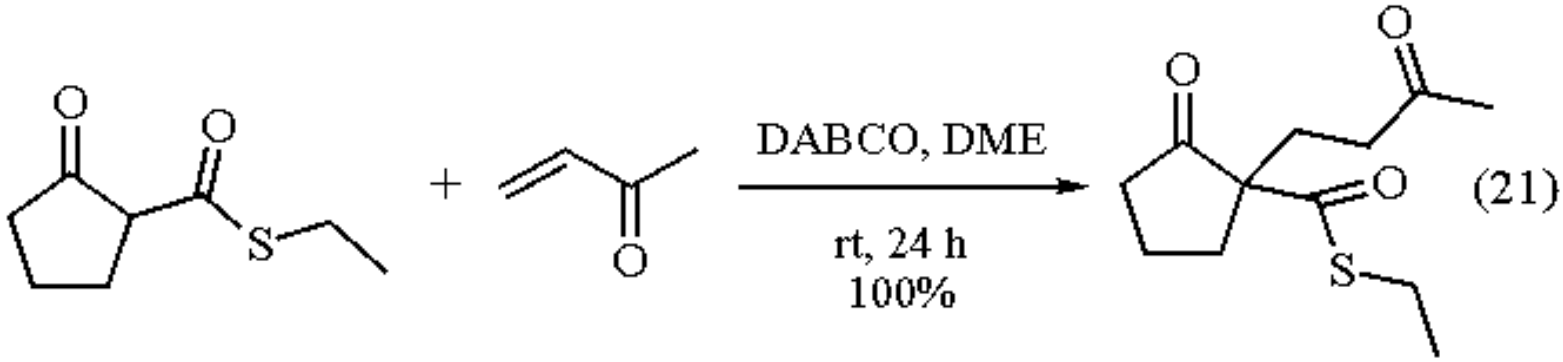

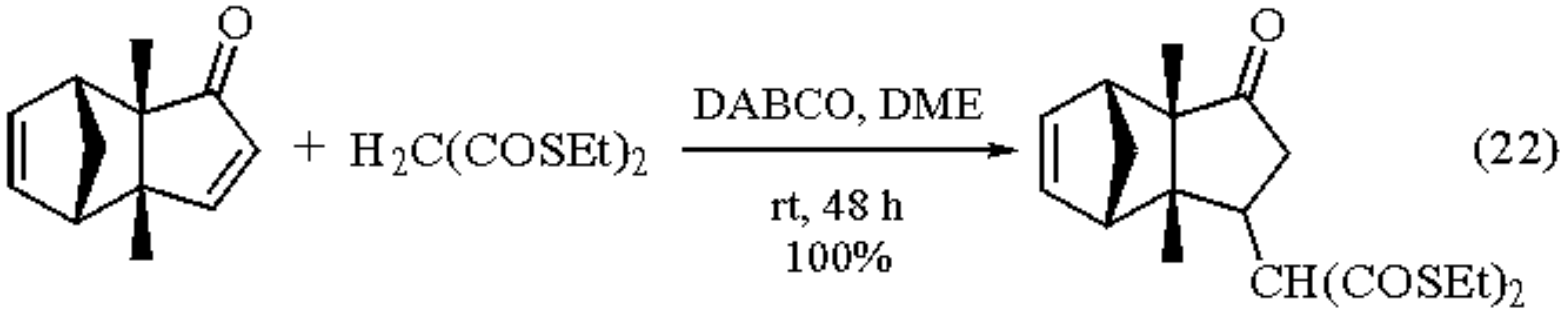

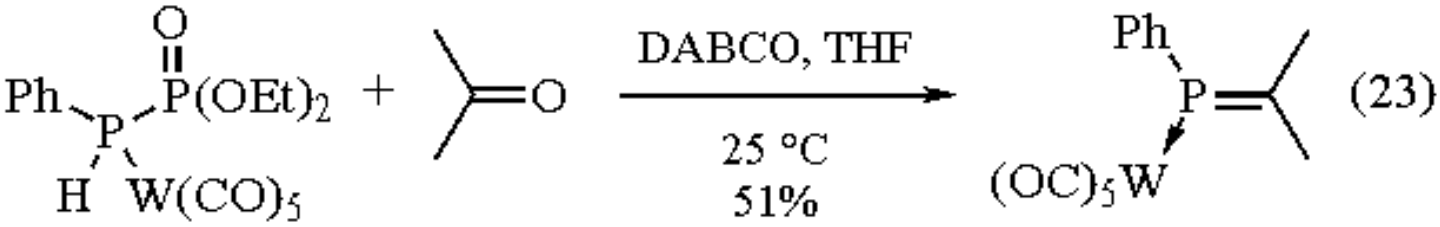

As a electron-donor reagent it forms a variety of useful adducts and complexes. The DABCO-$2Br_2$ complex (mp 155-60 °C, stable to air, light, and water) is a selective reagent for the oxidation of benzylic and secondary hydroxyls,[34] and for sulfides.[35] The DABCO-$2H_2O_2$ complex is an equivalent to anhydrous ***Hydrogen Peroxide***.[36] This on treatment with ***Chlorotrimethylsilane*** gives ***Bis(trimethylsilyl) Peroxide***, a useful reagent for the electrophilic hydroxylation of aromatic and heteroaromatic systems[37] and also for the facile conversion of sulfones to carbonyl compounds.[38]

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1,8-Diazabicyclo[5.4.0]undec-7-ene[1]

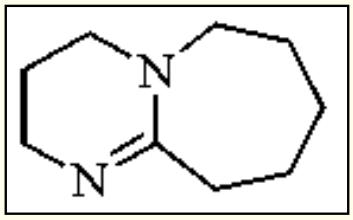

[6674-22-2] · $C_9H_{16}N_2$ · 1,8-Diazabicyclo[5.4.0]undec-7-ene · (MW 152.24)

(organic soluble base for elimination reactions, isomerizations, esterifications, amidations, etherifications, condensations, carboxylations/carbonylations, and halogenations)

Alternate Name: DBU.

Physical Data: bp 259-260 °C; *d* 1.0192 g cm^{-3}.

Solubility: readily sol water, ethanol, benzene, acetone, ethyl acetate, carbon tetrachloride, diethyl ether, dioxane, 1,4-butanediol, dimethyl sulfoxide; hardly sol petroleum ether.

Form Supplied in: clear, light yellow liquid.

Handling, Storage, and Precautions: stable at ambient temperatures, but is hygroscopic; overexposure to atmosphere results in water absorption which can lead to hydrolysis; rate of hydrolysis to *N*-(3-aminopropyl)-ε-caprolactam (10 wt% soln; molar ratio 1:76) is 3×10^{-4} $mol\%^{-1}$ min^{-1}; half-life for a 0.657 molar soln is 33 min at 35 °C; contact with undiluted product may cause skin irritation or burns.

Introduction.

1,8-Diazabicyclo[5.4.0]undec-7-ene is an organic soluble amidine base which has been used effectively, and under relatively mild conditions, for a variety of base-mediated organic transformations including eliminations, isomerizations, esterifications, amidations, etherifications, condensations, carboxylations/carbonylations, and halogenations. A related reagent, ***1,5-Diazabicyclo[4.3.0]non-5-ene*** (DBN), is used for similar reactions.

Elimination Reactions.

DBU has been used widely for dehydrohalogenations as well as for the introduction of unsaturation by elimination of sulfonic acids. Reactions generally proceed under mild conditions and without side reactions. Typical procedures use equimolar base and elevated reaction temperatures (generally 80-100 °C). Reaction solvents such as DMF, benzene,

and DMSO have been used with reaction times varying from several hours to several days. Products may be distilled directly from the reaction mixture or separated from the DBU salt byproduct by extraction with a nonpolar solvent. Terminal as well as internal double bonds can be introduced with a high degree of regioselectivity. Additionally, this method has been used to prepare functionalized alkenes such as vinyl halides and vinyl ethers. Alkynes are not typically prepared using DBU-mediated eliminations; propargyl ethers, however, are an exception.

Oediger and Möller introduced DBU in 1967 for the dehydrohalogenation of bromoalkanes. DBN was found to be less effective.[2] For example, treatment of 4-bromoheptane with equimolar DBU at 80-90 °C gave 3-heptene in 91% yield; with DBN the yield was 60%. Similar treatment of 2-bromooctane gave a 4:1 mixture of 2-octene and 1-octene in 84% yield; with DBN the yield was 40%.

DBU was used in the following one-pot procedure for converting β-disubstituted primary alkyl iodides to terminal alkenes.[3] DBN was also used effectively for this procedure. The THP-protected tosylate (**1**) was converted to the corresponding iodide with NaI in DMF; subsequent addition of 1.5 equiv of DBU and heating at 80 °C for 3-4 h afforded terminal alkene (**2**) in 82% overall yield from (**1**) (eq 1). For comparison, when (**1**) was transformed into the bromide and treated with ***Potassium t-Butoxide*** in DMSO at 50 °C, a 3:2 mixture of the terminal alkene and its rearranged trisubstituted isomer resulted.[4]

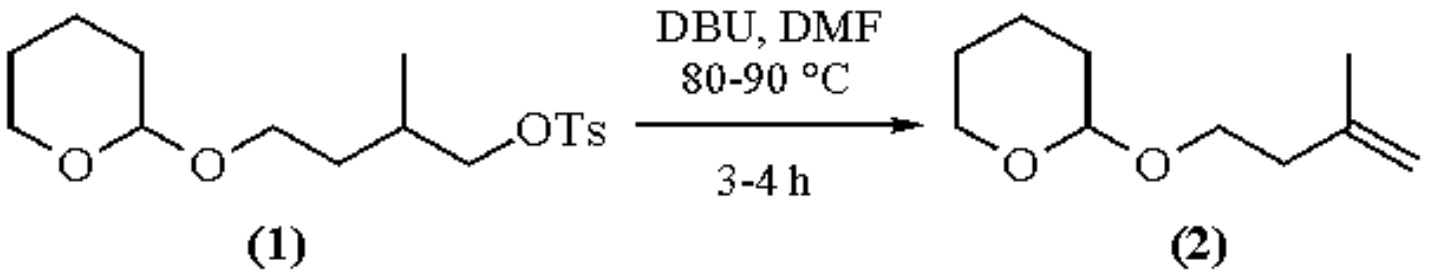

(1)

DBU was found to be an effective base for converting piperidine (**3**) into 3,4-dehydropiperidine (**4**) without formation of the undesired 2,3-dehydropiperidine in a synthesis of the alkaloid sedinine (eq 2).[5]

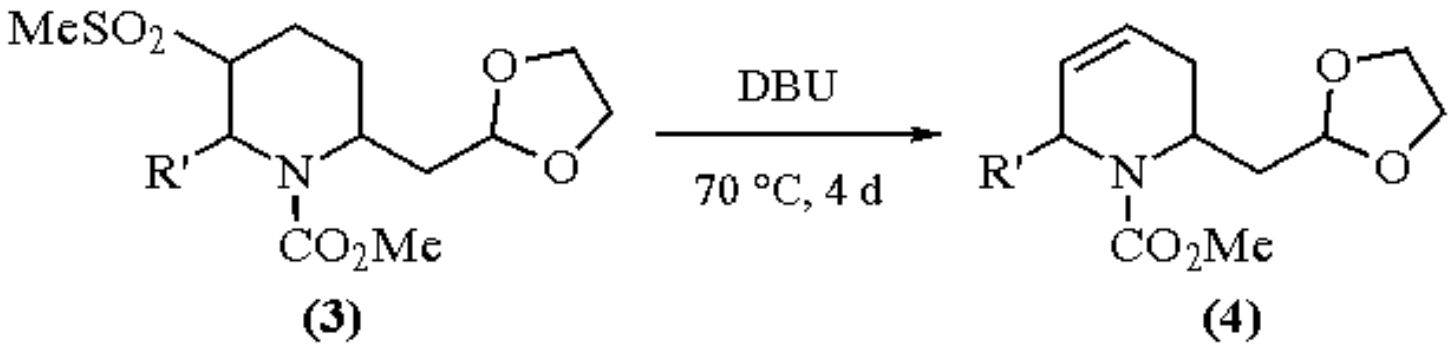

(2)

DBU has also been used to prepare (*E*)-1-iodo-1-alkenes from 1,1-diiodoalkanes.[6] In a representative procedure (eq 3), diiodobutane (**5**) was combined with equimolar DBU and heated to 100 °C until appearance of a brown solid (15-20 min). The product, (*E*)-1-iodo-1-butene (**6**), was isolated in 80% yield by distilling directly from the reaction mixture. Higher-boiling vinyl iodides required DMSO as reaction solvent and product extraction with pentane.

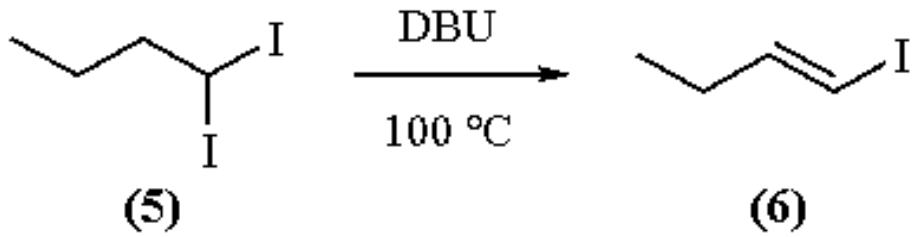

(3)

DBU is not typically used to convert vinyl halides into alkynes; in general, this conversion requires alkoxides, solid alkali, or alkali metal amides.[7] However, the (*Z*)-vinyl bromide (**7**: R = H) was nearly quantitatively converted into terminal alkynes (**8**) in 2 h with DBU in refluxing benzene; the corresponding (*E*) isomer did not react (eq 4).[8] When a (*Z/E*) mixture of (**7**) was treated with ***Potassium Carbonate*** in refluxing methyl ethyl ketone (MEK), only starting material was recovered. With β-oxygen substitution (R = CH_2OH), vinyl bromides (**7**) were quantitatively converted into alkynes in 1 h with either DBU in refluxing benzene or potassium carbonate in refluxing MEK.

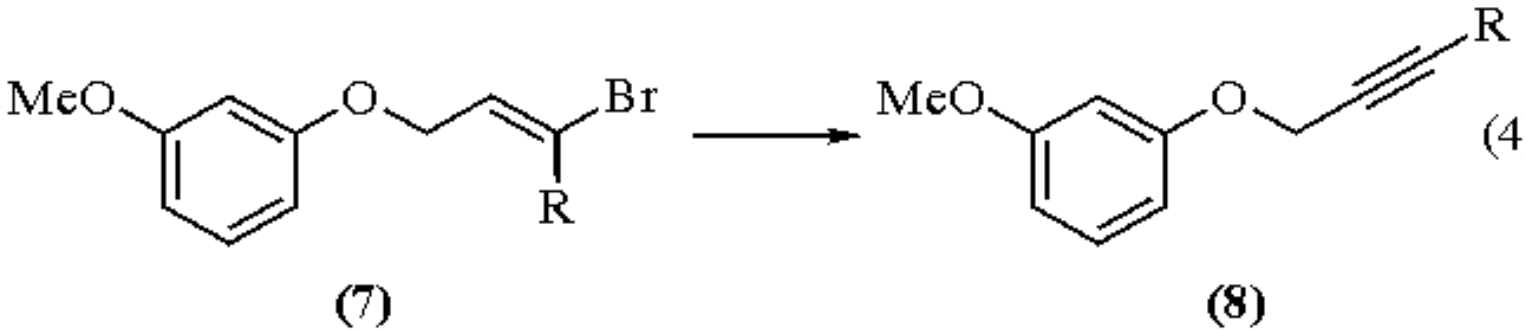

(4)

DBU has also been used to prepare alkenes from sulfonates. Heating tosylate (**9**) in solvent DBU for 30 min at 100 °C afforded the *cis* vinyl ether (**10**) in 72% yield (eq 5).[9] When (**9**) was treated with potassium *t*-butoxide in *t*-butanol for 30 min at 80 °C, the vinyl ether product was a 3:7 *cis*:*trans* alkene isomer mixture (72% yield).

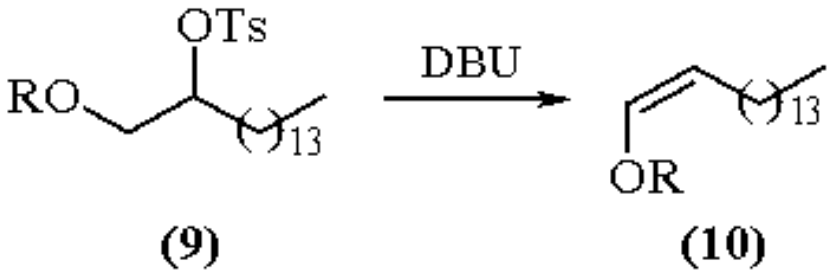

(5)

Otter used DBU to effect the elimination of methanesulfonic acid in the final step of his preparation of 1,3-dimethyl-6-propyluracil, a synthetic pyrimidine nucleoside (eq 6).[10]

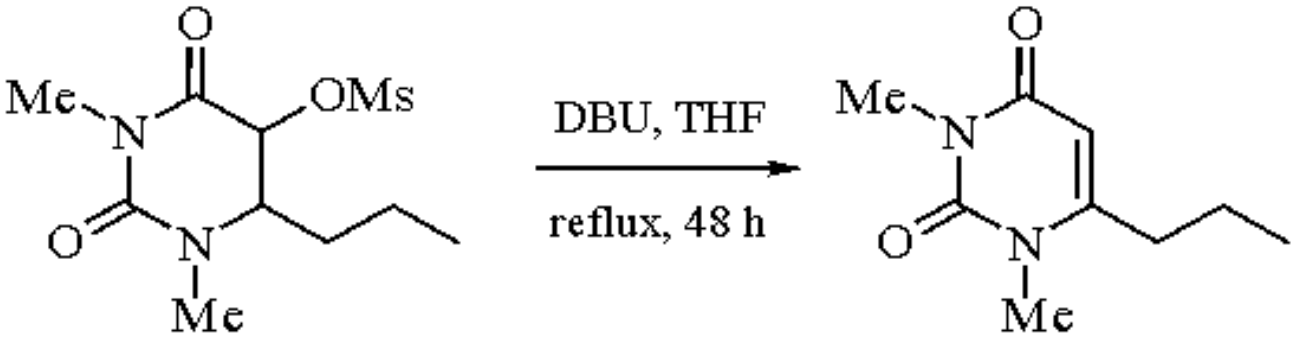

(6)

Isomerizations.

1,8-Diazabicyclo[5.4.0]undec-7-ene is used for base-mediated double bond migrations and epimerizations. Isomerizations generally require proton abstraction at a carbon α to a carbonyl group (or related functionality) and are thermodynamically controlled.

DBU was used to equilibrate a mixture of substituted pyrrolidin-2-ones in the final step of a herbicide synthesis.[11] The mixture of isomers (**11**) was allowed to stand for 1 h at rt with DBU in toluene to give the pure 3,4-*trans* isomer (**12**) in 96% yield (eq 7).

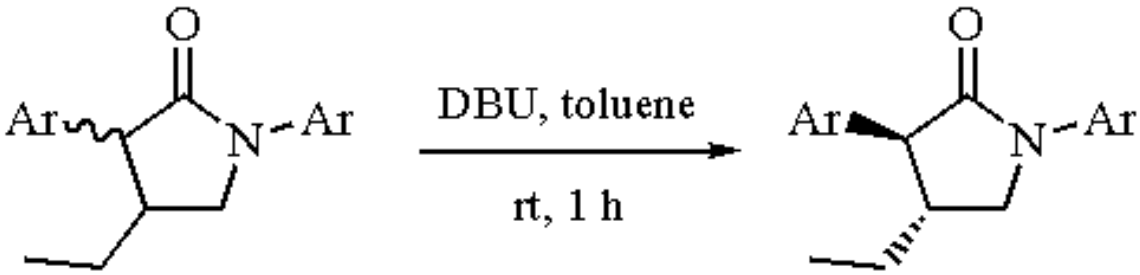

(11) (12)

(7)

Amidine bases have been used extensively for the equilibration of β-lactams. Although DBN appears to be the base of choice for such epimerizations,[12-17] the 7α-(dimethylamidino)-3-cephem ester 1α-oxide (**14**) was prepared via DBU epimerization of the corresponding 7β-isomer (**13**) (eq 8).[18]

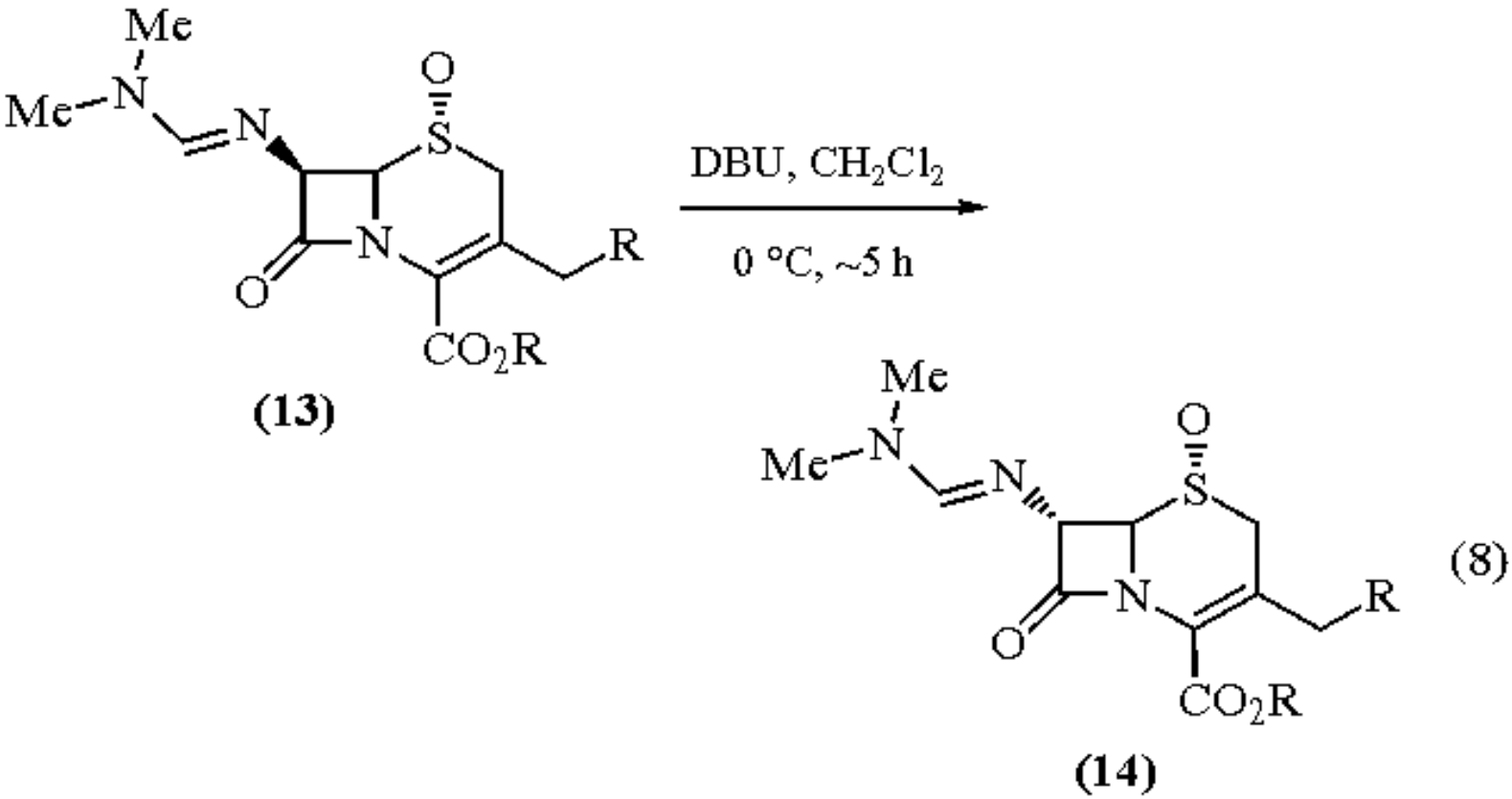

DBU has been employed to convert esters with β,γ-unsaturation into the corresponding α,β-unsaturated isomers.[19] Thus 3-pentenoate (**15**) underwent up to 60% isomerization to 2-pentenoate (**16**) in the presence of DBU at 100 °C (eq 9). Corresponding exposure of pure *cis*-2-pentenoate (**16**) to DBU at 130 °C for 4 h afforded a similar product mixture (53% *trans*-2-pentenoate, 40% of 3-pentenoate (**15**), and 7% recovered starting material), suggesting thermodynamic equilibrium.[20] For comparison, in a continuous process using ***4-Dimethylaminopyridine*** at reflux, up to 78% of the thermodynamically favored (**16**) was converted to (**15**) over the course of 30 h.

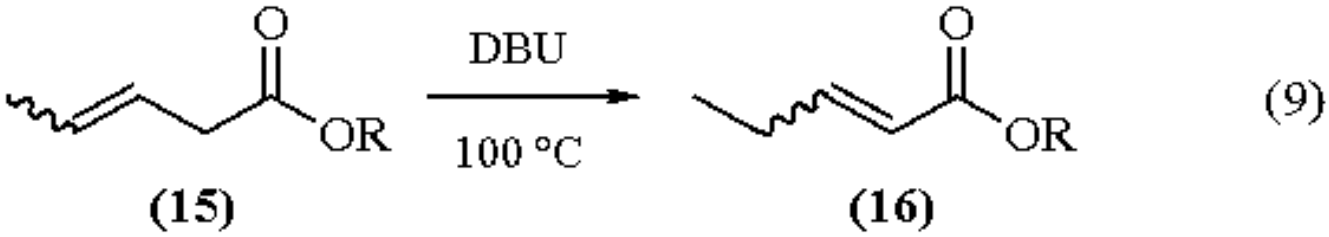

β,γ-Unsaturated nitriles (e.g. **17**) have been isomerized to the thermodynamically favored α,β-unsaturated nitriles (e.g. **18**) in the presence of catalytic DBU or DBN (eq 10).[21]

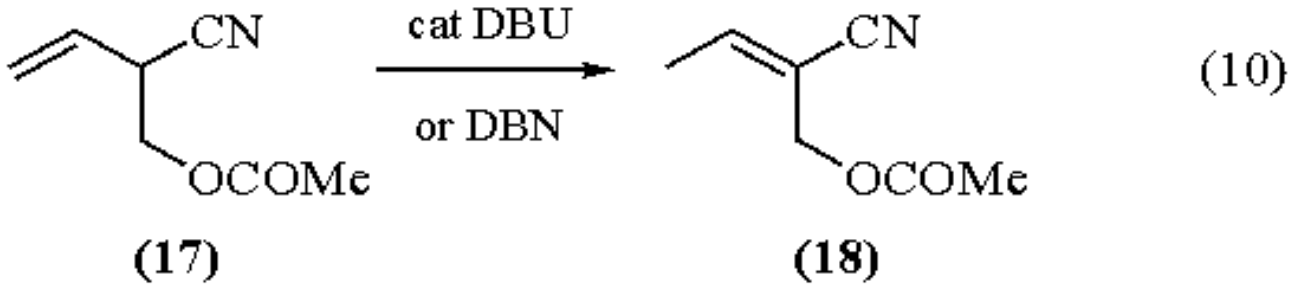

As part of a study directed toward the synthesis of dodecahedrane, DBU was used to effect the isomerization of bis-enone (**19**) into (**20**) in 90% yield (eq 11).[22] The mechanism was presumed to involve formation of the β,γ-unsaturated isomer of bis-enone (**19**).

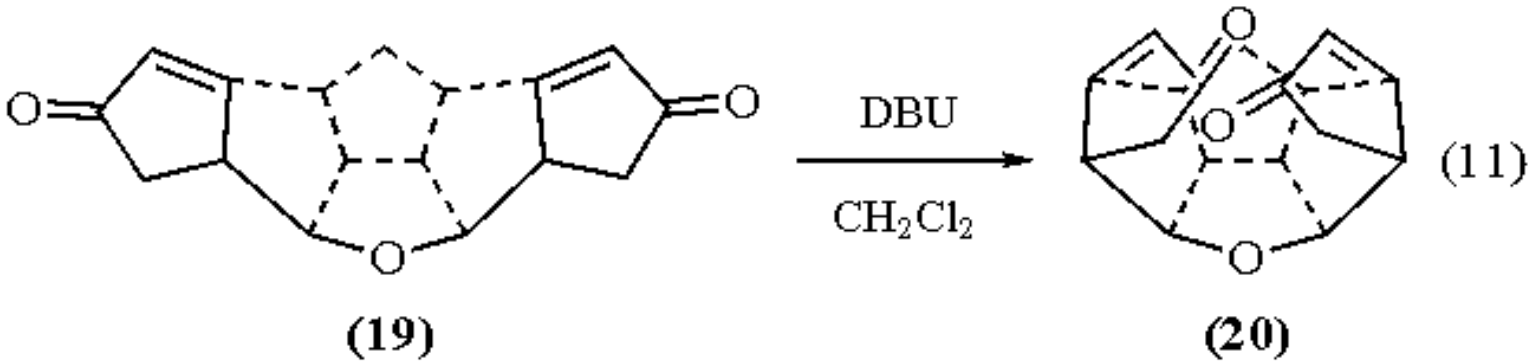

Several biomimetic methods for the conversion of amines to carbonyl compounds have used amidine bases to effect equilibration of the intermediate imine.[23-25] Rapoport used DBU in the oxidation of amines with 4-formyl-1-methylpyridinium benzenesulfonate (FMPBS).[25] As an example, phenylacetaldehyde (**22**) was obtained in 83% yield from β-phenylethylamine (**21**) after treatment with FMPBS and DBU in CH_2Cl_2/DMF (eq 12). ***Triethylamine*** was not effective as a DBU replacement except when the amine β-carbon had electron withdrawing substituents (e.g. acetophenone from α-phenylalanine).

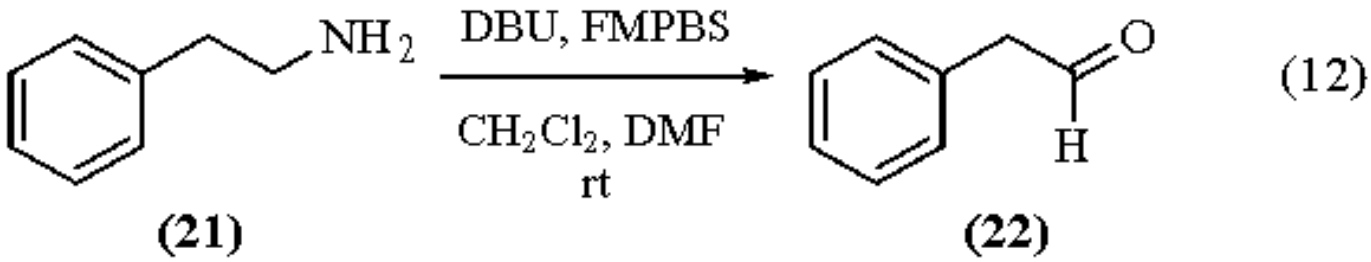

Esterifications, Amidations, and Etherifications.

DBU has been used to prepare esters[26] and amides[27] from carboxylic acids as well as ethers,[28] esters,[29] and carbamates[30] from alcohols. These procedures involve proton abstraction followed by reaction of the carboxylate or alkoxide with an alkyl halide, acylating agent, or other suitable electrophile. Esterifications and amidations are generally conducted at or near rt, whereas etherifications require elevated temperatures (60-80 °C).

In 1978, Ono reported a convenient procedure for the esterification of carboxylic acids using DBU.[26] Esters were produced in high yield from acids, alkyl halides, and DBU. The advantage of this procedure is that it provides mild conditions for esterification, it is not necessary to prepare the carboxylate anion in a separate step, and side reactions, especially dehydrohalogenation, are avoided. Amino acids have been esterified without racemization using this procedure. As a representative example, benzoic acid reacted with ethyl iodide in the presence of DBU for 1 h to give ethyl benzoate in 95% yield. The same reaction using triethylamine instead of DBU afforded essentially no ethyl benzoate. With benzyl bromide, benzoic acid, and DBU in DMSO, benzyl benzoate was formed quantitatively at 30 °C in 10 min.[31] Triethylamine, when substituted for DBU, afforded benzyl benzoate in 81% after 1 h at 30 °C; ***Pyridine*** afforded a 15% yield of benzyl benzoate after 6 h.

The high yields of ester afforded by this method make it attractive for polyester synthesis.[31] Thus isophthalic acid reacted with *m*-xylylene dibromide in the presence of 2 molar equiv of DBU in DMSO at 30 °C for 3 h to afford polyester (**23**) in high yield and viscosity (eq 13). Other organic bases such as triethylamine, pyridine, *N*,*N*-dimethylaminopyridine, or a DBU-pyridine mixture did not afford any polymer.

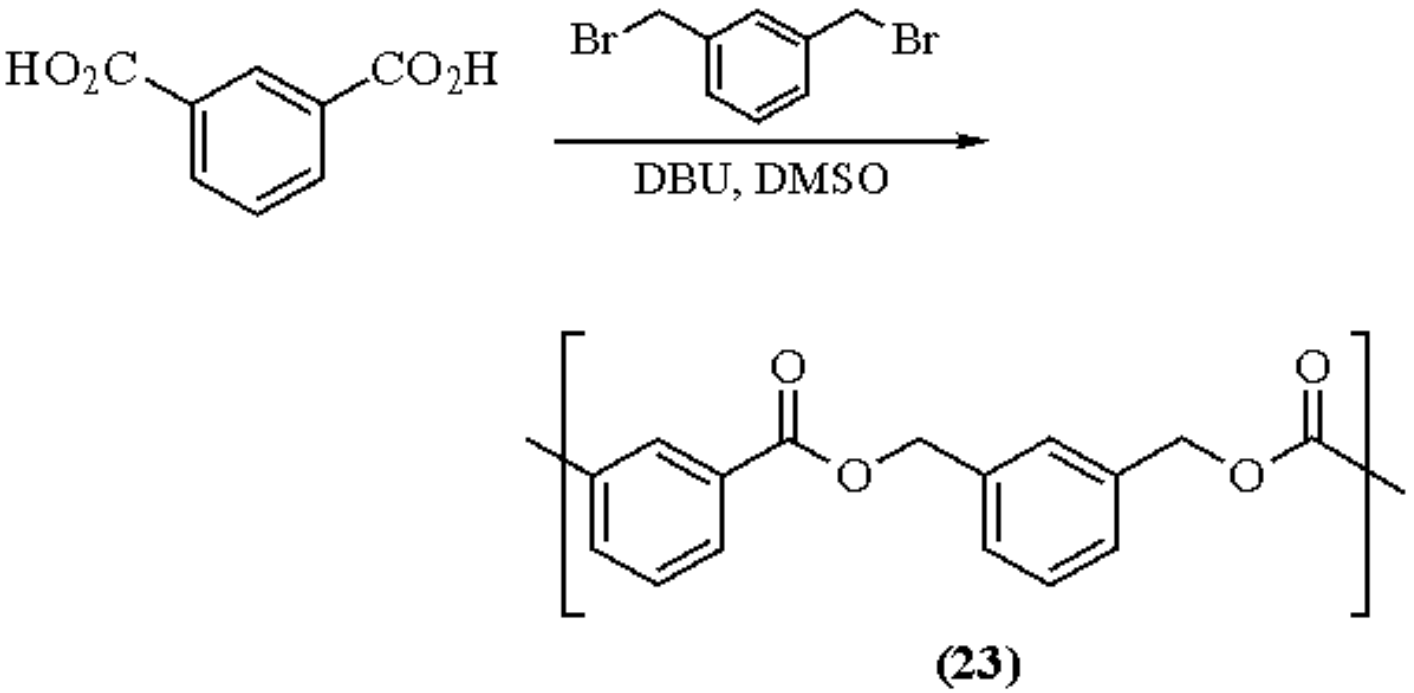

(13)

This method has also been used for the esterification of polymers.[28,32] As an example, poly(methacrylic acid) (**24**) reacted with *p*-bromomethylnitrobenzene in the presence of equimolar DBU in DMSO at 30 °C for 3 h to afford poly(methacrylate) (**25**) at 97 mol% esterification (eq 14).

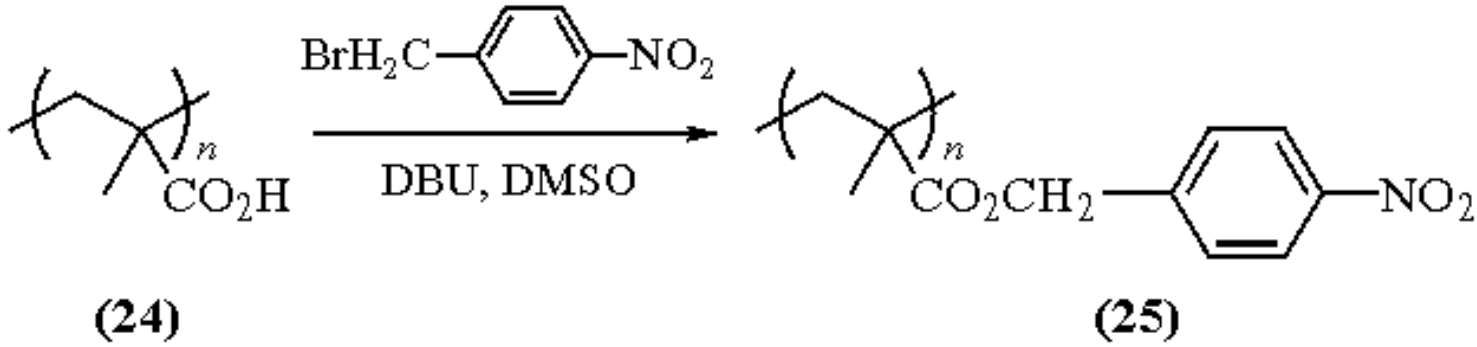

(14)

The etherification of poly(4-hydroxystyrene) (**26**) is related.[32] On treatment with equimolar *p*-bromomethylnitrobenzene and DBU in HMPA at 60 °C for 24 h, (**26**) was converted into poly[4-(4-nitrobenzyloxy)styrene] (**27**) at 98 mol% etherification (eq 15). Solvents such as DMF, DMSO, and NMP were less effective for this reaction, requiring longer reaction times, higher reaction temperatures, and excess reagent. For example, a high degree of etherification (>80%) using DMF as solvent required 2 molar equivalents each of *p*-bromomethylnitrobenzene and DBU at 80 °C for more than 24 h. No reaction was observed using triethylamine or pyridine instead of DBU.

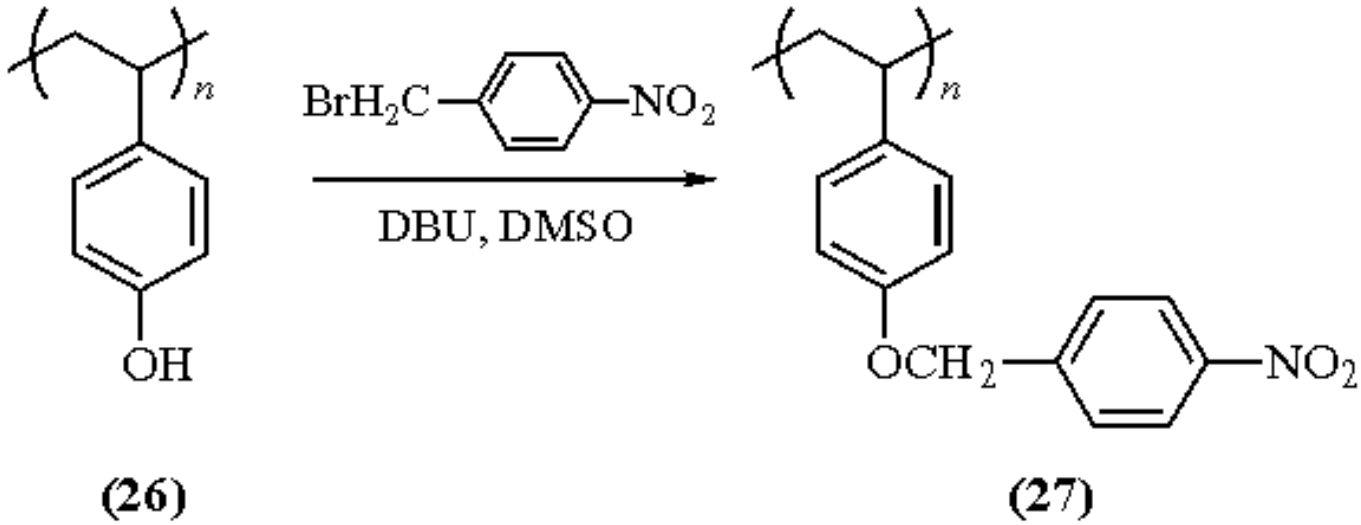

(15)

Polyimides containing pendant carboxylic acids have also been esterified using 1-phenethyl bromide and DBU.[33,34]

In an alternative approach to esterification, DBU was used to accelerate the reaction of *N*-acylimidazoles with *t*-butanol in a one-pot conversion of carboxylic acids into their *t*-butyl esters. The general reaction is outlined in eq 16. Acids were treated with 1 molar equiv of ***N,N´-Carbonyldiimidazole*** in DMF under a nitrogen atmosphere at temperatures from 40 to 80 °C and reaction times of 5 to 24 h. Products were extracted from the reaction mixtures with diethyl ether. In this manner, *t*-butyl benzoate, *t*-butyl cinnamate, and *t*-butyl heptanoate were prepared in 91%, 64%, and 68% yield, respectively. With sodium *t*-butoxide rather than DBU, there was competitive formation of 3-oxoalkanoic esters with acids having one or two protons at C-2.[35] A similar limitation was noted for the conversion of *N*-acylimidazoles to *t*-butyl esters using *t*-butanol and NBS.[36]

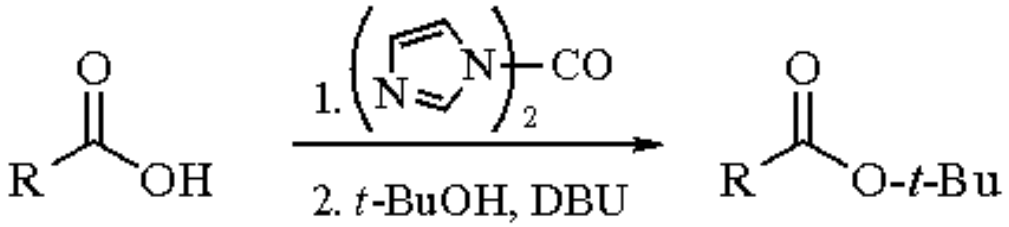

(16)

Enolizable acyl cyanides have been converted into 1-cyano-1-alkenyl esters upon treatment with tertiary amines (e.g. DBU, pyridine, dimethylamine, and ***1,4-Diazabicyclo[2.2.2]octane***) and carboxylic acid chlorides or anhydrides.[37] With acid chlorides, equimolar base was required, whereas only a catalytic amount of base was necessary for reactions involving acid anhydrides. As an example, propionyl cyanide was treated with a stoichiometric amount of DBU and acetyl chloride in methylene chloride at rt to afford 1-cyanovinyl acetate in 61% yield.

DBU has also been used for certain deesterifications. In the case of acetates, deacetylation with DBU occurs under relatively mild conditions (rt to 80 °C; 5-45 h).[38] The method only works for esters derived from acetic acid. Methanol is the solvent of choice, although dichloromethane or benzene may be added to improve reactant solubility. It was speculated, though not confirmed, that the mechanism involves formation of the desired alcohol by elimination of ketene. As an example, acetate (**28**) was deacetylated in 93% yield to alcohol (**29**) with DBU in methanol at rt for 24 h (eq 17). The same reaction using DBU in xylene afforded only starting material.[39]

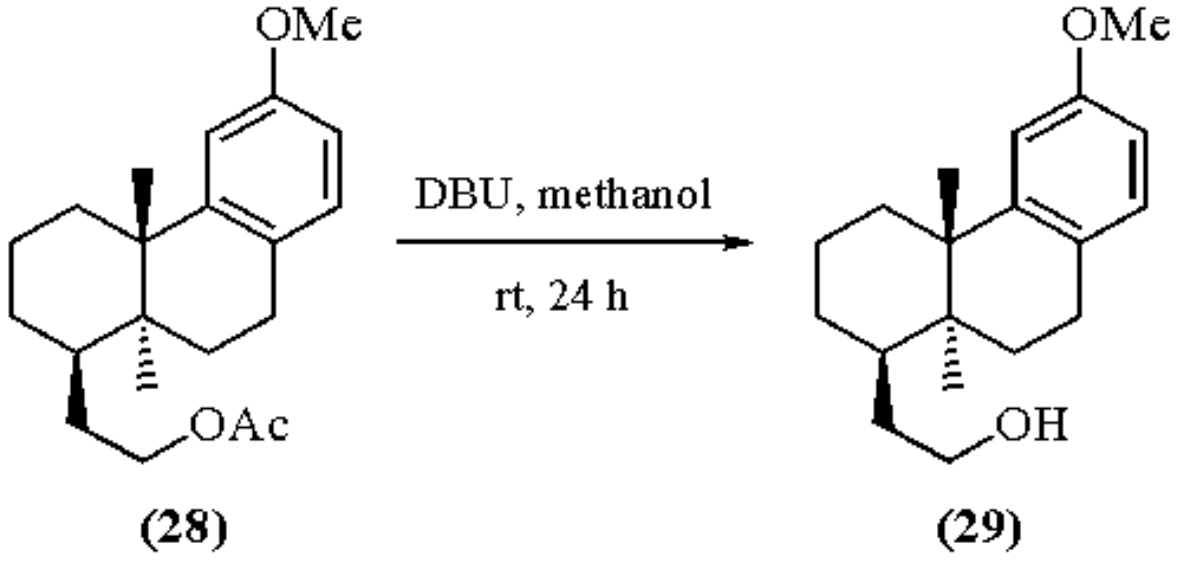

(17)

Methyl esters are cleaved with DBU. High reaction temperatures and extended reaction times are required; however, the corresponding acid is generally obtained in high yield (>90%) without the use of ionic nucleophiles such as ***Lithium Iodide***, lithium thiolate, or potassium *t*-butoxide.[39] Thus a solution of methyl mesitoate, 10 equiv of DBU, and 10 equiv of *o*-xylene was heated to 165 °C for 48 h, affording mesitoic acid which was isolated in 95% yield after ether extraction (eq 18).

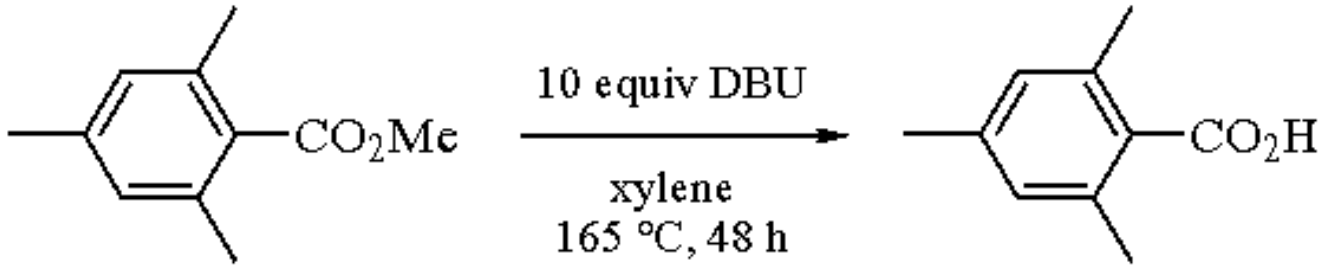

(18)

DBU was one of several effective bases used in an amide synthesis from *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride, primary or secondary amines, and carboxylic acids.[27] Other bases included ***1-Ethylpiperidine***, triethylamine, and *N*-ethylmorpholine. Reactions were conducted at rt for 1-2 h, avoiding racemization of optically pure substrates. Thus 3,3-dimethylacrylic acid and the acid salt of (*S*)-(-)-α-methylbenzylamine in DMA were treated with 2 equiv of DBU at rt over 30 min, then allowed to react at rt for 75 min to afford amide (**30**) in 75% yield (eq 19). Other methods require higher reaction temperatures (alkyl carbamates and alkyl amines afford amides at 200 °C in the presence of tertiary amines[40]), longer reaction times (***1,3-Dicyclohexylcarbodiimide***[41] and ***Diphenylphosphinic Chloride***[42] procedures require up to 12 h and result in only modest yields for similar conversions), or excess reagents or reactants (the cyanuric chloride method[43] requires excess acid and the *o*-nitrophenyl thiocyanate/***Tri-n-butylphosphine*** method[44] uses excess reagent and amine).

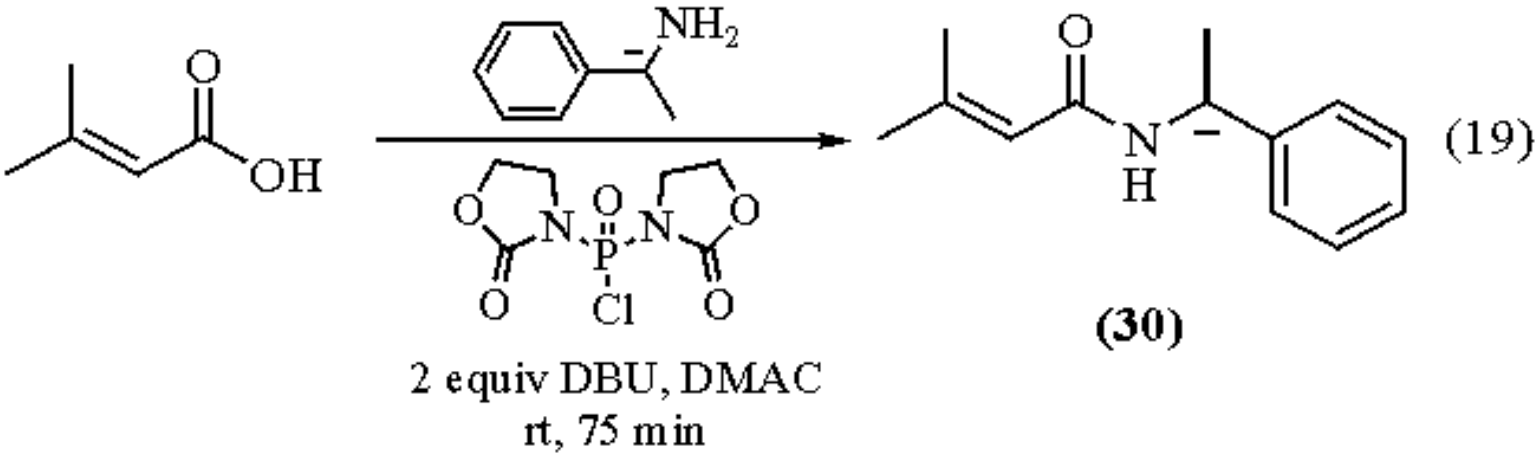

(19)

Condensations.

DBU has been used to effect condensations of active methylene compounds and other substrates containing active hydrogen. Reactions generally use equimolar DBU and aprotic solvents such as THF or benzene. Reaction times and temperatures vary.

DBU was shown to be an effective base for the Michael reaction of diethyl acetamidomalonate (**31**) with methyl acrylate in a synthesis of glutamic acid (eq 20).[45] ***1,1,3,3-Tetramethylguanidine*** and DBN were found to be equally effective. All resulted in the formation of glutamic acid derivative (**32**) quantitatively.

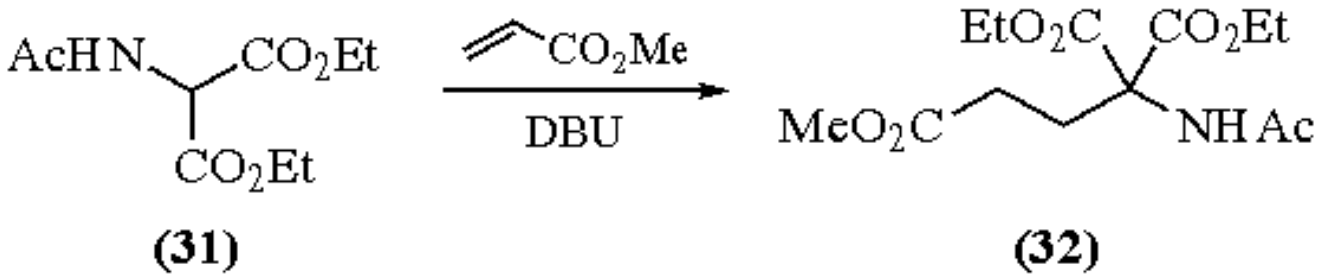

(20)

In the Knoevenagel condensation of ***Malonic Acid*** with hexanal, the β,γ-unsaturated isomer (**33**) was obtained with 94% selectivity and 56% yield after 10 h at 90 °C in the presence of equimolar DBU (eq 21).[46] Other bases selective for (**33**) included triethanolamine, triethylamine, ethylpiperidine, *N*,*N*-dimethylaniline, and ***2,6-Lutidine***. For comparison, pyridine, 3-methylpyridine, and 4-methylpyridine showed ~90% selectivity for the α,β-unsaturated isomer. A β,γ-unsaturated carbonyl compound was also obtained from the condensation of ***Formaldehyde*** with pentenone in the presence of catalytic DBU or DBN.[47] These results are interesting in view of the literature reports that β,γ-unsaturated carboxylates[19,20] and nitriles[21] are isomerized to the thermodynamically favored α,β-unsaturated isomers in the presence of DBU.

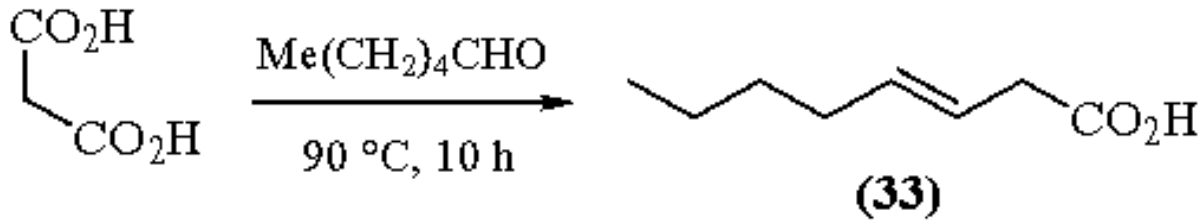

(21)

Diesters of homophthalic acid condensed with aromatic aldehydes in the presence of equimolar DBU in refluxing benzene for 6-10 h to give excellent yields of cinnamic esters. The reaction of dimethyl homophthalate with 3-benzyloxy-4-methoxybenzaldehyde to afford cinnamic ester (**34**) is representative (eq 22).[48] Sodium hydride, sodium alkoxides, and potassium acetate were all found to be ineffective for this reaction.

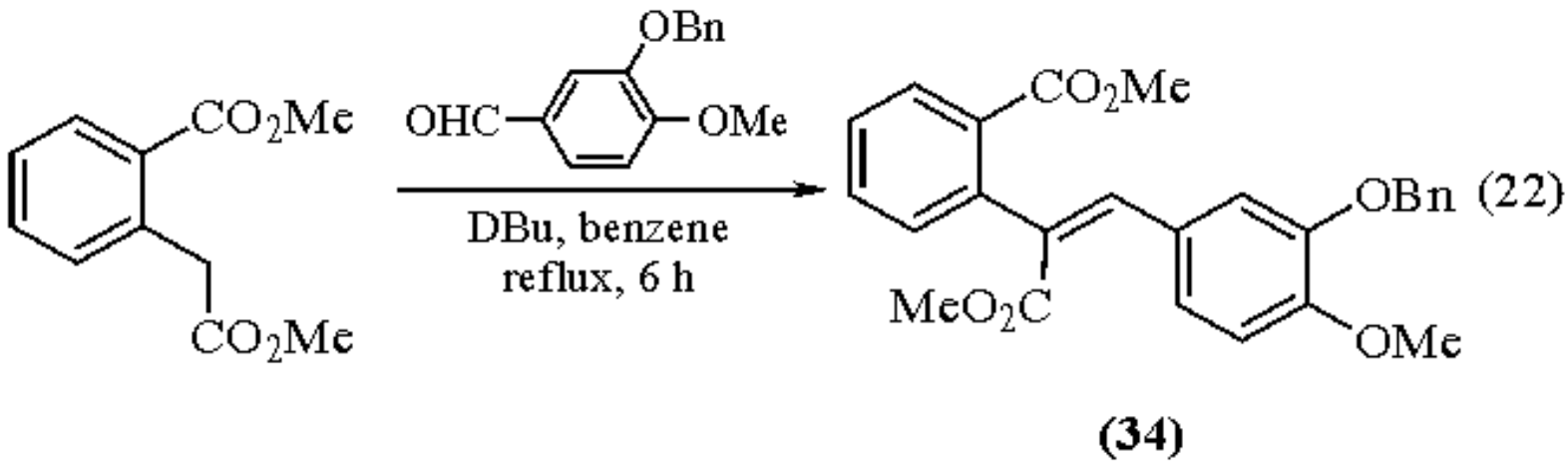

DBU catalyzed the asymmetric synthesis of δ-oxocarboxylic acids from (2*R*,3*S*)-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (**35**).[49] The Michael reaction of (**35**) with 2-cyclopenten-1-one afforded (+)-3-cyclopentanoneacetic acid (**36**) in moderate yield (43%) and high optical purity (96%) after hydrolysis and decarboxylation (eq 23). Trityllithium (***Triphenylmethyllithium***) or potassium *t*-butoxide afforded (**36**) in similar yields (30-50%) but poorer optical purity (7-76%).

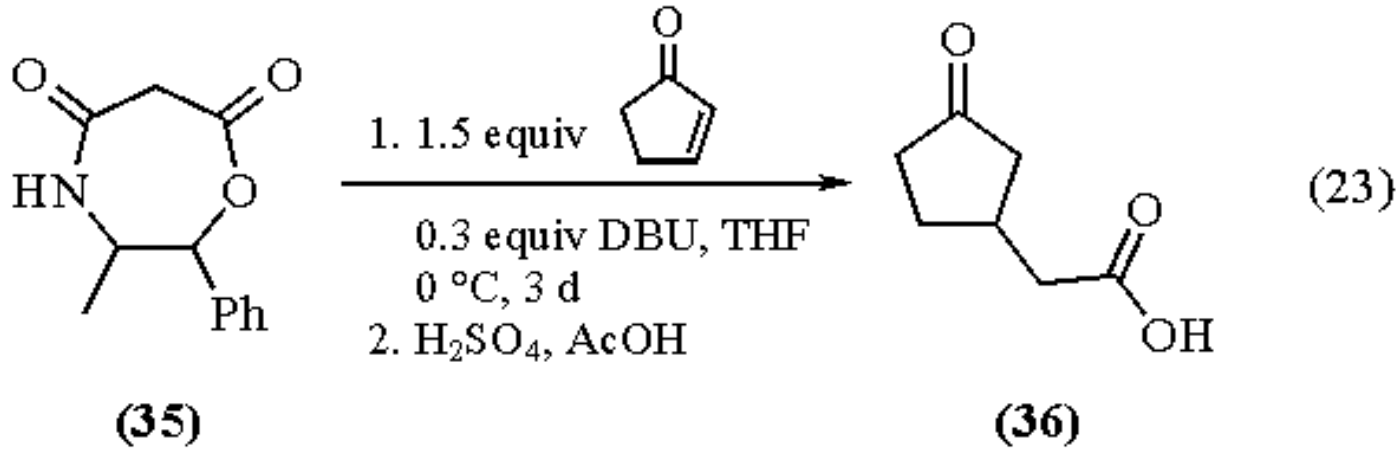

Carbonylations and Carboxylations.

DBU has been used to prepare amides or imides[50-52] and esters[53] via the sequential carbonylation/alkylation of amines and alcohols, respectively. Similarly, the carboxylation of amines and alcohols affords urethanes and carbonates.[54] Reactions use stoichiometric base and are catalyzed by palladium or nickel complexes. Product yields are generally high (80-100%). Carbonylations have been conducted in DMA at elevated temperatures (115-150 °C), whereas carboxylations have been performed at rt in a variety of solvents including methylene chloride, DMSO, THF, and glyme. Eqs (24) and (25) show the preparation of *N*-phenylbenzamide and allyl benzylethylcarbamate by these procedures. The efficacy of various bases was compared in the carboxylation/alkylation of benzylethylamine using a catalytic amount of tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$). DBU, *N*-cyclohexyl-*N*´,*N*´,*N*´´,*N*´´-

tetramethylguanidine, and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene were preferred. DBN afforded a modest 49% yield of urethane and essentially no urethane was formed using ***Diisopropylethylamine***.

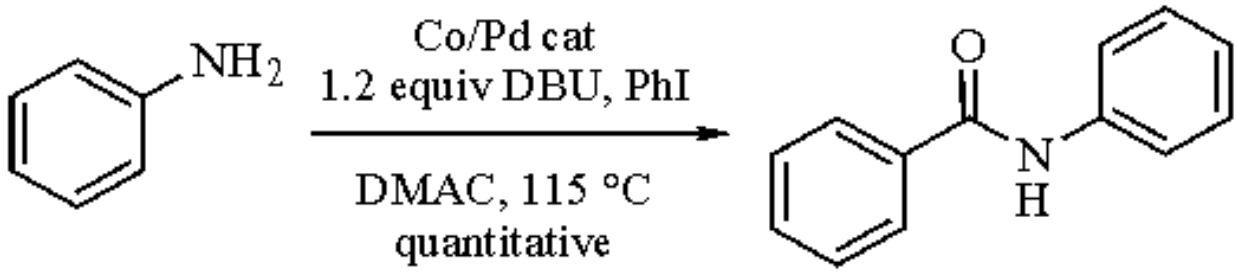

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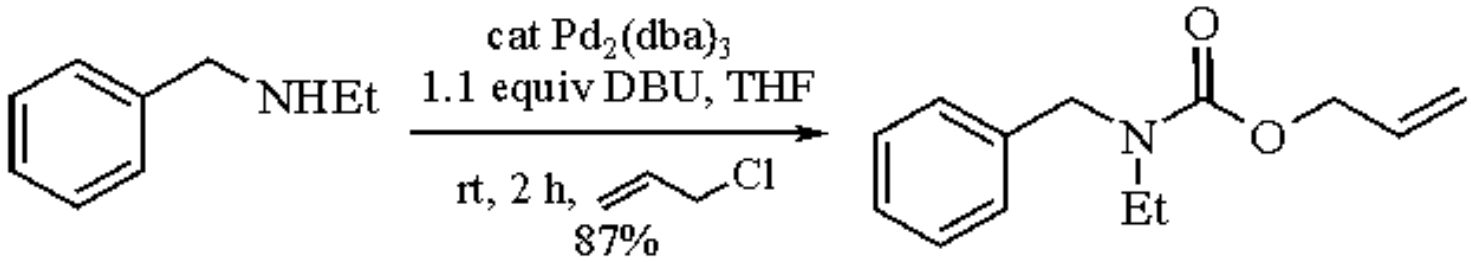

(25)

Methods for the preparation of thiocarbamates from alcohols, carbon disulfide, and alkylating agents[55] or via the sulfur-assisted carbonylation of alcohols[56] are related; these do not require a metal catalyst. Thus *S*-benzyl *O*-*n*-butylcarbonothionate was isolated in 86% yield after the carbonylation of *n*-butanol in THF at 80 °C for 4 h in the presence of 3 equiv of powdered sulfur and 5 equiv of DBU followed by esterification with 1.2 equiv of benzyl bromide (eq 26).

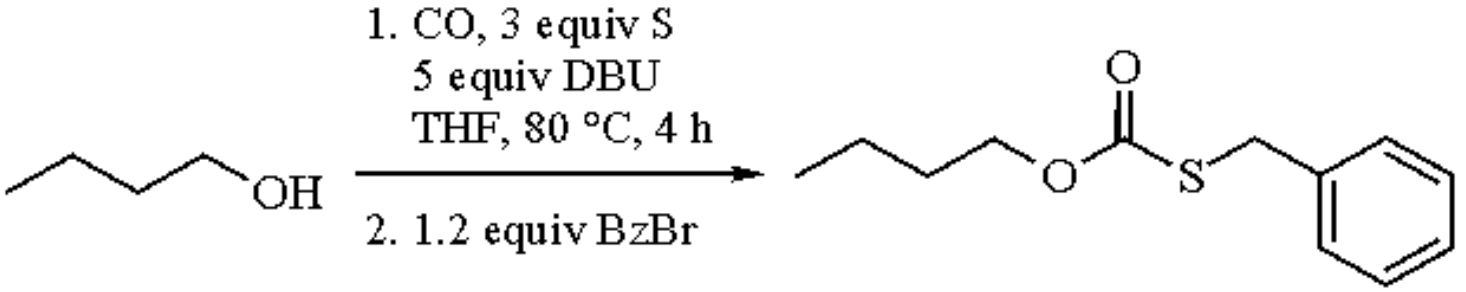

(26)

DBU has also been used in the nickel- or palladium-catalyzed coupling of alkenes with ***Carbon Dioxide***.[57,58] As an example (eq 27), isoprene was treated with $Pd(acac)_2$, a phosphine ligand, DBU, and tributyltin ethoxide for 84 h at 80 °C under CO_2 to afford an isomeric mixture of C-10 carboxylic acids (68% after esterification and purification). It was found that DBU and tributyltin ethoxide independently promote the reaction, but not as effectively as when used as a combination.

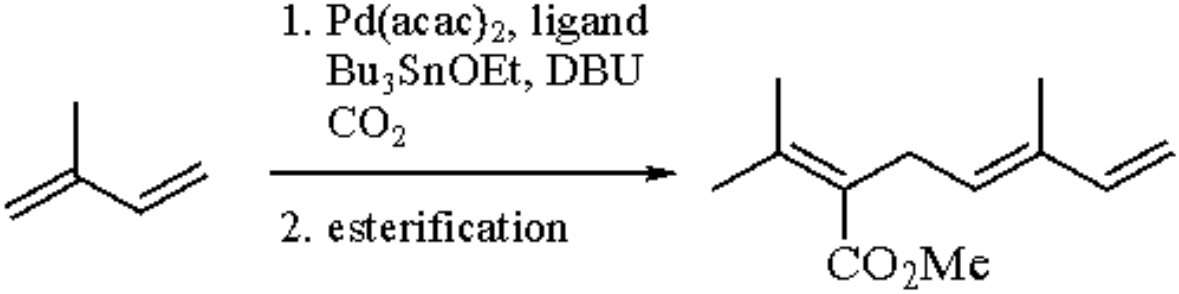

(27)

Halogenations.

DBU-based brominating agents such as DBU/bromine,[59] DBU/hydrobromide perbromide,[60] and DBU/bromotrichloromethane,[61,62] have been used to brominate enolizable substrates and aromatic compounds. As an example, 3-halomethylcephems (e.g. **38**), convenient intermediates for the synthesis of 3´-substituted cephalosporins, were prepared by treatment of *exo*-methylene cephems (e.g. **37**) with DBU/bromine in THF over the temperature range -80 to 0 °C (eq 28).

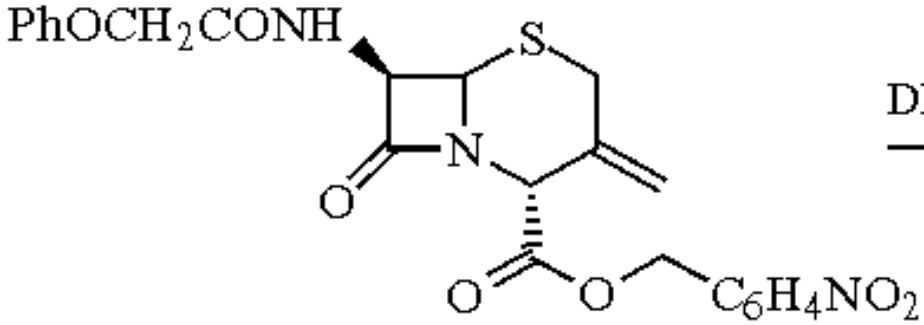

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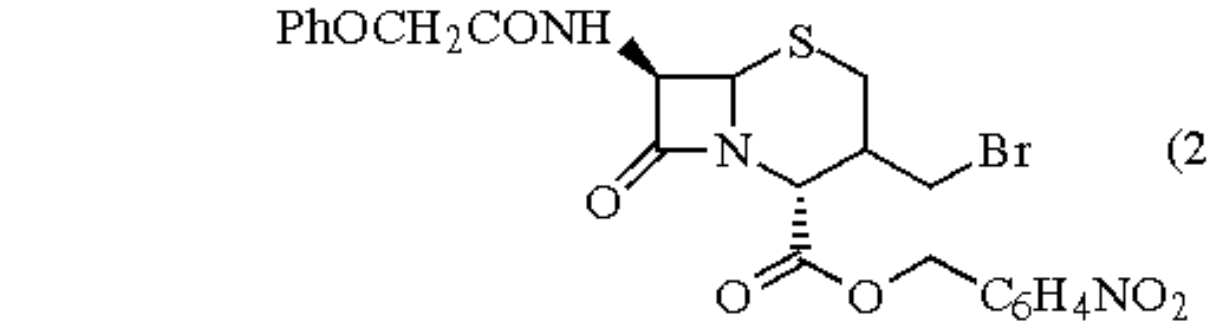

(28)

(38)

Miscellaneous.

A synthesis of phthalocyanines and metallophthalocyanines, interesting optical and electronic materials, involves the DBU-mediated reaction of alcohols with phthalonitrile at elevated temperature.[63-67] The alkoxy-3-iminoisoindolenine (**39**) is presumed to be an intermediate (eq 29). Thus phthalonitrile was treated with equimolar DBU in refluxing ethanol to afford the corresponding phthalocyanine as a blue crystalline compound. DBN was also shown to be effective for this transformation; neither pyridine nor 1,4-diazabicyclo[2.2.2]octane promoted the formation of

phthalocyanine.

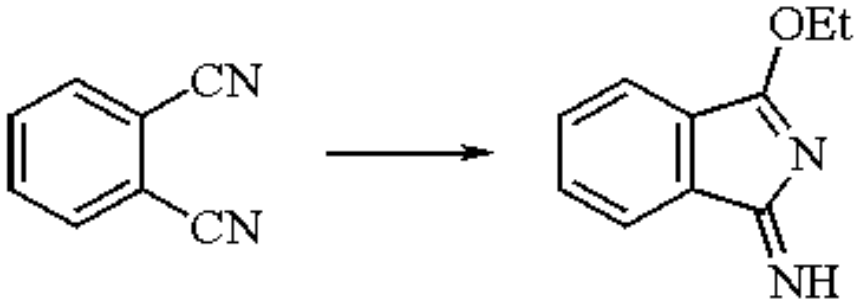

(29)

Carboxylic acids have been phosgenated in the presence of a variety of amine bases, including DBU, to afford acid chlorides.[68] Reactions are conducted with 2 mol% base at 80-100 °C. Yields of acid chlorides are generally greater than 90%.

DBU was used to promote the in situ formation of hydrogen selenide from ***Selenium***, ***Carbon Monoxide***, and water for selective reduction of α,β-unsaturated carbonyl compounds.[69] *N*-Methylpyrrolidine was also found to be effective. Thus benzylideneacetone afforded 4-phenylbutanone in 82% yield in the presence of DBU, selenium, and carbon monoxide at 50 °C or *N*-methylpyrrolidine at 80 °C after 24 h. Isophorone underwent selective reduction of the conjugated double bond and β-ionone was reduced to 4-(2,6,6-trimethyl-1-cyclohexenyl)-2-butanone.

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2,5-Diazido-3,6-di-*t*-butyl-1,4-benzoquinone[1]

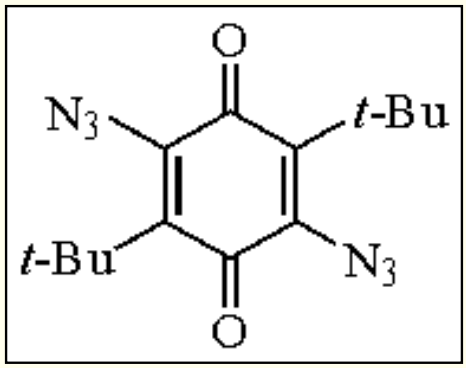

[29342-21-0] · $C_{14}H_{18}N_6O_2$ · 2,5-Diazido-3,6-di-*t*-butyl-1,4-benzoquinone · (MW 302.38)

(reagent for the preparation of *t*-butylcyanoketene,[2] a versatile ketene for reactions with a variety of ketenophiles[1])

Physical Data: mp 89-90 °C (dec).

Solubility: sol aromatic solvents which are used in the preparation of *t*-butylcyanoketene.

Analysis of Reagent Purity: IR (Nujol) 2110 (N_3), 1640 (CO) cm^{-1}; ^1H NMR ($CDCl_3$), δ 1.31 (s, *t*-Bu).

Preparative Method: 2,5-diazido-3,6-di-*t*-butyl-1,4-benzoquinone (**2**) is readily synthesized in five steps from commercially available 2,5-di-*t*-butyl-1,4-benzoquinone (**1**) in approximately 30% overall yield (eq 1-3).[2]

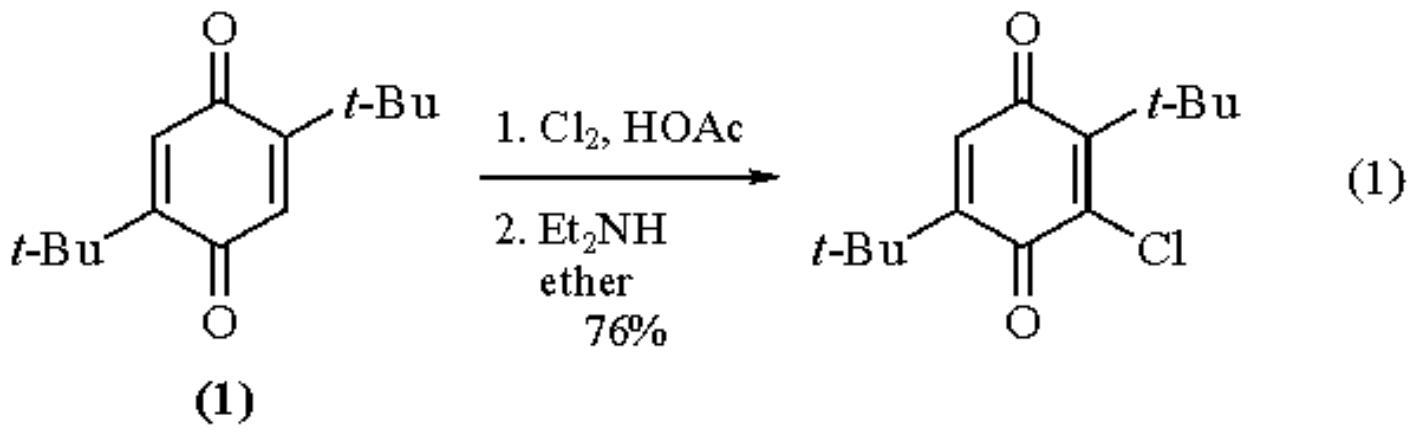

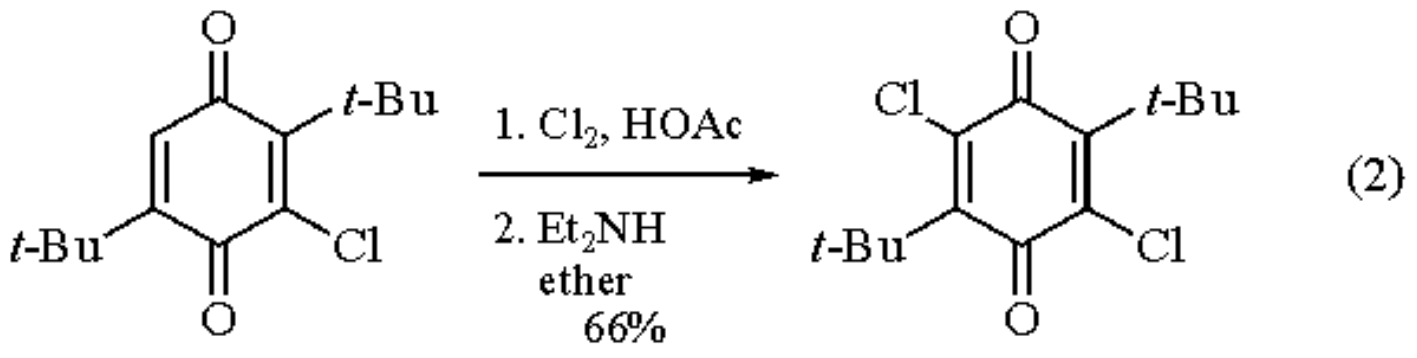

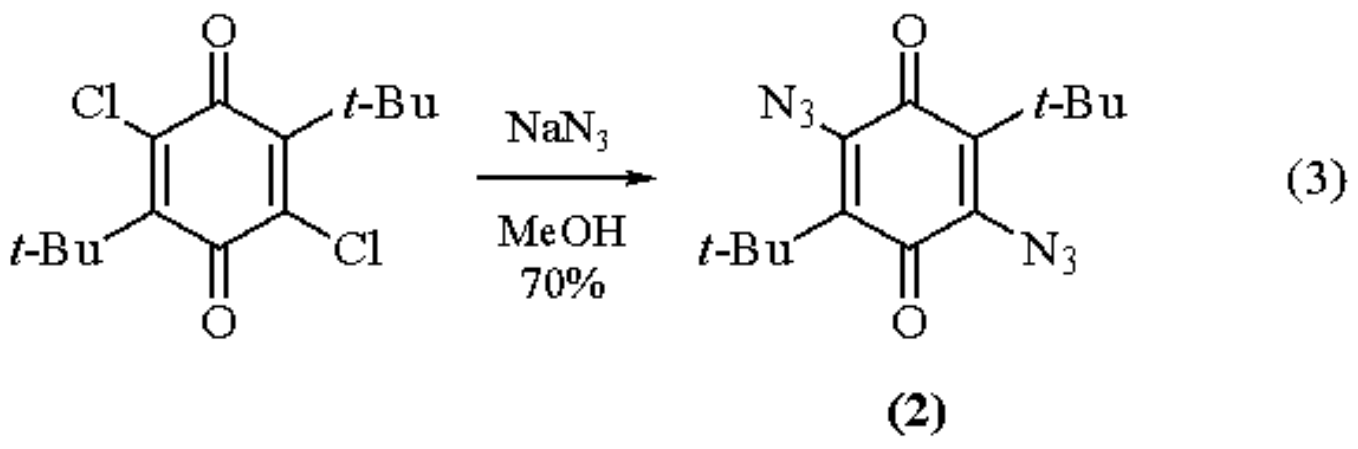

Purification: recrystallization from chloroform/ethanol.

Handling, Storage, and Precautions: during the course of any purification method that might be employed, the diazide should not be heated above 50 °C since decomposition occurs quite noticeably at that temperature. It is best to store the pure product below -5 °C in the dark since it undergoes a facile photochemical rearrangement to a cyclopentenedione.[2]

Thermolysis.

Upon heating in refluxing benzene, 2,5-diazido-3,6-di-*t*-butyl-1,4-benzoquinone (**2**) loses 2 mol of nitrogen to generate 2 mol of *t*-butylcyanoketene (TBCK, **3**) (eq 4). One advantage of this route over other classical routes to TBCK is the fact that external bases or metals are not employed. Also, when the thermolysis is accomplished in the presence of a ketenophile the concentration of TBCK is low, thus minimizing polymerization reactions.[2]

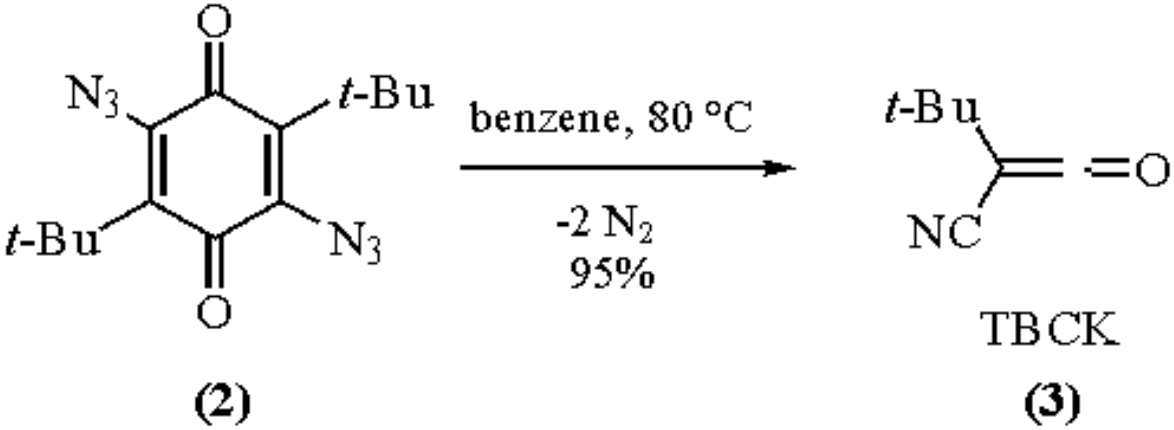

Cycloadditions.

TBCK does not undergo rapid self-condensation in benzene at 25 °C but rather cycloadds to a variety of ketenophiles including alkenes, imines, enol ethers and silyl enol ethers, alkynes, allenes, ketenes, isocyanides, stannylethynyl ethers, and a variety of heterocyclic compounds.

Cycloadditions with Alkenes.

Cycloadditions of TBCK to a variety of mono-, di-, and trisubstituted alkenes give good yields of the corresponding cyclobutanones. No examples of reactions of TBCK with tetrasubstituted alkenes have been reported.[1] The addition of TBCK to alkenes generally is stereoselective, resulting in the bulky *t*-butyl group *cis* to the larger group on the alkene. These findings best correspond to a concerted $_{\pi}2_a + {}_{\pi}2_s$ reaction mechanism.[1] The reactions of TBCK with styrene and cyclohexene demonstrate this highly stereoselective route to substituted cyclobutanones (eqs 5 and 6).[1,3]

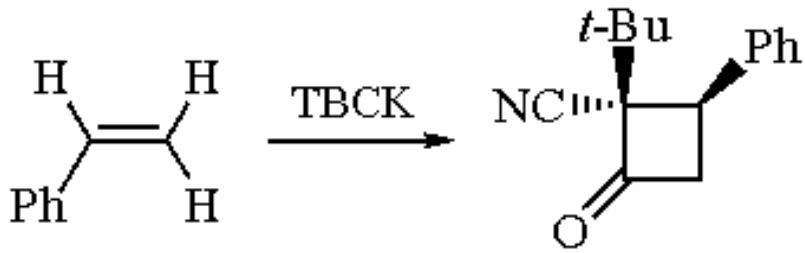

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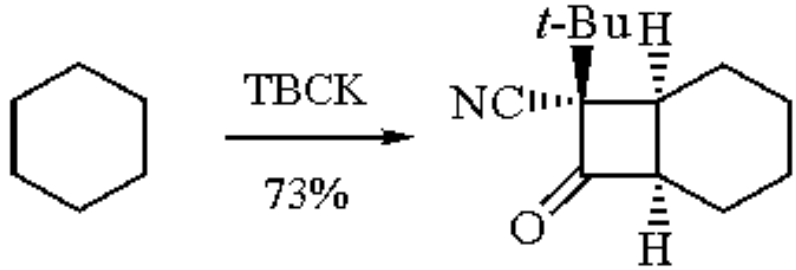

(6)

When stabilization of a zwitterionic intermediate is energetically favored, as in the addition of TBCK to *trans,trans*-2,4-hexadiene, a stepwise mechanism may be involved (eq 7).[1] The major product of this reaction appears to be cyclobutanone (**4**) and not (**5**), which would be the expected product if a concerted mechanism was involved. Other interesting products result from the reaction of TBCK with cyclic dienes. Addition to cyclohexa-1,3-diene and

bicyclo[2.2.1]heptadiene gives both the cyclobutanone product plus a formal oxy-Cope rearrangement product (eqs 8 and 9).[1,4]

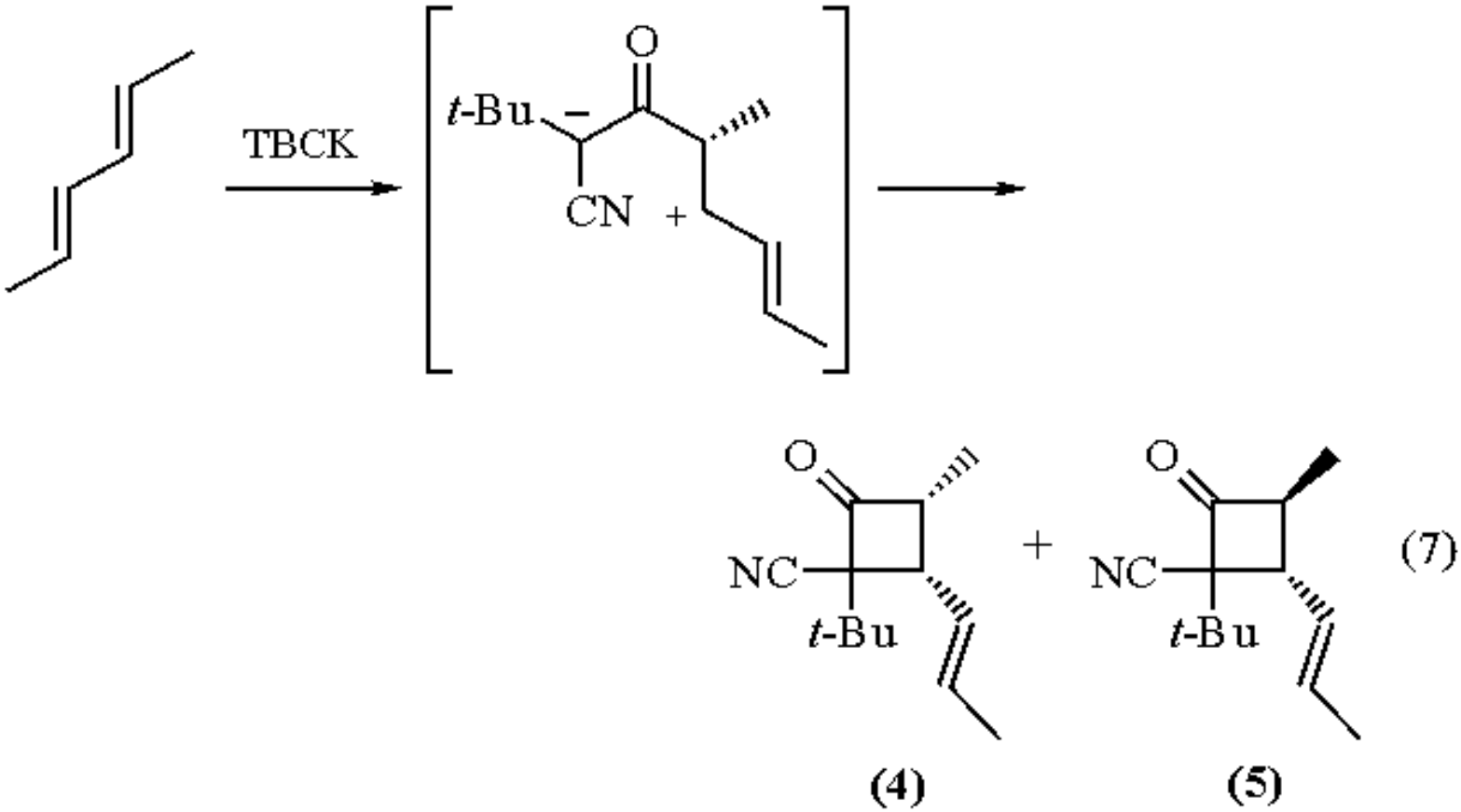

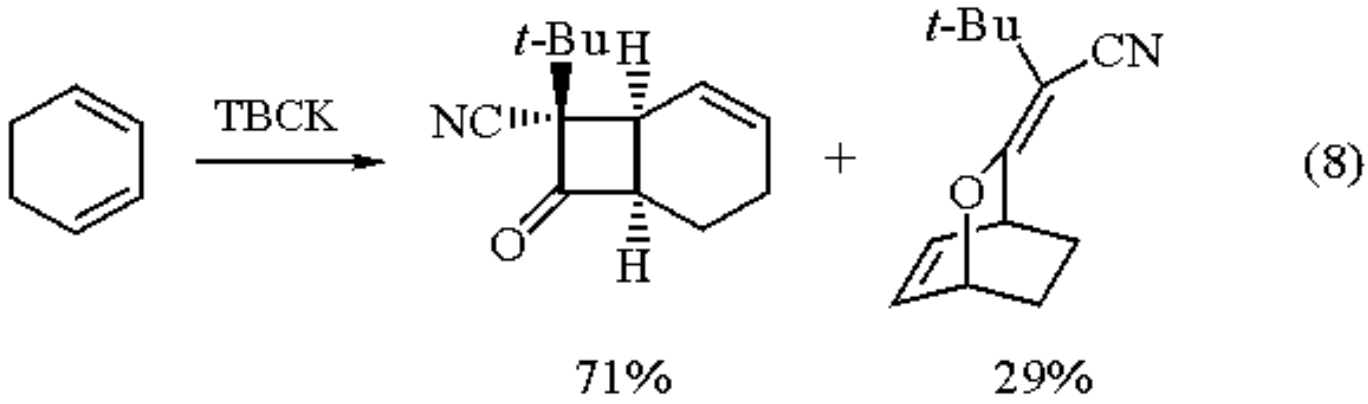

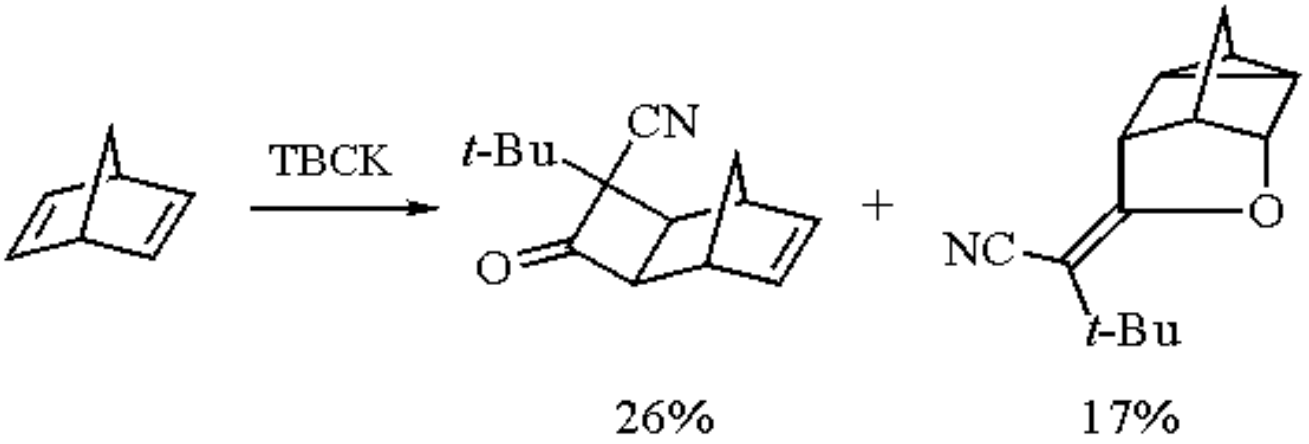

(9)

Cycloadditions with Imines.

Next to alkenes, the most studied ketenophiles of TBCK are formimidates, thioformimidates, and imines.[1] Reaction of a variety of imines such as *S*-ethyl-*N*-phenylthioformimidate with TBCK produces β-lactam products (**7**) stereospecifically; the products of these reactions are consistent with a stepwise mechanism involving a dipolar intermediate (**6**) (eq 10). In addition, 2:1 adducts are also frequently formed with imines (**8**) and (**9**) (eq 11).[1,5]

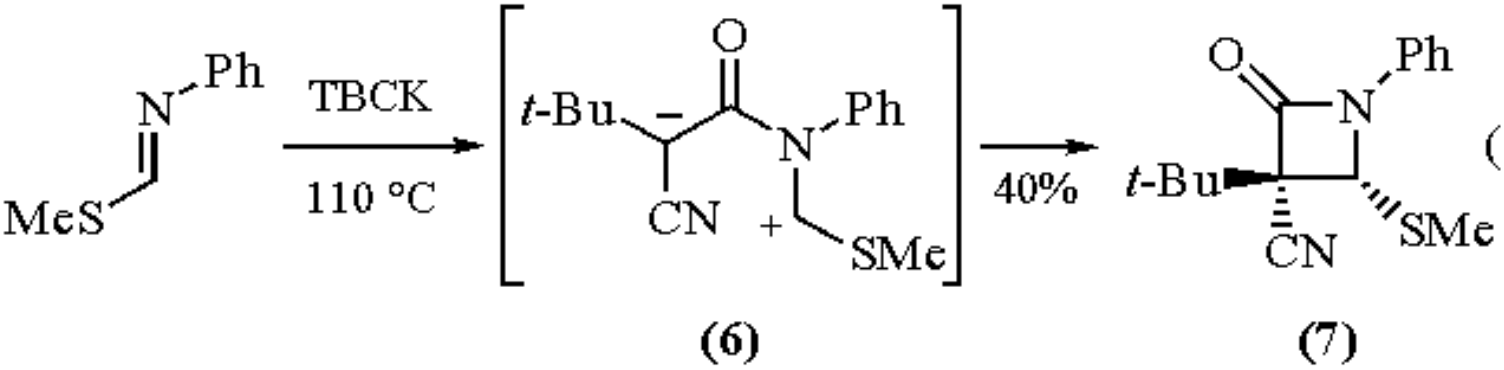

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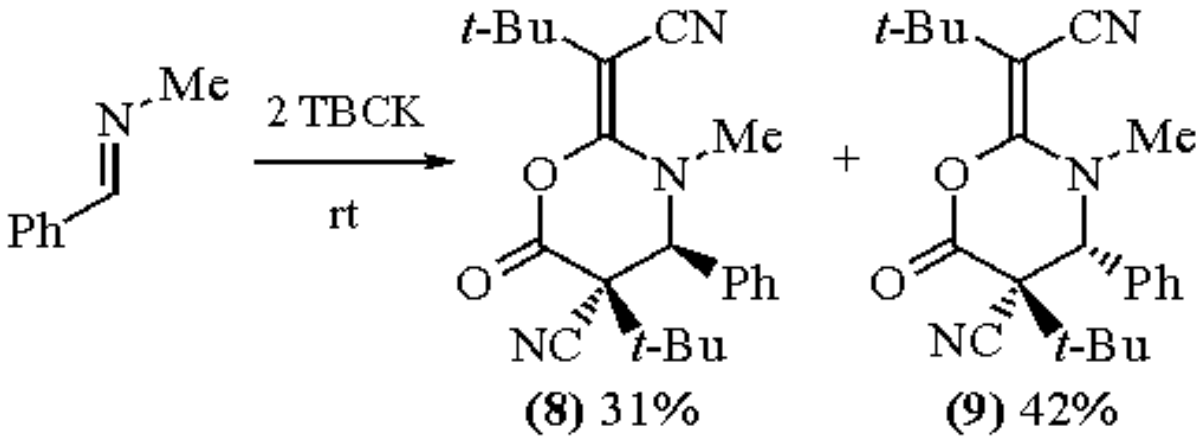

(11)

Cycloadditions with Enol Ethers and Silyl Enol Ethers.

Additions of TBCK to a variety of enol ethers typically give mixtures of stereoisomers.[1] Reaction with ethyl vinyl ether generates cyclobutanone products that could only reasonably arise from a dipolar intermediate (eq 12).[1]

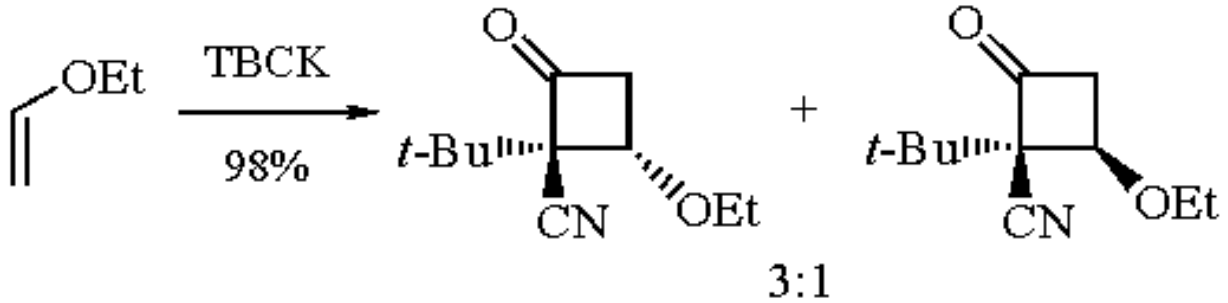

(12)

Additions to silyl enol ethers behave in an analogous fashion; a stepwise mechanism is involved.[6] However, different products arise depending on the steric congestion (H vs. Me) of the zwitterionic intermediate (**10**) and (**11**) formed in the reaction (eqs 13 and 14).[7]

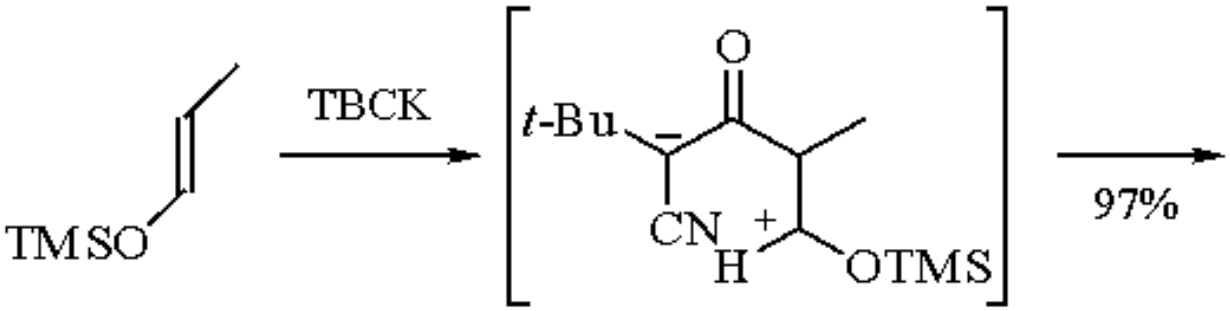

(10)

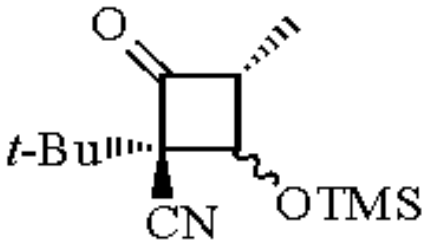

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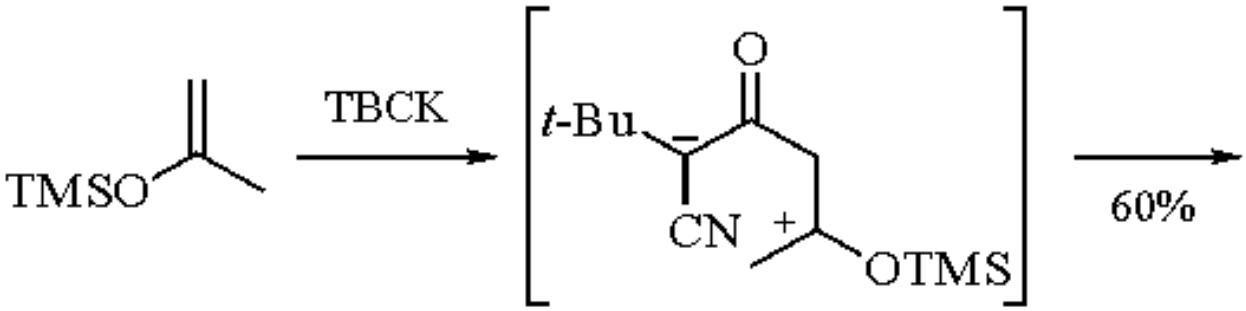

(11)

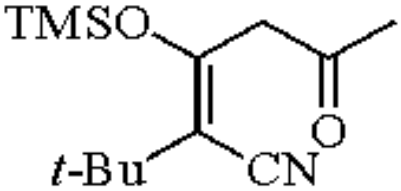

(14)

Cycloadditions with Alkynes.

Regiospecific cycloadditions of TBCK to simple alkynes give cyclobutenones, a transformation consistent with a concerted mechanism (eq 15).[1]

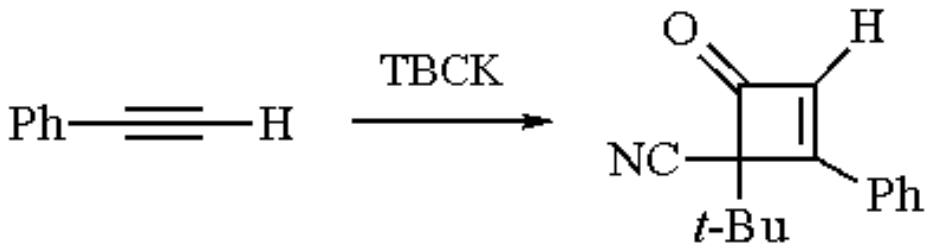

(15)

Cycloaddition with Allenes.

Cycloaddition of TBCK to allenes typically gives cyclobutanone products, as in the case of 1,1-dimethylallene (eq 16).[1] The varying ratios of regio- and stereoisomeric products lend credence to a zwitterionic intermediate.

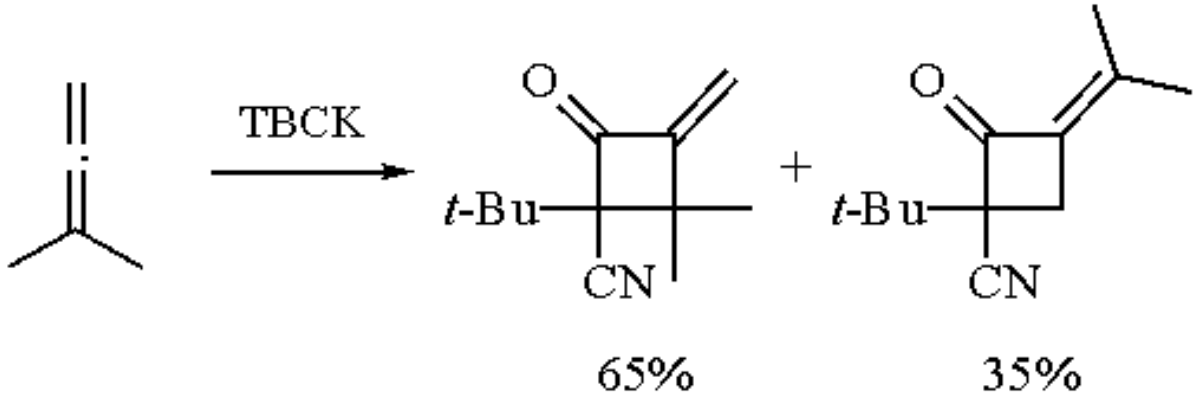

(16)

Cycloadditions with Ketenes.

Cycloaddition of TBCK to ketenes generally produces 1,3-cyclobutanedione products (eq 17), although oxetan-2-one products (**14**) can form if the steric demands on the zwitterionic intermediate (**13**) are lessened as in the case of methylketene (**12**) (eq 18).[8]

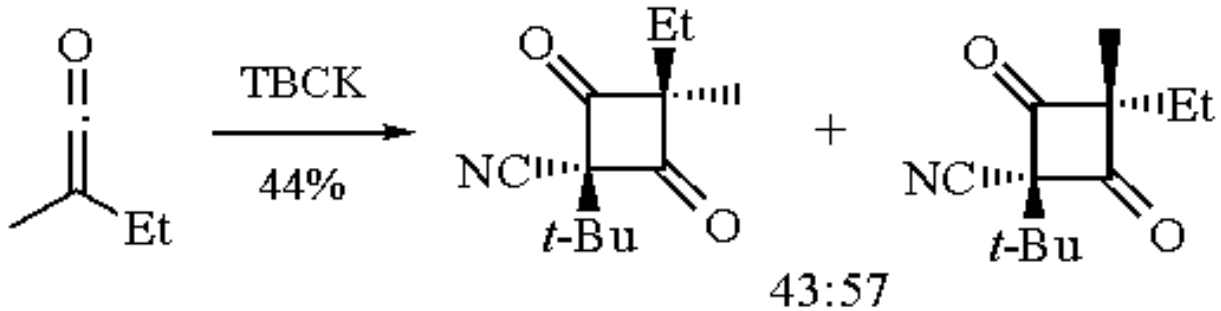

(17)

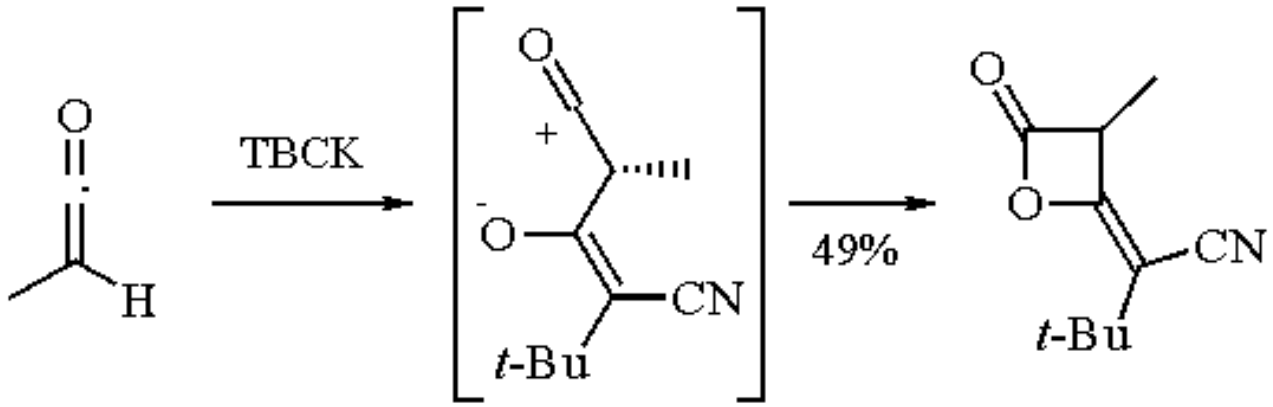

(18)

Cycloadditions with Isocyanides.

Cycloaddition of TBCK to isocyanides gives the 2:1 adducts (**15**), presumably by a stepwise mechanism (eq 19).[9] This adduct (**15**) rearranges to the iminolactone (**16**) in refluxing benzene and further thermolysis at 130 °C gives the butenolide (**17**).

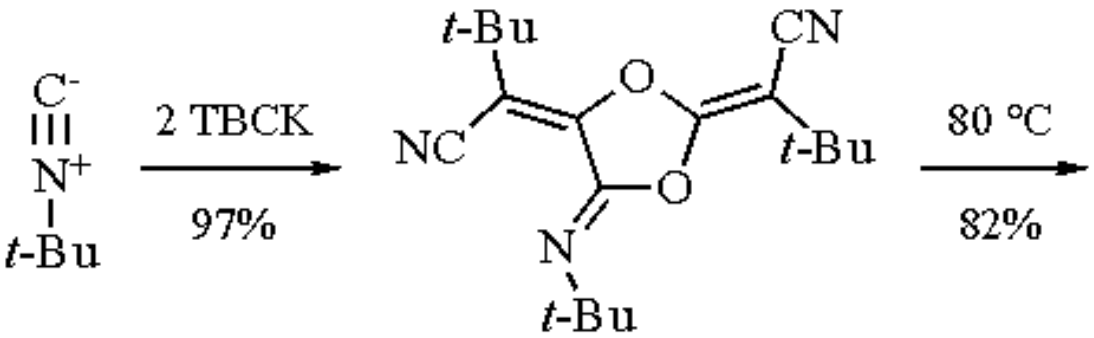

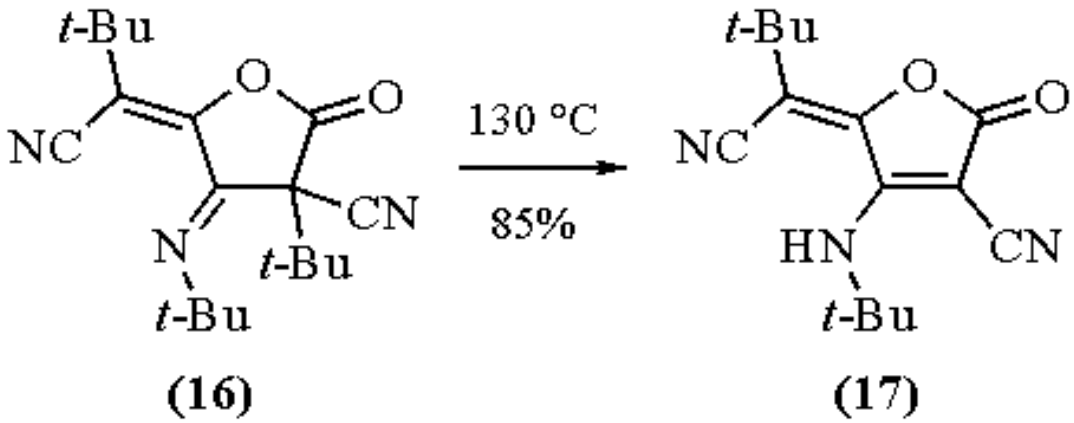

(19)

Cycloaddition with Stannylethynyl Ethers.

Cycloaddition of TBCK to various stannylethynyl ethers proceeds to zwitterionic intermediates (**18**) and (**19**) which are

in equilibrium and can either rearrange to the stannyl enol ether (**20**) or can add to another molecule of TBCK to form (**21**) (eq 20).[10]

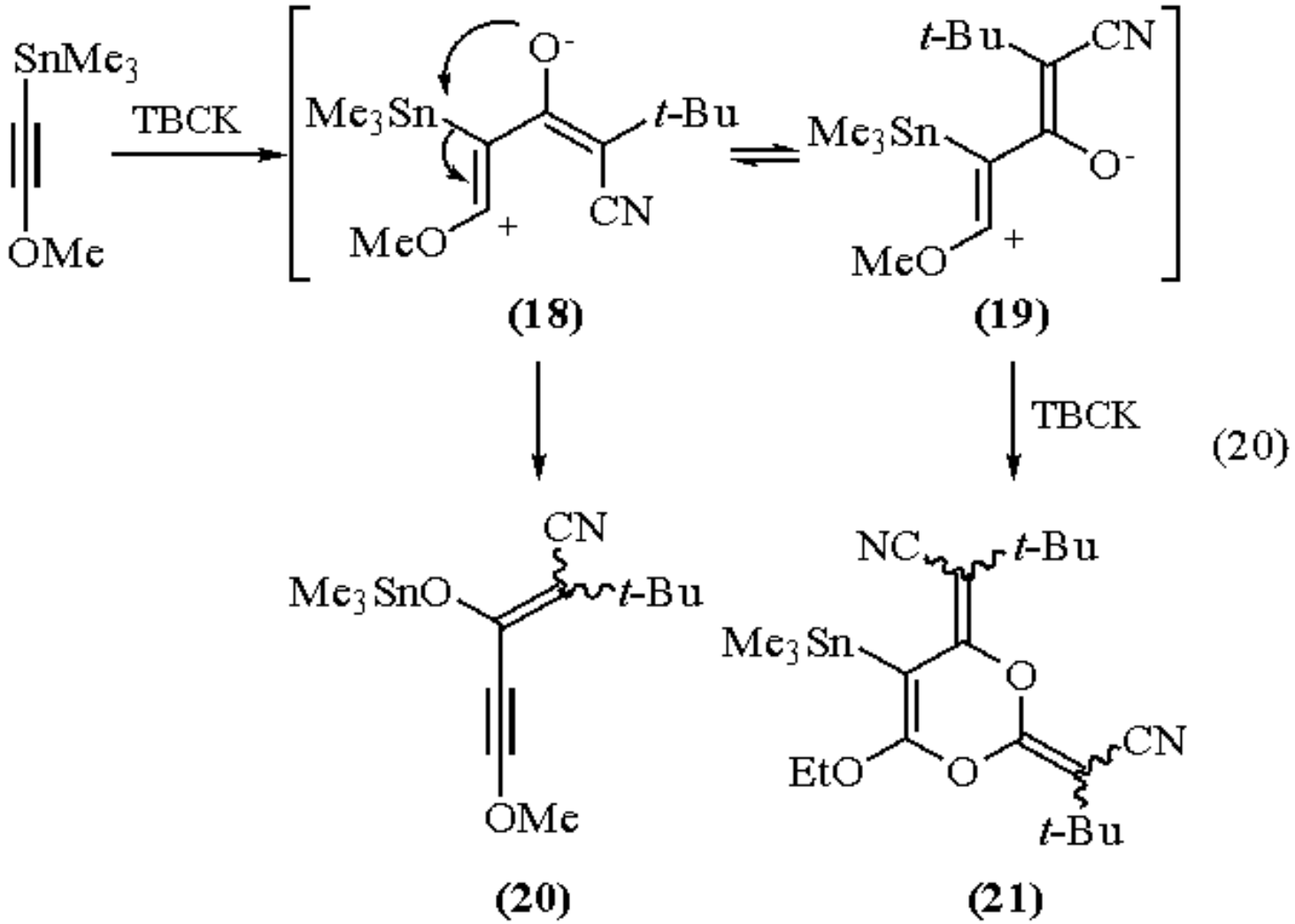

Miscellaneous Cycloadditions.

Cycloadditions of TBCK have been attempted with a host of compounds including 1-azirines,[1] *N*-oxides,[1,11] *N*-sulfiminoaziridines,[1] spirooxaziridines,[1] sulfurdiimides,[12] carbodiimides,[12] sulfinylamines,[12] and thiooxazoles.[13] All cycloadditions listed here appear to involve a stepwise dipolar mechanism.

Cycloreversions of Cyclobutanone Adducts.

A variety of cyclobutanone products derived from the cycloaddition of TBCK with alkenes have been thermolyzed to form the original ketenes and ketenophiles (eq 21).[14] These retro [2 + 2] reactions appear to be concerted processes due to the lack of appreciable solvent effects.

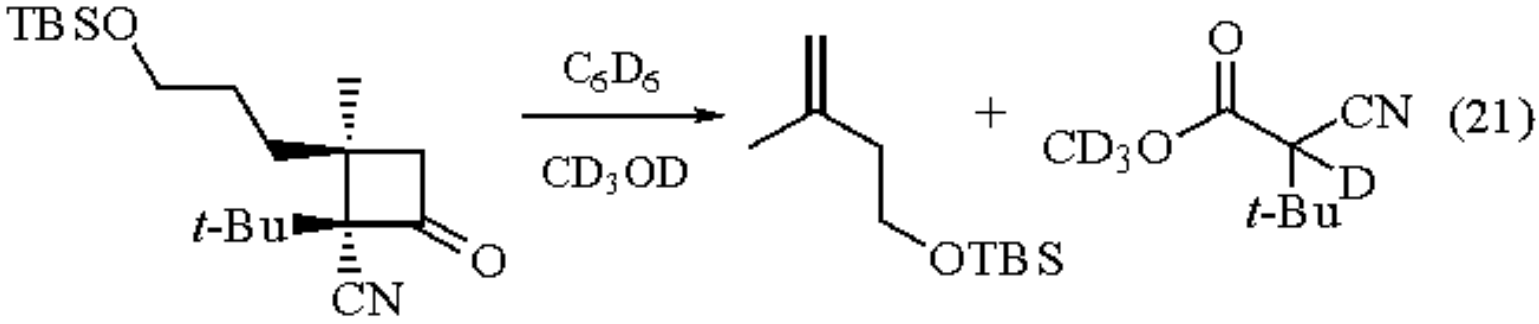

Related Reagents.

2,6-Di-t-butyl-1,4-benzoquinone.

---

1. Moore, H. W.; Gheorghiu, M. D. *CSR* **1981**, *10*, 289.
2. Weyler, W. Jr.; Duncan, W. G.; Liewen, M. B.; Moore, H. W. *OSC* **1988**, *6*, 210.
3. Weyler, W.; Duncan, W. G.; Moore, H. W. *JACS* **1975**, *97*, 6187.
4. Brook, P. R.; Hunt, K. *CC* **1974**, 1989.
5. Moore, H. W.; Hughes, G.; Srinivasachar, M. F.; Nguyen, N. V.; Schoon, D.; Tranne, A. *JOC* **1985**, *50*, 4231.
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Diazidotin Dichloride

$SnCl_2(N_3)_2$

[32006-05-6] · Cl_2N_6Sn · Diazidotin Dichloride · (MW 273.64)

(electrophilic activating agent for thioacetals[1])

Physical Data: white powder; explodes on heating without melting.

Solubility: insol CH_2Cl_2 and most org solvents; sparingly sol Me_3SiCl.

Form Supplied in: white or slightly yellow high polymer.

Analysis of Reagent Purity: IR spectroscopy; explodes under microanalytical N_2 determination.

Preparative Methods: from reaction of Me_3SiN_3 with $SnCl_4$ (1:1 to 2:1) in CH_2Cl_2 or pentane at rt,[2] or by oxidative addition of halogen azides to tin(II) chloride in CCl_4 at 0 °C.[3]

Purification: almost analytically pure after washing with solvent and drying in vacuo; does not crystallize or sublime.

Handling, Storage, and Precautions: the dry solid is sensitive to hydrolysis and should be stored in the absence of moisture. Contact with metal (spatula) must be avoided and the reagent should be used only behind a safety shield. Use in a fume hood.

Thiophilic Electrophile.

Generated in situ from ***Azidotrimethylsilane*** and ***Tin(IV) Chloride***, diazidotin dichloride converts thioacetals of cyclic ketones to imino thioethers (eq 1).[1] This one step process involves generation of a thionium ion, subsequent formation of an α-azido sulfide, and Schmidt rearrangement of the latter.

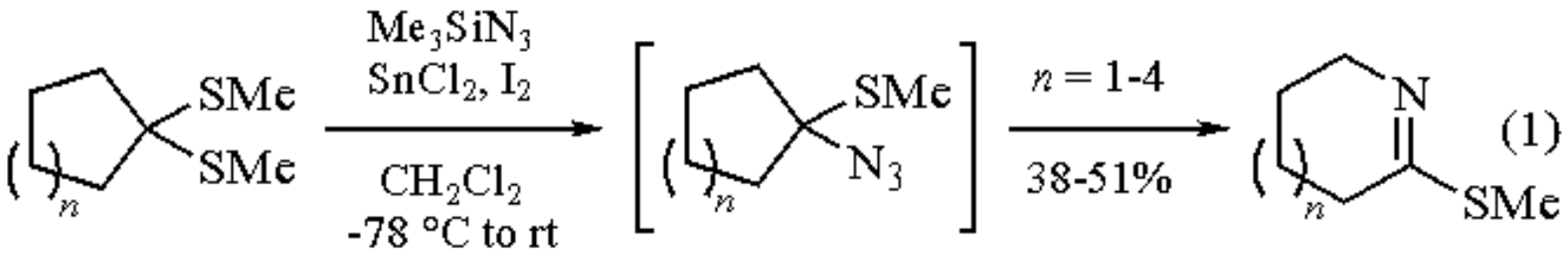

Addition of ***Sodium Azide*** instead of Me_3SiN_3 gives better yields of imino thioethers (50-83%), but in this case difficulties are encountered on a large scale (>10 mmol) because of the heterogeneous nature of the process. For small-scale reactions, appreciably better yields (to 95%) can be obtained by using 0.5 equiv of preformed diazidotin dichloride and 1 equiv of $SnCl_4$ in methylene chloride.[1]

Chemoselectivity of the process is reasonably high (eq 2)[1] and thus it is possible to reverse the normal reactivity pattern of thioacetal and ketone groups.

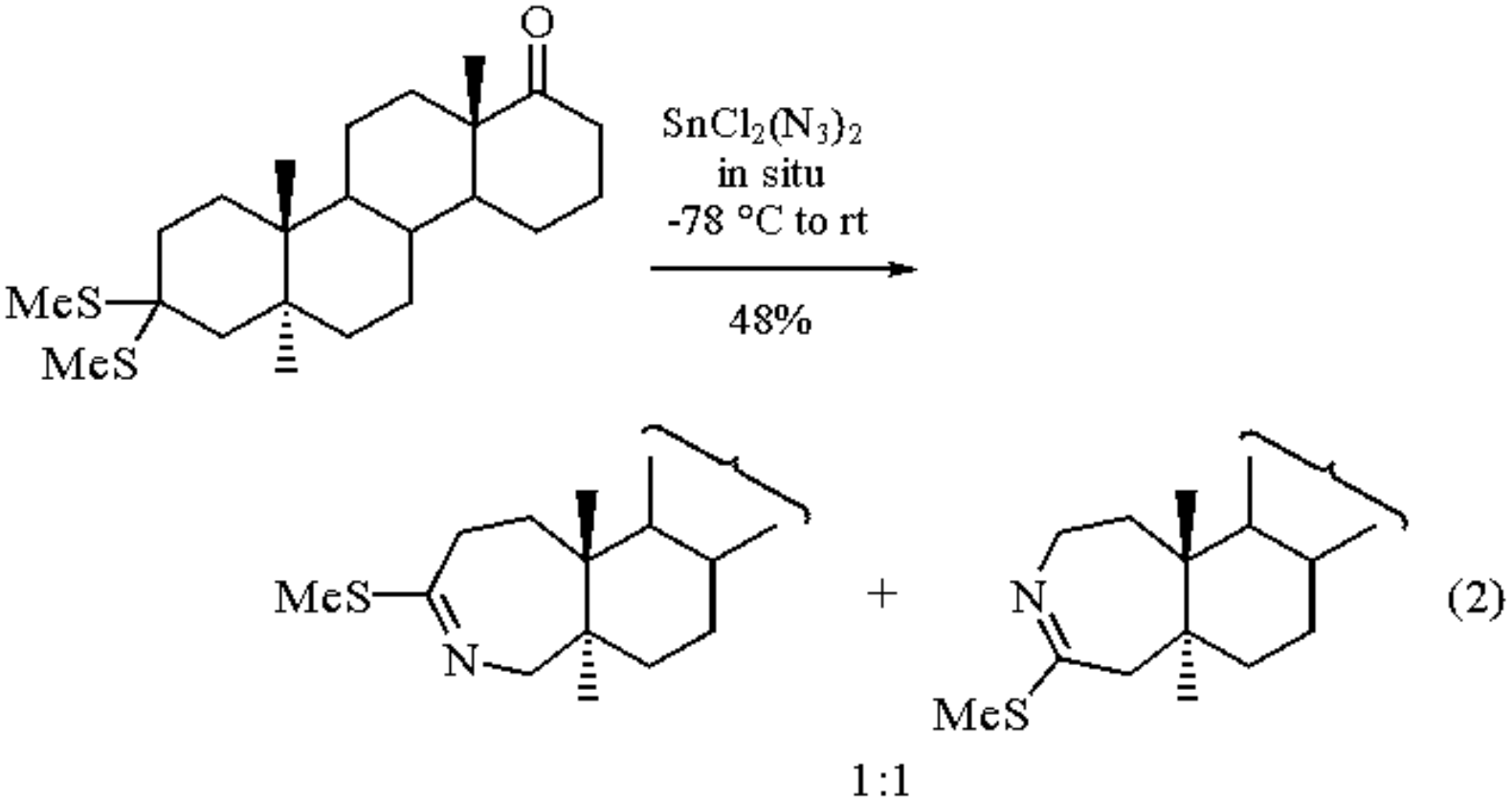

Lewis Acid Adducts.

Diazidotin dichloride forms at rt a reasonably stable 1:1 adduct with neat Me_3SiCl, precipitated as a white solid (eq 3).[2] The complex decomposes without melting on heating with quantitative elimination of Me_3SiCl and dissociates in solutions of organic solvents (by NMR).[2,3]

$$SnCl_2(N_3)_2 + Me_3SiCl \underset{\Delta,\ 80\text{-}90\ ^\circ C}{\overset{\text{in } Me_3SiCl}{\rightleftharpoons}} Cl_2Sn(N_3)_2 \cdot Me_3SiCl \quad (3)$$

---

1. Trost, B. M.; Vaultier, M.; Santiago, M. L. *JACS* **1980**, *102*, 7929.
2. Wiberg, N.; Schmidt, K. H. *CB* **1967**, *100*, 748.
3. Dehnicke, K.; Ruschke, P. *Z. Anorg. Allg. Chem.* **1978**, *444*, 54 (*CA* **1978**, *89*, 208 381v).

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Diazoacetaldehyde[1]

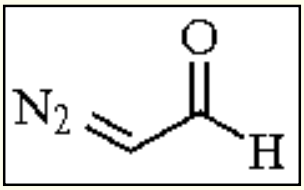

[6832-13-9] · $C_2H_2N_2O$ · Diazoacetaldehyde · (MW 70.06)

(cyclopropanation of alkenes;[2] condensation with organoboranes;[3] 1,3-dipolar cycloaddition with alkynes, yielding substituted pyrazoles[2,4])

Physical Data: bp 40 °C/10 mmHg: *d* 1.159 g cm^{-3}.

Solubility: sol water, ethanol, diethyl ether, THF, and dichloromethane; insol hydrocarbon solvents.

Preparative Methods: diazoacetaldehyde is not commercially available, but can be prepared from β-*N*-methylanilinoacrolein and ***p-Toluenesulfonyl Azide***.[2] A simple and convenient preparation involves the treatment of ***Acetic Formic Anhydride*** with ***Diazomethane*** in diethyl ether.[5]

Handling, Storage, and Precautions: extreme caution must be exercised when handling diazoacetaldehyde. It is thermally unstable and will detonate violently if overheated (do not expose to temperatures above 50 °C), emitting toxic fumes of NO_x. At low temperatures, diazoacetaldehyde can be stored for several weeks without noticeable decomposition. This reagent should only be handled in a fume hood.

Cyclopropanation.

Diazoacetaldehyde can serve as a source of formylcarbene. This reactive carbenoid can readily add to an alkene, giving rise to a cyclopropyl aldehyde. A number of catalysts have been examined to effect this addition, of which ***Copper(II) Acetylacetonate*** proved to be the most promising. The generation of the formyl carbenoid with $Cu(acac)_2$ in tetramethylethylene is accompanied by rapid addition to the alkene (eq 1).[2]

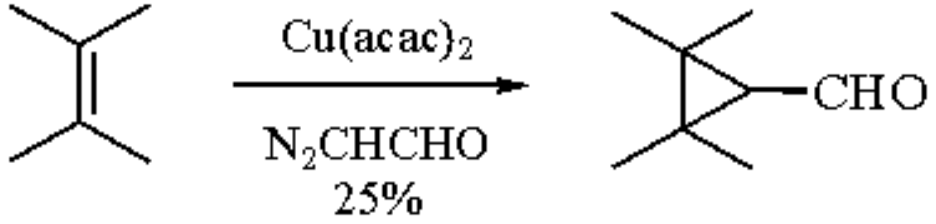

(1)

1,3-Dipolar Cycloaddition.

The uncatalyzed cycloaddition of diazoacetaldehyde with a suitable dipolarophile yields a substituted pyrazole.[4] Diazoacetaldehyde reacts with ***Dimethyl Acetylenedicarboxylate*** to give 3-formyl-4,5-dimethoxycarbonylpyrazole (eq 2).[2]

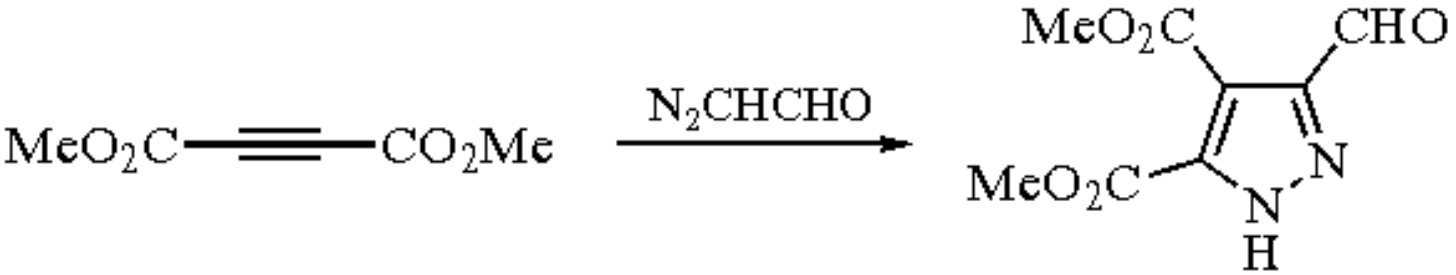

(2)

Condensation.

Addition of diazoacetaldehyde to an organoborane provides a convenient method for a two-carbon homologation of an alkene, via its organoborane derivative, to an aldehyde. This reaction possesses excellent regioselectivity with unsymmetrical alkenes. Terminal alkenes are successfully homologated to give exclusively primary alkyl substituents over secondary. The organoborane of cyclopentene is condensed with diazoacetaldehyde to give cyclopentylacetaldehyde (eq 3).[3] This reaction is conveniently carried out in a THF/water solvent to afford the aldehyde in excellent yield.

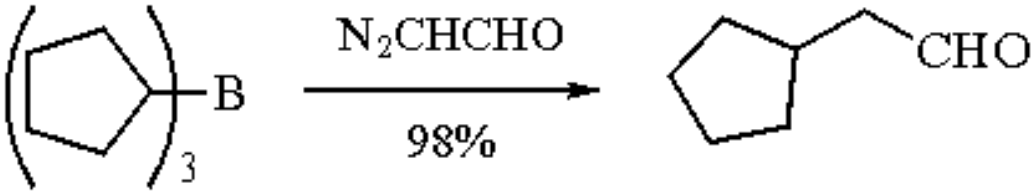

(3)

Related Reagents.

Diazoacetone; α-***Diazoacetophenone***; ***Ethyl Diazoacetate***; ***Methyl Diazoacetate***.

---

1. (a) *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978; Part 1 and Part 2.

(b) Regitz, M.; Maas, G. *Diazo Groups Properties and Synthesis*; Academic: New York, 1986.
2. Arnold, Z. *CC* **1967**, 299.
3. Hooz, J.; Morrison, G. F. *CJC* **1970**, *48*, 868.
4. For references regarding the formation of pyrazoles and pyrazolines with the dimethyl acetal of diazoacetaldehyde, see the following: (a) Abdallah, H.; Gree, R.; Carrie, R. *BSF(2)* **1985**, 794 (*CA* **1987**, *107*, 7111y). (b) Abdallah, H.; Gree, R.; Carrie, R. *CJC* **1985**, *63*, 3031 (*CA* **1986**, *104*, 5815v). (c) Abdallah, H.; Gree, R.; Carrie, R. *BSF(2)* **1984**, 338 (*CA* **1985**, *102*, 149 166r). (d) Abdallah, H.; Gree, R. *TL* **1980**, 2239 (*CA* **1980**, *93*, 204 529j).
5. Hooz, J.; Morrison, G. F. *OPP* **1971**, *3*, 227.

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Diazoacetone[1]

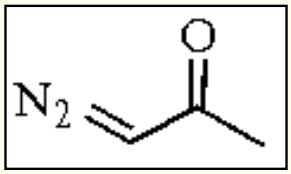

[2684-62-0] · $C_3H_4N_2O$ · Diazoacetone · (MW 84.09)

(cyclopropanation of alkenes,[2] furans,[3] and oxy alkenes;[4] condensation with carbonyls[5,6] and organoboranes;[7] 1,3-dipolar cycloaddition with acrylates[8] and alkynes,[9] yielding substituted pyrazolines and pyrazoles)

Physical Data: bp 49 °C/13 mmHg.

Solubility: sol diethyl ether, THF, DME, methanol, cyclohexane, benzene.

Preparative Methods: diazoacetone is not commercially available, but can be prepared from ***Acetyl Chloride*** and ***Diazomethane***.[10] An alternative method for preparation involves an alkaline acyl cleavage of 3-diazo-2,4-pentanedione.[11]

Handling, Storage, and Precautions: diazo ketones are known to be unstable at elevated temperatures (>50 °C) and should be handled in a fume hood. The health risks associated with diazoacetone have not been evaluated. At low temperatures diazoacetone can be stored without significant decomposition.

Cyclopropanation.

The metal-catalyzed decomposition of diazoacetone generates a reactive carbenoid species which readily adds to a variety of alkenes. This reaction can give rise to a cyclopropyl ketone in moderate yield or subsequently furnish a rearranged product. The catalyzed reaction between diazoacetone and a suitable alkene is often carried out neat or with cyclohexane as the solvent. The generation of the keto carbenoid with anhydrous ***Copper(II) Sulfate*** in cyclohexene is accompanied by rapid addition to the alkene (eq 1).[2] Diazoacetone addition to 1-ethoxycyclohexene is catalyzed efficiently with ***Copper Bronze*** at 90 °C for 2 h. Aqueous acid hydrolysis and ring opening yields a 1,4-diketone.[12] Addition of diazoacetone to furan, also catalyzed by copper bronze, furnishes a cross-conjugated dicarbonyl (eq 2).[3]

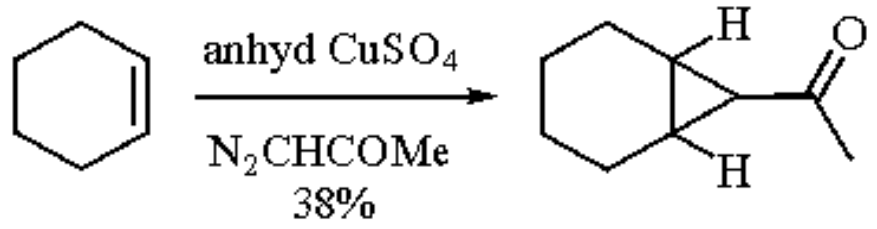

(1)

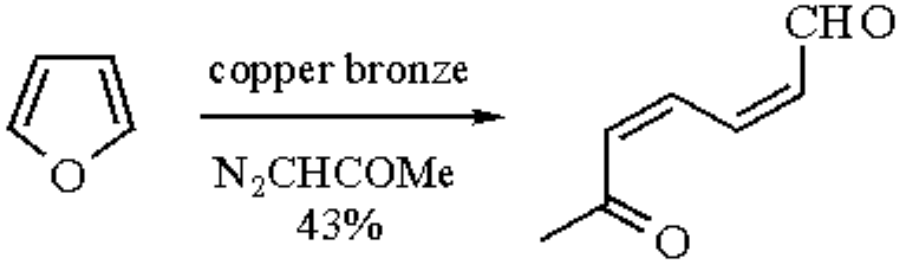

(2)

The catalyzed reaction of diazoacetone with the trimethylsilyl enol ether of cyclohexanone affords a regiospecific silyl enol ether formed through a silatropic retro-aldol (eq 3).[13] Cyclopropanation of a methyl enol ether in the presence of copper bronze yields a β-methoxycyclopropyl ketone.[14] Subsequent acid hydrolysis yields a 1,4-keto aldehyde (eq 4). The catalytic reaction between diazoacetone and 1-methoxy-1,3-butadiene provides only mild regioselectivity, with the predominant formation of the nonoxygenated cyclopropane.[15]

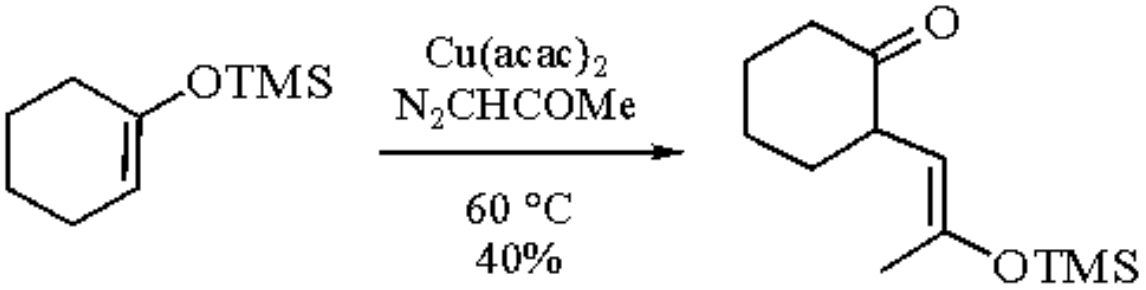

(3)

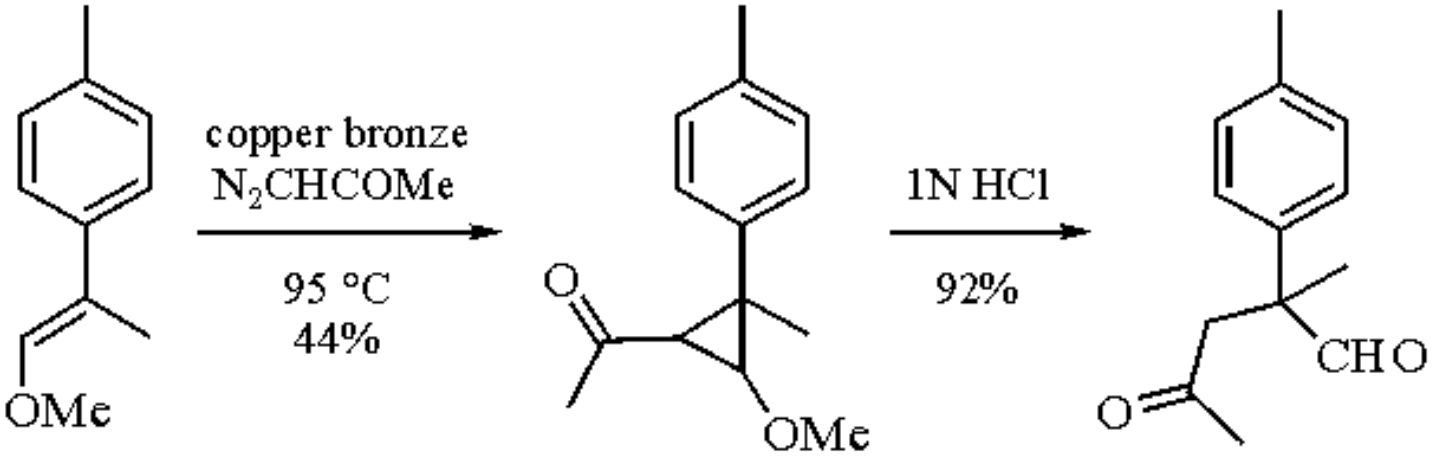

(4)

In addition to alkenes, diazoacetone can undergo catalytic insertion into a number of carbenoid acceptors. A substituted dihydrofuran is synthesized by the ***Copper(II) Acetylacetonate***-catalyzed insertion of diazoacetone into a ketene dimethyl acetal.[16] A benzyl ketone is obtained by the $Rh_2(O_2CCF_3)_4$-catalyzed addition of diazoacetone to benzene.[17] Cyclopropenes are formed through either catalytic or photolytic insertion into alkynes.[18,19]

Condensation.

Treatment of diazoacetone with ***Silver(I) Oxide*** in diethyl ether generates a diazomethyl carbon nucleophile that adds to most electrophiles in moderate to poor yields.[20] An improved result is seen with the condensation between diazoacetone and a ketone or aldehyde, conveniently effected under basic conditions to yield an α-diazo-β-hydroxycarbonyl.[5] 1,3-Diketones can be readily formed by the addition of 1-diazo-1-lithioacetone to an aldehyde followed by a catalytic transformation with $Rh_2(OAc)_4$ (eq 5).[21] This condensation process is quite efficient with excellent yields obtained for a variety of aldehydes. 1-Diazo-1-lithioacetone also reacts with lactones and thiolactones to give the corresponding diazo alcohol or diazo thiol. The respective 2-substituted 3-oxepanone or 2-substituted 3-thiopanone is formed upon heating in benzene with a catalytic amount of $Rh_2(OAc)_4$ (eq 6).[6,22]

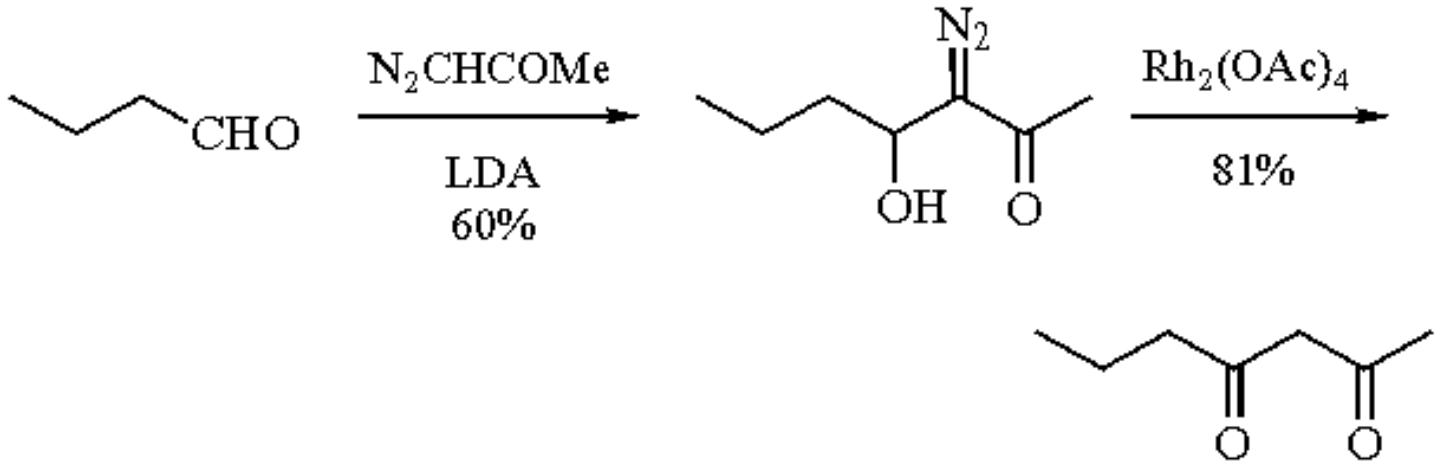

(5)

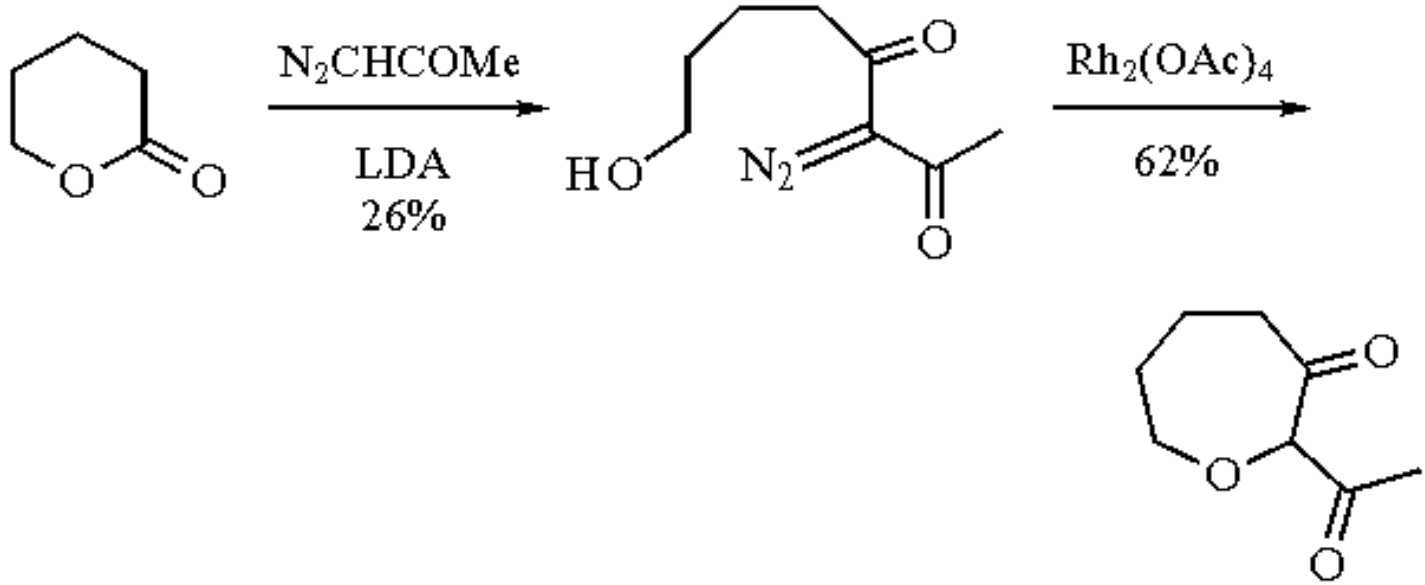

(6)

The addition of diazoacetone to an organoborane provides a convenient method for a three-carbon homologation of an alkene, via an organoborane, to a ketone or regiospecific enol borane.[7,23] This enol borane can be mono α-alkylated with certain electrophiles in the presence of lithium dimethylaminoethoxide (eq 7). Di- and polyalkylation products are not observed, nor is alkylation of the methyl terminus.

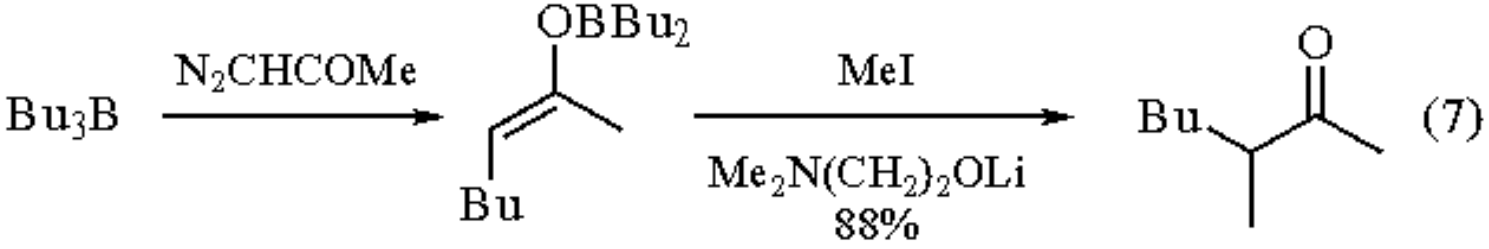

An α-alkoxy ketone or an α-thioketone is prepared by the insertion of the keto carbenoid of diazoacetone into the O-H or S-H bond of an alcohol or thiol.[24,25]

1,3-Dipolar Cycloaddition.

Diazoacetone can undergo an uncatalyzed 1,3-dipolar cycloaddition with a variety of dipolarophiles to yield pyrazoles or pyrazolines.[8,9,26] Reaction with an α-substituted acrylate under mild conditions yields a 3,5,5-trisubstituted pyrazoline in good yield (eq 8).[27]

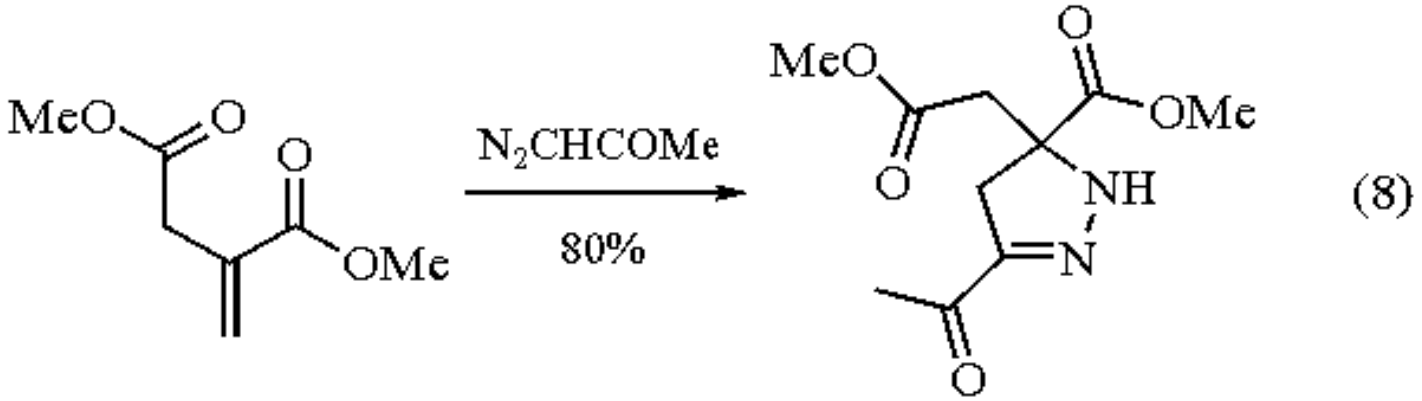

Related Reagents.

Diazoacetaldehyde; α-***Diazoacetophenone***; ***Ethyl Diazoacetate***; ***Methyl Diazoacetate***.

---

1. (a) Adams, J.; Spero, D. M. *T* **1991**, *47*, 1765. (b) *Carbene Chemistry*; Kirmse, W., Ed.; Academic: New York, 1971; Vol. 1. (c) *The Chemistry of Diazonium and Diazo Groups*; Patai, S. Ed.; Wiley: New York, 1978; Part 1 and Part 2. (d) Regitz, M.; Maas, G. *Diazo Groups Properties and Synthesis*; Academic: New York, 1986.
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13. Coates, R. M.; Sandefur, L. O.; Smillie, R. D. *JACS* **1975**, *97*, 1619.
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15. Wenkert, E.; Goodwin, T. E.; Ranu, B. C. *JOC* **1977**, *42*, 2137.
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17. McKervey, A. M.; Russell, N. D.; Twohig, F. M. *JCS(C)* **1985**, 491.
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19. Nefedov, O. M.; Dolgii, I. E.; Baidzhigitova; E. A. *IZV* **1975**, 2842 (*CA* **1976**, *84*, 121 933z).
20. Schollkopf, U.; Rieber, N. *CB* **1969**, *102*, 488 (*CA* **1969**, *70*, 86 980z).
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22. Moody, T. J.; Taylor, R. J. *T* **1990**, *46*, 6501.
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α-Diazoacetophenone[1]

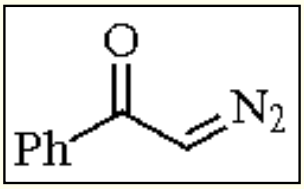

[3282-32-4] · $C_8H_6N_2O$ · α-Diazoacetophenone · (MW 146.16)

(precursor to carbenes and carbenoids;[2] reagent for preparation of sulfonium,[3] oxonium,[4] and pyridinium[5] ylides; 1,3 dipole for heterocycle synthesis;[6] reagent for Lewis acid or transition metal-mediated insertion reactions;[7] reagent for cyclopropanation of alkenes[8] and for aromatic annulation[9])

Physical Data: pale yellow rods, mp 49-50 °C.

Solubility: sol ether, THF; slightly sol pentane.

Form Supplied in: not commercially available.

Preparative Methods: an improved method of synthesis of diazo ketones has been recently published, via acylation of the lithium enolate of the ketone with ***2,2,2-Trifluoroethyl Trifluoroacetate*** and subsequent reaction with ***Methanesulfonyl Azide***.[10] Alternatively, acylation of diazomethane with aroyl chlorides in the presence of triethylamine provides a general method for the synthesis of aromatic diazo ketones.[11]

Handling, Storage, and Precautions: diazoacetophenone is a skin irritant; therefore direct contact should be avoided. Diazoacetophenone has shown microbial mutagenicity.

Ylide Formation.

Diazoacetophenone (and other diazo ketones) react under copper catalysis with sulfides to form sulfonium ylides, which may be trapped with electron-deficient alkenes for cyclopropanation (eq 1).[3a] Sulfonium ylides are also available by acid-catalyzed reaction with sulfides, followed by base treatment.[3b] Applied to cyclic sulfides, the ylides so formed can undergo [2,3]-rearrangement, allowing for ring expansion (eq 2).[3c]

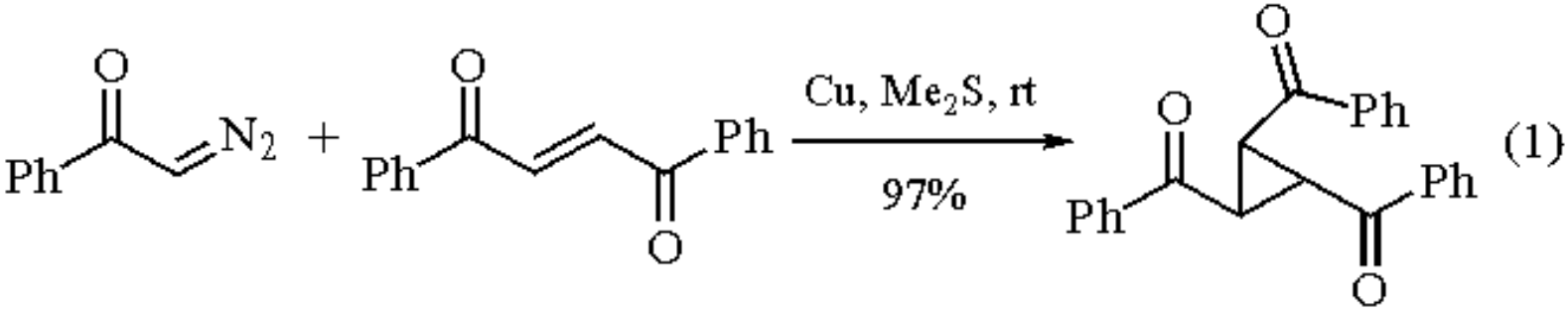

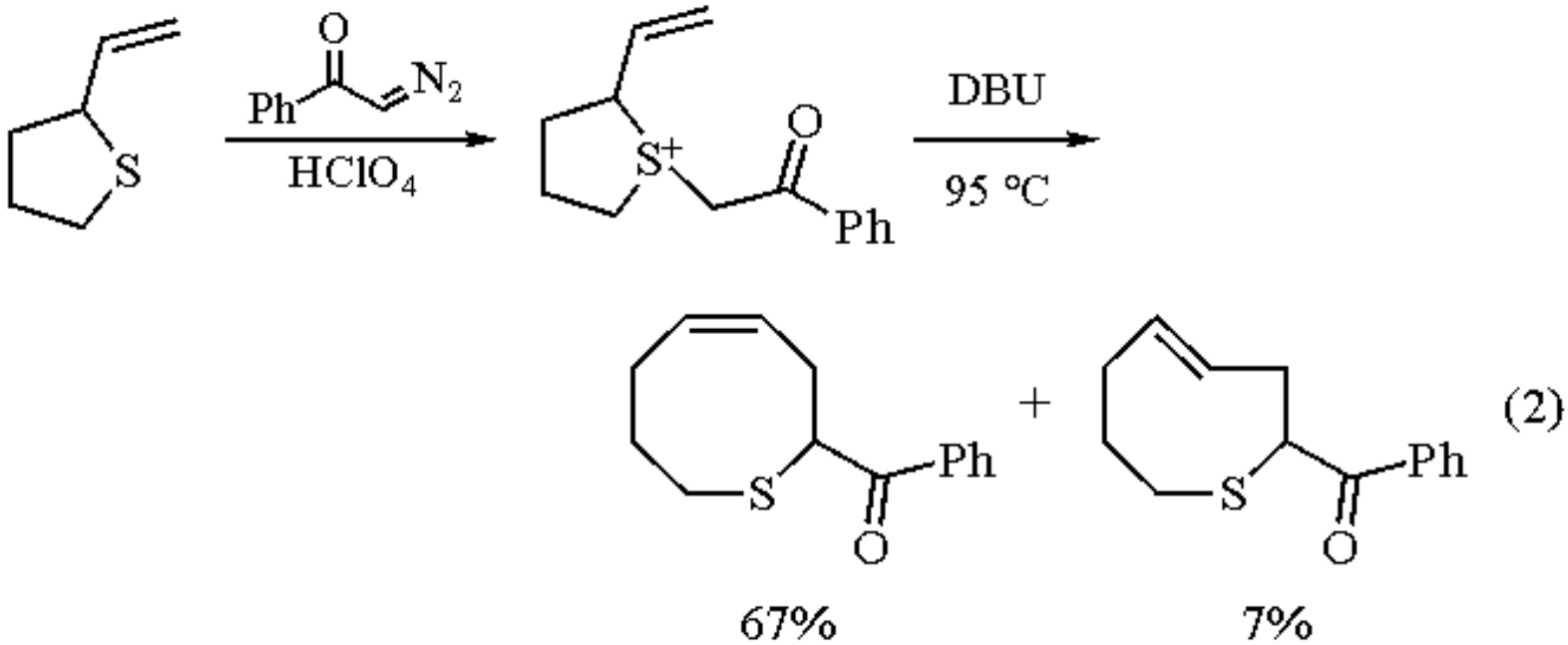

In a similar fashion, oxonium ylides, formed by rhodium(II)-catalyzed decomposition of diazoacetophenone in the presence of methyl allyl and methyl propargyl ethers, undergo [2,3]-rearrangement to provide methoxy keto alkenes (eq 3)[4a] and allenes (eq 4).[4b] Rhodium(II) perfluorobutyrate is often the preferred catalyst to minimize competing cyclopropanation.

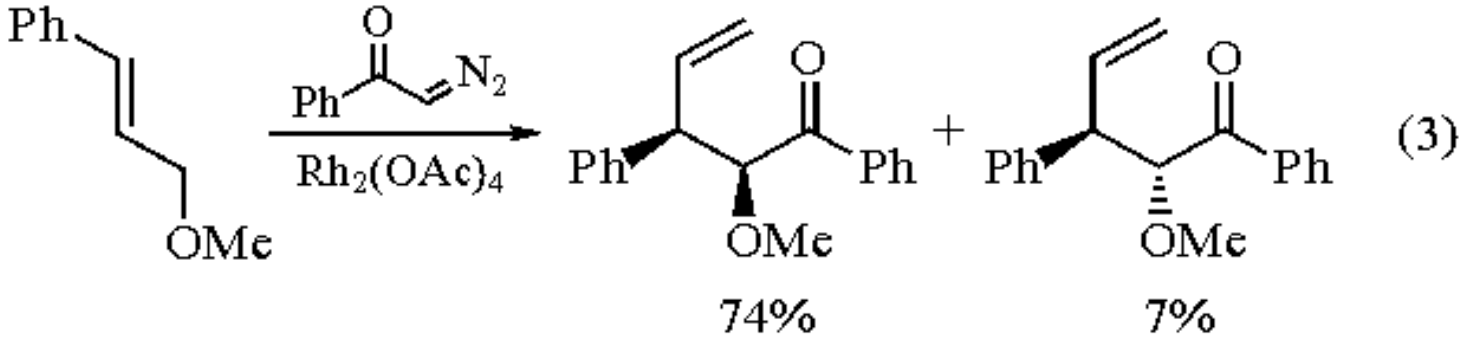

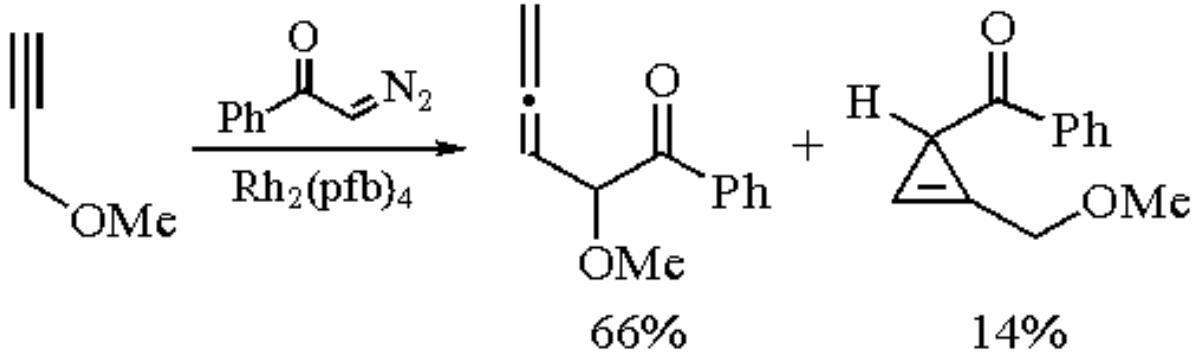

(4)

Decomposition of diazoacetophenone in the presence of 2-(methylthio)pyridine affords the pyridinium ylide, which undergoes 1,3-dipolar cycloadditions with a variety of dipolarophiles (eq 5).[5]

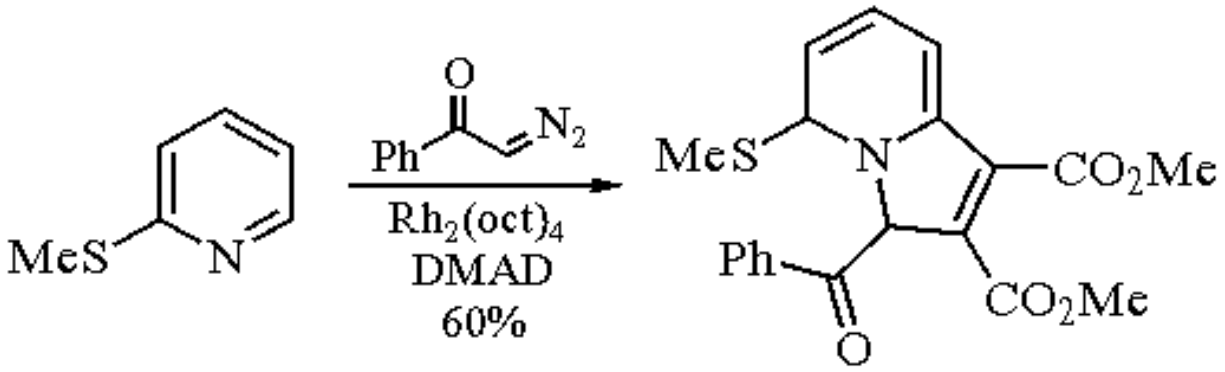

(5)

Heterocycle Formation.

Diazoacetophenone reacts with nitriles under Lewis acid (eq 6) or transition metal (eq 7) catalysis to afford oxazoles.[6a,b]

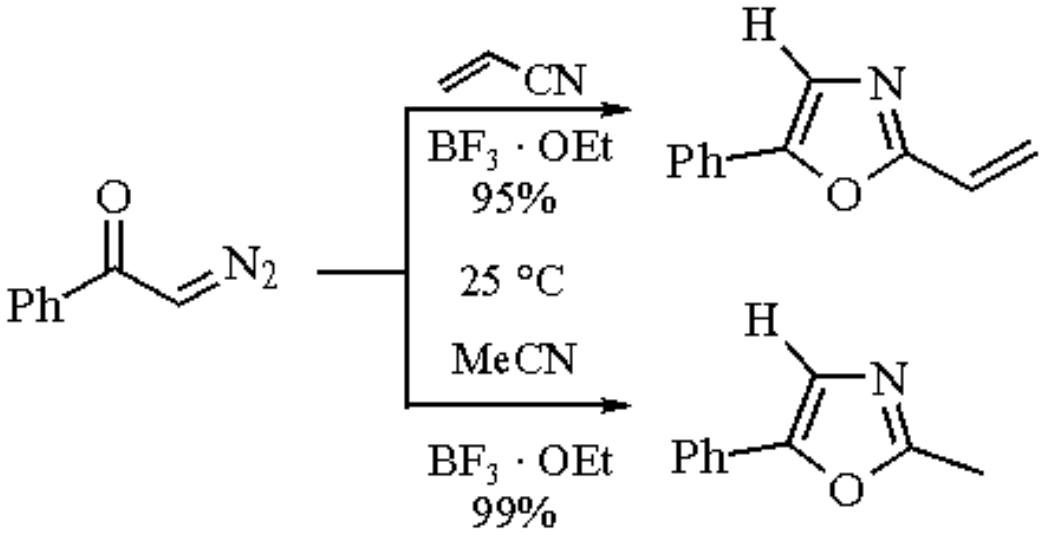

(6)

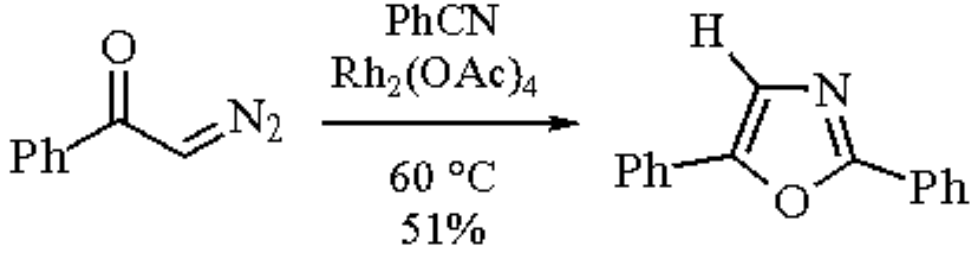

(7)

Alternatively, diazoacetophenone reacts with unsaturated nitriles and esters under pyridine catalysis to yield pyrazolines. The nitrile-derived pyrazolines undergo alkoxide-induced elimination of HCN to afford the 3-benzoylpyrazoles (eq 8).[6c] A variety of activated alkenes, including enamines,[6d] and vinyltriphenylphosphonium salts,[6e] can be readily converted to the corresponding pyrazolines and pyrazoles with diazoacetophenone (eq 9). Additionally, treatment of formamidines with diazoacetophenone affords the 4-benzoyl-1,2,3-triazole (eq 10).[12]

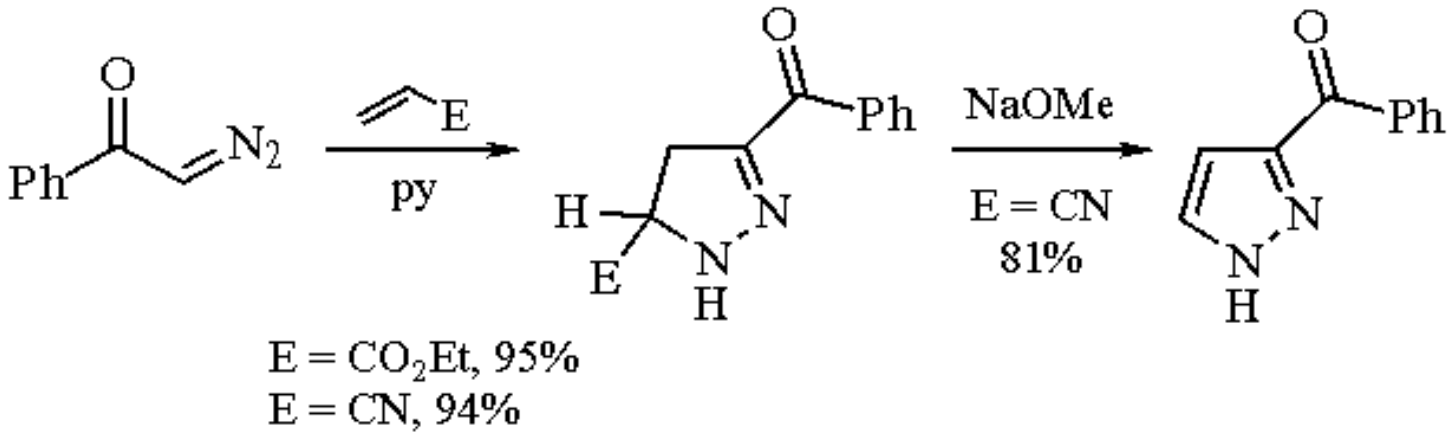

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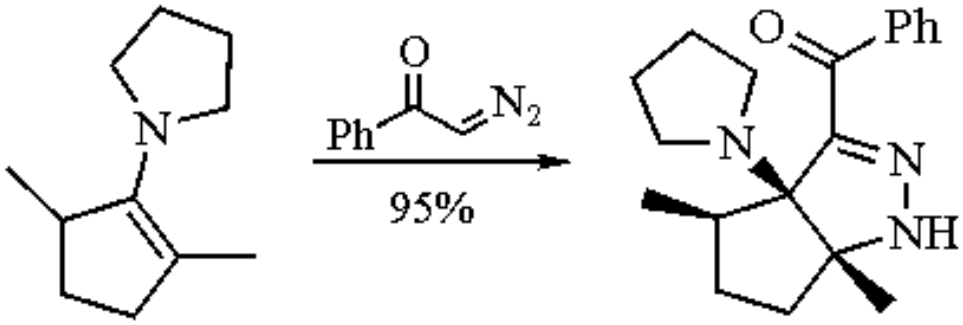

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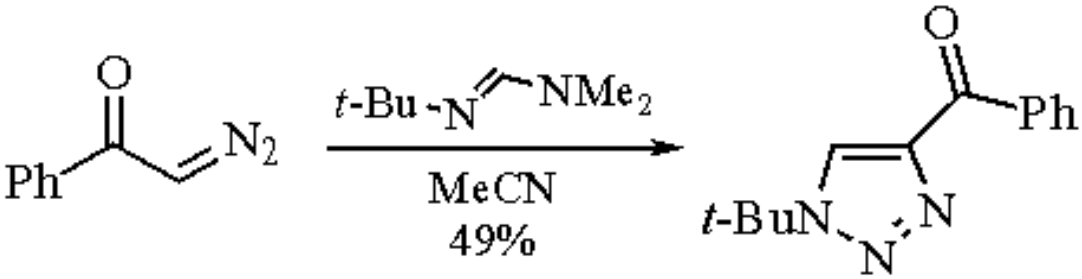

(10)

Insertion Reactions.

Diazoacetophenone (and other diazo ketones) reacts with a variety of compounds containing acidic X-H bonds under

Lewis acid and transition metal catalysis. Included are alcohols,[7a] thiols,[7b] and trialkylsilanes (eq 11).[7c] The latter forms a general synthesis of α-silylacetophenone (and α-silyl ketones). In similar fashion, diazoacetophenone reacts with trialkylboranes affording, selectively, the (*E*)-enol boronates (eq 12).[7d]

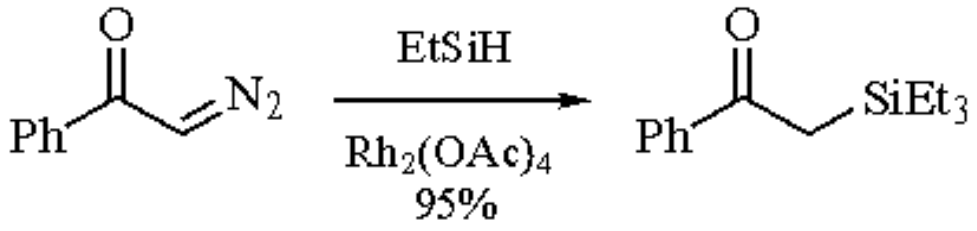

(11)

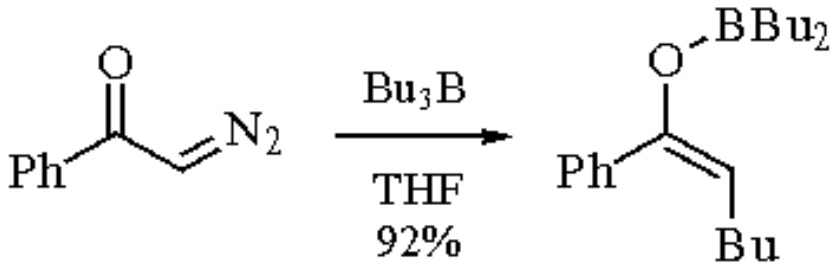

(12)

Cyclopropanation.

Diazoacetophenone is effective in transition metal-mediated cyclopropanation of a variety of alkenic compounds. For electron-deficient alkenes, molybdenum catalysts favor cyclopropane formation over competing pyrazoline formation (eq 13).[8a] Reaction with vinylboronic acid esters follows in similar fashion, with ***Palladium(II) Acetate*** as the catalyst of choice for the formation of benzoylcyclopropylboronic acid esters (eq 14).[8b]

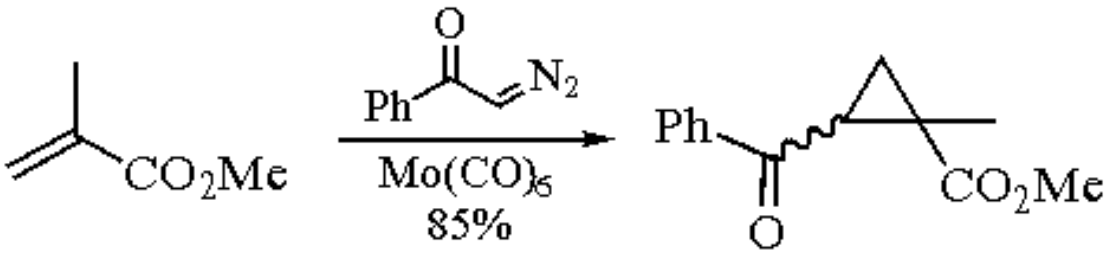

(13)

$(E):(Z) = 1.9$

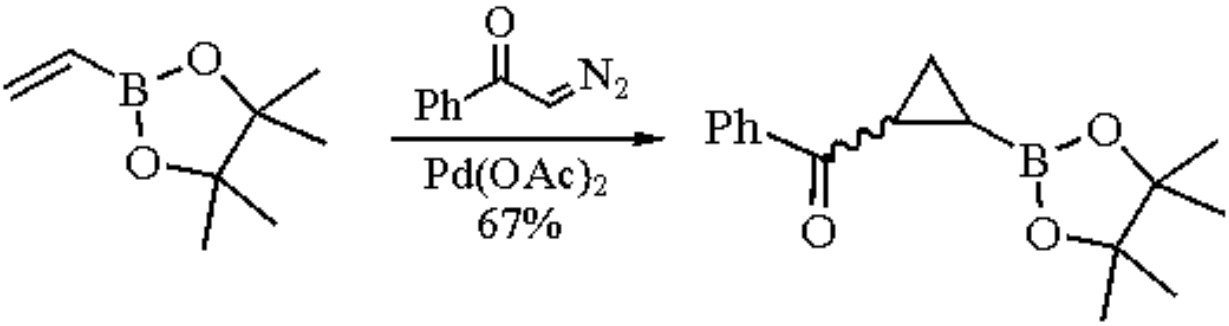

(14)

$(E):(Z) = 2.0$

Aromatic Annulation.

Diazo ketones have been utilized in a novel aromatic annulation protocol. The use of diazoacetophenone in this fashion allows for the conversion of alkynes into naphthol derivatives (eq 15).[9]

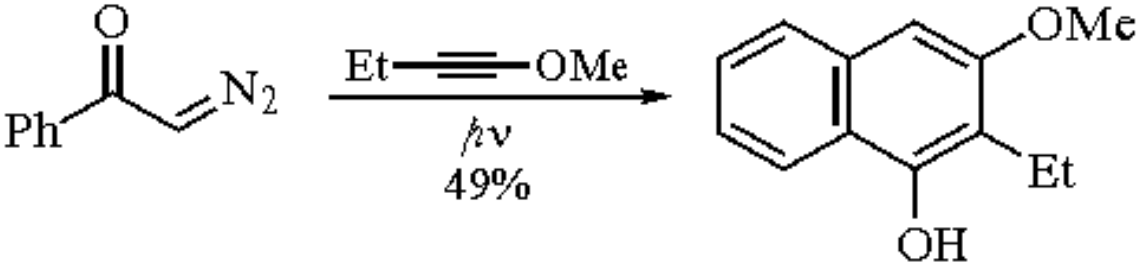

(15)

Related Reagents.

Diazoacetaldehyde; ***Diazoacetone***; ***Ethyl Diazoacetate***; ***Methyl Diazoacetate***.

---

1. Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic: Orlando, 1986.
2. Doyle, M. P.; Devia, A. H.; Bassett, K. E.; Terpstra, J. W.; Mahapatro, S. N. *JOC* **1987**, *52*, 1619.
3. (a) Quintana, J.; Torres, M.; Serratosa, F. *T* **1973**, *29*, 2065. (b) Flowers, W. T.; Holt, G.; Hope, M. A. *JCS(P1)* **1974**, 1116. (c) Vedejs, E.; Hagen, J. P.; Roach, B. L.; Spear, K. L. *JOC* **1978**, *43*, 1185.
4. (a) Doyle, M. P.; Bagheri, V.; Harn, N. K. *TL* **1988**, *29*, 5119. (b) Doyle, M. P.; Bagheri, V.; Claxton, E. E. *CC* **1990**, 46.
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6. (a) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliot, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *JOC* **1980**, *45*, 3657. (b) Ibata, T.; Fukushima, K. *CL* **1992**, 2197. (c) Doyle, M. P.; Colsman, M. R.; Dorow, R. L. *JHC* **1983**, *20*, 943. (d) Huisgen, R.; Reissig, H-U.; Huber, H.; Voss, S. *TL* **1979**, 2987. (e) Schweizer, E. E.; Labaw, C. S. *JOC* **1973**, *36*, 3069.
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8. (a) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *JOC* **1982**, *47*, 4059. (b) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *S* **1991**, 605.
9. Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *JACS* **1990**, *112*, 3093.
10. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *JOC* **1990**, *55*, 1959.
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5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione

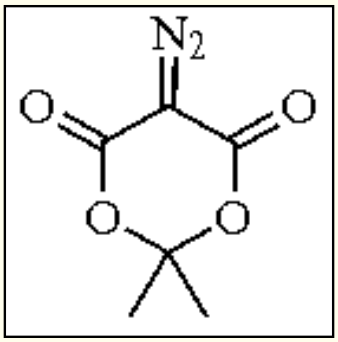

[7270-63-5] · $C_6H_6N_2O_4$ · 5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione · (MW 170.14)

(reagent for the synthesis of α-oxygenated ketenes for [2 + 2] cycloadditions with alkenes[2])

Alternate Name: diazo Meldrum's acid.

Physical Data: solid with a melting point of 90-91 °C.

Solubility: sol ether, dichloromethane, and acetonitrile.

Preparative Methods: most commonly by diazo transfer to Meldrum's acid. A number of procedures involving the use of sulfonyl azide reagents have been reported.[1] Typical procedures involve the addition of the sulfonyl azide to a solution of Meldrum's acid containing a tertiary amine base. Aqueous workup followed by chromatography on silica gel provide the diazo compound in yields ranging from 40 to 76%. A modification using KF on alumina is reported to provide a 90% yield of product.[1a] Diazo compounds are potentially explosive as are certain sulfonyl azides, such as tosyl azide. For this reason, extreme care must be observed in the synthesis and use of this compound, with all operations being conducted behind a blast shield in a fume hood.

Handling, Storage, and Precautions: in addition to the previously mentioned explosion hazard which this reagent presents, there are health related hazards that must also be considered. Diazo compounds, as a class, are toxic and irritating and can be sensitizers. They must be used in a well-ventilated fume hood and not come in contact with skin. For a description of the hazards associated with this class of compounds, see the handling and storage precautions listed for ***Diazomethane***.

Cycloadditions.

Diazo Meldrum's acid was at one time used for the synthesis of spiro activated cyclopropanes;[2] however, after the original report, it was found that the adduct formed was not the expected cyclopropane, but a cyclobutane which was

the result of ketene-alkene cycloaddition.[3] Thus photolysis at 254 nm promotes extrusion of N_2 to provide a carbene which undergoes a Wolff rearrangement to provide an α-alkoxy ketene. This then undergoes a [2 + 2] cycloaddition to provide the cyclobutane (eq 1). This reaction appears to work with a variety of alkenes including hindered alkenes such 1,3,3-trimethylcyclohexene (eq 2).

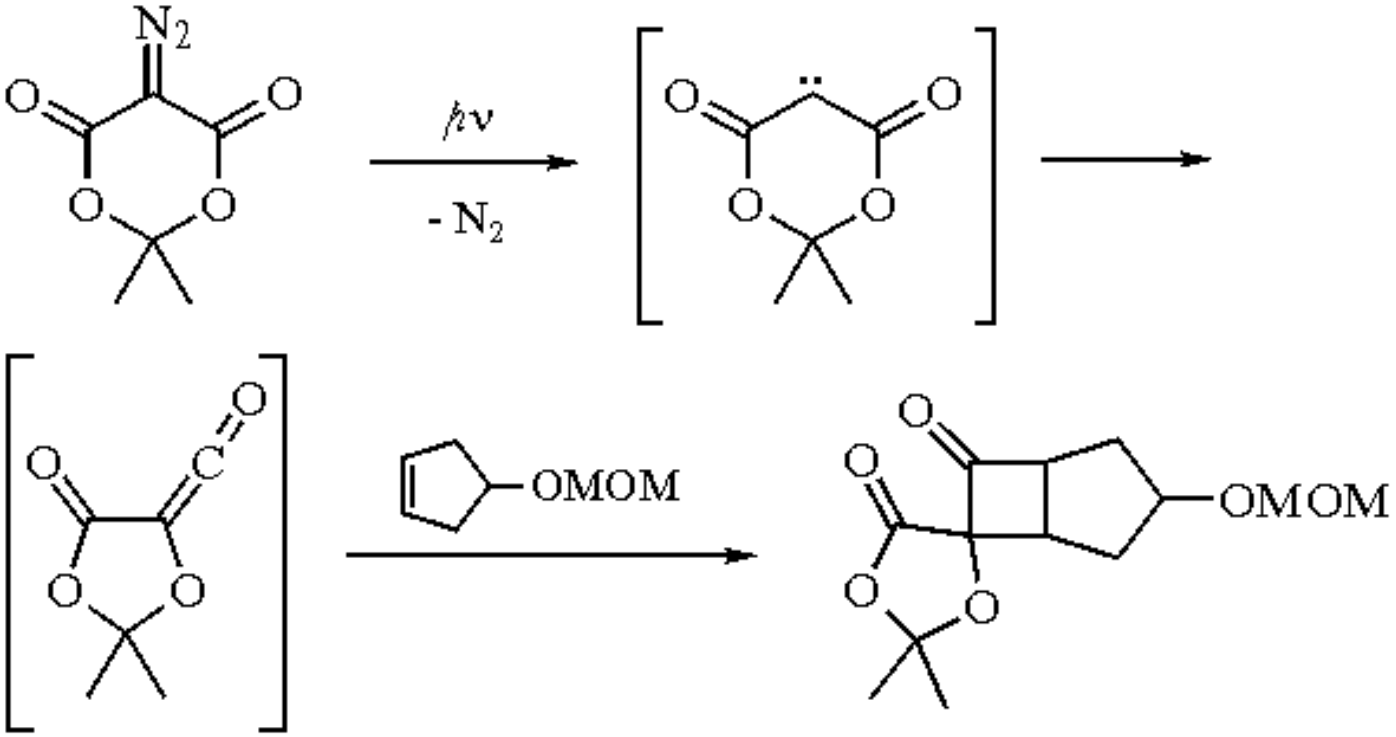

(1)

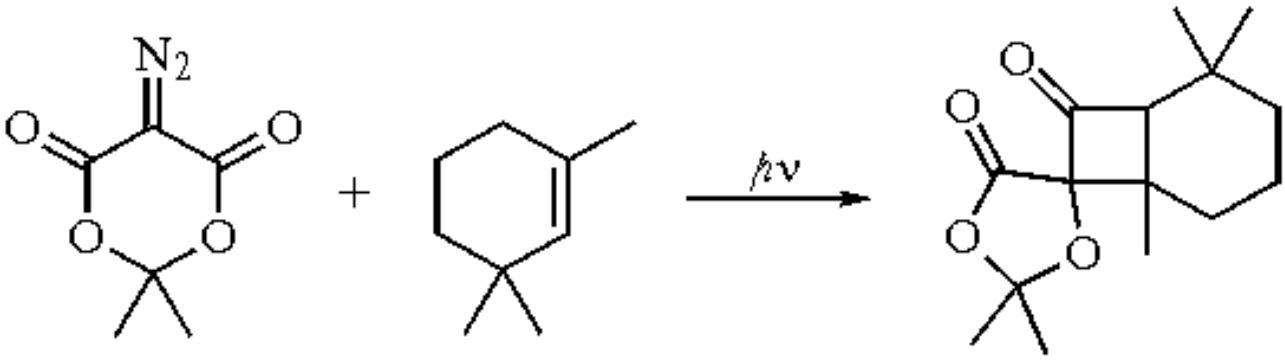

(2)

Related Reagents.

Dimethyl Diazomalonate; ***Ethyl Diazoacetate***; ***Methyl Diazoacetate***.

---

1. (a) Alloum, A. B.; Villemin, D. *SC* **1989**, *19*, 2567. (b) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *SC* **1987**, *17*, 1709. (c) Rao, Y. K.; Nagarajan, M. *IJC(B)* **1986**, *25B*, 735. (d) Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *SC* **1981**, *11*, 947. (e) Regitz, M.; Stadler, D. *LA* **1965**, *687*, 214. (f) Eistert, B.; Geiss, F. *CB* **1966**, *99*, 3128.
2. Livinghouse, T.; Stevens, R. V. *JACS* **1978**, *100*, 6479; Livinghouse, T.; Stevens, R. V. *CC* **1978**, 754; Stevens, R. V. *PAC* **1979**, *51*, 1317.

Diazomethane[1]

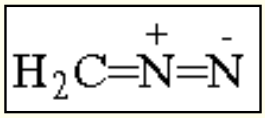

[334-88-3] · CH_2N_2 · Diazomethane · (MW 42.04)

(methylating agent for various functional groups including carboxylic acids, alcohols, phenols, and amides; reagent for the synthesis of α-diazo ketones from acid chlorides, and the cyclopropanation of alkenes[1])

Physical Data: mp -145 °C; bp -23 °C.

Solubility: diazomethane is most often used as prepared in ether, or in ether containing a small amount of ethanol. It is less frequently prepared and used in other solvents such as dichloromethane.

Analysis of Reagent Purity: diazomethane is titrated[2] by adding a known quantity of benzoic acid to an aliquot of the solution such that the solution is colorless and excess benzoic acid remains. Water is then added, and the amount of benzoic acid remaining is back-titrated with NaOH solution. The difference between the amount of acid added and the amount remaining reveals the amount of active diazomethane present in the aliquot.

Preparative Methods: diazomethane is usually prepared by the decomposition of various derivatives of *N*-methyl-*N*-nitrosoamines. Numerous methods of preparation have been described,[3] but the most common and most frequently employed are those which utilize ***N-Methyl-N-nitroso-p-toluenesulfonamide*** (Diazald®; **1**),[4] ***1-Methyl-3-nitro-1-nitrosoguanidine*** (MNNG, **2**),[5] or *N*-methyl-*N*-nitrosourea (**3**).[2]

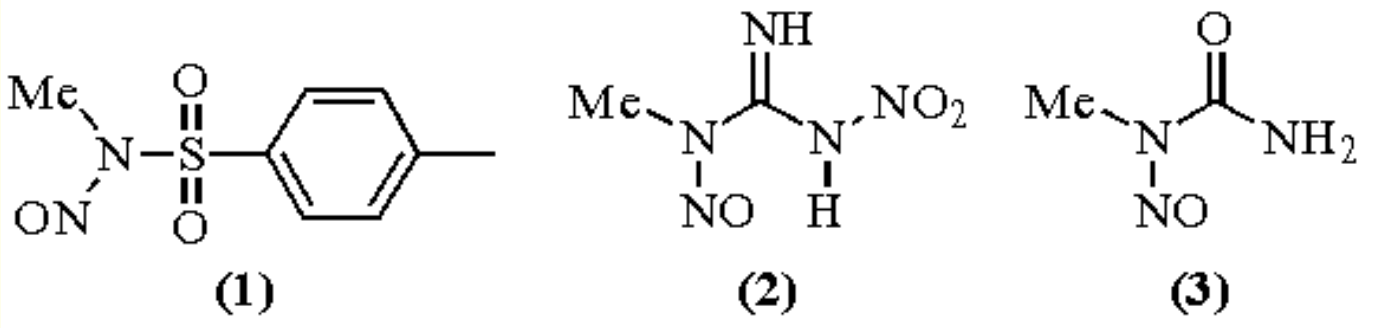

The various reagents each have their advantages and disadvantages, as discussed below. The original procedure[6] for the synthesis of diazomethane involved the use of *N*-methyl-*N*-nitrosourea, and similar procedures are still in use today. An advantage of using this reagent is that solutions of diazomethane can be prepared without distillation,[7] thus avoiding the most dangerous operation in other preparations of diazomethane. For small scale preparations (1 mmol or less) which do not contain any alcohol, a kit is available utilizing MNNG which produces distilled diazomethane in a closed environment. Furthermore, MNNG is a stable compound and has a shelf life of many years. For larger scale preparations, kits are

available for the synthesis of up to 300 mmol of diazomethane using Diazald as the precursor. The shelf life of Diazald (about 1-2 years), however, is shorter than that of MNNG. Furthermore, the common procedure using Diazald produces an ethereal solution of diazomethane which contains ethanol; however, it can be modified to produce an alcohol-free solution. Typical preparations of diazomethane involve the slow addition of base to a heterogeneous aqueous ether mixture containing the precursor. The precursor reacts with the base to liberate diazomethane which partitions into the ether layer and is concomitantly distilled with the ether to provide an ethereal solution of diazomethane. Due to the potentially explosive nature of diazomethane, the chemist is advised to carefully follow the exact procedure given for a particular preparation. Furthermore, since diazomethane has been reported to explode upon contact with ground glass, apparatus which do not contain ground glass should be used. All of the kits previously mentioned avoid the use of ground glass.

Handling, Storage, and Precautions: diazomethane as well as the precursors for its synthesis can present several safety hazards, and must be used with great care.[8] The reagent itself is highly toxic and irritating. It is a sensitizer, and long term exposure can lead to symptoms similar to asthma. It can also detonate unexpectedly, especially when in contact with rough surfaces, or on crystallization. It is therefore essential that any glassware used in handling diazomethane be fire polished and not contain any scratches or ground glass joints. Furthermore, contact with certain metal ions can also cause explosions. Therefore metal salts such as calcium chloride, sodium sulfate, or magnesium sulfate must not be used to dry solutions of the reagent. The recommended drying agent is potassium hydroxide. Strong light is also known to initiate detonation. The reagent is usually generated immediately prior to use and is not stored for extended periods of time. Of course, the reagent must be prepared and used in a well-ventilated hood, preferably behind a blast shield. The precursors used to generate diazomethane are irritants and in some cases mutagens and suspected carcinogens, and care should be exercised in their handling as well.

Methylation of Heteroatoms.

The most widely used feature of the chemistry of diazomethane is the methylation of carboxylic acids. Carboxylic acids are good substrates for reaction with diazomethane because the acid is capable of protonating the diazomethane on carbon to form a diazonium carboxylate. The carboxylate can then attack the diazonium salt in what is most likely an S_N2 reaction to provide the ester. Species which are not acidic enough to protonate diazomethane, such as alcohols, require an additional catalyst, such as ***Boron Trifluoride Etherate***, to increase their acidity and facilitate the reaction. The methylation reaction proceeds under mild conditions and is highly reliable and very selective for carboxylic acids. A typical procedure is to add a yellow solution of diazomethane to the carboxylic acid in portions. When the yellow color persists and no more gas is evolved, the reaction is deemed complete. Excess reagent can be destroyed by the addition of a few drops of acetic acid and the entire solution concentrated to provide the methyl ester.

Esterification of Carboxylic Acids and Other Acidic Functional Groups.

A variety of functional groups will tolerate the esterification of acids with diazomethane. Thus α,β-unsaturated carboxylic acids and alcohols survive the reaction (eq 1),[9] as do ketones (eq 2),[10] isolated alkenes (eq 3),[11] and amines (eq 4).[12]

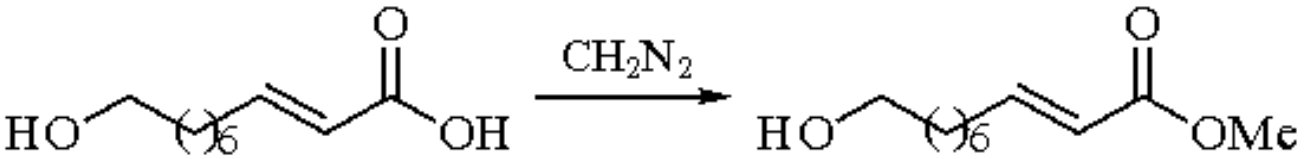

(1)

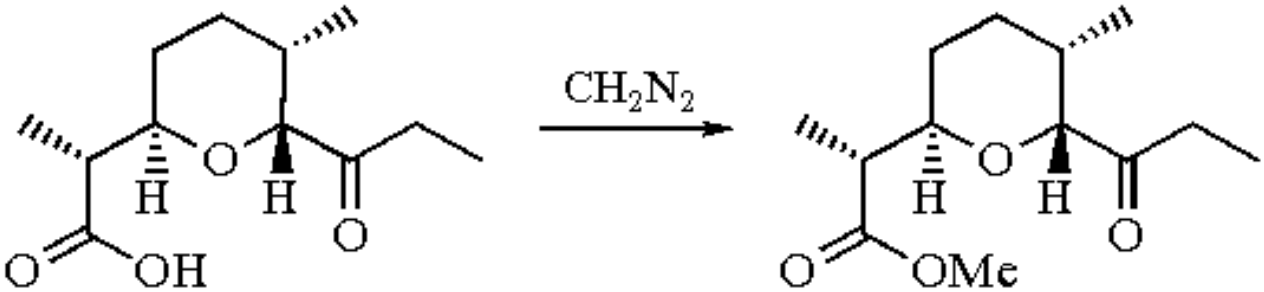

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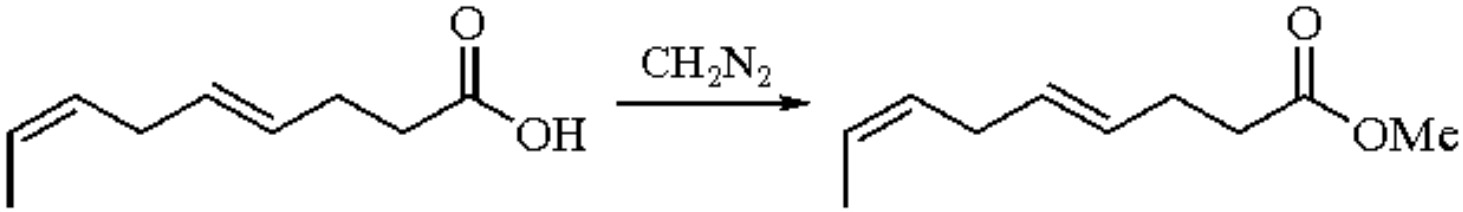

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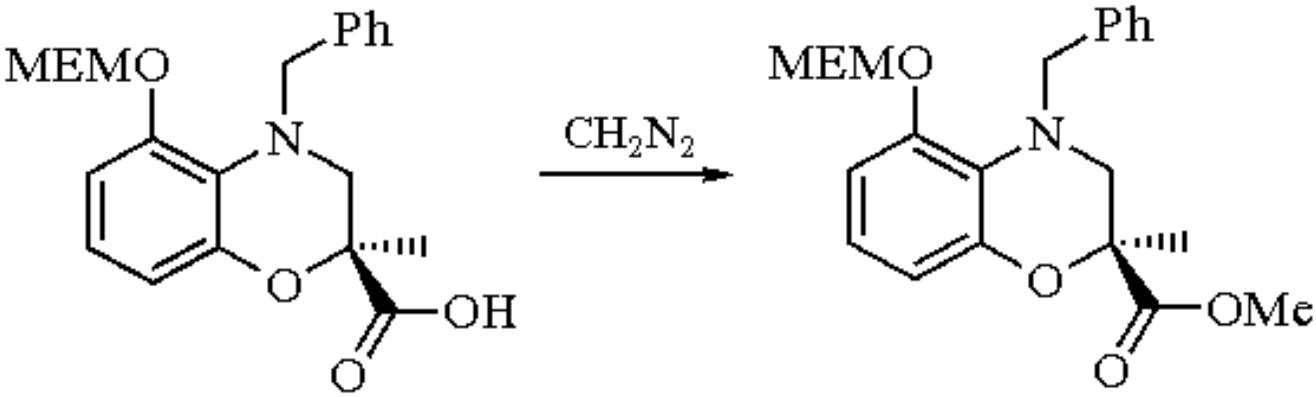

(4)

Other acidic functional groups will also undergo reaction with diazomethane. Thus phosphonic acids (eq 5)[13] and phenols (eq 6)[14] are methylated in high yields, as are hydroxytropolones (eq 7)[15] and vinylogous carboxylic acids (eq 8).[16] The origin of the selectivity in eq 6 is due to the greater acidity of the A-ring phenol.

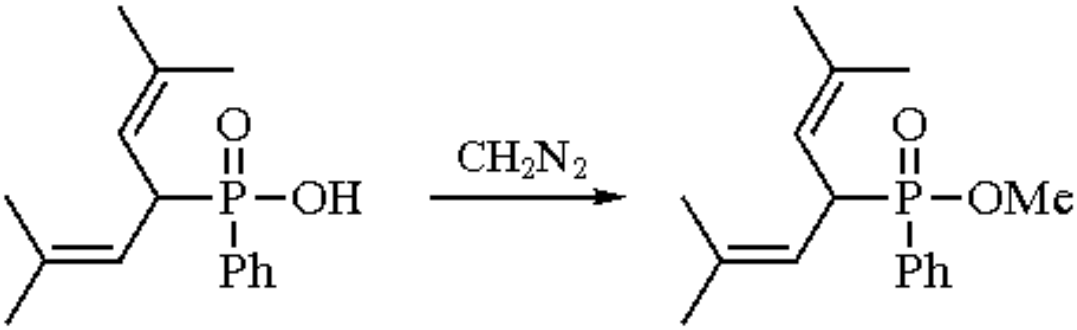

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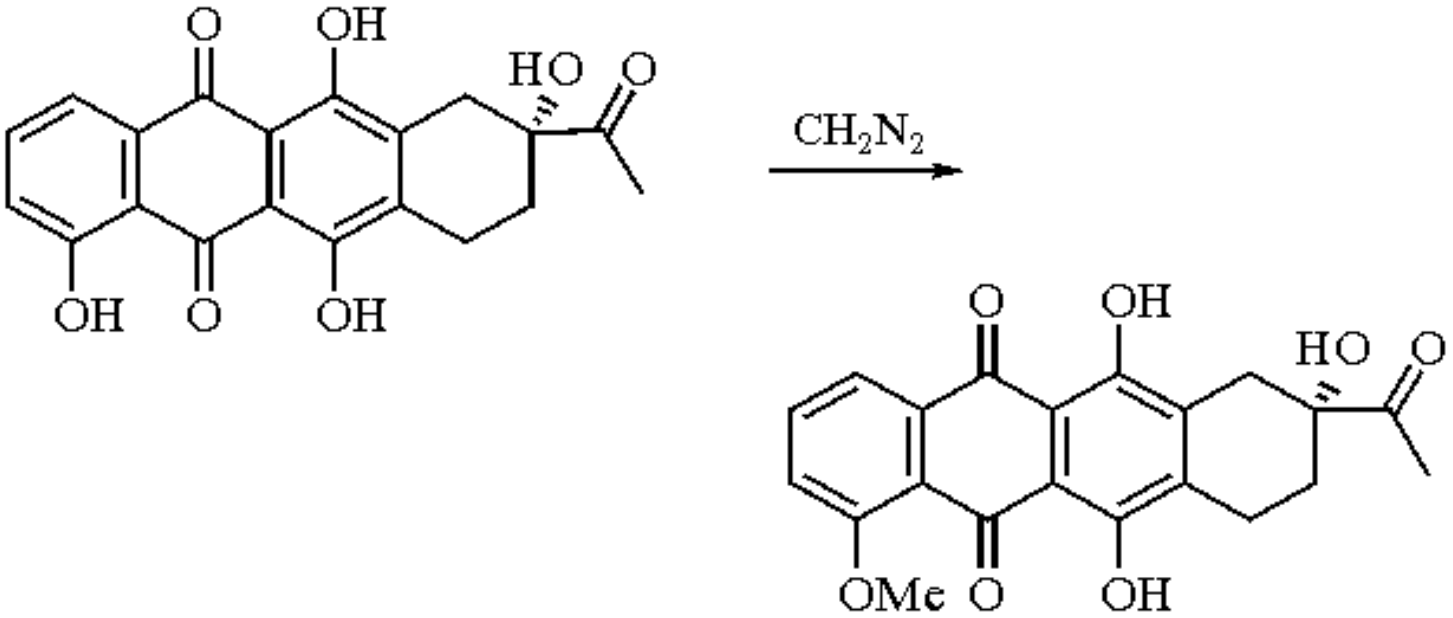

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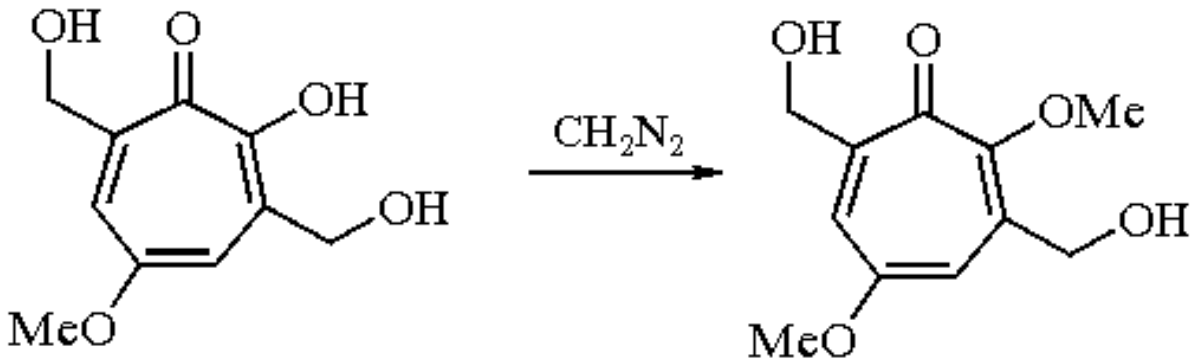

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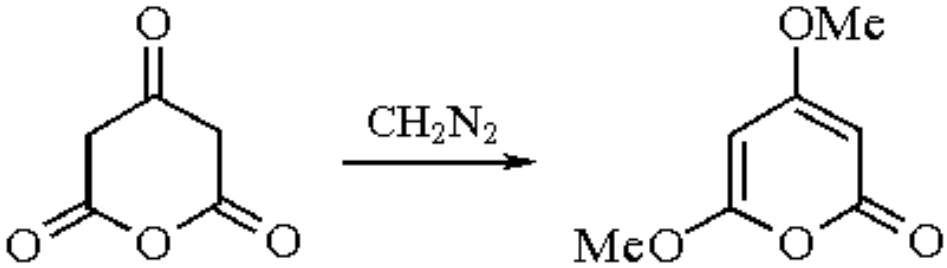

(8)

Selective monomethylation of dicarboxylic acids has been reported using ***Alumina*** as an additive (eq 9).[17] It is thought that one of the two carboxylic acid groups is bound to the surface of the alumina and is therefore not available for reaction. Carboxylic acids that are engaged as lactols will also undergo methylation with diazomethane to provide the methyl ester and aldehyde (eq 10).[18]

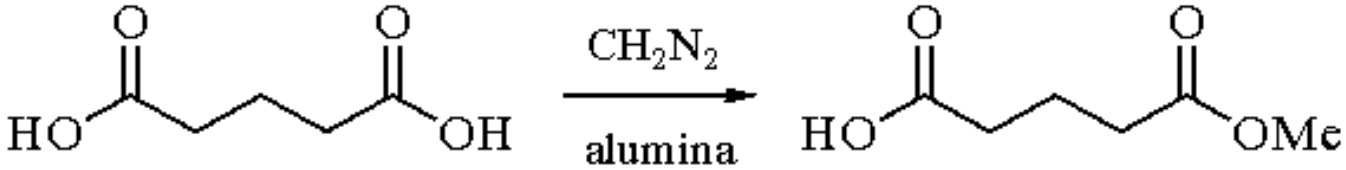

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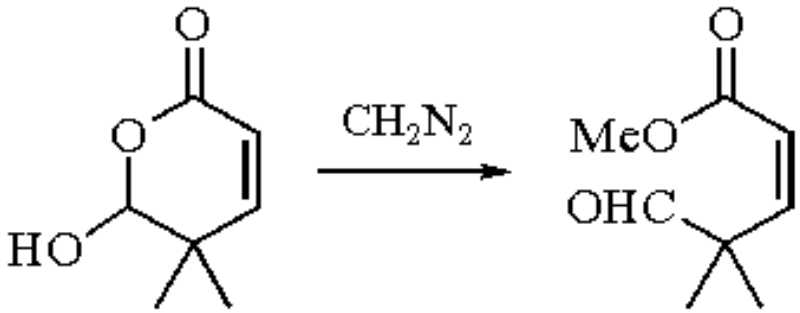

(10)

Methylation of Alcohols and Other Less Acidic Functional Groups.

As previously mentioned, alcohols require the addition of a catalyst in order to react with diazomethane. The most commonly used is boron trifluoride etherate (eq 11),[19] but ***Tetrafluoroboric Acid*** has been used as well (eq 12).[20] Mineral acids are not effective since they rapidly react with diazomethane to provide the corresponding methyl halides. Acids as mild as silica gel have also been found to be effective (eq 13).[21] Monomethylation of 1,2-diols with diazomethane has been reported using various Lewis acids as promoters, the most effective of which is ***Tin(II) Chloride*** (eq 14).[22]

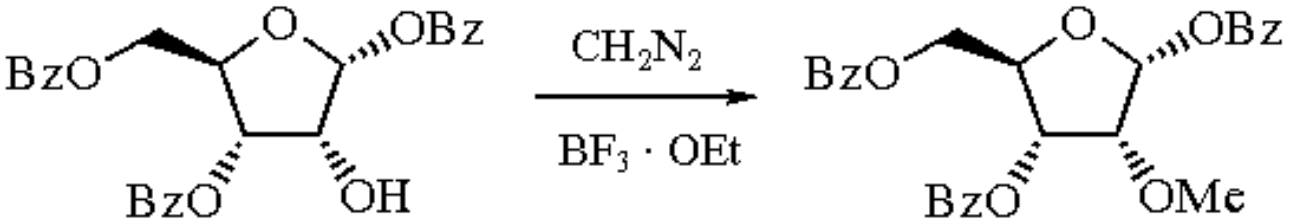

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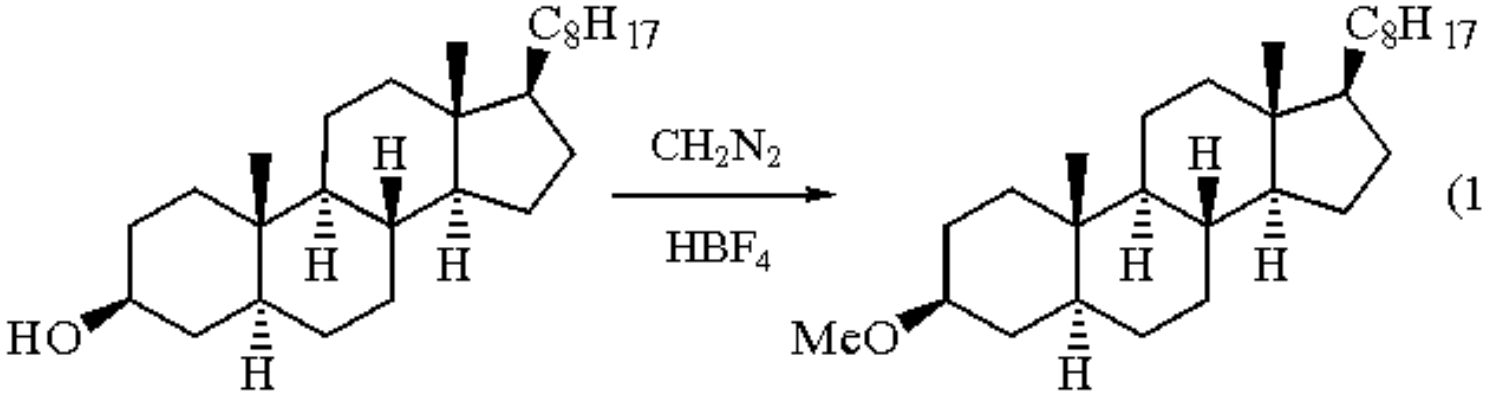

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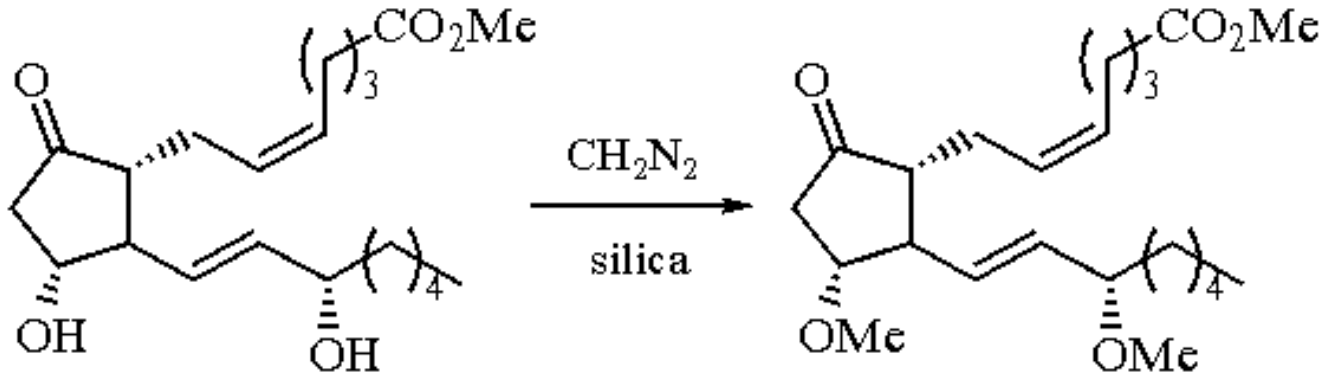

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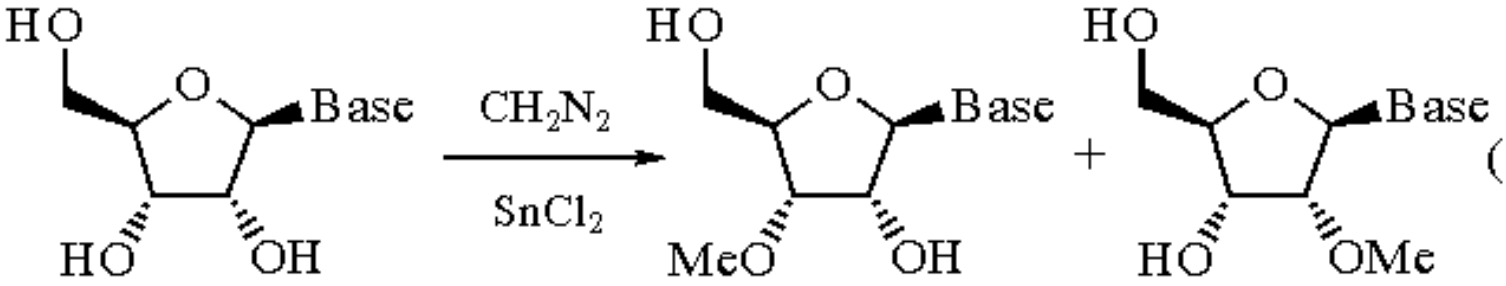

(14)

An interesting case of an alcohol reacting with diazomethane at a rate competitive with a carboxylic acid has been reported (eq 15).[23] In this case, the tertiary structure of the molecule is thought to place the alcohol and the carboxylic acid in proximity to each other. Protonation of the diazomethane by the carboxylic acid leads to a diazonium ion in proximity to the alcohol as well as the carboxylate. These species then attack the diazonium ion at competitive rates to provide the methyl ether and ester. No reaction is observed upon treatment of the corresponding hydroxy ester with diazomethane, indicating that the acid is required to activate the diazomethane.

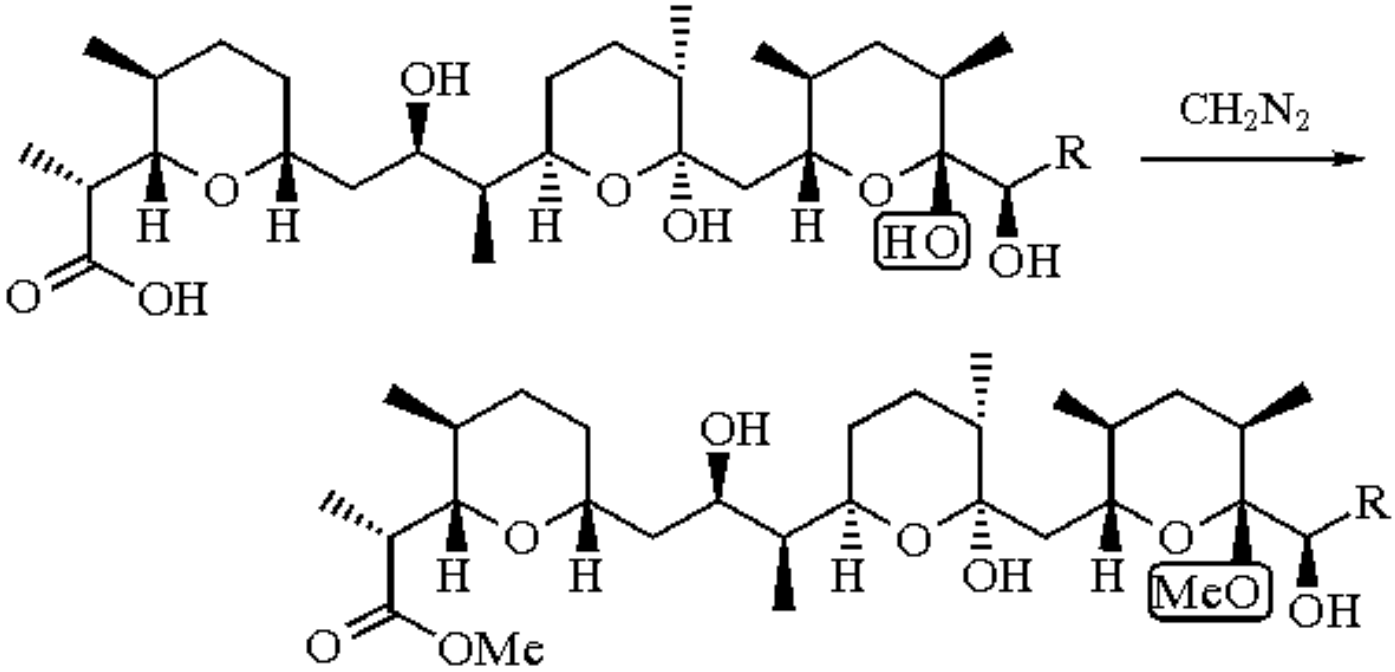

(15)

Amides can also be methylated with diazomethane in the presence of silica gel; however, the reaction requires a large excess of diazomethane (25-60 equiv, eq 16).[24] The reaction primarily provides *O*-methylated material; however, in one case a mixture of *O*- and *N*-methylation was reported. Thioamides are also effectively methylated with this procedure to provide *S*-methylated compounds. Finally, amines have been methylated with diazomethane in the

presence of BF_3 etherate, fluoroboric acid,[25] or copper(I) salts;[26] however, the yields are low to moderate, and the method is not widely used.

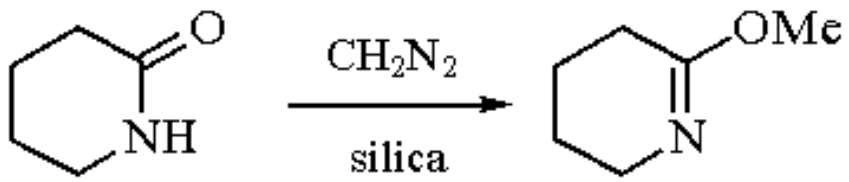

(16)

The Arndt-Eistert Synthesis.

Diazomethane is a useful reagent for the one-carbon homologation of acid chlorides via a sequence of reactions known as the Arndt-Eistert synthesis. The first step of this sequence takes advantage of the nucleophilicity of diazomethane in its addition to an active ester, typically an acid chloride,[27] to give an isolable α-diazo ketone and HCl. The HCl that is liberated from this step can react with diazomethane to produce methyl chloride and nitrogen, and therefore at least 2 equiv of diazomethane are typically used. The α-diazo ketone is then induced to undergo loss of the diazo group and insertion into the adjacent carbon-carbon bond of the ketone to provide a ketene. The ketene is finally attacked by water or an alcohol (or some other nucleophile) to provide the homologated carboxylic acid or ester. This insertion step of the sequence is known as the Wolff rearrangement[28] and can be accomplished either thermally (eq 17)[29] or, more commonly, by treatment with a metal ion (usually silver salts, eq 18),[30] or photochemically (eq 19).[31] It has been suggested that the photochemical method is the most efficient of the three.[32] As eqs 18 and 19 illustrate, retention of stereochemistry is observed in the migrating group. The obvious limitations of this reaction are that there must not be functional groups present in the molecule which will react with diazomethane more rapidly than it will attack the acid chloride. Thus carboxylic acids will be methylated under these conditions. Furthermore, electron-deficient alkenes will undergo [2,3] dipolar cycloaddition with diazomethane more rapidly than addition to the acid chloride. Thus when the Arndt-Eistert synthesis is attempted on α,β-unsaturated acid chlorides, cycloaddition to the alkene is observed in the product. In order to prevent this, the alkene must first be protected by addition of HBr and then the reaction carried out in the normal way (eq 20).[33] Cycloaddition to isolated alkenes, however, is not competitive with addition to acid chlorides.

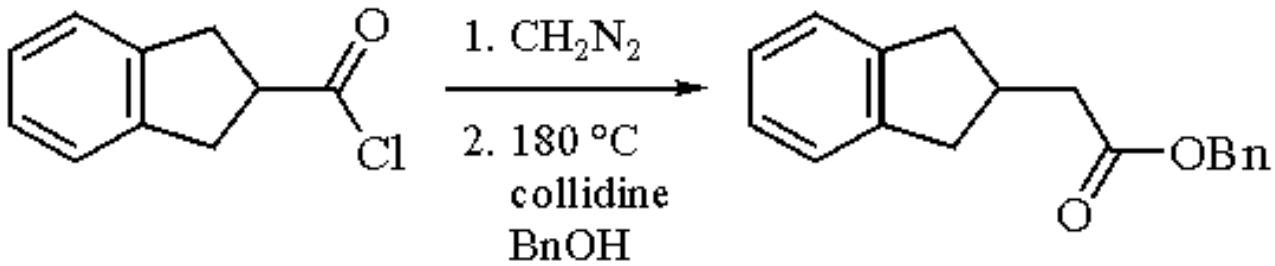

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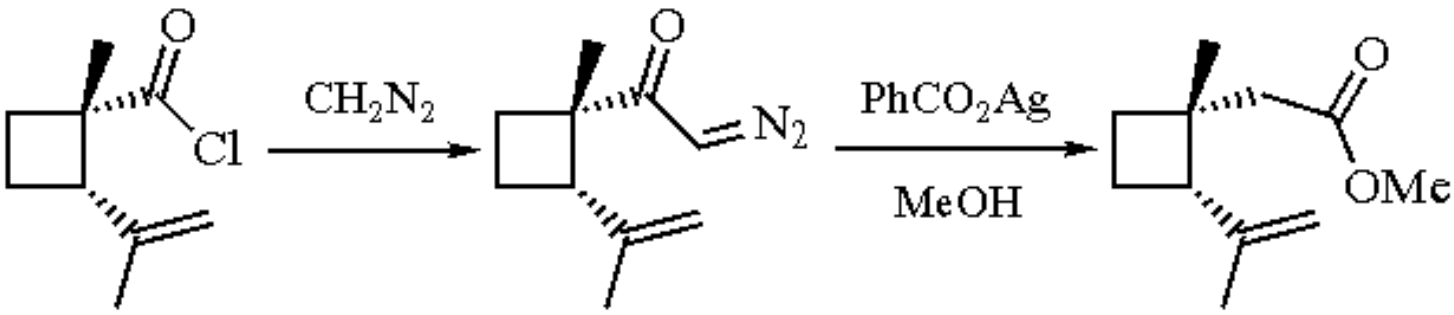

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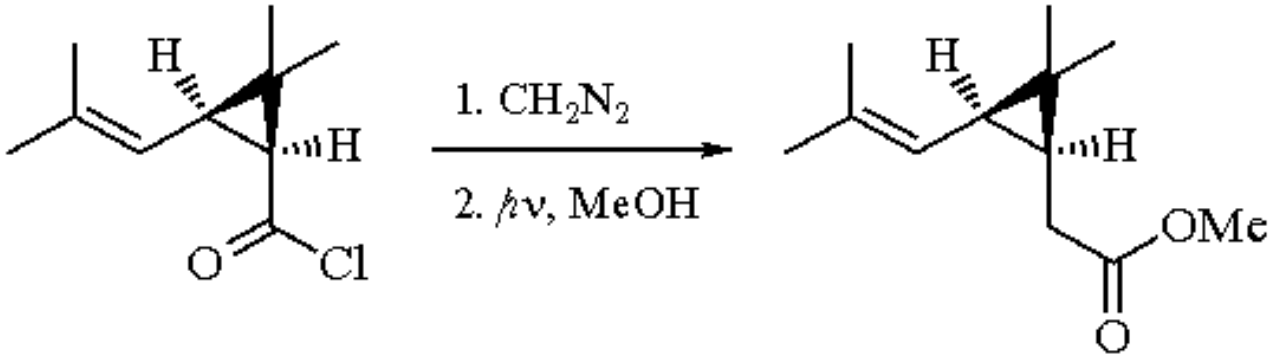

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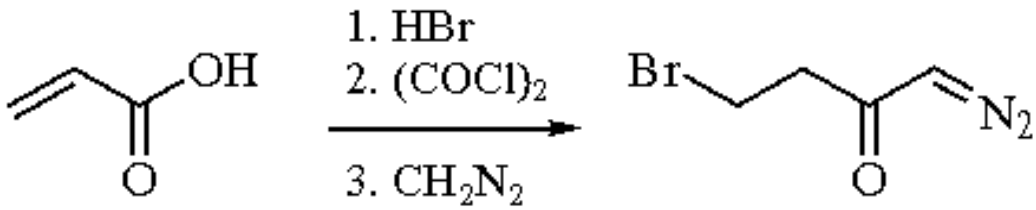

(20)

Other Reactions of α-Diazo Ketones Derived from Diazomethane.

Depending on the conditions employed, the Wolff rearrangement may proceed via a carbene or carbenoid intermediate, or it may proceed by a concerted mechanism where the insertion is concomitant with loss of N_2 and no intermediate is formed. In the case where a carbene or carbenoid is involved, other reactions which are characteristic of these species can occur, such as intramolecular cyclopropanation of alkenes. In fact, the reaction conditions can be adjusted to favor cyclopropanation or homologation depending on which is desired. Thus treatment of the dienoic acid chloride shown in eq 21 with diazomethane followed by decomposition of the α-diazo ketone with silver benzoate in the presence of methanol and base provides the homologated methyl ester. However, treatment of the same diazoketone intermediate with Cu^{II} salts provides the cyclopropanation products selectively.[34] This trend is generally observed; that is, silver salts as well as photochemical conditions (eqs 18 and 19) favor the homologation pathway while copper or rhodium salts favor cyclopropanation.[35] Using copper salts to decompose the diazo compounds, hindered alkenes as well as electron-rich aromatics can be cyclopropanated as illustrated in eqs 22 and 23,[36,37] respectively.

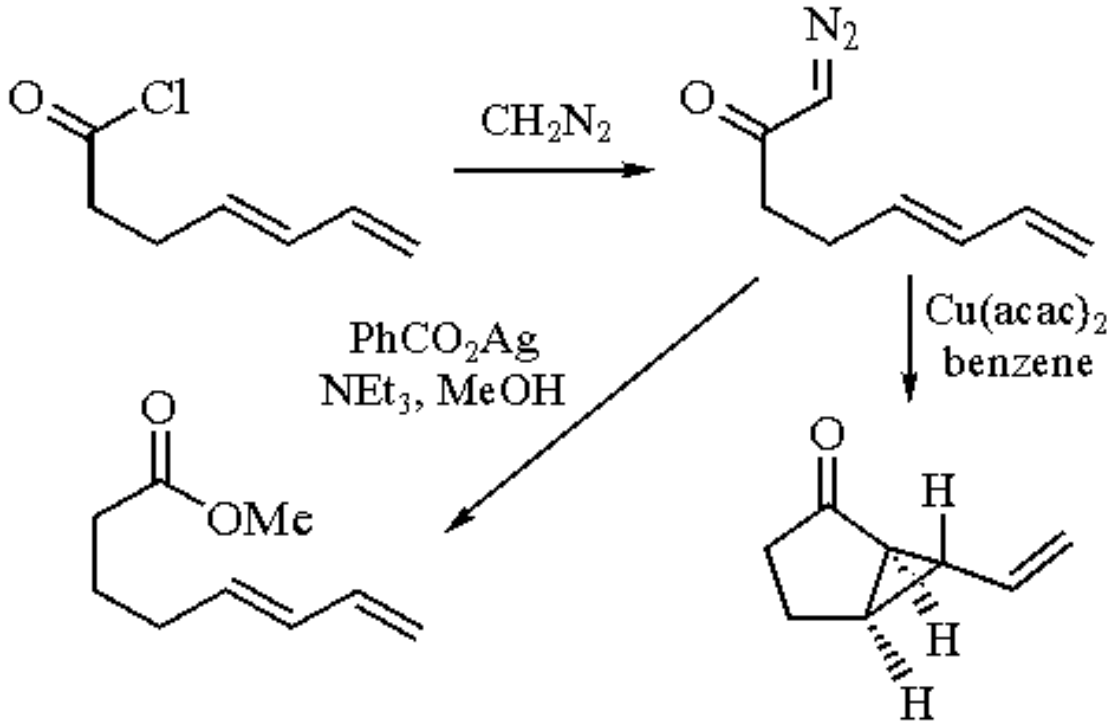

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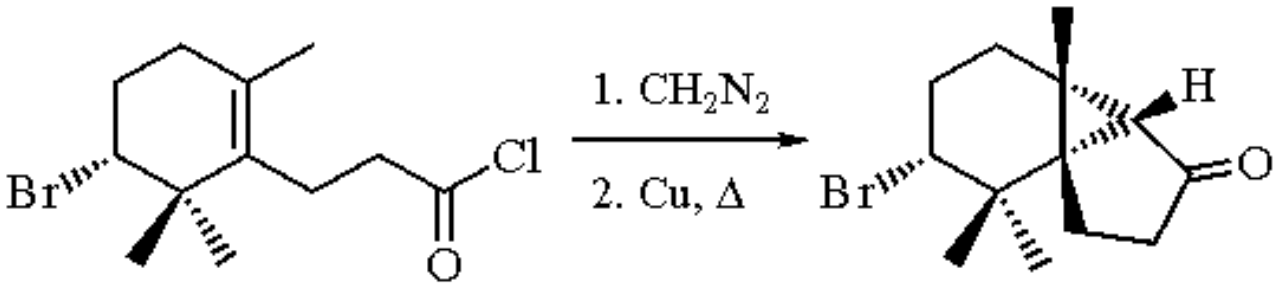

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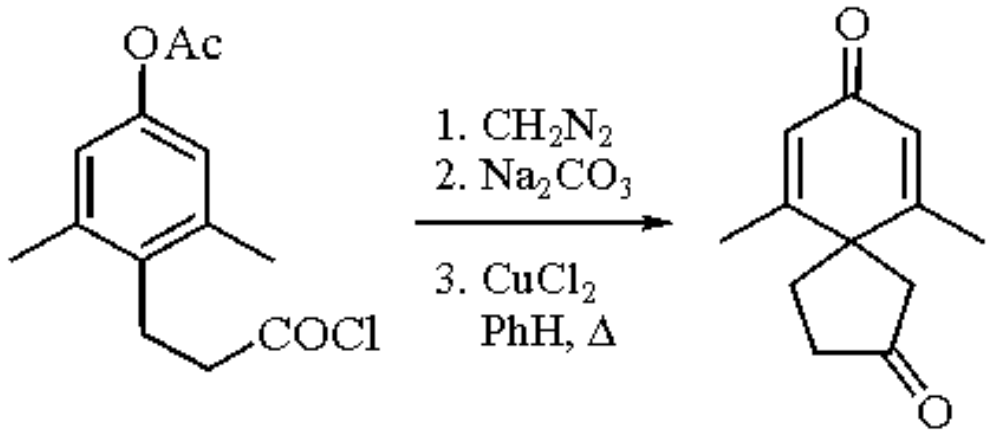

(23)

In addition to these reactions, α-diazo ketones will undergo protonation on carbon in the presence of protic acids[38] to provide the corresponding α-diazonium ketone. These species are highly electrophilic and can undergo nucleophilic attack. Thus if the proton source contains a nucleophile such as a halogen then the corresponding α-halo ketone is isolated (eq 24).[39] However, if the proton source does not contain a nucleophilic counterion then the diazonium species may react with other nucleophiles that are present in the molecule, such as alkenes (eq 25)[40] or aromatic rings (eq 26).[41] Note the similarity between the transformations in eqs 26 and 23 which occur using different catalysts and by different pathways. Also, eq 26 illustrates the fact that other active esters will undergo nucleophilic attack by

diazomethane.

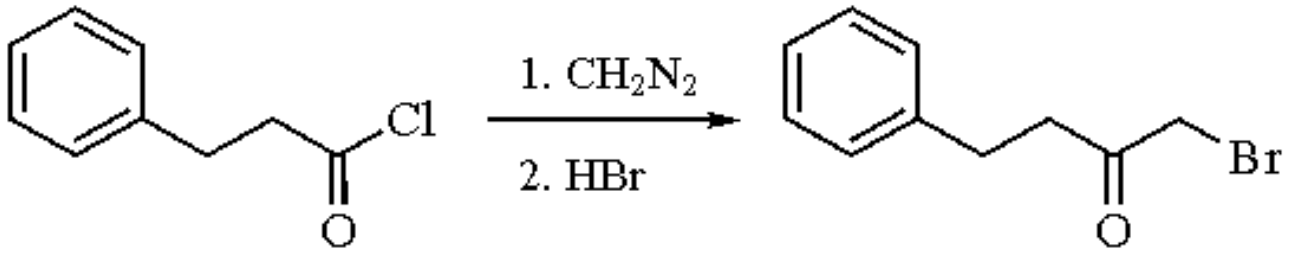

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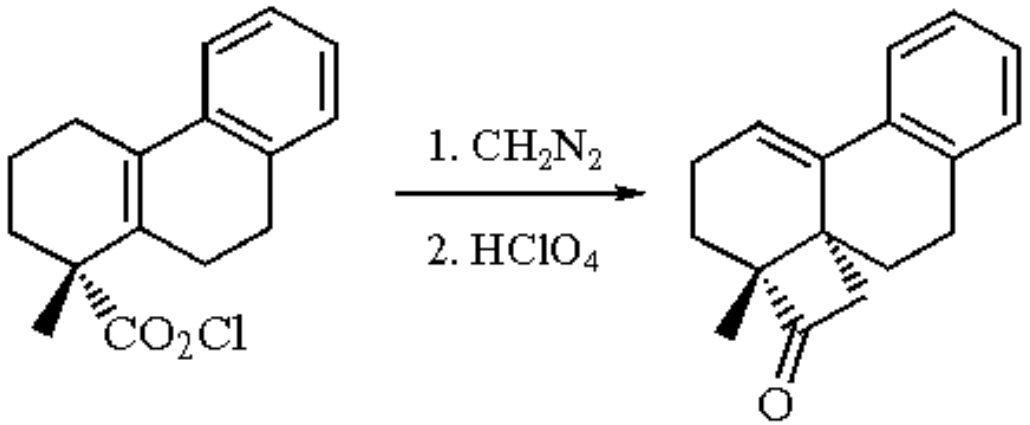

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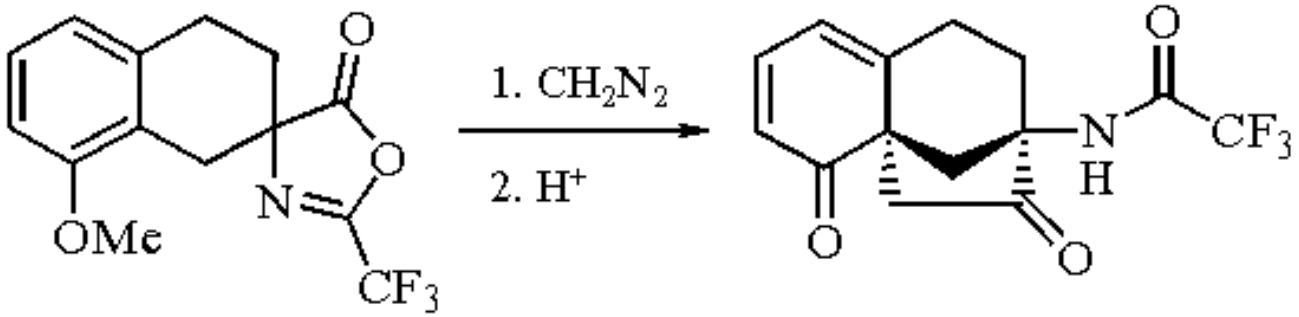

(26)

Lewis acids are also effective in activating α-diazo ketones towards intramolecular nucleophilic attack by alkenes and arenes.[42] The reaction has been used effectively for the synthesis of cyclopentenones (eq 27) starting with β,γ-unsaturated diazo ketones derived from the corresponding acid chloride and diazomethane. It has also been used to initiate polyalkene cyclizations (eq 28). Typically, boron trifluoride etherate is used as the Lewis acid, and electron-rich alkenes are most effective providing the best yields of annulation products.

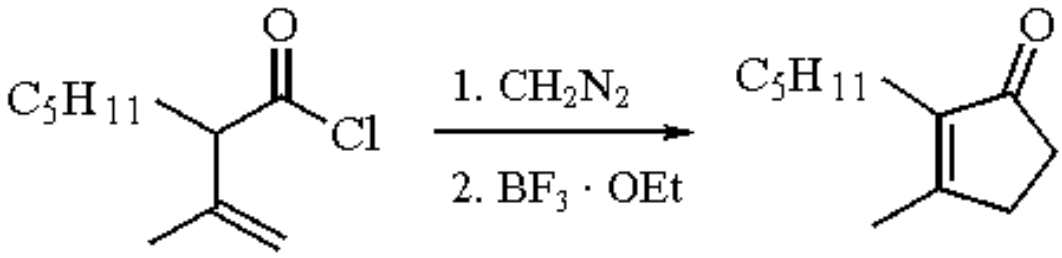

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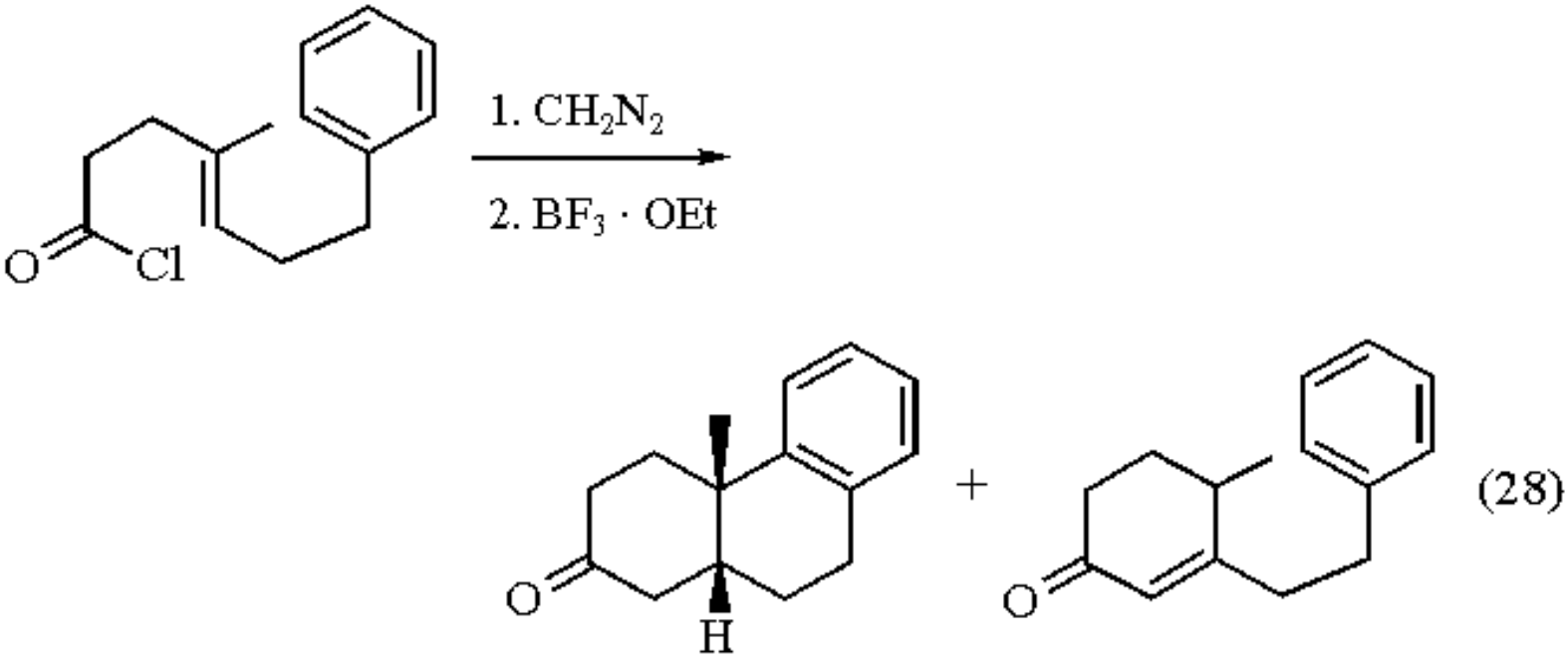

The Vinylogous Wolff Rearrangement.

The vinylogous Wolff rearrangement[43] is a reaction that occurs when the Arndt-Eistert synthesis is attempted on β,γ-unsaturated acid chlorides using copper catalysis. Rather than the usual homologation products, the reaction proceeds to give what is formally the product of a [2,3]-sigmatropic shift, but is mechanistically not derived by this pathway.[44] The mechanism is thought to proceed by an initial cyclopropanation of the alkene by the α-diazo ketone to give a bicyclo[2.1.0]pentanone derivative. This compound then undergoes a fragmentation to a ketene alkene before being trapped by the solvent (eq 29). Inspection of the products reveals that they are identical with those derived from the Claisen rearrangement of the corresponding allylic alcohols, and as such this method can be thought of as an alternative to the Claisen procedure. However, the stereoselectivity of the alkene that is formed is not as high as is typically observed in the Claisen rearrangement (eq 30), and in some substrates the reaction proceeds with no selectivity (eq 31).

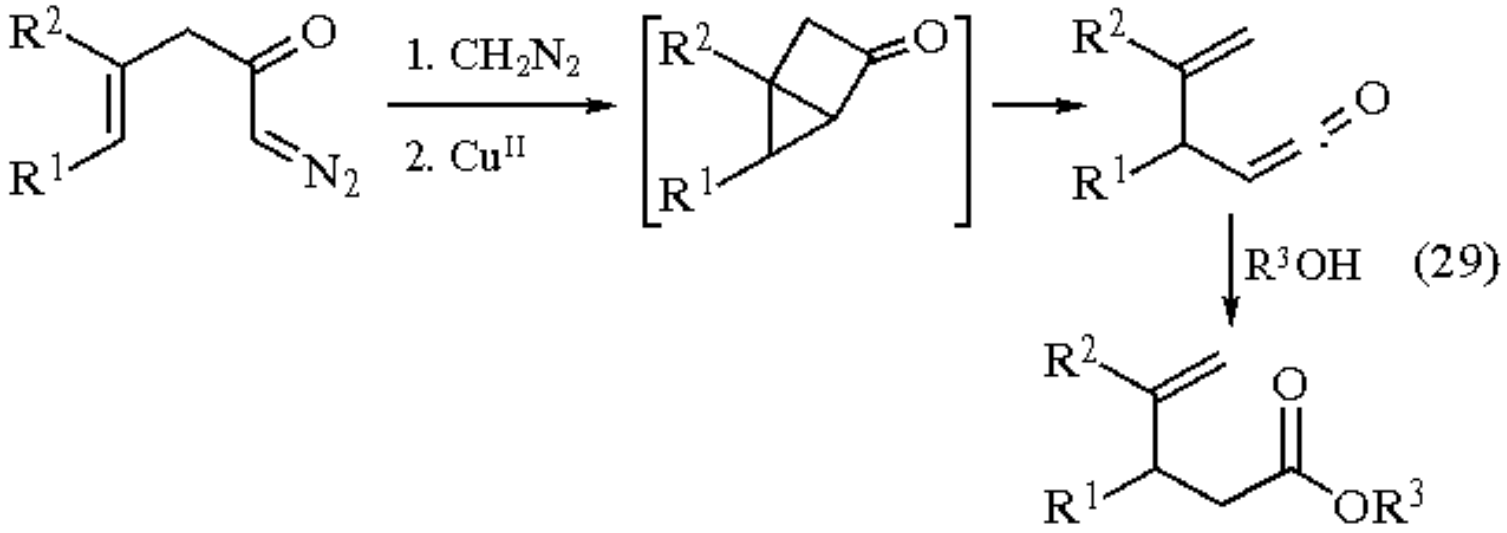

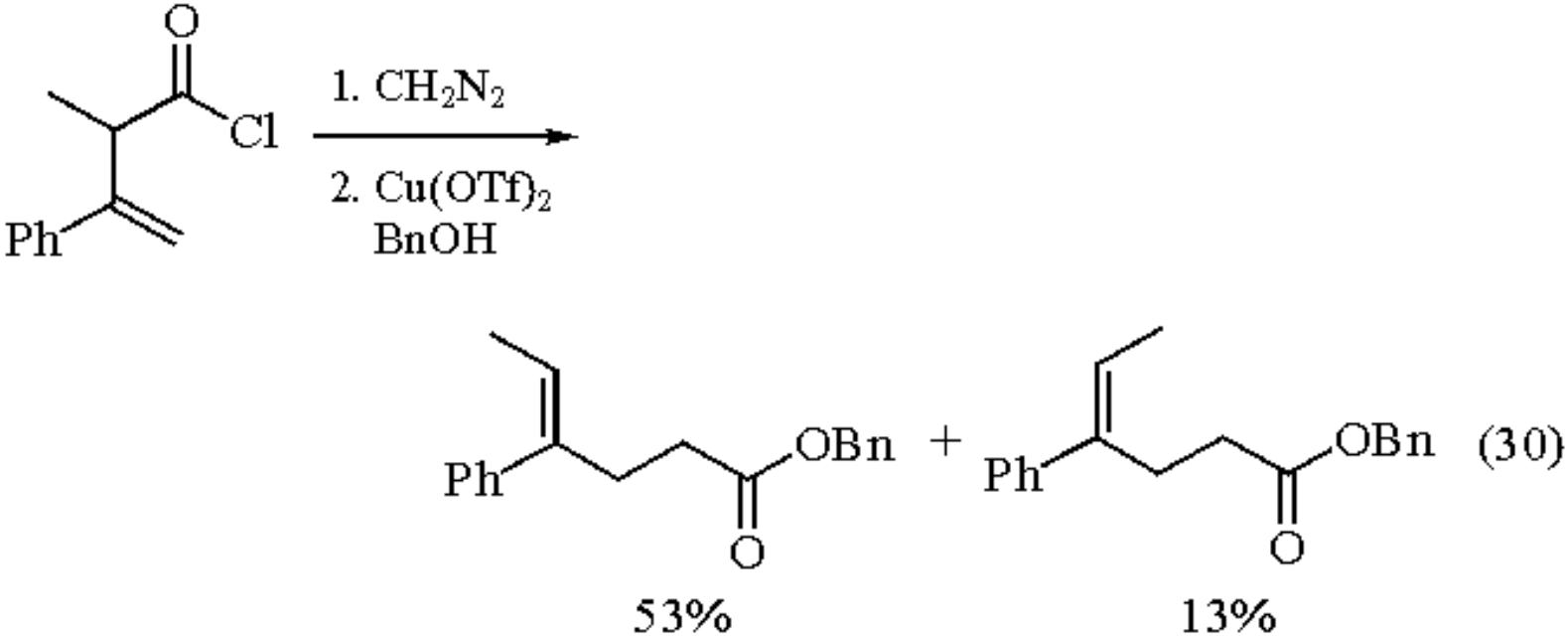

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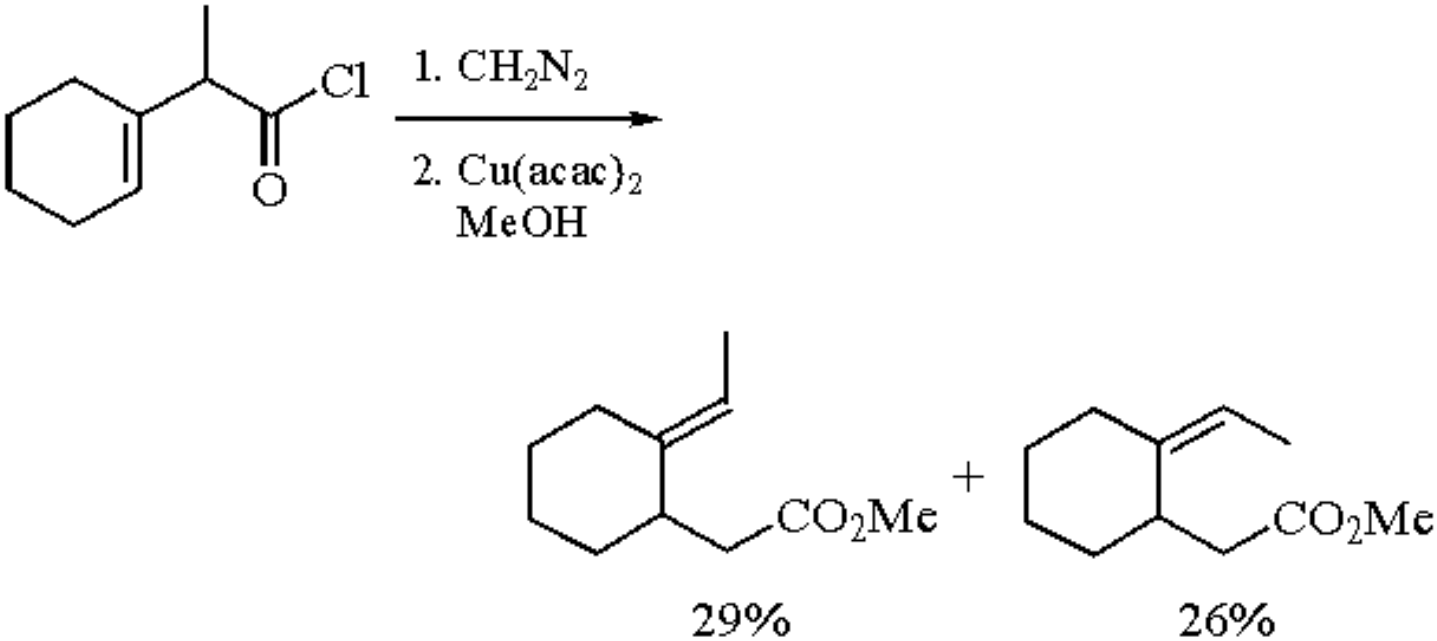

(31)

Insertions into Aldehyde C-H Bonds.

The α-diazo ketones (and esters) derived from diazomethane and an acid chloride (or chloroformate) will also insert into the C-H bond of aldehydes to give 1,3-dicarbonyl derivatives.[45] The reaction is catalyzed by $SnCl_2$, but some simple Lewis acids, such as BF_3 etherate, also work. The reaction works well for aliphatic aldehydes, but gives variable results with aromatic aldehydes, at times giving none of the desired diketone (eq 32). Sterically hindered aldehydes will also participate in this reaction, as illustrated in eq 33 with the reaction of ethyl α-diazoacetate and pivaldehyde. In a related reaction, α-diazo phosphonates and sulfonates will react with aldehydes in the presence of $SnCl_2$ to give the corresponding β-keto phosphonates and sulfonates.[46] This reaction is a practical alternative to the Arbuzov reaction for the synthesis of these species.

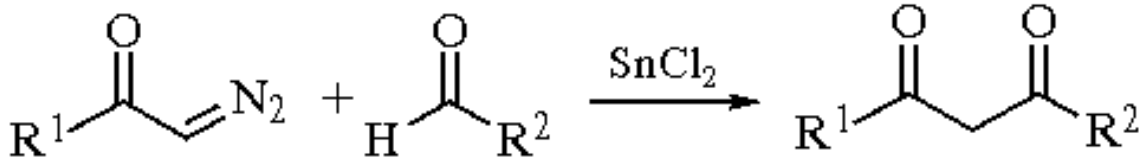

(32)

R^1	R^2	Yield (%)
Ph	H	88
Ph	$PhCH_2$	90
$PhCH_2CH_2$	Ph	0

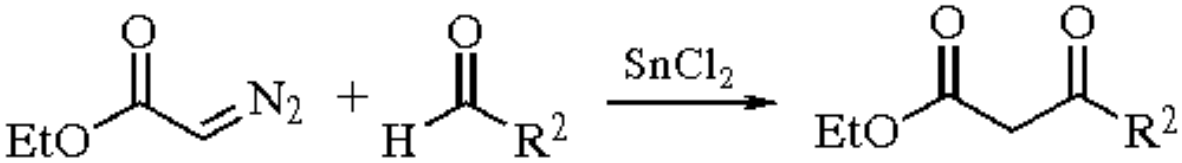

(33)

R^2	Yield (%)
t-Bu	65
Ph	50

Additions to Ketones.

The addition of diazomethane to ketones[47] is also a preparatively useful method for one-carbon homologation. This reaction is a one-step alternative to the Tiffeneau-Demjanow rearrangement[48] and proceeds by the mechanism shown in eq 34. It can lead to either homologation or epoxidation depending on the substrate and reaction conditions. The addition of Lewis acids, such as BF_3 etherate, or alcoholic cosolvents tend to favor formation of the homologation products over epoxidation.

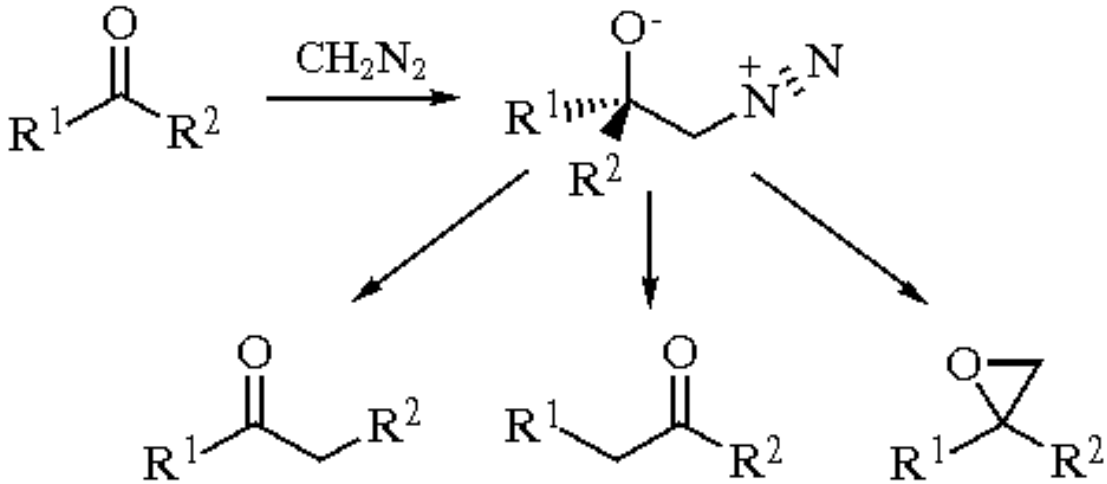

(34)

However, the reaction is limited by the poor regioselectivity observed in the insertion when the groups R^1 and R^2 in the starting ketone are different alkyl groups. What selectivity is observed tends to favor migration of the less substituted carbon,[49] a trend which is opposite to that typically observed in rearrangements of electron-deficient species such as in the Baeyer-Villiger reaction. Furthermore, the product of the reaction is a ketone and is therefore capable of undergoing further reaction with diazomethane. Thus, ideally, the product ketone should be less reactive than the starting ketone. Strained ketones tend to react more rapidly and are therefore good substrates for this reaction (eq 35).[50] This method has also found extensive use in cyclopentane annulation reactions starting with an alkene. The overall process begins with dichloroketene addition to the alkene to produce an α-dichlorocyclobutanone. These species are ideally suited for reaction with diazomethane because the reactivity of the starting ketone is enhanced due to the strain in the cyclobutanone as well as the α-dichloro substitution. Furthermore, the presence of the α-dichloro substituents hinders migration of that group and leads to almost exclusive migration of the methylene group. Thus treatment with diazomethane and methanol leads to a rapid evolution of nitrogen, and produces the corresponding α-dichlorocyclopentanone, which can be readily dehalogenated to the hydrocarbon (eq 36).[51] Aldehydes will also react with diazomethane, but in this case homologation is not observed. Rather, the corresponding methyl ketone derived from migration of the hydrogen is produced (eq 37).

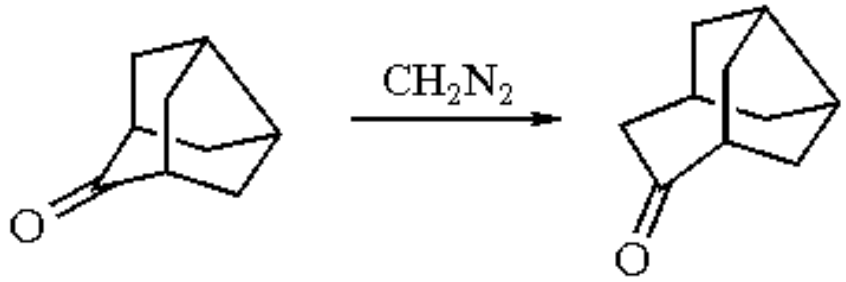

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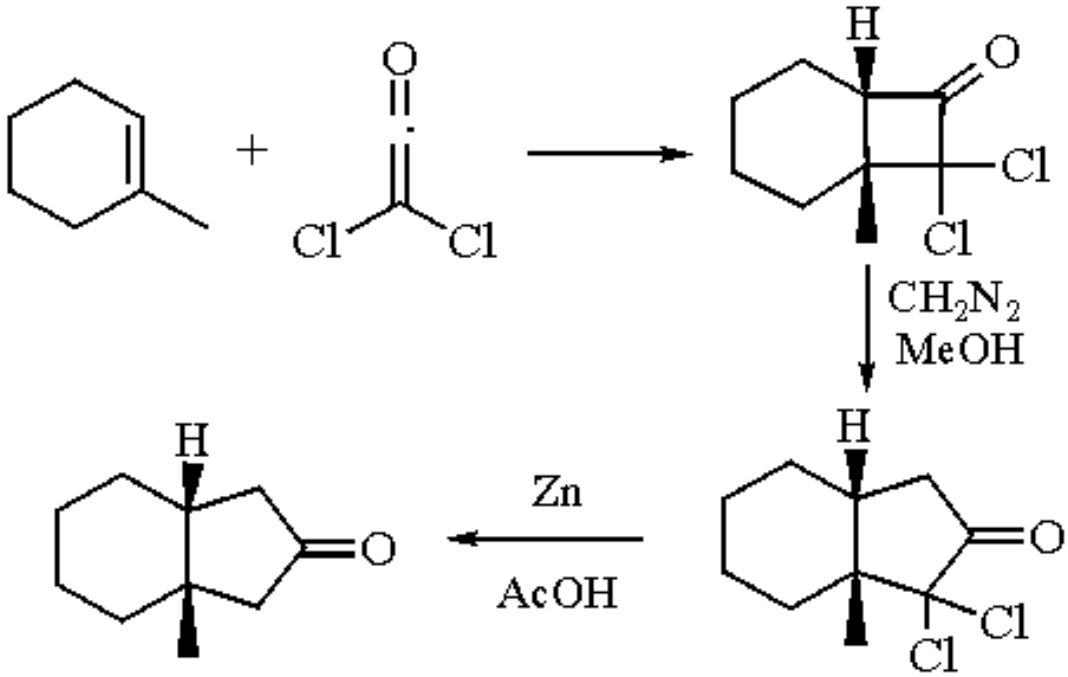

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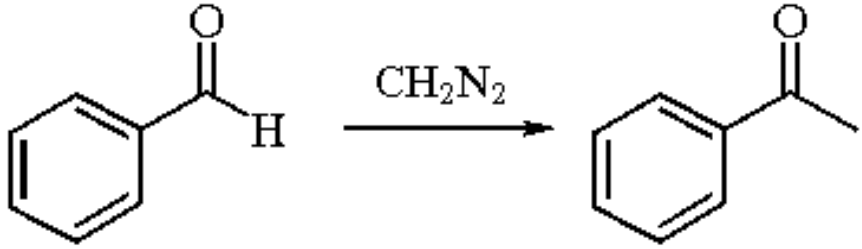

(37)

Cycloadditions with Diazomethane.

Diazomethane will undergo [3 + 2] dipolar cycloadditions with alkenes and alkynes to give pyrazolines and pyrazoles, respectively.[52] The reaction proceeds more rapidly with electron-deficient alkenes and strained alkenes and is controlled by FMO considerations with the HOMO of the diazomethane and the LUMO of the alkene serving as the predominant interaction.[53] In the case of additions to electron-deficient alkenes, the carbon atom of the diazomethane behaves as the negatively charged end of the dipole, and therefore the regiochemistry observed is as shown in eq 38. With conjugated alkenes, such as styrene, the terminal carbon has the larger lobe in the LUMO, and as such the reaction proceeds to give the product shown in eq 39. Pyrazolines are most often used as precursors to cyclopropanes by either thermal or photochemical extrusion of N_2. In both cases the reaction may proceed by a stepwise mechanism with loss of stereospecificity. As shown in eq 40, the thermal reaction provides an almost random product distribution, while the photochemical reaction provides variable results ranging from 20:1 to stereospecific extrusion of nitrogen.[54]

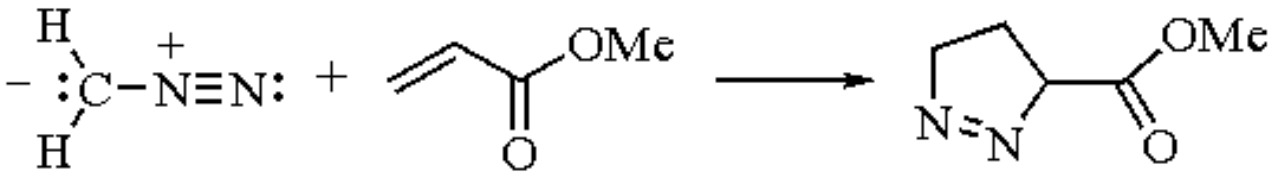

(38)

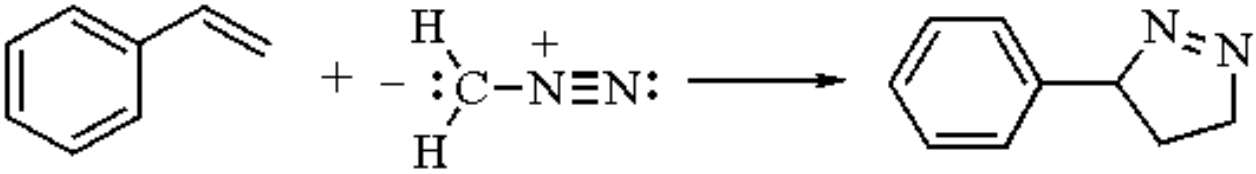

(39)

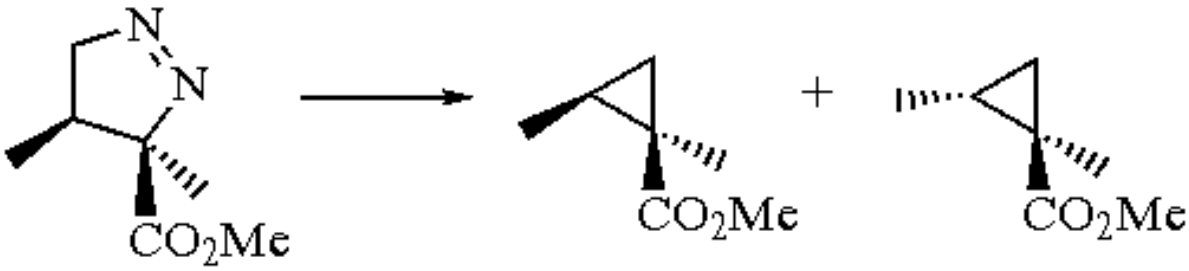

(40)

Δ	1.2:1
$h\nu$	20:1
	to >100:1

Cyclopropanes can also be directly synthesized from alkenes and diazomethane, either photochemically or by using transition metal salts, usually ***Copper(II) Chloride*** or ***Palladium(II) Acetate***, as promoters. The metal-mediated

reactions are more commonly used than the photochemical ones, but they are not as popular as the Simmons-Smith procedure. However, they do occasionally offer advantages. Of the two processes, the Cu-catalyzed reaction produces a more active reagent[55] which will cyclopropanate a variety of alkenes, including enamines as shown in eq 41.[56] These products can then be converted to α-methyl ketones by thermolysis. The cyclopropanation of the norbornenol derivative shown in eq 42 was problematic using the Simmons-Smith procedure and provided low yields, but occurred smoothly using the $CuCl_2$/diazomethane method.[57]

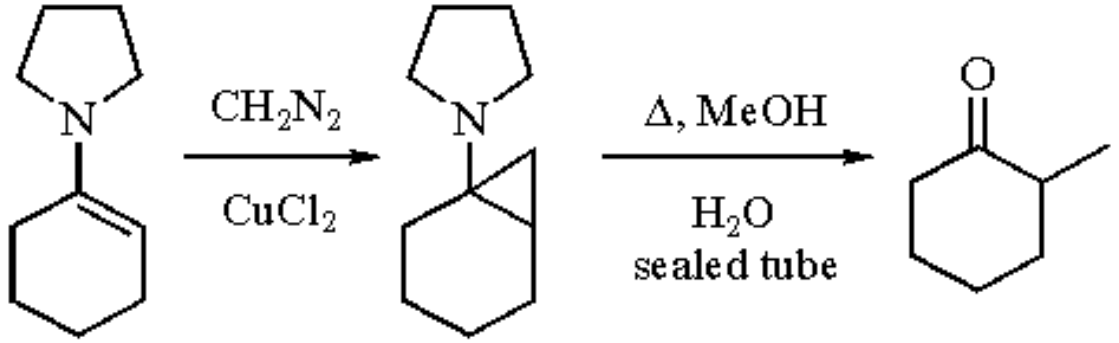

(41)

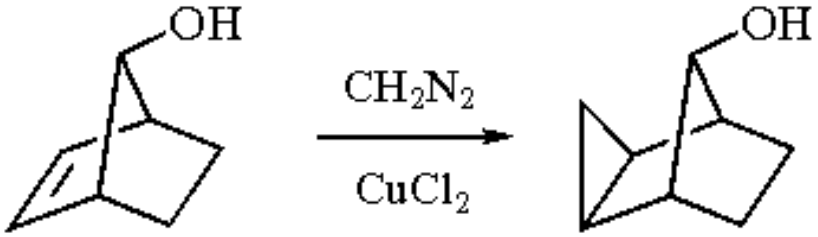

(42)

The $Pd(OAc)_2$-mediated reaction can be used to cyclopropanate electron-deficient alkenes as well as terminal alkenes. Thus selective reaction at a monosubstituted alkene in the presence of others is readily achieved using this method (eq 43).[58] The example shown in eq 44 is one in which the Simmons-Smith procedure failed to provide any of the desired product, whereas the current method provided a 92% yield of cyclopropane.[59]

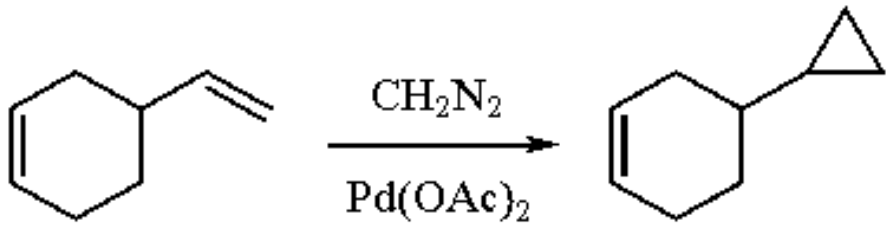

(43)

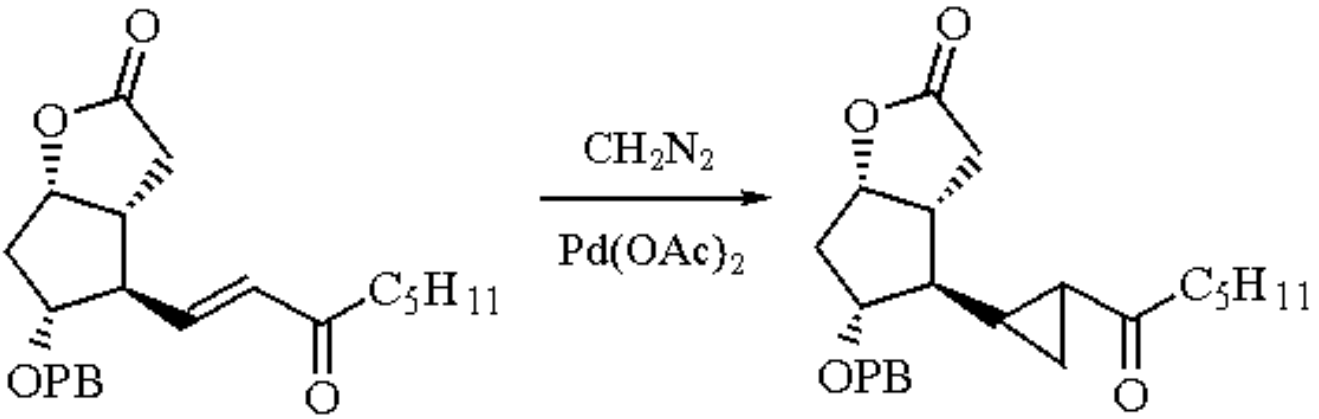

(44)

In the case of the photochemical reaction, irradiation of diazomethane in the presence of *cis*-2-butene provides *cis*-1,2-dimethylcyclopropane with no detectable amount of the *trans* isomer (eq 45).[60] This reaction is thought to proceed via a singlet carbene. However, if the same reaction is carried out via a triplet carbene, generated via triplet sensitization, then a 1.3:1 mixture of *trans* to *cis* dimethylcyclopropane is observed (eq 46).[61] The yields in the photochemical reaction are typically lower than the metal-mediated processes, and are usually accompanied by more side products.

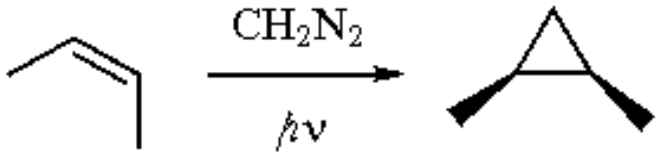

(45)

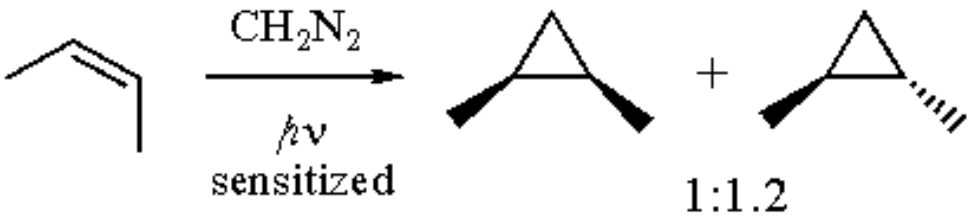

(46)

Additions to Electron-Deficient Species.

Diazomethane will also add to highly electrophilic species such as sulfenes or imminium salts to give the corresponding three-membered ring heterocycles. When the reaction is performed on sulfenes, the products are episulfones which are intermediates in the Ramberg-Backlund rearrangement, and are therefore precursors for the synthesis of alkenes via chelotropic extrusion of SO_2. The sulfenes are typically prepared in situ by treatment of a sulfonyl chloride with a mild base, such as ***Triethylamine*** (eq 47).[62] Similarly, the addition of diazomethane to imminium salts has been used to methylenate carbonyls.[63] In this case, the intermediate aziridinium salt is treated with a strong base, such as ***n-Butyllithium***, in order to induce elimination (eq 48).

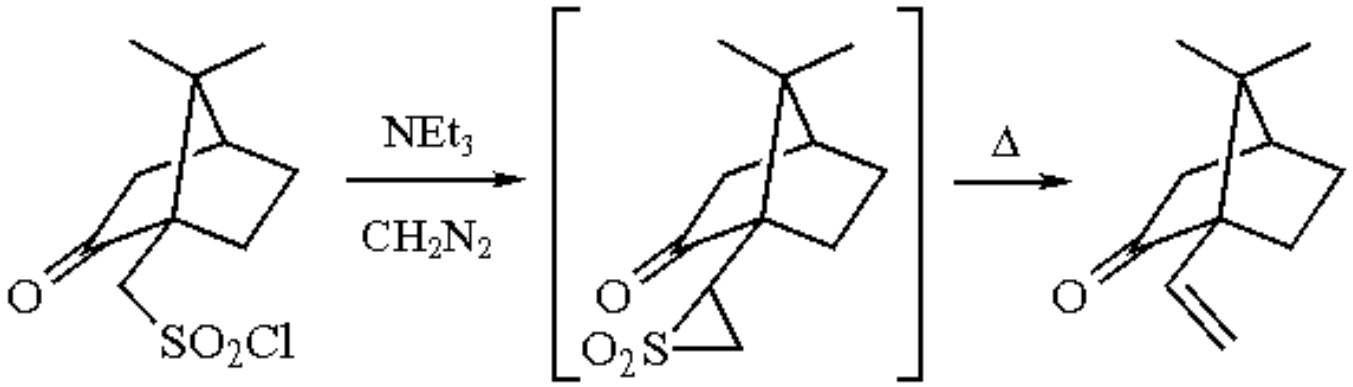

(47)

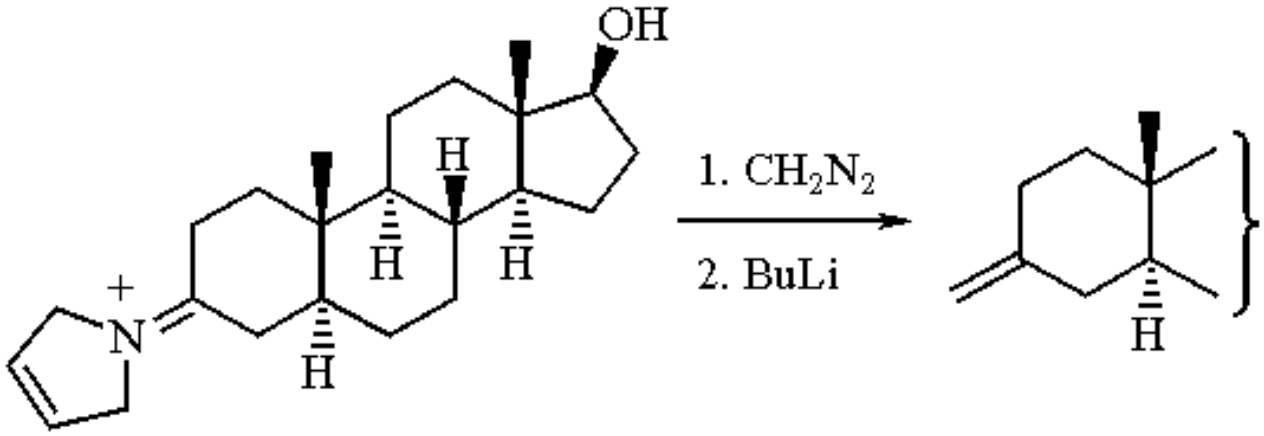

(48)

Miscellaneous Reactions.

Diazomethane has been shown to react with vinylsilanes derived from α,β-unsaturated esters to provide the corresponding allylsilane by insertion of CH_2 into the C-Si bond (eq 49).[64] The reaction has been shown to be stereospecific, with *cis*-vinylsilane providing *cis*-allylsilanes; however, the mechanism of the reaction has not been defined. Diazomethane has also been used in the preparation of trimethyloxonium salts. Treatment of a solution of dimethyl ether and trinitrobenzenesulfonic acid with diazomethane provides trimethyloxonium trinitrobenzenesulfonate, which is more stable than the fluoroborate salt.[65]

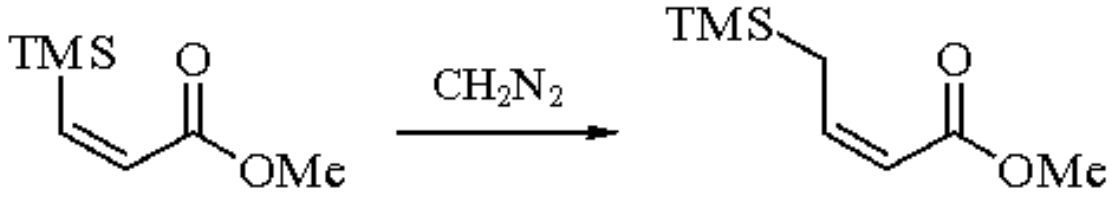

(49)

Related Reagents.

2-Diazopropane; ***Diphenyldiazomethane***; ***Phenyldiazomethane***; ***1-Diazo-2-propene***.

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2-Diazopropane

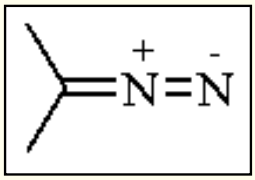

[2684-60-8] · $C_3H_6N_2$ · 2-Diazopropane · (MW 70.11)

(reagent for the cyclopropanation of alkenes[2])

Physical Data: the reagent is a gas at rt.

Solubility: the reagent is most commonly prepared and used as a solution in ether.

Analysis of Reagent Purity: titration with benzoic acid has been used to estimate the concentration of 2-diazopropane solutions; however, this method underestimates the yield by as much as 50% since the reaction of benzoic acid with the reagent is not quantitative. Spectrophotometric determination by measuring the absorbance at 500 nm has also been used; however, the ε value for this band is not precisely known.

Preparative Method: 2-diazopropane is most commonly prepared by the oxidation of ***Acetone Hydrazone*** with ***Mercury(II) Oxide*** in the presence of base.[1] The reaction is carried out in ether and the product is codistilled with the ether to provide an ethereal solution of the reagent which is used immediately. The reagent is unstable and undergoes a first-order decay with a half-life of 3 h at 0 °C. Diazo compounds are potentially explosive (especially on contact with objects containing rough or jagged surfaces such as ground glass) and for this reason extreme care must be observed in the synthesis and use of this compound with all operations being conducted behind a blast shield in a hood. Furthermore, the use of glassware which does not contain ground glass joints is essential.

Handling, Storage, and Precautions: in addition to the previously mentioned explosion hazard which this reagent presents, there are health related hazards that must also be considered. Diazo compounds, as a class, are toxic and irritating and can be sensitizers. They must be used in a well-ventilated fume hood and not come in contact with skin. For a description of the hazards associated with this class of compounds, see the handling and storage precautions listed for ***Diazomethane***.

Cyclopropanation of Alkenes.

2-Diazopropane is most commonly used to prepare *gem*-dimethylcyclopropyl derivatives. Like most diazoalkanes, this reagent will readily undergo cycloadditions with alkenes to provide the corresponding pyrazolines which can be induced to lose N_2 to provide the desired cyclopropanes. As with other dipolar cycloadditions, this reaction occurs most readily with electron-deficient alkenes. Extrusion of N_2 from these species can be accomplished photochemically, either by

direct irradiation or with the aid of a triplet sensitizer such as benzophenone.[2] Photochemical reactions without the sensitizer are typically slower, and can provide two side products, the retro cycloaddition to give the starting alkene, and the product of insertion into the vinylic C-H bond to provide the isopropyl-substituted alkene.[3] In some systems, thermal extrusion of N_2 also provides a substantial amount of the insertion product (eq 1). This is not always observed, however, and in certain cases thermal reactions can provide the desired cyclopropane in high yield.

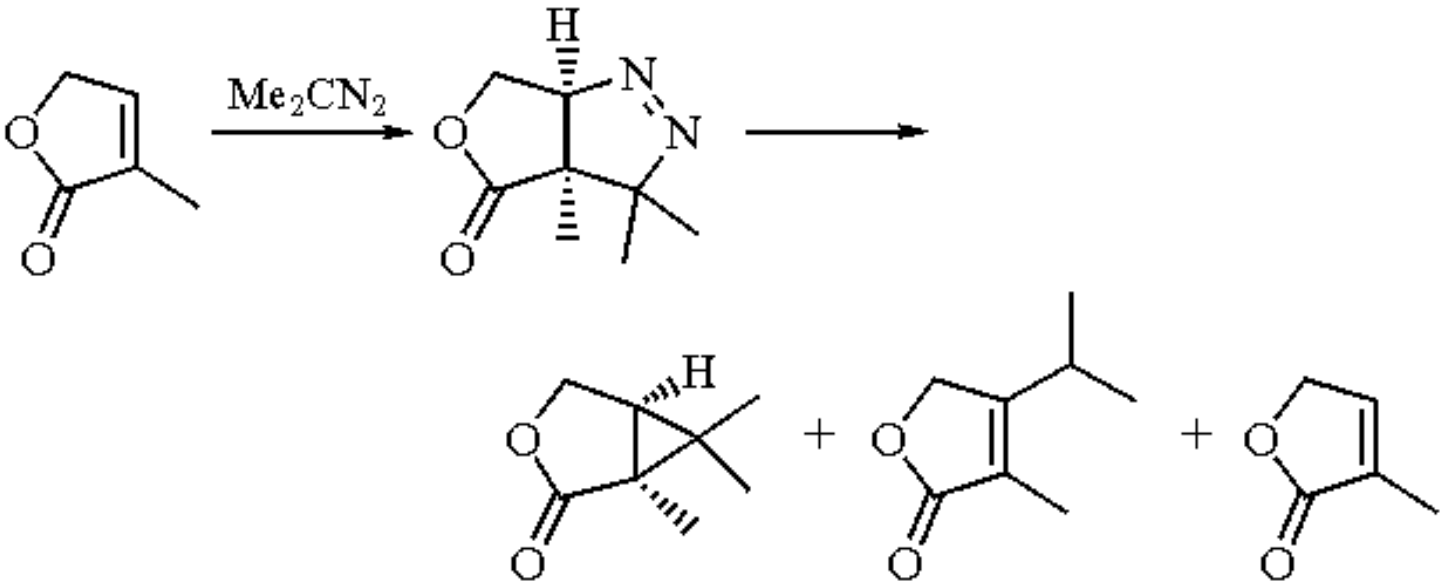

(1)

Δ, 70 °C	20%	80%	-
hν	62%	21%	17%
hν, sensitizer	>99%	-	-

The regiochemistry of the addition step of the reaction depends on the sterics of the system but, typically, the carbon of the diazoalkane adds to the more electrophilic β-carbon of the alkene. However, if this carbon is disubstituted, then the opposite regiochemistry can be observed, but frequently with diminished yields (eq 2).[4] Ultimately, the regiochemistry is inconsequential to the overall reaction because extrusion of N_2 provides the same cycloalkane in either case.

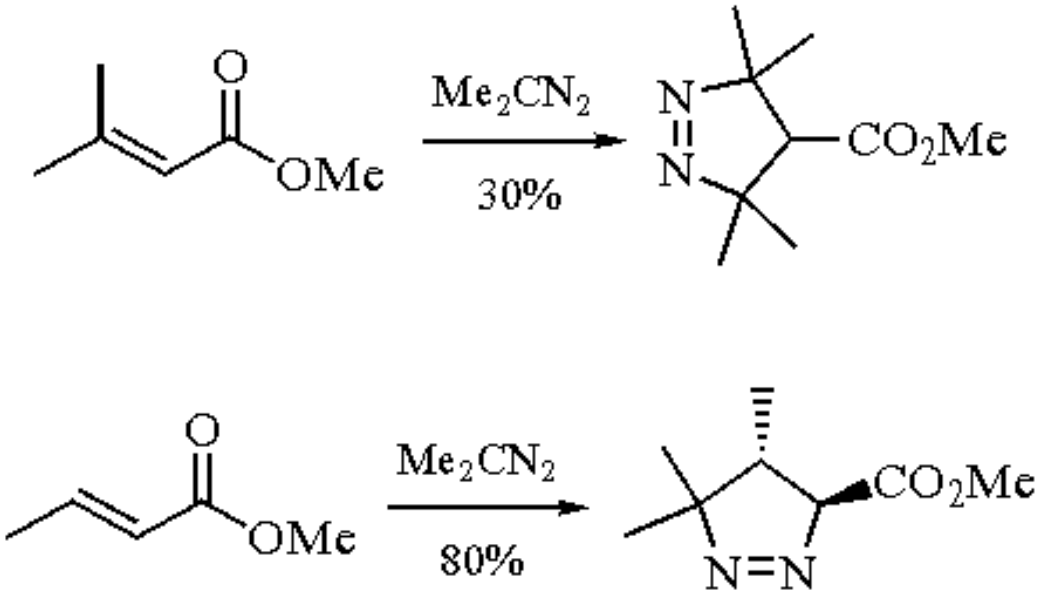

(2)

It is possible to cyclopropanate an electron-deficient alkene in the presence of an isolated alkene. Thus treatment of the steroid derivative shown in eq 3 with 2-diazopropane provided only addition to the conjugated alkene.[5] Photolysis of this compound provided the dimethylcyclopropane in 50% yield. Furthermore, differentiation between two electron-deficient alkenes on steric grounds is possible with this reagent. Thus addition of 2-diazopropane to the steroid derivative shown in eq 4 provided only the product of addition to the alkene containing a single substituent at the β-carbon. Photolysis again provided the desired cyclopropane, but in only 25% yield.

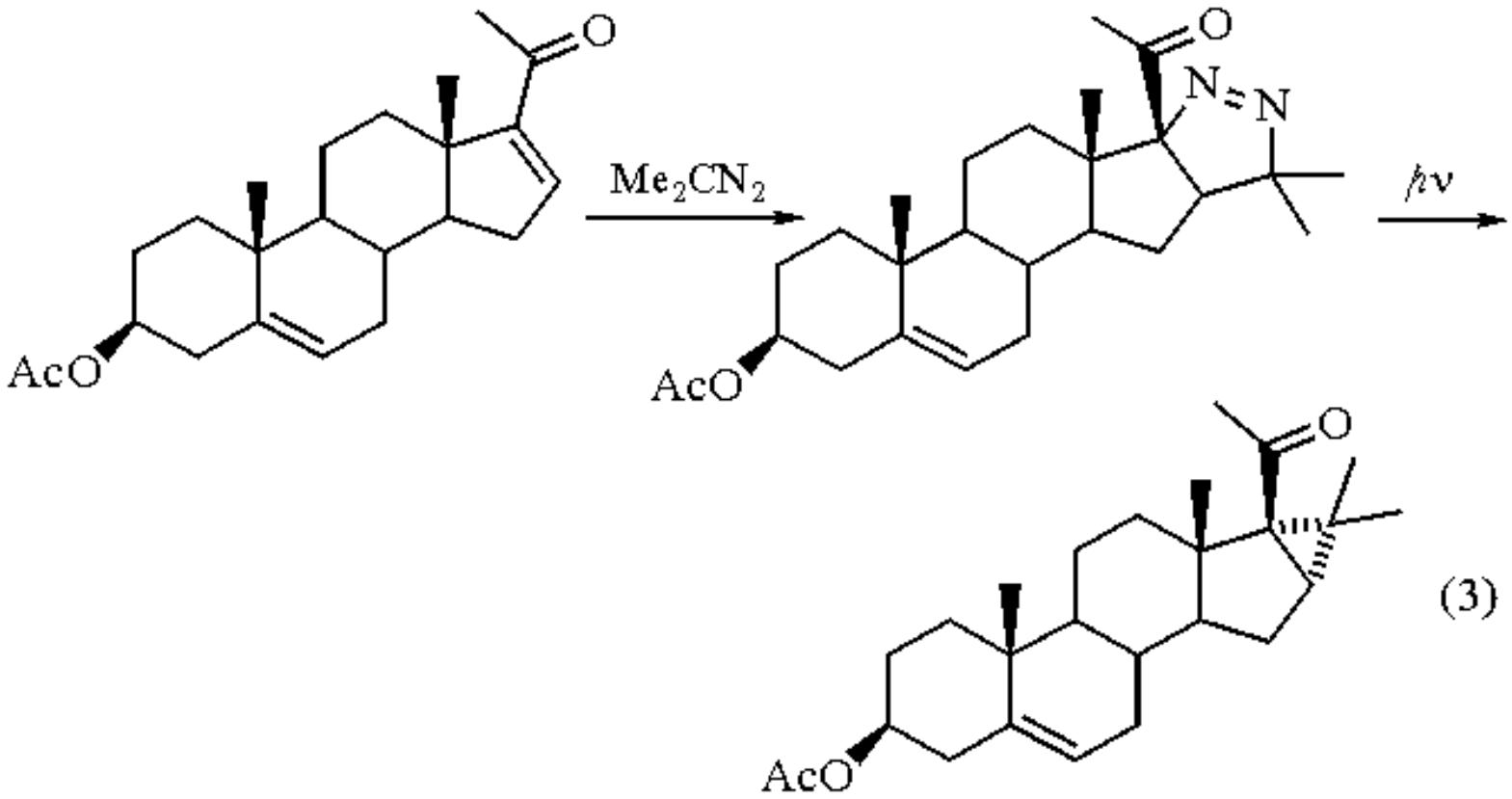

(3)

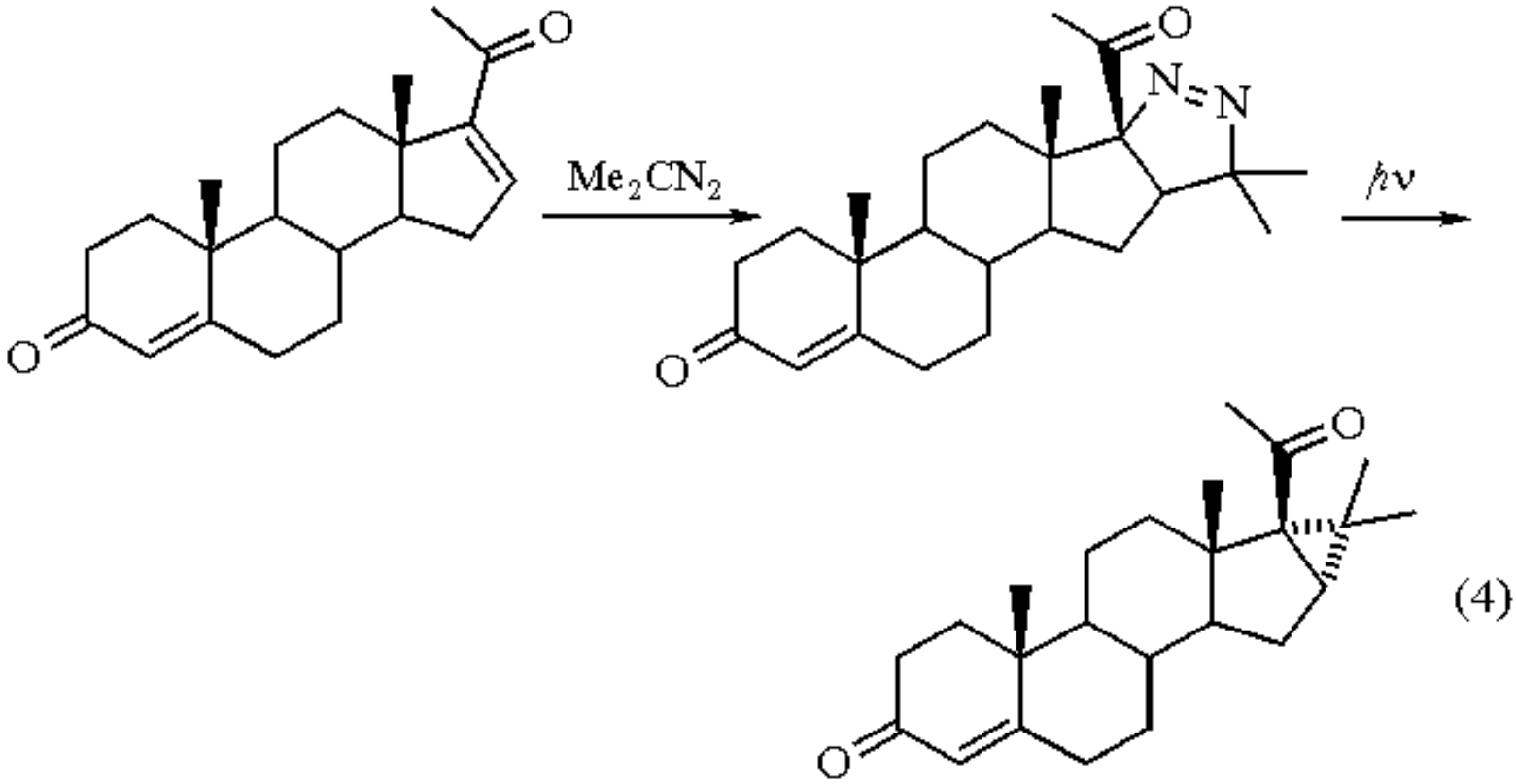

Strained alkenes will also undergo cycloadditions with 2-diazopropane (eq 5).[6] This particular case is interesting because the reagent adds predominantly to the more hindered face of the alkene, suggesting that the reaction is directed[7] by the acetate groups. In reactions with diazomethane the preference for addition to the more hindered face is even greater.

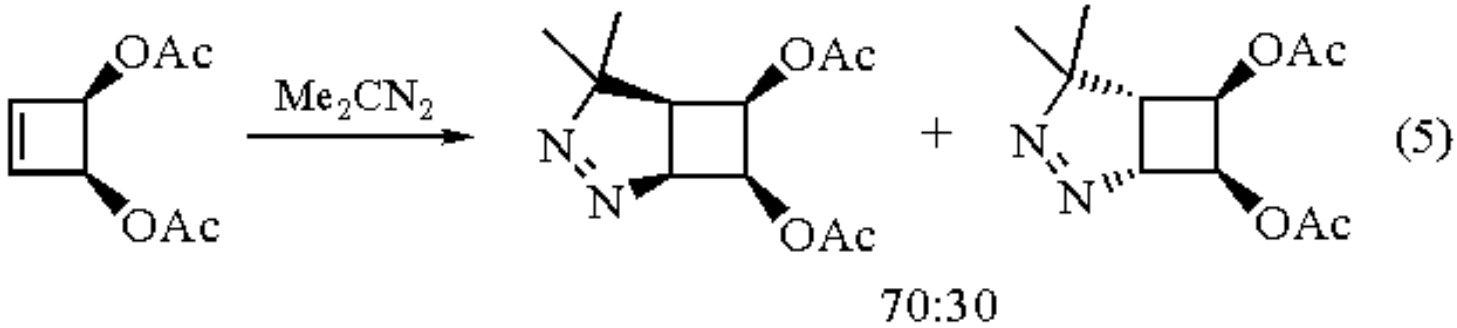

Additions of 2-diazopropane to chiral bicyclic lactams have also been explored (eq 6).[8] These reagents are known to add nucleophiles from the more hindered *endo* face of the alkene. Thus cyclopropanation with diphenylsulfonium isopropylide provided the expected *endo* product in a greater than 200:1 ratio. However, addition of 2-diazopropane provided a 1:1 mixture of *endo* and *exo* products. This difference in behavior has been explained on the basis of frontier molecular orbital theory.

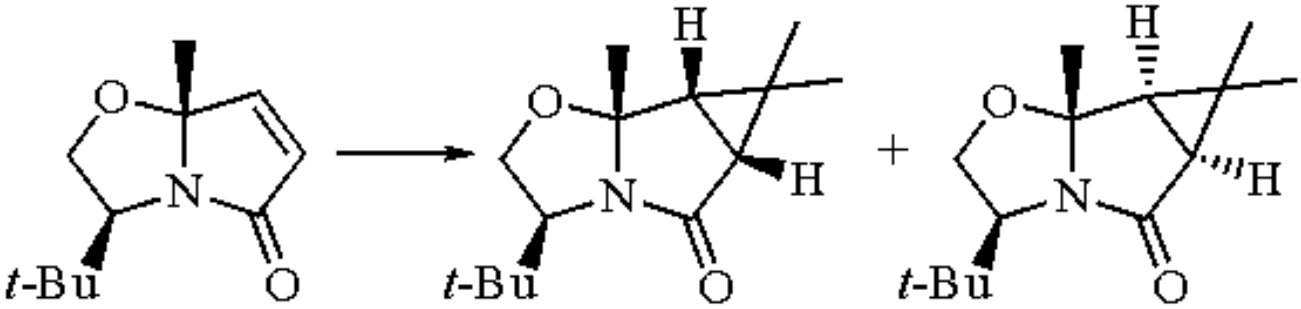

$Ph_2S{=}CMe_2$	>200:1
Me_2CN_2, $h\nu$	1:1

A similar loss in stereoselectivity was observed in the cyclopropanation of menthyl fumarates. Thus cyclopropanation with isopropylidenetriphenylphosphorane provided an 87:13 ratio of diastereomers while the use of 2-diazopropane provided a 53:47 mixture (eq 7).[9]

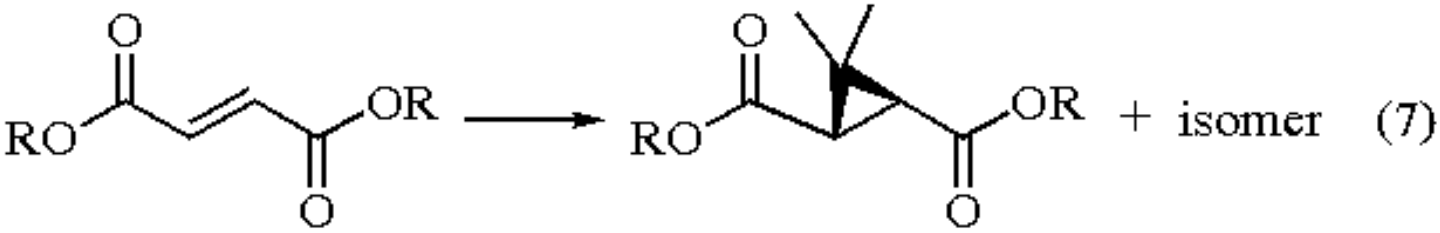

R = (-)-menthyl

$PPh_3{=}CMe_2$	87:13
Me_2CN_2, $h\nu$	53:47

The synthesis of α-cyclopropyl amino acids from suitably protected dehydro amino acids has been accomplished using 2-diazopropane.[10] The overall transformation is stereospecific with the (*Z*)-alkene isomer providing the corresponding *cis*-cyclopropane (eq 8). The regiochemistry in the cyclopropanation of tropone derivatives has been controlled by first converting the tropone to the dieneiron tricarbonyl complex. The uncomplexed alkene then reacts with 2-diazopropane to provide the pyrazoline which undergoes thermal extrusion of N_2 to give the desired cyclopropane (eq 9).[11]

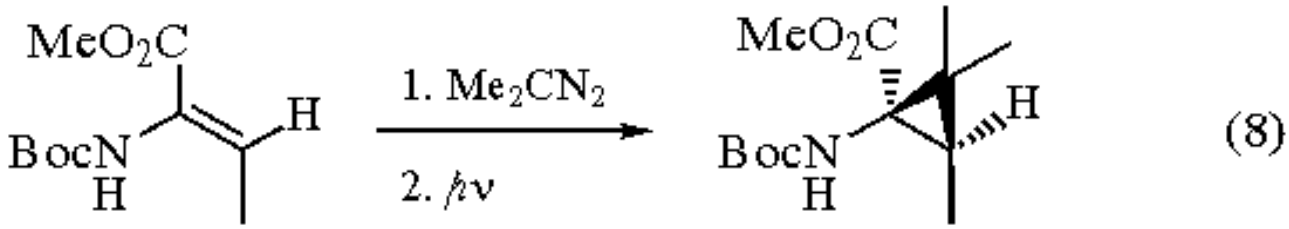

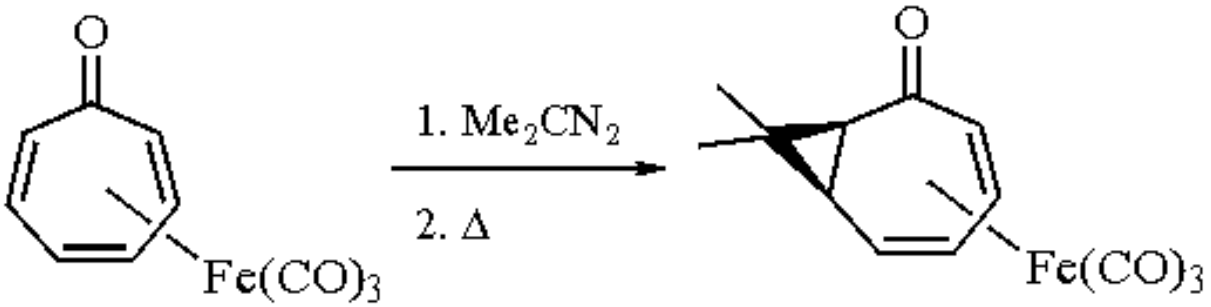

(9)

Cyclopropanation of Allenes.

Allenes are also suitable substrates for cyclopropanation by 2-diazopropane, with the most reactive substrates being those that are conjugated to an electron-withdrawing group. As with alkenes, the regiochemistry of the pyrazoline that is formed depends on the sterics of the system. With allenes that contain one or fewer carbon substituents at the γ-carbon, the carbon of the diazopropane will add to the more electron-deficient carbon of the double bond (eq 10). If the γ-carbon is disubstituted, then the opposite regiochemistry is observed (eq 11).[12]

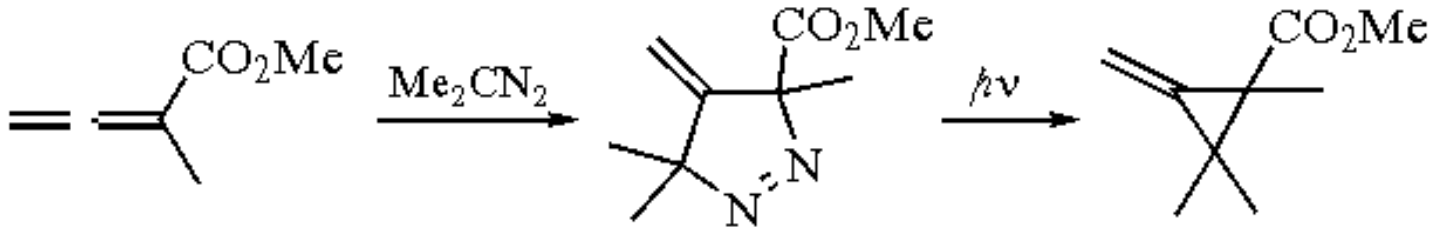

(10)

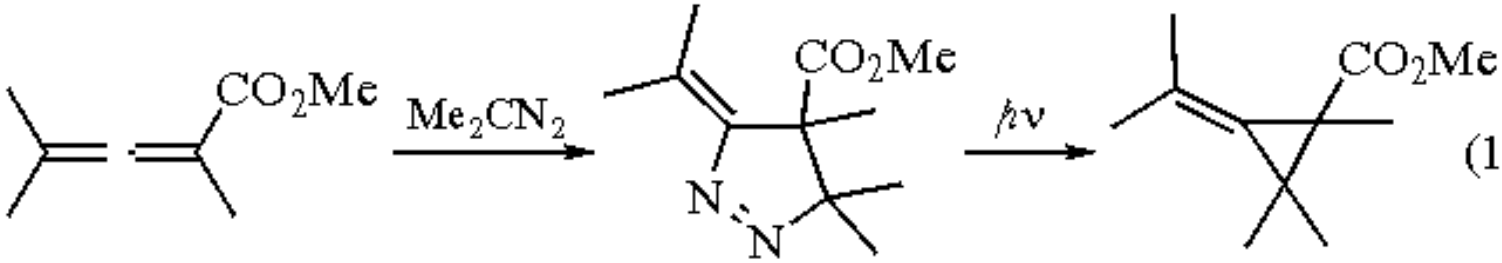

(11)

An interesting example of a cyclization to an allene which is not electron deficient has been reported.[13] Addition of 2-diazopropane to the allene shown in eq 12 provided the pyrazoline shown, which upon photolysis provided a 2:1 mixture of the two cyclopropanes in the equation. This synthesis was used to disprove an erroneous structure for the sex attractant of the American cockroach.

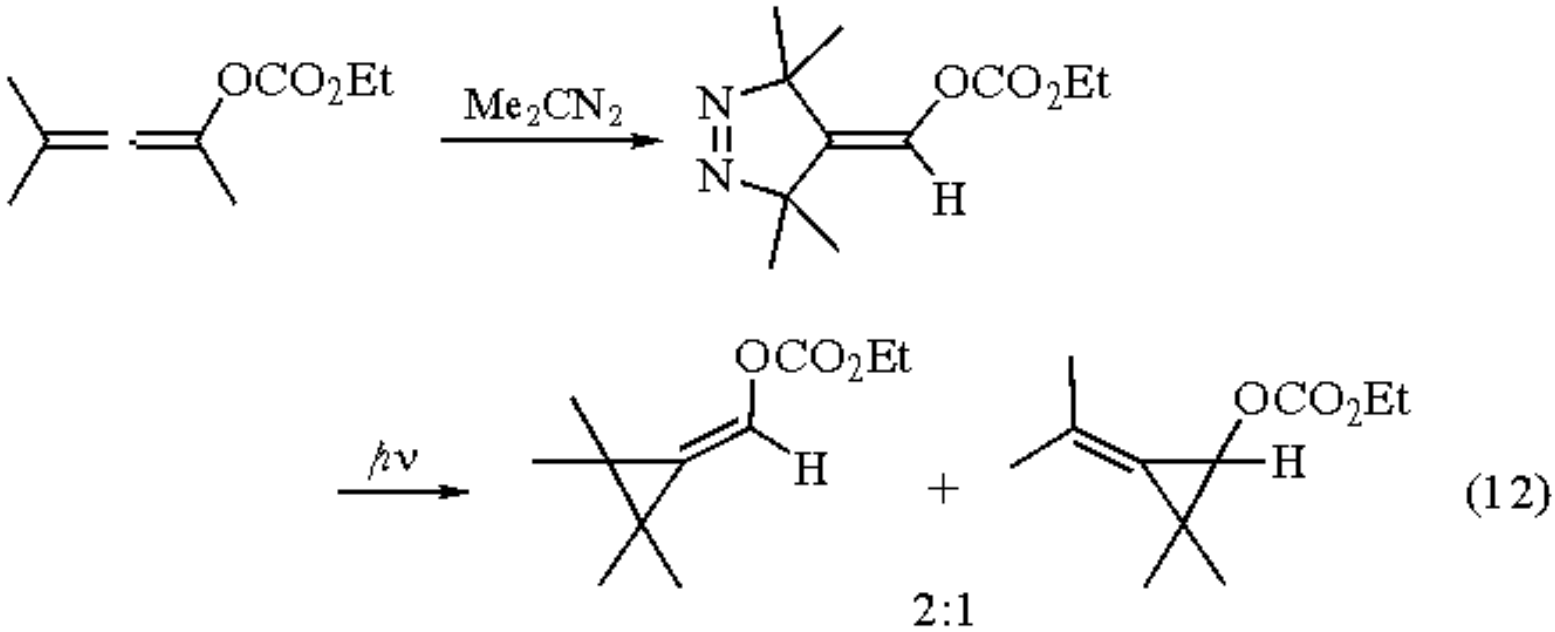

Cyclopropenation of Alkynes.

Alkynes can be converted to the corresponding cyclopropene via the pyrazole with 2-diazopropane. As with other systems, the reaction works best with electron-deficient alkynes, and the regiochemistry of the pyrazole that is formed depends on the sterics of the alkyne. Thus terminal alkynes provide the usual regiochemistry, whereas internal alkynes provide the opposite regiochemistry (eq 13).[14] Photolysis of the pyrazoles induces a rearrangement to a diazoalkene species which then undergoes photochemical extrusion of N_2 to give a carbene which inserts into the π-bond of the alkene to provide the cyclopropene (eq 14).

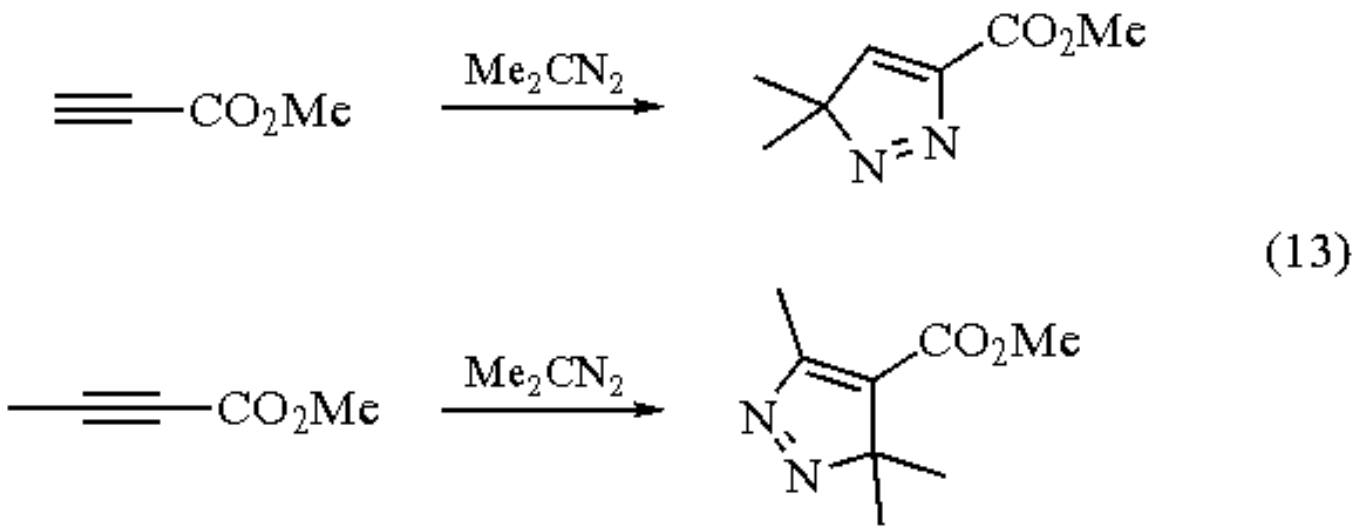

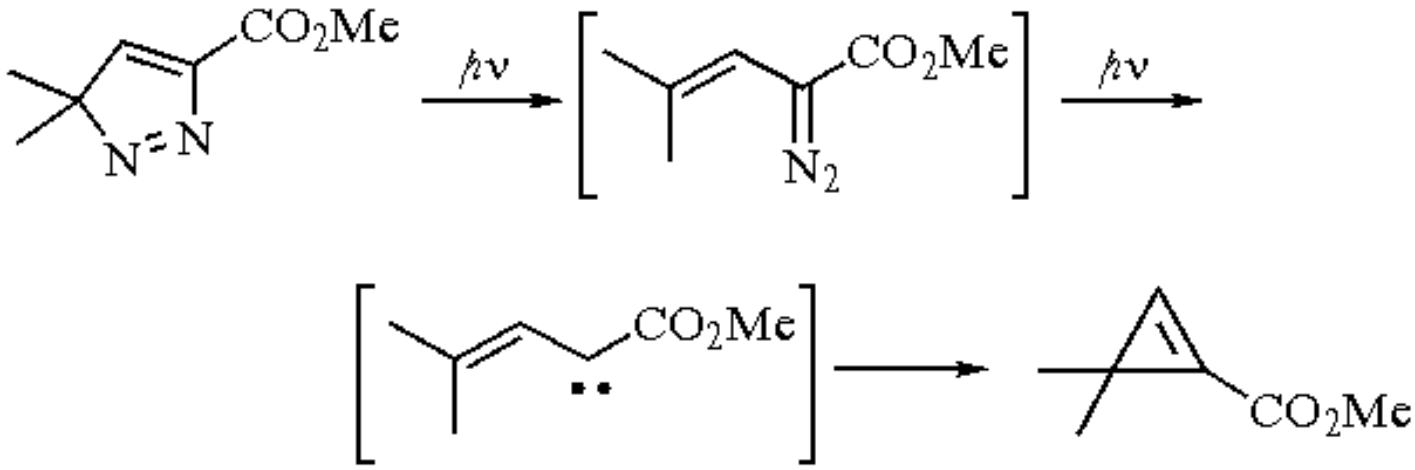

(14)

Evidence for the intermediacy of the diazoalkene has been obtained by trapping this species with acetic acid.[15] An interesting side reaction has been observed in reactions with trimethylsilyl-substituted alkynes. Irradiation of the pyrazole derived from these alkynes provides the expected carbene which, rather than inserting into the π-bond, inserts into the σ-bond of the acyl group to provide the product of a 1,2-acyl shift in high yield (eq 15).[16] The generality of this reaction has not yet been established. Other substrates that do not provide the cyclopropene are those that provide products which are sterically hindered. Thus irradiation of the pyrazole shown in eq 16 provides the product of insertion into the tertiary C-H bond rather than the alkene.[17]

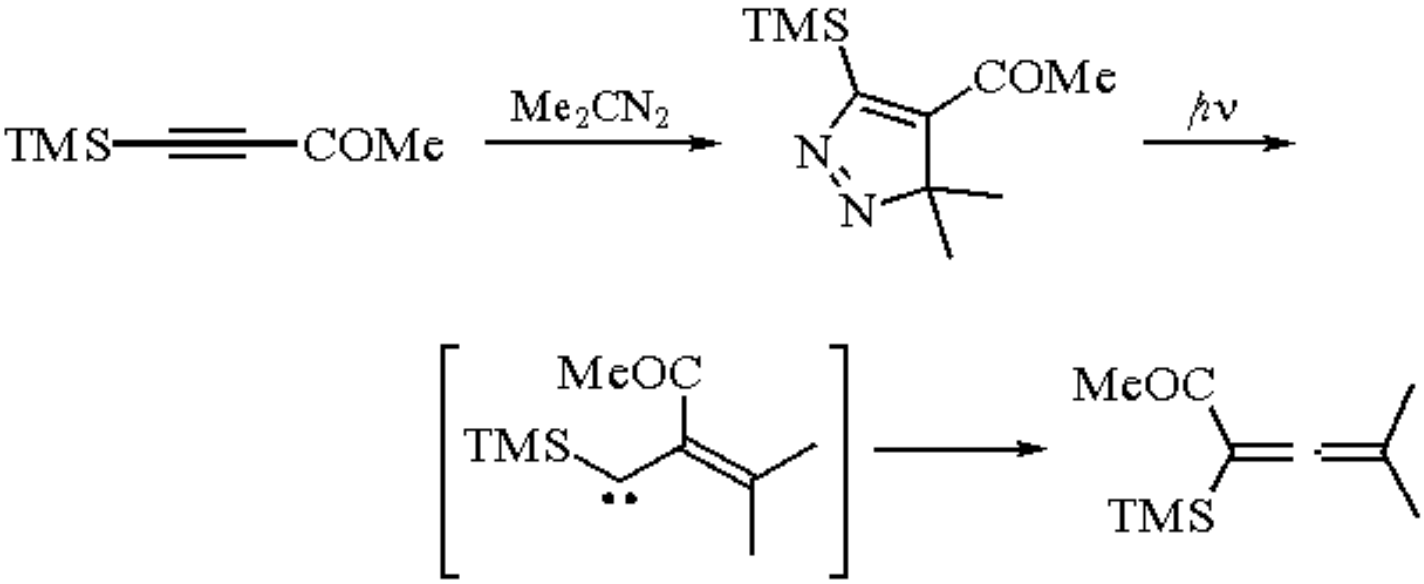

(15)

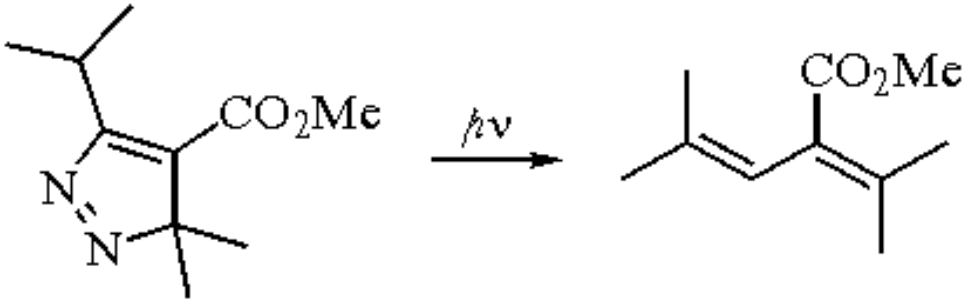

(16)

The cyclopropenes produced in this reaction have been used in the synthesis of *cis*-chrysanthemic methyl ester.[18] The key step involves cyclopropenation of the ene-yne shown in eq 17. Addition of 2-diazopropane to the alkyne occurs in

preference to the alkene to give both regioisomeric pyrazoles. Photochemical extrusion of N_2 from both isomers provides the desired cyclopropene. This was converted to *cis*-chrysanthemic methyl ester by diimide reduction of the more reactive cyclopropene alkene.

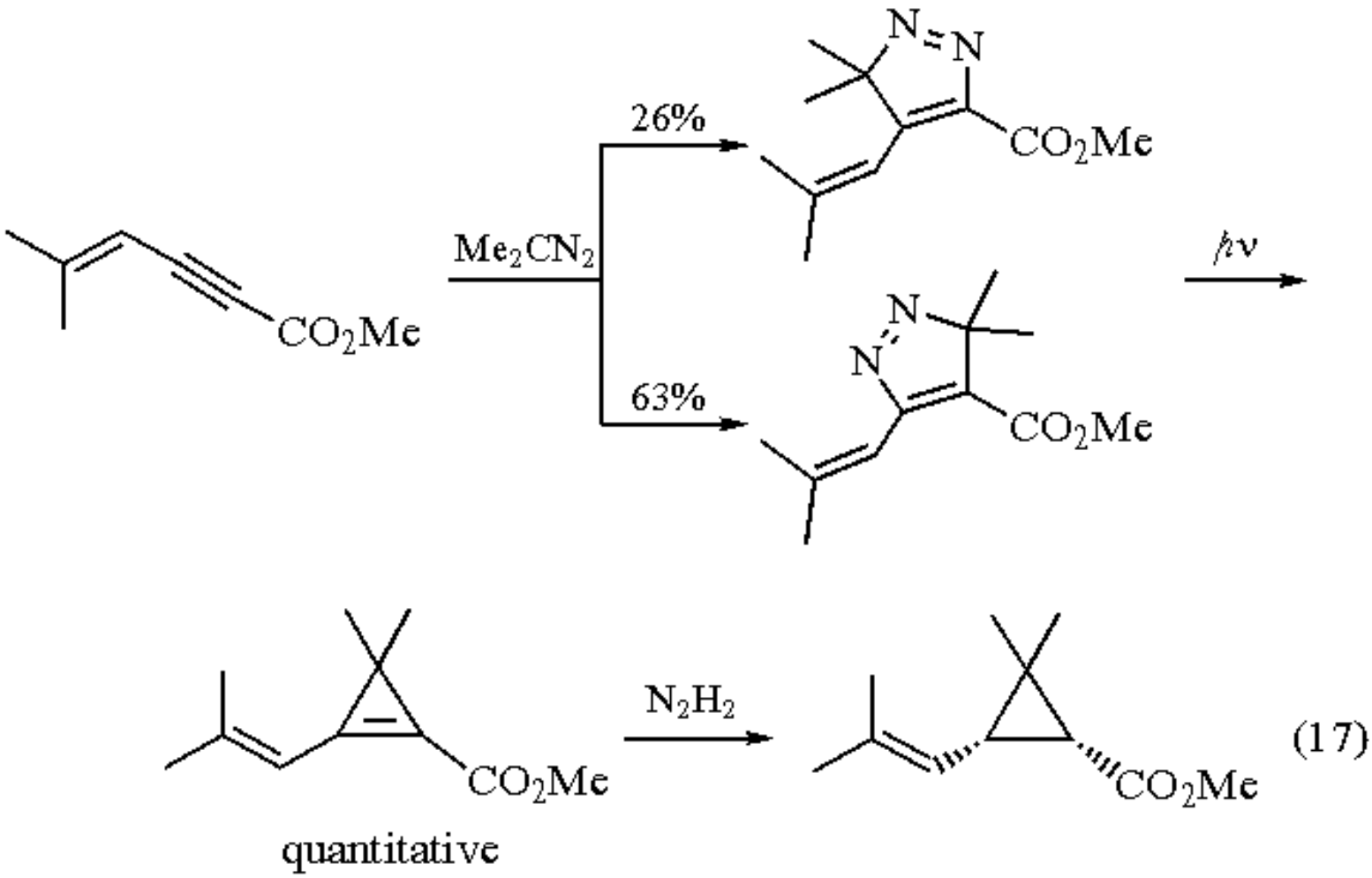

Another use for these cyclopropene reagents is a formal [3 + 2] annulation reaction which provides cyclopentenols. The process involves [2 + 2] cycloaddition of the cyclopropene with an eneamine to provide a strained bicyclic product which undergoes ring opening with acid and water to provide a cyclopentenol (eq 18).[19] This strategy has been employed in the synthesis of several natural products including hirsutene,[20] silphenene,[21] and dihydroilludine M.[22]

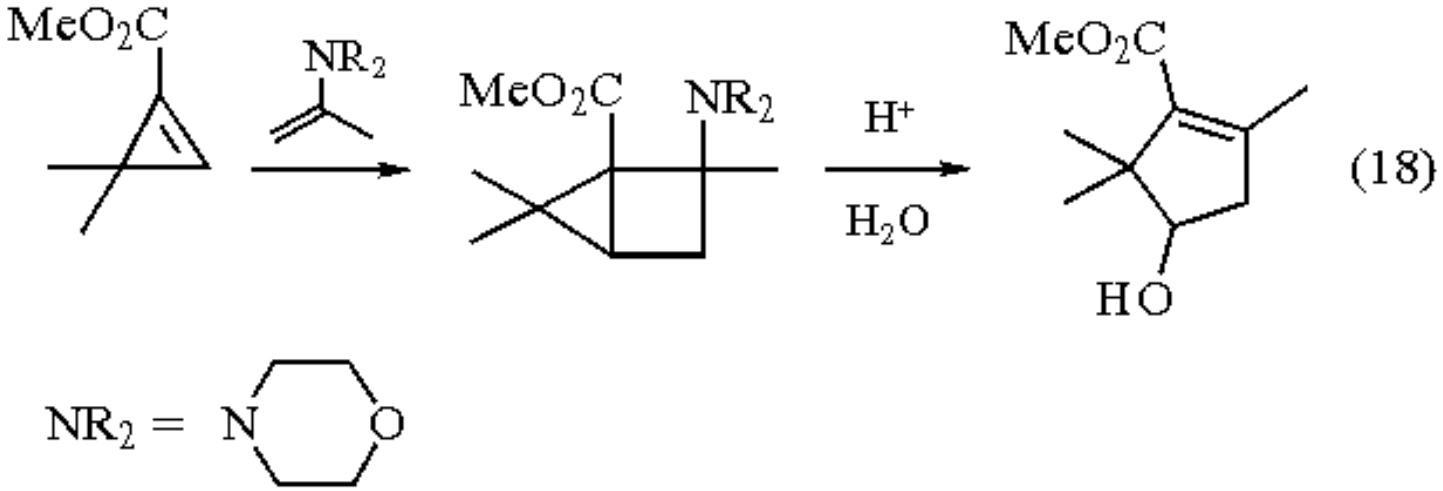

A disadvantage of this strategy is that with certain substrates, the cycloaddition product is accompanied by a substantial amount (at times the major product) of the product of Michael addition of the eneamine to the cyclopropylcarboxylate. A related annulation has therefore been developed which avoids this problem. This strategy involves the addition of 2-diazopropane to a cyclobutene to provide a similar bicyclic intermediate to that obtained previously. This species can also undergo acid-catalyzed ring opening with water (eq 19) to provide the cyclopentenol.[23]

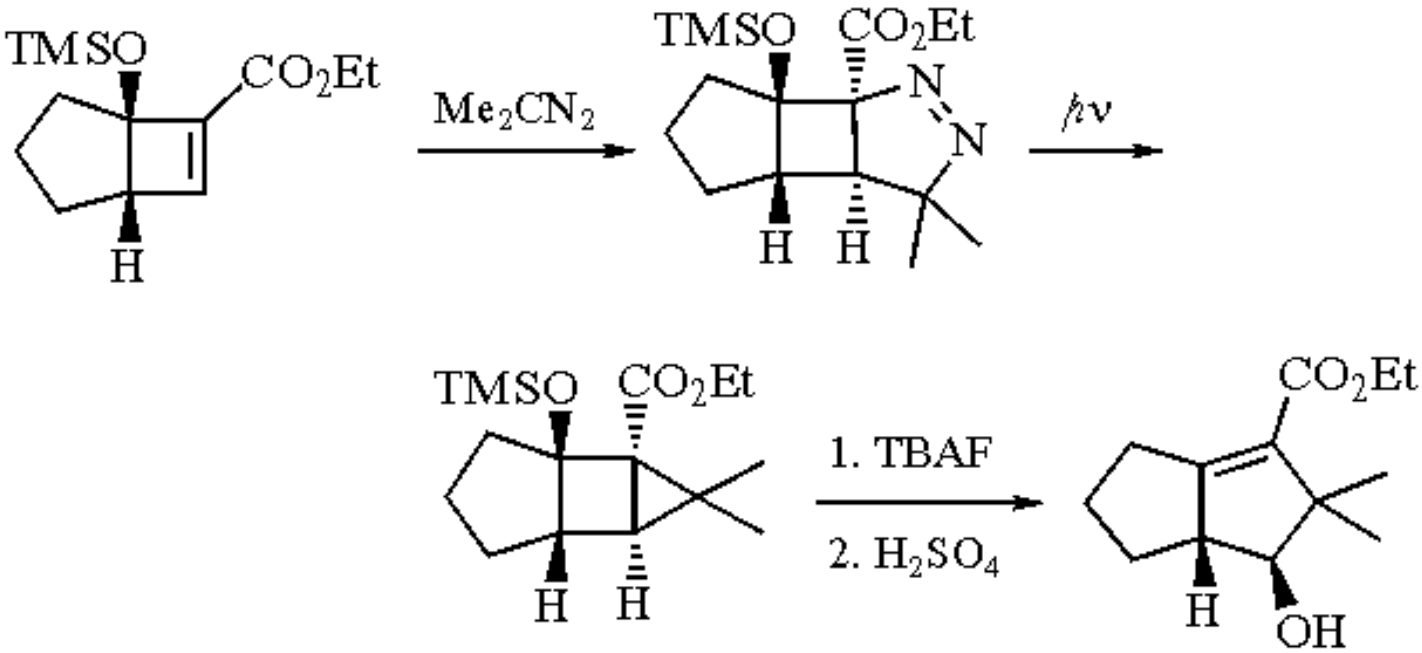

(19)

Insertion into Vinylic C-H Bonds.

A common side reaction which occurs during attempted cyclopropanation of alkenes with diazopropane is an overall insertion into a C-H bond of the alkene. This reaction is favored by thermal extrusion of N_2 and, for this reason, photolysis is the preferred method of decomposing pyrazolines to cyclopropanes (eq 1). However, it has been observed that alkenes which bear two electron-withdrawing groups will exclusively provide the insertion product upon reaction with 2-diazopropane with mild or no heating. The reaction has been used to introduce an isopropyl residue into 3-cyanocoumarins[24] and iron tricarbonyl complexes of acetyltropone[25] in excellent yield (eqs 20 and 21). Furthermore, it has been used in diminished yield to alkylate alkenes with a single electron-withdrawing group, as previously discussed.[26]

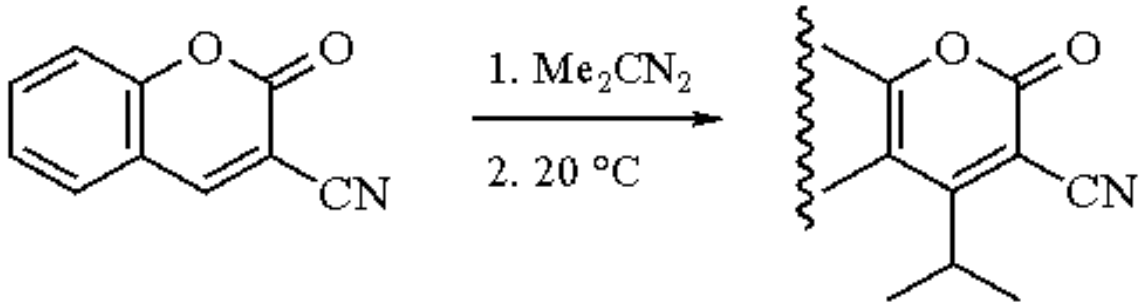

(20)

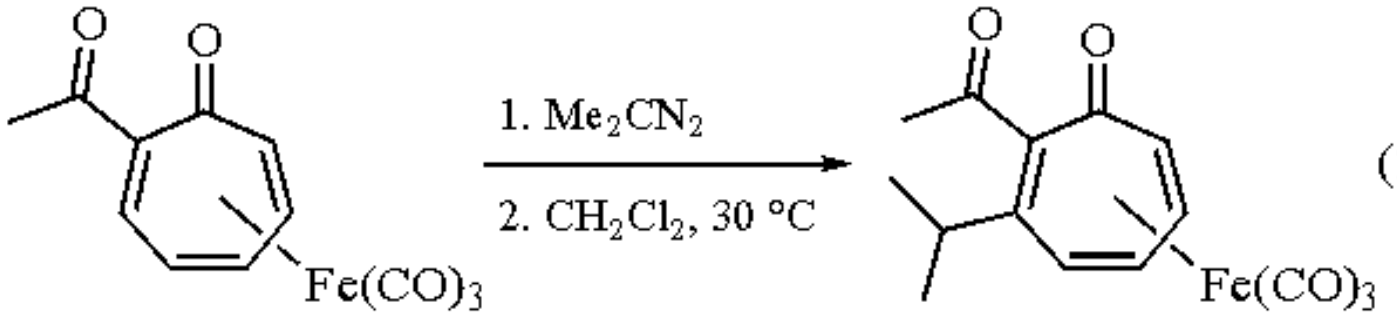

(21)

Miscellaneous Reactions.

Interestingly, 2-diazopropane is not commonly used to esterify carboxylic acids. The reaction has been studied with excess acetic acid and has been shown to proceed in 35%-52% yield based on the diazo compound, with the major byproduct being tetramethylethylene.[27] This should not be a serious problem to utilizing the reaction with other carboxylic acids since the byproduct is volatile. The reagent has been used to selectively esterify the more hindered carbonyl of a vinylogous acid when other reagents failed (eq 22).[28]

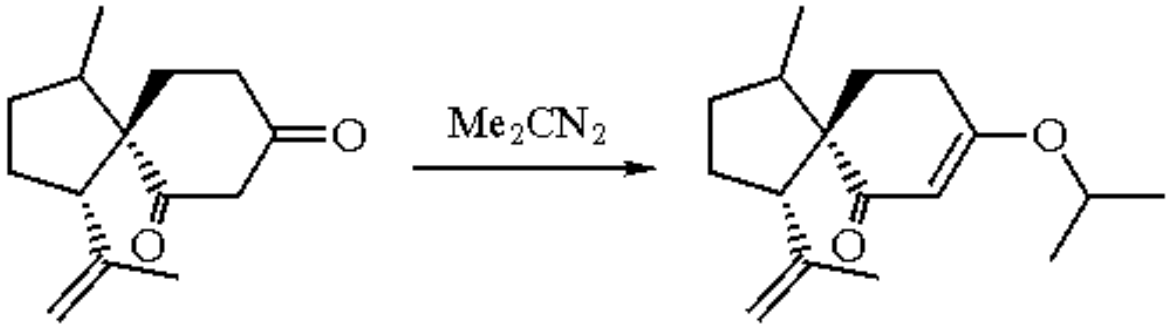

(22)

2-Diazopropane has also been used in the synthesis of episulfides from thioketones. The reaction works even for very hindered substrates (eq 23). Extrusion of sulfur with triphenylphosphine provides the corresponding alkene, thus rendering this a method for the synthesis of hindered alkenes.[29]

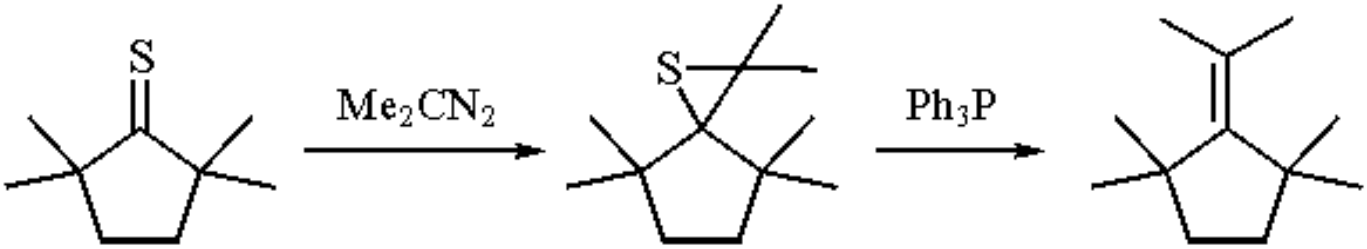

(23)

Related Reagents.

Diazomethane.

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1. Andrews, S. D.; Day, A. C.; Raymond, P.; Whitting, M. C. *OSC* **1988**, *6*, 392.

2. Franck-Neumann, M. *AG(E)* **1968**, *7*, 65.
3. This reaction is most common with highly electron-deficient alkenes, such as those bearing two electron-withdrawing groups, and is discussed in more detail later in this article.
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7. For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *CRV* **1993**, *93*, 1307.
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11. Saha, M.; Bagby, B.; Nicholas, K. M. *TL* **1986**, *27*, 915.
12. Andrews, S. D.; Day, A. C.; Inwood, R. N. *JCS(C)* **1969**, 2443.
13. Day, A. C.; Whitting, M. C. *JCS(C)* **1966**, 464. Day, A. C.; Whitting, M. C. *JCS(B)* **1967**, 991.
14. Day, A. C.; Inwood, R. N. *JCS(C)* **1969**, 1065.
15. Day, A. C.; Whitting, M. C. *JCS(C)* **1966**, 1719.
16. Padwa, A.; Wannamaker, W. *T* **1990**, *46*, 1145.
17. Dietrich-Buchecker, C.; Franck-Neumann, M. *T* **1977**, *33*, 751.
18. Franck-Neumann, M.; Dietrich-Buchecker, C. *TL* **1980**, *21*, 671.
19. Franck-Neumann, M.; Miesch, M.; Kempf, H. *S* **1989**, 820.
20. Franck-Neumann, M.; Miesch, M.; LaCroix, E. *TL* **1989**, *30*, 3529.
21. Franck-Neumann, M.; Miesch, M.; LaCroix, E. *TL* **1989**, *30*, 3533.
22. Franck-Neumann, M.; Miesch, M.; Barth, F. *TL* **1989**, *30*, 3537.
23. Franck-Neumann, M.; Miesch, M.; Gross, L. *TL* **1990**, *31*, 5027.
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25. Franck-Neumann, M.; Martina, B. D. *TL* **1978**, *19*, 5033.
26. For an additional example, see: McMoriss, T. C.; Ramakrishnan, S.; Arunachalam, T. *JOC* **1974**, *39*, 669.
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1-Diazo-2-propene

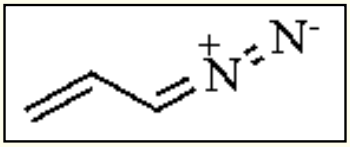

[2032-04-4] · $C_3H_4N_2$ · 1-Diazo-2-propene · (MW 68.08)

(reagent for the cyclopropanation of alkenes)

Alternate Name: vinyldiazomethane.

Solubility: vinyldiazomethane is most commonly prepared and used as a solution in ether or THF, or as an alcoholic solution in either of those solvents.

Analysis of Reagent Purity: the amount of active diazo compound contained in a solution has been determined by measuring the volume of nitrogen evolved upon reaction of an aliquot of the diazo compound with an excess of *p*-nitrobenzoic acid in THF.[3]

Preparative Methods: the reagent is most commonly prepared by the action of base on various *N*-allyl-*N*-nitroso derivatives. Thus ethyl-*N*-allyl-*N*-nitrosocarbamate has been used,[1] as has *N*-allyl-*N*-nitrosourea.[2] The reagent is light sensitive and should therefore be shielded from light during its preparation. It undergoes isomerization to pyrazole at rt[1c] and is therefore prepared immediately prior to use, and not usually stored for any length of time. Furthermore, it is potentially explosive and for this reason the chemist is advised to follow carefully the exact procedure given for a particular preparation and perform all operations behind a blast shield in a well ventilated fume hood.

Handling, Storage, and Precautions: in addition to the previously mentioned explosion hazard which this reagent presents, there are health related hazards that must also be considered. Diazo compounds, as a class, are toxic and irritating and can be sensitizers. They must be used in a well ventilated fume hood and not come in contact with skin. For a description of the hazards associated with this class of compounds, see the handling and storage precautions listed for ***Diazomethane***.

Cycloadditions.

Vinyldiazomethane is commonly used to prepare vinylcyclopropane derivatives from alkenes, either via transition metal-catalyzed cyclopropanation, or via an intermediate pyrazoline. In the case of the transition metal-catalyzed process, the product cyclopropane contains an alkene which can react further with the starting vinyldiazomethane. The procedure is therefore limited to alkenes which can be used in large excess, or which are substantially more reactive than the product alkene. Thus low boiling, electron-rich alkenes have been used in large excess with various copper(II)

salts as the catalysts.[3] Of the various copper salts examined, ***Copper(II) Trifluoromethanesulfonate***, copper(II) trifluoroacetate, and ***Copper(II) Hexafluoroacetylacetonate*** were found to provide low to moderate yields (12-40%) of the desired cyclopropane from cyclohexene. Copper(I) iodide and copper(II) chloride, carbonate, and sulfate were found to be ineffective. The reaction is stereospecific, with *cis*- and *trans*-alkenes providing the corresponding *cis*- and *trans*-cyclopropanes, respectively (eqs 1 and 2).

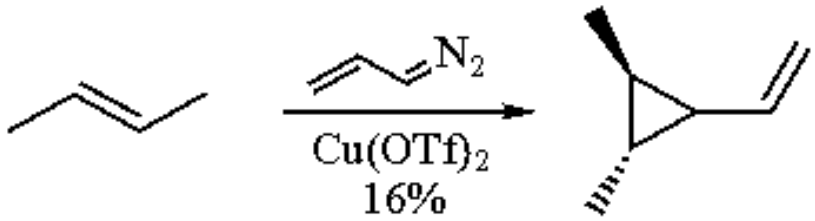

(1)

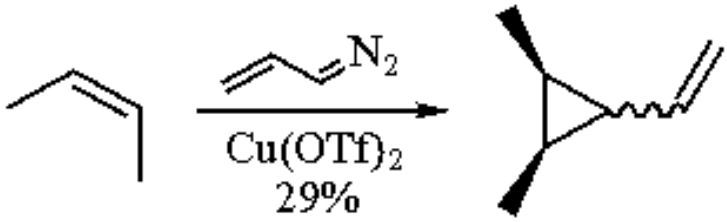

(2)

Rhodium(II) complexes have also been examined as catalysts for cyclopropanation, and have been found to be more effective than copper salts.[4] The reaction works well for enol ethers and dienol ethers, with cyclopropanation preferentially occurring at the alkoxy-substituted alkene (eq 3). The reaction has been used to prepare cycloheptadiene derivatives by cyclopropanation of dienes followed by [3,3]-sigmatropic rearrangement of the resulting divinylcyclopropane.

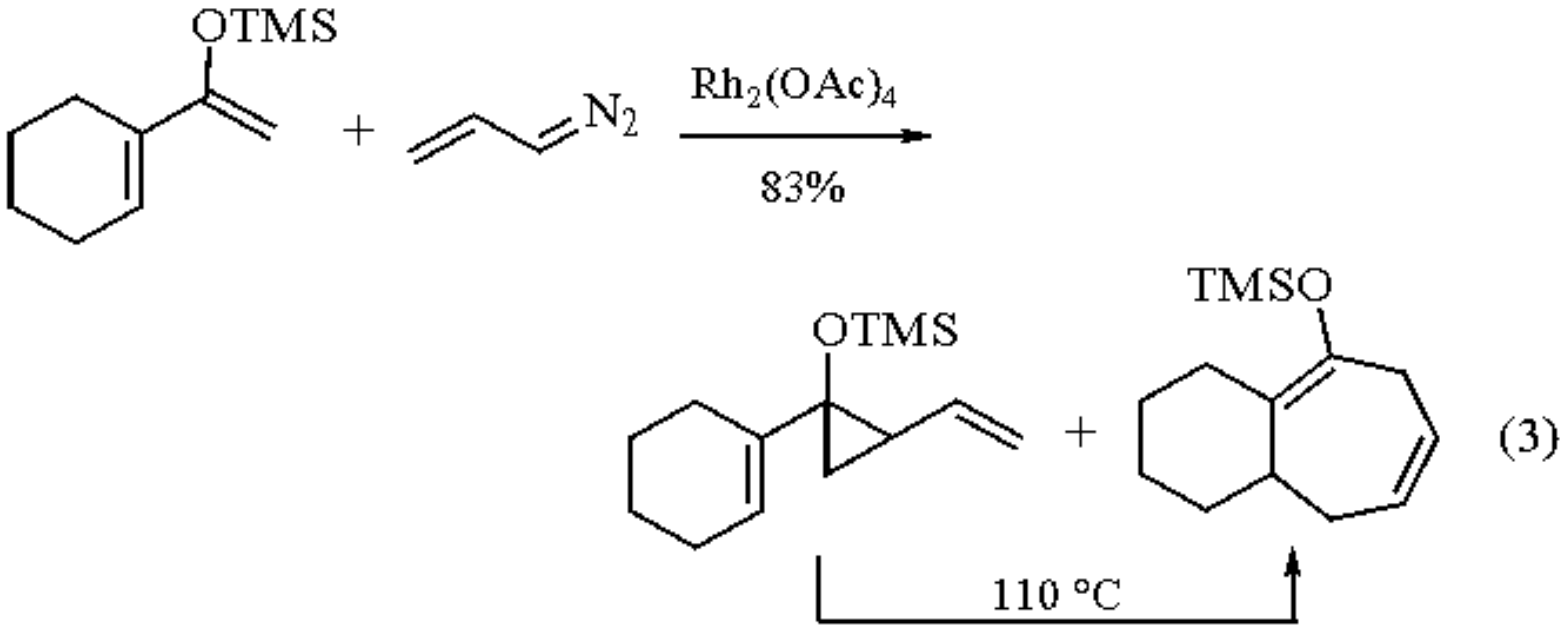

(3)

Vinyldiazomethane will readily undergo dipolar cycloaddition with electron-deficient alkenes to provide vinylpyrazolines.[5] Vinylpyrazolines are less stable than typical alkylpyrazolines, and will undergo loss of N_2 to provide the corresponding vinylcyclopropane with either thermal or photochemical activation. The reaction has been used to prepare vinylcyclopropyl steroid derivatives from Δ^{16}-20-oxo-steroid derivatives (eq 4).[2] Thermal extrusion of N_2

provides the desired cyclopropane in 90% yield.

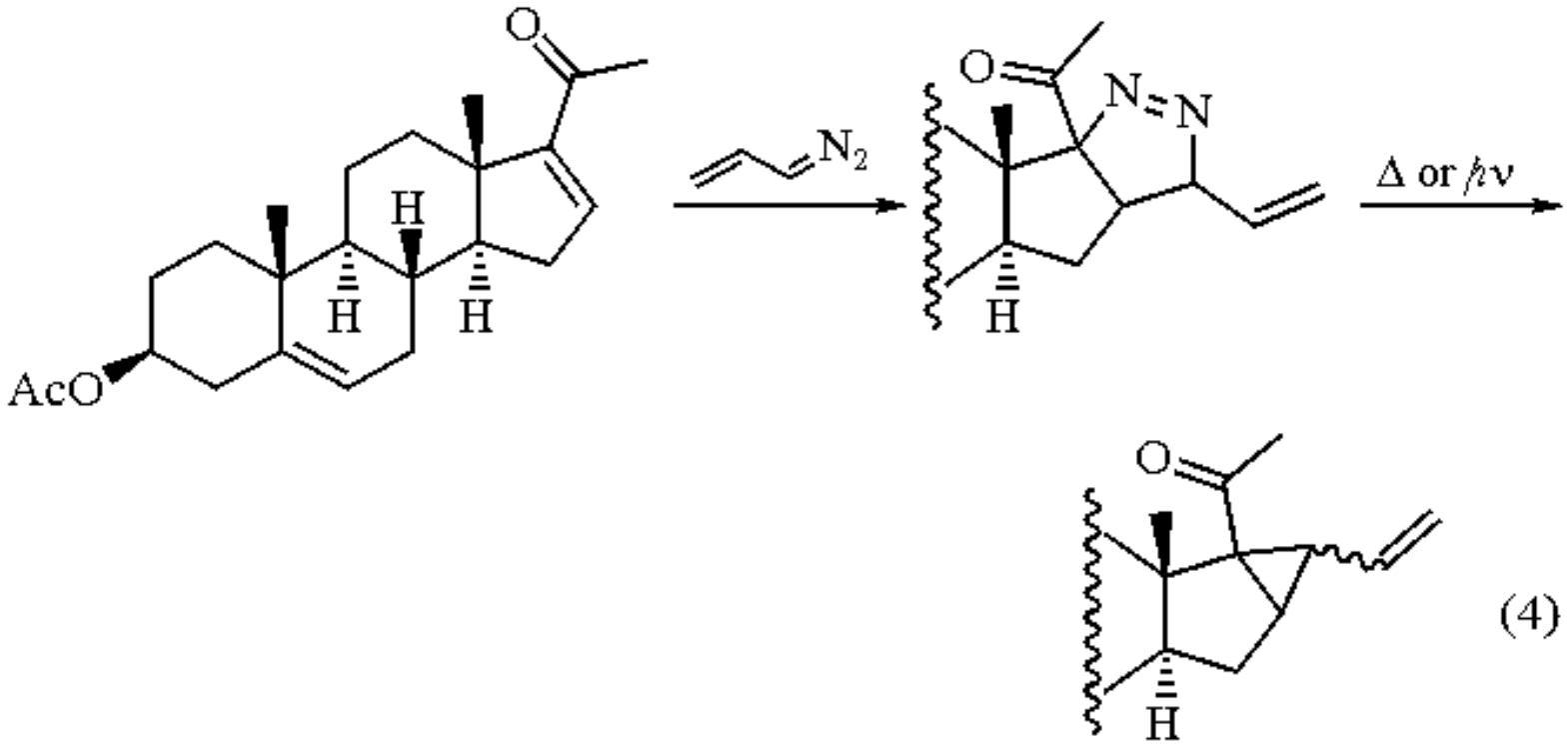

(4)

An interesting side reaction has been observed with alkenes that bear two electron-withdrawing substituents. These substrates do not provide the cyclopropane upon thermolysis, but give the product of insertion into C-H bonds on the carbon that is β to the carbonyl (eq 5).[6] This is a general reaction which will work with other diazoalkanes.

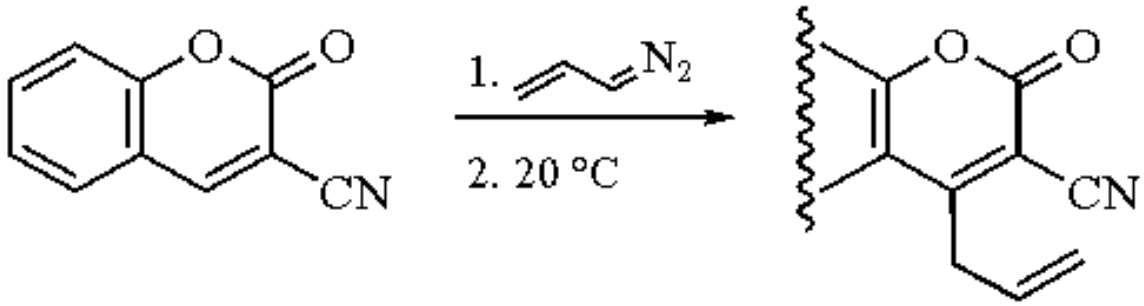

(5)

Conjugated dienes will also undergo dipolar cycloaddition with vinyldiazomethane. The reaction occurs preferentially at the less substituted alkene, as predicted by FMO theory.[7] The resulting pyrazolines undergo extrusion of N_2 at rt or below to provide the corresponding divinylcyclopropyl derivatives. These compounds will then undergo [3,3]-sigmatropic rearrangement to provide cycloheptadiene derivatives. The *cis*-divinylcyclopropanes undergo sigmatropic rearrangement very rapidly, at times below rt. This has hindered attempts to obtain kinetic data for these substrates. However, they can be synthesized by low temperature (-40 °C) photolysis of pyrazolines derived from vinyldiazomethane and conjugated dienes.[8] The reaction has been used to synthesize the algae metabolite dictyopterene D´ via a vinylcyclopropyl derivative (eq 6).[9]

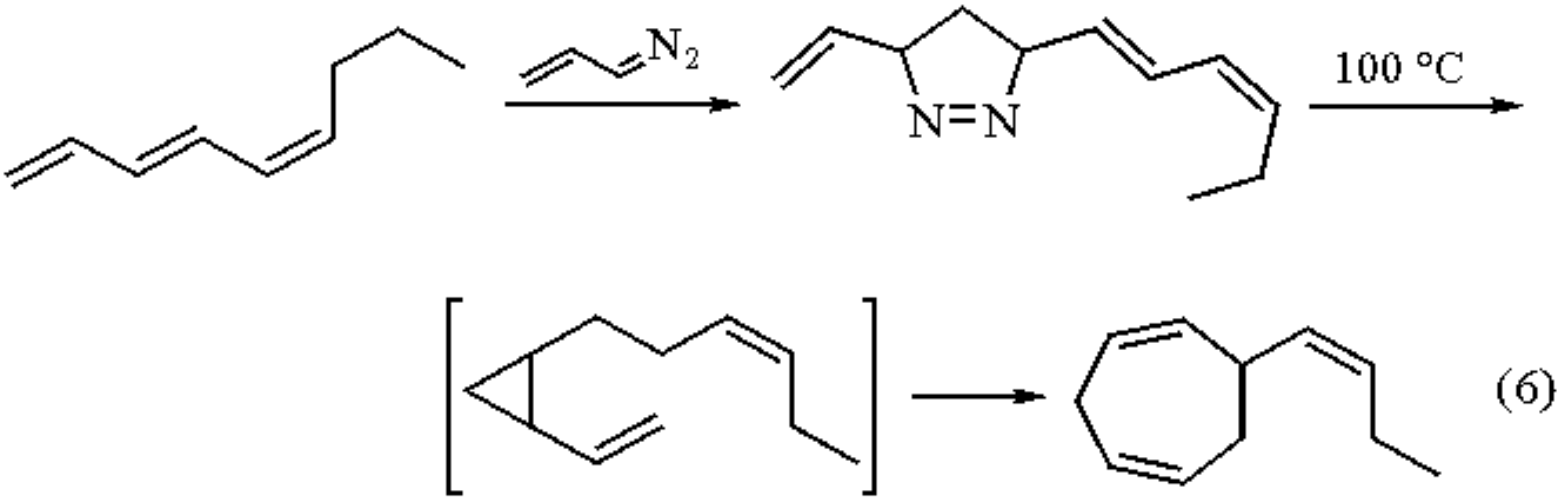

Allylation of Heteroatoms.

Vinyldiazomethane can be used to convert carboxylic acids to the corresponding allyl carboxylate.[1c,3] However, the reaction has not been widely utilized. An interesting example of the allylation of an alcohol has been reported.[10] Treatment of the vicinal steroidal diol shown in eq 7 with boric oxide provides the corresponding borate ester. Treatment of this compound with vinyldiazomethane provides the monoallyl ether with preferential reaction at the less hindered oxygen. Presumably, the reaction proceeds by protonation of the vinyldiazomethane by the borate ester to provide an allyldiazonium species which undergoes nucleophilic attack by oxygen.

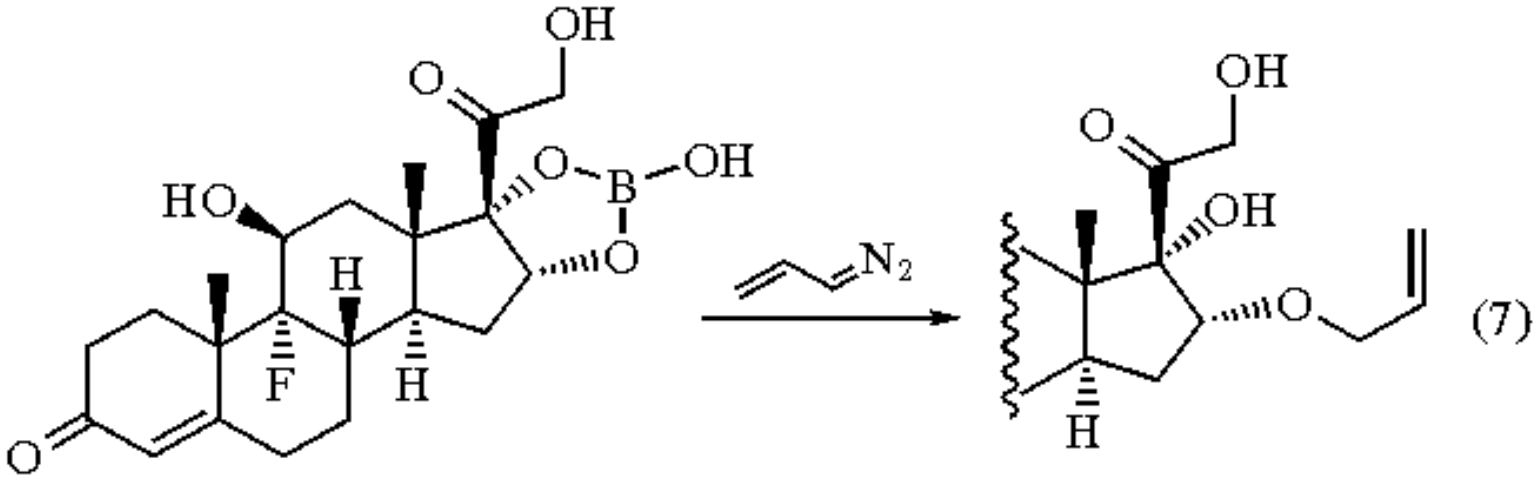

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1. (a) De Meijere, A.; Schulz, T-J.; Kostikov, R. R.; Graupner, F.; Murr, T.; Bielfeldt, T. *S* **1991**, 547. (b) Hooz, J.; Kono, H.; *OPP* **1971**, *3*, 47. (c) Brewbaker, J. L.; Hart, H. *JACS* **1969**, *91*, 711.
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Diazo(trimethylsilyl)methyllithium[1]

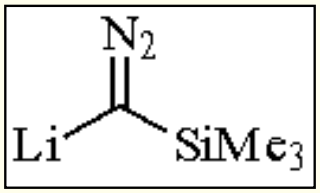

[84645-45-4] · $C_4H_9LiN_2Si$ · Diazo(trimethylsilyl)methyllithium · (MW 120.16)

(nucleophilic diazo species for introduction of one carbon; used in homologation and alkenylation of ketones,[2,4,5] preparation of diazo ketones,[6] acylsilanes,[7] vinylsilanes,[8] and heterocycles[9,10])

Alternate Names: lithiotrimethylsilyldiazomethane; trimethylsilyldiazomethyllithium.

Solubility: sol THF/hexane mixtures in which it is generated; precipitates out of ether/hexane.

Preparative Method: prepared in situ by lithiation of ***Trimethylsilyldiazomethane*** using ***n-Butyllithium***.

Handling, Storage, and Precautions: handle as for other organolithium reagents; stable in solution below 0 °C. Use in a fume hood.

Homologation Reactions of Ketones.

When generated in pentane/THF at -100 °C, diazo(trimethylsilyl)methyllithium reacts with ketones (three examples) and benzaldehyde to give the unstable 1-diazo-1-trimethylsilyl-2-alkanols (eq 1).[2] On gentle warming, the diazo alcohols rapidly lose N_2 to give trimethylsilyl epoxides. Since such epoxides readily give aldehydes on treatment with acid,[3] the method represents an overall homologation of a ketone to the next higher aldehyde.

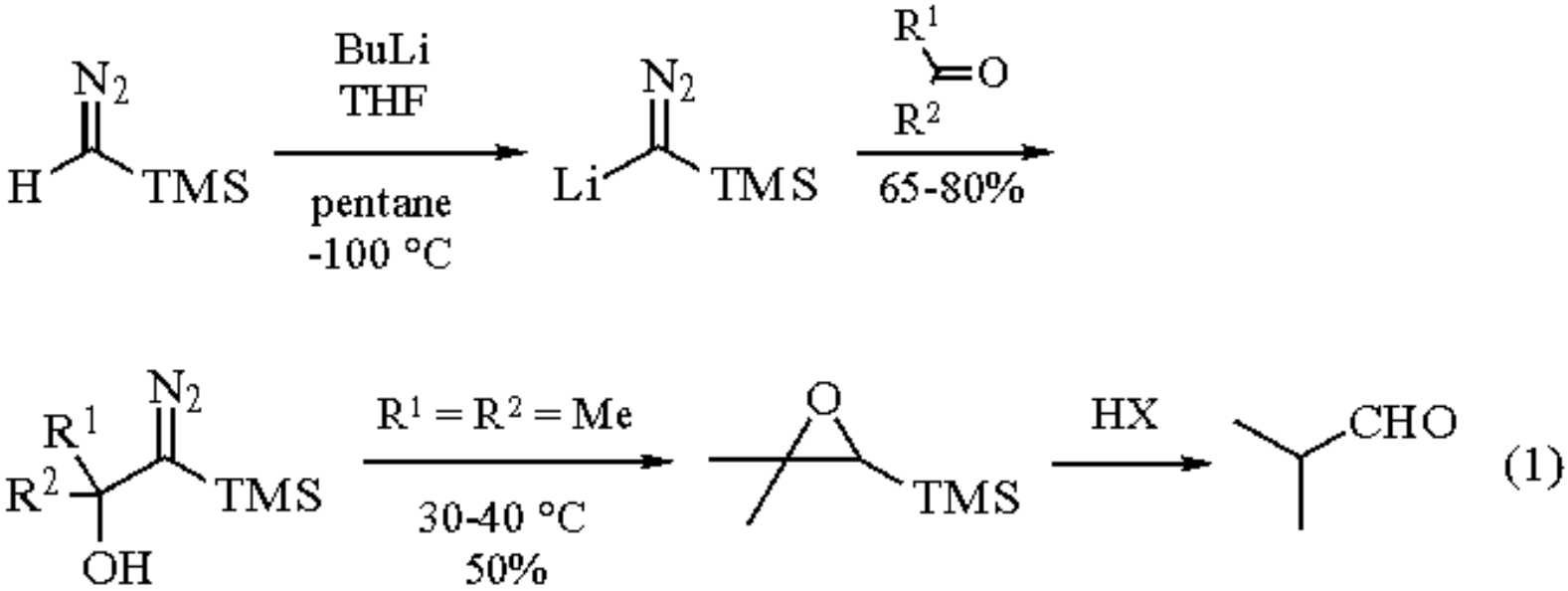

When diaryl ketones are used, diarylalkynes are formed in good yield (eq 2).[4] The reaction presumably proceeds via the diazoalkene followed by aryl migration with loss of nitrogen.

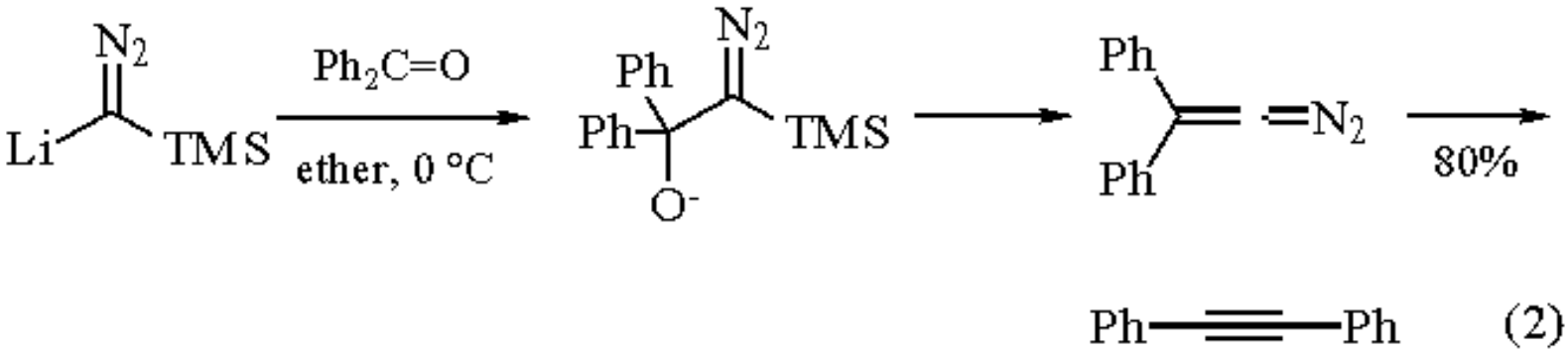

In contrast to the above, a more recent study, using slightly different conditions, reports that whereas aldehydes give terminal alkynes (eq 3), ketones give cyclopentene derivatives, presumably by intramolecular C-H insertion of intermediate alkylidenecarbenes (eq 4).[5] No detectable amounts of diazo alcohols or epoxysilanes were produced.

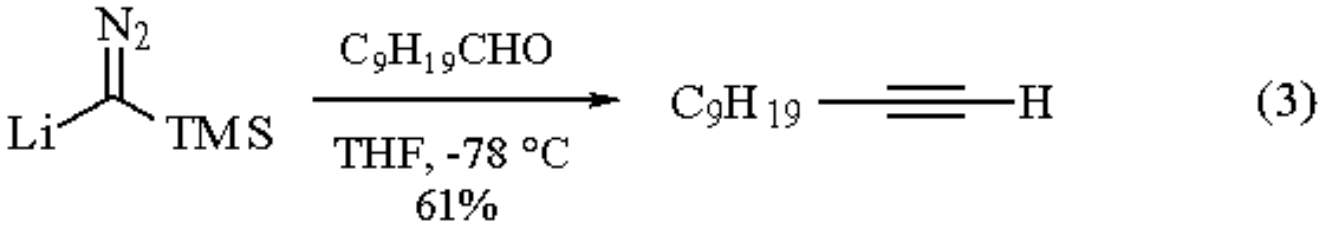

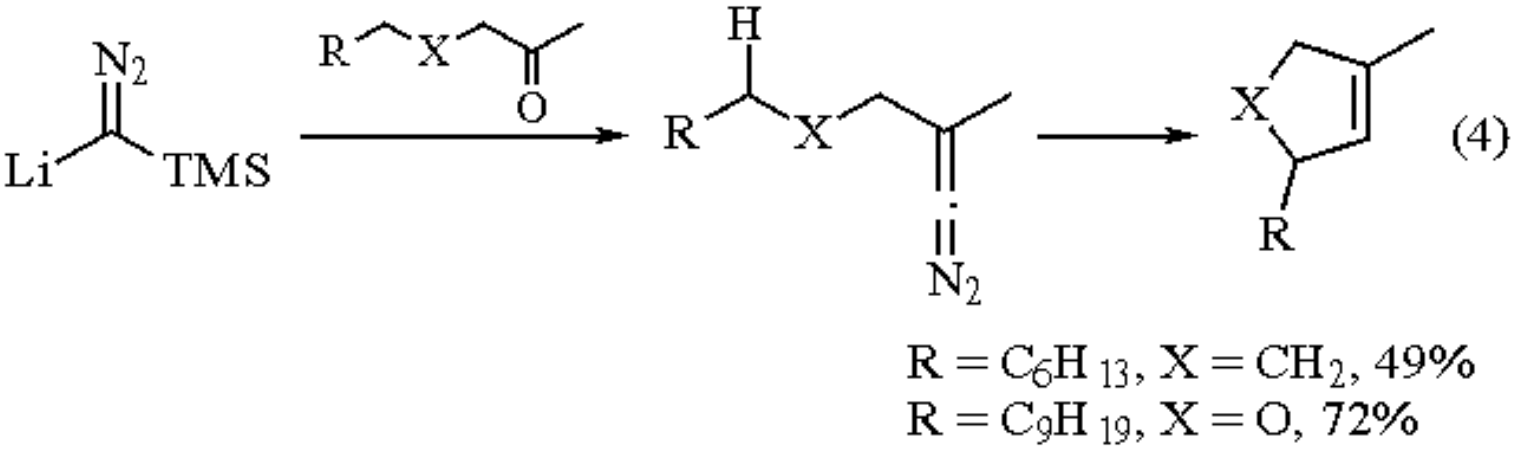

Preparation of Diazo Ketones.

Diazo(trimethylsilyl)methyllithium reacts with lactones to give the product of ring opening, the diazo alcohol, although the silyl group is lost during workup (eq 5).[6] The diazo alcohol can subsequently be cyclized to the corresponding oxepane by treatment with ***Dirhodium(II) Tetraacetate***.

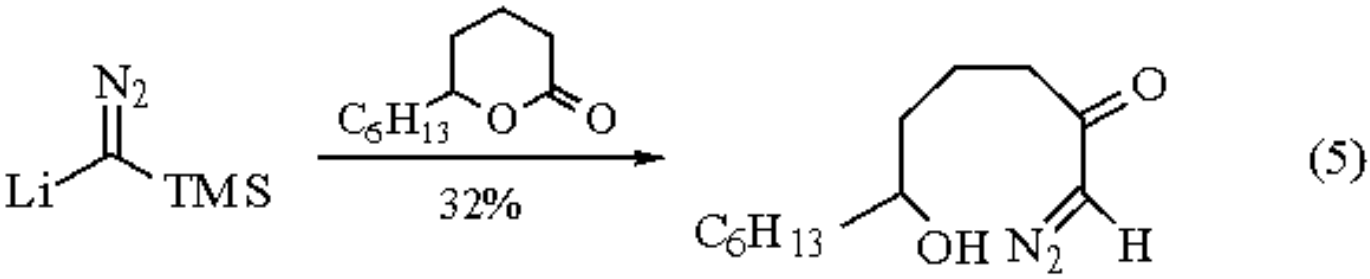

Preparation of Acylsilanes.

Diazo(trimethylsilyl)methyllithium is alkylated by a range of alkyl halides RX (R = alkyl, benzyl) to give the corresponding diazosilanes, which are oxidized to the acylsilanes in reasonable yield by treatment with ***m-Chloroperbenzoic Acid*** (eq 6).[7]

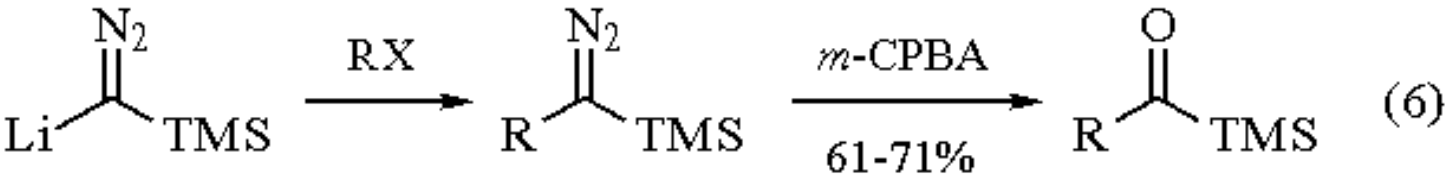

Preparation of Vinylsilanes ((*E*)-Trimethylsilylalkenes).

Treatment of trimethylsilyldiazoalkanes, obtained by alkylation of diazo(trimethylsilyl)methyllithium with RCH_2X, with ***Copper(I) Chloride*** gives excellent yields of (*E*)-1-trimethylsilylalkenes (eq 7).[8]

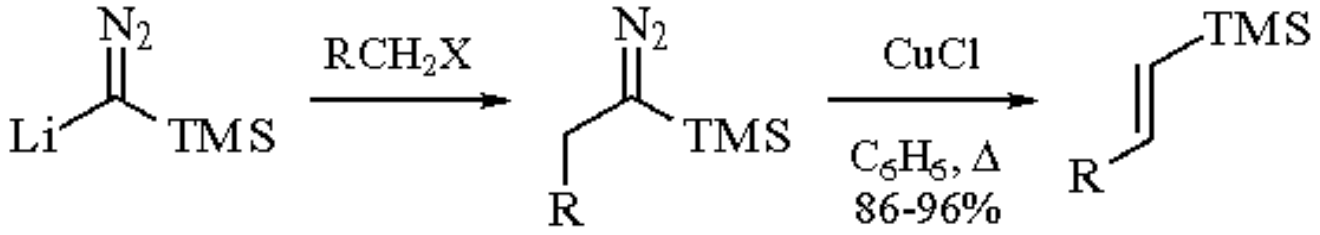

(7)

Preparation of Heterocycles.

On reaction with methyl esters, diazo(trimethylsilyl)methyllithium (2 equiv) gives 2-substituted 5-trimethylsilyltetrazoles in 50-90% yield (eq 8).[9a] Similarly, reaction with nitriles gives 1,2,3-triazoles in high yield (eq 9).[9b] Reaction with $(Me_3Si)_2C{=}PCl$ leads to 1,2,4-diazaphospholes (eq 10).[10]

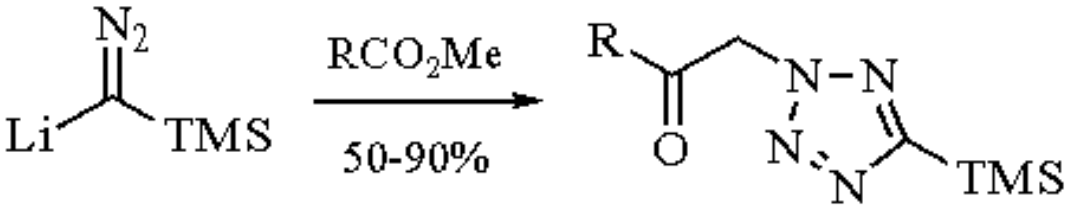

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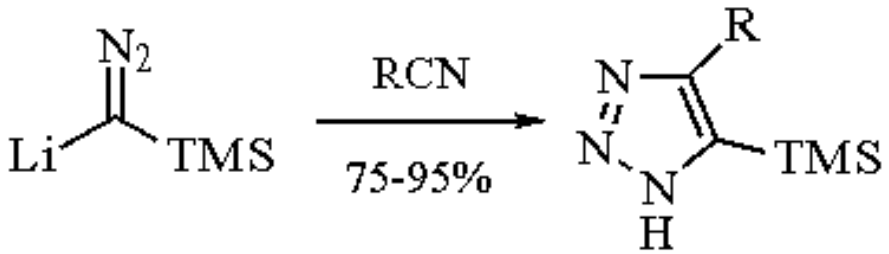

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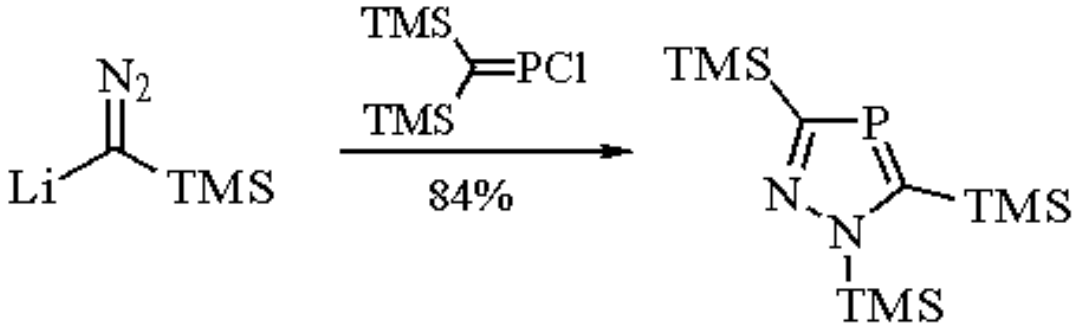

(10)

Related Reagents.

Triisopropylsilyldiazomethane can be similarly converted into its lithium derivative.[11] Diazo compounds containing tin (R_3SnCHN_2) and germanium (R_3GeCHN_2) are also known,[1] but have not been used in synthesis. Other lithiated diazo compounds (for example, see ***Ethyl Diazolithioacetate***) are covered elsewhere, as are other lithiated silanes.

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Dibenzenechromium

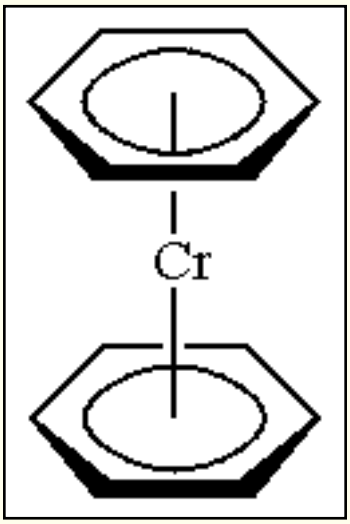

[1271-54-1] · $C_{12}H_{12}Cr$ · Dibenzenechromium · (MW 208.22)

(dehydrogenation catalyst[1])

Alternate Name: bis(η^6-benzene)chromium.

Physical Data: mp 284-285 °C.

Solubility: sol benzene; slightly sol ether.

Form Supplied in: brown-black crystals.

Purification: sublimed at 160 °C in vacuo.

Handling, Storage, and Precautions: air sensitive.

Dehydrogenation Catalyst.

Treatment of dibenzenechromium with potassium produces the corresponding radical anion (eq 1), which is an effective catalyst for the conversion of 1,4-cyclohexadiene to benzene (eq 2).[1] The scope and

limitations of the process have not been tested.

$$(C_6H_6)_2Cr \xrightarrow{K} [(C_6H_6)_2Cr]^{-}\cdot \quad (1)$$

(1)

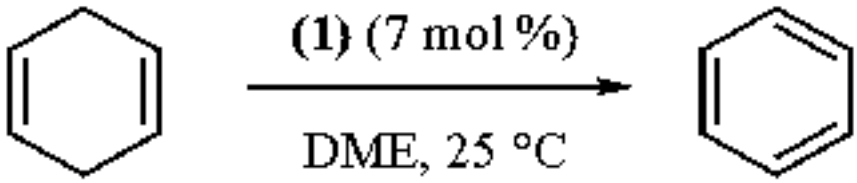

(2)

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Dibenzo-18-crown-6

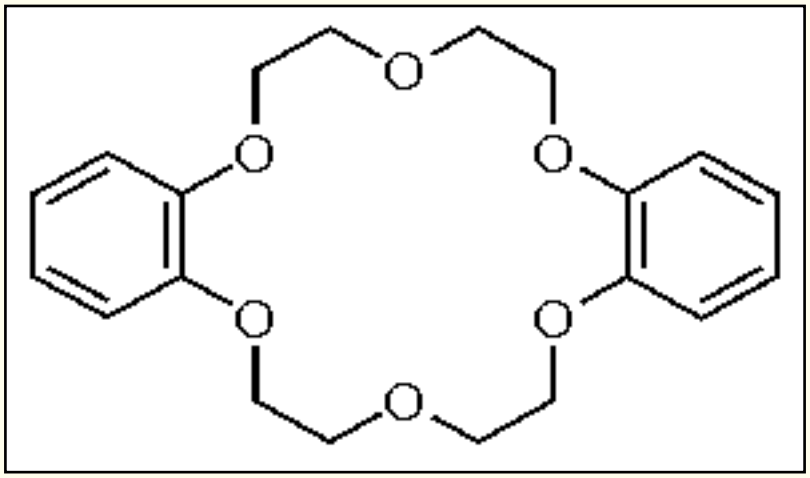

[14187-32-7] · $C_{20}H_{24}O_6$ · Dibenzo-18-crown-6 · (MW 360.41)

(solubilization and activation of a variety of potassium salts)

Physical Data: mp 162.5-163.5 °C. UV maxima: (MeOH solution) 223 nm (ε 17 500) and 275 nm (ε 5500). ^{1}H NMR: ($CDCl_3$) 6.8-7.0 ppm (8H multiplet) and 3.8-4.3 ppm (16H multiplet).

Form Supplied in: white fibrous needles.

Preparative Methods: dibenzo-18-crown-6 was first prepared in 39-48% yield from the reaction of catechol and bis(2-chloroethyl) ether using sodium hydroxide as the base and *n*-butanol as the solvent.[1] The ditosylate of diethylene glycol has been substituted for the dichloride with accompanying yields of 32-35%.[2]

Handling, Storage, and Precautions: toxic; use in a well-ventilated fume hood.

Complexation With Metal Salts.

The cavity diameter of dibenzo-18-crown-6 is estimated to be 2.6-3.2 Å, which is ideal for complexing with a potassium cation (ionic diameter 2.66 Å).[3] While the selectivity of dibenzo-18-crown-6 for

potassium salts is well documented, this macrocyclic multidentate ligand will also effectively complex with other alkali metal cations.[3] The solubility of potassium acetate in ***Acetonitrile*** is greater in the presence of dibenzo-18-crown-6 compared to ***18-Crown-6***.[4] The solubility of potassium acetate in the presence of a variety of other ligands was also reported. Arguments related to cavity diameter, lipophilicity, and rigidity were advanced to explain, at least partially, the observed structure-solubilization order.

Reactions.

Halides.

The catalytic activity of a number of macrocyclic polydentate ligands in the reaction of 1-octyl bromide with ***Potassium Iodide*** to produce the 1-octyl iodide has been reported.[5] Dibenzo-18-crown-6 appears to be less effective than ***Dicyclohexano-18-crown-6***.[5]

Oxygen Anions.

The reaction of potassium acetate activated by a wide variety of macrocyclic polydentate ligands with benzyl chloride in acetonitrile indicates that dibenzo-18-crown-6 is somewhat less effective than 18-crown-6 or dicyclohexano-18-crown-6.[4] At -45 °C in dry THF, sodium 3-(fluoren-9-ylidene)-2-phenylacrylate decarboxylated very slowly. In the presence of dibenzo-18-crown-6 the reaction proceeded at a rapid rate, indicating that the nature of the ion pair was critical in influencing the reaction rate profile.[6]

Dibenzo-18-crown-6 has been used in the reaction of an acetylated halo sugar with a series of alcohols catalyzed by ***Silver(I) Nitrate*** (Koenigs-Knorr reaction). The reaction proceeds in good yield with inversion of configuration.[7,8]

The rates of alkylation of potassium phenoxide with 1-bromobutane in dioxane at 25 °C in the presence of linear and cyclic polyether additives has been reported.[9] Dicyclohexano-18-crown-6 was more effective than dibenzo-18-crown-6. A comparison has been made between the rates of reaction of *t*-butoxide in *t*-butanol with 2-nitrofluorobenzene and 4-nitrofluorobenzene where the counter cation was potassium and potassium/dibenzo-18-crown-6 and the corresponding reaction of potassium methoxide in methanol.[10] Potassium methoxide was 30 times more reactive than ***Potassium t-Butoxide*** but in the presence of dibenzo-18-crown-6 the reverse was true.

Dibenzo-18-crown-6 is an effective phase-transfer catalyst in the reactions of 4-chloromethyl-1,3-dioxolane with mono- and dihydric phenols in the presence of metal hydroxides.[11]

The effect of dibenzo-18-crown-6 on the reaction of sodium 9-fluorenone oximate with ***Iodomethane*** in 33.5% acetonitrile and 66.5% *t*-butyl alcohol has been studied. The crown ether increased the fractional *O*-alkylation.[12,13]

Carbon Anions.

The effects of dibenzo-18-crown-6 on (a) the simultaneous base-catalyzed racemization, isotopic exchange, and isomerization of optically pure (-)-3-*t*-butyl-1-methylindene-1-*h* and its deuterated counterpart in the 1-position to 1-*t*-butyl-3-methylindene under a variety of conditions,[14] (b) the isotopic exchange and racemization of (-)-4-biphenylylphenylmethoxydeuteromethane with potassium *t*-butoxide,[15] (c) the stereochemistry accompanying the cleavage of (+)-4-phenyl-3,4-dimethyl-3-hexanol with potassium *t*-butoxide,[12] and (d) the rates of isotopic exchange and racemization of (+)-2-methyl-2,3-dihydro-2-deuterobenzo[*b*]thiophene 1,1-dioxide with potassium methoxide[12] have been reported.

The lithium, sodium, and potassium salts of 4*H*-cyclopenta[*def*]phenanthrene radical anion are considerably more stable in the presence of dibenzo-18-crown-6, especially when sodium or potassium is the counter cation.[16] The presence of crown also affected the rate of decay of the radical anion.

The use of dibenzo-18-crown-6 as a liquid-liquid phase-transfer catalyst in the generation and reaction of carbanions and halocarbenes has been studied.[17] Among the reactions studied were the alkylation of carbon acids, reactions involving trichloromethyl anions and dichloromethylene, reactions of carbanions with nitro compounds, and Darzens condensations.

Sulfur Anions.

The solid-liquid phase-transfer catalytic reaction between ***Benzyl Chloride*** and ***Potassium Thiocyanate*** produces a ratio of benzyl thiocyanate to benzyl isothiocyanate of 71:29 in the presence of dibenzo-18-crown-6.[18]

Reductions.

Studies related to the use of ***Sodium Borohydride*** in toluene in the reduction of a variety of ketones (acetophenone, cyclohexanone, methyl *n*-pentyl ketone, methyl isopropyl ketone) in the presence of equivalent amounts of dibenzo-18-crown-6, diglyme, or dimethoxyethane have been reported.[19] In general, the crown was the most effective ligand. Potassium borohydride required longer reactions times.

Oxidations.

The preparation of *N*-(arylsulfonyl)sulfoximines by oxidation of the sulfilimines with ***Sodium Hypochlorite*** in an aqueous methylene chloride-ethyl acetate two-phase system has been reported.[20]

The reaction of ***Potassium Chromate*** with primary alkyl halides in HMPA containing dibenzo-18-crown-6 at 100 °C produces aldehydes in good yields.[21] The chromate ion behaves as both a nucleophile and an oxidant.

The oxidation of 1-octene to *n*-heptanoic acid with a saturated aqueous ***Potassium Permanganate***-benzene two-phase system proceeds in 80% yield at rt in the presence of dibenzo-18-crown-6.[22]

Related Reagents.

18-Crown-6; ***Dicyclohexano-18-crown-6***.

---

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Charles L. Liotta

Dibenzoyl Peroxide[1-4]

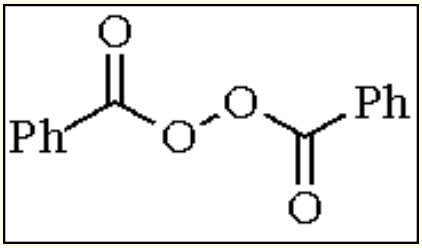

[94-36-0] · $C_{14}H_{10}O_4$ · Dibenzoyl Peroxide · (MW 242.23)

(initiator for radical reactions such as allylic and benzylic halogenation,[5] radical addition to carbon-carbon multiple bonds to form C-heteroatom (halogen, S, Si, Ge, P, and N) bonds,[2] C-H additions across multiple bonds[4] in an intermolecular[1] and intramolecular[6] fashion, homolytic aromatic substitution in electron-deficient heteroaromatics;[7] reagent for benzoyloxylation of enolates, enamines, and other electron-rich systems;[8] oxidizing agent for N, P, Si, S, and Se compounds; oxidizing agent in redox chain reactions with transition metals[9])

Alternate Name: DBP.

Physical Data: mp 103-106 °C (dec).

Solubility: sparingly sol water or alcohol; sol benzene, chloroform, and ethers.

Form Supplied in: white crystalline powder.

Analysis of Reagent Purity: the peroxide content can be established by iodometric titration.[10]

Handling, Storage, and Precautions: explosive; harmful if exposed by ingestion or skin contact; strong oxidizer; susceptible to explosion by shock, friction or heat; autoignition temperature 79 °C. *Caution*: all experiments involving peroxy compounds should be carried out behind a safety shield. Excess peroxide should be destroyed before working up the reaction.[11]

Introduction.

Dibenzoyl peroxide is a widely used initiator for radical reactions. It undergoes thermal homolytic cleavage of the O-O bond with a half-life of about 1 h at 95 °C (eq 1).[12] This homolysis may also be effected by light as well as transition metal catalysts.[9]

$$(PhCO_2)_2 \longrightarrow 2\ PhCO_2\cdot \longrightarrow Ph\cdot + CO_2 \qquad (1)$$

Initiator for Halogenation Reactions.

Even though DBP has been used as an initiator for functionalization of unactivated hydrocarbons (eq 2), more common are the applications for halogenations of allylic (eqs 3 and 4)[5,13] and benzylic (eq 5)[14] positions. DBP also serves as an initiator for halogenation of silanes by replacement of a Si-H bond.[15]

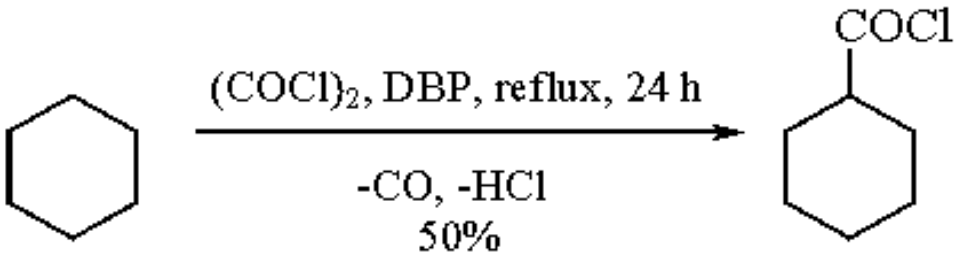

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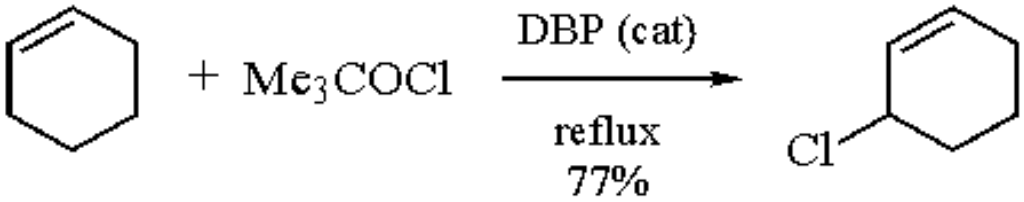

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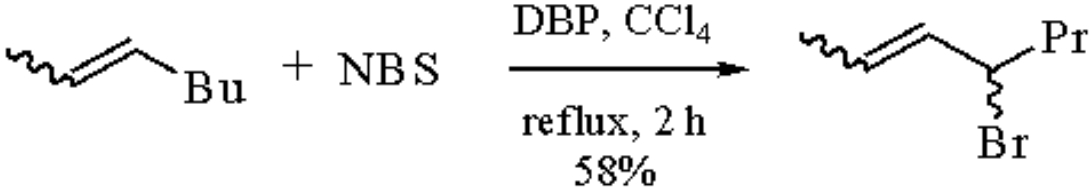

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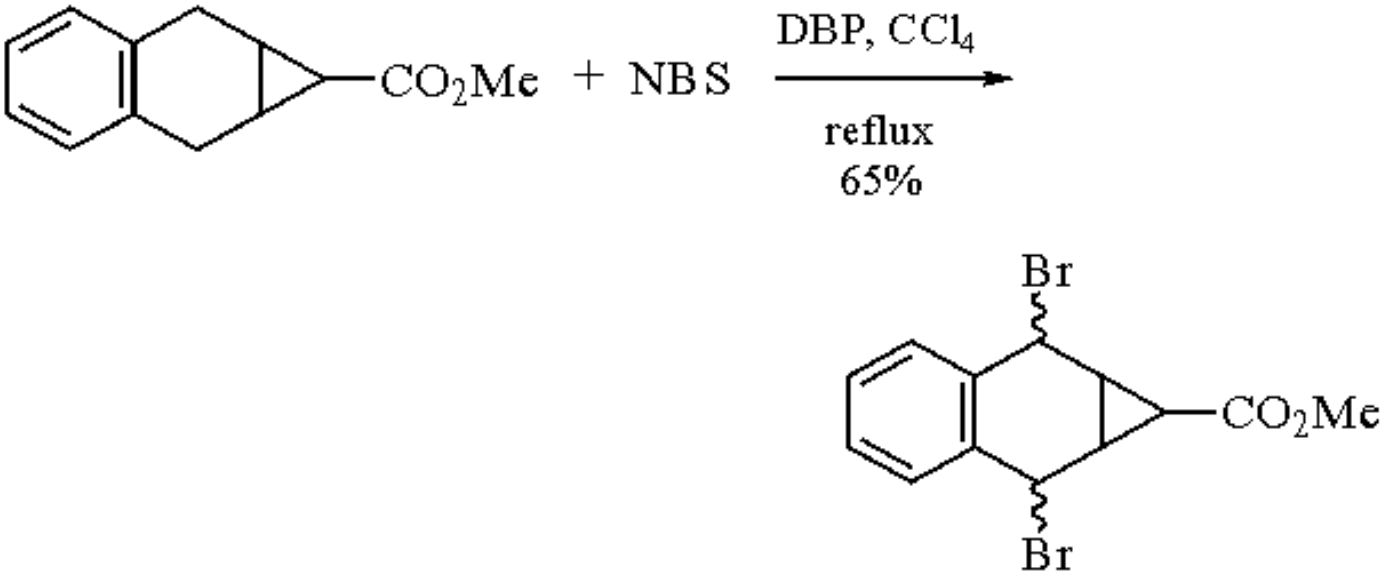

(5)

Initiator for Radical Additions to Unsaturated Compounds.

The primary steps in the radical addition of X-Y to unsaturated compounds are shown in eqs 6-10. By far the largest application of this reagent[16] is in radical chain polymerization of vinyl compounds such as vinyl chloride, vinyl acetate,

butadiene derivatives, styrene, and various acrylic monomers. The topic of polymerization is beyond the scope of this article. Excellent monographs and reviews dealing with this subject are available.[17]

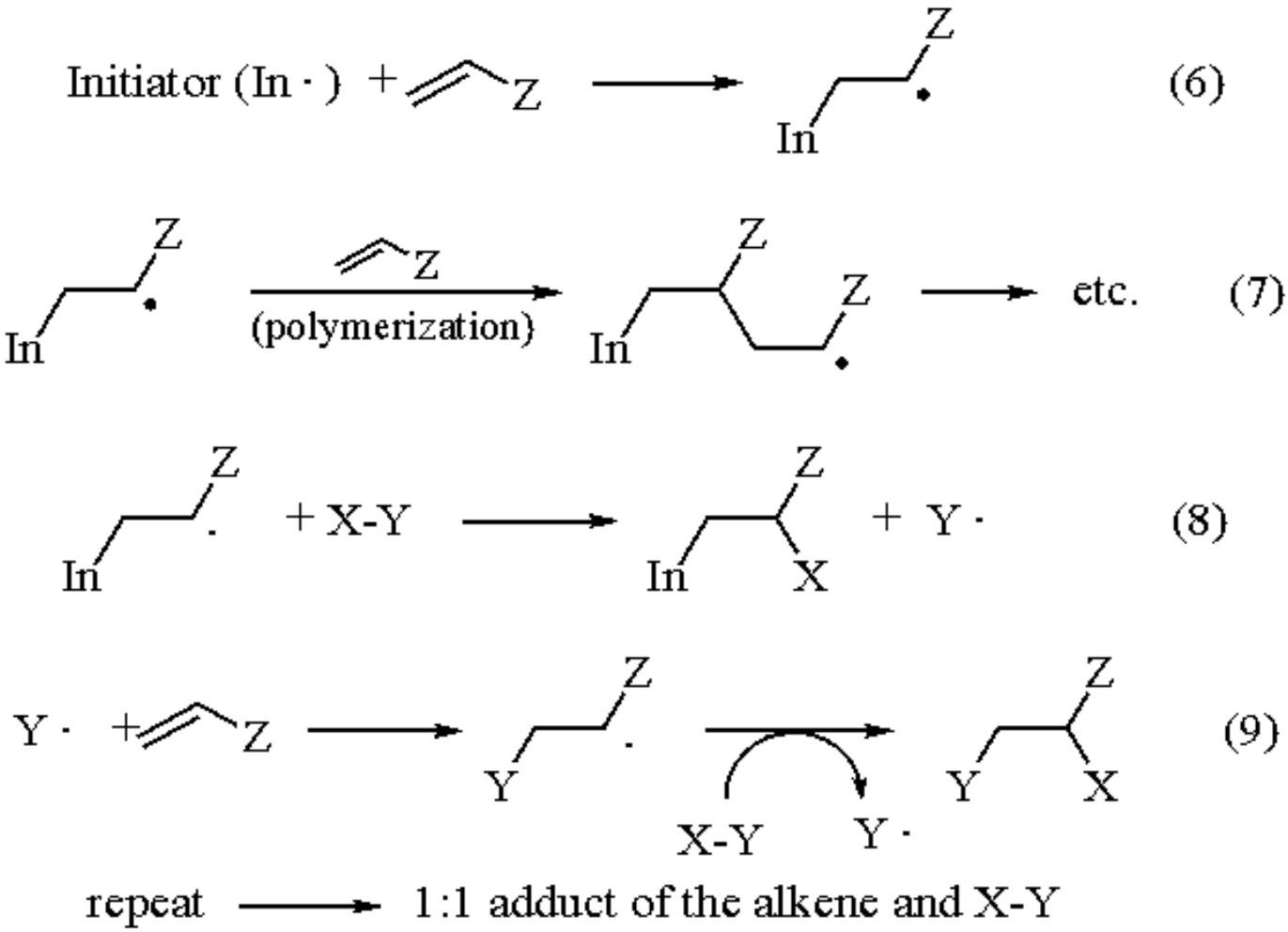

when X-Y contains an activated C-H:

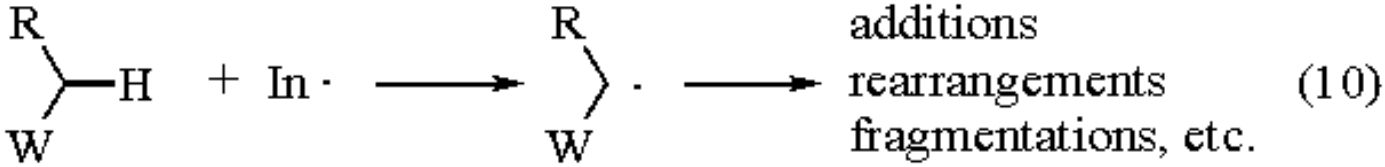

Formation of a 1:1 adduct (eq 9) will be favored when X-Y is an efficient chain transfer agent. For reactions of short chain lengths, an excess of X-Y and a steady concentration of the initiator should be present in the reaction medium.[2] Since the original discoveries of the anti-Markovnikov addition of HBr (eq 11),[18] and of carbon tetrachloride to alkenes (eq 12),[1] a large number of related reactions have been reported. DBP catalyzes the addition of a wide variety of X-Y type compounds to carbon-carbon multiple bonds. These include H-Br, thiols, mercapto acids, thiophosphoric acids, hydrogen sulfide, silanes, germanes, phosphorus halides, phosphorus acids and esters, and various oxides of nitrogen.[2] The important C-C bond-forming reactions are described below.

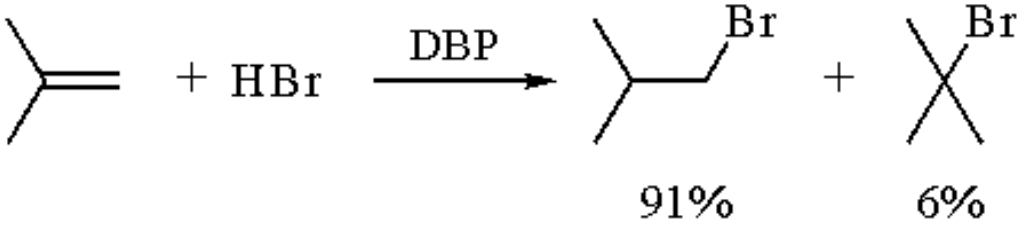

(11)

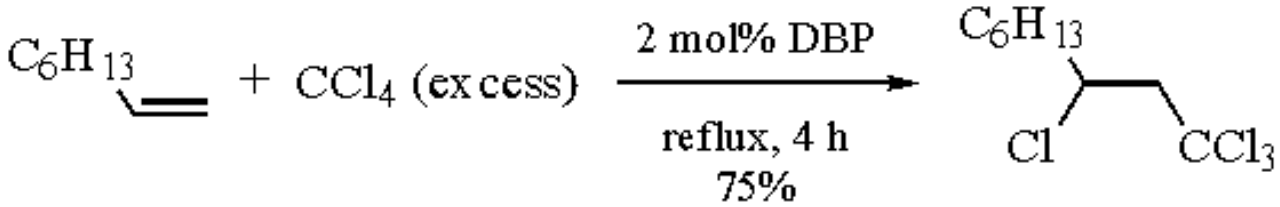

(12)

Intermolecular Carbon-Carbon Bond Forming Reactions.

When the compound X-Y contains an activated C-H bond, initiators such as DBP and di-*t*-butyl peroxide initiate the radical reactions by abstraction of this hydrogen (eq 10) from the substrate, and the resultant radical enters the radical chain cycle. Substrates of this kind are poor chain transfer agents and typically a higher concentration of the substrate and a steady supply of the initiator are needed for a viable reaction. Representative examples of carbon-carbon bond forming reactions initiated by DBP are listed in Table 1[11,41-45] (see also ***1,1-Di-t-butyl Peroxide***). A more complete list is available in two excellent reviews.[1,4]

Table 1 Intermolecular C-C Forming Reactions via Radicals

Precursor	Alkene	Reaction conditions	Product
MeOH	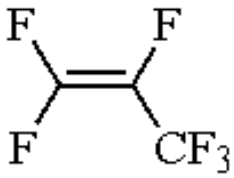	DBP (cat), 120 °C, 3h [11]	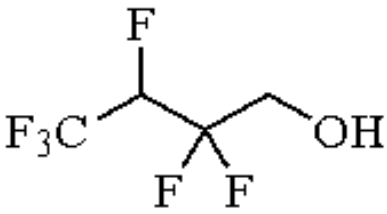 67%
	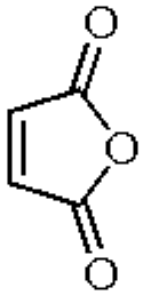	DBP (cat), 65 °C [41]	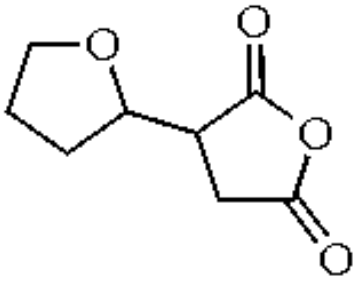 70%
			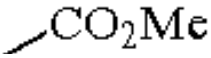

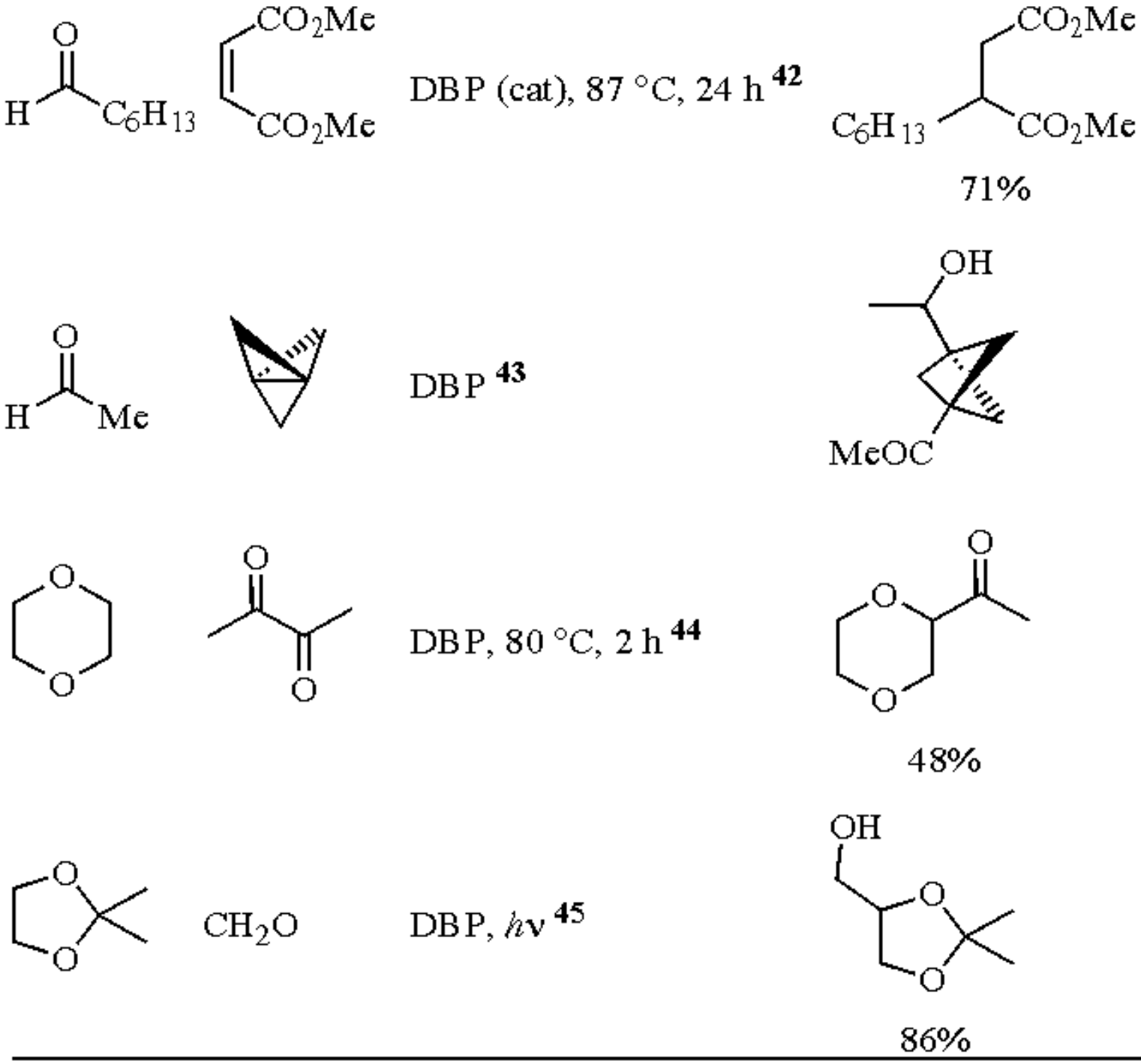

The intermolecular additions may be coupled to an intramolecular cyclization (eq 13)[19] or an S_H2 reaction.[20] The S_H2 reactions are useful for the synthesis of epoxy compounds (Scheme 1) or lactones (eq 14). Radicals from nitriles, ketones, ethers, and polyhaloalkanes also undergo similar addition-substitution reactions.

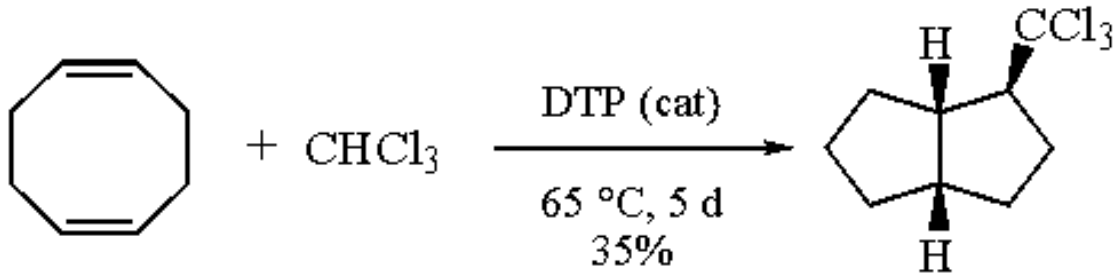

(13)

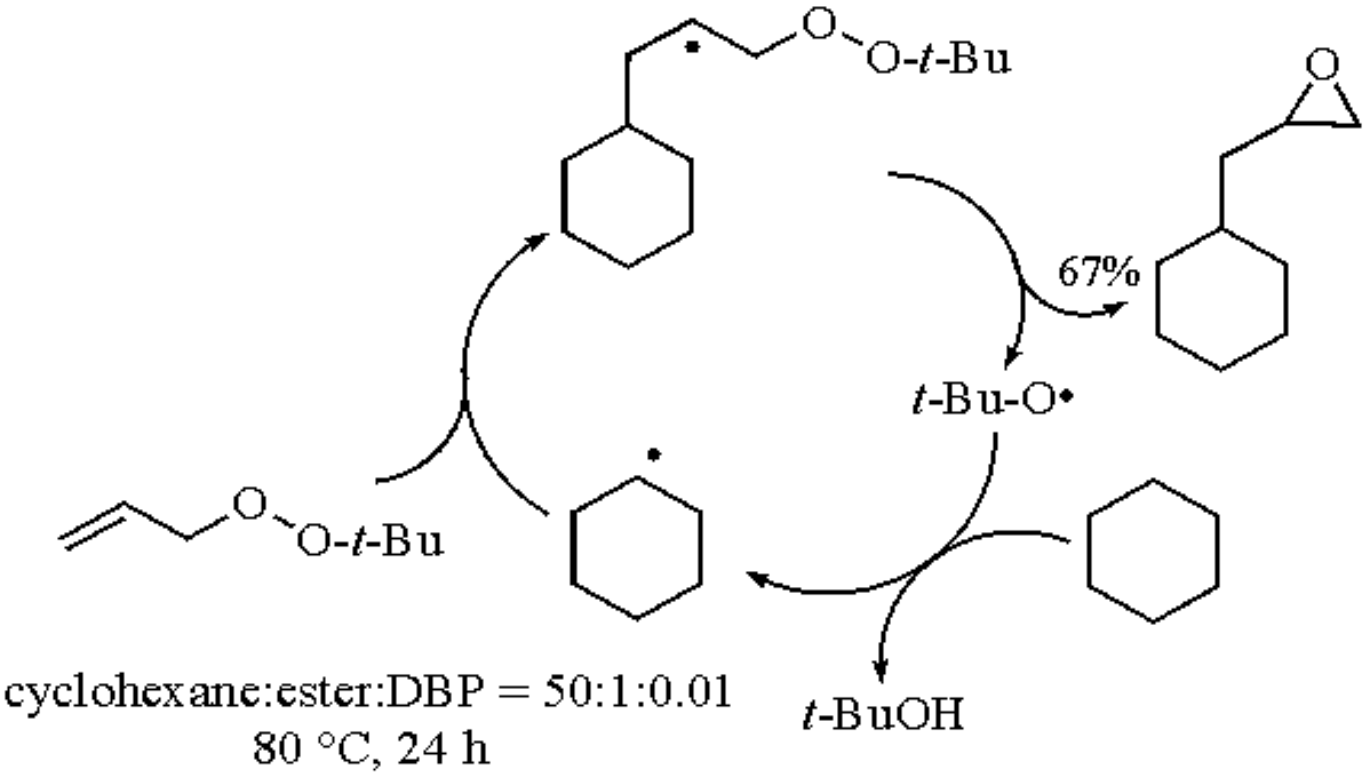

Scheme 1 Intermolecular addition-S_H2 reaction of peresters

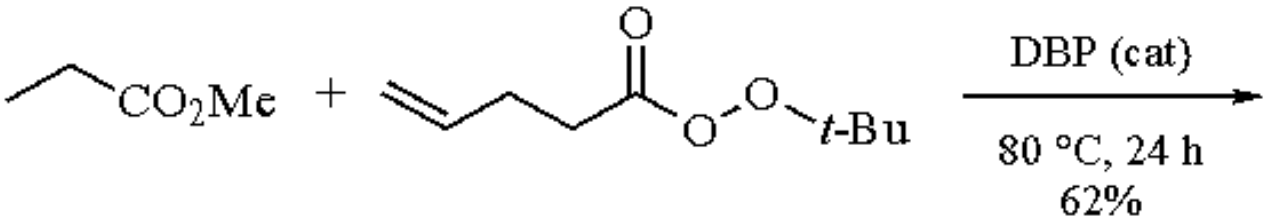

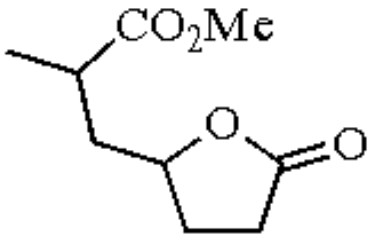

(14)

Addition of various α-carboxyl radicals to alkenes is best carried out with a high temperature initiator such as di-*t*-butyl peroxide, although reports of using DBP are known. This subject has been extensively reviewed.[21]

Intramolecular Additions.

The intramolecular versions of the C-H additions mentioned above have been extensively studied by Julia and co-workers (eqs 15 and 16).[6] These reactions, while not very practical from a synthetic standpoint, nonetheless have played a key role in the development of radical synthetic methodology.[22,23] A related cyclization (eq 17) was used by Barton and co-workers for the synthesis of a tetracycline intermediate.[24] An interesting variant of this reaction is the cyclization of geranyl acetate to a benzoyloxyfarnesyl acetate (eq 18).[25] The radical reaction is initiated by DBP and the Cu salt serves as an oxidant for

the final cyclized radical.

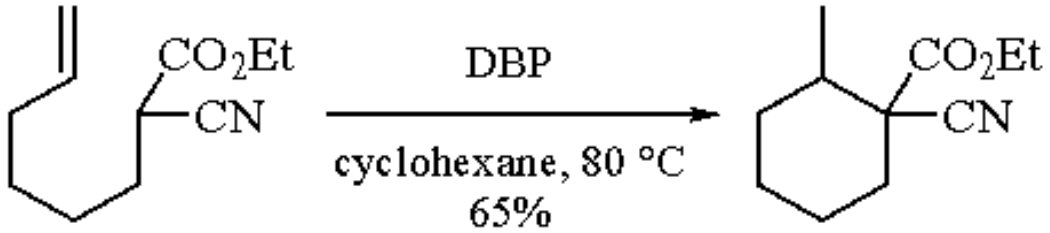

(15)

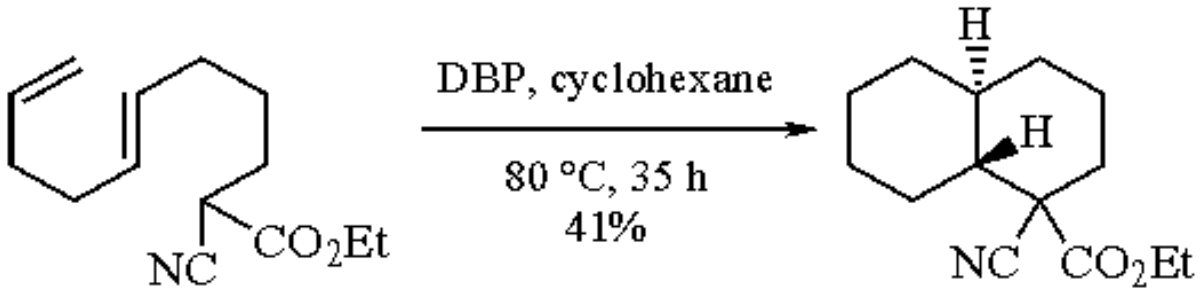

(16)

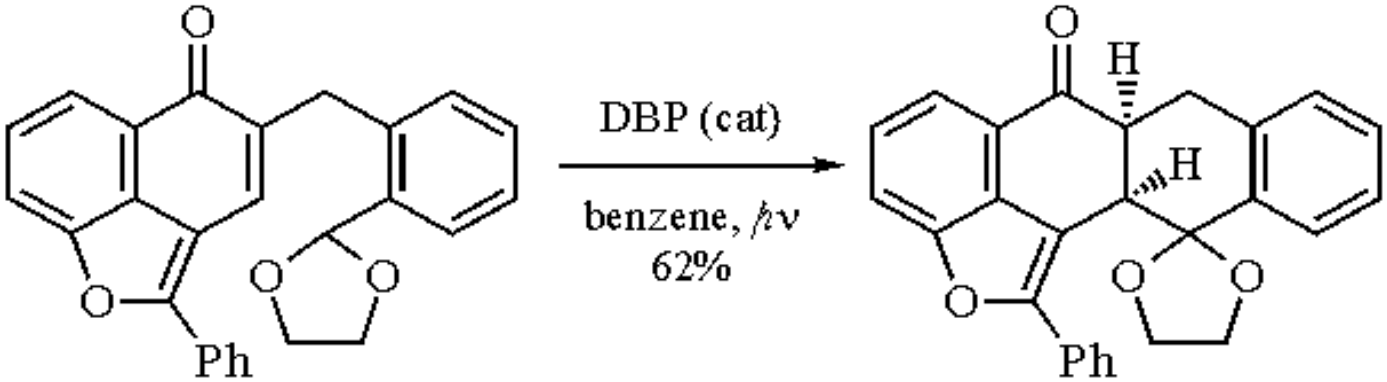

(17)

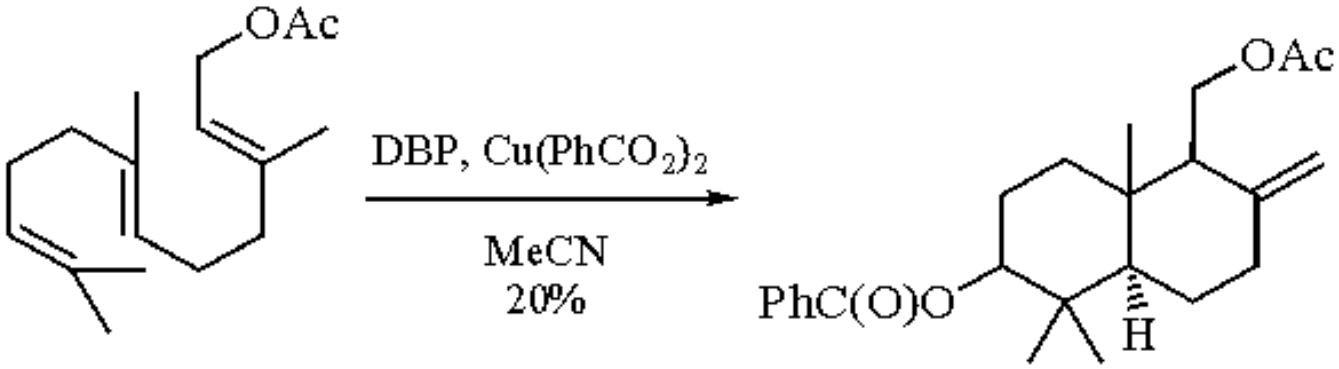

(18)

Initiator for Radical Additions to Electron-Deficient Heteroaromatic Compounds.

Minisci and co-workers have developed radical-mediated homolytic substitution reactions for various electron-deficient aromatic nuclei.[7] Radicals derived from alkyl halides, dioxane,[26] dimethylformamide,[27] and even cyclohexane[26] can be added to protonated heteroaromatic compounds. The addition of a cyclohexyl radical (eq 19) proceeds in good yields even when the reaction medium contains a large excess of chloroform and acetonitrile. The highly electrophilic nature of the

&bdot;CCl_3 and &bdot;CH_2CN completely inhibits the reaction towards the protonated heterocycle. Under these conditions, ethyl acetate gives the electrophilic radical &bdot;CH_2CO_2Et and the nucleophilic radical $MeCO_2$&bdot;CHMe, but only the latter adds.

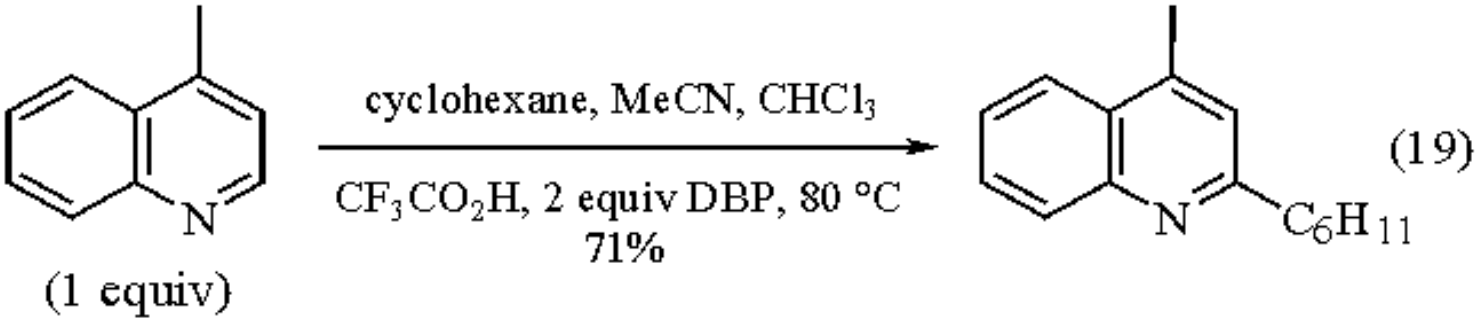

As an Oxidant.

Benzoyl peroxide oxidizes ethers to α-benzoyloxy ethers, and alkyl sulfides to α-benzyloxy sulfides (eq 20).[28] Tertiary amines are oxidized to amine oxides, while secondary amines give *N*-benzoyloxy amines (eq 21).[29] In the presence of a mild base, DBP acts as a very selective oxidizing agent for hydroquinones.[30] Aldehydes and benzylic positions are not affected. Two key steps in the Eschenmoser synthesis of the corrin nucleus make use of DBP (eqs 22 and 23).[31] Secondary alcohols are oxidized to ketones with dibenzoyl peroxide and ***Nickel(II) Bromide*** (eq 24).[32] A benzoyl peroxide-mediated annulation used by Kishi in the synthesis of sporidesmin B (eq 25)[33] is likely to be an ionic (vis-á-vis radical) reaction. A 1:1 mixture of DBP and ***Hexamethyldisilazane*** has been used as an epoxidizing agent for acid-sensitive alkenic substrates.[34]

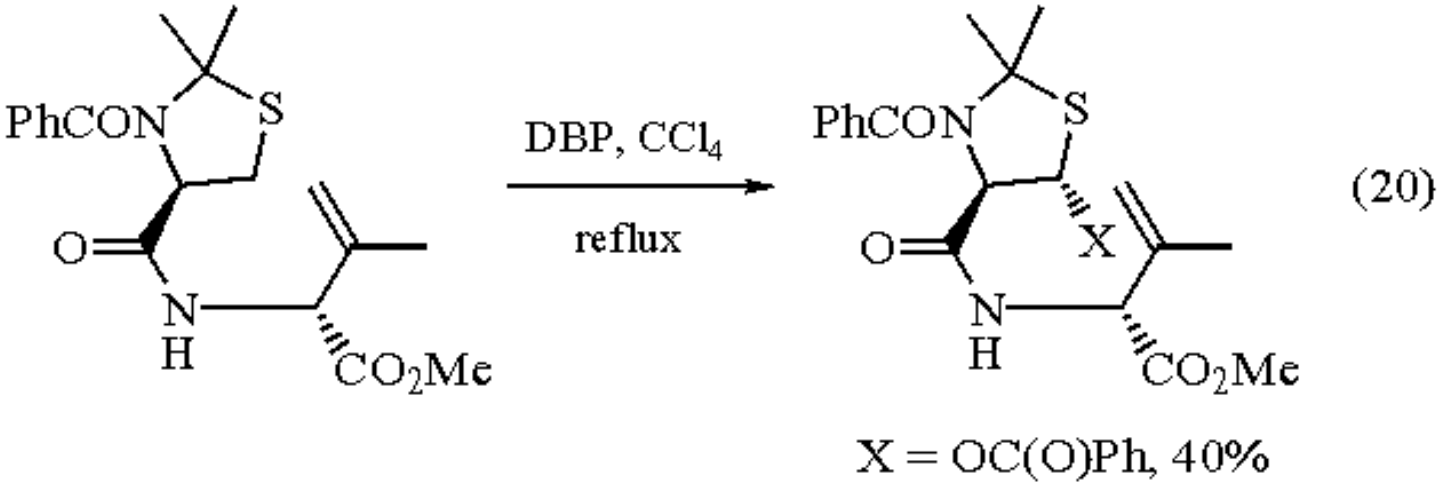

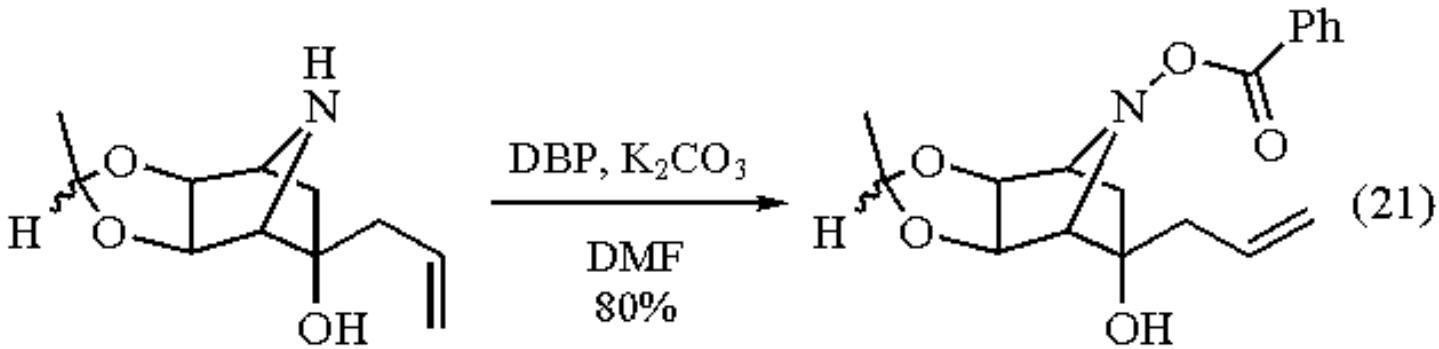

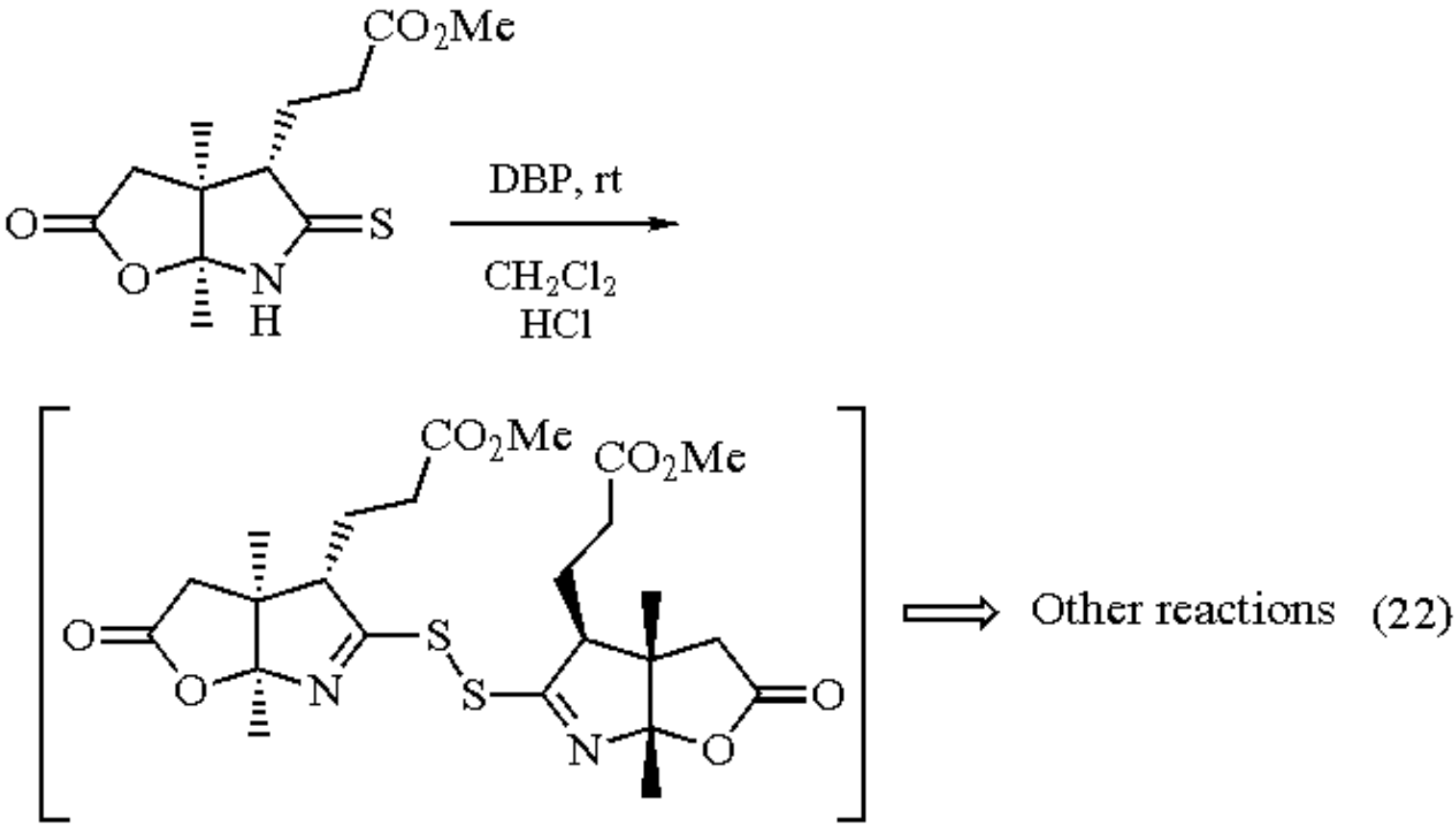
CO2Me
DBP, rt
CH2Cl2
HCl
CO2Me
CO2Me
Other reactions
(22)

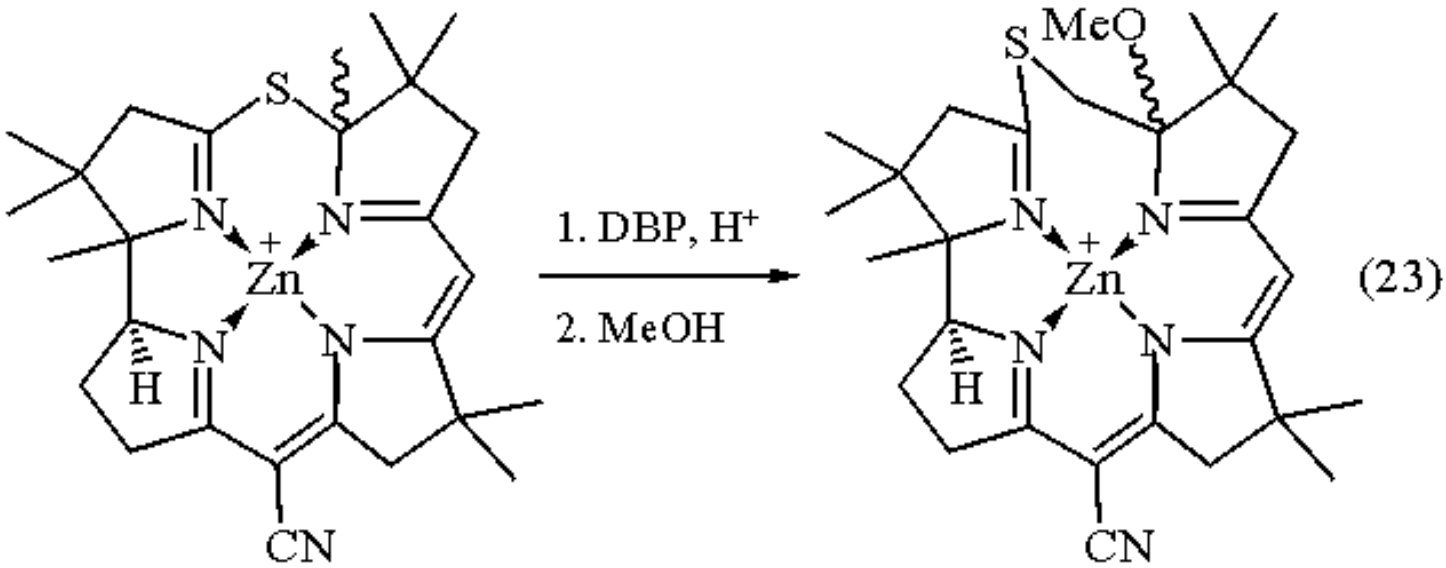
1. DBP, H+
2. MeOH
MeO
Zn
CN
(23)

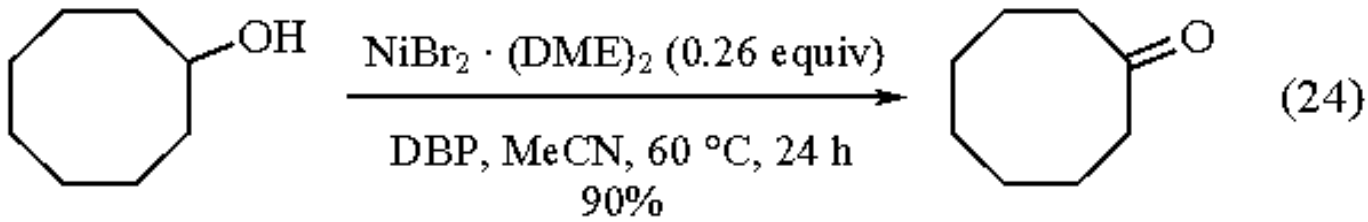
OH
NiBr2 · (DME)2 (0.26 equiv)
DBP, MeCN, 60 °C, 24 h
90%
(24)

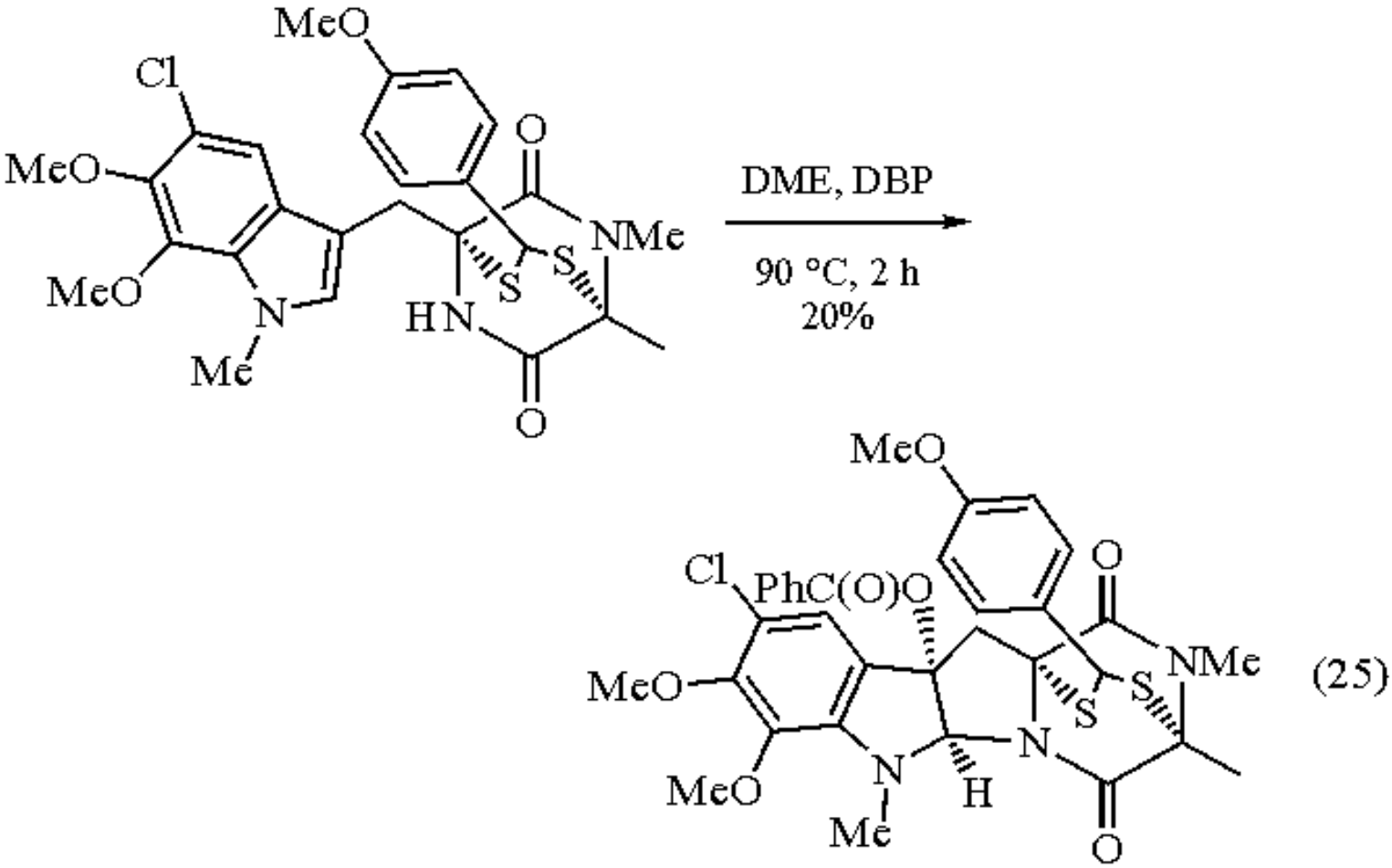

As a Benzoyloxylation Agent.[8]

Under catalysis by ***Iodine***, benzoyloxylation of aromatic and heteroaromatic compounds takes place. Nucleophilic compounds such as malonates,[35] phenols,[36] enamines, and indoles[37] also react with DBP to give benzoyloxylation products. Secondary amines are converted into *N*-benzyloxy amines (eq 20).[29] An improved protocol[38] for this reaction and an application for synthesis of N^5-hydroxy-L-ornithine[39] have appeared in the literature.

Benzoyl peroxide has been used for α-benzoyloxylation of an enolate (eq 26).[40]

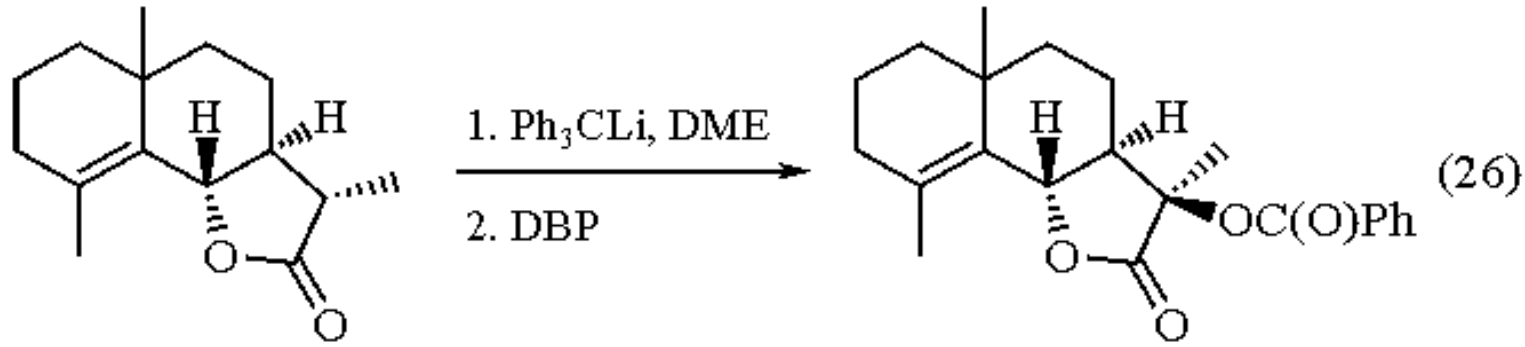

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Dibenzyl Azodicarboxylate[1]

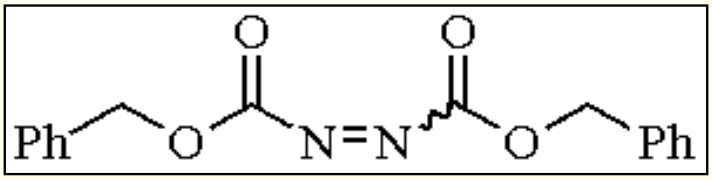

[2449-05-0] · $C_{16}H_{14}N_2O_4$ · Dibenzyl Azodicarboxylate · (MW 298.30)

(efficient diene in the hetero Diels-Alder reaction with furanoid and pyranoid glycals;[2] source of positive nitrogen, used in the preparation of α-hydrazino and α-amino acids from chiral lithium enolates[3])

Alternate Name: DBAD.

Physical Data: mp 44-46 °C.

Solubility: sol CH_2Cl_2; insol cyclohexane.

Form Supplied in: orange solid.

Hetero Diels-Alder Reaction.

Dibenzyl azodicarboxylate adds to furanoid and pyranoid glycals,[2] under irradiation at 350 nm in cyclohexane/CH_2Cl_2 solution, to provide [4 + 2] cycloadducts in high yields (eq 1). The photoisomerization[4] of *trans*-DBAD to the *cis* isomer is essential to allow the cycloaddition reaction to take place (eq 2). This cycloaddition reaction is highly stereoselective; the adduct is usually obtained as a single isomer. The approach of DBAD to the glycal double bond is directed by the orientation of the C-3 substituent to give the cycloadduct with the 2-amino function *trans* to the C-3 substituent. The cycloaddition reaction of DBAD and glycals allows, in a single operation, the introduction of an amino moiety at C-2 of a carbohydrate and a latent nucleofugal group at the C-1 position. The dibenzyl adducts, namely dihydrooxadiazines, can be efficiently opened by various nucleophiles such as alcohols, hydrides, and acids, in the presence of an activator (eq 1). The resulting hydrazides can then be converted to their corresponding free amines under hydrogenolysis conditions. This methodology has been applied to the synthesis of simple and complex 2-amino saccharides.[5] The cycloaddition reaction of DBAD with galactal and glucal was used for the synthesis of subunits of tunicamycin.[6]

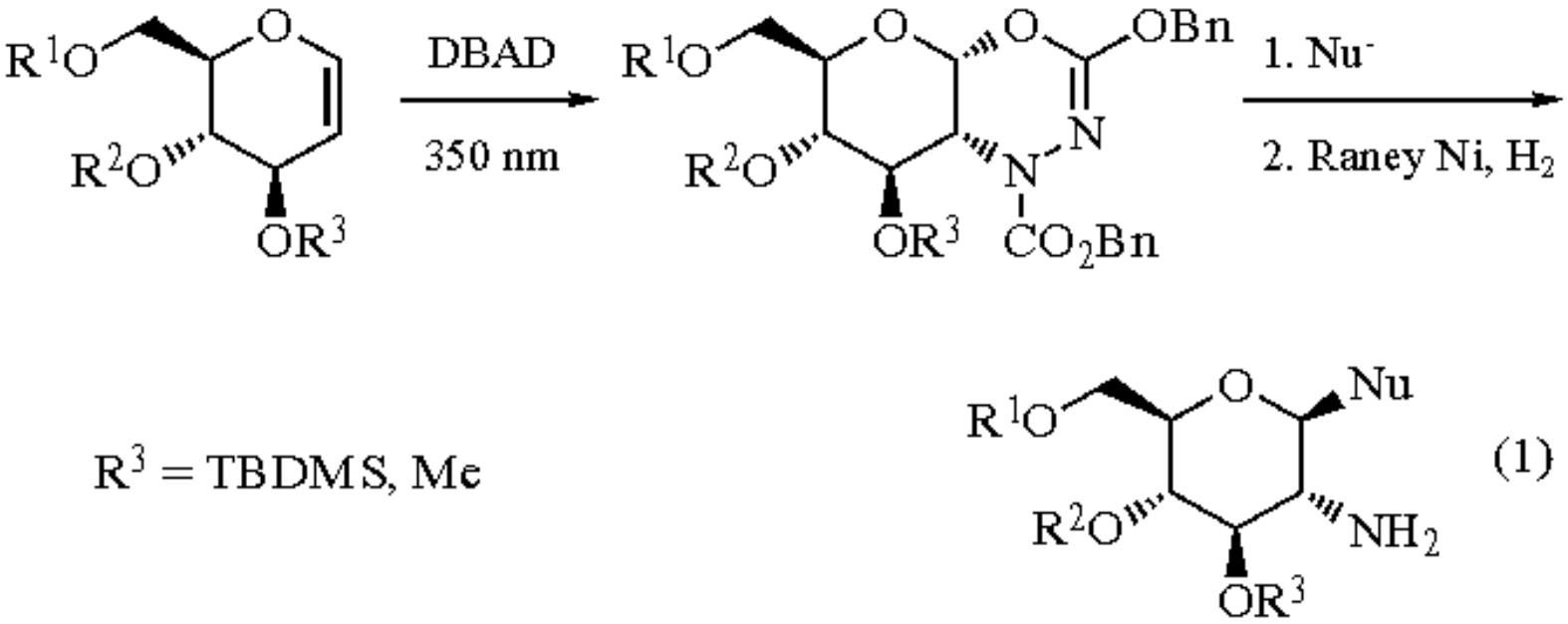

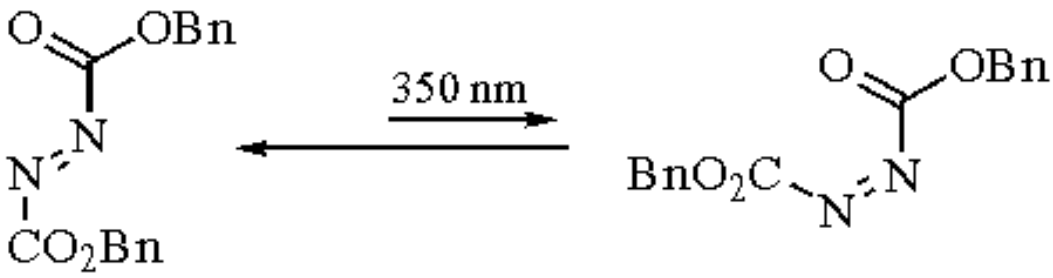

It has been observed that the rate of cycloaddition is related to the electronic nature of the C-3 substituent.[2a,b] The cycloaddition reaction does not take place with substrates having electron-withdrawing groups at the C-3 position.

Under thermal conditions, DBAD undergoes a [4 + 2] cycloaddition reaction with derivatized 2-oxazolones. The reaction shows moderate diastereofacial selectivity (eq 3).[7]

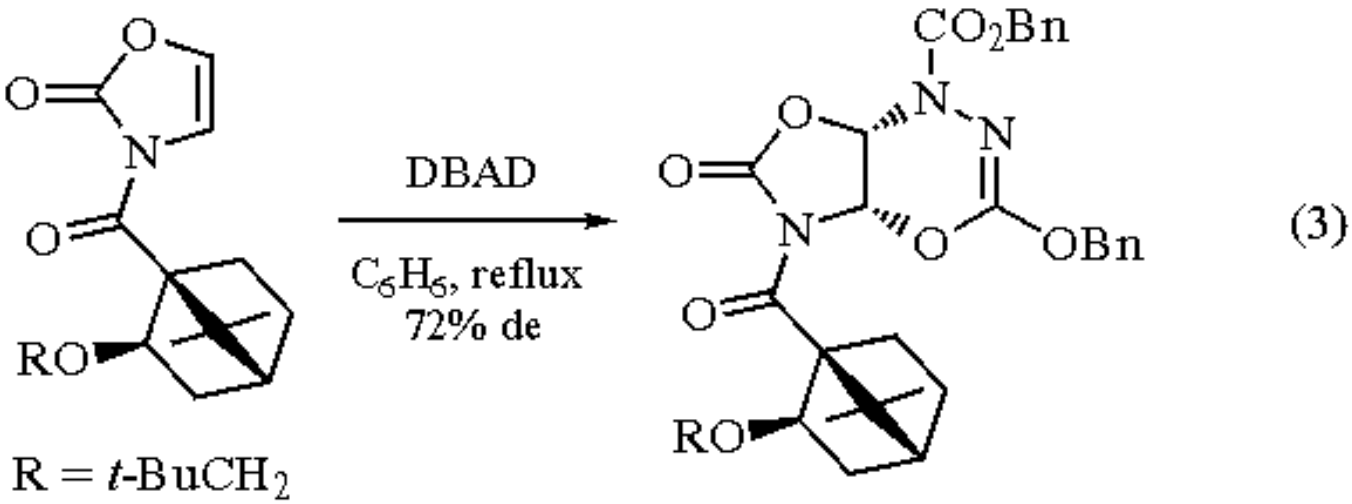

Synthesis of α-Hydrazino and α-Amino Acids.

DBAD is an efficient source of electrophilic nitrogen and has been used in the preparation of α-hydrazino and α-amino acids.[3] Aminated carboximides were obtained from the condensation of (*Z*)-lithium enolates of chiral carboximides with DBAD (eq 4). The selectivity observed in this amination reaction was generally greater than 85% de, depending on the bulk of the side chain (Me < CH_2Ph < *i*-Pr). Similar results were obtained in studies with other azodicarboxylates such as ***Di-t-butyl Azodicarboxylate***.[8] The aminated products were then converted to their corresponding α-hydrazino acids under hydrogenolysis conditions (***Palladium on Carbon***, H_2) and then to their free amines with ***Raney Nickel***/H_2.

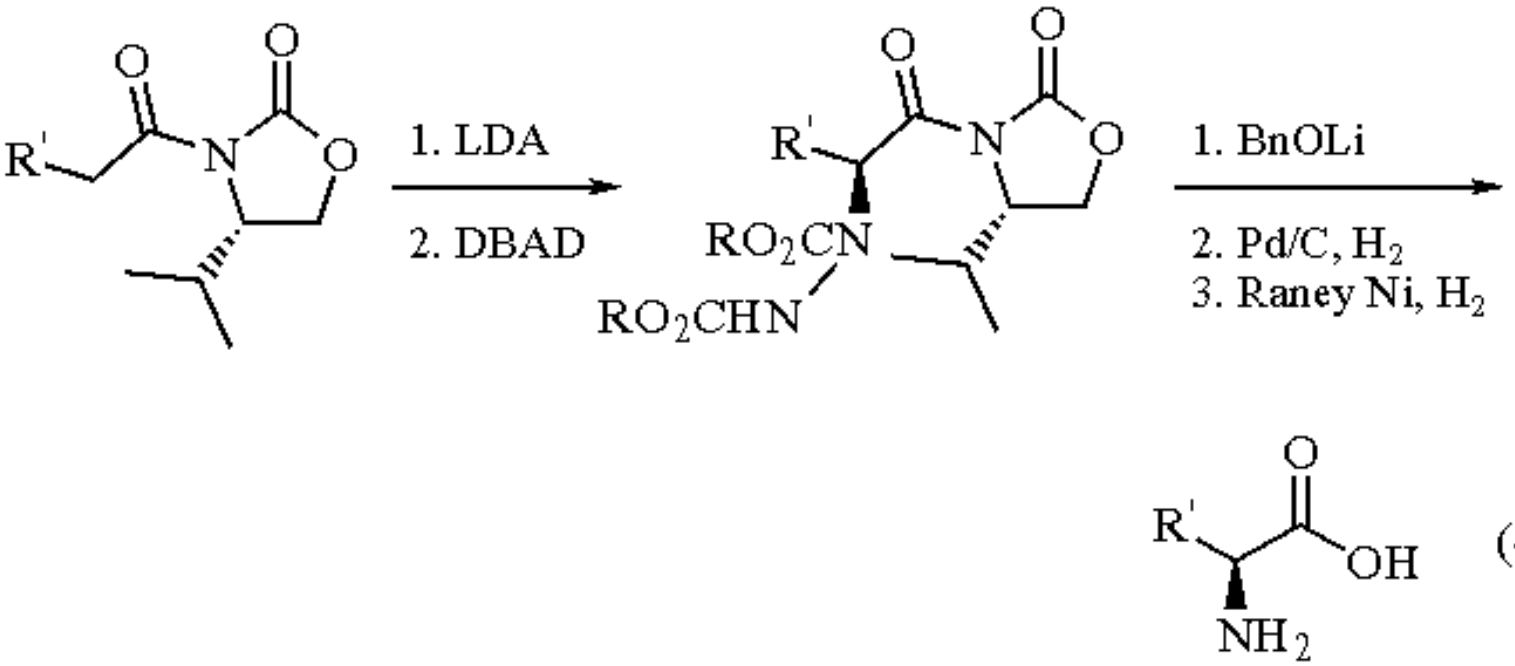

(4)

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Yves Leblanc

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Dibenzyl *N,N*-Diethylphosphoramidite

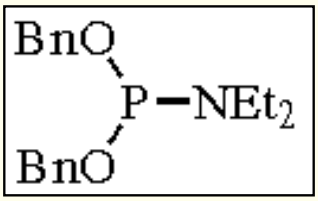

[67746-43-4] · $C_{18}H_{24}NO_2P$ · Dibenzyl *N,N*-Diethylphosphoramidite · (MW 317.40)

(phosphorylation of simple alcohols,[1] serine,[2] threonine,[3] and tyrosine;[4] synthesis of glycosyl phosphites and phosphates[5])

Physical Data: bp 131-132 °C/10^{-4} mmHg,[6] 150-152 °C/0.01 mmHg,[7] 154-156 °C/0.3 mmHg.[8]

Preparative Methods: by the reaction of dichloro *N,N*-diethylphosphoramidous acid with 2 equiv of benzyl alcohol.[3,7] An alternative synthesis, described on a 1 mol scale, combines phosphorus trichloride, diethylamine, and 2 equiv of benzyl alcohol in a one-pot reaction.[8] An earlier route to this reagent involved heating phosphorus hexaethyltriamide with 2 equiv of benzyl alcohol.[6]

Purification: by distillation at reduced pressure.

Handling, Storage, and Precautions: reported to be stable at rt and has been kept for at least 6 months.[5]

Preparation of Organic Phosphite and Phosphate Esters.

While dibenzyl *N,N*-diethylphosphoramidite will form phosphite triesters upon heating with 1,2-diacylglycerols in an uncatalyzed reaction (eq 1),[6] phosphitylation of alcohols has more recently been accomplished at ambient temperature in nearly quantitative yield in the presence of added 5-methyl-1*H*-tetrazole, 1*H*-tetrazole, or 1,2,4-triazole.[1,3,8] The phosphate triester has commonly been obtained by in situ oxidation of the phosphite ester intermediate using ***m-Chloroperbenzoic Acid***,[1] ***t-Butyl Hydroperoxide***,[3] or aqueous 30% ***Hydrogen Peroxide***.[8] *t*-Butyl dibenzyl phosphate has been obtained in excellent yield (eq 2).[1]

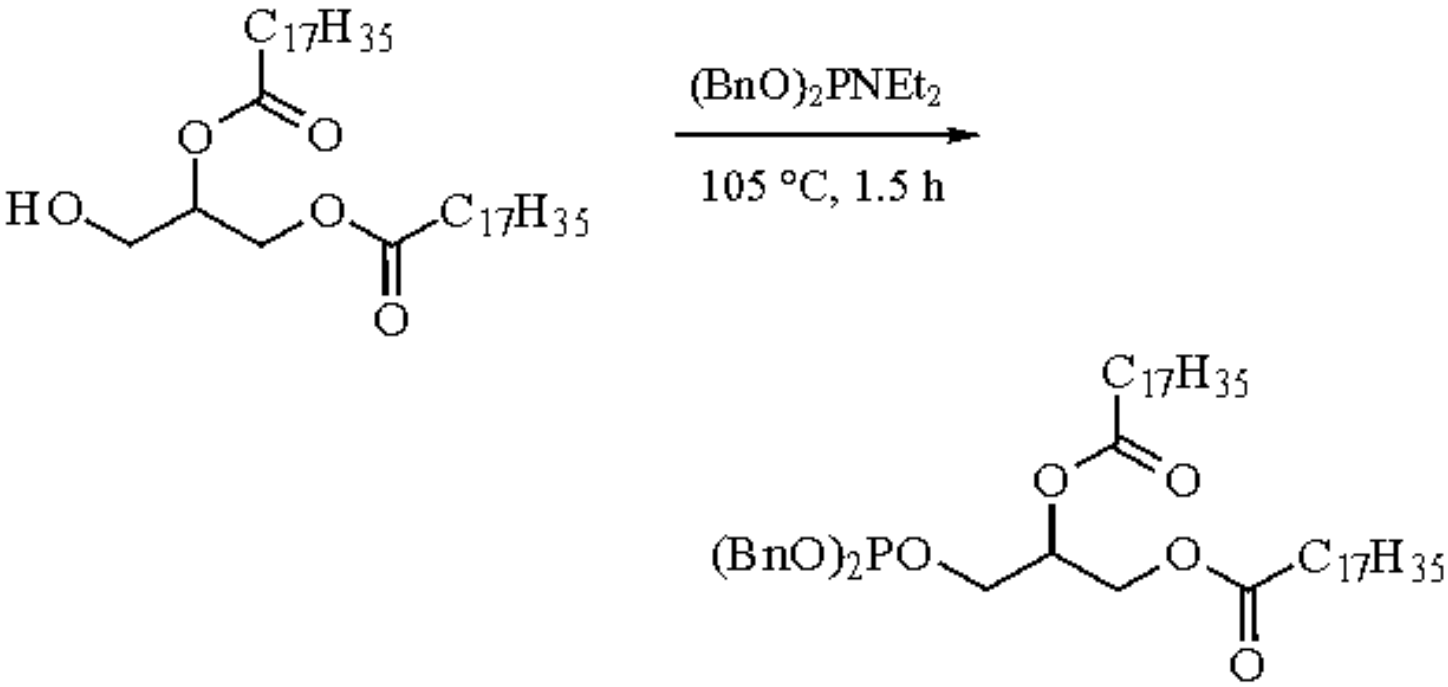

(1)

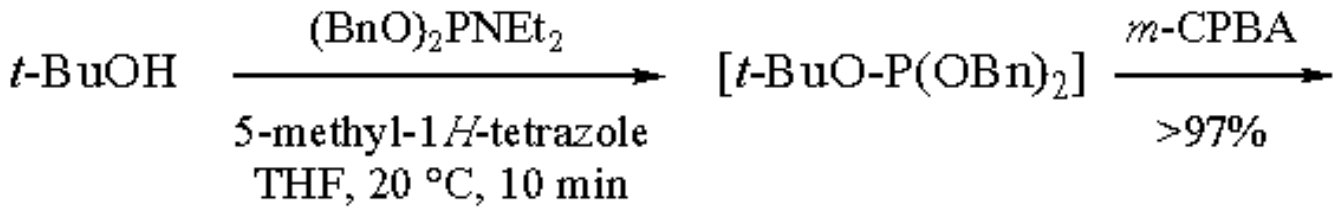

t-BuO-P(O)(OBn)$_2$ (2)

Protected serine and threonine derivatives have been phosphorylated for subsequent incorporation into peptides as the phosphate triesters (eq 3).[2,3,9,10] Similarly, dibenzyl *N*,*N*-diethylphosphoramidite has been used to prepare both Boc and Fmoc tyrosine derivatives for use in peptide synthesis.[4,11-14] Use of dibenzyl *N*,*N*-diethylphosphoramidite in phosphorylation of the side chain hydroxyls of serine- and threonine-containing peptides has been demonstrated.[2,7,15-18]

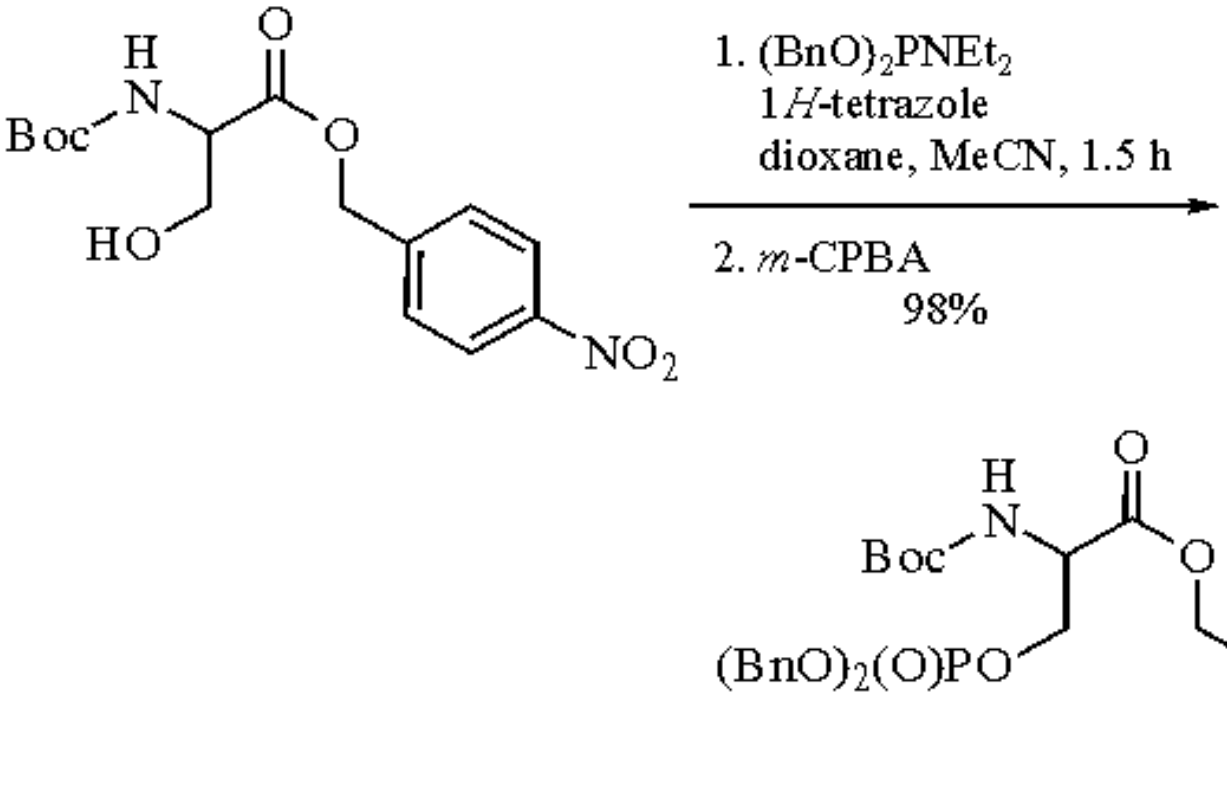

(3)

Dibenzyl *N*,*N*-diethylphosphoramidite has been used in phosphorylation sequences yielding dihydroxyacetone phosphate, D-*myo*-inositol 1,3,4,5-tetrakisphosphate (eq 4), and an inositol monophosphatase inhibitor.[8,19,20] Phosphitylation of the anomeric hydroxy groups of a series of sugars has been examined. The resulting glycosyl dibenzyl phosphites are effective as glycosylating reagents (eq 5), or they may be oxidized to the phosphates and used in the synthesis of sugar nucleotides.[5,21]

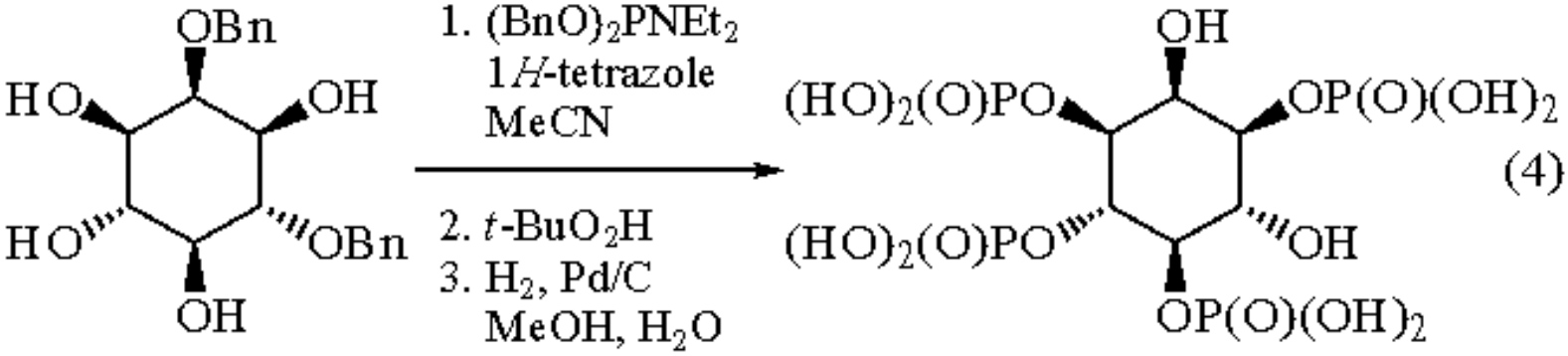

(4)

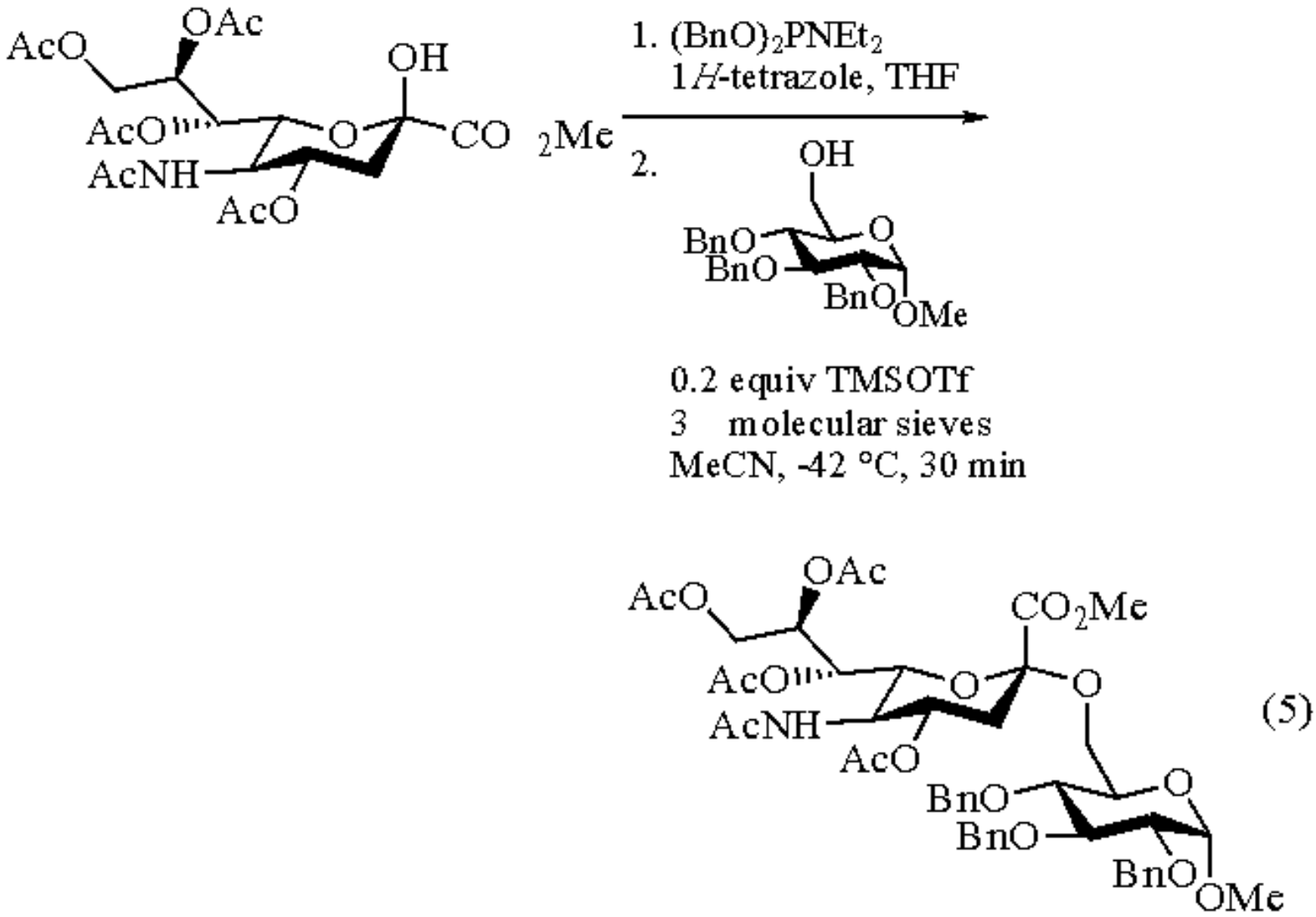

Related Reagents.

Dibenzyl N,N-Diisopropylphosphoramidite.

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Dibenzyl *N,N*-Diisopropylphosphoramidite[1]

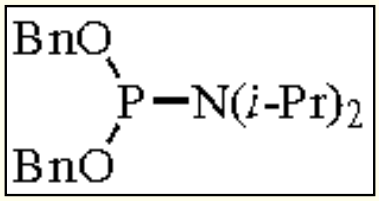

[108549-23-1] · $C_{20}H_{28}NO_2P$ · Dibenzyl *N,N*-Diisopropylphosphoramidite · (MW 345.42)

(phosphitylating reagent for alcohols; the resulting alkyl dibenzyl phosphite is transformed to the phosphoric monoesters by oxidation and subsequent debenzylation)[2]

Solubility: insol cold H_2O; sol CH_2Cl_2, THF, acetonitrile.

Analysis of Reagent Purity: NMR: δ_P ($CDCl_3$) +148.2.

Preparative Methods: there are several synthetic methods,[2-4] among which the reaction of benzyl alcohol with *N,N*-diisopropylphosphoramidous dichloride in the presence of *t*-amine in diethyl ether, THF, or dioxane is convenient.[5]

Purification: chromatography on silica gel.

Handling, Storage, and Precautions: can be stored in the absence of moisture and air for more than several months. A stock solution can be also prepared.

Phosphoric Monoester Synthesis.

Dibenzyl phosphoramidites such as dibenzyl *N,N*-diisopropylphosphoramidite (**1**) (see also ***Dibenzyl N,N-Diethylphosphoramidite***) react quickly with various alcohols in the presence of 1*H*-tetrazole at room temperature to afford the phosphorus triesters which are oxidized in situ with an oxidant such as ***m-Chloroperbenzoic Acid***, ***t-Butyl Hydroperoxide***, or 30% ***Hydrogen Peroxide*** to give the corresponding alkyl dibenzyl phosphoric triesters in excellent yields. The triesters are deprotected by simple and clean catalytic hydrogenolysis on a Pd catalyst such as ***Palladium on Carbon*** or ***Palladium(II) Hydroxide***. The usefulness of the sequence has been demonstrated by many examples which involve synthesis of phosphate derivatives of amino acids,[2,6] peptides,[7] sugars,[8] and cyclitols (eq 1).[4]

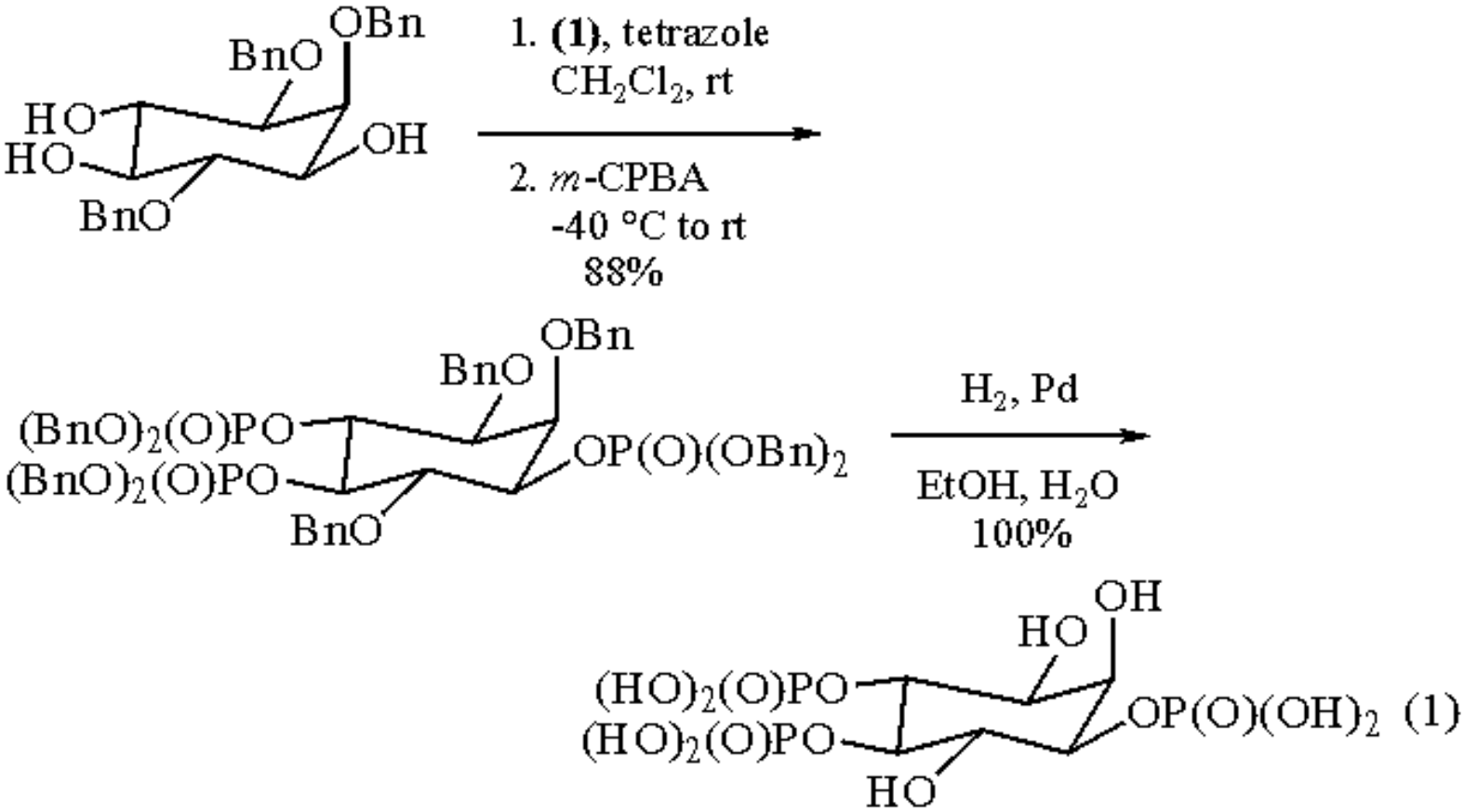

Dibenzyl phosphoric triesters are prepared alternatively by using ***Dibenzyl Phosphorochloridate***, tetrabenzyl pyrophosphate, or dibenzyl phosphorofluoridate. See also cyclic homologue of (**1**), ***o-Xylylene N,N-Diethylphosphoramidite***. These amidite reagents are more effective than P^V reagents, especially for phosphorylation of sterically hindered or base-sensitive alcohols, due to their high reactivity under milder conditions.

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1. For a related review, see Beaucage, S. L.; Iyer, R. P. *T* **1992**, *48*, 2223.
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Dibenzyl Phosphorochloridate[1]

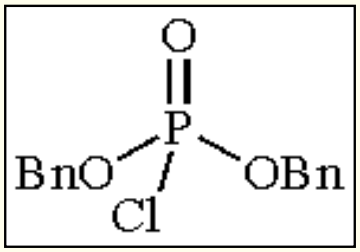

[538-37-4] · $C_{14}H_{14}ClO_3P$ · Dibenzyl Phosphorochloridate · (MW 296.69)

(phosphorylating reagent for alcohols,[2] phenols,[3] amines,[4] and amides;[5] removal of benzyl groups from the products affords phosphoric monoesters and monoamides respectively)

Alternate Name: BPC.

Physical Data: undistillable thick oil.

Analysis of Reagent Purity: NMR: δ_P +4.7, +3.5 ppm.

Preparative Methods: oxidative halogenation of dibenzyl phosphite using Cl_2 or *N*-chlorosuccinimide[6] yields dibenzyl phosphorochloridate (BPC). The reaction of dibenzyl hydrogen phosphate with PCl_5 is also used.[7] The latter procedure is employed for the preparation of *p*-substituted benzyl derivatives such as *p*-nitrobenzyl[8] and *p*-chlorobenzyl.[9] These substituted benzyl phosphates are crystalline and more stable than BPC but have reactivities similar to the parent chloridate.

Handling, Storage, and Precautions: dibenzyl phosphorochloridate may be stored in the cold but preferably prepared just prior to use. Distillation of the chloridate may cause violent decomposition.

Phosphorylation.

A variety of hydroxy compounds including nucleosides,[10] 1-hydroxy sugars (eq 1),[2] cyclitols,[11] and amino acids (eq 2),[12] as well as amines[4] and amides (eq 3),[5] have been phosphorylated with dibenzyl phosphorochloridate in the presence of a base, or after deprotonation, to afford the corresponding triesters and phosphoramidates, respectively.

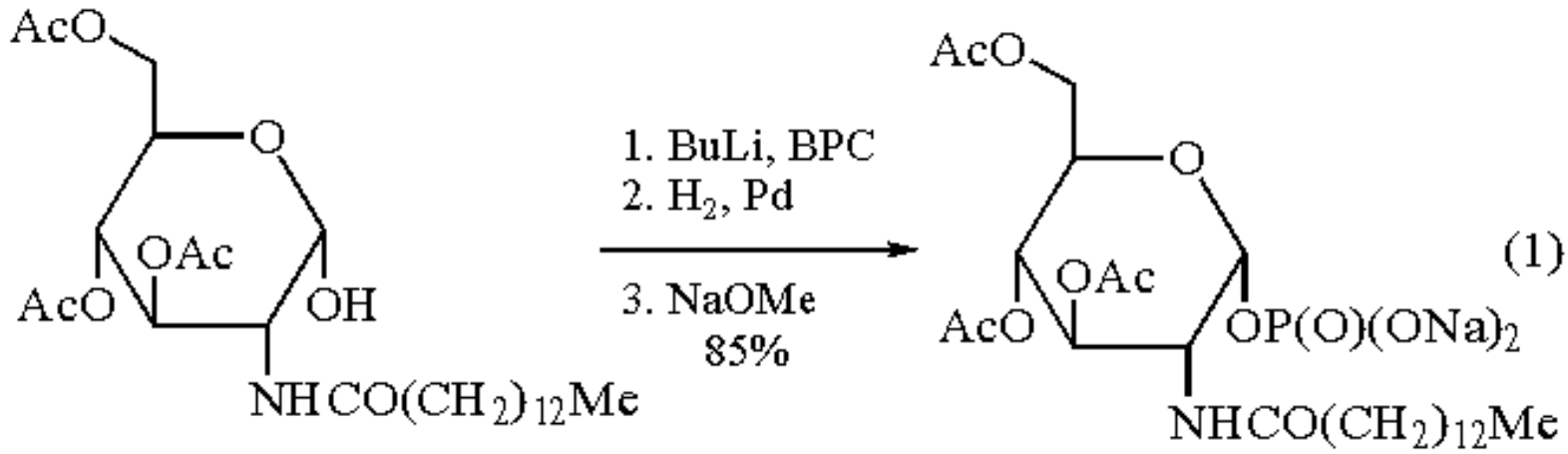

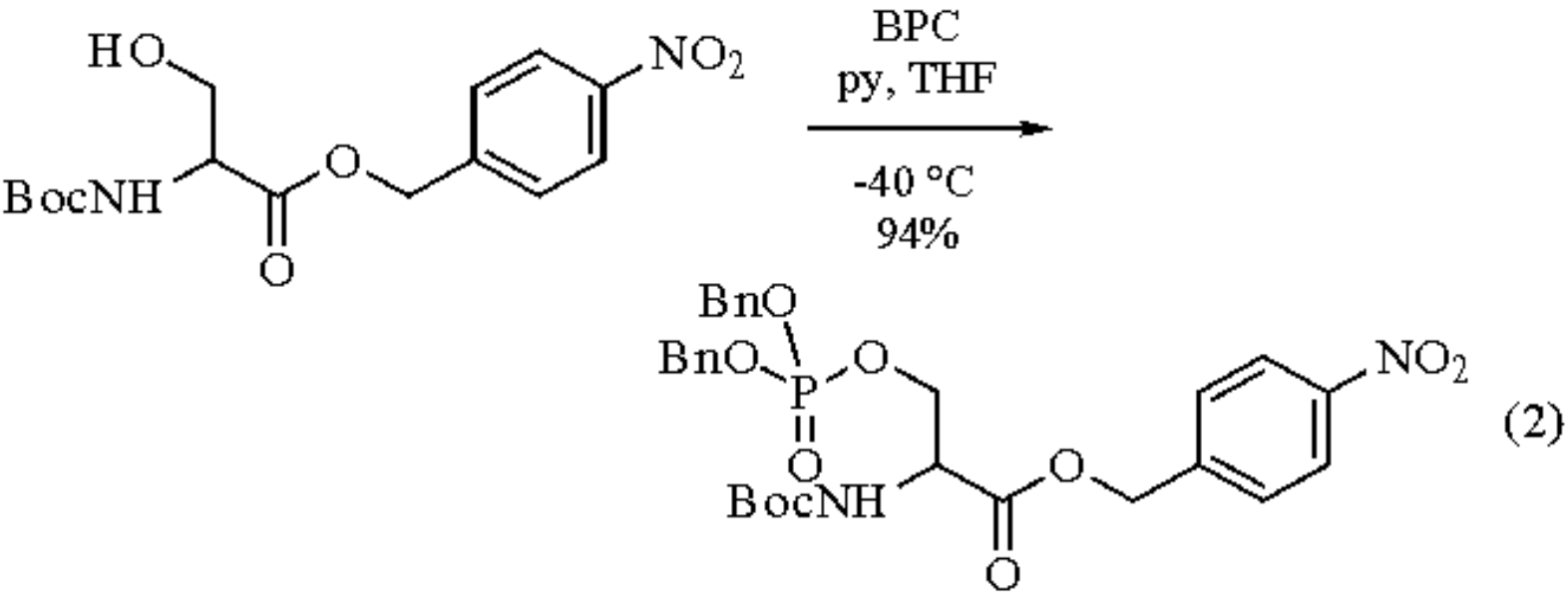

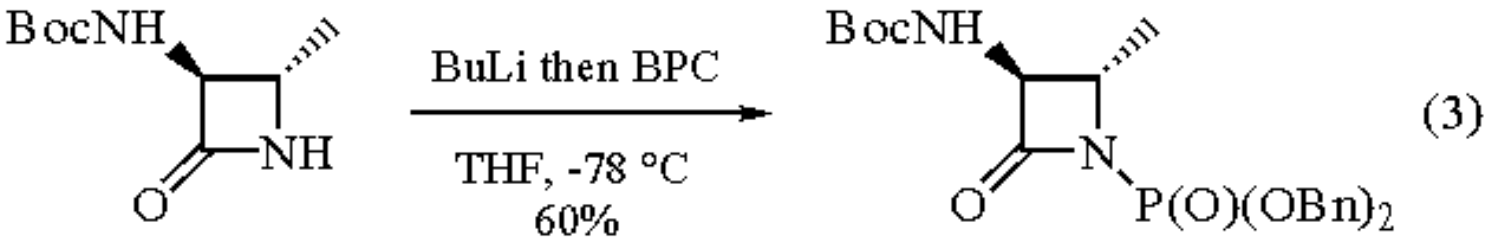

Deprotection of the dibenzyl phosphate derivatives is readily achieved by hydrogenolysis on a palladium catalyst such as ***Palladium on Carbon*** or Pd black, resulting in the formation of phosphoric monoesters and monoamides. Removal of the benzyl groups can be also carried out by ***Sodium-Ammonia***,[13] and ***Bromotrimethylsilane***[14] is useful when hydrogenation should be avoided. When removal of one of two benzyl groups is desired, various halides such as ***Sodium Iodide***[7] and other nucleophiles[15] are applied.

Synthetically Analogous Reagents.

Dibenzyl phosphorofluoridate (colorless oil), a fluoro analog of BPC, is prepared by the action of 2-fluoro-1-methylpyridinium *p*-toluenesulfonate on dibenzyl hydrogen phosphate or by the reaction of tetrabenzyl pyrophosphate with CsF.[16] Unlike BPC, and dibenzyl phosphorobromidate and -iodidate, the fluoridate can be purified by distillation

under reduced pressure (bp ca. 150 °C/0.2 mmHg) or chromatography on SiO_2. It reacts with alcohols and preferably with phenols in the presence of ***Cesium Fluoride*** (eq 4)[16] to give alkyl or aryl dibenzyl phosphates.

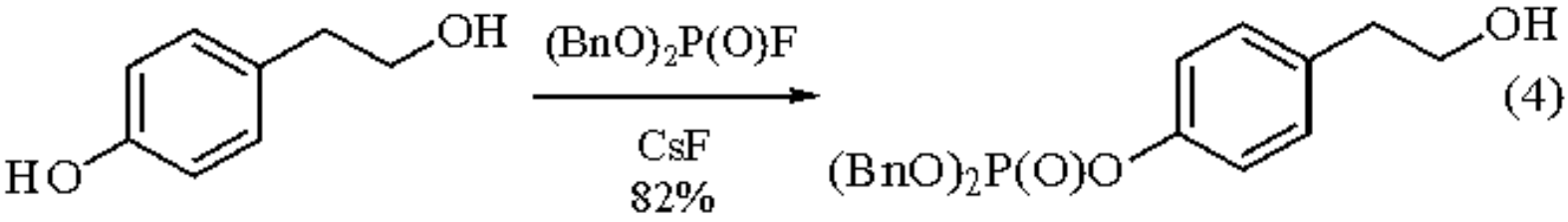

(4)

Tetrabenzyl pyrophosphate (needles, mp 60-61 °C), which is derived from dibenzyl hydrogen phosphate in the presence of ***1,3-Dicyclohexylcarbodiimide***,[17] can be used also for the phosphorylation of alcohols involving polyols (eq 5)[18] and amines. In the case of alcohols, generation of alkoxide by the action of strong bases such as ***n-Butyllithium***, ***Lithium Diisopropylamide***, ***Sodium Hydride***, or ***Potassium Hydride*** is necessary due to decreased reactivity relative to BPC. The pyrophosphate is crystalline solid and easy to handle, and can be stored in a desiccator.

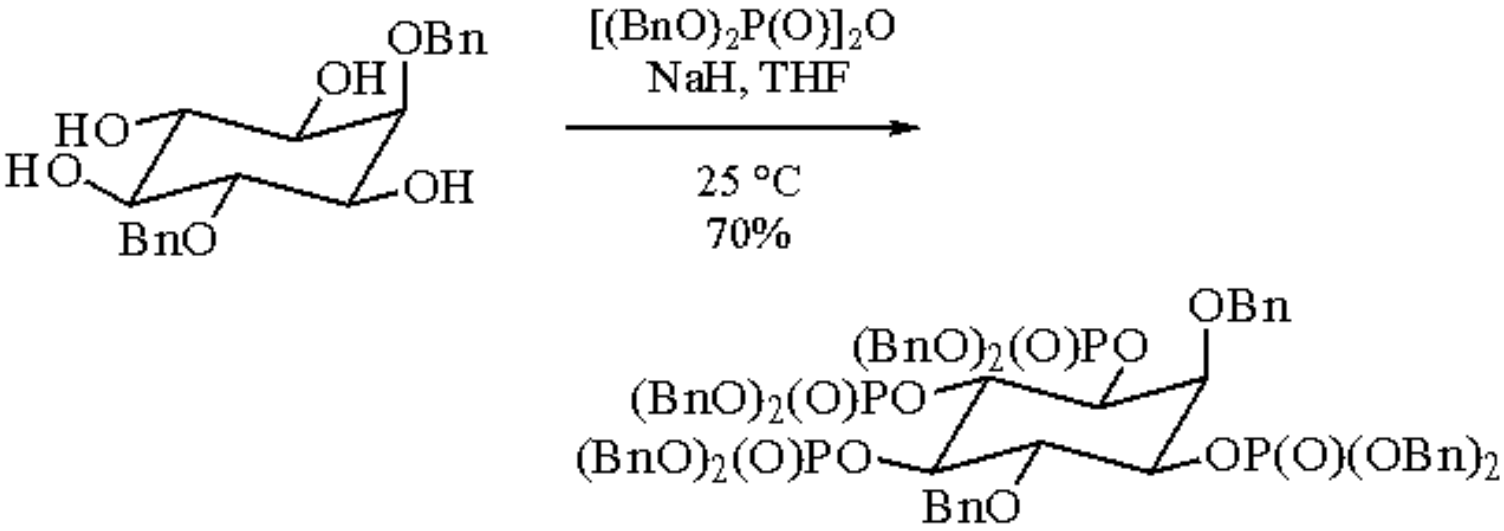

(5)

Related Reagents.

Dibenzyl N,N-Diethylphosphoramidite; ***o-Xylylene N,N-Diethylphosphoramidite***.

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Diborane

B_2H_6

[19287-45-7] · B_2H_6 · Diborane · (MW 27.67)

(strong reducing agent for many functional groups; extremely efficient hydroborating reagent)

Physical Data: bp -92.5 °C; mp -165.5 °C; *d* 0.437 g cm^{-3} (liquid at -92.5 °C); heat of vaporization 3.41 kcal mol^{-1} (at -92.5 °C).

Solubility: slightly sol pentane and hexane; forms BH_3 adduct with DMS, THF, and other ethers; reacts with H_2O and protic solvents, releasing flammable hydrogen gas.

Form Supplied in: commercially available as a compressed gas.

Analysis of Reagent Purity: supplied as either 99.99% or >99.0% B_2H_6.

Handling, Storage, and Precautions: diborane is a toxic, pyrophoric gas and must be stored and handled accordingly. Feed lines and reactors should be flushed with N_2 and kept free of moisture. Cylinders should be hard-piped directly to reactor. When not in use, cylinder valve should be securely closed and capped. Cold (-20 to 0 °C) storage is recommended to ensure product purity. Decomposition products include higher boron hydrides and hydrogen gas.

Diborane and Borane Reagents.

Borane complexes have been used in industrial-scale applications for years. In addition to their unique ability to add across carbon-carbon multiple bonds, boron hydrides reduce ketones, carboxylic acids, amides, and nitriles (eqs 1-3).[1] By the appropriate choice of borane reagent and reaction conditions, a significant degree of chemical selectivity can be achieved. This high level of selectivity and reactivity has found utility not only in classical organic synthesis,[2,3] but also in the area of asymmetric synthesis with the Corey-Itsuno catalyst serving as a prime example of a highly reactive and enantioselective reagent.[4]

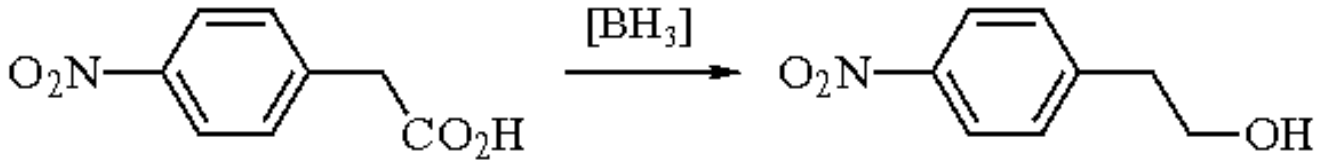

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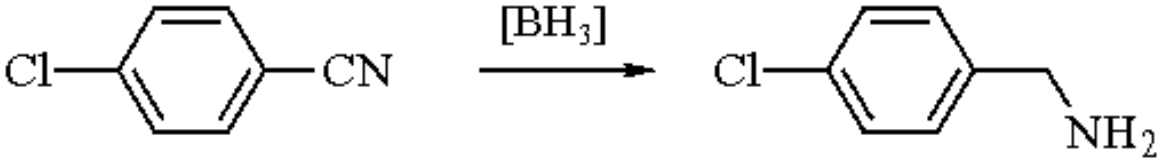

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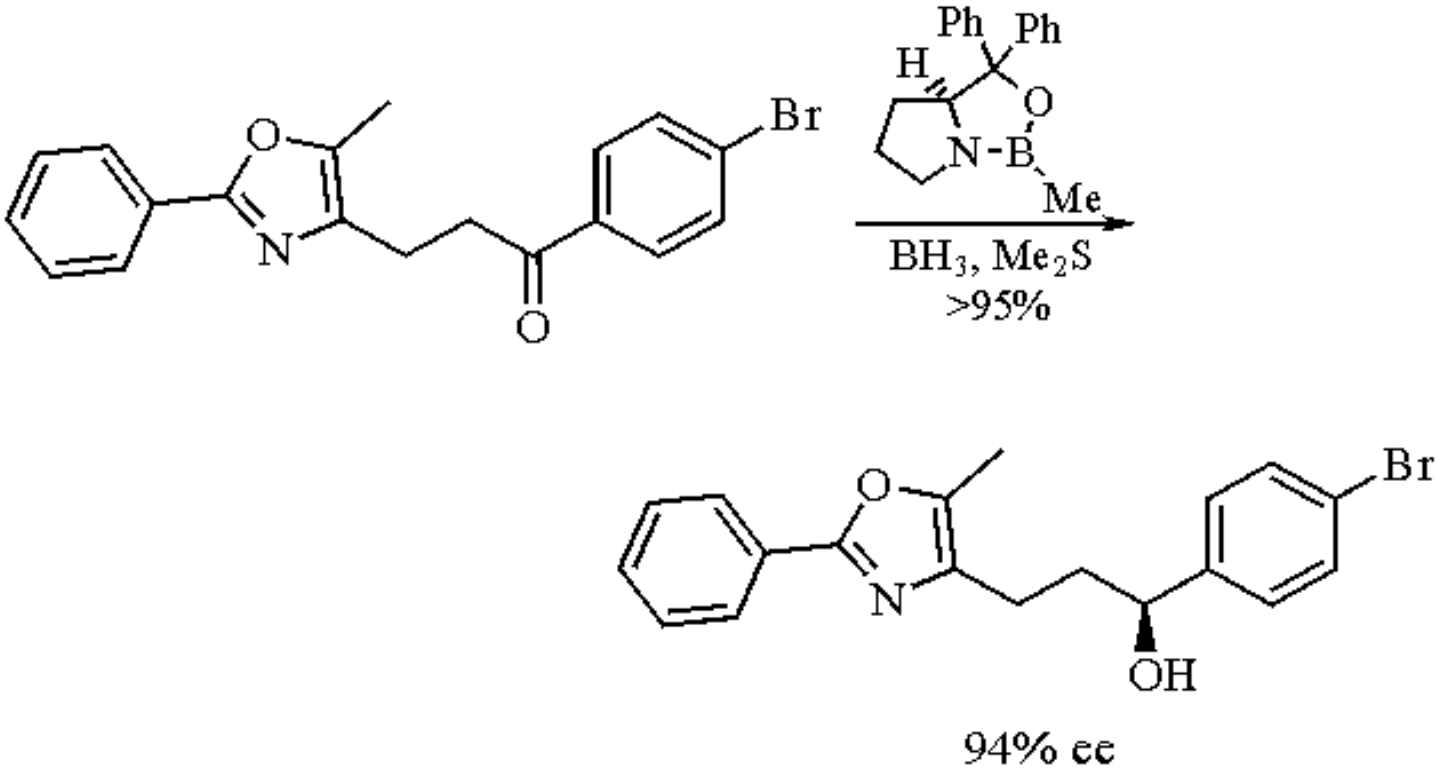

(3)

Chemically, diborane is the parent of all the borane complexes. Diborane will react with a Lewis base to form an adduct in which the electron pair from the Lewis base is donated to the borane. This complexation alters the reactivity of the borane, subsequently changing its physical form. Diborane is a gas with a boiling point of -92.5 °C, whereas the borane complexes are either liquids or solids. As illustrated in the molecular model (**1**), diborane has some unusual bonding characteristics. The boron is so electron deficient that it resorts to sharing the electrons in the B-H bond, giving rise to bridging hydrogens. This electron deficiency allows formation of borane complexes with Lewis bases such as tetrahydrofuran (THF), dimethyl sulfide (DMS), and amines (Scheme 1).

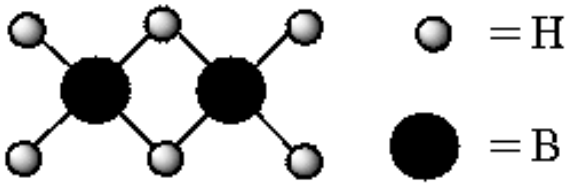

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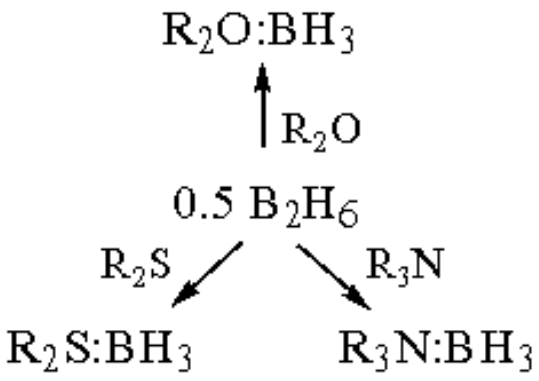

Scheme 1

In the search for better borane reagents, a variety of complexes have been synthesized; almost all fit under one of the three following classifications: ether-borane complexes, sulfide-borane complexes, or amine-borane complexes.

A general trend of borane complexes is that the stronger the Lewis base, the weaker the reducing power of the resulting borane.[5] ***Borane-Tetrahydrofuran*** (THFB) is more reactive than ***Borane-Dimethyl Sulfide*** (DMSB), which in turn is more reactive than most amine-boranes. When reducing a carboxylic acid or hydroborating a carbon-carbon double bond, THFB and DMSB are both effective reagents, while amine-boranes generally are not suitable choices.

Comparison of Borane Reagents.

THFB and DMSB, however, do have drawbacks which can be of some concern in an industrial setting. The maximum workable concentration for THFB is 1 molar. Therefore a large reactor volume is required to achieve the desired reduction. The low loading in a given size reactor, and ultimately solvent waste, increase the cost-per-pound of product.

DMSB is commercially available as a neat solution (~10M); thus solvent volume is determined by reactor loading of other reactants (substrate). However, anyone who has had the opportunity to use dimethyl sulfide can attest to the fact that the human nose can detect DMS in the ppm range. Various schemes have been used in an attempt to scrub the DMS from reaction streams, but none are truly effective.

When diborane is added to an ether solvent, ether-borane complexes are formed. If the solvent is THF, then THFB is formed in situ, and reacts in the same manner without the high dilution effect of using the 1M THFB solution. By using diborane rather than THFB, reactor loading can be increased, thereby reducing costs. Use of diborane will also reduce the amount of waste solvent remaining at the end of the process. The advantage of diborane over DMSB is the avoidance of odor control problems inherent in dimethyl sulfide, again reducing costs.

Although much of the literature describing borane reductions involves coordinating solvents such as ethers, diborane can be employed in nonpolar hydrocarbon solvents.[6-9] Table 1 shows an appreciable solubility of diborane in hexanes. It should be noted that the reactivity of diborane in hydrocarbons may be distinctly different from the reactivity of borane complexes. For example, because it is uncomplexed, diborane is generally much more reactive than sulfide boranes such as DMSB.

Table 1 Solubility of Diborane in Various Solvents

Solvent	Solubility (g B_2H_6/100 g solvent)	Temperature (°C)	B_2H_6 pressure (atm)
n-Pentane	0.996	19.6	0.958
n-Hexane	4.22	room	2.55
neo-Hexane	3.18	room	4
cis-Decalin	1.86	room	2.44
Mesitylene	0.323	25	0.653
Ethyl ether	1.1	20	1
1,4-Dioxane	3.37	room	2.38
Tetrahydrofuran	8.1	20	1

However, diborane should not be used in every reaction where THFB or DMSB are currently in use.

- 1)DMSB is a good choice if the reduction requires heat to push the reaction to completion, because DMSB is stable at higher temperatures than ether-borane complexes.
- 2)THFB is a good choice when addition of substrate to an excess of borane is required, and reactor loading is not a major concern. THFB solutions should not be heated above 50 °C, since diborane will be lost from the complex and reductive ring opening of the THF will occur.
- 3)Diborane is a good choice when it is desirable to add borane to the substrate in the reactor. With diborane, higher reactor loadings can be achieved than with either of the other two reagents.

Generally, if the reaction is fast at or below ambient temperature, diborane is an effective replacement for either THFB or DMSB.

The classic synthesis of ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) from *cis,cis*-1,5-cyclooctadiene (cod) serves as a good model for hydroboration reactions (eq 4). The route described in the literature[10] advises the use of DMSB in dimethoxyethane (DME). Following the hydroboration and removal of DMS, crystalline 9-BBN precipitates out of the DME solvent. Unfortunately, the resulting product is contaminated with the odor of dimethyl sulfide which is not readily removed from the 9-BBN. The use of THFB as the hydroborating reagent does alleviate the DMS odor, but the product remains solubilized as a dilute solution in THF and DME. When diborane is added as a gas to a DME solution of cod, the resulting 9-BBN is obtained as a clean crystalline product with a typical purity of >96%. No further processing is required from the diborane-produced 9-BBN.[11]

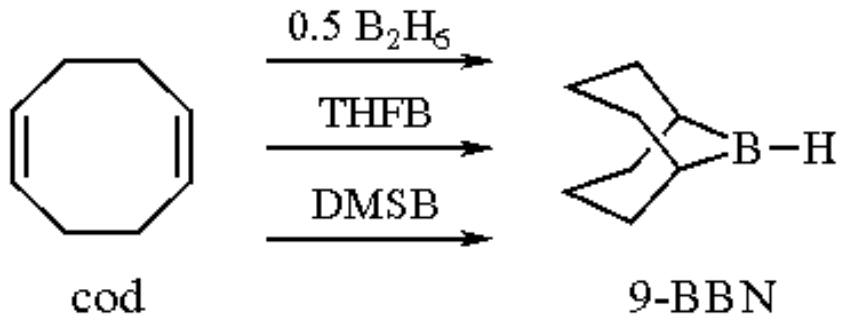

(4)

Reduction of a substituted xanthone to a xanthene, shown in eq 5, was accomplished using three borane reagents.[12] THFB was an effective reagent for this transformation, and was the most desirable for small-scale preparations because of its ease of use. The reduction utilizing DMSB could not be driven to completion. Diborane proved to be the most effective reagent and was highly desirable for commercial-scale synthesis of the xanthene. With the higher loading achievable using diborane, the THFB route was considered to be economically unfeasible.

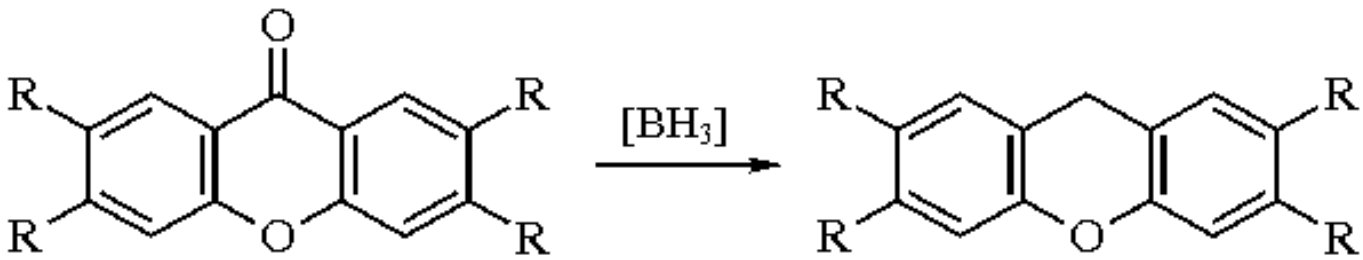

(5)

Practical Considerations.

Introduction of diborane into a reactor requires some careful consideration of the reactor system. Diborane, like almost all hydrides, is very reactive. It is critical that the reactor be under an inert gas, such as nitrogen, since diborane is a pyrophoric material. The addition of diborane to a solution is best accomplished by feeding gaseous diborane under the surface of the solvent. If the product formed by reaction of diborane is a solid, diborane can be added to the reactor head space provided that a back pressure on the reactor keeps it contained. Given a reactor which is free of oxygen and moisture, diborane is used as any other compressed gas.

Diborane cylinders are packaged in dry ice for shipment. The vapor pressure of diborane at -78 °C is 15 psig (776 Torr). This allows for a convenient method to control the pressure of diborane gas being fed to a reactor. The rate at which diborane is fed into the reactor is dictated by the thermodynamics and kinetics of the reaction, and the temperature constraints of the system.

Conclusion.

In many cases, diborane can be used as a cost effective reagent for reduction or hydroboration. Use of diborane in place of THFB can significantly increase the loading in a given reaction. Used in place of DMSB, it can eliminate the handling of dimethyl sulfide as a waste. All three reagents (diborane, THFB, and DMSB) have application in organic synthesis, and each should be evaluated for potential use.

Related Reagents.

Borane-Ammonia; ***Borane-Dimethyl Sulfide***; ***Borane-Pyridine***; ***Borane-Tetrahydrofuran***; ***Ephedrine-borane***;

Norephedrine-Borane.

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Dibornacyclopentadienyltrichlorozirconium[1]

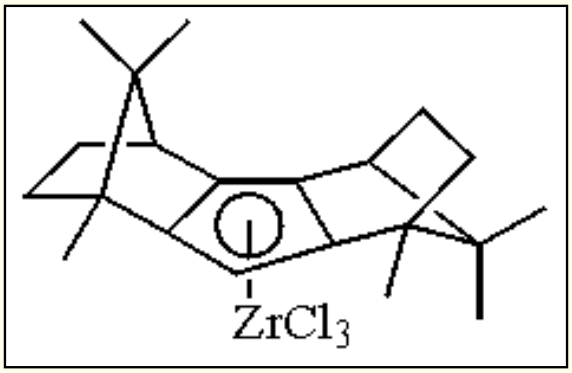

[126035-93-6] · $C_{21}H_{29}Cl_3Zr$ · Dibornacyclopentadienyltrichlorozirconium · (MW 479.07)

(chiral Lewis acid for enantioselective C-C coupling of pyruvic esters with active arenes[1])

Physical Data: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.73, 3.05 (4,4´-H), 0.8-1.0, 1.8-2.2, 2.68 (5,5´,6,6´-H), 6.11 (8-H), 0.26, 0.92, 0.93, 0.95, 1.19, 1.46 (1,1´,7,7´-CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz, ^1J(CH) in Hz): δ 11.6, 12.5 (1,1´-CH_3), 19.8, 20.6 (double intensity), 29.8 (7,7´-CH_3), 25.8 (122) and 00.0 (125; 5,5´), 32.1 (131) and 38.5 (137; 6,6´), 50.5 (149) and 51.6 (147; 4,4´), 55.8 (triple intensity), 68.6 (1,1´,7,7´), 106.4 (173; 8), 144.9, 146.9, 152.7, 159.7, 159.2 (2,2´,3,3´).

Solubility: sol dichloromethane.

Preparative Method: reaction of dibornacyclopentadienyllithium with $ZrCl_4$ (40% yield).[1]

Preparation.

Both the title zirconium catalyst (**1**), and the corresponding hafnium derivative (**2**) have been synthesized according to Scheme 1. Addition of 2 equiv of 2-bornen-2-yllithium (**4**) (generated via the Shapiro reaction[2] from (+)-camphor (**3**)) to ethyl formate gives bis(2-bornen-2-yl)methanol (**5**). Cyclization of alcohol (**5**) is carried out with ***Potassium Hydrogen Sulfate*** at 100-150 °C to afford dibornacyclopentadiene (**6**). Deprotonation of (**6**) with ***n-Butyllithium*** followed by reaction with ***Zirconium(IV) Chloride*** affords (**1**). Reaction with $HfCl_4$ affords (**2**).

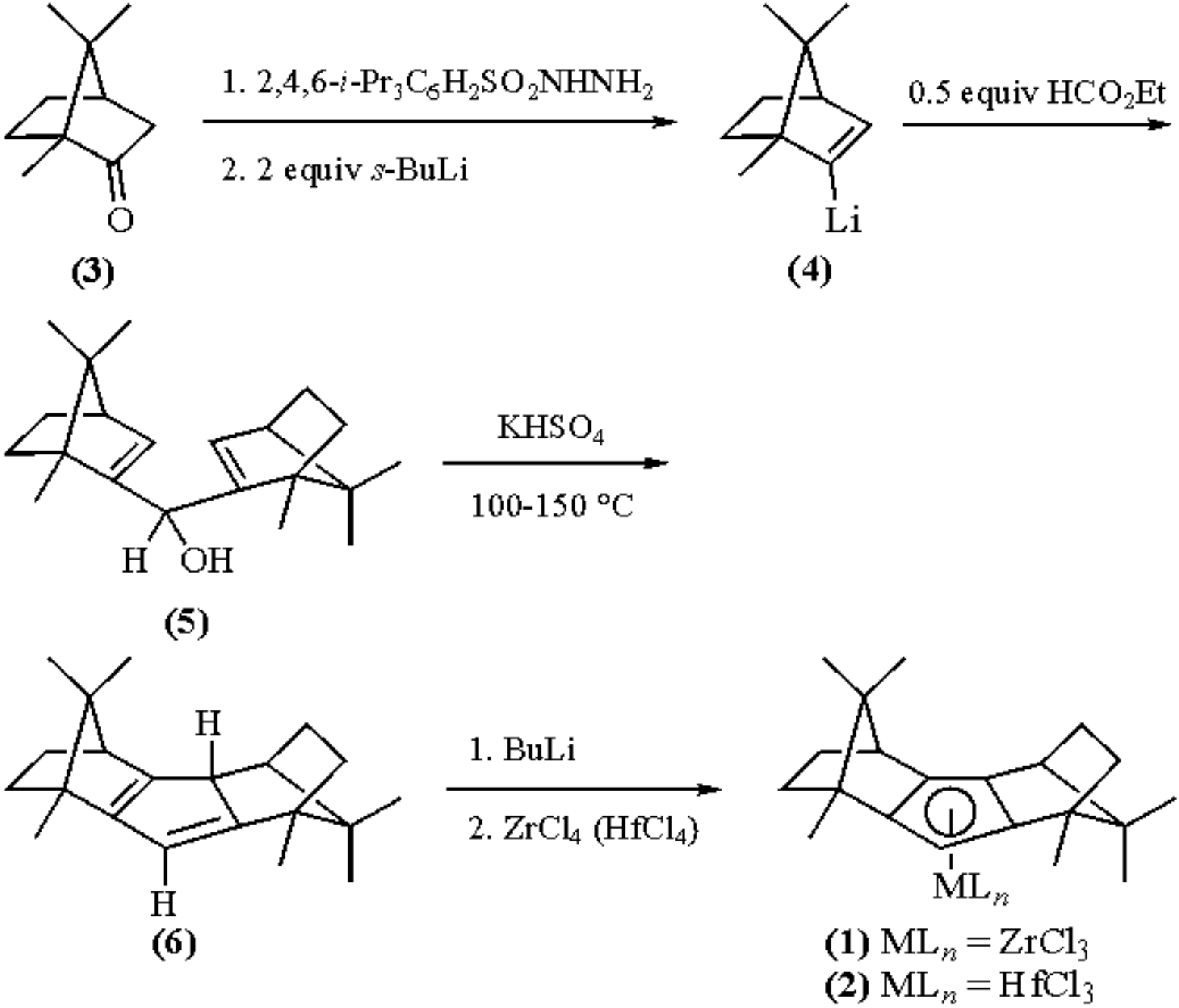

Scheme 1

Arylation of α-Keto Esters.

Zirconium complex (**1**) has been used as a catalyst for the synthesis of optically active 2-(2-hydroxyaryl)lactic acid ethyl ester (**7**) (eq 1).[1]

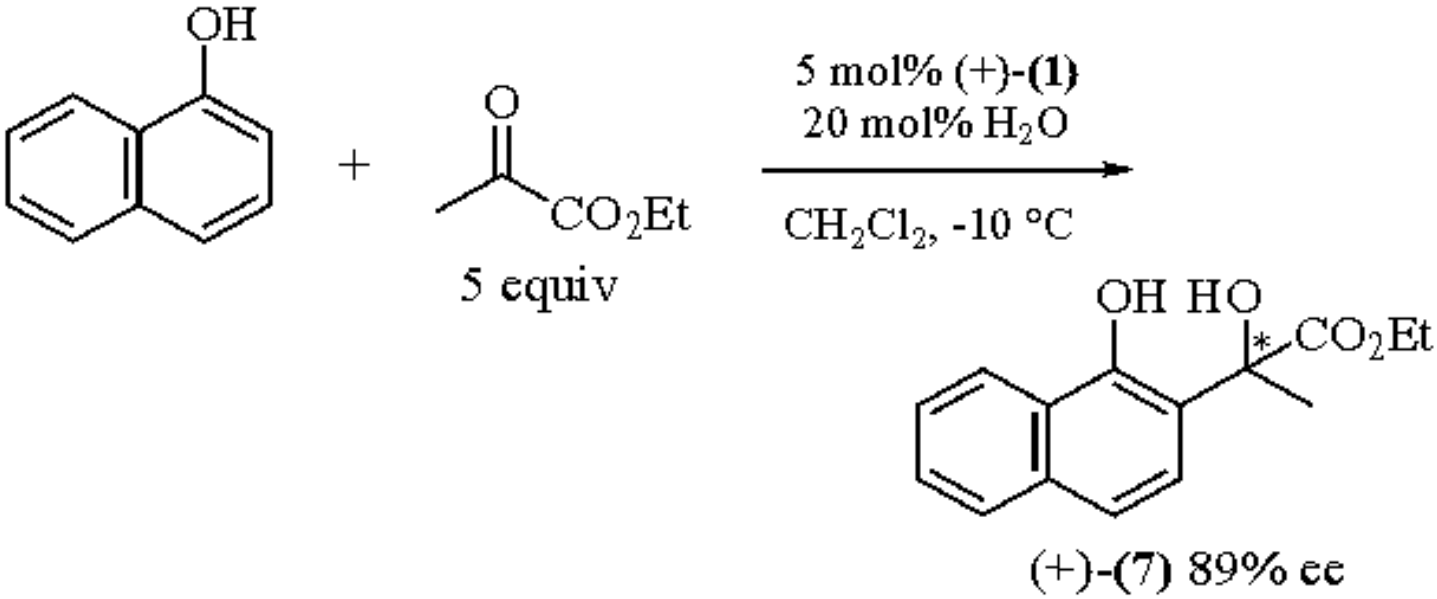

(1)

It was found that lowering the reaction temperature from rt to -10 °C resulted in an increased enantiomeric excess (from 27% ee to 54% ee). Surprisingly, the addition of small amounts of water (ca. 20 mol %) also increased the chiral induction observed (up to 89% ee).

---

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1,3-Dibromoacetone

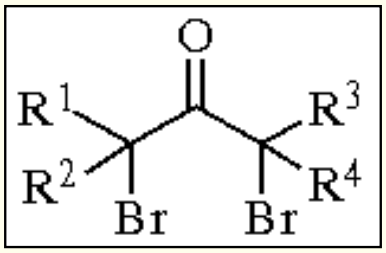

(**1**; R^1 = H, R^2 = H, R^3 = H, R^4 = H)

[816-39-7] · $C_3H_4Br_2O$ · 1,3-Dibromoacetone · (MW 215.87) (**2**; R^1 = H, R^2 = Br, R^3 = H, R^4 = Br)

[22612-89-1] · $C_3H_2Br_4O$ · 1,1,3,3-Tetrabromoacetone · (MW 373.66) (**3**; R^1 = Me, R^2 = Br, R^3 = H, R^4 = Br)

[27992-54-7] · $C_4H_4Br_4O$ · 1,1,3,3-Tetrabromo-2-butanone · (MW 387.69) (**4**; R^1 = Me, R^2 = H, R^3 = Me, R^4 = H)

[815-60-1] · $C_5H_8Br_2O$ · 2,4-Dibromo-3-pentanone · (MW 243.93) (**5**; R^1 = Me, R^2 = Me, R^3 = Me, R^4 = H)

[37010-00-7] · $C_6H_{10}Br_2O$ · 2,4-Dibromo-4-methyl-3-pentanone · (MW 257.95) (**6**; R^1 = Me, R^2 = Me, R^3 = Me, R^4 = Me)

[17346-16-6] · $C_7H_{12}Br_2O$ · 2,4-Dibromo-2,4-dimethyl-3-pentanone · (MW 271.98) (**7**; R^1 = Et, R^2 = H, R^3 = Me, R^4 = Me)

[69204-79-1] · $C_7H_{12}Br_2O$ · 3,5-Dibromo-2-methyl-3-hexanone · (MW 271.98) (**8**; R^1 = Et, R^2 = H, R^3 = Et, R^4 = H)

[36461-40-2] · $C_7H_{12}Br_2O$ · 3,5-Dibromo-4-heptanone · (MW 271.98) (**9**; R^1 = Me, R^2,R^3 = -$(CH_2)_3$-, R^4 = Me)

[56829-67-5] · $C_8H_{12}Br_2O$ · 2,6-Dibromo-2,6-dimethylcyclohexanone · (MW 283.99) (**10**; R^1 = *i*-Pr, R^2 = H, R^3 = Me, R^4 = Me)

[56829-66-4] · $C_8H_{14}Br_2O$ · 2,4-Dibromo-2,5-dimethyl-3-hexanone · (MW 286.01) (**11**; R^1 = *i*-Pr, R^2 = H, R^3 = *i*-Pr, R^4 = H)

[30957-25-6] · $C_9H_{16}Br_2O$ · 3,5-Dibromo-2,6-dimethyl-4-heptanone · (MW 300.03) (**12**; R^1 = *n*-Pr, R^2 = Me, R^3 = Me, R^4 = Me)

[56829-63-1] · $C_9H_{16}Br_2O$ · 2,4-Dibromo-2,4-dimethyl-3-heptanone · (MW 300.03) (**13**; R^1 = Et, R^2 = Me, R^3 = Et, R^4 = Me)

[56829-64-2] · $C_9H_{16}Br_2O$ · 3,5-Dibromo-3,5-dimethyl-4-heptanone · (MW 300.03) (**14**; R^1 = Ph, R^2 = H, R^3 = Me, R^4 = H)

[38651-07-9] · $C_{10}H_{10}Br_2O$ · 1,3-Dibromo-1-phenyl-2-butanone · (MW 306.00) (**15**; R^1 = *n*-Pr, R^2 = Me, R^3 = Et, R^4 = Me)

[56829-65-3] · $C_{10}H_{18}Br_2O$ · 3,5-Dibromo-3,5-dimethyl-4-octanone · (MW 314.06) (**16**; R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Me)

[64097-38-7] · $C_{11}H_{12}Br_2O$ · 1,3-Dibromo-4-methyl-1-phenyl-2-butanone · (MW 320.02) (**17**; R^1 = *t*-Bu, R^2 = H, R^3 = *t*-Bu, R^4 = H)

[23438-05-3] · $C_{11}H_{20}Br_2O$ · 3,5-Dibromo-2,2,6,6-tetramethyl-4-heptanone · (MW 328.09) (**18**; R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = H)

[958-79-2] · $C_{15}H_{12}Br_2O$ · 1,3-Dibromo-1,3-diphenyl-2-propanone · (MW 368.07)

(three-carbon units for reductive [3 + 2][14,15] and [3 + 4][14,16] cyclocoupling with certain alkenes and 1,3-dienes)

Alternate Name: 1,3-dibromo-2-propanone.

Physical Data: (**1**) mp 26-27 °C; bp 80-81 °C/9 mmHg.[1] (**2**) mp 37-38 °C; bp 129-130 °C/7 mmHg.[1] (**3**) mp 53-54 °C.[1] (**4**) bp 51-57 °C/3 mmHg,[2] 67-68 °C/8 mmHg,[1] 67-82 °C/10 mmHg,[3] 115-118 °C/45 mmHg.[4] (**5**) bp 40 °C/0.15 mmHg.[5] (**6**) bp 80 °C/5 mmHg,[6] 85-87 °C/10 mmHg,[7] 87-89 °C/10 mmHg.[8] (**7**) bp 42 °C/0.15 mmHg.[5] (**8**) bp 100-101 °C/17 mmHg,[9] 118-121 °C/25 mmHg.[4] (**9**) mp 27-28 °C; bp 64 °C/0.3 mmHg.[6,10] (**10**) bp 41 °C/1 mmHg,[11] 45 °C/0.3 mmHg,[6] 51 °C/0.1 mmHg.[5] (**11**) bp 145-147 °C/28 mmHg.[4] (**12**) bp 63 °C/0.6 mmHg.[6] (**13**) bp 68 °C/0.6 mmHg.[6] (**14**) mp 34-45 °C.[12] (**15**) bp 68 °C/0.6 mmHg.[6] (**16**) mp 59-60 °C.[12] (**17**) mp 69-70 °C.[4] 70-71 °C,[13] (**18**) mp 81-84 °C,[14] 112-114 °C.[14]

Solubility: freely or fairly sol most organic solvents.

Form Supplied in: colorless or slightly yellow liquid or crystals; usually prepared in the laboratory.

Purification: the pure liquid compounds can be obtained by distillation or passage through basic alumina, while the pure crystalline derivatives are obtainable by recrystallization.

Handling, Storage, and Precautions: dibromo ketones, especially cyclic analogs, are allergenic and

lachrymatory and hence should be handled in a well-ventilated hood. Use of rubber gloves is recommended for handling. Since the dibromo ketones are sensitive to moisture and light, they should be stored in a tightly stoppered brown bottle or a brown ampule in a refrigerator. Occasionally, the compounds bear deep yellow or orange color on long storage. All procedures of the iron carbonyl-promoted reactions, including workup, should be carried out in a well-ventilated hood.

Generation of 2-Oxyallyl Species.

Two-electron reduction of an α,α´-dibromo ketone, generating a reactive zwitterionic 2-oxyallyl or related species, is effected with many low-valent metallic reagents such as ***Sodium Iodide-Copper*** in acetonitrile,[17,18] ***Zinc/Copper Couple*** in DME or acetone,[19] ***Zinc/Silver Couple*** in THF,[20] and ***Nonacarbonyldiiron*** in benzene (eq 1).[21] A similar species is generated by the reduction with ***Sodium Iodide*** in acetone or acetonitrile.[13,22] The reactive C_3 intermediates undergo cycloaddition to certain alkenes or 1,3-dienes to give five- or seven-membered cyclic ketones, respectively.

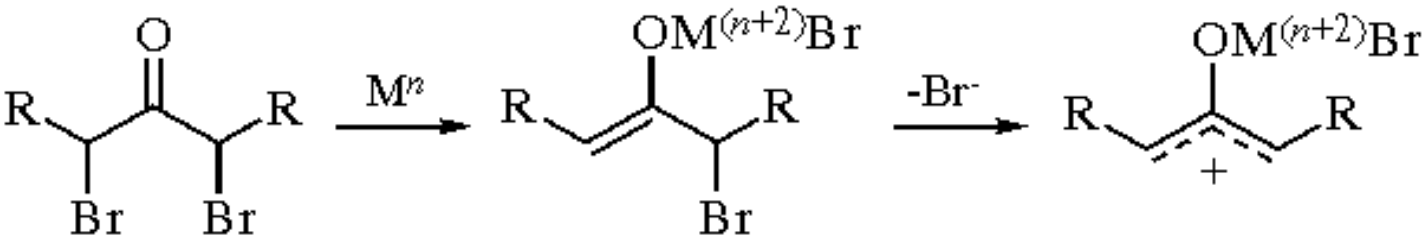

(1)

The [3 + 2 -> 5] Cyclocoupling Reactions.

Reduction of an α,α´-dibromo ketone with $Fe_2(CO)_9$ in the presence of an aryl-substituted alkene gives a 3-arylcyclopentanone (eq 2).[23] The reaction of an unsymmetrically substituted dibromo ketone proceeds with high regioselectivity.[24,25]

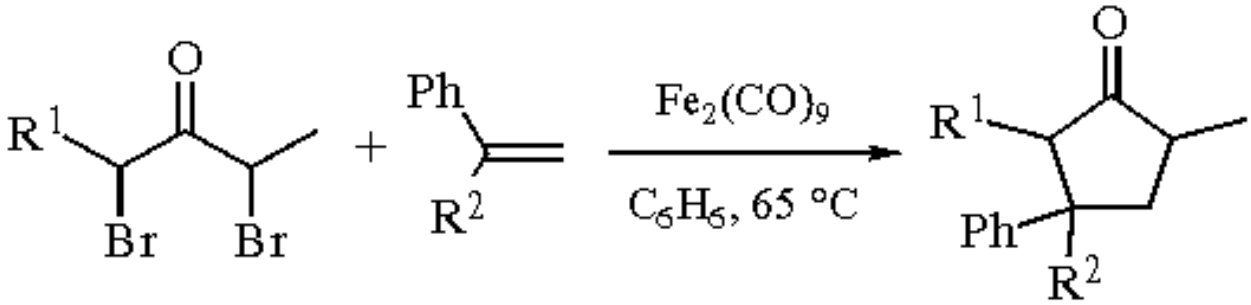

(2)

$R^1 = Me$; $R^2 = Ph$; 95%
$R^1 = Ph$; $R^2 = H$; 49%, 100% regioselective

Enamines serve as excellent C_2 substrates in the $Fe_2(CO)_9$-promoted cyclocoupling. Secondary dibromides initially form labile 3-aminocyclopentanones which readily eliminate amines to give 2-cyclopentenones (eq 3).[2,26] $Fe_2(CO)_9$ is the only efficient reducing agent for this cyclopentenone-forming reaction. The reaction with a tertiary dibromide gives a stable 3-aminocyclopentanone[26b,27] or 2-amino-5-alkylidenetetrahydrofuran.[26b] The latter type of product is obtained

by the reaction with 1,1-dimethoxyethylene promoted by Cu-NaI.[18]

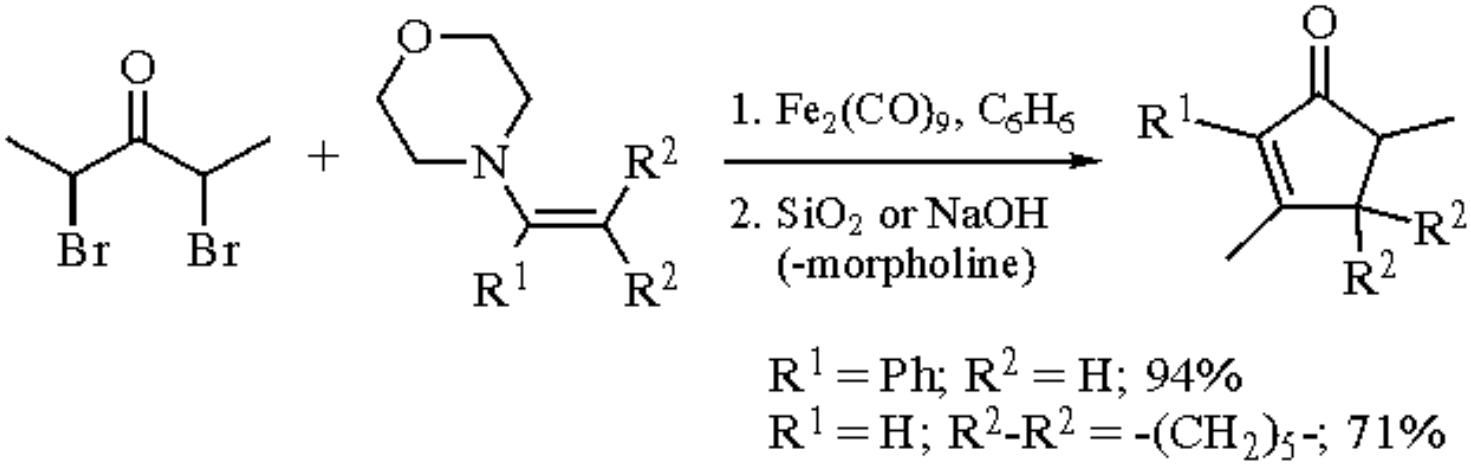

(3)

The secondary dibromides similarly cyclocouple with *N*,*N*-dimethylcarboxamides with the aid of $Fe_2(CO)_9$ to give 3(2*H*)-furanones (eq 4).[28] Use of Zn/Cu couple usually affords 2-amino-4-alkylidene-1,3-dioxolanes, which readily rearrange to the 3(2*H*)-furanones.[29] A similar 1,3-dioxolane product is formed in the reaction with a ketone promoted by ultrasonically dispersed Hg.[30] The NaI-assisted cyclocoupling with tetracyanoethylene or diethyl azodicarboxylate affords the corresponding five-membered products but in low yield.[13] Reduction of tertiary dibromo ketones with Zn/Cu couple[31] or $Fe_2(CO)_9$[14b] in the presence of acetonitrile produces 5-alkylidene-2-oxazolines in low yields.

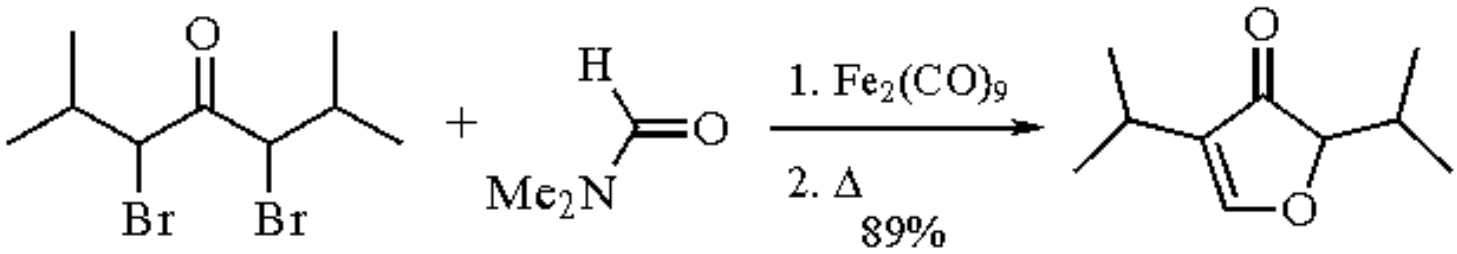

(4)

The $Fe_2(CO)_9$-aided [3 + 2] cyclocoupling with 2-methylpropene does not proceed smoothly,[32] while the intramolecular version gives a bicyclic product (eq 5).[33]

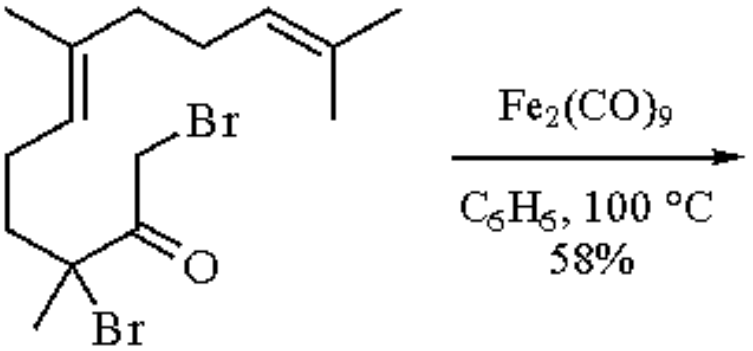

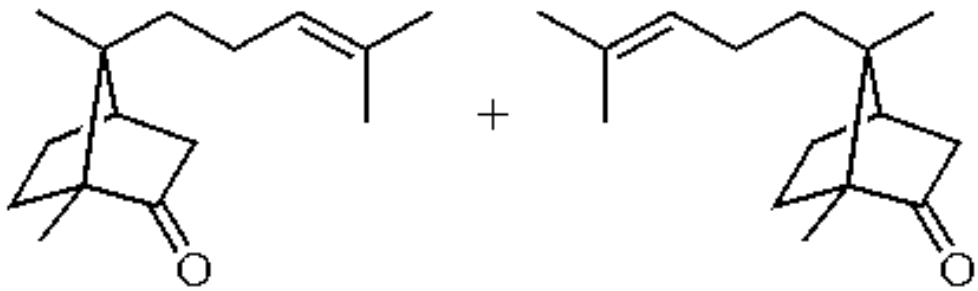

(5)

The [3 + 4 -> 7] Cyclocoupling Reactions.

Reduction of an α,α´-dibromo ketone with $Fe_2(CO)_9$ in the presence of open-chain 1,3-dienes affords the [3 + 4] products, 4-cycloheptenones.[34] High yields are obtained with the dienes having a high population of the *s-cis* conformation. The butadiene-$Fe(CO)_3$ complex acts as a good reducing agent and receptor (eq 6). $Fe(CO)_5$[34] or Zn/Cu couple[31,35] promotes the reductive coupling but less effectively.

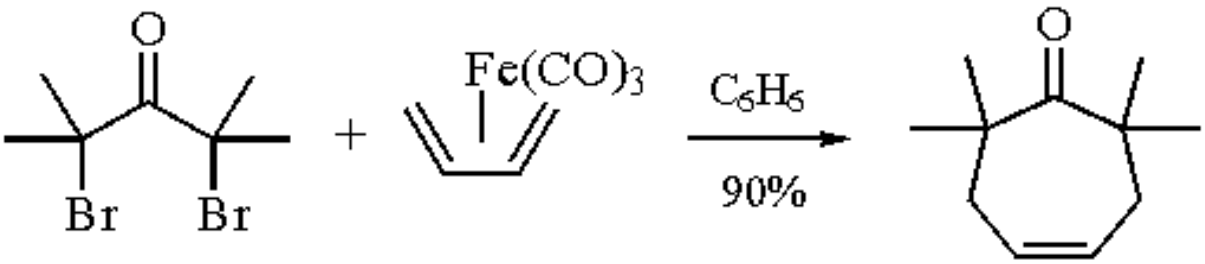

(6)

Substituted and unsubstituted cyclopentadienes,[13,17,19,22,31,34,36,37] 1,3-cyclohexadiene,[38] fulvenes,[17b] *N*-protected pyrroles,[34b,39-41] and furans,[13,17,19,22,34b,36,39,42-45] in which the diene is frozen to the *s-cis* conformation, serve as excellent C_4 components (eq 7). Intramolecular [3 + 4] reaction has also been achieved.[33,46] Pyrrole and its *N*-alkyl derivatives can be employed for the Cu-NaI assisted reaction of acyclic dibromo ketones,[39,41] whereas cyclic dibromides give the substitution products. The reaction using Zn/Cu couple or iron carbonyls results only in the substitution products.[34b,39,40a] The aromatic substitution of furan is often observed in the $Fe_2(CO)_9$-promoted reaction of cyclic dibromides.[34b]

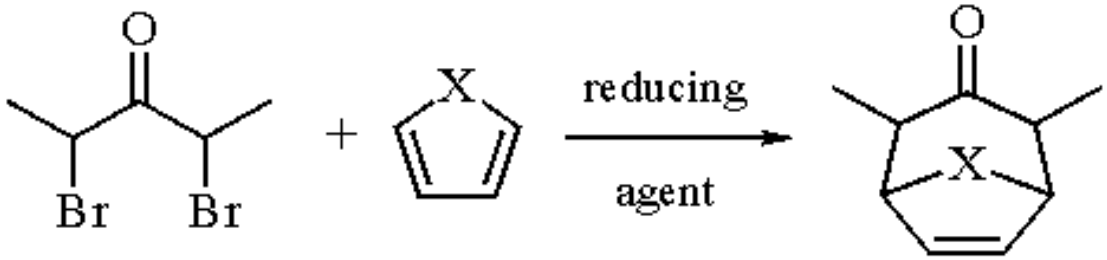

(7)

X	Reducing agent	Yield (%)
CH_2	Zn/Cu	65
CH_2	$Fe_2(CO)_9$	82
NMe	Cu, NaI	89
NCO_2Me	$Fe_2(CO)_9$	60
O	Cu, NaI	48
O	Zn/Cu	85
O	Zn/Ag	80
O	$Fe_2(CO)_9$	90

α,α´-Dibromoacetone itself cannot be used as the C_3 unit. However, ***1,1,3,3-Tetrabromoacetone*** acts as its synthetic equivalent. Iron carbonyls,[34b,37b,47,48] Zn-$(EtO)_3B$,[45b] Zn/Cu couple,[40c] or Zn/Ag couple[20,48c] promote the [3 + 4] cyclocoupling with reactive 1,3-dienes. Debromination of the resulting dibromo ketones with Zn/Cu couple and ammonium chloride in methanol gives the desired ketonic products (eq 8). This modification is generally applicable to the reaction of other methyl ketone polybromides.[20,36,34b,39,44,49]

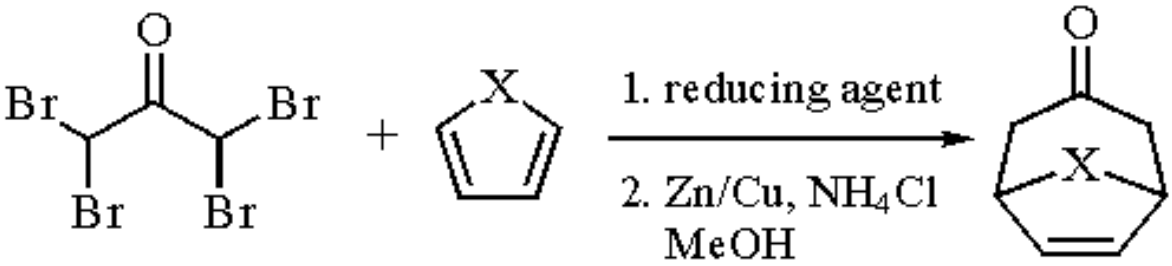

(8)

X	Reducing agent	Yield (%)
CH_2	$Fe(CO)_5$	60
NCO_2Me	$Fe_2(CO)_9$	57
O	Zn/Ag	55
O	$Fe_2(CO)_9$	63

Miscellaneous Reactions.

Reaction of α,α´-dibromo ketones and η^1-allyl(cyclopentadienyl)iron dicarbonyl affords substituted cyclohexanones (eq 9).[27] Reaction of the dibromide and an isocyanide assisted by Cu in benzene or Zn in pyridine-benzene provides a facile way to a 2-(*N*-alkylimino)cyclobutanone (eq 10).[50] Reaction of an α,α´-dibromo ketone and an organocuprate is used to prepare α-monoalkylated and α,α´-dialkylated ketones (eq 11).[42]

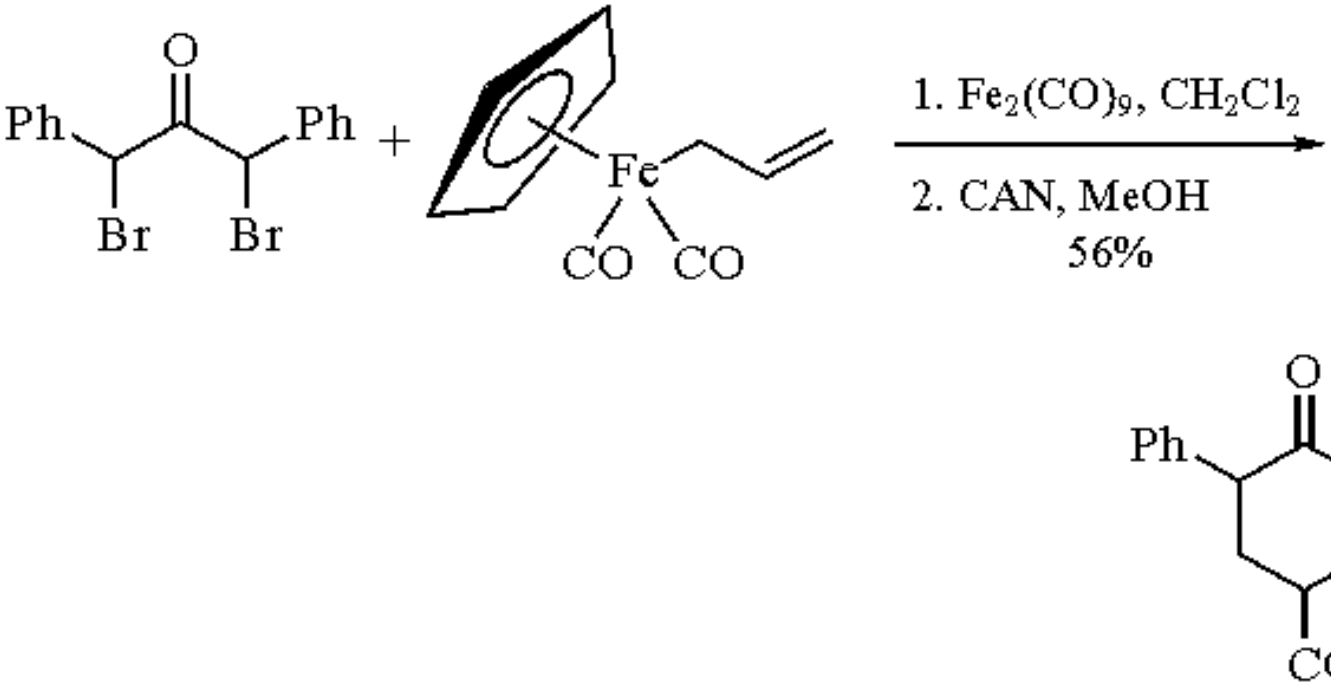

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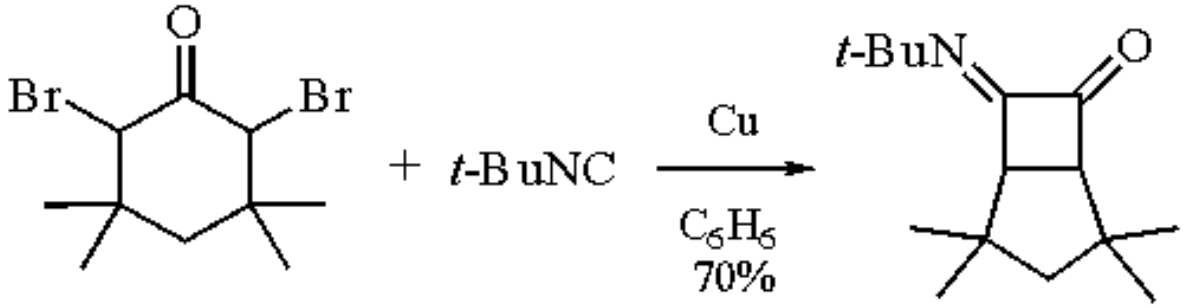

(10)

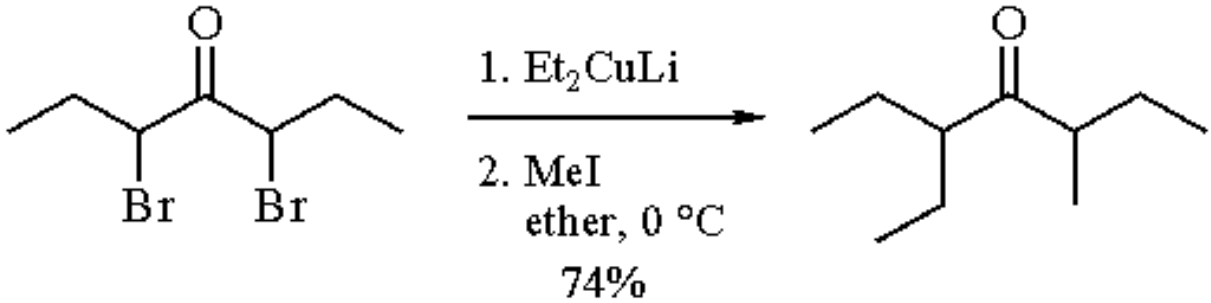

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Dibromoacetonitrile

$CHBr_2CN$

[3252-43-5] · C_2HBr_2N · Dibromoacetonitrile · (MW 198.84)

(reagent used to introduce an α-bromo acid[1] or ester moiety[1,2] directly on a substrate having a carbonyl group; can be also used for heterocyclic syntheses;[8,10] and other miscellaneous reactions[18,19])

Physical Data: bp 68-69 °C/24 mmHg; *d* 2.296 g cm^{-3}; n_D^{20} 1.5390.

Solubility: insol H_2O; sol ether, alcohol, THF.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: dibromoacetonitrile is reputed to be relatively toxic, lachrymatory, and light sensitive. Usual precautions of storage in darkness between 0-5 °C and handling in a fume hood are recommended.

Homologation of Carbonyl Groups into α-Bromo Acids or Esters.

Divergent pathways have been described in the Darzens reaction of aldehydes or ketones with ***Dichloroacetonitrile***[3] and dibromoacetonitrile[1] in a basic alcoholic medium. Whereas α-chlorinated glycidic imino ethers are obtained in the reaction with dichloroacetonitrile, α-bromo acids or α-bromo esters are the products of the Darzens reaction with dibromoacetonitrile. The reaction is carried out in one pot and leads to α-bromo acids or esters in rather good yields (eq 1).[1,2] The reaction combined with a subsequent substitution of the bromine by ammonia[4,5] or by potassium phthalimide[6] on the α-bromo carbonyl compound holds important synthetic potential for the conversion of a carbonyl group into an α-amino acid.

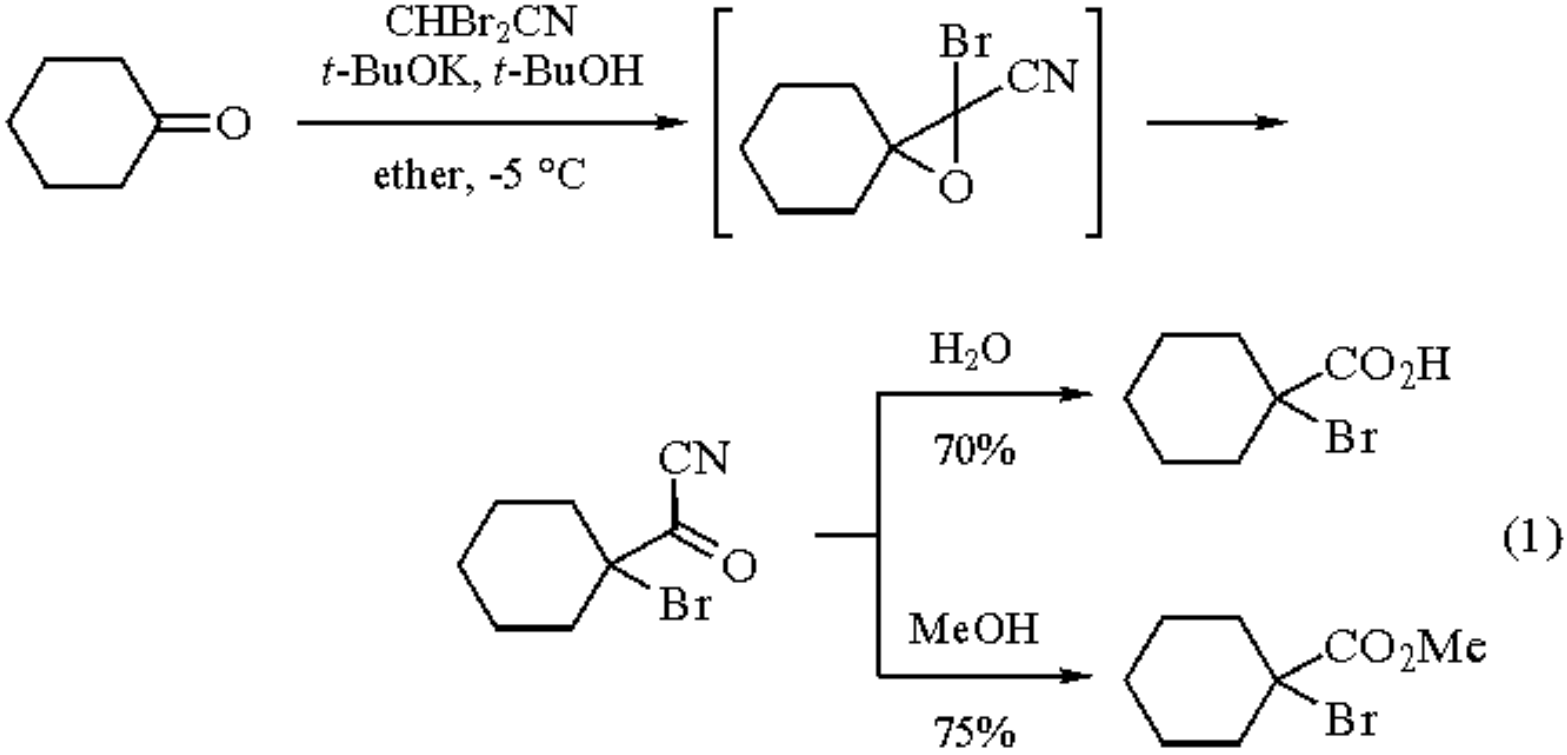

Heterocycle Syntheses.

Very few methods exist for the introduction of halogen at the 2- and 3-positions of the pyridine ring.[7] It was reported that dibromoacetonitrile adds smoothly under mild conditions to methacrolein, in the presence of a catalytic amount of ***Copper(I) Chloride*** and ***Tri-n-butylphosphine*** as co-catalysts, to afford an adduct that readily cyclizes to give 2,3-dibromo-5-methylpyridine. No trace of the primary adduct was detected in the isolated product (eq 2). Under the same reaction conditions, dichloroacetonitrile leads to a mixture of 2,3-dichloro-5-methylpyridine and 2,4-dichloro-4-methyl-5-oxopentanenitrile.[8]

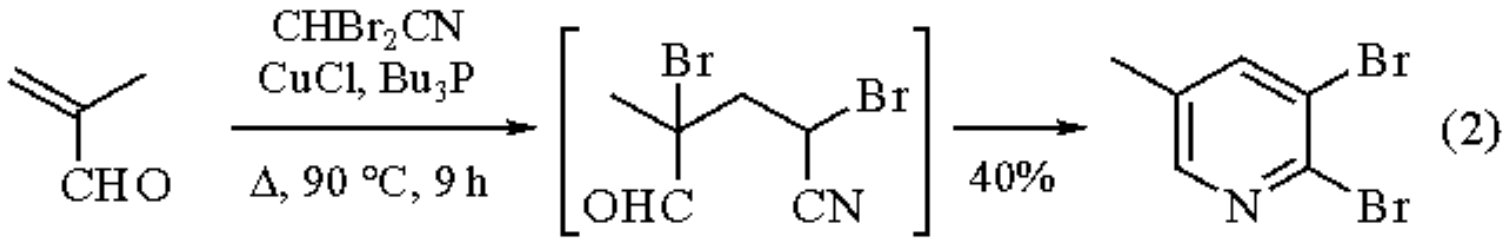

Special emphasis has also been given to the development of synthetic procedures for the preparation of polyhalogenation products from trialkyl-1,3,5-triazines.[9] Dibromoacetonitrile trimerizes in the presence of ***Aluminum Bromide*** in acidic medium and yields tris(dibromomethyl)-1,3,5-triazine (eq 3),[10] which constitutes the precursor of a synthetic equivalent of the unstable triformyl-1,3,5-triazine (eq 4) not previously isolated.[11,12] The alternative, classical method for the synthesis of tris(dibromomethyl)-1,3,5-triazine requires the availability of the trimethyl-1,3,5-triazine as starting material.[9]

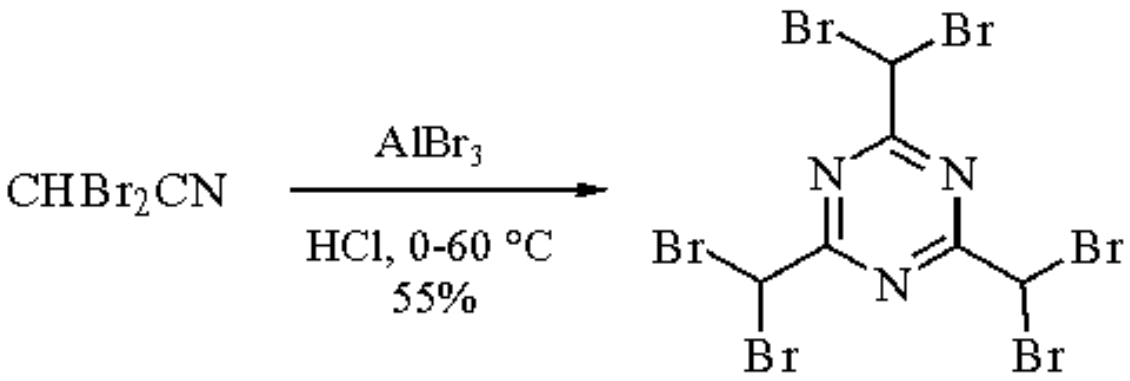

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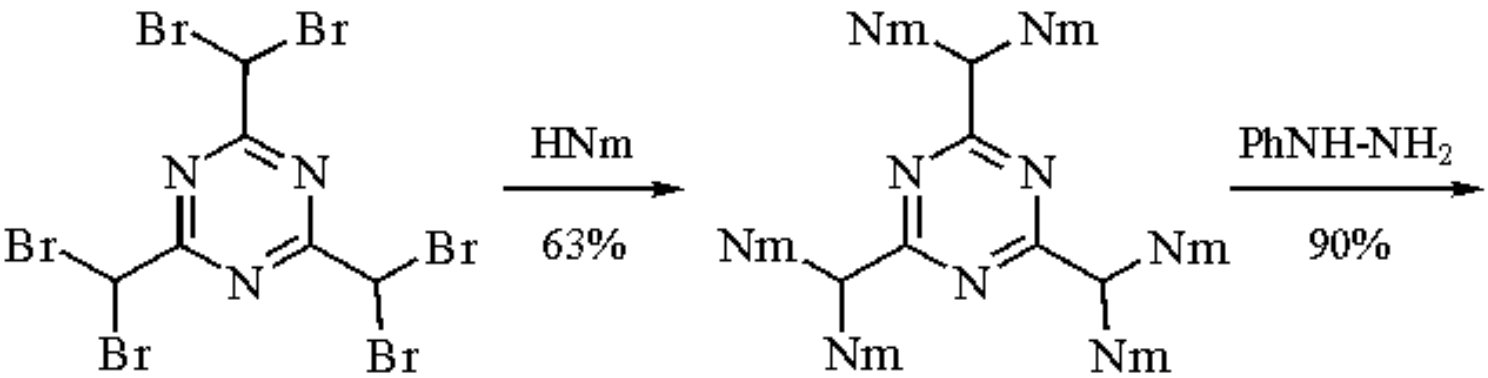

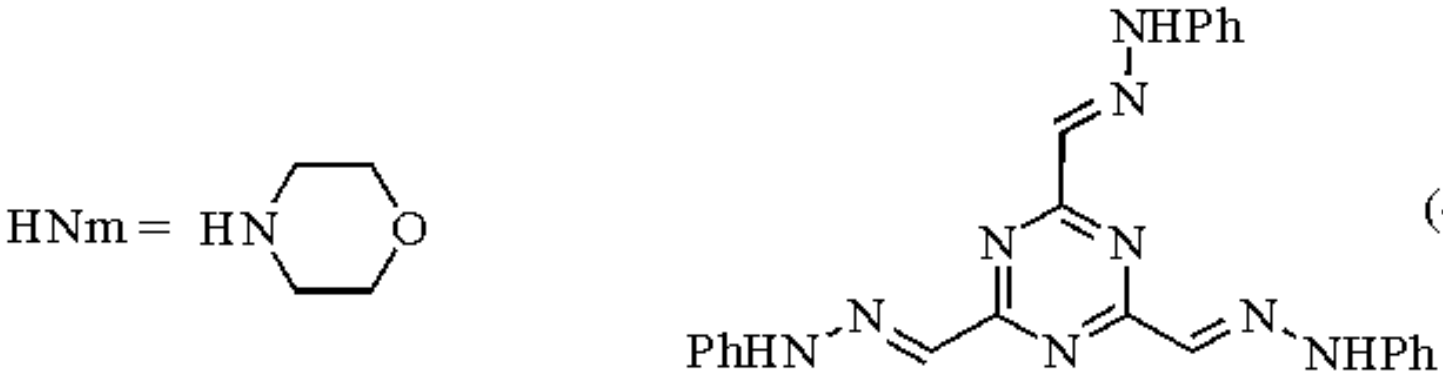

(4)

Miscellaneous Reactions.

Addition of HCN to nitriles having hydrogen atoms on the α-carbon atom occurs in only a few special cases.[13-15] For the addition to be successful, the cyano group has to be activated by one or more strongly electron-withdrawing groups on the α-carbon.[16,17] A selected example reports that dichloro- and dibromoacetonitrile react with HCN to give β,β-dihalo-α-aminoacrylonitriles, a new class of acrylonitrile compounds, in good yields (eq 5).[18]

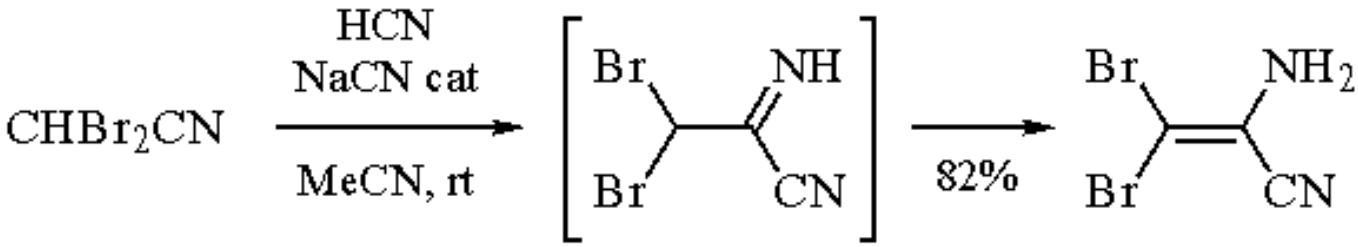

(5)

In certain reactions dibromoacetonitrile reacts as the bromocyanomethyl radical. For instance, $CHBr_2CN$ was used to prepare several 1-cyano-2-(trichloroethyl)cyclopropanes of importance in pyrethroid chemistry.[19] The sequence of reactions involves homolytic displacement of cobaloxime(II) from an allylcobaloxime(II) complex by the bromocyanomethyl radical (bis(dimethylglyoximato)pyridine = $(dmgH)_2py$). The bromocyanomethyl radical attacks regiospecifically at the γ-carbon of the allyl ligand to afford the 2-bromo-4-phenylpent-4-enenitrile (eq 6).[20] Subsequent treatment with the $((dmgH)_2py)$cobaltate(II) ion in aqueous methanol at ambient temperature (eq 7) and then with trichloromethanesulfonyl chloride leads to the corresponding 1-cyano-2-(trichloroethyl)cyclopropane (eq 8).[19]

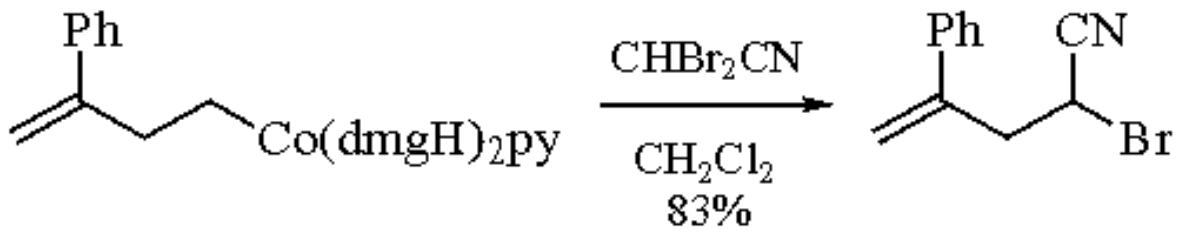

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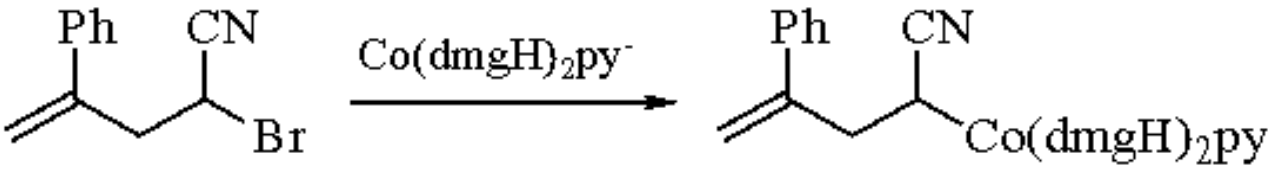

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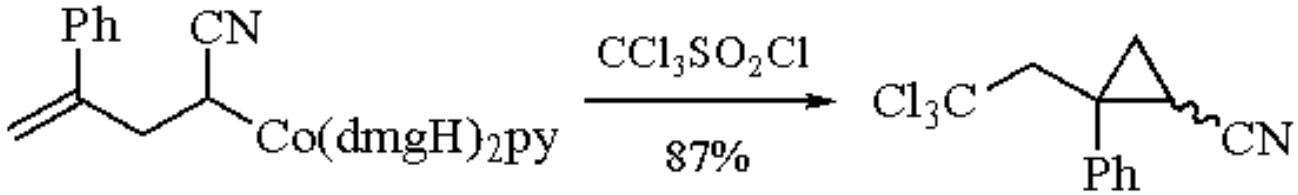

(8)

Related Reagents.

Dichloroacetonitrile; ***Ethyl Dibromoacetate***.

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Dibromoalane

Br_2AlH

[15576-93-9] · $AlBr_2H$ · Dibromoalane · (MW 187.80)

(reagent for reduction of acetals;[1,2] selective carbonyl reductions[3,4])

Physical Data: mp -15 °C; bp 95 °C under high vacuum.[5]

Solubility: sol benzene, chloroform, ether, THF.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: normally prepared in situ as a solution in ether and used without purification or analysis; however, the bis-THF adduct has been characterized by NMR, IR, and elemental analysis.[6]

Preparative Methods: generally prepared in situ from ***Lithium Aluminum Hydride*** (1 equiv) and ***Aluminum Bromide*** (3 equiv) in ether at 0 °C;[2,3] alternatively, the reagent can be prepared in pure form by reaction of ***Aluminum Hydride*** (1 equiv) with $AlBr_3$ (2 equiv) in ether followed by vacuum distillation.[5] The bis-THF adduct [$Br_2AlH.2(THF)$] is a stable crystalline compound (mp 64-67 °C) which can be prepared by either of the methods described above (substituting THF for ether as the solvent).[6]

Purification: by distillation; see above.

Handling, Storage, and Precautions: generally prepared in situ and used immediately; handle under dry nitrogen in a fume hood.

Reduction of Acetals.

Dibromoalane (**1**) is a useful reagent for the reductive cleavage of acetals to the corresponding hydroxy ethers. For example, reduction of a bicyclic acetal with (**1**) in ether afforded the *cis* and *trans* hydroxy ethers (*cis*:*trans* = 97:3) in 72% yield (eq 1).[1] Note that substitution of ***Dichloroalane*** or ***Diisobutylaluminum Hydride*** (DIBAL) for (**1**) in this reaction led to a decrease in the *cis*:*trans* product ratio (possibly due to the higher reaction temperatures required for these less reactive reagents).

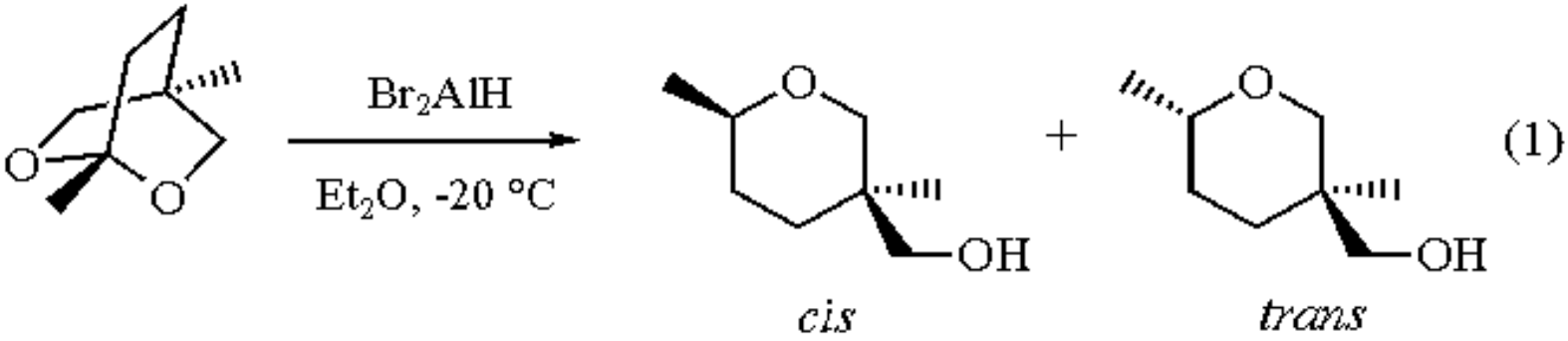

Chiral acetals can be reduced with dibromoalane to afford the corresponding ether with varying degrees of stereoselectivity. For example, reduction of the chiral acetal derived from cyclohexyl methyl ketone and (-)-(2*R*,4*R*)-2,4-pentanediol afforded the hydroxy ether as a 23:1 mixture of diastereomers in 99% yield (eq 2).[2] Dibromoalane generally gives better results than dichloroalane or DIBAL but stereoselectivity is somewhat lower with less hindered substrates. Note that the ethers generated by this reduction can subsequently be converted to the corresponding alcohol via an oxidation-elimination sequence (eq 3).[2] The net result of the overall sequence is thus a stereoselective reduction of the original ketone.

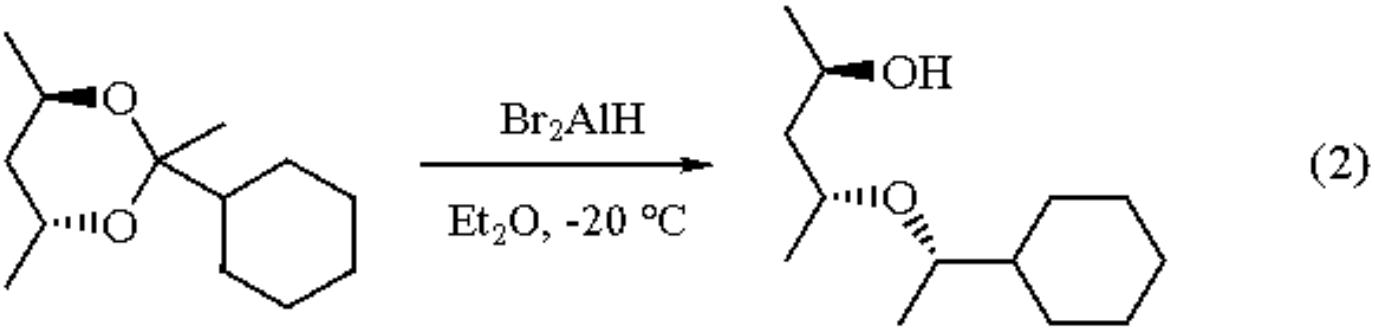

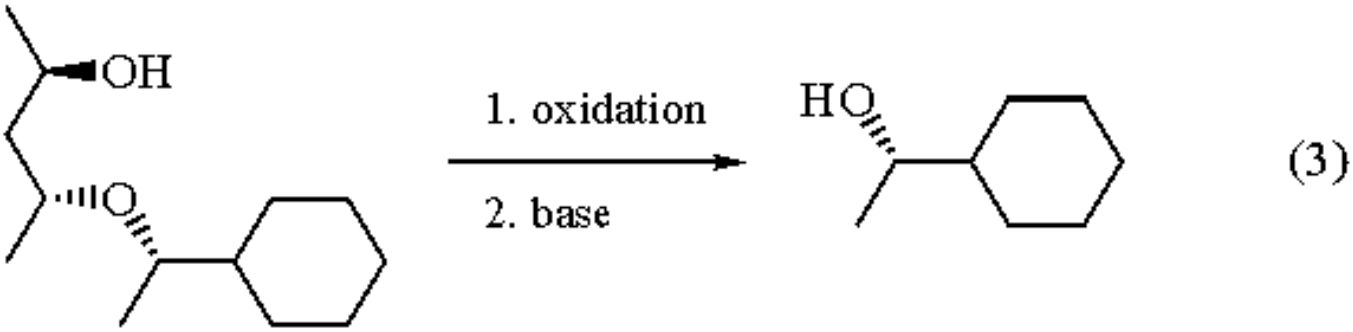

Selective Carbonyl Reduction.

Dibromoalane (**1**), in combination with a hindered alkoxyaluminum compound, is an excellent reagent for the selective reduction of a hindered ketone in the presence of a less-hindered ketone (eq 4).[3] The less hindered of the two ketones forms a complex with the alkoxyaluminum additive (e.g. ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)***), leaving the more hindered ketone accessible for reduction by the hydride reagent. A variety of hydride reagents may be used but (**1**) usually gives the best selectivity.[3]

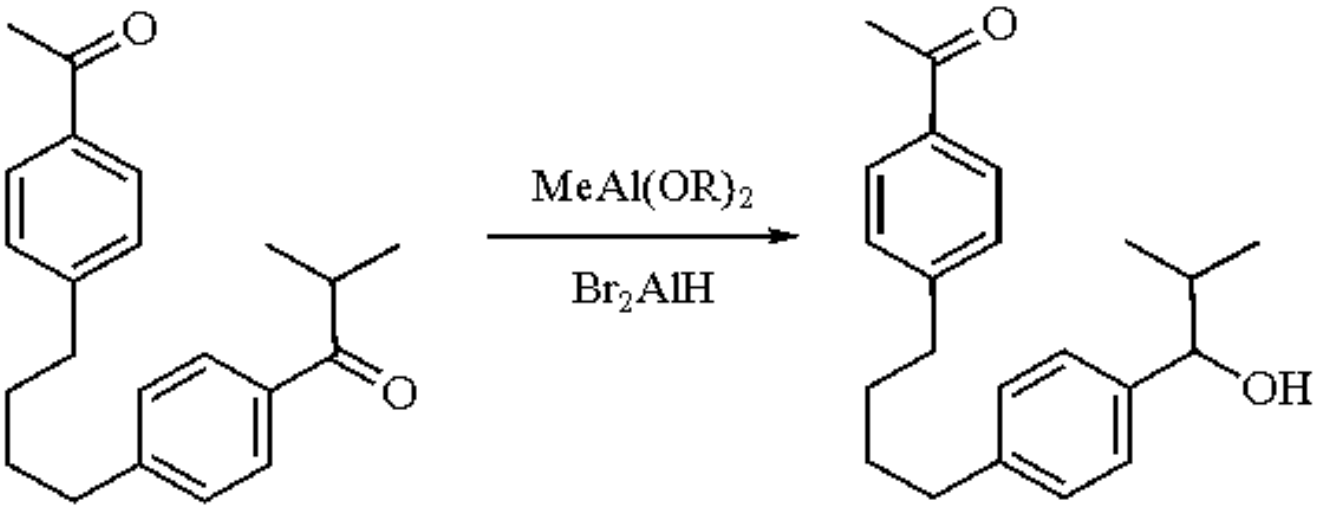

(4)

In combination with ***Copper(I) Iodide***, (**1**) can also effect 1,4-reduction of α,β-unsaturated ketones. However, lithium aluminum hydride/copper iodide is generally superior for this purpose.[4]

Related Reagents.

Dichloroalane; ***Diisobutylaluminum Hydride***; ***Lithium Aluminum Hydride-Copper(I) Iodide***.

---

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Dibromobis(triphenylphosphine)nickel(II)[1]

$NiBr_2(PR_3)_2$

(**1**; R = Ph)

[14126-37-5] · $C_{36}H_{30}Br_2NiP_2$ · Dibromobis(triphenylphosphine)nickel(II) · (MW 743.08) (**2**; R = Bu)

[15242-92-9] · $C_{24}H_{54}Br_2NiP_2$ · Dibromobis(tributylphosphine)nickel(II) · (MW 623.14) (**3**; R = Et)

[19224-77-2] · $C_{12}H_{30}Br_2NiP_2$ · Dibromobis(triethylphosphine)nickel(II) · (MW 454.81)

(catalysts for the cross-coupling reactions of various RX with Grignard reagents,[1] C-X bond reduction,[9,10] homocoupling of C_{sp^2} halides,[11] displacement of aryl halides,[2] and oligomerization of dienes[12,13])

Alternate Name: bis(triphenylphosphine)nickel(II) bromide.

Physical Data: (**1**) mp 222-225 °C; dark green. (**2**) mp 51-53 °C; red. (**3**) mp 106-107 °C; dark red.

Solubility: sol acetone, benzene, THF.

Form Supplied in: most nickel bromide phosphine complexes are commercially available.

Preparative Methods: conveniently synthesized by mixing a stoichiometric amount of ***Nickel(II) Bromide*** with the appropriate phosphine ligand.[15]

Handling, Storage, and Precautions: these complexes are somewhat air sensitive. Like other Ni^{II} compounds, they are cancer suspect agents and corrosive. These reagents should be handled in a fume hood.

General Considerations.

Most reactions promoted by ***Dichlorobis(triphenylphosphine)nickel(II)*** or related complexes can also be mediated by $NiBr_2(PPh_3)_2$ or the like. This section covers certain specific applications using the nickel bromide reagents.

Displacement Reactions.

Aryl triflates readily participate in an in situ generated Ni^0-catalyzed nucleophilic displacement with cyanide anion, thereby providing a convenient method for the preparation of aryl cyanides (eq 1).[2]

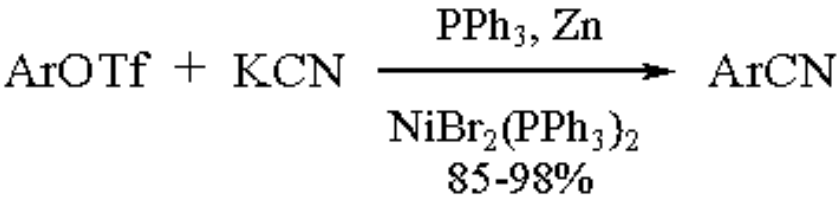

(1)

Reaction of allylic alcohols with morpholine in the presence of a catalytic amount of $NiBr_2(PPh_3)_2$ and ***Potassium t-Butoxide*** gives the corresponding amines in good yields (eq 2).[3]

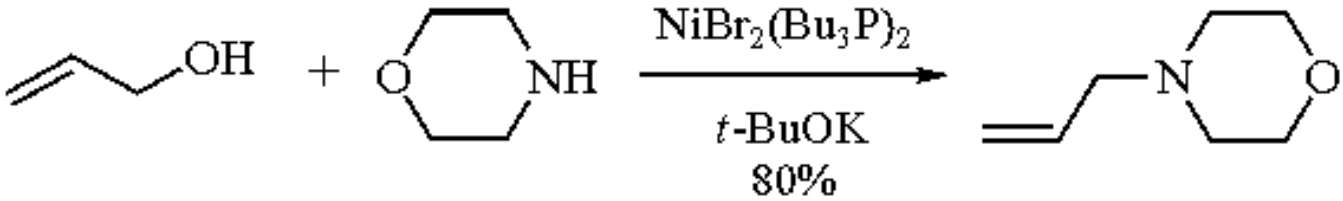

(2)

The regioselective rearrangement of propene oxide to propionaldehyde is reportedly promoted by $NiBr_2(PPh_3)_2$.[4] Surprisingly, the reaction of methylmagnesium iodide with *t*-BuO^- in the presence of $NiBr_2(PPh_3)_2$ yields isobutylene oxide (eq 3).[5]

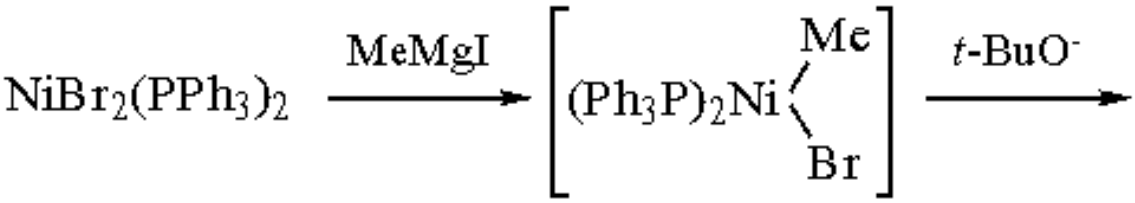

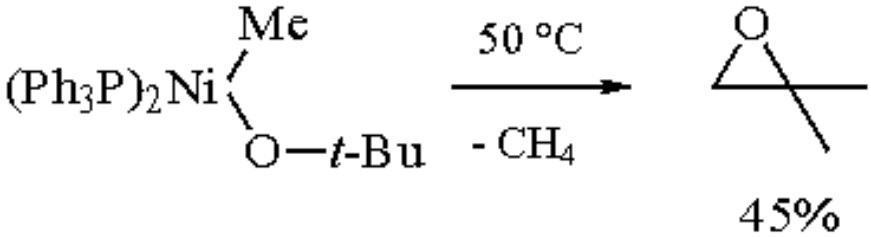

(3)

Cross-Coupling Reactions.

Most of the cross-coupling reactions that use nickel halide phosphine complexes as the catalyst are discussed in the article on ***Dichlorobis(triphenylphosphine)nickel(II)***.[1] The addition of the phosphine ligand to a solution of nickel bromide also serves as a useful catalytic system for this purpose.

In an electrochemical process, aryl halides react with α-haloacetic acid esters to give the corresponding arylacetic acid derivatives.[6] The reaction of (*E*,*E*)-1,4-dilithio-1,4-diphenyl-1,3-butadiene at -78 °C with $(Et_3P)_2NiBr_2$ produces the nickel complex of 1,2,5,6-tetraphenylcyclooctatetraene in good yield. The cot ligand can easily be liberated upon air oxidation.[7]

When chiral ligands are used, enantioselective cross-coupling reactions can be achieved. To illustrate, $NiBr_2$[(*S*)-(*R*)-PPFOME] has been used for the synthesis of chiral ternaphthyl (eq 4).[8]

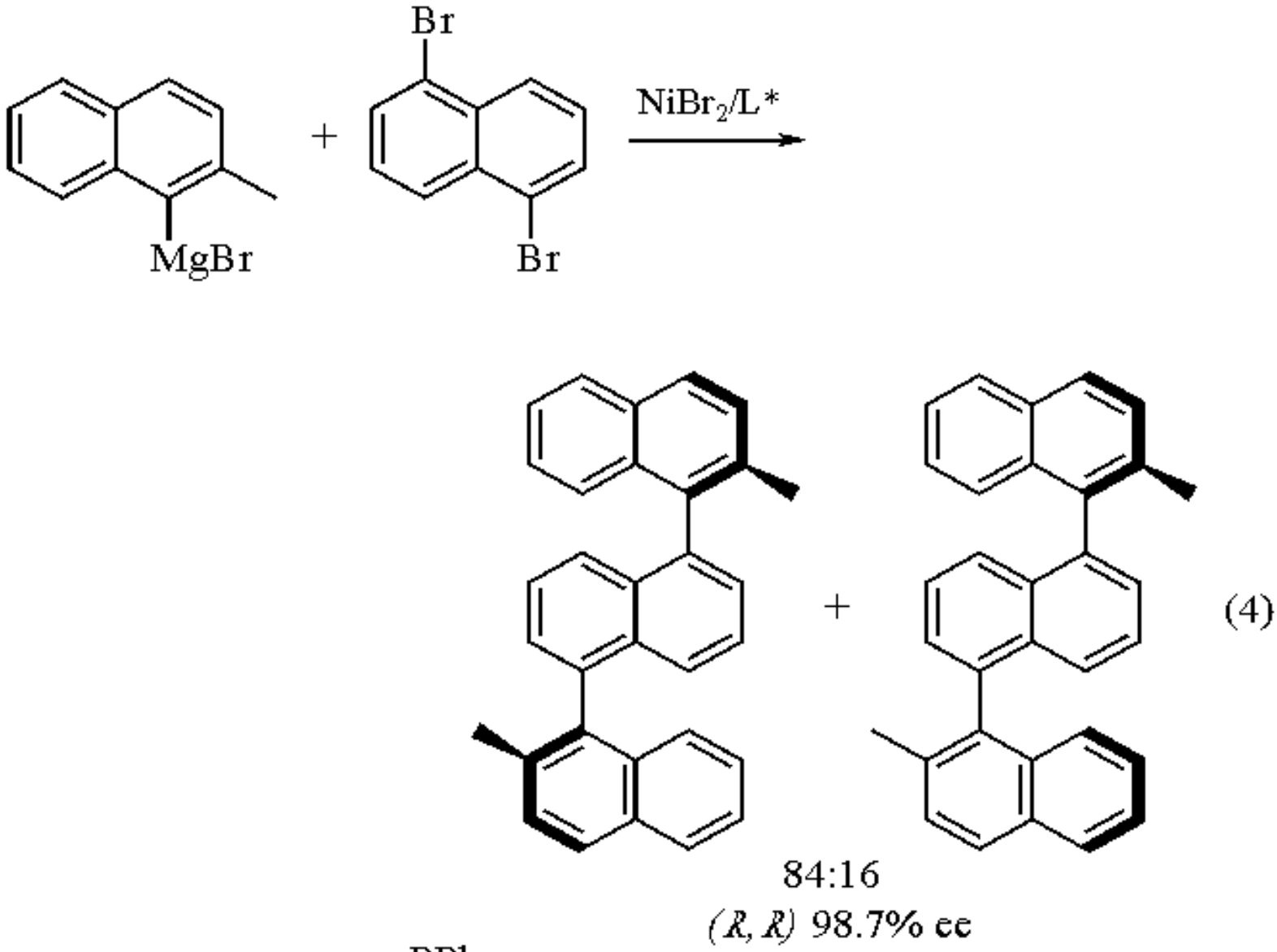

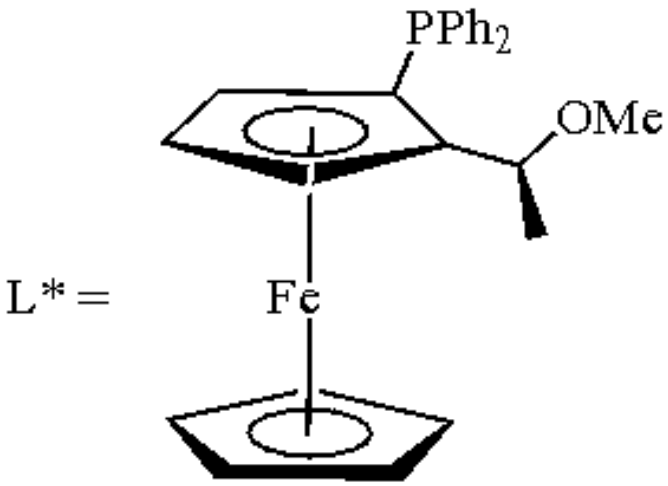

(*S*)-(*R*)-PPFOME

Reduction.

The carbon-sulfur bonds of thiols, thioethers, dithioacetals, and sulfoxides as well as sulfones are reduced upon treatment with $NiBr_2(PPh_3)_2$ and ***Lithium Aluminum Hydride*** in moderate to good yields.[1f,9] As sulfoxides and sulfones can readily be reduced to thioethers by low valent transition metal complexes or by complex hydrides,[10] it has been suggested that nickel reagents first reduce sulfoxides or sulfones to the corresponding sulfides which are further reduced under the reaction conditions. Therefore an excess amount of the reducing agent is usually required to effectively reduce these substrates.

The reaction of cumulenes with zero valent nickel catalyst generated in situ from $NiBr_2(PPh_3)_2$, zinc, and Ph_3P proceeds smoothly at rt to give the dimeric radialenes in moderate yield (eqs 5 and 6).[11]

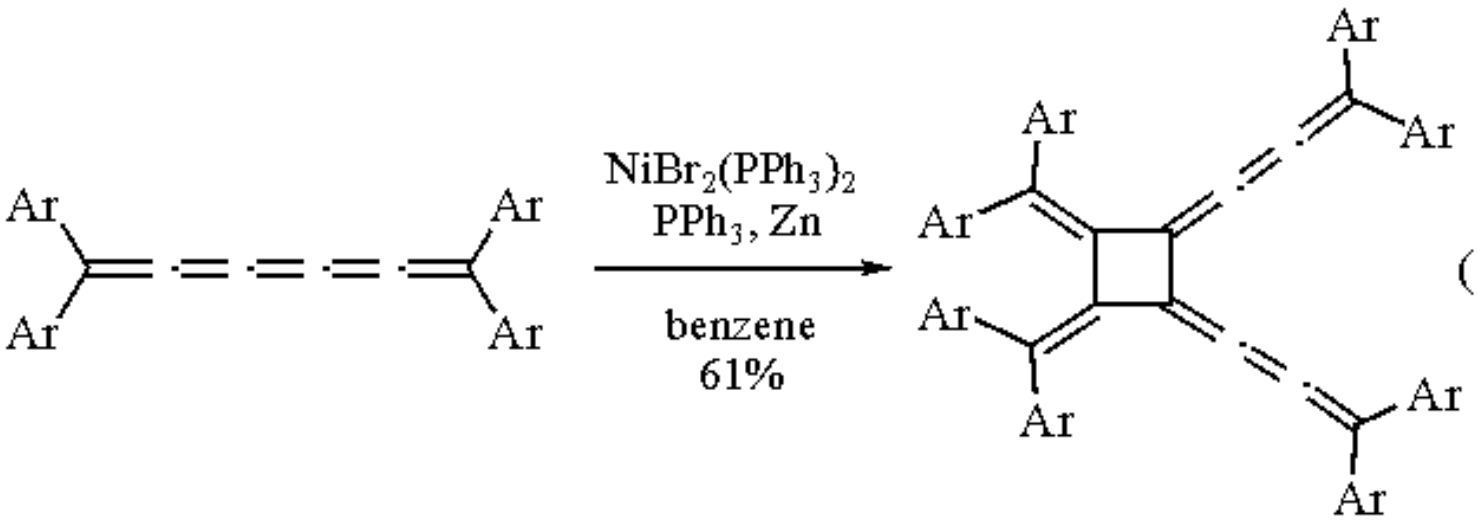

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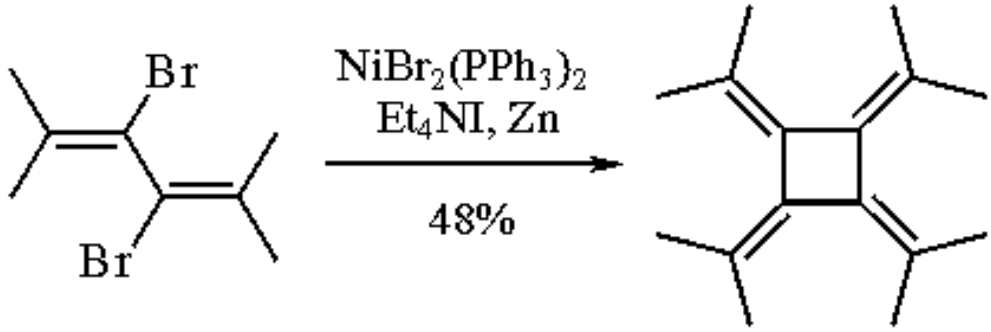

(6)

1,1-Dibromo-2,2-diphenylethylene also dimerizes under similar conditions in benzene to give the butatriene (eq 7).[11]

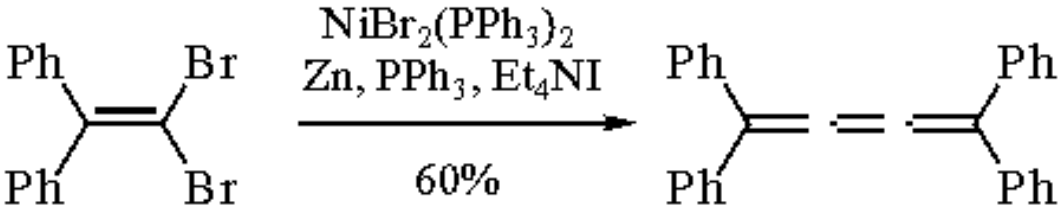

(7)

Although low valent nickel complexes are very useful for the dimerization and oligomerization of alkenes or

butadienes, the use of $NiBr_2(PPh_3)_2$ or related complexes for this purpose is relatively rare (eq 8), because a number of isomeric products are occasionally obtained.[12] Alternatively, $NiBr_2(PPh_3)_2$-***n-Butyllithium*** has been shown to catalyze the cyclodimerization of butadiene to give the five-membered ring product in excellent yield (eq 9).[13]

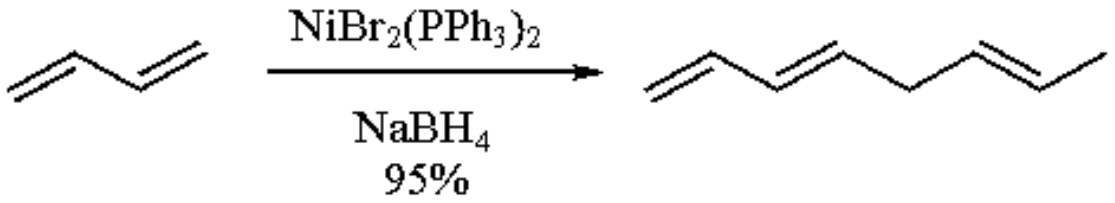

(8)

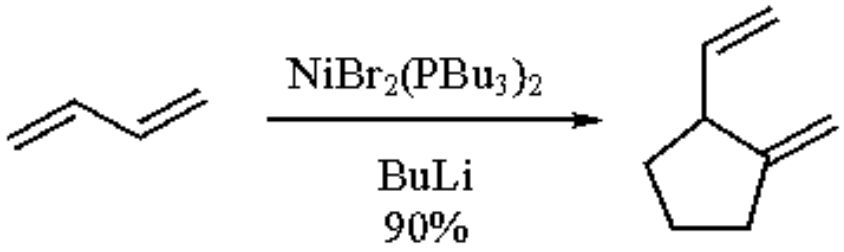

(9)

Allylic acetals react with allylzinc reagents in the presence of a catalytic amount of $NiBr_2(PPh_3)_2$ followed by treatment with electrophiles, leading to double functionalization of α,β-unsaturated acetals (eq 10).[14]

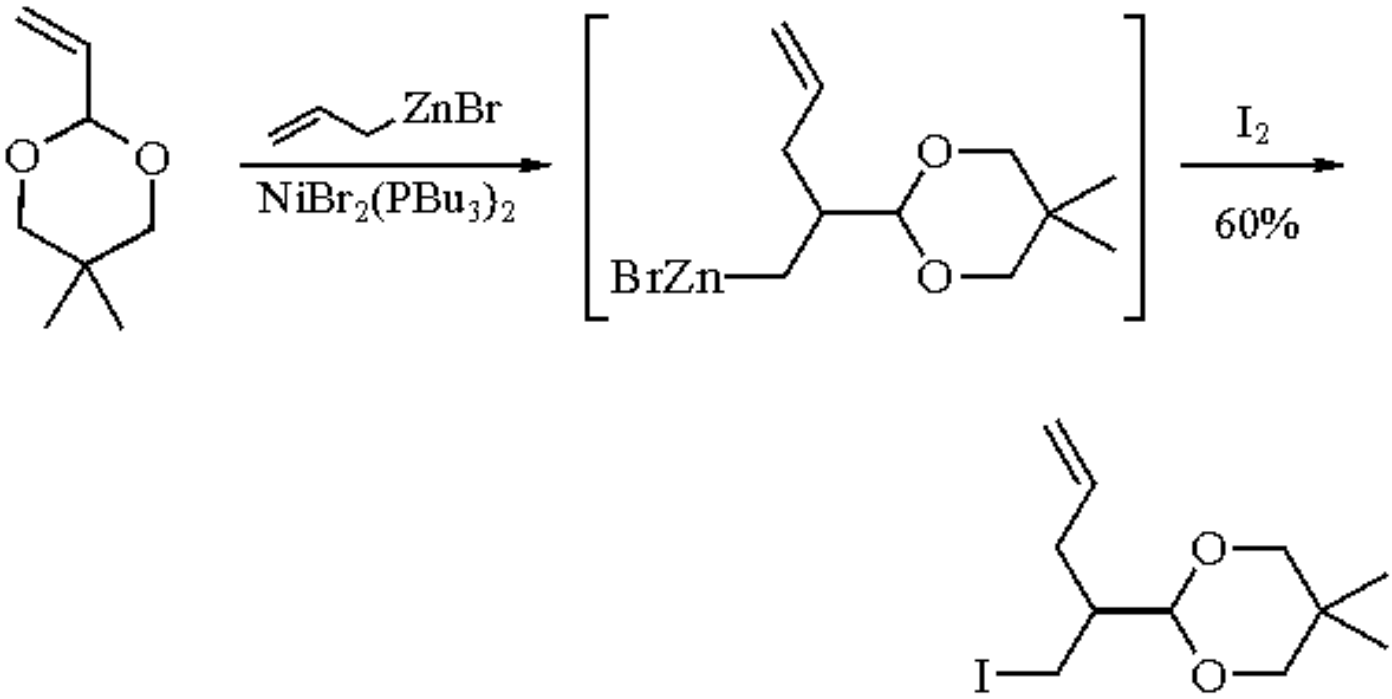

(10)

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Dibromobis(triphenylphosphine)palladium(II)[1]

$PdBr_2(PPh_3)_2$

(*cis*)

[25044-96-9] · $C_{36}H_{30}Br_2P_2Pd$ · Dibromobis(triphenylphosphine)palladium(II) · (MW 790.81) (*trans*)

[22180-53-6]

(catalyst for carbonylation of aromatic and vinylic bromides;[1-5] arylation of allylic alcohols;[6] silylation[7] and stannation[8] of aromatic bromides)

Physical Data: mp 230-250 °C (dec).

Solubility: sol acetonitrile, DMF, halogenated solvents.

Preparative Method: from commercially available $PdCl_2(PPh_3)_2$.[1b,1c]

Handling, Storage, and Precautions: hygroscopic, air sensitive in solution.

Carbonylation.

$PdBr_2(PPh_3)_2$ (**1**) is a catalyst that has been used for the carbonylation of aromatic bromides to give carboxylic acids.[2] Use of this reagent in a synthesis of anthranilic acids is shown in eq 1.

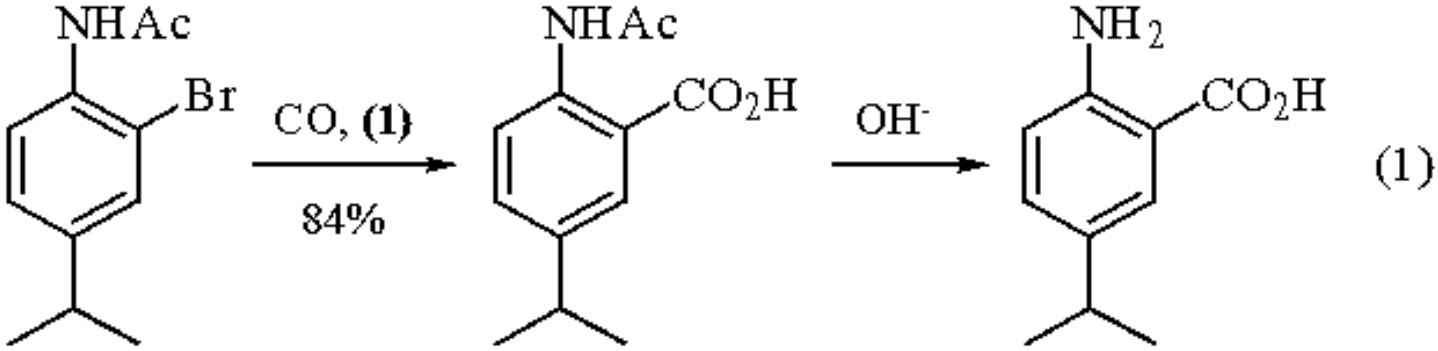

Aromatic and vinyl bromides have been carbonylated in the presence of amines to give amides (eq 2).[3]

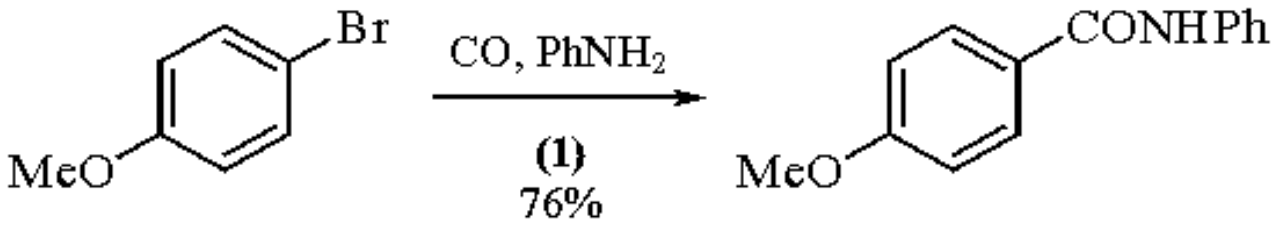

(2)

Carboxylic acid esters are formed from carbonylation of aromatic and vinylic bromides and iodides in the presence of an amine and an alcohol (eq 3).[4]

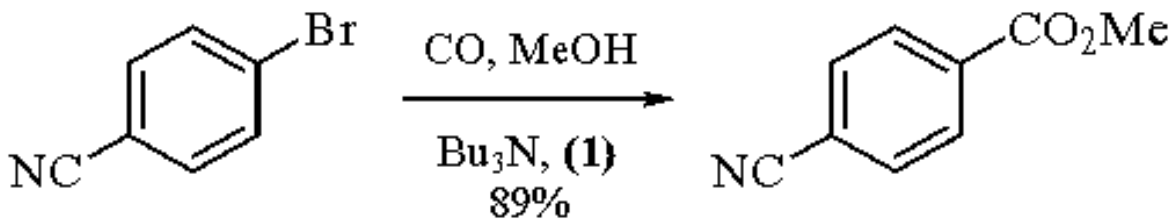

(3)

Aryl halides and vinyl halides react with carbon monoxide and hydrogen in the presence of amines and (**1**) to yield aldehydes (eq 4).[5]

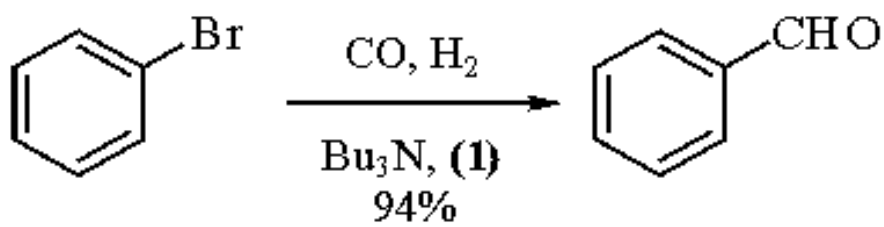

(4)

Arylation.

The title reagent has been used to couple aromatic halides with allylic alcohols (eq 5).[6] This process is formally equivalent to a conjugate addition between the halide and an unsaturated ketone.

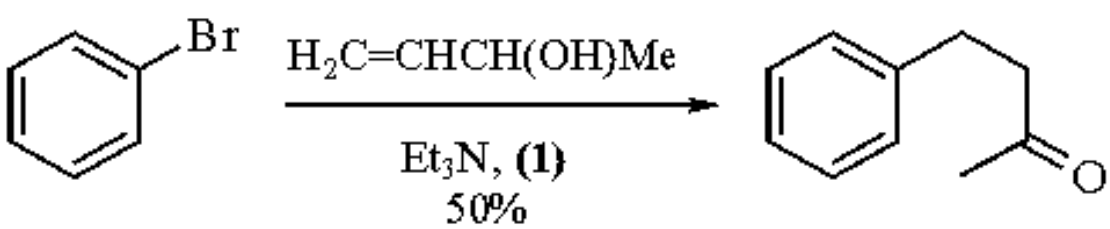

(5)

Silylation.

$PdBr_2(PPh_3)_2$ will catalyze the silylation of aromatic and alkyl bromides with disilanes (eq 6).[7]

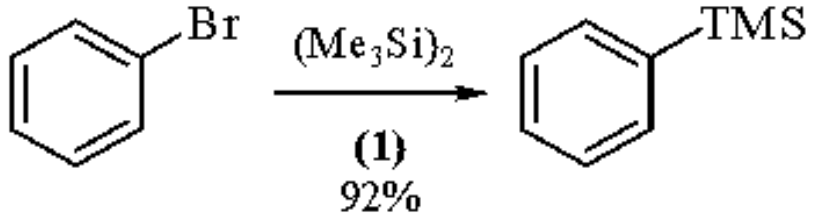

(6)

Stannation.

The title reagent has been used to prepare organostannanes from functionalized aromatic bromides and distannanes (eq 7).[8] The reaction is especially useful where normal Grignard or organolithium reagents cannot be used.

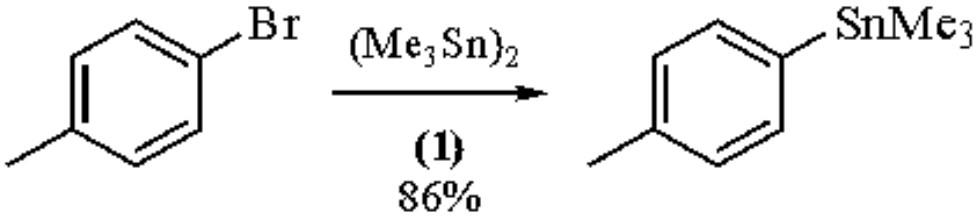

(7)

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Dibromoborane-Dimethyl Sulfide[1]

$BHBr_2.SMe_2$

[55671-55-1] · $C_2H_7BBr_2S$ · Dibromoborane-Dimethyl Sulfide · (MW 233.77)

(hydroborating agent providing access to alkyl-[2] and alkenyldibromoboranes[3] and boronic acids[2,4])

Alternate Name: DBBS.

Physical Data: mp 30-35 °C; bp 75 °C/0.1 mmHg.

Solubility: sol dichloromethane, carbon disulfide, carbon tetrachloride.

Form Supplied in: white solid or liquid, 7.8 M in $BHBr_2$.

Preparative Methods: by redistribution of $BH_3.SMe_2$ and $BBr_3.SMe_2$ or $BH_3.SMe_2$ and BBr_3;[5] by the reaction of bromine with $BH_3.SMe_2$ in CS_2.[6]

Analysis of Reagent Purity: ^1H NMR (CCl_4) δ 2.48, (CS_2) 2.69 ppm; ^{11}B NMR (CCl_4) δ -7.3 (d, J_{B-H} = 160 Hz),[5] (CS_2) -8.2 ppm.[6] Hydrolysis of an aliquot and measuring the hydrogen evolved according to the standard procedure.[7]

Handling, Storage, and Precautions: corrosive liquid; air and moisture sensitive; flammable; stench. Handle and store under nitrogen or argon. Stable indefinitely when stored under nitrogen at 25 °C. Reacts violently with water. This reagent should be handled in a fume hood.

Hydroboration of Alkenes.

Dibromoborane-dimethyl sulfide hydroborates alkenes directly without need for a decomplexing agent (see ***Dichloroborane Diethyl Etherate***) (eq 1).[2]

$$RCH{=}CH_2 + BHBr_2 \cdot SMe_2 \xrightarrow[71\text{-}93\%]{CH_2Cl_2} RCH_2CH_2BBr_2 \cdot SMe_2 \quad (1)$$

Regioselectivity of DBBS in the hydroboration of alkenes and derivatives is high, approaching ***9-Borabicyclo[3.3.1]nonane***, e.g. 1-hexene, styrene, 2-methyl-1-pentene, 2-methyl-2-butene and 4-(dimethylphenylsilyl)-2-pentene, react by placing the boron atom at the less hindered position with &egt;99% selectivity.[2,8a] Lower regioselectivity of the hydroboration-oxidation is observed if an excess of alkene is used, due to hydrobromination, which is a side reaction in the hydrolysis-oxidation step.[8b] The reactivity of DBBS toward structurally different alkenes and alkynes is different from that of other hydroborating agents (Table 1).[3,9]

Table 1 Relative Reactivity of Representative Alkynes and Alkenes with $BHBr_2{\cdot}SMe_2$, 9-BBN, and Sia_2BH

Compound	$BHBr_2{\cdot}SMe_2$	9-BBN	Sia_2BH
1-Octene	100	100	100
(*Z*)-3-Hexene	20	0.55	1.25
1-Hexyne	290	15	345
3-Hexyne	5900	0.74	208

Reactions of Alkyldibromoboranes.

Alkyldibromoboranes are versatile synthetic intermediates. They are resistant to thermal isomerization, a feature of considerable importance for the regio- and stereoselective synthesis of organoborane intermediates from highly labile alkenic structures.[10]

Standard oxidation of alkyldibromoboranes with alkaline ***Hydrogen Peroxide*** affords alcohols.[2,8b] Conversion of terminal alkenes to carboxylic acids using alkyldibromoboranes works well, although hydrolysis prior to oxidation is needed.[11] Chiral alkyldibromoboranes have been used as catalysts for the asymmetric Diels-Alder reaction.[12,13]

The hydridation-stepwise hydroboration procedure provides a convenient general approach to monoalkylbromoboranes, mixed dialkylbromoboranes, dialkylboranes, totally mixed trialkylboranes, ketones, alcohols (eq 2),[14] and stereodefined alkenes, dienes, and haloalkenes (see below). Mixed alkylalkenylalkynylboranes are also available by this methodology.[15]

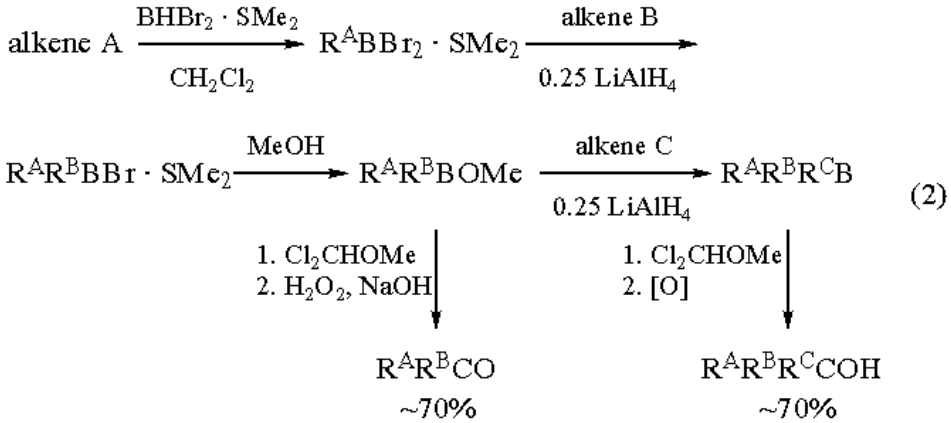

(2)

Hydrolysis and alcoholysis of alkyldibromoboranes provide simple access to alkylboronic acids and esters respectively,[4] which are important synthetic intermediates and reagents for protection of hydroxy groups of diols[16a-f] and derivatizing agents for GC and GC-MS analysis.[16g,h]

Selective Hydroboration of Dienes and Enynes.

The opposite reactivity trends of DBBS and other hydroborating agents makes possible the selective hydroboration of dienes (eq 3)[9] and enynes.[9] In conjugated systems, however, bromoboration of the triple bond is observed.[17]

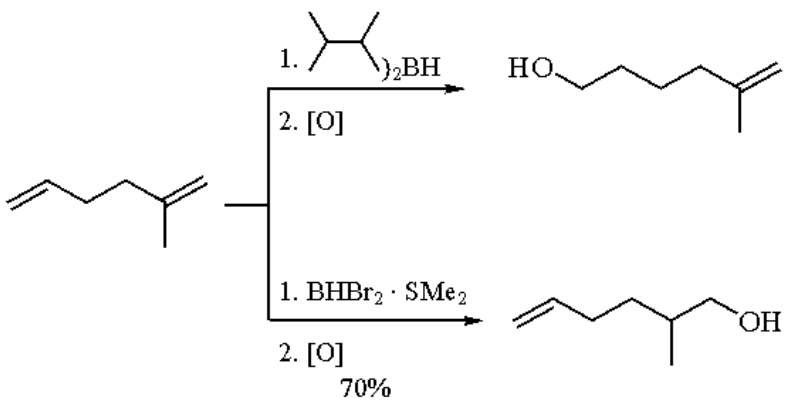

(3)

Reactions of Alkenyldibromoboranes and Alkenylalkylbromoboranes.

Synthesis of Alkenylboronic Acids, Alkenes, Aldehydes, and Ketones.

Alkenyldibromoboranes undergo many of the characteristic reactions of alkenylboranes. The presence of dimethyl sulfide does not interfere in their transformations. Protonolysis with acetic acid in refluxing dichloromethane gives the corresponding

alkene. Oxidation leads to aldehydes or ketones (eq 4).[3] Hydrolysis and alcoholysis yields alkenylboronic acids and esters, respectively.

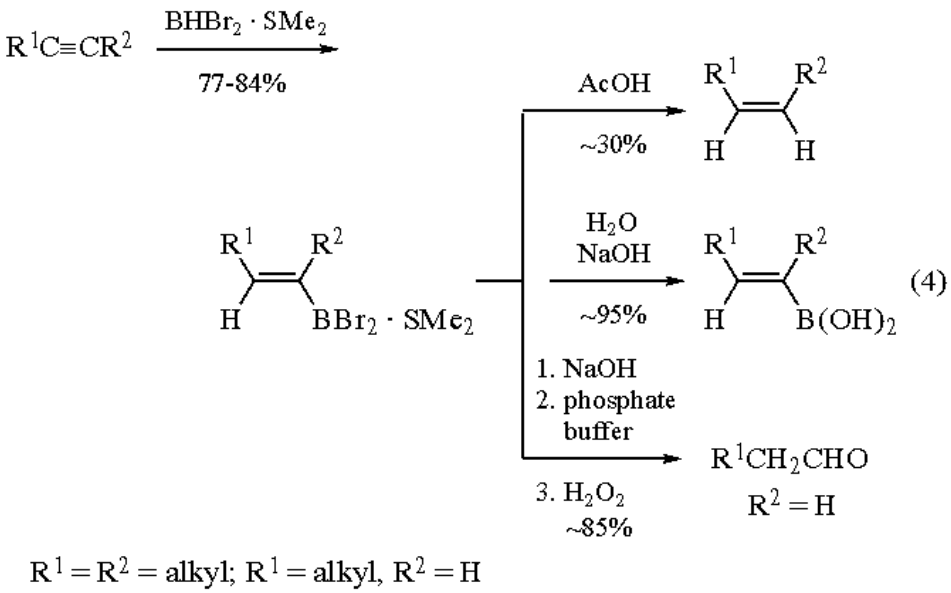

The (*E*)-alkenylboronic acids are directly available from 1-alkynes by hydroboration-hydrolysis (eq 4).[4] The (*Z*)-isomers are prepared from 1-bromo-1-alkynes by hydroboration-hydride reduction (eq 5).[18]

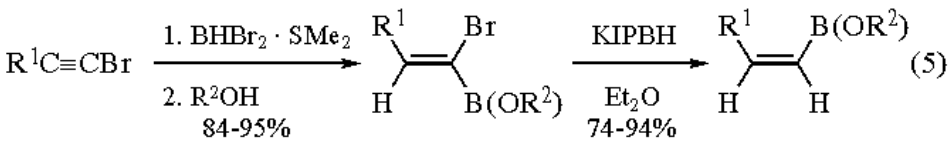

Synthesis of (*E*)- and (*Z*)-Alkenes, Trisubstituted Alkenes, 1,2-Disubstituted Alkenyl Bromides, Ketones, and Enolborates.

The synthesis of (*Z*)-alkenes, according to eq 4, is a simple, convenient method, provided the alkynic precursor is readily available. A general Zweifel (*E*)- and (*Z*)-alkene synthesis starts with 1-alkynes and 1-bromo-1-alkynes, respectively. The precursors are hydroborated with monoalkylbromoborane to give the corresponding alkylalkenylbromoboranes. Migration of the alkyl group completes the formation of the carbon skeleton (eq 6).[19-21] The procedure allows full utilization of the alkyl group.

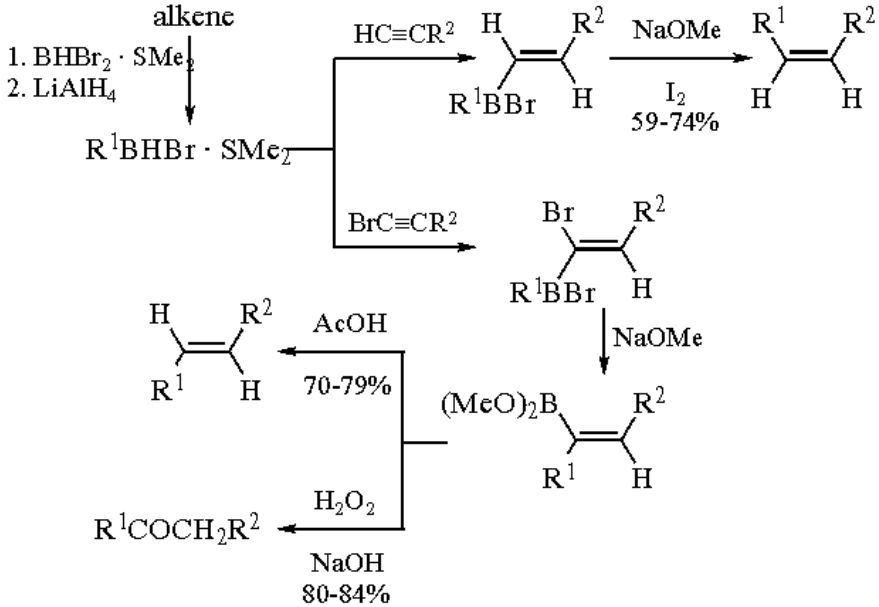

(6)

(*Z*)-9-Tricosene (muscalure), the sex pheromone of the housefly (*Musca domestica*), has been prepared by this method in 69% yield and >99% purity.[20,22] Extension of the methodology to trisubstituted alkenes is based on the iodine-induced migration of the second alkyl group R^3 (eq 7).[23]

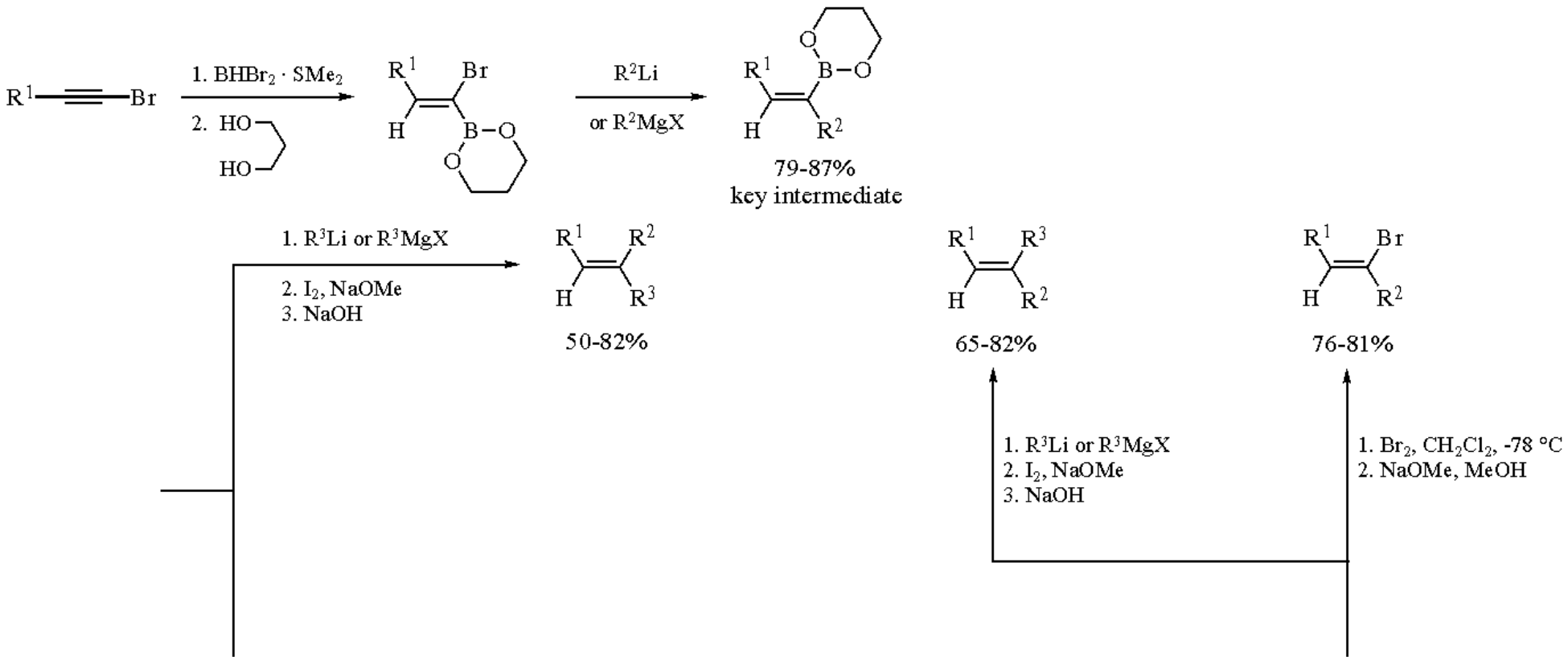

(7)

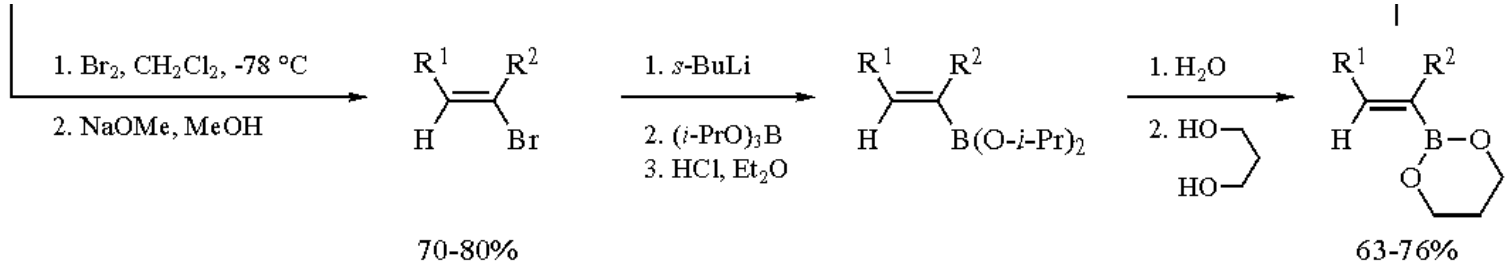

The key alkenylboronate intermediate used for the introduction of the R^3 group (eq 7) is of the same structure as the one shown in eq 6. The procedure works well both for alkyl and aryl R^3 groups. However, a methyl group shows poor migratory aptitude in these reactions.[20,23] If the two *trans*-alkyl groups in the product alkene are the same or differ significantly in steric bulk, an internal alkyne may serve as a starting material (eq 8).[24]

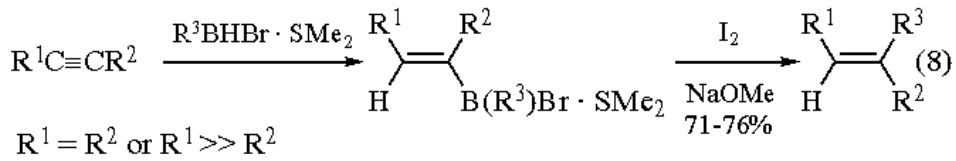

(8)

Other approaches to trisubstituted alkenes via organoboranes involve alkynyltrialkyl borates,[25] alkenyltrialkyl borates[26] or the cross-coupling reaction of alkenylboronic acids with alkyl halides.[27]

Both (*E*)- and (*Z*)-1,2-disubstituted alkenyl bromides can also be prepared by the methodology shown in eq 7.[28] The ***Boron Trifluoride Etherate***-mediated 1,4-addition of 1,2-disubstituted alkenylboronates affords γ,δ-unsaturated ketones (eq 9).[29] The boronates can also be converted into chiral enolborates for the enantioselective addition to aldehydes.[30]

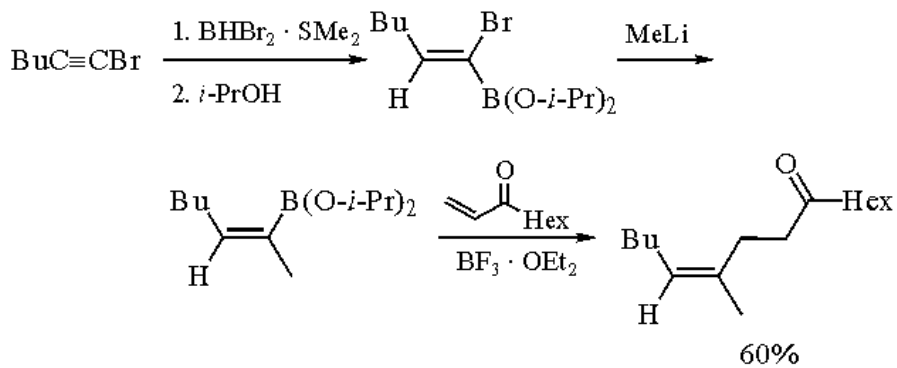

(9)

Synthesis of (*E*)- and (*Z*)-1-Halo-1-alkenes and α-Bromoacetals.

Stereodefined alkenyl halides are important starting materials for the synthesis of alkenyl Grignard[31] and lithium[32] derivatives, pheromones,[33] and (*E*,*E*)-, (*E*,*Z*)-, (*Z*,*E*)- and (*Z*,*Z*)-dienes by the cross-coupling reaction.[34] An efficient, general (*E*)- and (*Z*)-1-halo-1-alkene synthesis starts with 1-alkynes and 1-halo-1-alkynes respectively, which are converted into the corresponding (*E*)- and (*Z*)-alkenylboronic acids or esters via alkenyldibromoboranes, according to eqs 4 and 5. The alkenylboronic acids and esters react with halogens directly[35-38] or via alkenylmercurials[39] to give the haloalkenes in high stereochemical purity in 70-100% yield (eq 10). In some of these halogenation reactions, alkenyldibromoboranes can be used directly.[35,36] Alternatively, (*Z*)-1-halo-1-alkenes are simply obtained by hydroboration-protonolysis of 1-halo-1-alkynes with 9-BBN or ***Disiamylborane***.[40]

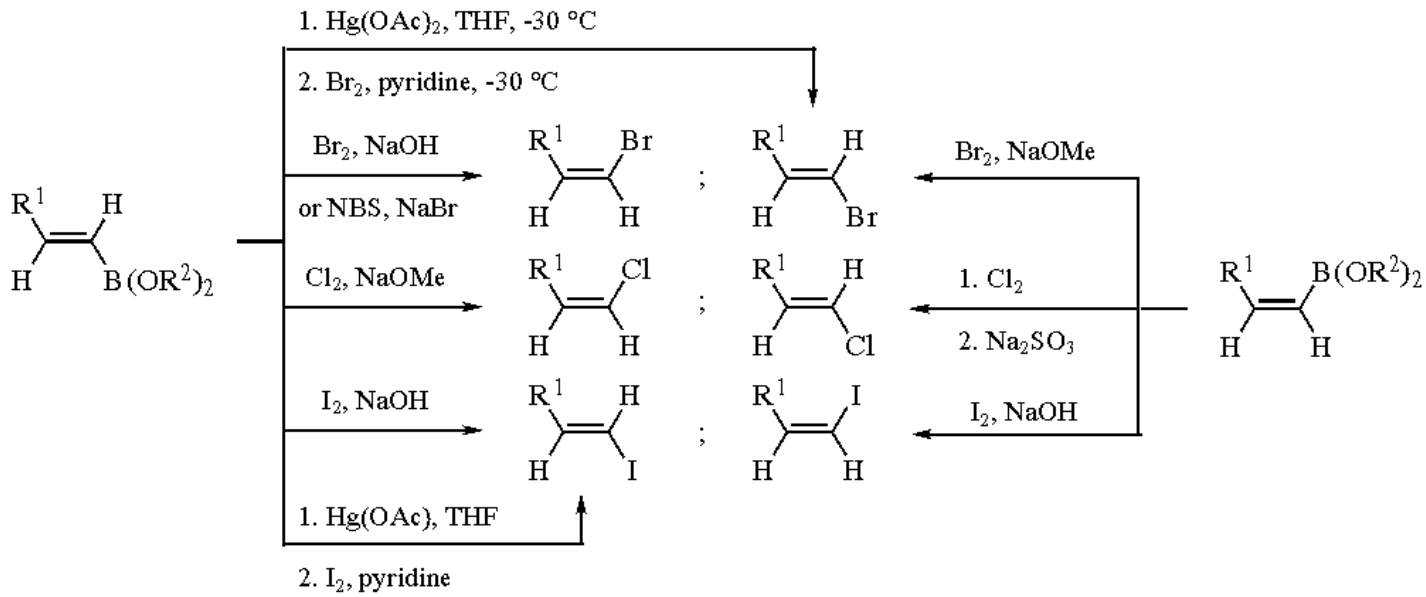

(10)

Synthesis of Conjugated Dienes.

The cross-coupling reaction of alkenylboronates with alkenyl halides is a general method for the synthesis of stereodefined 1,3-dienes (eq 11).[41]

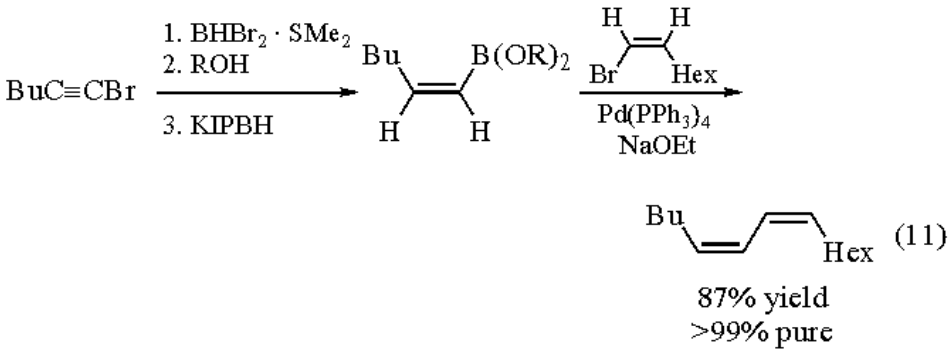

(11)

Other Applications.

DBBS is an excellent precursor for the formation of bulk powders and ceramic fiber coatings of boron nitride.[42] It has been used for the synthesis of the small carborane *closo*-2,3-$Et_2C_2B_5H_5$,[43] 3-*O*-carboranylcarbene,[44] silver and sodium isocyanoborohydrides,[45] and dications based on the hydrotris(phosphonio)borate skeleton.[46]

Related Reagents.

Dichloroborane-Dimethyl Sulfide.

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1,4-Dibromobutane

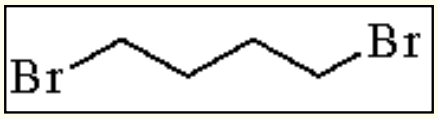

[110-52-1] · $C_4H_8Br_2$ · 1,4-Dibromobutane · (MW 215.92)

(useful for annulation as bis-electrophile[1] or as precursor to organobis(metallics)[2])

Alternate Name: tetramethylene dibromide.

Physical Data: bp 194-196 °C, 63-65 °C/6 mmHg; *d* 1.808 g cm^{-3}.

Solubility: sol THF, toluene, HMPA, benzene, DMF, Et_2O.

Form Supplied in: colorless liquid, 99%.

Analysis of Reagent Purity: ^1H NMR: δ 3.48 (m), 2.05 (m).

Handling, Storage, and Precautions: store in a cool dry place. Lachrymator; this reagent should be handled in a fume hood.

Uses as a Bis-Electrophile.

1,4-Dibromobutane reacts with a wide variety of nucleophiles to give displacement of one or both bromine atoms, depending upon the stoichiometry of the reaction. When 1 equiv of nucleophile is present, monoalkylation occurs. In general, subsequent functionalization of the remaining bromide is performed in the course of the synthesis. In this way the reagent is a precursor to many 1,4-difunctionalized butanes. When 2 equiv of nucleophile are used, symmetrically substituted butanes are the result. Many different nucleophiles have been utilized in these reactions. Carbon nucleophiles include alkynyl,[3] alkenyl,[4] allyl,[5] aryl,[6] benzyl,[7] and cyclopentadienyl anions.[8] In addition, a number of enolate anions have been alkylated including those derived from dissolving metal reductions of carbonyl-substituted arenes.[9] Heteroatom nucleophiles include halides,[10] alkoxides,[11] phenoxides,[12] and *N*-deprotonated amides.[13]

Electrophilic Annulation.

When two nucleophilic sites exist in the same molecule, 1,4-dibromobutane can react to form a ring. Typically these reagents are carboxylic acid derivatives having two geminal α-hydrogens. When 2 equiv of base are added, the dibromide reacts twice at the same carbon center to give a cyclopentane. If the acidic carbon is part of a pre-existing

ring, then a spirocycle is formed.[1] Esters,[14] ketones,[15] and nitriles[16] all work well for these annulation reactions, but any compound with two geminal acidic hydrogens can exhibit similar reactivity.[17] The iminonitrile (**1**) was annulated by this method in a route to cycloleucine (eq 1).[16] α,β-Unsaturated carbonyl compounds can react via their extended enolates at the α-position to give deconjugated annulated products[18] or, if the structure permits, at the α´-position.[19] If the nucleophilic moieties are vicinally related, fused-ring compounds are obtained.[20] This is the case for the isoquinoline formamidine (**2**), which is alkylated at its benzylic position with the aid of lithium chelation and then directly cleaved with ***Hydrazine*** to give a benzo[*a*]quinolizidine (eq 2).[21] Metallacyclopentenes, prepared by the reaction of 1,3-dienes with activated ***Magnesium***, react with 1,4-dibromobutane and lead to spiroannulated products.[22]

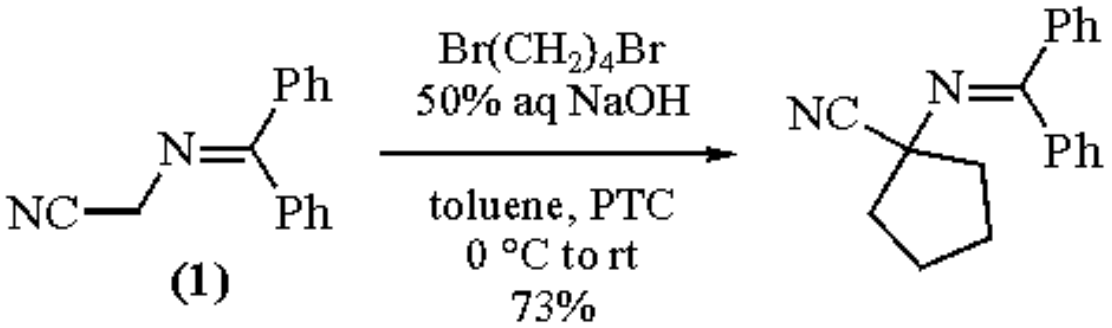

(1)

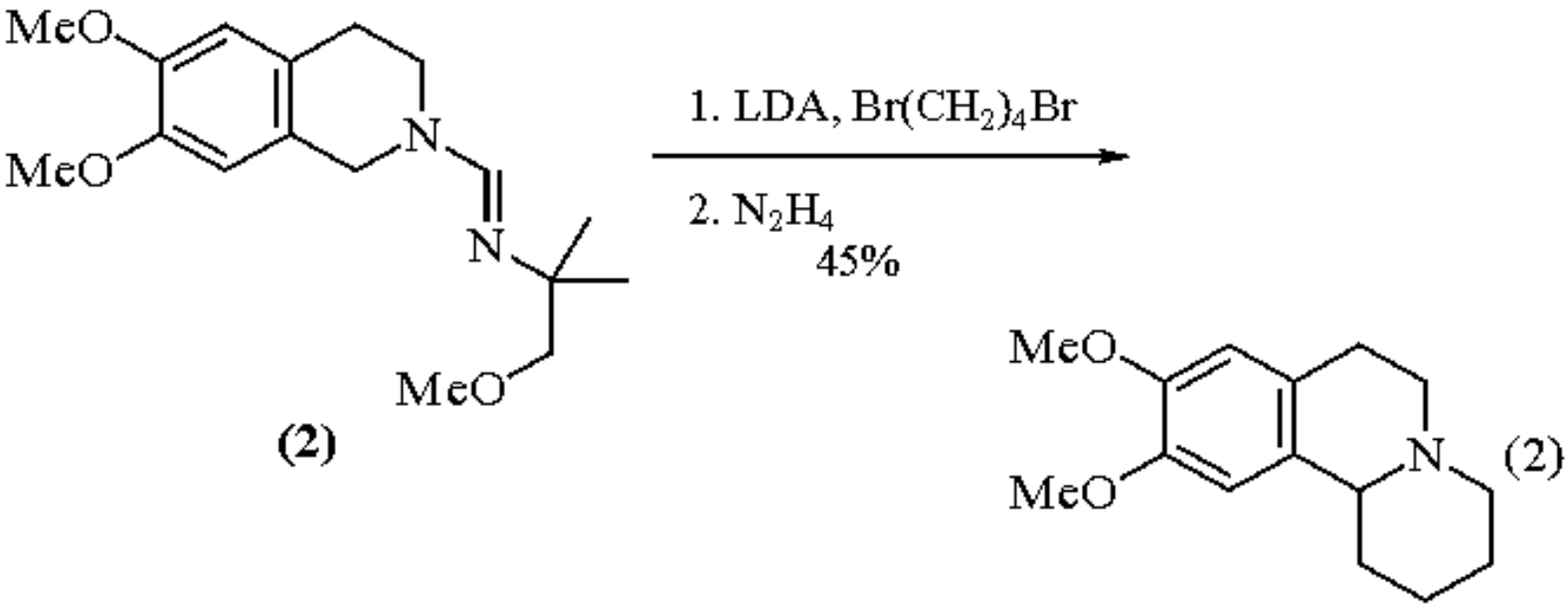

(2)

Formation and Uses of Organobis(metallics).

The electrophilic nature of 1,4-dibromobutane can be inverted by the formation of organobis(metallics). These compounds can be used with substrates bearing two electrophilic sites to form new rings. The bis-Grignard reagents have been used extensively. Reaction with esters and lactones gives cyclopentanols[23] and cyclic dicarboxylic acid anhydrides lead to spirolactones.[24] The bis-cuprate has been utilized in a novel class of spiroannulations via 1,4-addition to 3-halocycloalk-2-enones followed by elimination of the halide atom and a second 1,4-addition (eq 3).[25]

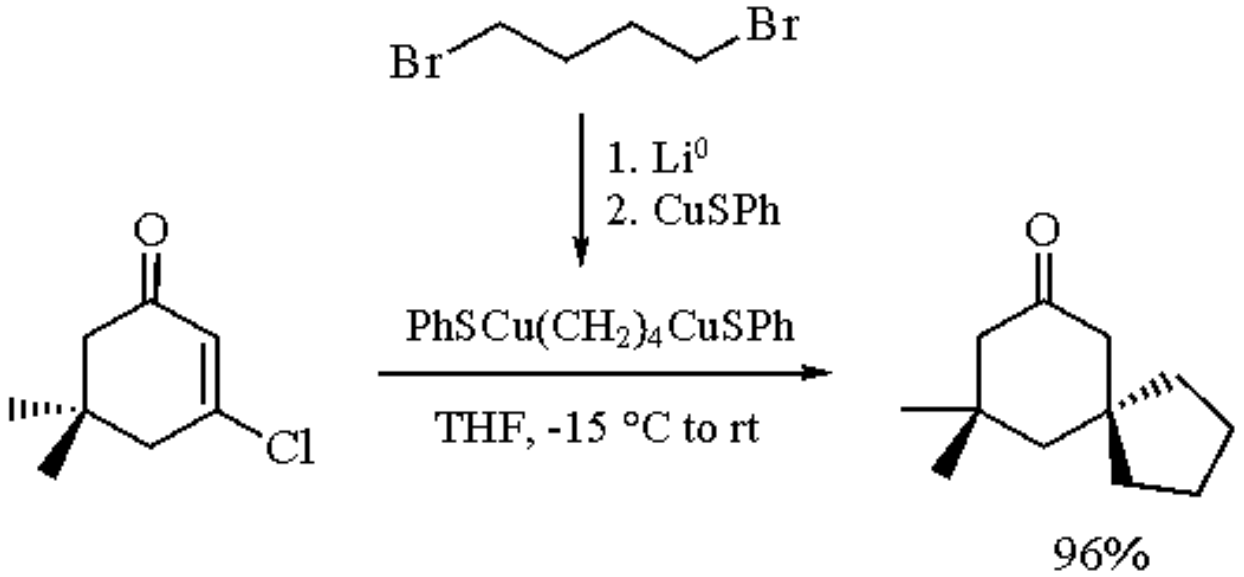

(3)

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Dibromodifluoromethane

CF_2Br_2

[75-61-6] · CBr_2F_2 · Dibromodifluoromethane · (MW 209.82)

(fluorinating reagent; can function as a precursor for the introduction of CF_2Br, CF_3, and $=CF_2$ groups into organic compounds)

Physical Data: bp 22.78 °C.[1]

Solubility: sol ether, acetone, alcohol, benzene.

Form Supplied in: colorless liquid.

Preparative Methods: dibromodifluoromethane is prepared by the reaction of $CFBr_3$ with AgF (50-60%),[2] by the reaction of CBr_4 with $SbBr_2F_3$ (80%),[3] or by the reaction of $CBrF_2CO_2Ag$ with Br_2 (81%).[4] Industrially, gas-phase reactions are employed to prepare CF_2Br_2. For example, CF_2Br_2 is formed from the reaction of CF_2H_2 and Br_2 at 500 °C,[5] the reaction of CF_2BrCl and HBr at 600 °C,[6] and the reaction of $ClCF_2C(O)CF_2Cl$ and Br_2 at 580-650 °C.[7]

Handling, Storage, and Precautions: use in a fume hood.

Addition to Alkenes and Alkynes.

Radical addition of CF_2Br_2 to alkenes and alkynes is initiated by irradiation,[8] metals,[9] boranes,[10] and peroxide[11] to give the corresponding adducts (eq 1). Reaction of CF_2Br_2 with an enamine (without any initiator) followed by hydrolysis produces α-bromodifluoromethylated ketones.[12]

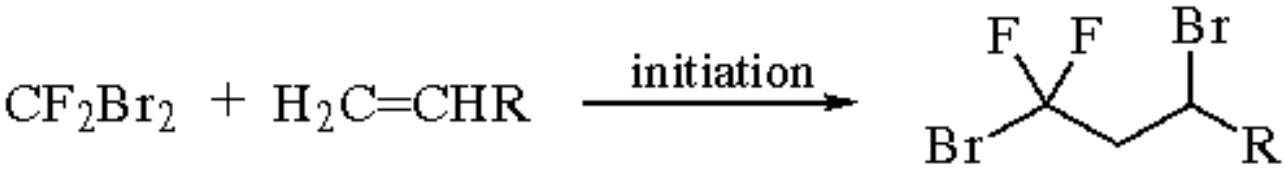

(1)

Reactions with Nucleophiles.

Treatment of carbanions, such as $[(EtO_2C)_2CR]^-$,[13] RC&tbond;C$^-$,[14] and $[PhCH{=}NC(Me)CO_2Me]^-$[15] with CF_2Br_2 gives the corresponding bromodifluoromethylated compounds. Reaction of CF_2Br_2 with phosphines or phosphites affords high yields of bromodifluoromethylphosphonium salts and bromodifluoromethylphosphonates, respectively (eqs 2 and 3).[16] CF_2Br_2 also reacts with sulfur and oxygen nucleophiles to produce bromodifluoromethyl sulfides[17] and ethers,[18] respectively. Reaction of pyrazole with CF_2Br_2 and NaH yields *N*1-bromodifluoromethylpyrazole.[19]

$$CF_2Br_2 + Nu \longrightarrow NuCF_2Br \qquad (2)$$

$$Nu = \text{carbanion}, RO^-, RS^-, Ph_3P, R^1R^2N^-$$

$$CF_2Br_2 + (RO)_3P \longrightarrow (RO)_2P(O)CF_2Br \qquad (3)$$

Difluoromethylenation.

CF_2Br_2 is a precursor in the Wittig reaction for the introduction of the $=CF_2$ moiety into organic molecules. In the presence of CF_2Br_2 and ***Hexamethylphosphorous Triamide*** or ***Triphenylphosphine***, aldehydes and ketones can be converted to the corresponding 1,1-difluoroalkenes (eq 4).[20] Alternatively, in the presence of phosphines or metals (***Zinc*** or Cd), treatment of the phosphonium salt $[R_3PCF_2Br]^+ Br^-$ with aldehydes and ketones also gives the corresponding 1,1-difluoroalkenes.[21]

$$CF_2Br_2 + 2\,R^1{}_3P + R^2COR^3 \longrightarrow R^2R^3C{=}CF_2 \qquad (4)$$

$$R^1 = Ph, NMe_2$$

Formation and Reactions of CF_3Cu.

CF_3Cu is readily prepared from CF_2Br_2. Treatment of CF_2Br_2 and Zn or Cd in DMF forms CF_3ZnX or CF_3CdX.[22] Metathesis of the CF_3ZnX or CF_3CdX with CuX gives the CF_3Cu reagent,[23] which couples with aryl and vinyl iodides, allyl chloride,[23] and activated aryl chlorides (eq 5 and 6).[24]

$$CF_2Br_2 + M \longrightarrow CF_3MX \xrightarrow{Cu^I} 'CF_3Cu' \qquad (5)$$

$$M = Zn, Cd; X = Br, CF_3$$

$$'CF_3Cu' + RY \longrightarrow RCF_3 \qquad (6)$$

$$Y = Cl, I; R = aryl, vinyl, allyl$$

Formation and Reactions of Difluorocarbene.

CF_2Br_2 is a precursor of difluorocarbene. In the presence of Zn or ***Lithium Aluminum Hydride-Titanium(IV) Chloride***, reaction of CF_2Br_2 with alkenes gives 1,1-difluorocyclopropane derivatives (eq 7);[25] difluorocarbene has been proposed as the active intermediate in the reaction. Alternatively, difluorocarbene has been generated from $[Ph_3PCF_2Br]^+ Br^-$ and fluoride ion, which is prepared from the reaction of CF_2Br_2 and triphenylphosphine (eq 8).[26] More conveniently, difluorocarbene has also been generated from CF_2Br_2, a tertiary phosphine, and fluoride ion.[26a] Treatment of aldehydes or ketones with the CF_2Br_2/Zn reagent gives *gem*-difluoroalkanes.[27]

$$CF_2Br_2 + R_2C{=}CR_2 \xrightarrow{Zn \text{ or } TiCl_4/LiAlH_4}$$

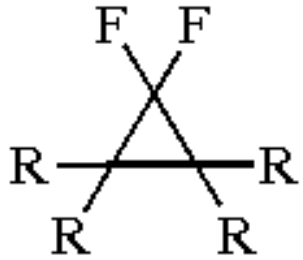

(7)

$$Ph_3PCF_2Br^+ Br^- + R_2C{=}CR_2 \xrightarrow{MF}$$

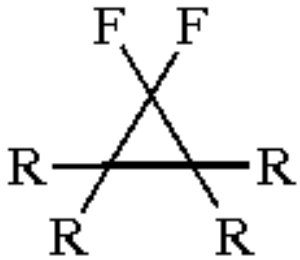

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5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione

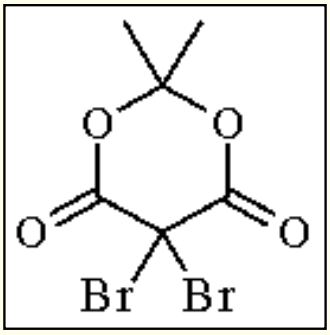

[66131-14-4] · $C_6H_6Br_2O_4$ · 5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione · (MW 301.92)

(selective α-bromination of aldehydes[1] and α´-bromination of α,β-unsaturated ketones;[1] reductive coupling to an ethylenetetracarboxylate[3,4])

Physical Data: mp 75-76 °C.

Solubility: sol diethyl ether, carbon tetrachloride, and most other organic solvents.

Form Supplied in: white solid.

Analysis of Reagent Purity: ^{1}H NMR; elemental analysis (Br).

Preparative Methods: by bromination of Meldrum's acid (***2,2-Dimethyl-1,3-dioxane-4,6-dione***)[2] (commercially available) with ***Bromine*** in the presence of ***Potassium Hydroxide*** or ***Sodium Hydroxide*** eq 1).[3]

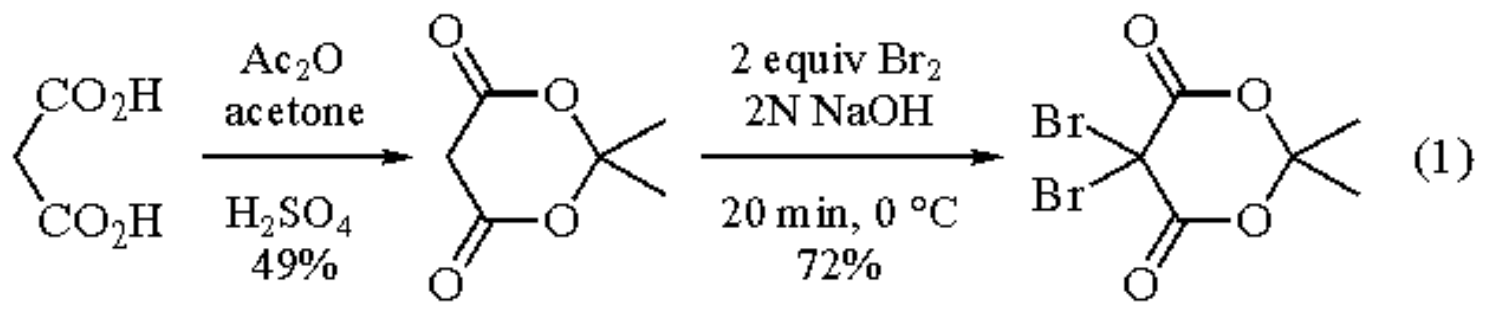

Purification: recrystallization from CCl_4.

Handling, Storage, and Precautions: can be stored for months at 0 °C.

Bromination of Aldehydes and Ketones.

This brominating reagent is especially useful for the synthesis of α-monobromoaldehydes[1] and the preparation of α´-brominated α,β-unsaturated ketones.[1] The bromination is usually carried out by stirring an ether solution of the reagent and the carbonyl compound (1:2 ratio) at rt. The bromination product is easily isolated by extracting the Meldrum's acid byproduct into aqueous sodium hydrogen carbonate. Heptanal is thus cleanly α-monobrominated (eq 2),[1] as are aldehydes having a methine at the α-position such as isobutanal and cyclohexanecarbaldehyde. Methyl ketones with no α´-hydrogens, such as acetophenone, are smoothly monobrominated as well.[1] However, the regioselectivity in the bromination of unsymmetrical ketones, e.g. 2-methylcyclohexanone and 4-methyl-2-pentanone, is not good, and this is not a synthetically useful process (eq 3).[1]

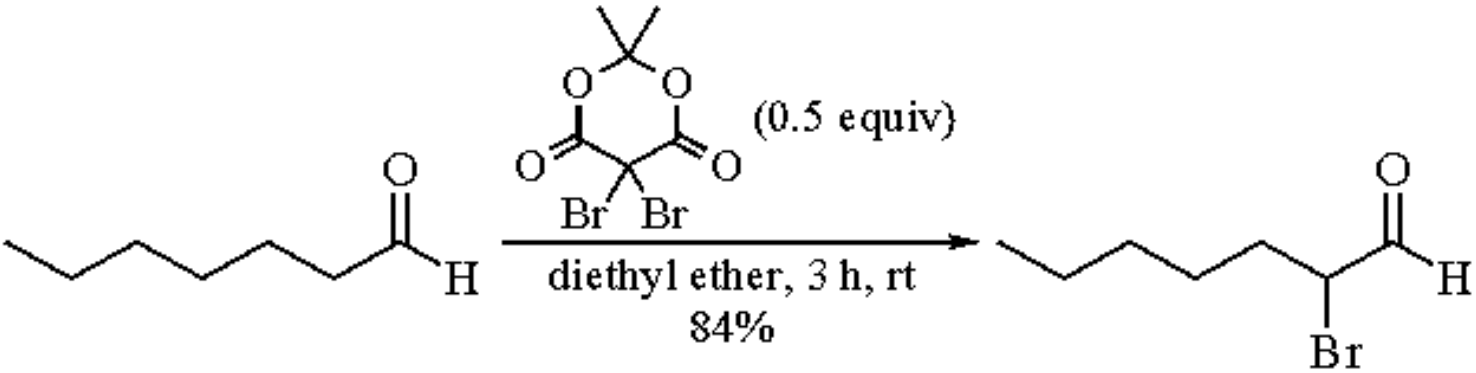

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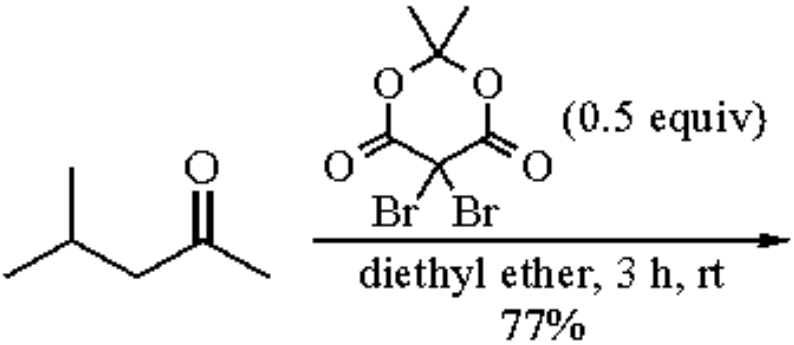

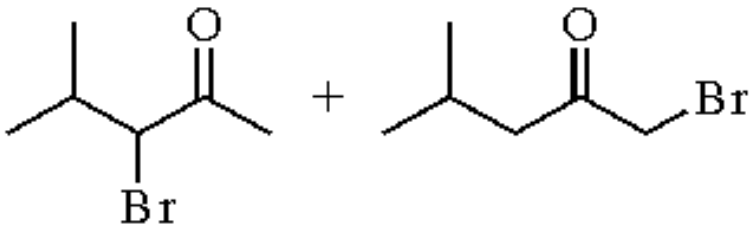

(3)

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5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione selectively monobrominates α,β-unsaturated ketones at the α´-position without side reactions, such as addition to the double bond or allylic bromination (eq 4).[1] In the case of ketones which enolize with difficulty, it is advantageous to enhance the rate of the reaction by the addition of catalytic amounts of ***Hydrogen Bromide*** or by heating to reflux. Representative selective brominations of some α,β-unsaturated ketones are presented in eqs 4-7.[1] In contrast, the bromination of 3-methyl-2-cyclopenten-1-one with this reagent in

5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione

CCl_4 under reflux gave no selectivity, resulting in 18% 5-bromo-, 11% 4-bromo-, 2% 5,5-dibromo- and 2% 4,5-dibromo-3-methyl-2-cyclopenten-1-one.[4]

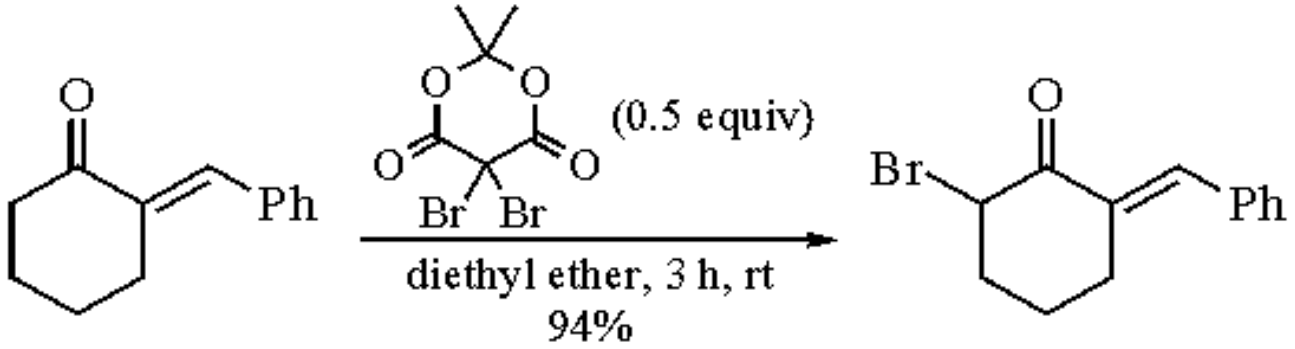

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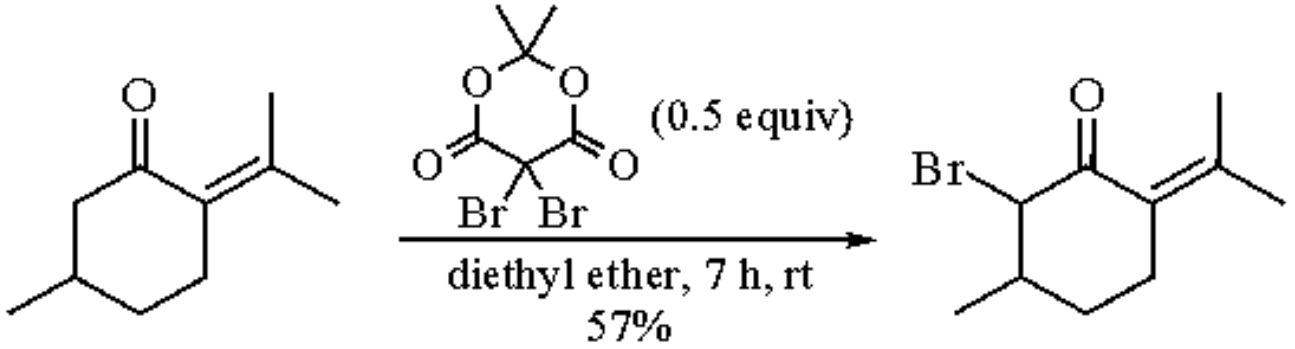

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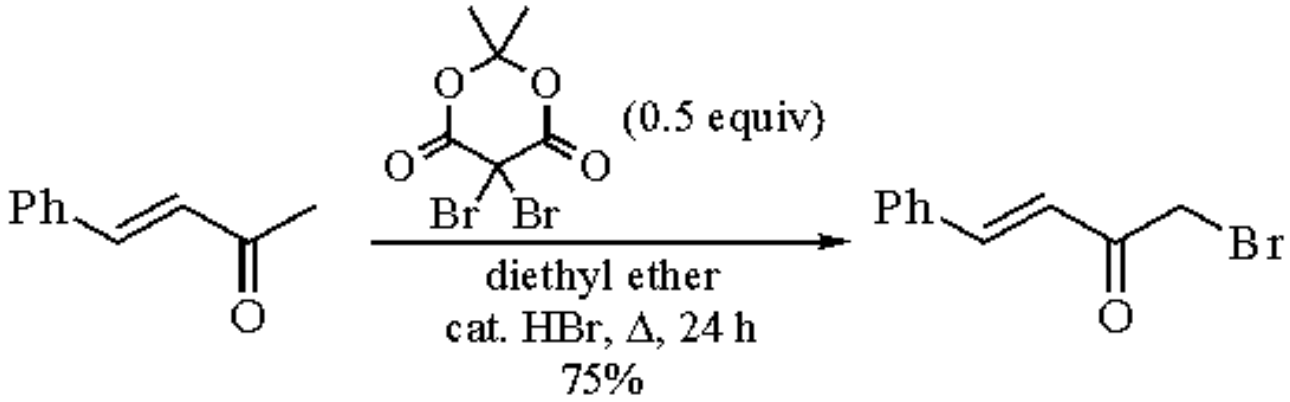

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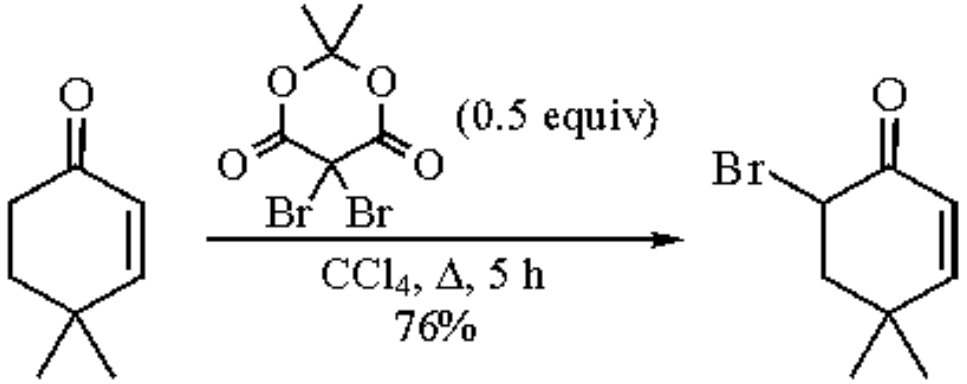

(7)

Synthesis of Ethylenetetracarboxylate.

Reductive coupling of 5,5-dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione takes place spontaneously in DMF at rt to afford diisopropylidene ethylenetetracarboxylate (eq 8).[3] It was subsequently reported that repeated attempts to prepare this diisopropylidene ethylenetetracarboxylate according to this procedure gave erratic results, and that more reliable results and improved yields could be obtained by adding 5-bromo-2,2-dimethyl-1,3-dioxane-4,6-dione to a solution of 1 equiv of 5,5-dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione in dry DMF which had been standing for 1 week in a well-illuminated place.[5] Dissolution of the 5-bromo derivative was quickly followed by the precipitation of the required ethylenetetracarboxylate in 57% yield (mp 230 °C, dec.) (eq 9).[5] This dimeric compound was used as a precursor to tricarbon monoxide via pyrolytic decomposition (eq 10).[6]

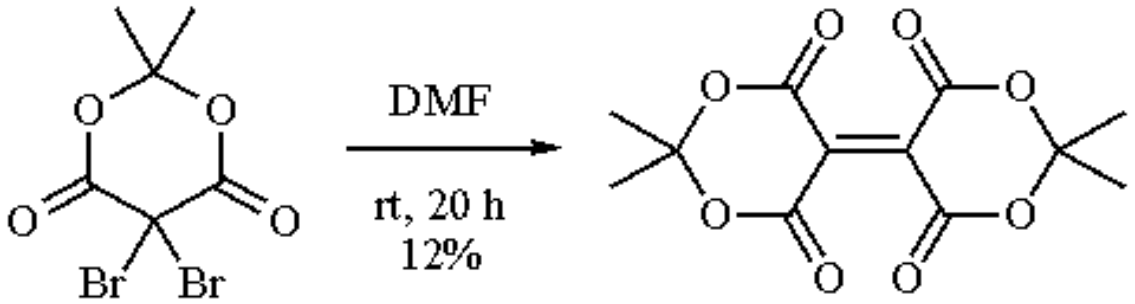

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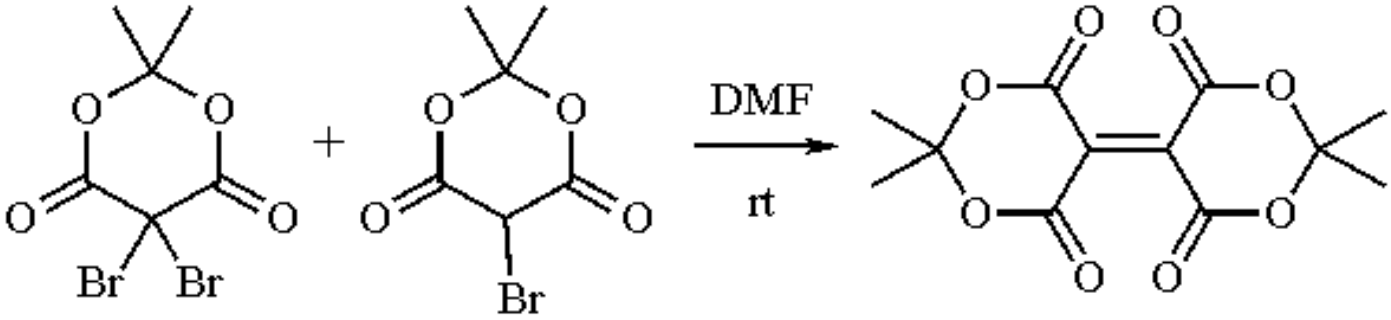

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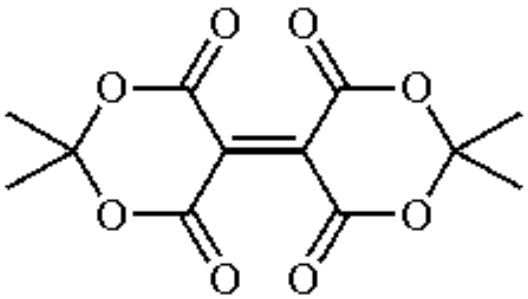

C_3O + acetone + CO_2 + CO (10)

Synthesis of Isocyanoamines.

5,5-Dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione reacts with *N*,*N*-disubstituted hydrazines to produce hydrazone derivatives, which serve as starting materials for dialkylisocyanoamines upon pyrolysis (eq 11).[7]

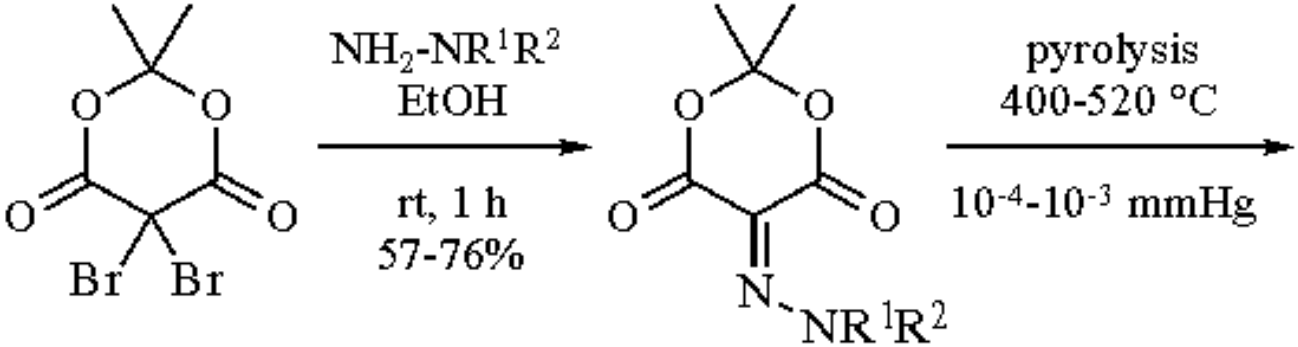

$R^1 = Me, Ph$
$R^2 = Me, H, Ph$

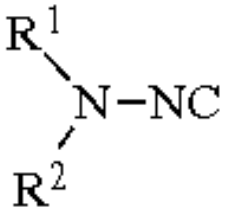

(11)

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1,3-Dibromo-5,5-dimethylhydantoin

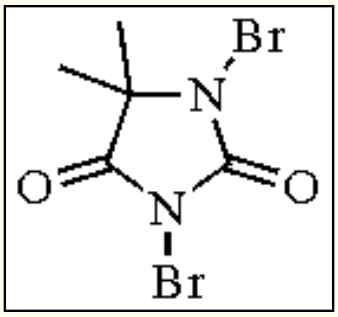

[77-48-5] · $C_5H_6Br_2N_2O_2$ · 1,3-Dibromo-5,5-dimethylhydantoin · (MW 285.93)

(benzylic bromination of arenes; bromoperoxylation and bromofluorination of alkenes)

Alternate Names: DBH; 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione; dibromantin.

Physical Data: mp 197-199 °C (dec).

Solubility: slightly sol acetone, THF, 1,4-dioxane, H_2O (hot), CCl_4 (reflux).

Form Supplied in: white powder or crystals; widely available.

Analysis of Reagent Purity: determined by the standard iodide-thiosulfate titration method.

Preparative Methods: DBH has been prepared by reaction of Br_2 (1 mol) with 5,5-dimethylhydantoin (0.5 mol) and NaOH (1 mol) in ice-water at 0 °C.[1a] 5,5-Dimethylhydantoin is widely available commercially, and can be prepared from KOCN, $(NH_4)_2CO_3$, and acetone in water at 85 °C.[1a] After removal of water and excess reagents by distillation, the resulting solution can be used directly for the preparation of DBH. 1,3-Dibromo-5-ethyl-5-methylhydantoin has also been prepared and has the advantage of greater solubility.[1b]

Purification: in an efficient fume hood (*caution*: bromine evolution), an impure sample of DBH (40 g) is dissolved as quickly as possible in 4 L of preheated water at 90-95 °C. The solution is filtered if necessary, and the filtrate is then immediately chilled well in an ice bath to effect crystallization. After most of the aqueous portion has been decanted, the white crystals are collected by filtration through a bed of ice and washed with water. The crystals are dried in vacuo (63-70% recovery).[1a]

Handling, Storage, and Precautions: 1,3-dibromo-5,5-dimethylhydantoin should be stored refrigerated and protected from light and moisture to avoid decomposition. DBH is an irritating solid and precautions should be taken to avoid inhalation of the powder or contact with skin.

Benzylic Bromination.

1,3-Dibromo-5,5-dimethylhydantoin has been used frequently for the radical bromination of benzylic positions of arenes and heterocycles. Using 0.5 molar equiv of DBH in CCl_4 at reflux in the presence of ***Dibenzoyl Peroxide***, high yields of the benzylic bromide are obtained under mild conditions. The use of DBH has been found to be advantageous for the preparation of particularly acid-sensitive benzylic bromides, as shown in eqs 1 and 2.[2,3] The use of NBS in the former case affords a debenzoylated product, while in the latter example, elimination of AcOH and HBr leads to the aromatized product. DBH was also found to be the most satisfactory reagent for the dehydrogenation of azlactones (eq 3).[4]

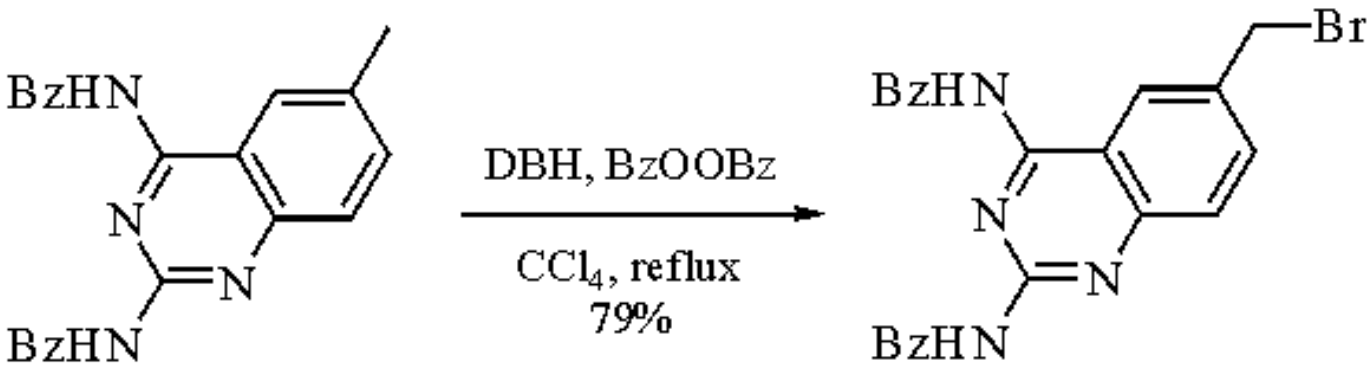

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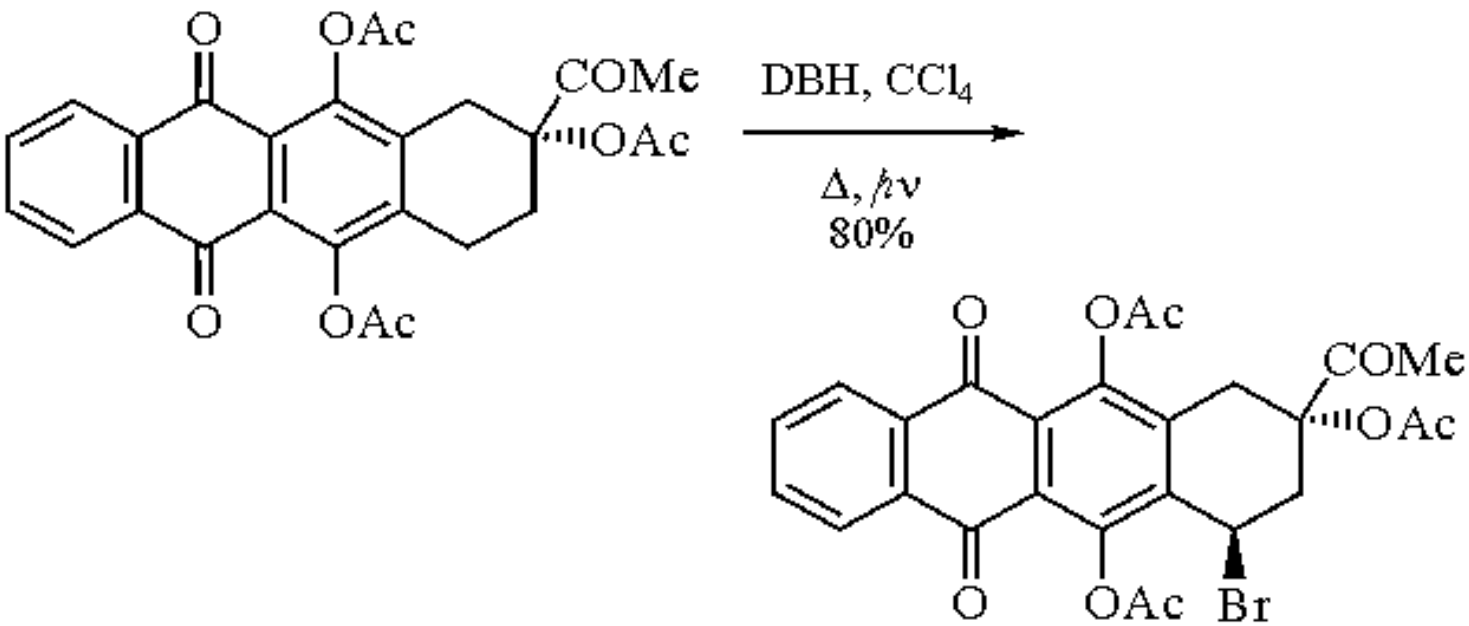

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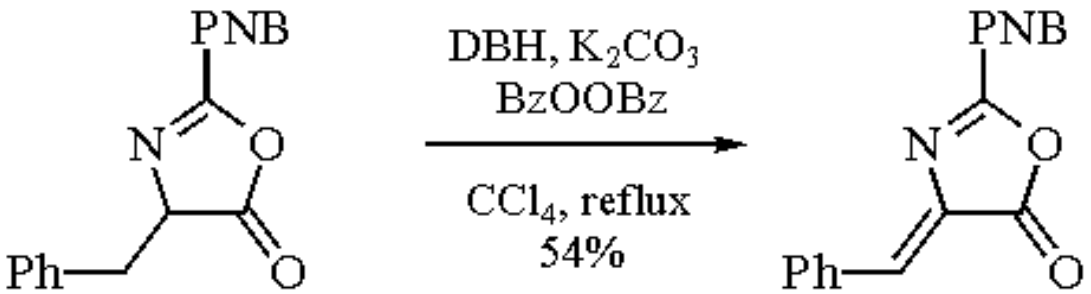

(3)

Electrophilic Bromination of Alkenes.

DBH is regularly substituted for ***N-Bromosuccinimide*** in industrial applications due to its low cost and high bromine content. Electrophilic brominations of alkenes often proceed in higher yield using DBH, as shown for the bromohydration of synthesis of epoxides via bromohydrins (eq 4).[5] DBH is the preferred reagent for the preparation of bromohydroperoxide precursors to 1,2-dioxetanes from alkenes using ***Hydrogen Peroxide***.[6] DBH has also been found to be the most effective reagent for the bromofluorination of alkenes in combination with ***Hydrogen Fluoride-Pyridine*** complex or ***Silicon(IV) Fluoride*** (eq 5).[7] Alkynes can be converted to (*E*)-bromofluoroalkenes with good stereoselectivity; these are suitable substrates for palladium-catalyzed coupling (eq 6).[8] In an analogous sense to the use of ***N-Iodosuccinimide***, DBH has been employed for the coupling of glycals to alcohols affording 2-bromoglycosides which can be converted to 2-deoxyglycosides.[9]

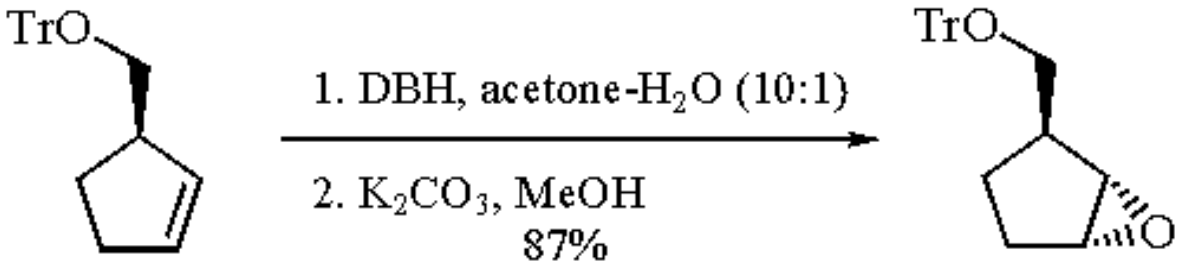

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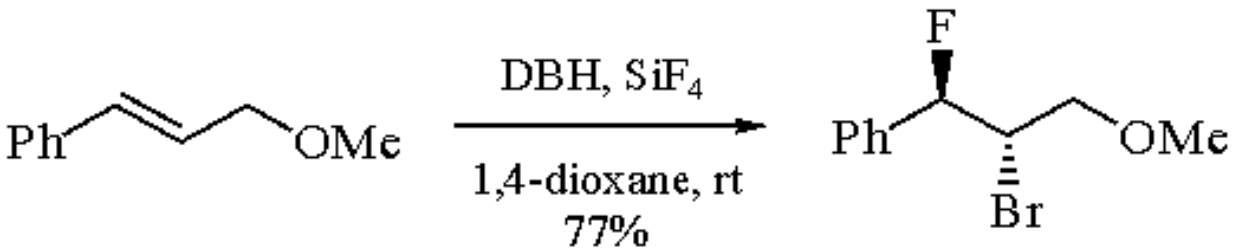

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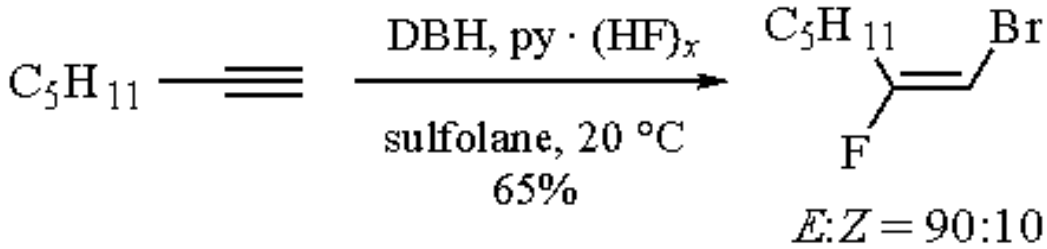

(6)

Electrophilic Bromination of Thioethers.

The use of DBH for the deprotection of dithioacetals and dithianes has been found to be superior to many other methods. Transacetalation of dithianes to diethyl acetals is achieved by treatment with 1 equiv of DBH in ethanol at rt.[10] In addition, dithiolanes can be converted to the corresponding geminal difluoro compounds in good yield by reaction with DBH and ***Pyridinium Poly(hydrogen fluoride)*** in dichloromethane at -78 °C.[11]

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1,2-Dibromoethane

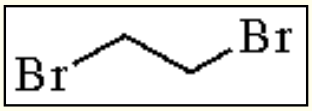

[106-93-4] · $C_2H_4Br_2$ · 1,2-Dibromoethane · (MW 187.86)

(used as an entrainment reagent[1,2] and for bromination of carbanions[5,7,8])

Alternate Name: ethylene dibromide.

Physical Data: bp 131.7 °C; mp 9-10 °C

Solubility: sol most organic solvents.

Form Supplied in: commercially available as a colorless liquid in 99% purity.

Analysis of Reagent Purity: NMR, GC, bp.

Purification: distillation.

Handling, Storage, and Precautions: 1,2-dibromoethane is toxic and carcinogenic. Exposure causes irritation of the skin, mucus membranes, eyes, and upper respiratory tract. Animal tests indicate that overexposure may cause reproductive disorders. Chronic toxic effects include damage to the liver, kidneys, and lungs. Contact with vapor should be avoided. This reagent should only be handled in a fume hood using proper protective equipment.

Entrainment Reagent.

1,2-Dibromoethane is commonly used to chemically activate ***Magnesium*** metal for use in forming Grignard reagents. It reacts with magnesium to expose a clean, reactive surface capable of converting otherwise unreactive halides into Grignard reagents.[1,2] When used as an entrainment reagent, 1,2-dibromoethane is added slowly so as to allow the halide with poor reactivity adequate time to react with freshly exposed magnesium surfaces. Pearson and Cowan's conversion of hexachlorobenzene to pentachlorobenzoic acid is a good example of this application (eq 1).[2] In this instance, 1,2-dibromoethane is added in dropwise fashion over a 48 h period to a refluxing mixture of hexachlorobenzene and magnesium turnings in ether. This reagent is often used in preference to other alkyl halides for entrainment because ethylene and $MgBr_2$ are produced as byproducts rather than a second Grignard reagent.

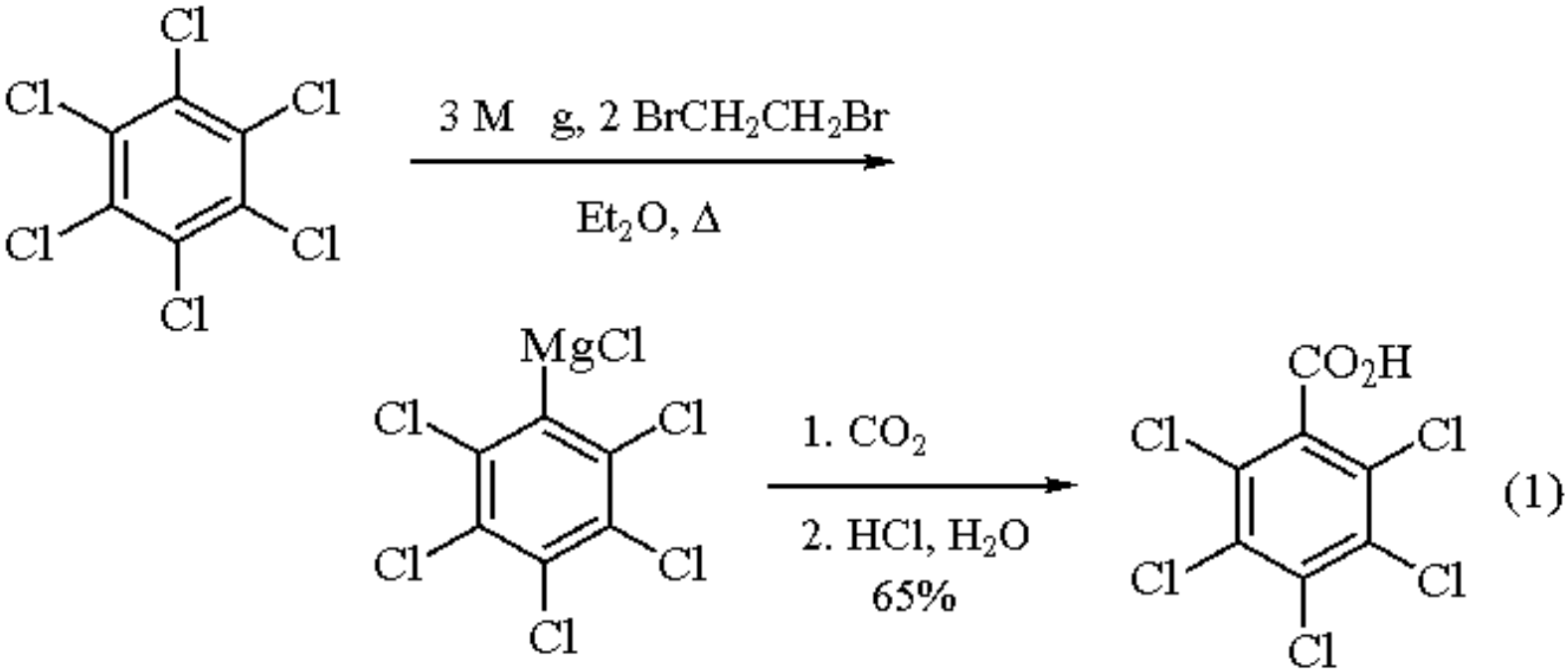

1,2-Dibromoethane is also a useful reagent for activating ***Zinc***.[3,4] For example, upon heating with this reagent in ethanol, zinc powder reacts exothermically to produce activated zinc that will reduce triple bonds to *cis*-double bonds in a variety of compounds (eq 2).[4] The zinc powder can be further activated by addition of a solution of ***Copper(I) Bromide*** and ***Lithium Bromide***.

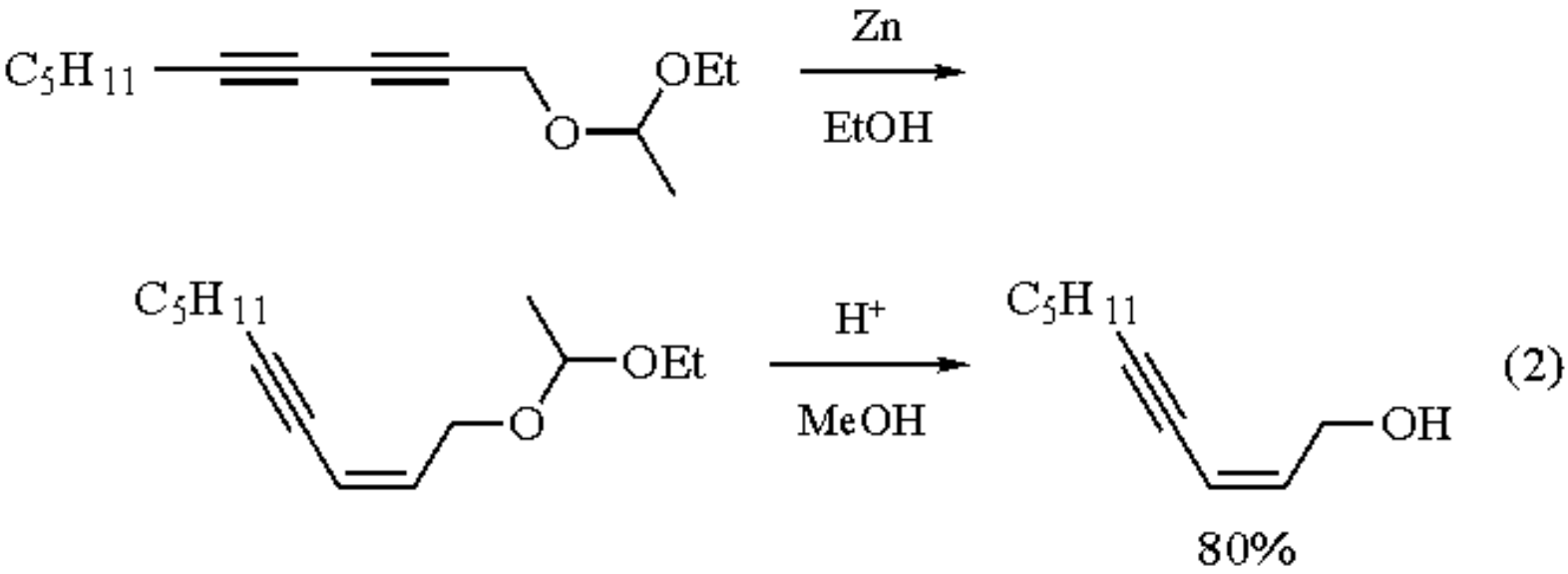

Reagent for Bromination of Carbanions.

This reagent can be used as a source of positive bromine for bromination of α-methyl lactone enolates.[5] Ourisson et al used this methodology effectively in the synthesis of α-methylene-γ-lactones, including (-)-frullanolide (eq 3). Because 1,2-dibromoethane is unreactive toward the lactone product, it may offer advantages over bromine. However, bromination of enolates by this reagent is not a general reaction. With many enolates, 1,2-dibromoethane acts instead as an alkylating agent.[6]

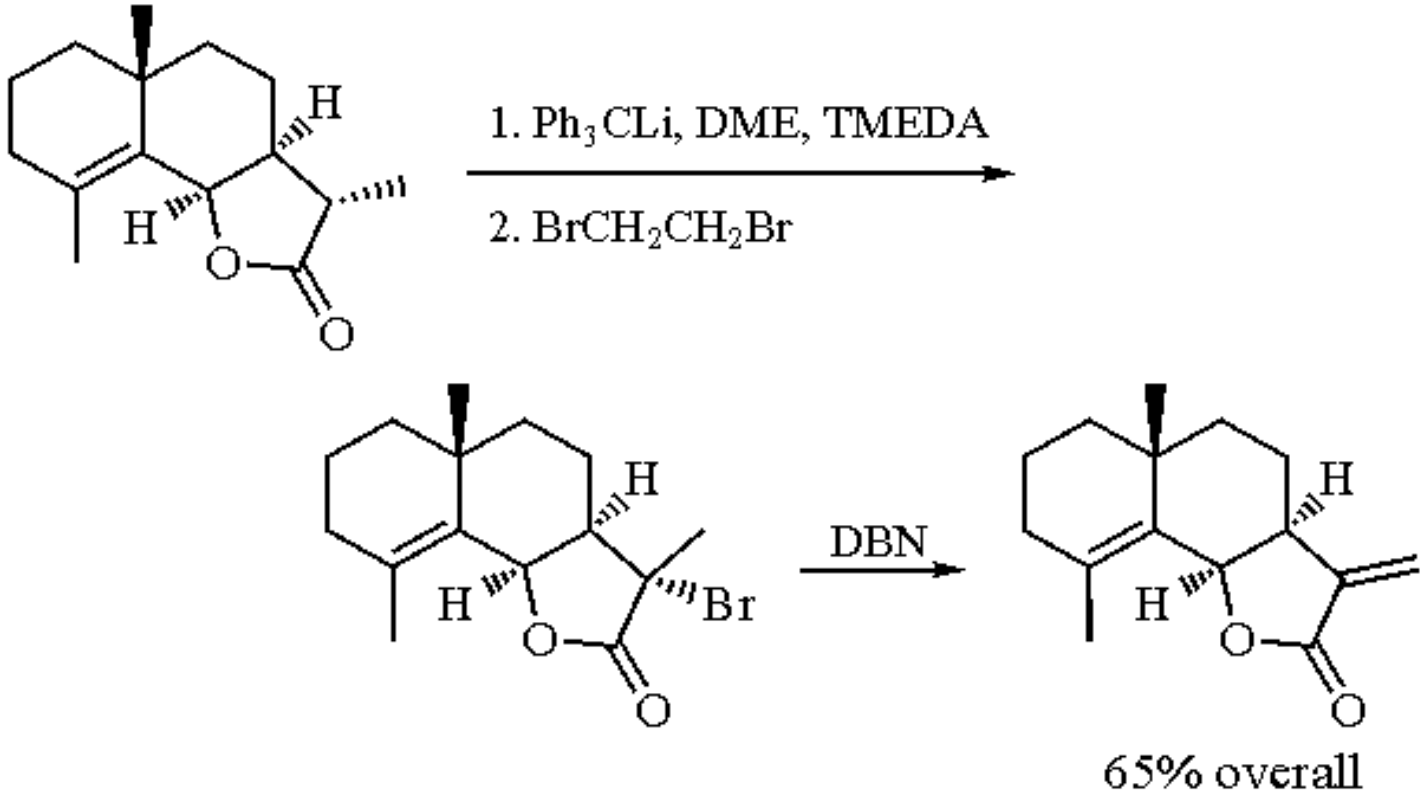

(3)

1,2-Dibromoethane also reacts with aryl-[7] and vinyllithiums[8] to produce the corresponding bromides in good yield. For example, Snieckus and Miah have used this reagent to efficiently convert lithiated *O*-pyridyl carbamates to the bromides (eq 4).

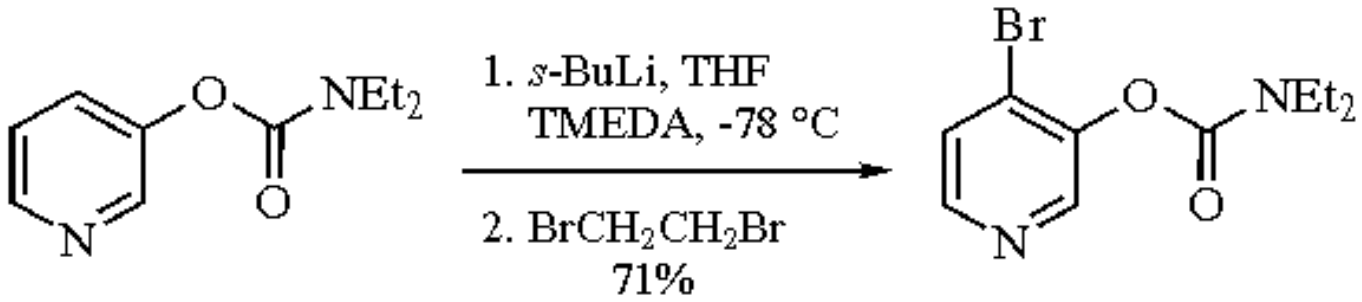

(4)

More recently, the reagent 1,2-dibromotetrafluoroethane, which often gives superior yields, has been used in a similar fashion for the bromination of anions.[9]

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1,1-Dibromo-2-ethoxycyclopropane

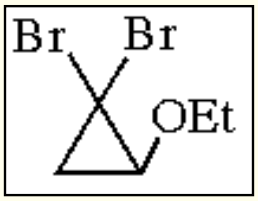

[55249-20-2] · $C_5H_8Br_2O$ · 1,1-Dibromo-2-ethoxycyclopropane · (MW 243.93)

(cyclopropyllithium reagent; cyclopropene precursor)

Alternate Name: 2,2-dibromocyclopropyl ethyl ether.

Physical Data: bp 45-48 °C/4 mmHg.

Analysis of Reagent Purity: ^{1}H NMR (CCl_4-Me_4Si, 60 MHz) δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.55-1.95 (m, 2H), 3.35-4.05 (m, 3H).

Preparative Method: [1] to a mixture of ethoxyethylene (1 equiv), *n*-Bu_3N (0.024 equiv), and $CHBr_3$ (1.5 equiv), is added aq. NaOH solution (50%, 6.25 equiv of NaOH) at rt. The reaction mixture is stirred for 48 h and poured into water and extracted with Et_2O. The organic phase is washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated using a rotary evaporator at 25 °C/60 mmHg. The residue is distilled at 25 °C/0.2 mmHg and further purified by silica gel column chromatography (petroleum ether/CH_2Cl_2 = 4:1) to give pure 1,1-dibromo-2-ethoxycyclopropane (**1**) (eq 1).

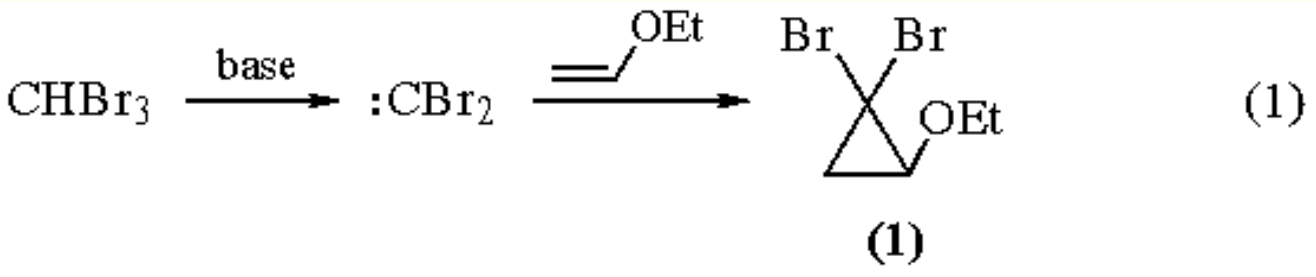

Purification: distillation followed by silica gel column chromatography.

Cyclopropylidenating Reagent.

A carbenoid reagent, 1-bromo-2-ethoxycyclopropyllithium (**2**), is generated from (**1**) upon treatment with 1 mol equiv of ***n-Butyllithium*** in THF at -95 °C. The lithium reagent reacts with various electrophiles to give 1-substituted

cyclopropane derivatives. The electrophile is introduced preferentially *cis* to the ethoxyl group.

The cyclopropyllithium (**2**) reacts with 2-cyclopentenone in a 1,2-addition manner to give the corresponding alcohol, which is converted into an ethanol adduct of chalicene (eq 2).[2]

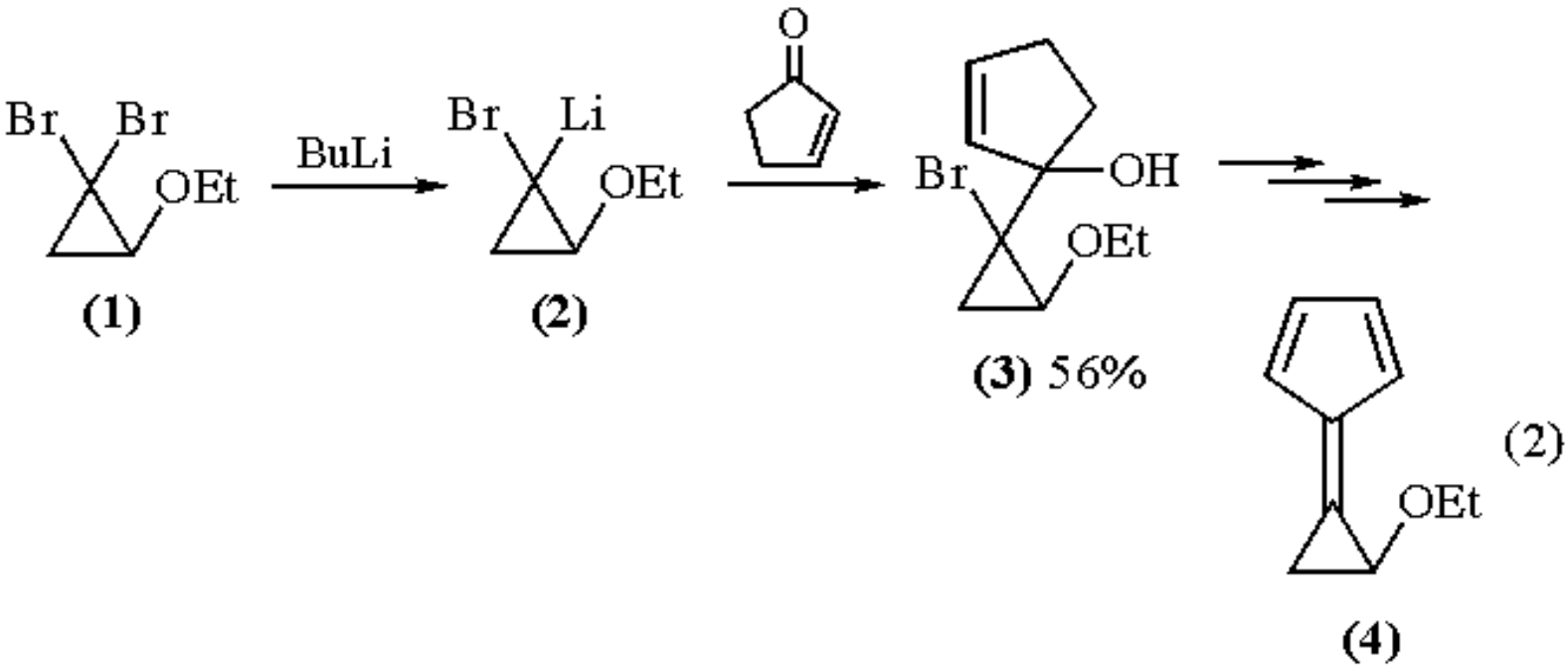

Cyclopropene Precursor.

Reduction of (**1**) with ***Zinc*** in methanol gives a mixture of *cis*- and *trans*-1-bromo-2-ethoxycyclopropane (**5**). The cyclopropane (**5**) is dehaloalkoxylated with ***Magnesium*** in THF at reflux to afford cyclopropene (**6**) (eq 3),[3] which is trapped with cyclopentadiene or bromine to give tricyclo[3.2.1.0^{2,4}]-6-octene (**7**) (eq 4) or *trans*-1,2-dibromocyclopropane (**8**) (eq 5), respectively.

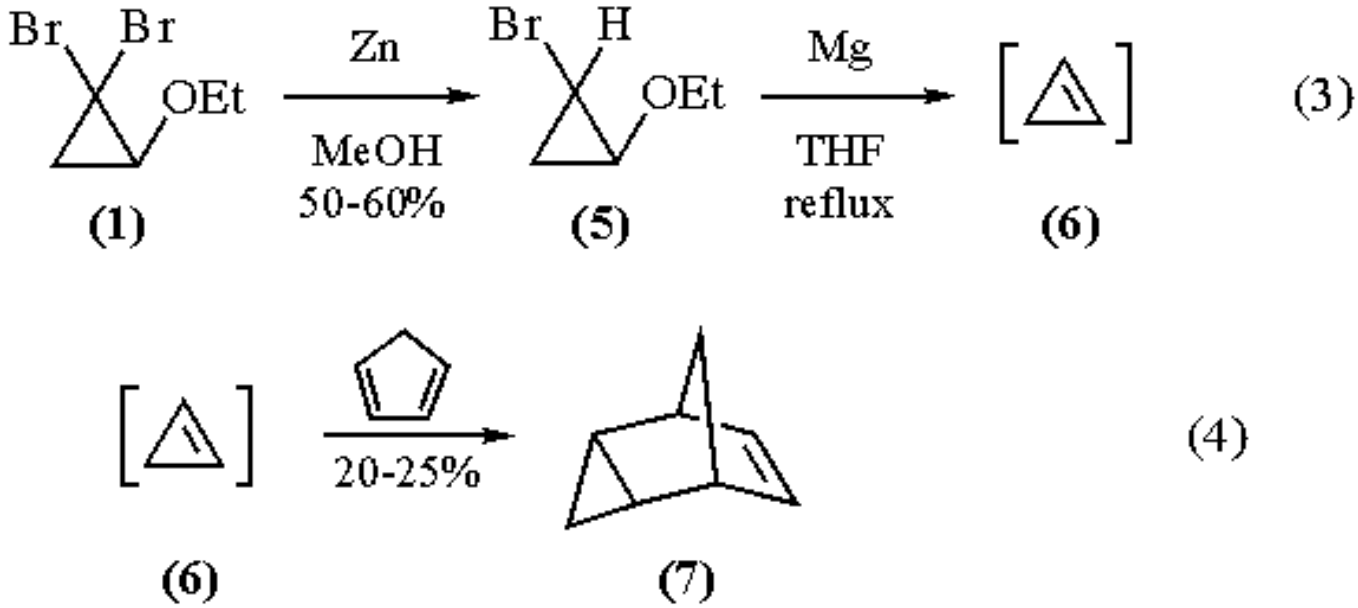

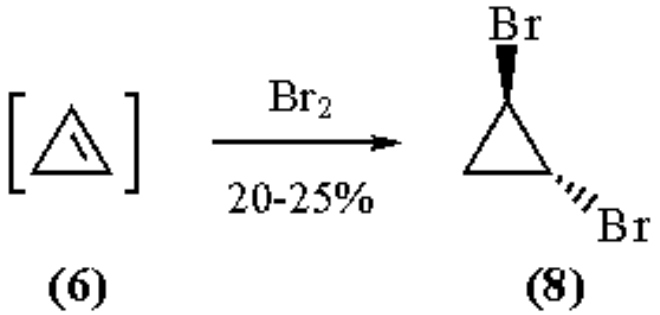

(5)

Solvolytic Ring Opening.[4]

Treatment of (**1**) with ***Sodium Ethoxide***/EtOH gives 3,3-diethoxy-1-propyne (**9**) (eq 6). When ***Potassium Fluoride*** is used as a base, 1,1,3-triethoxy-2-bromopropane (**10**) is the product (eq 7).

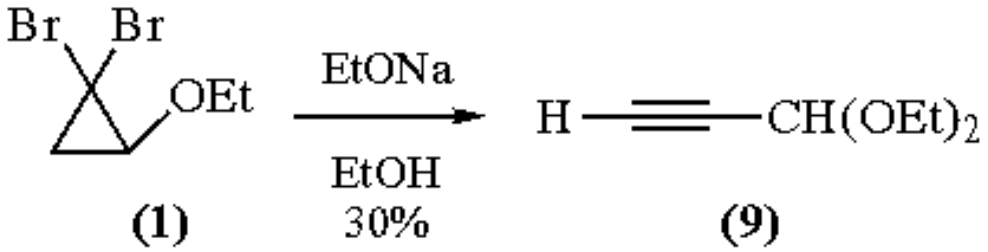

(6)

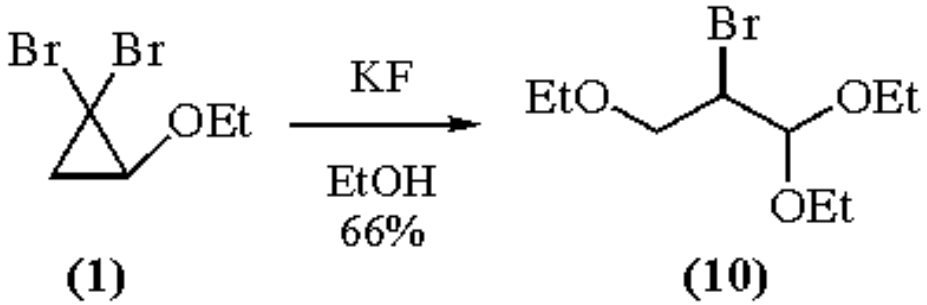

(7)

The 1-substituted cyclopropanes (**11**) undergo solvolysis in ethanol/***Potassium Carbonate*** to give 2-substituted 3,3-diethoxy-1-propene derivatives (**12**), which upon hydrolysis afford α-substituted acroleins (**13**) (eq 8). Thus the carbenoid reagent (**2**) is a synthetic equivalent of acrolein α-anion. This method is applied to the synthesis of β-sinensal (eq 9) and juvenile hormone JH-II.[5]

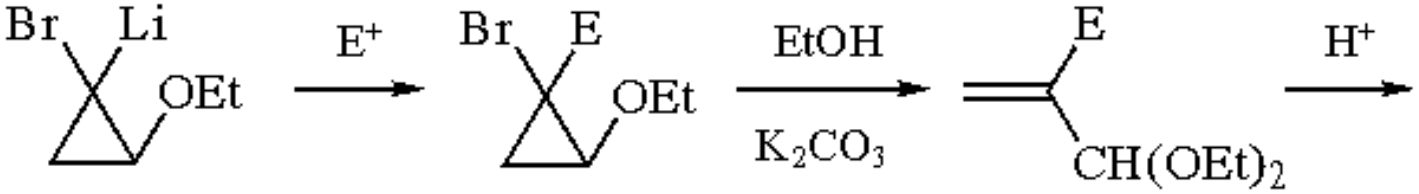

(2) **(11)** **(12)**

E = H, Br, TMS, SPh
n-HexCH(OH)-

74-93% from **(2)**

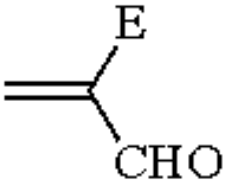

(8)

(13)
80-100%

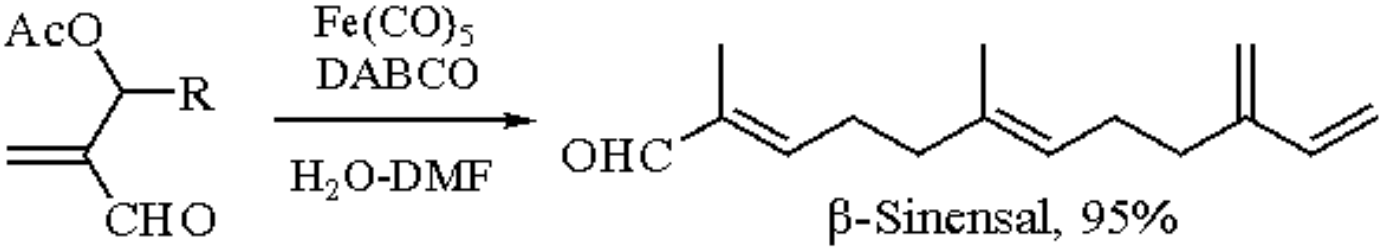

(9)

β-Sinensal, 95%

64% from **(1)**

R = $CH_2{=}CHC({=}CH_2)(CH_2)_2CH{=}C(Me)(CH_2)_2$

In ethanol containing ***Boron Trifluoride Etherate***, (**11**) are converted into 3-substituted 3-bromo-1,1-diethoxypropanes (**14**), which are used in the synthesis of jasmones (eq 10).[5]

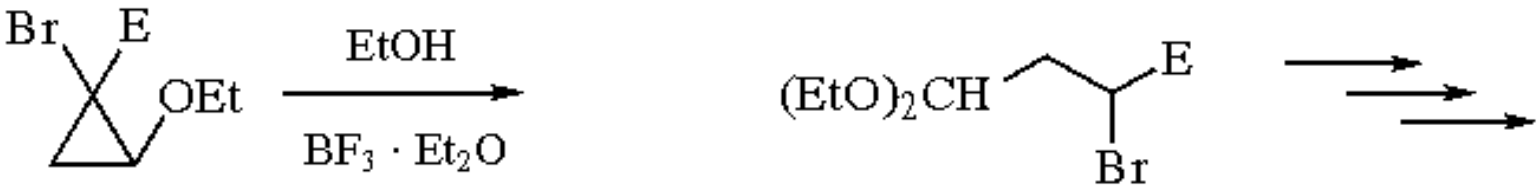

(11)

(14a) E = *n*-HexC(O), 74%
(14b) E = *(Z)*-EtCH=CHCH$_2$CH$_2$C(O), 77%

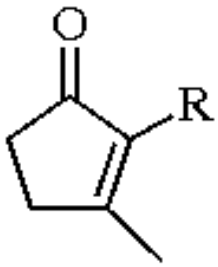

(10)

R = C_5H_{11} Dihydrojasmone
R = *(Z)*-EtCH=CHCH$_2$ *cis*-Jasmone

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1,3-Dibromoisocyanuric Acid

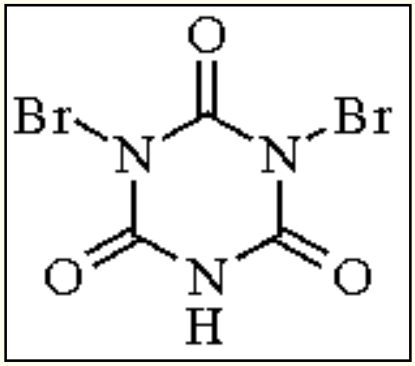

[15114-43-9] · $C_3HBr_2N_3O_3$ · 1,3-Dibromoisocyanuric Acid · (MW 286.87)

(electrophilic bromination of aromatic compounds, oximes)

Alternate Name: DBI.

Solubility: sol CH_2Cl_2, H_2SO_4.

Preparative Method: dibromoisocyanuric acid has been prepared by treatment of isocyanuric acid (0.1 mol) and LiOH (0.2 mol) with Br_2 (0.4 mol) in water (1 L) at 20 °C.[1] After vigorous stirring to effect dissolution of Br_2, the mixture is cooled slowly in a refrigerator for 24 h. The product is collected by filtration, washed with ice-cold bromine water, and then dried in vacuo, first over KOH, then over P_2O_5 (88% yield).

Handling, Storage, and Precautions: dibromoisocyanuric acid should be stored refrigerated and protected from light and moisture to avoid decomposition. DBI is an irritating solid and precautions should be taken to avoid inhalation of the powder or contact with skin.

Bromination of Aromatic Compounds.

Dibromoisocyanuric acid is reputed to be the most powerful reagent known for the electrophilic bromination of aromatic compounds. Nitrobenzene, which is brominated using ***Bromine***/Fe or ***N-Bromosuccinimide***/50% H_2SO_4 only at elevated temperatures, is converted to the *m*-bromo derivative (88% yield) upon reaction with DBI in conc. H_2SO_4 in 5 min at 20 °C. Similarly, *m*-dinitrobenzene, benzoic acid,

acetophenone, and trifluoroacetophenone (eq 1)[2] are all smoothly converted to the expected monobromides by reaction with 0.5 equiv of DBI in conc. H_2SO_4 at rt.[1] Due to the mild conditions of the reaction, alkyl groups attached to the aromatic ring are not affected (eq 2).[3] Furthermore, perbrominations of a variety of aromatic compounds may be achieved under more forcing conditions (eq 3).[4]

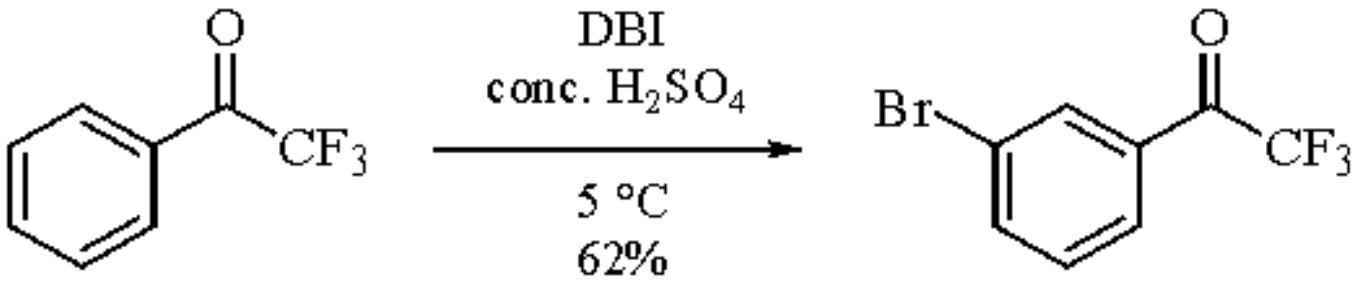

(1)

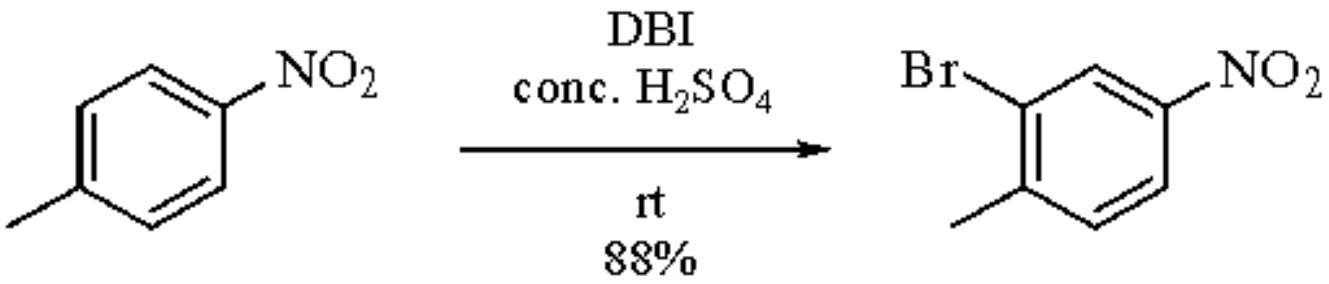

(2)

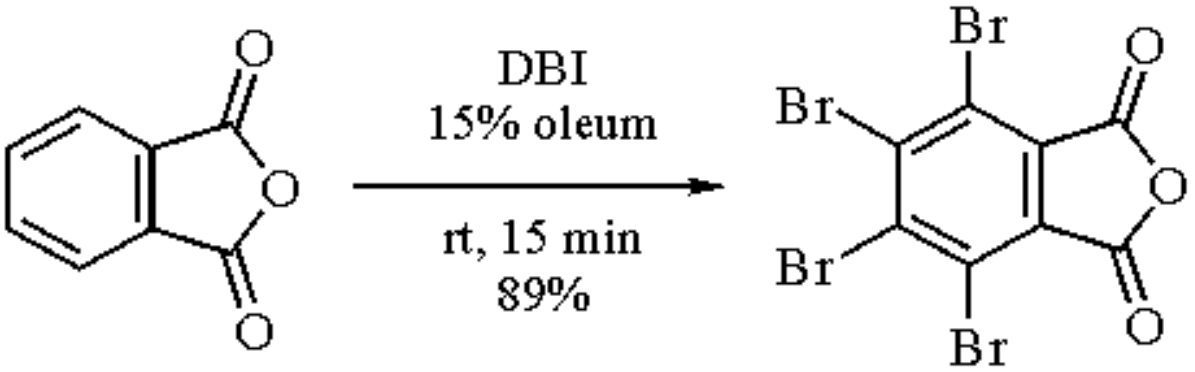

(3)

Bromination of Oximes and Preparation of Azoxy Compounds.

Reaction of oximes with DBI and $NaHCO_3$ in aqueous dioxane affords acceptable yields of the geminal bromonitro compounds (eq 4). The higher reactivity of DBI effects in situ oxidation of the bromonitroso intermediate to the bromonitro compound, in contrast to the reagents NBS and DBH (***1,3-Dibromo-5,5-dimethylhydantoin***) which require supplemental oxidation with ***Ozone***.[5] In the presence of amines as well as cyanamide and *O,O*-diethyl amidophosphate (eq 5), oxidative coupling of *C*-nitroso compounds by DBI leads to the formation of the corresponding azoxy compounds.[6]

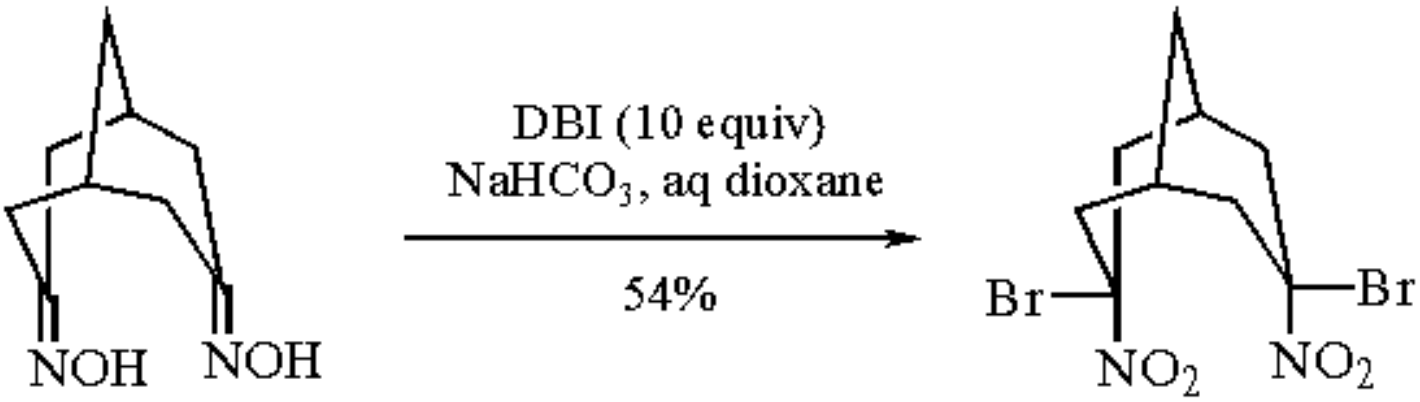

(4)

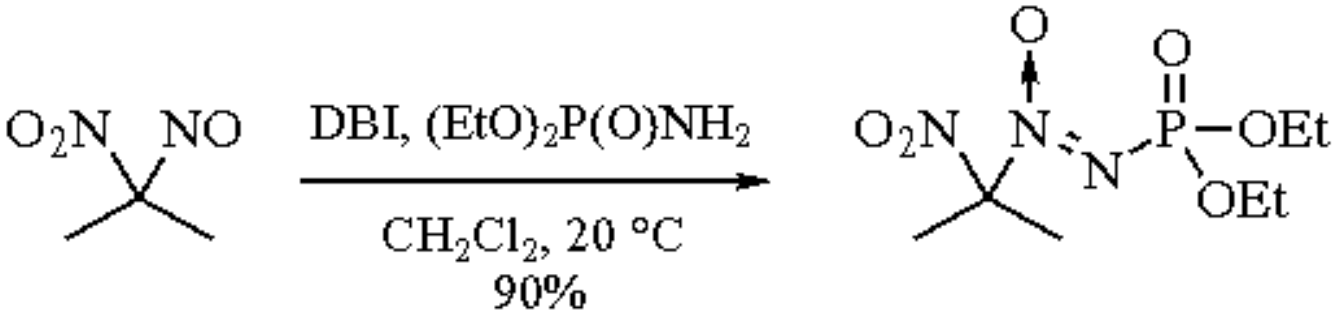

(5)

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Dibromomethane

CH_2Br_2

[74-95-3] · CH_2Br_2 · Dibromomethane · (MW 173.83)

(converts diols to cyclic methylene acetals;[1] reagent with Zn and $TiCl_4$ converts C=O to C=CH_2;[2,3] with Zn, cyclopropanates alkenes[4])

Alternate Name: methylene bromide.

Physical Data: mp -52.7 °C;[5] bp 96.95 °C;[6] *d*204 2.4921,[7] 2.496 g cm^{-3};[8] *n*20D 1.53559,[7] 1.5419.[8]

Solubility: sol water: 11.70 g L^{-1} (15 °C); 11.93 g L^{-1} (30 °C).[9]

Form Supplied in: commercially available.

Preparative Method: patents suggest manufacture from CH_2Cl_2 and HBr[10] or NaBr.[11]

Handling, Storage, and Precautions: toxicity hazard greater than CH_2Cl_2, less than CH_2I_2 or most alkyl bromides. Absorbed through skin;[12] mutagenic in Ames test[13] but not in assay in *Drosophila* because it kills the flies (LC_{50} 120 mg m^{-3} in air);[14] not hepatotoxic in mice ($CHCl_3$ is);[15] should be handled in a fume hood with the usual protective gloves and clothing.

General Behavior toward Nucleophiles.

The reactivity of dibromomethane toward nucleophiles is generally less than that of ordinary alkyl bromides, and falls between diiodomethane and dichloromethane. For example, toward PhSNa in MeOH, rates (10^4 *k*, s^{-1}, per C-X bond) at 0 °C are EtBr, 3.79; CH_2I_2, 1.19; CH_2Br_2 0.08; CH_2Cl_2, 0.0013 (extrapolated).[16] Toward NaI in acetone, rates (10^5 *k*, s^{-1}) at 50 °C are EtBr, 1700; CH_2Br_2, 69; CH_2Cl_2 0.2.[17] Accordingly, nucleophilic substitutions that are unsatisfactory with CH_2Cl_2 may proceed at useful rates with CH_2Br_2, which is much cheaper than CH_2I_2. Monosubstitution products of CH_2Br_2 are usually more reactive toward nucleophiles than CH_2Br_2 itself, and the net result is that disubstitution generally occurs unless the substituent is sufficiently branched to provide steric hindrance. Alkoxy substituents greatly accelerate the second substitution and make it impossible to isolate any monosubstitution product.[18]

For substitutions where the reactivity of CH_2Br_2 or CH_2I_2 is insufficient, it should be possible to use methylene ditosylate or methylene chlorotosylate,[18] though the reactions of these promising new reagents have not been

extensively studied yet.

Methylene Acetals.

Dibromomethane is particularly useful for making methylene acetals because the reaction is irreversible. Thus not only the usual *cis*-fused acetals but also the less stable *trans*-fused acetals can be made from carbohydrates (eq 1).[1] The basic phase transfer conditions are mild and compatible with much other functionality.

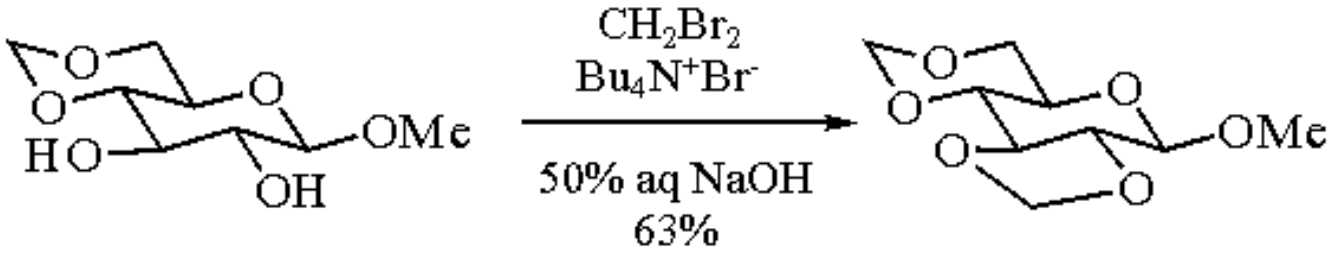

(1)

Similar reactions have been carried out with DMSO as solvent (eq 2).[19]

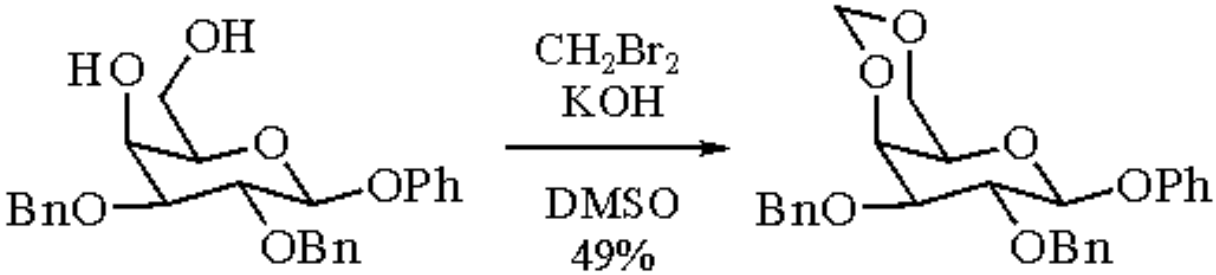

(2)

Analogous reactions with an alkyltrimethylammonium phase transfer catalyst provide methylene acetals of catechols (eq 3)[20] and monothioacetals of mercaptophenols (eq 4).[21]

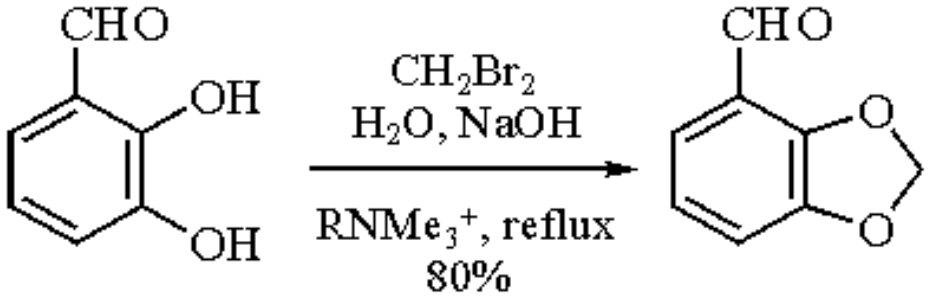

(3)

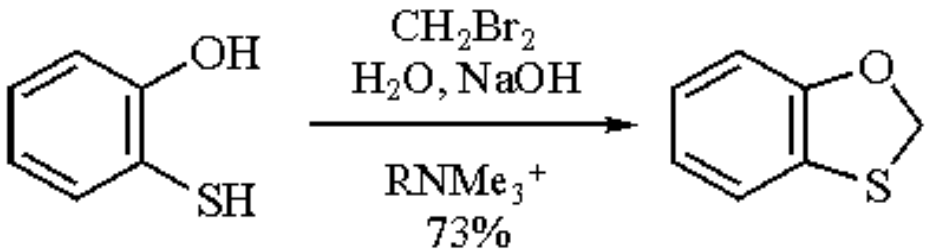

(4)

Reaction of phenol (PhOH) with CH_2Br_2, aqueous base, and a phase transfer catalyst ($Bu_4N^+X^-$) yields the methylene

acetal $CH_2(OPh)_2$ (90%).[22] Benzoic acid with NaOH and CH_2Br_2 in HMPA yields $CH_2(O_2CPh)_2$ (86%).[23]

Bromomethylation of Carbanions.

Enolates often provide sufficient steric hindrance to allow bromomethylation rather than disubstitution of CH_2Br_2. Recent and typical examples include a cyclobutanecarboxylic ester (eq 5)[24] and a tetralonecarboxylic ester (eq 6).[25]

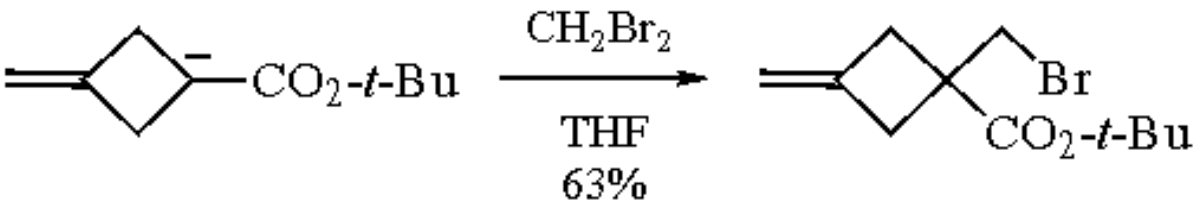

(5)

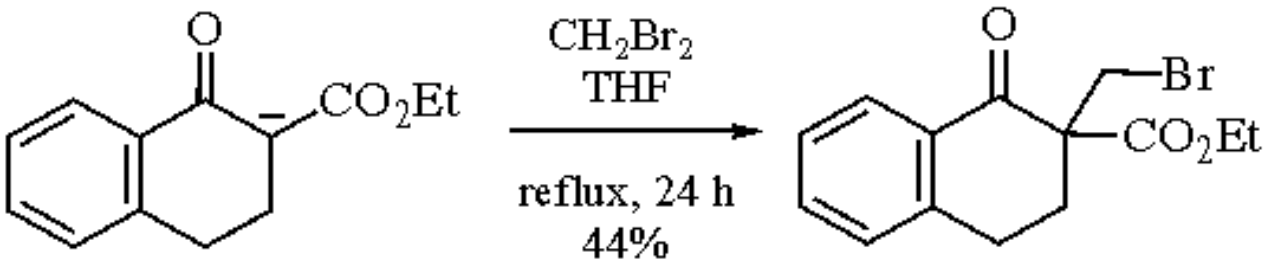

(6)

Bromomethylation of a chiral lithiated heterocycle provides intermediates useful in the asymmetric synthesis of unusual amino acids (eq 7).[26] Diastereomeric excesses were 84-95%.

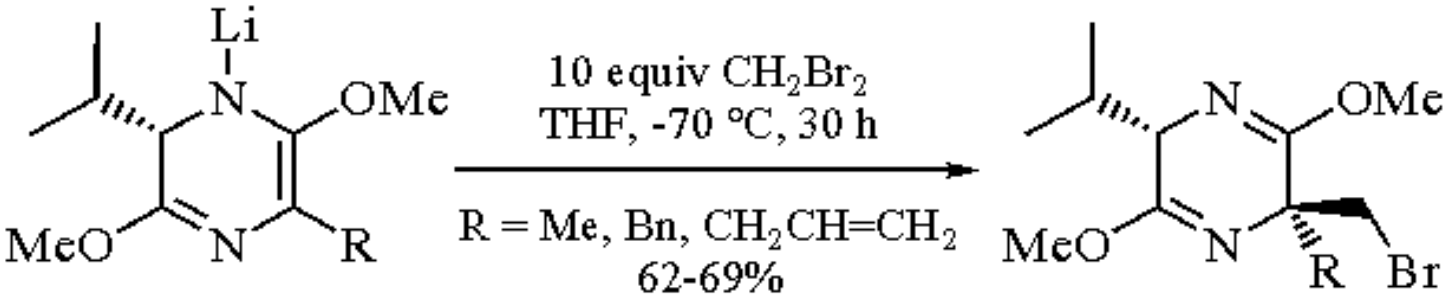

(7)

Cross coupling of ArMgBr with CH_2Br_2 in the presence of ***Copper(I) Bromide*** has yielded $ArCH_2Ar$ (60-90%).[27]

Methylenation of Carbonyls.

A remarkably mild and effective reagent for converting C=O to $C{=}CH_2$ is obtained by reaction of dibromomethane with Zn and $TiCl_4$ in THF (see ***Dibromomethane-Zinc-Titanium(IV) Chloride***).[2] Steric factors are minimal, and camphor was converted to the methylene derivative (92%).[2] The reagent is particularly useful because it does not enolize ketones, and for example reacted with a gibberellin-related intermediate to produce the methylene derivative (eq 8) where the normal Wittig reagent yielded mainly epimerized product.[28]

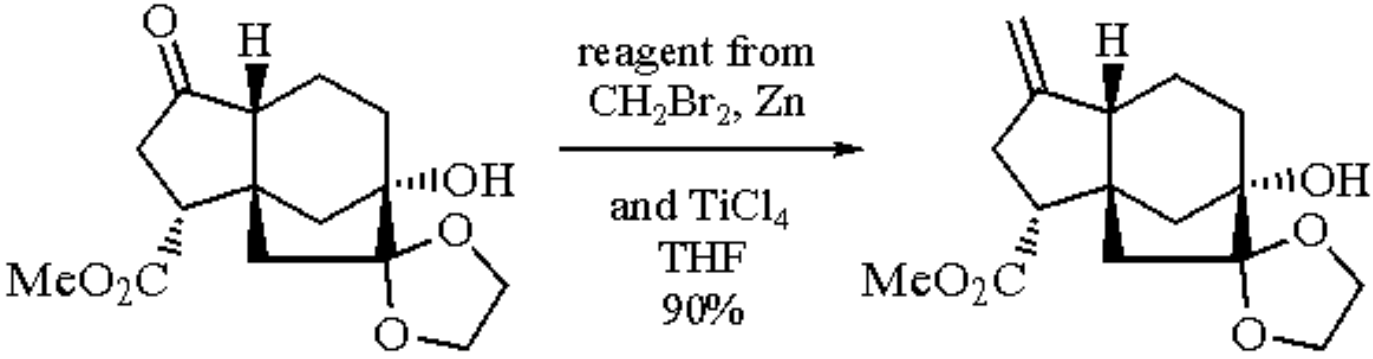

(8)

An *Organic Syntheses* procedure for the use of the CH_2Br_2-Zn-$TiCl_4$ reagent with (+)-isomenthone (eq 9) has been published.[3] It has been found best to add the $TiCl_4$ to the zinc and CH_2Br_2 in THF at -40 °C, then stir 3 days at 5 °C before use.

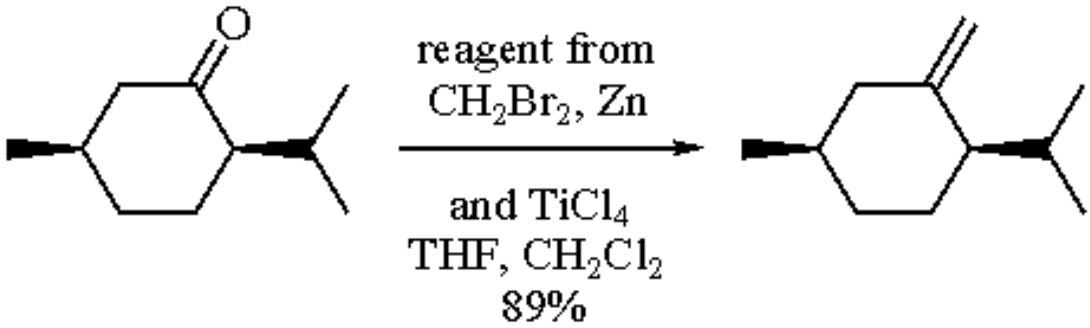

(9)

Other examples that illustrate the utility of this reagent include methylene-substituted nucleosides (eq 10)[29] and an intermediate for chiral synthesis derived from glucose (eq 11).[30]

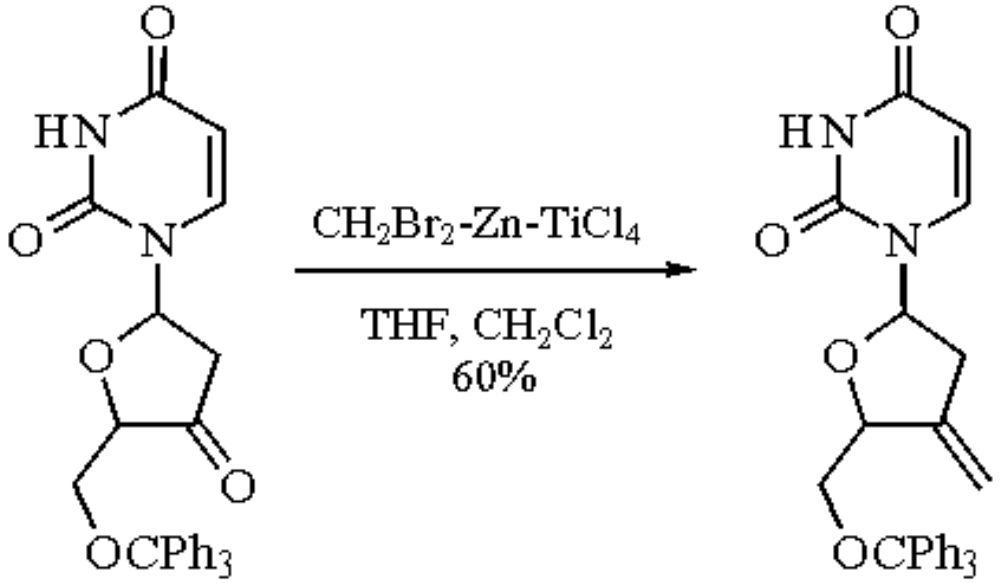

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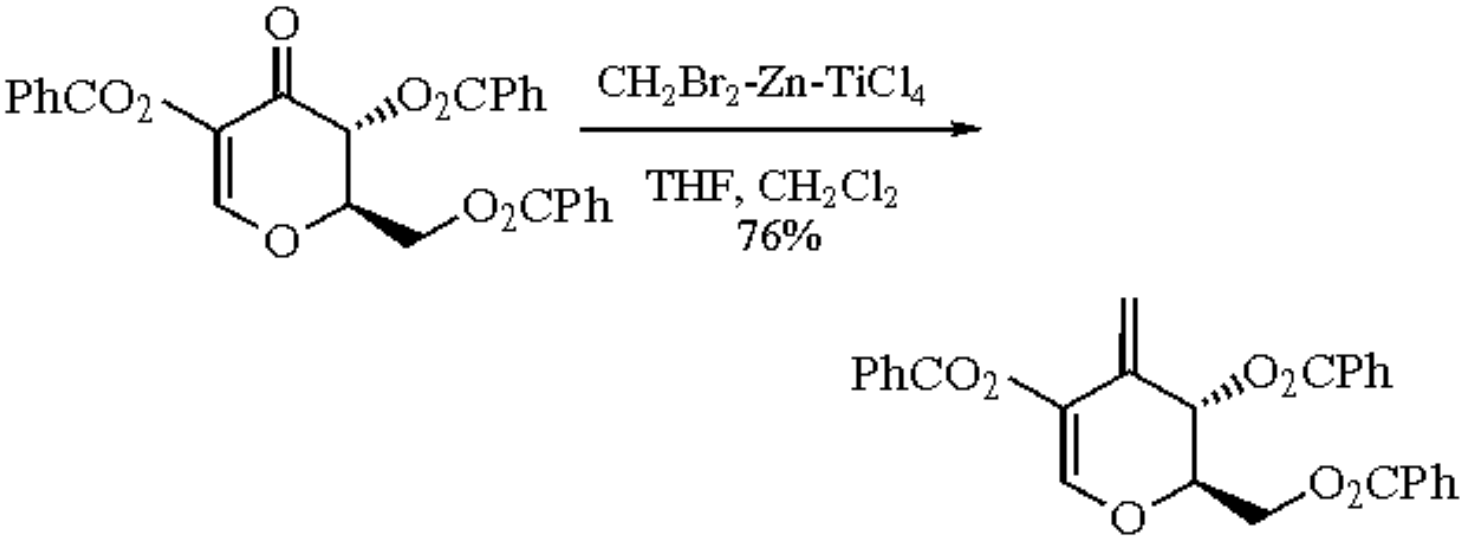

(11)

A related reagent from CH_2Br_2, Zn, and ***Dichlorobis(cyclopentadienyl)zirconium*** has been reported, though at the present stage of development it does not give as high yields.[31]

An earlier alternative for the methylenation of ketones was methylenebis(magnesium bromide), $CH_2(MgBr)_2$, or the corresponding iodide.[32] However, this reagent is difficult to prepare, requiring magnesium amalgam, and offers no advantage. It does have some use in the preparation of other methylenedimetallic compounds.[33]

Cyclopropanations.

Dibromomethane can be used in place of ***Diiodomethane*** in the Simmons-Smith cyclopropanation process. (Bromomethyl)zinc bromide is presumably the active intermediate. In order to obtain satisfactory yields, a number of processes for activating the zinc metal have been tested. The best activator in addition to ***Copper(I) Chloride*** now appears to be a small amount of ***Acetyl Chloride***, and previous methods have been declared obsolete.[4] Typical results are illustrated in eqs 12 and 13.

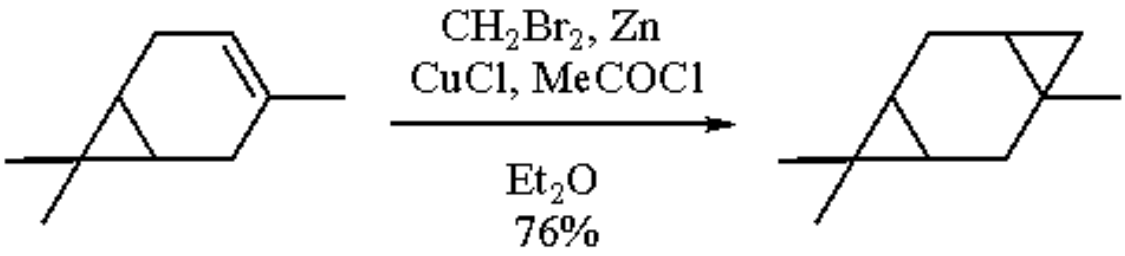

(12)

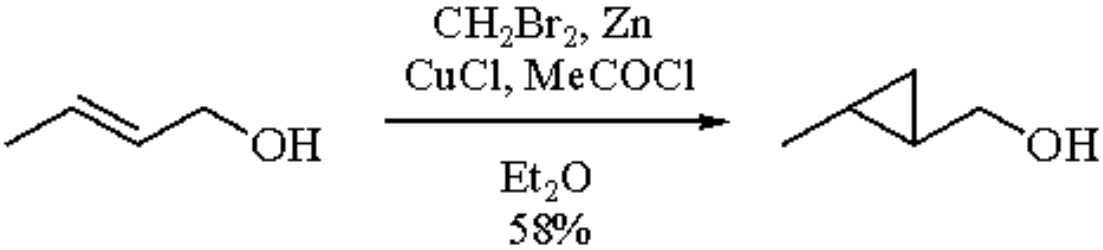

(13)

Previously tested methods of activating the zinc included ultrasound[34] and ***Titanium(IV) Chloride***.[35] Electrolytic

activation using a zinc anode has also proved successful,[36] though it appears to offer no significant advantage over less cumbersome methods.

Bromocarbene can be generated by treatment of CH_2Br_2 with ***Sodium Hexamethyldisilazide***, and converts alkenes to bromocyclopropanes in yields ~40%.[37] Bromochlorocarbene has been generated by treatment of CH_2Br_2 with $PhCCl_3$ and 60% aqueous KOH in the presence of the phase transfer catalyst Bu_4N^+, and converts alkenes in situ to bromochlorocyclopropanes (45-75%).[38]

Related Reagents.

Bromomethyllithium; ***Chloroiodomethane***; ***Dibromomethane-Zinc-Titanium(IV) Chloride***; ***Dibromomethyllithium***; ***Diiodomethane***; ***Iodomethylzinc Iodide***.

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Dibromomethane-Zinc/Copper Couple[1]

CH_2Br_2-Zn/Cu

(CH_2Br_2)

[74-95-3] · CH_2Br_2 · Dibromomethane-Zinc/Copper Couple · (MW 173.83) (Zn)

[7440-66-6] · Zn · Dibromomethane-Zinc/Copper Couple · (MW 65.39)

(reagent combination for cyclopropanations)

Alternate Name: bromomethylzinc bromide.

Physical Data: CH_2Br_2: mp -52 °C; bp 96-98 °C; *d* 2.477 g cm^{-3}. Zn: mp 419.5 °C; *d* 7.140 g cm^{-3}.

Solubility: sol Et_2O, THF.

Preparative Methods: the original method for the preparation of a ***Zinc/Copper Couple*** that will react with ***Dibromomethane*** calls for the formal preparation of the Zn/Cu couple from 30-mesh granular ***Zinc*** instead of zinc dust.[2] In this procedure, 35 g of granular zinc (30 mesh) is added to a hot solution of 50 mL of acetic acid containing 0.5 g of $CuOAc.H_2O$ (see ***Copper(I) Acetate***). The mixture is kept hot and shaken for 1-3 min. The acetic acid is carefully decanted from the couple. The couple is then washed with 50 mL of acetic acid and three 50 mL portions of Et_2O. The couple is shaken for 1 min with each washing. The Et_2O moistened couple is ready for use or can be dried with a stream of nitrogen. More recently a number of different methods for activation of the Zn/Cu couple have appeared. These newer modifications include the use of ultrasound[3] or catalytic amounts of ***Titanium(IV) Chloride***[4] or ***Acetyl Chloride***.[5] They require no prior preparation of the couple. The couple is prepared in situ by reaction of zinc dust and ***Copper(I) Chloride***.[6] The method of choice appears to be the acetyl chloride method.

Handling, Storage, and Precautions: CH_2Br_2 is toxic. Zn is a moisture-sensitive, flammable solid. When the reactions are complete, the reaction mixture is filtered from the zinc residue. It is recommended that the residue be wetted with water prior to disposal.

Cyclopropanations.

The use of CH_2Br_2 in place of the more commonly employed ***Diiodomethane*** in the cyclopropanation of an alkene[1] has the advantages that it is less expensive and more stable. It has not been used as extensively because of the lower reactivity of the dibromide with the various forms of the Zn/Cu couple. The first reported form of a Zn/Cu couple that would react effectively with the dibromide was made from granular zinc.[2] It suffered from long reaction times and lower yields in

comparison with the diiodomethane derived reagent. It was found that sonication could be used to effect cyclopropanations of alkenes with dibromomethane[3] and an in situ generated Zn/Cu couple prepared from Zn dust and CuCl.[6] The ultrasound method, however, suffered from irreproducibility. A more convenient method for activation involves the use of a catalytic amount (2 mol %) of $TiCl_4$. The use of more than 2% $TiCl_4$ results in unmanageable reactions. Activation of the couple with $TiCl_4$ is also effective when using diiodomethane. In either the dibromo- or diiodomethane reactions there is a competing formation of ethylene. This problem is greater for dibromomethane than for diiodomethane. The only drawback in the titanium mediated procedure is that it is not always tolerant of Lewis acid sensitive groups.[4] Acetyl chloride has been found to activate the Zn/Cu couple as well as $TiCl_4$ and has the advantage that Lewis acid sensitive groups are tolerated. This now appears to be the method of choice.[5] Table 1 shows the results[3-11] of some representative alkenes under some of the different cyclopropanation conditions. When the difference in yield between the diiodo and dibromo conditions are minimal and the alkene is not the limiting reagent, the dibromomethane conditions offer an inexpensive alternative. The somewhat lower yields obtained are offset by the cost savings.

Table 1 Comparison of Cyclopropanation Conditions for Various Alkenes

	Yield (%)					
	CH_2I_2 Zn/Cu	CH_2I_2 Zn/Cu $TiCl_4$[4]	CH_2Br_2 Zn/Cu	CH_2Br_2 Zn/Cu ultrasound[3]	CH_2Br_2 Zn/Cu $TiCl_4$[4]	CH_2Br_2 Zn/Cu AcCl[5]
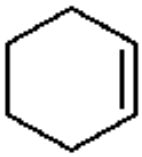	92[6]	69	61[2]	60	58	61
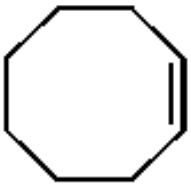	94[6]	90	56[2]	72	73	88
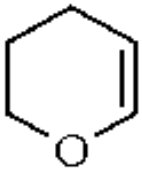	65[7]	<2	-	41	17	45
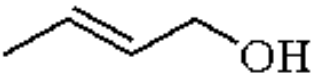	52[8]	42	68[11]	57	36	58
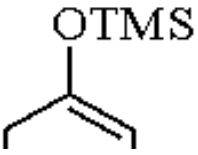	65[9]					60

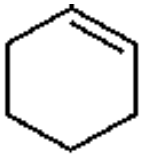	65[9]	-	-	-	-	60
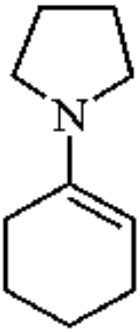	8[10]	-	-	-	-	22

The regioselectivity of the reagent in its reactions with limonene (eq 1) and 4-vinylcyclohexene (eq 2) has been studied. Using a ratio of diene:CH_2Br_2:Zn of 1:1:1.5, the major product of the reaction was recovered diene (47%). The monocyclopropanated products were isolated in ~28% yield with a 2.5:1.0 ratio of exocyclic cyclopropane:ring cyclopropane. There was little stereoselectivity observed in ring cyclopropanated products, with a 1:1.1 ratio of *cis* and *trans* isomers being produced. A small (4%) amount of biscyclopropanation was obtained under these conditions. If the diene:CH_2Br_2:Zn ratio was changed to 1:2:3, the amount of recovered diene decreases but the amount of biscyclopropane increased. For 4-vinylcyclohexene with the 1:1:1.5 ratio, the ring cyclopropane was favored over the exocyclic cyclopropane by 1.75:1. The combined yield of these two products is again low (~7%). The major product was recovered diene (53%).[12]

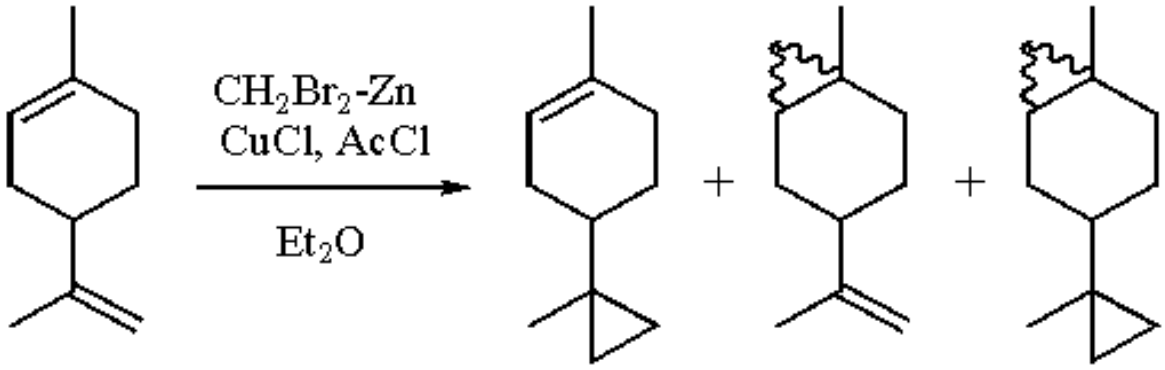

(1)

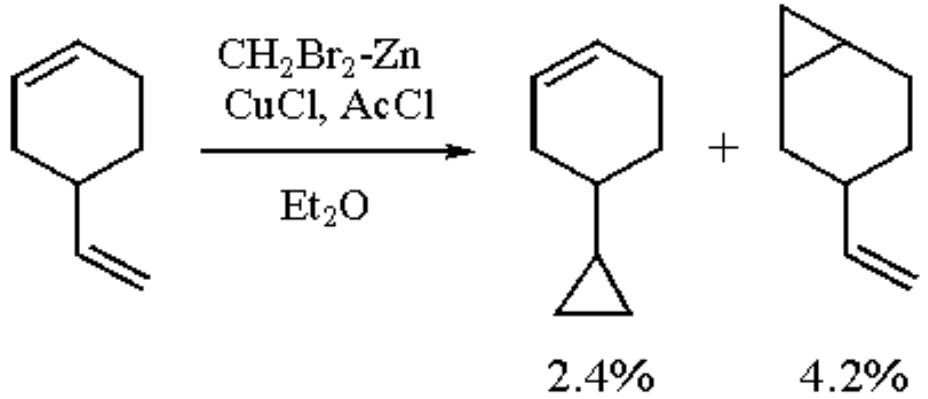

(2)

Miscellaneous.

Reaction of ***Triethylsilane*** with dibromomethane and Zn/Cu couple results in an insertion of methylene into the Si-H bond. The reaction with triethylsilane (eq 3) produces triethylmethylsilane. The reaction with diiodomethane produces the insertion product in 64% yield.[13]

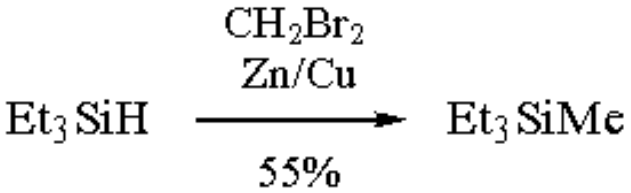

(3)

The ^{1}H and ^{13}C NMR data for bromomethylzinc bromide and bis(bromomethyl)zinc have been reported.[14]

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Dibromomethane-Zinc-Titanium(IV) Chloride[1]

CH_2Br_2-Zn-$TiCl_4$

(CH_2Br_2)

[74-95-3] · CH_2Br_2 · Dibromomethane-Zinc-Titanium(IV) Chloride · (MW 173.83) (Zn)

[7440-66-6] · Zn · Dibromomethane-Zinc-Titanium(IV) Chloride · (MW 65.39) ($TiCl_4$)

[7550-45-0] · Cl_4Ti · Dibromomethane-Zinc-Titanium(IV) Chloride · (MW 189.69)

(reagent for the methylenation of ketones[1-5] and aldehydes;[1] it methylenates highly enolizable[1,4,6] and sterically hindered ketones;[1] it selectively methylenates ketones and aldehydes in the presence of esters, while some variations allow the chemoselective methylenation of aldehydes and ketones;[7] in combination with TMEDA it methylenates esters and lactones;[1] similar reagents made from other 1,1-dibromoalkanes allow the alkylidenation of esters,[8] lactones,[8] silyl enol esters,[9] thioesters,[10] and amides[10])

Alternate Name: Lombardo's reagent.

Solubility: partially sol solvents usually used for the reaction (THF and CH_2Cl_2).

Form Supplied in: not available commercially.

Preparative Methods: Oshima method:[2,3] a suspension of ***Zinc*** dust (4.5 equiv) and ***Dibromomethane*** (1.5 equiv) in dry THF, stirred under N_2 at rt, is treated with a 1.0 M solution of ***Titanium(IV) Chloride*** (1.1 equiv) in CH_2Cl_2. After 15 min the resulting dark brown mixture is treated dropwise with a solution of the ketone (1 equiv) in dry THF, and the mixture is stirred at rt for 4-40 h. *Lombardo's reagent*:[4,5] to a suspension of Zn dust (4.3 equiv) and CH_2Br_2 (1.4 equiv) in dry THF, stirred under N_2 at -40 °C, is added dropwise neat $TiCl_4$. The mixture is then allowed to warm to 5 °C and is stirred for 1-3 days to produce a thick gray slurry of the active reagent. The cold slurry is added to a solution of the ketone in CH_2Cl_2 or THF. Usually, the reaction is complete within a few minutes.

Handling, Storage, and Precautions: moisture sensitive; decomposes at rt. Lombardo's reagent may be stored at -20 °C up to a year with only 5-10% loss of reactivity.

Methods for Carbonyl Methylenation.

The methylenation of aldehydes and ketones is often performed with the Wittig reagent, CH_2=PPh_3 (see ***Bis(cyclopentadienyl)dimethyltitanium***), or by the addition of other P-, Si-, or S-stabilized methylene anions.[11] As a result of the inherent basicity of these reagents, however, several limitations exist for their synthetic utility. Among the major drawbacks of the Wittig-type alkenation methods is their inability to alkenate readily enolizable carbonyls or substrates that undergo facile nucleophilic addition or elimination reactions. Furthermore, sterically hindered substrates are often methylenated only in low yields, while the alkenation of esters and lactones is usually not possible with these methods. Several alternative methylenation procedures have been developed that avoid most of the problems encountered with Wittig-type processes. Among these, the Tebbe reagent (see ***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***)[1,12] has been used for the methylenation of a variety of carbonyls, including aldehydes, enolizable ketones, esters, and lactones. This reagent, however, is not suitable for highly acid-labile substrates and requires strenuous inert-atmosphere techniques due to its high sensitivity to air and water. An experimentally convenient alternative to the Tebbe reagent is dimethyltitanocene (see ***Bis(cyclopentadienyl)dimethyltitanium***)[13] which is easier to prepare and handle and is suitable for the methylenation of both ketone and ester carbonyls, including highly enolizable and acid-labile substrates. Another widely used carbonyl methylenation procedure is the combination of CH_2Br_2-Zn-$TiCl_4$, which was first reported by Oshima,[2,3] and later modified by Lombardo[4,5] and Takai.[6,7]

According to the initial procedure,[2,3] a suspension of ***Zinc*** dust and ***Dibromomethane*** in THF are reacted with a solution of ***Titanium(IV) Chloride*** in CH_2Cl_2; after stirring for 15 min the dark brown mixture is combined with the carbonyl substrate in CH_2Cl_2 or THF. In this manner the completion of the methylenation reaction often requires prolonged stirring at rt. This in situ procedure is most effective for the methylenation of ketones and is less effective with aryl ketones and aldehydes, which undergo a competing pinacol-type reductive coupling.

Lombardo[4,5] found that prior low temperature aging of the CH_2Br_2-Zn-$TiCl_4$ system, which presumably alters the composition of the reagent, significantly speeds up the methylenation process and limits the exposure of the carbonyl substrate to Zn and $TiCl_4$. This methodology leads to increased methylenation yields and suppressed side reactions. The use of CD_2Br_2 or $^{13}CH_2Br_2$ in these reactions allows the incorporation of D or ^{13}C into the substrate.

Takai[6] has reported that a more reactive system consisting of ***Diiodomethane-Zinc-Titanium(IV) Chloride*** is very effective for the methylenation of highly enolizable ketones. Two other variations, CH_2I_2-Zn-Ti(O-*i*-Pr)$_4$ and CH_2I_2-Zn-Me_3Al, allow the chemoselective methylenation of aldehydes in the presence of ketones.[7]

Methylenation of Ketones.

The Oshima procedure effectively methylenates a variety of ketones which, under the usual Wittig conditions, are unreactive or give much lower yields. The presence of carboxylic ester groups, which often interfere with the Wittig methylenation of ketones, do not present such problems with this methylenation process. A similar advantage can exist over the use of the Tebbe reagent which also alkenates the ester functionality.[14] Due to the nonbasic conditions, this method is suitable for substrates that undergo facile enolization, such as β,γ-unsaturated ketones (eq 1)[15] and cyclopentanones (eq 2).[14]

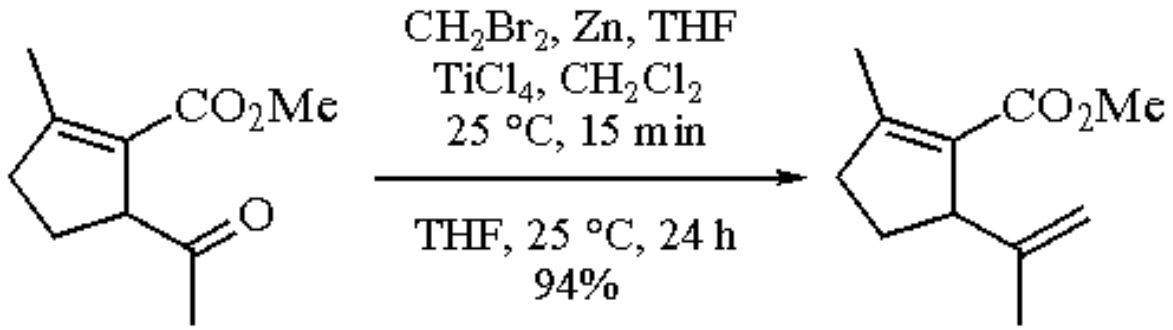

(1)

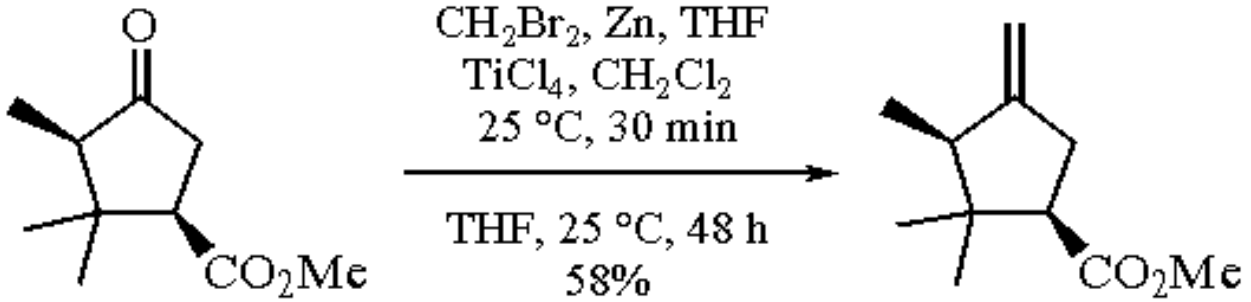

(2)

Lombardo's reagent is often the best choice for the methylenation of base-sensitive ketones. This system has been employed extensively in the synthesis of gibberellins[4,16,17] and related compounds. Although this type of bridged ketone is susceptible to enolization and epimerization, the desired alkenes are obtained in high yield without any loss of stereochemistry (eqs 3 and 4).[4,17] Free hydroxy and carboxylic acid groups are also tolerated by this reagent.

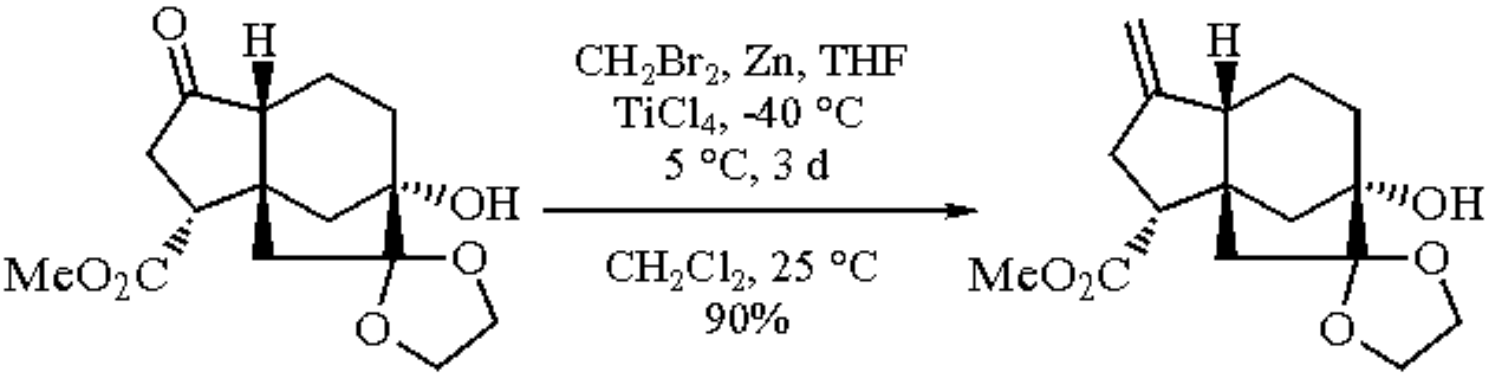

(3)

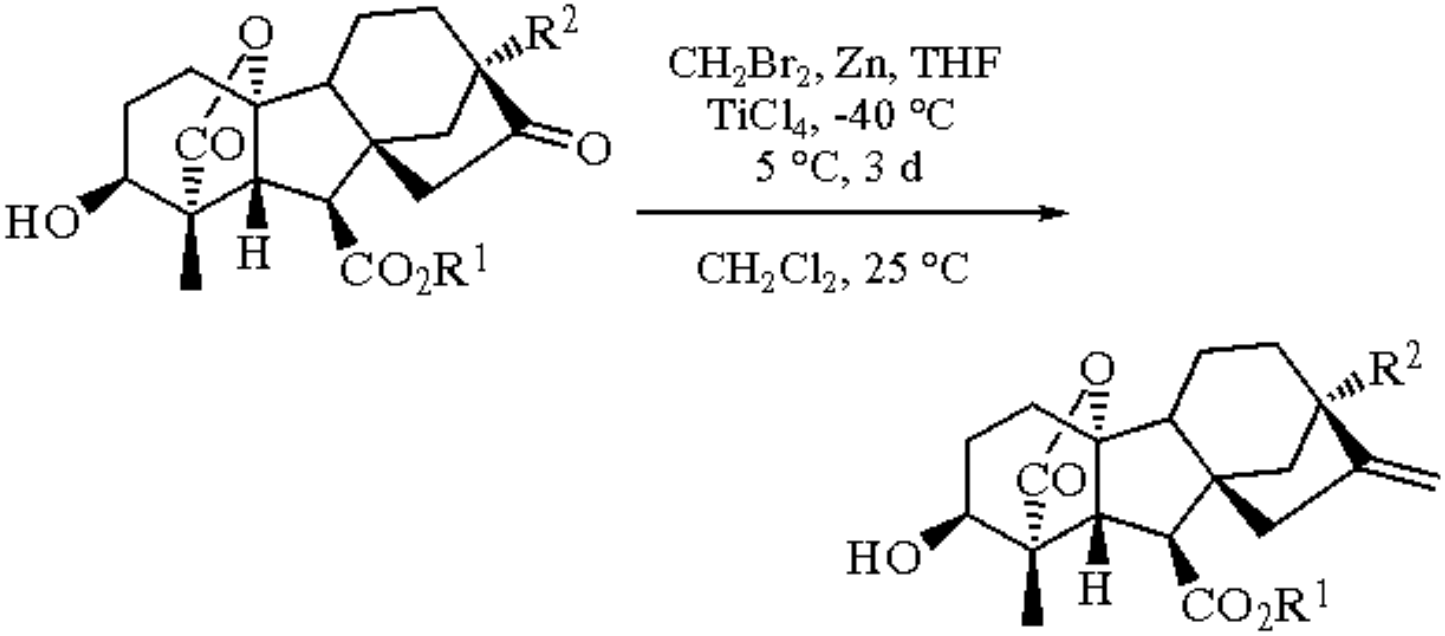

(4)

R^1	R^2	
Me	H	93%
H	H	80%
Me	OH	38%

This methylenation method proceeds without enolization of the carbonyl group, even in cases where this is a very facile process. For example, while Wittig-type methodologies often fail completely with β,γ-unsaturated ketones, the use of Lombardo's reagent gives excellent yields of the corresponding alkenes (eqs 5 and 6).[18,19]

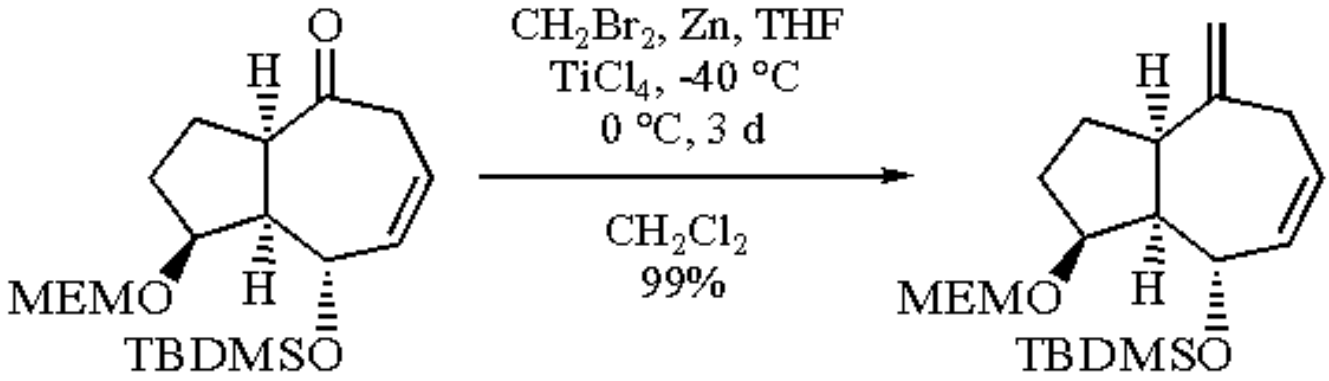

(5)

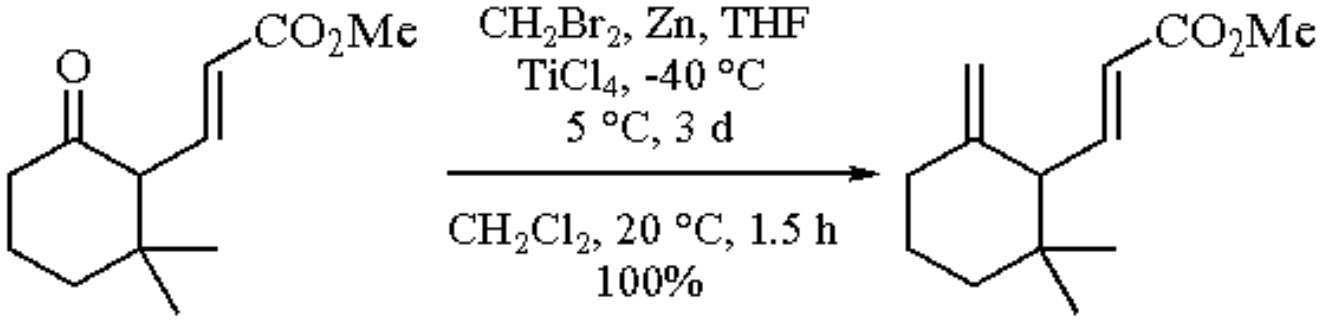

(6)

This reagent has been used widely in prostaglandin synthesis. A variety of cyclopentanones bearing the usual protective groups were successfully methylenated without epimerization or elimination of the β-silyloxy (eq 7)[20] or even β-acyloxy functionalities (eq 8).[21]

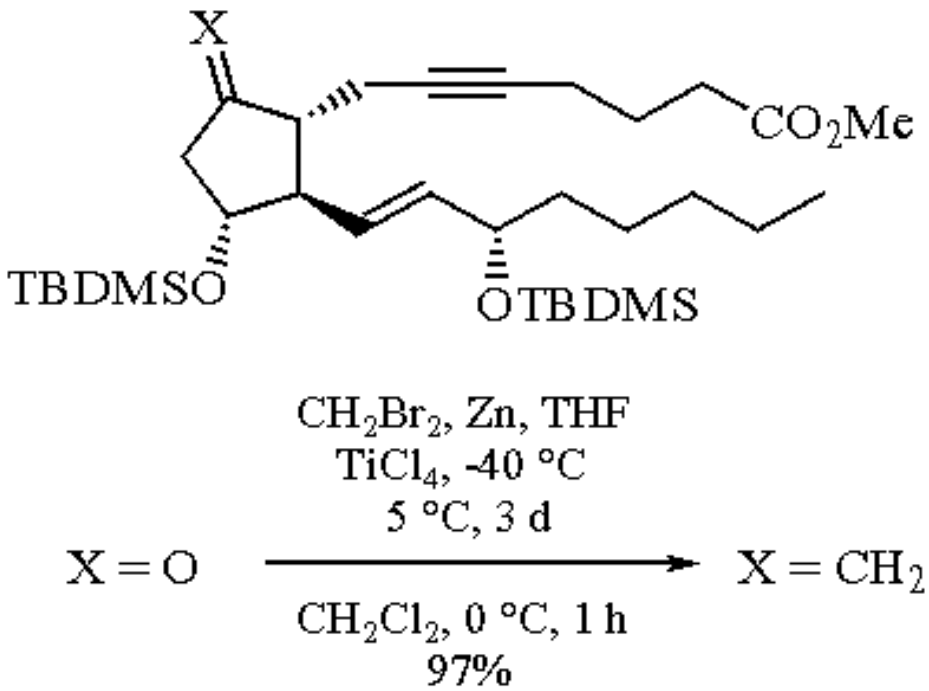

(7)

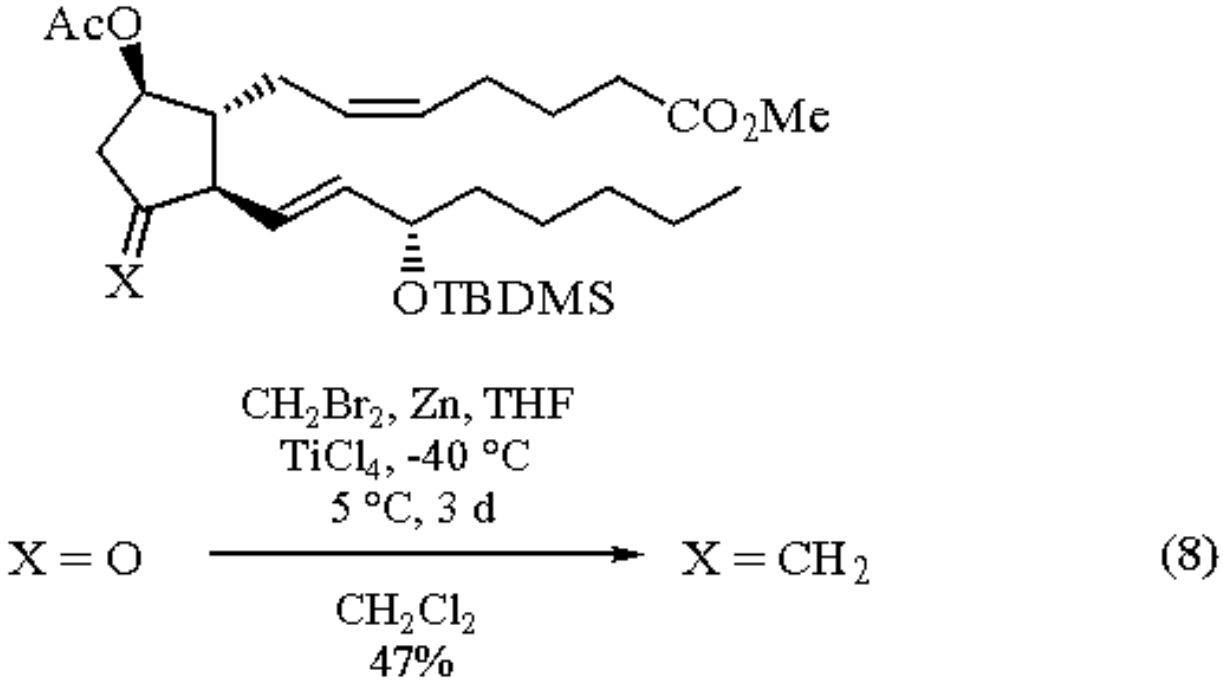

(8)

β-Acyloxy ketones are methylenated more efficiently with CH_2I_2-Zn-$TiCl_4$ (eq 9).[6]

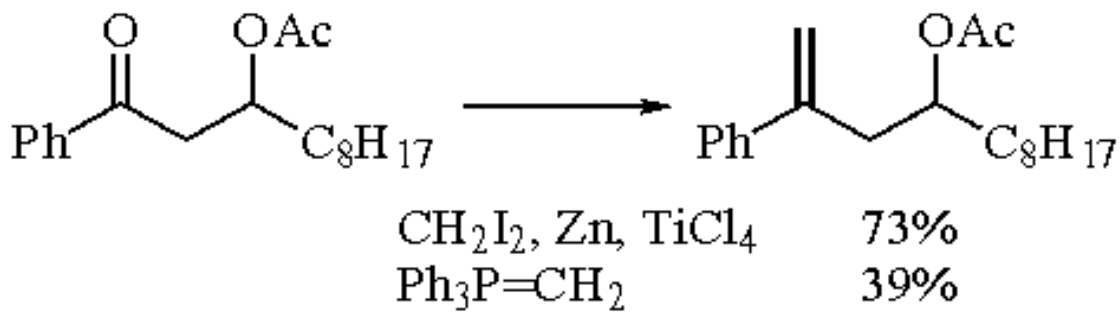

(9)

These reagents are also suitable for the methylenation of sterically hindered ketones (eq 10)[22] and enones (eq 11),[23] reactions that often fail with Wittig-type methods.

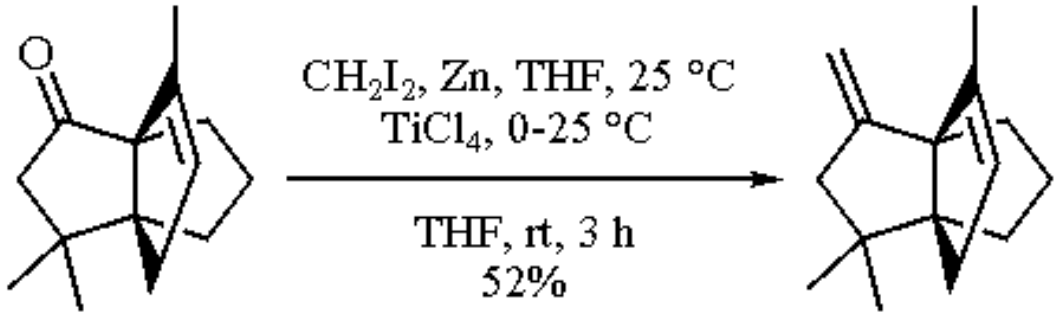

(10)

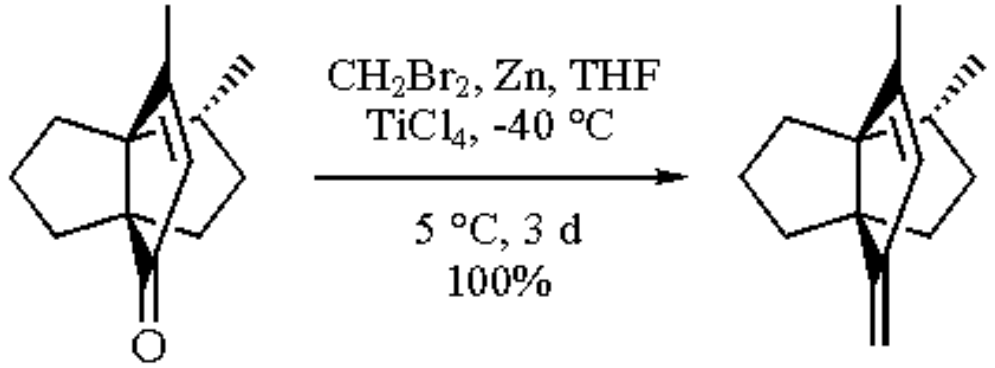

(11)

In some cases the methylenation products undergo subsequent cyclopropanation (eq 12),[24] a reaction that can be more efficient in the presence of copper.[25]

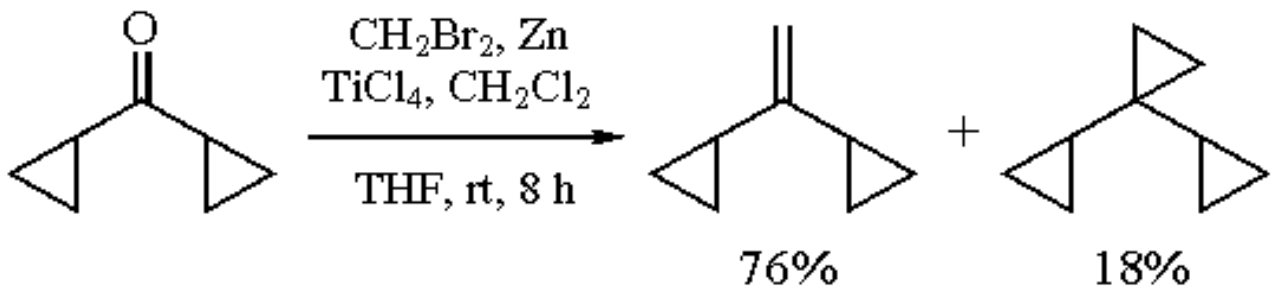

(12)

The CH_2I_2-Zn-$TiCl_4$ system is effective for the methylenation of nonracemic α-amino ketone derivatives (eq 13).[26]

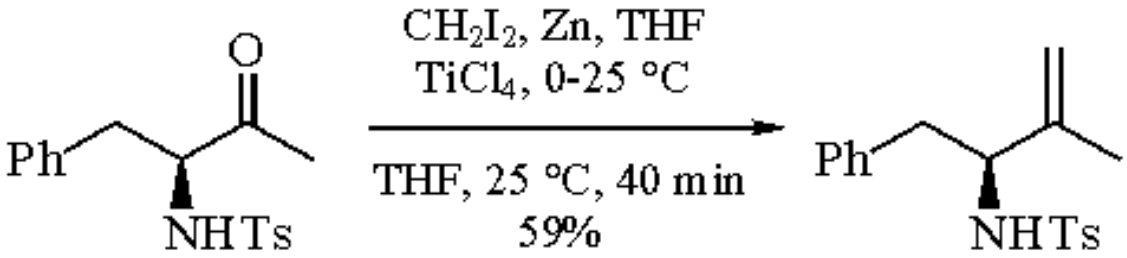

(13)

Substituents containing other heteroatoms, such as tin (eq 14),[27] sulfur (eq 15),[28,29] or selenium (eq 16),[29] are well tolerated in this process.

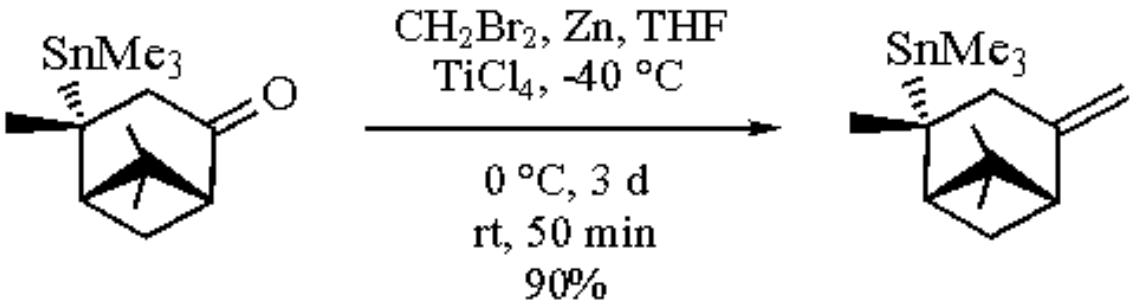

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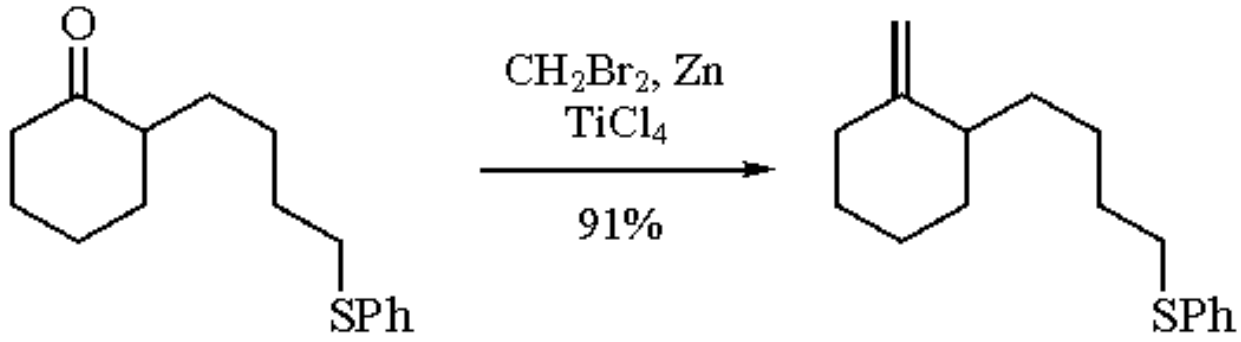

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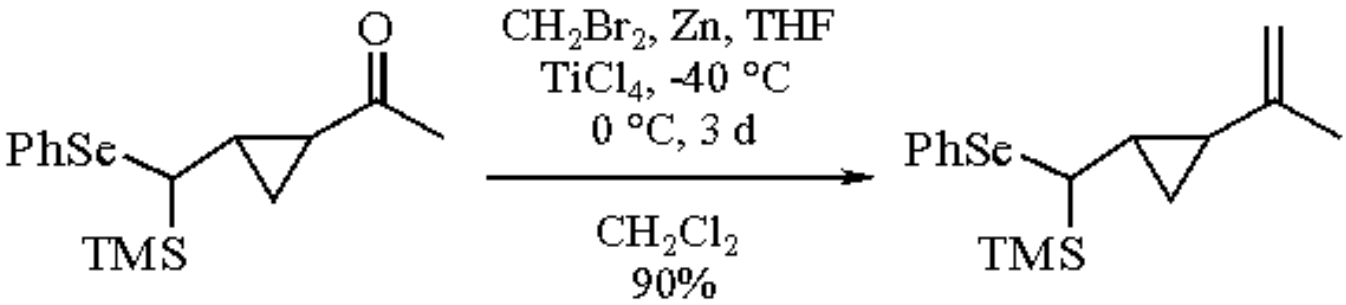

(16)

Methylenation of Aldehydes.

Aldehydes are not as good substrates as ketones for the methylenation with the CH_2Br_2-Zn-$TiCl_4$ system due to complications arising from reductive coupling of the carbonyl. In some cases, however, an aldehyde moiety can be methylenated even in the presence of the phosphonoacetate group (eq 17).[30]

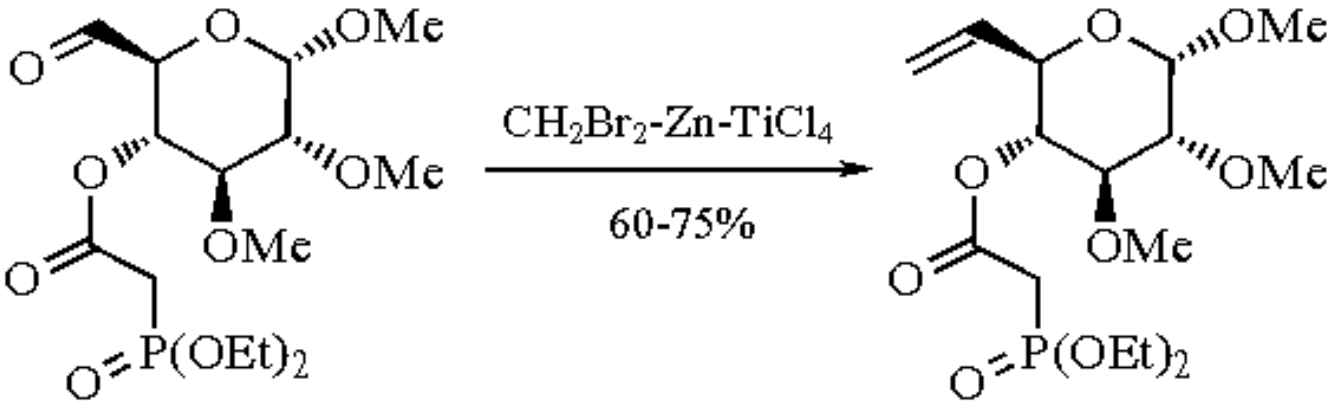

(17)

The chemoselective methylenation of aldehydes in the presence of ketones (eq 18) can be done with CH_2I_2-Zn-Ti(O-*i*-Pr)$_4$ or CH_2I_2-Zn-Me_3Al.[7] The reverse selectivity, i.e. the methylenation of a ketone in the presence of an aldehyde, can be accomplished by the in situ protection of the aldehyde with ***Titanium Tetrakis(diethylamide)***, followed by reaction with CH_2I_2-Zn-$TiCl_4$ and deprotection (eq 19).[7]

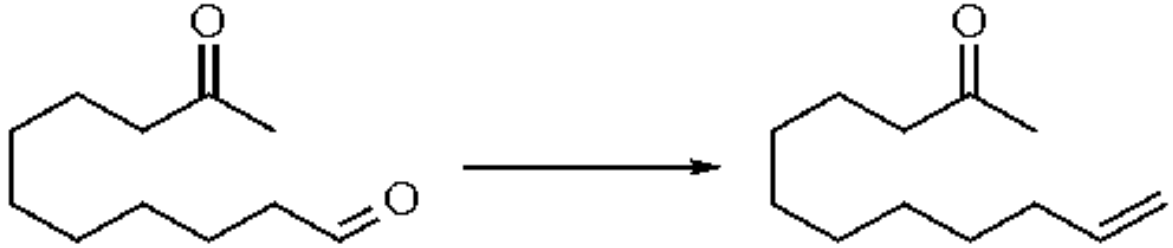

(18)

CH_2I_2-Zn-Ti(O-*i*-Pr)$_4$, 25 °C, 4 h 83%
CH_2I_2-Zn-$AlMe_3$, 25 °C, 3 h 96%

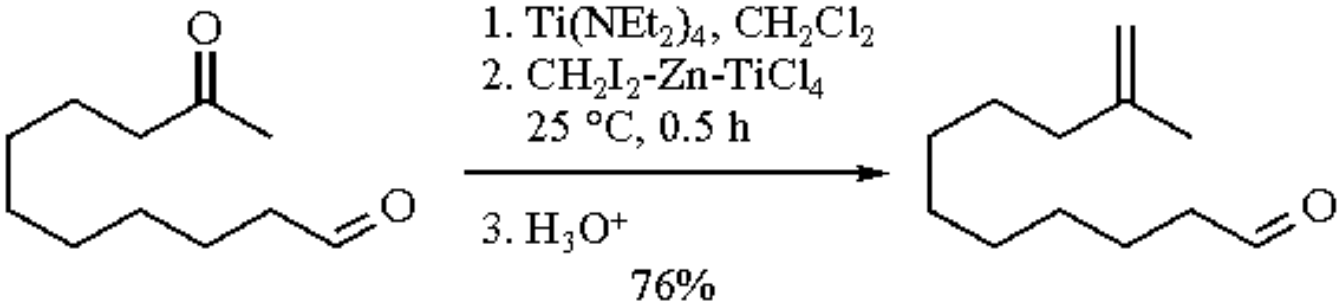

(19)

Methylenation of Esters.

The CH_2Br_2-Zn-$TiCl_4$ reagent is selective for ketones and aldehydes, and it alkenates these carbonyls in the presence of esters. Although the reagent of choice for the methylenation of esters and lactones is often the Tebbe reagent[1,12] or dimethyltitanocene,[13] it is possible to alkenate esters with the CH_2Br_2-Zn-$TiCl_4$ system if TMEDA is mixed with $TiCl_4$ prior to its exposure to Zn and CH_2Br_2.[8] These conditions were used to convert allyl esters to allyl enol ethers (eq 20)[31] and to alkenate carbohydrate ester intermediates (eq 21).[32]

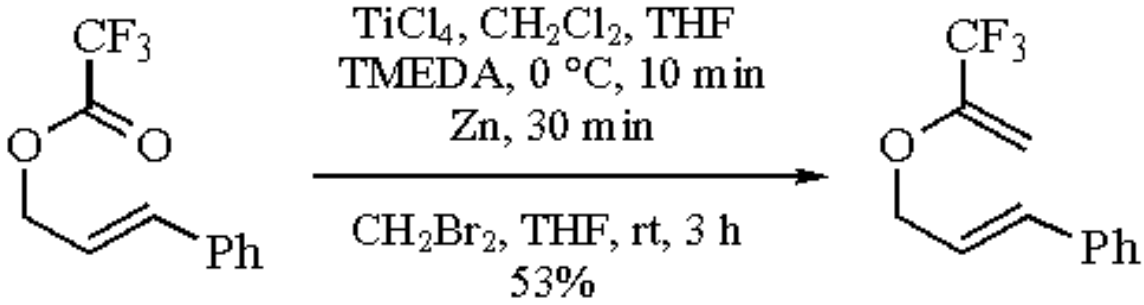

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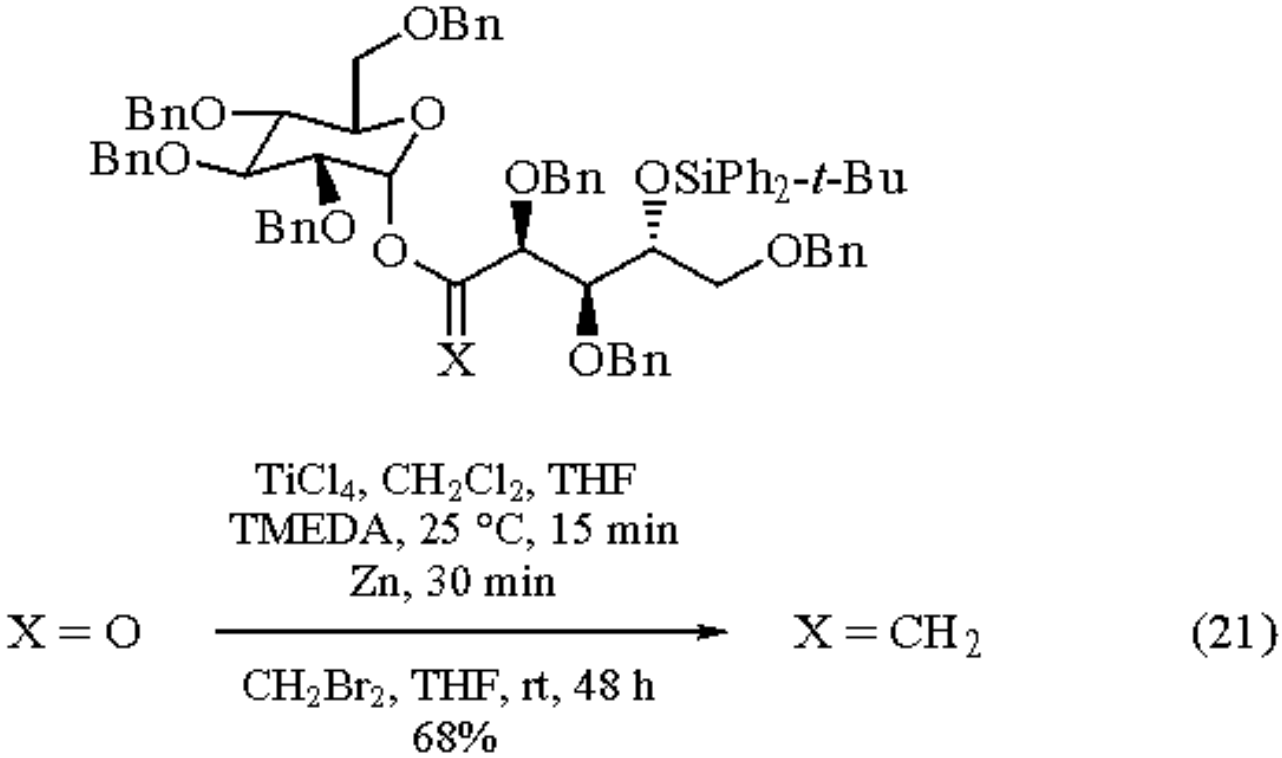

A lactone methylenation was similarly accomplished by using an excess of all of the ingredients (eq 22).[33]

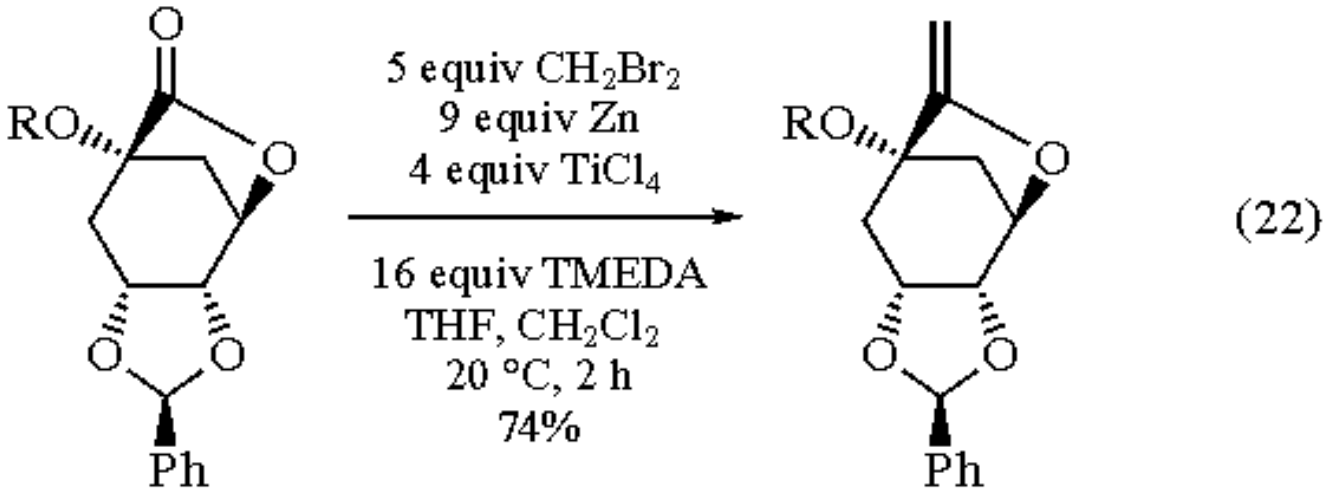

Alkylidenation of Carbonyl Compounds.

This methodology was extended to the alkylidenations of carbonyls by the use of 1,1-dihaloalkanes in the presence of TMEDA.[8] In this manner, esters and lactones are converted to the corresponding enol ethers in good yields and with (*Z*) selectivities (eq 23).[8] This type of reaction was utilized in a synthesis of spiroacetals (eq 24).[34]

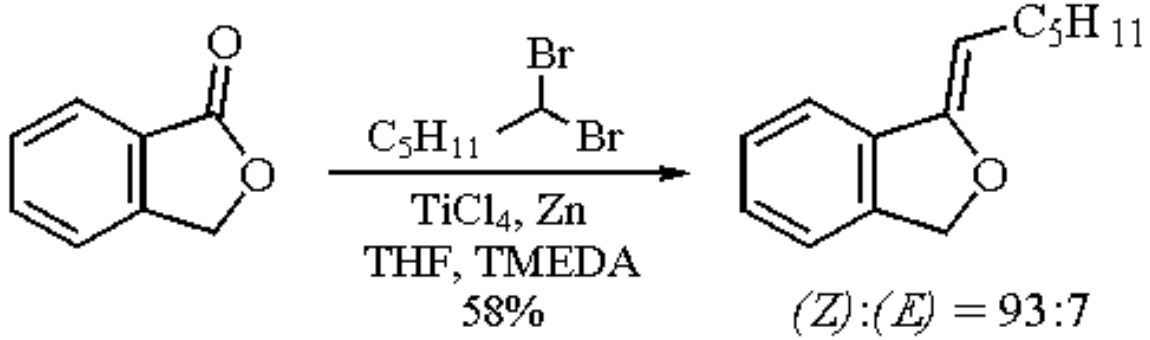

(23)

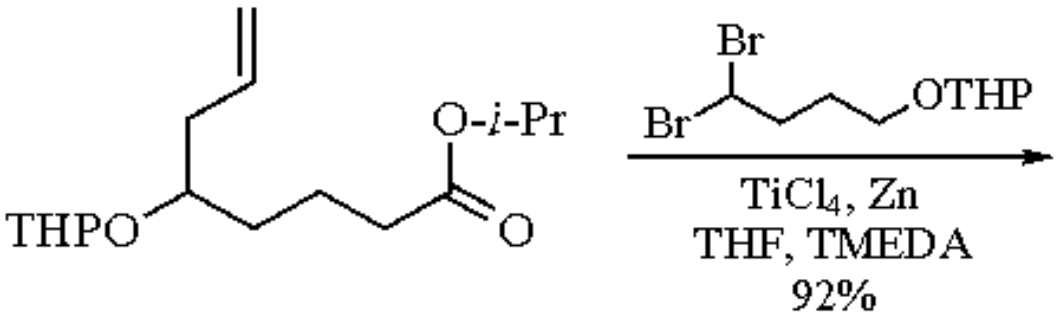

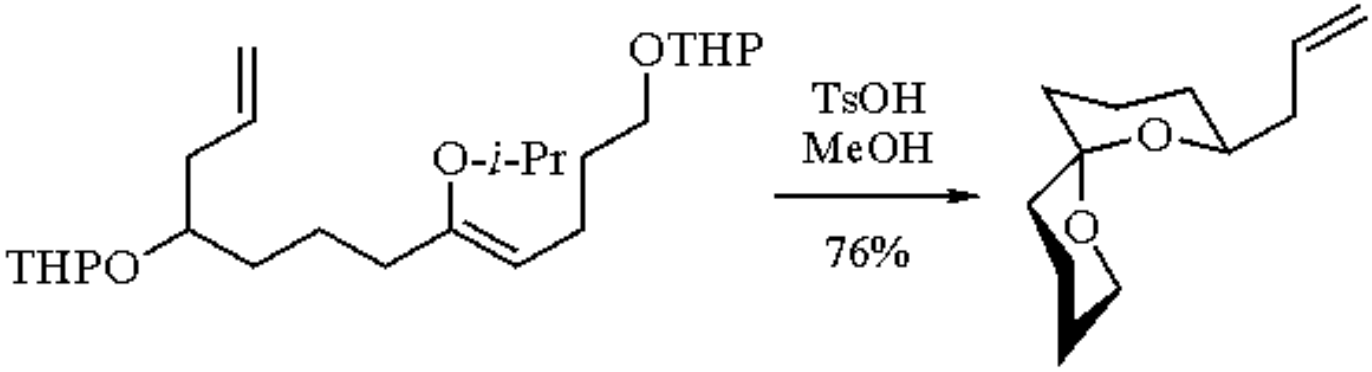

(24)

Silyl esters afford silyl enol ethers when they are subjected to these conditions with the geometry of the products being predominantly (*Z*) (eq 25).[9]

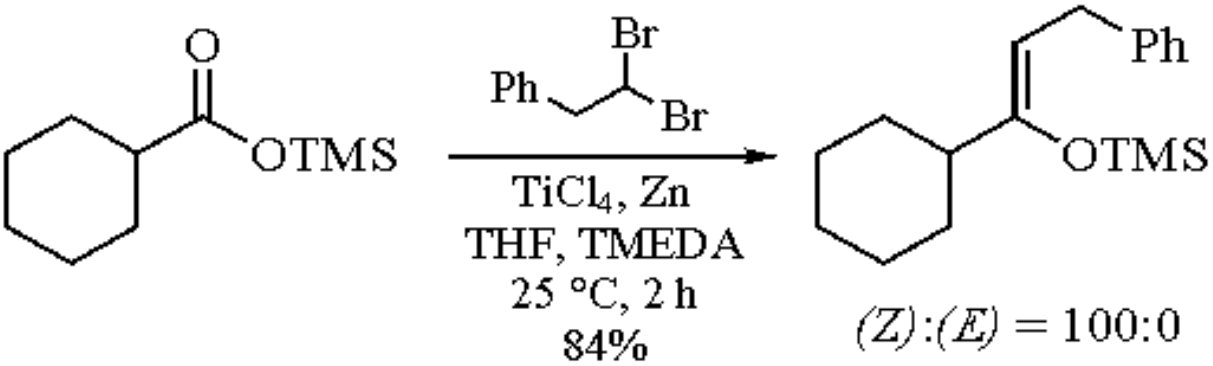

(25)

Alkylidenation of thioesters (eq 26) and amides (eq 27), to produce alkenyl sulfides and enamines respectively, is also possible with this methodology.[10]

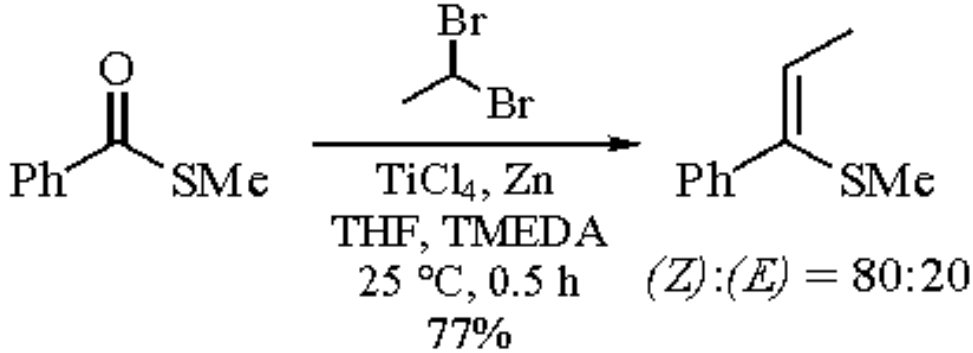

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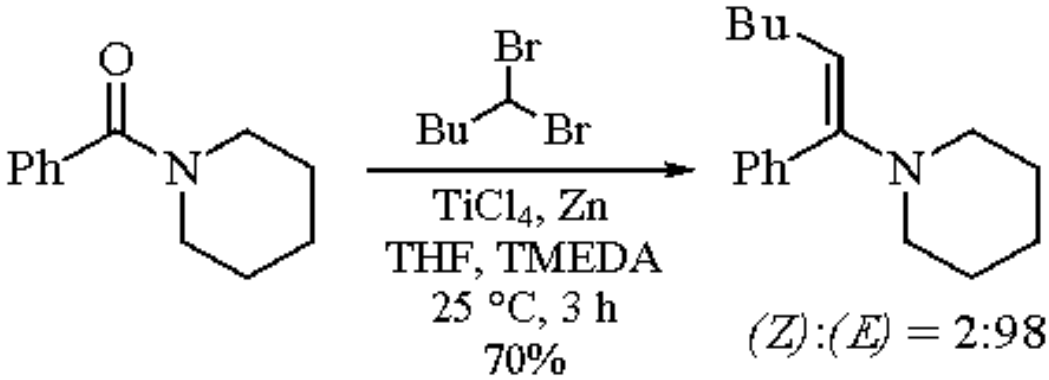

(27)

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University of Southern California, Los Angeles, CA, USA

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[Dibromo(methoxycarbonyl)methyl]phenylmercury[1]

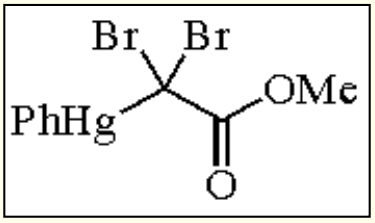

[22060-04-4] · $C_9H_8Br_2HgO_2$ · [Dibromo(methoxycarbonyl)methyl]phenylmercury · (MW 508.56)

(by thermolysis, transfers **:**$CBrCO_2Me$ to alkenes, giving cyclopropanes,[2] and to silanes, inserting into Si-H bond[2,3])

Physical Data: mp 154-156 °C (dec).

Solubility: sol THF, $CHCl_3$, chlorobenzene, benzene.

Analysis of Reagent Purity: spectroscopic data: IR,[3] ^{1}H NMR.[3]

Preparative Method: reaction of $HCBr_2CO_2Me$ with ***Phenylmercury(II) Chloride*** and ***Potassium t-Butoxide*** in THF at -60 °C,[2,3] according to the general method to prepare phenyl(trihalomethyl)mercurials.[4] The yield, though typically in the range of 55%, can be as high as 68%.

Purification: recrystallization from chloroform/hexane (1:1).

Handling, Storage, and Precautions: flame-dried glassware and an atmosphere of dry nitrogen are used for the reactions. Organomercury compounds should be carefully handled, and skin contact and inhalation should be particularly avoided. All reactions must be conducted in a well-ventilated fume hood.

Cyclopropanation of Alkenes.

The observed high thermal stability of $PhHgCBr_2CO_2Me$ (**1**) restricts its application in synthesis. An additional drawback is related to the long reaction times and high reaction temperatures required, which results in significant side reactions, as is clear from the disparity between the amounts of phenylmercury(II) bromide recovered and the cyclopropane formed. Nevertheless, the cyclopropanation of several alkenes has been reported.[3] For instance, reaction of cyclooctene with (**1**) in chlorobenzene gives rise to the cyclopropane derivative (eq 1), with greater yields of cyclopropane ring formation as the reaction temperature is raised (50% at reflux, 19% at 130 °C).

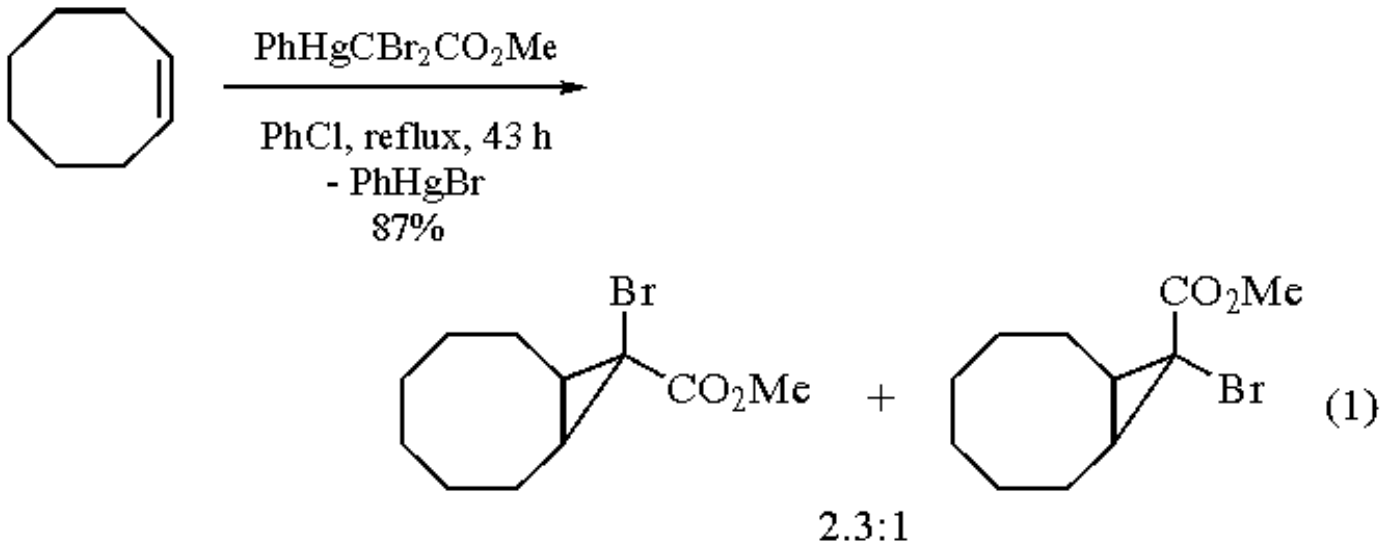

Allyltrimethylsilane is also an efficient partner for (**1**) in the cyclopropanation process (eq 2).[3] The cyclopropane product is formed as a mixture of stereoisomers in a 1.5:1 ratio. The major isomer has been tentatively assigned to that having a *syn* disposition for the Me_3SiCH_2 and Br groups on the basis of the larger steric bulk of the CO_2Me group.

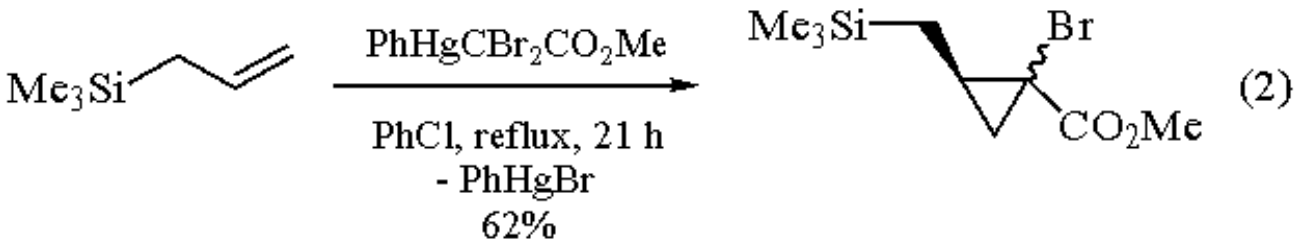

Trisubstituted alkenes gave very modest yields. Thus 2-methyl-2-butene affords 9% of cyclopropane formation, while phenylmercury(II) bromide is recovered in 92% after 24 h at 130 °C in chlorobenzene.[3]

Insertion into Si-H Bond.

This is another representative reaction for α-haloorganomercurials that is also observed for (**1**) (eq 3).[3]

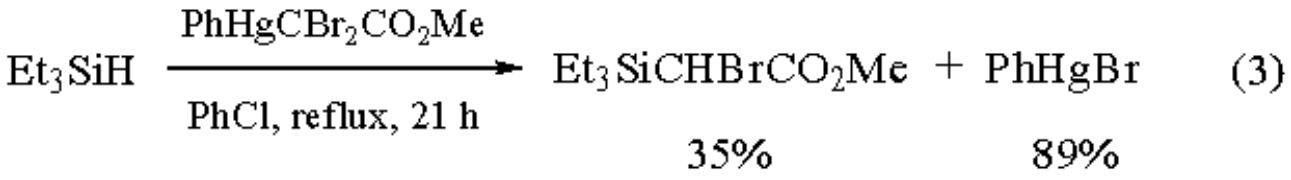

In spite of the limitations found, $PhHgCBr_2CO_2Me$ is an interesting reagent to transfer the functional divalent $CBrCO_2Me$ group to several alkenes.

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1. (a) Seyferth, D. *PAC* **1970**, *23*, 391. (b) Seyferth, D. *ACR* **1972**, *5*, 65. (c) Zeller, K.-P.; Straub, H. *MOC* **1974**, *13/2b*, 351. (d) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985; Chapter X, pp 327-413.
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Dibromomethyllithium

$LiCHBr_2$

[37555-63-8] · $CHBr_2Li$ · Dibromomethyllithium · (MW 179.77)

(reagent used for bromocyclopropanation, nucleophilic dibromomethylation, ring expansion, bromomethylenation, chain elongation)

Physical Data: low temperature ^{13}C and ^{6}Li NMR data are available,[1] as are matrix IR data.[2]

Preparative Methods: solutions of the title compound can be obtained by treatment of ***Dibromomethane*** with slightly less than 1 equiv of ***Lithium Diisopropylamide*** in THF/ether (1:3) at -100 °C for 15 min.[3] Amine-free solutions may be obtained by deprotonation of CH_2Br_2 with ***Dichloromethyllithium*** in THF at -100 °C.[4]

Handling, Storage, and Precautions: the reagent is generally stable from -110 to about -80 °C depending on the solvent. There is evidence that carbenoids of this nature show greater thermal stability in THF than in ether.[5] Further, transmetalation with ***Titanium Tetraisopropoxide*** is reputed to give a reagent with greater thermal stability,[5e] although subsequent reports confirming this have not appeared.

General Considerations.

Alkyllithiums bearing halogens on the α-carbon are frequently referred to as carbenoids, reflecting a major mode of reactivity. Good general reviews of such species are available.[6] At very low temperatures, however, the reagent reacts like a typical alkyllithium.

Cyclopropanations.

When α-haloorganolithium reagents are treated with alkenes, a rapid low temperature reaction takes place resulting from α-elimination of LiX to a carbene followed by cyclopropanation of the alkene (see also ***2,2,2-Tribromoethyl Chloroformate***, ***Trichloromethyllithium***, and ***Dichloromethyllithium***). This mode of reactivity has been reported for both $LiCHBr_2$ and $NaCHBr_2$ (eq 1).[7] Yields were reported only for the organosodium reagent and were generally moderate. Details of this process were sketchy.

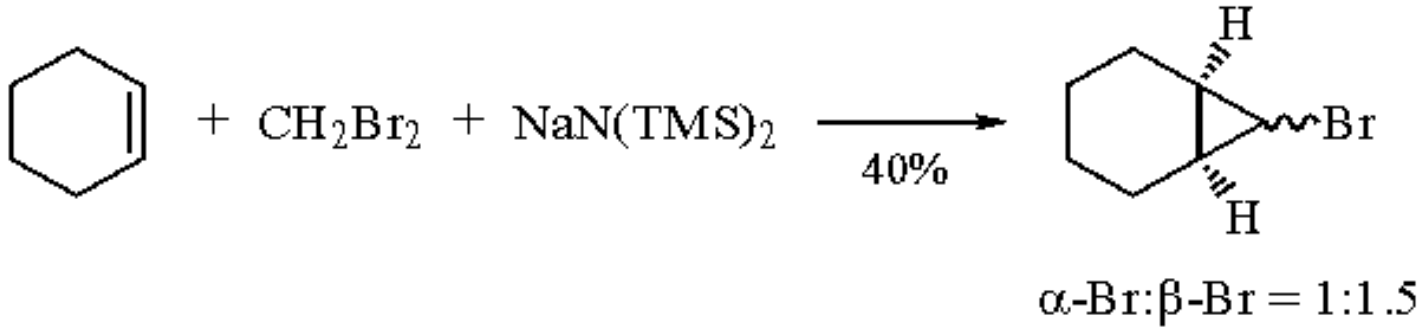

(1)

An apparently noncarbenic bromocyclopropanation of fulvenes has been described by Grohmann.[8] When LDA was slowly added to a THF solution of a fulvene and CH_2Br_2 at -75 °C followed by slow warming to 0 °C, a mixture of *cis*- and *trans*-halospiro[2.4]heptadienes were formed (eq 2). Evidence indicates a nucleophilic addition-displacement mechanism as opposed to a carbene reaction. A related reaction involving ring enlargement of silacycles has also been reported.[9]

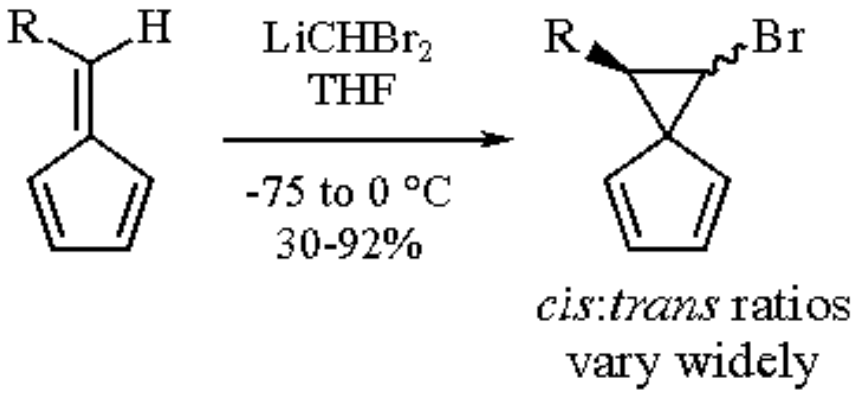

(2)

Nucleophilic Additions to Carbonyls and Subsequent Processes.

As with ***Tribromomethyllithium***, ***Trichloromethyllithium***, and ***Dichloromethyllithium***, $LiCHBr_2$ can be generated in the presence of aldehydes and ketones when a solution of CH_2Br_2 and the carbonyl compound in THF is treated with 2 equiv of lithium dicyclohexylamide at -78 °C (eq 3). Addition of $LiCHBr_2$ to the carbonyls forms dibromocarbinols in excellent yield.[10] Alternatively, $LiCHBr_2$ may be generated by the LDA method followed by addition of the aldehyde or ketone.[3a] Such intermediates are quite versatile, undergoing a variety of synthetically useful transformations.

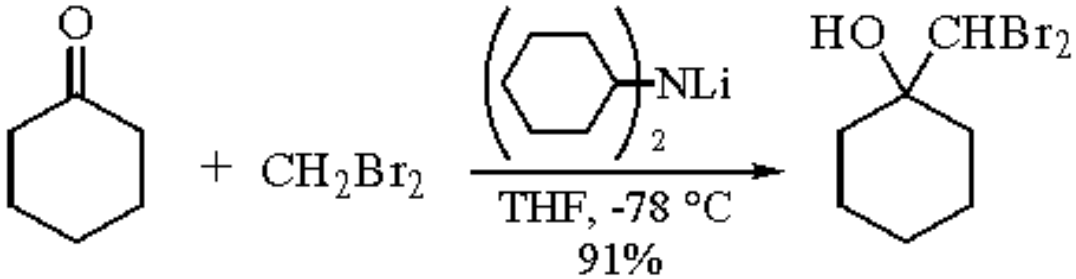

(3)

Preparation of Terminal Bromoalkenes.

Treatment of such dibromo alcohols with excess Zn dust and 2-6 equiv of HOAc (see ***Zinc-Acetic Acid***) in CH_2Cl_2 at reflux provides the bromoalkene as a mixture of (*E*) and (*Z*) isomers.[11] Overall yields for the two-step process are generally >40% (eq 4). Kobrich had previously reported similar alkene forming processes whereby elimination proceeds via the trimethylsilyl ether derivatives of the alcohol adducts (Scheme 1).[12] Treatment with LDA at -100 °C promoted loss of TMS-OH and formation of terminal dibromoalkenes in good yield, while treatment with ***n-Butyllithium*** at the same temperature promoted Li-halogen exchange and elimination of TMSO-Li to give a mixture of monobromoalkenes.

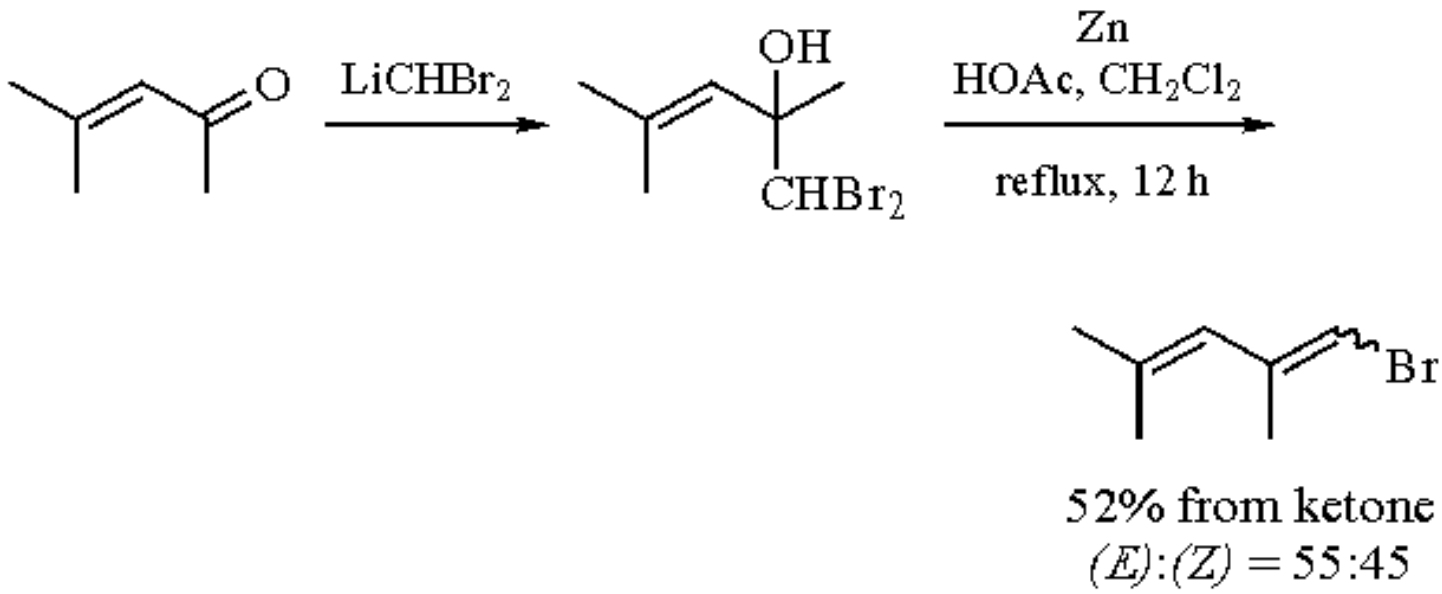

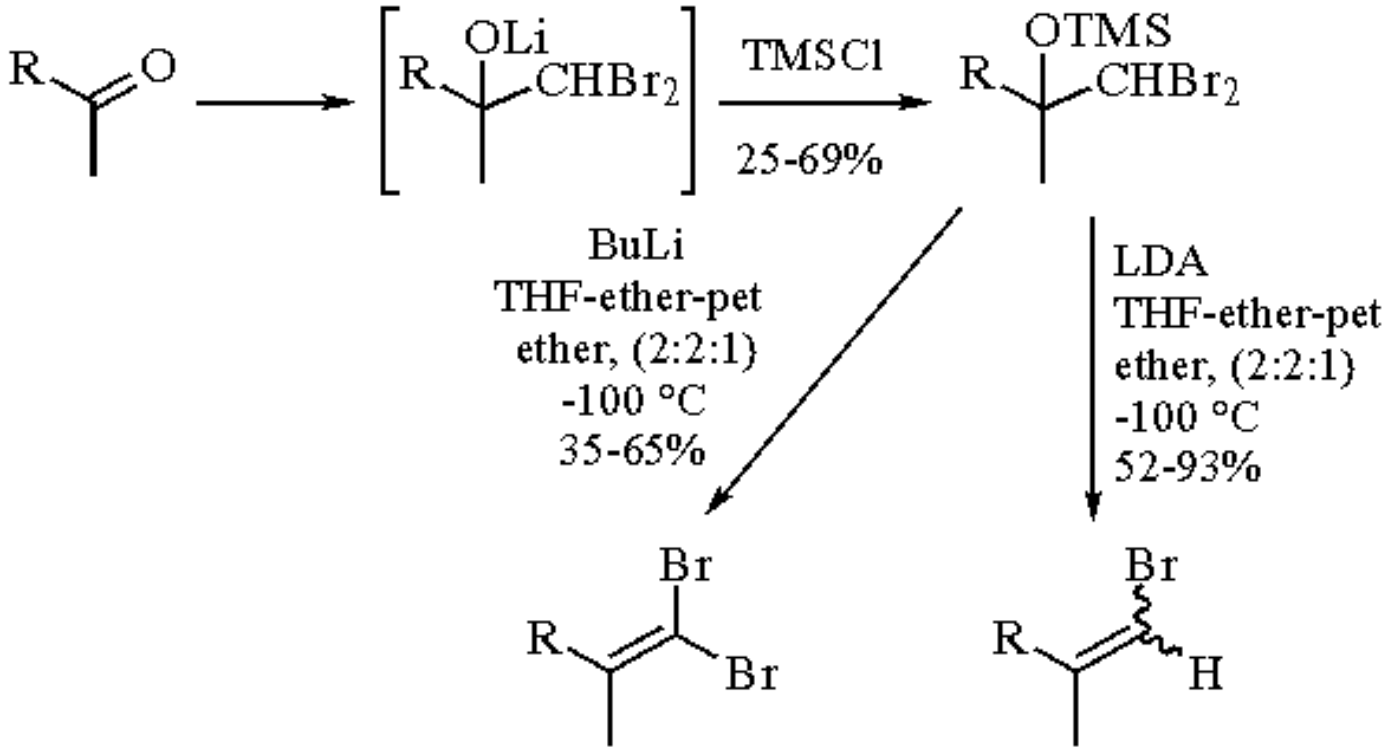

Scheme 1

Preparation of α,α-Dibromo Ketones.

The dibromo alcohols have been oxidized with the Swern reagent (***Dimethyl Sulfoxide-Oxalyl Chloride***), ***Pyridinium Dichromate***, or ***Pyridinium Chlorochromate*** to the corresponding ketones in 44-60% yield (eq 5).[13] A higher yield process is the direct addition of $LiCHBr_2$ to esters, proceeding in 68-78% yield.[14]

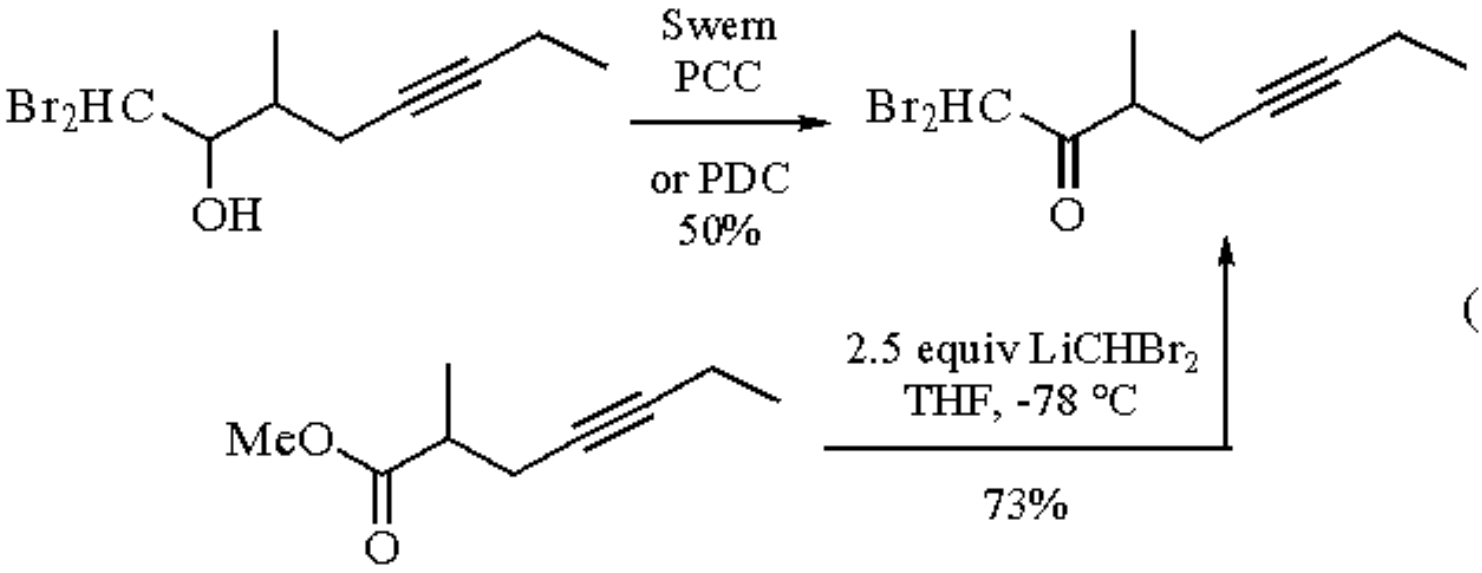

(5)

Ring Expansions of Derived β-Oxidocarbenoids.

A facile ring expansion (Scheme 2) has been developed by Nozaki[15] based on a well-known carbene rearrangement. Dibromo alcohols such as (**1**) can be treated with 2 equiv of *n*-BuLi in THF at low temperature to generate the alkoxycarbenoid (**2**). This can undergo α-elimination to the carbene (**3**) which undergoes ring-expanding rearrangement to enolate (**4**), eventually resulting in the ring-expanded ketone (**5**). Yields are good to excellent. There is some regioselectivity in the rearrangement step (eq 6).[16] For example, the dibromo alcohol (**6**) provides the ketone (**7**) as the major product, resulting from migration of the more substituted center. This appears to be general, although there are clear temperature and solvent effects on the degree of regioselectivity.

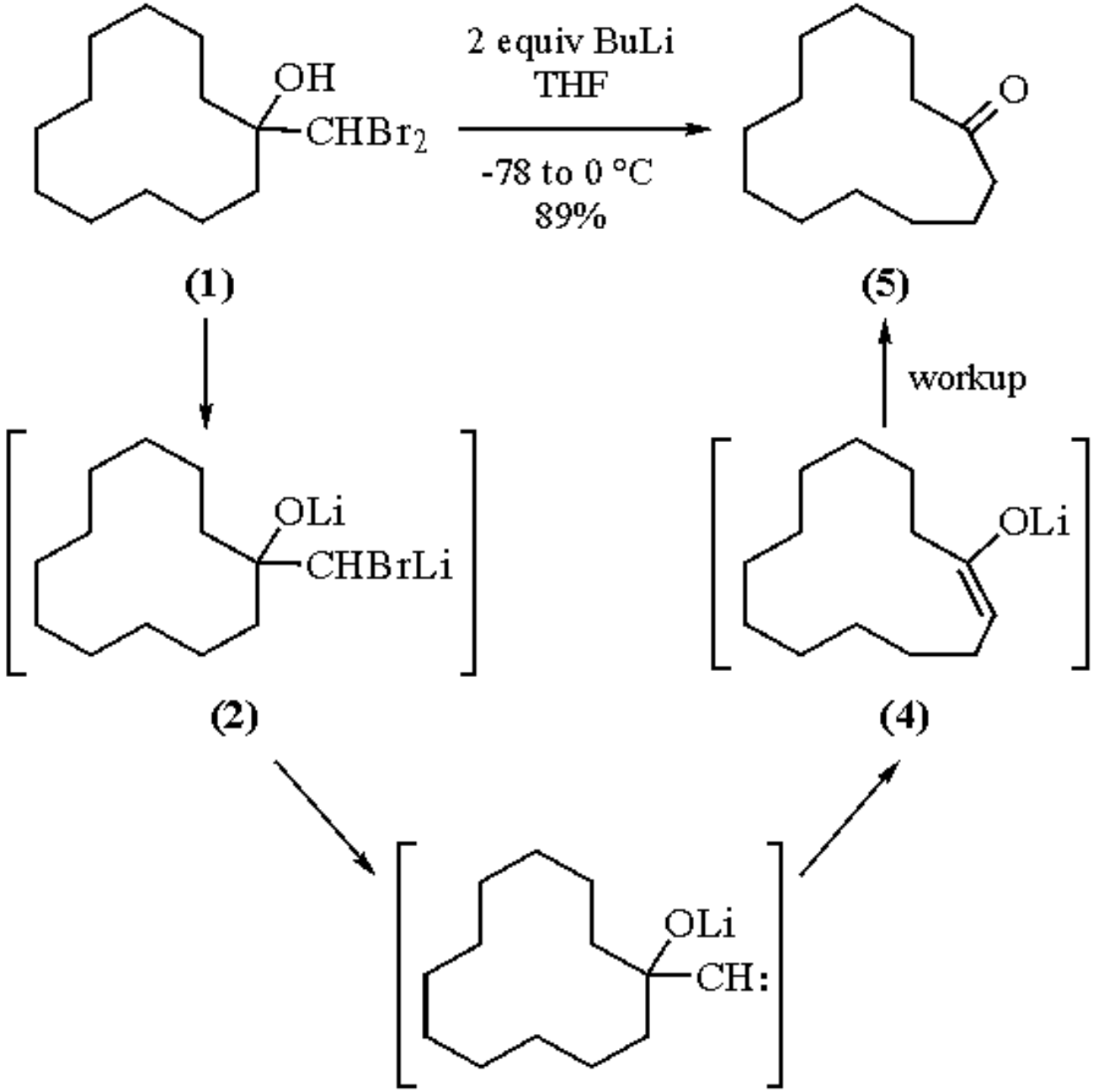

Scheme 2

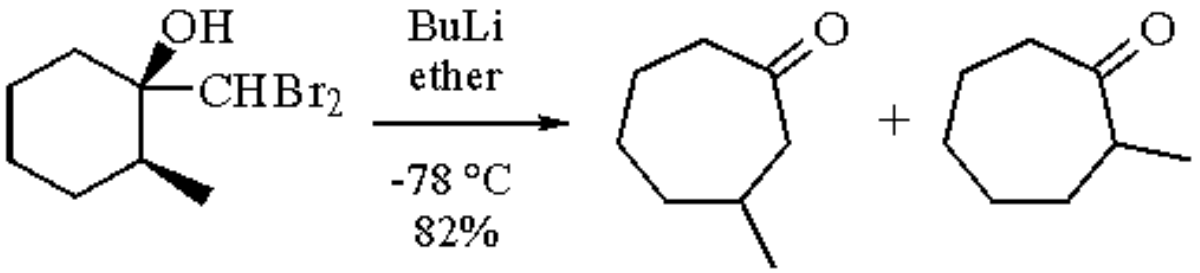

(6)

(6) (7) 95:5

In addition, cyclic conjugated enones undergo expansion by migration of the unsaturated group to give β,γ-unsaturated cyclic ketones. However, there is a lack of regiospecificity with conjugated cyclopropyl ketones as substrates.[17] An analogous ring expansion occurs if intermediate lithioalkoxides such as (**8**) are deprotonated with an amide base like ***Lithium 2,2,6,6-Tetramethylpiperidide*** (eq 7).[18] In these cases the result is a ring expanded α-bromo ketone.

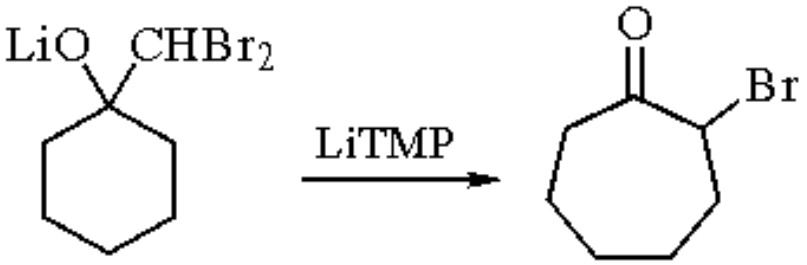

(7)

(8)

Ester Homologation.

Related to this rearrangement is an ester homologation process developed by Kowalski which proceeds without isolation of intermediates.[19] In this procedure, $LiCHBr_2$ is generated using LiTMP and is added to an ester at low temperature. A second addition of excess base promotes the collapse to the enolate (**10**) which undergoes Li-halogen exchange to the carbenoid (**11**). Fritsch-Buttenberg-Wiechell rearrangement of the derived (**12**) gives the ynolate (**13**) which is quenched into acidic ethanol, eventually giving the homologated ester (Scheme 3). Lactones also undergo the process. The intermediate ynolate (**13**) may be captured by silyl halides, resulting in one of the few methods of preparing ynol silyl ethers (**14**) (Scheme 4). Such species have been utilized in a stereoselective alkenation alternative to the Wadsworth-Emmons process (**14**) -> (**15**).[20]

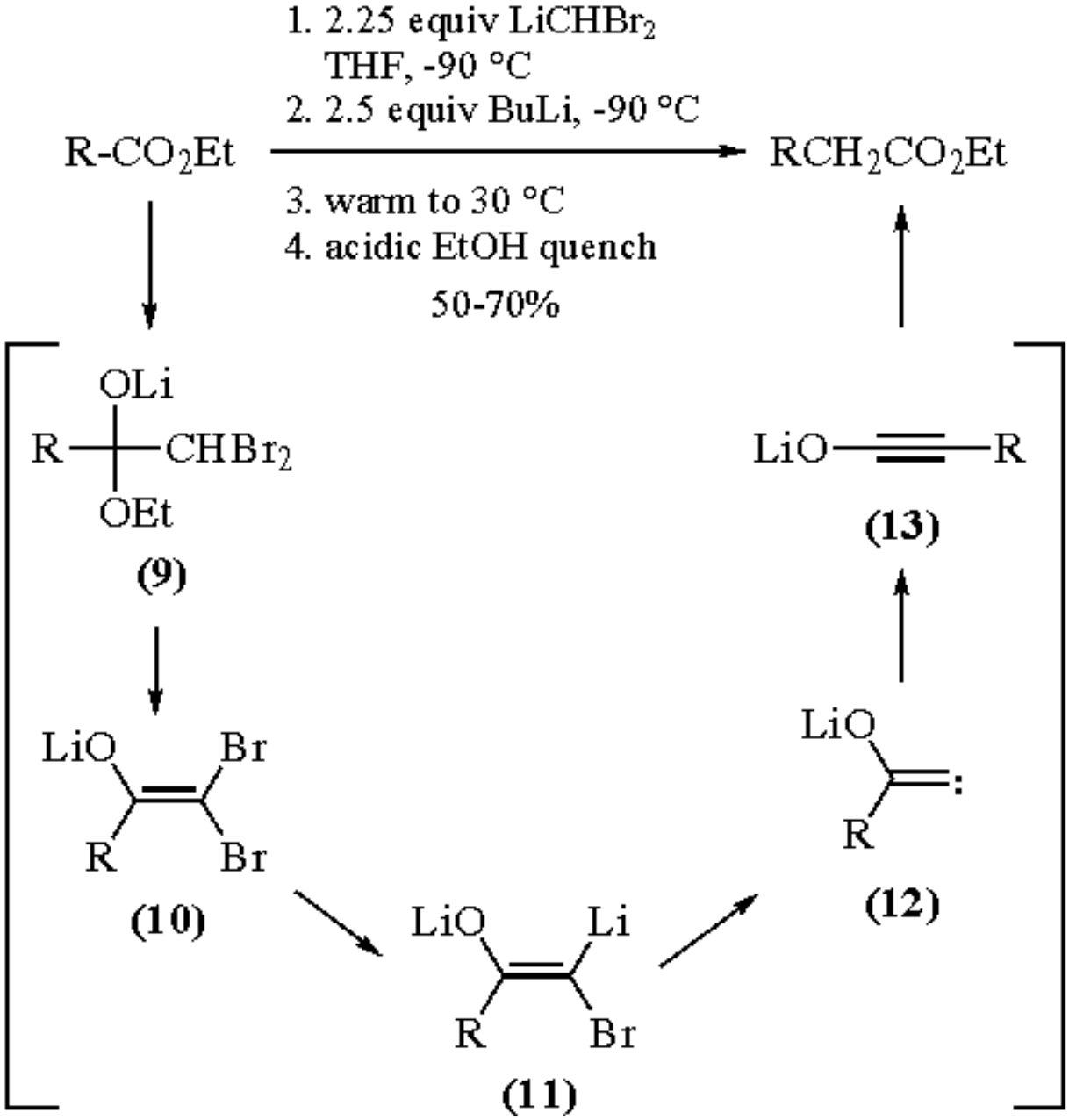
1. 2.25 equiv LiCHBr2
THF, -90 °C
2. 2.5 equiv BuLi, -90 °C
R-CO2Et
RCH2CO2Et
3. warm to 30 °C
4. acidic EtOH quench
50-70%
OLi
R
CHBr2
OEt
(9)
LiO
R
(13)
LiO
Br
R
Br
(10)
LiO
Li
R
Br
(11)
LiO
R
(12)

Scheme 3

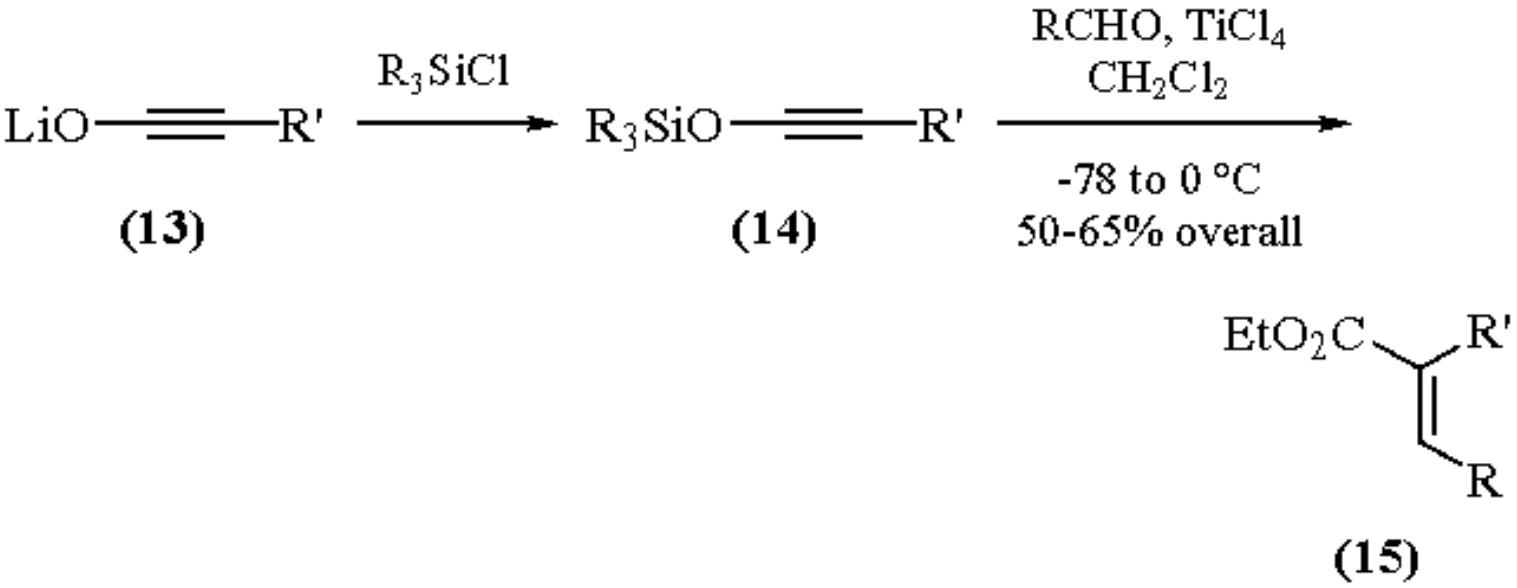

Scheme 4

Alkylation with Alkyl Halides.

$LiCHBr_2$ reacts well with alkyl bromides, iodides, and other active alkylating agents at low temperature to provide dibromoalkanes in good yield (eq 8).[21]

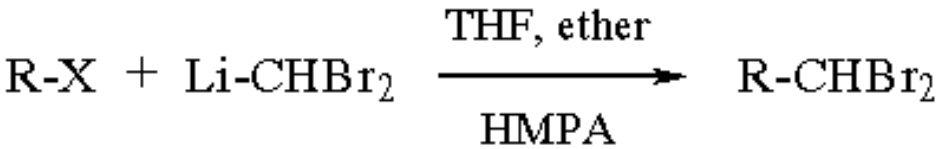

(8)

R-X	Yield (%)
BnBr	74
BuI	69
allyl bromide	59
TMSCl	71
Ph_3GeBr	78

Chain Homologation of Boronic Esters.

$LiCHBr_2$ is capable of chain elongating boronic esters to give α-bromoboronic esters, useful intermediates in synthesis. Treatment of a boronic ester, generally of the cyclic variety, with $LiCHBr_2$ at low temperature and allowing it to stand at rt for a period of hours results in the familiar B -> C migration of an alkyl group in the ate complex (**17**) with expulsion of bromine to form a boronic ester (**18**) elongated by a bromomethylene group (Scheme 5). Boronic esters (**18**) are quite stable intermediates which undergo facile displacement of the halide by nucleophiles with inversion of

configuration, providing more highly functionalized boronic esters.[22]

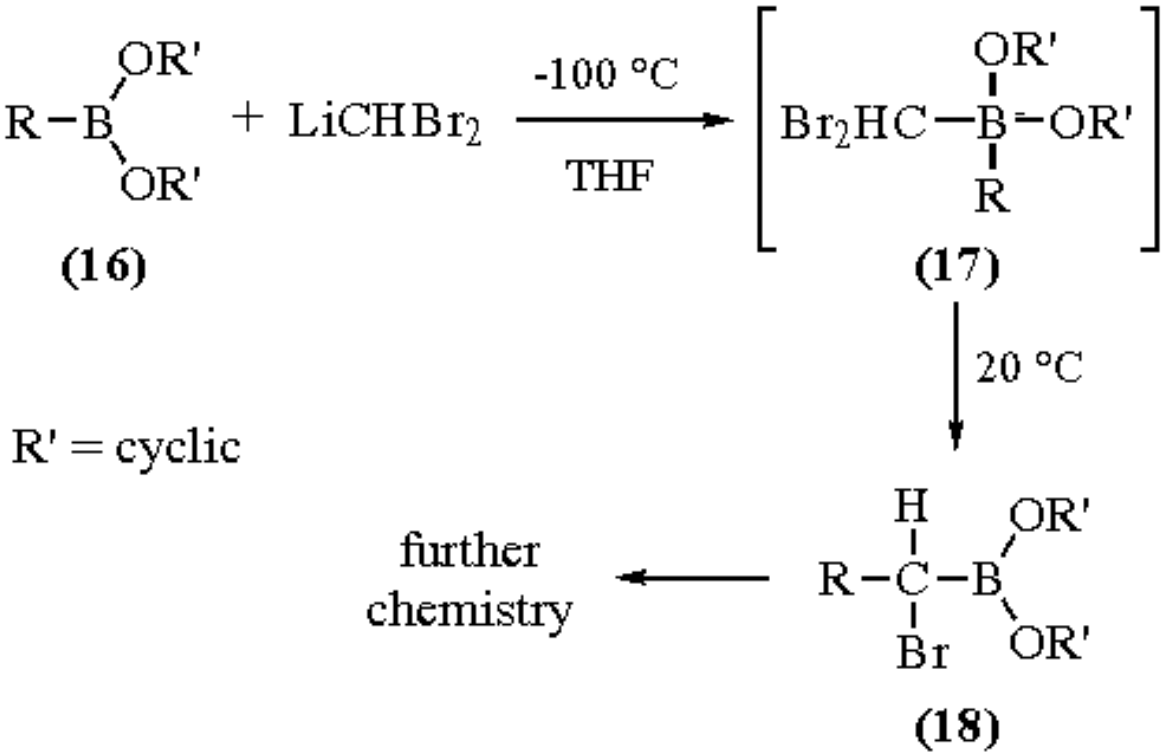

Scheme 5

Use of optically active boronic esters provides the opportunity for asymmetric induction at the newly formed chiral carbon. Ate complexes of pinanediols undergo nearly enantiospecific ***Zinc Chloride***-catalyzed migration of alkyl groups, resulting in production of a new versatile chiral carbon.[23] It was found that $LiCHBr_2$ gives better yields and diasteromeric ratios than $LiCHCl_2$ in the migration step.[24] Also, Br was found to be more readily displaced by $LiOCH_2Ph$, enabling more efficient syntheses of small carbohydrates by an iterative approach. This is illustrated in the first few steps of a synthesis of (+)-ribose, (**19**) -> (**21**), which proceed in excellent yield and stereoselectivity (Scheme 6).

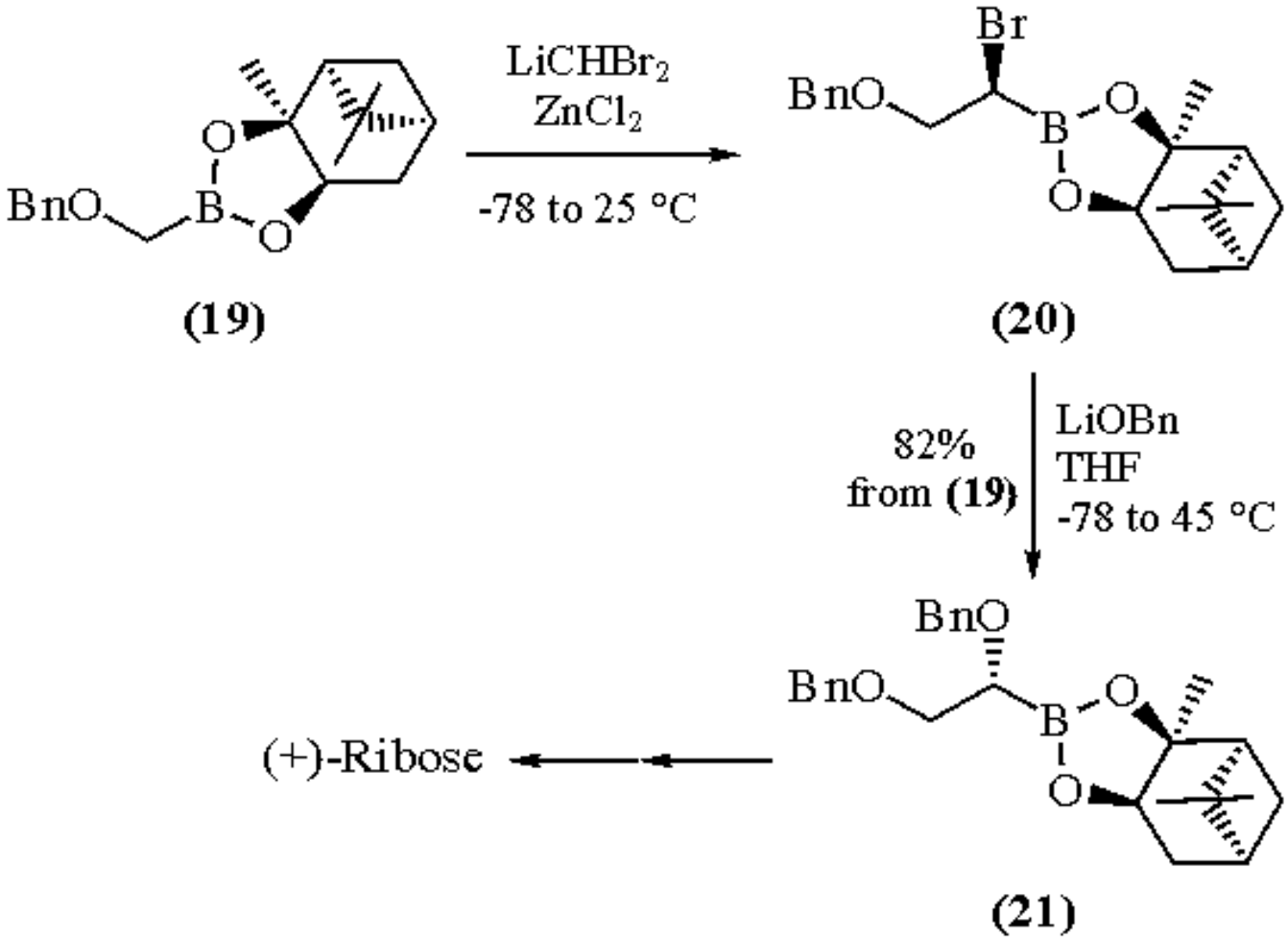

Scheme 6

Related Reagents.

Bromomethyllithium; ***Chloromethyllithium***; ***Dichloromethyllithium***; ***2,2,2-Tribromoethyl Chloroformate***; ***Trichloromethyllithium***.

---

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(Dibromomethyl)trimethylsilane

$Me_3SiCHBr_2$

[2612-42-2] · $C_4H_{10}Br_2Si$ · (Dibromomethyl)trimethylsilane · (MW 246.03)

(reagent for the preparation of vinylsilanes)

Alternate Name: trimethyl(dibromomethyl)silane.

Physical Data: bp 49.5-51.5 °C/12 mmHg; *d* 1.519 g cm^{-3}.[1b]

Solubility: sol most organic solvents.

Preparative Method: to a dry, 1.0 L three-neck flask, equipped with a mechanical stirrer, a pentane thermometer, a nitrogen inlet tube, and a pressure-equalizing addition funnel, was added 62.0 g (0.245 mol) of ***Bromoform*** and 300 mL of dry THF. The reaction was cooled to -90 °C and 0.25 mol of isopropylmagnesium chloride in 200 mL of THF was added during 30 min at such a rate that the temperature was kept at -80 °C or below. The reaction was stirred at -90 °C for 15 min and then 0.25 mol of ***Chlorotrimethylsilane*** in 100 mL of THF was added at such a rate that the temperature did not exceed -80 °C. After 1 h, the reaction was allowed to warm to rt. The reaction mixture was hydrolyzed with saturated NH_4Cl solution until large lumps of salt cake formed. The organic layer was poured off, dried over anhydrous Na_2SO_4, and distilled at atmospheric pressure to remove most of the THF. A trap-to-trap distillation of the residue at 0.1 mmHg was followed by distillation through an 11 in. Vigreux column. The fraction boiling at 49.5-51.5 °C/12 mmHg was collected, affording 47.9 g (79%) of (dibromomethyl)trimethylsilane.[1a]

Lithium-Halogen Exchange.

Reaction of (dibromomethyl)trimethylsilane with ***n-Butyllithium*** at -110 °C results in the formation of trimethylsilylbromomethyllithium. The silane and the *n*-BuLi are added simultaneously in order to suppress side reactions. Treatment of the intermediate lithium reagent with ***Chlorotrimethylsilane*** (eq 1) or mercury(II) bromide (eq 2) affords bis(trimethylsilyl)bromomethane or bis(trimethylsilylbromomethyl)mercury, respectively. If the lithium reagent is allowed to warm in the presence of cyclohexene, the only reaction observed is an alkylation with the *n*-butyl bromide formed in the exchange reaction. The alkylated product is formed in 89% yield.[1a]

$$TMSCHBr_2 \xrightarrow[\text{2. TMSCl}]{\text{1. BuLi, -110 °C}} (TMS)_2CHBr \qquad (1)$$

52%

$$TMSCHBr_2 \xrightarrow[\text{2. } HgBr_2]{\text{1. BuLi, -110 °C}} (TMSCHBr)_2Hg \qquad (2)$$

44%

In an alternative procedure, the lithium reagent was obtained by reaction with ***Lithium*** metal. Subsequent reaction with a trialkylborane (eq 3) followed by oxidation provided access to α-hydroxysilanes. The yields are good for simple trialkylboranes but are diminished as the alkyl groups become more hindered.[2]

$$TMSCHBr_2 \xrightarrow[\text{3. } H_2O_2,\ OH^-]{\text{1. 2 equiv Li, THF; 2. } (C_5H_{11})_3B} TMSCH(OH)C_5H_{11} \qquad (3)$$

79%

Deprotonation.

(Dibromomethyl)trimethylsilane can be deprotonated with ***Lithium Diisopropylamide*** at -78 °C. Reaction of the intermediate anion with *n*-butyl iodide (eq 4) furnished the alkylated product in 93% yield.[3,4] If the anion was allowed to warm to 20 °C in the absence of an electrophile, the bis(trimethylsilyl)ethylene (eq 5) was produced.[4]

$$TMSCHBr_2 \xrightarrow[\text{2. BuI}]{\text{1. LDA, -78 °C}} TMSCBr_2Bu \qquad (4)$$

93%

$$TMSCHBr_2 \xrightarrow[\text{2. 20 °C}]{\text{1. LDA, -78 °C}} TMSBrC{=}CBrTMS \qquad (5)$$

50%

Vinylsilanes.

Two reports have appeared on the formation of the 1,1-di-Grignard reagent using ***Magnesium Amalgam***. In the first

report, the di-Grignard, prepared indirectly from the dizinc reagent, was combined with cyclohexanone to produce the vinylsilane in 40% yield.[5] In the second, satisfactory results were obtained only with the non-enolizable benzophenone (eq 6). Cyclohexanone afforded only 13% of the vinylsilane. In addition, the di-Grignard was treated with ***Chlorotrimethylstannane*** to furnish bis(trimethylstannyl)trimethylsilylmethane in 94% yield.[6]

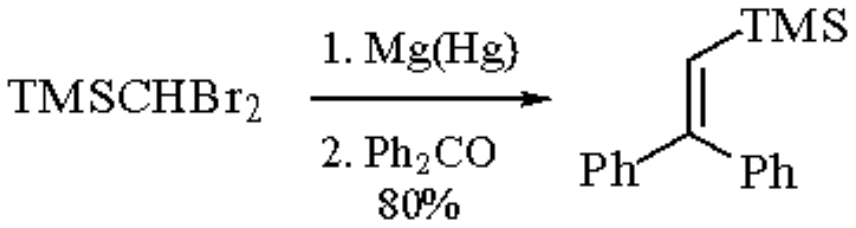

(6)

The *gem*-dichromium reagent was prepared by reduction of the dibromide with ***Chromium(II) Chloride***. This reagent will stereoselectively produce (*E*)-alkenylsilanes in excellent yield. The reagent can chemoselectively react with an aldehyde (eq 7) in the presence of a ketone.[7]

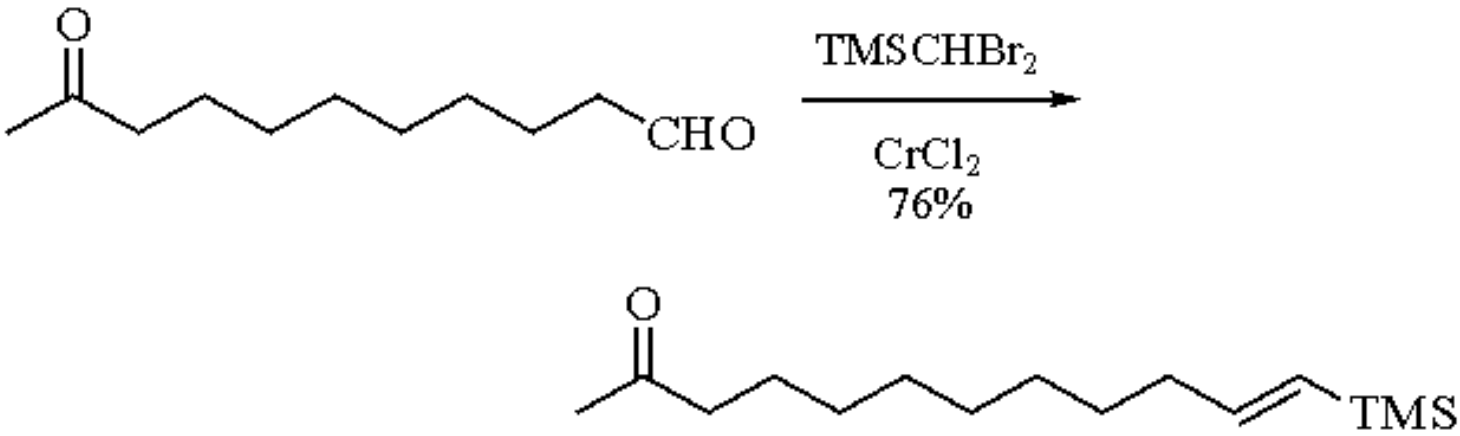

(7)

Esters (eq 8) and thioesters (eq 9) can be silylmethylenated by the action of the dibromide with low-valent titanium prepared from ***Titanium(IV) Chloride*** and ***Zinc***. The reaction produces β-hetero-substituted vinylsilanes and was (*Z*) selective.[8]

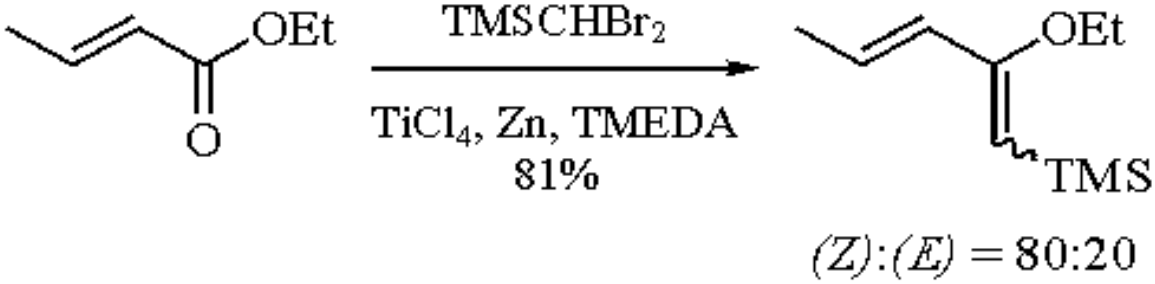

(8)

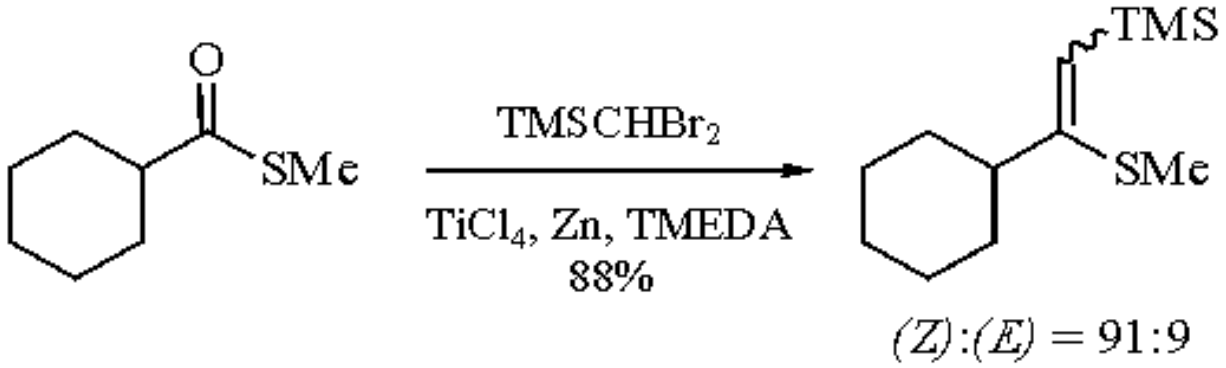

(9)

Miscellaneous.

The kinetics of the cleavage of the dibromomethyl group by ammonia buffer have been reported.[9]

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2,4-Dibromo-3-pentanone[1]

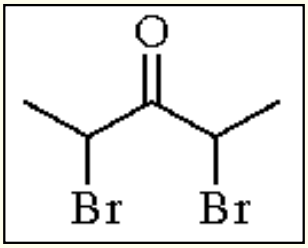

[815-60-1] · $C_5H_8Br_2O$ · 2,4-Dibromo-3-pentanone · (MW 243.93)

(a good source of the dimethyloxyallyl cation; especially useful for [4 + 3] and [3 + 2] cycloadditions[1])

Physical Data: bp 194-5 °C/732 mmHg; *d* 1.771 g cm^{-3} (18 °C).

Solubility: quantitative data unavailable. Sol moderately polar to polar organic solvents.

Form Supplied in: not generally commercially available and should be prepared as needed.[2,3]

Analysis of Reagent Purity: obtained as a mixture of (+)-, (-)-, and *meso* isomers which can be assayed by NMR.

Handling, Storage, and Precautions: is a powerful lachrymator and a skin irritant. If contact with the skin occurs the affected area should be thoroughly washed with soap followed by a solution of sodium bicarbonate.[2]

[4 + 3] Cycloadditions.

The chemistry of 2,4-dibromo-3-pentanone (**1**) is dominated by its ability to form oxyallylic cations (**2**) and (**3**) under a variety of conditions (eq 1). Though other reaction pathways are possible, these intermediates, particularly (**2**), have been used in most cases as dienophiles in a [4 + 3] cycloaddition with dienes.[1] 2,4-Dibromo-3-pentanone serves as a prototype for other polyhalogenated ketones which exhibit similar chemistry (see ***1,1,3,3-Tetrabromoacetone***).

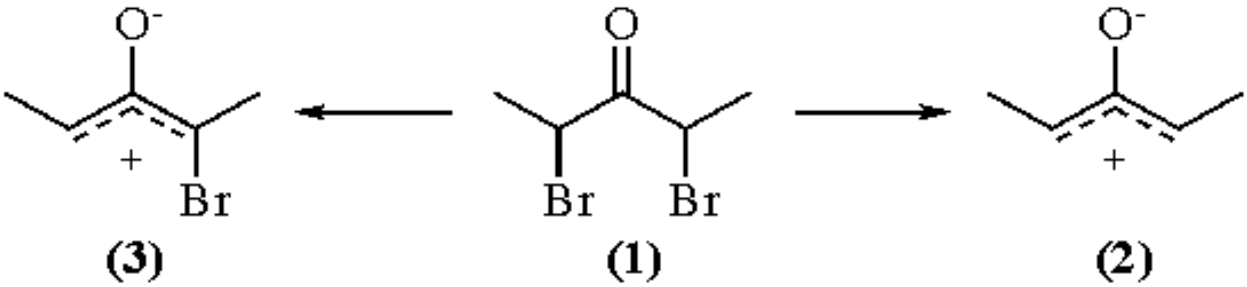

(1)

The reactivity of (**2**) is determined to a considerable extent by the reaction conditions under which it is generated. Of particular importance is the nature of the reagent used in the reductive debromination of (**1**). Reagents which have found

application in this process include ***Diethylzinc***,[4] ***Zinc/Copper Couple***,[5] ***Sodium Iodide-Copper***,[2,5b] ***Nonacarbonyldiiron***,[1c,3] ***Cerium(III) Chloride-Tin(II) Chloride***,[6] and ***Zinc/Silver Couple***.[7] These reagents preclude the formation of (**2**) as such and require inclusion of a counterion(s) which, in combination with solvent and other effects, modifies the reactivity of (**2**) with respect to scope, yield, and stereoselectivity in its [4 + 3] cycloaddition reaction with various dienes.

For the reaction of (**2**) with furan, expected products include isomers of 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**4**) (eq 2). Table 1 summarizes the results obtained with several different reagents. Yields are generally high and stereoselectivity good in most cases. The need for excess furan in many of these processes limits the generality of the reaction. The high stereoselection in the Zn/Ag reaction is noteworthy.[7] All of the methods are convenient, though concerns about the toxicity and expense of nonacarbonyldiiron make its use less attractive.

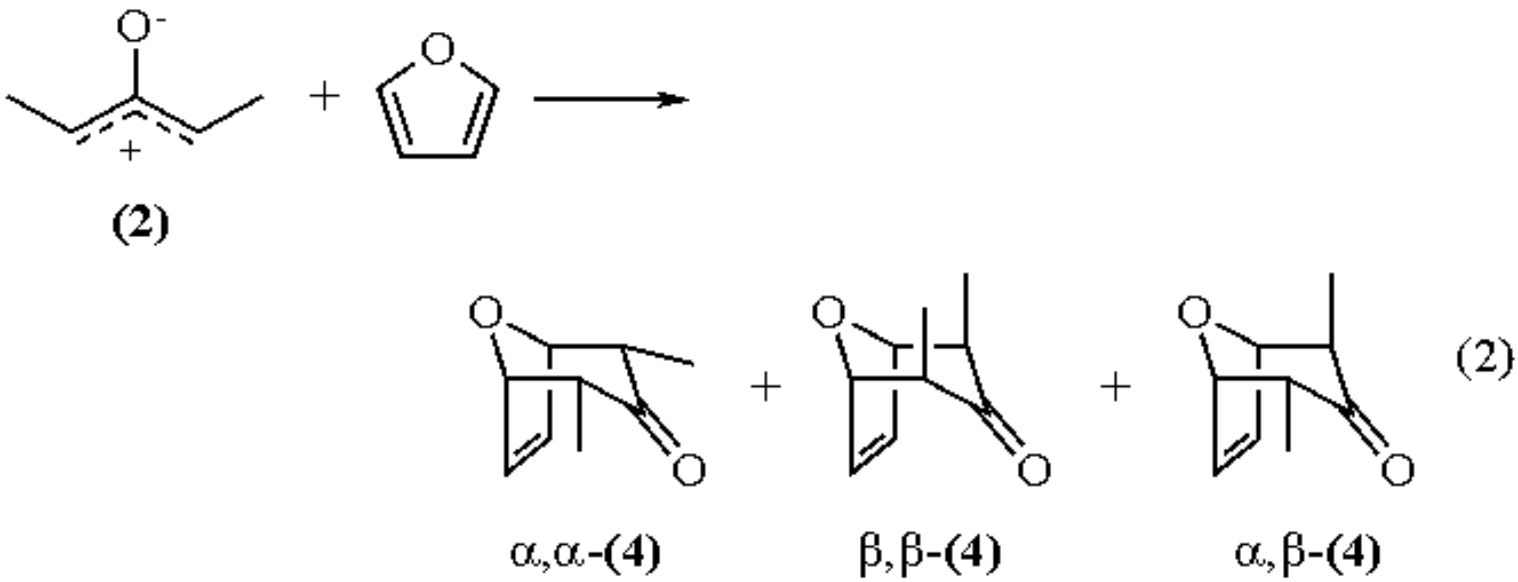

Table 1 Reaction of (2) with Furan (eq 2)

Reagent	Furan	Product ratio of (4) a,a:b,b:a,b	Yield (%)
Et_2Zn	Solvent	9:1:0	53[4]
$Fe_2(CO)_9$	Solvent	1:1.3:0	90[3b]
NaI, Cu	4 equiv	30:1:2	80[2,5b]
$CeCl_3$, $SnCl_2$	10 equiv	6.2:2.8:1	90[6]
Zn/Ag	10 equiv	1:0:0	80[7]
Zn/Cu	10 equiv	9:1:1	85[2a]

A variety of other furans have successfully undergone [4 + 3] cycloaddition with (**2**). However, it appears that an

exhaustive study of substituent effects on the cycloaddition process has not been made. The reaction of pinofuran (**5**) with (**2**) gave (**6**) as a mixture of isomers, resulting from a sterically controlled approach of the oxyallyl *anti* to the *gem*-dimethyl group of (**5**), but through both extended and compact transition states (eq 3).[8]

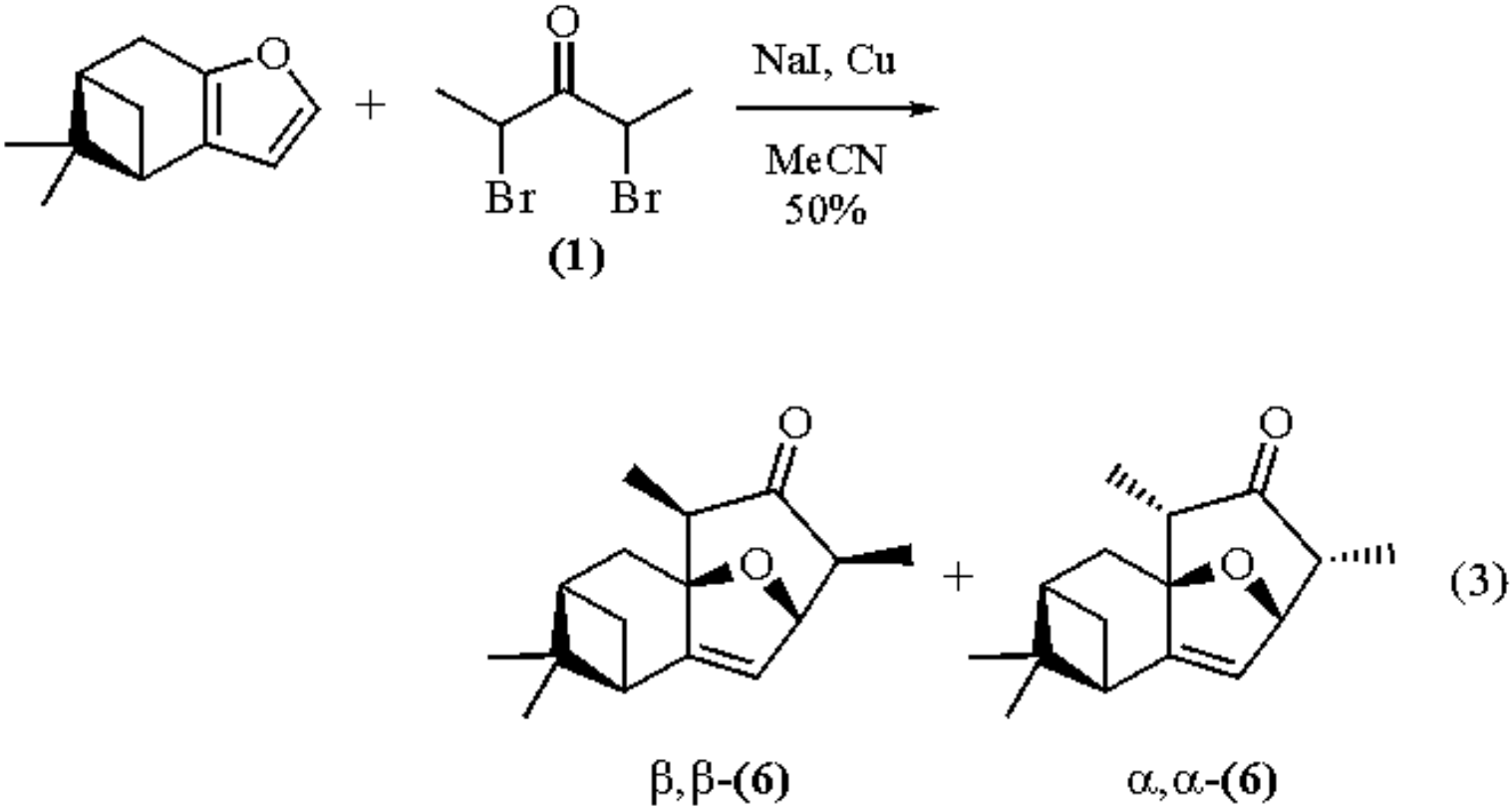

The cycloadducts derived from (**2**) and various furans have found considerable application in synthesis. They have been used in the synthesis of the Prelog-Djerassi lactone,[9] nonactic acid,[10] and fragments of rifamycin S[11] and ionomycin[12] and hold considerable promise as templates for the stereoselective synthesis of polyfunctional acyclic systems.[13]

Other dienes have been used to trap (**2**). Cyclopentadienes,[3b,5c] fulvenes,[5c,14] anthracenes,[15] and acyclic butadienes[3b] have been successfully employed, especially with (**2**) generated using the reaction of (**1**) with $Fe_2(CO)_9$ (eq 4). Iron tricarbonyl complexes of the dienes may also be used to both generate (**2**) and subsequently trap it. Cycloadducts from the reaction of (**2**) with acyclic butadienes have been converted in a general fashion to tropones and tropolones.[16]

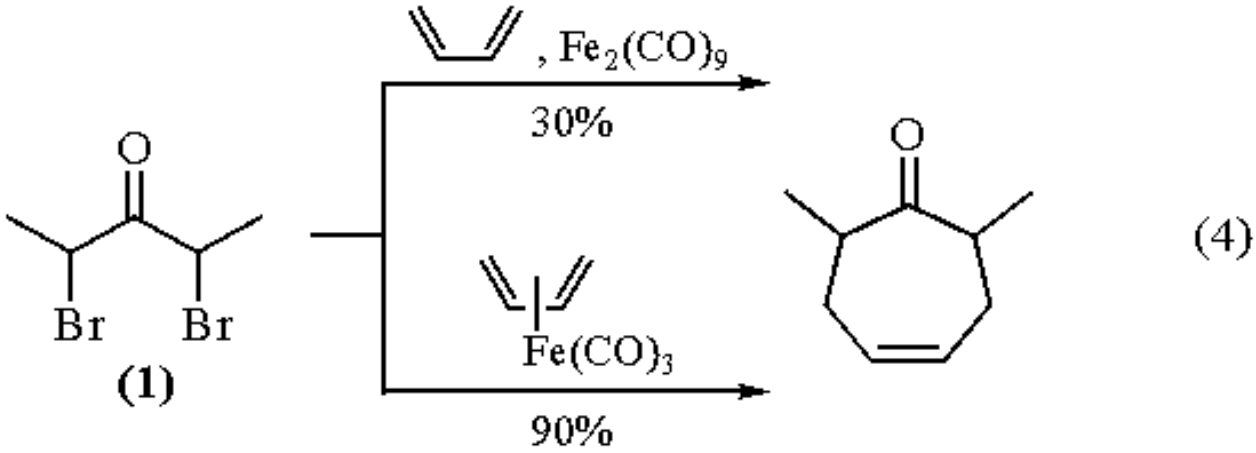

Pyrroles can also be effective traps for (**2**), leading to [4 + 3] cycloadducts. *N*-Methylpyrrole gave a [4 + 3] cycloadduct

upon reaction with (**2**) generated from NaI/Cu but only Friedel-Crafts substitution products with the oxyallyl generated from Zn/Cu or $Fe_2(CO)_9$ (eq 5).[3b,17] Better results were obtained in the latter case using *N*-methoxycarbonyl- or *N*-acetylpyrroles (eq 6).[18]

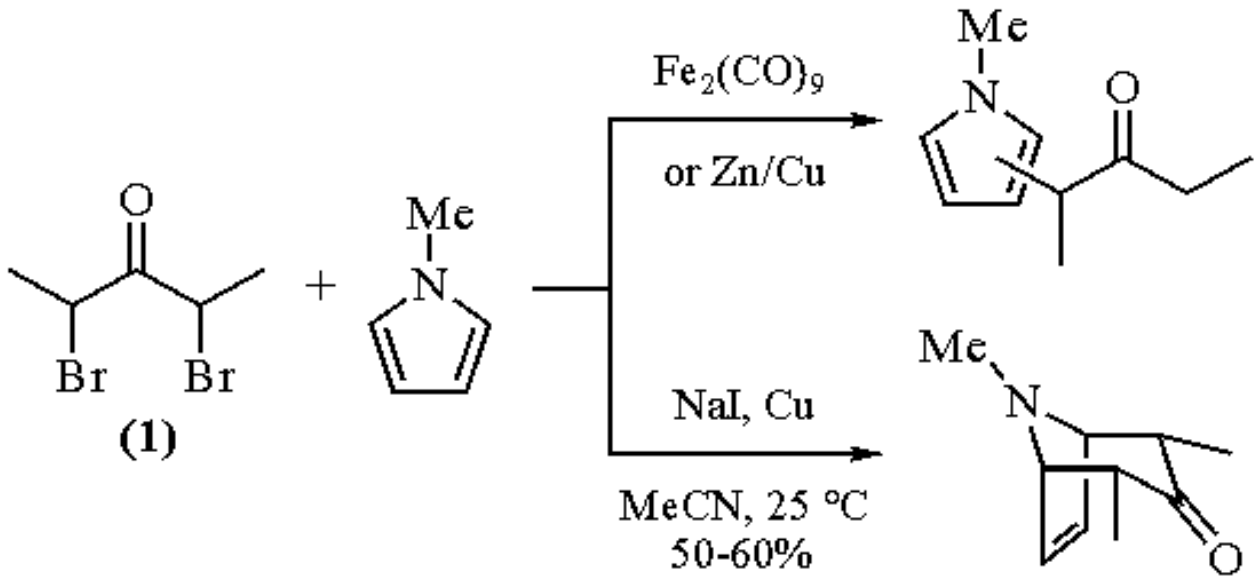

(5)

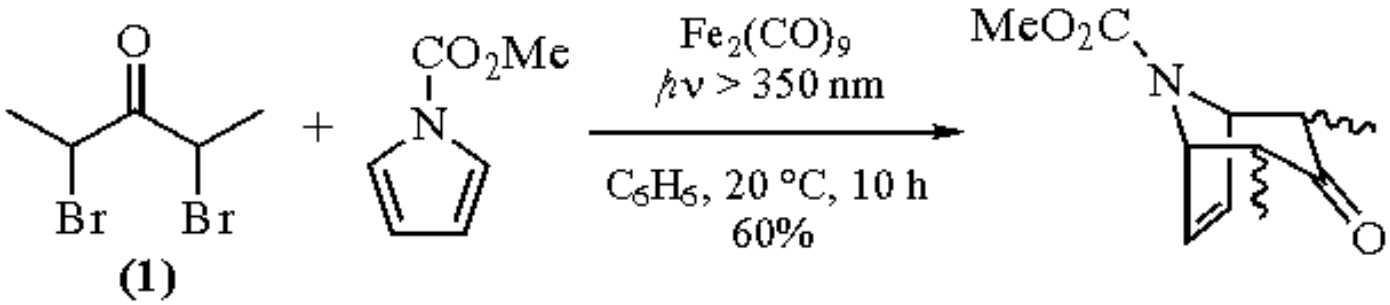

(6)

Generally, thiophenes give only Friedel-Crafts substitution products upon attempted [4 + 3] cycloaddition with oxyallyls.[1] However, 2,5-dimethylthiophene gave [4 + 3] cycloadducts with (**2**) generated from $Fe_2(CO)_9$ (eq 7).[19] This result strongly suggests that the use of substituted thiophenes in [4 + 3] cycloaddition processes may be generally feasible.

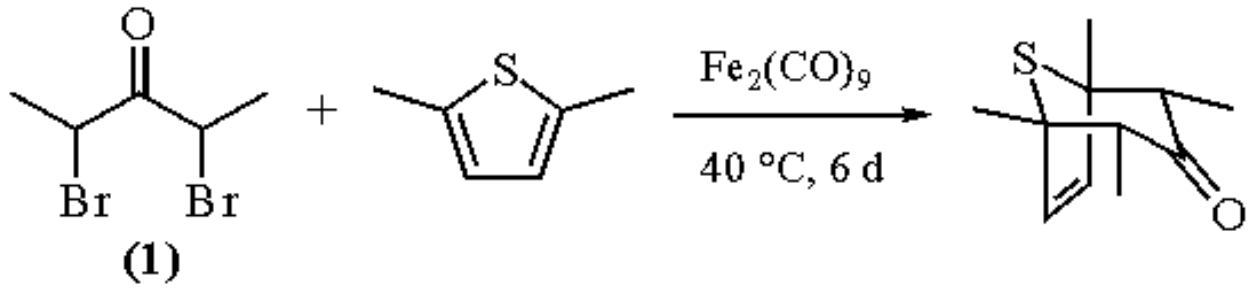

(7)

More unusual heterocycles, including selenophene and tellurophene,[19] diphenylisobenzofuran and *N*-*t*-butylisoindole,[20] and 1-phenyl-1-thio-3,4-dimethylphosphole,[21] have been used to trap (**2**). In the latter case, an unexpected hydrolysis took place in the course of the reaction to give bicycle (**7**) as the sole [4 + 3] cycloadduct, albeit in low yield (eq 8).

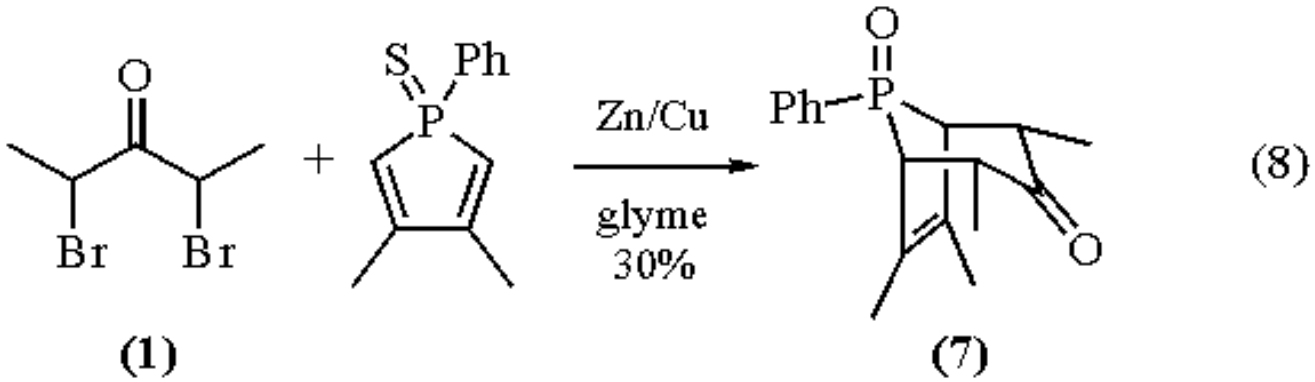

[3 + 2] Cycloadditions.

The trapping of (**2**) with π-systems in a [3 + 2] sense has been the subject of a number of studies. The reaction of (**2**) with morpholino enamines has been shown to lead to cyclopentenones in a general fashion (eq 9).[3a,22] ***Iron-Graphite*** ($C_{24}Fe$) has been introduced as a reagent for the conversion of (**1**) to (**2**) in the context of this annulation process.[23] Related cycloadditions also occur with *N*,*N*-bis-silyl enamines and *N*-tosyl enamines (eq 10).[24,25]

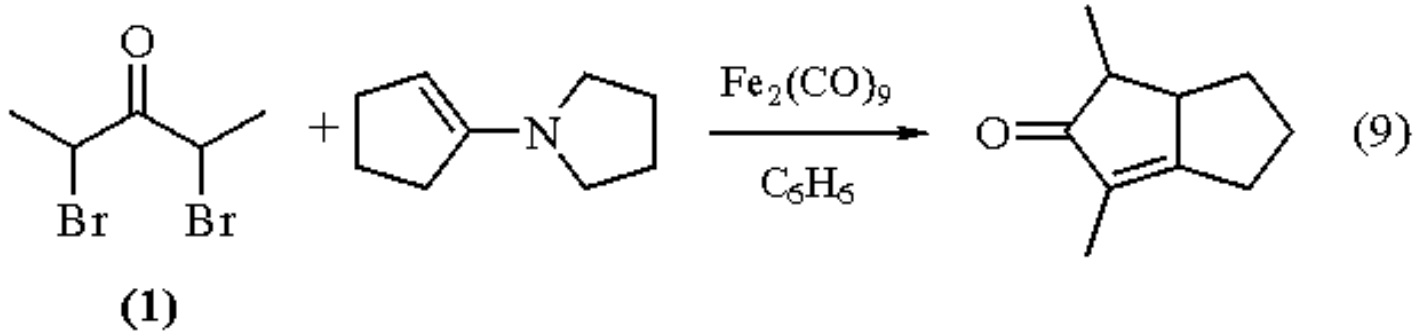

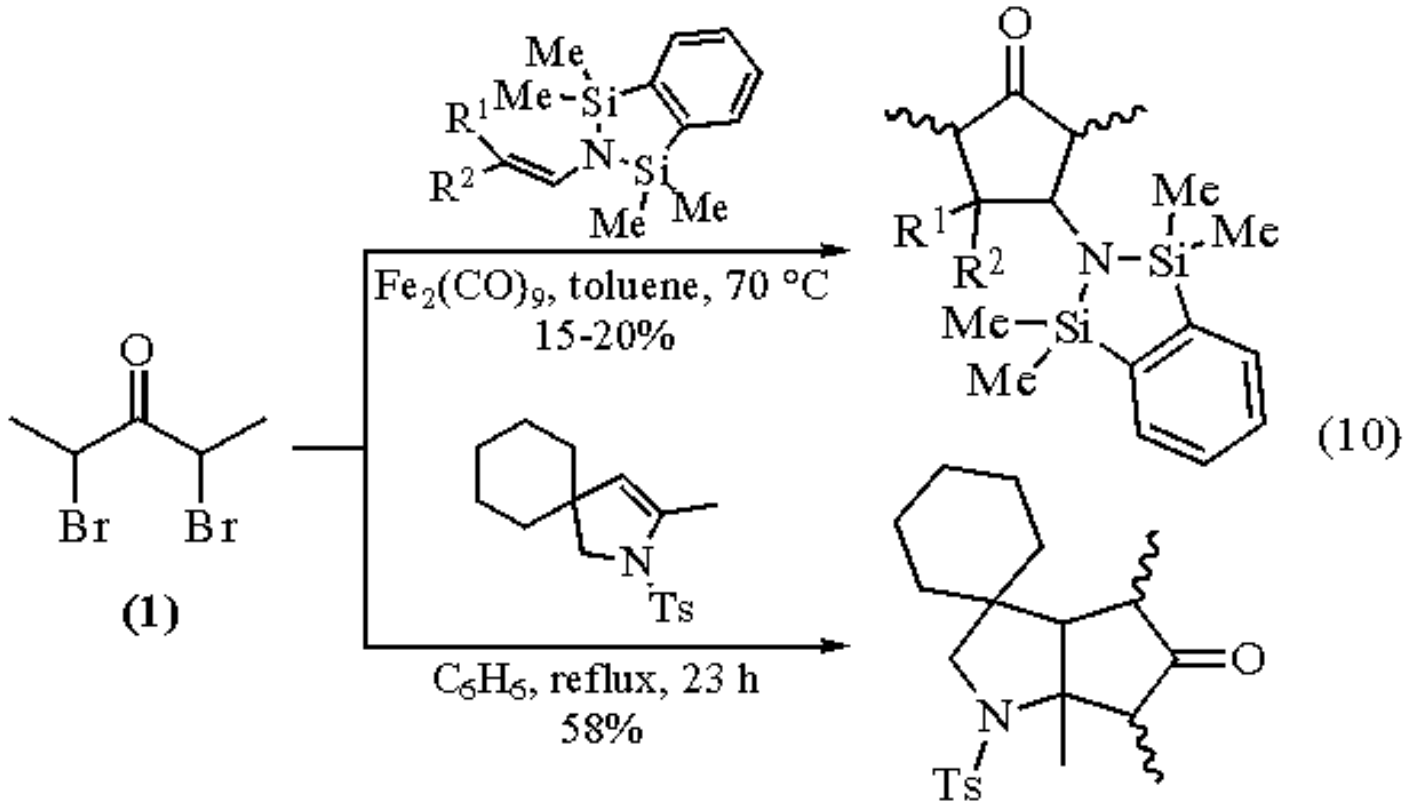

Aromatic alkenes are also capable of trapping (**2**) to afford cyclopentanones (eq 11).[26] Dienes can also exhibit regioselectivity characteristic of [3 + 2] cycloadditions in their reactions with (**2**).[27]

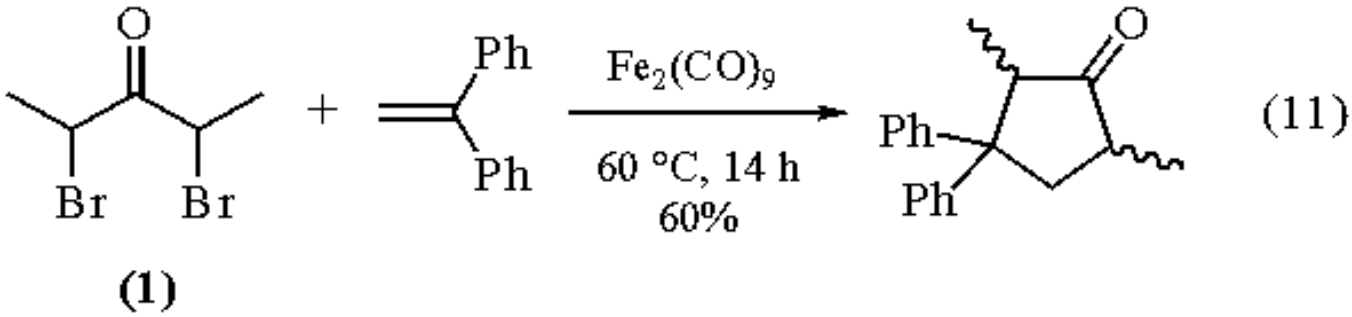

A general synthesis of 3(2*H*)-furanones based on the reaction of (**2**) with dimethylamides has been developed (eq 12).[28] An interesting example is the synthesis of (**8**), which, while derived from (**2**), is also a precursor of this species (eq 13).[29]

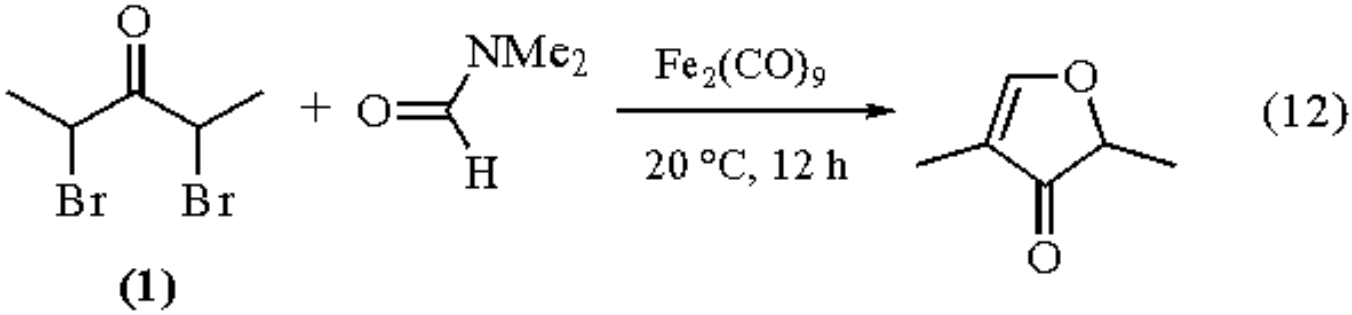

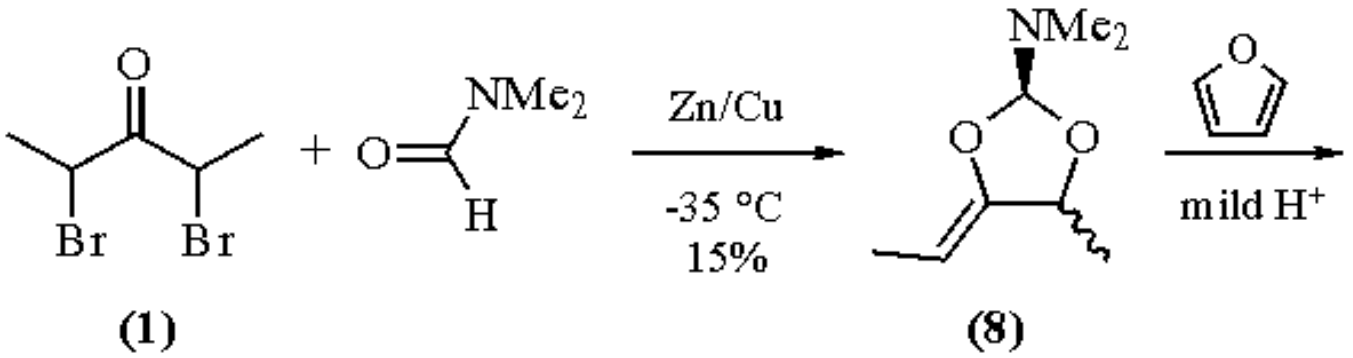

(13)

The reaction of (**2**) with 1,1-dimethoxyethylene resulted in the formation of heterocycle (**9**) in high yield (eq 14). Attempted trapping with alkynes did not produce [3 + 2] cycloadducts but led to low yields of substituted allenes (eq 15).[30]

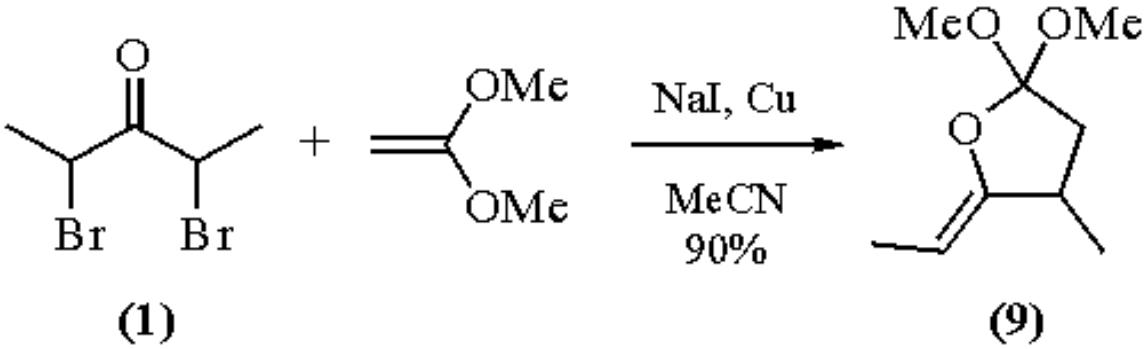

(14)

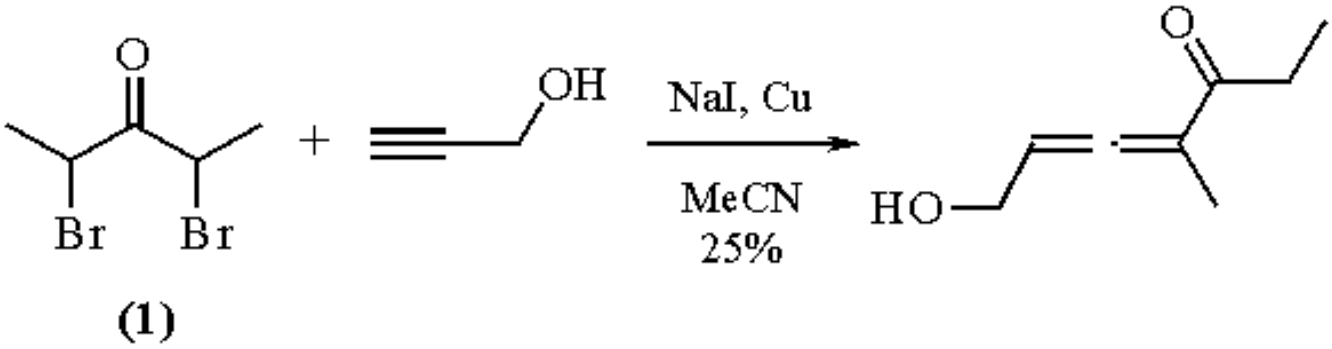

(15)

[3 + 3] Cycloadditions.

Only one example of this type of reaction with (**2**) has been reported. Reaction of (**2**) with η^1-allyl(cyclopentadienyl)dicarbonyliron in the presence of $Fe_2(CO)_9$ followed by oxidation resulted in the synthesis of 2,6-dimethyl-4-methoxycarbonylcyclohexanone in low yield (eq 16).[25]

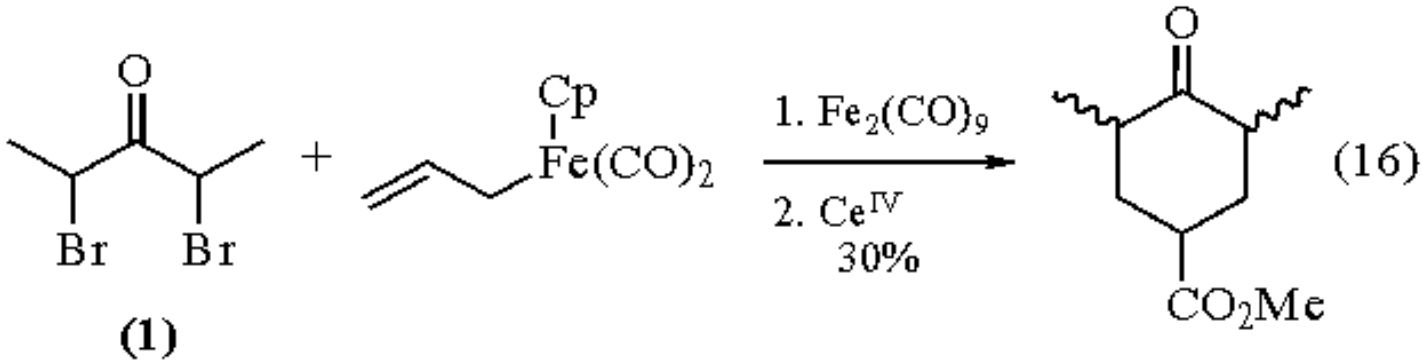

Miscellaneous Reactions.

A number of other synthetically useful transformations of (**1**) have been developed. Treatment of (**1**) with isopropylamine gave imino ketone (**10**) and diimine (**11**) in 72% yield in a ratio of 98:2 (eq 17).[31] All proposed mechanistic possibilities for this transformation involve oxyallylic species, including (**2**) and (**3**).

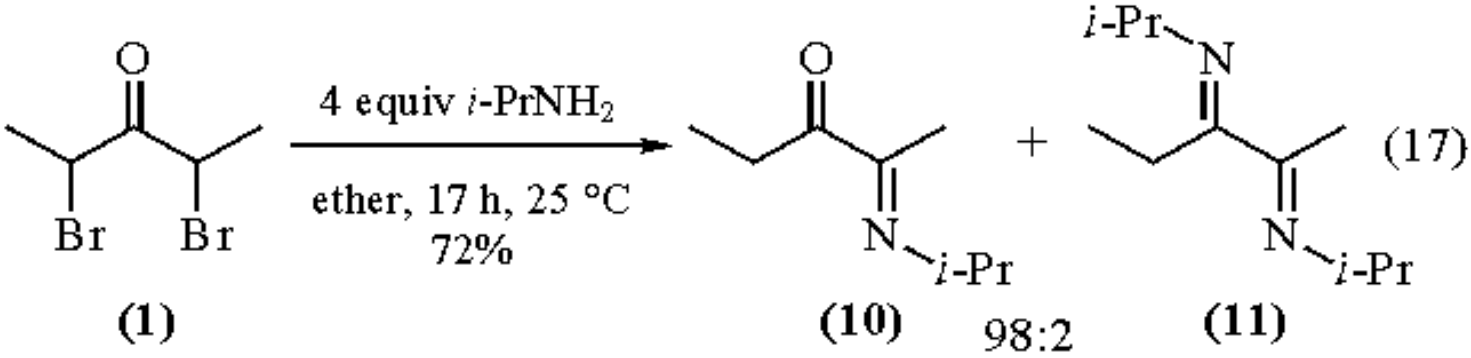

Nucleophilic trapping of (**2**) with methanol served to support the intermediacy of this oxyallyl in various cycloaddition processes (eq 18).[32] This trapping reaction has not been synthetically exploited.

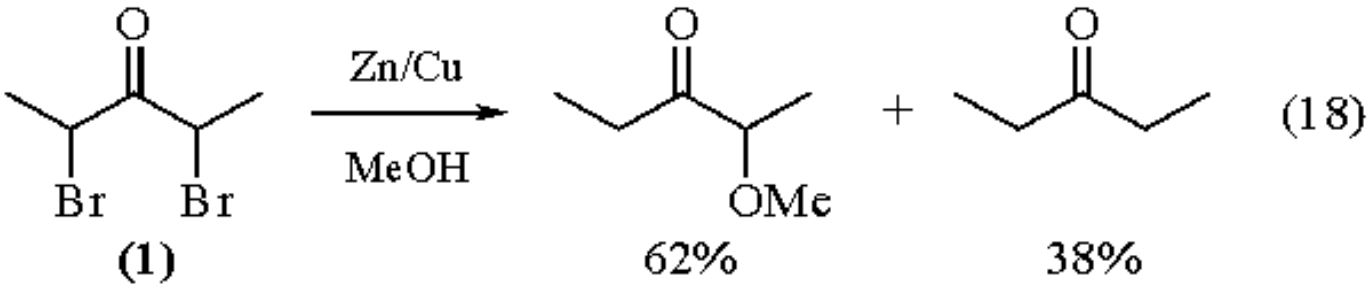

A palladium-mediated reductive dehalogenation of (**1**) may hold promise as a new means of generating (**2**).[33] An electrochemical reduction of (**1**) apparently resulted in the formation of a cyclopropanone which was nucleophilically trapped under the reaction conditions (eq 19).[34]

2,4-Dibromo-3-pentanone

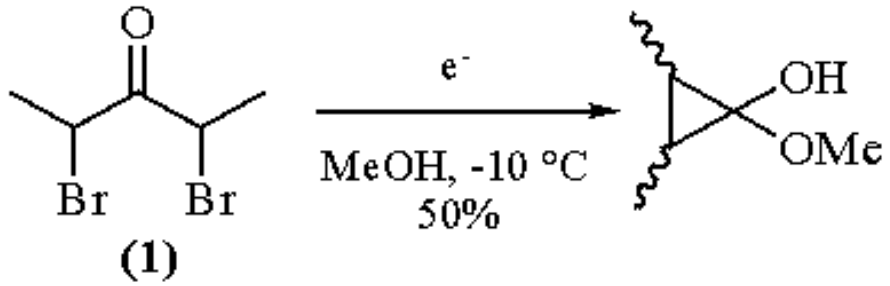

(19)

Finally, treatment of (**1**) with cuprates resulted in a unique reductive alkylation. Alkylative trapping of the resulting enolate gave reasonable yields of ketones not easily accessible by other routes (eq 20).[35]

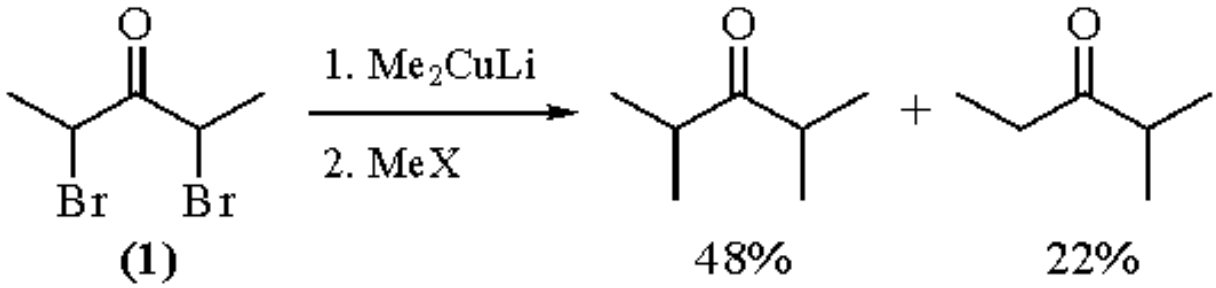

(20)

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1,3-Dibromo-2-pentene

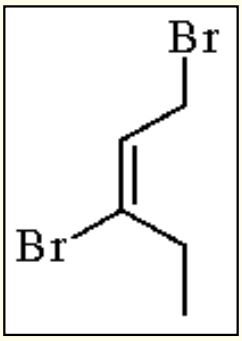

[59838-04-9] · $C_5H_8Br_2$ · 1,3-Dibromo-2-pentene · (MW 227.93)

(ethyl vinyl ketone equivalent used in the synthesis of sesquiterpenes)

Physical Data: bp 88 °C/3 mmHg.

Form Supplied in: colorless liquid stabilized with silver wool.

Preparative Method: is prepared in two steps from commercially available 2-pentyn-1-ol (eq 1). Reduction of the alkynic alcohol with ***Lithium Aluminum Hydride*** in the presence of ***Sodium Methoxide*** followed by bromination of the intermediate aluminate afforded the vinyl bromide which was then converted to the final product by treatment with ***Phosphorus(III) Bromide*** in pyridine.[1]

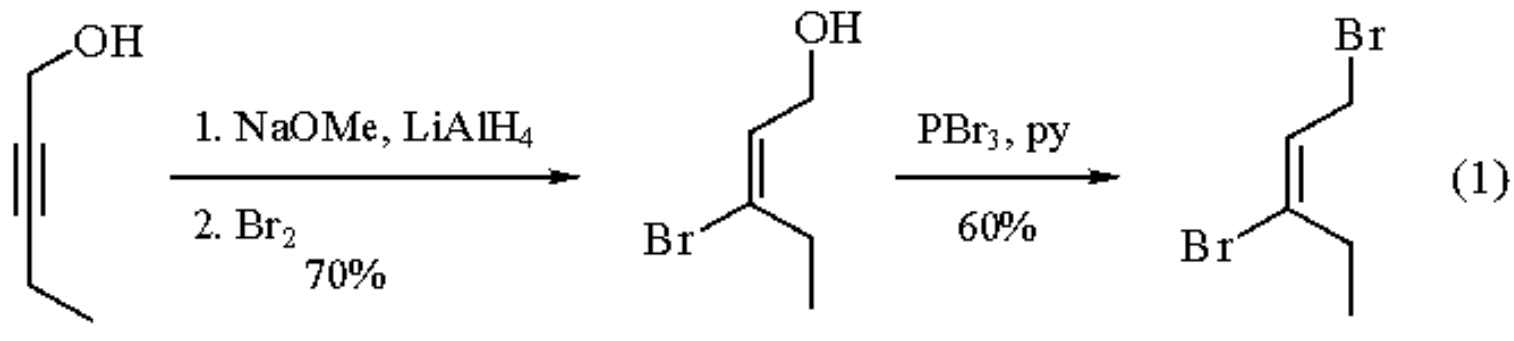

Handling, Storage, and Precautions: lachrymator; stored cold in an amber bottle to protect from light. Use in a fume hood.

Ethyl Vinyl Ketone Equivalent.

1,3-Dibromo-2-pentene has been used as an ethyl vinyl ketone equivalent in cases where a Michael addition to the unsaturated ketone failed. β-Cyperone was synthesized using this strategy via alkylation of 6-methyl-3-butylthio-2-cyclohexen-1-one using ***Lithium Diisopropylamide*** as the base to yield the 6,6-dialkylated enone system in 60% yield (eq

2). Further elaboration resulted in the synthesis of the target sesquiterpene.[1]

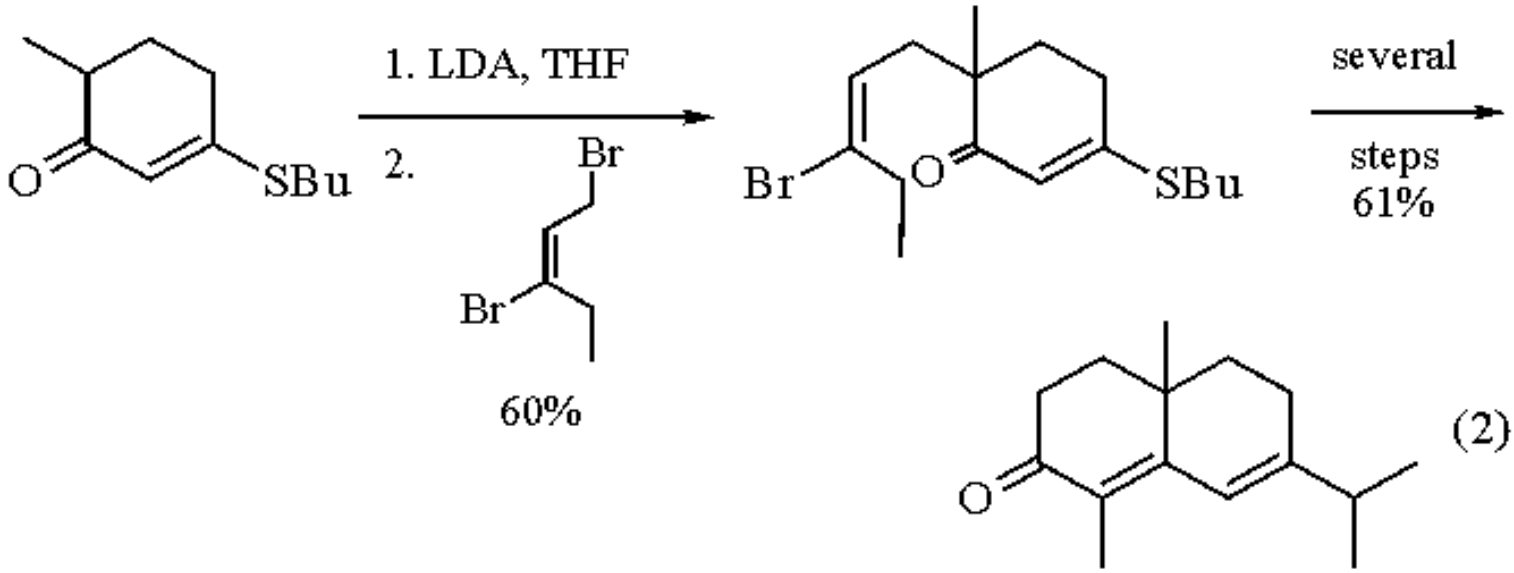

In a related strategy, 1,3-dibromo-2-pentene was used as a building block in the synthesis of compounds related to sclerosporal (eq 3). Alkylation of (-)-carvone with the allylic bromide using ***Potassium t-Butoxide*** as base in refluxing benzene afforded two stereoisomeric products in 55% and 22% yields. These isomers could be separated by chromatography and subsequently converted to the known enones which were dehydrogenated and photochemically rearranged to guaienones.[2]

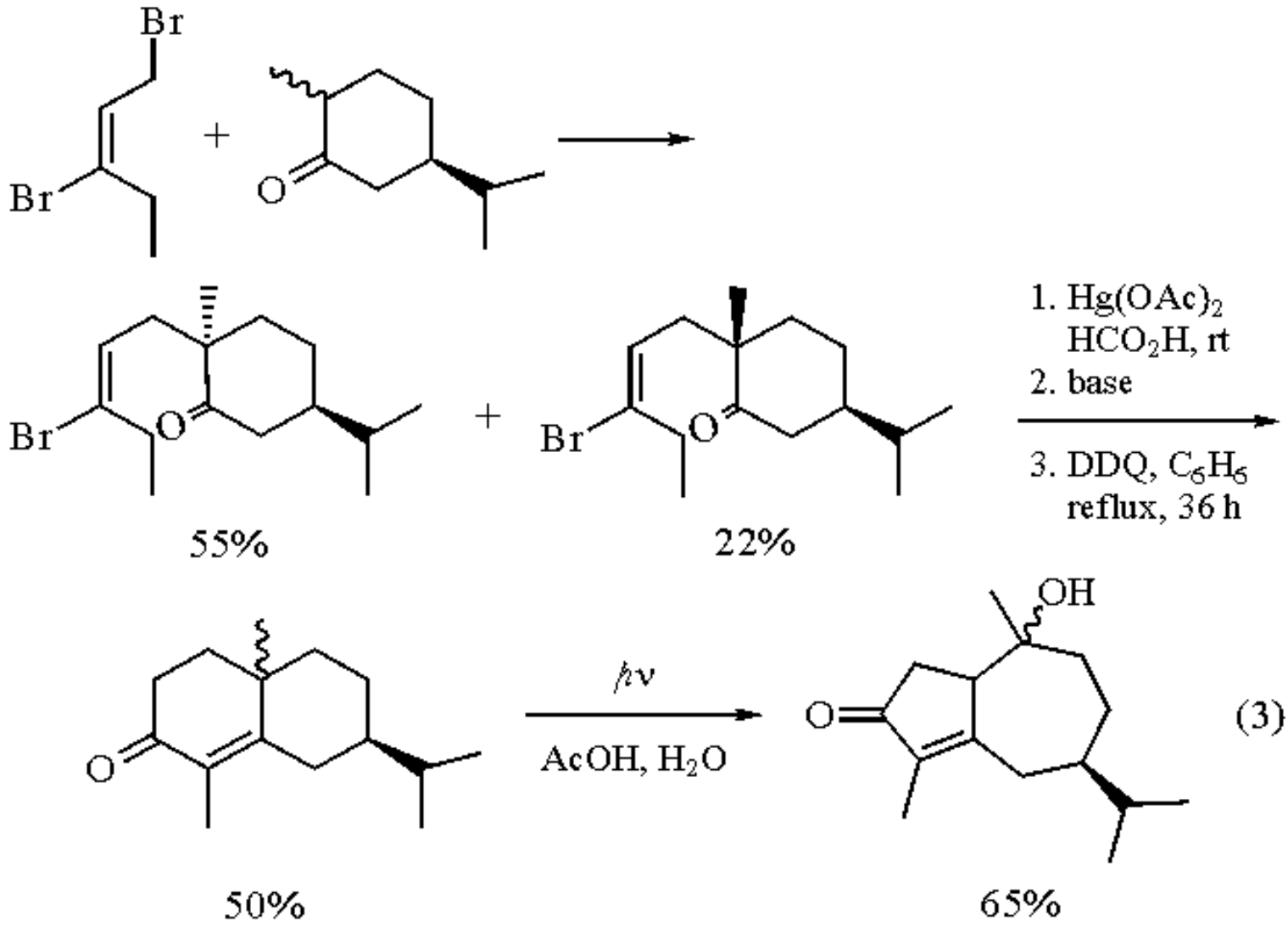

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1,1-Dibromopentyllithium[1]

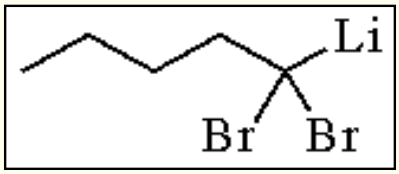

[41294-30-8] · $C_5H_9Br_2Li$ · 1,1-Dibromopentyllithium · (MW 235.88)

(used in conjunction with *n*-butyllithium for homologation of carbonyl compounds[1])

Solubility: sol ether, THF.

Preparative Method: prepared by the reaction of 1,1,1-tribromopentane with butyllithium in THF-ether at -100 °C.[1]

Handling, Storage, and Precautions: stable only at very low temperature (-100 °C); cannot be stored.

Homologation of Ketones.

1,1-Dibromo-1-pentyllithium adds readily to aldehydes or ketones. In the presence of a second equiv of ***n-Butyllithium***, a further lithium carbenoid[2,3] can be generated which undergoes a rearrangement in which a preferential migration of a hydrogen over an organic group is observed (eq 1). After hydrolysis, a mixture of two isomeric carbonyl compounds is observed (eqs 2 and 3). In some cases, only one rearrangement product is produced (eq 4)[1]. The reaction can be extended to other 1,1-dibromides (eq 5),[1] as well as to the performance of ring expansions (eq 6).[1] The related homologation of esters using ***Dibromomethyllithium*** has been extensively investigated.[4]

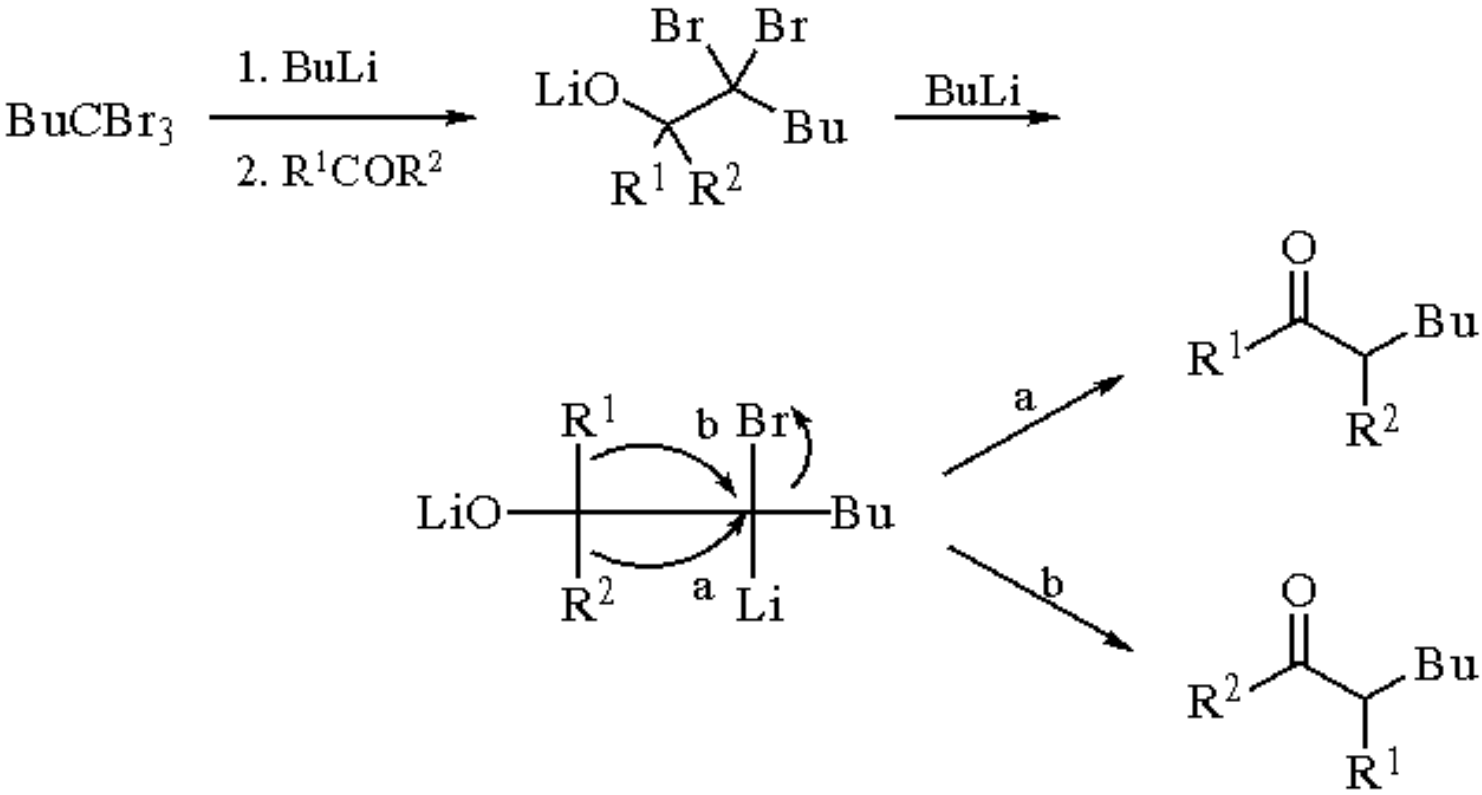
BuCBr3
1. BuLi
2. R1COR2
Br Br
LiO
Bu
R1 R2
BuLi
R1
b Br
LiO
Bu
R2
a Li
a
b
O
R1
Bu
R2
O
R2
Bu
R1

(1)

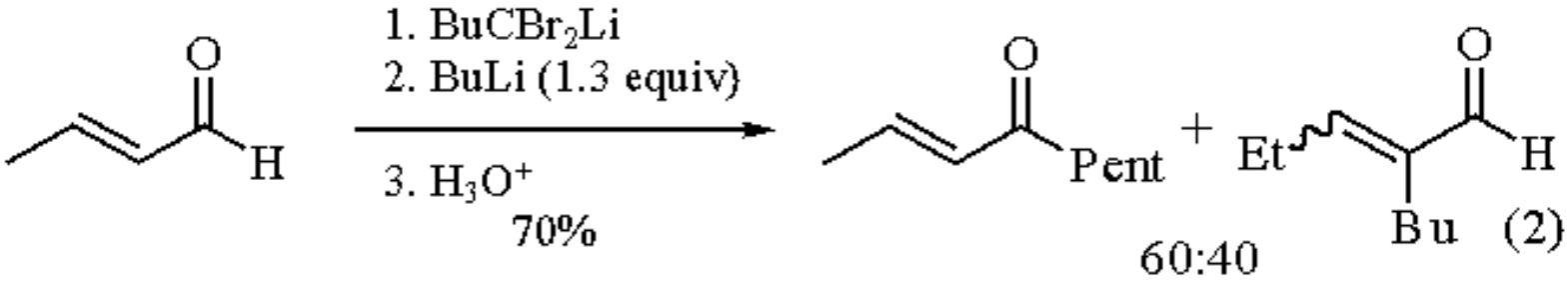
O
H
1. BuCBr2Li
2. BuLi (1.3 equiv)
3. H3O+
70%
O
Pent
+
Et
O
H
Bu
60:40

(2)

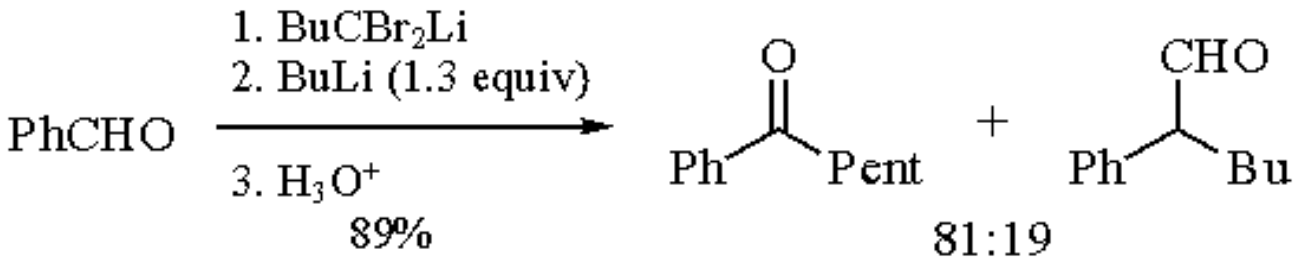
PhCHO
1. BuCBr2Li
2. BuLi (1.3 equiv)
3. H3O+
89%
O
Ph
Pent
+
CHO
Ph
Bu
81:19

(3)

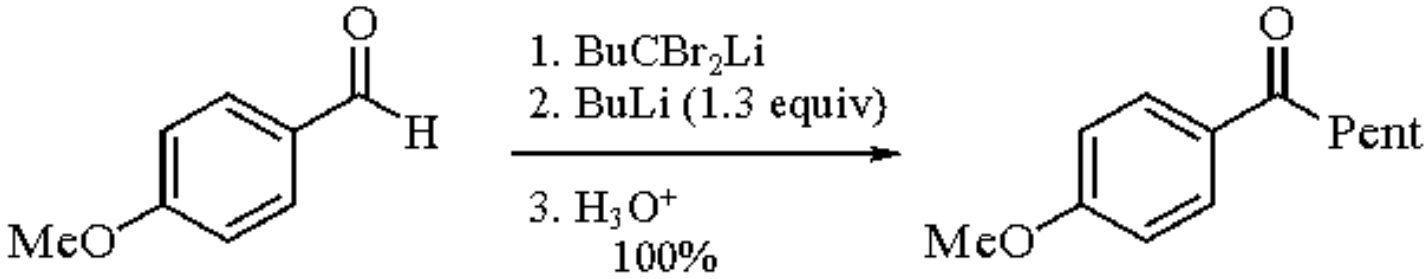
O
H
MeO
1. BuCBr2Li
2. BuLi (1.3 equiv)
3. H3O+
100%
O
Pent
MeO

(4)

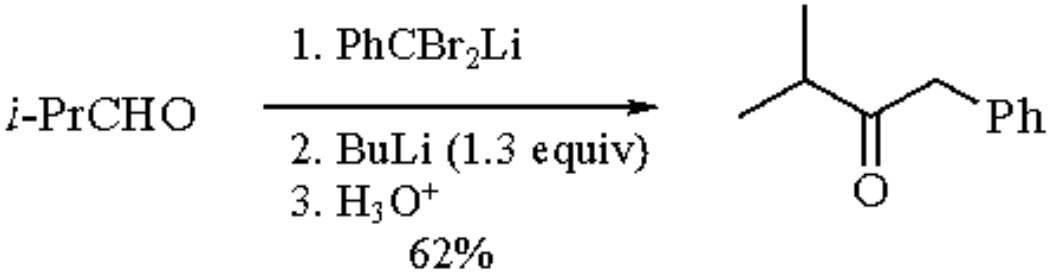

(5)

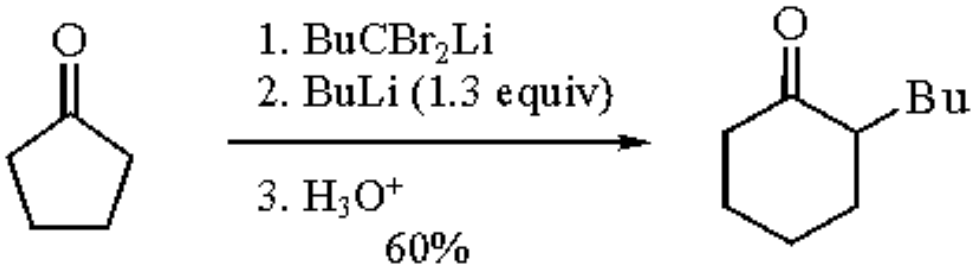

(6)

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1. Villiéras, J.; Perriot, P.; Normant, J. F. *S* **1979**, 968.
2. (a) Villiéras, J.; Bacquet, C.; Normant, J. F. *JOM* **1972**, *40*, C1. (b) *JOM* **1973**, *97*, 325. (c) Villiéras, J.; Bacquet, C.; Normant, J. F. *BSF* **1975**, 1797. (d) Köbrich, G.; Grosser, J. *TL* **1972**, 4117. (e) Villiéras, J.; Reliquet, A.; Normant, J. F. *JOM* **1978**, *144*, 263. (f) Villiéras, J.; Reliquet, A.; Normant, J. F. *S* **1978**, 27.
3. (a) Villiéras, J. *BSF* **1967**, *1511*, 1520. (b) Villiéras, J.; Rambaud, M.; Tarhouni, R.; Kirschleger, B. *S* **1981**, 68. (c) Villiéras, J.; Kirschleger, B.; Tarhouni, R.; Rambaud, M. *BSF* **1986**, 470. (d) Villiéras, J.; Tarhouni, R.; Kirschleger, B.; Rambaud, M. *BSF* **1985**, 825. (e) Villiéras, J.; Rambaud, M.; Kirschleger, B.; Tarhouni, R. *BSF* **1985**, 837.
4. (a) Kowalski, C. J.; Haque, M. S. *JACS* **1986**, *108*, 1325. (b) Kowalski, C. J.; Lal, G. S. *TL* **1987**, *28*, 2463. (c) Kowalski, C. J.; Lal, G. S. *JACS* **1988**, *110*, 3693. (d) Kowalski, C. J., Reddy, R. E. *JOC* **1992**, *57*, 7194.

Paul Knochel

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2,3-Dibromopropene

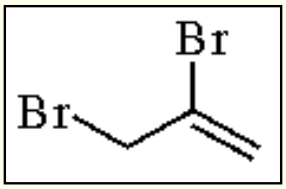

[513-31-5] · $C_3H_4Br_2$ · 2,3-Dibromopropene · (MW 199.87)

(a bifunctional reagent, widely employed in coupling reactions, and as a precursor of key intermediates for cycloaddition reactions)

Alternate Names: 1,2-dibromo-2-propene; 2-bromoallyl bromide.

Physical Data: bp 140-142 °C; 75-76 °C/75 mmHg; 42-43 °C/18 mmHg; *d* 2.045 g cm^{-3}; *n*20D 1.544.

Form Supplied in: colorless oil; commercially available.

Purification: may be distilled under atmospheric pressure with very slight decomposition, but becomes highly colored on standing in a glass-stoppered bottle.

Handling, Storage, and Precautions: irritating to skin, eyes, and respiratory system. Use in a fume hood.

Introduction.

Interesting products can be prepared by taking advantage of the different reactivity of the allylic and vinylic halogen atoms. The products obtained can be further elaborated in a variety of manners, frequently leading to polycycles.

Coupling Reactions with Organometallic Reagents.

The allylic and the vinylic bromine atoms of 2,3-dibromopropene (**1**) can be selectively substituted in two consecutive cross-coupling steps.[1] Thus 1,1-disubstituted ethylenes (**2**) can be easily prepared by first adding the appropriate Grignard reagent to a solution of (**1**) in THF at rt. After completion of the coupling reaction, a catalytic amount of $NiCl_2$(dppp) is added, and a solution of the second Grignard reagent is added to the mixture containing the intermediate alkenyl bromide (eq 1).

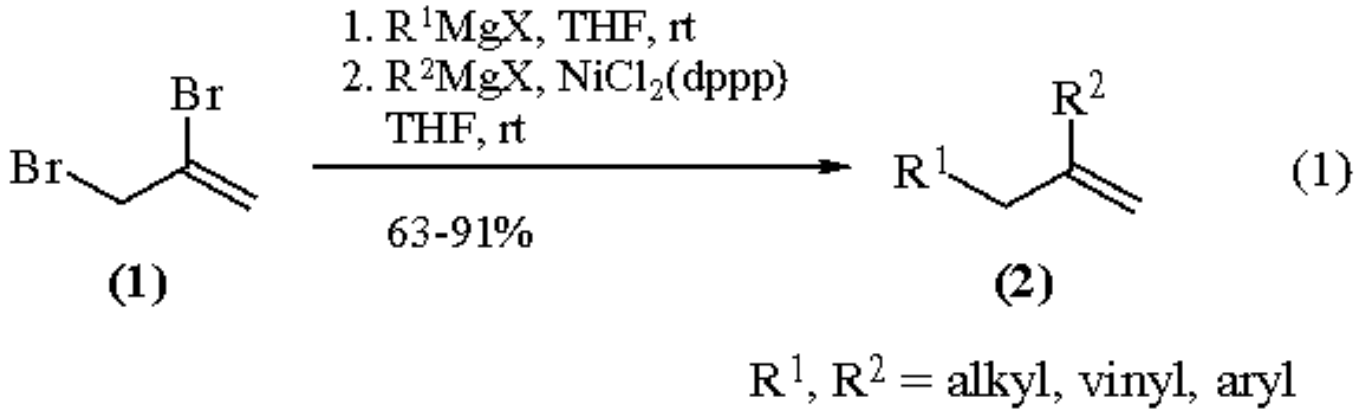

The allylic bromide can be also substituted by terminal alkynes in the presence of a catalytic amount of a copper(I) salt and tetra-*n*-butylammonium chloride[2] or by alkenylcopper reagents.[3,4] Highly functionalized 2-bromo-1-alkenes are prepared[5] by Cu^{I}-catalyzed reaction of functionalized organozinc halides. Alkylation (***Lithium Diisopropylamide***, THF/HMPA) of methyl 2-(trimethylstannyl)-1-cyclohexene-3-carboxylate with 2,3-dibromopropene affords the ester (**3**) which can be smoothly cyclized to compound (**4**) by using 2-3 equiv of ***Copper(I) Chloride*** in DMF at 60-70 °C (eq 2).[6]

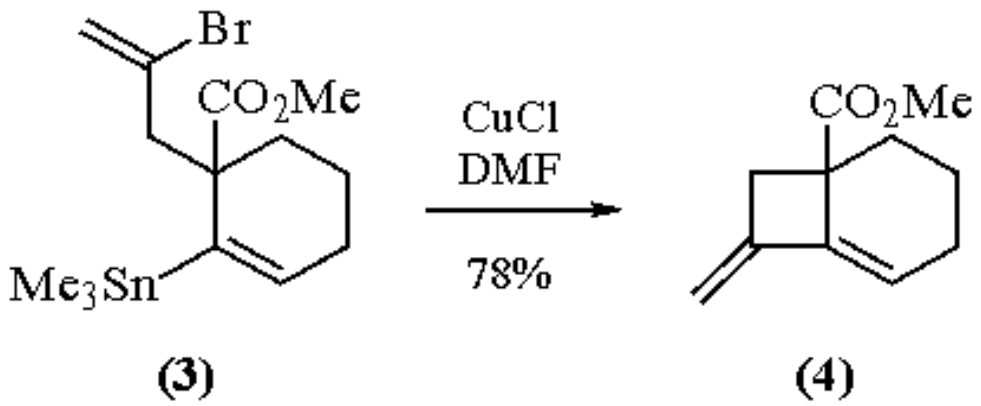

The coupling reactions are widely utilized for the synthesis of several intermediates (e.g. **5**-**8**) (eq 3), which are versatile reagents in cycloaddition reactions. In particular, (**5**) is synthesized[7] in two steps: 2,3-dibromopropene is coupled with ***Trimethylsilylmethylmagnesium Chloride*** and the intermediate obtained, after transformation into a Grignard reagent, is combined with vinyl bromide in the presence of a Ni^{II} catalyst. Product (**6**) is formed by combining lithium (trimethylsilyl)cyanocuprate in a 3:1 THF-HMPA mixture at 0 °C with 2,3-dibromopropene.[8] An alternative synthesis of (**6**) requires treatment of (**1**) with ***Trichlorosilane*** and Et_3N in the presence of a catalytic amount of CuCl, and direct addition of the allyltrichlorosilane to an ether solution of ***Methylmagnesium Bromide***.[9] Diene (**7**) can be obtained by oxidative dimerization of the cuprate derived from (**6**).[10] Compound (**6**) can be also directly transformed, by a coupling reaction, into the diene (**8**).[11]

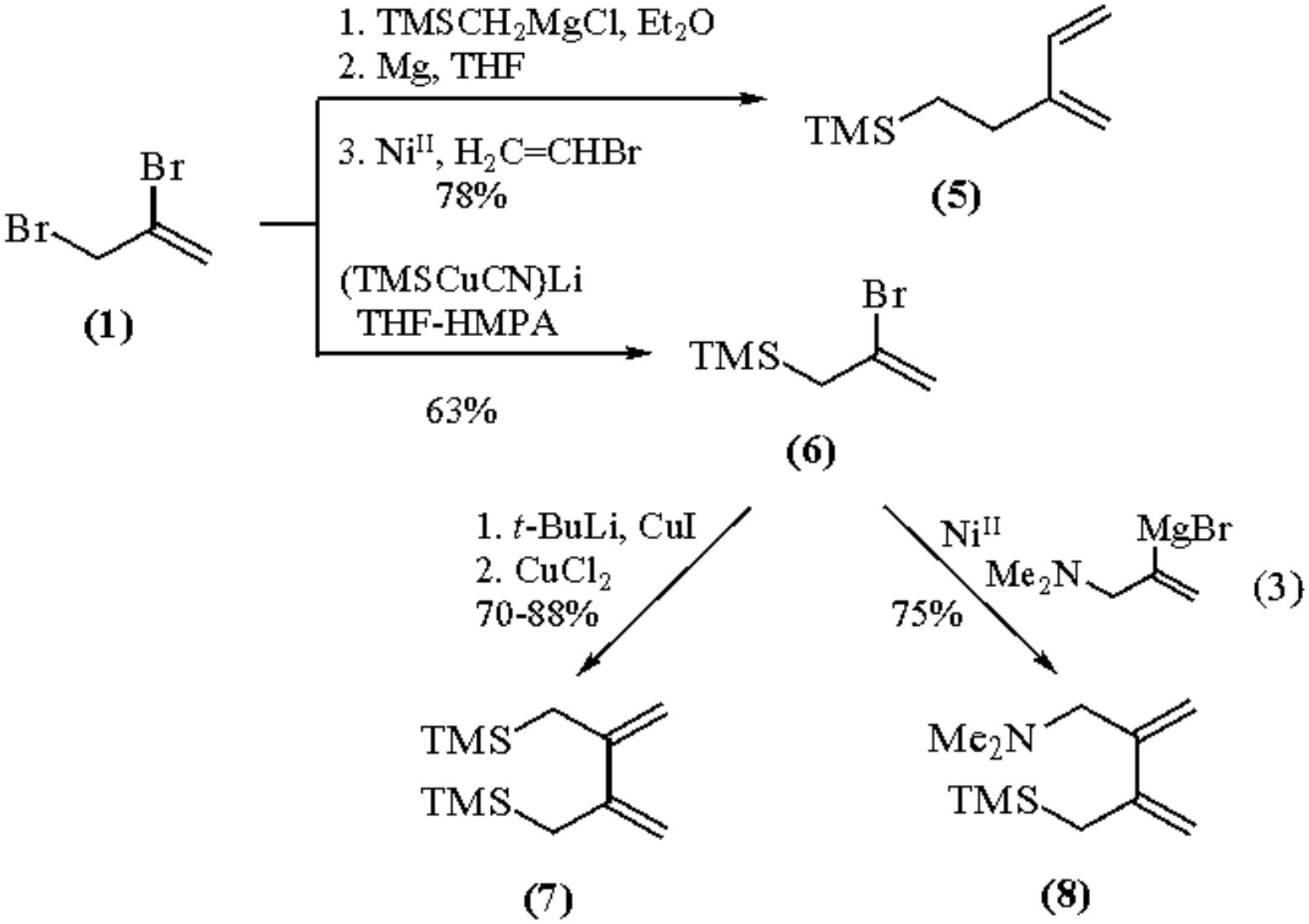

Dienes (**5**) and (**8**) work well in consecutive Diels-Alder reactions.[7,12] In particular, (**5**) reacts with two dienophiles via consecutive cycloaddition-1,2-elimination-cycloaddition, leading to the polycycle reported in eq 4. Furthermore, the diene (**7**) represents a conjunctive reagent for tandem Diels-Alder cycloaddition (eq 5).[10]

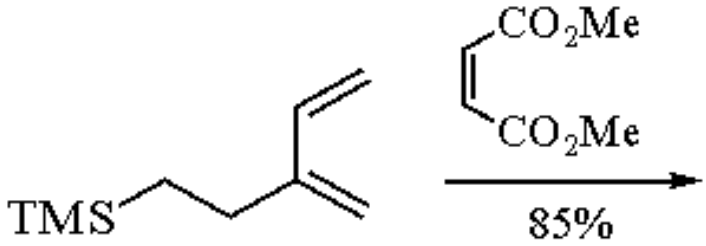
CO2Me
CO2Me
TMS
85%

(5)

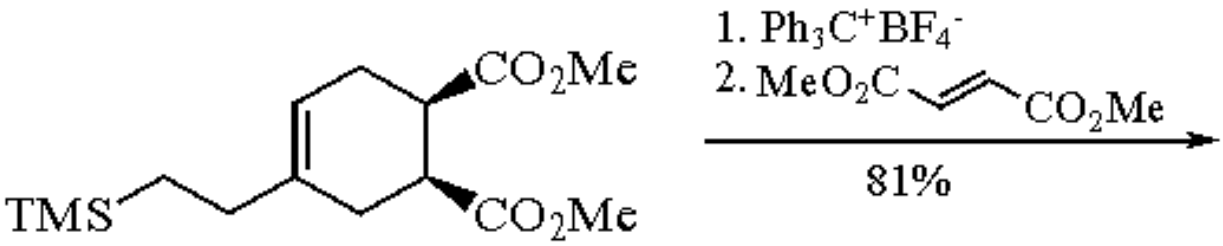
CO2Me
CO2Me
TMS
1. Ph3C+BF4-
2. MeO2C
CO2Me
81%

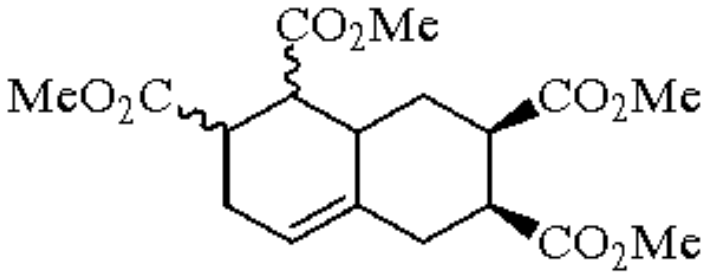
CO2Me
MeO2C
CO2Me
CO2Me

(4)

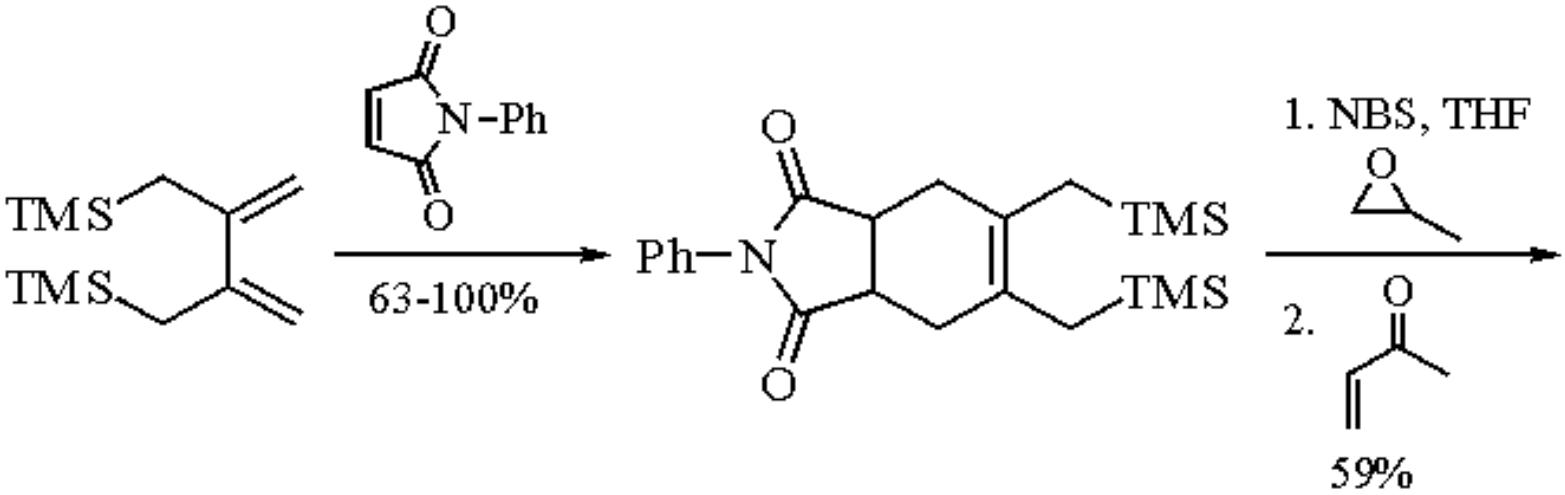
TMS
TMS
N-Ph
63-100%
Ph-N
TMS
TMS
1. NBS, THF
2.
59%

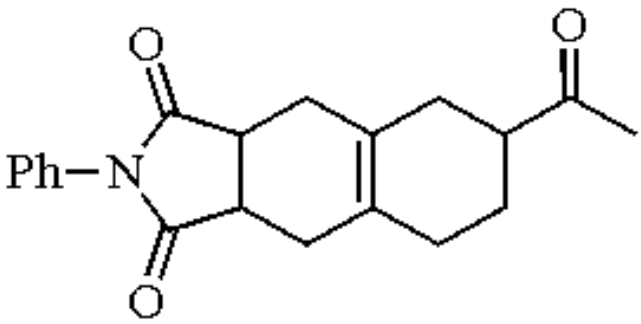
Ph-N

(5)

Sequential alkylation of the 9-fluorenyl anion with 1-bromo-2,4-pentadiene and with 2,3-dibromopropene leads to (**9**),[13] which under Heck reaction conditions affords (**10**) (eq 6).

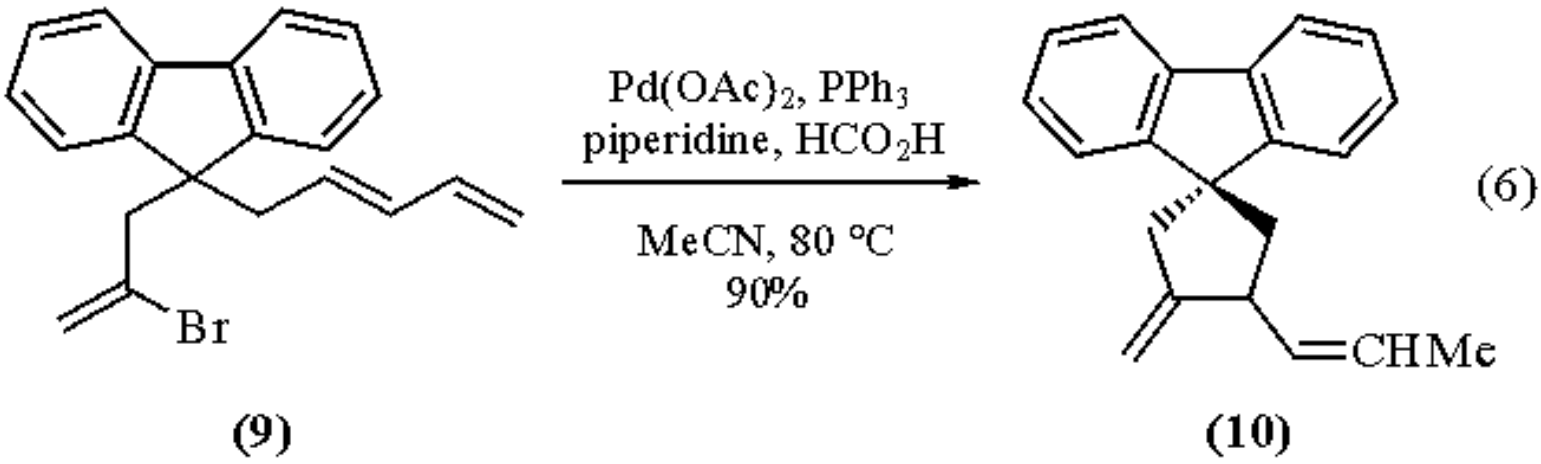

Reactions with Nitrogen Nucleophiles.

α-Methylene-β-lactams are synthesized from various 2-bromoallylamine derivatives using a catalytic amount of ***Palladium(II) Acetate*** and ***Triphenylphosphine*** under pressure of CO (eq 7).[14] Other procedures involving the use of 2,3-dibromopropene and nitrogen nucleophiles have been reported.[15-18]

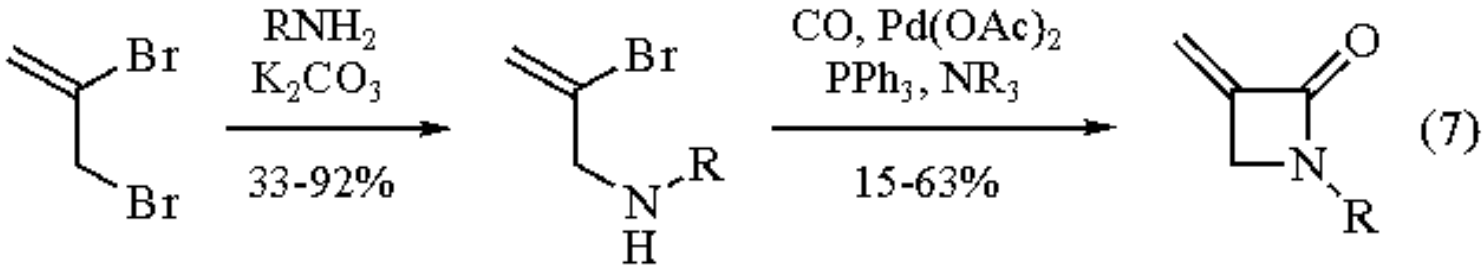

Reactions with Oxygen and Sulfur Nucleophiles.

Intramolecular radical cyclization reactions are widely used in organic synthesis for the construction of carbocycles.[19] A rapid access to the hexahydrobenzofuran unit of avermectin A_{2b},[20] which has a high antiparasitic activity, is shown in eq 8, where an important step is the construction of a 2-bromoallyl ether by phase transfer allylation with 2,3-dibromopropene.[21]

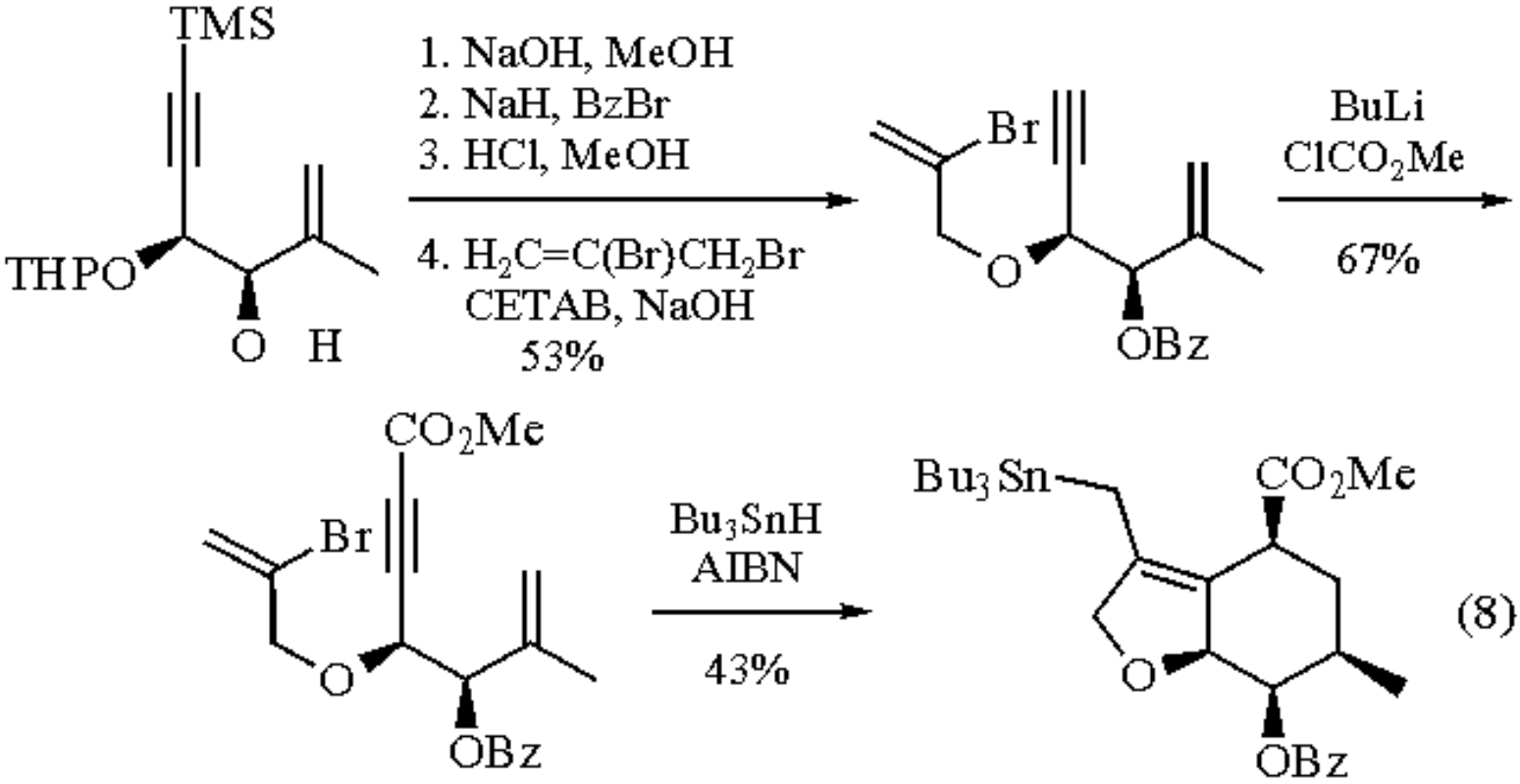

Reaction of PhSNa with 2,3-dibromopropene leads to 3-phenylthio-2-bromopropene, a useful reagent for radical allylations.[22]

Related Reagents.

2,3-Dichloropropene.

---

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3. Wang, K. K.; Chu, K.-H.; Lin, Y.; Chen, J.-H. *T* **1989**, *45*, 1105.
4. Piers, E.; Tillyer, R. D. *JCS(P1)* **1989**, 2124.
5. Zhu, L.; Shaughnessy, K. H.; Rieke, R. D. *SC* **1993**, *23*, 525.
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11. Hosomi, A.; Otaka, K.; Sakurai, H. *TL* **1986**, *27*, 2881.
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19. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986.
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α,α´-Dibromo-*o*-xylene

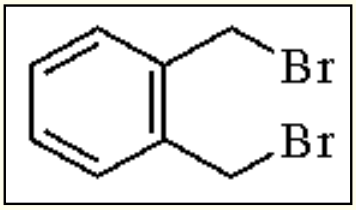

[91-13-4] · $C_8H_8Br_2$ · α,α´-Dibromo-*o*-xylene · (MW 263.97)

(a source of *o*-quinodimethane, a highly reactive diene useful in Diels-Alder reactions;[1] an electrophile for the synthesis of carbo- and heterocyclic compounds including macrocycles (cyclophanes, crown ethers, hemispherands, spherands),[2] cryptands,[3] hemicarcerands,[4] vaulted cappedophanes,[5] bicyclic compounds,[6] spirocyclic compounds;[7] a protective group reagent for diols[8])

Alternate Name: 1,2-bis(bromomethyl)benzene.

Physical Data: mp 95 °C ($CHCl_3$-EtOH); bp 140 °C/20 mmHg; *d* 1.960 g cm^{-3}; dipole moment (hexane, 20 °C) 1.98 D.

Solubility: sol ethanol, ether, chloroform; slightly sol petroleum ether.

Form Supplied in: commercially available as a solid.

Purification: recrystallization from 95% ethanol (3 mL g^{-1}), petroleum ether (bp 60-80 °C) (19 mL g^{-1}), chloroform (1 mL g^{-1}). Column chromatography (silica gel, cyclohexane-ethyl acetate).

Handling, Storage, and Precautions: avoid moisture; corrosive (forms HBr on hydrolysis); lachrymator; not mutagenic in Ames test; decontaminate by soaking apparatus, etc. in alcoholic alkali for 24 h or longer.

Precursor of *o*-Quinodimethane.

A reductive 1,4-elimination[1] of two bromide ions generates the reactive diene which can be intercepted by dienophiles and by iron[9] or cobalt[10] carbonyl reagents to form stable complexes. The elimination may be accomplished by activated ***Zinc***,[11] particularly with ultrasonication at rt (eq 1),[12] activated ***Nickel***,[13] ***Sodium Iodide***[14] in DMF, sodium benzenetellurolate,[15] ***Chromium(II) Chloride***,[16] and elemental ***Copper***[17] (as the *t*-butyl isocyanide complex). The dibromide is a precursor of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**2**)[18] and 1,4-dihydro-2,3-benzoxathiin 3-oxide (**3**),[19] which yield *o*-quinodimethane on thermolysis (eqs 2 and 3).

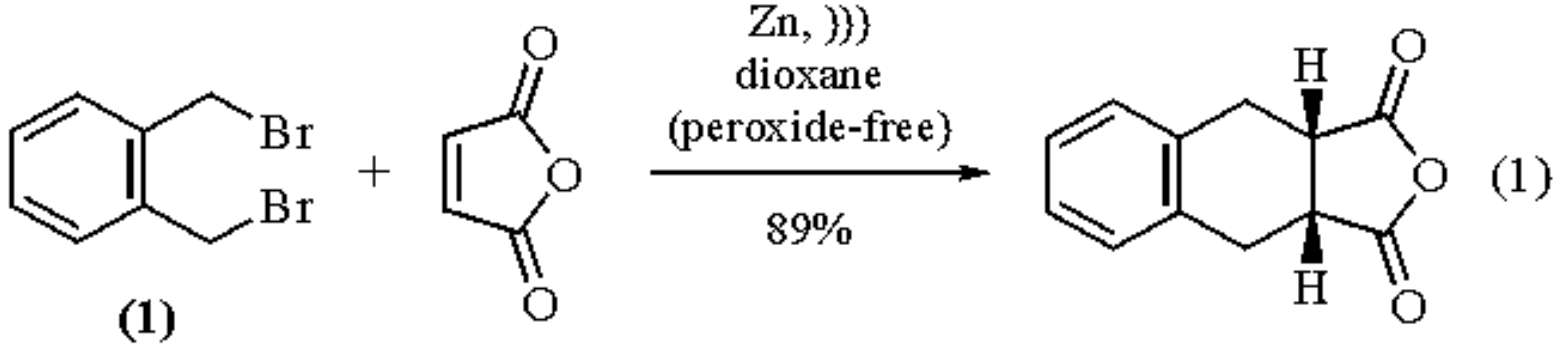
Br
Br
(1)
O
O
O
Zn,))))
dioxane
(peroxide-free)
89%
H
O
O
H
O
(1)

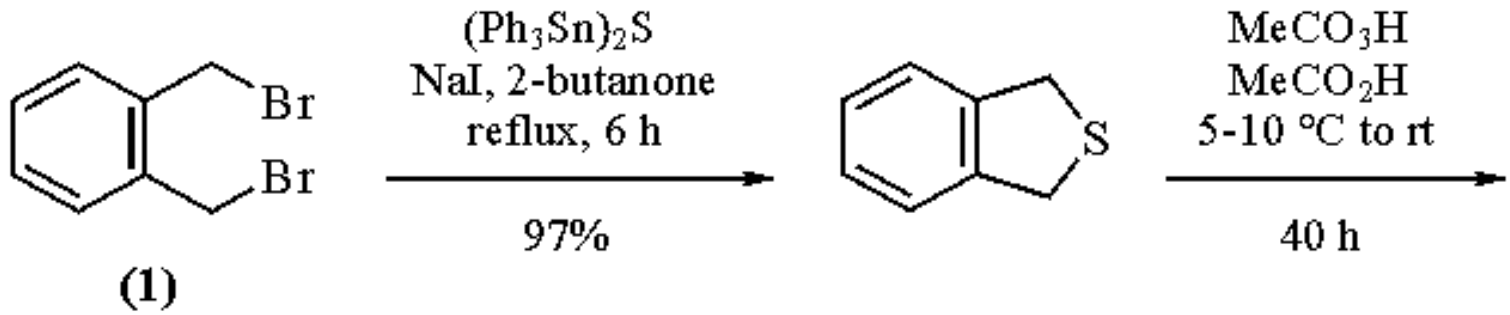
Br
Br
(1)
$(Ph_3Sn)_2S$
NaI, 2-butanone
reflux, 6 h
97%
S
$MeCO_3H$
$MeCO_2H$
5-10 °C to rt
40 h

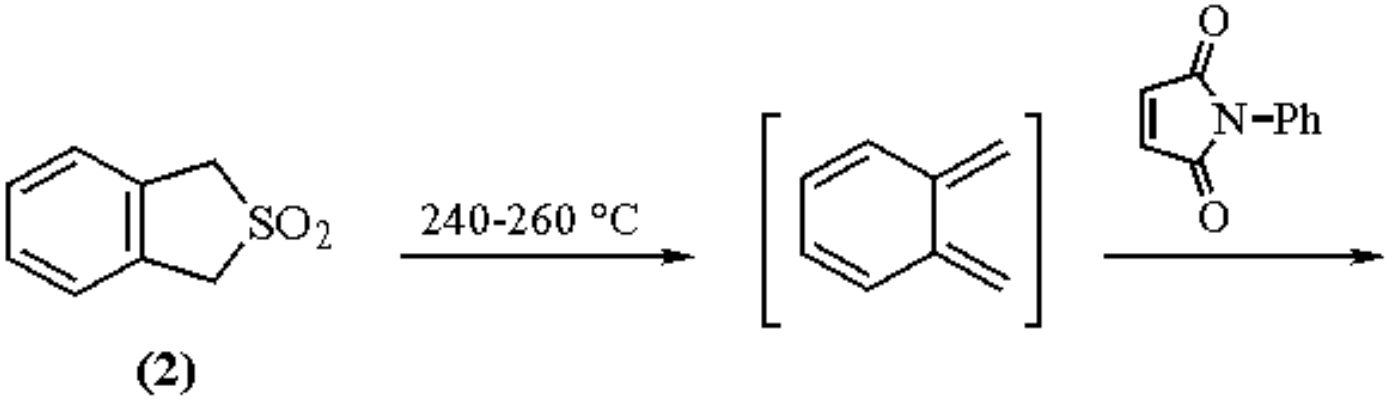
SO_2
(2)
240-260 °C
O
N-Ph
O

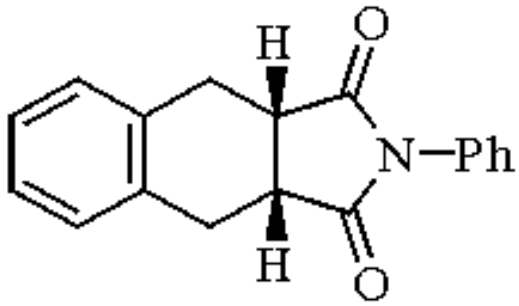
H
O
N—Ph
H
O
(2)

78%

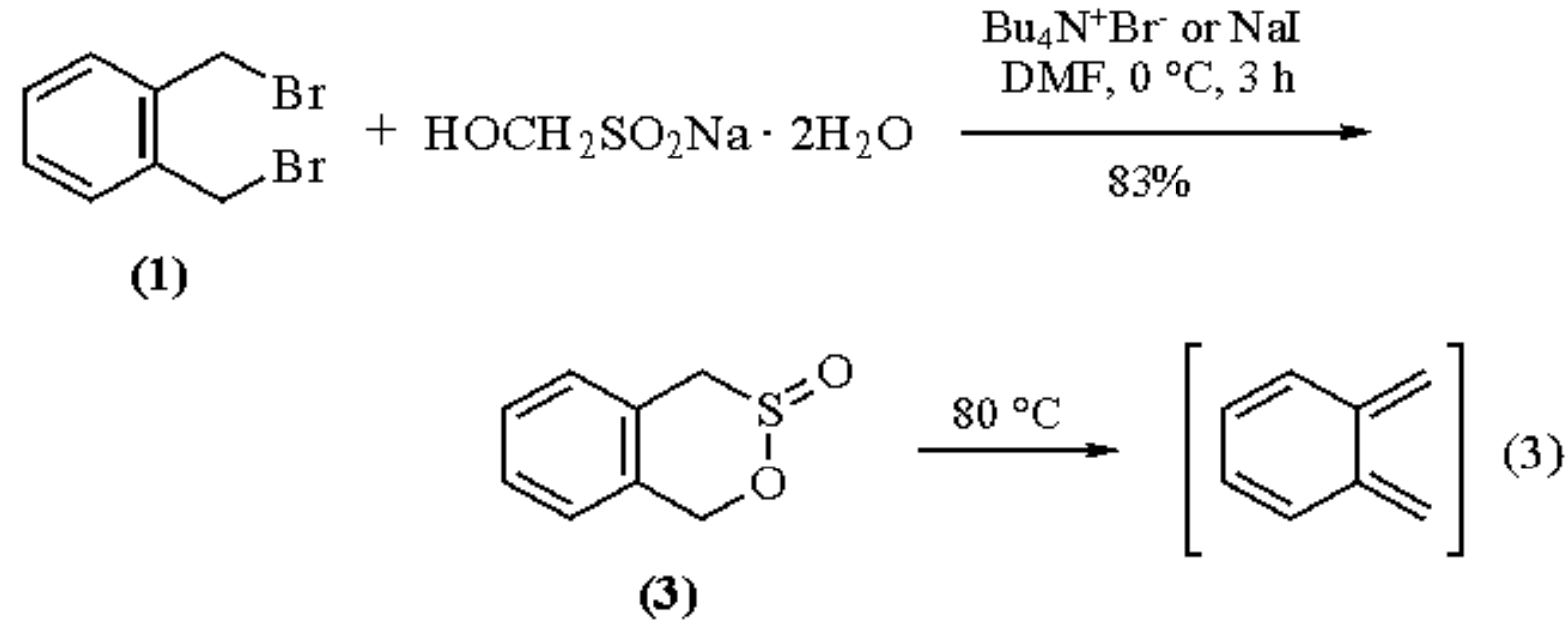

Cyclization Reactions.

Any reagent capable of functioning as a bis-nucleophile can, in principle, yield a cyclic product with (**1**). Benzocyclobutene may be formed in reactions yielding *o*-quinodimethane,[18a] and fused ring compounds containing five or more atoms in the second ring are available from (**1**). Examples of various fused ring compounds obtained from (**1**) are as follows: five-membered (eqs 2 and 4),[18b,20] six-membered (eqs 3 and 5),[19a,19b,21] seven-membered (eq 6),[22] and eight-membered (eq 7).[23] The attachment of larger rings is not uncommon, as shown in eq 8 for a macrocycle.[2d]

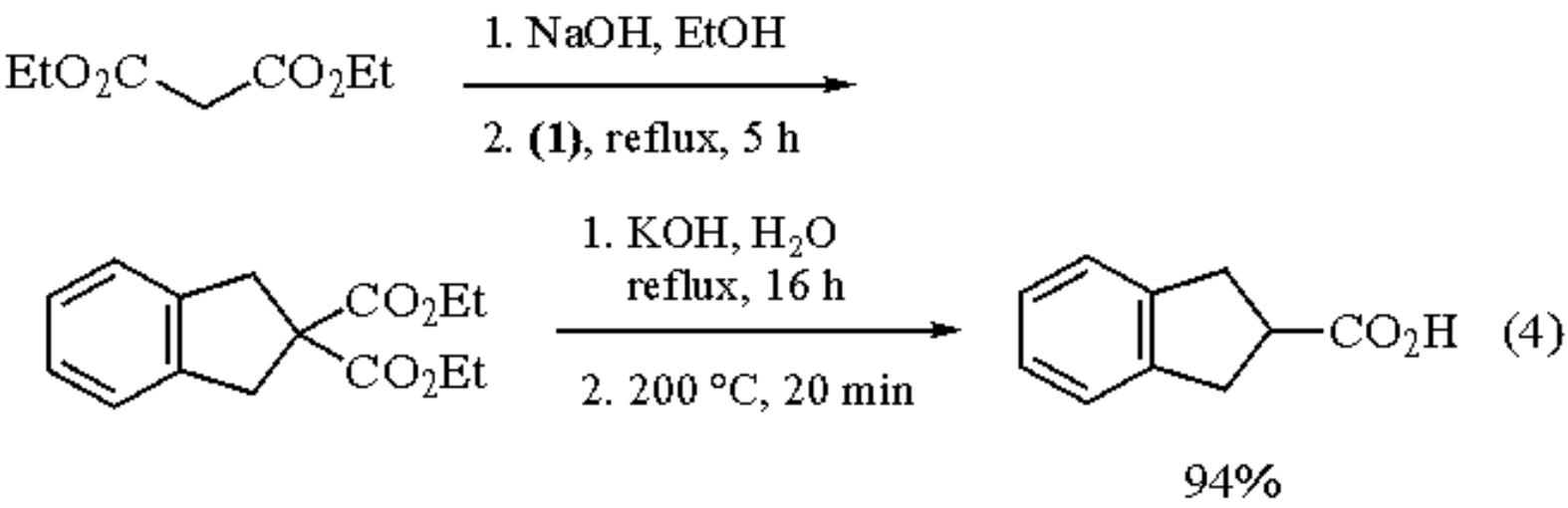

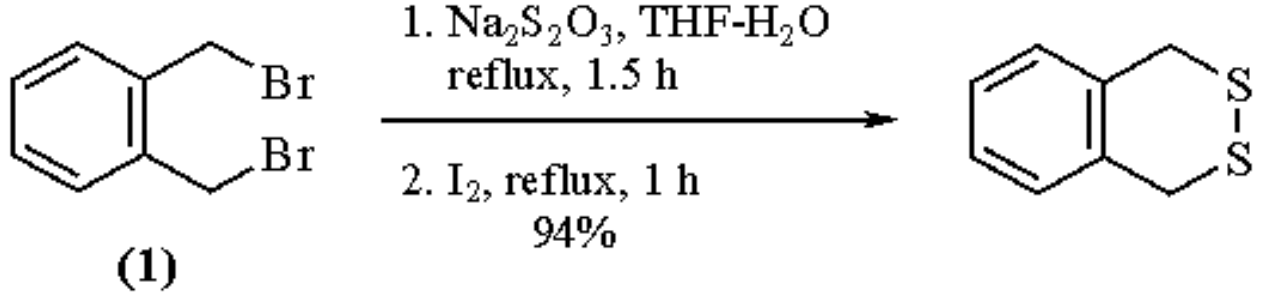

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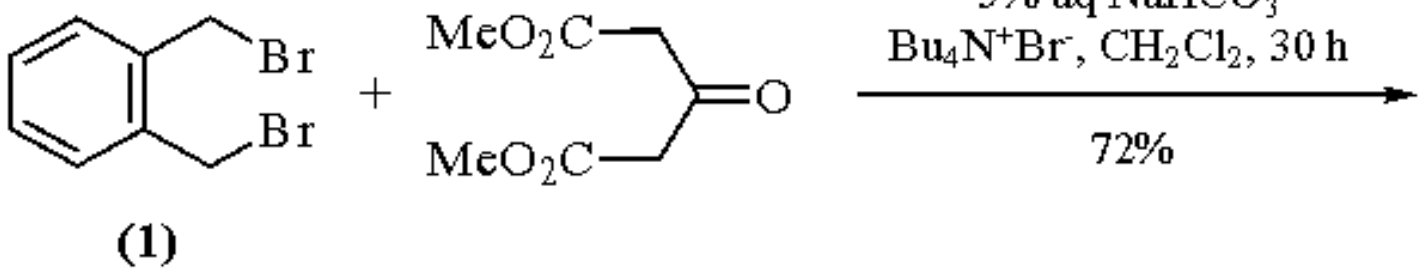

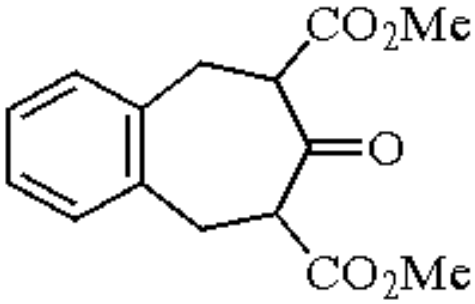

(6)

mixture of isomers

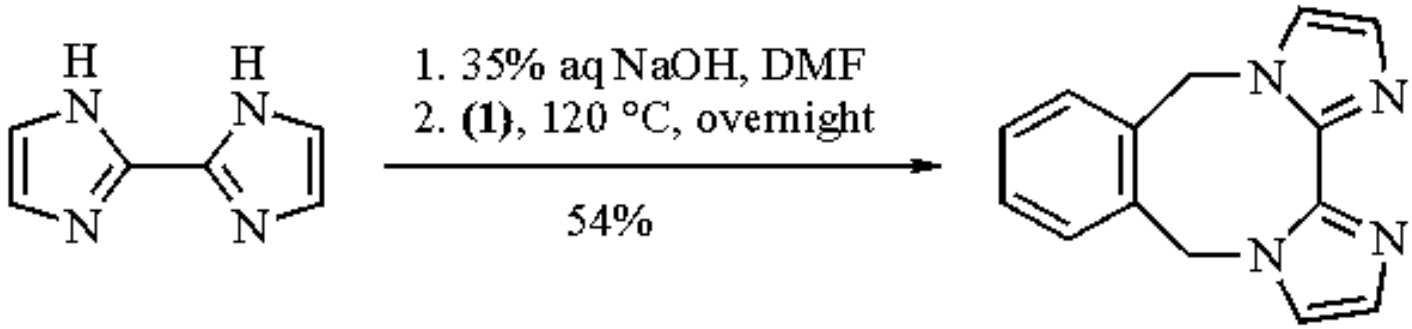

(7)

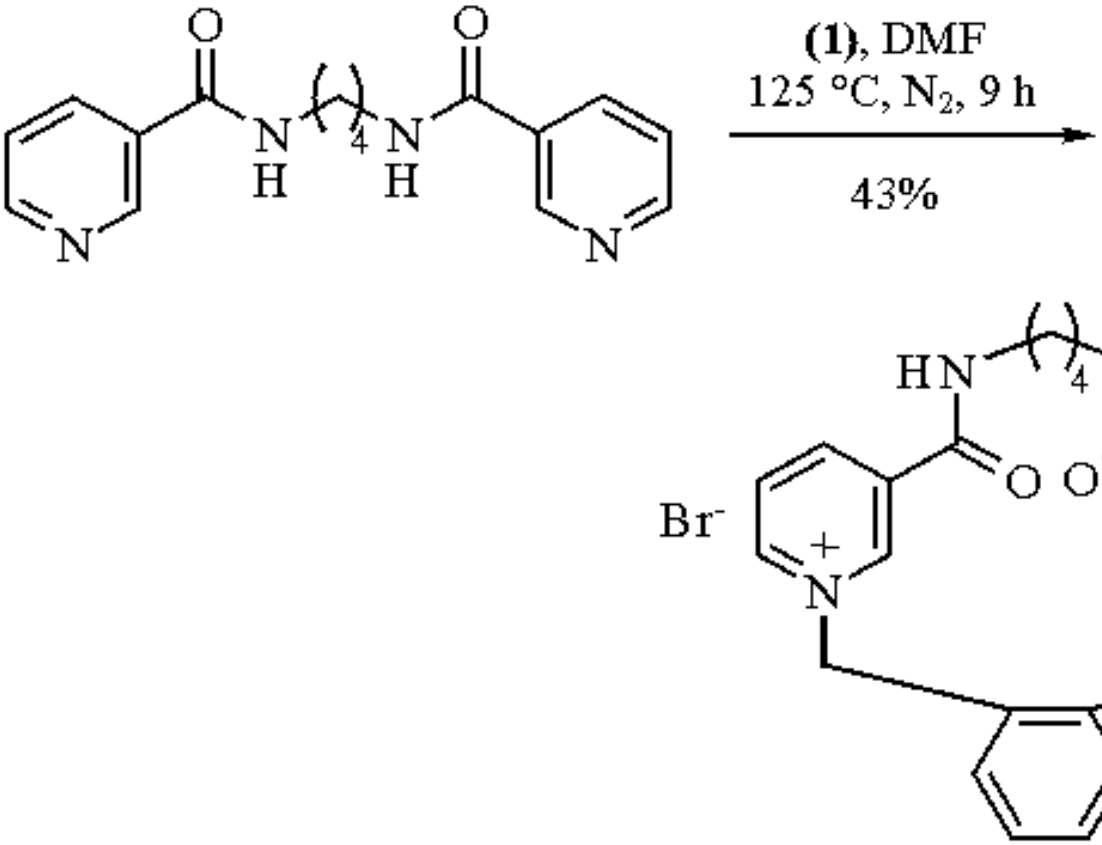

(8)

Bicyclic ring systems have been obtained by the appropriate choice of nucleophile (e.g. the cryptand shown in eq 9),[3a] and spirocyclic compounds have been prepared (eq 10).[7b] Four molecules of (**1**) were used in a critical step in the construction of a globe-shaped hemicarcerand by uniting two bowl-like units via reaction with eight phenolic hydroxy groups on the rims of the two bowls.[4] A monensin ionophore bridged by treatment with (**1**) shows excellent chiral recognition ability for salts of amino acids and amines.[2g]

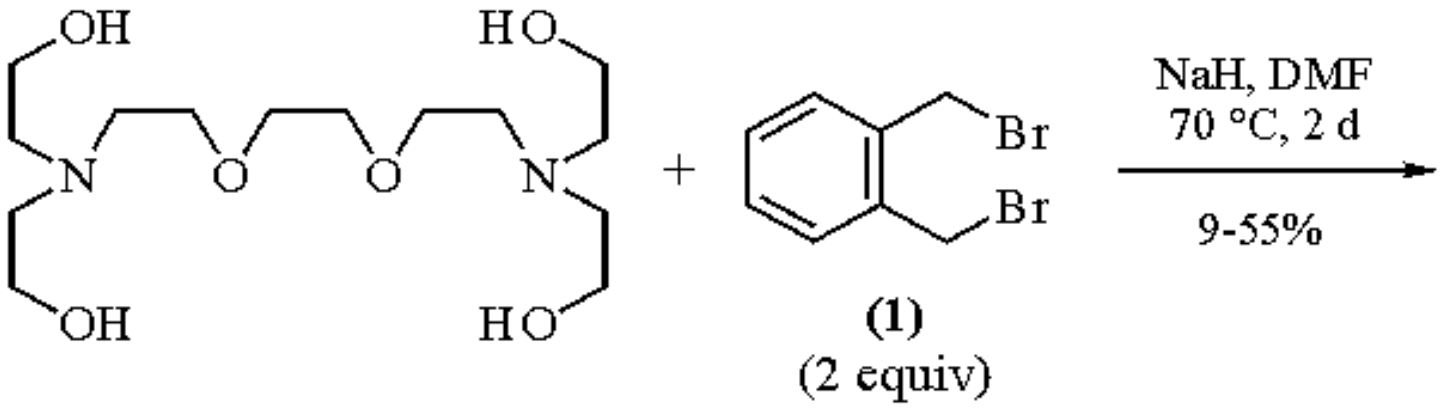

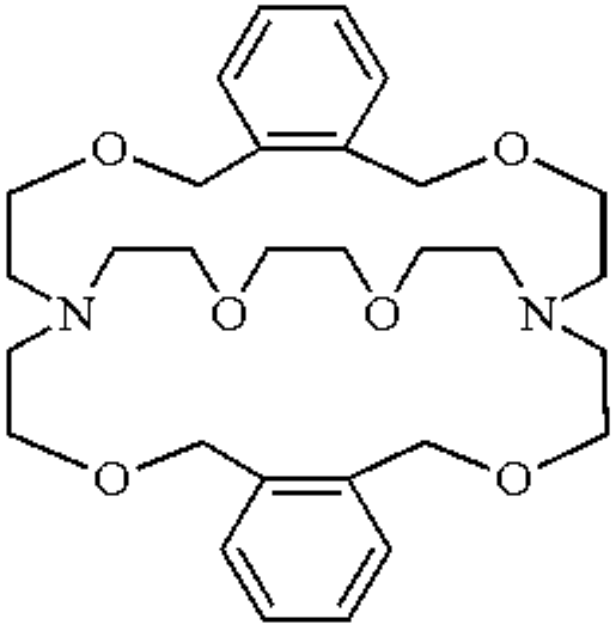

(9)

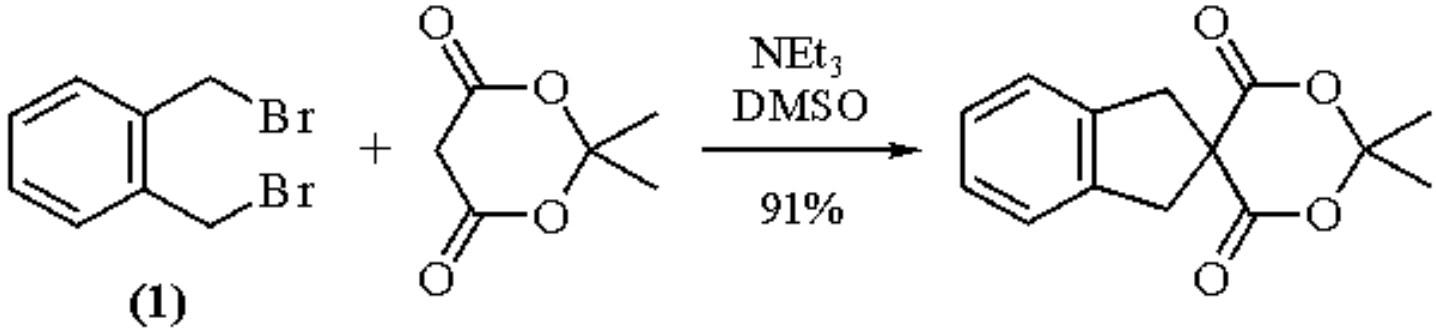

(10)

In addition to undergoing cyclizations with nucleophiles, (**1**) also dimerizes in 65% yield to 1,2;5,6-dibenzocyclooctadiene by treatment with 2 equiv of ***Ethylenebis(triphenylphosphine)nickel(0)*** at -20 °C in ether[2f] and in 80% yield by ultrasonication with ***Lithium*** in THF.[24]

Protective Group Reagent for Diols.

1,2- and 1,3-diols containing primary or secondary alcohol functions, catechols, and ene-1,2-diols are protected by reaction with (**1**). Deprotection involves hydrogenolysis of the protecting group (eq 11).[8]

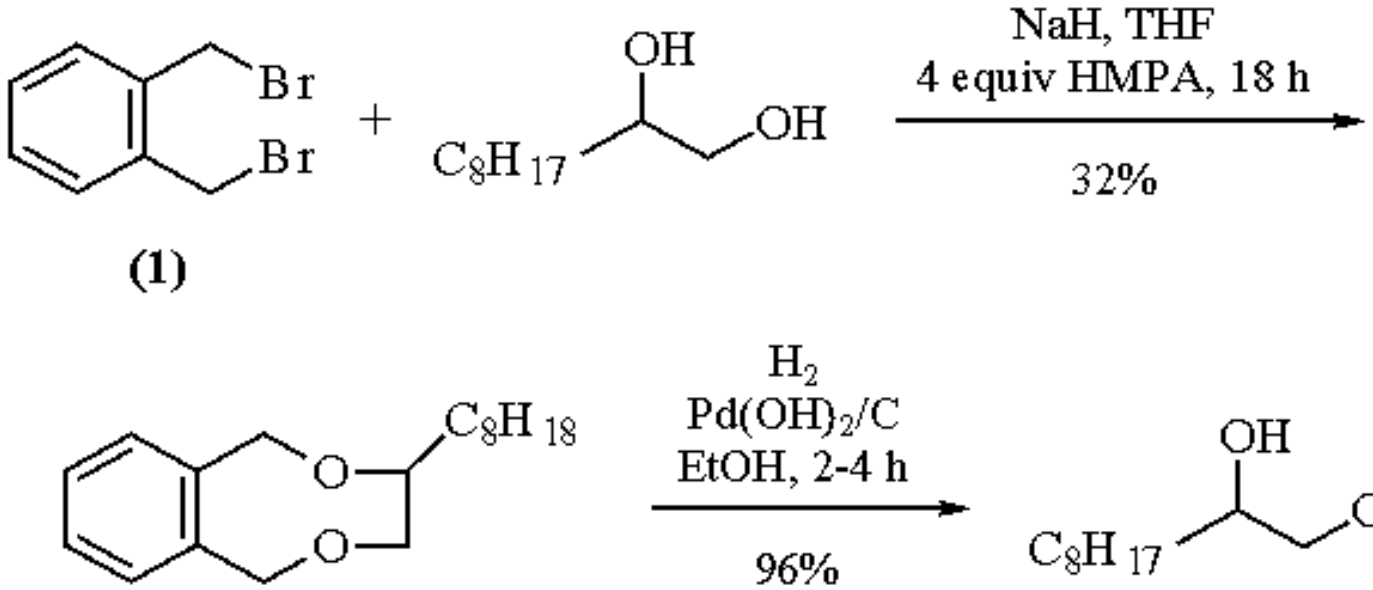

(11)

Miscellaneous Uses.

The dichloride rather than dibromide (**1**) is preferable for synthesis of the bis-Grignard reagent which is obtained in good yield, especially by treatment with Mg(anthracene)$(THF)_3$ in THF, hexane, or toluene under moderately high dilution to forestall Wurtz coupling.[25] A 75% yield of *o*-dibenzylbenzene is obtained by Friedel-Crafts reaction of (**1**) catalyzed by ***Aluminum Chloride-Nitromethane***.[26] Yields are poor if $AlCl_3$ alone is used.

Related Reagents.

1,3-Dihydrobenzo[c]thiophene 2,2-Dioxide.

---

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Di-*t*-butoxyacetylene

***t*-BuO-C&tbond;C-O-*t*-Bu**

[66478-63-5] · $C_{10}H_{18}O_2$ · Di-*t*-butoxyacetylene · (MW 170.25)

(a synthon for oxocarbons,[1] it transfers a protected enediol fragment by cycloaddition)

Physical Data: mp 8.5 °C; bp 30 °C/0.05 mmHg; *n*25D = 1.4365.

Solubility: completely sol hydrocarbons, ethers, chlorinated solvents, and ethyl acetate; insol water.

Form Supplied in: pale yellow oil; not commercially available.

Analysis of Reagent Purity: IR (CCl_4) cm^{-1}: 2972, 2922, 1470, 1450, 1390, 1367, 1301, 1263, 1245, 1150, 825; ^1H NMR (CCl_4) δ: 1.31 (s, CH_3).

Preparative Methods: from 1,2-dichloro-1,2-dimethoxyethane[2] or from *trans*-2,3-dichloro-1,4-dioxane.[2b,3] This latter procedure has been thoroughly optimized[4] and involves six steps, beginning with dioxane.

Purification: usual impurities can be removed by column chromatography on neutral alumina using a column refrigerated at 0 °C and eluting with pentane under N_2 pressure.

Handling, Storage, and Precautions: most conveniently stored as a solid at -20 °C. It slowly decomposes at rt through elimination of 2-methylpropene.[5]

Cycloadditions and Cyclooligomerizations of Di-*t*-butoxyacetylene.

Different carbenes equivalent to CO add to di-*t*-butoxyacetylene (**1**) to afford di-*t*-butoxycyclopropenone (**2**) (eq 1).[1,6] This compound has been quantitatively converted to deltic acid (dihydroxycyclopropenone) by treatment with ***Trifluoroacetic Acid*** (TFA).

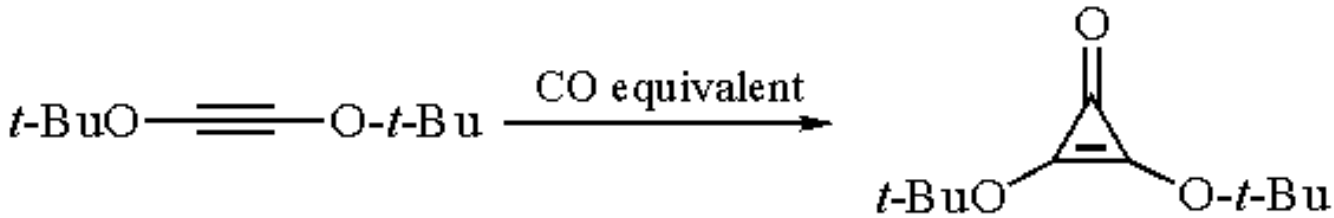

(1)

(1) **(2)**

CO equivalent	Source	Yield (%)
CCl_2	$CHCl_3$, aq NaOH, TEBA	12-26
CClF	$CHCl_2F$, aq KOH, 18-crown-6	21-27

Simple heating under reflux of a benzene solution of (**1**) leads to the quantitative formation of 2,3,4-tri-*t*-butoxycyclobutenone (**3**) via a [2 + 2] cycloaddition with thermally generated *t*-butoxyketene (eq 2).[6] Compound (**3**) has been converted to 3-hydroxycyclobutene-1,2-dione (semisquaric acid) by trifluoroacetolysis,[7] and to 3,4-dihydroxycyclobutene-1,2-dione (squaric acid) by an oxidation-trifluoroacetolysis sequence.[6] The cyclodimerization of (**1**) can be also induced by Pd^{II}. Di-*t*-butyl squarate is obtained and converted without isolation to squaric acid by treatment with TFA (eq 3).[7]

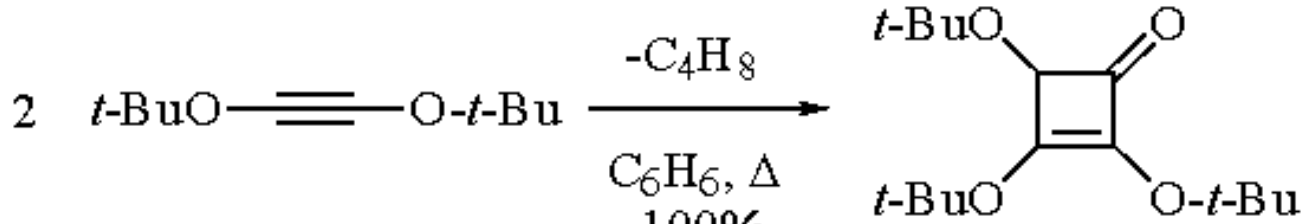

(2)

(1) **(3)**

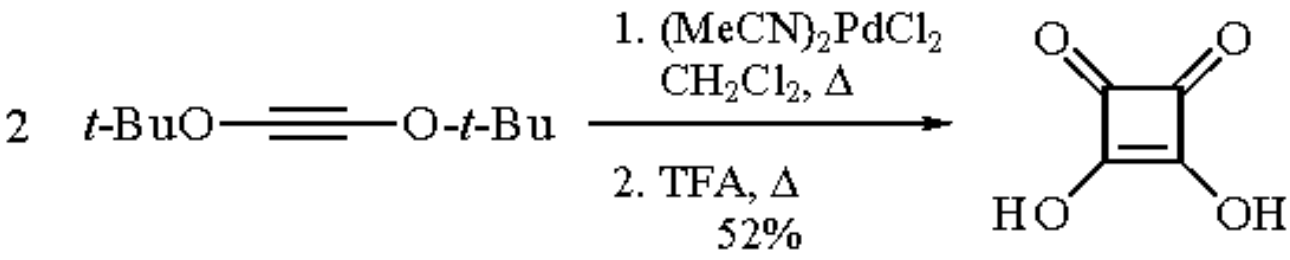

(3)

(1)

Both ***Dicarbonyl(cyclopentadienyl)cobalt(I)*** and ***Nonacarbonyldiiron*** efficiently induce cyclopentadienone formation from (**1**) (eq 4).[7,8] Demetalation of complex (**4**) leading to tetra-*t*-butoxycyclopentadienone has been achieved electrochemically,[9] whereas complex (**5**) is most conveniently demetalated with ***Trimethylamine N-Oxide***.[8] Tetra-*t*-butoxycyclopentadienone has been converted to 2,4,5-trihydroxycyclopent-4-ene-1,3-dione (hydrocroconic acid) and to 4,5-dihydroxycyclopent-4-ene-1,2,3-trione (croconic acid).[8,9]

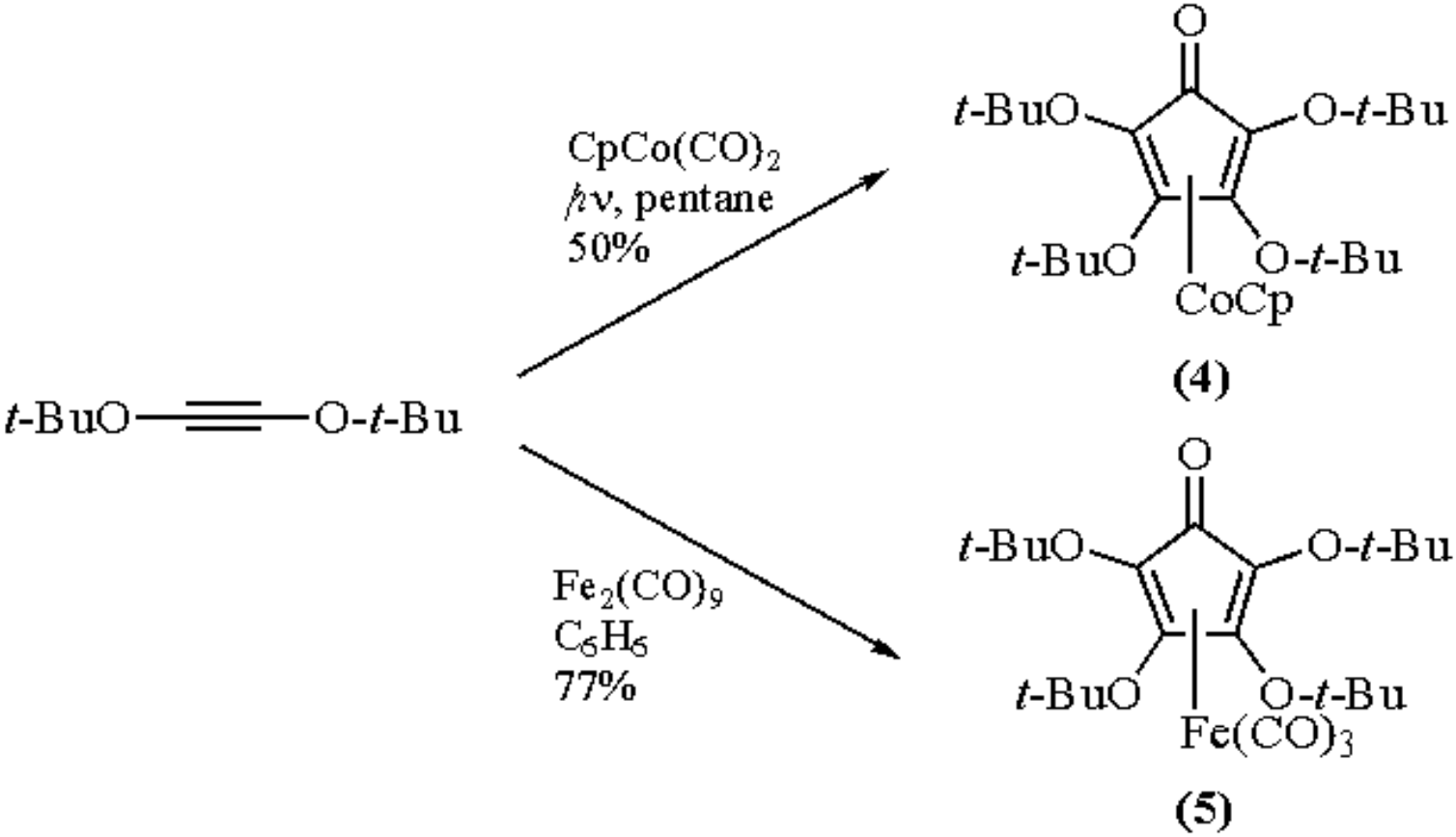

(4)

Catalytic amounts of ***Octacarbonyldicobalt***[6] or, better, ***Tetracarbonylnickel***,[1,10] induce cyclotrimerization of (**1**) leading to hexa-*t*-butoxybenzene (**6**) under unusually mild conditions (eq 5). Trifluoroacetolysis of (**6**) affords quantitatively hexahydroxybenzene, the classical precursor of 5,6-dihydroxycyclohex-5-ene-1,2,3,4-tetrone (rhodizonic acid).

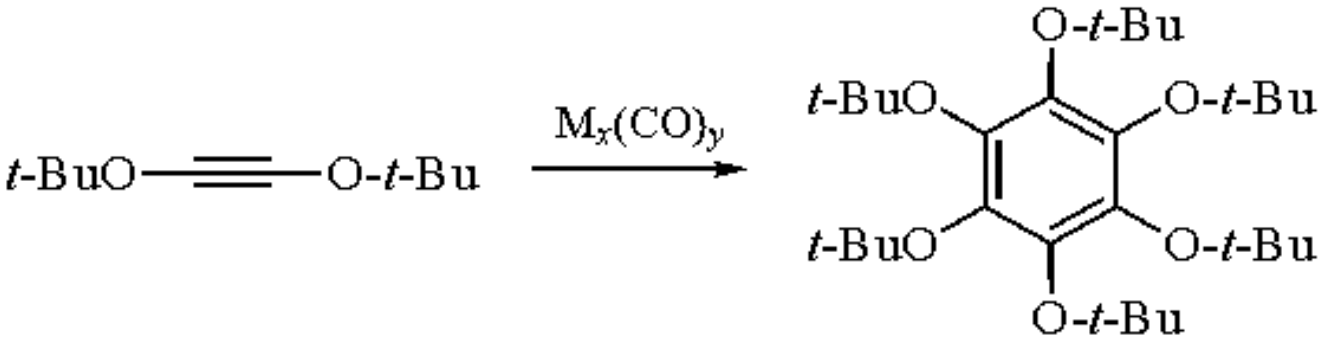

(5)

(1) **(6)**

$M_x(CO)_y$	Yield (%)
5% $Co_2(CO)_8$, pentane	5
10% $Ni(CO)_4$, THF	60

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1,3-Dibutoxy-1-lithio-1-propene[1]

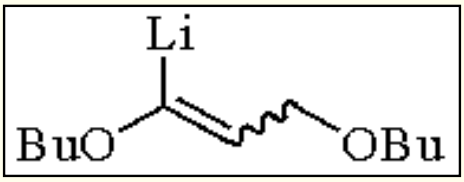

[-] · $C_{11}H_{21}LiO_2$ · 1,3-Dibutoxy-1-lithio-1-propene · (MW 192.23)

(nucleophilic reagent equivalent to an umpoled enone formed from 1,3-dibutoxypropene and *t*-butyllithium)

Solubility: sol THF/HMPA.

Preparative Method: metalation of 1,3-dibutoxypropene with *t*-BuLi in THF/HMPA.[1]

Handling, Storage, and Precautions: sensitive to air, water, and temperature.

A mixture of (*E*)- and (*Z*)-1,3-dibutoxypropene is prepared[1] from 1,3-dichloro-2-hydroxypropane, through the formation of the known dibutyl ether of glycerol[2] and the generation of the final alkene mixture (*Z*/*E* = 4:1) through elimination of the tosylate (eq 1). The exclusive formation of the vinyl anion (e.g. 1,3-dibutoxy-1-lithio-1-propene) is observed when the isomeric mixture is treated with ***t-Butyllithium*** in THF/HMPA (10:1) at -65 °C (eq 1). Gould and Rossi[3] used theoretical calculations to suggest a weakened α-vinyl C-H bond in the (*Z*)-1,3-dibutoxypropene. Methylated products are observed in the same (*Z*/*E*) ratio (i.e. 4:1) as the starting alkenes (eq 1). Other alkylations with low molecular weight primary bromides or iodides give 70-90% yields of products alkylated at the vinyl position. Other electrophiles such as carbonyls or epoxides were not examined. The overall process corresponds to the generation of a synthetic equivalent of a carbonyl enone synthon (eq 2). This umpoled synthon has been investigated extensively and includes such synthetic equivalents as (**1**),[4] (**2**),[5] and (**3**).[6]

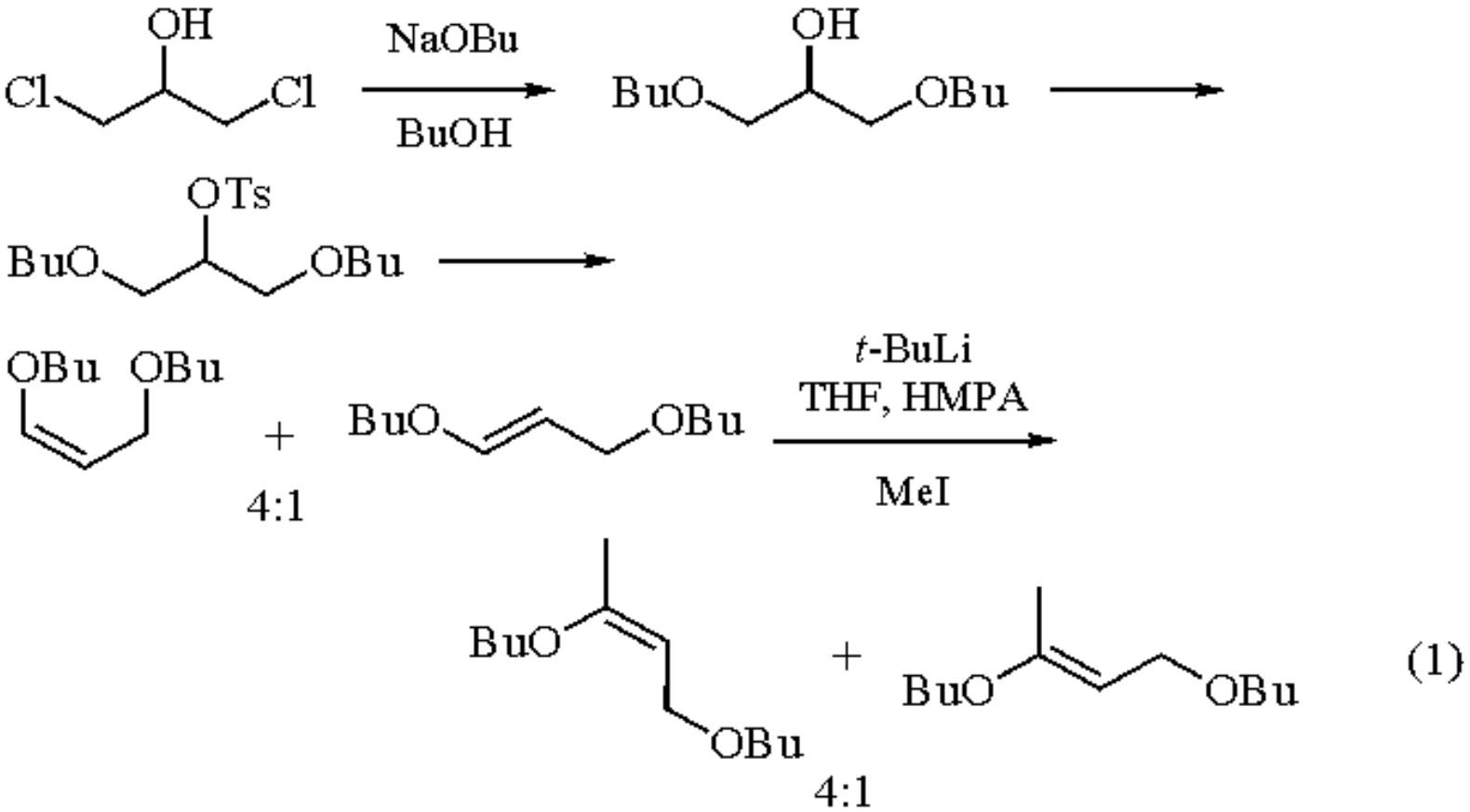

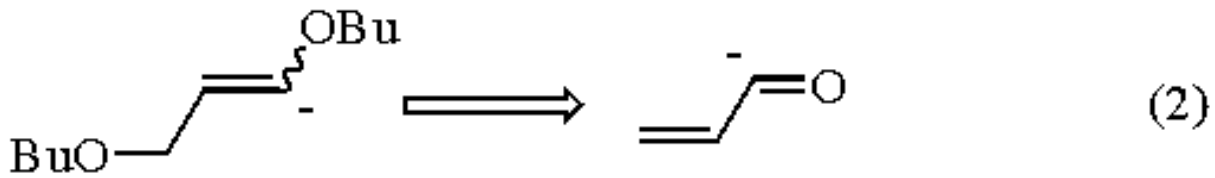

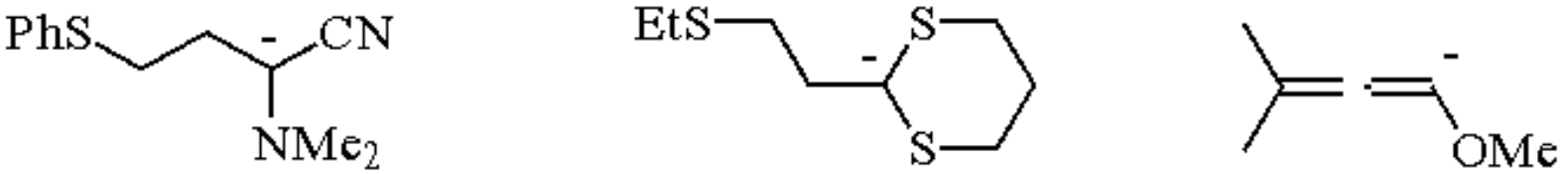

(1) **(2)** **(3)**

This work contrasts with that of Funk (eq 3),[7] where the allylic metalation and alkylation of 4*H*-1,3-dioxin provides a 3-acylvinyl equivalent. Theoretical calculation of bond energies for the 1,3-dioxin system was not performed. Vinyl anions are observed for other cyclic vinyl ethers.[8,9] 1,3-Hetero allylic systems, e.g. (**4**)[10] and (**5**),[11] containing sulfur also provide the allylic carbanion.

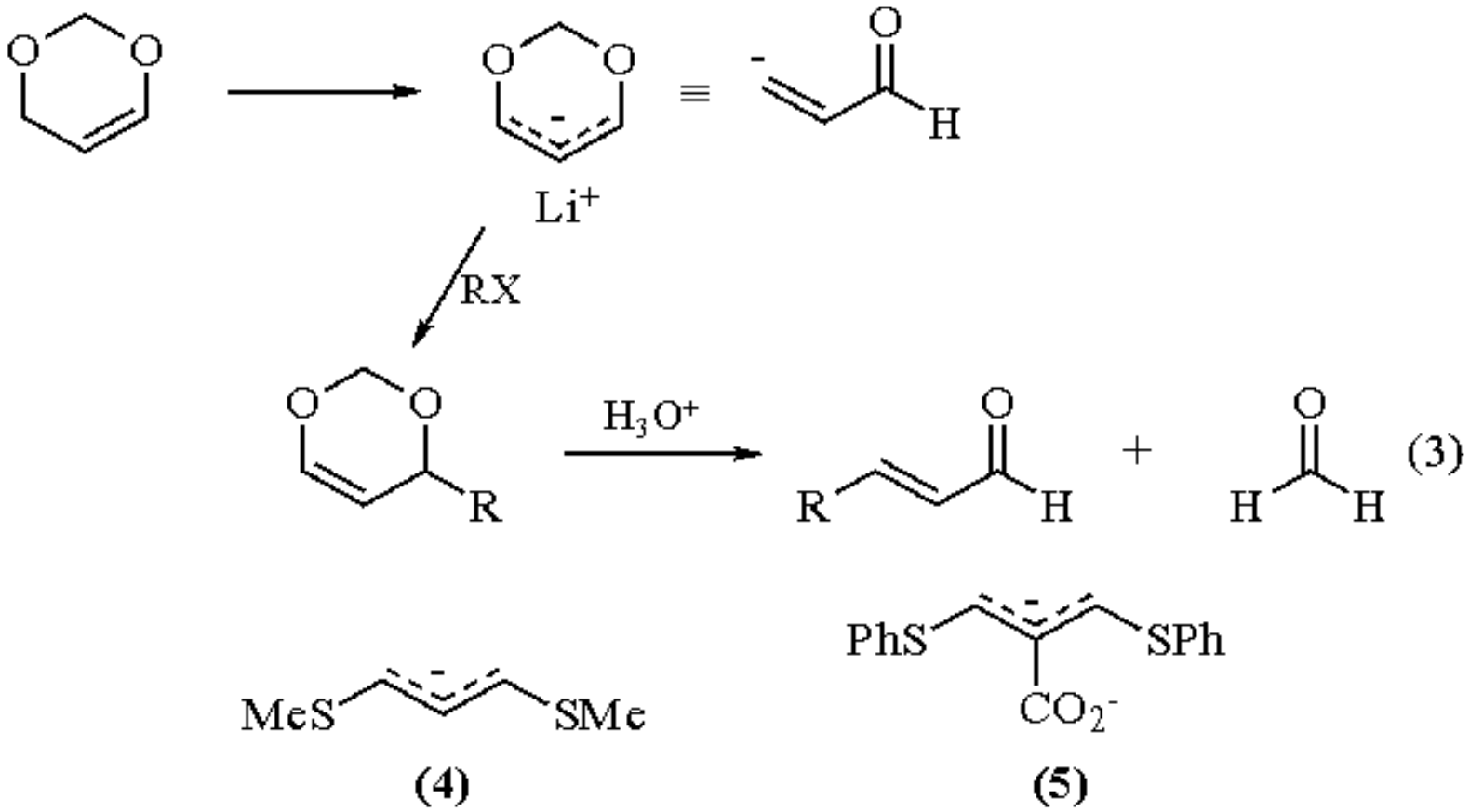

Related Reagents.

1-Ethoxy-1-(trimethylsilyloxy)cyclopropane; ***1-Methoxyallenyllithium***; ***(E)-3-Methylthio-2-propenyl p-Tolyl Sulfone***.

---

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Dibutylamine

Bu_2NH

[111-92-2] · $C_8H_{19}N$ · Dibutylamine · (MW 129.28)

(strong hindered base capable of catalyzing water elimination with $SOCl_2$,[1] detosylation,[2] isomerization around a double bond,[3] rearrangement of epoxides,[4] and cyclocondensations[5])

Physical Data: mp -62 °C; bp 159 °C; *d* 0.767 g cm^{-3}; *n*20D 1.4170; p*K*H_2Oa 11.25.

Solubility: very sparingly sol H_2O; sol most organic solvents.

Preparative Methods: from butyl bromide and ammonia;[5b] separation of the mono-, di-, and tributylamines is required.

Form Supplied in: liquid; commercially available.

Purification: can be dried over and distilled from fresh potassium hydroxide immediately before use.

Handling, Storage, and Precautions: is a flammable, colorless liquid. Harmful by inhalation and by eye and skin contact.

Purification of Carboxylic Acids.

Dibutylamine can be used for the purification of diterpene carboxylic acids,[6] long-chain fatty acids,[7] and benzoic acids.[8] The free carboxylic acids can be regenerated by treatment of the amine salts in ethanol with ***Acetic Acid***. Other secondary amines (e.g. diisopentylamine,[6] diisobutylamine[6b]) can also be used.

Eliminations.

Dibutylamine can also be used in different elimination reactions as a hindered strong base. When 1,1,1-trichloro-2-methyl-2-propanol is treated with 4 equiv of ***Thionyl Chloride***, a catalytic amount of dibutylamine at reflux then affords pure 3,3,3-trichloro-2-methyl-1-propene in good yield by water elimination, similar to ***t-Butylamine***, ***Triethylamine***, aniline, and dimethylaniline (eq 1).[1] In the presence of other amines, such as octylamine, ***Piperidine***, ***Pyridine*** or tetramethylammonium chloride, isomerized product is also formed.

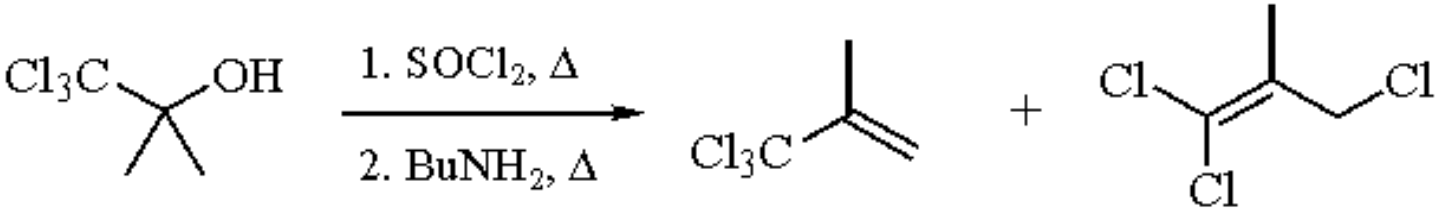

(1)

The base-catalyzed detosylation rate of 1-(*p*-toluenesulfonyl)-2-propyl *p*-toluenesulfonate depends on the polarity of the solvent used (eq 2).[2] In acetonitrile and 50% aqueous dioxane the strongest catalytic base is dibutylamine, followed by hexylamine and triethylamine. In solvents with a medium dielectrict constant (e.g. chloroform, chlorobenzene), the above the order is reversed.[2]

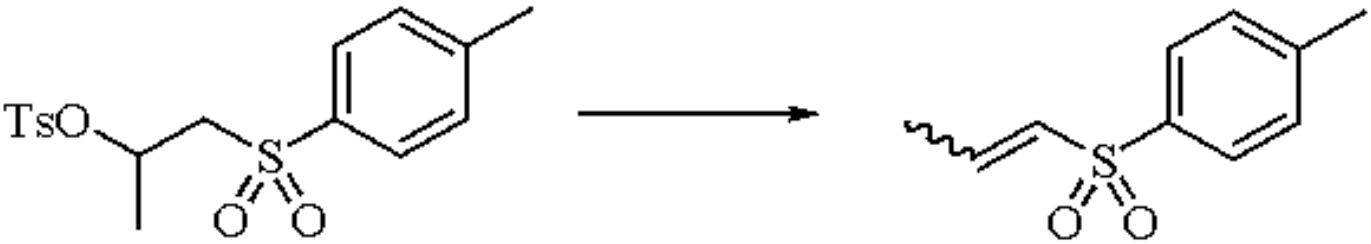

(2)

Isomerizations, Rearrangements.

For the amine-catalyzed nucleophilic isomerization of ethyl *cis*-2-cyano-3-(2-methoxyphenyl)acrylate to the *trans* derivative (eq 3)[3] in benzene the order of reactivity of the amines is dibutylamine > dipropylamine > diisobutylamine > tributylamine > diisopropylamine > triethylamine > pyridine > ***2,6-Lutidine***. This isomerization can also be influenced by solvent[3] and other oxygen[9] and carbon nucleophiles.[9]

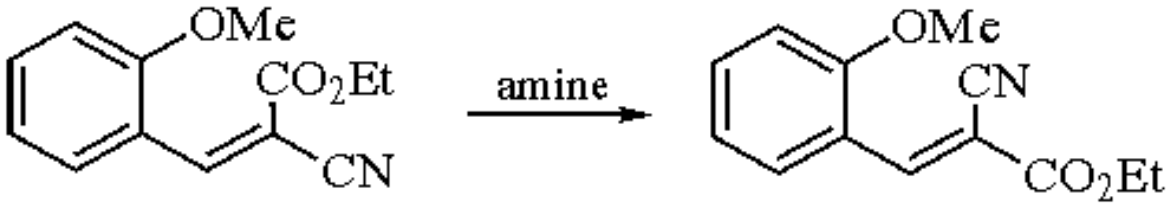

(3)

Base-induced rearrangement of epoxides with lithium alkylamides can yield allylic alcohols, isomerized derivatives, ketones, or, by direct nucleophilic substitution, amine alcohols. Cyclohexene oxide (**1**) gives 2-cyclohexen-1-ol (**2**) near quantitatively with lithium dibutylamide[4] (prepared in situ from a 15% solution of ***n-Butyllithium*** in hexane and an ethereal solution of dibutylamine) or lithium dipropylamide, while other lithium amides afford low to moderate yields of the allylic alcohol (**2**), very little ketone (**3**) and 3-cyclohexen-1-ol (**5**), and extensive amounts of the amino alcohol adduct (**4**) (eq 4).

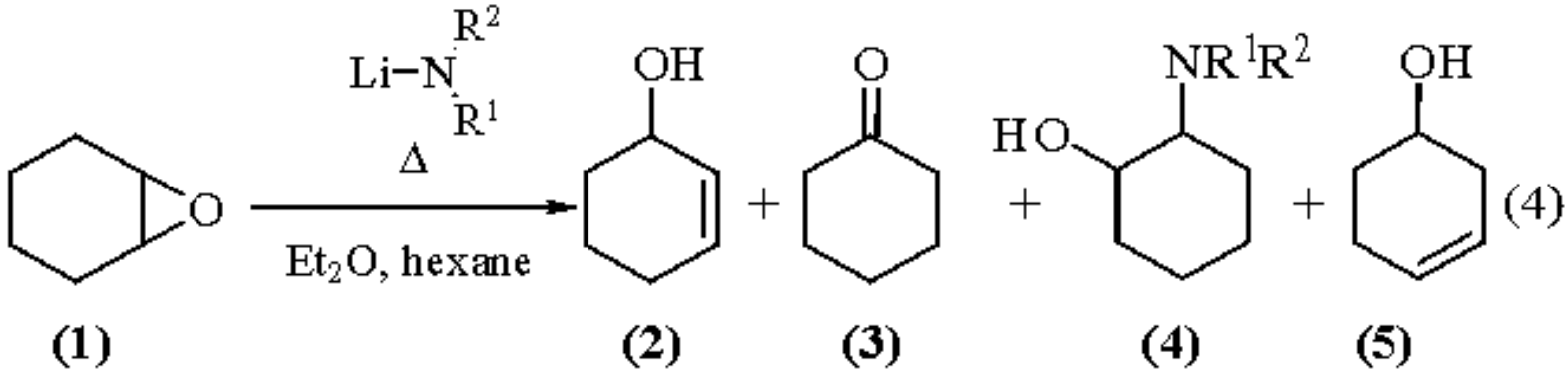

R^1	R^2	Reaction time (h)	Yield (%)			
H	Pr	17	15	0.5	77	trace
H	*i*-Pr	41	75	0.5	10	5
H	*i*-Bu	48	77	-	19	4
Et	Et	2	86	3	10	-
i-Pr	*i*-Pr	3	38	33	28	-
Pr	Pr	2	99	<0.5	-	<0.5
Bu	Bu	4	97	-	3	<0.5
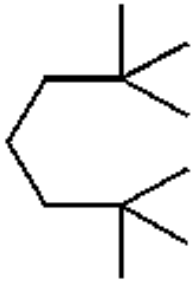		0.5	31	62	7	-

Cyclocondensations.

2-Unsubstituted 3-nitro-2*H*-chromenes can be prepared in fair to excellent yields either by the reaction of 2-hydroxybenzaldehydes and ***Nitroethylene*** in boiling chloroform, or by the reaction of 2-hydroxybenzaldehydes, 2-nitroethanol, and 2 equiv of phthalic anhydride in boiling toluene in the presence of 0.2-0.5 equiv of dibutylamine (eq 5).[5] Other amines, like ***Diisopropylethylamine*** and ***1,4-Diazabicyclo[2.2.2]octane***, lead to a rapid polymerization of nitroethylene. Ammonium chlorides[10] like dibutylammonium, diisopropylammonium, diethylammonium, dioctylammonium, piperidinium, and morpholinium chlorides in boiling isopentyl acetate lead to lower yields or more difficult purification.

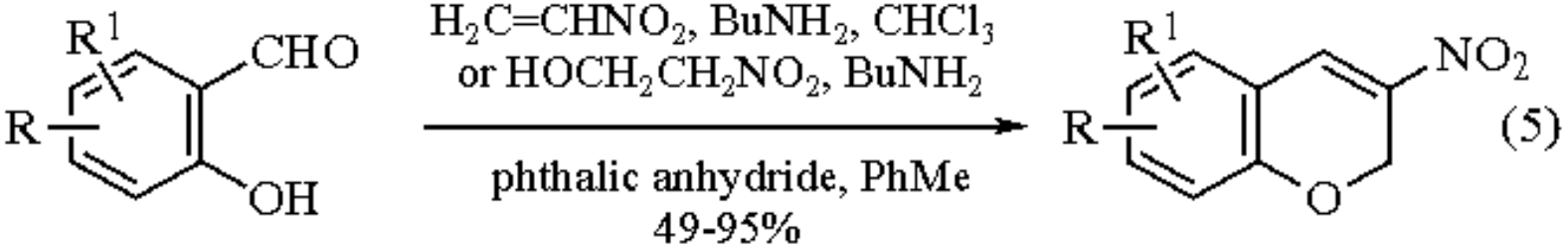

1. Kudinger, D. G.; Pledger, H.; Ott, L. E. *JACS* **1955**, *77*, 6659.
2. Pearson, R. G.; Vogelsong, D. C. *JACS* **1958**, *80*, 1048.
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4. Kissel, C. L.; Rickborn, B. *JOC* **1972**, *37*, 2060.
5. (a) Al Neirabeyeh, M.; Koussini, R.; Guillaumet, G. *SC* **1990**, *20*, 783. (b) Werner, E. A. *JCS* **1919**, *115*, 1010.
6. (a) Burgstahler, A. W.; Worden, L. R. *JACS* **1961**, *83*, 2587. (b) Burgstahler, A. W.; Worden L. R. *JACS* **1964**, *86*, 96.
7. Mod, R. R.; Magne, F. C.; Skau, E. L. *J. Am. Oil Chem. Soc.* **1959**, *36*, 616.
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Di-*t*-butyl Azodicarboxylate[1]

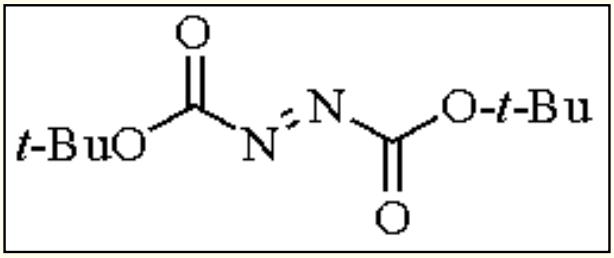

[870-50-8] · $C_{10}H_{18}N_2O_4$ · Di-*t*-butyl Azodicarboxylate · (MW 230.26)

(reagent for the electrophilic amination[2] of enolates; Diels-Alder dienophile)

Alternate Names: DBAD; TBAD.

Physical Data: mp 90-92 °C.

Solubility: sol most organic solvents.

Form Supplied in: yellow solid; widely available.

Preparative Method: a detailed description is given in *Organic Syntheses*.[3]

Handling, Storage, and Precautions: light sensitive; more stable than its methyl or ethyl analogs.

Reactions with Carbon Nucleophiles.

Although the electrophilic reactivity of azodicarboxylates towards C-nucleophiles was recognized long ago,[4] the first reaction of di-*t*-butyl azodicarboxylate (**1**) with an organometallic reagent was reported only in 1961. The addition of *t*-butylmagnesium chloride to DBAD, to give the protected *t*-butylhydrazine (**2**) in 50% yield (eq 1), has been described.[5] This type of reaction is not limited to aliphatic Grignard reagents; aryllithium and aryl Grignard reagents (**3**) add analogously to DBAD to afford arylhydrazines (**5**) after final deprotection (eq 2).[6]

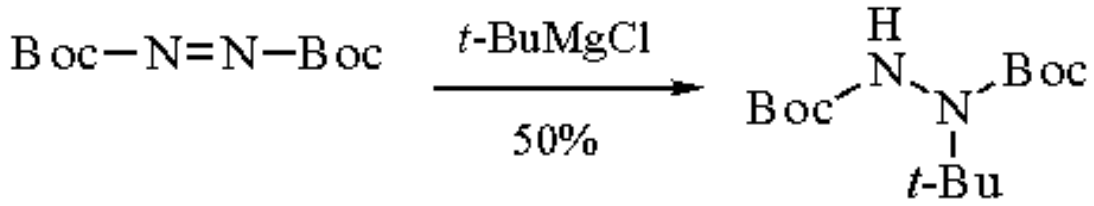

(1)

(1) (2)

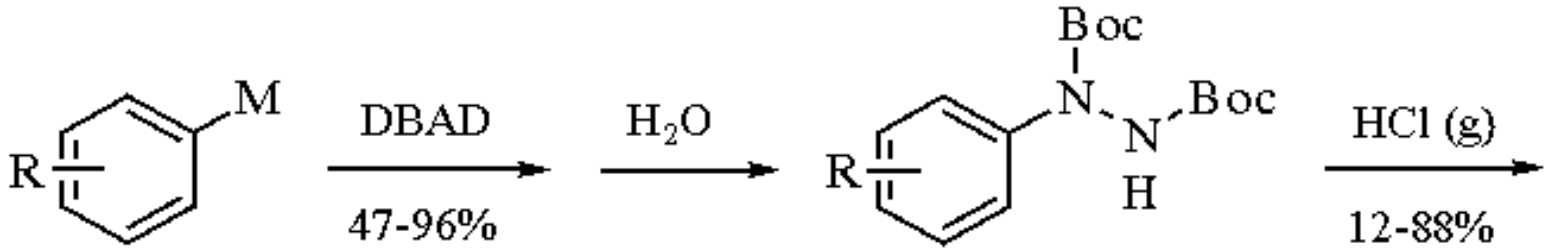

(3) (4)

M = Li, MgBr
R = OMe, SMe, CF_3, CF_3CH_2, etc

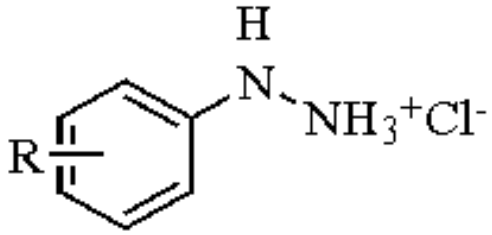

(2)

(5)

Although in principle other azodicarboxylates give the same reaction, the advantage of using DBAD is the ease of removal of the protecting group. The *t*-butoxycarbonyl (Boc) group is readily cleaved by ***Trifluoroacetic Acid*** or ***Hydrogen Chloride***, whereas the harsher acidic or basic conditions required for the removal of methyl or ethyl analogs can interfere with the hydrazine moiety. A comparison of anionic attack on DBAD and related azodicarboxylates with subsequent deprotection is available (eq 3).[7] Deprotonation of the chiral carboximides (**6**) followed by reaction with azodicarboxylates produces the hydrazino acid precursors (**7**) in high yields. Dimethyl and diethyl azodicarboxylate give only moderate diastereoselectivity, whereas the dibenzyl and di-*t*-butyl derivatives afford excellent stereoselection. The phenylalanine-derived carboximide (**8**) adds DBAD upon deprotonation with ***Lithium Diisopropylamide*** in a similar fashion (eq 4).[8]

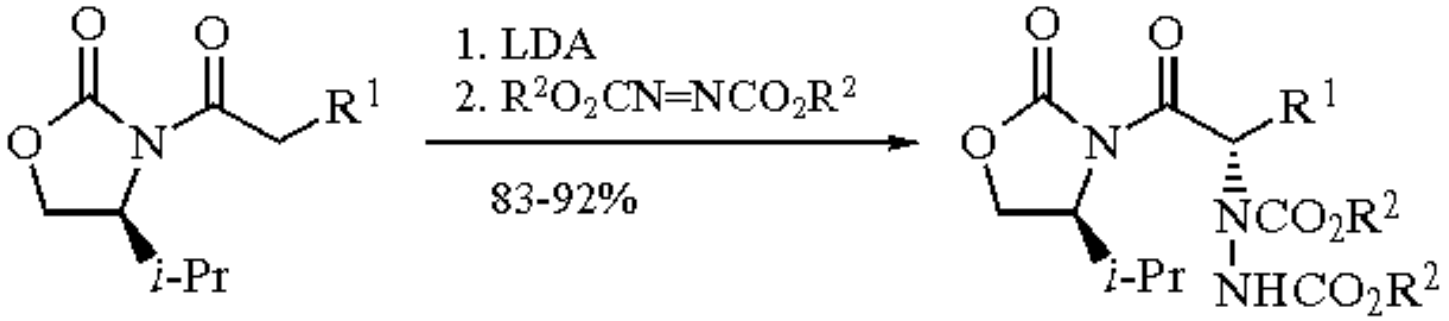

(3)

(6) **(7)**

R^1 = Me, Bn, *i*-Pr

R^2 = Me, 38% de
R^2 = Et, 50% de
R^2 = *t*-Bu, Bn, 90-94% de

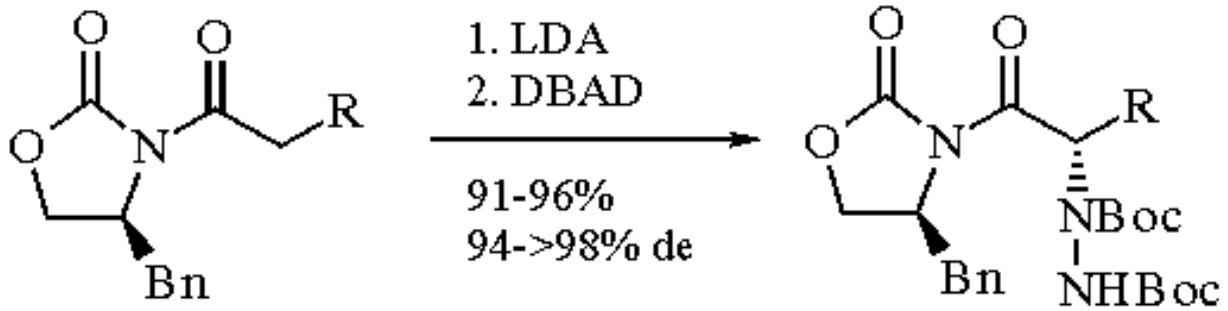

(4)

(8) R = Me, Bn, *i*-Pr, *t*-Bu, Ph, allyl **(9)**

Heterocycles (**7**) and (**9**) can each be cleaved to either (*S*)-α-hydrazino acids (**10**) or, if desired, to (*S*)-α-amino acids (**11**), both of which are obtained in enantiomerically pure form within detection limits (eq 5). Since the enantiomers of (**6**) and (**8**) are readily available, (*R*)-α-amino acids and (*R*)-α-hydrazino acids can also be made. This approach has allowed generation of [^{14}C]phenylalanine[9] and 2-adamantylalanine.[10] An elegant application of this methodology is seen in the synthesis of (*R*)- and (*S*)-piperazic acids (eq 6).[11] Deprotonation and reaction of the carboximide (**12**), derived from 5-bromovaleric acid, with DBAD produces an aza anion capable of displacing bromide to give, upon final deprotection, (*S*)-piperazic acid (**15**) as a single isomer. Its enantiomer was made using the antipode of the chiral auxiliary. The asymmetric synthesis of 1,6-dihydropiperazic acid has been elaborated in a similar way; however, its TFA salt was reported to be unstable.[12]

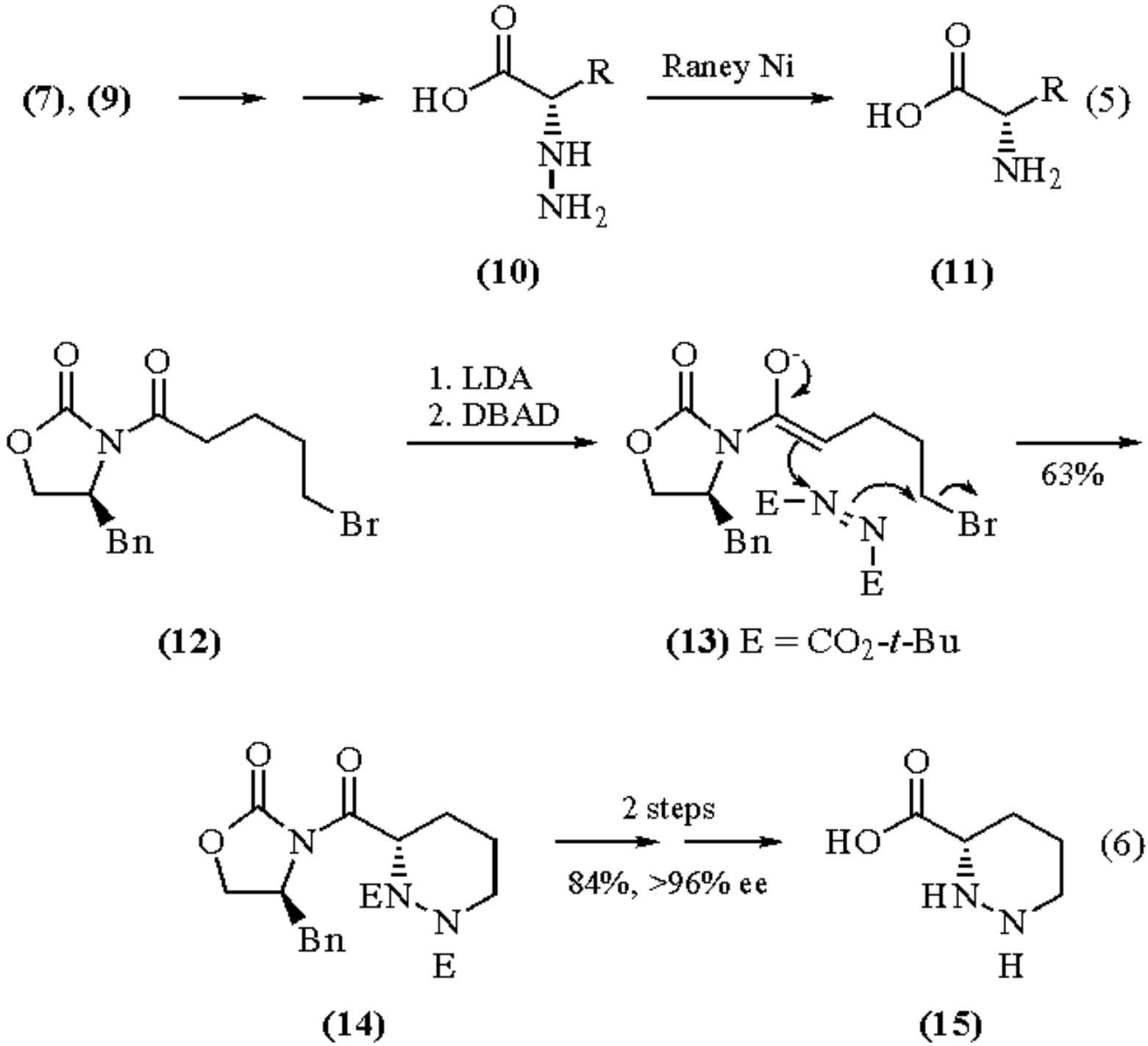

Several related syntheses of either α-amino acids or α-hydrazino acids have been developed, all of them using electrophilic amination of enolates to construct the stereogenic center at the α-carbon. 10-Sulfonamidoisobornyl esters (**16**) are useful tools for such processes.[13] These esters can be selectively deprotonated at -78 °C and converted to their corresponding *O*-silyl ketene acetals, which upon Lewis acid promoted addition of DBAD yield the amination products (**17**) in high yields (eq 7). These compounds are generally obtained with high stereoselectivity, and are diastereomerically pure after chromatography. α-Amino acids are synthesized from these precursors via a four-step procedure; the amino acids (**18**) are nearly enantiomerically pure (ee &egt; 95%).

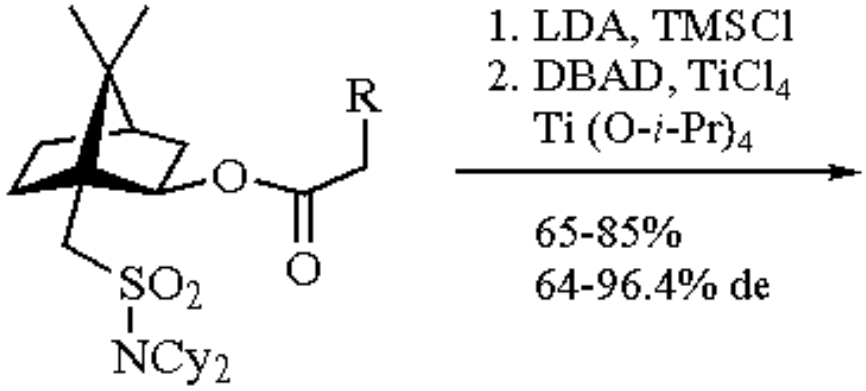

(16)

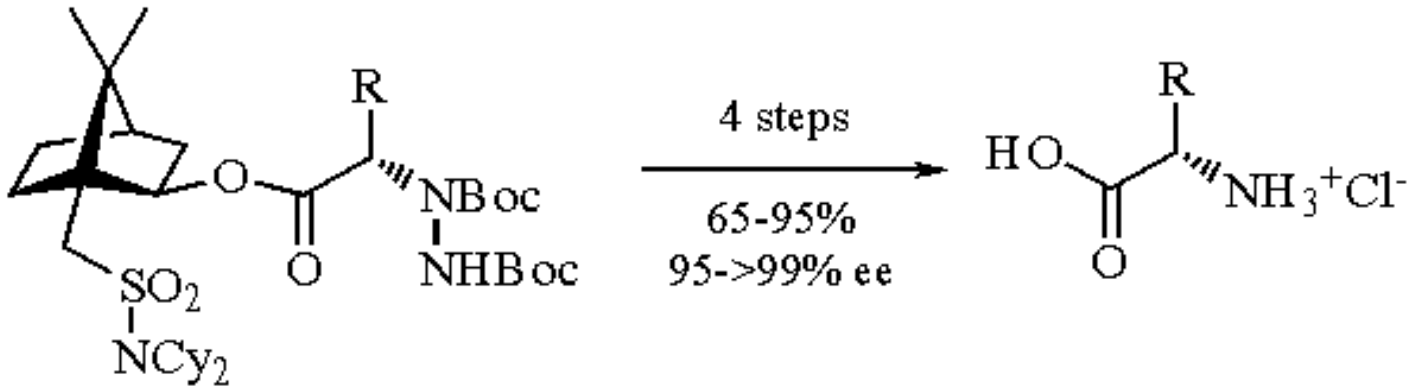

(7)

(17) **(18)**

R = alkyl, *i*-alkyl, Bn, 1-adamantyl-CH_2

(1R,2S)-N-Methylephedrine is also a suitable chiral auxiliary for the diastereoselective amination of *O*-silyl ketene acetals.[14] The silyl ketene acetals (**19**), derived from corresponding esters and *N*-methylephedrine, react smoothly with a preformed DBAD/***Titanium(IV) Chloride*** complex to generate the hydrazino derivatives (**20**) (eq 8). The major diastereomers are chromatographically separated and converted to their corresponding α-hydrazino acids (**21**) (from which a single isomer can also be obtained by recrystallization) or to the α-amino acids (**22**), respectively. Both (**21**) and (**22**) are obtained in good yields as single enantiomers.

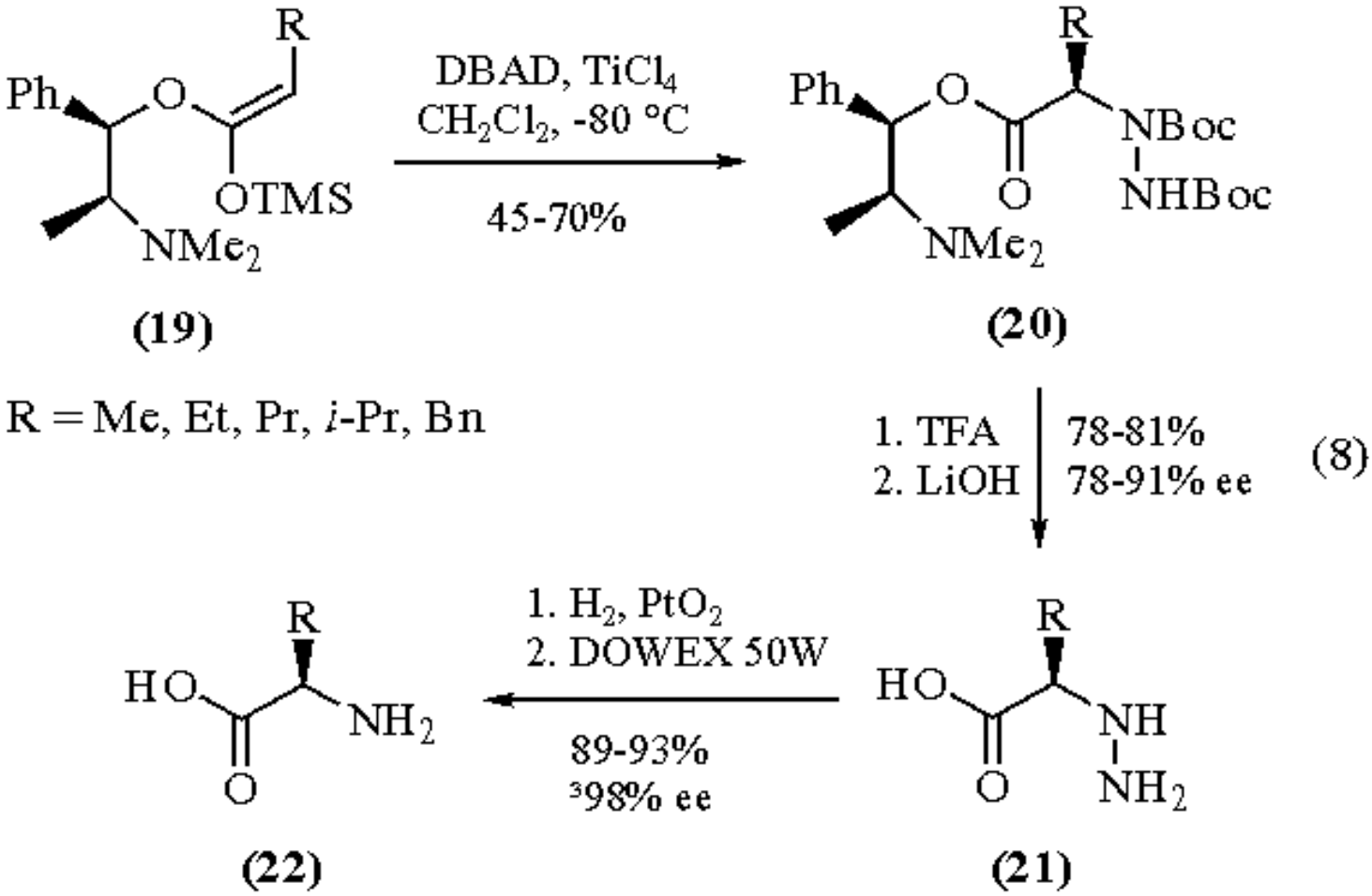

β-Hydroxy esters (**23**), available in both enantiomeric forms, can be deprotonated at the α-carbon without protection of the hydroxy group. These react with DBAD to give an easily separable mixture of *syn*- and *anti*-adducts. The *anti*-adduct (**24**) is formed in up to 88% de (eq 9).[15] These adducts are very useful tools since compounds with *anti* (allo) stereochemistry are not easily accessible by other established methods for amino acid synthesis. As in the previous cases, either amino acids or hydrazino acids are obtainable via several deprotection steps. One compound, (**26**; R = Me), was synthesized as a single enantiomer, but the others were initially prepared as racemic mixtures. Subsequently, as an application of this method, D-*ribo*-C_{18}-phytosphingosine was stereoselectively synthesized.[15b] Closely related processes were published afterwards and show analogous results.[16]

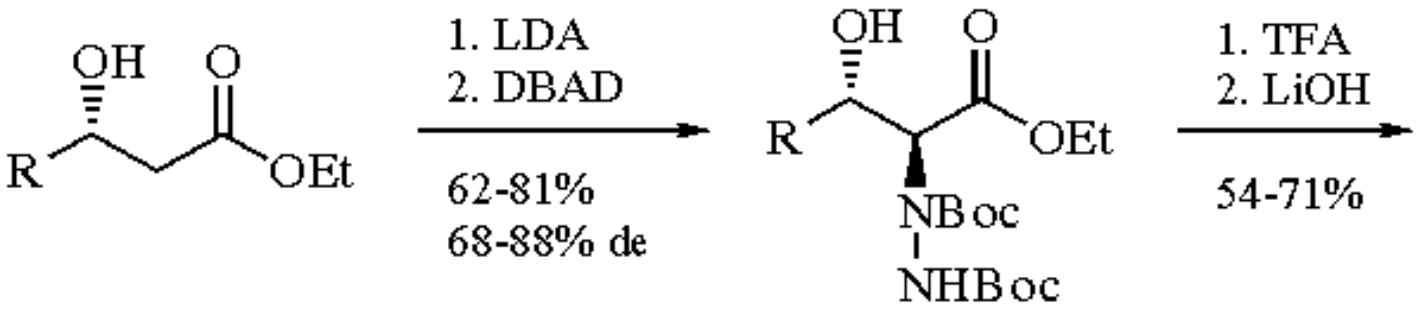

(23) (24)

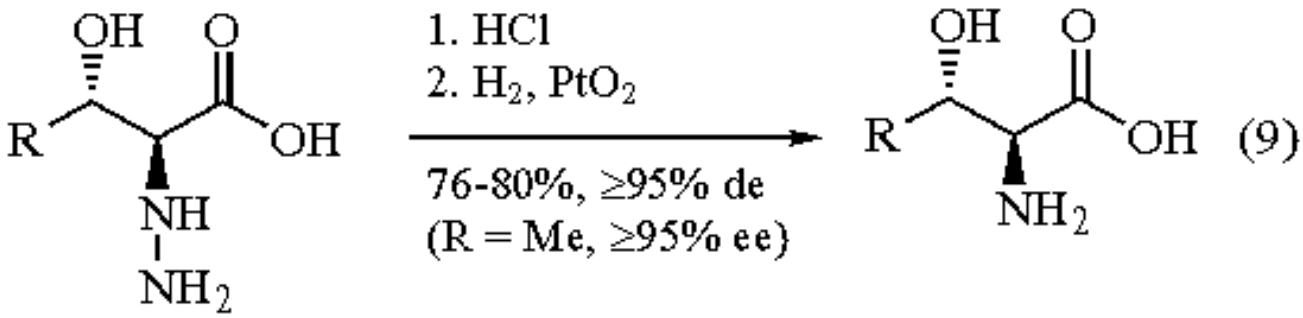

(25) (26)

R = Me, CF_3, hexyl, Cy

(*S*)-Trifluorothreonine methyl ester (**28**) has been synthesized from (**27**) using a related approach (eq 10).[17] Although an additional bulky *t*-butyl group is required for stereoinduction, this method gives the amination products with complete control of stereochemistry. Subsequent deprotection and hydrogenation reactions yield the desired product (**28**). A diastereoselective synthesis of (-)-2,3-diaminobutanoic acid from β-aminobutanoic acid has also been described (eq 11).[18] The synthesis of enantiomerically pure β-aminobutanoic acid is described in the same contribution, but the amination reaction of the protected derivative (**29**) with DBAD was performed on the racemic mixture, giving only one diastereomer (**30**) as a mixture of enantiomers. Several deprotection steps produced the desired (-)-2,3-diaminobutanoic acid as its diastereomerically pure hydrochloride (**32**).

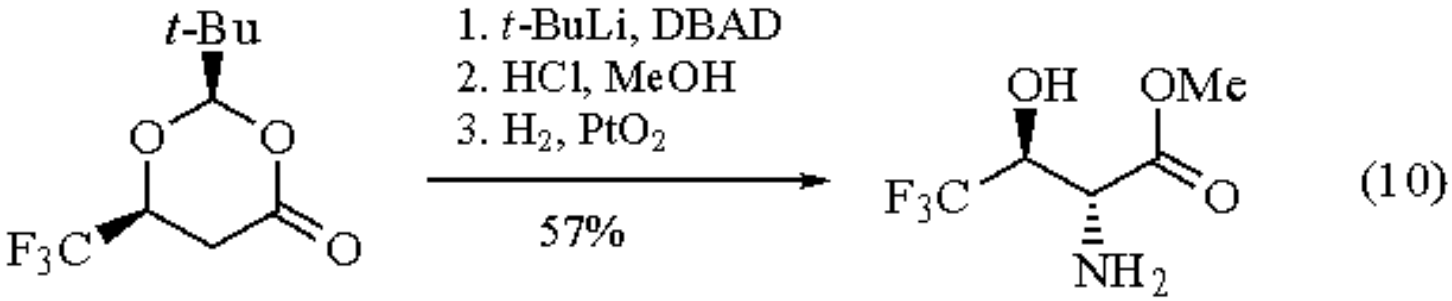

(27) (28)

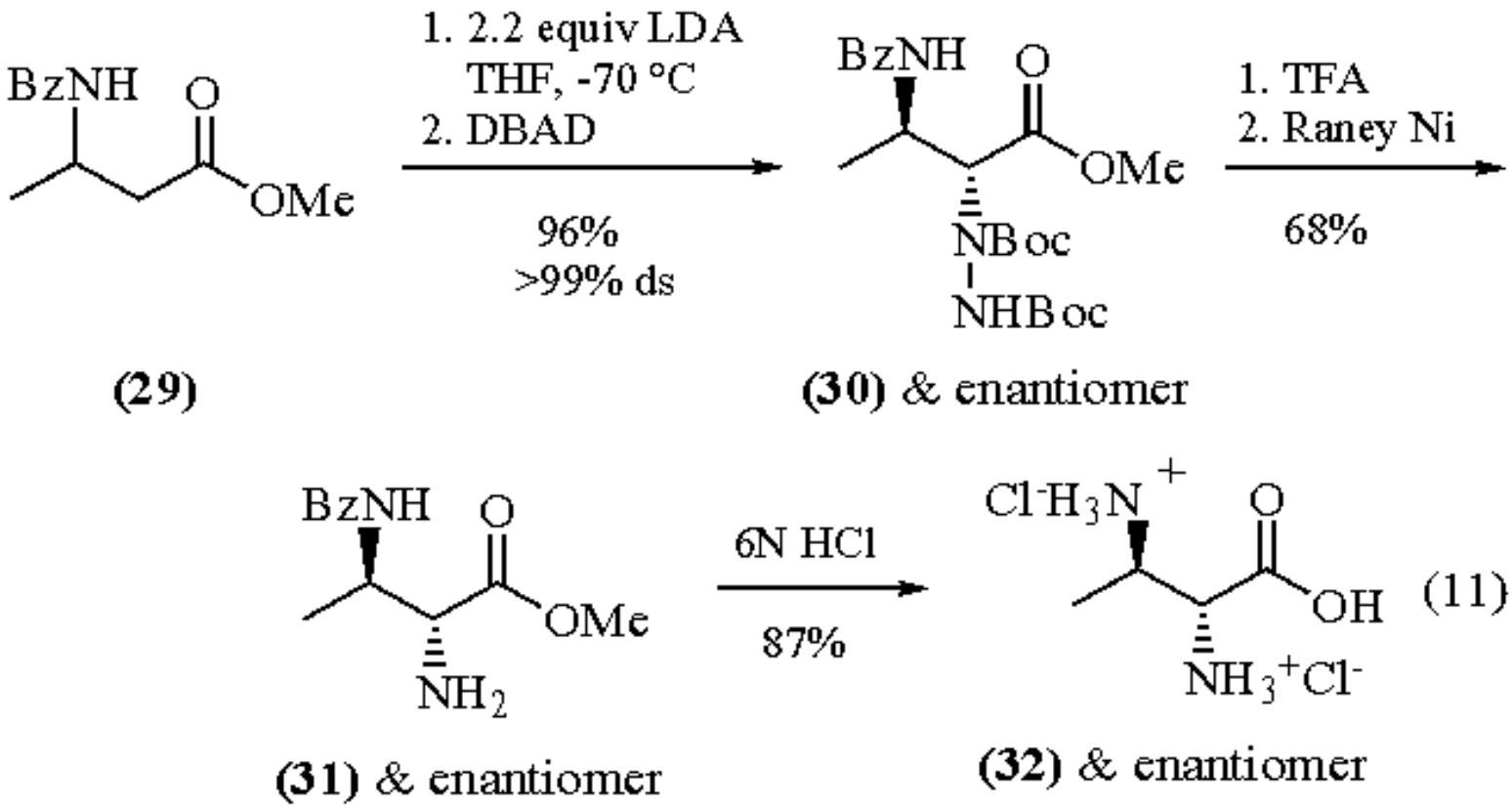

Methyl dithioacetate (**33**), upon deprotonation with ***n-Butyllithium***, is a suitable nucleophile for reaction with DBAD (eq 12).[19] The amination product (**34**), a precursor of α-amino thioacids, was obtained in 57% yield along with 15% of a side product resulting from attack of DBAD at the sulfur atom of the intermediate thioenolate.

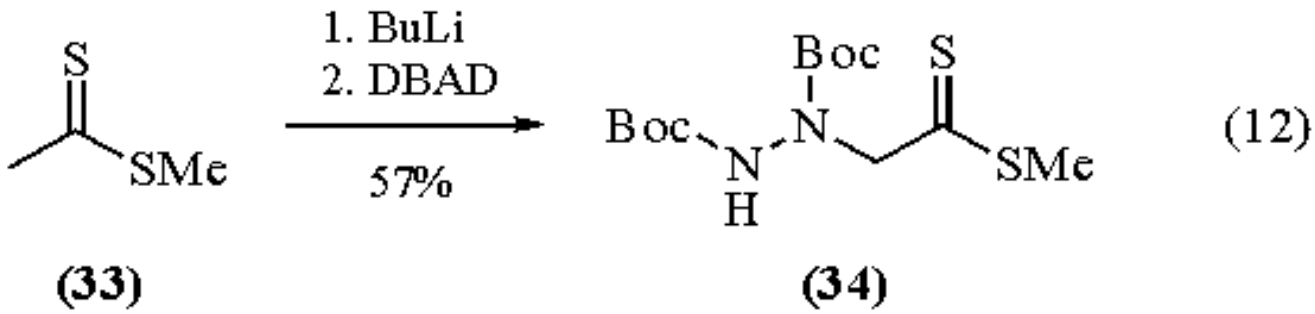

The procedures described above demonstrate the potential for electrophilic amination of enolates with DBAD to yield various α-amino acids or α-hydrazino acids with high optical purity. However, other condensations with carbanions have been published recently. After deprotonation with *n*-BuLi, the 1,2-oxazine (**35**) attacks DBAD with high γ-selectivity to produce (**36**) (eq 13).[20] Carbonyl compounds and D_2O also show high γ-selectivity, whereas alkyl halides react primarily in the α-position. The oxazine (**36**) is useful as a precursor of a 1,4-diamino compound.

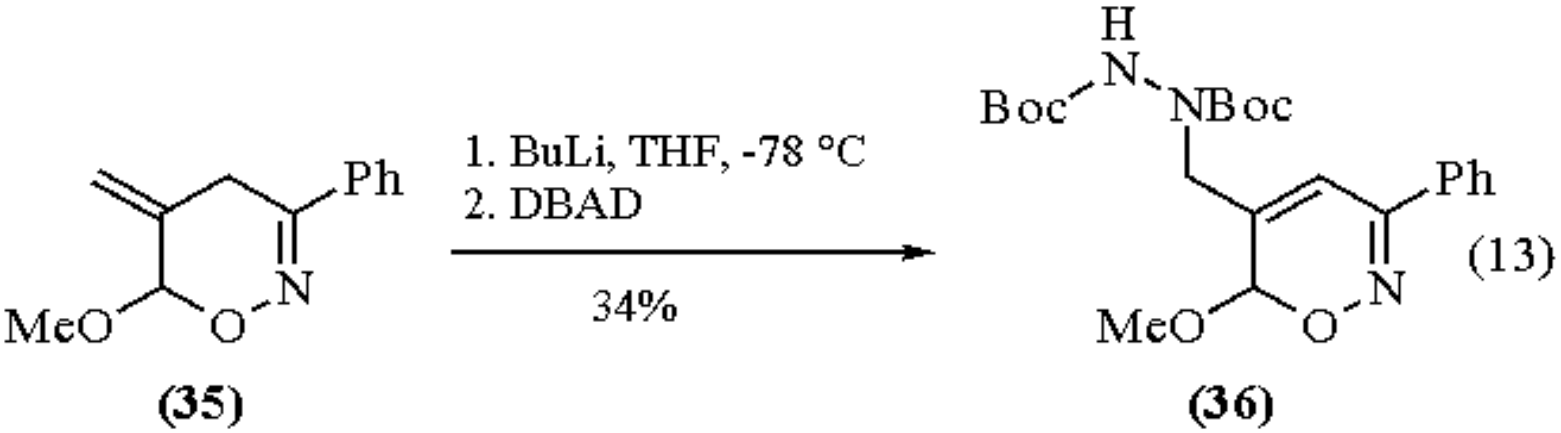

Reactions with Sulfur Nucleophiles.

Thiols readily react with DBAD to form sulfenohydrazides.[21] For example, *t*-butyl thiol (**37**) adds to the azodicarboxylate upon treatment with catalytic amounts of sodium alcoholate to give the sulfenohydrazide (**38**). These compounds can transfer a thio moiety to thiols. For example, attack by a second sulfur nucleophile, such as cysteine (**39**) (eq 14), leads to *t*-butyl thiocysteine (**40**). The overall result is a selective (and reversible) protection of cysteine at sulfur, thus providing an alternative to the commonly used protecting groups (e.g. trityl). A useful application is the synthesis of unsymmetrical cystine peptides (**44**) (eq 15).[21] A cysteine-containing peptide (**41**) is activated by DBAD, and the resulting sulfenohydrazide (**42**) is attacked by a different cysteine-containing peptide (**43**), to link two peptide chains via a disulfide. Several biologically important unsymmetrical cystine peptides and derivatives were prepared by this procedure.

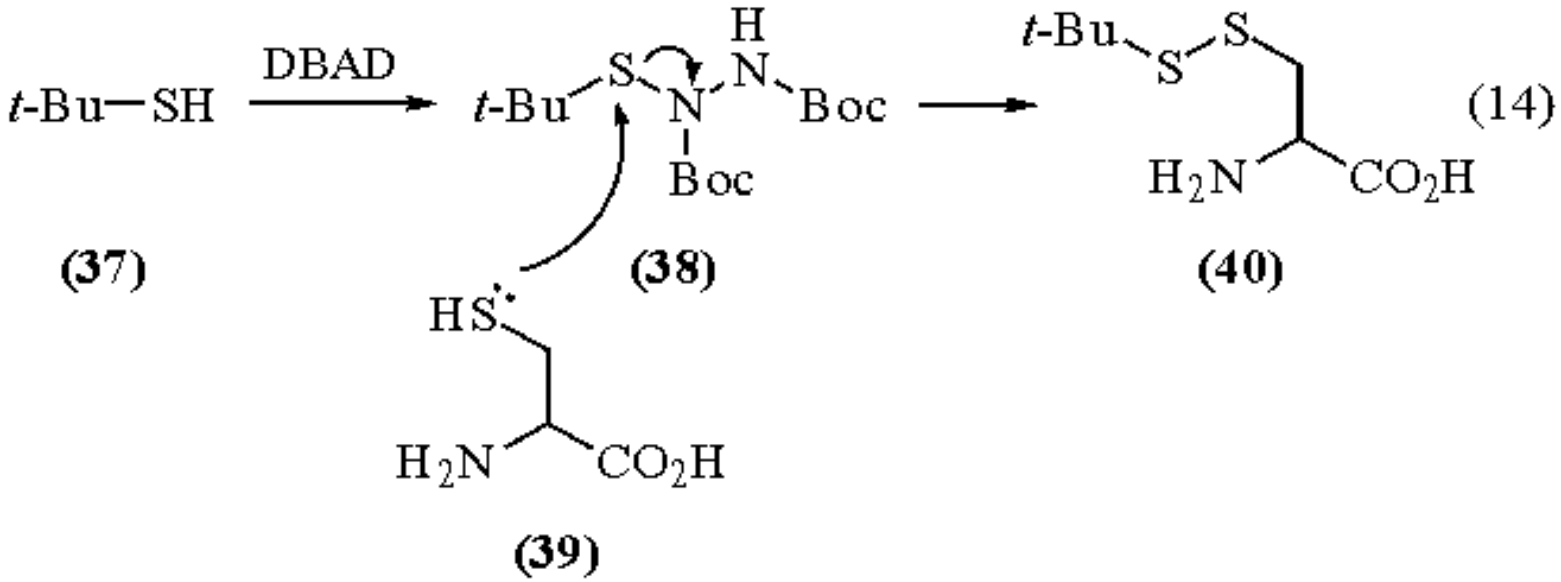

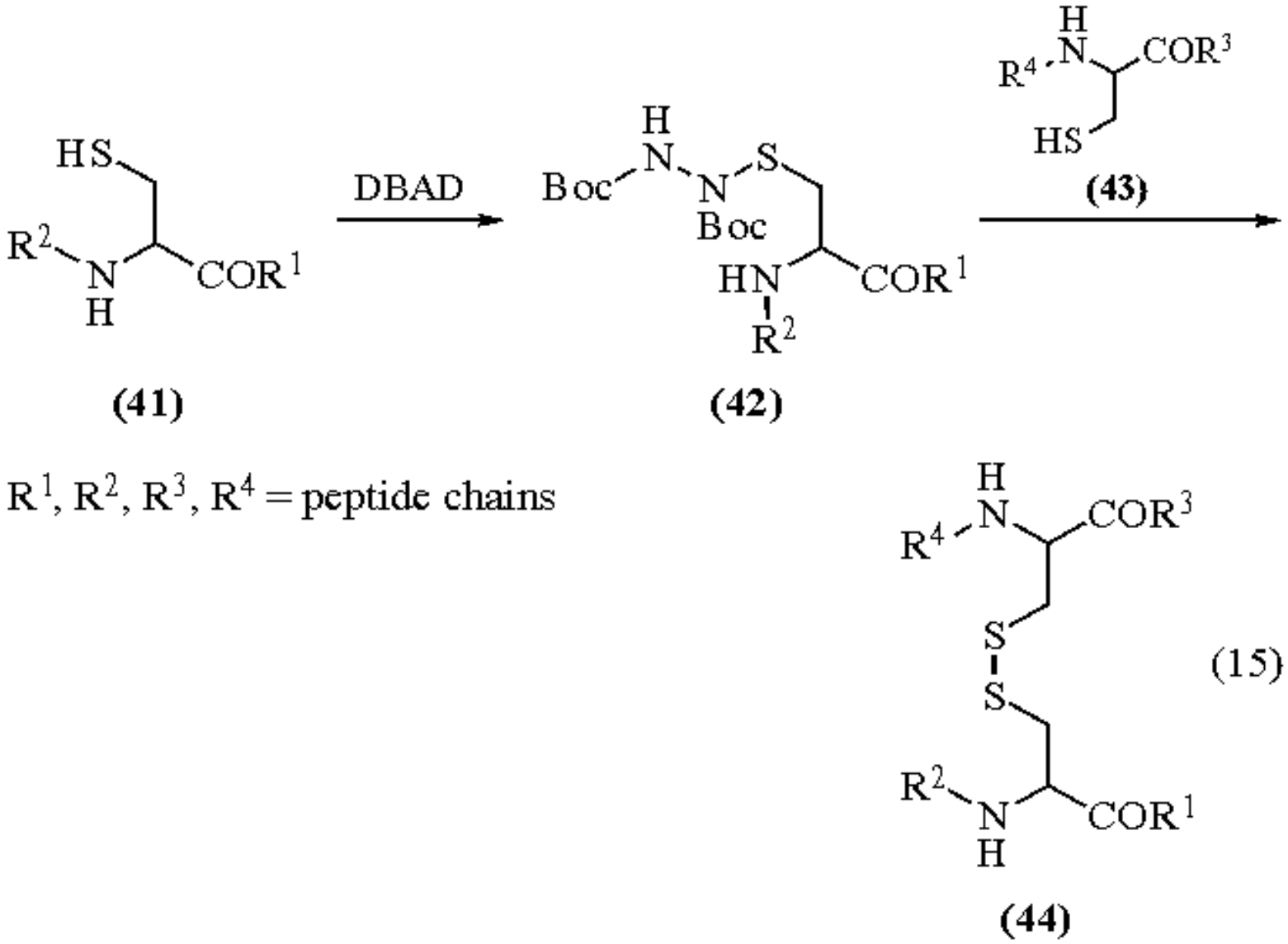

Sulfides (**45**) react with azodicarboxylates to yield adducts (**47**), where the addition has not proceeded in the manner described above, but rather to the carbon adjacent to the sulfur (eq 16).[22] Some of these reactions require the addition of ***Dibenzoyl Peroxide*** and/or UV irradiation to initiate the process. The reactivity order for hydrogens adjacent to sulfur atoms appears to be CH_2CO_2Me > benzyl > methyl, thus suggesting a carbanionic intermediate or transition state. The authors consider that association of the sulfide with the azo linkage might be accompanied by proton transfer to generate the ylide (**46**) in one step. Subsequent rearrangement furnishes the functionalized sulfides (**47**), providing a method to oxidize carbon atoms adjacent to sulfur; thus (**47**) can be considered a compound with a masked carbonyl group.

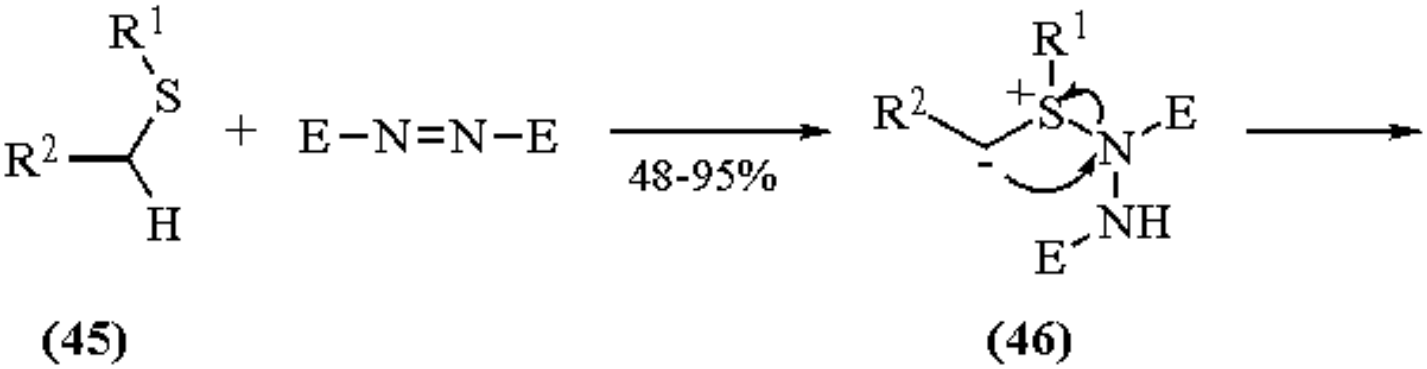

(45) (46)

$R^1 = Bn, Me, Et$
$R^2 = CO_2Me, Bn, alkyl$
$R^3 = Me, Bn, t\text{-}Bu$
$E = CO_2R^3$

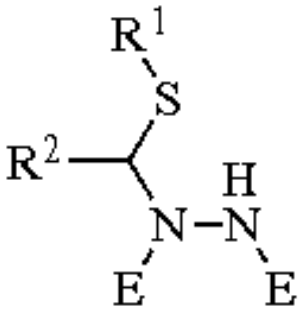

(16)

(47)

Diels-Alder[23] and Related Cycloadditions.

Azodicarboxylates have been long known to react with dienes in a [4 + 2] cycloaddition.[24] DBAD undergoes a variety of cycloadditions, e.g. Diels-Alder reactions, but is somewhat less reactive in these processes than its methyl or ethyl counterparts due to the bulky Boc groups. However, since the two Boc groups are more easily cleaved in the later steps of a reaction sequence than methoxycarbonyl groups, DBAD is still an attractive dienophile. In addition, DBAD has a higher thermal stability than its methyl or ethyl analog (e.g. dimethyl azodicarboxylate has to be distilled behind a safety shield). The condensation of cyclopentadiene with diethyl azodicarboxylate has been known since 1925, but the reaction can be done with DBAD in a similar manner (eq 17).[5,25] Several substituents and an additional keto function do not affect cycloadditions with azodicarboxylates, but interestingly, the intermediate Diels-Alder adducts rearrange and give oxadiazines (**52**) (eq 18).[26]

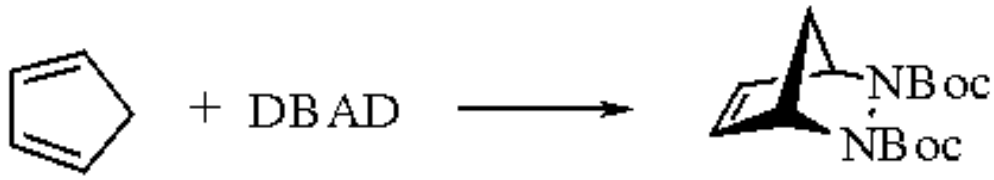

(17)

(48) (1) (49)

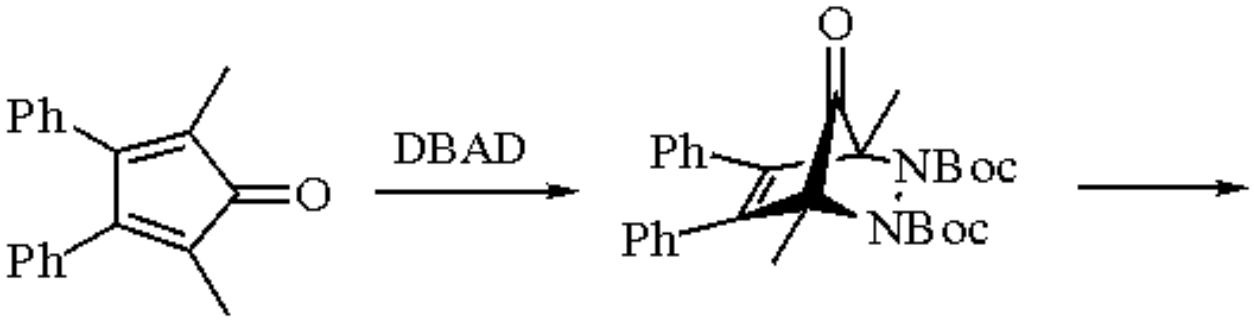

(50) (51)

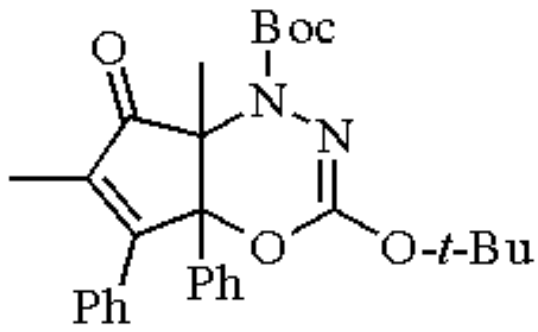

(18)

(52)

o-Quinoidal bismethylene arenes like (**54**) are very reactive dienes, which are prepared in situ via iodide-induced 1,4-elimination, and can be trapped with various dienophiles. The use of DBAD in this case leads to pyridazines (**55**) (eq 19).[27] A related reaction affords tetrahydroindeno[1,2-*d*]pyridazine (**58**). The process involves a similar 1,4 elimination of the precursor (**56**) followed by subsequent cycloaddition (eq 20).[28]

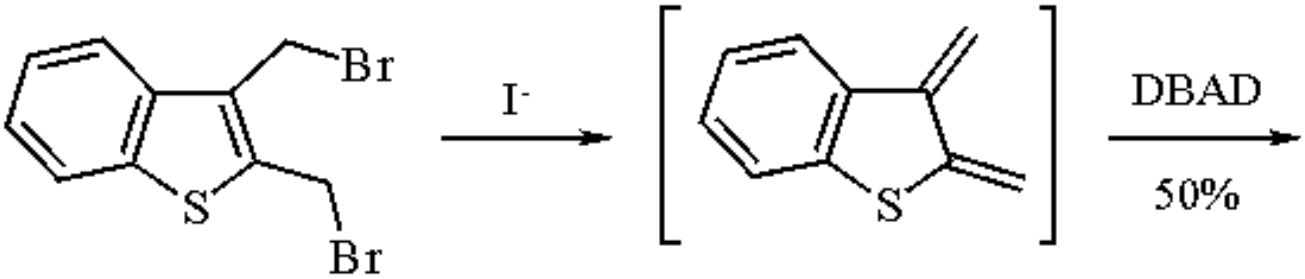

(53) (54)

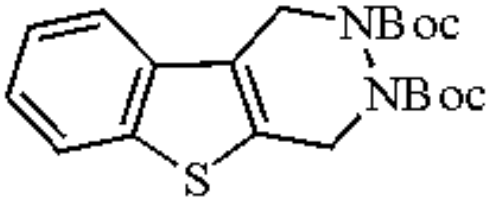

(19)

(55)

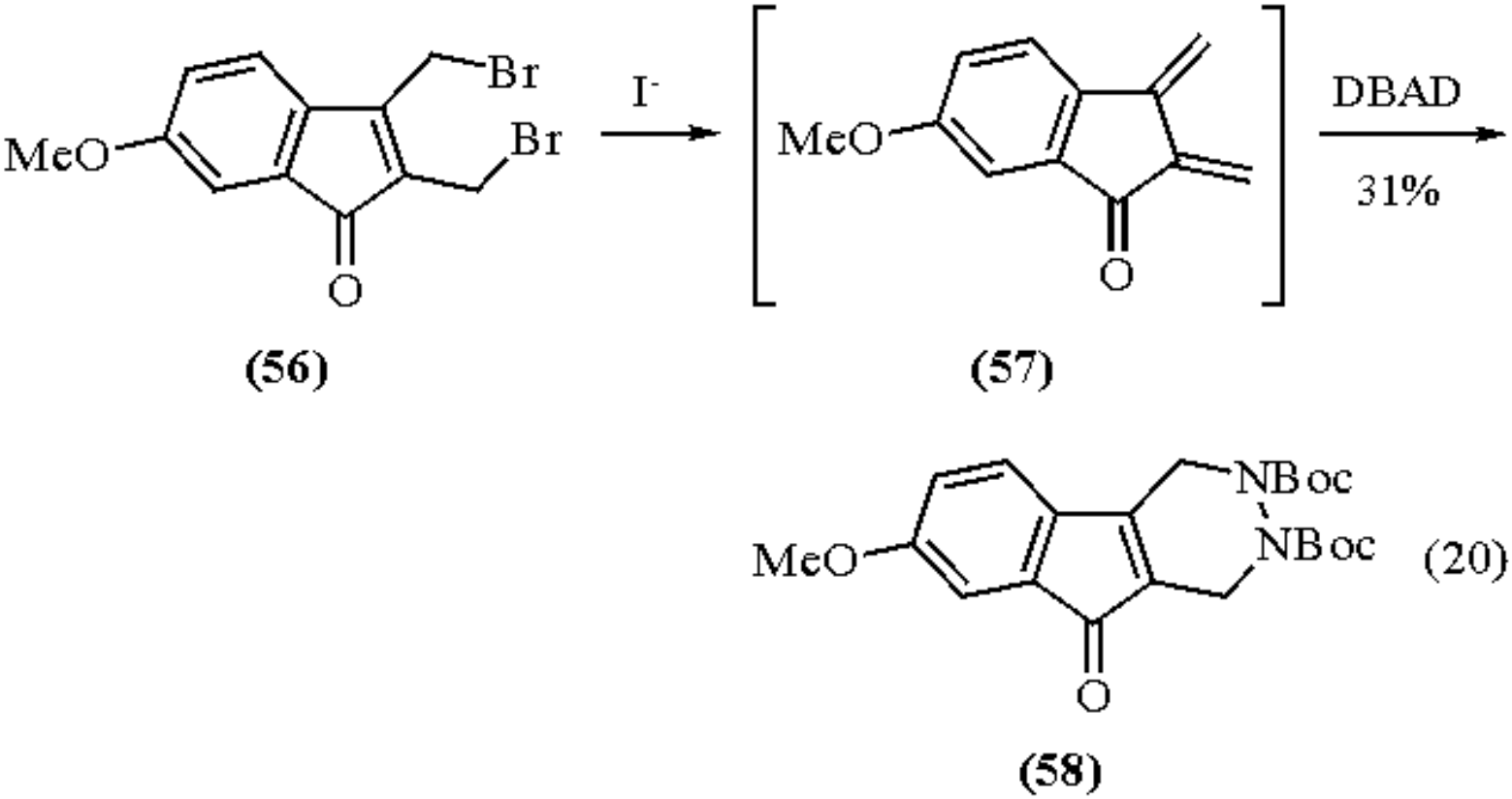

The thermal valence isomerization between the benzenoid structure (**59**) and the *o*-quinoidal structure (**60**) allows a range of [8 + 2] cycloadditions; condensation with DBAD leads to 2*H*-3,4-dihydro-1,2,3-benzothiadiazine (**61**) (eq 21).[29] 2-Vinyl-1,4-benzodioxin (**62**) undergoes facile Diels-Alder reaction with DBAD to produce the hydrazino aminal derivative (**63**) (eq 22).[30] 3-Vinylpyridines, 4-vinylpyridines, and 2-vinylthiophene undergo similar cycloadditions with DBAD.[31]

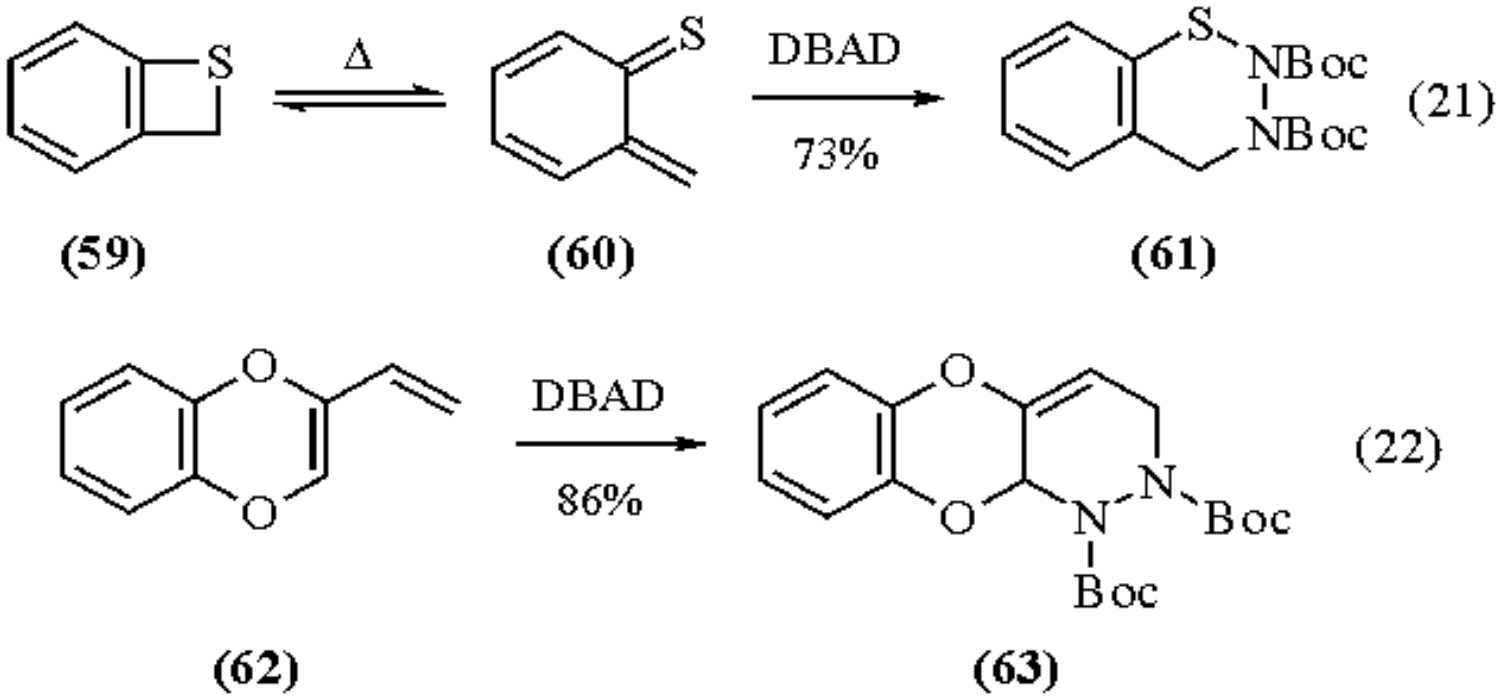

Mitsunobu-Type Reactions.

One of the most common reactions for dimethyl and diethyl azodicarboxylate is the Mitsunobu reaction.[1b] Surprisingly, very little is known about Mitsunobu reactions using DBAD. Only one publication, studying the mechanism of the Mitsunobu reaction, describes a comparative study of several azodicarboxylates, concluding that such reactions can be performed using DBAD.[32] A Mitsunobu-type reaction has been published recently, starting from alcohol (**64**). Treatment with triphenylphosphine and DBAD gives the hydrazine derivative (**65**) in one step (eq 23), presumably by a displacement reaction of the intermediate hydrazide anion and the triphenylphosphine/alcohol adduct.[33]

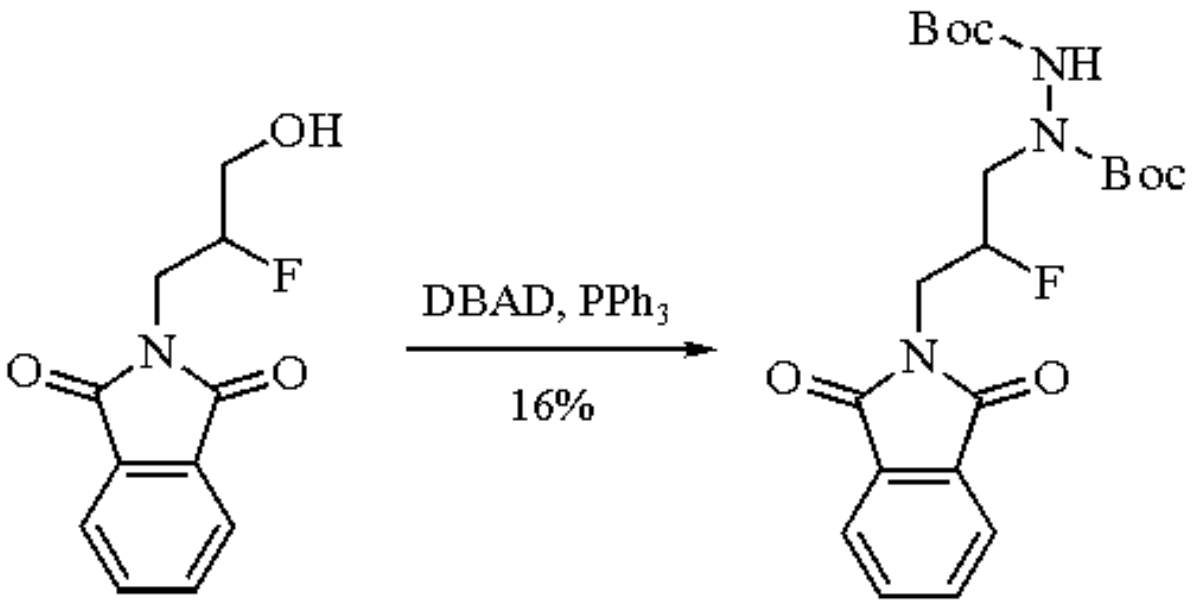

(64) (65) (23)

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Diethyl Azodicarboxylate.

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3,5-Di-*t*-butyl-1,2-benzoquinone

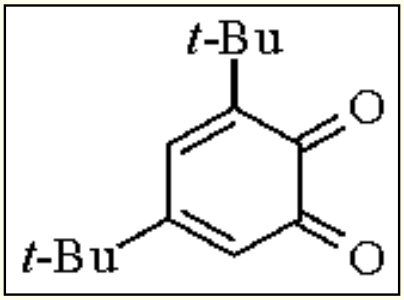

[3383-21-9] · $C_{14}H_{20}O_2$ · 3,5-Di-*t*-butyl-1,2-benzoquinone · (MW 220.31)

(reacts with primary amines to give different products depending on the alkyl substituent: benzoxazoles from primary amines and α-amino acids; ketones from *s*-alkyl primary amines; dioxazepines from cyclopropylamines; aromatic aldehydes from *vic*-aminobenzyl alcohols; skatole from tryptophan)

Alternate Name: DTBBQ.

Physical Data: mp 114-115 °C.

Solubility: sol most organic solvents; insol water.

Form Supplied in: dark red needles; commercially available.

Analysis of Reagent Purity: by TLC (silica gel plate Bakerflex-IBF, hexane/methylene chloride (1:1), R_f 0.53);[5] UV-vis λ_{max} 402 (ε = 821).[3]

Preparative Methods: by PbO_2 oxidation of 3,5-di-*t*-butylcatechol;[7] by chemical and electrochemical oxidation of 3,5-di-*t*-butyl-2-hydroxyaniline.[3]

Purification: recrystallization from toluene or by vacuum sublimation.

Handling, Storage, and Precautions: avoid exposure to light; toxicity unknown.

General Characteristics.

As a result of the steric hindrance caused by two *t*-butyl groups, the reactions are centered at the less hindered carbonyl, producing an unstable quinoneimine which is prone to a spontaneous aromatization. All reactions occur under mild conditions. In several reactions DTBBQ mimics pyridoxal.[8]

Reactions with Amines.

Primary alkyl primary amines, e.g. benzylamine[1] and ethanolamine,[2] react with DTBBQ to give benzoxazole derivatives via a quinoneimine and a Schiff base that undergoes cyclization and dehydrogenation with DTBBQ present in excess (eq 1).

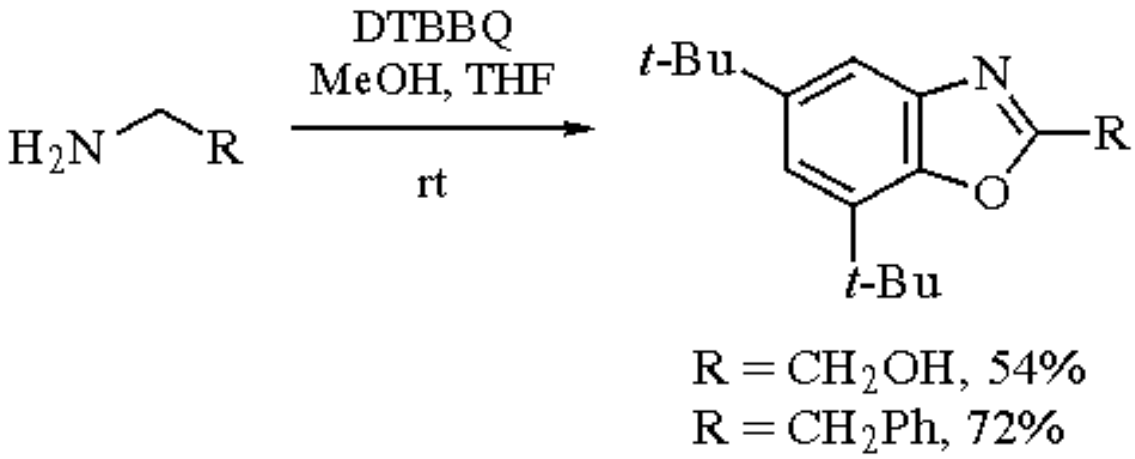

(1)

s-Alkyl primary amines undergo oxidative deamination (Corey's reaction) to give ketones produced in 84-97% yield. A small quantity of a phenoxazinone derivative is responsible for the pink color of the reaction mixture (eqs 2 and 3).[1,3]

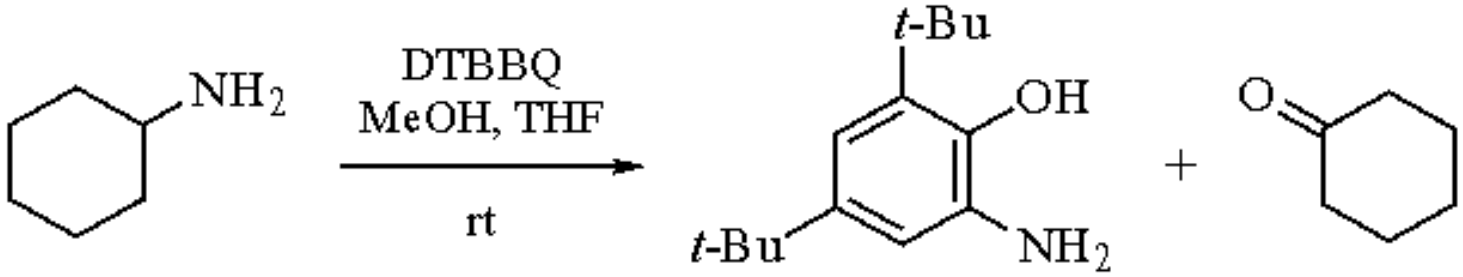

(2)

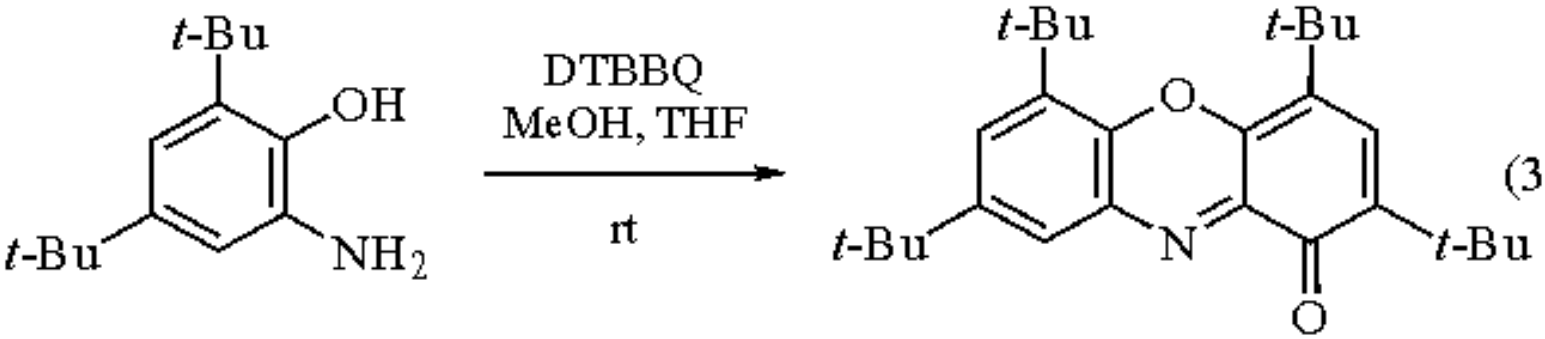

(3)

The tertiary cyclopropyl primary amine 1-phenylcyclopropylamine reacts via a ring-opening step to form a substituted dibenzoxazepine and an azospirodecatrienone (eq 4). Also the products obtained with cyclopropylamine show evidence of ring cleavage.[4]

3,5-Di-t-butyl-1,2-benzoquinone

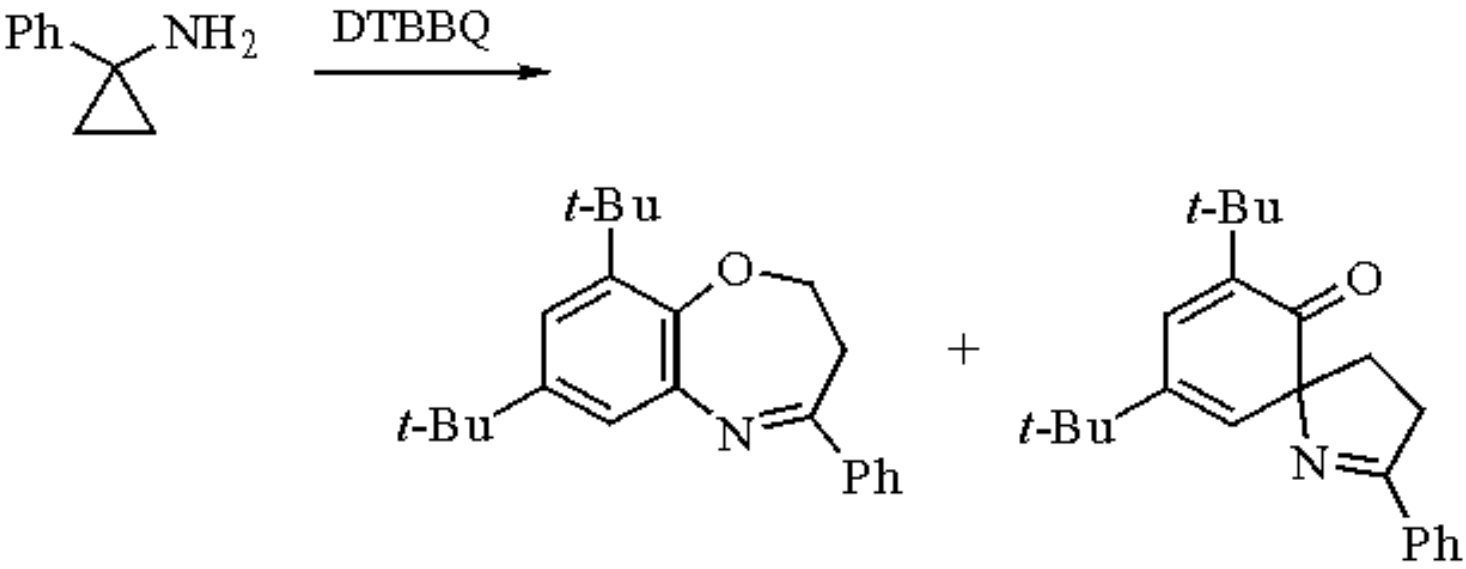

(4)

Vicinal aminobenzyl alcohols with 2 equiv of DTBBQ undergo C-C bond cleavage to form the respective aromatic aldehydes and benzoxazoles in high yields (eq 5). With an equimolar ratio of the reactants, benzaldehyde condenses with a portion of the amino alcohol to give the Schiff base (**1**).[2,6]

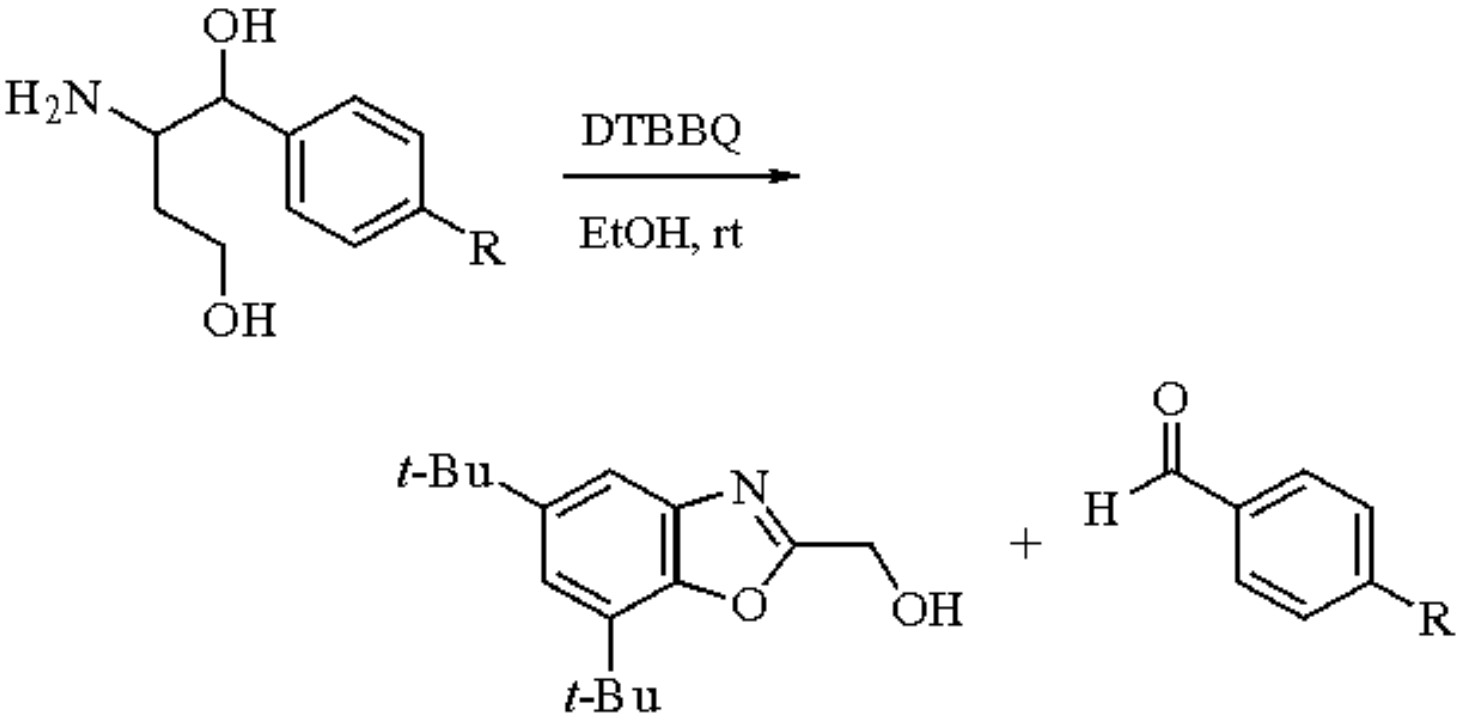

(5)

R = SMe	91:95
R = H	95:91

3,5-Di-t-butyl-1,2-benzoquinone

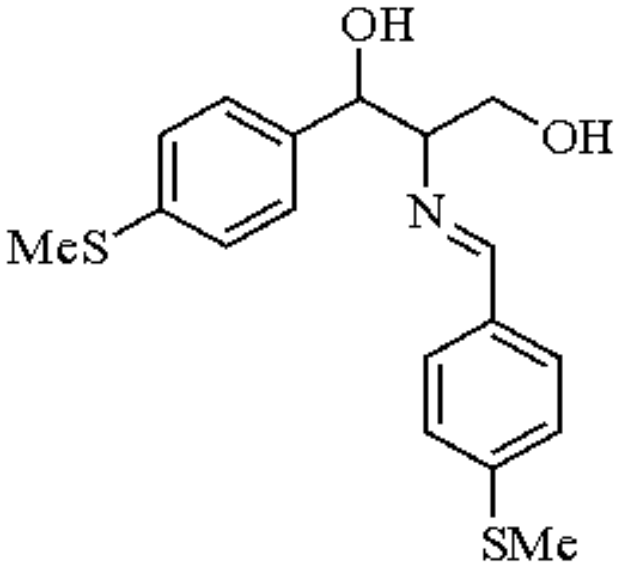

(1)

α-Amino acids form 2-substituted benzoxazoles via a decarboxylation step.[5] Tryptophan is an exception, undergoing retroaldol cleavage and formation of skatole (eqs 6 and 7).[6]

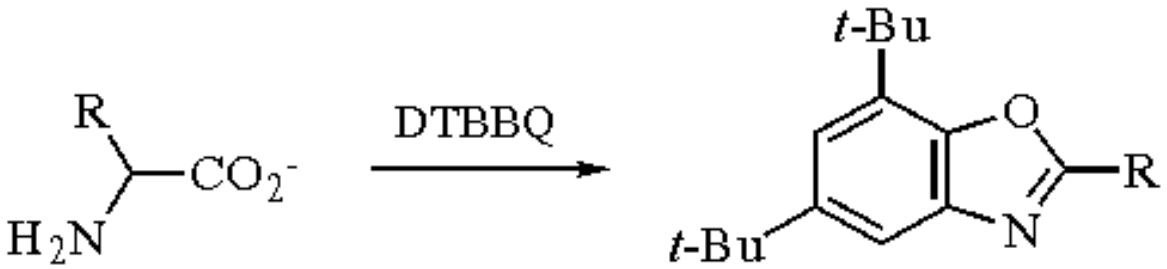

(6)

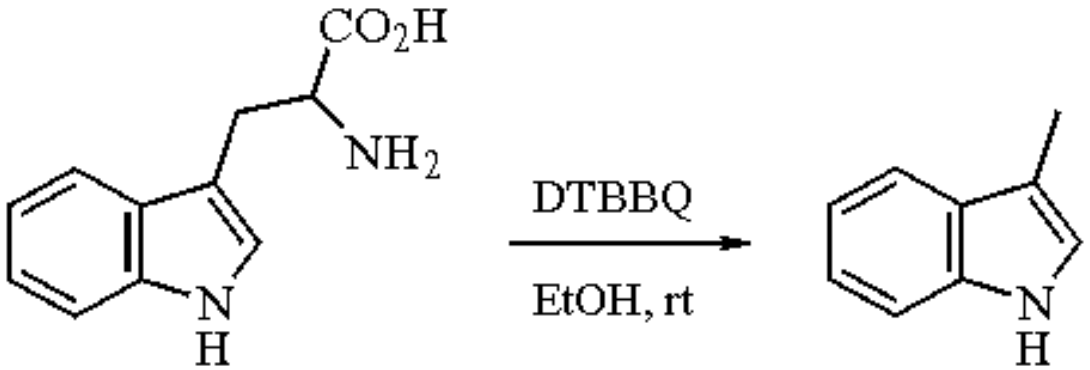

(7)

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2,6-Di-*t*-butyl-1,4-benzoquinone[1]

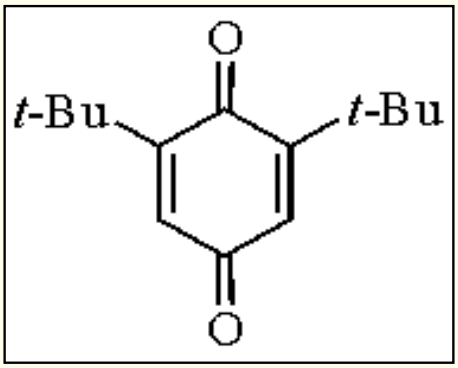

[719-22-2] · $C_{14}H_{20}O_2$ · 2,6-Di-*t*-butyl-1,4-benzoquinone · (MW 220.31)

(precursor for 4-aryl-2,6-di-*t*-butylphenols;[2] for 4-alkynyl-2,6-di-*t*-butylphenols;[3] oxidation of amines to amides via oxygenation of 4-(*N*-arylmethyleneamino)-2,6-di-*t*-butylphenols[4])

Physical Data: mp 65-67 °C.

Solubility: insol H_2O; sol organic solvents.

Form Supplied in: yellow solid.

Analysis of Reagent Purity: TLC, NMR.

Preparative Method: Co(salen)-catalyzed oxygenation of 2,6-di-*t*-butylphenol in DMF.[1]

Purification: silica gel column chromatography; recrystallization from hexane.

Preparation of 4-Substituted 2,6-Di-*t*-butylphenols.

2,6-Di-*t*-butyl-1,4-benzoquinone (**1**) is conveniently utilized for the preparation of a variety of 4-substituted 2,6-di-*t*-butylphenols. The reaction of (**1**) with Grignard reagents derived from aryl bromides, alkynes, and ***Ethylmagnesium Bromide*** gives the corresponding 1,4-quinols (**2**) in >90% yield from aryl Grignard reagents[2] and in 65-77% yield from RC&tbond;CMgBr (R = Ph, *n*-Bu, *t*-Bu).[3] The reduction of (**2**) with ***Zinc***/HCl in ethanol then affords the corresponding phenols (**3**) in 74-96% yield (eq 1).[3]

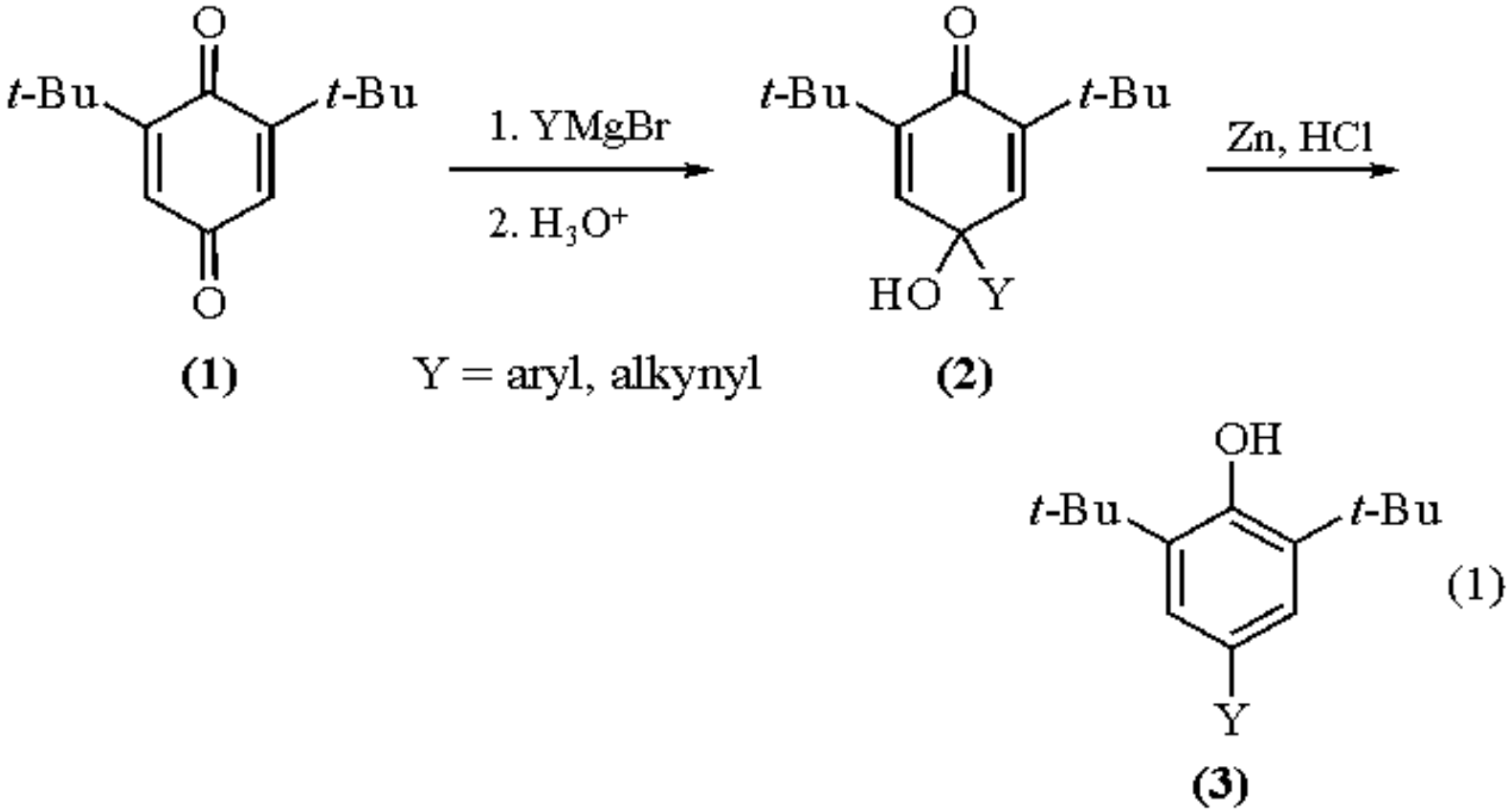

(1)

Oxidation of Amines to Amides.

Quinone (**1**) can conveniently be used for the selective oxidation of an α-methylene group in amines to give the corresponding amides, normally a difficult transformation. Treatment of (**1**) with $ArCH_2NH_2$ in ethanol at reflux first leads to 4-(*N*-arylmethyleneamino)-2,6-di-*t*-butylphenol (**4**) (eq 2) (yields: Ar = Ph (82%), 4-MeC_6H_4 (61%), 4-$MeOC_6H_4$ (72%), 4-ClC_6H_4 (49%), 3-pyridyl (62%), 2-furyl (42%)).[4] Base-promoted oxygenation of (**4**) then affords (**1**) and the corresponding amide (eq 2). The yield of amide depends on the reaction conditions; oxygenation with ***Potassium t-Butoxide*** in *t*-BuOH provides the amide in 36-85% yield, but the recovery of (**1**) is only 10% because (**1**) is unstable under the conditions. On the other hand, the use of ***Potassium Hydroxide*** in ethanol leads to the amide in 15-79% yield with better recovery of (**1**) (70%).[4] The oxygenation of (**5**) with Co(salpr) in dichloromethane reveals that hydroperoxide (**5**) is a likely intermediate in this reaction.[5]

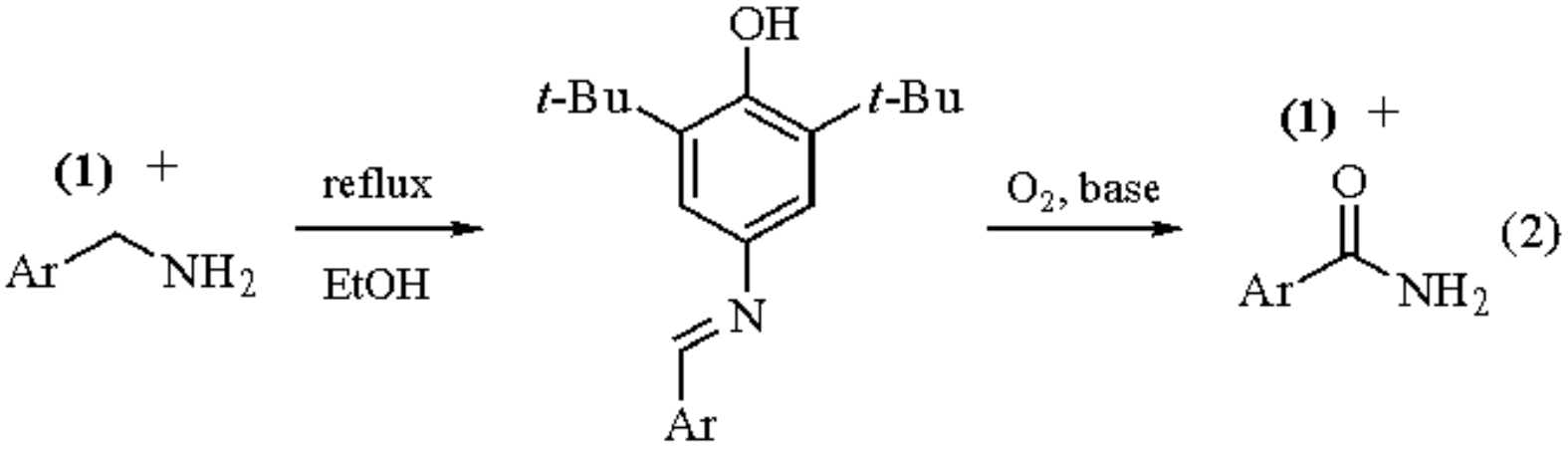

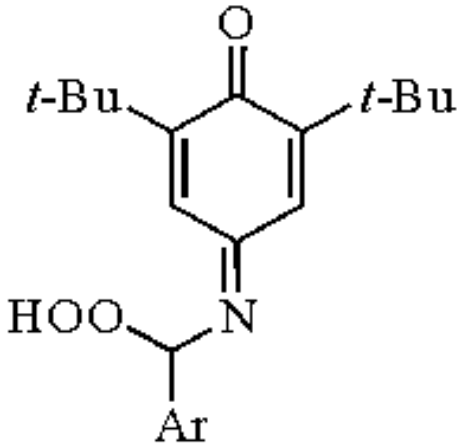

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Di-*n*-butylboryl Trifluoromethanesulfonate

***n*-Bu_2B-OSO_2CF_3**

[60669-60-4] · $C_9H_{18}BF_3O_3S$ · Di-*n*-butylboryl Trifluoromethanesulfonate · (MW 274.11)

(Lewis acid for the preparation of vinyloxyboranes,[1-6] boryl azaenolates;[7,8] catalyst for macrolactonization[9])

Physical Data: bp 60 °C/2.0 mmHg.

Solubility: sol common inert organic solvents such as Et_2O, CH_2Cl_2, and hexane.

Form Supplied in: 1.0 M solution in CH_2Cl_2 and Et_2O.

Preparative Method: ***Trifluoromethanesulfonic Acid*** is added slowly to an equimolar amount of ***Tri-n-butylborane*** with gentle warming (50 °C) until butane evolution commences. The remaining acid is added at such a rate to maintain a reaction temperature of less than 50 °C. After the addition is complete, the mixture is stirred for an additional 30 min at 25 °C and then the product is isolated by vacuum distillation.[1c]

Handling, Storage, and Precautions: the neat liquid as well as solutions are moisture and air sensitive. Therefore the material should be stored and transferred under a dry inert atmosphere. Use in a fume hood.

Vinyloxyboranes (Boron Enolates).

Dibutyl vinyloxyboranes are conveniently prepared from active methylene carbonyl containing compounds utilizing Bu_2BOTf in combination with a sterically hindered amine base. Typically the base, ***Diisopropylethylamine*** or ***2,6-Lutidine*** (2,6-lut), and Bu_2BOTf are premixed in Et_2O or CH_2Cl_2 at -78 °C and then the carbonyl component is added. Enolate generation is allowed to occur over the next 15-30 min at temperatures ranging from -78 °C to 0 °C, resulting in the formation of vinyloxyboranes which are suitable for reaction with aldehydes in a crossed aldol reaction. Other boryl triflate reagents have similar or complimentary utility in this process (see ***9-Borabicyclononyl Trifluoromethanesulfonate*** (9-BBNOTf) and ***Dicyclopentylboryl Trifluoromethanesulfonate*** ($(c\text{-}C_5H_9)_2BOTf$)).

With unsymmetrical methyl ketones, use of Bu_2BOTf and *i*-Pr_2NEt results in the regioselective formation of the vinyloxyborane at the least hindered carbon. However, if 9-BBNOTf and 2,6-lut are used, the regioselectivity of vinyloxyborane formation is reversed (eq 1).[10]

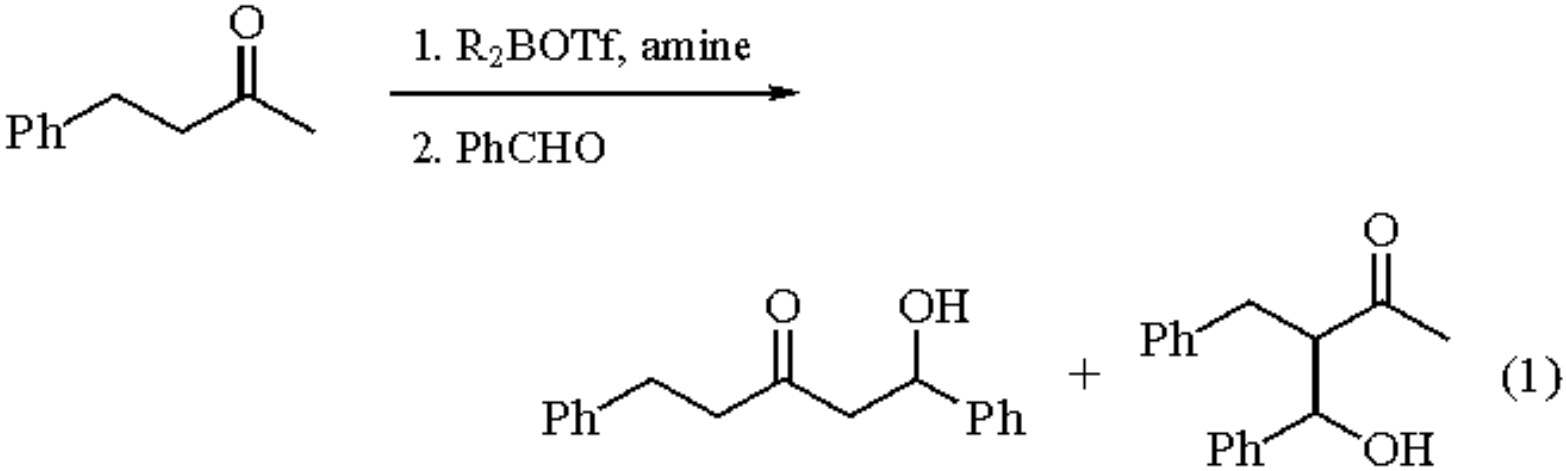

Bu_2BOTf, *i*-Pr_2NEt	100:0
9-BBNOTf, 2,6-lut	12:88

The relative stereochemistry of the two new chiral centers formed in the aldol product is a direct consequence of the vinyloxyborane enolate geometry with *Z*(O) enolates affording the 2,3-*syn* aldol products and the *E*(O) vinyloxyboranes leading to the 2,3-*anti* isomers. As a result, a number of studies have examined the effects of various boryl triflates and amines on the ratio of kinetic enolates formed. In general, it has been found that with a given base, more sterically hindered boryl triflates lead to increased amounts of the *E*(O) enolate. For example, when 3-pentanone is treated with Bu_2BOTf or $(c\text{-}C_5H_9)_2BOTf$ in the presence of *i*-Pr_2NEt, the ratio of *Z*(O):*E*(O) enolates drops from 32:1 to 4:1 (eq 2).[1c]

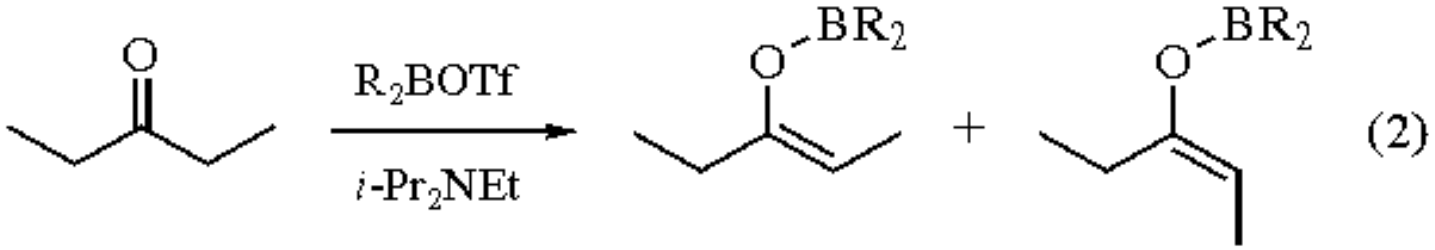

R_2	
Bu_2	>97:3
$(c\text{-}C_5H_9)_2$	82:18

With ketones in which no combination of boryl triflate and amine produces a vinyloxyborane of predominately one geometry, Bu_2BOTf has been utilized to catalyze the exchange with a trimethylsilyl enol ether of defined stereochemistry (eq 3). In order to maintain high stereoselectivity in the subsequent aldol reaction, it is necessary to remove the TMSOTf byproduct prior to the addition of the aldehyde (eq 3).[11]

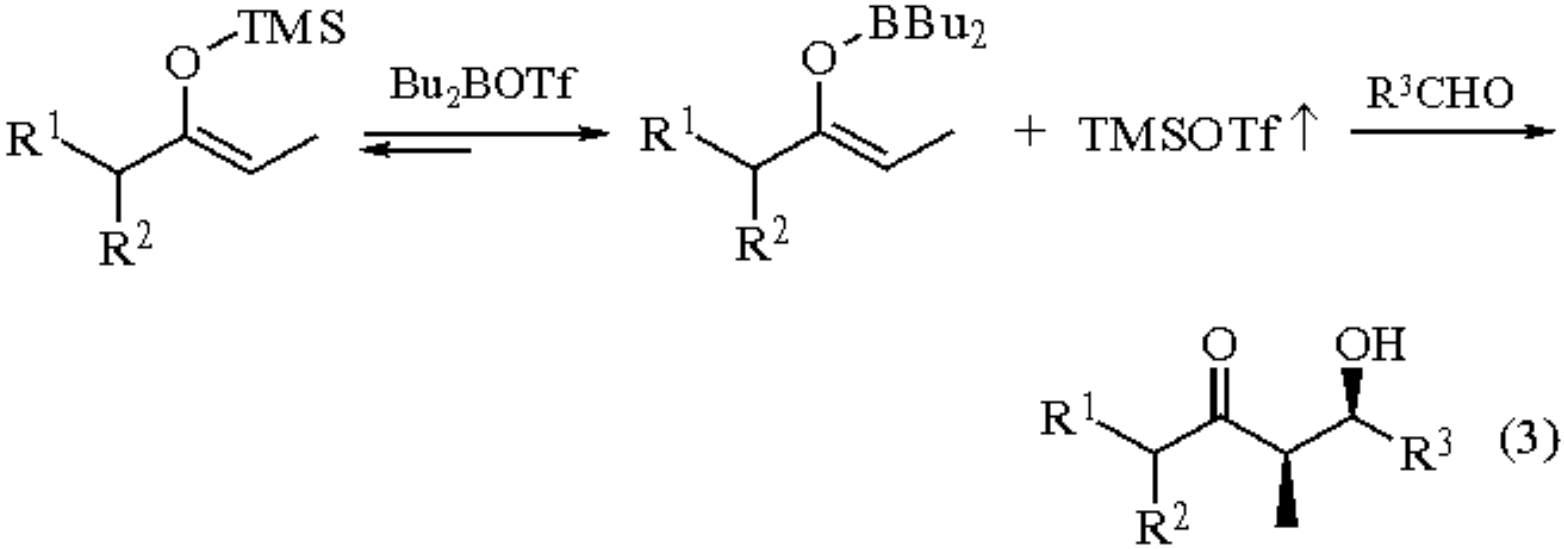

Probably the greatest utility of this reagent has been in the stereoselective formation of chiral vinyloxyboranes with defined enolate geometries from which the absolute stereochemistry of the new chiral centers formed in the aldol process are controlled. A number of chiral masked propionate equivalents useful for the synthesis of polypropionate-like natural products have been developed for this purpose. Chiral α-hydroxy ethyl ketones derived from both enantiomers of hexahydromandelic acid have been shown to form the *Z*(O) vinyloxyborane stereospecifically with 9-BBNOTf, Bu_2BOTf, and $(c\text{-}C_5H_9)_2BOTf$. However, the size of the ligands attached to boron has a measurable effect upon the extent of the enantioselectivity achieved in the aldol process, as exemplified in eq 4.[1b]

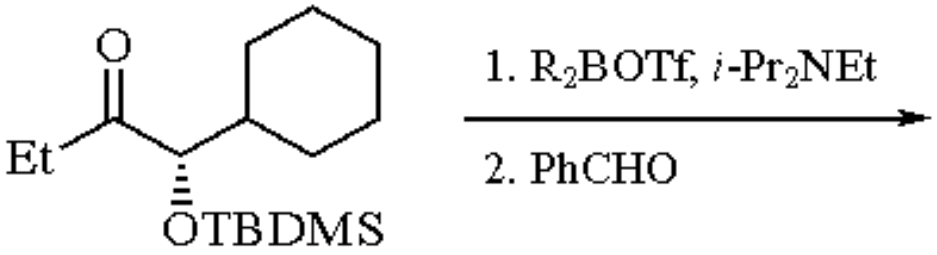

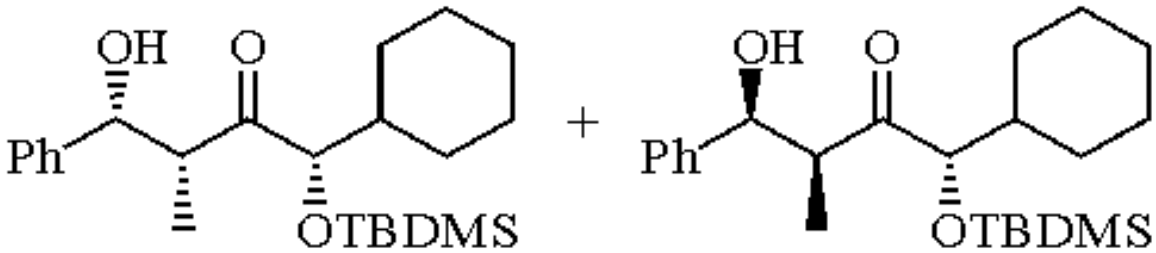

(4)

R_2	
9-BBN	14:1
Bu_2	40:1
$(c\text{-}C_5H_9)_2$	75:1

The other major class of chiral boron enolate reagents developed for this purpose employs a propionate unit attached to a chiral auxiliary. These are typified by the chiral oxazolidinones derived from α-amino alcohols initially developed by Evans (eq 5),[2a] with subsequent variants involving thiazolidinethiones, oxazolidinethiones,[3] sultams,[4] and camphor-derived oxazolidinones[2b] being reported more recently.

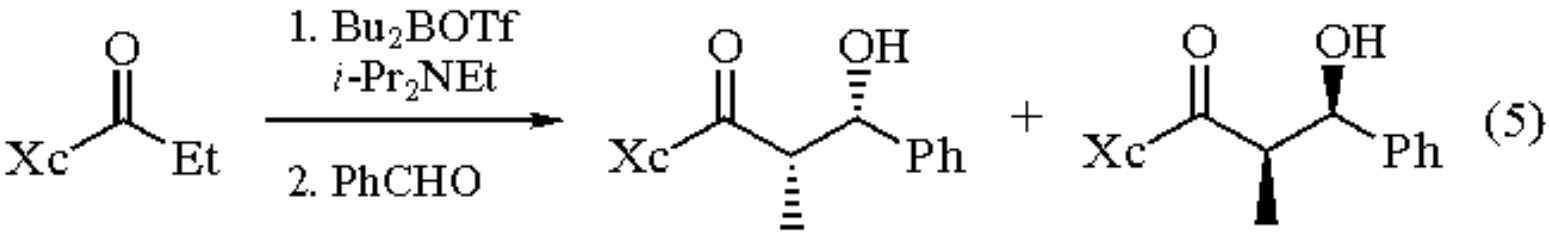

Xc		
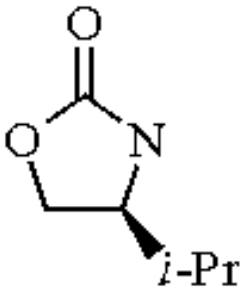	>500:1	88%
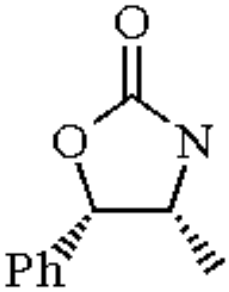	<1:500	89%

Other functional groups which can be utilized for further synthetic manipulation are well tolerated on the chiral vinyloxyborane. These have included thioethers,[12a] selenoethers,[12b] carboxylic esters,[2a] and halogens. For example, the bromoacetyl oxazolidinone in eq 6 has been utilized in a Darzens-like condensation for the enantioselective synthesis of *cis*-substituted epoxides.[12c] This procedure is complemented by the synthesis of *trans*-substituted epoxide derivatives from the *E*(O) vinyloxyborane derived from α-bromo-*t*-butylthioacetate.

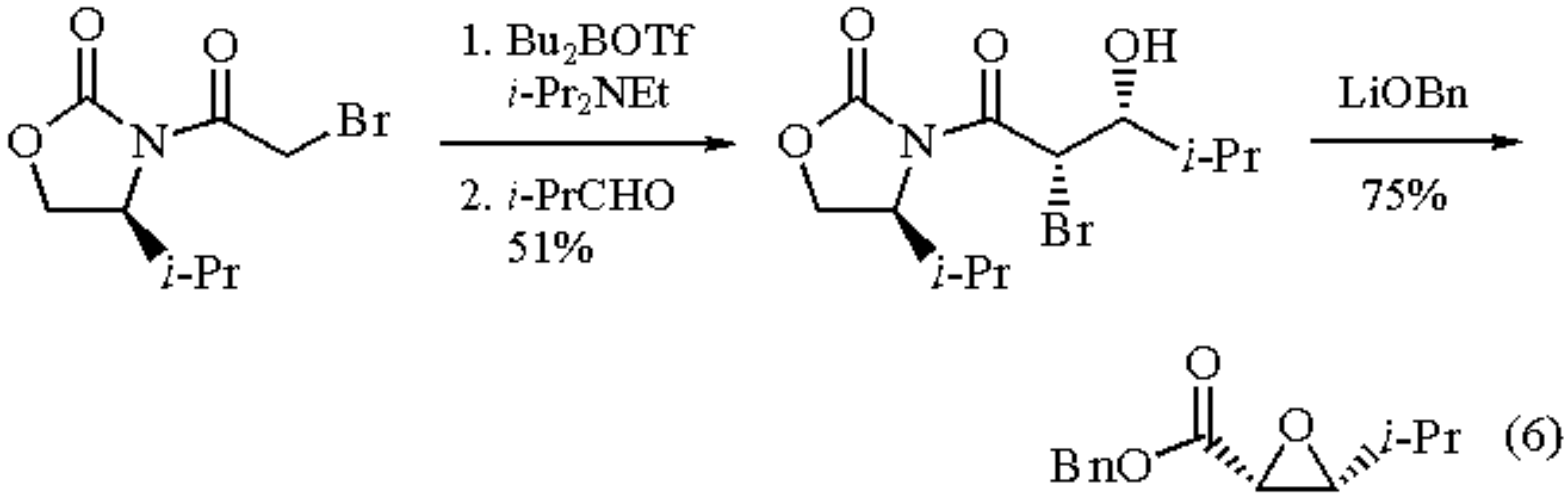

Vinyloxyboranes also react with electrophiles other than aldehydes. For example, the chiral vinyloxyborane generated

from an *N*-propionyloxazolidinone, Bu_2BOTf, and *i*-Pr_2NEt reacts with ***N-Bromosuccinimide*** to produce the chiral bromide shown in eq 7 as the principal adduct.[13] High enantioselectivity has also been achieved in sulfenylation and selenation reactions with chiral boron enolates, an example of which is shown in eq 8.[14]

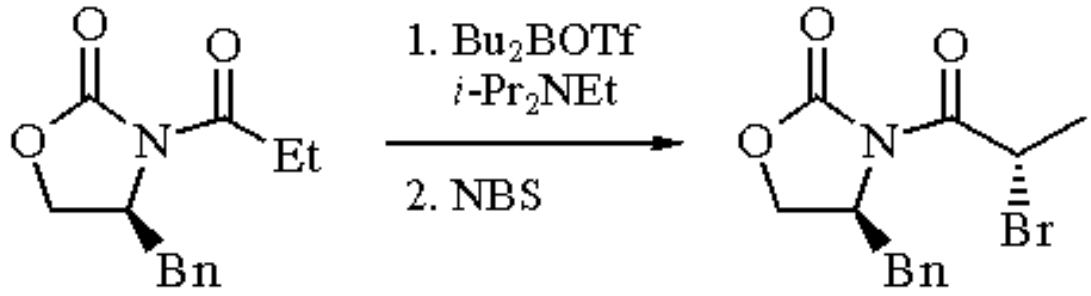

(7)

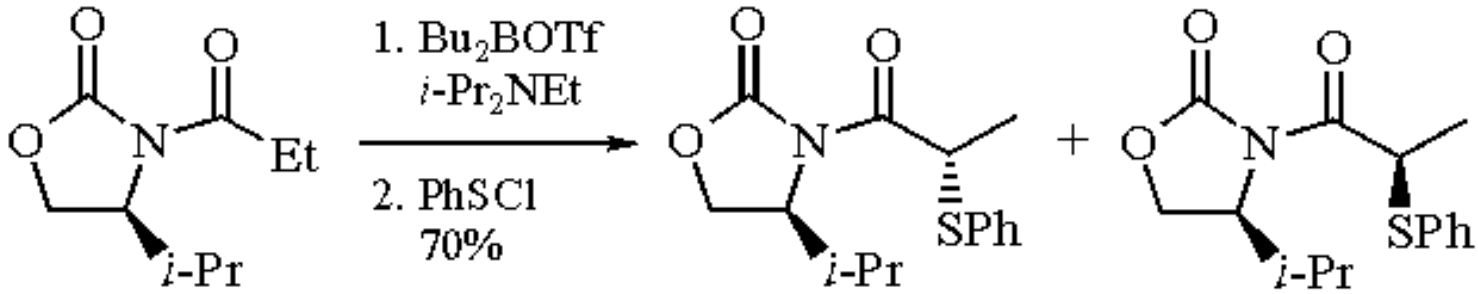

(8)

88:12

The boron enolate of *t*-butyl thioacetate has been employed in the condensation with a variety of Schiff bases to produce β-amino acid derivatives. Reported yields range from 40-80% and the conditions are sufficiently mild to allow for the preparation of a highly functionalized intermediate used in the synthesis of bleomycin (eq 9).[5] The boron component of various vinyloxyboranes is also capable of activating ***Bis(dimethylamino)methane***, resulting in a convenient one-pot procedure for the preparation of β-dimethylamino carbonyl compounds (eq 10).[15]

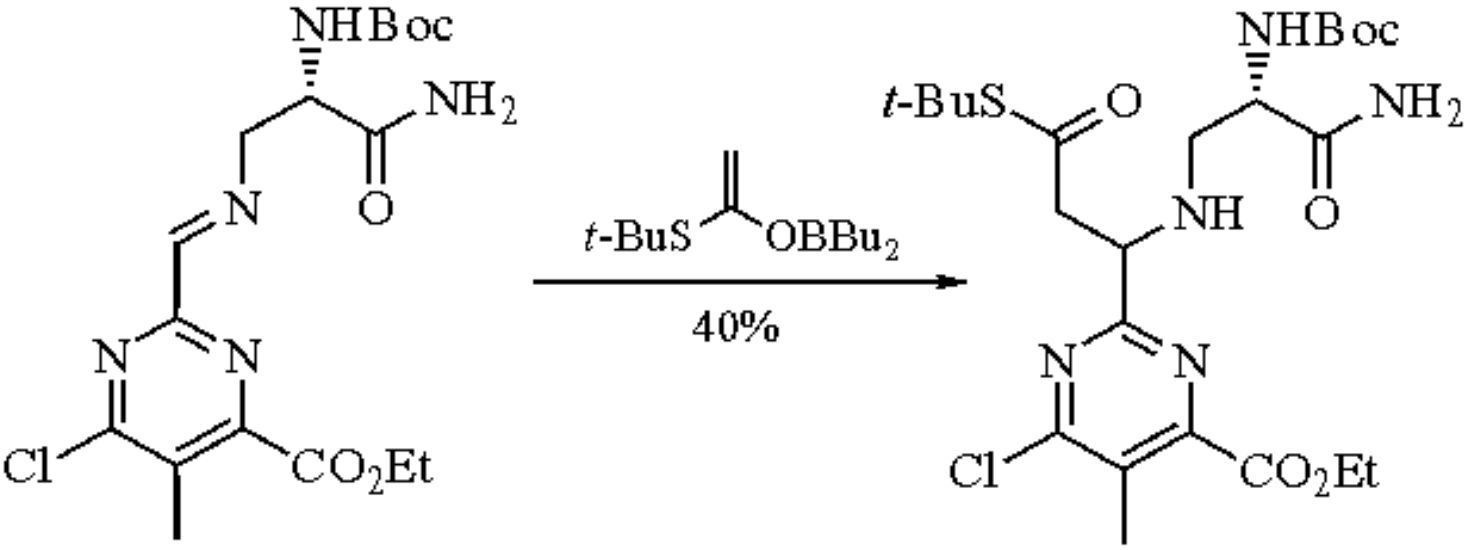

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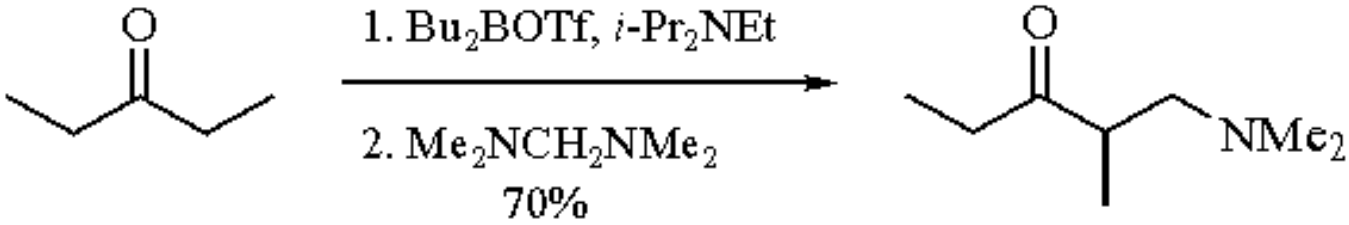

(10)

Simple carboxylic esters are not active enough to form enolates in the reaction with a boryl triflate and an amine; however, glycolate and thioglycolate esters are readily transformed into vinyloxyboranes which upon further reaction with aldehydes yield predominately the 2,3-*syn* aldol products (eq 11).[6]

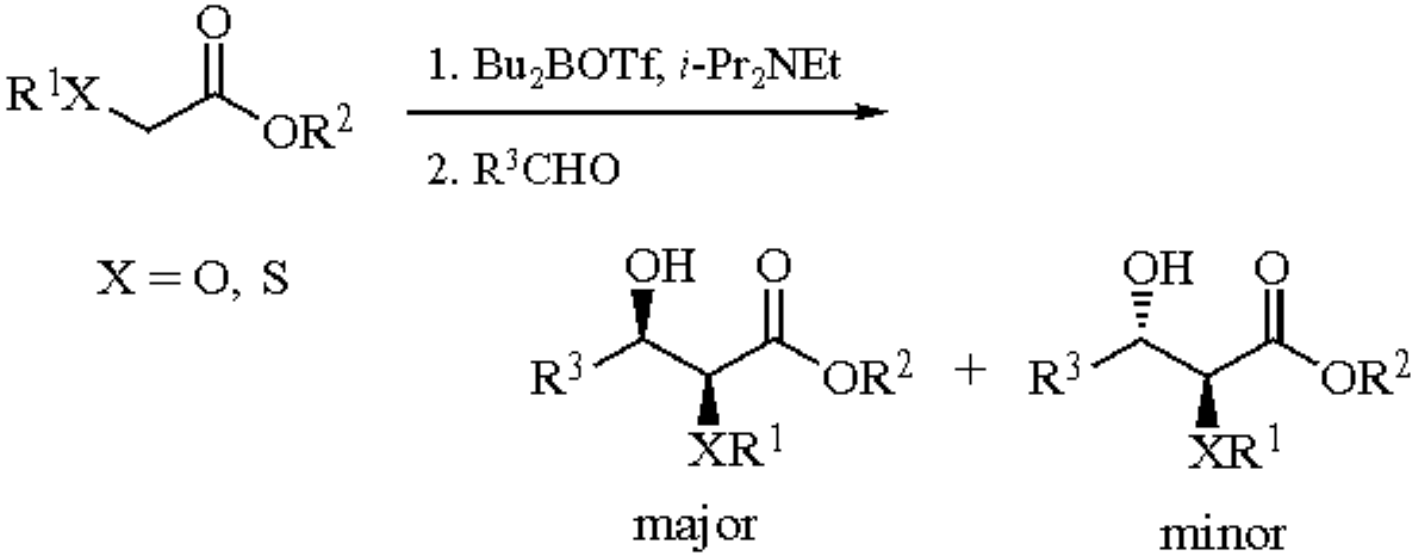

(11)

Boryl Azaenolates.

Nitrile derivatives react with Bu_2BOTf and *i*-Pr_2NEt to produce enolates which condense with various substituted benzaldehydes to yield β-hydroxy nitrile products. Poor yields result when aliphatic aldehydes are utilized as reactants, thus limiting the scope of this reaction.[7] 2-Ethylpyridine yields predominately the 2,3-*syn* aldol product when the enolate is generated with Bu_2BOTf in the presence of ***Triethylamine*** (eq 12). No reaction occurs when *i*-Pr_2NEt is used.[8]

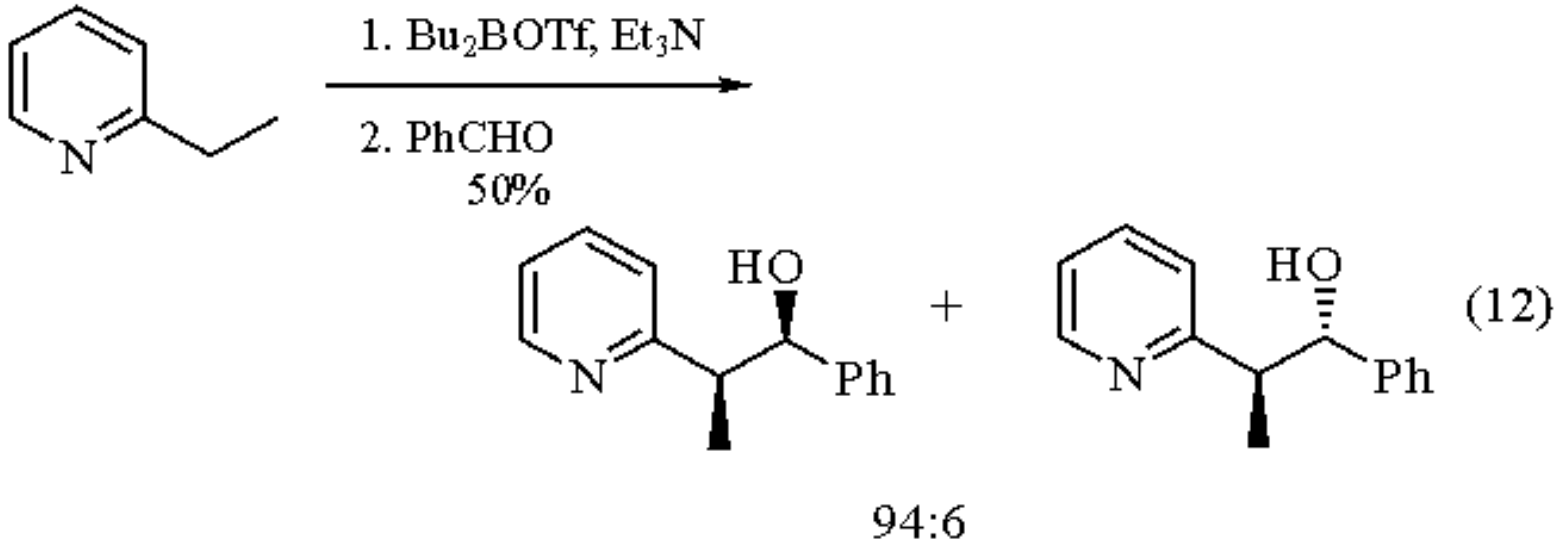

Macrolactonization.

Trimethylsilyl o-trimethylsilyloxycarboxylates cyclize to the corresponding macrolides in the presence of 1 equiv of a dialkylboryl triflate. Pr_2BOTf gives higher yields of product than either Et_2BOTf or Bu_2BOTf (eq 13).[9]

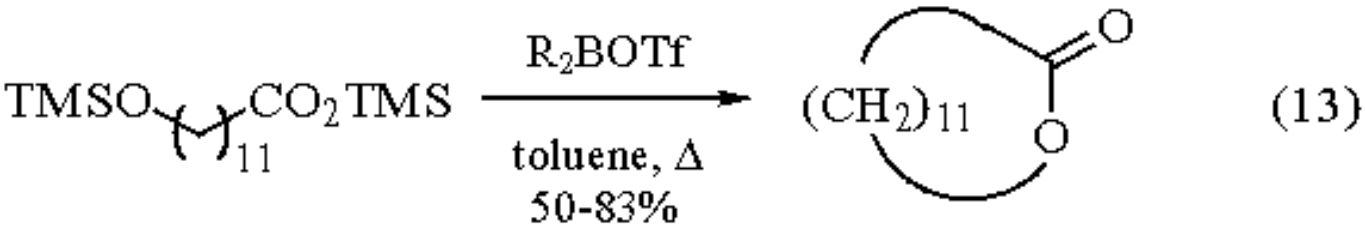

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1. (a) Mukaiyama, T.; Inoue, T. *CL* **1976**, 559. (b) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *JACS* **1981**, *103*, 1566. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *JACS* **1981**, *103*, 3099.
2. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *JACS* **1981**, *103*, 2127. (b) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C. Huang, T.-Y. *JACS* **1993**, *115*, 2613.
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7. Hamana, H.; Sugasawa, T. *CL* **1982**, 1401.
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11. Kuwajima, I.; Kato, M.; Mori, A. *TL* **1980**, *21*, 4291.
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13. Evans, D. A.; Ellman, J. A.; Dorow, R. L. *TL* **1987**, *28*, 1123.
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15. Nolen, E. G.; Aliocco, A.; Vitarius, J.; McSorley, K. *CC* **1990**, 1532.

Di-*t*-butyl Chromate[1]

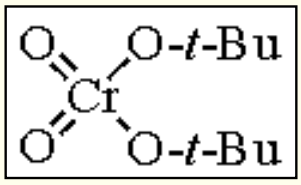

[1189-85-1] · $C_8H_{18}CrO_4$ · Di-*t*-butyl Chromate · (MW 230.22)

(selectively oxidizes allylic methylene groups to carbonyl groups; oxidizes alcohols to aldehydes and ketones)

Alternate Name: *t*-butyl chromate.

Physical Data: red crystals; oil at rt; mp -5 to 0 °C.

Solubility: sol CH_2Cl_2, C_6H_6, BuOH, *t*-BuOH, CCl_4, petroleum ether, C_6H_6 or CCl_4 or $Cl_2C{=}CCl_2/Ac_2O$/HOAc.

Preparative Method: prepared from *t*-butanol and ***Chromium(VI) Oxide*** or ***Chromyl Chloride***.

Handling, Storage, and Precautions: should be used as prepared. Chromium(VI) compounds are toxic and should be handled with care; the mutagenicity of Cr^{VI} compounds is well documented.[1f] Use in a fume hood.

Oxidation of Allylic Methylene Groups to Carbonyl Groups.

Good to excellent yields of α,β-unsaturated ketones have been obtained from the di-*t*-butyl chromate oxidation of allylic methylene groups.[2-4] The oxidation of cyclohexene affords cyclohexen-3-one and benzoquinone (eq 1).[2] Carvomenthene (**1**) is oxidized to carvotanacetone (**2**) and piperitone (**3**) (eq 2).[5-7] Similarly, verbenone may be obtained from β-pinene in 40% yield[7] and limonene (**4**) affords carvone (**5**) and isopiperitenone (**6**) (eq 3).[8]

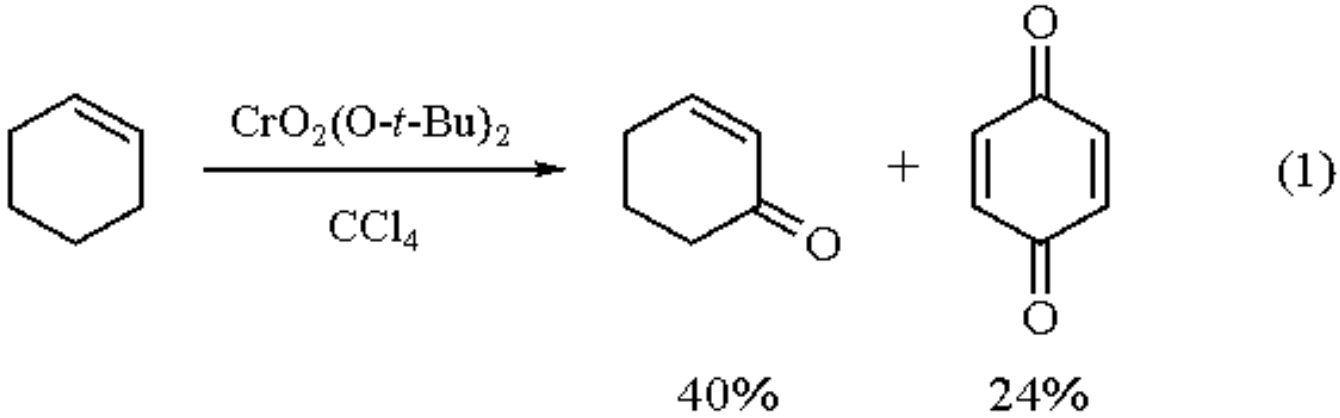

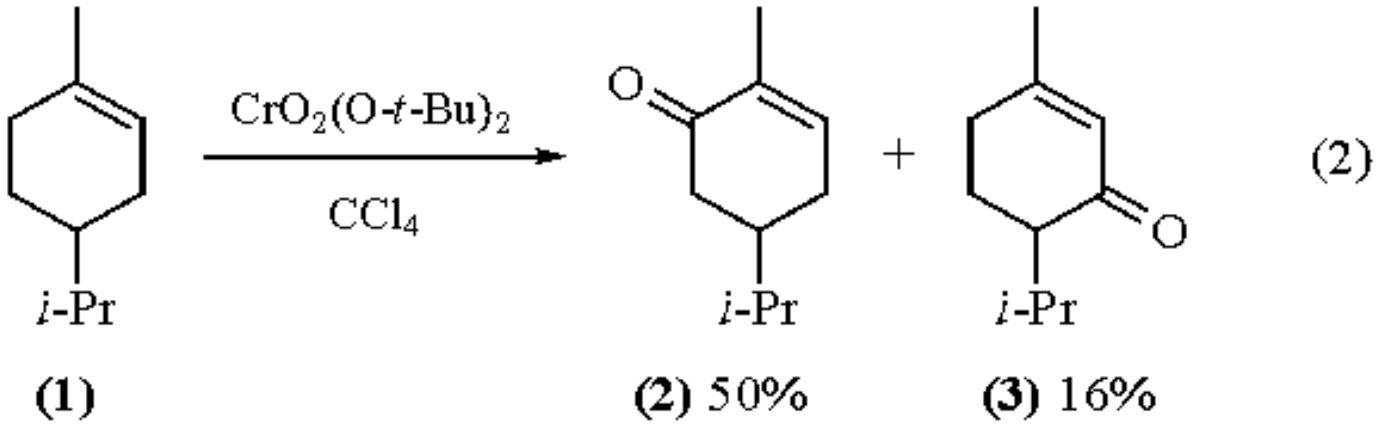

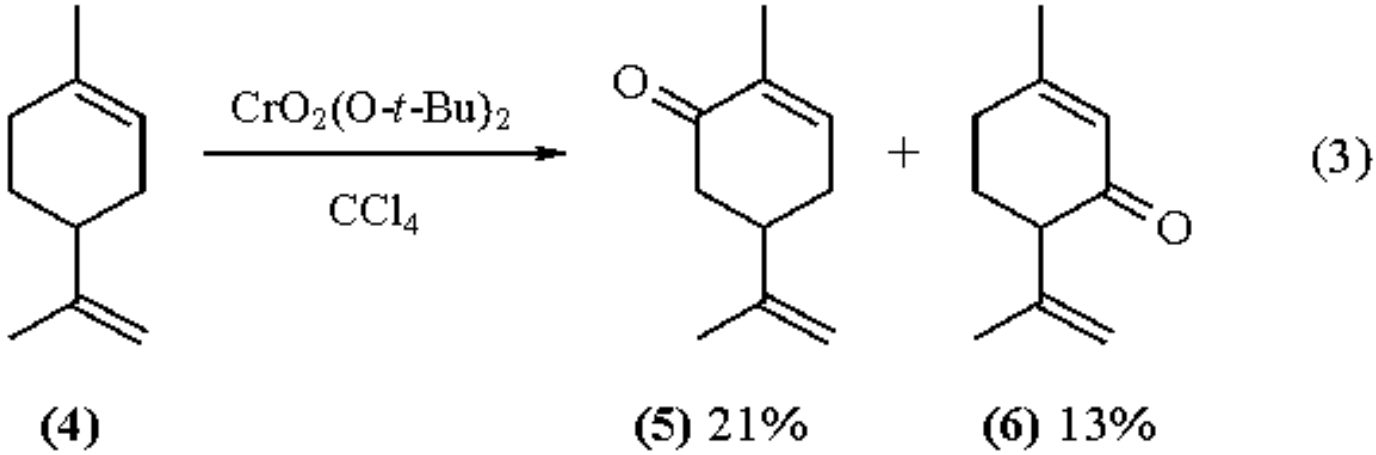

Di-*t*-butyl chromate, in refluxing *t*-butanol, oxidizes α-ionone (**7**) to small amounts of the α,β-unsaturated ketone (**8**) and 1-hydroxy-4-keto-α-ionone (**9**) in 23-27% yield (eq 4).[9] Allylic methine carbon-hydrogen bonds are more resistant to oxidation than methylene carbon-hydrogen bonds in nonpolar solvents. Ketone (**8**) is obtained (14%, 14 days) in tetrachloromethane at 0 °C. The hydroxy ketone (**9**) was converted into abscisic acid, which is a plant hormone involved in flower and leaf abscission. Di-*t*-butyl chromate is superior to ***Chromium(VI) Oxide*** or ***Potassium Permanganate*** for oxidation of (+)-car-3-ene (**10**) to (-)-car-3-en-5-one (**11**) (eq 5).[10] Di-*t*-butyl chromate does not attack methylene groups adjacent to the cyclopropane ring, as (-)-*cis*-carane and (+)-caren-3-ol are stable under the experimental conditions.

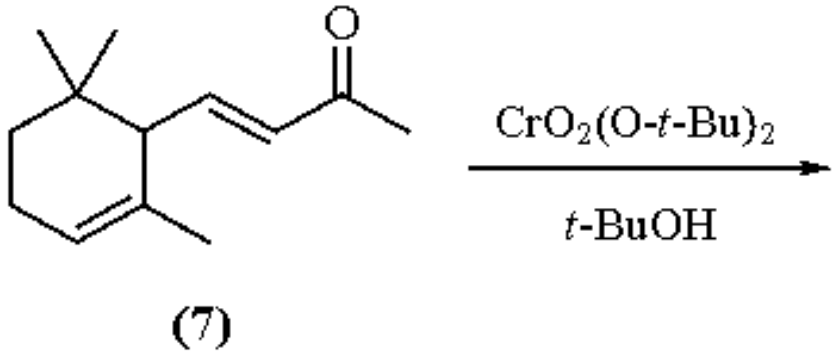

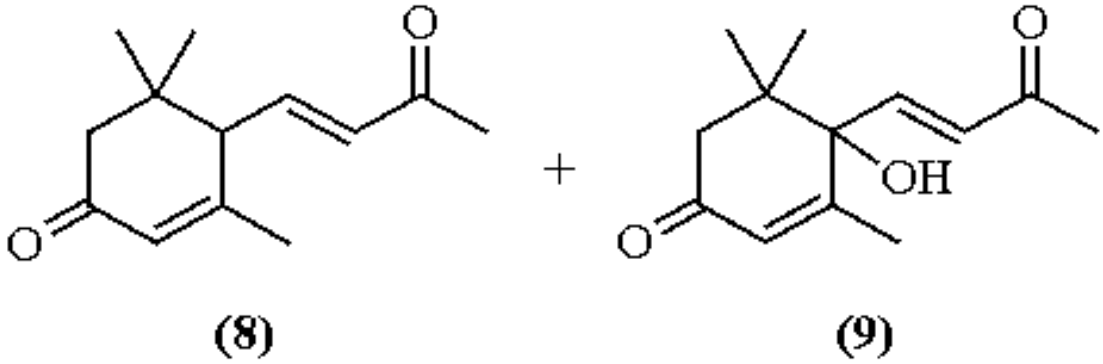

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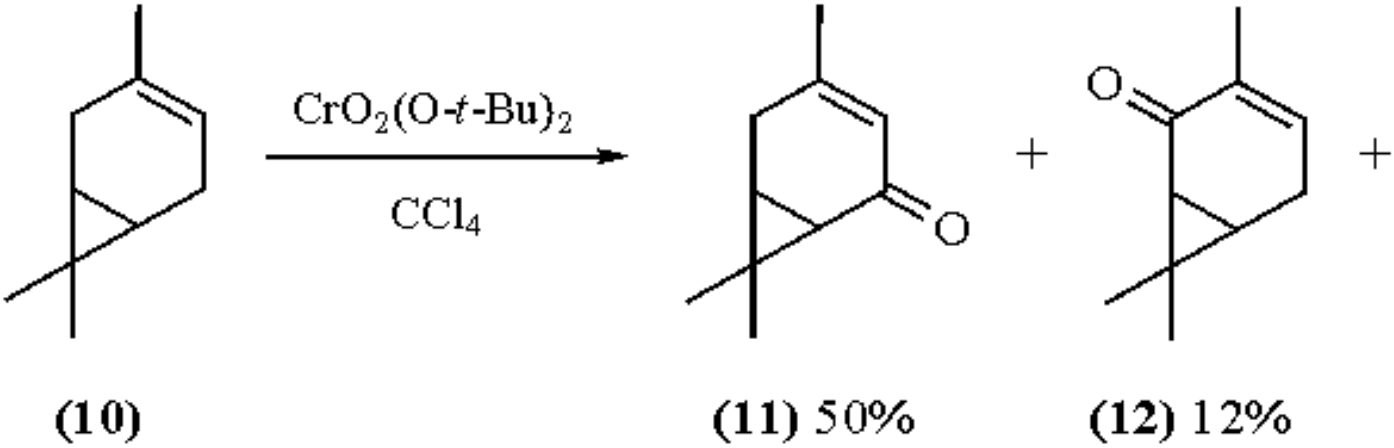

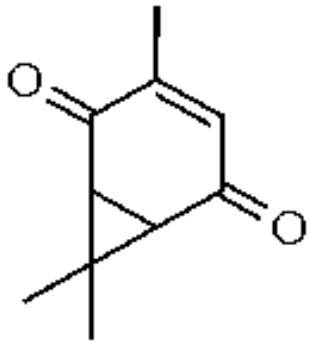

(5)

Di-*t*-butyl chromate was found superior to ***Selenium(IV) Oxide*** or ***Dipyridine Chromium(VI) Oxide*** for oxidation of the trienone (**14**) to (**15**) (eq 6).[11] Compound (**16**) is used in the synthesis of yomogin. Oxidation of the 1,4-diene (**17**)

affords dienones (**18**) and (**19**) in the ratio 1:3 (65% total yield, eq 7).[12] Complementary regioselectivity (**18**/**19** = 9:1, 70% yield) is obtained with ***Pyridinium Chlorochromate*** (PCC). Chromium(VI) oxide-pyridine gave results similar to di-*t*-butyl chromate.

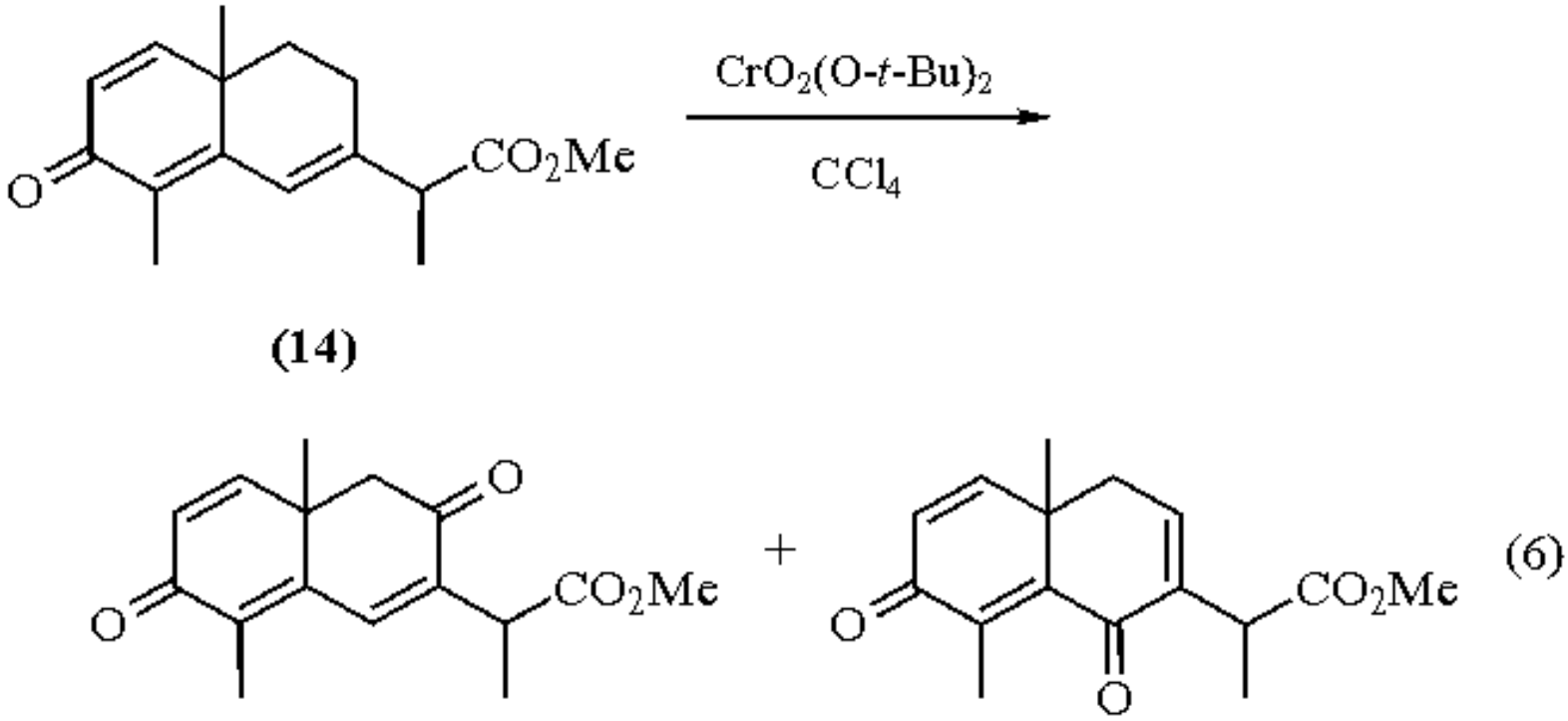

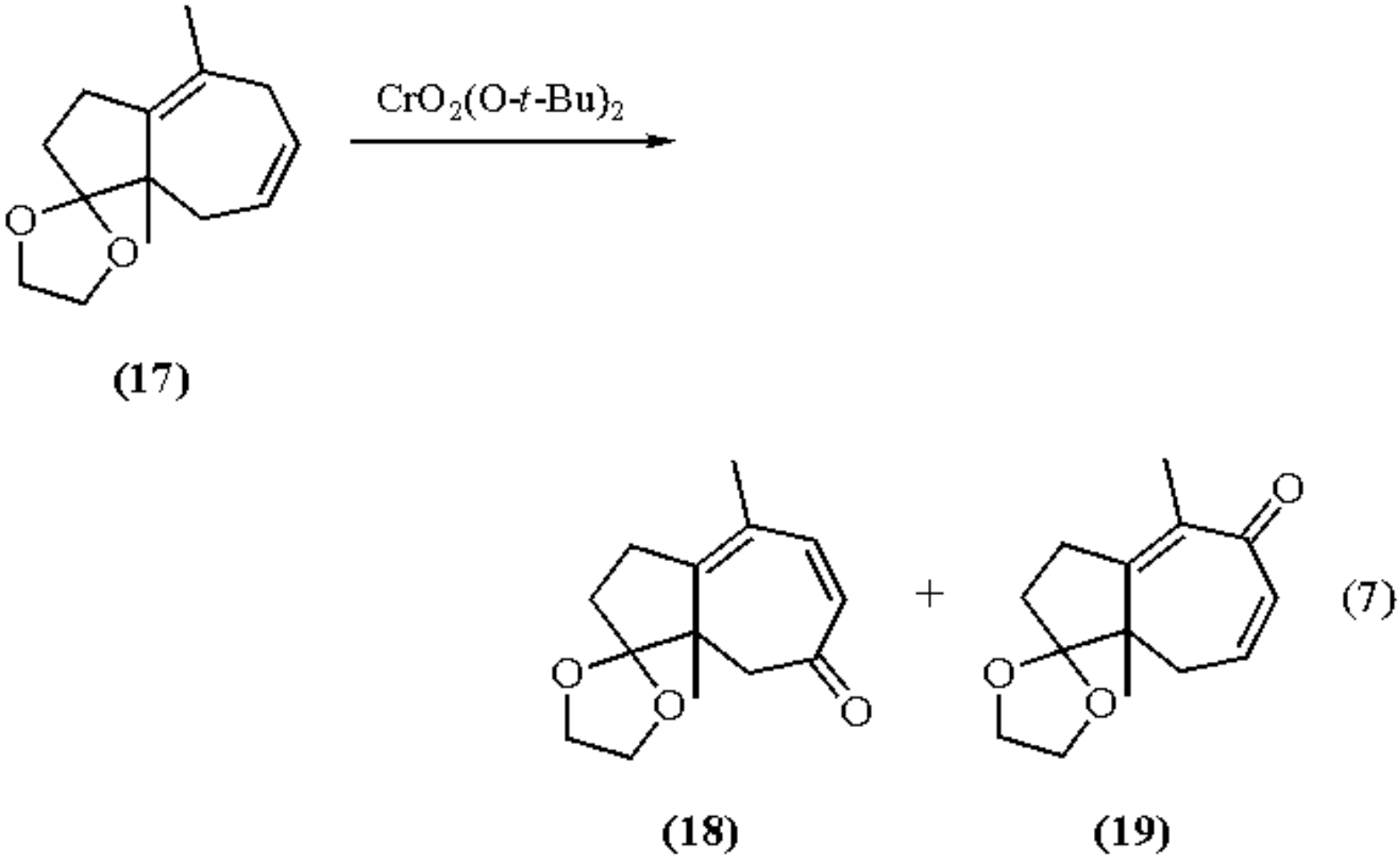

The 17β-epimer of Δ^1-5β-pregnen-20-one (**20**) was converted to progesterone (**21**) by oxidation with di-*t*-butyl chromate in tetrachloroethylene/Ac_2O/HOAc (eq 8).[13] Selective hydrogenation of progesterone (**21**) afforded 5β-pregnane-3,20-dione. Pregnenolone acetate (**22**) is oxidized at the C-7 position to afford (**23**) (eq 9).[4] Similarly, 3β,21-diacetoxypregn-5-ene-20-one has been oxidized to 3β,21-diacetoxypregn-5-ene-7,20-dione (71%).[4] Di-*t*-Butyl chromate oxidizes cholesteryl acetate (**24**) to (**25**) (eq 10).[2,14-16] 3β-Substituted (20*S*)-20-[(benzenesulfonyl)methyl]pregn-5-en-7-ones, which are useful as intermediates for hormones, growth regulators, and calcium metabolism, were prepared by allylic oxidation of the pregn-5-enes with di-*t*-butyl chromate in acetic anhydride/acetic acid.[17]

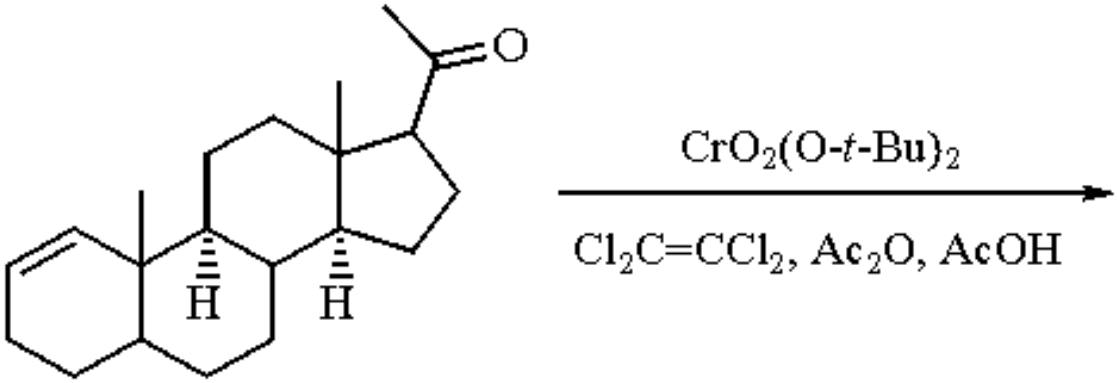

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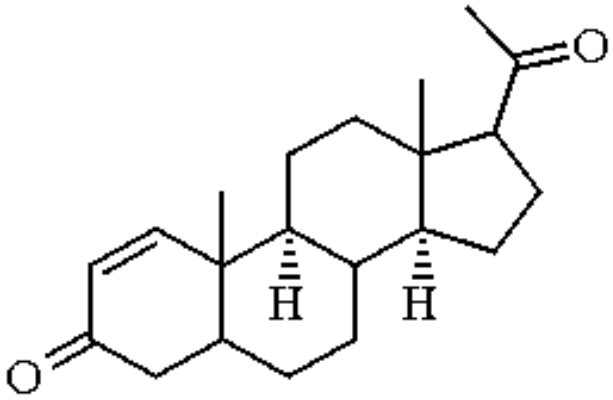

(8)

(21) 60%

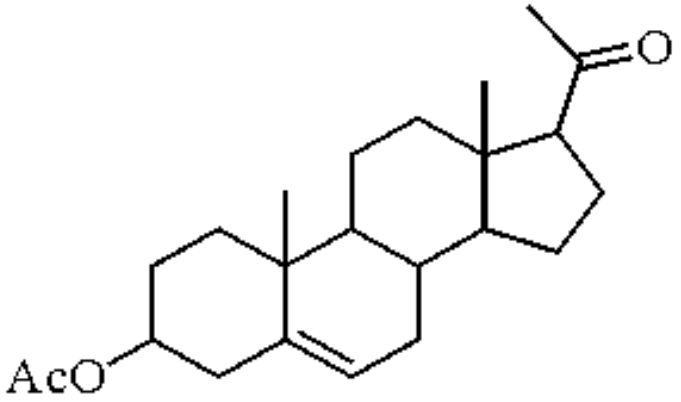

(22)

$$\xrightarrow[CCl_4,\ Ac_2O,\ AcOH]{CrO_2(O\text{-}t\text{-}Bu)_2}$$

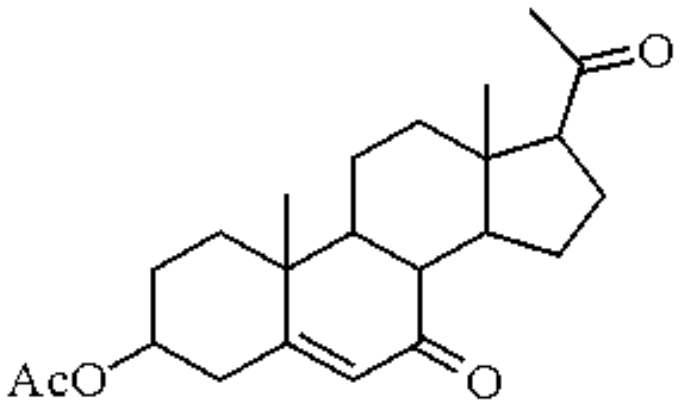

(23) (9)

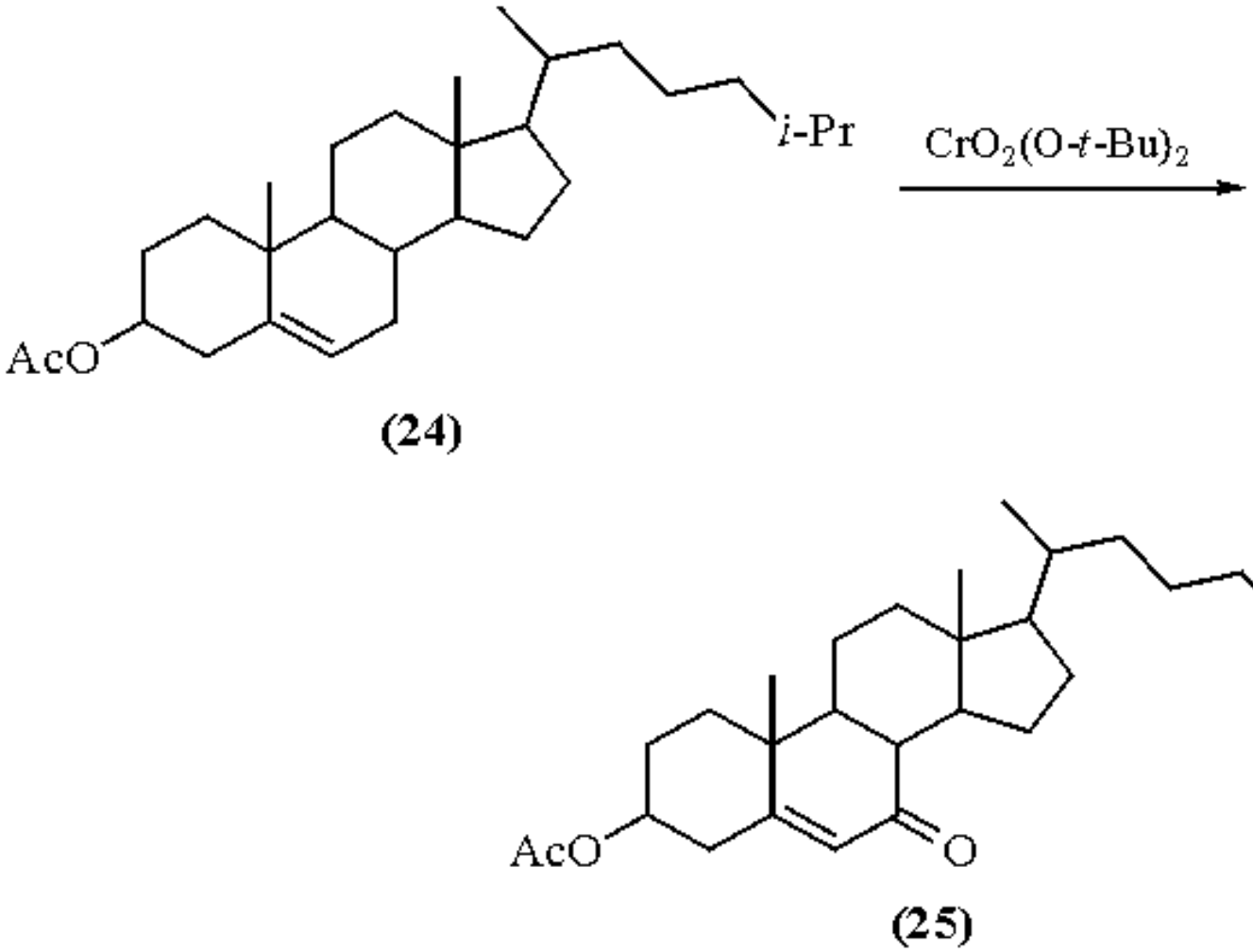

(10)

Allylic oxidation of steroidal glycosides by di-*t*-butyl chromate affords the corresponding carbonyl compounds in high yields.[18] Oxidation of a methylene group adjacent to a double bond or aromatic ring to a carbonyl group was effected in a group of diterpenes and triterpenes.[19]

Oxidation of tetrasubstituted alkenes generally leads to a mixture of products. For example, methyl 13β-abiet-8(9)-en-18-oate is oxidized to five products in tetrachloromethane.[20]

Di-*t*-butyl chromate oxidizes the substituted ether (**26**) to the 2,6-naphthoquinone derivative (**27**) in low yield (eq 11).[6] Presumably the methyl group is oxidized to a carboxyl group which undergoes decarboxylation.

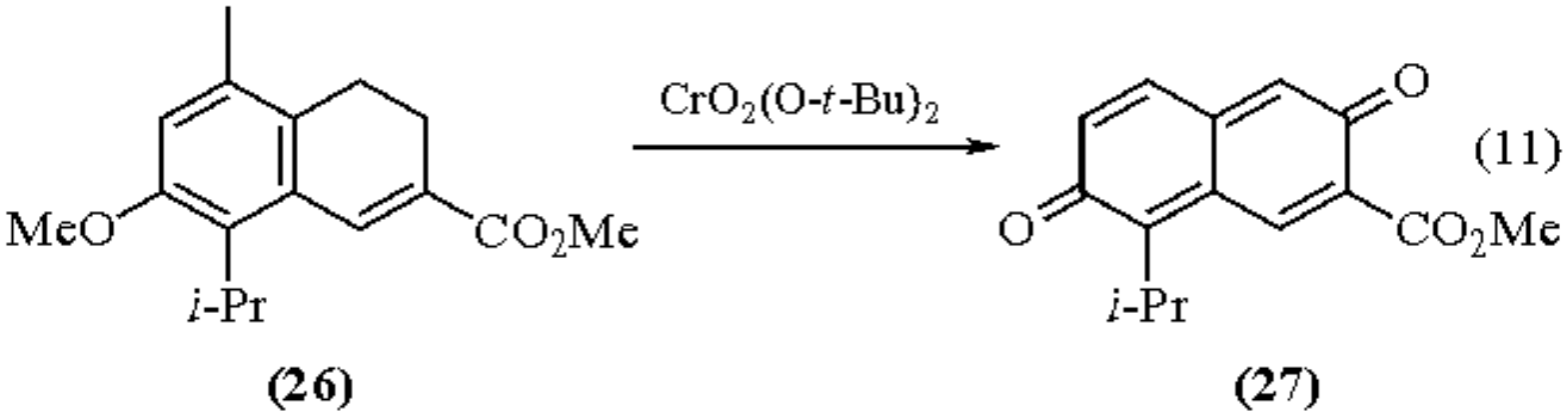

(11)

Conjugated homoannular dienes are oxidized to α-diketones. 3β-Benzoyloxy-4,4,9-trimethyl-1,2,3,4,8,9-hexahydronaphthalene (**28**) is oxidized to the corresponding 6,7-dione (**29**) in tetrachloromethane containing acetic anhydride and acetic acid (eq 12).[21] Similarly, (+)-occidentalol, a sesquiterpene containing a homoannular diene, is oxidized to four products in benzene containing acetic anhydride and glacial acetic acid.[22]

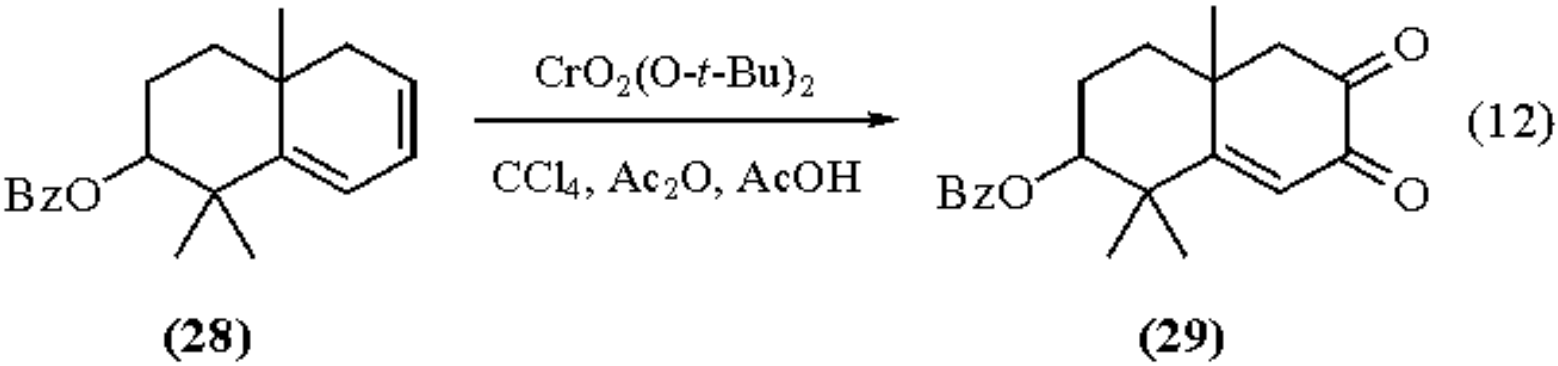

Oxidation of Alcohols to Aldehydes and Ketones.

Di-*t*-butyl chromate oxidizes alcohols in nonpolar solvents.[23,24] Although aliphatic primary alcohols are oxidized to the corresponding aldehydes in low yields, allylic and benzylic primary alcohols give aldehydes in good to excellent yields. Cyclohexanol affords cyclohexanone (89%), cyclohexane-1,2-diol yields adipic acid, and cyclic vicinal glycols with one secondary and one tertiary hydroxy group are oxidized at the secondary position to give the corresponding hydroxy ketones.[25] The ultrasound-mediated di-*t*-butyl chromate ester oxidation of alcohols in dichloromethane affords aldehydes and ketones in excellent yields.[26]

The oxidation of alcohols with anhydrous ***Di-t-butyl Chromate-Pyridine*** gives high yields of aldehydes and ketones and permits large scale reactions.[27,28] The use of excess di-*t*-butyl chromate in the presence of 3,5-dimethylpyrazole selectively oxidized an allylic methylene position to a carbonyl group in the final step in the synthesis of (-)-solavetivone.[29]

Other Applications.

In CCl_4/Ac_2O/HOAc, di-*t*-butyl chromate is more effective than ***Ruthenium(VIII) Oxide*** in converting spiroethers to spirolactones.[30]

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Di-*t*-butyl Chromate-Pyridine

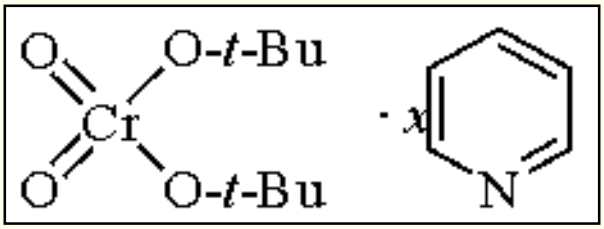

[1189-85-1] · $C_8H_{18}CrO_4$ · Di-*t*-butyl Chromate-Pyridine · (MW 230.22)

[110-86-1] · C_5H_5N · Di-*t*-butyl Chromate-Pyridine · (MW 79.10)

(reagent for oxidizing alcohols and silyl ethers to aldehydes and ketones)

Alternate Name: *t*-butyl chromate-pyridine; chromyl chloride-pyridine-*t*-butanol.

Preparative Methods: prepared in situ from chromyl chloride, pyridine, and *t*-butanol to afford the tripyridine (x = 3) complex[1] or from chromium(VI) oxide, *t*-butanol, and pyridine to yield a complex which may contain 1 to 3 equivalents (x = 1-3) of pyridine.[2]

Handling, Storage, and Precautions: all chromium(VI) reagents must be handled with care; the mutagenicity of Cr^{VI} compounds is well documented.[3] This reagent should be handled in a fume hood.

Oxidation of Alcohols to Carbonyl Compounds.

Addition of ***Chromyl Chloride*** to a solution of pyridine in dichloromethane, cooled in a dry ice-acetone bath, gave a strong oxidizing mixture which oxidized primary alcohols to aldehydes in good to excellent yields on a small scale.[1] Addition of *t*-butanol generated a milder oxidant which could be ***Di-t-butyl Chromate*** or a di-*t*-butyl chromate-tripyridine complex.[1,4,5] This reagent is suitable for both small and large scale reactions. Cinnamyl alcohol, cyclododecanol, citronellol (eq 1), 1-dodecanol, and geraniol (eq 2) are oxidized to the corresponding carbonyl compounds in 86, 97, 93, 99, and 100% yield, respectively.[1] Although this reagent is inferior to the Collins reagent (see ***Dipyridine Chromium(VI) Oxide***) for oxidizing allylic alcohols owing to isomerization of the carbon-carbon double bond (eq 2), it offers advantages for the oxidation of simple saturated primary alcohols.

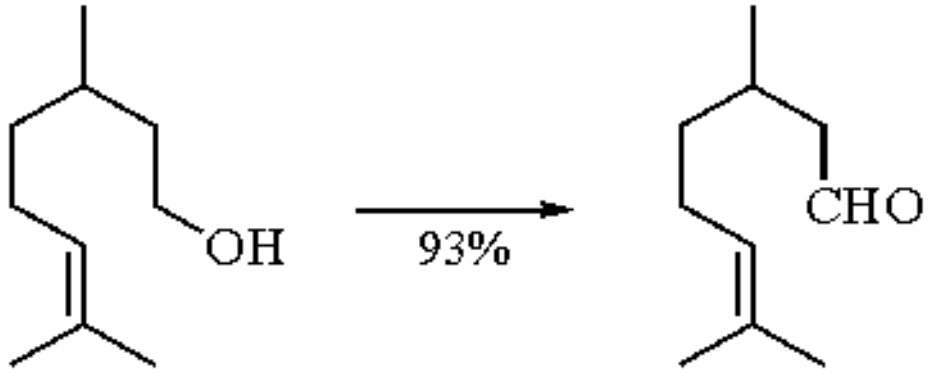

(1)

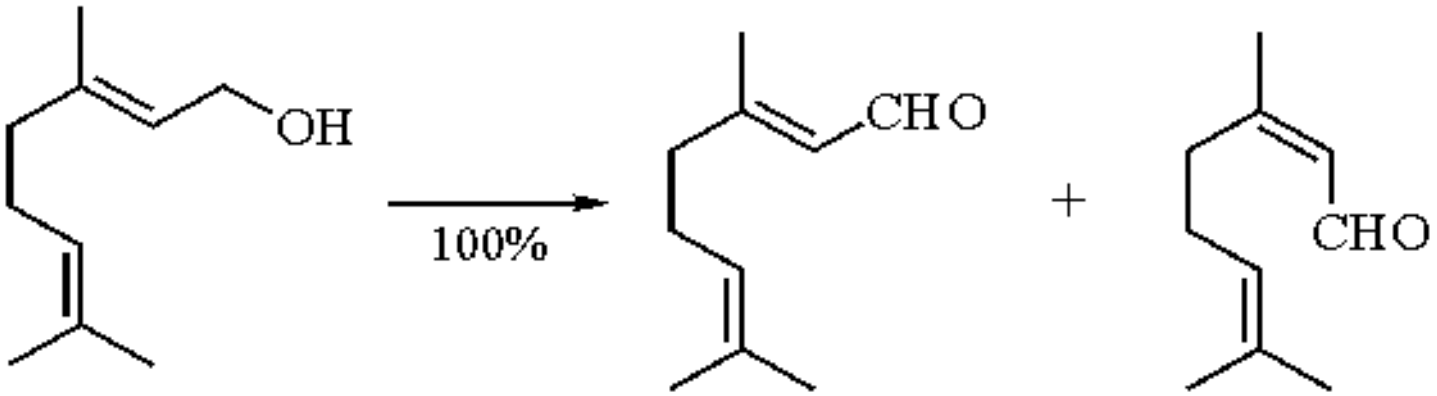

(2)

3:1

The reagent prepared from chromium(VI) oxide oxidizes primary trimethylsiloxy groups to aldehydes and does not attack acid-labile groups, double bonds, ether groups, or allylic methylene groups in the same molecule.[3] Although secondary silyl ether groups are oxidized to ketones by the reagent, they are stable to the experimental conditions used for the oxidation of primary silyl ether groups. For example, (±)-[(1*R*,2*S*,3*R*,5*S*)-2-[(trimethylsiloxy)methyl]-3-(trimethylsiloxy)-6-oxabicyclo[3.3.0]octan-7-one is oxidized to (±)-[(1*R*,2*S*,3*R*,5*S*)-2-formyl-3-(trimethylsiloxy)-6-oxabicyclo[3.3.0]octan-7-one.

It is of interest to note that di-*t*-butyl chromate oxidizes primary aliphatic alcohols in benzene or petroleum ether at room temperature to a mixture of the aldehyde, acid, and the ester of the acid.[5] It oxidizes cinnamyl alcohol and geraniol to the corresponding aldehydes in 61 and 77% yield, respectively.[5]

---

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5. Suga, T.; Kihara, K.; Matsuura, T. *BCJ* **1965**, *38*, 893.

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Di-*t*-butyl Dicarbonate

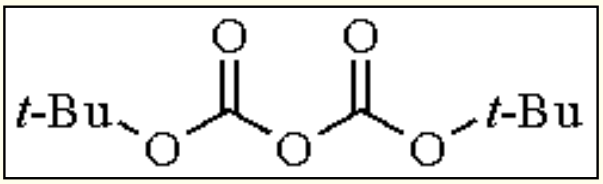

[24424-99-5] · $C_{10}H_{18}O_5$ · Di-*t*-butyl Dicarbonate · (MW 218.25)

(efficient *t*-butoxycarbonylating agent for amines,[1,2] phenols, and thiols; *t*-butoxycarbonylation of alcohols, amides,[3] lactams, carbamates[4] and NH-pyrroles[5] occurs in the presence of 4-dimethylaminopyridine)

Alternate Names: di-*t*-butyl pyrocarbonate; Boc anhydride; Boc_2O.

Physical Data: mp 22-24 °C; bp 56-57 °C/0.5 mm Hg; fp 37 °C; *d* 0.950 g cm^{-3}; n_D^{20} 1.4103.

Solubility: insol cold H_2O; sol most organic solvents such as decalin, toluene, CCl_4, THF, dioxane, alcohols, acetone, MeCN, DMF.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: IR 1810 and 1765 cm^{-1}; NMR 1.50 (CCl_4).

Preparative Method: prepared by the action of ***Phosgene*** on potassium *t*-butyl carbonate, followed by conversion of the obtained di-*t*-butyl tricarbonate under the action of basic catalysts such as ***1,4-Diazabicyclo[2.2.2]octane***.[6]

Handling, Storage, and Precautions: the liquid is flammable and must be stored in a refrigerator in the absence of moisture. Do not heat above 80 °C.

t-Butoxycarbonylation of Amines.

Owing to the instability of the corresponding chloride (***t-Butyl Chloroformate***), the Boc_2O reagent is widely used for the introduction of the *t*-butoxycarbonyl amino protecting group (Boc). This group is easily removed under moderately acidic conditions such as treatment with ***Trifluoroacetic Acid***, or by thermolysis. The Boc-NHR group is not hydrolyzed under basic conditions and is inert to many other nucleophiles.[1] Therefore the use of this amino protecting group is not limited to amino acid and peptide synthesis; it has been extended to the synthesis of amino sugars, alkaloids, etc. The great importance of the *t*-butyl carbamate function in peptide synthesis is not only due to the ease of its cleavage, but also to the fact that the oxazolones formed from the activated *N*-alkoxycarbonyl amino

acids do not usually epimerize (racemize) during coupling with amines.[7]

Boc_2O reacts smoothly and rapidly with amino compounds in organic solvents, or aqueous organic solvent mixtures, to form pure derivatives in high yields, the only byproducts being the innocuous and easily removable *t*-butanol and carbon dioxide (eq 1). Innumerable examples are available.[8-11] ***Hydroxylamine*** slightly accelerates the reaction through the in situ formation of the Boc-ONH_2 intermediate.[12] The reaction is also accelerated by sonication of the amine salts.[13]

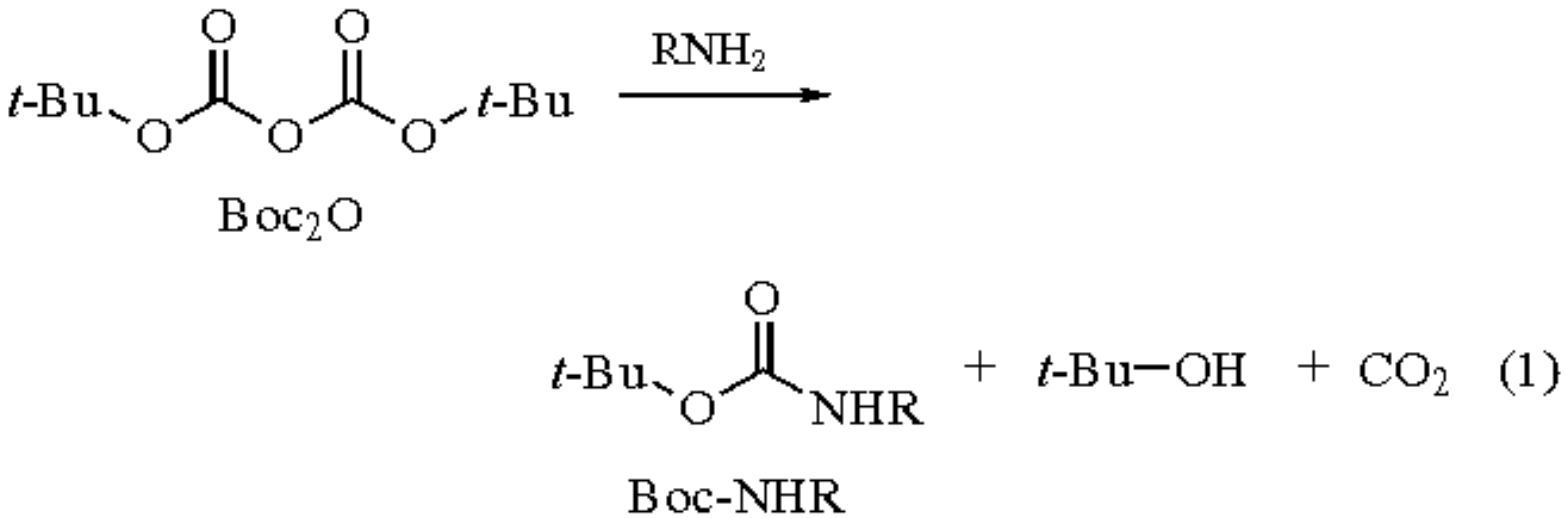

Aliphatic,[14] alicyclic,[15] aromatic,[16,17] and heterocyclic amines[18,19] have been *t*-butoxycarbonylated under a variety of conditions. Anilines are sometimes heated at reflux in THF to obtain the corresponding Boc derivatives in good yields. However, *t*-butoxycarbonylation also occurs at rt,[17] and 4-aminobenzoic acid reacts in DMF/aq NaOH at rt.[20] The Boc-NHR substituent is an *ortho*-directing group in heteroatom-facilitated lithiations of aromatic and heterocyclic amines.[16,18,19,21] Reaction of the resultant carbanions (eq 2), as well as that of the analogous benzylic carbanions, with electrophiles is a powerful method for the synthesis of substituted anilines and heterocycles.[16,22]

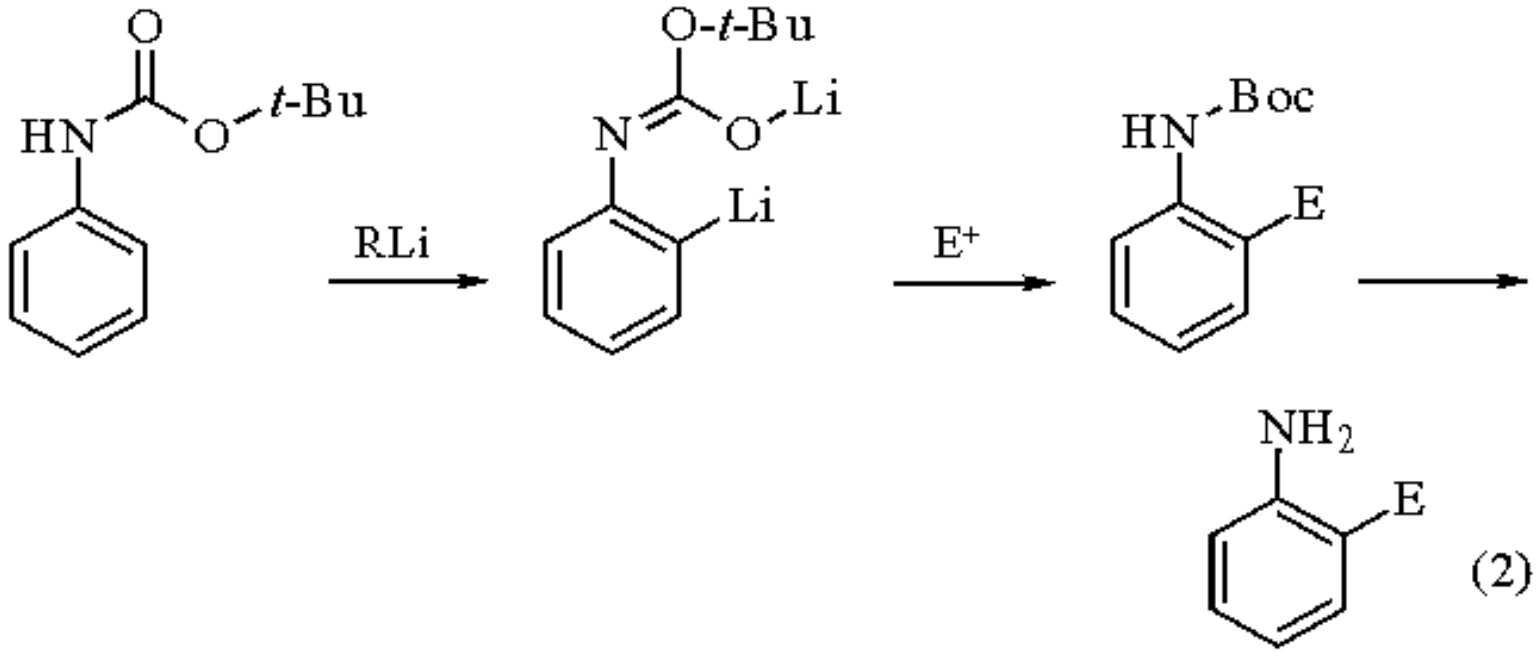

Asymmetric deprotonation of Boc-pyrrolidine with ***s-Butyllithium/(-)-Sparteine*** gives a chiral organolithium reagent, which undergoes reaction with electrophiles to give enantiomerically enriched products.[23] The sequence of equatorial α-lithiation followed by an electrophilic substitution of a series of *N*-Boc cyclic amines provides amines which are substituted adjacent to the nitrogen atom.[15]

A suspension of 4-dimethylaminopyridinium fluoroborate in ethyl acetate reacts with Boc_2O to give the corresponding 1-*t*-butoxycarbonyl-4-dimethylaminopyridinium salt, which is an efficient water-soluble agent for the *t*-butoxycarbonylation of amines (eq 3).[24]

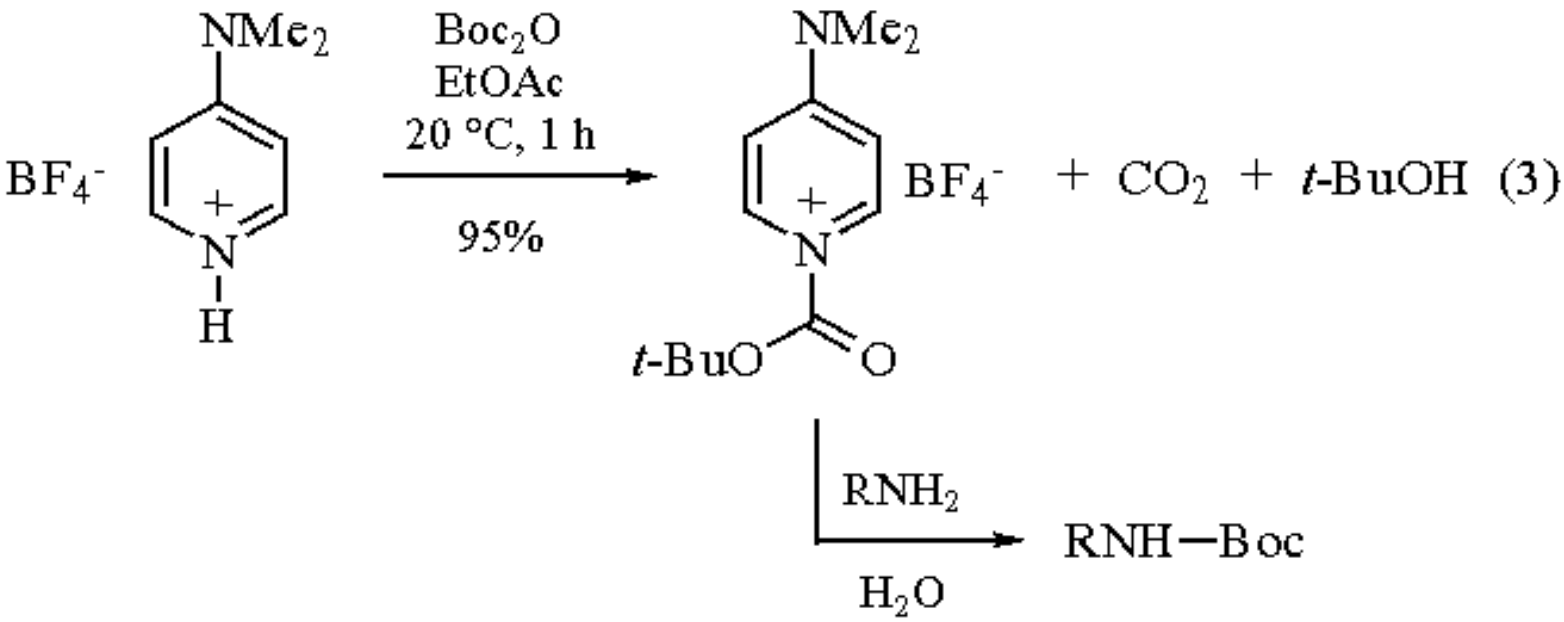

Interesting chemo- and regioselective alkoxycarbonylation of polyfunctional substrates, e.g. diamines, amino alcohols, and amino acids, can be achieved under mild conditions. Treatment of α,o-alkanediamines (6-10 molar excess) with the reagent in dioxane or acetone as solvent leads to the corresponding mono-Boc diamines in 75-90% yields (eq 4).[25,26]

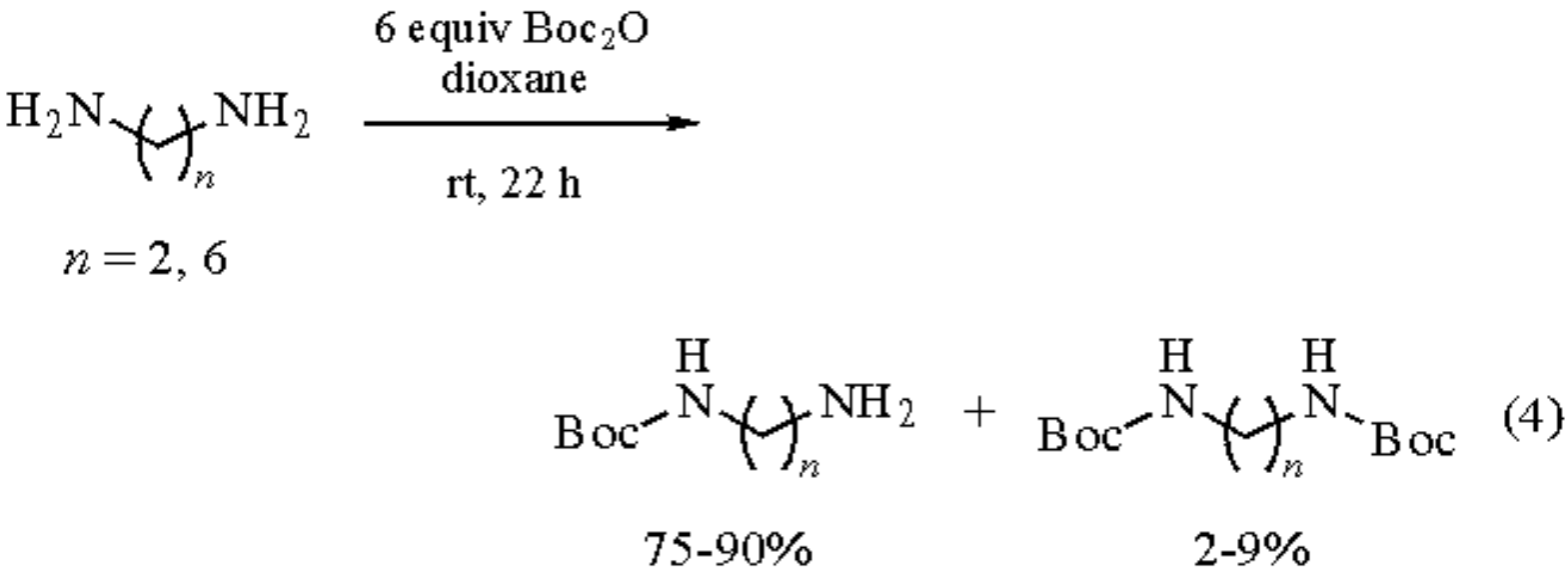

*N*ε-Boc-L-lysine has been selectively prepared from the copper complex of lysine.[27] This complex, as well as that

of N^{δ}-Boc-L-ornithine, has been directly benzyloxycarbonylated to give the corresponding α-Cbz-ε-Boc amino acids (eq 5).[28]

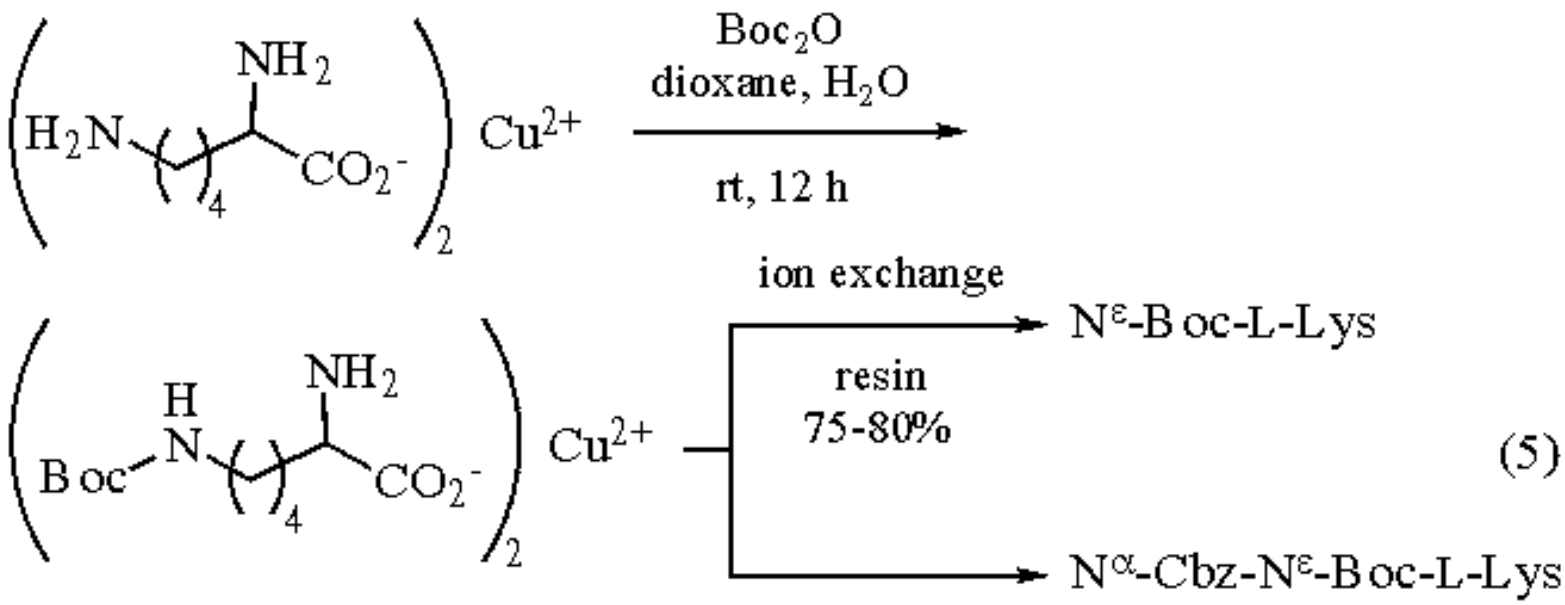

In CH_2Cl_2 at low temperature, selective *t*-butoxycarbonylation of a β-amino- in the presence of an α-amino-ester function has been recently realized (eq 6).[29]

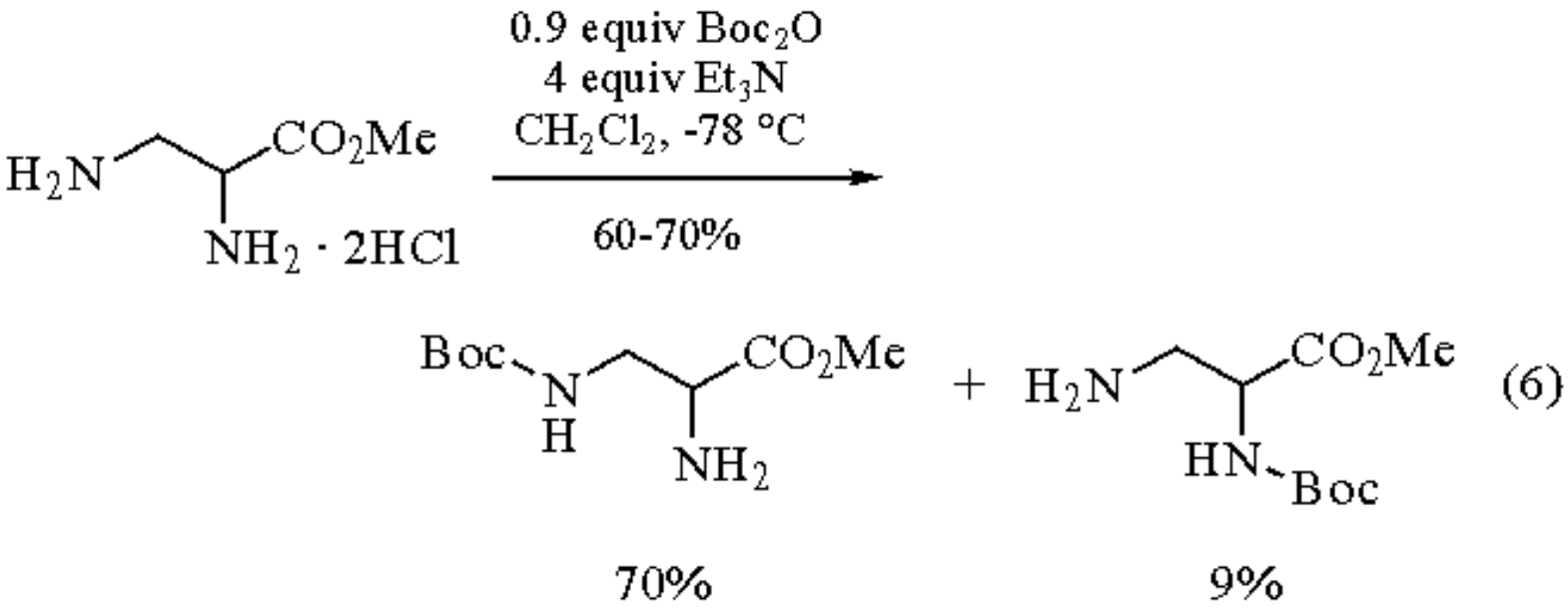

The substitution of a secondary amino group in the presence of a primary amine has been performed by an indirect route: formation of the labile Schiff base of the primary amine and then *t*-butoxycarbonylation of the secondary nitrogen (eq 7).[30] Selective protection of polyamines may also be achieved by an indirect route in the presence of DMAP (see below).

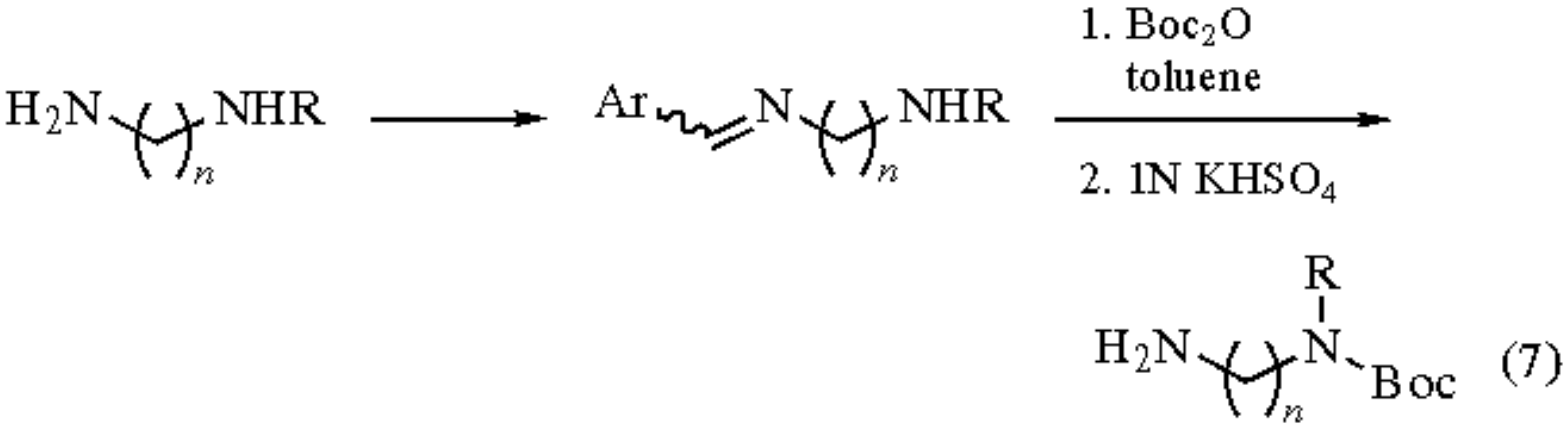

The Boc_2O reagent has been widely used for the *N*-protection of amino acids and peptides. When a carboxylic acid function is present in the molecule, 1 equiv of base (NaOH, Et_3N, Triton B) is necessary (eq 8).[10,11,31]

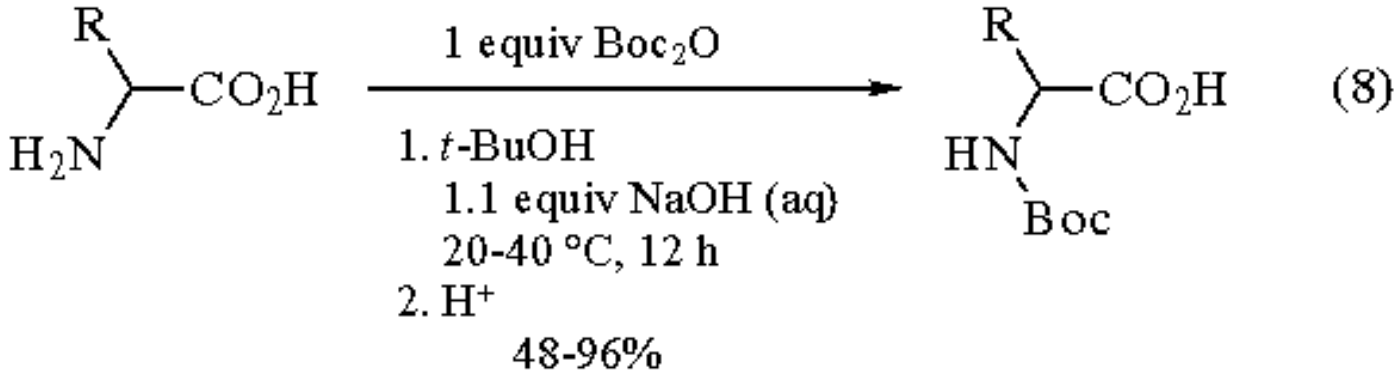

To avoid loss of the *O*-labeling, trialkylammonium salts of amino acids have been *t*-butoxycarbonylated in dry methanol or DMF.[32] *N*-*t*-butoxycarbonylation of an alkaline labile and hindered 2,2-dimethylthiazolidine-4-carboxylic acid has been performed in acetonitrile (eq 9).[33]

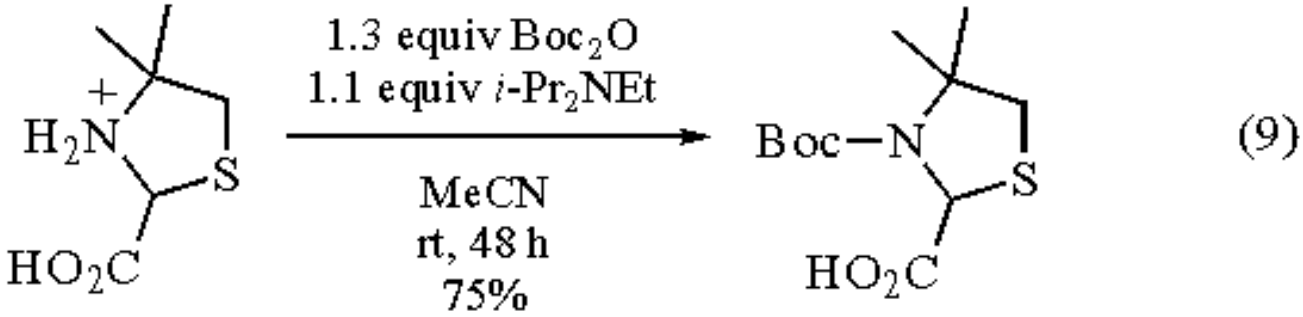

In the presence of pyridine, a free carboxylic function reacts with the reagent to give a mixed anhydride (see below). This reaction also occurs during the acylation of an amino acid salt with Boc_2O and is responsible for the formation of small amounts of dipeptide byproducts by aminolysis of the mixed anhydride intermediate (eq 10).[34]

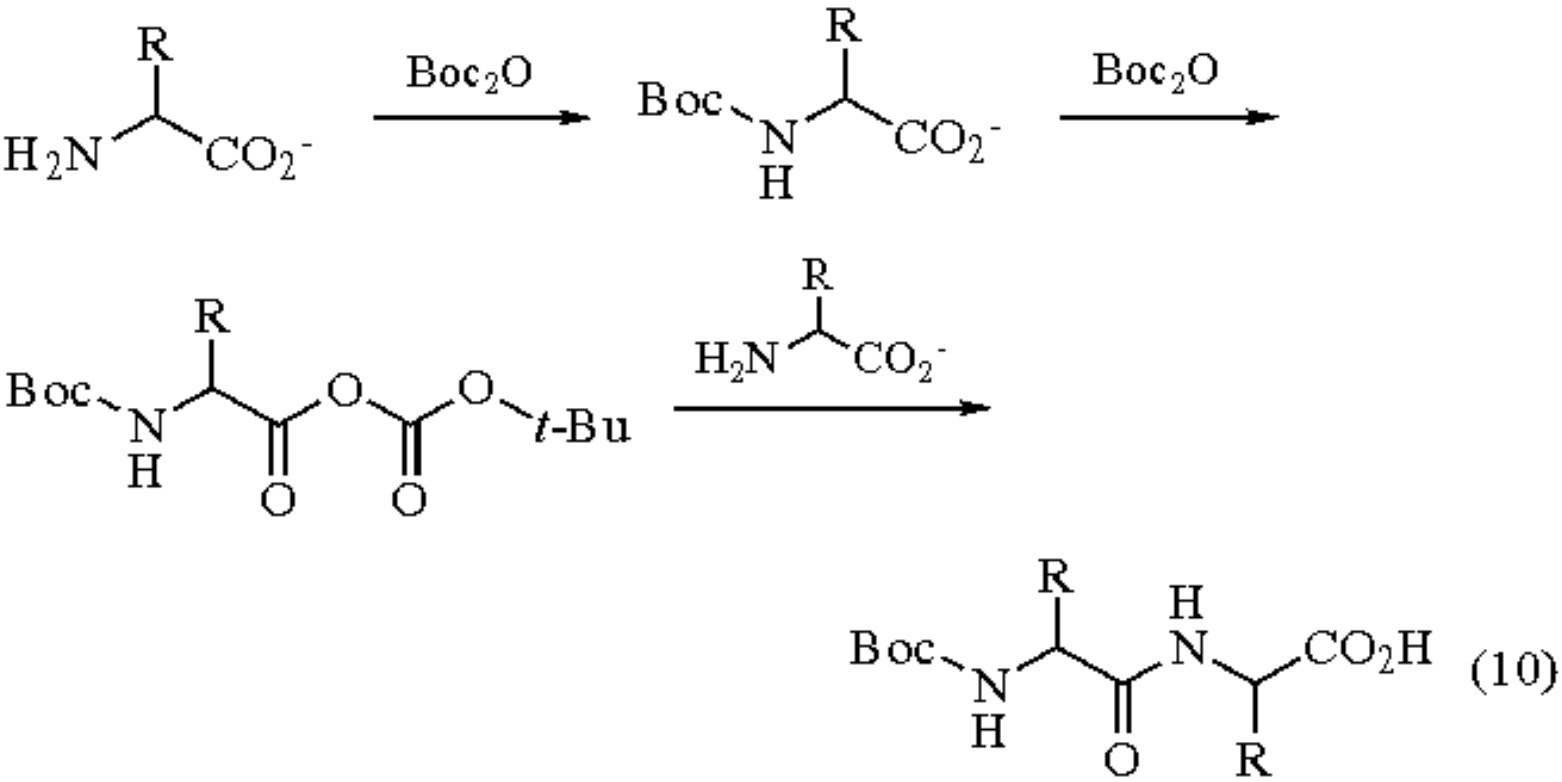

t-Butoxycarbonylation of phenolic amino acids in aqueous ***Potassium Hydroxide*** gives the *N*,*O*-bis-Boc derivatives.[35] Under phase-transfer conditions, selective *N*-*t*-butoxycarbonylation of tyrosine ethyl ester has been observed (see below). The SH group of cysteine,[36] the imidazole of histidine,[37] and even the guanidine function of arginine[38] have been acylated. Boc_2O has been used for the chemical modification of histidine residues of proteins.[39] For the *t*-butoxycarbonylation of insulin, Boc_2O is much more reactive than the corresponding succinimidyl and *p*-nitrophenyl esters.[40] Bamberger ring-cleavage of the imidazole nucleus slowly occurs in the presence of ***Potassium t-Butoxide***.[41] Selective *N*-protection of amino alcohols is also easily performed (eq 11).[42]

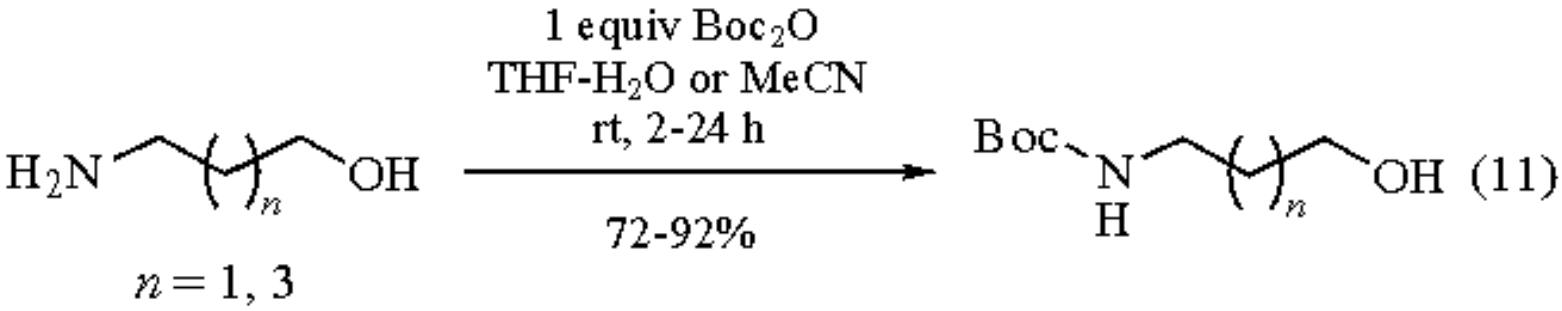

At pH 10.3, hydroxylamine itself gives the *O*-substituted product,[12] whereas treatment of *N*-alkylhydroxylamines in dioxane furnishes the *N*-Boc derivatives (eq 12).[43] The *O*-Boc hydroxylamine[12,44] as well as *O*-Boc oximes[45] are themselves efficient *t*-butoxycarbonylating agents.

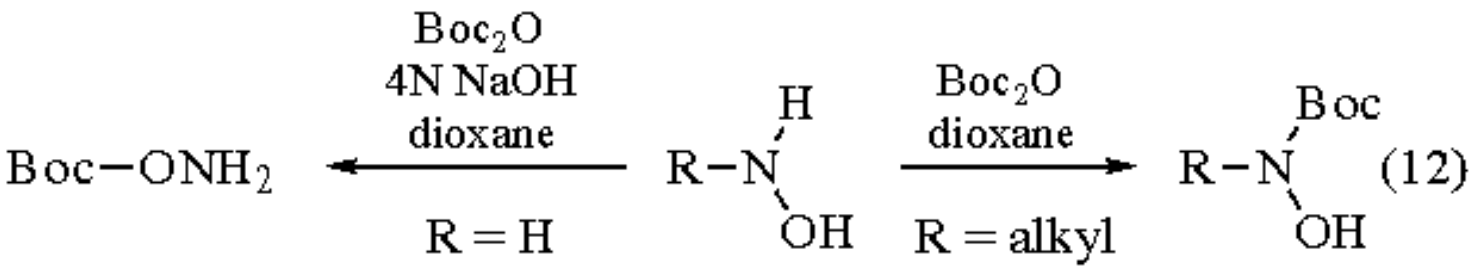

Hydrazines and hydrazides are acylated by the reagent.[46] The mono-Boc derivatives of hydrazine or phenylhydrazine, obtained in isopropanol, react further with Boc_2O in benzene or dioxane to give the $(Boc\text{-}NR)_2$ diacylated derivatives. Regioselective N^{α}-protection of ethyl hydrazinoacetate is performed at 0 °C and the product used for the synthesis of hydrazino peptides (eq 13).[47]

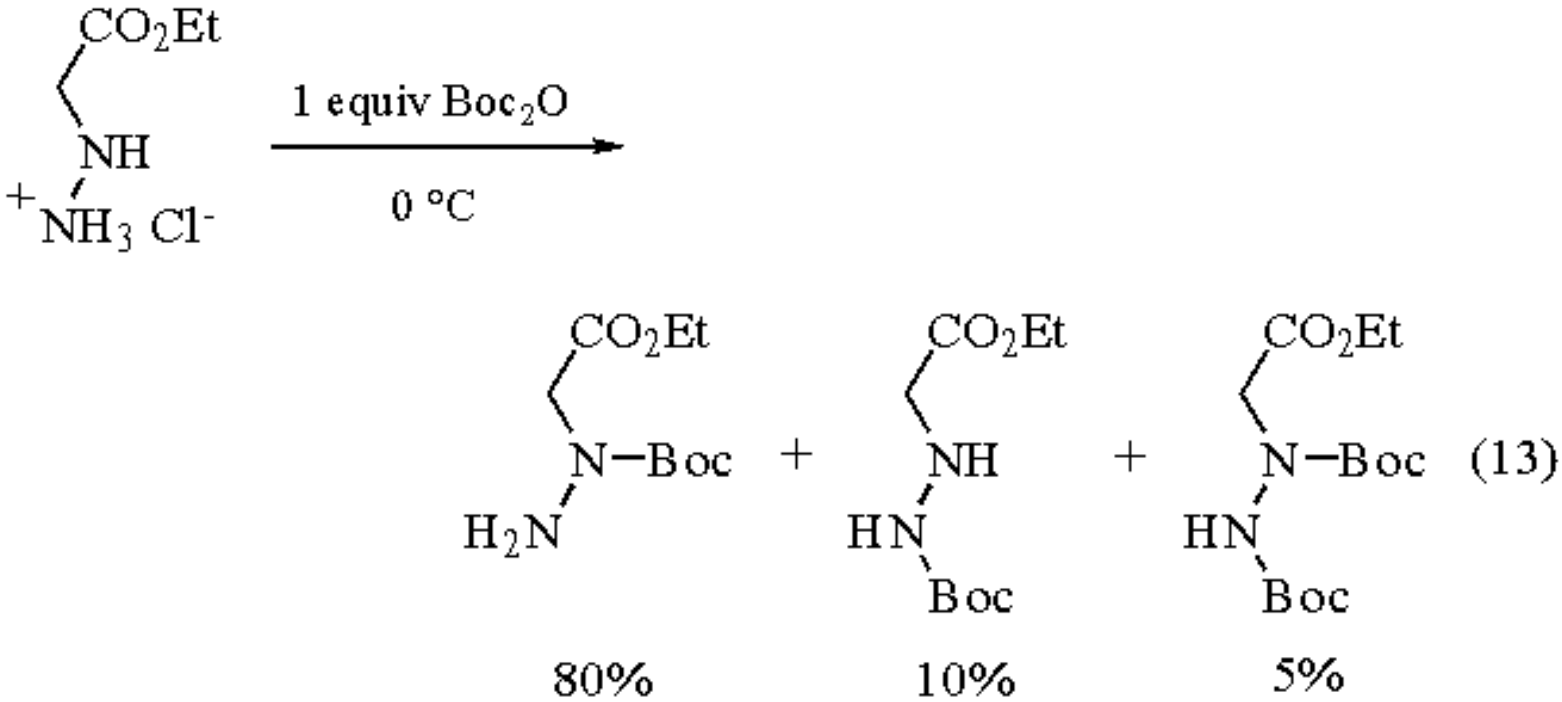

Boc-amines can also be prepared directly from azides by hydrogenation in the presence of Boc_2O (eq 14).[48]

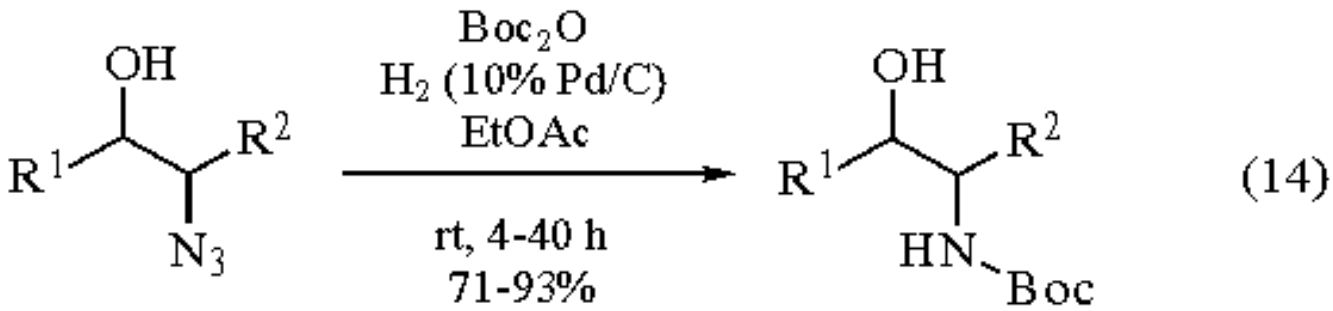

The alkylation of Boc-amines, particularly that of the more acidic Boc-anilines[17] and the selective alkylation of *N*-Boc amino acids,[49-51] has been done by using an alkylating agent and ***Sodium Hydride*** or ***Silver(II) Oxide*** as a base. For the *N*-perbenzylation of *N*-Boc peptides a P4-phosphazene base (see ***Phosphazene Base P_4-t-Bu***) has been used at -100 °C.[52]

Exchange of Amino-Protecting Groups.

N-Benzyloxycarbonyl (Cbz) and 9-fluorenylmethyloxycarbonyl (Fmoc) amino protecting groups are also widely used in peptide synthesis.[2] The choice of protecting groups, and hence of the conditions for their cleavage (Cbz: hydrogenolysis or HBr/HOAc; Fmoc: piperidine or F^-)[1] plays a key role in the planning of a synthesis. For instance, orthogonal protection (Boc/Cbz or Fmoc/Boc or Cbz) is of crucial importance in the case of the trifunctional amino acids. For a given peptide segment, chemoselective transformation of an amino protecting group into another one under neutral conditions may be very useful for the synthesis.

In the presence of a slight excess of Boc_2O, conversion of a benzyl carbamate into a *t*-butyl carbamate has been achieved by catalytic hydrogenation,[53] or by the use of cyclohexadiene as an hydrogen donor (eq 15).[54] The catalytic transfer hydrogenation is the more selective: benzyl and BOM ethers are stable under the reaction conditions. The Cbz -> Boc transformation can also be performed using triethylsilane and a palladium catalyst.[53] The replacement of a Fmoc group by a Boc group has recently been achieved by the in situ cleavage of the Fmoc group with ***Potassium Fluoride*** in DMF (eq 15).[55]

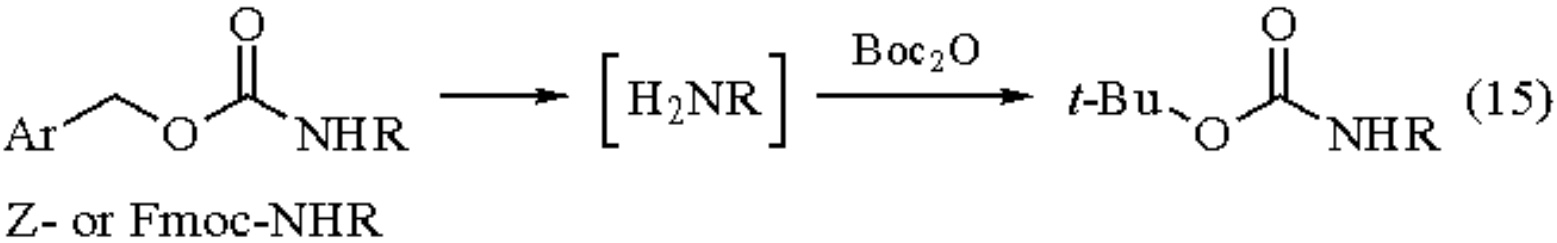

Ar = Ph

H_2, 5% Pd/C, MeOH, rt, 5-40 h, 93-95%

1,4-cyclohexadiene, 10% Pd/C, EtOH, rt, 0.3-5 h, 86-96%

Et_3SiH, $Pd(OAc)_2$, Et_3N, EtOH, rt, 15-30 h, 91-97%

Ar = 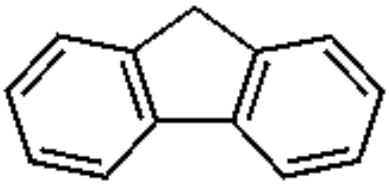 KF, Et_3N, DMF, rt, 5-10 h, 84-93%

t-Butoxycarbonylation of Phenols, Alcohols, Enols, and Thiols.

In alkaline media the nucleophilic phenolate salts are easily *t*-butoxycarbonylated.[35,56] Acylation of *p*-dimethylsulfoniophenol gives a sulfonium salt which is a new water-soluble *t*-butoxycarbonylating agent for amino acids.[57] Under anhydrous conditions, thiolate salts are also substituted in good yields using the Boc_2O reagent.[56] Under phase-transfer conditions, *t*-butoxycarbonylation of phenols as well as enols, thiols, or alcohols can be realized. For phenols, enols, and thiols, K_2CO_3 (powder)/18-crown-6/THF are the best experimental conditions. Biphasic

conditions (Bu_4NHSO_4/CH_2Cl_2/aq. NaOH) are also effective with sluggish alcoholic groups.[56] Using 1 equiv of Boc_2O, selective *N*-*t*-butoxycarbonylation of tyrosine ethyl ester can be achieved. *N*,*S*-Bis(Boc)-cysteine ethyl ester has also been prepared.[56] The *t*-butoxycarbonylation of alcohols to give alkyl *t*-butyl carbonates is efficiently catalyzed by DMAP.[58]

t-Butoxycarbonylation of Amides, Lactams, and Carbamates.

In the presence of ***4-Dimethylaminopyridine***, Boc_2O is a strong acylating agent able to react with the weakly nucleophilic amide and carbamate groups under anhydrous conditions. The reaction probably involves a 1-*t*-butoxycarbonyl-4-dimethylaminopyridinium ion intermediate (eq 3).[24] This enhanced reactivity has led to numerous interesting synthetic applications. A wide range of amides, lactams, and urethanes have been converted to the corresponding Boc derivatives using Boc_2O as reagent and DMAP as catalyst.

Secondary amides and lactams react with Boc_2O in the presence of both ***Triethylamine*** and DMAP in CH_2Cl_2 to give stable *N*-*t*-butoxycarbonylated products (eq 16).[3] In the reaction of disubstituted pyrrolidones, the yields are much higher using THF as solvent than with dichloromethane.[59]

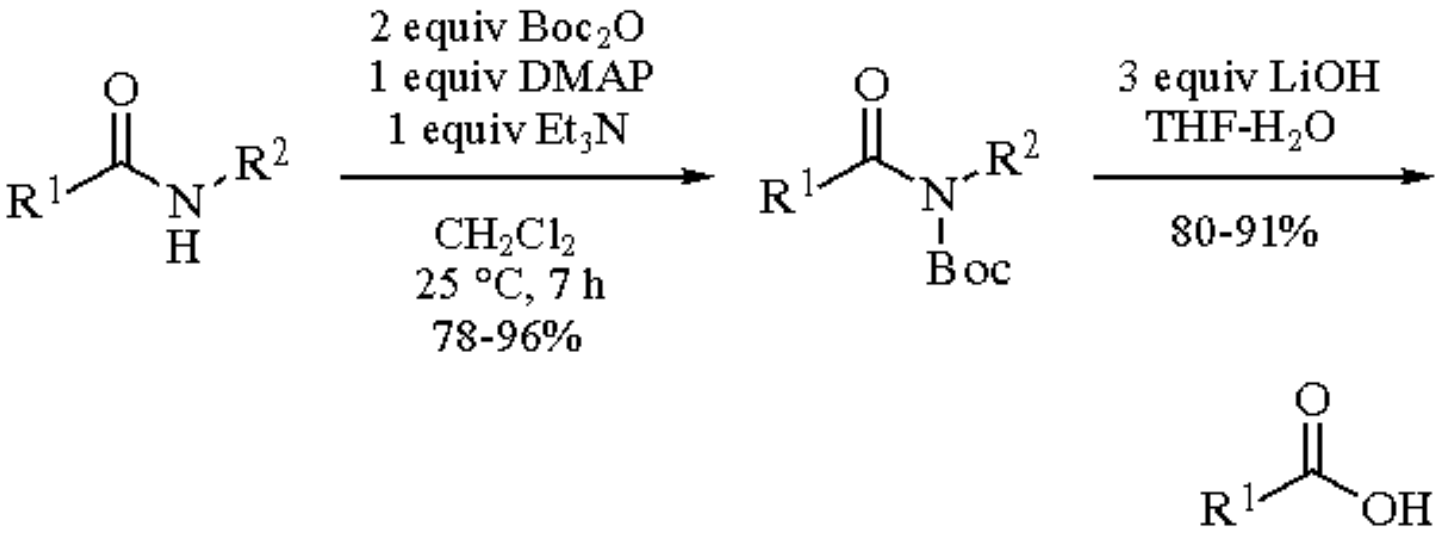

(16)

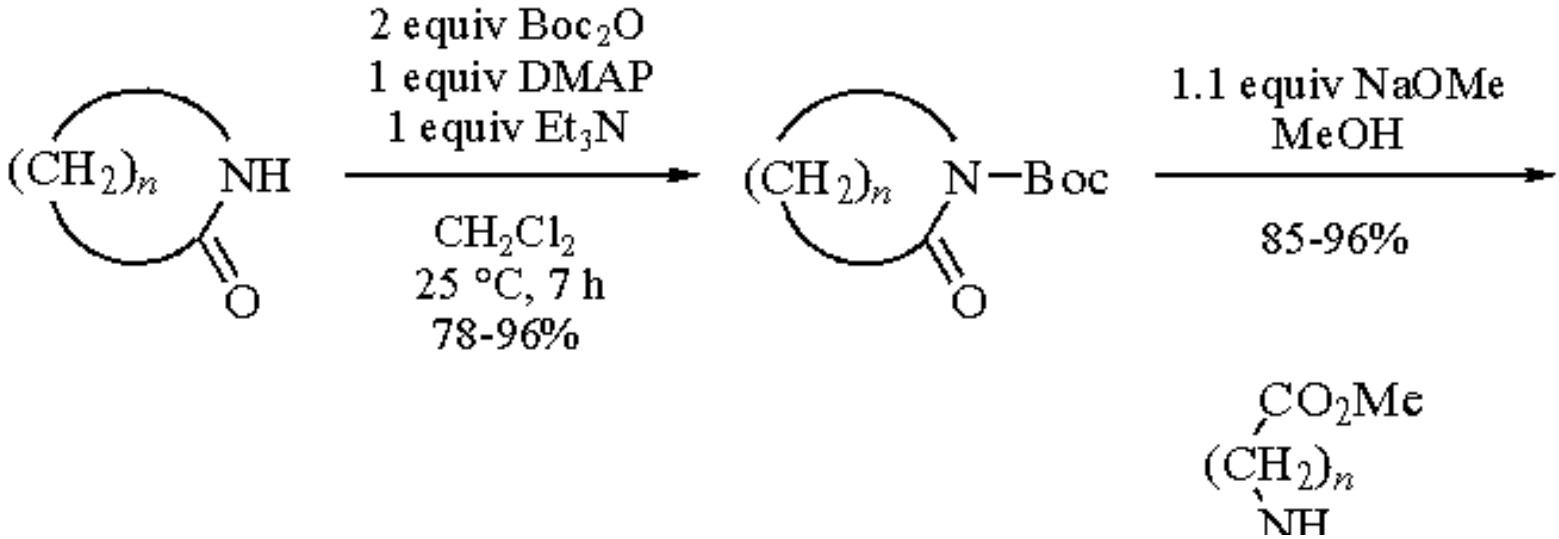

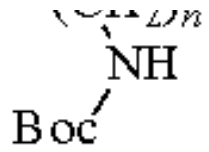

Exhaustive acylation of a series of secondary amides has also been performed with Boc_2O in dry acetonitrile at ambient temperature using DMAP as catalyst. The method has some steric limitations. For instance, it is retarded in the case of the *ortho*-substituted benzamides. The reaction has been extended to the acylation of carbamates and other amide type functions: sulfonamides, sulfenamides, and phosphinamides.[60] β-Lactams are also *N*-protected in good yields (eq 17).[61]

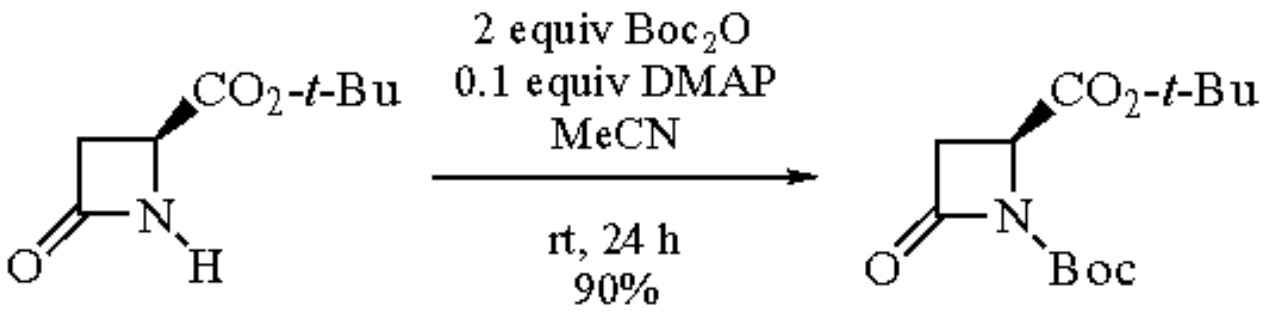

(17)

Primary carboxamides react with 2 equiv of Boc_2O and 1 equiv of DMAP to give isolable *N*-acylimidodicarbonates which are acylating agents for amines (eq 18).[62] Formamide itself furnishes the unstable di-*t*-butyl *N*-formylimidodicarbonate (eq 19).[63]

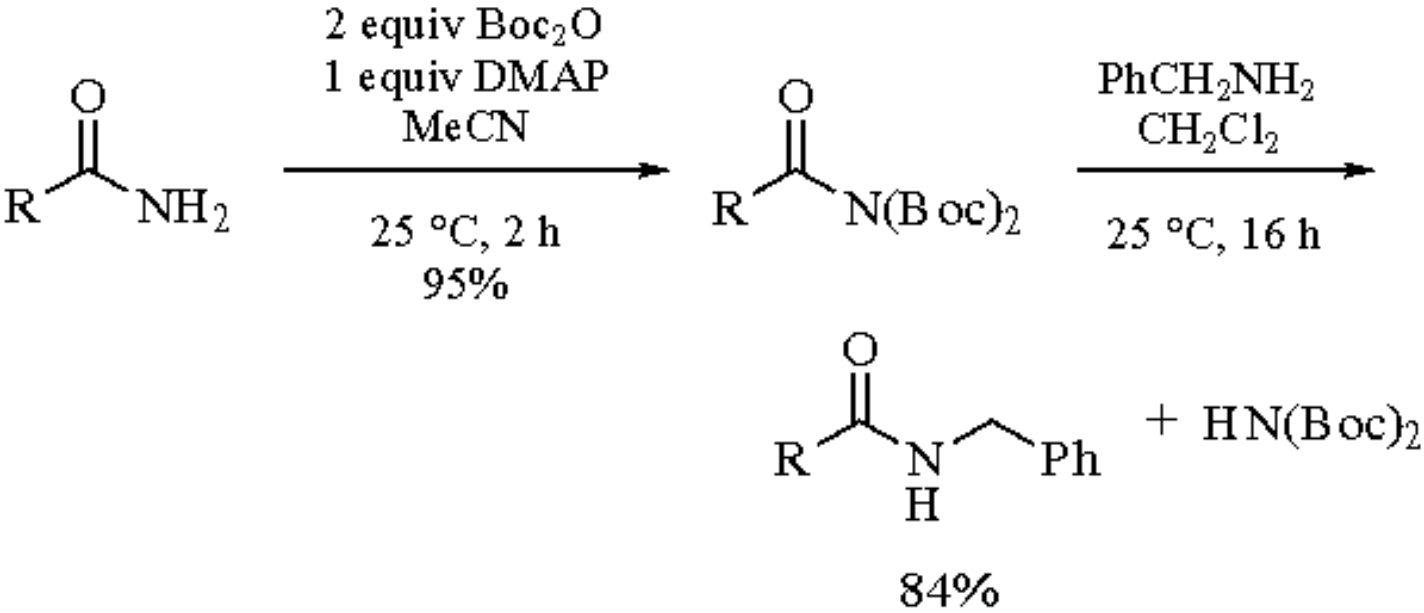

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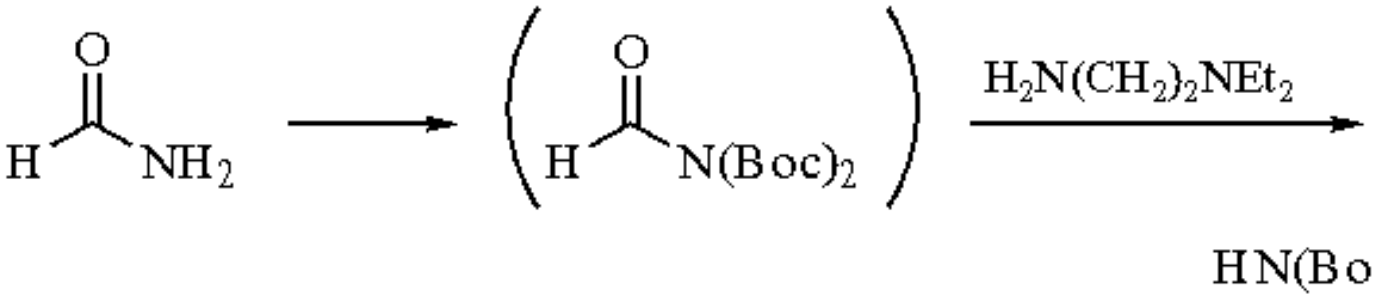

(19)

Grieco has shown that the regioselective hydrolysis or methanolysis of *N*-*t*-butoxycarbonyl derivatives of amides and lactams affords the corresponding carboxylic acids or methyl esters, respectively (eq 16).[3] ***1,1,3,3-Tetramethylguanidine*** efficiently catalyzes the methanolic cleavage.[64] Grieco's method has been applied to a formal synthesis of gabaculine, in which ***Lithium Hydroxide*** treatment induces both sulfoxide elimination and lactam cleavage (eq 20).[65]

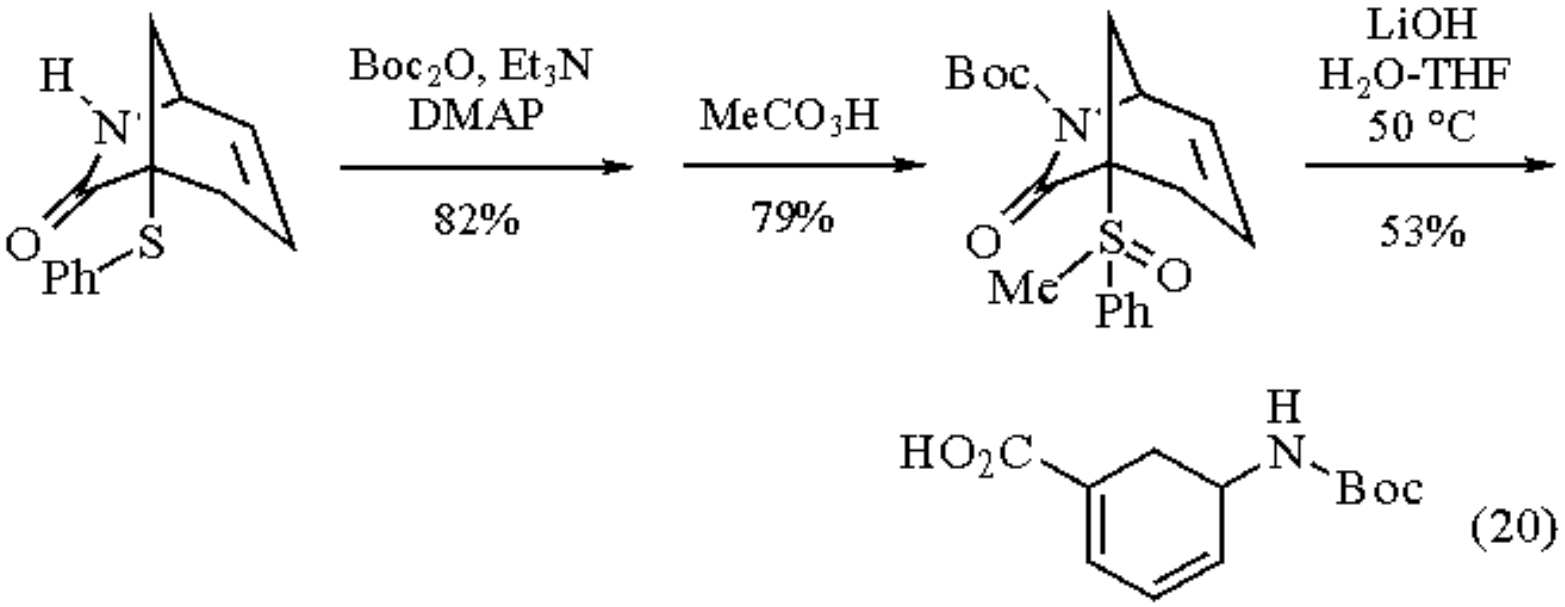

(20)

Other regioselective attacks at the acyl function are known. Aminolysis of substituted pyrrolidones gives the corresponding *N*-Boc γ-amino acid amides.[59] The *N*-Boc five- to eight-membered lactams are cleaved with Grignard reagents at the endocyclic carbonyl group to give o-Boc-amino ketones,[66-68] which can be deprotected with TFA and cyclized with NaOH to yield cyclic imines.[67] Regioselective ring opening of the *N*-Boc-pyroglutamate ethyl ester with the lithium enolates of carboxylic esters, dithiane anion, alcohols, amines, and thiols occurs without epimerization.[69-71] Selective cleavage of cyclic carbamates gives *N*-protected amino alcohols (eq 21). In this reaction, methyl ester substituents are not transformed into acids by using ***Cesium Carbonate*** as a base.[72]

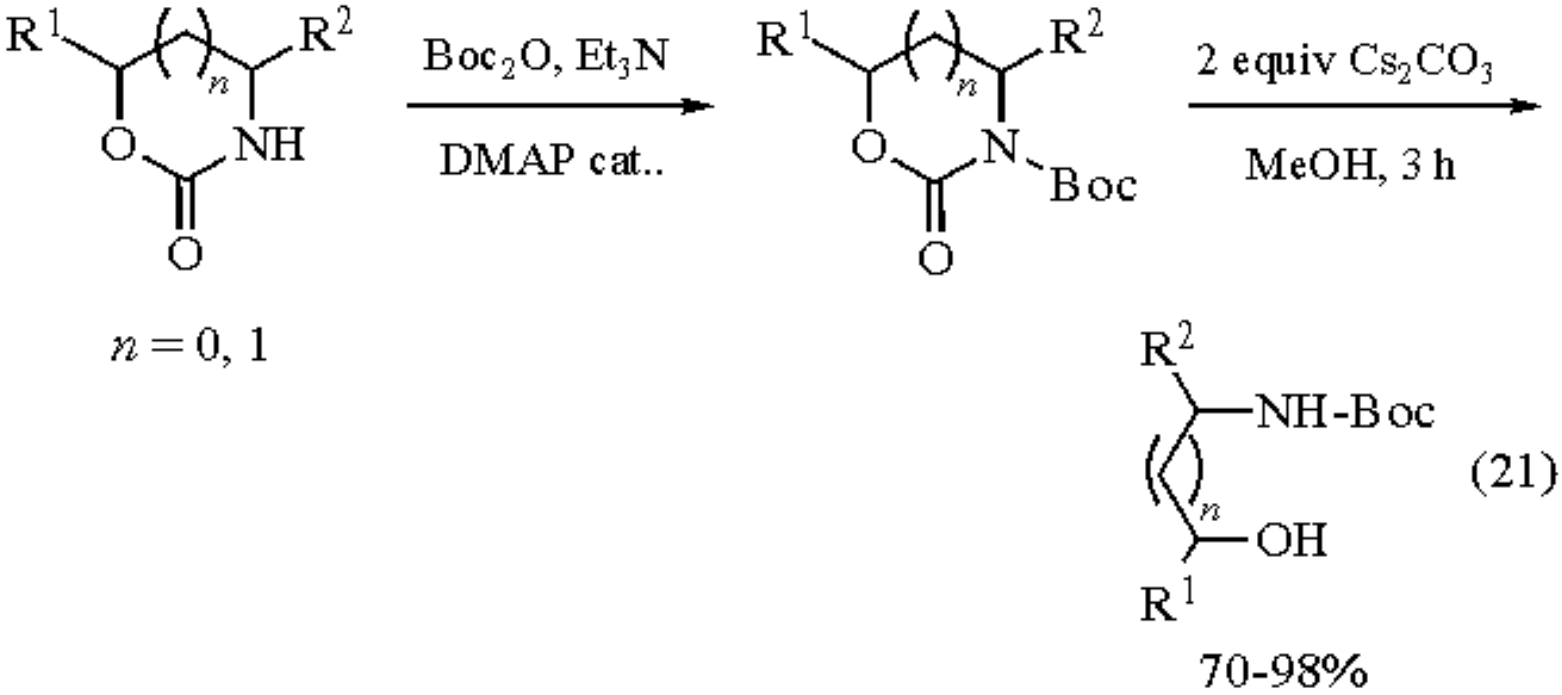

(21)

The selective deacylation of *N*-Boc carboxamides has also been achieved by aminolysis to give *N*-Boc amines. 2-Diethylaminoethylamine in acetonitrile is particularly convenient, but other conditions such as hydrazine in methanol can also be used.[64,73] Aminolysis of di-*t*-butyl *N*-formylimidodicarbonate affords di-*t*-butyl imidodicarbonate, $HN(Boc)_2$ (eq 19).[63] This compound, as well as the unsymmetrical benzyl *t*-butyl imidocarbonate, has been used as a substitute for ***Phthalimide*** in the Gabriel and Mitsunobu reactions to give primary amines. Compared to the classical method, which requires the hydrazinolysis of the phthaloyl protecting group, the main advantage of these novel Gabriel reagents is the much milder and rather specific conditions for the final deprotection step.[74] The lithium salt of $HN(Boc)_2$ has also been used in a palladium-catalyzed allylic amination.[75] Labeled di-*t*-butyl imidodicarbonate leads to ^{13}C and ^{15}N glycine derivatives.[76] Alkylation with triflates prepared from α-hydroxy acid esters gives ^{15}N-labeled chiral Boc-amino acids suitable for the synthesis of labeled peptides.[77]

t-Butoxycarbonylation of benzyl or allyl *N*-Boc or *N*-Cbz amino acid esters using Boc_2O/DMAP gives *N*-bis(alkoxycarbonyl) amino acid esters. Specific cleavage of the allyl protecting group with ***Chlorotris(triphenylphosphine)rhodium(I)***, or hydrogenolysis of the benzyl ester function, respectively, gives N^{α}-benzyloxycarbonyl, N^{α}-*t*-butoxycarbonyl or N^{α}-di-*t*-butoxycarbonyl amino acids (eq 22).[78,79]

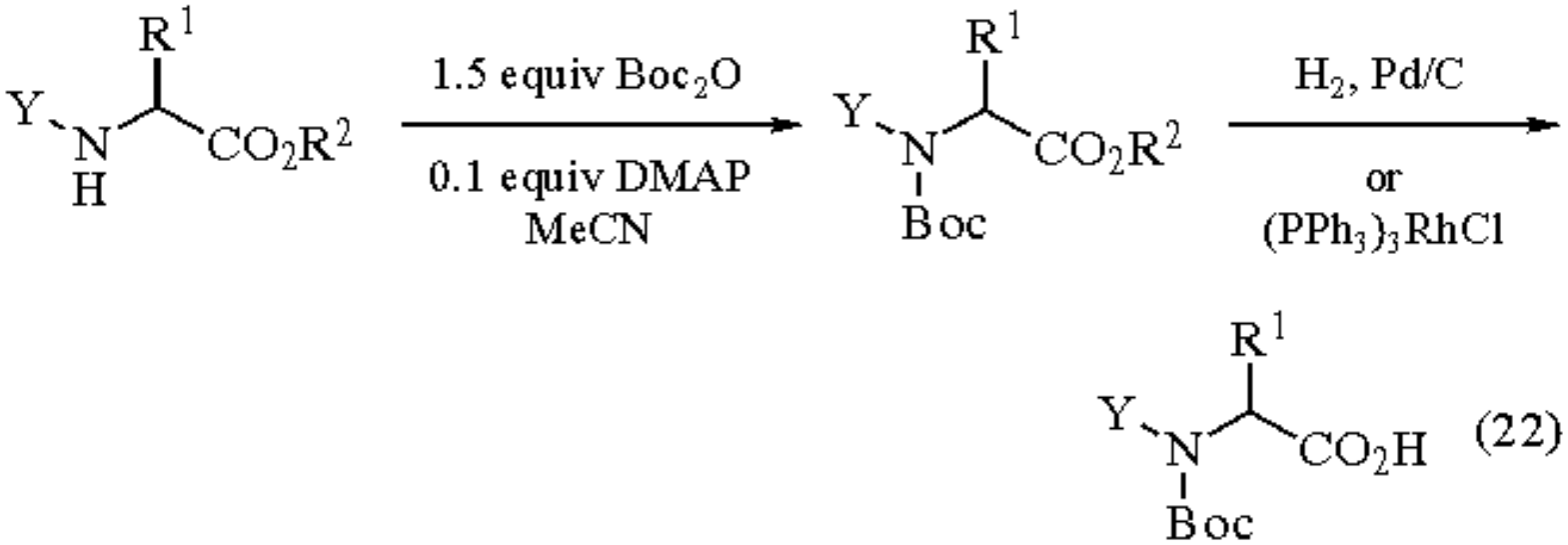

where H_2, Pd/C is used, R^2 = Bn, Y = Boc
where $(PPh_3)_3RhCl$ is used, R^2 = allyl, Y = Cbz or Boc

The di-*t*-butoxycarbonyl amino acids have been applied to solution peptide synthesis using the ***1,3-Dicyclohexylcarbodiimide*** or *p*-nitrophenyl ester method in DMF for coupling[79]

Reaction of a bis(alkoxycarbonyl)amino acid pyridinium salt with cyanuric fluoride at -30 °C gives a *N*-bis(alkoxycarbonyl)amino acid fluoride (eq 23). Owing to the high electronegativity and small size of the fluorine atom, this derivative is an efficient acylating agent for amines and pyrrole anions.[80] Use of the Vilsmeier reagent instead of cyanuric fluoride leads to a chemically and optically pure *N*-Boc or *N*-Cbz amino acid *N*-carboxy anhydride (Boc- or Cbz-NCA) without the use of phosgene and the unstable *t*-butyl chlorocarbonate (eq 23).[80] Peptide synthesis with these urethane protected amino acid *N*-carboxy anhydrides (U-NCAs) is a very clean reaction which liberates only CO_2 as a byproduct.[81]

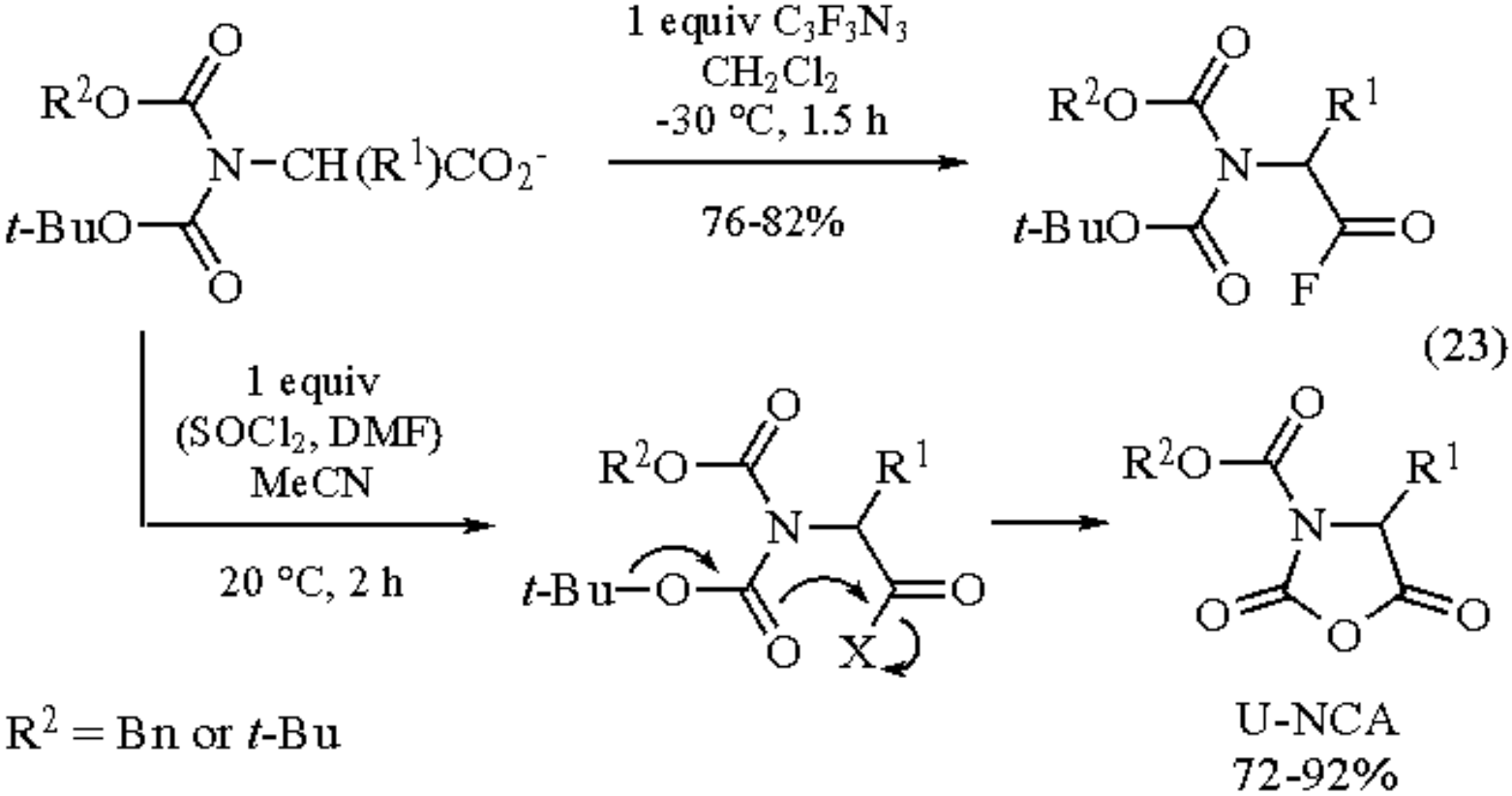

(23)

Treatment with $Boc_2O/DMAP_{cat}$ allows exhaustive *N*-*t*-butoxycarbonylation of some peptides.[82] The *t*-butoxycarbonylation of the internal amide bonds favors the cyclization of the peptides.[83] Interestingly, one Boc group can be selectively removed from a bis(Boc)-amine[75,76] with a slight excess of trifluoroacetic acid. Use of the $Boc_2O/DMAP_{cat}$/MeCN conditions also allows selective protection of mixed primary-secondary diamines. *t*-Butoxycarbonylation of a *N*,*N*´-bis(benzyloxycarbonyl)diamine followed by hydrogenolysis of the Cbz groups furnishes the *t*-butoxycarbonylated derivative of the primary amino function (eq 24).[84] Analogous strategies have been used for the selective indirect acylation of polyamines such as spermidine.[85,86]

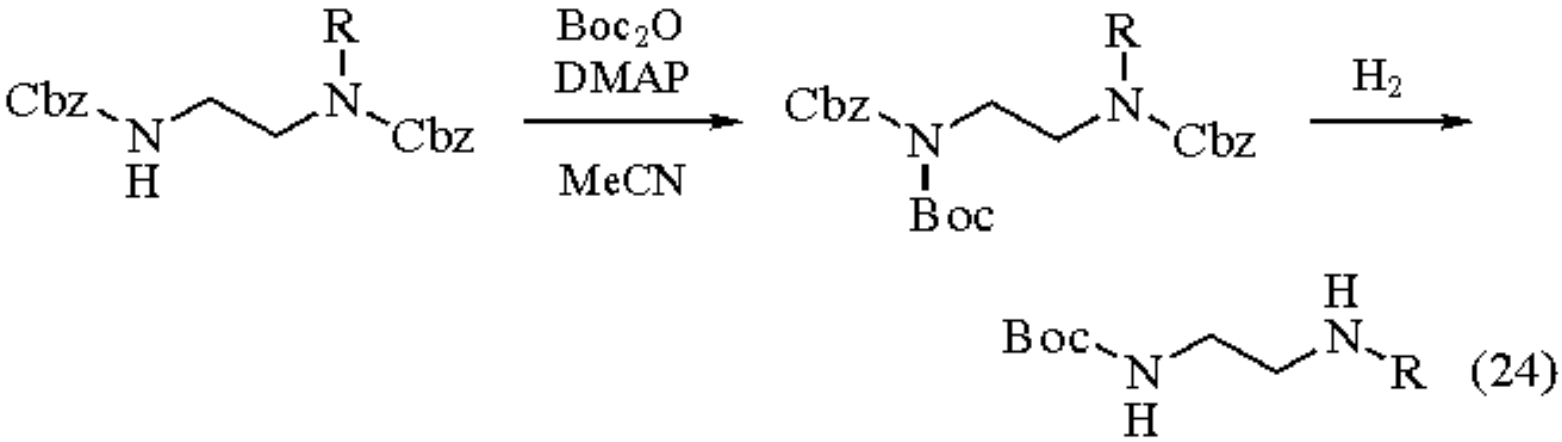

(24)

The *t*-butoxycarbonylation of the sodium salt of thiourea does not require DMAP catalysis. The resulting *N*,*N*´-bis(*t*-butoxycarbonyl)thiourea reacts with amines to give bis(*t*-butoxycarbonyl)guanidines (eq 25).[87]

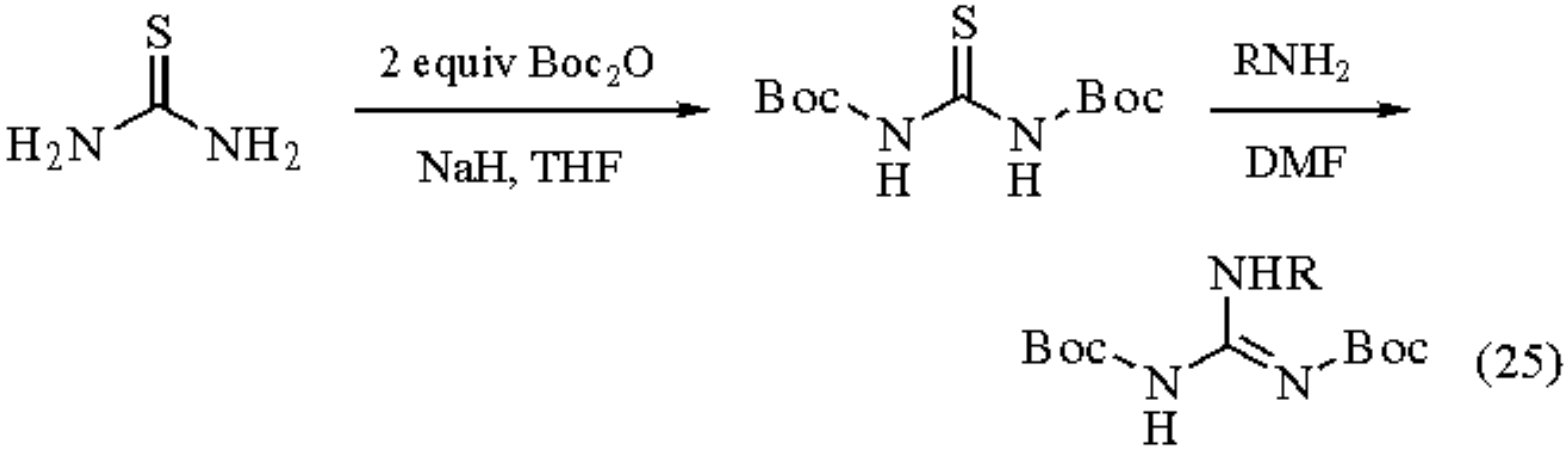

Sequential diacylation of 1-guanidinylpyrazole gives the *N*,*N*´-bis(Boc)-guanidinylpyrazole, which is also an efficient reagent for the conversion of amines to protected monosubstituted guanidines and therefore for the synthesis of arginine-containing peptides from their ornithine counterparts (eq 26).[88]

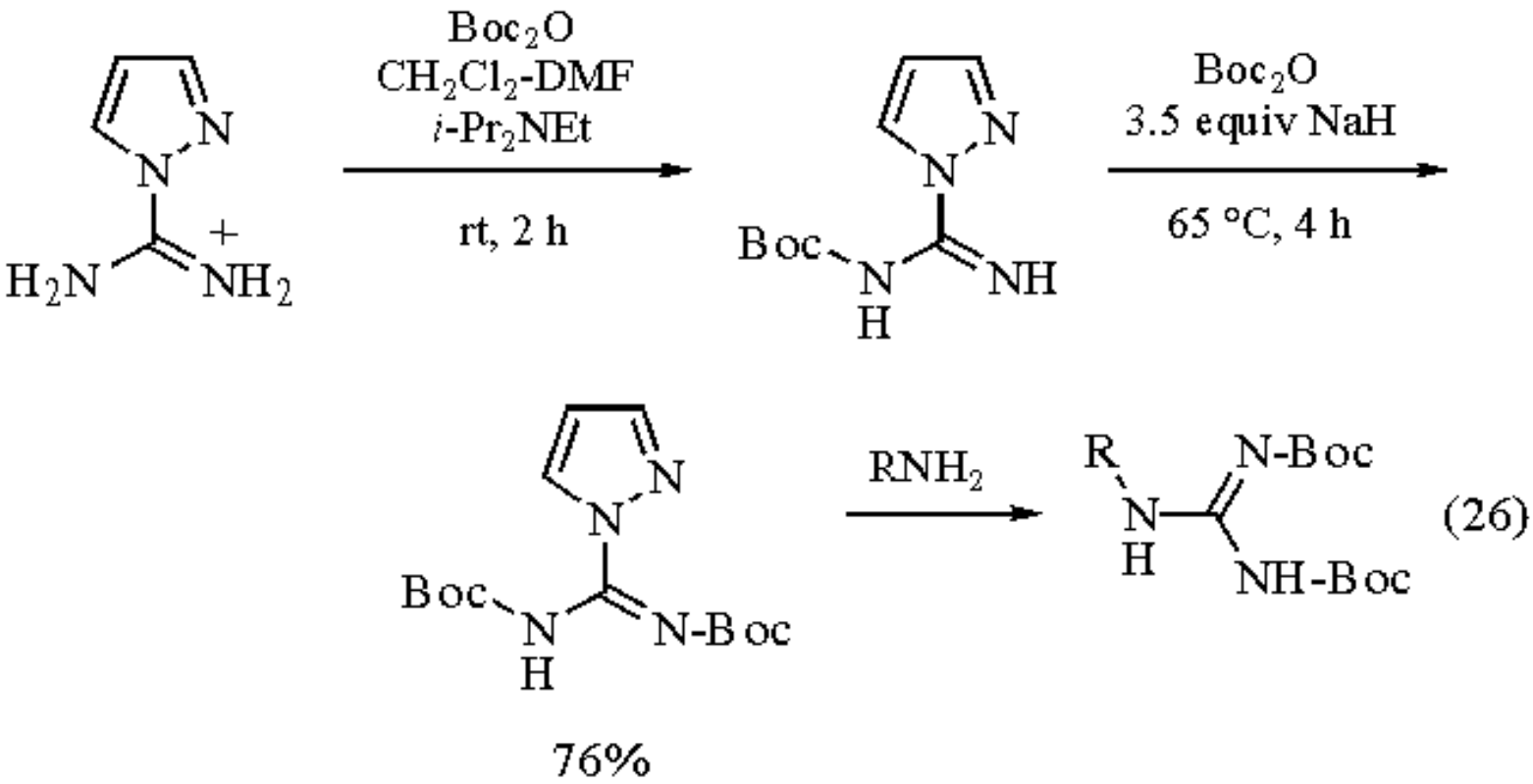

N-*t*-Butoxycarbonylation of Pyrroles and Indoles.

A series of substituted pyrroles and indoles[89-92] react smoothly with Boc_2O in the presence of catalytic amounts of DMAP in CH_2Cl_2 or acetonitrile to give the corresponding *N*-Boc pyrrole or indole derivatives. The *N*-*t*-butoxycarbonylation allows direct lithiation α to the indole and pyrrole nitrogen at low temperature. Alternatively, lithium-halogen exchange of *N*-Boc-2-bromopyrroles generates the *N*-protected 2-lithiopyrroles (eq 27).[91] After reaction with an electrophile, the Boc protecting group is easily removed either by methoxide ion in methanol or by thermolysis.[90,93]

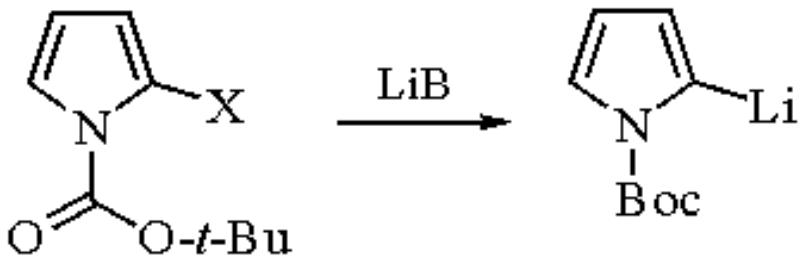

(27)

X = H, LiB = lithium tetramethylpiperidide
X = Br, LiB = BuLi

In the reaction with Boc_2O/DMAP, N^{α}-Boc-tryptophan methyl ester affords the N^{α},N^{in}-di-Boc derivative in almost quantitative yield. This product has been used in peptide synthesis. Moreover, selective cleavage of the N^{α}-Boc group is possible in the presence of the N^{in}-Boc function by using 2.7 N HCl in dioxane.[94]

Activation of the Carboxyl Group. Formation of Esters and Anhydrides.

In the presence of ***Pyridine*** in aprotic solvents, the carboxyl function of a carboxylic acid or a *N*-Boc-amino acid is activated with the Boc_2O reagent. The resulting mixed anhydride can react further with one molecule of the starting acid to give a symmetrical anhydride. At an equimolar ratio of the acid and the Boc_2O reagent a mixture of the mixed and the symmetrical anhydrides is formed. If 2 equiv of acid are used, the symmetrical anhydride becomes the main reaction product. Addition of certain nucleophilic agents to the Boc_2O/carboxylic acid/pyridine mixture leads to the acylation of the nucleophile (eq 28).[58]

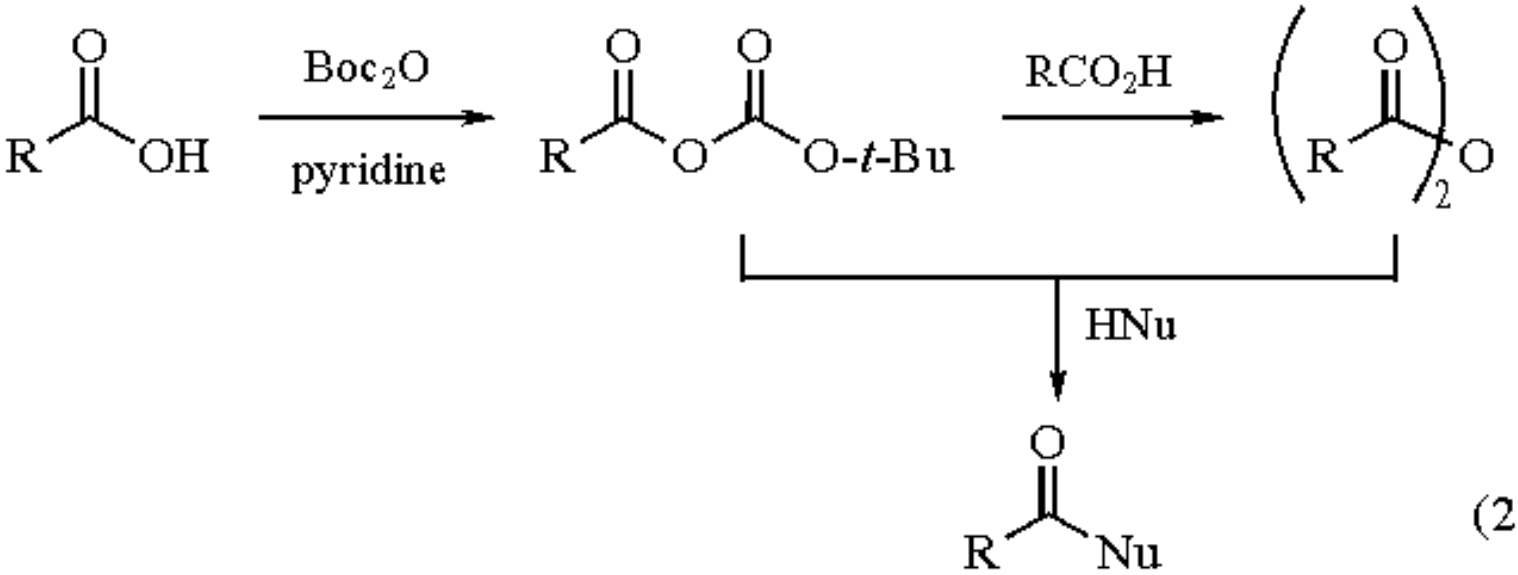

(28)

From a preparative point of view, it is essential that Boc_2O reacts much more rapidly with the carboxylate function than with the nucleophile. The reaction has been applied to the synthesis of aryl and alkyl esters and anilides such as *o*-nitrophenyl, benzyl, or trifluoroethyl esters and *p*-nitroanilides of *N*-protected amino acids. The formation of esters derived from secondary alcohols (benzhydryl, menthyl, or cholesteryl esters) is accelerated by addition of DMAP.

Depsipeptides are obtained in good yields. DMAP is a necessary catalyst for the synthesis of *t*-butyl esters and the esterification of *N*-protected amino acids occurs without epimerization.[58]

t-Butoxycarbonylation of Carbanions.

Preferential *C*-*t*-butoxycarbonylation of diethyl acetamidomalonate occurs by treatment with $Boc_2O/DMAP_{cat}$ in acetonitrile (eq 29).[60] From the reaction of the potassium salt of diphenylphosphinyl isocyanide and Boc_2O in CH_2Cl_2 at -70 °C, the corresponding Wittig-Horner reagent, *t*-butyl (diphenylphosphinyl)isocyanoacetate, is formed in near quantitative yield.[95] Similarly, treatment of α-lithioalkylphosphonates with Boc_2O gives *C*-*t*-butoxycarbonylated enolates which react with aldehydes to give substituted *t*-butyl acrylates.[96] The lithium salt of the Schiff base derived from the aminomethyldiphenylphosphine oxide reacts with Boc_2O at low temperature to give the imine of *t*-butyl α-(diphenylphosphinoyl)glycinate.[97]

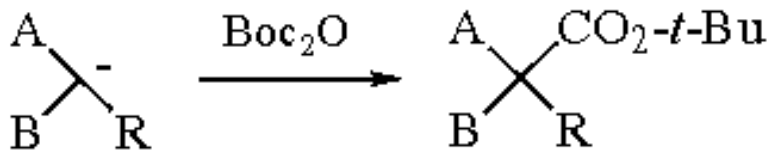

(29)

A = B = CO_2Et		R = NHAc	MeCN	rt	93%
A = Ph_2PO	B = N=C	R = H	CH_2Cl_2	-70 °C	92%
A = $(Et_2O)_2PO$	B = alkyl	R = H	THF	-78 °C	quant.
A = Ph_2PO	B = N=CPh	R = H	THF	-60 °C	80%

t-Butoxycarbonylation of Imines.

In previous examples, the acylation occurred either at the amino function[30] or at the carbanionic center[97] and not at the imine function. However, the reaction of a nucleophilic imine possessing an electron-releasing substituent (Ar = *p*-$MeOC_6H_4$) with Boc_2O in ethanol proceeds through the intermediacy of an *N*-alkoxycarbonyl iminium ion to give an α-ethoxy carbamate (eq 30). As the trapping of the iminium ion by the alcohol is a reversible process, the α-ethoxy *t*-butyl carbamate is a precursor of the electrophilic *N*-Boc iminium ion in an intermolecular condensation with propargyltrimethylsilane.[98]

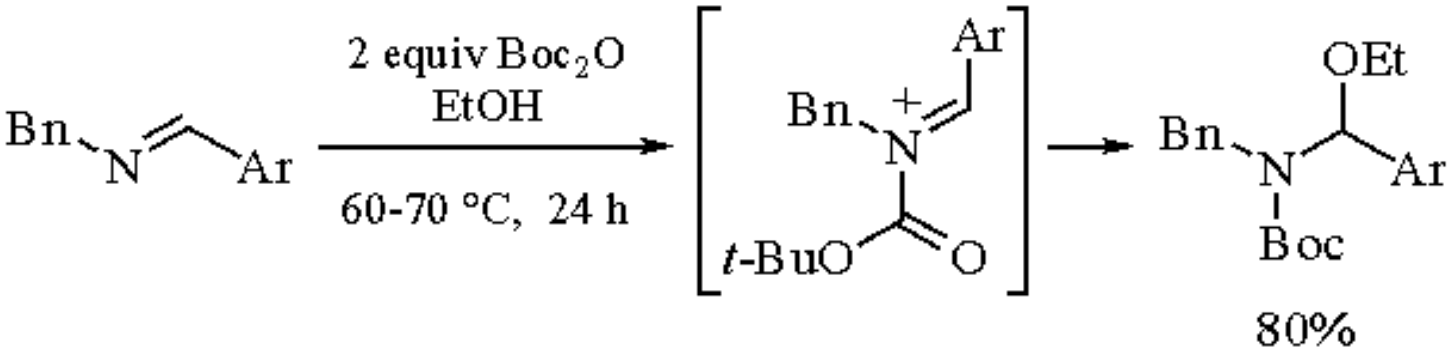

(30)

Related Reagents.

1-(t-Butoxycarbonyl)imidazole; ***1-N-(t-Butoxycarbonyl)-1H-benzotriazole 3-N-Oxide***; ***2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile***; ***N-(t-Butoxycarbonyloxy)phthalimide***; ***N-(t-Butoxycarbonyloxy)succinimide***; ***1-t-Butoxycarbonyl-1,2,4-triazole***; ***t-Butyl Azidoformate***; ***t-Butyl Chloroformate***.

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Di-*t*-butyldichlorosilane

t-Bu_2SiCl_2

[18395-90-9] · $C_8H_{18}Cl_2Si$ · Di-*t*-butyldichlorosilane · (MW 213.22)

(reagent for the protection of diols; used as a silylene precursor)

Physical Data: mp -15 °C; bp 190 °C/729 mmHg; *d* 1.009 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: liquid.

Preparative Methods: can be conveniently prepared by chlorination of di-*t*-butylsilane ($CCl_4/PdCl_2$ (cat), 85%)[1,2] but various other methods of preparation have been reported.[3-6]

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; reacts with hydroxylic solvents, corrosive; lachrymator. Use in a fume hood.

Protection of Alcohols.

The presence of the bulky *t*-butyl groups in di-*t*-butyldichlorosilane has been found to increase the Si-C bond lengths slightly and to widen the CSiC bond angles by 11.1° relative to ***Dichlorodimethylsilane*** as determined by electron diffraction and molecular mechanics calculations.[7]

The di-*t*-butylsilylene protecting group for diols was introduced by Trost and Caldwell[4] and used in a total synthesis of deoxypillaromycinone.[5] It is introduced by the reaction of di-*t*-butyldichlorosilane with a 1,2- or 1,3-diol in acetonitrile in the presence of ***Triethylamine*** and ***1-Hydroxybenzotriazole*** (HOBt) at 45-90 °C (eq 1). For a related, highly reactive reagent see ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***.

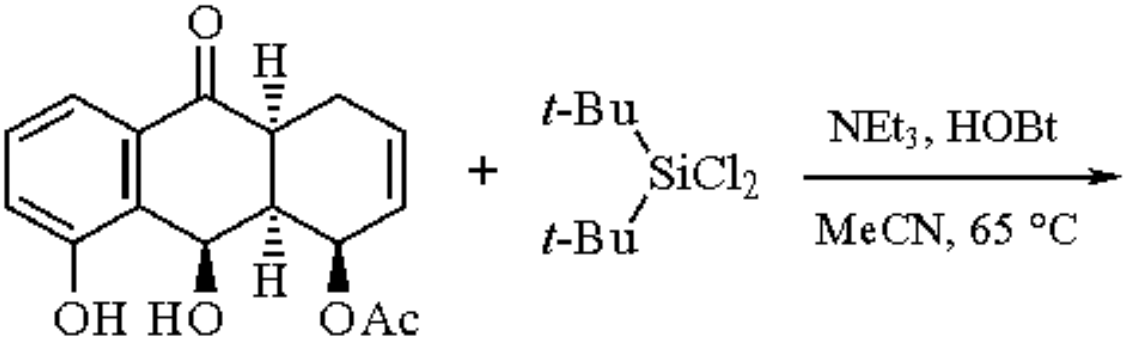

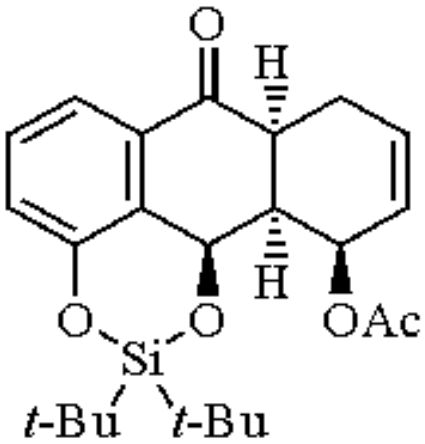

(1)

When at least one of the hydroxy groups is phenolic or primary, reactions proceed smoothly at 25-65 °C, but when both hydroxy groups are secondary, more forcing conditions (95 °C, sealed tube) are required. In all cases, yields range from 64% to 85%. No examples have been reported with tertiary alcohols. ***Pyridinium Poly(hydrogen fluoride)*** is used for deprotection and under those conditions a *t*-butyldimethylsilyl ether and a β-hydroxy ketone are unaffected (eq 2).

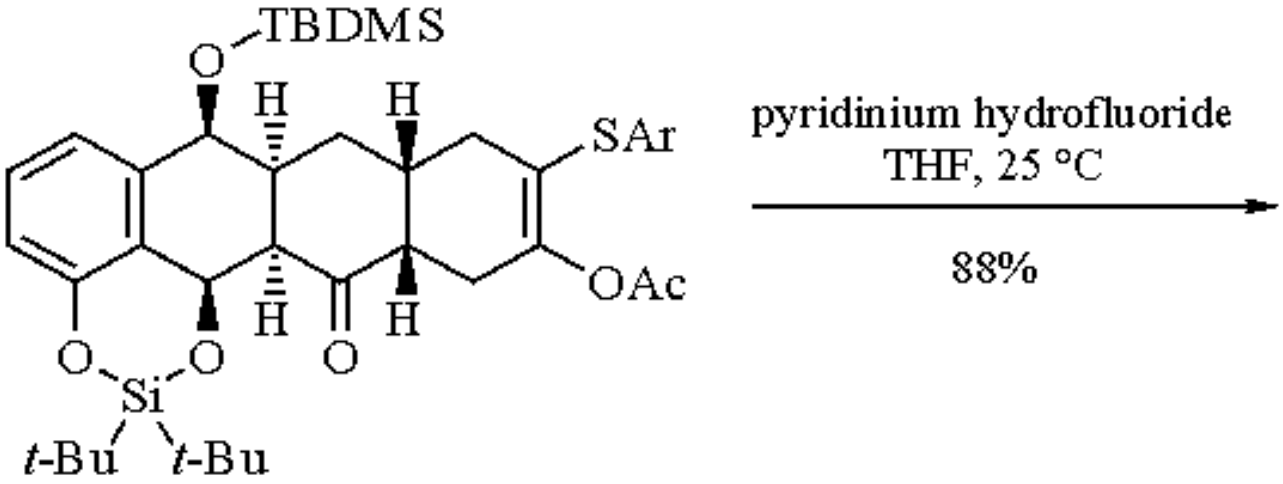

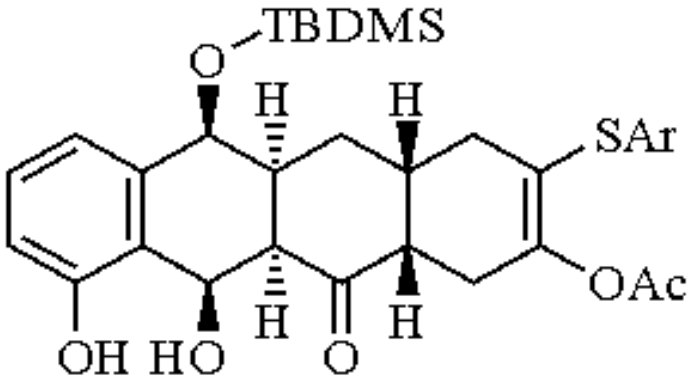

(2)

This protecting group has seen limited use but has been applied in ribonucleoside chemistry.[8-10] The reagent reacts slowly with nucleosides in the presence of imidazole/DMF but formation of the more reactive di-*t*-butylsilyl dinitrate in situ, followed by addition of cytidine, results in a protected 3´,5´-silylene derivative in excellent yield (90%) (eq 3). The protecting group can be removed conveniently with tributylamine hydrofluoride.[11]

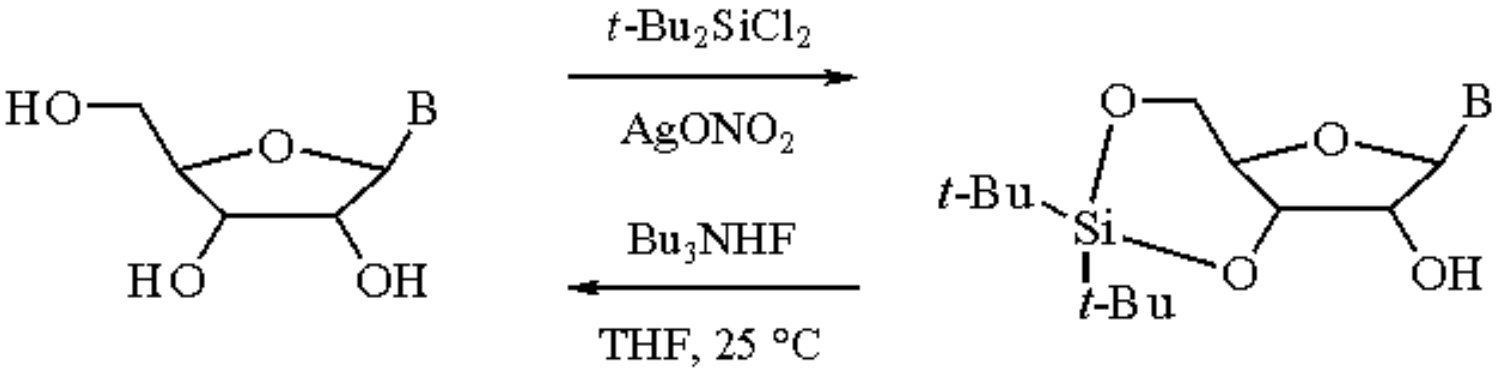

(3)

A one-pot procedure has been reported for the selective protection of a secondary alcohol over a primary alcohol in a 1,3-diol in 2´-deoxynucleosides (eq 4).[12,13]

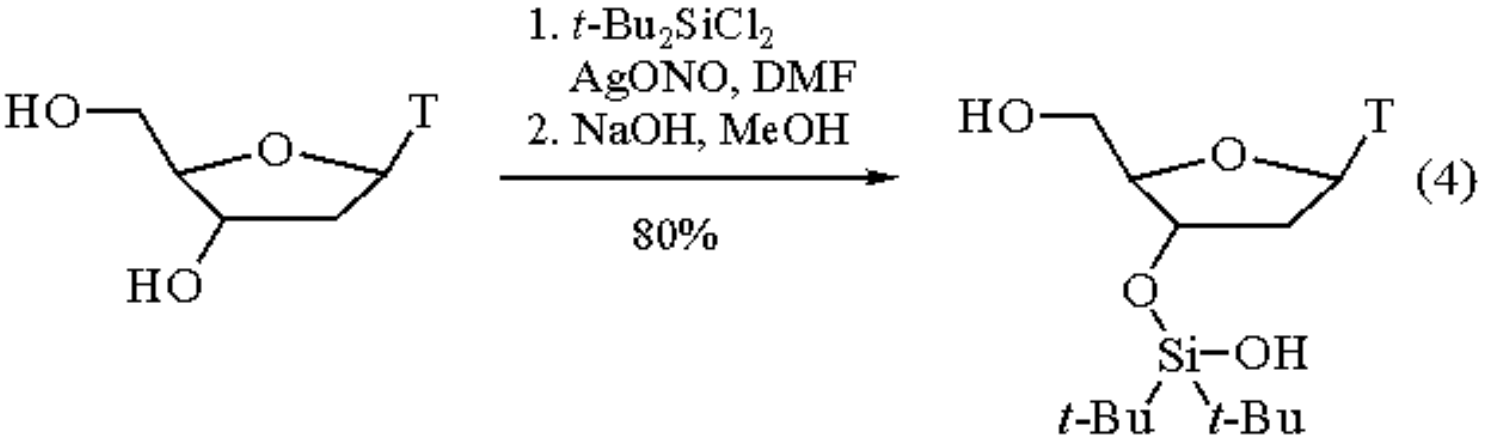

Derivatization of Diols and Hydroxy Acids.

Di-*t*-butyldichlorosilane has been used to derivatize α-hydroxy acids, β-hydroxy acids, alkylsalicyclic acids, anthranilic acid, catechols, and 1,2- and 1,3-diols for analysis by gas chromatography-electron impact mass spectrometry (eq 5).[14,15] These derivatives are useful for separation. The major fragmentation is that of Si-C bonds. The 1,2-diol in the antibiotic sorangicin has also been derivatized with di-*t*-butyldichlorosilane.[16]

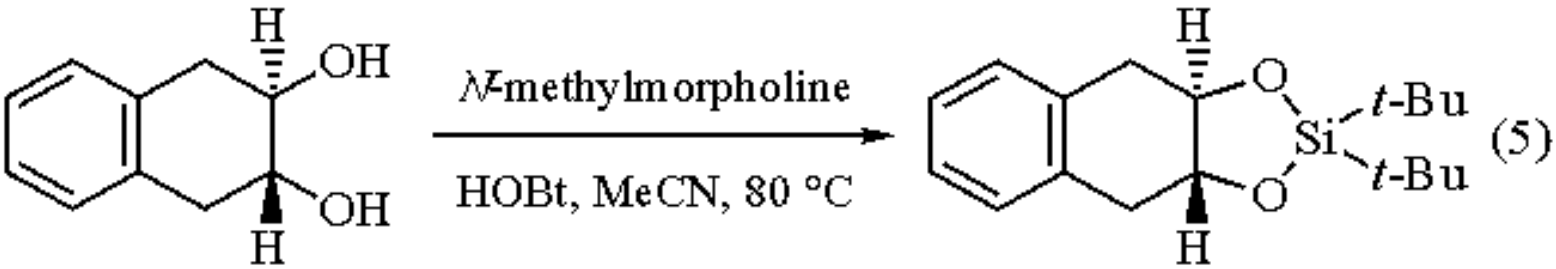

m/z 304 (M^+), 247 (M^+ - Bu), 205 (B, 247 - C_3H_6)

Silylene Precursor.

Di-*t*-butyldichlorosilane can be reduced using ***Lithium***/THF to give a putative silylene derivative that will react with double bonds to give 1,1-silirane derivatives[17-19] or react with triethylsilane to give an Si-H insertion product (eq 6).[17]

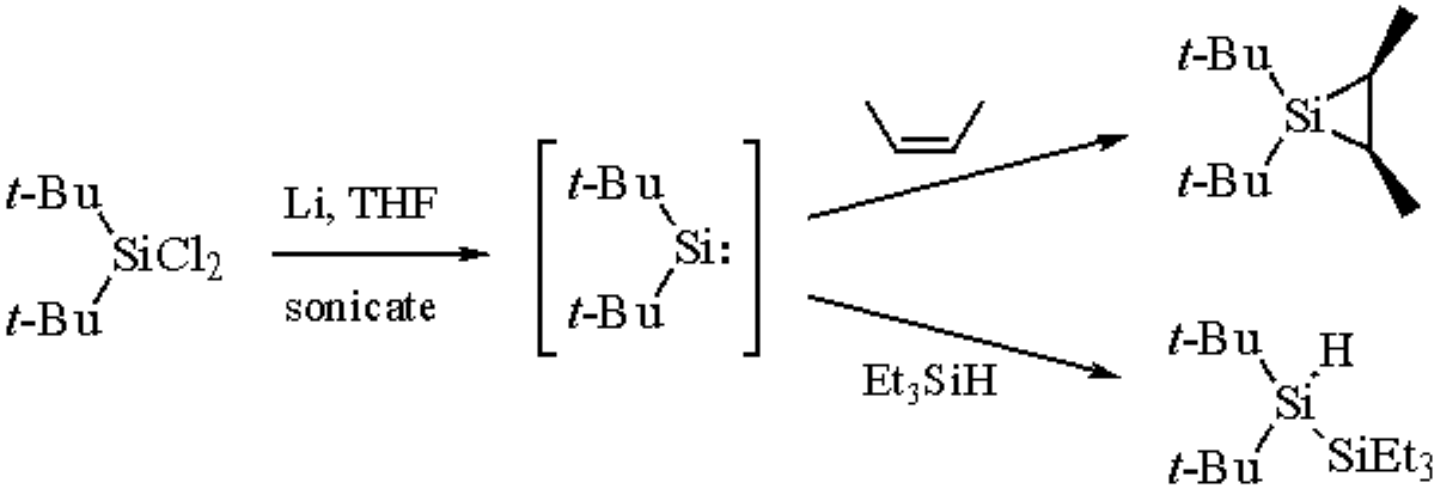

(6)

Reaction of di-*t*-butyldichlorosilane with ***Lithium Naphthalenide*** in DME gives compound (**1**) which upon irradiation gives, in addition to naphthalene, tetra-*t*-butyldisilene that subsequently reacts with 2,3-dimethylbutadiene to give a Diels-Alder adduct along with a product arising from an ene reaction (eq 7).[20]

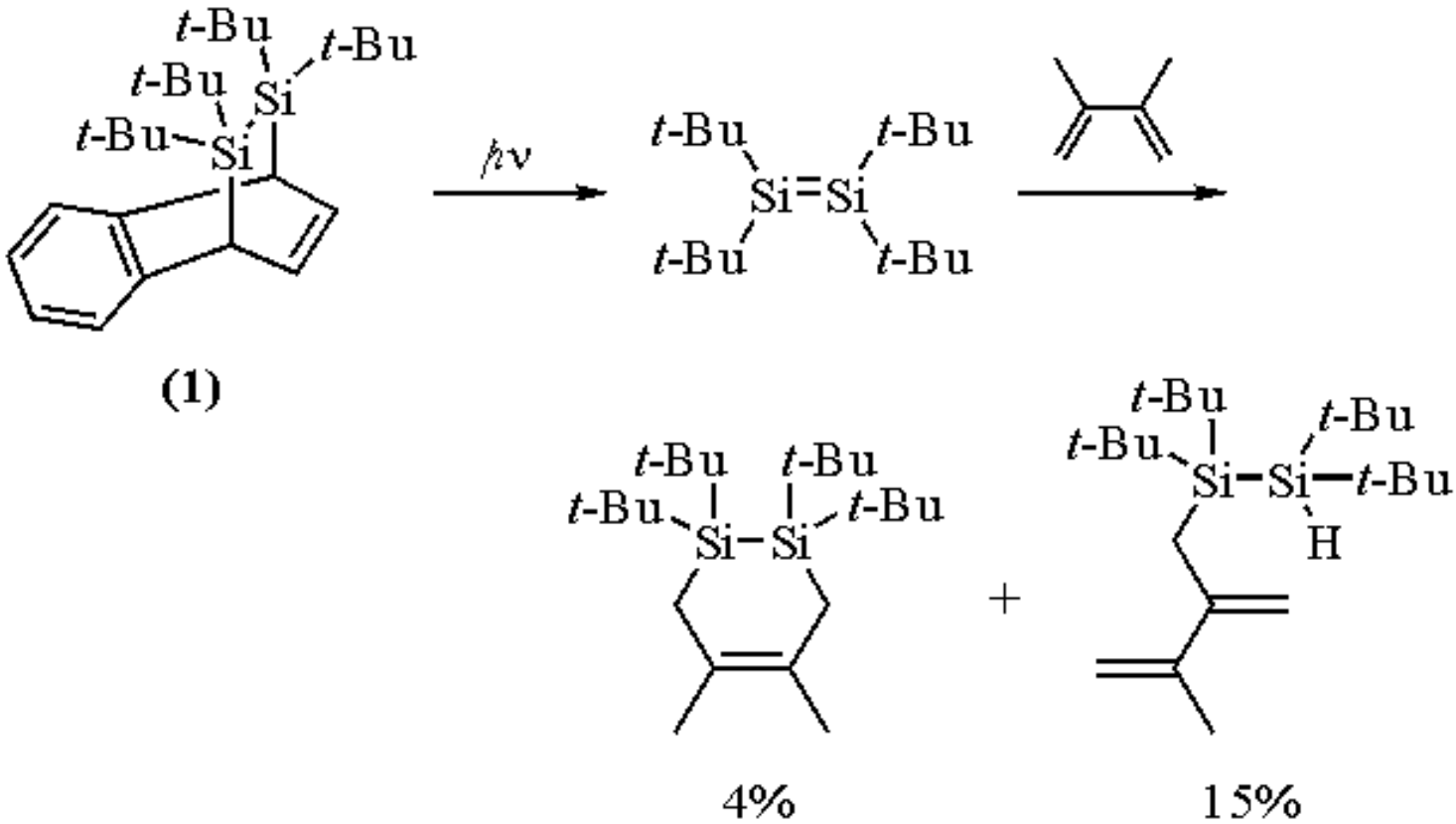

(1)

(7)

Reduction of di-*t*-butyldichlorosilane with lithium in THF at 0 °C in the presence of an excess of ***Dichlorodimethylsilane*** gives compound (**2**).[21] Reaction of di-*t*-butyldichlorosilane with lithium and 1,4-diaza-1,3-butadienes gives 1,3-diaza-2-sila-4-cyclopentenes (eq 8).[22]

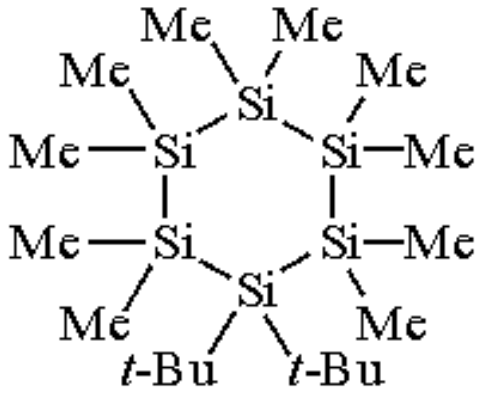

(2)

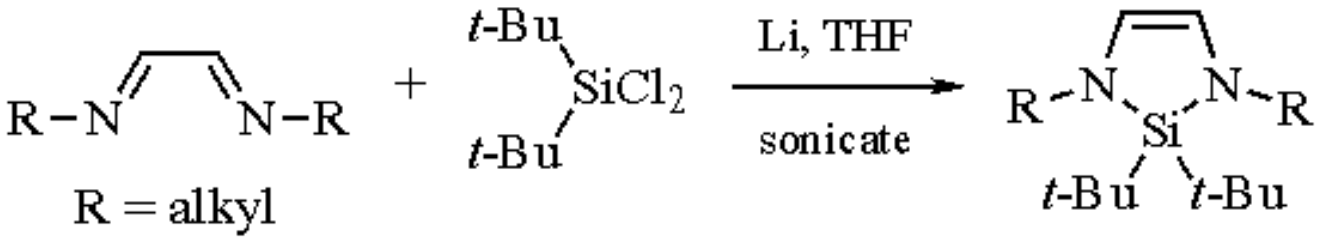

(8)

Other Substitution Reactions.

The chlorine atoms in di-*t*-butyldichlorosilane can be replaced with various nucleophiles. Di-*t*-butyldifluorosilane has been prepared by using SbF_3,[23,24] ZnF_2,[25] or $(NH_4)_2SiF_6$.[26,27] Reaction of di-*t*-butyldichlorosilane with ***Lithium Aluminum Hydride*** gives di-*t*-butylsilane[28] and reaction with ***Sodium Azide*** gives di-*t*-butyldiazidosilane; upon irradiation this gives a putative di-*t*-butylsilylene which undergoes various reactions depending on the conditions.[29] Reactions of di-*t*-butyldichlorosilane with LiPHMe[30] and $LiPH_2$[31] yield (**3**) and (**4**), respectively.

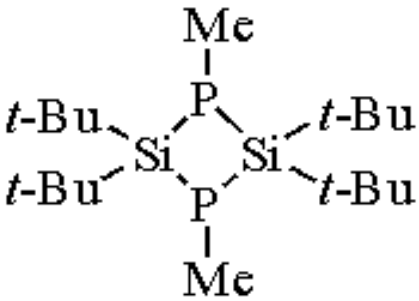

(3)

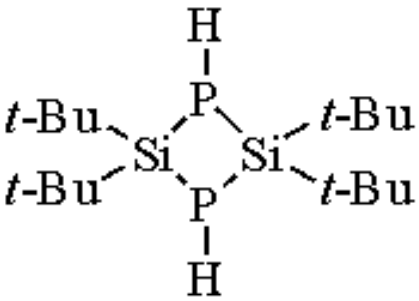

(4)

Treatment of di-*t*-butyldichlorosilane with ***Trimethylsilyllithium*** gives di-(*t*-butyl)bis(trimethylsilyl)silane.[32]

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Di-*t*-butyl Hyponitrite[1]

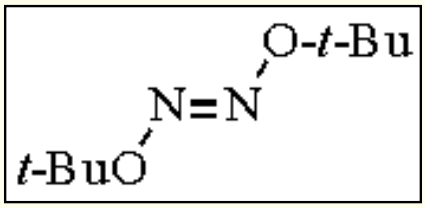

[14976-54-6] · $C_8H_{18}N_2O_2$ · Di-*t*-butyl Hyponitrite · (MW 174.24) (*E*)

[82554-97-0]

(a convenient, low-temperature source of *t*-butoxyl radicals;[1] induces serial cyclization of polyunsaturated hydroperoxides,[2] rearrangement of allylic hydroperoxides,[3] and reduction of alkyl halides or dialkyl sulfides with Et_3SiH;[4] used in radical-trapping experiments;[5] and as initiator for dimerization[6] and polymerization[7])

Alternate Names: DTBN; TBHN; DBH.

Physical Data: white crystals mp 84.5 °C (dec);[1d] volatile (0.1 mmHg at rt).[1a]

Solubility: insol H_2O; sol common organic solvents (e.g. hexane, benzene, toluene, CCl_4, and EtOH).

Analysis of Reagent Purity: NMR ($CDCl_3$, δ) ^1H 1.33 (s); IR (cm^{-1}) 2959, 1368, 1183, 995;[1a] for IR and Raman band assignments, see Ogle et al.;[8] UV (λ_{max}, pentane) 223.4 nm (ε 7140 M^{-1} cm^{-1});[1d] the *trans* structure has been established by X-ray analysis.[8]

Preparative Method: obtained in 80-90% yield by reaction of sodium hyponitrite with *t*-BuBr in the presence of ***Iron(III) Chloride*** or ***Zinc Chloride***.[9] The preparation of sodium hyponitrite (from Na, benzophenone, and nitric oxide)[10a] must be performed with extreme care.[10b]

Handling, Storage, and Precautions: although DTBN appears to be insensitive to scratching and is considered as safe,[1a] it can detonate when struck.[1d] Mixtures of DTBN with formamides undergo violent reaction or explosion when heated at 60-70 °C.[6] Due to the potential risk of explosion, it is strongly recommended that all operations involving DTBN be carried out behind a safety shield using tongs, gloves, and a safety mask. Since DTBN is quite volatile, most of the unchanged material can be conveniently removed at the end of a reaction by flushing the mixture with N_2 or Ar.[5,11a] Solid DTBN can be kept intact for several months at -10 °C or below.

Thermal Decomposition.

DTBN is used as a clean source of *t*-butoxyl radicals in the temperature range of 20 to 90 °C (eq 1).[1b] Decomposition probably involves a simultaneous two-bond scission.[1c,d] In low viscosity solvents, 4-10% of *t*-butoxyl radicals are wasted through cage recombination to form di-*t*-butyl peroxide.[1a,b] Compared to ***Di-t-butyl Peroxyoxalate*** (DBPO), which also delivers *t*-butoxyl radicals at rt, DTBN decomposes more slowly and is far less sensitive to shock or scratching.[1a] From published data,[1a] the half-life ($t_{1/2}$) of DTBN in isooctane is calculated to be ca. 425 min at 45 °C ($t_{1/2}$ of DBPO at 45 °C in benzene is about 44 min).[12] Unlike DBPO, DTBN is resistant to induced decomposition in both protic and aprotic solvents even at high concentrations.[1a]

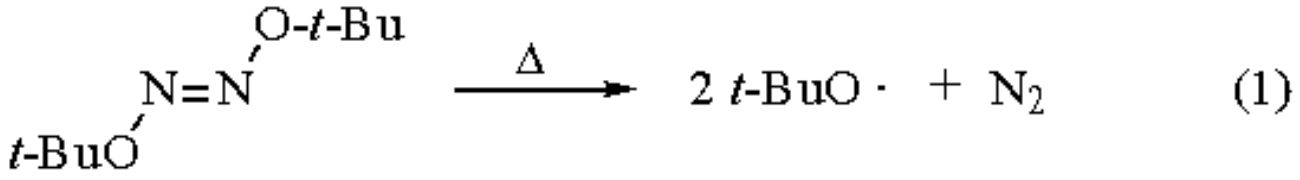

Peroxyl Radical Serial Cyclizations.

In the presence of DTBN and oxygen, polyunsaturated hydroperoxides undergo multiple cyclizations to form polycyclic peroxides.[2,13] Thus compound (**1**) cyclizes by a 6-*exo*-trig mode to afford, after selective reduction of the resulting hydroperoxides (**2**), five diastereomeric hydroxy-bis-1,2-dioxanes (**3**) in nearly 70% overall yield (eq 2).[2] Similarly, bis-1,2-dioxolanes are accessible from suitable substrates through a 5-*exo* closure.[13] For a more detailed discussion and further examples of peroxyl radical cyclizations, see ***Di-t-butyl Peroxyoxalate***.

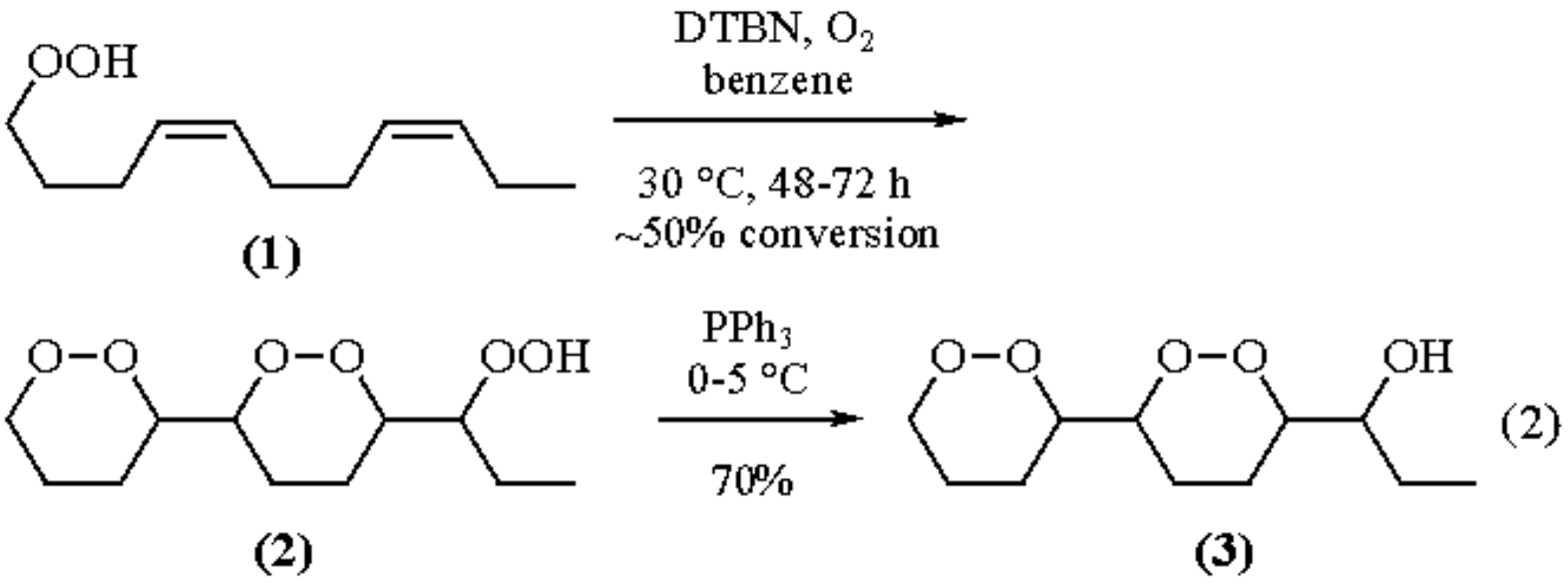

Allylic Hydroperoxide Rearrangement.

The [2,3]-rearrangement of allylic hydroperoxides is catalyzed by radical initiators or by light.[3] With few exceptions,[14] DTBN is particularly effective in accelerating the process at 20-40 °C.[3,15] Rearrangement is highly stereoselective at rt, as illustrated by the transformation of (**4**) (>99% ee) into a 1.7:1 mixture of (**4**) and (**5**), which are obtained with ee's of 97-99% (eq 3).[15a] Both experimental[15b] and theoretical[16] results suggest that an allyl radical-dioxygen pair is involved.

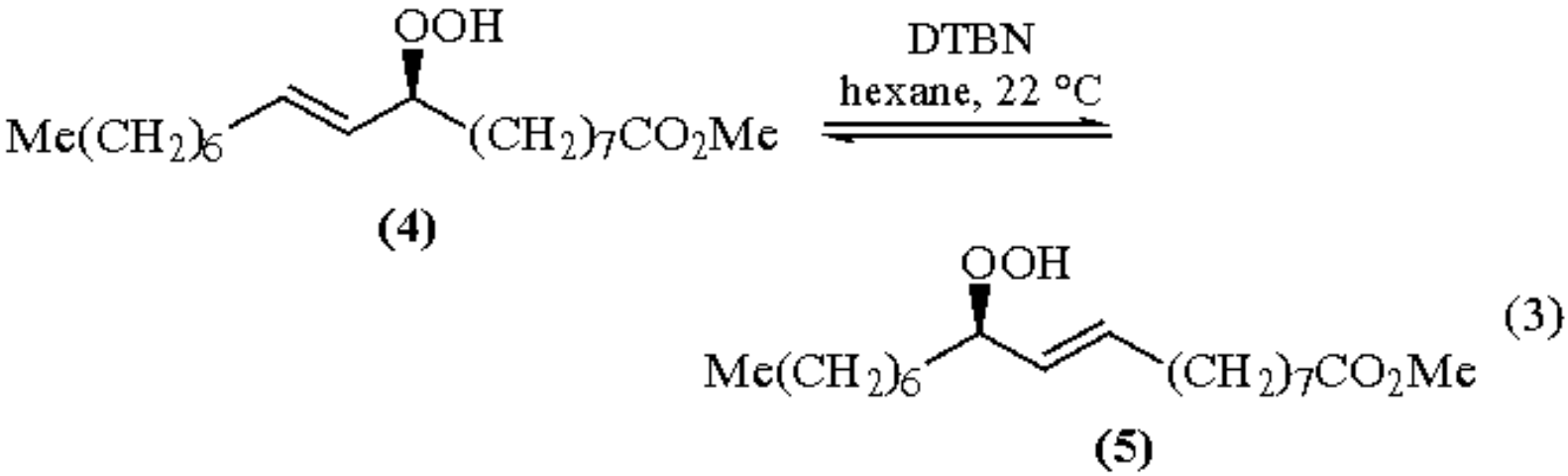

Radical Chain Reductions.[4]

Saturated primary, secondary, or tertiary alkyl halides undergo essentially quantitative reduction to the corresponding alkanes upon treatment with DTBN, ***Triethylsilane***, and *t*-dodecanethiol (mixture of isomers). An example is shown in eq 4. Likewise, dialkyl sulfides are reduced to alkanes in excellent yields. The thiol acts as a polarity reversal catalyst which mediates hydrogen-atom transfer from the silane to the alkyl radical.

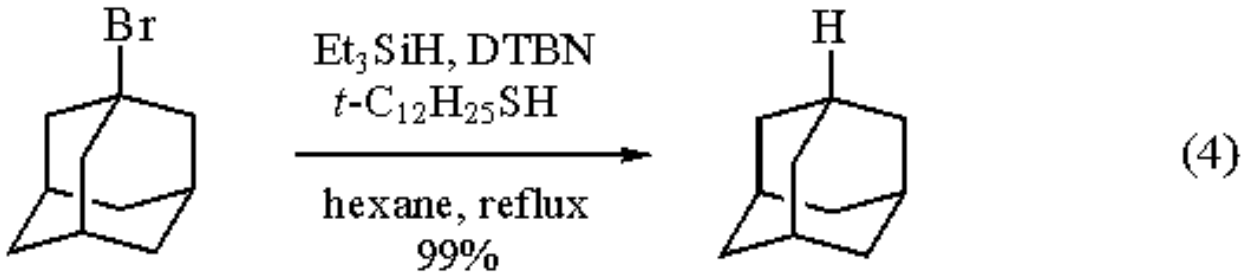

Miscellaneous Applications.

In several cases, dimerization of organic compounds can be achieved in better yields by using DTBN instead of conventional initiators such as ***1,1-Di-t-butyl Peroxide*** or acetyl peroxide (eq 5).[6]

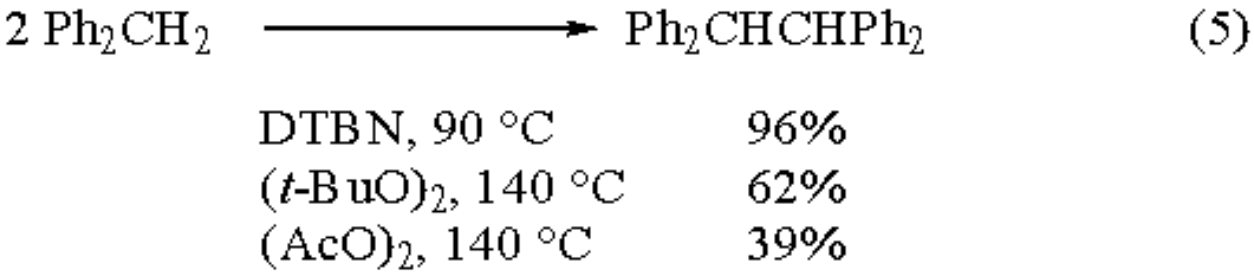

DTBN is also used as an initiator for autoxidation,[11] radical polymerization,[7,17] and in radical-trapping experiments.[5]

Related Reagents.

t-Butyl Hydroperoxide; ***Dibenzoyl Peroxide***; ***1,1-Di-t-butyl Peroxide***; ***Di-t-butyl Peroxyoxalate***; ***m-Nitrobenzenesulfonyl Peroxide***; ***p-Nitrobenzenesulfonyl Peroxide***; ***Triethylsilane***.

---

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Dibutylmagnesium

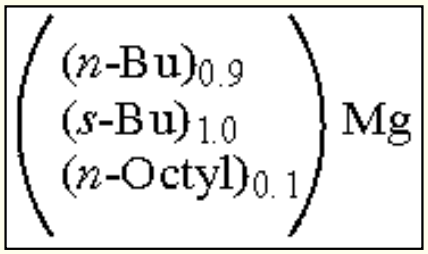

[3988-32-8] · $C_8H_{18}Mg$ (mainly) · Dibutylmagnesium · (MW 145 (av))

(magnesiating agent of various activated C-H bonds[1] and protic functional groups; can be halogenated to make finely divided anhydrous magnesium chloride or bromide)

Alternate Name: DBM.

Physical Data: waxy solid; for 1 M heptane solution, *d* 0.72 g cm^{-3}, viscosity 0.91 cP at 25 °C and 0.76 cP at 35 °C.

Solubility: moderately sol (<1.3 M) aliphatic and aromatic hydrocarbons; highly sol ethereal solvents; reacts exothermically with water and protic solvents.

Form Supplied in: available as 0.7-1 M solution in heptane.[2]

Analysis of Reagent Purity: determined by total alkalinity and magnesium content using standardized EDTA. Will react with oxygen to form soluble alkoxides which could lead to incorrect assay.

Preparative Method: via a two-step process (eq 1).[3,4]

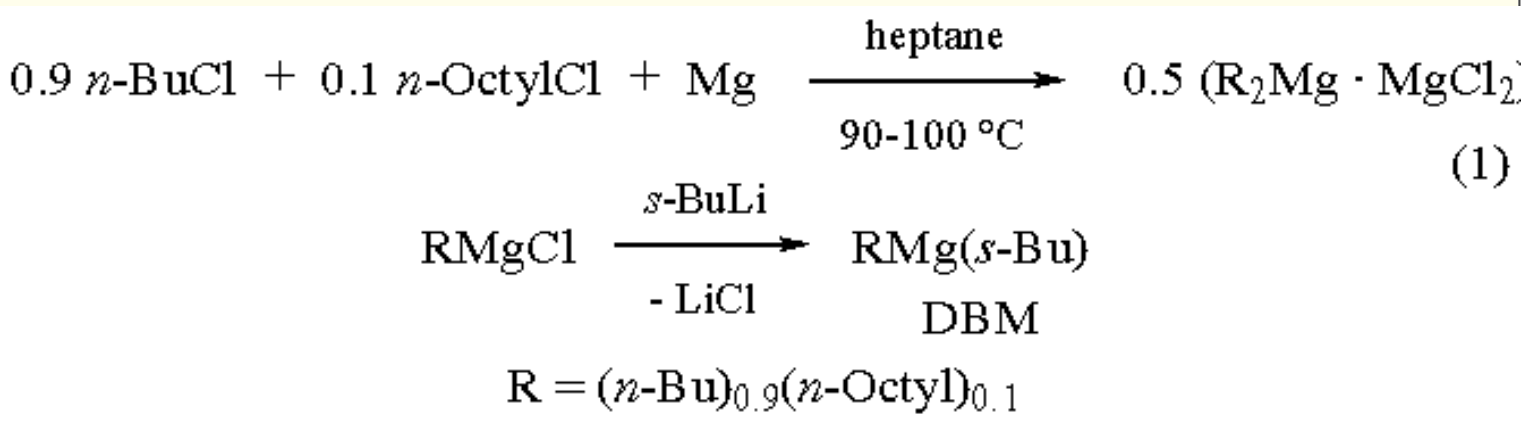

Handling, Storage, and Precautions: commercial solution is stable indefinitely if kept cool and sealed under inert atmosphere; however, isolated solids are pyrophoric. Main hazard is possibility of solvent ignition due to exothermic reaction between dibutylmagnesium and water in any form (including moist air).

Introduction.

Dibutylmagnesium is a stable and Lewis base-free organomagnesium composition. Hydrocarbon solubility of DBM results from the 1:1 ratio of *n*-alkyl to *s*-butyl groups. In synthesis, DBM is used as a metalating or magnesiating agent. Care must be taken to ensure that both equivalents of alkyl groups react because the second equivalent reacts more slowly than the first.

Magnesiation of Hydrocarbyl Substrates.

Cyclopentadiene (eq 2) and phenylacetylene (eq 3) are metalated with DBM.[1] Magnesiated substrates of cyclopentadiene undergo metathesis with transition metal halides.[5] Although sulfones[1] and α-picoline[6] derivatives can be magnesiated in heptane, toluene and triphenylmethane cannot.[1]

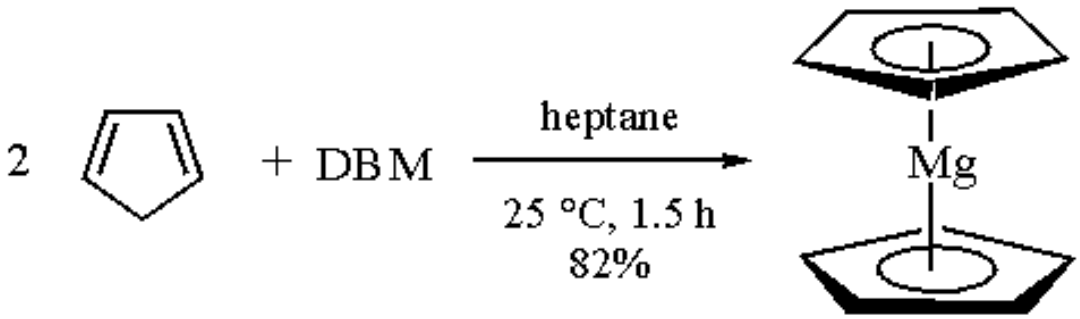

(2)

$$2\ PhC{\equiv}CH + DBM \xrightarrow[\text{25 °C, 1 h; 93\%}]{\text{heptane}} (PhC{\equiv}C)_2Mg \qquad (3)$$

Magnesiation of More Acidic Substrates.

Carboxylic acids,[7] alcohols,[5,8] and amines[5,9] can be deprotonated with DBM. Metalation of β-branched secondary amines, such as ***Diisopropylamine*** and ***2,2,6,6-Tetramethylpiperidine***, produce magnesium bis-organoamides which are hydrocarbon soluble.[9] Several magnesium organoamides have been used for magnesiation, reduction,[10] and amidation.[11]

Finally, DBM has many uses in polymerization, e.g. it provides a source of magnesium chloride[12] for Ziegler-Natta catalysts. For synthesis, anhydrous and Lewis base-free magnesium bromide is easily prepared at 30-45 °C by controlled, sparged addition of anhydrous HBr (2.01 mol) to 0.5 M DBM in heptane (2.0 mol). When the resulting slurry becomes acidic, excess HBr is removed by reflux with proper scrubbing. The solids are isolated, washed with pentane, and dried by an inert gas using an enclosed filter.

Related Reagents.

Bromomagnesium Diisopropylamide; ***t-Butylmagnesium Chloride***; ***Bromomagnesium Diethylamide***; ***Ethylmagnesium Bromide***; ***Isopropylmagnesium Bromide***; ***Methylmagnesium N-Cyclohexylisopropylamide***.

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Terry L. Rathman

FMC Corporation Lithium Division, Bessemer City, NC, USA

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(2,6-Di-*t*-butyl-4-methylphenoxy)methylaluminum Trifluoromethanesulfonate

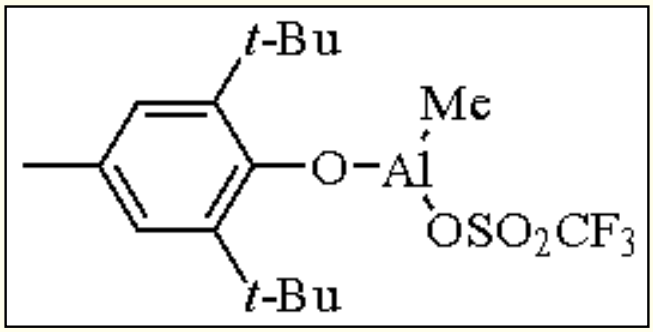

[82866-56-6] · $C_{17}H_{26}AlF_3O_4S$ · (2,6-Di-*t*-butyl-4-methylphenoxy)methylaluminum Trifluoromethanesulfonate · (MW 410.43)

(designer Lewis acid for allylic ether cleavage and its application to biogenetic-type terpene synthesis[1])

Solubility: sol toluene and CH_2Cl_2; slightly sol hexane.

Form Supplied in: prepared and used in situ.

Preparative Method: treatment of 2,6-di-*t*-butyl-4-methylphenol in dry CH_2Cl_2 with a 1-2 M hexane solution of ***Trimethylaluminum*** at -78 °C for 10 min and at 0 °C for 30 min affords ***Dimethylaluminum 2,6-Di-t-butyl-4-methylphenoxide*** which, after cooling to -78 °C, is reacted with ***Trifluoromethanesulfonic Acid*** (TfOH). Upon warming to 0 °C, gas evolution is observed to give a pink solution after further stirring at 0 °C for 30 min.[2]

Handling, Storage, and Precautions: the dry solid and solutions are flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Intramolecular Prenyl Transfer Reaction.

This modified organoaluminum reagent has been developed for effecting the intramolecular version of prenyl transfer reactions.[2] Thus reaction of isopentenyl prenyl ether with the highly oxygenophilic organoaluminum reagent in CH_2Cl_2 at 25 °C enables head-to-tail condensation, resulting in formation of the two C_{10} alcohols in a 1:3 ratio (eq 1). Conventional strong Lewis acids such as ***Titanium(IV) Chloride***, ***Tin(IV) Chloride***, and ***Boron Trifluoride Etherate***

readily attack both ethereal oxygen and alkenes in isopentenyl prenyl ether to furnish a number of side-reaction products. With weaker acids it is difficult to cleave the allylic C-O bond of isopentenyl prenyl ether. Clearly, the present oxygenophilic aluminum reagent is strong enough to coordinate to the ether oxygen, but not to double bonds. It could thus play a key role in promoting a combined C-O bond fission/rearrangement. In addition, the bulky 2,6-di-*t*-butyl-4-methylphenoxy group in the aluminum reagent may assist anchimerically the through-space interaction of the π-electron orbital of the prenyl cation via a six-membered transition state.

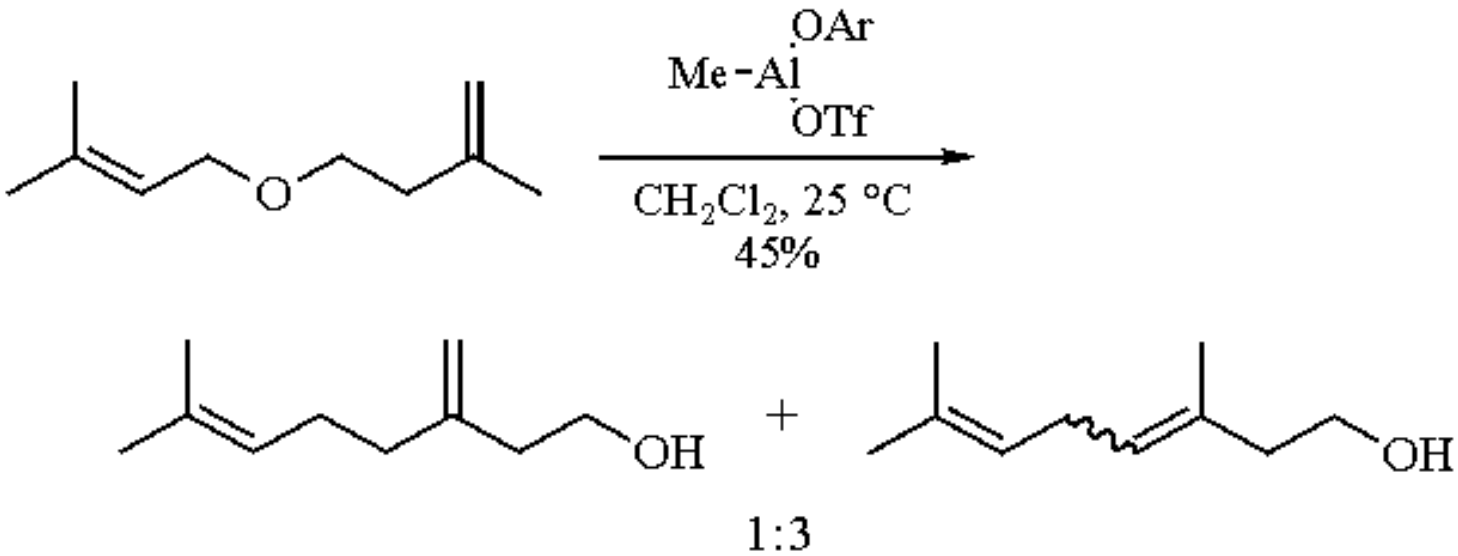

(1)

Ar = 2,6-di-*t*-butyl-4-methylphenyl

The organoaluminum reagent can also effect the biogenetic-type head-to-head condensation of C_5 units. Thus treatment of diprenyl ether with the reagent at 0 °C for 1.5 h affords the C_{10} alcohol lavandulol exclusively, in 33% yield (eq 2). This method provides a very simple route to lavandulol, hitherto accessible only by multi-step synthesis.[3]

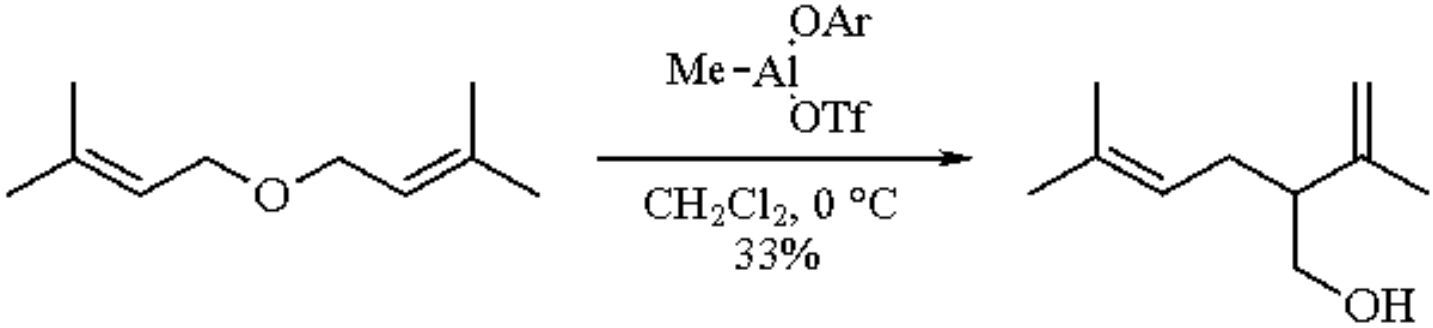

(2)

Asymmetric Cyclization.

Biogenetic-type asymmetric cyclization of (*R*)-(+)-binaphthol mononeryl ether to optically active limonene can be realized using this type of reagent in $CFCl_3$ at -130 °C (eq 3). Among various oxygenophilic organoaluminum triflates examined, (2,4,6-tri-*t*-butylphenoxy)isobutylaluminum trifluoromethanesulfonate gives the best result.[4]

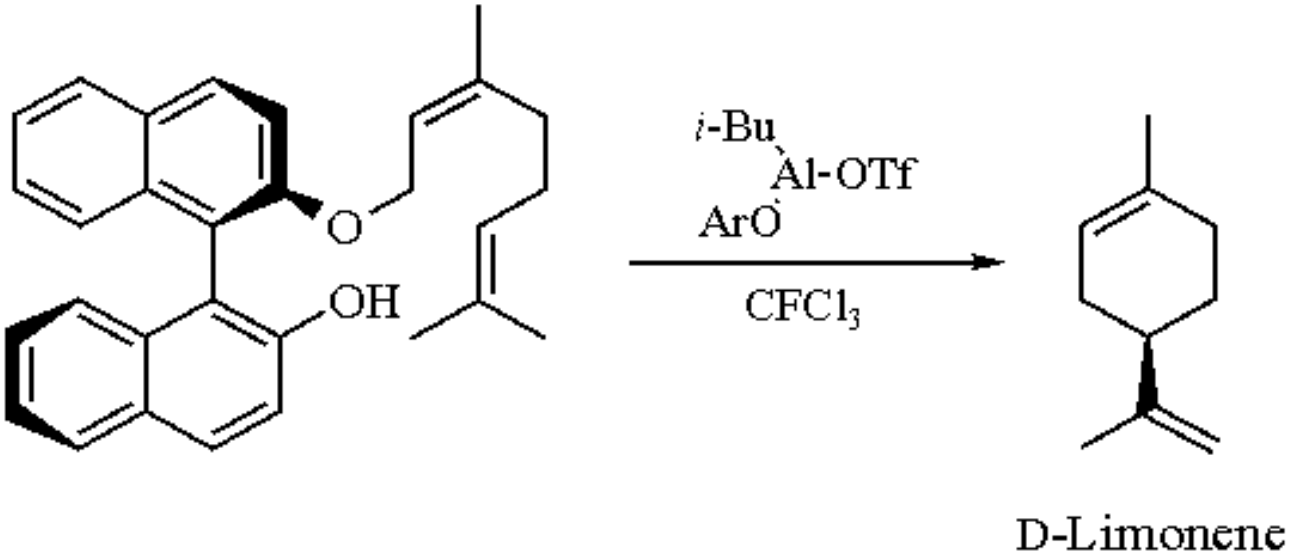

(3)

i-Bu_2OTf	39% ee
i-$BuAl(OTf)_2$	40% ee

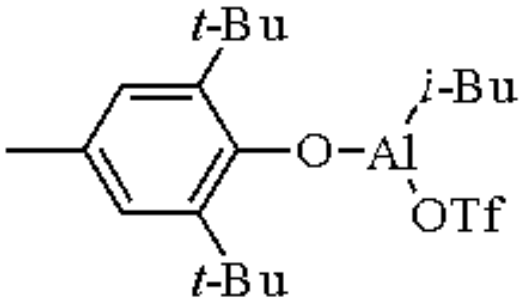

64% ee

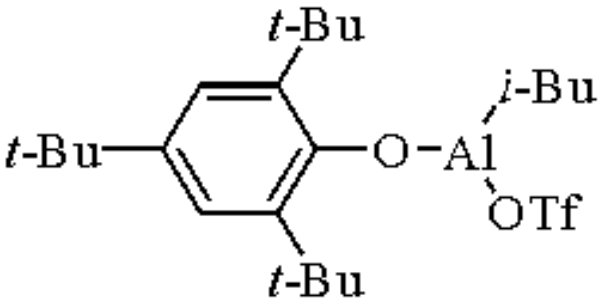

77% ee

Asymmetric cyclization of (*R*)-(+)-binaphthol (*Z*,*Z*)-monofarnesyl ether can be executed equally well with this aluminum reagent, giving (+)-β-bisabolene in 76% ee (eq 4).

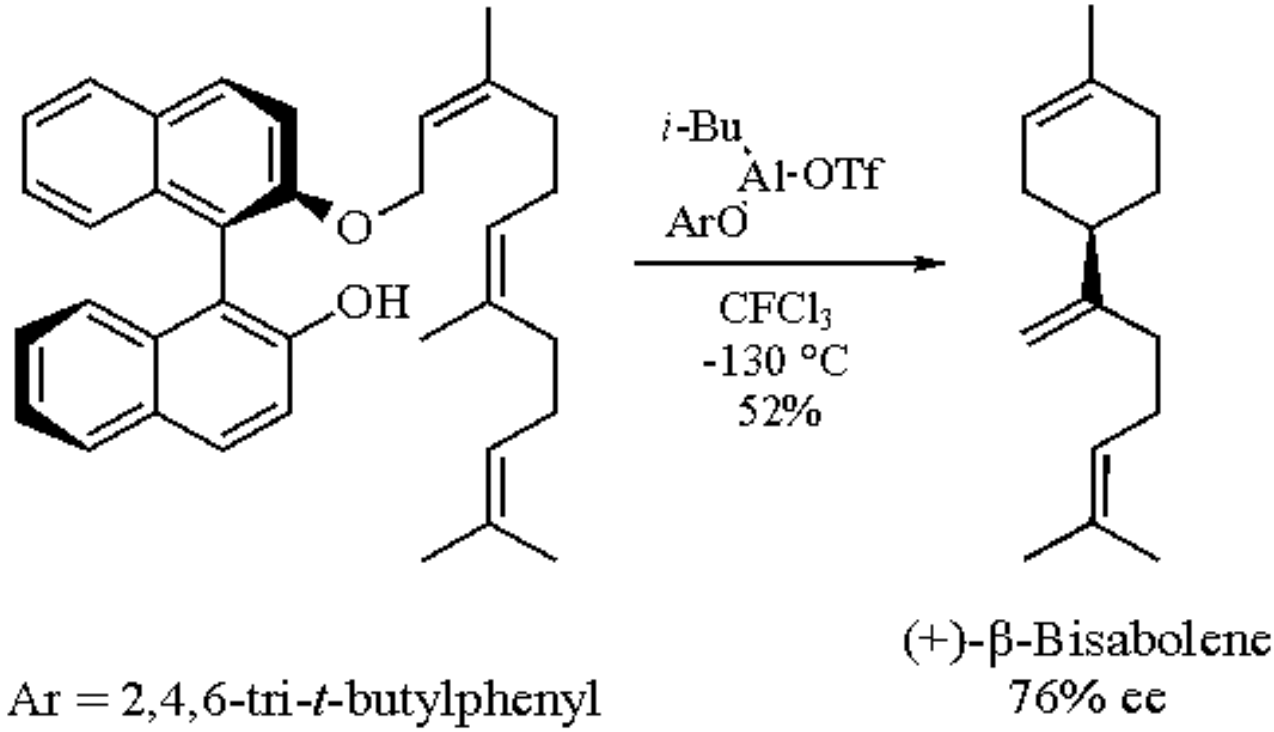

(4)

Polymerization.

The aluminum reagent possesses high activity in both cationic polymerization and electrophilic reactions.[5]

---

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Di-*t*-butylmethylsilyl Trifluoromethanesulfonate[1]

t-$Bu_2MeSiOSO_2CF_3$

[105866-92-0] · $C_{10}H_{21}F_3O_3SSi$ · Di-*t*-butylmethylsilyl Trifluoromethanesulfonate · (MW 306.42)

(bulky trialkylsilylating agent; useful for preparation of hydrolytically stable, sterically congested enol silyl ethers and silyl carboxylic esters; t-Bu_2MeSi- also serves as a reactivity control element)

Alternate Name: DTBMSOTf.

Physical Data: colorless, water-sensitive liquid; bp 63-65 °C/1.5 mmHg.

Solubility: sol THF, Et_2O.

Form Supplied in: not available commercially.

Preparative Method: addition of ***Trifluoromethanesulfonic Acid*** (TfOH) to neat di-*t*-butylmethylsilane[2] at 4 °C, stirring 16 h at 20 °C, followed by distillation in vacuo.[1]

Purification: vacuum distillation through a Vigreux column.

Handling, Storage, and Precautions: stable in the absence of moisture. Fumes in moist air, producing TfOH by hydrolysis. Owing to the high corrosivity of TfOH, breathing the vapor or the fumes produced by reaction with moist air should be avoided. Use in a fume hood.

Enol Silylation.

Di-*t*-Butylmethylsilyl triflate converts a hydroxymethylene ketone into the corresponding DTBMS enol silyl ether (eq 1).[1] DTBMS ethers were prepared previously by the reaction of alcohols with DTBMS perchlorate.[2] The bulky substituents on silicon suppress 1,4-addition of MeLi to the DTBMS ethers of hydroxymethylene ketones. Thus the proportion of 1,2-adduct versus 1,4-adduct improves as the steric bulk of the silyl substituents increases from trimethylsilyl (TMS) to *t*-butyldimethylsilyl (TBDMS) to DTBMS enol ethers (eq 2).[1] Dehydration in conjunction with hydrolysis of the DTBMS enol ether group delivers an α,β-unsaturated aldehyde in excellent yield (eq 3).

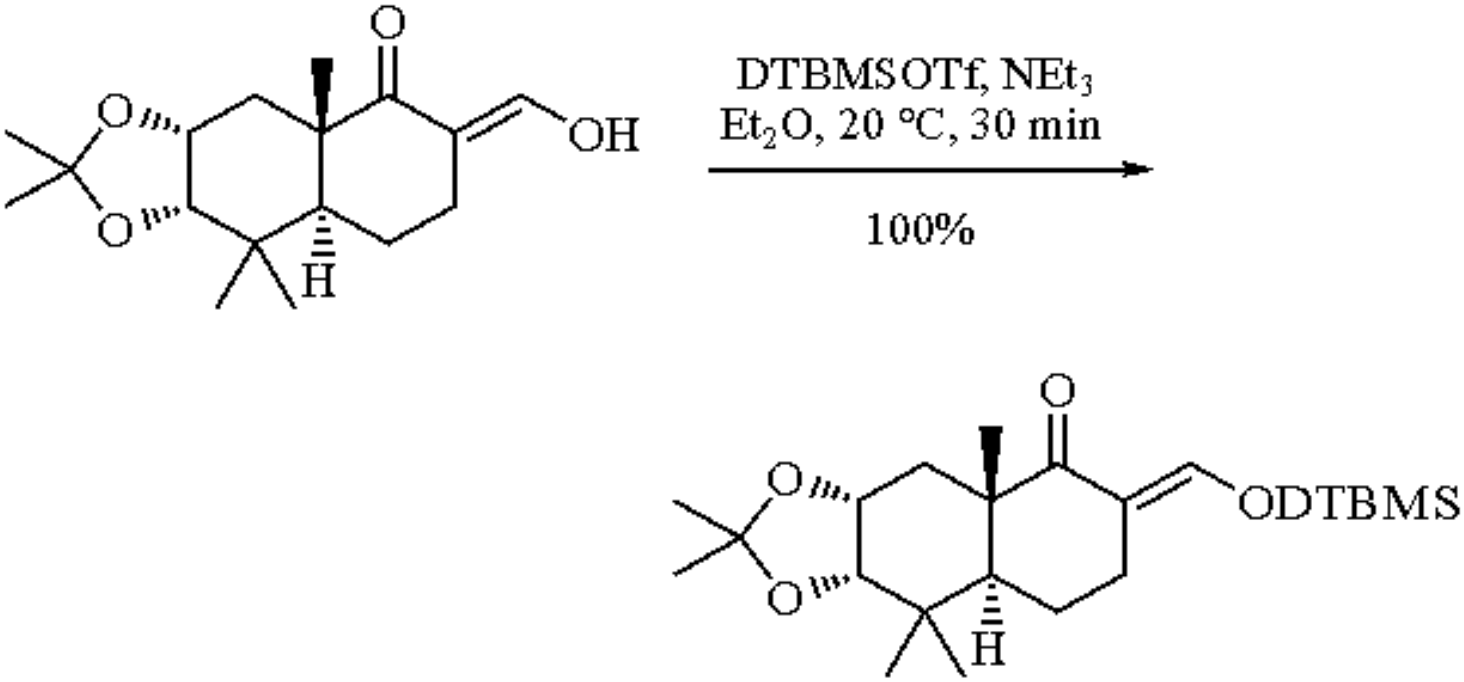

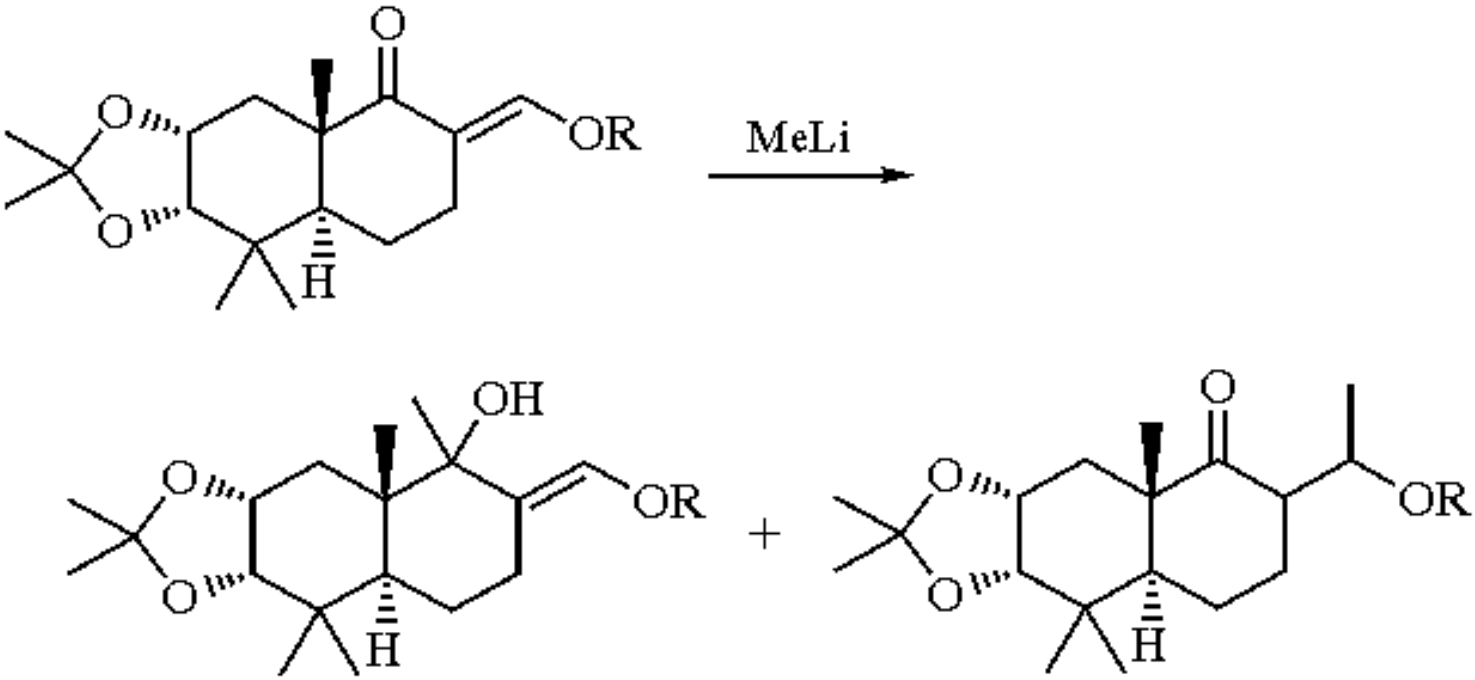

R = TMS	59%	39%
R = TBDMS	70%	25%
R = DTBMS	90%	10%

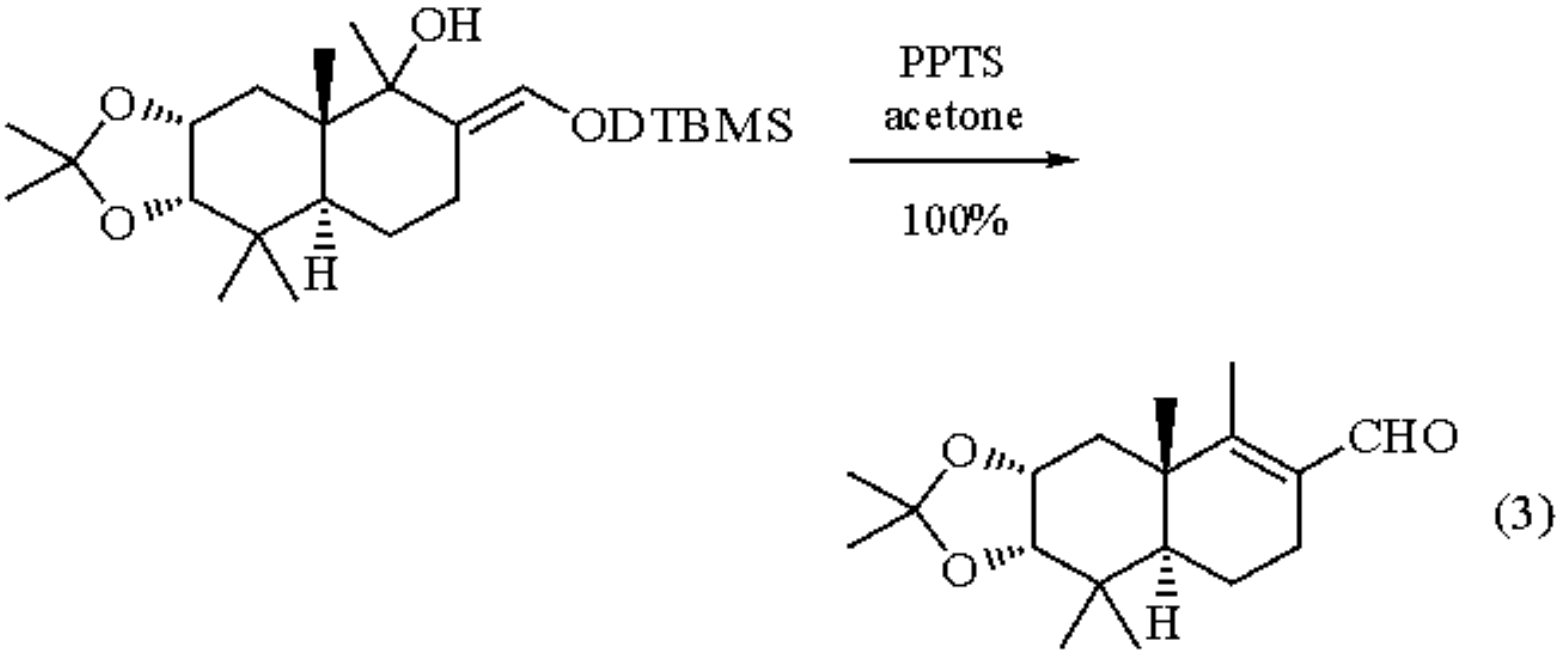

TMSCl accelerates the conjugate addition of Grignard reagents catalyzed by copper salts.[3] Therefore the influence of silyl substituents on the reaction of 2-cyclohexenone with ***Ethylmagnesium Bromide*** in the presence of a chiral nonracemic copper catalyst was examined (eq 4).[4] The anticipated silyl enol ether intermediate was rapidly hydrolyzed in the workup, delivering optically active 3-ethylcyclohexanone. The bulky silyl reagent, DTBMSOTf, afforded better enantioselectivities than TMSCl in the addition of EtMgBr to cyclohexenone (eq 4). However, for the reaction with *n*-BuMgBr, enantioselectivities obtained with TMSCl, DTBMSOTf, and Ph_2(*t*-Bu)SiCl were 51% ee, 40% ee and 78% ee, respectively. The ability of the silyl reagent structure to influence the enantioselectivity suggests that a silylated species is involved in the rate-determining step of the conjugate addition.

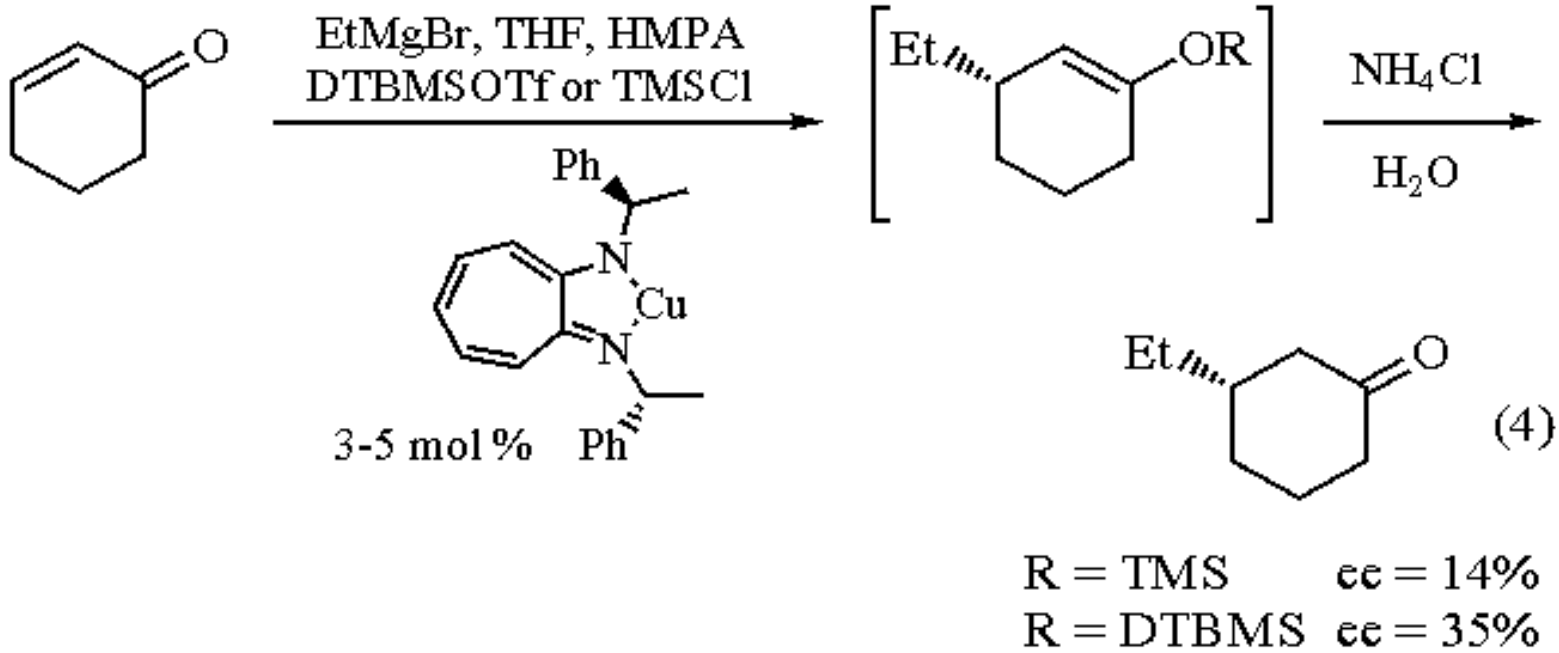

Silyl Esterification.

Carboxylic acids are converted into DTBMS esters by treatment with DTBMSOTf and ***Triethylamine*** in THF (eq 5). Although hydroxy carboxylic acids can be selectively converted to hydroxy silyl carboxylic esters (eq 5), the extraordinary stability of DTBMS esters allows an alternative route. Thus silyl esterification of a tetrahydropyranyloxy carboxylic acid followed by selective removal of the THP ether protecting group by treatment with ***Pyridinium p-Toluenesulfonate*** in ethanol[5] delivers a hydroxy DTBMS ester (eq 6).[1]

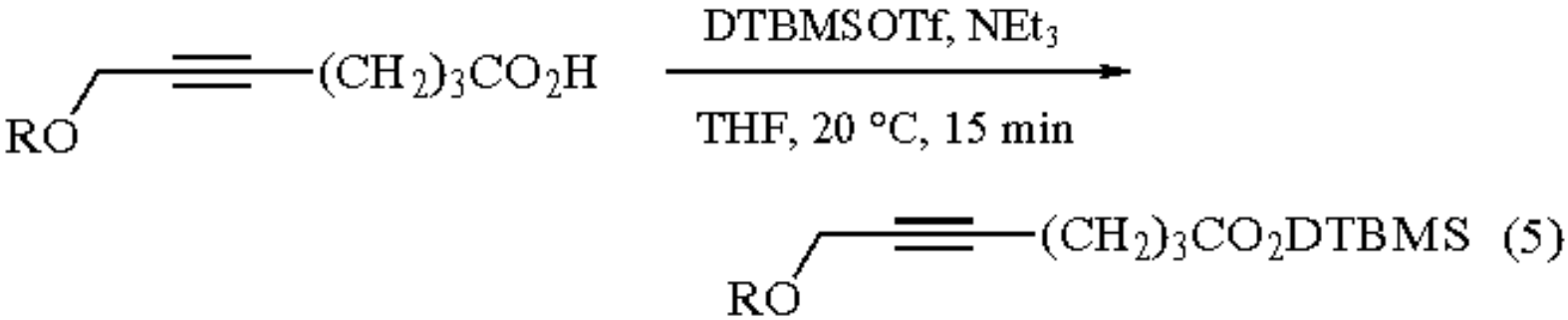

R = H, 44%
R = THP, 92%

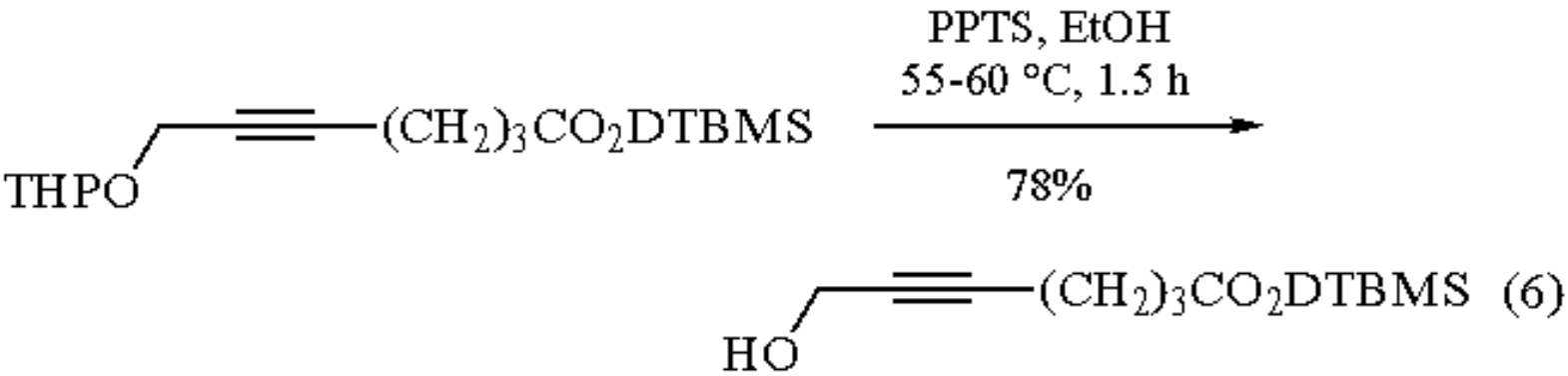

The bulky substituents on silicon confer resistance to nucleophilic attack at the carbonyl group of DTBMS esters. Thus selective reduction of a butyrolactone in the presence of a *t*-butyl or DTBMS ester gives a much better yield than the corresponding methyl ester (eq 7).[1,6]

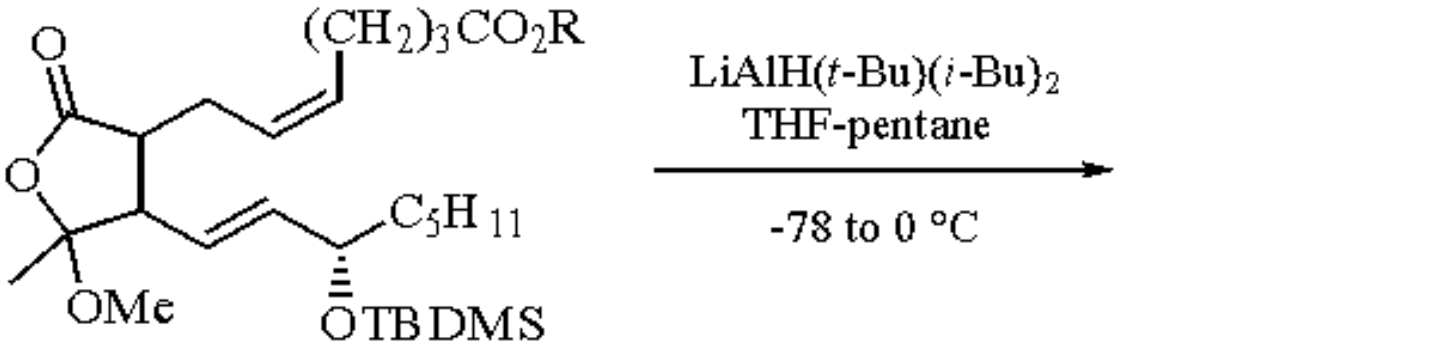

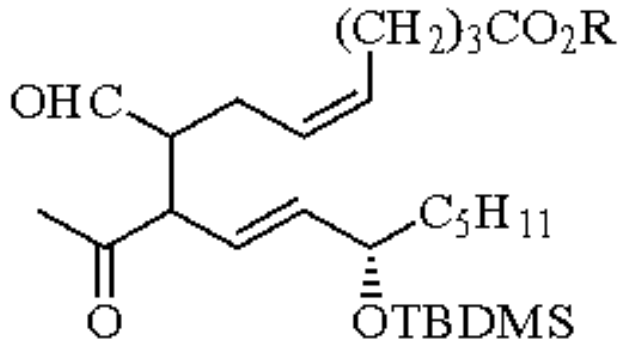

(7)

R = Me, 20%
R = *t*-Bu, 50%
R = DTBMS, 49%

Removal of the DTBMS ester protecting group under mild acidic conditions is achieved in better yield than removal of the *t*-butyl group, but in neither case can deprotection be accomplished without concomitant dehydration (eq 8).[1,6]

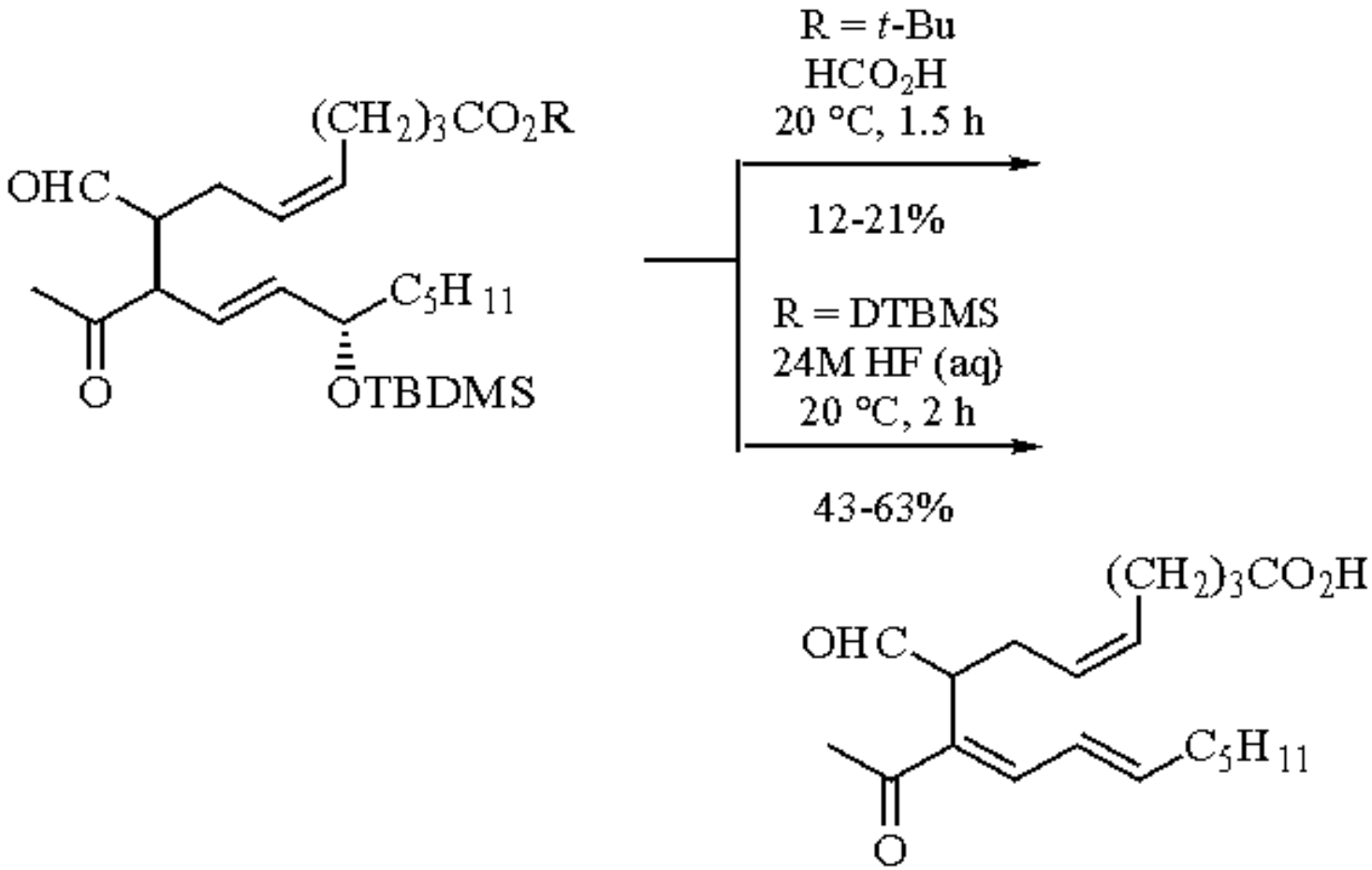

(8)

Conversion of DTBMS esters to carboxylic acids can also be achieved by treatment with ***Tetra-n-butylammonium Fluoride*** in wet THF. Under these conditions, both TBDMS ether and DTBMS ester protecting groups are removed (eq 9).[1]

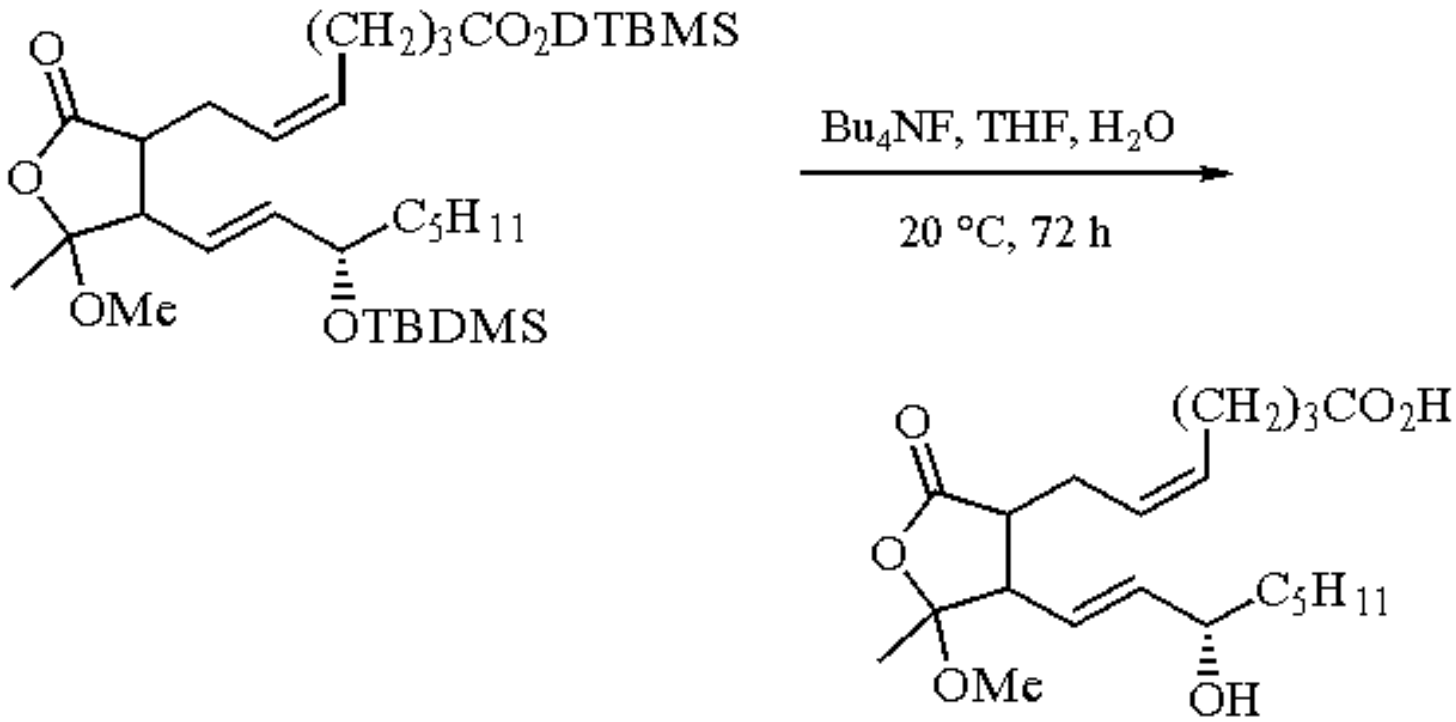

(9)

1. Bhide, R. S.; Levison, B. S.; Sharma, R. B.; Ghosh, S.; Salomon, R. G. *TL* **1986**, *27*, 671.
2. Barton, T. J.; Tully, C. R. *JOC* **1978**, *43*, 3649.
3. Corey, E. J.; Boaz, N. W. *TL* **1985**, *26*, 6015.
4. Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *OM* **1990**, *9*, 3178.
5. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *JOC* **1977**, *42*, 3772.
6. Levison, B. S.; Miller, D. B.; Salomon, R. G. *TL* **1984**, *25*, 4633.

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1,1-Di-*t*-butyl Peroxide[1-3]

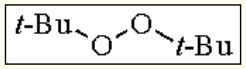

[110-05-4] · $C_8H_{18}O_2$ · 1,1-Di-*t*-butyl Peroxide · (MW 146.23)

(radical initiator, initiates anti-Markovnikov addition of HX to alkenes (X = halogen, S, Si, P);[4] initiates, by H-abstraction, the following radical reactions of compounds with an activated C-H bond: (a) dehydrodimerization;[5,6] (b) intra-[7] and intermolecular additions[3,8,9] to alkenes, alkynes, and carbonyl compounds; (c) addition to protonated heterocycles;[10,11] (d) fragmentation;[12,13] mediates alcohol deoxygenation via silane reduction of esters[14] and chlorohydrin formation by reaction with $TiCl_4$ and alkene[15])

Alternate Names: *t*-butyl peroxide; DTBP.

Physical Data: bp 109 °C/760 mmHg, 63 °C/119 mmHg; *d* 0.796 g cm^{-3}.

Solubility: freely soluble in organic solvents.

Form Supplied in: clear colorless liquid.

Analysis of Reagent Purity: Kropf describes various procedures (chemical and chromatographic) for the analysis of peroxides.[1b]

Handling, Storage, and Precautions: explosive; harmful if exposed by inhalation or skin contact; strong oxidizer; flammable; keep away from heat. Caution: All experiments involving peroxy compounds should be carried out behind a safety shield. Use in a fume hood.

General Discussion.

Di-*t*-butyl peroxide is a commonly used initator for radical reactions. It undergoes facile unimolecular thermal decomposition to the *t*-butoxy radical, which in turn fragments to a methyl radical and acetone. The half-lives of DTBP are approximately 3 h at 140 °C and 24 h at 120 °C.[2] Accordingly, radical reactions that proceed at 110-150 °C can be initiated by DTBP, since a steady concentration of the initiating radical would be available for the reactions. Alkoxy radicals are electrophilic and they initiate the reaction by abstraction of a C-H bond α to a heteroatom. The resultant radicals undergo a variety of carbon-carbon bond forming reactions, including polymerization.[16] Scheme 1 shows the primary steps involved in useful C-C bond forming reactions. Use of precursors having an activated C-H bond is advantageous for this purpose, since the chain-transfer step also produces the primary adducts along with the propagating radical, which is also one of the reactants. However, because of the high bond energy associated with the C-H bond, these types of compound are poor H-atom donors. Chain lengths of these reactions are generally short; the use of a large excess of the C-H precursor and a steady supply of the initiator are important for success in many instances.

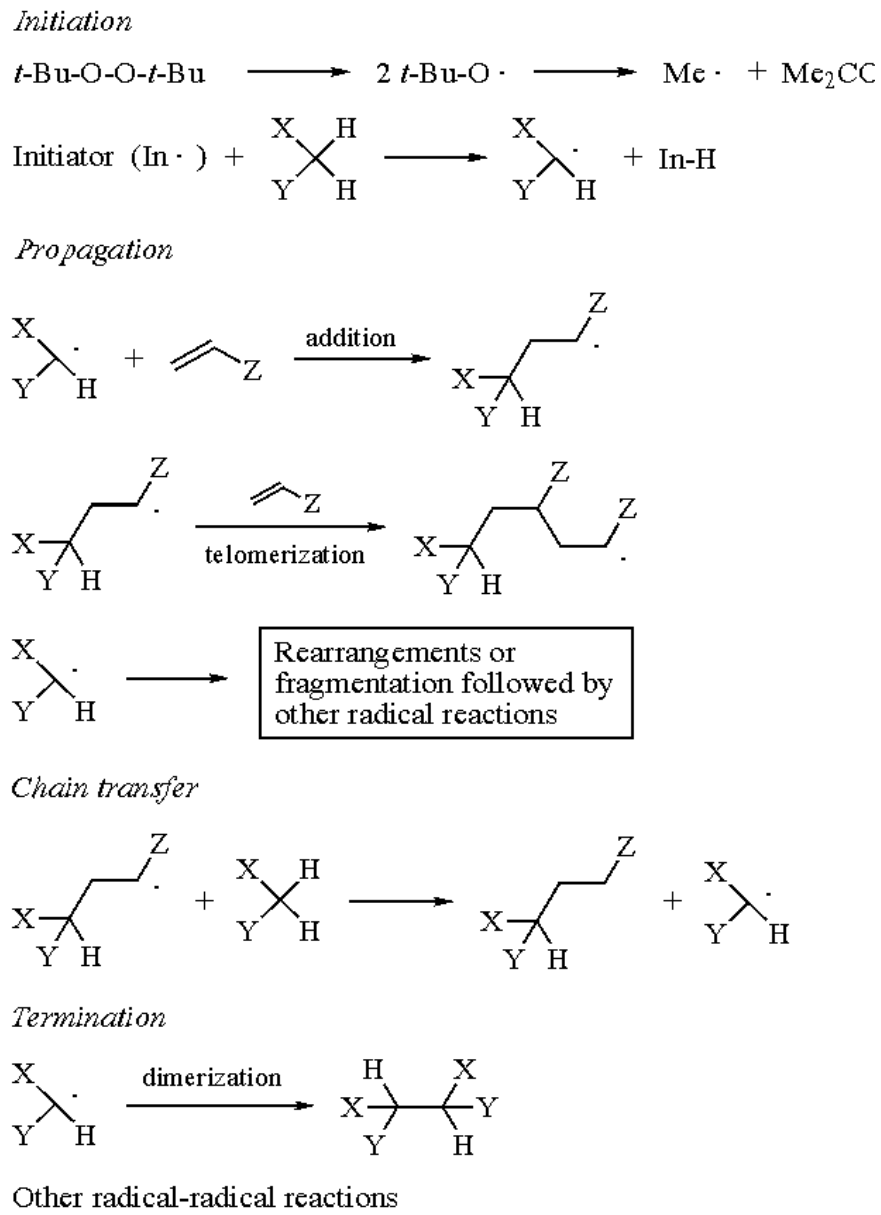

Scheme 1 Primary radical processes

Abstractions of H adjacent to ethers and amines are important examples, the heteroatom adjacent to the site of reaction providing a favorable polar contribution to the transition state for abstraction by the electrophilic oxy radical, and providing stabilization for the product radical. Examples of the use of DTBP in this way include the study of anomeric radicals by Ingold and co-workers (eq 1),[17] and a synthesis of substituted tetrahydrofurans (eq 2).[18]

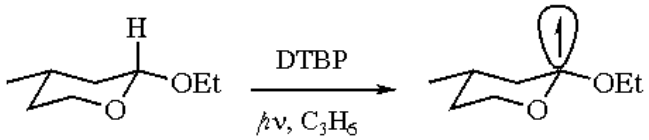

(1)

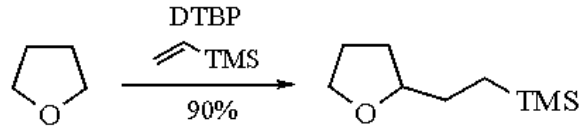

(2)

In the first case the radicals were generated by UV photolysis of the reaction mixture in the cavity of the NMR instrument used for studying the configuration at the anomeric center. By contrast, the substitution of THF was carried out under more typical thermal conditions by heating in a sealed autoclave. In this study it was found that similar substitution of tetrahydro-2-furanone could also be carried out, although generally in modest yield.

Hydrogen atom abstraction from amino acid derivatives is especially facile, since the resulting captodative radicals are highly stabilized. Treatment of an alanine derivative with DTBP led to a mixture of an α-methylated product and a diastereomeric mixture of dimers (eq 3).[19] The first product is formed as a result of radical combination between the captodative amino acid radical and a methyl radical formed by scission of a *t*-butoxy radical. Substitution of protected dipeptides can be carried out using this approach, by including an alkylating agent such as toluene in the reaction medium (eq 4).[20] The reaction relies on the action of biacetyl (***2,3-Butanedione***) as a photoinitiator, hydrogen atom abstraction occurring preferentially at glycine residues.

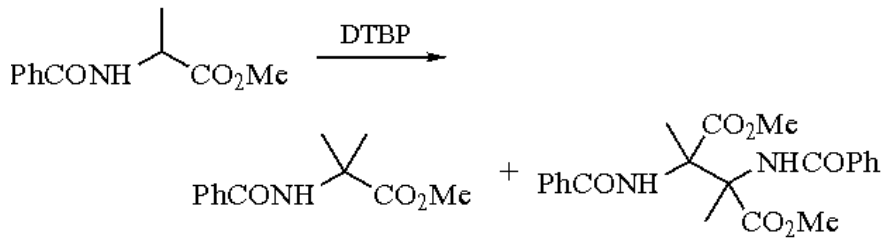

(3)

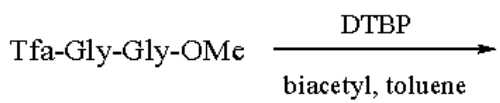

Tfa-Phe-Gly-OMe + Tfa-Gly-Phe-OMe + Tfa-Phe-Phe-OMe (4)

30% 29% 10%

Reactions involving phosphorus centered radicals derived from diethyl hydrogen phosphite are also initiated by DTBP under thermal conditions (eq 5).[21] Under modified reaction conditions, diphosphonate products, resulting from further addition to the initially formed unsaturated phosphonate, were also observed.

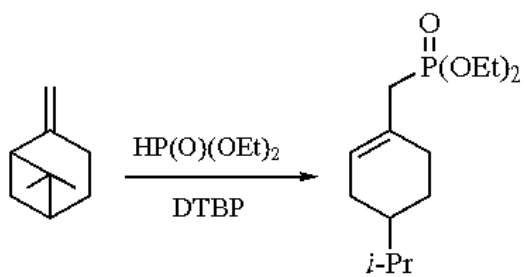

(5)

Typical reactions of radicals with alkene acceptors, initiated by DTBP and used in synthesis, are listed below.

Intermolecular Additions.

The radical chain nature and the anti-Markovnikov regiochemistry of radical addition reactions were originally discovered by Kharasch in the 1930s. Since then, these reactions have been used extensively for the formation of carbon-carbon[3,8] and carbon-heteroatom[4] bonds. Substrates that are suitable for the former include polyhalomethanes, alcohols, ethers, esters, amides, and amines. The prototypical examples compiled in Table 1 are from reviews by Walling[8] and Ghosez et al.[3]

Table 1 Intermolecular C-C Bond Forming Reactions via Radicals

Precursor	Alkene	Reaction conditions	Product(s)
EtOH	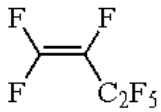	DTBP, 120 °C, 48 h	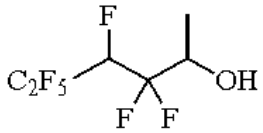 60%
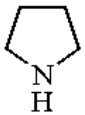	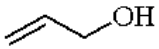	DTBP, 120 °C, 48 h	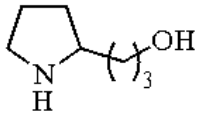 54%
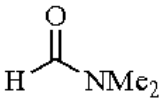	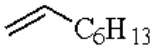	DTBP, 132 °C, 18 h	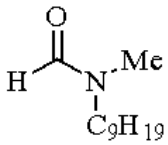 + 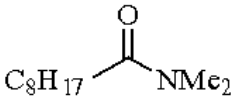 22% 34%
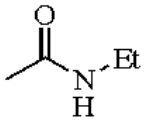	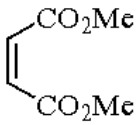	DTBP, 0.01 equiv, 6 h	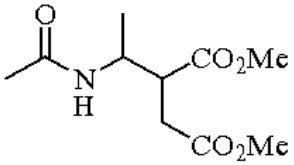 87%
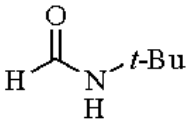	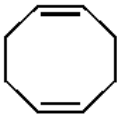	DTBP, 137 °C, 24 h	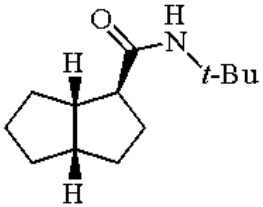
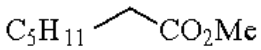	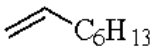	DTBP, 150 °C	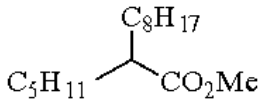 56%
			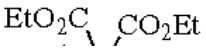

1,1-Di-t-butyl Peroxide

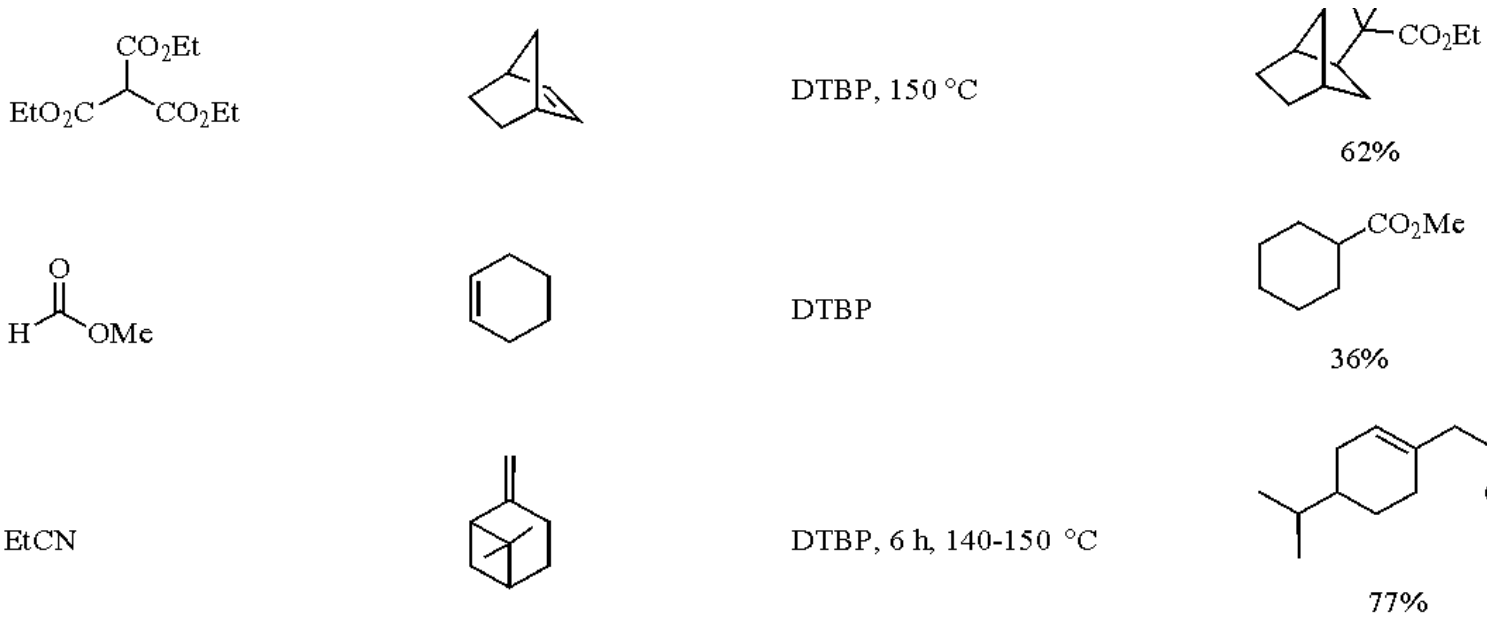

Among the other notable applications are addition of the radical from diethyl malonate to alkynes and alkenes (eq 6),[9] addition of a 1,3-dioxalane-derived radical to formaldehyde (eq 7),[22] and addition of *s*-alcohols to alkenes (eq 8).[23] Novel radical mediated alkylations of a dipeptide makes use of DTBP as an initator (eqs 9 and 10).[20]

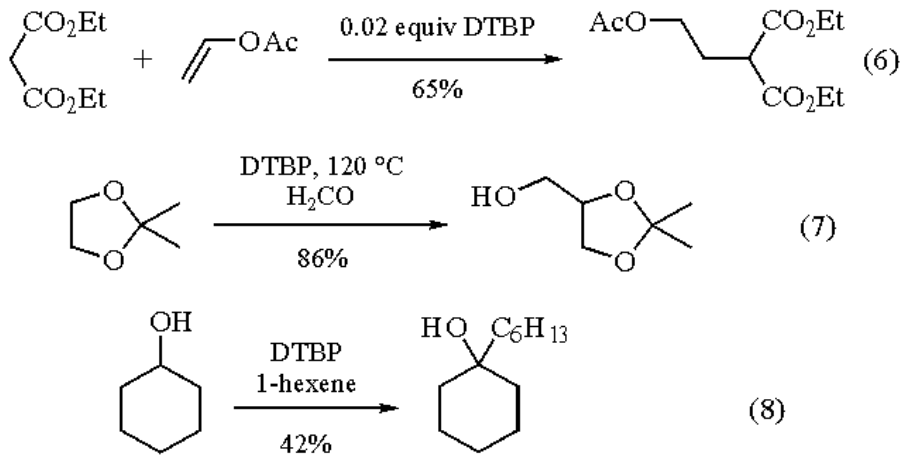

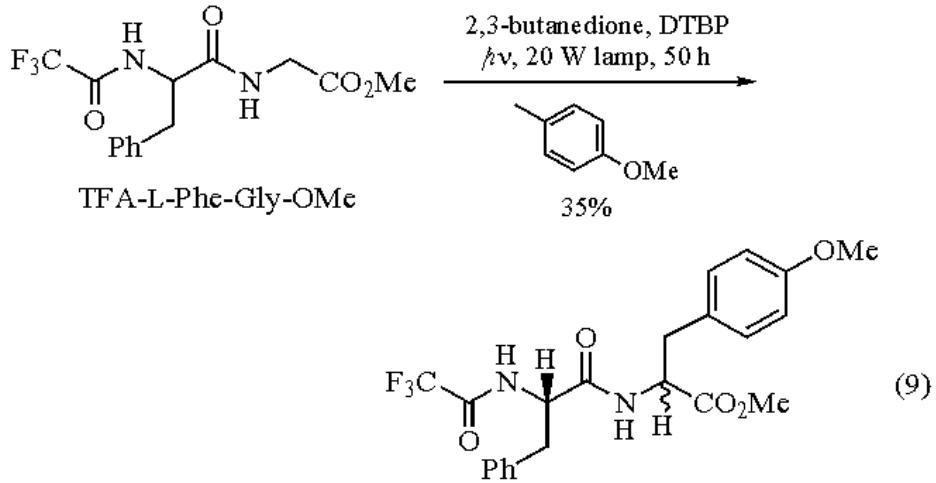

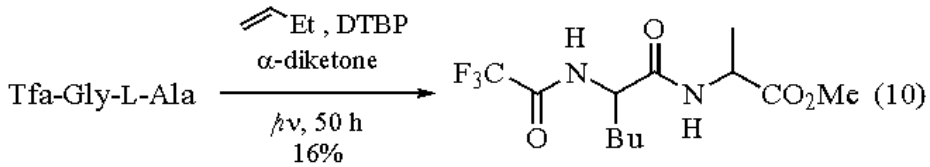

Intramolecular Addition Reactions.

Early studies by Julia and his co-workers on the cyclization of hexenyl (eq 11) and heptenyl radicals played a key role in the development of radical synthetic methodology, and many of the earlier studies were conducted with peroxides as initiators.[7] Cyclization of stabilized radicals such an malonates and cyanoesters are reversible, and the course of ring closure can be controlled by the appropriate choice of precursors and reaction conditions. Thus the cyanoacetate in eq 12[24] with 2 equiv of DTBP gives the products shown, whereas under kinetic conditions, using the tin hydride method, a different product distribution is obtained (eq 13).

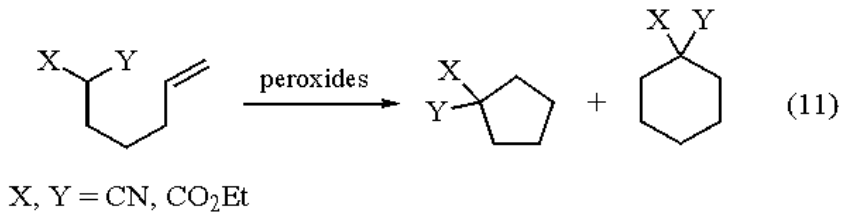

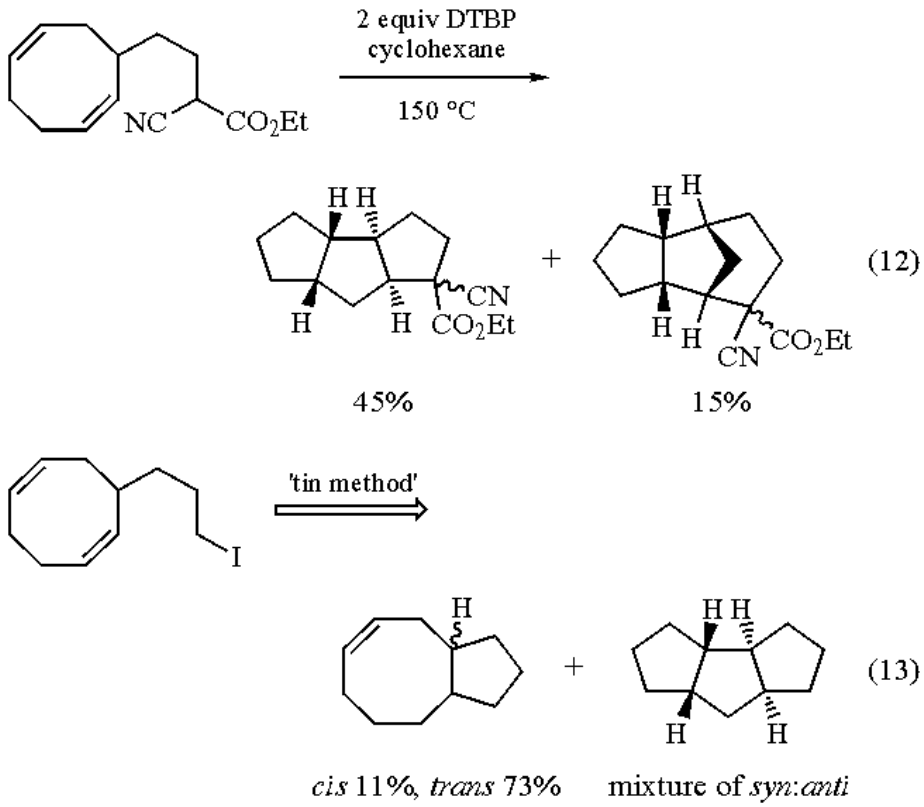

Dehydrodimerization.

Radicals that are stabilized by an α-heteroatom, when produced in sufficiently high concentrations, will undergo dimerization. Use of DTBP is particularly effective for dehydrodimerizations of polyhaloalkanes,[25] alcohols, ethers,[5,25] amides, and esters (Table 2).[5,6] Viehe, who pioneered this work, has used α-*t*-butylmercaptoacrylonitrile as a trapping agent for the above mentioned C-centered radicals.[26] The adduct radical is stabilized by captodative effects[27] and do not participate in further chain transfer chemistry. These radicals undergo ready dimerization, thereby providing a facile route to compounds with a four-carbon bridge between the original radicals (eq 14).

Table 2 Dimerization of Radicals

Precursor	Reaction conditions	Products
$PhCH_2OH$	DTBP, 140 °C, 10 h	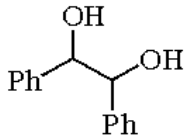 69%
	DTBP, 135 °C	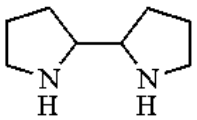

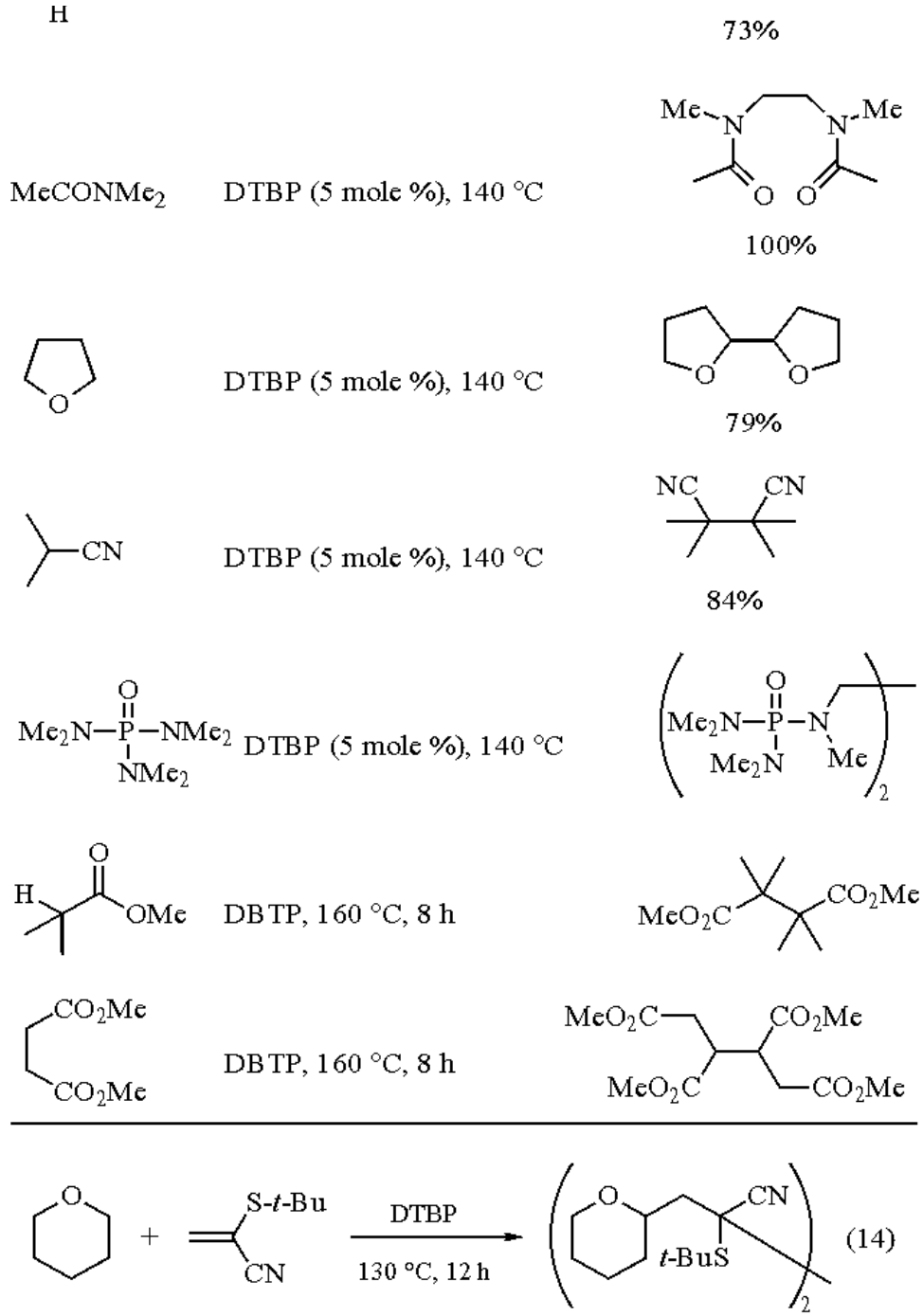

Fragmentation Reactions.

The tetrahydrofuranyl radical undergoes fragmentation at 140 °C to give an open-chain acyl radical. The THF radical as well as the rearranged radical are trapped by excess of alkene (eq 15).[12] Benzylidene acetals undergo similar fragmentation to give a benzoate ester (eq 16).[13]

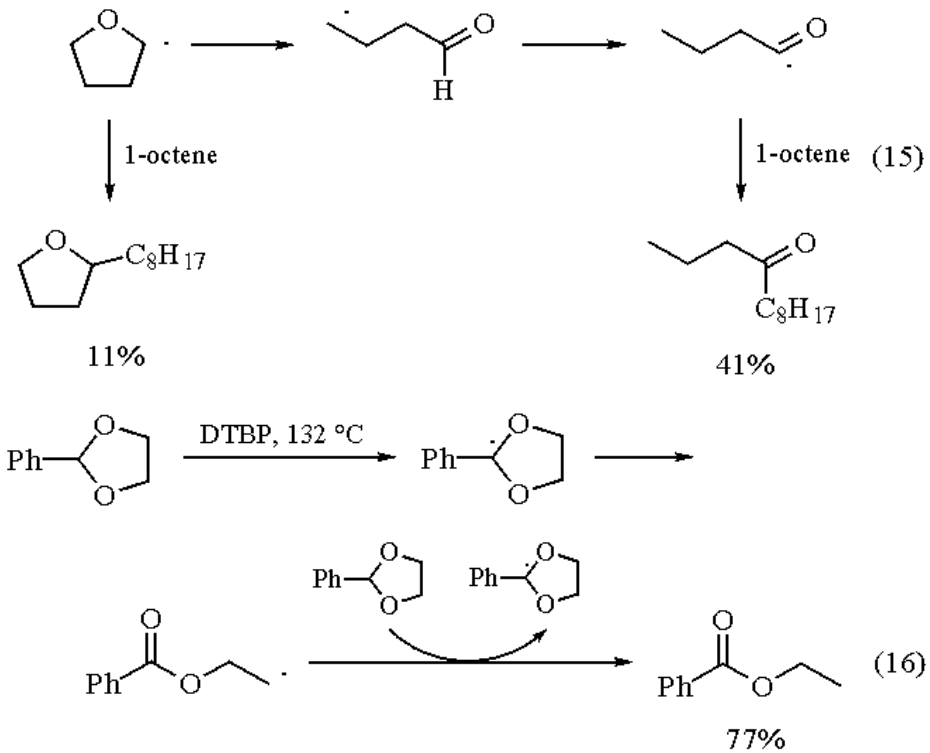

Homolytic Substitution Reactions.

Alkylation of electron-deficient heteroaromatic compounds developed by Minisci and co-workers is a powerful method for their functionalization.[10,28] Three examples are illustrated in eqs 17, 18 and 19. The product distribution often depends on the oxidant used. For example, as shown in eq 19, DTBP gives a 1:2 mixture of two products (A and B) upon alkylation of 4-methylquinoline. ***t-Butyl Hydroperoxide*** and Fe^{II} salts give almost exclusively the dimethylaminocarbonyl radical adduct A (eq 19).[11]

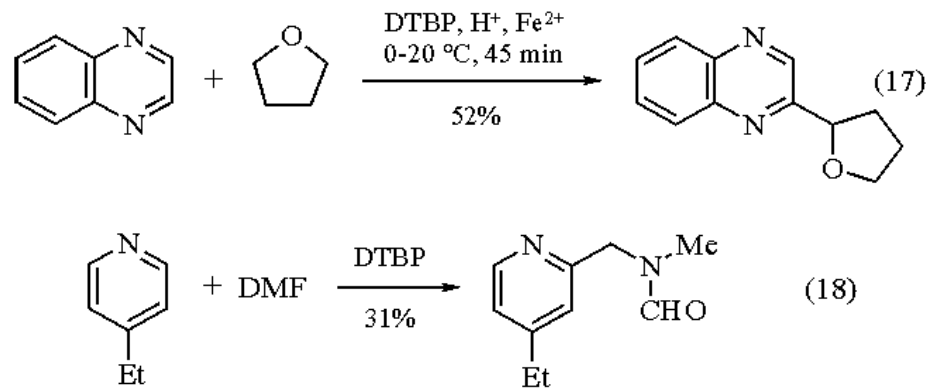

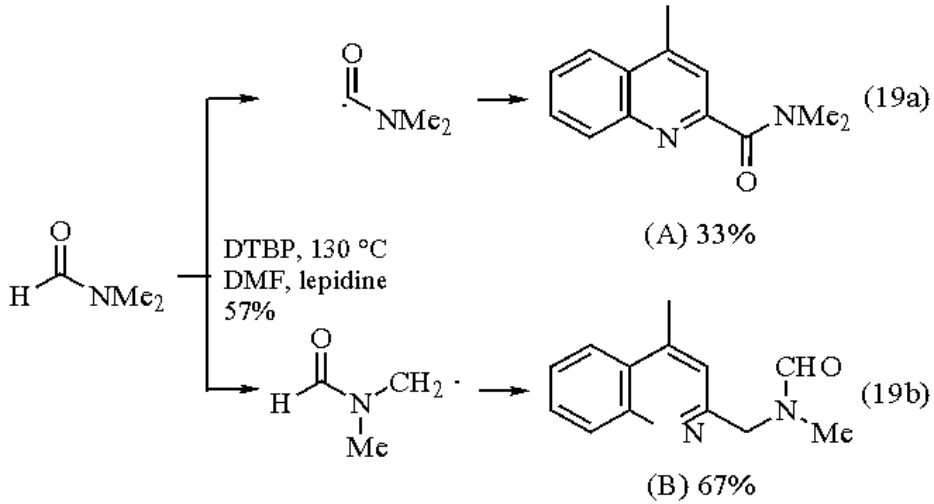

Miscellaneous Reactions.

DTBP has been used as a hydrosilylation catalyst,[4] even though catalysis[29] by transition metal complexes have largely replaced the radical methods. DTBP has also been used as an oxidant for silanes.[30,31] Other applications of DTBP include its use as an initiator for radical mediated deoxygenation of alcohols via the corresponding chloroformate[32] or acetate ester[14] (eq 20). It has also been used as an initiator for the reduction of lactones and esters to ethers using ***Trichlorosilane***.[33] In a rare example of a nonradical reaction, DTBP has been used in conjunction with ***Titanium(IV) Chloride*** for the formation of chlorohydrin from alkenes (eq 21).[15]

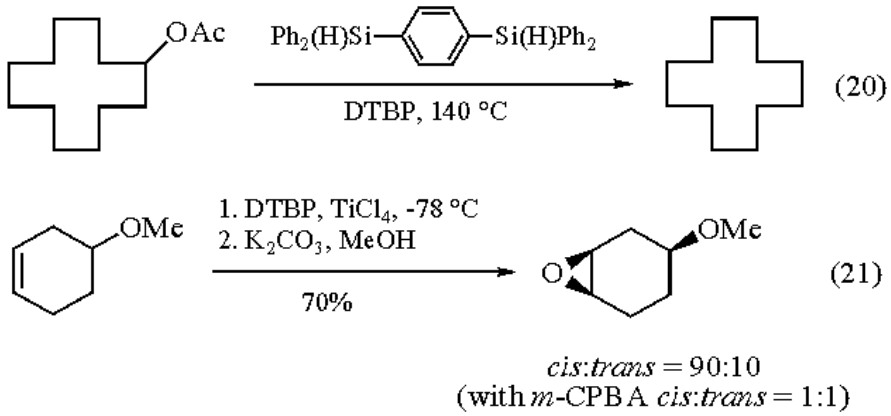

The carbonylation reaction of disulfides, catalyzed by ***Octacarbonyldicobalt***, normally leads to the production of thioesters. However, in the presence of DTBP and in the absence of CO the reaction takes an alternative course, with benzyl disulfides undergoing clean desulfurization to give the corresponding sulfides (eq 22).[34]

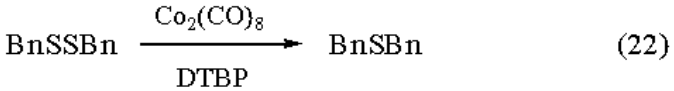

DTBP has also been employed in palladium catalyzed carbonylation reactions. Depending on the type of catalyst used, or on the reaction conditions, the carbonylation reaction of primary amines can be used to prepare either ureas (eq 23)[35] or carbamate esters (eq 24).[36]

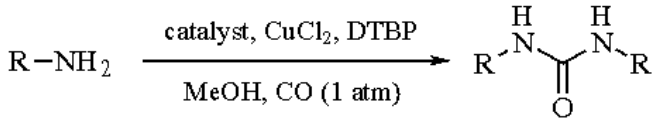

(23)

catalyst = montmorillonite(bipyridyl)palladium(II) acetate

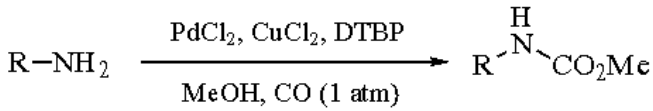

(24)

Using the ***Palladium(II) Chloride*** system, the reaction involving secondary amines was found to give mixtures of carbamate ester and an oxamate ester resulting from double carbonylation.[36] Analogous carbonylations of alcohols can lead to a range of products, including dialkyl carbonates, oxalates, and succinates.[37]

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Di-*t*-butyl Peroxyoxalate[1]

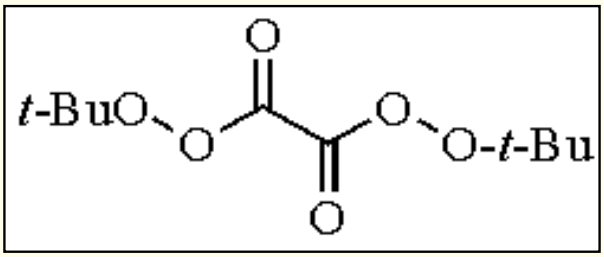

[1876-22-8] · $C_{10}H_{18}O_6$ · Di-*t*-butyl Peroxyoxalate · (MW 234.25)

(useful for clean, low-temperature generation of *t*-butoxyl radicals;[1] induces cyclization of alkenyl hydroperoxides;[2] used in radical-trapping experiments,[3] and as initiator for alkene autoxidation[4] and polymerization[5])

Alternate Name: DBPO.

Physical Data: white crystals, mp 50.5-51.5 °C (dec).[1a]

Solubility: sol most organic solvents (e.g. CH_2Cl_2, CCl_4, PhH, PhCl, and pentane).

Analysis of Reagent Purity: NMR (C_6D_6, δ) ^{1}H: 1.12 (s), ^{13}C: 25.7, 85.4 (no signal is observed for the carbonyl carbon);[6] iodometric titration.[1a]

Preparative Methods: readily obtained by reaction of ***Oxalyl Chloride*** with *t*-butyl hydroperoxide and pyridine in anhydrous pentane.[1a,7] It is recommended to collect the crystals of DBPO on a precooled filter (-78 °C).

Handling, Storage, and Precautions: the preparation and manipulation of DBPO must be conducted behind a safety shield. Tongs, gloves, and safety masks should be used throughout every operation. DBPO is highly sensitive to scratching or shock especially when the crystals are dry.[1a] In one instance, a violent explosion occurred during the transfer of solvent-wetted, recrystallized DBPO from one glass vessel to another.[4a,b] Consistent with the risk of explosion, it is recommended to use the reagent as prepared. If it must be stored, it should be kept in a flask under Ar at -20 °C or below. Ethers should not be used as solvents since they are known to accelerate perester decomposition.[1a] For most applications, benzene is the best solvent. Chemists new to the manipulation of organic peroxides are urged to read the appropriate literature before commencing experimental work.[8]

Thermal Decomposition.

DBPO is a convenient source of *t*-butoxyl radicals in the temperature range of 20 to 60 °C (eq 1). Its half-life ($t_{1/2}$) in benzene is about 1470 min at 20 °C and 6.8 min at 60 °C.[1a] Thermal decomposition is believed to proceed via concerted three-bond cleavage.[1,5,9] In low viscosity solvents such as pentane or benzene, about 5% of *t*-butoxyl radicals are wasted through cage recombination to give di-*t*-butyl peroxide.[10]

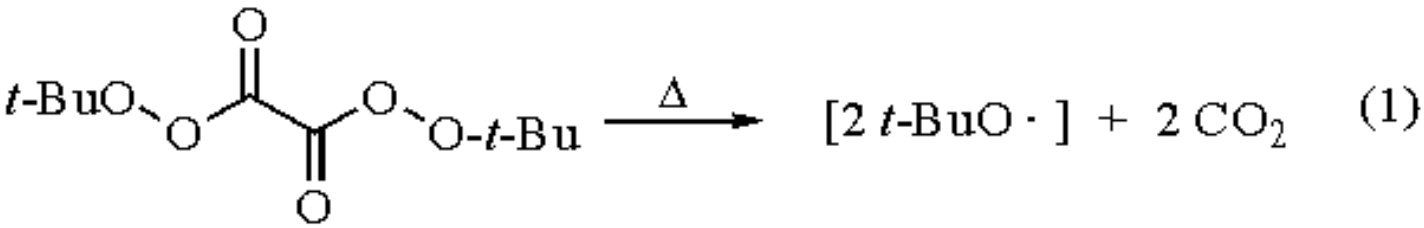

Peroxyl Radical Cyclizations.

On a per hydrogen basis, *t*-butoxyl radicals abstract hydrogen 200-1000 times faster from a hydroperoxyl than an allylic methylene or methyl.[11] Thus specific peroxyl radicals are accessible on treatment of alkenyl hydroperoxides with DBPO. Intramolecular addition to the alkene, followed by oxygen entrapment of the resultant carbon-centered radical and hydrogen atom transfer, leads to cyclic peroxides.[2] By this method, 1,2-dioxolanes (eq 2)[12] and 1,2-dioxanes (eq 3)[13] are obtained in modest yields. In general, there is a strong bias for *exo* cyclization[2,14,15] and, when there is a choice, the 5-*exo*-trig mode is preferred over the 6-*exo*-trig.[16] Although DBPO is the most frequently used initiator for these reactions,[16,17] ***Di-t-butyl Hyponitrite*** is also effective.[18] Further, similar transformations have been achieved at -20 to 5 °C with ***Copper(II) Trifluoromethanesulfonate***-octanoic acid in MeCN.[19]

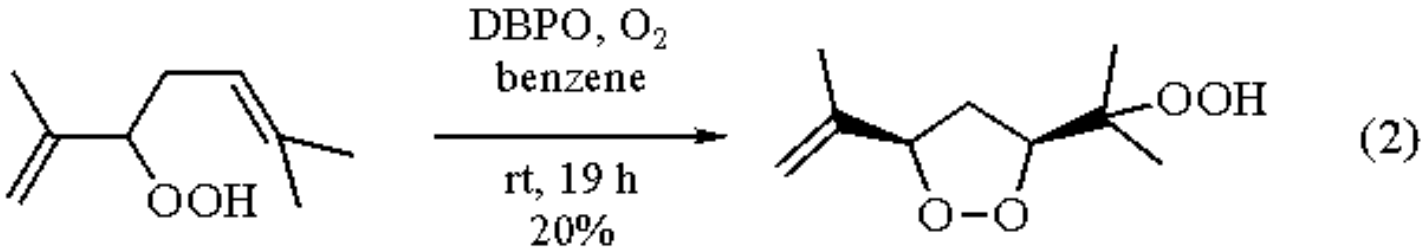

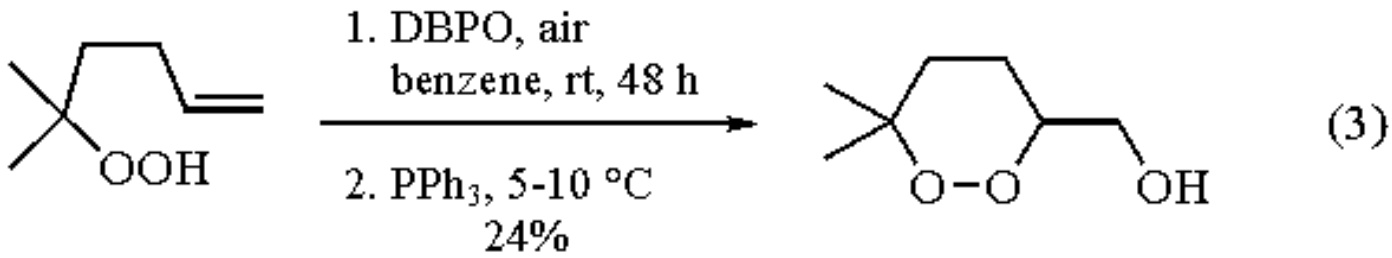

A mechanistically related approach to 1,2-dioxolanes relies on DBPO-initiated thiol-oxygen cooxidation with 1,4-dienes (eq 4)[20] or 1,3,6-trienes.[21,14]

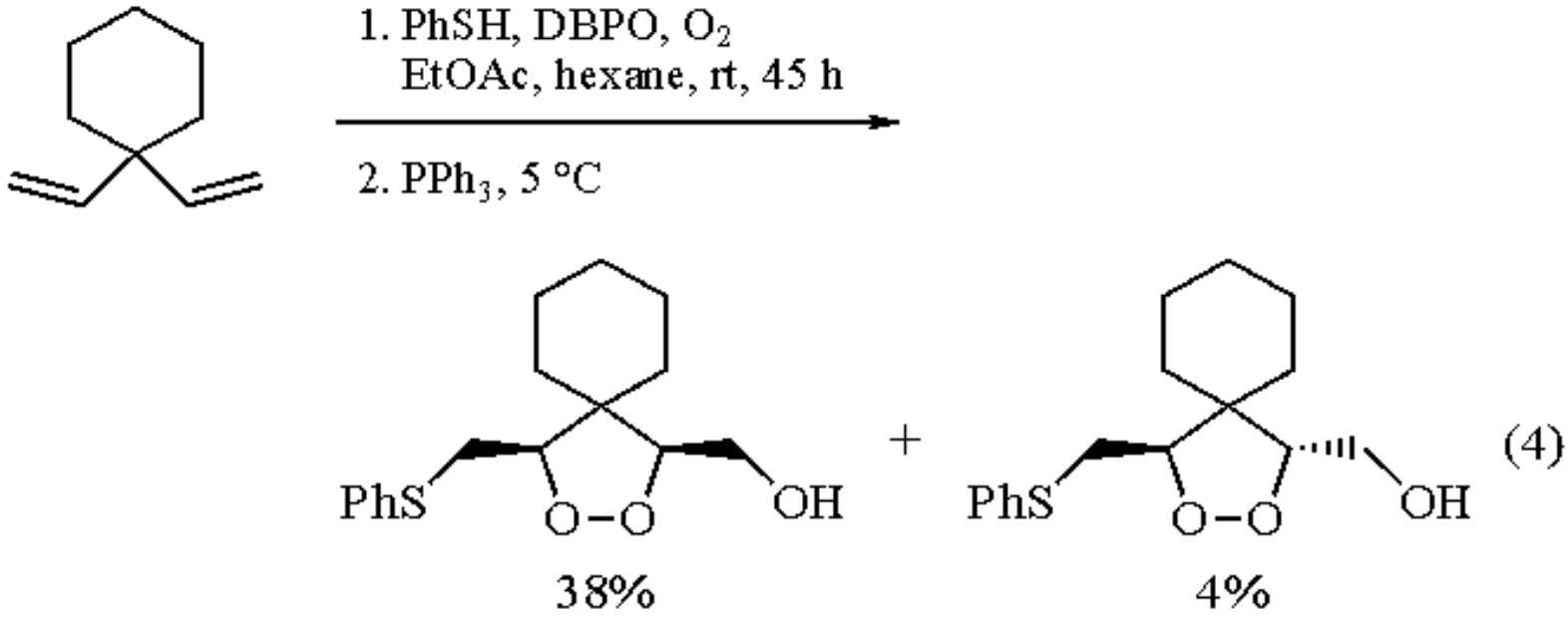

Autoxidation.

The use of DBPO in conjunction with an excess of ***t-Butyl Hydroperoxide*** (TBHP) allows clean autoxidation of simple alkenes at 30-50 °C to provide allylic hydroperoxides (eq 5).[4] The main role of TBHP is to trap product peroxyl radicals as hydroperoxides, thereby preventing side-reactions.[4a,b] Unlike auto-initiated autoxidation, which often leads to complex mixtures containing many nonperoxide products,[4a] the DBPO-TBHP procedure is of comparable preparative value to the widely utilized singlet oxygen route.[4c]

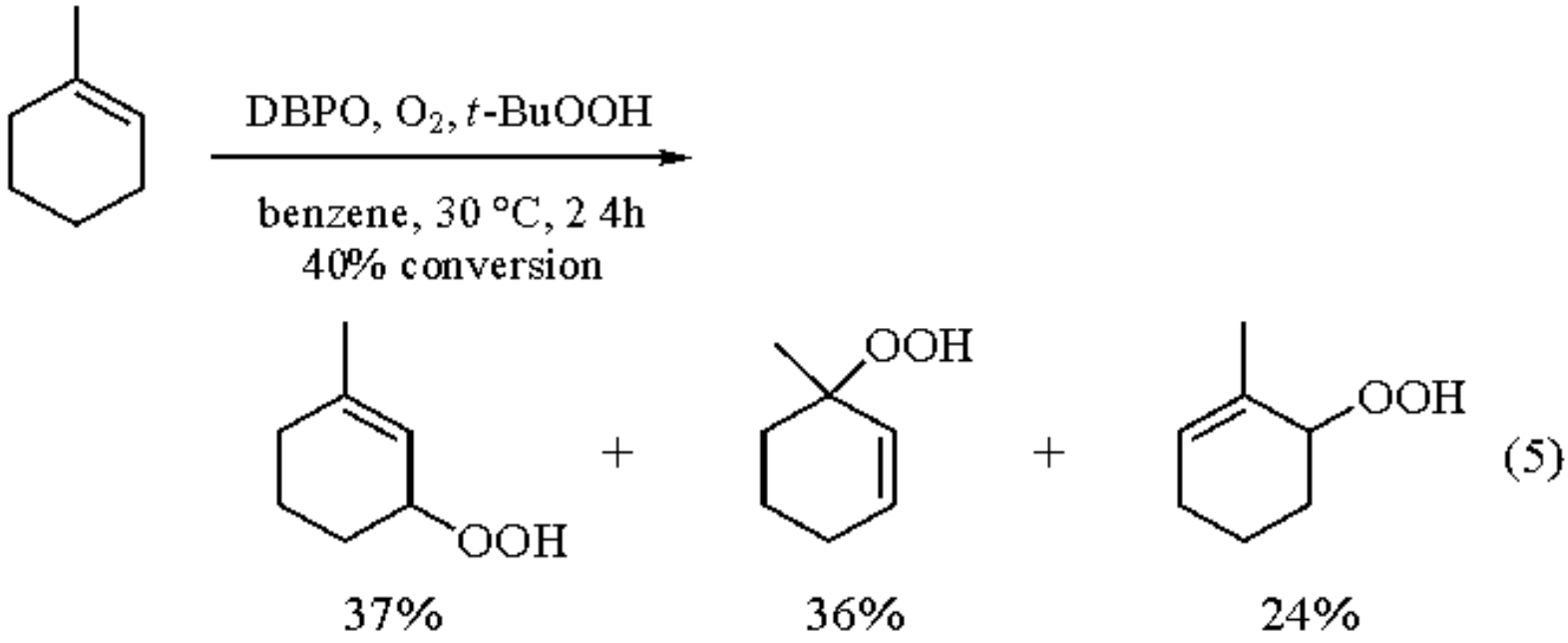

Homolytic Alkylation.

Aldoximes bearing electron-withdrawing groups undergo *C*-alkylation upon treatment with DBPO in a hydrogen donor solvent at 60 °C (eq 6).[22] The alkylation of heteroaromatic compounds with alkyl bromides can be realized in a highly

regioselective fashion by using DBPO in conjunction with phenylsilane and ***Trifluoroacetic Acid*** (eq 7).[23] Other initiators, such as TBHP, ***1,1-Di-t-butyl Peroxide***, or ***Dibenzoyl Peroxide***, are less effective than DBPO.[23]

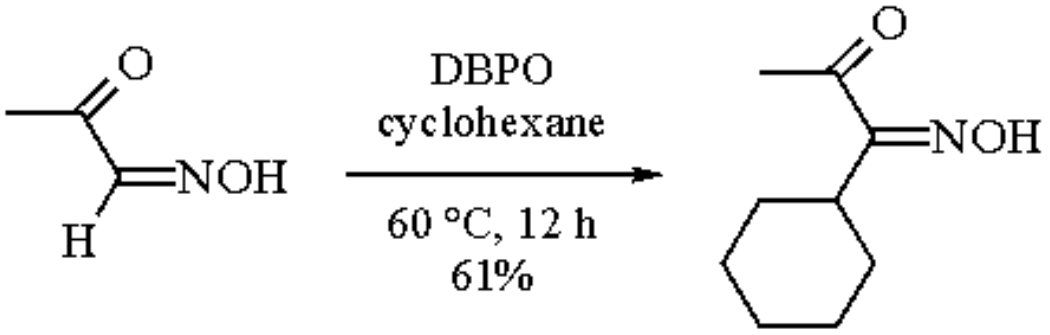

(6)

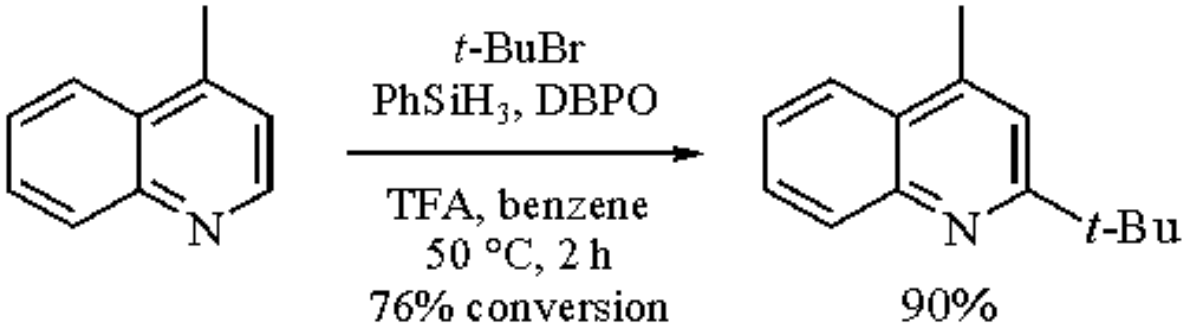

(7)

Miscellaneous Applications.

DBPO has been extensively employed as a low-temperature initiator for radical polymerization and related mechanistic studies,[5,24] as well as in radical-trapping experiments.[3] It is also known to accelerate rearrangement of allylic hydroperoxides[25] and to effect oxidative coupling of phenols.[26] For an equally useful reagent for producing *t*-butoxyl radicals at rt and a comparison with DBPO, see ***Di-t-butyl Hyponitrite***.

Related Reagents.

t-Butyl Hydroperoxide; ***Dibenzoyl Peroxide***; ***Di-t-butyl Hyponitrite***; ***1,1-Di-t-butyl Peroxide***; ***m-Nitrobenzenesulfonyl Peroxide***; ***p-Nitrobenzenesulfonyl Peroxide***.

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2,6-Di-*t*-butylpyridine[1]

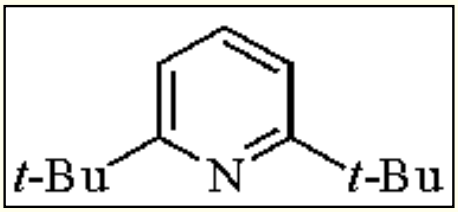

[585-48-8] · $C_{13}H_{21}N$ · 2,6-Di-*t*-butylpyridine · (MW 191.32)

(weak base and proton scavenger;[2-4] prevention of acid-catalyzed side reactions;[5-7] vinyl triflate synthesis[8,9])

Alternate Names: 2,6-bis(1,1-dimethylethyl)pyridine; BDMEP.

Physical Data: mp 2.2 °C; bp 100-101 °C/23 mmHg; *n*20D 1.4733; pK_a 3.58 (50% EtOH);[2] pK_a 0.81 (DMSO).[3]

Solubility: insol H_2O; sol alcohol, acetone, and hexane.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: potentially toxic; handle with care. Use in a fume hood.

Proton Scavenger.

BDMEP has high basicity in the gas phase,[4] but is an abnormally weak base in solution.[2,3] The low basicity of BDMEP is due to steric hindrance of solvation.[10] Therefore BDMEP forms an HCl salt and compounds with Br_2, but does not react with MeI or BF_3.[2]

BDMEP has been used to prevent acid-catalyzed side reactions or nucleophilic reactions by the base in the synthesis of [*trans*-2,3-*trans*-5,6-$^2H_4$]-1,4-dioxane (eq 1),[5] labeled [1-^{13}C]acid chlorides (eq 2),[6] steroidal dienes,[11] and divinyl ketones. In the last case, Amberlyst/15 pretreated with BDMEP was used (eq 3).[7]

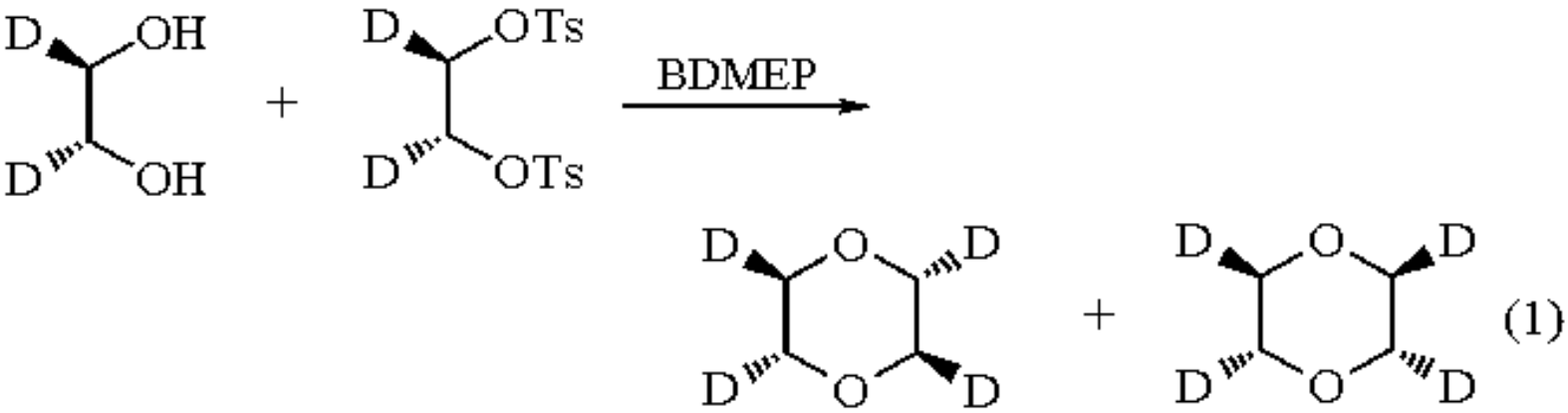

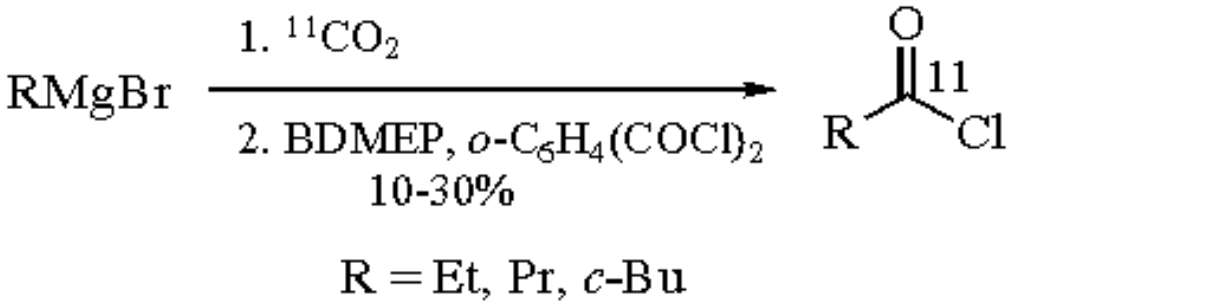

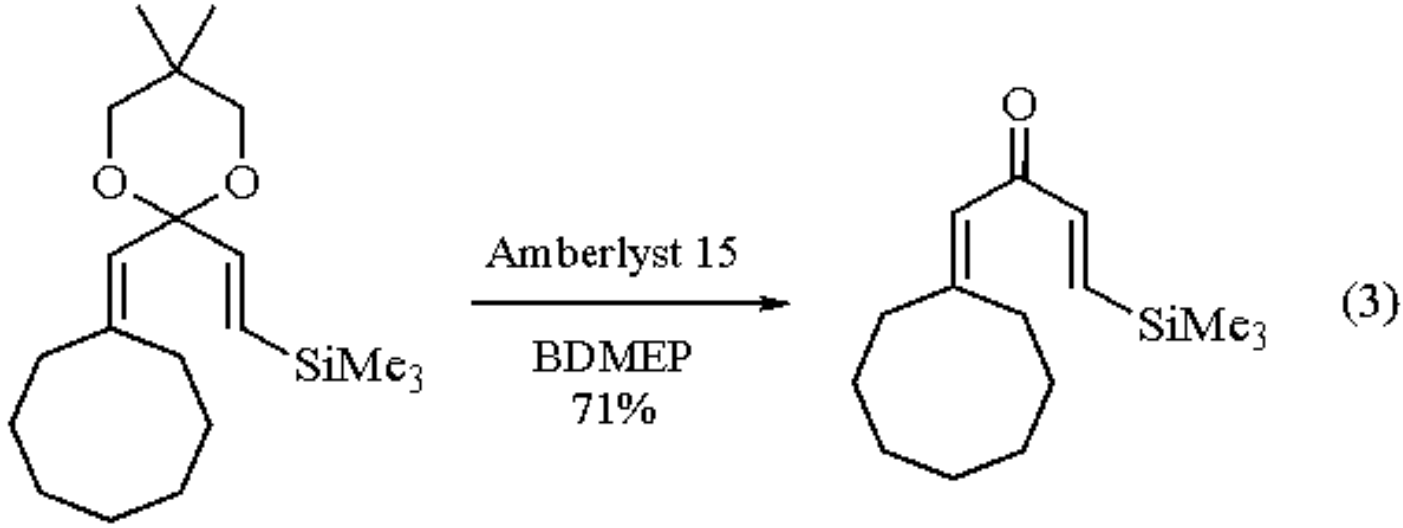

Catalysis of Enolization and Addition Reactions.

It has been shown that BDMEP and its analogs (e.g. 4-methyl-BDMEP) can be used to prepare vinyl triflates from carbonyl compounds and triflic anhydride.[12] Good results were obtained with a polymer-bound BDMEP, which may be easily recycled (eq 4).[8] Intermediate vinylsilanes have been obtained from 2,3-dihydro-4*H*-pyran-4-one derivatives. These have been used in Diels-Alder reactions with alkynes to prepare silyl phenyl ethers (eq 5).[9] In the presence of BDMEP, formaldehyde acetals react with trimethylsilyl enol ethers to form β-alkoxy ketones (eq 6).[13]

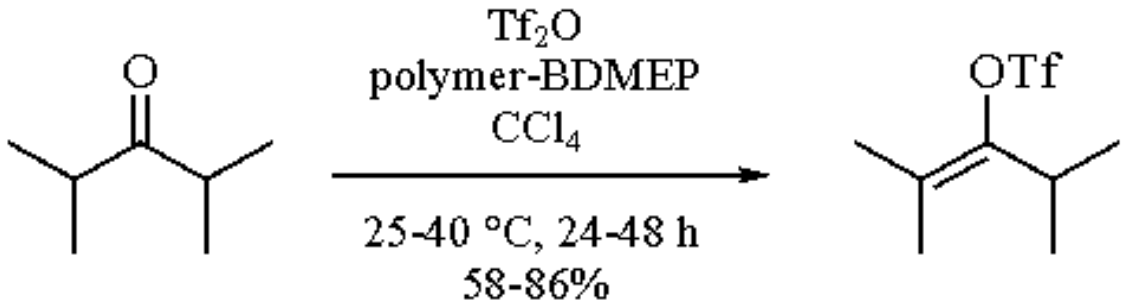

(4)

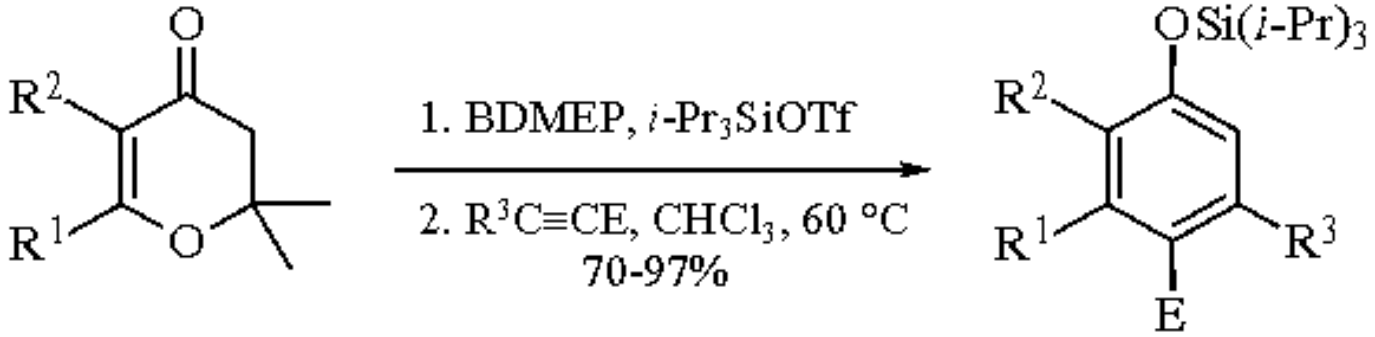

(5)

$R^1 = Ph, t\text{-}Bu, p\text{-}MeOC_6H_4$; $R^2 = H, CO_2Et$; $R^3 = H, PhCO, CO_2Me$; $E = PhCO, CO_2Me, CO_2Et$

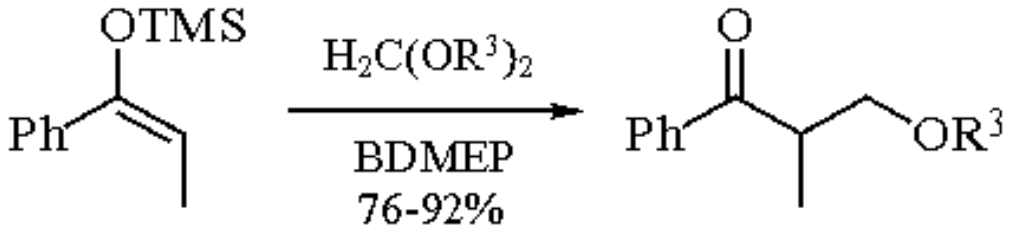

(6)

$R^3 = Me, Bn$

Inhibition of Acid-Catalyzed Reactions.

BDMEP was used to eliminate protic acid catalysis in aminium cation-radical initiated Diels-Alder reactions of dienes,[14] and vinylcyclopropane-cyclopentene isomerizations.[15] Cationic polymerization of isobutene and α-methylstyrene by Ziegler-type catalysts in the presence of BDMEP resulted in a polymer with a higher molecular weight and noticeably narrower molecular weight distribution.[16]

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Di-*t*-butylsilyl Bis(trifluoromethanesulfonate)

t-$Bu_2Si(OSO_2CF_3)_2$

[85272-31-7] · $C_{10}H_{18}F_6O_6S_2Si$ · Di-*t*-butylsilyl Bis(trifluoromethanesulfonate) · (MW 440.44)

(reagent for the protection of diols)

Physical Data: bp 73-75 °C/0.35 mmHg; *d* 1.208 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: liquid.

Preparative Method: by the treatment of di-*t*-butylchlorosilane with ***Trifluoromethanesulfonic Acid***, followed by distillation (71% yield).[1]

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; reacts with hydroxylic solvents; corrosive.

Protection of Alcohols.

Di-*t*-butylsilyl bis(trifluoromethanesulfonate) is a reagent for the selective protection of polyhydroxy compounds. This reagent reacts with 1,2-, 1,3-, and 1,4-diols under mild conditions to give the corresponding dialkylsilylene derivatives in high yield (0-50 °C, 79-96%). Deprotection is conveniently achieved by using aqueous ***Hydrofluoric Acid*** in acetonitrile (eq 1).

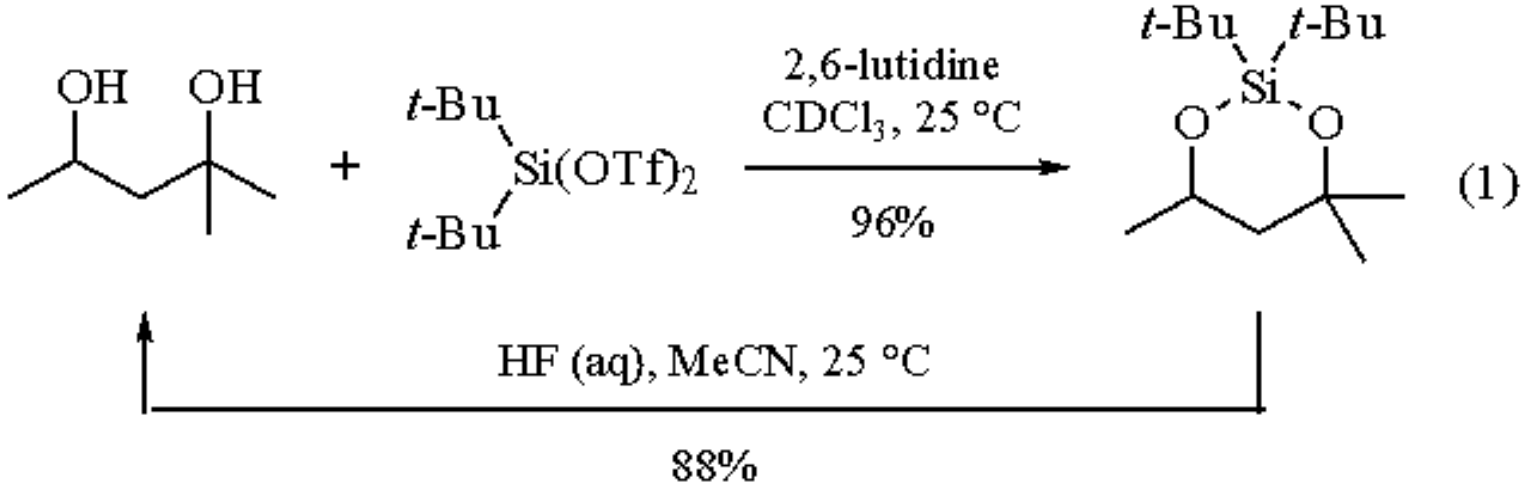

Unlike ***Di-t-butyldichlorosilane***, this reagent reacts with hindered alcohols. Even pinacol reacts to give the silylene derivative (100 °C, 24 h, 70%). Di-*t*-butylsilylene derivatives of 1,2-diols are more reactive than those of 1,3- and 1,4-diols and undergo rapid hydrolysis (5 min) in THF/H_2O at pH 10, while the 1,3- and 1,4-derivatives are unaffected at pH 4-10 (22 °C) for several hours. This protecting group is stable under the conditions of PDC oxidation of alcohols (CH_2Cl_2, 25 °C, 27 h) and tosylation of alcohols (pyridine, 25 °C, 27 h).

The reagent has seen limited use for the protection of alcohols but has been used to protect nucleosides (eq 2).[2-5] The procedure consists of sequential addition of the ditriflate and ***Triethylamine*** to the nucleoside in DMF. The choice of solvent is critical.

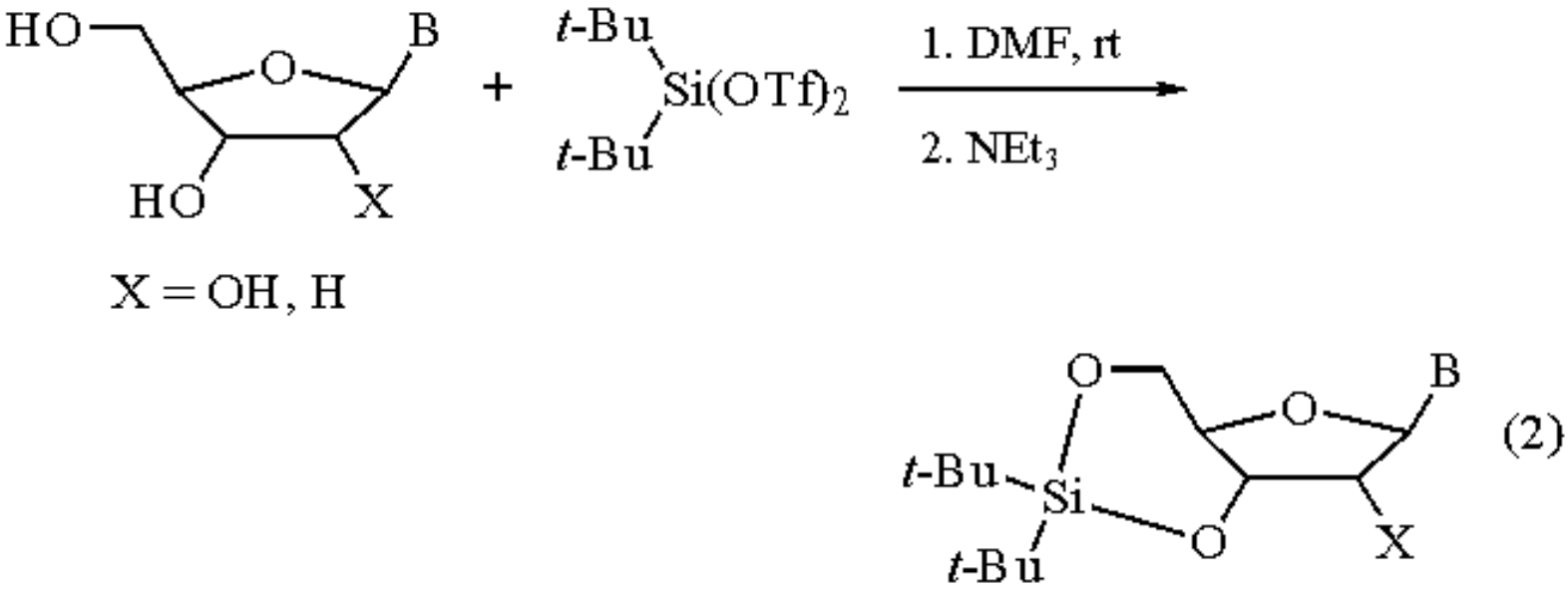

The ribonucleosides of uracil, adenine, and guanine give the protected derivative in 94-95% yield.[2] Cytidine gives a low yield of the desired product under these conditions. Subsequent studies suggested that O^2 of cytosine participates in the reaction. Addition of ***Trifluoromethanesulfonic Acid*** or ***Silver(I) Trifluoromethanesulfonate*** at 0 °C prior to addition of the silylating agent results in a 99% yield of the desired derivative.[3] The derivatives are acid sensitive, presumably due to the proximity of the 2´-hydroxy group. Acetylation, tetrahydropyranylation, methoxytetrahydropyranylation, and silylation of the 2´-hydroxy group are accomplished without affecting the dialkylsilylene protecting group. The 2´-deoxyribonucleosides, including 2´-deoxycytidine, can also be prepared by the aforementioned procedure (yields 90-99%). These cyclic silylene derivatives of nucleosides can be deprotected

conveniently using tributylamine hydrofluoride in THF (5 min, 1 M, rt, 20 equiv).[4] A one-pot procedure has been reported for simultaneously protecting the 2´-, 3´-, and 5´-hydroxys of a ribonucleoside, which utilizes the acid generated upon silylating the 3´- and 5´-hydroxys for catalyzing the formation of a THP acetal at the 2´-position (eq 3).[5]

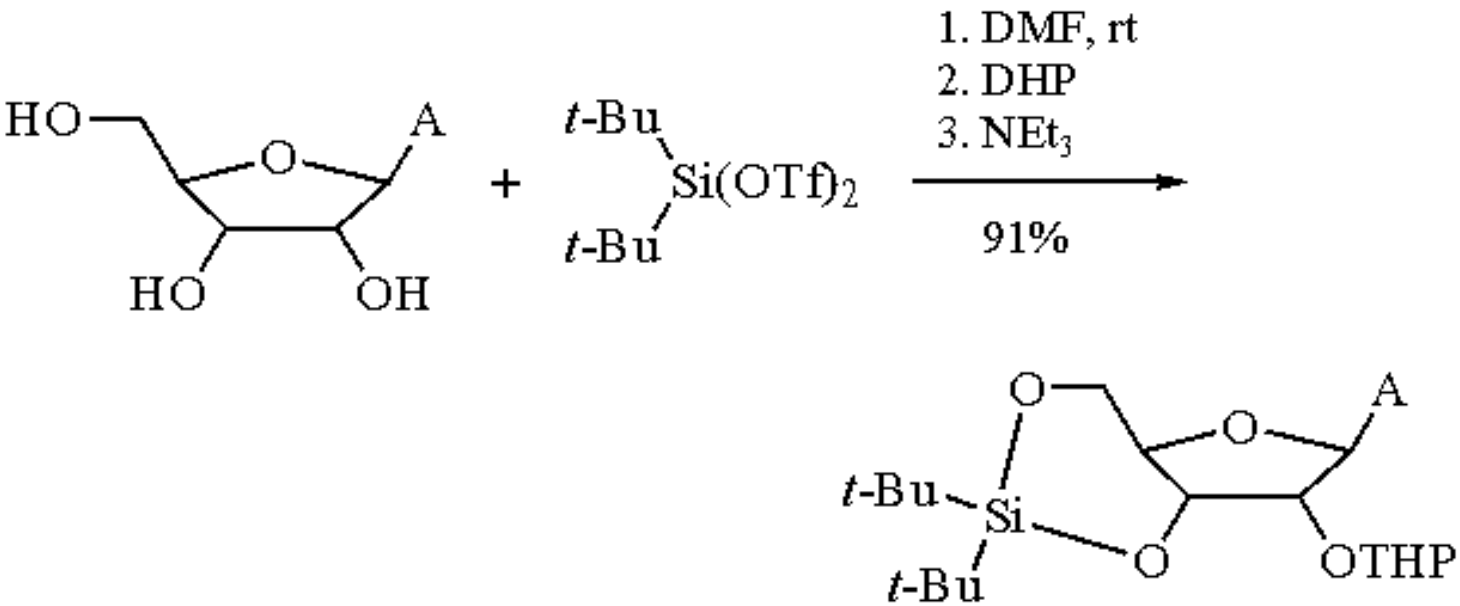

(3)

Derivatization of Alcohols.

Di-*t*-butylsilyl bis(trifluoromethanesulfonate) has been used to derivatize hindered diols, to give derivatives such as (**1**), for analysis by gas chromatography-electron impact mass spectrometry.[6] The major fragmentation is that of the Si-C bonds.

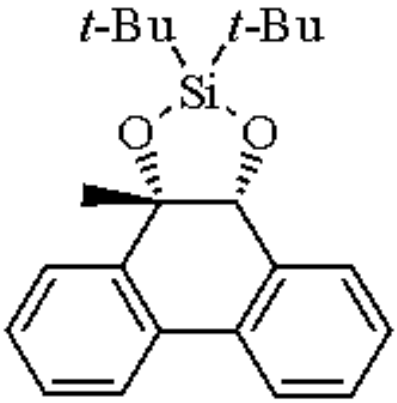

(1)

m/z 366 (M^+), 309 (M^+ - Bu), 191 (*B*)

Reagent in Enantioselective Additions.

In a study of enantioselective conjugate addition to cyclohexanone it was found that the presence of HMPA and various silyl reagents markedly increases the enantioselectivity (eq 4).[7] Di-*t*-butylsilyl bis(trifluoromethanesulfonate) gives a 67% yield and 40% ee but ***t-Butyldiphenylchlorosilane*** gives a 97% yield and 78% ee.

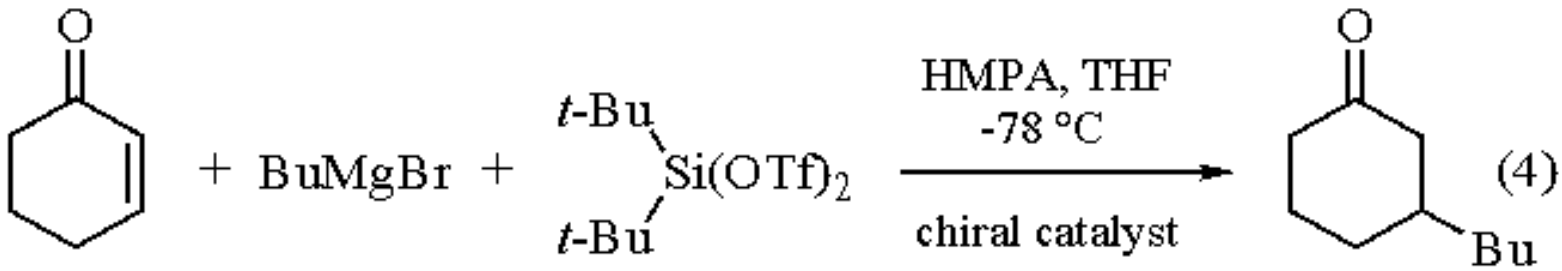

Other Substitution Reactions.

An extremely hindered silyl reagent, tri-*t*-butylsilyl trifluoromethanesulfonate, was prepared from di-*t*-butylsilyl bis(trifluoromethanesulfonate) and ***t-Butyllithium*** (eq 5).[8] This reagent might find use in the protection of alcohols.

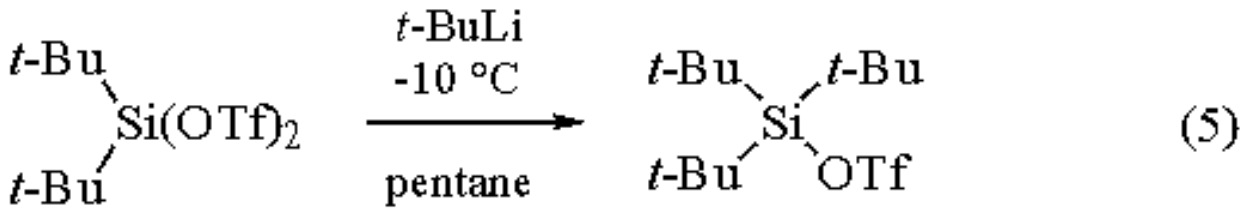

In conjunction with the study of alkyl-substituted silyl triflates, (**2**) and (**3**) have been prepared from the corresponding alkynyllithium reagents and di-*t*-butylsilyl bis(trifluoromethanesulfonate).[9]

(2) **(3)**

The preparation of other derivatives of di-*t*-butylsilyl bis(trifluoromethanesulfonate) using germanium[10] and phosphorus[11] nucleophiles has been reported and provides bifunctional silanes such as (**4**) and (**5**).

(4) **(5)**

X = -C≡CPh, -$SiPh_3$, -$N(TMS)_2$, -PHPh, -O-*i*-Pr, -SPh

A compound closely related to di-*t*-butylsilyl bis(trifluoromethanesulfonate) is di-*t*-butylchlorosilyl

trifluoromethanesulfonate, which has been used to tether two structurally different alcohol derivatives in order to effect an intramolecular Diels-Alder reaction (eq 6).[12]

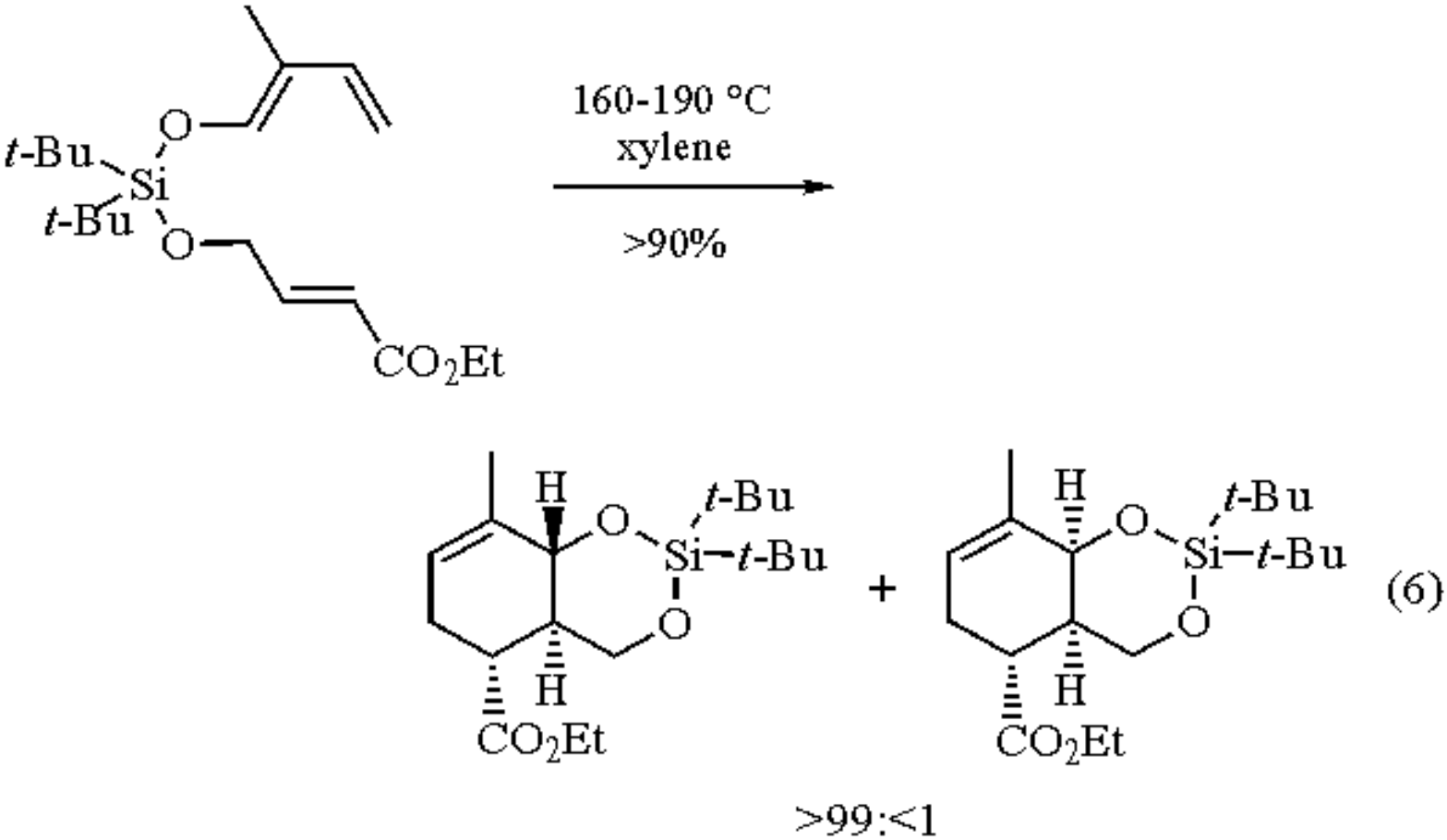

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2,2-Dibutyl-2-stanna-1,3-dithiane[1]

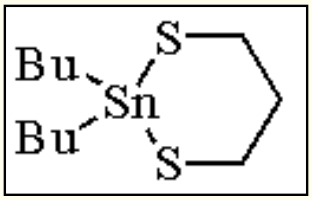

[7191-32-4] · $C_{11}H_{24}S_2Sn$ · 2,2-Dibutyl-2-stanna-1,3-dithiane · (MW 339.20)

(reagent for synthesizing 1,3-dithianes from aldehydes and acetals[2,3])

Alternate Name: DSDT.

Physical Data: mp 63-64 °C; bp 170 °C/0.5 mmHg.

Solubility: insol H_2O; sol most organic solvents.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 6H, *J* = 7.32 Hz), 1.61 (m, 14H), 2.94 (t, 4H, *J* = 6.10 Hz); ^{13}C NMR ($CDCl_3$) δ 13.40, 24.51, 26.50, 27.82, 30.16.

Preparative Method: to a CH_2Cl_2 solution (400 mL) of Bu_2SnCl_2 (45.8 g, 0.15 mol) and $HS(CH_2)_3SH$ (15.1 mL, 0.15 mol) is added Et_3N (41.8 mL, 0.3 mol) at 0 °C. The solution is stirred at rt overnight and diluted with CH_2Cl_2 (200 mL). The combined solution is washed with H_2O (200 mL × 2). The organic layer is dried (Na_2SO_4) and evaporated. Distillation of the residue affords DSDT (39.5 g, 78%): bp 170 °C/0.5 mmHg.

Handling, Storage, and Precautions: stable in air and to moisture and thus can be handled and stored in air; odorless.

Synthesis of 1,3-Dithianes from Aldehydes and Acetals.[2,3]

Treatment of aldehydes with DSDT (1.2 equiv) in the presence of $Bu_2Sn(OTf)_2$ (DBTT) in 1,2-dichloroethane affords 1,3-dithianes in 70-99% yields (eq 1). ***Boron Trifluoride Etherate*** may also be used in this procedure; however, use of DBTT results in cleaner reactions and better yields. 1,3-Dithianes are conventionally prepared with ***1,3-Propanedithiol*** under acidic conditions and are occasionally contaminated by yellow-colored byproducts. No such byproducts are detected in reactions with DSDT. Of more synthetic value is the mildness of the reaction. Acid-labile substrates can be successfully employed: aldehydes having siloxy or tetrahydropyranyloxy groups, which are unmasked under conventional reaction conditions, are converted to 1,3-dithianes smoothly. However, α,β-unsaturated aldehydes undergo isomerization of the double bond.

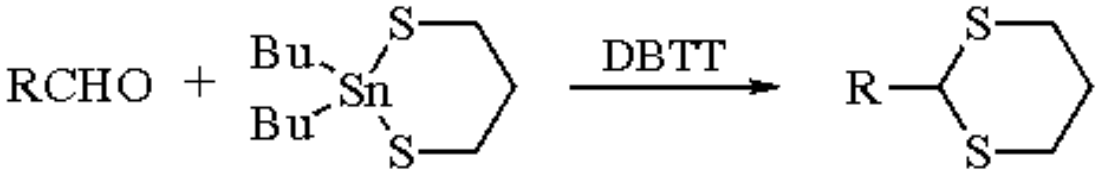

(1)

The reactions with acetals also proceed smoothly (eq 2). 1,3-Dithiolanes are obtained by an analogous procedure employing 2,2-dialkyl-2-stanna-1,3-dithiolanes in place of DSDT. In some respects this method is comparable to the Evans' thiosilane protocol,[4] which, however, is applied to carbonyls only; no reaction with acetals has been described. Moreover, the following merits of the present dithioacetalization method are worthy of note. Thiostannanes can be readily prepared from various organotin sources such as oxides, alkoxides, and halides. They are entirely air and moisture stable and, thus, can be used even in the presence of water. Because they are odorless, they can be stored in the air.

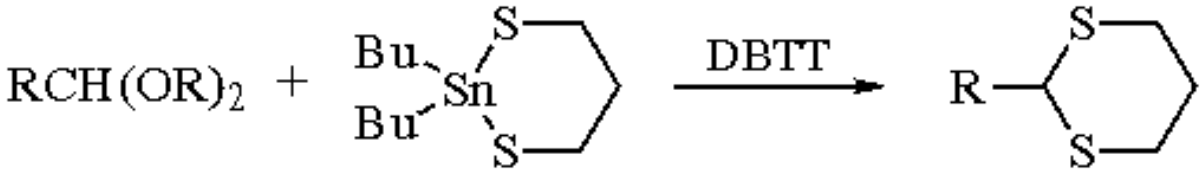

(2)

Differentiation between Carbonyls and Acetals.

In competition reactions employing an equimolar mixture of various types of carbonyls and acetals, one of the substrates reacts preferentially. Representative results are described briefly in the following sections.

Competition between Aldehydes and Ketones (or Acetals).

An aldehyde reacts preferentially over a ketone (eq 3), while the preference is reversed in the reaction of the corresponding acetals (eq 4). The reaction of the carbonyl is initiated by coordination of the carbonyl to tin. Thus the enhanced reactivity of the aldehyde can be accounted for by the fact that the aldehyde forms a complex with tin more readily than the ketone does. In contrast, the reaction of the acetal proceeds via an oxocarbenium ion, which is generated from ketone acetals more easily than from aldehyde acetals.

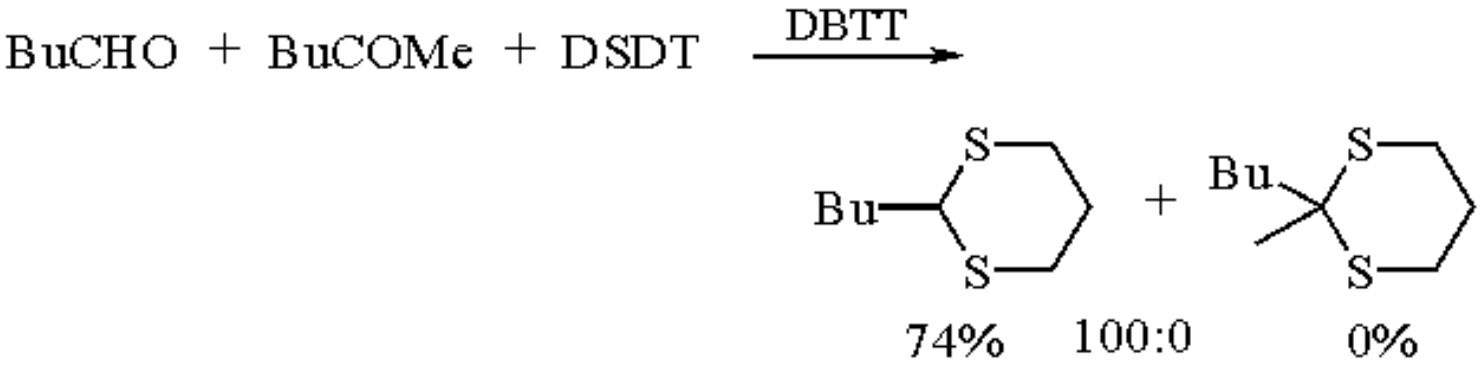

(3)

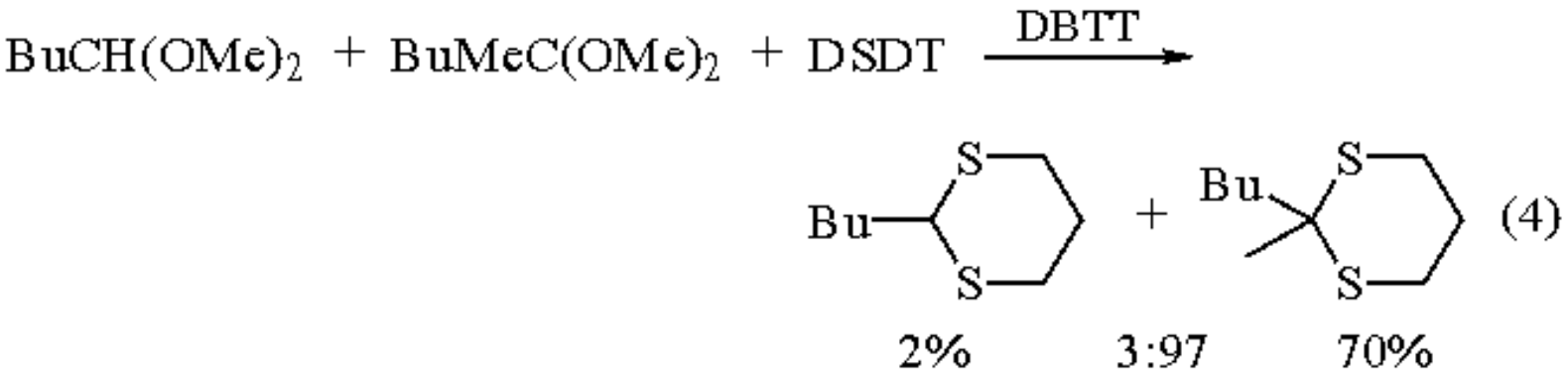

Competition between Aldehydes.

Differentiation between two of the same type of carbonyl functions often requires highly elaborate methods. Organotin triflates effect such differentiations successfully. As shown in eq 5, competition between benzaldehyde and pentanal leads to predominant formation of the 1,3-dithiane of the latter.

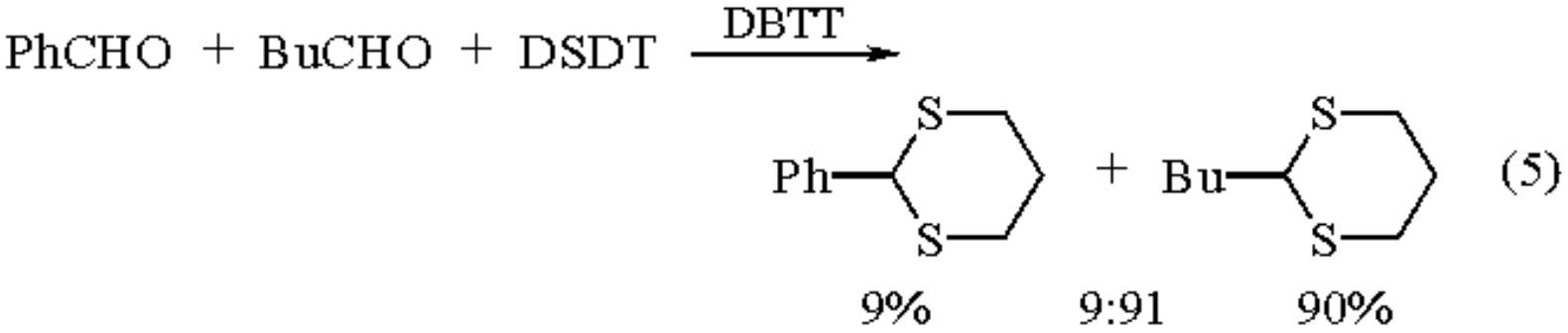

Competition between Acetals.

An aromatic acetal can be differentiated from an aliphatic acetal (eq 6).

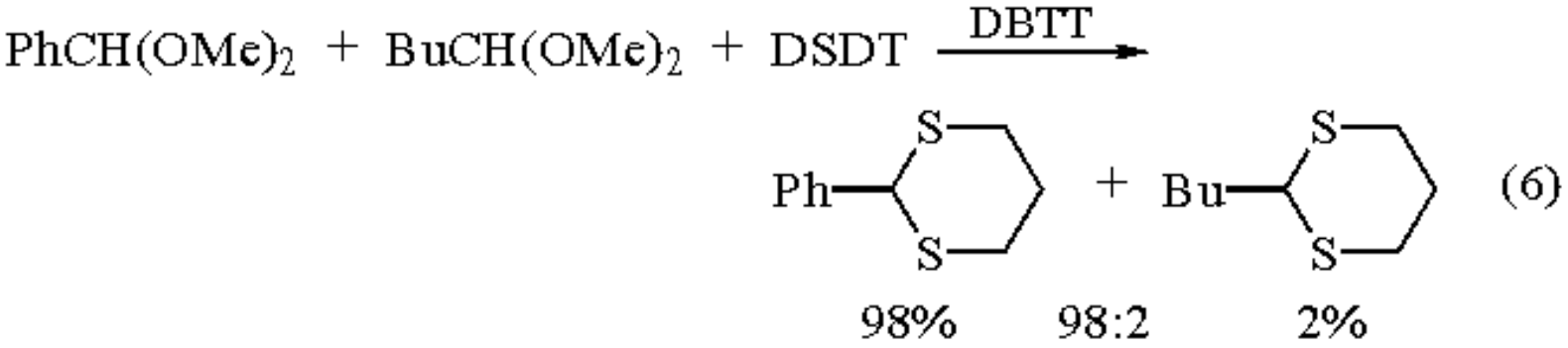

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Dibutyl Telluride[1]

R_2Te

(R = *n*-Bu)

[38788-38-4] · $C_8H_{18}Te$ · Dibutyl Telluride · (MW 241.83) (R = *i*-Bu)

[83817-01-0]

(nucleophilic agent for the synthesis of telluronium salts, which undergo many transformations;[2] used as a halophilic[3] and reducing[4] reagent)

Physical Data: *n*-Bu_2Te bp 75-76 °C/4 mmHg; *i*-Bu_2Te bp 68-70 °C/6 mmHg.

Solubility: insol H_2O, ethanol; sol ether, petroleum ether, THF, etc.

Preparative Methods: dibutyl telluride and diisobutyl telluride are prepared from *n*-butyl bromide and isobutyl bromide with ***Sodium Telluride***, which is prepared in situ from ***Tellurium*** powder, rongalite (***Sodium Hydroxymethanesulfinate***), and ***Sodium Hydroxide*** in H_2O.[5]

Handling, Storage, and Precautions: stored and handled under N_2. Care should be taken in handling Bu_2Te and *i*-Bu_2Te; because of their bad smell, experiments should be carried out in an efficient fume hood.

Organotelluronium Salts.

The reaction of dibutyl telluride or diisobutyl telluride with halides affords telluronium salts, which can mediate the syntheses of alcohols, alkenes, epoxides, and cyclopropanes.

Formation of Alcohols.

Treatment of the telluronium salts with an alkyl- or aryllithium reagent results in a lithium-tellurium exchange reaction via an unstable transient tetraorganyltellurium intermediate. The in situ generated lithium species react with carbonyl compounds to give various alcohols in high yields. In this way, homobenzylic alcohols,[6] β-hydroxy nitriles,[7] and (trimethylsilyl)propargyl alcohols[8] are synthesized in excellent yields (eq 1-3).

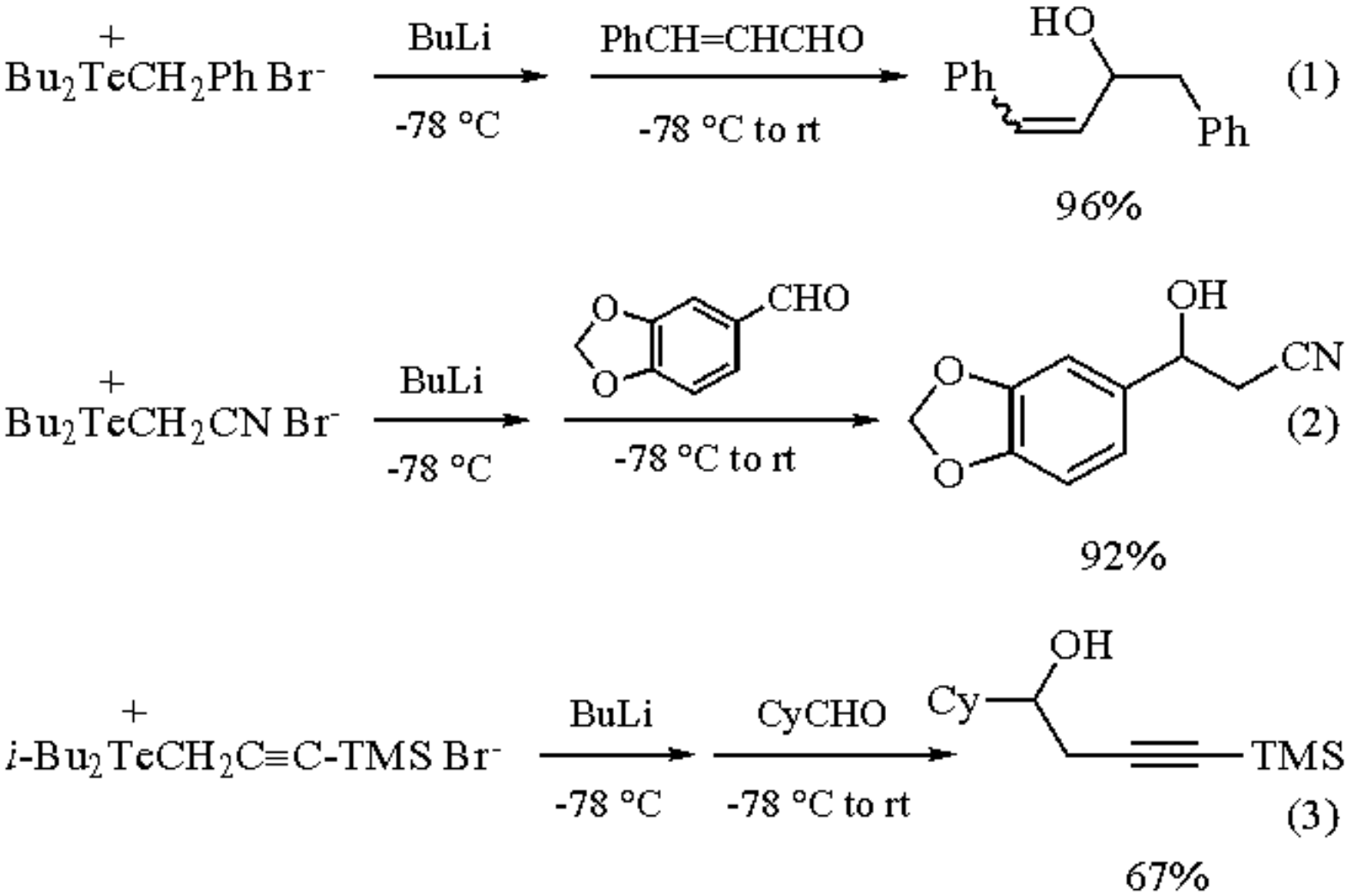

Formation of Alkenes via Telluronium Ylides.

Stabilized telluronium ylides, formed from telluronium salts with ***Potassium t-Butoxide***, react with carbonyl compounds to give α,β-unsaturated esters,[9] carboxamides,[10] ketones, and nitriles[11] in high yields (eq 4).

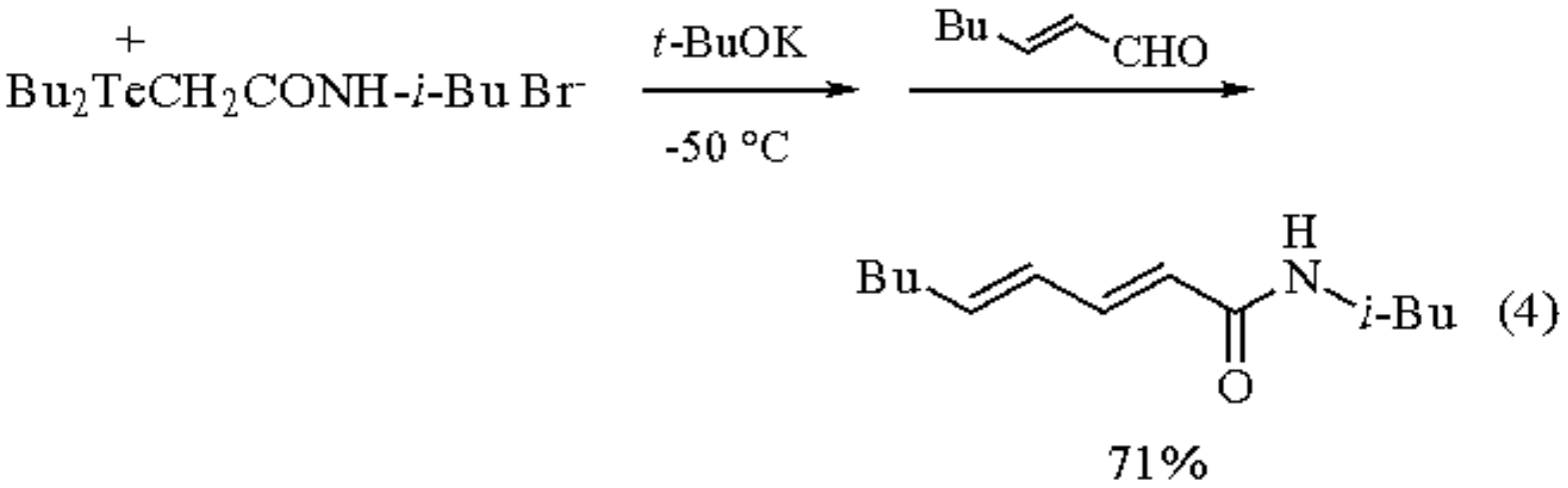

Due to the ease of conversion of dibutyl telluride to the telluronium salts, these alkenation reactions can be carried out

at rt in a one-pot procedure. Thus α,β-unsaturated carboxylic acid amides can be obtained in excellent yields with high (*E*) stereoselectivity.[12] The dibutyl telluroxide formed during the reaction can be reduced back to dibutyl telluride by ***Triphenyl Phosphite***. Thus alkenes can be obtained using a catalytic amount of dibutyl telluride (eq 5).[13]

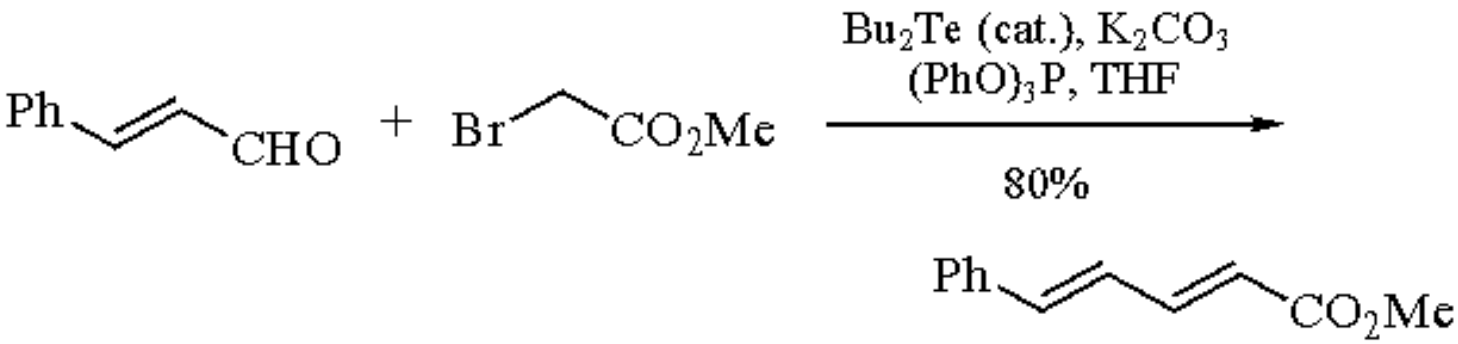

(5)

Dibutyl or diisobutyl telluride reacts with carbenes or nitrenes to form telluronium ylides or tellurimides, which react with carbonyl compounds to afford alkenes or *N*-tosylimines (eqs 6 and 7).[14,15]

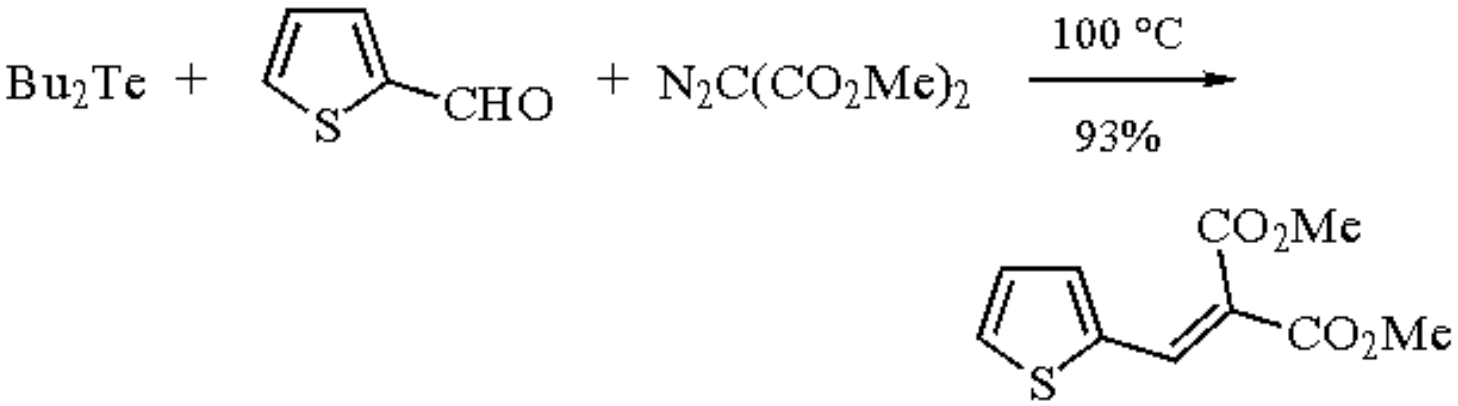

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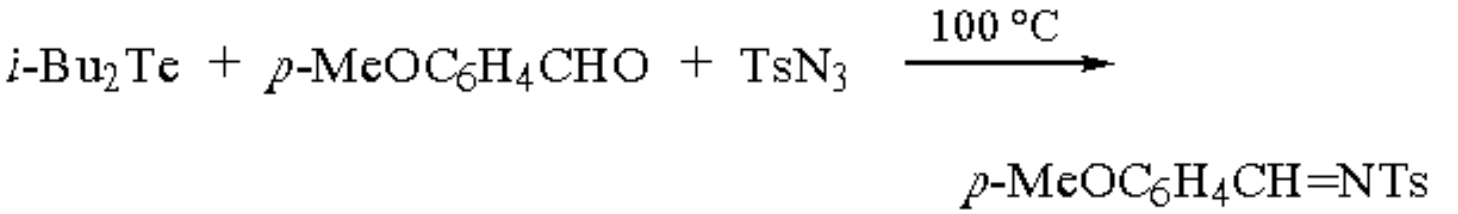

(7)

Formation of Epoxides via Telluronium Ylides.

Diisobutyltelluronium allylide, generated from allyldiisobutyltelluronium bromide, reacts with aldehydes to give vinyl epoxides in good yields.[16] In the presence of ***Cesium Carbonate*** the epoxidation reaction can be promoted by a catalytic amount of diisobutyl telluride (eq 8).[17] Allyl[18] and propargyl[8,18] telluronium ylides can also be formed by deprotonation with ***Lithium 2,2,6,6-Tetramethylpiperidide*** (eq 9), giving high *cis* selectivity in some cases.

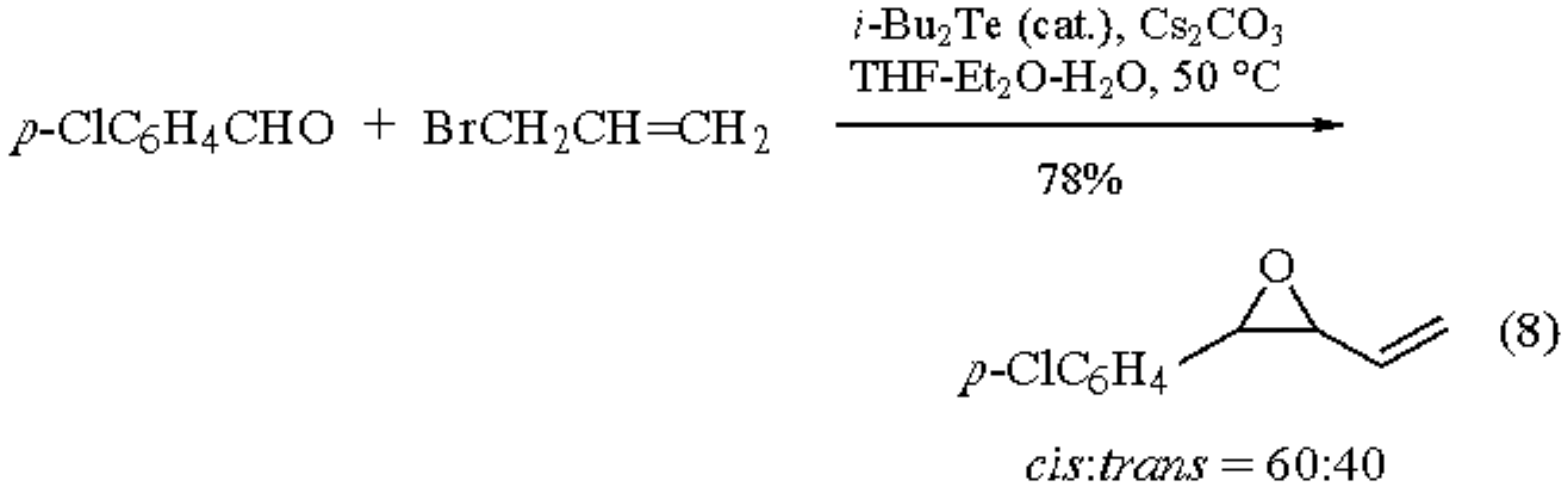

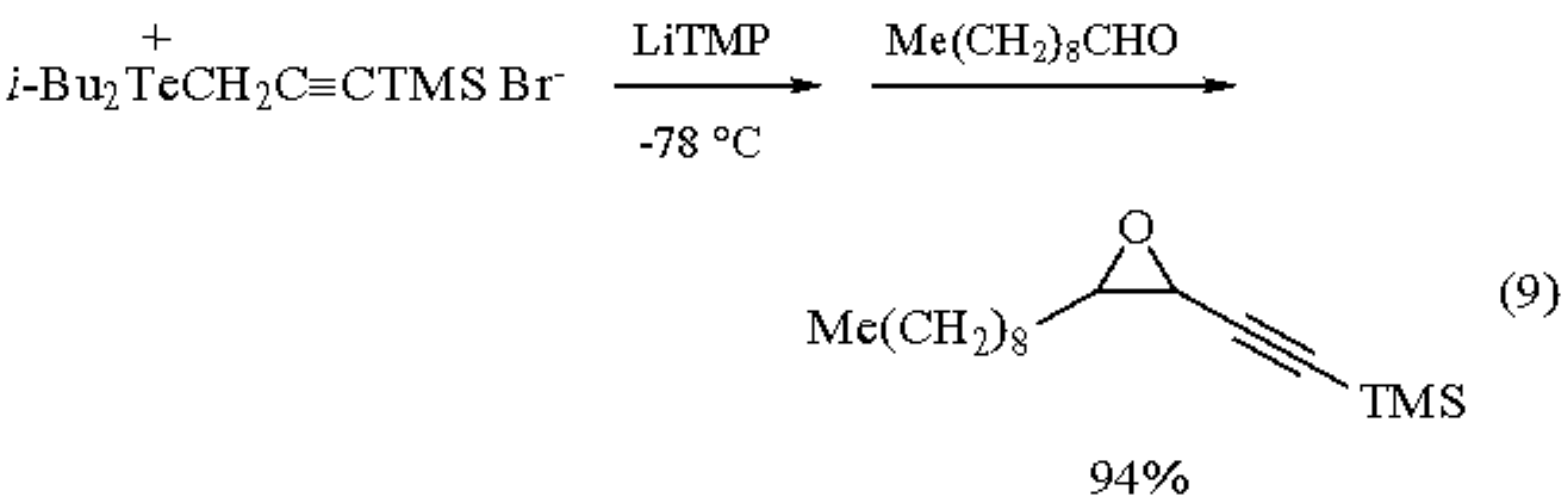

Formation of Cyclopropane Derivatives via Telluronium Ylides.

Trimethylsilylated diisobutyltelluronium allylide reacts with α,β-unsaturated esters to afford trimethylsilylvinylcyclopropane derivatives via Michael addition in excellent yields with high stereoselectivity (eq 10).[19,20]

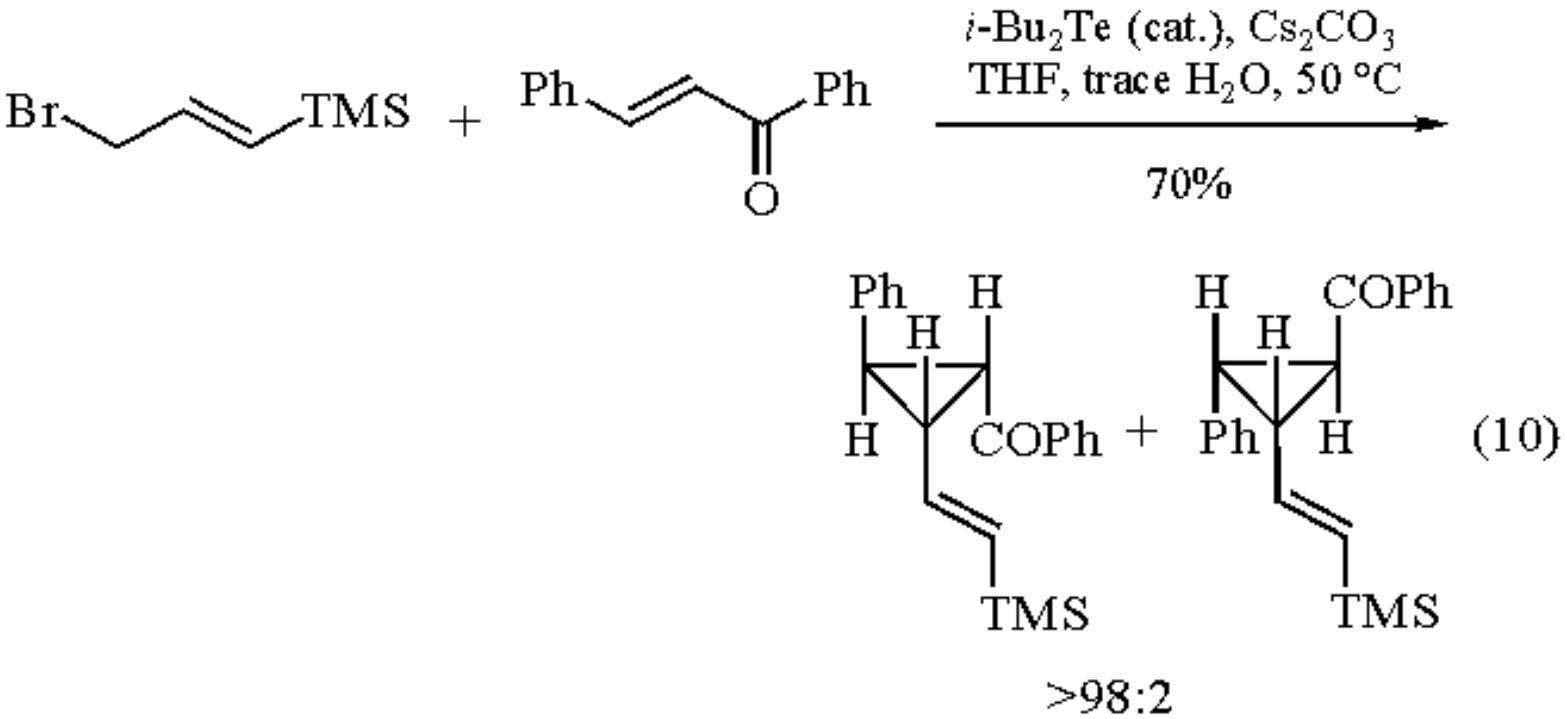

Halophilic Reactions of Dibutyl Telluride.

Owing to the great halophilicity of dibutyl telluride, several alkenation reactions have been developed. Thus in the presence of dibutyl telluride, (iodomethyl)triphenylphosphonium iodide reacts with aldehydes to afford the methylenation products (eq 11).[3] A one-pot reaction of α-halo esters, malonic esters, nitriles, and ketones with aldehydes gives α,β-unsaturated esters, nitriles, and ketones in high yields (eq 12).[11,21-23] A similar reaction of ***Diethyl Dibromomalonate*** with electron-deficient alkenes affords cyclopropanation products (eq 13).[23]

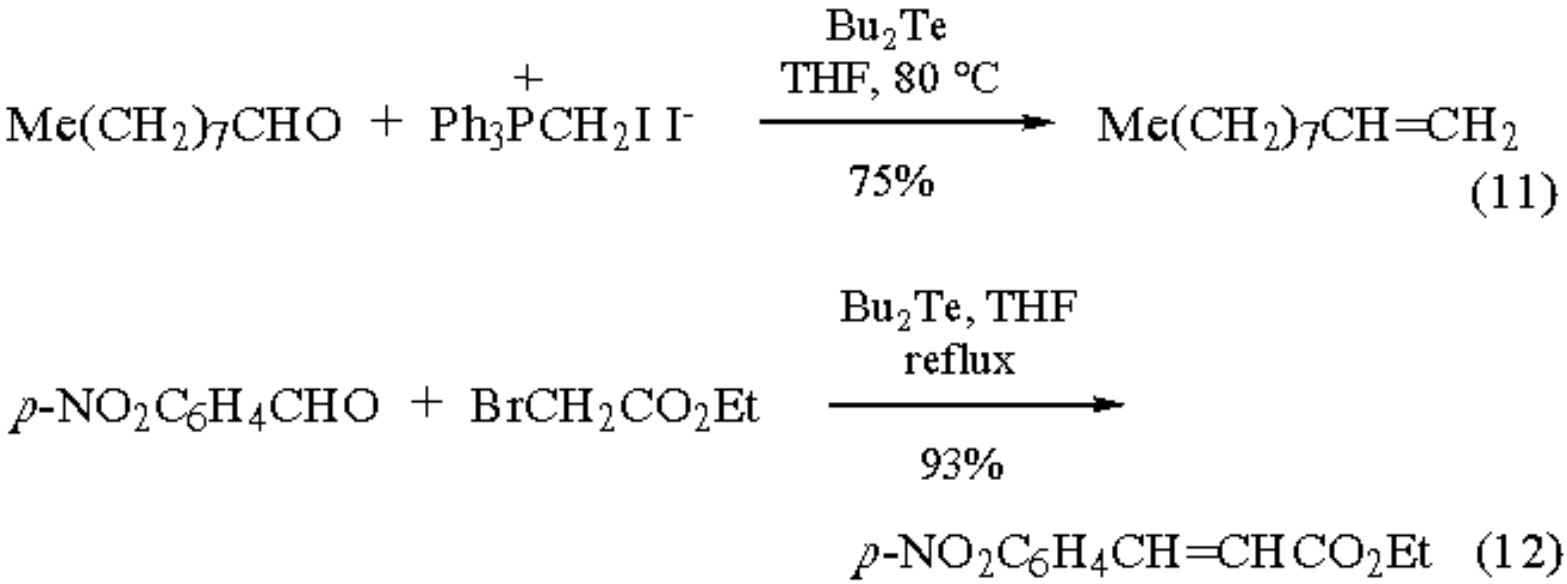

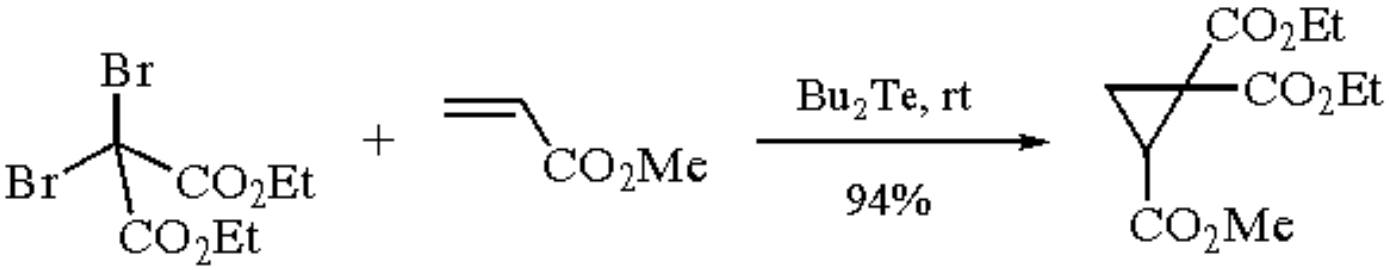

(13)

Reducing Agent.

Diisobutyl telluride reduces ***Titanium(IV) Chloride*** to ***Titanium(III) Chloride***, which can mediate pinacolizations, carbonyl reductions, and reductive aromatization (eq 14).[4]

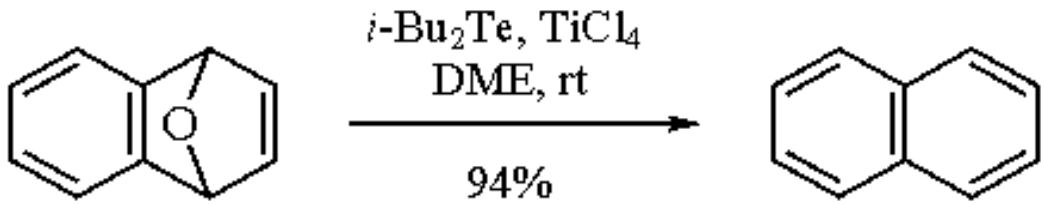

(14)

Related Reagents.

Tri-n-butylstibine; ***Triphenylphosphine***.

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18. Zhou, Z. L.; Huang, Y. Z.; Shi, L. L. *CC* **1992**, 986.
19. Huang, Y. Z.; Tang, Y.; Zhou, Z. L.; Huang, J. L. *CC* **1993**, 7.
20. Huang, Y. Z.; Tang, Y.; Zhou, Z. L.; Xia, W.; Shi, L. P. *JCS(P1)* **1994**, 893.
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Shanghai Institute of Organic Chemistry, China

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Di-*n*-butyltin Oxide[1,2]

Bu_2SnO

[818-08-6] · $C_8H_{18}OSn$ · Di-*n*-butyltin Oxide · (MW 248.92)

(converts diols to *O*-stannylene acetals[2] which undergo regioselective acylation, alkylation, oxidation, and condensation with activated carboxylic acid derivatives; activates α,o-hydroxy acids and α,o-amino acids for lactone and lactam formation, respectively;[3] mediates epoxidation of allylic alcohols by *t*-butyl hydroperoxide;[4] catalyzes $TMSN_3$ addition to nitrile;[5] useful as a source of tin for Otera transesterification[6] and organotin phosphate condensate[7] catalysts)

Alternate Name: DBTO.

Physical Data: mp >300 °C.

Solubility: insol most organic solvents with which it does not react. However solvents like toluene, benzene, and methanol are routinely used for reactions of hydroxylic substrates.

Form Supplied in: white powder.

Handling, Storage, and Precautions: toxic and irritant;[8,9] use in a fume hood.

Introduction.

Di-*n*-butyltin oxide, because of its biocidal and antifouling properties, is one of the most widely used industrial chemicals.[9] It is the final product of hydrolysis of dialkyltin halides (eq 1) and exists as an amorphous polymeric solid insoluble in nonreacting solvents. A reticulated network (**1**) consisting of four-membered rings of alternating tin and oxygen has been suggested as a possible structure for this compound.[10] The interaction of diorganotin oxides with various biomolecules like amino acids, peptides, carbohydrates, and nucleic acid components has been reviewed[9] and is beyond the scope of this article.

$$R_2SnX_2 \longrightarrow R_2Sn(X)OSn(X)R_2 \longrightarrow R_2(X)SnOSnR_2(OH) \longrightarrow R_2SnO \quad (1)$$

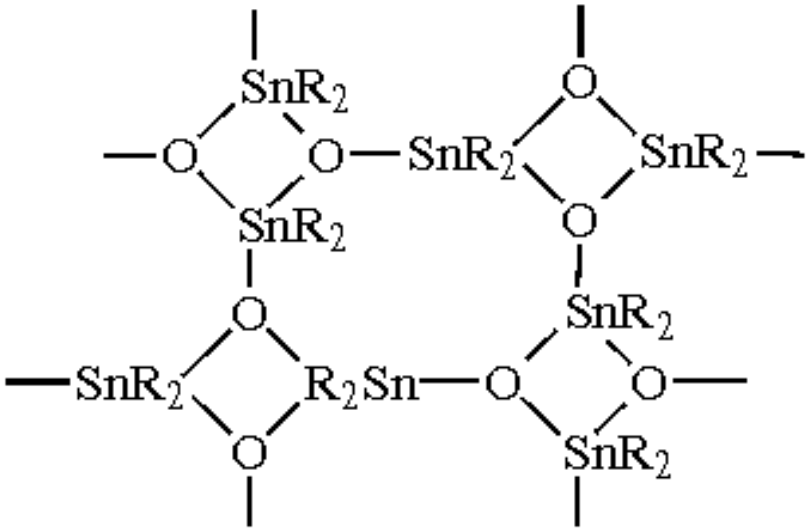

(1)

Formation and Reactions of Dibutylstannylenes.

By far the largest application of DBTO in organic chemistry is in the generation and reactions of stannylenes from polyhydroxy compounds. Dibutylstannylenes are prepared in nearly quantitative yields by heating stoichiometric amounts of DBTO and the polyol in a solvent such as benzene or toluene with concomitant removal of water (eq 2).[11] Compounds (**2**)[12] and (**3**)[13] are other prototypical stannylenes that have been prepared by this method. Formation and reactions of 1,6-stannylenes from monosaccharides have also been reported recently.[14] While the stannylene from ethylene glycol (eq 2) is an infinite coordination chain polymer with hexacoordinated Sn,[15] the stannylenes from cyclohexane-1,2-diols and the methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**3**)[16] are dimeric (e.g. **4**).

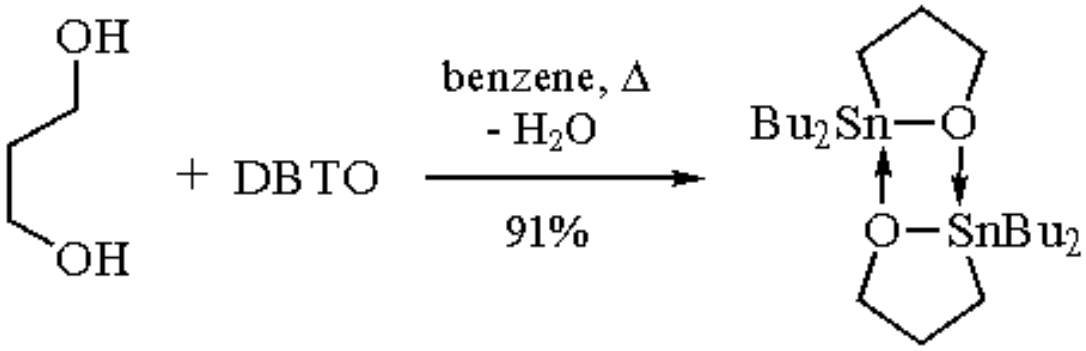

(2)

mp 223-226 °C

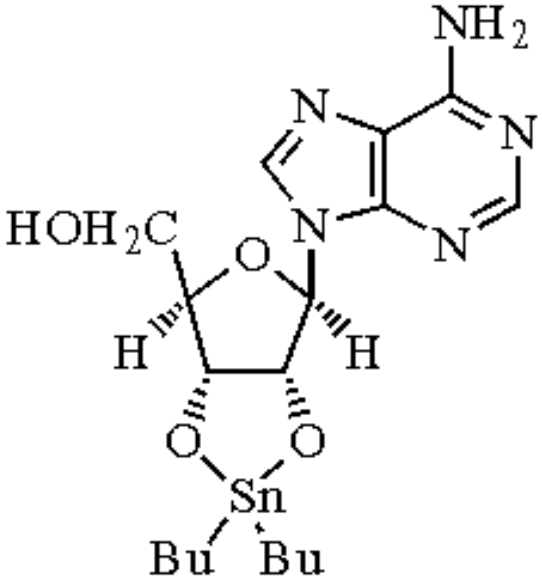

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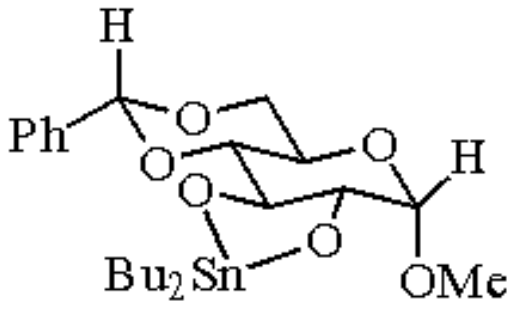

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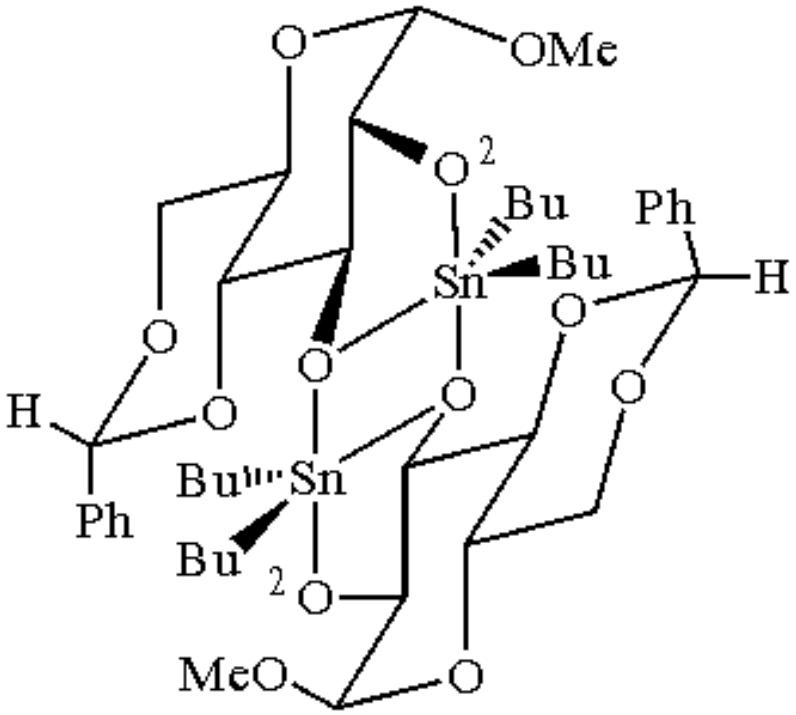

(4)

Regioselective Alkylation, Acylation, and Sulfonylation.

Synthetic applications of stannylenes have followed the elegant studies of Moffatt[17] and Ogawa,[18] who showed that the inherent differences in the nucleophilicities of carbohydrate hydroxys can be amplified by the formation of trialkyltin ethers. Several selective acylations and alkylations could thus be accomplished. Further it was noted that while acylation proceeds without any catalyst, alkylation is a sluggish reaction and needs assistance from tetrabutylammonium halides (eq 3).[19]

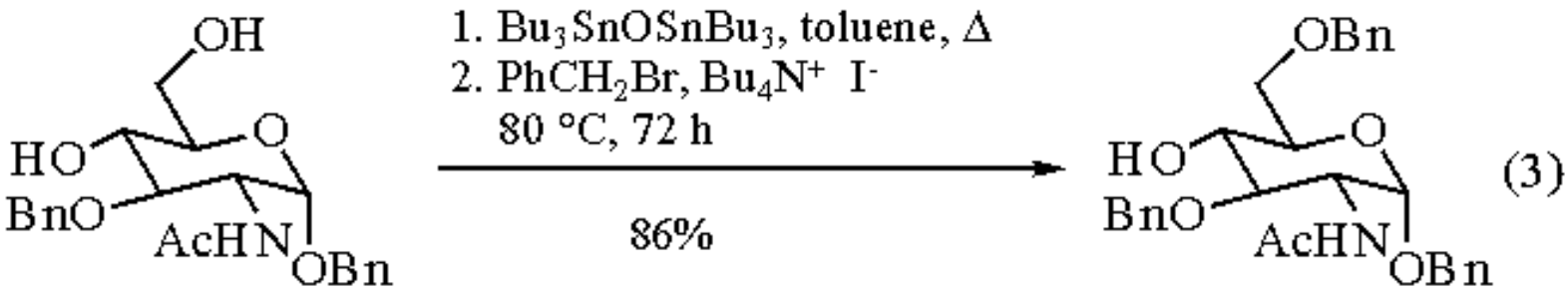

Reactions of stannylene (**2**) are typical and are shown in eq 4.[2]

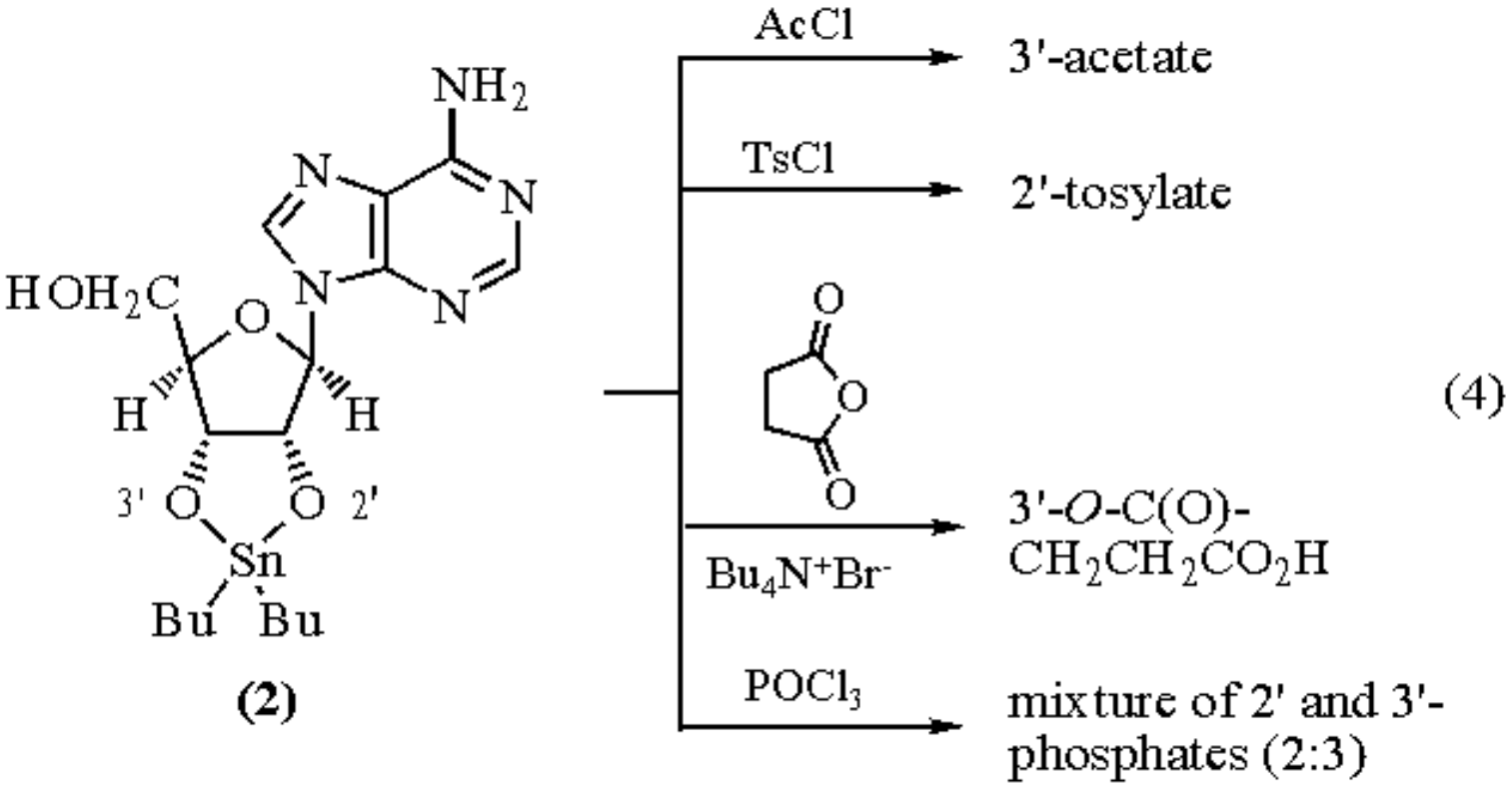

The stannylene (**3**) reacts with benzoyl chloride or tosyl chloride to give the corresponding 2-*O*-derivative (eq 5). The alkylation is less selective.[20] Use of nonpolar solvents and tetrabutylammonium halide has been a significant improvement (eq 6) in this alkylation procedure.[21] Several other examples of selective acylation and alkylations are given by David and Hanessian.[2] An intramolecular ether formation using DBTO has been used for the synthesis of octosyl acid.[22] Monoacylation of dimethyl L-tartrate has been carried out using this procedure (eq 7).[23] Two highly readable accounts of how the anomer composition and stoichiometry of reagents affect the regiochemistry of acylation[24] and tosylation[25] have recently appeared.

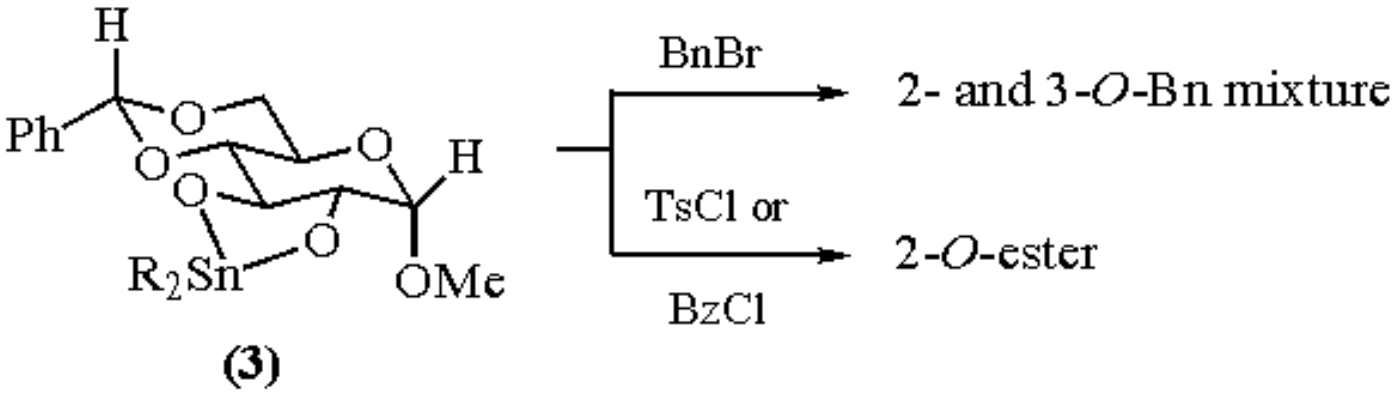

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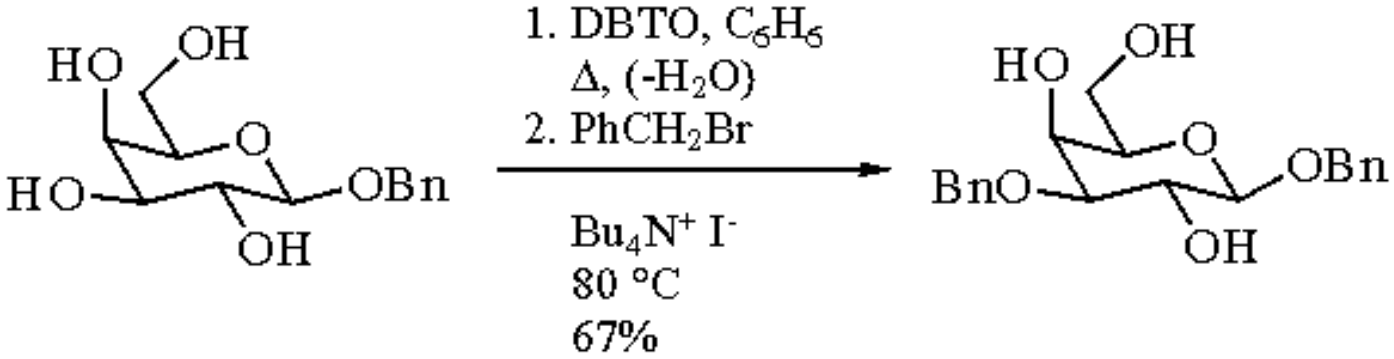

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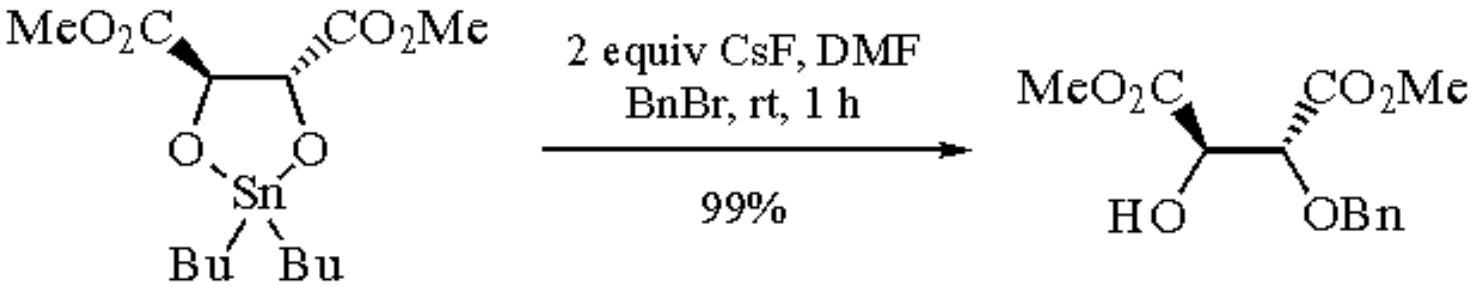

(7)

(also reactions with *t*-BuCOCl and TBDMS-Cl)

The structure of the dimeric complex (**4**) has been used to explain the observed preferential reactivity of the C-2 hydroxy groups.[2] It is argued that the divalent oxygens that occupy the axial position within the tin cordination sphere (i.e. this case, the C-2 oxygens) are not only more nucleophilic, but also are more accessible sterically. It is believed that the orientational preference of the hydroxy group is related to its acidity, and thus by forming a Sn complex with the more acidic hydroxy group in the axial position, its reactivity towards nucleophiles is enhanced. The stannylene procedure can be used to reverse the stereochemistry of the classical monoacylation regiochemistry observed in some unsymmetrical diols.[26]

Regioselective Oxidation.

Following the original discovery by David and Thieffrey,[27] several stannylenes have been oxidized by bromine to acyloins (eq 8). Hanessian employed this reaction for the synthesis of a densely functionalized intermediate which was converted into (+)-spectinomycin.[28] A detailed study of monooxidation of unprotected carbohydrates has also appeared.[29] Stannylenes are oxidized the same way as diols, with ***Sodium Periodate*** and ***Lead(IV) Acetate***.[2]

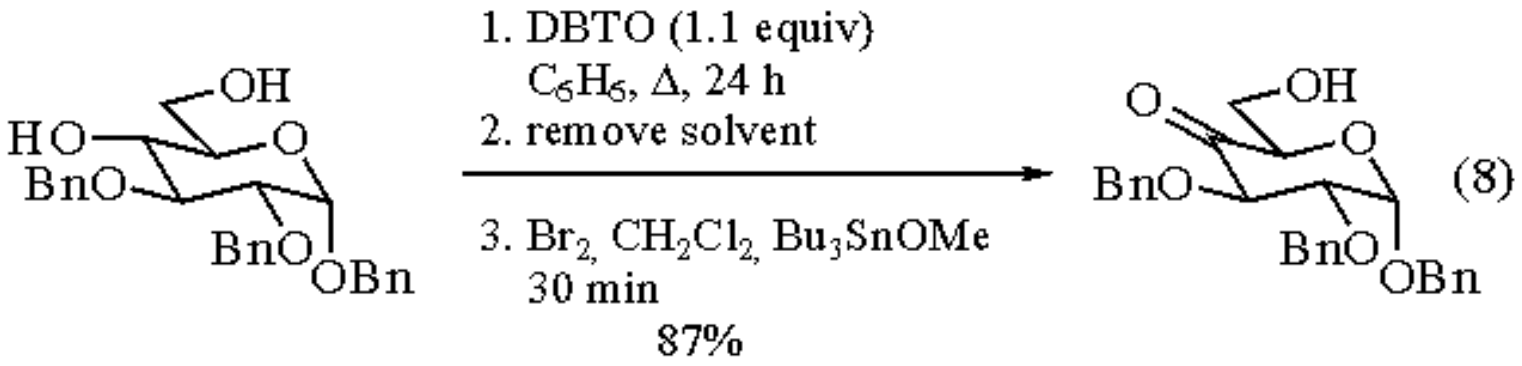

Esterification Catalyst.

In the presence of DBTO, alcohols react with carboxylic acids to give esters[30] and the reaction can be extended to make lactones and lactams (eqs 9 and 10).[3] It should be noted that the stereochemistry of the alcohol center is unaffected. A template-driven extrusion process, in which an intermediate where the hydroxy and the carboxyl groups are brought into close proximity by tin oxide, has been proposed for this reaction.

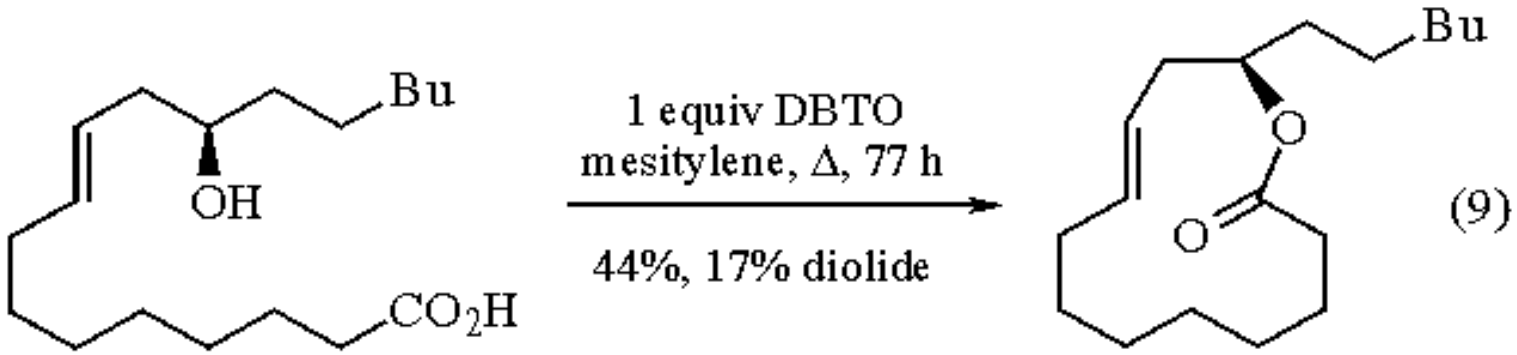

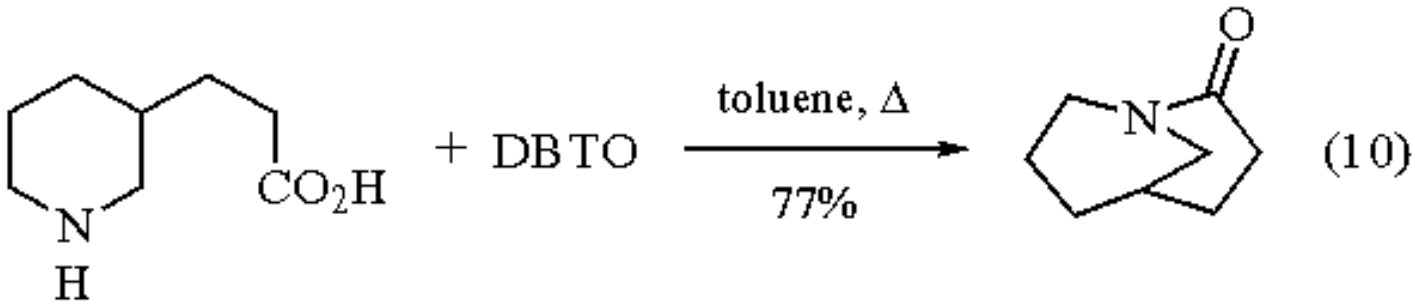

Stannylenes derived from diols react with bifunctional carboxylic acid derivatives to give macrocyclic polyolides of various sizes.[31,32] This approach has been used for the synthesis of (+)-dicrotaline (eq 11).[33]

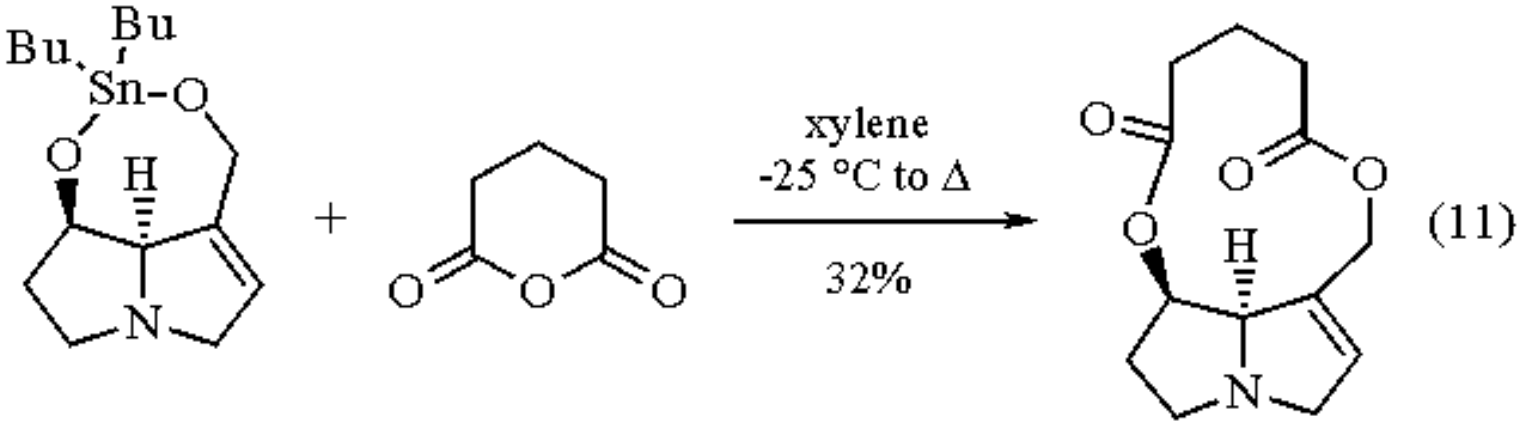

Dibutyltin oxide is the best source of tin for the Otera transesterification catalysts (eq 12),[6] which have found wide use in organic synthesis. DBTO has also been used as a catalyst for hydrolysis of amides in very sensitive molecules, where other procedures have failed.[34]

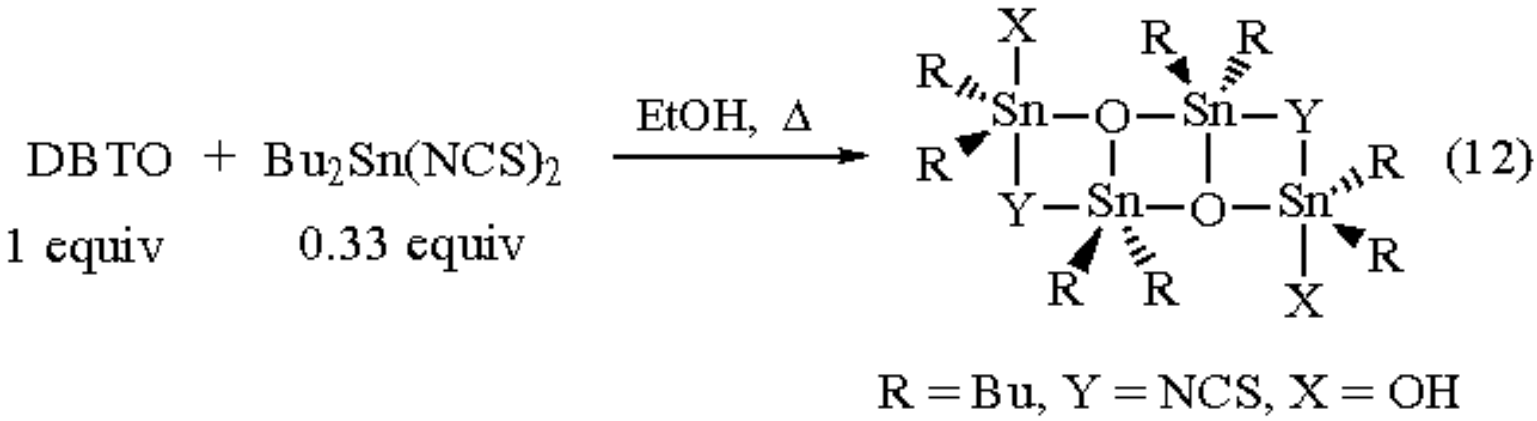

Catalyst in Oxidation Reactions.

DBTO has been used as a catalyst in Fe^{III}-mediated oxidation of thiols to disulfides, even though ***Tri-n-butyl(methoxy)stannane*** seems to be better suited for this purpose.[35] Epoxidation of terminal alkenes in a two-phase system (chloroform-water) containing H_2O_2/ammonium molybdate/DBTO has also been reported.[36] A combination of DBTO and ***t-Butyl Hydroperoxide*** oxidizes allylic alcohols with moderate regio- and stereoselectivity.[4] Tri- and tetrasubstituted double bonds are most easily oxidized and the selectivities are comparable to those of the corresponding ***Vanadyl Bis(acetylacetonate)*** mediated reactions.

Miscelleneous Applications.

The method of choice for the regioselective opening of benzylic and tertiary epoxides with alcohols (eq 13) appears to be a reaction mediated by organotin phosphate condensate (OPC), which is readily prepared from DBTO and tributyl phosphate.[7] DBTO catalyzes rearrangement of 3-hydroxy-2-oxo carboxylic acid esters (eq 14), a reaction reminiscent of a similar one mediated by the enzyme reductoisomerase.[37] DBTO has been used as a catalyst for the addition of ***Azidotrimethylsilane*** to nitriles[5] for the production of tetrazoles (eq 15).

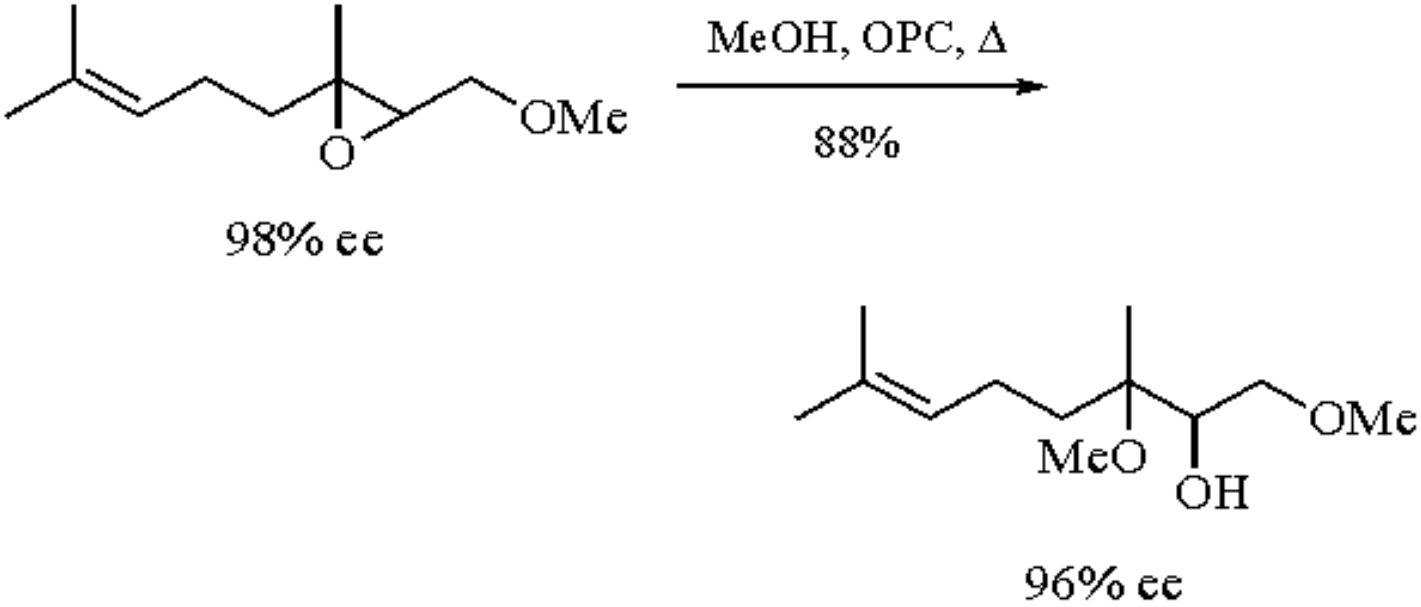

(13)

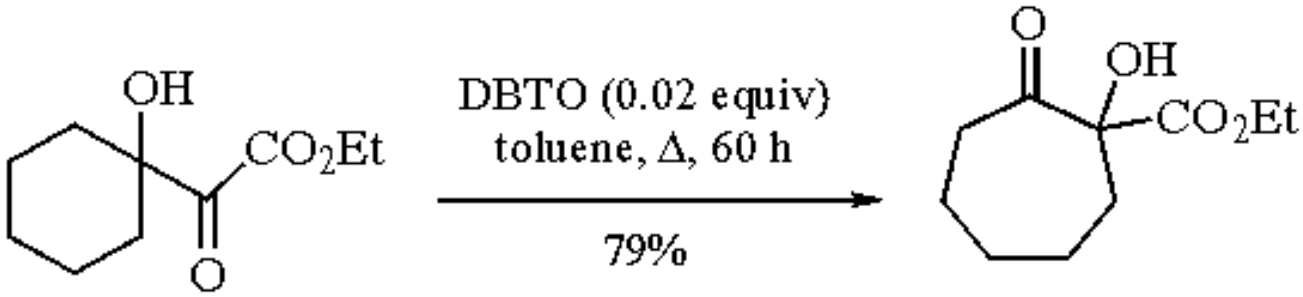

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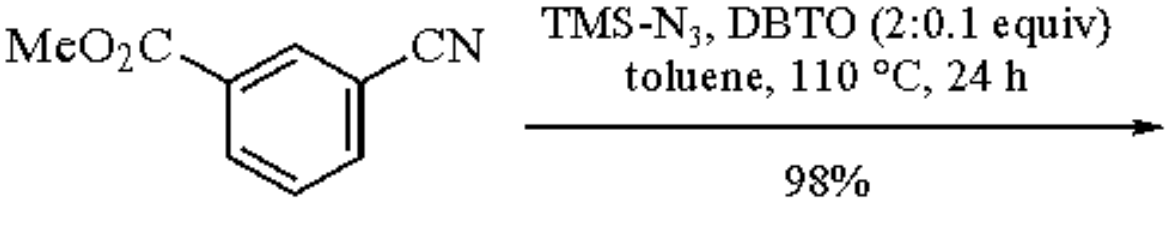

(15)

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Di-*n*-butylbis(cyclopentadienyl)zirconium

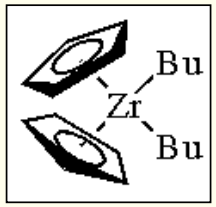

[80005-41-0] · $C_{18}H_{28}Zr$ · Di-*n*-butylbis(cyclopentadienyl)zirconium · (MW 335.64) (*n*-BuLi)

[109-72-8] · C_4H_9Li · Di-*n*-butylbis(cyclopentadienyl)zirconium · (MW 64.06) (*n*-BuMgCl)

[693-04-9] · C_4H_9ClMg · Di-*n*-butylbis(cyclopentadienyl)zirconium · (MW 116.87) (Cl_2ZrCp_2)

[1291-32-2] · $C_{10}H_{10}Cl_2Zr$ · Di-*n*-butylbis(cyclopentadienyl)zirconium · (MW 292.32)

(a reagent generated in situ as a $ZrCp_2$ equivalent useful for the preparation of $ZrCp_2$ π-complexes containing alkynes,[1,2] alkenes,[1,2] dienes,[5] aldehydes,[14] and nitriles as well as five-membered zirconacycles and their bicyclic and polycyclic derivatives)

Alternate Name: di-*n*-butylzirconocene.

Physical Data: Cl_2ZrCp_2; mp 245 °C.

Form Supplied in: *n*-BuLi: solutions in cyclohexane, hexanes and pentane. *n*-BuMgCl: solutions in diethyl ether and THF. Cl_2ZrCp_2: colorless crystals. All are commercially available.

Preparative Methods: generated in situ by the addition of 2 equiv of ***n-Butyllithium*** in hexanes or pentane, or *n*-BuMgCl in diethyl ether or THF, to ***Dichlorobis(cyclopentadienyl)zirconium*** dissolved in THF at -78 °C in an inert atmosphere of N_2 or Ar.

Handling, Storage, and Precautions: *n*-butyllithium and *n*-butylmagnesium chloride are sensitive to air, moisture, and a wide variety of heterofunctional and carbofunctional compounds. They must be used and stored under an inert atmosphere of N_2 or Ar. Zirconocene dichloride may be handled in air, but it is advisable to avoid extensive exposure to air, moisture, and light. Use in a fume hood.

Reaction of *n*-Butyllithium with Cl_2ZrCp_2.

The reaction of Cl_2ZrCp_2 with 2 equiv of *n*-BuLi in THF at -78 °C cleanly produces *n*-Bu_2ZrCp_2 (**1**) in essentially quantitative yield within 1 h.[1] At or above 0 °C, (**1**) decomposes smoothly to form thermally unstable (1-butene)zirconocene (**2**), which can be stabilized with PMe_3 and other phosphines to give the corresponding 1-butene-zirconocene-phosphine complex (eq 1). Some such complexes, e.g. $(EtCH{=}CH_2)ZrCp_2(PMe_3)$ (**3**), have been isolated and fully identified.[1c,2] Detailed studies of the decomposition reaction of dialkylzirconocenes indicate that the reaction is first-order, unimolecular,[3] and nondissociative.[4] Thus neither free $ZrCp_2$ nor free alkene is formed during the conversion of dialkylzirconocenes into alkene-zirconocene complexes. In the absence of any other reagents, $(EtCH{=}CH_2)ZrCp_2(PMe_3)$, which exists as an 80:20 to 90:10 mixture of the distal and proximal stereoisomers (**3a** and **3b**), respectively, further decomposes at 50 °C to give a dimeric species (**4**), which is relatively stable and inert to various compounds.[2] Unstabilized alkene-zirconocene complexes are even more prone to a similar dimerization. Consequently, the generation and use of these compounds, e.g., (**2**) and (**3**) is best carried out in the presence of additional reagents that can react with alkene-zirconocene derivatives in a synthetically desirable manner before decomposition of the zirconocene complexes

occurs.

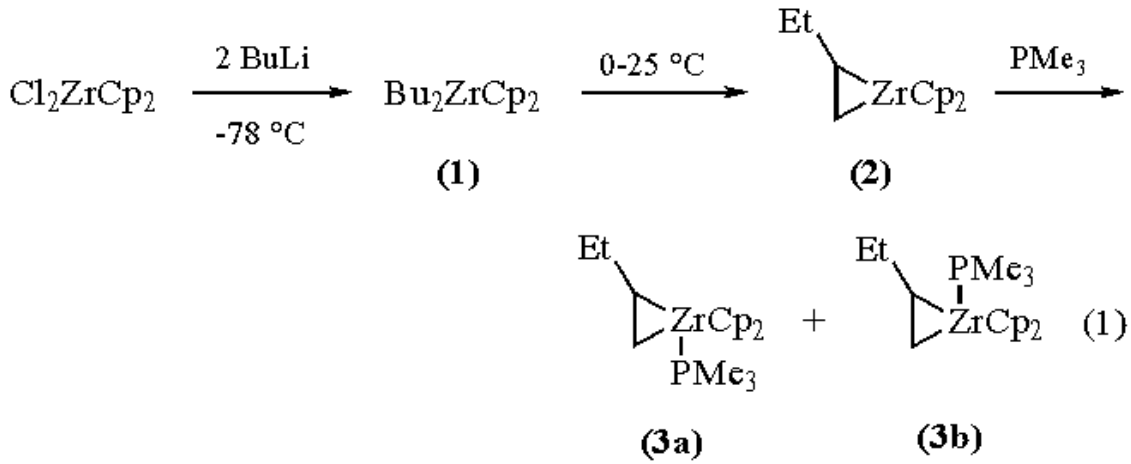

Alkene Displacement Reactions.

The 1-butene-zirconocene complexes (**2**) and (**3**) can react with alkynes,[1,2] alkenes,[1,2] and conjugated dienes[5] to give the corresponding π-complexes with concomitant expulsion of 1-butene. Even some single-bonded reagents, e.g. silanes,[6] allyl ethers,[7] and propargyl ethers,[8] can react similarly with (**2**) or (**3**) to give oxidative addition products with extrusion of 1-butene. Some representative examples are shown in Scheme 1. The complexes (**4**), (**5**),[1b] (**6**),[10] (**7**),[2,9] (**8**),[6] and (**9**)[11] have been fully identified by spectroscopic and other analytical methods, including X-ray analysis.

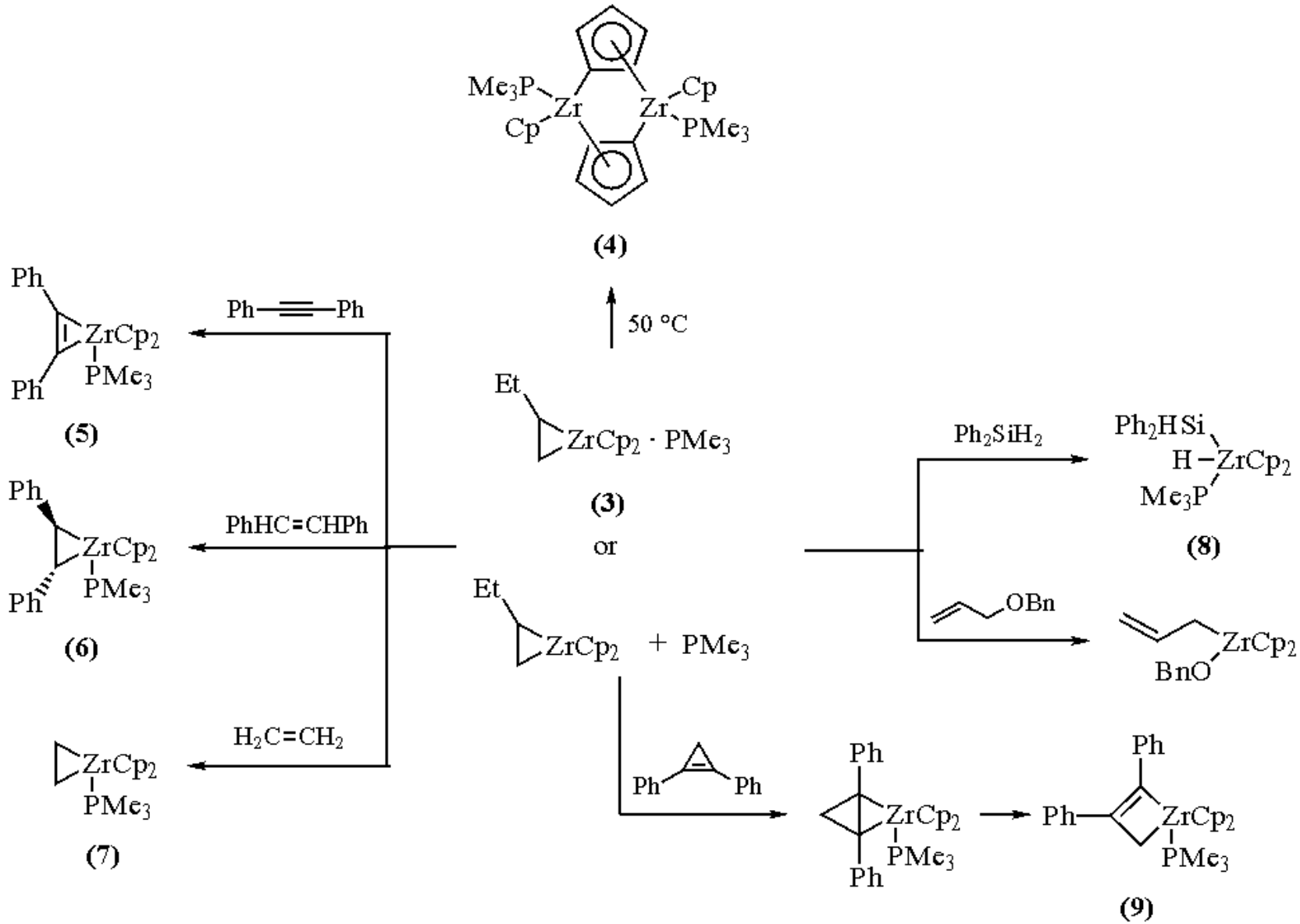

Scheme 1

Synthesis of Five-Membered Zirconacycles via (1-Butene)zirconocene.

Depending on substrate structures, quantities, and whether or not other reagents, such as phosphines, are present, the reactions of (1-butene)zirconocene with π-compounds, such as alkynes, alkenes, dienes, aldehydes, and nitriles, may give either displacement products as discussed above or five-membered zirconacycles with or without incorporation of 1-butene. Although the exact courses of these reactions depend on various kinetic and thermodynamic factors and often are difficult to predict, the following results indicate some general trends for prediction. In general, 1-butene is a relatively weak and readily displaceable ligand, as shown above. However, in cases where the 1-butene displacement products are relatively unhindered, 1-butene may ultimately be incorporated to give five-membered zirconacycles. Some reagents may be capable of directly interacting with (**2**) to give the corresponding five-membered zirconacycles with incorporation of 1-butene. Some of these reactions are shown in Scheme 2. The

reactions of (**2**) with alkenes have been shown to give thermodynamically equilibrated products,[12,13] In the thermally equilibrated products, alkyl groups prefer to be β to the Zr atom, while aryl and alkenyl groups end up in the α-position, as in (**10**)-(**12**). In the aldehyde reaction, the sterically less hindered C-Zr bond must selectively react with aldehydes to produce (**13**) in an irreversible manner.[14]

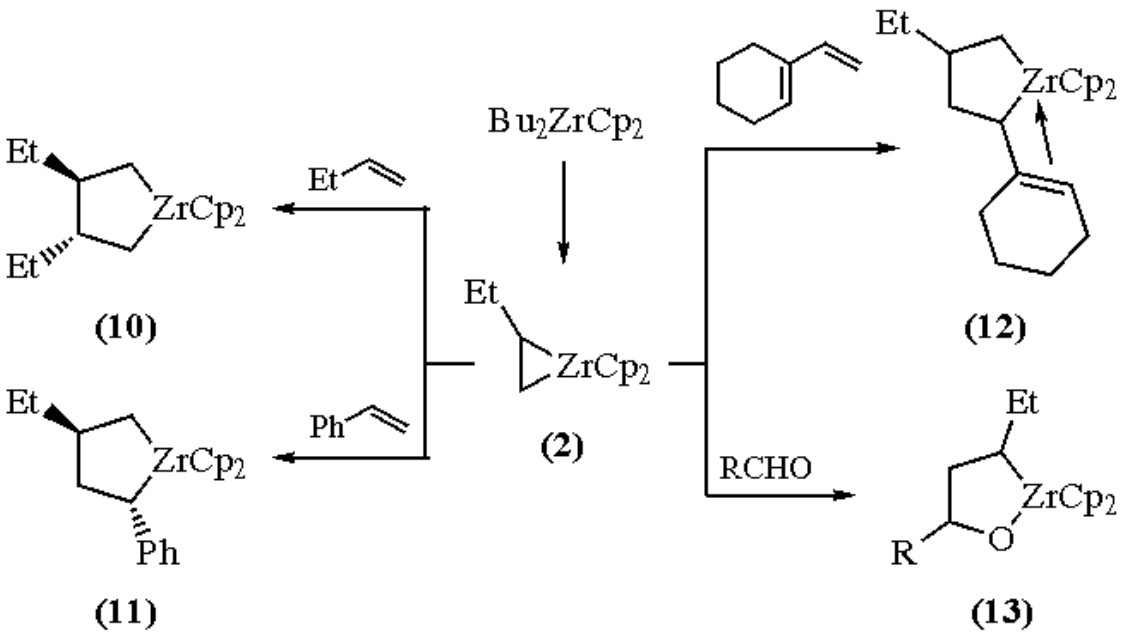

Scheme 2

Synthetically more useful are those reactions in which five-membered zirconacycles are formed with extrusion of 1-butene. Particularly attractive are the bicyclization reactions of nonconjugated enynes,[15-17] diynes,[1,18,19] and dienes[20-22] as well as related heterocycle-producing reactions (Scheme 3).[23] These products can be readily converted to a variety of organic derivatives via various reactions including protonolysis, iodinolysis, and carbonylation (Scheme 4).[1,12-23] The intermolecular versions of these reactions are more difficult to control. Nonetheless, some highly favorable and clean results have been obtained with selected alkenes.[24] In some of these reactions (Scheme 3), zirconacyclopentanes are undoubtedly the initial products which then undergo ring contraction and reexpansion to give the final zirconacyclopentenes and other products.

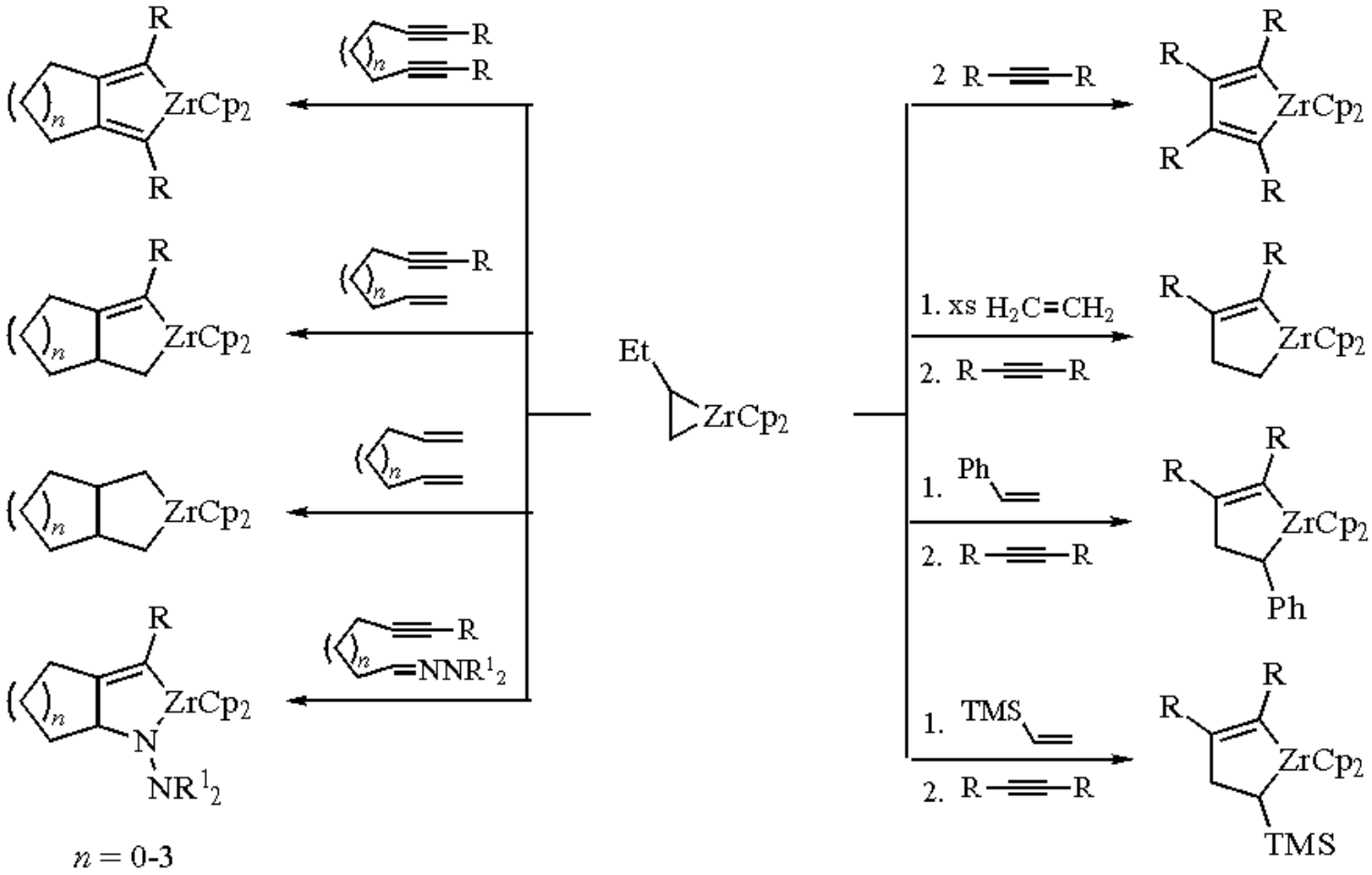
R
ZrCp2
n
Et
2 R—≡—R
1. xs H2C=CH2
2. R—≡—R
1. Ph
2. R—≡—R
1. TMS
2. R—≡—R
Ph
TMS
=NNR12
N
NR12
n = 0-3

Scheme 3

Di-n-butylbis(cyclopentadienyl)zirconium

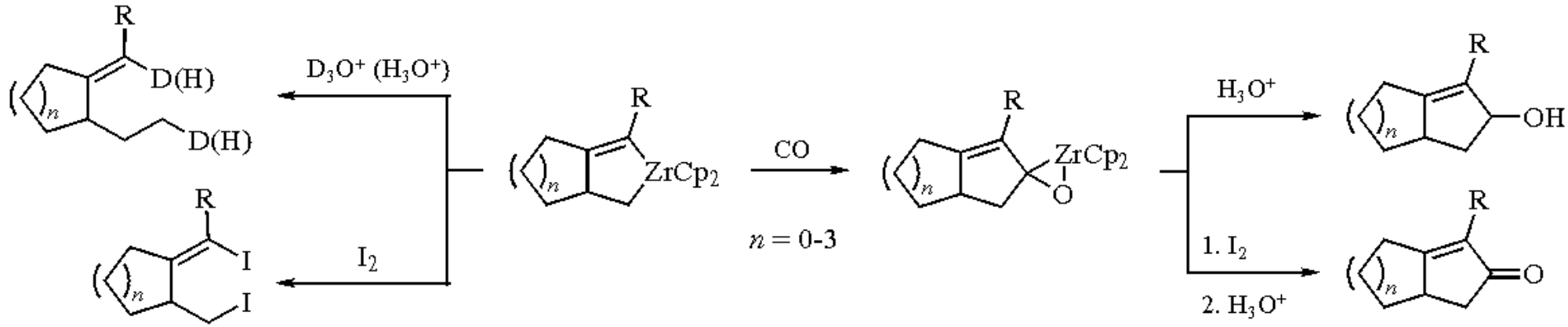

Scheme 4

The Zr-promoted bicyclization reactions of enynes and dienes have been applied to the efficient synthesis of some complex natural products, e.g. phorbol (**14**),[25] pentalenic acid (**15**),[26] iridomyrmecin (**16**),[27] and dendrobine (**17**).[28]

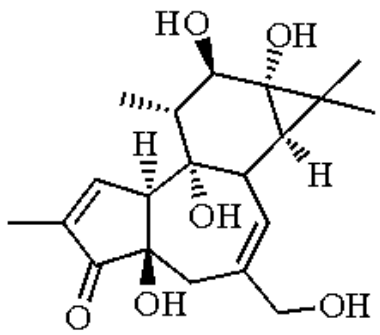

(14)

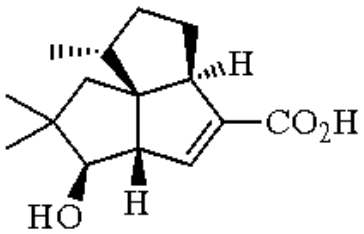

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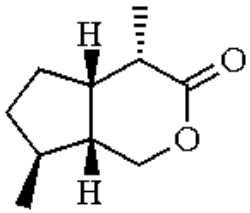

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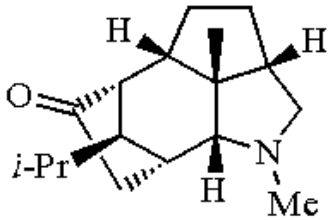

(17)

Zirconocene derivatives derived from *n*-BuMgCl and Cl_2ZrCp_2 effectively catalyze cyclic[29,30] and acyclic[31] dimerization of alkenes, as exemplified by eq 2. Significant differences between Et_2ZrCp_2[30,32-34] and higher dialkylzirconocenes such as $(n\text{-Bu})_2ZrCp_2$ have been noted.

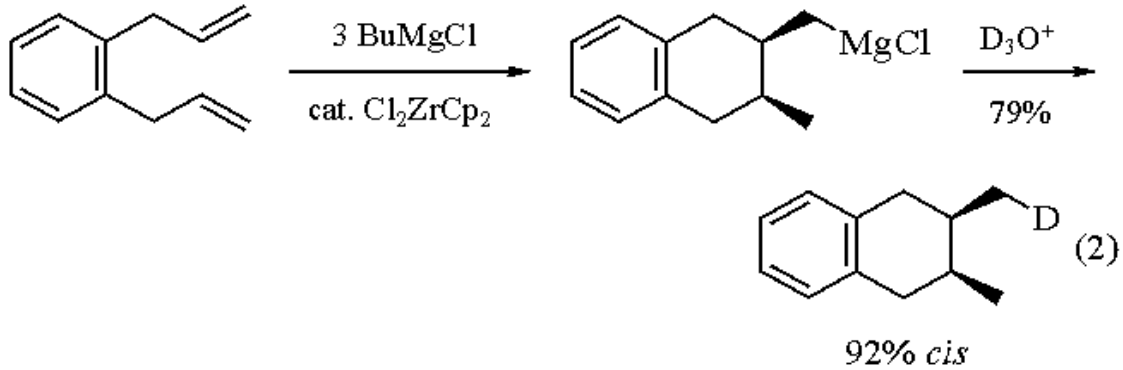

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Dicarbonylbis(cyclopentadienyl)hafnium[1]

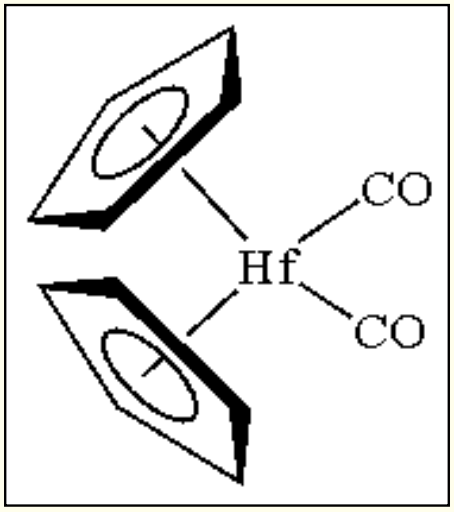

[59487-86-4] · $C_{12}H_{10}HfO_2$ · Dicarbonylbis(cyclopentadienyl)hafnium · (MW 364.70)

(couples alkynes to form hafnacyclopentadienes[3])

Physical Data: subl at 80 °C/10^{-4} mmHg.[2a]

Solubility: sol hydrocarbons, THF.

Analysis of Reagent Purity: IR, NMR.[2]

Preparative Method: reduction of ***Dichlorobis(cyclopentadienyl)hafnium*** with ***Magnesium Amalgam*** under CO atmosphere.[2b]

Purification: hexane solution is filtered through alumina and cooled to -20 °C to induce crystallization; sublimation at 80 °C/10^{-4} mmHg.[2]

Handling, Storage, and Precautions: store and handle under an inert atmosphere. Use in a fume hood.

Dicarbonylbis(cyclopentadienyl)hafnium reacts with alkynes to form hafnacyclopentadiene complexes (eq 1), which may be isolated and purified prior to further manipulations.[3] Carbonylated products are not observed, indicating that the carbonyl ligands serve only as labile ligands which are lost during the reaction. Hafnacyclopentadiene complexes prepared by alternate methods have been converted into various 1,3-butadienes (see also ***Dichlorobis(cyclopentadienyl)hafnium***).

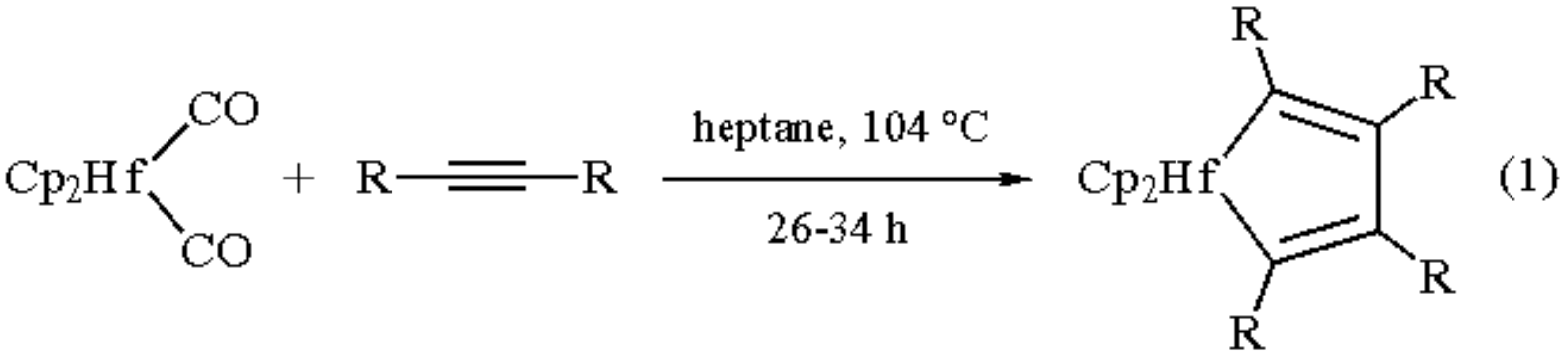

R = Ph, 68%; R = C_5F_5, 71%; R = Et, 74%

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1. (a) Cardin, D. J. In *Dictionary of Organometallic Compounds*; Buckingham, J., Ed.; Chapman & Hall: London, 1984; Vol. 2, p 1009. (b) Cardin, D. J.; Lappert, M. F.; Raston, C. L.; Riley, P. I. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 3, pp 610-616. (c) Pez, G. P.; Armor, J. N. *Adv. Organomet. Chem.* **1981**, *19*, 1. (d) Sikora, D. J.; Macomber, D. W.; Rausch, M. D. *Adv. Organomet. Chem.* **1986**, *25*, 317.
2. (a) Thomas, J. L.; Brown, K. T. *JOM* **1976**, *111*, 297. (b) Sikora, D. J.; Moriarty, K. J.; Rausch, M. D. *Inorg. Synth.* **1990**, *28*, 248.
3. Sikora, D. J.; Rausch, M. D. *JOM* **1984**, *276*, 21.

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Dicarbonylbis(cyclopentadienyl)titanium[1]

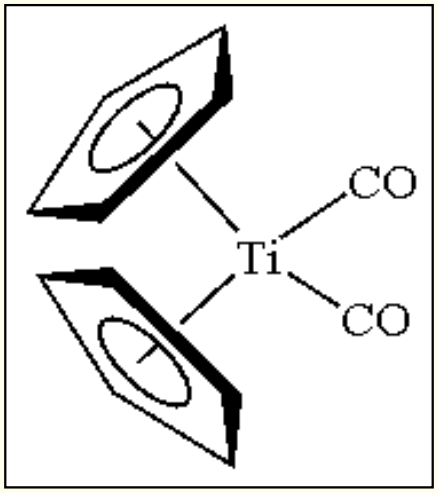

[12129-51-0] · $C_{12}H_{10}O_2Ti$ · Dicarbonylbis(cyclopentadienyl)titanium · (MW 234.09)

(deoxygenates sulfoxides;[3] forms alkenes by reductive coupling of aromatic aldehydes;[4a] reduces alkynes[5])

Physical Data: mp 90 °C (dec), subl 40-80 °C/0.001 mmHg.[1a]

Solubility: sol most common organic solvents; reacts with $CHCl_3$ and CH_2Cl_2.

Analysis of Reagent Purity: IR, NMR.[2]

Preparative Method: reduction of ***Dichlorobis(cyclopentadienyl)titanium*** with ***Magnesium Amalgam*** under CO atmosphere.[2]

Purification: recrystallization from toluene or sublimation at 40-80 °C/0.001 mmHg.

Handling, Storage, and Precautions: pyrophoric; store and handle under an inert atmosphere.[1a] Use in a fume hood.

Deoxygenation of Sulfoxides.

Sulfoxides are readily deoxygenated by dicarbonylbis(cyclopentadienyl)titanium to form sulfides in high yield.[3] It is noteworthy that this deoxygenation is not accompanied by byproducts that sometimes result from Pummerer rearrangement in other methods. A range of alkyl and aryl sulfoxides are reduced in yields which are generally higher than 80% (see eq 1, for example).

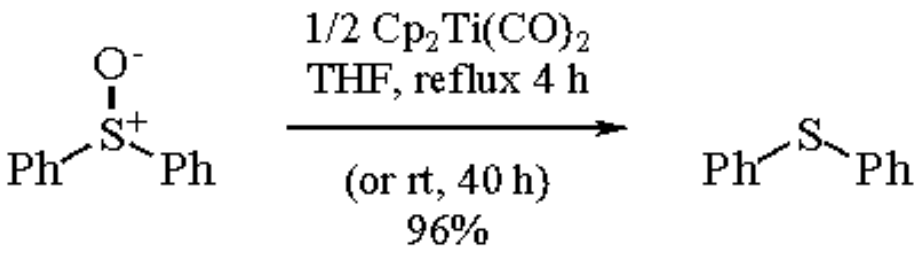

(1)

Reductive Coupling of Aromatic Aldehydes.

Reductive coupling of aromatic aldehydes forms stilbene derivatives in good yields (eq 2).[4a] These reactions apparently proceed through the intermediacy of pinacol derivatives which are often observed as byproducts of the reaction, especially at short reaction times, and in the presence of substoichiometric quantities of dicarbonylbis(cyclopentadienyl)titanium. Related reductive dimerizations have also been reported for diethyl ketomalonate,[4b] *N,N´*-di-*p*-tolylcarbodiimide,[4b] and carbon disulfide.[4c]

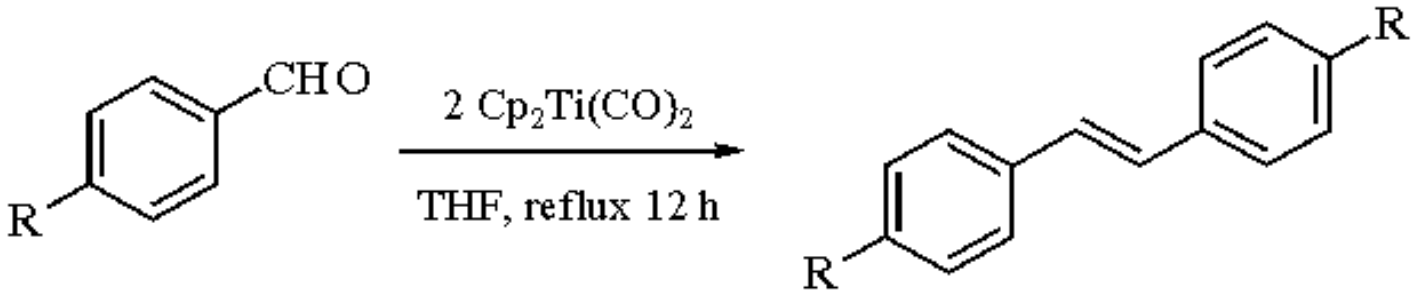

(2)

R = H, 98%; R = Me, 99%; R = Cl, 59% (88% with 4 equiv $Cp_2Ti(CO)_2$)

Reduction of Alkynes.

Terminal alkynes are hydrogenated to terminal alkenes using dicarbonylbis(cyclopentadienyl)titanium as the catalyst. Aryl alkynes are reduced to the corresponding ethane derivatives under the same conditions (Table 1).[5a] A more potent catalyst is obtained by treating $Cp_2Ti(CO)_2$ with ***Diphenylacetylene***. The resulting π-acetylene complex rapidly and completely reduces diphenylacetylene, styrene, *trans*-stilbene, 1-octene, and 1,4-diphenylbutadiene to the corresponding ethane derivatives.[5b]

Table 1 Hydrogenation of Alkynes with Catalytic Dicarbonylbis(cyclopentadienyl)titanium

Substrate	Product	Yield (%)
Acetylene	No reaction	
1-Pentyne	1-Pentene	95
1-Hexyne	1-Hexene	90
t-Butylacetylene	3,3-Dimethylbut-1-ene	40
	2,2-Dimethylbutane	60
3-Heptyne	No reaction	
Phenylacetylene	Ethylbenzene	95
Diphenylacetylene	Dibenzyl	90

Stoichiometric alkyne reductions have also been reported. Low yields of *cis* alkenes are obtained by treatment of internal alkynes with $Cp_2Ti(CO)_2$ in wet hexane followed by cleavage of the resulting complex with HCl in CH_2Cl_2.[5c] The reaction of several unsaturated diacids with $Cp_2Ti(CO)_2$ gave the corresponding saturated carboxylate complexes in fair to excellent yields, rather than the expected unsaturated complexes.[5d]

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1. (a) *Dictionary of Organometallic Compounds*; Macintyre, J. E., Ed.; Chapman & Hall: London, 1988; 4th Suppl., p 239. (b) Bottrill, M.; Gavens, P. D.; McMeeking, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 3, pp 285-291. (c) Sneeden, R. P. A. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 8, p 28. (d) Tkatchenko, I. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 8, p 219. (e) Pez, G. P.; Armor, J. N. *Adv. Organomet. Chem.* **1981**, *19*, 1. (f) Sikora, D. J.; Macomber, D. W.; Rausch, M. D. *Adv. Organomet. Chem.* **1986**, *25*, 317.
2. Sikora, D. J.; Moriarty, K. J.; Rausch, M. D. *Inorg. Synth.* **1990**, *28*, 248.
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Dicarbonylbis(cyclopentadienyl)zirconium[1]

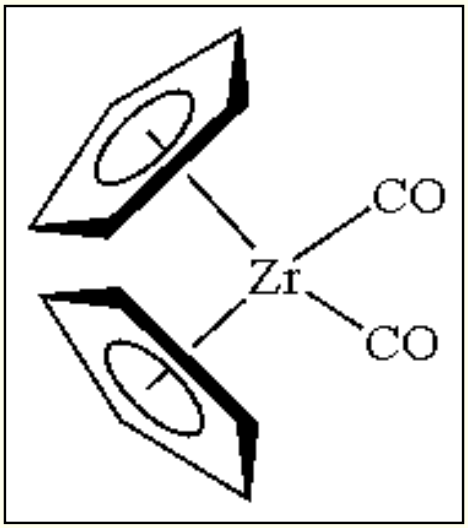

[59487-85-3] · $C_{12}H_{10}O_2Zr$ · Dicarbonylbis(cyclopentadienyl)zirconium · (MW 277.44)

(couples alkynes to form zirconacyclopentadienes[3])

Physical Data: subl 70 °C/10^{-2} mmHg.[1a]

Solubility: sol hydrocarbons, THF.

Analysis of Reagent Purity: IR, NMR.[2]

Preparative Method: reduction of ***Dichlorobis(cyclopentadienyl)zirconium*** with ***Magnesium Amalgam*** under CO atmosphere.[2]

Purification: hexane solution is filtered through alumina and cooled to -20 °C to induce crystallization; sublimation at 70 °C/10^{-2} mmHg.[2]

Handling, Storage, and Precautions: store and handle under an inert atmosphere. Use in a fume hood.

Dicarbonylbis(cyclopentadienyl)zirconium is one of several zirconocene derivatives which give zirconacyclopentadiene complexes when reacted with alkynes (eq 1) (see also ***Bis(cyclopentadienyl)diphenylzirconium*** and ***Dichlorobis(cyclopentadienyl)zirconium***).[3] Zirconacyclopentadiene complexes may be isolated and purified prior to further manipulations. Significantly, CO insertion usually does not occur, except when the reaction is done in a closed vessel (thereby preventing escape of CO).

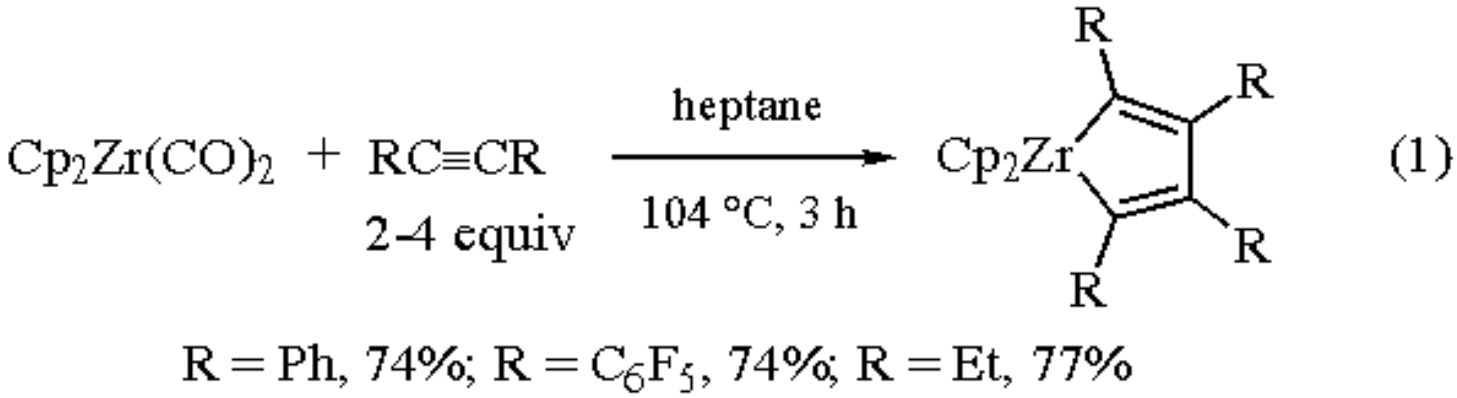

A number of reagents, including ***Hydrogen Chloride***, ***Iodine***, and ***Carbon Monoxide***, stereospecifically replace the metal to form substituted 1,3-butadienes.[4] For example, the zirconacyclopentadiene (**1**) reacts with HCl to give (*Z*,*Z*)-1,2,3,4-tetrakis(pentafluorophenyl)butadiene (eq 2).[3]

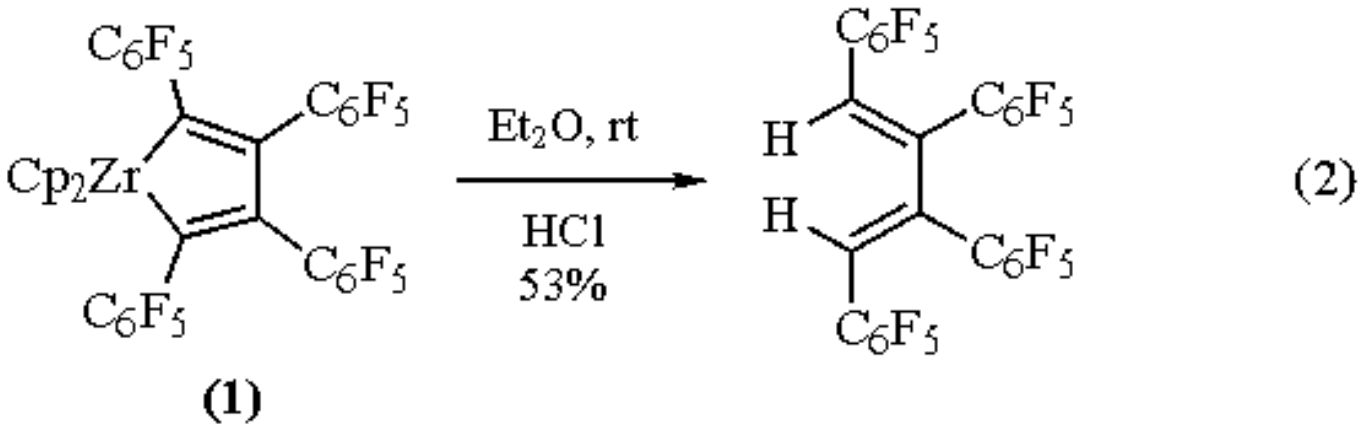

Zirconacyclopentadiene complexes have also been reported to react with excess alkyne producing expanded zirconacycles, and eventually alkyne oligomers and polymers.[5]

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1. (a) Cardin, D. J. In *Dictionary of Organometallic Compounds*; Buckingham, J., Ed.; Chapman & Hall: London, 1984; Vol. 2, p 2453. (b) Cardin, D. J.; Lappert, M. F.; Raston, C. L.; Riley, P. I. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 3, pp 610-616. (c) Pez, G. P.; Armor, J. N. *Adv. Organomet. Chem.* **1981**, *19*, 1. (d) Sikora, D. J.; Macomber, D. W.; Rausch, M. D. *Adv. Organomet. Chem.* **1986**, *25*, 317.
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3. Sikora, D. J.; Rausch, M. D. *JOM* **1984**, *276*, 21.
4. Most zirconacyclopentadiene complexes have been prepared from the other reagents cited in the text; the interested reader should refer to these sections for methods to form dienes from the zirconacyclopentadiene complexes.
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Thomas E. Snead

Dicarbonylbis(triphenylphosphine)nickel(0)

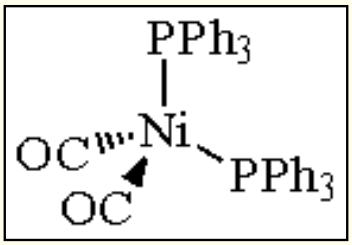

[13007-90-4] · $C_{38}H_{30}NiO_2P_2$ · Dicarbonylbis(triphenylphosphine)nickel(0) · (MW 639.32)

(carbonylation of vinyl and aryl halides;[1,2] oxidative bisdecarboxylation;[3-5] oligomerization reactions;[6-8] homo-Diels-Alder reactions)

Physical Data: mp 213-218 °C (dec).

Solubility: sol HMPA, THF, diglyme, triglyme, benzene, acetonitrile, ethanol, cyclohexane.

Form Supplied in: nonvolatile, light-yellow, air-stable solid.

Preparative Methods: by treating ***Tetracarbonylnickel*** with 2 equiv of ***Triphenylphosphine***[6] or by dissolving ***Dichlorobis(triphenylphosphine)nickel(II)*** in ethanol and treating it with CO in the presence of MeSNa.[10]

Purification: recrystallize from benzene.

Handling, Storage, and Precautions: catalytic activity decreases with storage. Likely to be toxic, similar to nickel carbonyl, but low volatility makes it easy to avoid ingestion.[1,11] Use in a fume hood.

Carbonylation Reactions.

The title reagent (**1**) is useful in the preparation of α-methylene lactones from appropriately substituted vinyl halides (eqs 1-3).[1] These reactions are commonly carried out at reflux under an inert atmosphere in THF using stoichiometric quantities of (**1**), triethylamine, and the substrate. The byproducts of this reaction are HBr and regenerated zerovalent nickel, so the process is formally catalytic in nickel. Attempts, however, to make this synthetic method catalytic have been unsuccessful.

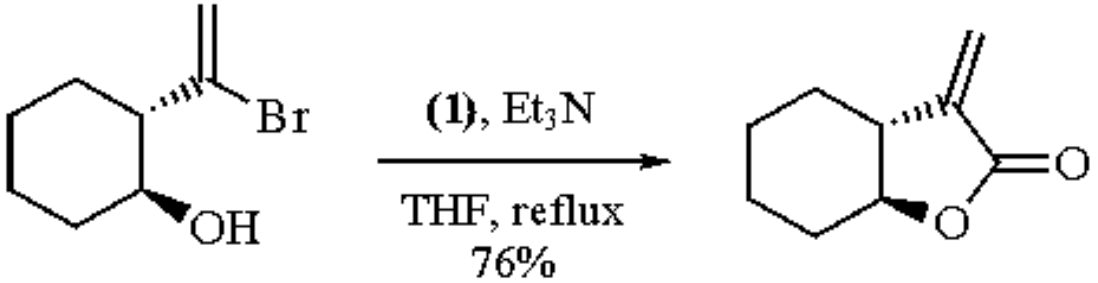

(1)

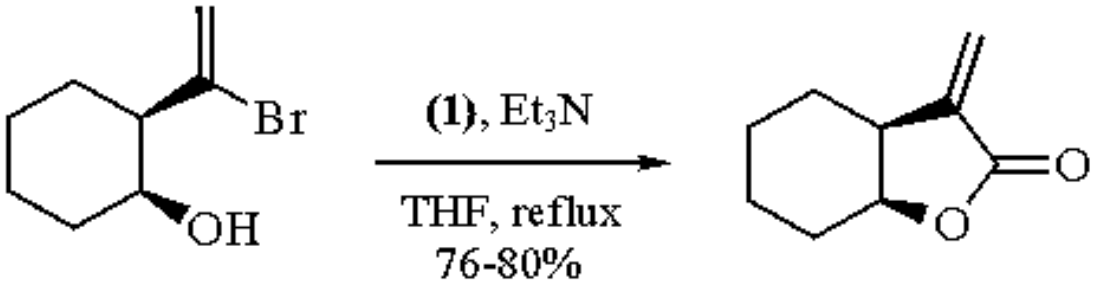

(2)

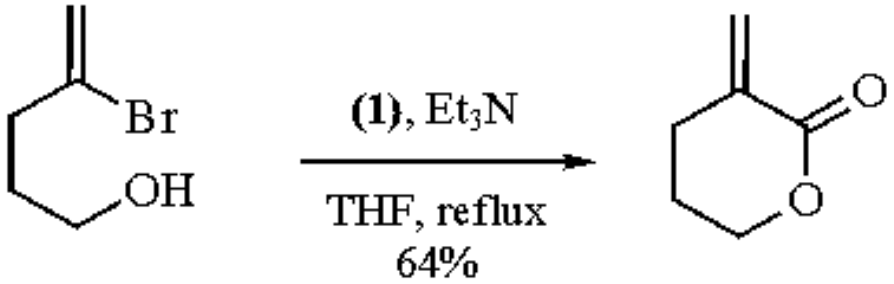

(3)

The title reagent has also been used in the carbonylation of aryl halides (eqs 4 and 5).[2] These reactions normally proceed at 120 °C in HMPA and 20 atm CO pressure. This process proceeds efficiently with ***Tetramethylstannane*** yet fails when Ph_4Sn is used under analogous conditions.

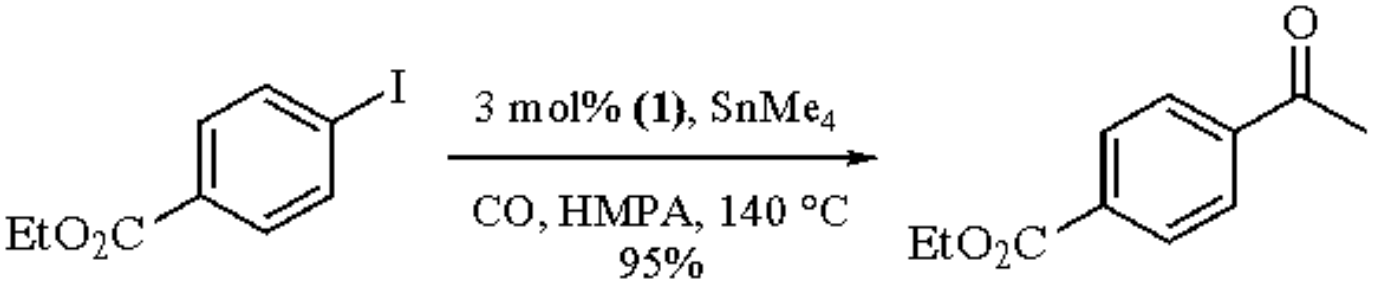

(4)

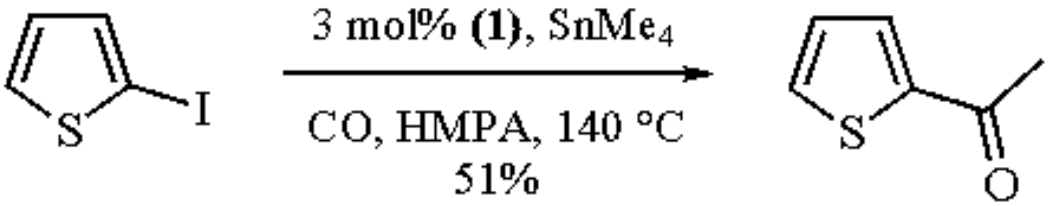

(5)

Oxidative Bisdecarboxylation.

This reaction using (**1**) has been used to prepare norbornenes (eq 6)[3,4] and other bicyclic compounds[5] from anhydride and thioanhydride precursors. These reactions are typically run in refluxing diglyme with stoichiometric (**1**). The application of this chemistry to other systems has been less effective particularly when the substrate contains abstractable β-hydrogens.[3]

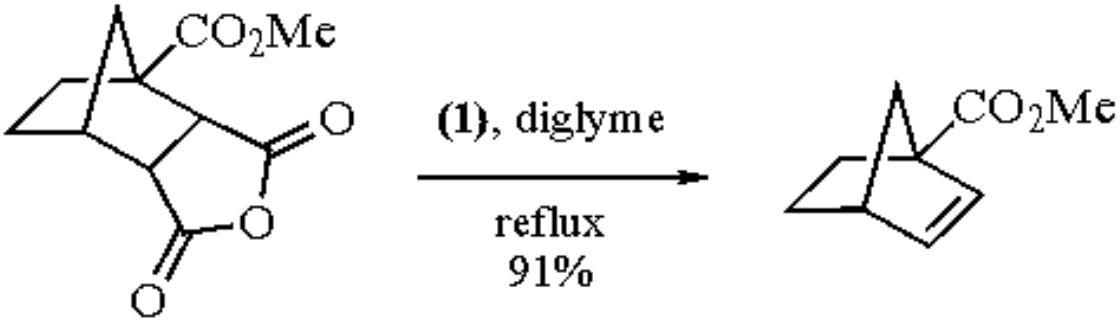

(6)

Cycloligomerization Reactions.

Complex (**1**) catalyzes the trimerization of alkynes to aromatic compounds (eq 7) under pressure in benzene.[6] The selective dimerization of butadiene to 4-vinylcyclohexene is mediated with catalytic (**1**) under CO pressure in high yield (eq 8).[7] When this process is allowed to proceed under acetylene pressure, a 4:1 mixture of 1,5-cyclooctadiene and 4-vinylcyclohexene is obtained in moderate yield (55%).[8]

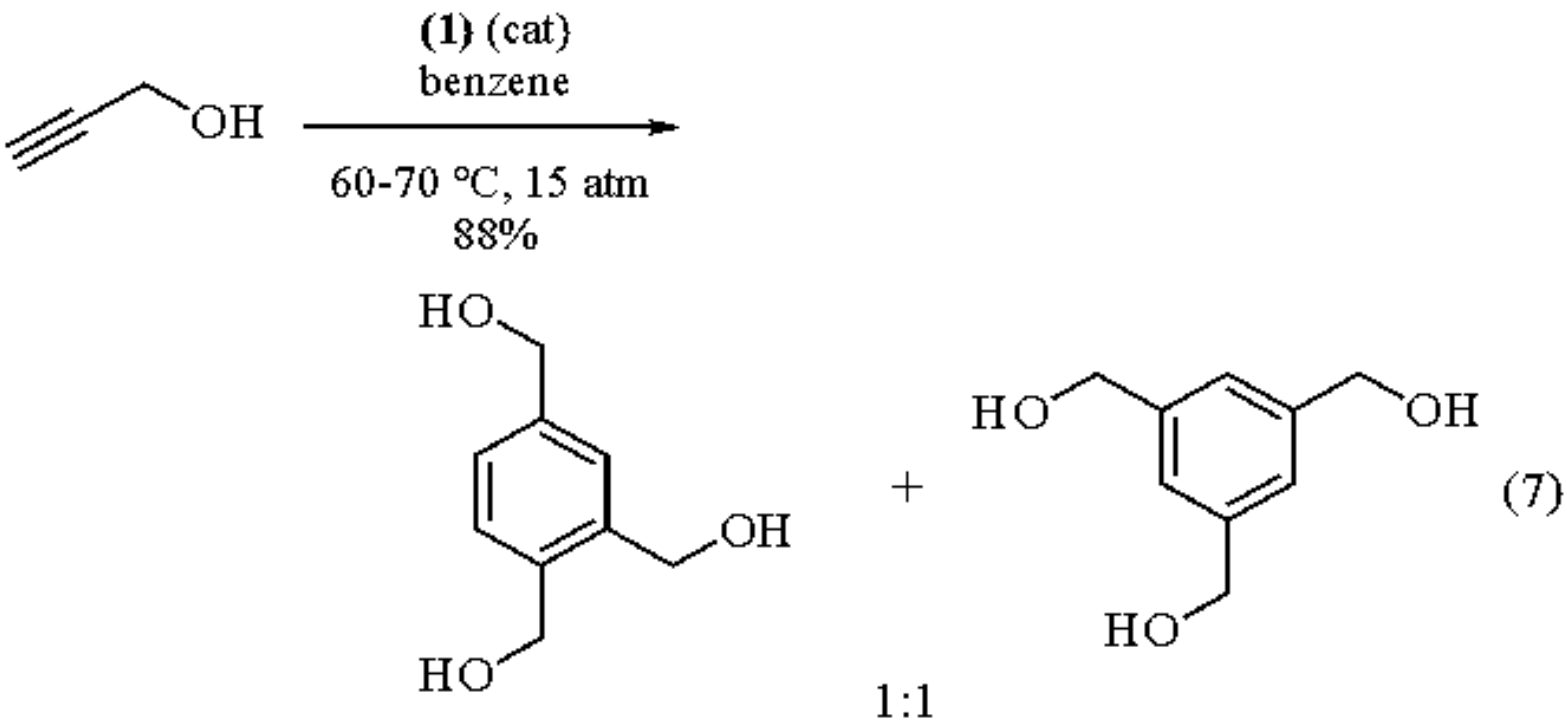

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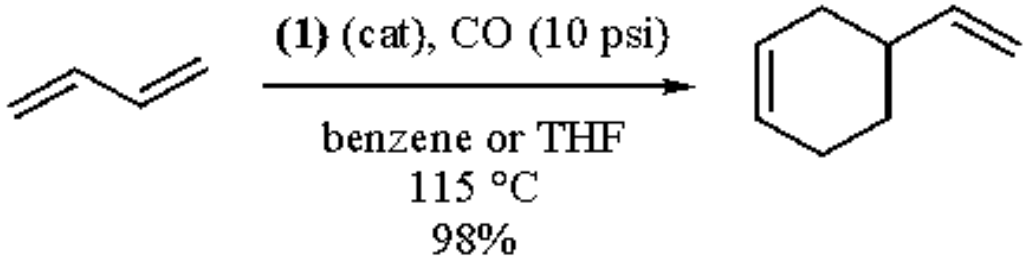

(8)

Homo-Diels-Alder Reactions.

The title reagent (**1**) catalyzes the homo-Diels-Alder condensation of vinyl compounds with norbornadiene (eq 9).[9] This process is typically carried out in a sealed tube while heating to 120 °C for 15 h.

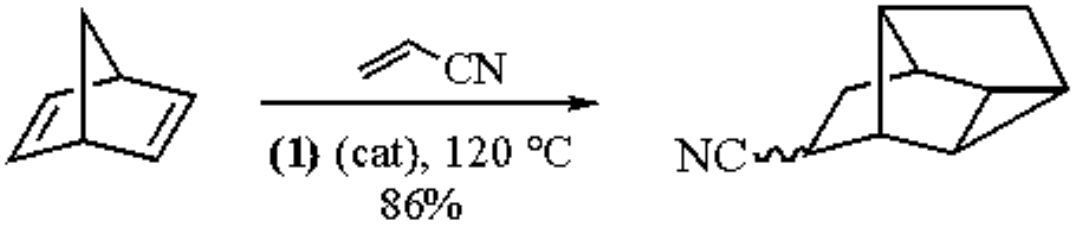

(9)

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Dicarbonyl(cycloheptadienyl)(triphenyl phosphite)iron Hexafluorophosphate

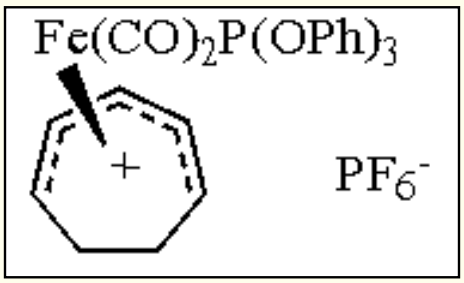

[85956-40-7] · $C_{27}H_{24}F_6FeO_5P_2$ · Dicarbonyl(cycloheptadienyl)(triphenyl phosphite)iron Hexafluorophosphate · (MW 660.27)

(synthesis of functionalized cycloheptadienes)

Physical Data: obtained as an amorphous powder.

Solubility: sol CH_2Cl_2, MeCN, acetone.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: IR (MeCN) 2067, 2028 cm^{-1}; ^1H NMR (CD_3CN) δ 7.49 (15H, m, $P(OPh)_3$), 6.36 (1H, t, *J* = 6.5 Hz, 3-H), 6.03 (2H, m, 2-H, 4-H), 4.92 (2H, m, 1-H, 5-H), 2.65 (2H, m, *endo*-6-H, *endo*-7-H), 1.80 (2H, m, *exo*-6-H, *exo*-7-H).

Preparative Methods: ***Triphenylmethyl Hexafluorophosphate*** (124 g) is dissolved in the minimum volume of dry CH_2Cl_2 and to that solution, dicarbonyl(cycloheptadiene)(triphenyl phosphite)iron[1] (150 g) is added. The mixture is swirled to dissolve the complex and set aside at rt for 2 h. The product is precipitated by pouring the mixture into wet ether, collected by filtration, and washed thoroughly with wet ether to afford pure (**1**) (190 g, 99%). The corresponding tetrafluoroborate salt is prepared from dicarbonyl(η^4-cycloheptatriene)(triphenyl phosphite)iron and ***Tetrafluoroboric Acid***.[2]

Regio- and Stereocontrolled Functionalization of Cycloheptadiene.[1,3]

By reacting the dienyl complex (**1**) with a range of nucleophiles, a variety of substituted cycloheptadienes are obtained. The addition of nucleophile is stereospecific, *trans* to the $Fe(CO)_2P(OPh)_3$ group. The regioselectivity of the

addition to the complex (**1**) is strongly dependent on the nature of the nucleophile, soft nucleophiles attacking C-1 and hard nucleophiles attacking C-2 of the dienyl ligand. For example, hard nucleophiles such as lithium or magnesium alkyls give predominant C-2 addition to give complexes (**2**) in good to excellent yield (eq 1), while organocuprate reagents (soft nucleophiles) result in predominant, in many cases exclusive, C-1 addition to give diene complexes (**3**) (eq 2).

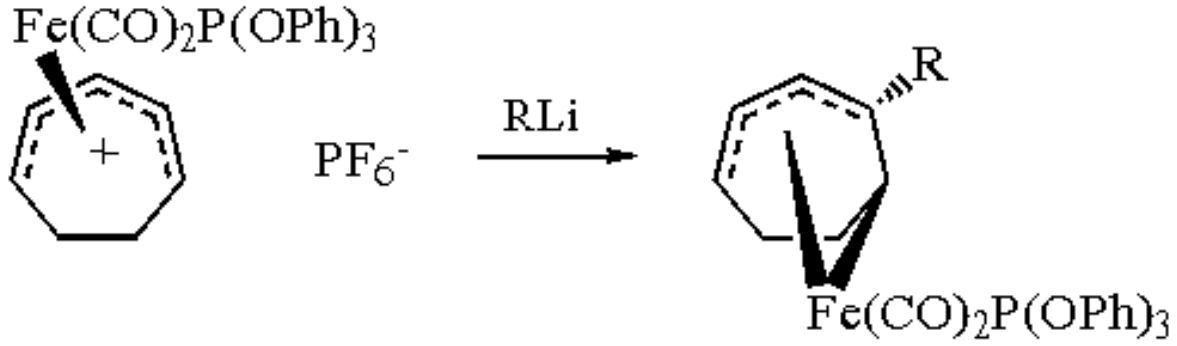

(1)

(1)

(2a) R = Me
(2b) R = Bu
(2c) R = Ph

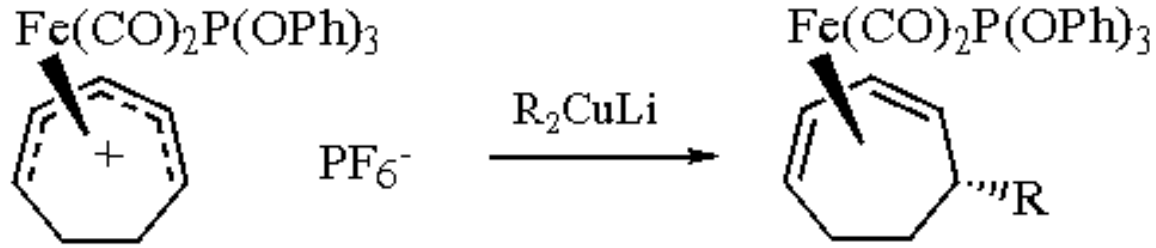

(2)

(1)

(3a) R = Me
(3b) R = Bu
(3c) R = Ph

The dienyl complexes also undergo very clean, high-yielding addition of stabilized enolates, $NaCH(CO_2Me)_2$, $NaCH(COMe)CO_2Me$, $NaCH(SO_2Ph)CO_2Me$, and $NaCH(CN)CO_2Me$, to give diene complexes (**4**) as the exclusive products (eq 3).

(3)

(1)

(4a) $R = R^1 = CO_2Me$

(4b) $R = COMe,\ R^1 = CO_2Me$

(4c) $R = SO_2Ph,\ R^1 = CO_2Me$

(4d) $R = CN,\ R^1 = CO_2Me$

To expand the synthetic utility, the monosubstituted diene complexes can be converted to the dienyl complexes (**5**) with the triphenylmethyl carbocation (eq 4) and reacted with nucleophiles to give disubstituted cycloheptadienes. The reactions with (**5**) are stereospecific, regiospecific, and give high yields. For example, reactions of (**5**) with alkyllithium, Grignard reagents, and cuprates give products (**6**) of C-1 addition, *cis* to the already present substituent (eq 4). As expected, the complex (**5**) also reacts with stabilized enolates to give stereochemically defined disubstituted complexes (**6e-h**) in very high yield (eq 4).

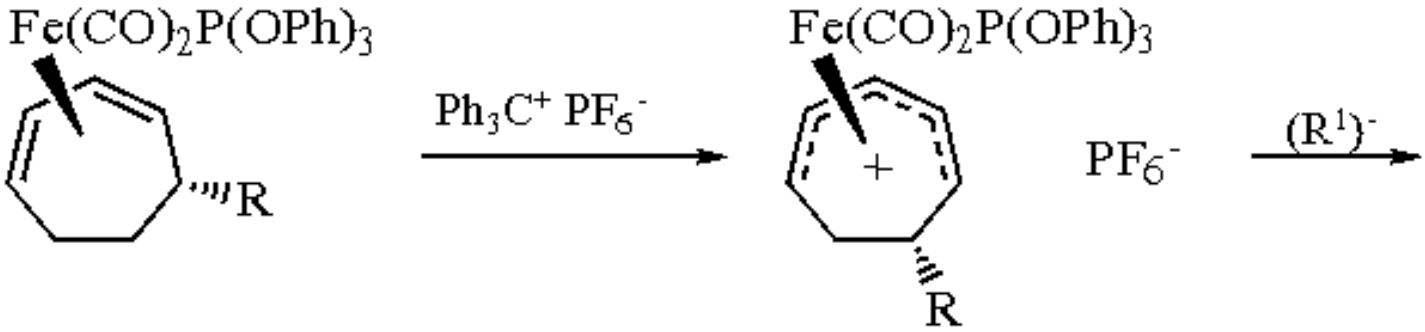

(3a) R = Me
(3b) R = Bu

(5)

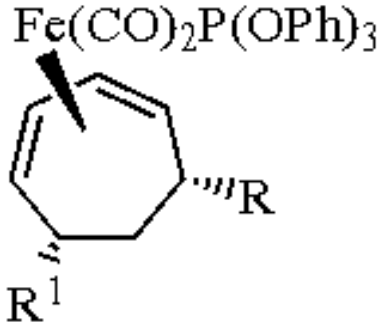

(4)

(6a) R = R^1 = Me
(6b) R = Me, R^1 = Bu
(6c) R = Me, R^1 = Ph
(6d) R = Me, R^1 = $CH_2CH{=}CH_2$
(6e) R = Me, R^1 = $CH(CO_2Me)_2$
(6f) R = Me, R^1 = $CH(COMe)CO_2Me$
(6g) R = Me, R^1 = $CH(SO_2Ph)CO_2Me$
(6h) R = Bu, R^1 = $CH(CO_2Me)_2$

The complex (**1**) is a better reagent for preparing functionalized cycloheptadiene than its tricarbonyl analog, where yields of the products are very low with very poor regioselectivities.

Stereocontrolled Multiple Functionalization of Cycloheptadiene.[4]

The complex (**1**) is also used for the preparation of stereocontrolled trisubstituted cycloheptadiene complex (**10**) (eq 5). Deprotonation of complex (**1**) provides the η^4-triene complex (**7**) in quantitative yield. Hydroboration of the

complex (**7**) gives a single alcohol (**8**) in 92% yield. The alcohol is converted to the ketone (**9**) in 81% yield by Swern oxidation. The ketone is used for the stereospecific synthesis of multiply functionalized cycloheptadiene complex (**10**) in two steps (eq 5).

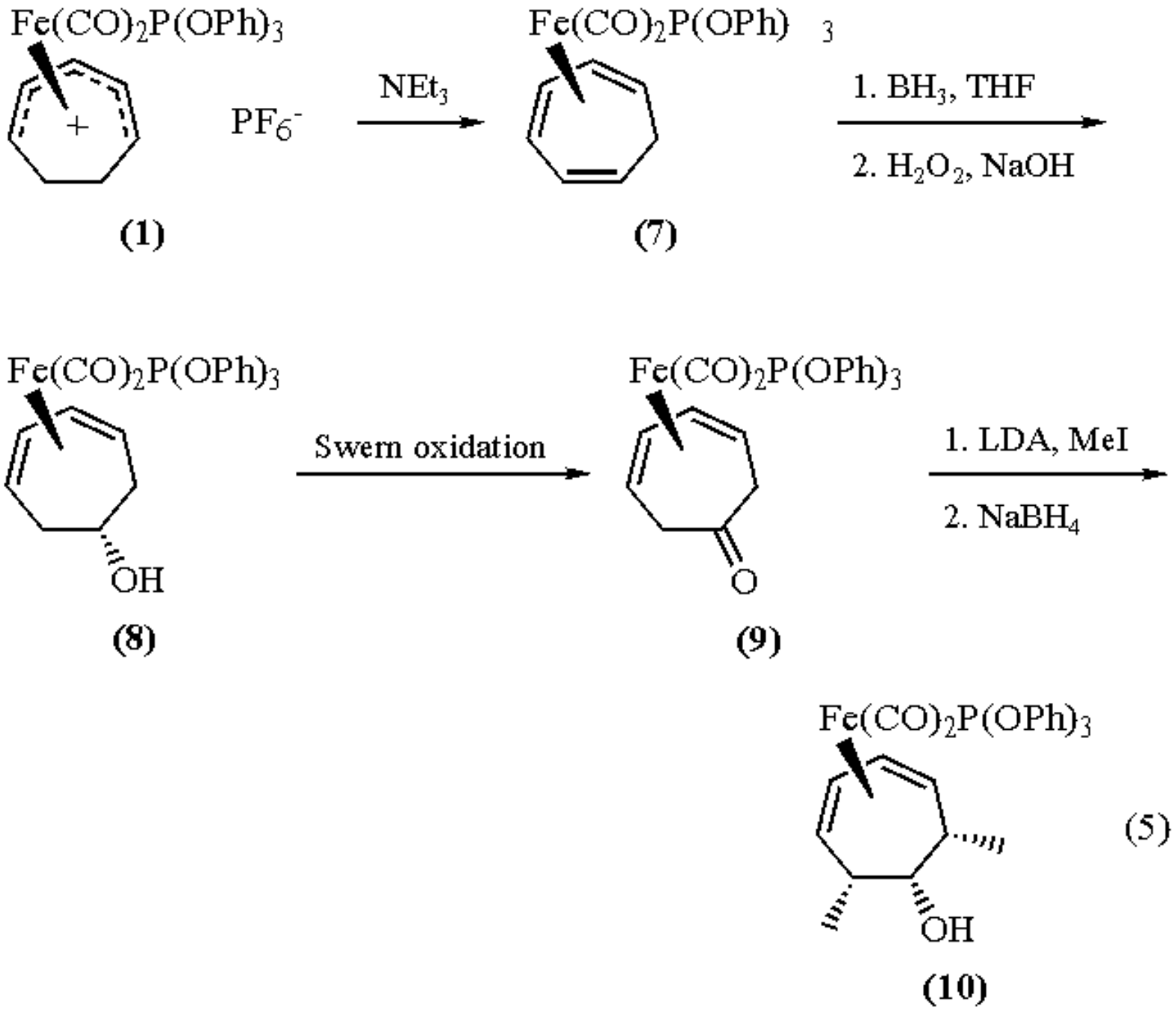

Asymmetric Synthesis of Cycloheptadienes.[5]

The complex (**1**) is also used in the preparation of optically active mono- and disubstituted cycloheptadiene iron complexes with sulfoximine chiral auxiliaries (eq 6). The treatment of the enolate anion of ester (**11**) with (**1**) gives the diene complex (**12**) as a mixture of diastereomers (98-99% yield). The desulfonylation of (**12**) gives up to 50% ee of monoester (**13**) in 80-83% yield. The optically active monoester (**13**) is used for the preparation of optically active disubstituted dienes (**14**) in good yield (eq 6).

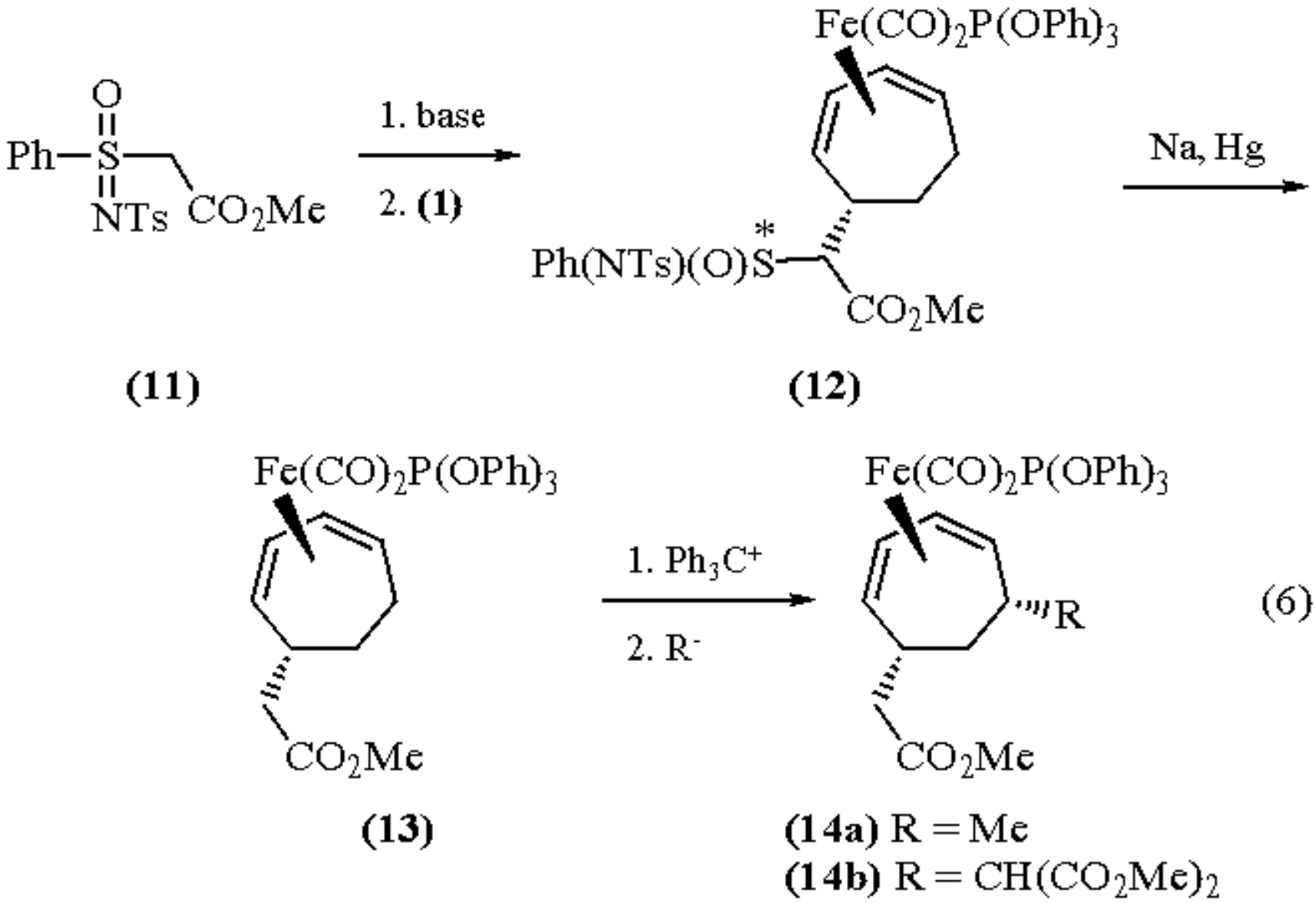

Synthesis of Precursors of Biologically Active Compounds.

Dimethylcycloheptadiene complex (**6a**) serves as an intermediate for the synthesis of (+)-Prelog-Djerassi lactonic acid (**15**) (eq 7).[6] This lactone is isolated as a degradative product of methymycin and related compounds, narbomycin, picromycin, and neomethymycin.[7] The racemic monoester complex (**14a**) has been utilized as an intermediate for the synthesis of precursor (**16**) of the antibiotic carbomycin B (eq 8).[8] The monoester (**14a**) has also been used as an intermediate for the synthesis of the lactone (**17**), a subunit of the antibiotic tylosin (eq 9).[6]

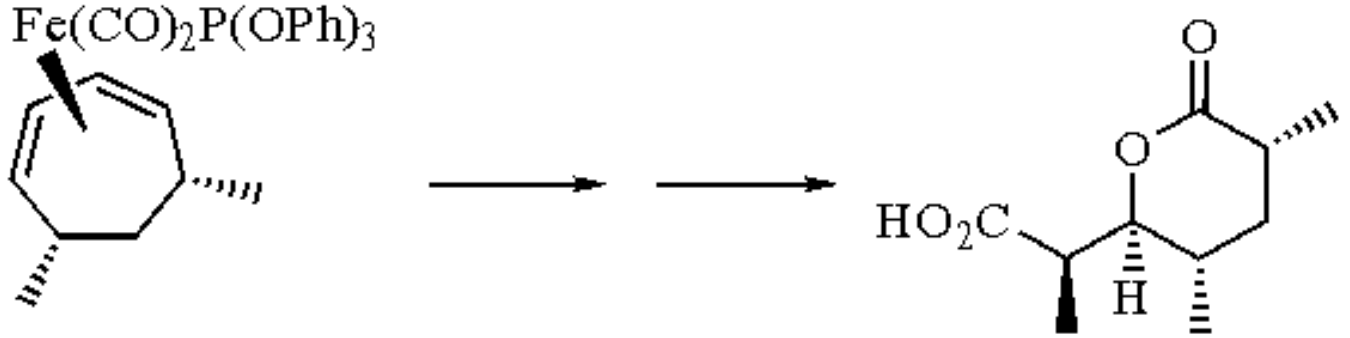

(7)

(6a) **(15)**

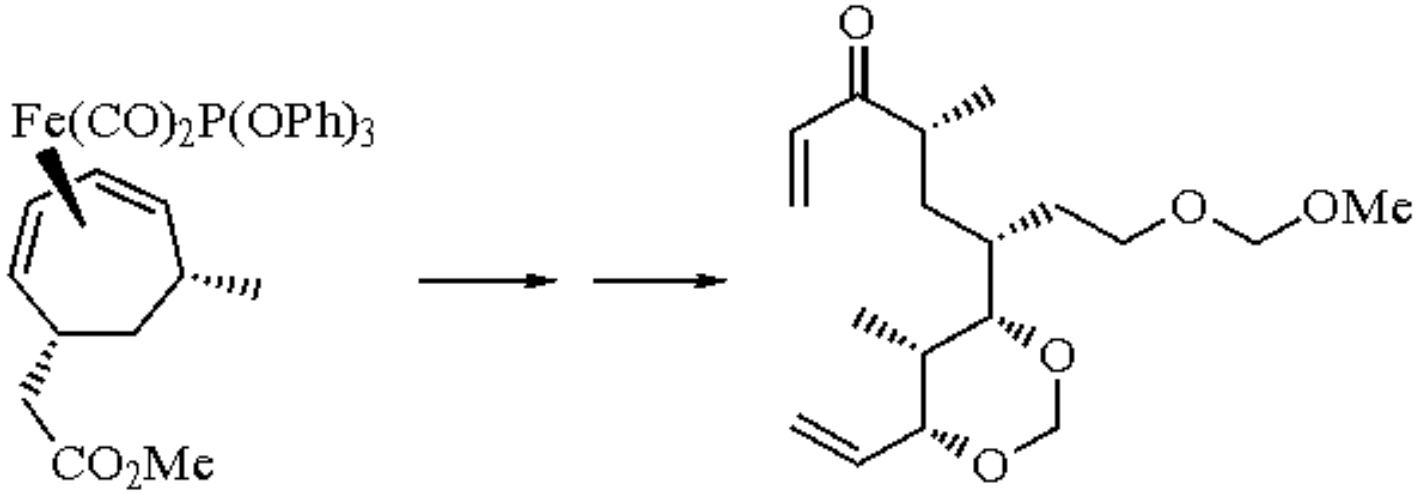

(8)

(14a) **(16)**

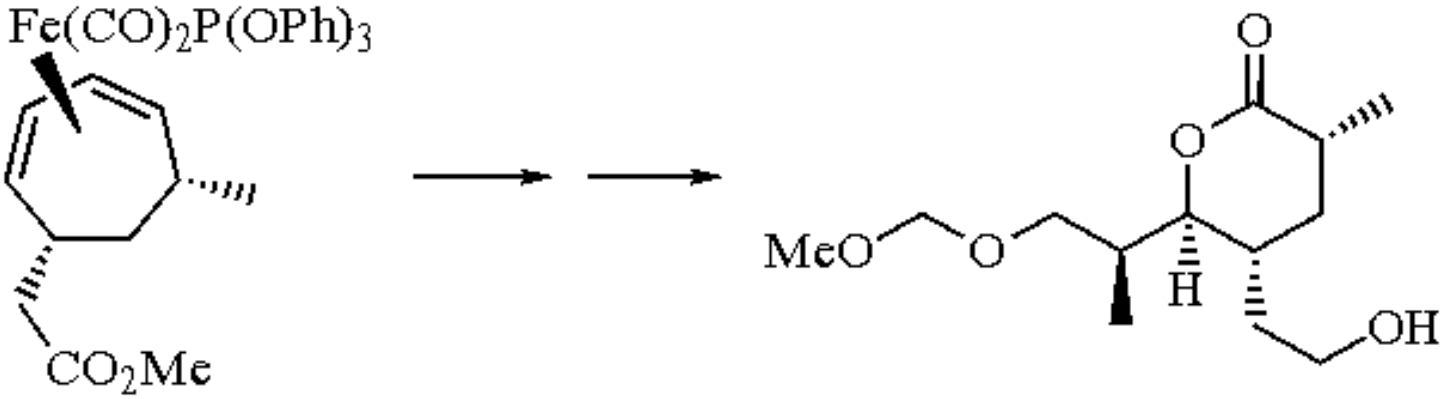

(9)

(14a) **(17)**

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2. Pearson, A. J.; Chen, B. *JOC* **1985**, *50*, 2587.
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Dicarbonyl(cyclohexadiene)(cyclopentadienyl)molybdenum Tetrafluoroborate

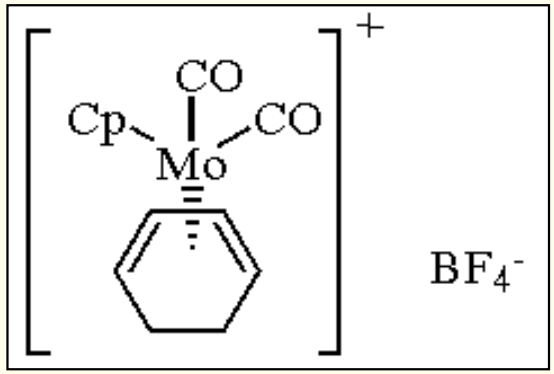

(BF_4 salt)

[115252-55-6] · $C_{13}H_{13}BF_4MoO_2$ · Dicarbonyl(cyclohexadiene)(cyclopentadienyl)molybdenum Tetrafluoroborate · (MW 383.99) (PF_6 salt)

[84117-10-2] · $C_{13}H_{13}F_6MoO_2P$ · Dicarbonyl(cyclohexadiene)(cyclopentadienyl)molybdenum Hexafluorophosphate · (MW 442.15) (cation)

[84117-09-9] · $C_{13}H_{13}MoO+2$ · Dicarbonyl(cyclohexadiene)(cyclopentadienyl)molybdenum Tetrafluoroborate · (MW 297.18)

(reagent for stereocontrolled multiple functionalization of cyclohexene rings[1])

Physical Data: dec >300 °C.

Solubility: sol most polar organic solvents; very sol methylene chloride; insol diethyl ether and alkanes.

Form Supplied in: yellow crystals generally prepared by user from $Mo(CO)_6$.

Analysis of Reagent Purity: carbonyl stretching bands at 2017 and 1962 cm^{-1} (CH_2Cl_2) are characteristic.

Preparative Methods: straightforwardly prepared in 97% yield by hydride abstraction from $CpMo(CO)_2$(cyclohexenyl),[2] which in turn is

prepared following a procedure developed for the parent allyl complex by Hayter[5] (>70% yield). This involves reflux of $Mo(CO)_6$ in acetonitrile to produce $Mo(CO)_3(MeCN)_3$, addition of 3-bromo-1-cyclohexene, and subsequent treatment with lithium cyclopentadienide.

Handling, Storage, and Precautions: should be handled under nitrogen or argon. The crystals can be handled in air for short periods with no significant decomposition. Solutions of the compound are air sensitive, but can be handled with brief exposure to air or can be reduced in volume with a rotary evaporator. Use in a fume hood.

Introduction.

The use of this versatile reagent was originally developed by Faller and his co-workers[2] and has been applied extensively in organic syntheses by Pearson[3] and Liu.[4]

Hydride Abstraction From the Allyl Complex.

Hydride abstraction is one of several important processes that establish the routes available for multiple functionalization of the ring (eq 1).

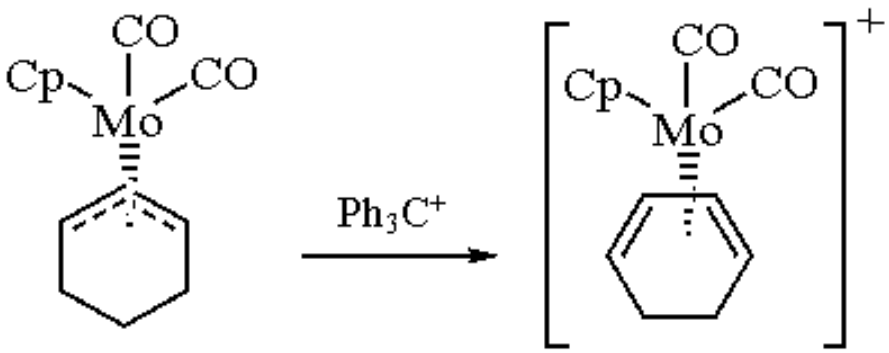

(1)

Nucleophilic Addition to the Cationic Diene Complex.

The positive charge on the diene complex makes it susceptible to nucleophilic attack, which occurs on the side of the ring opposite to the metal. This yields a new substituted η^3-cyclohexenyl complex, which can undergo a second hydride abstraction-nucleophilic addition process to yield a disubstituted η^3-cyclohexenyl species (eq 2).[2,3] Most soft nucleophiles, such as dimethyl malonate, cyanoborodeuteride, or enamines, are effective. Reactions with Grignard reagents provide access to the methyl and phenyl derivatives.

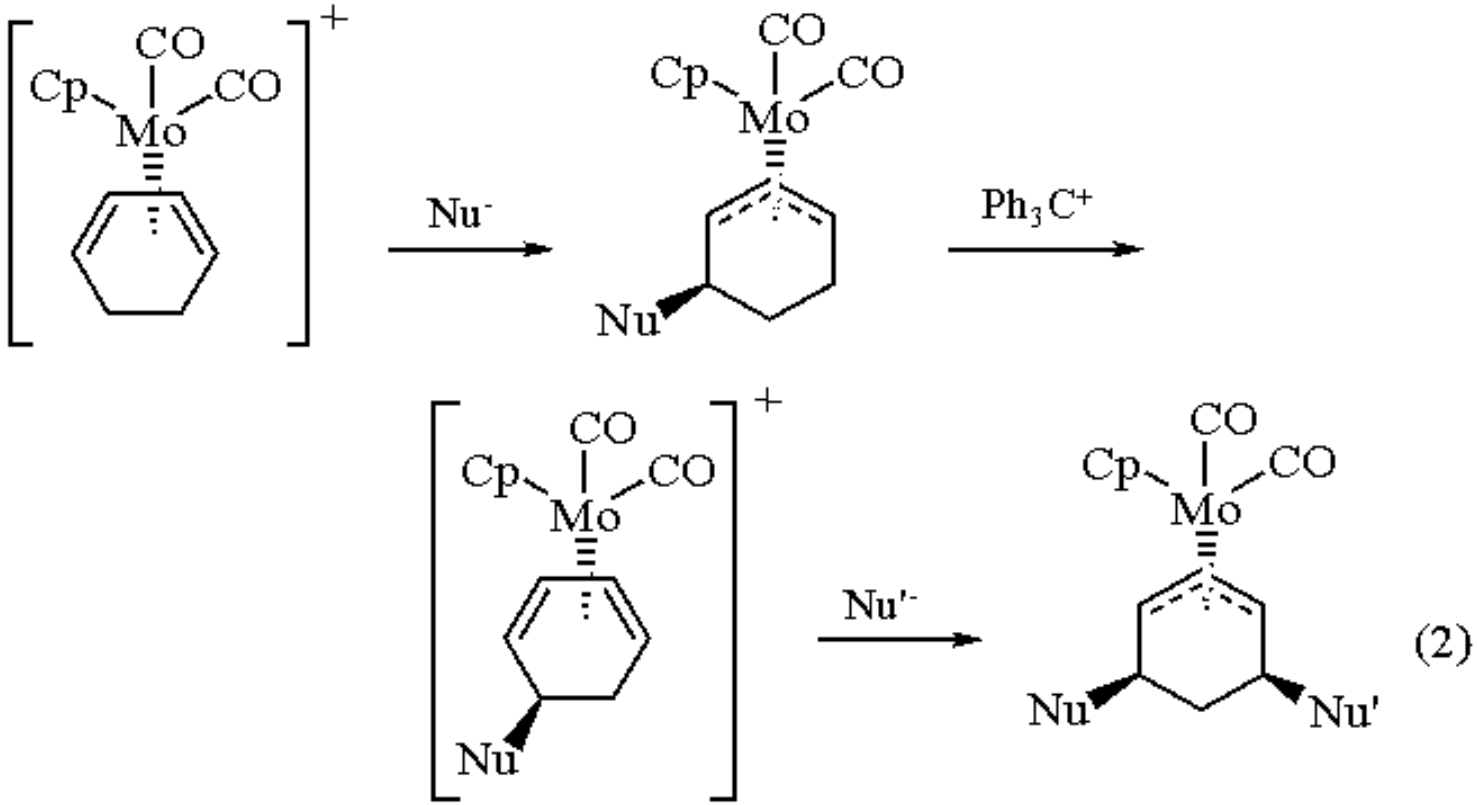

Deprotonation of the Cationic Diene Complex.

The positive charge on the complex renders the methylene protons adjacent to the bound double bonds acidic. Treatment with ***Triethylamine*** yields the η^3-cyclohexadienyl complex (eq 3).[6] Usually in this type of system both additions and abstractions of hydride occur on the side of the ring opposite to the metal.

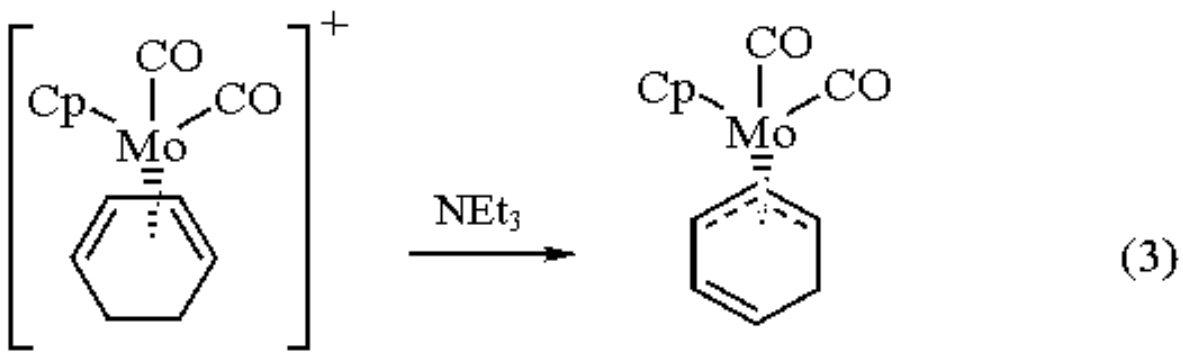

Further Functionalization of the Ring.

The availability of the η^3-cyclohexadienyl complexes allows further elaboration of the ring. For example, the η^3-cyclohexadienyl complex undergoes a ***Boron Trifluoride***-promoted ene reaction with aldehydes (-40 °C, toluene) (eq 4).[4]

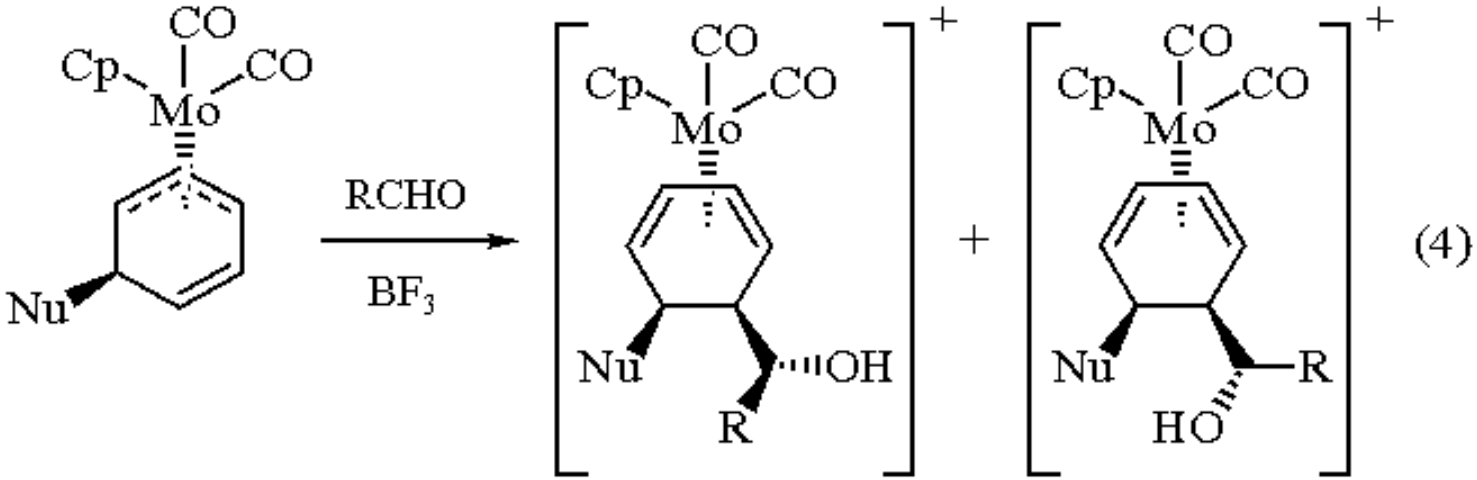

An alternative to activation of the ring to nucleophilic attack is replacement of a carbonyl in the η^3-cyclohexenyl complexes by NO^+ (eq 5).[7] Usually the addition occurs *cis* to the nitrosyl, although a number of factors can affect the stereochemistry of the addition.[8]

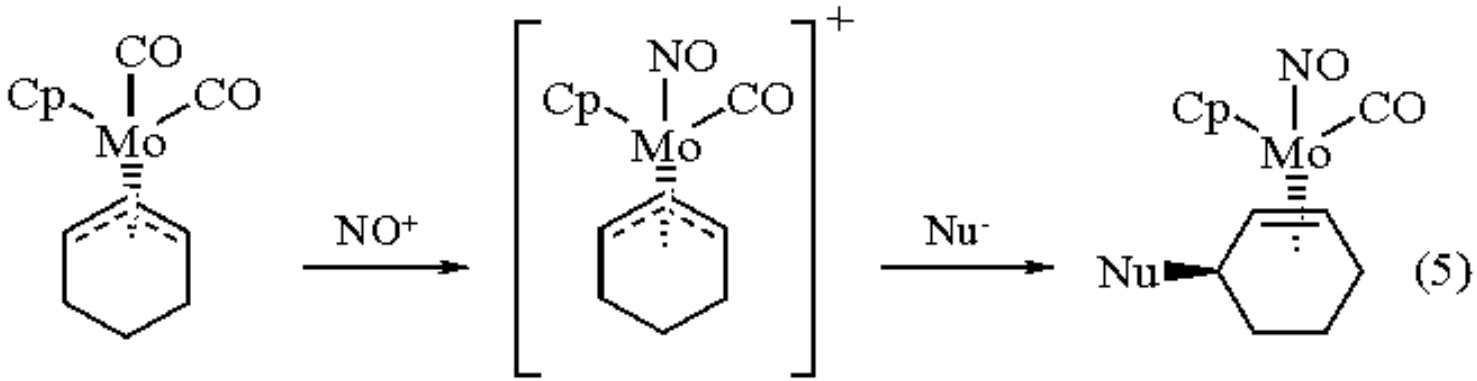

Removal of the Metal.

The functionalized cyclohexadiene can be decomplexed by oxidation of the cationic complex with Et_3NO. Another alternative is to prepare the cyclohexene complex via NO^+ addition to the η^3-cyclohexenyl dicarbonyl and treat this with another nucleophile or cyanoborohydride to produce the η^2-alkene

complex. These η^2-alkene complexes can be oxidized by ***Cerium(IV) Ammonium Nitrate*** (buffered with acetate)[9] or air[7] to yield the decomplexed cyclohexene. Pearson has also developed an iodolactonization methodology for decomplexation of the ring which is applicable in some cases (eq 6).[9]

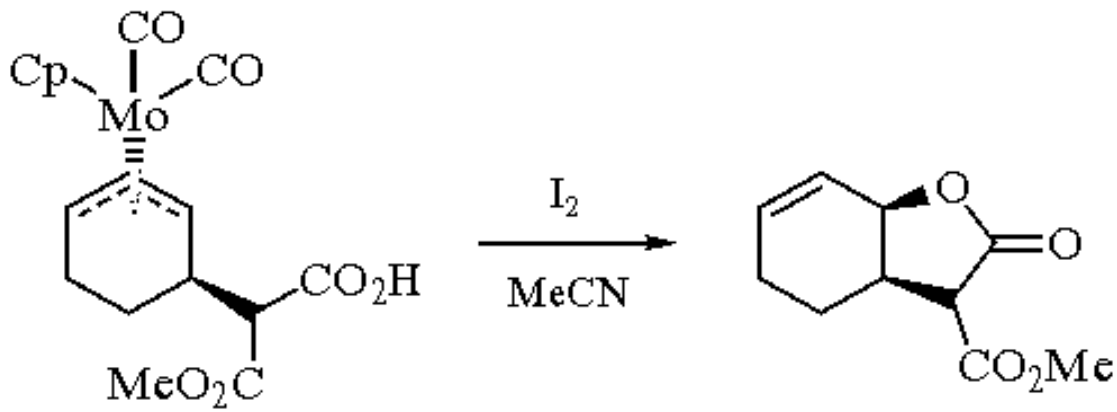

(6)

Enantioselective Syntheses.

The sequential additions to the complexed cyclohexadienyl moiety should allow the development of a powerful strategy for asymmetric syntheses of substituted six-membered rings. Since the parent $[CpMo(CO)_2(cyclohexenyl)]^+$ complex has a plane of symmetry, attention has focused on obtaining nonracemic substituted derivatives. The η^4-cyclohexadiene complex is essentially a *meso* structure since the bound alkenic carbons are all stereogenic centers. It follows that diastereoselectivity would be observed for one side or the other of a given face of the ring in nucleophilic attack by chiral nucleophiles. Moderate de's (78%) have been obtained on selective addition of (+)-*t*-butyldimethylsilyl sulfoximinyl ester enolates.[10] The products then contain three new stereogenic centers, with the $S_{(S)}$-enolate yielding primarily the (*S*,*S*,*S*)-product (eq 7).

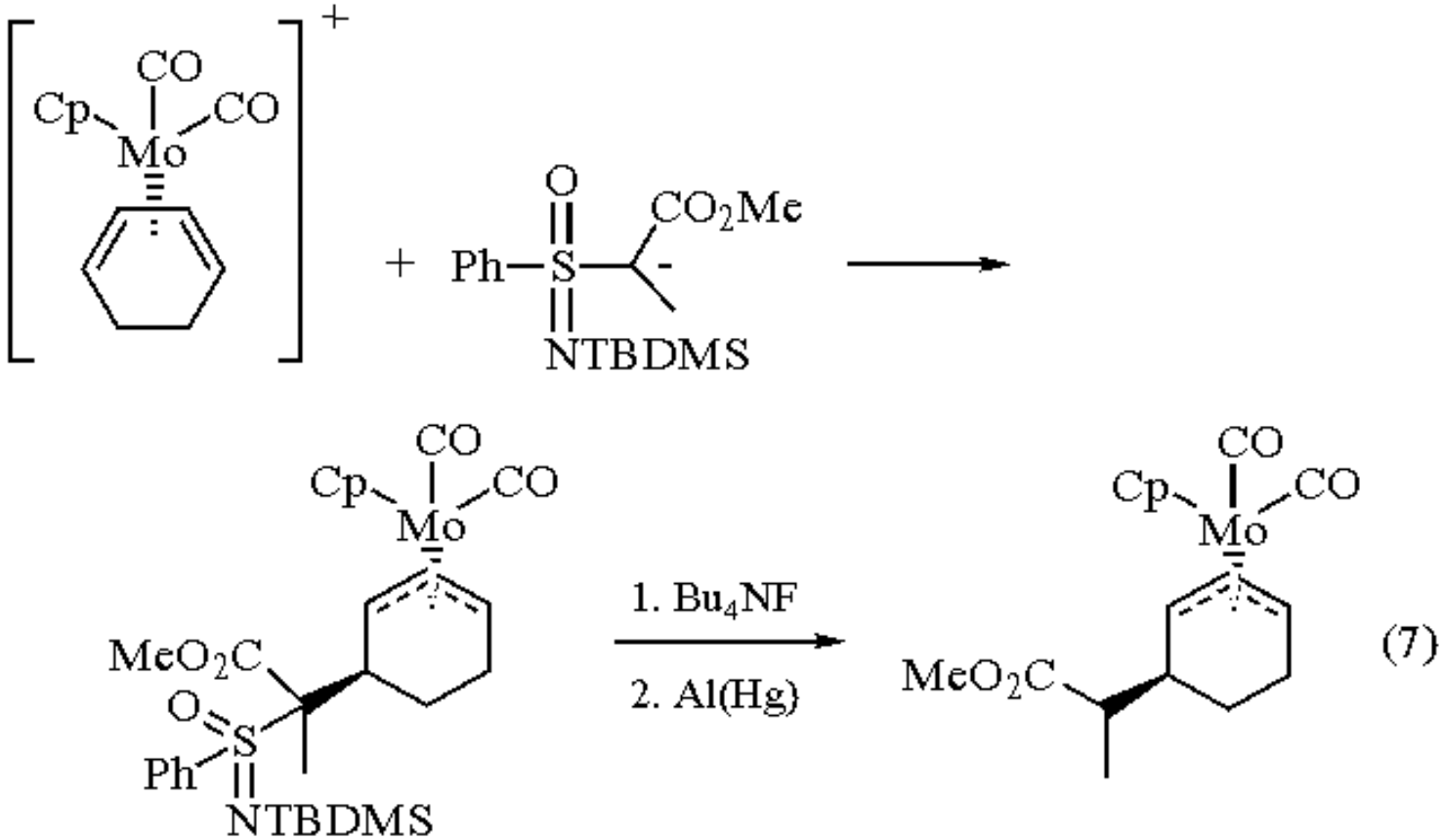

Since the addition of chiral allylic acetates[11,12] and presumably phosphonates[13] to $Mo(CO)_3(MeCN)_3$ apparently occurs with retention of configuration, an alternative route into asymmetric cyclohexenols would be the use of enantiomerically pure cyclohexenols as starting materials. Although this has not yet been exploited extensively, Liebeskind[12] recently reported stereocontrolled syntheses of a number of dihydropyrans and tetrahydropyrans using the $[CpMo(CO)_2(oxacyclohexadienyl)]^+$ system.

---

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Dicarbonyl(cyclopentadienyl)cobalt(I)

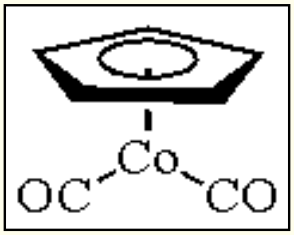

[12078-25-0] · $C_7H_5CoO_2$ · Dicarbonyl(cyclopentadienyl)cobalt(I) · (MW 180.05)

(catalyst, especially for alkyne trimerization and cotrimerization;[3-5] source of a wide range of cyclopentadienylcobalt complexes and of cyclopentadienones, pyridones,[10] etc.)

Alternate Names: cyclopentadienyldicarbonylcobalt; cyclopentadienylcobalt dicarbonyl.

Physical Data: bp 139-140 °C/710 mmHg; 37-38.5 °C/2 mmHg.

Solubility: very sol all common org solvents; insol H_2O.

Form Supplied in: dark red liquid; available commercially.

Preparative Methods: synthesized quantitatively from ***Octacarbonyldicobalt*** and ***Cyclopentadiene***[1] or from ***Bis(cyclopentadienyl)cobalt*** and ***Carbon Monoxide***.[2]

Handling, Storage, and Precautions: somewhat air sensitive; toxic; best stored under CO or inert gas (N_2, Ar) at low temperature (<0 °C). Use in a fume hood.

General Remarks.

Many of the reactions in which $CpCo(CO)_2$ acts as catalyst involve dissociation of CO to leave the catalytically active species, regarded as CpCo. As this can readily arise from other $CpCoL_2$ complexes (e.g. L = PR_3, $P(OR)_3$, C_2H_4; L_2 = diene) or from Cp_2Co, useful reactions of the phosphine complexes are included here and the entries for ***Bis(cyclopentadienyl)cobalt*** and ***(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)***, the preferred catalyst for pyridine synthesis, should also be consulted.

Catalytic Reactions.

General.

Dicarbonylcyclopentadienylcobalt is the most widely used catalyst for alkyne cyclotrimerization and can effectively catalyze such related processes as pyridine synthesis from two alkyne molecules and one nitrile molecule, cyclohexadiene synthesis from two alkyne molecules and one alkene molecule, and participate in the (usually stoichiometric) formation of cyclopentadienones from two alkyne molecules and CO. It is known that the first step in these processes is the thermally or photochemically induced dissociation of CO and there is strong evidence for intermediate formation of bis(alkyne) complexes (eq 1) which can react with the third substrate molecule to give the above products.

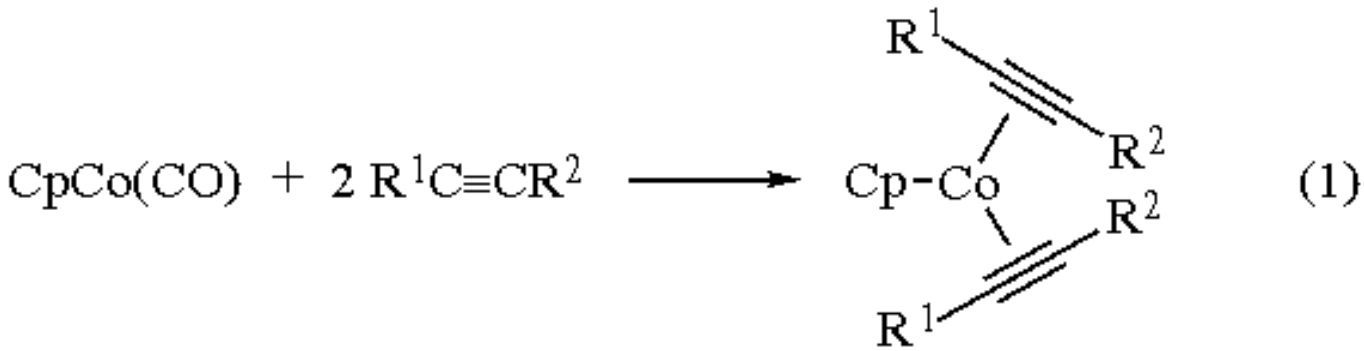

The reaction in eq 1 must be assumed to proceed by coordination of one alkyne, followed by dissociation of the second CO. Although monoalkyne complexes $CpCo(CO)(R^1C_2R^2)$ have not been isolated from such systems, their analogs, $CpCo(PPh_3)(R^1C_2R^2)$ are well known. They are accessible, inter alia, by the sequence shown in eqs 2 and 3,[3,4] followed by eq 4.[5]

$$CpCo(CO)_2 + PR_3 \longrightarrow CO + CpCo(CO)(PR_3) \qquad (2)$$

$$ClCo(PR_3)_3 + CpLi \longrightarrow PR_3 + CpCo(PR_3)_2 \qquad (3)$$

$$CpCoL(PR_3) + R^1C{\equiv}CR^2 \longrightarrow L + CpCo(PR_3)(R^1C_2R^2) \qquad (4)$$

$$L = CO \text{ or } PR_3$$

The products $CpCo(PR_3)(R^1C_2R^2)$ also yield bis(alkyne) complexes $CpCo(R^1C_2R^2)_2$ on further treatment with alkyne.[6] It is uncertain whether cyclization of these bis(alkyne) complexes to cobaltacyclopentadiene systems (eq 5) precedes or is induced by addition of the third ligand L. When L is a third alkyne this leads to the immediate precursor of the aromatic cyclotrimerization product; it is also the step which determines the regiochemistry of that product. The cobaltacyclopentadienes arising according to eq 5 have been well characterized for L = PPh_3, but the compounds with L = alkyne, nitrile, alkene, or CO presumably collapse rapidly to the above-mentioned endproducts. In the cases where these are dienes (eqs 6 and 7), these can remain bound as stable complexes, but arenes and 2-substituted pyridines are too readily displaced by alkyne, regenerati ng the bis(alkyne) complexes $CpCo(R^1C_2R^2)_2$ and making the reactions catalytic. Only very exceptionally (eq 8) has an η^4-arene complex been isolated.[7]

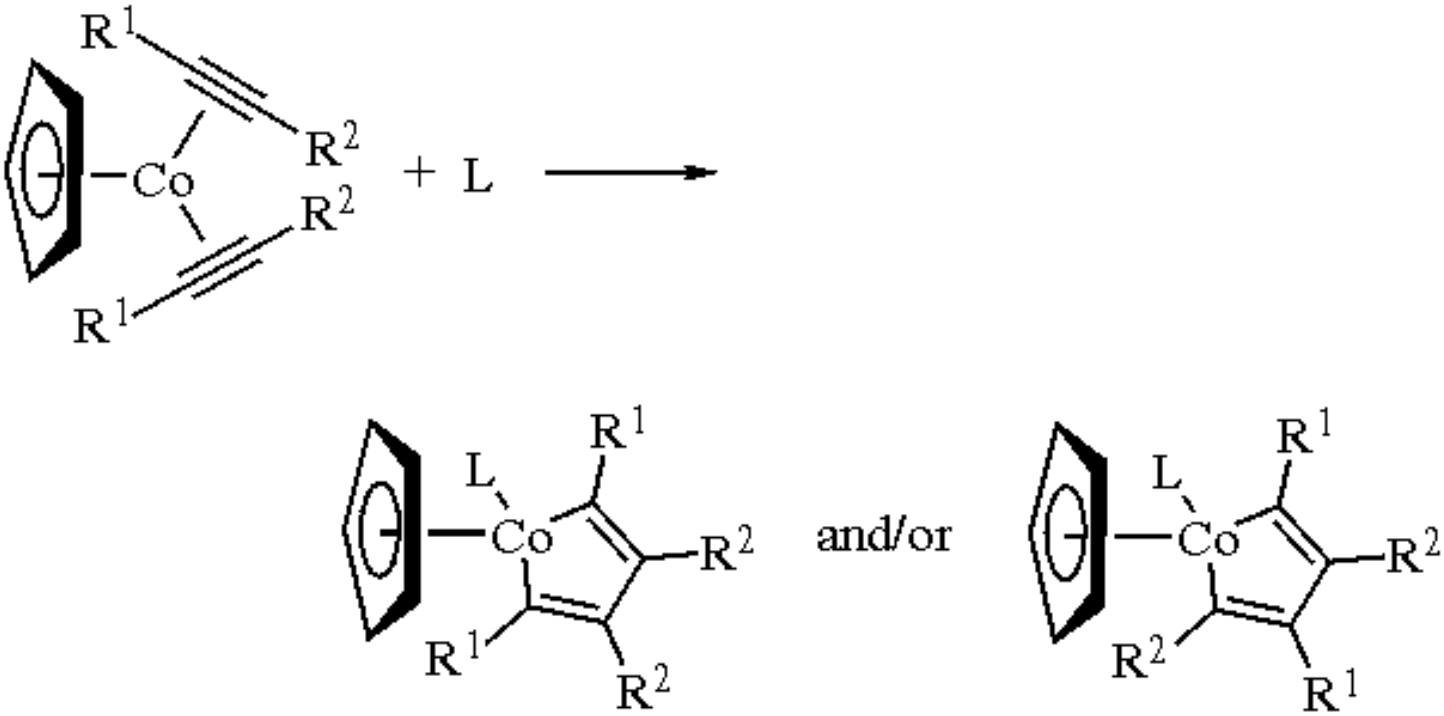

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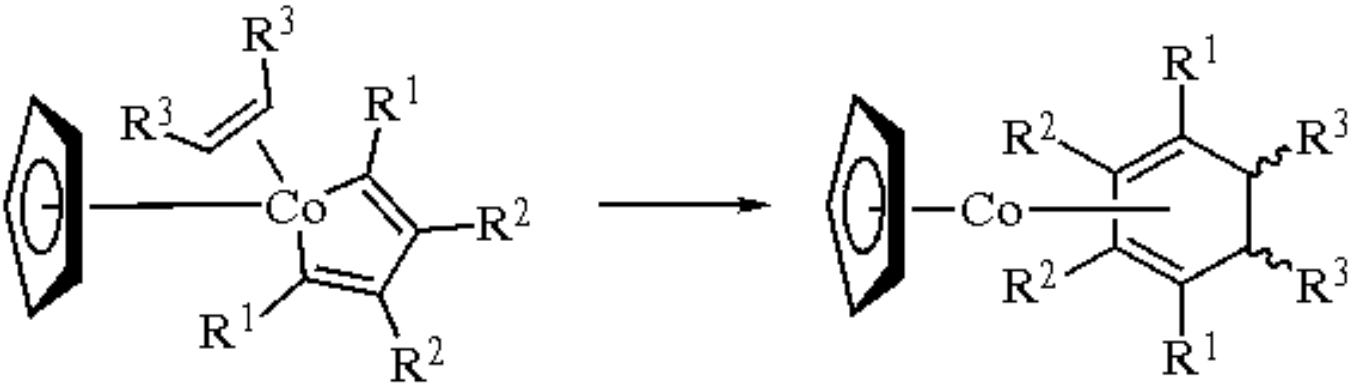

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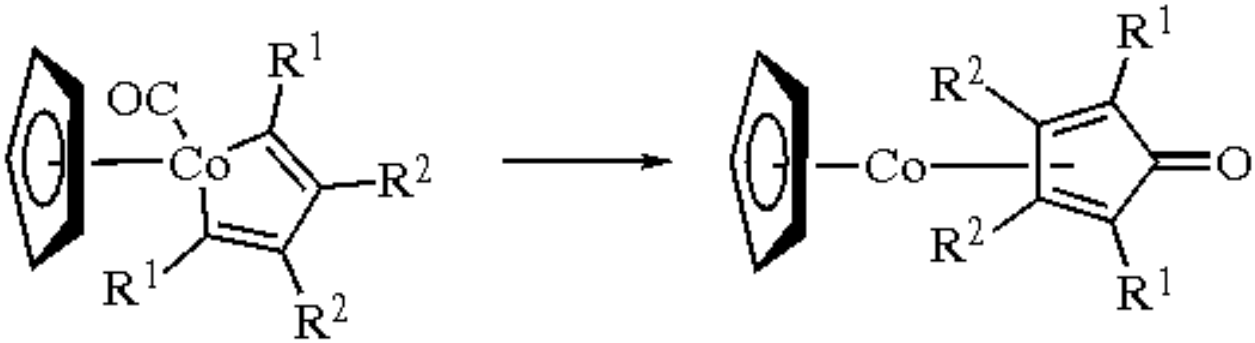

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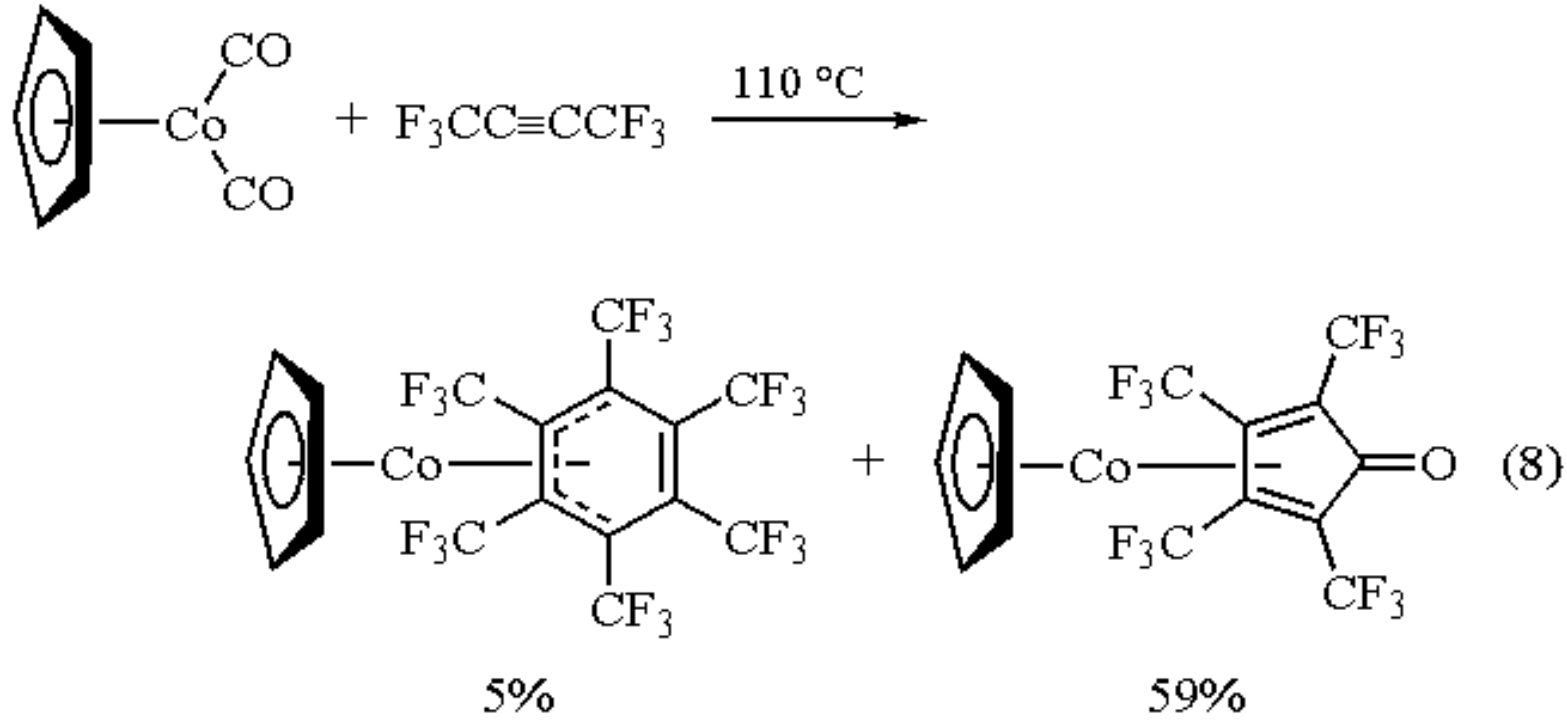

Cyclotrimerization, Including Mixed Cyclotrimerization of Alkynes.

Simple cyclotrimerizations can be achieved efficiently with a wide range of metal carbonyl[8] and other complexes. With unsymmetrical alkynes, different catalysts may lead to widely different regioselection. Thus whereas $CpCo(CO)_2$ converts diphenyl-1,3-butadiyne chiefly to the unsymmetrical trimer (eq 9), use of ***Dicarbonylbis(triphenylphosphine)nickel(0)*** gives exclusively the symmetrical isomer (83%).[9]

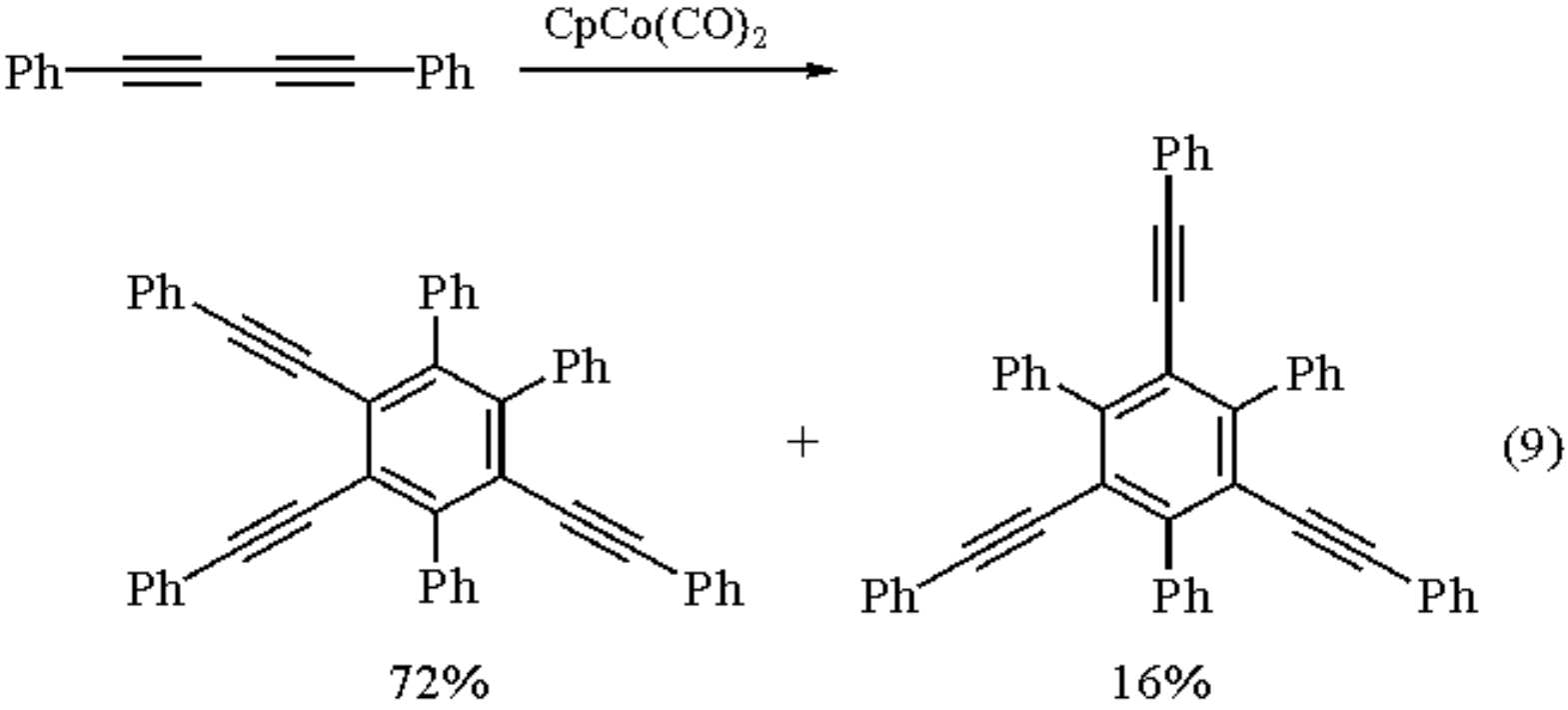

However, the special value of $CpCo(CO)_2$ with respect to trimerization arises from its ability to promote controlled mixed trimerization reactions when one alkyne molecule carries bulky substituents, e.g. trimethylsilyl, and cannot undergo self-trimerization, apparently for steric reasons. It is then possible to employ that bulky alkyne in excess, e.g. in reactions with dialkynes, so as to suppress their trimerization (eq 10) in favor of the mixed condensation (eq 11). Surprisingly, when a polymer-supported form of the catalyst was substituted, only the reaction in eq 10 was observed (e.g. with $n = 3$). With $CpCo(CO)_2$ itself, many high-yielding examples of reactions of the type in eq 11, have been studied and reviewed.[10]

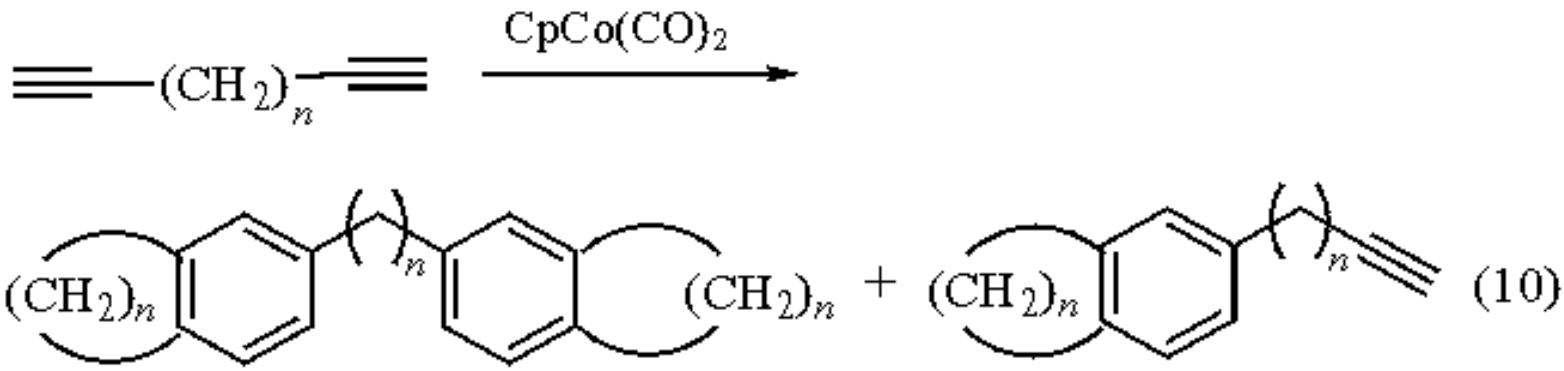

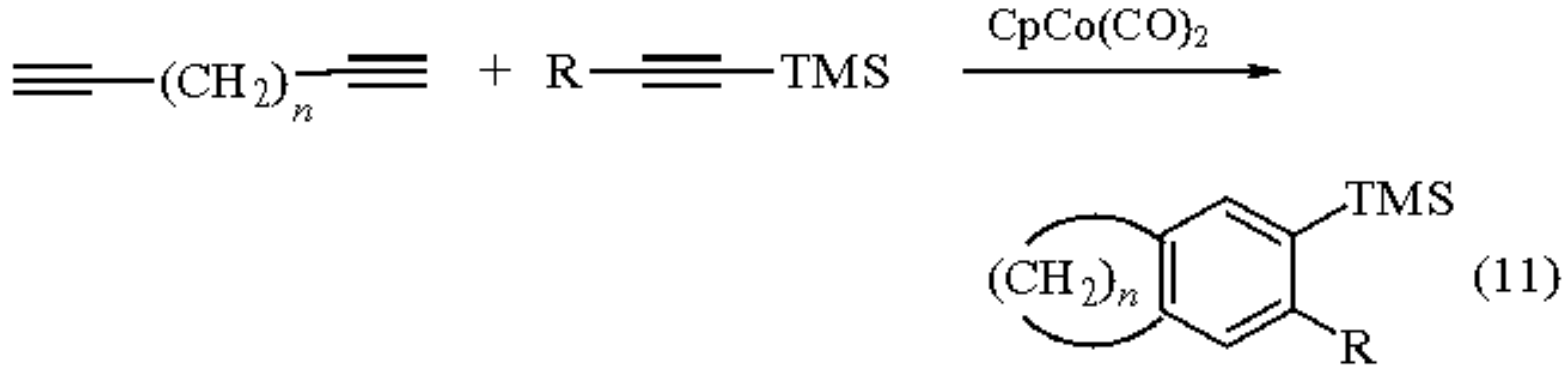

Examples include the remarkably efficient formation of benzocyclobutenes from 1,2,4,5-tetraethynylbenzene (eq 12) and the reaction of an enediyne designed as a steroid synthon (eq 13); in the latter case the intermediate benzocyclobutene is not isolated but ring opens as shown to allow an intramolecular Diels-Alder reaction. The product was converted to (±)-estrone in 80% yield via selective protodesilylation at the 2-position with ***Trifluoroacetic Acid*** followed by replacement of the second silyl group by OH using ***Lead(IV) Trifluoroacetate***. The alternative protodesilylation under basic conditions (using ***Potassium t-Butoxide***) or replacement of $SiMe_3$ by halogens adds to the versatility of such silyl-substituted products in synthesis. Approaches to other natural products are exemplified for protoberberine-type isoquinoline alkaloids (eq 14). This example also illustrates the highly regioselective formation of the more sterically demanding arene as a result of the initial coupling of the least hindered alkynic carbons.[10]

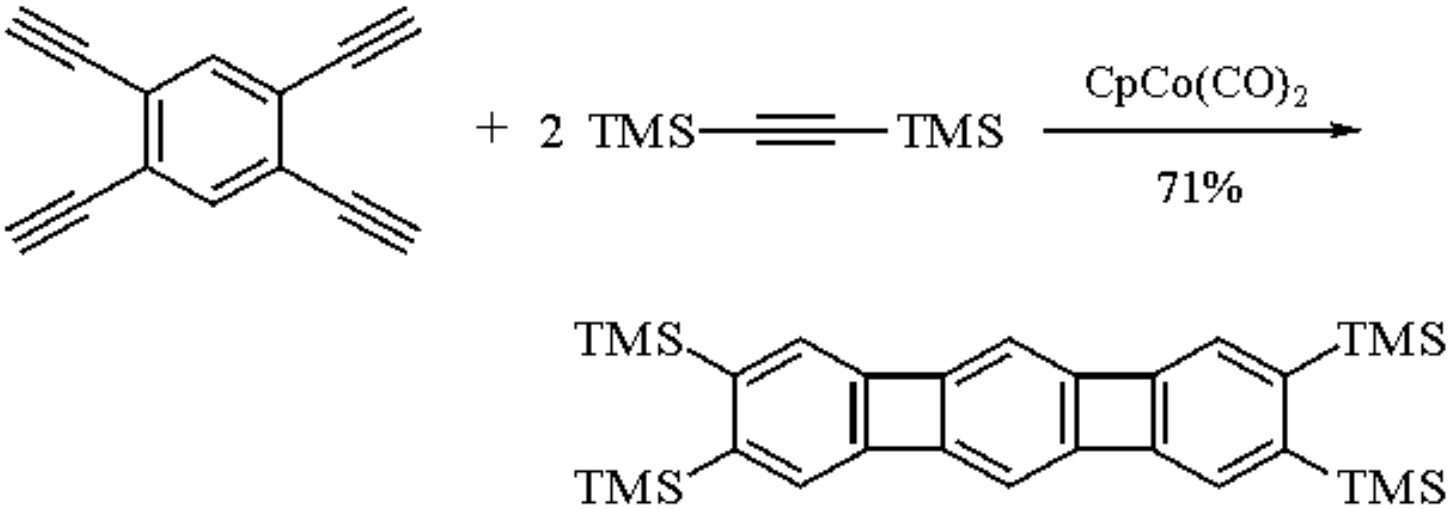
+ 2 TMS TMS
CpCo(CO)2
71%
TMS
TMS
TMS
TMS

(12)

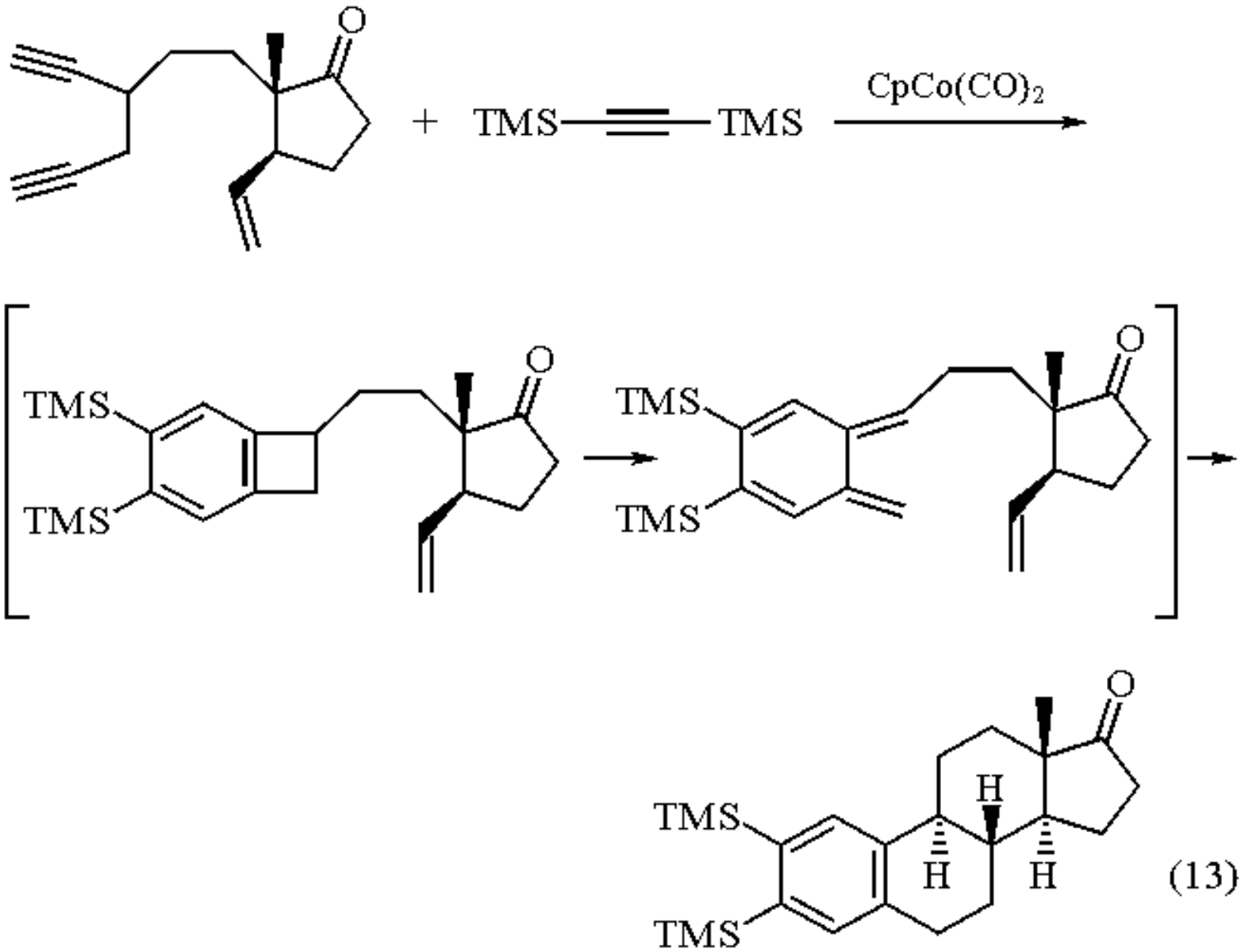
O
+ TMS TMS
CpCo(CO)2
TMS
TMS
O
TMS
TMS
O
O
TMS
TMS
H
H
H

(13)

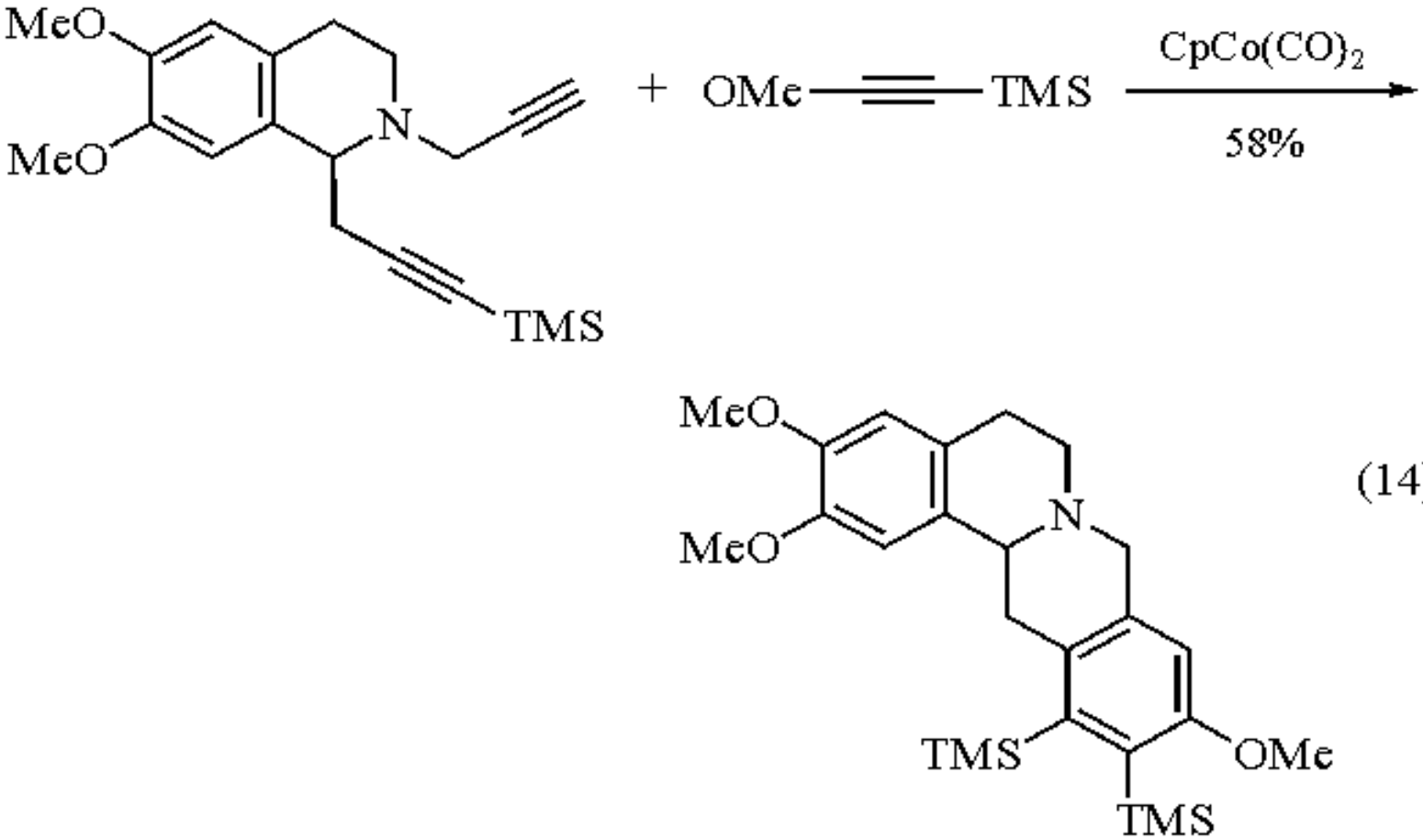

(14)

Pyridine Synthesis.

Dicarbonylcyclopentadienylcobalt-catalyzed reactions have been reviewed;[10] see ***(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)***, the more frequently used catalyst, for a fuller discussion. As in cyclotrimerization (cf. e.g. eq 14), high regioselectivity is often observed; an example is shown in eq 15.[10]

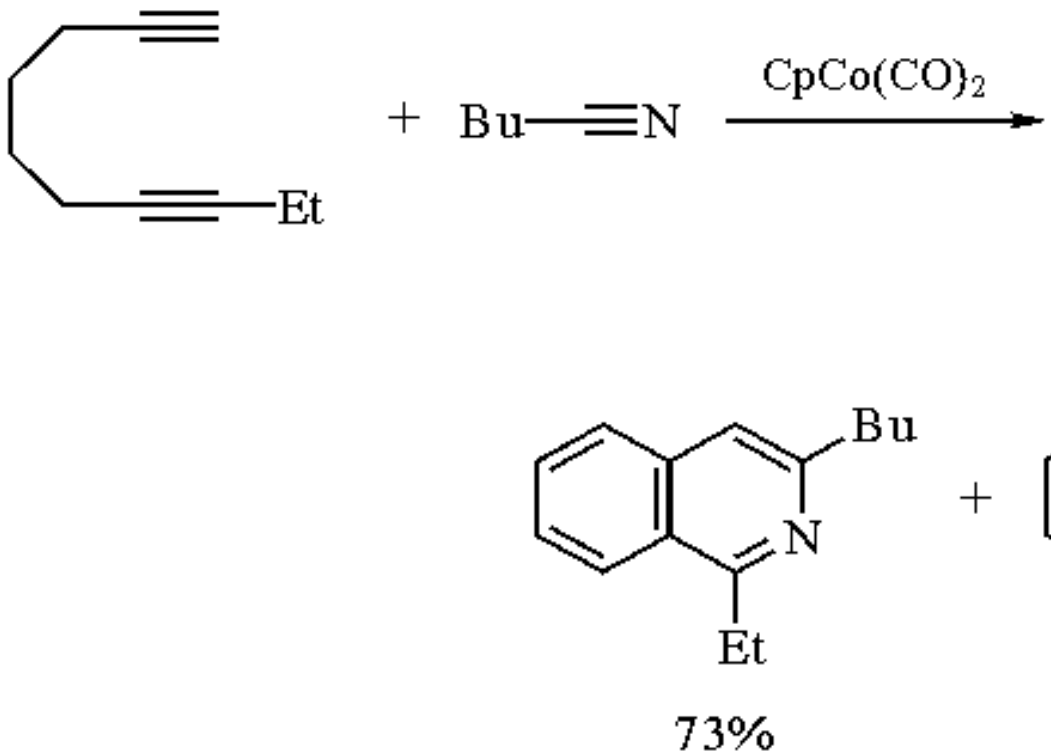

Pyridones result from alkynes and alkyl isocyanates, but with low regioselectivity.[10] This problem is avoided in condensations using o-alkynyl isocyanates (eq 16).[11]

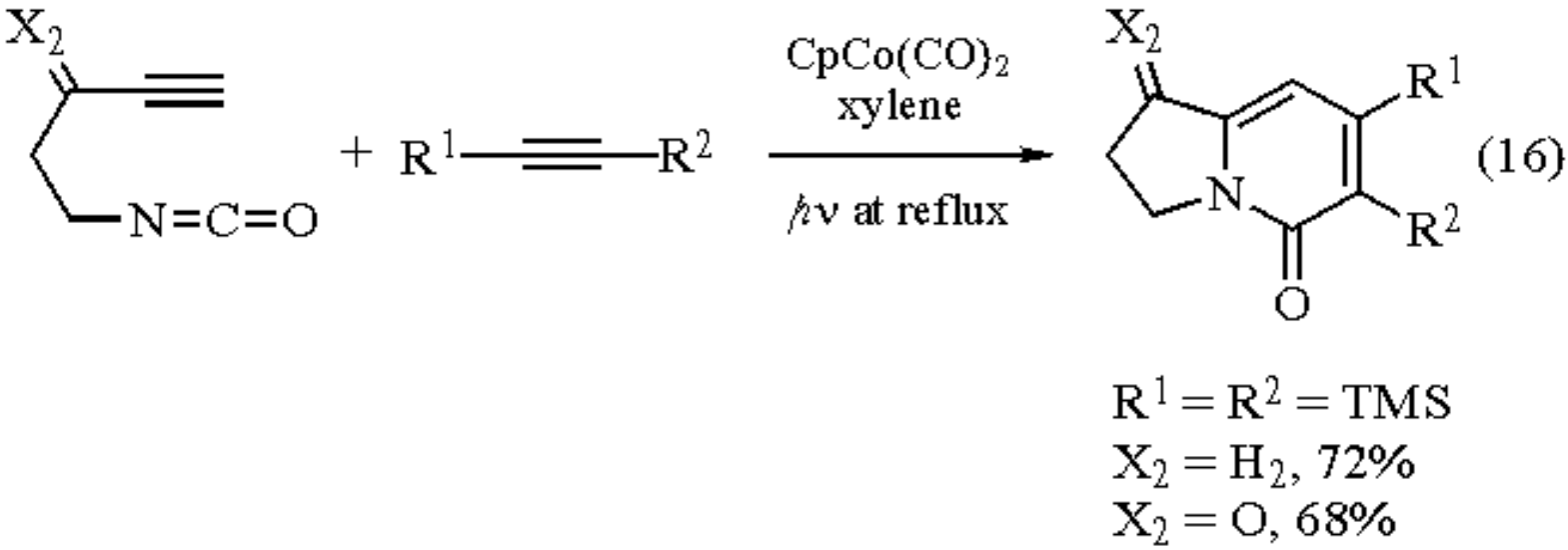

Other Catalytic Reactions.

Dicarbonylcyclopentadienylcobalt and ***Octacarbonyldicobalt*** are alternative catalysts for pyrrole synthesis from alkynes and ***Cyanotrimethylsilane*** (eq 17).[12] The known addition of ***Phenyl Isocyanide*** to the complex $CpCo(PPh_3)(PhC_2Ph)_2$ (eq 18)[13] may provide a model for this reaction, which may be initiated by isomerization of Me_3SiCN to Me_3SiNC and continue as in eq 19.

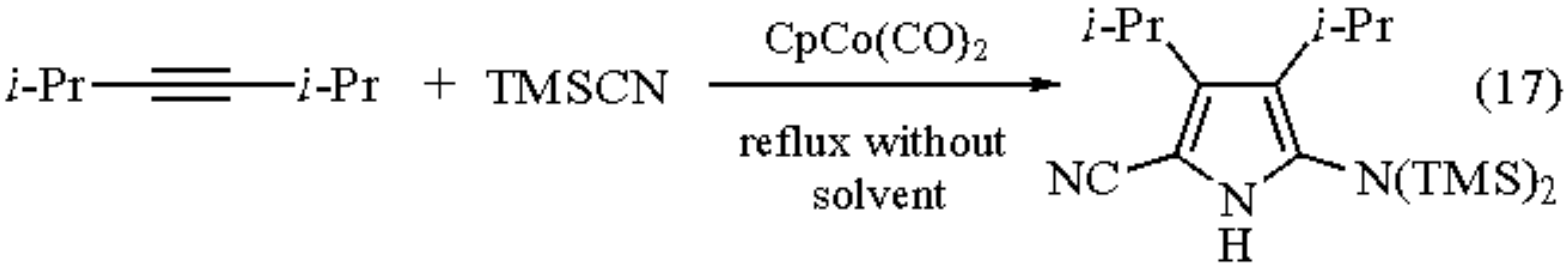

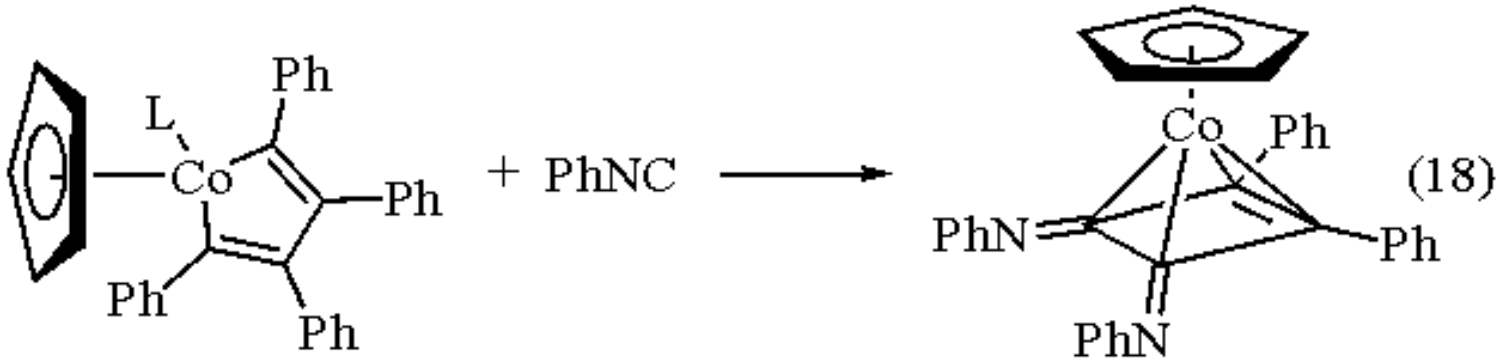

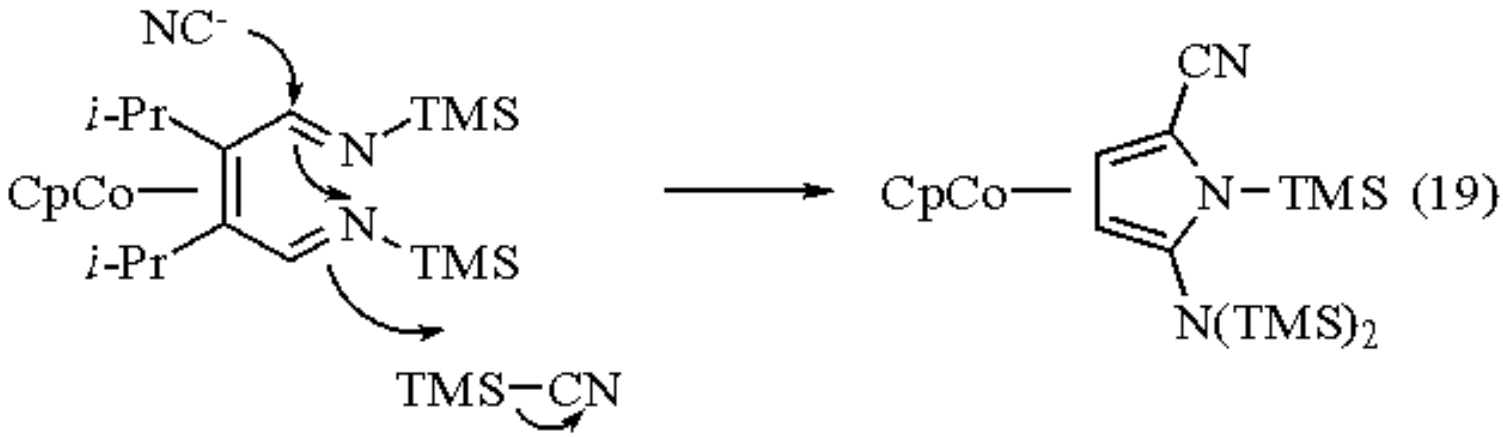

Stoichiometric Reactions.

Cyclohexadiene Formation.

As noted above, highly substituted cyclohexadienes can be obtained (eq 6) by treating the isolated cobaltacyclopentadiene complexes with a range of terminal alkenes or dimethyl maleate; subsequent oxidation using cerium(IV) salts liberates the free dienes.[14,15] The complex formed from $MeN(CMe_2C_2Me)_2$ and $CpCo(PPh_3)_2$ has similarly been added to diethyl fumarate.[16] Cyclohexadiene complexes are obtained more commonly and conveniently, without isolation of cobaltacyclopentadienes. Thus tolan or dimethyl acetylenedicarboxylate reacts with norbornene and $CpCo(CO)_2$ according to eq 20 to yield mixtures of two stereoisomeric complexes.[17]

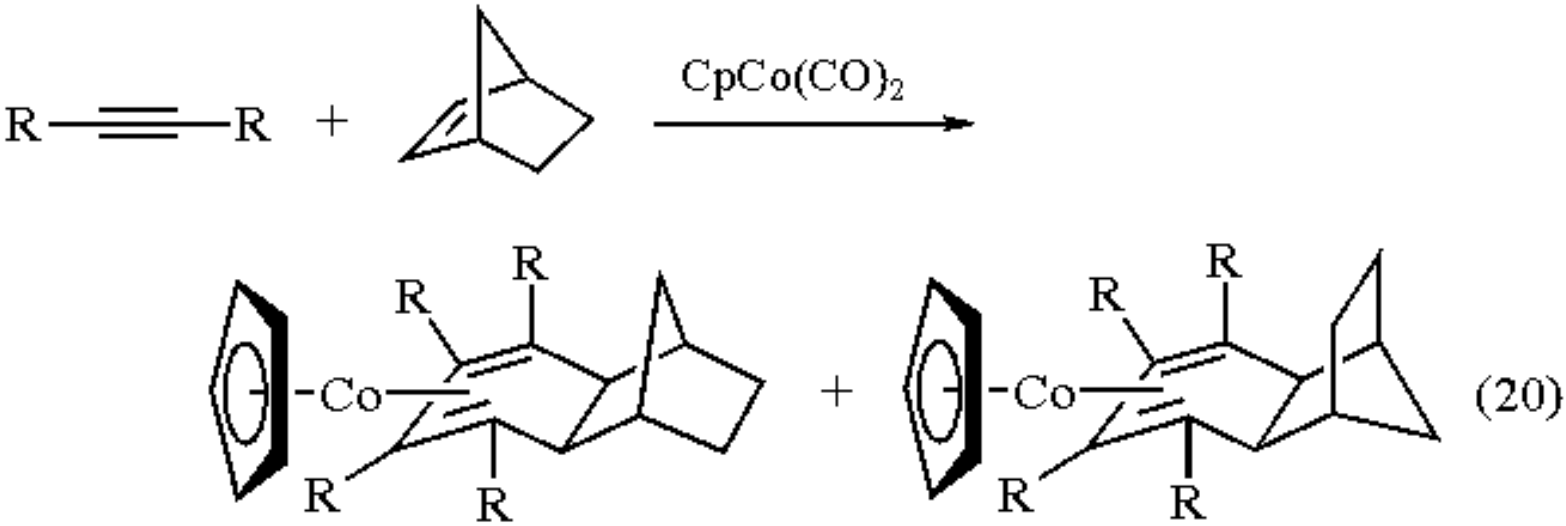

R = Ph or CO_2Me

Alkynes or diynes have been added in similar fashion to uracil derivatives (eqs 21 and 22).[18]

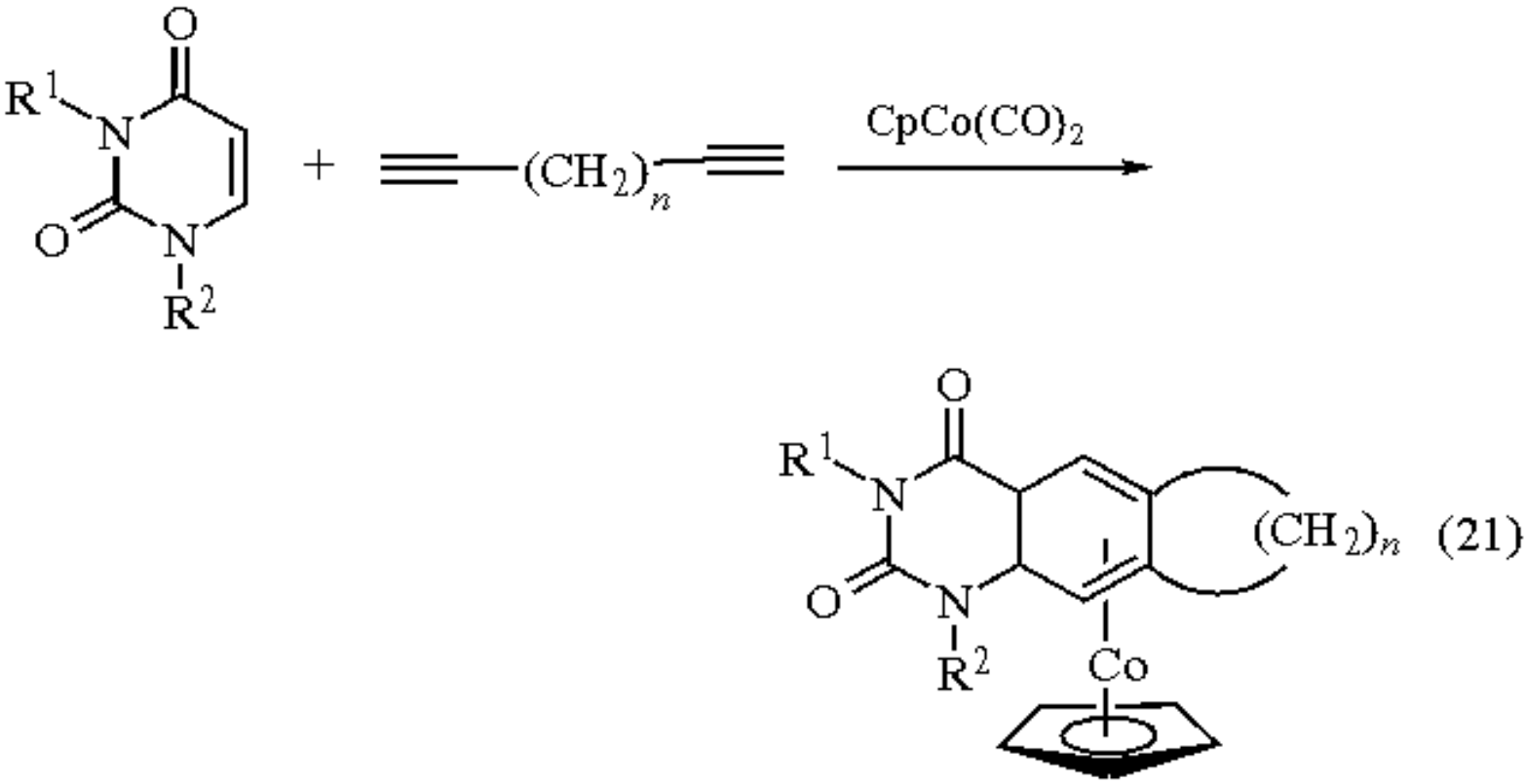

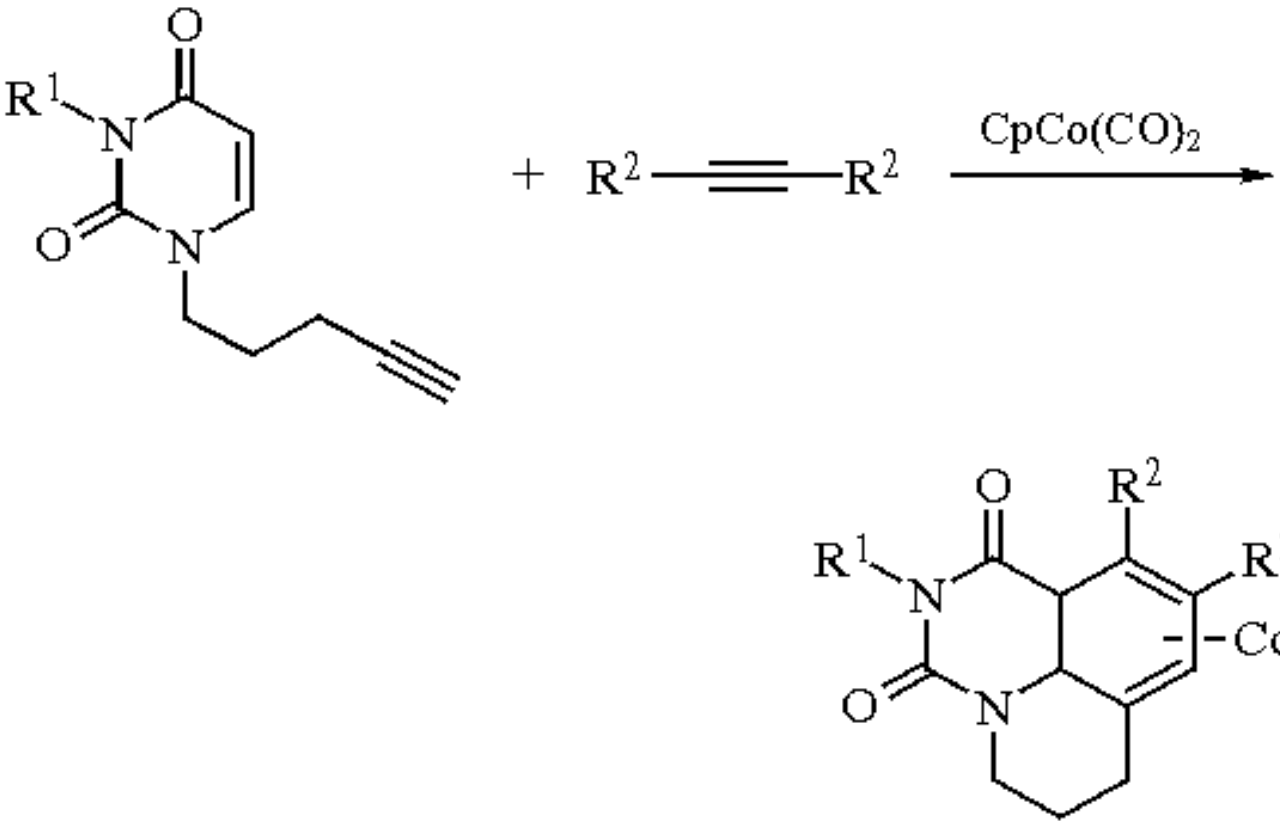

(22)

Even the 2,3-bond of *N*-acylindoles can function as the ene component in such condensations (eq 23).[19] The free tetracyclic ligand was liberated from the resultant complex in excellent yield by ***Copper(II) Chloride*** or ***Iron(III) Chloride*** oxidation and the aromatized ligand was obtained when Ce^{IV} was used. Cyclization of enediynes[10] (eq 24) has been followed by liberation of the organic ligands using oxidation with $CuCl_2/Et_3N$ and by other transformations.[20] An efficient approach to steriods by enediyne cyclization is shown in eq 25.[21] The free organic ligand is liberated from the resultant cobalt complex in 81% yield by oxidation.

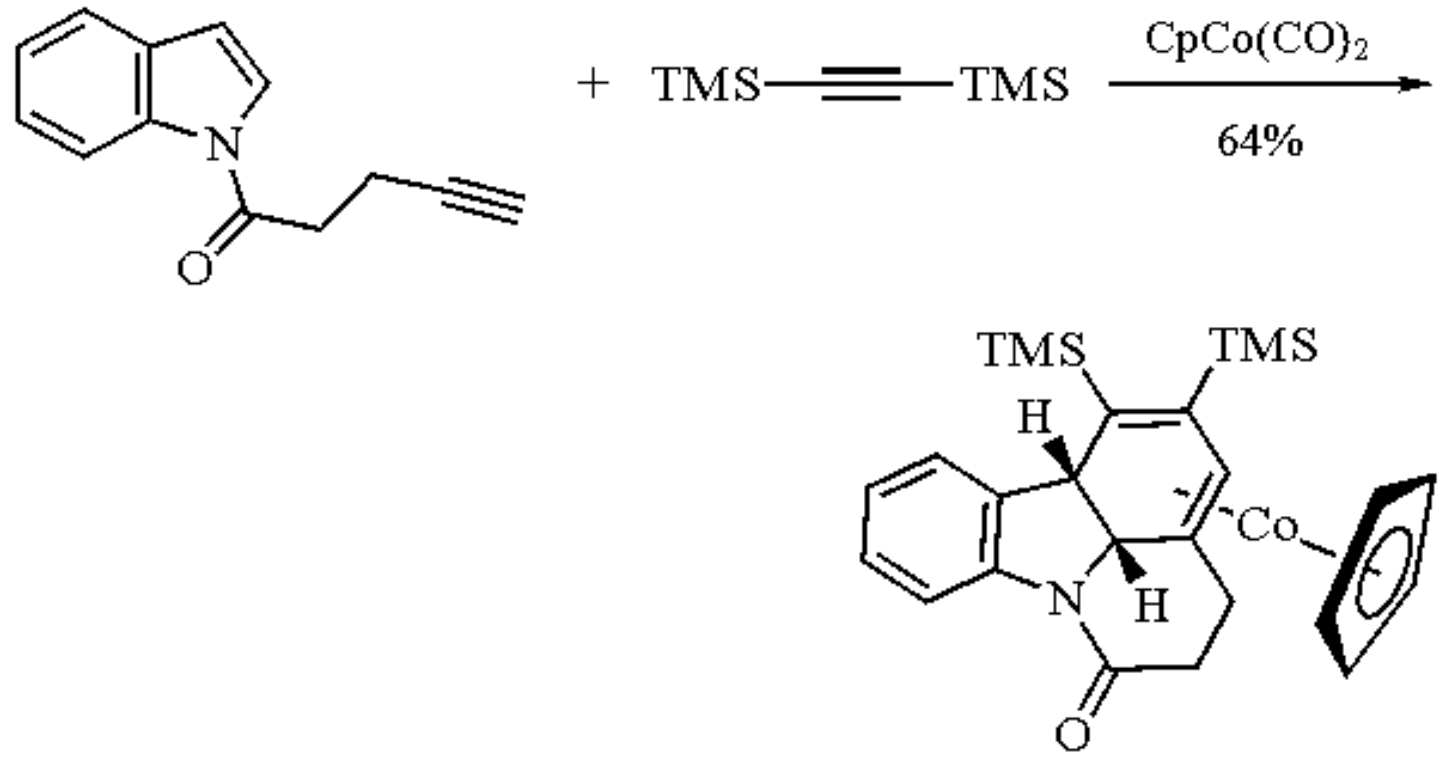

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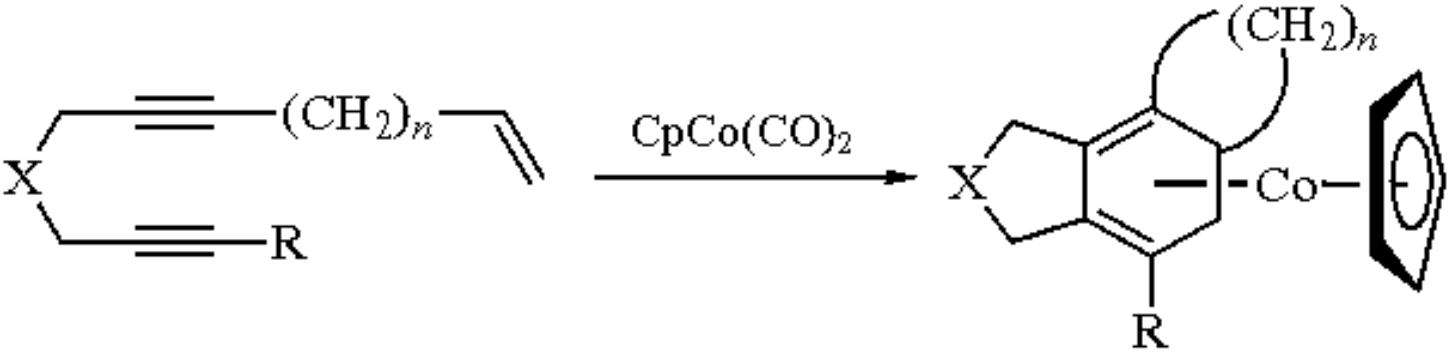

(24)

$X = CH_2CH_2$ or O, $n = 3$ or 4, R = H or TMS

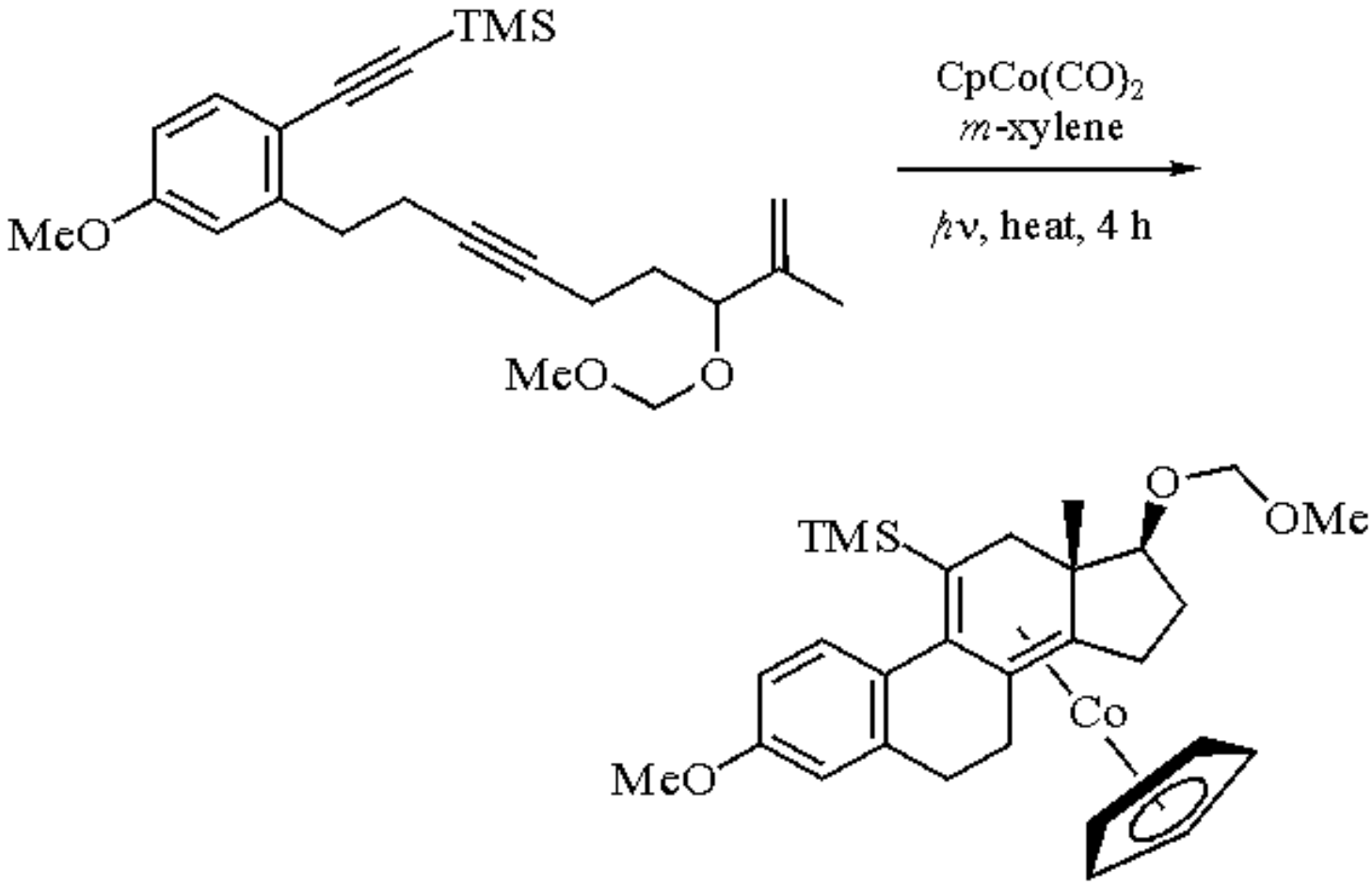

(25)

The sequence of steps for cyclohexadiene formation can be altered as in eq 26 followed by eq 27.[22,23] Again $CuCl_2$ proves to be an efficient oxidizing agent to liberate the free cyclohexadiene with only a small amount of aromatization, whereas the use of cerium(IV) leads to extensive dehydrogenation.[23] Loss of PPh_3 from the cobaltacyclopentene intermediate (eq 27) is assisted in this case by coordination of an ester carbonyl. The same intermediates also add carbon monoxide or isocyanides, yielding cyclopentenones or aminocyclopentadienes, respectively (eq 28).[23]

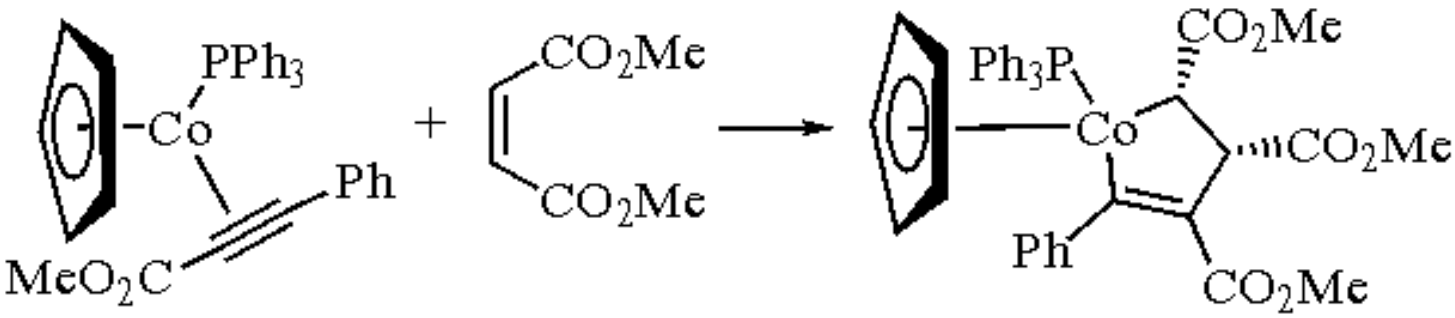

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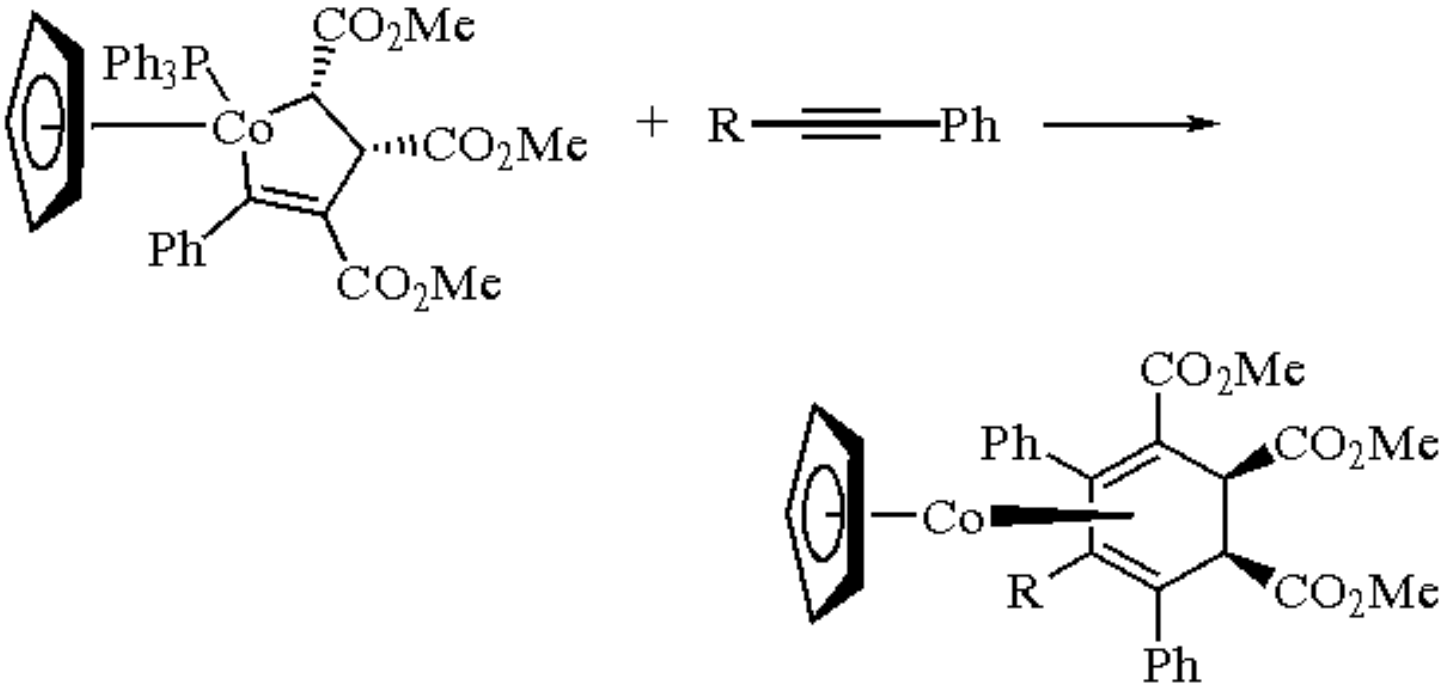

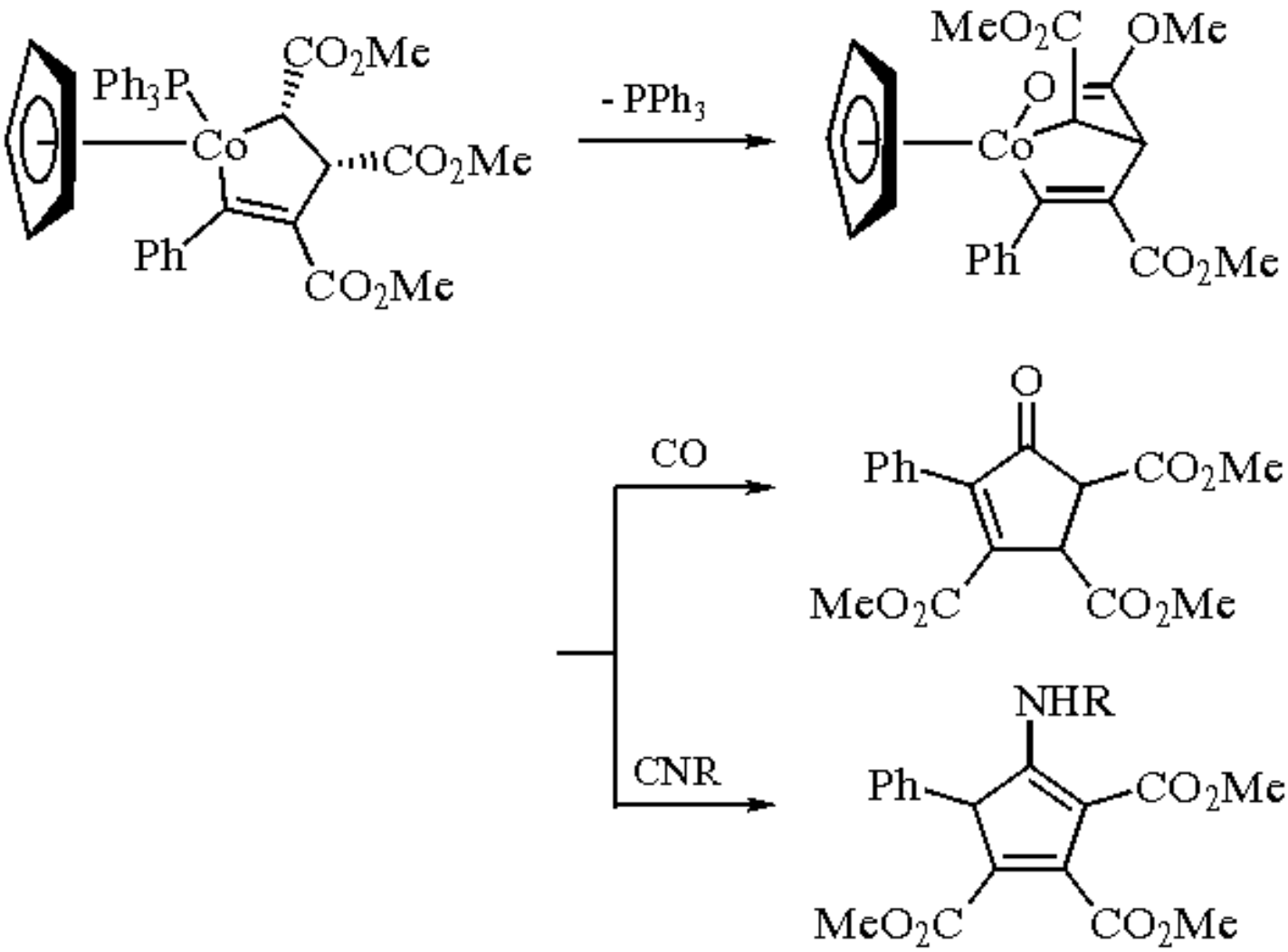

Pyran Synthesis.

Under photochemical conditions, ketones (or aldehydes) can take the place of alkenes and add to diynes to yield pyrans. Examples include the addition of acetone to 1,7-octadiyne (eq 29) with the more reactive maleic anhydride substituted catalyst and the tricyclization of a diynone (eq 30). In the latter case a ring-opened product accompanies the pyran.[24] In other examples an ynone is condensed with a silylalkyne (eq 31).[24]

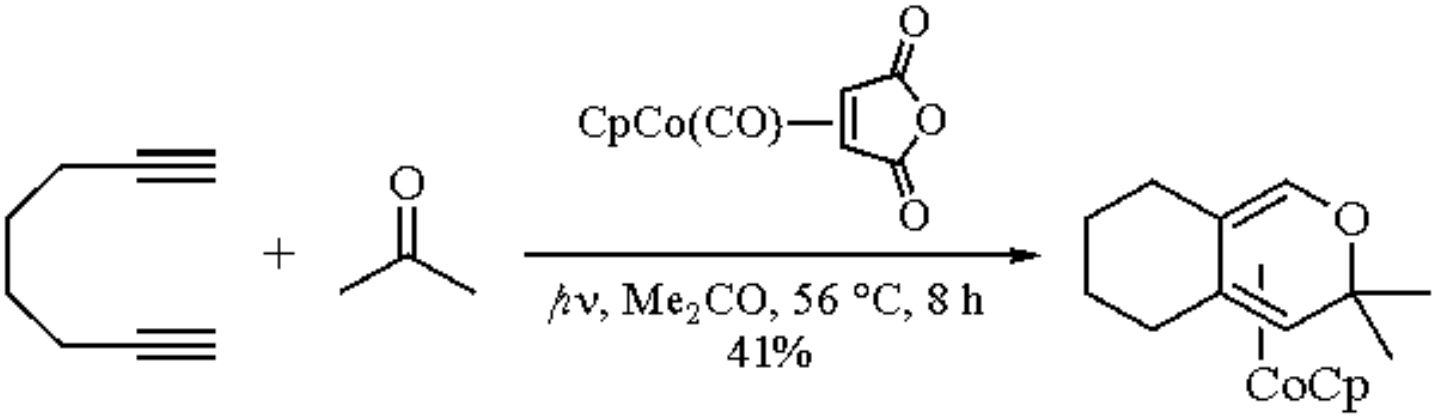

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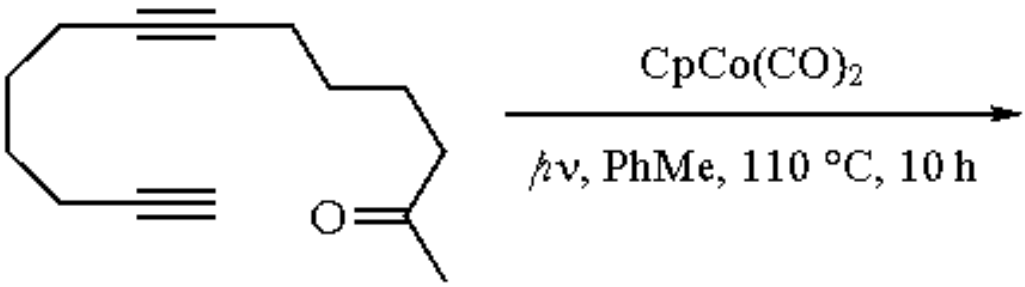

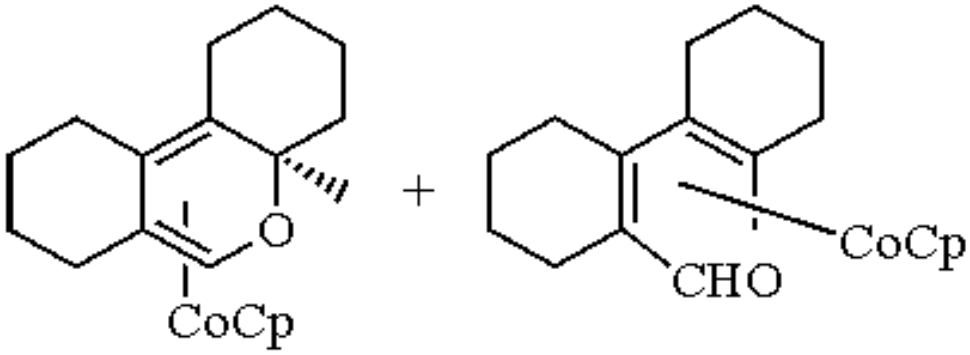

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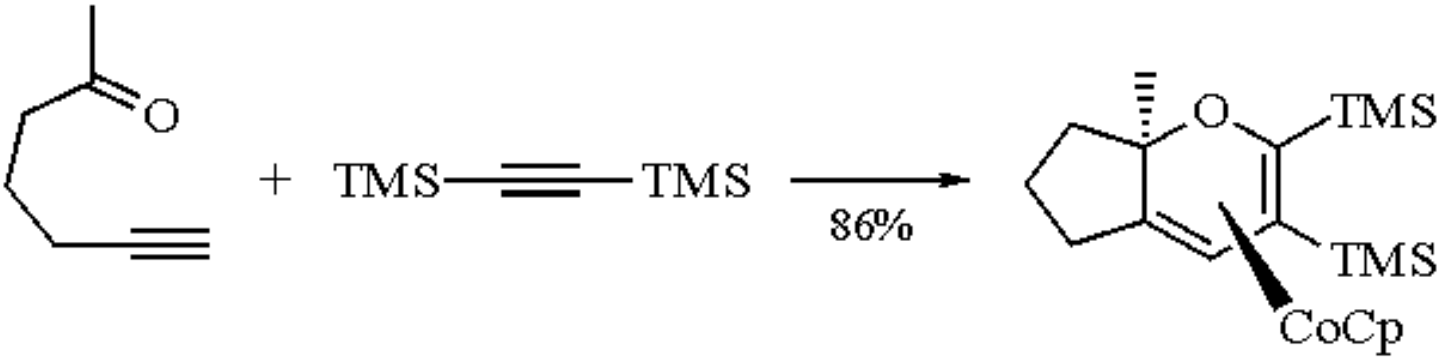

(31)

Formation of Cyclopentadienone Complexes and

Competing Reactions.

(Cyclopentadienone)cyclopentadienylcobalt derivatives are major products of the reaction of $CpCo(CO)_2$ with internal alkynes and terminal alkynes, RC_2H, which have bulky groups, R. Irradiation was used to obtain the earliest examples (eq 32, R = Me or Ph)[25] and remains the method of choice in most cases, but thermal activation has also been widely used. Three other types of product are frequently produced under thermal conditions: (cyclobutadiene)cyclopentadienylcobalt, cyclopentadienyl(*p*-quinone)cobalt, and (cyclopentadienyl)maleylcobalt derivatives. Formation of the cyclobutadiene complexes has been reviewed.[26] CO-free precursors, e.g. ***(1,5-Cyclooctadiene)(cyclopentadienyl)cobalt(I)***, are preferable for this purpose since they cannot yield the other products, but $CpCo(CO)_2$ can also give excellent yields as in the examples shown in eqs 33 and 34.[27,28] The latter example contrasts with the low-temperature photochemical reaction of the same precursors (eq 35).[29] Liberation of the free dienone from the product by Ce^{IV} oxidation as well as partial or complete displacement of $SiMe_3$ by Br or H[30] emphasizes the synthetic utility of such reactions.

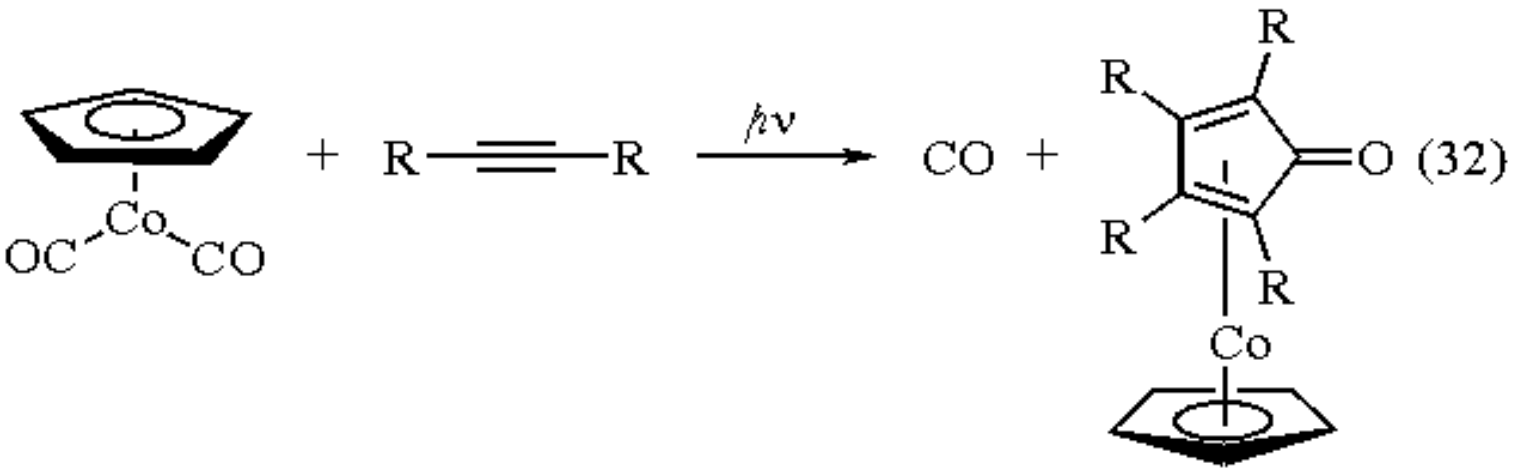

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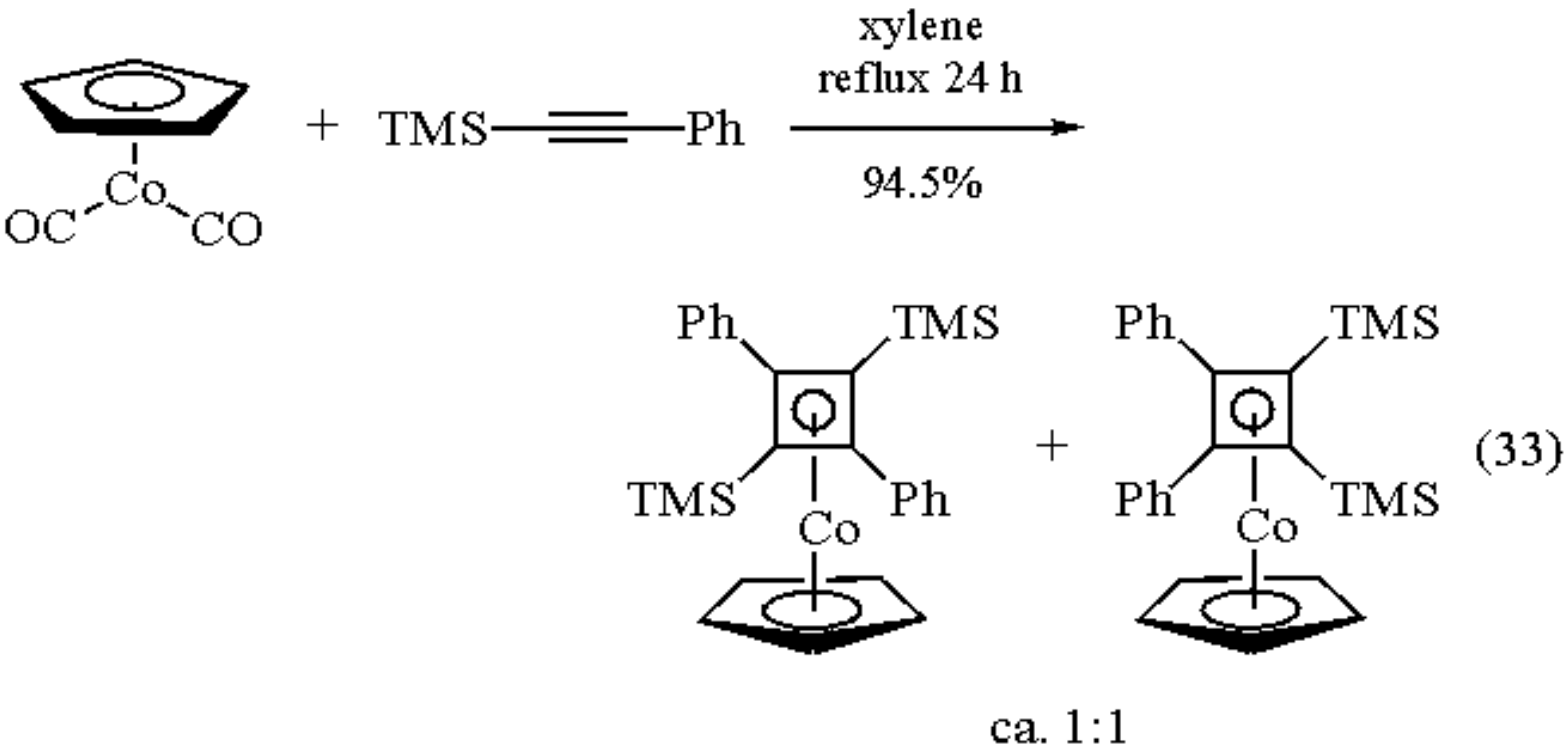

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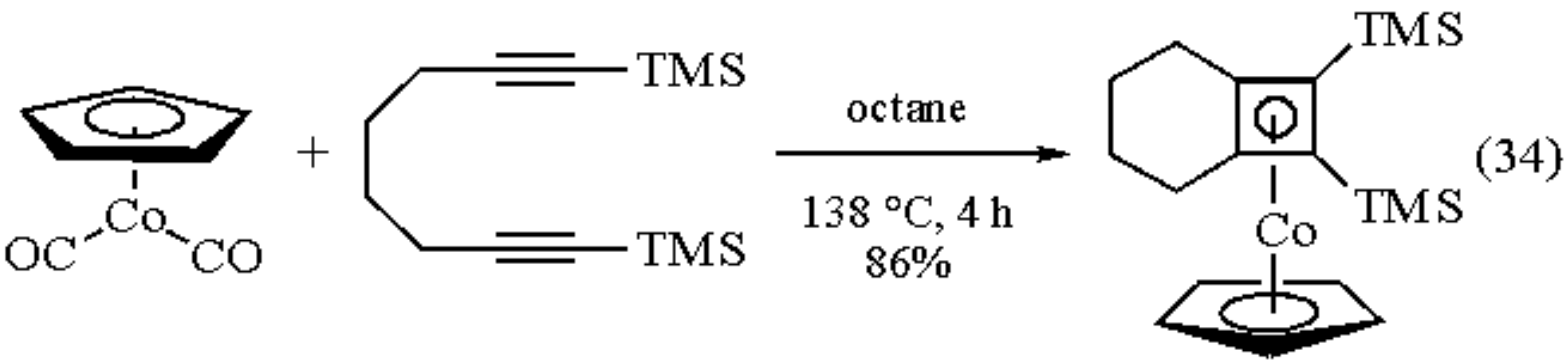

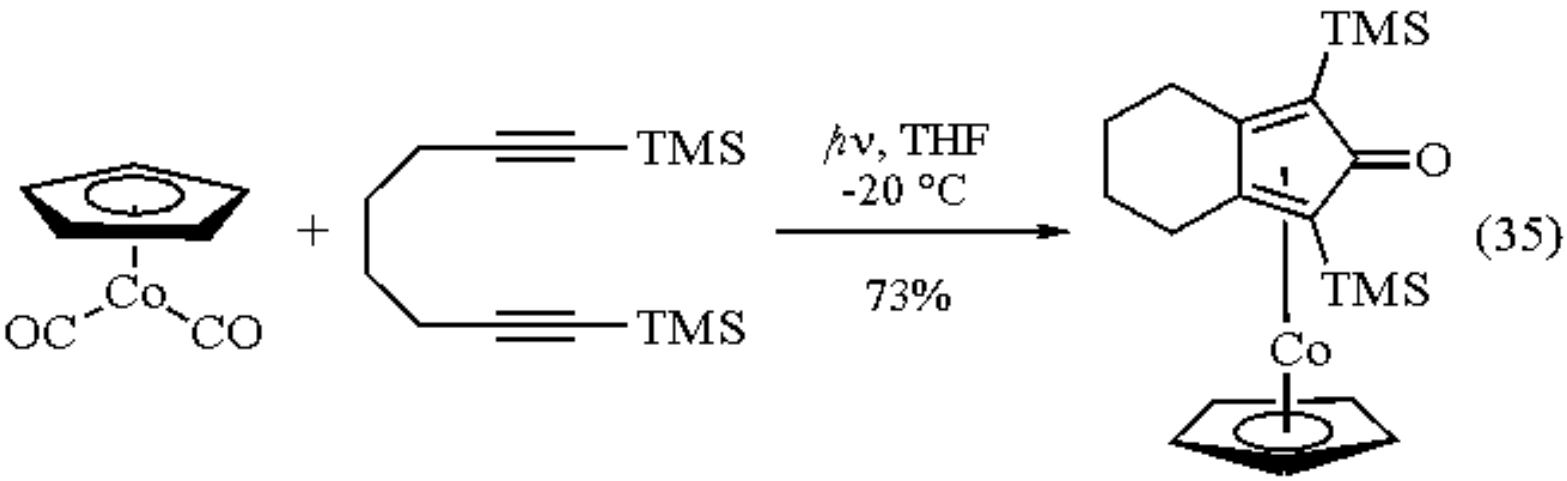

The reaction of 2-butyne under thermal conditions (eq 36)[31] shows that quinone complexes are formed more quickly than cyclopentadienone complexes and perhaps decarbonylate to the latter under the reaction conditions. Similarly at 100 °C, 3-hexyne yields the tetraethylquinone complex but at 110-130 °C it yields the tetraethylcyclopentadienone complex as the major product.[32] In a series of alkynes, MeC_2R, both the electronegativity and size of R affects the product ratios.[33] The maleyl complexes appear only as minor products (eq 36) and hence cannot be considered to be synthetically significant.

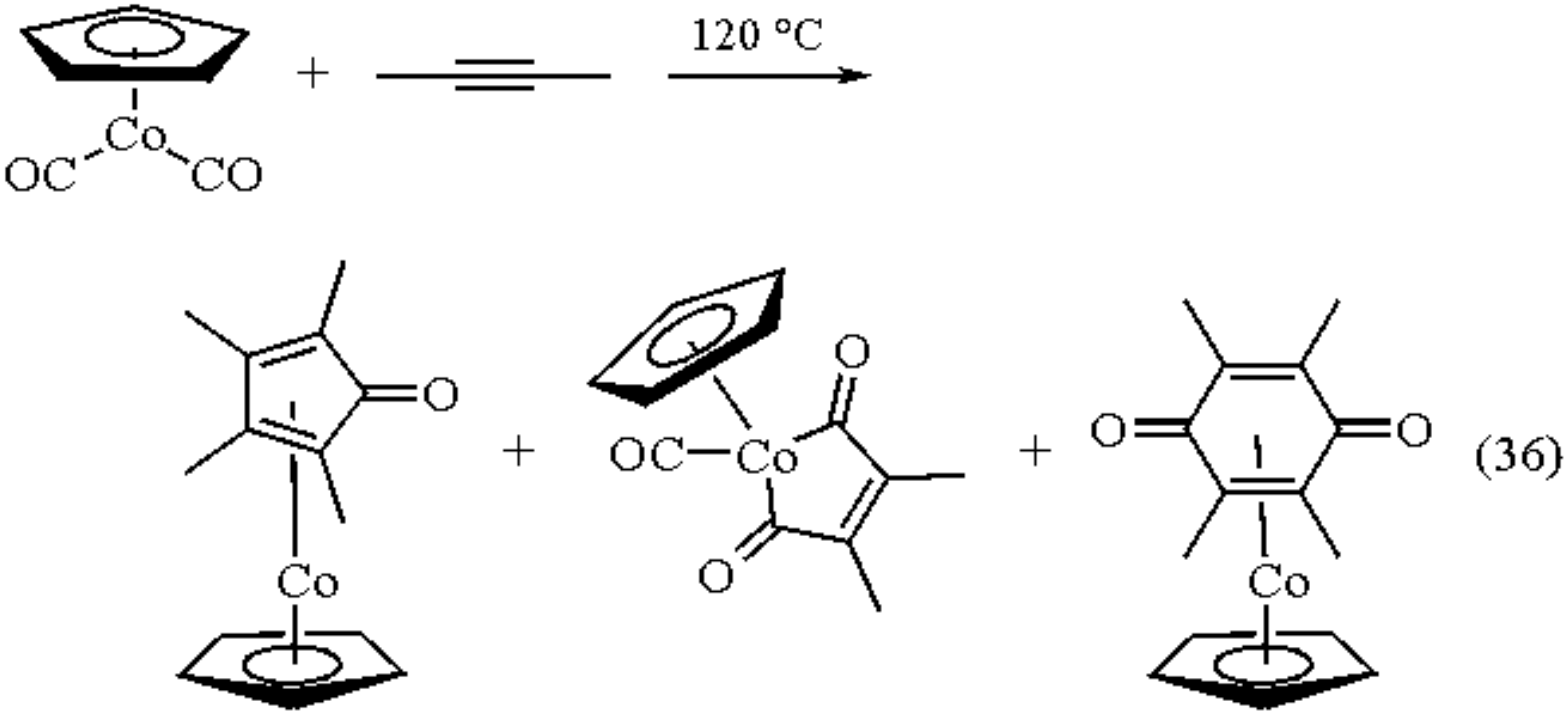

(36)

yields after 19 h 3:3:27%
yields after 90 h 62:1:16%

Tolerance of highly polar substituents is illustrated by the reaction of di-*t*-butoxyacetylene (eq 37).[34] The ionic catalyst, [K(crown)][CpCo(CO)CN], obtained from [K(crown)]CN and $CpCo(CO)_2$, has been used[35] in the reaction with tolan, but although the conditions were fairly mild (reflux in butyronitrile), the modest yield (43%) of the tetraphenylcyclopentadienone complex does not encourage use of this procedure.

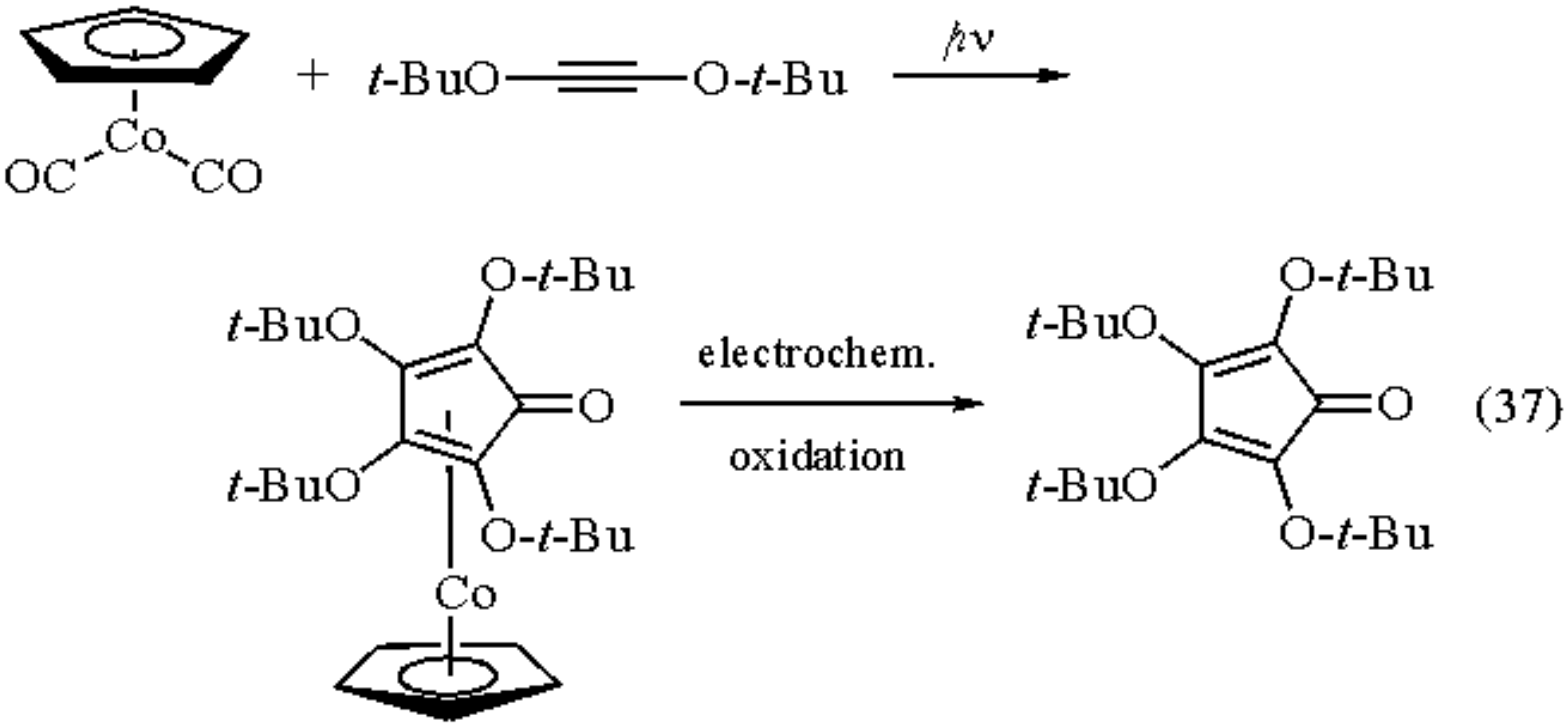

(37)

In contrast to its efficient incorporation into cyclobutabenzenes (see above), $Me_3SiC_2(CH_2)_2C_2SiMe_3$ gives a very complex mixture of (largely polynuclear) cyclobutadiene and cyclopentadienone complexes in the absence of added alkyne.[28] Presumably the monomeric cyclobutenocyclopentadienone is too strained, whereas a derivative with four methyl substituents on the cyclobutene ring is formed as the sole product according to eq 38.[36]

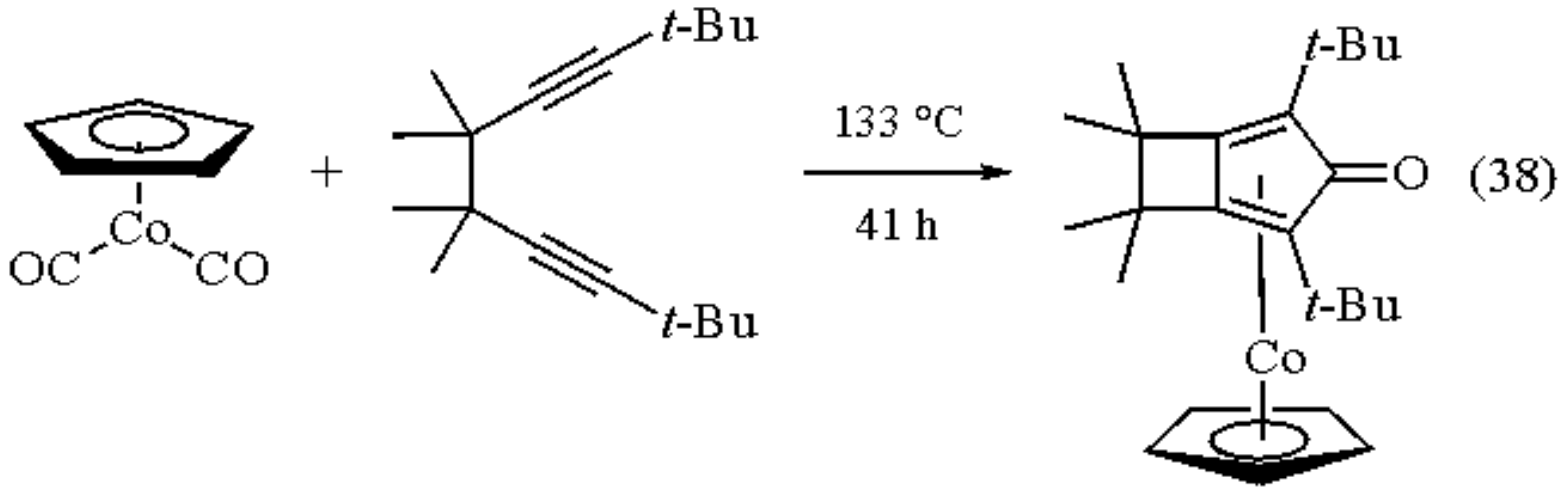

When the terminal alkyne Me_3SiC_2H is used, the 2,5-disubstituted cyclopentadienone complex is the major product (eq 39)[29] (a 76% yield is reported[37] under only marginally different conditions) with $CpCo(CO)_2$, but the corresponding 2,4-disubstituted compound predominates in the product from $(C_5Me_5)Co(CO)_2$.[29]

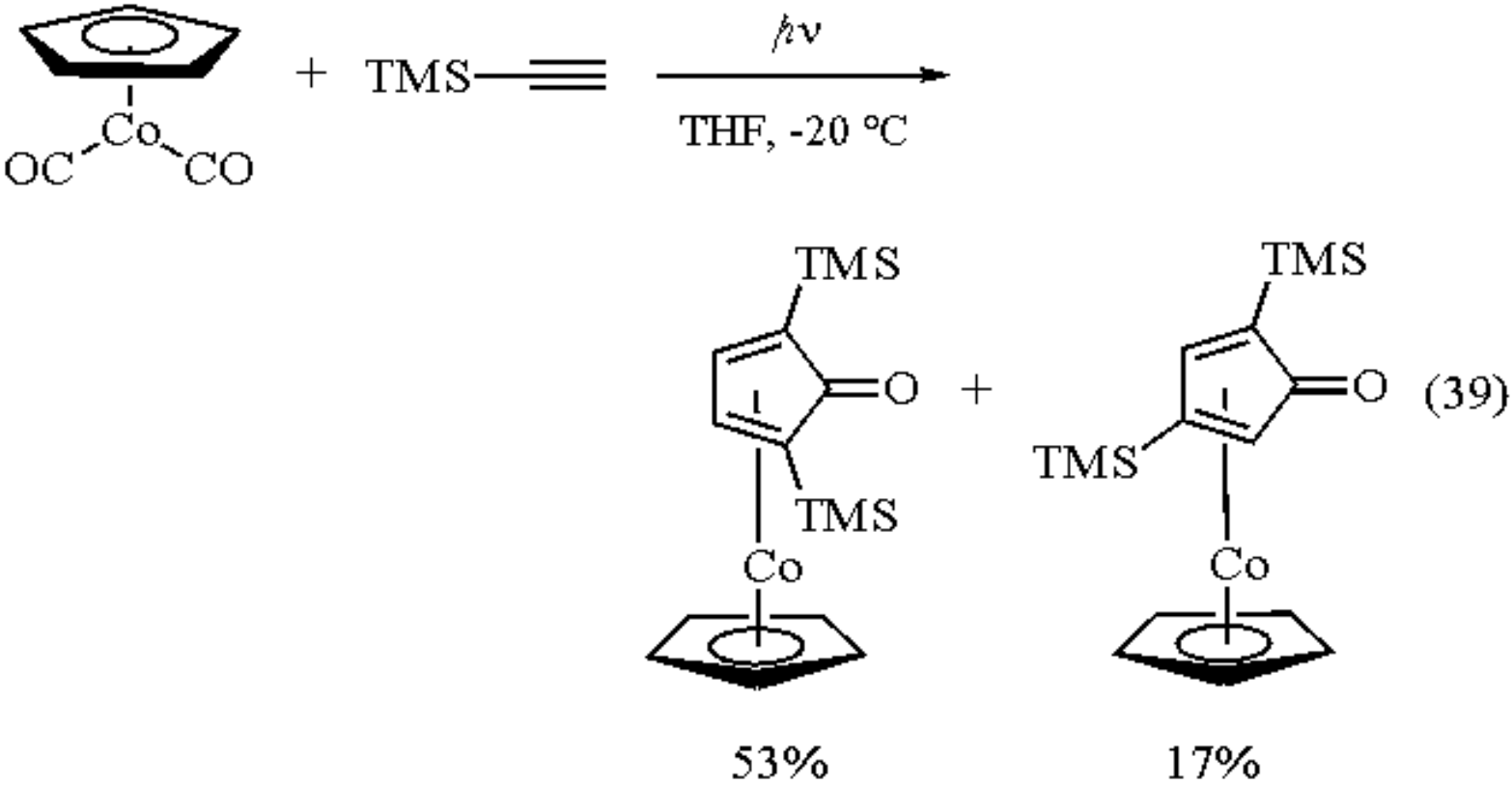

In a reaction closely analogous to the CO insertion, cobaltacyclopentadienes react with isocyanides to give iminocyclopentadiene complexes, e.g. according to eq 40.[38]

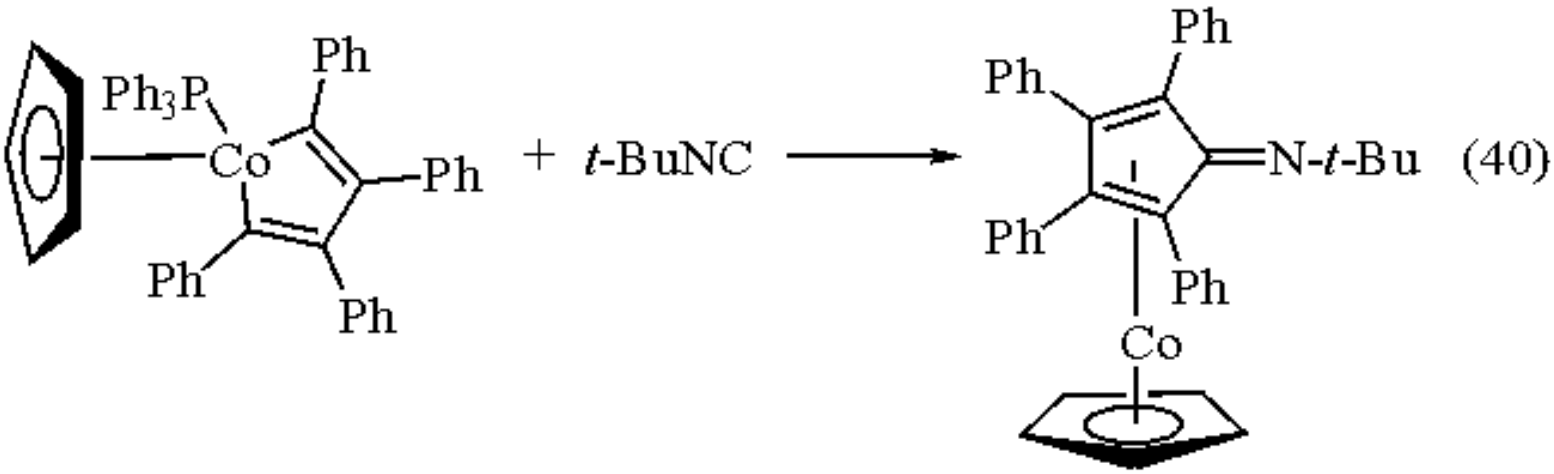

Other Products from Cobaltacyclopentadienes.

In addition to the above alkene and CO insertions, isolated cobaltacyclopentadienes have been shown to react with diazo compounds to yield cyclopentadiene complexes and hence substituted cyclopentadienes (e.g. eq 41),[39] and similarly with azides to yield pyrroles (eq 42).[40] Acid azides, $RCON_3$, react similarly to give the corresponding *N*-acylpyrroles while tosyl azide reacts according to eq 43.[40]

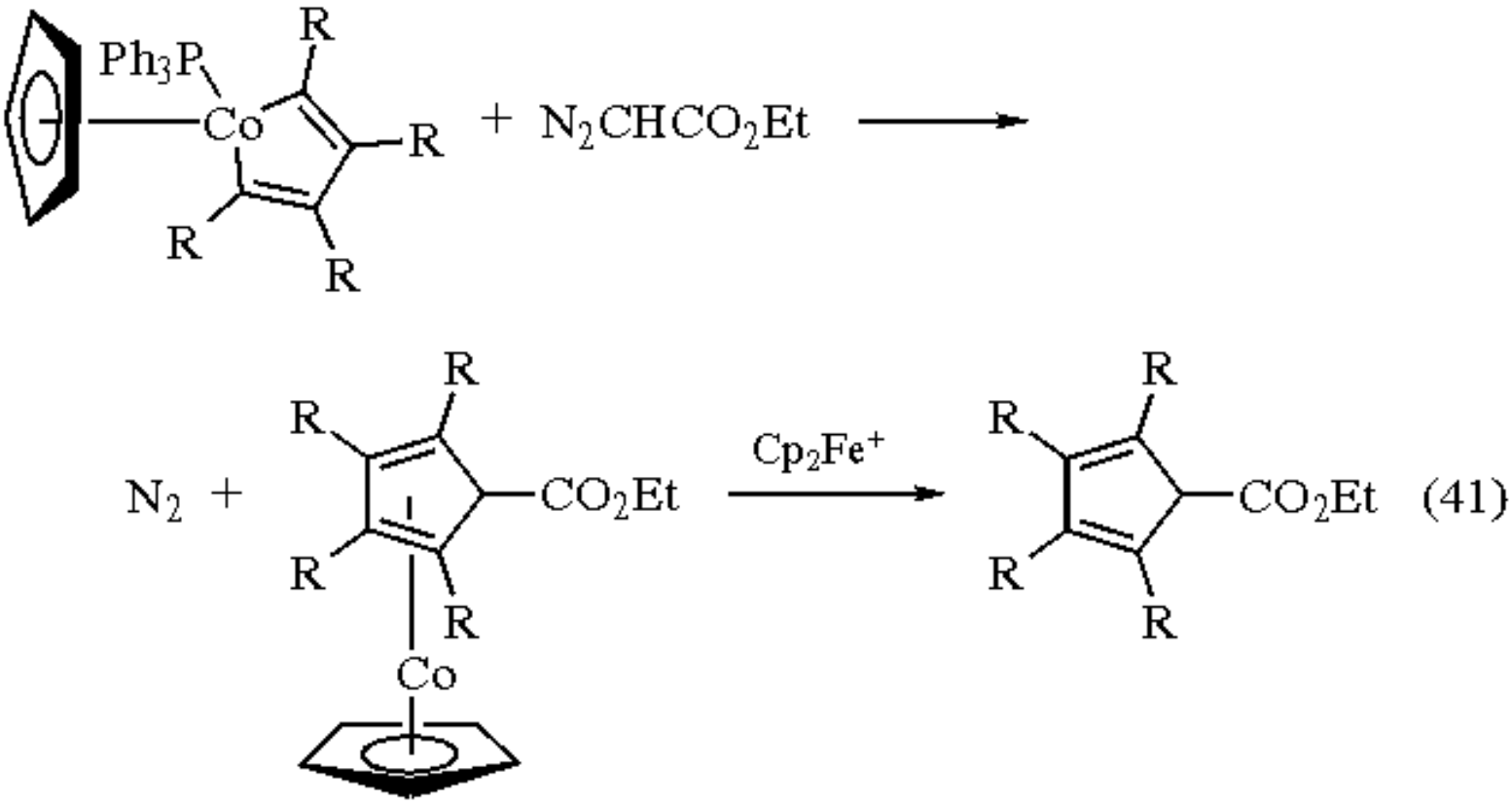

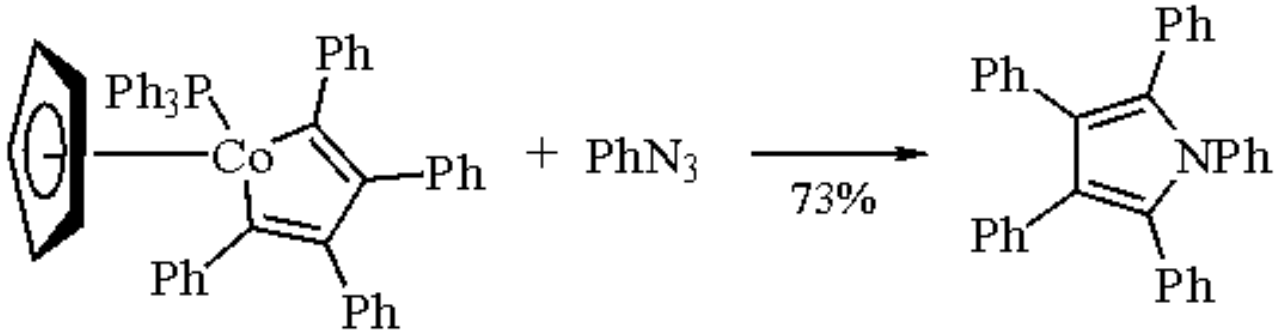

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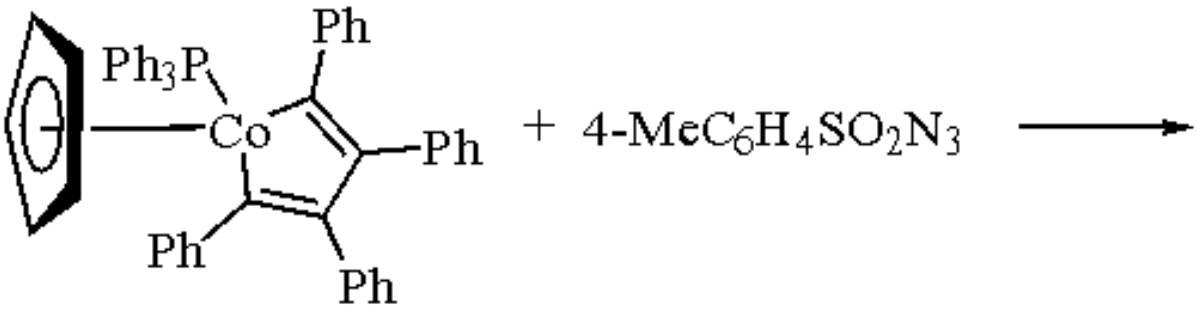

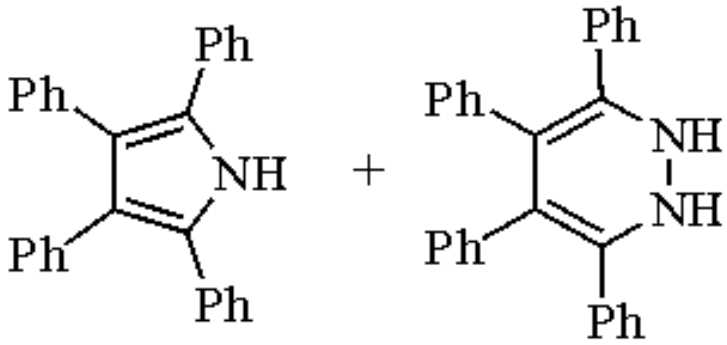

(43)

Reaction with sulfur yields thiophenes (eq 44).[41] Replacement of triphenylphosphine by phosphites also results in ring formation, leading to cyclic 1-alkoxyphosphole oxide complexes (as mixtures of two stereoisomers) with loss of alkyl groups (eq 45).[42]

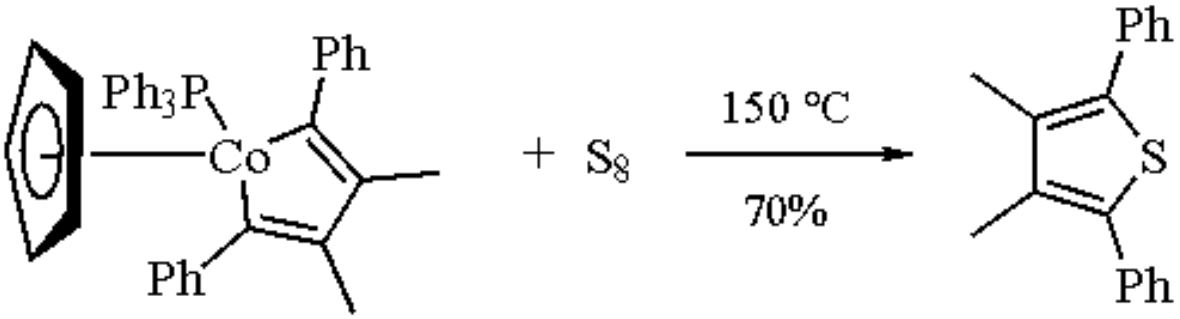

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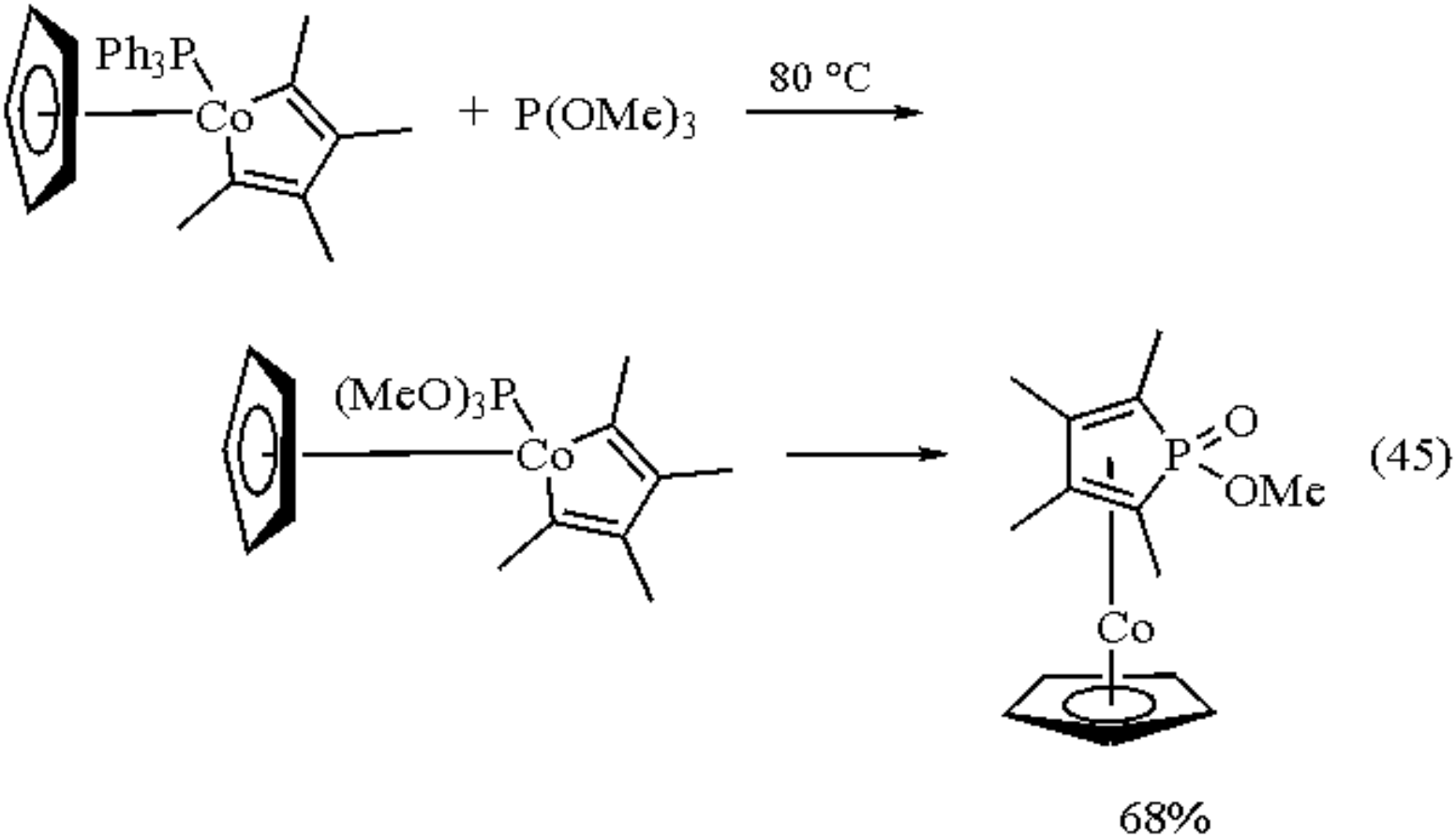

(45)

Oxidation of the tetraphenyl- or dimethyldiphenylcobaltacyclopentadiene complex with ground-state oxygen at 70 °C or singlet oxygen at room temperature yields dibenzoyldiphenylethylene or 2,3-dibenzoyl-2-butene, respectively, via the corresponding CpCo complex (eq 46).[43]

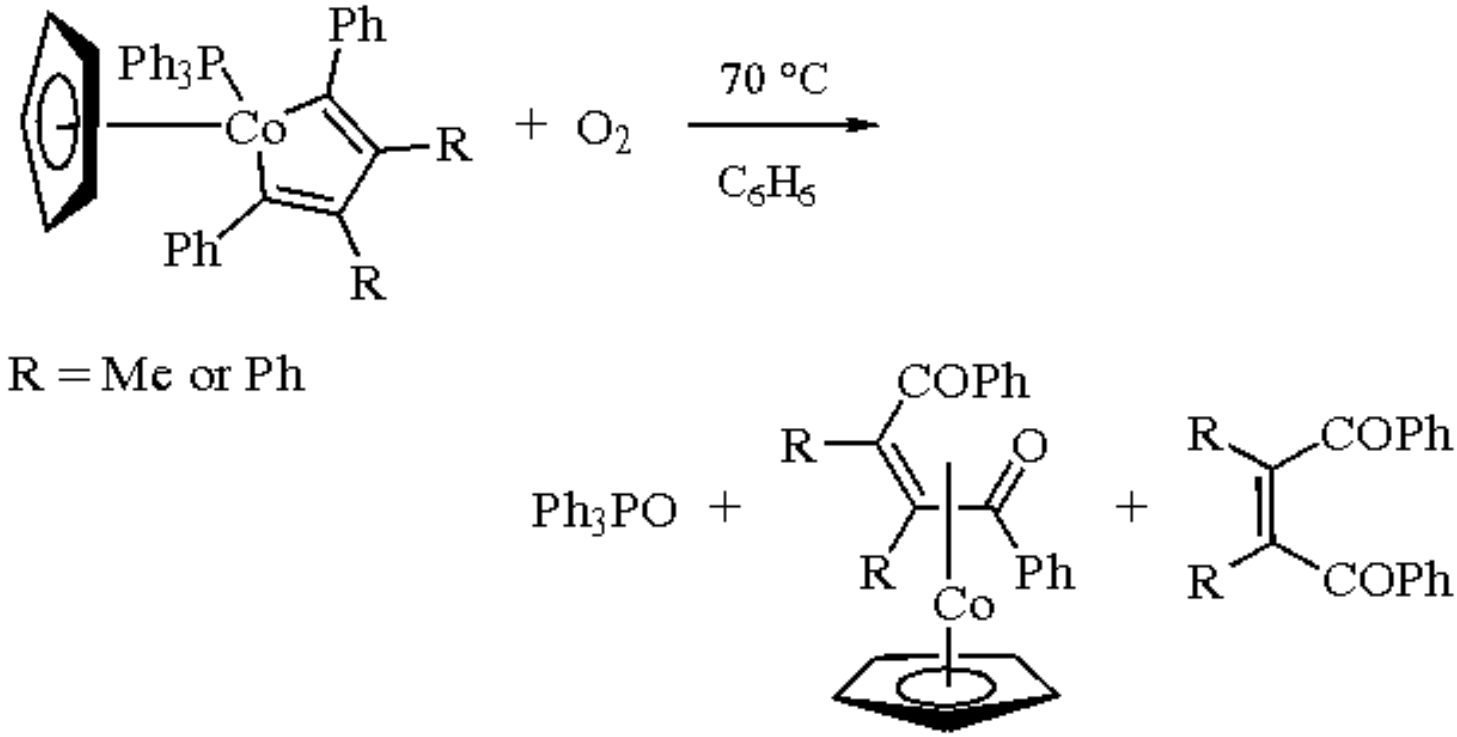

(46)

Insertion Reactions.

Cyclobutenediones react smoothly when heated with $CpCo(CO)_2$ to yield cobaltacyclopentenediones (eqs 47 and 48). Both the cyclopentadienyl complex and its pentamethyl derivative have been used with benzocyclobutenedione.[44] As shown in eq 48, despite the high temperature required the latter reaction proceeds quantitatively. The product complexes react photochemically with alkynes to give complexes of benzoquinones from which the free quinone may be liberated by cerium(IV) oxidation (eq 49).[44]

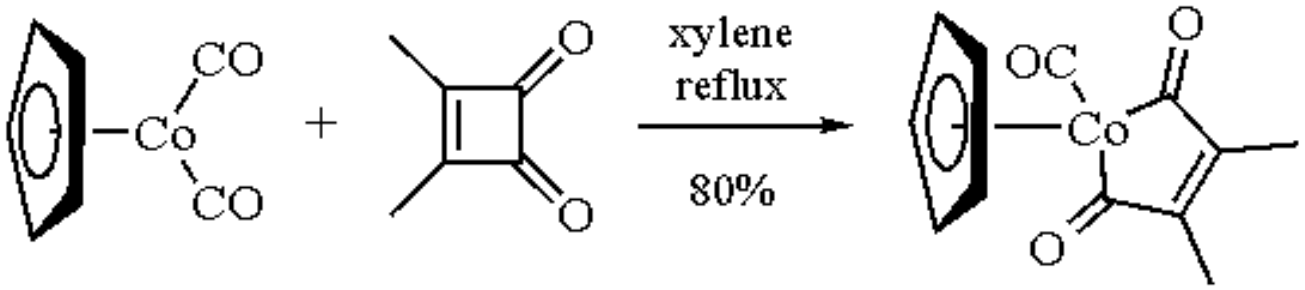

(47)

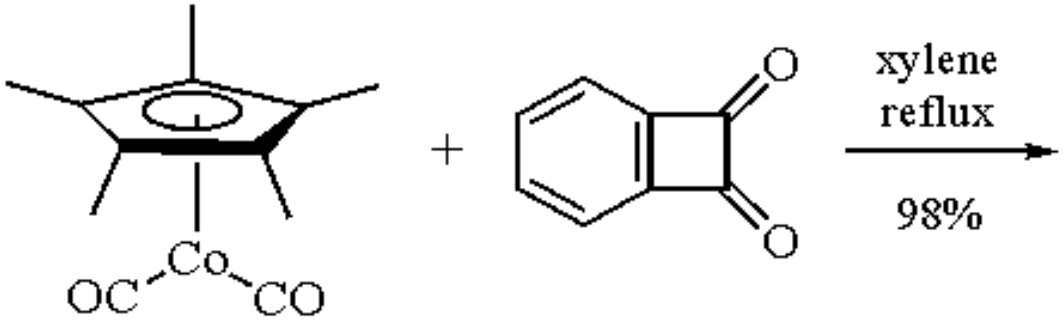

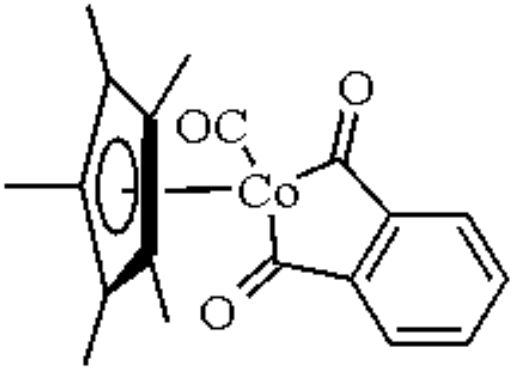

(48)

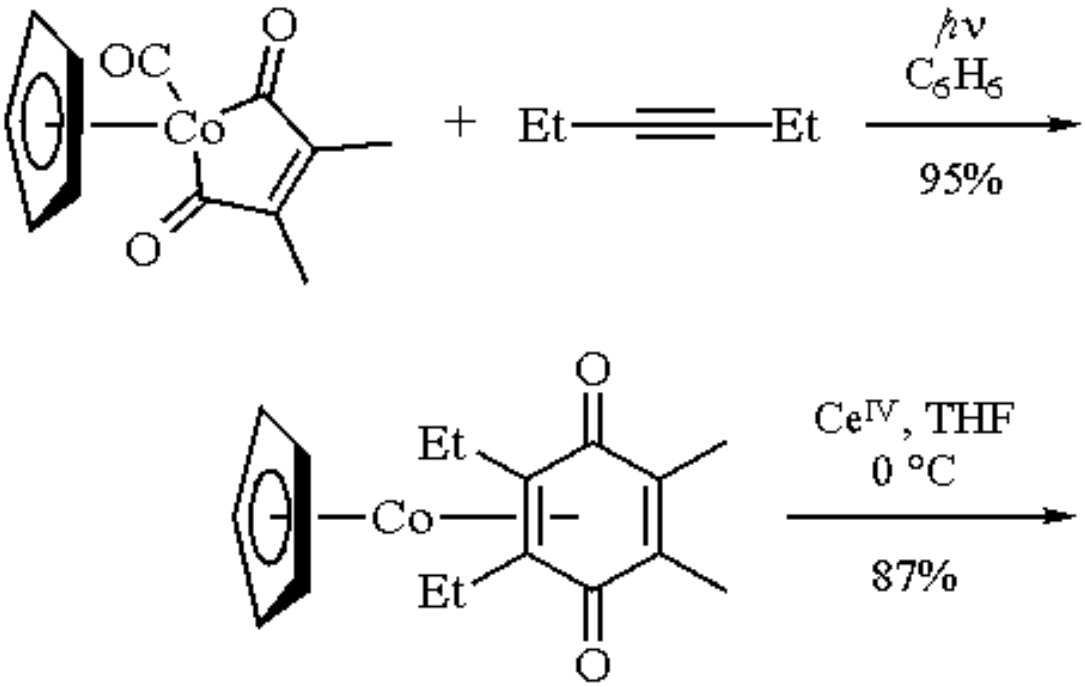

(49)

The related insertion into cyclobutenones has been effected using indenylbis(triphenylphosphine)cobalt (eq 50), initially yielding ketene complexes which add alkynes to give phenols.[45]

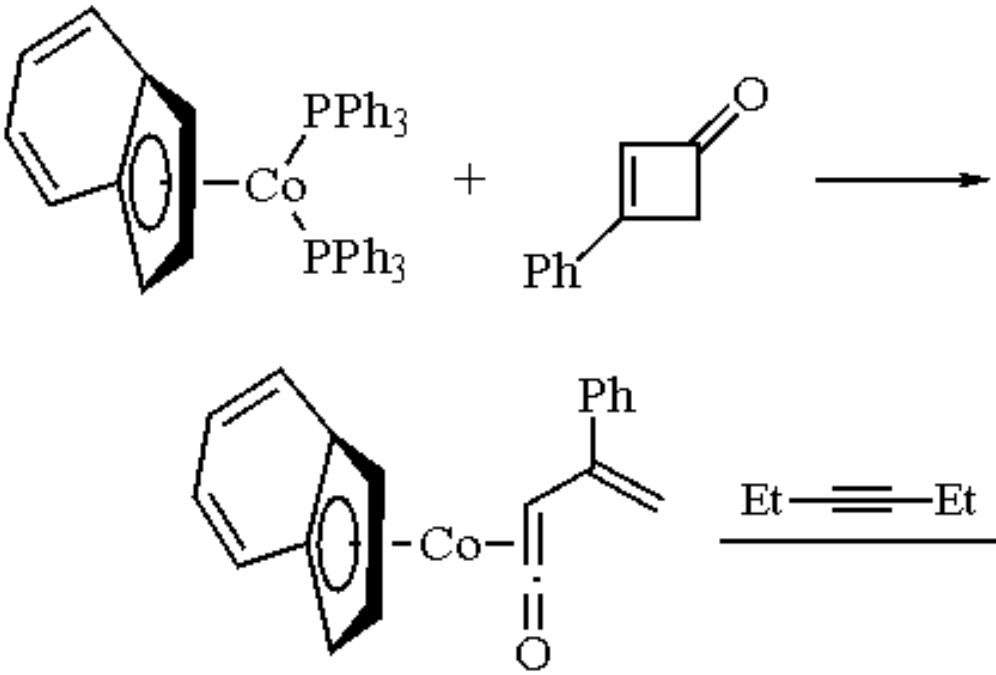

(50)

Another four-membered ring is expanded when $CpCo(CO)_2$ adds to a disilacyclobutene, e.g. in the reaction sequence shown in eq 51. The initially formed complex reacts photochemically with butadiene or its derivatives, at low temperature merely replacing the CO ligand, but at 60 °C giving disilacyclooctadienes.[46]

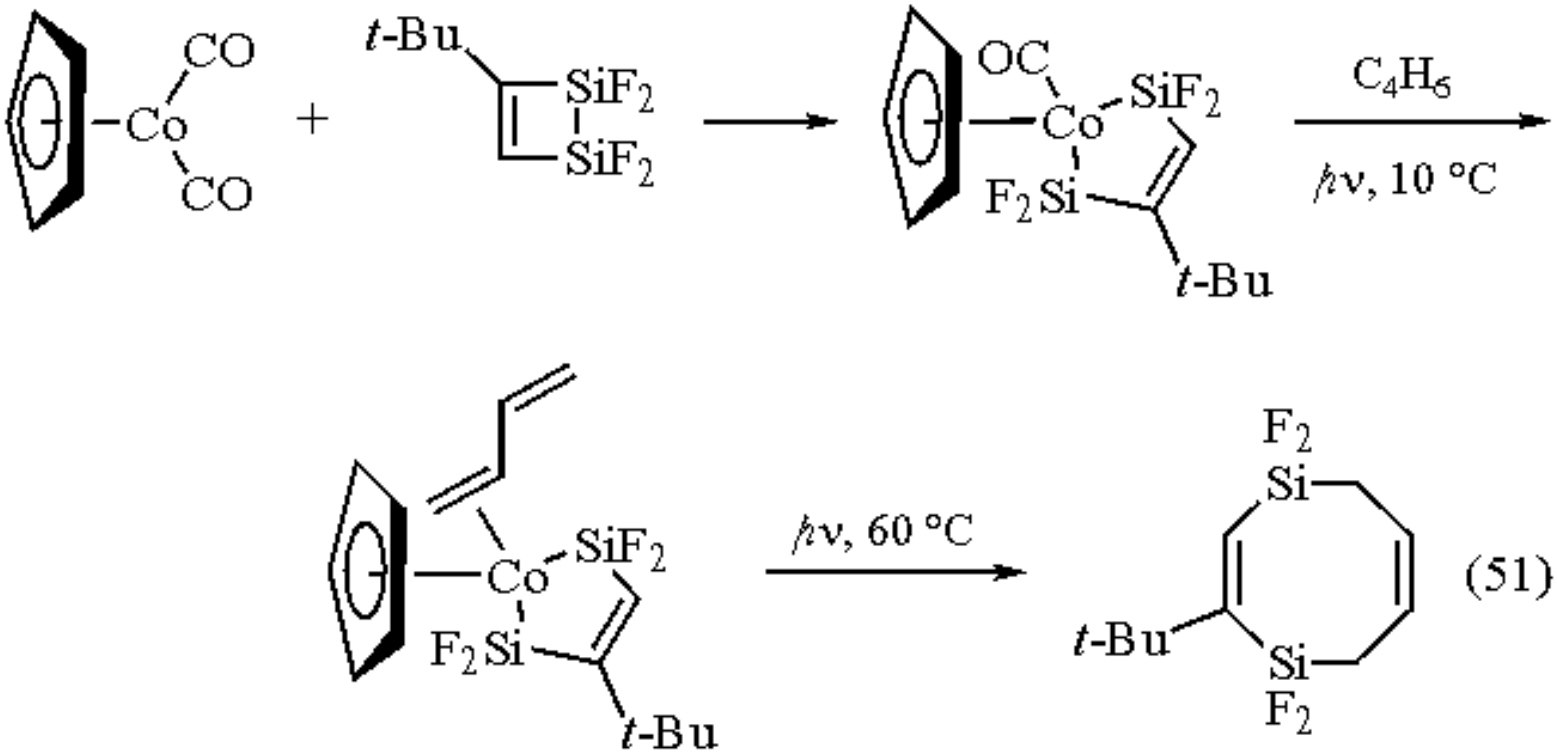

Miscellaneous Reactions.

Azoarenes react with $CpCo(CO)_2$ as exemplified for azobenzene (eq 52). The complexes formed may be carbonylated to yield *N*-arylbenzimidazolones (eq 53).[47] Most diazoalkanes react according to eq 54 yielding dinuclear, methylene-bridged complexes,[48] but diethyl diazomalonate yields a cobaltafuranone complex (eq 55).[49]

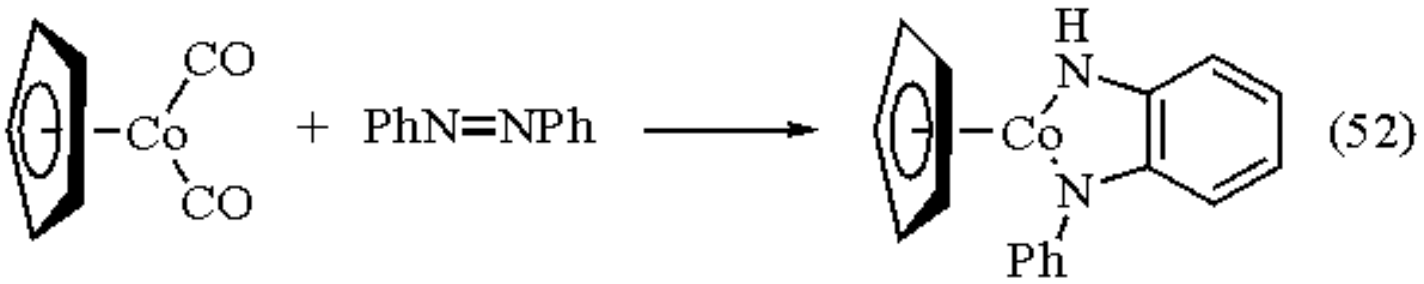

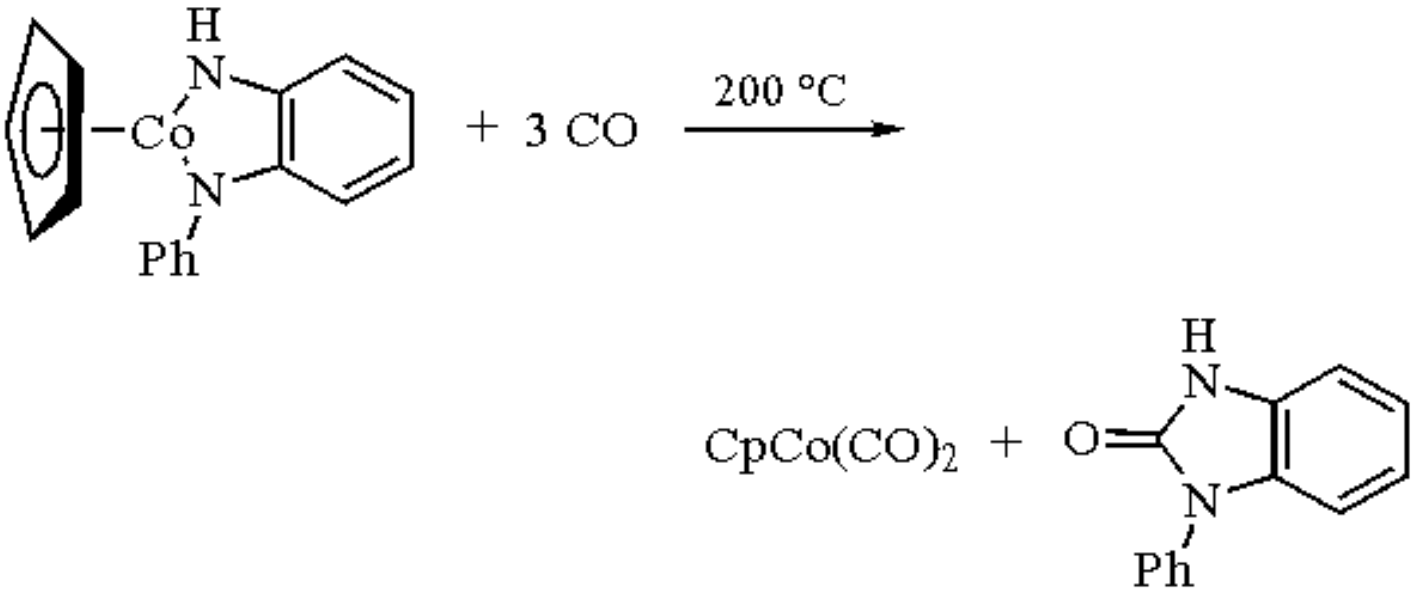

(53)

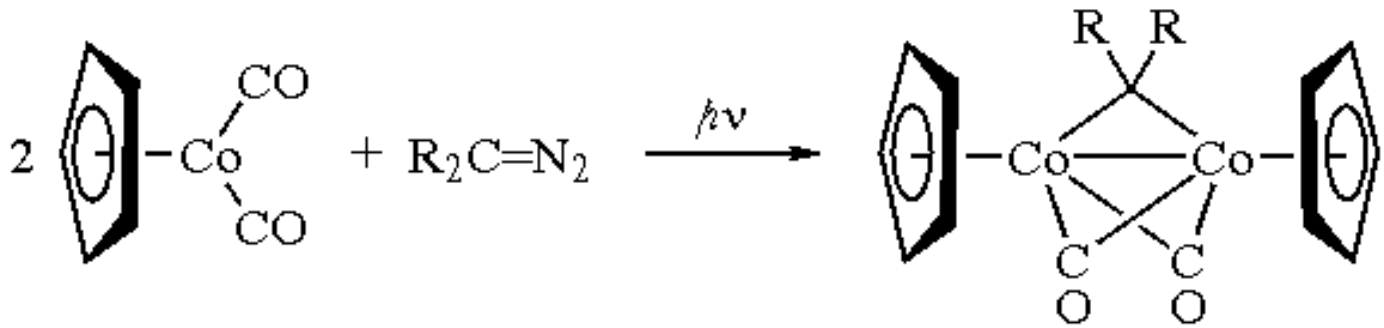

(54)

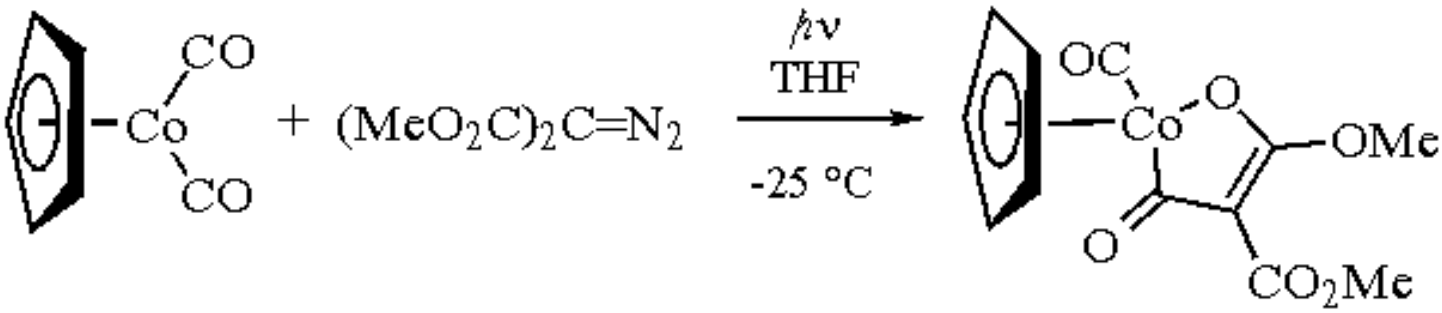

(55)

The products of the reaction in eq 55 and other cobaltacycles, formed inter alia from alkyne complexes (eq 56)[50] or from the isocyanide-phosphine complexes, $C_5H_5Co(PMe_3)(RNC)$,[51] have not been utilized in further reactions which would constitute synthetically useful transformations of the organic fragments.

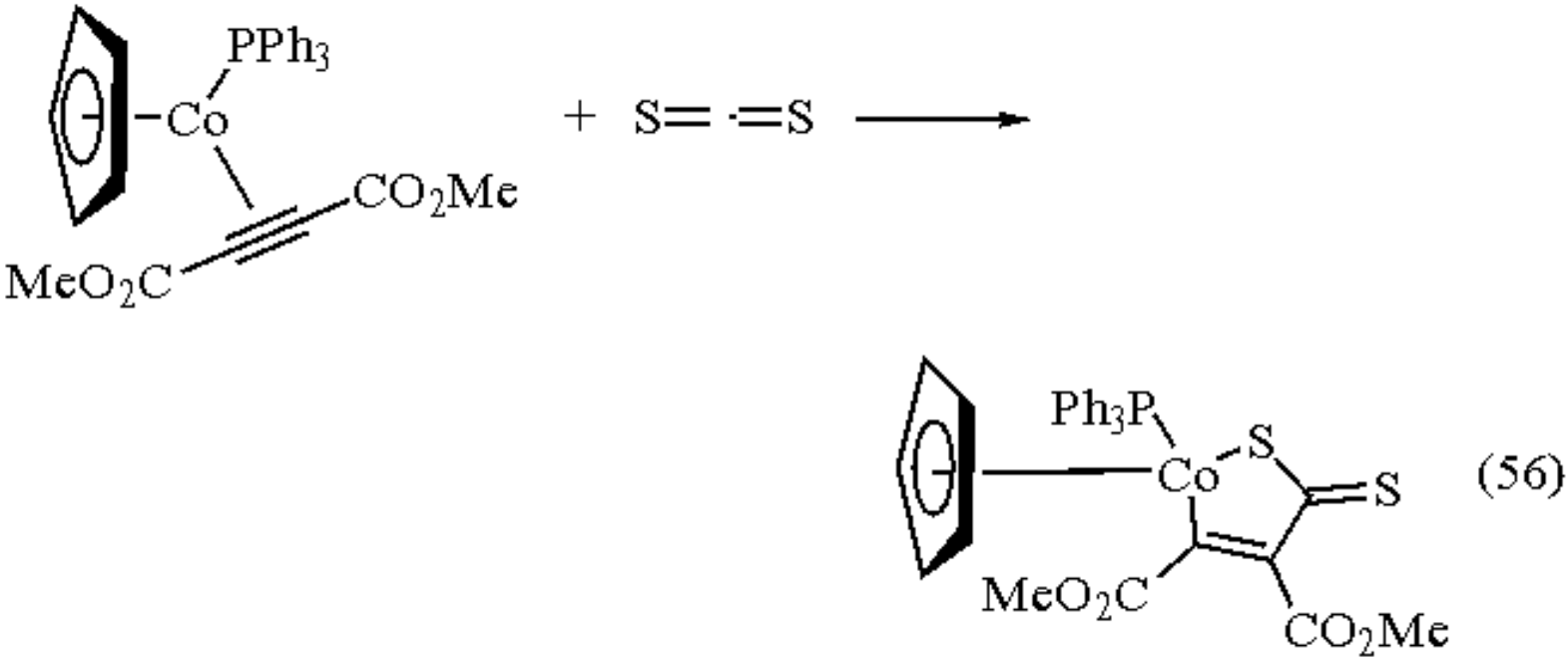

Dicarbonylcyclopentadienylcobalt is the source (via reaction with 3,4-dichlorocyclobutene or with photopyrone) of the cyclobutadiene complex $(C_5H_5)Co(C_4H_4)$ whose substitution reactions provide potential routes to many cyclobutadiene derivatives; however, it is not known to have any advantages in this respect over the more commonly used ***Tricarbonyl(cyclobutadiene)iron***.[26]

Dicarbonylcyclopentadienylcobalt is reduced by ***Sodium*** metal to the salt of a dinuclear radical anion (eq 57).[52] Alkyl halides convert this anion to dialkyl complexes (eq 58) which react with carbon monoxide, yielding ketones and regenerating $CpCo(CO)_2$ (eq 59).[53] Use of dihalides in this sequence leads to cyclic ketones; thus the complex obtained from 1,3-diiodopropane affords cyclobutanone (eq 60), but the same intermediate can be used to generate cyclopropane on treatment with iodine (eq 60).[54] In the case of the product from dibromo-*o*-xylene, $C_6H_4(CH_2Br)_2$, the initial complex disproportionates at 22 °C and the product is carbonylated (eq 61), whereas direct carbonylation of the intermediate leads to dimeric hydrocarbon products (eq 62).[55]

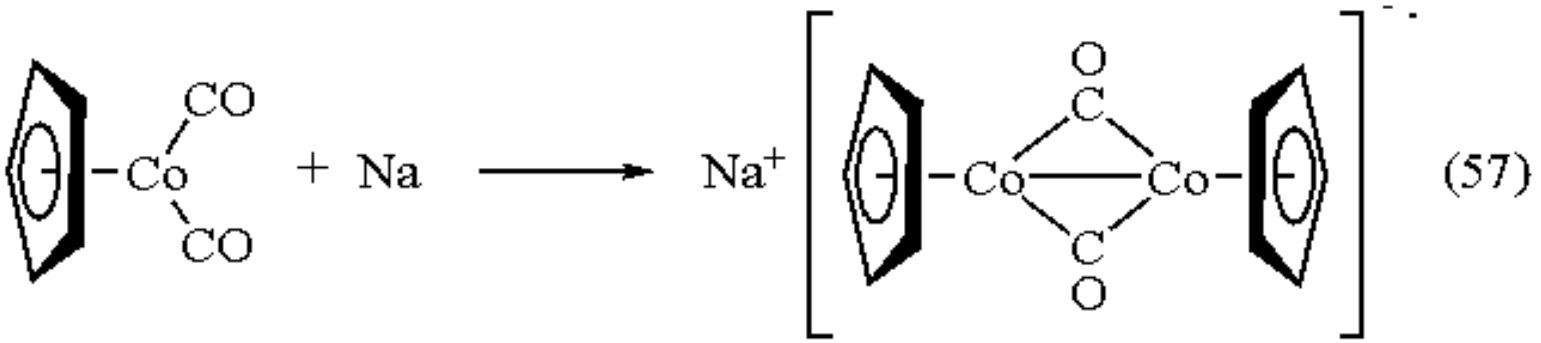

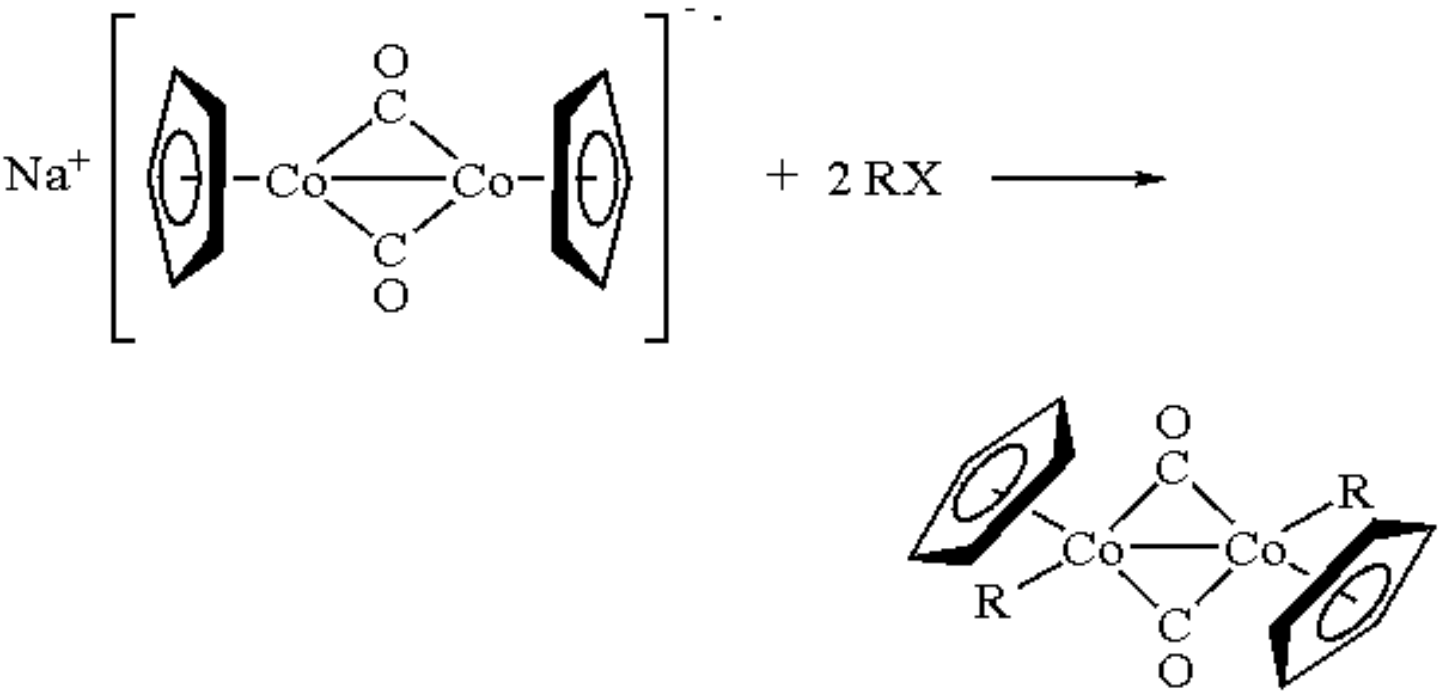
Na+
Co
Co
O
C
C
O
+ 2 RX
R
R

(58)

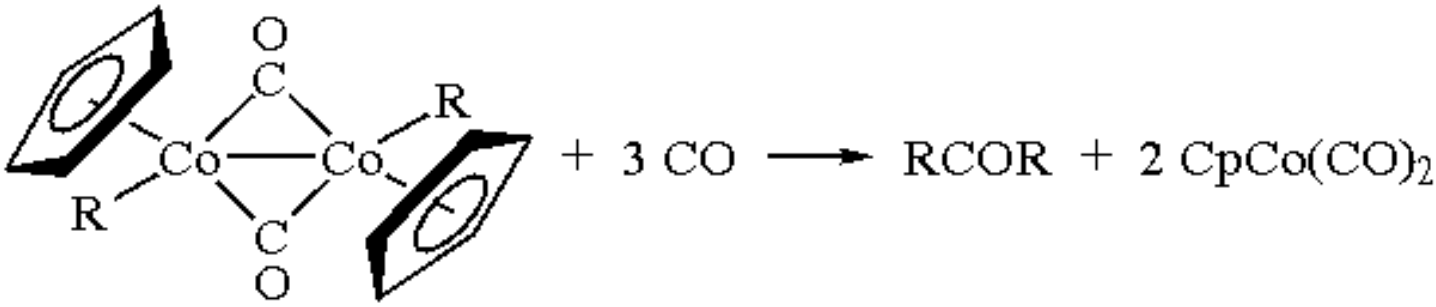
Co
Co
O
C
C
O
R
R
+ 3 CO
RCOR + 2 CpCo(CO)2

(59)

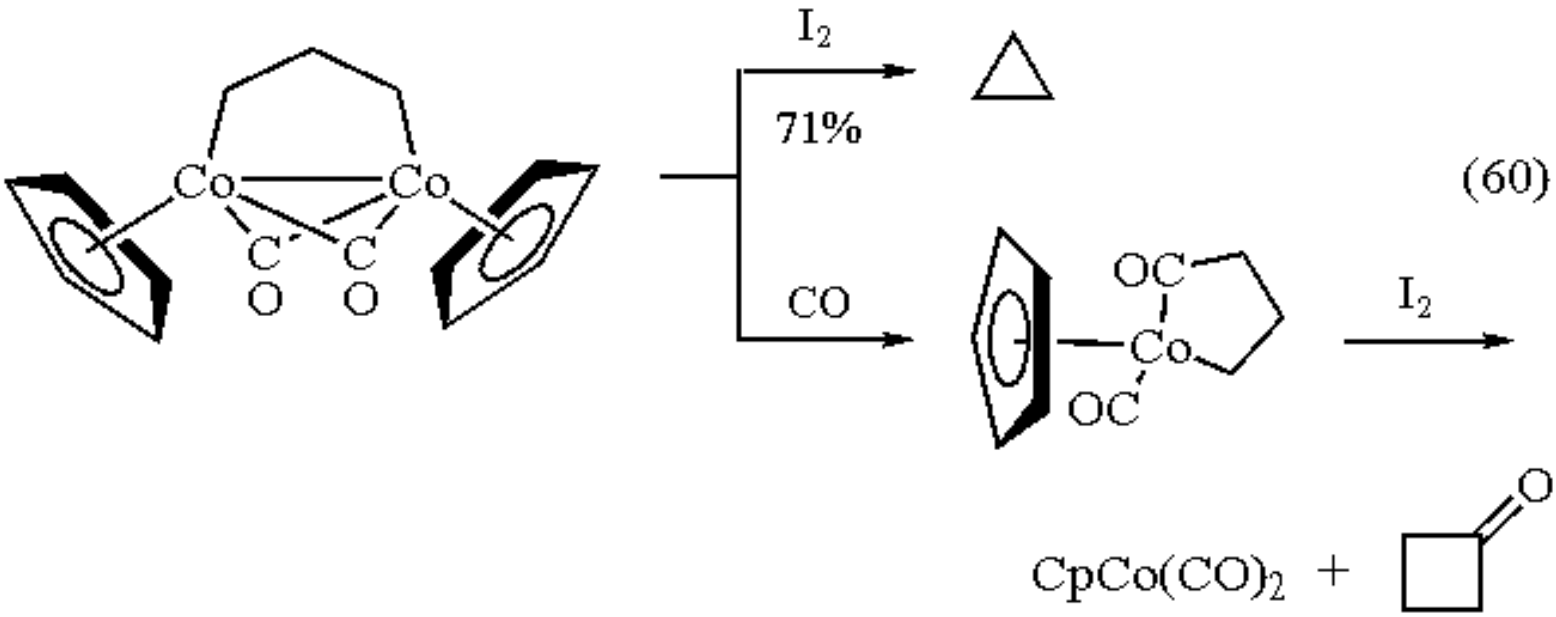
Co
Co
C
C
O
O
I2
71%
CO
OC
Co
OC
I2
CpCo(CO)2 +
O

(60)

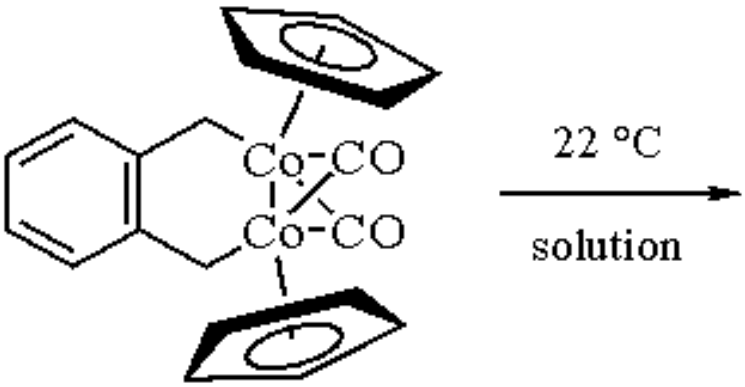

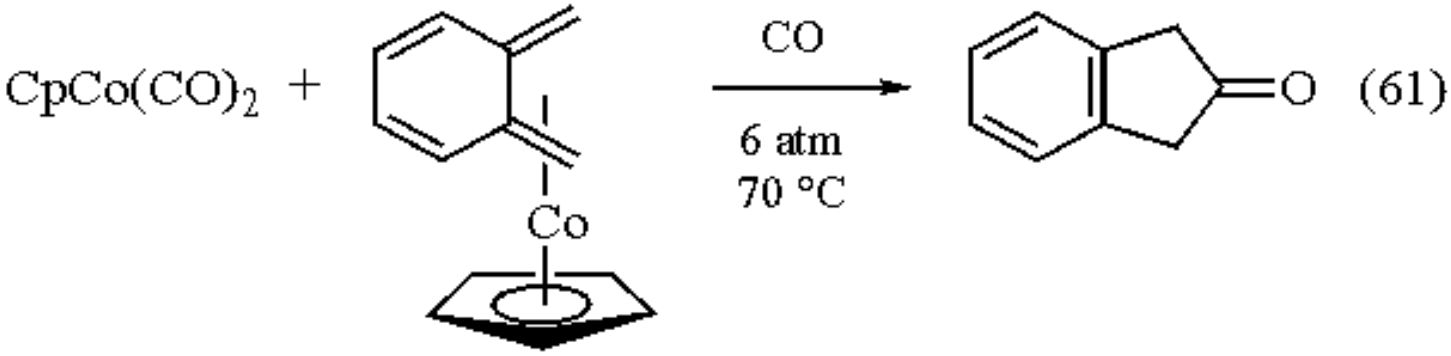

(61)

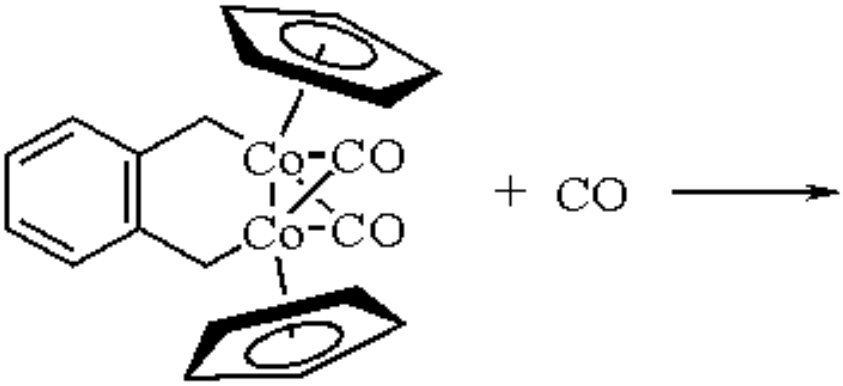

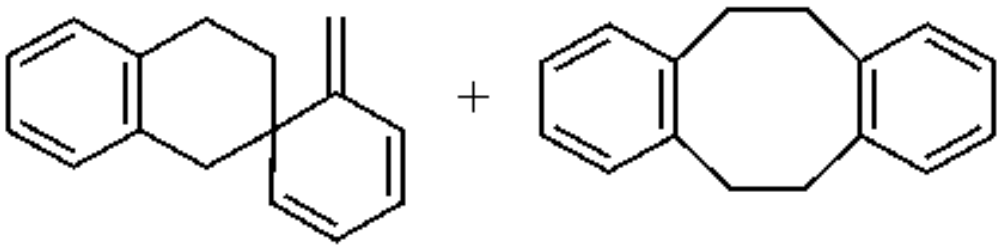

(62)

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Dicarbonyl(cyclopentadienyl)[(dimethylsulfonium)methyl]iron Tetrafluoroborate[1]

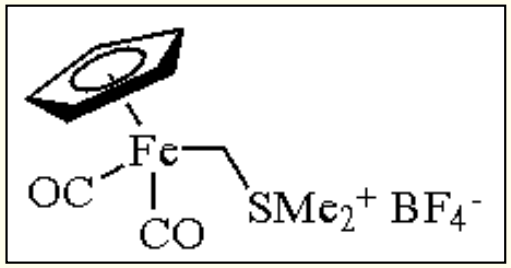

[72120-26-4] · $C_{10}H_{13}BF_4FeO_2S$ · Dicarbonyl(cyclopentadienyl)[(dimethylsulfonium)methyl]iron Tetrafluoroborate · (MW 339.93)

(stable precursor of a cationic carbene, or methylene, complex of iron; reacts directly with alkenes to give cyclopropanes[2])

Physical Data: mp 129-130 °C; *d* 1.57 g cm^{-3}.

Solubility: insol or slightly sol most solvents at rt; sol very polar solvents such as nitromethane at rt; sol other polar solvents (e.g. dioxane) at reflux.

Form Supplied in: yellow-orange powder or crystals.

Analysis of Reagent Purity: ^1H NMR.

Preparative Methods: the preparation of this reagent has gone through several revisions and improvements since its introduction in 1979. The most recently improved preparations[3] are satisfactory for large-scale applications and have been adapted for commercial use. In a one-pot operation, the stable, crystalline, dinuclear complex $[Cp(CO)_2Fe]_2$ is reductively cleaved with sodium dispersion to generate a THF solution of the highly nucleophilic sodium ferrate, $Na[Cp(CO)_2Fe]$. This species is immediately alkylated with chloromethyl methyl sulfide, and the resulting iron alkyl, $Cp(CO)_2FeCH_2SMe$, is subjected to *S*-alkylation with methyl iodide. Finally, the resulting sulfonium salt, initially produced as an iodide, is subjected to in situ anion exchange and simultaneous crystallization by treatment with hot aqueous $NaBF_4$, followed by cooling to give the reagent as a yellow-orange, or amber-colored, crystalline solid (eq 1) which has been characterized spectroscopically and by single-crystal X-ray diffraction.[4] The anion exchange is performed in order to assure that a nonnucleophilic counterion is present during the subsequent cyclopropanation reactions; a nucleophilic anion such as iodide may apparently intercept reactive intermediates on the pathway leading to the desired cyclopropane products. A remarkable property of the reagent is its unusually high stability compared to most other organometallic reagents. This point is especially clear from the fact that it can be recrystallized from hot water exposed to the air.

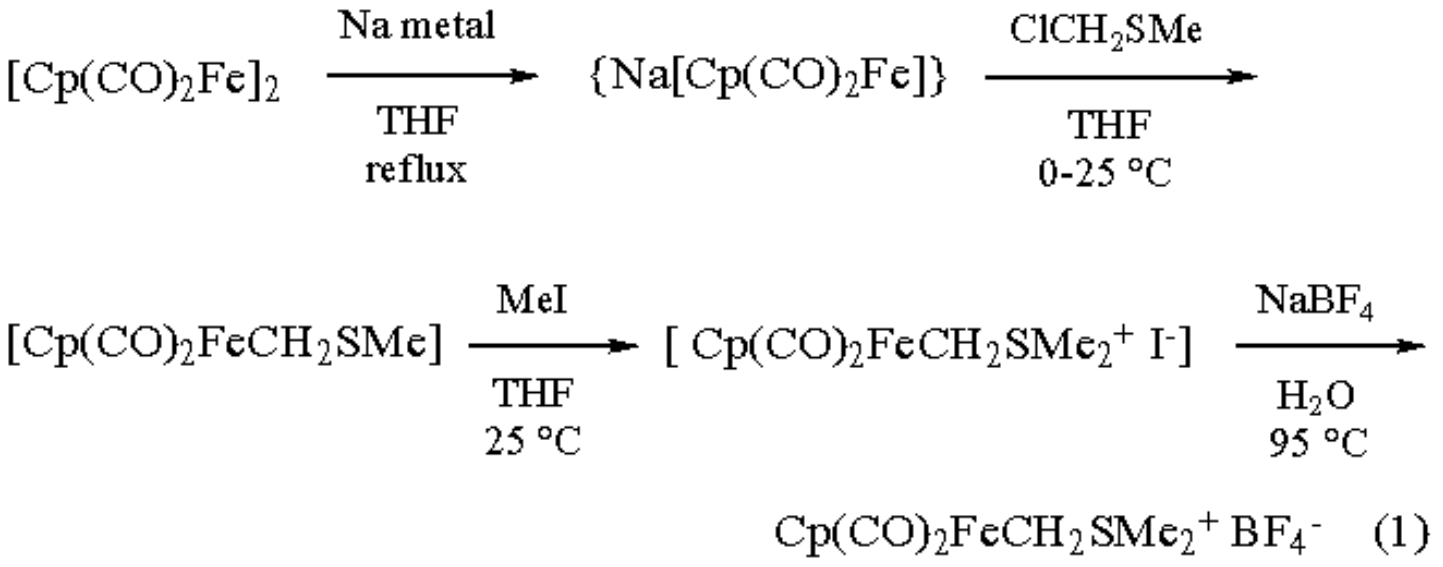

Purification: recrystallization from nitromethane, acetone, or other polar solvents.

Handling, Storage, and Precautions: stable indefinitely as a solid, even when exposed to air; slowly decomposes in solution if exposed to air for long periods of time (although reactions with alkenes can be done in the presence of air and even moisture); decomposes upon heating to release dimethyl sulfide (stench). Use in a fume hood.

Alkene Cyclopropanation.

Once this reagent has been prepared (or purchased commercially) it can be used directly in reactions with a wide range of alkenes without the need for using any further activation agents in order to obtain cyclopropanes (eq 2). An iron carbene complex is apparently generated as a reactive intermediate upon dissociation of dimethyl sulfide which ultimately recombines with the iron moiety to give the principal byproduct of the reaction.

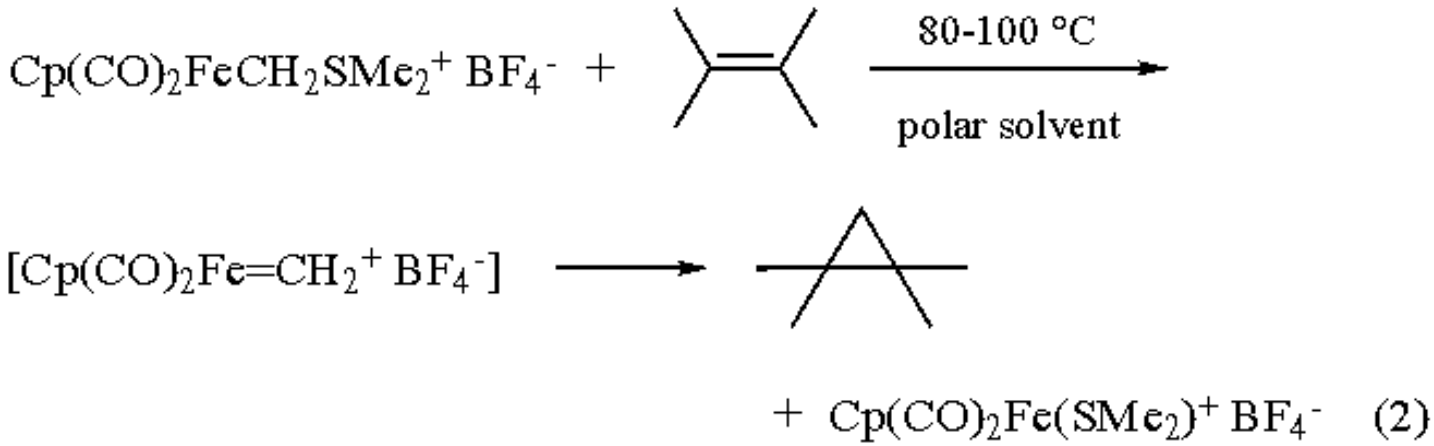

The procedure is very simple; the reagent and the alkene are mixed with a polar solvent and then heated in the temperature range of typically 80-100 °C for a few hours. Among the solvents that have been used successfully are 1,4-dioxane, DMF, ethanol, and nitromethane. The last of these, nitromethane, typically and reproducibly gives the highest yields of cyclopropanes. Excess reagent is commonly used to assure complete conversion of alkene to cyclopropane; 2 mol equiv is usually sufficient, but in some cases of less reactive alkene substrates the use of 3 mol equiv is necessary for obtaining optimum yields of cyclopropanes. The products are isolated very easily by adding pentane or another suitable nonpolar solvent to the cooled reaction mixture to precipitate the organometallic byproducts. Filtration of the mixture and use of routine distillation or chromatographic purification techniques then provide the cyclopropanes.

The reaction occurs most efficiently with mono- and disubstituted alkenes. More highly substituted alkenes generally react too slowly and exhibit very poor conversion to cyclopropanes. Some illustrative examples of efficient cyclopropanation are gathered in Table 1. Entries 1[2] and 2[2] are representative of relatively simple, nonfunctionalized alkenes. Entries 3[5] and 4[6] indicate both compatibility with other simple functional groups (ethers, sulfides, and acetals have also been used[2]) and the typical selectivity of an electrophilic reagent for more electron-rich alkenes in the presence of electron-deficient double bonds.

Table 1 Cyclopropanation of Alkenes with $Cp(CO)_2FeCH_2SMe_2^+$ BF_4^-

Entry	Alkene	Product	Yield (%)
1	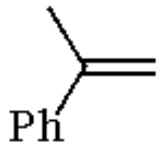	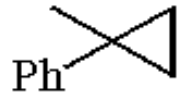	83
2	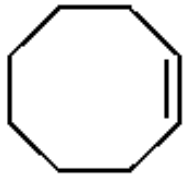	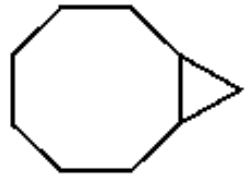	88
3	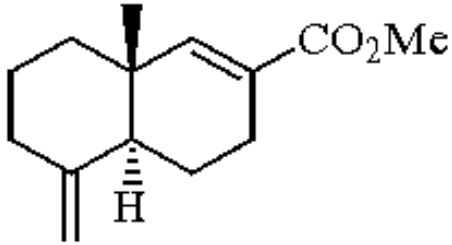	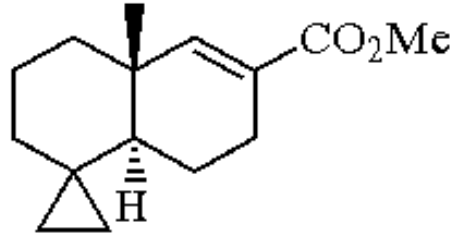	86
4	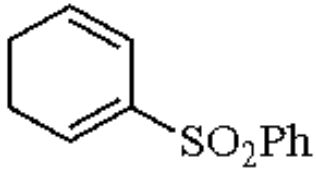	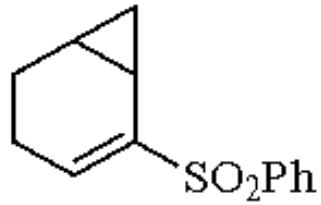	68

Alternative Reagents.

The classical method for the addition of a simple methylene group to an alkene is the Simmons-Smith reaction.[7] Indeed, it is still probably the most highly used

method for effecting this transformation. It is compatible with a wide range of functional groups, and it appears to be less sensitive to the degree of double bond substitution than the present iron reagent. On the other hand, the Simmons-Smith reagent appears to show reactivity towards both electron-deficient and electron-rich alkenes in some cases; the selectivity is less pronounced than in the case of the iron reagent. More specifically, the conversions shown in entries 3 and 4 of Table 1 were also attempted with the Simmons-Smith reagent, but the iron reagent gave superior results.[5,6] A minor disadvantage of the Simmons-Smith reaction is that the active reagent must be prepared freshly before use from ***Diiodomethane*** and ***Zinc/Copper Couple*** or related combinations of sometimes air-sensitive reagents,[8] whereas the iron reagent can be stored as a highly stable solid for indefinite periods of time before use and then be used directly with no further activation being necessary. ***Diazomethane*** may also be used as an alternative reagent,[1c] but the hazards and difficulties of preparing and handling this reagent are well known.

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1. (a) Brookhart, M.; Studabaker, W. B. *CRV* **1987**, *87*, 411. (b) Helquist, P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, 1991; Vol. 2, pp 143-194. (c) Helquist, P. *COS* **1991**, *4*, 951.
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8. Maruoka, K.; Fukutani, Y.; Yamamoto, H. *JOC* **1985**, *50*, 4412.

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Dicarbonyl(cyclopentadienyl)(isobutene)iron Tetrafluoroborate

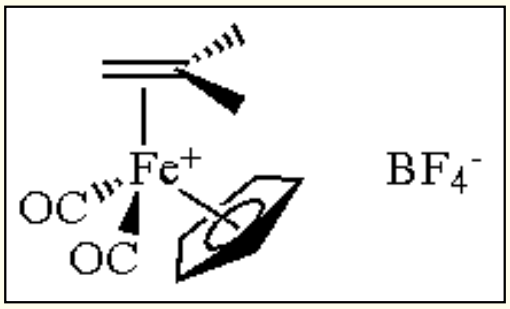

[41707-16-8] · $C_{11}H_{13}BF_4FeO_2$ · Dicarbonyl(cyclopentadienyl)(isobutene)iron Tetrafluoroborate · (MW 319.87)

(exchange reagent for synthesis of Fp-alkene$^+$ and Fp-alkyne$^+$ complexes; Fp$^+$ protecting group for alkenes; cycloadditions of alkenes and alkynes)

Physical Data: yellow-orange crystalline solid.

Solubility: sol CH_2Cl_2, THF; insol Et_2O, benzene, hexane; decomposes at varying rates in DMSO, $MeNO_2$, MeCN, acetone, and other coordinating solvents.

Analysis of Reagent Purity: ^{1}H NMR (CD_3CN): δ 5.52 (Cp), 3.81 (=CH_2), 1.84 (CH_3). ^{13}C NMR (CD_3CN): δ 209 (CO), 118 (=*C*Me_2), 87 (Cp), 51 (=CH_2), 26 (Me).[2] NMR shifts are highly solvent dependent.

Preparative Method: by reaction of NaFp (Fp = $CpFe(CO)_2$) with methallyl chloride followed by protonation of the resulting alkyl complex with HBF_4 (eq 1).[1]

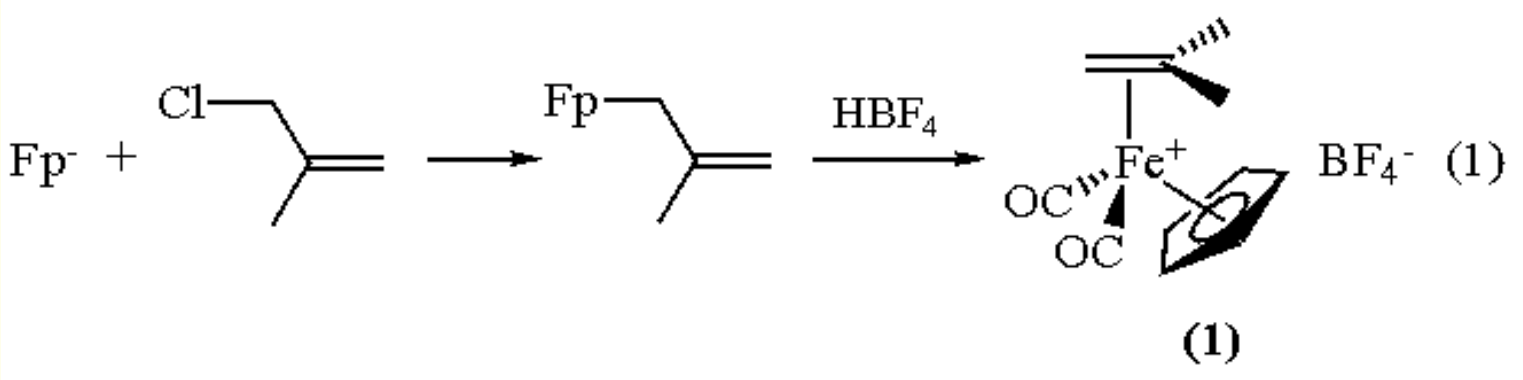

Handling, Storage, and Precautions: stable indefinitely under Ar or N_2 at 0 °C.

Alkene Exchange.[3]

Isobutene-Fp^+ BF_4^- is a convenient reagent for the synthesis of Fp-alkene$^+$ complexes. Exchange reactions occur readily in 1,2-dichloroethane (65-70 °C) or CH_2Cl_2 (at reflux) to form π-complexes with a wide variety of alkenes,[4] dienes,[5] allenes,[6] and alkynes,[7] and to form σ-complexes with heteroatomic donors (eq 2).[8]

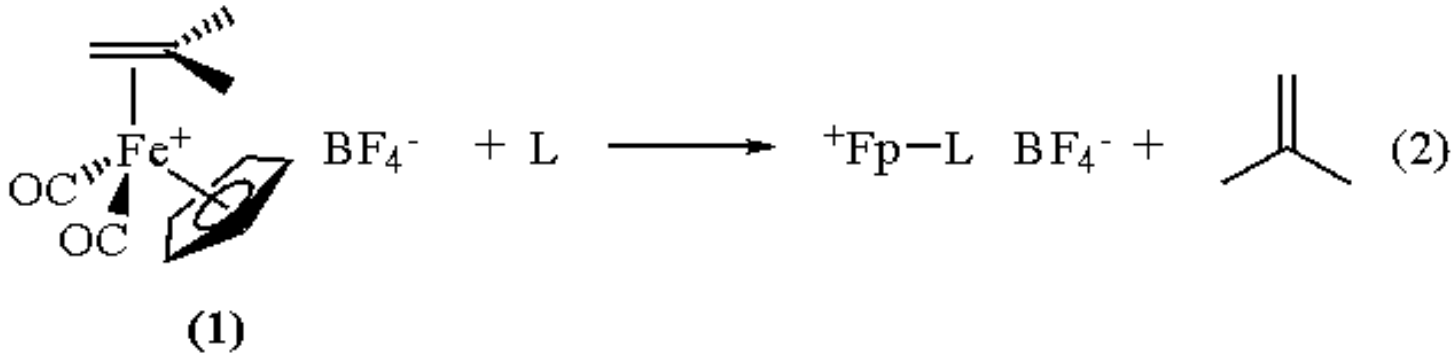

Protecting Group for Alkenes.

Isobutene-$FpBF_4$ has also been used successfully to protect alkenes from hydrogenation[3] and halogenation (eq 3).[9]

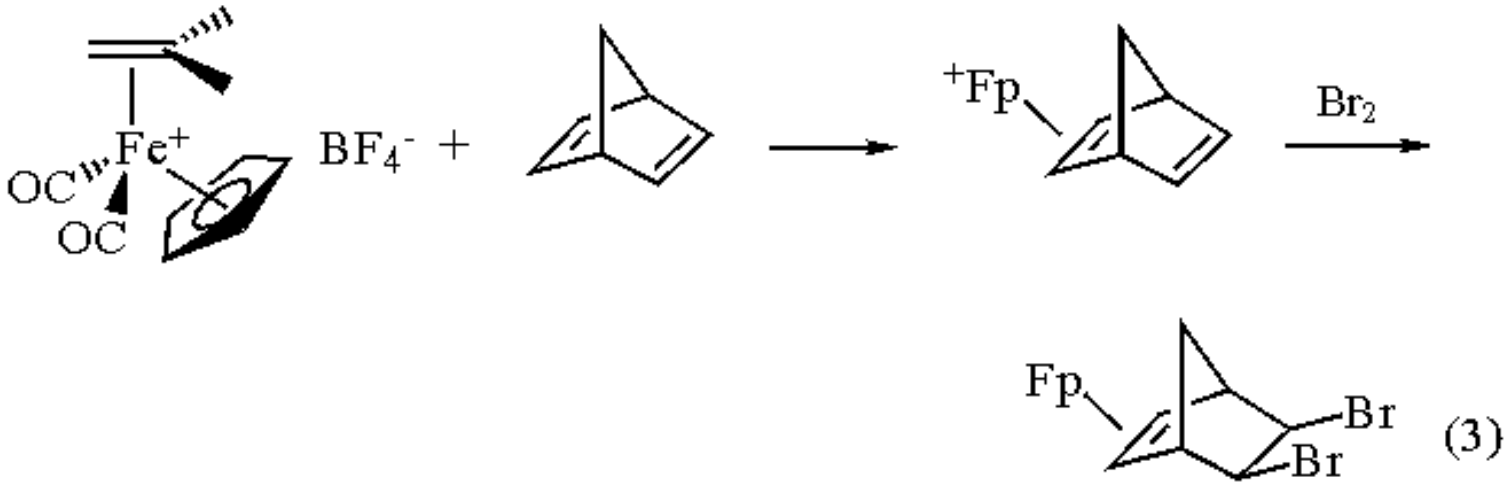

Activation of Alkynes and Allenes; Ring Formation.[10]

Reaction of isobutene-$FpBF_4$ with homopropargylic alcohols or hydroxyallenes gives substituted dihydrofurans, as their Fp complexes (eq 4).

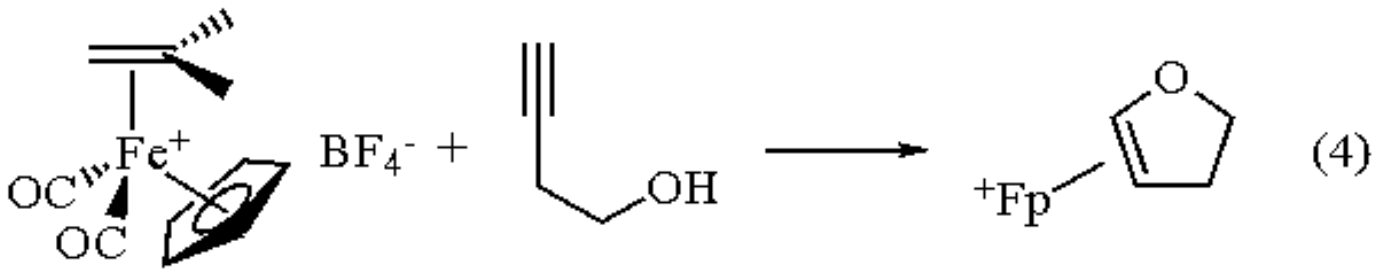

Isobutene-$FpBF_4$ has also been reported to catalyze the cycloaddition of alkynic esters to alkenes to give cyclobutenes and lactones (eq 5).[11] The complex Fp-THF^+ BF_4^- has been used in a similar fashion.[12]

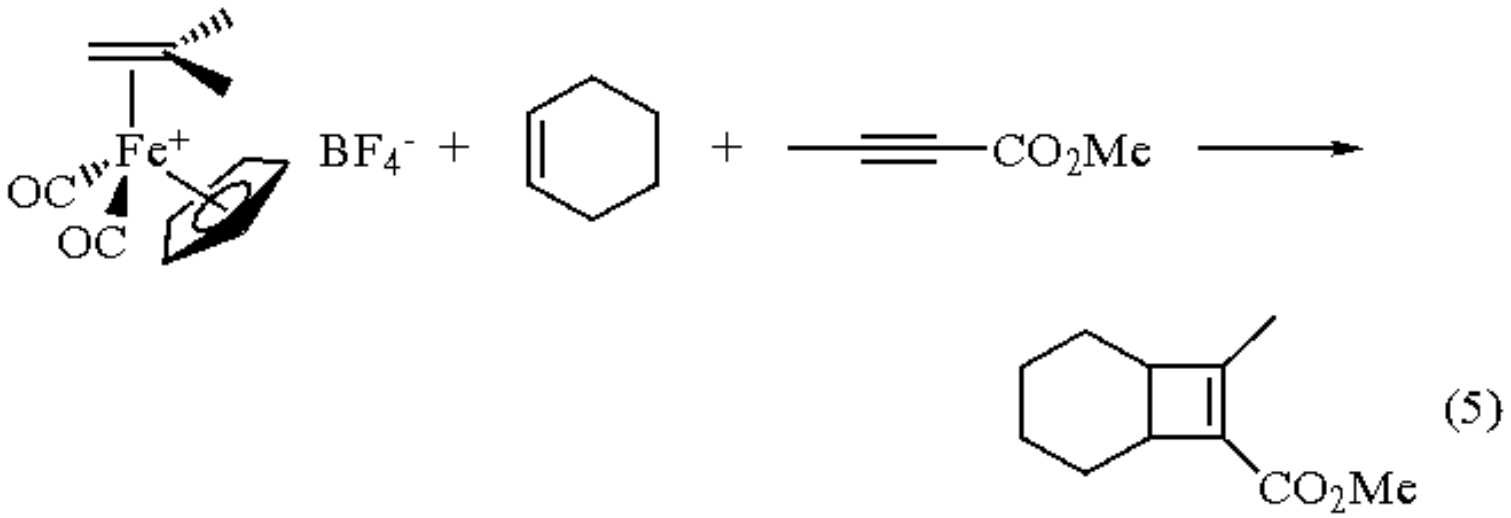

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1. (a) Giering, W. P.; Rosenblum, M. *JOM* **1970**, *25*, C71. (b) Rosenblum, M.; Giering, W. P.; Samuels, S-B. *Inorg. Synth.* **1990**, *28*, 207.
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Mark M. Turnbull

Dicarbonyl(cyclopentadienyl)(1-phenylthioethyl)iron[1]

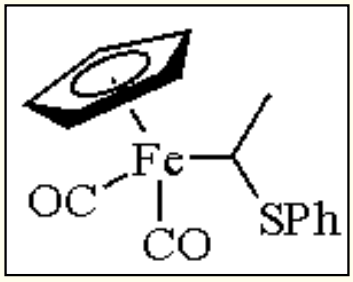

[77418-50-9] · $C_{15}H_{14}FeO_2S$ · Dicarbonyl(cyclopentadienyl)(1-phenylthioethyl)iron · (MW 314.18)

(stable precursor of a cationic methylcarbene, or ethylidene, complex of iron; for conversion of alkenes into methyl-substituted cyclopropanes[2])

Physical Data: mp 59 °C.

Solubility: sol most common solvents; methylene chloride is the solvent of choice.

Form Supplied in: yellow crystals.

Analysis of Reagent Purity: ^{1}H and ^{13}C NMR.

Preparative Methods: the stable, crystalline, dinuclear complex $[Cp(CO)_2Fe]_2$ is reductively cleaved with sodium amalgam to generate a THF solution of the highly nucleophilic sodium ferrate, $Na[Cp(CO)_2Fe]$. This species is immediately alkylated with 1-chloroethyl phenyl sulfide to give $Cp(CO)_2FeCH(Me)SPh$, which is purified chromatographically to give the reagent as a yellow, crystalline solid (eq 1) which has been characterized spectroscopically.[2] An alternative preparation employs the addition[4] of methyllithium or methylmagnesium bromide to the stable, readily available, phenylthiocarbene complex $Cp(CO)_2Fe{=}CHSPh^+\ PF_6^-$.[5]

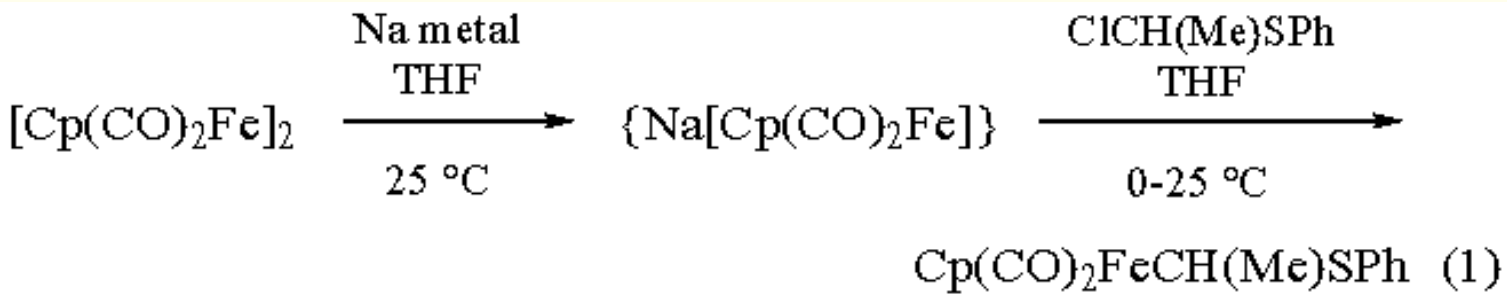

Purification: silica gel chromatography.[3]

Handling, Storage, and Precautions: stable indefinitely as a solid when protected from air; can be exposed to air for short periods of time (weighing, setting up reactions, etc.) without noticeable decomposition; decomposes in solution if exposed to air.

Alkene Cyclopropanation.

Alkenes undergo reaction with the iron reagent in the presence of reactive methylating agents such as ***Trimethyloxonium Tetrafluoroborate***[6] (*caution*: volatile, highly toxic alkylating agent) to give methyl-substituted cyclopropanes (eq 2). The reaction apparently occurs via *S*-methylation of the iron reagent to produce a sulfonium salt, which in turn undergoes dissociation of thioanisole to generate a carbene complex of iron as the reactive intermediate.

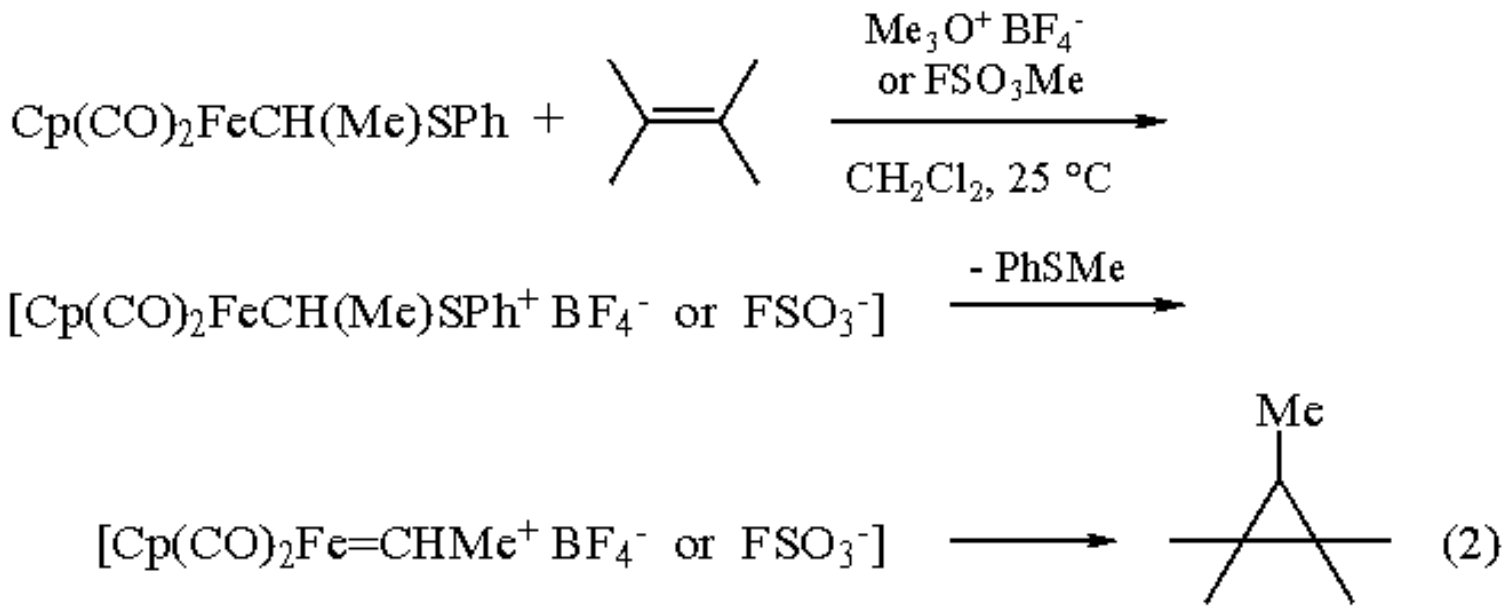

The iron reagent and the alkene are normally used in equimolar amounts, but a slight excess of the methylating agent (total of 1.25 mol equiv) is usually employed to permit optimum conversion to products. The cyclopropane products are isolated very easily by adding pentane or another suitable nonpolar solvent to the reaction mixture to precipitate the organometallic byproducts. Filtration of the mixture and use of routine distillation or chromatographic purification techniques then provides the cyclopropanes.

The product yields are typically modest, usually being in the range of 40-70%. The reaction occurs best with mono- and disubstituted alkenes. More highly substituted alkenes generally react too slowly and exhibit very poor conversion to cyclopropanes. Some illustrative examples are gathered in Table 1.[2] Two important stereochemical features of these reactions are: (1) the stereospecific retention of configuration of the initial alkene double bond upon conversion to the cyclopropanes (see entry 4); and (2) the notable preference for *endo* or *syn* stereoselectivity with respect to the orientation of the reagent-derived methyl group in the cyclopropanes (see entries 1, 2, and 4).

Table 1 Cyclopropanation of Alkenes with $Cp(CO)_2FeCH(Me)SPh$

Entry	Alkene	Product	Yield (%)
1	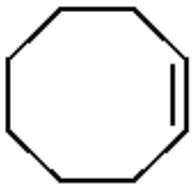	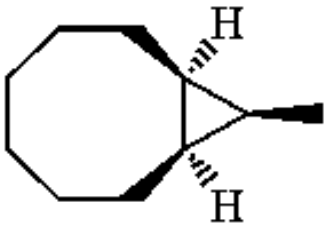	73
2	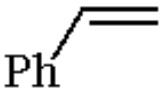		67
3	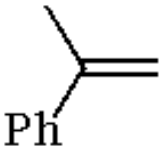	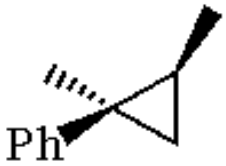 + *exo*-methyl (2.4:1)	65
4			43

Alternative Reagents.

The classical method for the cyclopropanation of alkenes is the Simmons-Smith reaction.[7] Indeed, this reaction is still probably the most highly used method for effecting this transformation. It is compatible with a wide range of functional groups, and it appears to be less sensitive to the degree of double bond substitution than the present iron reagent. However, the Simmons-Smith reaction has been used most commonly for transfer of the parent methylene group. Extensions to more highly substituted alkylidene groups have been limited in investigation. When ethylidene transfer has been studied,[8] poor *endo* stereoselectivity is seen compared to the present iron reagent. The same observation of lower stereoselectivity has been made for a more recent, aluminum-based modification of the Simmons-Smith reaction.[9] Diazoalkanes may also be used as alternative reagents,[1c] but the hazards and difficulties of preparing and handling these reagents are well-known. Much more closely related to the present reagent is the iron derivative, $Cp(CO)_2FeCH(Me)OMe$.[1a,10] Results of cyclopropanations using either of the iron reagents are quite comparable.

1. (a) Brookhart, M.; Studabaker, W. B. *CRV* **1987**, *87*, 411. (b) Helquist, P. In *Advances in Metal-Organic Chemistry*, Leibeskind, L. S., Ed.; JAI: London, 1991; Vol. 2, pp 143-194. (c) Helquist, P. *COS* **1991**, *4*, 951.
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Dichlorine Monoxide[1]

Cl_2O

[7791-21-1] · Cl_2O · Dichlorine Monoxide · (MW 86.91)

(powerful chlorinating reagent; induces ene-type and aromatic ring/side chain chlorination)

Alternate Names: chlorine oxide; hypochlorite.

Physical Data: mp -116 °C; fp -120.6 °C; bp 2.0 °C; pale orange-yellow gas.

Solubility: sol carbon tetrachloride, water (contact with water forms hypochlorous acid), ether, benzene, CH_2Cl_2, ethyl acetate, dioxane.

Form Supplied in: usually prepared as needed, as a solution in CCl_4.[2]

Analysis of Reagent Purity: iodometric titration.[2,3]

Preparative Methods: gaseous dichlorine monoxide is prepared by passing ***Chlorine*** through a column containing dry yellow ***Mercury(II) Oxide***.[2,4] A carbon tetrachloride solution of dichlorine monoxide is obtained as follows:[2,5] into a solution of chlorine in carbon tetrachloride is added 3.36 g of dry yellow mercury(II) oxide per gram of chlorine (1.1 mol/mol of chlorine) at 25 °C. After being stirred for 45 min at this temperature, the solids are removed by filtration through a coarse sintered-glass funnel to give a solution of dichlorine monoxide in ca. 75% yield.

Handling, Storage, and Precautions: explosions of the gas may result from a spark, by heating, or by contact with rubber, cork, or other forms of organic matter. A carbon tetrachloride solution is easier to obtain and safer to handle. It can be stored for a long time at -78 °C, but decomposes at a moderate rate at rt. Strong oxidant. Use in a fume hood.

Chlorination of Alkanes and Alkenes.

Gas-phase chlorinations of alkanes such as methane and propane with dichlorine monoxide have been reported.[6] More conveniently, a carbon tetrachloride solution of the reagent can be used for chlorination of various saturated compounds, such as 1-chlorobutane, 1-chloropropane, and butyronitrile.[7] Each mole of dichlorine monoxide produces nearly 2 moles of chlorinated products and 1 mole of water. In the dark, a very long induction period is required, but this is significantly shortened by exposure to light or addition of ***Azobisisobutyronitrile*** (AIBN). A radical chain reaction mechanism has been proposed (eqs 1-7).

$$Cl_2O \longrightarrow Cl\cdot + ClO\cdot \quad (1)$$

$$ClO\cdot + RH \longrightarrow HOCl + R\cdot \quad (2)$$

$$R\cdot + Cl_2O \longrightarrow RCl + ClO\cdot \quad (3)$$

$$HOCl \longrightarrow Cl\cdot + \cdot OH \quad (4)$$

$$RH + Cl\cdot \longrightarrow R\cdot + HCl \quad (5)$$

$$HCl + HClO \longrightarrow H_2O + Cl_2 \quad (6)$$

$$R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot \quad (7)$$

The chlorination of alkenes with dichlorine monoxide usually gives a mixture of allylic chlorides, β-chloroalkanols, α-chloroalkanones, and other products.[1] For instance, the reaction of Cl_2O with a large excess of cyclohexene at -20 °C in the dark proceeds instantaneously to give a mixture of the addition and substitution products (eq 8).[8]

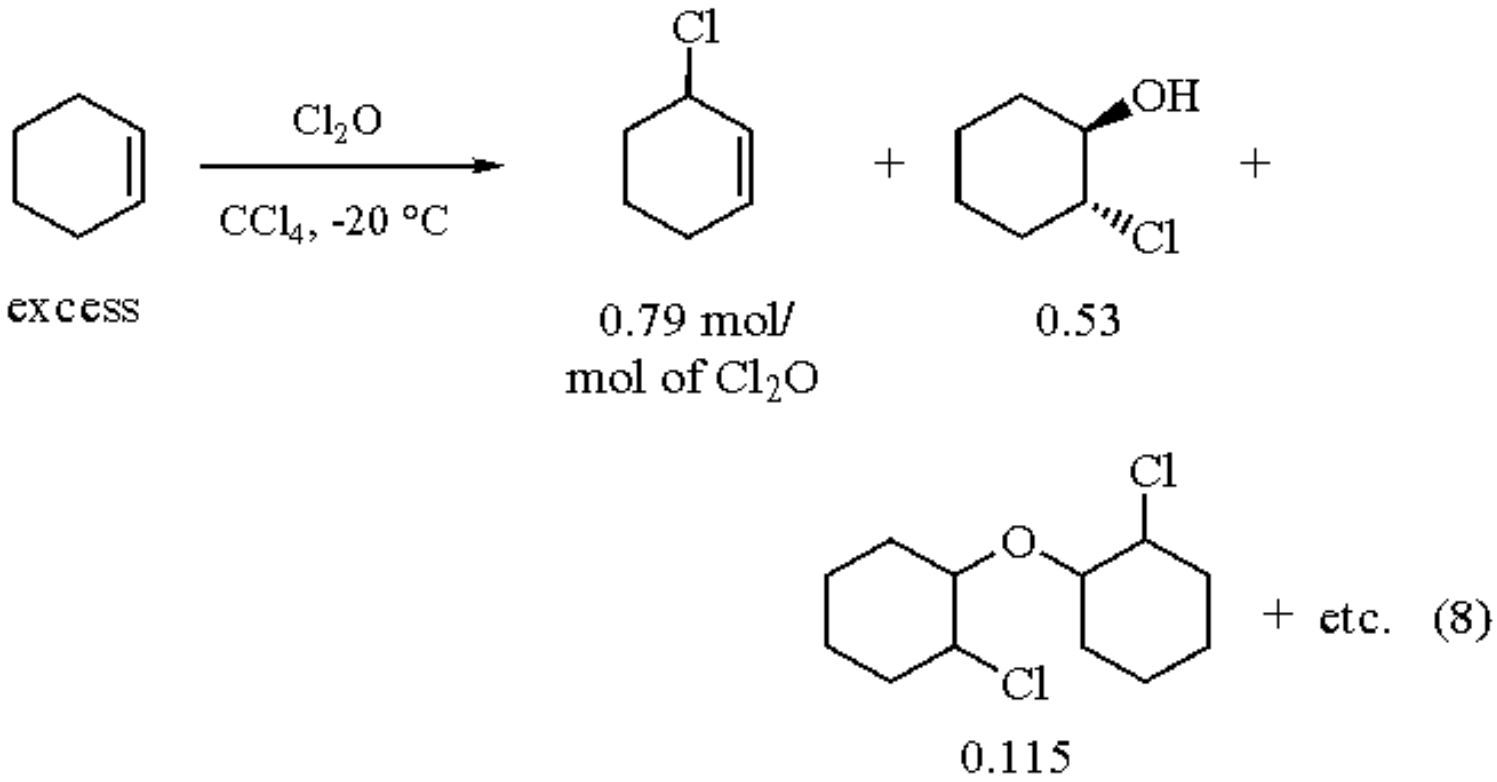

Ene-Type Chlorination.[9]

Ene-type chlorination of alkenes with dichlorine monoxide in various organic solvents, such as methylene chloride, diethyl

ether, benzene, dioxane, and ethyl acetate, proceeds smoothly at ambient conditions, affording the corresponding allylic chlorides in good to excellent yields. Each reaction is completed by use of 0.5 mol equiv of dichlorine monoxide, indicating that both chlorine atoms are utilized in the chlorination. Double ene-type chlorination is also performed by use of 1 mol equiv of the reagent (eq 9).

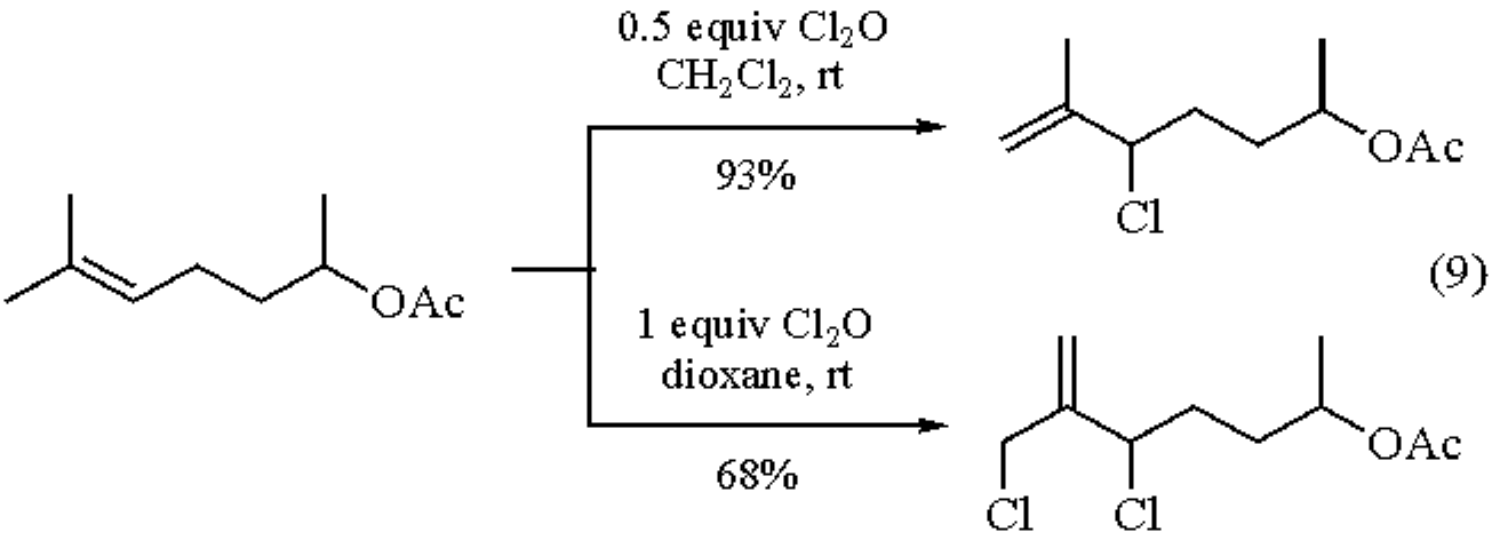

(9)

The ene-type chlorination proceeds in a highly regio- and chemoselective manner; indeed, ene-type chlorination of the terminal double bond of azetidinone derivatives is achieved by treatment with dichlorine monoxide at rt for 10 min, affording the desired chlorinated products in 85-93% yields (eqs 10 and 11).

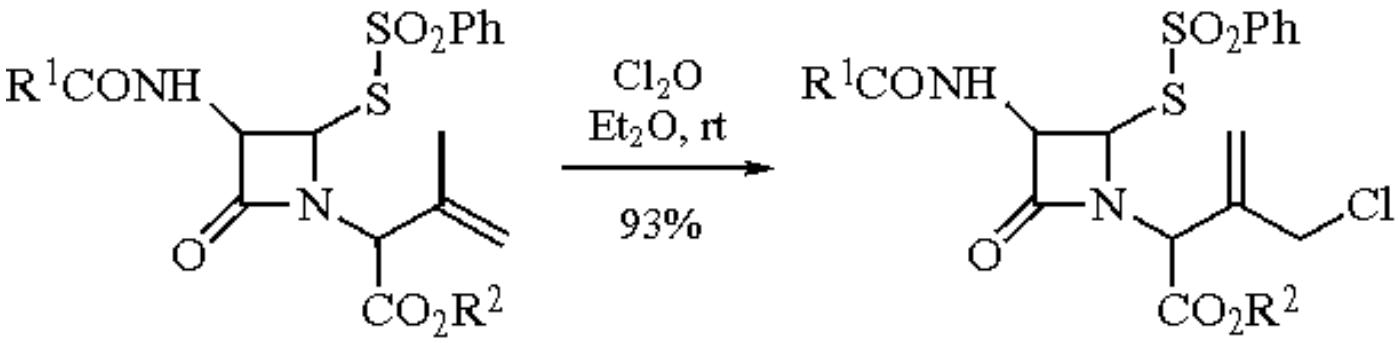

(10)

$R^1 = PhOCH_2$, $R^2 = CH_2Ph$

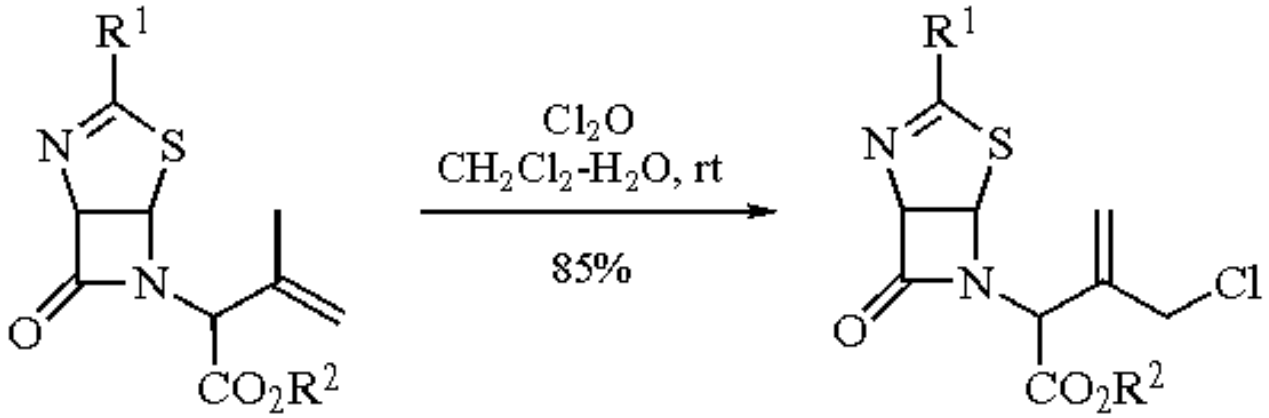

(11)

$R^1 = PhCO,\ R^2 = CH_2Ph$

Side Chain or Ring Chlorination of Aromatic Compounds.[10]

Dichlorine monoxide is a powerful and selective reagent for either side chain or ring chlorination of inactive aromatic substrates; it gives excellent yields under mild conditions where conventional reagents fail or require harsh conditions. For instance, side chain chlorination of inactive alkyl aromatic compounds, such as *p*-nitrotoluene, can be performed by treatment with dichlorine monoxide in carbon tetrachloride at 25 °C for 96 h, affording the corresponding tri- or dichlorinated compounds in high purity (see Table 1). At 75 °C, the reaction affords equivalent yields in about 3 h.

Table 1 Chlorination of Inactive Alkyl Aromatic Compounds with Cl_2O in CCl_4

Substrate	Product	Yield (%)
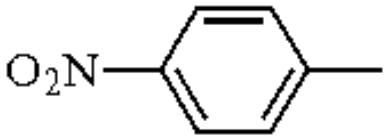		99[a]
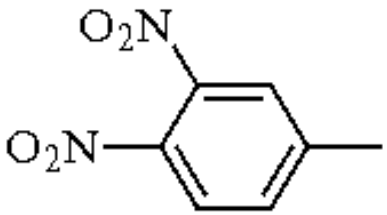	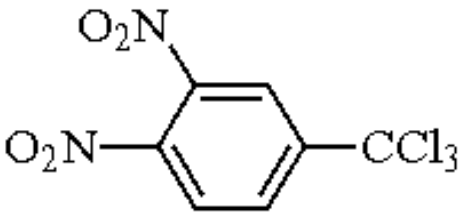	89[b]
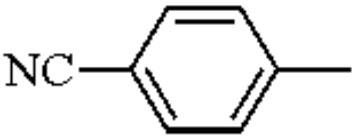	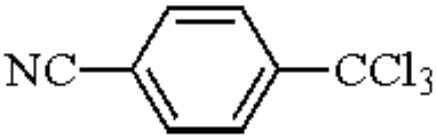	99[a]
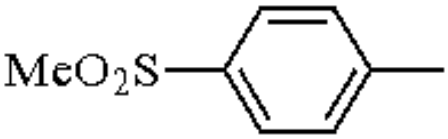	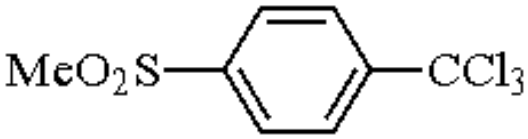	96[b]
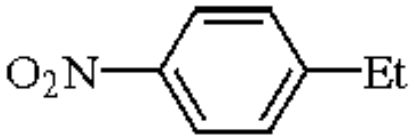	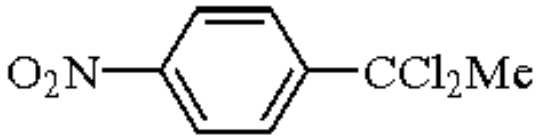	100[b]
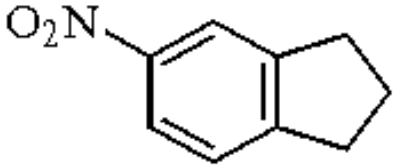	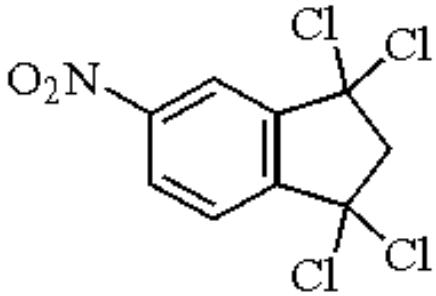	97[b]

[a] Reaction temperature 25 °C. [b] Reaction temperature 75 °C.

Exclusive ring chlorination of inactive aromatic compounds e.g. *p*-nitrotoluene, proceeds smoothly at 0-50 °C if a strong protic acid, e.g. H_2SO_4, is added to the Cl_2O reaction medium. Dichlorine monoxide is among the most reactive and

selective agents known for chlorination of inactive aromatic ring systems; the degree of chlorination is controlled by the quantity of dichlorine monoxide employed, yielding mono- and perchlorinated products, respectively (Table 2). The mechanistic aspects of the reaction have been studied based on isotope effects, linear free-energy relationships, and related kinetics.

Table 2 Chlorination of Inactive Aromatic Rings with Cl_2O/Acid at 20-40 °C

Substrate	Product	Acid	Yield (%)
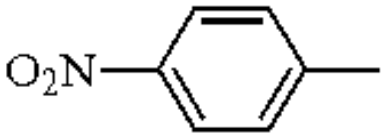	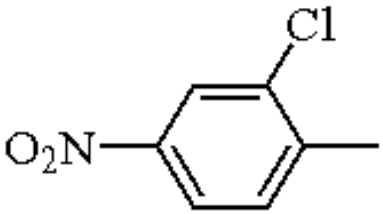	H_2SO_4	99[a]
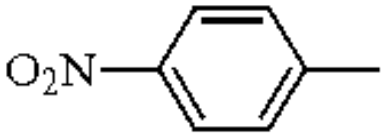	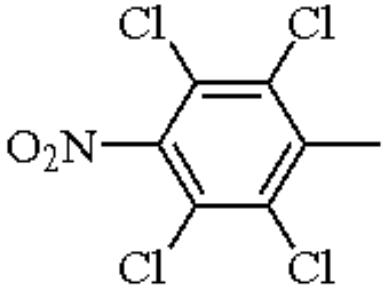	CF_3SO_3H	97[b]
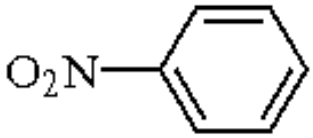	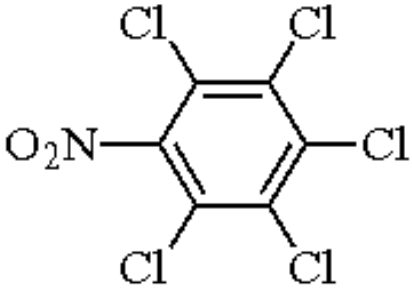	H_2SO_4	94[b]
	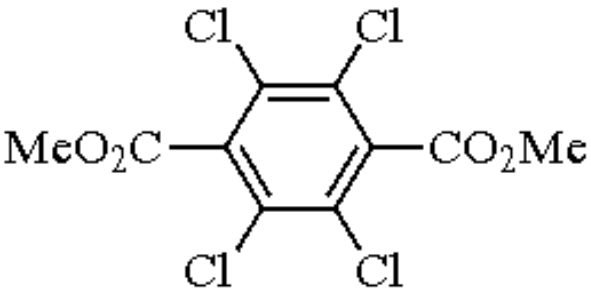	CF_3SO_3H	99[b]

Cl Cl

[a] 0.5 equiv of Cl_2O. [b] >2.5 equiv of Cl_2O.

Chlorinations of phenols, aryl ethers,[1] sulfamides,[11] lignin,[12] hydrazines,[13] cyanic acid,[14] and polymers[15] with dichlorine monoxide have been investigated. The reactions are conducted in carbon tetrachloride, yielding mono- and/or polychlorinated products.

Bleaching.[16]

Dichlorine monoxide has been found to be an effective reagent for the bleaching of wood pulp and textiles. This method promises not only to increase process efficiency, but also reduce stream pollution significantly.

Related Reagents.

t-Butyl Hypochlorite; ***Chloramine***; ***Chlorine***; ***Chlorine-Chlorosulfuric Acid***; ***Dimethyl Sulfide-Chlorine***; ***Chlorine-Pyridine***; ***N-Chlorosuccinimide***; ***Sulfuryl Chloride***.

---

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Sigeru Torii & Hideo Tanaka

Okayama University, Japan

1,3-Dichloroacetone[1]

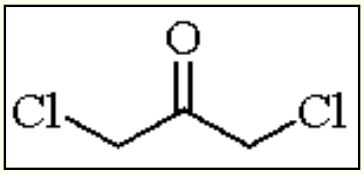

[534-07-6] · $C_3H_4Cl_2O$ · 1,3-Dichloroacetone · (MW 126.97)

(starting material for the synthesis of cyclopropanols[2] and cyclopropenones[3])

Alternate Name: 1,3-dichloro-2-propanone.

Physical Data: mp 39-41 °C; bp 173 °C; *d* 1.383 g cm^{-3}.

Solubility: sol organic solvents.

Form Supplied in: solid; commercially available.

Handling, Storage, and Precautions: highly corrosive and toxic. Use in a fume hood.

The reagent is useful as starting material for a simple one-pot synthesis of many 1-arylcyclopropanols (eq 1).[4,5] In this procedure the initially formed 1,3-dichloro-2-aryl isopropoxide is reduced to the 1-aryl cyclopropoxide by low-valent iron, generated in situ by the reaction of ***Ethylmagnesium Bromide*** with ***Iron(III) Chloride***.[6] The general method can be extended to the synthesis of 1-alkylcyclopropanols by using an excess of ***Lithium*** powder as the reducing agent in place of the EtMgBr/$FeCl_3$.[7] A somewhat related synthesis of 1-alkyl- or 1-arylcyclopropanols makes use of the reaction of ethyl 3-bromopropionate with 1 equiv of Grignard reagent in the presence of 2 equiv of ***Samarium(II) Iodide***.[8]

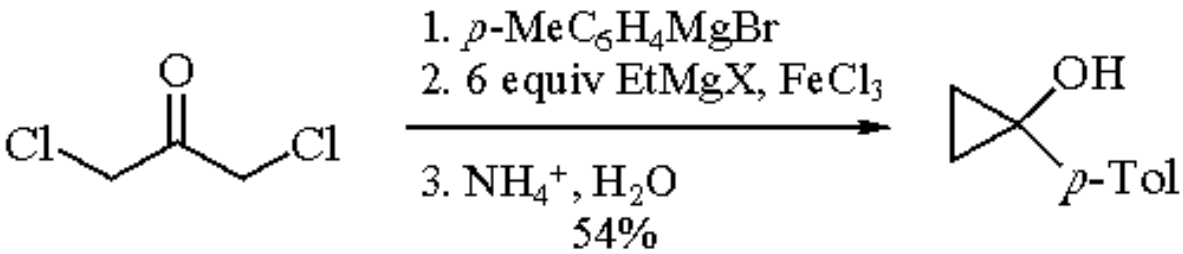

(1)

1,3-Dichloroacetone also serves as the starting reagent in a general synthesis of cyclopropenones and their acetals (eq 2).[3] The initially formed cyclopropenone acetal (**1**) can be alkylated a second time if desired, and then hydrolyzed to a dialkylcyclopropenone.

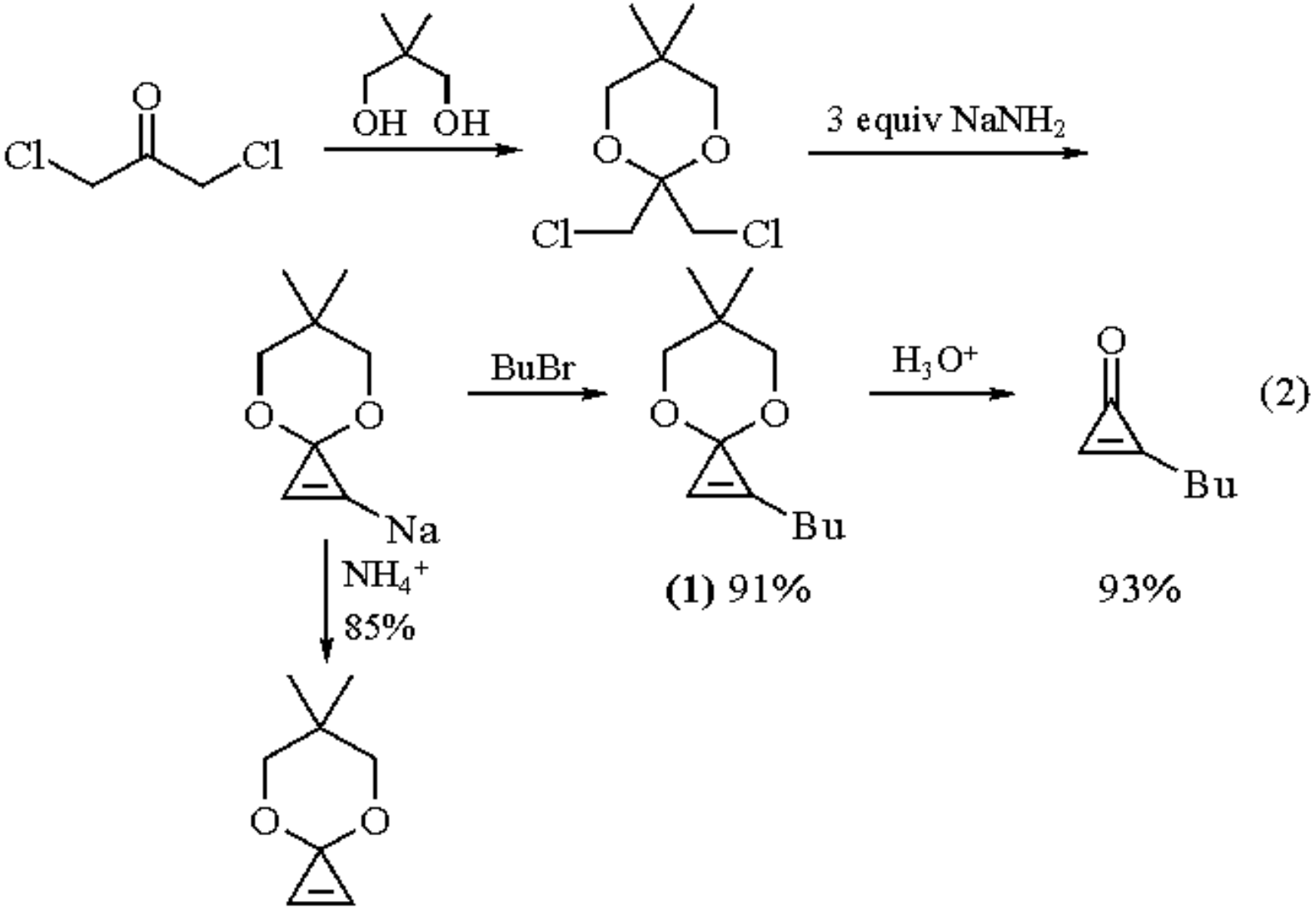

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1. No review of the chemistry of 1,3-dichloroacetone has been published. For a review of the chemistry of cyclopropanols, see: Gibson, D. H.; DePuy, C. H. *CRV* **1974**, *74*, 605. For a review of the chemistry of cyclopropenones, see: Potts, K. T.; Baum, J. S. *CRV* **1974**, *74*, 189.
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Charles H. DePuy

University of Colorado, Boulder, CO, USA

Dichloroacetonitrile

Cl_2CHCN

[3018-12-0] · C_2HCl_2N · Dichloroacetonitrile · (MW 109.94)

(used in synthesis of α-chloro- and α,α-dialkyl-substituted nitriles;[1] building block for synthesis of pyrimidines[2] and pyridines;[3] undergoes Darzens reaction with aldehydes and ketones[4])

Physical Data: bp 110-112 °C; *d* 1.369 g cm^{-3}.

Solubility: insol H_2O; sol hexane, benzene, EtOH, ether, acetone, CH_2Cl_2.

Form Supplied in: colorless liquid; commercially available.

Handling, Storage, and Precautions: lachrymator; avoid inhalation of vapors or skin contact; flammable (toxic fumes); possible mutagen. Store under N_2. Since Cl_2CHCN is a byproduct of drinking water disinfection with chlorine, its toxicity has been studied in detail.[5] Use in a fume hood.

Alkylation of dichloroacetonitrile with trialkylboranes (eq 1) (R = primary or secondary alkyl) affords α-chloro nitriles or α,α-dialkyl-substituted nitriles in good yield.[1] The use of the hindered phenoxide base (p*K* 11.7) is advantageous because it minimizes self-condensation of both starting nitrile and the product. Since nitriles are readily hydrolyzed to acids, this procedure represents an alternative to the classical malonic ester synthesis.[6]

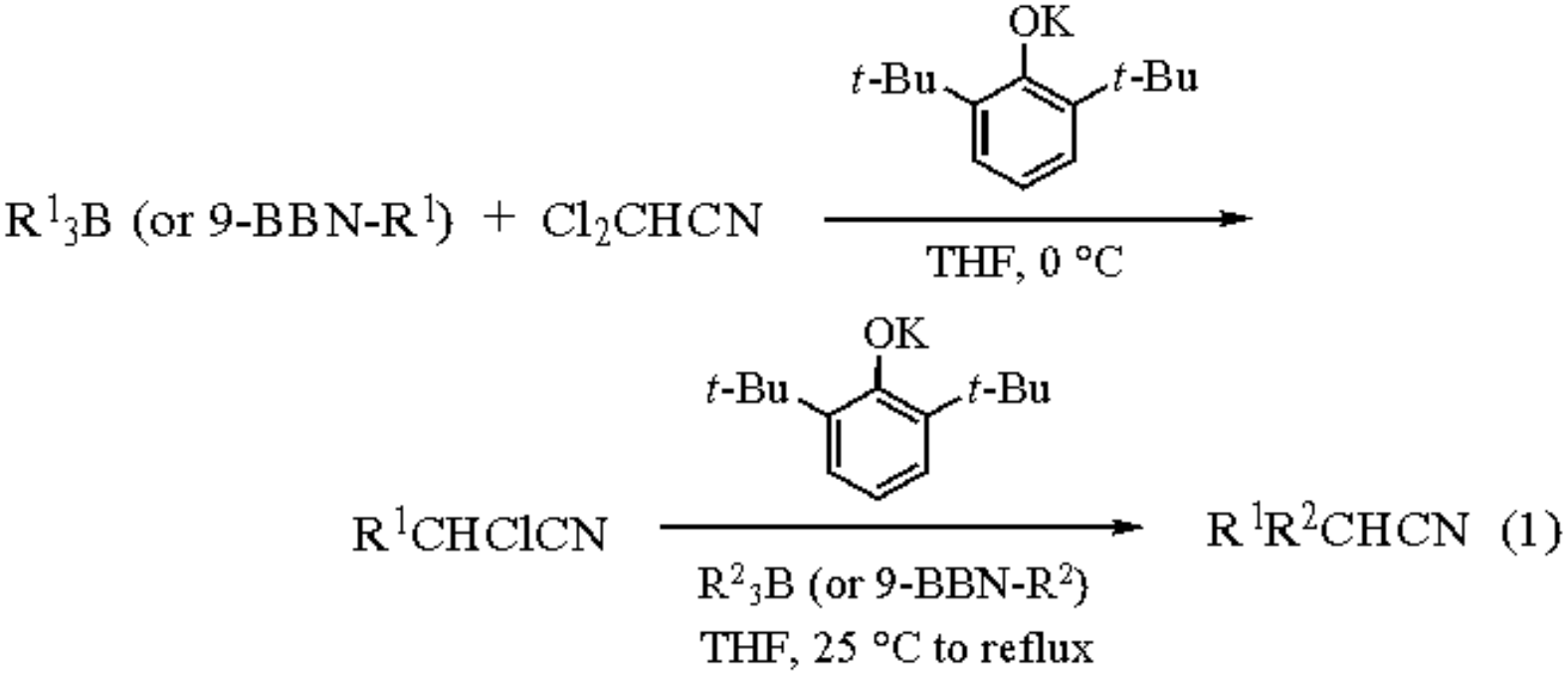

Treatment of 2-amino aromatic nitriles with Cl_2CHCN affords either 4-chloro- or 4-aminopyrimidines depending on the substrate (eq 2).[2] Halogenated pyridines are obtained via the copper-catalyzed addition of Cl_2CHCN to methacrolein (eq 3).[3] The first step of eq 3 represents a special case of the more general reaction in which copper salt-catalyzed addition of Cl_2CHCN to alkenes yields a variety of 2,4-dichlorobutyronitriles,[7] via an oxidation-reduction chain mechanism.

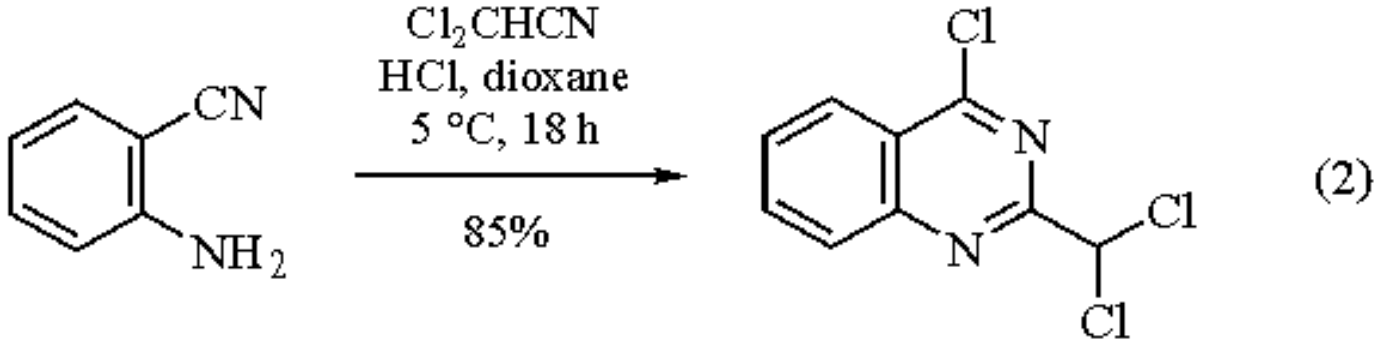

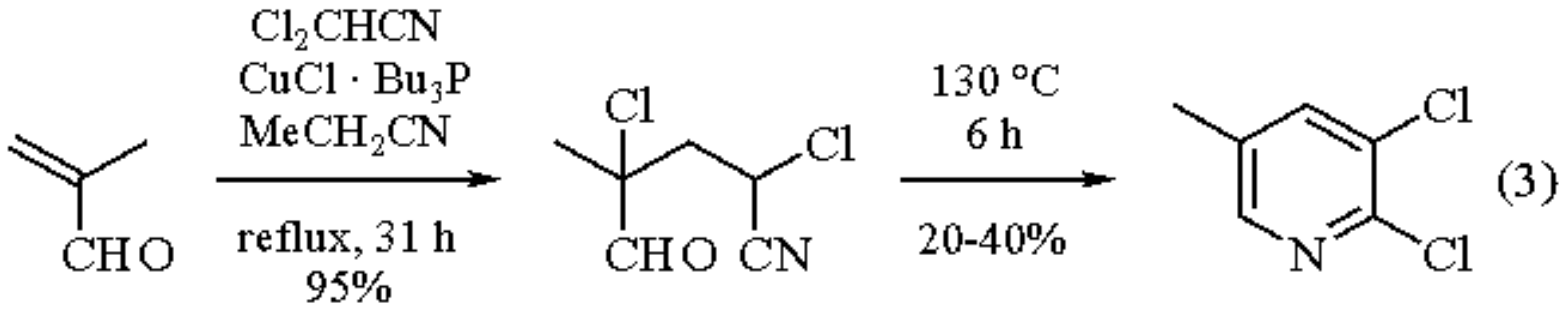

Aldehydes and ketones condense with Cl_2CHCN in the presence of alkoxide bases at -78 °C to afford isolable α,α-dichloro-β-hydroxy nitriles in good yield (eq 4).[4] At higher temperatures the chloroglycidimidates are obtained. Analogous reactions utilizing nonnucleophilic bases allow retention of the nitrile functionality.[4,8]

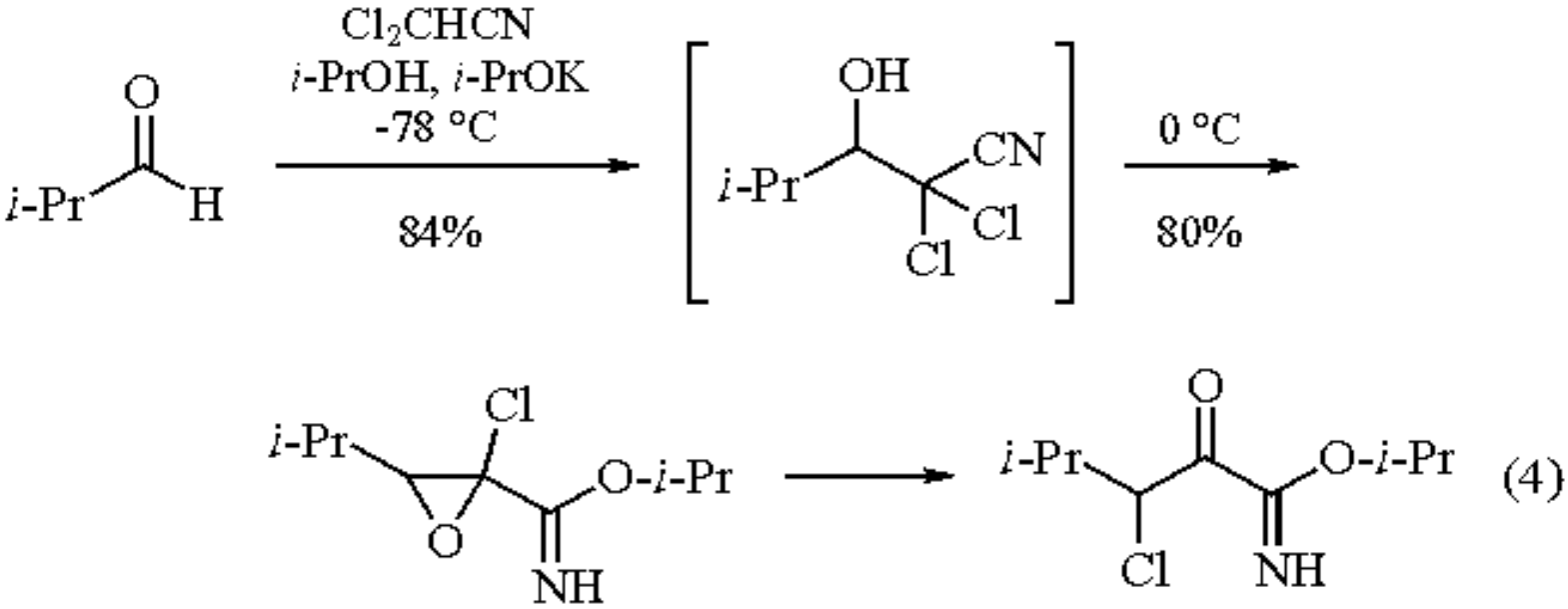

Reaction of Cl_2CHCN with ***Hydrogen Cyanide*** (or, more safely, with ***Acetone Cyanohydrin***) yields a versatile enamino nitrile which can form Schiff bases, be acylated, react with thiolates and alkoxides, and (in two steps) form amino-substituted oxazoles (eq 5).[9]

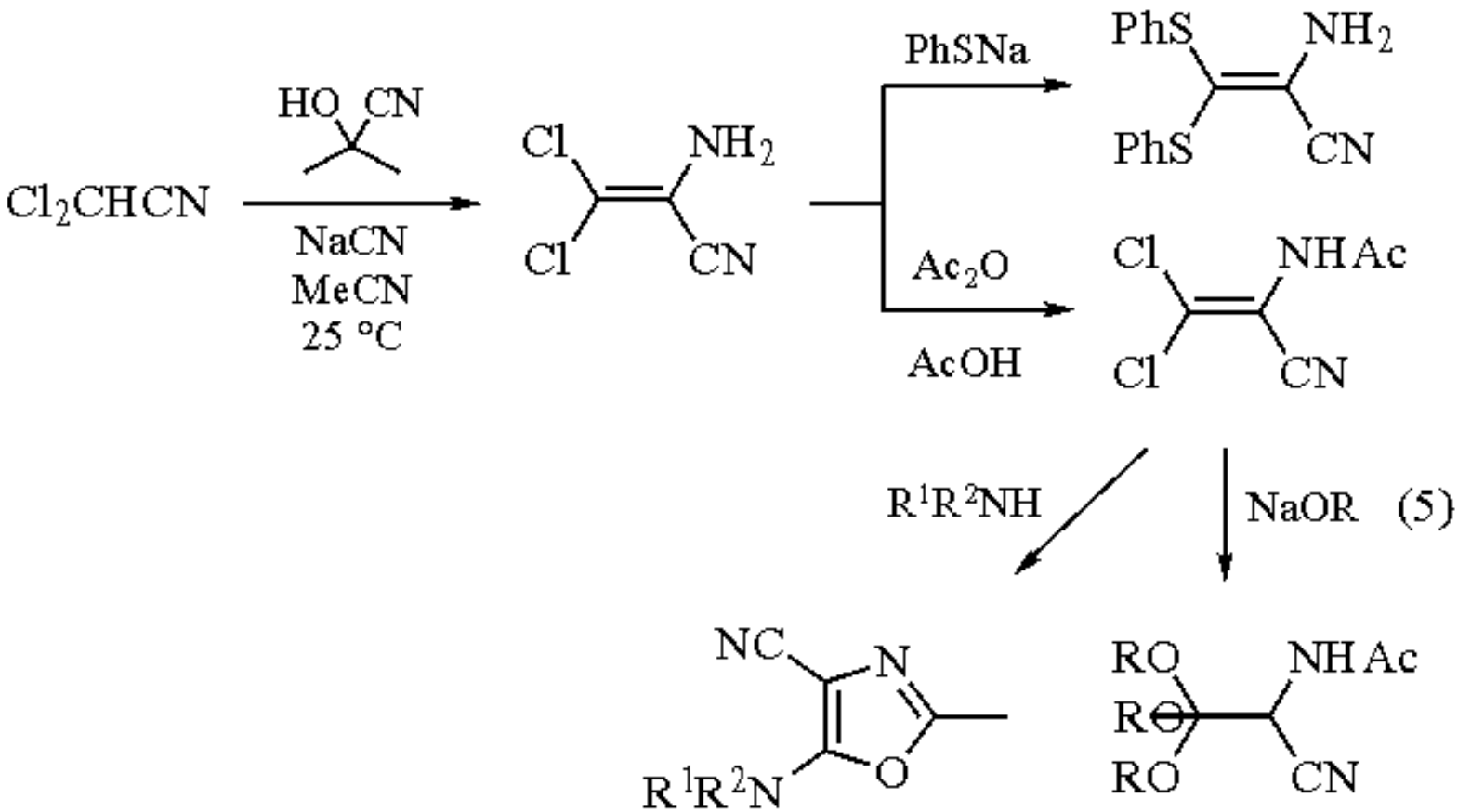

The dimerization of Cl_2CHCN in the presence of HCl gives an *N*-(α-chloroalkenyl)alkylamidine hydrochloride, which upon treatment with ***Phosgene*** provides an unusual 4(3*H*)-pyrimidinone (eq 6).[10] Novel selenium-containing heterocycles are available via Diels-Alder cyclization of selenoaldehydes prepared in good yield from Cl_2CHCN (eq 7).[11]

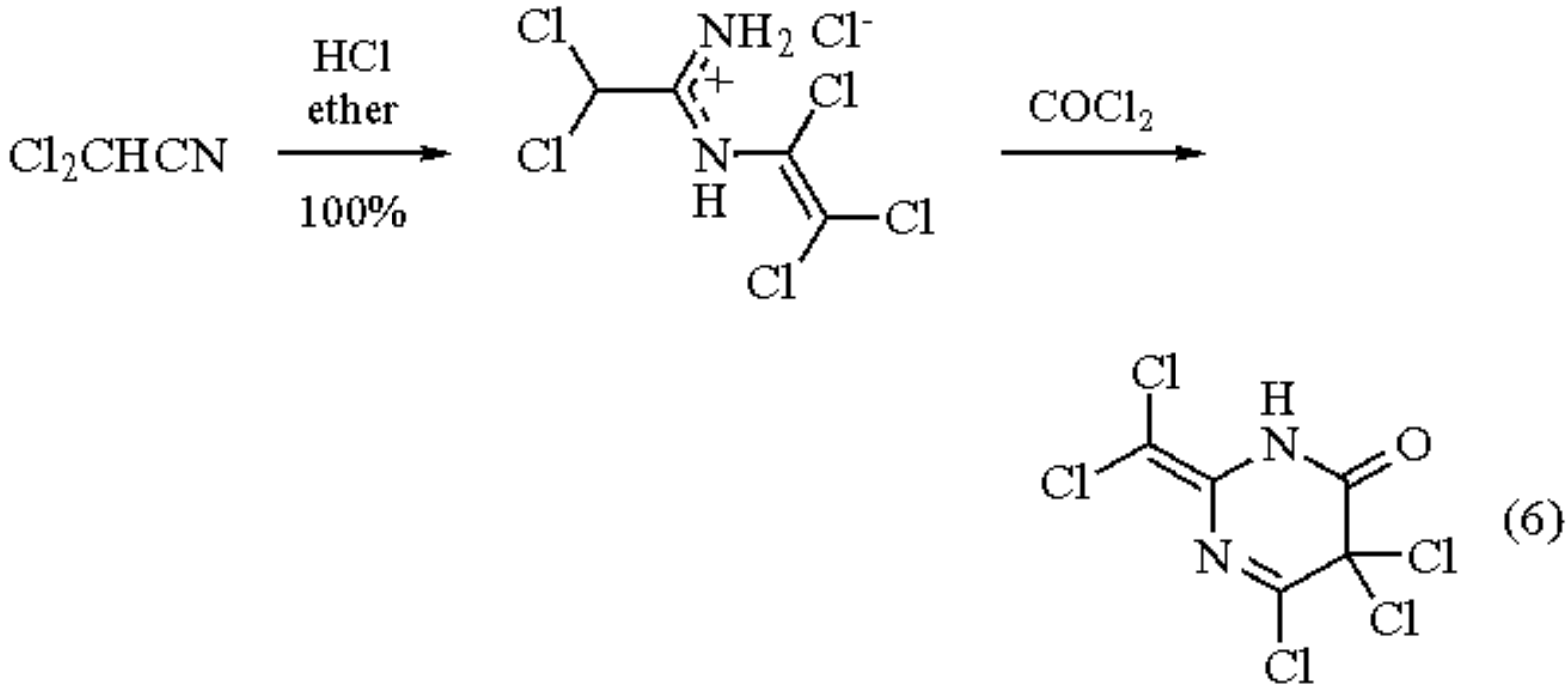

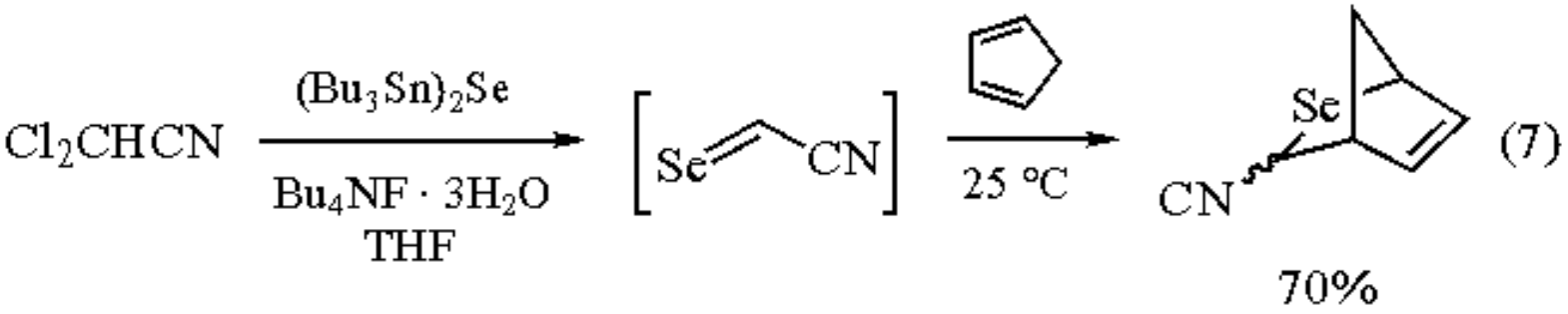

Related Reagents.

Dibromoacetonitrile; ***Ethyl Dibromoacetate***; ***Methyl Dichloroacetate***.

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Dichloroalane

Cl_2AlH

[13497-97-7] · $AlCl_2H$ · Dichloroalane · (MW 98.90)

(reduction of acetals,[1] orthoesters,[2] oxazolidines,[3] and ozonides;[4] hydrogenolysis of ethers,[5] and alcohols;[6] ring opening of epoxides[7] and oxetanes;[8] reduction of ketones,[9] azetidinones,[10] and phosphonates;[11] hydroalumination of alkenes[12])

Physical Data: bp 95 °C in high vacuum.[13a]

Solubility: sol benzene, chloroform, ether, THF.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: normally prepared in situ as a solution in ether and used without purification or analysis; however, the bis-THF adduct has been characterized by NMR, IR, and elemental analysis.[13b]

Preparative Methods: generally prepared in situ from ***Lithium Aluminum Hydride*** (1 equiv) and ***Aluminum Chloride*** (3 equiv) in ether at 0 °C;[4,11b] alternatively, can be prepared in pure form by reaction of AlH_3 (1 equiv) with $AlCl_3$ (2 equiv) in ether followed by vacuum distillation.[13a] The bis-THF adduct [$Cl_2AlH.2(THF)$] is a stable crystalline compound (mp 90-95 °C) which can be prepared by either of the methods described above (substituting THF for ether as the solvent).[13b]

Purification: by distillation.

Handling, Storage, and Precautions: generally prepared in situ and used immediately; handle under dry nitrogen in a fume hood.

Reduction of Acetals, Orthoesters, and Oxazolidines.

Dichloroalane (**1**) may be used for the reduction of acetals to ethers.[1] However, ***Dibromoalane*** is generally superior for this purpose. For the reduction of orthoesters to acetals, either (**1**) or alane (AlH_3) is suitable (eq 1).[2] Similarly, oxazolidines may be reduced to amino alcohols with either (**1**) or alane.[3] Substitution of alane for (**1**) may result in a different stereochemical outcome in some cases.[2,3]

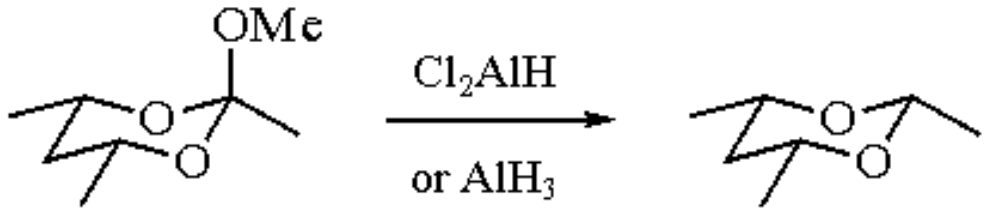

(1)

Reduction of Ozonides to Ethers.

Ozonides can be reduced to ethers with (**1**) in low to moderate yields (varying amounts of diol are obtained as the major byproduct) (eq 2).[4] Substitution of ***Sodium Borohydride-Trifluoroacetic Acid*** for (**1**) in this reaction results in considerable differences in product ratios and yields.

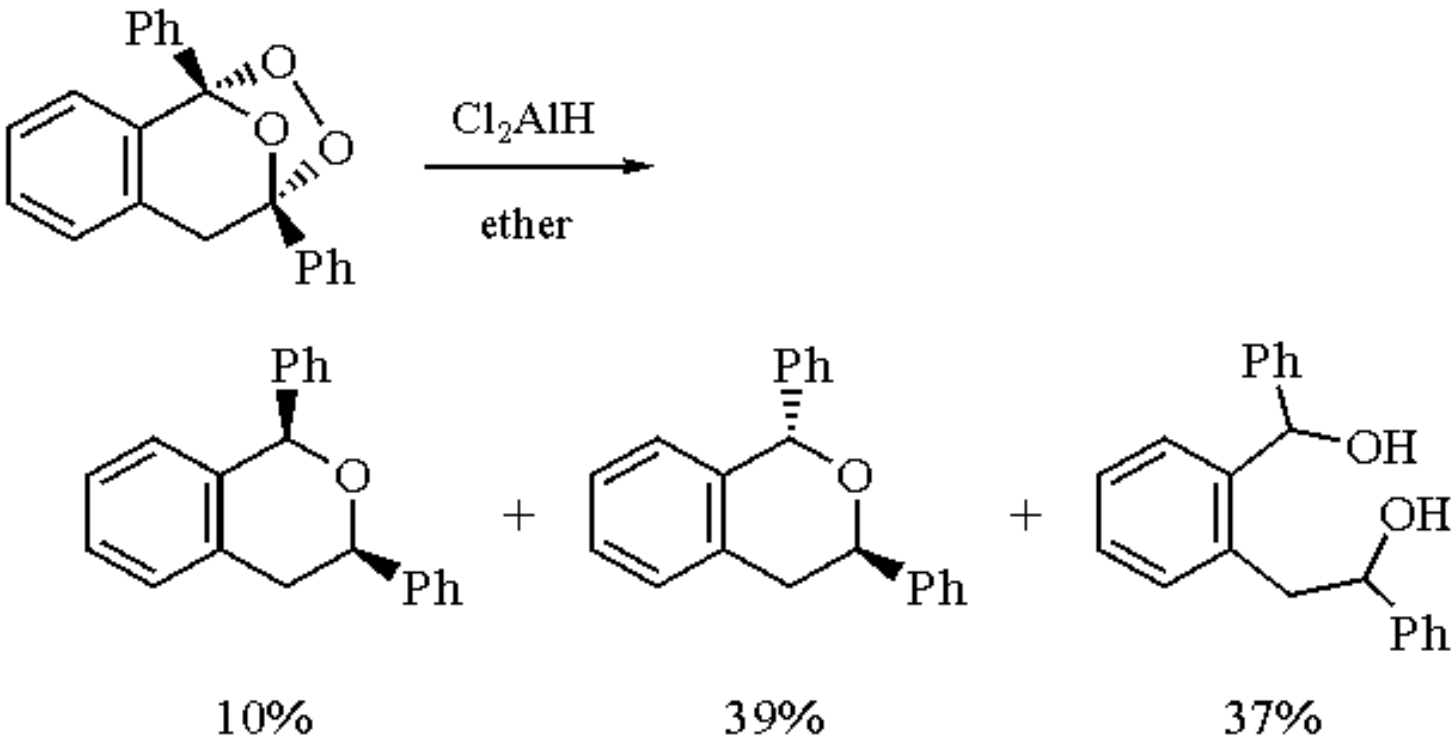

(2)

Hydrogenolysis of Fluorenyl Ethers and Benzylic/Allylic Alcohols.

Dichloroalane (**1**) reductively cleaves fluoren-9-yl ethers in refluxing dichloromethane/ether (eq 3).[5] The necessity of elevated temperatures may lead to formation of byproducts in some cases. Benzylic alcohols (and some chlorides) can also be cleaved by reaction with (**1**), although the necessary conditions are again relatively harsh and byproduct formation is common.[6a] Catalytic hydrogenolysis (H_2, ***Palladium on Carbon***) is probably superior for most substrates. Limited examples of hydrogenolysis of allylic alcohols with (**1**) also exist.[6b]

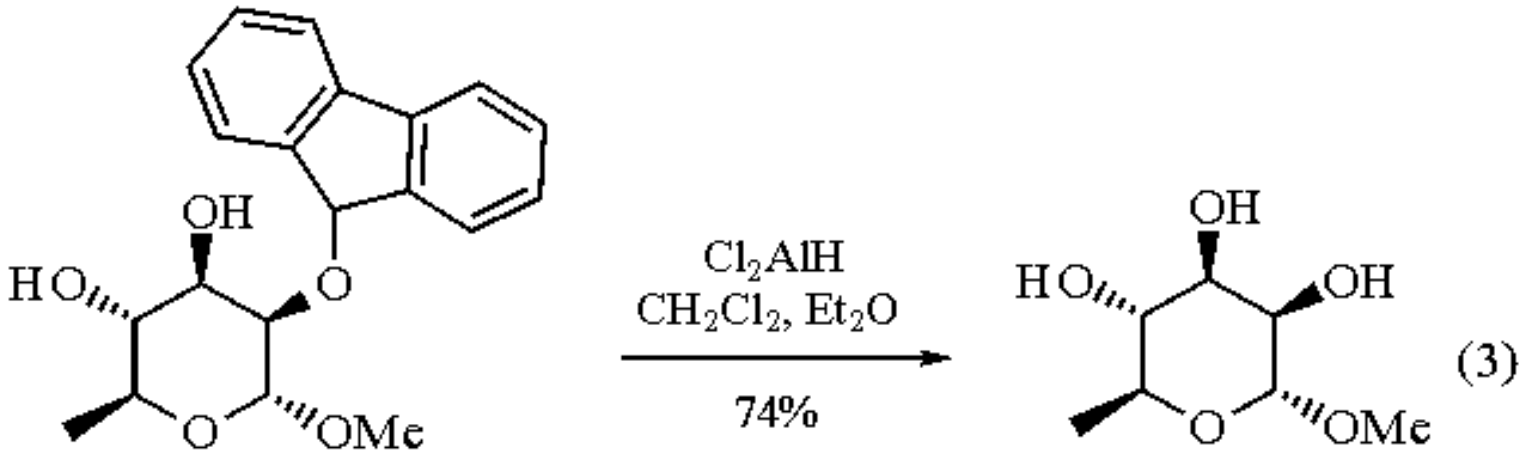

Ring Opening of Epoxides and Oxetanes.

Dichloroalane (**1**) has been used to reduce epoxides, although rearrangement and/or byproduct formation is common due to the Lewis acidity of the reagent.[7] For example, attempted reduction of an alkene-substituted cyclohexane epoxide afforded predominantly cyclized products with no reduced product present (eq 4).[7a] The best reduction substrates are phenyl-substituted epoxides with limited rearrangement options.[7c] Similar results have been reported for reduction of oxetanes with (**1**).[8]

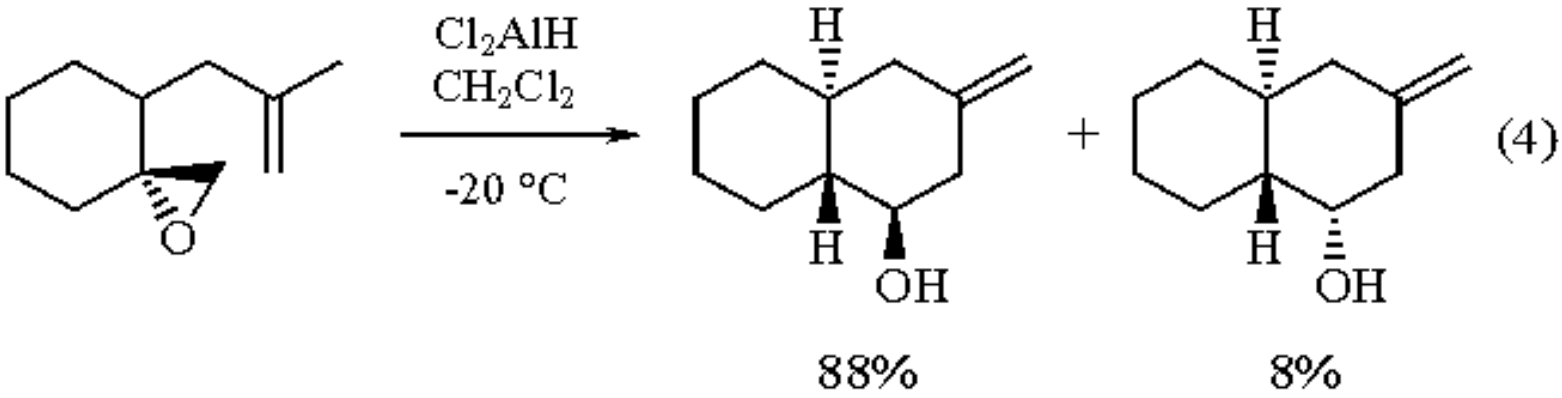

Reduction of Ketones.

In combination with ***Copper(I) Iodide***, (**1**) can effect 1,4-reduction of α,β-unsaturated ketones. However, lithium aluminum hydride/copper iodide is generally superior for this purpose.[9a] There are several examples of the reduction of ketones with (**1**).[9b,c,d] However, (**1**) has no apparent advantage over more readily accessible hydride reagents (e.g. sodium borohydride or lithium aluminum hydride) for this purpose. Dibromoalane is superior to (**1**) for selective reduction of the more hindered of two ketones.[9e]

Reduction of Azetidinones to Azetidines.

Azetidin-2-ones can be efficiently reduced with (**1**) in refluxing ether to afford azetidines in excellent yield (eq 5).[10] This reagent is markedly superior to other reducing agents for this purpose.

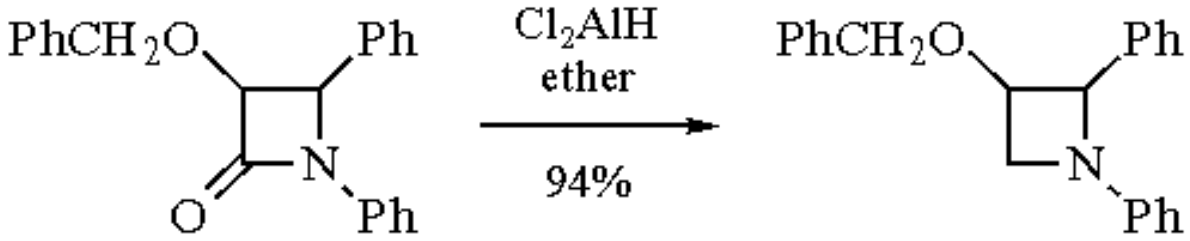

(5)

Reduction of Phosphonates to Phosphines.

Dichloroalane (**1**) is an excellent reagent for the preparation of alkynylphosphines,[11a] allenylphosphines,[11a] or vinylphosphines[11b] by reduction of the corresponding phosphonates. For example, vinylphosphine has been prepared on a gram scale by reduction of a vinylphosphonate with (**1**) (eq 6).[11b] Attempts to effect this reduction with lithium aluminum hydride or alane were unsuccessful.

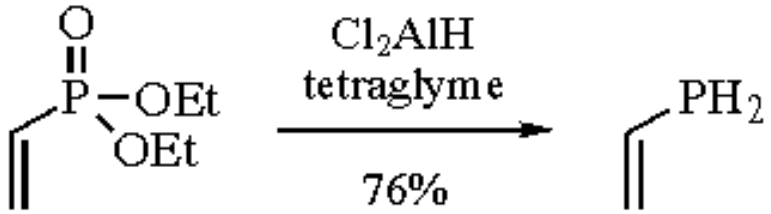

(6)

Hydroalumination of Alkenes.

Alkylaluminum species derived by reaction of (**1**) with alkenes can react with a variety of electrophiles. The net result of this process is the addition of HX across the double bond in an anti-Markovnikov sense. The reaction may be catalyzed by an organoborane[12a] or a transition metal hydride.[12b] For example, organoborane-catalyzed hydroalumination of 1-dodecene with (**1**) followed by reaction of the intermediate organoaluminum species with ***Bromine*** affords 1-bromododecane in excellent yield (eq 7).[12a]

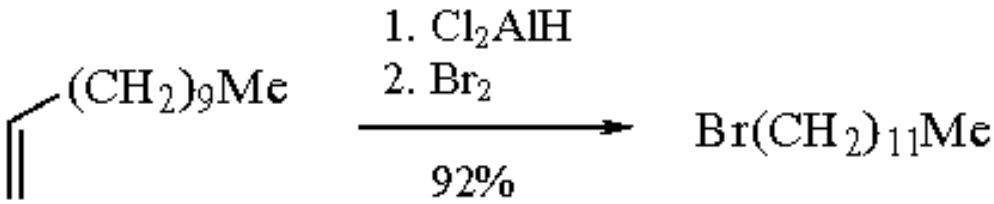

(7)

Bis(dialkylamino)alanes are also excellent reagents for this purpose and may be superior to (**1**).[12b] It is possible to obtain alcohols via hydroalumination-oxidation of alkenes,[12c] but hydroboration-oxidation is preferred for this transformation. It has also been reported that propargylic ethers and amines can be reduced to the corresponding *trans* allylic ethers and amines by the action of (**1**).[12f] However, (**1**) appears to be inferior to other hydride reagents for this purpose.

Related Reagents.

Aluminum Hydride; ***Dibromoalane***; ***Lithium Aluminum Hydride-Copper(I) Iodide***.

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1. (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *TL* **1983**, *24*, 4581. (b) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *JOM* **1985**, *285*, 83. (c) Zajac, W. W., Jr.; Byrne, K. J. *JOC* **1972**, *37*, 521. (d) Loewen, P. C.; Makhubu, L. P.; Brown, R. K. *CJC* **1972**, *50*, 1502.
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1,1-Dichloroallyllithium

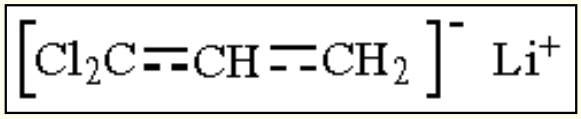

[51522-97-5] · $C_3H_3Cl_2Li$ · 1,1-Dichloroallyllithium · (MW 116.90)

(ambient allyl anion; reacts with a variety of electrophiles to give α- and/or γ-substituted products;[1-5] can serve as a ketone annulating agent to form cyclopentenones;[5] an equivalent of chlorovinyl carbene[6])

Solubility: sol THF.

Preparative Methods: 1,1-dichloroallyllithium (**2**) can be prepared[1] by the lithium-halogen exchange reaction between *n*-butyllithium and 3,3,3-trichloropropene (**1**) at -105 °C (eq 1), but transmetalation of 3,3-dichloro-2-propenyltriphenyllead (**3**) with *n*-butyllithium in THF at -95 °C is cleaner (eq 2).[1]

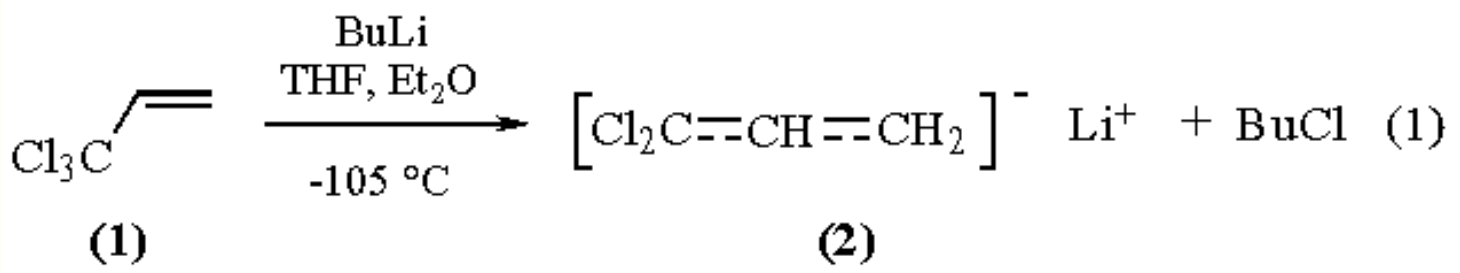

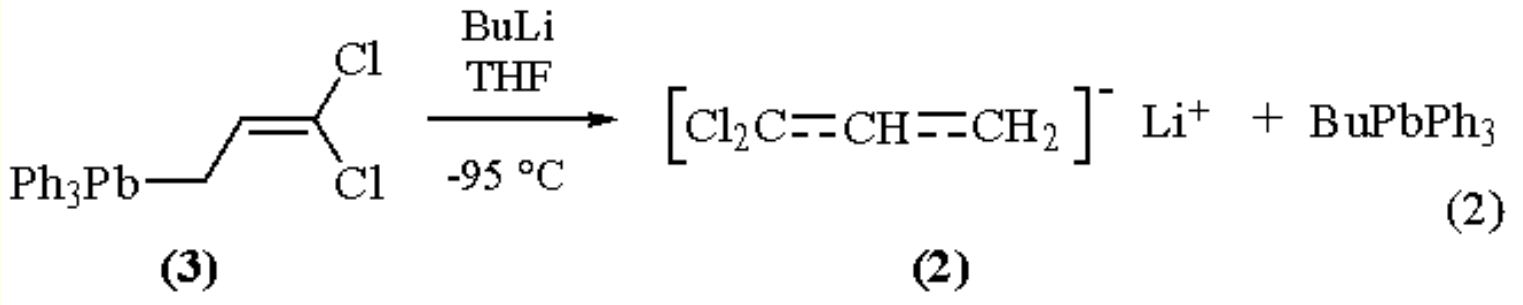

Handling, Storage, and Precautions: highly unstable; generated only at -95 °C, in the presence of electrophiles in an inert atmosphere. Use in a fume hood.

Reaction of (**2**) with ***Chlorotrimethylsilane*** gave exclusively the α-silylated product (**4**) in 99% yield (eq 3). In contrast, the γ-isomer (**5**) was the sole product when (**2**) was treated with Me_3SnBr (eq 4).

(2) **(4)**

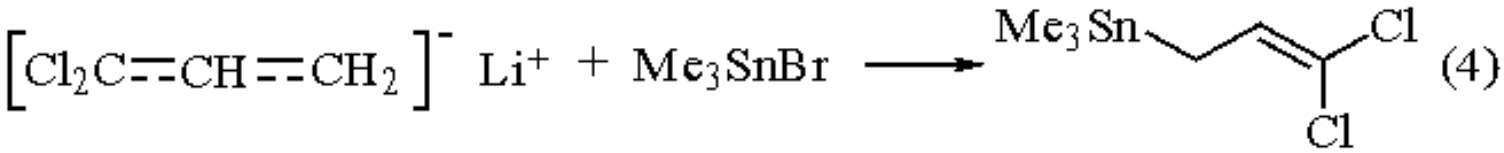

(2) **(5)**

Similar regioselective reaction was observed with $HgCl_2$ to afford a γ-mercurated product (i.e. CCl_2=CH-CH_2HgCl) in 83% yield, while its reaction with iodomethane yields the corresponding α-alkylated product (i.e. $MeCCl_2$-CH=CH_2) in 98% yield. Only trimethylchlorogermane gives a mixture (5.66:1) of α- and γ-isomers.[1]

The reaction of (**2**) with ketones is governed by the ambident nucleophilic character of (**2**), whose two reacting termini differ substantially in terms of both steric and electronic factors. Several ketones and aldehydes give either exclusive α- or γ-products, with two exceptions (PhCHO, PhCOMe) where a mixture of both isomers is obtained in each case (eq 5). The regioselectivity can be explained on the basis of HSAB principle.[2,3] There is also a strong effect of the counterion. When (**2**) is generated by treatment of 3,3-dichloro-1-propene with ***Lithium Diisopropylamide***, benzaldehyde gives mostly γ-product, whereas with ***Potassium t-Butoxide*** present, mostly α-product is obtained (eq 6).[4]

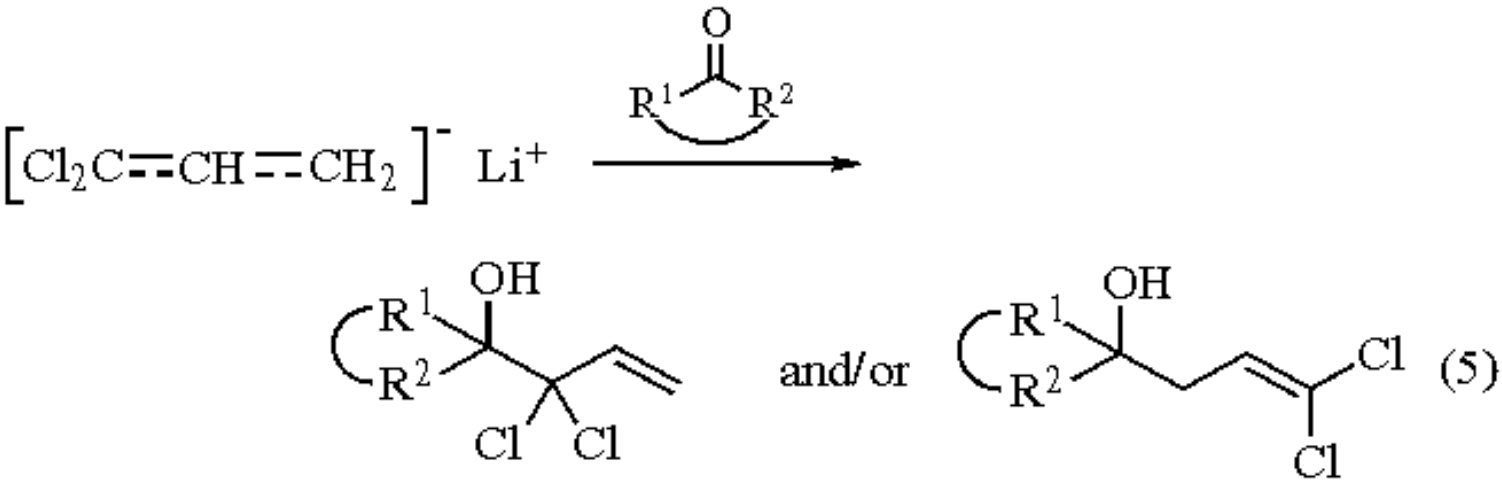

(6) $R^1 = R^2 =$ alkyl

(7) $R^1 = Ph, R^2 = H$
$R^1 = R^2 = Ph$
$R^1 = R^2 = CF_3$

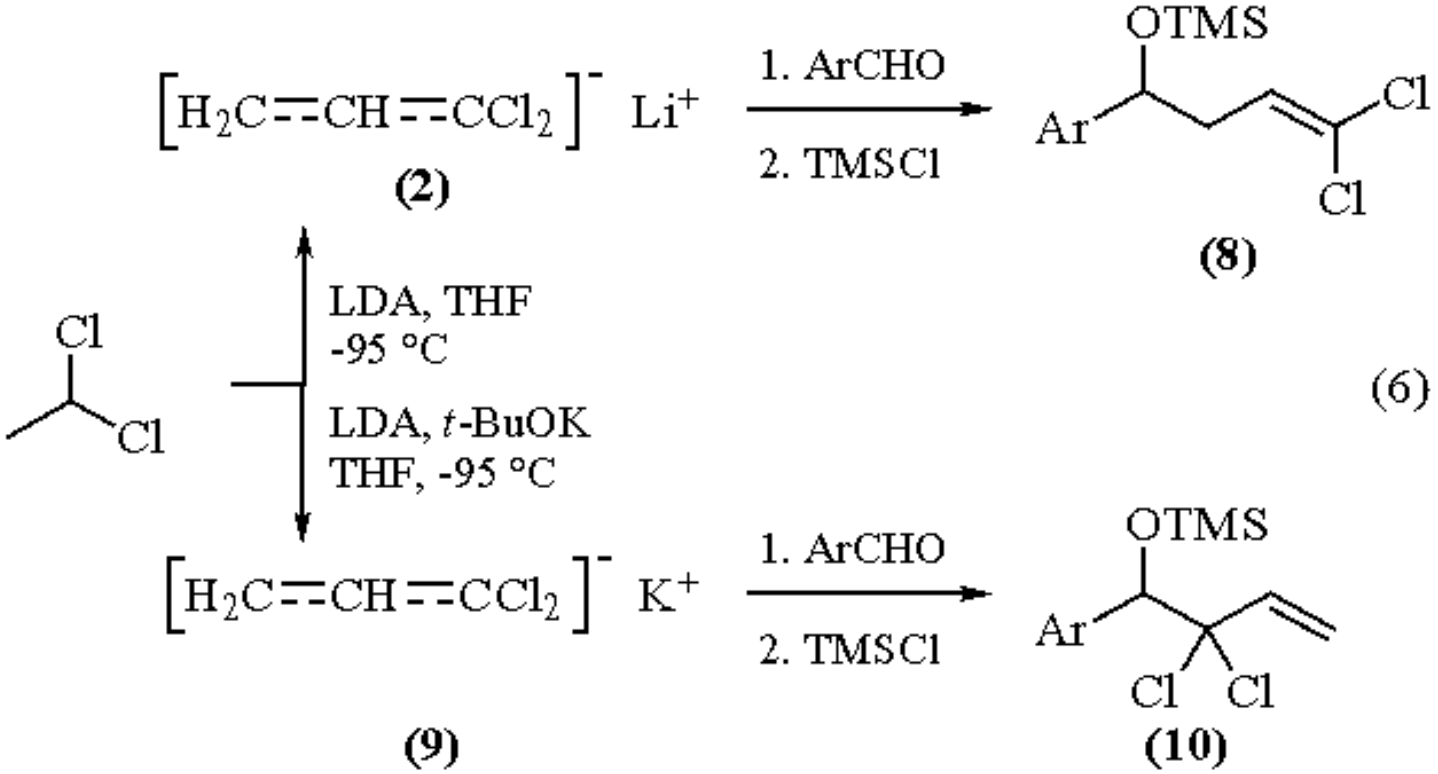

Ar = Ph, *p*-$CF_3C_6H_4$, *o*-ClC_6H_4, *p*-ClC_6H_4 , *o*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-MeC_6H_4, *p*-MeC_6H_4

The reaction of (**2**) with both cyclic and acyclic ketones gives dichlorohomoallylic alcohols (**11**) exclusively. The alcohols have been transformed to the cyclopentenones (**14**) in good yields (eq 7).[5] This conversion is a modified Nazarov cyclization.

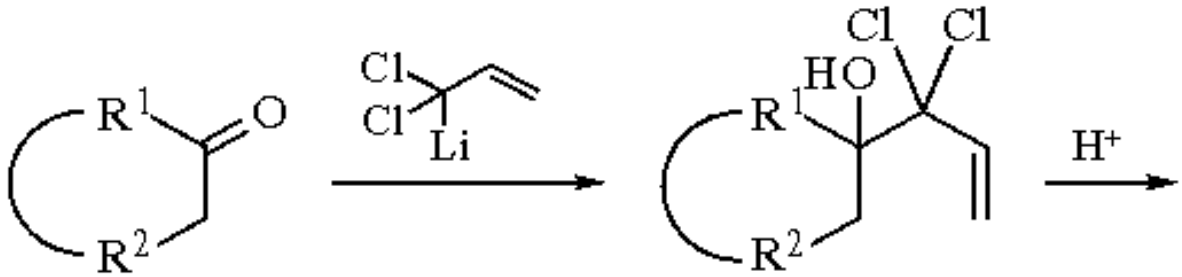

(11)

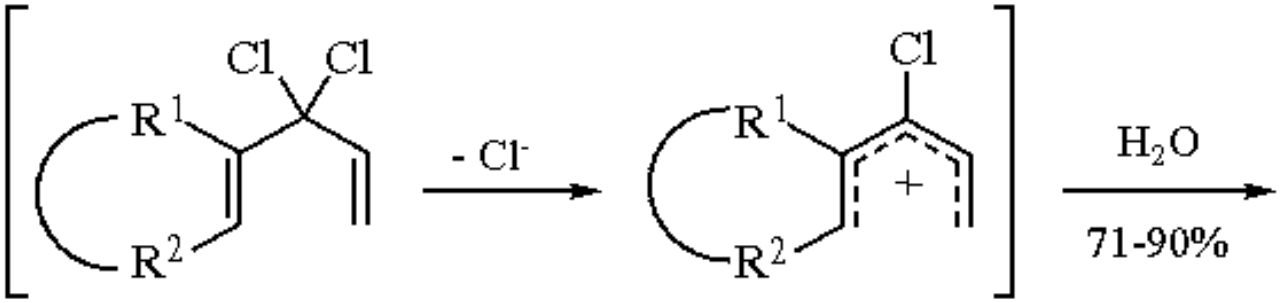

(12) **(13)**

$R^1 = R^2 = -(CH_2-)_n$ $n = 4, 5, 6, 10$
$R^1 = Me$; $R^2 = C_5H_{11}$

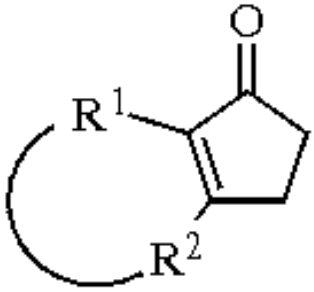

(7)

(14)

The anion (**2**) generated by treatment of 3,3-dichloropropene with ***Lithium 2,2,6,6-Tetramethylpiperidide*** in the presence of alkenes yields, after hydrolytic work-up, the corresponding *gem*-chlorovinylcyclopropanes (**15**) (eq 8) in good yields.[6] With 1,3-butadiene a mixture of *cis*- and *trans*-1-chloro-1,2-divinylcyclopropanes is formed. The *cis* isomer (**16**) (eq 9), however, rapidly undergoes Cope rearrangement to the chloroheptadiene (**17**) in 31% yield.

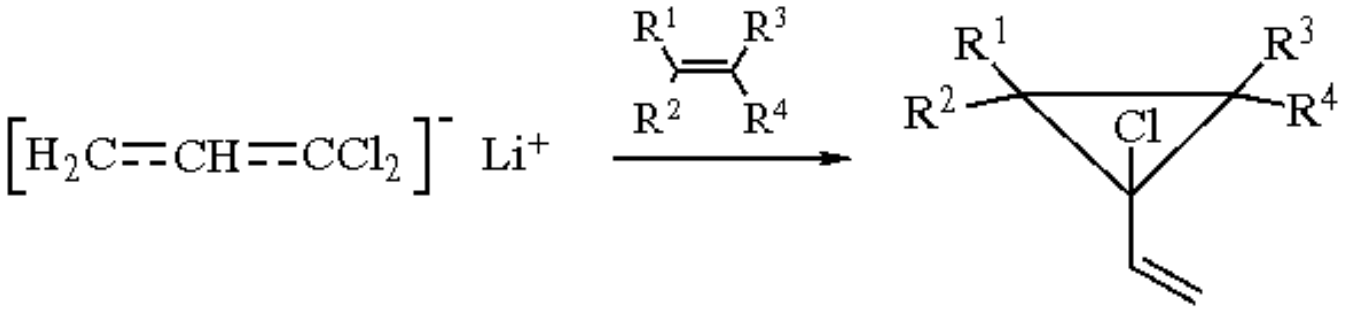

(8)

(15) $R^1 = R^2 = R^3 = R^4 = H, Me$

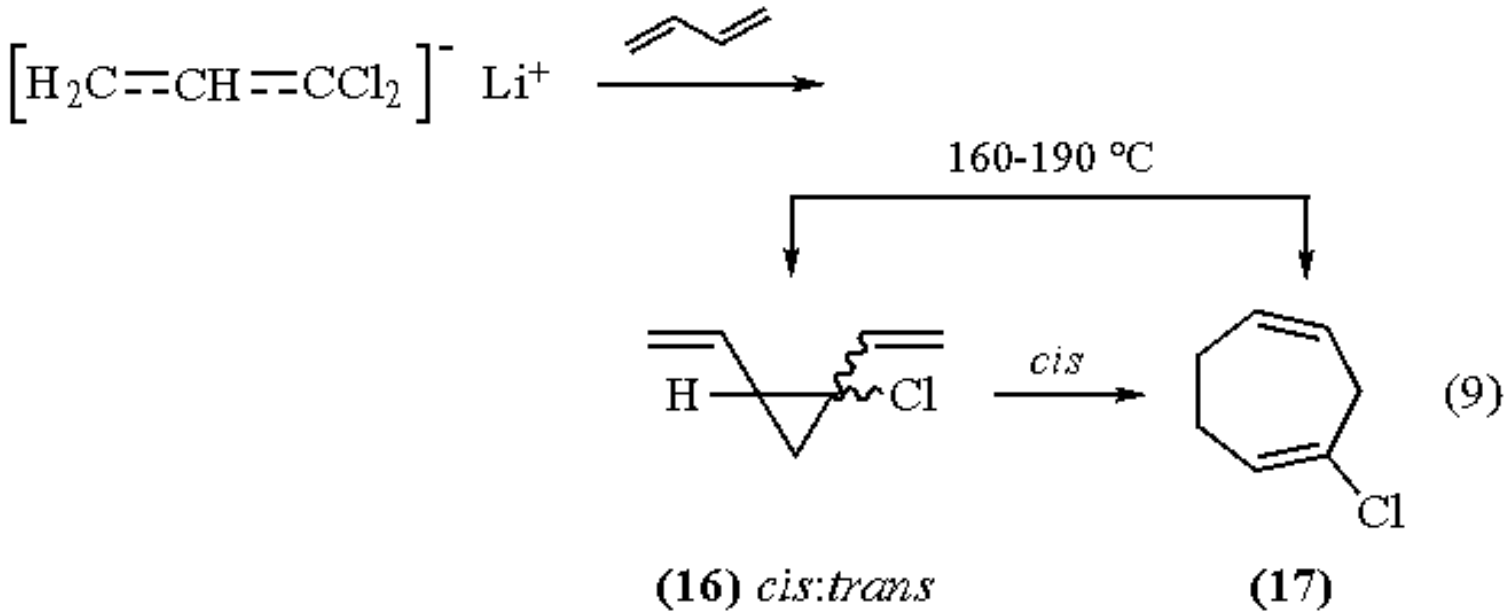

1,1-Difluoroallyllithium (**19**) is of interest as a reagent for the introduction of fluorine into organic molecules. It was first generated[7,8] at -95 °C in THF by treating 3,3-difluoroallyltrimethyltin (**18**) with ***n-Butyllithium*** (eq 10). The reagent is unstable, even at -95 °C to -130 °C, in the absence of an electrophile. However, when (**19**) is generated in the presence of Me_3SiCl, the corresponding α-silylated product (Me_3SiCF_2-CH=CH_2) is obtained in 75% yield. A more effective route to (**19**) involves the Li/Br exchange reaction of CH_2=CH-CF_2Br with BuLi (eq 11) in the presence of various electrophiles.[9]

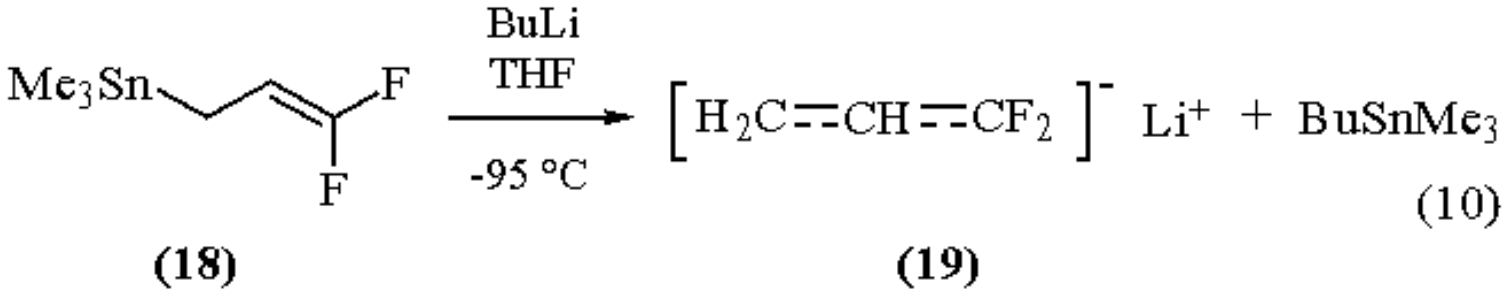

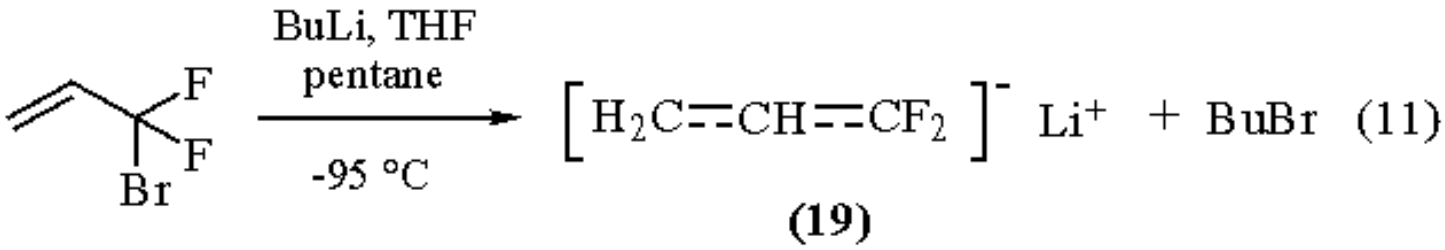

Chlorosilanes, aldehydes, ketones, and esters give α-substituted products such as (**18**) from esters and (**20**) from ketones and aldehydes (eq 12).[10]

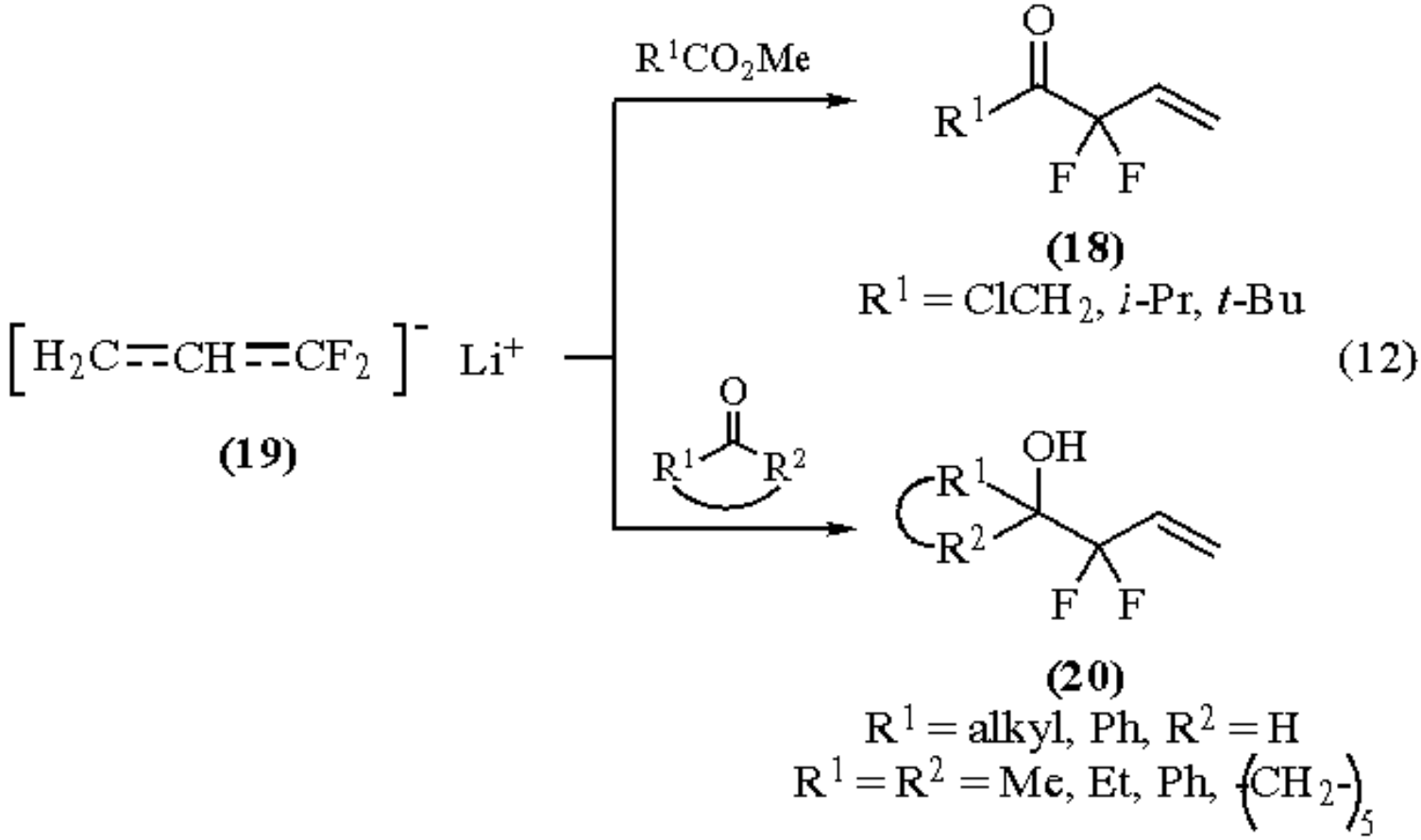

Related Reagents.

1-Chloroallyllithium; ***Dichloromethyllithium***; ***Trichloromethyllithium***.

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1. Seyferth, D.; Murphy, G. J.; Woodruff, R. A. *JOM* **1974**, *66*, C29.
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Dichloroaluminum Phenoxide[1]

$PhOAlCl_2$

[33715-52-5] · $C_6H_5AlCl_2O$ · Dichloroaluminum Phenoxide · (MW 190.99)

(Lewis acid catalyst for carbocyclic ring-expansion reactions)

Physical Data: trimeric structure in benzene solution; forms a stable 1:1 complex with benzonitrile as a yellowish-white solid.

Solubility: sol benzene and methylene chloride.

Preparative Methods: the reagent should be freshly prepared in situ by the careful addition of commercially available dichloromethylaluminum to a 0 °C solution of 1 equiv of phenol in CH_2Cl_2, making provision for the evolution of methane.

Handling, Storage, and Precautions: moisture sensitive; should be prepared and handled under an inert atmosphere. Use in a fume hood.

Ring Expansions.

Dichloroaluminum phenoxide is a powerful Lewis acid that has been shown to be superior to dichloromethylaluminum as a catalyst for the one-carbon ring enlargement of α-(trimethylsilylmethyl)cycloalkanecarbaldehydes to the corresponding α-(trimethylsilylmethyl)cycloalkanones (eq 1).[2] This 1,2-migration is facilitated in part by stabilization of an incipient carbocation by the β-silicon substituent.

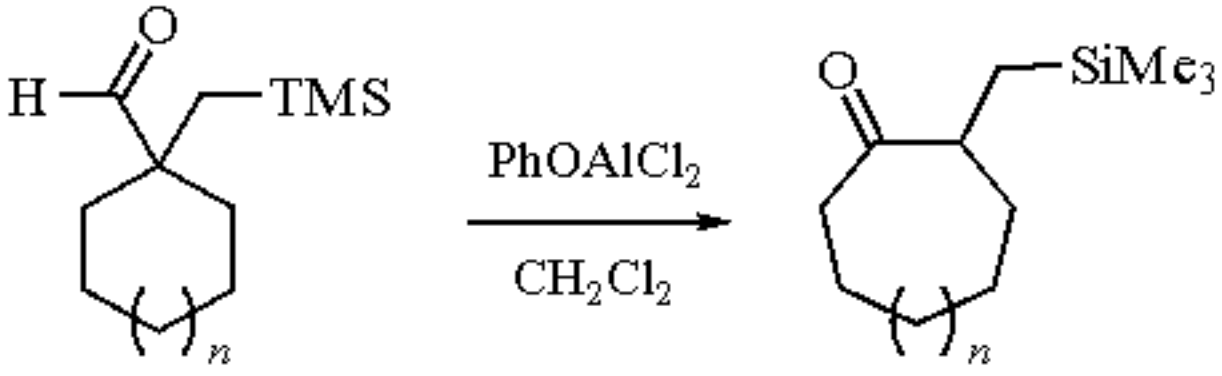

(1)

$n = 1$, 100%
$n = 3$, 97%
$n = 7$, 85%

In a related process, treatment at 0 °C of a methylene chloride solution of 1-acyl-2-vinylcyclobutanes (eqs 2 and 3) with the reagent leads to a two-carbon ring enlargement, affording the corresponding 4-acylcyclohexenes.[3] As before, the oxygenophilic character of this aluminum reagent facilitates the formation of a stabilized carbocationic intermediate.

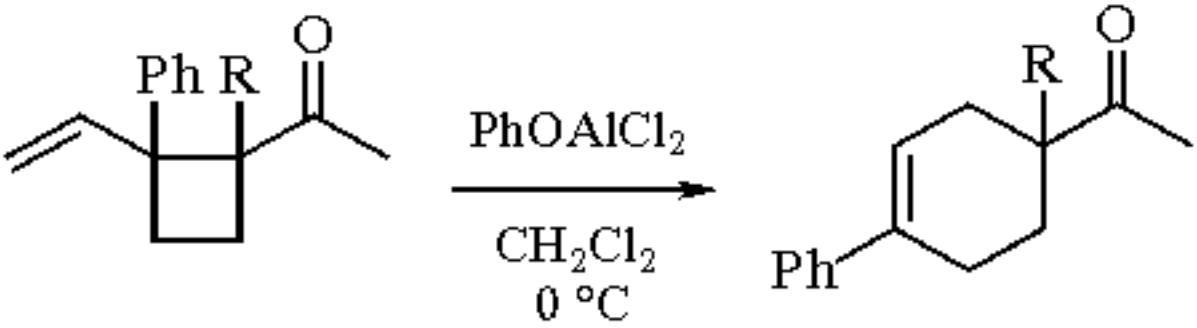

(2)

R = H, Me, 67%

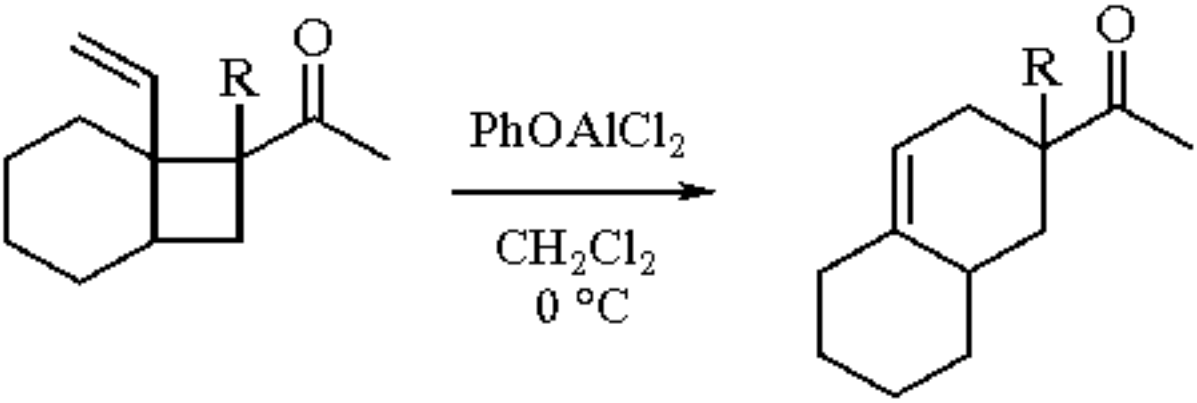

(3)

R = H, 75%
R = Me, 53%

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Di-μ-chlorobis(1,5-cyclooctadiene)diiridium(I)[1]

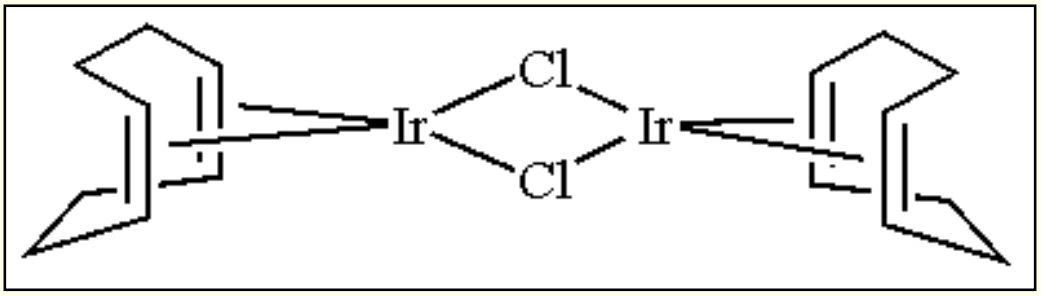

[12112-67-3] · $C_{16}H_{24}Cl_2Ir_2$ · Di-μ-chlorobis(1,5-cyclooctadiene)diiridium(I) · (MW 671.71)

(active catalyst precursor for Claisen rearrangements,[2] [2 + 2] cycloadditions,[3] hydrosilations,[4] and hydroboration[5] reactions)

Physical Data: mp 190 °C (dec); ^{1}H NMR ($CDCl_3$) δ 4.22 (m, =C*H*$_2$), 2.15 (m, C*H*$_2$), 1.40 (C*H*$_2$).[6]

Solubility: sparingly sol acetone; sol CH_2Cl_2 and toluene; insol diethyl ether.

Form Supplied in: orange-red crystalline solid.

Preparative Method: a solution of 6 mL of 1,5-cyclooctadiene in 35 mL of ethanol and 20 mL of water is added to 2.0 g of $IrCl_3.3H_2O$ in a round-bottomed flask. The mixture is refluxed under nitrogen for 24 h, during which time an orange-red product precipitates from solution. The mixture is cooled to rt and di-μ-chlorobis(1,5-cyclooctadiene)diiridium(I) is collected by filtration, washed with cold methanol, and dried in vacuo at 25 °C for 8 h.[1]

Handling, Storage, and Precautions: the dry solid is moderately air-stable.

Claisen Rearrangements.[2]

Cope and Claisen [3,3]-sigmatropic thermal rearrangements are of considerable utility in synthetic organic

chemistry. Although such reactions proceed at high temperatures (ca. 200 °C), transition metals can be employed to accelerate the rearrangements. Indeed, $[Ir(\mu\text{-}Cl)(1,5\text{-cod})]_2$ is a fairly active catalyst precursor for the rearrangement of allyl imidates to allyl amides,[2a] as well as allylic thionobenzoates to allylic thiolobenzoates[2b] under mild conditions. Reactions are not selective, as both [3,3]- and [1,3]-rearrangement products are generated in approximately equal amounts (eq 1). Use of palladium(II) complexes circumvents this complication, giving exclusive [3,3] regioselectivity. The mechanism of iridium(I) catalysis seems to involve carbonium ion intermediates formed by allyl-oxygen bond cleavage.

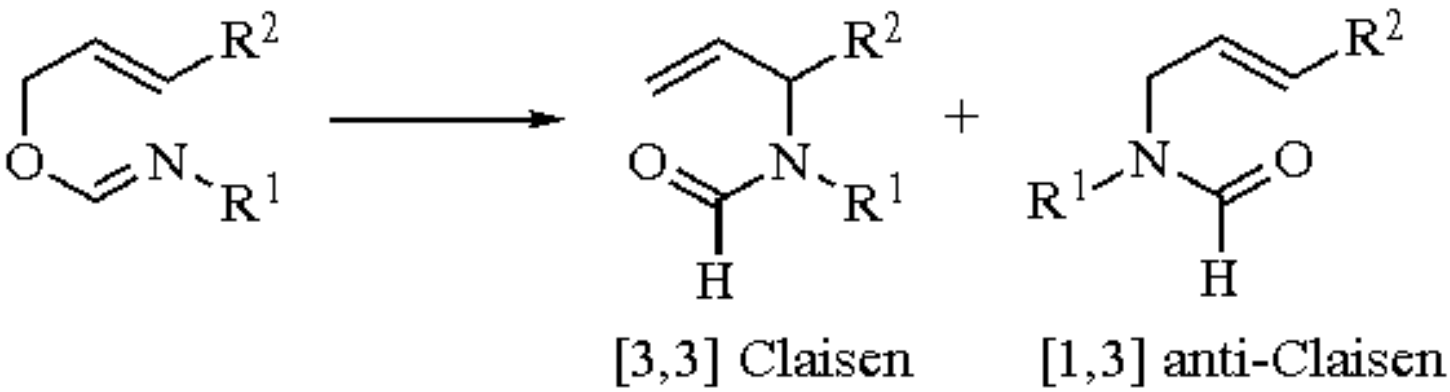

(1)

In another rearrangement reaction, $[Ir(\mu\text{-}Cl)(1,5\text{-cod})]_2$ can be used in conjunction with ***Iodomethane*** to catalyze the isomerization of methyl formate to acetic acid (eq 2).[7] Reactions are conducted in a carboxylic acid solvent. Water inhibits acetic acid formation and allows an alternative pathway to proceed that affords methane and carbon dioxide as principal products.

$$HCO_2Me + RCO_2H \longrightarrow HCO_2H + RCO_2Me \qquad (2)$$

[2 + 2] Cycloaddition Reactions.

The dimerization of bicyclo[2.2.1]heptadiene is promoted by $[Ir(\mu\text{-}Cl)(1,5\text{-cod})]_2$, giving exclusive formation of a dimer with *exo-trans-exo* configuration (eq 3).[3] Evidence has been presented that suggests this dimerization proceeds via a metal-carbon σ-bonded intermediate.

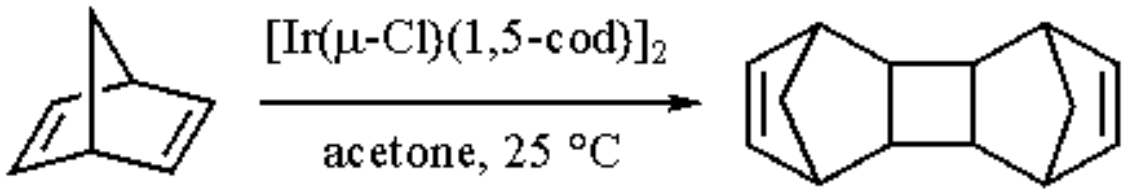

(3)

H-X Additions.

Hydrosilation of allylic halides with ***Triethoxysilane*** carried out in the presence of a catalytic amount of

$[Ir(\mu\text{-}Cl)(1,5\text{-cod})]_2$ affords predominantly halopropyltrialkoxysilanes.[4] Disilane formation is observed, however, in analogous hydrosilations of 1-hexene using H_2SiEt_2.[7] Finally, while $[Ir(\mu\text{-}Cl)(1,5\text{-cod})]_2$ can be used to catalyze the hydroboration of vinylarenes, selectivities are poor and product distributions are complicated by significant amounts of alkane formation derived from hydrogenation of the substrate.[5] Regioselectivities for this reaction are dependent upon the nature of the catalyst precursor employed.[8]

---

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Dichlorobis(cyclopentadienyl)hafnium[1]

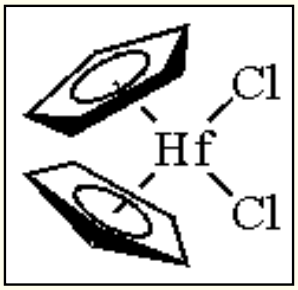

[12116-66-4] · $C_{10}H_{10}Cl_2Hf$ · Dichlorobis(cyclopentadienyl)hafnium · (MW 379.59)

(starting material to prepare many kinds of hafnocene(II or IV) derivatives;[2] in combination with Ag^I salt, is an effective activator for glycosyl fluoride[3])

Physical Data: mp 230-233 °C.

Solubility: sol aromatic solvents, chloroform; slightly sol THF, ether; insol hexanes.

Form Supplied in: colorless crystals; commercially available.

Analysis of Reagent Purity: ^{1}H NMR (THF-d_8) δ 6.62 (s, C_5H_5).

Handling, Storage, and Precautions: the dry solid is reasonably stable to air and moisture and can be handled in an ordinary manner. However, it should be stored in a tightly-sealed nitrogen-flushed bottle to preclude moisture.

Transmetalation and Generation of Cp_2Hf Equivalent.

Cp_2HfCl_2 is an important starting material for the preparation of Hf^{IV} and Hf^{II} derivatives, just as ***Dichlorobis(cyclopentadienyl)zirconium*** is used to prepare zirconium compounds. While the chemistry of Cp_2ZrCl_2 and its derivatives is well-developed, a corresponding surge in the study of hafnium compounds has not ensued. In general, the chemistry of Cp_2HfCl_2 and its derivatives is similar to that of zirconium. Transmetalation reactions of Cp_2HfCl_2 with organometallics containing lithium, sodium, potassium, and magnesium are a general method to prepare $Cp_2Hf(R)Cl$ and Cp_2HfR_2 (R = alkyl, alkenyl, aryl, and alkynyl) (eq 1).[2,4] Alkylhafnocenes are thermally more stable than the corresponding alkylzirconocenes in the solid state and in solution. For example, while dibutylzirconocene rapidly eliminates butane to give a zirconocene-butene complex, thermolysis of the hafnocene analog at 80 °C is required for this process.[2a] Heating *n*-butyl-*t*-butylhafnocene at 45 °C in the presence of trimethylphosphine gives a hafnocene-isobutene complex, which reacts with diphenylacetylene to give an alkyne complex. It also promotes C-H

bond activation with benzene or alkoxide (eq 2).[2a] Alkyl-alkene coupling (eq 3)[2b] and skeletal rearrangement by C-C bond activation[5] to form hafnacyclopentanes have been reported. Generation of Cp_2Hf equivalent can be achieved by reduction of Cp_2HfCl_2 with ***Magnesium-Mercury(II) Chloride***[6] or 2 equiv ***n-Butyllithium***.[2] This Cp_2Hf reacts with a series of unsaturated compounds (alkyne and alkene) through a ligand exchange process to give a hafnocene complex; this reaction has been applied to bicyclizations of nonconjugated dienes, enynes, and/or diynes (eq 4).[6]

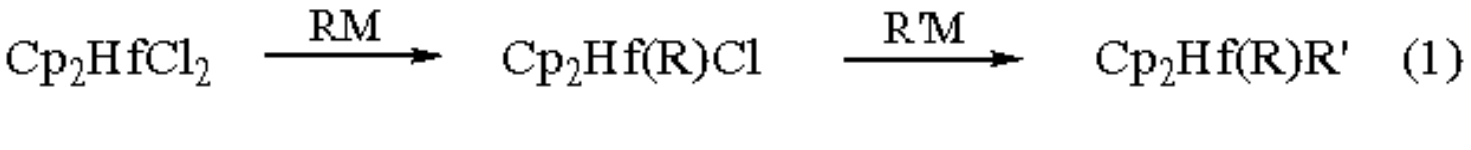

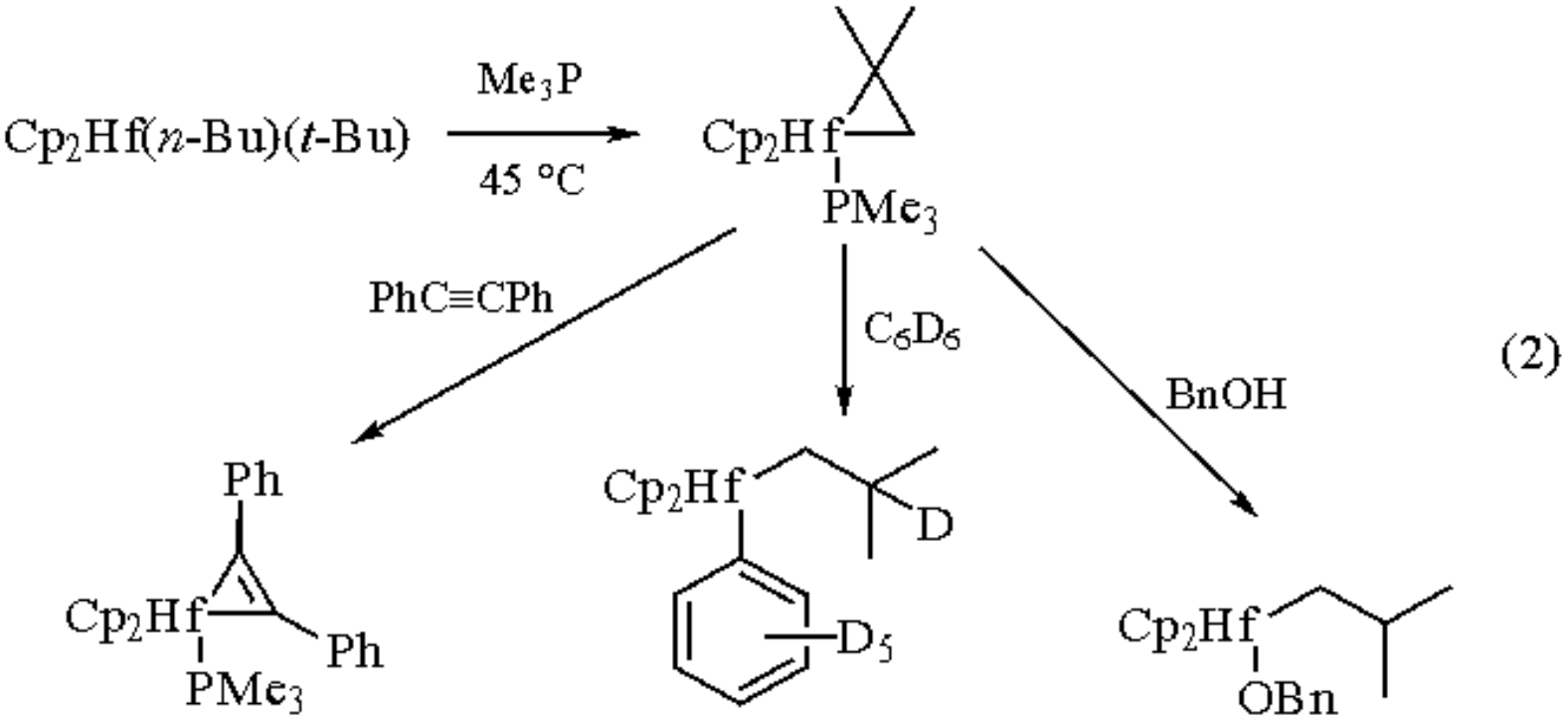

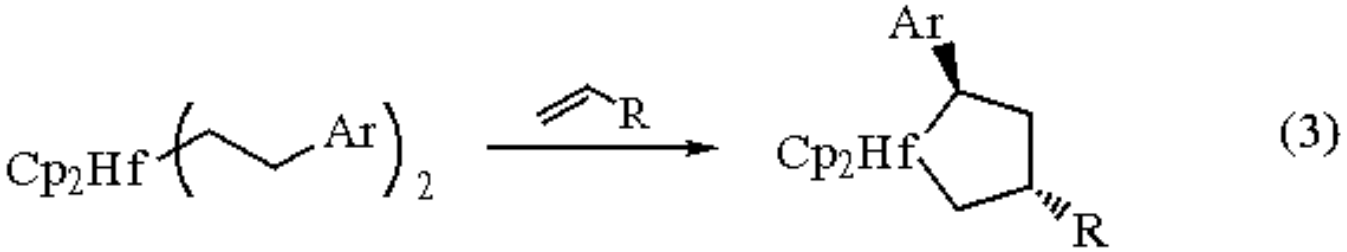

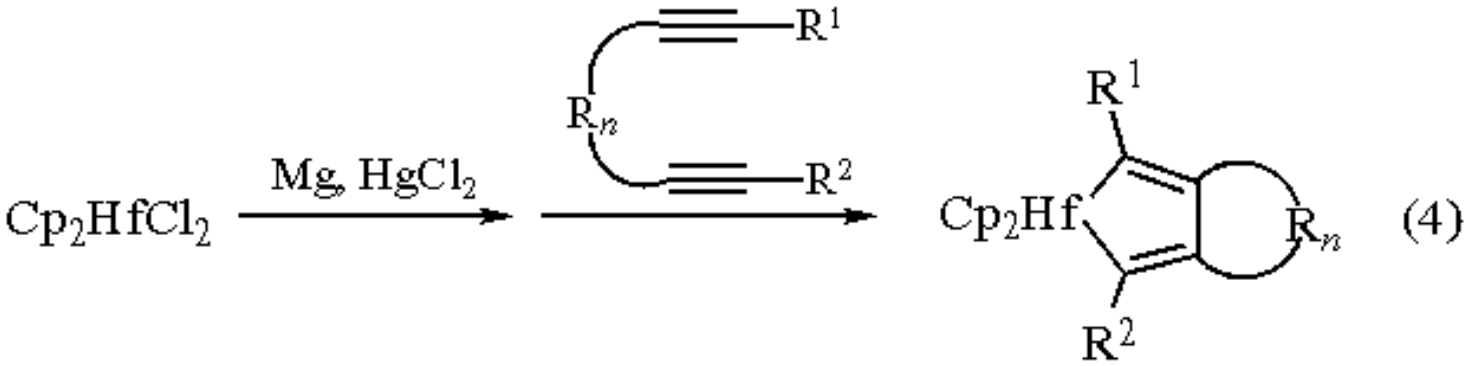

Glycosidation.

The combination of metallocene dichloride (Cp_2ZrCl_2 or Cp_2HfCl_2) and silver salt (AgX: X = ClO_4, OTf, BF_4) is a highly effective reagent system for activating glycosyl fluoride to give the *O*-,[7] *C*-,[8] or *N*-glycoside[9] stereoselectively under mild conditions (eq 5). Selection of the center metal (Zr or Hf), the molar ratio of metallocene dichloride and Ag^I salt, and the solvent used are crucial factors for controlling the reactivity and stereoselectivity in this glycosidation reaction.[7a,10] The Cp_2HfCl_2 based activators are more reactive than the Cp_2ZrCl_2 ones[9] and the former are more effective than the latter in the case of amino sugar derivatives.[11] Regio- and stereocontrolled *C*-aryl glycosidation of phenols based on the *O*-*C* glycoside rearrangement is efficiently carried out by using the Cp_2HfCl_2-***Silver(I) Perchlorate*** system (eq 6).[12] The high β-selectivity achieved without neighboring group assistance in glycosyl fluoride is a key synthetic advantage of these reagent systems.

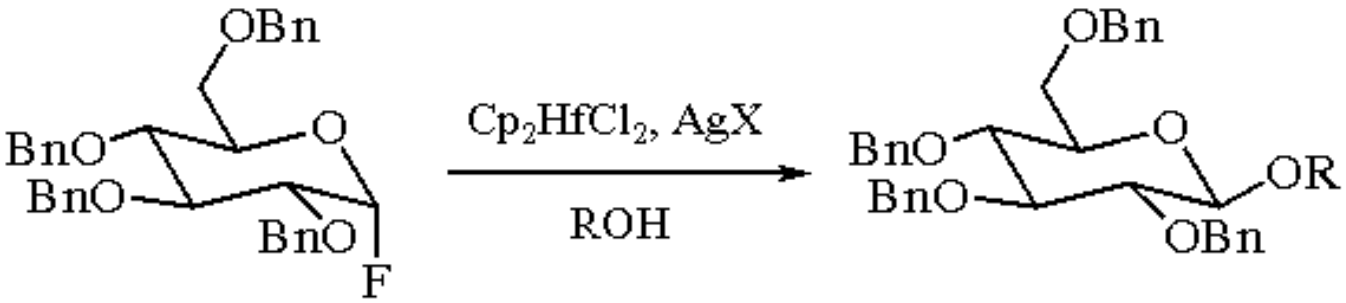

(5)

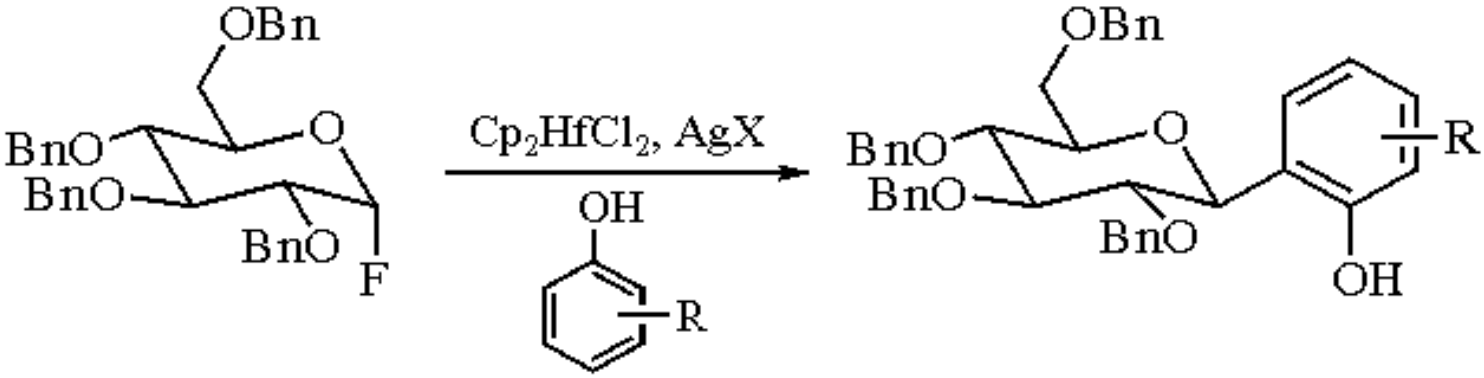

(6)

Related Reagents.

Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts; ***Dichlorobis(cyclopentadienyl)titanium***; ***Dichlorobis(cyclopentadienyl)zirconium***.

---

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Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts[1]

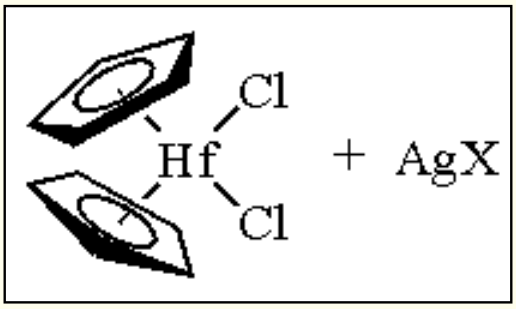

(Cp_2HfCl_2)

[12116-66-4] · $C_{10}H_{10}Cl_2Hf$ · Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts · (MW 379.59) ($AgClO_4$)

[7783-93-9] · $AgClO_4$ · Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts · (MW 207.32) ($AgOSO_2CF_3$; AgOTf)

[2923-28-6] · $CAgF_3O_3S$ · Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts · (MW 256.93) ($AgBF_4$)

[14104-20-2] · $AgBF_4$ · Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts · (MW 194.68) ($AgPF_6$)

[26042-63-7] · AgF_6P · Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts · (MW 252.83)

(can activate glycosyl fluorides for *O*-glycosidation;[2] can convert aryl *O*-glycosides to the corresponding aryl *C*-glycosides[3])

Physical Data: see entries for ***Dichlorobis(cyclopentadienyl)hafnium*** and individual silver salts.

Handling, Storage, and Precautions: the reagents are combined just before use by adding the Ag salt to a solution of Cp_2HfCl_2. $AgClO_4$ leads to the best reactivity, but has a potential hazard of explosion.[4] AgOTf is recommended as a safe alternative with slightly decreased reactivity. Other silver salts (e.g. $AgBF_4$, $AgPF_6$, $AgAsF_6$) are less effective, but sometimes offer unique stereochemical preferences.[2,3] Molecular sieves 4Å are often used for removal of water in small scale runs, but are not necessarily essential.

Glycosyl fluorides are widely used in glycoside synthesis, because of their stability, ease of handling and availability

of specific activation methods.[5] Although ***Tin(II) Chloride***-$AgClO_4$[5a] is most often utilized, the extremely high reactivity offered by Cp_2HfCl_2-$AgClO_4$[2] renders it the promoter of choice for the glycosidation of sterically demanding substrates. Intermediate cationic hafnocene complexes are believed to be the origin of the high reactivity, which led to the finding that the use of the combination in 1:2 ratio leads to an even more increased reactivity (eq 1).[2d] The efficiency of this new protocol is clearly demonstrated in the synthesis of oligo- or even polysaccharides.[6e]

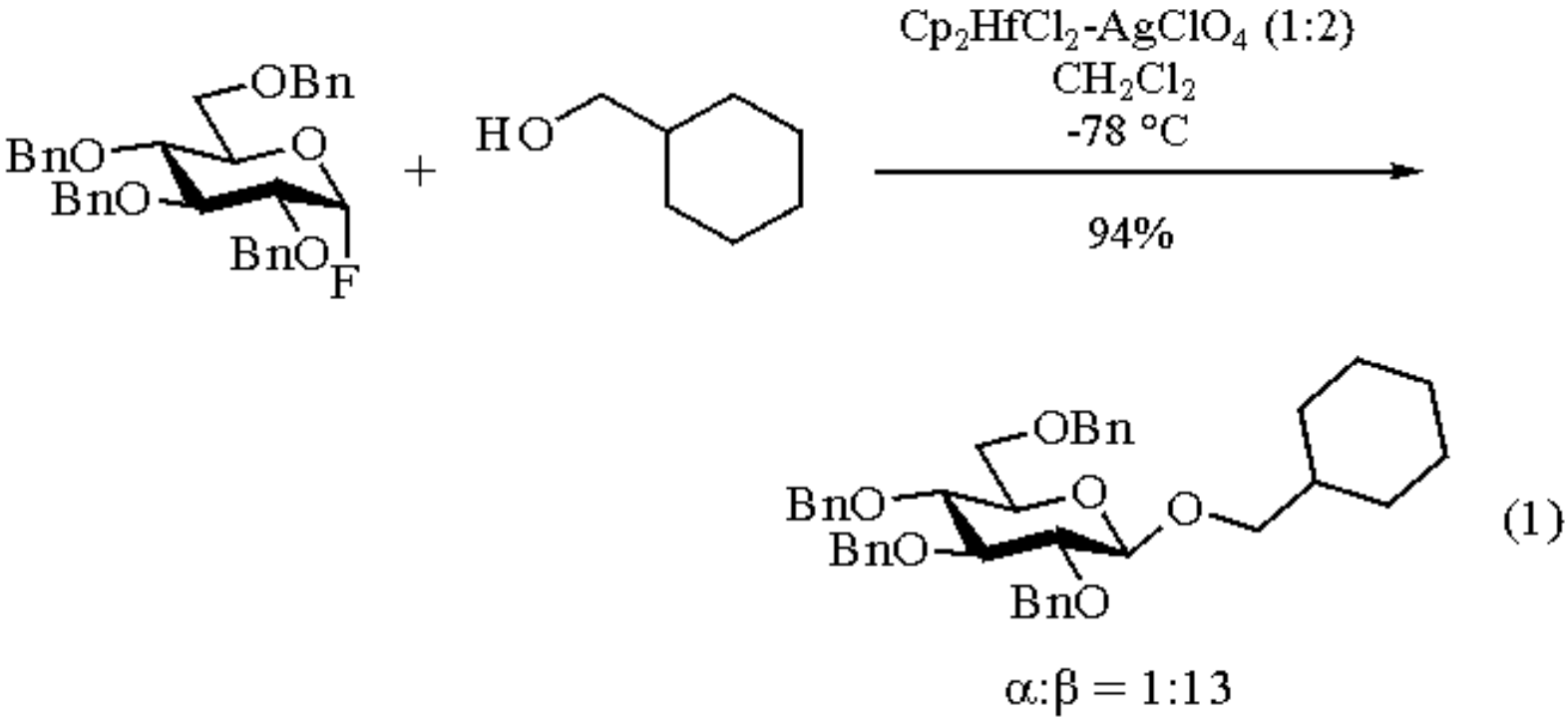

(1)

A number of useful applications are reported for the synthesis of various classes of glycoconjugates ranging from macrolides, e.g. (**1**),[2a,b,c] to oligosaccharide structures embedded in glycolipids.[6] One of the highlights in the latter context is the block synthesis of sialyl Le^X related oligosaccharides via the coupling of the glycosyl fluoride (**2**).[6a,b] Applicability to glycosidation of amino sugars is another notable feature of this activation method.[2b,c,6]

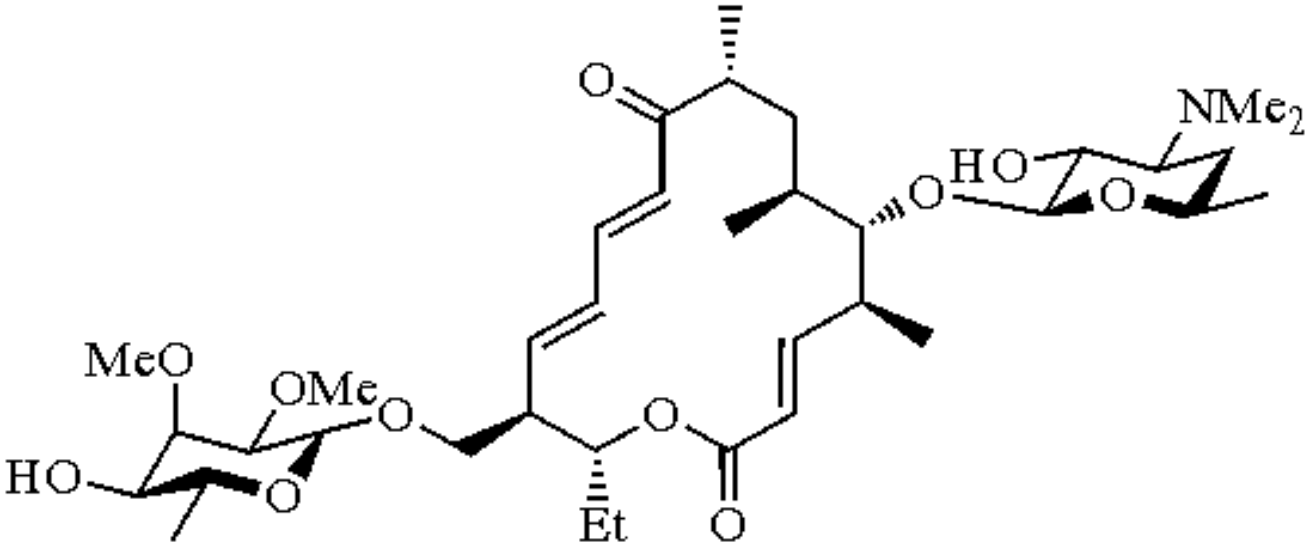

(1)

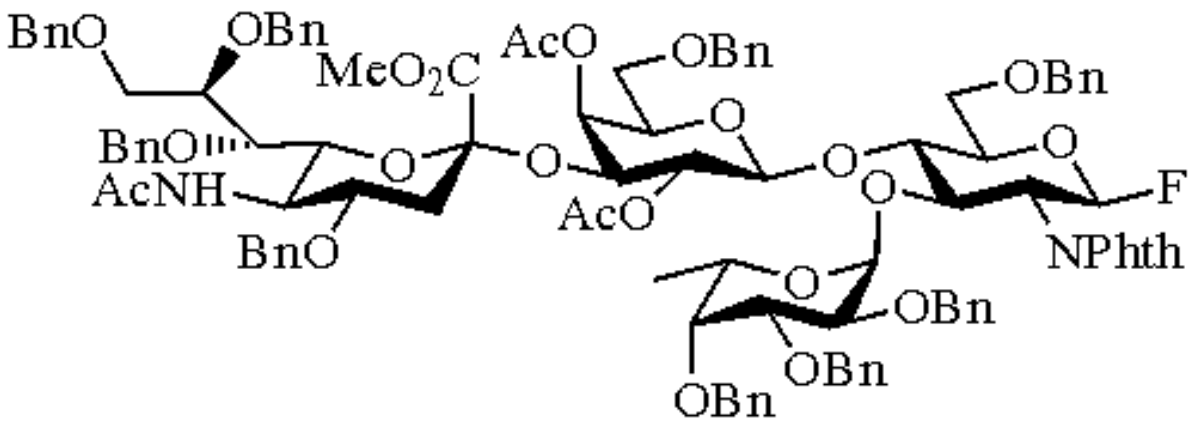

(2)

A Lewis acid-mediated synthetic reaction of aryl *C*-glycosides is reported, which involves (1) the initial formation of aryl *O*-glycosides at low temperature, and (2) its in situ rearrangement to the corresponding aryl *C*-glycosides (eq 2).[3] A particularly useful feature is that the C-C bond is formed regioselectively at the position *ortho* to the phenol.

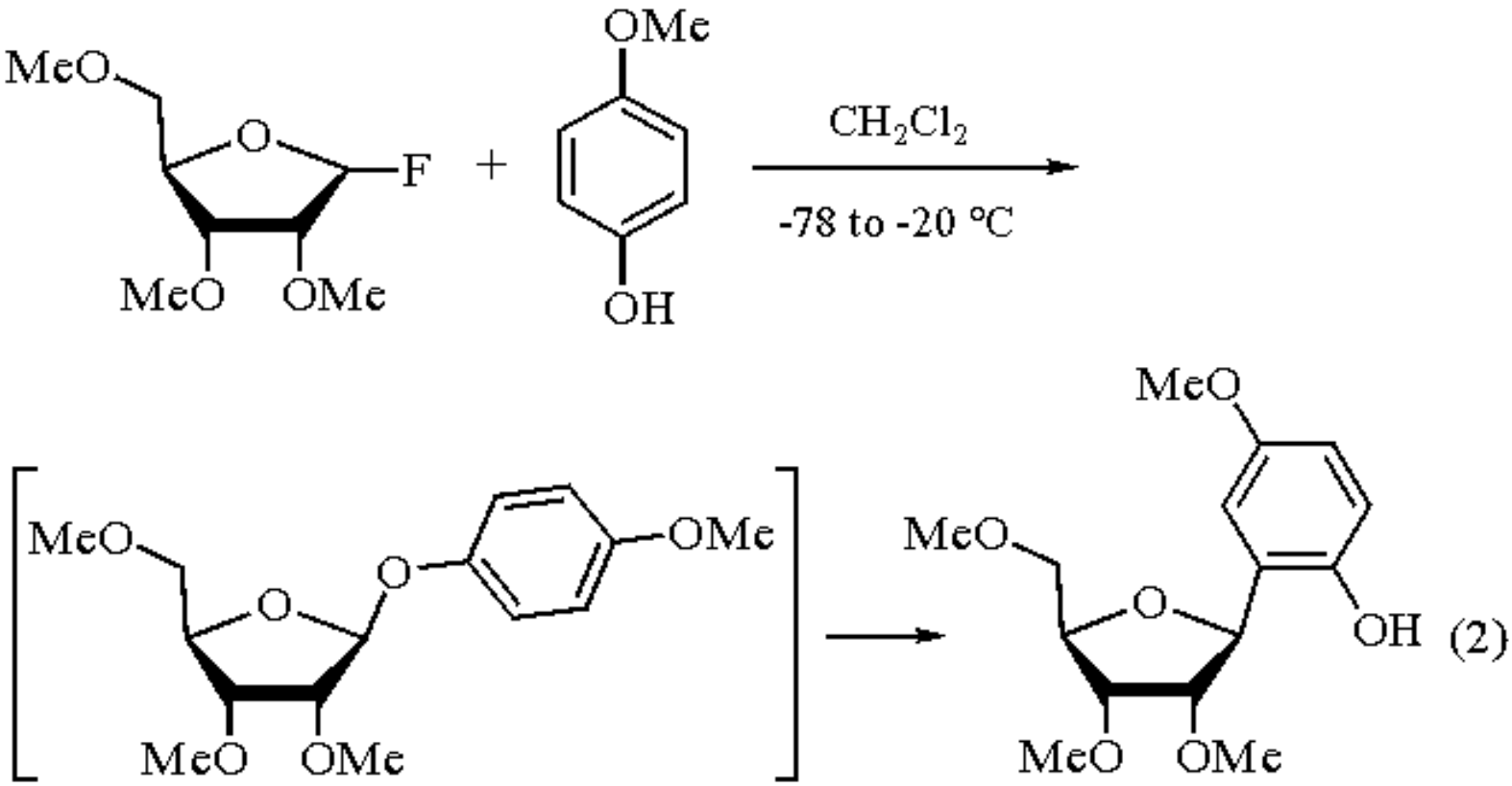

(3)

(2)

Cp_2HfCl_2-$AgClO_4$, 79% $\alpha:\beta = 1:9$
$BF_3 \cdot OEt_2$, 50% $\alpha:\beta = 1:1$ + **(3)** 41%

Both processes can be promoted by general Lewis acids, but Cp_2HfCl_2-$AgClO_4$ is prominent in terms of the reactivity and stereoselectivity. These features are well illustrated by their application in the total syntheses of vineomycinone

B_2 methyl ester (**4**)[7] and gilvocarcin M (**5**).[8] Donor solvents, such as Et_2O or MeCN, retard the second step, thereby providing a useful synthetic method for aryl *O*-glycosides.[3b]

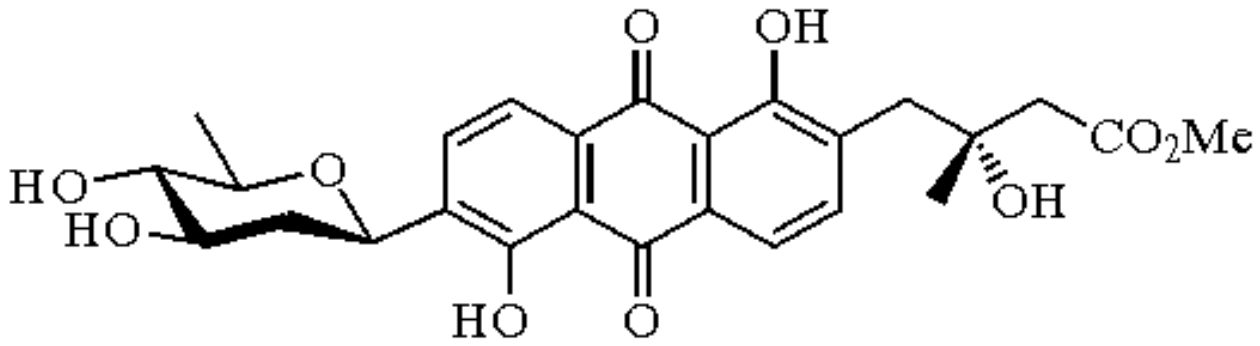

(4)

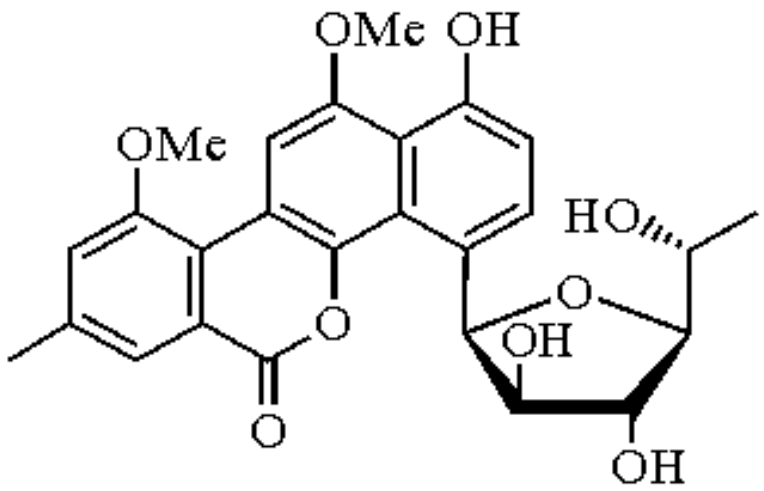

(5)

Cp_2HfCl_2-$AgClO_4$ is useful in nucleoside synthesis via the coupling of glycosyl fluorides and bis(trimethylsilyl)uracil (eq 3).[9]

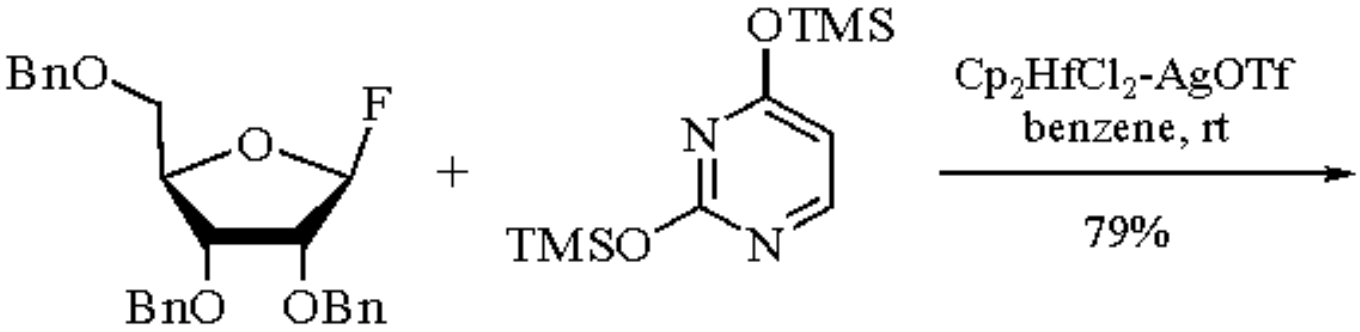

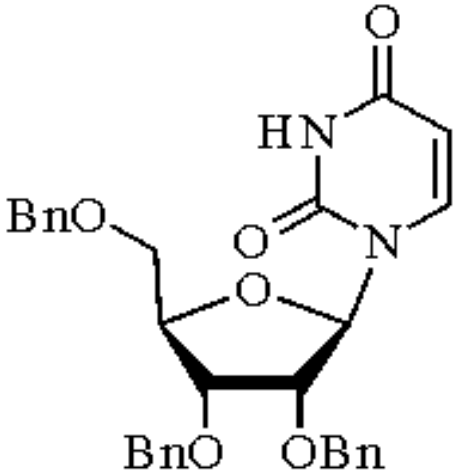

(3)

$\alpha:\beta = 5:95$

Related Reagents.

Dichlorobis(cyclopentadienyl)hafnium; ***Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts***.

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Dichlorobis(cyclopentadienyl)titanium[1]

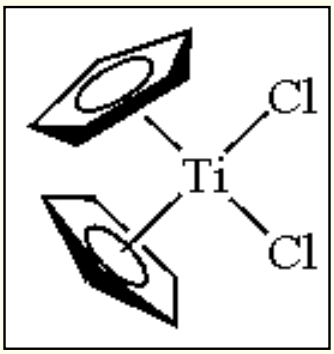

[1271-19-8] · $C_{10}H_{10}Cl_2Ti$ · Dichlorobis(cyclopentadienyl)titanium · (MW 248.98)

(used in hydrometalation and reduction; pinacol coupling reagent; carbometalation reagent; deoxygenation reagent; addition to carbonyls; Lewis acid catalyst; alkenation reagent)

Alternate Name: titanocene dichloride.

Physical Data: mp 289 °C; *d* 1.600 g cm^{-3}.

Solubility: sol toluene, chloroform, alcohol, and other hydroxylic solvents; sparingly sol water, petroleum ether, benzene, ether, carbon disulfide, carbon tetrachloride.

Form Supplied in: purple solid; commercially available.

Preparative Methods: see Wilkinson and Birmingham[2a] and Clearfield et al.[2b]

Handling, Storage, and Precautions: moisture sensitive; irritant; combustible.

Hydromagnesiation of Alkenes and Alkynes.[3]

Hydromagnesiation of alkynes, where metal hydride addition occurs with *syn* stereochemistry, can be carried out with *i*-BuMgCl and 1-10 mol % of Cp_2TiCl_2 (eq 1).[4] Eq 2 illustrates the hydromagnesiation product of a silylalkyne formed after equilibration, where the C-Mg bond is formed α to the silyl unit (or aryl group with aryl alkylalkynes)[5] and *syn* to the magnesium alkoxide (presumably because of heteroatom-metal coordination).[6] The carbon-metal bond may then be used in reactions with a variety of electrophiles (e.g. ketones, alkyl or allyl halides).[7] The synthesis of dihydrojasmone represents one of the applications of titanium-catalyzed hydromagnesiation.[7a]

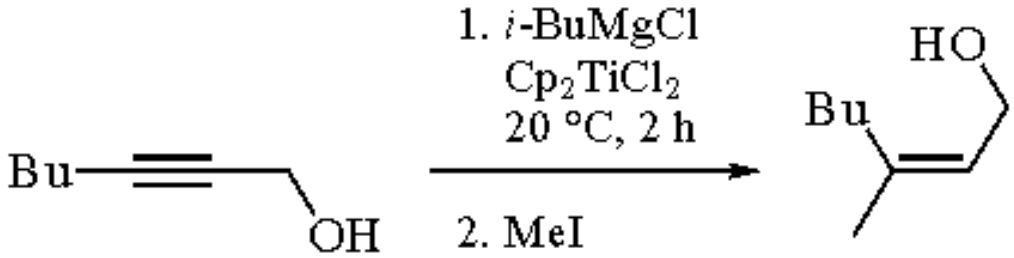

(1)

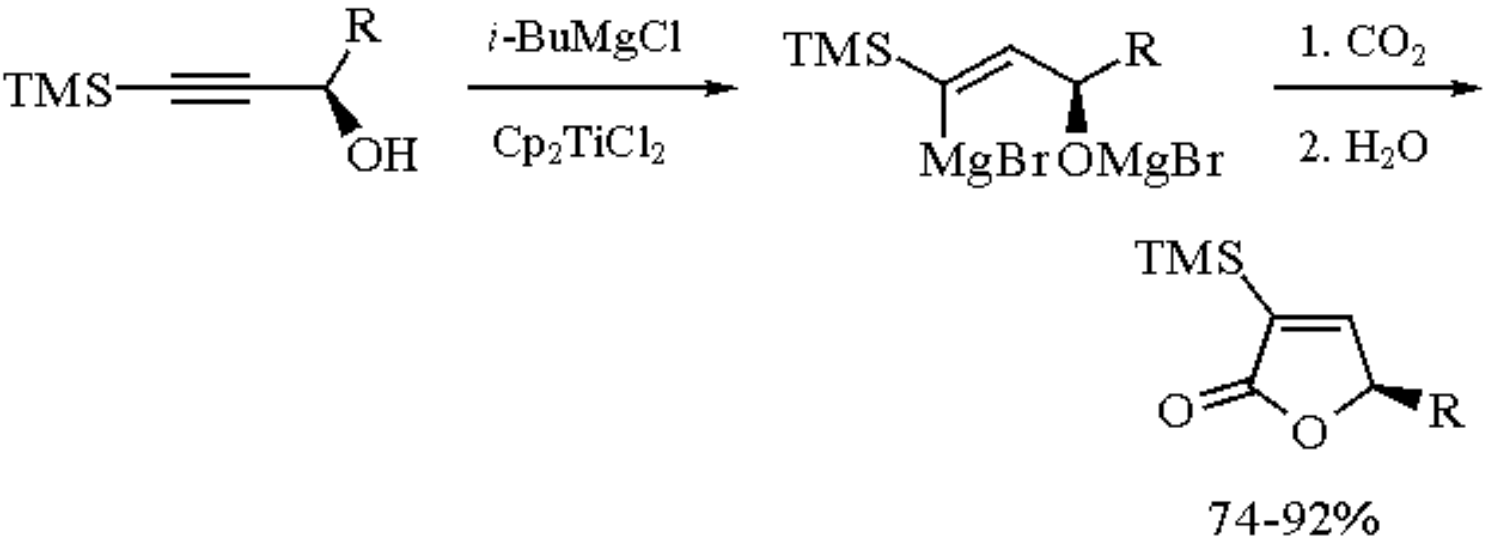

(2)

Hydromagnesiation of allylic and homoallylic alcohols is catalyzed by Cp_2TiCl_2 as well; however, this transformation is only operative with monosubstituted alkenes, wherein a primary C-Mg bond is generated (eq 3).[8] MgH_2 and 5 mol % Cp_2TiCl_2 have been used in the hydromagnesiation of terminal alkenes (>90% yield).[9] In addition, as shown below, Cp_2TiCl_2 catalyzes the hydrometalation of conjugated dienes to afford allyl Grignard reagents, which may then be utilized for further functionalization (eq 4).[10]

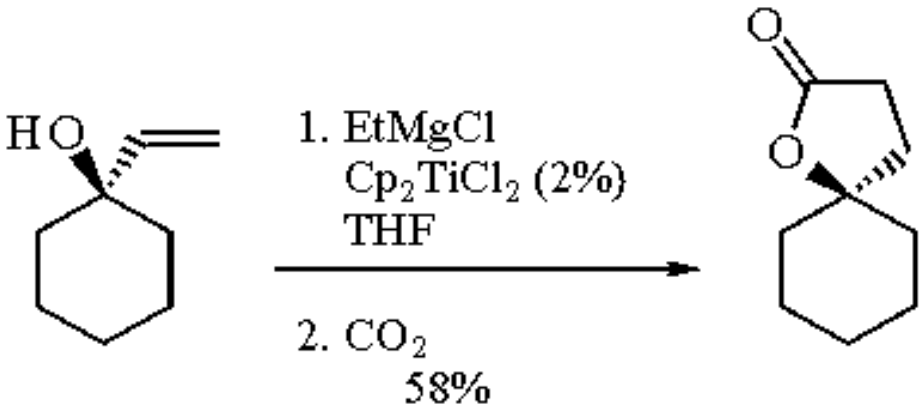

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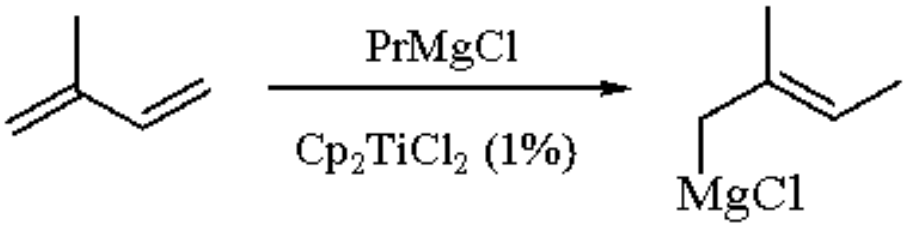

(4)

Hydroalumination of Alkenes.

Cp_2TiCl_2 is an effective catalyst for hydroalumination of mono- and disubstituted alkenes (representative aluminum hydrides: ***Bis(diisopropylamino)aluminum Hydride*** and ***Lithium Aluminum Hydride***).[11]

Hydrogenation Catalysts.

Titanocene dialkyls (formed by the addition of alkyllithiums to Cp_2TiCl_2) are effective alkene hydrogenation catalysts. Catalytic activity is enhanced when polymer-supported titanocene is used.[12]

Reduction of Carbonyls.

As shown in eqs 5 and 6, in the presence of 1-3 mol % of Cp_2TiCl_2, *i*-BuMgCl is an effective carbonyl-reducing agent.[13] Carboxylic acids and esters are reduced to aldehydes[14] and alcohols,[15] respectively. When methyl and ethyl Grignard reagents are employed, competing direct alkylation occurs. The proposed reducing agent is Cp_2TiH, and the reaction is most effective with saturated carbonyls. Aryl and benzylic acids are suitable substrates, whereas α,β-unsaturated acids are recovered unchanged.

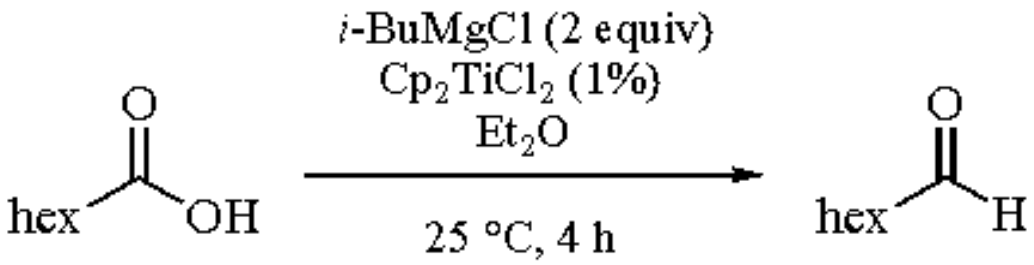

(5)

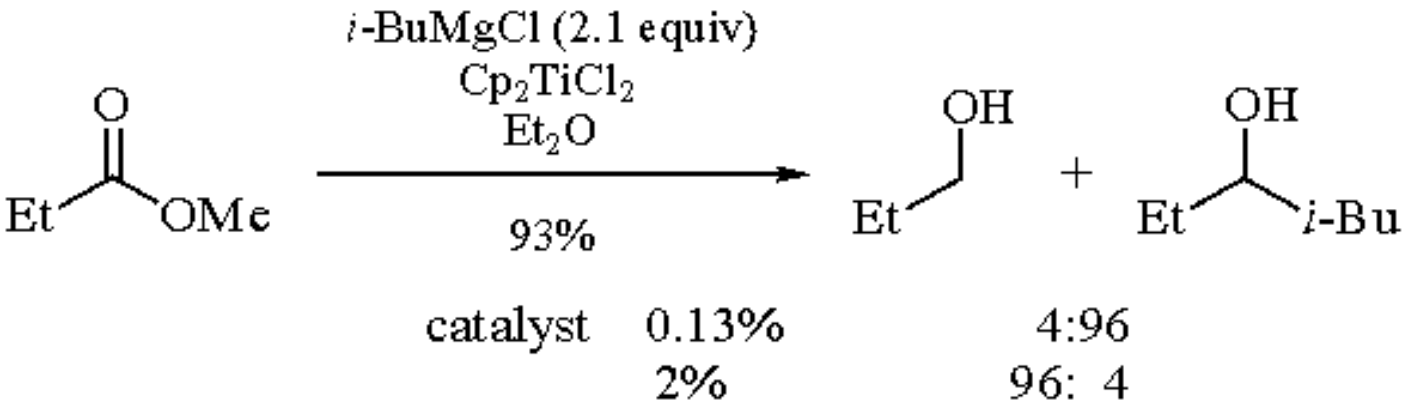

(6)

Reduction of Bromides.

Treatment of vicinal dibromides with 2 equiv of Cp_2TiCl_2 and excess ***Zinc*** affords the corresponding alkene in high yield (eq 7).[16] Alternatively, Cp_2TiCl_2 may be used catalytically (20 mol %) but longer reaction times are required. Stoichiometric amounts of Cp_2TiCl_2 and *i*-PrMgCl effect coupling of allylic and benzylic bromides (eq 8) and debromination of α-bromo ketones (eq 9).[17] In addition, debromination of aryl and vinyl bromides proceeds

selectively and quantitatively in the presence of catalytic amounts of Cp_2TiCl_2 (2-5 mol %) and excess *i*-PrMgCl (eq 10).[18] The proposed mechanism involves insertion of Cp_2TiH into the carbon-bromine bond, followed by reductive elimination of the product alkene.

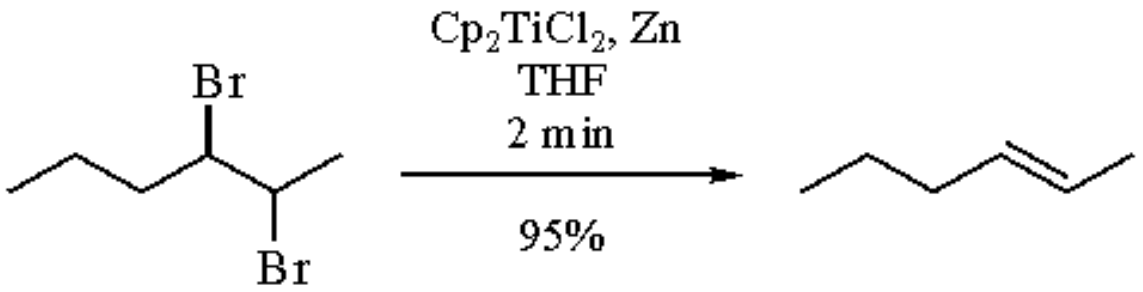

(7)

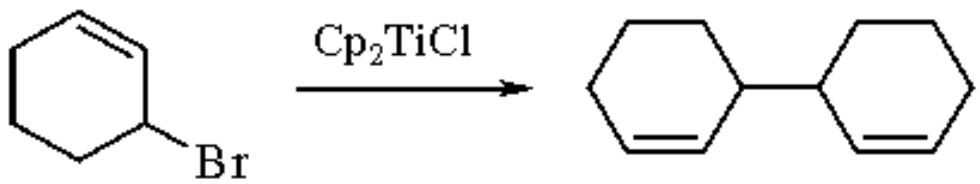

(8)

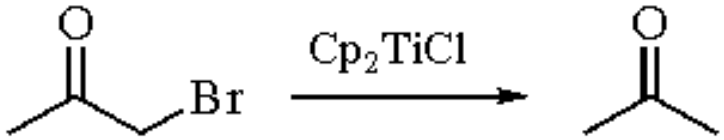

(9)

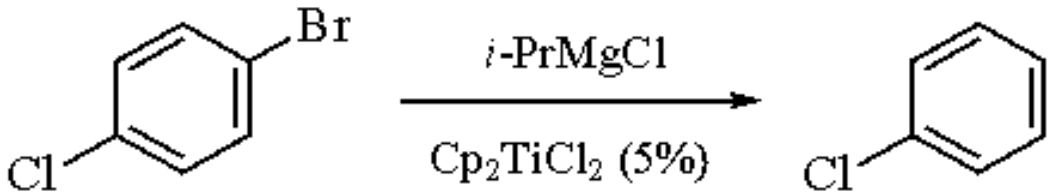

(10)

Pinacol Coupling Reactions.

Stereoselective pinacol coupling reactions can be effected by a complex derived from Cp_2TiCl_2 and *s*-BuMgCl[19] or ***Magnesium***.[20] Coupling of aromatic and α,β-unsaturated aldehydes typically provides >90% yield and >50:1 *threo*:*erythro* (eq 11), whereas saturated aldehydes are unreactive. Pinacol coupling with diaryl ketones has also been achieved;[21] the reaction is stoichiometric in Cp_2TiCl_2 and the active organometallic agent is believed to be a Ti^{III} species.

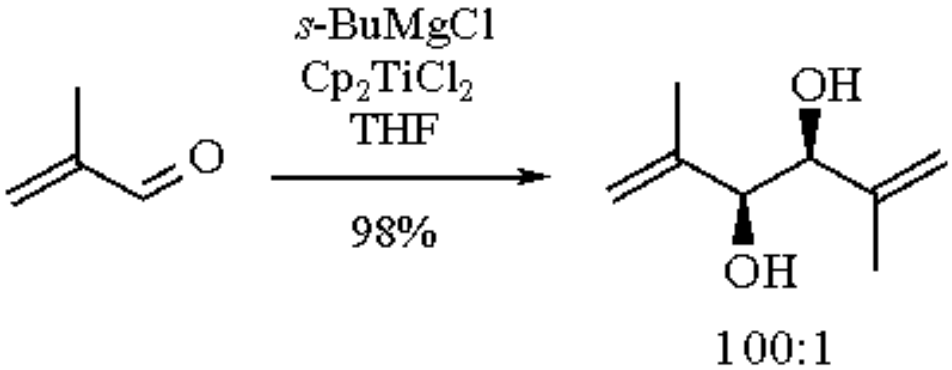

(11)

Carbometalation Reactions.

As shown in eq 12, reaction of *syn*-1,2-dimethyltitanacyclobutane with I_2 affords the corresponding alkyl iodide; subsequent intramolecular carbometalation affords *syn*-1,2-dimethylcyclopropane stereoselectively.[22] Reaction of Cp_2TiCl_2 with ***Trimethylaluminum***, ***Dimethylaluminum Chloride***, or ***Diethylaluminum Chloride*** and silyl alkynes[23] proceeds smoothly (25 °C, 2 h) to afford a carbon-metal bond α to the silyl group (eq 13).[24] Similar reactions with terminal alkenes afford 1,1-disubstituted alkenes (eq 14).[25] As shown in eq 15, selective formation of five- and six-membered ring carbocycles may be accomplished through an alkene or alkyne insertion into a carbon-titanium bond.[26]

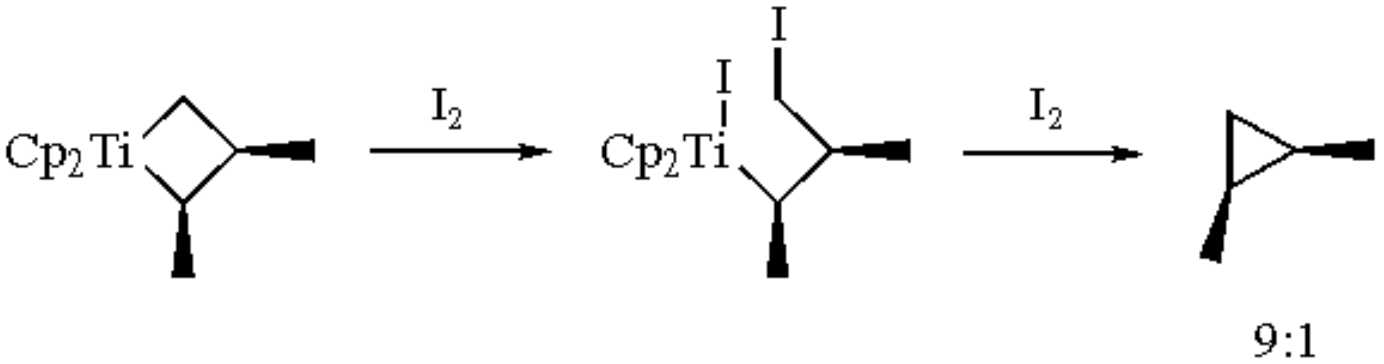

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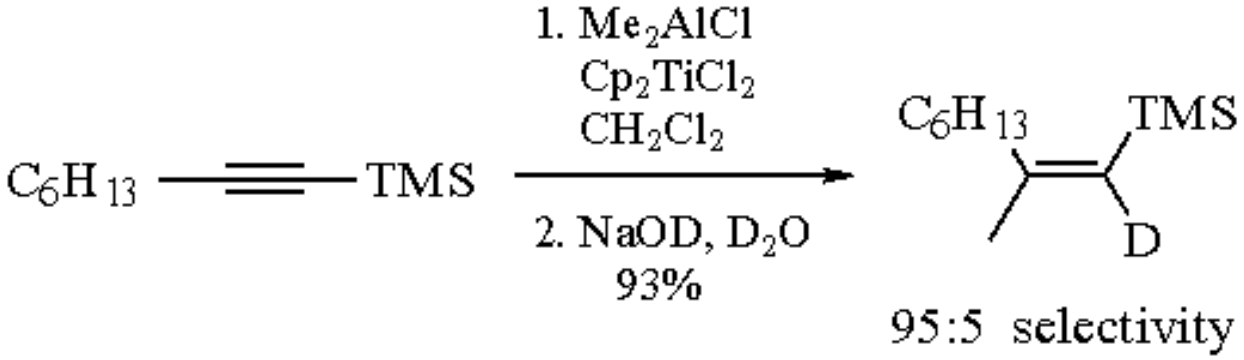

(13)

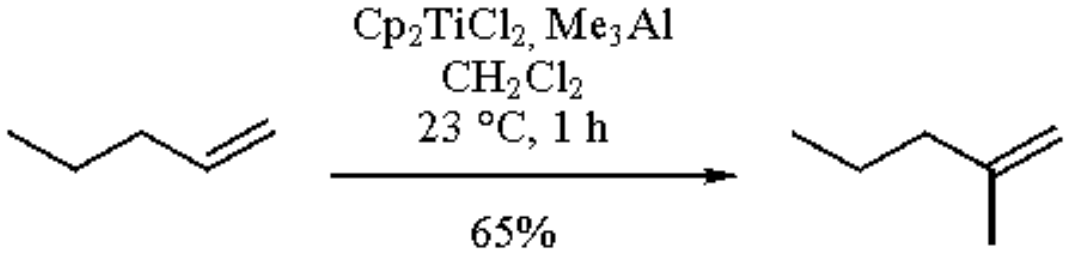

(14)

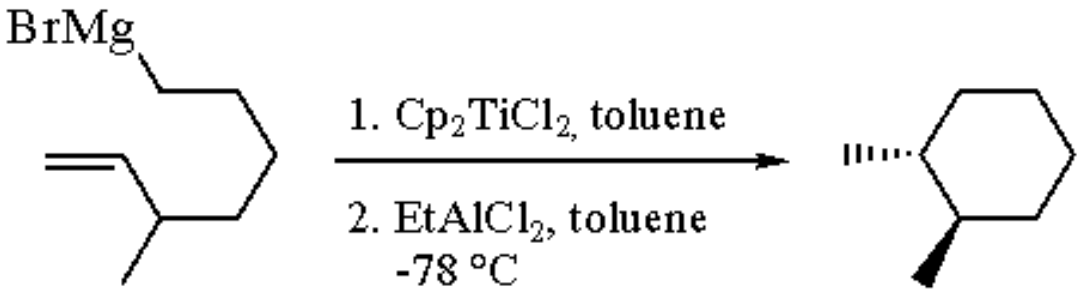

(15)

99:1

Cyclization of diynes and enynes to five- and six-membered rings has been effected by dibutyltitanocene (eq 16).[27] Such cyclization reactions are stoichiometric in Ti and may not be extended to dienes. As shown in eq 17, treatment of an epoxide with Cp_2TiCl (from Cp_2TiCl_2 and Zn powder) in the presence of an alkene results in alkene alkylation. This reaction has been carried out inter-[28] and intramolecularly.[29] The levels of stereocontrol for the intermolecular reactions are generally low (~2:1). Cp_2TiCl_2 and *i*-PrMgBr catalyze the intramolecular cyclization reaction of 1,5-dienes (eq 18;[30] these transformations proceed only when the two alkenes are monosubstituted.

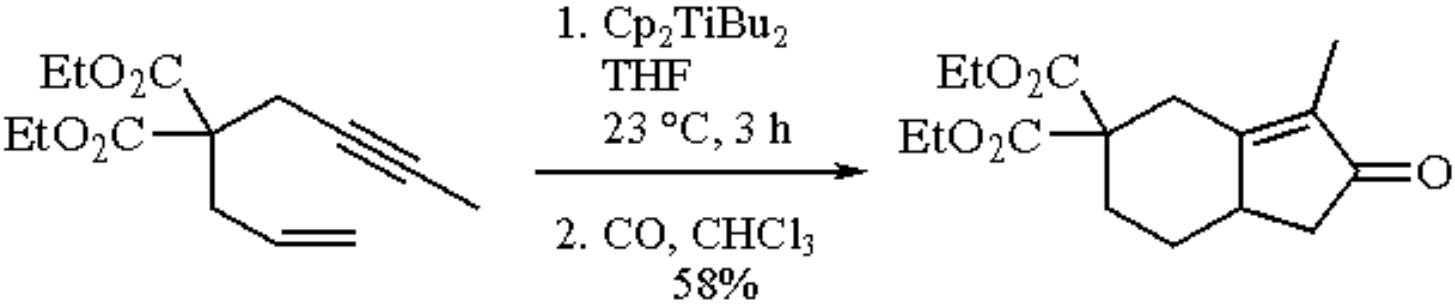

(16)

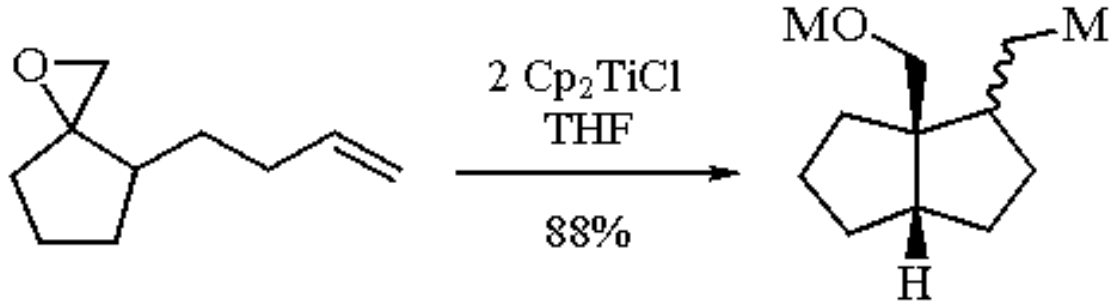

(17)

M = Cp_2TiCl

endo:*exo* = 90:10

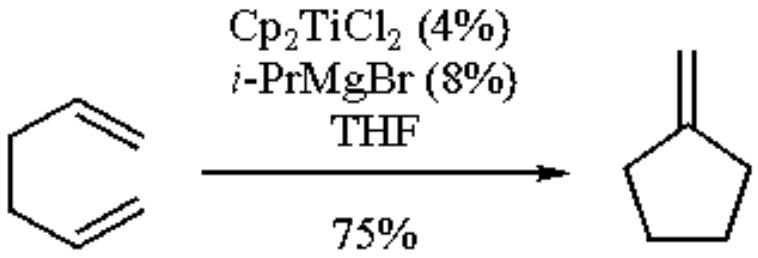

(18)

Deoxygenation Reactions.

As shown in eqs 19 and 20, treatment of aldehydes, esters, and epoxides with Cp_2TiCl_2 (10 equiv, pretreated with Na sand) affords deoxygenated adducts in good yields.[31] The titanocene reagent is ineffective when alcohols, alkoxides, or acyclic ethers are employed as substrates. A complementary reductive deoxygenation for diaryl and aryl alkyl ketones and alcohols has also been reported (eq 21).[32]

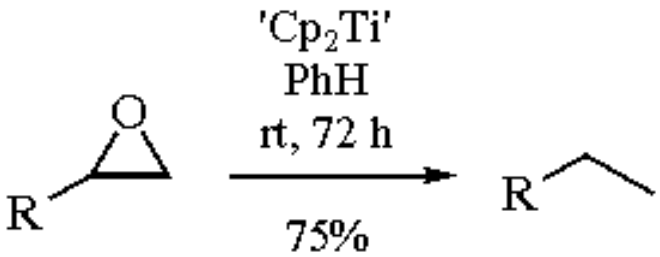

(19)

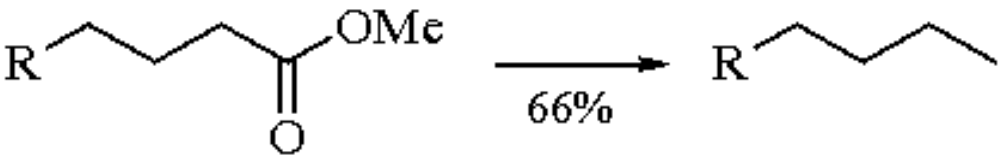

(20)

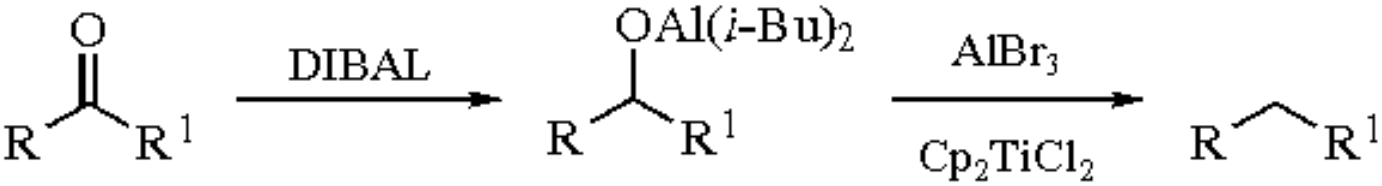

(21)

Cp_2TiCl cleaves epoxides by a radical mechanism, affording the regiochemistry opposite to that obtained from the corresponding nucleophilic epoxide opening. In addition, as illustrated in eq 22, depending on the reaction conditions, various epoxides may either be regioselectively converted to the alcohol, or reduced to the derived alkenes.[33]

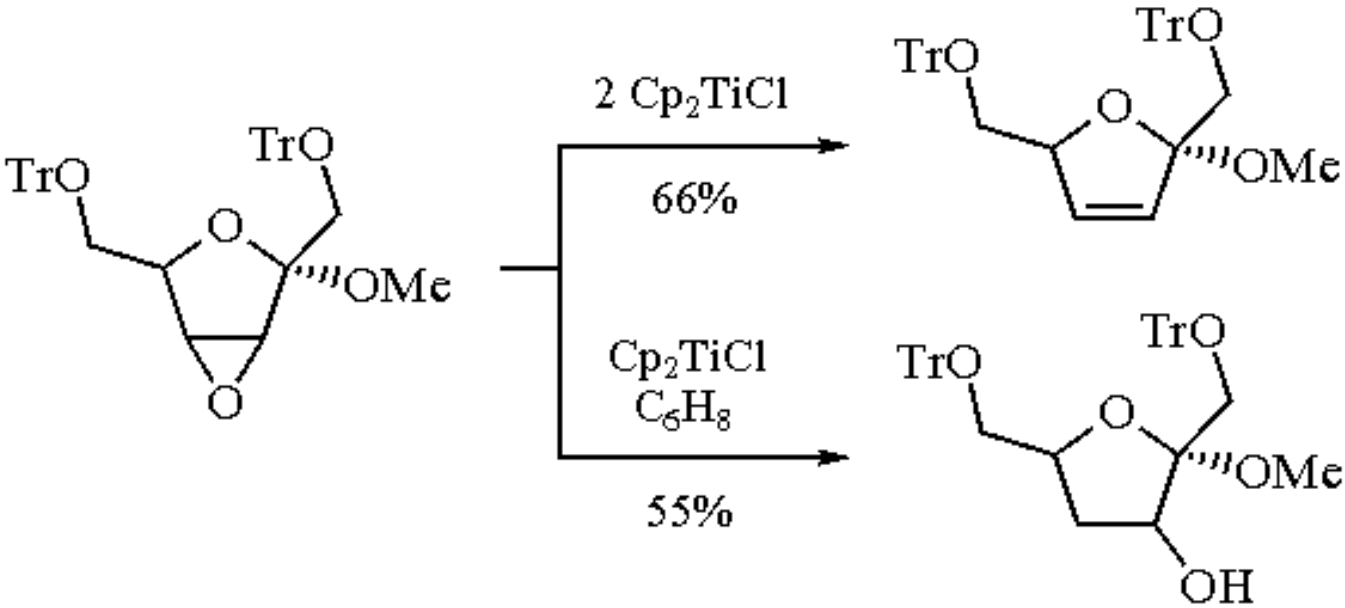

(22)

Addition of Alkyl Titanocenes to Carbonyls.

Alkylation of aldehydes and ketones with π-allyltitanium complexes (stoichiometric, eq 23) formed from Cp_2TiCl_2 and various dienes (see eq 4) affords *anti* homoallylic alcohols selectively.[34] Such π-allyltitanium reagents do not react with esters or alkyl halides. Similar alkylation reactions have been carried out with trimethylsilyl[35] and 1,3-disubstituted allyl anions.[36] Addition to aldehydes (eq 24) followed by hydroxy-silyl elimination yields *cis,trans* or *trans,trans* alkenes (basic or acidic conditions, respectively).

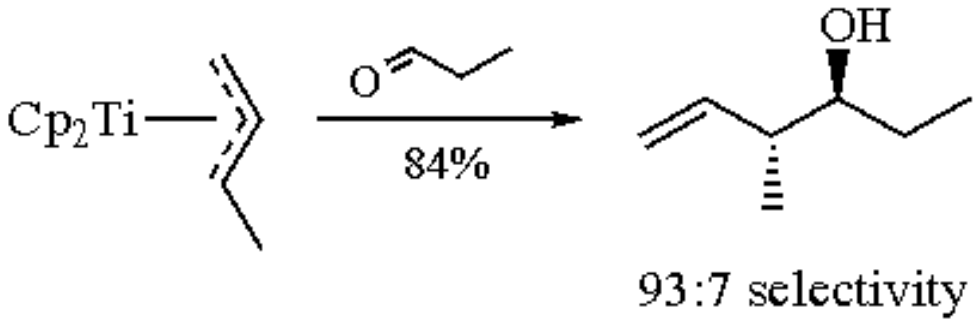

(23)

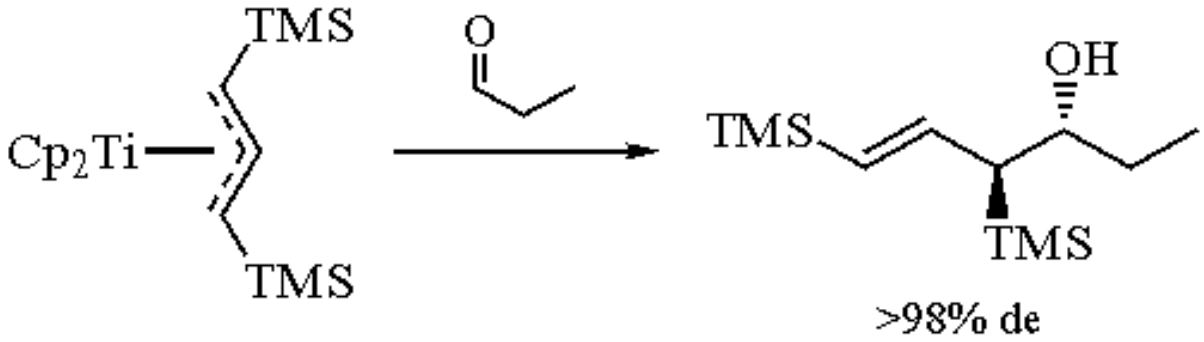

(24)

Lewis Acid Catalysis with Titanocene Derivatives.[37]

$[Cp^*_2Ti(H_2O)_2](CF_3SO_3)_2$, a readily made derivative of $Cp^*_2TiCl_2$,[38] is an effective catalyst (1%) for Diels-Alder cycloadditions (eq 25); these cycloadditions may be carried out in the presence of water. $Cp_2Ti(CF_3SO_3)_2$ (made from Cp_2TiCl_2 and ***Silver(I) Trifluoromethanesulfonate*** catalyzes aldol reactions as well.[39]

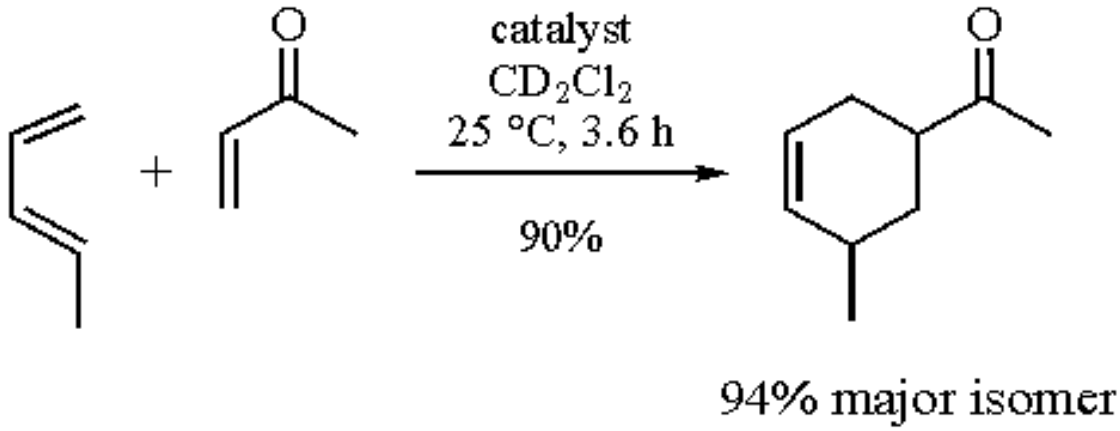

(25)

Alkenation Reactions.

Me_3Al addition to Cp_2TiCl_2 affords an Al-Ti bimetallic complex (Tebbe's reagent, see ***μ-Chlorobis(cyclopentadienyl)(dimethylaluminum)-μ-methylenetitanium***) which has been used for methylenation of ketones, esters (eq 26), and alkenes.[40] A variety of alkyl groups have been used on titanium to achieve similar alkenations.[41]

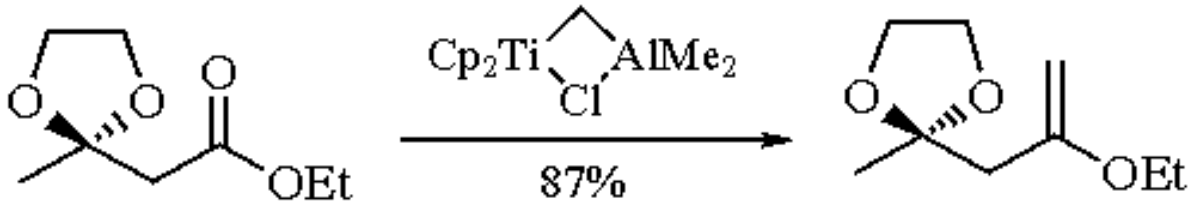

(26)

Titanocene dichloride reacts with $CH_2(MgBr)_2$ to yield a magnesium analog of Tebbe's reagent; the Mg complex is used to convert alkenes and alkynes to the derived titanacyclobutanes and -butenes, respectively.[42] The combination of alkenation of carbonyls and formation of titanacyclobutanes leads to the synthesis of substituted allenes (eq 27), where stoichiometric amounts of the titanacyclobutane are utilized.[43] Titanacyclobutane has been shown to serve as a catalyst for ring opening metathesis polymerization reactions.[44]

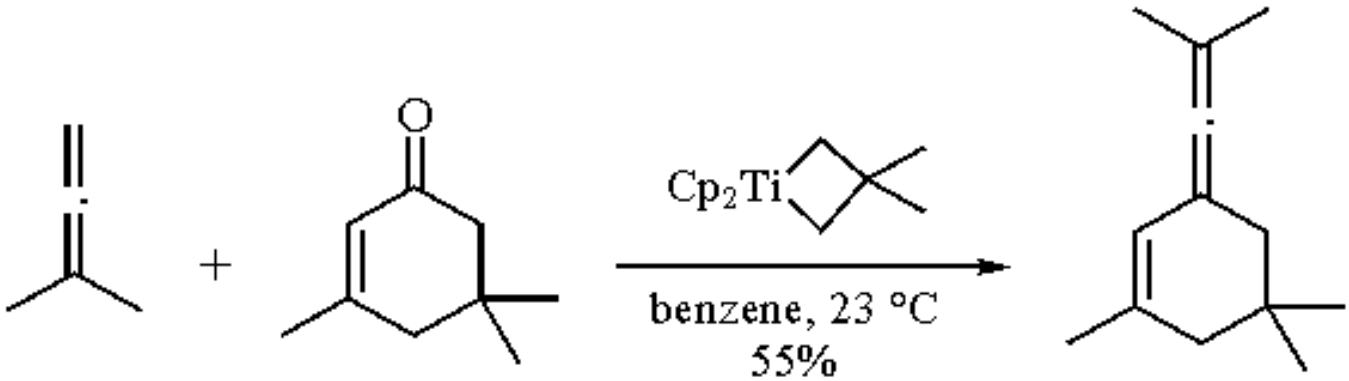

(27)

Nitrogen fixation reactions have been accomplished with various titanocene systems. For example, titanocene-benzyne complexes react with molecular nitrogen to provide aniline and NH_3, albeit in low yield.[45]

---

1. For a recent discussion of chemistry of chiral titanocene complexes, see: (a) Halterman, R. L. *CRV* **1992**, *92*, 965. For a discussion of chemistry of noncyclopentadienyl Ti complexes, see: (b) Duthaler, R. O.; Hafner, A. *CRV* **1992**, *92*, 807. For a review of low valent Ti complexes (carbonyl coupling), see: (c) McMurry, J. E. *CRV* **1989**, *89*, 1513. For Cp_2TiCl_2 and Et_2AlCl catalysis of Ziegler-Natta type polymerizations, see: (d) Benedek, I. *Stud. Cercet. Chim.* **1973**, *21*, 263. For general references to Ti-mediated or -catalyzed reactions, see: (e) Sato, F. *Fundamental Research in Homogeneous Catalysis*; Plenum: New York, 1978, vol. 2, p 81. (f) Pearson, A. J. *Metallo-Organic Chemistry*; Wiley: Chichester, 1985. (g) Wailes, P. C.; Coutts, R. S. P.; Weigold, H. *Organometallic Chemistry of Titanium, Zirconium and Hafnium*; Academic: New York, 1974.
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Dichlorobis(cyclopentadienyl)zirconium[1]

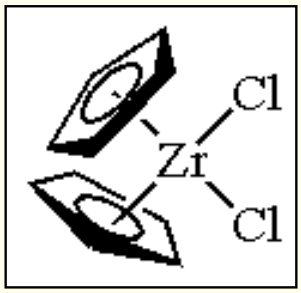

[1291-32-3] · $C_{10}H_{10}Cl_2Zr$ · Dichlorobis(cyclopentadienyl)zirconium · (MW 292.32)

(good starting material to prepare many kinds of zirconocene(II or IV) derivatives;[2] in combination with organometallics (Al, Zn, or Mg) it is a catalyst for stereo- and regioselective alkylation of unsaturated compounds;[3] in combination with an Ag^I salt (AgX; X = ClO_4, OTf, BF_4) it is an effective activator for glycosyl fluorides; in combination with MAO, it is a good catalyst for polymer synthesis[4])

Physical Data: mp 247-249 °C; sublimes at 150-180 °C.

Solubility: sol aromatic solvents, chloroform; slightly sol THF, ether; insol hexanes.

Form Supplied in: colorless crystals; widely available.

Analysis of Reagent Purity: ^{1}H NMR (THF-d_8) δ 6.62 (s, C_5H_5).

Handling, Storage, and Precautions: the dry solid is reasonably stable to air and moisture and can be handled in the ordinary manner. However, it should be stored in a tightly sealed nitrogen-flushed bottle.

Hydrozirconating Agent.

Cp_2ZrCl_2 is a very important starting material for the preparation of Zr^{IV} and Zr^{II} derivatives. Cp_2ZrCl_2 is a key compound for the preparation of the so called Schwartz reagent (***Chlorobis(cyclopentadienyl)hydridozirconium***),[5] which is a versatile hydrozirconating agent. Among the methods for reduction of Cp_2ZrCl_2,[6] an economical method for the isolation (eq 1)[7] and a method for the generation[8] of Cp_2ZrHCl in situ (eq 2) are recommended for organic synthesis.

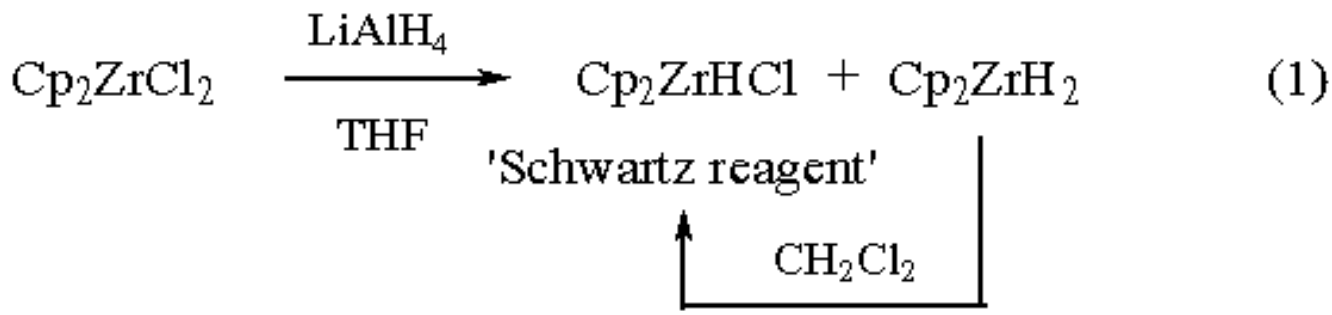

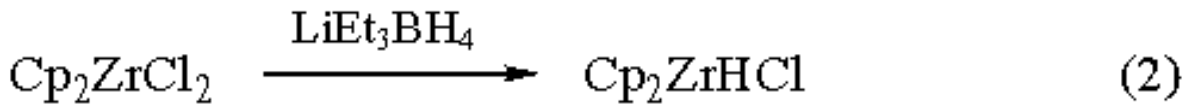

Transmetalation.

Transmetalation of Cp_2ZrCl_2 with organometallics containing lithium, sodium, potassium, and magnesium appears to be a general method to prepare Cp_2ZrR_2 (R =alkyl, allyl, benzyl, alkenyl, aryl, and alkynyl). The reaction of 1 mol of organometallic with 1 mol of Cp_2ZrCl_2 to produce Cp_2ZrRCl requires precise reaction conditions and judicious choice of organometallic to avoid the formation of Cp_2ZrR_2 (eq 3). One example of the importance of reaction conditions and the ligand to obtain a Cp_2ZrRCl-type compound is seen in a contrasting pair of reactions (eqs 4 and 5).[9]

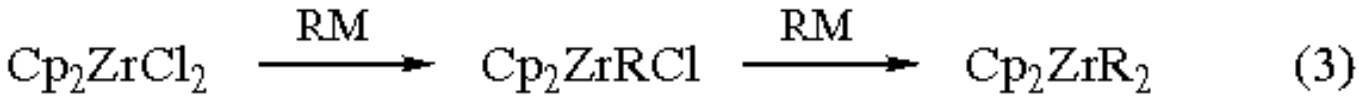

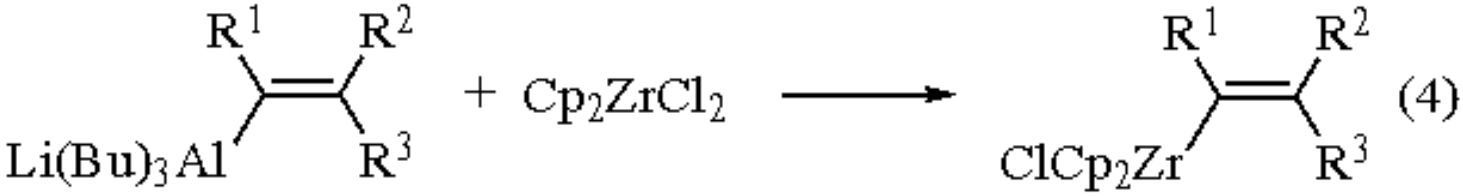

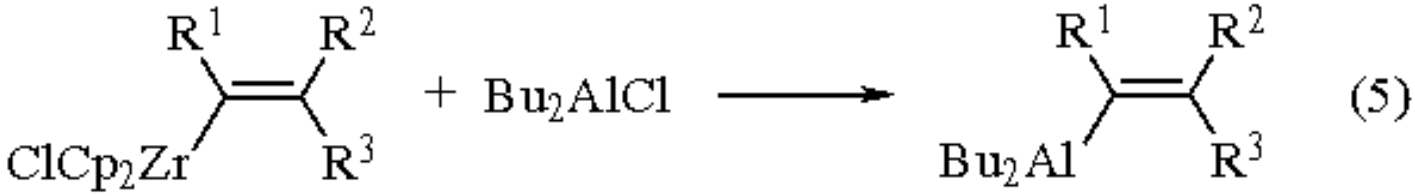

Carbometalation Catalyst.

In a valuable synthetic transformation, stereo- and regioselective addition of organometallics to unsaturated compounds can be catalyzed by Cp_2ZrCl_2 to give carbometalated compounds. Reaction of terminal or internal alkynes with organoaluminum in the presence of Cp_2ZrCl_2 gives the *syn* addition products (>98%) in good to excellent yields (eq 6).[10] The reactions of terminal alkynes with ***Trimethylaluminum*** are regioselective, with the addition of the methyl group to the internal carbon (95%), but the regioselectivity drops to the 75-85% range for other alkyl groups.

Although addition of organozinc can also be catalyzed by Cp_2ZrCl_2, higher yields are obtained using Cp_2ZrI_2 (eq 7).[11] These regio- and stereoselective carbometalations have been applied to the synthesis of natural products.[12] Interestingly, in the Cp_2ZrCl_2-catalyzed carboalumination, the addition of 1-2 equiv of water to the reaction mixture significantly increases the rate of the carboalumination.[13] The effect of the added water is considered to be due to formation of an oxo-bridged dimer and not to formation of methylaluminoxane, which is a cocatalyst for the polymerization of α-alkenes. When an alkyl group of R_3Al has β-hydrogens, hydroalumination via hydrozirconation becomes a serious side reaction.[14] It can, however, be suppressed by the use of the R_2AlCl-Cp_2ZrCl_2 reagent system. With *i*-Bu_3Al and Cp_2ZrCl_2, a clean hydroalumination is observed.[15]

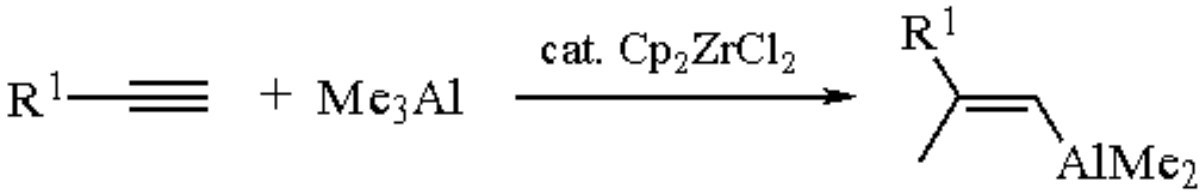

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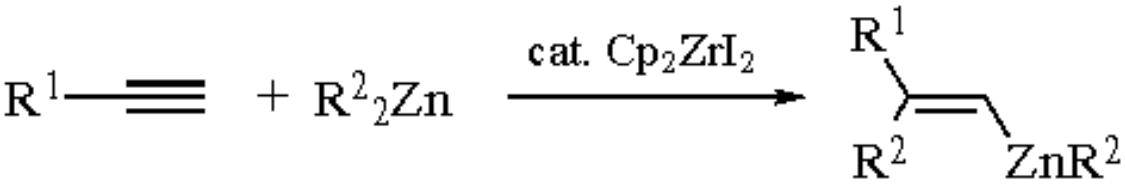

+ regioisomer (7)

Carbometalation of alkenes catalyzed by Cp_2ZrCl_2 proceeds using aluminum (eq 8) and/or magnesium reagents (eq 9). The carbomagnesation reaction of alkenes is known to proceed through a totally different process from that of the carboalumination of alkynes (eq 10).[16] That is, prior formation of a zirconocene-ethylene complex by the reaction of Cp_2ZrCl_2 with ***Ethylmagnesium Bromide*** and the subsequent coupling reaction with vinyl compounds has been confirmed. The stereochemistry and rate of ethyl magnesation are influenced by the presence of an allylic or homoallylic oxygen functionality (eqs 11 and 12).[17]

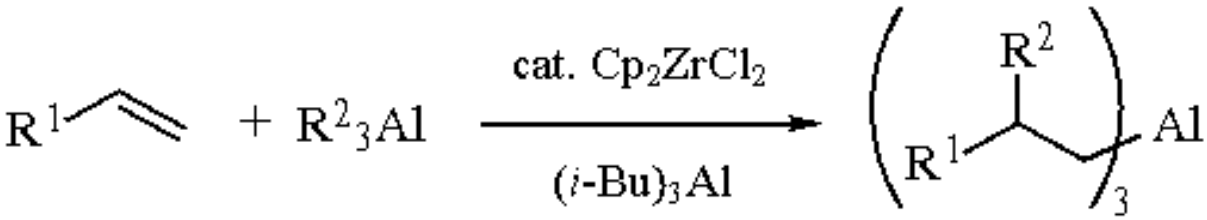

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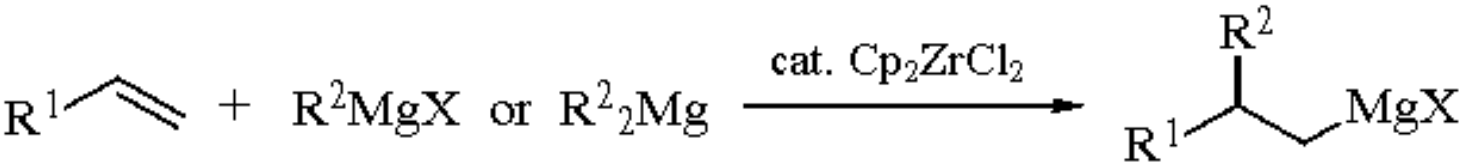

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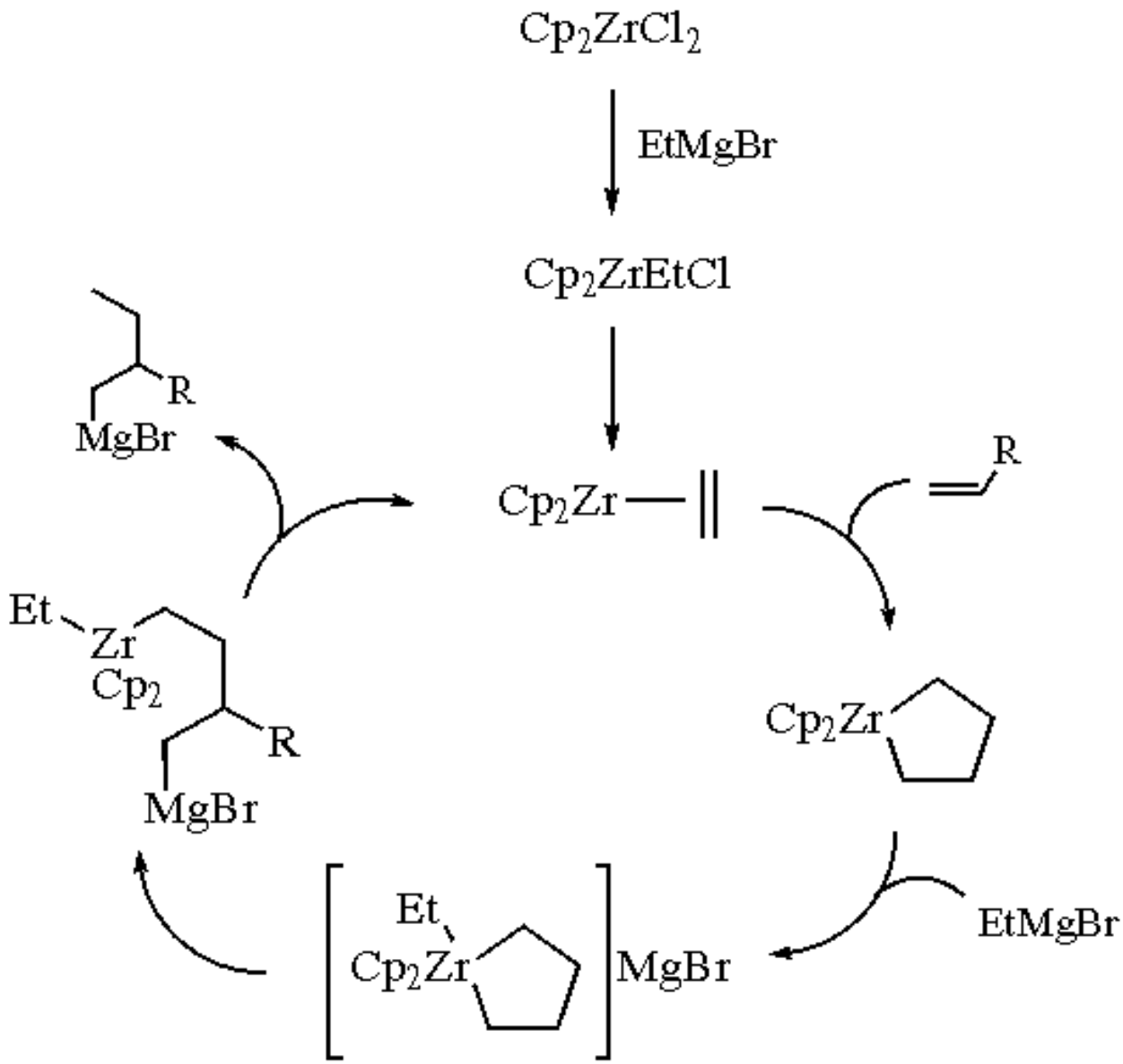

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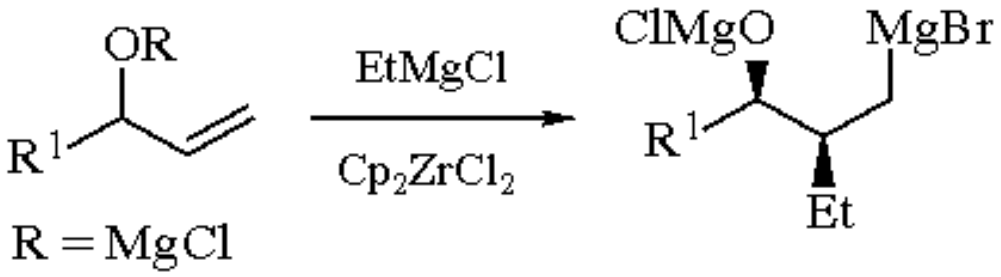

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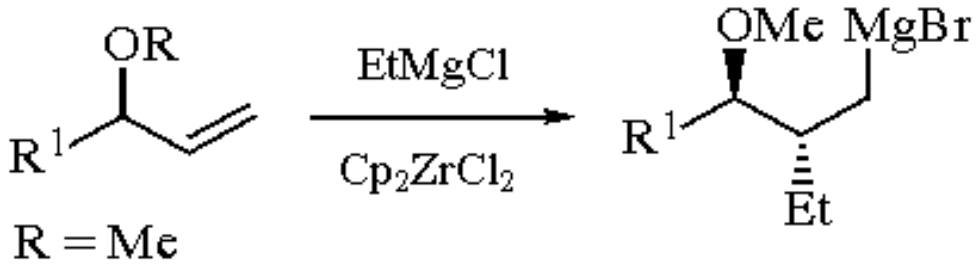

(12)

Generation of Cp_2Zr and its Equivalent.

Generation of Cp_2Zr can be achieved by reduction of Cp_2ZrCl_2 with ***Magnesium-Mercury(II) Chloride*** (eq 13)[18] or 2 equiv ***n-Butyllithium*** (eq 14).[19] The latter method is recommended since the metal reduction of Cp_2ZrCl_2 is prone to a side reaction leading to Zr^{III} species.[20] Low valent Zr^{II} generated with 2 equiv *n*-BuLi exists as a Cp_2Zr-butene complex (eq 15). The Cp_2Zr-butene complex reacts with a series of unsaturated compounds (alkynes, alkenes,[10b,21] imines,[22] and azadienes[23]) through a ligand exchange process to give the desired zirconocene complexes (eqs 16 and 17). Therefore the Cp_2Zr-butene complex is often called zirconocene equivalent (Cp_2Zr). When the reaction of Cp_2Zr with an unsaturated compound is hampered by the presence of the butene, which is released in situ by ligand exchange, use of ***t-Butyllithium*** instead of *n*-BuLi is recommended.[24] The isobutene generated in situ by ligand exchange in the modified procedure is much less reactive than butene toward the Cp_2Zr-substrate complex. The Cp_2Zr equivalent is largely applied to bicyclizations of nonconjugated dienes, enynes, and/or diynes (eq 18).[21] These Cp_2Zr-promoted cyclizations, which proceed with high regio- and stereoselectivity,[25] have been applied to the syntheses of many natural products.[26]

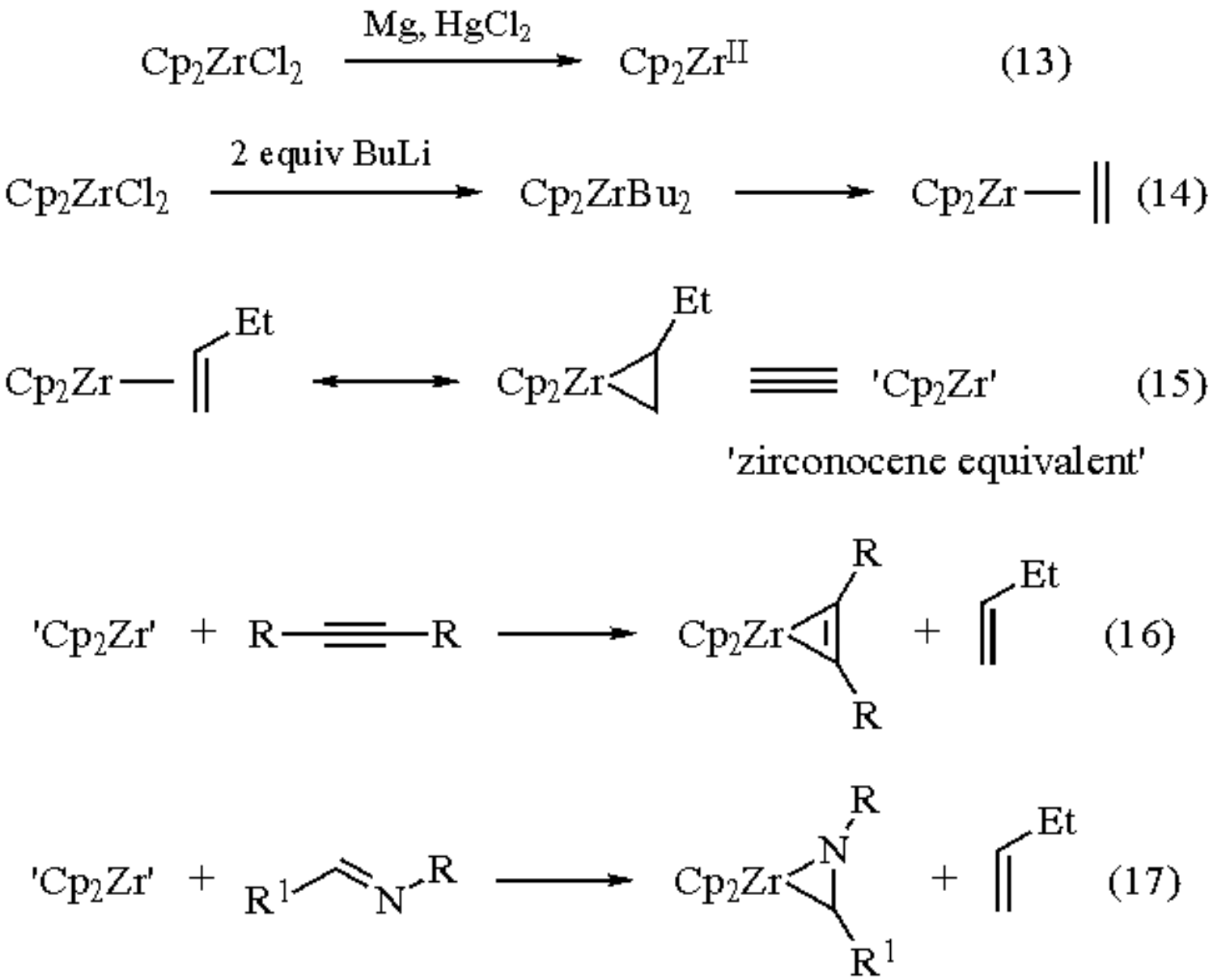

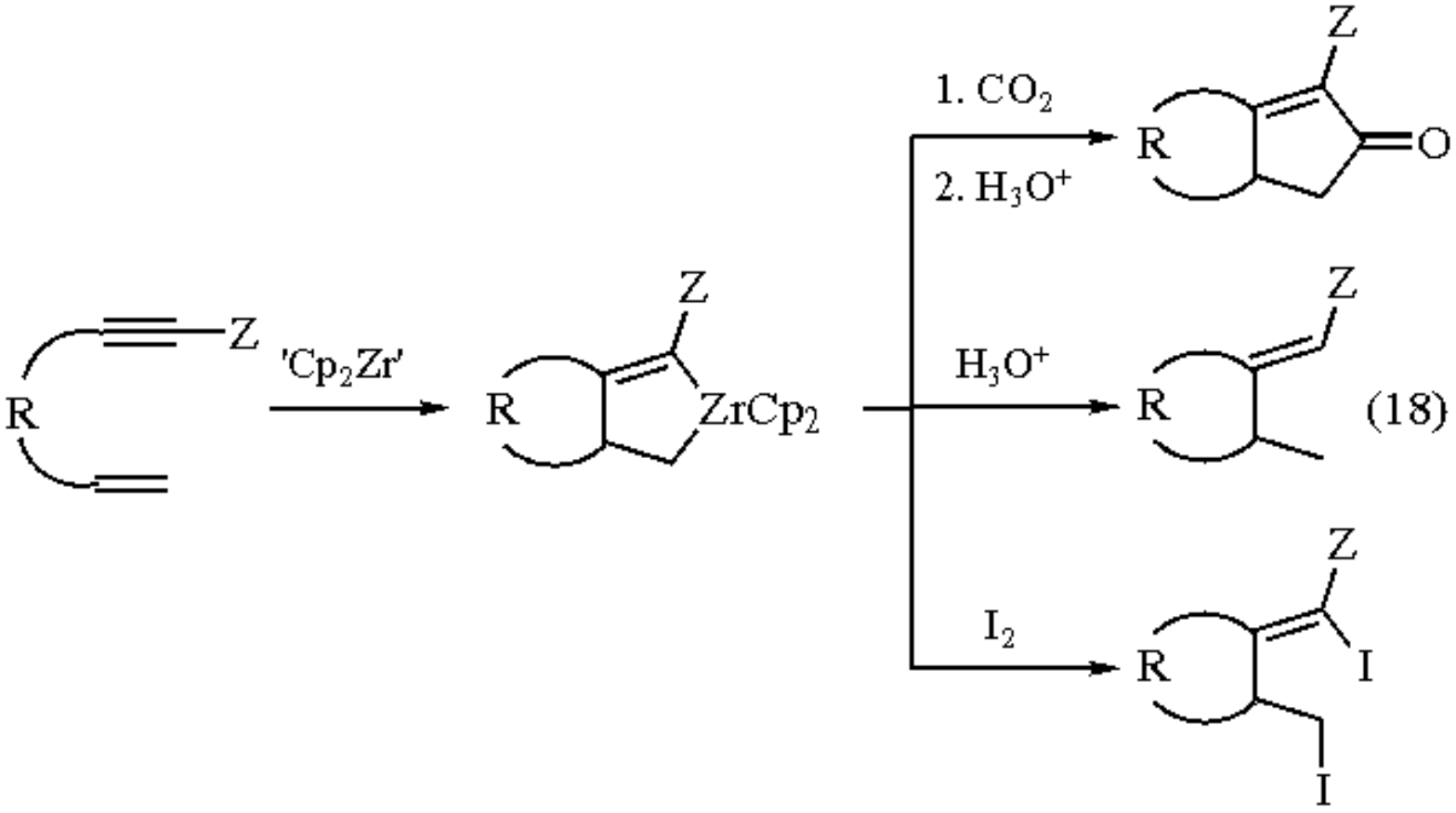

(18)

Apart from the Cp_2Zr-mediated cyclization chemistry, various allylic zirconium derivatives can be generated from allylic ethers and Cp_2Zr (eq 19).[27] This process is a result of the initial formation of zirconacyclopropane and the subsequent elimination of a β-alkoxyl group. In a similar way, the generation of allenic[28] and γ-alkoxyallylic[29] zirconium has been achieved from propargylic ethers and acrolein diethyl acetal, respectively. Allylic zirconium derivatives can also be generated in situ by the metal-exchange reaction of allylic Grignard reagents with Cp_2ZrCl_2.[30] The reactivity of these allylic or allenic zirconium species towards carbonyl compounds is much larger than that of other alkyl zirconocene derivatives. In general, the nucleophilic reactivity of the organozirconium compound having a cyclopentadienyl ligand is low. The Cp_2ZrCl_2/2 mol *n*-BuLi reagent, which generates the zirconocene equivalent in situ, is also applicable as a efficient catalyst in the hydrosilylation of alkenes,[31] Tishchenko reaction[32] of aldehydes, and a cross-aromatization of cyclohexanone derivatives.[33]

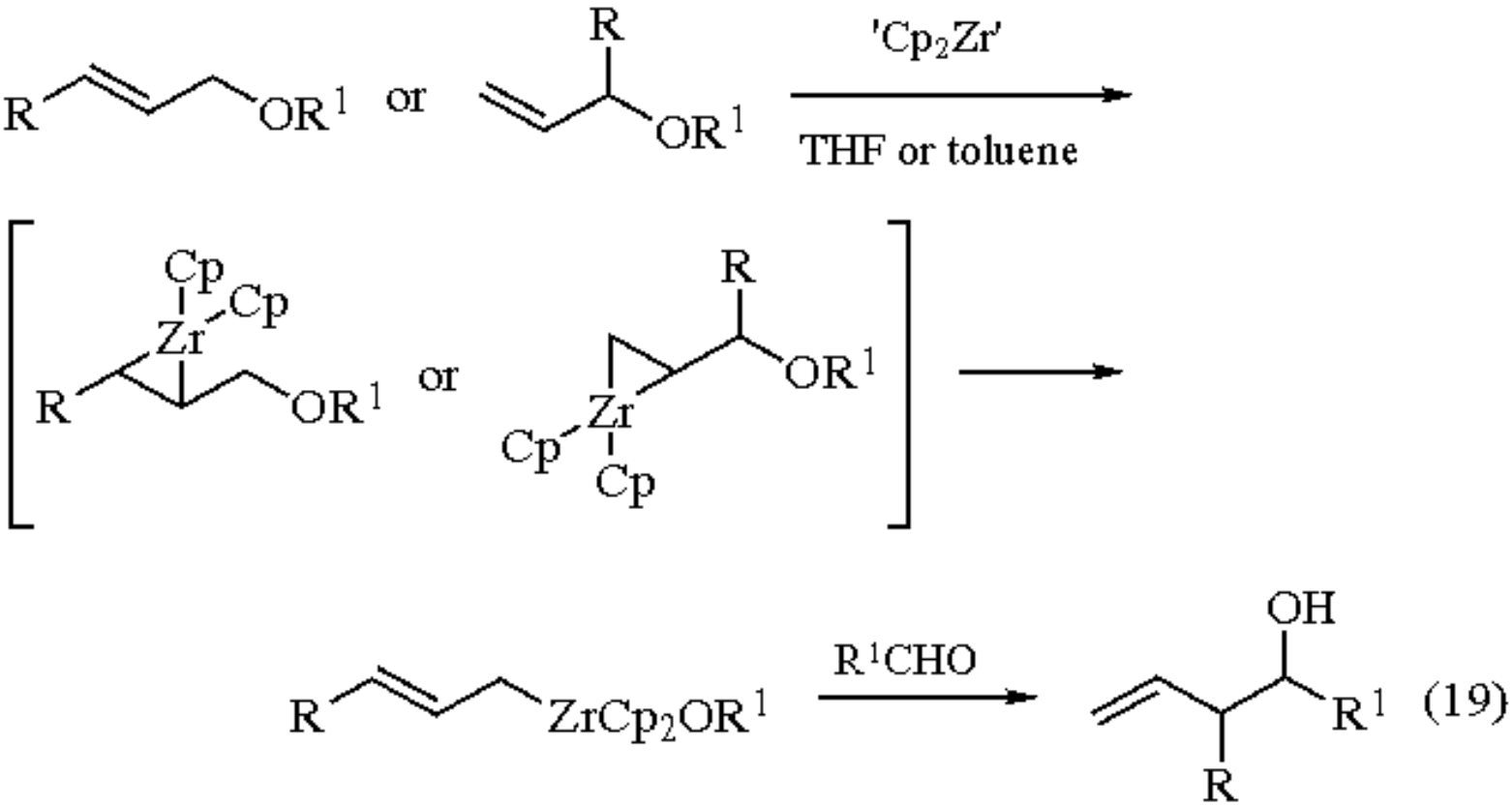

Zirconium Enolate.

Cp_2ZrCl_2 is often used to generate very important metal enolates. Zirconocene enolates generated in situ from lithium enolates of carbonyl compounds play a very important role in the stereoselectivity of the products in the crossed aldol reaction (eq 20)[34] and [2,3]-Wittig rearrangements (eq 21).[35] In the aldol reactions a zirconium enolate reacts with carbonyl compounds to give aldol products in a highly *erythro* selective manner regardless of the geometry of the enolate. The rationale for the excellent selectivity in these reactions can be explained by the σ-bond angle, geometry of the coordination site, and the oxophilic nature of zirconocene(IV) derivatives.[36]

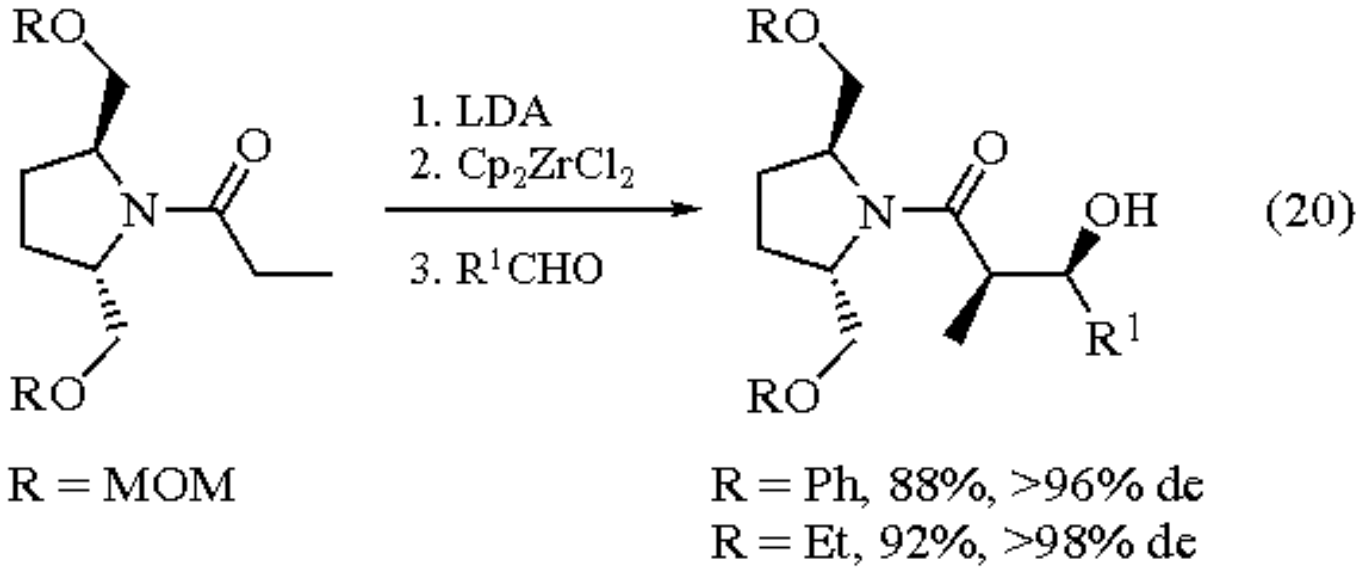

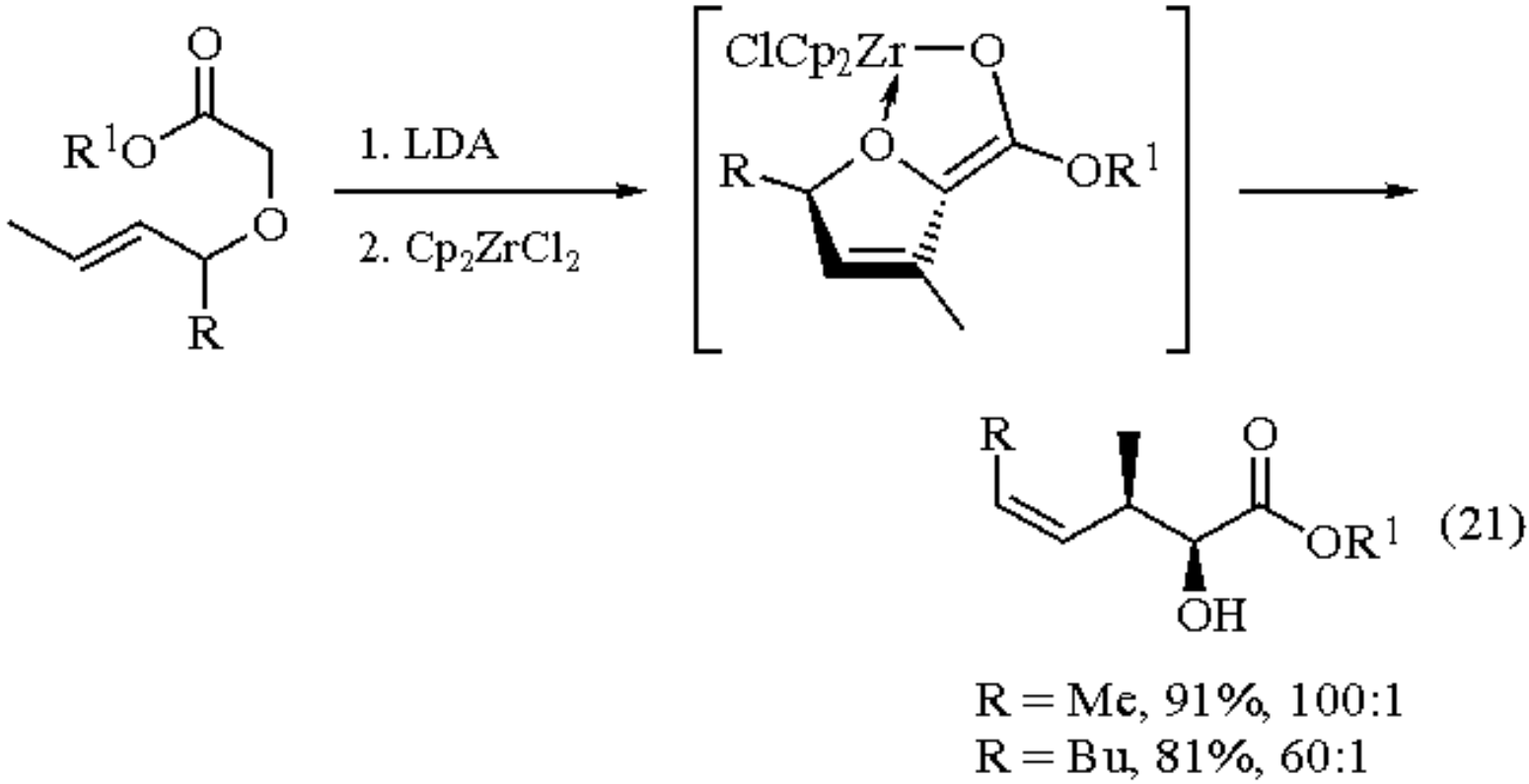

Glycosidation.

The combination of Cp_2ZrCl_2 and a silver salt (AgX, X = ClO_4, OTf, and BF_4) is a highly effective reagent system for activating glycosyl fluoride to give the *O*-[37] or *C*-glycoside[38] stereoselectively under very mild conditions (eq 22). This activation process is presumed to involve a cationic zirconocene species as an actual activator (eq 23) and has been applied to the synthesis of a natural product.[37]

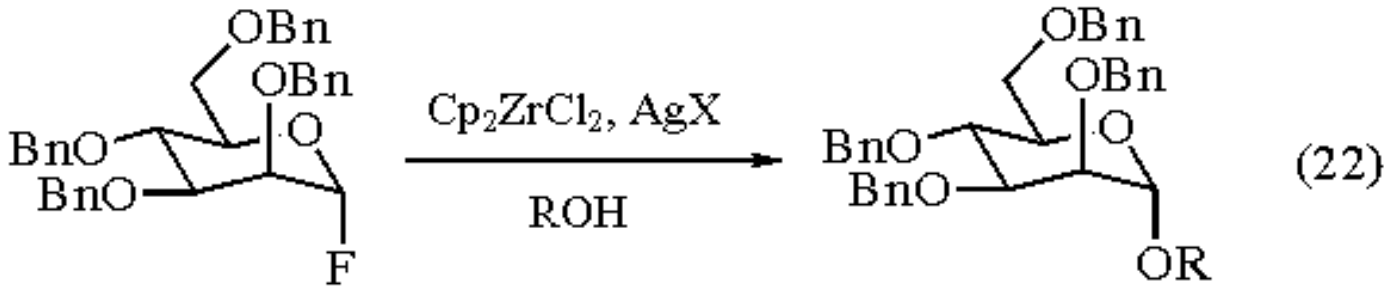

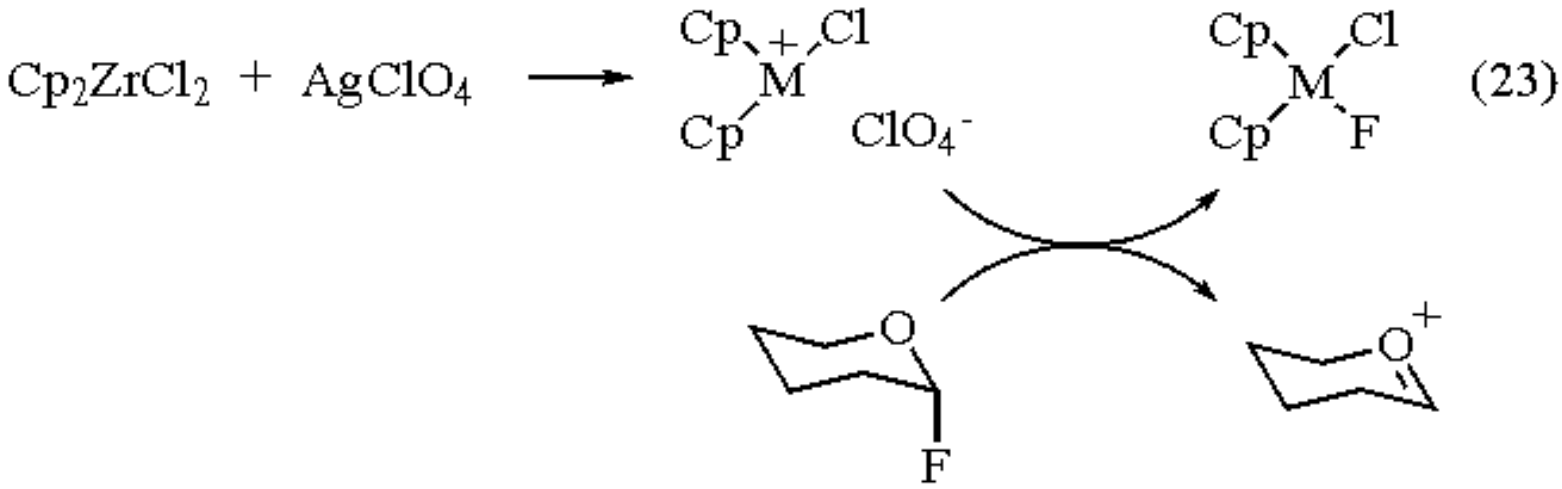

Methylenation of Carbonyls.

The methylenation of carbonyls (aldehydes, ketones, and enones) is effectively carried out by treating the carbonyls with Cp_2ZrCl_2, CH_2X_2 (X = Cl or Br), and ***Zinc*** powder (eqs 24 and 25).[39] This system is presumed to form a bimetallic complex. This bimetallic complex attacks the carbonyl compound to afford metallaoxacyclobutane, which rapidly collapses to zirconocene oxide and the methylenated product (eq 26). Unlike the Tebbe reagent (μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***),[40] this zirconium system does not successfully methylenate esters and lactones.

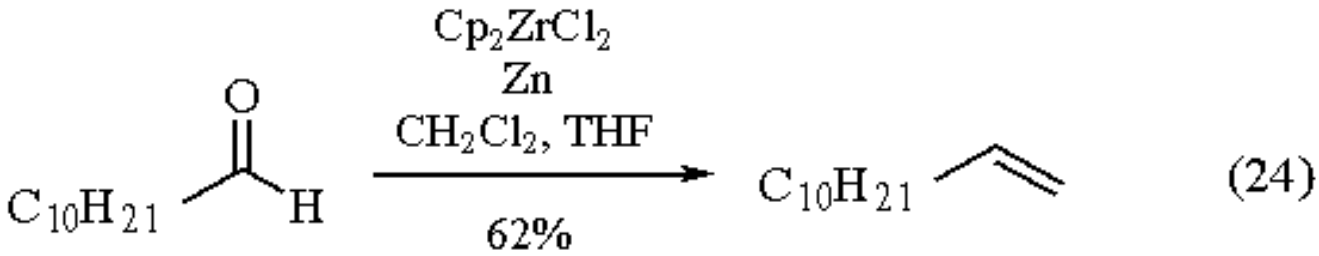

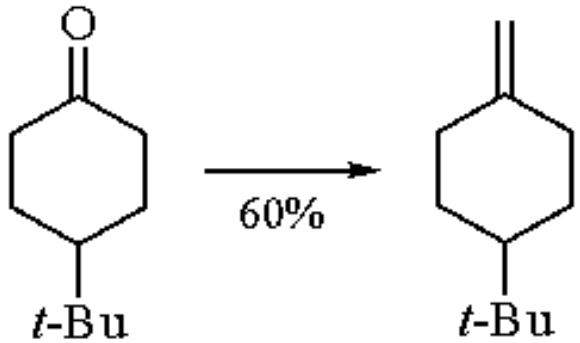

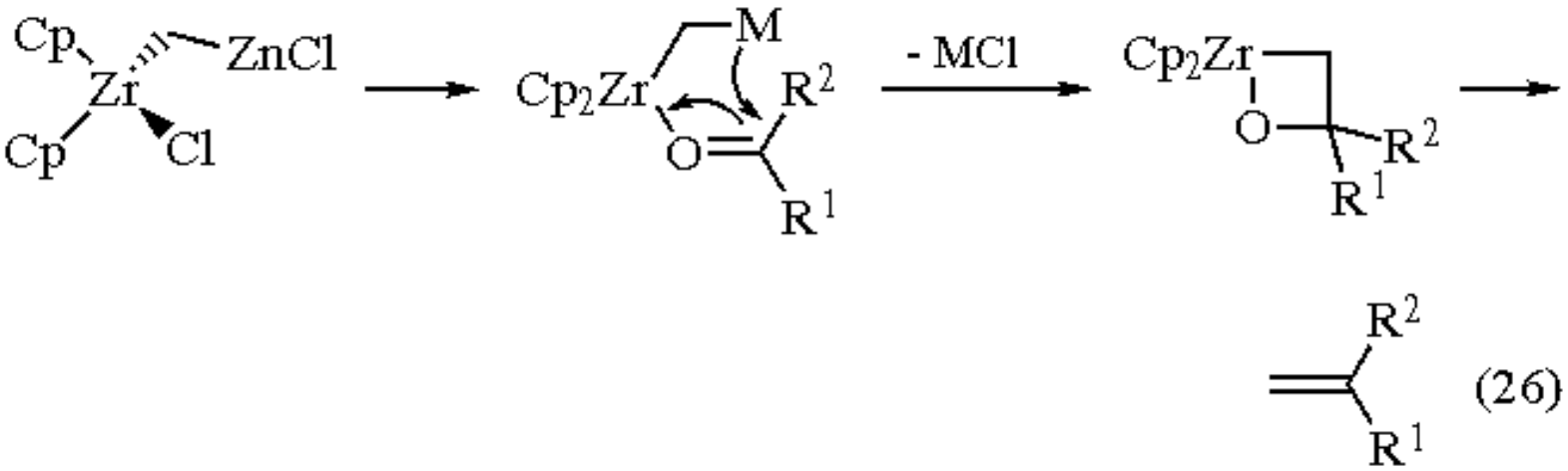

Polymerization Catalyst.

Another important application of Cp_2ZrCl_2 as a catalyst is found in polymer chemistry. The combination of Cp_2ZrCl_2 and methylaluminoxane (MAO) is a famous system (Ziegler-type system) for polymerization of ethylene to polyethylene.[41]

Related Reagents.

Chlorobis(cyclopentadienyl)hydridozirconium; ***Dichlorobis(cyclopentadienyl)titanium***; ***Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts***; ***Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane***.

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Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts[1]

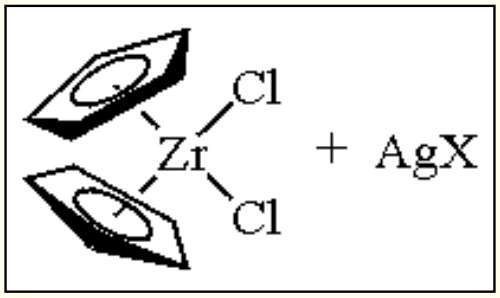

(Cp_2ZrCl_2)

[1291-32-3] · $C_{10}H_{10}Cl_2Zr$ · Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts · (MW 292.32) ($AgClO_4$)

[7783-93-9] · $AgClO_4$ · Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts · (MW 207.32) ($AgOSO_2CF_3$; AgOTf)

[2923-28-6] · $CAgF_3O_3S$ · Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts · (MW 256.93) ($AgBF_4$)

[14104-20-2] · $AgBF_4$ · Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts · (MW 194.67) ($AgPF_6$)

[26042-63-7] · AgF_6P · Dichlorobis(cyclopentadienyl)zirconium-Silver(I) Salts · (MW 252.83)

(activates glycosyl fluorides for *O*-glycoside synthesis;[2] effects Friedel-Crafts coupling of glycosyl fluorides with arenes to give aryl *C*-glycosides[3])

Physical Data: see entries for ***Dichlorobis(cyclopentadienyl)zirconium*** and individual silver salts.

Handling, Storage, and Precautions: the reagents are combined just before use by adding the Ag salt to a solution of Cp_2ZrCl_2. ***Silver(I) Perchlorate*** leads to the best reactivity but has a potential hazard of explosion.[4] ***Silver(I) Trifluoromethanesulfonate*** is recommended as a safe alternative with slightly decreased reactivity. Other silver salts (e.g. ***Silver(I) Tetrafluoroborate***, $AgPF_6$, $AgAsF_6$) are less effective, but sometimes offer unique stereochemical preferences.[2d] Molecular sieves 4A are often used for removal of water in small scale runs but are not necessarily essential.

Cp_2ZrCl_2-$AgClO_4$ is used for the activation of glycosyl fluorides which, upon reaction with alcohols (glycosyl acceptors), give various *O*-glycosides.[1,2] The reactivity is slightly less than its hafnium counterpart, Cp_2HfCl_2-$AgClO_4$ (see ***Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts***). Use of the combination in a 1:2 ratio increases the reactivity.[2d] A number of useful applications have been reported for the synthesis of various classes of glycoconjugates, ranging from macrolides[2] to oligosaccharide structures embedded in glycopeptides or glycolipids.[5] Fine tuning of the reactivity/stereoselectivity[2,5] can be made by the suitable choice of the solvent, the metal center (Zr or Hf), and also the silver salt (eqs 1 and 2).

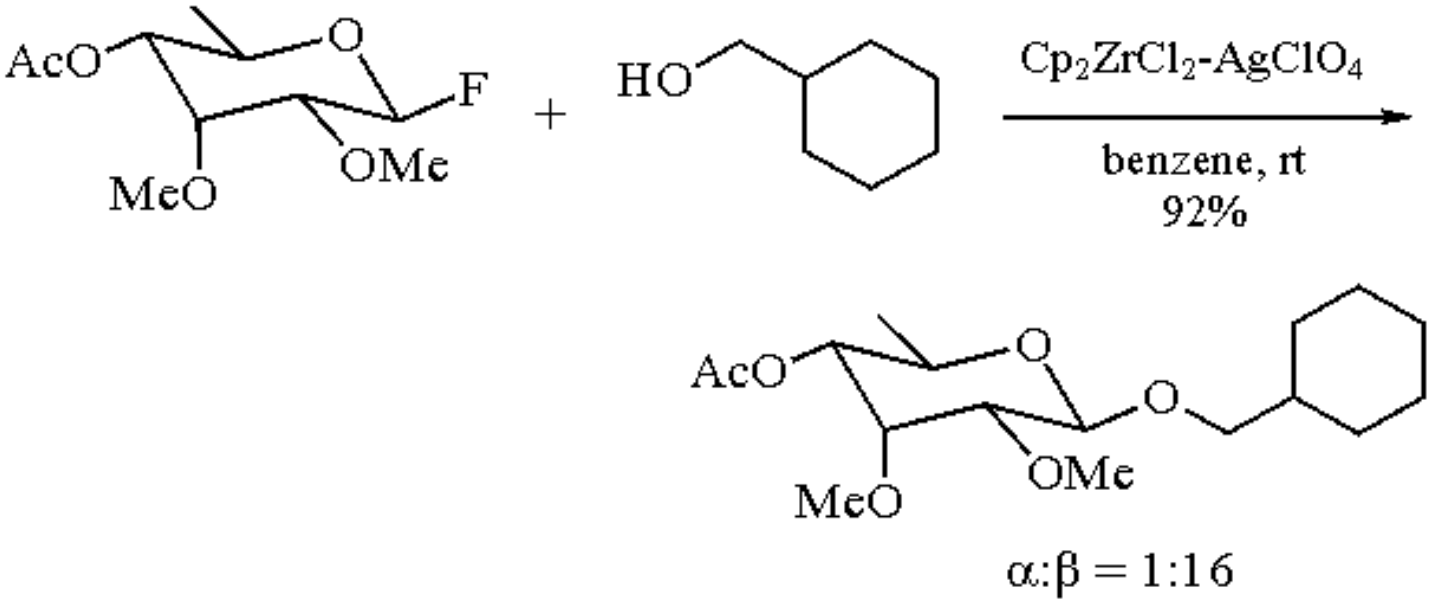

(1)

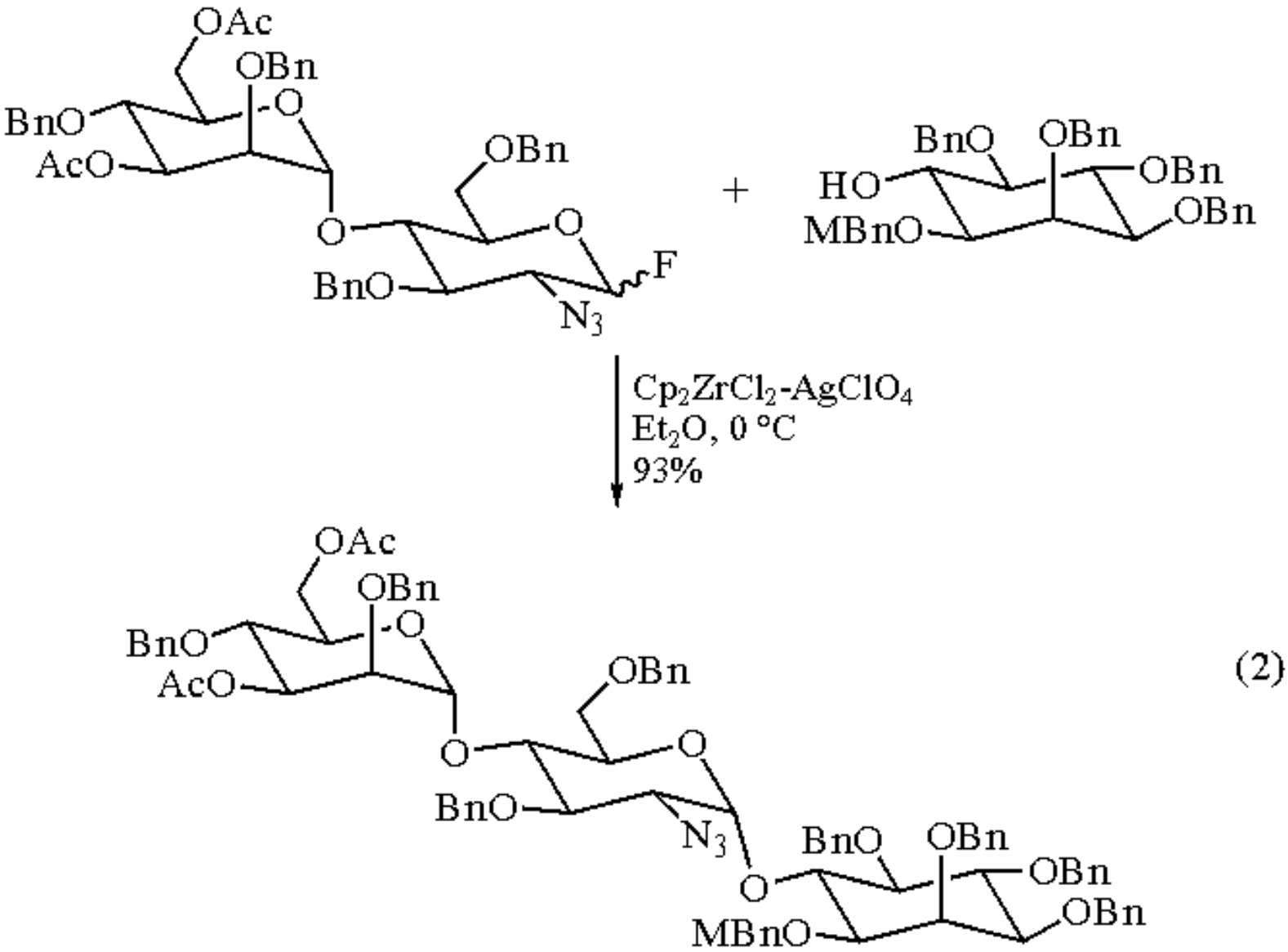

(2)

α:β = 3.7:1

MBn = 4-methoxybenzyl

Cp_2ZrCl_2-$AgClO_4$ effects Friedel-Crafts coupling of glycosyl fluorides with activated aromatic compounds to give aryl *C*-glycosides (eq 3).[3] The hafnium counterpart is often too reactive.

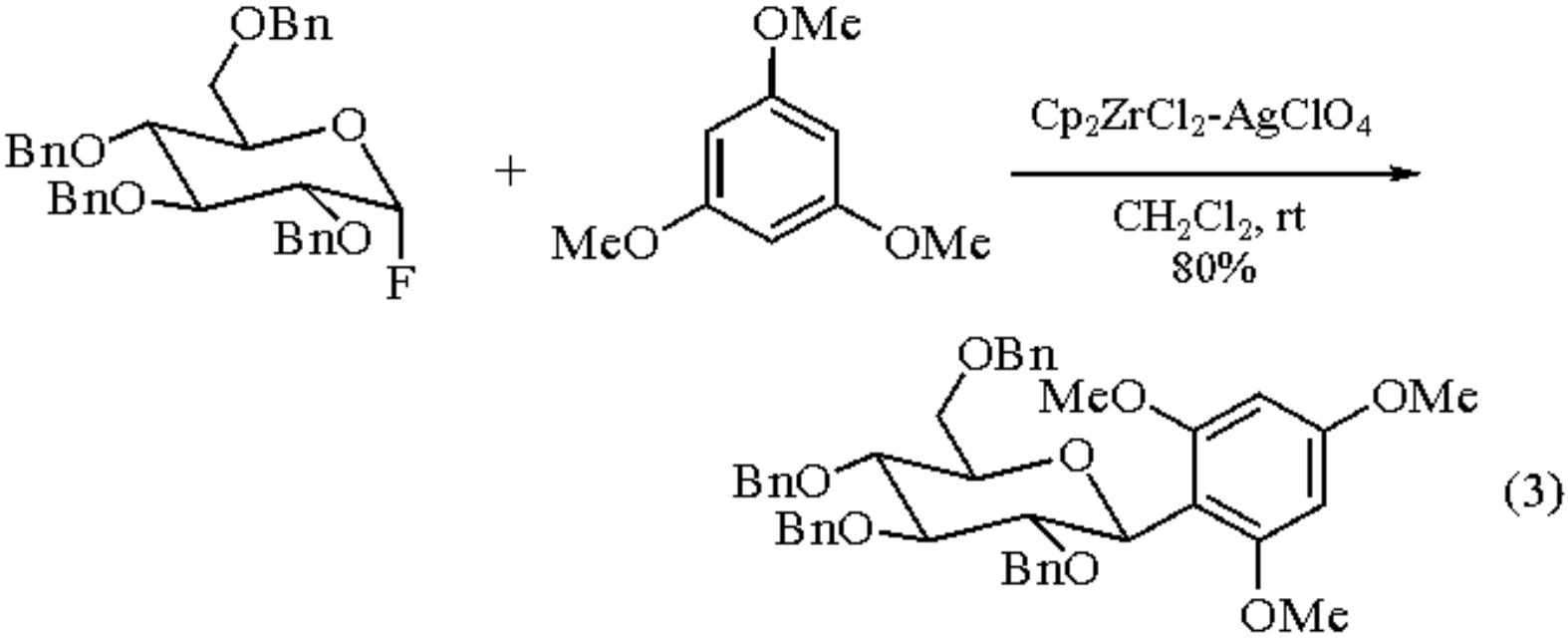

Related Reagents.

Dichlorobis(cyclopentadienyl)hafnium-Silver(I) Salts; ***Dichlorobis(cyclopentadienyl)zirconium***.

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Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane[1]

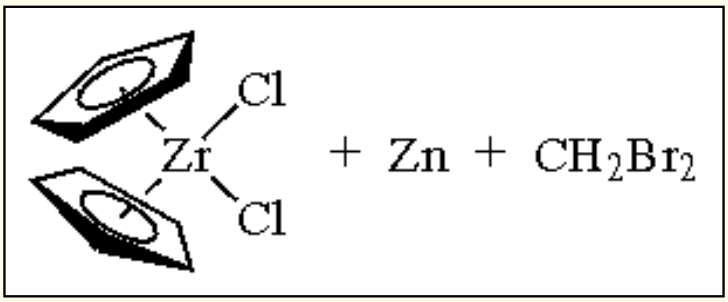

(Cp_2ZrCl_2)

[1291-32-3] · $C_{10}H_{10}Cl_2Zr$ · Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane · (MW 292.32) (Zn)

[7440-66-6] · Zn · Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane · (MW 65.37) (CH_2Br_2)

[74-95-3] · CH_2Br_2 · Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane · (MW 173.85)

(methylenating reagent for aldehydes, ketones, and enones[1])

Physical Data: Cp_2ZrCl_2: mp 245 °C. Zn: mp 419.5 °C; *d* 7.14 g cm^{-3}. CH_2Br_2: mp -52 °C; bp 96-98 °C; *d* 2.477 g cm^{-3}.

Solubility: Cp_2ZrCl_2: sol THF, CH_2Cl_2, and $CHCl_3$. Zn: insoluble in organic solvents. CH_2Br_2: miscible in common organic solvents.

Form Supplied in: Cp_2ZrCl_2: white crystalline powder; widely available. Zn: metallic gray granules or powder. CH_2Br_2: clear, colorless liquid.

Preparative Method: prepared in situ.

Handling, Storage, and Precautions: Cp_2ZrCl_2: store under N_2. Zn: flammable solid. CH_2Br_2: harmful if inhaled or swallowed; may cause irritation.

The reagent is prepared in situ by the addition of ***Dibromomethane*** to a mixture of ***Zinc***, ***Dichlorobis(cyclopentadienyl)zirconium***, and the aldehyde or ketone in dry THF. Typical reaction time is 3 h at room temperature.[1,3] The yield of methylenated products is good with enones, aldehydes, and ketones (Table 1), but the

reagent will not methylenate lactones or esters.[1]

Table 1 Conversion of Carbonyls (X = O) to Alkenes (X = CH_2) using $Cp_2Zr_2Cl_2$-CH_2Br_2-Zn[a]

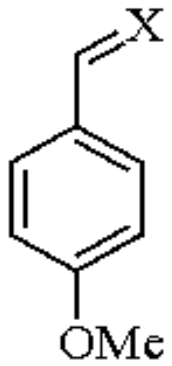

1 h (64%)

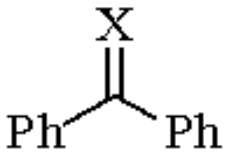

2 h (76%)

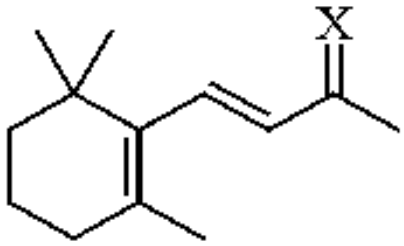

2 h, 76%

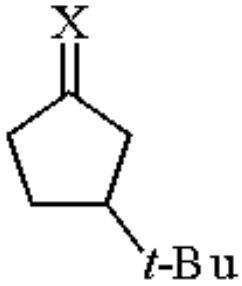

4 h, 57%

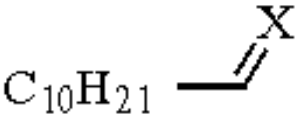

3 h, 62% (70%)

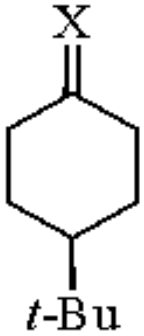

6 h, 60% (80%)

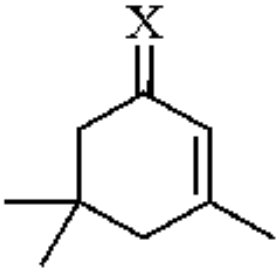

3 h (88%)

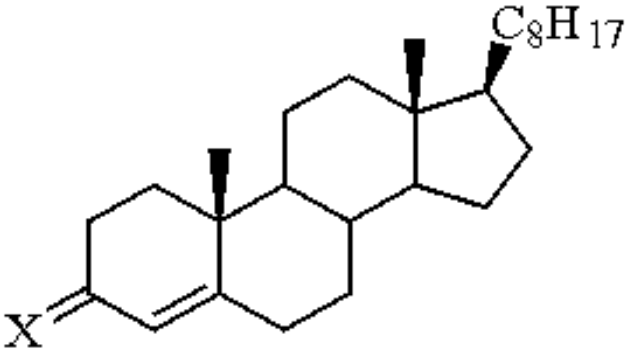

3 h, 64%

[a] The yields in parentheses are VPC yields

The reagent has also been used on readily enolizable ketones in the presence of hydroxyl and secondary amide protons (eq 1) where the Wittig reaction and Peterson alkenation were not successful.[2]

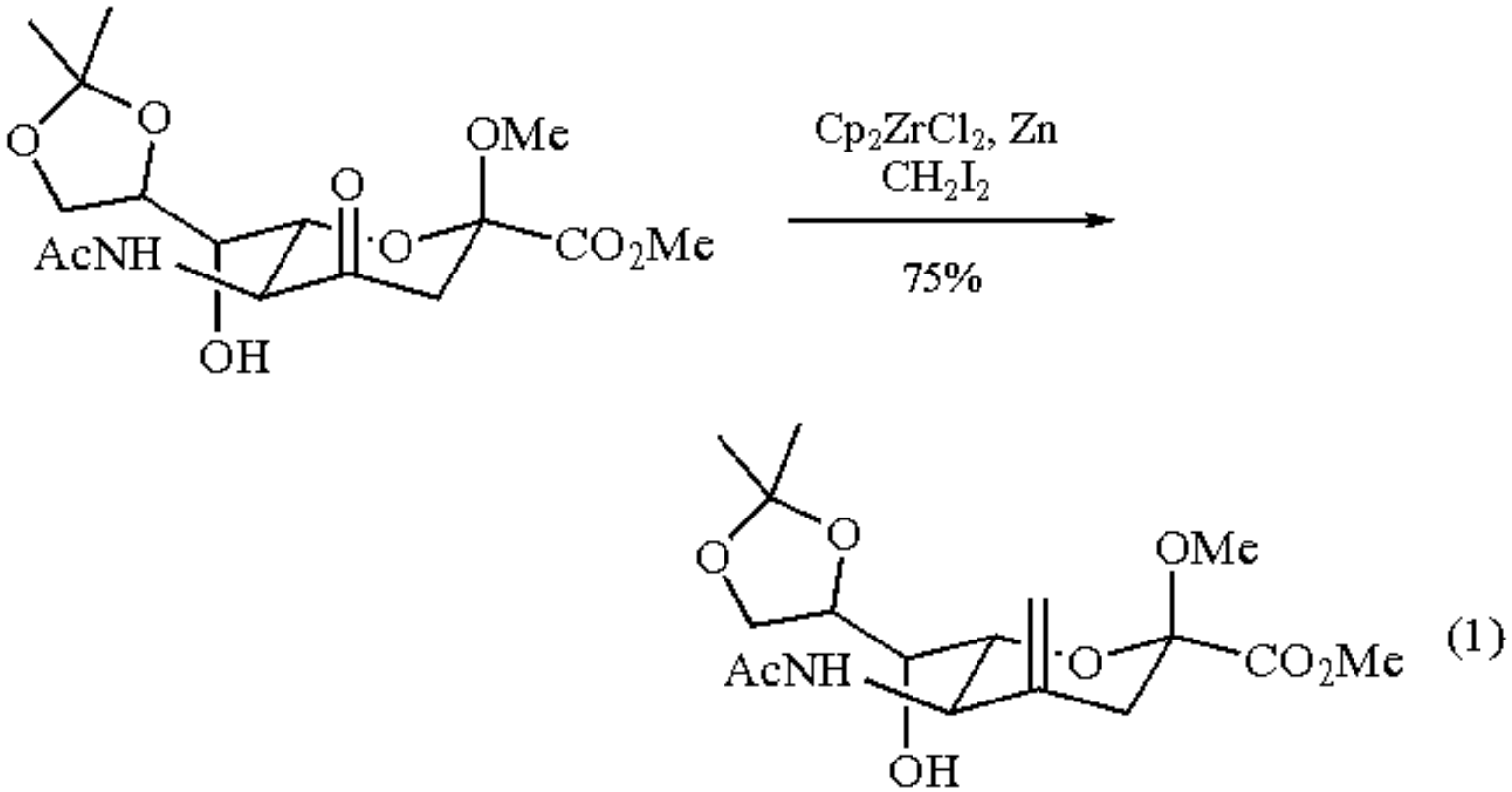

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Dichloro[1,4-bis(diphenylphosphino)butane]nickel(II)

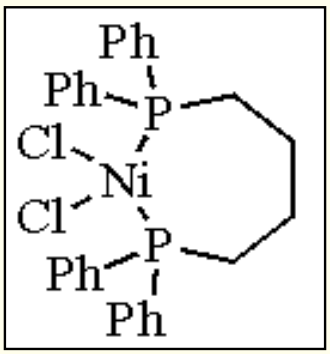

[18750-53-3] · $C_{28}H_{28}Cl_2NiP_2$ · Dichloro[1,4-bis(diphenylphosphino)butane]nickel(II) · (MW 556.07)

(catalyst for allylic alkylation[1] of stable enolates, dialkylation[2] of dithioacetals and electrochemical carboxylation of terminal alkynes[3])

Physical Data: light fawn-colored powder.

Solubility: sol benzene. *Drying:* the powder can be dried under vacuum.[4]

Preparative Method: prepared by adding a solution of $NiCl_2.6H_2O$ in *n*-butanol to a solution of 1,4-bis(diphenylphosphino)butane (dppb) in *n*-butanol and refluxing until the complex drops out of solution as a light purple powder.

Handling, Storage, and Precautions: should be stored in dry, dark-colored bottles under an inert atmosphere.

Allylic Alkylation.

The title reagent has been used to catalyze alkylation of stabilized enolates with allylic acetates. The regioselectivity depends on the ligands present around nickel.[1] For example, 1,4-diphenylphosphinobutane (dppb) shows better regioselectivity than 1,2-diphenylphosphinoethane (dppe) in the nickel-catalyzed alkylation of *trans*-2-buten-1-yl acetate with the anion of malonic ester even though the stereoselectivity is about the same (eq 1).[5]

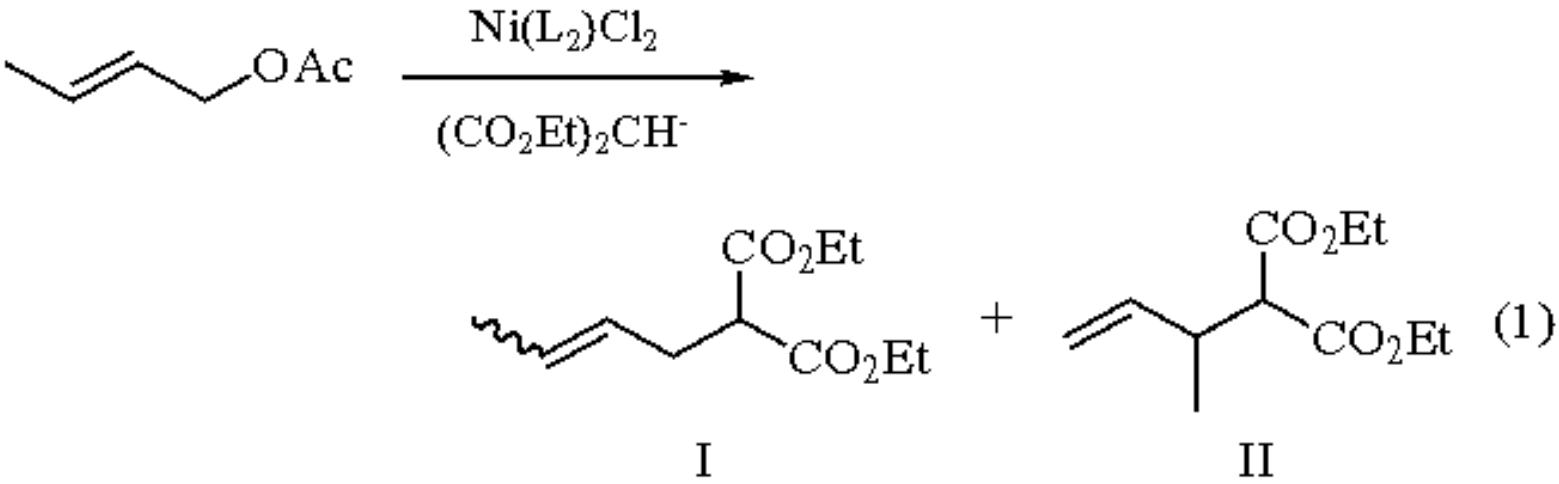

Ligand	Yield	I (*E*:*Z*)	II
dppb	97	98 (81:19)	2
dppe	78	72 (80:20)	28

Regioselective Alkylation of Allylic Dithioacetals.

$NiCl_2$(dppb) shows higher regioselectivity than triphenylphosphine in the dialkylation of dithioacetal derivatives of α,β-unsaturated carbonyl compounds with Grignard reagents. The *gem*-dimethylation of cinnamaldehyde dithioacetal with MeMgI using $NiCl_2$(dppb) as a catalyst occurs regiospecifically in 90% yield (eq 2).[2] In contrast, ***Dichlorobis(triphenylphosphine)nickel(II)*** gives a 70/30 mixture of the *gem*-dimethyl adduct and 1-phenylbutadiene. Generally, the regioselectivity of all nickel catalysts decreases as the size of the 2-substituent on the allylic moiety increases.[2]

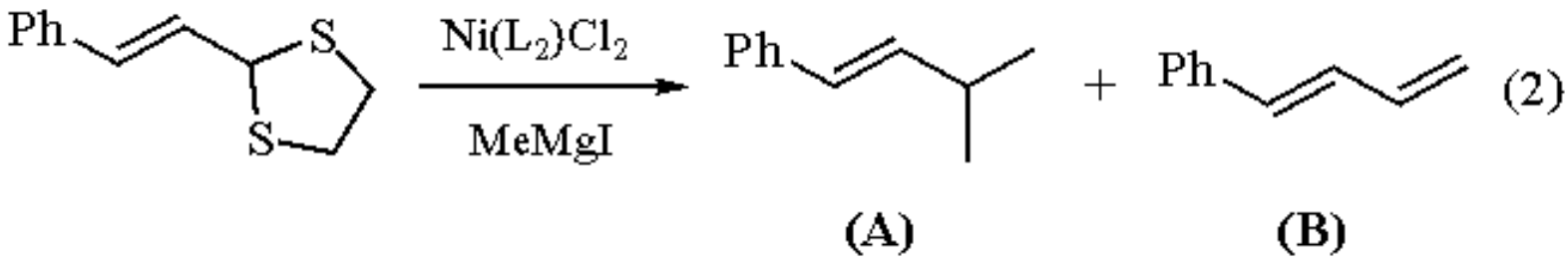

Ligand	Yield	A:B
dppb	90	100:0
PPh_3	85	70:30

Electrochemical Carboxylation of Terminal Alkynes.

The product ratio in nickel-catalyzed electrochemical carboxylations of terminal alkynes depends strongly on the ligand.[3] For example, 1-octyne has been electrochemically carboxylated with $NiCl_2$(dppb) to give the diacid only (eq 3), whereas $NiCl_2$(dppe) gives a mixture of alkynyl acid and trihexylbenzene (eq 4).[3]

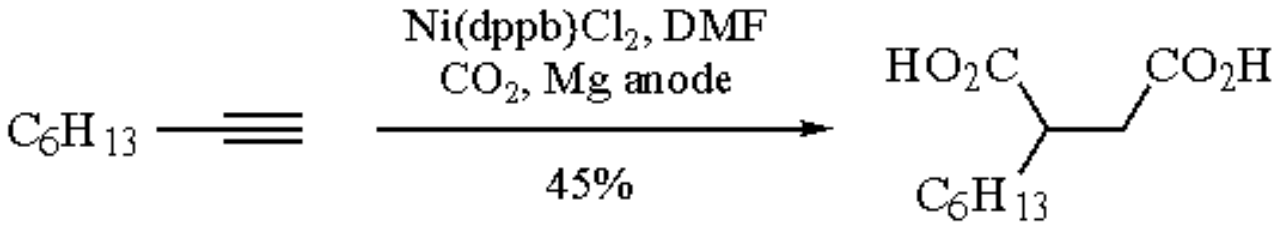

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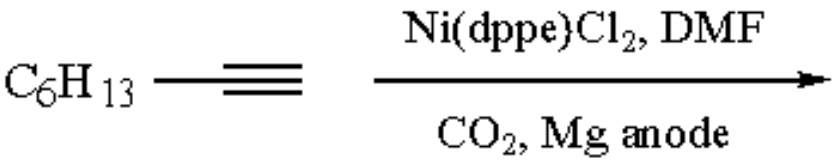

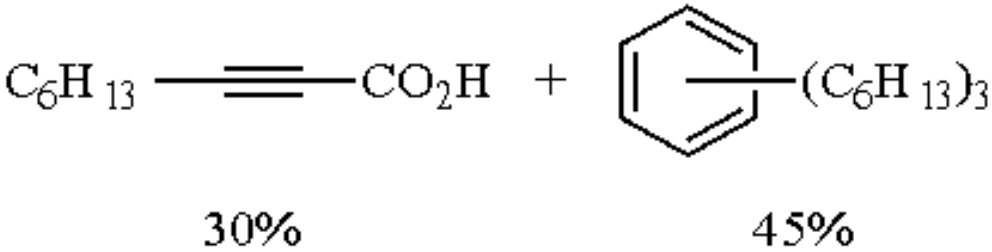

(4)

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Dichloro[1,4-bis(diphenylphosphino)butane]palladium(II)

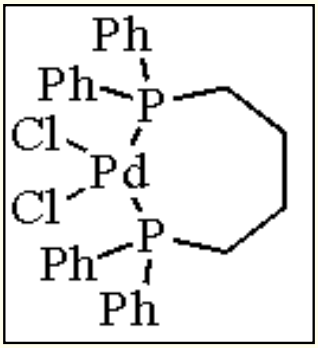

[29964-62-3] · $C_{28}H_{28}Cl_2P_2Pd$ · Dichloro[1,4-bis(diphenylphosphino)butane]palladium(II) · (MW 603.80)

(useful for the catalysis of styrene carbonylation,[1] coupling of alkyl Grignard reagents with organic halides,[2] selective monoalkylation of organic polyhalides,[3] and modification of the dihalovinyl moiety of synthetic pyrethroids[4])

Solubility: commonly used in ethanol, benzene, and ethereal solvents.

Form Supplied in: cream colored powder.

Preparative Methods: can be prepared conveniently in situ by mixing the bidentate phosphine ligand and $(PhCN)_2PdCl_2$ in either benzene or chloroform.[1] The preparation of $(dppb)PdCl_2$ is also possible through the reaction of $PdCl_2$ with dppb in acetone, a process that slowly forms the catalyst as a white precipitate which can be isolated in 51% yield.[5] Preparation of the hydrate complex is possible via the reaction of $Na_2[PdCl_4]$ with dppb in a mixture of CH_2Cl_2 and water.[5]

Handling, Storage, and Precautions: hygroscopic.

Carbonylation of Styrene.

One of the earliest uses of $(dppb)PdCl_2$ was for the catalytic carbonylation of styrene (eq 1).[1] The product distribution from this reaction depends on the nature of the phosphine ligand, $Ph_2P(CH_2)_nPPh_2$, and was examined for n = 1-6 and 10 (the n = 2 ligand did not show catalytic activity). The selectivity appears to depend on the coordinating power of the phosphine ligand, where strongly coordinating bidentate ligands (n = 3 or 4) create a steric environment that suppresses formation of the branched ester (**2**). The highest selectivity for the formation of (**2**) is obtained with a derivative of the dppb ligand, DIOP (***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane***).

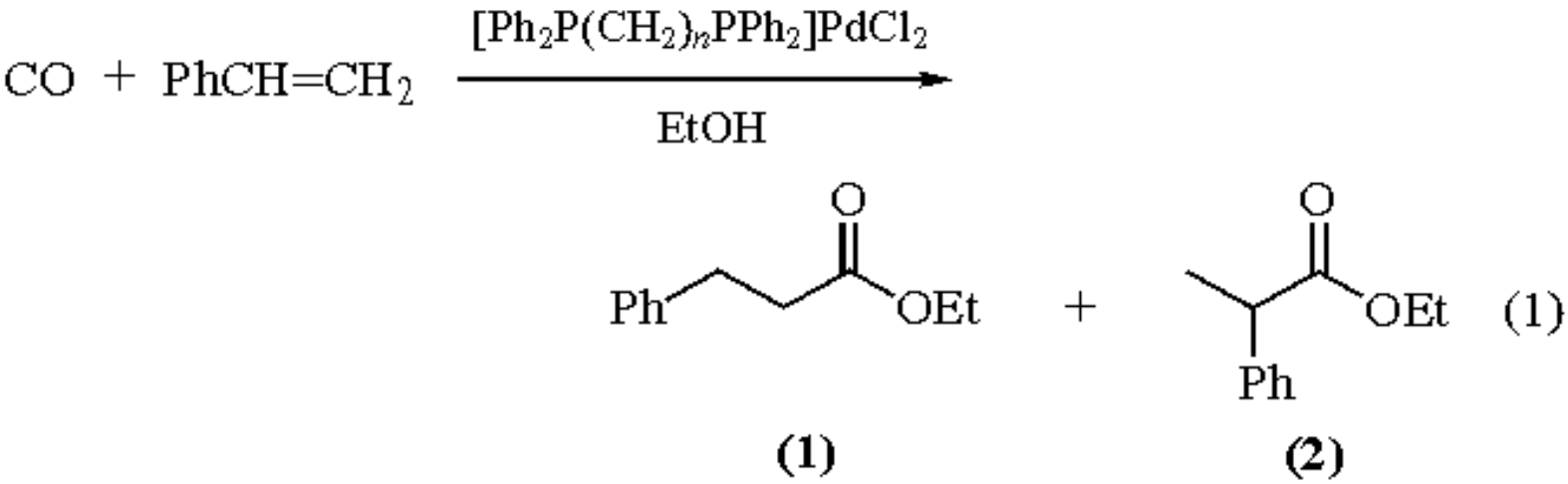

n	1	3	4	5	6	10	DIOP
(1)	33%	12%	22%	37%	78%	88%	23%
(2)	29%	29%	48%	42%	16%	5%	67%

Coupling Reactions.

Investigation of the activity of various bisphosphine-Pd and -Ni complexes in the coupling of *s*-butylmagnesium chloride with aryl or vinyl bromides shows that (dppb)$PdCl_2$ is relatively selective (eq 2).[2] In comparison, ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***, (dppf)$PdCl_2$, is far more effective. The increased selectivity of the dppf ligand is attributed to the larger P-Pd-P angle and smaller Cl-Pd-Cl angle imposed by the presence of the ligand. Overall, the selectivity for the ligands is: (dppf)$PdCl_2$ >> (dppb)$PdCl_2$ &egt; (dppp)$PdCl_2$ > $(PPh_3)_4Pd$ > $(PPh_3)_2PdCl_2$ > (dppe)$PdCl_2$. Although (dppp)$NiCl_2$ is the most selective nickel catalyst for such transformations, (dppf)$PdCl_2$ is even more effective. The use of these catalysts allows for coupling with secondary alkyl groups and with alkyl groups containing β-hydrogens.[2]

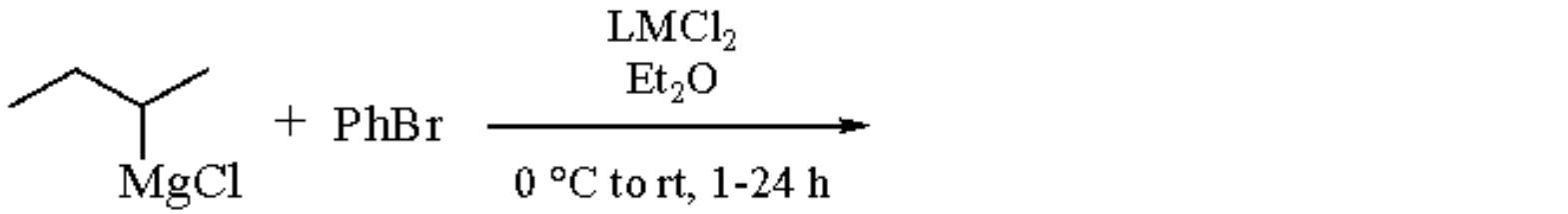

LM	(3)	(4)
(dppf)Pd	95%	0%
(dppb)Pd	51%	25%
(dppp)Ni	29%	3%

The use of (dppb)$PdCl_2$ promotes selective monoalkylation of organic polyhalides to produce 1-substituted (*Z*)-1-chloroalkenes from 1,1-dichloro-1-alkenes and either Grignard or organozinc reagents (eq 3).[3] Alkyl, aryl, and heteroaryl Grignard or zinc reagents are effective in this coupling reaction. Even trichloroethylene undergoes this coupling reaction at the expected position. The regioselectivity of this reaction depends upon the presence of substituent R^1.[3] In addition, the use of $(PPh_3)_2PdCl_2$ rather than (dppb)$PdCl_2$ gives mainly diarylation products. This procedure provides a viable alternative to Wittig alkenation for the preparation of unsymmetrically trisubstituted alkenes since aldehydes can easily be transformed into 1,1-dichloroalkenes.

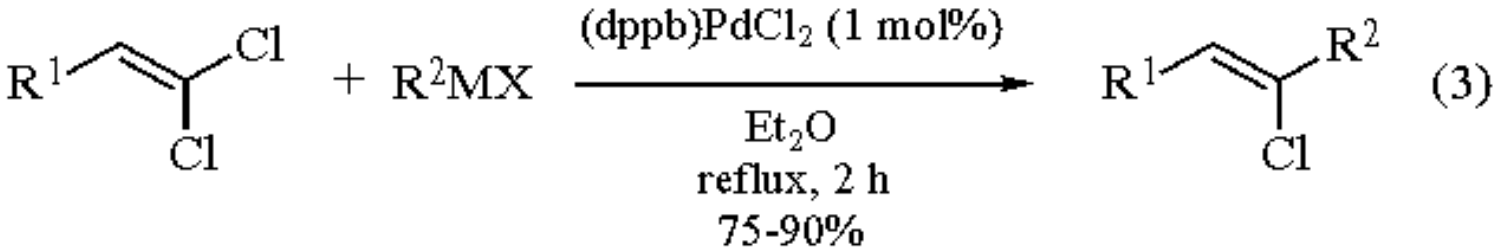

R^1 = Ph, 4-$MeOC_6H_4$, 2-thienyl, Me, Cl; R^2MX = PhMgBr, 4-$MeOC_6H_4MgBr$, PhZnCl, 4-ClC_6H_4MgBr, *n*-BuZnCl, *n*-hexylMgBr

Work toward modification of the dihalovinyl moiety of synthetic pyrethroids such as permethrin, cypermethrin, and deltamethrin, which are present in many household and agricultural insecticides, has progressed due to the application of similar palladium catalyzed coupling reactions.[4] The reaction of an organozinc complex in the presence of (dppb)$PdCl_2$ provides a pathway for the direct stereoselective transformation of (2,2-dihalovinyl)dimethylcyclopropanecarboxylates into [(*Z*)-2-substituted 2-halovinyl]dimethylcyclopropanecarboxylates (eq 4).[4]

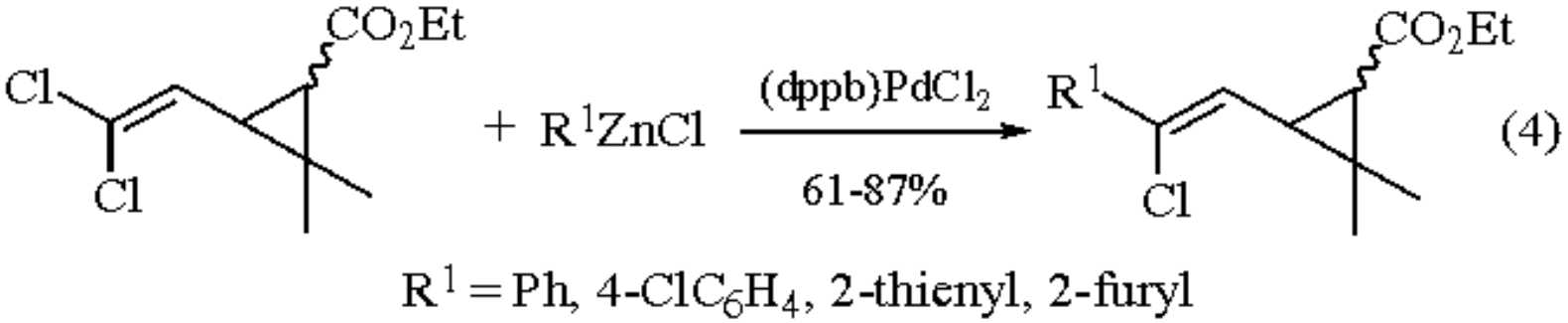

Similar reactions are known for the catalytic system formed from $Pd(OAc)_2$ and dppb. This system is used for affecting regioselective hydrocarboxylation of alkenes,[6] and for regioselective arylation of unsymmetrical alkenes[7] and acyclic enol ethers.[8]

In addition, the combination of $(dppb)PdCl_2$ and CuO has been shown to be a useful catalytic system for the Stille cross coupling of 2-tributylstannylpyridine with halobenzenes and aromatic heterocyclic halides.[9]

Related Reagents.

Dichloro[1,4-bis(diphenylphosphino)butane]palladium(II); ***Dichloro[1,2-bis(diphenylphosphino)ethane]palladium(II)***; ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***; ***Tetrakis(triphenylphosphine)palladium(0)***.

---

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Dichloro[1,2-bis(diphenylphosphino)ethane]palladium(II)

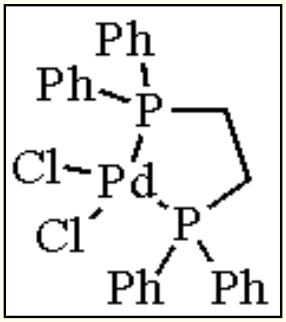

[19978-61-1] · $C_{26}H_{24}Cl_2P_2Pd$ · Dichloro[1,2-bis(diphenylphosphino)ethane]palladium(II) · (MW 575.75)

(catalyst for carbonylation[1] and biscarbonylation[2,3] of aryl halides with amines)

Alternate Names: [1,2-bis(diphenylphosphino)ethane]palladium(II) chloride; dichloro[ethylenebis(diphenylphosphino)]palladium(II).

Physical Data: mp >300 °C.

Form Supplied in: orange powder; available from several suppliers.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$-DMSO-d_6) δ 3.5 (t, CH_2), δ 3.8 (q, CH_2); ^{1}H NMR ($CDCl_3$) δ 3.45 (t, CH_2), δ 3.6 (q, CH_2); ^{31}P NMR (121.5 MHz, CH_2Cl_2) 58.3 (s).

Preparative Methods: prepared by treating commercially available K_2PdCl_2 (in DMF) with bis(diphenylphosphino)ethane (in CH_2Cl_2).[4,5] It can also prepared from K_2PdCl_2 (in H_2O) and bis(diphenylphosphino)ethane (in CH_2Cl_2) using Bu_4NCl (in CH_2Cl_2) as a phase-transfer catalyst.[6]

Purification: recrystallization from DMF-ether.

Handling, Storage, and Precautions: moisture sensitive.

N-Substituted Phthalimides.

The title reagent is useful in carbonylation and coupling of *o*-dihalo aromatics and primary amines to form *N*-substituted phthalimides.[1] Optimal conditions for the reaction of *o*-diiodobenzene and aniline use DMA (0.2 M),

115 °C, 90 psi of CO, 3% $PdCl_2$(dppe), and 2.4 equiv of DBU (eq 1). This procedure tolerates a wide variety of functional groups and gives a good yield of desired products. An exception is the reaction of aniline with 1,2-dibromocyclopentene under the above conditions, which has been reported to give a variety of products.

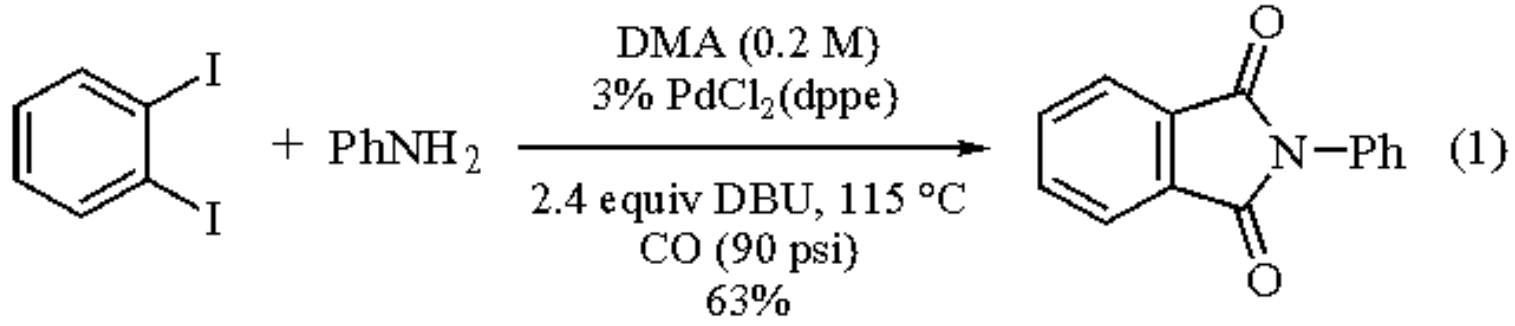

α-Keto Amides.

The title reagent is used as a catalyst to prepare α-keto amides and amides from aryl halides upon treatment with secondary amines and ***Carbon Monoxide*** (eq 2).[2,3] These reactions are most commonly carried out without solvent at 100 °C at 10 atm of CO using a 1:3:0.1 molar ratio of aryl halide/secondary amine/$PdCl_2$(dppe).

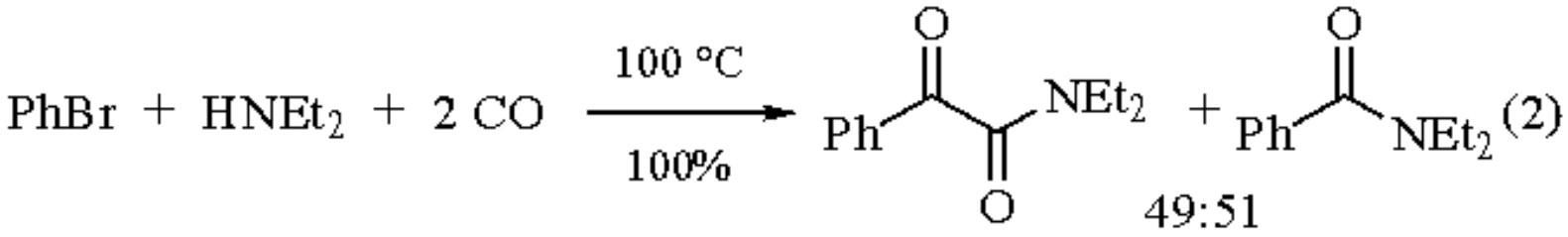

Allylation of Allylic Alcohols.

Allylation of carbonyl compounds is carried out via the formation of π-allylpalladium complexes using the title reagent as a catalyst and ***Tin(II) Chloride*** as a reducing agent (eq 3).[7] The reactivity order of allylating agents is allylic carbonate > allylic alcohol > allylic acetate and that of carbonyl compounds is aldehyde > ketone. Polar solvents such as DMF, DMSO, or ***1,3-Dimethyl-2-imidazolidinone*** (DMI) are preferred for higher regioselectivity.

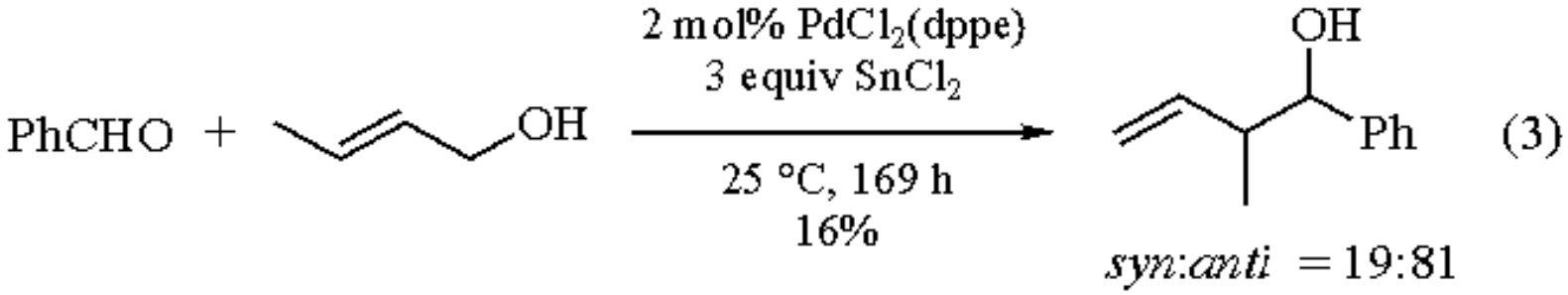

Other Uses.

The title reagent is used as a catalyst for cross coupling of primary, secondary, and tertiary Grignard and alkylzinc reagents with organic halides, but results are reported to be unsatisfactory.[8,9] ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)*** [$PdCl_2$(dppf)] is the preferred catalyst in the case of primary and secondary Grignard and alkyl zinc reagents,[8] whereas 1,1´-[bis(diphenylphosphino)ferrocene)]nickel(II) chloride is an effective catalyst in the case of tertiary alkyl Grignard reagents.[9] Allylic *p*-tolyl sulfones are desulfonylated to the corresponding alkanes in moderate yield by ***Lithium Triethylborohydride*** in the presence of a catalytic amount of the title reagent under mild conditions with preservation of the original stereochemistry. Dichloro[1,3-bis(diphenylphosphino)propane]palladium(II) [$PdCl_2$(dppp)] gives better results in the desulfonylation.[10]

Related Reagents.

$PdCl_2(PPh_3)_2$ has shown similar results in carbonylation and coupling of *o*-dihalo aromatics and primary amines to form *N*-substituted phthalimides, but ***Palladium(II) Chloride***, ***Palladium(II) Acetate***, $PdCl_2$.2MeCN, and $PdCl_2$.2BzCN have shown inferior results.[1] ***Dichlorobis(methyldiphenylphosphine)palladium(II)*** and $PdCl_2(PBuPh_2)_2$ are reported to be more effective as catalysts among the palladium complexes containing tertiary phosphine ligands.[2] ***Bis(benzonitrile)dichloropalladium(II)*** is a better catalyst for carbonyl allylation using allylic alcohols because of its stability towards air and moisture.[7]

---

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Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)

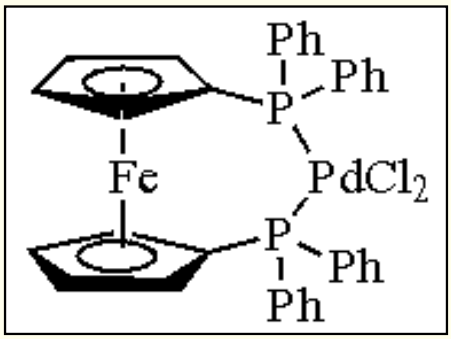

[72287-26-4] · $C_{34}H_{28}Cl_2FeP_2Pd$ · Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II) · (MW 731.72)

(catalyst for cross-coupling reactions)

Physical Data: mp 265-268 °C (dec).

Solubility: sol ether, THF, benzene.

Form Supplied in: reddish brown solid; commercially available.

Purification: recrystallization from $CHCl_3$ under inert atmosphere.

Handling, Storage, and Precautions: the complex is an irritant; store under an inert atmosphere.

Cross Coupling.

Like other Pd^{II} and Ni^{II} phosphine complexes, $PdCl_2$(dppf) is a very useful catalyst for the cross-coupling reactions of vinyl or aryl halides or triflates with Grignard reagents, leading to carbon-carbon bond formation.[1] $PdCl_2$(dppf)-catalyzed reaction of vinyl bromide with *s*-BuMgCl gives exclusively the desired coupling product (eq 1), while other Pd catalysts also yield isomerized and reduced by-products.[1a] (*E*)-1-Bromo-1-alkenes are more reactive than the (*Z*)-isomers.[1c] Selective monoalkylation of dichlorobenzene under refluxing conditions using $PdCl_2$(dppf) catalyst has been recorded.[2] Whereas palladium catalysts are usually unreactive in cross couplings of organosulfur compounds,[3] reactions of 2-methylthio-4,4-dimethyl-2-oxazoline with aryl Grignard reagents are catalyzed efficiently by $PdCl_2$(dppf) (eq 2).[4] Phototoxic terthiophenes have been prepared and the SMe group remains intact under the reaction conditions (eq 3).[5] Organozinc reagents behave similarly in these cross coupling reactions.[6] $PdCl_2$(dppf) has been found to catalyze iodine-zinc exchange reactions which lead to an interesting Pd-catalyzed intramolecular carbozincation of alkenes (eq 4).[7] It is

noteworthy that various functional groups remain intact under these conditions.

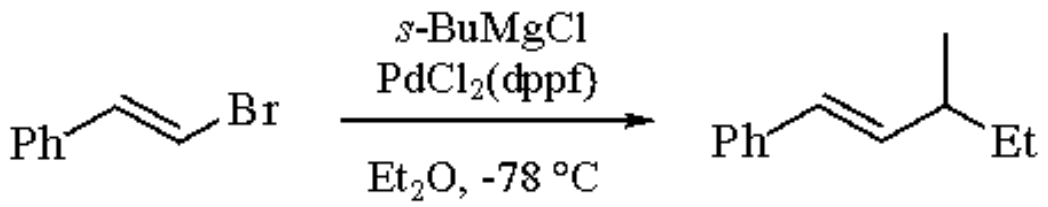

(1)

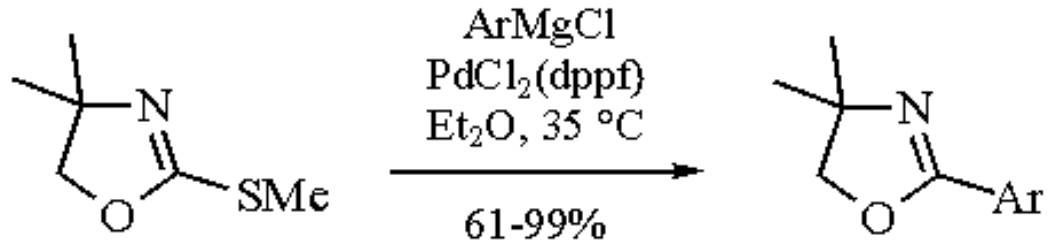

(2)

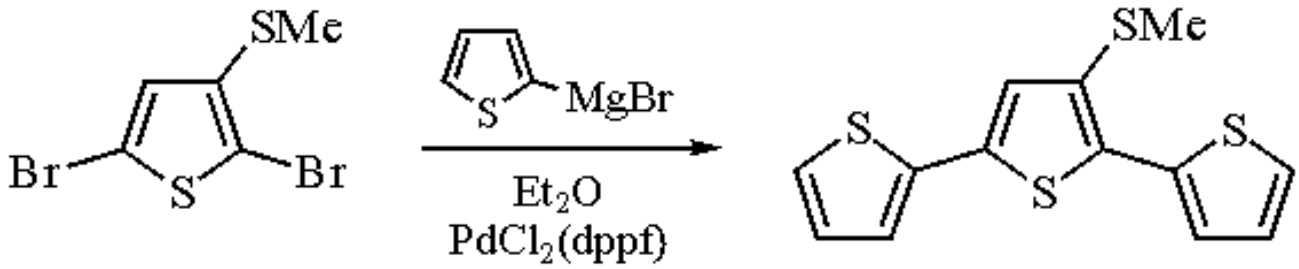

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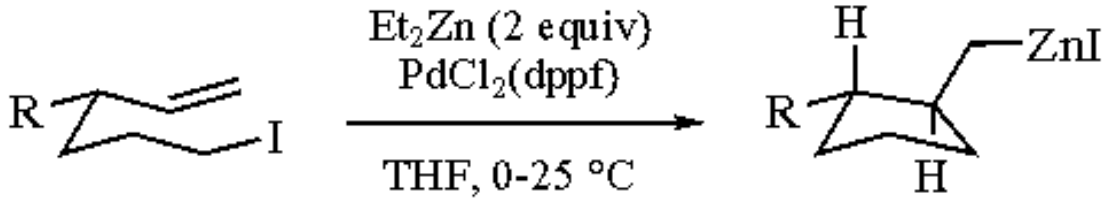

(4)

Aliphatic iodides are reduced upon treatment with alkyl Grignard reagents in the presence of $PdCl_2$(dppf) catalyst.[8] Aryl triflates are efficiently reduced by ***Sodium Borohydride*** or ***Ammonium Formate*** in the presence of $PdCl_2$(dppf).[9]

$PdCl_2$(dppf) also promotes the Stille reaction[10,11] as well as the Suzuki reaction.[12] Selective alkyl transfer in the Stille coupling reaction is effectively catalyzed by $PdCl_2$(dppf) (eq 5).[10a] Distannanes have been found to promote the $PdCl_2$(dppf) catalyzed allylation of aryl halides with allyl acetate.[10b] Intramolecular cyclization and cross coupling of alkynic aryl triflates with organotin reagents is promoted by $PdCl_2$(dppf) (eq 6).[10c] The $PdCl_2$(dppf)-catalyzed inter- and intramolecular coupling reactions of vinyl or aryl triflates with organostannanes in the presence of carbon monoxide and ***Lithium Chloride*** takes place under mild conditions to give good yields of vinyl or aryl ketones (eq 7).[11] Similar reactions have been performed with aryl triflates (eq 8).[13]

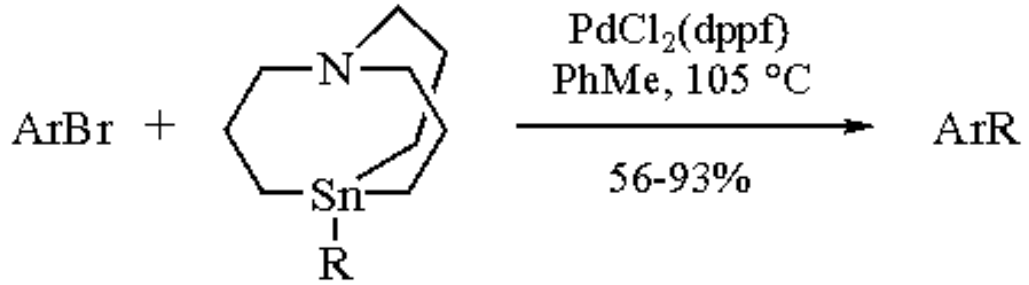

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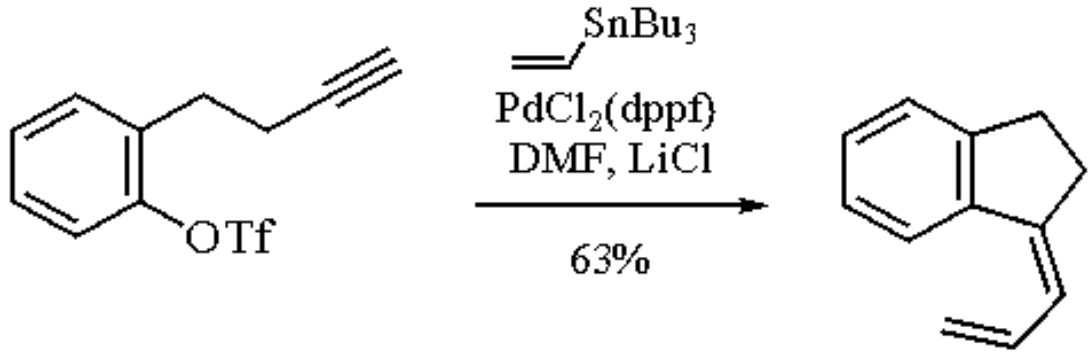

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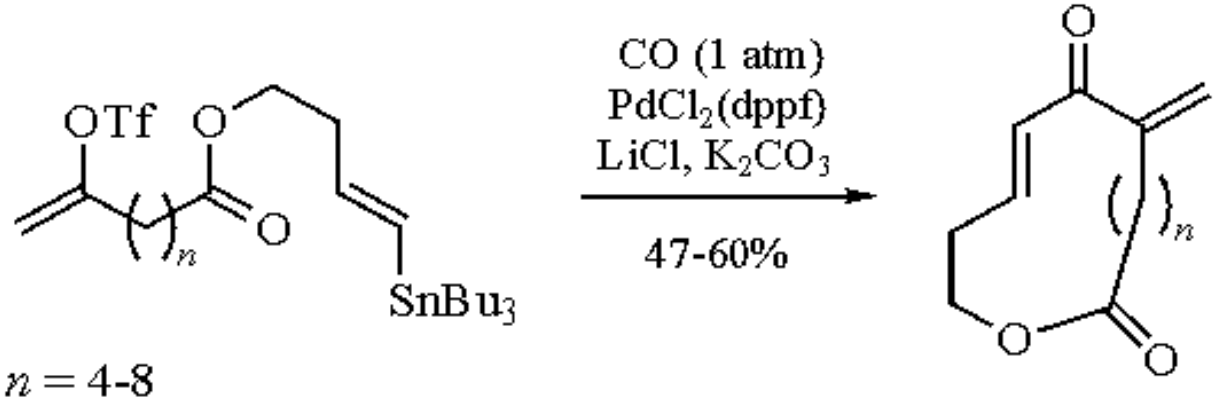

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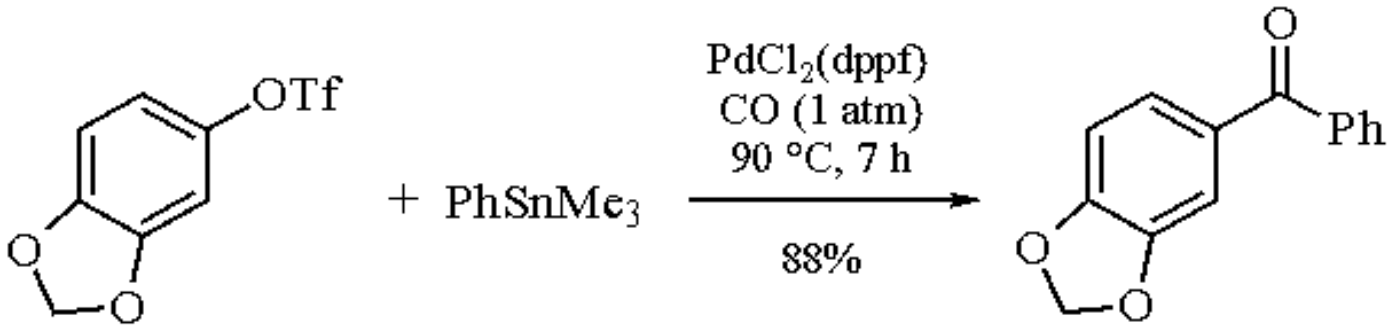

(8)

The title reagent has also been used to hydroesterify trimethylsilylalkynes, affording conjugated vinylsilanes in good yield (eq 9).[14]

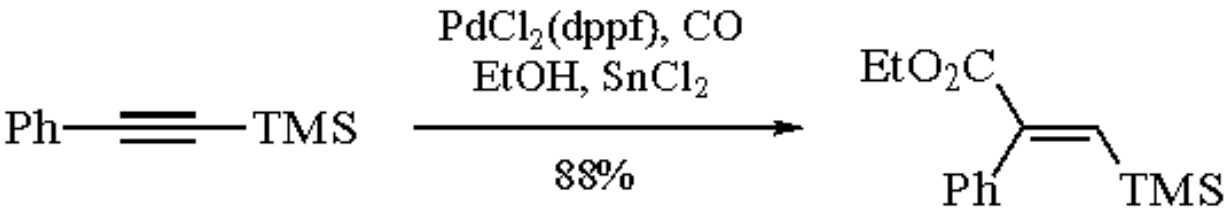

(9)

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Dichlorobis(methyldiphenylphosphine)palladium(II)

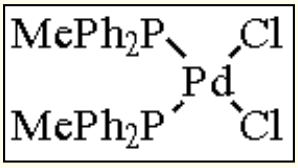

[52611-08-2] · $C_{26}H_{26}Cl_2P_2Pd$ · Dichlorobis(methyldiphenylphosphine)palladium(II) · (MW 577.75)

(catalyst for biscarbonylation of aryl halides with amines[3,4])

Alternate Name: bis[(diphenylphosphino)methane]palladium(II) chloride.

Physical Data: ^{1}H NMR ($CDCl_3$) δ 4.2 (t, CH_3).

Preparative Methods: by treating commercially available K_2PdCl_2 (in DMF) with methyldiphenylphosphine (in CH_2Cl_2),[1] or from K_2PdCl_2 (in H_2O) and methyldiphenylphosphine (in CH_2Cl_2) using Bu_4NCl (in CH_2Cl_2) as a phase-transfer catalyst.[2]

α-Keto Amides.

The title reagent ($PdCl_2$(dppm)) is one of the most effective catalysts among transition-metal complexes for the preparation of α-keto amides and amides from aryl halides by treatment with secondary amines and carbon monoxide.[3,4] These reactions are most commonly carried out without solvent at 100 °C at 10 atm of CO using a 1:3:0.1 molar ratio of aryl halide/secondary amine/$PdCl_2$(dppm) (eq 1).

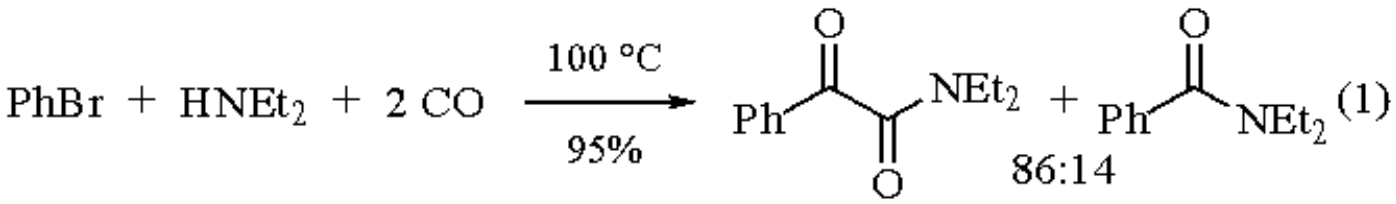

The reactivity of phenyl halides decreases in order of PhI > PhBr > PhCl,[3] although the selectivity of biscarbonylation is higher with the bromo than with the iodo derivative.[4] Introduction of electron-withdrawing substituents into the para position of phenyl halides enhances the reactivity but decreases the selectivity for α-keto amides.[3] Amines with high basicity ($pK_b < 4$) are essential for accomplishing the catalytic biscarbonylation. Sterically hindered amines favor formation of the α-keto amides.[3]

Related Reagents.

$PdCl_2(PBuPh_2)_2$ has shown good results in the formation of α-keto amides from aryl halides upon treatment with secondary amines with ***Carbon Monoxide***.[3]

---

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Dichlorobis(triphenylphosphine)nickel(II)[1]

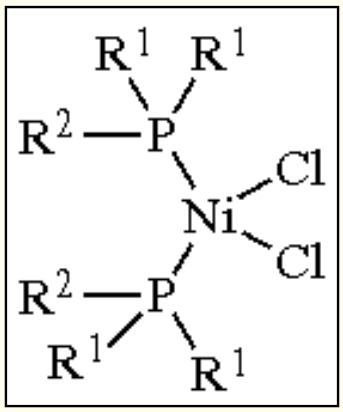

$NiCl_2(PPh_3)_2$ (R^1 = Ph, R^2 = Ph)

[14264-16-5] · $C_{36}H_{30}Cl_2NiP_2$ · Dichlorobis(triphenylphosphine)nickel(II) · (MW 654.18) $NiCl_2(PEt_3)_2$ (R^1 = Et, R^2 = Et)

[17523-24-9] · $C_{12}H_{30}Cl_2NiP_2$ · Dichlorobis(triethylphosphine)nickel(II) · (MW 365.91) $NiCl_2(PBu_3)_2$ (R^1 = Bu, R^2 = Bu)

[15274-43-8] · $C_{24}H_{54}Cl_2NiP_2$ · Dichlorobis(tributylphosphine)nickel(II) · (MW 534.23) $NiCl_2$(dppe) (R^1 = Ph, R^2,R^2 = -$(CH_2)_2$-)

[14647-23-5] · $C_{26}H_{24}Cl_2NiP_2$ · Dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) · (MW 528.02) $NiCl_2$(dppp) (R^1 = Ph, R^2,R^2 = -$(CH_2)_3$-)

[15629-92-2] · $C_{27}H_{26}Cl_2NiP_2$ · Dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) · (MW 542.05) $NiCl_2$(dppb) (R^1 = Ph, R^2,R^2 = -$(CH_2)_4$-)

[18750-53-3] · $C_{28}H_{28}Cl_2NiP_2$ · Dichloro[1,4-bis(diphenylphosphino)butane]nickel(II) · (MW 556.07) $NiCl_2$(dppf) (R^1 = Ph, R^2,R^2 = -$(C_5H_4)Fe(C_5H_4)$-)

[67292-34-6] · $C_{34}H_{28}Cl_2FeNiP_2$ · Dichloro[1,1´-bis(diphenylphosphino)ferrocene]nickel(II) · (MW 683.99)

(catalysts for the cross-coupling reactions of various RX with Grignard reagents,[1-34] C-X bond reduction,[35,36] homocoupling of C_{sp^2} halides,[37-40] displacement of aryl halides,[41] and oligomerization of dienes[47])

Physical Data: $NiCl_2(PPh_3)_2$: dark green; mp 205-206 °C. $NiCl_2(PEt_3)_2$: dark red; mp 112-113 °C. $NiCl_2(PBu_3)_2$: red; mp 48-49 °C. $NiCl_2$(dppe): orange; mp 263-265 °C. $NiCl_2$(dppp): red; mp 213 °C (dec). $NiCl_2$(dppb): light violet; mp 270-272 °C. $NiCl_2$(dppf): dark green; mp 283-284 °C.

Solubility: sol benzene, acetone, THF, hot alcohol.

Preparative Methods: most nickel chloride phosphine complexes are commercially available. They can also be conveniently synthesized by mixing the stoichiometric amount of $NiCl_2$ with the appropriate phosphine ligand.[48]

Handling, Storage, and Precautions: nickel chloride phosphine complexes are corrosive and cancer suspect agents. Most of these complexes are air stable in solid form. Handle in a fume hood.

Cross-Coupling Reactions.

Transition metal catalyzed cross-coupling reactions of R-X with organometallic nucleophiles are well documented.[1] R can be an aryl, vinyl, or allyl group, and X can be any leaving group ranging from the more reactive triflates and halides to less labile thioalkoxides, sulfoxides, sulfones, hydroxides, alkoxides, and even amido groups. Aryl, vinyl, as well as alkyl Grignard reagents are commonly used organometallic nucleophiles. These reactions provide extremely versatile carbon-carbon bond formation processes. Eqs 1-4 summarize representative examples.[2-4] Even acid chlorides undergo the cross-coupling reaction (eq 5).[5]

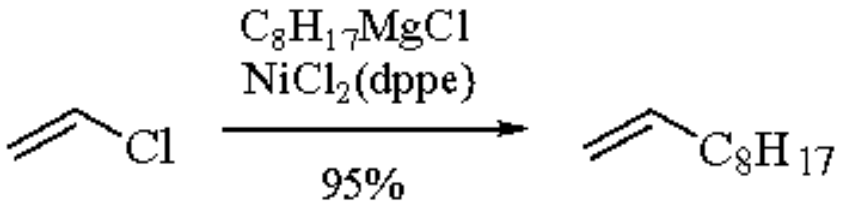

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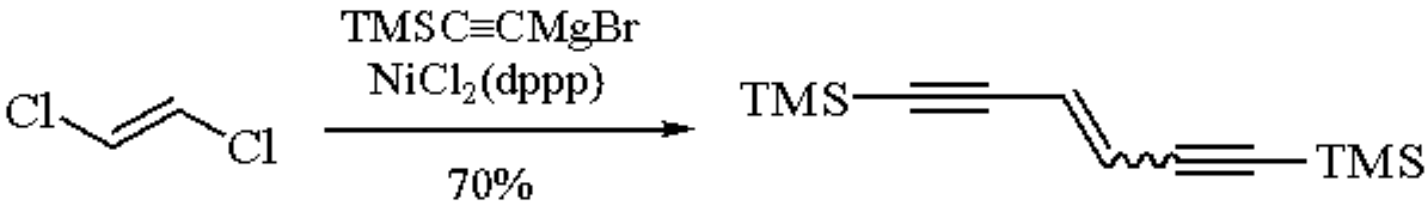

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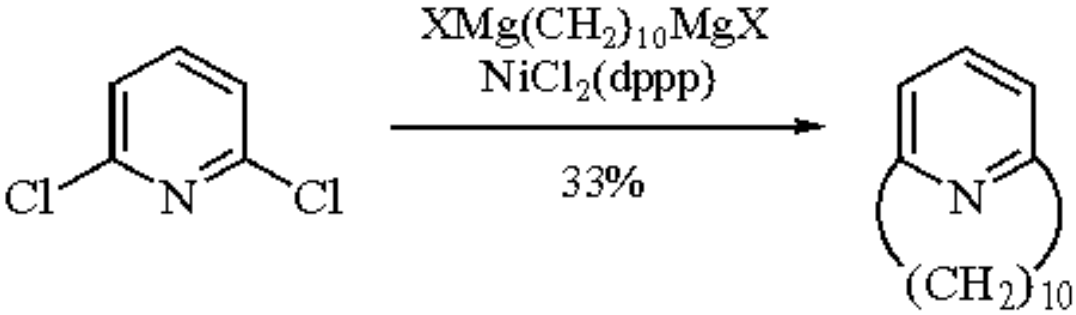

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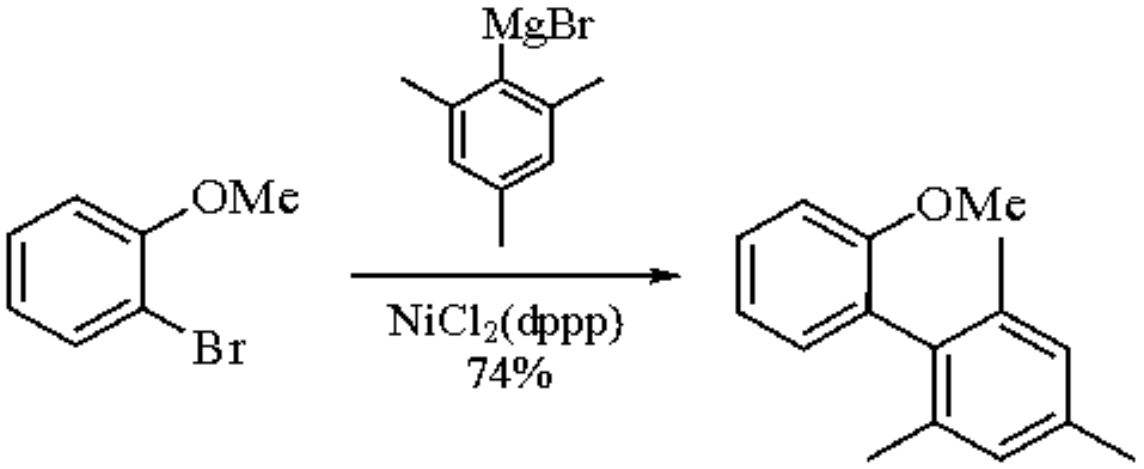

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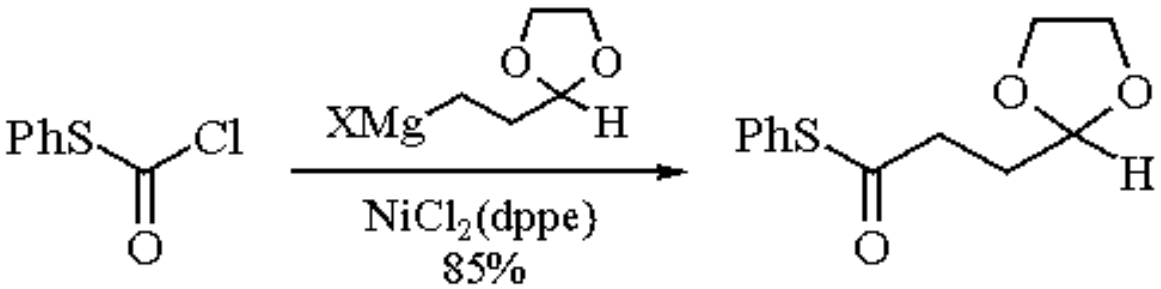

(5)

Palladium and nickel complexes are the most useful catalysts for this purpose. Although nickel compounds without phosphine ligands can mediate cross-coupling reactions, those bearing phosphine ligands occasionally give much better results, with bidentate phosphine ligands providing the greatest catalytic activity for simple aryl, vinylic, or allyl substrates.

The choice of catalyst is particularly important for reactions of secondary alkyl Grignard reagents. When secondary Grignard reagents that bear β-hydrogens are employed, competitive β-hydride elimination results in the formation of both reduced and isomerized byproducts. These side reactions are particularly bothersome in reactions with hindered alkenyl halides. It is noteworthy that the use of the $NiCl_2$(dppf) catalyst can minimize these side reactions by accelerating the rate of desired reductive elimination relative to undesired β-elimination.[6] For example, $NiCl_2$(dppf) is the most selective catalyst for the cross-coupling reaction of β-bromostyrene with *t*-BuMgCl, giving (*E*)-β-*t*-butylstyrene exclusively (eq 6).[6] Other nickel complexes, $NiCl_2(PPh_3)_2$, $NiCl_2$(dppe), $NiCl_2$(dppp), and $NiCl_2$(dppb), also catalyze the coupling reaction, but it is accompanied occasionally by *t*-butyl isomerization to give (*E*)-β-isobutylstyrene as a byproduct. Moreover, there are only limited cases which are known for the cross-coupling reactions of alkyl iodides with Grignard reagents. $NiCl_2$(dppf) again demonstrates a unique reactivity for this transformation.[7] It is interesting to note that only neopentyl iodide can undergo coupling reactions with aromatic Grignard reagents (eq 7). Other coupling reactions including the activation of aliphatic carbon-sulfur bonds will be discussed later.

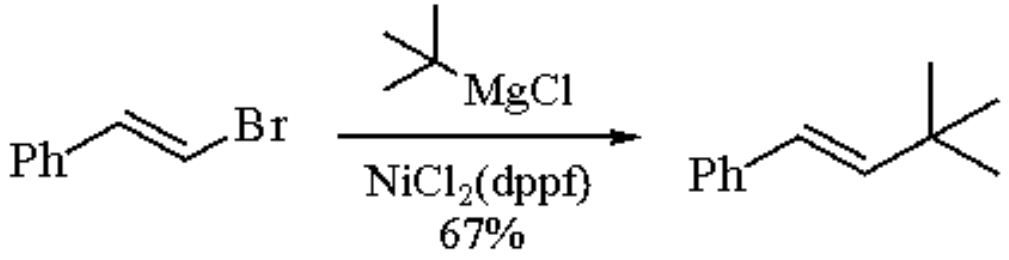

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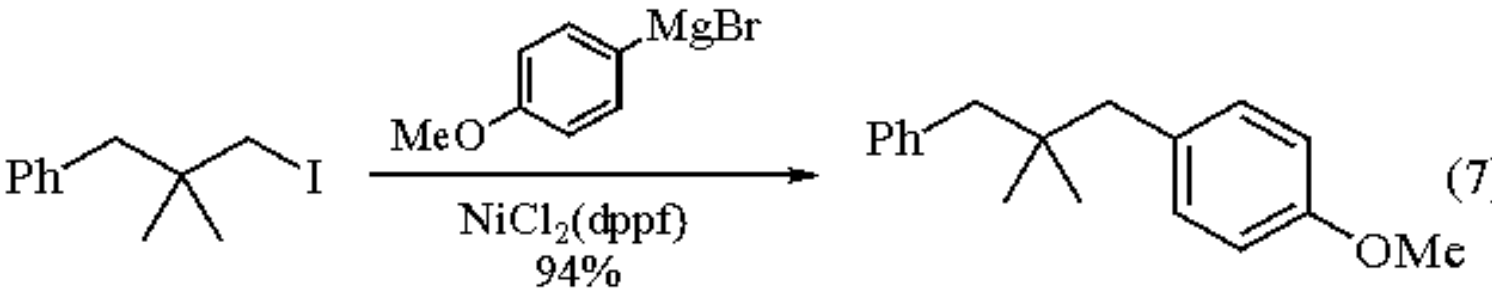

(7)

In general, reactions of alkenyl halides exhibit predominant retention of alkene geometry (eq 8),[8] while reactions of alkenyl Grignard reagents are complicated by competing (*Z*) to (*E*) isomerization.[1]

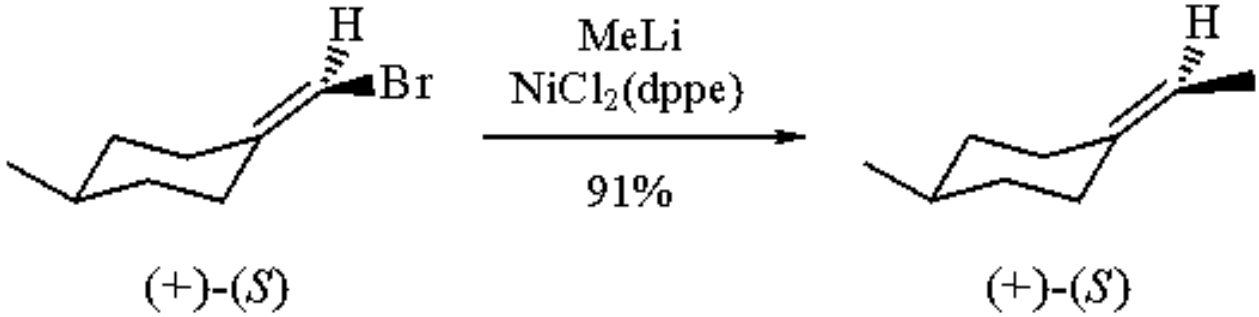

(8)

Coupling reactions of unsymmetric allylic substrates normally gives a mixture of isomers. However, when a zinc reagent is used, allyl chlorides undergo regioselective displacement reactions giving S_N2-like products predominantly, if not exclusively (eq 9). It is noted that copper-catalyzed reactions give S_N2' substitution products selectively.[9]

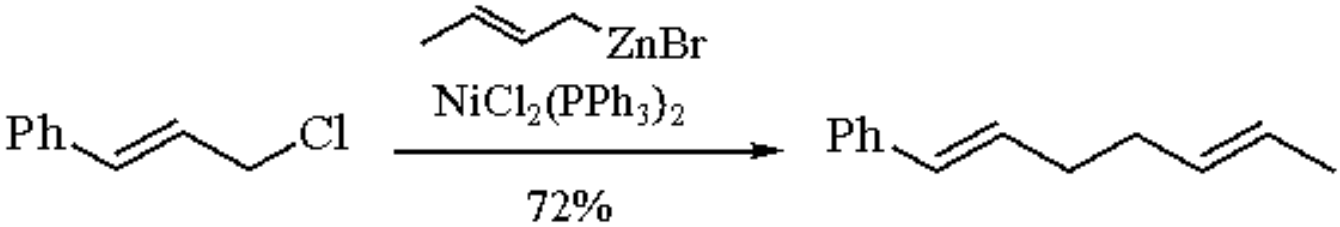

(9)

Vinyl and aryl ethers also react with Grignard reagents under nickel catalysis, although they are less reactive than the corresponding bromides.[10] Reactions of dihydrofuran and dihydropyran derivatives with Grignard reagents, giving homoallylic and bishomoallylic alcohols, respectively, are particularly noteworthy (eqs 10 and 11).[11] Retention of alkene geometry is predominantly observed. Silyl enol ethers[12a] and enol phosphates[12b,c] behave similarly.

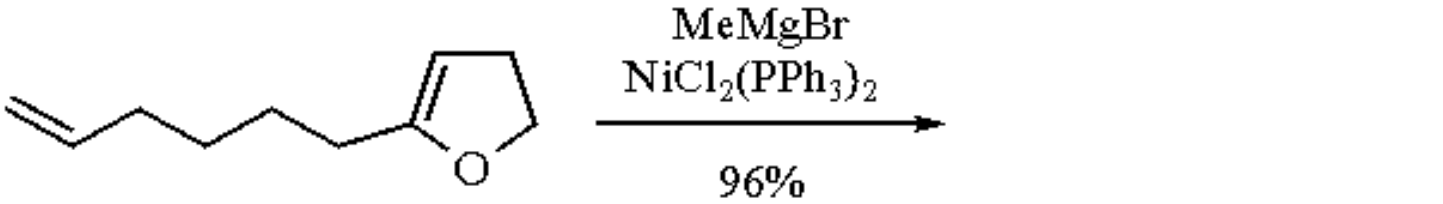

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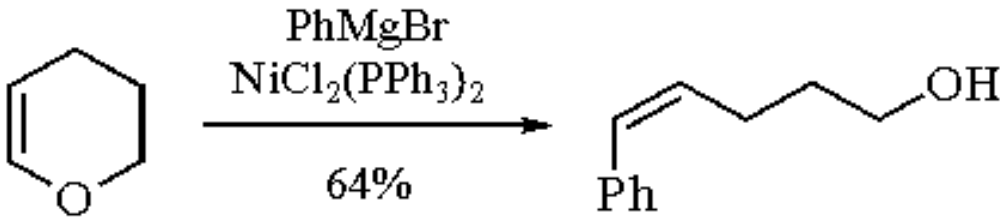

(11)

Allylic alcohols also give the corresponding coupling products upon treatment with a Grignard reagent in the presence of the nickel catalyst (eq 12),[1e,13] and propargylic ethers yield the allene products (eq 13).[14a] It is noteworthy that soft nucleophiles can also displace the allylic ethers in the presence of the nickel catalyst (eq 14).[14b]

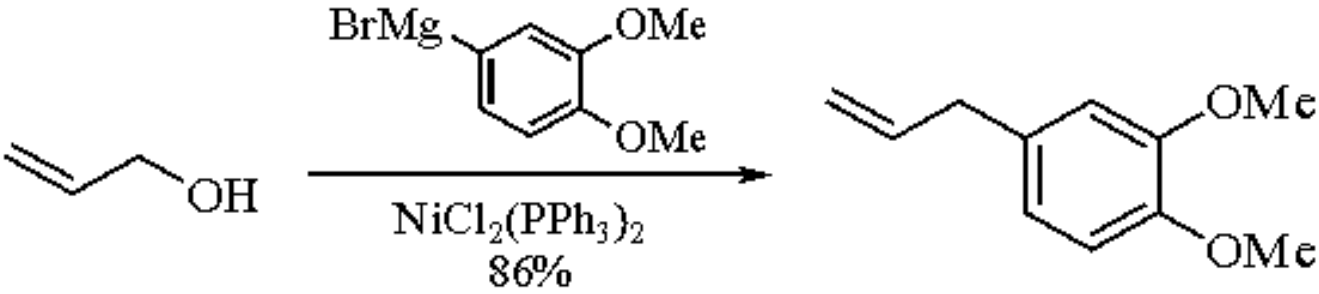

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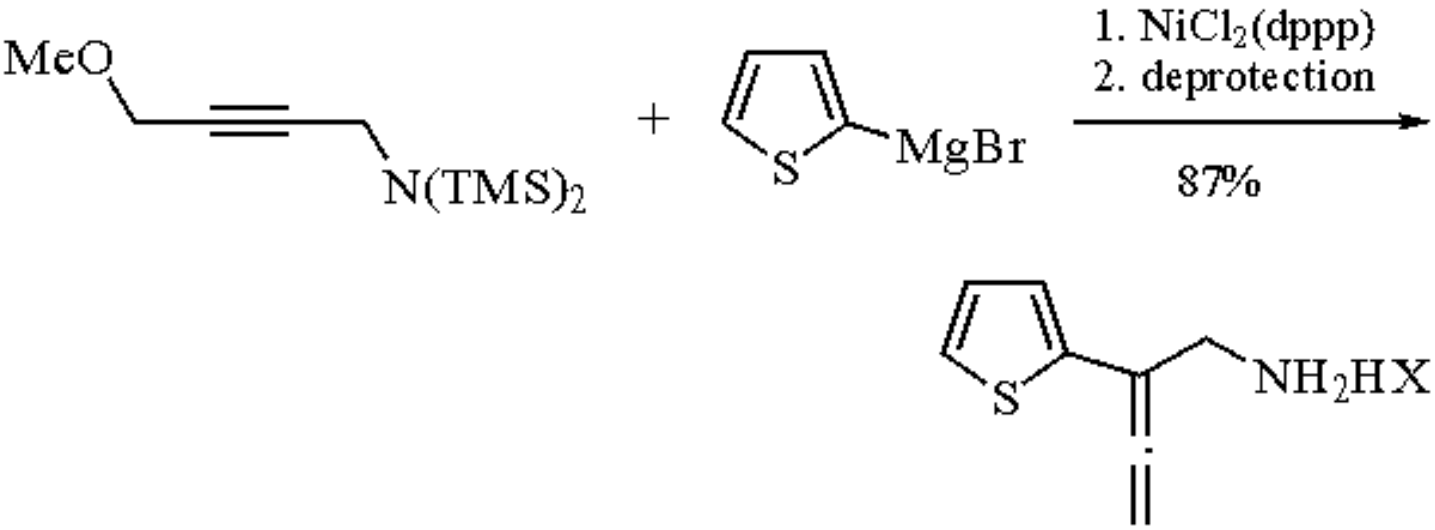

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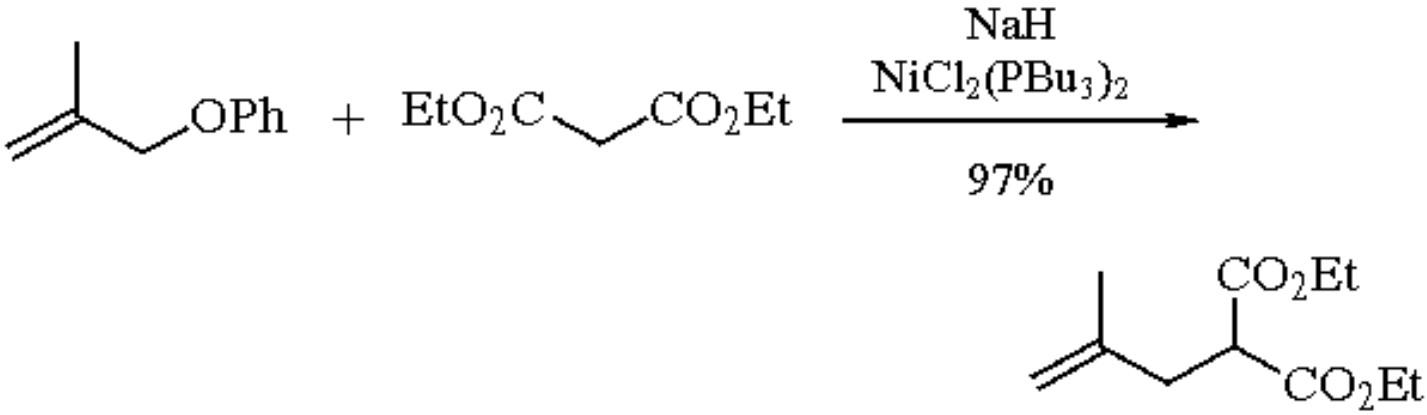

(14)

The nickel-catalyzed substitution of vinyl sulfides by Grignard reagents forms the basis of a procedure for the stereoselective synthesis of alkenes by sequential cross-coupling reactions (eq 15).[1c-g,15,16] The cross-coupling reactions of thiophenes under the same conditions lead to stereoselective synthesis of substituted butadienes (eq 16).[15d,e] Unlike halide and triflate leaving groups, where palladium is also effective, the nickel catalyst plays a unique role in the displacement of the carbon-sulfur bonds. Thiols, sulfoxides, sulfones, as well as sulfonates also undergo coupling reactions smoothly (eq 17).[15] Among vinylic substrates, the reactivity trend of various leaving groups in these nickel-catalyzed cross-coupling reactions appears to be in the following order: I > Br > SR > Cl > OR.

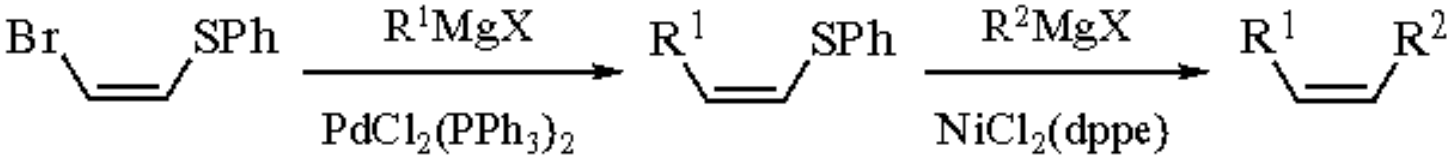

(15)

R^1, R^2 = alkyl, aryl, vinyl

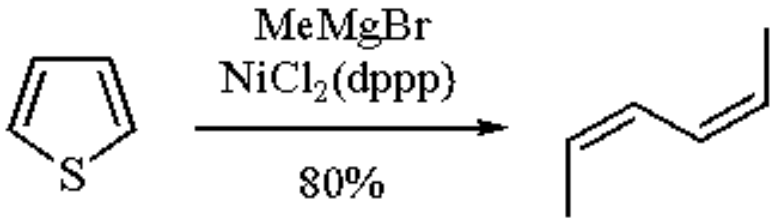

(16)

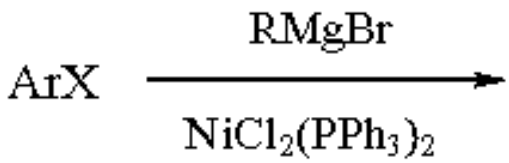

(17)

X = SH, SOMe, SO_2Me, $SO_3C_6H_4Me$

Optically active alkenylsulfoximines undergo nickel-catalyzed cross-coupling with organozinc reagents in the presence of an additional magnesium, lithium, or zinc salt. The reaction proceeds with more than 98% retention of alkene geometry (eq 18).[17]

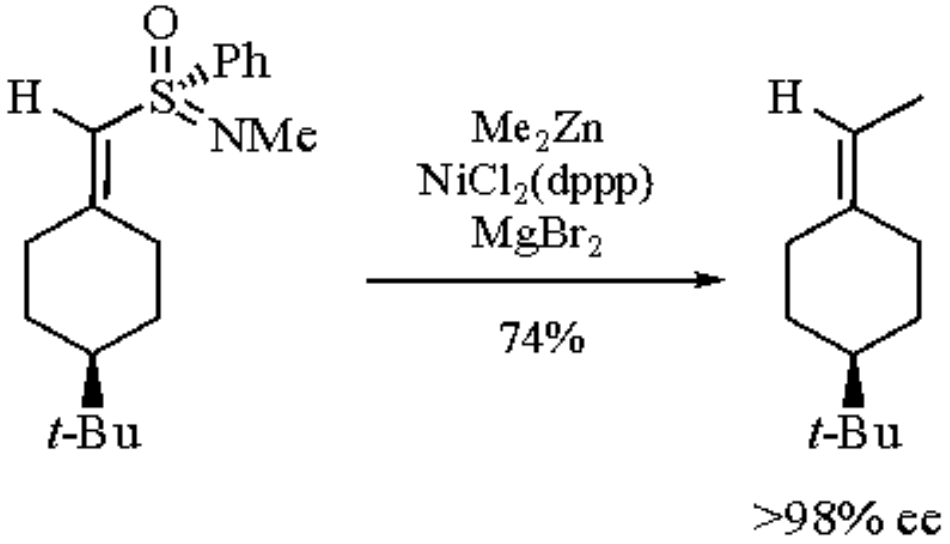

(18)

Dithioacetals have two carbon-sulfur bonds attached to the same carbon atom. Sequential displacements of these two bonds in allylic substrates (eq 19) and *o*-amino-substituted benzylic substrates (eq 20) result in the net conversion of a carbonyl equivalent into a geminal dimethylated product.[1f,g,18] It is noteworthy that only nickel complexes containing bidentate ligands catalyze the desired geminal dimethylation. When $NiCl_2(PPh_3)_2$ is used, a mixture of alkenation and dimethylation products is obtained.

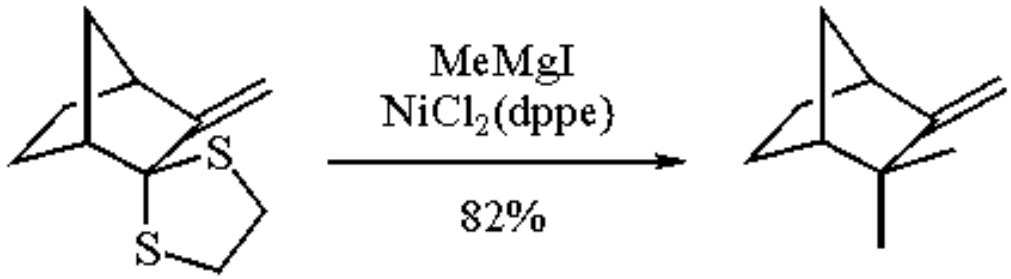

(19)

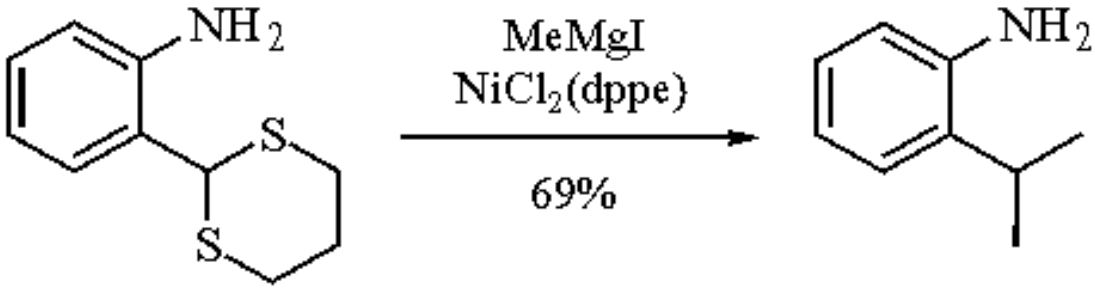

(20)

As mentioned earlier, β-hydride elimination is a major side reaction in the cross-coupling. However, this elimination process has been used in cross-coupling reactions of dithioacetals leading to alkenation products.[1g] In this case, one of the carbon-sulfur bonds is substituted by a carbon-carbon bond, and subsequently the second carbon-sulfur bond is eliminated to produce an alkene (eq 21).[1f,g,19] In this respect, $NiCl_2(PPh_3)_2$ is the best catalyst and the sulfur leaving group may coordinate to the nickel catalyst throughout the catalytic process.[20] The reaction has particularly useful applications for the synthesis of various silyl-substituted alkenes and dienes (eqs 22 and 23).[21] When the cyclopropyl Grignard reagent is employed, the reaction provides an interesting ring opening route for the synthesis of substituted dienes (eq 24).[22] This reaction demonstrates an interesting example using cyclopropyl anion as an allyl anion synthon. Reactions of dithioacetals with allylmagnesium halides under similar conditions, on the other hand, afford

1,4-pentadienes as the predominant, if not exclusive, products.[21b] Benzylic and allylic orthothioesters also give the corresponding alkylative alkenation products in satisfactory yields.[21c,e]

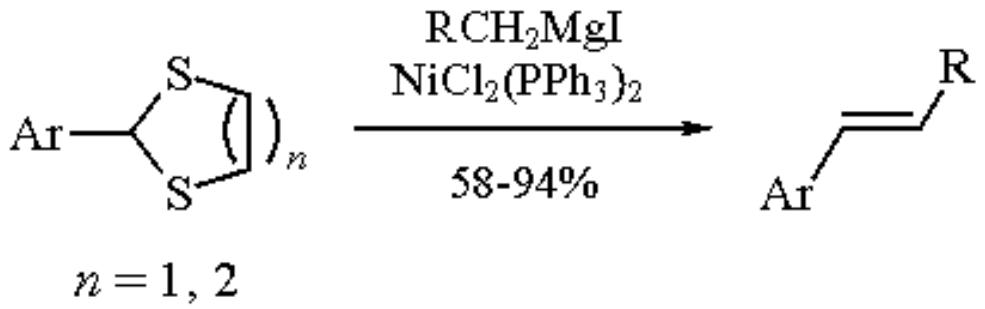

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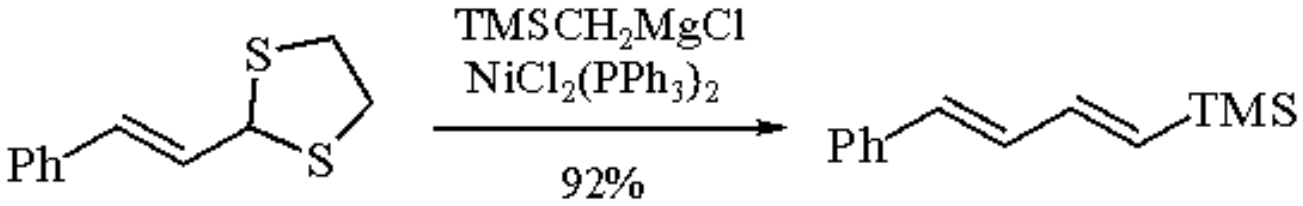

(22)

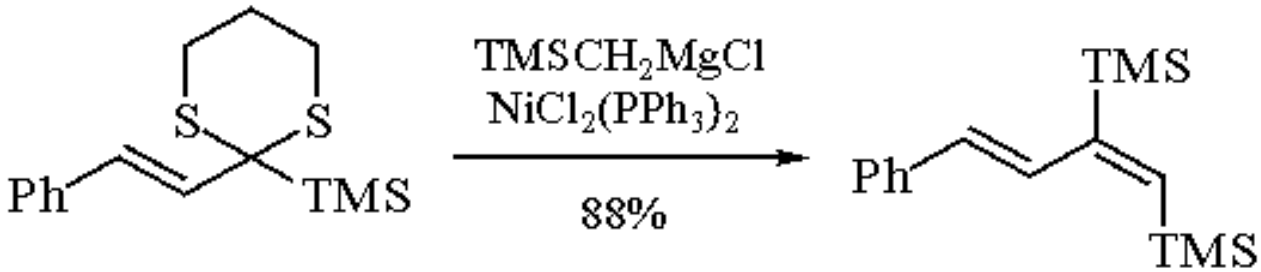

(23)

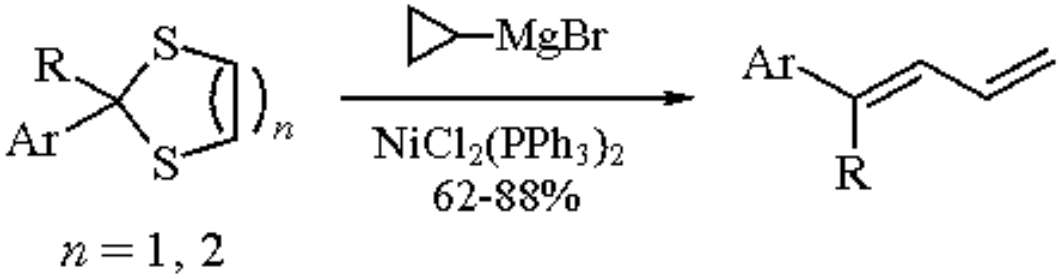

(24)

Whereas simple aliphatic dithioacetals do not undergo the cross-coupling reaction, tetrathioorthocarbonate interestingly serves as a C^{4+} synthon under these reaction conditions.[23] For example, tris(trialkylsilyl)isobutene is conveniently synthesized as shown in eq 25. When an appropriately located heteroatom is present for chelation of the nickel catalyst, aliphatic dithioacetals can also undergo cross-coupling reactions. Depending on the nature of the substrates, bisdithioacetals undergo either selective monoalkenation or a tandem coupling process via an allylic dithioacetal intermediate (eqs 26 and 27).[24]

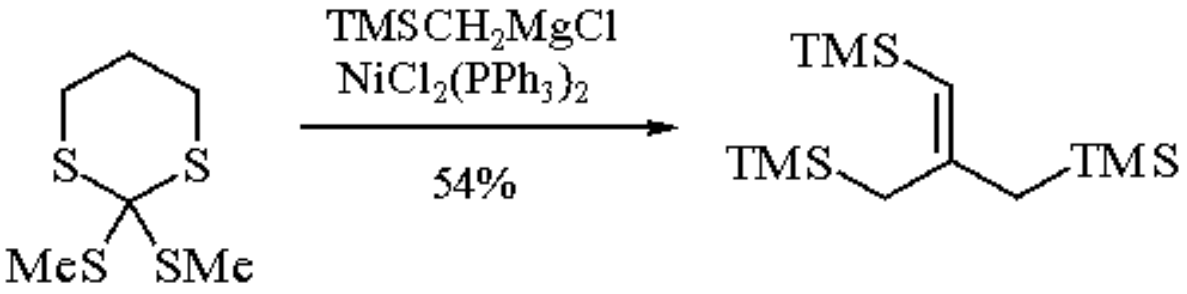

(25)

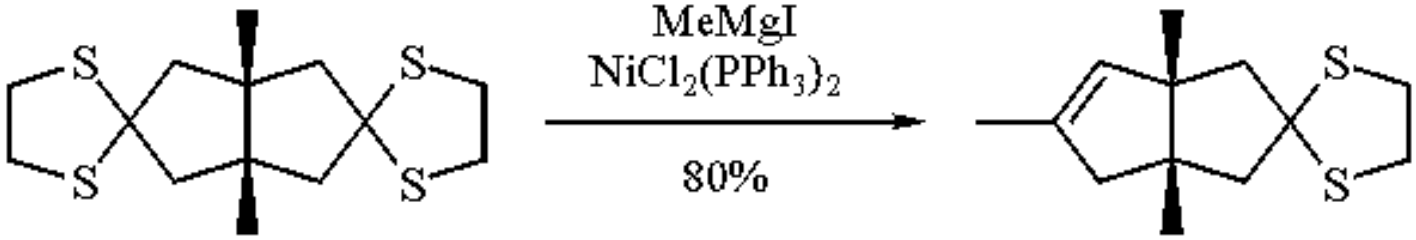

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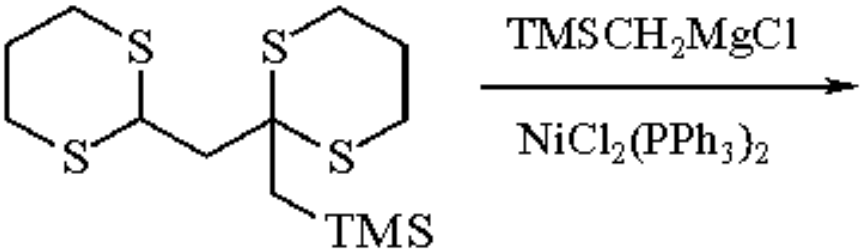

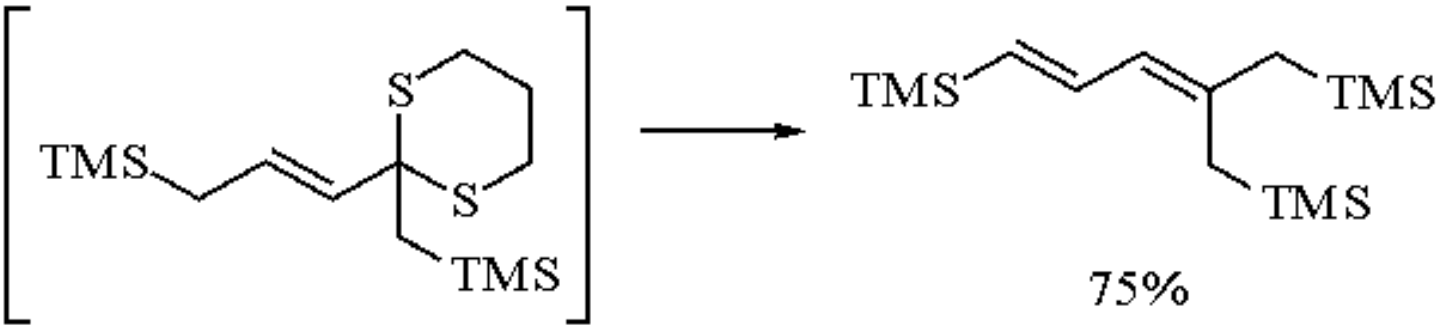

(27)

Since the reaction medium is basic, benzylic dithioacetal-*S*-oxides undergo a Pummerer-type rearrangement followed by the reaction with the Grignard reagent to give the dithioacetals which then undergo the nickel-catalyzed alkenation process to yield the corresponding alkylative alkenation products (eq 28).[25]

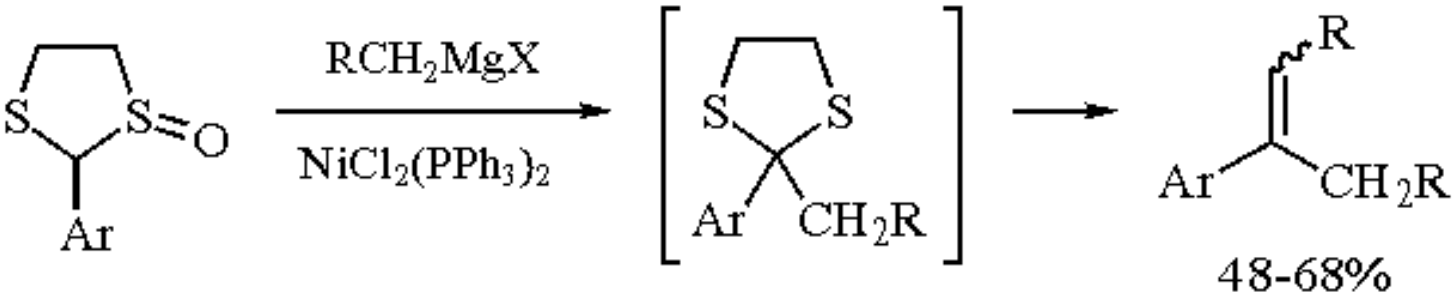

(28)

Carbon-tellurium bonds can be replaced[26] and quarternary ammonium ion can also serve as a leaving group in the

nickel-catalyzed cross-coupling reactions (eq 29).[27]

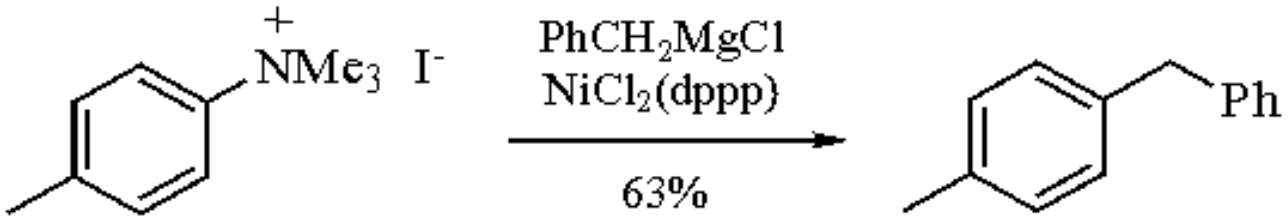

(29)

Cross-coupling reactions of Si-O and Si-H bonds with Grignard reagents are also catalyzed by nickel complexes (eqs 30 and 31).[28,29]

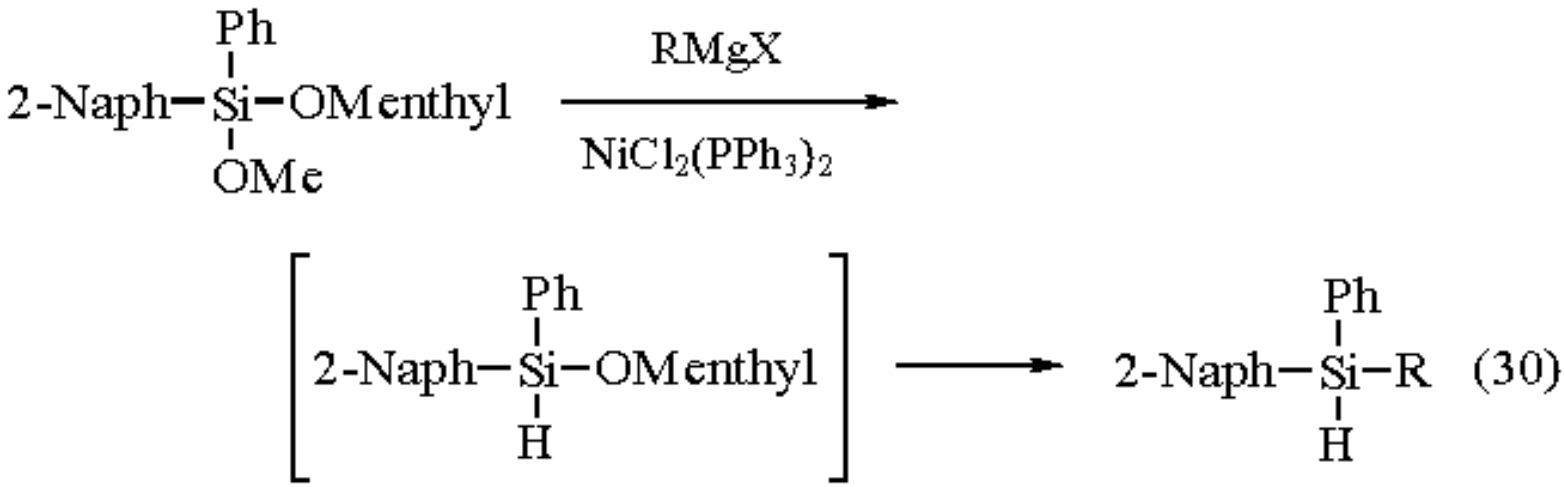

(30)

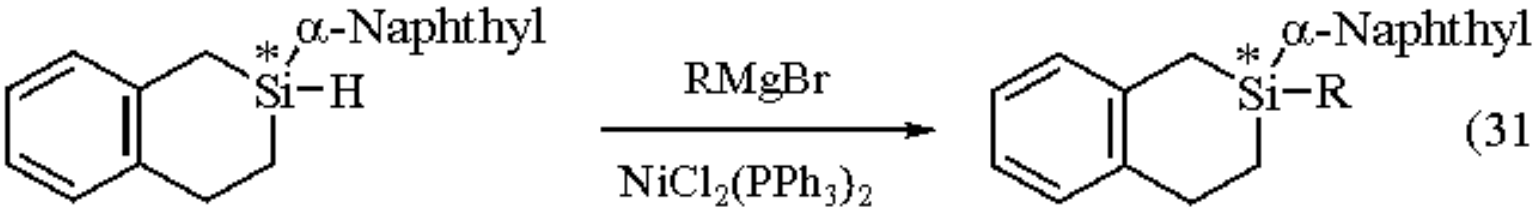

(31)

Cross-Coupling Reactions Using Chiral Ligands.

When chiral phosphine ligands are used, the coupling reaction can be enantioselective.[1l-n] Thus the cross-coupling reaction of 3-cyclohexenyl ether with EtMgBr yields the corresponding hydrocarbons with excellent selectivity when [(*S*,*S*)-chiraphos]$NiCl_2$ is employed (eq 32).[30]

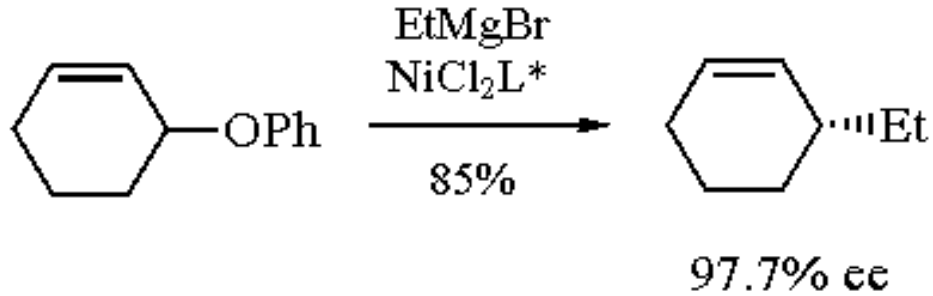

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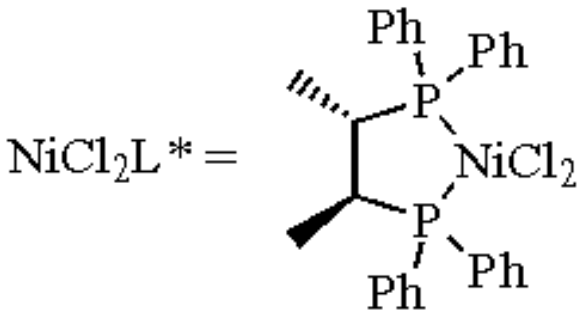

The cross-coupling reaction between 1-phenylethylmagnesium bromide and vinyl bromide in the presence of a [(*S*,*S*)-norphos]$NiCl_2$ catalyst yields the corresponding coupling product in 95% yield with 67% ee (eq 33).[31]

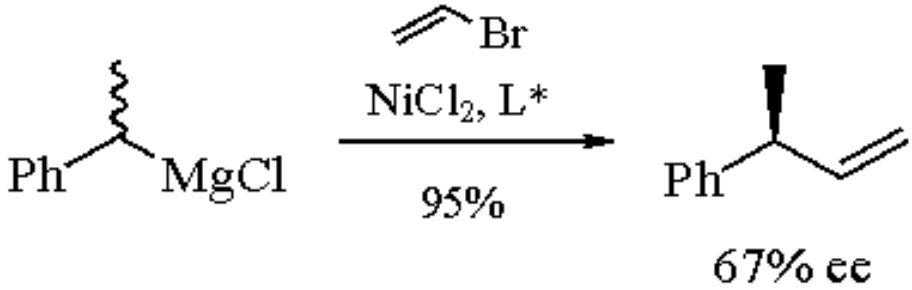

(33)

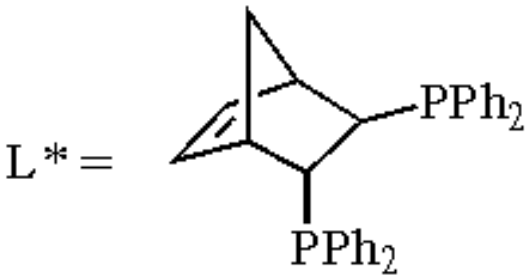

Higher enantioselectivities are achieved when certain chiral aminophosphines derived from amino acids are used. In general, ligands derived from (*S*)-amino acids give rise to the (*S*)-product, but it has been reported that this trend is reversed in the presence of ZnX_2. It is worth noting that a sulfide-containing side chain appended to the dimethylaminophosphine ligands improves the enantioselectivity. The sulfide moiety offers a third site for coordination to the metal, and such intramolecular participation would accelerate the rate of reductive elimination, minimizing the loss of enantiomeric purity resulting from competitive β-elimination (eq 34).[32]

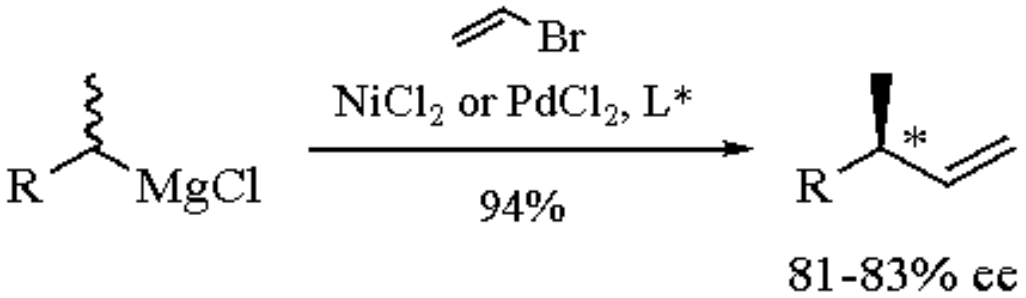

(34)

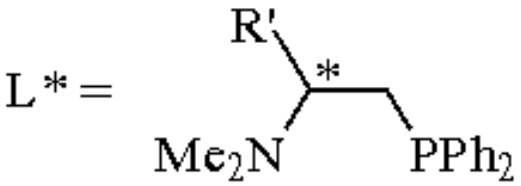

R = *p*-Tol, *p*-(*i*-Bu)C_6H_4, *p*-PhC_6H_4, Ph
R' = *i*-Pr, *t*-Bu, *s*-Bu, Cy, MeS$(CH_2)_3$

It is particularly noteworthy that cross-coupling reactions of 1-bromonaphthalenes with 1-naphthyl Grignard reagents in the presence of a ferrocene-based chiral nickel catalyst [(*S*)-(*R*)-PPFOMe]$NiCl_2$ furnish a useful entry for the preparation of a various chiral binaphthyl derivatives (eq 35).[33] Chiral ternaphthyl derivatives are obtained similarly.[33] It is interesting to note that other ferrocene-based chiral ligands do not behave well under the reaction conditions.[34]

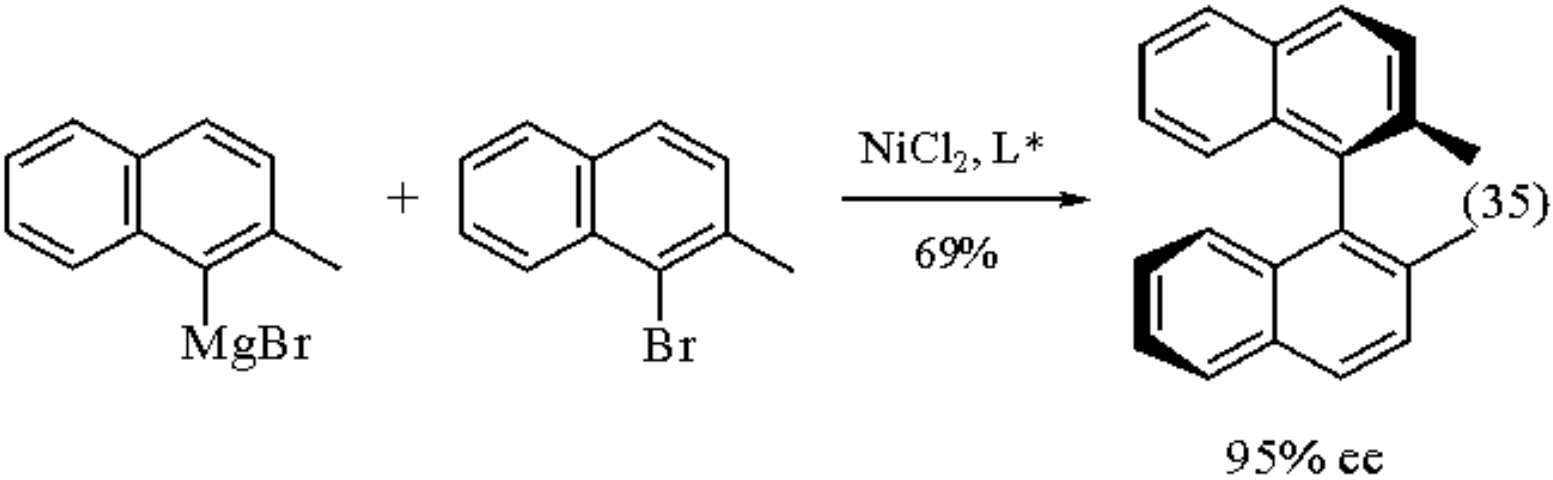

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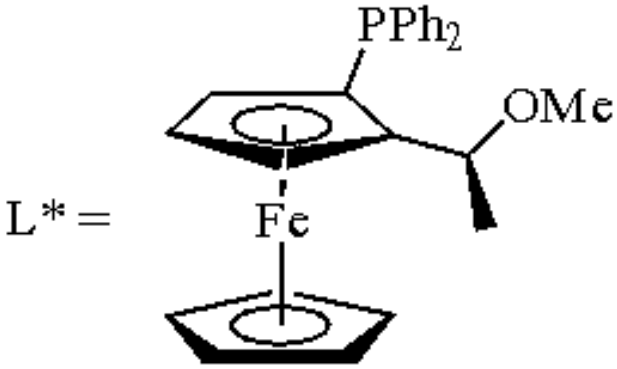

[(*S*)-(*R*)-PPFOMe]

Reduction.

Nickel hydride species, generated in situ from the reaction of secondary Grignard reagents and $NiCl_2(PPh_3)_2$ catalyst, are active for the reductive cleavage of the carbon-sulfur bonds (eq 36).[35] Vinylic or aryl thiols, sulfides, sulfoxides, and sulfones can be reduced with ease under these conditions. The reduction is stereospecific, with no over reduction being detected. Si-X bonds are also reduced under similar conditions.[36]

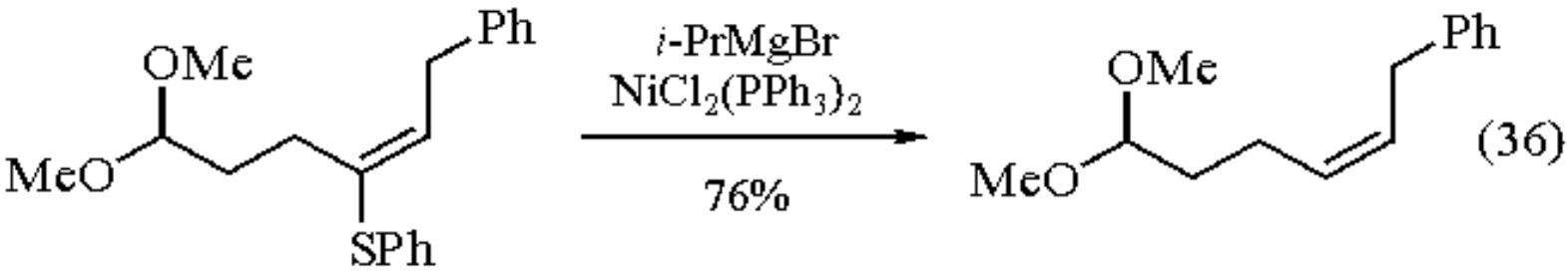

Homocoupling.

A Ni^0 catalyst generated in situ from the reduction of $NiCl_2(PPh_3)_2$ with zinc promotes homocoupling of aryl or vinyl halides in good yields (eq 37).[37,38] DMF is the most suitable solvent. Esters, amides, ketones, aldehydes, and ether functionalities are stable under the reaction conditions. Bicinnamyl is obtained from cinnamyl chloride in 50% yield.[38] (*E*/*Z*) isomerization may occur in the homocoupling of alkenyl halides.[38b] Et_4NI or KI or thiourea have been shown to assist the reduction of Ni^{II} with zinc and also to convert the alkenyl bromides to the corresponding alkenyl iodides.[38e,f] The extension of this reaction to the synthesis of heterocyclic biaryls, such as bipyridyls and bithienyls, has been executed.[39] The generation of a Ni^0 species by electrochemical reduction of $NiCl_2(PPh_3)_2$ is useful for the reductive homocoupling of aryl bromides.[40]

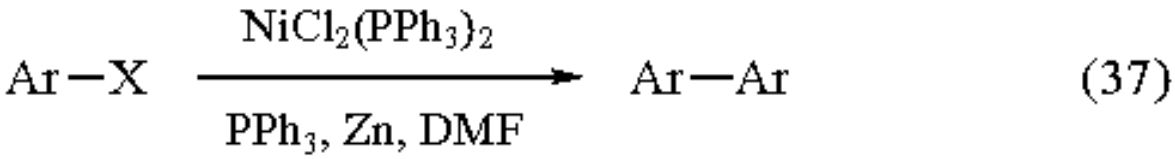

Displacement.

Aryl bromides are readily displaced by iodide in the presence of nickel catalysts.[38e,f] In a similar manner, carbon-sulfur bonds are produced when an aryl iodide is treated with thiourea in the presence of a Ni^0 catalyst generated in situ from the reaction of $NiCl_2(PEt_3)_2$ and ***Sodium Cyanoborohydride*** (eq 38).[41] Hydrolysis of the thiouronium salt gives the corresponding thiols.

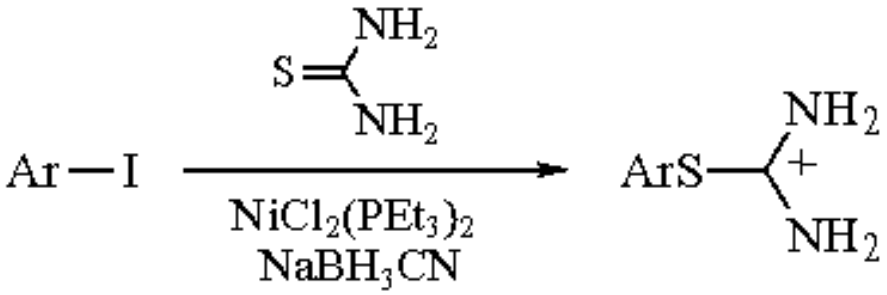

(38)

Reductive Heck-Like Reactions.

In the presence of the zinc, $NiCl_2(PPh_3)_2$ promotes reductive coupling reactions of aryl bromides with excess α,β-unsaturated esters in the presence of pyridine and a trace amount of water (eq 39).[42] Alkyl bromides also give similar coupling products.

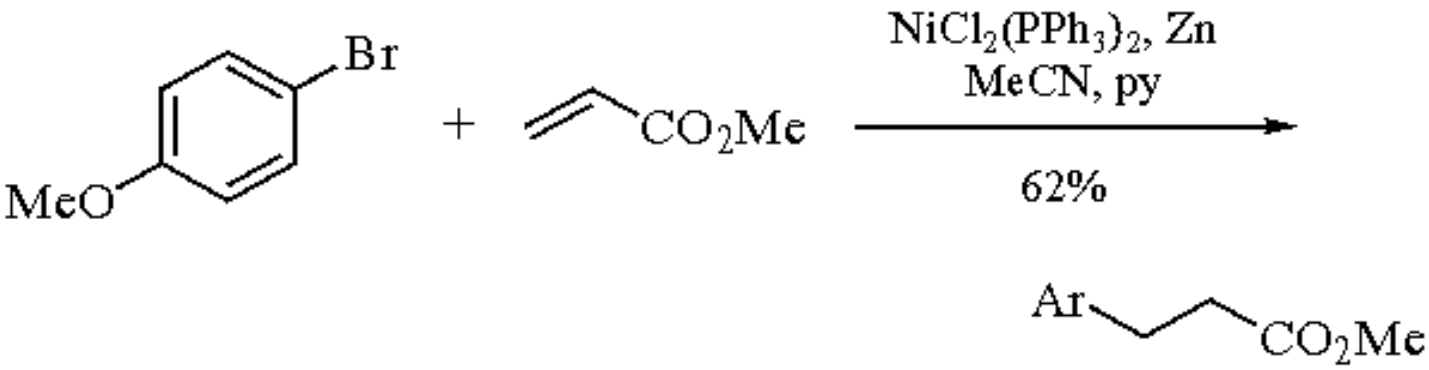

(39)

Miscellaneous.

Octa-1,7-diynes bearing ester groups on the terminal positions react with propargyl alcohols in the presence of stoichiometric amounts of a nickel(0) reagent derived from $NiCl_2(PPh_3)_2$ and ***n-Butyllithium*** to give tetralin lactones in moderate yields (eq 40).[43]

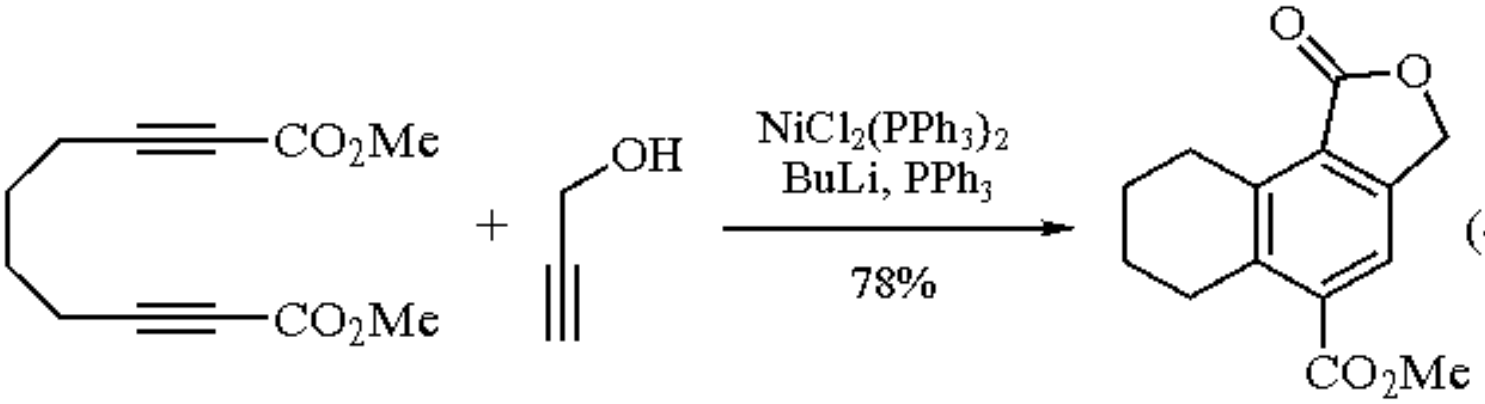

(40)

The formation of ketones from reaction of a carboxylic acid with a Grignard reagent is catalyzed by $NiCl_2$(dppe) (eq 41).[44] The *cis* addition of the Grignard reagent to triple bond is also catalyzed by $NiCl_2(PPh_3)_2$ (eq 42).[45] Elimination of HBr from a terminal bromo compound is reportedly promoted by $NiCl_2(PPh_3)_2$ (eq 43).[46]

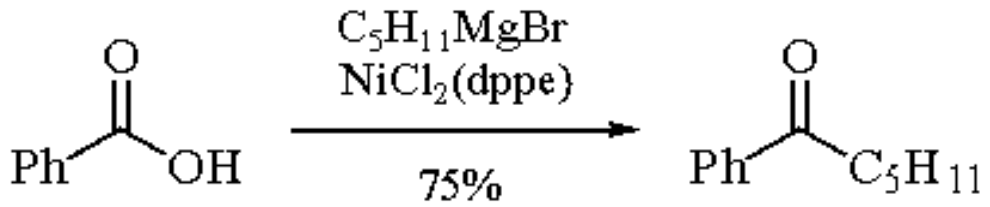

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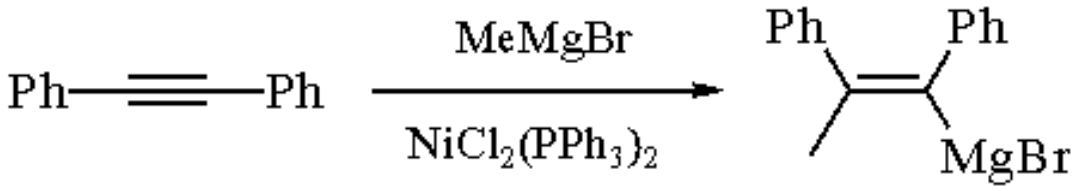

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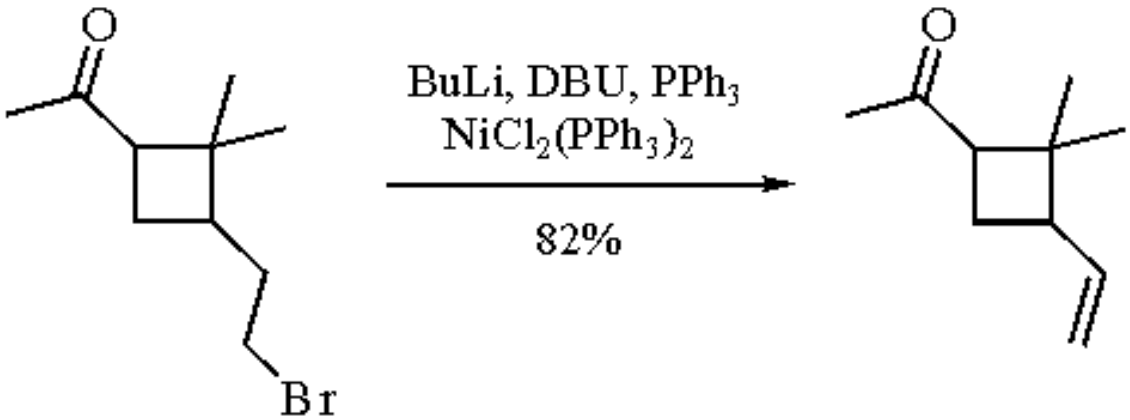

(43)

Although low-valent nickel complexes are very useful for dimerization and oligomerization of alkenes, the use of $NiCl_2(PPh_3)_2$ or related complexes for this purpose is relatively rare (eq 44). Occasionally, a number of isomeric products are obtained.[47]

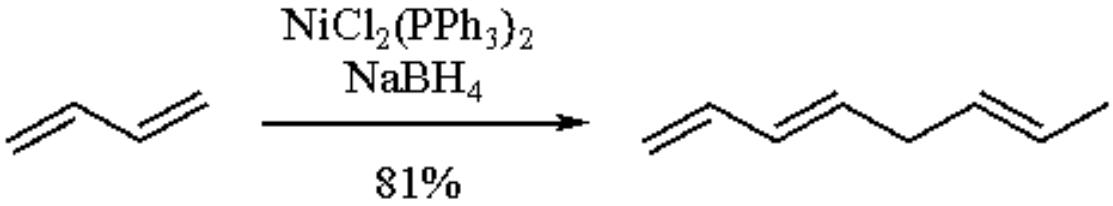

(44)

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Tien-Yau Luh & Tien-Min Yuan

Dichlorobis(triphenylphosphine)platinum(II)-Tin(II) Chloride

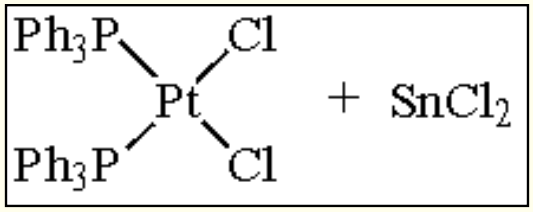

($PtCl_2(Ph_3P)_2$)

[10199-34-5] · $C_{36}H_{30}Cl_2P_2Pt$ · Dichlorobis(triphenylphosphine)platinum(II)-Tin(II) Chloride · (MW 790.58) (*cis*)

[15604-36-1] (*trans*)

[14056-88-3] ($SnCl_2.2H_2O$)

[10025-69-1] · Cl_2Sn · Dichlorobis(triphenylphosphine)platinum(II)-Tin(II) Chloride · (MW 225.63)

(a homogeneous catalyst for hydroformylation,[1] hydrogenation, and isomerization of alkenes)

Physical Data: cis-$PtCl_2(Ph_3P)_2$: mp 310 °C (dec); *trans*-$PtCl_2(Ph_3P)_2$: mp > 300 °C; $SnCl_2.2H_2O$: mp 37.7 °C (dec), bp 652 °C, *d* 2.710 g cm^{-3}.

Solubility: $SnCl_2.2H_2O$ sol alcohol, ether.

Form Supplied in: $PtCl_2(Ph_3P)_2$: solid; $SnCl_2.2H_2O$: white crystals, widely available.

Handling, Storage, and Precautions: $PtCl_2(Ph_3P)_2$: irritant, hygroscopic; $SnCl_2.2H_2O$: corrosive, toxic.

Hydroformylation.

In combination with an excess of tin(II) chloride as cocatalyst, $PtCl_2(Ph_3P)_2$[2] catalyzes the hydroformylation[1,3] of a variety of α-alkenes in high yield and selectivity (eq 1).

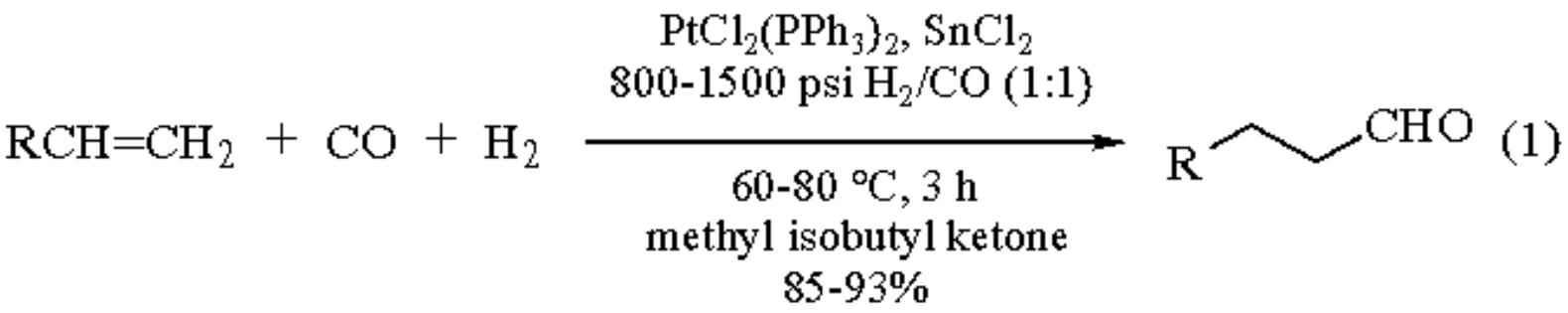

The yields and the selectivity for linear aldehydes depend on alkene structure, temperature, H_2/CO pressure, and solvent composition. Cyclic alkenes have also been hydroformylated (e.g. cyclopentene, 79% yield). Competing alkene isomerization (ca. 7%) and reduction to the alkane (ca. 4%) are generally observed. The catalytic activity of this system has been enhanced by the use of various other ligands in place of triphenylphosphine.[1,3] Good chemo- and regioselectivity can be obtained in the hydroformylation of functionalized alkenes (eq 2).[4] Enantioselective hydroformylations have been achieved using chiral phosphine ligands.[5]

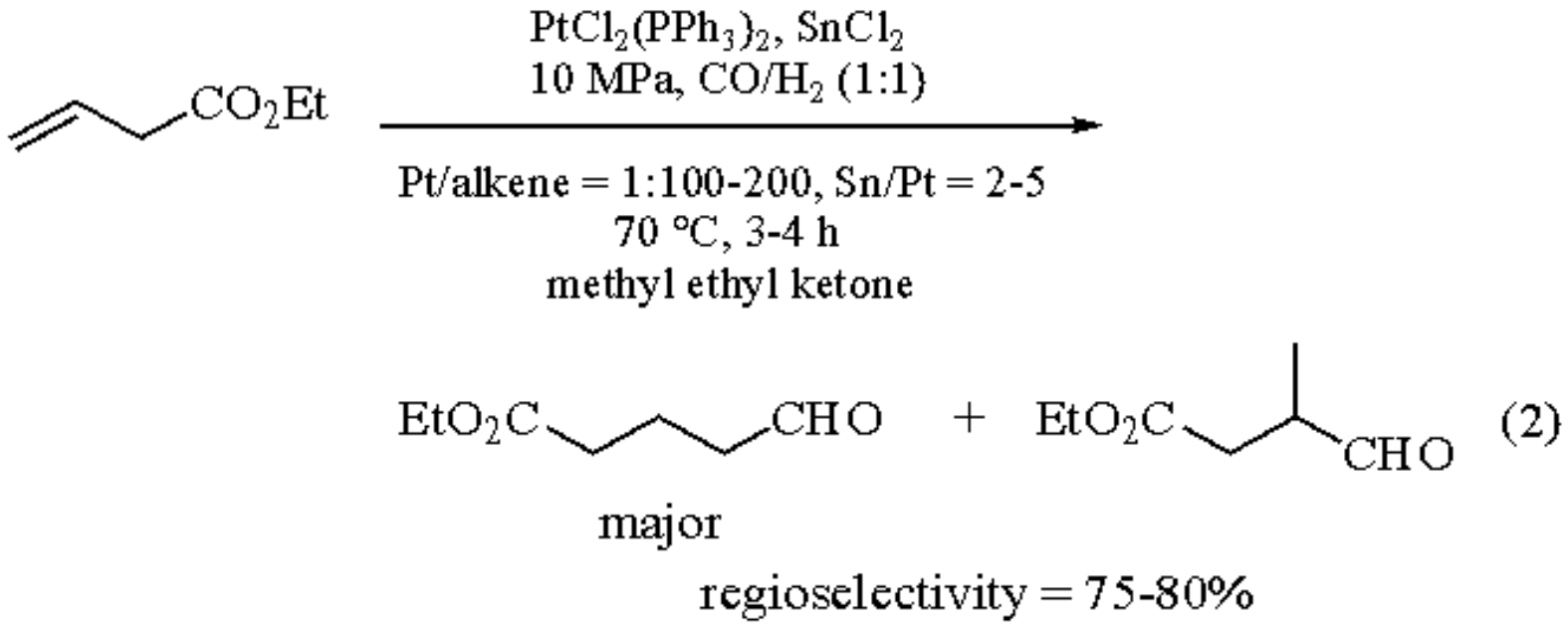

The mechanism of this hydroformylation has been investigated and some putative intermediates have been identified.[6] When the reaction is carried out in ethanol in the absence of H_2, terminal esters are obtained, but in low yield.[7] More effective catalysts for this alkoxycarbonylation have been developed.

Hydrogenation.

This catalyst system has been utilized for the hydrogenation of nonaromatic polyalkenes to monoenes.[8] The reaction proceeds via migration of the double bonds into conjugation, followed by reduction. The ability of this catalyst to place double bonds into conjugation has been exploited for the conversion of 1,5-cyclooctadiene to 1,3-cyclooctadiene, and for placing the double bonds of methyl linoleate into conjugation.[9]

Miscellaneous Reactions.

The catalyst system promotes the conversion of primary alkylamines to the corresponding dialkylamines.[10] It has also been reported that in methanol this system rearranges steroidal allylic alcohols to the allyl methyl ethers (eq 3).[11]

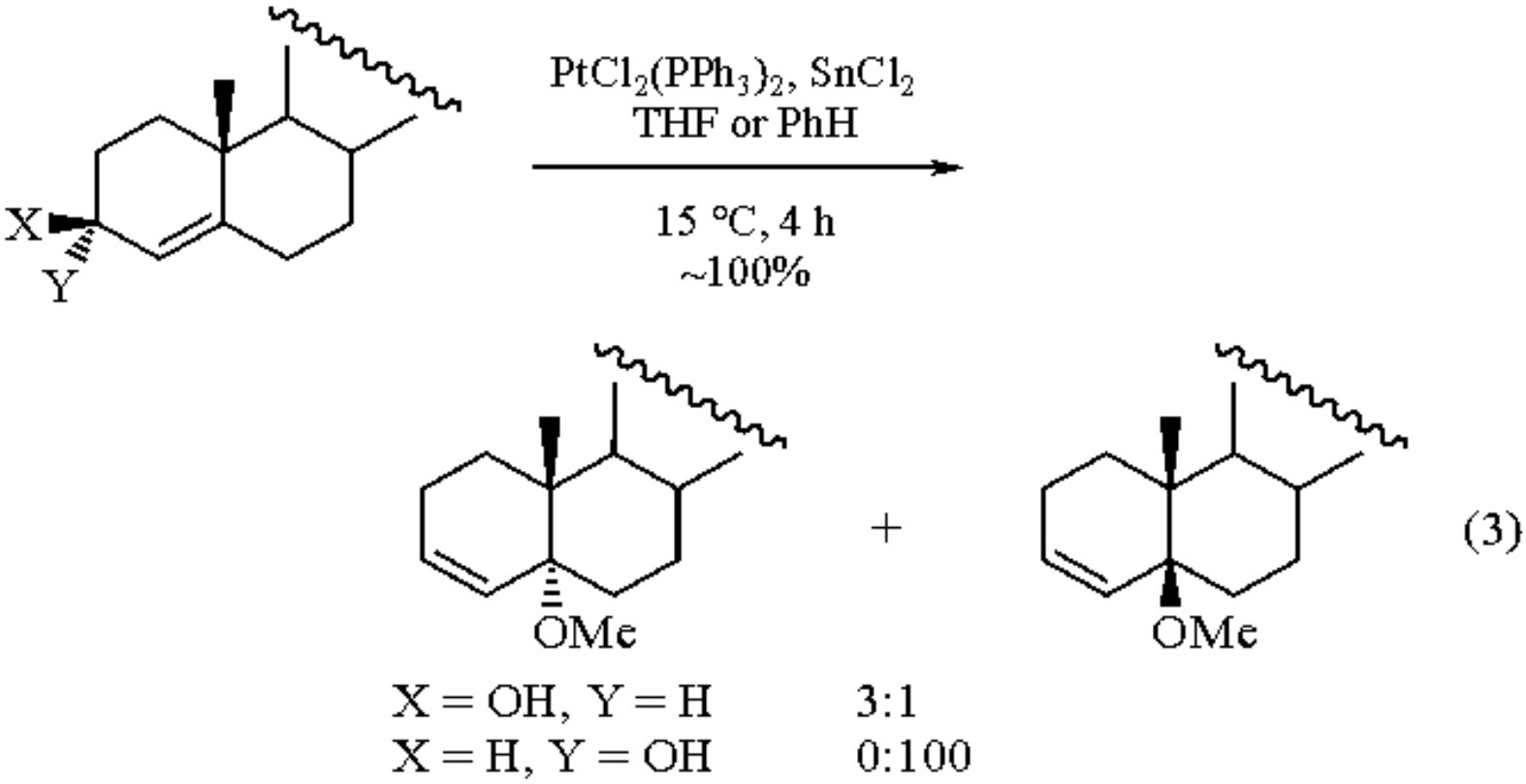

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Surendra P. Singh, Venkat Krishnamurthy & Viresh H. Rawal

Dichlorobis(tri-*p*-tolylphosphine)palladium(II)

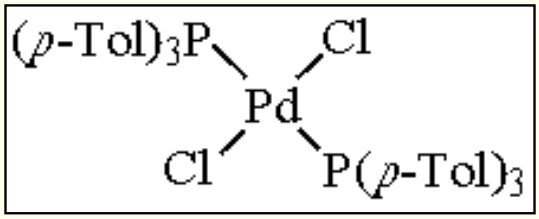

[60802-43-9] · $C_{42}H_{42}Cl_2P_2Pd$ · Dichlorobis(tri-*p*-tolylphosphine)palladium(II) · (MW 786.06)

(catalyst for linear carbonylation of α-alkenes with alcohols[2-4])

Alternate Name: trans-dichlorobis(tri-*p*-tolylphosphine)palladium(II).

Preparative Method: by treating an aqueous solution of commercially available K_2PdCl_2 with tri-*p*-tolylphosphine in dichloromethane using Bu_4NCl as a phase-transfer catalyst.[1]

Linear Carboxylic Acid Esters.

The title reagent has been used in bimetallic complexes with Group 14 metal halides for linear carbonylation of α-alkenes with alcohols.[2-4] Several alkyl and aryl esters of alkanoic acids have been prepared by reaction of α-alkenes with carbon monoxide and nucleophilic co-reactants using $Et_4N^+SnCl_3^-$ and $[(p\text{-Tol})_3P]_2PdCl_2$ as a catalyst system. In a typical procedure, a mixture of 1-octene (400 mmol), ethanol (400 mmol), $Et_4N^+SnCl_3^-$ (40 mmol), and $[(p\text{-Tol})_3P]_2PdCl_2$ (4 mmol) was heated for 3-6 h at 80-95 °C under nitrogen while introducing CO at 1500 psi to give 84% ethyl nonanoate with 91% conversion and 83% selectivity (eq 1).[2]

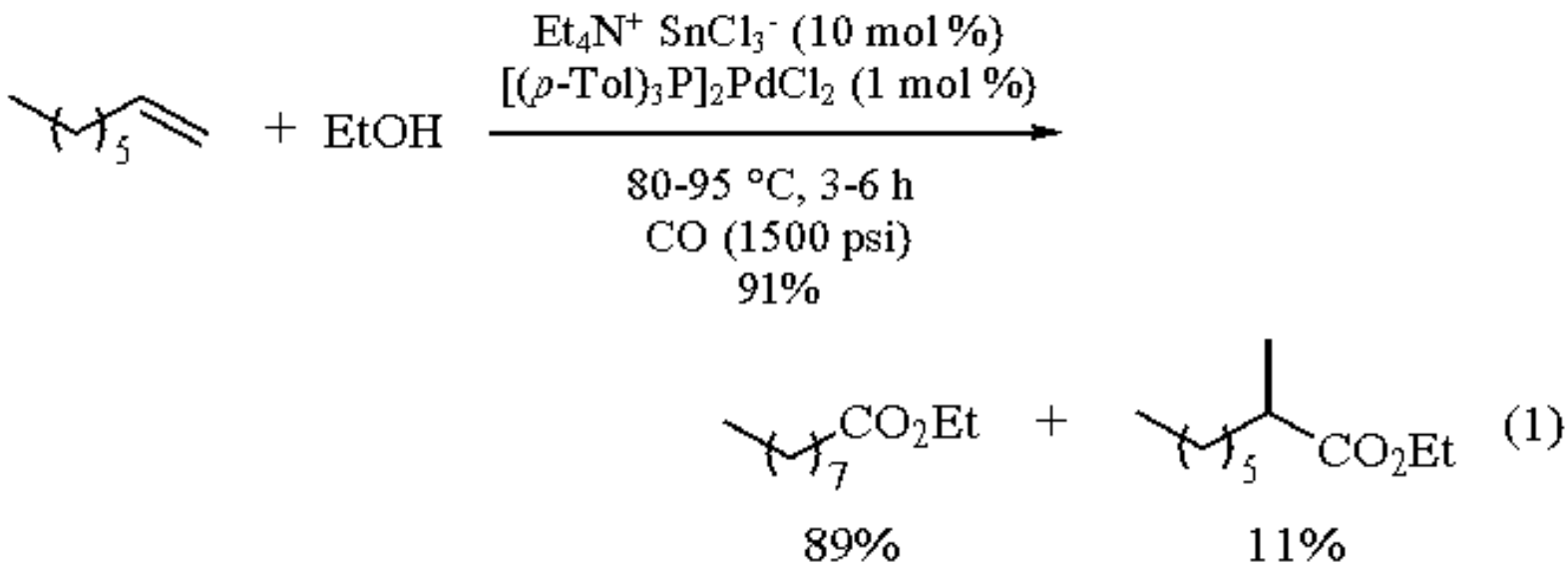

Arylacetones.

The title reagent has been used as a catalyst in aromatic acetonylation to obtain arylacetones from acetonyltri-*n*-butyltin (prepared from ***Tri-n-butyl(methoxy)stannane*** and ***Isopropenyl Acetate*** in situ, eq 2) and aryl halides.[5] In a typical procedure, a solution of methoxytributylstannane (15 mmol), isopropenyl acetate (15 mmol), aryl bromide (10 mmol), and the palladium complex (0.1 mmol) in toluene (5 mL) was heated for 5 h (eq 3).

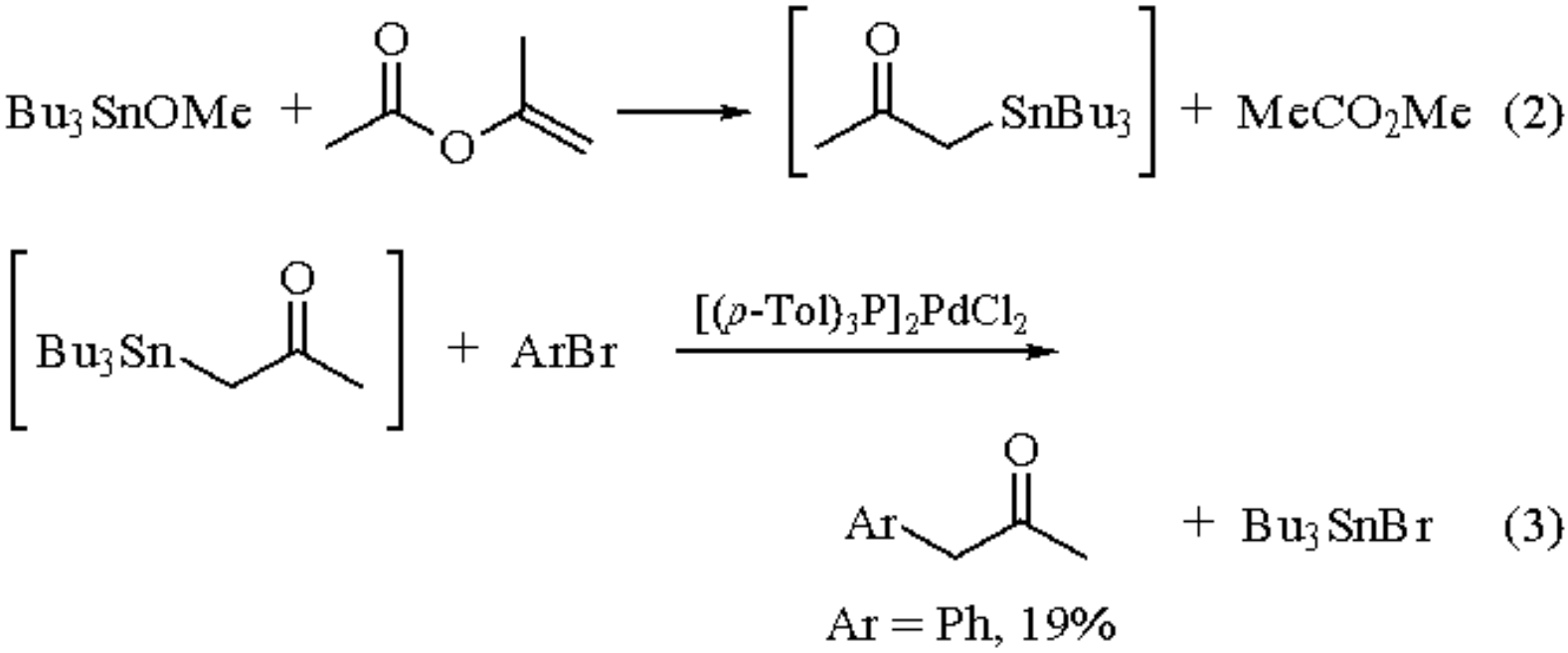

Related Reagents.

$(Ph_3As)_2PtCl_2$-$SnCl_2$ has been used for linear carbonylation of α-alkenes with alcohols and has shown good regioselectivity.[6] $(Ph_3P)_2PdCl_2$-$SnCl_2$ has also been reported to give similar results.[4] ***Dichlorobis(tri-o-tolylphosphine)palladium(II)*** is a preferred catalyst in aromatic acetonylation to prepare arylacetones.[5]

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Dichlorobis(tri-*o*-tolylphosphine)palladium(II)

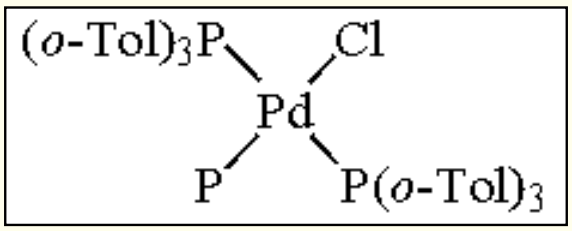

[40691-33-6] · $C_{42}H_{42}Cl_2P_2Pd$ · Dichlorobis(tri-*o*-tolylphosphine)palladium(II) · (MW 786.07)

(catalyzes arylation of organozinc reagents;[1] catalyzes carbon-carbon bond formation via stannyl enolates;[2] catalyzes aromatic cyanomethylation and amination[3])

Physical Data: mp 285-295 °C (yellow crystals from toluene).[4]

Preparative Method: prepared by stirring $PdCl_2$ and P(*o*-Tol)$_3$ in methanol at rt for 2 h.[4,5]

Arylation of Organozinc Reagents.

The coupling of organozinc reagents with electron-rich (eq 1) or electron-deficient (eq 2) aryl iodides proceeds in good yield with Pd catalysis.[1] $PdCl_2[P(o\text{-Tol})_3]_2$ is superior to $PdCl_2(PPh_3)_2$ (see ***Palladium(II) Chloride***) and ***Tetrakis(triphenylphosphine)palladium(0)*** because biaryls are not produced during the reaction. This catalyst is not useful, however, for coupling organozinc compounds with vinyl iodides or triflates. Zinc-substituted aromatic ketones also react with aryl iodides under $PdCl_2[P(o\text{-Tol})_3]_2$ catalysis in excellent yield (eq 3).[6] Enantiomerically pure, protected 3-aryl-α-amino acids can be prepared by coupling a protected zinc homoenolate with an aryl iodide under Pd catalysis (eq 4).[7] The sterically smaller catalyst $PdCl_2(PPh_3)_2$ produces the desired product in only 15% yield.

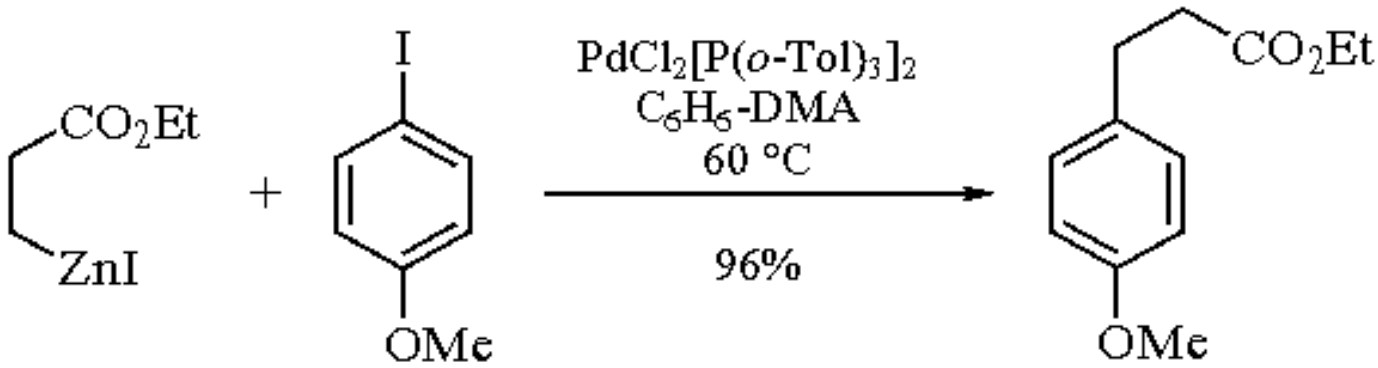

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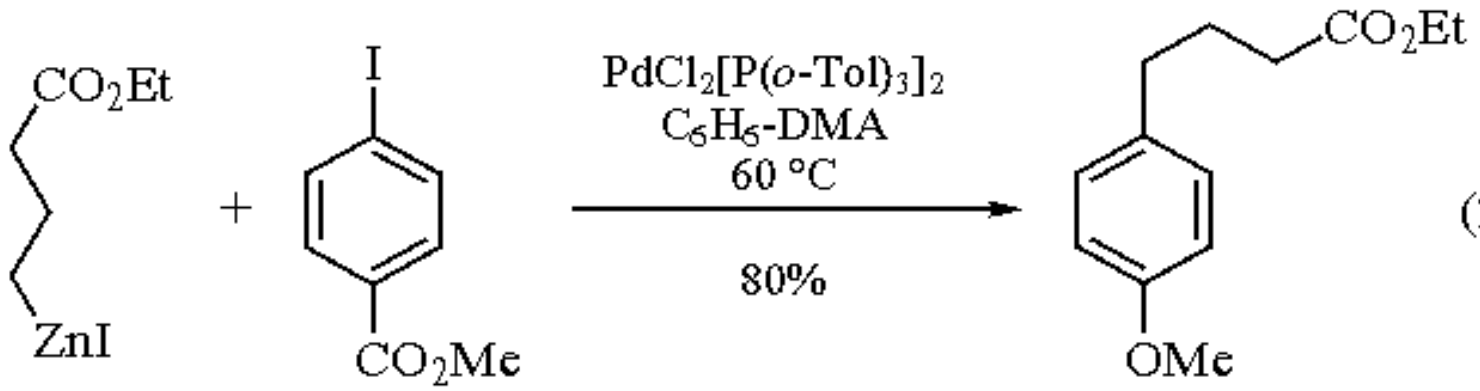

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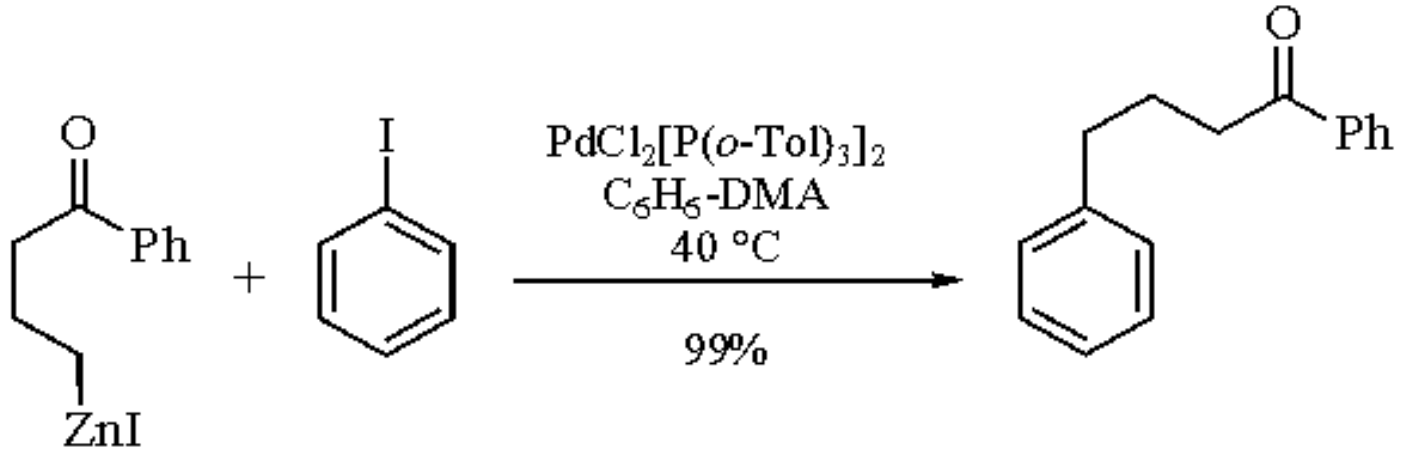

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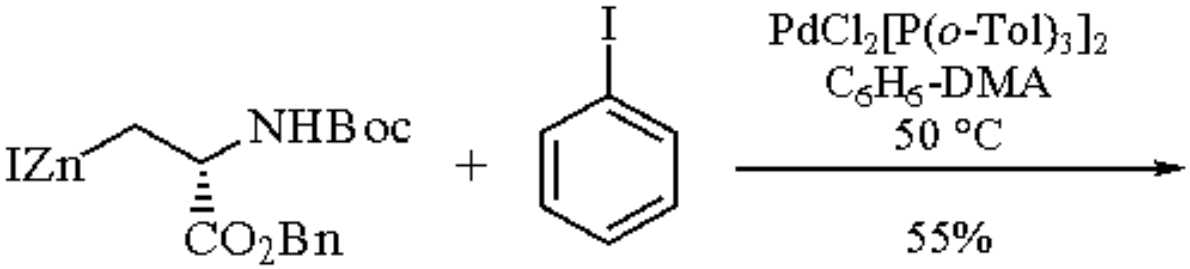

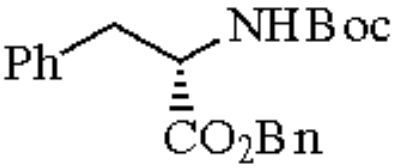

(4)

Carbon-Carbon Bond Formation via Stannyl Enolates.

Tri-*n*-butyltin enolates, generated in situ by treatment of enol acetates with ***Tri-n-butyl(methoxy)stannane*** undergo $PdCl_2[P(o\text{-Tol})_3]_2$-catalyzed coupling with vinyl bromides (eq 5)[2] or bromobenzene (eq 6).[8] Although the reaction is sensitive to steric hindrance caused by substituents on the enol acetate, the number and position of substituents on the vinyl bromide does not have a serious effect on the product yield. The configuration of the alkenyl bromide is completely retained in the product.

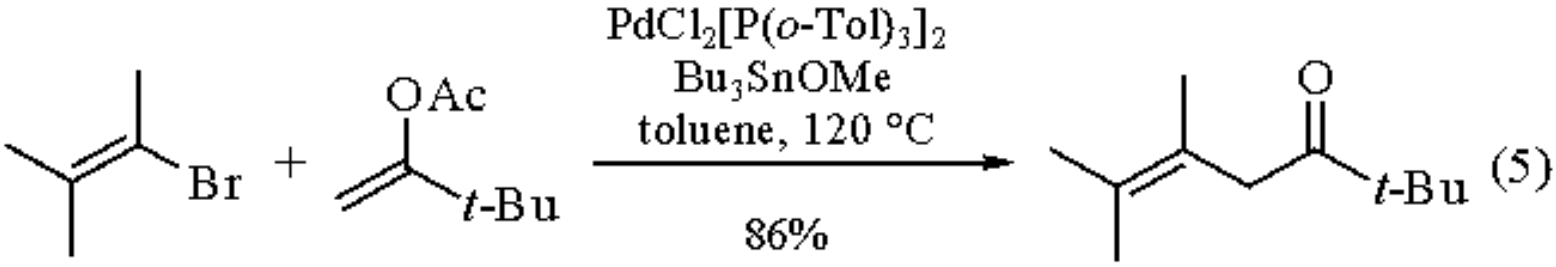

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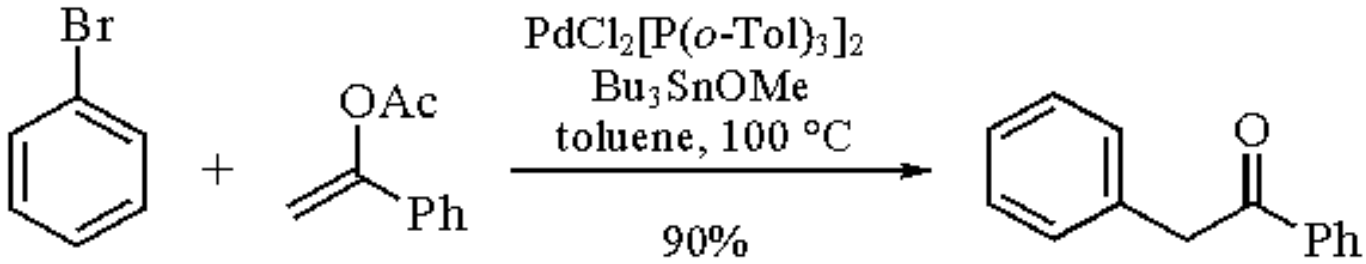

(6)

Stannyl enolates, generated in situ from silyl enol ethers by Bu_3SnF-mediated silyl/stannyl exchange, undergo $PdCl_2[P(o\text{-Tol})_3]_2$-catalyzed aldol reactions with aromatic (eq 7) and aliphatic aldehydes.[9] The products are isolated as the hydroxy ketones. Tin enolates produced from silyl enol ethers can also be coupled with both electron-deficient (eq 8) and electron-rich aryl bromides with almost equal success.[10] The silyl/stannyl exchange induced by Bu_3SnF is useful only for silyl enol ethers of methyl ketones. The remarkable difference in reactivities may arise from the steric repulsion between the alkyl group(s) attached to the alkenic moiety and the approaching tributyltin fluoride. This relative reaction rate phenomena has been utilized for the $PdCl_2[P(o\text{-Tol})_3]_2$-catalyzed chemoselective desilylation of silyl enol ethers (eq 9).[11]

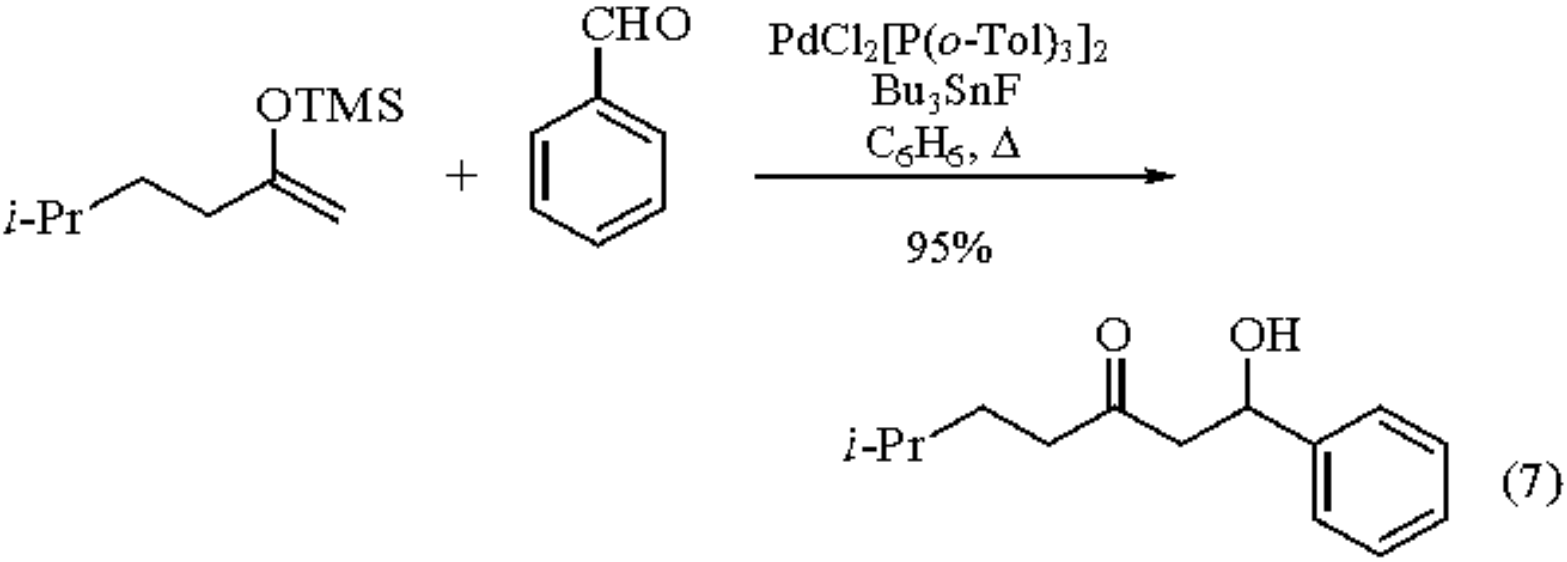

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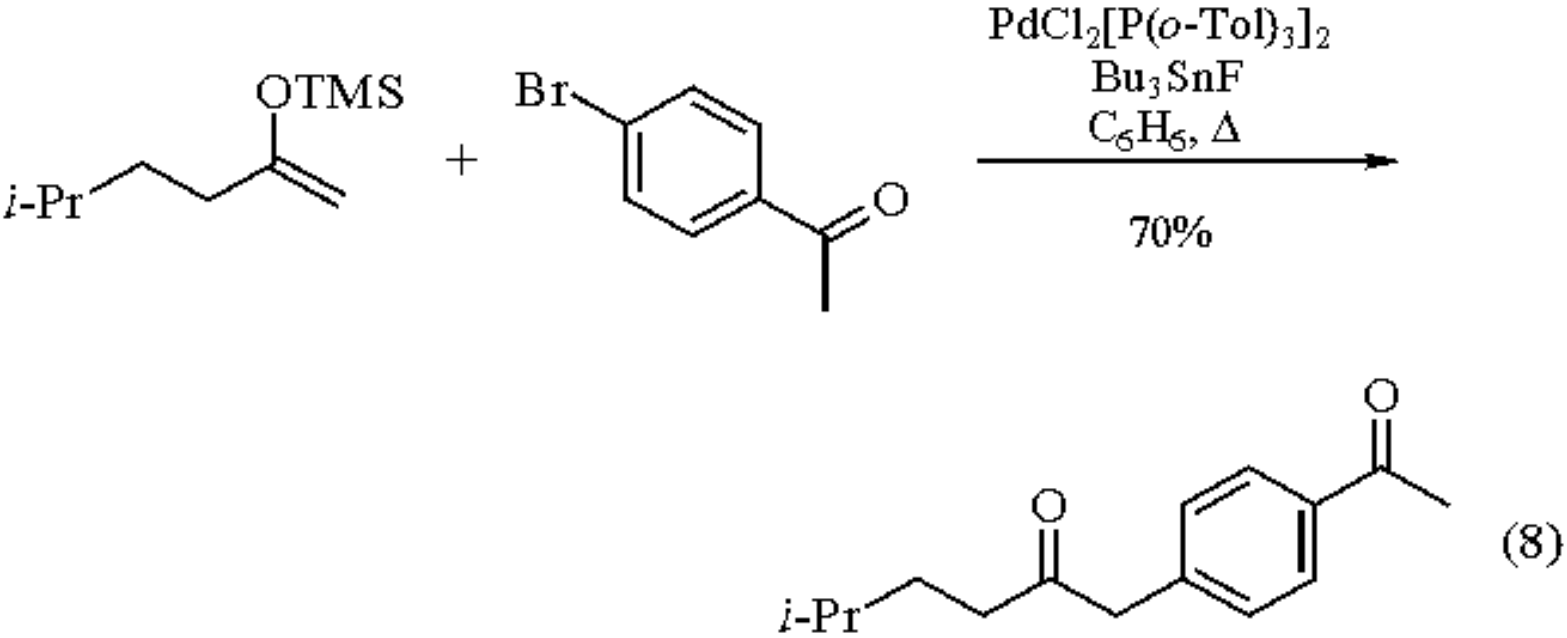

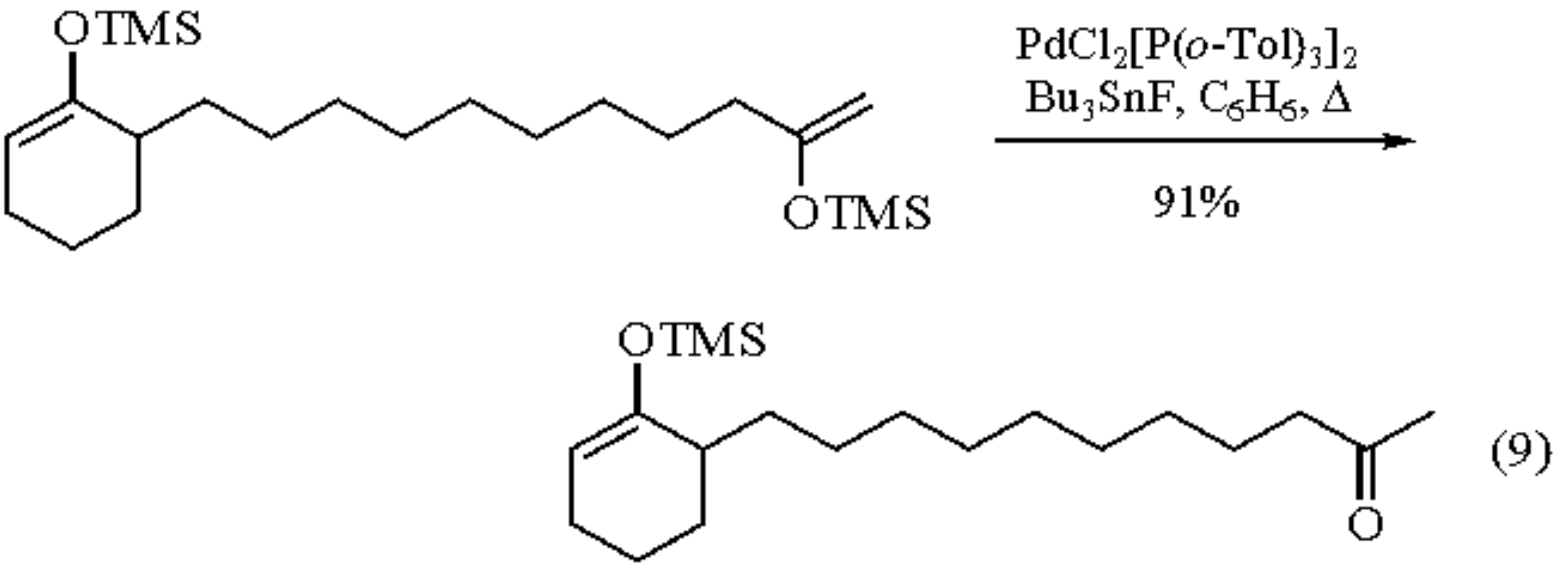

Aromatic Cyanomethylation and Amination.

Aryl bromides react with cyanomethyltributyltin in the presence of $PdCl_2[P(o\text{-Tol})_3]_2$ catalyst to afford cyanomethylated products (eq 10).[3] The aryl bromides can be substituted with methyl, methoxy, or chloro groups, but not π-electron withdrawing groups such as nitro. Bromobenzene can be aminated with *N*,*N*-diethylaminotributyltin (eq 11).[12] The best catalyst is $PdCl_2[P(o\text{-Tol})_3]_2$ and the reaction also gives good yields with methyl substituted bromobenzenes.

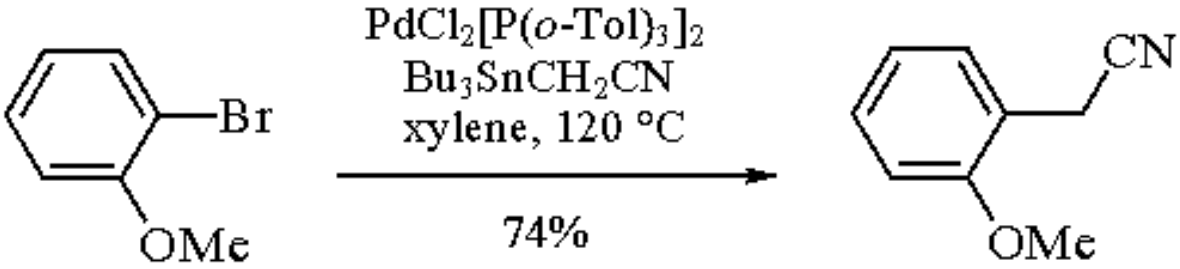

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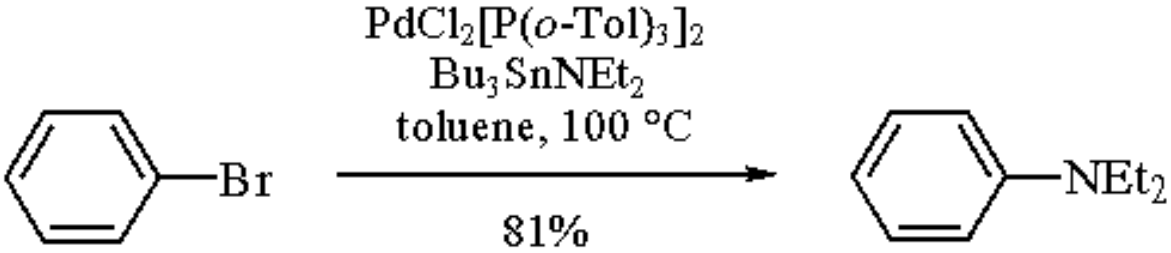

(11)

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Dichloroborane Diethyl Etherate[1]

$BHCl_2.OEt_2$

[41156-66-5] · $C_4H_{11}BCl_2O$ · Dichloroborane Diethyl Etherate · (MW 156.85)

(hydroborating agent providing access to alkyldichloroboranes and alkenyldichloroboranes;[2] reagent for deoxygenation of sulfoxides[3] and cleavage of cyclic acetals[4])

Physical Data: bp 59 °C/1.5 mmHg;[5] mp -30 to -25 °C.[6,7]

Solubility: sol benzene, carbon tetrachloride, diethyl ether; not miscible with pentane.

Analysis of Reagent Purity: the hydride content is determined by hydrolyzing an aliquot and measuring the hydrogen evolved according to the standard procedure.[8] The chloride is estimated by hydrolyzing an aliquot and titrating the HCl produced with $NaHCO_3$ using methyl orange as indicator. Coulometric titration has also been used for the determination of $BHCl_2.OEt_2$.[9a] ^{11}B NMR: δ, ppm 8.1;[9b] 7.9 (J_{B-H} = 152 Hz).[9c]

Preparative Methods: an approximately 1.5 M solution in diethyl ether can be prepared by the reaction of ***Lithium Borohydride*** with ***Boron Trichloride***.[2] The neat reagent can be isolated by removing excess diethyl ether. It is a colorless liquid, 6.6 M in $BHCl_2$, containing about 4-6 mol % of $BCl_3.OEt_2$ as impurity. Less conveniently, $BHCl_2.OEt_2$ can also be prepared by reacting BCl_3 with ***Diborane*** in the presence of diethyl ether.[6,7] The deuterated reagent is known.[7]

Handling, Storage, and Precautions: corrosive, flammable, air- and moisture-sensitive liquid. Reacts violently with water. The reagent is not stable over long periods of time, cleaving the ether solvent at a significant rate, even with storage at 0 °C. The neat reagent is not stable for more than 2 days at rt. Handle in a fume hood.

Hydroboration of Alkenes and Dienes.

The reaction of alkenes with dichloroborane diethyl etherate is slow and accompanied by disproportionation. In contrast, dichloroborane reacts readily with alkenes in the gas phase.[10] Apparently, strong complexation with ether significantly decreases the reactivity. This difficulty can be circumvented by the addition of boron trichloride, a strong Lewis acid, liberating dichloroborane from the complex with instantaneous precipitation of $BCl_3.OEt_2$ (eq 1).[2] (For direct hydroboration of alkenes, see ***Dibromoborane-Dimethyl Sulfide***).

$$\text{alkene} + BHCl_2 \cdot OEt_2 + BCl_3 \xrightarrow[77\text{-}97\%]{\text{pentane}} RBCl_2 + BCl_3 \cdot OEt_2\downarrow \quad (1)$$

The pentane solution contains essentially pure alkyldichloroborane applicable directly for further transformations. Alternatively, the product can be isolated by distillation. The directive effects of $BHCl_2.OEt_2$ are comparable to ***Monochloroborane Diethyl Etherate***, e.g. 1-hexene and styrene react, placing the boron atom at the terminal position with 99.3% and 96.3% selectivity, respectively. Alkyldichloroboranes can also be prepared by the redistribution reaction.[11,12]

Ethyl Diazoacetate reacts readily with aryl- and alkyldichloroboranes to give the corresponding two-carbon homologated ethyl esters. Essentially quantitative yields are obtained in the reactions of aryldichloroboranes (eq 2).[13]

$$PhBCl_2 + N_2CH_2CO_2Et \xrightarrow[2.\ ROH]{1.\ THF,\ -25\ °C,\ -N_2} PhCH_2CO_2Et \quad (2)$$

The homologations of alkyldichloroboranes proceed in the range of 57-71% yield, so in these cases this procedure has little advantage over that involving the more conveniently synthesized dialkylchloroboranes (see ***Monochloroborane Diethyl Etherate***). A remarkable enhancement of reactivity relative to trialkylboranes is observed in the reaction of alkyldichloroboranes with organic azides. Secondary amines are formed in 84-100% yields (eq 3).[14,15]

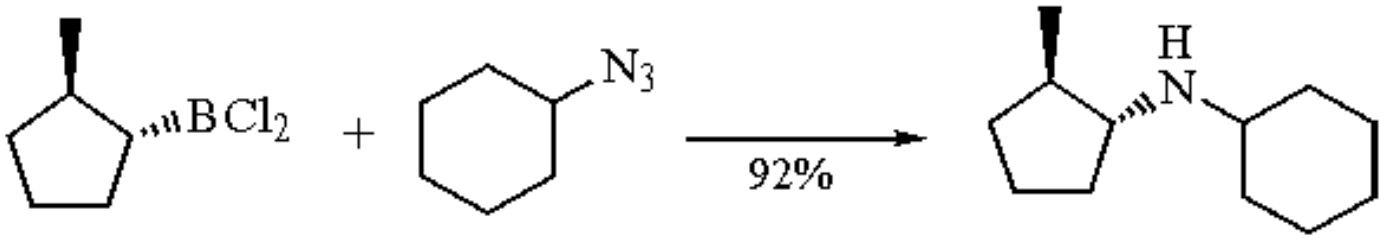

(3)

An extension of this reaction to 2-iodoalkyl azides provides β-iodo derivatives of secondary amines which undergo ring closure upon treatment with base, producing the corresponding *N*-alkylaziridines in 73-94% yields (eq 4).[15,16]

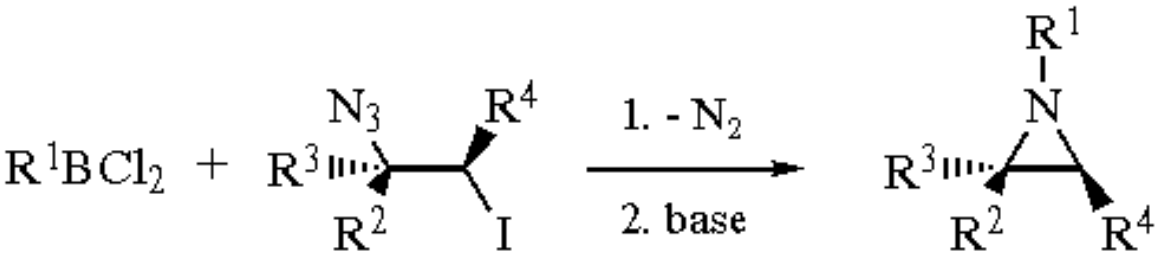

(4)

The procedure is not applicable to 1-azido-2-iodophenylpropane, which undergoes elimination of β-methylstyrene under the reaction conditions.[15] In all of the reactions described above the migrating group retains its configuration. Optically active amines can be prepared from optically active alkyldichloroboranes.[17] Another useful transformation of alkyldichloroboranes is the controlled oxidation with oxygen, providing hydroperoxides (eq 5).[18,19] The reaction is a radical process and the configuration of the alkyl group is not completely retained.

$$RBCl_2 + O_2 \xrightarrow[\text{84-94\%}]{Et_2O,\ -15\ ^\circ C} ROOH \qquad (5)$$

Dihydroboration of allene with dichloroborane diethyl etherate gives a 1,3-dibora product which can be transformed into the 1,2-diborole derivative.[20]

Hydroboration of Alkynes.

The monohydroboration of alkynes with dichloroborane diethyl etherate in the presence of an equimolar amount of boron trichloride gives alkenyldichloroboranes (eq 6),[2] which can be transformed into alkenylboronates, alkenes, or ketones by alcoholysis, protonolysis, and oxidation, respectively.

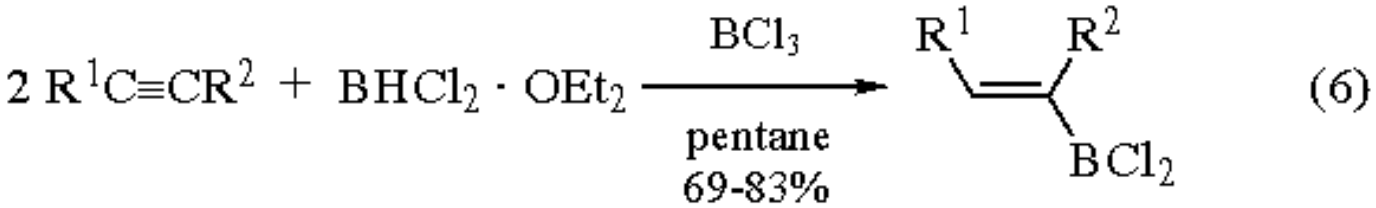

$$R^1 = R^2 = \text{alkyl};\ R^1 = \text{alkyl},\ R^2 = H$$

α-Silyl ketones are obtained from 1-trimethylsilyl-1-alkynes.[21] A 10-40% excess of the silylalkyne is necessary to minimize dihydroboration. The dihydroboration of alkynes with dichloroborane diethyl etherate has been studied only briefly.[2,22] 1-Alkynes are hydroborated to 1,1-diboraalkanes (eq 7).[22]

$$RC{\equiv}CH + 2\,BHCl_2 \cdot OEt_2 + 2\,BCl_3 \xrightarrow[\text{30\%}]{\text{pentane, -30 °C}} RCH_2CH(BCl_2)_2 \quad (7)$$

Deoxygenation of Sulfoxides and Cleavage of Cyclic Acetals.

Aliphatic sulfoxides are rapidly deoxygenated to the corresponding sulfides in excellent yields by dichloroborane in THF at 0 °C.[3] Other reducible functionalities, such as ketones, esters, and amides, are not affected. Since dichloroborane in THF is a very poor hydroborating agent,[23,24] unsaturated sulfoxides might be expected to undergo selective reduction. Cyclic acetals are cleaved under mild conditions[4] (see also ***Monochloroborane Diethyl Etherate*** and ***Monochloroborane-Dimethyl Sulfide***).

Related Reagents.

Dibromoborane-Dimethyl Sulfide; ***Dichloroborane-Dimethyl Sulfide***; ***Monochloroborane Diethyl Etherate***; ***Monochloroborane-Dimethyl Sulfide***.

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Dichloroborane-Dimethyl Sulfide[1]

$BHCl_2.SMe_2$

[63462-42-0] · $C_2H_7BCl_2S$ · Dichloroborane-Dimethyl Sulfide · (MW 144.85)

(hydroborating agent suitable for the hydroboration of labile alkenic structures;[2] provides access to alkyldichloroboranes and alkenyldichloroboranes[3,4])

Alternate Name: DCBS.

Physical Data: d_4^{20} = 1.255 g cm^{-3}.

Solubility: sol benzene, carbon tetrachloride, dichloromethane, diethyl ether, THF.

Form Supplied in: colorless to pale yellow liquid.

Analysis of Reagent Purity: hydrolyze an aliquot and measure the hydrogen evolved according to the standard procedure.[7a] ^{11}B NMR (CCl_4): δ, ppm, 2.0;[7b] 1.7 (d);[7c] 2.2 (d, J_{B-H} = 157.42 Hz).[5]

Preparative Methods: by redistribution of ***Borane-Dimethyl Sulfide*** (BMS) and $BCl_3.SMe_2$.[5] A mixture containing $BHCl_2.SMe_2$ (73%) and BMS, $BH_2Cl.SMe_2$, and $BCl_3.SMe_2$ is obtained by the reaction of BMS with Ph_3CCl.[6]

Handling, Storage, and Precautions: corrosive, air- and moisture-sensitive, flammable liquid; stench. Reacts violently with water. Handle and store under nitrogen or argon. Stable indefinitely when stored under nitrogen at 25 °C. Destructive to upper respiratory tract, eyes, and skin. Handle in a fume hood.

Hydroboration of Alkenes and Alkynes.

The hydroboration of alkenes with dichloroborane-dimethyl sulfide (DCBS) in refluxing dichloromethane produces considerable quantities of R_2BCl and R_3B as impurities, presumably as the result of disproportionation of the reagent. The addition of boron trichloride liberates dichloroborane and the hydroboration proceeds cleanly at 25 °C (eq 1)[3] (see ***Dibromoborane-Dimethyl Sulfide*** for direct hydroboration of alkenes).

$$RCH{=}CH_2 + BHCl_2 \cdot SMe_2 + BCl_3 \xrightarrow[\text{69-85\%}]{\text{pentane, 25 °C}} RCH_2CH_2BCl_2 + BCl_3 \cdot SMe_2\downarrow \quad (1)$$

DCBS is highly regioselective,[8] exhibiting the directive effects similar to those observed for ***Monochloroborane Diethyl Etherate***.[9] Alkyldichloroboranes are readily isolated by distillation under vacuum. Methanolysis provides the corresponding alkylboronic esters (eq 2).[3] Alkenylboronic esters can be obtained from alkynes (eq 3).[4]

$$RCH_2CH_2BCl_2 \xrightarrow{MeOH} RCH_2CH_2B(OMe)_2 \quad (2)$$

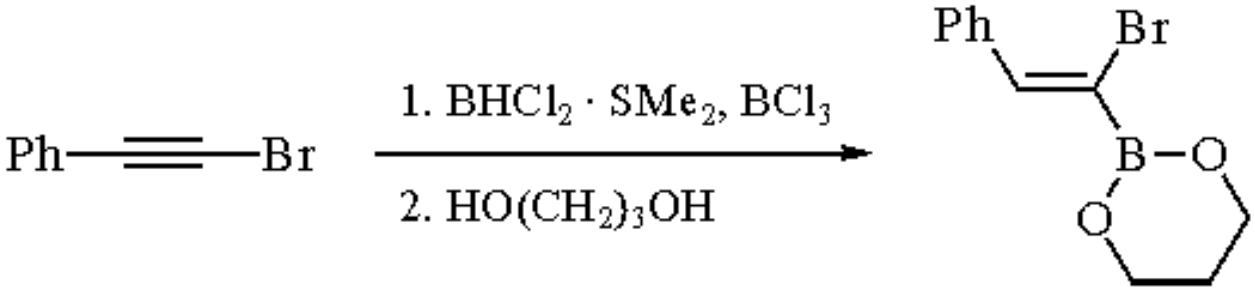

(3)

A characteristic feature of alkyldichloroboranes is their exceptional resistance to thermal isomerization, making possible the regio- and stereoselective synthesis of organoborane intermediates from highly labile alkenic structures. Thus the organoborane intermediate initially formed in the hydroboration of 1-methylcyclooctene with ***Borane-Tetrahydrofuran*** undergoes facile isomerization, even at 0 °C, to a mixture of regio- and stereoisomeric organoboranes (eq 4).[10] In contrast, the hydroboration of 1-methylcyclooctene with DCBS at 0 °C affords cleanly *trans*-(2-methylcyclooctyl)dichloroborane in excellent yield and purity (eq 5).[2]

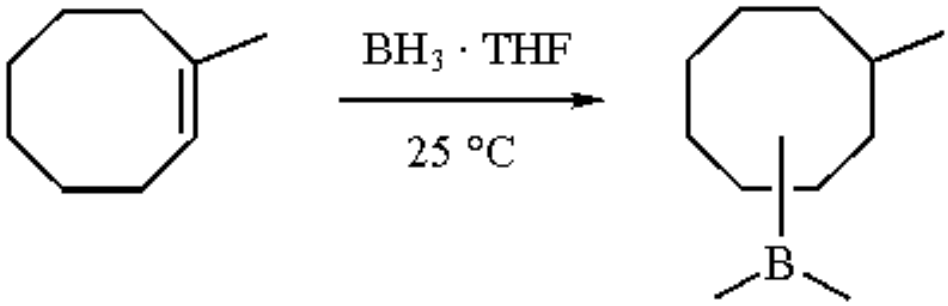

(4)

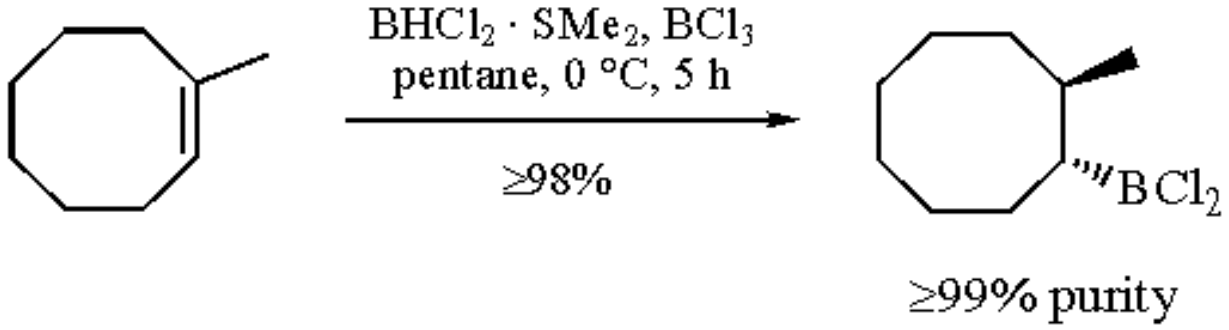

(5)

An intramolecular version of the reaction of alkyldichloroboranes with organic azides has been employed in a highly stereoselective synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines (eq 6)[11] (for the synthesis of other secondary amines, see ***Dibromoborane-Dimethyl Sulfide*** and ***Dichloroborane Diethyl Etherate***).

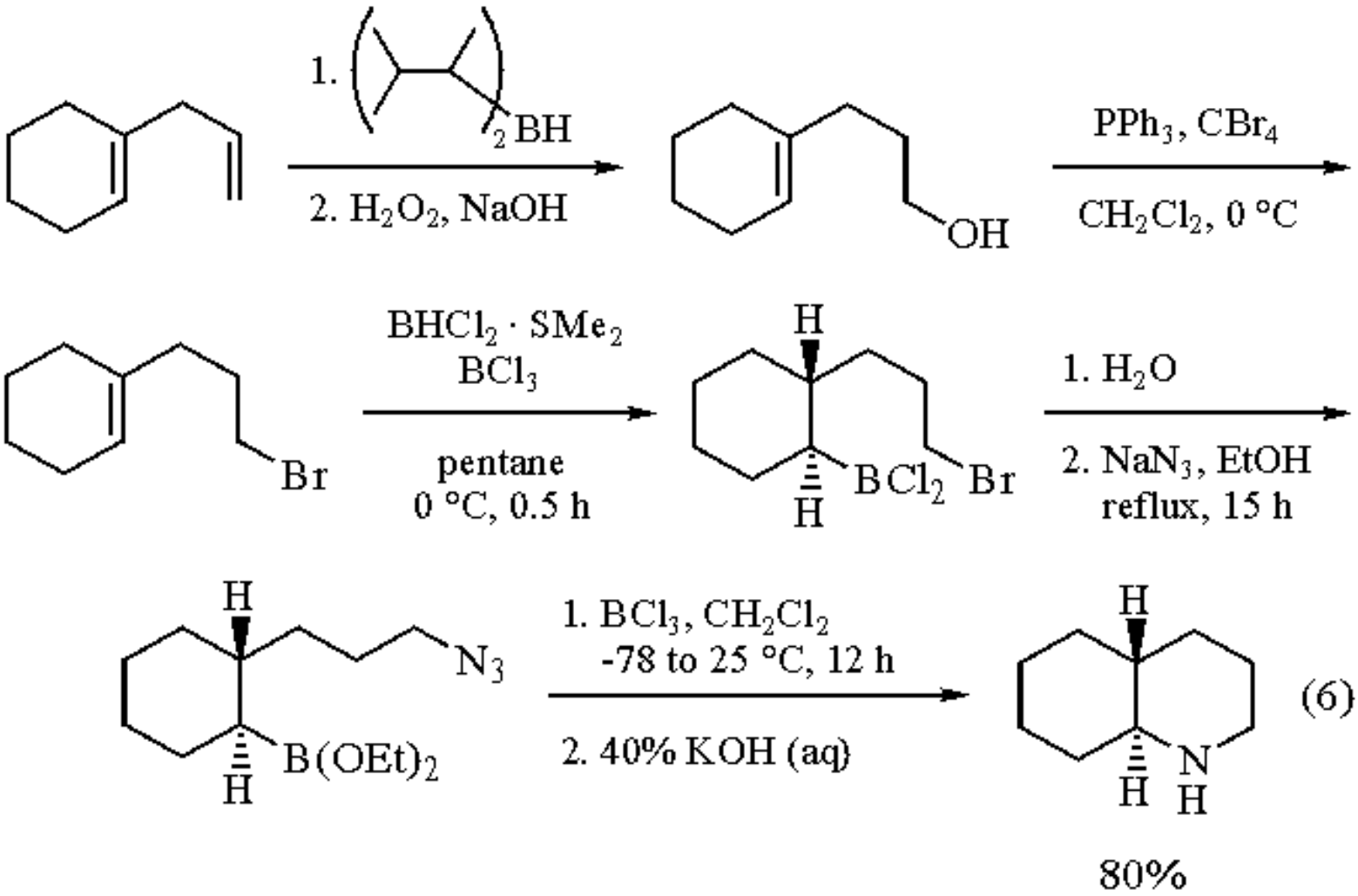

(6)

Alkyldichloroboranes can be converted into a host of valuable organoborane intermediates via the hydridation-stepwise hydroboration procedure.[12] The procedure enables a general synthesis of unsymmetrical dialkylboranes and totally mixed trialkylborane intermediates for the synthesis of ketones and tertiary alcohols, respectively.[12b]

Transmetalation.

The reagent has been used in the synthesis of bis(2,4,6-triisopropylphenyl)borane ($(trip)_2BH$) by the transmetalation reaction (eq 7).[13] $(Trip)_2BH$ belongs to the family of highly hindered borane reagents like dimesitylborane.[14] It is a rare example of a monomeric disubstituted borane.[13]

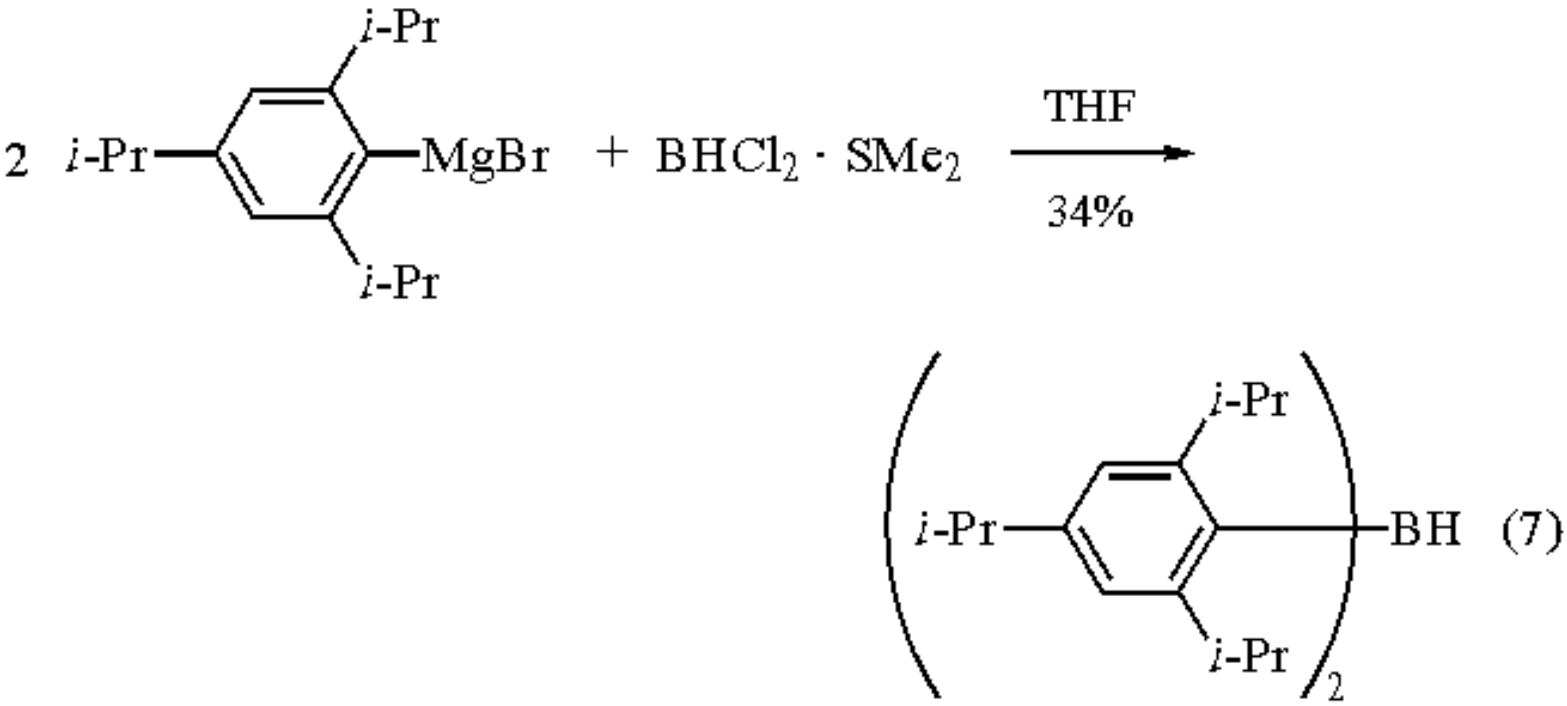

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1,4-Dichloro-2-butanone

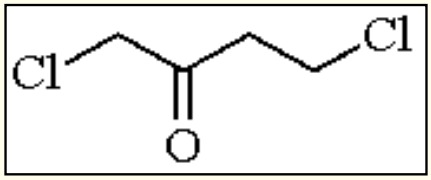

[16714-78-6] · $C_4H_6Cl_2O$ · 1,4-Dichloro-2-butanone · (MW 141.00)

(reactive electrophile, precursor for 1,4-disubstituted 2-butanones and 2-butenones)

Alternate Name: 2-chloroethyl chloromethyl ketone.

Physical Data: bp 65 °C/3 mmHg; vap. *d* 4.9 g cm^{-3}.[1]

Solubility: freely sol organics; may react with amides, amines, alcohols, sulfoxides, water.

Form Supplied in: neat liquid.

Analysis of Reagent Purity: IR, UV, NMR (δ 3.08, 2H, t, *J* = 6 Hz; 3.71, 2H, t, *J* = 6 Hz; 4.00 ppm, 2H, s).[2]

Preparative Methods: can be prepared by the Friedel-Crafts acylation of ethylene with ***Chloroacetyl Chloride*** catalyzed by ***Aluminum Chloride***[4] or the treatment of 2-chloropropionyl chloride with ***Diazomethane*** followed by concentrated HCl.[5] The Friedel-Crafts process can be used with other alkenes and acid chlorides to yield α,β´-dichloroalkyl ketones.[4]

Handling, Storage, and Precautions: highly irritating to the skin, eyes, and mucous membranes via oral inhalation and skin contact. A lacrimator type of military poison. Dangerous; when heated to dec, burns and emits highly toxic fumes of chlorides.[3] Use in a fume hood.

Alkylation Reactions.

The title reagent (**1**) can react at either of the halide positions or at the carbonyl. With weak nucleophiles such as alkoxide,[6] acetate,[6] thiolate,[7] or phthalimide,[8] (**1**) yields (**2**) or (**3**). Compound (**2**) can be converted into (**3**) with base treatment. Diamine (**2**) (X = NH_2) has been converted into histamine (eq 1).[8] The carbonyl group of (**1**) is the electrophilic site in reactions with organolithium or Grignard reagents. The intermediate alkoxide can be converted into a diorganolithio trianion which can be trapped with several electrophiles (eq 2).[9]

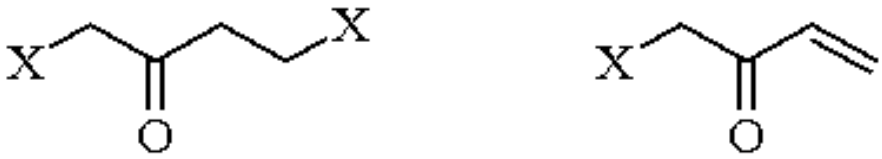

(2) (3)

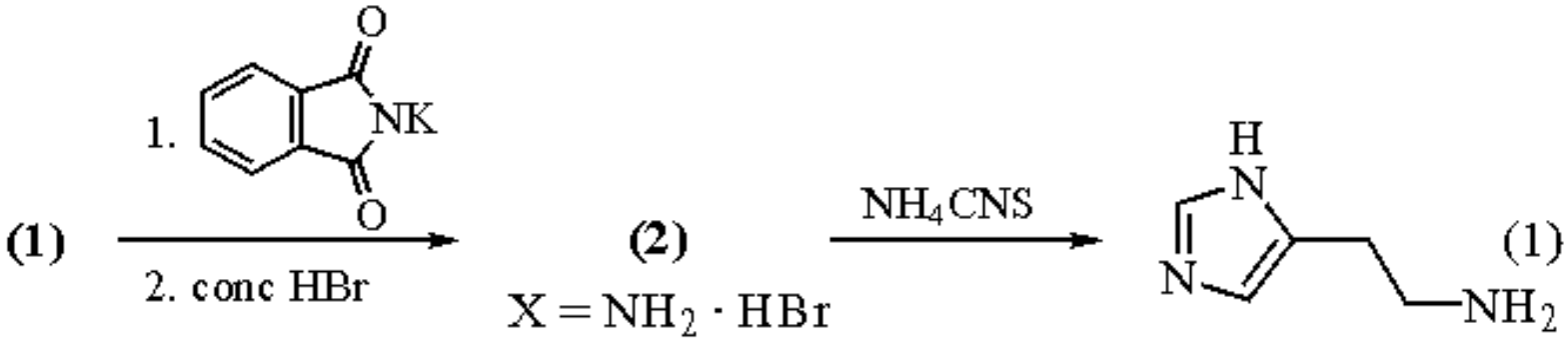

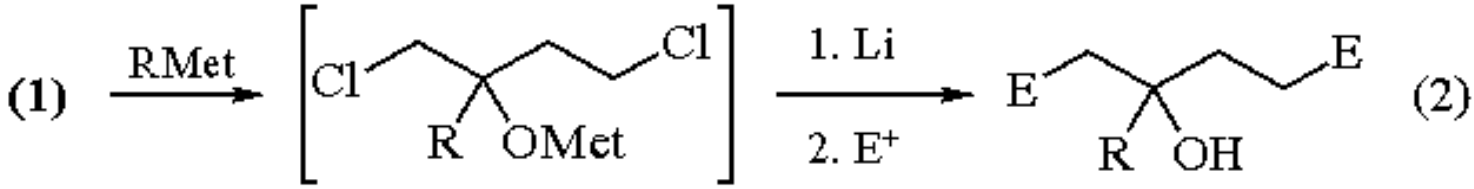

Enones such as (**3**) have found extensive use as the dienophiles in Diels-Alder reactions.[10] They should also be valuable 2π electron components in other cycloadditions. Compound (**1**) was used to generate (**3**) (X = Cl) in situ for a Robinson annulation with β-dicarbonyls (eq 3).[11] The normal aldol product is trapped in about 50% yield to afford an epoxy ketone. This process has been called epoxyannulation. Other examples of epoxyannulation have included treatment of enolates with ***2-Chloroacrylonitrile***[12a] or 1-butadienylsulfonium salts[12b] and the cyclization of o-ketosulfonium salts.[12c,d]

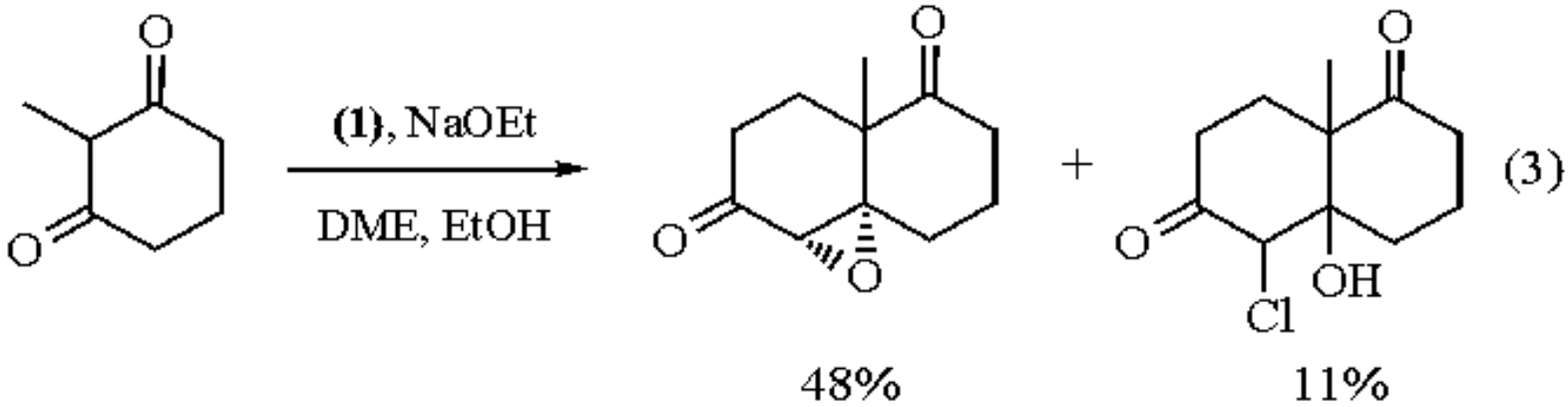

The other major use of (**1**) has been to construct functionalized azoles. Although only thiazoles[13] (eq 4) appear to have been reported, oxazoles and imidazoles should be available from (**1**) since other chloromethyl ketones yield all of these azoles.[14]

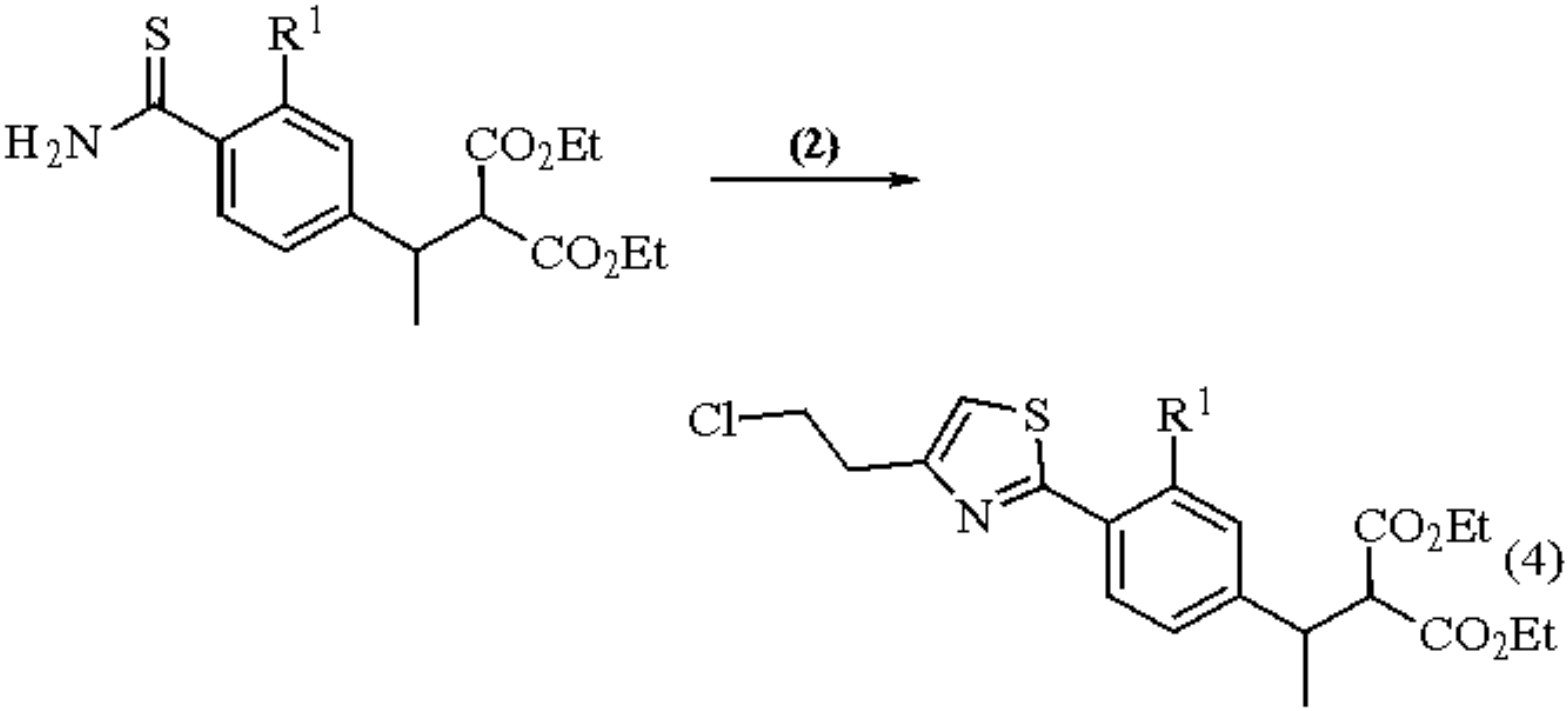

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1,4-Dichloro-2-butene

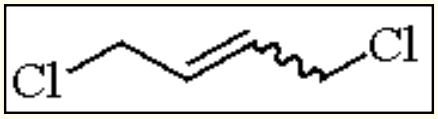

(*cis/trans*)

[764-41-0] · $C_4H_6Cl_2$ · 1,4-Dichloro-2-butene · (MW 125.00) (*cis*)

[1476-11-5] (*trans*)

[110-57-6]

(a versatile four-carbon synthon useful in cycloalkylations[1-7] and cycloadditions[11-14]; forms heterocyclic systems in reactions with heteroatom nucleophiles[15-18])

Physical Data: cis (95%): mp 48 °C; bp 152 °C; *d* 1.188 g cm^{-3}. *trans* (98%): bp 74-76 °C/40 mmHg; *d* 1.183 g cm^{-3}. *cis*/*trans* (95%): bp 72-75 °C/40 mmHg; *d* 1.183 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: available as neat liquid as pure *cis* or *trans* forms and a *cis*/*trans* mixture.

Handling, Storage, and Precautions: flammable liquid; lachrymator, irritant, and corrosive, handle in a fume hood.

Carbocycles via Dianion Alkylations.

gem-Dianions generated from active methylene compounds react with *trans*-1,4-dichloro-2-butene to give vinylcyclopropanes, which can be thermally rearranged to cyclopentenes (**1**) (eq 1).[1] If the malonates are chiral, optically active cyclopropanes are formed.[2] Acetoacetic ester in place of malonate yields cyclohepten-4-one (**2**) (eq 2) after alkaline hydrolysis.[4]

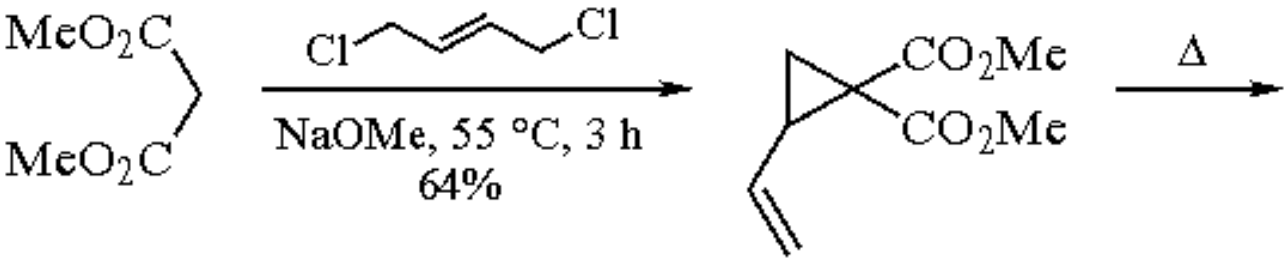

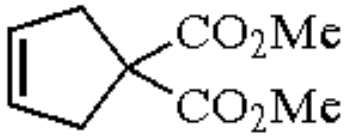

(1)

(1)

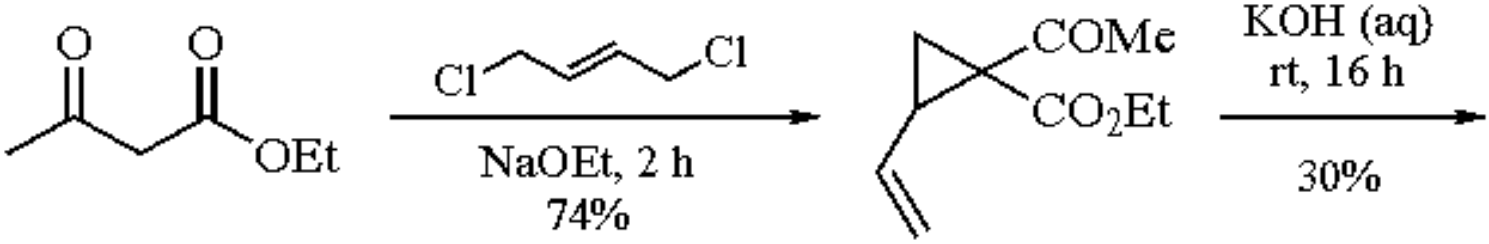

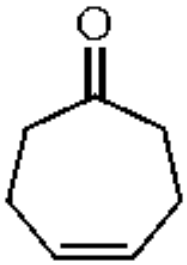

(2)

(2)

cis-1,4-Dichloro-2-butene, on the other hand, yields the cyclopentene exclusively, or a mixture with the vinylcyclopropane, depending on the active methylene compound (eq 3).[3]

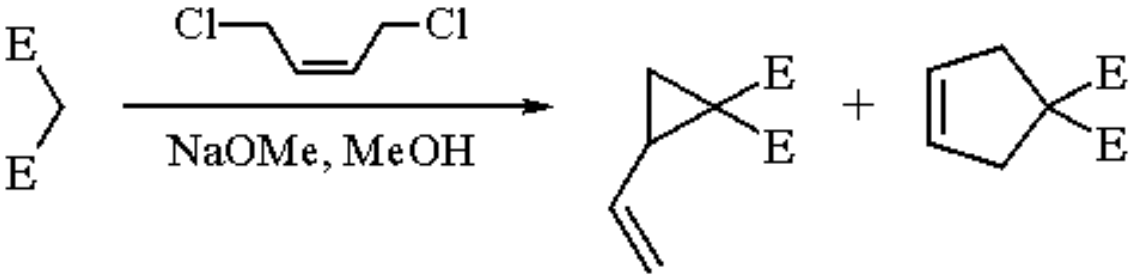

(3)

E = CN	0:100
E = CO_2Me	42:58

Reactions with *vic*-diester dianions or with 1,3-dianions afford monocyclic[6,7] (**3**), (**4**), or fused carbocycles[5,8] (**5**), depending on the anionic compound (eqs 4-6). Bicyclo[4.*n*.1] ring systems are easily made by use of enolates[9] or enamines[10] where reactions in the carbonyl form prove difficult.

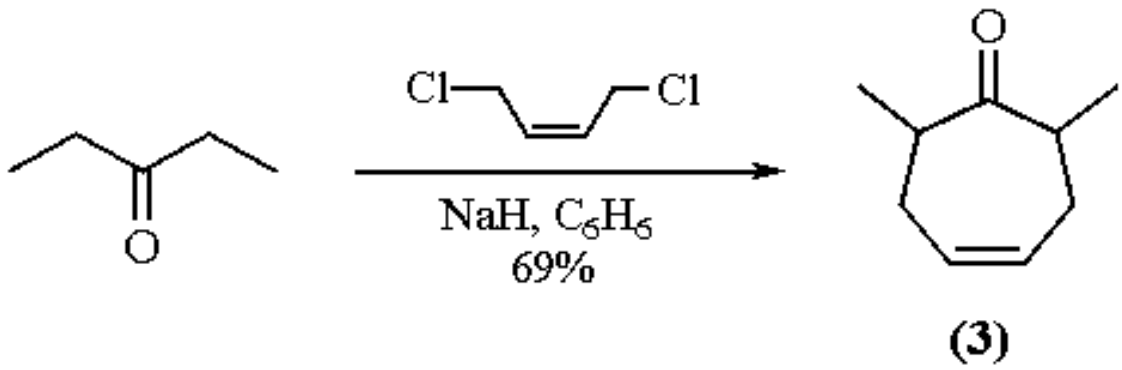

(4)

(3)

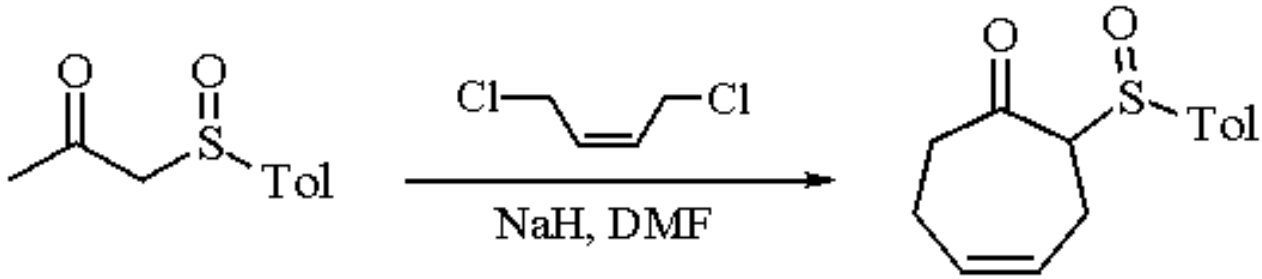

(5)

(4)

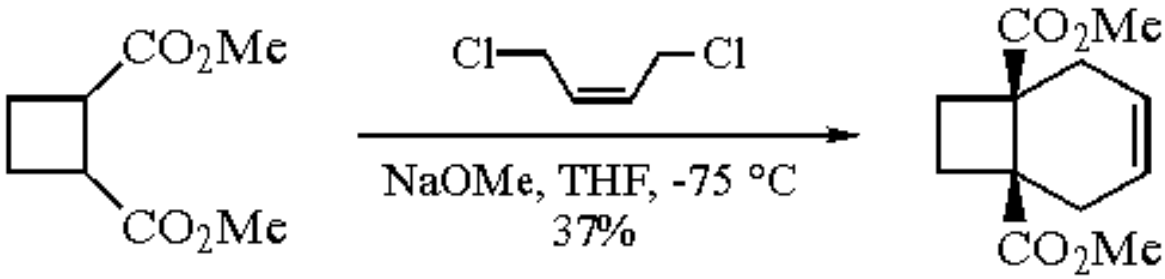

(6)

(5)

Carbocycles via Cycloadditions.

[2 + 2] Additions.

Trans-1,4-Dichloro-2-butene adds to fused cyclopentenones to produce a tricyclic system (eq 7).[11]

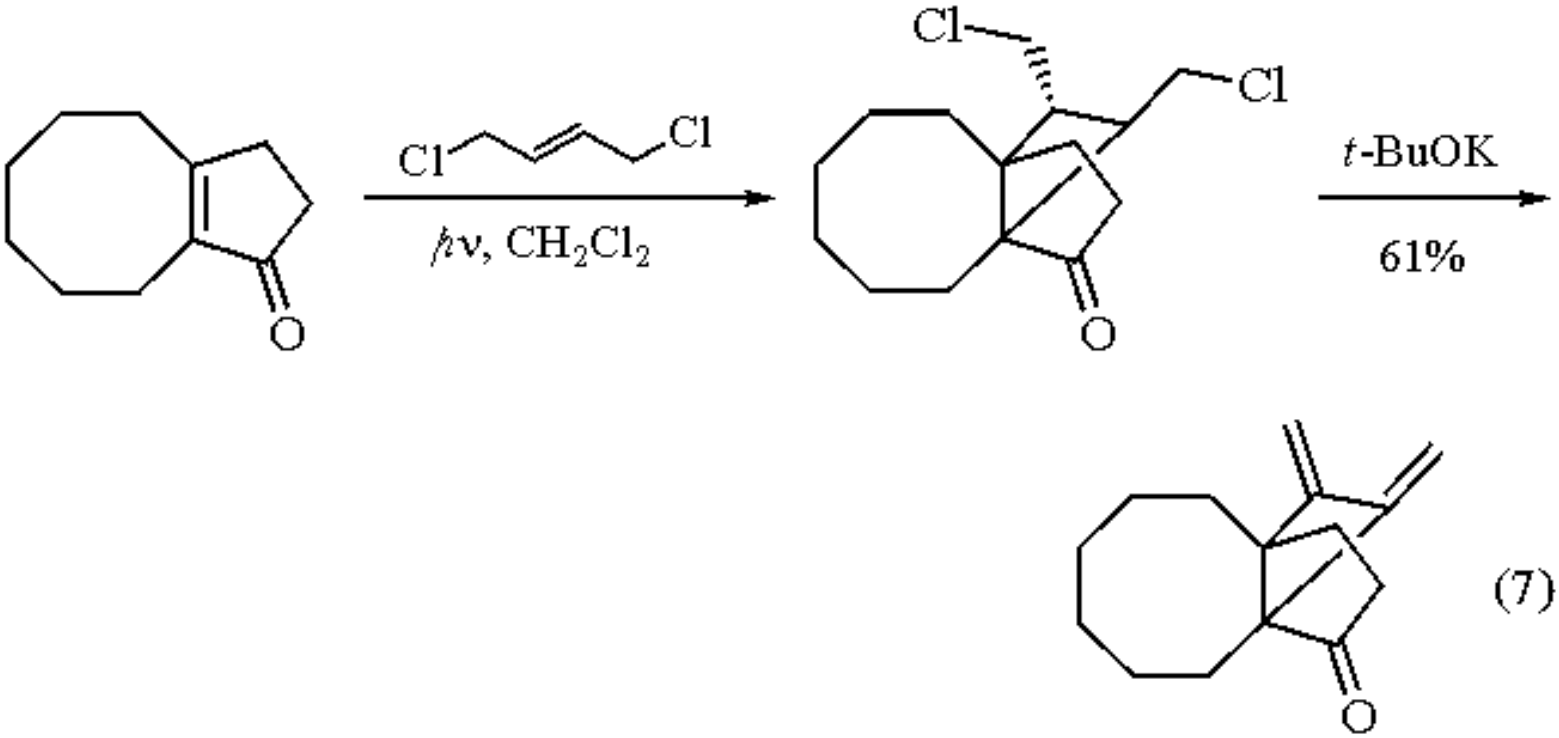

(7)

Using *trans*-1,4-dichloro-2-butene, access to *anti*-tricyclo[3.1.0.0^{2,4}]hexanes is made very easy.[12] The route is via a [2 + 2] addition to maleic anhydride, followed by two intramolecular displacements.

[4 + 2] Additions.

Reactions with anthracene give benzocarbocycles, providing quick access to the triptycenes (eq 8).[13]

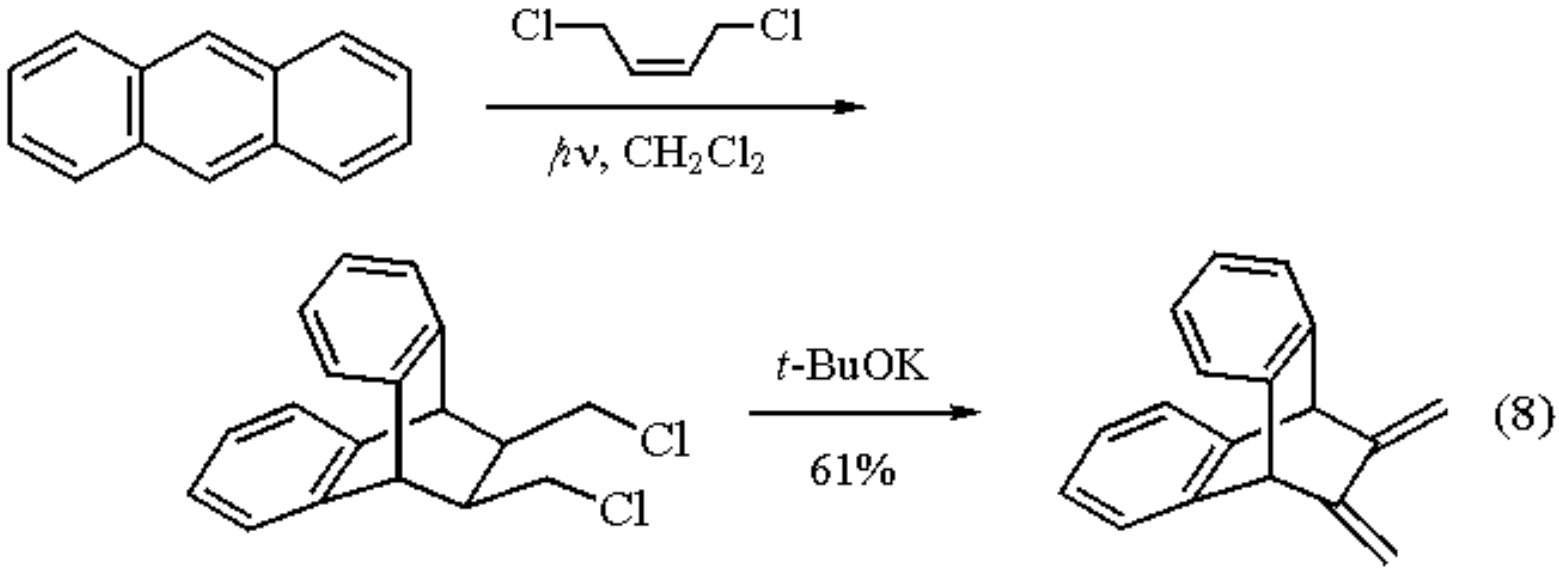

(8)

The synthetic utility of these cycloadditions is further enhanced by the base-induced dehydrohalogenation to generate new 1,4-diene units.

cis-1,4-Dichloro-2-butene is easily converted to an electron-rich diene on treatment with sodium aryloxide. This

reaction has been used in the synthesis of phyllanthocin (eq 9).[14]

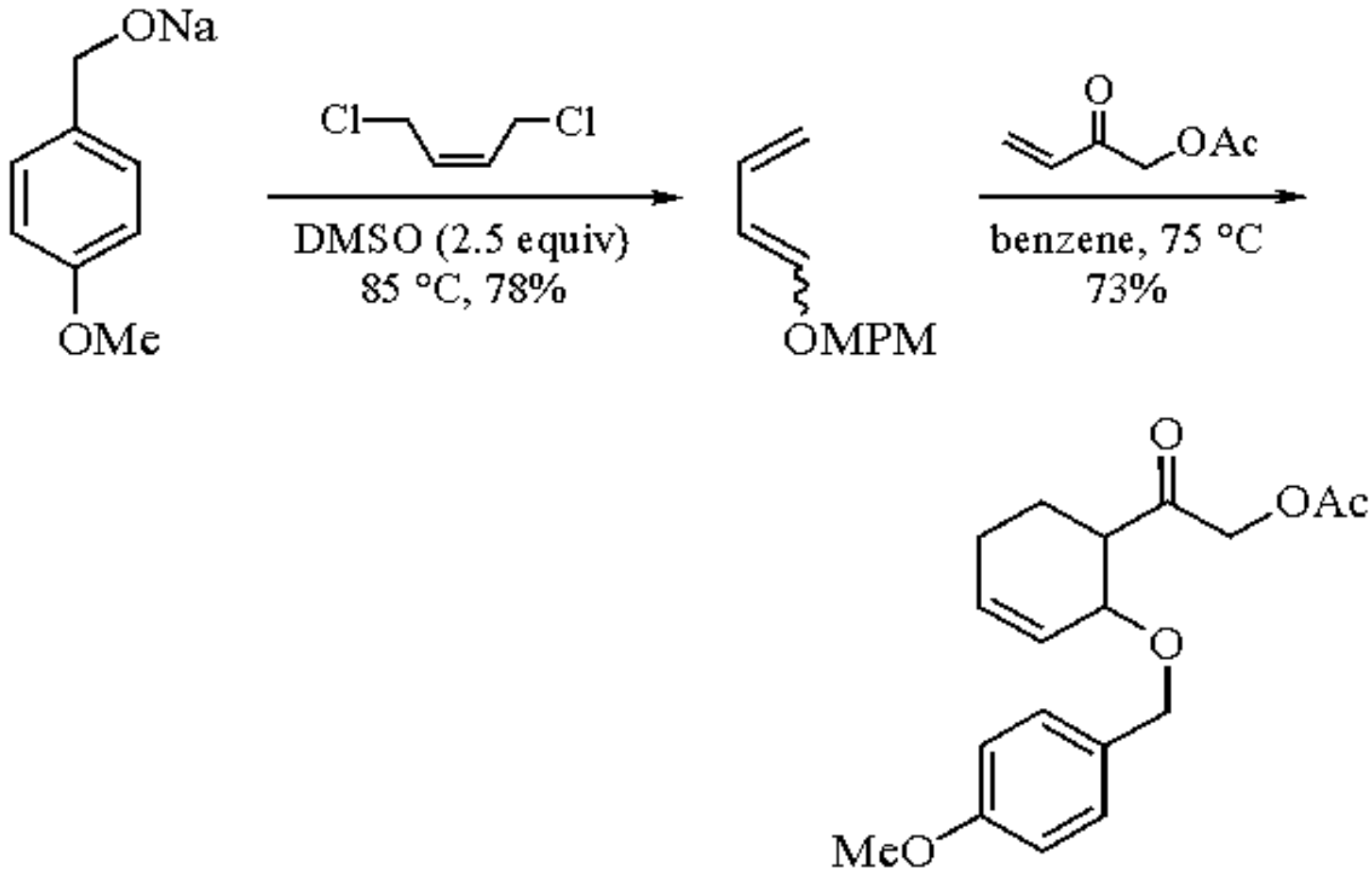

(9)

Synthesis of Heterocycles.

cis-1,4-Dichloro-2-butene affords 1,4-dihydropyrroles with ammonia or amines (eq 10).[15,16]

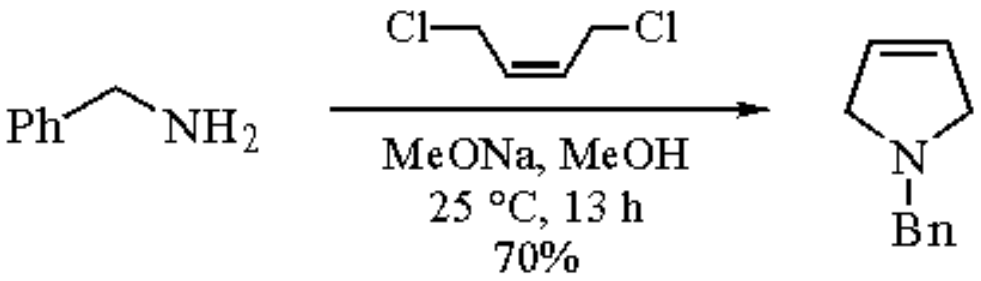

(10)

Similarly, tetrahydropyridines are accessible using diethyl acetamidomalonates (eq 11).[17]

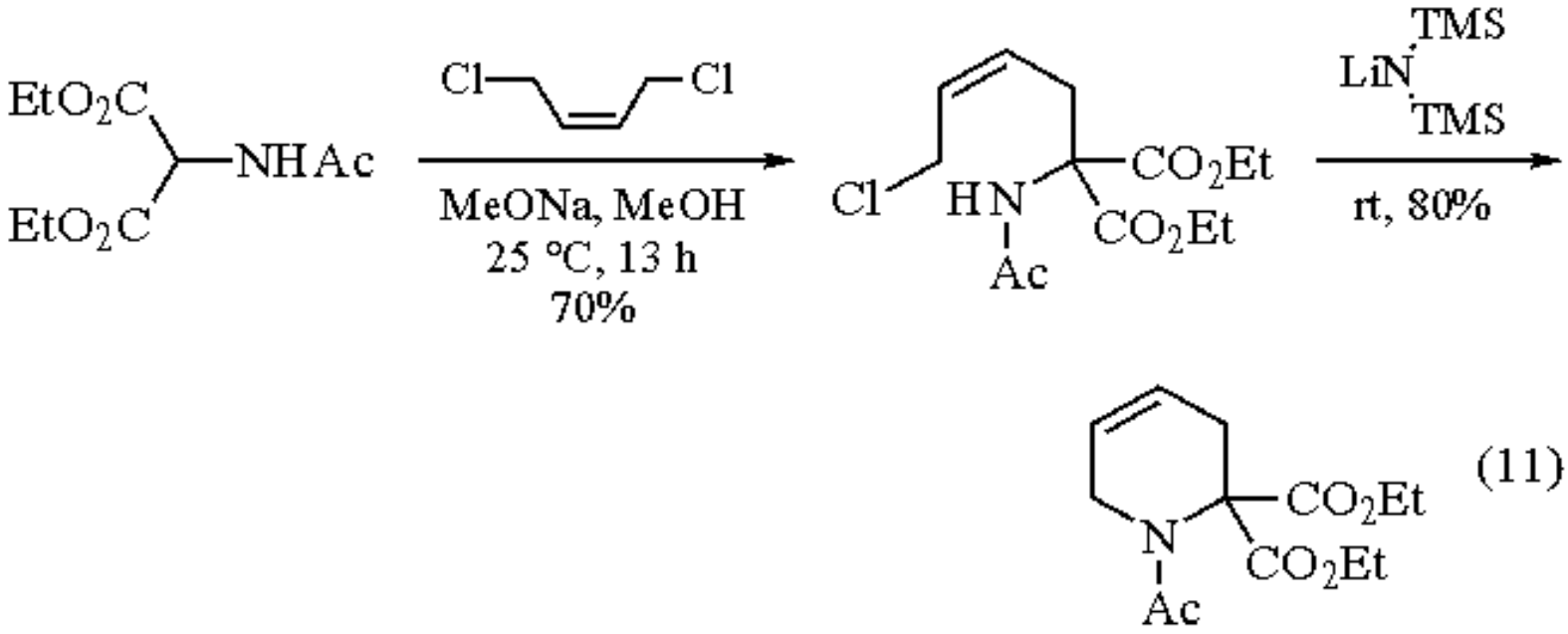

(11)

1,3-Butadienylphosphonium dichloride (obtained by treating 1,4-dichloro-2-butene with PPh_3) reacts with α-mercapto aldehydes or ketones, leading to unexpected vinylthiophenes (eq 12).[18]

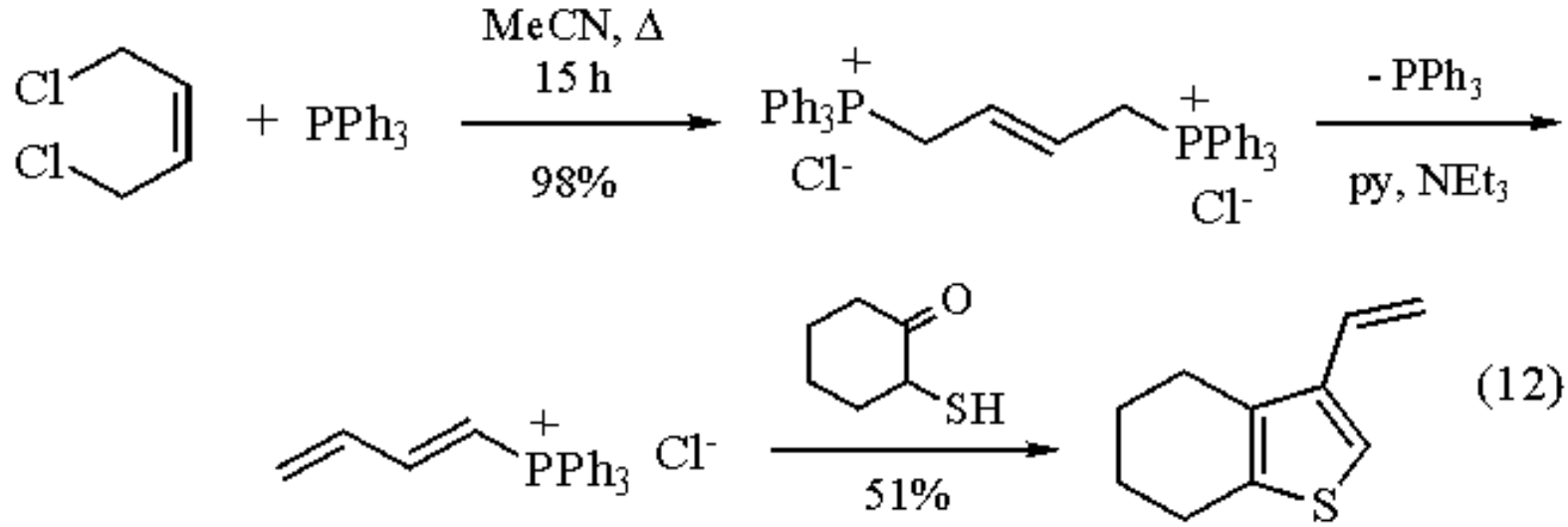

(12)

The bis Wittig salt is formed extremely easily with 1,4-dichloro-2-butene, but not with its dibromo counterpart.

6-*trans*-Styryl-3-azabicyclo[3.1.0]hexane.[19]

This reagent has been made by a novel N to C transannular rearrangement following an intramolecular carbenoid insertion starting from 1,1-dichloro-*cis*-2,3-bis(chloromethyl)cyclopropane, obtained by dichlorocarbene addition to *cis*-1,4-dichloro-2-butene.

The reagent is a good source of enyne carbanions,[20a] generated using ***Lithium Amide***/liq NH_3, which can be used for C-C bond formations (eq 13).[20b]

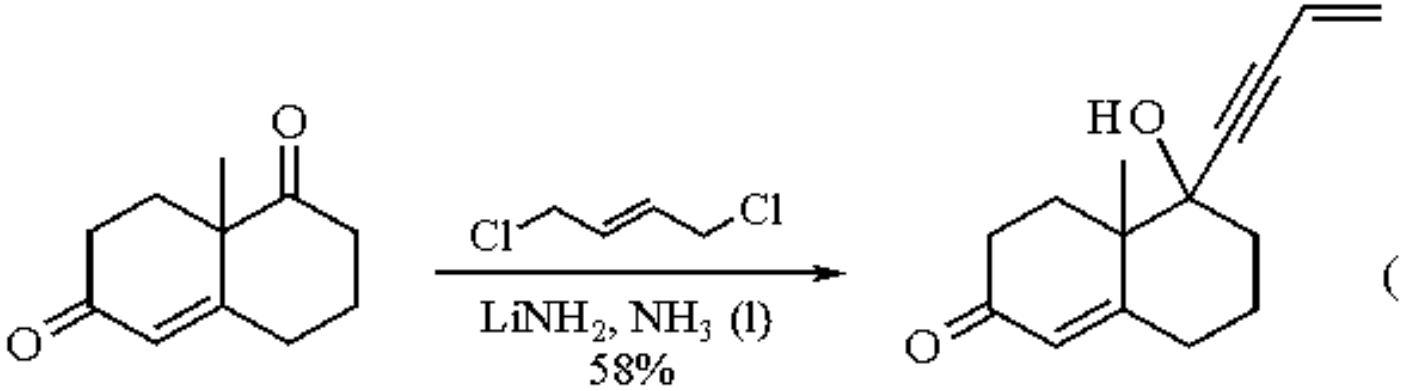

(13)

The reagent also finds use as a coupling promoter to obtain biaryls from aryl Grignard reagents.[21]

Related Reagents.

1,4-Dibromobutane; ***1,4-Dichloro-2-butyne***.

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1,3-Dichloro-2-butene

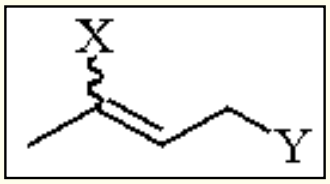

(**1**) (*E*/*Z*) (X = Cl, Y = Cl)

[926-57-8] · $C_4H_6Cl_2$ · 1,3-Dichloro-2-butene · (MW 125.00) (*E*)-(**1**) (X = Cl, Y = Cl)

[7415-31-8] (*Z*)-(**1**) (X = Cl, Y = Cl)

[10075-38-4] (**2**) (*E*/*Z*) (X = Cl, Y = Br)

[51430-83-2] · C_4H_6BrCl · 1-Bromo-3-chloro-2-butene · (MW 169.45) (**3**) (*E*/*Z*) (X = Cl, Y = I)

[54201-06-8] · C_4H_6ClI · 3-Chloro-1-iodo-2-butene · (MW 216.45) (*E*)-(**4**) (X = Br, Y = Br)

[86365-83-5] · $C_4H_6Br_2$ · 1,3-Dibromo-2-butene · (MW 213.90) (*Z*)-(**4**) (X = Br, Y = Br)

[86365-84-6] (*E*)-(**5**) (X = I, Y = Cl)

[135663-74-0] · C_4H_6ClI · 1-Chloro-3-iodo-2-butene · (MW 216.45) (*Z*)-(**5**) (X = I, Y = Cl)

[138174-48-8] (*Z*)-(**6**) (X = I, Y = I)

[134005-20-2] · $C_4H_6I_2$ · 1,3-Diiodo-2-butene · (MW 307.90)

(aldol, alkenyl radical, organopalladium/Heck annulations; methyl ketone precursor; alkyne precursor; alkenyl organometallic precursor; allylic nucleophile precursor)

Alternate Name: Wichterle reagent (**1**).

Physical Data: (*E*)-(**1**) bp 40 °C/20 mmHg; (*Z*)-(**1**) bp 35 °C/20 mmHg; (*Z*)-(**4**) bp 66 °C/13 mmHg.

Preparative Methods: see appropriate reference: (**1**),[2a,3] (**2**),[7a] (**3**),[12a] (**4**),[14b,15d,e] (**5**),[15c,f] (**6**).[15a]

Handling, Storage, and Precautions: reagent (**1**) shows an acute LD_{50} (inhalation, 4 h) of 546 ppm in rats.[2a] Acute and chronic toxicity to the kidney and other major organs is well established.[2] As low molecular weight allylic halides, these reagents can be expected to be lachrymatory, irritating to and absorbed through

the skin and mucous membranes, especially hazardous via inhalation, and suspect carcinogens. The usual stability order I < Br < Cl applies for both X and Y. The iodoallyl reagent (**3**) is photolabile;[12a] the iodoalkenyl reagent (*Z*)-(**5**) is reported to decompose above 25 °C.[15f]

Annulation (Aldol); Methyl Ketone Precursor.[4-10]

In 1948, Wichterle reported that treatment of a chloroalkenyl keto ester with concentrated sulfuric acid resulted in cyclization (eq 1),[4a] effecting a formal equivalent of the Robinson annulation with 1,3-dichloro-2-butene (**1**) serving as a substitute for ***Methyl Vinyl Ketone*** (MVK). The Wichterle reaction has proven useful in many syntheses in which MVK gives poor results due to polymerization or other side reactions. The alkylation step has been performed with unstabilized as well as stabilized enolates and with enamines. The Roussel-Uclaf synthesis of 19-norprogesterone, which exploited the selective condensation of pyrrolidine with a cyclohexenone in the presence of a saturated methyl ketone, is exemplary (eq 2).[4b] In this case, the allylic iodide (**3**) was formed in situ; the bromo (**2**) or iodo derivative (**3**) is often prepared in a separate Finkelstein reaction. Although (*E*)-(**1**) and (*Z*)-(**1**) are more reactive than allyl chloride to substitution with ***Potassium Iodide*** or ***Sodium Ethoxide***,[3a] (**3**) failed a demanding test of regioselective alkylation of a sterically hindered enolate (eq 3).[4c] Catalytic ***Tetrakis(triphenylphosphine)palladium(0)*** has been shown to enhance the reactivity of (**1**), allowing regioselective alkylation of potassium enoxyborates.[4d]

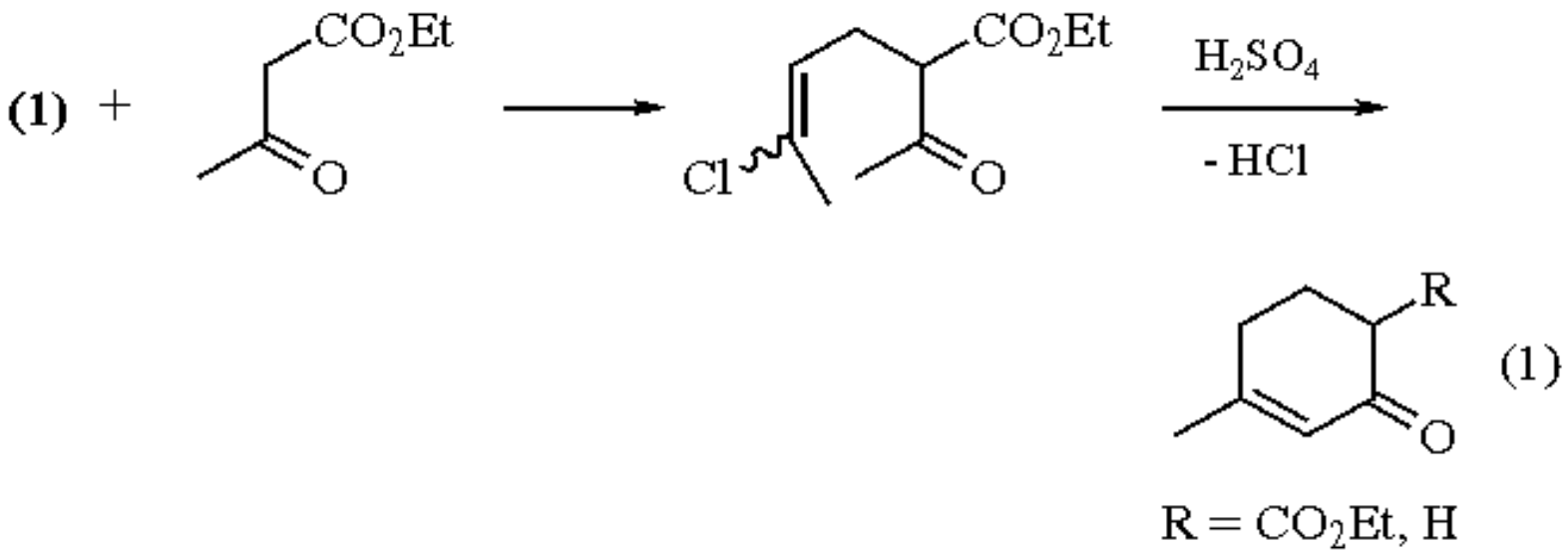

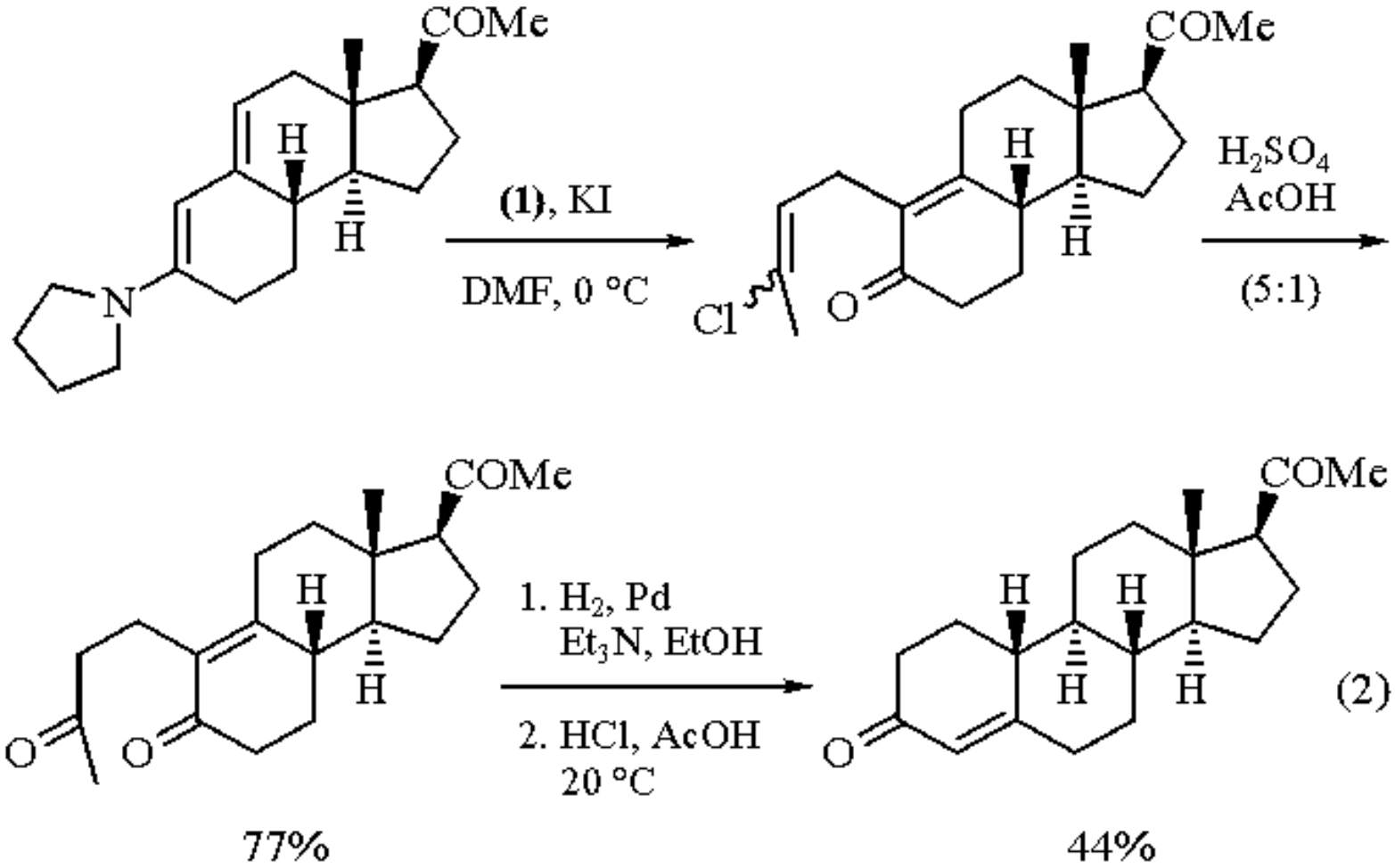

(2)

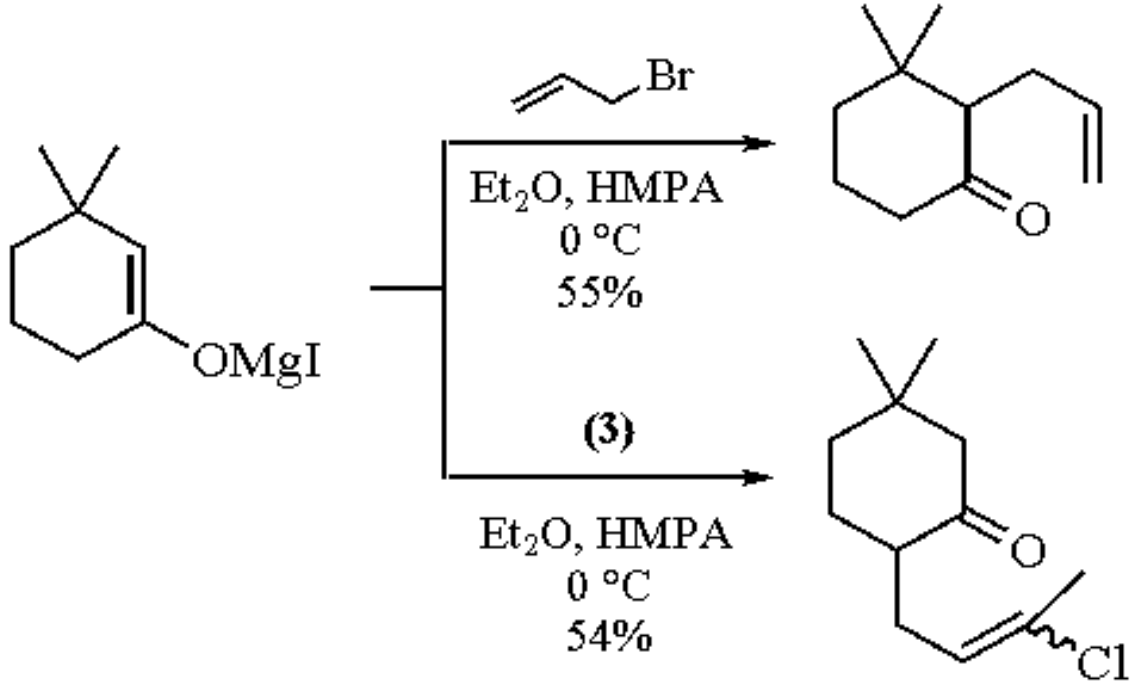

(3)

When concentrated H_2SO_4 is used for solvolysis, high yields are favored by short (<1 h) reaction times at 0 °C, use of a diluent (CH_2Cl_2), and rapid dilution upon aqueous workup.[5a,b] Starting ring size, substitution, and unsaturation affect the course of cyclization.[5] Saturated ketones tend to cyclize to bridged bicyclic enones, sometimes (eq 4)[5a] to

the exclusion of the usually desired fused product. Unsaturation can prevent premature cyclization (eq 5);[5a] in eq (2), a bridged enone would violate Bredt's rule. Fused products can be obtained from saturated ketones by using milder acidic conditions (eq 6).[5d,7a] Treatment with Hg^{II} salts or ***Titanium(IV) Chloride*** is often preferred,[4d] giving the dione which is cyclized in a separate aldol step (e.g. eqs 7 and 8). Chloroalkenes also react with carbocations intramolecularly as cyclization terminators, but are inferior to fluoroalkenes in this role.[6]

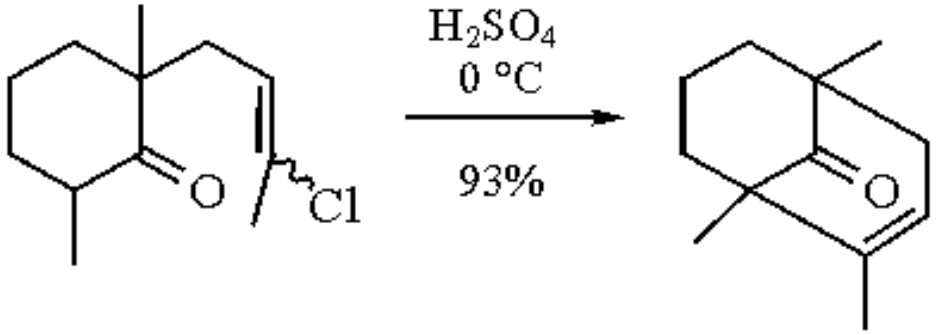

(4)

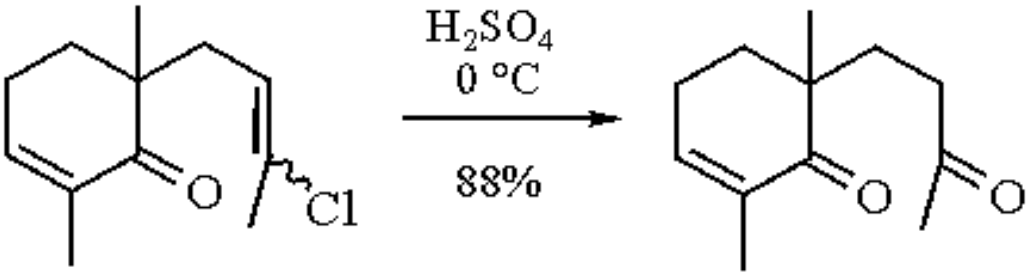

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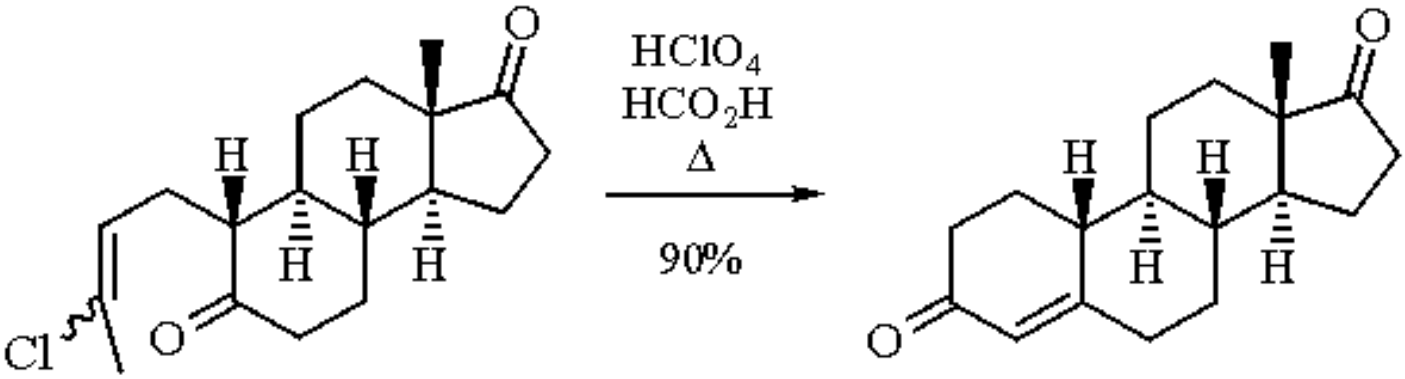

(6)

Reductive alkylation by (**2**) of a dienone (eq 7),[7b] or related enedione,[7a] proceeded regio- and stereoselectively to provide a concise synthesis of adrenosterone. The stabilized Michael acceptor α-(trimethylsilyl)-MVK[7c] failed in this case. Alkylation of an optically active β-hydroxybutyrate dianion proceeded with high *anti* selectivity to form a quaternary chiral center (eq 8);[8a,b] the 1,5-diketone thereby obtained could be cyclized to either regioisomeric cyclohexenone by varying aldol conditions. Phase-transfer alkylation of a 1-indanone in the presence of a *Cinchona* alkaloid-derived chiral catalyst proceeded with pronounced enantioselectivity, again leading to a chiral quaternary enone after cyclization (eq 9).[8c] Reaction of a lithiothiomethyl phosphonate with (**1**), followed by a second lithiation and condensation with an aldehyde, afforded in one flask a dienic 1,4-diketone precursor (eq 10).[8d]

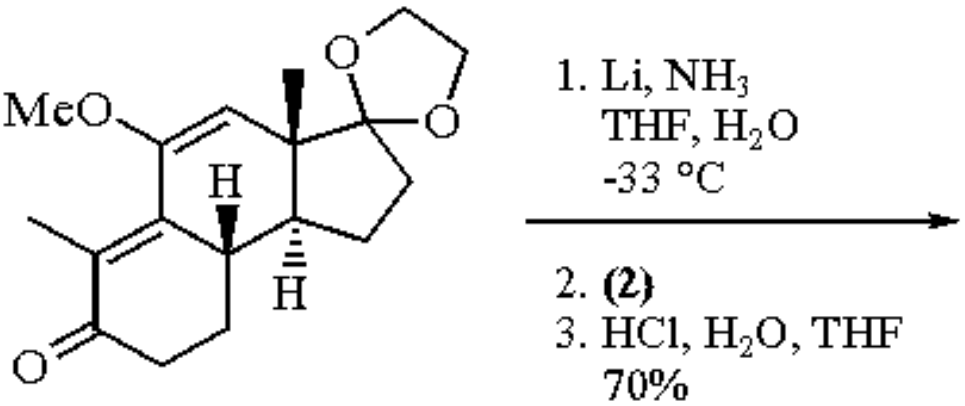
MeO
O
O
H
H
O
1. Li, NH3
THF, H2O
-33 °C
2. (2)
3. HCl, H2O, THF
70%

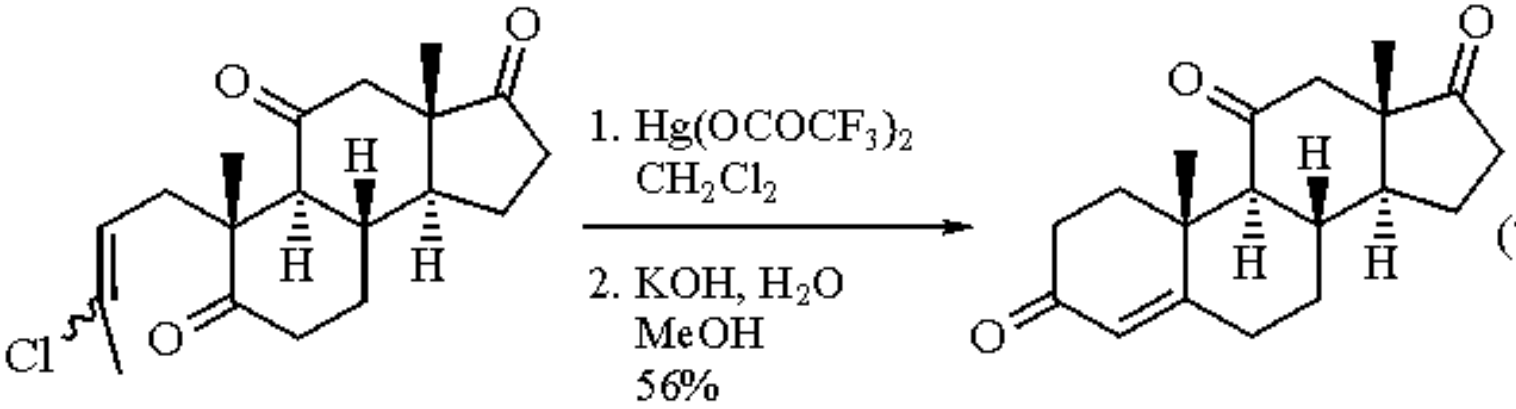
O
O
H
H
H
Cl
O
1. Hg(OCOCF3)2
CH2Cl2
2. KOH, H2O
MeOH
56%
O
O
H
H
H
O

(7)

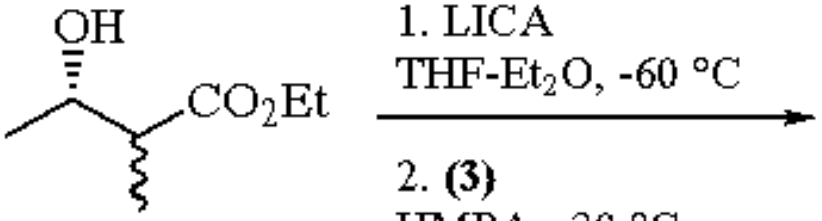
OH
CO2Et
1. LICA
THF-Et2O, -60 °C
2. (3)
HMPA, -30 °C
53%

(3*S*, 2*RS*)

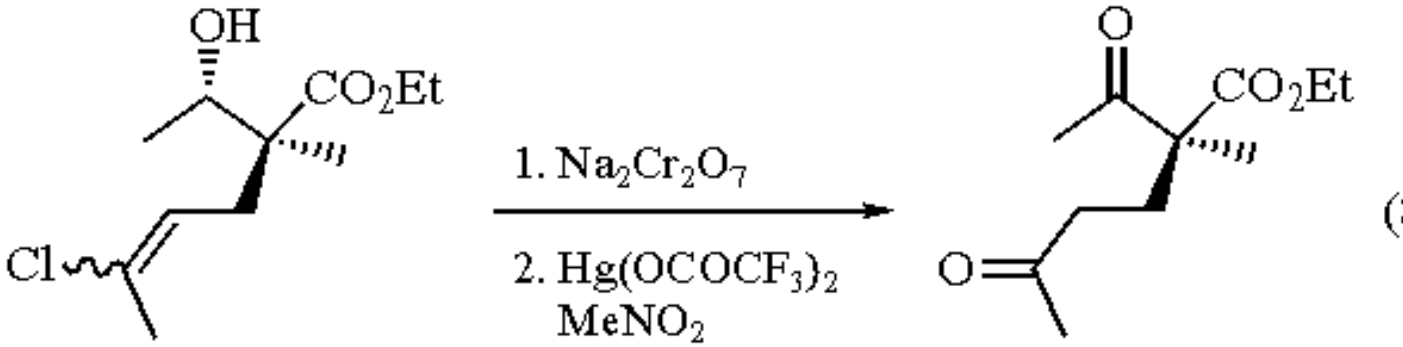
OH
CO2Et
Cl
1. Na2Cr2O7
2. Hg(OCOCF3)2
MeNO2
60%
O
CO2Et
O

93:7

(8)

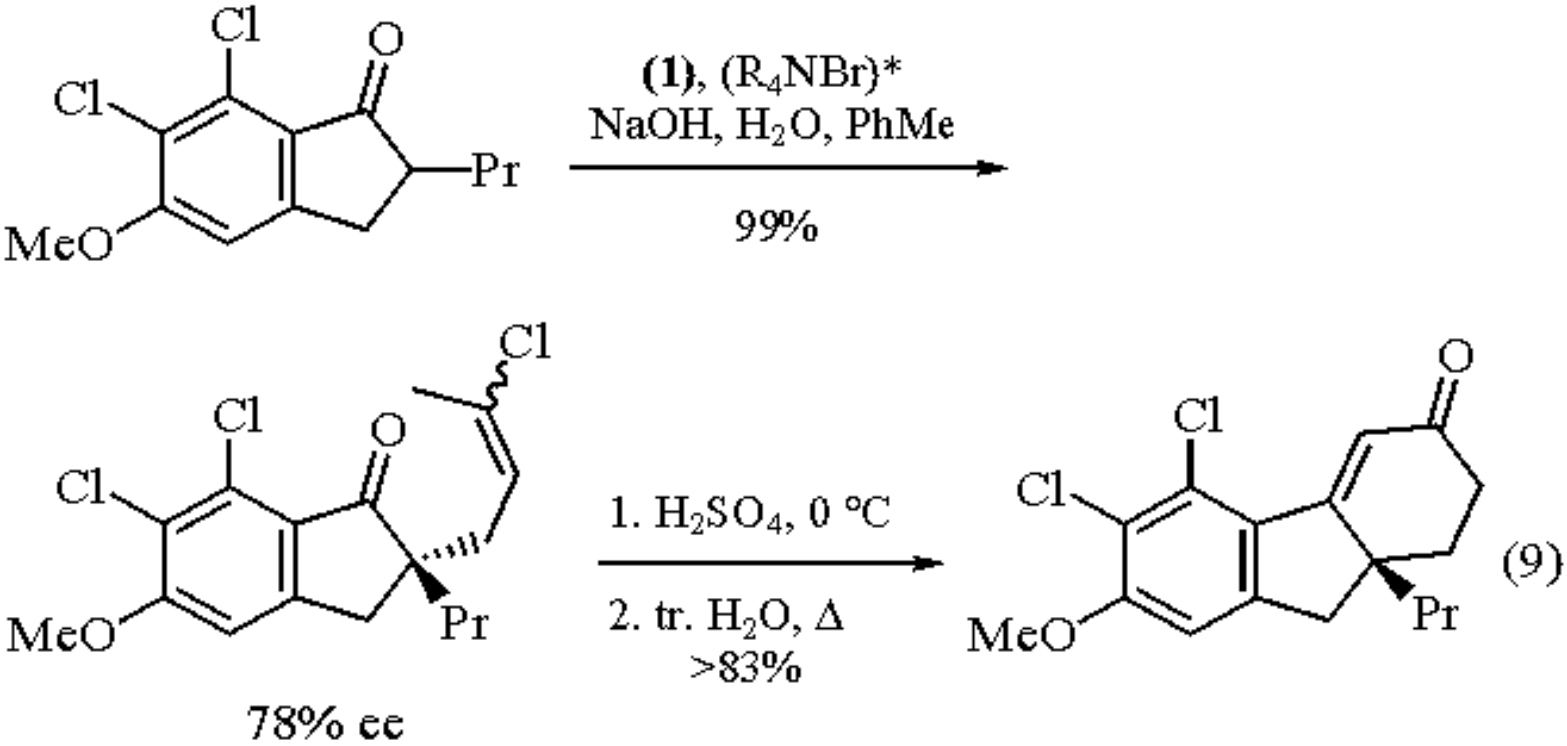

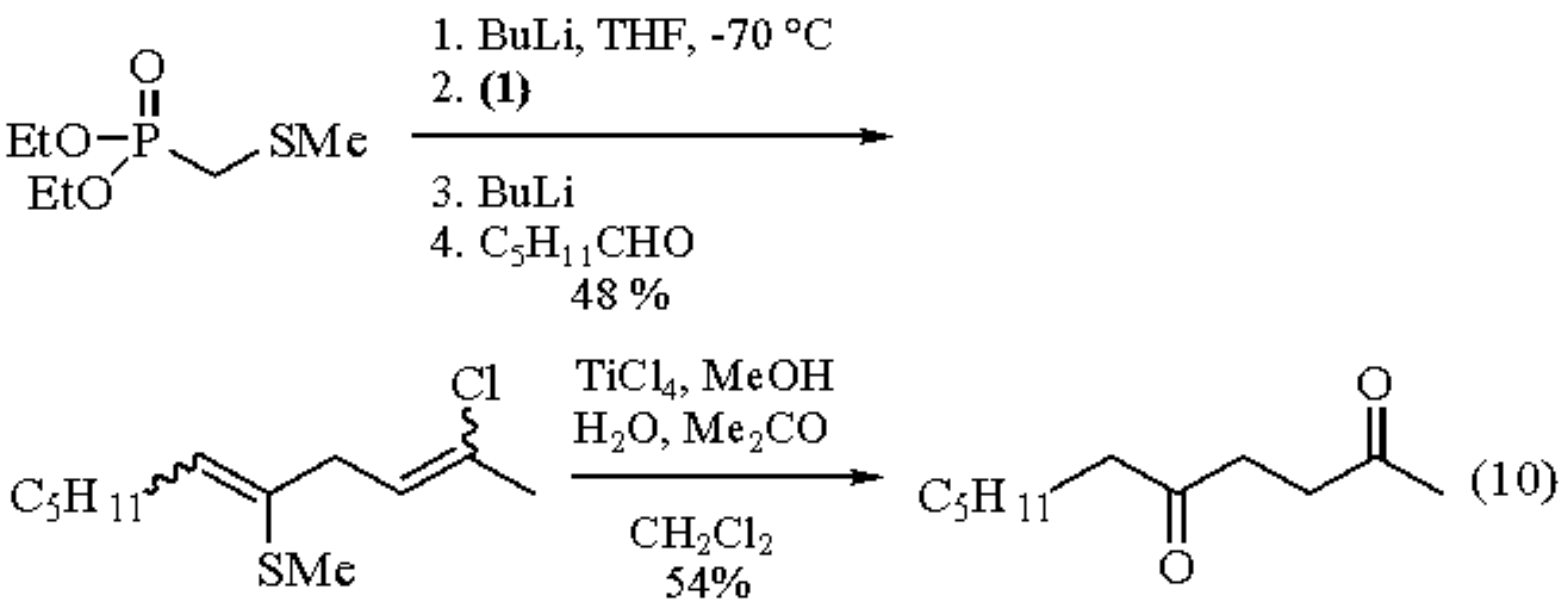

The Wichterle reaction has found use in heterocyclic synthesis, of the pyrido[1,2-*a*]benzimidazole system (eq 11).[10a] En route to camptothecin, a planned aldol cyclization route to a dihydropyridone using ***Methyl Magnesium Carbonate*** (MMC) took an unexpected course, via transient benzylic methoxycarbonylation (eq 12).[10b] In a model study for mesembrine synthesis, alkylation with (**1**) followed by a regioselective imide reduction paved the way to an iminium ion cyclization (eq 13).[10c]

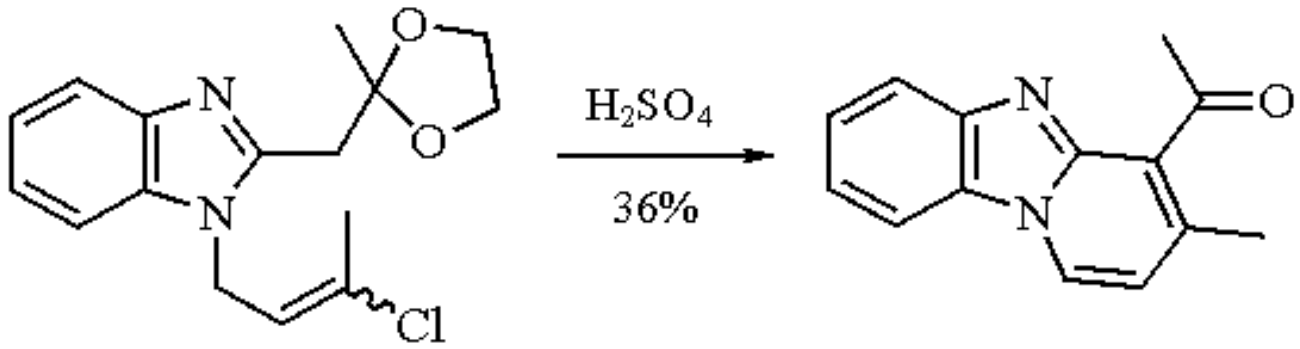

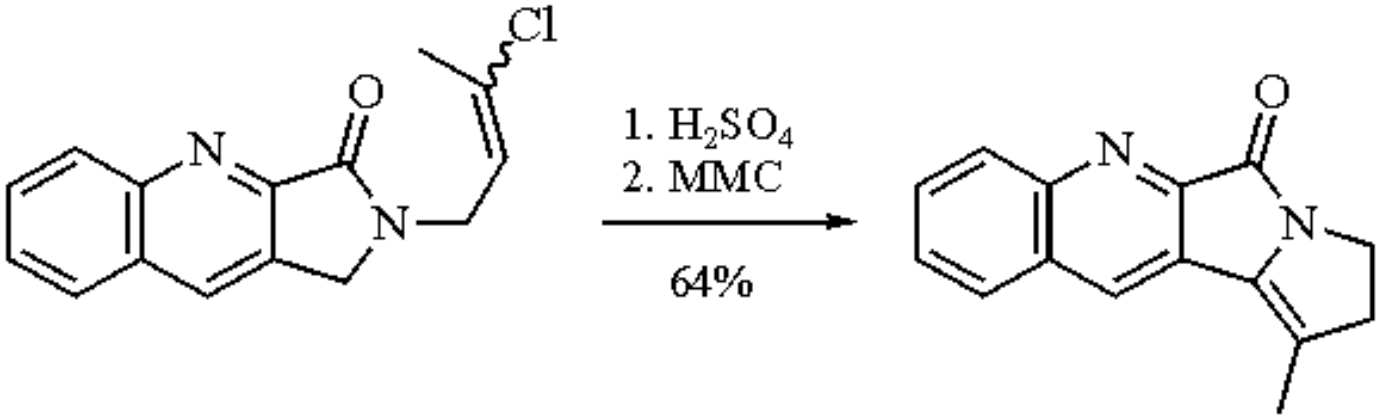

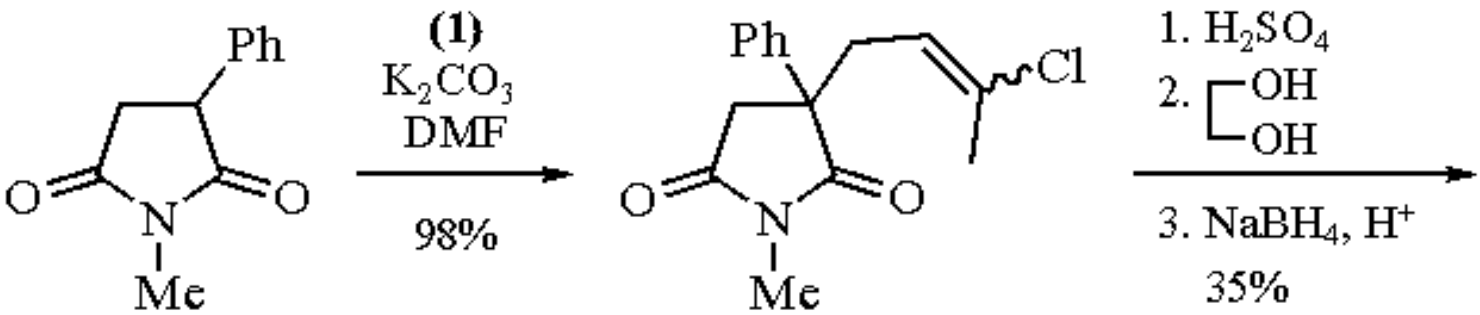

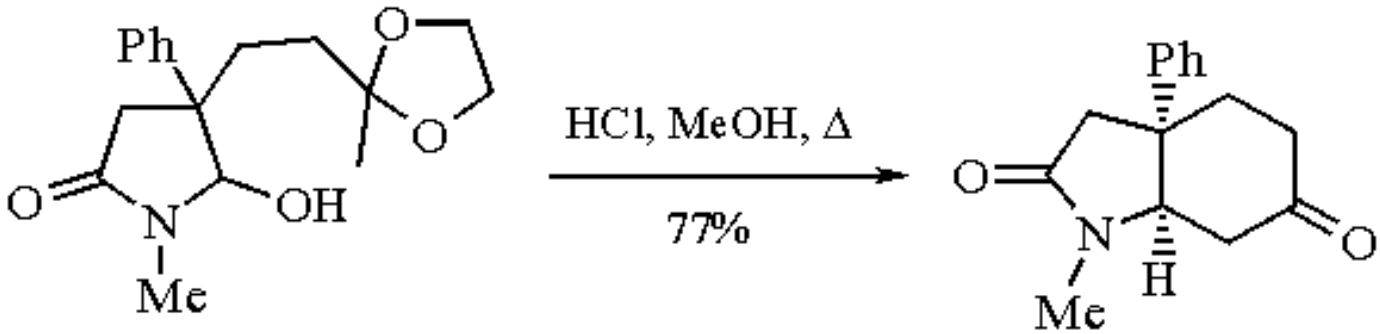

Alkyne Precursor.[11,12]

Vigorous basic treatment of (**1**) provides vinylacetylene (eq 14).[11a] Under appropriate conditions, chloroalkenes derived from (**1**) are transformed into either the internal (eq 15)[11b] or terminal alkyne (eq 16).[12a-c] δ,ε-Alkynyl ketones undergo reductive[12a,b] or photochemical cyclization;[12c] Hg^{II}-catalyzed hydration to the 1,5-diketone is an alternative to direct hydrolysis of the chloroalkene.[12d]

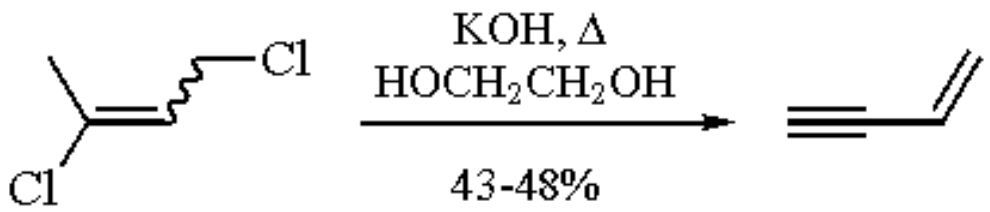

(14)

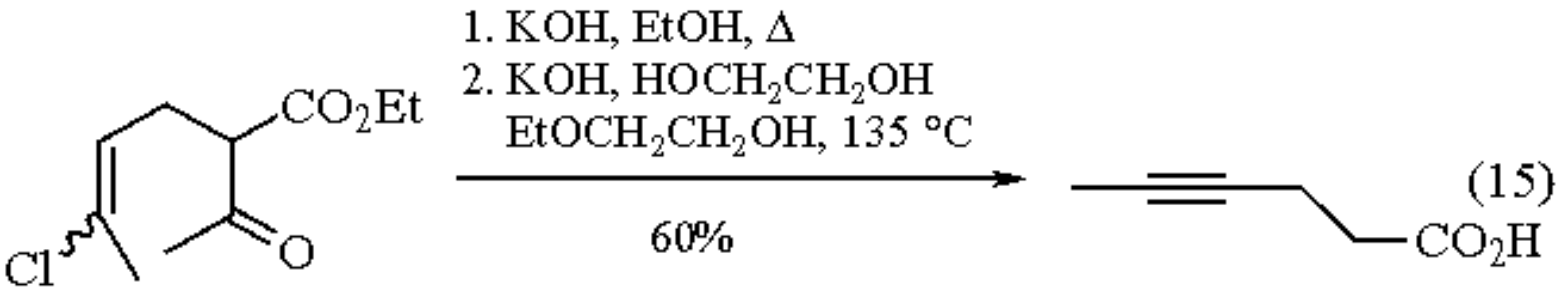

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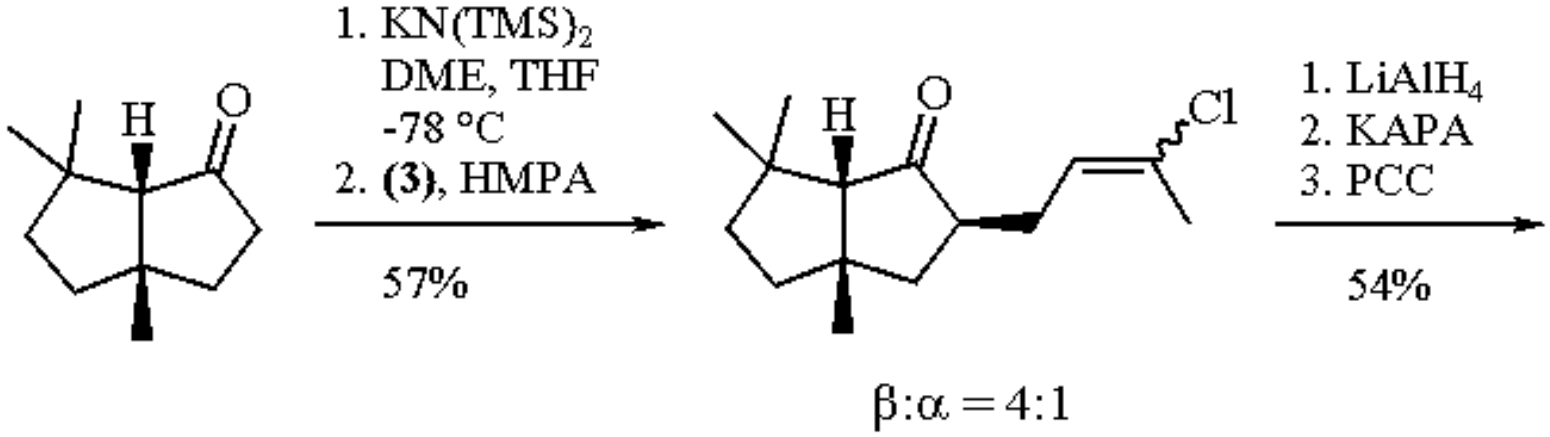

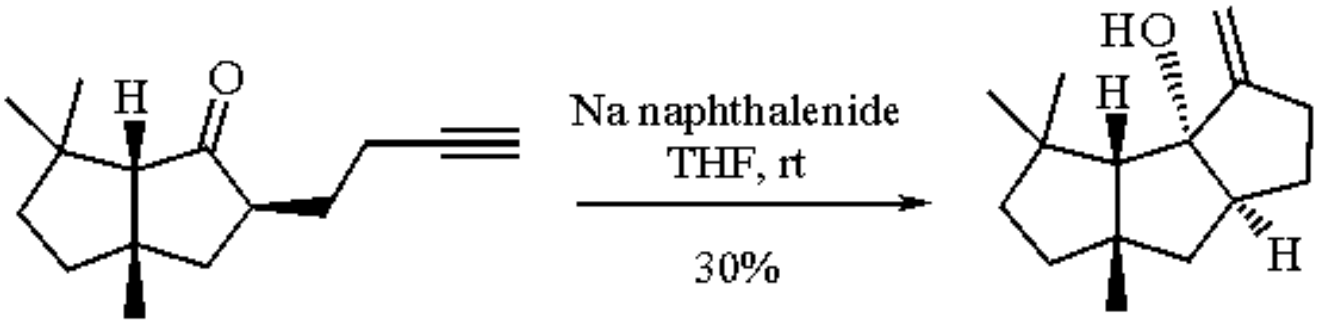

(16)

Allylic Nucleophile.[13]

The allyllithium derivative of (**1**) can be prepared at -90 °C via an allyllead intermediate;[13a] preparation of the Grignard reagent in the usual way, near rt, presumably results in decomposition. Electrochemical coupling of (**1**) with $ClSiMe_2Ph$ yields the allylsilane.[13b] Reaction of (**3**) with Ph_3P gives the phosphonium salt and thence the phosphorane unexceptionally.[13c]

Alkenyl Radical Cyclization.[14]

Treatment of an iodo- or bromoalkene with ***Tri-n-butylstannane*** generates the alkenyl radical which can add intramolecularly to a double bond (eqs 17 and 18).[14a,b] A strong preference for enolate alkylation *syn* to the double bond (eq 18)[14b] was exploited. The (*E*)-bromoalkene can be used because alkenyl radical inversion is rapid.

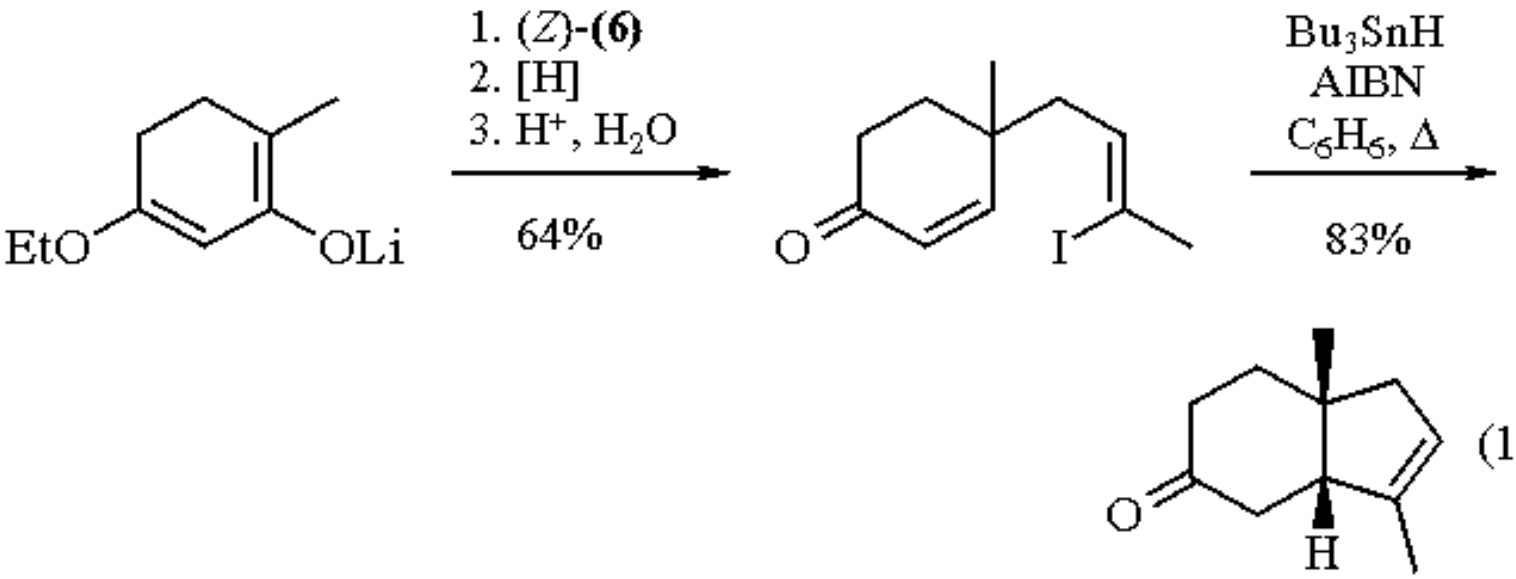

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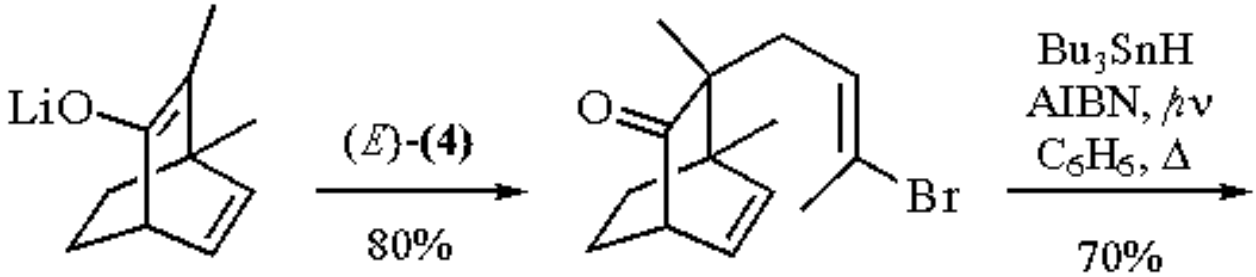

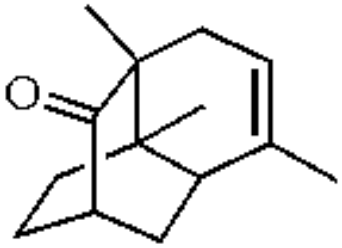

(18)

Alkenyl Organometallic Precursor.[15]

Eq 19[15a,b] demonstrates use of a catalytic intramolecular Heck reaction of a (*Z*)-iodoalkene in a cyclopentene annulation sequence. Cyclization of the related (1-alkenyl) triflate using the chiral ligand *S*-BINAP gave the *exo*-methylene product in 80% ee. En route to rapamycin, reagent (*E*)-(**5**) provided an allylic sulfone that was deployed sequentially in a Cr^{II}-mediated (Nozaki-Kishi) aldehyde addition and a Julia coupling (eq 20).[15c]

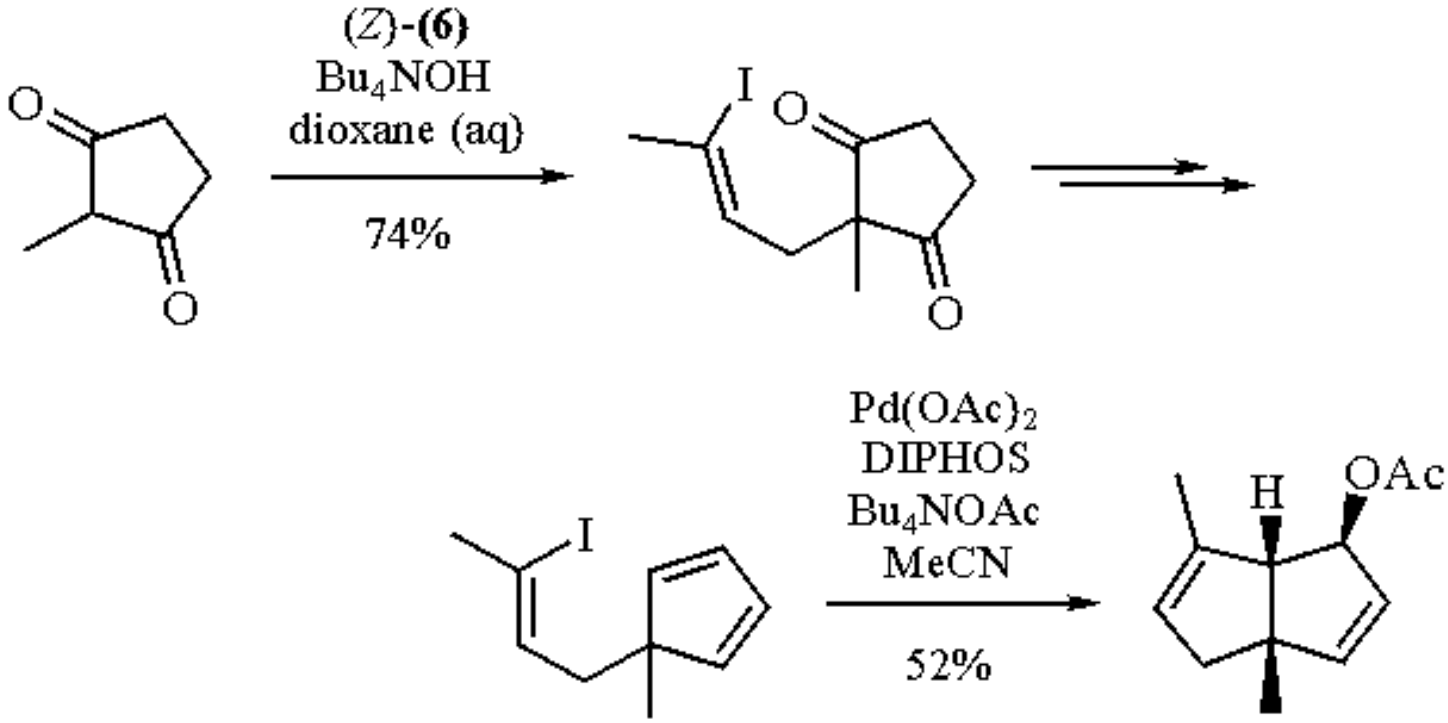

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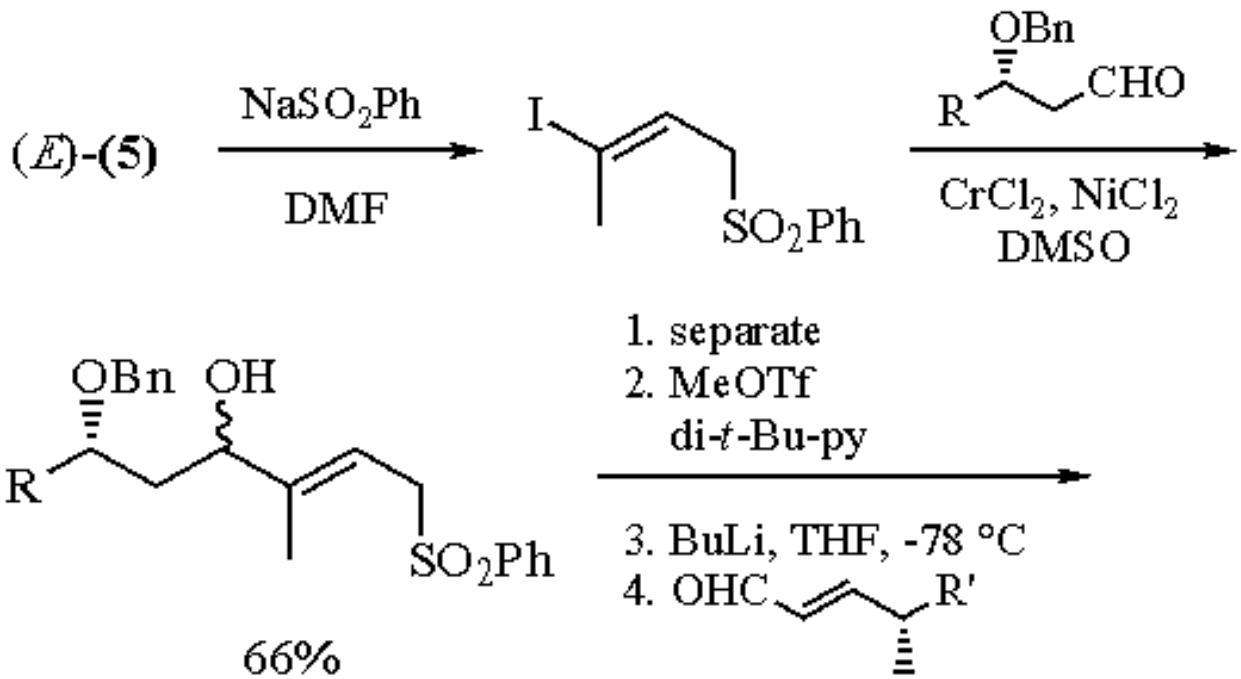

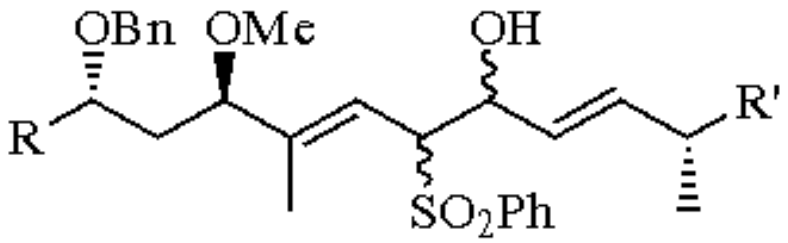

(20)

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15. (a) Kagechika, K.; Ohshima, T.; Shibasaki, M. *T* **1993**, *49*, 1773. (b) Kagechika, K.; Shibasaki, M. *JOC* **1991**, *56*, 4093. (c) Chen, S.-H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *JOC* **1991**, *56*, 5834. (d) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *JOC* **1983**, *48*, 3894. (e) Asao, K.; Iio, H.; Tokoroyama, T. *TL* **1989**, *30*, 6401. (f) Cristofoli, W. A.; Keay, B. A. *TL* **1991**, *32*, 5881.

Raymond E. Conrow

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1,4-Dichloro-2-butyne

$ClCH_2$-C&tbond;C-CH_2Cl

[821-10-3] · $C_4H_4Cl_2$ · 1,4-Dichloro-2-butyne · (MW 122.98)

(undergoes electrophilic additions, 1,3-dipolar additions,[17] trimerizations;[19] source of four-carbon synthons such as butadienes[3-5,8-10] and allenes;[16] serves as coupling promoter[18])

Physical Data: colorless liquid, bp 165-168 °C; *d* 1.258 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: neat liquid of high purity.

Preparative Method: conveniently prepared by treating 1,4-butynediol with ***Thionyl Chloride***.[1] However, as a precautionary measure the medium is diluted with CH_2Cl_2 and cooled to -30 °C before adding thionyl chloride to avoid hazards associated with the exothermicity of the reaction.[2]

Handling, Storage, and Precautions: flammable liquid, lachrymator, and irritant; use in a fume hood.

Substituted Butadienes.

A variety of polysubstituted 1,3-butadienes are conveniently prepared by a two-step sequence involving addition-elimination (eq 1). Thus halogens/pseudohalogens,[3] aryl selenosulfonates,[4] and silanes[5] can be added followed by reductive dehalogenation with ***Zinc***. These functionalized butadienes can be used as dienes in cycloadditions[3,6] and in the synthesis of allenes[4] (eq 2). Silylbutadienes find use as adhesion promoters[5] and in complexes with iron tricarbonyl undergo unprecedented diacylations under Friedel-Crafts conditions.[7]

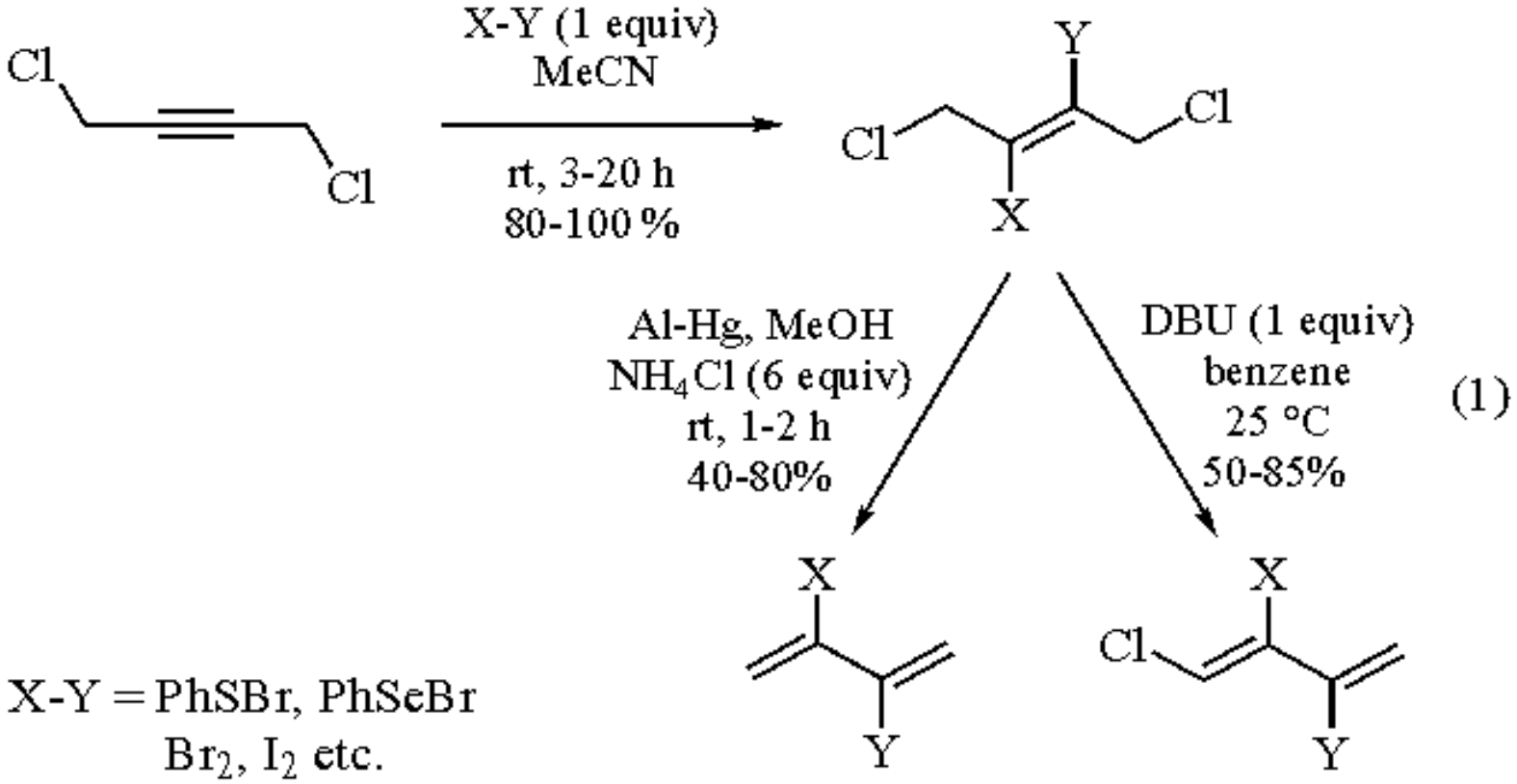
X-Y (1 equiv)
MeCN
rt, 3-20 h
80-100 %
Al-Hg, MeOH
NH4Cl (6 equiv)
rt, 1-2 h
40-80%
DBU (1 equiv)
benzene
25 °C
50-85%
(1)
X-Y = PhSBr, PhSeBr
Br2, I2 etc.

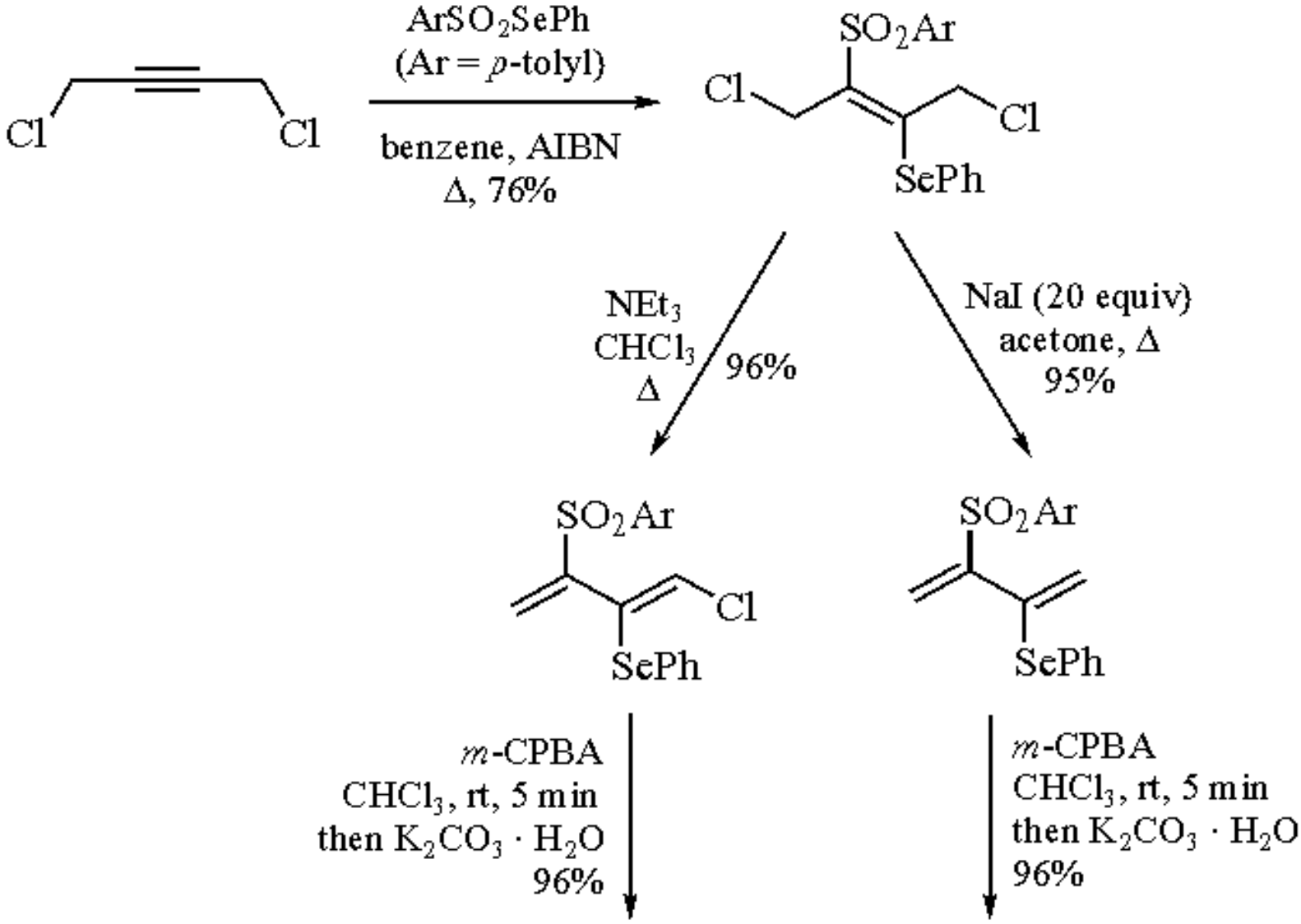
ArSO2SePh
(Ar = p-tolyl)
benzene, AIBN
Δ, 76%
NEt3
CHCl3
Δ
96%
NaI (20 equiv)
acetone, Δ
95%
m-CPBA
CHCl3, rt, 5 min
then K2CO3 · H2O
96%
m-CPBA
CHCl3, rt, 5 min
then K2CO3 · H2O
96%

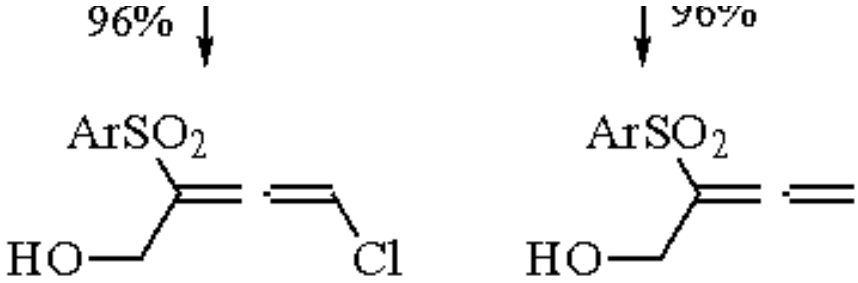

(2)

2,3-Disubstituted butadienes are also accessible by Grignard addition[8] or by thermal rearrangement,[9] while alkylborane addition[10] is a means of obtaining 2-alkylbutadienes (eq 3).

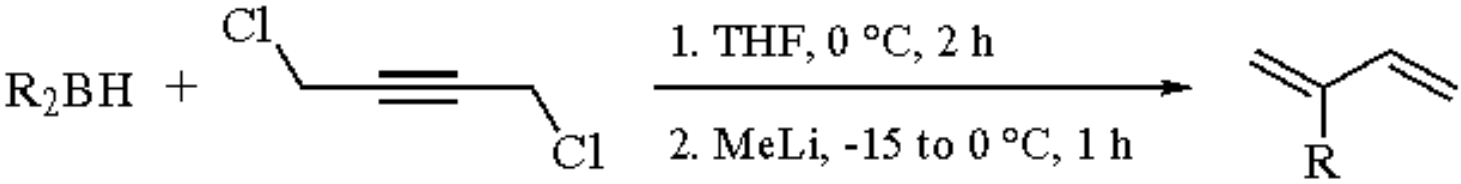

(3)

Bisalkynes.

With ***Sodium Amide***, the bisacetylide anion is formed, which on being quenched with ***Iodomethane*** gives 1,3-pentadiyne.[11] Alternatively, the carbanion can be treated with a carbonyl compound to obtain dialkynyl alcohols. In one instance a dialkynyl alcohol has been elaborated to a hydroxy fatty acid (eq 4)[12] and in the other, following a different strategy, to a marine natural product.[13]

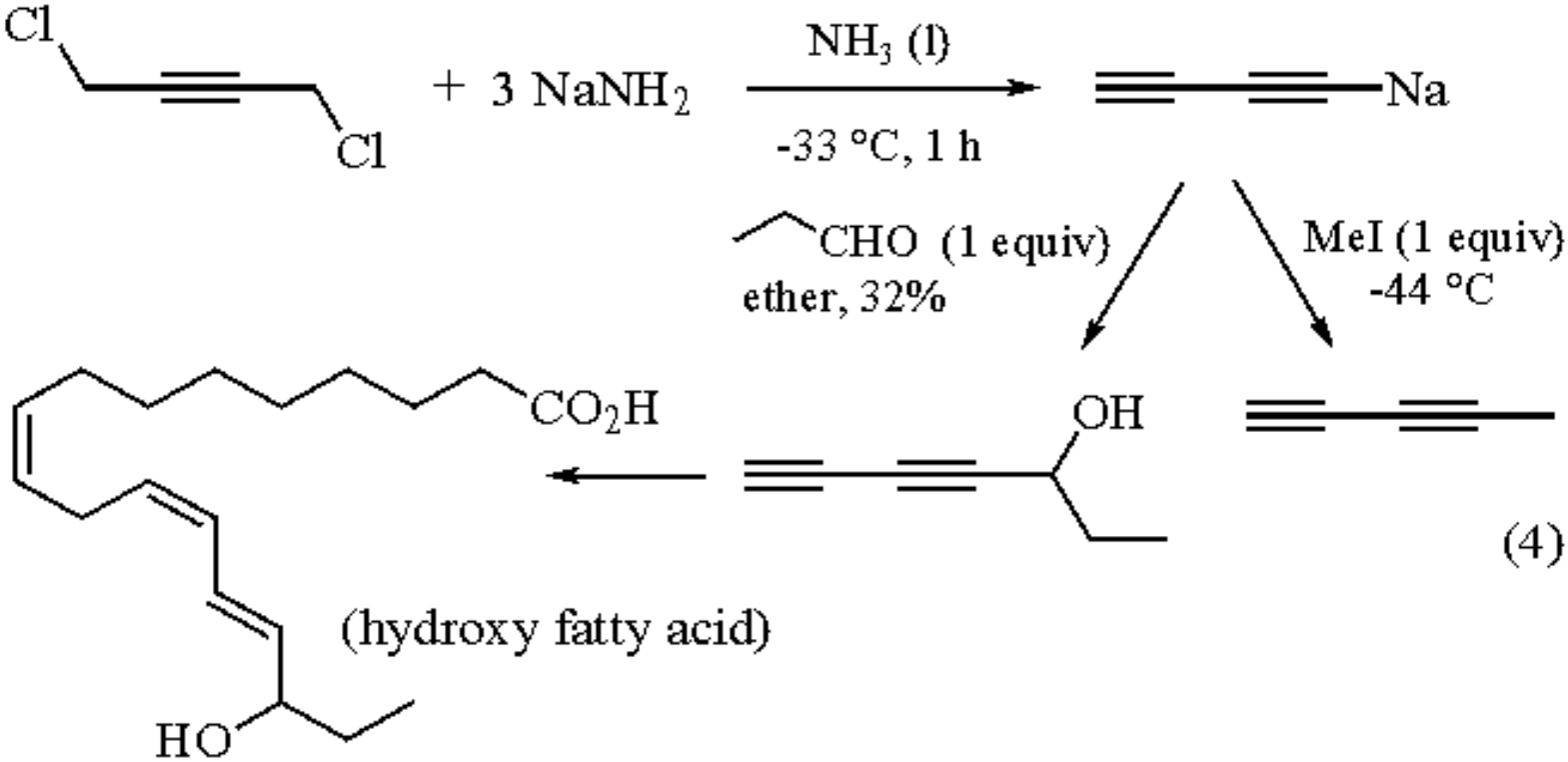

(4)

Fused Carbocycles.[14]

Polycyclic compounds are accessible by successive addition of two carbenes under rhodium catalysis (eq 5).

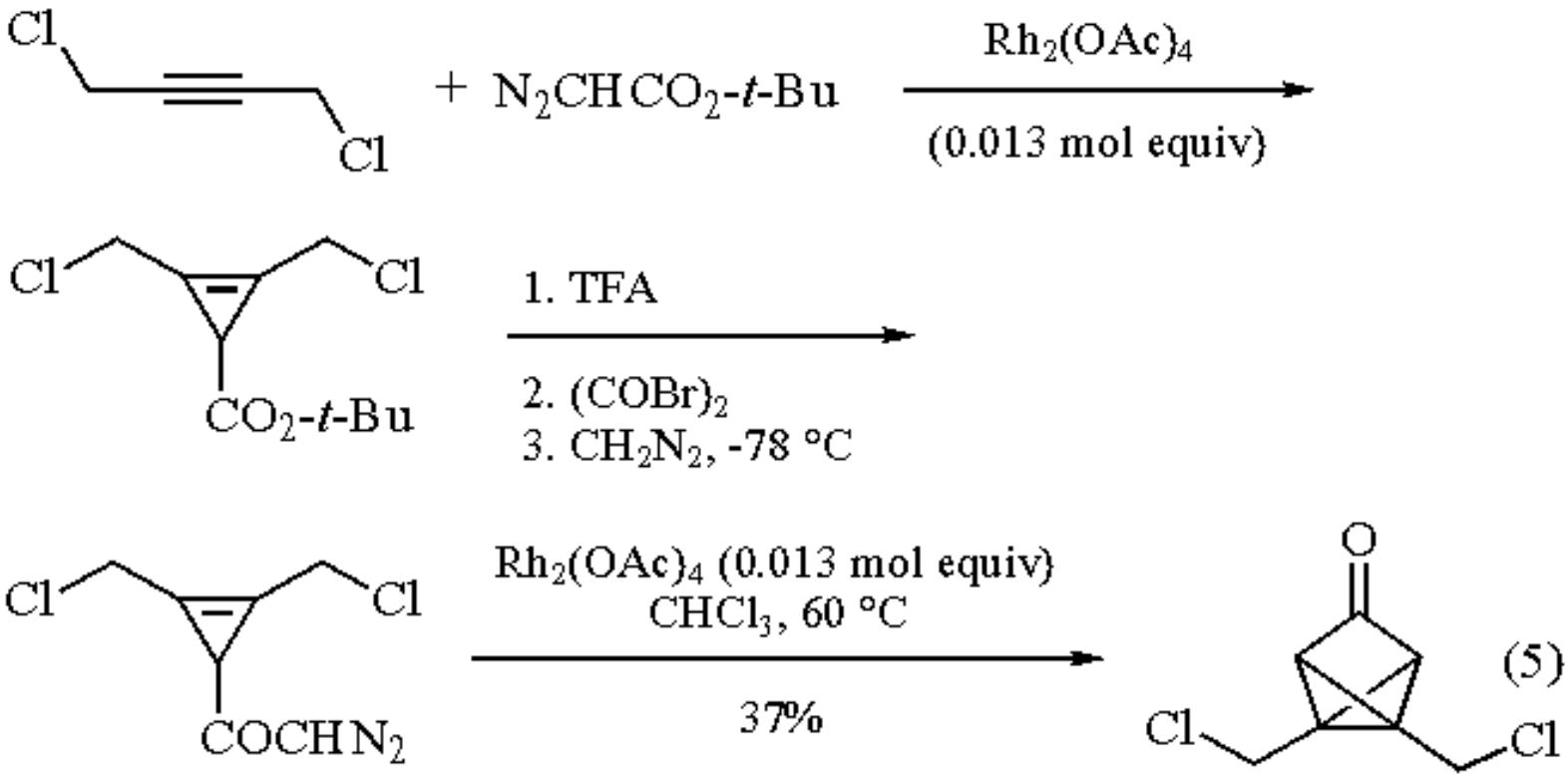

Cumulated Trienes.[15]

These can be obtained by addition of dithiocarbonate followed by desulfurization, as an alternative to the traditional Zn reduction (eq 6).

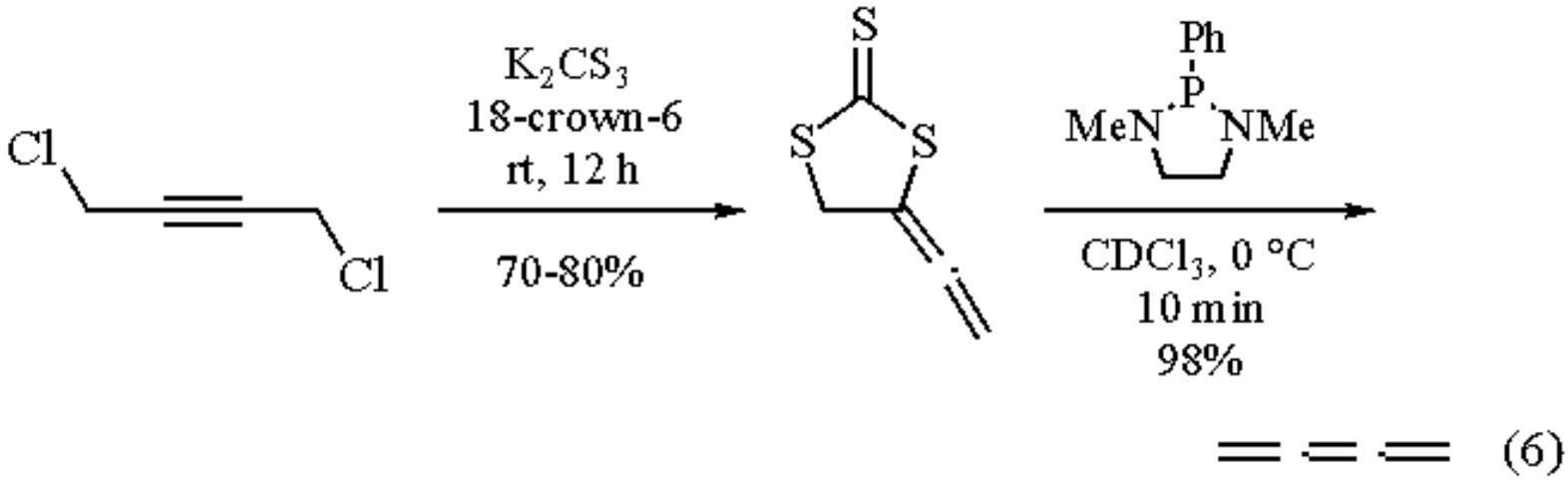

A novel allenol nucleoside[16] with pronounced anti-HIV activity is synthesized making use of the base-catalyzed alkyne-allene rearrangement. The allene nucleoside can be cyclized to the dideoxydidehydronucleoside under more basic conditions (eq 7).

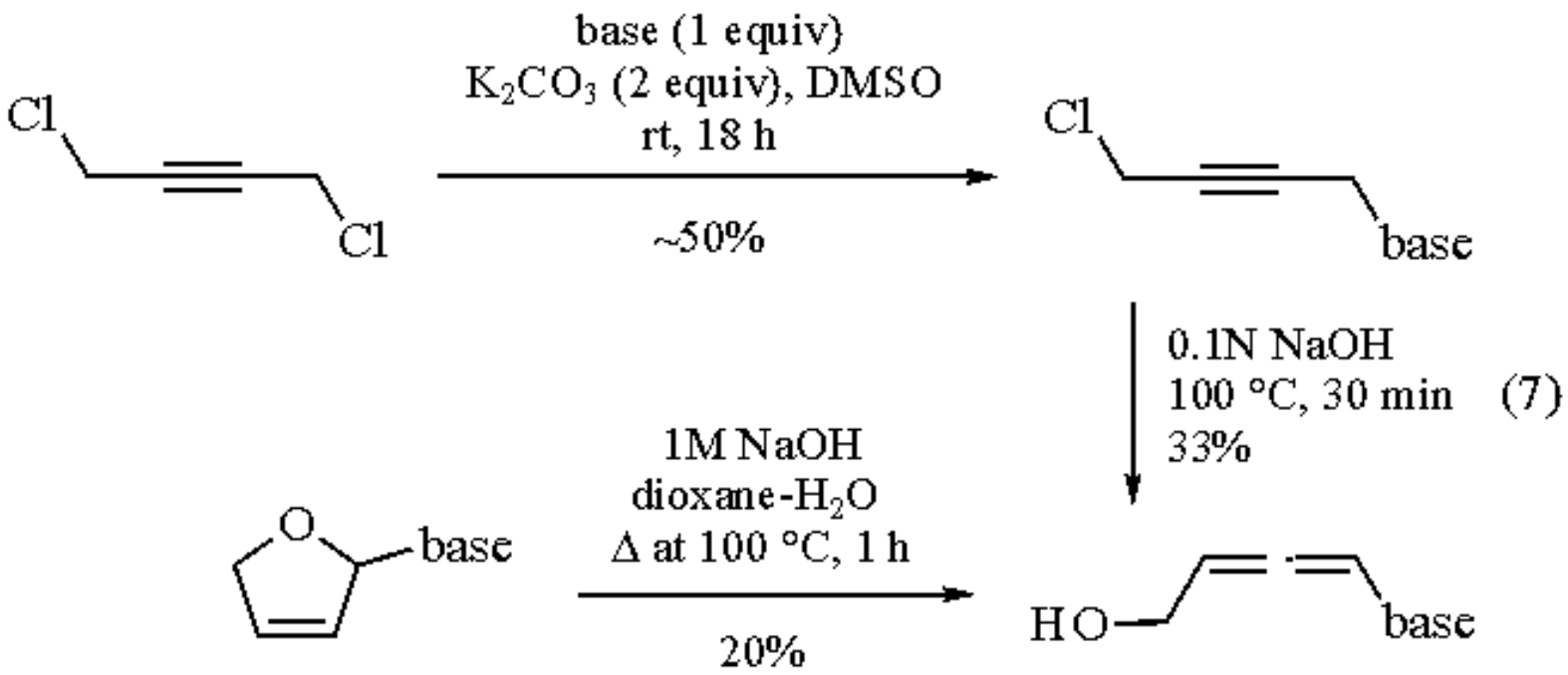

1-Glycosyl(halomethyl)-1,2,3-triazoles.[17]

These are useful as potential alkylating agents in cancer chemotherapy and can be obtained by a 1,3-dipolar addition of the reagent to a glycosyl azide.

The reagent is used as a coupling promoter to obtain biaryls from aryl Grignard reagents.[18] 1,4-Bisthioglycosyl-2-butene trimerizes under transition-metal catalysis to give cluster glycosides.[19]

Related Reagents.

1,4-Dichloro-2-butene.

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Dichloro(1,5-cyclooctadiene)palladium(II)

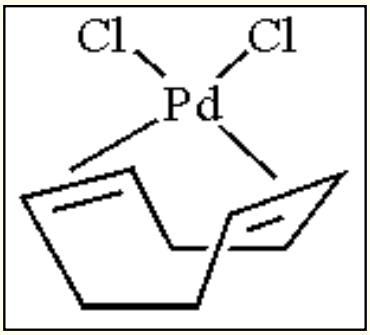

[12107-56-1] · $C_8H_{12}Cl_2Pd$ · Dichloro(1,5-cyclooctadiene)palladium(II) · (MW 285.49)

(alcohol protection; synthesis of carbamates, bicyclooctanes; alkene carbonylation)

Physical Data: yellow solid, mp 210 °C (dec).

Solubility: slightly sol $CHCl_3$, tetrahydrothiophene 1,1-dioxide (sulfolane), and nitrobenzene.

Preparative Method: prepared in 96% yield by treating ***Palladium(II) Chloride*** with 1,5-cyclooctadiene in concentrated hydrochloric acid.[1]

Purification: recrystallization from methylene chloride.

Handling, Storage, and Precautions: the reagent is air-stable.

Protection of Hydroxyl Groups.

Alcohols can be protected as acetals by treatment with 2-benzyloxy-1-propene in the presence of the title reagent (**1**) as catalyst in very good yields (eq 1).[2] This protection strategy is useful for the following reasons: (a) both the protection and the regeneration of the alcohols are carried out under neutral conditions; (b) primary hydroxyl groups are selectively protected; (c) the acetal prepared is stable toward organometallic reagents, including hydrides, and alkaline hydrolytic conditions. This methodology has been extended to the preparation of mixed orthoesters from allylic alcohols and ketene acetals in the presence of (**1**) as catalyst (eq 2).[3] These orthoesters can be used to prepare γ,δ-unsaturated esters by the Claisen rearrangement.[3]

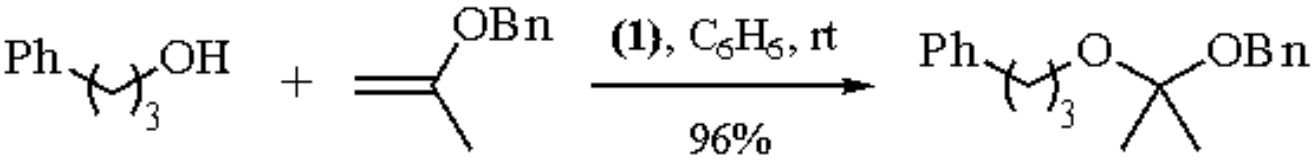

(1)

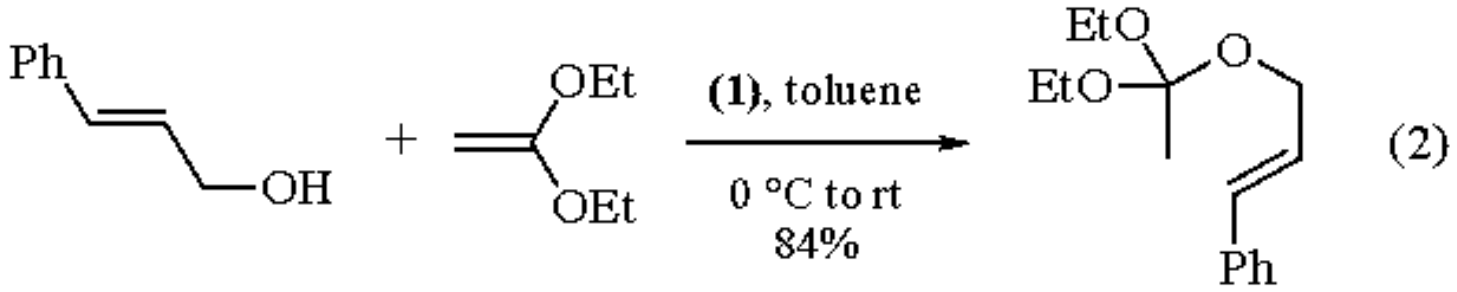

Preparation of 4-Cyclooctenylcarbamates.

Carbamates such as ethyl carbamate react with (**1**) to give the corresponding 4-cyclooctenylcarbamate in moderate yields (eq 3).[4]

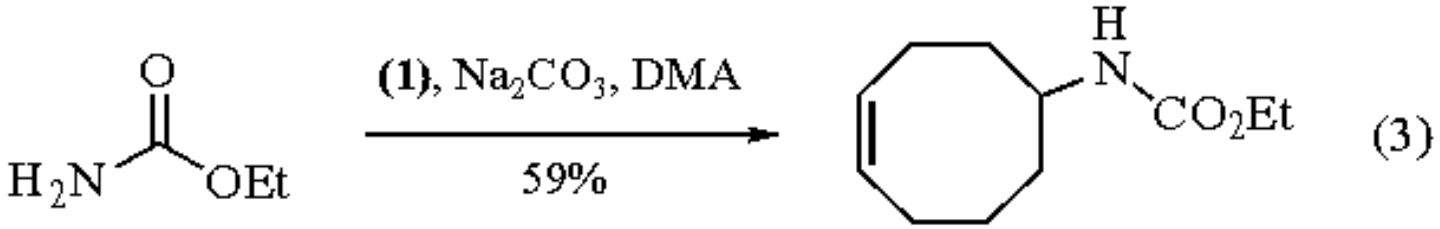

Alkene Carbonylation.

Reagent (**1**) reacts with aqueous ***Sodium Carbonate*** to give a hydroxypalladation enyl complex (**2**), which on carbonylation in water gives exclusively *trans*-2-hydroxy-5-cyclooctenecarboxylic acid β-lactone (eq 4).[5] Carbonylation of (**2**) in methanol gives the *trans*-hydroxy ester (**3**) (eq 5).

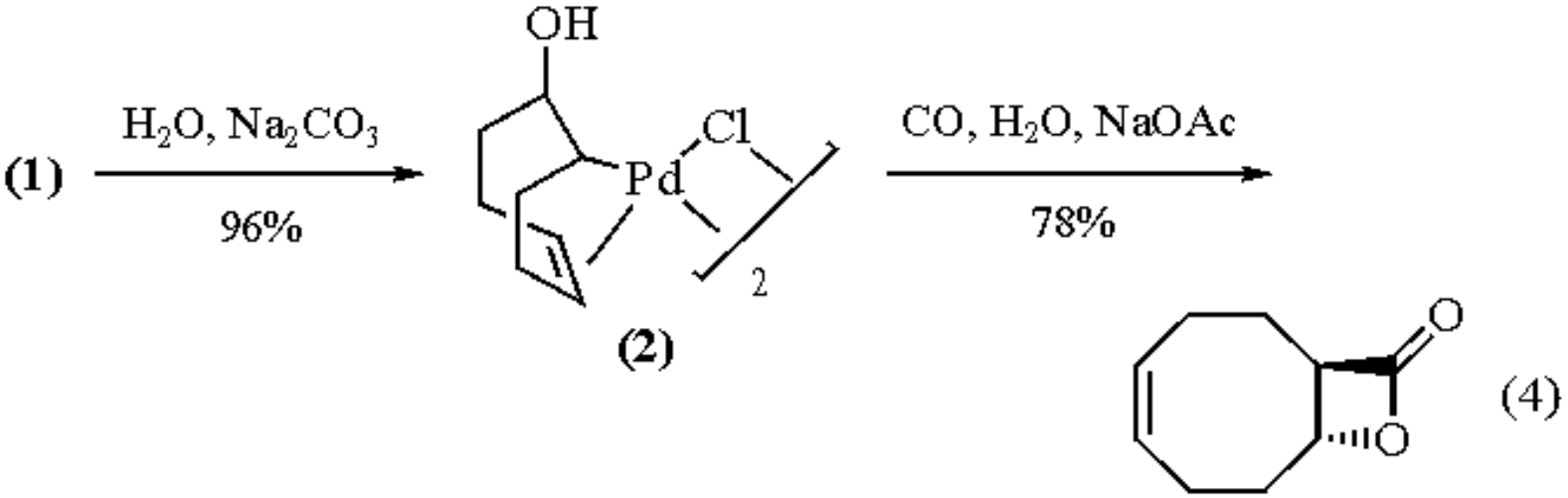

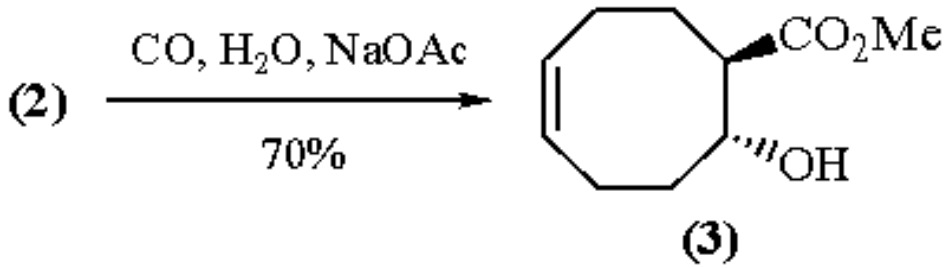

(5)

Synthesis of Bicyclo[3.3.0]octanes.

Treatment of (**1**) with excess of ***Diethyl Malonate*** in the presence of ***Sodium Hydride*** in DMSO gives tetraethyl bicyclo[3.3.0]octane-2,6-dimalonate as the major product in a transannular reaction (eq 6).[6]

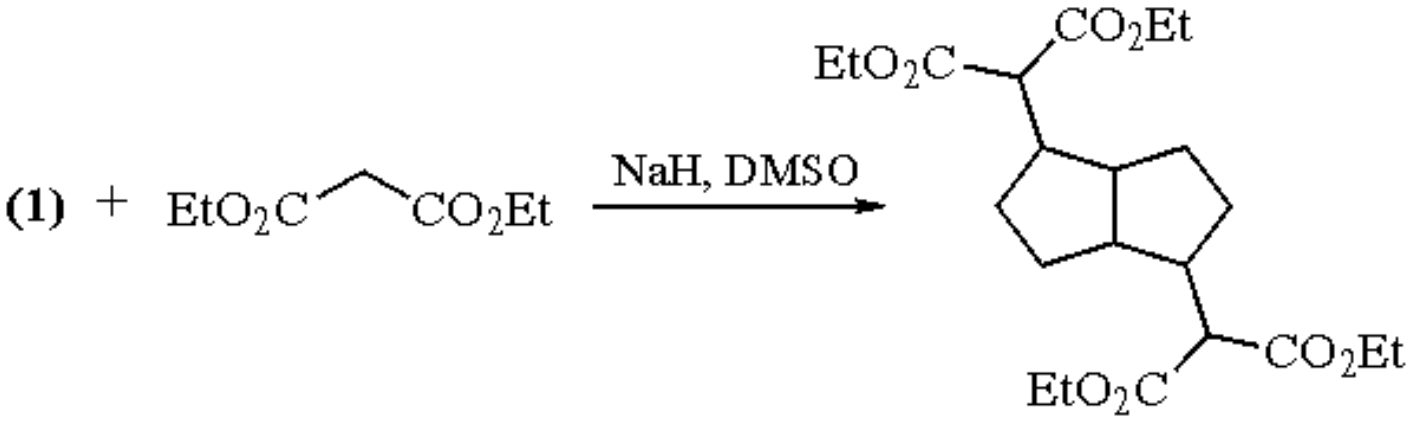

(6)

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2. Mukaiyama, T.; Ohshima, M.; Murukami, M. *CL* **1984**, 265.
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2,3-Dichloro-5,6-dicyano-1,4-benzoquinone[1]

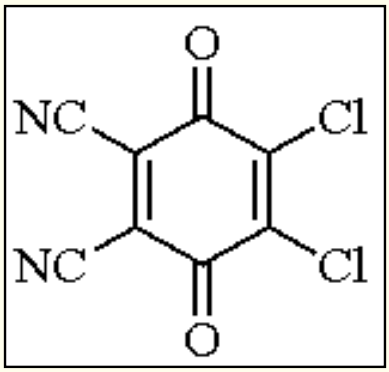

[84-58-2] · $C_8Cl_2N_2O_2$ · 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone · (MW 227.01)

(powerful oxidant, particularly useful for dehydrogenation to form aromatic[1a-d] and α,β-unsaturated carbonyl compounds;[1] oxidizes activated methylene[1a-c] and hydroxy groups[1b] to carbonyl compounds; phenols are particularly sensitive[1c])

Alternate Name: DDQ.

Physical Data: mp 213-216 °C; E_0 &AApprox; 1000 mV.

Solubility: very sol ethyl acetate and THF; moderately sol dichloromethane, benzene, dioxane, and acetic acid; insol H_2O.

Form Supplied in: bright yellow solid; widely available.

Analysis of Reagent Purity: UV (λ_{max} [dioxane] 390 nm) and mp.

Purification: recrystallization from a large volume of dichloromethane.

Handling, Storage, and Precautions: indefinitely stable in a dry atmosphere, but decomposes in the presence of water with the evolution of HCN. Store under nitrogen in a sealed container.

Introduction.

Quinones of high oxidation potential are powerful oxidants which perform a large number of useful reactions under

relatively mild conditions. Within this class, DDQ represents one of the more versatile reagents since it combines high oxidant ability with relative stability[1] (see also ***Chloranil***). Reactions with DDQ may be carried out in inert solvents such as benzene, toluene, dioxane, THF, or AcOH, but dioxane and hydrocarbon solvents are often preferred because of the low solubility of the hydroquinone byproduct. Since DDQ decomposes with the formation of hydrogen cyanide in the presence of water, most reactions with this reagent should be carried out under anhydrous conditions.[1a]

Dehydrogenation of Hydrocarbons.

The mechanism by which quinones effect dehydrogenation is believed to involve an initial rate-determining transfer of hydride ion from the hydrocarbon followed by a rapid proton transfer leading to hydroquinone formation.[1d] Dehydrogenation is therefore dependent upon the degree of stabilization of the incipient carbocation and is enhanced by the presence of functionality capable of stabilizing the transition state. As a consequence, unactivated hydrocarbons are stable to the actions of DDQ while the presence of alkenes or aromatic moieties is sufficient to initiate hydrogen transfer.[1d,2] The formation of stilbenes from suitably substituted 1,2-diarylethanes[3] and the synthesis of chromenes by dehydrogenation of the corresponding chromans (eq 1)[4] are particularly facile transformations. Similar reactions have also found considerable utility for the introduction of additional unsaturation into partially aromatized terpenes and steroids, where the ability to control the degree of unsaturation in the product is a particular feature of quinone dehydrogenations.[5] Moreover, the ability to effect exclusive dehydrogenation in the presence of sensitive substituents such as alcohols and phenols (eq 2)[5b] illustrates the mildness of the method and represents a further advantage.

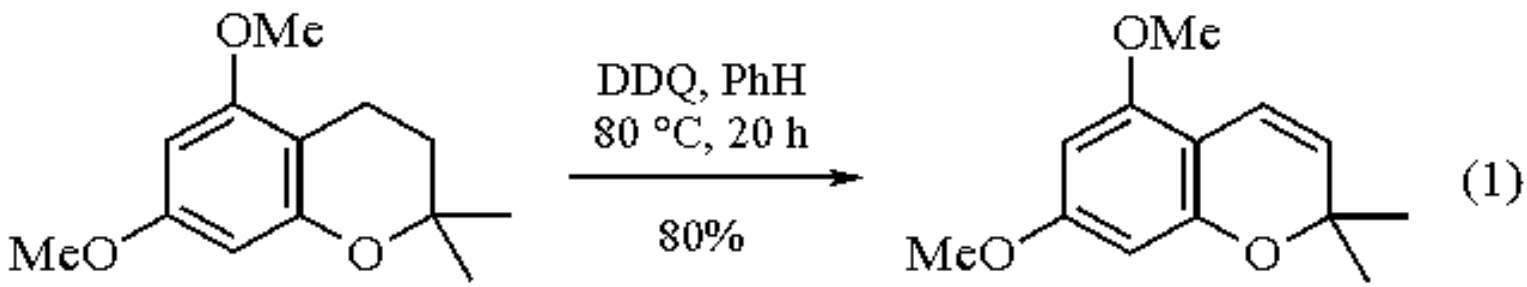

(1)

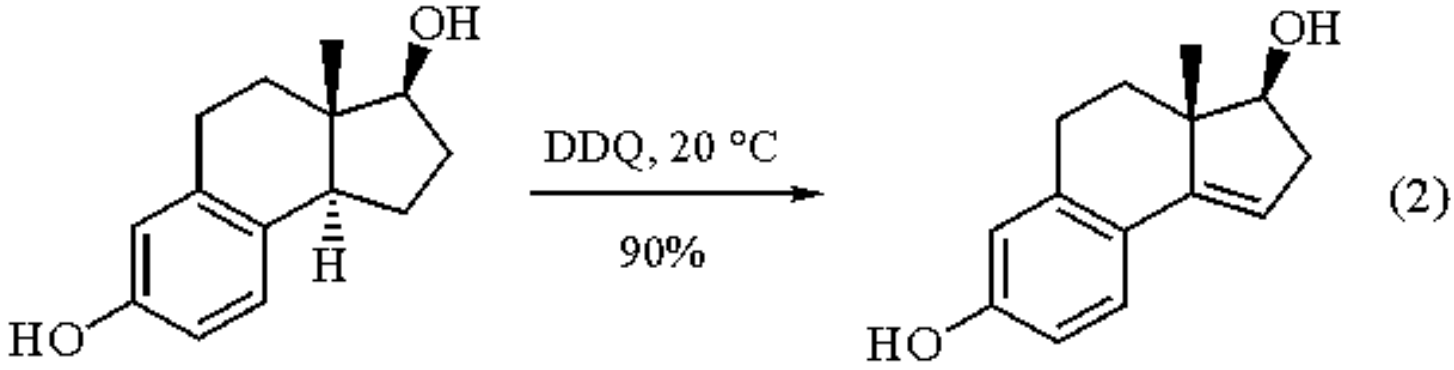

(2)

DDQ is a particularly effective aromatization reagent and is frequently the reagent of choice to effect facile dehydrogenation of both simple (eq 3)[6] and complex hydroaromatic carbocyclic compounds.[1d,7] Skeletal rearrangements are relatively uncommon features of quinone-mediated dehydrogenation reactions, but 1,1-dimethyltetralin readily undergoes aromatization with a 1,2-methyl shift when subjected to the usual reaction

conditions (eq 4).[8] Wagner-Meerwein rearrangements have also been observed in the aromatization of steroids (eq 5), although in this instance considerably longer reaction times are required.[9] Such reactions provide a unique method for the aromatization of cyclic systems containing quaternary carbon atoms without the loss of carbon.

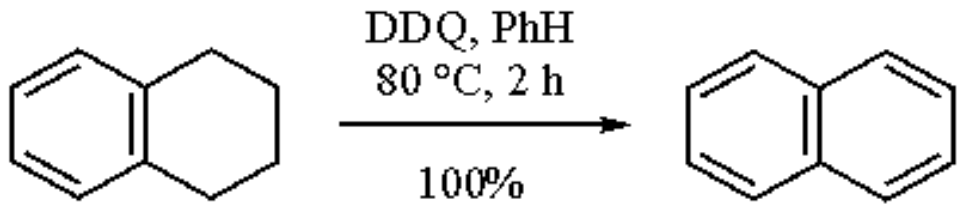

(3)

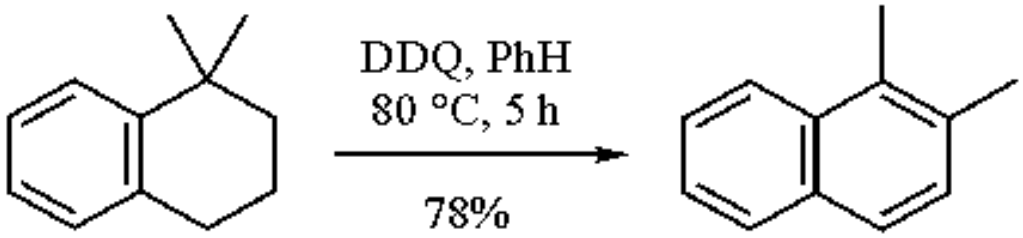

(4)

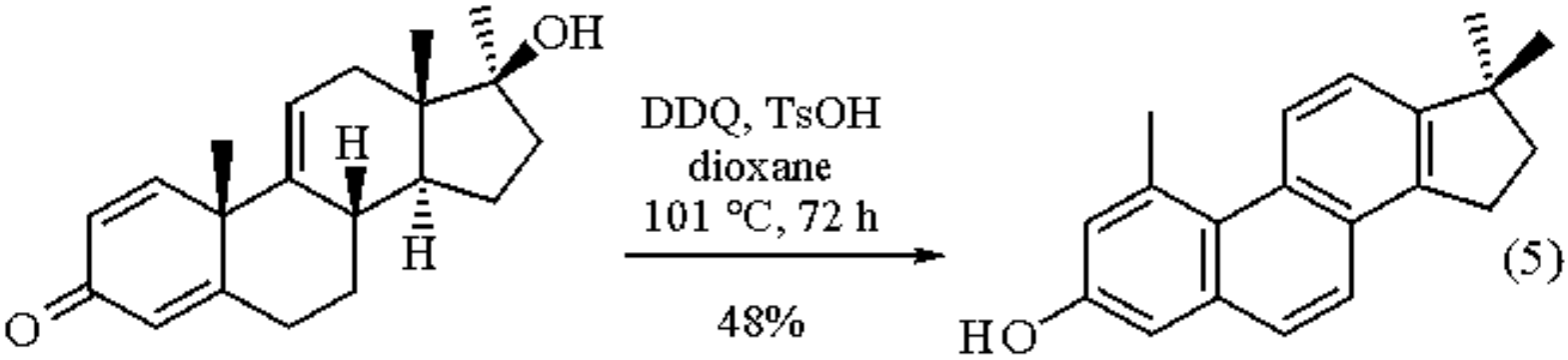

(5)

DDQ is also an effective reagent for the dehydrogenation of hydroaromatic heterocycles, and pyrroles,[10] pyrazoles,[11] triazoles,[12] pyrimidines,[13] pyrazines,[14] indoles,[15] quinolines,[16] furans,[17] thiophenes,[18] and isothiazoles[19] are among the many aromatic compounds prepared in this manner. Rearomatization of nitrogen heterocycles following nucleophilic addition across a C=N bond (eq 6)[13] is a particularly useful application of DDQ,[13,16] and similar addition and reoxidation reactions in acyclic systems have also been reported.[20]

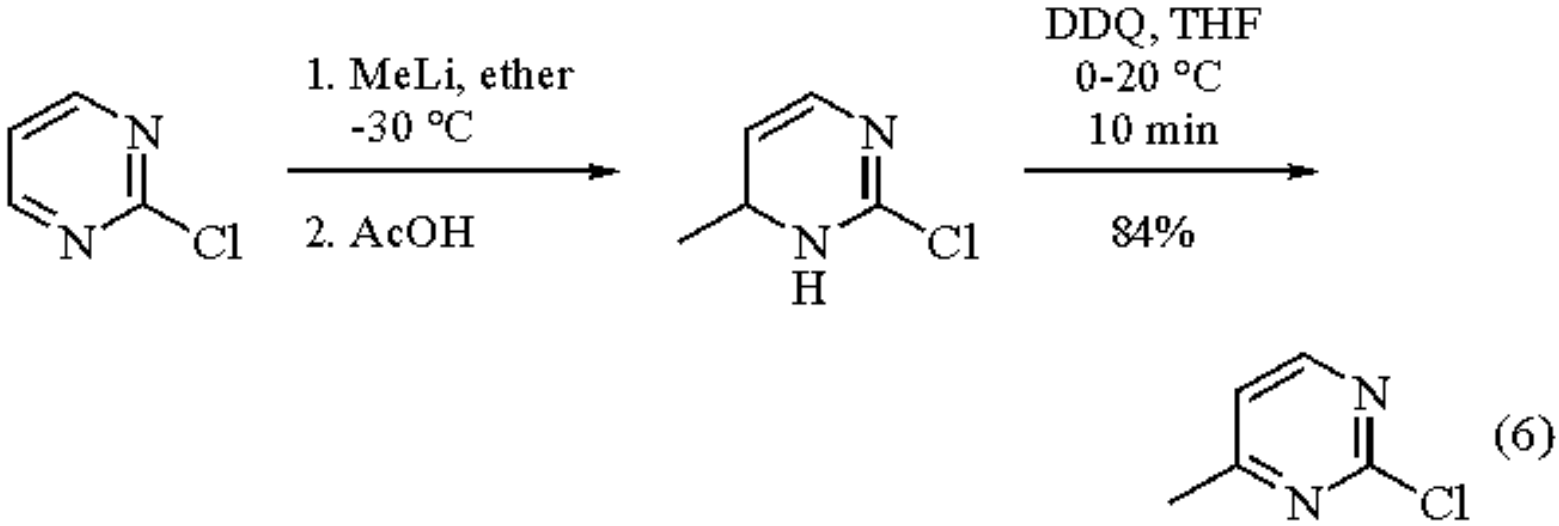

One particularly important use of DDQ has been in the dehydrogenation of reduced porphyrins, where the degree of aromatization of the product is highly dependent on the relative reagent:substrate stoichiometry.[1b] Under optimal conditions, excellent yields of partially or fully conjugated products may be isolated.[1b,21] The formation of porphyrins from tetrahydro precursors on reaction with 3 equiv of DDQ under very mild conditions (eq 7) typifies one of the more commonly described transformations.[21] More recently, DDQ has been used as part of a one-pot sequence for the formation of porphyrins from simple intermediates, although the overall yields in such reactions are generally comparatively low.[22]

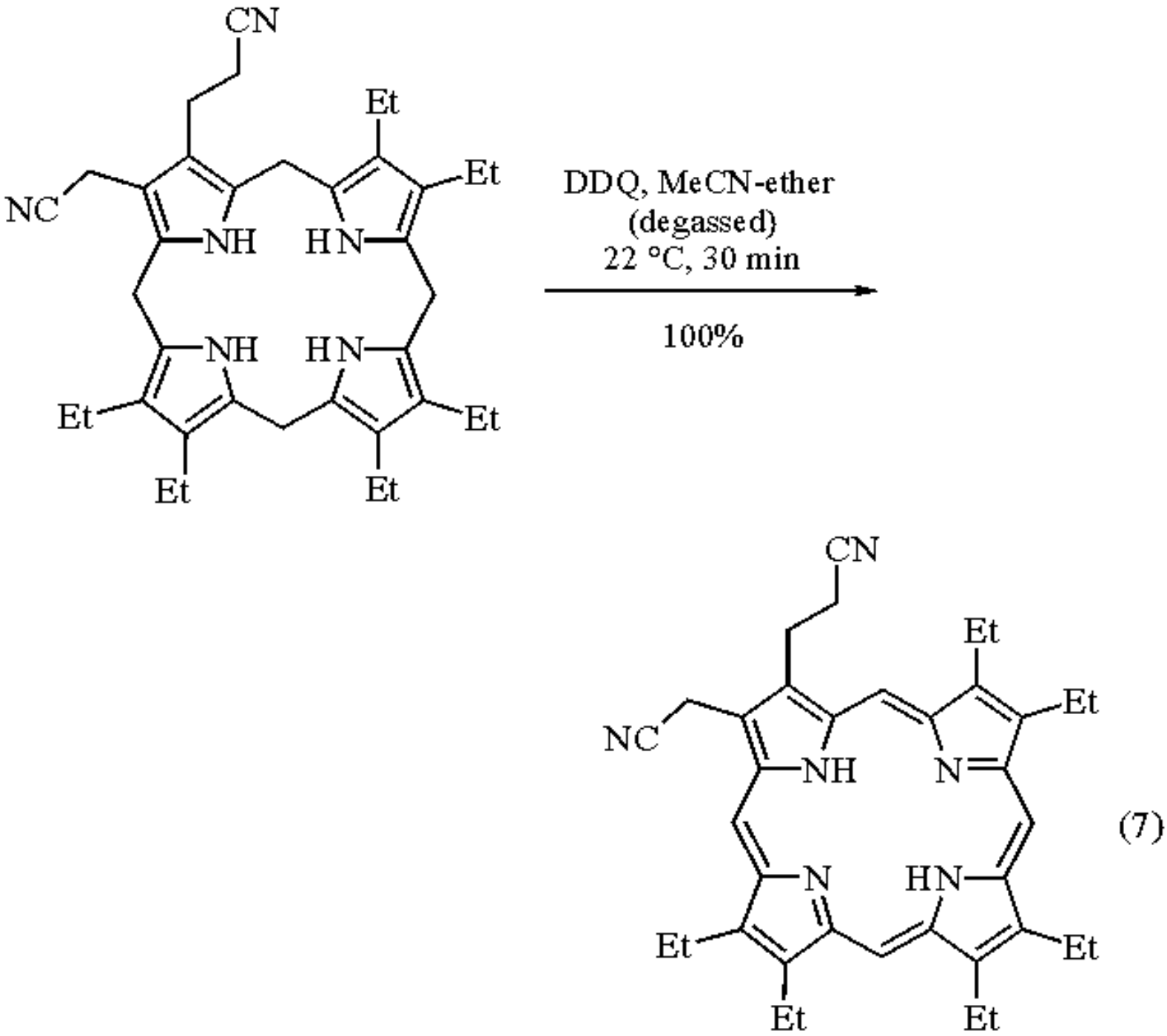

(7)

In addition to the formation of neutral aromatic compounds, DDQ is also an effective agent for the preparation of the salts of stable aromatic cations. High yields of tropylium (eq 8) and triphenylcyclopropenyl (eq 9) cations have been isolated in the presence of acids such as perchloric, phosphoric, and picric acid,[23] and oxonium,[24] thioxonium,[23,25] and pyridinium[23,26] salts may be prepared in reasonable yields from appropriate starting materials under essentially similar conditions. The formation of the perinaphthyl radical has been reported on oxidation of perinaphthalene with DDQ under neutral conditions,[23] although such products are not usually expected.

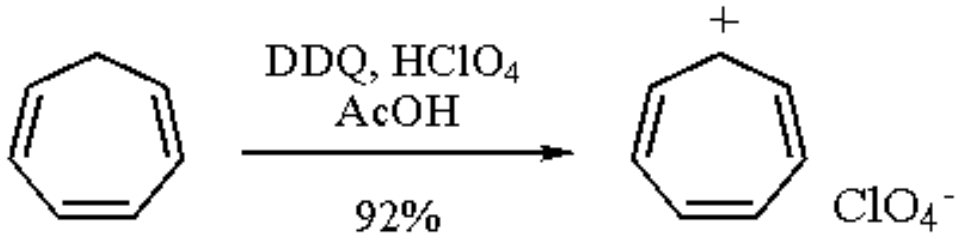

(8)

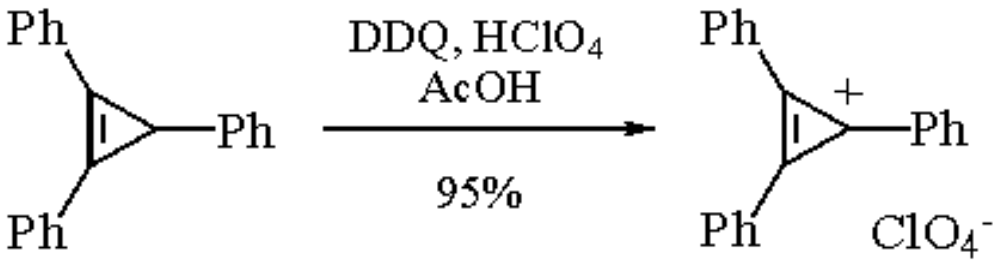

(9)

Dehydrogenation of Carbonyl Compounds.

DDQ and other high oxidation potential quinones are versatile reagents for the synthesis of α,β-unsaturated carbonyl compounds,[1e] a reaction that has found extensive application in the chemistry of 3-keto steroids.[1b] The regiochemical course of this dehydrogenation is highly dependent on the initial steroidal geometry; thus the 5α- and the 5β-series usually furnish Δ^1- and Δ^4-3-keto steroids, respectively (eq 10).[1b] The selection of one isomer over the other is likely to reflect the relative steric crowding of the C-4 hydrogen atom in the two series, but other factors may play a role in those instances where the anticipated product is not formed.[1b]

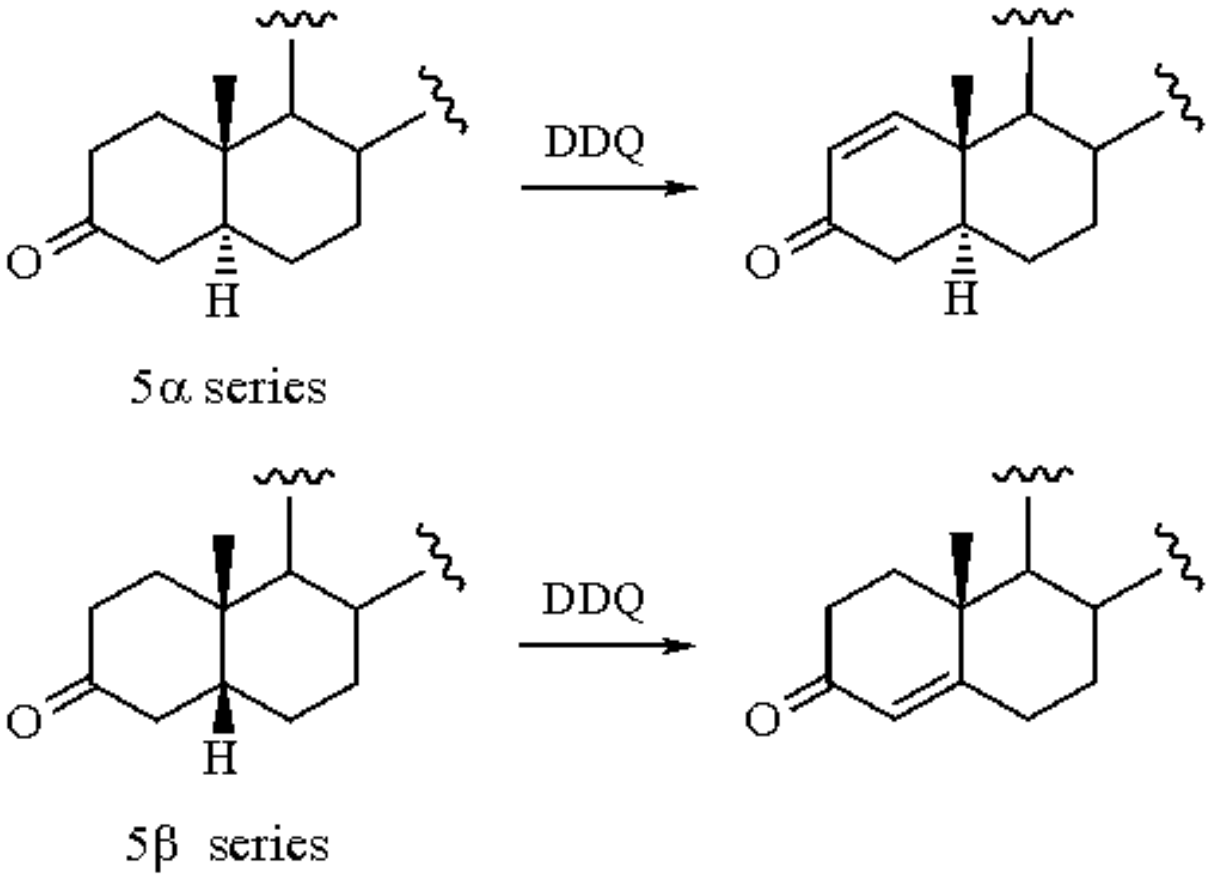

(10)

A rather more unusual situation exists during the dehydrogenation of Δ^4-3-keto steroids where the product formed is dependent on the oxidizing quinone. Thus whereas DDQ gives the $\Delta^{4,6}$ ketone, chloranil and a number of other quinones yield only the $\Delta^{1,4}$ isomer (eq 11), a result that has been rationalized on the basis of DDQ proceeding via the kinetic enolate while less reactive quinones proceed via the thermodynamic enolate.[27]

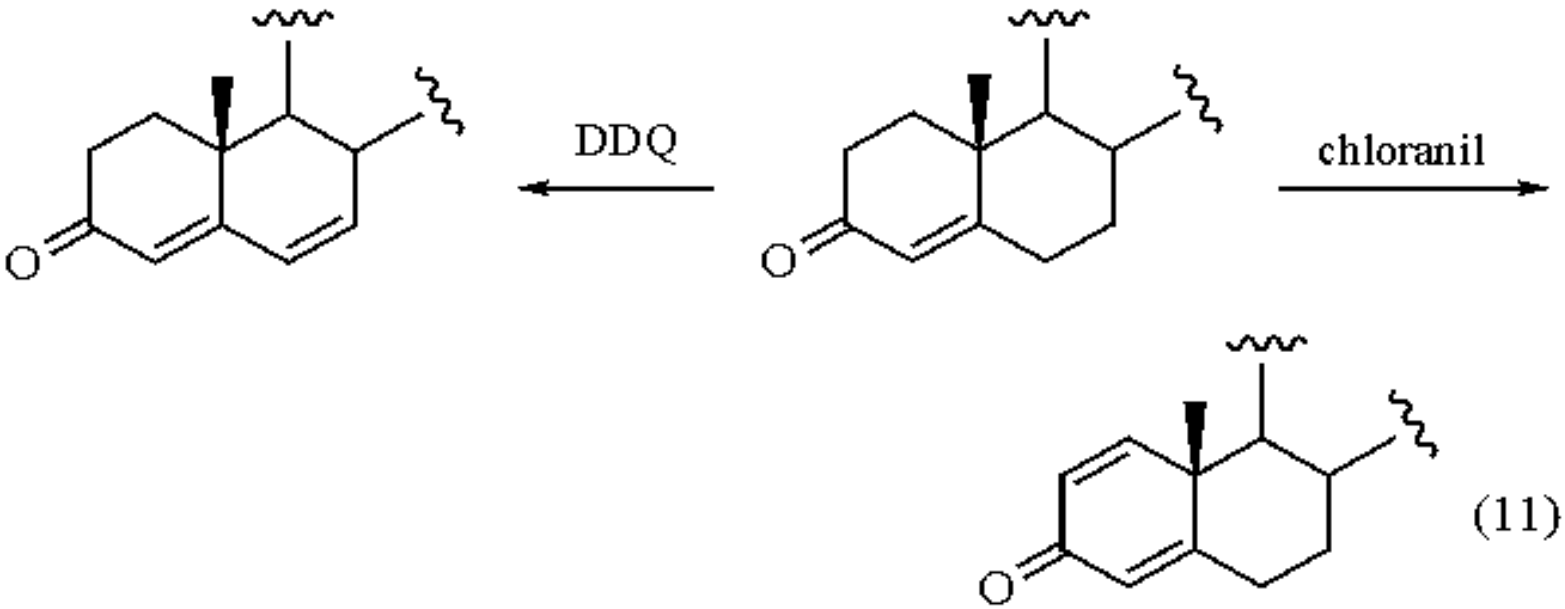

(11)

While DDQ is an effective reagent for the formation of α,β-unsaturated steroidal ketones, the dehydrogenation of cyclohexanones to the corresponding enone only proceeds well when the further reaction is blocked by *gem*-dialkyl substitution.[1b,28] Tropone, by contrast, has been prepared from 2,4-cycloheptadienone (eq 12), although the yield was somewhat low.[29] Heterocyclic enones such as flavones[30] and chromones[31] may be efficiently prepared from flavanones and chromanones, respectively, under similar conditions to those used for the dehydrogenation of steroids, and the dehydrogenation of larger ring heterocyclic ketones has been described.[32] Ketone enol ethers have also been shown to undergo facile dehydrogenation to α,β-unsaturated ketones with DDQ, although the nature of the product formed may be dependent on the presence or absence of moisture.[33] Prior formation of the silyl enol ether is a potentially more versatile procedure that has been shown to overcome the problems generally associated with the dehydrogenation of unblocked cyclohexanones (eq 13),[34] particularly when the acidic hydroquinone formed during the reaction is neutralized by the addition of ***N,O-Bis(trimethylsilyl)acetamide*** (BSA)[34] or a hindered base.[35] Preparation of the enone derived from either the kinetic or the thermodynamic enolate is possible in this manner.[34,35a]

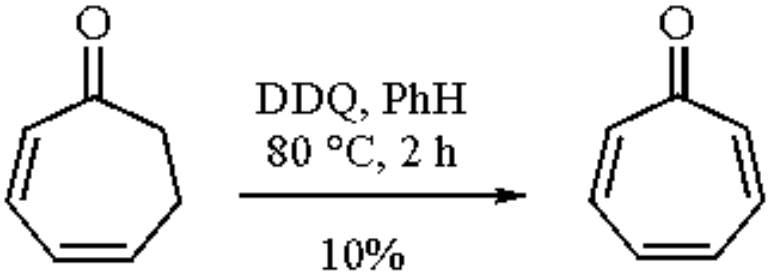

(12)

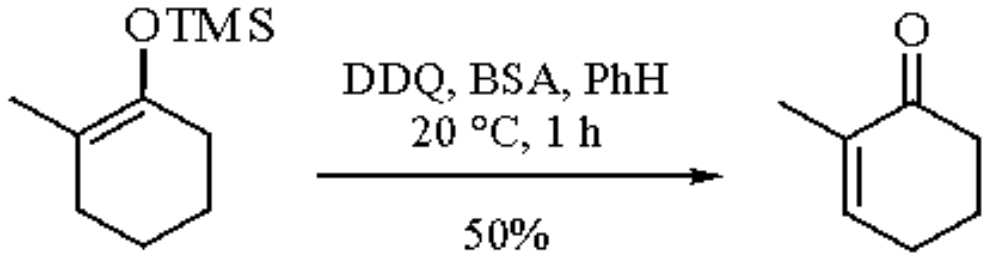

(13)

Quinone dehydrogenation reactions of carbonyl compounds are mostly limited to the more readily enolized ketones, and analogous reactions on esters[36] and amides[37] require stronger conditions and are far less common unless stabilization of the incipient carbonium ion is possible. Oxidation in the presence of the silylating agent bis(trimethylsilyl)trifluoroacetamide (BSTFA) considerably improves the dehydrogenation of steroidal lactams (eq 14) by facilitating the breakdown of the intermediate quinone-lactam complex.[38] Similar dehydrogenations of carboxylic acids are rare, but reaction of the α-anion of carboxylate salts generated in the presence of HMPA has given modest yields of a number of α,β-unsaturated fatty acids.[39]

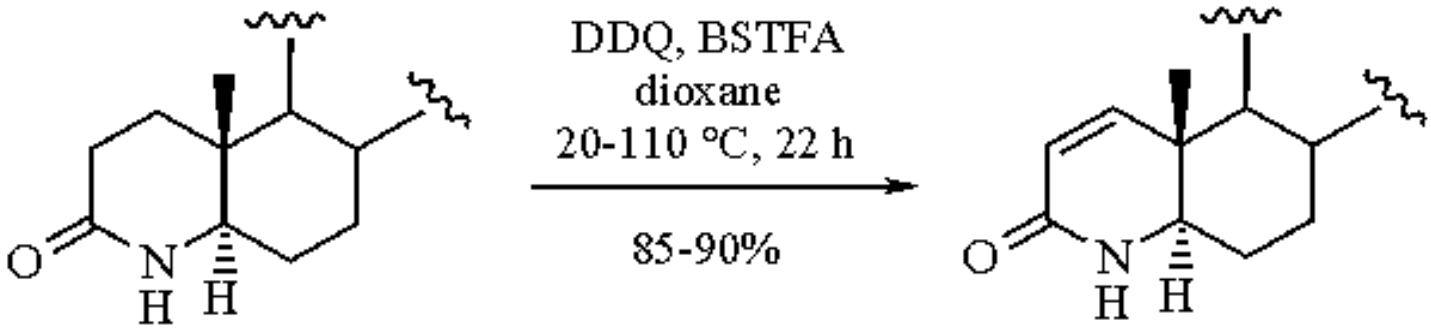

(14)

Oxidation of Alcohols.

Saturated alcohols are relatively stable to the action of DDQ in the absence of light, although some hindered secondary alcohols have been oxidized in reasonable yield on heating under reflux in toluene for extended periods of time (eq 15).[40] It has been suggested that oxidation proceeds in this instance as a result of relief of steric strain.[40] Allylic and benzylic alcohols, on the other hand, are readily oxidized to the corresponding carbonyl compounds,[1b,41] and procedures have been developed which utilize catalytic amounts of the reagent in the presence of a stoichiometric amount of a second oxidant.[42] Since the rate of oxidation of allylic alcohols is greater than that for many other reactions,[43] the use of DDQ provides a selective method for the synthesis of allylic and benzylic carbonyl compounds in the presence of other oxidizable groups.

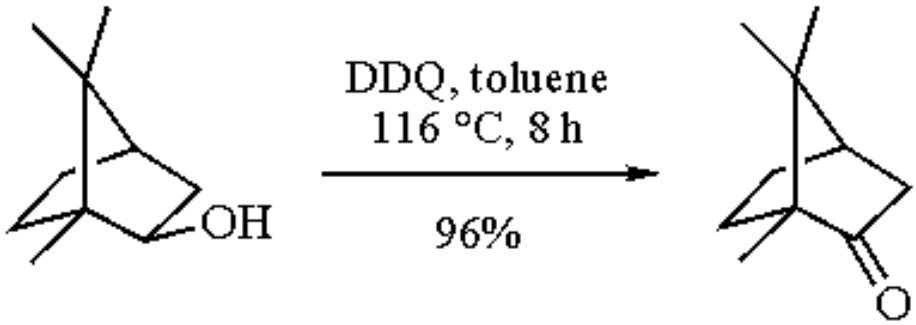

(15)

Benzylic Oxidation.

The oxidation of benzylic alkyl groups proceeds rapidly in those instances in which stabilization of the incipient carbonium ion is possible[44,45] and a number of polycyclic aromatic compounds have been oxidized in good yield to the corresponding benzylic ketones on brief treatment with DDQ in aqueous acetic acid at rt.[44] The reaction is postulated to proceed via an intermediate benzylic acetate which is hydrolyzed and further oxidized under the reaction conditions.[44] It is interesting that 1-alkylazulenes, which are cleaved by many of the more common oxidants, are cleanly oxidized following a short exposure to DDQ in aqueous acetone (eq 16), while under the same conditions no oxidation of C-2 alkyl substituents takes place.[46] As expected, the oxidation was shown to be disfavored by the presence of strongly electron-withdrawing substituents.[46]

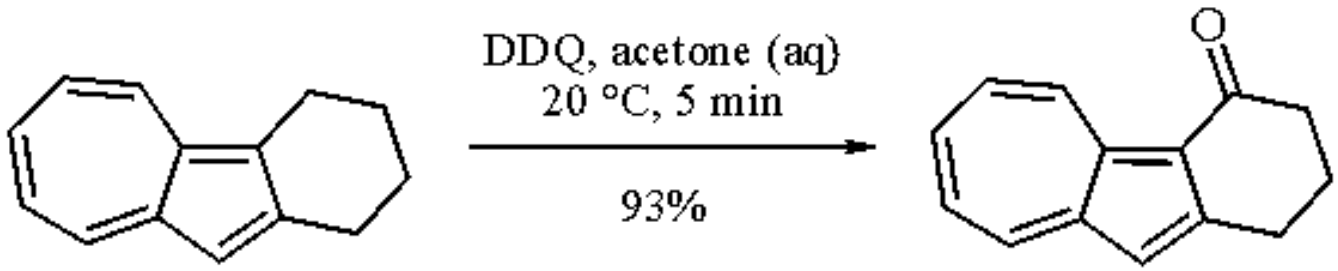

(16)

The stabilization of benzylic carbonium ions is also a feature of arenes containing electron-donating substituents, especially those having 4-alkoxy or 4-hydroxy groups, and such compounds are particularly effective substrates for oxidation by DDQ. Thus 6-methoxytetralone has been prepared in 70% yield from 6-methoxytetralin on treatment with DDQ in methanol,[47] although it is possible to isolate intermediate benzylic acetates if the oxidation is carried out in acetic acid (eq 17).[48] An interesting variant of the oxidation in inert solvents in the presence of either ***Cyanotrimethylsilane***[49] or ***Azidotrimethylsilane***[50] results in the isolation of good to excellent yields of benzyl cyanides and azides, respectively.

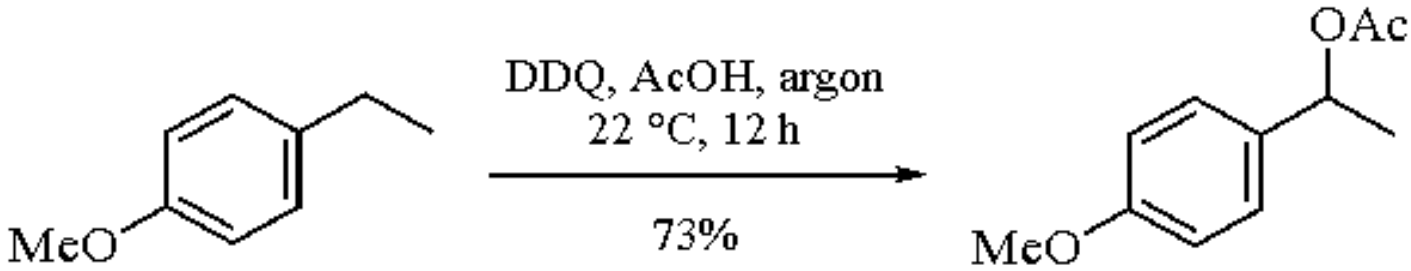

(17)

Benzylic oxidation of alkoxybenzyl ethers is particularly facile, and since some of the more activated derivatives are cleaved under conditions which leave benzyl, various ester, and formyl groups unaffected, they have found application in the protection of primary and secondary alcohols.[51] Deprotection with DDQ in dichloromethane/water follows the order: 3,4-dimethoxy > 4-methoxy > 3,5-dimethoxy > benzyl and secondary > primary, thus allowing the selective removal of one function in the presence of another.[51] 2,6-Dimethoxybenzyl esters are readily cleaved to the corresponding acids on treatment with DDQ in wet dichloromethane at rt, whereas 4-methoxybenzyl esters are stable under these conditions.[52] Oxidative cleavage of N-linked 3,4-dimethoxybenzyl derivatives with DDQ has also been demonstrated.[53]

DDQ is a powerful oxidizing agent for phenols, and carbonium ion stabilization via the quinone methide makes

benzylic oxidation of 4-alkylphenols a highly favored process.[47,54] With methanol as the solvent it is possible to isolate α-methoxybenzyl derivatives in reasonable yield.[55]

Phenolic Cyclization and Coupling Reactions.

The oxidation of phenolic compounds which either do not possess benzylic hydrogen atoms, or which have an alternative reaction pathway, can result in a variety of interesting products. Cyclodehydrogenation reactions leading to oxygen heterocycles represent a particular application of phenolic oxidation by DDQ, and is common when intramolecular quenching of the intermediate phenoxyl radical is possible (eqs 18-20).[56-59] These reactions necessarily take place in nonpolar solvents and have given such products as coumarins,[56] chromenes (eq 18),[57] benzofurans (eq 19),[58] and spiro derivatives (eq 20).[59]

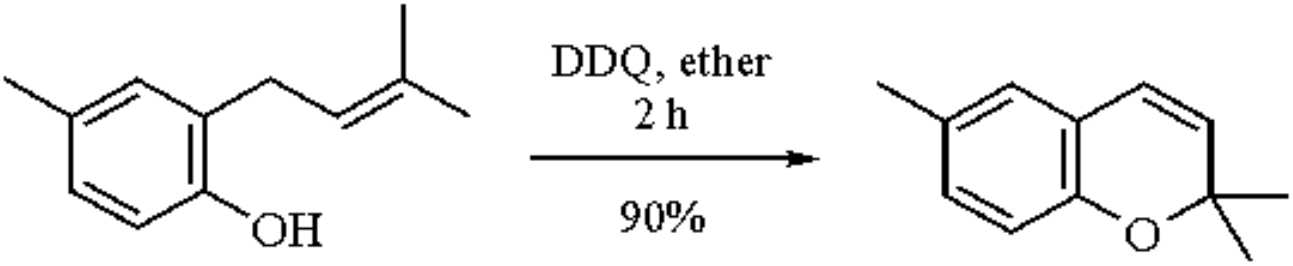

(18)

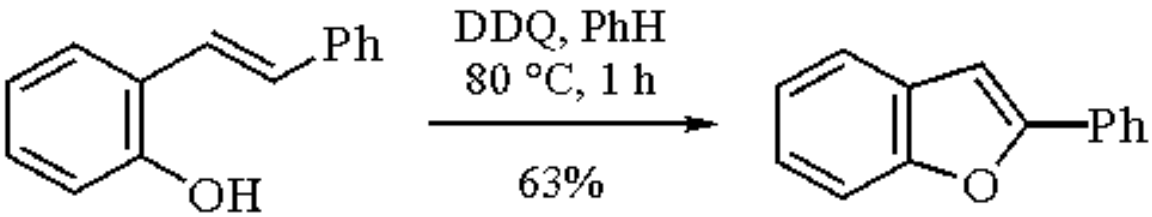

(19)

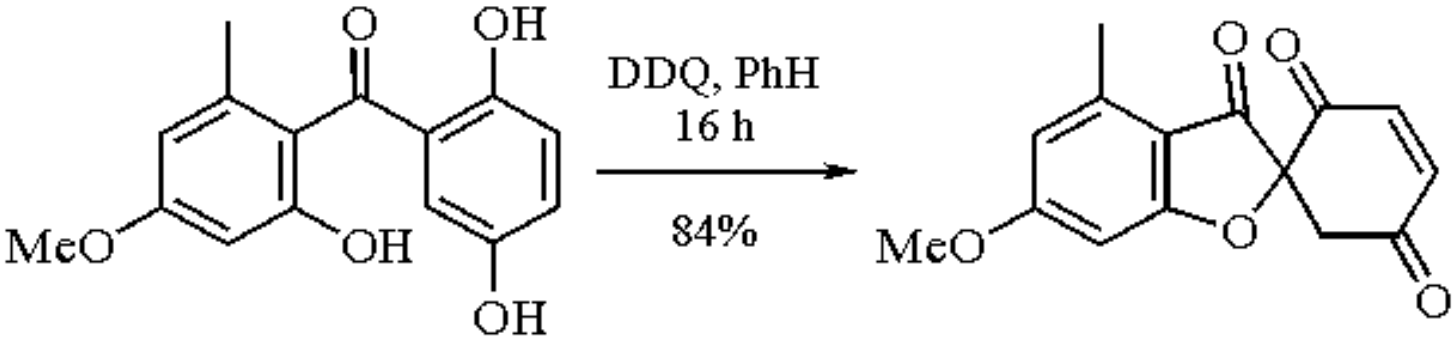

(20)

Phenols and enolizable ketones that cannot undergo α,β-dehydrogenation may afford intermolecular products arising from either C-C or C-O coupling on treatment with DDQ in methanol.[60] 2,6-Dimethoxyphenol, for example, results predominantly in oxidative dimerization (eq 21), while the hindered 2,4,6-tri-*t*-butylphenol generates the product of quinone coupling (eq 22).[60] Various other unusual products have been observed on DDQ oxidation of phenols and enolic compounds, their structure being dependent on that of the parent compound.[41,60,61]

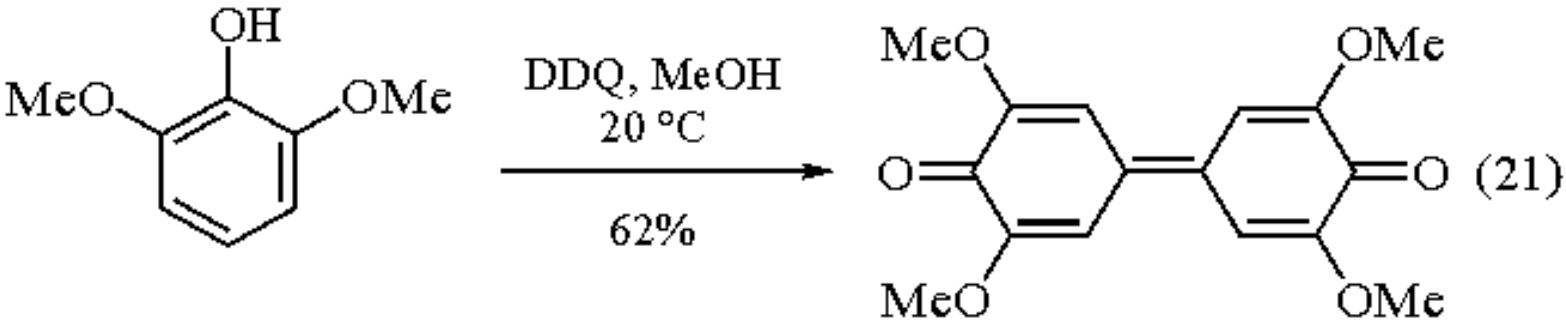

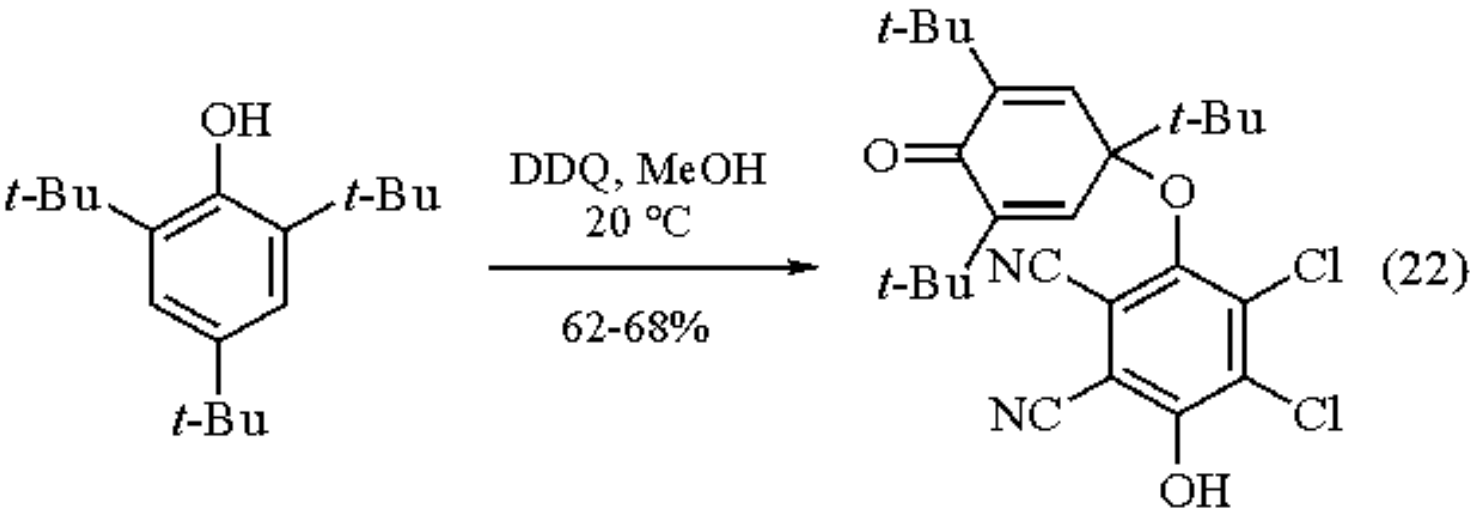

Miscellaneous Reactions.

In addition to the key reactions above, DDQ has been used for the oxidative removal of chromium,[62] iron,[63] and manganese[64] from their complexes with arenes and for the oxidative formation of imidazoles and thiadiazoles from acyclic precursors.[65] Catalytic amounts of DDQ also offer a mild method for the oxidative regeneration of carbonyl compounds from acetals,[66] which contrasts with their formation from diazo compounds on treatment with DDQ and methanol in nonpolar solvents.[67] DDQ also provides effective catalysis for the tetrahydropyranylation of alcohols.[68] Furthermore, the oxidation of chiral esters or amides of arylacetic acid by DDQ in acetic acid provides a mild procedure for the synthesis of chiral α-acetoxy derivatives, although the diastereoselectivity achieved so far is only 65-67%.[69]

While quinones in general are well known dienophiles in Diels-Alder reactions, DDQ itself only rarely forms such adducts.[70] It has, however, been shown to form 1:1 adducts with electron-rich heterocycles such as benzofurans and indoles where it forms C-O and C-C adducts, respectively.[71]

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SmithKline Beecham Pharmaceuticals, Epsom, UK

Dichlorodi-μ-methoxybis(pyridine)dicopper

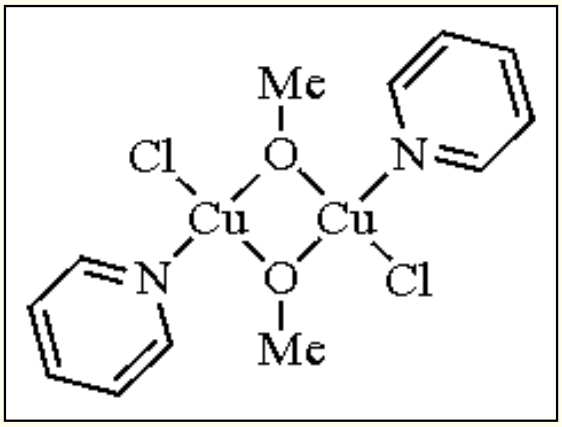

[15338-24-6] · $C_{12}H_{16}Cl_2Cu_2N_2O_2$ · Dichlorodi-μ-methoxybis(pyridine)dicopper · (MW 418.27)

(oxidizing agent for aromatic alcohols;[1] useful in preparation of muconic acid monoesters and mononitriles;[2] preparation of cyclic orthoesters,[3] cyclic imides,[2a] and lactones[1d,2a,4])

Alternate Names: chloromethoxy(pyridine)copper *[28733-06-4]*; di-μ-chlorodimethoxybis(pyridine)dicopper *[15094-30-1]*.

Solubility: modestly sol pyridine; slightly sol methanol, NMP, DMF.

Form Supplied in: green solid.

Preparative Methods: easily prepared by oxidation of ***Copper(I) Chloride*** using O_2 in methanol/pyridine solution (eq 1).[5] There are several other methods for obtaining this reagent, or generating it in situ without isolation (eqs 2-4).[5,6]

$$4\ CuCl + O_2 + >4\ C_5H_5N \xrightarrow[rt]{MeOH} \underset{\textbf{(1)}}{2\ [(C_5H_5N)CuClOMe]_2} \quad (1)$$

$$4\ CuCl + O_2 + 4\ MeOH \xrightarrow[rt]{py} \underset{\textbf{(1)}}{[(C_5H_5N)CuClOMe]_2} \quad (2)$$

$$(C_5H_5N)_2CuCl_2 + NaOMe \xrightarrow{MeOH} [(C_5H_5N)CuClOMe]_2 \quad (3)$$

(1)

$$(C_5H_5N)_2CuCl_2 + Cu(OMe)_2 \xrightarrow{MeOH} [(C_5H_5N)CuClOMe]_2 \quad (4)$$

(1)

Handling, Storage, and Precautions: the freshly prepared dry solid may be stored briefly at rt and weighed without special precautions. The crystals may be stored indefinitely at rt when sealed under a dry N_2 atmosphere to preclude moisture.

Introduction.

The reagent (**1**) is a selective oxidizing agent for phenol and catechol derivatives, as well as for *o*-benzoquinones. Pyridine is the preferred solvent. In the solid state (**1**) exists as methoxy-bridged dimers.[7]

Oxidative Cleavage of Catechol in the Presence of Water or Oxygen.

Under anaerobic conditions in a pyridine solution of water, methanol, and 3 mol equiv of (**1**), catechol rapidly undergoes a four-electron oxidative ring opening to *cis,cis*-muconic acid monomethyl ester at rt (eq 5).[1d,3] 4-Substituted catechols and *o*-benzoquinones are also readily cleaved to the corresponding muconic acid ester (eq 6). *o*-Methoxyphenols are unreactive.

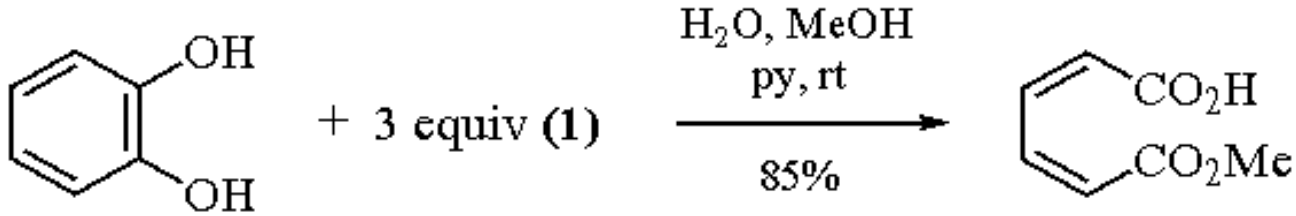

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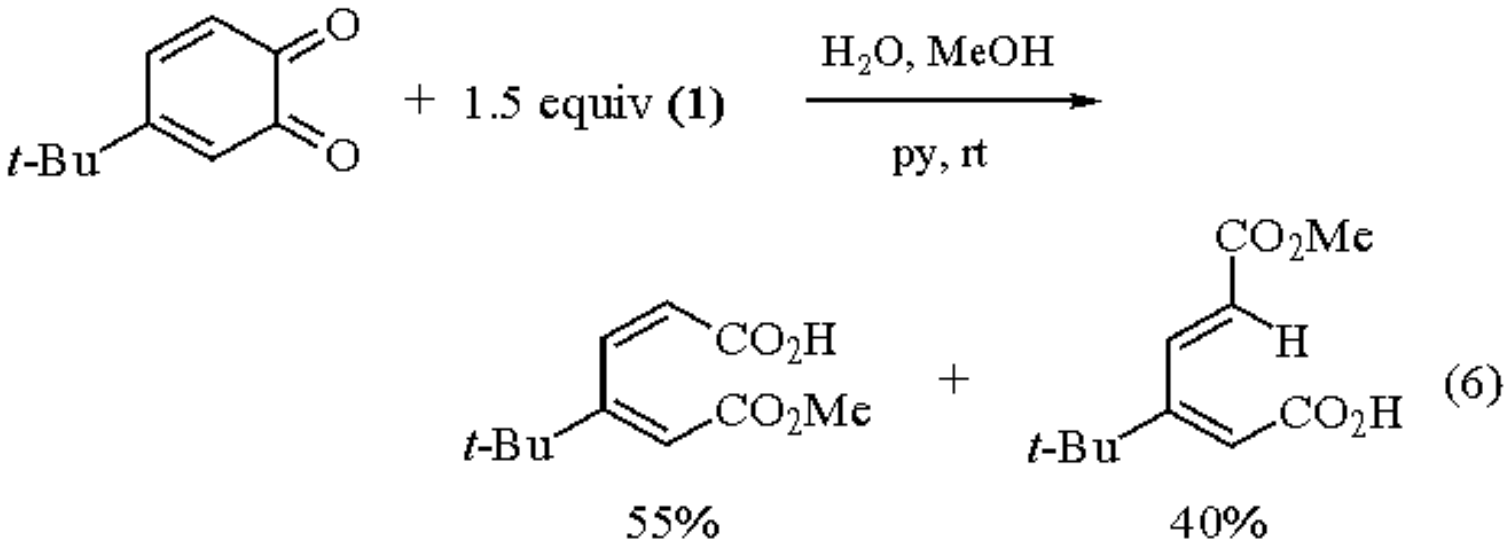

The same cleavage reactions occur in the presence of oxygen. Thus by using different alcohols in the method of eq 2 for generating (**1**) in situ, monoalkyl and monoaryl esters of muconic acid are available (eq 7).[1d] Interestingly, phenol undergoes a net six-electron oxidative ring opening only in the presence of oxygen, and at a much slower rate than the other aromatic derivatives already mentioned.

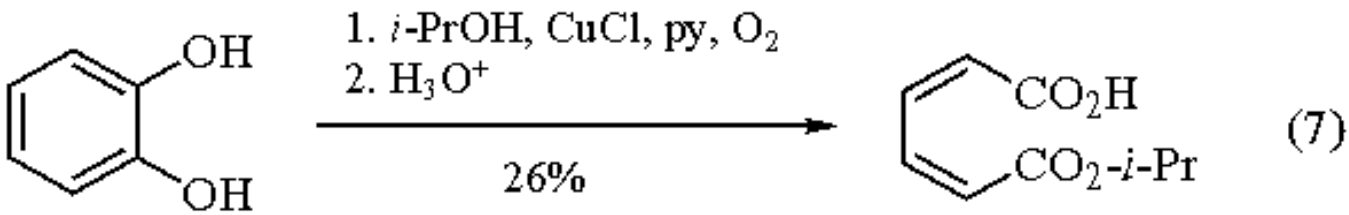

Overall, (**1**) reacts as a two-electron oxidant, and the suggestion that this oxidant system exemplifies the activation of molecular oxygen[1a-c] is inconsistent with experimental findings.[1d,3,8] Mechanistic studies continue to probe the complex interaction of O_2 with similar copper species.[9]

Oxidations in the Presence of Ammonia.

In the presence of ammonia, (**1**) oxidizes catechols and *o*-benzoquinones to a ring-expanded cyclic imide (eq 8).[2a] Replacing MeOH with ammonia in the method of eq 2 generates a reactive Cu^{II} oxidant, related to (**1**), that cleaves phenols, catechols, and *o*-benzoquinones to muconic acid mononitriles (eq 9).[2,10]

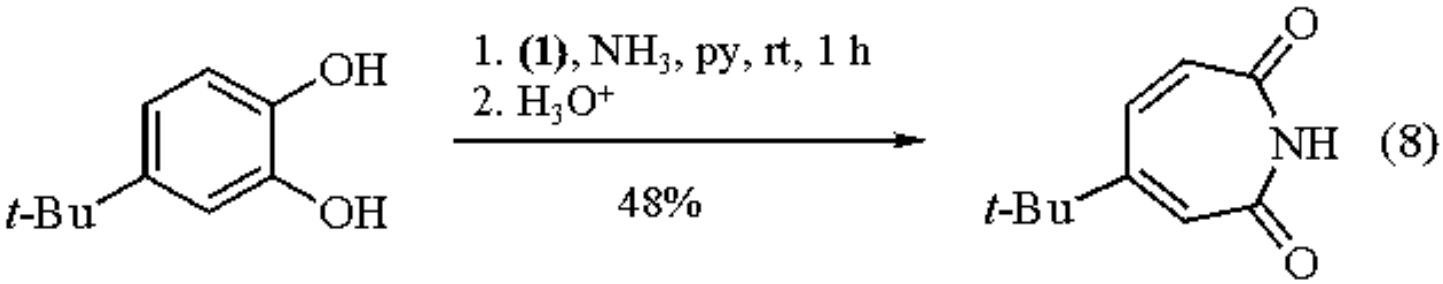

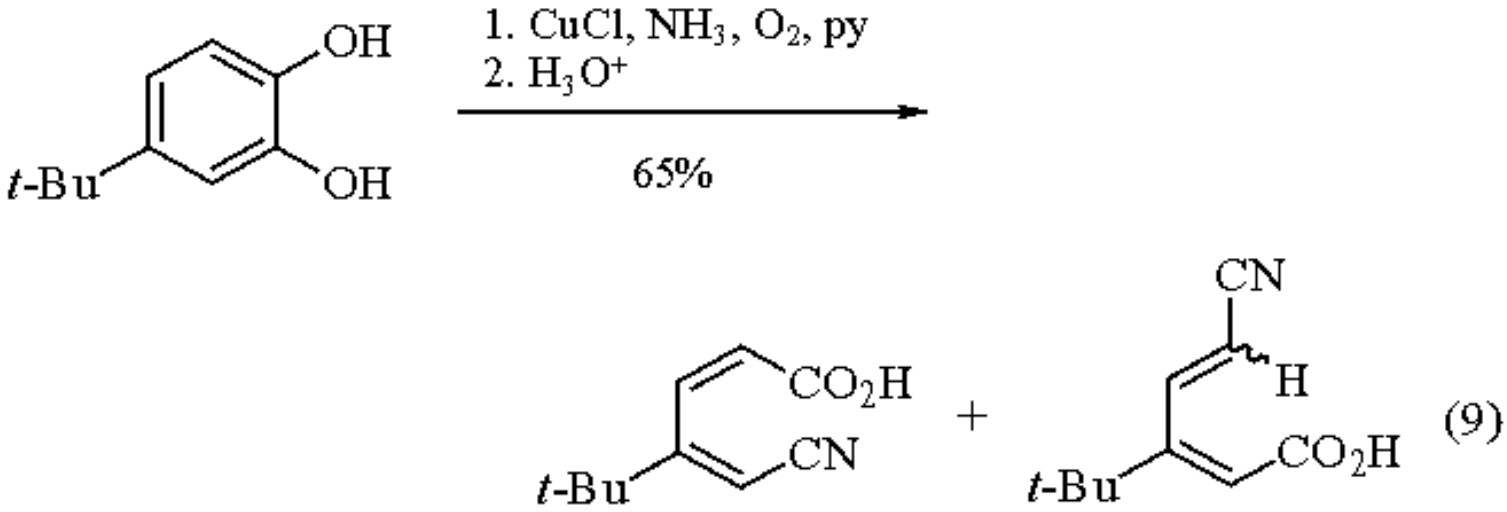

Oxidations Under Anaerobic, Anhydrous Conditions.

Under combined anaerobic/anhydrous reaction conditions in pyridine, phenol undergoes no net oxidation in the presence of (**1**), whereas catechol polymerizes, possibly by forming unstable quinone intermediates. However, 4-*t*-butylcatechol or 4-*t*-butyl-6-substituted catechols are subjected overall to a six-electron oxidation, forming a novel cyclic orthoester ester (eq 10).[3] Under similar conditions, cyclic anhydrides cleave to a mixture of muconic acid monoester isomers, except in the case of the di-*t*-butyl anhydride, in which ring opening, lactonization, and chlorination occur (eq 11).[4]

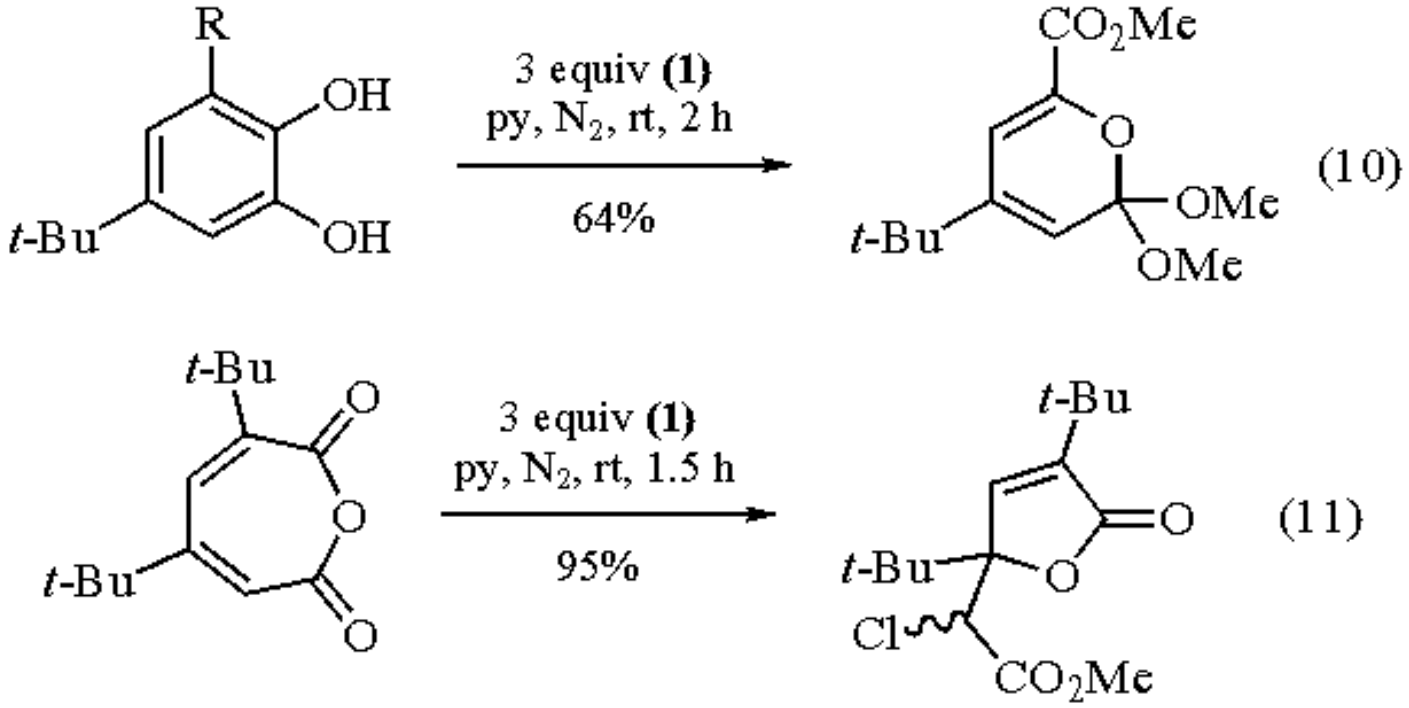

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Dichlorodimethylsilane[1]

Me_2SiCl_2

[75-78-5] · $C_2H_6Cl_2Si$ · Dichlorodimethylsilane · (MW 129.06)

(additive for pinacol cyclization;[2] protecting group for diols[3] and carbonyl compounds;[4] precursor for a wide variety of silicon-based reagents)

Physical Data: mp -76 °C; bp 70-71 °C; *d* 1.064 g cm^{-3}.

Solubility: sol chlorinated solvents and ethereal solvents; reacts with protic solvents.

Form Supplied in: liquid form from laboratory to commercial scale (typical purities >95%).

Purification: can be purified by distillation.

Handling, Storage, and Precautions: reacts with water, amines, alcohols, amides, and other protic species with the evolution of hydrogen chloride. Use in a fume hood.

Pinacol Reaction.

Dichlorodimethylsilane (**1**) allows clean pinacol cyclization of a keto aldehyde to occur without competition from an aldol reaction (eq 1).[2]

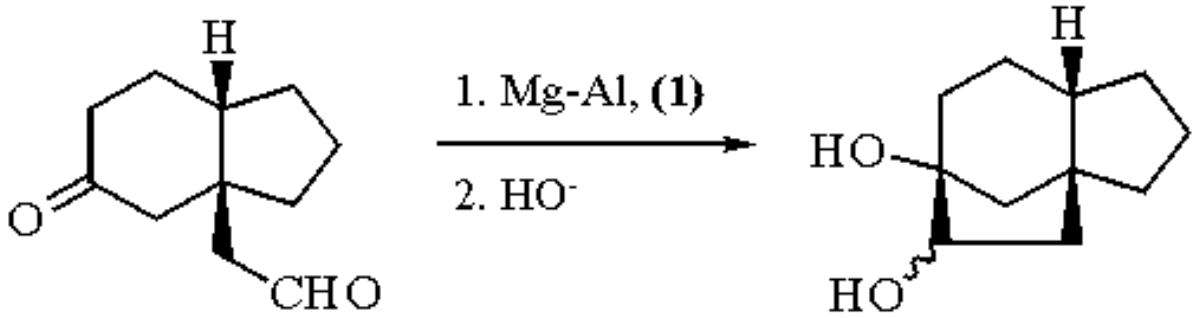

(1)

Protection.

The success of the pinacol cyclization is due to the formation of a siliconide, the silicon equivalent of an acetonide.

Reaction of a diol with (**1**) in the presence of base also provides these cyclic silicon compounds (eq 2).[3,5] However, the labile dimethylsiliconide does not afford a widely applicable form of protection for this functional group, although it has found some use with pericyclic reactions.[6]

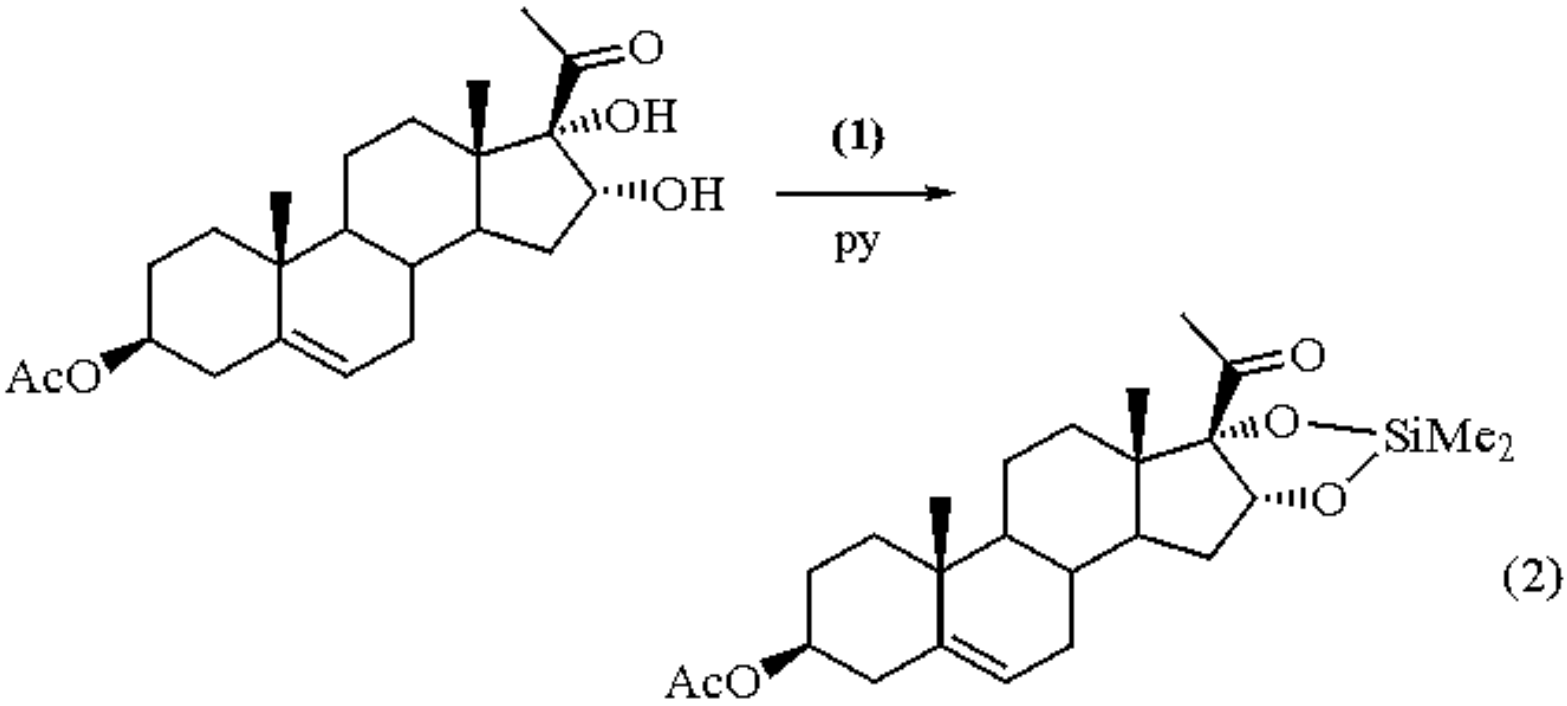

Enolates derived from aldehydes can also form bisenol ethers with (**1**), but the reaction fails with aldehydes containing four or fewer carbons.[7] Ketone lithium enolates provide bisenol ethers in good yields when treated with (**1**). These bisenol ethers can then be employed in further reactions such as intramolecular aldol reactions.[8] The formation of bisenol ethers by treatment of ketones with the silyl dichloride (**1**) in the presence of ***Triethylamine*** and ***Sodium Iodide*** has been advocated. However, the yields can still be variable and the use of *N*,*N*-diethylaminodimethylchlorosilane is suggested as a superior silylating agent.[4] The lithium enolate derived from pinacolone reacts with an equivalent of (**1**) to provide the monoenol silyl chloride that can then be treated with a wide variety of oxygen and nitrogen based nucleophiles.[9] Chiral enol ethers are also available through the use of the dichloride (**1**) as the silicon source (eq 3).[10]

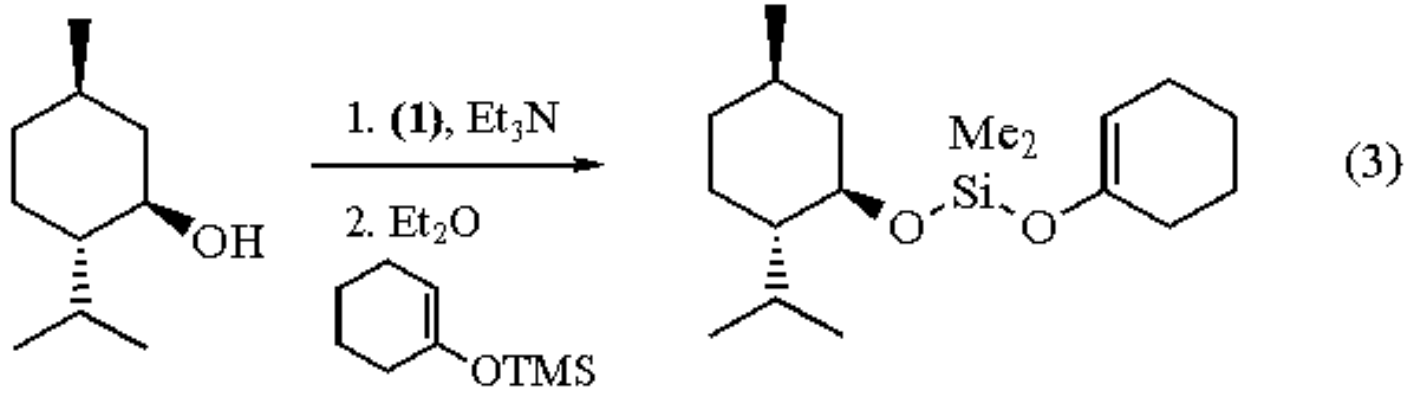

Silanes.

Dichlorodimethylsilane (**1**) is a precursor to a wide variety of silicon reagents. For example, reaction with an

organometallic reagent, such as phenyl- or *t*-butyllithium, results in the corresponding silyl chloride (eq 4).[11] Many of these silyl chlorides have found application for the protection of functional groups.[12]

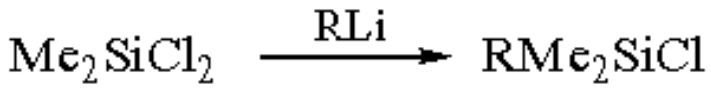

(4)

The presence of two leaving groups allows for the introduction of two different nucleophilic species.[13] In addition to carbon, heteroatom nucleophiles have been used.[14] A wide variety of heterocyclic derivatives are available when difunctional, nucleophilic compounds are treated with (**1**) (eq 5).[15] The synthetic potential of all of these derivatives is as wide as organosilicon chemistry.[16]

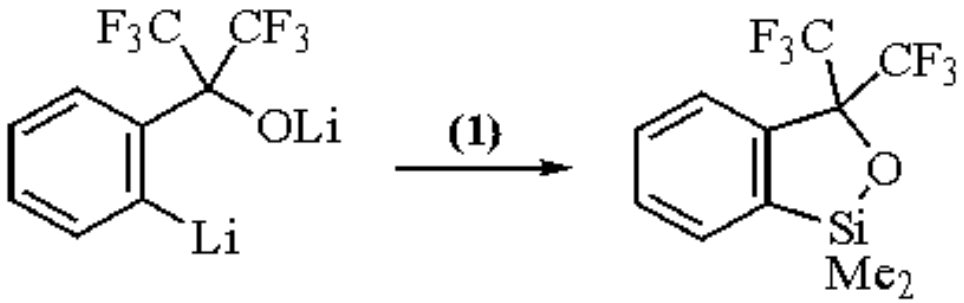

(5)

The dichloride (**1**) has also found widespread application for the formation of polysiloxanes and other high molecular weight silanes.[17] In addition to water, the chlorine atoms can be displaced by a wide variety of nucleophiles to provide some useful reagents, such as dimethyldiacetoxysilane.[18]

A controlled reaction of dichloride (**1**) with lithium in THF affords dodecamethylsilane,[19] a reagent that has been used for the preparation of silyl enol ethers through photolytic cleavage.[20] Silanes and polysilanes are readily available from the addition of an organometallic species to (**1**). Thus the bisvinylsilane (**2**) can be prepared from (**1**) (eq 6).[21]

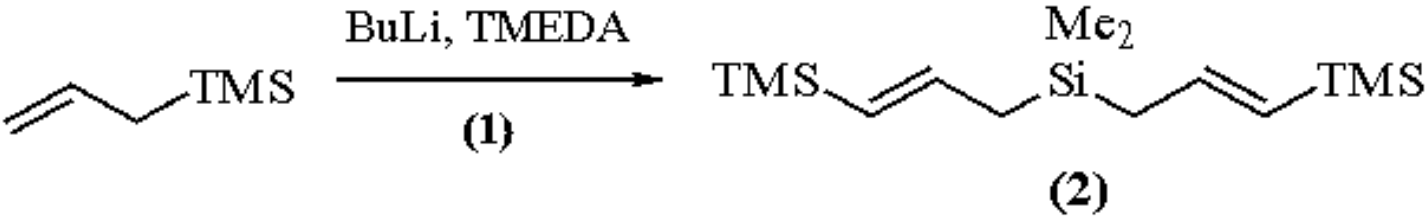

(6)

Related Reagents.

Di-t-butyldichlorosilane; ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***.

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Dichloro(ethoxy)oxovanadium(V)

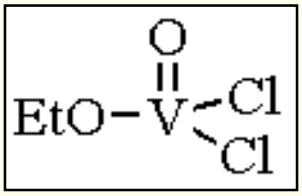

[1801-77-0] · $C_2H_5Cl_2O_2V$ · Dichloro(ethoxy)oxovanadium(V) · (MW 182.91)

(Lewis acid capable of one-electron oxidation; effects oxidative cleavage and oxidative coupling reactions)

Physical Data: bp 32-34 °C/1 mmHg; yellow liquid;[1] *d*204 1.47 g cm^{-3}.

Solubility: sol most organic solvents such as alcohol, dichloromethane, hexane.

Preparative Method: $VO(OEt)Cl_2$ is prepared by addition of ethanol to ***Vanadyl Trichloride***.[2]

Handling, Storage, and Precautions: moisture sensitive; should be handled under dry inert atmosphere and refrigerated in the dark to prevent decomposition (orange fumes). Avoid breathing the vapor; skin irritant and corrosive. Use in a fume hood.

Introduction.

$VO(OR)Cl_2$ (R = Et, *i*-Pr, etc.) are Lewis acids with one-electron oxidation capability, which effect oxidative transformations of carbonyl and organosilicon compounds in organic solvents. These oxovanadium(V) compounds have widely been used as catalysts in copolymerization.

Oxidation of Carbonyl Compounds.

The regioselective oxidative α-cleavage of cyclic ketones is catalyzed by $VO(OEt)Cl_2$ in ethanol under oxygen to give diesters or keto esters (eq 1).[2] The presence of α,β-unsaturation alters the reaction course. Oxidation of 2-cyclohexen-1-ones is induced by $VO(OEt)Cl_2$ in ethanol, resulting in dehydrogenative aromatization to ethyl aryl ethers. An oxovanadium compound obtained from $VO(OEt)Cl_2$ and ***Silver(I) Trifluoromethanesulfonate*** or ***Trimethylsilyl Trifluoromethanesulfonate*** is more efficient in the latter

reaction.[3] In the case of α,β-unsaturated ketones such as 2-cyclopenten-1-ones and 1-acetyl-1-cyclohexene, allylic oxidation is achieved to introduce an oxo or alkoxy group at the γ-position as exemplified by the formation of 4-methyl-4-cyclopentene-1,3-dione (eq 2).[4] 2-Phenylglycine derivatives undergo the $VO(OEt)Cl_2$-induced oxidative deamination and/or decarboxylation to give ethyl benzoate and ethyl phenylglyoxylate.[5]

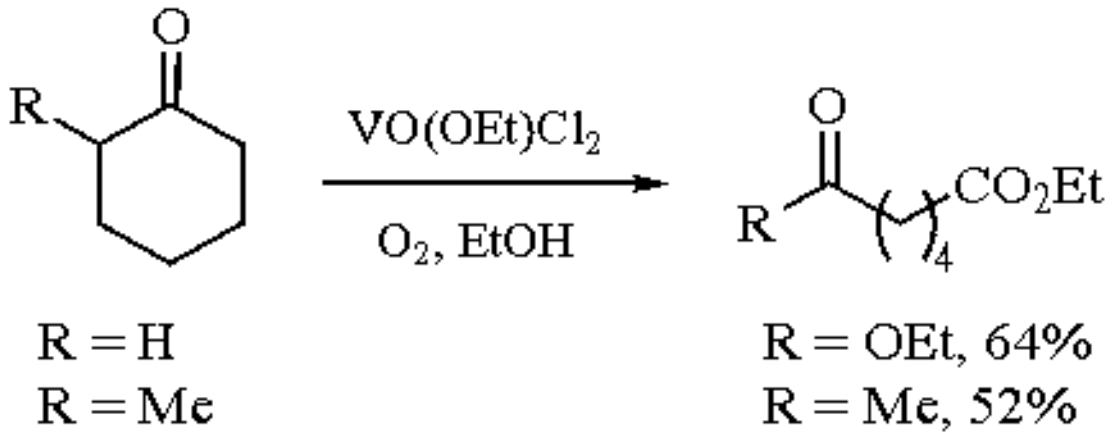

(1)

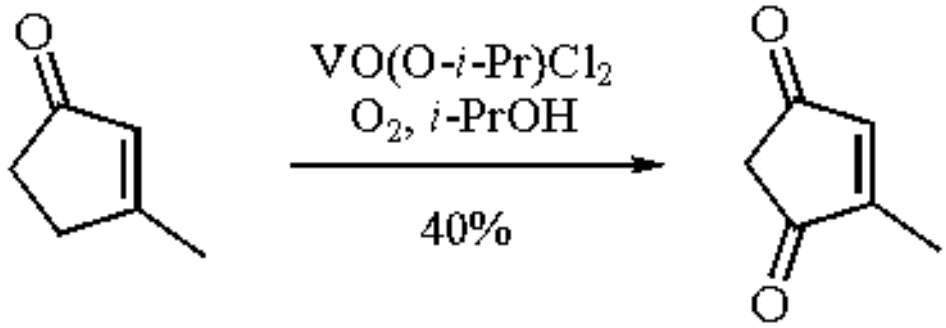

(2)

Oxidative cleavage of cyclobutanone in the presence of ***Copper(II) Chloride*** or $BrCCl_3$ affords ethyl 4-chloro- or ethyl 4-bromobutanoate (eq 3).[6] 1-Chlorooctan-4-one is produced upon addition of ***n-Butyllithium*** followed by oxidative fragmentation (eq 4). Conjugate addition of the ethoxycarbonylpropyl fragment occurs in the presence of electron-deficient alkenes such as acrylonitrile or methacrylonitrile (eq 5). The oxidative coupling of diketene and styrenes gives ethyl 2-methyl-4,5-dihydrofuran-3-carboxylates.[7]

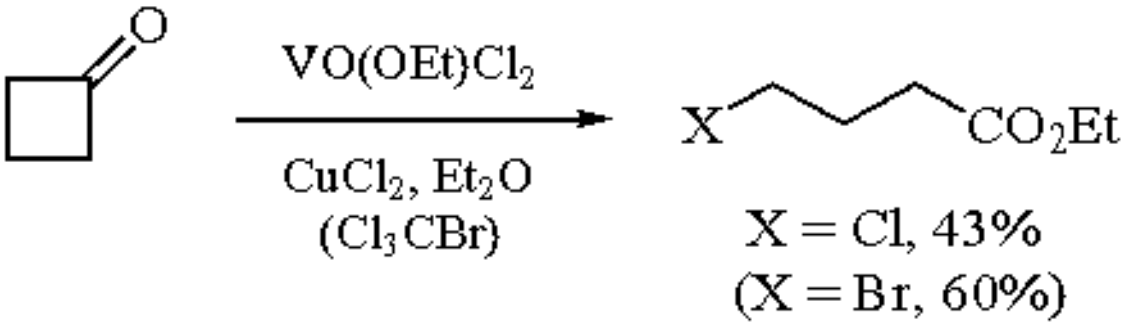

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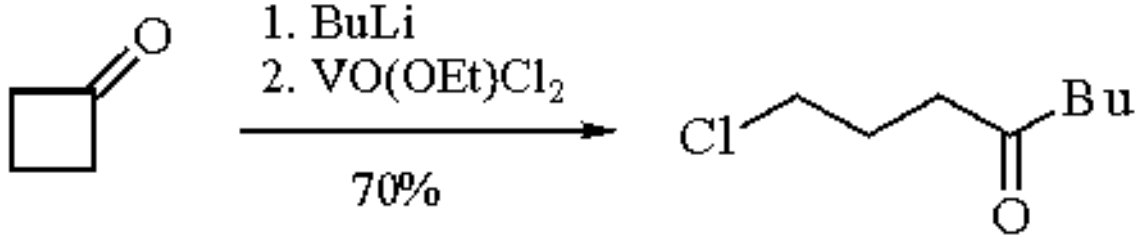

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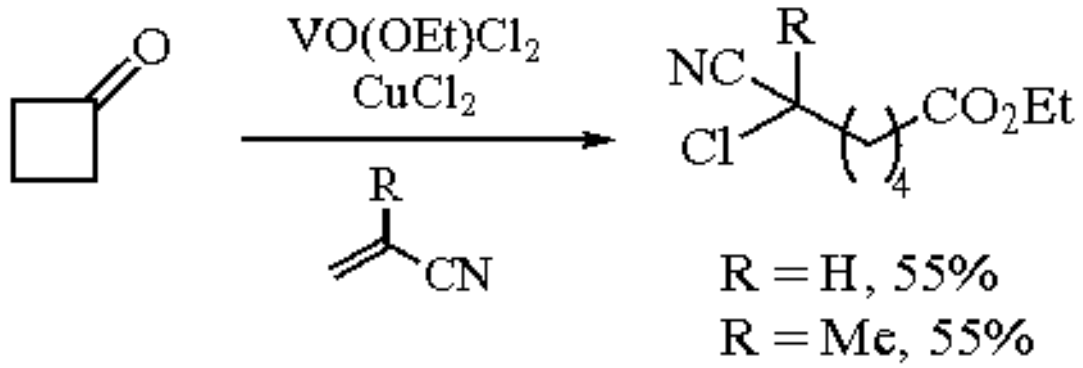

(5)

Oxidation of Organosilicon Compounds.

Oxidative desilylation can be selectively performed by one-electron oxidation with $VO(OEt)Cl_2$. Silyl enol ethers undergo $VO(OEt)Cl_2$-induced oxidative dimerization and cross-coupling reactions, affording symmetrical and unsymmetrical 1,4-diketones (eq 6).[8] Allylsilanes dimerize regioselectively to 1,4-dialkyl-1,5-hexadienes (eq 7).[9]

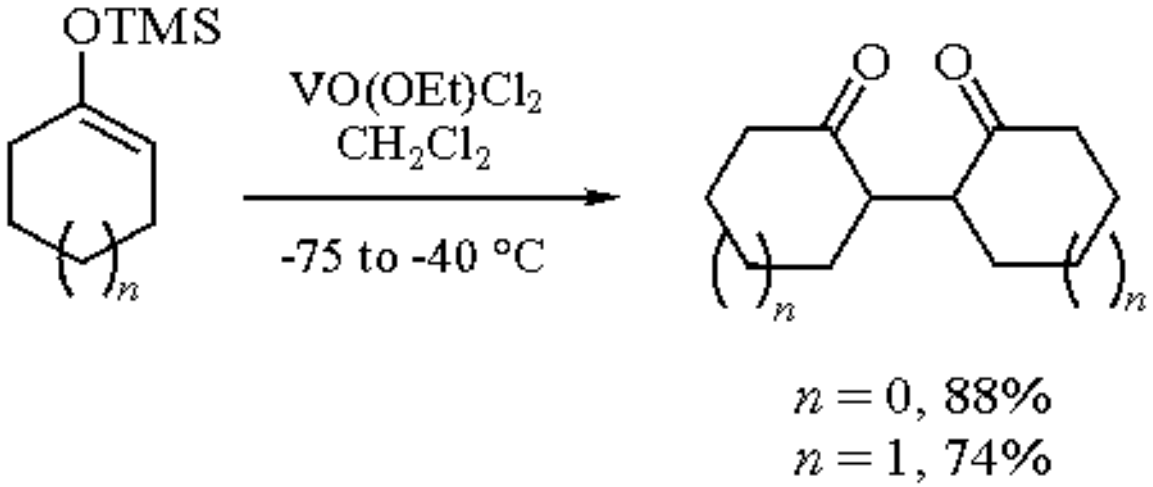

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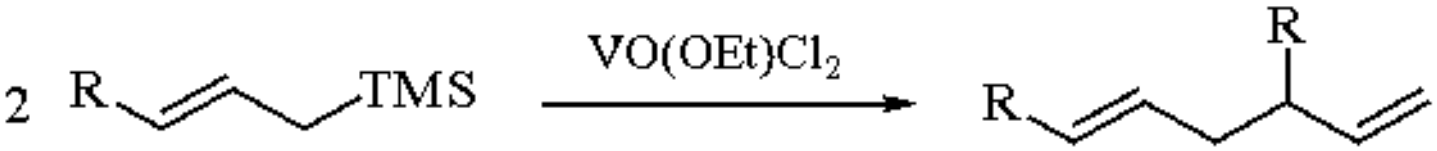

(7)

Related Reagents.

Copper(I) Trifluoromethanesulfonate; ***Lead(IV) Acetate***; ***Silver(I) Oxide***; ***Vanadyl Trichloride***.

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1,2-Dichloroethylene[1]

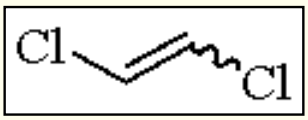

(*E*)

[156-60-5] · $C_2H_2Cl_2$ · 1,2-Dichloroethylene · (MW 96.94) (*Z*)

[156-59-2]

(useful reagent for the synthesis of chloroenynes, enediynes, chlorodienes, conjugated trienes, and tetraenes)

Physical Data: mp -80.5 °C (*Z*), -50 °C (*E*); bp 60.3 °C (*Z*), 48.4 °C (*E*); *d* 1.284 g cm^{-3} (*Z*), 1.257 g cm^{-3} (*E*).

Solubility: insol water; sol alcohol, ether, and most other organic solvents.

Form Supplied in: colorless liquid; widely available. *Drying:* before use, (*E*)- or (*Z*)-1,2-dichloroethylene must be distilled under an inert atmosphere.

Handling, Storage, and Precautions: (*E*)- or (*Z*)-1,2-dichloroethylene has a slightly acrid odor; it is gradually decomposed by air, light, and moisture, forming HCl; it must be stored in a refrigerator. Exposure to vapor may produce nausea and weakness. Use in a fume hood.

Derived Organolithium Reagents.

(*E*)-1,2-Dichloroethylene can be metalated with ***n-Butyllithium*** at -110 °C to give, after carboxylation, (*E*)-2,3-dichloroacrylic acid (eq 1).[2] With (*Z*)-1,2-dichloroethylene the reaction leads to lithium chloroacetylide, which can be trapped with an appropriate electrophile (eq 2).[3,4]

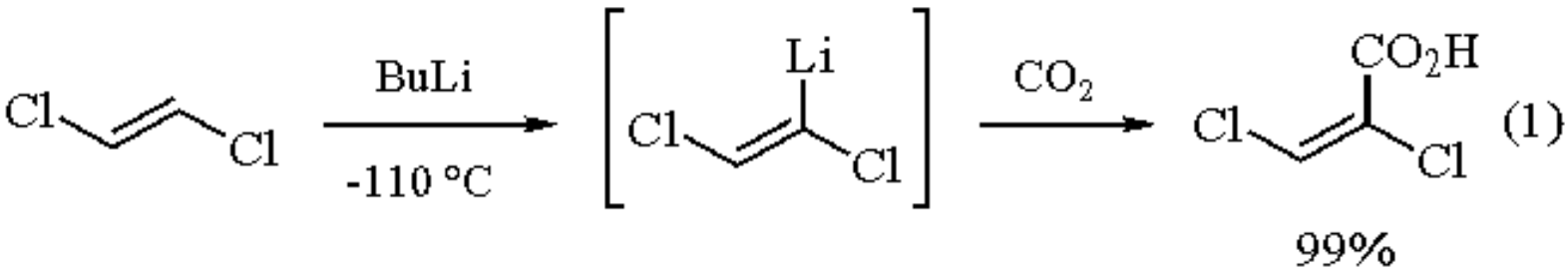

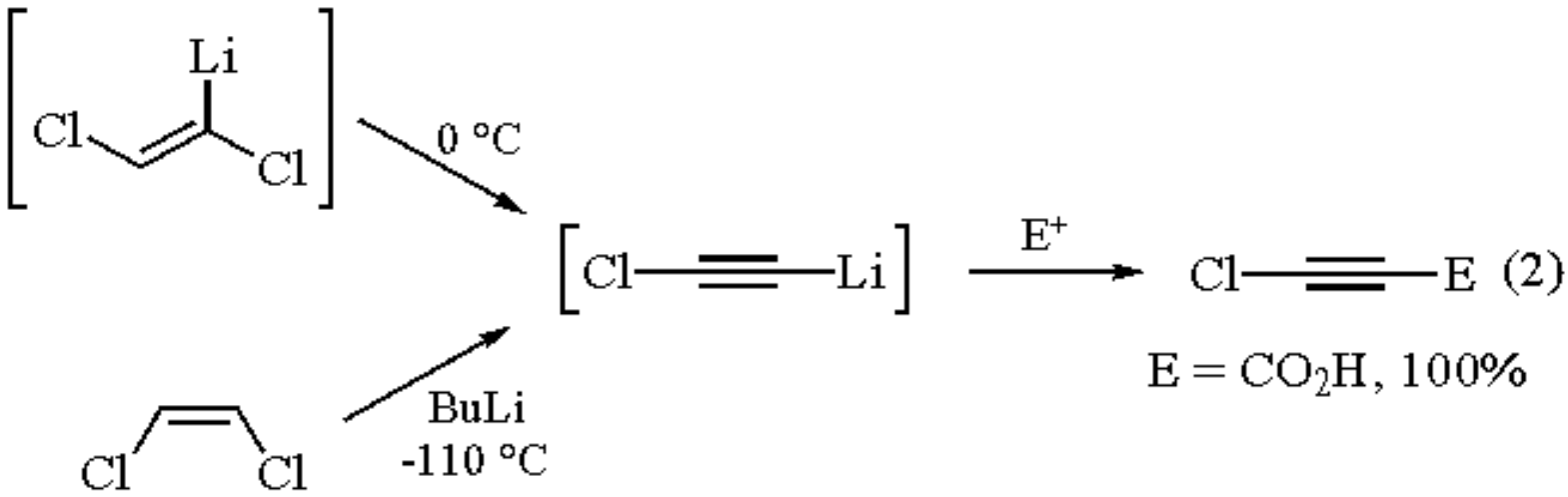

Acetylene Equivalent.

Reaction of (*E*)-1,2-dichloroethylene with enones leads to dichlorocyclobutanes and, after reduction, to cyclobutenes (eq 3).[5]

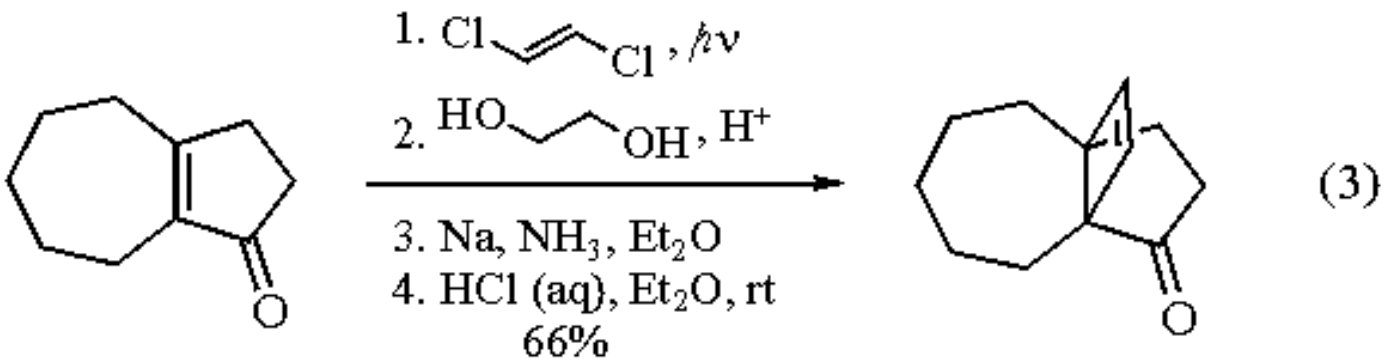

Coupling Reactions.

When treated with nucleophilic agents such as sodium arenethiolate,[6] sodium acetate,[7] or lithium diphenylphosphide,[8] (*Z*)- or (*E*)-1,2-dichloroethylene lead to disubstituted products (eq 4).

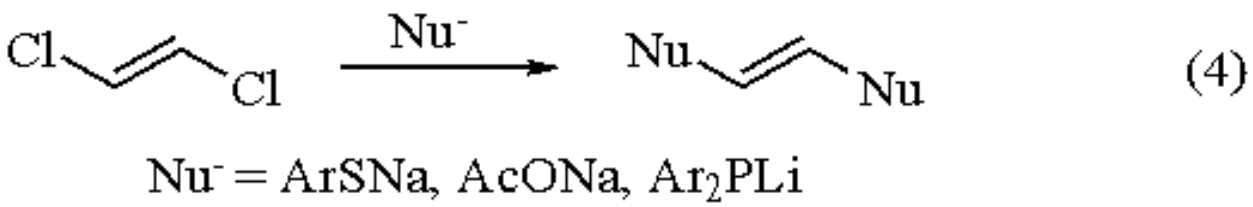

The nickel- or palladium-catalyzed coupling reaction between organometallics and (*Z*)- or (*E*)-1,2-dichloroethylene[9,10] allows for the preparation of vinyl chlorides (eqs 5 and 6).[10a,b]

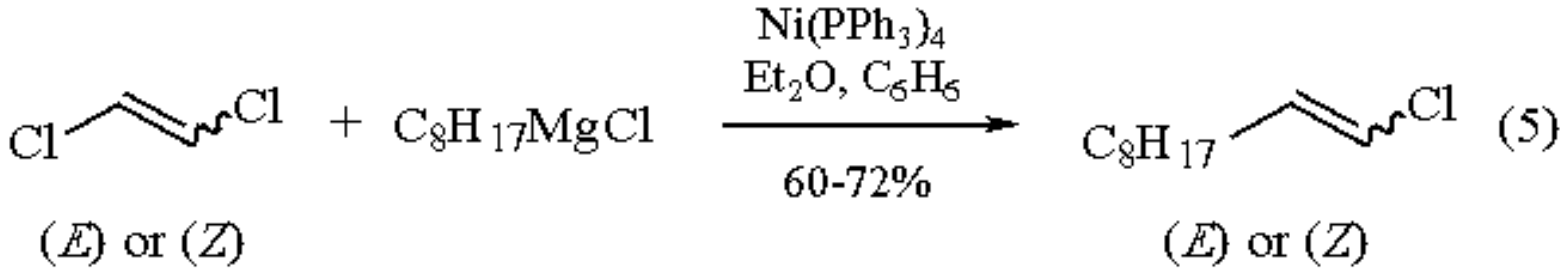

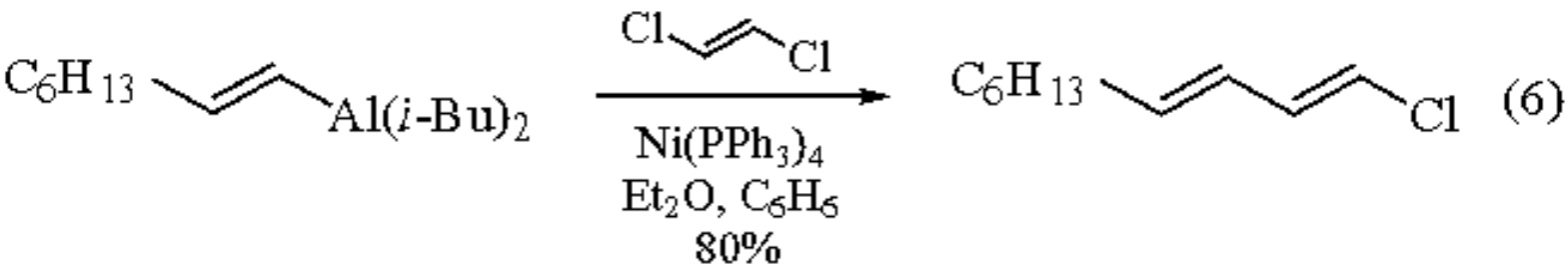

The stereospecific Pd/Cu-catalyzed cross-coupling reaction[10,11] of terminal alkynes with (*E*)- or (*Z*)-1,2-dichloroethylene is a chemoselective and efficient route to (*E*) or (*Z*) conjugated chloroenynes or enediynes (eq 7).[10b]

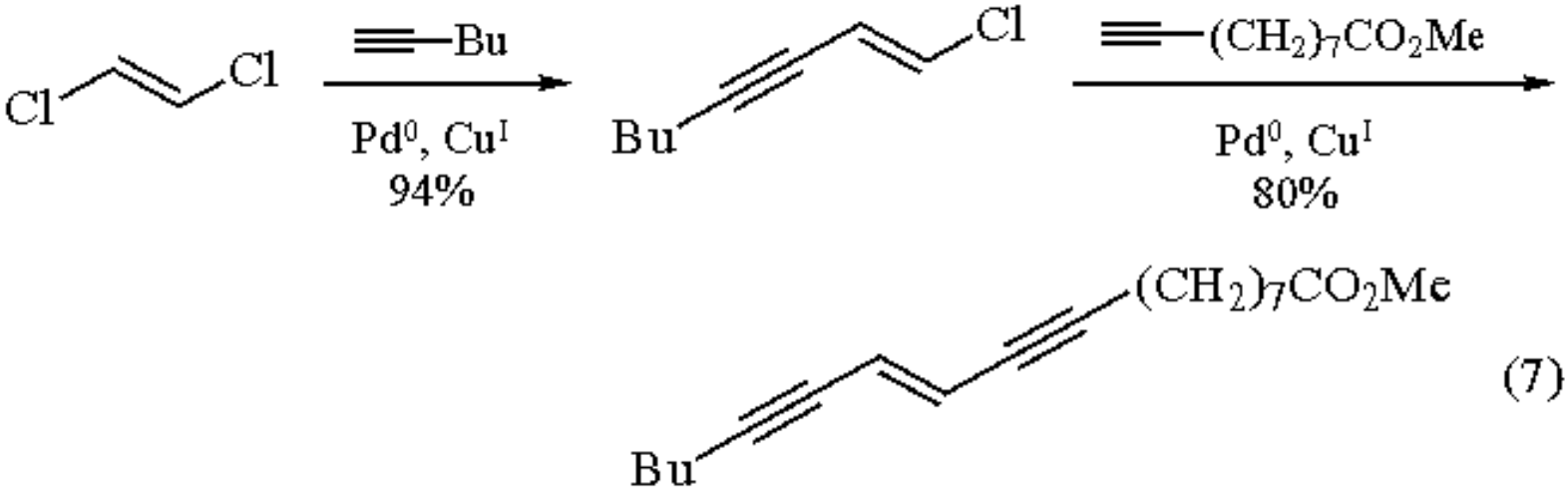

Applications to the synthesis of esperamycins and related substances[12] have been described (eq 8).[12a]

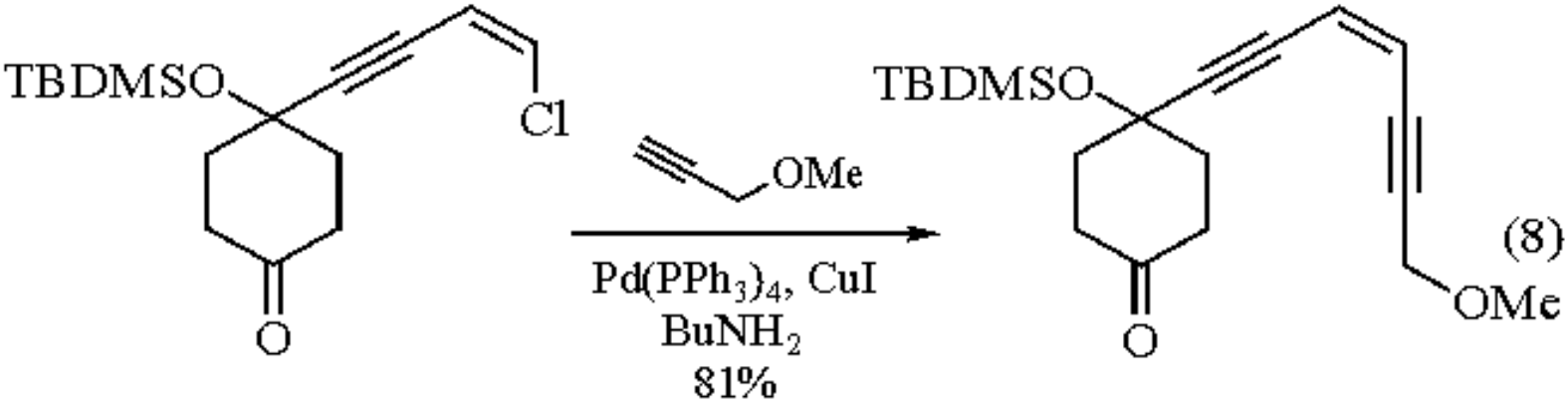

(*Z*)-Chloroenynes are converted into 1,3-diynes under mild conditions by treatment with ***Tetra-n-butylammonium***

Fluoride (eq 9).[13]

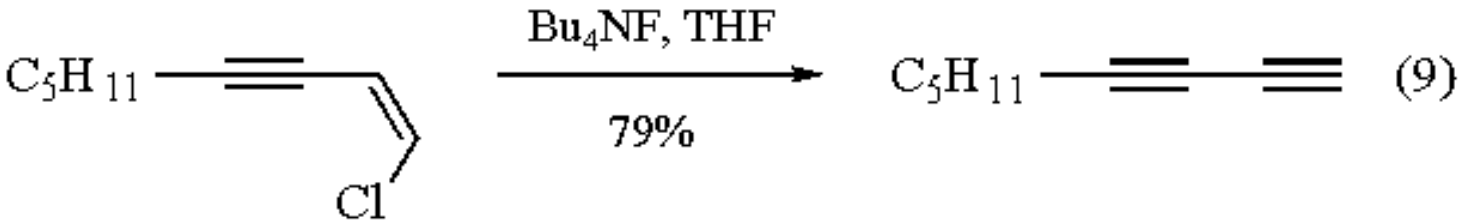

Selective reduction of enediynes, dienynes, and trienynes, prepared from 1,2-dichloroethylenes, allows for the stereocontrolled synthesis of conjugated trienes[14] (eq 10)[10b] and tetraenes (eq 11)[15] having a defined geometry.

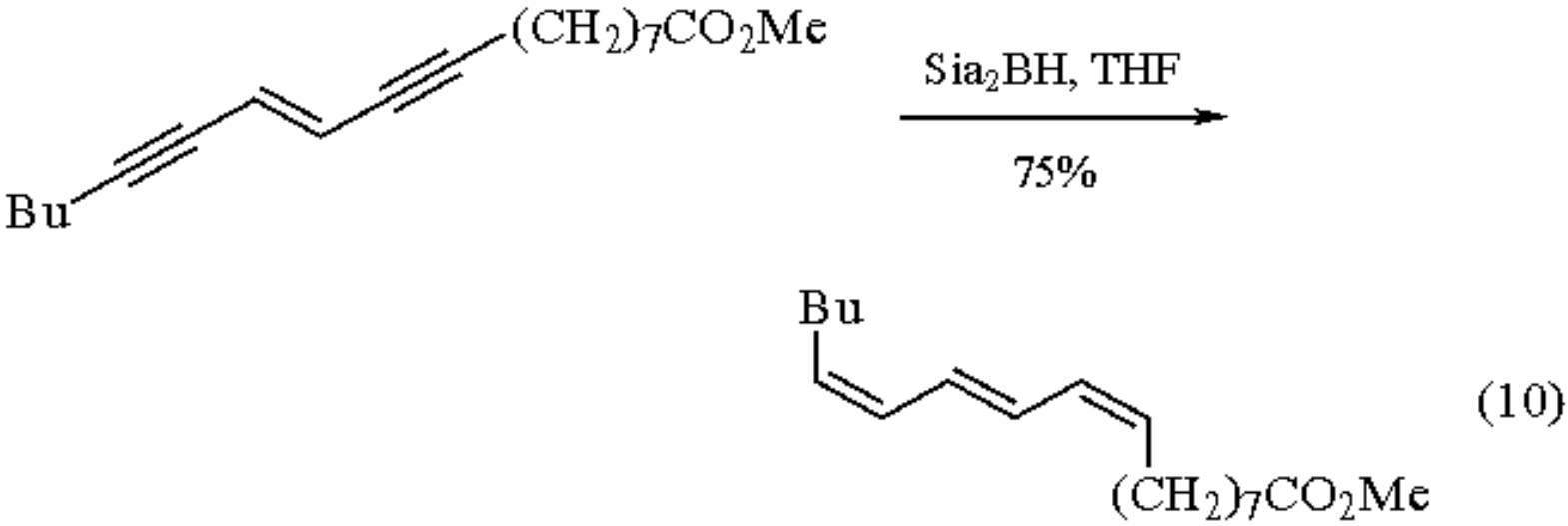

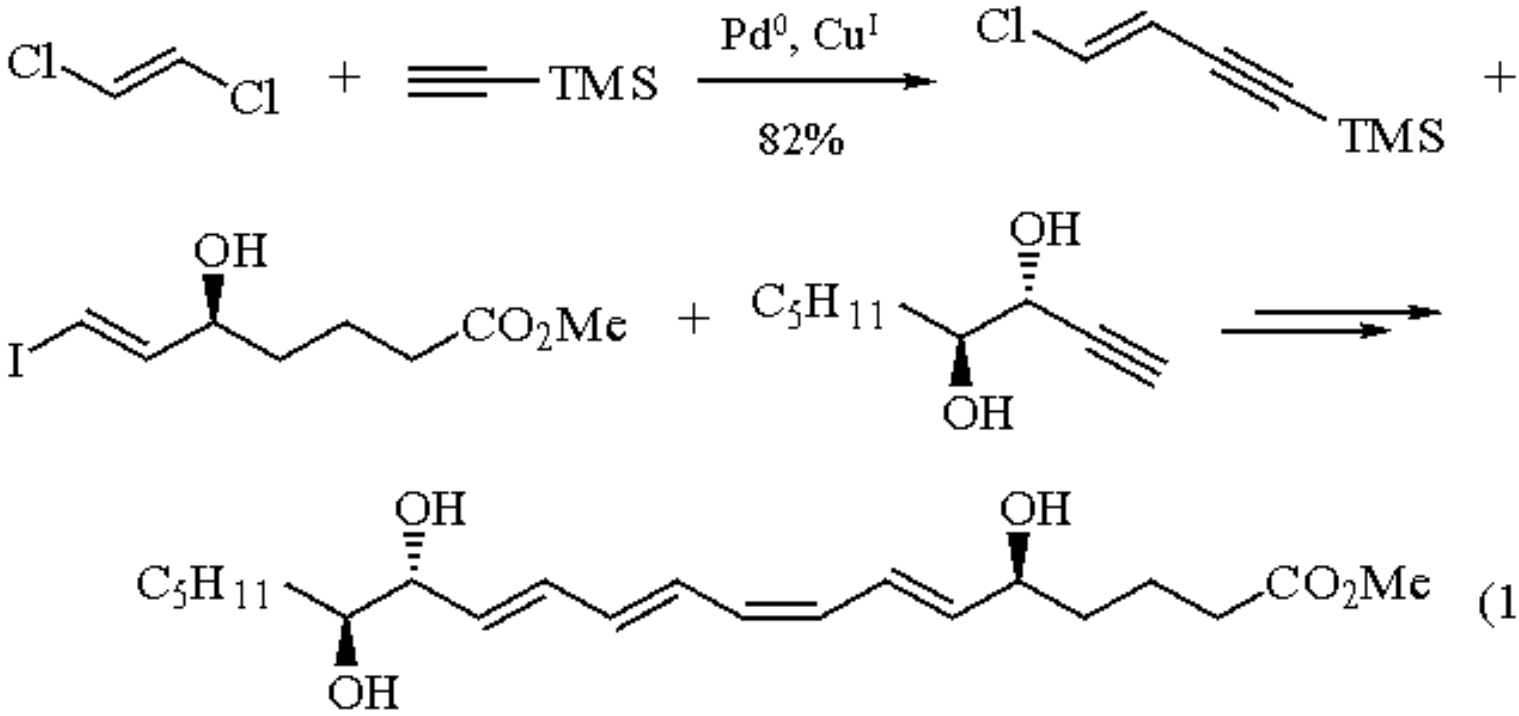

Related Reagents.

1-Chloro-2-iodoethylene.

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(-)-Dichloro(ethylene)(α-methylbenzylamine)platinum(II)

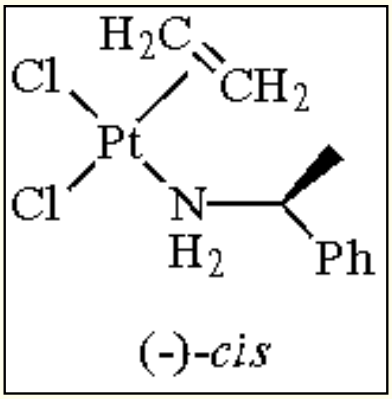

(**1**) (-)-*cis*

[12084-44-5] · $C_{10}H_{15}Cl_2NPt$ · (-)-Dichloro(ethylene)(α-methylbenzylamine)platinum(II) · (MW 415.22)
(**2**) (-)-*trans*

[12084-42-3]

(determination of % ee of alkenes and allenes via ^{195}Pt NMR;[1] resolution of alkenes;[2] asymmetric epoxidation of alkenes[3])

Physical Data: trans isomer: mp 71 °C, [α]21D + 15.5-16.9° (*c* 1.0, CH_2Cl_2), usually obtained as a viscous oil but can be crystallized upon further purification;[2g] *cis* isomer: mp 164 °C, [α]25D -54.5° (*c* 1.3, acetone), obtained as pale green-yellow needles.[4]

Solubility: both the *cis* and *trans* isomers are sol acetone and dichloromethane.

Analysis of Reagent Purity: trans isomer: ^{1}H NMR (CD_2Cl_2) δ 7.39 (s, 5H), 4.62 (t, *J* = 30.5 Hz, 4H), 1.78 (d, *J* = 6.5 Hz, 3H);[2g] for ^{13}C and ^{195}Pt NMR data see Pregosin et al.[5]

Preparative Methods: trans isomer: synthesized from Zeise's salt [K_2PtCl_3(ethylene)] by adding (+)- or (-)-α-methylbenzylamine under acidic conditions;[2g] *cis* isomer: synthesized by adding 2 equiv of (+)- or (-)-α-methylbenzylamine to an aqueous solution of K_2PtCl_4 and then exposing this material to ethylene under pressure.[4]

Purification: trans isomer: chromatography over silica with CH_2Cl_2 as eluent;[2g] *cis* isomer: recrystallization from 1:1 acetone/*n*-heptane or toluene.[4]

Handling, Storage, and Precautions: both isomers are air and water stable.

Determination of % ee via ^{195}Pt NMR.

The *cis* chiral complex has been used to determine enantiomeric purity of asymmetric allenes[1a] and allylic alcohols and ethers[1b] via complexation and ^{195}Pt NMR spectroscopy. The complexes (**3**) and (**4**) are generated by displacement of ethylene from (**1**) by the alkene; recovery of the alkene and (**1**) is effected by the reverse sequence employing excess ethylene.[1b]

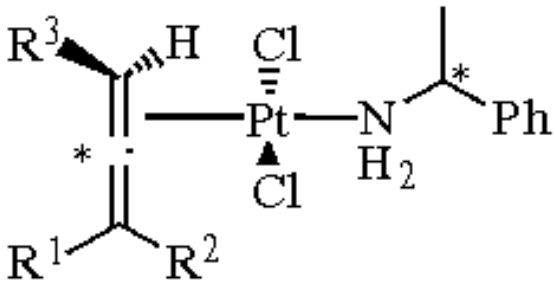

(3)

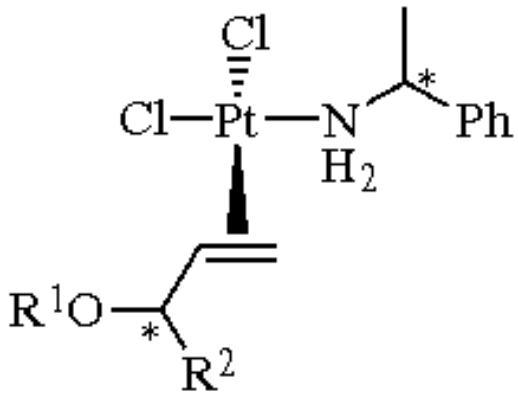

(4)

Resolving Agent.

A variety of chiral alkenes have been resolved via complexation and crystallization including alkenes (**5**)-(**7**) (via **1**),[2a] *cis*,*trans*-1,5-cyclooctadiene (**8**) (via **2**),[2b] 2-vinyltetrahydropyran (**9**) (via **1**),[2c,d] 1,2-cyclononadiene (**10**) (via **2**),[2e] *trans*-cyclooctene (**11**) (via **2**),[2f] and spiro[3.3]hepta-1,5-diene (**12**) (via **2**).[2g]

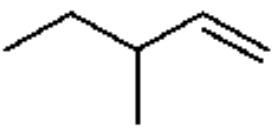

(5) 24% ee

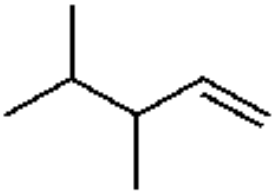

(6) 93% ee

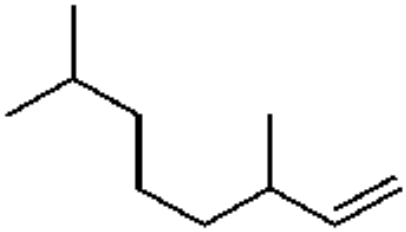

(7) 42% ee

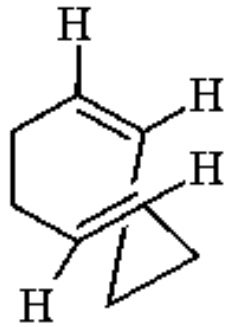

(8) 80% ee

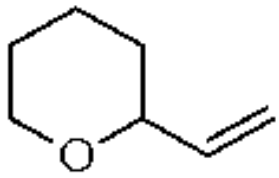

(9) 92% ee

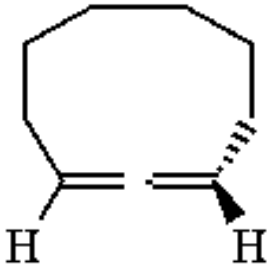

(10) 44% ee

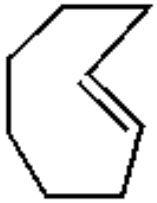

(11) >99% ee

(12)

Asymmetric Epoxidation.

McKervey and co-workers have effected the asymmetric epoxidation of humulene. Complexation of humulene with (**2**) in a 1:2 ratio followed by peracid oxidation gave (-)-humulene 1,2-epoxide in 37% ee (eq 1).[3]

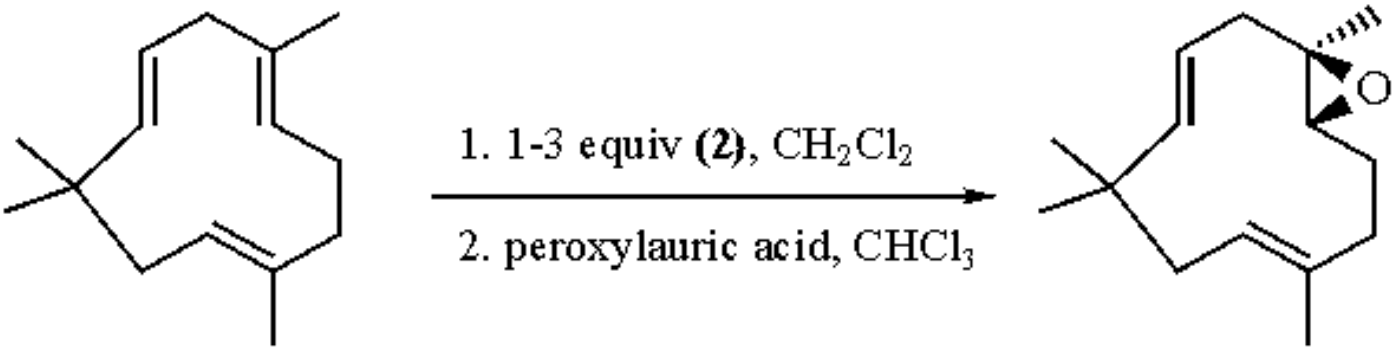

(1)

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Dichloro[2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]palladium(II)

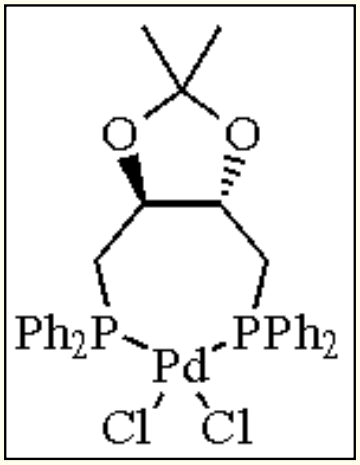

(2*R*,3*R*) or (-)

[63598-08-3] · $C_{31}H_{32}Cl_2O_2P_2Pd$ · Dichloro[2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane]palladium(II) · (MW 675.87) (2*S*,3*S*) or (+)

[59634-23-0]

(chiral catalyst used in asymmetric hydrocarboxylation[1] or hydroalkoxycarbonylation reactions,[2] allylation of β-diketones or β-keto esters,[3] double carbonylation,[4] cross-coupling reactions,[5] preparation of optically active Pd^0 derivatives and their subsequent reactions[6])

Alternate Name: (DIOP)$PdCl_2$.

Physical Data: crystalline pale yellow solid; ((-)-(2*R*,3*R*)-DIOP)$PdCl_2$, $[\alpha]_D$ -7.9° ($CHCl_3$, *c* 1.0);[6b] mp 278-279 °C (dec).[7b]

Solubility: sol dichloromethane; insol heptane.

Analysis of Reagent Purity: for ((-)-(2*R*,3*R*)-DIOP)$PdCl_2$: crystal structure,[7a] ^{1}H NMR,[6b,7b] ^{13}C NMR,[6b] ^{31}P NMR.[6b]

Preparative Methods: prepared from commercially available ***Palladium(II) Chloride*** and (-)-(2*R*,3*R*)-***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane*** in ether,[7a] or by treating a stoichiometric

amount of (-)-(2*R*,3*R*)-DIOP in ethanol with Li_2PdCl_4 in water,[5] or from (+)-(2*S*,3*S*)-DIOP and $Pd(PhCN)_2Cl_2$ in benzene[6b] or acetone.[3c]

Handling, Storage, and Precautions: relatively stable to air oxidation.

Asymmetric Hydrocarboxylation.

The title reagent was used in the first example of an asymmetric hydrocarboxylation (eq 1).[1a,1c] With the α-methylstyrene, the straight chain isomer was formed. The regiospecificity was much less pronounced, however, for other alkenic substrates.[1b] The influence of some reaction variables on the reaction shown in eq 1 was studied. For example, the presence of a solvent such as THF or benzene, the alcohol source, the effect of CO pressure, the effect of substitution on the phenyl ring, the $PdCl_2$/DIOP molar ratio, or the presence of PPh_3 along with DIOP, were varied to improve the optical yield.[1c-e]

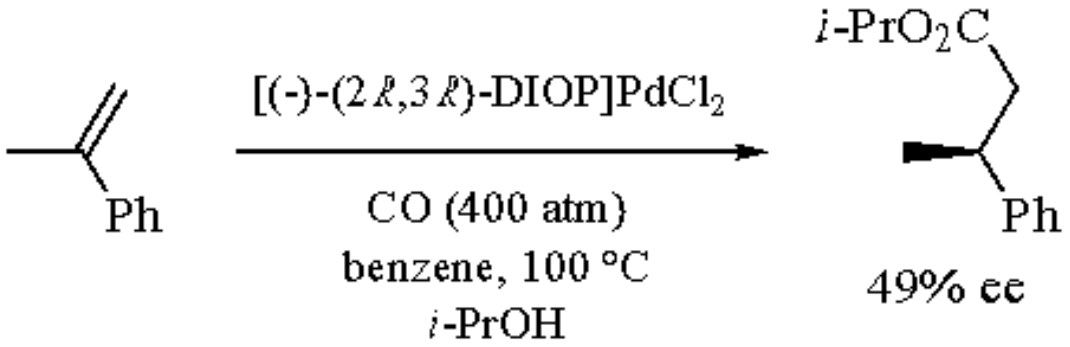

(1)

Methyl methacrylate has been hydromethoxycarbonylated with ((-)-(2*R*,3*R*)-DIOP)$PdCl_2$ as a catalyst to afford (*S*)-dimethyl succinate with excellent regioselectivity, but only modest enantioselectivity (eq 2).[2a,2b]

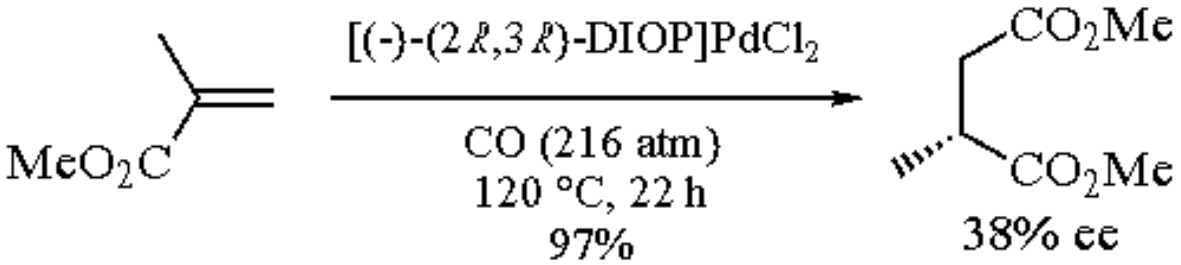

(2)

Asymmetric Allylic Alkylation.

In early investigations of Pd-mediated allylations of alkenes and allylic acetates, Trost and his co-workers used (+)-(2*S*,3*S*)-DIOP along with $PdCl_2$ or $Pd(PPh_3)_4$ and obtained optical yields in the range of 12-46%.[3a,3b] In the allylation of β-diketones or β-keto esters using allyl phenyl ether or allylic esters, use of the title reagent as a chiral catalyst afforded allylated compounds in good yields, but with low enantioselectivity (eq 3).[3c]

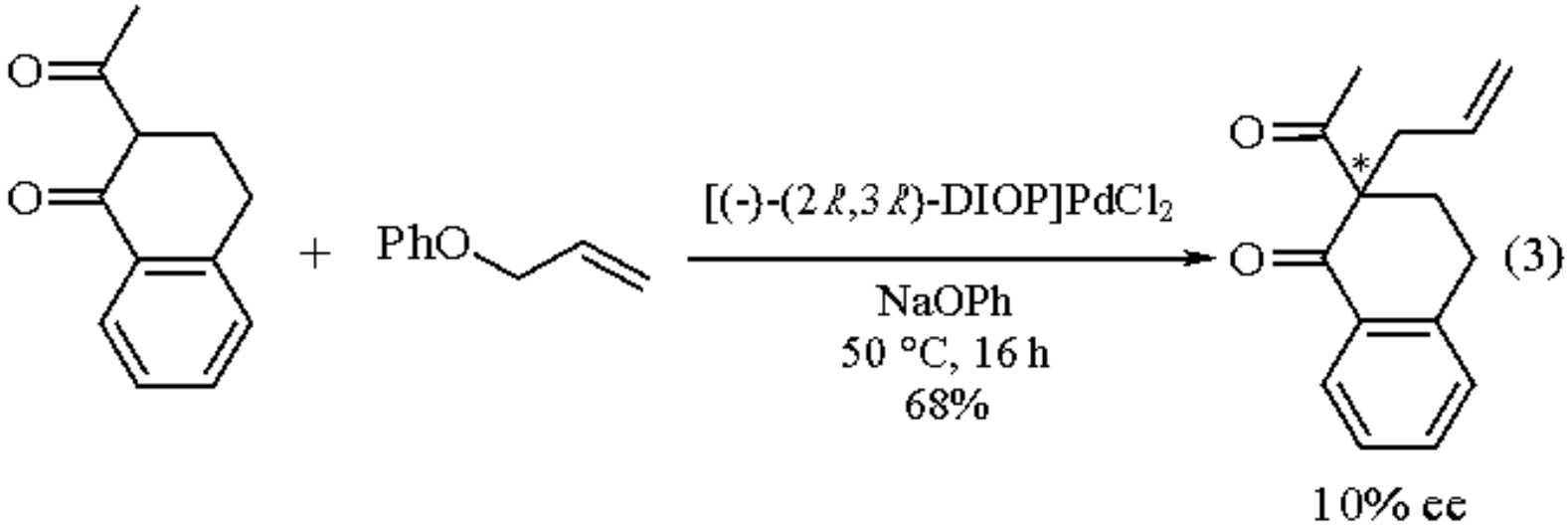

Double Carbonylation of Aryl Halides.

(DIOP)$PdCl_2$ catalyzed the double carbonylation of phenyl iodide in the presence of diethylamine to afford the α-ketoamide in a very good yield along with a minor amount of the benzamide derivative (eq 4).[4]

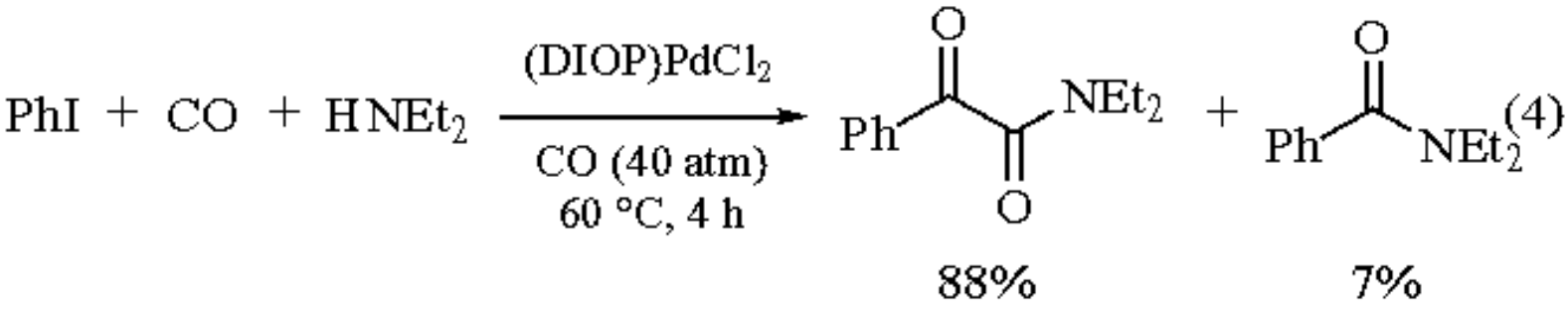

Cross-Coupling of Halides.

4,4-Dimethyl-1-phenylpenta-1,2-diene has been prepared using a ((-)-(2*R*,3*R*)-DIOP)$PdCl_2$-catalyzed cross-coupling reaction, although low enantioselectivity was observed (eq 5).[5]

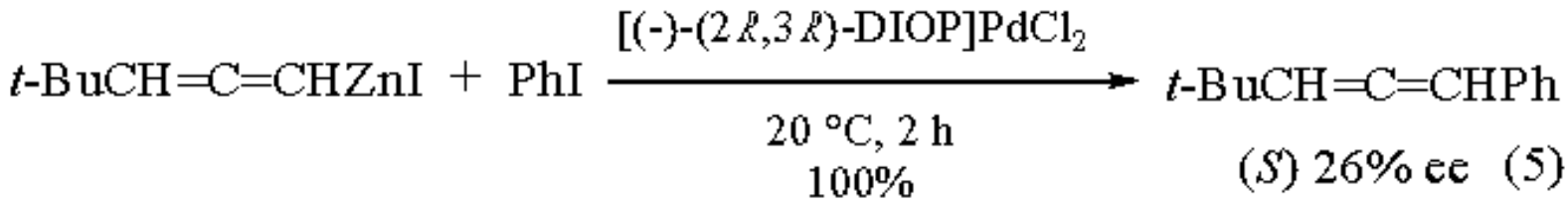

Other Pd^0 Derivatives and Related Reactions.

Other chiral palladium complexes, such as $(DIOP)_2Pd^0$ or (DIOP)(alkene)Pd^0, can be prepared from (DIOP)$PdCl_2$.[6a,6d] These catalysts have afforded low levels of asymmetric induction (10% ee) in the hydrocyanation of norbornene derivatives.[6b,6c]

Oxirane Formation.

The reaction of acetonyltributyltin with α-bromoacetophenone to yield 2-acetonyl-2-phenyloxirane has been investigated using ((+)-(2*S*,3*S*)-DIOP)$PdCl_2$ as a catalyst, but no asymmetric induction was observed.[8]

---

1. (a) Botteghi, C.; Consiglio, G.; Pino, P. *C* **1973**, *27*, 477. (b) Consiglio, G.; Marchetti, M. *C* **1976**, *30*, 26. (c) Consiglio, G.; Pino, P. *C* **1976**, *30*, 193. (d) Consiglio, G. *JOM* **1977**, *132*, C26. (e) Consiglio, G.; Roncetti, L. *Chirality* **1991**, *3*, 341.
2. (a) Consiglio, G.; Kollár, L.; Kölliker, R. *JOM* **1990**, *396*, 375. (b) Consiglio, G.; Nefkens, S.; Pisano, C.; Wenzinger, F. *HCA* **1991**, *74*, 323
3. (a) Trost, B. M.; Dietsche, T. J. *JACS* **1973**, *95*, 8200. (b) Trost, B. M.; Strege, P. E. *JACS* **1977**, *99*, 1649. (c) Fiaud, J. C.; Gournay, A. H.; Larcheveque, M.; Kagan, H. B. *JOM* **1978**, *154*, 175.
4. Kobayashi, T.; Tanaka, M. *JOM* **1982**, *233*, C64.
5. De Graaf, W.; Boersma, J.; Van Koten, G.; Elsevier, C. J. *JOM* **1989**, *378*, 115.
6. (a) Brown, K.; Chaloner, P. A. *JOM* **1981**, *217*, C25. (b) Elmes, P. S.; Jackson, W. R. *AJC* **1982**, *35*, 2041. (c) Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *OM* **1988**, *7*, 1761. (d) Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *CC* **1987**, 1309.
7. (a) Gramlich, V.; Consiglio, G. *HCA* **1979**, *62*, 1016. (b) Chaloner, P. A. *JOM* **1984**, *266*, 191.
8. Pri-Bar, I.; Pearlman, P. S.; Stille, J. K. *JOC* **1983**, *48*, 4629.

Ronan Guével

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Dichloroketene[1]

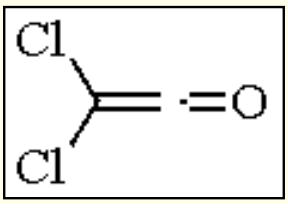

[4591-28-0] · C_2Cl_2O · Dichloroketene · (MW 110.93)

(dichloroacetylating agent;[2] undergoes cyclizations with numerous substrates[3])

Solubility: sol ether, pentane, hexane.

Form Supplied in: not commercially available.

Preparative Methods: typically prepared in situ by dehalogenation of trichloroacetyl halides or dehydrohalogenation of dichloroacetyl halides. Elimination of dichloroacetyl chloride with ***Triethylamine*** affords the desired ketene,[4] although material formed in this manner is of limited reactivity.[5] Reduction of ***Trichloroacetyl Chloride*** with ***Zinc/Copper Couple*** activated with either ***Phosphorus Oxychloride***[6] or ***1,1-Dimethoxyethane***[7] provides fully reactive dichloroketene. Recently, thermal activation of ***Zinc*** dust was used to generate dichloroketene.[8]

Handling, Storage, and Precautions: given the propensity of dichloroketene to dimerize or polymerize, the reagent must be made and used immediately. Polymeric material is obtained on heating or concentration of solutions of dichloroketene, and anhydrous conditions must be maintained.

Dichloroacetylation.

In his original preparation of dichloroketene, Brady formed the reagent in the presence of aniline to form the corresponding acetanilide (eq 1).[2] Given the wealth of methods to perform this transformation, this is of limited synthetic utility.

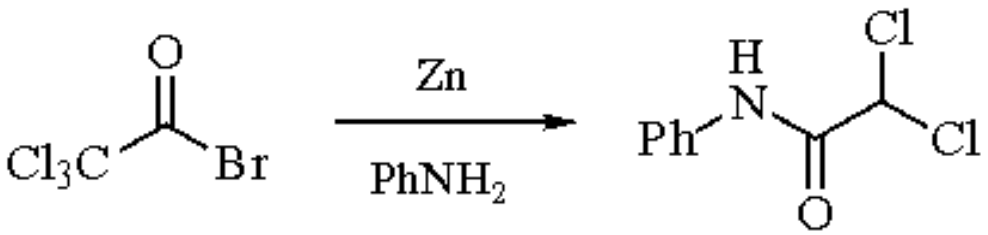

(1)

Cyclizations.

The propensity of dichloroketene to undergo cycloaddition reactions with a variety of π-systems has rendered this reagent a powerful synthon.[1,3] Treatment of dichloroketene with numerous alkenes such as 1-pentene causes a [2 + 2] cycloaddition to occur (eq 2).[9] These cyclizations have been shown to occur in a *syn* fashion, as reaction of dichloroketene with *cis*- and *trans*-cyclooctene affords the corresponding *cis* and *trans* bicyclic products (eqs 3 and 4).[10] The cycloadditions of dichloroketene are often sensitive to the method of preparation. For example, conjugated dienes react with dichloroketene in a [2 + 2] fashion to form cyclobutanones, but the ketene must be generated by the dehydrohalogenation of dichloroacetyl chloride, as Lewis acids promote the polymerization of most dienes (eq 5).[11] In fact, the cyclization of acid sensitive alkenes such as vinyl ethers and styrene can only be realized with dichloroketene formed in this fashion.[3a,9] Cyclizations with tri- and tetrasubstituted alkenes are also possible, although in this case the dichloroketene must be generated from activated zinc (eq 6).[12] The cyclobutanones formed in this manner can undergo a vast array of transformations (see below).

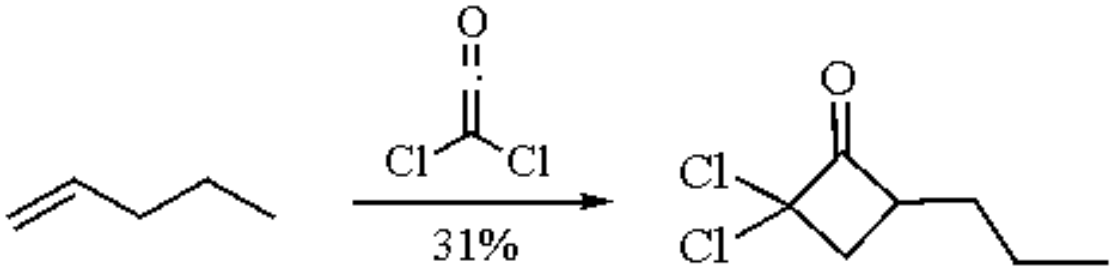

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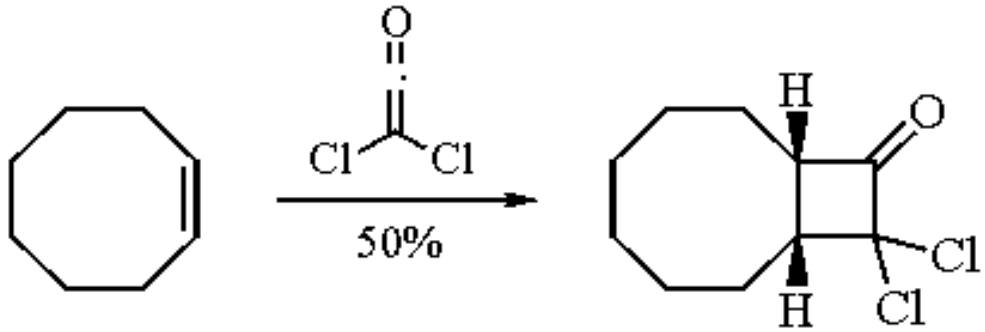

(3)

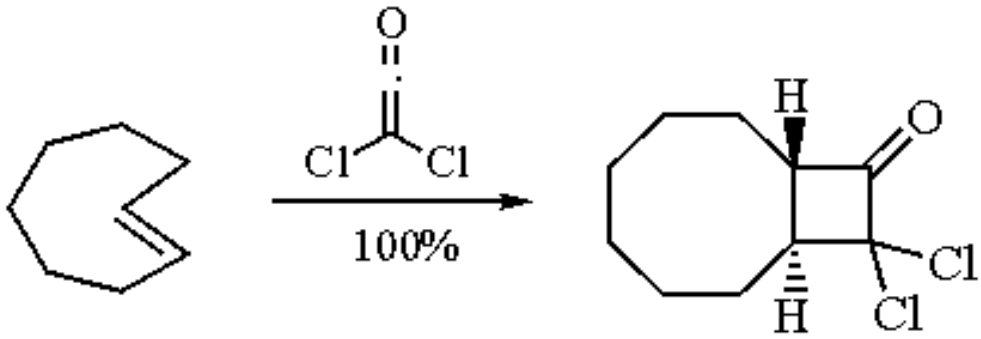

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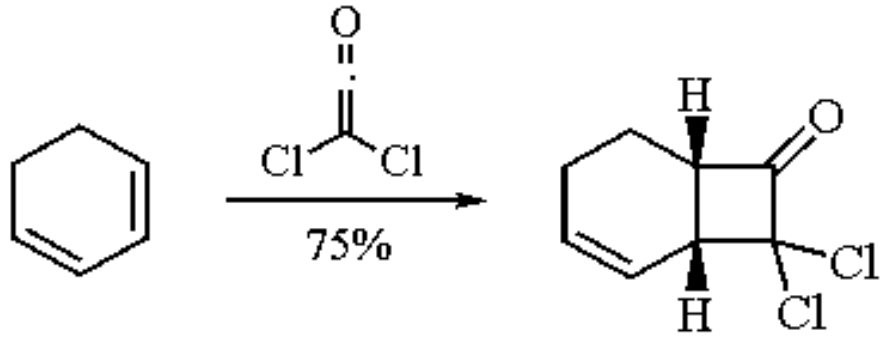

(5)

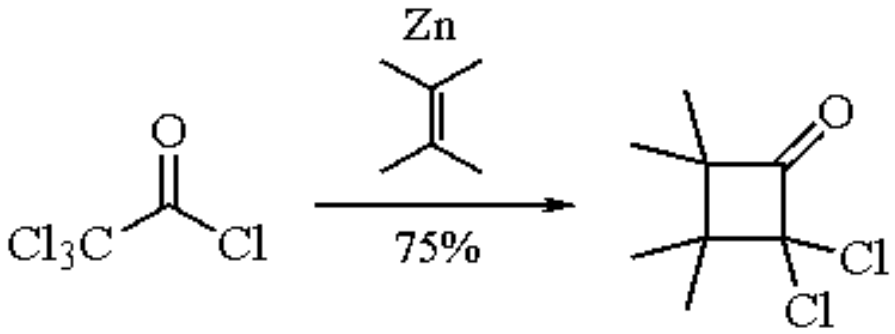

(6)

Cyclization of dichloroketene with unsymmetrical alkenes typically occurs in a regiospecific fashion. For example, cyclization of 1-methylcyclohexene with dichloroketene gives a single product (eq 7).[12] Exocyclic methylenes undergo facile conversion to the corresponding cyclobutanones, allowing easy access to spiro compounds (eq 8).[13]

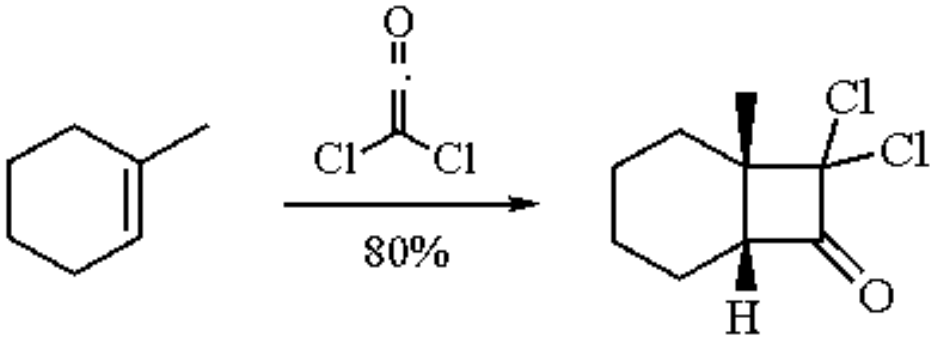

(7)

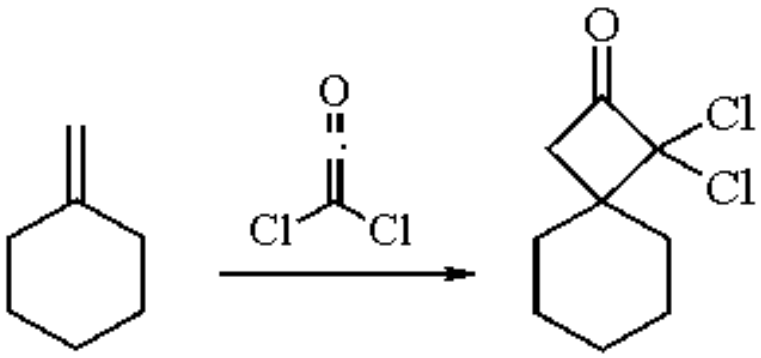

(8)

Dichloroketene also reacts with carbonyls to generate 2-oxetanones.[1,3] However, the method of preparation of the ketene is critical. Cyclohexanone, for example, is smoothly converted to the corresponding β-lactone on exposure to dichloroketene prepared via the activated zinc pathway (eq 9).[14] It has been proposed that the zinc present in the reaction activates the ketone carbonyl toward cycloaddition.[15] Dehydrohalogenation of dichloroacetyl chloride in the

presence of acetone does not lead to useful product. However, dichloroketene generated in this fashion reacts readily with monosubstituted benzaldehydes (eq 10).[16] The 3,3-dichloro-2-oxetanones formed in this fashion can be made to undergo thermolysis under elevated temperatures, resulting in the generation of dichlorostyrenes (eq 11).[16] Cycloalkanones react with dichloroketene to form spirolactones (eq 12).[17] Thermolysis leads to exocyclic dichloroalkenes, and ***Sodium-Ammonia*** reduction affords the exocyclic methylene (eq 13).[17] This provides a useful complement to the methodology developed by Wittig and Tebbe. The chlorinated β-lactones formed via these cycloadditions are useful synthetic intermediates (see below).

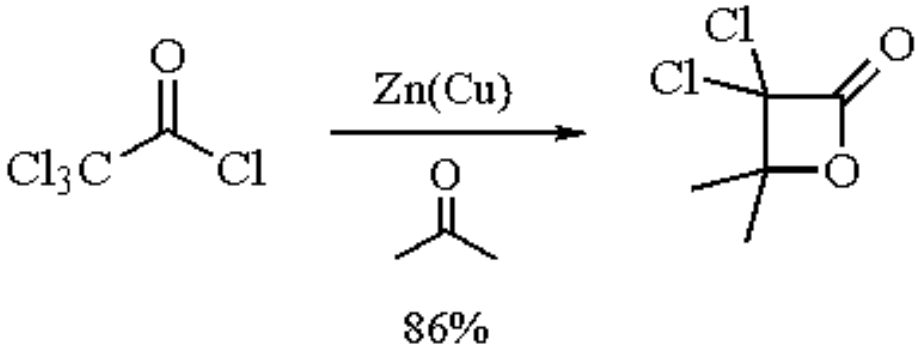

(9)

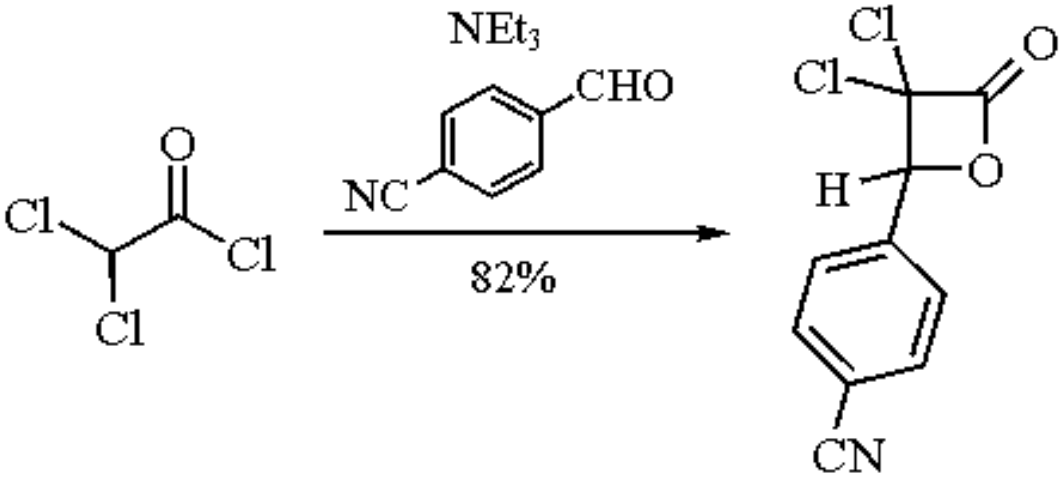

(10)

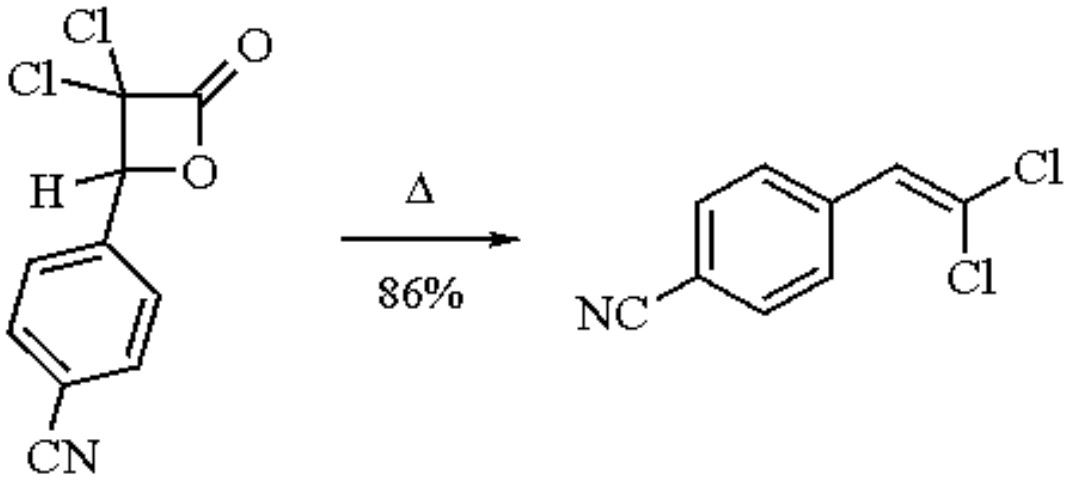

(11)

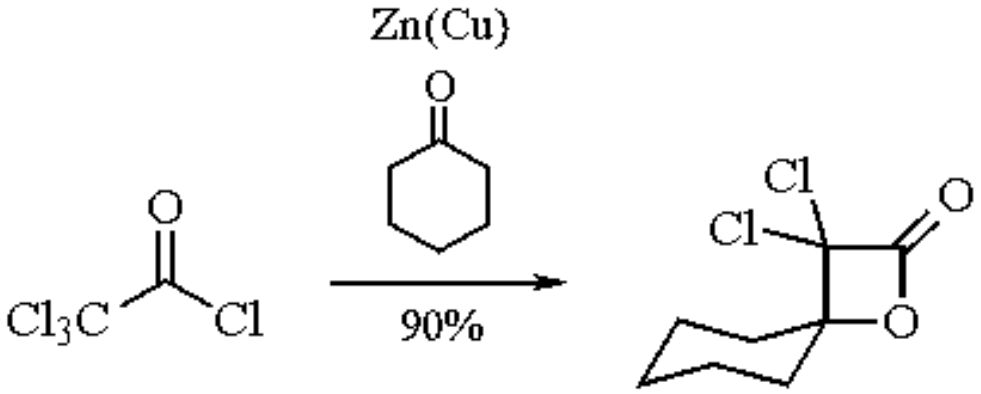

(12)

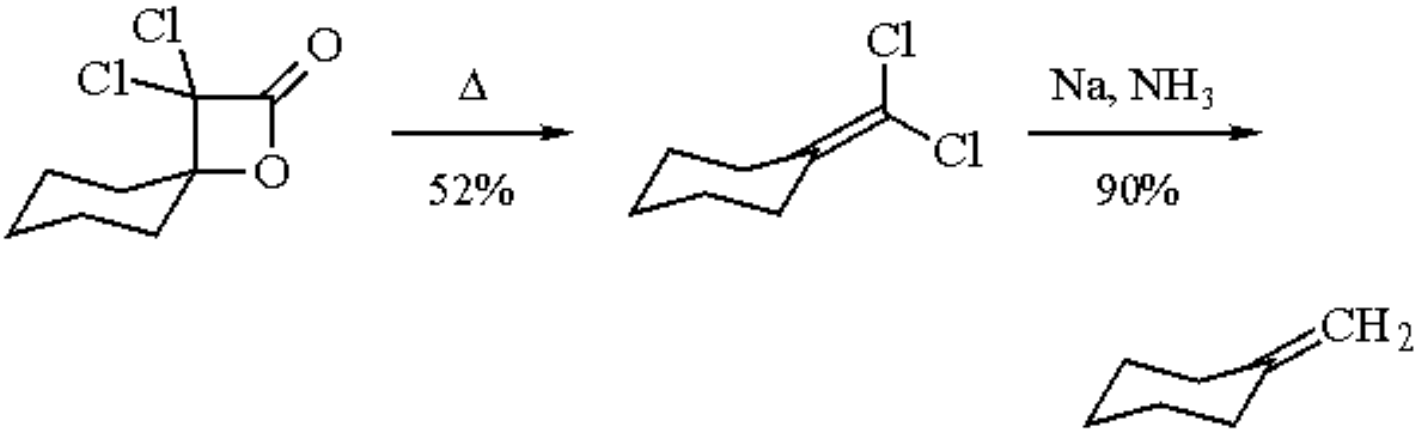

(13)

Dichloroketene undergoes [2 + 2] cyclizations with numerous other unsaturated compounds. Imines, for example, serve as excellent cycloaddition partners, providing a rapid route to the synthesis of β-lactams (eq 14).[18] Diimides also react readily with dichloroketene to form β-iminoazetidinones (eq 15).[19] Addition of trichloroacetyl chloride to alkynes in the presence of activated zinc yields 2-cyclobutenones (eq 16).[7] These reactions also occur in a regiospecific manner. Ethoxyacetylene adds to dichloroketene, and subsequent hydrolysis gives the vinylogous acid (eq 17).[20] Cyclization of vinyl ethers with dichloroketene gives a single product, and chiral ethers have been used to generate optically pure cyclobutanones (eqs 18 and 19).[21,22] α-Alkylidenecyclobutanones can be formed on cyclization of dichloroketene with allenes (eq 20).[23]

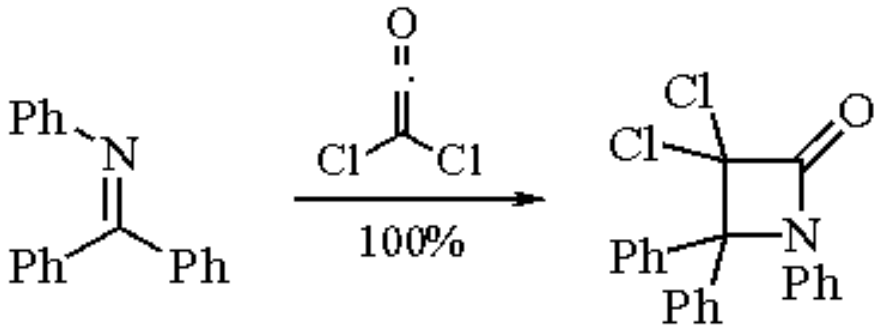

(14)

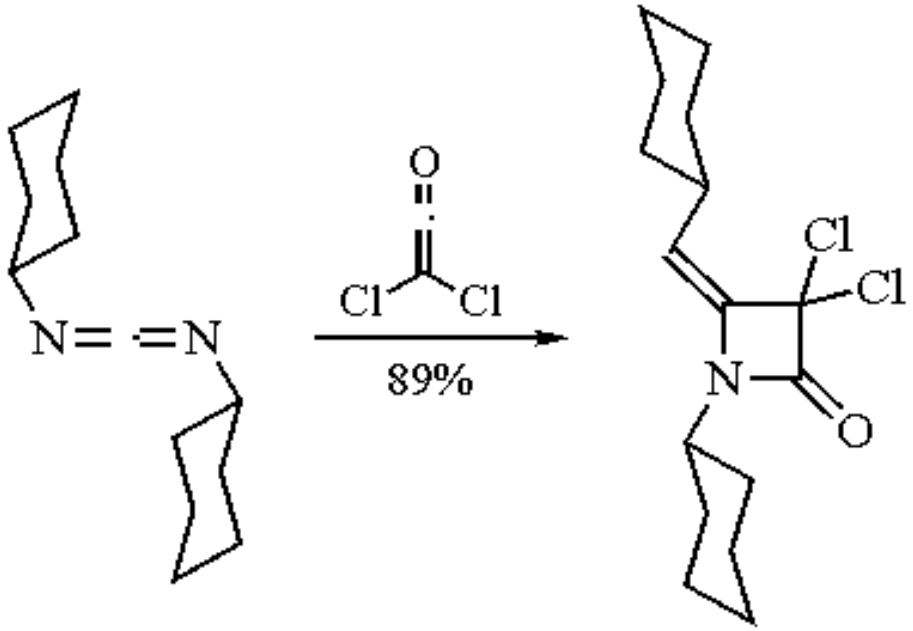
N= =N
O
Cl Cl
89%
Cl
Cl
N
O

(15)

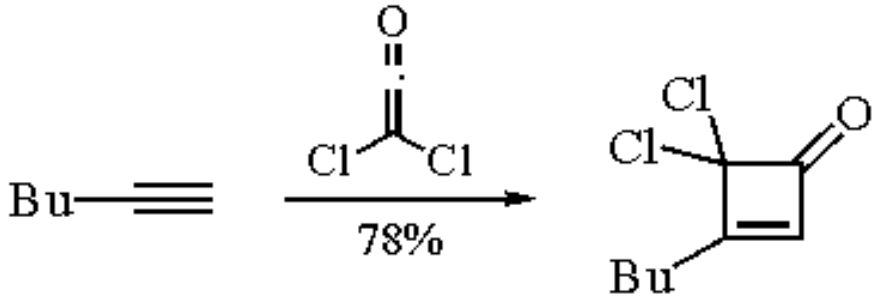
Bu
O
Cl Cl
78%
Cl
Cl
O
Bu

(16)

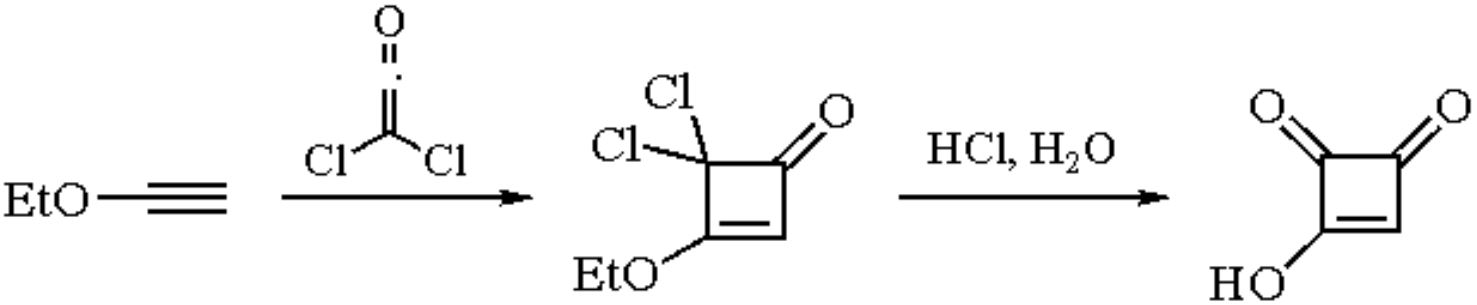
EtO
O
Cl Cl
Cl
Cl
O
EtO
HCl, H2O
O
O
HO

(17)

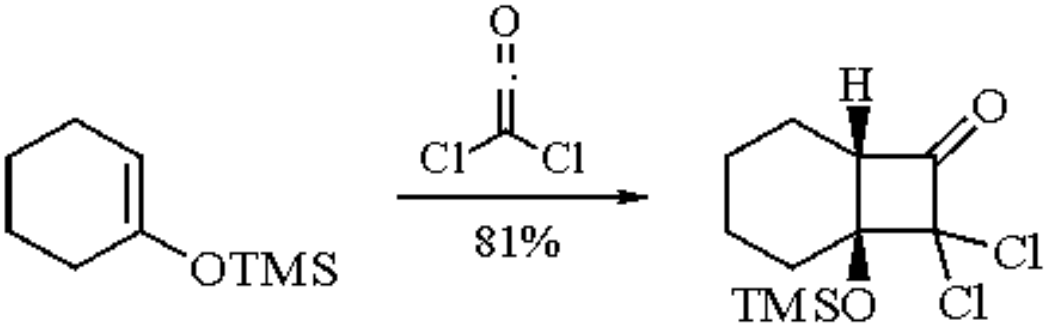
OTMS
O
Cl Cl
81%
H
O
Cl
TMSO
Cl

(18)

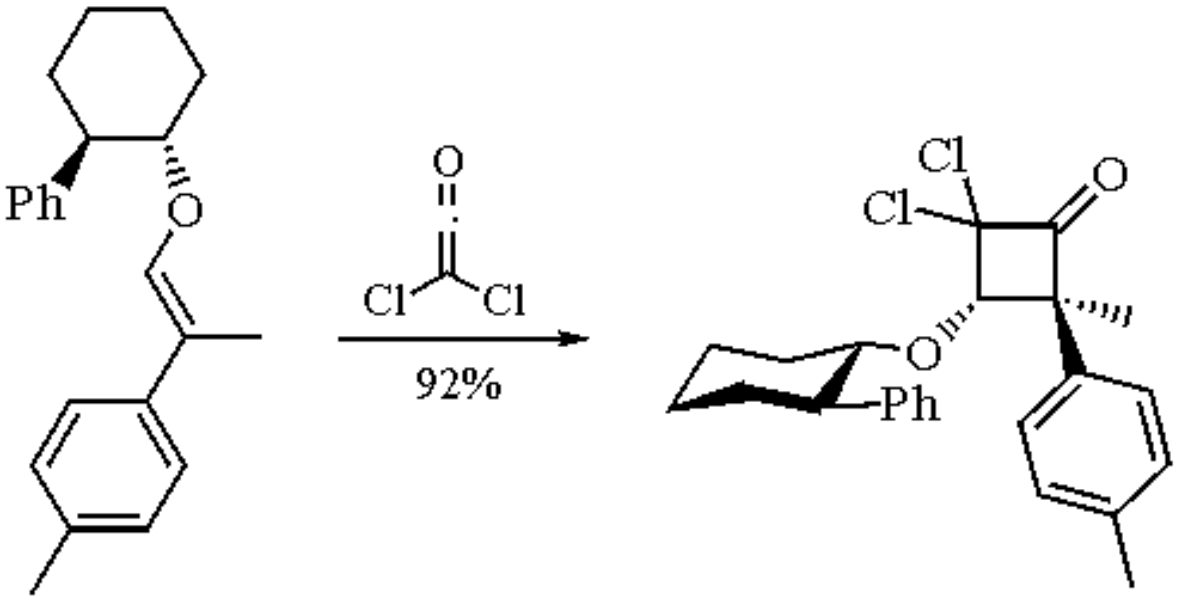

(19)

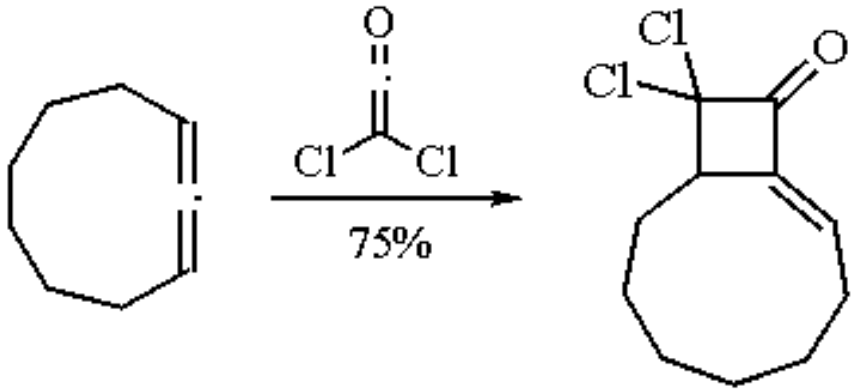

(20)

While [2 + 2] cyclizations are more common, dichloroketene does undergo [4 + 2] cycloaddition reactions in some cases. For example, β-dialkylamino-α,β-unsaturated enones add in an apparent [4 + 2] sense and, upon elimination of hydrogen chloride, furnish 2-pyrones (eq 21).[24] Some imines are also substrates for this reaction, and 2-pyridones can be prepared (eq 22).[25]

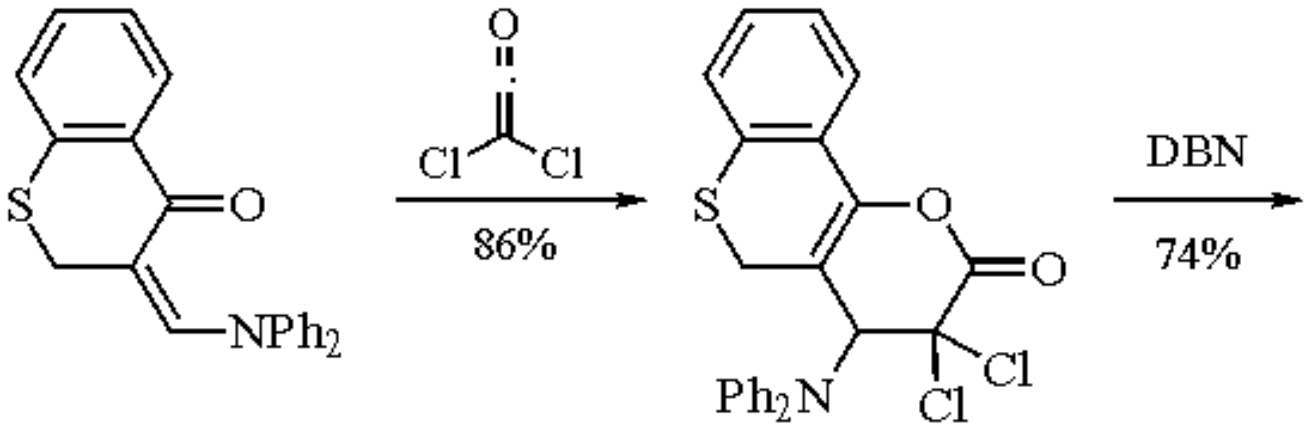

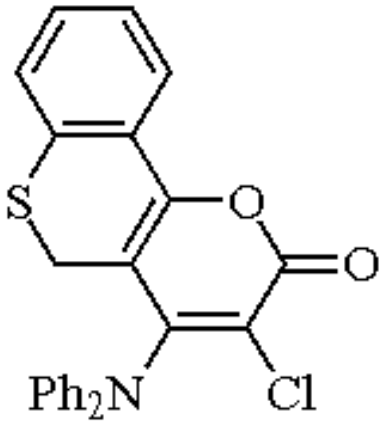

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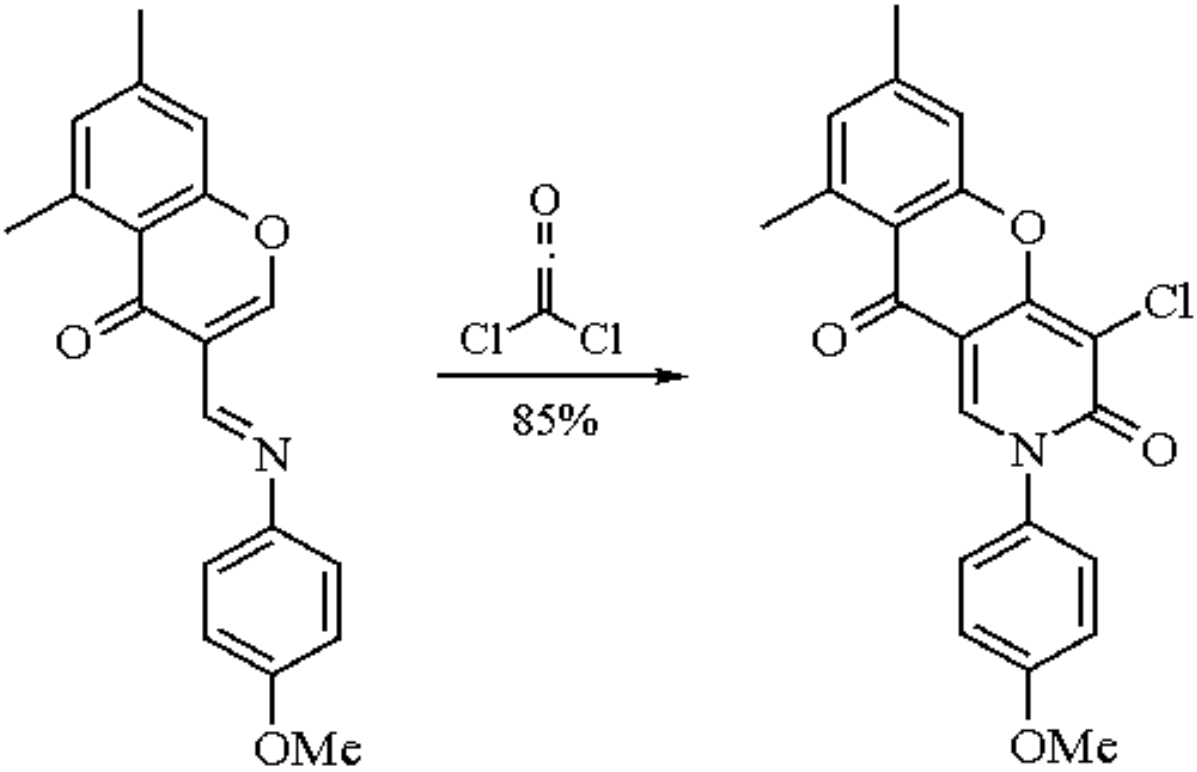

(22)

Reaction of vinyl sulfoxides with dichloroketene gives a novel synthetic route to butyrolactones (eq 23).[26] With the ready availability of optically pure sulfoxides, this provides an asymmetric source of γ-lactones (eq 24).[27] Allylic ethers and sulfides react with dichloroketene via a Claisen-type rearrangement to give esters, albeit in modest yields

(eq 25).[28] This method can be used as a novel entry into macrolide synthesis (eq 26).[29]

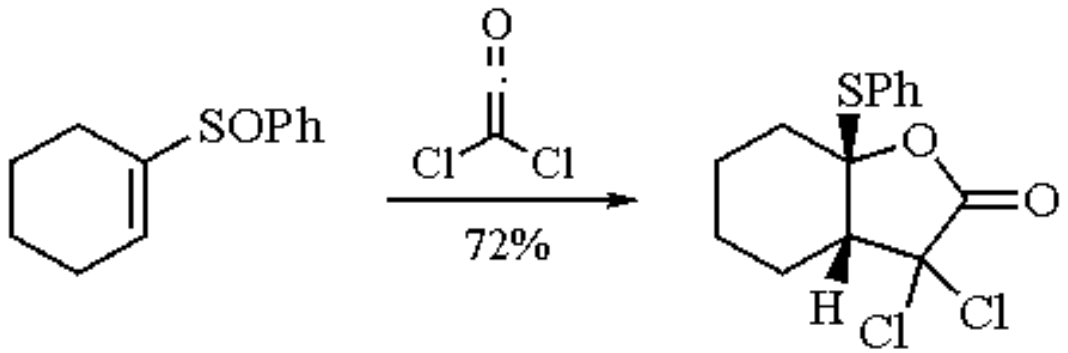

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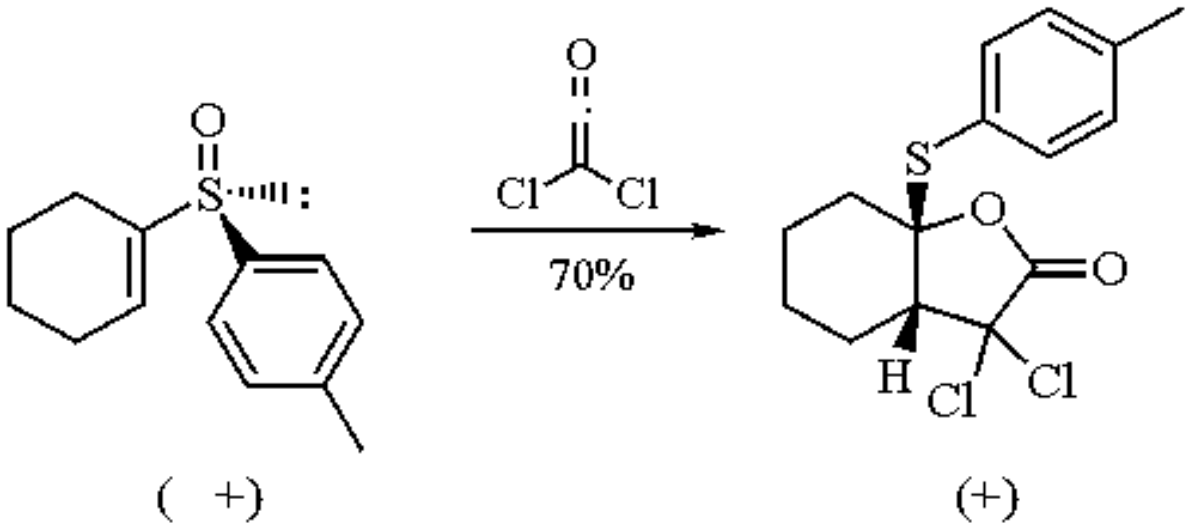

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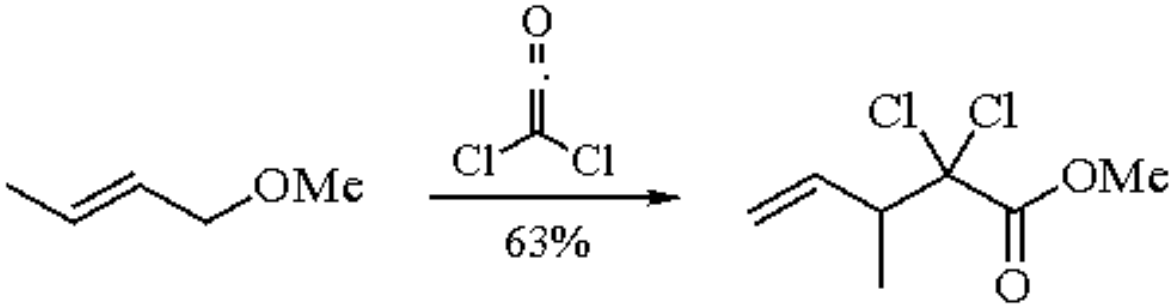

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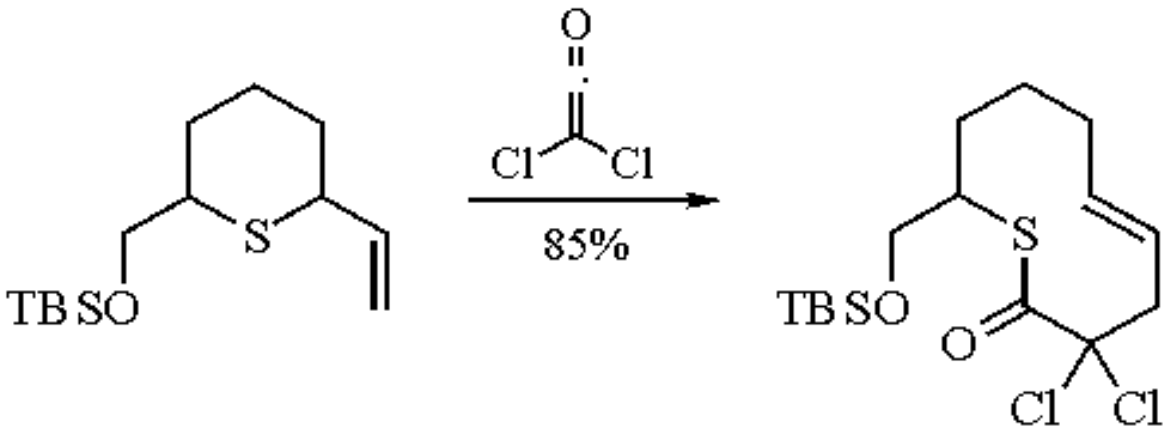

(26)

Reactions of Dichloroketene Adducts.

The cycloadduct of cyclopentadiene with dichloroketene can be hydrolyzed to furnish tropolone (eq 27).[30] This is a fairly mild and general reaction, and a number of annulated tropolones can be formed in this fashion (eq 28).[3,31]

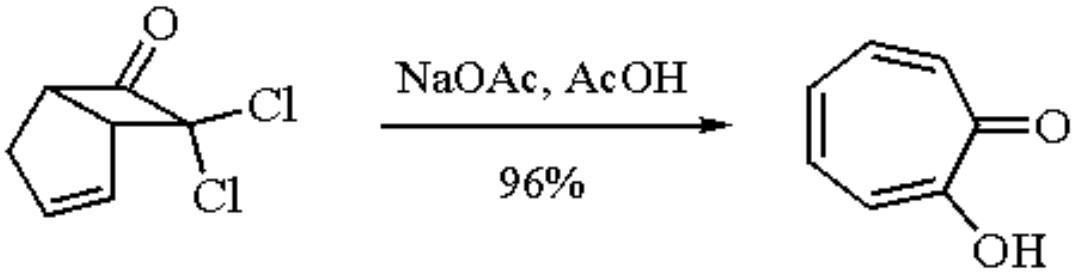

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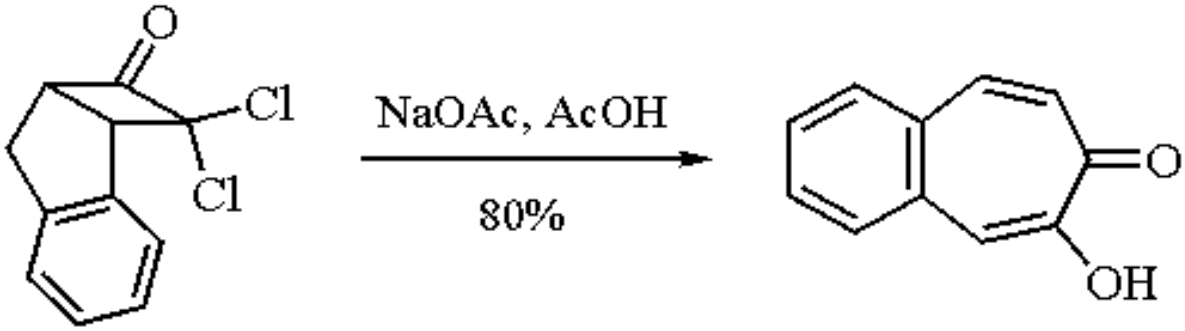

(28)

The reductive removal of one or both of the chlorine atoms of dichloroketene cycloadducts lends considerable flexibility to the synthetic utility of this reagent.[3,4,32] Reduction of the cyclopentadiene addition product with ***Tri-n-butylstannane*** or ***Zinc-Acetic Acid*** gave the bicyclo[3.2.0]heptenone (eq 29).[4] This compound can also be selectively reduced to give exclusively the *endo*-monochloro derivative (eq 30).[33,34] The facile removal of both chlorine substituents renders dichloroketene as a synthetic equivalent of the parent ketene. Since dichloroketene is considerably more reactive than ketene and can be made from inexpensive starting materials, it is superior to ketene in most cases.[1,3] In addition, many of the other adducts can also undergo dehalogenation, providing easy access to the β-lactones, β-lactams, and spiroalkanones (eq 31).[35] In fact, these compounds are substrates for many of the same reactions known for the cyclobutanones.[1,3,4]

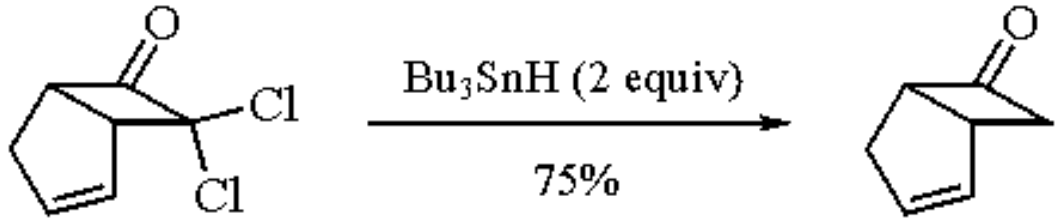

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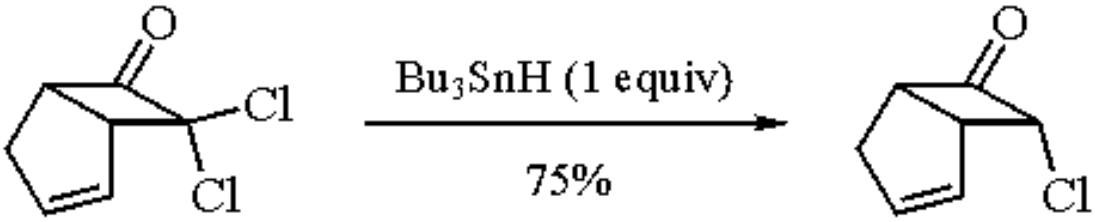

(30)

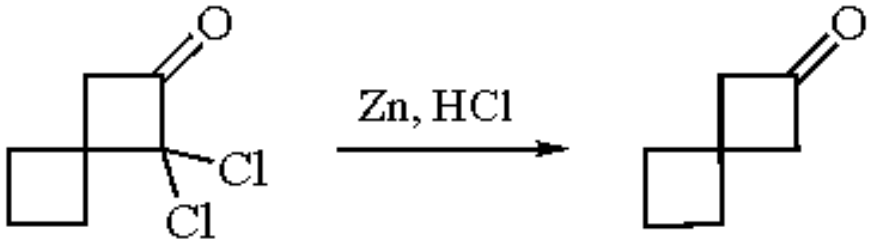

(31)

The dichlorocyclobutanones can easily be expanded or contracted, thereby providing a synthetic source of cyclopropanes or cyclopentanes. Reaction of diazomethane with the cycloadduct of cyclohexene and dichloroketene results in the formation of the corresponding cyclopentanone (eq 32).[36] These can undergo several reactions, including dehalogenation (eq 33),[36] reductive alkylation (eq 34),[37] and conversion to cyclopentenes (eq 35).[38,39]

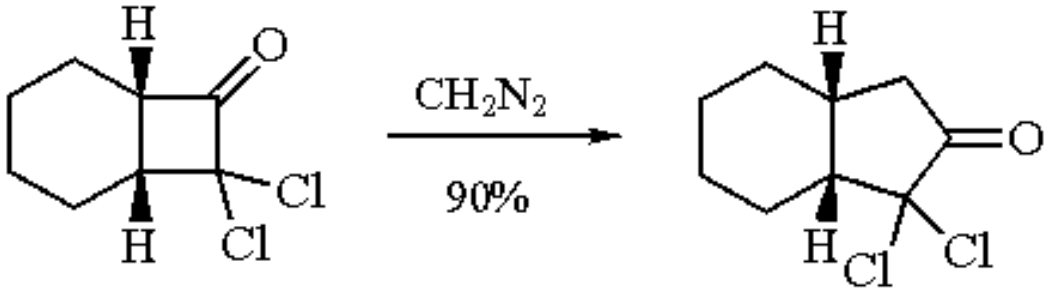

(32)

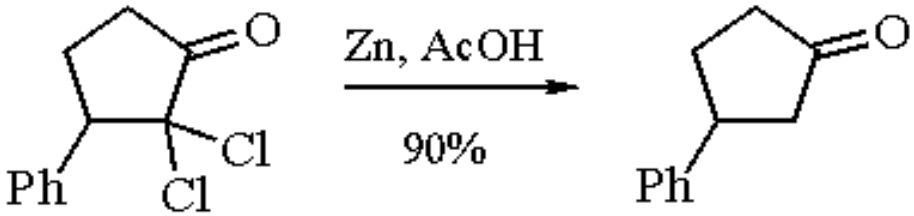

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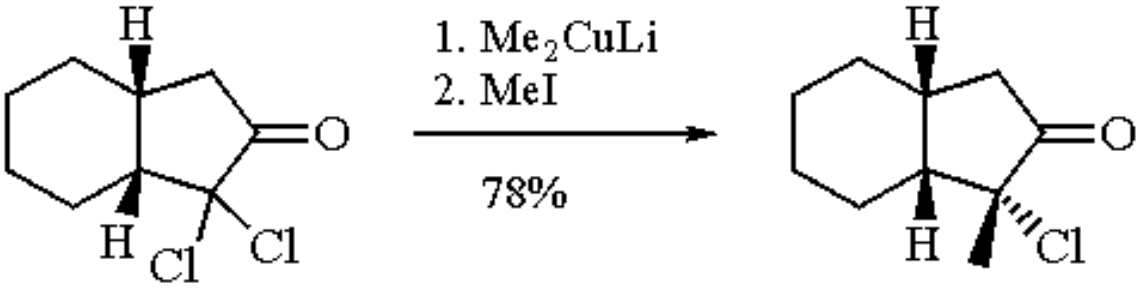

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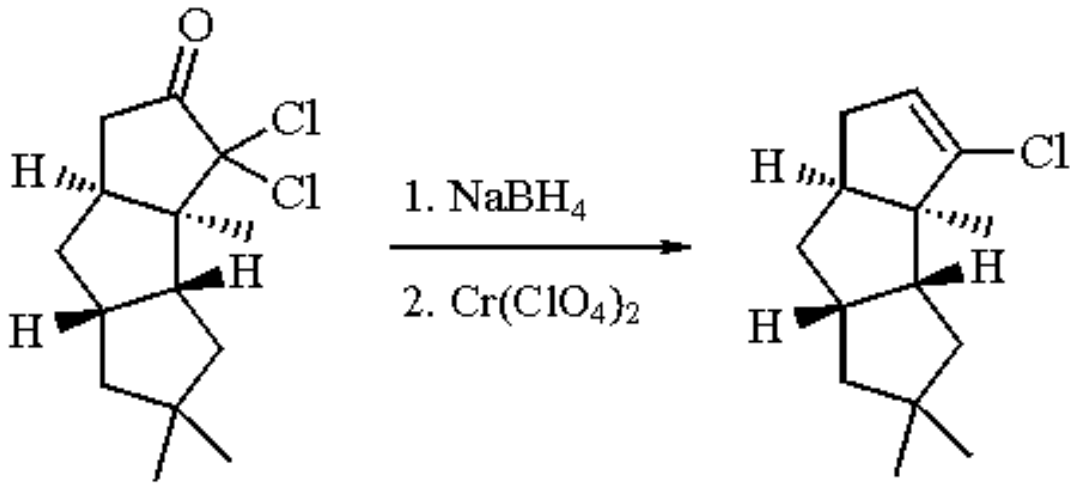

(35)

While these reactions are well precedented for the cyclopentanones, most are also amenable to the cyclobutanones.[1,3,4] Ring contractions of α-chlorocycloalkanones via Favorskii rearrangements are well known.[40] Direct exposure of dichloroketene cycloadducts to strong base, however, does not typically lead to ring contraction but rather to ring cleavage (eq 36).[41] One method that has been developed to circumvent this shortcoming is the reduction of the carbonyl of the cyclobutanone followed by treatment with base, which causes ring contraction to the corresponding cyclopropane carbaldehyde (eq 37).[42] Both *endo*- and *exo*-carbaldehydes can be made in this manner.[43]

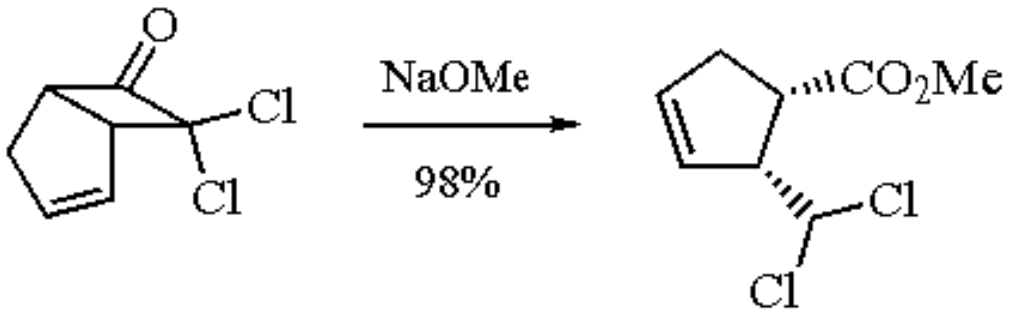

(36)

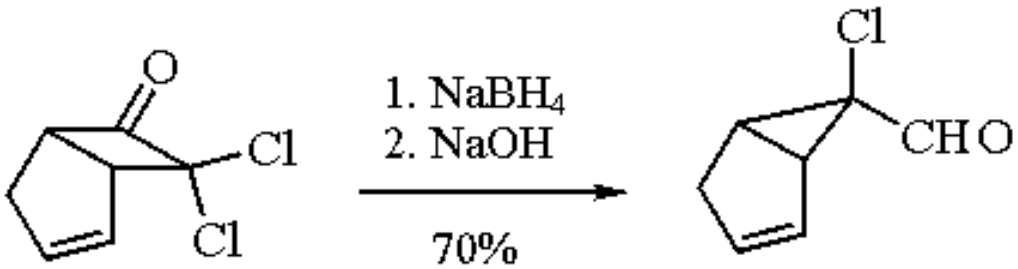

(37)

An alternative method of ring expansion is via oxidation. Baeyer-Villiger oxidation of the cyclobutanone adducts supplies a synthetic route to *cis*-bicyclic lactones (eq 38).[44] Ring expanded lactams can also be made, with migration of either of the alkyl substituents (eqs 39 and 40).[45]

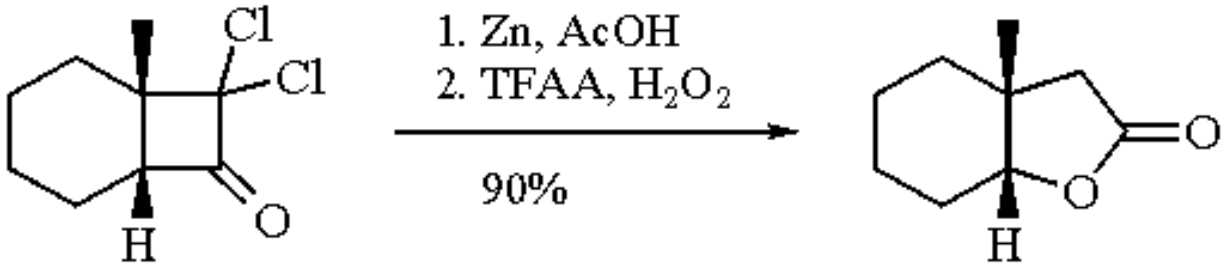

(38)

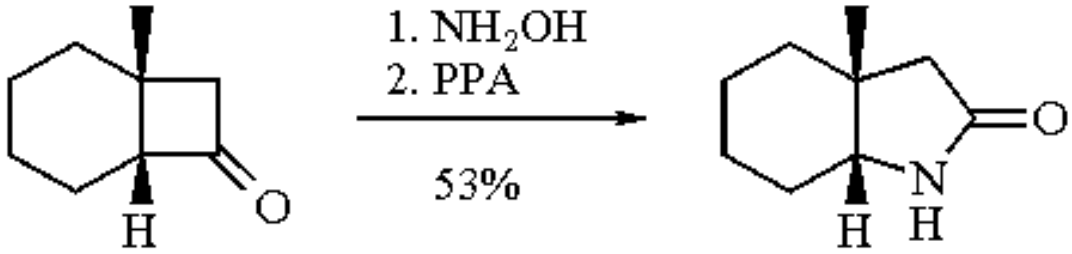

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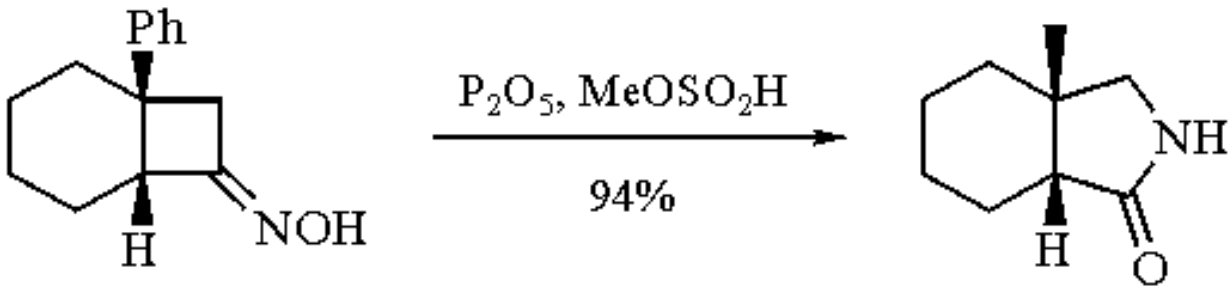

(40)

The dichlorocyclobutanones can be converted into several other useful materials. Following reductive removal of the chlorines, ***Selenium(IV) Oxide*** generates the 1,2-cyclobutanediones (eq 41).[46] Lithium-halogen exchange followed by acetylation of the enolate and ***Ruthenium(VIII) Oxide*** oxidation affords a one-pot conversion to vicinal dicarboxylic acids (eq 42).[47] In tandem with the cycloaddition of dichloroketene, this provides a mild and general method for *syn*-vicinal dicarboxylations. In a similar fashion, the α-chloroenol acetates can be isolated (eq 43).[48] Thermolysis of these compounds results in a retrocyclization reaction to give exclusively the (*Z*)-α-chloroenone (eq 44).[48]

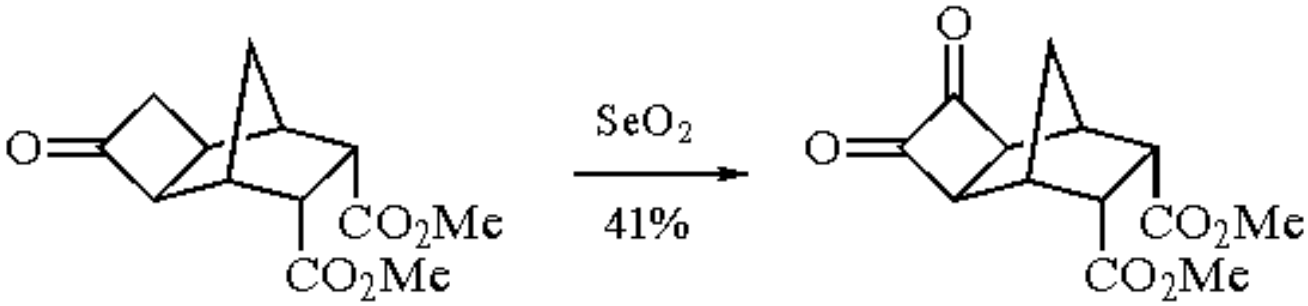

(41)

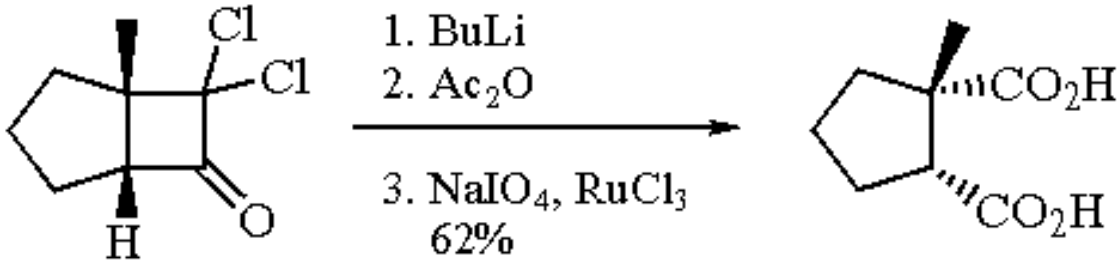

(42)

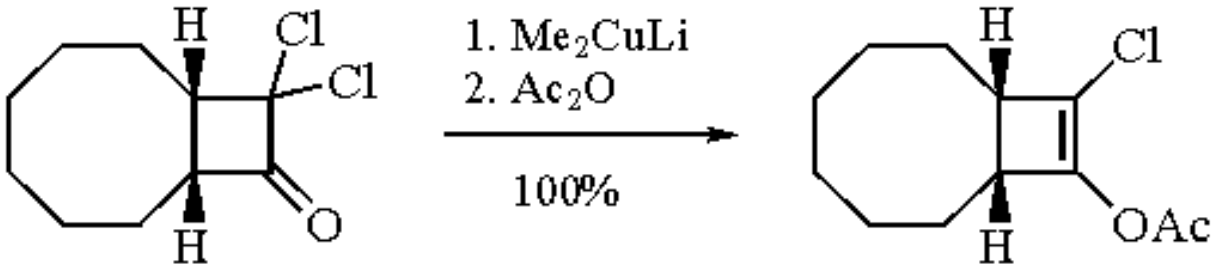

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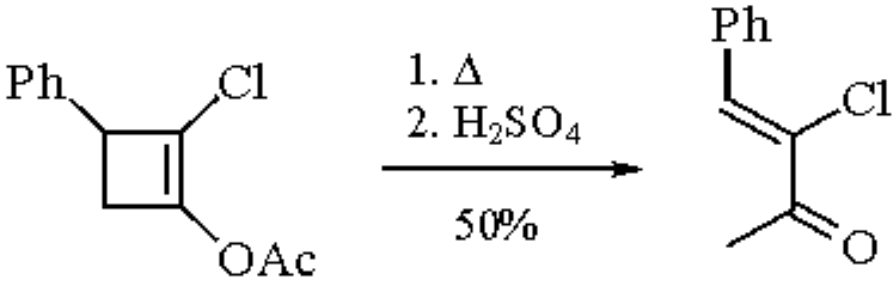

(44)

Related Reagents.

Chlorosulfonyl Isocyanate; ***Diiodomethane-Zinc-Titanium(IV) Chloride***; ***Trichloroacetyl Chloride***; ***Zinc/Copper Couple***.

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James W. Leahy

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Diisopropyl (Dichloromethyl)boronate[1]

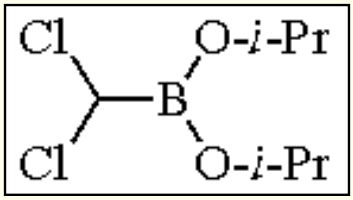

[63360-99-5] · $C_7H_{15}BCl_2O_2$ · Diisopropyl (Dichloromethyl)boronate · (MW 212.91)

(reacts with RLi to form α-chloroalkyl boronic esters;[2] chiral 1,2-diol ester derivatives react highly stereoselectively with RLi to form chiral α-chloroalkyl boronic esters[1])

Physical Data: bp 65 °C/10 mmHg,[2] 50-52 °C/5 mmHg;[3] *n*25D 1.4208.[2]

Form Supplied in: commercially available as pure liquid.

Preparative Method: addition of LDA to CH_2Cl_2 and triisopropyl borate in THF at -78 °C, then anhydrous HCl, filtration, and fractional distillation.[3]

Handling, Storage, and Precautions: is hydrolyzed to (dichloromethyl)boronic acid on contact with atmospheric moisture, and should be stored well sealed under nitrogen. It can be transferred and weighed in air without difficulty. The toxicity is unknown, but it should be regarded as a typical reactive alkyl halide.

Reagent Preparation.

The first preparation of diisopropyl (dichloromethyl)boronate was from preformed Cl_2CHLi, generated from BuLi and CH_2Cl_2 in THF at -100 °C, which was treated with $B(OMe)_3$ and worked up with aqueous acid and ether to yield crude (dichloromethyl)boronic acid, which was esterified with 2-propanol (60%).[2]

The most efficient method reported is the dropwise addition of ***Lithium Diethylamide*** to a vigorously stirred solution of CH_2Cl_2 and ***Triisopropyl Borate*** in THF with the internal temperature kept strictly below 0 °C with an ice-salt bath, followed by vacuum distillation of the diethylamine and THF, treatment with diethyl ether, anhydrous HCl, filtration under an inert atmosphere, and distillation of diisopropyl (dichloromethyl)boronate (69%) (eq 1).[3] The preparation works equally well at -78 °C with ***Lithium Diisopropylamide*** in place of $LiNEt_2$ (yield 70%), except that diisopropylamine is not as easily removed by distillation as diethylamine, and the voluminous amine salt is a nuisance to filter.

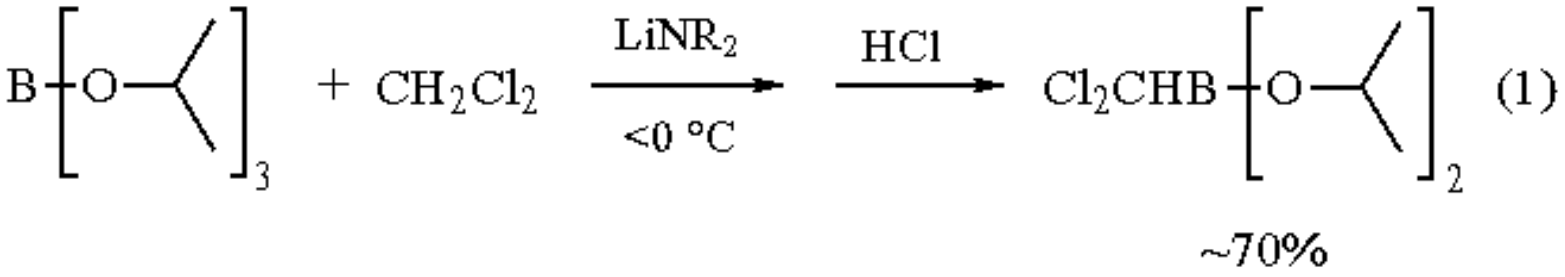

Diol Esters.

1,2-Diols or 1,3-diols react rapidly and irreversibly with diisopropyl (dichloromethyl)boronate[4,5] or (dichloromethyl)boronic acid.[2,6] For example, transesterification with (*R*,*R*)-2,3-butanediol readily yields [4*R*-(4α,5β)]-2-(dichloromethyl)-4,5-dimethyl-1,3,2-dioxaborolane (**1**) (eq 2).[4] The 1,3,2-dioxaborolanes can be purified by vacuum distillation,[2-6] and the (4*S*)-4,5-dicyclohexyl derivative can be recrystallized.[7]

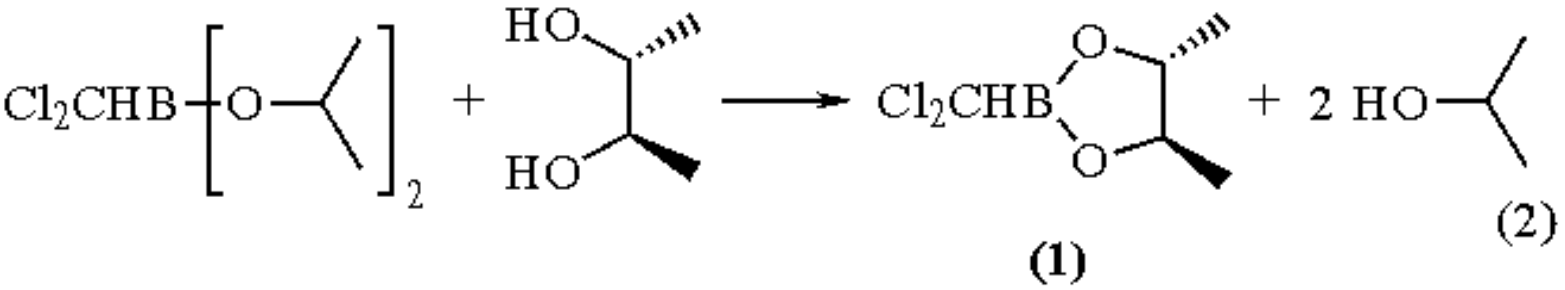

α-(Chloroalkyl)boronic Esters.

Diisopropyl (dichloromethyl)boronate reacts with organolithium reagents to form α-(chloroalkyl)boronic esters, which can be oxidized to aldehydes or treated with a second mole of RLi to form *s*-alkylboronic esters.[2]

1,3,2-Dioxaborolanes are generally easier to handle than diisopropyl boronic esters and have been employed in all of the more recent chemistry of this type.[1] For example, 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with vinylmagnesium chloride yields 2-(1-chloroallyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (eq 3).[8] The 2-(dibromomethyl) analog behaved similarly.[8]

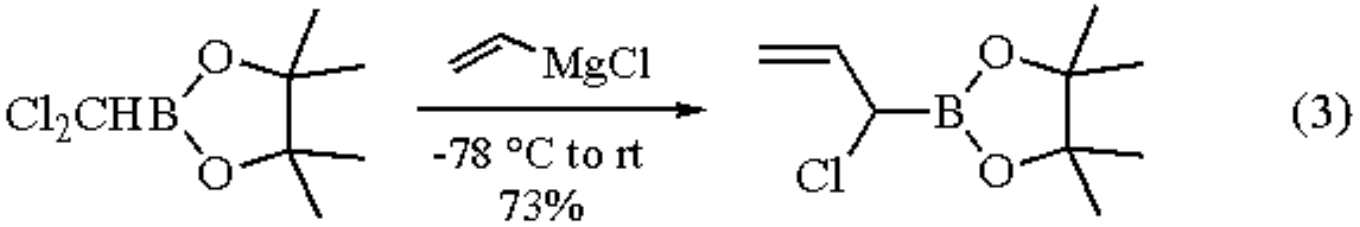

2-(Dichloromethyl)-1,3,2-dioxaborolanes and -1,3,2-dioxaborinanes have been reduced with ***Tri-n-butylstannane*** to the corresponding 2-chloromethyl derivatives,[5] though better routes to these compounds now exist (see ***Pinacol (Chloromethyl)boronate***).

The most useful 1,2-diol esters are those having C_2 symmetry, systematically named (4α,5β)-2-(dichloromethyl)-4,5-dialkyl-1,3,2-dioxaborolanes. With Grignard or lithium reagents these yield [2(*S**),4α,5β]-2-(1-chloroalkyl)-4,5-dialkyl-1,3,2-dioxaborolanes.[1,4] For example, [4*R*-(4α,5β)]-2-(dichloromethyl)-4,5-dimethyl-1,3,2-dioxaborolane (**1**) with ***n-Butyllithium*** yields intermediate borate (**2**), which rearranges at rt in the presence of ***Zinc Chloride*** to form {4*R*-[2(*S**),4α,5β]}-(1-chloropentyl)-4,5-dimethyl-1,3,2-dioxaborolane (**3**) (eq 4).[4] Diastereomeric excesses (de's) in this reaction as well as those with other lithium or Grignard reagents are generally ~90%.[4]

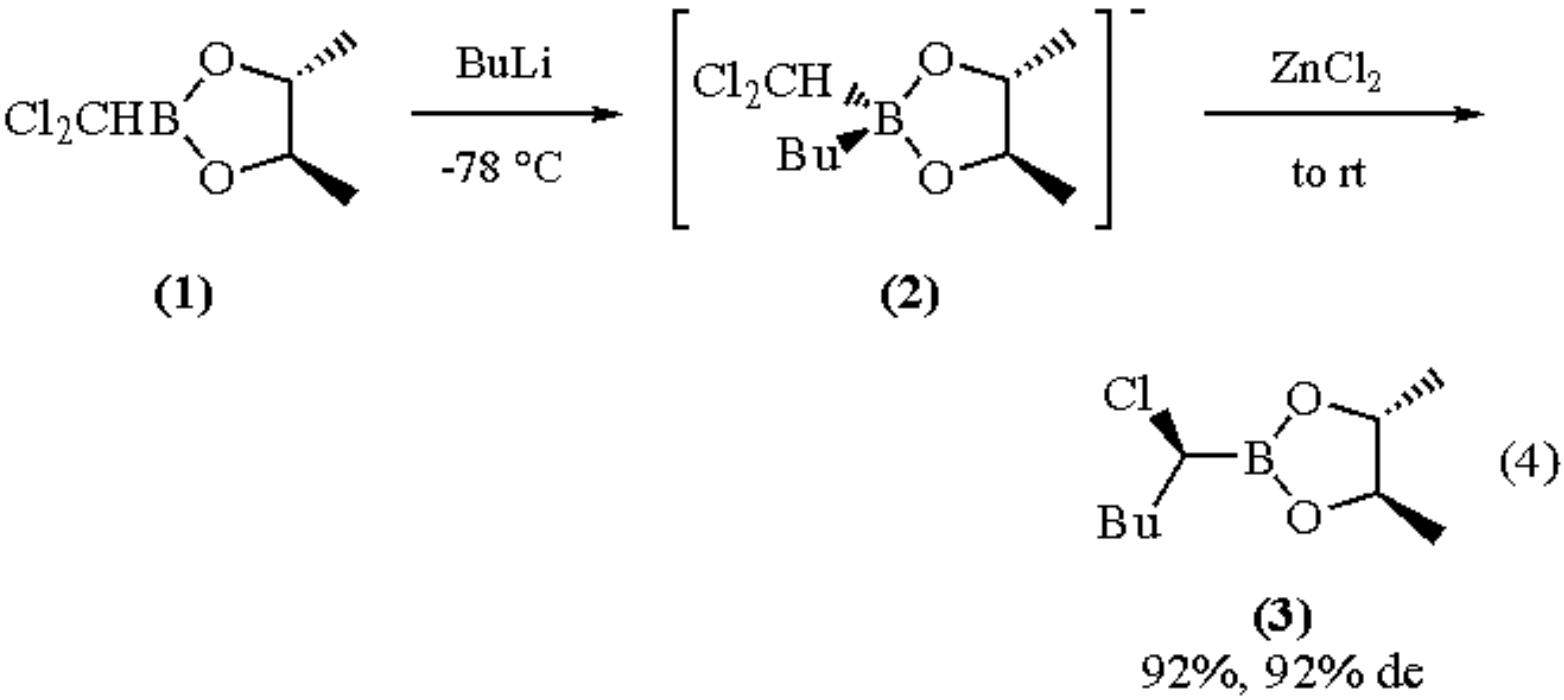

Higher stereoselectivities were obtained with larger 4,5-substituents on the dioxaborolane (eq 5). [4*S*-(4α,5β)]-4,5-Diisopropyl-2-(dichloromethyl)-1,3,2-dioxaborolane (**4a**) of ~95-98% ee and a series of Grignard or lithium reagents yielded (α*S*)-α-chloroethyl boronic esters (**5a**) in &egt;92-94% ee and de.[9] The measurement technique was inadequate to establish the true de's, which later work suggests may be 98-99% (see Alternative Route below).

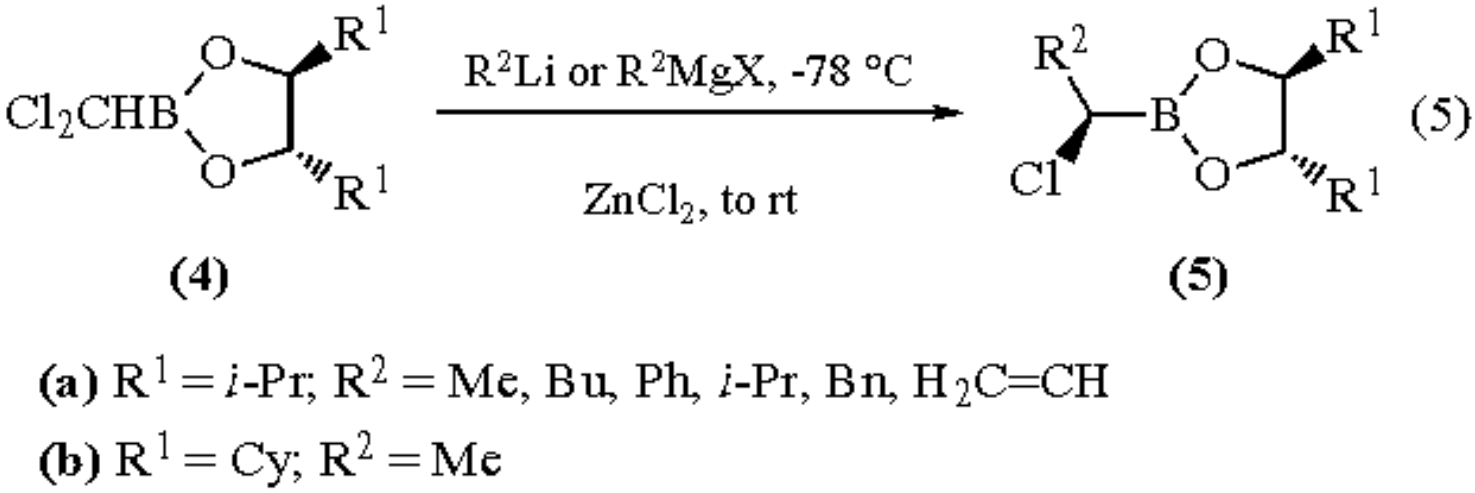

(a) $R^1 = i$-Pr; R^2 = Me, Bu, Ph, *i*-Pr, Bn, $H_2C{=}CH$

(b) R^1 = Cy; R^2 = Me

A higher de, &egt;99%, has been reported for conversion of [4*S*-(4α,5β)]-2-(dichloromethyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**4b**) via the (α*S*)-α-chloroethyl boronic ester (**5b**) (eq 5) to the (*Z*)-(α*R*)-α-methyl-2-butenyl boronic ester (**6**) (eq 6).[7]

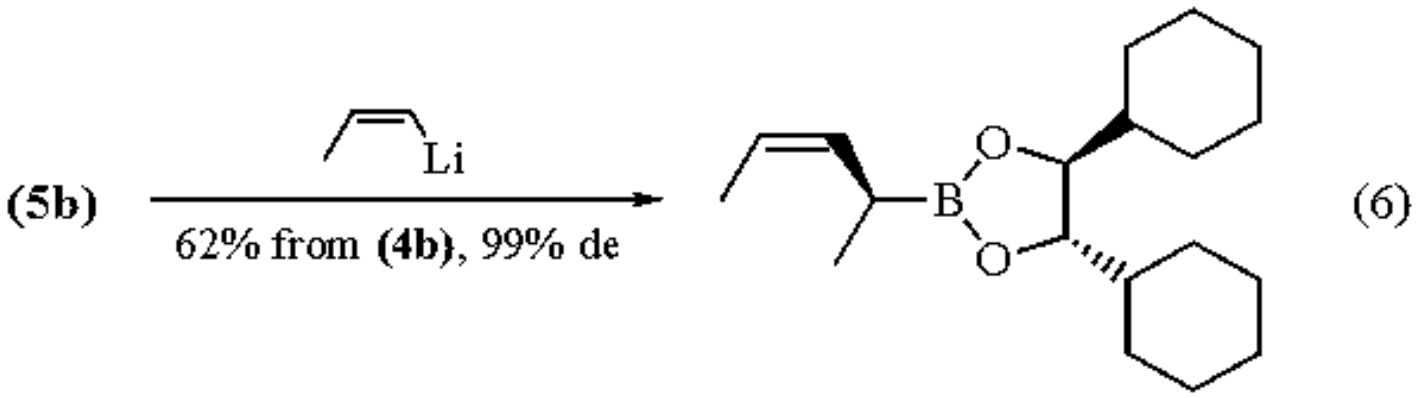

(6)

Limitations.

The more easily accessible 4,5-diphenyl analog of (**4**) does not yield satisfactory diastereoselection (62-72% de).[10] Problems have been encountered in the attempted utilization of this chemistry for the preparation of α-chloroallylic boronic esters. Although vinylmagnesium chloride with (**1**) yielded 73% of (α*S*)-α-chloroallylboronic ester of >82% de,[10] attempted use of 1-propenylmagnesium halides led to allylic rearrangement of the initially formed α-chlorocrotylboronic esters if zinc chloride was used or led to low de's if it was not.[11] An unrelated enantioselective synthesis of α-halocrotylboronic esters was devised.[11,12]

Alternative Route.

It is important to note that the C_2 symmetry of [4*R*-(4α,5β)]-2-(dichloromethyl)-4,5-dimethyl-1,3,2-dioxaborolane (**1**) makes both faces of the boron atom equivalent, and that there is only one diastereomer of the derived borate complex (**2**). Thus the mode of assembly of (**2**) does not matter, and the reaction of [4*R*-(4α,5β)]-2-butyl-4,5-dimethyl-1,3,2-dioxaborolane (**7**) with ***Dichloromethyllithium*** (eq 7) yields the same intermediate (**2**) as that from (**1**) and butyllithium in (eq 4) and produces (**3**) in similar yield and diastereomeric purity.[4]

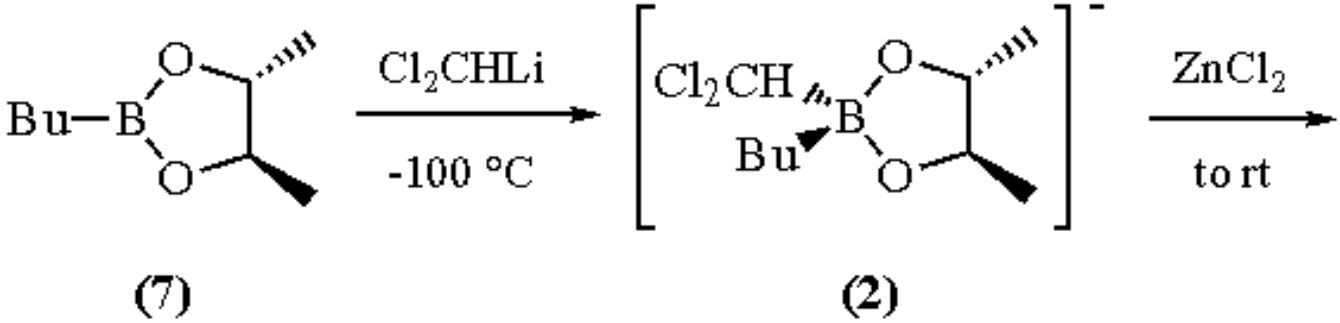

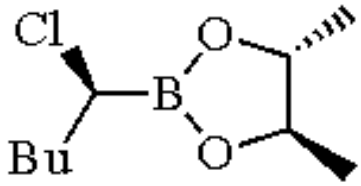

(7)

(3) 90% de

The use of [4*S*-(4α,5β)]-2-alkyl-4,5-diisopropyl-1,3,2-dioxaborolanes (**8**) in this alternative route has led to *s*-alkylboronic esters (**10**) of 99.8% de (eq 8).[13] It was shown that the de was enhanced in the reaction of the chloro intermediate (**9**) with R^2MgX. It should be noted that (**9**) (eq 8) is the same as (**5a**) (eq 5). In addition to the conversion of (**9**) to (**10**) by organometallic reagents, useful products are obtained from (**9**) with a variety of other nucleophiles.[1,14]

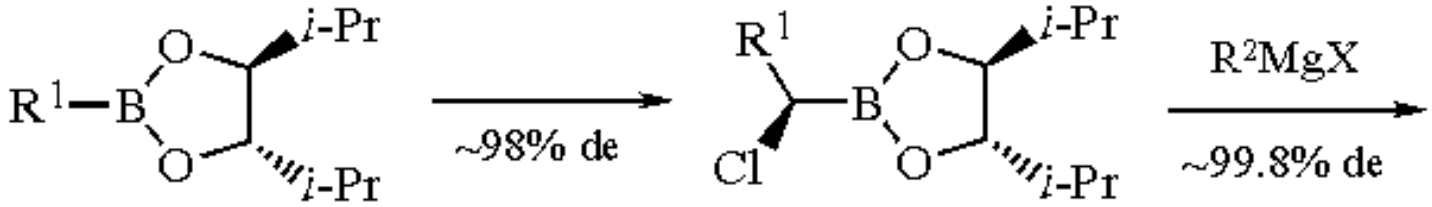

(8) **(9)**

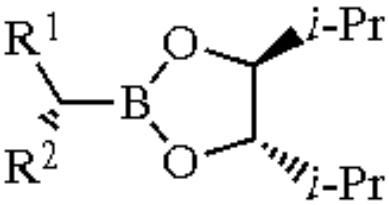

(8)

(10)

With chiral dioxaborolanes that lack C_2 symmetry, the two faces of the boron atom are nonequivalent, and entirely different results may be obtained depending on the route to the borate intermediate. Pinanediol derived from either enantiomer of α-pinene is a relatively inexpensive and effective chiral director. Reaction of dichloromethyllithium with (*S*)-pinanediol alkylboronates (**11**) leads to borates (**12**), which rearrange in the presence of zinc chloride to α-chloroalkylboronic esters (**13**) having de's in the 97-99% range (eq 9).[15] This chemistry provides a broadly useful method of asymmetric synthesis.[1,16]

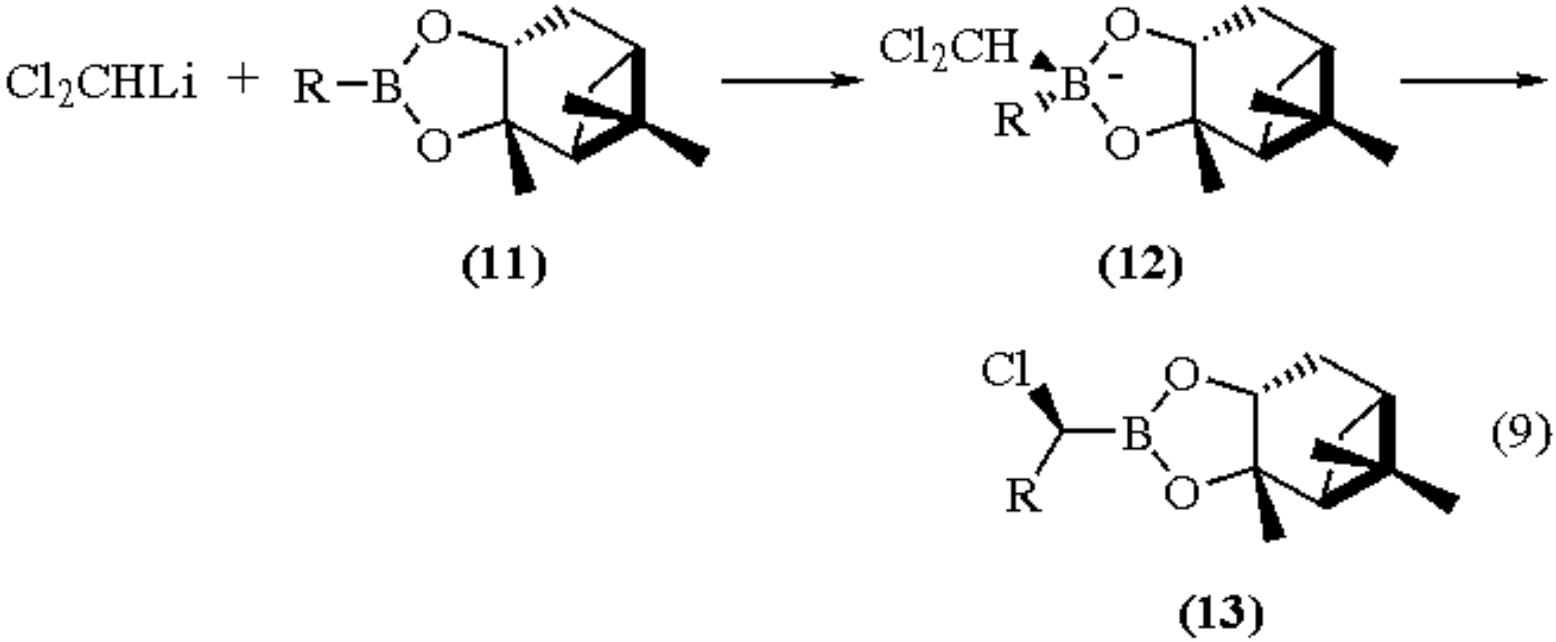

In contrast, reactions of pinanediol dichloromethylboronate (**14**) with alkylmagnesium halides yield borate intermediates (**15**) diastereomeric to (**12**), which rearrange to gross mixtures of diastereomers (**13**) and (**16**) (eq 10).[6] Accordingly, (**14**) is not useful for asymmetric synthesis.

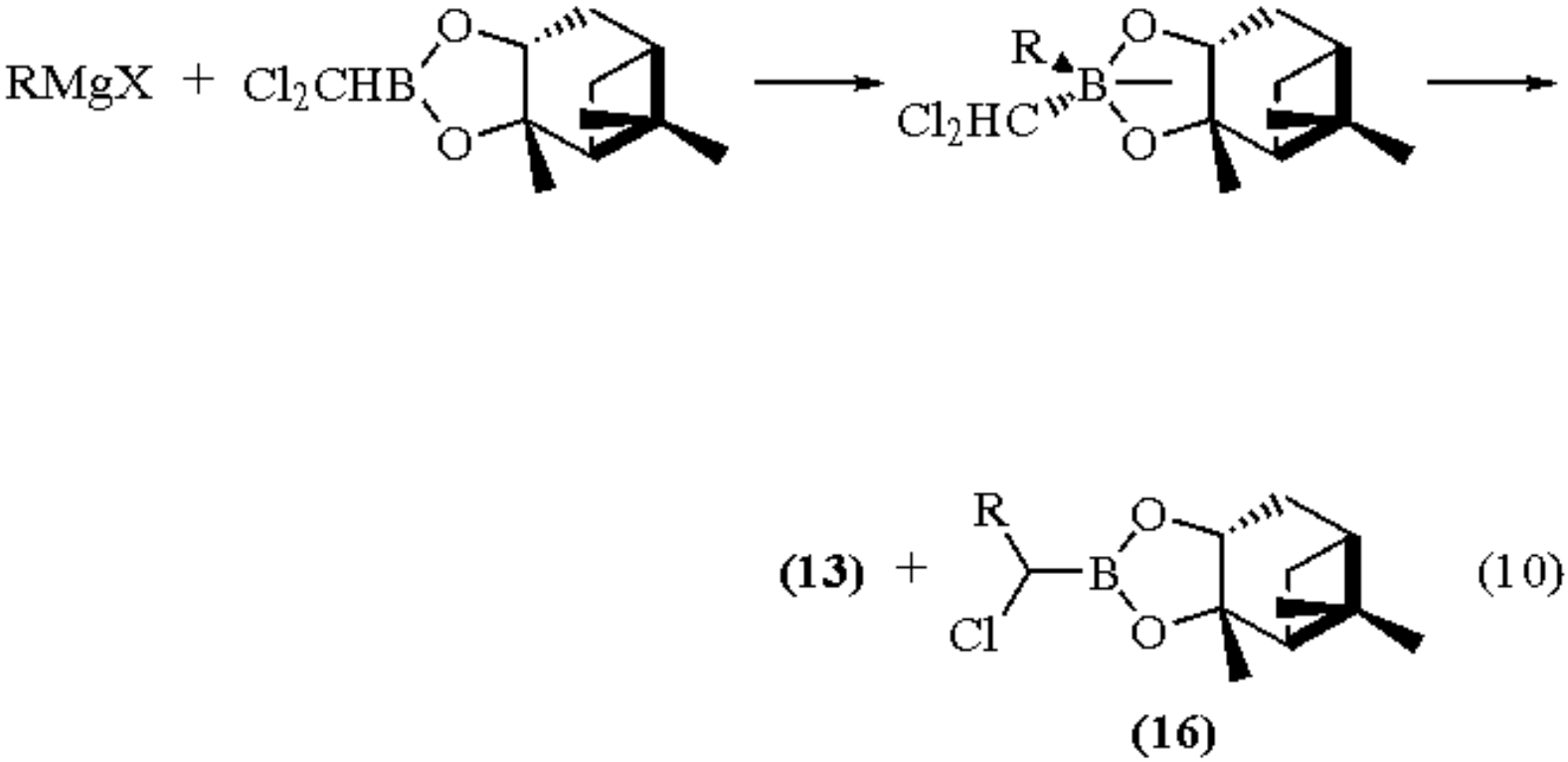

Dimethyl (1,1-dichloroethyl)boronate, $CH_3CCl_2B(OMe)_2$, has been prepared[3] and converted to the pinanediol ester.[17] Pinanediol (1,1-dichloroethyl)boronate does not yield useful asymmetric inductions, and the alternative route via pinanediol boronates (**11**) and (1,1-dichloroethyl)lithium did so only when R = Ph.[17] Pinanediol (1,1-dichloroethyl)boronate has been converted to the (1-chlorovinyl)boronate.[18]

Related Reagents.

Dichloromethyllithium; ***Pinacol (Chloromethyl)boronate***.

---

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N-Dichloromethylene-*N,N*-dimethyliminium Chloride[1]

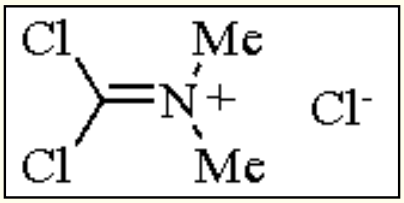

[33842-02-03] · $C_3H_6Cl_3N$ · *N*-Dichloromethylene-*N,N*-dimethyliminium Chloride · (MW 162.46)

(converts alcohols into halides;[5] useful in heterocycle synthesis;[20-22] reacts with active methylenes to afford α-chloroenamines[1,30])

Alternate Names: PI; phosgeniminium chloride.

Physical Data: mp ~186 °C (dec); 194-196 °C from acetonitrile (sublimation).[2]

Solubility: sol liquid SO_2, thionyl chloride (for NMR measurements), nitromethane, acetonitrile; sparingly sol chloroform, dichloromethane, and polychloroethanes; insol benzene, ether, toluene; THF and dioxane are slowly decomposed; protic solvents and DMSO react violently.

Form Supplied in: white solid, commercially available. Dimethylcarbamoyl chloride and complexed HCl may be present.

Analysis of Reagent Purity: hydrolysis and titration, NMR (CD_3NO_2) δ = 4.07 ppm.

Preparative Methods: chlorination of ***Dimethylthiocarbamoyl Chloride*** using ***Chlorine***,[1,2] ***Phosphorus(V) Chloride***,[2,3] ***Phosgene*** or ***Sulfuryl Chloride***.[1] When exposed to excess chlorine the title reagent forms a yellow complex, PI.Cl_2.[2,4] Dimethyldithiuram and dithiocarbamates are also cheap starting materials for the preparation of the reagent.[3,4]

Purification: washing with dry dichloromethane and drying on a rotary evaporator at 40-60 °C/12 mmHg.

Handling, Storage, and Precautions: moisture sensitive. In the absence of moisture, has a shelf life of a few years. The reaction apparatus should be flame dried. The hydrolysis product, dimethylcarbamoyl chloride, is reportedly mutagenic.

Reactions with Alcohols, Amines, and Thiols.

Alcohols are invariably converted to the corresponding alkyl halides since the intermediate alkoxychloromethyleniminium salts are unstable when treated with PI. With phenols and thiols, selective mono- and disubstitution are possible.[5-7] Diols lead to cyclic iminium carbonates, which are opened by the chloride counterion in a strictly S_N2 fashion. This has important implications in carbohydrate chemistry. One free hydroxy group is replaced stereo- and regioselectively by a chlorine atom, leading to chlorodeoxy sugars. *Vic*-diols form iminium carbonates, which give chloro-*O*-carbamoyldeoxy sugars in a selective fashion (eq 1).[8]

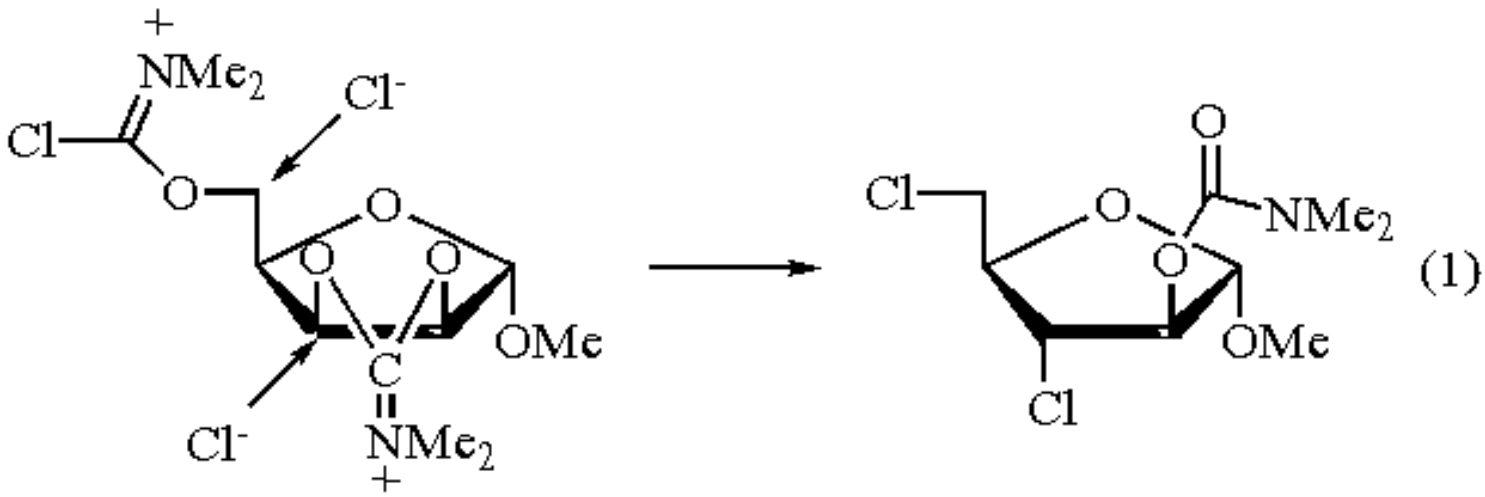

Bromodeoxy sugars are available on treatment with the PI-$FeCl_3$ complex and subsequent addition of ***Lithium Bromide***.[9] Recent developments have been detailed by Copeland[10] and Benazza.[11] Carboxylic and even sulfonic acids are converted smoothly to the corresponding chlorides.[1] ***Hydrogen Selenide*** affords *N*,*N*-dimethyldiselenocarbamate, which may be converted to 1,3-diselenolium salts, the starting materials for selenafulvalene-type organic conductors (eq 2).[12]

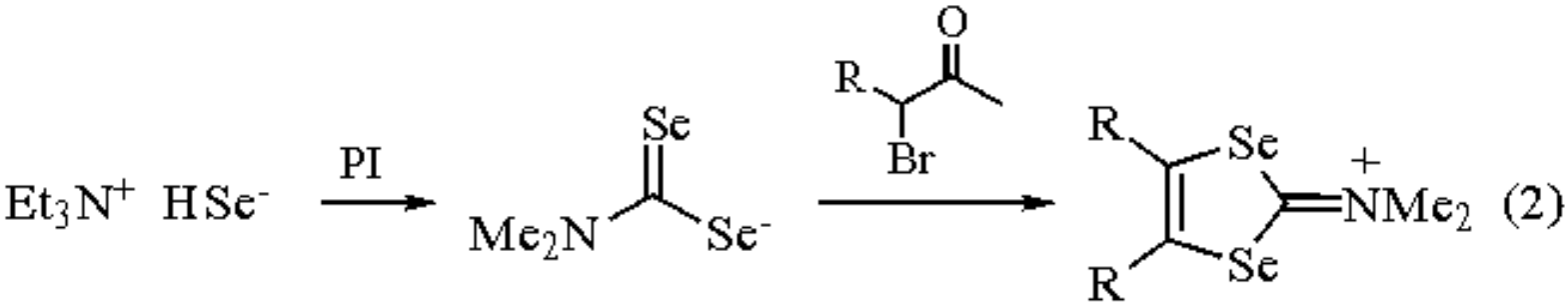

The reagent even reacts with unreactive primary and secondary amines, e.g. tosylamides,[13] to give the corresponding chloroformamidines or chloroformamidinium salts.[1]

Primary enamines react both at the nitrogen and at the nucleophilic carbon atom, thereby forming versatile azapentamethine cyanines (eq 3).[14]

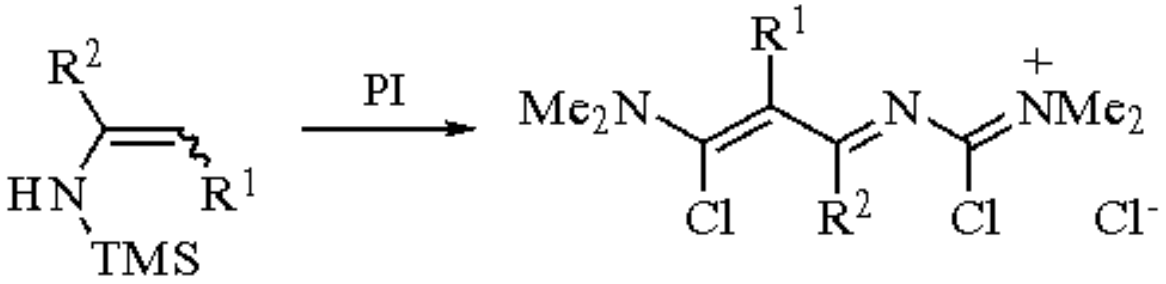

(3)

Substituted nitriles lead, in the presence of HCl, to analogous compounds (R = Cl).[15] Dimethylcyanamide adds smoothly to PI giving 1,3-dichloro-2-azatrimethine cyanines, which have found widespread use in heterocyclic synthesis (eq 4).[1,16] Carbodiimides form nonconjugated adducts (eq 5).[17]

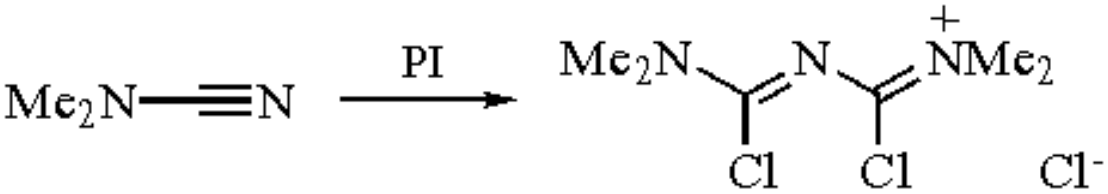

(4)

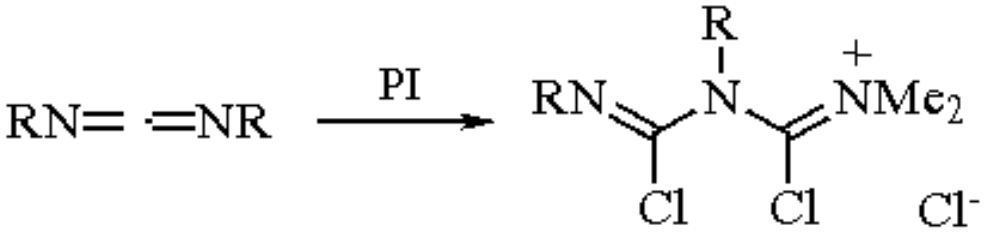

(5)

Chloroazidoiminium salts are obtained from PI and ***Azidotrimethylsilane***.[18] They transfer a diazonium group to nucleophilic aromatic substrates, whereas diazo transfer occurs with activated methylene compounds.[19]

Heterocycle Synthesis.

PI salts have almost unlimited potential in heterocyclic chemistry, readily forming cyclic systems with 1,4- and 1,5-bisnucleophilic compounds (eqs 6-8).[20-22]

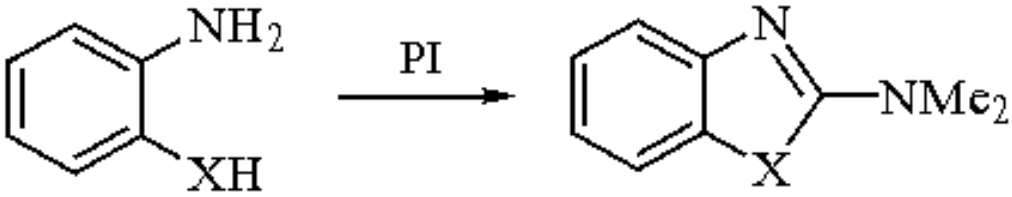

X = O, N, S

(6)

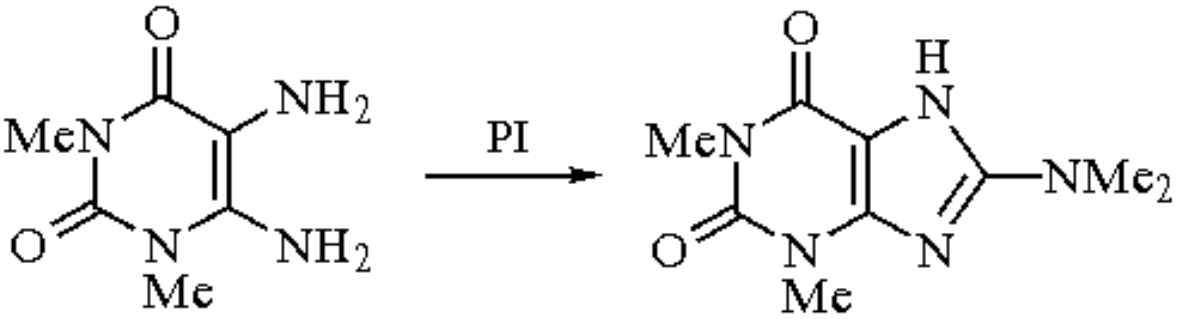

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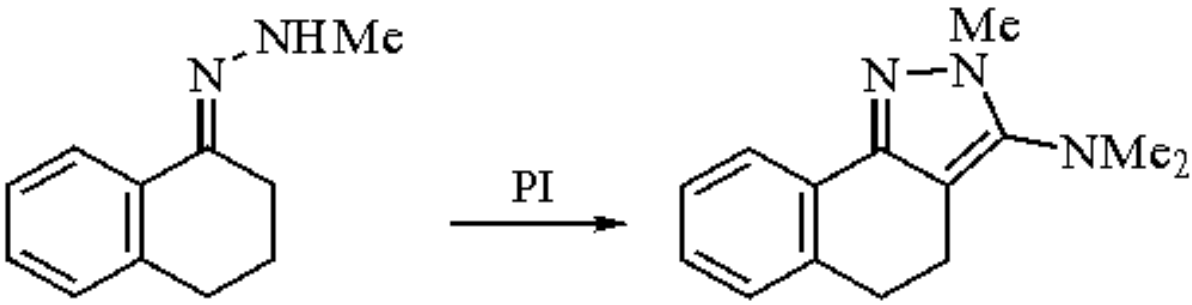

(8)

Ester or cyano groups (after prior addition of HCl) can also act as nucleophiles (eqs 9 and 10).[23,24]

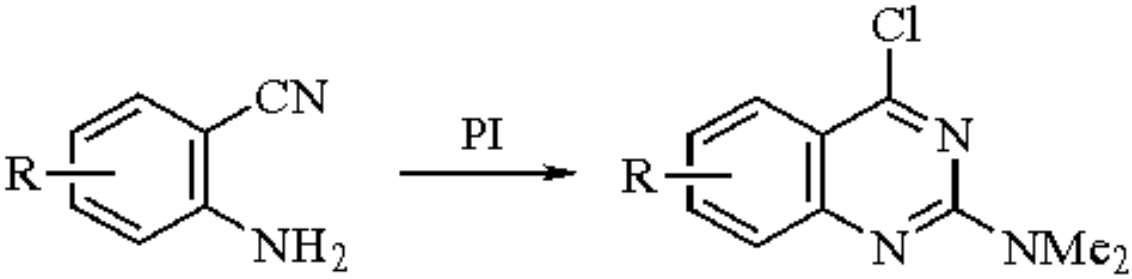

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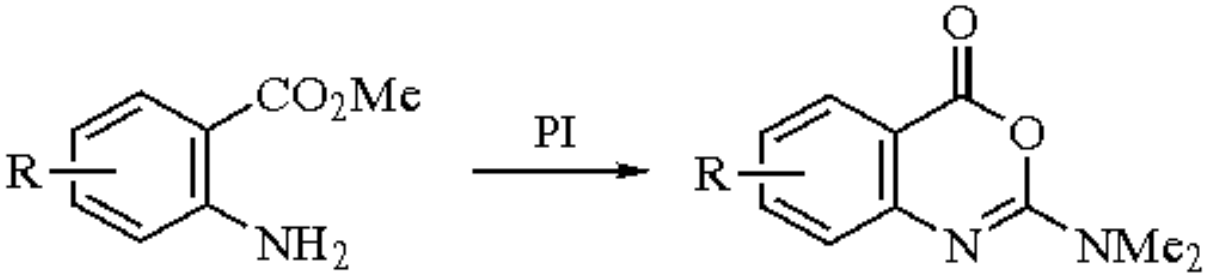

(10)

ortho-Hydroxybenzonitriles lead, after hydrolysis, to 2-dimethylamino-1,3-benzoxazines.[25] Aliphatic enamino esters and nitriles react completely analogously to their aromatic counterparts (eq 11).[26,27]

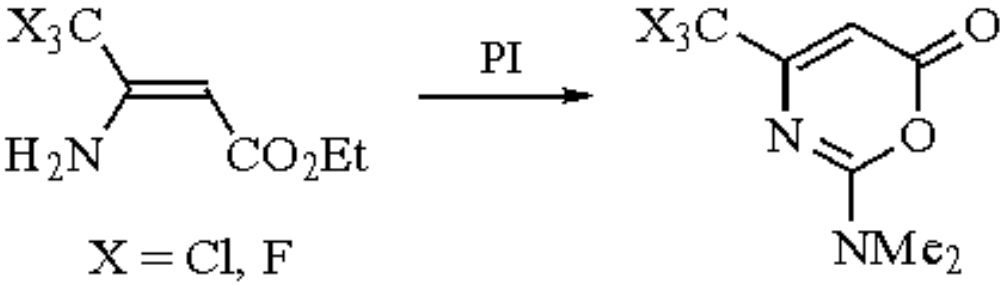

(11)

Reactions with Carbon Nucleophiles.

Ketones react smoothly with PI in refluxing chloroform to form the corresponding chlorides of 3-chloroacrylamides (eqs 12 and 13).[1]

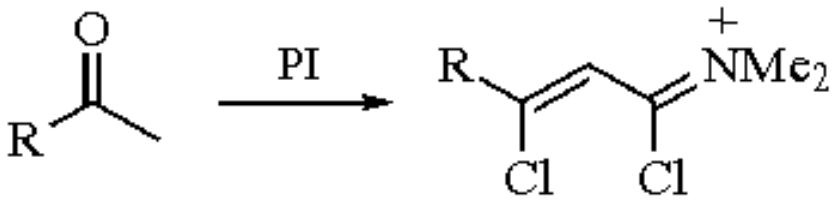

(12)

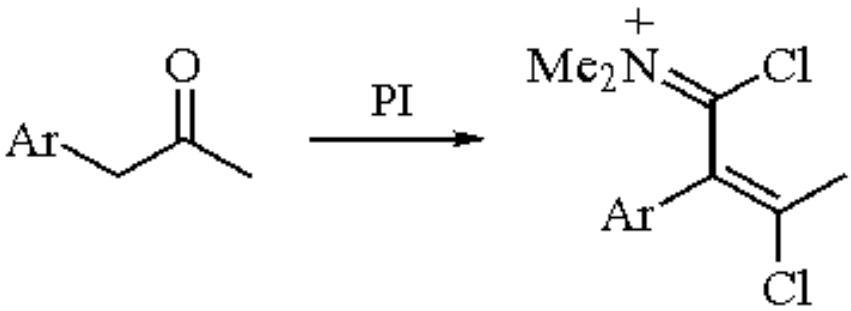

(13)

Cyclic ketones react too, but the reagent is very sensitive to steric hindrance. Aliphatic ketones (e.g. acetone) lead to complicated mixtures. Acid chlorides probably react via ketene intermediates, affording α-chloro-β-chlorocarbonylenamines.[28] Diphenylketene leads to 4,4-dichloroazetidin-2-one.[28]

Only very activated (hetero) aromatics undergo *C*-acylation with PI. Thus 1,3-dimethoxybenzene is acylated, generating the corresponding amide chloride, which can be hydrolyzed to the amide or, interestingly, thermolyzed to the nitrile (eq 14).[29] In this manner, PI can be considered as a $[CN]^+$ equivalent. Similar chemistry is observed with electron-rich indoles[29] and pyrroles.[30]

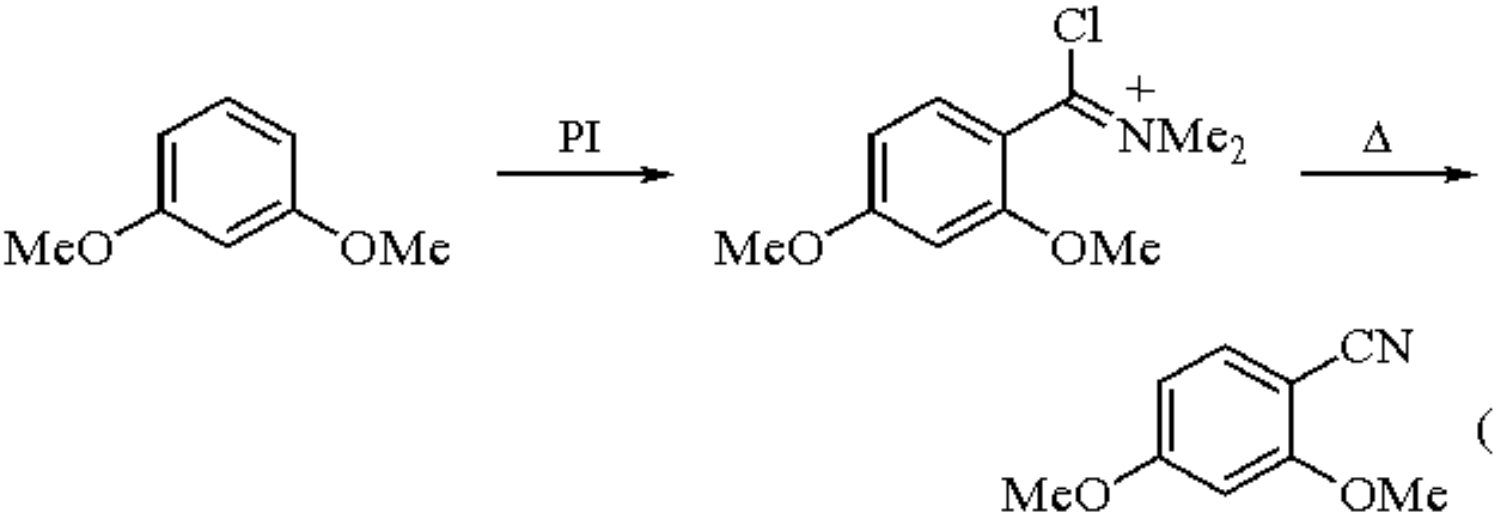

(14)

Activated methylene groups condense readily with PI to form push-pull α-chloroenamines.[1,30] This transformation is also successful for vinylogous methyl and methylene groups in ethylidene malononitriles and cyanoacetates (eq 15).[31]

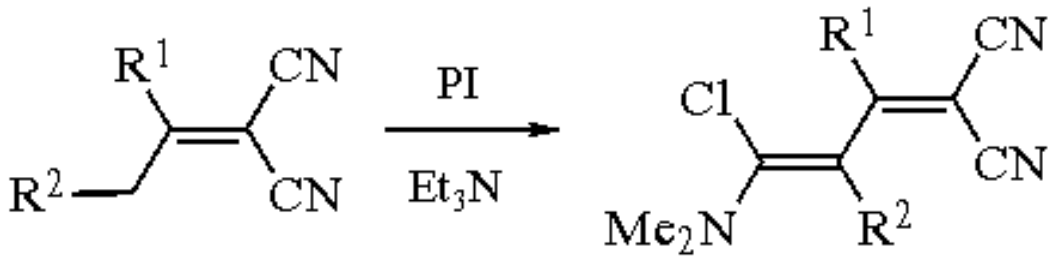

(15)

Cyanoacetate condensation products cyclize spontaneously to aminocyanopyrones, via attack by the ester group.[31] Tricyanomethane reacts at the cyano nitrogen.[32]

Enamines react readily with PI to give trimethine cyanines.[1] Vinylogous aminofulvenes undergo attack on the cyclopentadiene moiety.[33] 1,2,3,4-Tetrachloro-1,3-cyclopentadiene[34] and 4,5-dichlorocyclopent-4-ene-1,3-dione[35] afford the corresponding chlorodimethylaminofulvene and fulvenequinone, respectively.

As a reasonably strong chlorinating agent, PI transforms tertiary amides into amide chlorides. Substituted acetamides react further to give the very versatile 1,3-dichlorotrimethine cyanines (eq 16).[36] Vinylogous acetamides (e.g. crotonamide) react as well (eq 17).[30,37] This reaction does not occur when R is a strong electron-withdrawing group (e.g. NO_2, ester, CF_3). Tertiary lactams produce unsymmetrical trimethine cyanines.[1,30,38]

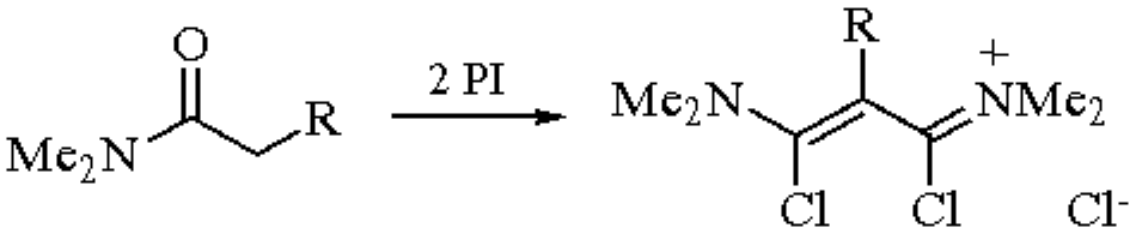

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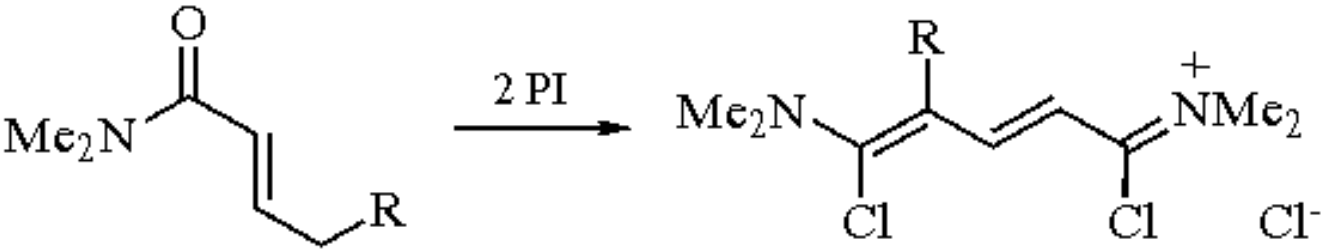

(17)

Secondary acetamides (or ketenimines) lead to versatile *N*-α-chlorovinyl chloroformamidinium salts (eq 18).[1,39]

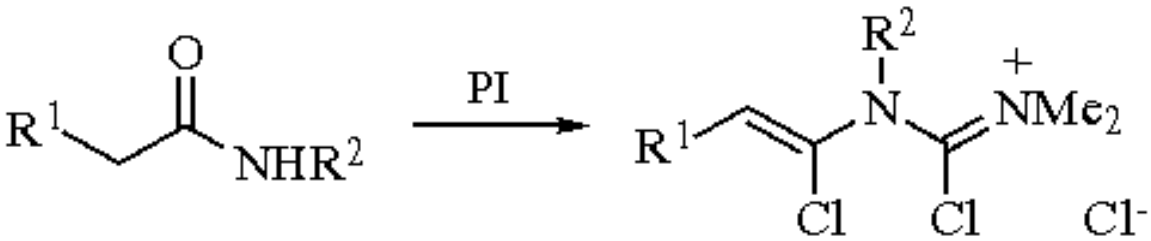

(18)

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Dichloromethylenetriphenylphosphorane[1]

$Ph_3P{=}CCl_2$

[6779-08-4] · $C_{19}H_{15}Cl_2P$ · Dichloromethylenetriphenylphosphorane · (MW 345.21)

(Wittig reagent for the formation of 1,1,-dichloroalkenes from aldehydes and ketones)

Physical Data: yellow powder, mp 115 °C (dec).

Solubility: sol THF and ether; insol hydrocarbons; reacts with acidic protons.

Handling, Storage, and Precautions: the ylide is generally prepared in situ and used immediately, but the solid can be stored under N_2 for several days. It reacts with air, water, or other acidic protons.

Preparation of the Ylide.

The dichloromethylene Wittig reagent can be prepared in three different ways:

- 1)reaction of Ph_3P with dichlorocarbene (generated from base and $CHCl_3$);
- 2)reaction of Ph_3P with CCl_4 or $BrCCl_3$;
- 3)deprotonation of the phosphonium salt $Ph_3{+}PCHCl_2\ X^-$ with strong base.

Preparation from Phosphines and Dichlorocarbene.

Dichloromethylenetriphenylphosphorane was first prepared by generation of dichlorocarbene (from ***Chloroform*** and ***Potassium t-Butoxide***) in the presence of ***Triphenylphosphine*** (eq 1).[2] Under these conditions, dichlorocarbene is immediately trapped by the phosphine to give the ylide as a suspension in heptane. This method has been used to transform aliphatic[2,3] and aromatic[2,4] aldehydes and ketones to the corresponding dichloroalkenes in yields of 50-80%. For best results the *t*-butanol formed during ylide generation should be removed by vacuum distillation prior to carbonyl condensation.[4]

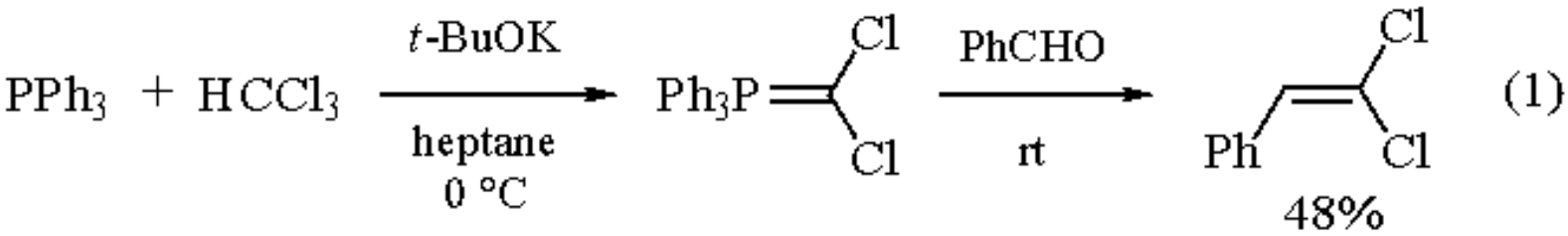

Preparation from Phosphines and Tetrahalomethane.

The most popular method for synthesis of dichloromethylenetriphenylphosphorane is the reaction of Ph_3P with a large excess of CCl_4 in the presence of a carbonyl compound.[5] The ylide is formed in situ and reacts with the substrate to give dichloroalkenes (eq 2).[6] Recent improvements include the use of $BrCCl_3$ in place of carbon tetrachloride[7,8] and acetonitrile as solvent.[9]

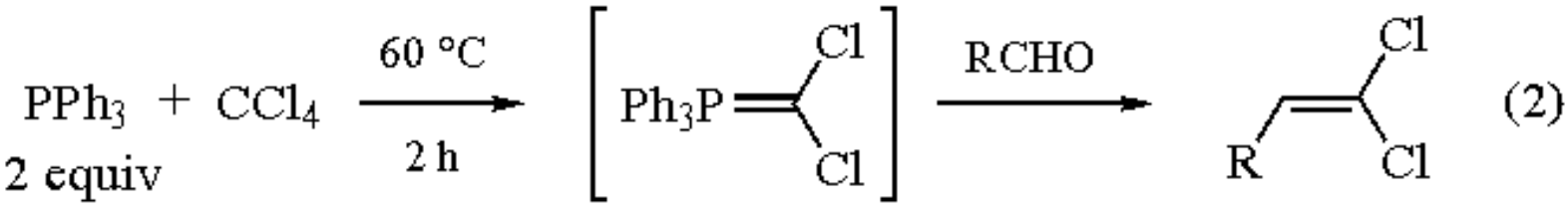

Aldehydes,[5,10] ketones,[5,9] and keto esters[9] react under these conditions to give good yields of the $R_2C{=}CCl_2$ products. A useful variation of the reaction used ***Hexamethylphosphoric Triamide*** in place of triphenylphosphine,[8,11] although under these conditions certain ketones did not react.[8] Synthetic applications of the ylide include preparation of steroid derivatives[8,10] and insecticide analogs.[12,13]

Preparation from Phosphonium Salt and Base.

The dichloromethyltriphenylphosphonium salt has been prepared from triphenylphosphine and $BrCHCl_2$[2] or more simply from reaction of 2 equiv Ph_3P with CCl_4 in the presence of a small amount of water (eq 3).[14] Only a few Wittig reactions have been reported for the ylide formed by phosphonium salt deprotonation. Treatment of the salt with ***Sodium Hydride*** in THF gave the dichloro ylide, which was then used to convert a 4-substituted cyclohexanone into the dichloromethylene derivative in 57% yield (eq 4).[9] When phenyllithium was used to form the ylide, reaction with benzophenone did not afford any of the expected dichloroalkene.[2]

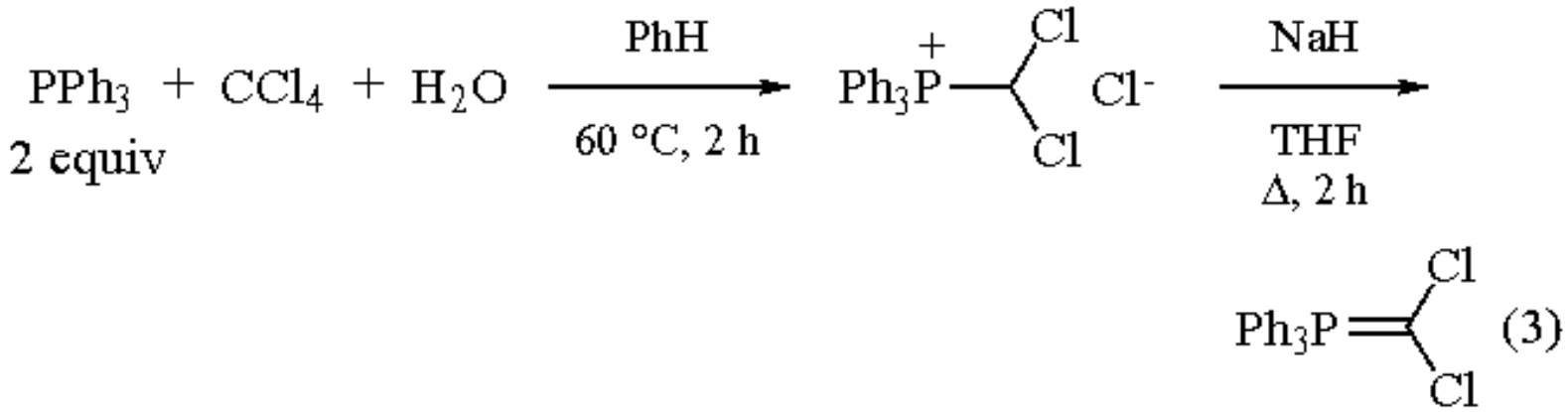

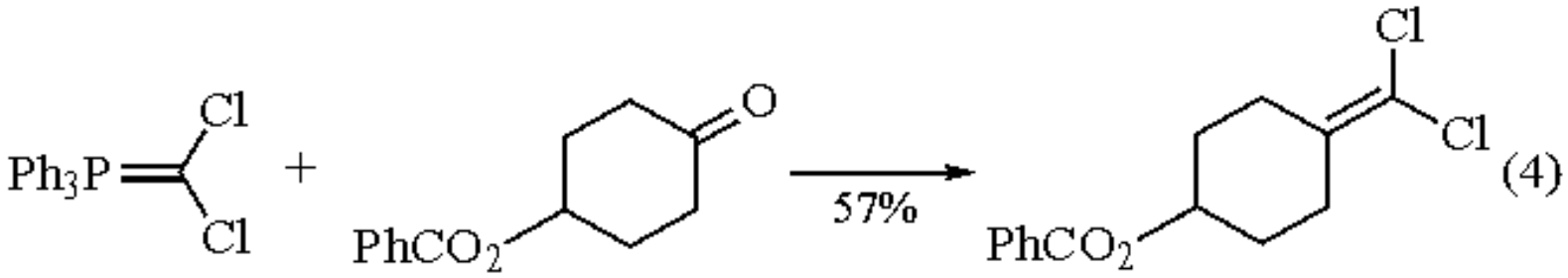

Alternatives to the Wittig reaction for the formation of dichloroalkenes from carbonyl compounds include the Horner-Emmons reaction of Cl-substituted phosphonate anions,[15] and a unique example of the Peterson alkenation reaction[16] using the lithium anion of TMS-$CHCl_2$. The above reactions generally use aldehydes or ketones as substrates; Wittig reaction of other carbonyl compounds such as esters with this ylide have not been reported. For an example of alkenation with a lactone, see Chapleur.[11]

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Dichloromethyllithium

$LiCHCl_2$

[2146-67-0] · $CHCl_2Li$ · Dichloromethyllithium · (MW 90.87)

(reagent used for chlorocyclopropanation, nucleophilic dichloromethylation, ring expansion, α-chloro aldehyde preparation, α-hydroxy aldehyde preparation, chain homologation)

Physical Data: low temperature ^{13}C and ^{6}Li NMR data are available,[1] as are matrix IR data.[2]

Preparative Methods: solutions of the title compound can be obtained by treatment of CH_2Cl_2 with ***n-Butyllithium*** in THF/ether/pentane (4:1:1) at -110 °C for 20 min;[3] alternate conditions include *n*-BuLi-***N,N,N´,N´-Tetramethylethylenediamine*** as the base in ether/THF (60:40) for 1 h at -90 °C.[4] One may also deprotonate CH_2Cl_2 with amide bases at -100 to -78 °C.[5]

Handling, Storage, and Precautions: the reagent is generally stable from -110 to about -80 °C, depending on the solvent. There is evidence that carbenoids of this nature show greater thermal stability in THF than in ether.[6] Solutions of $LiCHCl_2$ in THF/ether mixtures of greater than about 20% (v/v) THF are quite stable for ~20 h at -74 °C.[6a] Further, transmetalation with ***Titanium Tetraisopropoxide*** is reputed to give a reagent with greater thermal stability,[6e] although subsequent reports confirming this have not appeared.

General Considerations.

Alkyllithiums bearing halogens on the α-carbon are frequently referred to as carbenoids, reflecting a major mode of reactivity. Good general reviews of such species are available.[7] At very low temperatures, however, the reagent reacts like a typical alkyllithium. The reactivity of $LiCHCl_2$ is mirrored by ***Dibromomethyllithium*** in many respects. It is noteworthy that $LiCHCl_2$ has been used as a base in the generation of other carbenoids, including $LiCHBr_2$.[8]

Cyclopropanations.

Unlike the carbenoids $LiCHBr_2$, ***Tribromomethyllithium***, and ***Trichloromethyllithium***, $LiCHCl_2$ has not been reported as a general precursor to chlorocarbene for use in cyclopropane synthesis. An apparently noncarbenic bromocyclopropanation of fulvenes has been described by Grohmann.[9] When ***Lithium Diisopropylamide*** was slowly added to a THF solution of a fulvene and CH_2Cl_2 at -75 °C followed by slow warming to 0 °C, a mixture of *cis*- and *trans*-halospiro[2.4]heptadienes was formed (eq 1).

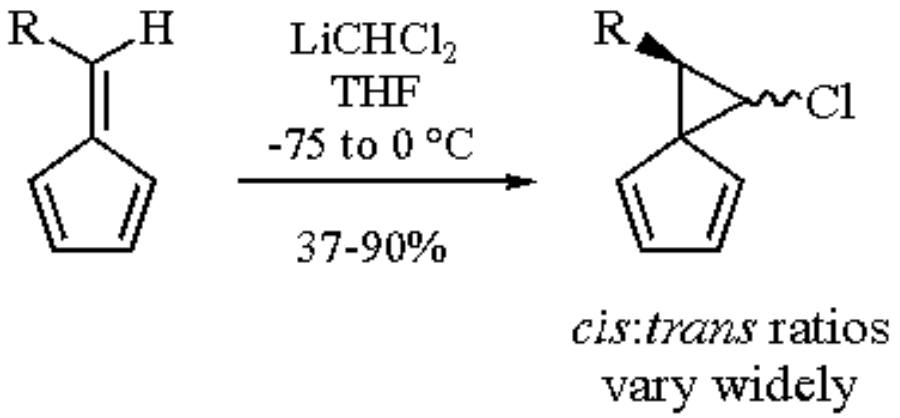

(1)

Alternatively, $LiCHCl_2$ may be preformed and the fulvene added slowly at -95 °C. Evidence indicates a nucleophilic addition-displacement mechanism as opposed to a carbene reaction. A related reaction involving ring enlargement of silacycles has also been reported.[10]

Nucleophilic Dichloromethylation Reactions.

$LiCHCl_2$ is an excellent reagent for incorporating the dichloromethyl group into molecules via nucleophilic displacement and addition reactions. Alkylation of primary alkyl halides proceeds well (eq 2).[4,11] The reaction of the terminal dichlorides with 3 equiv of *n*-BuLi/THF at -30 to -40 °C results in production of the terminal alkynes in good yield (eq 3).

$$\text{R-X} + LiCHCl_2 \xrightarrow[\text{TMEDA or HMPA}]{\text{THF, ether}} RCHCl_2 \qquad (2)$$

R-X	% yield	
$3\text{-}ClC_6H_4CH_2Br$	62	
$C_{12}H_{25}Br$	92	
$Cl(CH_2)_3Br$	89	(Br displaced)
$PhCH{=}CHCH_2Br$	70	
Et_2CHCH_2I	55	

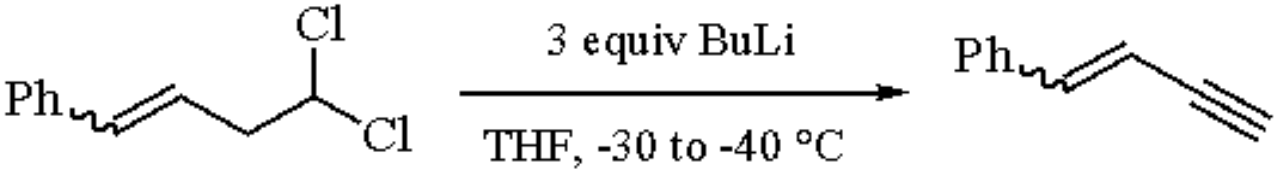

(3)

Carbonyl addition reactions are also quite facile. As with other α-haloorganolithiums, $LiCHCl_2$ may be generated by

deprotonation with lithium dicyclohexylamide in the presence of aldehydes and ketones to subsequently provide polyhalomethylcarbinol adducts in excellent yield (eq 4).[12] The adducts may be trapped in situ by ***Chlorotrimethylsilane*** to provide silyl ethers[13] which serve as precursors to terminal dichloroalkenes on treatment with *n*-BuLi in THF/ether/petroleum ether at -110 °C (eq 5).[14]

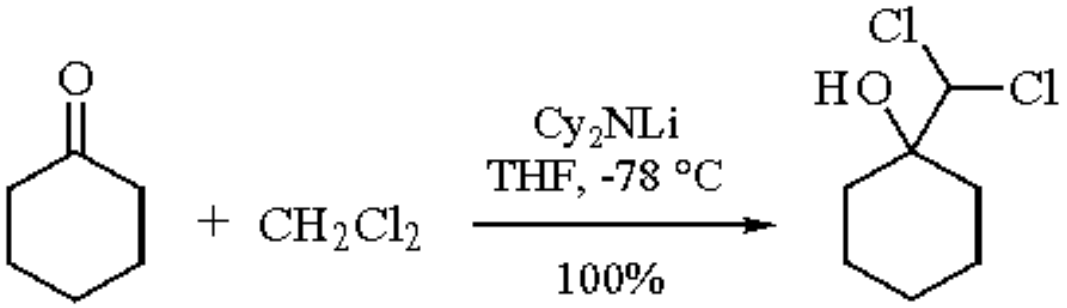

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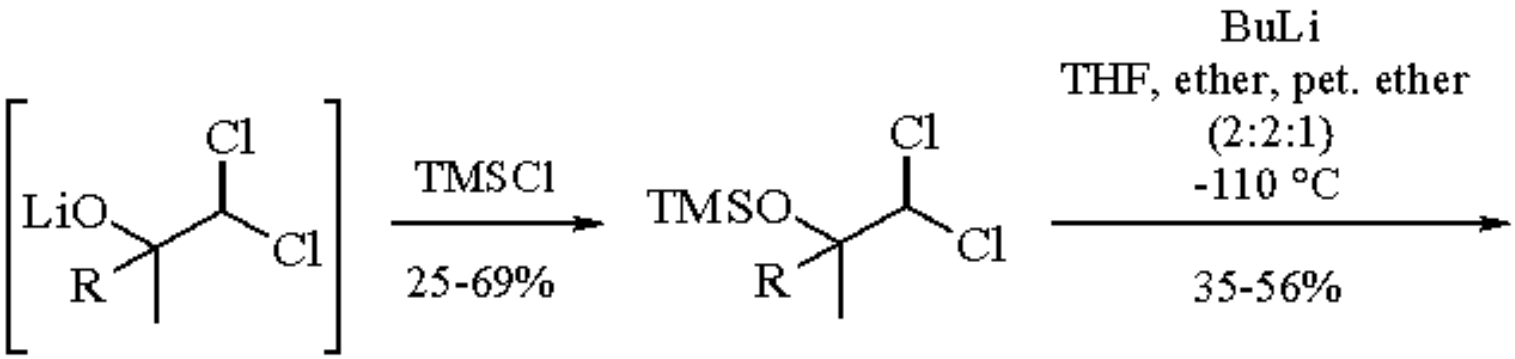

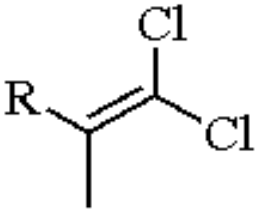

(5)

α-Chloro Ketones and Ring Expansions by Fritsch-Buttenberg-Wiechell Rearrangement.

The intermediate lithioalkoxides have been treated with *n*-BuLi, which results in deprotonation of the halogen-containing carbon to generate another carbenoid intermediate (Scheme 1). Such species undergo synthetically useful carbene rearrangements. For example aldehyde-$LiCHCl_2$ adducts undergo migration of hydrogen to provide one-carbon homologated α-chloro ketones in 50-70% overall yield (eq 6).[15] ***Lithium Piperidide*** may also be used as the base in this process.[15b] Side products may include α-chloro aldehydes via migration of the alkyl group instead of hydrogen, although these tend to be minor products. Cyclic ketones undergo an analogous reaction, resulting in ring expanded α-chloro ketones (eq 7). Symmetrical acyclic ketones also undergo the transformation in good yield. A rough migratory aptitude order has been determined. An analogous series of reactions occurs with carbonyl-$LiCHBr_2$ adducts (see ***Dibromomethyllithium***).

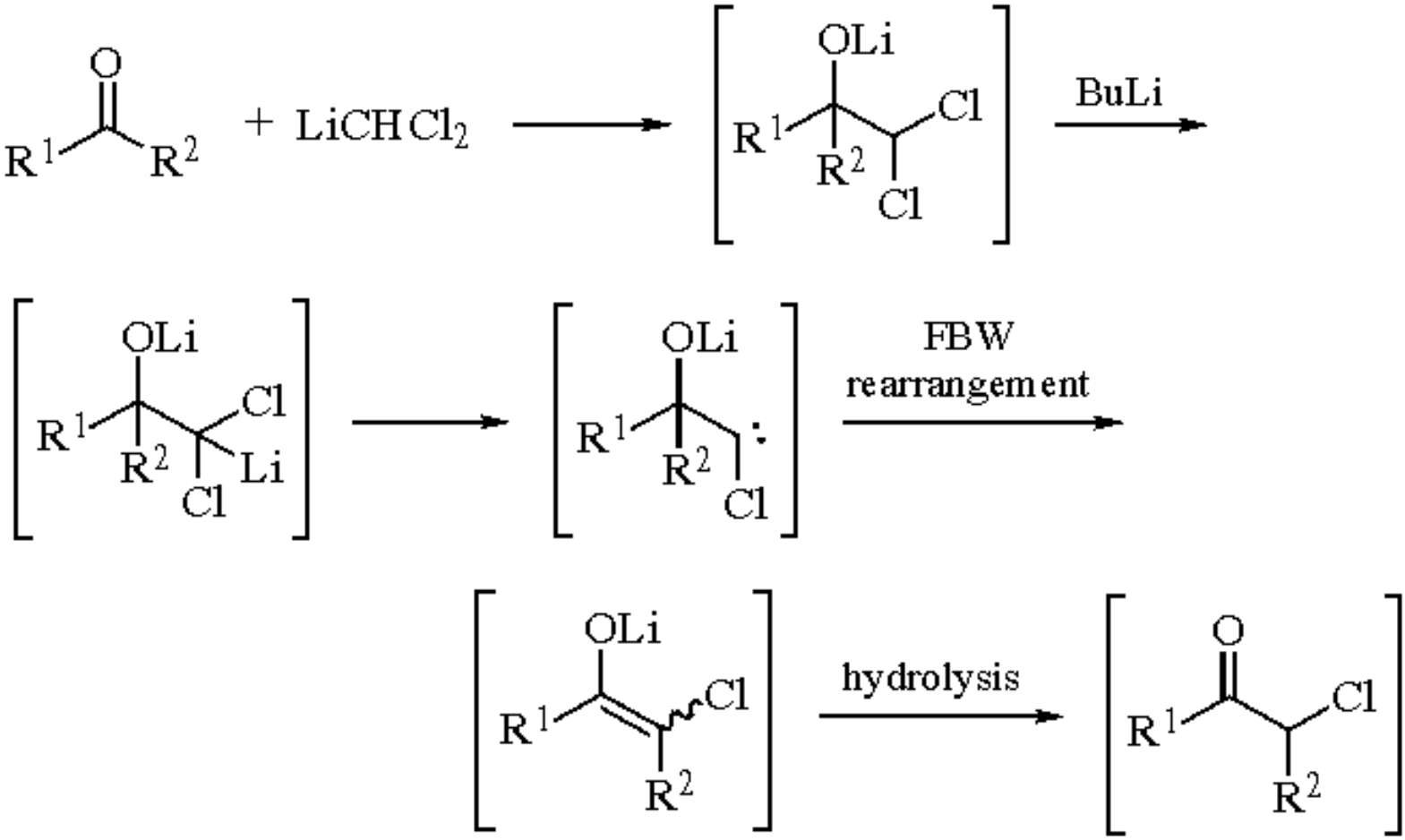

migratory aptitude: H > Ph > R_3C, R_2CH > RCH_2

Scheme 1

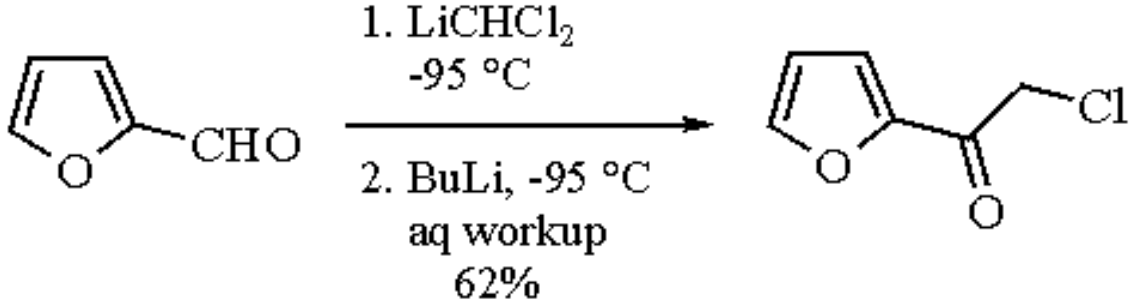

(6)

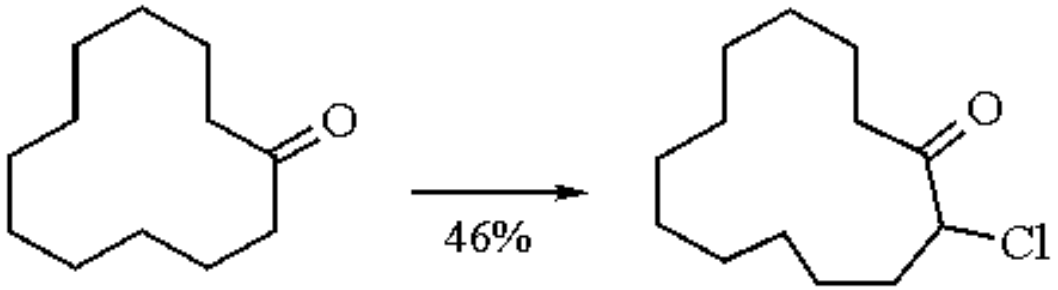

(7)

Rearrangements to α-Chloro Aldehydes.

If the aldehyde-$LiCHCl_2$ adducts (**1**) are heated in refluxing THF, the α-chloro aldehydes (**3**) are formed, presumably by ring opening of intermediate α-chlorooxiranes (**2**). Elimination of HCl from (**3**) results in α,β-unsaturated aldehydes in overall 50-80% yield (Scheme 2). Cyclic ketones also undergo the transformation in good yield.[16]

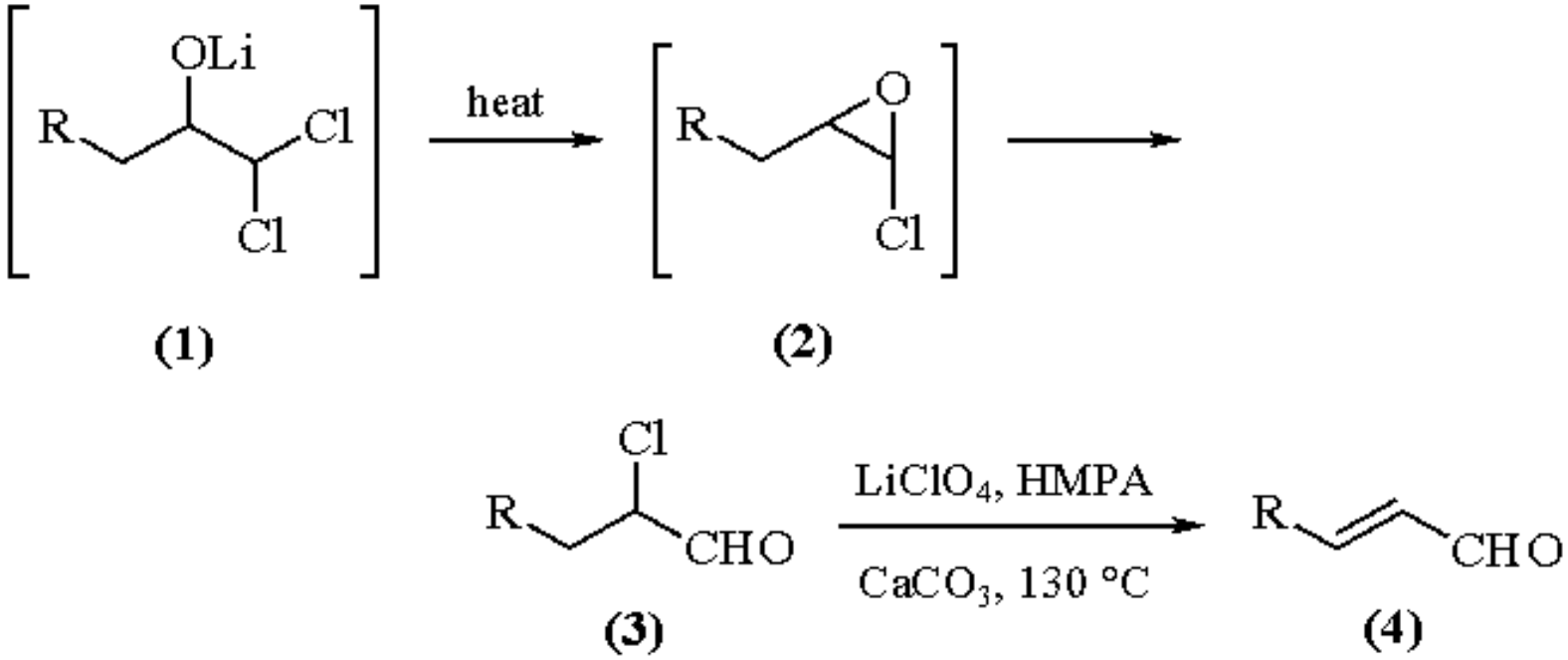

Scheme 2

α-Hydroxy Aldehyde Preparation.

Hydrolysis of $LiCHCl_2$-phenyl alkyl ketone adducts provides α-hydroxy aldehydes in moderate yield (eq 8).[17] Oxidation of the aldehydes with ***Potassium Permanganate*** gives rise to the corresponding carboxylic acids in poor yield.

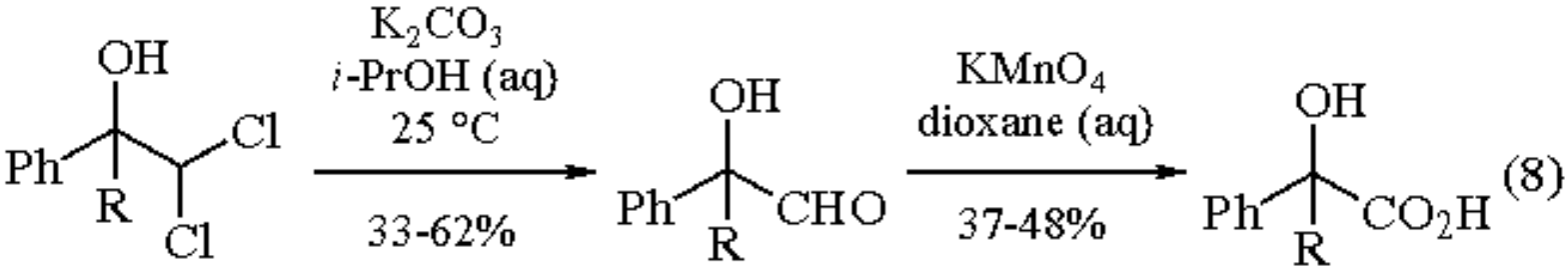

Reaction with Esters to Provide α,α-Dichloromethyl Ketones.

Esters undergo an addition-elimination process when treated with $LiCHCl_2$ to provide α,α-dichloromethyl ketones in moderate yields (eq 9).[18] Reaction with acyl chlorides gives dichloromethyl ketones, bis(dichloromethyl)carbinols, and/or α-chloro-β-(dichloromethyl)oxiranes, depending on the substrate and the reaction conditions.[19]

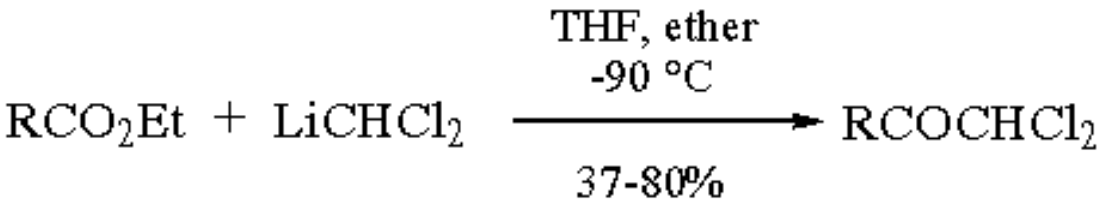

(9)

Chain Homologation of Boronic Esters.

$LiCHCl_2$ is capable of chain elongating boronic esters to give α-chloroboronic esters, useful intermediates in synthesis. Treatment of a boronic ester, generally of the cyclic variety, with $LiCHCl_2$ at low temperature and allowing it to stand at rt for a period of hours results in the familiar B -> C migration of an alkyl group in the ate complex (**6**), with expulsion of a chlorine resulting in a boronic ester (**7**) elongated by a chloromethylene group (Scheme 3). A variety of procedures were examined in order to optimize the process and it was concluded by Brown that in situ generation by deprotonating CH_2Cl_2 with LDA at 0 °C in the presence of the boronic ester was the method of choice for this homologation.[5b] Boronic esters (**7**) are quite stable intermediates which undergo facile displacement of the halide by nucleophiles with inversion of configuration, providing more highly functionalized boronic esters (eq 10).[20]

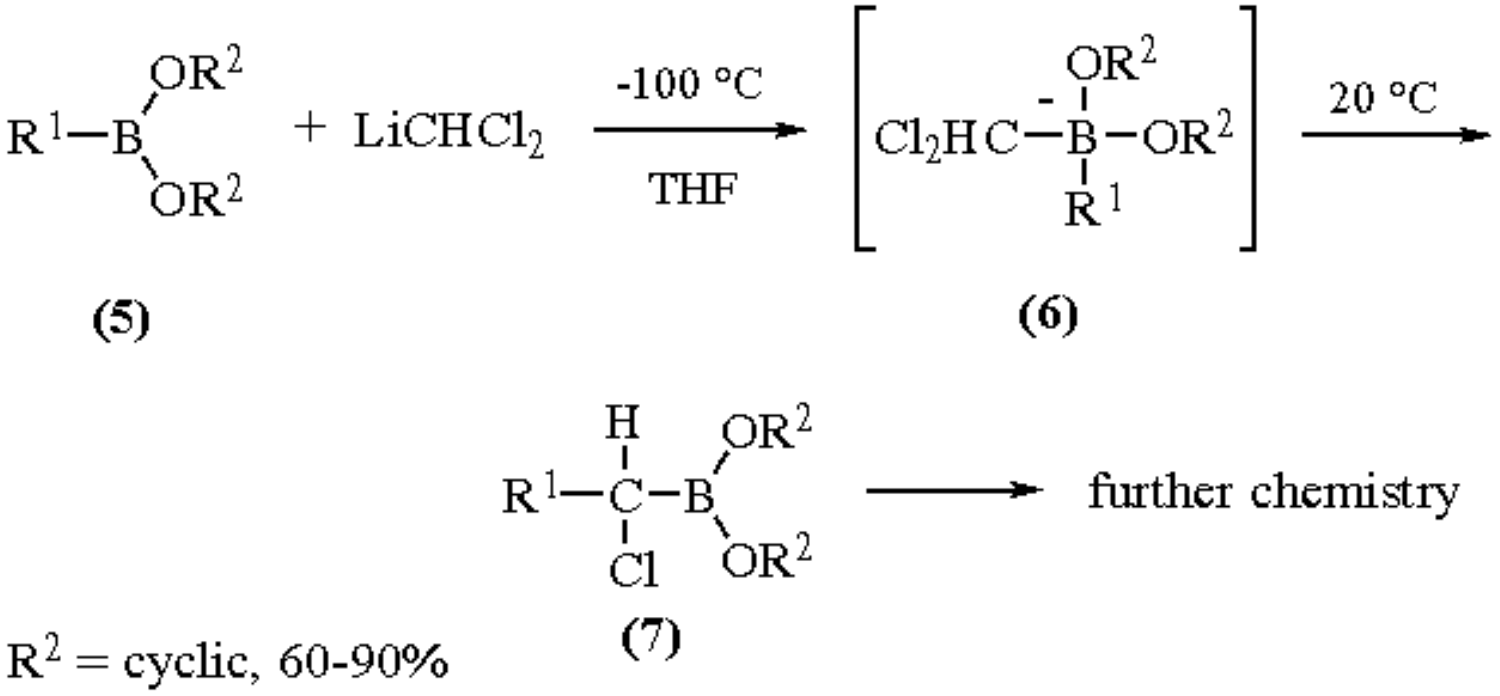

Scheme 3

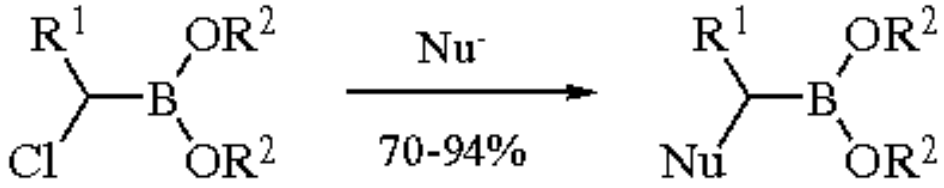

(10)

(7) (8)

Nu = NaSPh, $LiOCH_2Ph$
BuLi, PhMgBr, enolates

Use of optically active boronic esters provides the opportunity for asymmetric induction at the newly formed chiral carbon. Ate complexes of pinanediols undergo nearly enantiospecific ***Zinc Chloride*** catalyzed migration of alkyl groups, resulting in production of a new versatile chiral carbon.[21] The utility of this technology can be seen in a synthesis of (+)-*exo*-brevicomin (**9** -> **15**) (Scheme 4). The final product was obtained contaminated with only 3% of an epimer, indicative of the stereospecificity of the three migration and two displacement steps. Subsequent reports state that $LiCHBr_2$ gives better yields and diastereomeric ratios than $LiCHCl_2$ in the migration step.[22] Also, Br was found to be more readily displaced by $LiOCH_2Ph$, enabling more efficient syntheses of small carbohydrates by an iterative approach.

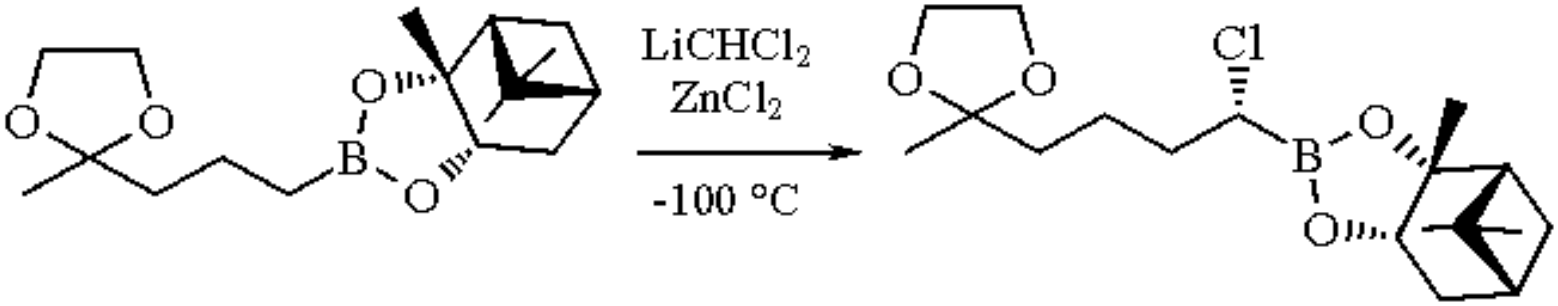

(9) (10)

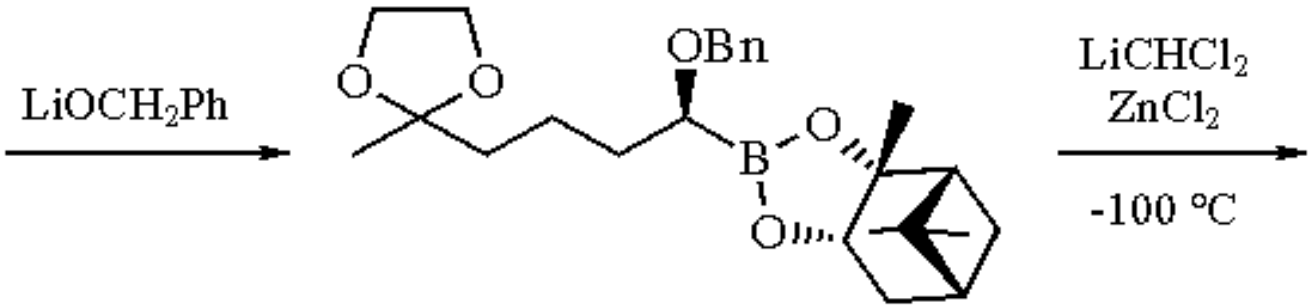

(11)
94% from **(9)**

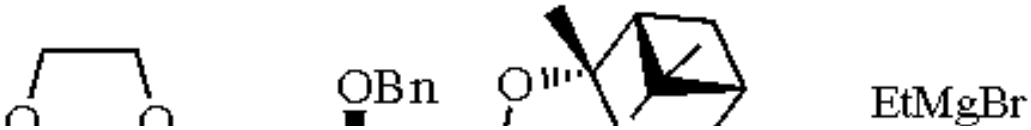

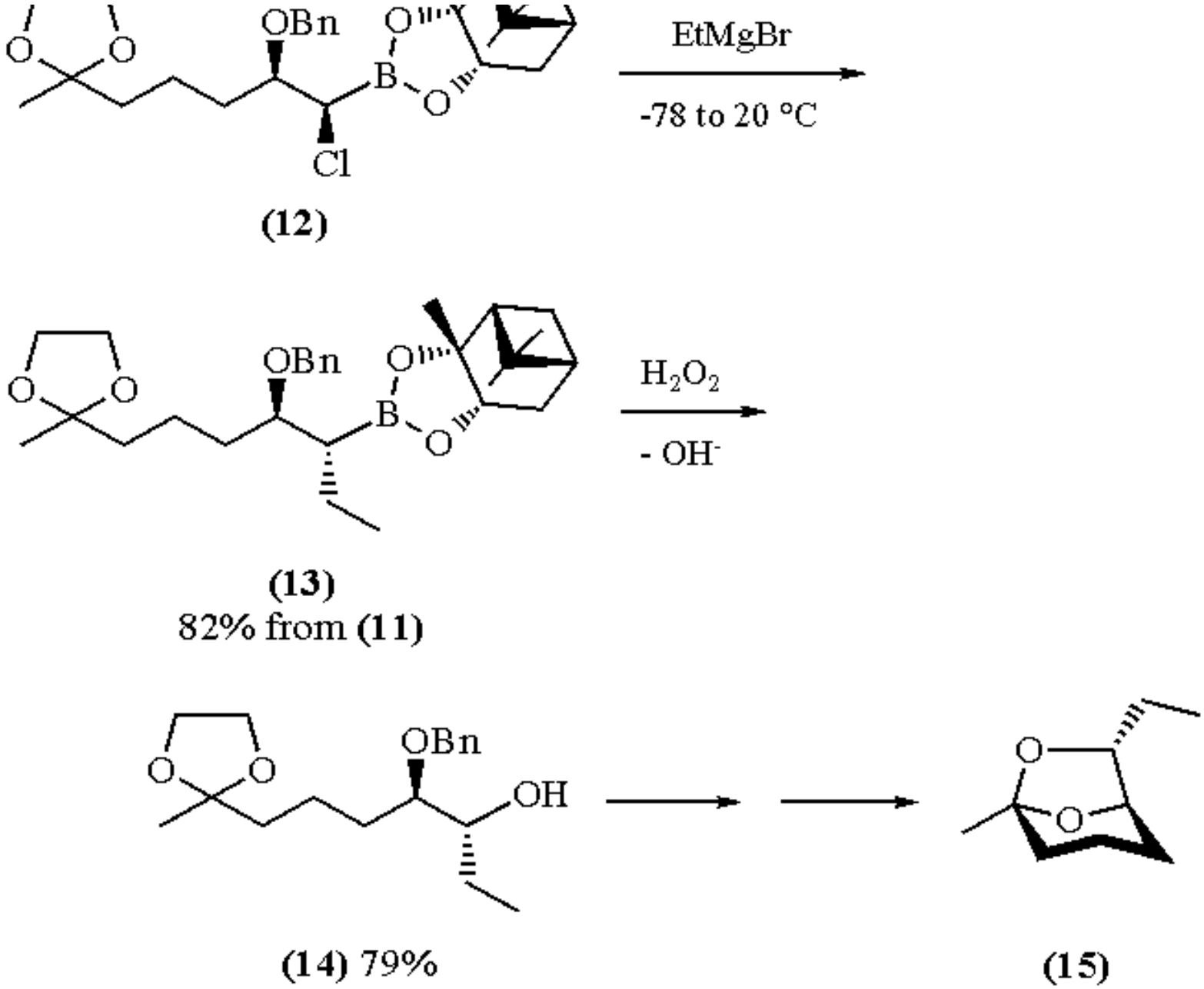

Scheme 4

Related Reagents.

Bromomethyllithium; ***Chloromethyllithium***; ***Dibromomethyllithium***; ***Tribromomethyllithium***; ***Trichloromethyllithium***.

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Dichloromethyl Methyl Ether

$MeOCHCl_2$

[4885-02-3] · $C_2H_4Cl_2O$ · Dichloromethyl Methyl Ether · (MW 114.96)

(carbon monoxide equivalent in reactions with boranes and borinates; formylating reagent for aromatic compounds and vinylsilanes; formation of α-keto acid chlorides)

Alternate Names: dichloromethoxymethane; DCME.

Physical Data: bp 85 °C; *d* 1.271 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: commercially available in 98% purity.

Preparative Method: from ***Methyl Formate*** and ***Phosphorus(V) Chloride***.[1]

Purification: by distillation.

Handling, Storage, and Precautions: dichloromethyl methyl ether is moisture sensitive, a lachrymator, and a suspect carcinogen. Handle in a fume hood.

Carbon Monoxide Equivalent.

Dichloromethyl methyl ether functions as a carbon monoxide equivalent in the reaction with boranes to yield tertiary alcohols. The reaction works well with both symmetrical and unsymmetrical boranes and for boranes containing tertiary alkyl groups (eq 1).[2,3] Hindered lithium alkoxides are the preferred bases.

$$Bu_3B + MeOCHCl_2 \xrightarrow[\text{94\%}]{\text{1. } LiOCEt_3 \text{ 2. } H_2O_2, NaOH} Bu_3COH \qquad (1)$$

A similar reaction occurs with borinate esters to yield ketones.[4] This reaction has been used in a facile synthesis of bicyclo[3.3.0]nonan-9-one from ***9-Borabicyclo[3.3.1]nonane*** (eq 2).[5] The insertion reaction proceeds with retention of

configuration of the migrating alkyl groups and provides a route to optically active ketones from chiral borinates and boronates (eq 3).[6] This reaction is applicable to the enantioselective synthesis of α-alkynyl ketones[7] and alkenones,[8] and as in the reaction of boranes with dichloromethyl methyl ether, hindered lithium alkoxides are the preferred bases. Borinates also undergo an elimination-rearrangement reaction to yield alkenes on treatment with dichloromethyl methyl ether and heat or ***Silver(I) Nitrate*** (eq 4).[9]

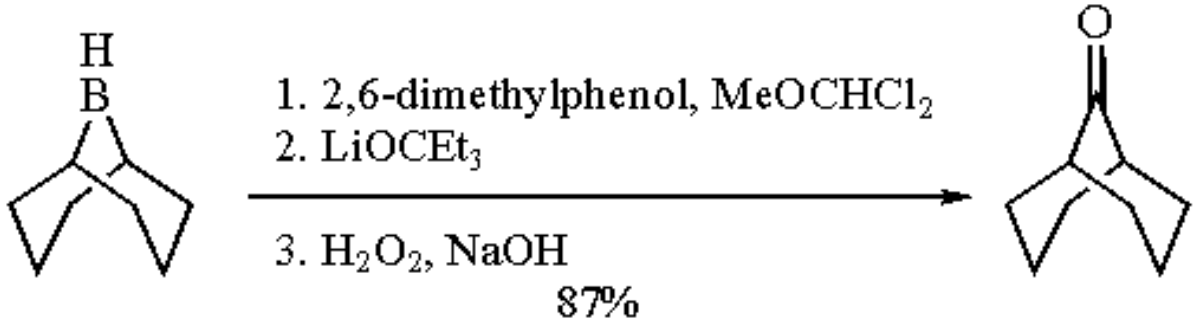

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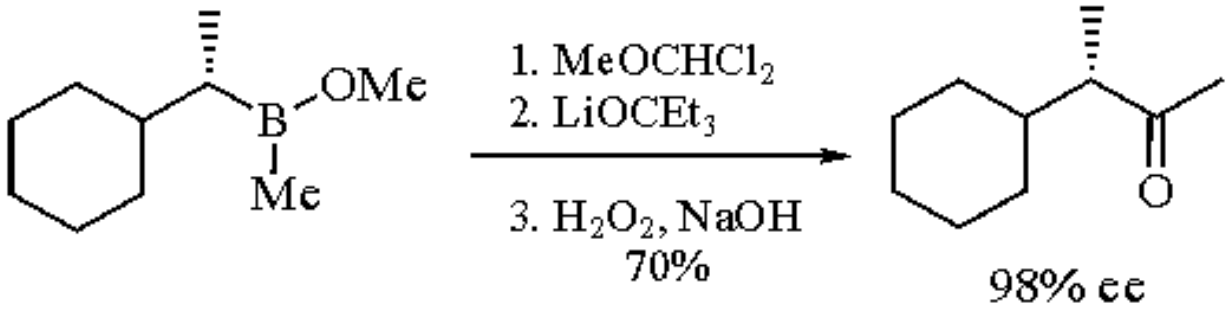

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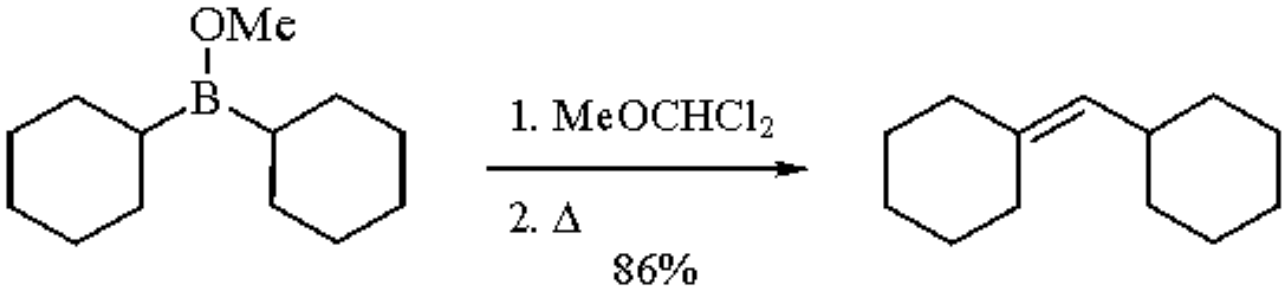

(4)

Formylation of Aromatic Compounds.

Dichloromethyl methyl ether has been used extensively to formylate aromatic compounds.[10-12] The reaction works well for the formylation of arenes and heterocycles such as indoles and pyrroles. ***Titanium(IV) Chloride*** has generally been used as the Lewis acid but an improved procedure recommending ***Tin(IV) Chloride*** has been reported.[13] A typical example is shown in eq 5.[14]

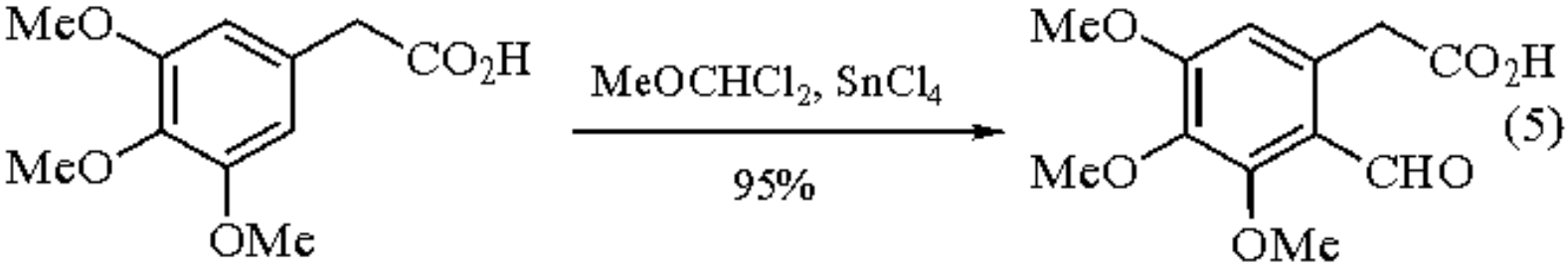

Formylation of Vinylsilanes.

Vinylsilanes are formylated by reaction with dichloromethyl methyl ether, providing a route to α,β-unsaturated aldehydes (eq 6).[15,16] This reaction is also works well for the synthesis of dienals from 1-trimethylsilyl-1,3-dienes.[17]

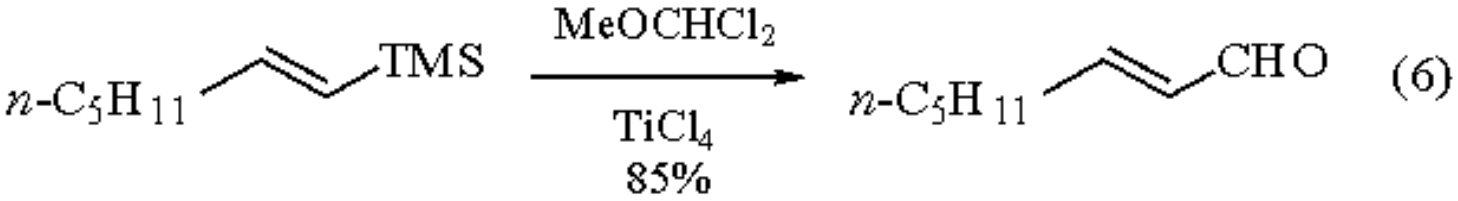

α-Keto Acid Chlorides.

Dichloromethyl methyl ether is used in the preparation of α-keto acid chlorides. Conventional reagents such as oxalyl chloride or phosphorus halides give poor results (eq 7).[18]

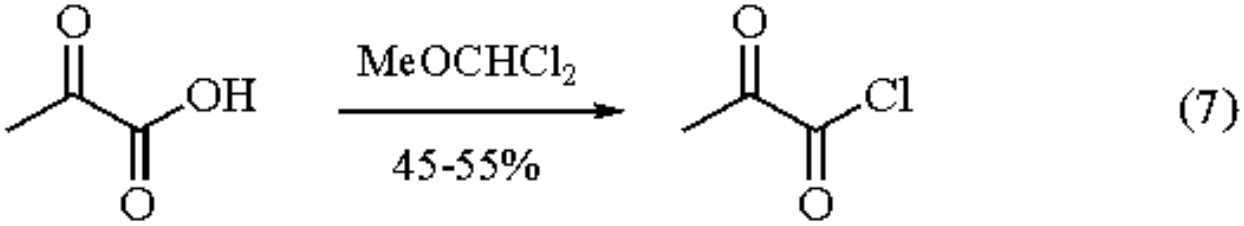

Related Reagents.

Carbon Monoxide; ***N-Dichloromethylene-N,N-dimethyliminium Chloride***; ***Potassium Cyanide***.

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1,1-Dichloro-2,2,2-trimethyl-1-phenyldisilane

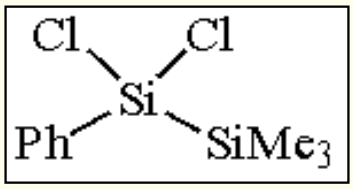

[57519-88-7] · $C_9H_{14}Cl_2Si_2$ · 1,1-Dichloro-2,2,2-trimethyl-1-phenyldisilane · (MW 249.29)

(silylating agent for π-allylpalladium complexes[1] and palladium-catalyzed allylic silylation, giving allylsilanes;[2] for asymmetric 1,4-disilylation of α,β-unsaturated ketones, giving optically active β-hydroxy ketones after oxidation[3])

Physical Data: bp 50-60 °C/0.5 mmHg.

Solubility: sol THF, benzene.

Form Supplied in: oil, with some 1-chloro-2,2,2-trimethyl-1-phenyldisilane.[2]

Analysis of Reagent Purity: NMR, MS.

Preparative Method: the disilane is prepared in 75% yield by selective chlorodephenylation of 2,2,2-trimethyl-1,1,1-triphenyldisilane with ***Hydrogen Chloride*** in the presence of a catalytic amount of ***Aluminum Chloride*** in benzene.[2,4]

Purification: fractional distillation.

Handling, Storage, and Precautions: the disilane reacts with air and water, and should be kept sealed to preclude decomposition. The reagent is a potential acidic corrosive. It should be handled in a well ventilated hood.

1,4-Disilylation of α,β-Unsaturated Ketones.

In the presence of palladium-phosphine catalysts such as ***Tetrakis(triphenylphosphine)palladium(0)***, the unsymmetrically substituted disilane $PhCl_2SiSiMe_3$ reacts with α,β-unsaturated ketones in refluxing benzene to give γ-(phenyldichlorosilyl) silyl enol ethers, which can be converted into β-(phenyldiethoxysilyl) ketones by treatment with ethanol and ***Triethylamine*** (eq 1).[3] Oxidation of the phenyldiethoxysilyl group with ***Hydrogen Peroxide*** in the presence of fluoride gives β-hydroxy ketones in high yields. γ-(Phenyldimethylsilyl) lithium enolates, generated by treatment of the γ-(phenyldichlorosilyl) silyl enol ethers with ***Methyllithium***, undergo alkylation with alkyl halides to give β-(phenyldimethylsilyl)-α-alkyl ketones with high *anti* selectivity (eq 2). These β-(phenyldimethylsilyl) ketones are subjected to fluorodephenylation followed by oxidation to give *anti*-β-hydroxy-α-alkyl ketones. The 1,4-addition of the disilane is enantioselective when catalyzed by

$PdCl_2$[(*R*)-BINAP], thereby providing optically active *anti*-β-hydroxy-α-alkyl ketones with 66-92% ee (Table 1).[3a]

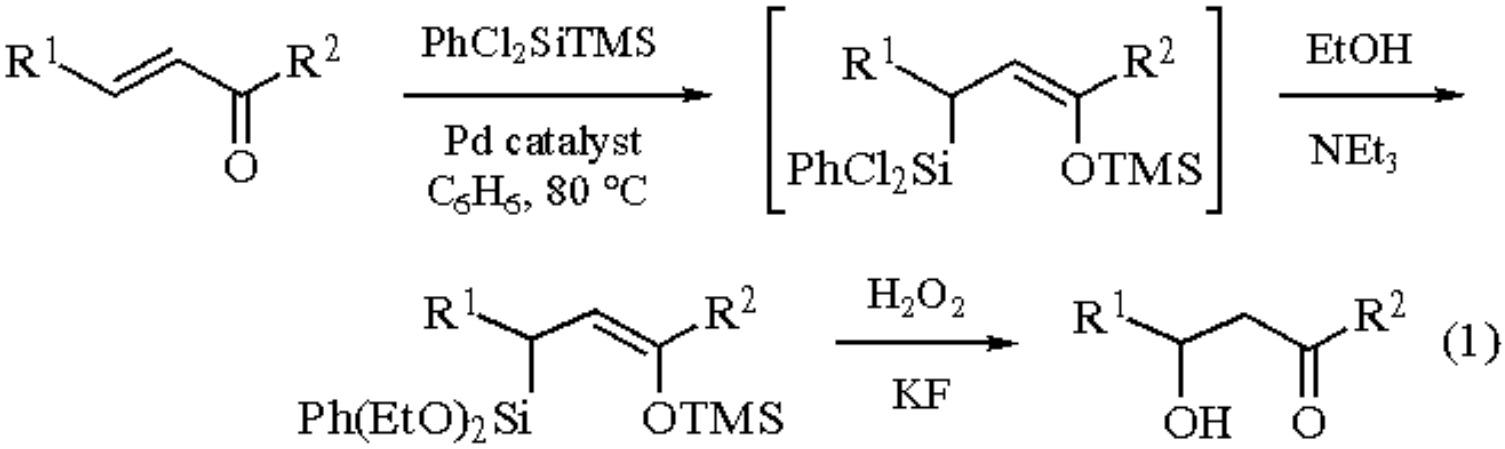

Pd catalyst = $Pd(PPh_3)_4$, $PdCl_2$[(*R*)-BINAP]

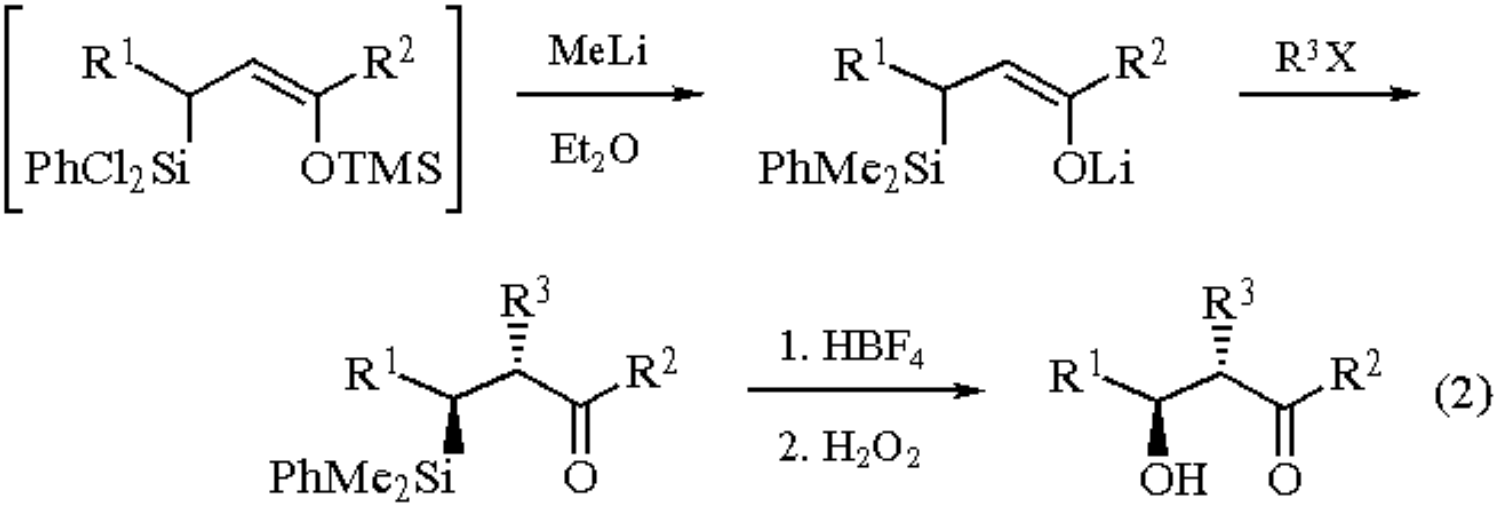

Table 1 b-Hydroxy Ketones Prepared via the Asymmetric Disilylation of Enones

R^1	R^2	R^3	Yield of b-hydroxy ketone (%)	% ee
Me	Ph	H	90	87
Me	Ph	Me	70	85
Me	4-$MeOC_6H_4$	H	81	92
i-Pr	Ph	H	100	86
Ph	Me	H	83	78
Ph	Me	Me	78	45
Me	Me	H	74	69
Me	Me	Bn	74	66

Silylation of π-Allylpalladium Complexes and Palladium-Catalyzed Allylic Silylation.

The disilane is a highly reactive reagent for the silylation of π-allylpalladium complexes, producing phenyldichloro(allyl)silanes in high yields.[1] The retention of configuration observed in the silylation of an optically active π-allylpalladium complex indicates that the silylation occurs by way of a π-allyl(phenyldichlorosilyl)palladium intermediate (eq 3). Palladium-catalyzed allylic silylation of allylic chlorides is also effected with the disilane reagent. In the presence of 1 mol % of palladium catalyst coordinated with triphenylphosphine or ***1,1´-Bis(diphenylphosphino)ferrocene*** (dppf), the silylation gives allylsilanes in high yields (eq 4).[2] The functionalized allylsilanes may be oxidized to allylic alcohols.

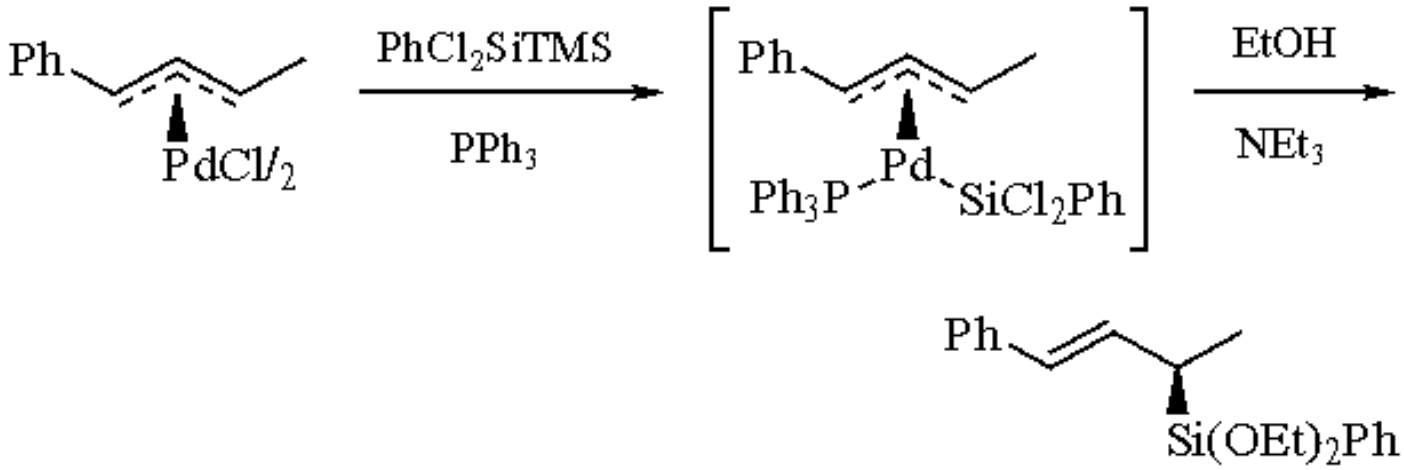

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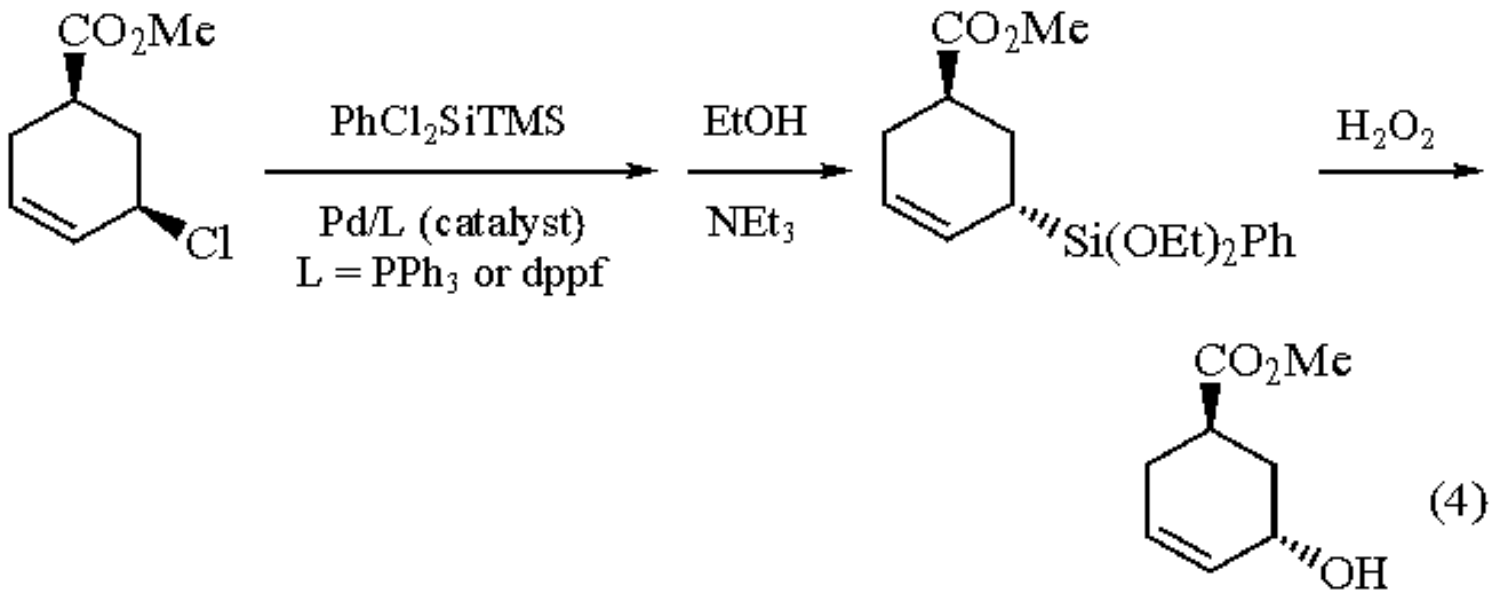

(4)

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2,3-Dichloropropionaldehyde

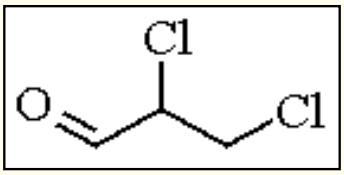

[10140-89-3] · $C_3H_4Cl_2O$ · 2,3-Dichloropropionaldehyde · (MW 126.97)

(undergoes condensation reactions, ene reactions, 1,2-additions; α-chloro nitrone precursor)

Alternate Name: 2,3-dichloropropanal.

Physical Data: bp 45 °C/12 mmHg; n_D^{20} 1.4762; d^{20} 1.3712 g cm^{-3}.

Solubility: sol most common organic solvents such as hexane, ether, THF, methylene chloride, ethanol, etc.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: NMR.

Preparative Methods: the reagent is best prepared by bubbling an equimolar amount of dry ***Chlorine*** gas into neat ***Acrolein*** at 5 °C.[2] The reaction temperature thereby rises spontaneously and is kept at 40 °C until the reaction has ended. Spinning band distillation at reduced pressure (12 mmHg) affords pure 2,3-dichloropropionaldehyde as a colorless liquid in 65% yield.

Handling, Storage, and Precautions: as the reagent is prone to polymerization it should be used as prepared for best results. For a limited time it can be stored under nitrogen at 5 °C in tightly sealed bottles. Use in a fume hood.

Condensation Reactions.

In the presence of Lewis acid catalysts such as ***Aluminum Chloride*** or ***Tin(IV) Chloride***, 2,3-dichloropropionaldehyde undergoes ene reactions[1] with acyclic[3-5] and cyclic alkenes[6,7] to afford alkenyl-substituted dichlorohydrins (eqs 1 and 2), which after treatment with base can easily be converted to the corresponding epichlorohydrins (eq 1).[6] With unsymmetrical alkenes such as 1-methylcyclohexene a mixture of products is obtained (eq 2),[7] in which the regioisomer resulting from methylene hydrogen abstraction dominates.

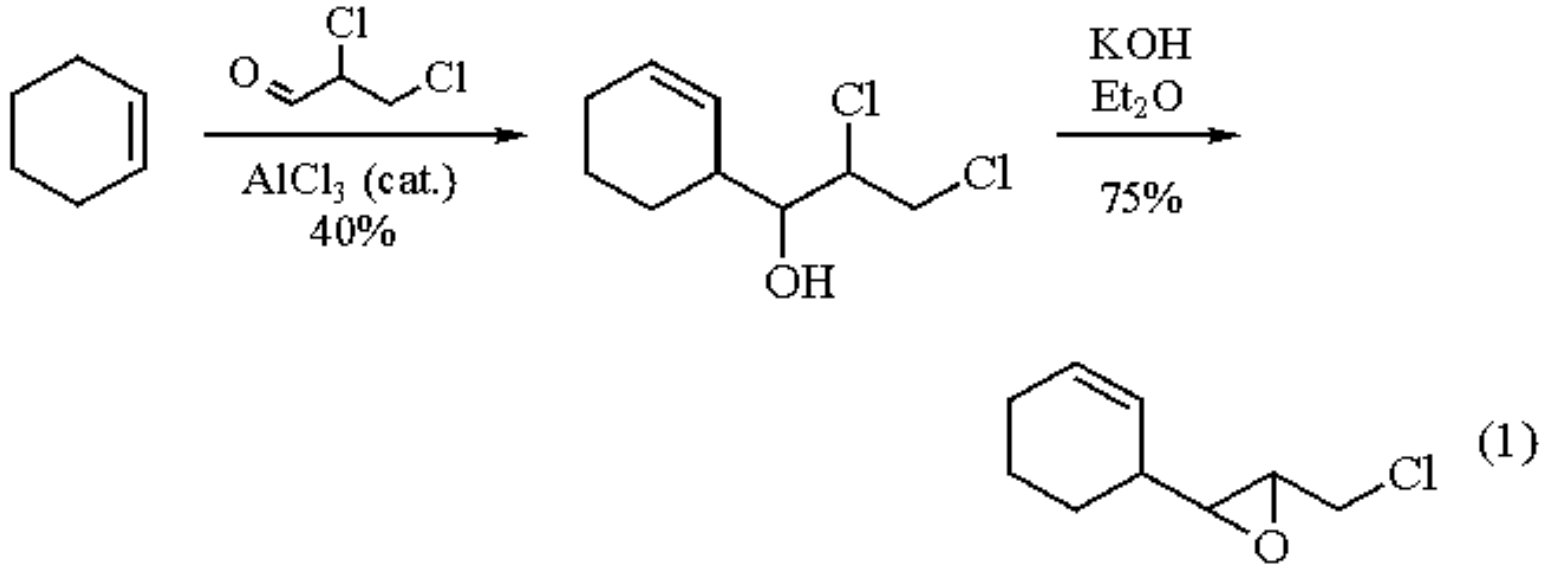

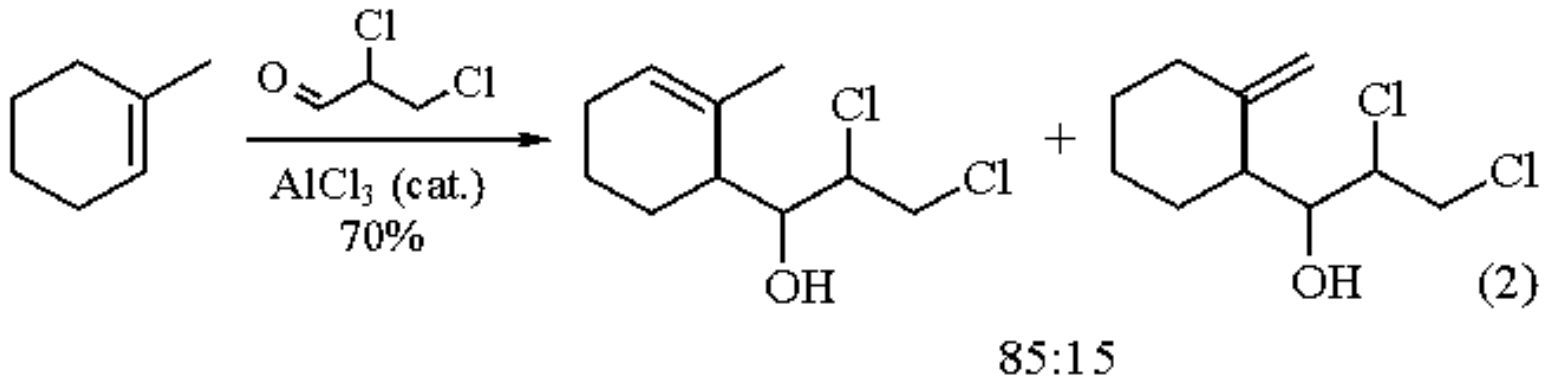

Asymmetric induction (70-75% ee) has been achieved in this ene reaction if a chiral catalyst such as (-)-menthoxyaluminum dichloride is employed.[4] In the absence of alkenes, Lewis acids such as $AlCl_3$ or ***Triethylaluminum*** initiate at low temperature the polymerization of the reagent to give high molecular weight poly[oxy(2,3-dichloropropylidene)].[8]

Similarly substituted dichlorohydrins or epichlorohydrins can also be generated by the addition of Grignard reagents to 2,3-dichloropropionaldehyde (eq 3).[9,10]

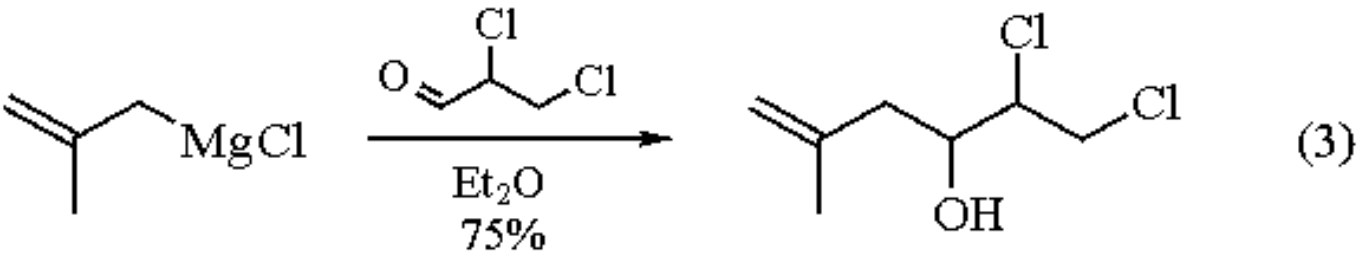

Precursor to Other Reagents.

Besides its role as precursor for the preparation of 2-chloroacrolein or its diethyl acetal (eq 4),[2] the reagent has also served as an intermediate to 2,3-dichloro-*N*-cyclohexylpropanaldonitrone.[11] The latter, which is formed upon treatment of the reagent with *N*-cyclohexylhydroxylamine, is able to undergo Ag^+-induced stereospecific *cis* additions to isolated

double bonds,[11] thus formally entering a Diels-Alder reaction with inverse electron demand. The resulting cyanide-trapped addition products are obtained as diastereomeric mixtures, which then may be converted in two steps to α-methylene-γ-butyrolactones in good yields (eq 5), thereby providing a preparative route to this unit often encountered in natural products. When the same α,β-dichloro nitrone is combined with a quinoidal vinologous ester system, an unusual course of the cycloaddition reaction is observed.[12]

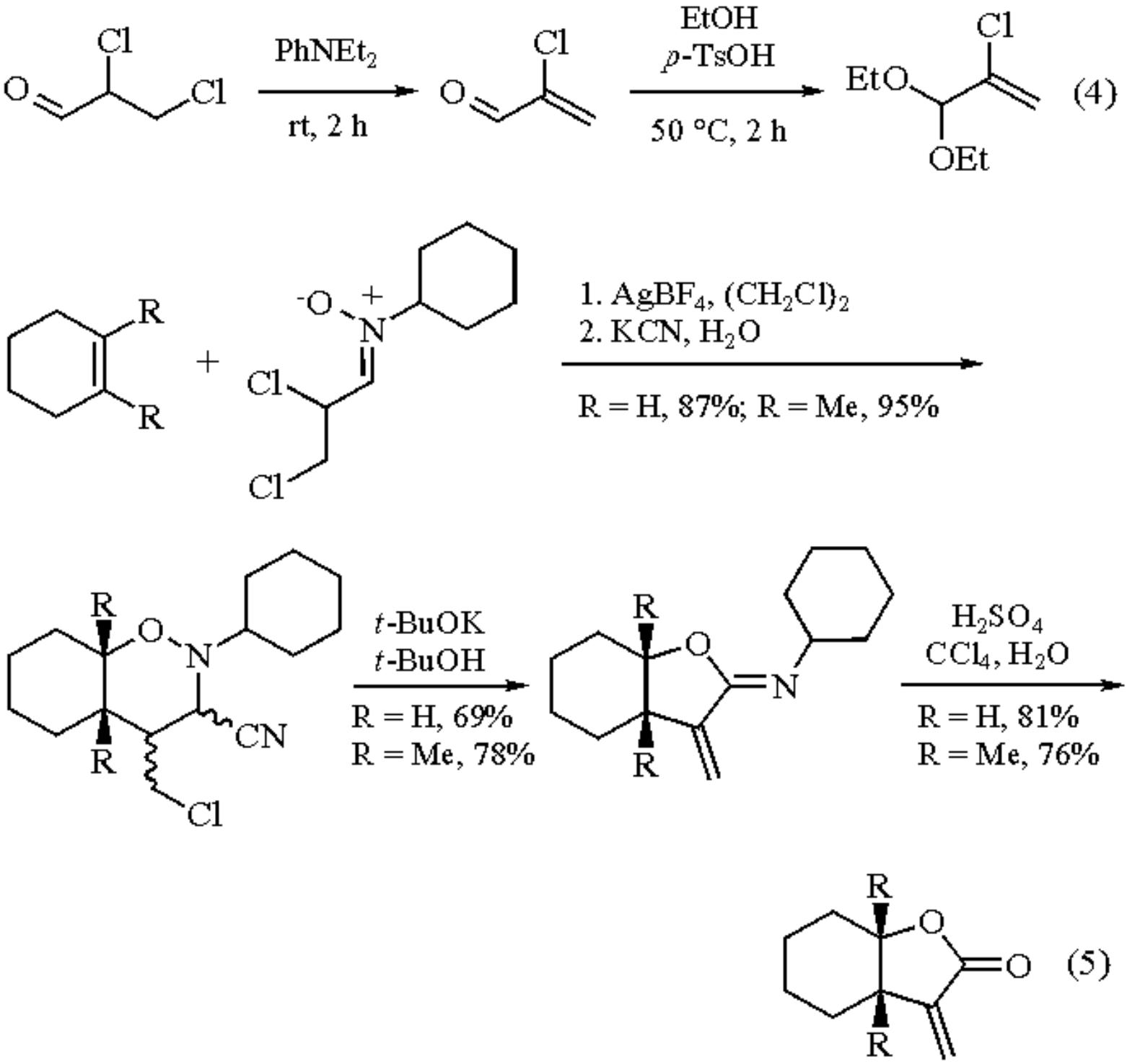

Finally, 2,3-dichloropropionaldehyde has also served as a precursor for the preparation of pyrazoles[13] and a new type of phosphorus-containing betaine.[14]

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1,3-Dichloropropene

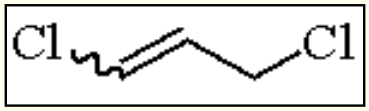

(*E*)

[10061-02-6] · $C_3H_4Cl_2$ · 1,3-Dichloropropene · (MW 110.97) (*Z*)

[10061-01-5]

(bifunctional alkylating agent)

Alternate Name: 1,3-dichloropropylene.

Physical Data: (*E*) isomer: bp 112 °C; *d*204 1.224 g cm^{-3}. (*Z*) isomer: bp 104.3 °C; *d*204 1.217 g cm^{-3}.

Solubility: sol ethers, hydrocarbons; slightly sol H_2O.

Form Supplied in: available as a mixture of (*E*) and (*Z*) isomers.

Handling, Storage, and Precautions: flammable liquid; suspect carcinogen. Handle in a fume hood.

Bifunctional Alkylating Agent.

1,3-Dichloropropene can be functionalized at each terminus by either nucleophiles or electrophiles. Most nucleophiles react with this reagent, as well as other 1,3-dihalopropenes, in an S_N2 substitution reaction to yield terminal vinyl halides that are unreactive towards further substitution.[1] Bis-substitutions with thiolate,[2a] selenate,[2a] or formate[2c] anions are effected under strongly basic conditions, leading to the useful propenone synthons 1,3-bis(phenylthio)- or 1,3-bis(phenylseleno)propene.[2a,b] Functionalized copper-zinc reagents, RCu(CN)ZnX, add to 1,3-dichloropropene with a high degree of S_N2' selectivity (>98%) to afford bis-functionalized alkenes in good to excellent yields with good stereoselectivity for formation of the (*E*) isomer (eq 1).[3]

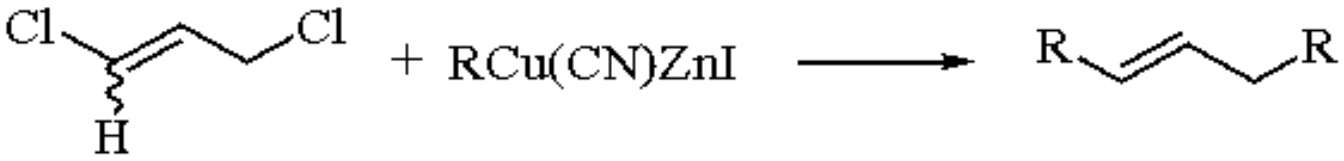

(1)

R	(*E*):(*Z*)	Yield (%)
$(CH_2)_3CN$	87:13	88
$(CH_2)_6OAc$	70:30	80
CH_2Ph	100:0	94
CH_2-2-thienyl	100:0	84

Under Arbuzov conditions a 1,3-dienyl phosphonate results from reaction of 1,3-dichloropropene with triethyl phosphite.[6]

Terminal bis-trimethylsilylation of 1,3-dichloropropenes can be effected by metalation with ***Lithium Diisopropylamide***, with in situ trapping by ***Chlorotrimethylsilane*** in THF/ether mixtures at -75 °C (eq 2).[4]

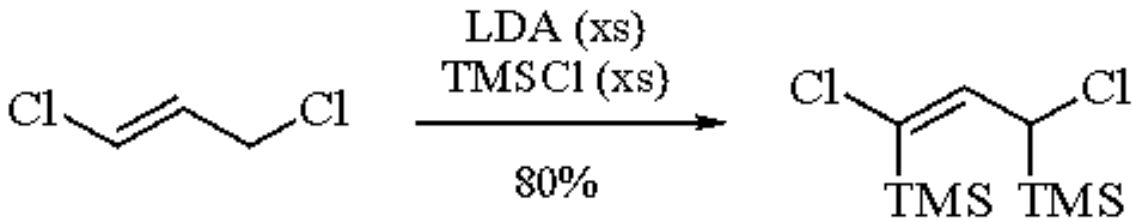

(2)

A simple synthesis of 1,3-butadienes in moderate yields and excellent stereoselectivity (*trans*:*cis* > 95:5) is accomplished by reaction of aldehydes or ketones with 1,3-dichloropropene and ***Zinc*** powder in an aqueous medium (eq 3).[5]

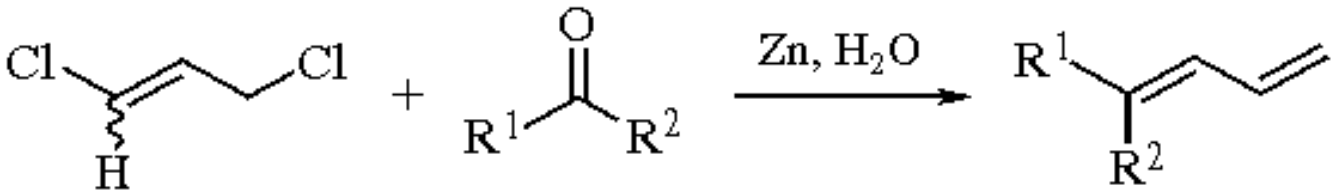

(3)

R^1	R^2	Yield (%)
Ph	H	53
$(CH_2)_2Me$	H	53
CH=CHPh	H	38
Ph	Me	53

Homoallylic alcohols result from addition to aldehydes that is mediated by ***Samarium(II) Iodide*** (eq 4).[7]

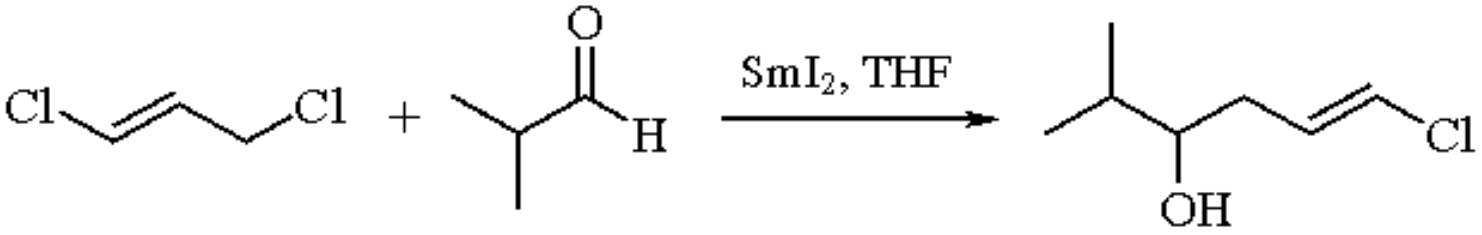

(4)

Vinylcyclopropanes are obtained in moderate yields by reaction of 1,3-dichloropropenes with α,β-unsaturated esters in the presence of ***Copper-t-Butyl Isocyanide*** complexes in benzene at 80 °C (eq 5).[8]

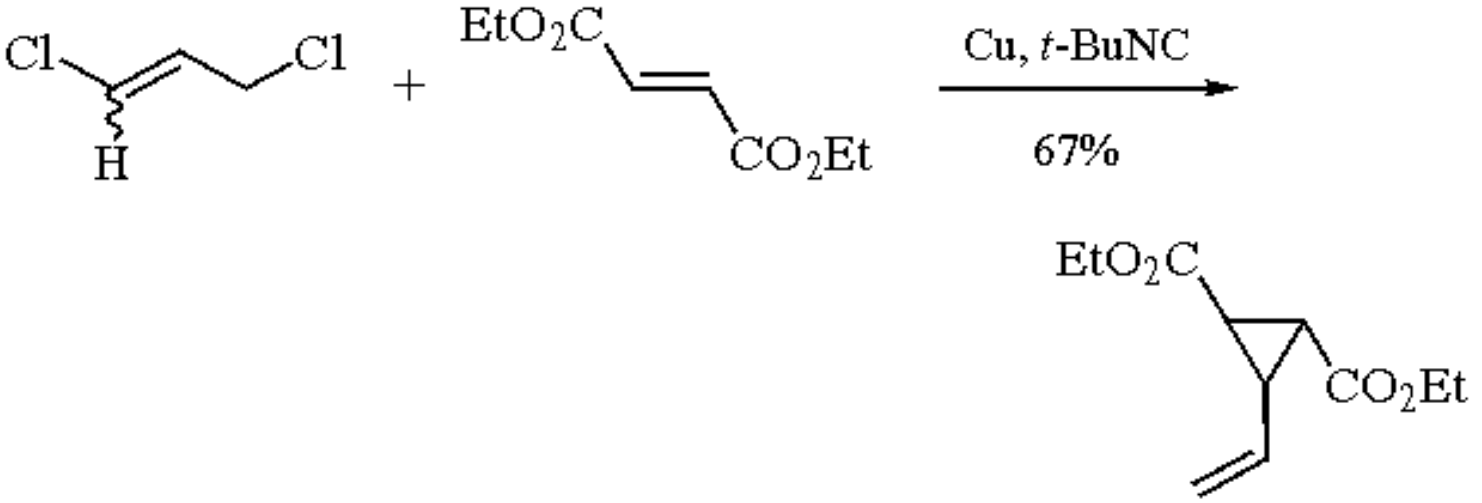

(5)

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2,3-Dichloropropene

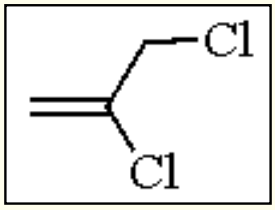

[78-88-6] · $C_3H_4Cl_2$ · 2,3-Dichloropropene · (MW 110.97)

(general purpose alkylating agent)

Physical Data: bp 94 °C; n_D 1.4611; *d* 1.204 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Preparative Method: can be prepared from 1,2,3-trichloropropane in 87% yield by the elimination of hydrogen chloride, using NaOH in a refluxing aqueous or ethanolic solution.[1] Recently it has been shown that the addition of quaternary basic salts such as $[Me(CH_2)_7]_3$+NMe Cl^- can improve the yield (94%) and selectivity of the elimination.[2]

Handling, Storage, and Precautions: highly flammable liquid (fp 10 °C); toxic; corrosive. Use in a fume hood.

Alkylations.

2,3-Dichloropropene (**1**) is a general purpose alkylating agent, useful for the incorporation of allyl side chains. Additions to carbonyl enolate anions are common,[3,4] for instance in the final stages of the total synthesis of (-)-hypnophilin (eq 1).[5]

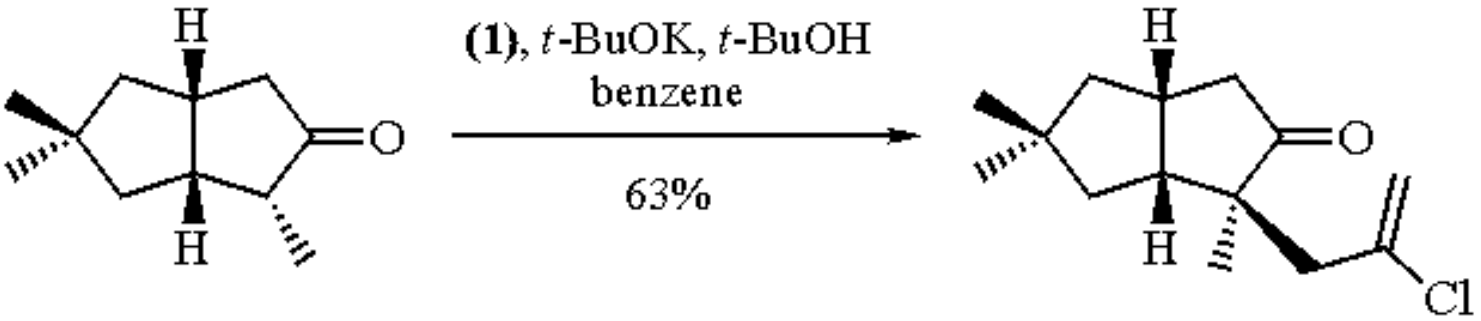

(1)

The additions of (**1**) to alcohols,[6] amines,[7] sulfones,[8] ketimines,[9] and Schiff bases[10] are also known.

In a number of cases the disposition of the (2-chloro)allyl side chain allows the alkylation to be followed by a Claisen rearrangement,[6,11,12] for instance in the bis(chloroallyl) ether (**3**) of anthrarufin (**2**) (eq 2).[13]

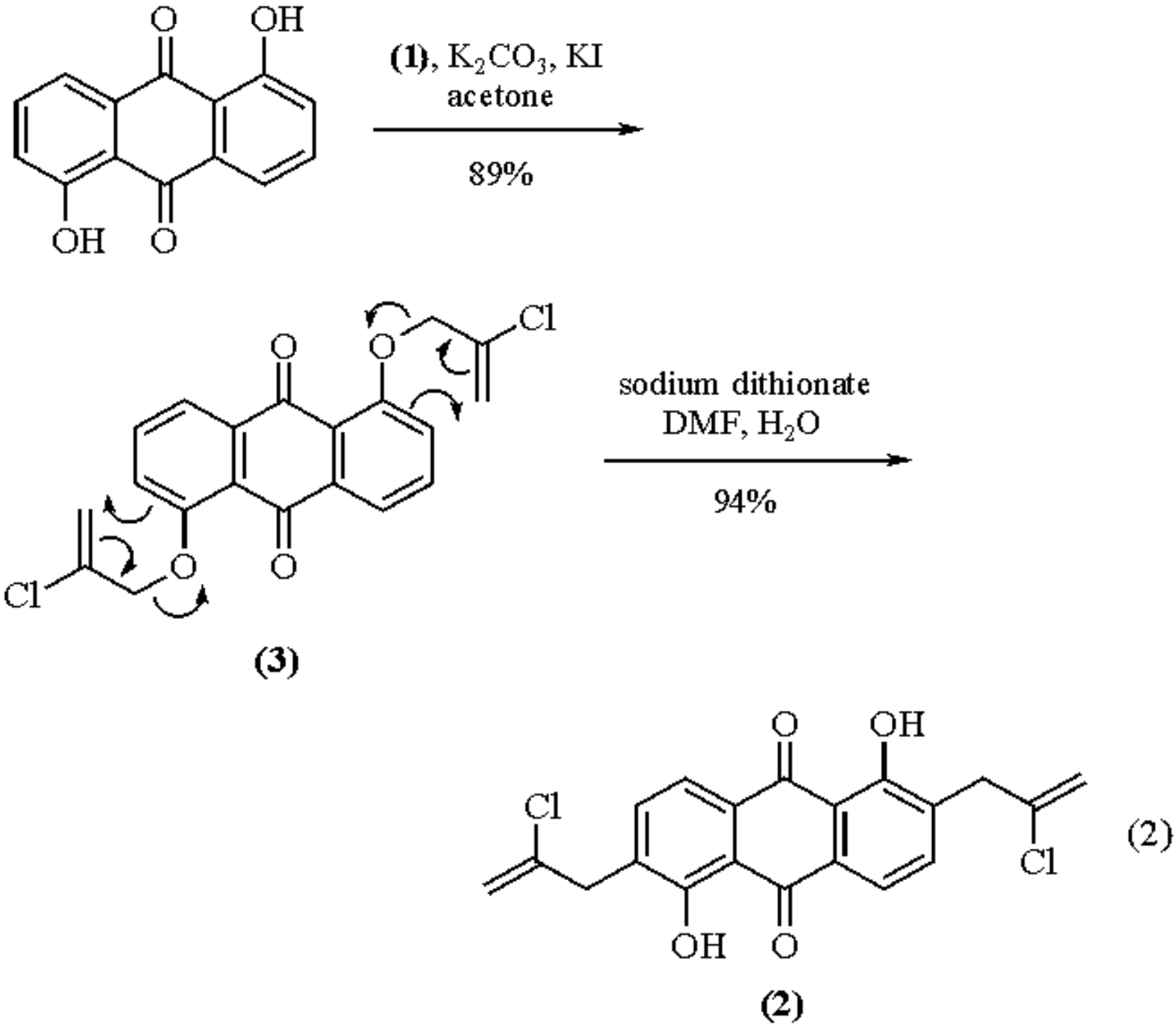

Grignard Reactions.

2,3-Dichloropropene also undergoes alkylation reactions with Grignard reagents.[14-16] This has been used in the synthesis of cyclic ketones by cyclization of the allyl side chain onto an alkene using 97% ***Formic Acid*** (eq 3).[17]

2,3-Dichloropropene

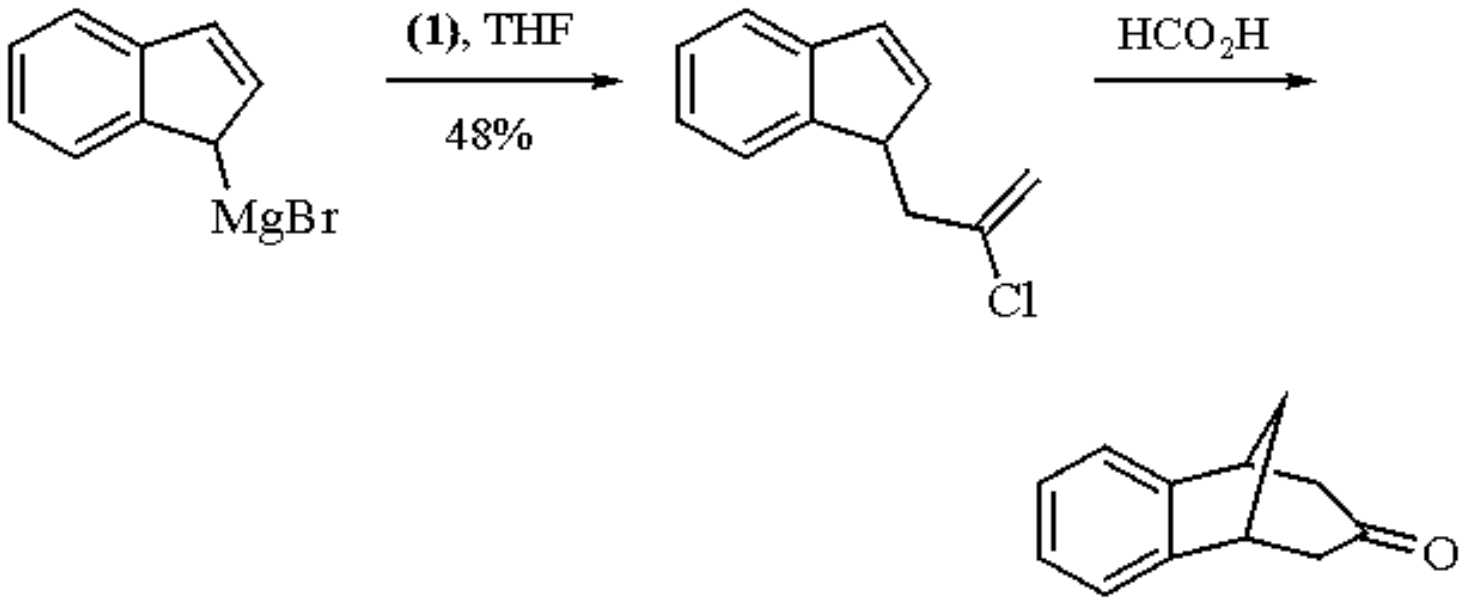

(3)

Palladium Coupling Reactions.

Cyclization of alkynylanilines to indoles under palladium catalysis, in the presence of allyl chlorides, gives 3-allylindoles in good yields (eq 4).[18] The reaction mixture must contain proton scavengers to avoid trapping of the intermediate organopalladium species by H^+.

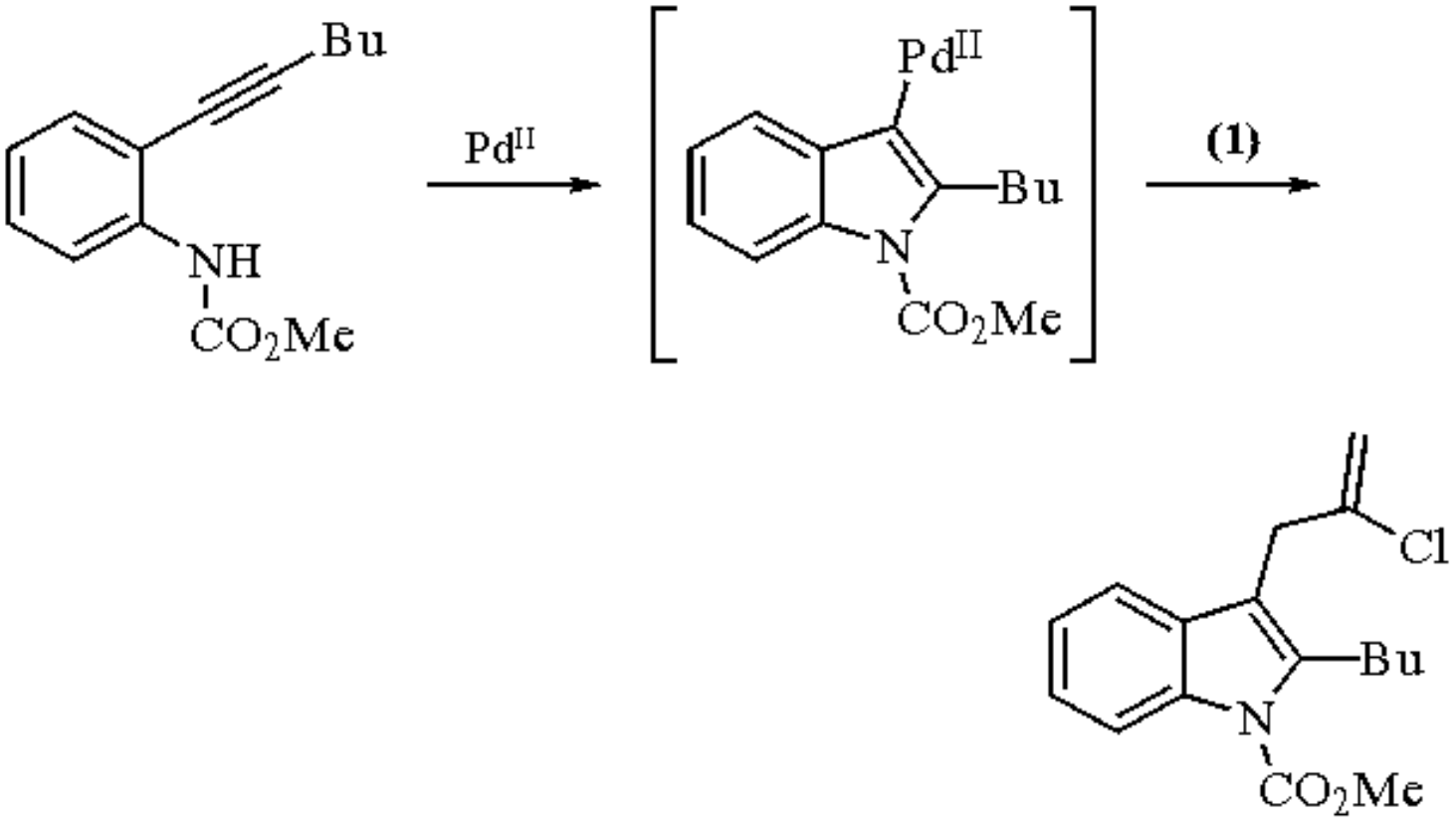

(4)

Allene Formation.

Although many routes to ***Allene*** are described in the literature, most give a mixture of allene and methylacetylene. However, reductive elimination of 2,3-dichloropropene with ***Zinc*** dust gives allene in a reproducible manner in good yield, with 2-chloropropene as the only impurity (eq 5).[19]

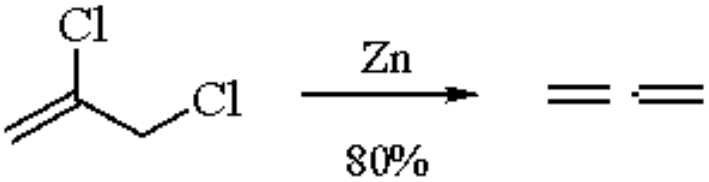

(5)

Aryl Coupling Reactions.

2,3-Dichloropropene acts as an electron acceptor in the radical coupling of aryl Grignard reagents (eq 6).[20] The high yield and avoidance of toxic thallium compounds give this method an advantage over other aryl coupling reactions. This method has been extended to the production of aryl polymers. Poly(*p*-phenylene) (PPP) has been produced using 2,3-dichloropropene and difunctional aryl Grignards (eq 7).[21]

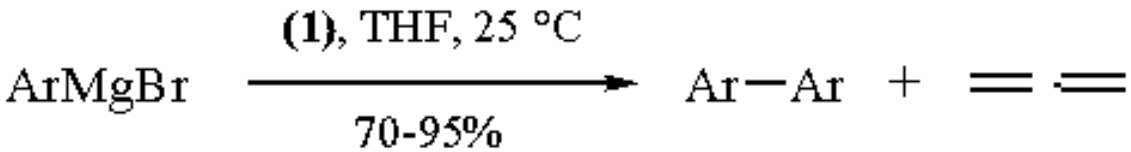

(6)

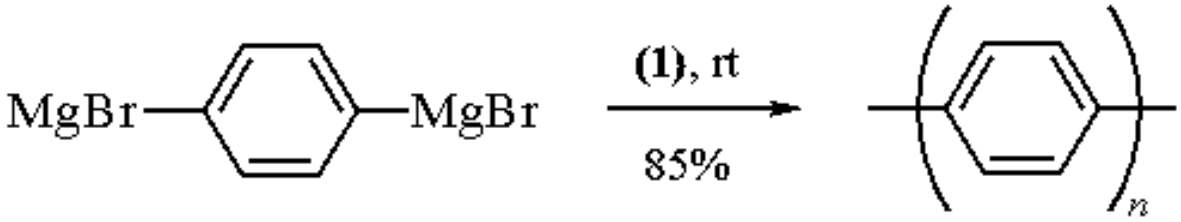

(7)

Halogen Substitution.

In the presence of ***Sodium Iodide***, 2,3-dichloropropene undergoes halogen exchange in the 3-position (eq 8).[22]

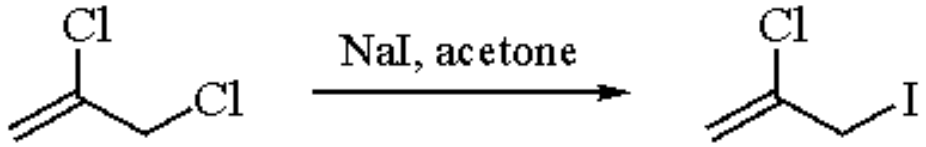

(8)

Organometallic Compounds.

2,3-Dichloropropene has been shown to undergo oxidative addition to form complexes with transition metals, for instance with ruthenium.[23]

Radical Reactions.

Functionalized cyclopentanes can be prepared from vinylcyclopropanes and 3-substituted propenes (e.g. **1**) by both photochemical and DBU initiation methods (eq 9).[24]

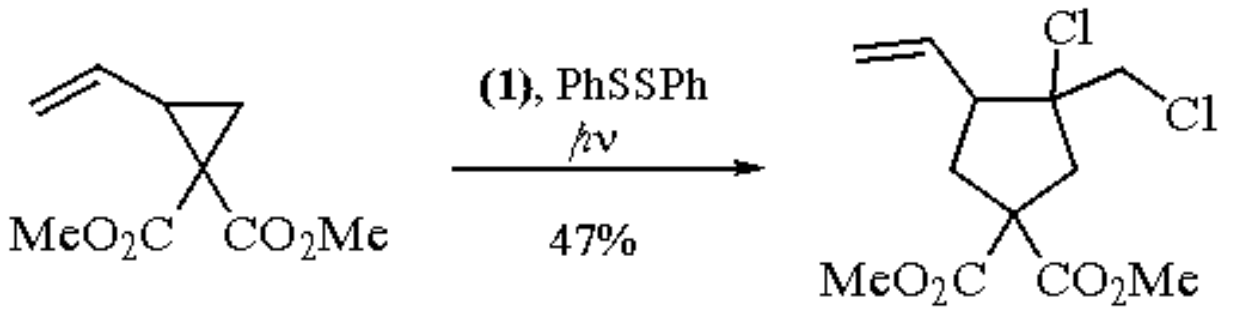

(9)

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1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane

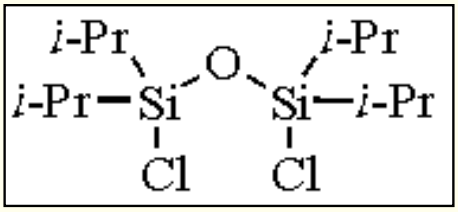

[69304-37-6] · $C_{12}H_{28}Cl_2OSi_2$ · 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane · (MW 315.43)

(simultaneous protection of the 3´- and 5´-hydroxyl functions of furanose nucleosides;[2,3] protecting group for carbohydrates;[4,5] protecting group reagent for open-chain polyhydroxy compounds;[6] preparation of cyclic bridged peptides[7])

Alternate Name: TIPSCl.

Physical Data: bp 70 °C/0.5 mmHg; *d* 0.986 g cm^{-3}.

Solubility: unaffected by water, 0.3M TsOH in dioxane, 10% TFA in chloroform, 5M NH_3 in dioxane-water (4:1), or isobutylamine-methanol (1:9), or tertiary amines (Et_3N, pyridine).

Form Supplied in: liquid; commercially available.

Preparative Method: can be prepared starting from ***Trichlorosilane*** by treatment with *i*-PrMgCl, H_2O, and ***Acetyl Chloride***.[1]

Handling, Storage, and Precautions: the liquid is corrosive and moisture sensitive.

Protection of the 3´- and 5´-Hydroxy Functions.

The reagent design was based upon the fact that triisopropylsilyl chloride reacts 1000 times faster with primary alcohols than secondary alcohols. Thus in the case of 3´,5´-dihydroxy nucleosides the reagent initially silylates at the 5´-position. This is then followed by intramolecular reaction with the secondary alcohol at the 3´-position to give the doubly protected derivative (eq 1).[2,3,8]

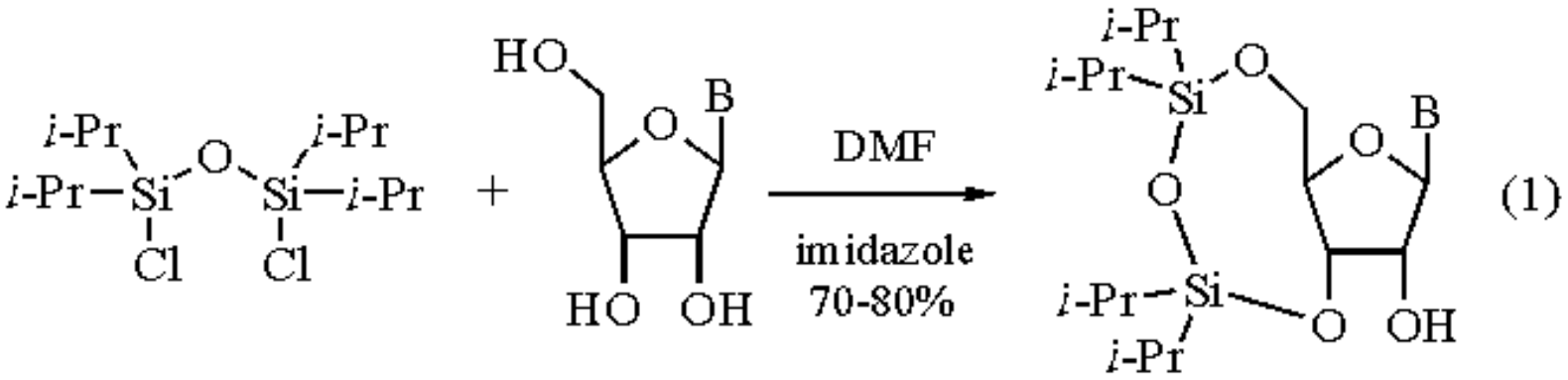

Rendering this protecting group of further utility is the fact that, in DMF under acidic conditions, silyl migration occurs affording the 2´,3´-disilyl derivative (eq 2).[4] This migration has been employed in the synthesis of carbohydrates (eq 3).[5,9]

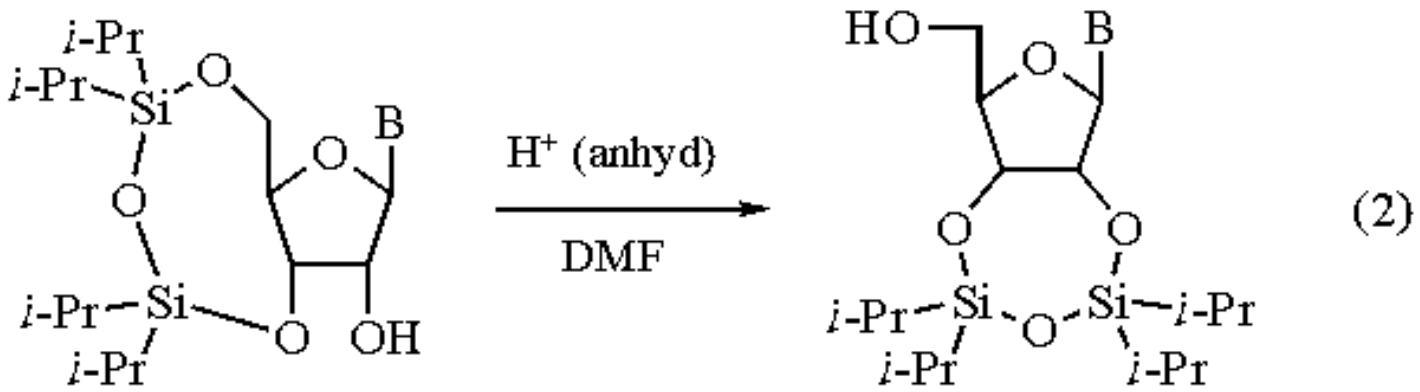

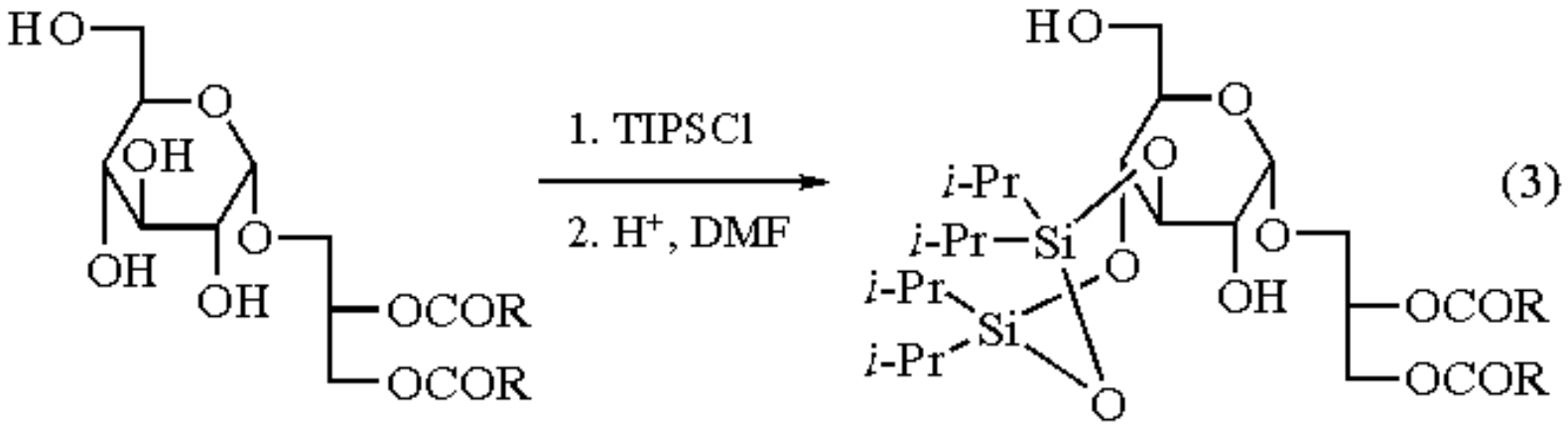

Protection of Open-Chain Polyhydroxy Compounds.

The utility of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane was extended to include open-chain polyhydroxy compounds. Glycerol reacted to form the eight-membered ring (eq 4) while the D-erythropentose derivative gave only the seven-membered ring (eq 5).[6] This strategy was used as a key step in the synthesis of the steroid 19-norcanrenone.[10]

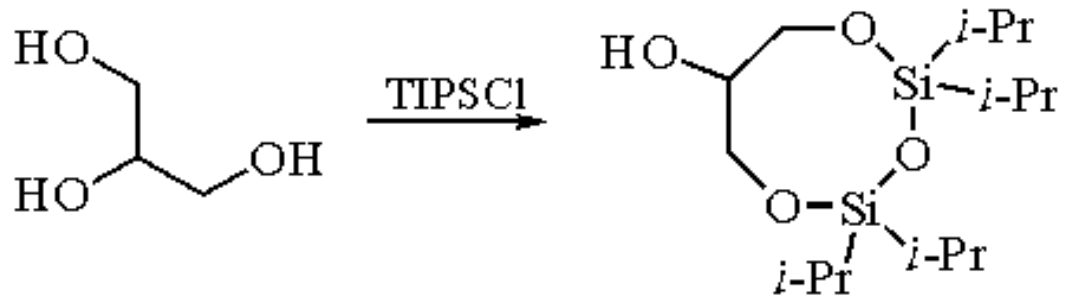

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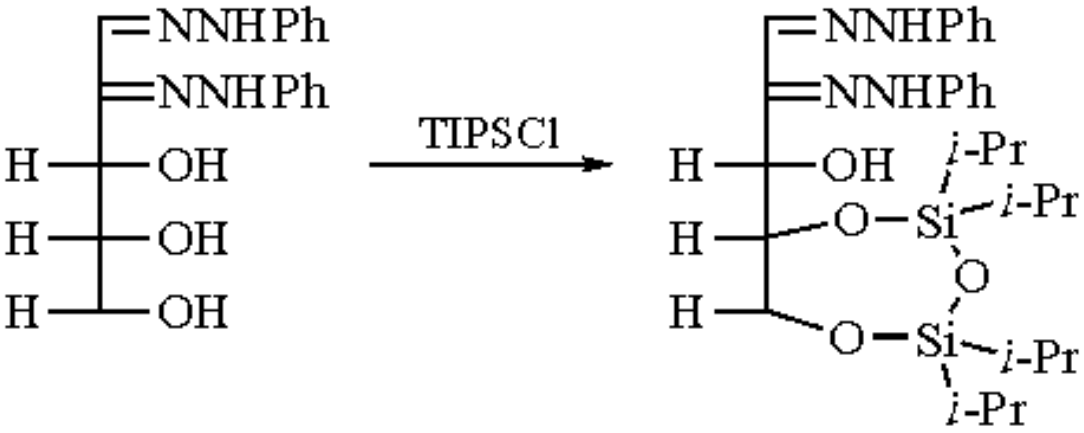

(5)

Preparation of Cyclic Bridged Peptides.

As part of a study aimed at improving the transport of peptides by derivatization with silyl reagents, the feasibility of restricting the conformational mobility of the enkephalin peptide backbone by bridging two serine residues with a disiloxane bridge was investigated. TIPSCl was chosen due to its specificity for primary alcohols as well as its ability to bridge secondary alcohols if present in the correct spatial environment.[7] Thus the solution phase syntheses of protected [Ser^2,Ser^5]- and [D-Ser^2,Ser^5]enkephalins were carried out followed by the reaction of the two free hydroxy groups in each with TIPSCl to afford the bridged disiloxane structures.

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Dichlorotitanium Diisopropoxide[1]

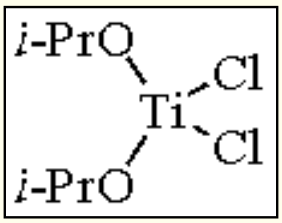

[762-99-2] · $C_6H_{14}Cl_2O_2Ti$ · Dichlorotitanium Diisopropoxide · (MW 236.962)

(a Lewis acid commonly used for the preparation of chiral titanium complexes;[2-5] a highly effective catalyst for Diels-Alder reactions,[4] [2 + 2] cycloadditions,[4] and carbonyl-ene reactions,[5] including asymmetric versions of these processes; reagent for the formation of titanium enolates;[6,7] component of catalysts used for the stereoselective additions of cyanide[3,8] and allyltin[9] nucleophiles to aldehydes[2])

Alternate Name: dichlorodiisopropoxytitanium.

Physical Data: crystalline solid.

Solubility: sol CH_2Cl_2, toluene, and other solvents.

Preparative Method: prepared by adding slowly at rt an equimolar amount of ***Titanium(IV) Chloride*** to a hexane solution of ***Titanium Tetraisopropoxide***; following mixing, during which heat is evolved, the mixture is allowed to stand at rt for 6 h and the precipitate is collected and washed with hexane; dibromotitanium diisopropoxide is prepared similarly.[10]

Purification: recrystallization from hexane, followed by drying under vacuum.[11,12]

Handling, Storage, and Precautions: corrosive; moisture sensitive; use in a fume hood; can be stored under nitrogen in pure form or in solution.

Preparation of Chiral Titanium Complexes.[2-5]

A variety of Lewis acid promoted transformations which are mediated by titanium complexes can take place with significant enantiocontrol by incorporating chiral nonracemic alkoxy ligands on titanium. One of the most common titanium sources for the synthesis of these derivatives is the title reagent (**1**), although ***Chlorotitanium Triisopropoxide*** and ***Titanium Tetraisopropoxide*** are also used. Usually, the two isopropoxy groups are replaced with a chiral diol either by the azeotropic removal of isopropyl alcohol or by simply mixing (**1**) and the chiral diol in the presence of 4Å molecular sieves. The latter method has been used successfully in several catalytic asymmetric

reactions. Among the most effective catalysts for this purpose are the titanium complexes derived from (**1**) and (*S*)- or ***(R)-1,1´-Bi-2,2´-naphthol*** (BINOL) (eq 1)[5,12] and TADDOL, a bulky tartrate-derived diol (eq 2).[3,4,13]

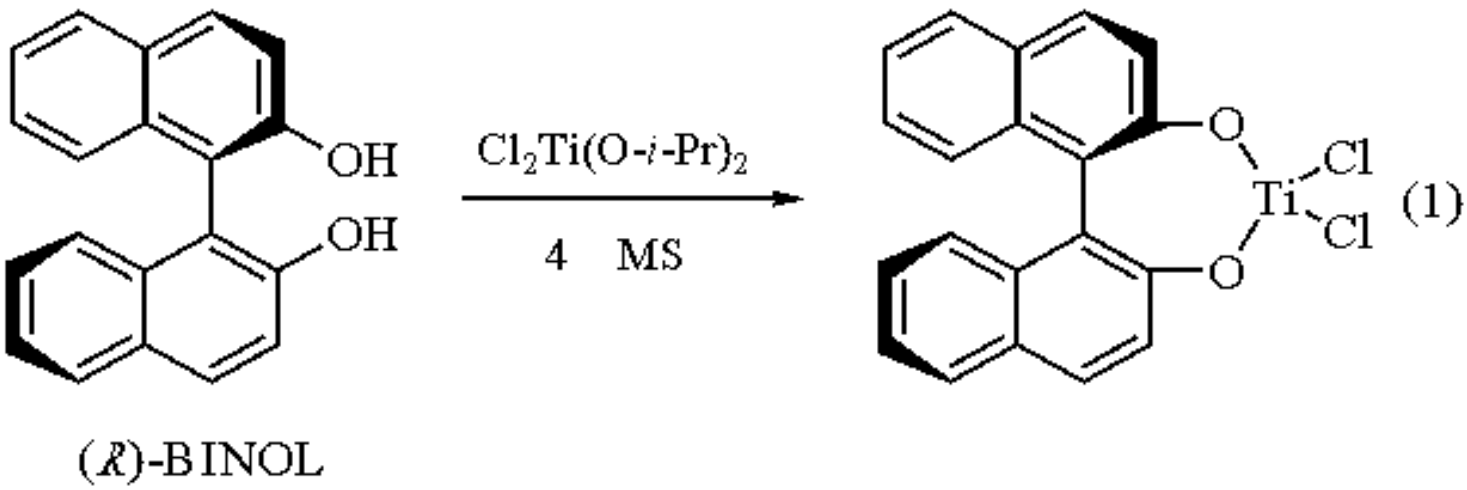

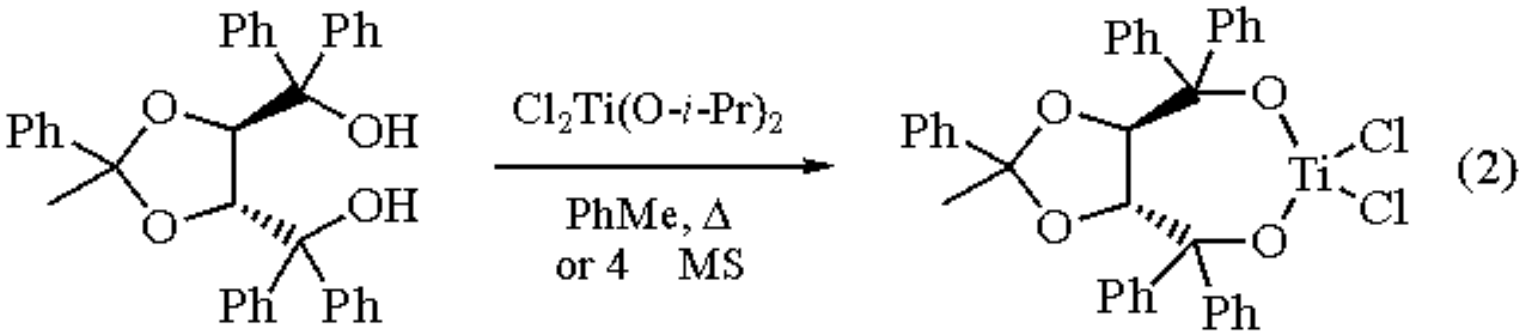

[4 + 2] Cycloadditions.

Even when they are generated in situ, the above titanium complexes are very effective catalysts for the asymmetric Diels-Alder reactions of certain dienes and dienophiles, such as acyloxyoxazolidinones (eq 3).[13]

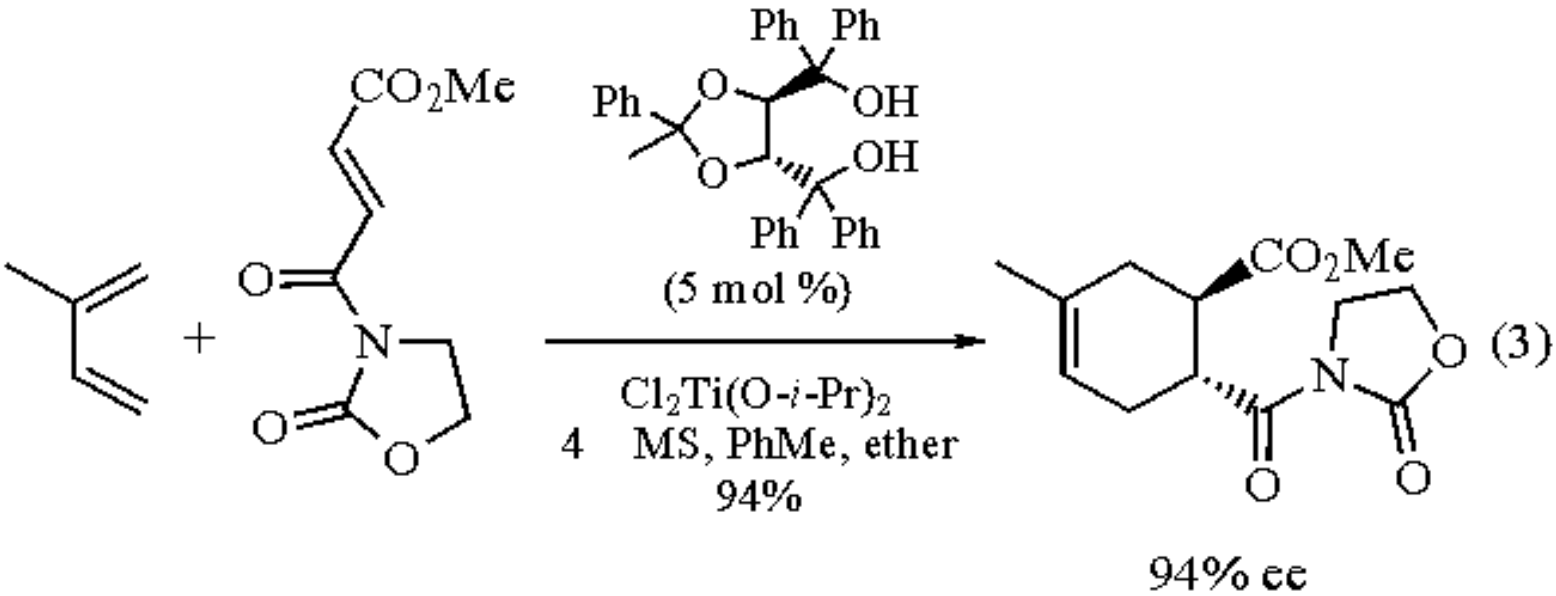

Very high enantioselectivity is observed in the Diels-Alder reactions of some chiral dienophiles in the presence of (**1**) (eq 4).[14]

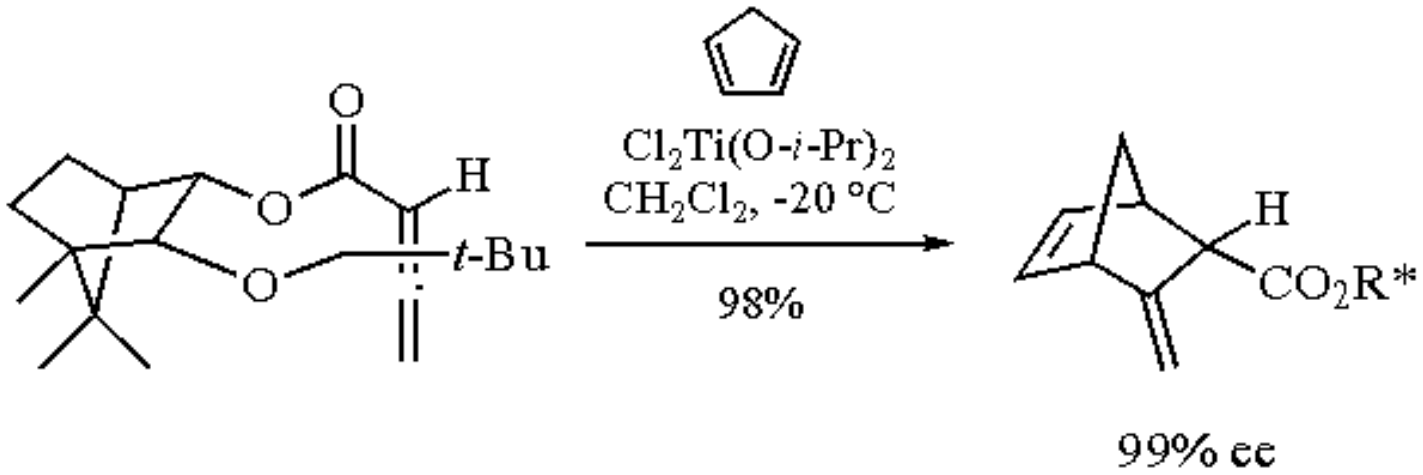

The reagent derived from (**1**) and BINOL is an excellent catalyst for the hetero Diels-Alder reactions of glyoxylates (eq 5).[5,15]

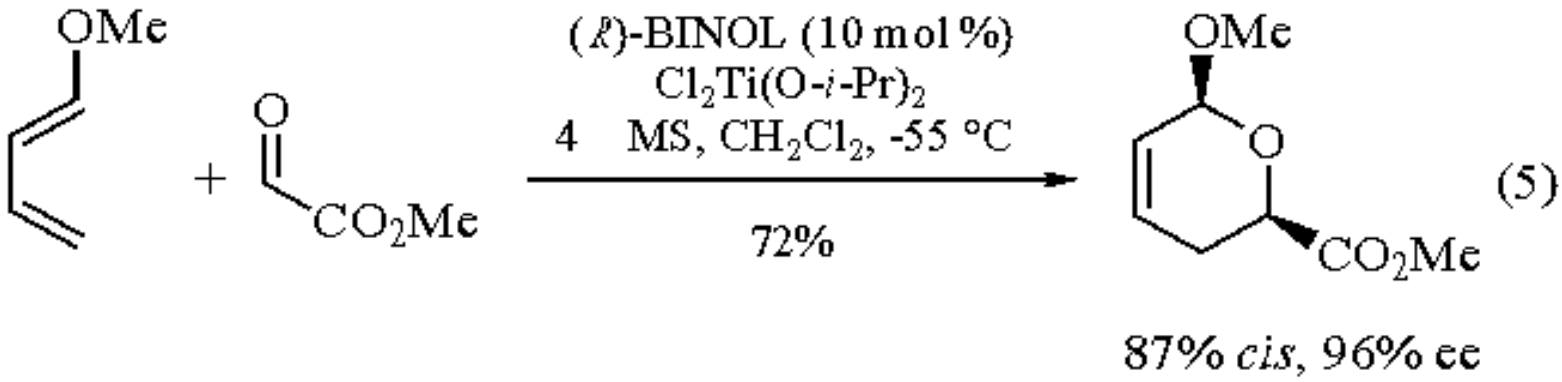

[2 + 2] Cycloadditions.[3,4]

The chiral titanium derivative in eq 2 is an efficient catalyst for the asymmetric [2 + 2] cycloadditions of alkynyl,[16] allenyl,[17] and alkenyl sulfides (eq 6).[18]

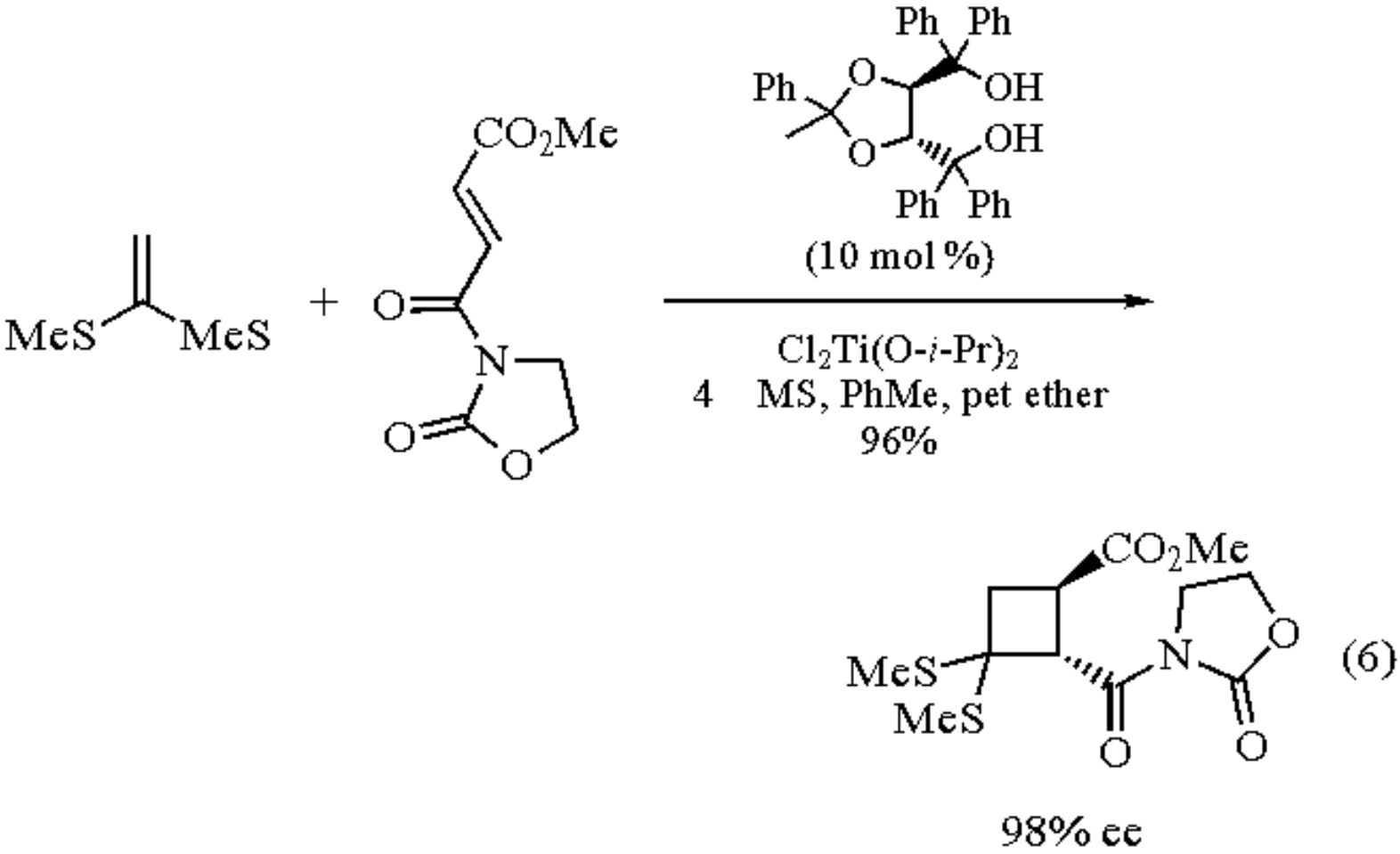

Carbonyl-Ene Reaction.[5]

The combination of (**1**) with BINOL (eq 1) is a very effective catalyst for the asymmetric carbonyl-ene reaction of glyoxylates (eq 7).[11] The bromo analog of (**1**) is also effective in this process.[11,12] The kinetic resolution of racemic alkenes, the desymmetrization of symmetrical dialkenes, as well as certain intramolecular variants of this reaction,[19] proceed with equally high diastereo- and enantioselectivity.[5] Similar ene-type products are also obtained during the addition of silyl enol ethers to glyoxylates.[20]

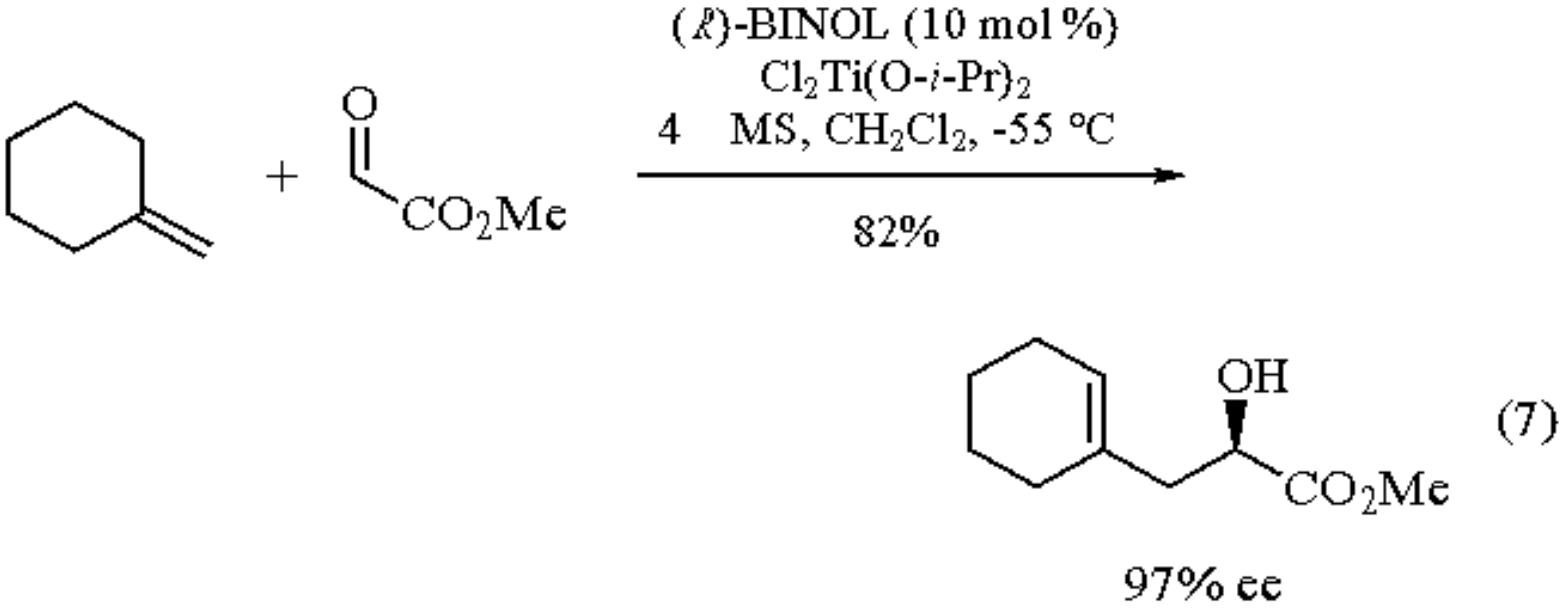

Titanation of Enolates.

The enolates derived from the imines of α-amino esters in the presence of (**1**) or ***Chlorotitanium Triisopropoxide*** react with α,β-unsaturated carbonyl compounds to form pyrrolidine derivatives.[6,21] They also react with aldehydes to form *anti*-amino alcohol products upon hydrolysis of the intermediate oxazolidines (eq 8).[7]

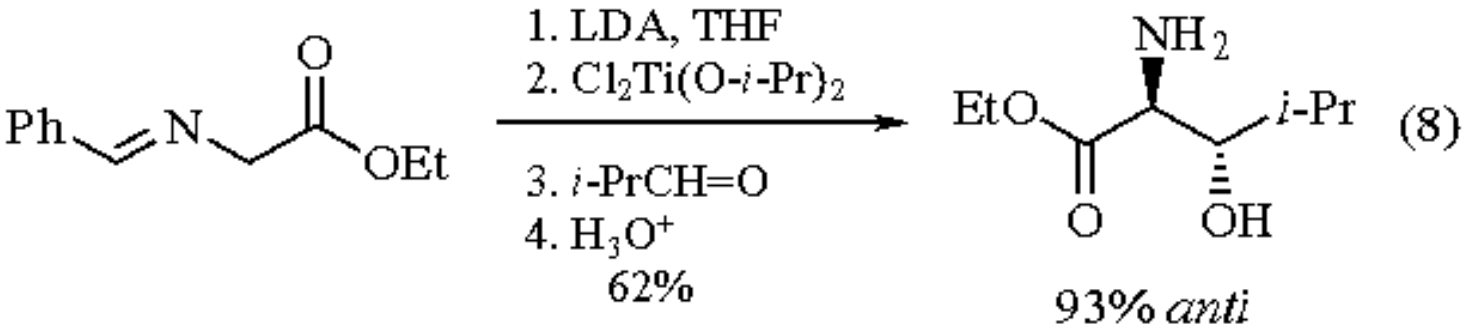

Enantioselective Additions to Aldehydes.

The chiral titanium complexes formed in situ from (**1**) can efficiently catalyze the asymmetric addition of cyanide,[3,8] as well as allyltin nucleophiles to aldehydes (eq 9).[9]

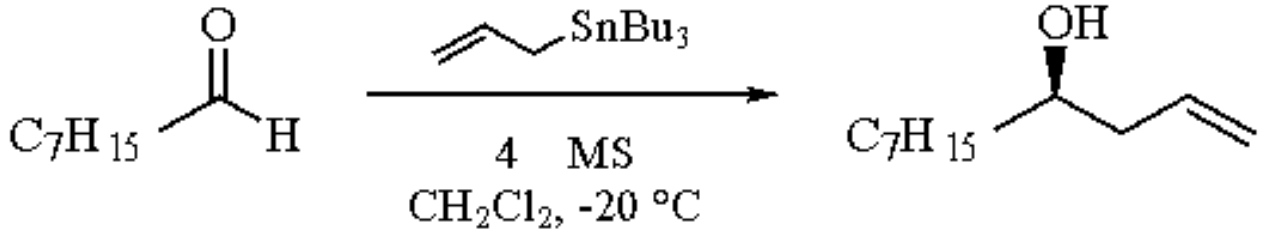

(9)

20 mol % $Cl_2Ti(O\text{-}i\text{-}Pr)_2$ 0%
20 mol % $Cl_2Ti(O\text{-}i\text{-}Pr)_2$, (*S*)-BINOL 81% (97% ee)

Related Reagents.

(R)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide; ***Chlorotitanium Triisopropoxide***.

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1,3-Dichloro-2-trimethylsiloxy-1-butene

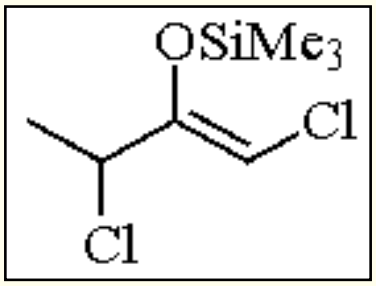

[80422-55-5] · $C_7H_{14}Cl_2OSi$ · 1,3-Dichloro-2-trimethylsiloxy-1-butene · (MW 213.18)

(1,3-dichloro-2-butanone equivalent; presursor of 1-chloro-3-methyl-2-oxyallyl cation;[1] substrate for double alkylation or selective arylation[2])

Alternate Name: [2-chloro-1-(chloromethylene)propoxy]trimethylsilane.

Physical Data: colorless oil; bp 54.5-55.5 °C/5 mmHg; IR (neat) 1630 cm^{-1} ($\nu_{C=C}$); ^1H NMR (60 MHz, CCl_4) δ 0.31 (s, 9H, $SiMe_3$), 1.60 (d, *J* = 6.6 Hz, 3H, allylic methyl), 4.40 (q, *J* = 6.6 Hz, 1H, allylic), and 5.56 (s, 1H, alkenic).

Solubility: sol common organic solvents (THF, Et_2O, CH_2Cl_2, $MeNO_2$).

Preparative Method: a solution of 1,3-dichloro-2-butanone (14 g, 0.1 mol) in ether (25 mL) is added dropwise into a stirred mixture of ***Chlorotrimethylsilane*** (12 g) and ***Triethylamine*** (12 g) in ether (100 mL) at ambient temperature. The mixture is stirred under reflux for 7 h and poured into ice water. The organic layer is washed with cold water, dried ($MgSO_4$), and concentrated. Distillation of the resulting oil under reduced pressure (5 mmHg) gives the reagent (18 g, 83%), which is exclusively of (*Z*) configuration;[1] the stereochemistry of the enol silylation depends on the solvent and base employed.[3] 1-Chloro-2-trimethylsiloxy-1,3-butadiene is sometimes an impurity (less than 5%).

Handling, Storage, and Precautions: the reagent is sensitive to moisture, especially under acidic conditions. If protected from moisture, it can be stored for years without significant decomposition.

2-Oxyallyl Cation.

Silver perchlorate induces ionization of this reagent, generating the 1-chloro-3-methyl-2-(trimethylsiloxy)allyl cation, which reacts with ***Furan*** or ***Cyclopentadiene*** to give corresponding seven-membered bicyclic ketones.[1] Thus a treatment of the reagent (5 mmol) with ***Silver(I) Perchlorate*** (2 equiv) in nitromethane in the presence of furan (25 mmol) and calcium carbonate (15 mmol as a buffer) yields 2-chloro-4-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one as a mixture of two stereoisomers bearing an axial Cl group (eq 1); with cyclopentadiene, a mixture of all four possible stereoisomers is formed (76%). Electrophilic substitution instead of cycloaddition occurs when the reaction with furan is carried out in THF/ether (1:2) in place of nitromethane (eq 2).

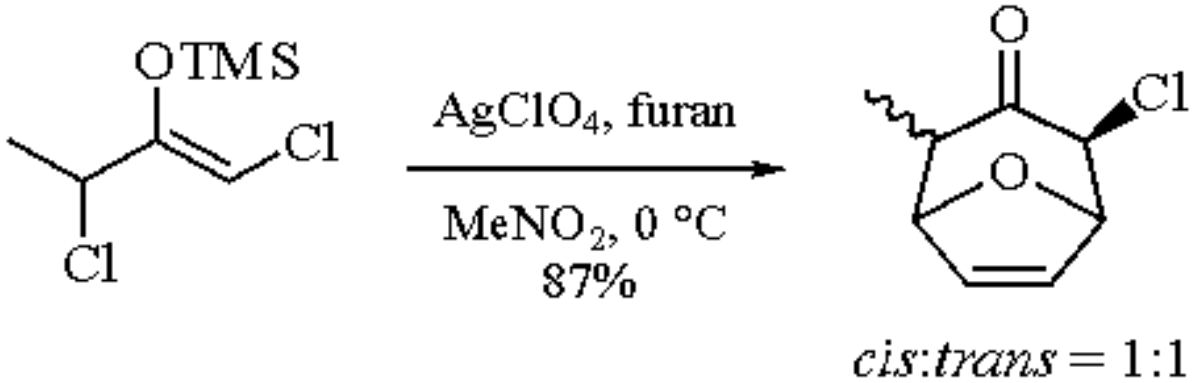

(1)

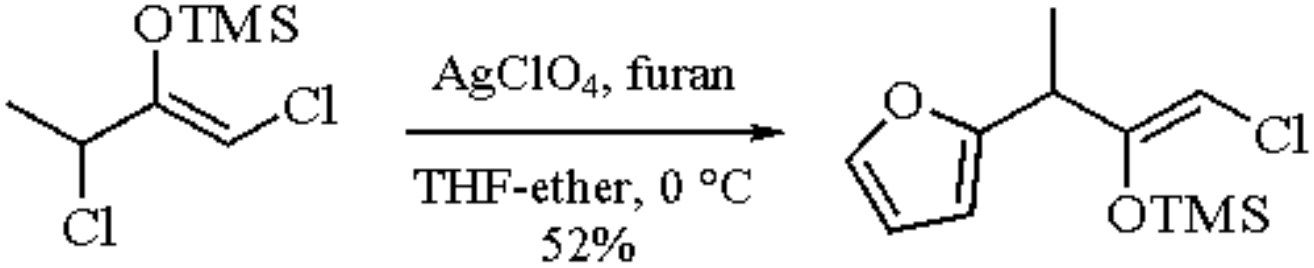

(2)

Alkylation and Arylation.

Reaction with 2 equiv of alkyl Grignard reagents in the presence of 10% ***Copper(I) Iodide*** in THF/HMPA (10:1) results in double alkylation via successive S_N2' displacements (eq 3). The allylic chlorine is selectively replaced with an aryl group upon treatment with 2.5 equiv of bis(aryl)copper(I) lithium in ether (eq 4).[2]

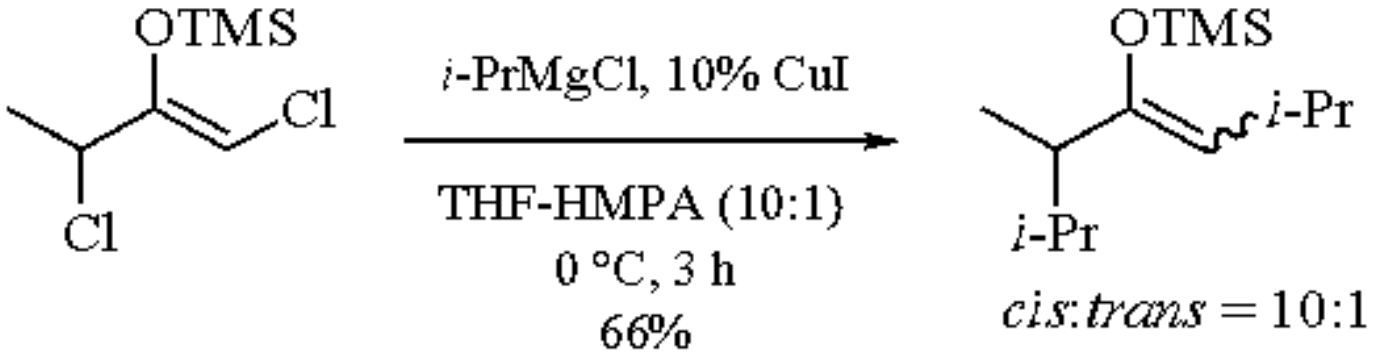

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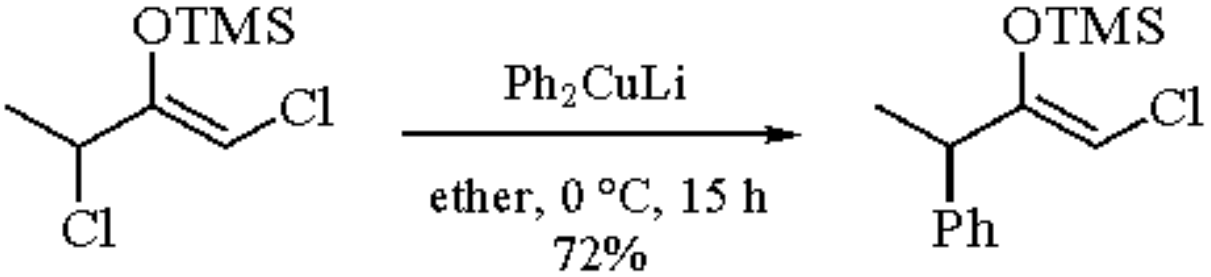

(4)

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Dichlorotris(triphenylphosphine)ruthenium(II)[1a]

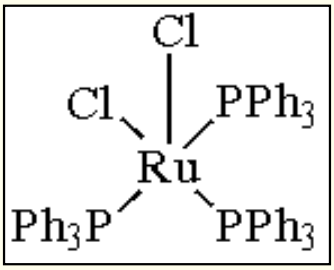

[15529-49-4] · $C_{54}H_{45}Cl_2P_3Ru$ · Dichlorotris(triphenylphosphine)ruthenium(II) · (MW 958.86)

(used in the hydrogenation of nitro groups,[10,12] imines,[15] and ketones,[14] and the selective oxidation of alcohols[21-23])

Physical Data: mp 132-134 °C.

Solubility: sol toluene, benzene, CH_2Cl_2.

Form Supplied in: red-brown or shiny black crystals.

Preparative Method: by refluxing hydrated ***Ruthenium(III) Chloride*** and ***Triphenylphosphine*** in ethanol according to the procedure of Wilkinson.[1b]

Carbocycles.

The title reagent (**1**) is a versatile homogeneous catalyst. It is used in the reduction, oxidation, cyclization, and isomerization of a variety of organic compounds. It is an effective catalyst for the Kharasch addition of a range of halogenated substances to alkenes.[3,4] α-Chloro-γ-lactones (eq 1)[5a] or carbocyclic α,γ-dichloroesters[5b] are formed by reaction of alkenic α,α-dichloro acids and esters in the presence of (**1**). The process occurs through a metal-complex radical and provides highly functionalized products. The reagent is also used in radical cyclizations of *N*-allylacetamides[6-8] and the stereoselective addition cyclization of 1,6-dienes (eq 2).[9] The synthesis of α,β-unsaturated ketones from primary alcohols and allyl acetates is catalyzed by (**1**).[10]

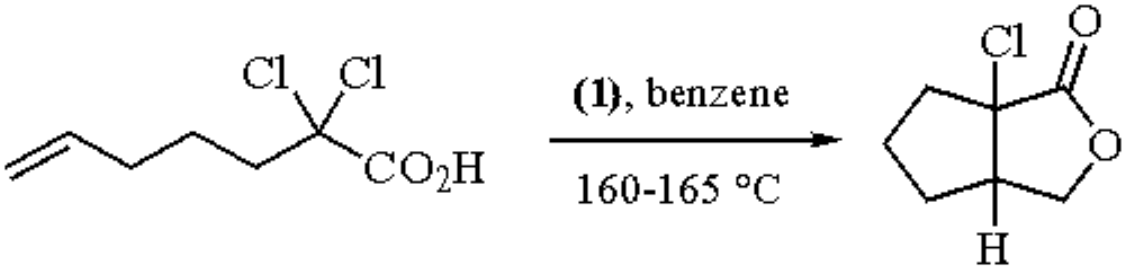

(1)

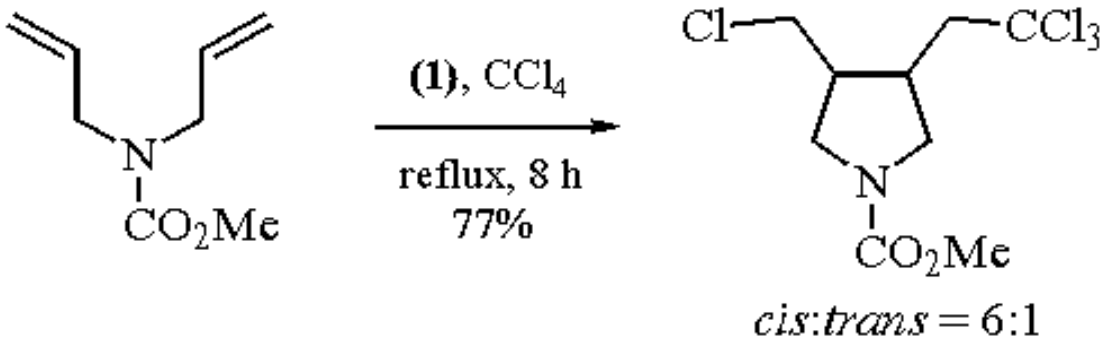

(2)

Reductions.

The reagent (**1**) can promote hydrogen transfer from alcohols,[14,15] acids,[17] and amides, as well as other hydrogen donors, to activated double bonds,[14,15] carbonyl compounds, and nitro groups. It is an efficient homogeneous catalyst for the hydrogenation of nitroalkanes to amines,[11] nitroarenes to amino arenes,[12,13] and imines to amines (eq 3).[16]

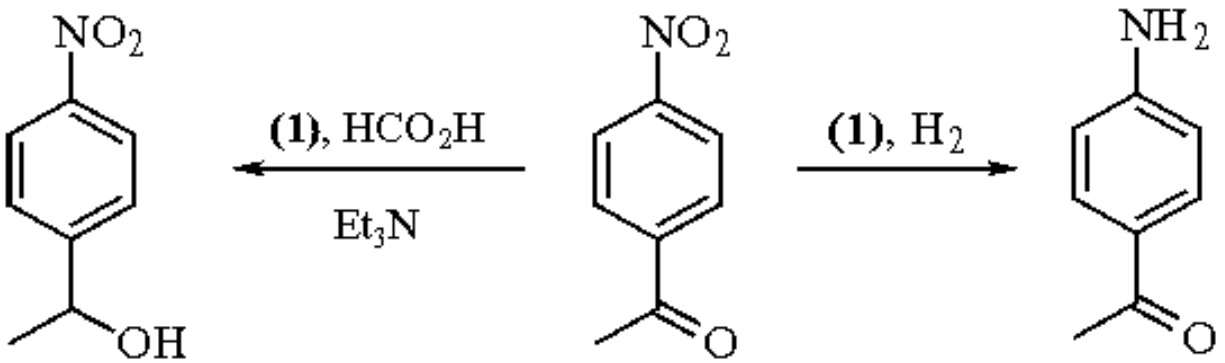

(3)

The ruthenium-catalyzed reduction of diallyl-α-oxalyl carboxylates with ***Formic Acid*** provides α-hydroxycarboxylic acids in good yields.[17]

Oxidations.

The reagent (**1**) can catalyze the oxidation of alkanes to tertiary alcohols,[18] amides to *t*-butyldioxyamides,[19] and tertiary amines to α-(*t*-butyldioxy)alkylamines[20] using ***t-Butyl Hydroperoxide***. *N*-Demethylation of tertiary methylamines is accomplished by hydrolysis of the α-(*t*-butyldioxy)alkylamine (eq 4). Alcohols have been oxidized to aldehydes and ketones in the presence of (**1**) and oxidants such as ***Bis(trimethylsilyl) Peroxide***,[21] molecular ***Oxygen***,[22] ***Acetone***,[23a] or ***N-Methylmorpholine N-Oxide***.[23b]

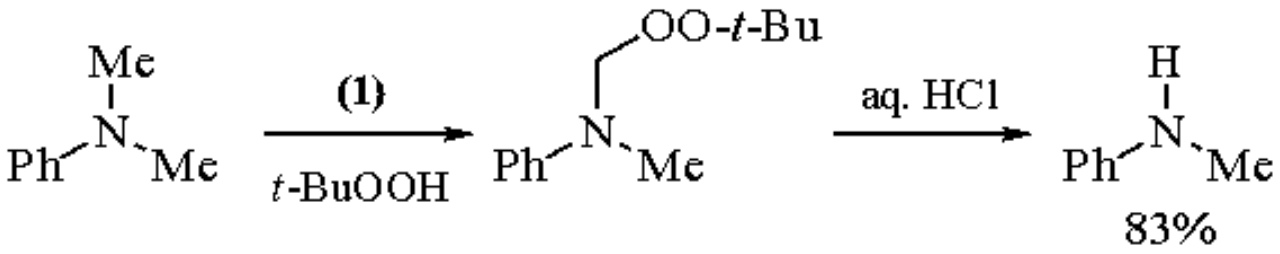

(4)

Isomerizations.

The reagent (**1**) catalyzes the isomerization of α,β-ynones to (*E*,*E*)-α,β,γ,δ-dienones,[24] allylic alcohols to ketones,[25a] and 2-ynols to α,β-unsaturated aldehydes.[25b] The Claisen rearrangement of unsymmetrical diallyl ethers is catalyzed by (**1**) to yield α,δ-unsaturated aldehyes or ketones.[25c]

The reagent can be immobilized on a polystyrene support. The immobilized complex can be reused, thereby making this heterogeneous system more efficient than the homogeneous one. This heterogeneous catalyst has been used in the isomerization of allylarenes.[2,26]

Heterocycles.

The reagent (**1**) is used in the *N*-alkylation of NH groups of azoles with alcohols under neutral conditions,[27] and in the synthesis of indoles[28] via an intramolecular *N*-alkylation. It is also used in the syntheses of important biologically active compounds such as imidazo[1,2-*a*]pyridines (eq 5).[29] Other important heterocycles such as 1,3-disubstituted 2,3-dihydroimidazol-2-ones are effectively prepared from *N*,*N*-disubstituted ureas and vicinal diols in presence of (**1**).[30] The reagent catalyzes the oxidation of the vicinal diol to the corresponding acyloin, and condensation of the urea with the acyloin followed by dehydration yields the desired product (eq 6).[31]

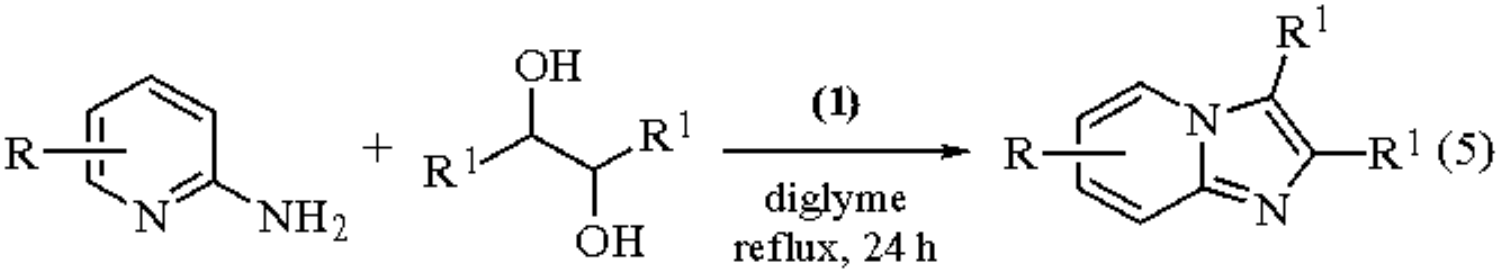

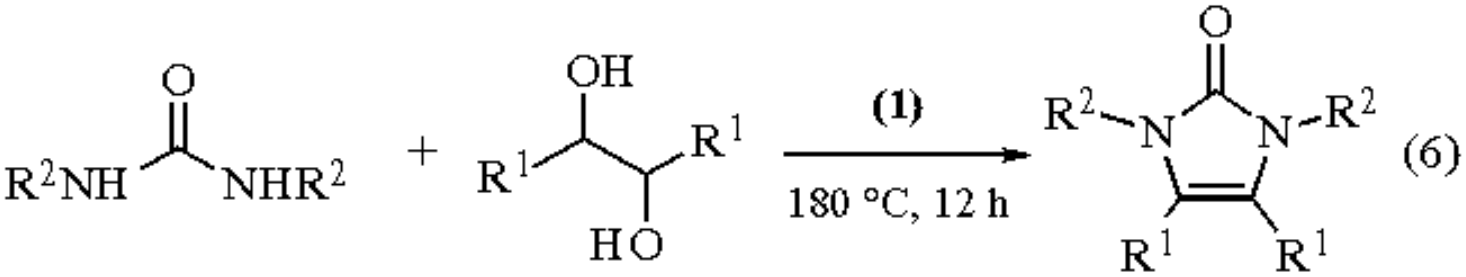

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N,N-Dichlorourethane[1]

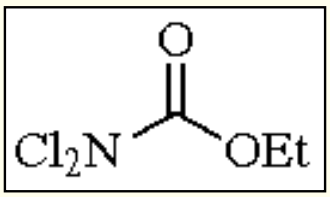

[13698-16-3] · $C_3H_5Cl_2NO_2$ · *N,N*-Dichlorourethane · (MW 157.98)

(stable but reactive pseudohalogen which adds to alkenes to give β-chlorocarbamates;[1] useful for the chlorination of tertiary hydrocarbons[2] and activated aromatics[3])

Alternate Name: DCU.

Physical Data: bp 55-56 °C/15 mmHg; 74-76 °C/15 mmHg;[6] *d* 1.349 g cm^{-3}.

Solubility: insol H_2O; sol benzene, acetic acid, acetonitrile.

Form Supplied in: liquid; widely available; purity of commercial material 90-98%.

Analysis of Reagent Purity: by iodometric titration for positive halogen.[5,6]

Purification: vacuum distillation affords the reagent with a purity of >99.5%.[6]

Handling, Storage, and Precautions: lachrymatory liquid; fairly stable in the dark for at least several weeks at 25 °C.[6,7] Store under inert atmosphere. This reagent should be handled in a fume hood.

Addition to Alkenes to give β-Chlorocarbamates.

Simple alkenes add DCU by a radical mechanism to afford, initially, β-chloro-*N*-chlorocarbamates, which are hydrolyzed to β-chlorocarbamates. Terminal alkenes give the products of anti-Markovnikov addition in 50-80% yields.[6,7] For example, 1-hexene provides *N*-(2-chloro-*n*-hexyl)carbamate (eq 1).[6]

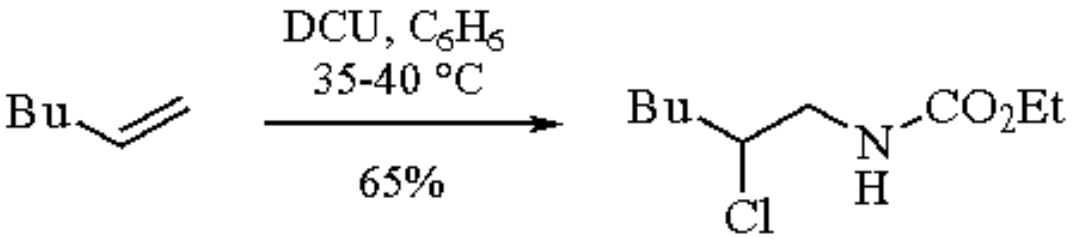

(1)

Addition to nonterminal alkenes is complicated by competing allylic chlorination; in these cases, yields of β-chlorocarbamates are generally only 30-40% (eq 2).[6] Styrene and *trans*-stilbene give better yields of addition products with DCU (80% and 65%, respectively).[6]

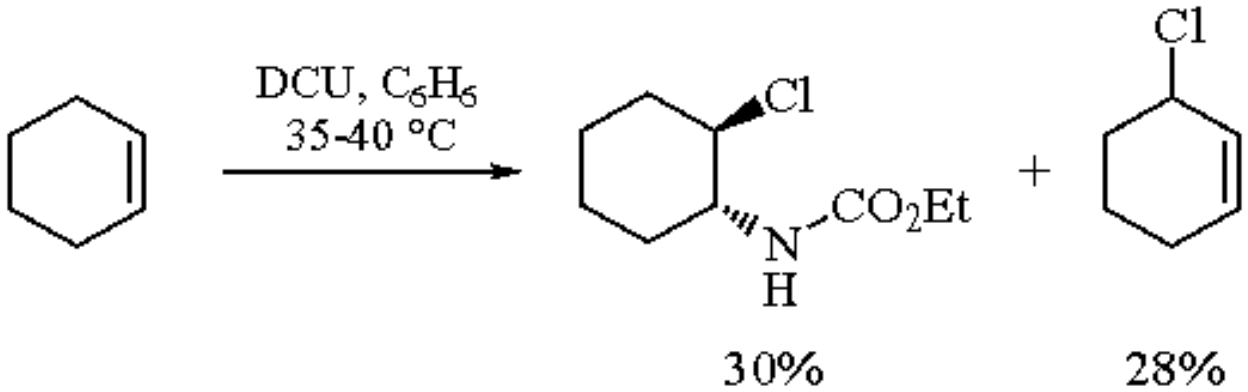

(2)

The β-chlorocarbamate products are useful intermediates for conversion to oxazolidones (eq 3) or aziridines (eq 4).[7,8]

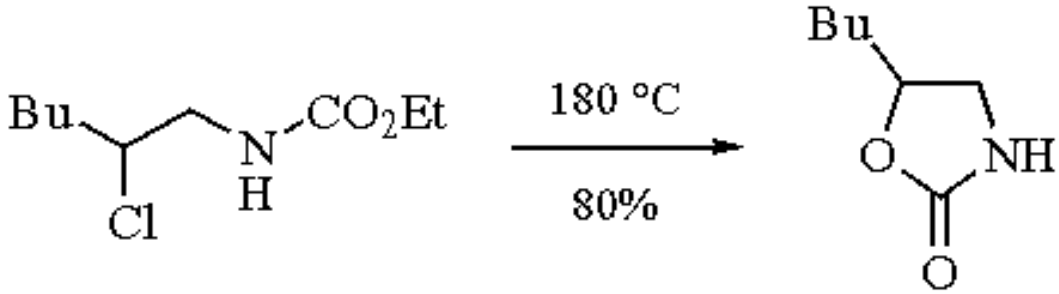

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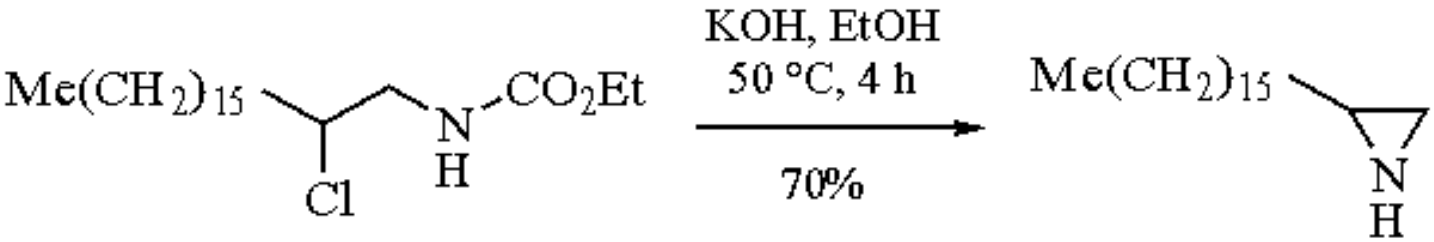

(4)

The addition of DCU to indenes,[9,10] unsaturated silanes,[11] and a variety of alkenes containing electron-withdrawing groups[12] has been described. A review of the addition reactions of DCU with alkenes has been published.[1]

Chlorination of Tertiary Hydrocarbons.

Unactivated tertiary hydrogens in some steroids can be selectively replaced with chlorine by reaction with DCU under

UV irradiation. The resulting chlorides have been treated with ***Silver(I) Perchlorate*** to afford alkenes (eq 5),[2] or hydrolyzed to alcohols (eq 6).[13]

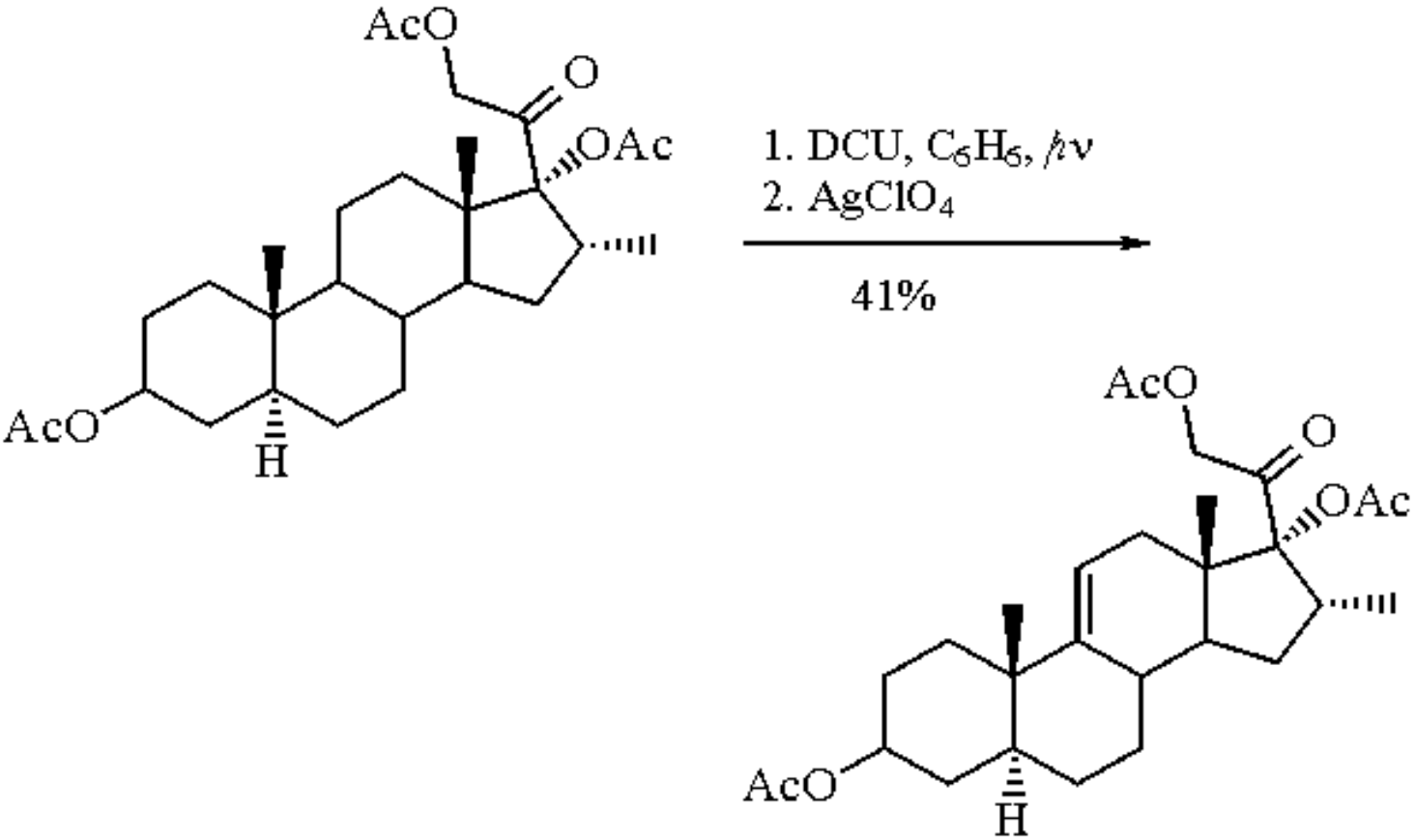

(5)

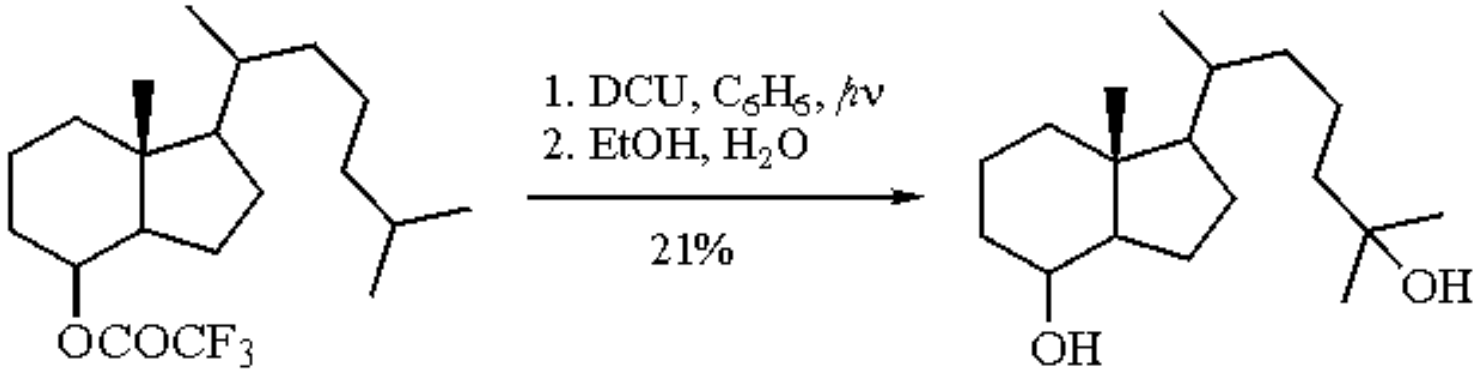

(6)

Chlorination of Activated Aromatics.

Anisole gives 4-chloroanisole in high yield with DCU; 2,4-dichloroanisole is also formed (eq 7).[3] Selective monochlorination of some isoflavones has been reported.[14]

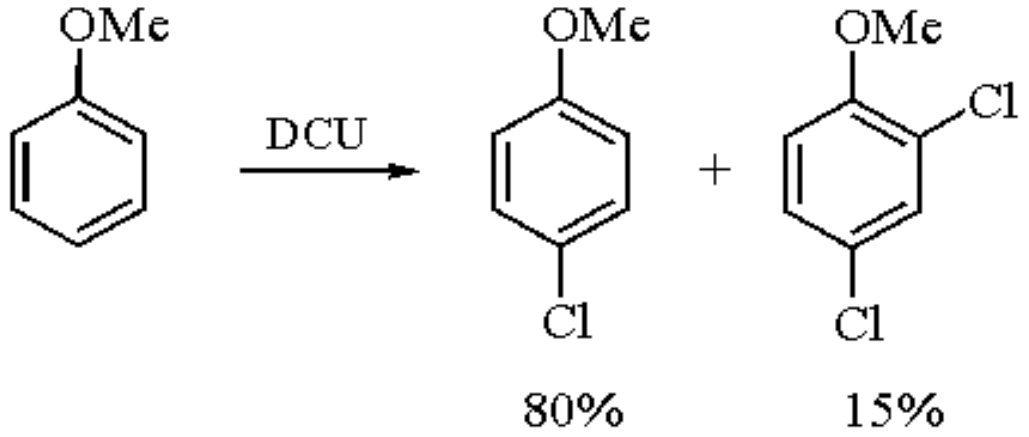

(7)

Other Reactions.

Organoboranes afford alkyl chlorides with DCU;[4] however, other reagents, such as ***Chloramine-T*** or ***Trichloramine*** are generally more effective. 2-Substituted indoles give chlorinated 2-indolinones with DCU.[15] Nitroso derivatives are oxidized with DCU in the presence of ***Copper(II) Bromide*** to provide azoxy compounds.[5] Alkyl ethers can undergo cleavage reactions with DCU, to afford β-chloro(biscarbamates).[3]

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Dichlorovinylene Carbonate[1]

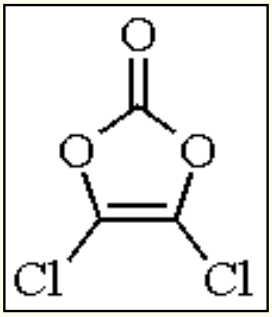

[17994-23-9] · $C_3Cl_2O_3$ · Dichlorovinylene Carbonate · (MW 154.94)

(dienophile for aromatics;[1] 1,2-dione synthesis;[2] ketene generation[3])

Alternate Name: 4,5-dichloro-1,3-dioxolen-2-one.

Physical Data: mp 19 °C; bp 39-40 °C/10 mmHg.

Solubility: sol acetone, benzene, xylene.

Preparative Method: by chlorination/dechlorination of ethylene carbonate.[2,4]

Handling, Storage, and Precautions: lachrymator; may be stored indefinitely in the refrigerator; slowly decomposes to CO and oxalyl chloride in the liquid state or in dilute aprotic solvents; decomposes at rt with phosphorus nucleophiles.

Reactivity Pattern.

Dichlorovinylene carbonate (**1**) is used primarily as a dienophile (weak) in thermal and photocycloaddition reactions. Once formed, the cycloadducts are hydrolyzed to give 1,2-dione or glyoxylic acid derivatives that are generally used as precursors of target molecules. As such, it may be considered a synthon for dicarbon suboxide (eq 1).

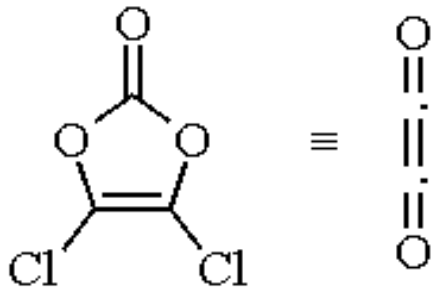

(1)

Cycloaddition Reactions.

Benzene, anthracene, and phenanthrene derivatives undergo cycloadditions with (**1**) to give 1,2- or 1,4-adducts. Acetophenone is generally used as the photosensitizer.[5] Typical chemistry is illustrated (eq 2) by its photocycloaddition with benzene to give adduct (**2**) that was then hydrolyzed to dione (**3**).[2]

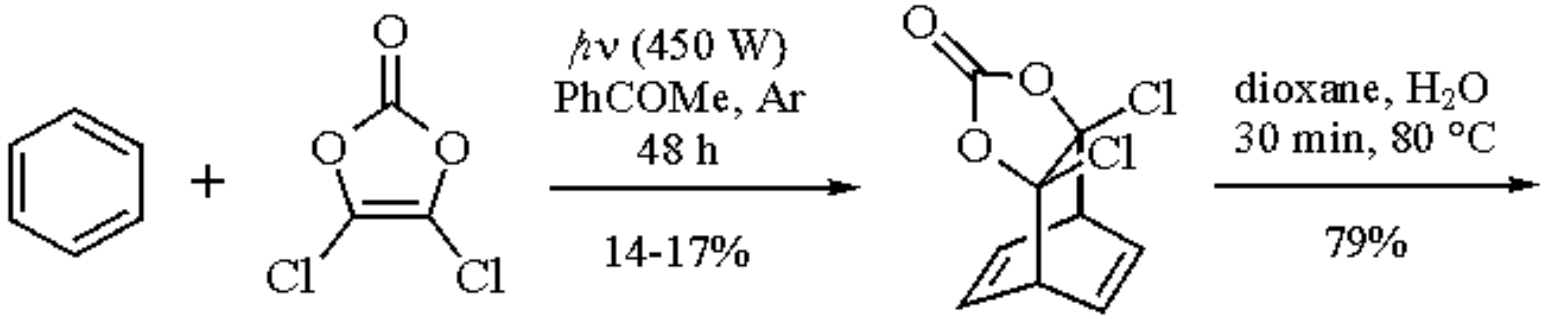

(1) (2)

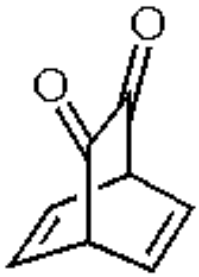

(2)

(3)

Phenanthrene and (**1**) give predominately one stereoisomer (shown) in a [2 + 2] photoreaction. Hydrolysis to the diketone followed by a benzilic acid rearrangement gives the cyclopropyl-α-hydroxy acid (eq 3).[6]

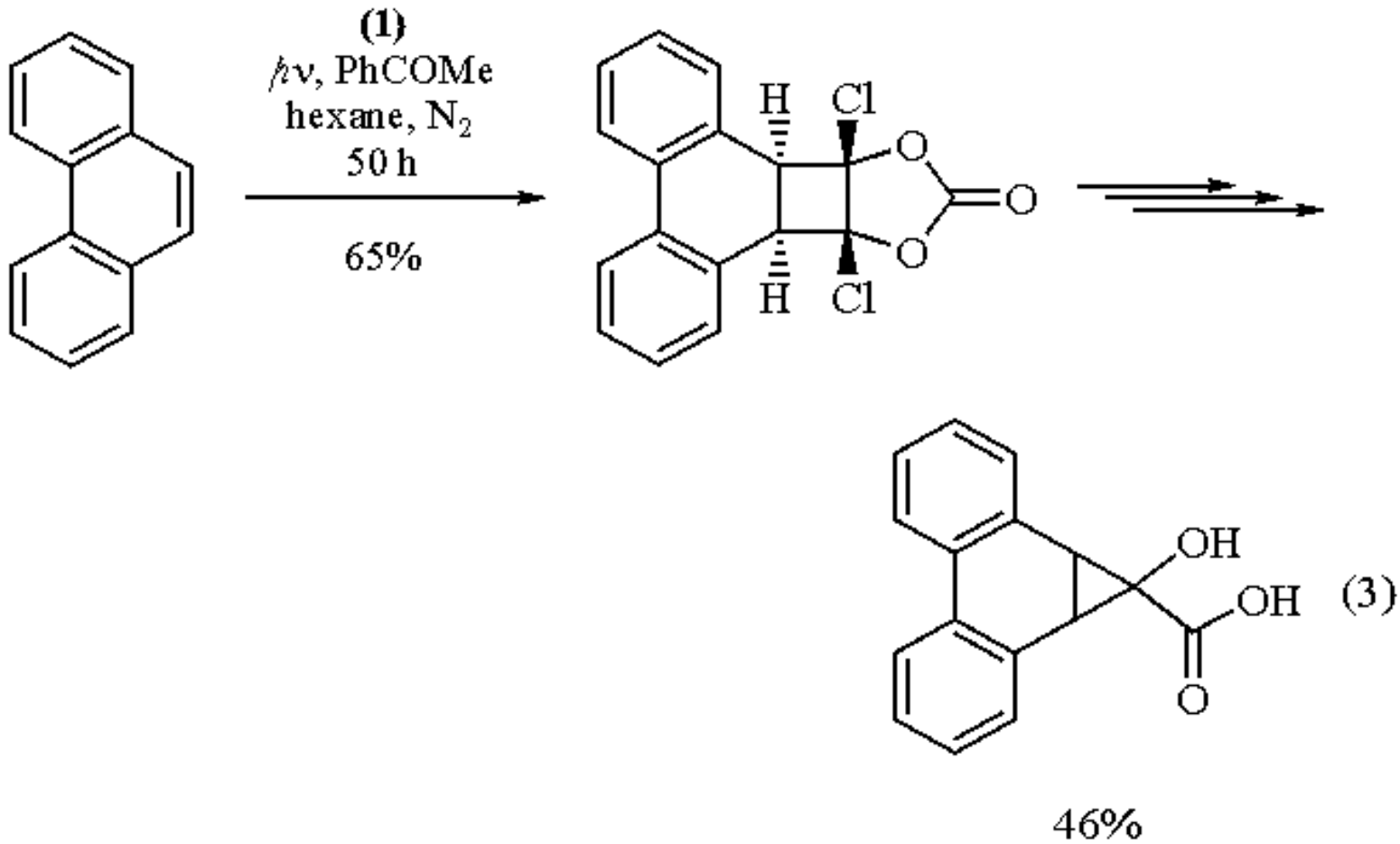

With anthracene, a thermal cycloaddition (refluxing in *p*-xylene) gives a 1,4-adduct (84%) and its dione (78%) upon hydrolysis (eq 4; X = H).[7] Ketene derivatives are available through this chemistry (eq 4; X = OMe).[3]

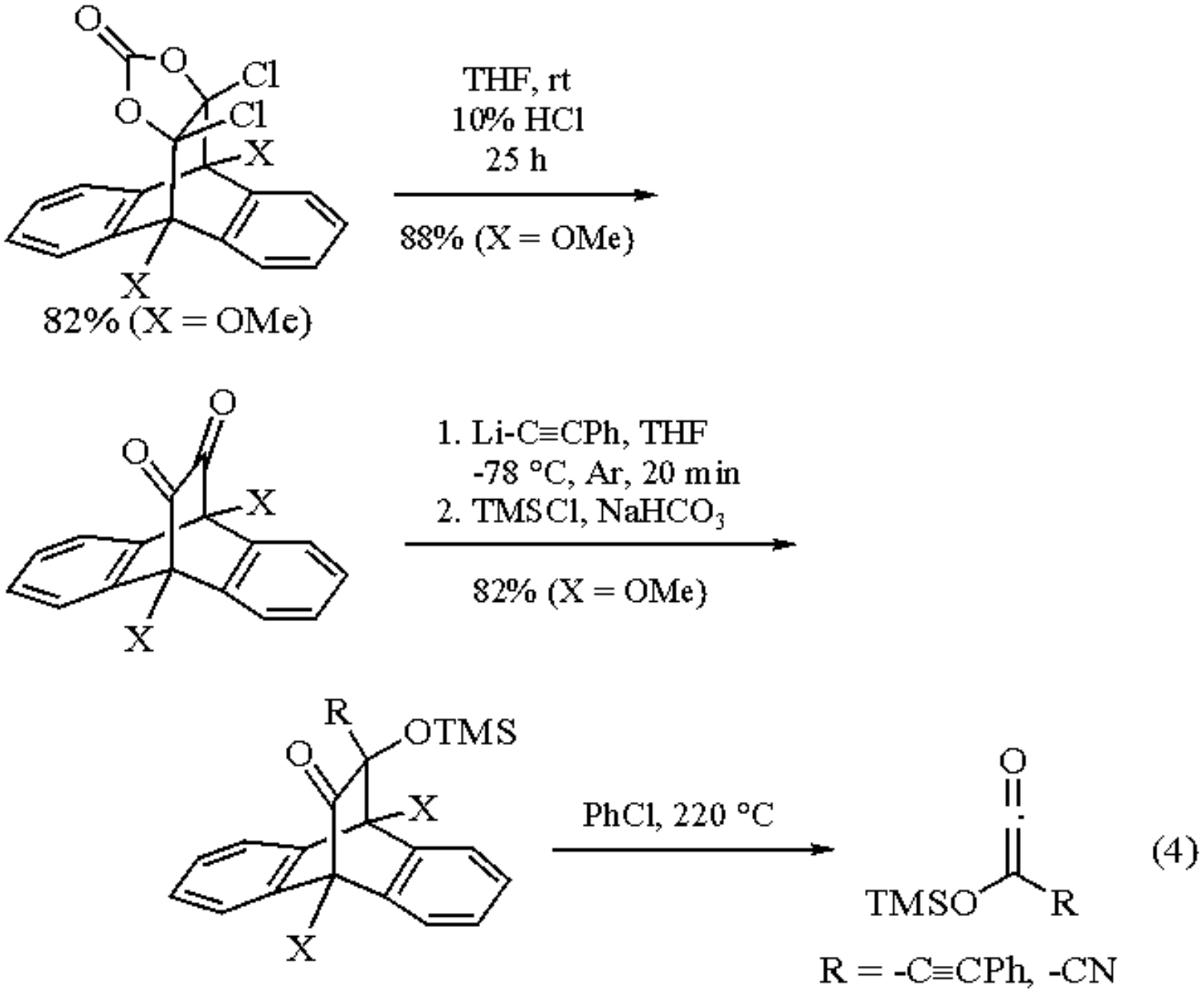

(4)

Alkenes,[8] alkynes,[1,9] and dienes[7,10] undergo cycloaddition as well. Eq 5 shows a two-step synthesis of a cyclobutenedione derivative[11] (see ***N,N-Diethyl-1-propynylamine*** for an alternate route). Less substituted alkenes such as ethylene also work well in this type of reaction.[8]

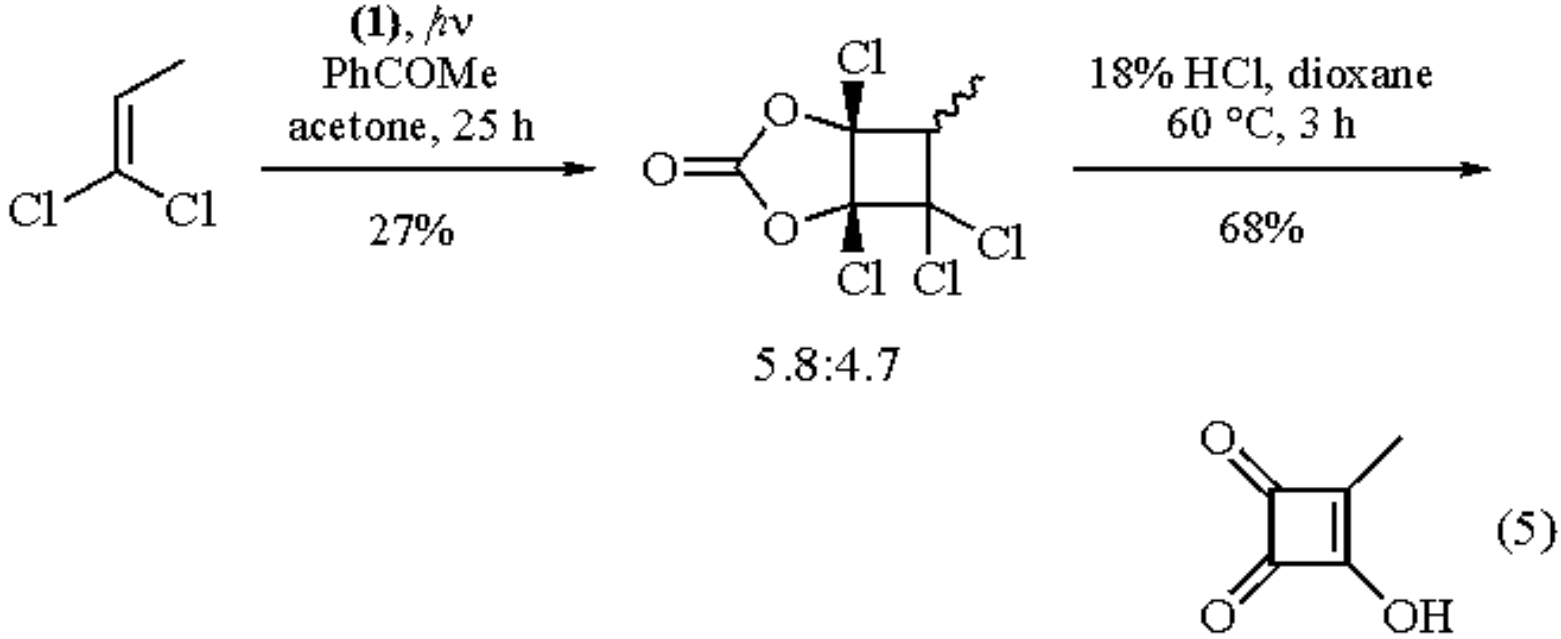

Cyclopentadienes give bicyclo[2.2.1]heptenediones in thermal [4 + 2] cycloadditions (eq 6),[12] where intermediate adducts are usually a mixture of *endo* and *exo* products. Addition rates depend on the cyclopentadiene used. Acyclic dienes tend to add in a [2 + 2] manner.[10] Other reactions include addition to norbornenes,[13] annulenes,[14] 3-phospholenes,[15] and *o*-benzoquinones.[16]

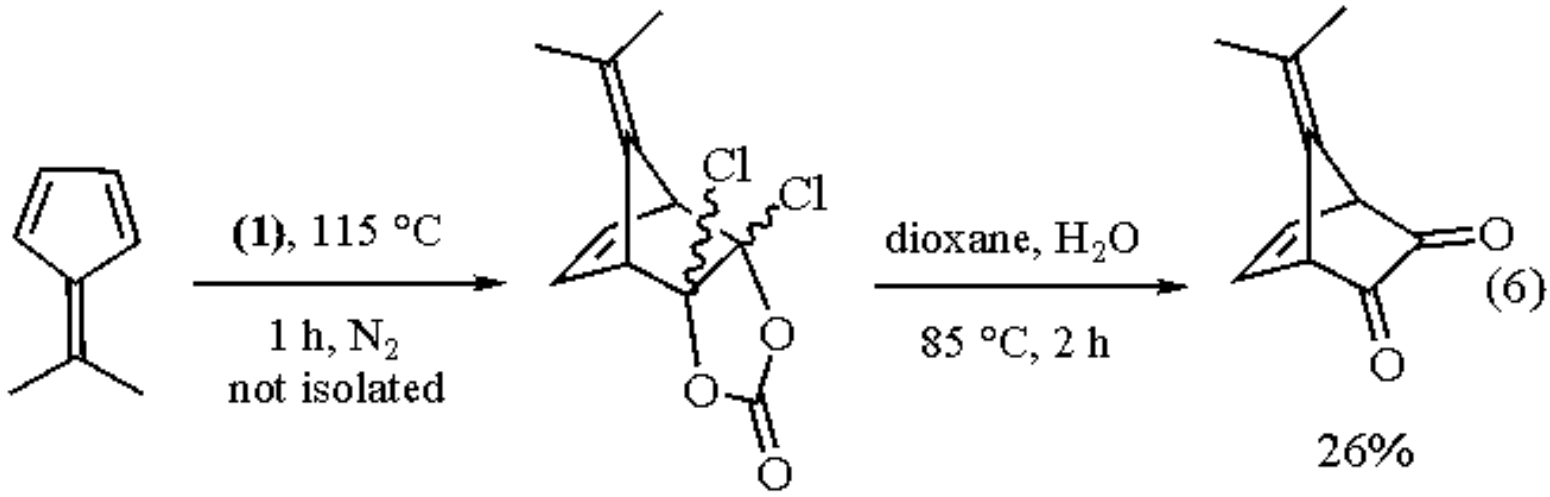

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Dicyanoacetylene[1]

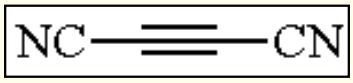

[1071-98-3] · C_4N_2 · Dicyanoacetylene · (MW 76.06)

(nucleophilic addition;[4,5] [4 + 2] cycloaddition reactions;[2] metal complexes insertion reactions[3])

Physical Data: bp 76.5 °C; mp 20.5 °C; *d* 0.9703 g cm^{-3}; IR 2268 cm^{-1} (w), 2212 cm^{-1} (m).

Solubility: sol all organic liquids.

Form Supplied in: clear colorless liquid.

Preparative Methods: see eq 1.

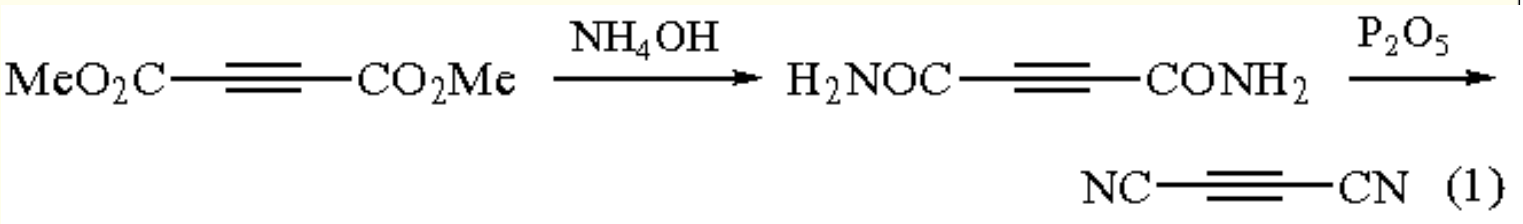

Purification: by simple vacuum sublimation or atmospheric distillation.

Handling, Storage, and Precautions: the solid compound can be stored indefinitely at dry-ice temperatures and is handled at rt. It is much more sensitive to the presence of oxygen, a polymerization or condensation reaction probably taking place.

Nucleophilic Addition.

Dicyanoacetylene is very susceptible to nucleophilic addition reactions. Thus it reacts at or below rt with ammonia and primary and secondary amines. The stereochemical aspects of this reaction have been investigated in the case of the piperidine and only the product of *cis* addition could be detected (eq 2).[4] Preference for *cis* stereochemistry has also been observed in the addition reaction of methanol and isopropyl alcohol. *t*-Butyl alcohol gives an equal mixture of both isomers (eq 3).[5]

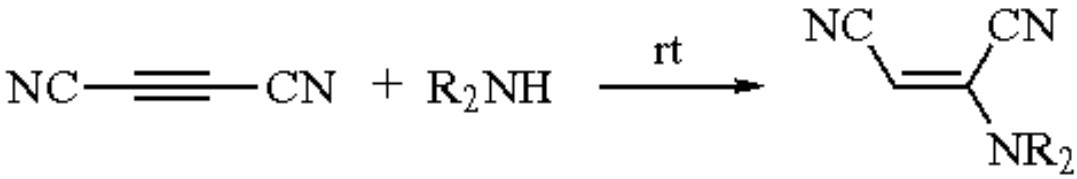

(2)

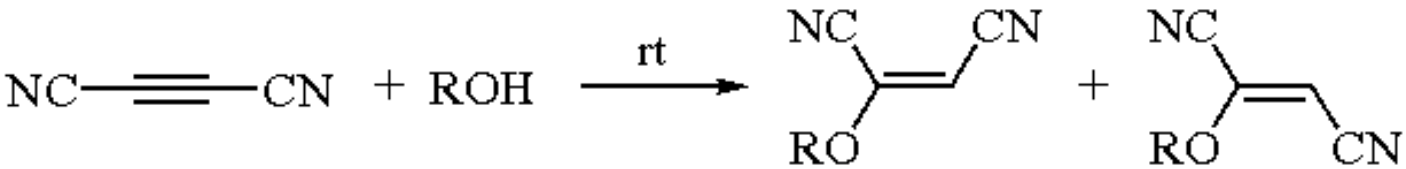

(3)

Dicyanoacetylene also reacts readily with hydrogen halides and halogens. They add to dicyanoacetylene at rt to give halodicyanoethylenes of unspecified stereochemistry. Addition of bromine to dicyanoacetylene affords the *trans* adduct in 57% yield (eq 4).[6]

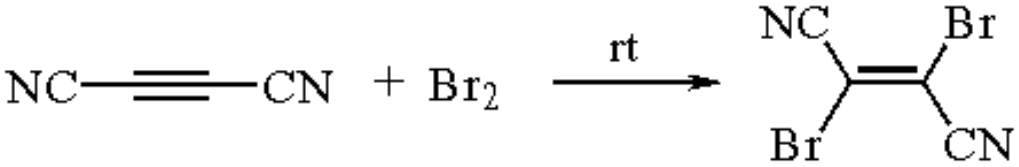

(4)

[4 + 2] Cycloaddition.

Because of the nature of the electron deficiency of the π-system of dicyanoacetylene, it is a more active dienophile than any other activated alkyne including hexafluoro-2-butyne and acetylenedicarboxylate esters. It has the added advantage over the latter of being thermally more stable, and any excess is readily removed due to its low boiling point. Although no direct comparison has been made, it seems likely that dicyanoacetylene is also more reactive in most Diels-Alder reactions than ***Maleic Anhydride*** and ***Tetracyanoethylene***; in fact it is probably only surpassed by benzyne, and some of the cyclic azo compounds. It reacts with cyclopentadiene, 1,3-cyclohexadiene, and butadiene at or below rt[7] and adds, albeit with decreasing ease, to anthracene, naphthalene, and even benzene itself. The latter addition requires heating at 180 °C for extended periods and the yields are low. However, the reaction can be catalyzed with ***Aluminum Chloride*** and ***Aluminum Bromide***. High yields of the adduct are obtained at rt; small amounts of phenylmaleo- and phenylfumaronitrile, the products of a Friedel-Crafts addition of dicyanoacetylene to benzene, are also isolated (eqs 5 and 6).

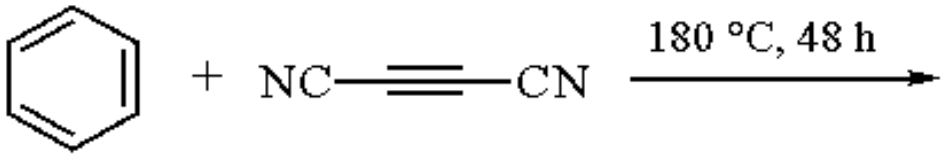

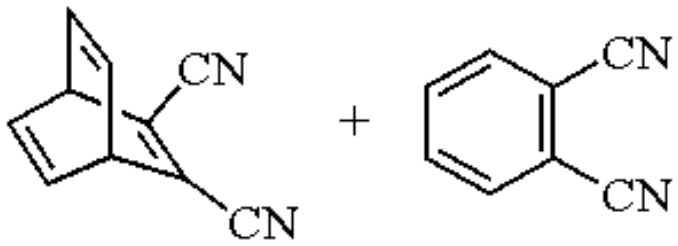

+ HC≡CH (5)

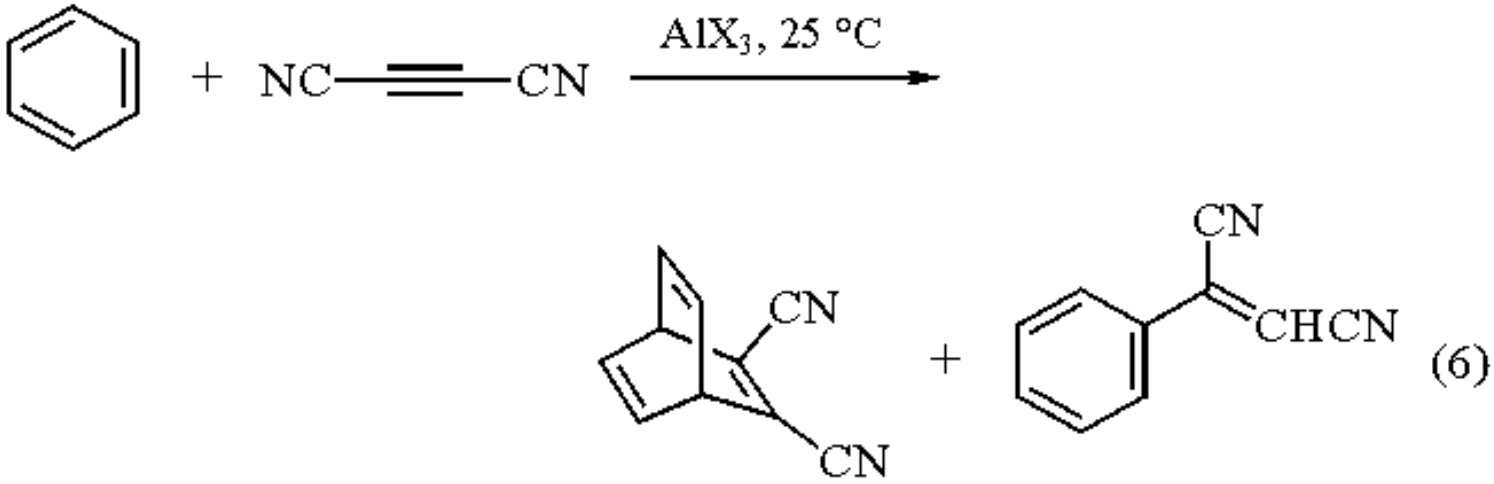

Dicyanoacetylene reacts with styrenes by sequential Diels-Alder addition and ene reaction to give adducts as illustrated (eq 7).[8] The intermediate adduct from a 1:1 molar ratio of starting materials could not be isolated. The reaction again occurs under exceptionally mild conditions.

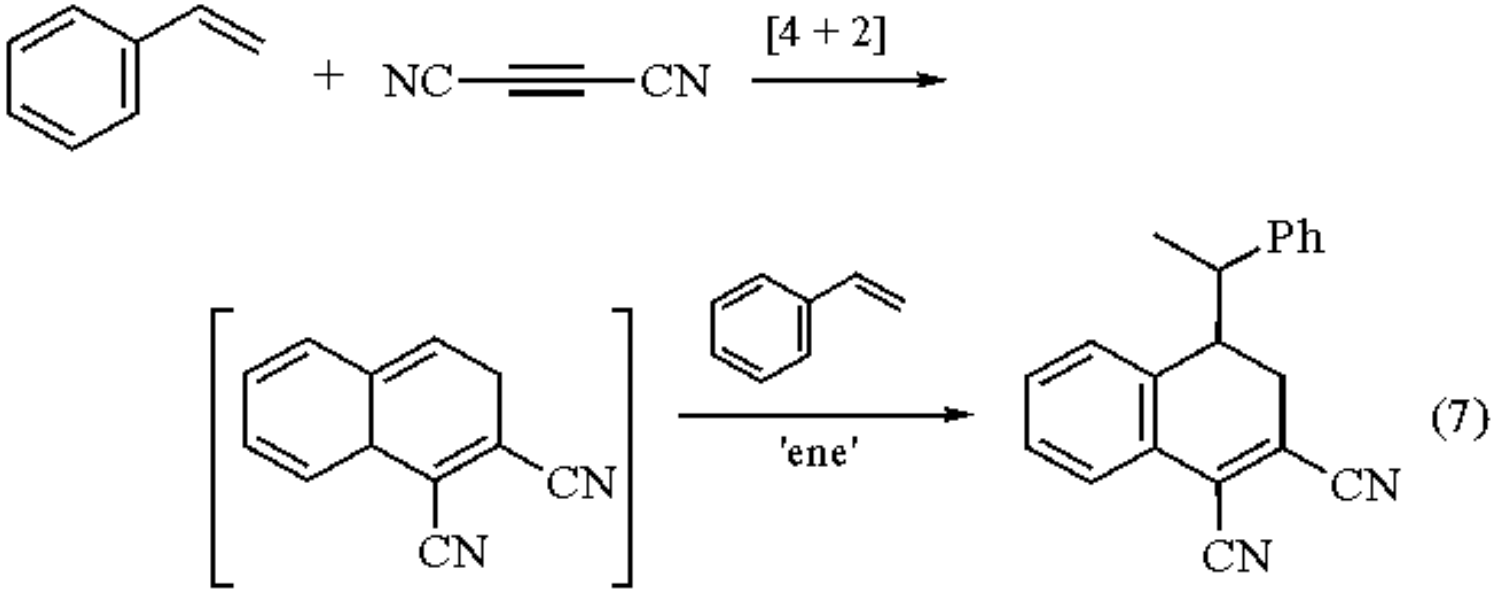

Dicyanoacetylene reacts at rt with quadricyclane (eq 8)[9] and norbornadiene (eq 9)[10] in good yields. With bicyclo[2.1.0]pentane it undergoes both a cycloaddition and an ene reaction (eq 10).[11]

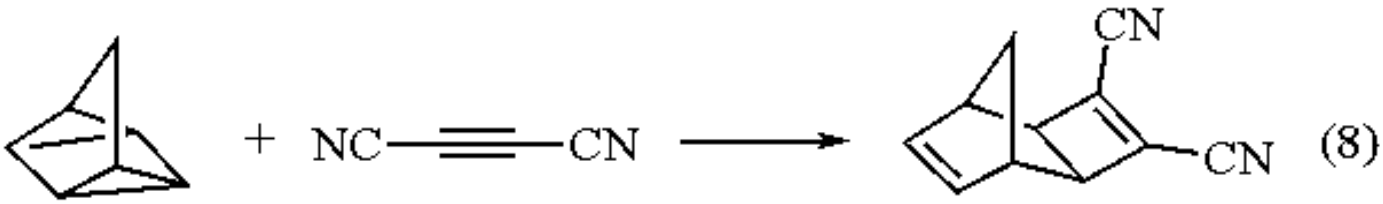

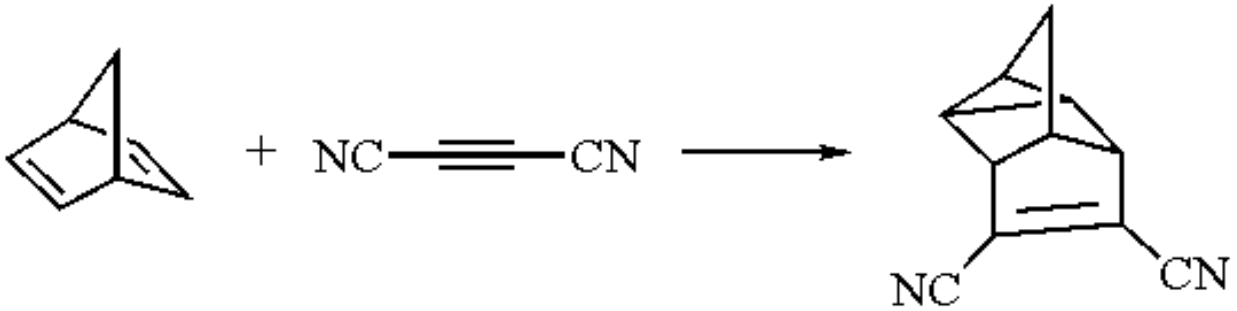

(9)

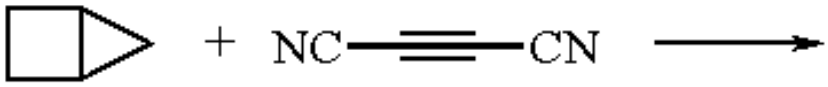

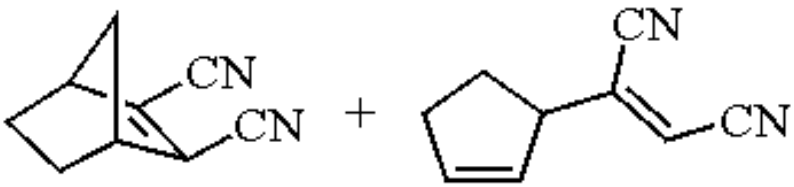

(10)

Other examples of the high reactivity of dicyanoacetylene in the Diels-Alder reaction are its additions to furan and furan derivatives,[12] fulvenes,[13] 1,4-diphenylnaphthalene,[14] cyclooctatetraene,[15] and [2.2]paracyclophane.[16] Dicyanoacetylene acts as a 1,3-dipolarophile in reactions with diazomethane,[17] ethyl diazoacetate,[18] and benzonitrile oxide.[19]

In more recent studies, dicyanoacetylene was reacted with more complicated systems. It can react with linear fused aromatic and heteroaromatic compounds with good regioselectivity. The example shows its reaction with anthra[2,3-*b*]thiophene in refluxing toluene to give an 82% yield of cycloaddition adduct (eq 11).[20]

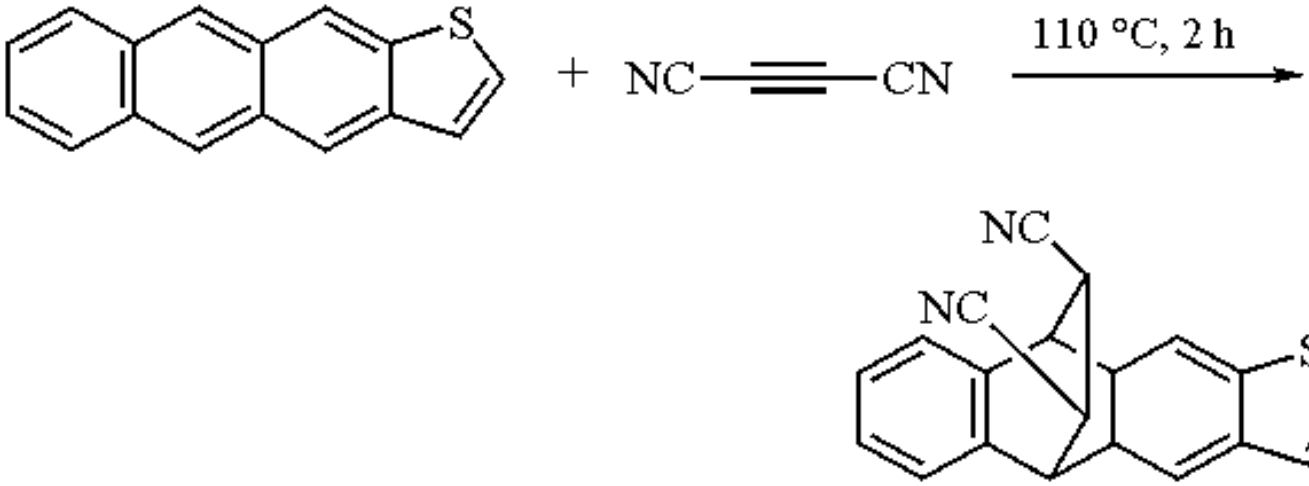

(11)

Under promoted conditions, dicyanoacetylene reacts with *syn-o,o´*-dibenzene derivatives at rt to give domino- and pincer-type products. This specific reaction gives exclusive domino-type product; in some other cases the ratio could be lower (eq 12).[21]

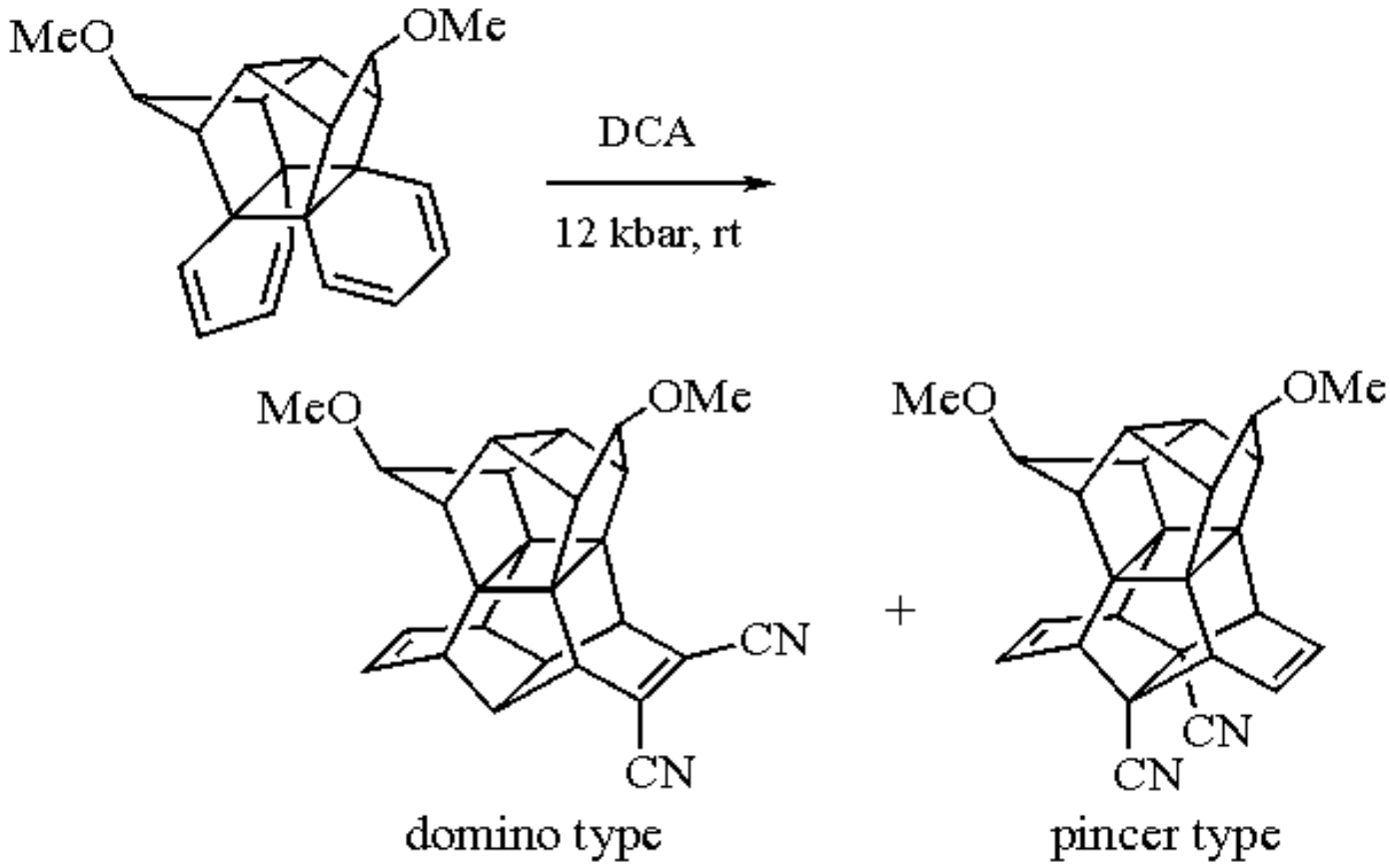

(12)

Vinylcycloheptatriene derivatives also undergo Diels-Alder reactions with dicyanoacetylene exclusively via the cycloheptatriene form to give 68-96% yields of adducts (eq 13).[22]

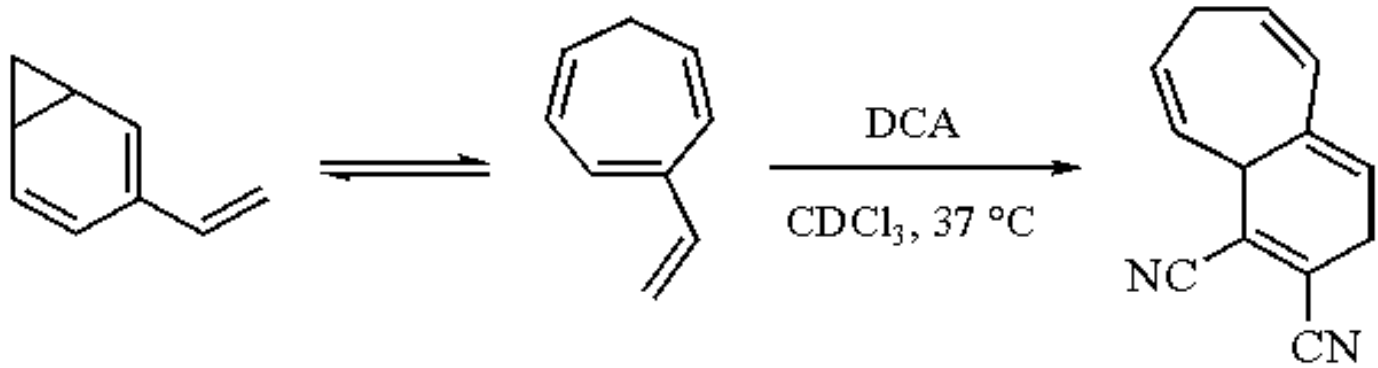

(13)

With excess of cyclopentadiene, *anti*-sesquinorbornene can be made through the Diels-Alder reaction with dicyanoacetylene in good yield (eq 14).[23]

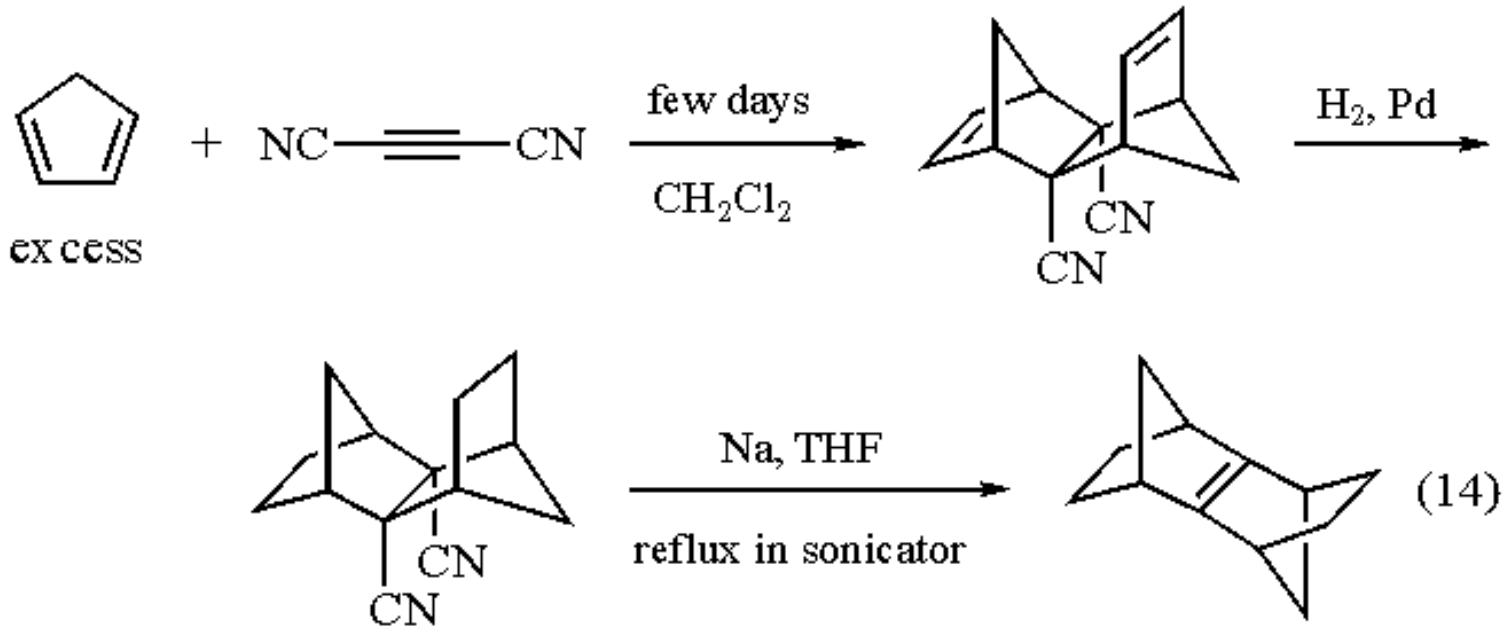

(14)

Reactions of antiaromatic compounds such as cyclobutadiene and azete with dicyanoacetylene yields Dewar benzene and 1-Dewar pyridine derivatives in fairly good yields. They can be converted by irradiation to benzene and pyridine intermediates (eqs 15 and 16).[24]

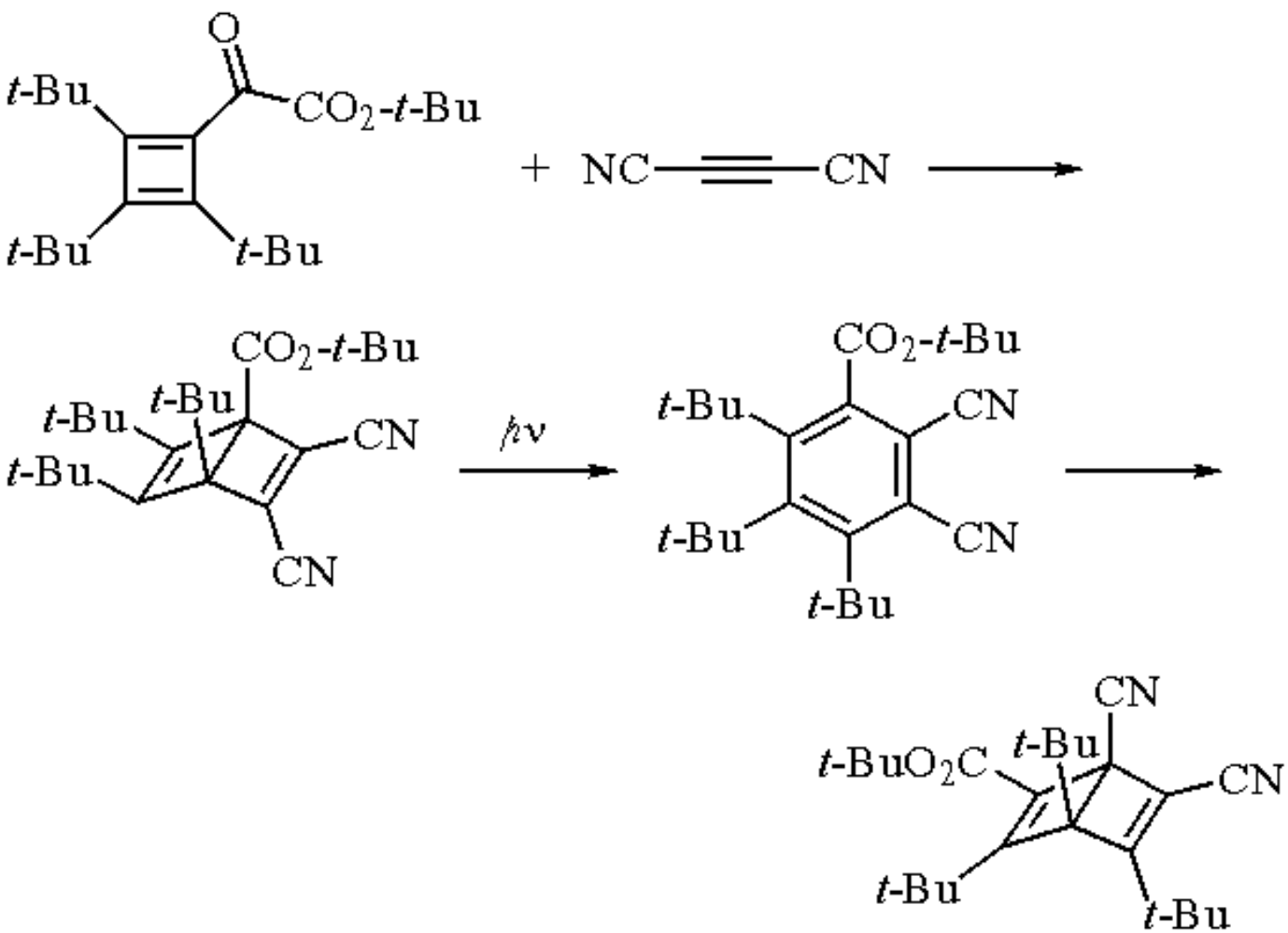

(15)

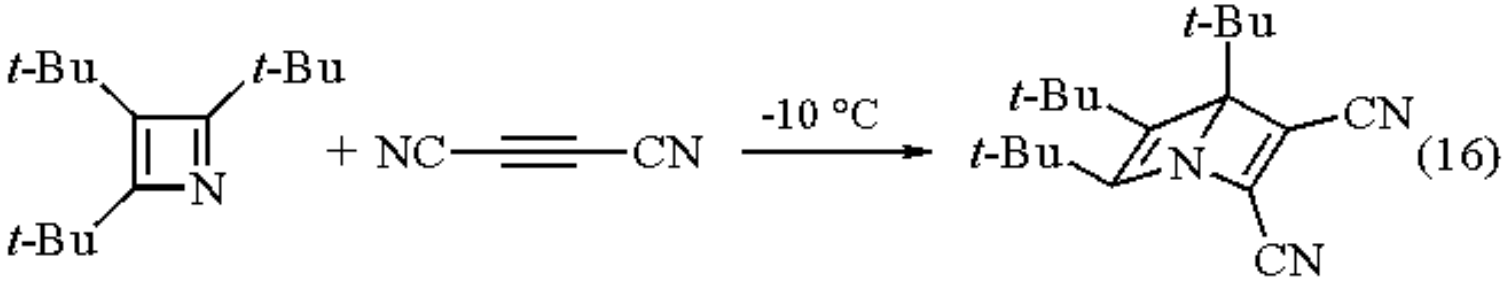

Dicyanoacetylene also serves as an important starting material in the synthesis of 1*H*-cyclopropa[*l*]phenanthrene (eq 17).[25]

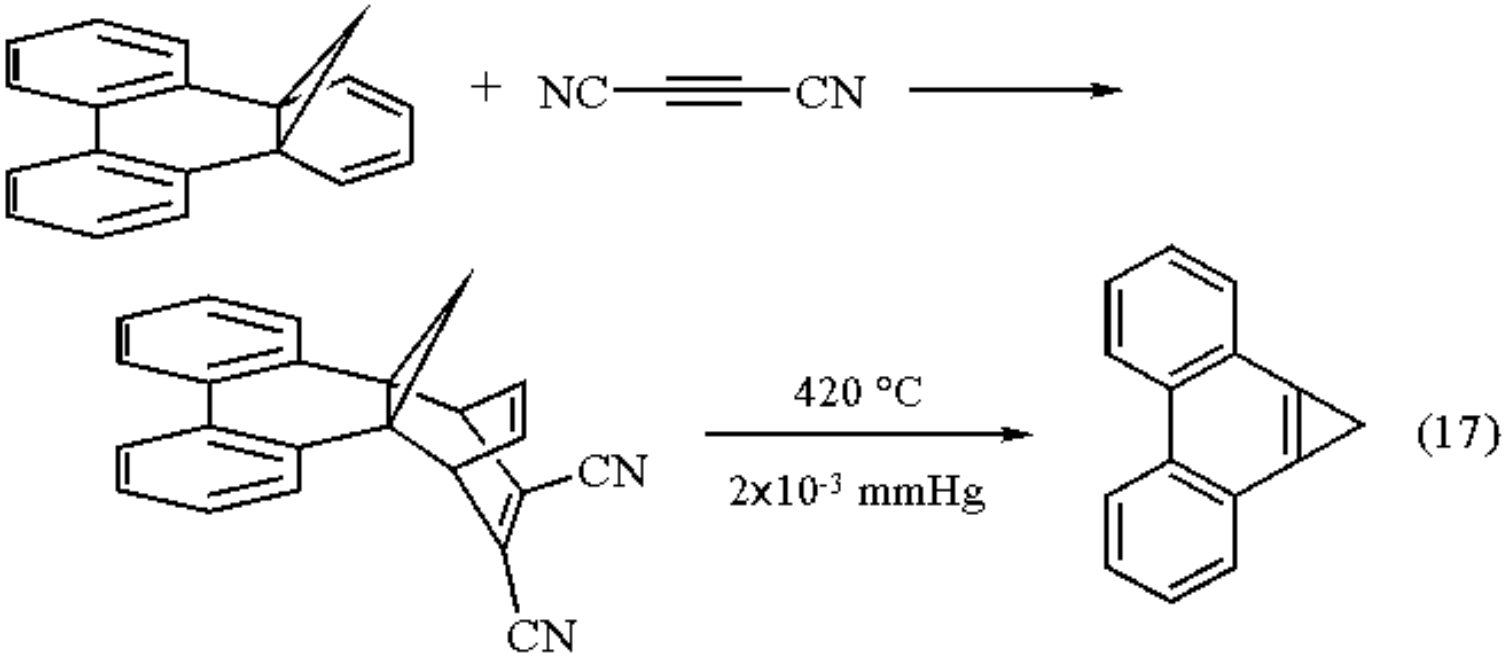

Treatment of a solution of $[2_2](1,4)$cyclophane in CH_2Cl_2 with dicyanoacetylene in the presence of $AlCl_3$ afforded 15,16-dicyano$[2_2](1,6)$cyclooctatetraenyl(1,4)cyclophane in 33% yield (eq 18).[26]

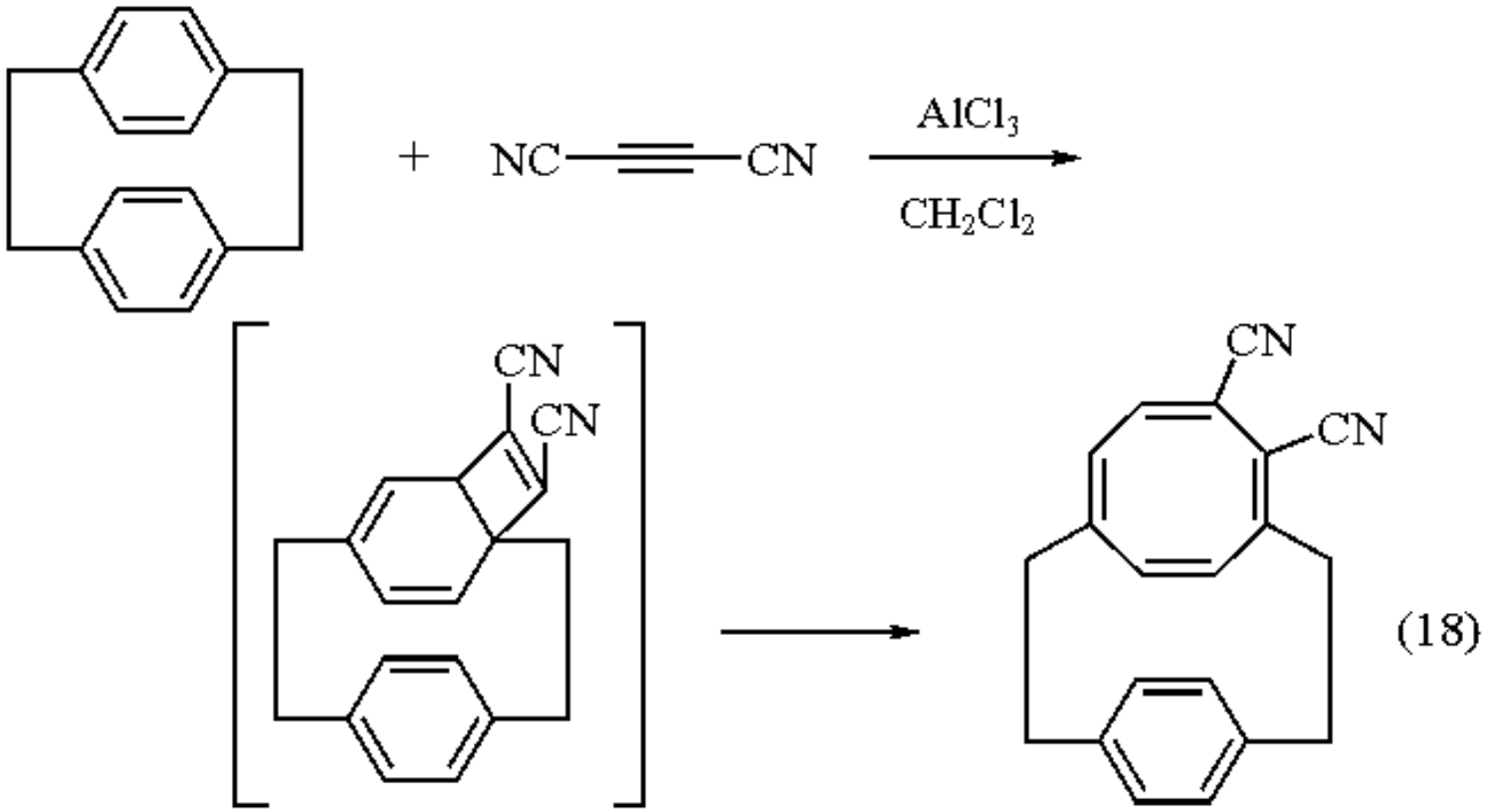

(18)

Radical Reaction with [1.1.1]Propellane.

The reaction of [1.1.1]propellane with dicyanoacetylene in chloroform proceeds extremely rapidly. It involves initial attack of the alkene under the flap of the bicyclopentane to produce a biradical intermediate which leads to the final product (eq 19).[27]

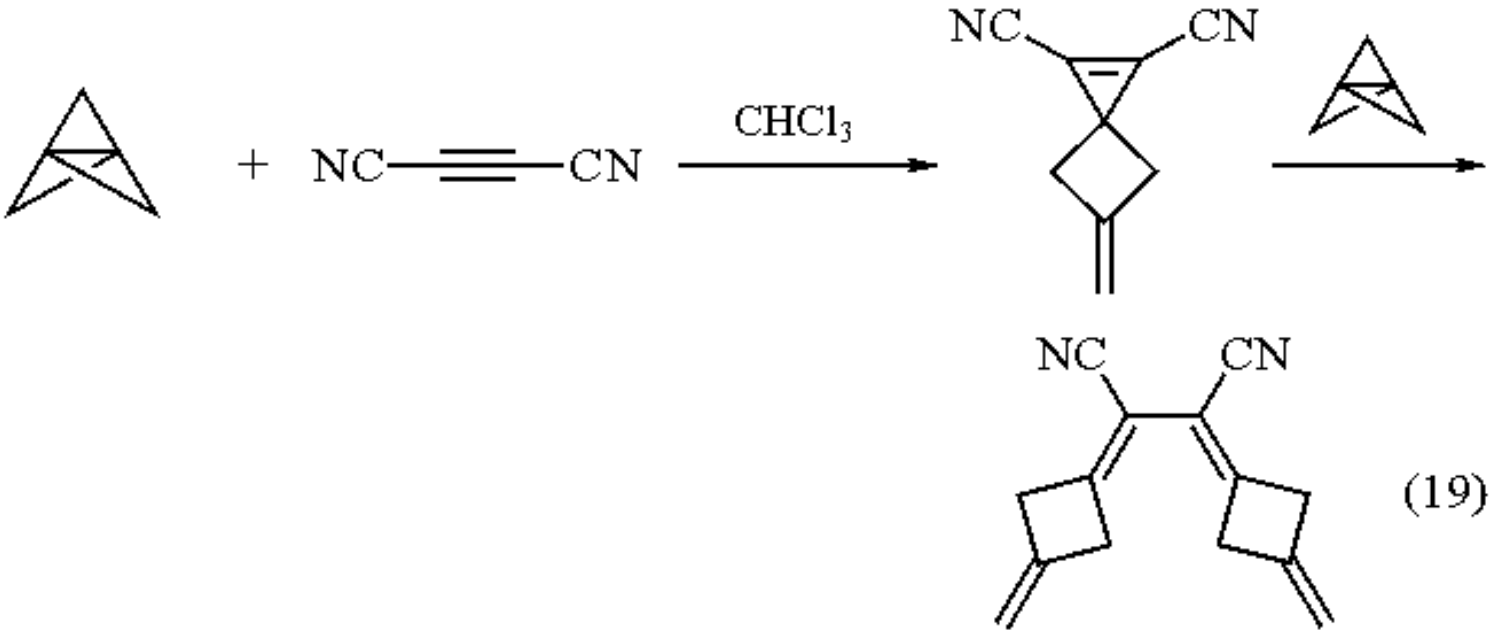

(19)

Cyclosubstitution Reaction.

On heating in toluene, 4,4-disubstituted 1,3-thiazole-5(4*H*)-thiones and dicyanoacetylene undergo a cyclosubstitution reaction to yield 2-methylidene-1,3-dithiol derivatives in 63% yield (eq 20).[28]

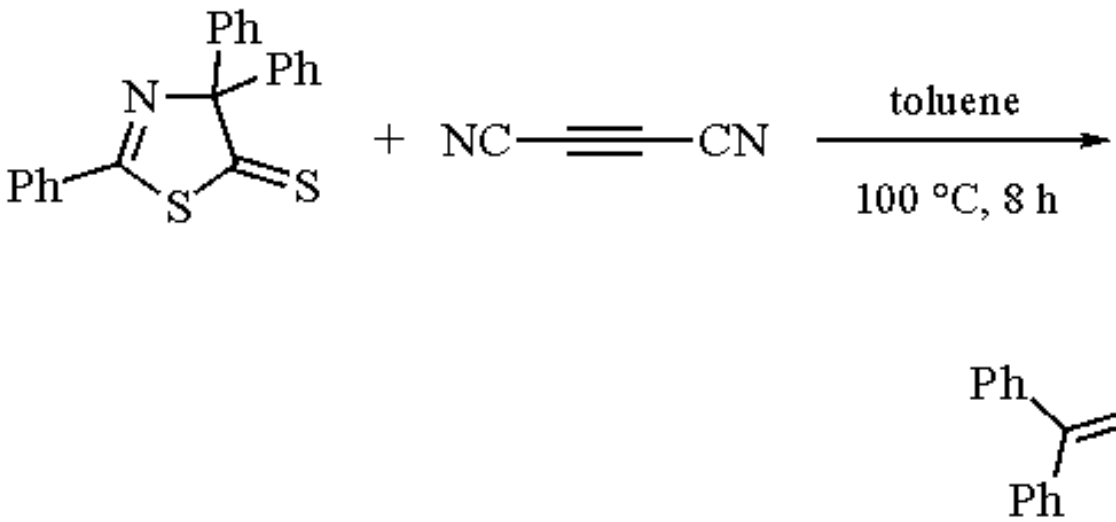

(20)

The regioselectivity of the cycloaddition of tetrasulfur tetranitride to dicyanoacetylene has been shown to favor 2,4-addition across nitrogen, or 1,5-addition across sulfur (eq 21).[29]

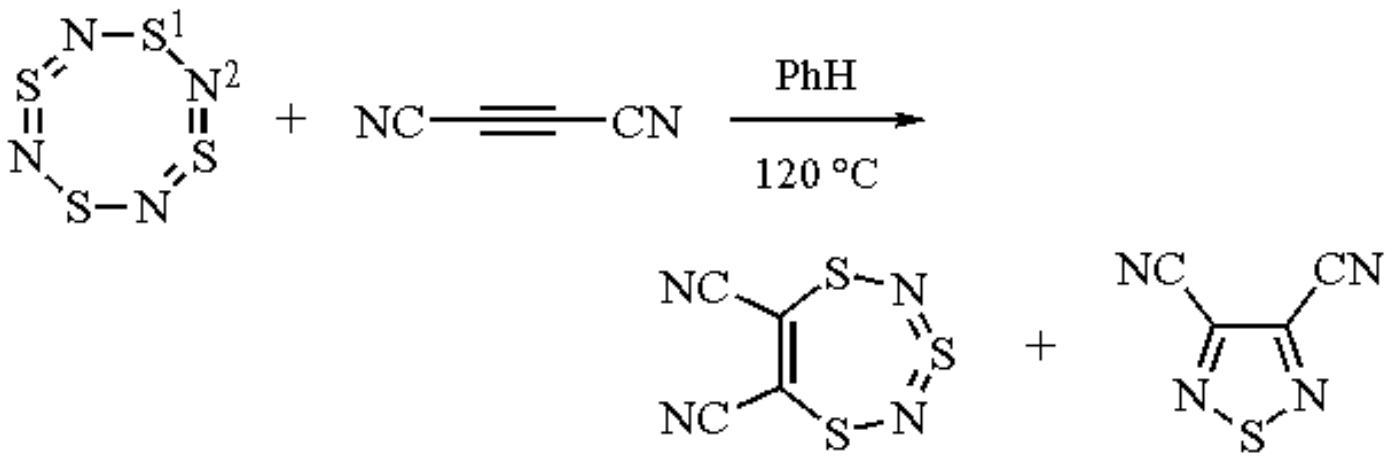

(21)

Photolysis.

Cycloaddition reactions of dicyanoacetylene with different alkenes not only can be initiated by heating and Lewis acids, but also can be promoted by photolysis. Subjected to UV radiation with ethylene, it forms 2,3-dicyano-1,3-butadiene at 254 nm (eq 22) or 1,2-dicyano-1-cyclobutene at 185 nm (eq 23).[30]

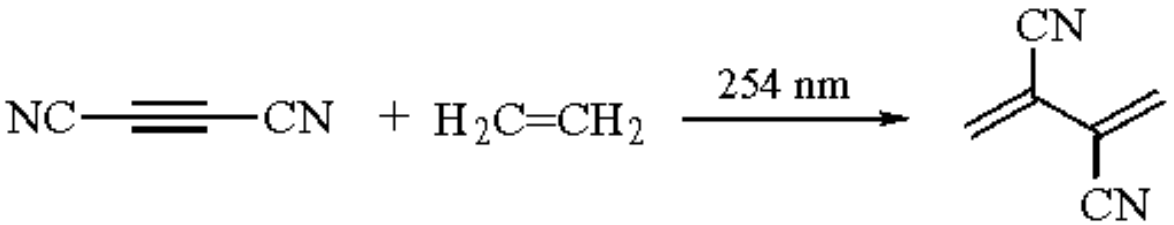

(22)

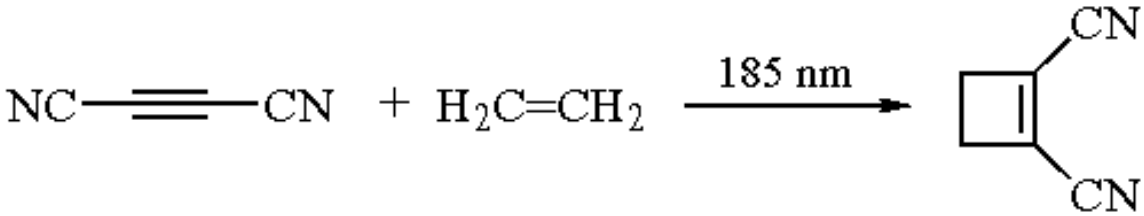

(23)

Metal Complex Insertion Reactions.

Insertion of alkynes into transition metal-hydride bonds is a key step in many important catalytic processes such as hydrogenation or polymerization. It also receives considerable attention by virtue of its utility in organic synthesis. Many transition metal complexes of Groups 6-10 play an important role in alkyne dimerization, oligomerization, and polymerization reactions, and in the formation of organometallic complexes that may be precursors for these reactions.[31] It was thus of interest to study the reactions of cyanoalkynes towards these metals (Zr, Nb, Mo, W, Re, Fe, Co, Ni). The following are just a few examples of metal complexes with dicyanoacetylene (eqs 24-26).[32-34]

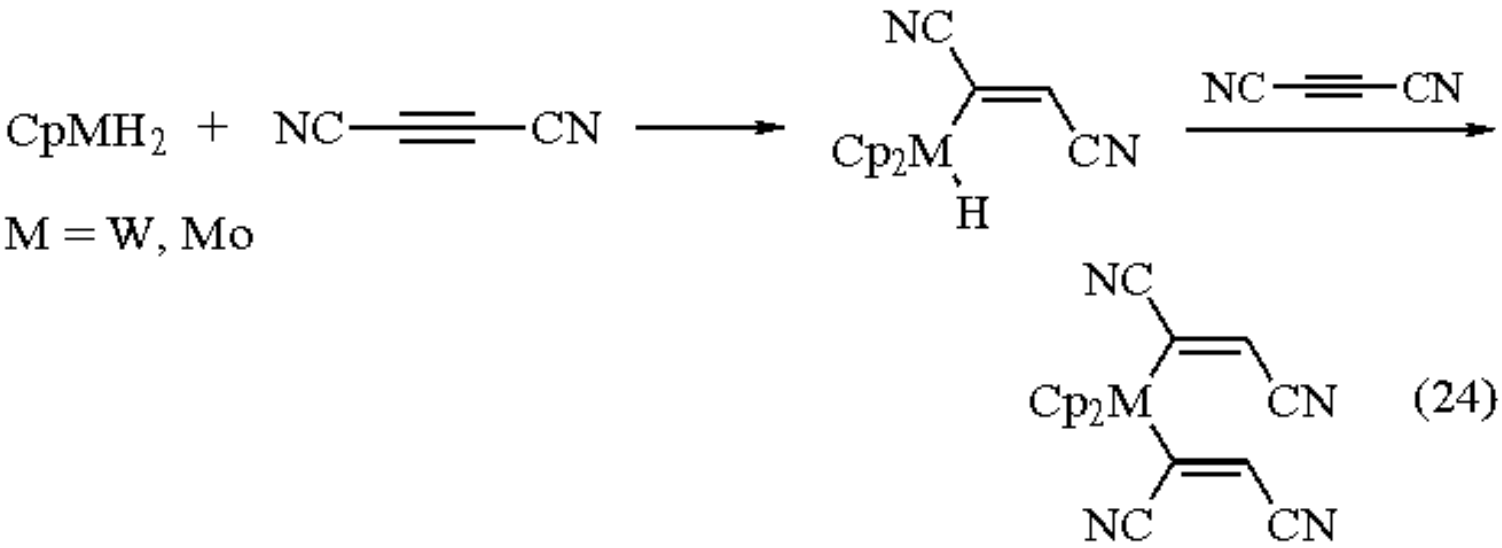

(24)

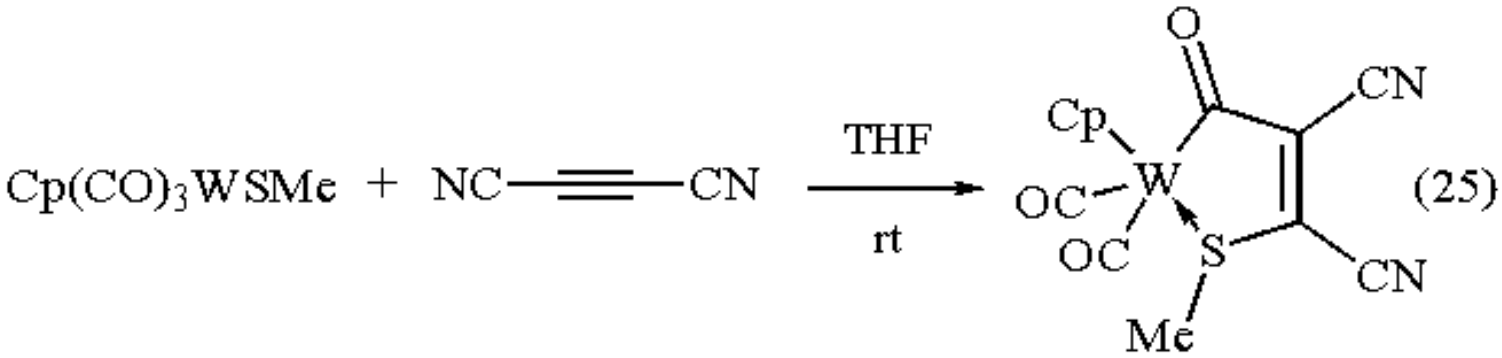

(25)

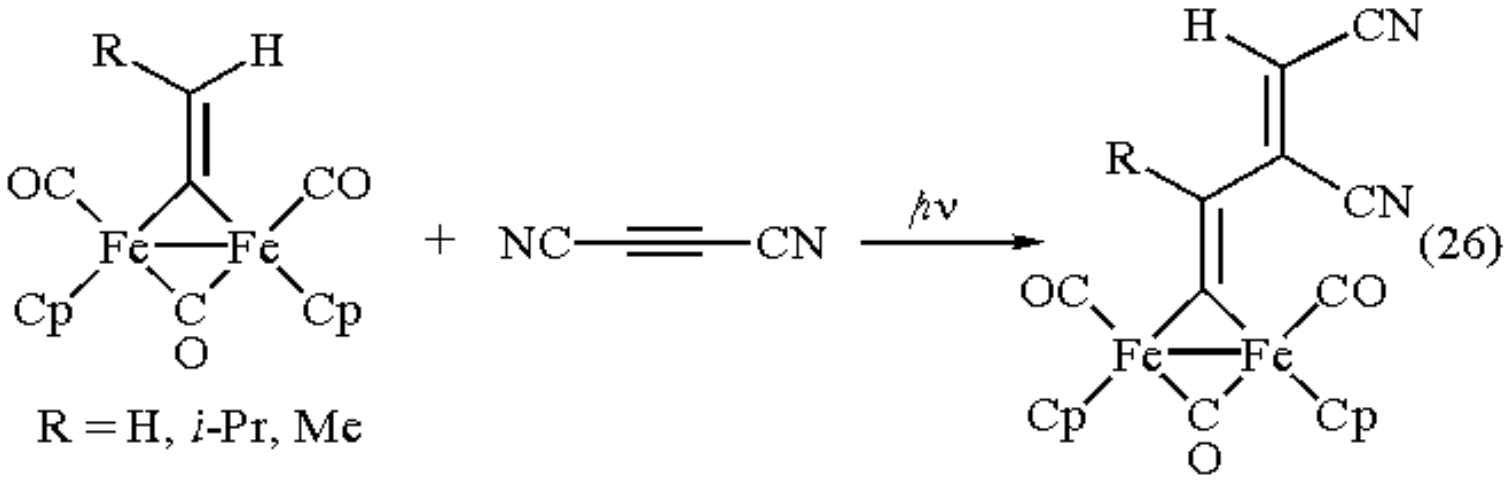

Related Reagents.

1,2-Dicyanocyclobutene; ***Dimethyl Acetylenedicarboxylate***; ***Maleic Anhydride***; ***Tetracyanoethylene***.

---

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Dicyanobis(triphenylphosphine)nickel(II)[1]

$Ni(PPh_3)_2(CN)_2$

[21946-42-9] · $C_{38}H_{30}N_2NiP_2$ · Dicyanobis(triphenylphosphine)nickel(II) · (MW 635.31)

(nickel(II) complex useful for the oligomerization of norbornadiene[2] and the isomerization of alkenes[3])

Physical Data: mp 212 °C (dec).

Solubility: only sparingly sol most organic solvents; most sol CH_2Cl_2.

Preparative Method: dry nickel(II) cyanide (11 g) was refluxed in 1 L ethanol with 78 g ***Triphenylphosphine*** for 48 h. The yellowish-gray $Ni(CN)_2$ turned to a light yellow coarse crystalline mass. The solvent was decanted and the solid was rinsed with ethanol to remove unreacted PPh_3. The remaining solid product was dried, extracted with CH_2Cl_2, and filtered to exclude insoluble $Ni(CN)_2$. Removal of solvent provided 39 g (62%) of light yellow crystals.[4]

Handling, Storage, and Precautions: air stable. Store at rt.

Oligomerization of Norbornadiene.

Dicyanobis(triphenylphosphine) nickel(II) catalyzes the [2 + 2 + 2] cycloaddition between norbornadiene and electron-deficient alkenes and alkynes. Thus norbornadiene (**1**) reacts with acrylonitrile in the presence of the nickel catalyst to give a 93% yield of the homo-Diels-Alder adduct (**2**) as a mixture of epimers (eq 1).[4] This catalyst is similar to ***Dicarbonylbis(triphenylphosphine)nickel(0)***, which gives 86% yield in the same reaction, but is easier to handle due to its lack of oxygen sensitivity (see also ***Bis(acrylonitrile)nickel(0)*** and ***Bis(1,5-cyclooctadiene)nickel(0)***.[5] Alkynes also form adducts with norbornadiene; however, the yields are lower than with alkenes.

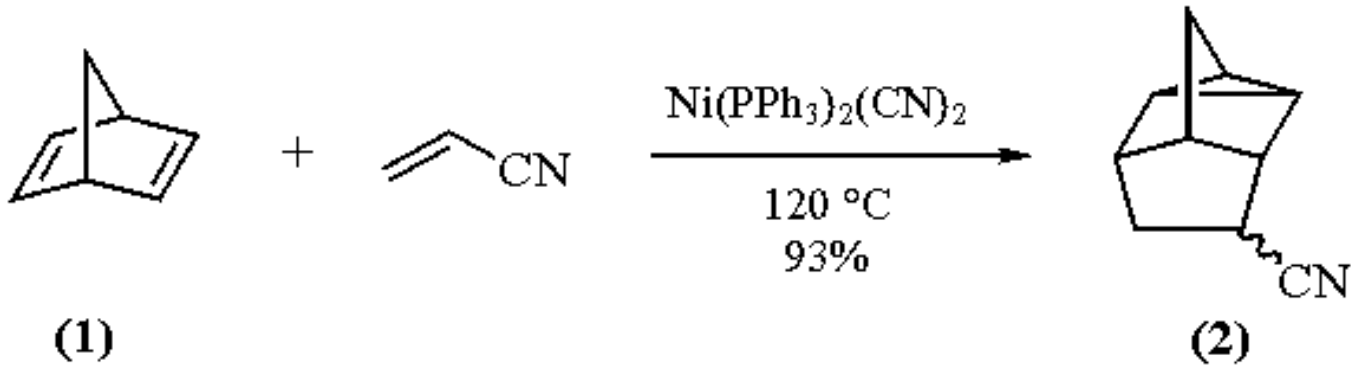

(1)

Isomerization of Alkenes.

When this complex is combined with ***Sodium Borohydride***, it can be used as a catalyst for the isomerization of alkenes. The mechanism occurs through nickel hydride addition across the alkene and subsequent β-hydride elimination. Acceptance of another hydride by the organonickel intermediate followed by reductive elimination leads to overall hydrogenation of the alkene. In this way, dimethyl maleate is converted to a 95:5 mixture of the isomerized product, dimethyl fumarate, and the hydrogenated product, dimethyl succinate (eq 2).[6] Other nickel(II) cyanide complexes such as $Ni(CN)_2$(phen) and $Ni(CN)_4^{2-}$ give rise to greater proportions of hydrogenated product. With $Ni(CN)_2(PPh_3)_2$, 1,5-cyclooctadiene can be isomerized to a mixture of 1,4- and 1,3-cyclooctadiene with no trace of the hydrogenated byproduct.

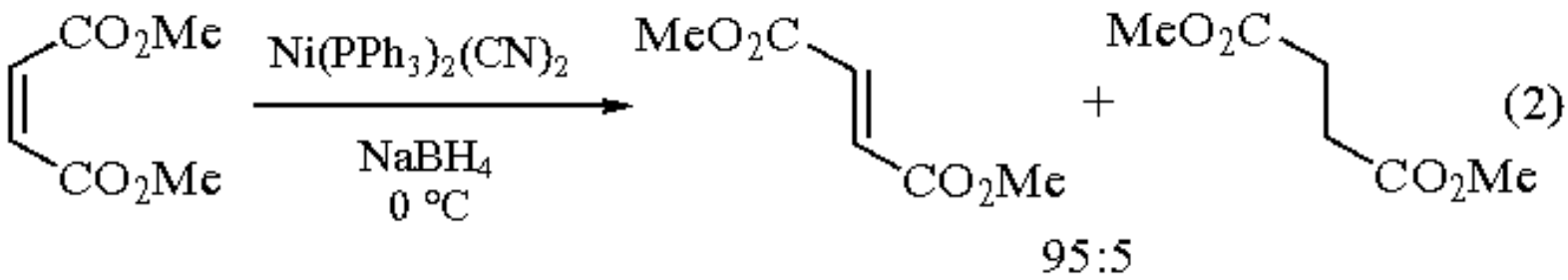

(2)

A *cis* selectivity was observed for the isomerization of 1-butene to 2-butene.[3] With $Ni(CN)_2(PPh_3)_2$, the *cis* isomer was favored by a factor of 2:1. Greater *cis* selectivities were observed for some cobalt complexes and other nickel(II) catalysts. These selectivities are dependent upon the cone angle of the phosphorus ligand, the size of the anionic ligands, and the steric congestion in the organometallic complexes.

---

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1,2-Dicyanocyclobutene

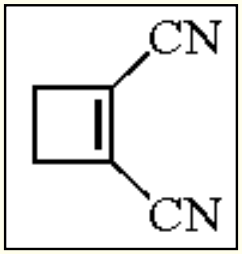

[3716-97-0] · $C_6H_4N_2$ · 1,2-Dicyanocyclobutene · (MW 104.11)

(reactive dienophile in [4 + 2],[1] [3 + 2],[2] and [2 + 2][3] Diels-Alder additions; reactive diene in [4 + 2] inverse electron demand Diels-Alder additions upon in situ thermolytic cleavage to 2,3-dicyanobutadiene)

Alternate Name: cyclobutene-1,2-dicarbonitrile.

Physical Data: bp 58-60 °C/0.06 mmHg; *n*20D 1.4926; *d*420 1.033 g cm^{-3}; IR (neat) cm^{-1}: 3002, 2957, 2230, 1612, 1422, 1251, 1169, 1003, 623; ^1H NMR δ 2.91 (s, 2H).

Solubility: insol H_2O; sol most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Preparative Methods: may be prepared by several methods.[4] The most convenient involves the chlorination of 1,2-dicyanocyclobutane with ***Phosphorus(V) Chloride*** followed by dechlorination with ***Triethylamine*** in refluxing benzene to give the reagent in good yield[1,5] (eq 1).

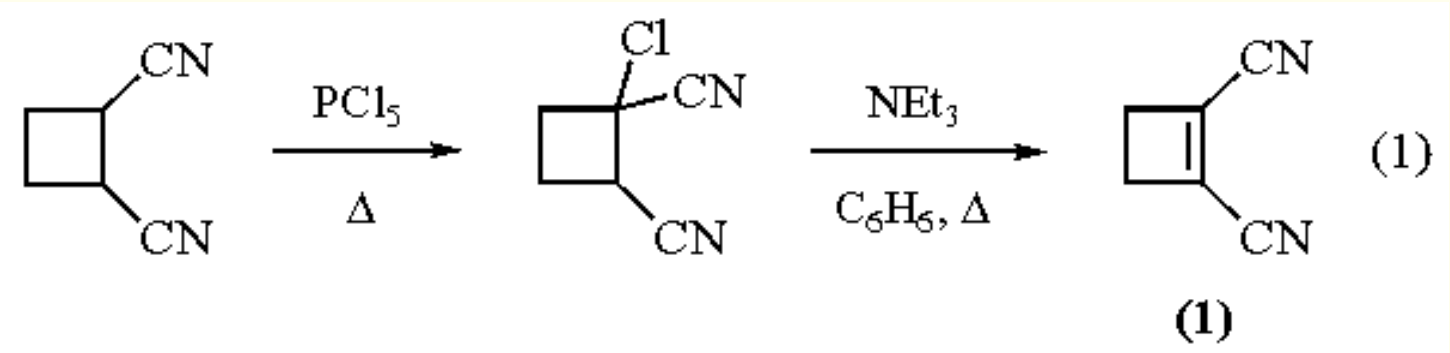

Purification: prepared by the method described, the reagent may be used directly for most cycloadditions. To remove trace impurities (1-4%) and obtain the pure compound, stir for 4 h over Raney cobalt under N_2 at 70 °C, then distill directly under vacuum; purity may be assessed by gas chromatography.[5]

Reactive Dienophile.

1,2-Dicyanocyclobutene (**1**) functions as a reactive dienophile in [4 + 2] cycloadditions to numerous diene systems. *Endo* versus *exo* selectivity is dependent on the presence of sp^3 carbon atoms in the diene (eqs 2-4).[1] The reactions are generally run without solvent.

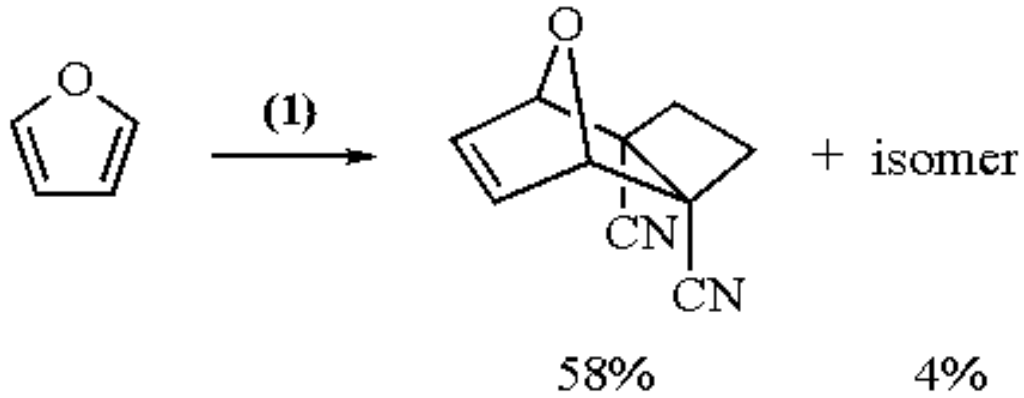

(2)

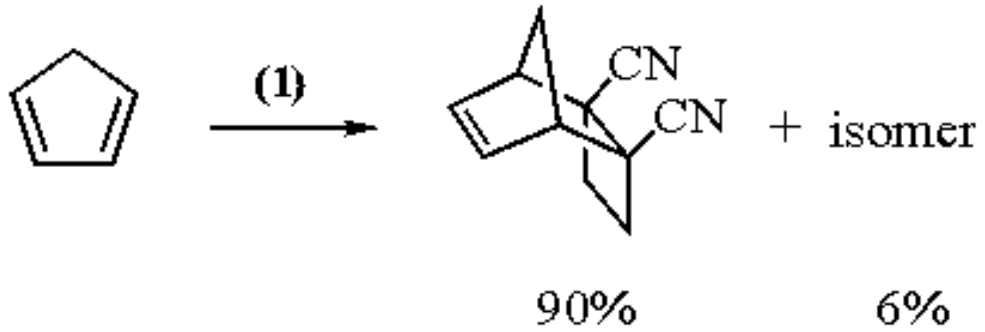

(3)

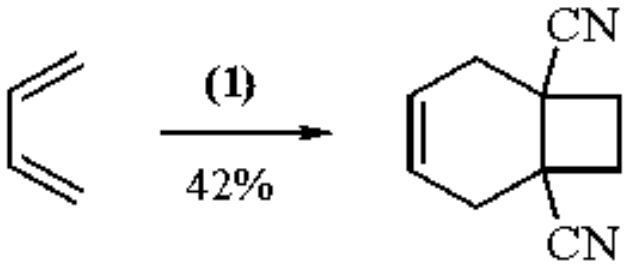

(4)

1,2-Dicyanocyclobutene is easily converted to 2,3-dicyanobutadiene (eq 5). Thermolytic cleavage in situ generates the diene which undergoes inverse electron demand Diels-Alder cycloaddition to a number of dienophiles.[1,5] The in situ generation procedure has the advantage of avoiding the tendency of the diene to polymerize in the pure state (eqs 6-8).

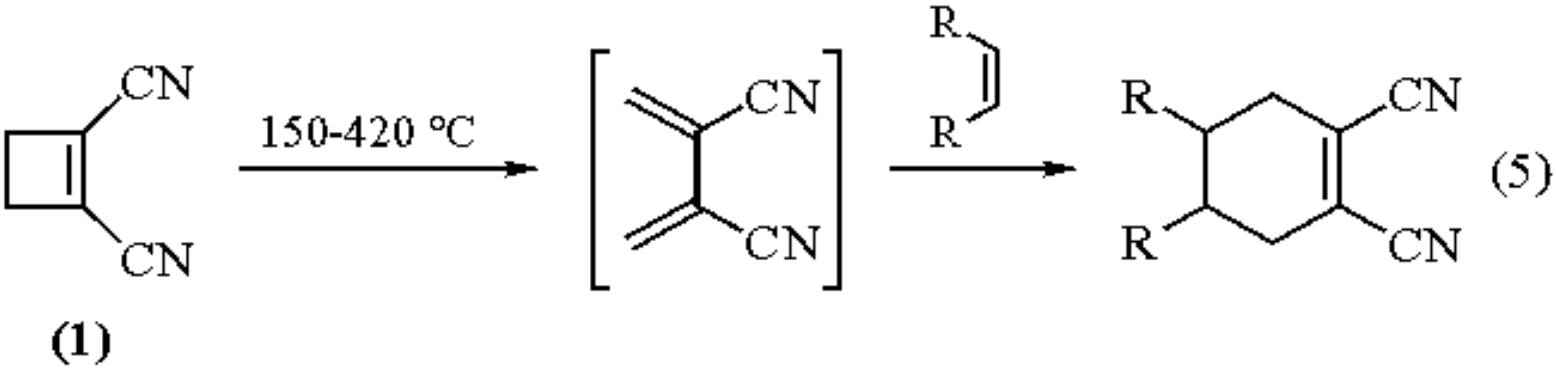

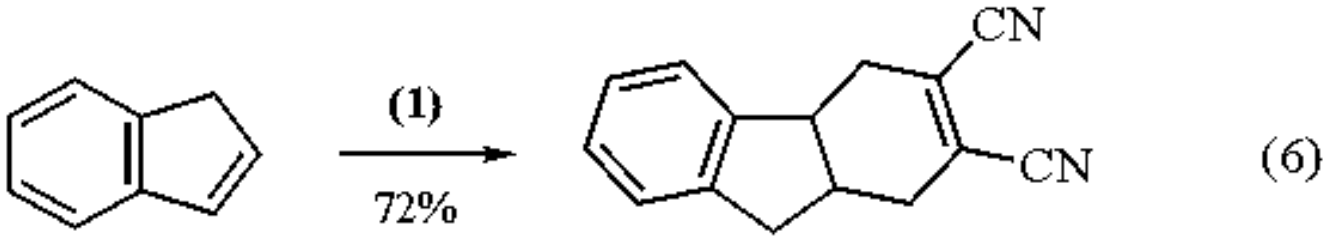

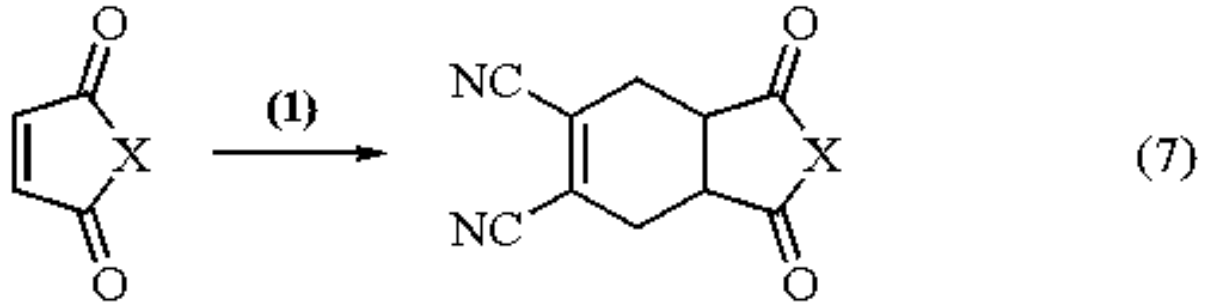

X = O, 58%
X = NEt, 50%

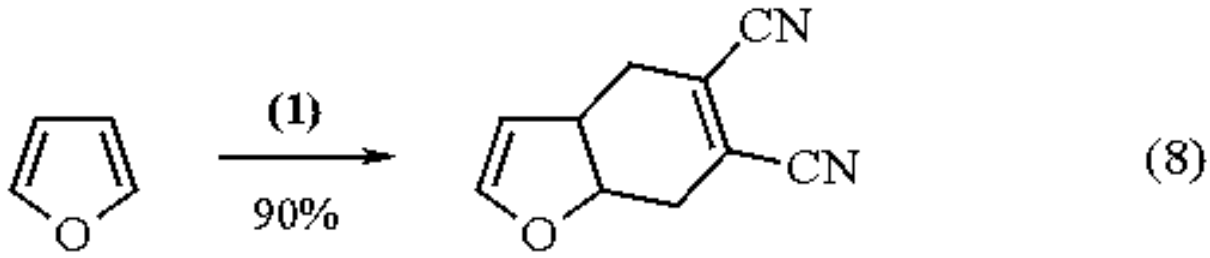

1,2-Dicyanocyclobutene also undergoes [3 + 2] cycloadditions with diazomethane and ethyl diazoacetate (eq 9).[2,3] Yields were not reported.

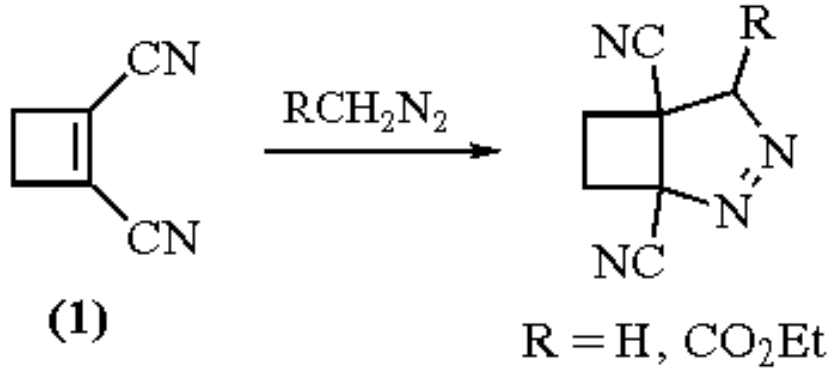

(9)

Photocatalyzed [2 + 2] cycloadditions of 1,2-dicyanocyclobutene with various alkenes have been demonstrated.[3] The reagent is strongly absorbent at 234 nm in acetonitrile, and the high degree of ring strain allows it react where other alkenes do not. Yields are moderate (eq 10).

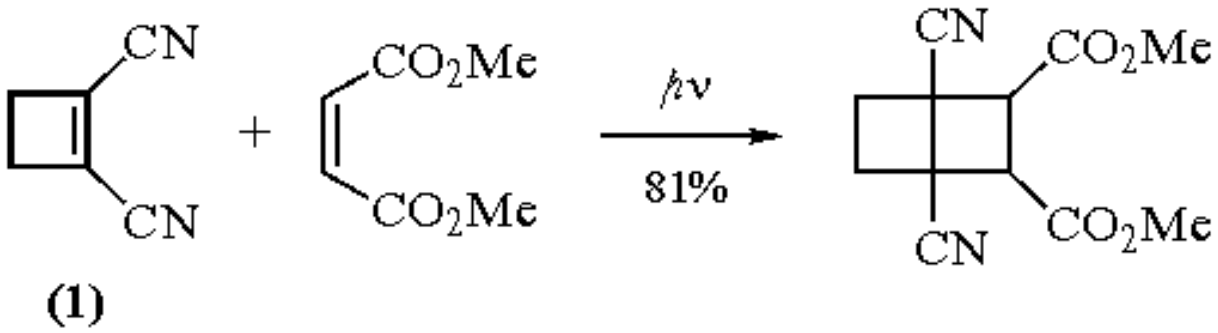

(10)

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2. Cobb, R. L.; Mahan, J. E. *JOC* **1977**, *42*, 2597.
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4. (a) Prinzbach, H.; Martin, H-D *C* **1973**, *23*, 37. (b) Greene, J. L.; Godfrey, M. US Patent 3 336 354, 1967 (*CA* **1968**, *68*, 21 598v). (c) Greene, J. L.; Standish, N. W.; Gray, N. R. US Patent 2 275 676, 1966 (*CA* **1967**, *66*, 10 637y).
5. Bellus, D.; Bredow, K.; Sauter, H.; Weis, C. *OS* **1978**, *58*, 67.

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Dicyanodimethylsilane

$Me_2Si(CN)_2$

[5158-09-8] · $C_4H_6N_2Si$ · Dicyanodimethylsilane · (MW 110.19)

(protecting reagent of β-diketones[1,2] and β-hydroxy ketones,[1,3] diols, and alcohols[4])

Physical Data: mp 85-87 °C; bp 108-109 °C/54 mmHg.

Solubility: sol dichloromethane, chloroform; slightly sol ether.

Preparative Methods: dicyanodimethylsilane is conveniently prepared by the reaction of dibromodimethylsilane[5] or ***Dichlorodimethylsilane***[6] with ***Silver(I) Cyanide***. ***Lithium Cyanide***,[4] ***Sodium Cyanide***,[7] and ***Potassium Cyanide***[7] can also be used in place of silver cyanide. A method which uses ***Hydrogen Cyanide*** as a source of cyano groups[8] and a procedure which utilizes transcyanation with ***Cyanotrimethylsilane*** have also been reported.[9] Dicyanodimethylsilane is obtained as colorless crystals via these methods.

Handling, Storage, and Precautions: dicyanodimethylsilane reacts instantly with water to form highly toxic hydrogen cyanide and siloxane oligomers. Therefore it should be handled carefully in a fume hood. If possible, it is recommended that CH_2Cl_2 solutions of this reagent be transferred by using syringe techniques.

Reaction with β-Diketones.

While enol silylations and cyanosilylations of β-diketones with cyanotrimethylsilane often give mixtures of products, the reactions with dicyanodimethylsilane give 5-cyano-2,6-dioxa-1-silacyclohex-3-enes in good yields (eq 1).[1] For enolizable β-diketones, the concurrent silylation and cyanosilylation takes place immediately without catalysts. On the other hand, ***Zinc Iodide*** catalysis is effective for reactions with less easily enolizable β-diketones (eq 2). Methyl 2,4-dioxopentanoate also reacts with dicyanodimethylsilane to give the corresponding cyclic product.[2] Treatment of the adducts in methanol (rt, overnight) furnishes the parent 1,3-diketones in good yields. Taking advantage of the stepwise nature of the methanolysis, a formal cyanosilylation can be achieved by treating the adduct with 1 equiv of methanol in dichloromethane at rt (eq 3).[1]

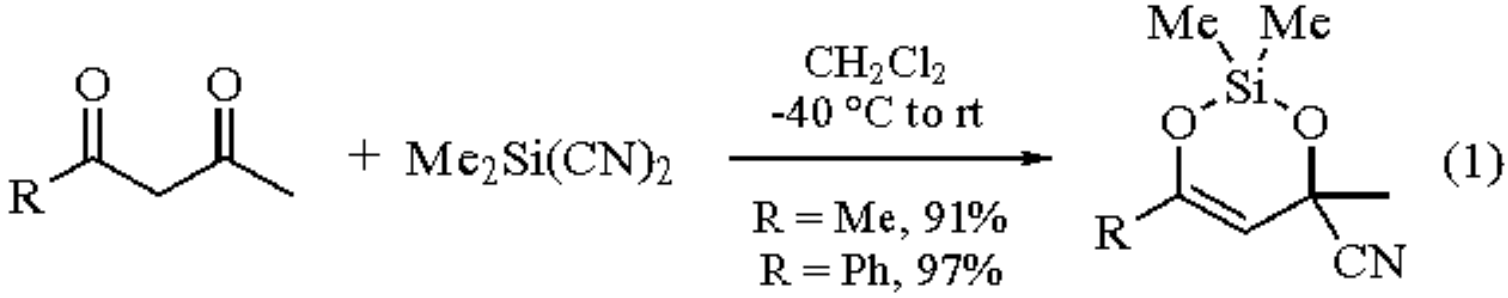

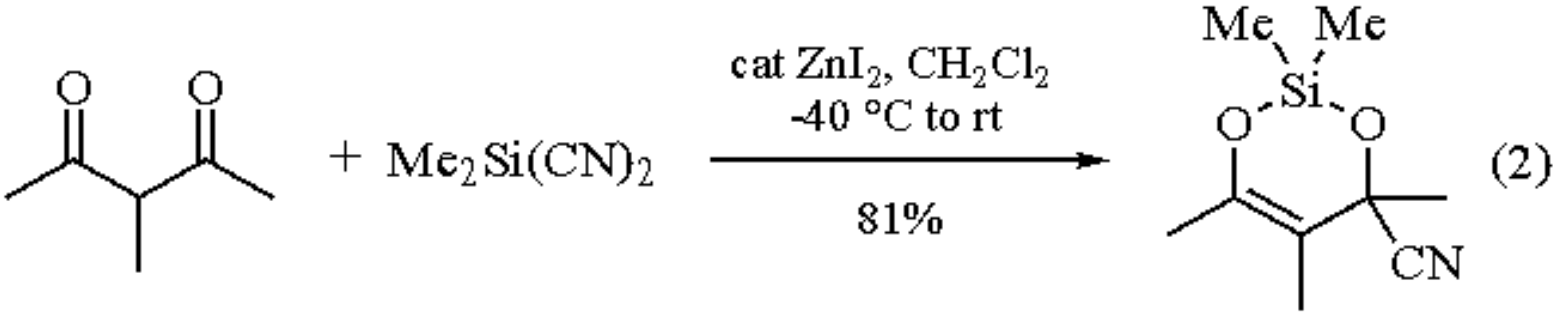

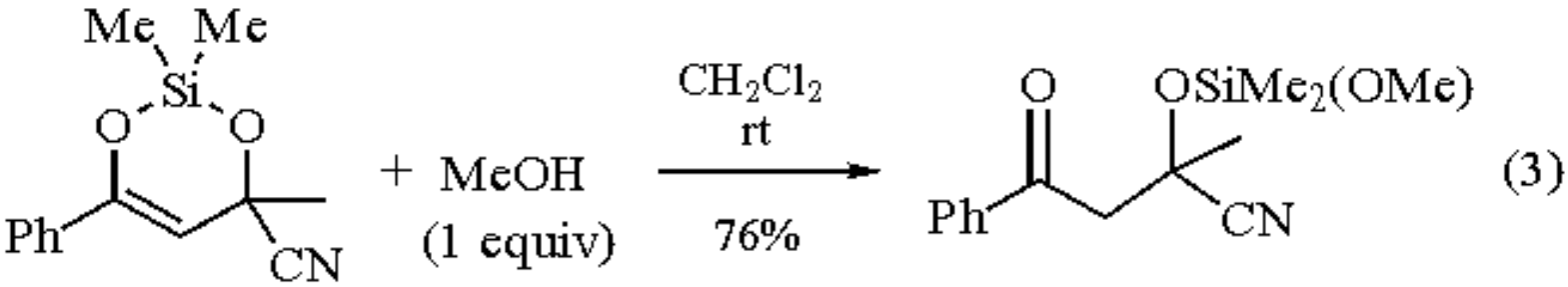

Reaction with β-Hydroxy Ketones and Alcohols.

The reaction of dicyanodimethylsilane with diacetone alcohol occurs according to eq 4.[1] The reaction, which is initiated at -78 °C, proceeds by way of the indicated cyanodimethylsilyl ether. When warmed to rt, the intermediate silyl ether cyclizes to give a mixture of the cyanosilylation product and the cyclic enol silyl ether. The cyanosilylation of secondary β-hydroxy ketones is highly diastereoselective (eq 5).[3] After desilylation, the cyanohydrins are obtained with high *syn* selectivity (de > 95%). The stereochemical result is rationalized by assuming a silyl-bridged chair-type transition state. Dicyanodimethylsilane reacts readily with alcohols, with liberation of hydrogen cyanide, to give bis(alkoxy)silanes in high yields (eq 6).[4]

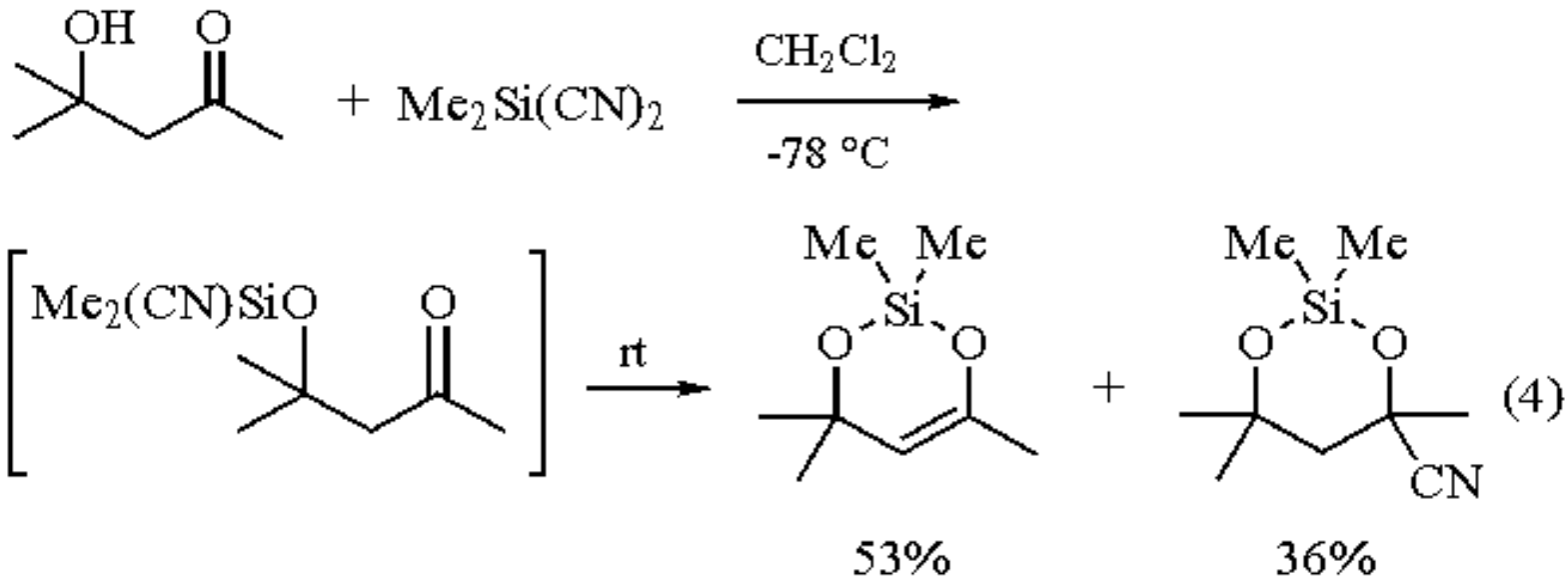

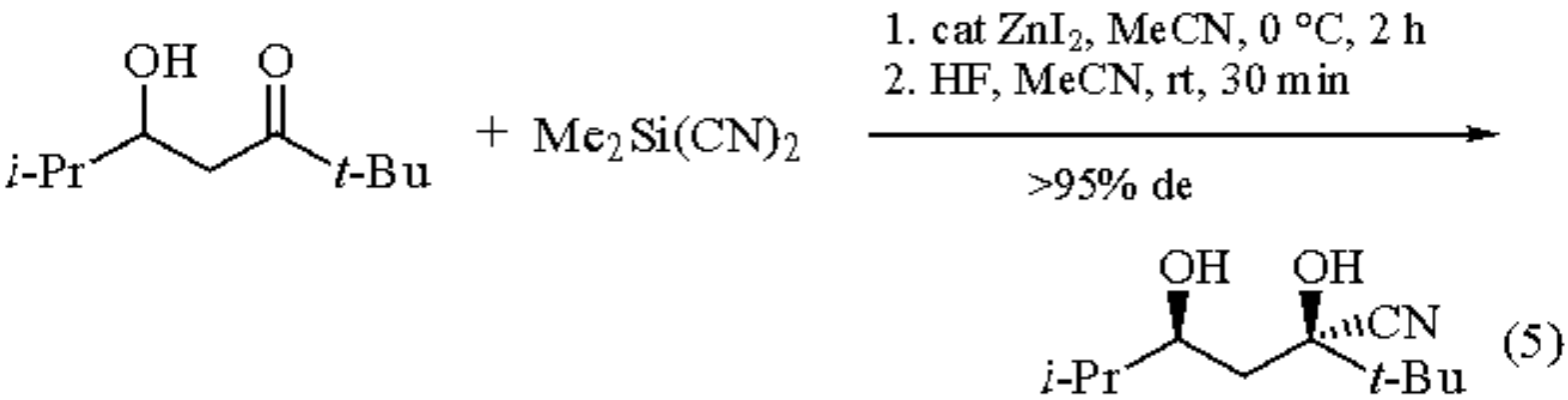

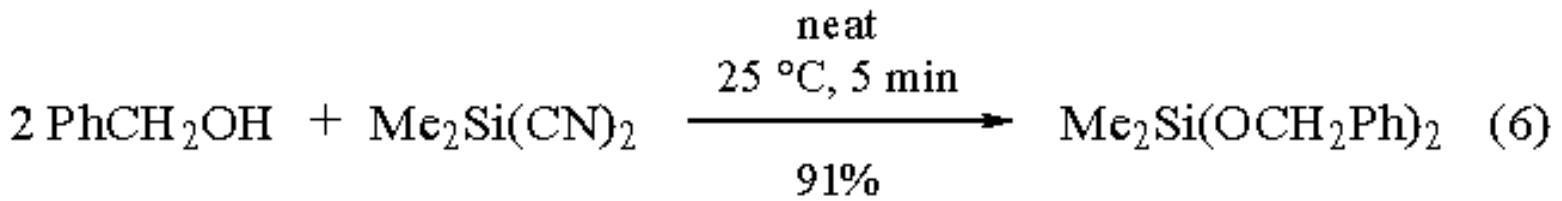

Dicyanodiethylsilane, Dicyanodiphenylsilane, and Dicyanomethylphenylsilane.

Dicyanodimethylsilane, dicyanodiethylsilane,[7,10] dicyanodiphenylsilane,[7,11] and dicyanomethylphenylsilane[12] are a family of related $R_2Si(CN)_2$ reagents that can be used as protecting groups for bifunctional compounds. The silyl-protection of 1,2- and 1,3-diols with these dicyanosilanes is well documented, affording the corresponding five- and six-membered ring compounds (eqs 7 and 8).[4] The reaction of dicyanomethylphenylsilane with ketones is reported to give biscyanosilylated products, but the yield is modest due to competitive aldol condensations.[12]

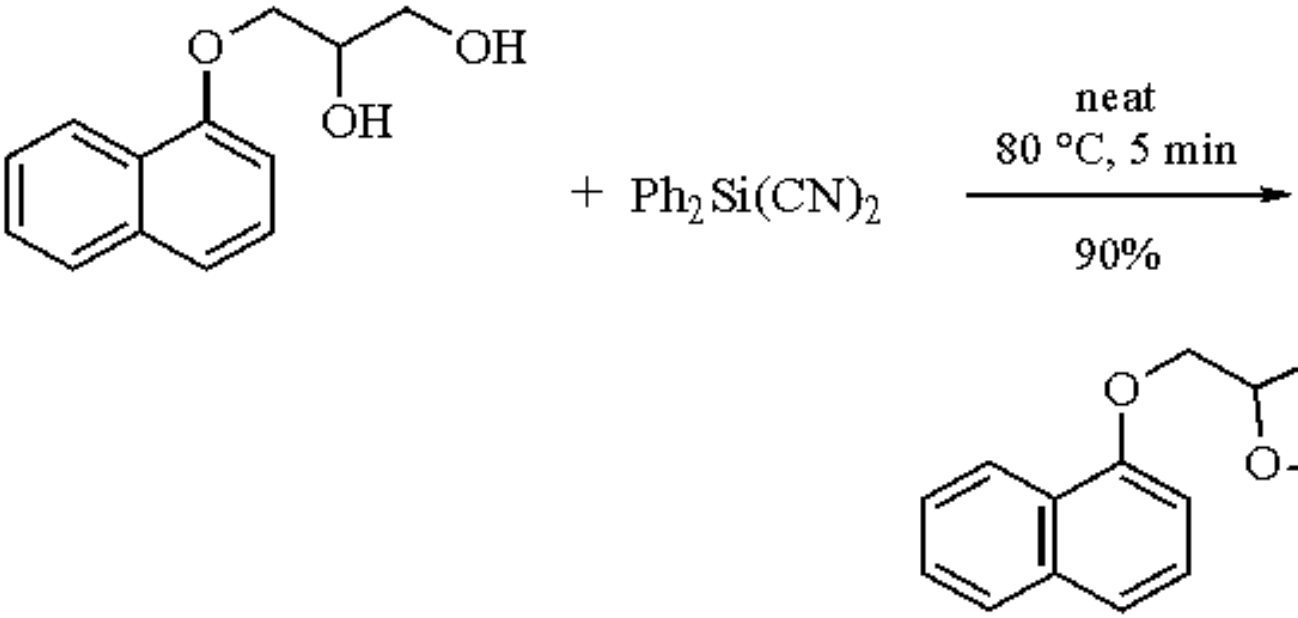

(7)

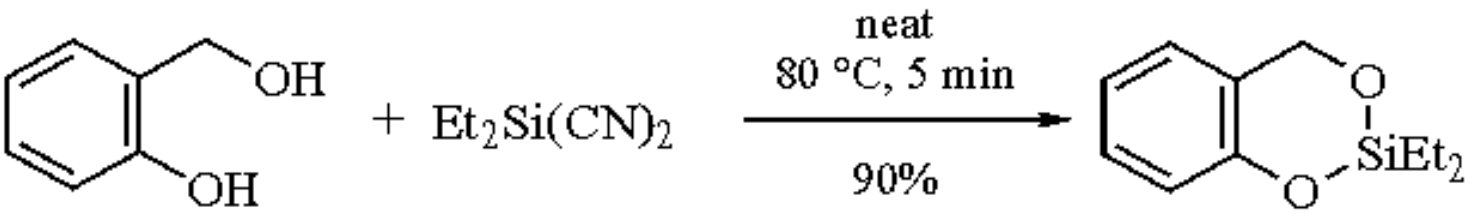

(8)

Related Reagents.

Di-t-butyldichlorosilane; ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***; ***Dichlorodimethylsilane***.

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1. Ryu, I.; Murai, S.; Shinonaga, A.; Horiike, T.; Sonoda, N. *JOC* **1978**, *43*, 780.
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12. Neef, H. *JPR* **1974**, *316*, 817.

Ilhyong Ryu

Osaka University, Japan

Dicyclohexylborane[1]

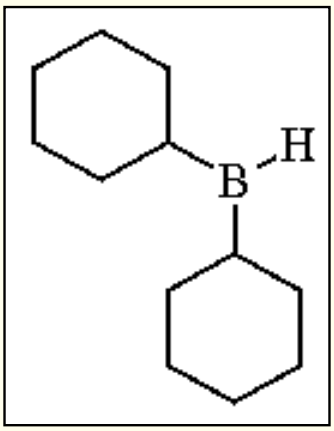

[1568-65-6] · $C_{12}H_{23}B$ · Dicyclohexylborane · (MW 178.12)

(reagent for the reduction of ketones[2] and α,β-unsaturated ketones;[3] used for the hydroboration of alkynes, alkenes, and allenes[4])

Physical Data: mp 103-105 °C.

Solubility: sol THF, diethyl ether, dichloromethane, pentane.

Analysis of Reagent Purity: a method to determine reagent purity by hydrogen gas evolution is available.[26]

Preparative Methods: is a stable white solid available via the hydroboration of cyclohexene with either ***Borane-Tetrahydrofuran*** or ***Borane-Dimethyl Sulfide***.[5] Recently, dicyclohexylborane has been prepared via the hydroboration of cyclohexene with borane-1,4-thioxane.[6]

Purification: may be purified by sublimation under vacuum.[5a]

Handling, Storage, and Precautions: must be used immediately upon generation or stored as a solid under dry nitrogen.[7] Use in a fume hood.

Reduction of Ketones and α,β-Unsaturated Ketones.

Dicyclohexylborane has proven to be a useful reagent for the stereoselective reduction of cyclic, bicyclic, and polycyclic ketones.[2] In reductions of substituted cyclic ketones this reagent often displays stereoselectivities that are opposite to those observed for the hydride reagents. For example, the reduction of 2-methylcyclohexanone with dicyclohexylborane in THF yields predominantly the *cis* diastereomer, while the reduction with ***Lithium Aluminum***

Hydride in THF leads to preferential formation of the *trans* diastereomer (eq 1).

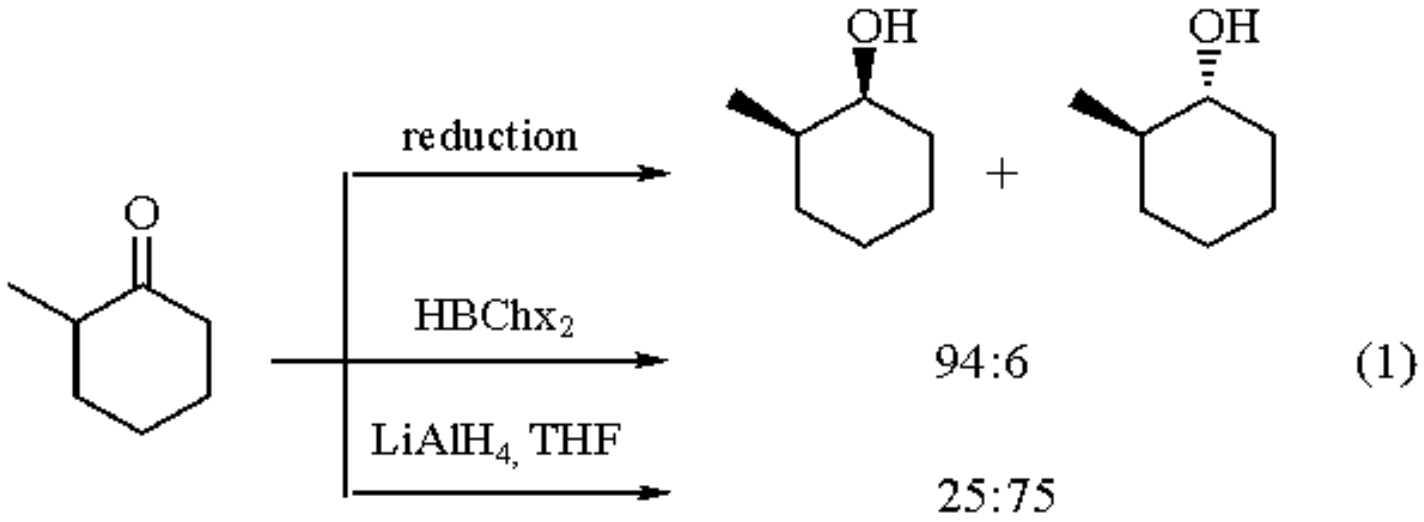

Dicyclohexylborane has also been used to obtain (*Z*)-vinyloxyboranes via the conjugate reduction of (*E*)-α,β-unsaturated ketones (eq 2). Treatment of the hydroboration mixture with aldehydes has allowed the preparation of stereochemically pure *syn* aldols in good yields.[3] Similar reactivity has also been demonstrated with catecholborane.[8]

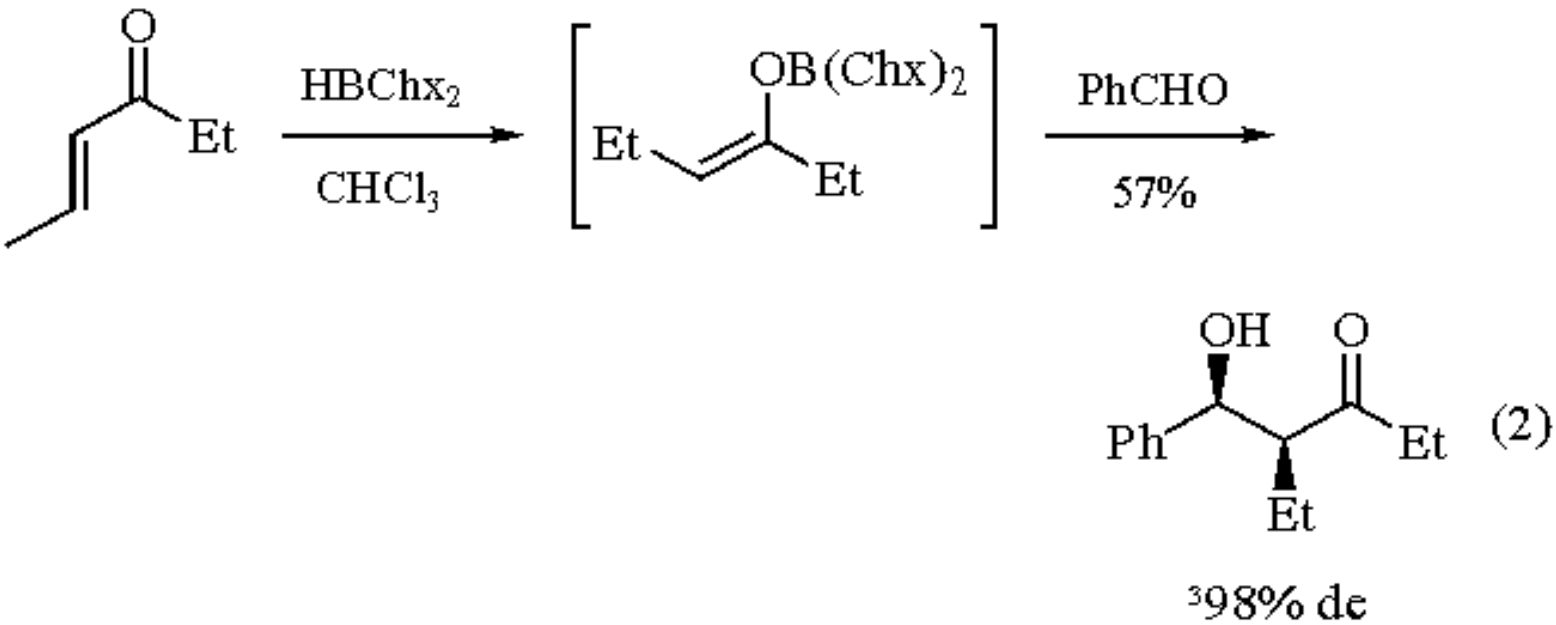

Hydroboration of Alkenes and Allenes.

Dicyclohexylborane has found many applications in the hydroboration of alkenes. It may be used to advantage for the hydroboration of sterically hindered alkenes where other regioselective hydroborating agents (e.g. ***Disiamylborane*** and ***Diisopinocampheylborane***) may suffer from significant amounts of retrohydroboration. In addition, dicyclohexylborane is less prone to isomerization than disiamylborane although the regioselectivity characteristics of the two reagents are comparable. The sterically encumbered nature of the reagent also allows for the possibility of selective hydroboration of different alkenes within the same molecule, although selective monohydroboration of conjugated dienes may be difficult.[4a]

The transformations of the trialkylborane products deriving from the hydroboration of alkenes have been extensively reviewed.[1,4] The trialkylborane products may be converted to alkenes, alkyl halides, alcohols, amines, aldehydes, ketones, and carboxylic acids. Trialkylboranes readily undergo isomerization at elevated temperatures, thus making it possible to isomerize an internal alkene to a terminal one.[1,4,9] Brown has extensively studied and optimized conditions for the hydroboration of vinyl and propenyl heterocycles with dicyclohexylborane as well as other representative hydroborating reagents.[10] Although dicyclohexylborane has not seen the widespread use that other hydroborating reagents have, virtually all of the transformations described for trialkylboranes may be adapted to trialkylboranes derived from hydroboration of alkenes with this reagent; this is particularly useful if a highly discriminating hydroboration reagent is desired. Some of its recent applications for the hydroboration of alkenes and allenes are outlined below.

A synthesis of carboxylic acids via the hydroboration of terminal alkenes has recently been developed (eq 3).[11] Several hydroborating reagents were evaluated for this transformation and it was determined that dicyclohexylborane and thexylborane are the reagents of choice.

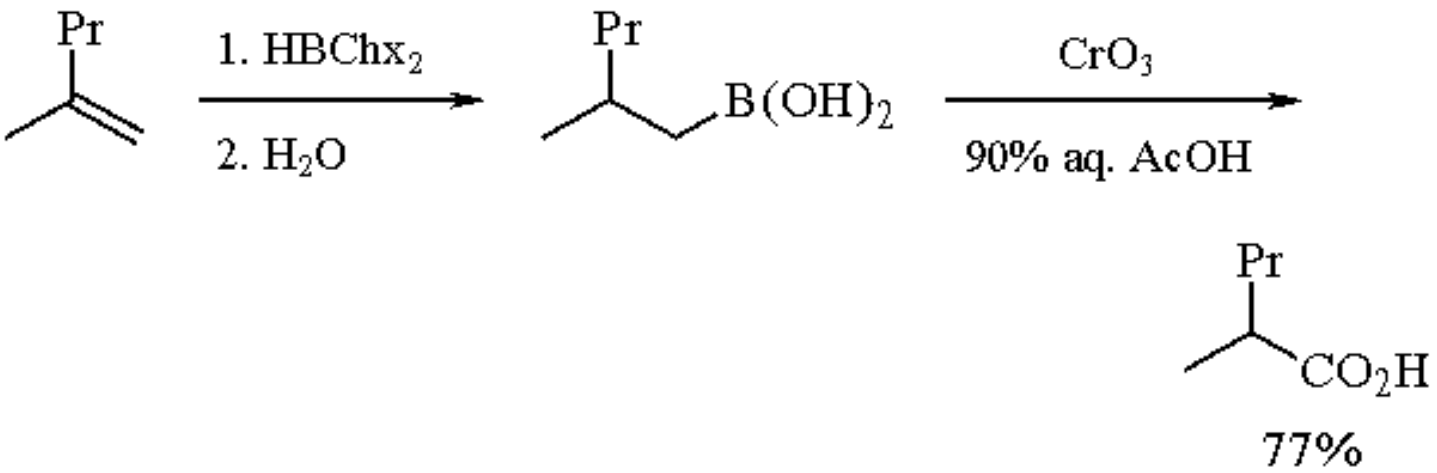

(3)

Dicyclohexylborane has shown useful levels of diastereoselection in the hydroboration of steroidal alkenes (eq 4).[2b] Several hydroborating reagents were studied, including ***Thexylborane***, ***9-Borabicyclo[3.3.1]nonane***, disiamylborane, and ***Borane-Dimethyl Sulfide***. Only the sterically hindered bis(*trans*-2-methylcyclohexyl)borane proved to be superior to dicyclohexylborane in this application.

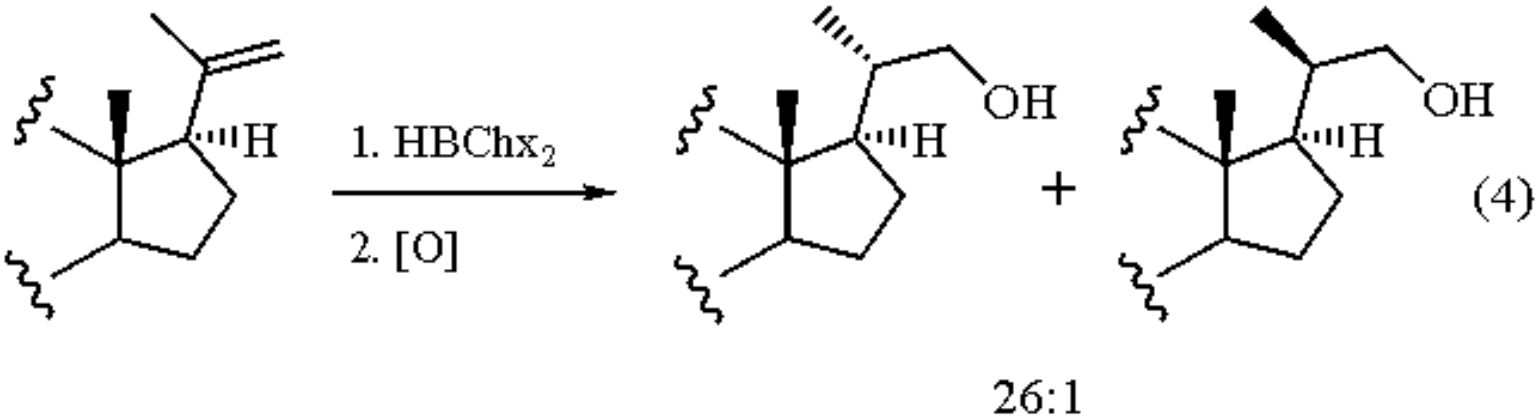

(4)

Allenes have also been used as substrates in reactions mediated by dicyclohexylborane.[12] The types of hydroboration products obtained in these reactions have been found to depend upon the type of allene employed. For example,

internal allenes yield preferentially vinylborane products with dicyclohexylborane, whereas 9-BBN will result in preferential formation of allylboranes.[12a] Terminal allenes give rise to allylborane products.[12a]

Hydroboration of Alkynes.

Dicyclohexylborane is an extremely useful reagent for the hydroboration of alkynes. The transformations of the resulting vinylboranes have been reviewed.[1,4] Both terminal and internal alkynes react readily with dicyclohexylborane to provide the corresponding vinylborane. Dihydroboration, which is often a problem with reagents such as 9-BBN, is kept to a minimum even with excess reagent.[13] Conjugated diynes may be monohydroborated with dicyclohexylborane.[14] In addition, it is possible to selectively reduce an alkyne in the presence of an alkene,[14,15] and hydroboration of alkynes in the presence of other functional groups is possible.[16]

Alkyl group transfer reactions of vinylborane intermediates have proven to be of enormous value in organic synthesis. Perhaps the most well known of these transformations is the Zweifel *cis*-alkene synthesis.[17] Treatment of the dialkylborane adduct with ***Sodium Hydroxide*** and ***Iodine*** results in the transfer of an alkyl group and the formation of the *cis*-alkene (eq 5).

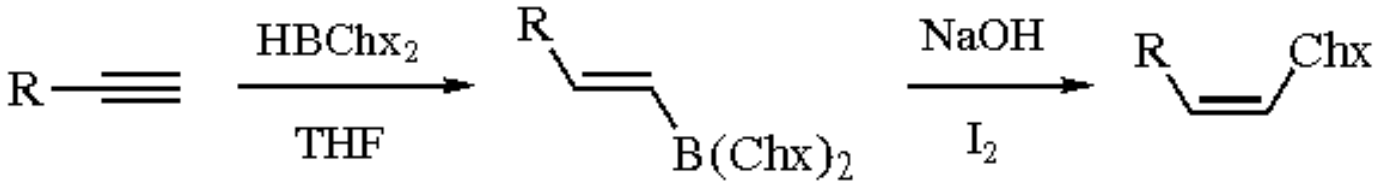

(5)

The capacity of alkyl groups to migrate from boron ate complexes have made possible the stereoselective synthesis of several additional alkene derivatives from vinylboranes.[1,4] In addition, methods have been developed for the coupling of alkenyldialkylboranes via alkenylcopper intermediates which leads to the stereoselective production of (*E*,*E*)-[18] and (*Z*,*Z*)-1,3-dienes[19] as well as 1,4-dienes (eq 6).[20]

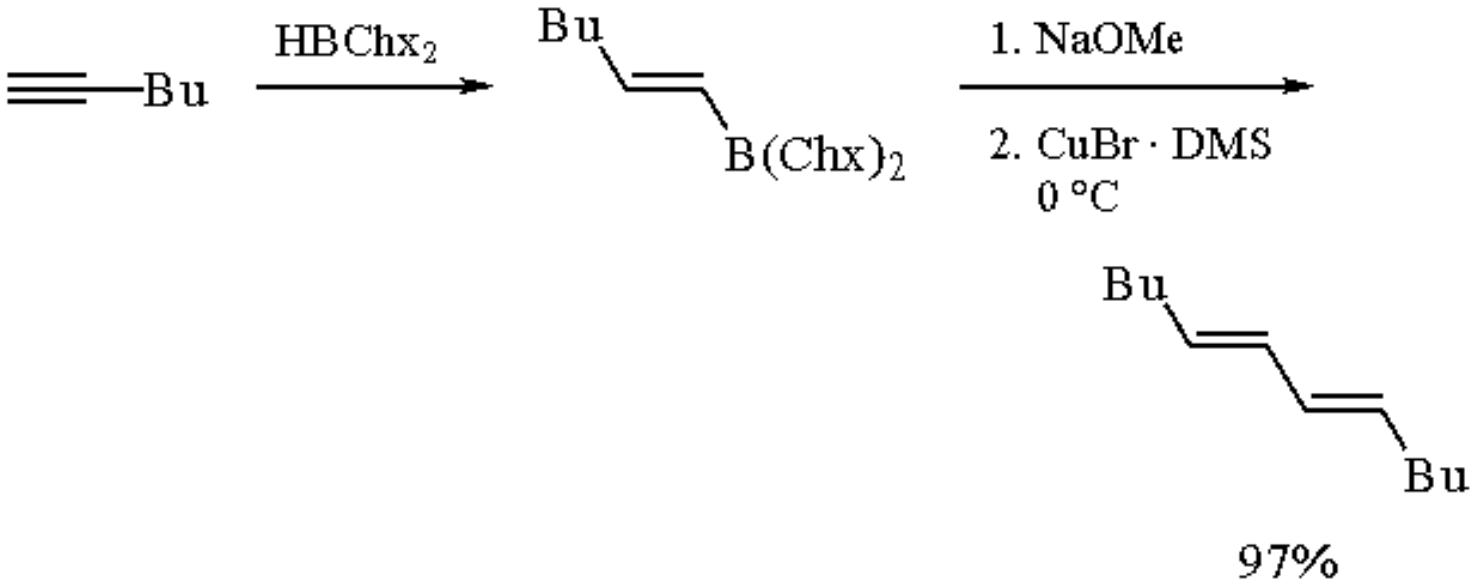

(6)

Several recent applications of dicyclohexylborane for the hydroboration of alkynes have been reported. The alkenyldialkylborane intermediates have been converted into 2-alkylbuta-1,3-dienes,[21] (*E*)-1-alkenylboronic esters,[22]

α,β-unsaturated nitriles,[23] and (*Z*)-1-halo-1-alkenes.[24] Several additional hydroboration applications have been reported.[25]

---

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1,3-Dicyclohexylcarbodiimide[1]

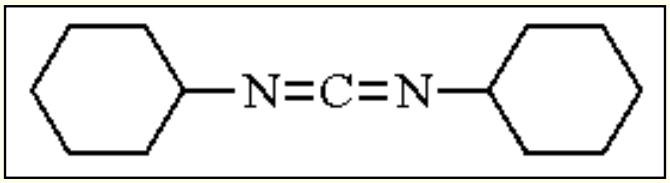

[538-75-0] · $C_{13}H_{22}N_2$ · 1,3-Dicyclohexylcarbodiimide · (MW 206.33)

(powerful dehydrating agent commonly used for the preparation of amides,[2] esters,[3] and anhydrides;[4] used with DMSO for the mild oxidation of alcohols to ketones;[5] used in the dehydrative conversion of primary amides to nitriles,[6] β-hydroxy ketones to α,β-unsaturated ketones,[7] and can effect the stereochemical inversion of secondary alcohols[8])

Alternate Name: DCC.

Physical Data: mp 34-35 °C; bp 122-124 °C.

Solubility: highly sol dichloromethane, THF, acetonitrile, DMF.

Form Supplied in: opalescent solid; widely available.

Handling, Storage, and Precautions: is an acute skin irritant in susceptible individuals. Because of its low melting point, it is conveniently handled as a liquid by gentle warming of the reagent container. It should be handled with gloves in a fume hood, and stored under anhydrous conditions.

Amide Formation.

Since the initial reports,[9,10] DCC has become the most common reagent in peptide synthesis[2,11,12] and in other amide bond-forming reactions of primary and secondary amines with carboxylic acids. The mechanism is considered to be well understood.[2,5]

Typically, DCC (1.1 equiv) is added to a concentrated solution (0.1-1.0 M) of the carboxylic acid (1.0 equiv), amine (1.0 equiv), and catalyst (when used) in methylene chloride or acetonitrile at 0 °C. The hydrated DCC adduct, dicyclohexylurea (DCU), quickly precipitates and the reaction is generally complete within 1 h at rt. The solvents THF and DMF can be used, but are reported to reduce reaction rates and encourage the formation of the *N*-acylurea side product, as well as increasing racemization in chiral carboxylic acids.[13-16] If the amine is initially present as the salt (i.e. amine hydrochloride), it may be neutralized by adding 1 equiv of ***Diisopropylethylamine*** prior to adding DCC; however, the addition of tertiary amines (particularly ***Triethylamine***) can facilitate *N*-acylurea formation and

racemization.[2] Racemization occurs via the formation of an oxazalone intermediate.[2] The addition of coupling agents (acylation catalysts) such as ***1-Hydroxybenzotriazole*** (HOBt),[17] 1-hydroxy-7-azabenzotriazole (HOAt),[18] ***N-Hydroxysuccinimide*** (HOSu),[19] and 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one[20] can generally ameliorate both problems. These additives are required for the coupling of sterically hindered components, or when the amine is weakly nucleophilic.

Another potential problem with DCC is that at the completion of the reaction some DCU remains in solution with the product, necessitating additional purification. Water-soluble carbodiimide derivatives such as ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-p-toluenesulfonate***[21] and ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride*** (EDCI)[22] obviate this problem, as they are removed by a simple extraction. Many newer coupling agents have been developed for peptide synthesis and other acylation reactions. These include ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (BOP),[23] ***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate*** (HBTU),[24] ***Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride***[25] (BOP-Cl), and (1*H*-1,2,3-benzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP).[26] In addition to linear and polymeric amides, lactams of various ring sizes have been synthesized using these methods (eq 1).[27]

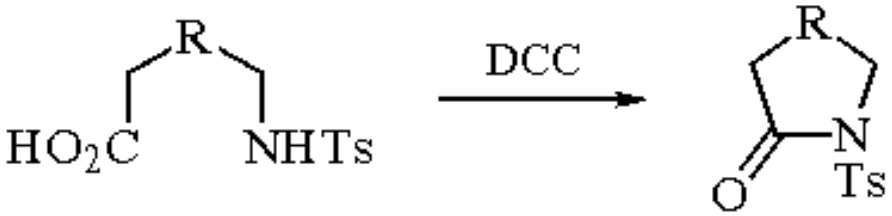

(1)

$R = (CH_2)_n$, $n = 0\text{-}6$

Ester and Thioester Formation.

These reactions occur through the same *O*-acylurea or anhydride active intermediate as in the amide coupling reactions, and the discussion of associated problems applies here as well. In general, alkyl and (particularly) aryl thiols can be efficiently coupled to carboxylic acids using DCC.[28] Reactions of primary and secondary alcohols proceed reliably, but require the presence of an acylation catalyst. This is usually ***4-Dimethylaminopyridine*** (DMAP),[29,30] (see also ***1,3-Dicyclohexylcarbodiimide-4-Dimethylaminopyridine***), but others have been used including 4-pyrrolidinopyridine[31] and pyridine (solvent) with catalytic ***p-Toluenesulfonic Acid***.[32] The acylation of more hindered alcohols often results in reduced yields; however, even *t*-butanol can be acylated, providing a useful route to *t*-butyl esters.[3,31] Various other carbodiimide derivatives have also been used in the preparation of esters.[33,34] As with amides, which are not limited to intermolecular reactions, a wide variety of lactones can also be synthesized.[35,36]

Anhydride Formation.

Among other anhydride-forming reagents, including ***Acetic Anhydride***, ***Trifluoroacetic Anhydride***, and ***Phosphorus(V) Oxide***, DCC is one of the simplest, mildest, and most effective reagents for the preparation of symmetrical anhydrides,[4,37] including formic anhydride,[38] which is useful in the preparation of formamides (eq 2).

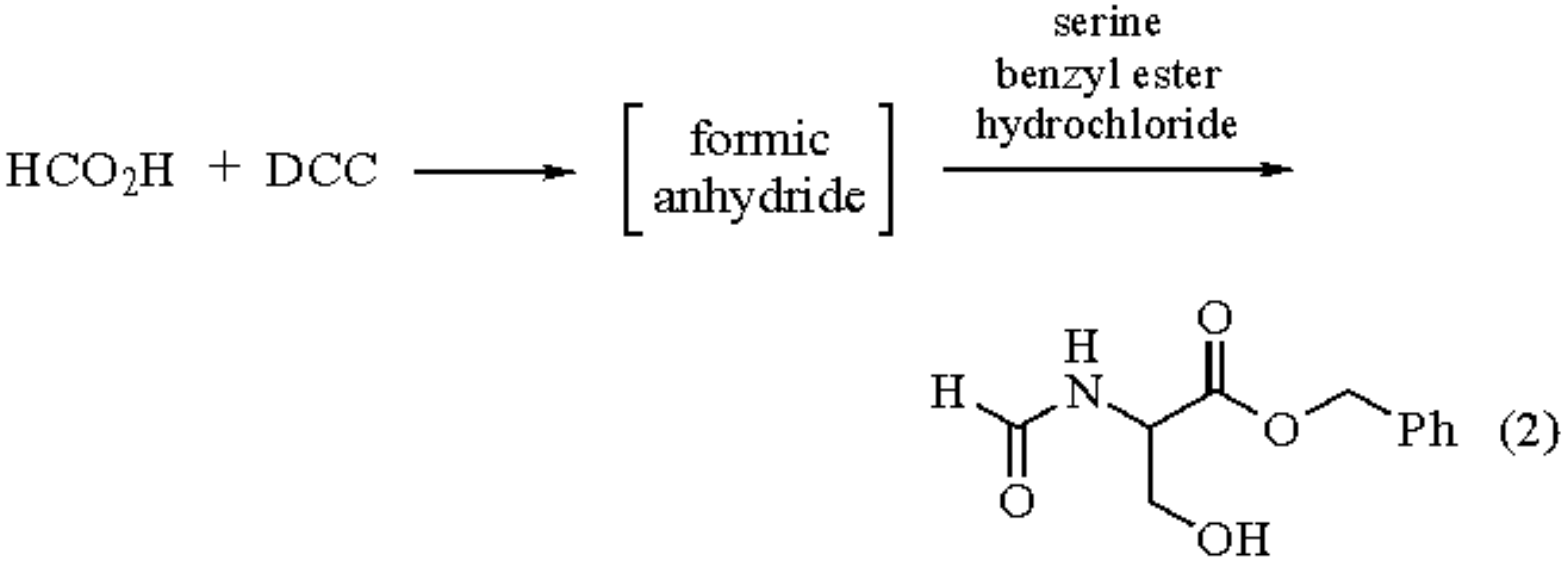

Anhydride formation is associated with each of the reaction types involving carboxylic acids. The anhydride is often the reactive species, to the extent that it competes with the *O*-acylurea or covalent catalyst adduct (see discussion of amide bond formation reactions).

Sulfinate and Phosphate Esters.

Anhydrides of sulfinic and sulfonic acids[39,40] and phosphate monoesters can be prepared using DCC. Further reaction with alcohols or phenols gives the corresponding sulfinates[41] and phosphate diesters.[42,43] Pyrophosphates can be prepared from mono- and disubstituted phosphate esters.[44] Reaction of activated sulfinates with amines gives the corresponding sulfinamides.[45]

Oxidation of Alcohols to Aldehydes and Ketones: Moffatt Oxidation.

The oxidation of primary and secondary alcohols[46] to aldehydes and ketones, respectively, can be carried out by reaction with DMSO activated by DCC (see ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***).[5,47,48] In comparison to the many metal-mediated oxidative reactions, the Moffatt oxidation is carried out under very mild conditions, and has found widespread use for reactions in the presence of sensitive functional groups (eq 3).[49] In addition, over-oxidation of aldehydes to form carboxylic acids is not observed. Under typical reaction conditions, a solution of the alcohol (1 equiv), DCC (3 equiv), and a proton source (pyridinium trifluoroacetate) (0.5 equiv) is stirred in DMSO or DMSO/benzene overnight at rt. After quenching the reaction with aqueous acetic acid and removing DCU by filtration, the product can be isolated by extraction. In modifications of this reaction,[46] DCC can be replaced by other DMSO-activating agents including acetic anhydride (see ***Dimethyl Sulfoxide-Acetic Anhydride***),[50] trifluoroacetic anhydride (see ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***),[51] and oxalyl chloride (see ***Dimethyl Sulfoxide-Oxalyl Chloride***).[52,53]

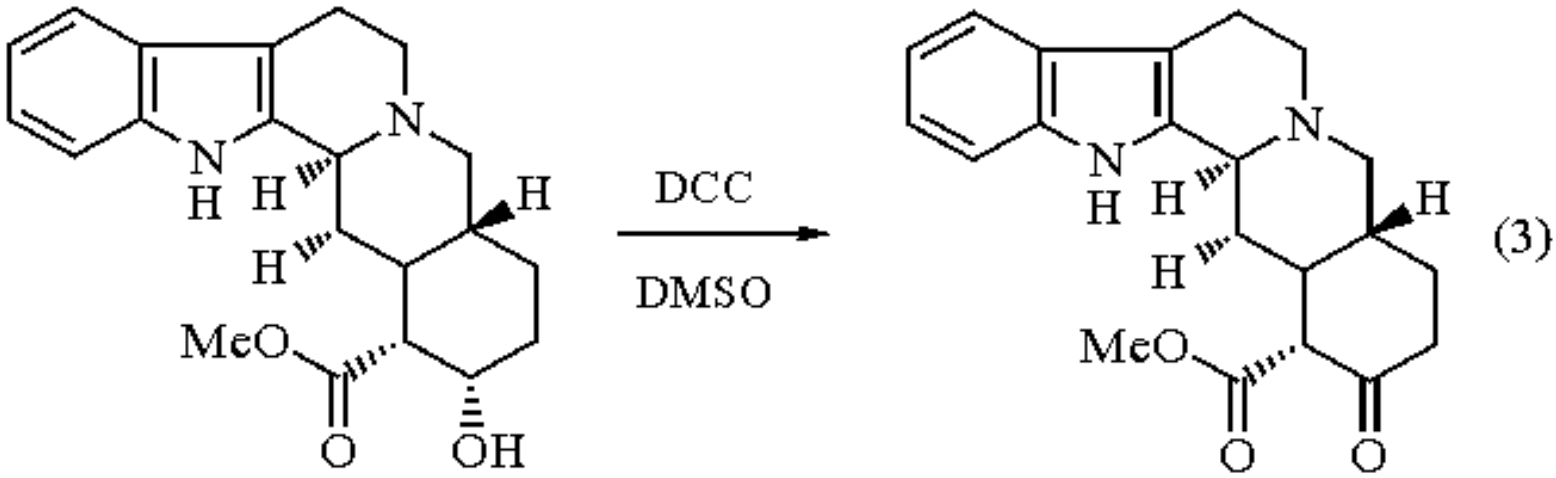

Dehydrative-Type Couplings.

Because of the power of DCC as a dehydrating agent, it has found many uses in a variety of other dehydrative coupling reactions. These include the reaction of primary amines with DCC and ***Carbon Dioxide*** or ***Carbon Disulfide*** to form ureas (eq 4)[54] or isothiocyanates (eq 5),[55] respectively.

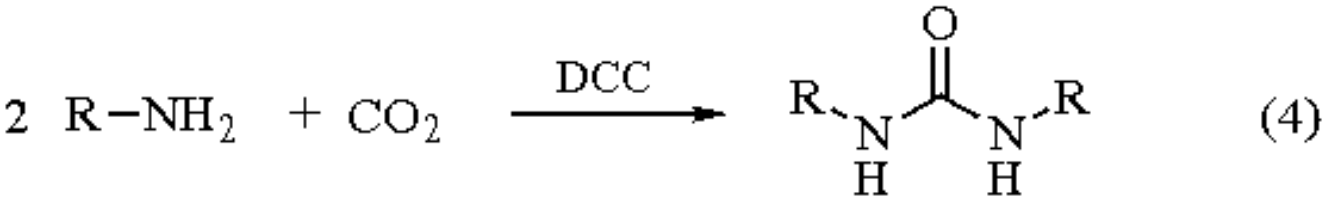

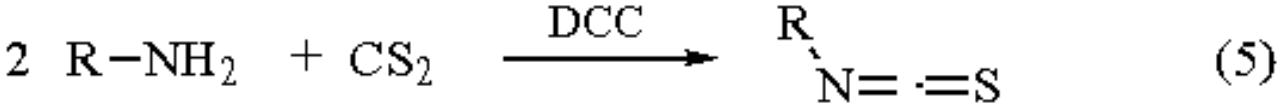

Symmetrical peroxides can be synthesized from benzoic acid derivatives and hydrogen peroxide (eq 6).[56] Unsymmetrical peroxides can be synthesized from the corresponding carboxylic acid and peroxy acid.[56]

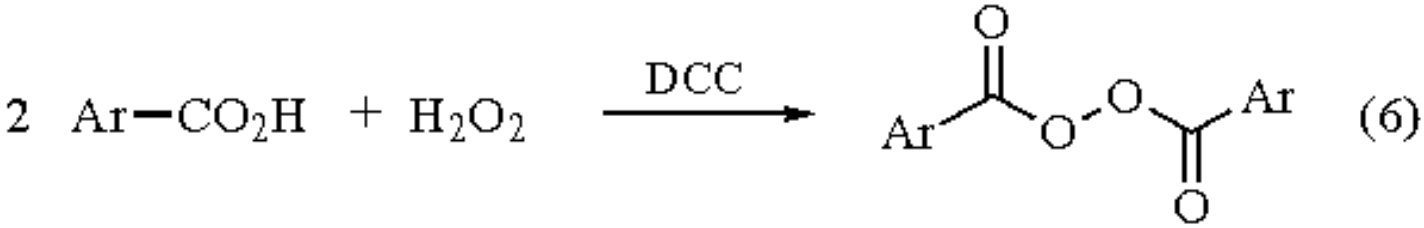

Aromatic and aliphatic alcohols and thiophenols can be coupled to form ethers (eq 7)[57,58] and thioethers (eq 8),[59,60] respectively, using DCC.

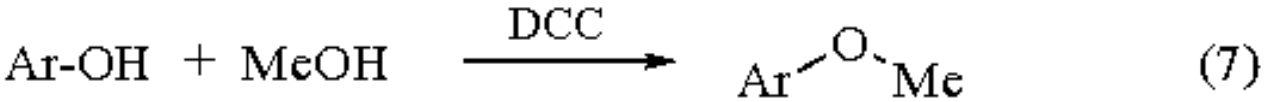

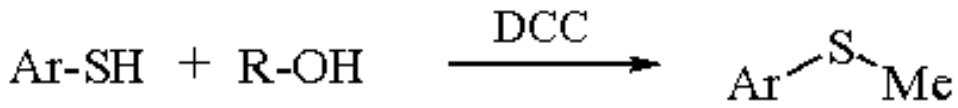

(8)

In cases where sensitivity of the compound precludes the formation of an acid chloride, α-diazo ketones can be synthesized by the DCC-mediated coupling of diazomethane to carboxylic acids (eq 9).[61,62]

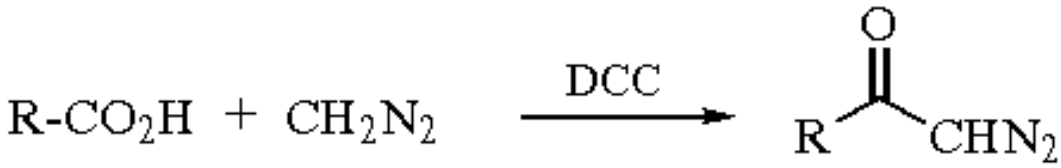

(9)

Dehydration to Alkenes, Epoxides, Nitriles, and Ketenes.

β-Hydroxy ketones and β-hydroxy esters can be dehydrated, using DCC, to α,β-unsaturated ketones (eq 10)[7,63] and esters (eq 11),[64] respectively. Cyclopropanes can be synthesized by the dehydration of γ-hydroxy ketones (eq 12).[65]

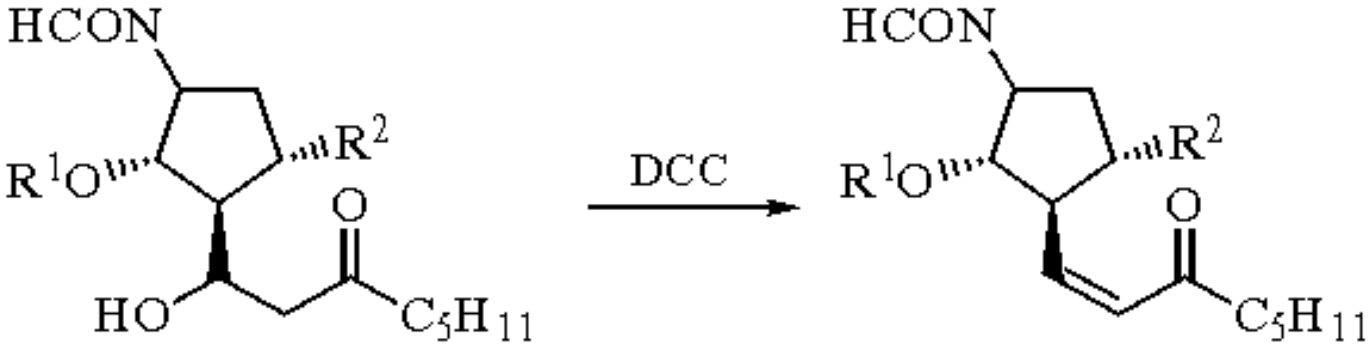

(10)

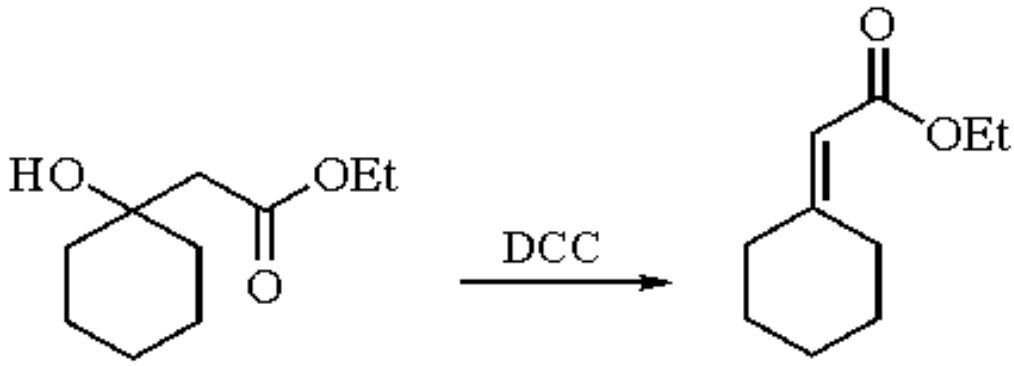

(11)

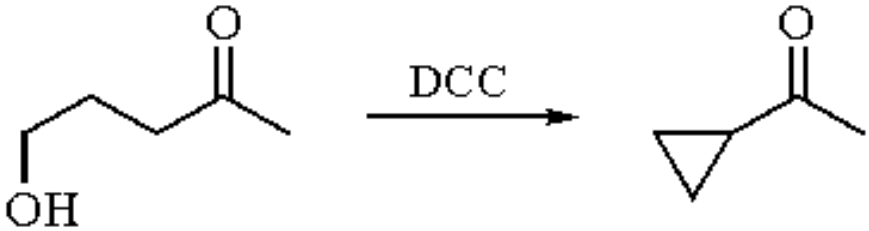

(12)

Other dehydration reactions include the conversion of primary amides to nitriles,[6] aldehydes to nitriles (via the hydroxylamine) (eq 13),[66,67] and carboxylic acids to ketenes (eq 14).[68]

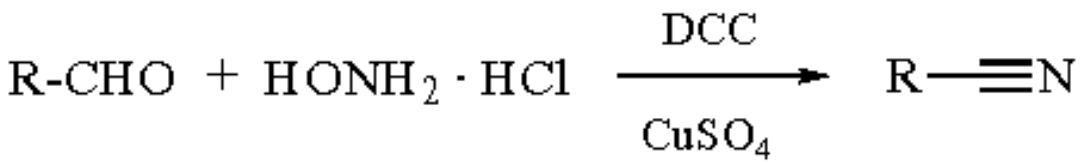

(13)

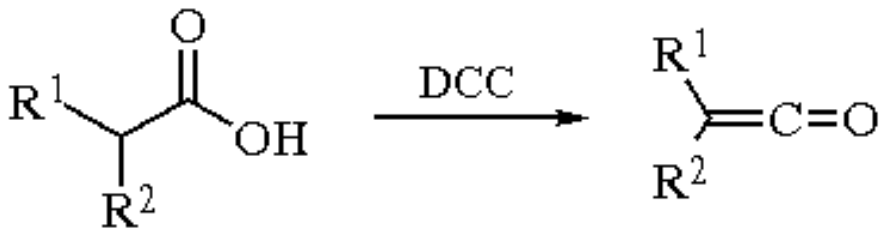

(14)

Dehydroxylation of Alcohols.

Alcohols and phenols can be dehydroxylated to the corresponding alkane by hydrogenation of the *O*-acylurea adduct formed from the reaction of the alcohol with DCC (eq 15).[69,70]

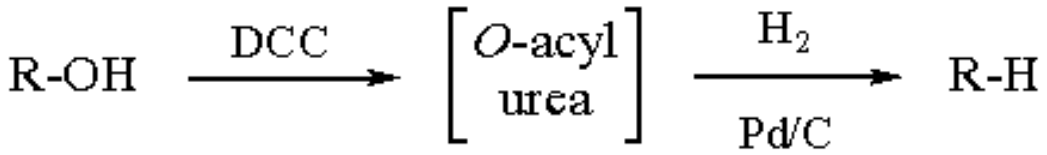

(15)

Inversion of Secondary Alcohols.

Secondary alcohols can be stereochemically inverted by formylation (or esterification) with DCC, followed by saponification (eq 16).[8]

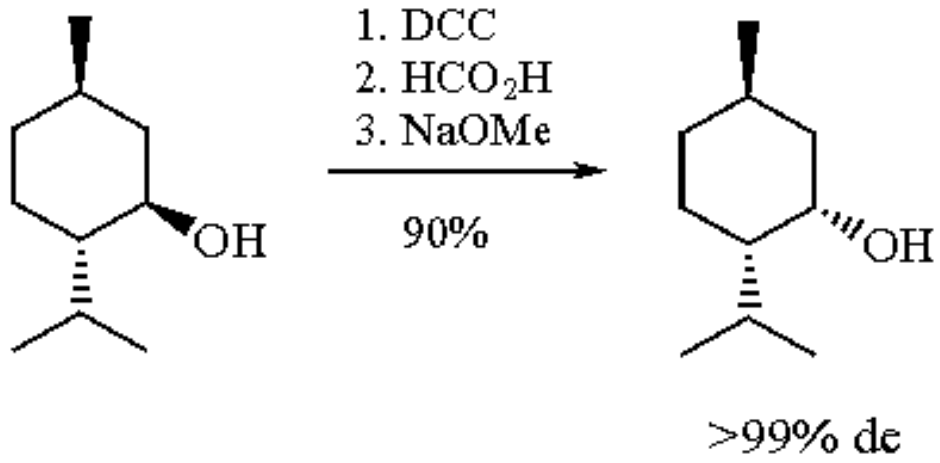

(16)

Heterocyclization Reactions.

DCC has frequently been used both as a reagent and as a reactant in the synthesis of heterocycles.[1] For example, DCC-mediated cyclodesulfurative annulation reactions[71] have been used to synthesize guanosine-type nucleotide analogs (eq 17).[72]

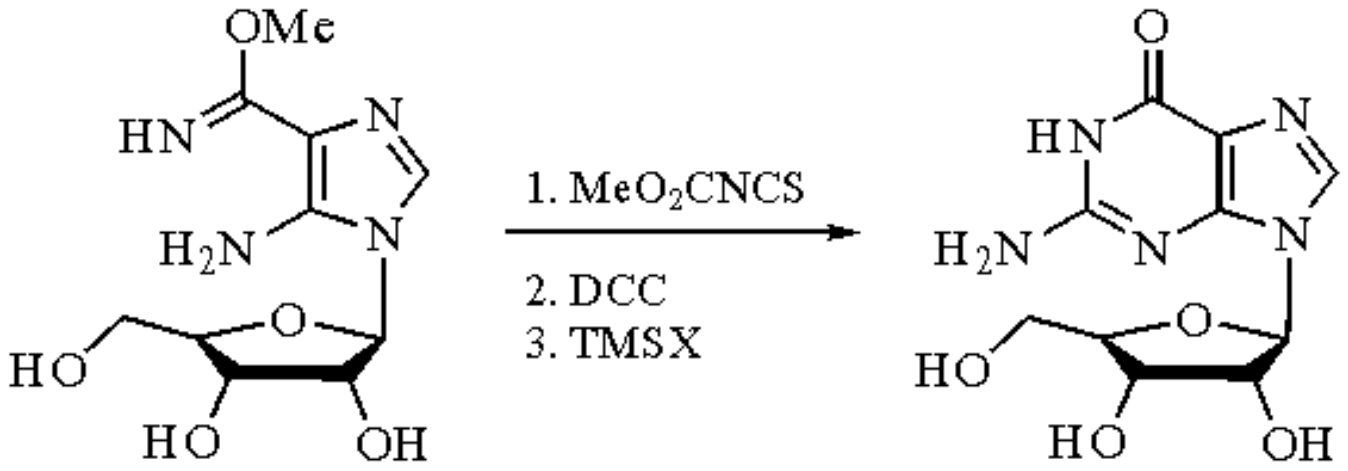

(17)

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Jeffrey S. Albert & Andrew D. Hamilton

1,3-Dicyclohexylcarbodiimide-Copper(I) Chloride[1]

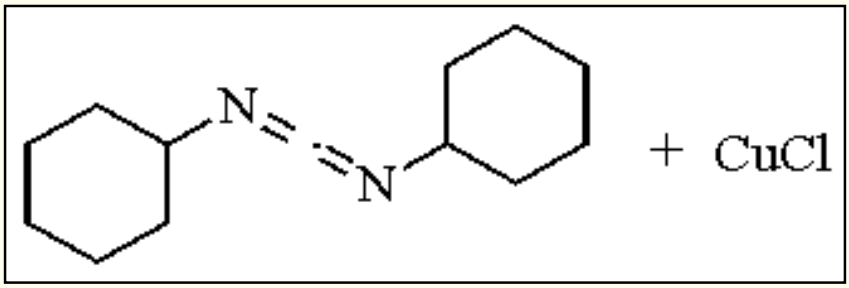

(DCC)

[538-75-0] · $C_{13}H_{22}N_2$ · 1,3-Dicyclohexylcarbodiimide-Copper(I) Chloride · (MW 206.33) (CuCl)

[7758-89-6] · ClCu · 1,3-Dicyclohexylcarbodiimide-Copper(I) Chloride · (MW 99.00)

(dehydrating reagent used for preparation of α,β-enones,[2,3] enimines,[4] and nitroalkenes;[5] used for esterification of secondary alcohols with inversion of configuration[6])

Physical Data: for details see individual entries for ***1,3-Dicyclohexylcarbodiimide*** and ***Copper(I) Chloride***.

Dehydration.

DCC in the presence of a catalytic amount of CuCl efficiently dehydrates alcohols with a β-substituted acceptor group. Reaction of β-hydroxy ketones, 2-hydroxyimines, and nitroaldols with DCC/CuCl affords α,β-unsaturated ketones (60-80% yield) (eq 1),[2,3] enimines (31-75% yield) (eq 2),[4] and nitroalkenes (60-99% yield) (eq 3),[5] respectively.

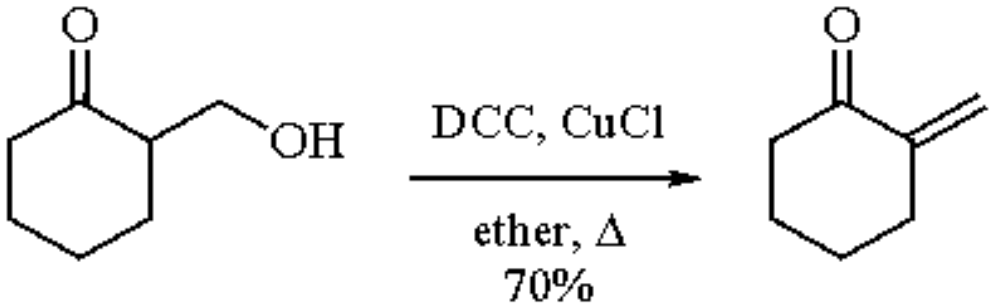

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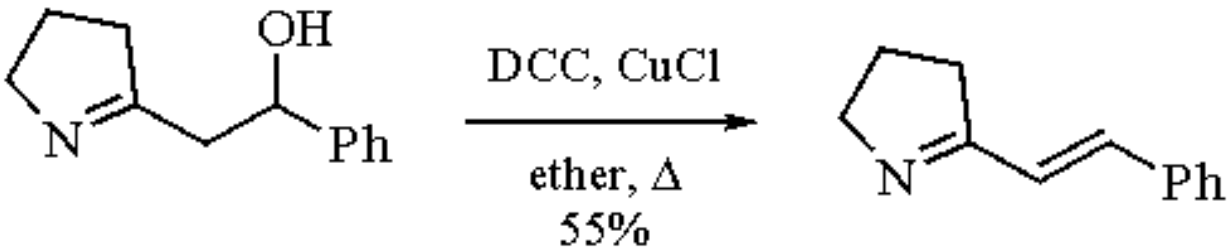

(2)

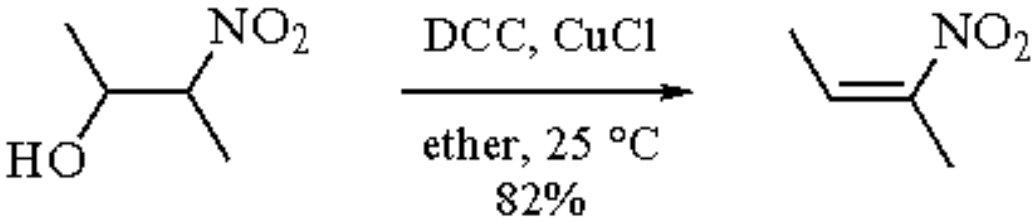

(3)

The mild reaction conditions provide an alternative to methods utilizing acidic conditions that promote polymerization and interfere with other functional groups. Yields for the DCC/CuCl method are comparable to the acidic conditions.[2-5]

α-Cyclopropyl ketones (eq 4) can be prepared by DCC/CuCl dehydration of γ-hydroxy ketones[7] which compares to other methods, e.g. alkylation of γ-chloro ketones or Simmons-Smith cyclopropanation of α,β-unsaturated ketones. A drawback to this method is the formation of dihydrofurans in the event of ketone enolization (eq 5). This phenomenon offers insight into the reaction mechanism, suggesting a *syn* elimination of H_2O.[3,8]

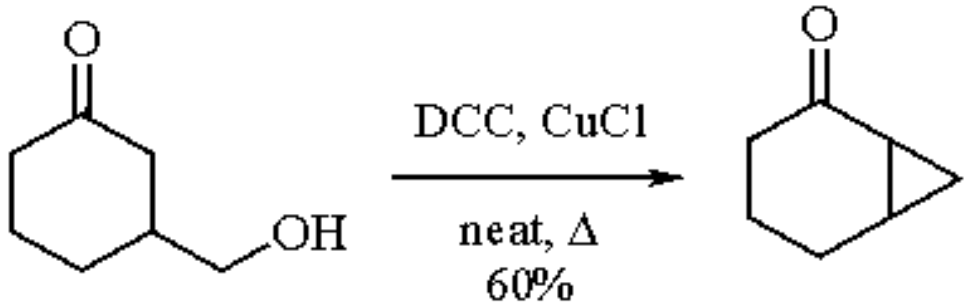

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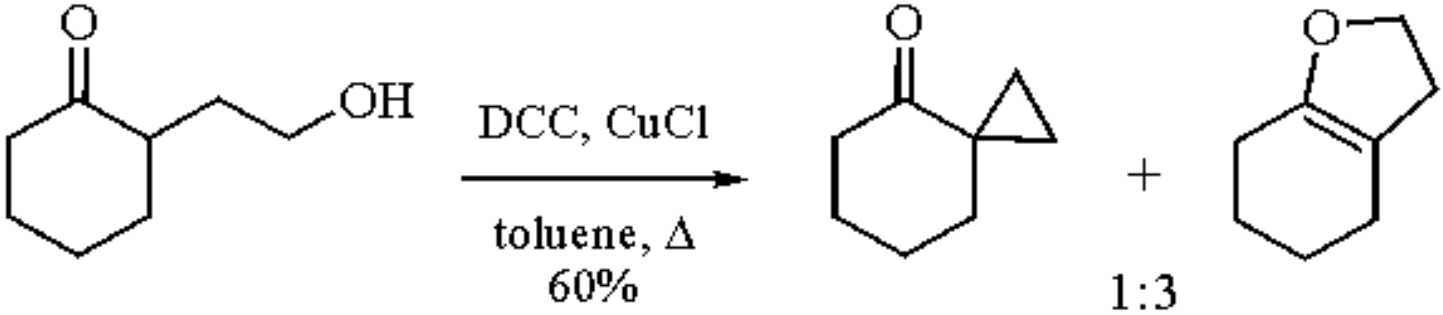

(5)

Esterification.

DCC/CuCl reacts with secondary alcohols (eq 6), affording an isourea ether or carbamidate adduct (**1**). Treatment of (**1**) with a carboxylic acid gives an ester with inverted configuration[9] in good yield (50-83%) with high enantioselectivity (>99% ee)[6] and compares to the Mitsunobu procedure.[10] Saponification of the resulting ester produces an alcohol with inversion of configuration, which is a viable alternative to existing methods.[11]

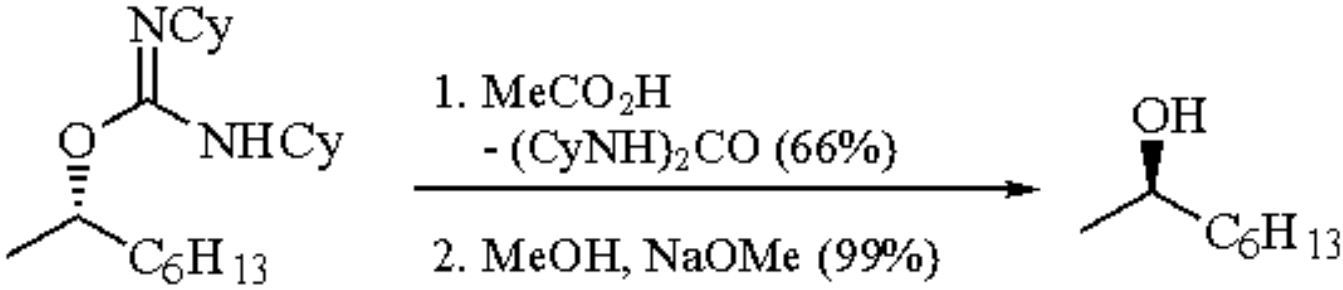

(6)

(1)

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1,3-Dicyclohexylcarbodiimide-4-Dimethylaminopyridine[1]

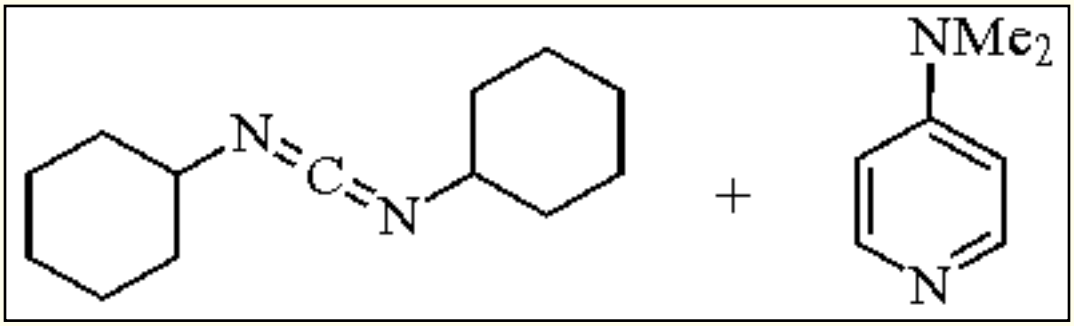

(DCC)

[538-75-0] · $C_{13}H_{22}N_2$ · 1,3-Dicyclohexylcarbodiimide-4-Dimethylaminopyridine · (MW 206.33) (DMAP)

[1122-58-3] · $C_7H_{10}N_2$ · 1,3-Dicyclohexylcarbodiimide-4-Dimethylaminopyridine · (MW 122.17)

(powerful dehydrating mixture used for the preparation of esters,[2] lactones,[3,4] and amides from carboxylic acids and alcohols or amines)

Alternate Name: DCC/DMAP.

Physical Data: DCC: mp 34-35 °C; bp 122-124 °C. DMAP: mp 108-110 °C.

Solubility: DCC: highly sol dichloromethane, THF, acetonitrile, DMF. DMAP: sol dichloromethane, THF, acetonitrile, DMF, ethyl acetate.

Form Supplied in: DCC: opalescent solid; widely available. DMAP: yellow to tan crystals; widely available.

Handling, Storage, and Precautions: DCC is an acute skin irritant in susceptible individuals. Because of its low melting point, it is conveniently handled as a liquid by gentle warming of the reagent container. It should be handled with gloves in a fume hood, and stored under anhydrous conditions. DMAP causes skin and eye burns, and is readily absorbed through the

skin. It should be handled with gloves in a fume hood and stored under dry conditions.

Ester Synthesis.

The combination of the powerful dehydrating agent ***1,3-Dicyclohexylcarbodiimide*** (DCC) and the nucleophilic acylation catalyst ***4-Dimethylaminopyridine*** (DMAP)[1] is widely used in the preparation of esters from carboxylic acids and alcohols. The coupling of carboxylic acids with phenols, thiophenols, and thiols can generally be carried out in the absence of any acylation catalyst,[5] but reactions with alcohols do require a catalyst. DMAP is most commonly used, although other related derivatives such as 4-pyrrolidinopyridine (PPY) have in some cases been more effective.[6] These reactions are quite general, although yields typically decrease as steric bulk increases. *t*-Butyl esters can frequently be synthesized in yields greater than 80%.[6-8] To facilitate purification of the product, water-soluble carbodiimides such as ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride*** (EDCI)[9] can be used in place of DCC.

Under typical conditions, DCC (1.1 equiv) is added to a concentrated solution (0.1-1.0 M) of the carboxylic acid (1.0 equiv), alcohol (1.0-3.0 equiv), and DMAP (0.01-0.10 equiv) in dichloromethane or dichloromethane/DMF at 0 °C. After 1 h the solution is allowed to warm to rt and stirring is continued for an additional 1-5 h. After removal of the precipitated dicyclohexylurea (DCU) by filtration, the product can be recovered by extraction.

Because DMAP and its related derivatives (in conjunction with a coupling agent) are such powerful acylating agents, racemization has frequently been observed in reactions with chiral carboxylic acids, particularly with amino acids. For example, in the synthesis of the *t*-butyl ester of Boc-Asp(OBz)-CO_2H, greater than 60% racemization was observed[2] using EDCI with DMAP (0.5 equiv). The degree of racemization is highly dependent upon the components, and generally increases with steric bulk. Racemization can be suppressed by using low temperatures, short reaction times, and a minimum of DMAP.

The role of DMAP in these reactions is two-fold. First, the pyridine nitrogen can undergo nucleophilic attack upon the *O*-acyl active ester, forming the *N*-acylpyridinium. This charge-separated adduct facilitates electrophilic attack of the nucleophile and increases the leaving group ability. The second role of DMAP is its function as a base (pK_a9.70). As such, it can assist in the deprotonation of the nucleophile. If DMAP is used in stoichiometric amounts, it can be used to neutralize acids formed if the activating agent is an anhydride rather than a carbodiimide.

Lactones.

DCC/DMAP has been frequently used in the synthesis of lactones of various ring sizes. The reaction

conditions and considerations are essentially the same as for ester formation. In several cases, however, the catalyst was effective only when used as the hydrochloride or trifluoroacetate salt.[4,10,11]

Amides.

Although amide bond formation reactions can often be carried out without any acyl-transfer catalyst, the use of DMAP can dramatically increase the reaction rate. For example, the rate of reaction between *m*-chloroaniline and benzoyl chloride was increased by a factor of nearly 6×10^3 when pyridine was replaced by DMAP as the catalyst.[12] However, DMAP is not frequently used for this purpose[13] because of the potential for racemization with chiral carboxylic acids. In these cases, less powerful acyl-transfer catalysts are used.

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Dicyclohexano-18-crown-6

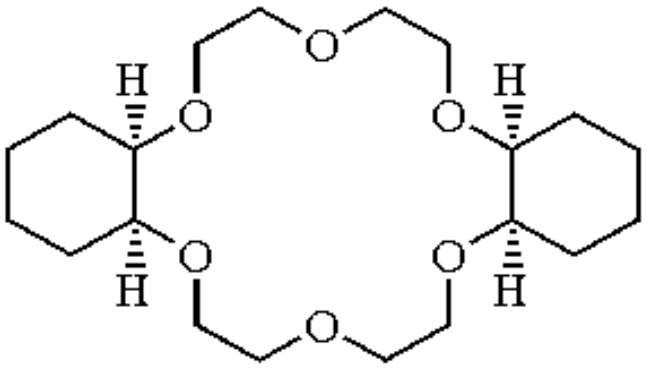

cis-syn-cis

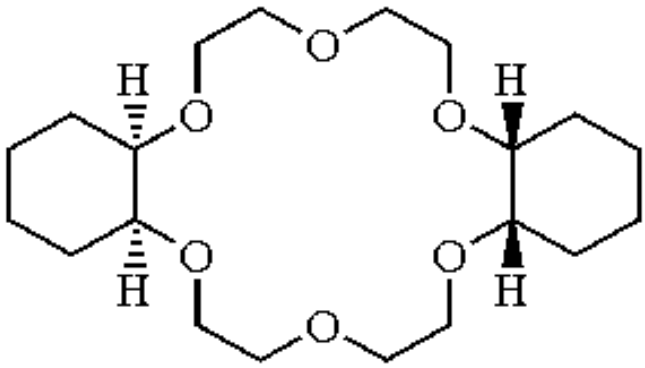

cis-anti-cis

(*cis-syn-cis*)

[15128-65-1] · $C_{20}H_{36}O_6$ · Dicyclohexano-18-crown-6 · (MW 372.50) (*cis-anti-cis*)

[56468-35-0]

(complexation agent; promoter of halide reactions, carbon, oxygen, and sulfur anion reactions, eliminations, oxidations, and reductions)

Physical Data: mp 38-54 °C (mixture of isomers); *cis-syn-cis* isomer mp 61-62 °C; *cis-anti-cis* isomer (two forms) mp 69-70 °C and 83-84 °C. ^{1}H NMR: (mixture of isomers, C_6D_6) 3.3-4.0 ppm (20H multiplet) and 0.9-2.2 ppm (16H multiplet).

Form Supplied in: all isomers are colorless crystals.

Preparative Methods: a mixture of diastereomers is prepared in 58-69% yield by the hydrogenation of ***Dibenzo-18-crown-6*** in *n*-butanol over 5% ruthenium on alumina at 1000 psi.[1] This mixture has been separated into the *cis-syn-cis* and *cis-anti-cis* isomers.[2] Direct synthesis of the *trans-syn-trans* (mp 120-121 °C) and *trans-anti-trans* (mp 77-80 °C) isomers from *trans*-1,2-cyclohexanediol has been reported.[3,4]

Handling, Storage, and Precautions: toxic orally; eye and skin irritant, with possible permanent injury; absorbed by skin. Use in a fume hood.

Complexation With Metal Salts.

The cavity diameter of dicyclohexano-18-crown-6 is estimated to be 2.6-3.2 Å, which is ideal for complexing with a potassium cation, which has an ionic diameter of 2.66 Å. While the selectivity of dicyclohexano-18-crown-6 for potassium

salts is well documented, this macrocyclic multidentate ligand will also effectively complex with other alkali metal cations.[5]

Reactions.

Halides.

The ***Potassium Fluoride***/dicyclohexano-18-crown-6 promoted elimination reaction of *cis*-β-bromo-*p*-styrene in the solvents ***Acetonitrile***, ***N,N-Dimethylformamide***, and *n*-butyl cellosolve has been studied.[6]

The reaction of dimethyl 2-chloroethylene-1,1-dicarboxylate with potassium fluoride/dicyclohexano-18-crown-6 in sulfolane produces dimethyl 2-fluoroethylene-1,1-dicarboxylate.[7] Modest yields of dechlorodecarboxymethylation products promoted by potassium chloride/dicyclohexano-18-crown-6 in sulfolane have also been observed (eq 1).[7]

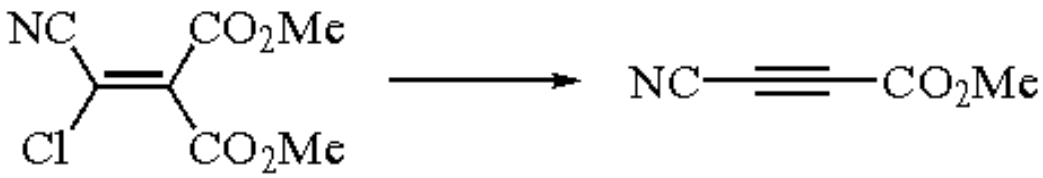

(1)

Dicyclohexano-18-crown-6 enhances the reactivity of potassium bromide and ***Potassium Iodide*** in nucleophilic substitution and elimination reactions.[8] Second-order kinetics are observed for the reaction of *n*-butyl brosylate with bromide and iodide ions in ***Acetone***. Potassium iodide/dicyclohexano-18-crown-6 complex acts as a base in aprotic solvents.[8] Reaction with 2-bromooctane in DMF at 100 °C for 6 h produced only 2-octene in 75-80% yield. In acetone the crown complex of potassium iodide gives a low yield of 2-octene; the major product is mesityl oxide from the condensation of acetone.

Dicyclohexano-18-crown-6 was used as a liquid-liquid phase transfer catalyst in the reaction of the mesylate of 1-octanol, 1-bromooctane, 1-iodooctane, and the mesylate of 2-octanol with a variety of sodium and potassium halides in the form of saturated aqueous solutions.[9] The relative nucleophilicity of the halides is $I^- > Br^- > Cl^- > F^-$; secondary substrates react more slowly than primary; excess iodide quantitatively displaces bromide. In general, dicyclohexano-18-crown-6 shows greater anion activation than ***Dibenzo-18-crown-6***.[10]

Oxygen Anions.

A wide variety of *p*-bromophenacyl esters have been synthesized by the reaction of potassium carboxylates with *p*-bromophenacyl bromide in acetonitrile or benzene in the presence of dicyclohexano-18-crown-6.[11-13] Sodium salts give excellent yields of product but the reaction times are longer.

Dicyclohexano-18-crown-6 activates potassium acetate more in its reaction with benzyl chloride than does ***18-Crown-6*** or dibenzo-18-crown-6.[14]

Sterically hindered esters of 2,4,6-trimethylbenzoic acid can be saponified with the ***Potassium Hydroxide***/dicyclohexano-18-crown-6 complex in aromatic hydrocarbons. The reaction proceeds by acyl-oxygen cleavage.[15] It was subsequently reported that using this procedure only 11% of the anions in toluene were hydroxide: the major species was methoxide ion.[16] Reaction of this solution with *o*-dichlorobenzene produced *o*-chloroanisole. The reaction was shown to be consistent with an addition-elimination aromatic nucleophilic substitution mechanism.

The rates of alkylation of potassium phenoxide with 1-bromobutane in dioxane in the presence of a series of linear and cyclic polyether additives have been compared.[17] Dicyclohexano-18-crown-6 is more effective than 18-crown-6 and dibenzo-18-crown-6.

The rates of reaction of ***Potassium t-Butoxide*** with 2-nitrofluorobenzene and 4-nitrofluorobenzene has been studied in the absence and presence of dicyclohexano-18-crown-6.[18] Upon addition of a molar equivalent of crown, the rate of reaction of 2-nitrofluorobenzene increased by a factor of 3, and that of 4-nitrofluorobenzene by a factor of 2000.[18]

The rates of reaction of a number of oxygen nucleophiles with *p*-nitrophenyl phosphinate and with *p*-nitrophenyl benzoate in toluene containing dicyclohexano-18-crown-6 have been reported. The anions studied include *t*-$BuOO^-K^+$, *t*-BuO^-K^+, *n*-$BuOO^-K^+$, and *p*-$MeC_6H_4O^-K^+$.[19]

Potassium Superoxide was successfully solubilized in ***Dimethyl Sulfoxide***, benzene, THF, and DMF containing dicyclohexano-18-crown-6.[20,21] Reaction with primary and secondary alkyl halides, tosylates, and mesylates was reported to produce reasonable yields of dialkyl peroxides.[21] Alcohol side products accompanied peroxide formation. Using (-)-(*R*)-2-octyl bromide it was demonstrated that the superoxide radical anion, as well as the intermediate alkyl peroxy anion, reacted with the alkyl halide with inversion of configuration.

Dicyclohexano-18-crown-6 is an effective phase transfer catalyst in the reactions of 4-chloromethyl-1,3-dioxolane with substituted mono- and dihydric phenols in the presence of metal hydroxide bases.[22]

Carbon Anions.

Dicyclohexano-18-crown-6 is used as a liquid-liquid phase-transfer catalyst in the reaction of ***Potassium Cyanide*** with 1-chlorooctane[10] and in the alkylation of phenylacetone with *n*-butyl bromide using 50% aqueous sodium hydroxide.[10] A series of kinetic studies involving the alkylation of sodio diethyl *n*-butylmalonate with *n*-butyl bromide in the solvents benzene and cyclohexane in the presence of varying concentrations of dicyclohexano-18-crown-6 has been reported.[23] In benzene solution containing only 0.036 M dicyclohexano-18-crown-6 the alkylation rate is equal to that observed in neat DMF. The addition of dicyclohexano-18-crown-6 to the alkali metal salts of ***Ethyl Acetoacetate*** in dioxane causes the destruction of ionic agglomerates and formation of monomeric ion pairs.[23] In the reaction of this enolate with ethyl tosylate a marked acceleration of rate is observed in the presence of the crown.[24]

The phase-transfer catalytic methylation of deoxybenzoin by ***Dimethyl Sulfate*** produces an oxygen-to-carbon alkylation ratio of approximately unity in the presence of dicyclohexano-18-crown-6.[25] Similar results were obtained with 18-crown-6.

Eliminations.

The effect of ionic association upon positional and geometrical orientation in base-promoted β-elimination processes from 2-butyl halides and *p*-toluenesulfonate systems in solvents of low polarity has been extensively explored.[24] The results of the reactions of 2-bromobutane and 2-butyl *p*-toluenesulfonate with a number of base-solvent systems to produce 1-butene and *cis*- and *trans*-2-butene in the presence and absence of dicyclohexano-18-crown-6 has been reported.[26]

The competition between *syn* and *anti* elimination in the reaction of *trans*-2-phenylcyclopentyl tosylate with potassium *t*-butoxide in *t*-butyl alcohol has been investigated.[24] The 1-phenylcyclopentene was produced by a *syn* elimination, while the 3-phenylcyclopentene was produced via an *anti* pathway. Using 0.1 M potassium *t*-butoxide, 89% *syn* elimination was realized; in the presence of an equivalent quantity of dicyclohexano-18-crown-6, however, the *syn* product was reduced to 30%.

Base association effects have been studied using conformationally mobile systems. The effect of dicyclohexano-18-crown-6 on the *syn* vs. *anti* elimination in the reaction of 4,4,7,7-tetramethylcyclodecyl bromide and tosylate,[27] chlorocyclodecane,[28] and 5-decyltosylate[29] has been reported.

The stereochemical course of reaction of *cis*- and *trans*-1-methoxy-d_3-2-*d*-acenaphthene with potassium *t*-butoxide is dependent on the nature of the counter cation.[30] The amount of *syn* elimination decreases in the order $Li^+ > K^+ > Cs^+ > NMe_4^+ > K^+$-crown. It is believed that the elimination mechanism proceeds through a carbanion intermediate.

The effect of dicyclohexano-18-crown-6 on the base-promoted *syn* and *anti* elimination pathways on the diastereomeric 1-deutero-2-fluoro-2-phenylthioethyl phenyl sulfone has been reported.[31] The bases used were potassium phenoxide in dioxane and sodium *t*-butoxide in benzene/*t*-butanol. With potassium phenoxide, in the absence of crown the *syn* elimination pathway dominates, while in the presence of crown the *anti* pathway becomes more important. The corresponding reaction with sodium *t*-butoxide shows little or no effect of crown on the stereochemical course of reaction.

Sulfur Anions.

Dicyclohexano-18-crown-6 serves as an efficient phase transfer catalyst in the reaction of thiophenoxide (see ***Thiophenol***) with 1-bromooctane under liquid-liquid phase-transfer catalytic conditions.[32]

Oxidations.

Dicyclohexano-18-crown-6 solubilizes ***Potassium Permanganate*** in benzene.[33] The solid complex was isolated but it was unstable and slowly decomposed to adipic acid. The solubilized permanganate provides a convenient, mild, and efficient oxidant for a wide variety of organic compounds, e.g. alkenes, alcohols, aldehydes, and alkyl aromatics.

The reaction of ***Potassium Chromate*** with primary alkyl halides in ***Hexamethylphosphoric Triamide*** containing dicyclohexano-18-crown-6 produces aldehydes in good yields.[34] The chromate functions both as a nucleophile and an oxidant.

Reductions.

Dicyclohexano-18-crown-6 has been employed as a liquid-liquid phase transfer catalyst in the reduction of 2-octanone in a benzene/aqueous ***Sodium Borohydride*** two-phase system.[10]

The solubilization of ***Potassium*** and cesium metals in THF and diethyl ether using dicyclohexano-18-crown-6 has been reported.[35] Metal concentrations of approximately 0.0001 M were obtained using 0.005 M solutions of crown. Solution of the metals in THF was carried out at rt, while solution of potassium in diethyl ether was conducted at -78 °C. At -78 °C the THF solutions were stable for days. Optical absorption spectra indicated that the major anionic species in the presence of the crown was the alkali metal anion, M^-.

The solubility enhancement of sodium and potassium metals in secondary amines and in straight and branched chain ethers in the presence of dicyclohexano-18-crown-6 has been studied.[36] The alkali metal anions Na^- and K^- were identified from optical spectra.

Related Reagents.

18-Crown-6; ***12-Crown-4***; ***15-Crown-5***; ***Dibenzo-18-crown-6***.

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Dicyclohexyl(ethyl)amine

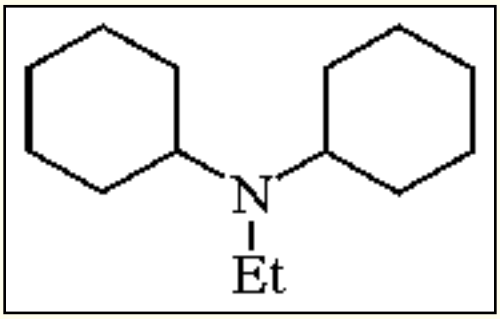

[7175-49-7] · $C_{14}H_{27}N$ · Dicyclohexyl(ethyl)amine · (MW 209.37)

(highly basic, nonnucleophilic amine; useful in alkylation of amines[3] and in dehydrohalogenations;[6] proton acceptor in esterifications[7])

Physical Data: bp 132-134.2 °C/10 mmHg; *d* 0.909 g cm^{-3}; fp 230 °C; absorbs CO_2 from the air.

Solubility: sol acetone, cyclohexane, 1,2-dichloroethane, dichloromethane.

Preparative Method: although commerically available in small quantities, the reagent can be conveniently prepared from dicyclohexylamine and diethyl sulfate.[1,2]

Alkylation of Amines.

Dicyclohexyl(ethyl)amine is an excellent hindered (Hünig's) base. Compatible alkylating agents include alkyl halides, dialkyl phosphates, and trialkyloxonium species.

Dialkylation of aniline with butyl bromide in the presence of dicyclohexyl(ethyl)amine proceeds in high yield (90-180 °C, 3 h, 97%).[3] Alkylation of amine hydrochlorides can be effected using this base and ***Dimethyl Sulfate***, as demonstrated in the final step of the total synthesis of (±)-terramycin.[4] The alkylation of 2-methylbenzimidazole with trialkyloxonium tetrafluoroborate in the presence of dicyclohexyl(ethyl)amine yields 1,3-dialkyl-2-methylbenzimidazolium tetrafluoroborates (0 °C, 70-90%).[5]

Dehydrohalogenation.

Dehydrohalogenation of alkyl halides proceeds in high yields in the presence of dicyclohexyl(ethyl)amine. *n*-Dodecyl bromide yields 1-dodecene (190 °C, 20 h, 98%). The reaction is applicable to the dehydrohalogenation of α-halo ethers to yield the corresponding enol ethers. Similar results can be obtained with other hindered amines, although yields are often inferior.[6]

Proton Acceptor.

Dicyclohexyl(ethyl)amine has been used as a proton acceptor, or proton sponge, in the preparation of esters of carboxylic acids. The reaction is applicable to the derivatization of low-melting fatty acids as their highly crystalline phenacyl bromides. Phenacyl esters are rapidly prepared in high yields (60 °C, 5 min, ~90%.[7] Similarly, methyl and ethyl esters of carboxylic acids can be prepared on micro or preparative scale by alkylation with a dialkyl sulfate: $EtCy_2N + ROS(O_2)OR$ (5 min, steam bath, 84-97%).[8] The procedure is particularly useful as an alternative to ***Diazomethane*** esterification when the latter is inappropriate. The present amine is advantageous over more commonly available alternatives, such as tris(hydroxypropyl)amine, in that it does not remove dimethyl sulfate as the quaternary ammonium salt, and hence can be used in excess. The proton scavenging ability of dicyclohexyl(ethyl)amine is also exploited in the Friedel-Crafts silylation of ferrocene, where it suppresses the protodesilylation reaction and hence allows maximal yields to be achieved (80 °C, 4 h, 36%).[9]

Acylation of alkenes by acetyl hexachloroantimonate yields β,γ-unsaturated ketones. As a buildup of acid is detrimental to the outcome of the reaction, a proton scavenger is necessary. The present amine maximizes yield of the desired product (-50 °C to -25 °C, 1 h, 83%).[10]

Arylated alkenes can be obtained, in good yield, by reaction of aroyl chlorides with activated alkenes in the presence of a hindered amine, such as dicyclohexyl(ethyl)amine, and a catalytic quantity of ***Palladium(II) Acetate***.[11]

Dicyclohexyl(ethyl)amine favors the organopalladium arylation of allylic alcohols by suppressing the formation of halides from the allylic alcohols and hydrogen chloride generated during the course of the reaction.[12] Similar effects are observed in the arylation of crotyl acetate.[13] Yields are in any case modest.

Alkoxycarbonylation.

Alkoxycarbonylation of alkyl halides, sulfates, and sulfonates can be carried out, in modest yields, in the presence of ***Carbon Monoxide***, an alcohol, a hindered base such as dicyclohexyl(ethyl)amine, and a catalytic quantity of ***Sodium Tetracarbonylcobaltate*** (50 °C, 1 atm, 16-20 h, 20-56%).[14] More

nucleophilic bases yield instead the corresponding amides by competitive nucleophilic attack.

Similarly, reaction of trimethylene oxide, carbon monoxide, and tetracarbonylhydridocobalt followed by treatment with dicyclohexyl(ethyl)amine yields γ-butyrolactone (0 °C, 3 h).[15]

Related Reagents.

Diisopropylethylamine; ***2,6-Lutidine***; ***Triethylamine***.

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N,N´-Dicyclohexyl-4-morpholinecarboximidamide

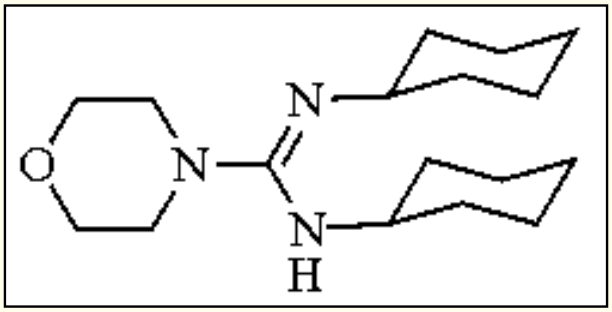

[4975-73-9] · $C_{17}H_{31}N_3O$ · *N,N´*-Dicyclohexyl-4-morpholinecarboximidamide · (MW 293.45)

(strong base; used as a catalyst for phosphorylation reactions in nucleoside chemistry)

Alternate Names: N,N´-dicyclohexyl-4-morpholineformamidine; DMC.

Physical Data: mp 105.5 °C.

Solubility: sol pyridine.

Form Supplied in: white powder.

Preparative Methods: easily prepared by refluxing morpholine and ***1,3-Dicyclohexylcarbodiimide***.[1]

Phosphorylating Reagent.

DMC is a strong base that acts as a catalyst for phosphorylating reactions. It can be used to increase the solubility of salts of nucleoside 5´-phosphoromorpholidates, and to catalyze their cyclization to cyclic 3´,5´-nucleoside phosphates in the presence of DCC (eq 1).[2]

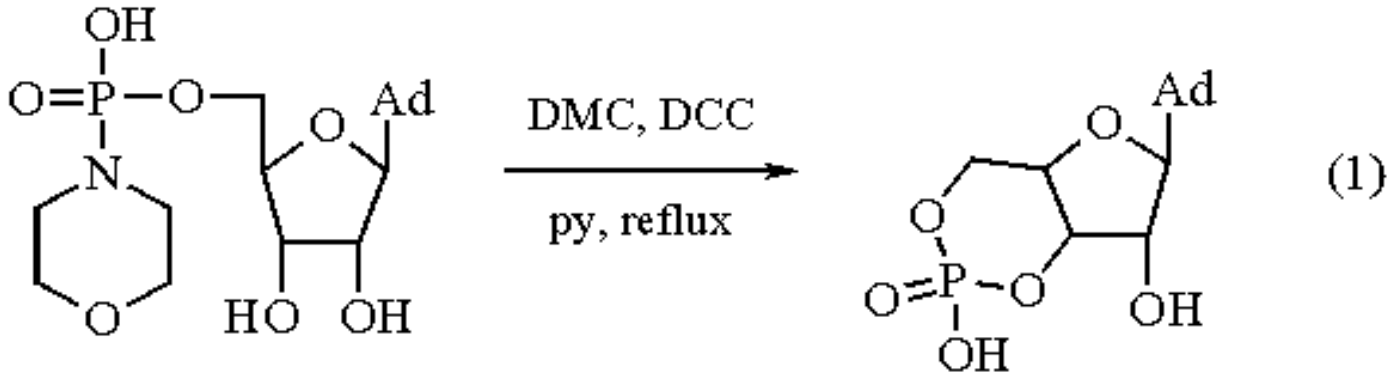

Reaction of DMC salts of nucleoside 5´-phosphoromorpholidates with phosphomonoesters gives nucleoside diphosphate derivatives.[3] Similar reactions have been used for the synthesis of neosamine *C*-nucleoside diphosphates (eq 2).[4]

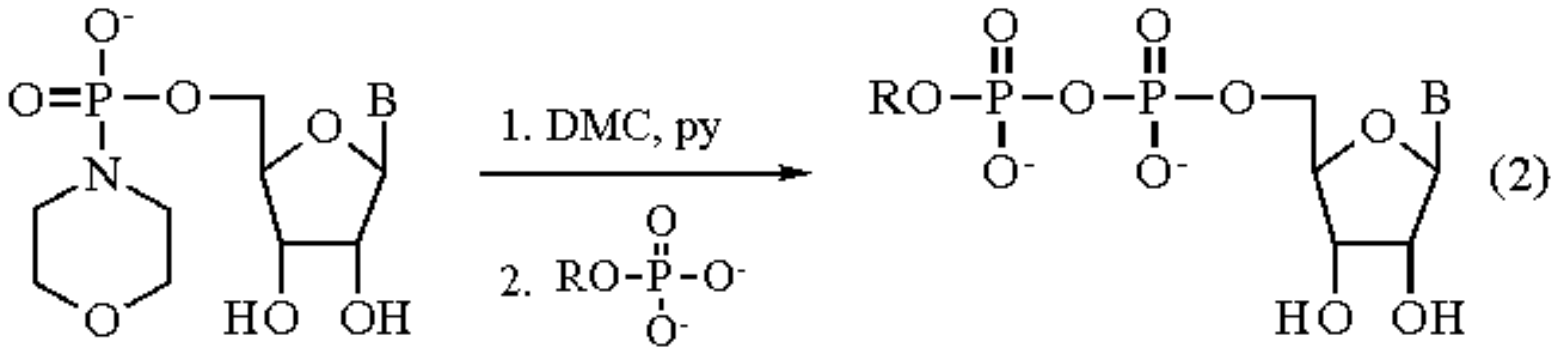

Preliminary formation of a morpholidate is not a necessary requirement and cyclization to 3´,5´-monophosphate derivatives is possible from DMC salts of the corresponding 5´-monophosphate. Ring closure is obtained by action of DCC in dry pyridine (eq 3).[5]

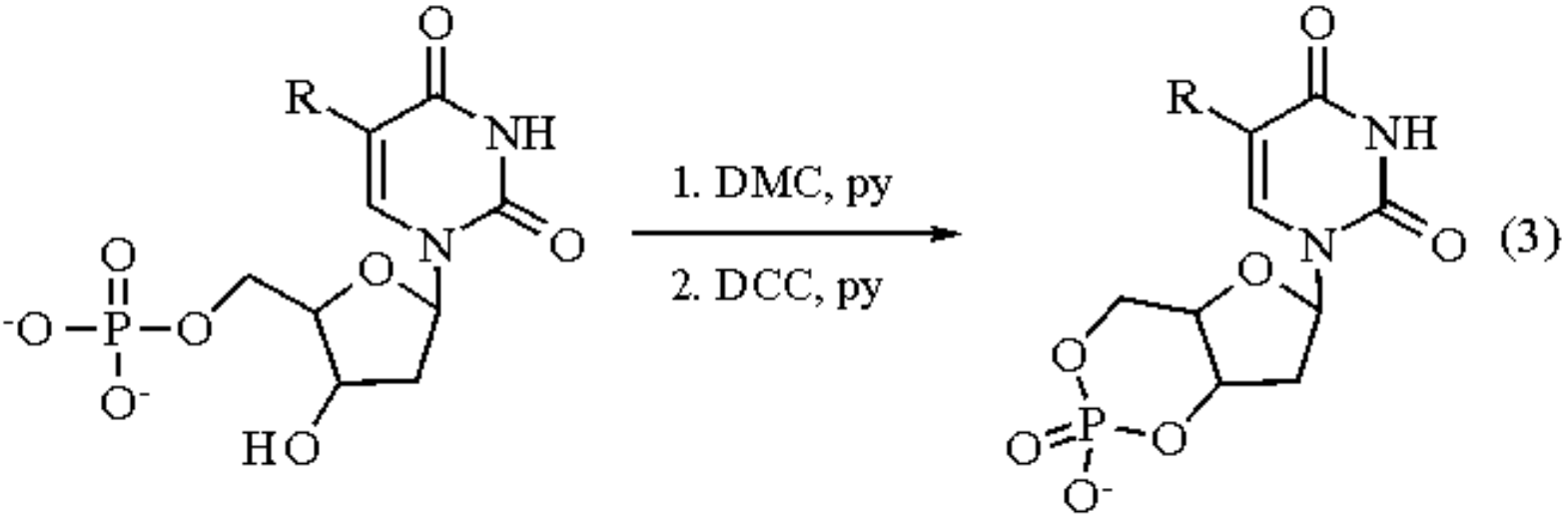

Catalyst for Acylation Reactions in Nucleoside Chemistry.

DMC catalyzes acylation of nucleosides by carboxylic anhydrides. As an example, reaction with succinic anhydride

gives a mixture of isomers but refined conditions have been described to yield N^6-succinyl adenosine (eq 4).[6]

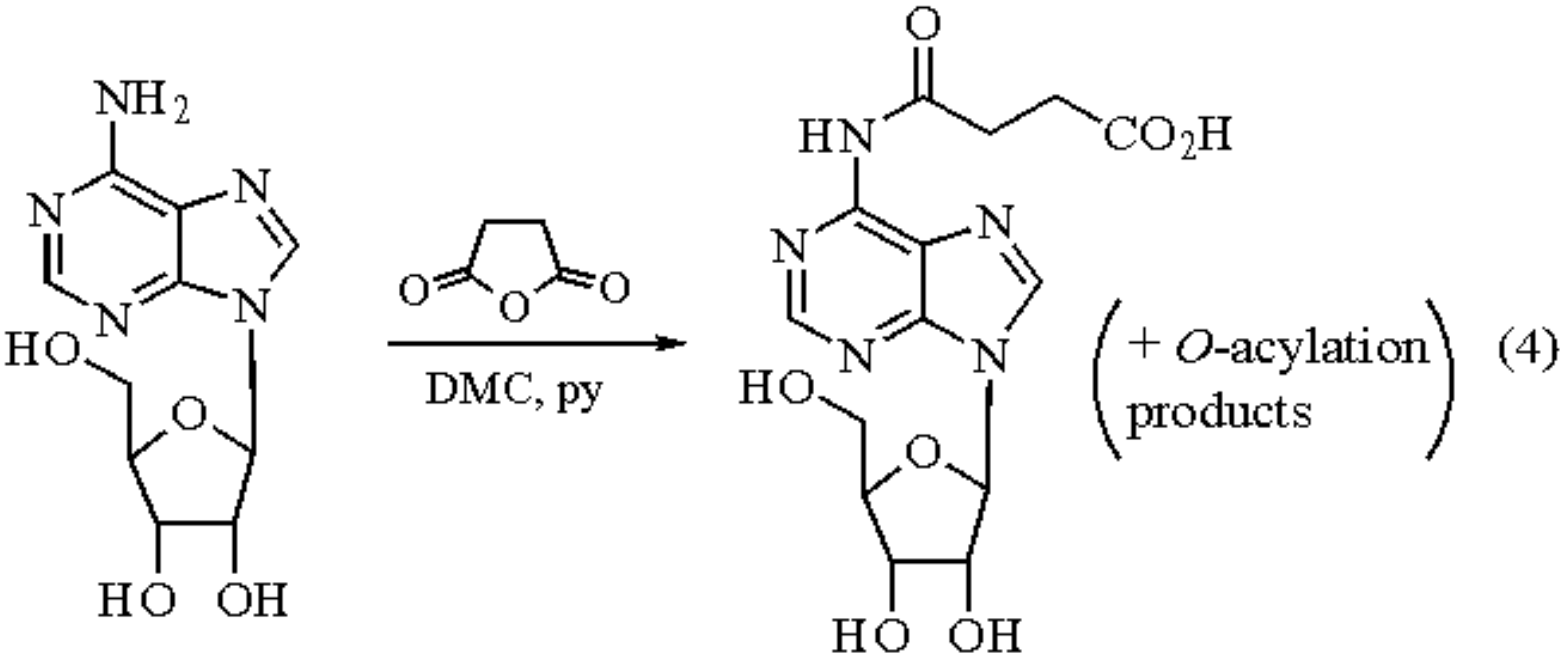

DMC allows simultaneous 2-hydroxybenzylation and phosphorylation when used together with methylthio-4*H*-1,2,3-benzodioxaphosphorin 2-oxide (MTBO) (eq 5).[7]

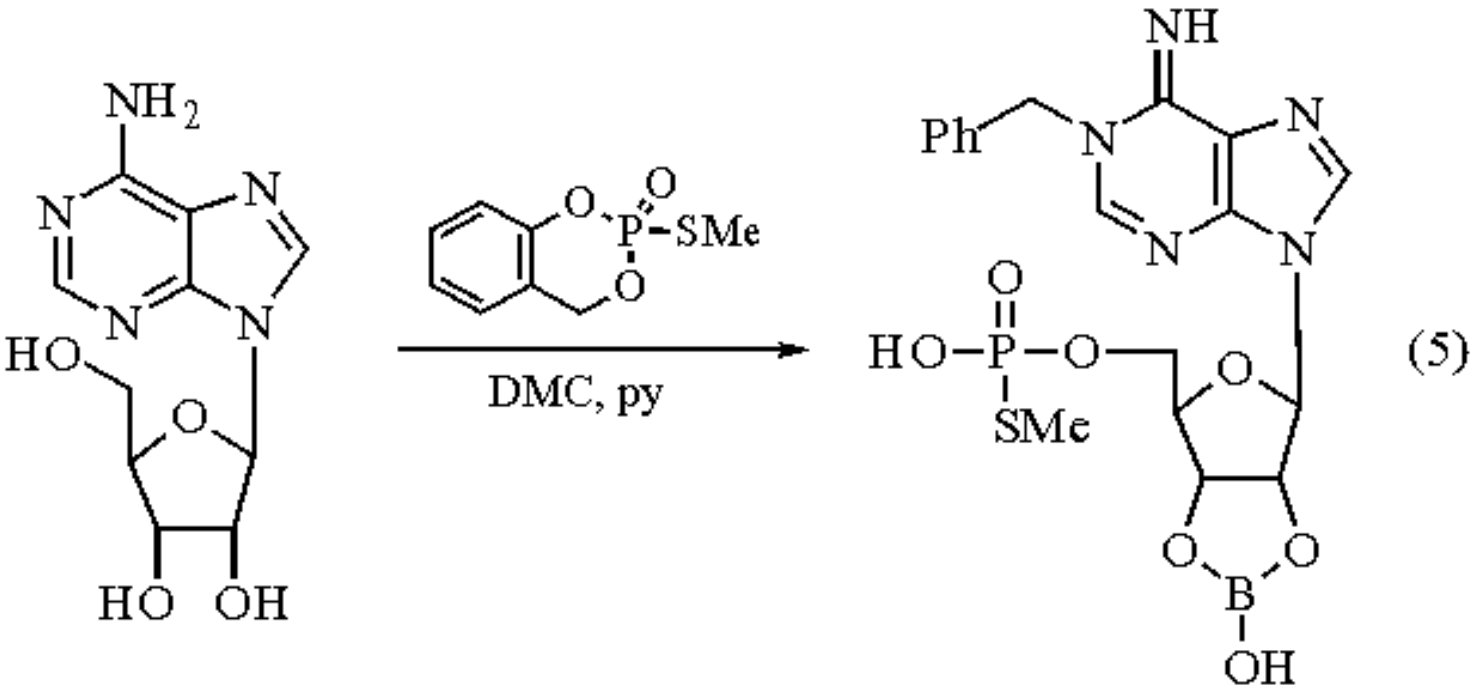

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10-Dicyclohexylsulfonamidoisoborneol[1]

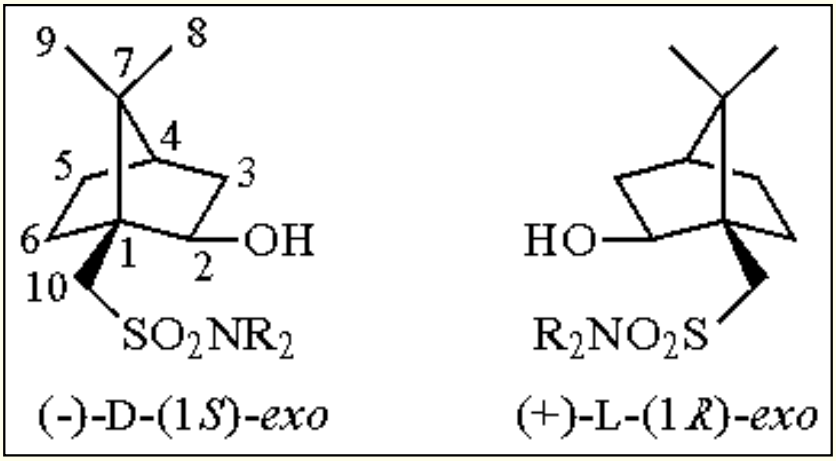

(1*S*)-*exo*; R = cyclohexyl

[96303-88-7] · $C_{22}H_{39}NO_3S$ · 10-Dicyclohexylsulfonamidoisoborneol · (MW 397.69) (1*S*)-*exo*; R = isopropyl

[89156-11-6] · $C_{16}H_{31}NO_3S$ · 10-Diisopropylsulfonamidoisoborneol · (MW 317.55)

(chiral auxiliary: enoate derivatives undergo stereoselective Diels-Alder[2,3] and 1,3-dipolar[3] cycloadditions and 1,4-cuprate additions;[4] enol ether derivatives undergo stereoselective [2 + 2] cycloadditions with dichloroketene;[5] ester enolate derivatives participate in stereoselective imine condensation,[6] alkylation,[4a] aldolization,[7] acetoxylation,[8] halogenation,[9] and amination[10] reactions)

Physical Data: R = cyclohexyl: mp (from hexane) 163-164 °C; [α]21D -25.7 (*c* = 0.76, EtOH). R = isopropyl: mp (from hexane) 102-103 °C; [α]21D -34.4 (*c* = 4.74, EtOH).

Form Supplied in: white crystalline solids.

Preparative Methods: crystalline, enantiomerically pure 10-diisopropyl- and 10-dicyclohexylsulfonamidoisoborneol auxiliaries are readily prepared from the appropriate enantiomer of ***10-Camphorsulfonyl Chloride*** by successive amidation and *exo* selective reduction (eq 1).[2]

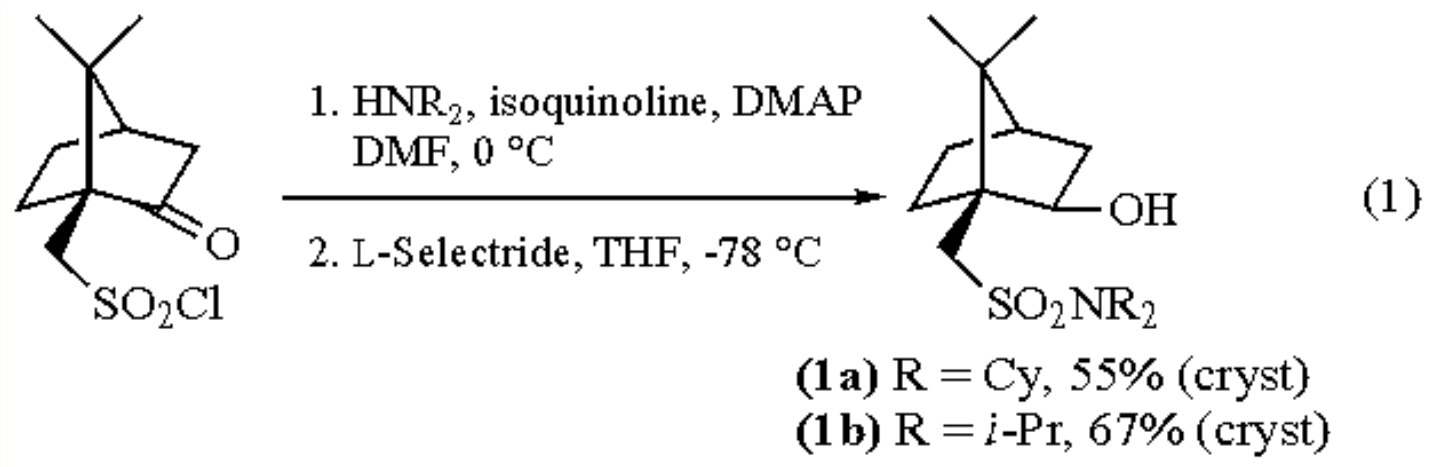

Simple acyl derivatives are prepared in good yields from carboxylic acids using Mukaiyama's ***2-Chloro-1-methylpyridinium Iodide*** coupling reagent[2] or from carboxylic acid chlorides using ***Silver(I) Cyanide***.[9a] The former method is also suitable for the preparation of enoyl derivatives, although a Horner-Wadsworth-Emmons reaction has also been employed for this purpose.[4b] The *cis*-propenyl enol ether derivative of 10-diisopropylsulfonamidoisoborneol was prepared by base-promoted isomerization of the corresponding allyl ether (the preparation of which was not described).[5]

Handling, Storage, and Precautions: these reagents are stable indefinitely at ambient temperature in sealed containers.

Introduction.

The 10-dialkylsulfonamidoisoborneol auxiliaries exert a powerful topological bias over the π-facial reactivity of enoate, enol ether, and ester enolate derivatives in a wide range of asymmetric transformations. However, the subsequently developed ***10,2-Camphorsultam*** chiral auxiliary outperforms these auxiliaries both in terms of stereoinduction and ease of nondestructive cleavage for most applications. Consequently, only transformations for which the 10-dialkylsulfonamidoisoborneol auxiliaries are particularly advantageous, or for which the analogous transformations of the 10,2-camphorsultam have not been reported, are described here. It should be noted, however, that the origin of the stereoinduction provided by these two camphor-derived auxiliaries is fundamentally different;[1] hence key references for all transformations are provided above.

Reactions of Enoate, Enol Ether, and Acyl Derivatives.

1,4-Organocopper Addition (Alkene to β-Functionalized Product).[4]

Tri-*n*-butylphosphine-stabilized organocopper reagents add in a conjugate fashion to *trans*-enoate derivatives of the 10-dicyclohexylsulfonamidoisoborneol auxiliary from the less hindered C(α)-*si* π-face with excellent selectivity (eq 2) (Table 1). This type of reaction has formed the basis of several natural product syntheses.[4]

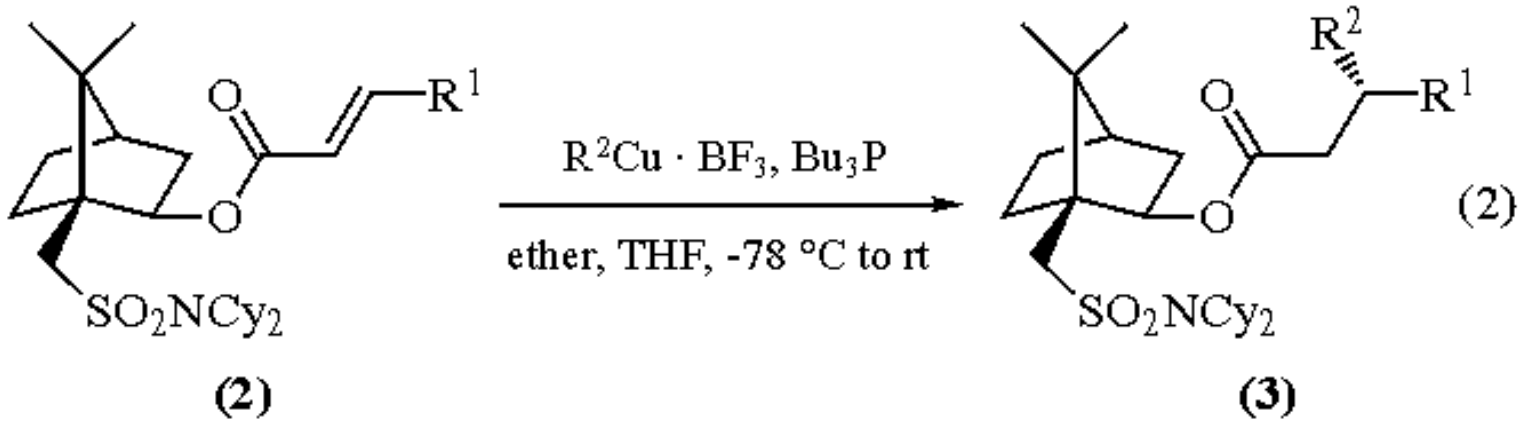

Table 1 Conjugate Addition of Organocopper Reagents (**2**) ® (**3**)

R^1	R^2	Yield (%)	de (%)
Bu	Me	93	97
Me	Bu	89	97
Pr	Me	89	94
Me	Pr	98	95
Me	CH_2=CH	80	98
Me	CH_2=CMe	84	94

[2 + 2] Dichloroketene Addition (Enol Ether to β-Alkoxy-α-dichlorocyclobutanone).[5]

Of six different chiral auxiliaries screened for their ability to control stereochemistry in the reaction of dichloroketene with derived *cis*-propenyl enol ethers, the 10-diisopropylsulfonamidoisoborneol auxiliary was the best. Thus, following ring expansion of the initially formed cyclobutanone (**4**) with ***Diazomethane-Chromium(II) Perchlorate***, α-chloro-γ-methylcyclopentenone was isolated in ~60% yield and 80% ee [C(α)-*si* face attack of the ketene] (eq 3). The auxiliary was also recovered in unspecified yield.

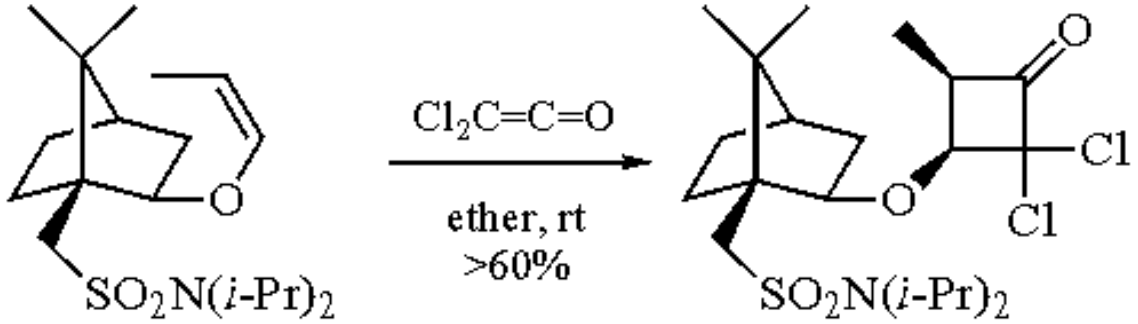

(3)

(4)
80% de
(major isomer shown)

Imine Condensation (Acyl Species to β-Lactam).[6]

Lithium enolates of acyl 10-diisopropylsulfonamidoisoborneols condense with *N*-aryl aldimines to give *cis*-disubstituted β-lactams with 56-92% ee, accompanied by 2.5-9% of their *trans* isomers (in undetermined ee) (eq 4) (the key step in a synthesis of the carbapenem antibiotic (+)-PS-5). Menthol was found to be a less efficient auxiliary for this application.[6]

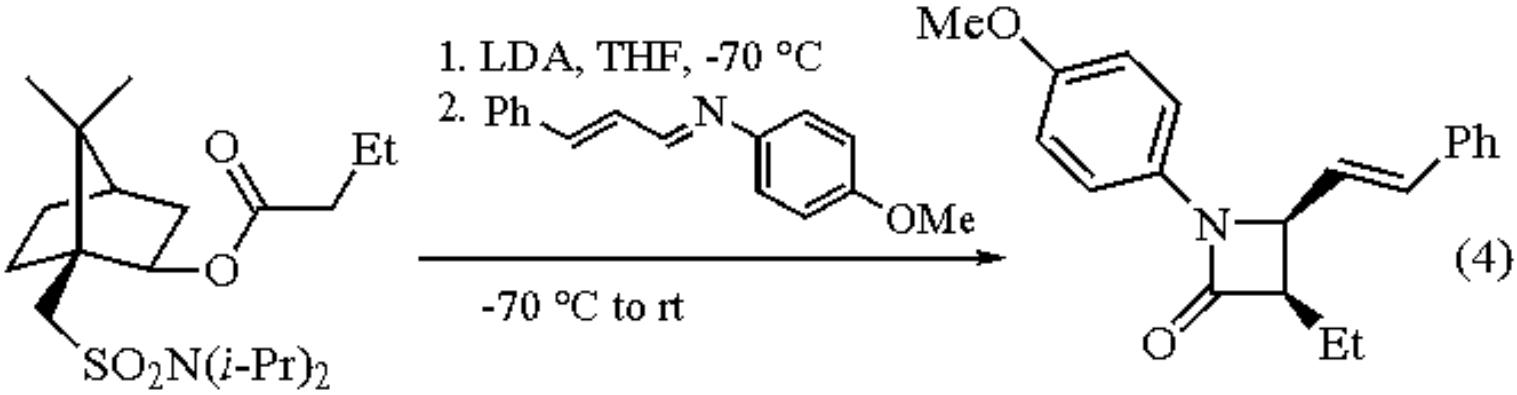

(4)

79% (FC), 91% ee
(+ recovered auxiliary 95%)

α-Acetoxylation and α-Halogenation (Acyl Species to α-Acetoxy or α-Halo Acyl Product).[8,9]

α-Acetoxylations of *O*-silyl enol ether derivatives of acyl 10-dicyclohexylsulfonamidoisoborneols with ***Lead(IV) Acetate*** proceed in high yield with excellent π-facial stereocontrol (95-100% de, with C(α)-*re* topicity).[8] Mechanistically related α-halogenations with *N*-halosuccinimides also proceed smoothly to afford α-halo acyl products in 76-96% de, but with C(α)-*si* topicity.[9] The observed topicities are consistent with initial attack of the electrophilic species from the less hindered C(α)-*si* face to give transient plumbonium/bromonium/chloronium ions. The plumbonium intermediates undergo S_N2-type attack by acetate at the β-position, whereas the bromonium/chloronium intermediates fragment with retention at C(β).[9a] The stereofacial influence of the auxiliary overrides any preexisting β-stereocenter. Hence, consecutive alkylcopper conjugate addition, then α-acetoxylation or α-bromination, allows the concise and stereocontrolled formation of two contiguous

stereocenters. α-Acetoxy ester derivative (**6**) formed in this way is a precursor to a key intermediate for the synthesis of the elm bark beetle pheromone (eq 5), and α-bromo ester derivative (**7**) was converted via azide displacement, trans-esterification, and hydrogenolysis into L-*allo*-isoleucine (eq 6).[9b] α-Halo esters are also useful precursors of enantiomerically pure epoxides.[9a]

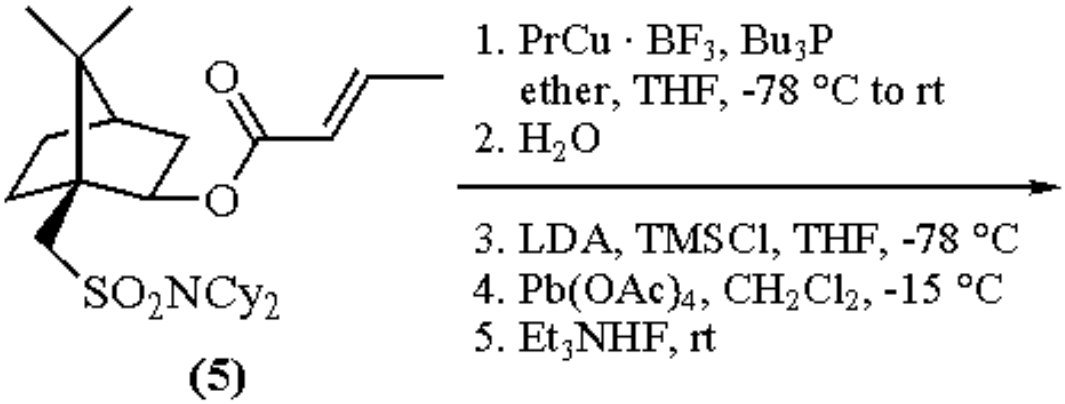

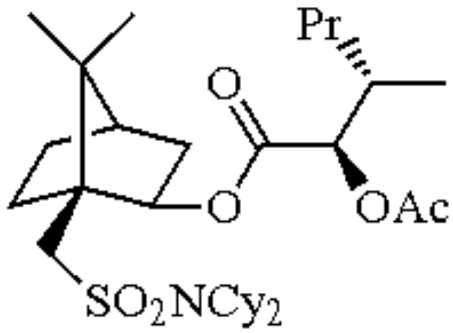

(5)

(6)

66% (cryst)

97% de C(α), 92% de C(β) (crude)

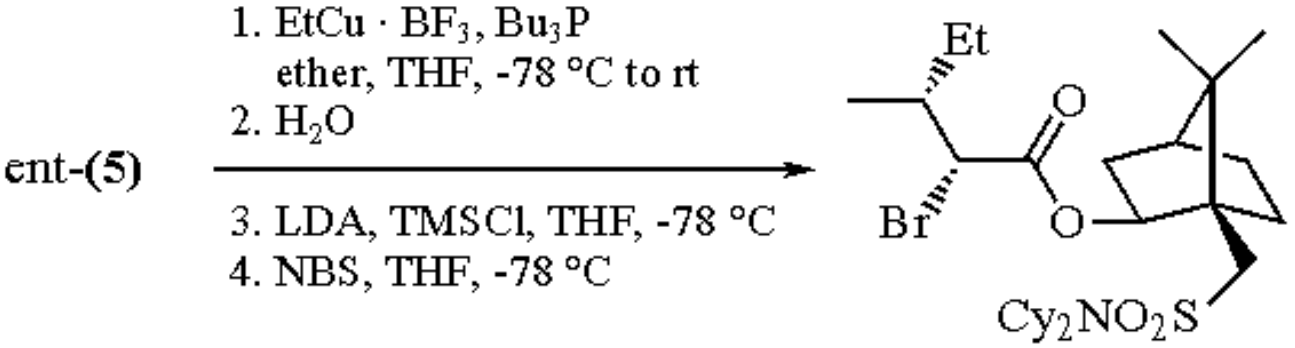

(6)

(7)

60% (cryst)

99.3% de C(α), 97.8% de C(β)

α-Amination (Acyl Species to α-Amino Acyl Product).[10]

Although asymmetric bromination and stereospecific azide displacement of *O*-silyl enol ethers of acyl 10-dicyclohexylsulfonamidoisoborneols (as described above) is a generally applicable route to optically active α-amino acids,[9b] a complementary and more direct approach to this important class of compounds is via electrophilic amination of these same compounds using ***Di-t-butyl Azodicarboxylate*** (DBAD). The initially formed α-(di-*N*-Boc-hydrazido)amino acid derivatives (**8**) (eq 7) may be efficiently converted to the corresponding α-amino acid hydrochlorides by successive deacylation, hydrogenolysis, transesterification, and hydrolysis. This reaction sequence has been shown to be efficient for the preparation of a wide range of α-amino acids in excellent enantiomeric purity[10] and compares favorably with closely related methods using alternative auxiliaries.[11]

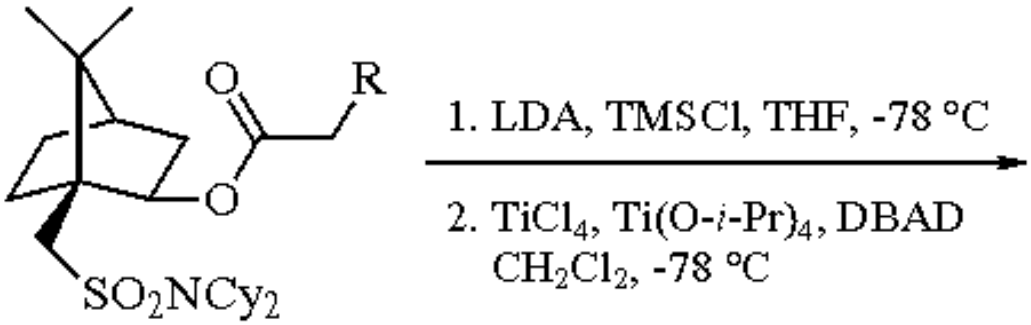

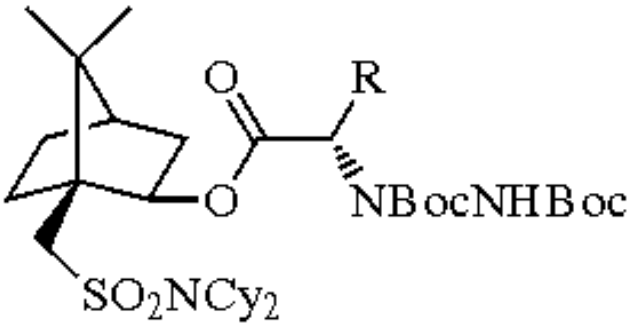

(7)

(8)

R = Me, Et, Pr, *i*-Pr, Bu, *i*-Bu, Bn, Cy

69-84% (FC) [92.6-96.4% de (crude)]

Nondestructive Auxiliary Cleavage.

The hindered ester linkage present in acyl derivatives of 10-dialkylsulfonamidoisoborneols is less readily cleaved than the corresponding sulfonamidic linkage of *N*-acyl-10,2-camphorsultam derivatives. However, it can be hydrolyzed and the auxiliary recovered intact under basic conditions using ***Potassium Hydroxide***[7] or ***Potassium Carbonate***[8] in MeOH, ***Sodium Hydroxide*** in aq EtOH,[4a] or ***Lithium Hydroxide*** in aq THF. Elevated temperatures are required to achieve acceptable reaction rates for all but the latter procedure which, although sluggish at ambient temperature, was employed for unmasking sensitive aldol products.[7] Nonbasic transesterification using $Ti(OBn)_4$/BnOH affords benzyl esters which may be subject to hydrogenolysis to give the corresponding carboxylic acids.[9b] Alternatively, transesterification with $Ti(OEt)_4$/EtOH[10b] may be followed by hydrolysis under acidic conditions.[10]

Primary alcohols can be obtained by hydride reduction using either ***Lithium Aluminum Hydride*** in ether[2,8] or $Ca(BH_4)_2$ in THF,[9a] and this latter reagent is compatible with halogen functionality. A dimethyl tertiary alcohol was obtained by addition of 2 equiv of methyllithium in ether.[4b]

Related Reagents.

α-***Methyltoluene-2,α-sultam***.

---

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Dicyclopentylboryl Trifluoromethanesulfonate

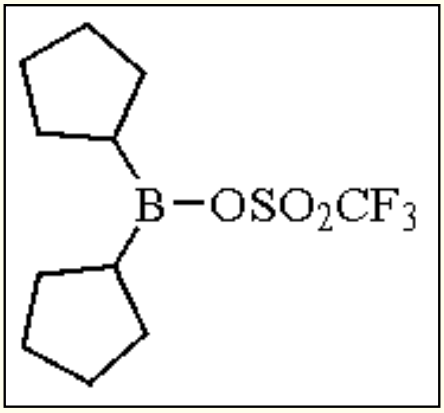

[72251-50-4] · $C_{11}H_{18}BF_3O_3S$ · Dicyclopentylboryl Trifluoromethanesulfonate · (MW 298.13)

(Lewis acid for the preparation of vinyloxyboranes[1-4])

Alternate Name: dicyclopentylboryl triflate.

Physical Data: colorless liquid, bp 70-72 °C/1.0 mmHg.

Solubility: sol common inert organic solvents such as Et_2O, CH_2Cl_2, and hexane.

Form Supplied in: 0.5 M solution in CH_2Cl_2.

Preparative Method: ***Trifluoromethanesulfonic Acid*** is added dropwise to an equimolar amount of tricyclopentylborane, with intermittent cooling to maintain the reaction temperature at approximately rt. Upon completion of the addition the reaction is stirred at rt for an additional 30 min followed by isolation of the product by vacuum distillation.[2b]

Handling, Storage, and Precautions: the neat liquid as well as solutions are moisture and air sensitive. Therefore the material should be stored and transferred under a dry inert atmosphere.

Vinyloxyborane Enolates.

Dicyclopentyl vinyloxyboranes are conveniently prepared from active methylene carbonyl compounds utilizing $(c\text{-}C_5H_9)_2BOTf$ in combination with a sterically hindered amine base. Typically the base, ***Diisopropylethylamine*** or ***2,6-Lutidine*** (2,6-lut), and reagent are premixed in Et_2O or CH_2Cl_2 at -78 °C to 0 °C and then the carbonyl component is

added. Enolate generation is allowed to occur over the next 15-30 min, resulting in the formation of vinyloxyboranes which are suitable nucleophiles for reaction with aldehydes in a crossed aldol reaction. Other boryl triflate reagents have been shown to have similar or complementary utility in this process (see ***9-Borabicyclononyl Trifluoromethanesulfonate*** (9-BBNOTf) and ***Di-n-butylboryl Trifluoromethanesulfonate*** (Bu_2BOTf)).

The relative stereochemistry of the two new chiral centers formed in the aldol product is a direct consequence of the vinyloxyborane enolate geometry with *Z*(O) enolates affording the 2,3-*syn* aldol products and the *E*(O) vinyloxyboranes leading to the 2,3-*anti* isomers. Consequently, a number of studies have examined the effects of various boryl triflates and amines on the ratio of kinetic enolates formed. In general, it has been found that with a given base, the more sterically hindered boryl triflates increase the selectivity for the formation of the *E*(O) enolate. For example, when the vinyloxyboranes of ethyl cyclohexyl ketone are generated with $(c\text{-}C_5H_9)_2BOTf$ or 9-BBNOTf in the presence of $i\text{-}Pr_2NEt$, reaction of the resulting enolates with benzaldehyde results in a ratio of crossed aldol products which varies dramatically. As shown in eq 1, the enolate derived from $(c\text{-}C_5H_9)_2BOTf$ yields a preponderance of the 2,3-*anti* aldol product while that from 9-BBNOTf produces almost exclusively the 2,3-*syn* isomer.[1]

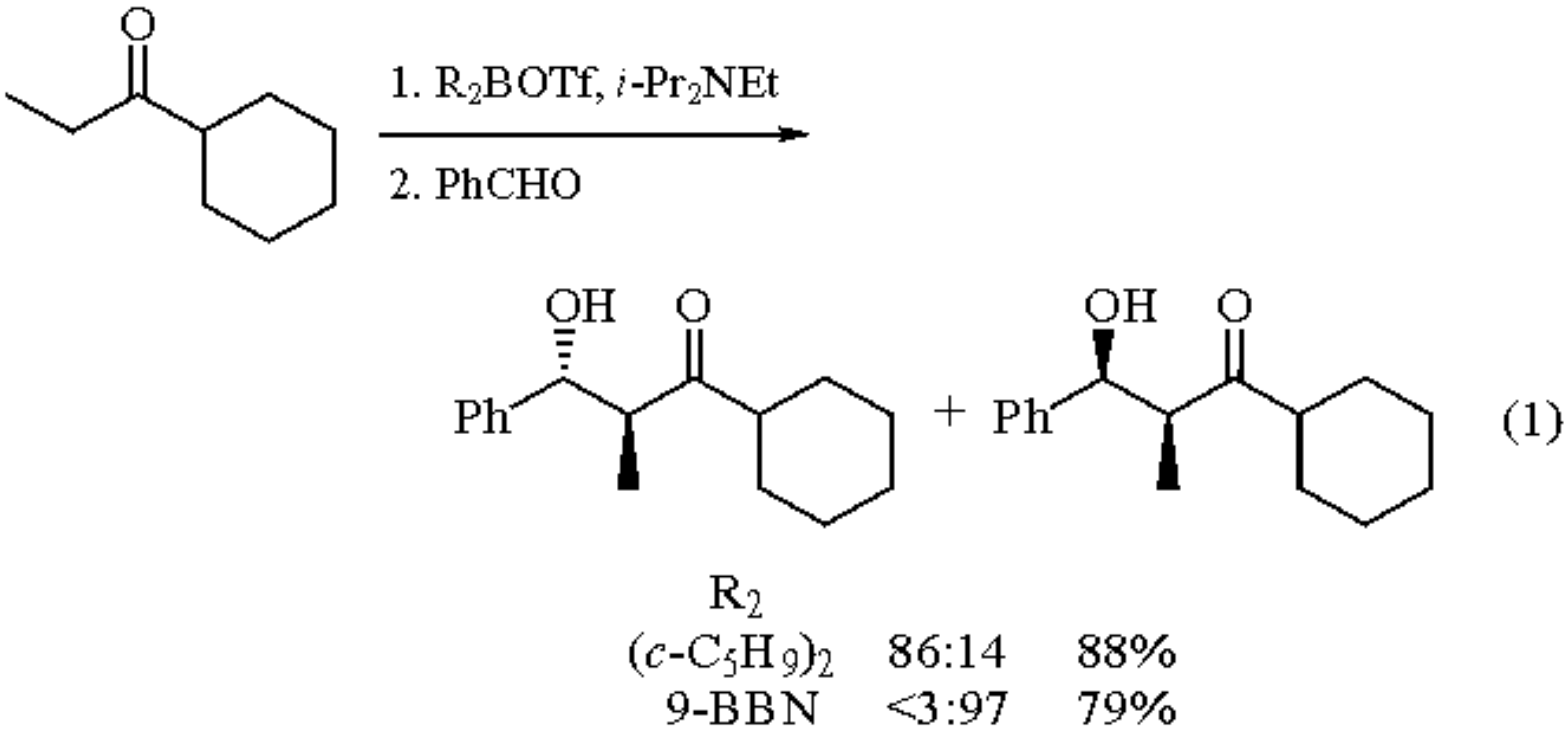

The propionate synthon *S*-*t*-butyl propanethioate upon reaction with $(c\text{-}C_5H_9)_2BOTf$ and $i\text{-}Pr_2NEt$ yields selectively the *E*(O) vinyloxyborane. Condensation of this enolate with various aldehydes affords the crossed aldol products, with the 2,3-*anti* diastereomer predominating (eq 2).[2] This combination of enolate substrate and reactants complements the results obtained from *S*-phenyl propanethioate, 9-BBNOTf, and $i\text{-}Pr_2NEt$ in which the 2,3-*syn* aldol product predominates (see ***9-Borabicyclononyl Trifluoromethanesulfonate***). Other functionality is also well tolerated on the thioester enolates. For example, the *E*(O) enolate derived from *t*-butyl α-bromothioacetate has been utilized in a Darzens-like condensation that selectively yields the *trans*-substituted epoxides (eq 3).[3] This procedure complements the synthesis of *cis*-substituted epoxide derivatives which are produced via aldol reactions of the *Z*(O) vinyloxyborane derived from a bromoacetyl oxazolidinone (see ***Di-n-butylboryl Trifluoromethanesulfonate***).

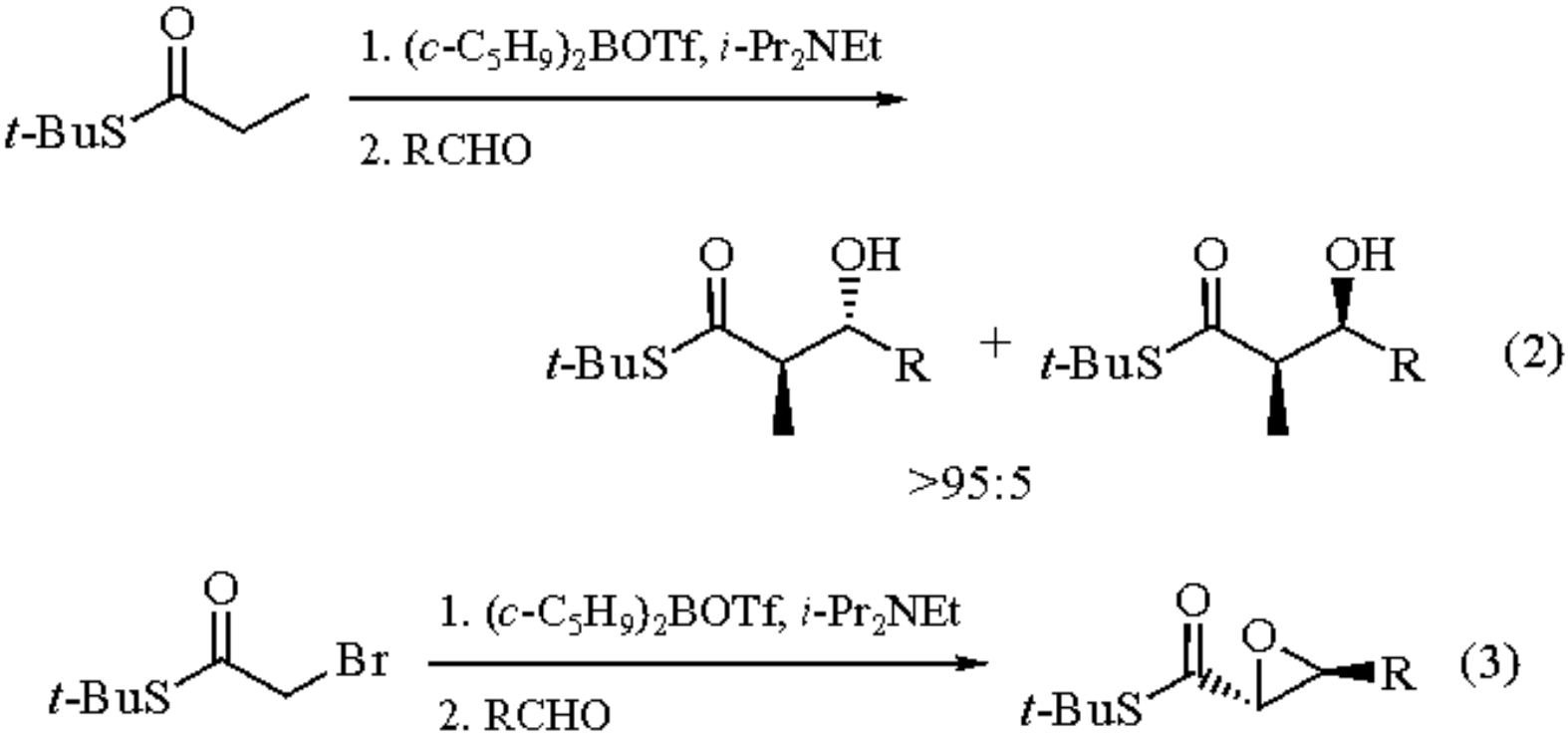

Probably the greatest utility of this reagent has been in the stereoselective formation of chiral vinyloxyboranes with defined enolate geometries from which the absolute stereochemistry of the new chiral centers formed in the aldol process are controlled. A number of chiral masked propionate equivalents useful for the synthesis of polypropionate-like natural products have been developed for this purpose. Chiral α-hydroxy ethyl ketones derived from both enantiomers of hexahydromandelic acid are such reagents and have been shown to form the *Z*(O) vinyloxyborane stereospecfically with 9-BBNOTf, Bu_2BOTf, and $(c\text{-}C_5H_9)_2BOTf$. However, the size of the ligands attached to boron does have a measurable effect upon the extent of the enantioselectivity achieved in the aldol process, as exemplified in (eq 4).[4]

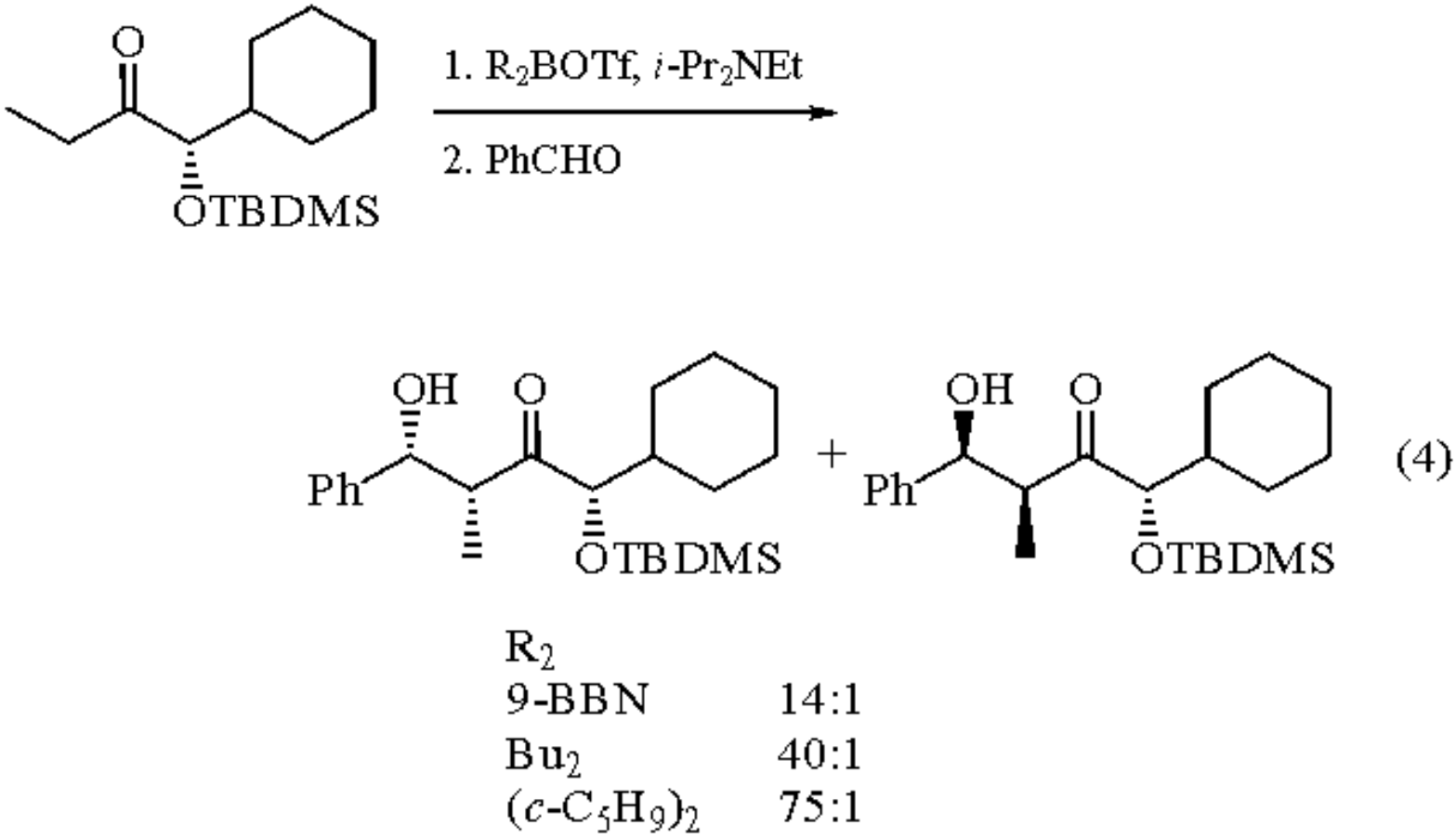

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1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene[1]

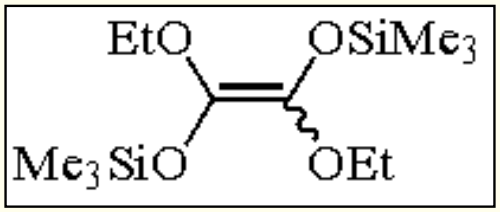

[90054-58-3] · $C_{12}H_{28}O_4Si_2$ · 1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene · (MW 292.52)

(synthetic equivalent of the acyl anion $^-C(O)CO_2Et$; useful in $ZnCl_2$-mediated nucleophilic additions to aldehydes and ketones,[1] Michael additions to enones,[1] and substitution reactions of S_N1-active alkyl halides[1] and carboxylic acid chlorides[2])

Physical Data: bp 68-70 °C/5 mmHg.

Solubility: sol CH_2Cl_2, toluene, THF.

Preparative Method: can be prepared in one step from ***Diethyl Oxalate*** using the Rühlmann version[2] of the acyloin condensation (eq 1).[3] Although a yield of 64% of isolated product was reported,[3] this could not be reproduced in a careful series of experiments.[1,4] Rather, yields of 21-25% are consistently obtained (0.1-1.0 molar scale).[1,4] The product consists of a (*Z*/*E*) isomeric mixture which is of no consequence for synthetic applications.

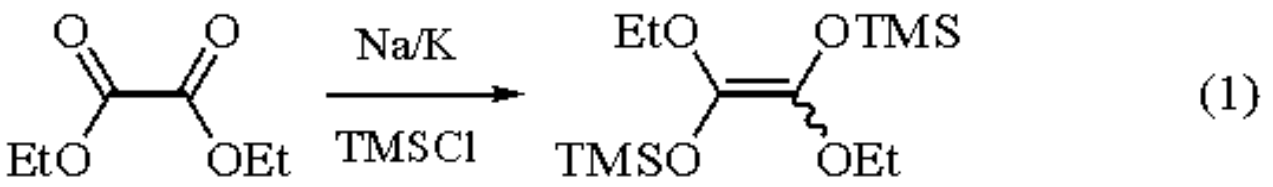

Handling, Storage, and Precautions: somewhat air and moisture sensitive and should therefore be handled and stored under an atmosphere of an inert gas such as N_2 and in nonprotic solvents. Use in a fume hood.

Reactions Forming Carbon-Carbon Bonds.

The reagent described herein has the structural features of an *O*-silyl ketene acetal, and it therefore undergoes the typical reactions known for this class of compounds, especially Lewis acid-mediated C-C bond-forming processes.[5] Since the reagent is extremely electron rich[6] and therefore very reactive, catalytic amounts of mild Lewis acids such as

ZnX_2 suffice.[1,4] The nucleophile which reacts with electrophilic organic substrates is a special case of an acyl anion equivalent (synthon) (**1**).

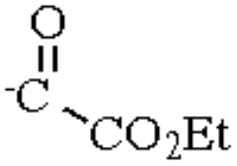

(1)

Group transfer-type[7] of Mukaiyama aldol addition[8] to aldehydes or ketones affords the isolable *O*-silylated aldol adducts, which can be hydrolyzed under acidic conditions to provide α-keto esters in high yield (eq 2).[1] In the case of aldehydes the initial products are *O*-silyl-protected reductones.[1]

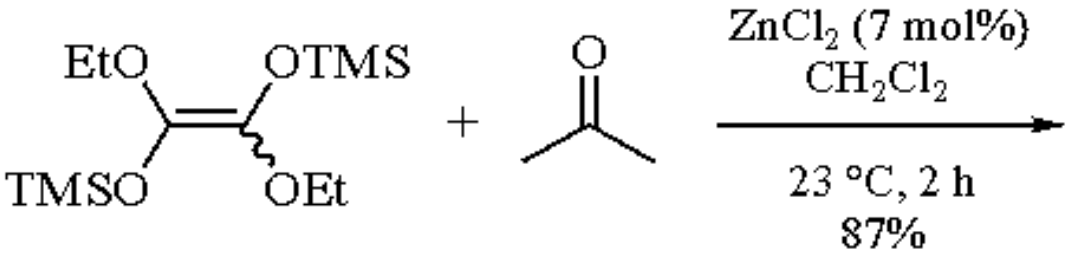

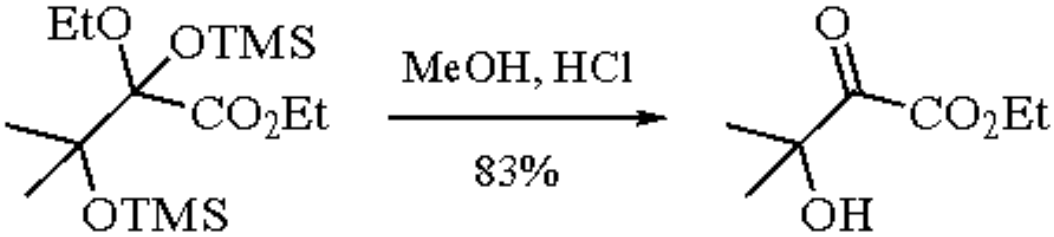

(2)

Group transfer-type of Michael additions to α,β-enones are just as smooth, with acidic workup affording α,δ-diketo esters (eq 3).[1,4]

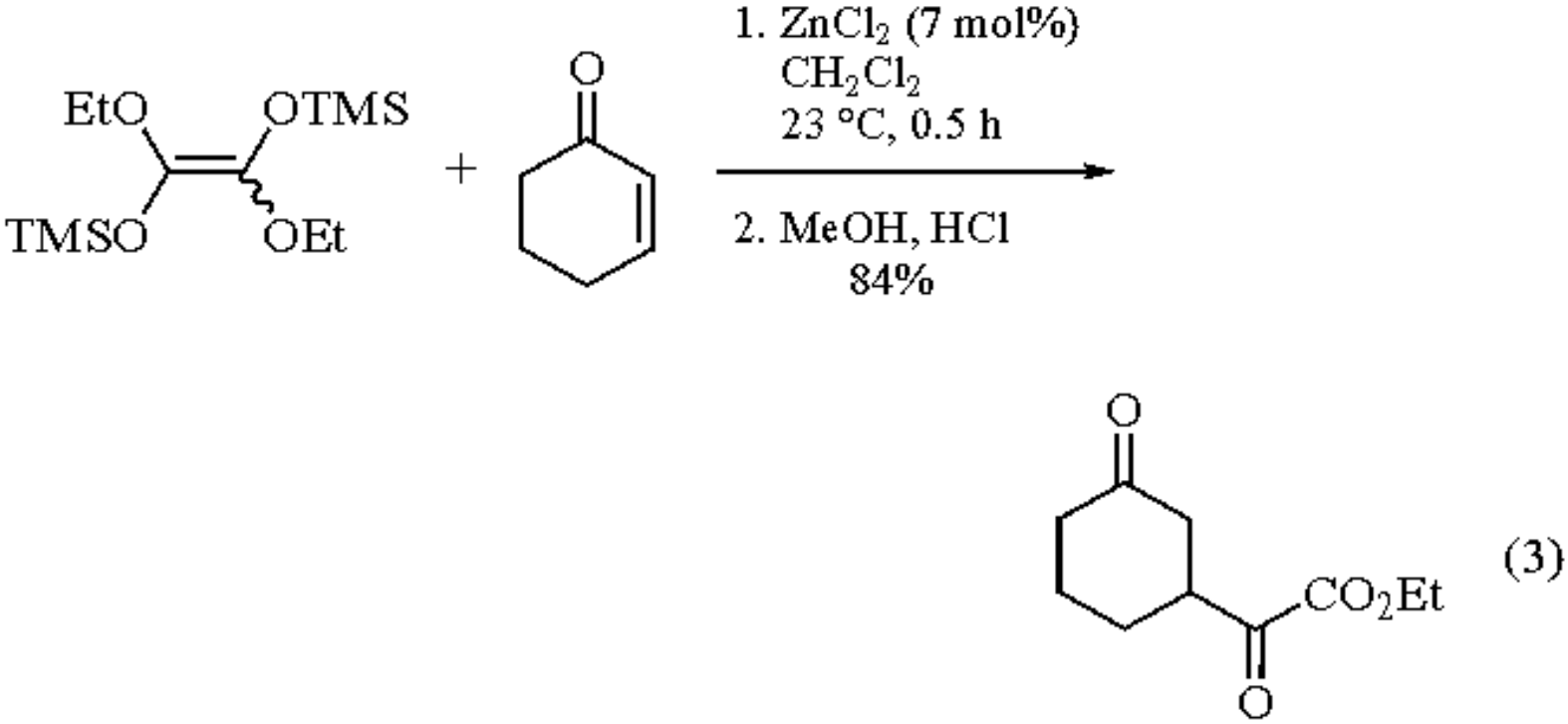

(3)

S_N1-active alkyl halides require longer reaction times (typically 3-6 h),[1,4] and the yields are lower. *t*-Butyl chloride and adamantyl bromide have been used successfully, but the generality of the procedure needs to be demonstrated (eq 4). In contrast, acylation reactions using a wide variety of carboxylic acid chlorides have been carried out (eq 5).[9,10] The initial products are protected forms of α,β-diketo esters which can be isolated in yields of 72-93%. Deprotection is accomplished using MeOH/HCl.[9,10] The products are vicinal tricarbonyl compounds having the usual characteristic chemical properties such as rapid formation of hydrated derivatives.[11] The protected forms can be used directly in the synthesis of heterocycles.[9,10]

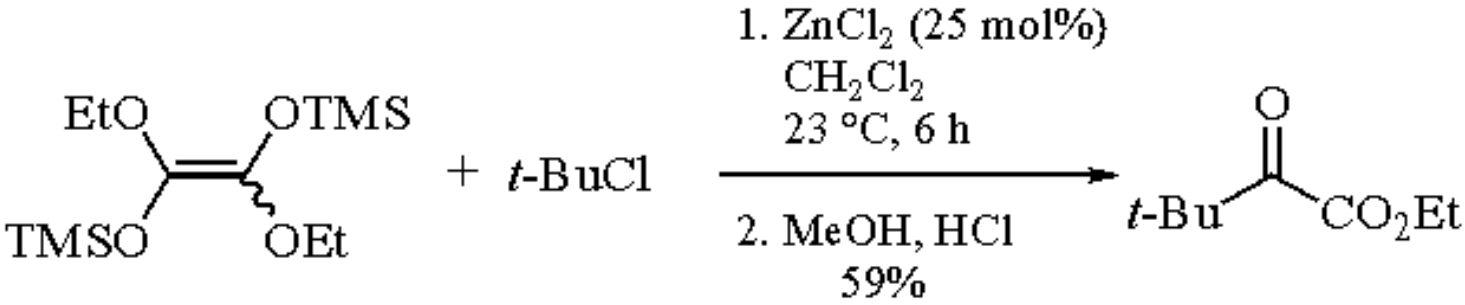

(4)

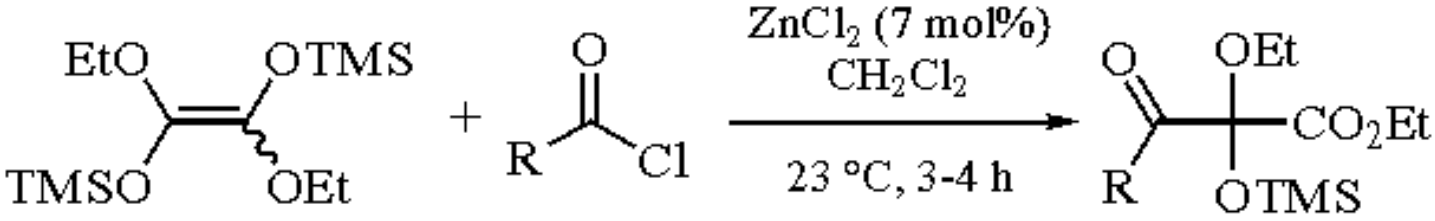

(5)

R = Me, 72%; R = Ph, 82%;
R = *o*-Me-C_6H_4, 91%;
R = *i*-Pr, 93%; R = *t*-Bu, 88%

In summary, the title compound, readily available from diethyl oxalate, is a synthetically useful synthon in various C-C bond-forming reactions, requiring only catalytic amounts of mild Lewis acids such as ***Zinc Chloride***. Alternatives to such an acyl anion equivalent include dithiane derivatives of glyoxylic acid esters, which have not been tested as widely and which require some synthetic effort in the final deprotection step.[12]

Related Reagents.

Ethyl Diethoxyacetate; ***Glyoxylic Acid Diethyl Dithioacetal***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene Diethyl Acetal***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Methyl Glyoxylate***; ***8-Phenylmenthyl Glyoxylate***; ***Tetramethoxyethylene***; ***Tris(trimethylsilyloxy)ethylene***.

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Diethoxymethyl Acetate[1]

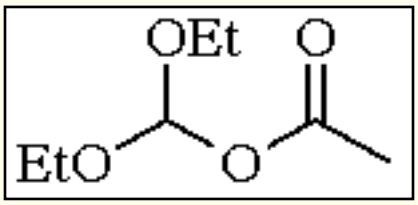

[14036-06-7] · $C_7H_{14}O_4$ · Diethoxymethyl Acetate · (MW 162.19)

(reactive orthoformic acid derivative in which the acetate group can be easily substituted by a variety of nucleophiles, e.g. alkoxy, amino, thiolo, and carbon nucleophiles[1])

Alternate Name: DEMA.

Physical Data: mp 27 °C; bp 70 °C/15 mmHg; *d* 0.993 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: colorless liquid or solid of 99% purity; widely available.

Preparative Method: best prepared from triethyl orthoformate and formic acid/acetic anhydride.[2]

Handling, Storage, and Precautions: the compound is sensitive to moisture and should be handled and stored under dry conditions. At temperatures above 120 °C it decomposes into ethyl acetate and ethyl formate.

DEMA is often used as a more reactive alternative for ***Triethyl Orthoformate***. In contrast to the latter it reacts under neutral or basic conditions with nucleophiles due to the better leaving ability of the acetoxy group compared to the ethoxy group. The acetate group can be easily exchanged for other carboxylic groups, leading to different diethoxymethyl esters.[2] Reactions with alcohols or thiols under basic conditions yield mixed orthoformates (eq 1).[1,3]

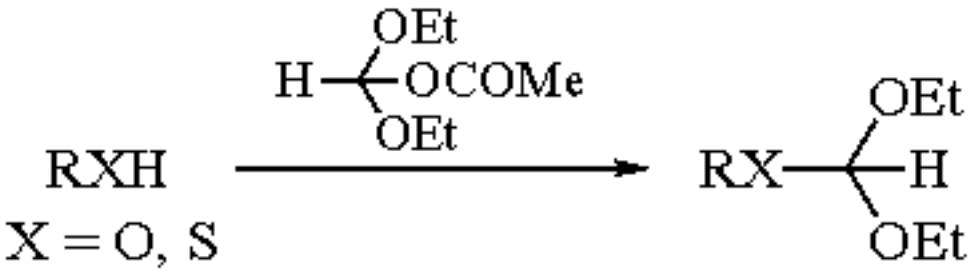

(1)

Preparation of the same compounds from triethyl orthoformate needs acid catalysis, which also leads to disproportionation of the formed mixed orthoester. The high reactivity of DEMA with amines is used in the synthesis of heterocyclic ring systems, e.g. formation of purines from vicinal diamines (eq 2).[4]

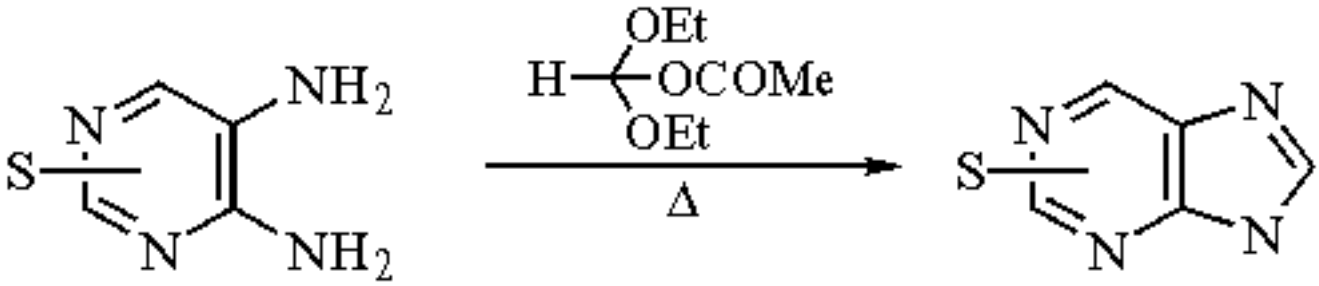

(2)

Analogous results have been reported for the synthesis of pyrimidines.[5] In the older literature, mixtures of triethyl orthoformate and acetic anhydride have been used, from which DEMA is supposed to be formed in situ.[1] The same holds for the reaction of acidic methynes with DEMA or triethyl orthoformate/acetic anhydride, leading to acetals or enol ethers (eq 3).

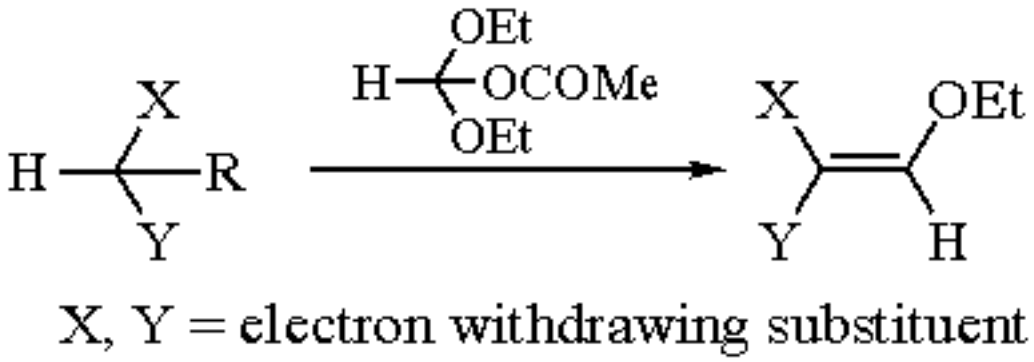

(3)

The advantages of the in situ procedures over pure DEMA have not been systematically investigated. The applicability of DEMA in the synthesis of acetals from the reaction with Grignard reagents has been demonstrated,[6] and the results compared with those of the related reagent ***Diethyl Phenyl Orthoformate***. It has been demonstrated that, prepared in this way, α-stannyl acetals (eq 4) are useful synthons in further synthesis.

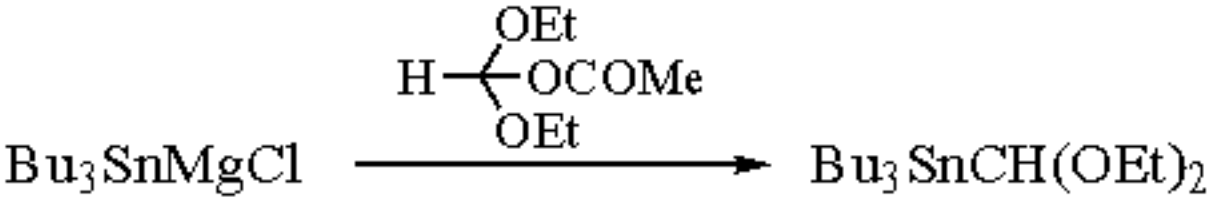

(4)

DEMA has also been used for the introduction of an acetoxy group in the synthesis of the related reagent 2-acetoxy-1,3-dioxolane (eq 5).[7]

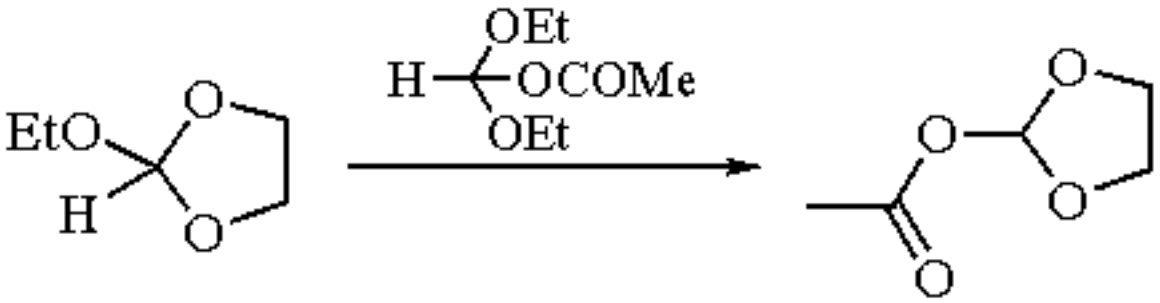

(5)

Diethoxymethyl formate, which is easily prepared from DEMA,[2] has been used in one of the first syntheses of formic anhydride.[8]

Related Reagents.

Acetic Anhydride; ***Acetic Formic Anhydride***; ***Diethyl Phenyl Orthoformate***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Triethyl Orthoformate***.

---

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(Diethoxymethyl)diphenylphosphine Oxide

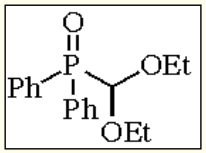

[20570-20-1] · $C_{17}H_{21}O_3P$ · (Diethoxymethyl)diphenylphosphine Oxide · (MW 304.32)

(readily accessible Horner-Wittig reagent for the conversion of aldehydes and ketones into homologous *O,O*-ketene acetals[1])

Physical Data: mp 77-79 °C; NMR: ^{31}P δ -25.5 ppm (H_3PO_4 = 0 ppm); ^{13}C δ(CH) 104.7 ppm; ^{1}H δ(CH) 4.98 ppm.

Solubility: sol benzene, THF, and ether.

Analysis of Reagent Purity: ^{31}P NMR; mp.

Preparative Method: the reagent (**1**) can be conveniently prepared by reaction of ***Chlorodiphenylphosphine*** with ***Triethyl Orthoformate***.[2] Adduct (**2**) is formed in a fast, exothermic, step. Upon heating, an Arbuzov reaction occurs to give the phosphine oxide (eq 1). Other *O,O*-acetals of formyldiphenylphosphine oxide can be prepared equally well.[2]

The usual procedure is for chlorodiphenylphosphine (88.2 g, 0.4 mol) to be added dropwise to triethyl orthoformate (59.3 g, 0.4 mol) over a period of 45 min. Subsequent heating of the reaction mixture (2 h, 110 °C) leads to formation of 24 g (93% of theory) of ethyl chloride. Upon cooling, a practically quantitative yield of (**1**) is obtained, mp 74-77 °C. Addition of some solvent, when (**1**) starts precipitating, avoids the formation of a solid cake that is hard to remove from the reaction flask. Crystallization from benzene/petroleum ether (80-110) affords the pure phosphine oxide.

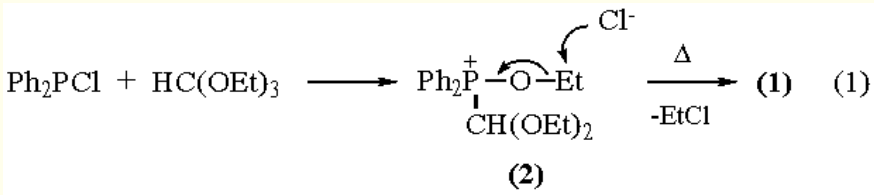

Handling, Storage, and Precautions: infinitely stable at rt. It should be protected from moisture.

Synthesis of Ketene *O,O*-Diethyl Acetals.

Aldehydes and ketones, aliphatic as well as aromatic and α,β-unsaturated, can be converted into their homologous ketene *O,O*-diethyl acetals by Horner-Wittig reaction with the anion of (**1**).[1,3] This conversion represents a considerable improvement over existing methods.[4] The metalation of (**1**) with ***Lithium Diisopropylamide*** as well as subsequent reactions of the anion should be carried out at below -90 °C as the anion is unstable at higher temperatures. Best results are obtained if the intermediate adducts (**3**) are isolated and subsequently treated with a potassium base to bring the Horner-Wittig reaction to completion (eq 2). By applying a water-free workup procedure, the ketene *O,O*-diethyl acetals (**4**) are obtained in the yields listed in Table 1. Also included in this table are some characteristic ^{13}C and, where applicable, ^{1}H NMR data of the ketene acetals. These products are sufficiently pure for most applications. Analytically pure ketene acetals can be obtained by distillation, but only at appreciable loss of product.

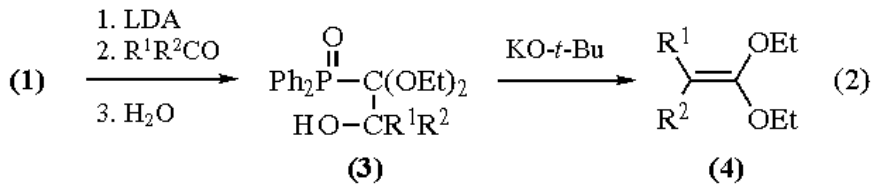

Table 1 Ketene *O*,*O*-Diethyl Acetals **(4)** Prepared According to Eq 2

Entry	R^1	R^2	Yield (%) crude (distilled)	NMR $\delta(H_\beta)$	$\delta(C_\alpha)$	$\delta(C_\beta)$	Bp (°C/mmHg (kPa))	n_D (°C)
1	Ph	H	85 (48)	4.62	158.5	80.4	72/0.09 (0.012)	1.5373 (22)
2	*p*-$MeOC_6H_4$	H	80 (69)	4.66	157.6	80.6	134/5 (0.67)	1.5368 (21)
3	Cy	H	68 (43)	3.41	156.8	87.8	110/10 (1.33)	1.4518 (22)
4	$Ph(CH_2)_2$	H	65 (32)	3.68	158.0	79.6	136/10 (1.33)	1.4939 (22)
5	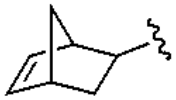	H	- (50)	3.30	156.9	86.5	70/0.1 (0.013)[a]	1.4761 (22)
6	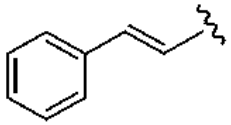	H	65 (25)	4.62	159.9	82.4	109/0.5 (0.067)	1.5924 (26)
7	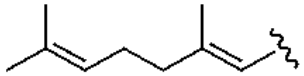	H	75 (38)	4.50	157.8	79.3	91/0.07 (0.009)	1.4864 (23)
8	Ph	Me	50 (20)	-	153.3	98.9	60/0.08 (0.011)	1.5129 (24)
9	$Me_2C{=}C(CH_2)_2$	Me	76 (27)	-	151.6	98.8	107/10 (1.33)	1.4457 (22)
10	$-(CH_2)_5-$		90 (66)	-	148.7	103.7	93/10 (1.33)	1.4530 (22)
11	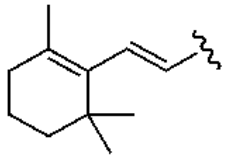	Me	- (39)	-	153.8	100.1	113/0.15 (0.02)	1.5099 (26)
12	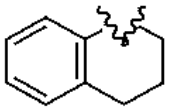		58 (29)	-	152.4	99.3	102/0.3 (0.04)	1.5478 (23)
13			- (45)	-	145.6	111.4	60/0.1 (0.013)	1.4896 (24)

[a] Short-path distillation.

In contrast to ketene *S*,*S*- and *S*,*O*-acetals,[5] the possibilities to prepare ketene *O*,*O*-acetals by Horner-Wittig or Peterson alkenation reactions appear to be restricted to phosphine oxides. Attempts to lithiate the corresponding phosphonates failed.[5] Horner-Wittig synthesis of ketene *O*,*O*-acetals is not restricted to the diethoxy compounds (**4**). Other (dialkoxymethyl)phosphine oxides perform equally well. The use of phosphine oxide (**5**), prepared in analogy to (**1**) from 2-ethoxy-5,5-dimethyl-1,3-dioxane,[2] can be especially advantageous because the corresponding ketene acetals have higher melting points. The reported examples (corresponding to entries 1, 10 and 13 in Table 1) are solids that can be conveniently purified by crystallization.[1]

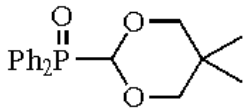

(5)

General Procedure.

To a solution of (**1**) (3.04 g, 10 mmol) in 200 mL of THF/diethyl ether (3:1), cooled to -100 °C, is added a solution of LDA (1.17 g, 11 mmol) in 25 mL of THF.[1,3] After stirring for 1 min, a solution of 10 mmol of the carbonyl compound in 25 mL of THF is added to the deeply colored solution at such a rate that the temperature of the reaction mixture is kept at all times below -90 °C. After stirring for an additional 5 min at this temperature, the mixture is quenched by the addition of 40 mL of water. After warming to rt, solid ***Potassium Carbonate*** is added and the organic layer is separated and dried. Evaporation of the solvents at reduced pressure affords the adducts (**3**) in almost quantitative yields. To a solution of the adduct in 50 mL of THF, ***Potassium t-Butoxide*** (1.23 g, 11 mmol) in 50 mL of THF is added in one portion. After stirring for 1 h at rt, the solvent is removed at temperatures not exceeding 40 °C. The residue is taken up in 100 mL of hexane. After centrifugation, the solution is decanted. Upon evaporation of the solvent, the ketene acetal is obtained as a pale yellow oil.

---

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(Diethoxyphosphoryl)difluoromethyllithium

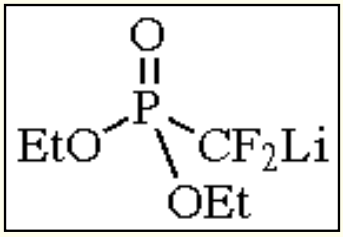

[94993-99-4] · $C_5H_{10}F_2LiO_3P$ · (Diethoxyphosphoryl)difluoromethyllithium · (MW 194.04)

(useful for the introduction of $(EtO)_2P(O)CF_2$ and $=CF_2$ into organic compounds)

Preparative Methods: by the deprotonation of diethyl difluoromethylphosphonate with LDA at -78 °C,[1] or generated in situ from diethyl bromodifluoromethylphosphonate and BuLi.[2]

Reaction with Carbonyl Compounds.

Deprotonation of diethyl difluoromethylphosphonate with ***Lithium Diisopropylamide*** at -78 °C gives the carbanion of diethyl difluoromethylphosphonate, which is only stable at or below -78 °C.[1] Reaction of the carbanion of diethyl difluoromethylphosphonate with aldehydes and ketones at -78 °C followed by decomposition (heating THF solution) of the intermediate forms the corresponding 1,1-difluoroalkenes.[1,3] The intermediate could be trapped by electrophiles, such as proton[1,4] and acid chlorides,[5] to form the corresponding phosphonates (eq 1).

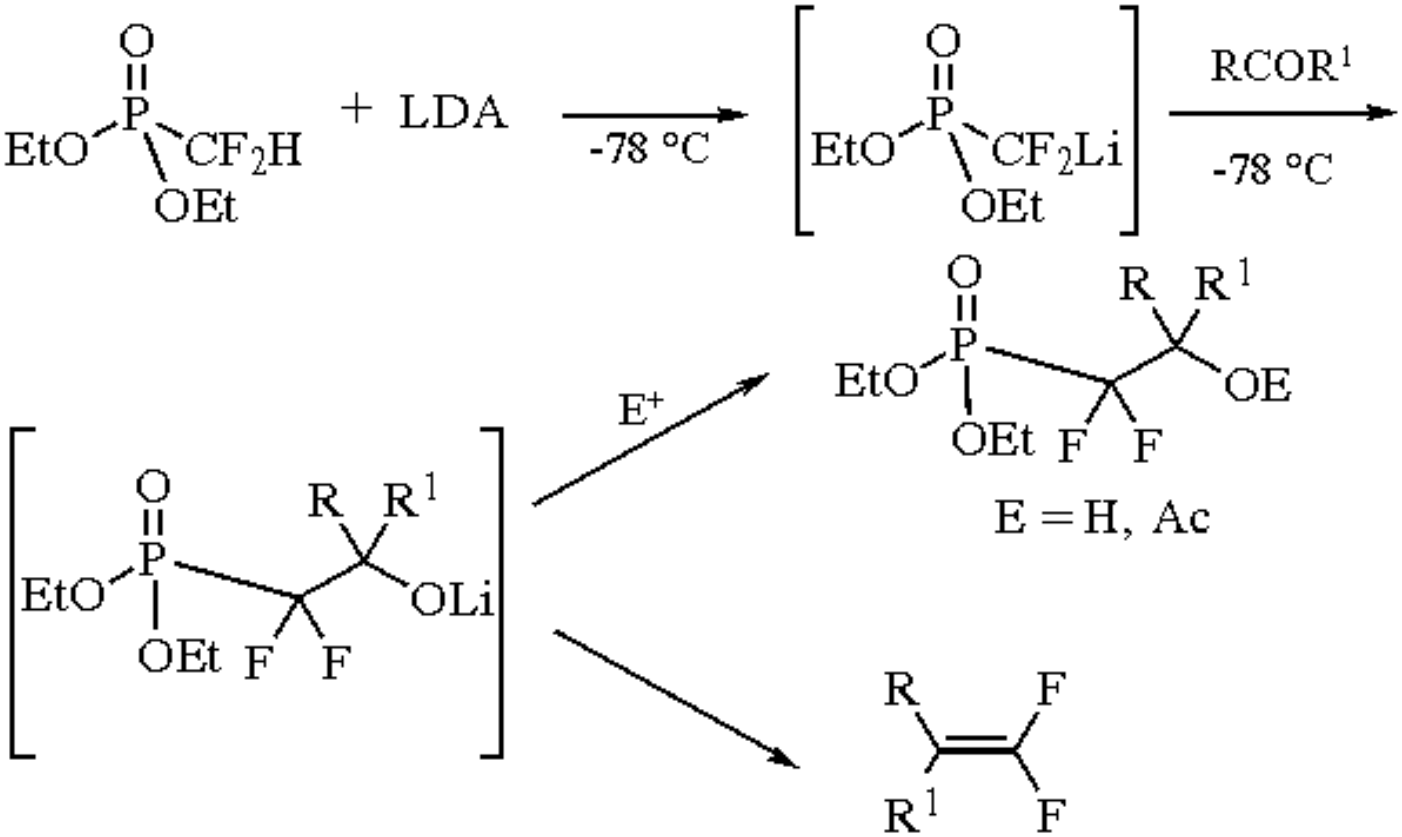

(1)

Reaction with Alkyl and Allyl Halides, and Alkyl Triflates.

The carbanion of diethyl difluoromethylphosphonate also reacts with alkyl halides,[1,6-8] alkyl triflates,[9] oxalate,[10] and allyl bromide[1] to form the corresponding 1,1-difluoro phosphonates (eq 2).

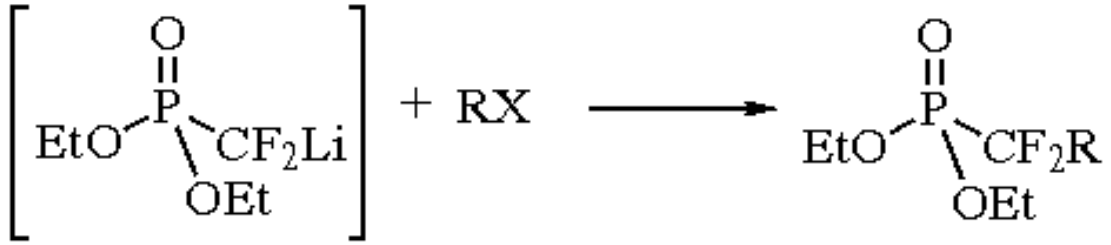

(2)

R = alkyl, allyl; X = I, Br, Tf

Reaction with Other Electrophiles.

The carbanion of diethyl difluoromethylphosphonate can be trapped with ***Chlorotrimethylsilane*** or trialkylchlorostannane to produce the corresponding trimethylsilylated and trialkyltin-substituted 1,1-difluoro phosphonates (eq 3).[1]

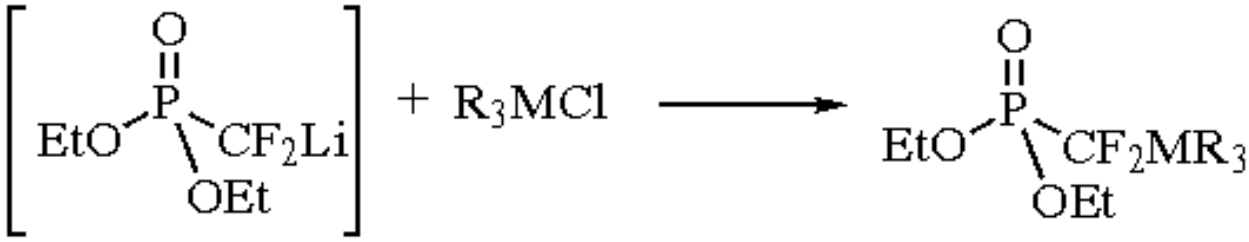

(3)

R = alkyl; M = Si, Sn

The carbanion also reacts with diethyl chlorophosphate or benzoyl chloride to give the corresponding α,α-difluoro bisphosphonate and β-ketophosphonate, respectively (eq 4).[1,11,12] Treatment of the carbanion of diethyl difluoromethylphosphonate with ***Carbon Dioxide*** at -78 °C leads to the formation of the carboxylic acid. The thiocarboxylic acid was formed by a similar reaction of the carbanion with ***Carbon Oxysulfide*** (eq 5).[13] The carbanion reacts in a 1,4-addition with 4-chloro-β-nitrostyrene to give the nitro phosphonate (eq 6).[14]

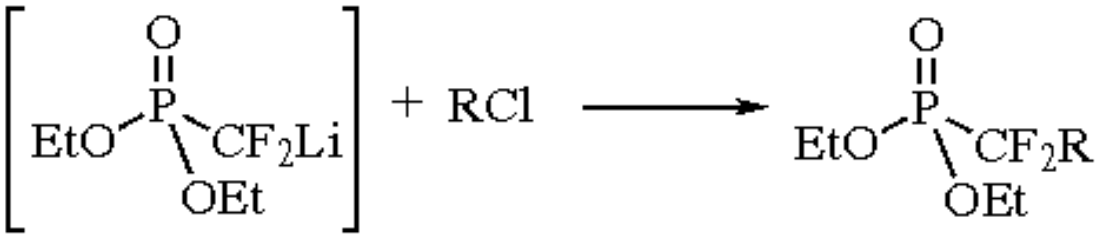

(4)

R = $(EtO)_2P(O)$, PhCO

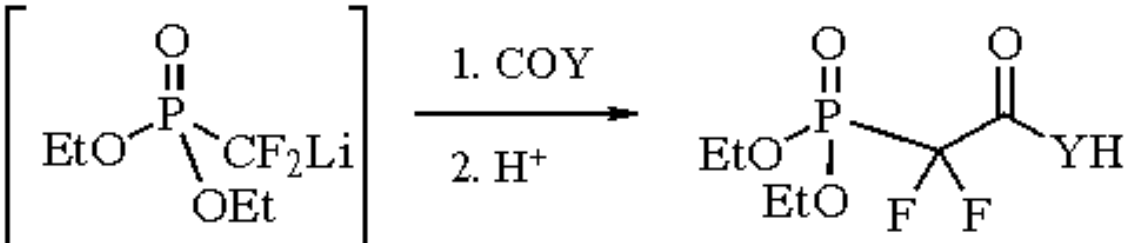

(5)

Y = O, S

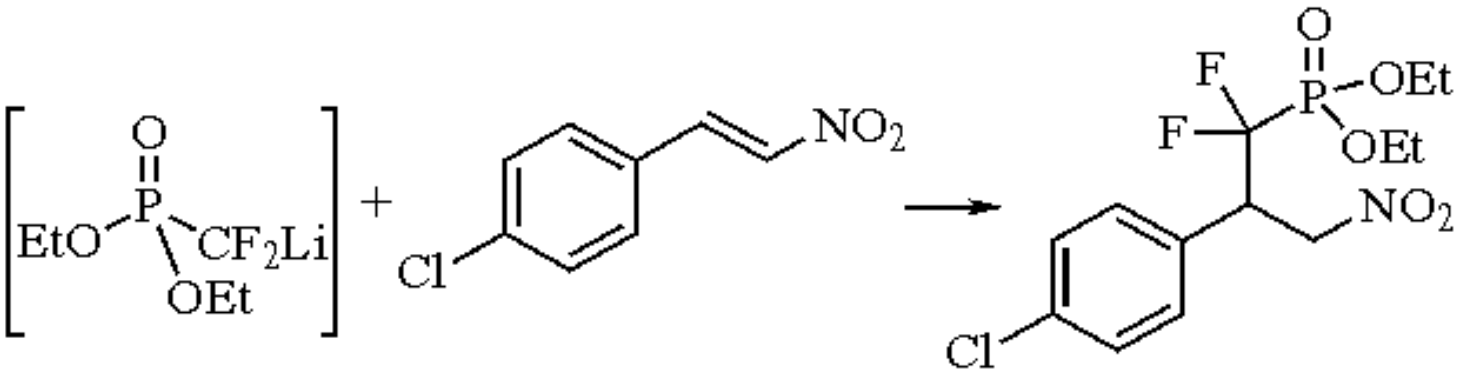

(6)

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(Diethoxyphosphoryl)acetonitrile Oxide

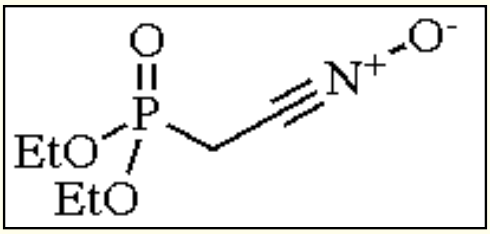

[113847-95-3] · $C_6H_{12}NO_4P$ · (Diethoxyphosphoryl)acetonitrile Oxide · (MW 193.14)

(nitrile oxide bearing an additional functionality)

Preparative Method: the reagent is a highly reactive intermediate and cannot be isolated. It is generated in situ from (diethoxyphosphoryl)acetaldehyde oxime[1] by bromination with ***N-Bromosuccinimide*** and elimination with ***Triethylamine***,[2] and used in synthesis by trapping with a coexisting dipolarophilic reagent.

Handling, Storage, and Precautions: Use in a well ventilated fume hood.

3-Acylisoxazoline Synthesis.

(Diethoxyphosphoryl)acetonitrile oxide, like other nitrile oxides, undergoes exclusive regioselective cycloadditions to monosubstituted alkenes to give 5-substituted 3-(phosphorylmethyl)isoxazolines which can be regioselectively lithiated with ***Lithium Diisopropylamide*** at the side chain and then alkylated in good yields (eq 1).[2,3] The alkylated products can be further lithiated with ***n-Butyllithium***. Air oxidation of the lithiated intermediates gives 3-acylisoxazolines in good yields. Horner-Emmons alkenations of the lithiated 3-phosphorylmethylisoxazolines and alkylated derivatives offer a convenient synthetic route to 3-[(*E*)-1-alkenyl)]isoxazolines.[3]

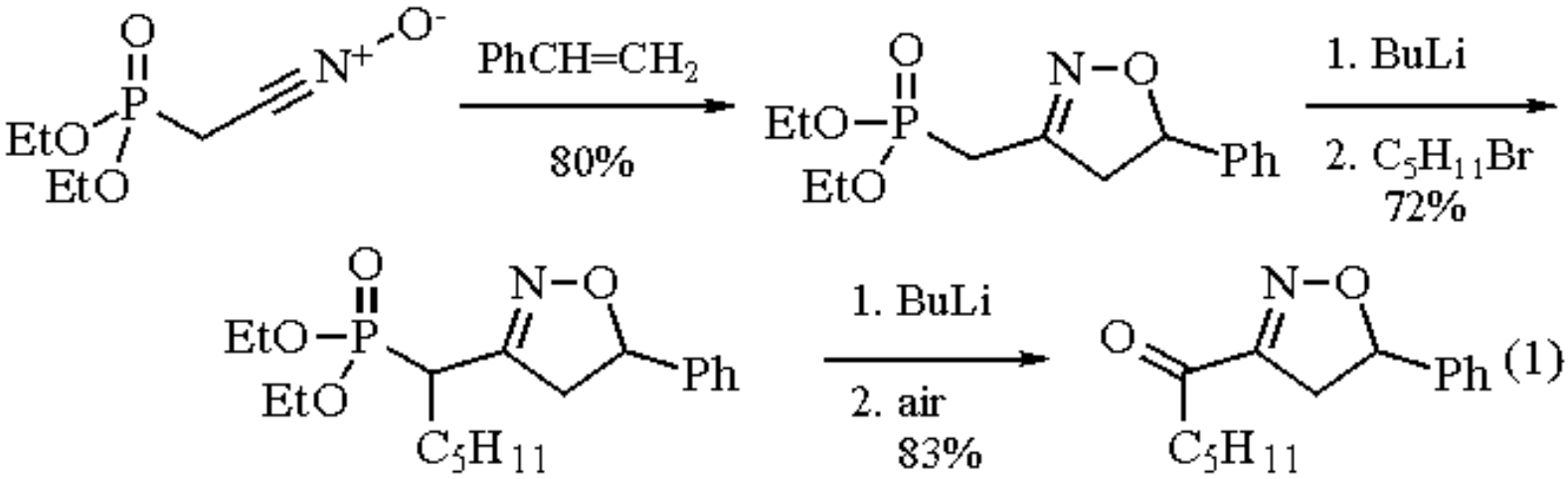

Furanone Synthesis.

Cycloaddition reactions of (diethoxyphosphoryl)acetonitrile oxide with unprotected propargylic alcohols proceed smoothly to give 5-(1-hydroxyalkyl)isoxazoles. The adduct to 1-methyl-3-butyn-2-ol is then lithiated with butyllithium at the side chain (-78 °C, THF), alkylated with ***Iodomethane*** (-78 °C, 94%), and finally reduced with ***Raney Nickel*** to cause a cleavage of the nitrogen-oxygen bond (W-2, ethanol, AcOH, rt) to give 5-(phosphorylmethyl)-3(2*H*)-furanones (eq 2).[4] These compounds are useful for the synthesis of 5-[1-(*E*)-alkenyl]-3(2*H*)-furanone derivatives through a Horner-Emmons alkenation procedure. One application has been shown by the effective synthesis of geiparvarin (eq 2).[4]

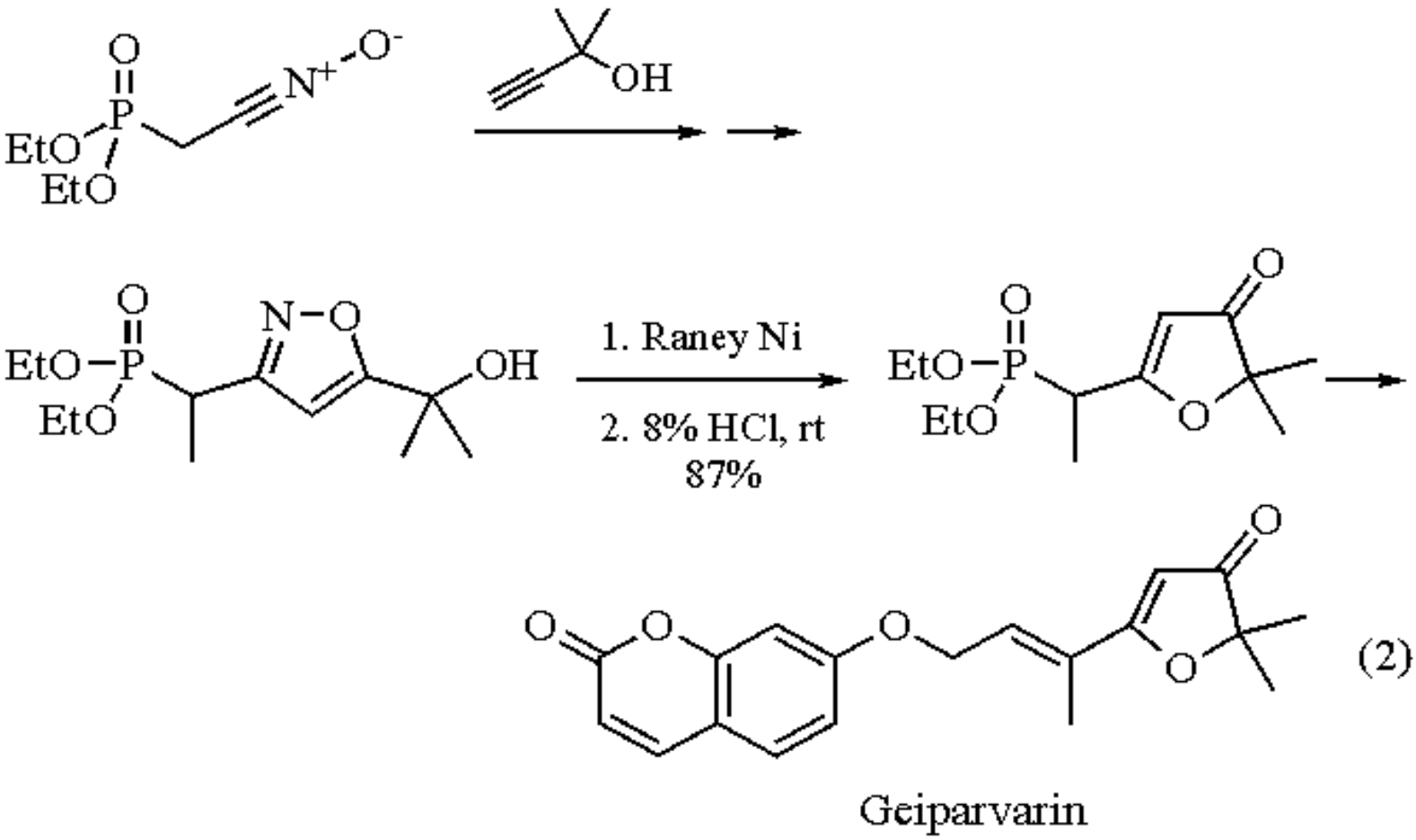

Furan Synthesis.

Cycloadditions of (diethoxyphosphoryl)acetonitrile oxide to THP-protected allylic alcohols followed by alkylation of the phosphorus-stabilized anion produces 5-(1-hydroxyalkyl)isoxazolines. These can be reductively cleaved and aromatized (sodium acetate in AcOH) to give 2-(1-phosphoryl)alkylfurans (eq 3) whose Horner-Emmons alkenations lead to 2-[1-(*E*)-alkenyl)furan derivatives.[5]

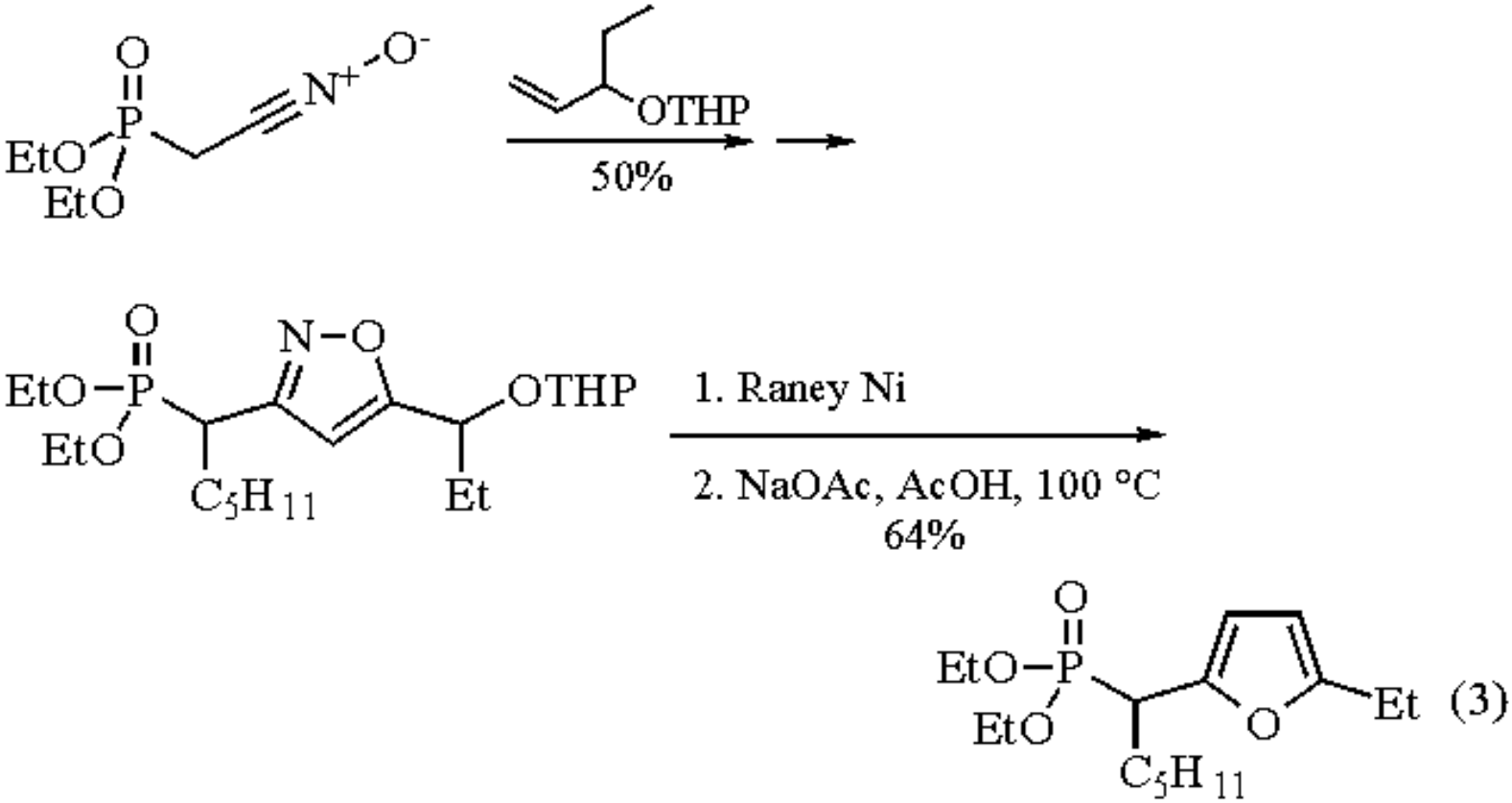

Synthetic applications to 2-hydroxy-4-oxo-5-alkenoates,[6] 5-[(*E*)-1-alkenyl]-3-hydroxy-4,5-dihydro-2(3*H*)-furanones,[6] (*Z*)-5-alkylidene-2(5*H*)-furanones,[6] and (*E*)-4-oxo-5-alkenoates[7] have also been reported.

---

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3,3-Diethoxy-1-propene[1]

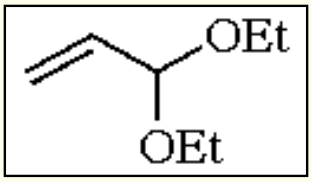

[3054-95-3] · $C_7H_{14}O_2$ · 3,3-Diethoxy-1-propene · (MW 130.19)

(reagent for ethoxyallylation of activated carbonyl compounds;[2,3] forms enol ethers with organocopper reagents;[4-6] acrolein equivalent for ionic Diels-Alder reaction;[7] precursor for ethoxyallyl cation;[7] acrolein synthon for Heck coupling with halides[8,9])

Alternate Name: acrolein diethyl acetal.

Physical Data: bp 125 °C; *d* 0.862 g cm^{-3}.

Solubility: slightly sol water; very sol ethanol and ether.

Form Supplied in: clear liquid, 95% pure; widely available.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 6H, *J* = 7 Hz), 3.5 (m, 2H), 3.6 (m, 2H), 4.85 (d, 1H, *J* = 2 Hz), 5.26 (d, 1H, *J* = 7 Hz), 5.38 (d, 1H, *J* = 11 Hz), 5.85 (m, 1H).

Purification: generally used as supplied; can be purified by distillation at atmospheric pressure from anhydrous sodium carbonate.

Handling, Storage, and Precautions: store under nitrogen.

Introduction.

The extreme reactivity of acrolein, which often results in extensive polymerization under many reaction conditions, is moderated by an acetal function in 3,3-diethoxy-1-propene (**1**) and thus (**1**) is a useful three-carbon reagent for many synthetic transformations.

Ethoxyallylation.

Thermal reaction of active methylene compounds with (**1**) furnishes ethoxyallyl products (eq 1).[2] In a detailed study it was found that the reaction was sluggish for the less acidic β-keto esters, but was effectively catalyzed by ***Nickel(II)***

Acetylacetonate (Ni(acac)$_2$) (eq 2).[3] The mechanism of this transformation is believed to involve a Claisen rearrangement of the initially formed mixed acetal; however, direct *C*-alkylation of the substrate at the γ-position of the ethoxyallyl cation is also possible.

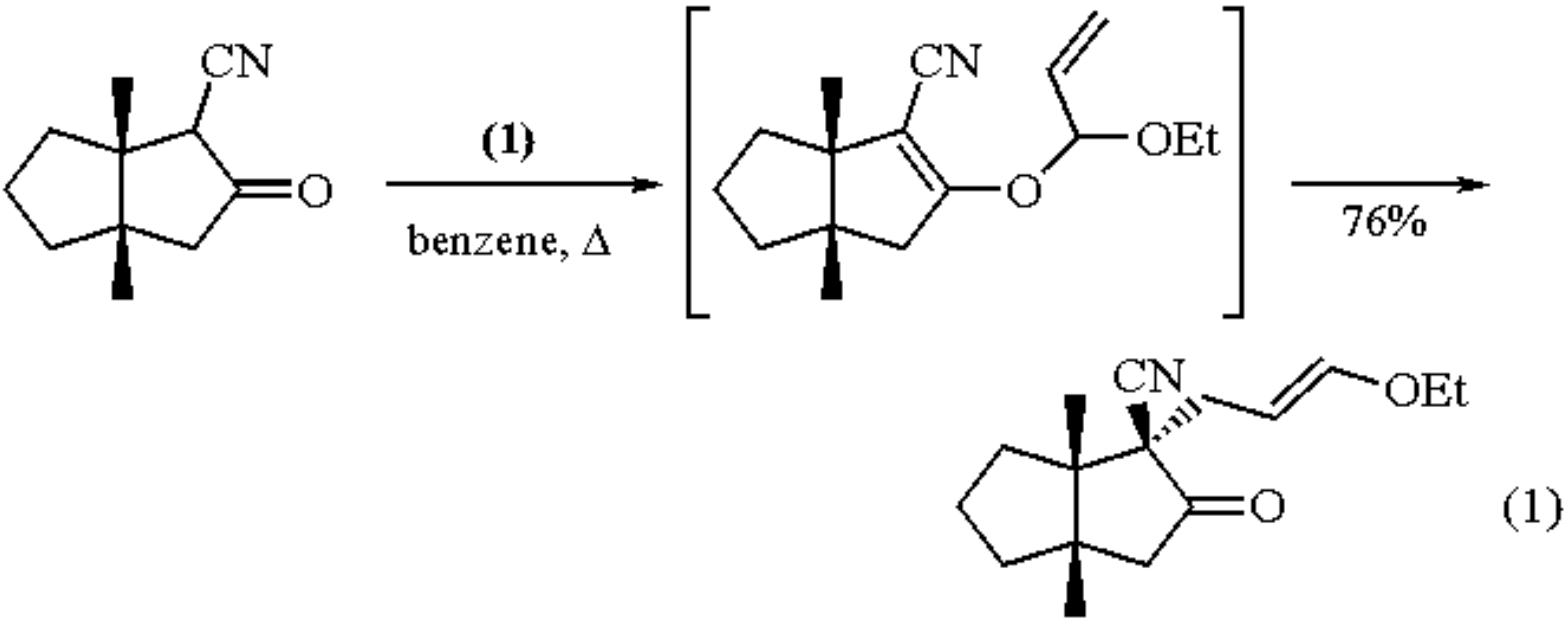

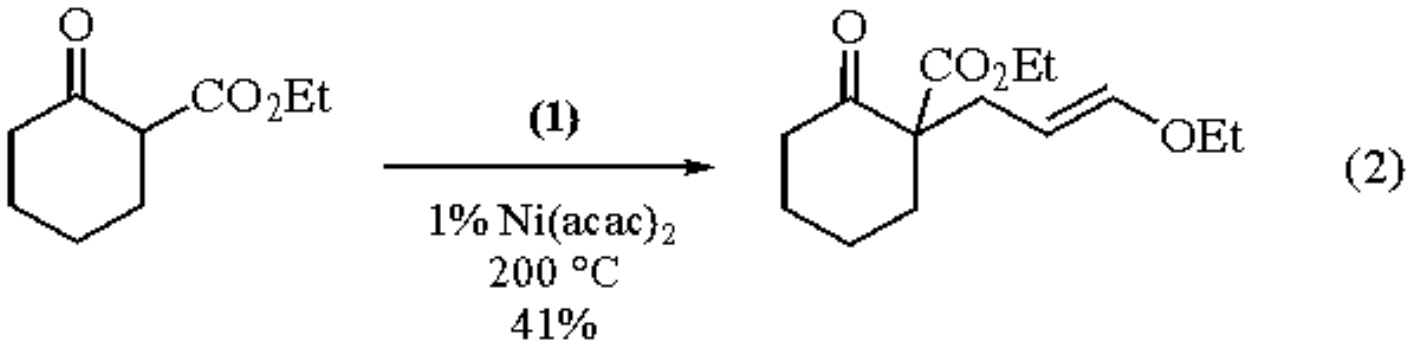

Allylic Displacement.

Copper(I) Bromide catalyzed additions of Grignard reagents to (**1**) give mostly (*Z*)-enol ethers, which are hydrolyzed to the corresponding aldehyde by aq HCl (eq 3).[4] In a later study it was shown that the (*E*) isomers predominate if a Lewis acid-modified organocopper reagent is used,[5] and in another report a nickel(II) phosphine catalyst (NiCl$_2$(dppp)) gave only the (*E*) isomer.[6]

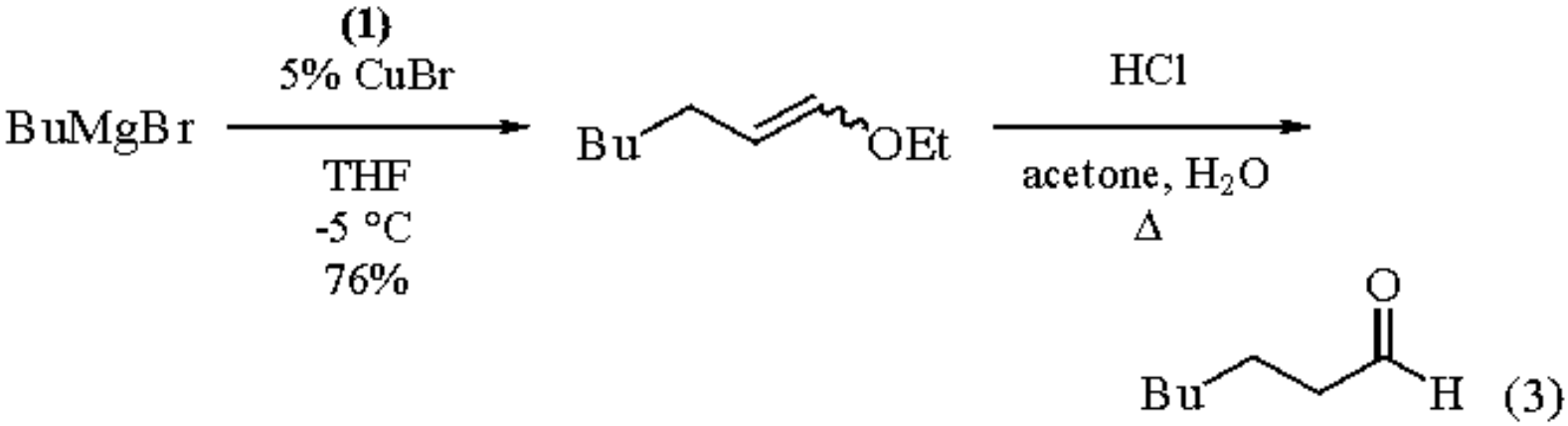

Ionic Diels-Alder Reaction.

The ethoxyallyl cation produced by ionization of (**1**) is a very potent dienophile which reacts with a variety of dienes below 0 °C to give Diels-Alder adducts (eq 4).[7] The yields of the addition products generally improved when a cyclic acetal (2-vinyl-1,3-dioxolane) was used.[7]

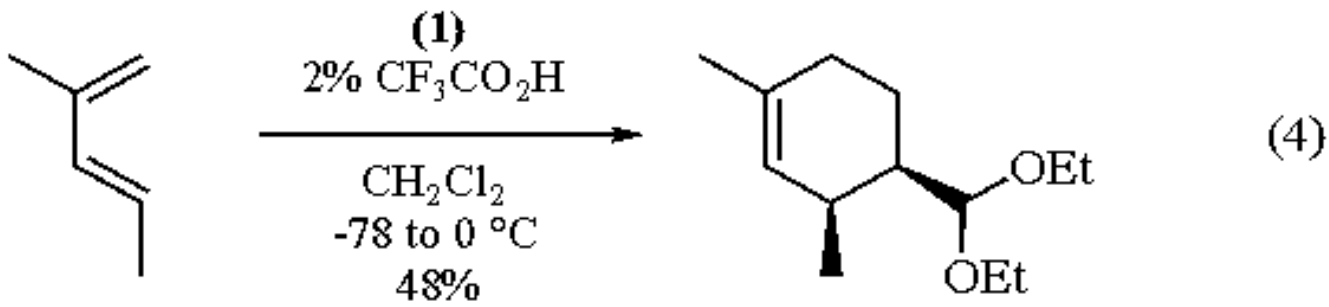

Heck Coupling.

The palladium-catalyzed (***Palladium(II) Acetate***, Pd(*o*-Tol)$_3$) coupling of (**1**) with aryl and vinyl halides in the presence of secondary amines such as piperidine and morpholine proceeds smoothly, in contrast to acrolein and other α,β-unsaturated aldehydes which tend to polymerize.[8,9] The reaction with vinyl halides furnishes a mixture of acetals and aminoacetals which are hydrolyzed to dienals by aqueous acid (eq 5).[8] However, with aryl halides the products are ethyl esters, probably arising from hydrolysis of the ketene acetal formed by elimination of the acetal hydrogen (eq 6).[9] With an isolated arylpalladium complex, formation of an aldehyde and its cyclization to a quinoline derivative are also reported.[10]

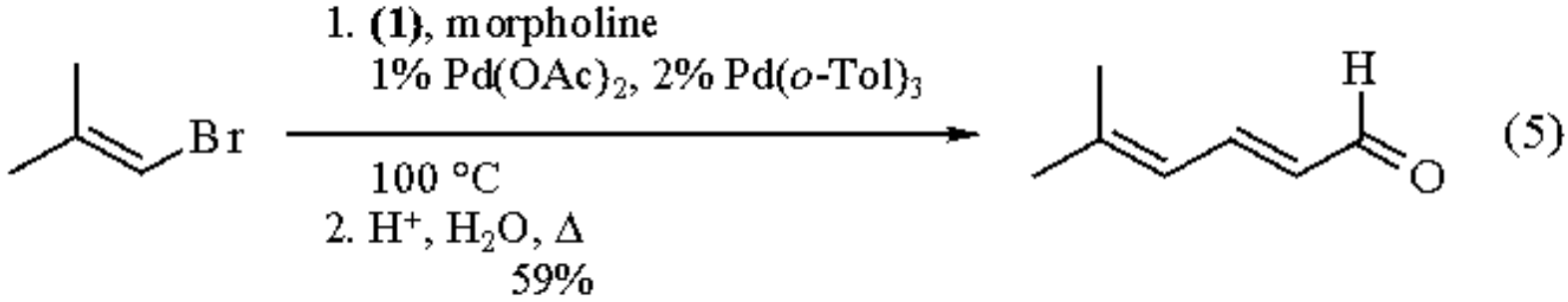

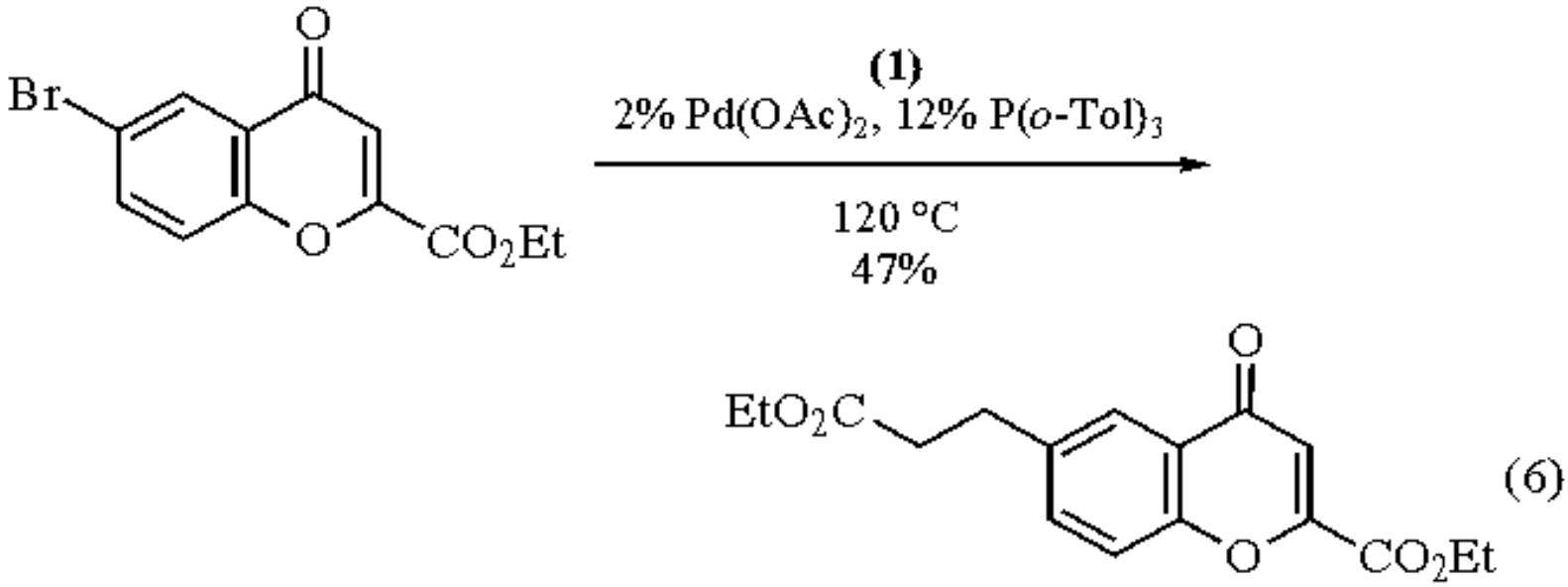

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3,3-Diethoxy-1-propen-2-ylcopper

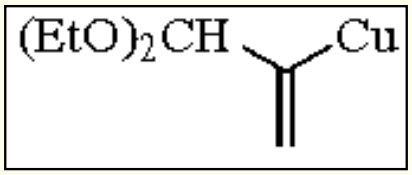

[57428-12-3] · $C_7H_{13}CuO_2$ · 3,3-Diethoxy-1-propen-2-ylcopper · (MW 192.72)

(reagent for the synthesis of α-methylene lactones;[1] 1,2-addition of the 2-substituted acrolein moiety;[2] 1,4-addition of the 2-substituted acrolein moiety[3])

Alternate Name: 1-(diethoxymethyl)vinylcopper.

Preparative Method: by reaction of 2-lithio-3,3-diethoxy-1-propene and copper iodide in THF at -55 °C.

Handling, Storage, and Precautions: sensitive to air and moisture; decomposes above -20 °C. Use in a fume hood.

The discovery of natural products containing the α-methylene lactone moiety stimulated the development of several 2-metallo acrylate and acrolein derivatives. Marino and Farina prepared 3,3-diethoxy-1-propen-2-ylcopper from the corresponding functionalized vinyl lithio reagent and 1 equiv of ***Copper(I) Iodide*** in THF at -55 °C and examined the reactivity of this reagent with cyclohexene monoepoxide.[1] The neutral copper reagent gave predominantly the *anti* 1,4-addition product in good yield. Formation of the homocuprate reagent from copper iodide using 2 equiv of the lithio anion gave a more reactive reagent that led to the *anti* 1,2-adduct as the major product. Mixed cuprates employing the nontransferable *t*-butylacetylene or cyano ligands were also prepared; the lower order cyanocuprate gave the lowest yields in the addition reaction, but was as selective for the 1,4-addition product as the neutral copper reagent (eq 1). The regioselectivity for 1,2-addition was enhanced using the homocuprate and carrying out the reaction in ether instead of THF. After hydrolysis of the acetal, the 1,2- and 1,4-adducts were stereospecifically converted to *trans*- or *cis*-α-methylene lactones, respectively, by oxidation to the acrylate and subsequent ring closure (eqs 2 and 3).

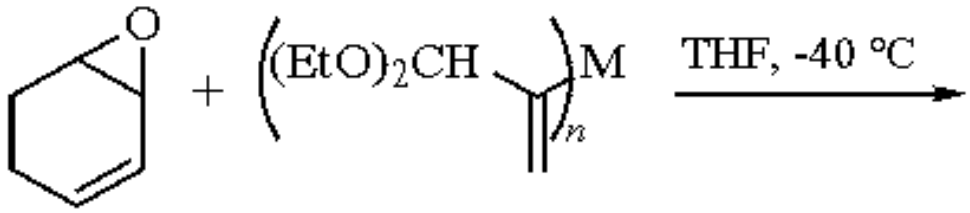

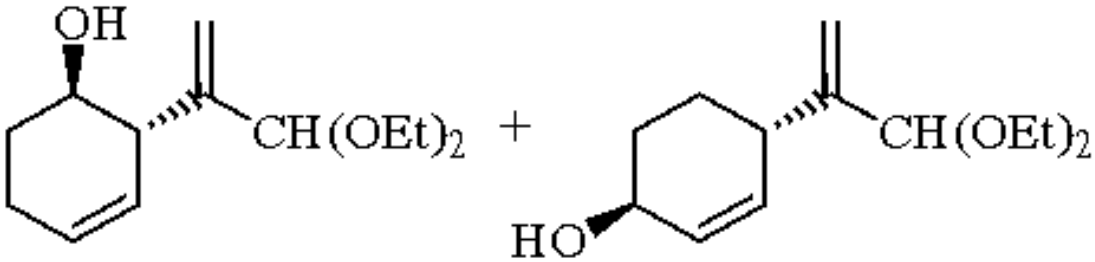

(1)

M	*n*	1,2:1,4	Yield (%)
Cu	1	0.6	71
Cu(Li)	2	1.5 (THF), 2.7 (Et_2O)	94
Cu(CC-*t*-Bu)	1	1.5	72
Cu(CN)Li	1	0.7	50

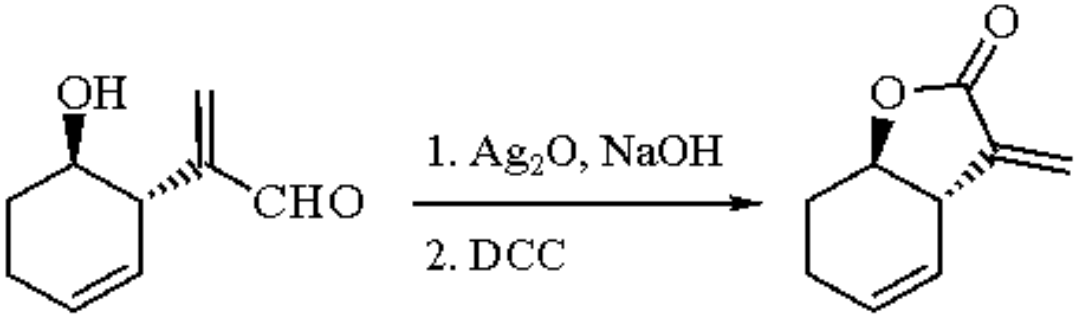

(2)

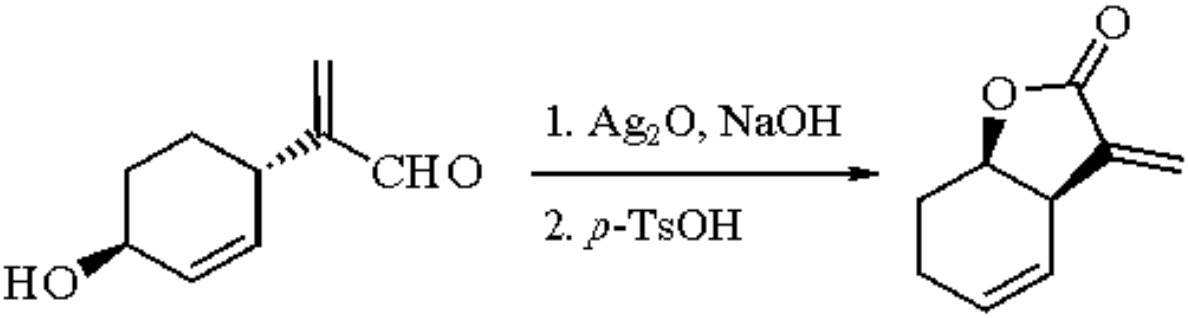

(3)

Grieco and co-workers also compared the reactivity of the 3,3-diethoxy-1-propen-2-ylcopper reagent and the thiophenoxy mixed cuprate in reactions with allyl halides (eq 4).[2] Both the neutral copper and cuprate reagents appeared to be specific for reaction with allylic halides and did not react with either benzyl bromide or 1-iodo-*trans*-oct-1-ene. Interestingly, the thiophenoxy mixed cuprate provided the 1,4-addition product with cyclohexenone (eq 5), while the neutral copper reagent resulted only in 1,2-addition to cyclohexenone (eq 6).

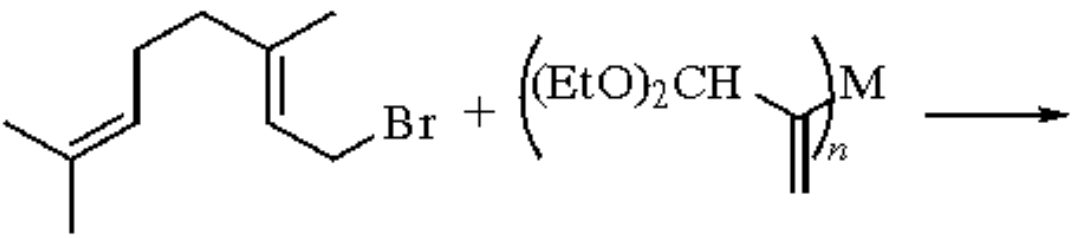

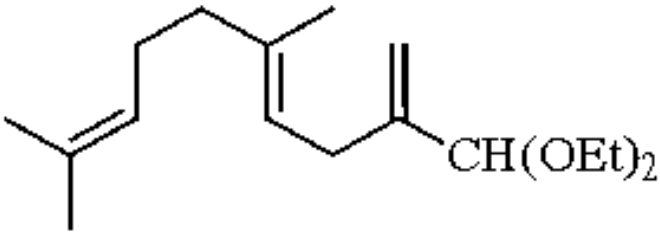

(4)

M = Cu, 85%
M = Cu(SPh)Li, 90%

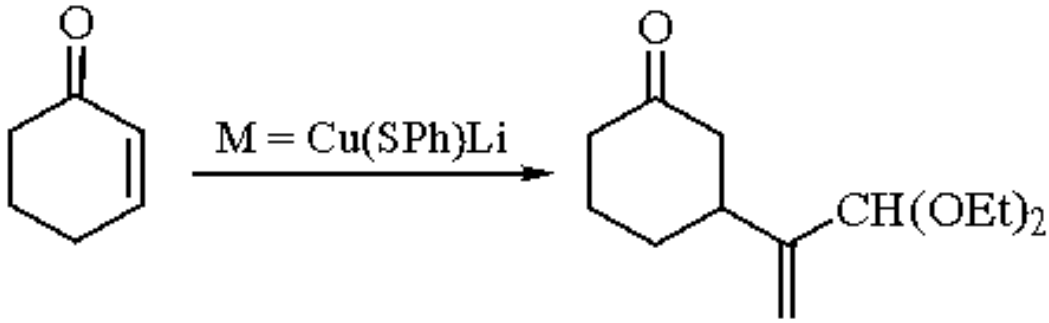

(5)

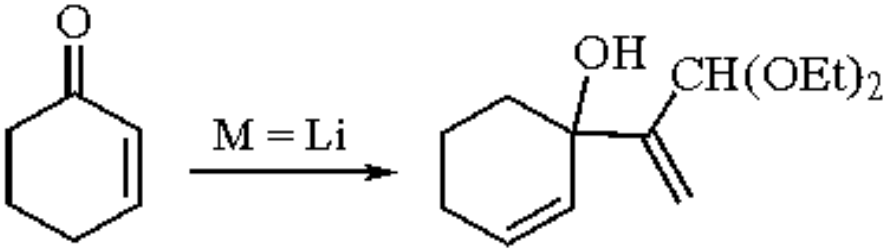

(6)

The reactivity of the neutral copper reagent toward carbonyls was also employed by Roush and Peseckis in the synthesis of 2-substituted acrolein derivatives, which underwent intramolecular Diels-Alder reaction to provide angularly oxygenated perhydroindenes.[4] Boeckman and Ramaiah observed better results in 1,4-addition reactions using the *t*-butylalkynic mixed cuprate reagent.[3] Lower yields of 1,4-addition were observed in reactions with β-substituted cyclohexenones or sterically hindered enones such as 4-*t*-butylcyclohexenone. It was also indicated that 3,3-diethoxy-1-propenylcuprate reagents did not react with primary or secondary alkyl bromides, vinyl bromides, or iodides; the major product isolated in attempted alkylation reactions was the 1,4-diene resulting from oxidative dimerization.

Conjugate addition reactions of the homocuprate derived from 2-lithio-3,3-diethoxy-1-propene have been reported in the synthesis of (+)-hanegokedial (eq 7),[5] and in an approach to ciliarin (eq 8).[6] 1,4-Addition of the cuprate to the cycloheptenone derivative, with in situ trapping of the derived enolate with gaseous ***Formaldehyde***, led to the α,β-

dialkylated product in good yield. The 1,4-addition stereochemistry was controlled by the cyclopropyl substituent, while the alkylation of the enolate led to a mixture of isomers. In the approach to ciliarin, stereospecific conjugate addition to the unsaturated lactone was achieved using in situ ***Chlorotrimethylsilane***. The chemistry of 2-metallo acrylates[7] and β-substituted acrylates[8] has also been developed. These functionalized cuprates exhibit atypical cuprate reactivity, favoring 1,2- over 1,4-addition in reactions with enones; however, reactions with acid chlorides provide α,α´-dienyl ketones in good yield.[9]

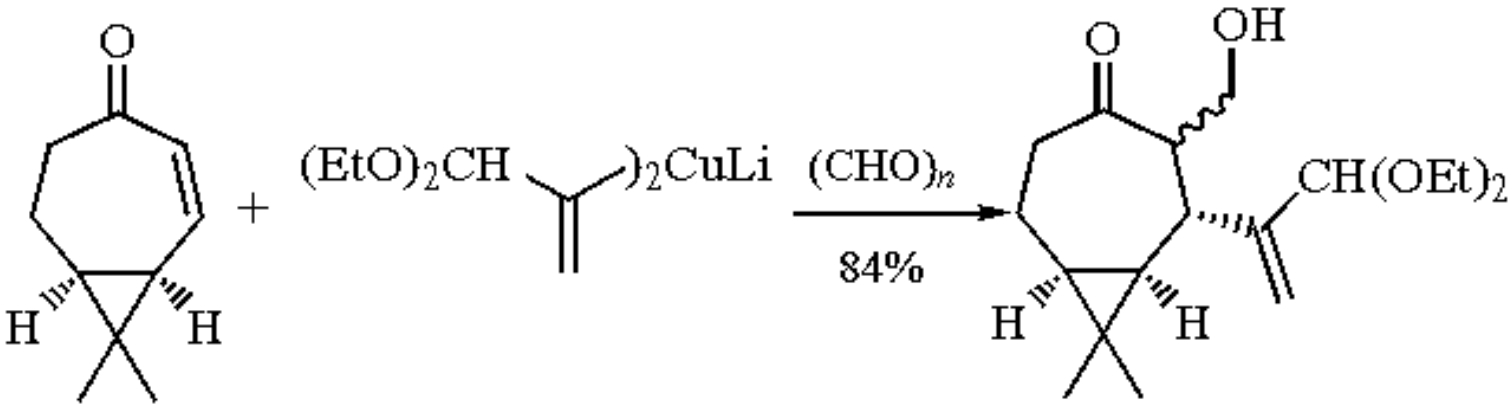

(7)

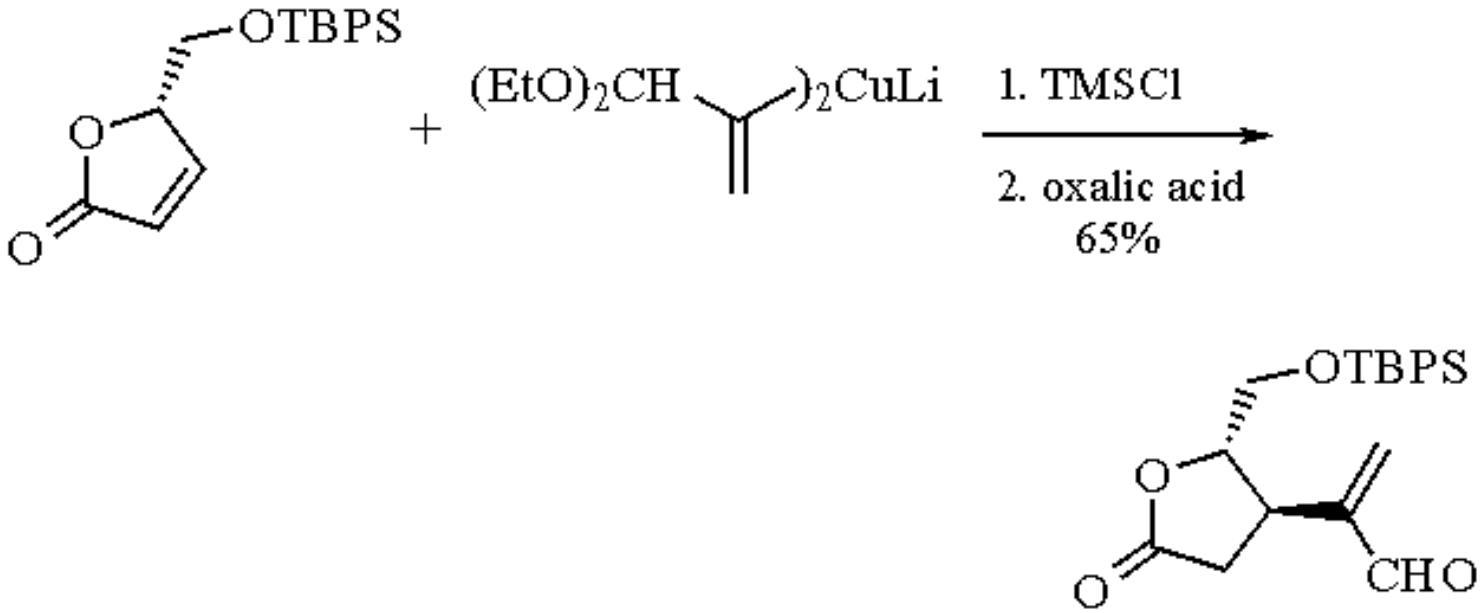

(8)

Related Reagents.

Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate; ***Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate***; ***Lithium Divinylcuprate***; ***Vinylcopper***.

---

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3,3-Diethoxy-1-propyne

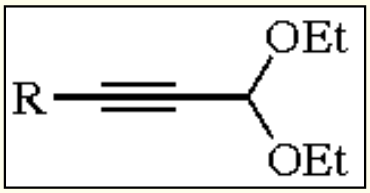

(R = H)

[10160-87-9] · $C_7H_{12}O_2$ · 3,3-Diethoxy-1-propyne · (MW 128.17) (R = Li)

[51756-42-4] · $C_7H_{11}LiO_2$ · 3,3-Diethoxy-1-propyne · (MW 134.10)

(intermediate for the synthesis of unsaturated and polyunsaturated compounds and numerous heterocycles[1])

Alternate Names: propiolaldehyde diethyl acetal; propargylaldehyde diethyl acetal.

Physical Data: bp 138-139.5 °C; *d* 0.894 g cm^{-3}.

Solubility: sol standard organic solvents.

Form Supplied in: colorless liquid; commercially available.

Analysis of Reagent Purity: IR: 3260, 2125 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.24 (t, *J* = 7, 6H), 2.58 (d, *J* = 2, 1H), 3.71 (q of d, *J* = 7, 2, 4H), 5.21 (d, *J* = 2, 1H).

Preparative Methods: the synthesis of this reagent can be accomplished according to eq 1. The dehydrobromination step can be carried out with ***Potassium Hydroxide*** in ethanol,[2] with ***Sodium Amide*** in liquid ammonia,[3] or by using ***Sodium Hydroxide*** in the presence of a phase transfer agent.[1a,4] 3,3-Diethoxy-1-propyne can also be prepared according to eq 2.[5]

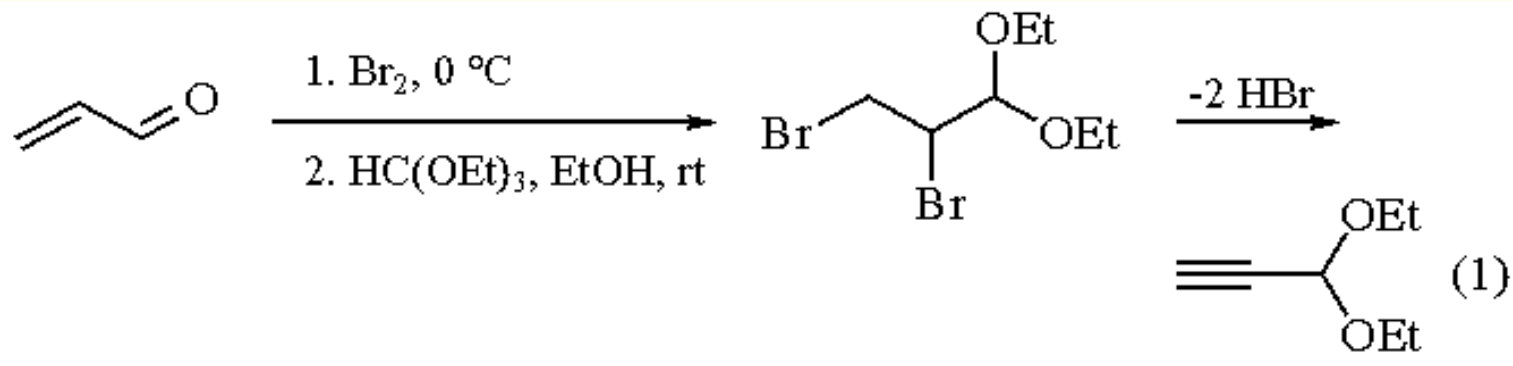

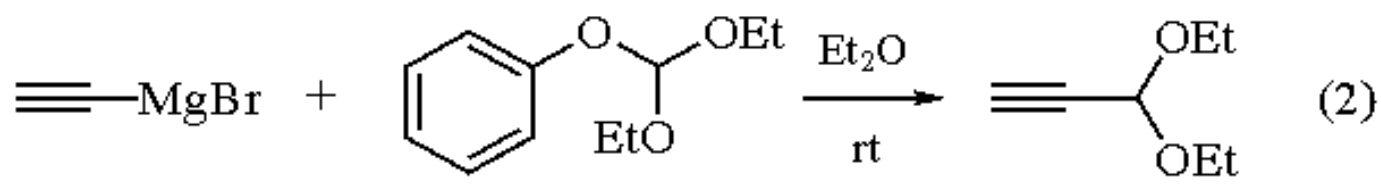

The lithio derivative, named (3,3-diethoxy-1-propynyl)lithium, is easily prepared by reaction of 1 equiv of a saturated lithium compound (e.g. ***n-Butyllithium***) with a solution of the acetal in ether or THF.[6]

Purification: by distillation at reduced pressure, bp 95-96 °C/170 mmHg.[1a]

Handling, Storage, and Precautions: should be stored in a refrigerator and protected from moisture.

Alkylation Reactions.

Reaction of the lithio derivative with organic halides and carbonyl compounds leads to the synthesis of unsaturated and polyunsaturated acetals and aldehydes.[6-8] Alkylation can also be performed by reaction of 3,3-diethoxy-1-propyne with halides (catalyzed by transition metal compounds)[9] or by Cadiot-Chodkiewicz coupling.[10]

Addition Reactions.

Interesting results are obtained by addition of organocuprates to 3,3-diethoxy-1-propyne owing to the regio- and stereoselectivity of the reaction (eq 3).[11,12]

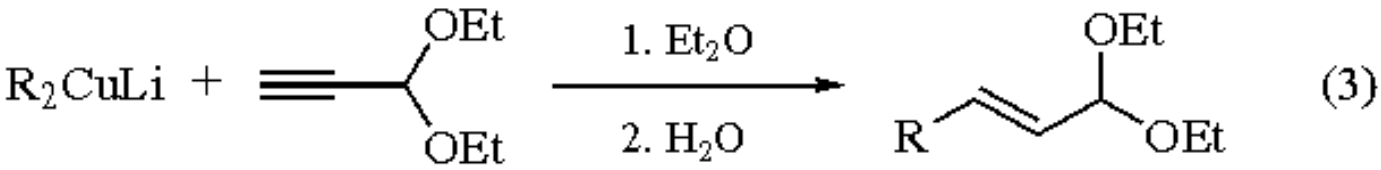

Recently, the stannocupration of 3,3-diethoxy-1-propyne has been found to lead to a bifunctional adduct, providing a useful synthon for further synthetic elaboration (eq 4).[13,14]

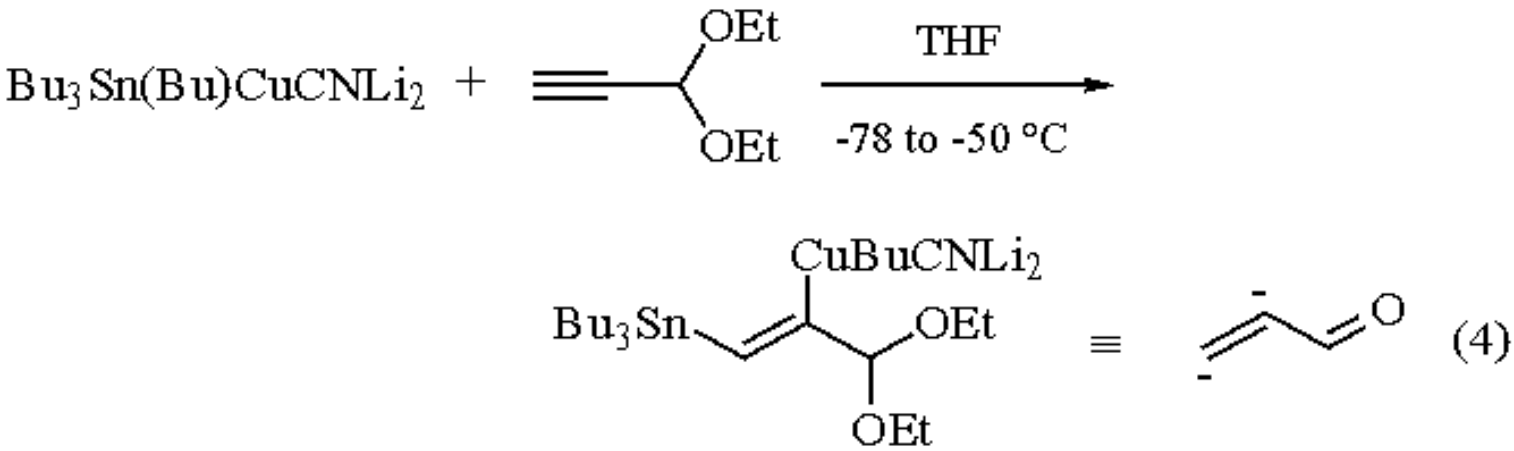

Heterocycle Synthesis.

The acetal and its lithio derivative have been used in the synthesis of numerous heterocyclic compounds, including furans,[8,9a] pyrazoles (eq 5),[15] isoxazoles,[16] and triazoles.[2]

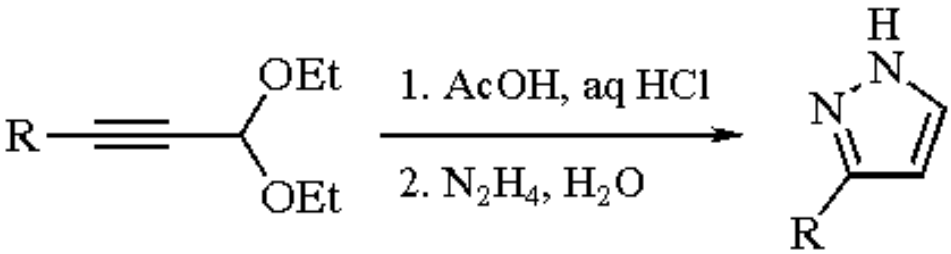

(5)

Some natural products have been synthesized by using 3,3-diethoxy-1-propyne and its lithio derivative as intermediates.[12,17-20]

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Diethyl Acetamidomalonate

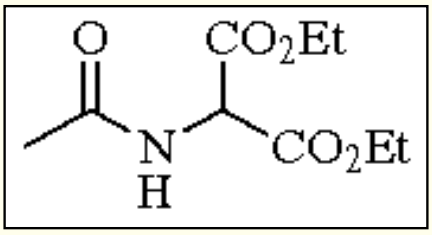

[1068-90-2] · $C_9H_{15}NO_5$ · Diethyl Acetamidomalonate · (MW 217.22)

(glycine anion equivalent for amino acid synthesis)

Physical Data: mp 95-96 °C.

Form Supplied in: commercially available.[1]

Amino Acid Synthesis.

Diethyl acetamidomalonate is the starting material for the classical Sörensen synthesis of amino acids, first reported in 1903.[2-4] The protected glycinate is deprotonated with base [typically ***Sodium Ethoxide***/EtOH or ***Sodium Hydride*** in THF, DMF or DMSO; more recently by phase-transfer catalysis (PTC)[5-13]], reacted with an electrophile (generally an alkyl halide or Michael acceptor), hydrolyzed and then decarboxylated (eq 1).[14] Although the second ester group acidifies the α-proton and avoids the common problem of dialkylation of an active methylene compound,[15] it is not possible to induce chirality at the α-carbon of amino acid derivatives by carbon-carbon bond formation with diethyl acetamidomalonate.[16]

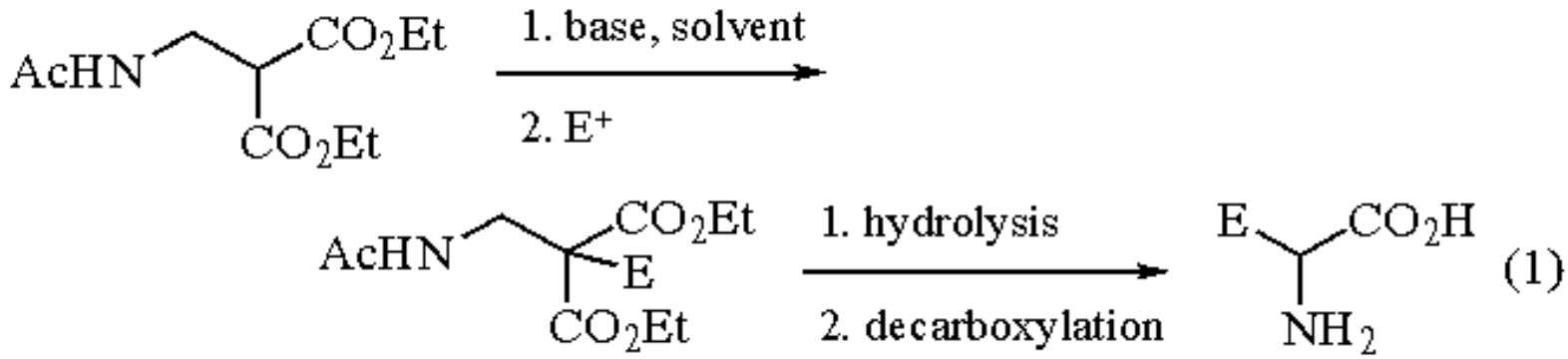

E^+ = alkyl halide, carbonyl compound, imine, Michael acceptor, other electrophiles

Numerous examples of this methodology exist and a brief listing of recent reports serves to highlight the possibilities in terms of reaction types (alkylations,[5,6,9,13,17-54] 1,2-carbonyl or imine additions,[55,56] Michael additions,[7,8,10-12,57,58] and an arylation[59]).

Amino acids with the following side chains have been produced by the Sörensen method: alkane,[19,21,26,30,60] alkene,[6,7,11,17,23,25,31,34,42,54,60-63] alkyne,[6,39,51,53,60,62] aromatic,[8,10,12,18,22,24,25,27,32,34,35,37,38,40,41,46,48,50,54,60] carbocycle,[61] fluoro,[6,35,52,57,58,64] halo (Cl, Br),[5,9,13,22,23,43,48,52] heterocycle,[17,20,28,29,37,43-45,49,52,55,57,59,60,64] iron,[18] ^{13}C label,[30,56] ^{2}H label,[40,56] ^{3}H label,[19,22] ^{15}N label,[49] nitrogen,[5,9-11,20,23,24,29,38,40-45,50,52,55-57,59,60,65,66] oxygen,[5,7,8,10-13,17,20,22,24,27-29,31,33,35-38,43-46,48-50,52,55,57-60,62,64,66] phosphorus,[5,48,50,52,60] platinum,[65] pro(cyclic imino),[5,9,37,42,47] sulfur,[7,23,33,44,45] and tin.[51]

New synthetic methodologies, such as catalytic enantioselective synthesis, are of special interest. Examples include phase-transfer catalyzed Michael addition to give (**1**) in 68% ee,[8,12] and palladium-catalyzed allylation to give (**2**) in up to 97% ee.[17,25,34,54] The chiral catalysts are a quaternarized *Ephedra* alkaloid derivative and a chiral phosphine ligand, respectively. In both of these cases the enantioselective reaction occurs at the indicated β-carbon center. Palladium-catalyzed carbopalladation of allenes to form 1,3-diene-containing amino acid derivatives,[63] conversion of the normally nucleophilic malonate into an electrophile by bromination followed by reaction as a glycine cation equivalent with a variety of nucleophiles,[60,62,66] and the synthesis of either heterocycles[67,68] or polymers[69] using compounds prepared from the parent malonate have also been reported.

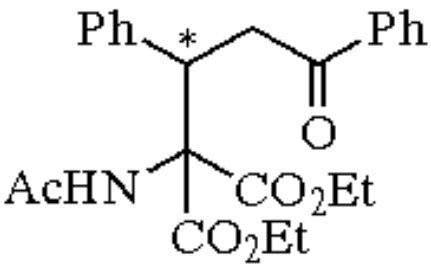

(1)

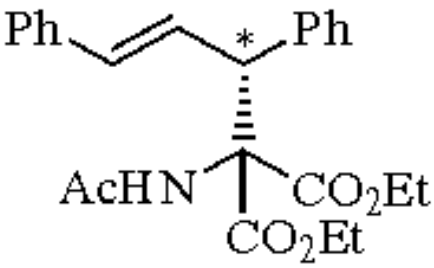

(2)

As noted above, the amino acid derivatives prepared by this methodology are achiral at the α-carbon. Recently, kinetic resolution by enantioselective hydrolysis with enzymes has been used for the direct preparation of the individual enantiomers.[61,70-73]

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***Diethyl Malonate***.

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Diethyl Acetonylmalonate

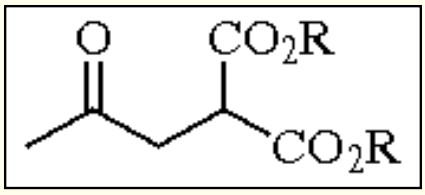

(R = Et)

[23193-18-2] · $C_{10}H_{16}O_5$ · Diethyl Acetonylmalonate · (MW 216.23) (R = Me)

[24889-15-4] · $C_8H_{12}O_5$ · Dimethyl Acetonylmalonate · (MW 188.18)

(doubly functionalized reagent, the ketone acting as an internal trapping agent after the reaction of the malonate anion;[1] for synthesis of five-membered rings)

Alternate Names: diethyl acetylmethylmalonate; diethyl 2-oxopropylmalonate.

Physical Data: R = Et: bp 102 °C/0.9 mmHg; R = Me: bp 75 °C/0.1 mmHg.

Preparative Methods: a detailed procedure reports the alkylation of ***Diethyl Malonate*** by chloroacetone on a 100 g scale, giving diethyl acetonylmalonate (**1**) with a yield of 55% after distillation.[1] Since chloroacetone is toxic and highly irritating to the eyes, skin, and mucous membranes,[2] an alternative procedure using ***Isopropenyl Acetate***, a mild irritant and a much less toxic compound than chloroacetone, should be seriously considered. Thus the reaction of dimethyl malonate with isopropenyl acetate in the presence of ***Cerium(IV) Ammonium Nitrate*** (CAN) followed by a mild basic treatment affords dimethyl acetonylmalonate in a yield of 82% on a 5-10 g scale (eq 1).[3] This procedure offers advantages regarding the yield and reaction conditions, and it uses available starting materials.

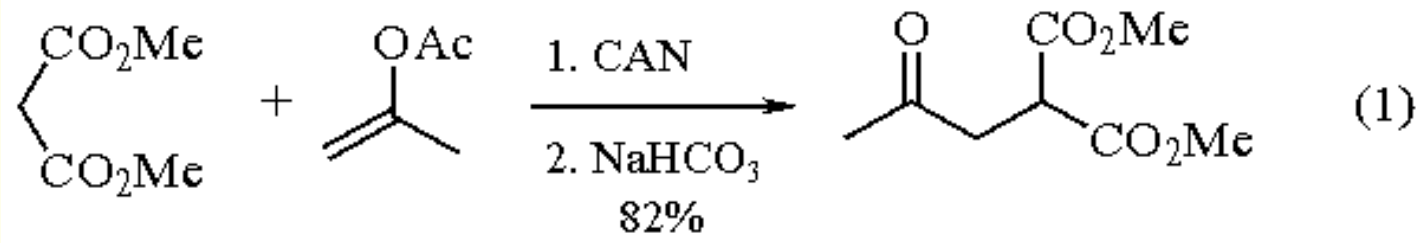

Handling, Storage, and Precautions: use in a fume hood.

Alkylation.

In a study toward the synthesis of ryanodine, Deslongchamps et al. reported the protection of the keto group of (**1**) and alkylation with 2-chlorocyclopentanone. Acid treatment of the crude product accomplishes the hydrolysis of the esters and acetal functions, decarboxylation, aldol condensation, and dehydration (eq 2).[1]

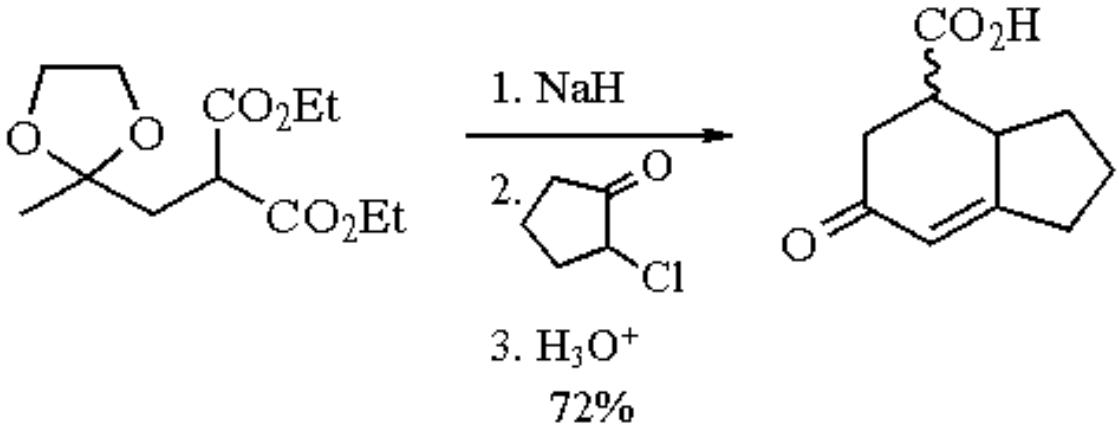

(2)

Michael Addition.

The conjugate addition of the potassium salt of (**1**) with ***2-Chloroacrylonitrile*** gives an intermediate which reacts with the keto group to give an epoxide by an intramolecular Darzens condensation (eq 3).[4] The reaction works equally well with methyl α-chloroacrylate. With α,β-unsaturated aldehydes, the Michael addition is followed by an intramolecular aldol reaction which can lead to lactonization (eq 4) or, as in the case of ***Acrolein***, dehydration (eq 5).[5] The sodium salt of (**1**) adds in a 1,4-fashion to α-diethoxyphosphoryl-$\Delta^{\alpha,\beta}$-butenolide to give an intermediate which reacts by an intramolecular Horner-Emmons reaction, providing an α,β-carbocyclic fused γ-lactone by a very simple route (eq 6).[6]

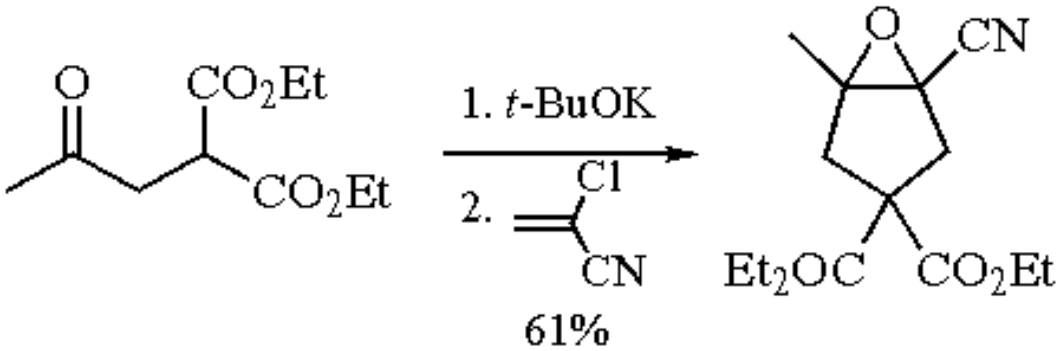

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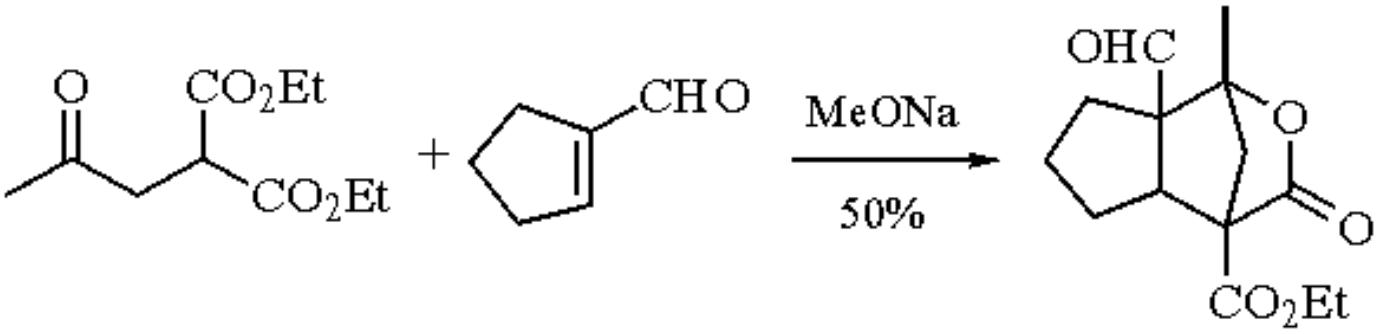

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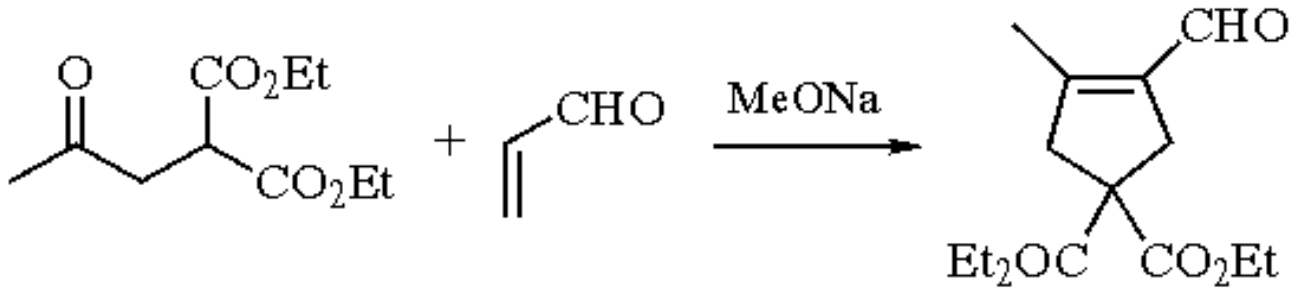

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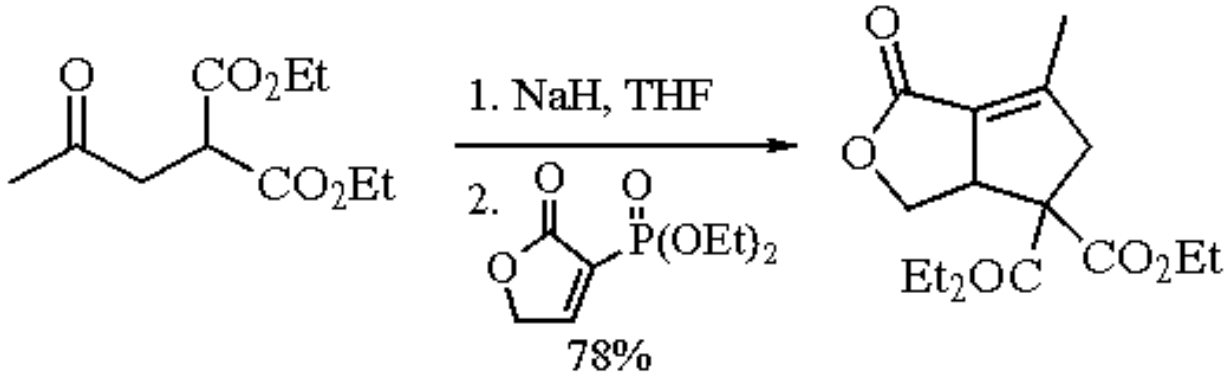

(6)

Conjugate Addition on Vinylphosphonium Compounds.

Treatment of the sodium salt of (**1**) with ***Vinyltriphenylphosphonium Bromide*** generates an intermediate phosphorane which undergoes an intramolecular Wittig reaction to give a cyclopentene derivative in good yield (eq 7).[7] Similarly, other phosphonium reagents such as (1-phenylthiovinyl)triphenylphosphonium chloride and 1-cyclobutenyl)triphenylphosphonium perchlorate can be used to synthesize cyclopentanones (eq 8)[8] and cyclobutane annulated compounds (eq 9),[9] respectively.

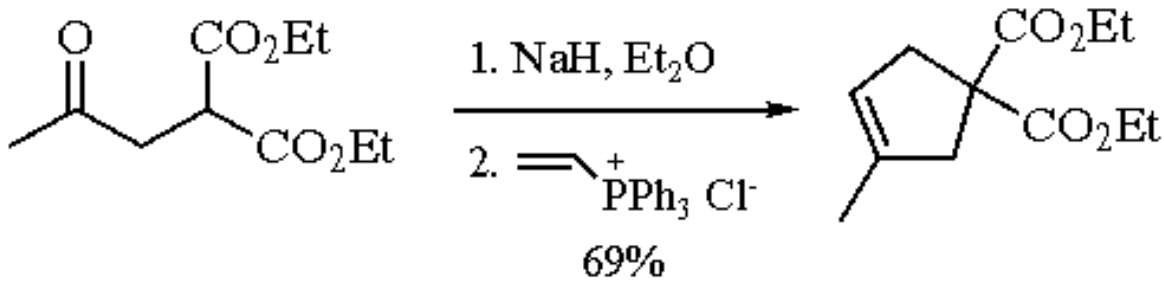

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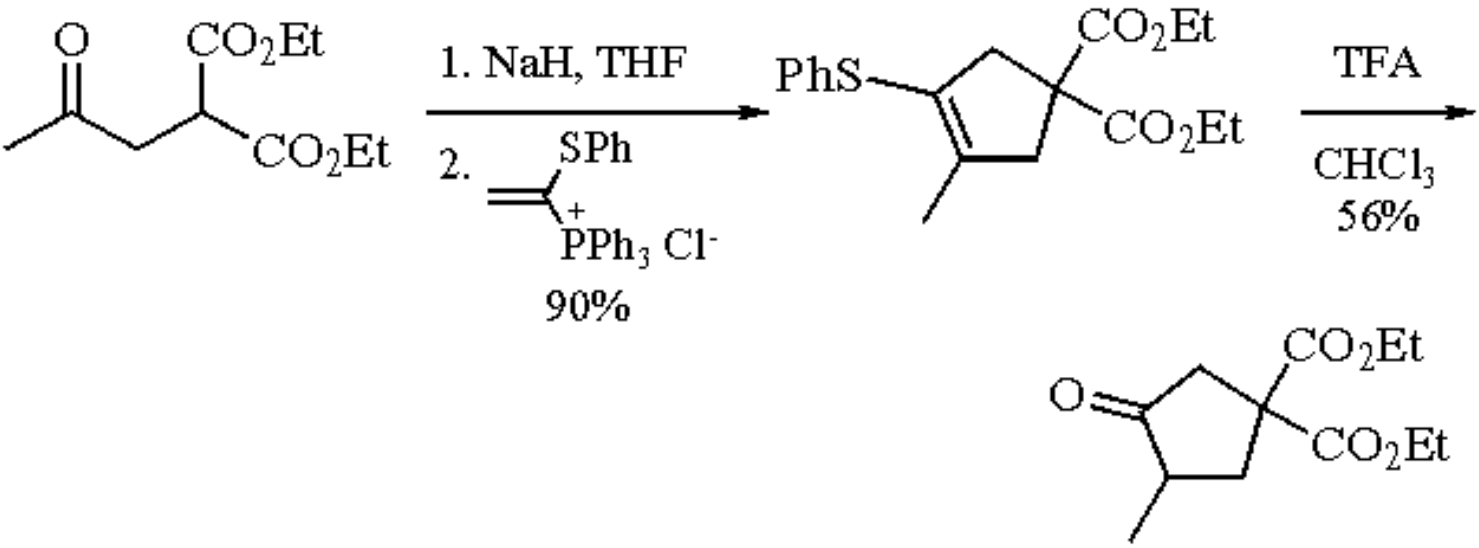

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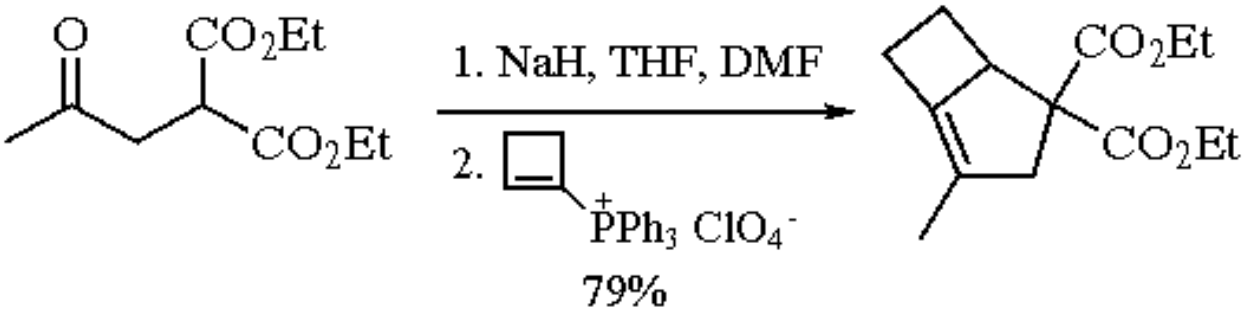

(9)

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Diethyl Acetonylphosphonate

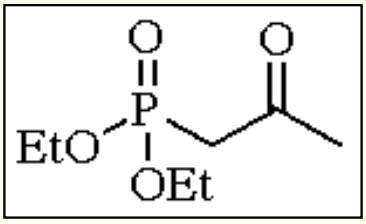

[1067-71-6] · $C_7H_{15}O_4P$ · Diethyl Acetonylphosphonate · (MW 194.17)

(Horner-Emmons reagent for the conversion of aldehydes and ketones to α,β-unsaturated methyl ketones;[1] can react via the corresponding derived metallic dianions to yield other β-ketophosphonates[2])

Alternate Name: diethyl acetylmethylphosphonate.

Physical Data: bp 126 °C/9 mmHg; *d* 1.010 g cm^{-3}; *n*D20 1.4330; δ ^{31}P 93.7 ppm (from P_4O_6 as reference),[3] -20 ppm (from 85% H_3PO_4 as external reference).[4]

Solubility: sol THF, ether, dichloromethane, chloroform.

Form Supplied in: colorless liquid.

Horner-Emmons Reagent.

Diethyl acetonylphosphonate is a very efficient reagent for the preparation of a variety of α,β-unsaturated methyl ketones via the Horner-Emmons modification[5] of the Wittig reaction and has the advantage over the equivalent Wittig ylide of much greater reactivity.[1] The corresponding derived sodium anion that realizes the carbonyl alkenation is usually obtained in aprotic medium with a limited range of solvents and bases, such as ***Sodium Hydride***/THF, NaH/DME,[6] or ***Sodium Hydroxide***/DMF.[7]

Excellent yields are obtained from aldehydes, often leading to exclusive *trans* stereochemistry for the α,β-unsaturated ketones formed (eq 1).[8] The lower electrophilic behavior of ketones combined with the increased steric hindrance results in lower yields,[6] and therefore allows, in the case of keto aldehydes, a chemoselective aldehyde alkenation (eq 2).[9]

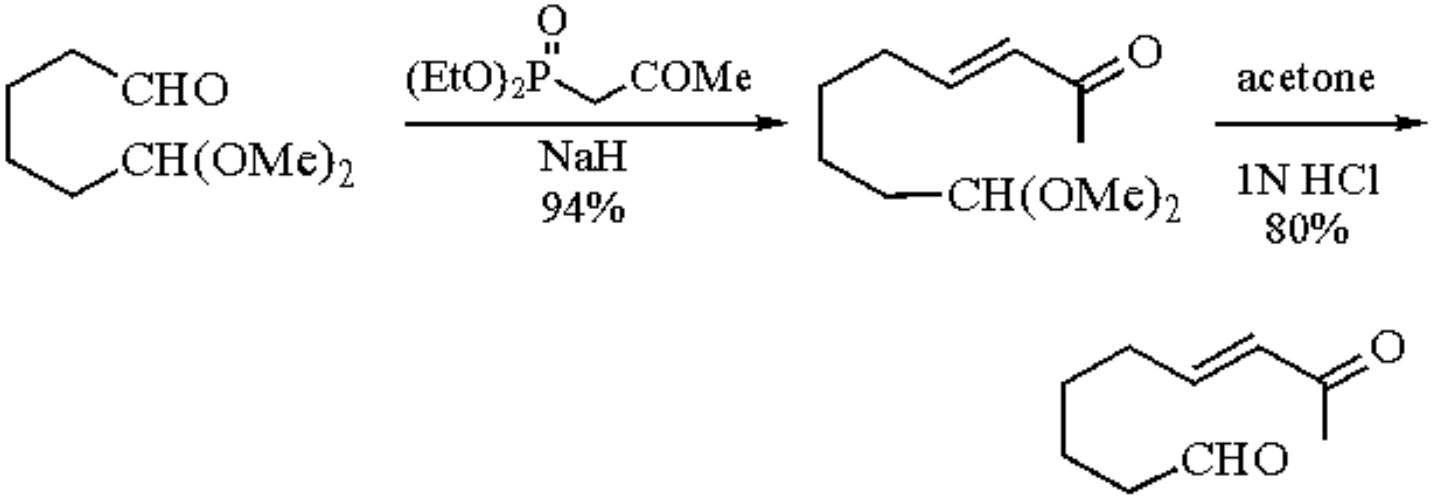

(1)

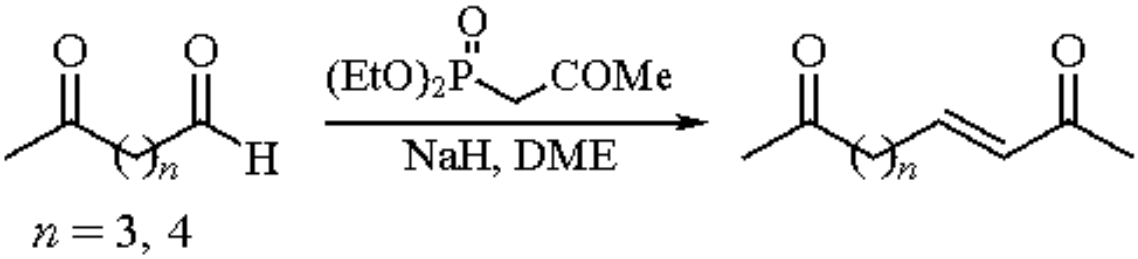

(2)

Often the carbonyl alkenation with diethyl acetonylphosphonate is part of a multistep synthesis of natural or bioactive products (eqs 3-5).[10-12]

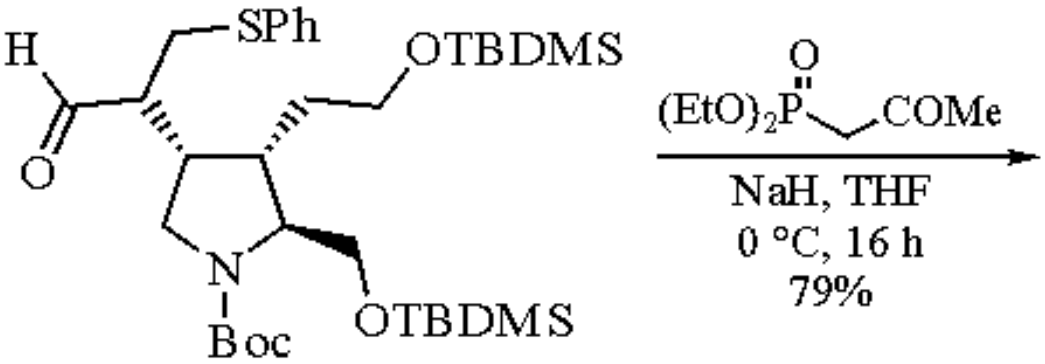

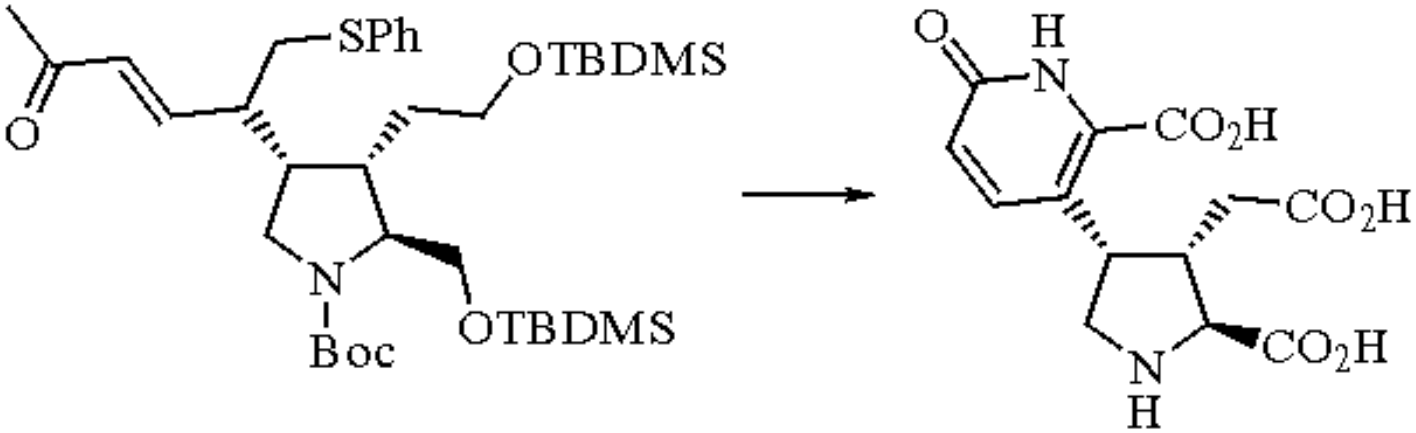

Acromelic acid (3)

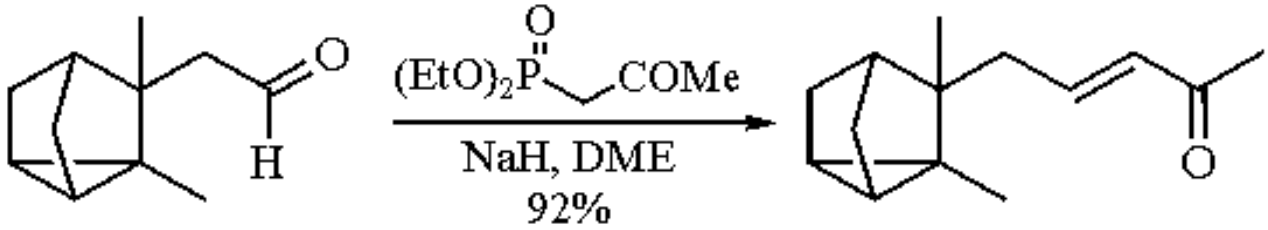

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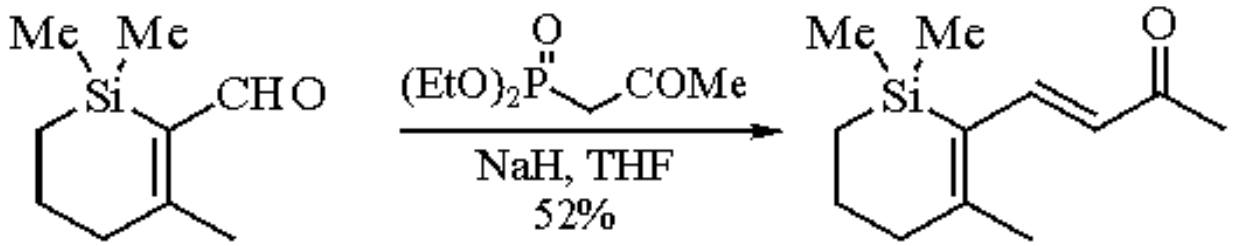

(5)

Diethyl acetonylphosphonate has also been used in an annulation sequence for building a cyclohexadienone ring onto a cyclic ketone (eq 6).[13]

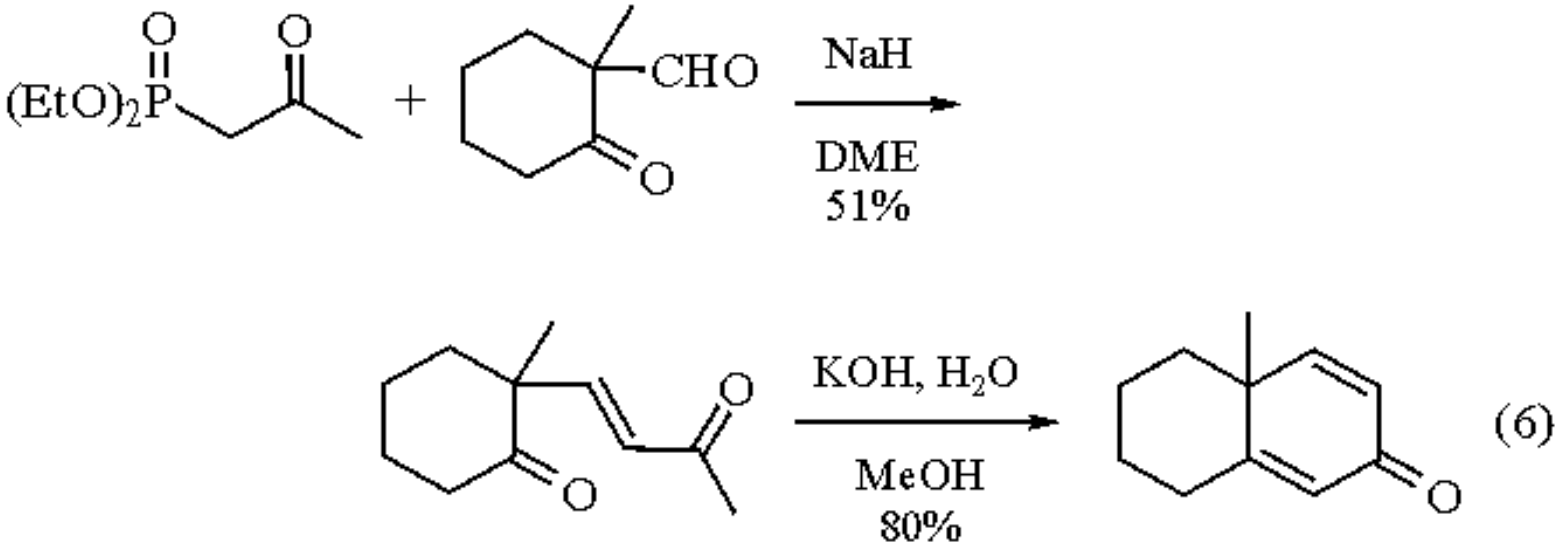

(6)

The Horner-Emmons reaction with diethyl acetonylphosphonate can be carried out in a protic solvent such as ethanol, with ***Potassium Hydroxide***[14] or ***Potassium Carbonate***[15] as base. Recently, two-phase liquid-liquid or solid-liquid procedures have been described and often represent a significative improvement for the Horner-Emmons reaction. Typical results are obtained in water, in the absence of organic solvents, using 6 M potassium carbonate as base (eq 7).[16]

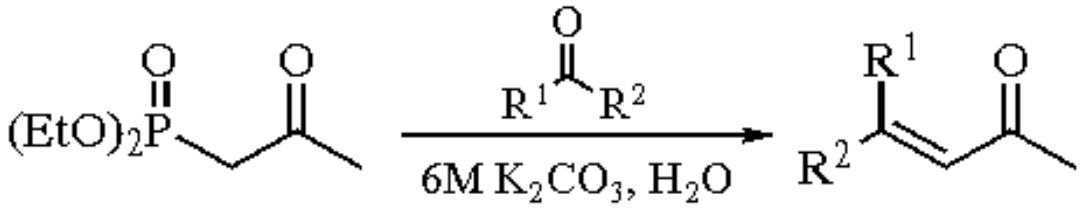

(7)

R^1	R^2	Base	Temperature	Times	Yield (%)
Et_2CH	H	6M K_2CO_3	100 °C	10 min	93
Et_2CH	H	6M K_2CO_3	20 °C	15 h	90
$-(CH_2)_5-$		6M K_2CO_3	20 °C	18 h	62

Under similar heterogeneous conditions, an aqueous solution of glutaraldehyde gives 1-acetyl-1-cyclohexen-6-ol (eq 8).[17]

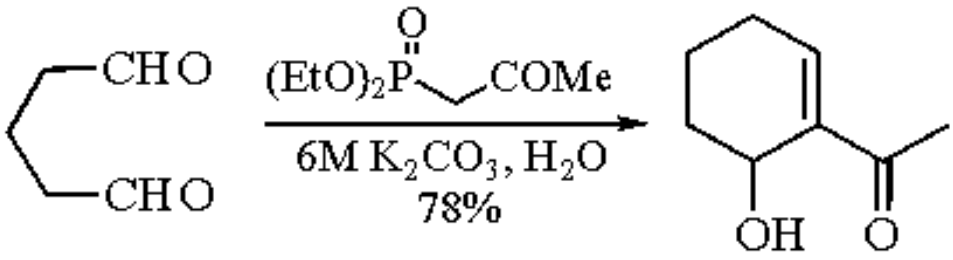

(8)

α-Labeled α,β-unsaturated methyl ketones (%D > 95%) can also be prepared with this procedure in the presence of 6 M K_2CO_3 in deuterium oxide solution at rt (eq 9).[18]

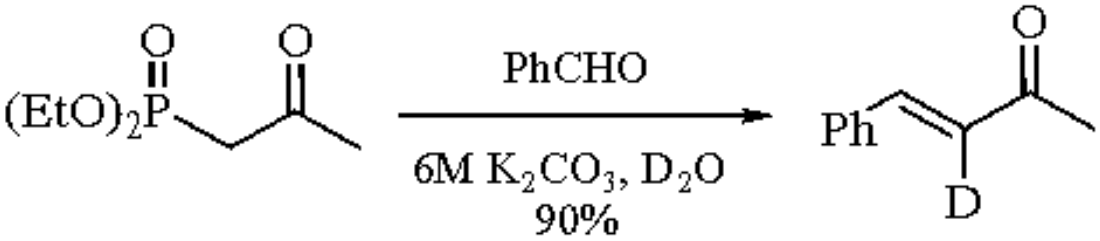

(9)

Microcrystalline ***Barium Hydroxide*** C200 [$Ba(OH)_2.0.8H_2O$, or $Ba(OH)_2.0.2H_2O$] has been used in very efficient solid-liquid Horner-Emmons reactions with β-ketophosphonates.[19] Under these conditions, Claisen-Schmidt and Horner-Emmons syntheses of acyclic enones using, respectively, acetone and diethyl acetonylphosphonate as reagents have been compared. The comparison shows that the Horner-Emmons reaction is more efficient and selective, while the Claisen-Schmidt condensation leads to a mixture of enone and dienone. The (*E*) stereoselectivity of the reaction is the same in both cases (eq 10).[20]

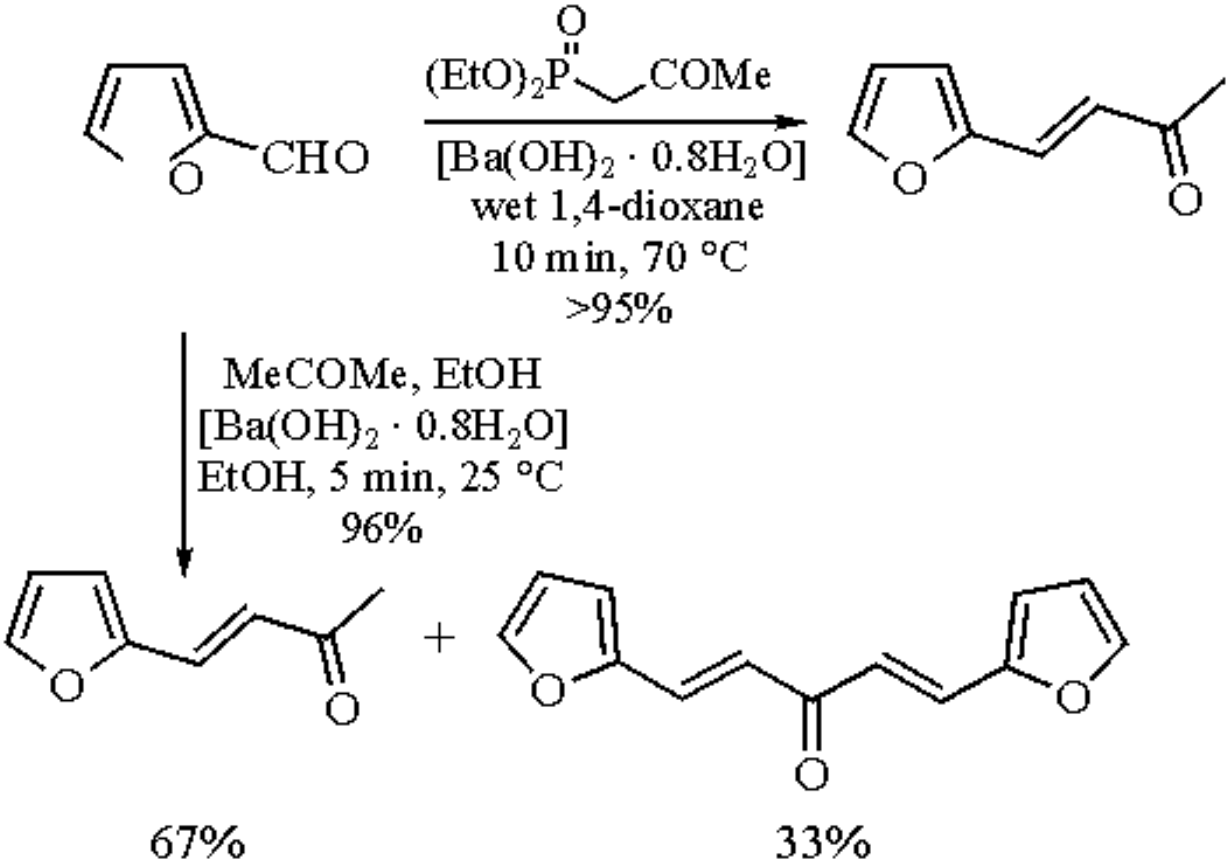

(10)

Preparation of Other β-Ketophosphonates.

α-Substituted or γ-substituted alkyl β-ketophosphonates can be prepared from, respectively, the monoanion[21] or the dianion of diethyl acetonylphosphonate. Prior α-alkylation of the sodium enolate, before the carbonyl alkenation step, is often employed (eq 11).[22]

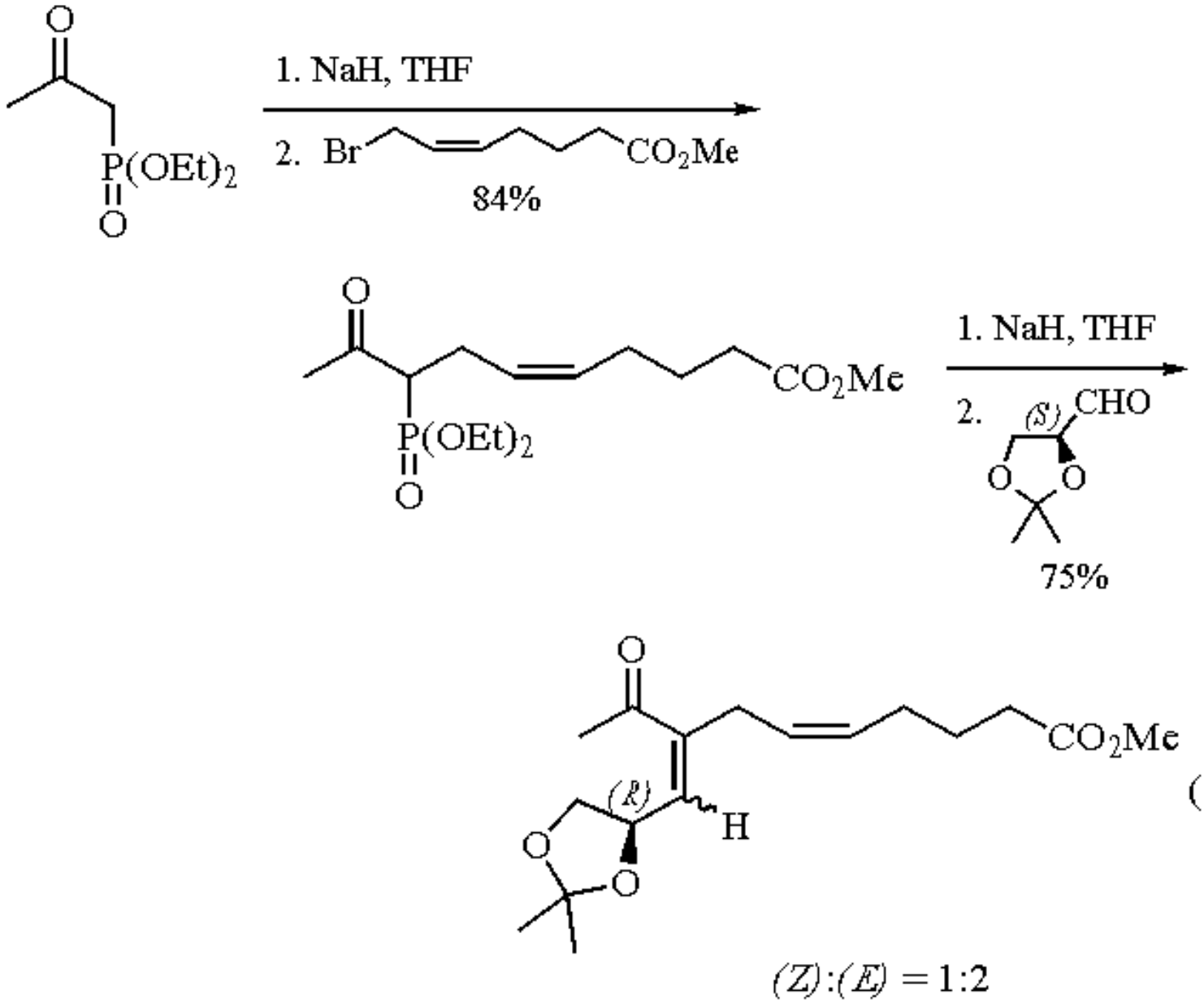

(11)

Prior α-alkylation is also required for other subsequent reactions as, for instance, an intramolecular aza-Wittig (Staudinger) reaction (eq 12).[23]

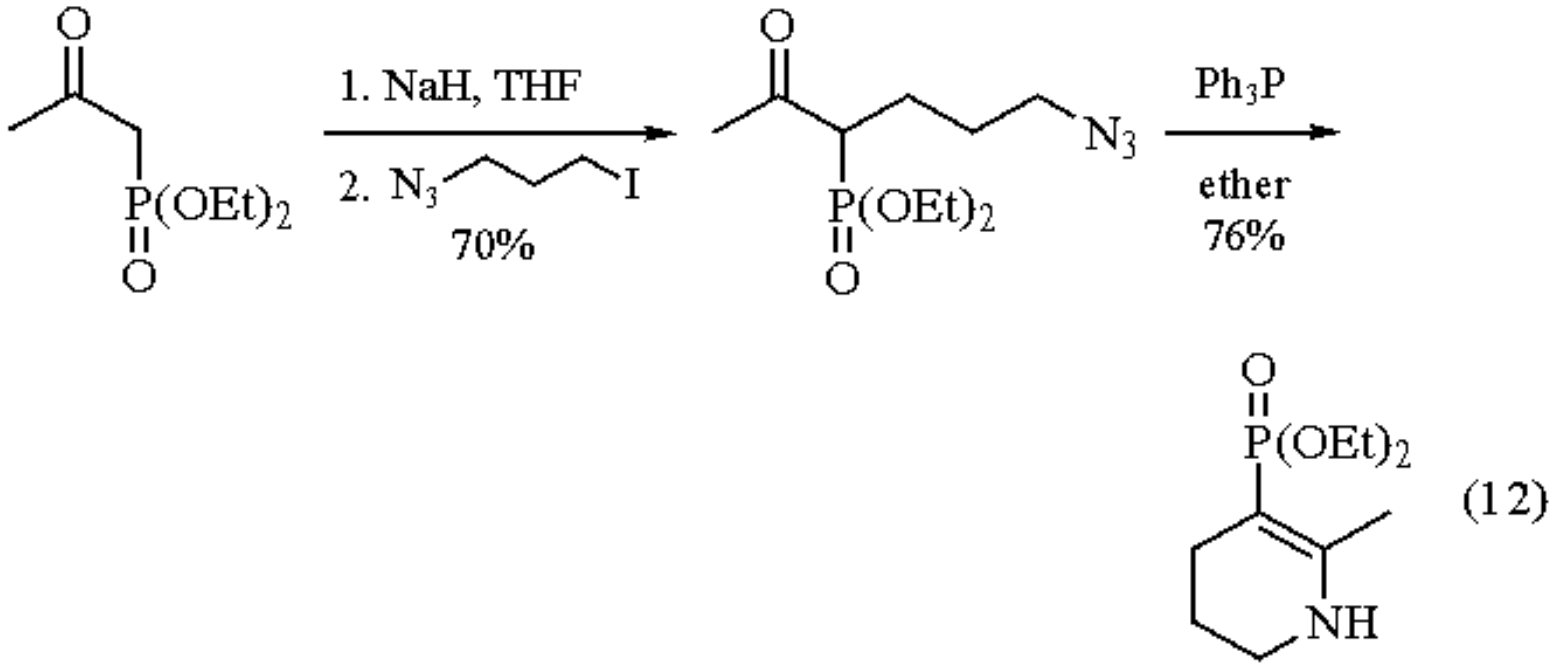

If desired, the dianion generated from diethyl acetonylphosphonate by successive treatment with NaH and ***n-Butyllithium*** can be alkylated at the γ-position with homoallyl bromide to yield diethyl 2-oxo-6-hepten-1-ylphosphonate (eq 13).[2a] Other examples of this γ-alkylation have been described with the dianion derived from diethyl acetonylphosphonate.[2b]

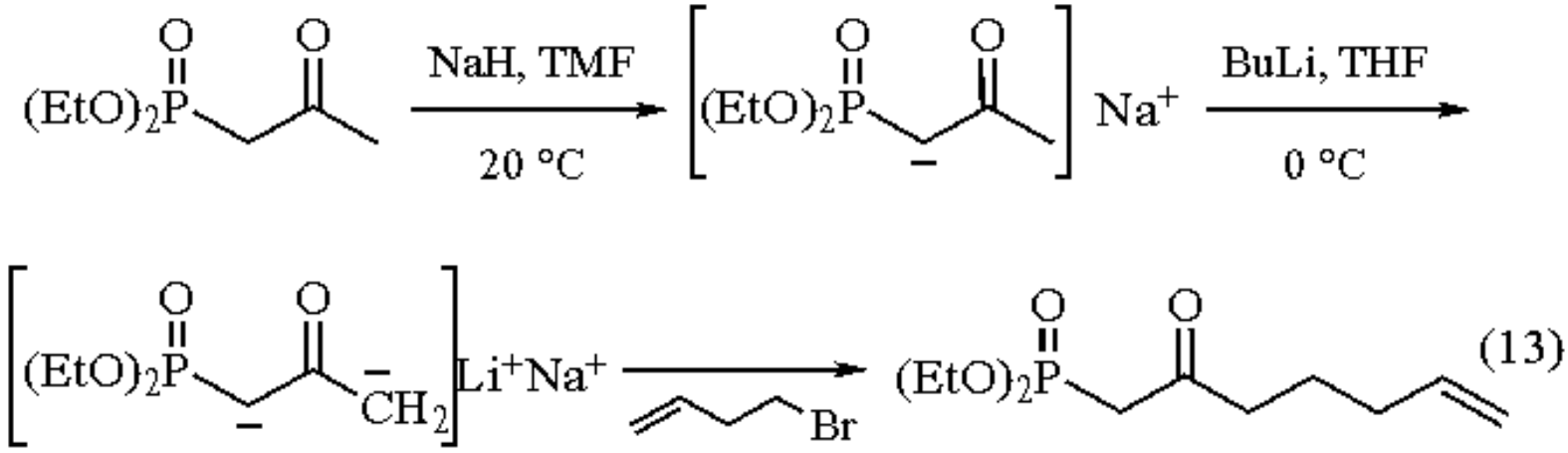

The Derived Metallic Dianion as Reagent.

The dianion derived from diethyl acetonylphosphonate gives γ-hydroxyalkylation with carbonyl compounds. After dehydration, the resulting 2-oxo-3-alkenylphosphonates serve as heterodienes in thermal reactions with vinyl ethers, leading ultimately to 5-substituted 2-phosphinyl-2-cyclohexen-1-ones.[24] Formed on the surface of solid K_2CO_3/MeOH, in the presence of ***Iodine***, the dianion can be exclusively γ-iodinated and gives in situ a novel ambident iodinated dianion where the two CH groups have approximately equivalent reactivity. Aromatic aldehydes react with this last intermediate in a simultaneous Horner-Emmons and Darzens reaction to yield epoxy enones (eq 14).[25]

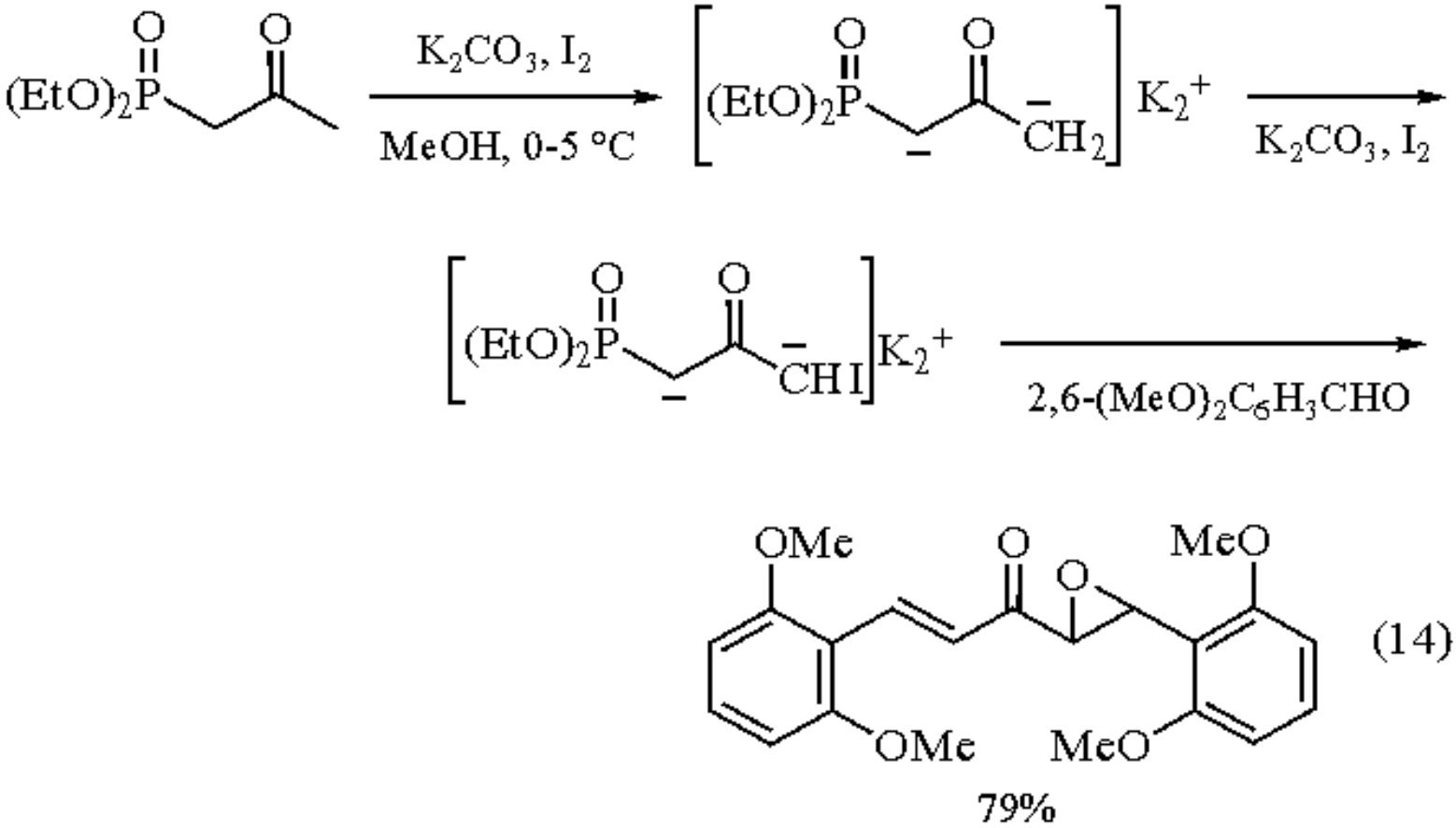

(14)

The dianion can be also formylated or acylated with ethyl esters or acyl chlorides in the γ-position to yield diethyl 2,4-dioxoalkylphosphonates. The deprotonation is carried out with NaH/THF at 20 °C with 1 equiv of sodium hydride followed by 2 equiv of ***Lithium Diisopropylamide*** at 0 °C. The excess of LDA is essential for a quantitative formation of the dianion because of proton transfer from the acylated product (eq 15).[26]

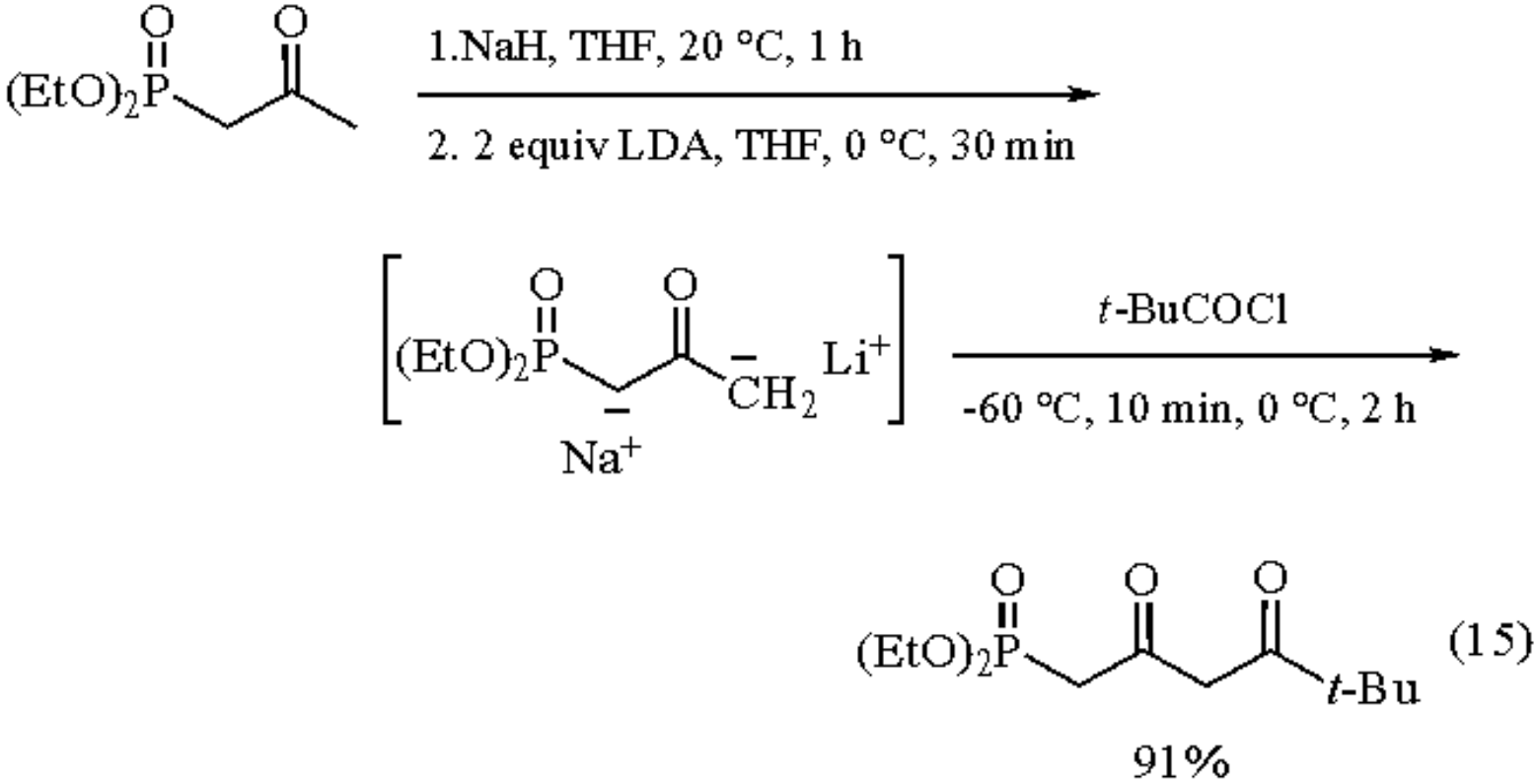

Miscellaneous Reactions.

Diethyl acetonylphosphonate can be used to prepare indolylphosphonates via a Fischer cyclization.[27] It also undergoes reductive amination in the presence of an amine and ***Sodium Cyanoborohydride*** in MeOH at pH 7-7.5 to yield the corresponding β-amino phosphonates (eq 16).[28]

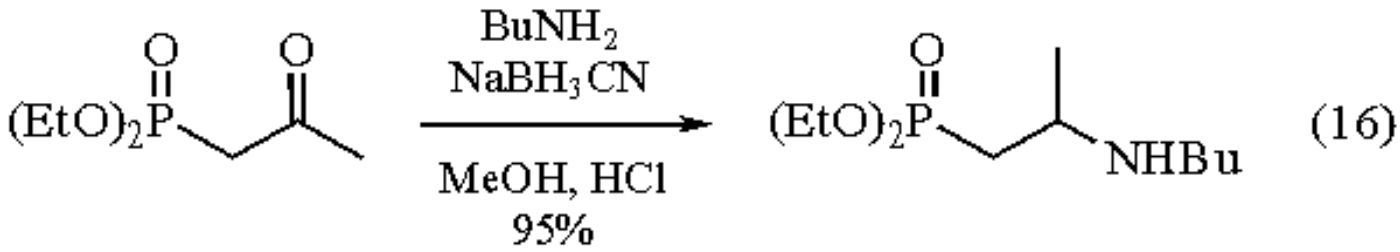

Strecker reaction leads to phosphonate analogs of α-methylaspartic acid.[29] Diethyl nitromethylphosphonate is obtained from the reaction between diethyl acetonylphosphonate and HNO_3/Ac_2O in 70% yield.[30]

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Diethylaluminum Chloride[1]

Et_2AlCl

[96-10-6] · $C_4H_{10}AlCl$ · Diethylaluminum Chloride · (MW 120.56)

(strong Lewis acid that can also act as a proton scavenger; reacts with HX to give ethane and EtAlClX)

Alternate Names: chlorodiethylaluminum; diethylchloroalane.

Physical Data: mp -50 °C; bp 125 °C/50 mmHg; *d* 0.961 g cm^{-3}.

Solubility: sol most organic solvents; stable in alkanes or arenes.

Form Supplied in: commercially available neat or as solutions in hexane or toluene.

Analysis of Reagent Purity: solutions are reasonably stable but may be titrated before use by one of the standard methods.[1e]

Handling, Storage, and Precautions: must be transferred under inert gas (Ar or N_2) to exclude oxygen and water. Use in a fume hood.

Introduction.

The general properties of alkylaluminum halides as Lewis acids are discussed in the entry for ***Ethylaluminum Dichloride***. Dialkylaluminum halides are less acidic than alkylaluminum dihalides. Et_2AlCl is much cheaper than ***Dimethylaluminum Chloride*** and is used more frequently than Me_2AlCl since comparable results are usually obtained. In some cases, most notably the ene reactions of carbonyl compounds, use of Me_2AlCl is preferable since its methyl groups are less nucleophilic than the ethyl groups of Et_2AlCl, which can act as a reducing agent.

Catalysis of Diels-Alder Reactions.

Et_2AlCl has been extensively used as a Lewis acid catalyst for Diels-Alder reactions. *N*-Acyloxazolidinones can form both 1:1 (eq 1) and 1:2 complexes with Et_2AlCl (eq 2).[2] The 1:2 complex is ~100 times as reactive as the 1:1 complex and gives greater *endo* selectivity and higher de. Me_2AlCl gives similar selectivity with fewer byproducts.

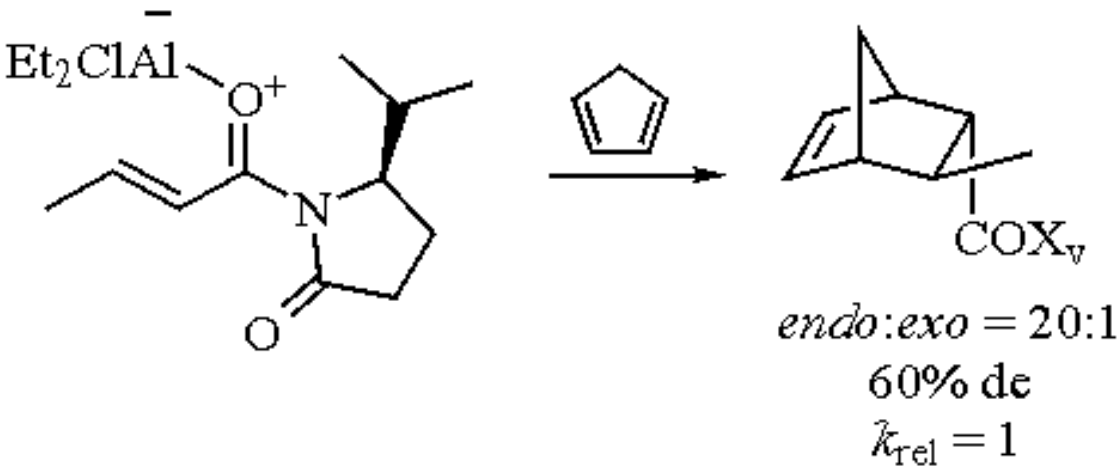

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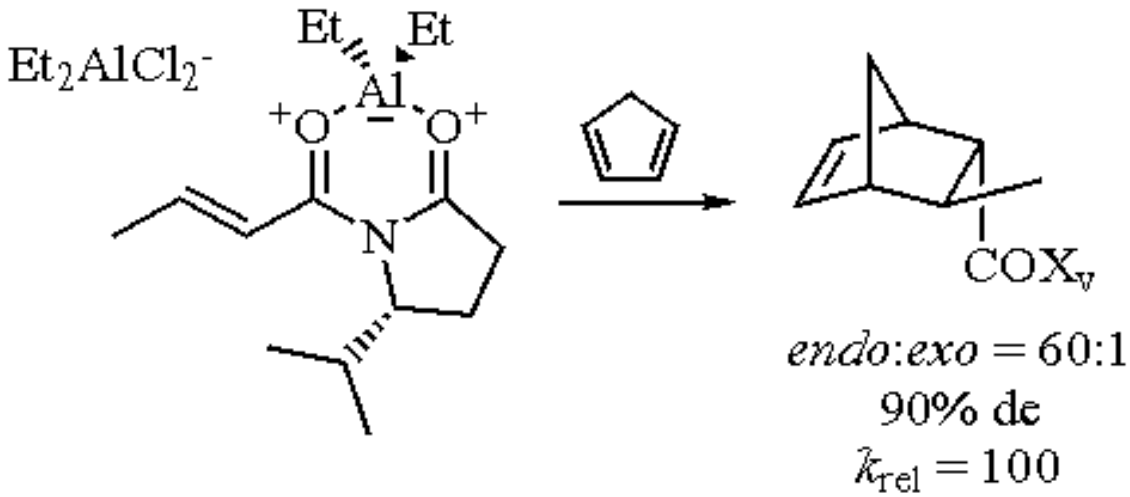

(2)

Et_2AlCl has been extensively used as a Lewis acid catalyst for intermolecular[3] and intramolecular[4] Diels-Alder reactions with α,β-unsaturated ketones and esters as dienophiles. It also catalyzes inverse electron demand Diels-Alder reactions of alkenes with quinone methides[5] and Diels-Alder reactions of aldehydes as enophiles.[6]

Catalysis of Ene Reactions.

Et_2AlCl has been used as a catalyst for ene reactions with ethyl propiolate as an enophile,[7] for intramolecular ene reactions of aldehydes,[8] and for intramolecular ene reactions with α,β-unsaturated esters as enophiles (eq 3).[3e,9]

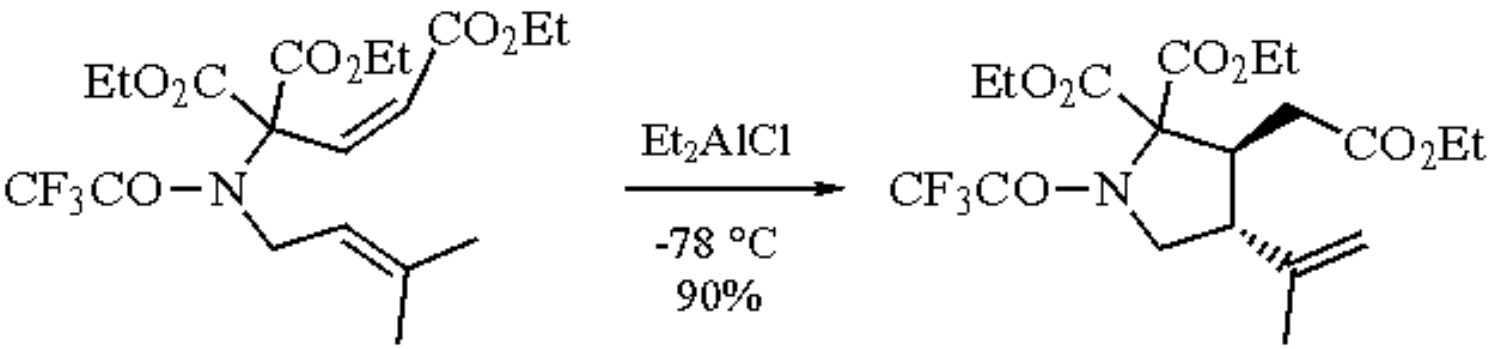

(3)

Catalysis of Claisen and Vinylcyclopropane Rearrangements.

Et_2AlCl has been used as a catalyst for Claisen rearrangement of aryl allyl ethers.[10] The rearrangement of 2-vinylcyclopropanecarboxylate esters to cyclopentenes is catalyzed by Et_2AlCl (eq 4).[11]

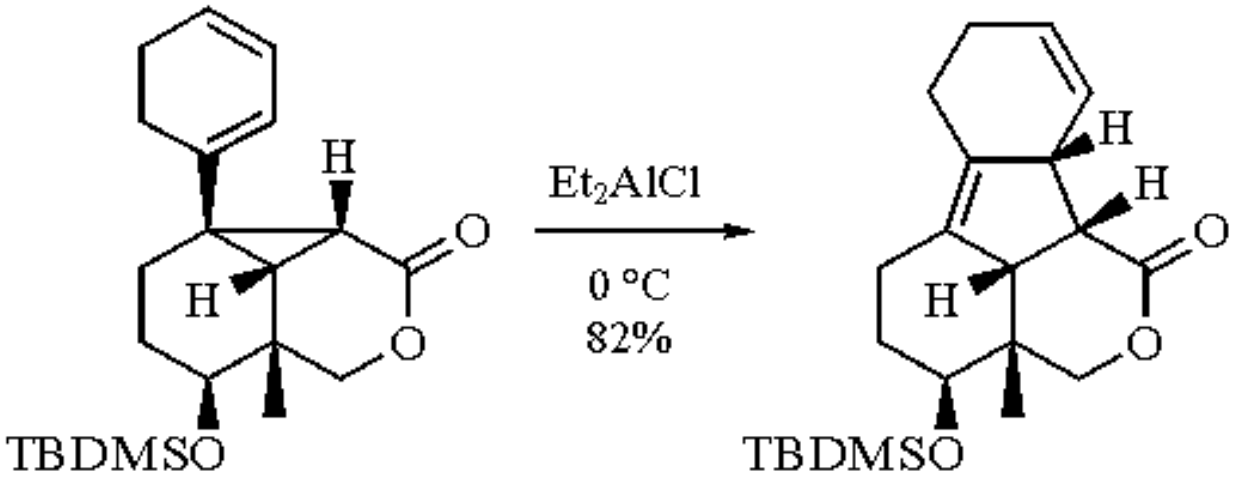

(4)

Generation of Electrophilic Cations.

Complexation of Et_2AlCl to ketones and aldehydes activates the carbonyl group toward addition of a nucleophilic alkyl- or allylstannane or allylsilane.[12] Et_2AlCl has been used to initiate Beckmann rearrangements of oxime mesylates. The ring-expanded cation can be trapped intermolecularly by enol ethers and cyanide and intramolecularly by alkenes (eq 5).[13]

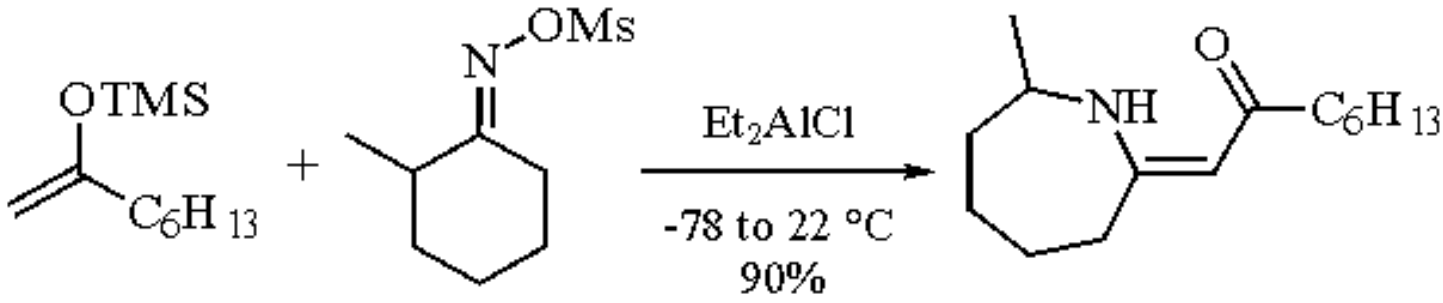

(5)

Formation and Reaction of Aluminum Enolates.

Et_2AlCl has been used in modified Reformatsky reactions. Aldol adducts are obtained in good yield by reaction of an α-bromo ketone with a ketone in the presence of ***Zinc*** and Et_2AlCl in THF (eq 6).[14] Lithium enolates of esters do not react with epoxides. Reaction of lithium enolates with Et_2AlCl affords aluminum enolates that react with epoxides at the less substituted carbon (eq 7).[15]

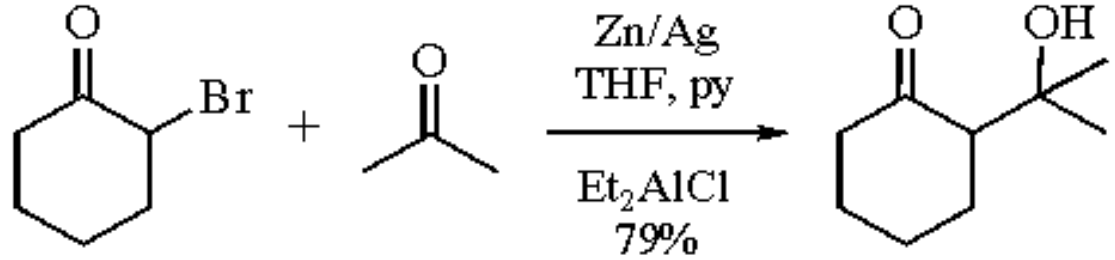

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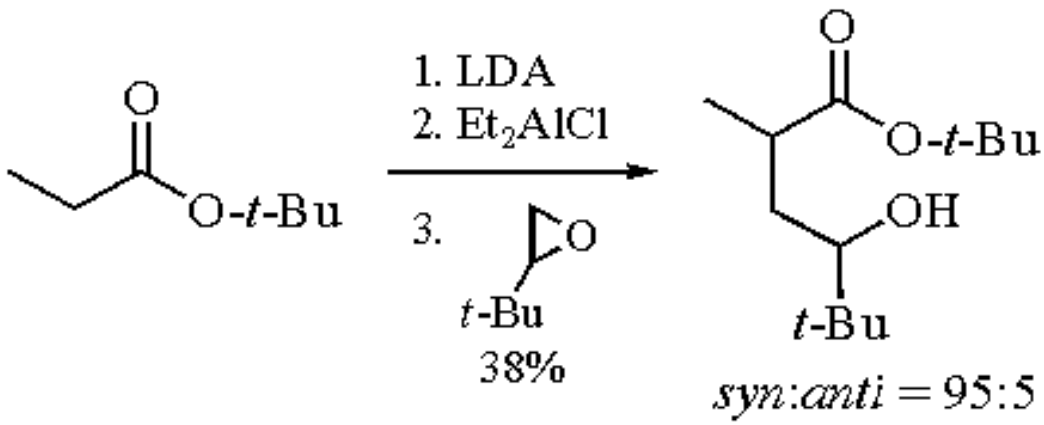

(7)

Formation and Reaction of Alkynylaluminum Reagents.

Lithium acetylides react with Et_2AlCl to form LiCl and diethylaluminum acetylides. The aluminum acetylides are useful reagents for carrying out S_N2 reactions on epoxides (eq 8)[15c,16] and undergo conjugate addition to enones that can adopt an *S-cis* conformation (eq 9).[17]

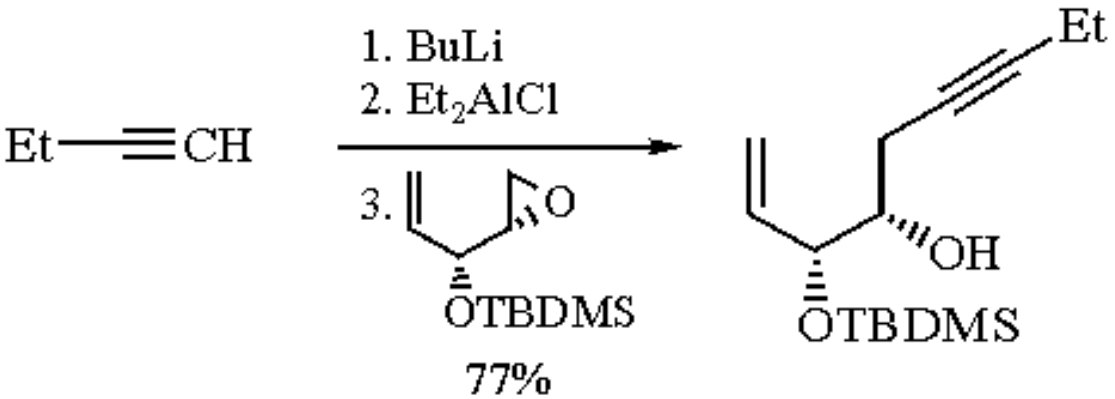

(8)

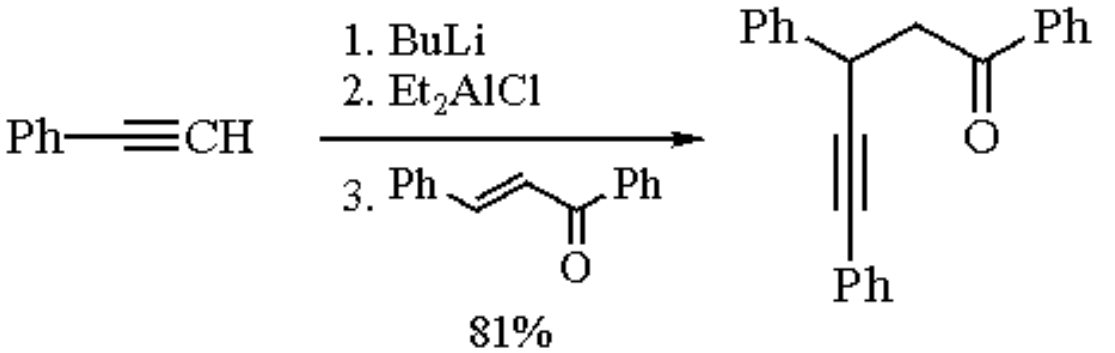

(9)

Reaction as a Nucleophile.

Et_2AlCl reacts analogously to ***Ethylmagnesium Bromide*** and transfers an ethyl group to many electrophiles. Since EtMgBr and ***Ethyllithium*** are readily available, use of Et_2AlCl to deliver an ethyl group is needed only when the stereochemistry of addition is an important issue. High levels of asymmetric induction are obtained in the conjugate addition of Et_2AlCl to unsaturated acyloxazolidinones with carbohydrate-derived chiral auxiliaries (eq 10).[18] Et_2AlCl opens epoxides to chlorohydrins.[19]

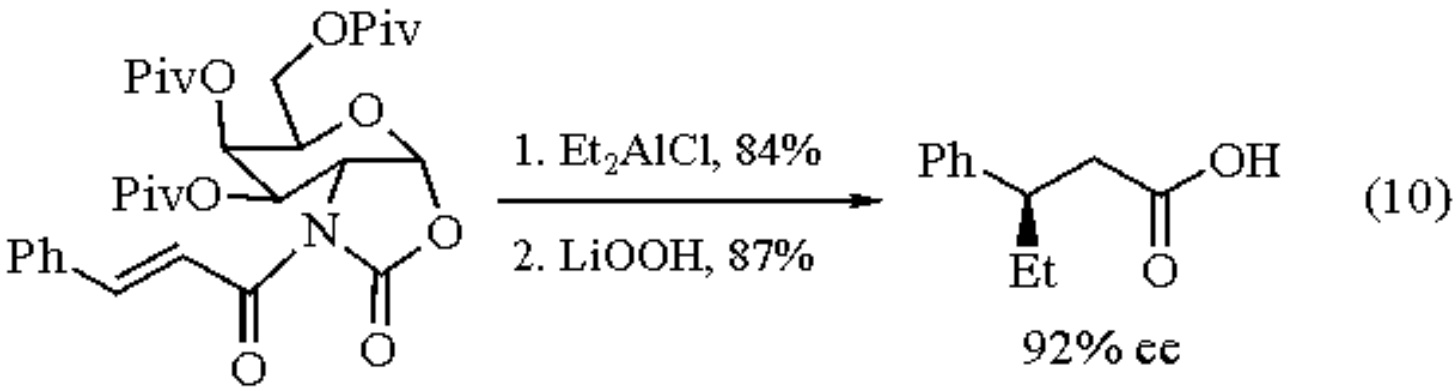

Related Reagents.

Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS.

---

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9. (a) Oppolzer, W.; Robbiani, C.; Bättig, K. *T* **1984**, *40*, 1391. (b) Oppolzer, W.; Mirza, S. *HCA* **1984**, *67*, 730.
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H. M. L.; Hu, B. *JOC* **1992**, *57*, 3186.
12. (a) McDonald, T. L.; Delahunty, C. M.; Mead, K.; O'Dell, D. E. *TL* **1989**, *30*, 1473. (b) Denmark, S. E.; Weber, E. J. *JACS* **1984**, *106*, 7970. (c) Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, N. W. *TL* **1987**, *28*, 3285.
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Diethylaluminum Cyanide[1]

Et_2AlCN

[5804-85-3] · $C_5H_{10}AlN$ · Diethylaluminum Cyanide · (MW 111.12)

(hydrocyanation of α,β-unsaturated ketones;[2] preparation of α-cyanohydrins from carbonyl compounds[3])

Physical Data: bp 162 °C/0.02 mmHg; colorless syrup; exists as a tetra- or pentamer in boiling benzene or diisopropyl ether and as a dimer in boiling THF.

Solubility: sol benzene, toluene, diisopropyl ether.

Form Supplied in: solution in toluene.

Preparative Method: by reaction of ***Triethylaluminum*** with a slight excess of ***Hydrogen Cyanide*** below rt.[1]

Handling, Storage, and Precautions: highly toxic. It can be stored as 1-2 M solutions in benzene, toluene, or diisopropyl ether. Use in a fume hood.

Hydrocyanation of α,β-Unsaturated Ketones.

Diethylaluminum cyanide is a reagent for the conjugate hydrocyanation of α,β-unsaturated ketones. The reaction is carried out simply by adding a stock solution of the reagent to a solution of the substrate α-enone in an aprotic solvent with ice cooling, and then allowing the reaction mixture to stand at rt (eqs 1 and 2).[2,3] This hydrocyanation is reversible and therefore can be controlled both kinetically and thermodynamically; that is, the product is kinetically controlled in the early stage.

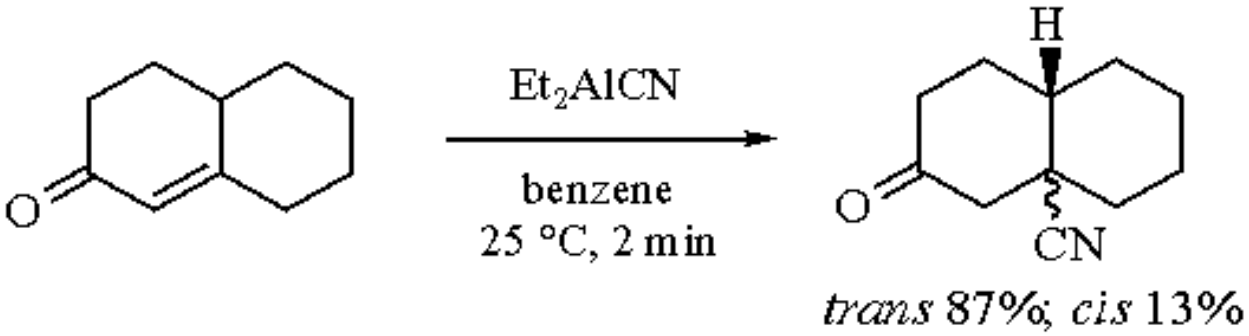

(1)

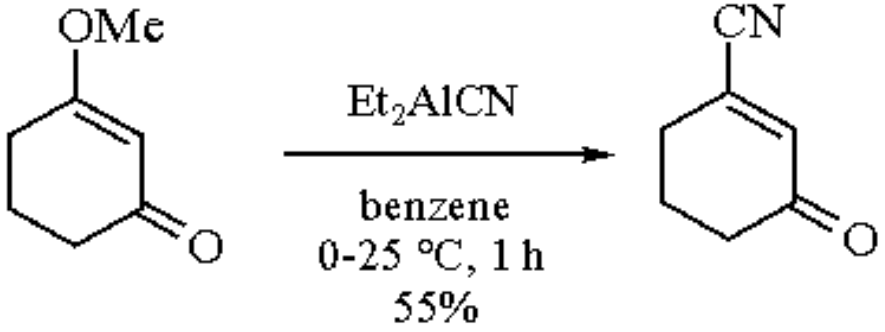

(2)

Preparation of α-Cyanohydrins from Carbonyl Compounds.

The preparation of cyanohydrins from ketones and aldehydes of low reactivity can be effected with Et_2AlCN (eq 3).[4]

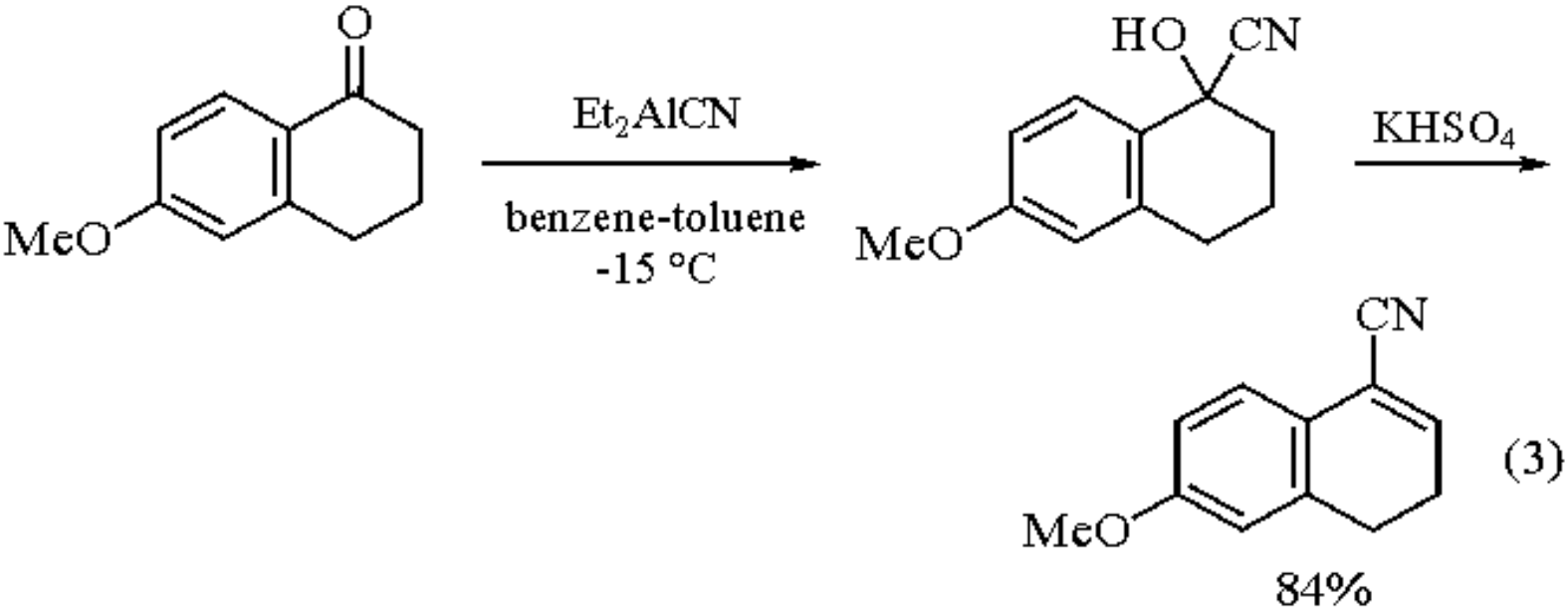

(3)

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Diethylaluminum Ethoxide[1]

Et_2AlOEt

[1586-92-1] · $C_6H_{15}AlO$ · Diethylaluminum Ethoxide · (MW 130.17)

(base for aldol condensations;[2] reducing agent for preparation of Ni catalysts[3])

Physical Data: colorless liquid; dimeric structure; mp 2.5-4.5 °C; bp 108-109 °C/10 mmHg; *d* 0.850 g cm^{-3}.

Solubility: sol hydrocarbons and ether.

Form Supplied in: commercially available, usually as a 25% solution in toluene.

Handling, Storage, and Precautions: the reagent itself is pyrophoric and its solutions are highly flammable and air and moisture sensitive and should be handled under an inert atmosphere. Use in a fume hood.

Aldol Condensations.

Diethylaluminum ethoxide is a useful base for promoting intramolecular aldol condensations in highly hindered systems. Thus 10 equiv of the reagent in toluene solution are used for effecting the condensation of polycyclic diketones (eqs 1 and 2).[2] Other bases fail to give any appreciable amount of the corresponding cyclization products.

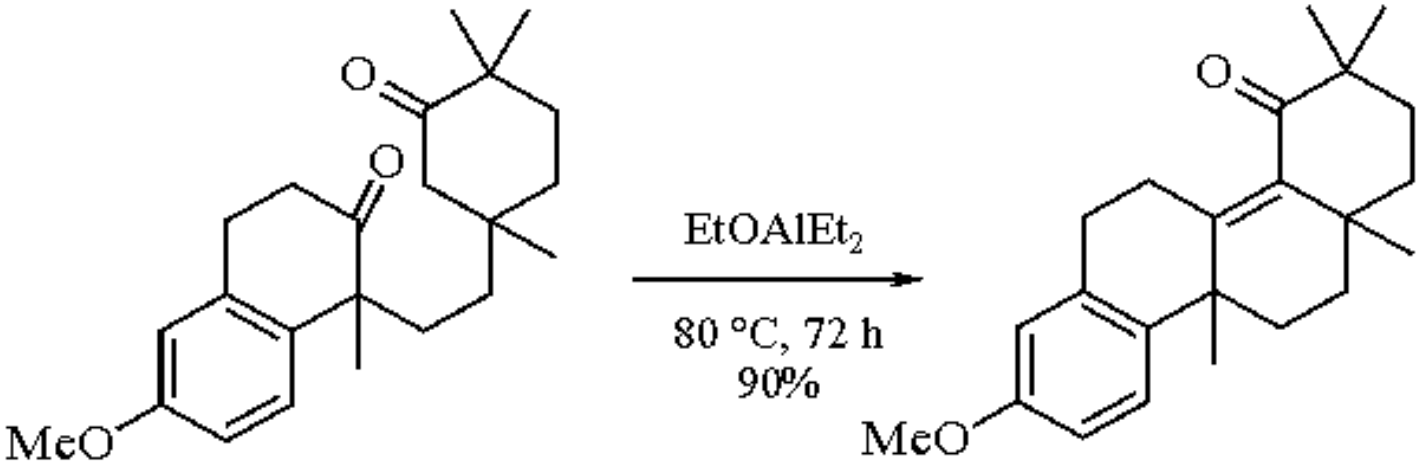

(1)

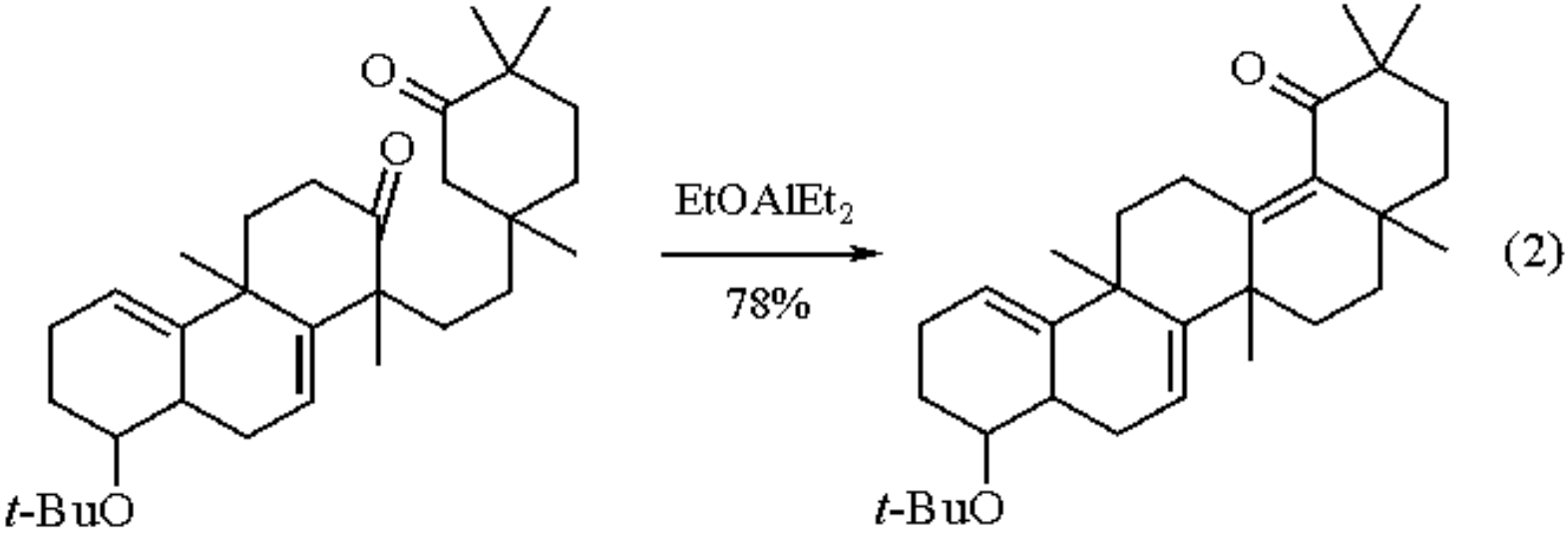

Reducing Agent.

When used to reduce $Ni(acac)_2$ to Ni^0, the reagent gives a selective catalyst for the [4 + 4] cyclodimerization of pentadienoic acid esters in the presence of 1,3-butadiene (eq 3).[3] Use of other reducing agents gives lower selectivity and greater amounts of [4 + 2] products.

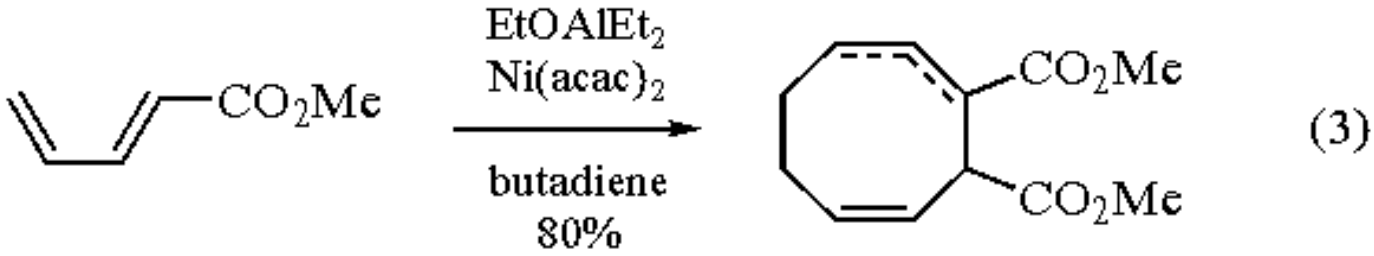

The reagent has also been used as a cocatalyst for terminal alkene isomerizations.[4]

---

1. Hirabayashi, T.; Sakakibara, T.; Ishii, Y. *JOM* **1972**, *35*, 19.
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Diethylaluminum Ethoxyacetylide

Et_2Al-C&tbond;C-OEt

[59212-00-9] · $C_8H_{15}AlO$ · Diethylaluminum Ethoxyacetylide · (MW 154.19)

(functionalized alane for the ring opening of epoxides to *trans*-ethoxyalkynyl alcohols which can be converted to *trans*-fused γ-lactones[1-3])

Solubility: sol toluene.

Preparative Method: prepared in situ by treating lithium ethoxyacetylide (generated from the reaction of equimolar amounts of ***n-Butyllithium*** and ***Ethoxyacetylene***) with an equivalent amount of ***Diethylaluminum Chloride*** in toluene at -40 °C (eq 1).[1]

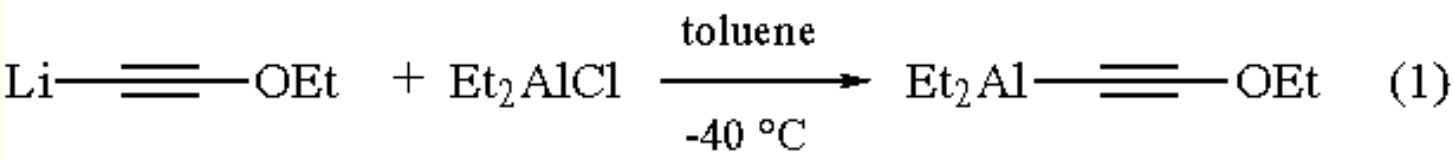

Epoxide Ring Opening and γ-Lactone Formation.

Initial studies using cyclohexene oxide and 2,3-epoxy-*trans*-decalin indicated that ring opening occurs via a *trans*-diaxial pathway (eqs 2 and 3). The stereochemistry in each case was demonstrated by converting the intermediate *trans*-ethoxyethynyl alcohols into the *trans*-γ-lactones. This reaction presumably proceeds via the corresponding hydroxy esters (eqs 4 and 5).[1]

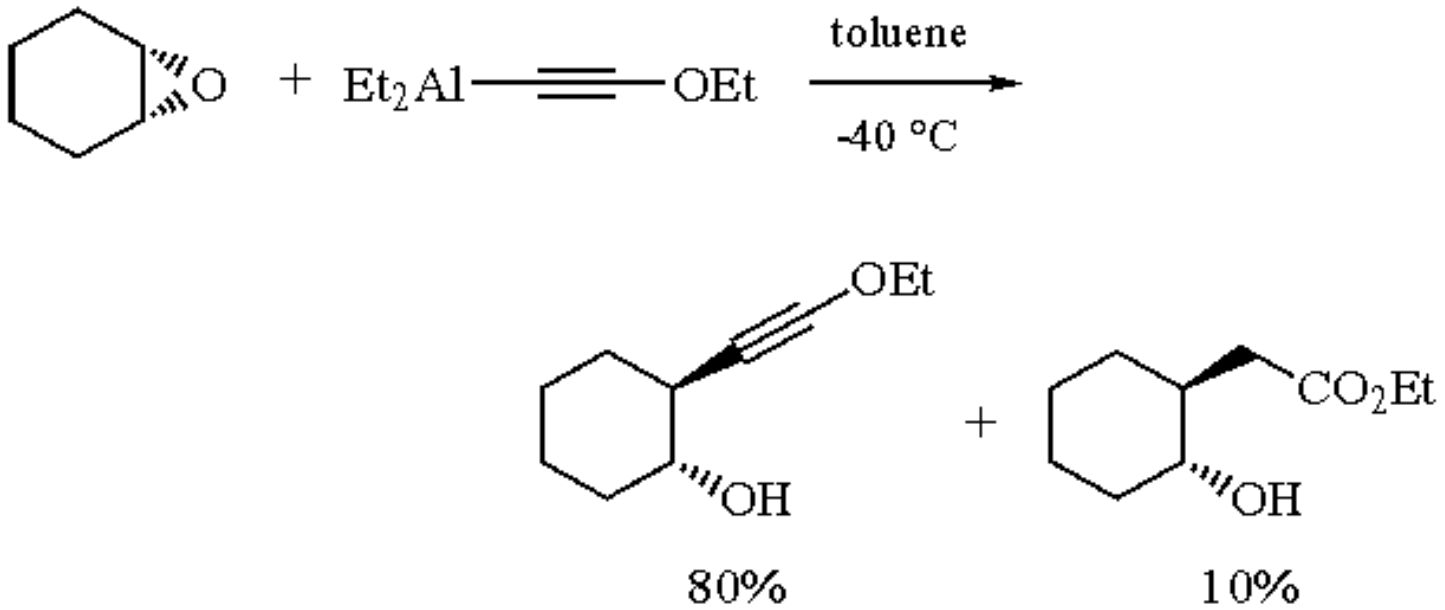
O
+ Et2Al
OEt
toluene
-40 °C
OEt
OH
+
CO2Et
OH
80%
10%

(2)

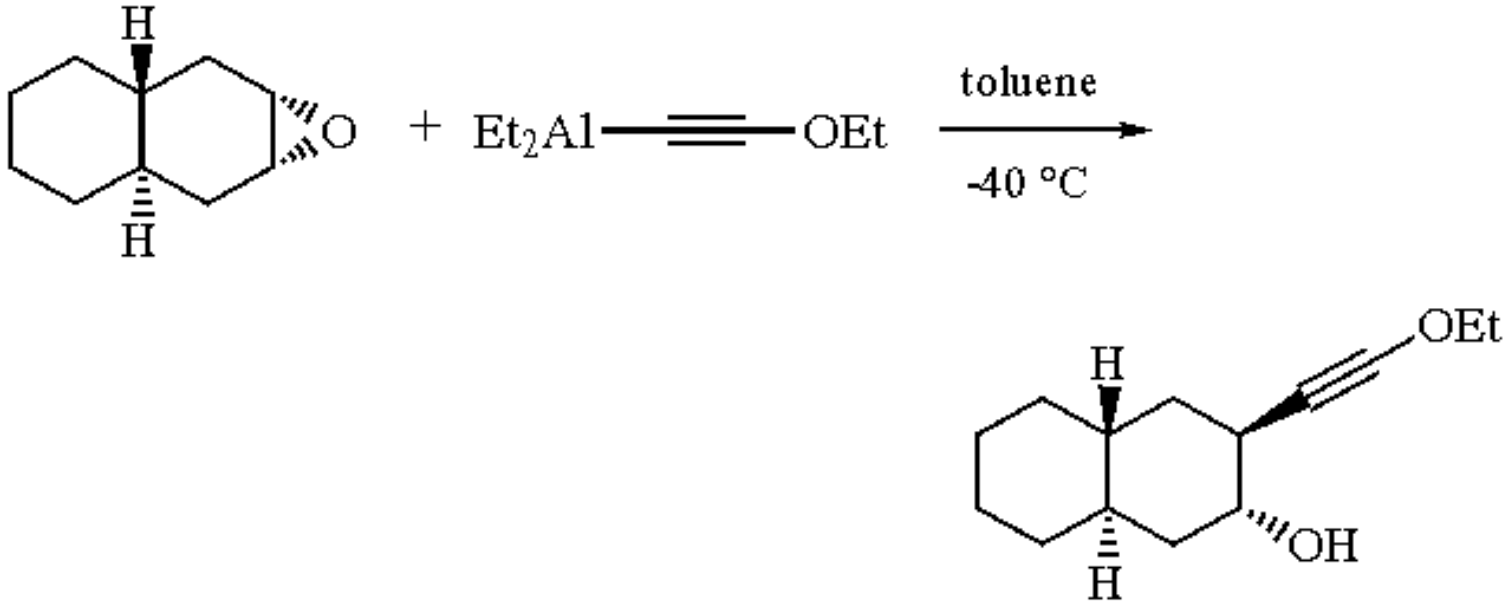
H
O
H
+ Et2Al
OEt
toluene
-40 °C
H
OEt
OH
H

(3)

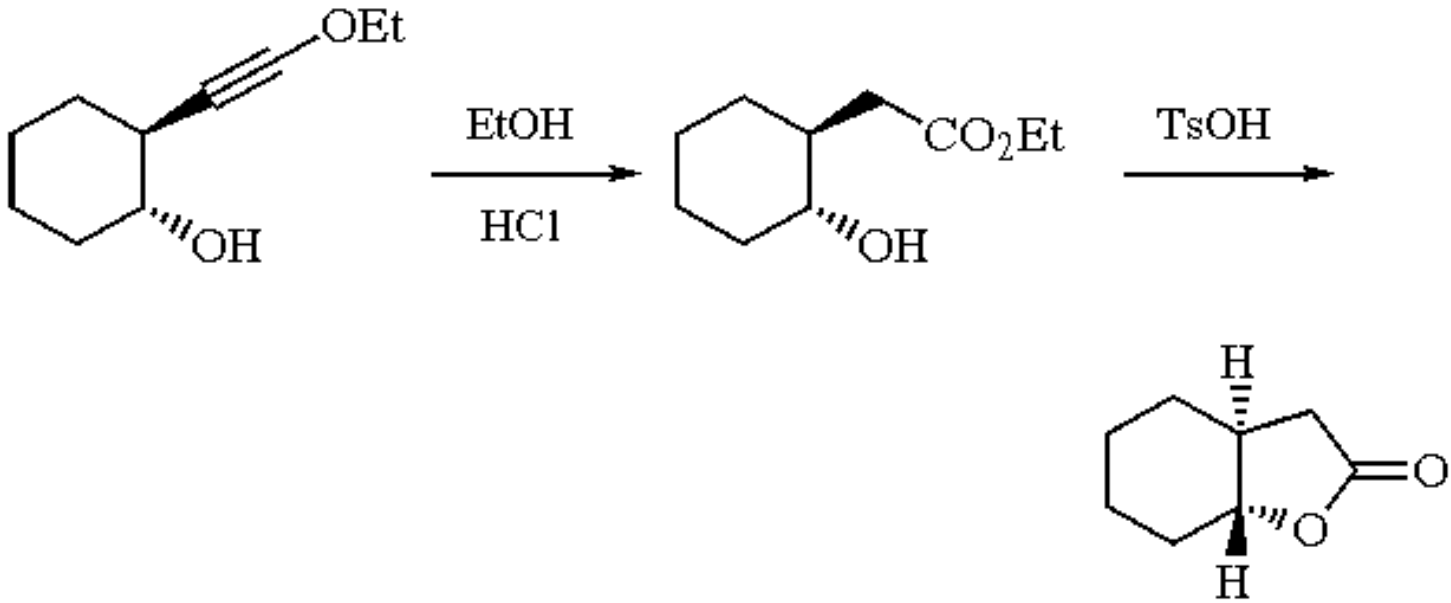
OEt
OH
EtOH
HCl
CO2Et
OH
TsOH
H
O
O
H

(4)

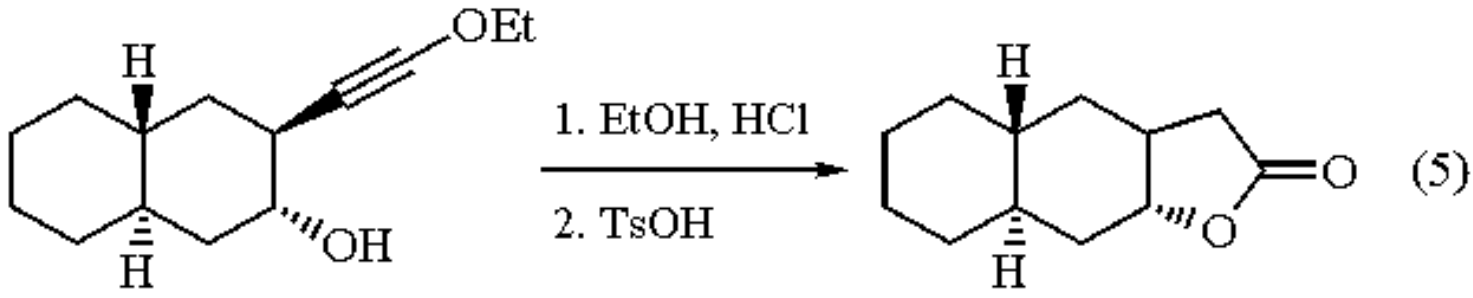

In an extension of this methodology, the epoxide ring opening was investigated in the presence of a neighboring oxygen functionality and a variety of α-hydroxycyclohexene epoxides were reacted with the alane reagent. The resultant *trans*-ethoxyalkynyl alcohols were converted into the corresponding ethyl esters by treatment with HCl/ethanol, and lactonization was effected with TsOH-benzene to give the *trans*-γ-lactones in 50-60% yield (eq 6).[2]

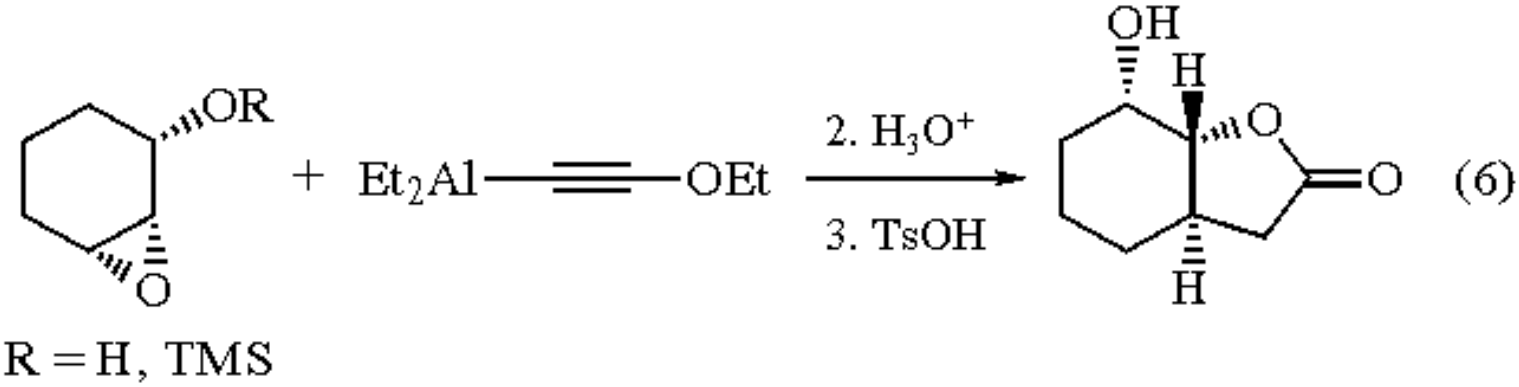

The ring opening of the α-oxygenated epoxides by the alane reagent was interpreted as being *trans*-diaxial in nature, assuming a preferred equatorial conformation of the neighboring oxygen substituent. It was noted that the course of the reaction is mainly dependent upon the stereochemical relationship of the oxy function and the epoxide and, to an insignificant extent, upon whether or not the oxygen was initially in the form of a hydroxyl or a trimethylsilyl ether. In this case, no directing effect of the neighboring oxygen functionality on the alane was observed since the attack occurs *trans* to the oxygen.

---

1. Danishefsky, S.; Kitahara, T.; Tsai, M.; Dynak, J. *JOC* **1976**, *41*, 1669.
2. Danishefsky, S.; Tsai, M.; Kitahara, T. *JOC* **1977**, *42*, 394.
3. Bartel, S.; Bohlmann, F. *TL* **1989**, *30*, 685.

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Diethylaluminum Iodide

Et_2AlI

[2040-00-8] · $C_4H_{10}AlI$ · Diethylaluminum Iodide · (MW 212.01)

(ethylating agent; catalyst)

Alternate Names: diethyliodoaluminum; diethyliodoalane.

Physical Data: bp 118-120 °C/4 mmHg; *d* 1.609 g cm^{-3}.

Solubility: sol toluene, benzene.

Form Supplied in: colorless liquid; commercially available, either neat or in toluene solution.

Preparative Methods: by reaction of ***Triethylaluminum*** and ***Aluminum Iodide*** in THF or benzene.[1]

Handling, Storage, and Precautions: moisture-sensitive and pyrophoric. Reacts with water to form an explosive and flammable gas. Extremely harmful if vapors are inhaled. The reagent is absorbed through skin. Wear gloves. Corrosive. Air-sensitive; must be stored under inert atmosphere. Use in a fume hood.

Addition to a Carbonyl Group.

In using the reagent to deliver the ethyl group to a carbonyl, there appears to be a preference for equatorial attack on cyclohexanones (eq 1).[1] A preference was also noted for 1,2-attack over 1,4-attack (eq 2).

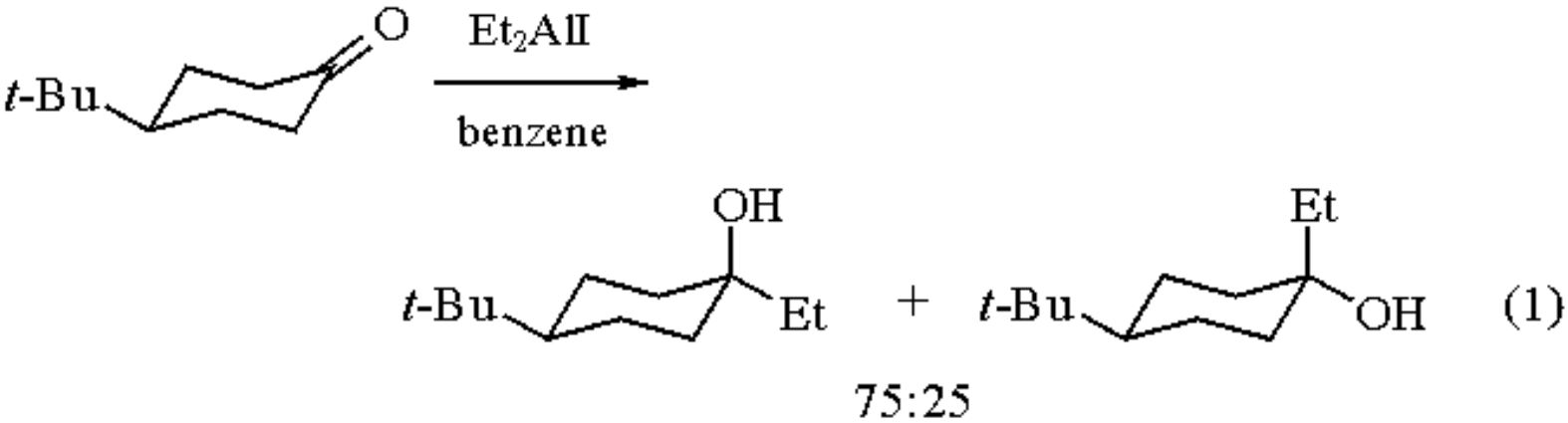

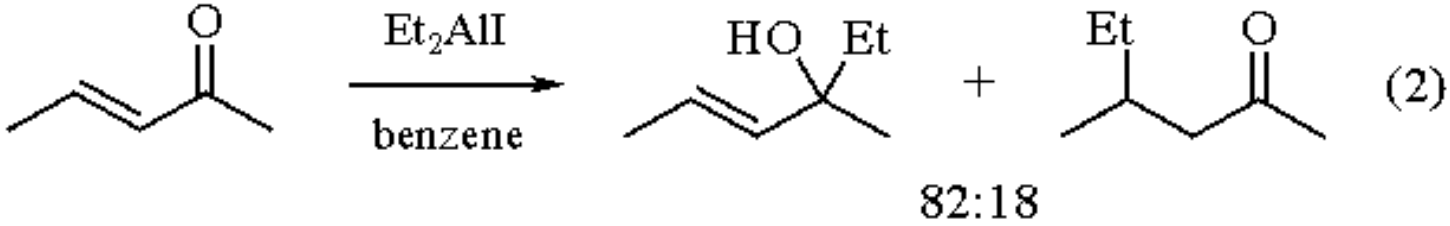

Addition to a Carbanion.

An alkylation-deoxygenation reaction provides an interesting approach to substituted alkenes from epoxides (eq 3).[2]

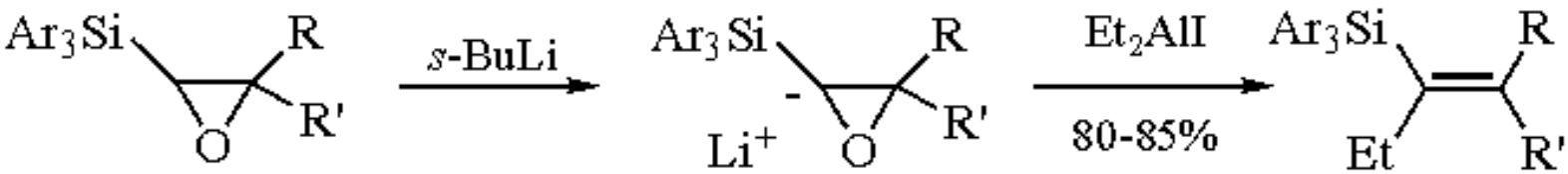

(3)

R = R' = H, 3%*; R = Me, R' = H, 13%*; R = H, R' = Me, 92%
* Major product has I adding rather than Et

Aldol-Type Reactions.

Diethylaluminum iodide-catalyzed reaction of aldehydes with α,β-unsaturated carbonyl compounds provides a useful entry into molecules of the types shown in eqs 4-7.[3]

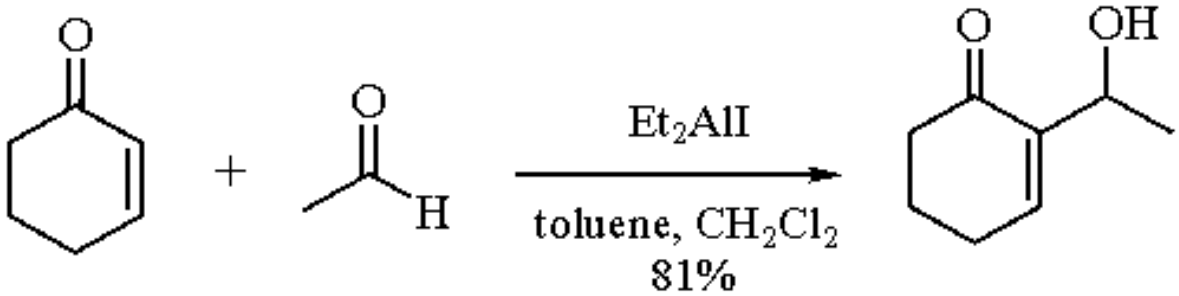

(4)

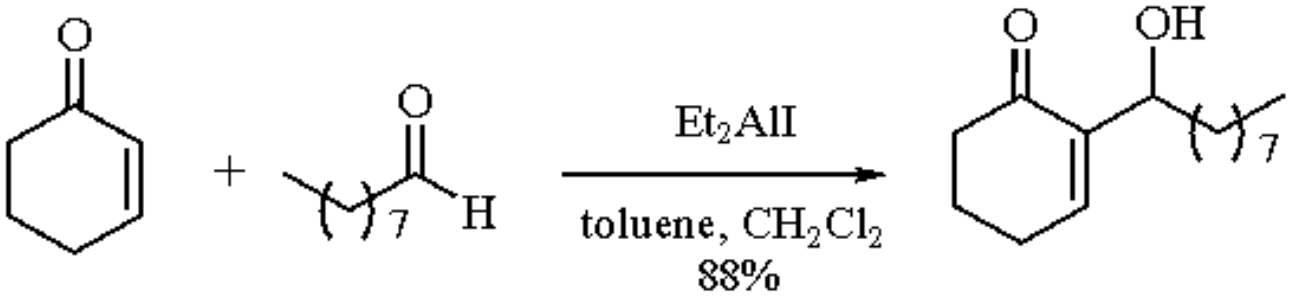

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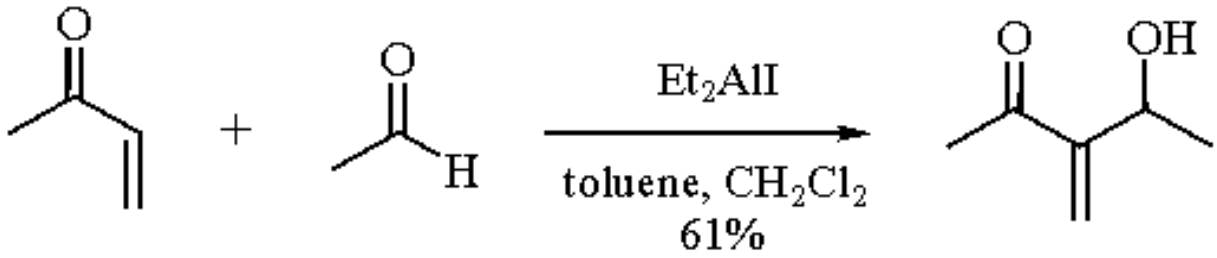

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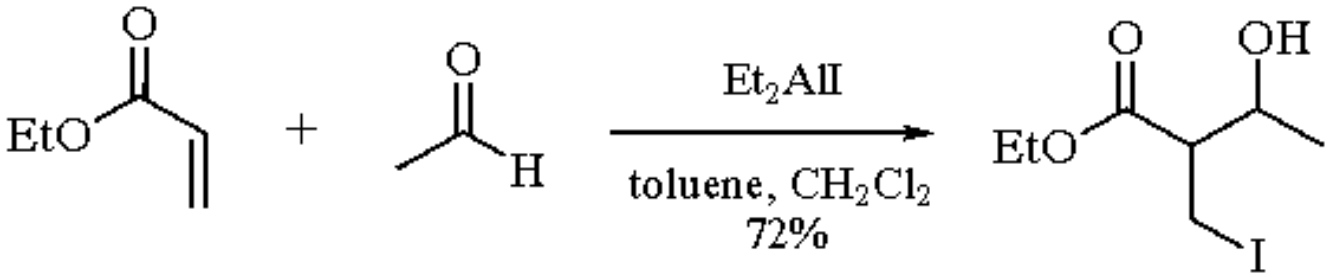

(7)

Beckmann Rearrangement.

Diethylaluminum iodide is a useful catalyst for conversions of the general type shown in eq 8.[4]

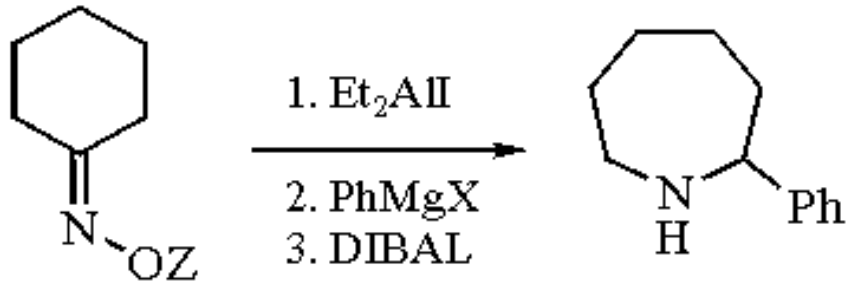

(8)

Z = Ms, 81%; CO_2Et, 17%; Ac, 0%

Related Reagents.

Diethylaluminum Chloride; ***Dimethylaluminum Chloride***; ***Dimethylaluminum Iodide***; ***Ethylaluminum Dichloride***; ***Methylaluminum Dichloride***.

---

1. Ashby, E. C; Noding, S. A. *JOC* **1979**, *44*, 4792.
2. Taniguchi, M.; Oshima, K.; Utimoto, K. *TL* **1991**, *32*, 2783.
3. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *BCJ* **1981**, *54*, 274.
4. Ishida, Y.; Sasatani, S.; Maruoka, K.; Yamamoto, H. *TL* **1983**, *24*, 3255.

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Colby College, Waterville, ME, USA

Diethylaluminum 2,2,6,6-Tetramethylpiperidide

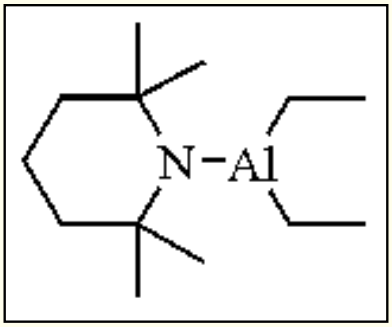

[54159-47-6] · $C_{13}H_{28}AlN$ · Diethylaluminum 2,2,6,6-Tetramethylpiperidide · (MW 225.35)

(combined Lewis acid-base reagent for oxygen-containing functional groups; can isomerize epoxides[1] and oxetanes;[3] can function as a base;[4] can enolize *meso*-cyclic acetals[5])

Alternate Name: DATMP.

Solubility: sol benzene, toluene, hexane, CH_2Cl_2.

Form Supplied in: prepared and used in situ.

Preparative Method: prepared in situ from ***Diethylaluminum Chloride*** and ***Lithium 2,2,6,6-Tetramethylpiperidide*** in benzene at 0 °C.[1]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. Use in a fume hood.

Isomerization of Epoxides to Allylic Alcohols.

This reaction is usually carried out with a lithium dialkylamide base (see ***Lithium Diethylamide***). However, organoaluminum amides of the type $Et_2AlNR^1R^2$ are also highly effective because of the high affinity of aluminum for oxygen. Among various organoaluminum amides, DATMP is the most satisfactory with respect to reactivity and selectivity.[1] The reagent effects the isomerization of (*E*)-cyclododecene oxide to (*E*)-2-cyclododecen-1-ol in 99% yield under very mild conditions (eq 1). The effectiveness of DATMP is clearly demonstrated by comparison with other organoaluminum amides in the conversion of (*E*)-cyclododecene oxide to (*E*)-2-cyclododecen-1-ol in benzene at 0 °C for 1 h: $Et_2AlN(i\text{-}Pr)_2$, 65%; Et_2AlNCy_2, 36%; Et_2AlNEt_2, 5%; $i\text{-}Bu_2AlNPh_2$, 48%; $i\text{-}Bu_2AlNMePh$, 69%; $i\text{-}Bu_2AlN(i\text{-}Pr)_2$, 30%. 6,7-Epoxygeraniol and squalene terminal epoxide give (*E*)-3,7-dimethyl-2,7-octadiene-1,6-diol and

(6*E*,10*E*,14*E*,18*E*)-2,6,10,15,19,23-hexamethyl-1,6,10,14,18,22-tetracosahexaen-3-ol, respectively, in high yields under very mild conditions (eqs 2 and 3). Notably, no cyclized byproducts are observed in these two cases. Unfortunately, the oxides of cyclopentene, cyclohexene, and cycloheptene are stable under similar reaction conditions.

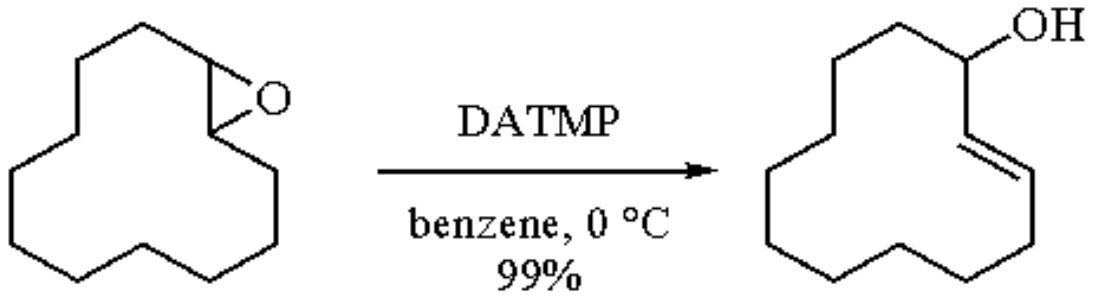

(1)

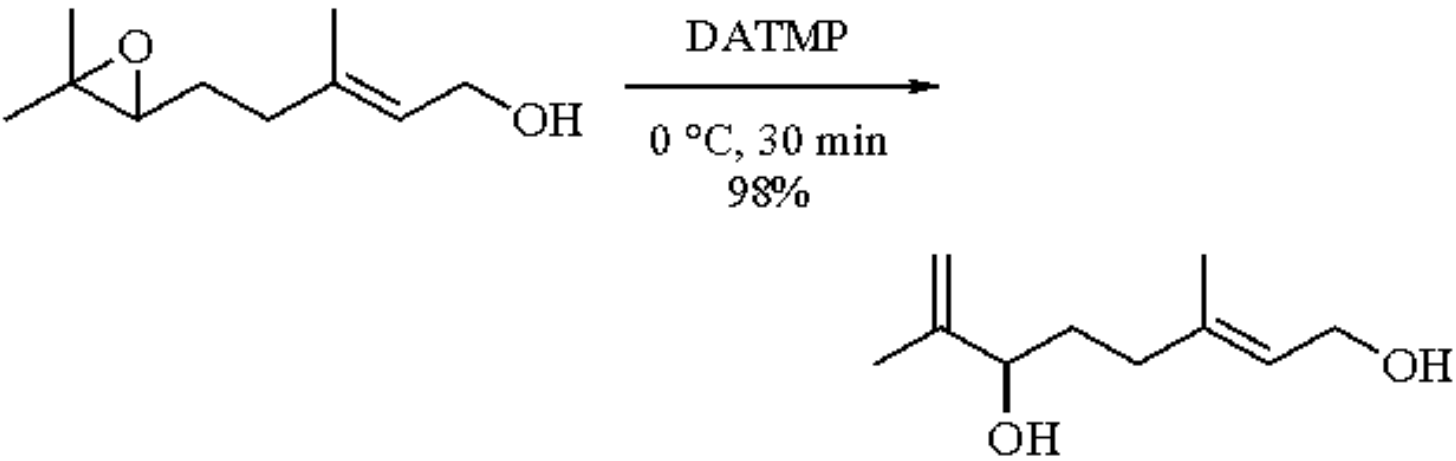

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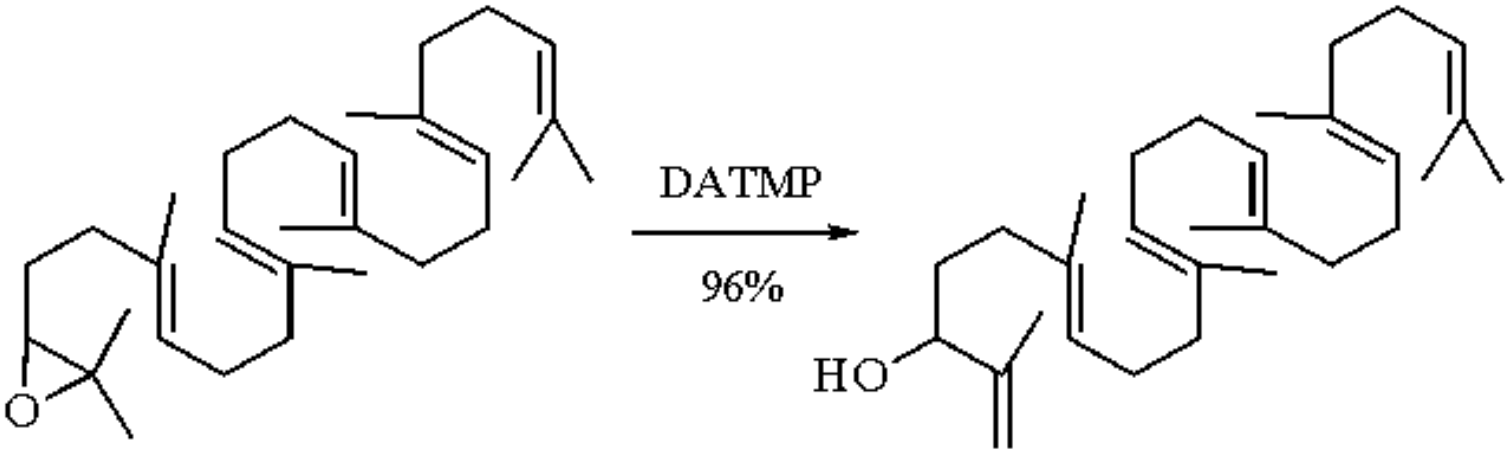

(3)

DATMP enables the regioselective isomerization of trisubstituted epoxides. Thus (*Z*)-6-methyl-5-undecene oxide is converted to the disubstituted allylic alcohol in high yield, while its (*E*)-isomer is transformed mainly into the trisubstituted allylic alcohol (eqs 4 and 5).[1] The bulk of the amide base may play a significant role in determining the course of the isomerization.

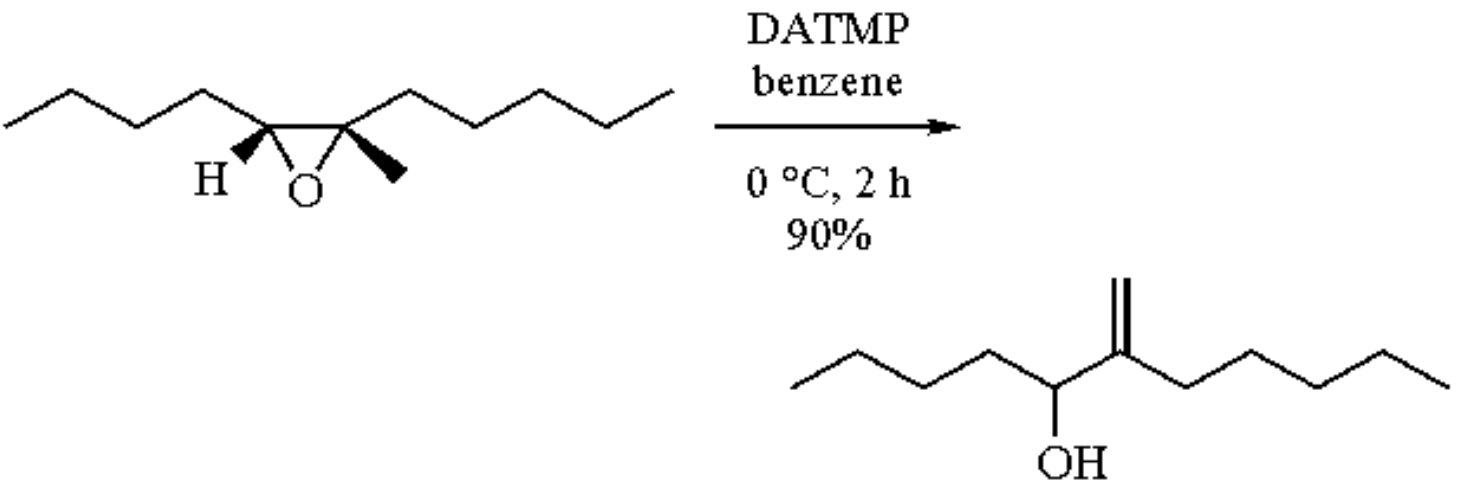

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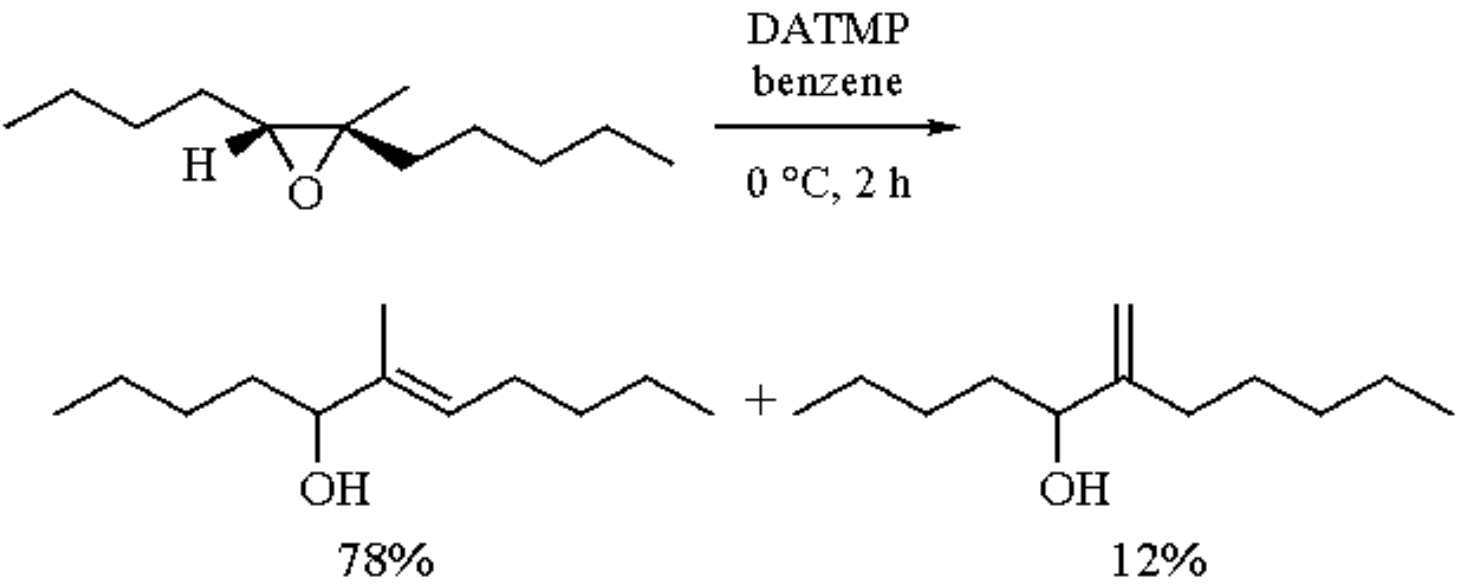

(5)

The remarkable selectivity inherent in DATMP is further demonstrated by the selective transformation of diepoxyfarnesol. Thus diepoxyfarnesol gives (*E*)-3,11-dimethyl-7-methylene-2,11-dodecadiene-1,6,10-triol upon exposure to lithium diethylamide, while treatment of the diepoxide with DATMP affords (2*E*,7*E*)-3,7,11-trimethyl-2,7,11-dodecatriene-1,6,10-triol as the sole isolable product (eq 6).

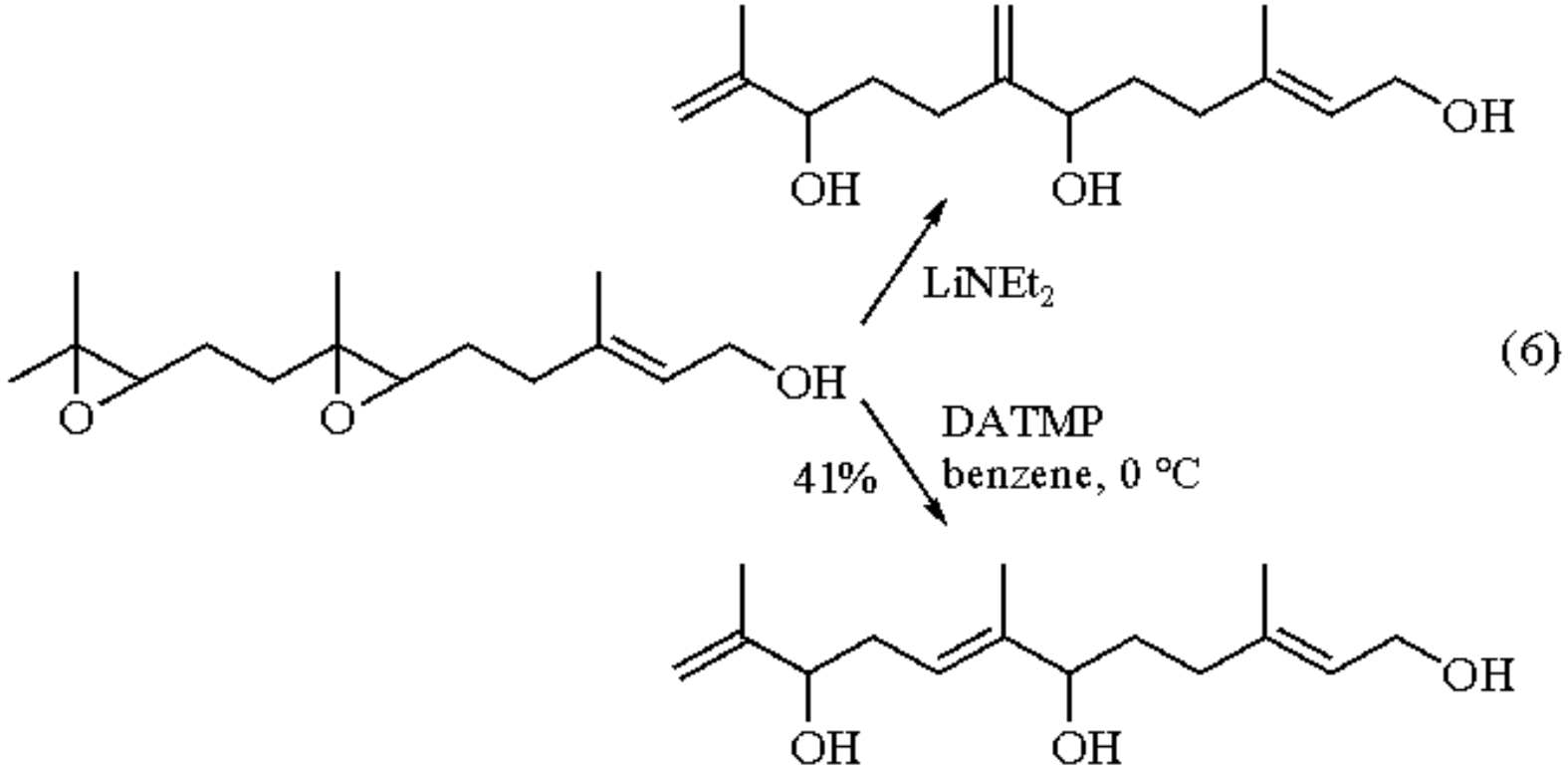

1,3-Diene Synthesis.

DATMP has been applied to a 1,3-diene synthesis which involves: (1) epoxidation of an allylic alcohol with ***t-Butyl Hydroperoxide*** in the presence of a vanadium catalyst followed by trimethylsilylation; (2) selective epoxide opening by means of DATMP and subsequent desilylation, producing a 3-ene-1,2-diol; and (3) removal of both hydroxy groups through bromination with a mixture of ***Phosphorus(III) Bromide*** and ***Copper(I) Bromide*** followed by ***Zinc*** debromination.[2] The reaction sequence has been used for the synthesis of β-myrcene from nerol, *trans*-β-ocimene from geraniol, and α- and β-farnesenes from their biological precursors (eqs 7 and 8). A C_{12} sex pheromone of red bollworm moth has been prepared efficiently using this methodology.

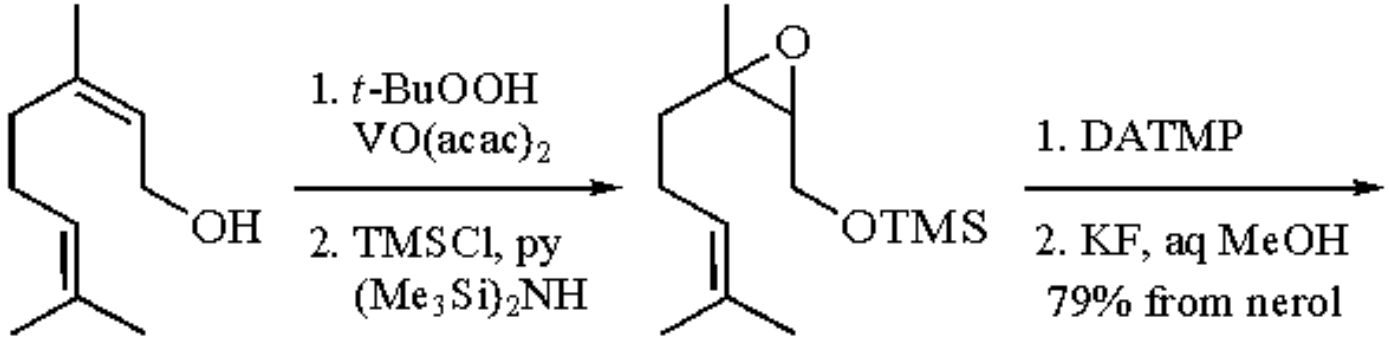

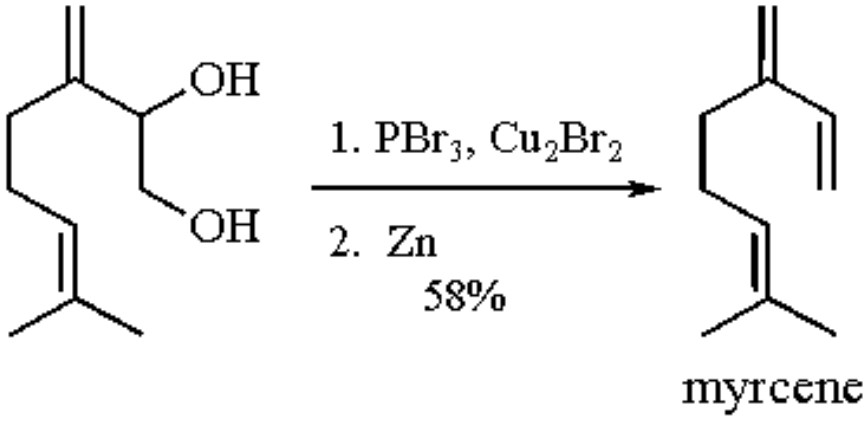

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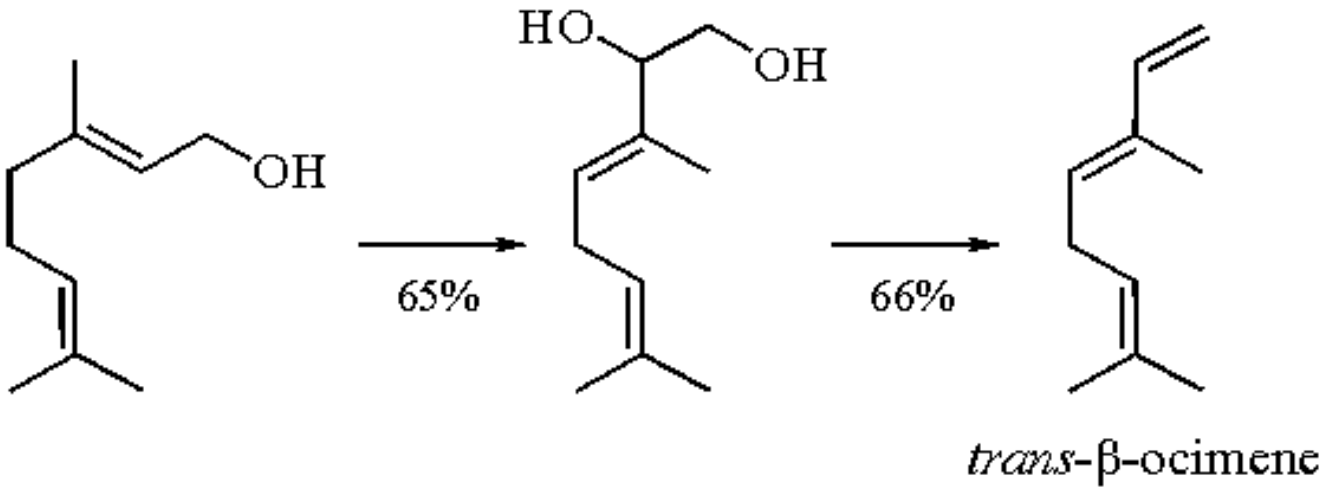

(8)

Conversion of Oxetanes to Homoallylic Alcohols.

Oxetanes can also be cleaved by organoaluminum amides, particularly by diethylaluminum methylanilide, providing (*E*)-homoallylic alcohols (eqs 9 and 10).[3] A higher reaction temperature and a longer reaction time are required compared to the epoxide cleavage. With this methodology, a fundamental medium ring sesquiterpene, humulene, has been synthesized in a highly stereoselective manner (eq 11).

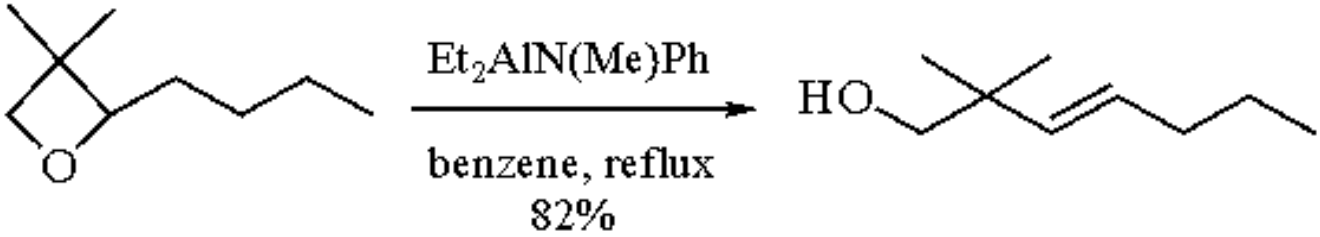

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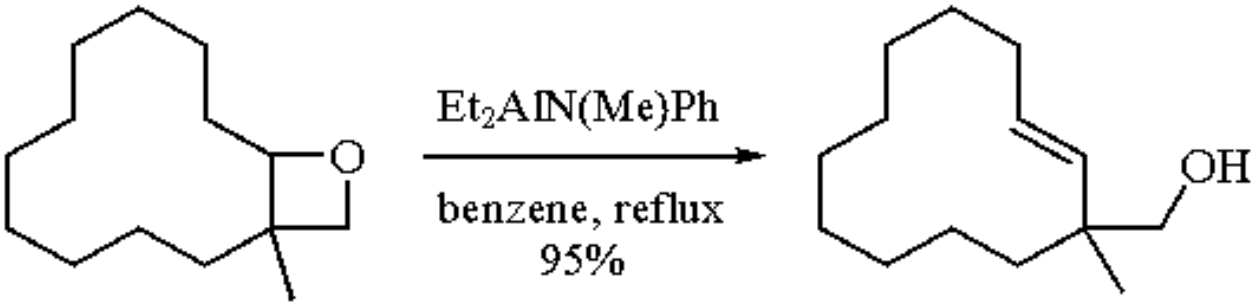

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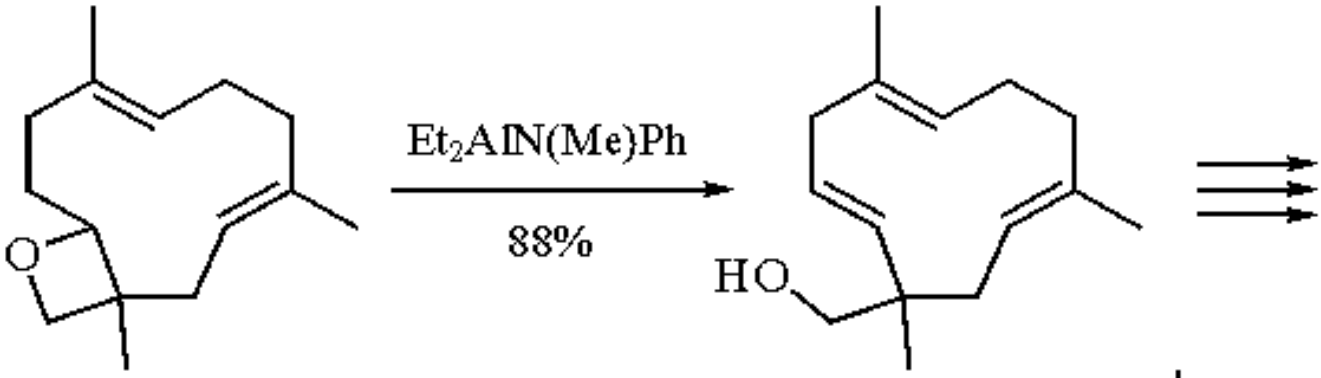

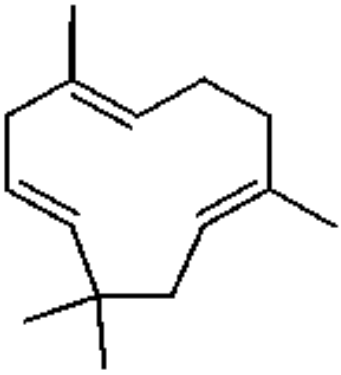

(11)

humulene

Aluminum Enolates.

Organoaluminum enolates are conveniently prepared from carbonyl substrates such as ketones and *t*-butyl acetate using DATMP as the base. Subsequent addition of aldehydes and ketones affords the desired aldol adducts in good yields (eqs 12 and 13).[4]

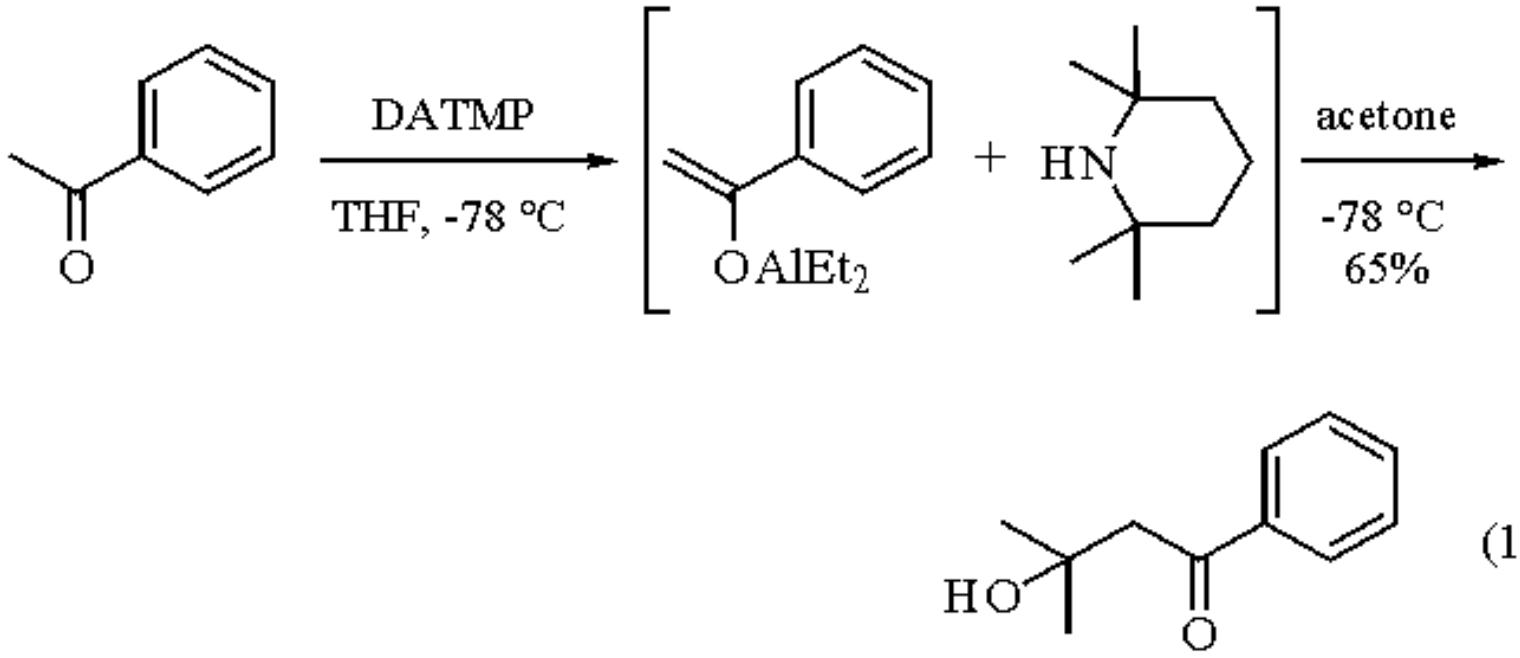

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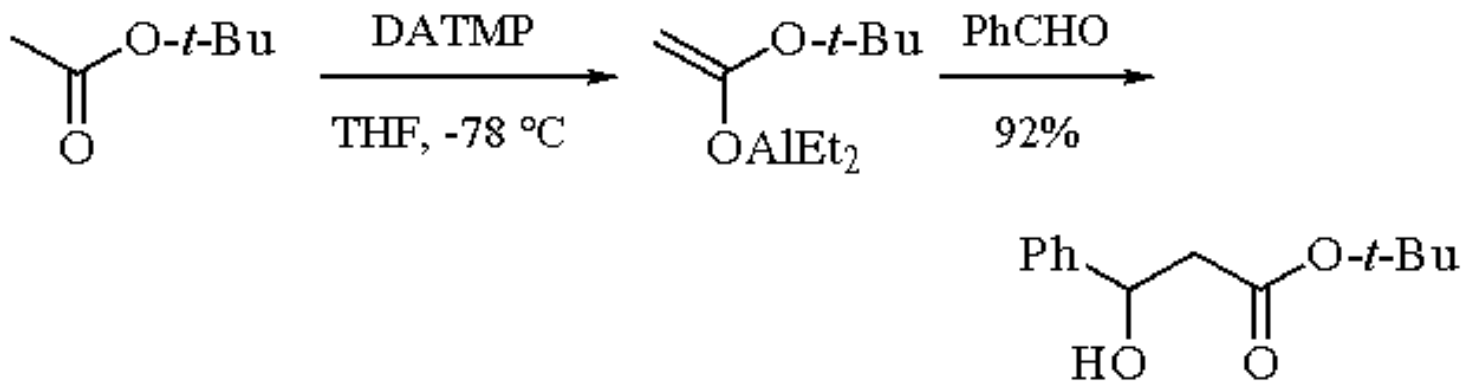

(13)

Asymmetric enolization of *meso*-cyclic acetals of (2*R*,4*R*)-pentanediol is effected with a series of trialkylaluminums and organoaluminum amides (eq 14).[5] Among a series of organoaluminum amides, diisobutylaluminum *t*-butyl(*t*-butylcyclohexylmethyl)amide is most effective for this transformation.

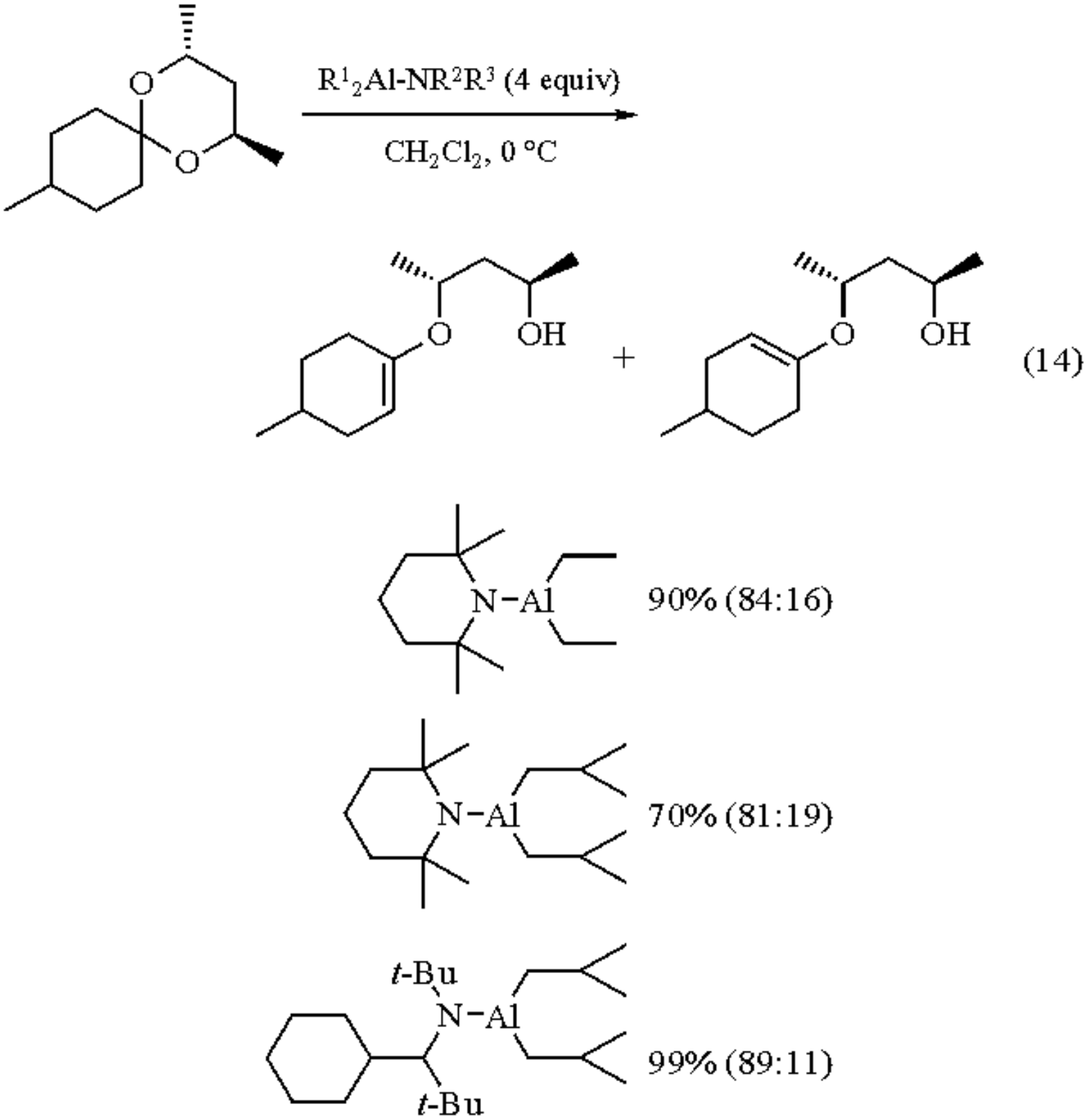

Polymerization.

The DATMP reagent can be used as a polymerization catalyst for ethylene and propylene.[6]

1. (a) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *JACS* **1974**, *96*, 6513. (b) Yasuda, A.; Yamamoto, H.; Nozaki, H. *BCJ* **1979**, *52*, 1705.
2. (a) Tanaka, S.; Yasuda, A.; Yamamoto, H.; Nozaki, H. *JACS* **1975**, *97*, 3252. (b) Yasuda, A.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *BCJ* **1979**, *52*, 1752.
3. Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *JACS* **1977**, *99*, 3864.
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6. Langer, A. W.; Burkhardt, T. J.; Steger, J. J. *Polym. Sci. Technol.* **1983**, 225.

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Diethylaluminum Thiophenoxide[1]

Et_2AlSPh

[58921-09-8] · $C_{10}H_{15}AlS$ · Diethylaluminum Thiophenoxide · (MW 194.30)

(preparation of *O*,*S*-acetals, catalyst for Claisen rearrangements;[3,4] 1,4-addition to vinyl epoxides[7])

Solubility: sol hexane, toluene.

Form Supplied in: generated in situ from commercially available materials.

Preparative Method: prepared by the reaction of ***Triethylaluminum*** in toluene with 1.2 equiv of ***Thiophenol*** (0 °C, 20 min),[2] or similarly in hexane solution (25 °C, 20 min).[3]

Handling, Storage, and Precautions: moisture sensitive. It is typically prepared in situ and used directly. Use in a fume hood.

Claisen Rearrangement.[3,4]

Allyl vinyl ethers undergo Claisen rearrangement in the presence of 2.5 equiv of the title reagent in 67-86% yields under extremely mild conditions (15 min to 1 h, 25 °C), as shown in eq 1. Similar results are obtained with ***Diethylaluminum Chloride-Triphenylphosphine***, but no rearrangement is observed with Et_2AlSEt. The (*E*/*Z*) selectivity is not impressive; better selectivity is observed with sealed tube thermolyses.[4]

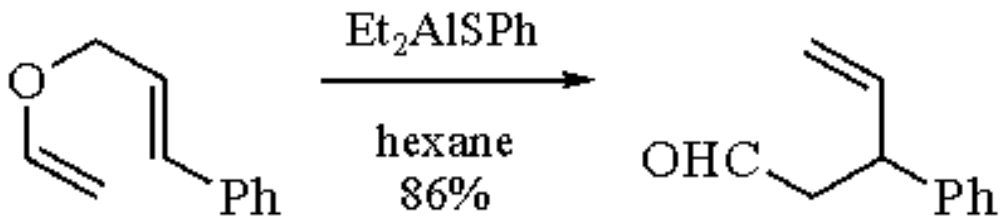

(1)

1,3-Cycloalkanediones.[5]

δ-Alkylidene-δ-lactones and an ε-alkylidene-ε-lactone have been converted to 1,3-diones, probably

via aluminum enolates (eq 2). These reactions are also effected with dimethylaluminum thioethoxide and ***Dimethylaluminum Methylselenolate***, but less effectively with iodomagnesium thiophenoxide and lithium thiophenoxide.

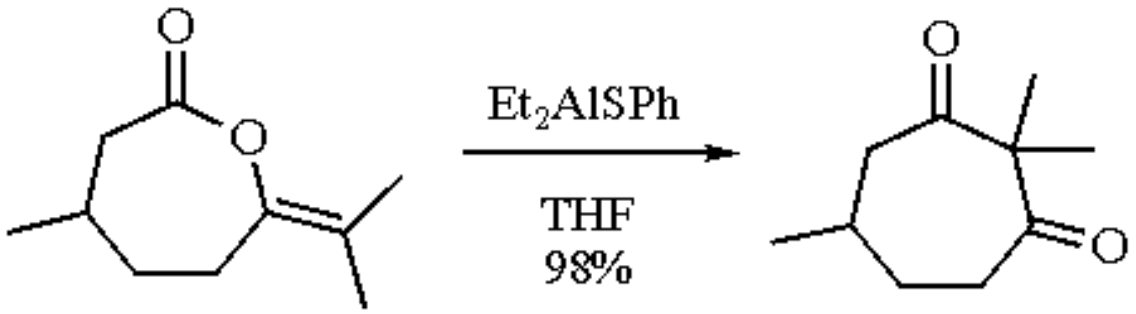

(2)

O,S-Acetals.[2,6]

Acetals have been cleanly converted to *O,S*-acetals in 63-89% yields using diethylaluminum thiophenoxide (eqs 3-5).

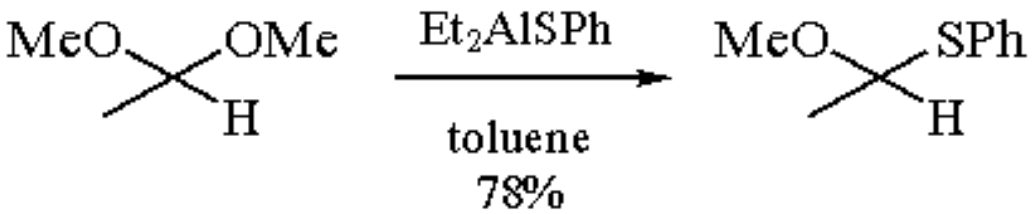

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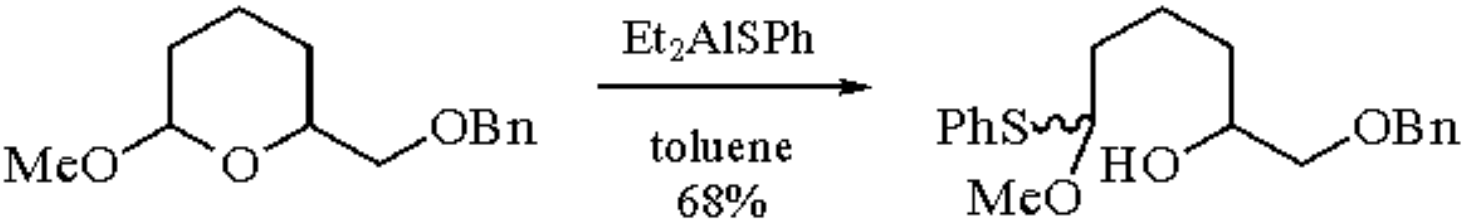

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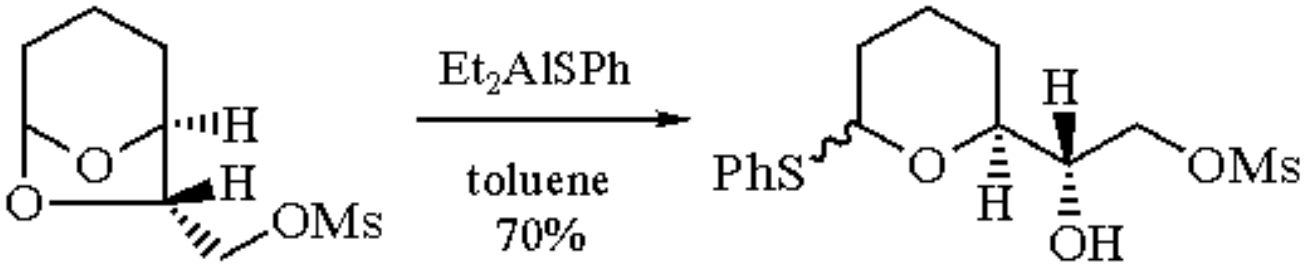

(5)

Reaction with Vinyl Epoxides.[7]

The reagent adds regio- and stereoselectively to vinyl epoxides in 1,4-fashion to afford (*Z*)-4-phenylthio-2-buten-1-ols at rt (eq 6). Performing the reaction at -78 °C in toluene or using polar solvents such as ether and

THF results in much reduced regio- and stereoselectivity. This stereoselectivity complements the reaction of the same vinyl epoxides with ***Thiophenol*** and ***Triethylamine*** in methanol, which gives almost exclusively the (*E*)-isomer. The products can be alkylated at the 4-position or converted into furans by oxidation with ***Lead(IV) Acetate***.

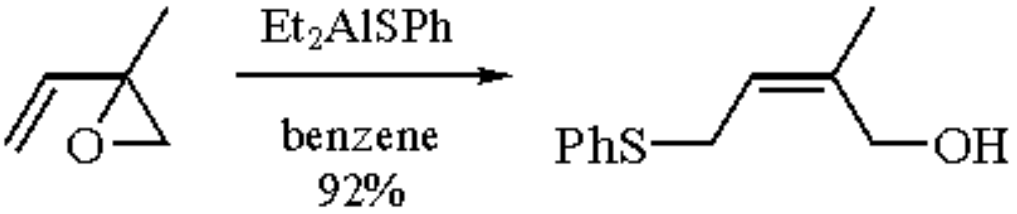

(6)

Rearrangement of Pinacol Monoacetates.[8]

Upon treatment with the title reagent, vicinal diol derivatives afford rearrangement products with different regioselectivity when compared to acid-catalyzed pinacol rearrangement. For example, 1,1-diphenyl-2-acetoxy-1-hydroxypropane affords 72% of 2-phenylpropiophenone and 24% of 2,2-diphenylacetone, while 1,1-diphenyl-1,2-dihydroxypropane affords 80% of 2,2-diphenylacetone as the sole product upon acid catalysis (eqs 7 and 8).

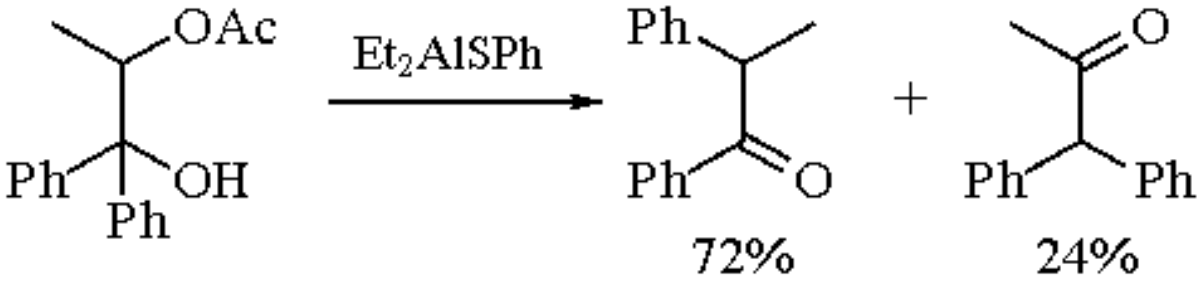

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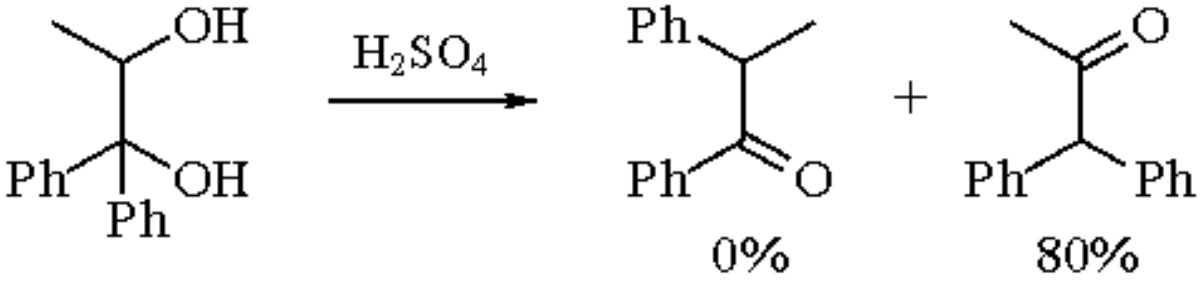

(8)

2-Methyl-5-methylene-2-vinyltetrahydrofuran and 2,5-dimethyl-2-vinyl-2,3-dihydrofuran afford 3-methyl-1-phenylthio-2-hepten-6-one (eq 9).[9]

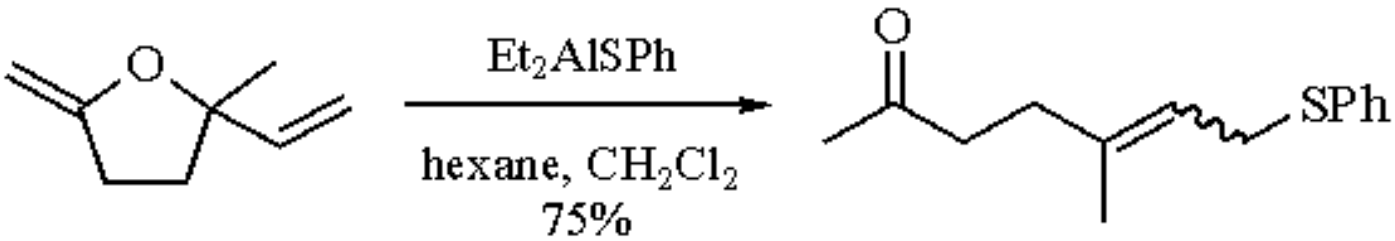

(9)

1. Fieser, M. *FF 10*, 281; *11*, 542; *12*, 343.
2. Masaki, Y.; Serizawa, Y.; Kaji, K. *CL* **1985**, 1933.
3. Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *BCJ* **1984**, *57*, 446.
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N,N-Diethylaminoacetonitrile[1]

Et_2NCH_2CN

[3010-02-4] · $C_6H_{12}N_2$ · *N,N*-Diethylaminoacetonitrile · (MW 112.17)

(application as formyl anion and formaldehyde dianion equivalents; synthesis of α-amino nitriles, α-amino-β-hydroxy nitriles, aldehydes, ketones, and α,β-enals)

Physical Data: bp 53 °C/10 mmHg,[2] 61-63 °C/14 mmHg,[3] 170 °C;[4] *d* 0.866 g cm^{-3}.

Solubility: sol water and most common organic solvents.

Form Supplied in: liquid; commercially available.

Preparative Method: prepared from diethylamine, formaldehyde, sodium cyanide, and sodium disulfite.[3]

Handling, Storage, and Precautions: is an organic cyanide and should be handled with due care in a fume hood.

Lithiation.

Lithio-*N,N*-diethylaminoacetonitrile *[67685-64-7]* is generated from *N,N*-diethylaminoacetonitrile using ***Lithium Diisopropylamide*** in ether or THF at -78 °C.

Alkylation.

Lithio-*N,N*-diethylaminoacetonitrile functions as a formyl anion equivalent. Other analogs of *N,N*-diethylaminoacetonitrile having different alkyl groups on nitrogen have been reviewed elsewhere.[1] Alkylation of *N,N*-diethylaminoacetonitrile with alkyl chlorides, bromides, iodides, and tosylates,[5,6] as well as Michael acceptors, and hydrolysis of the monoalkylation and dialkylation products with ***Oxalic Acid***,[5] ***Copper(II) Sulfate***,[5,7] or ***Hydrochloric Acid***[6] in aqueous THF, furnishes aldehydes and ketones, respectively. Oxalic acid[5] will not hydrolyze dialkylation products unless β,γ-unsaturation is present. The deprotection method using copper(II) sulfate leaves acetal groups intact and allows the preparation of keto aldehyde acetals (eq 1).[5] Alkylation with allylic bromides followed by hydrolysis proceeds with concomitant isomerization of the alkene to afford α,β-unsaturated aldehydes.[8] Similar alkylations with epoxides followed by acid-catalyzed hydrolysis proceed with concomitant dehydration to provide α,β-unsaturated aldehydes.[5] An unusual addition to azulene and a subsequent oxidation and hydrolysis of the amino nitrile

with aqueous ***Silver(I) Nitrate*** furnishes a mixture of 4- and 6-azulenecarbaldehydes.[9]

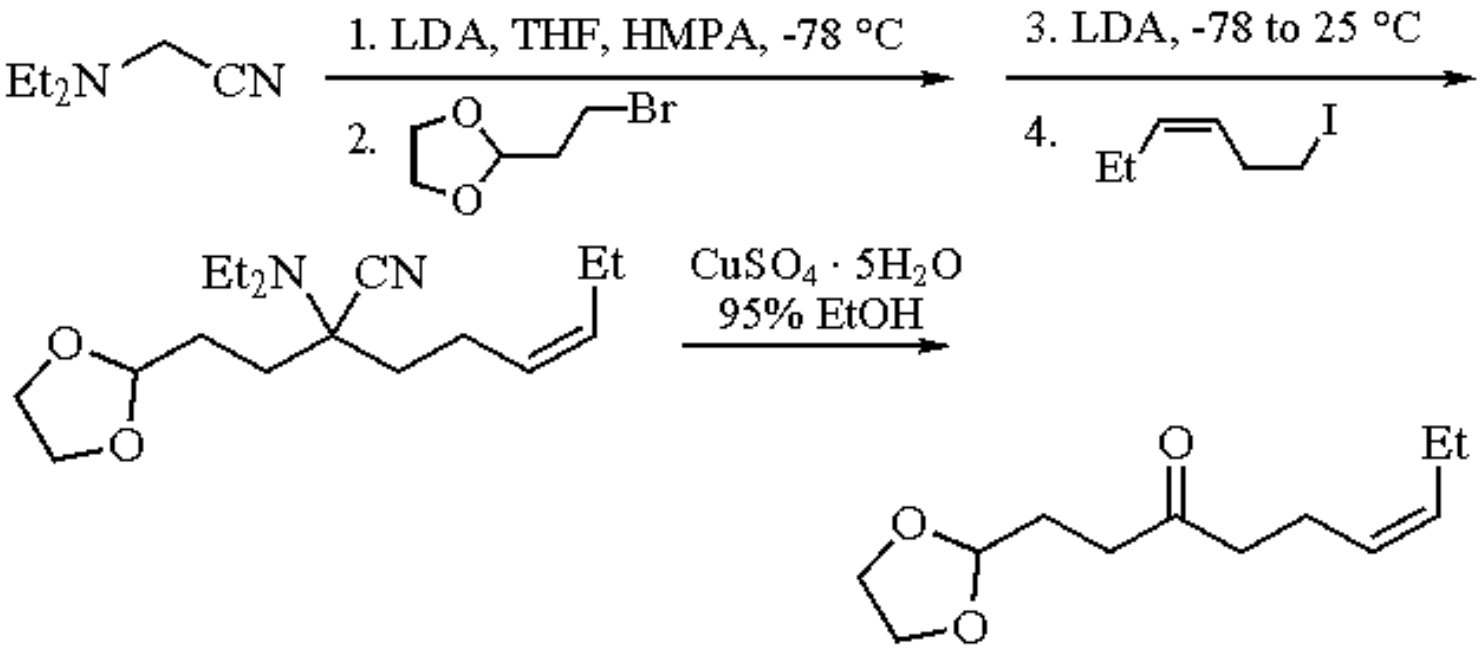

(1)

In contrast to *N*,*N*-diethylaminoacetonitrile, alkylations[10] of *N*,*N*-dimethylaminoacetonitrile with allylic halides proceed through *N*-alkylation and subsequent [2,3]-sigmatropic rearrangement. However, alkylation with 2-octyl iodide occurs at carbon.[11] Addition of lithio-*N*,*N*-diethylaminoacetonitrile to saturated[12-14] or α,β-unsaturated carbonyl compounds[15] leads to diastereomeric β-hydroxy-α-diethylamino nitriles, and a subsequent dehydration affords α-(diethylamino)acrylonitriles in modest yield.[13]

Reactions with Heteroelectrophiles.

The anion of *N*,*N*-diethylaminoacetonitrile reacts with ***Dimethyl Disulfide***[16] and ***Chlorotrimethylgermane***[17] to give the α-methylthio and α-trimethylgermyl derivatives, respectively. Direct silylation of the anion of *N*,*N*-diethylaminoacetonitrile with ***Chlorotrimethylsilane*** failed,[12] but the LDA-induced rearrangement of a silylammonium salt[12] formed from *N*,*N*-diethylaminoacetonitrile and chlorotrimethylsilane gives the α-trimethylsilyl derivative (eq 2).[18]

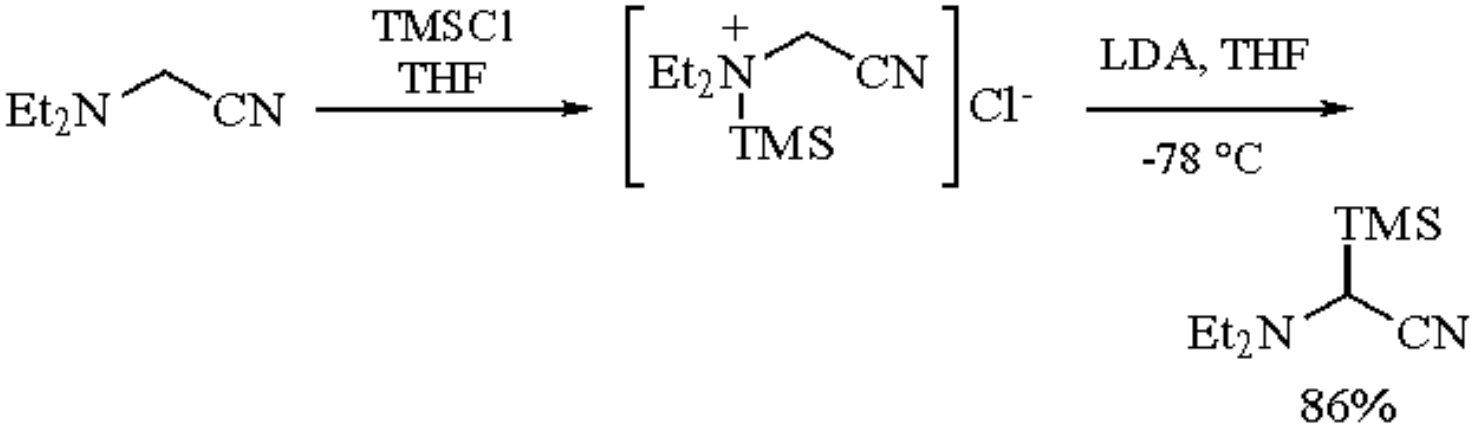

(2)

Other Reactions.

N,*N*-Diethylaminoacetonitrile undergoes a Ritter reaction with 1-adamantol[19] to give an α-(diethylamino)acetamide, and participates in a ***Bis(cyclopentadienyl)cobalt***-catalyzed reaction with acetylene to form 2-(diethylaminomethyl)pyridine.[20]

Related Reagents.

N,N-Dimethyldithiocarbamoylacetonitrile; ***2-(2,6-Dimethylpiperidino)acetonitrile***; ***(4aR)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin***; ***2-Lithio-1,3-dithiane***; ***Methoxyacetonitrile***; ***Nitromethane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***; ***2-(Trimethylsilyl)thiazole***.

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N,N-Diethylaminodimethylsilane

$Et_2NSiHMe_2$

[13686-66-3] · $C_6H_{17}NSi$ · *N,N*-Diethylaminodimethylsilane · (MW 131.29)

(reagent for intramolecular hydrosilation of allyl alcohols[1] and intermolecular hydrosilation of 1,7-diynes[2])

Physical Data: bp 112 °C/760 mmHg; *n*20D 1.4087; *d*204 mr3000.7505 g cm^{-3}.

Solubility: sol common aprotic organic solvents.

Preparative Method: by treatment of commercially available ***Chlorodimethylsilane*** ($ClMe_2SiH$) and diethylamine in the presence of triethylamine in ether, followed by filtration and distillation.

Handling, Storage, and Precautions: moisture sensitive and corrosive. Must be stored under nitrogen in a tightly capped bottle in a freezer and transferred or weighed quickly via syringe. Use in a fume hood.

Intramolecular Hydrosilation Agent.

For a detailed description of the intramolecular hydrosilation procedure, see ***1,1,3,3-Tetramethyldisilazane***. *N,N*-Diethylaminodimethylsilane is a useful reagent for the conversion of hydroxy groups of allyl or homoallyl alcohols into hydrodimethylsilyl ethers for use in intramolecular hydrosilation reactions. In some cases, *N,N*-diethylaminodimethylsilane gives superior results compared to the more commonly employed 1,1,3,3-tetramethyldisilazane (eq 1).[1]

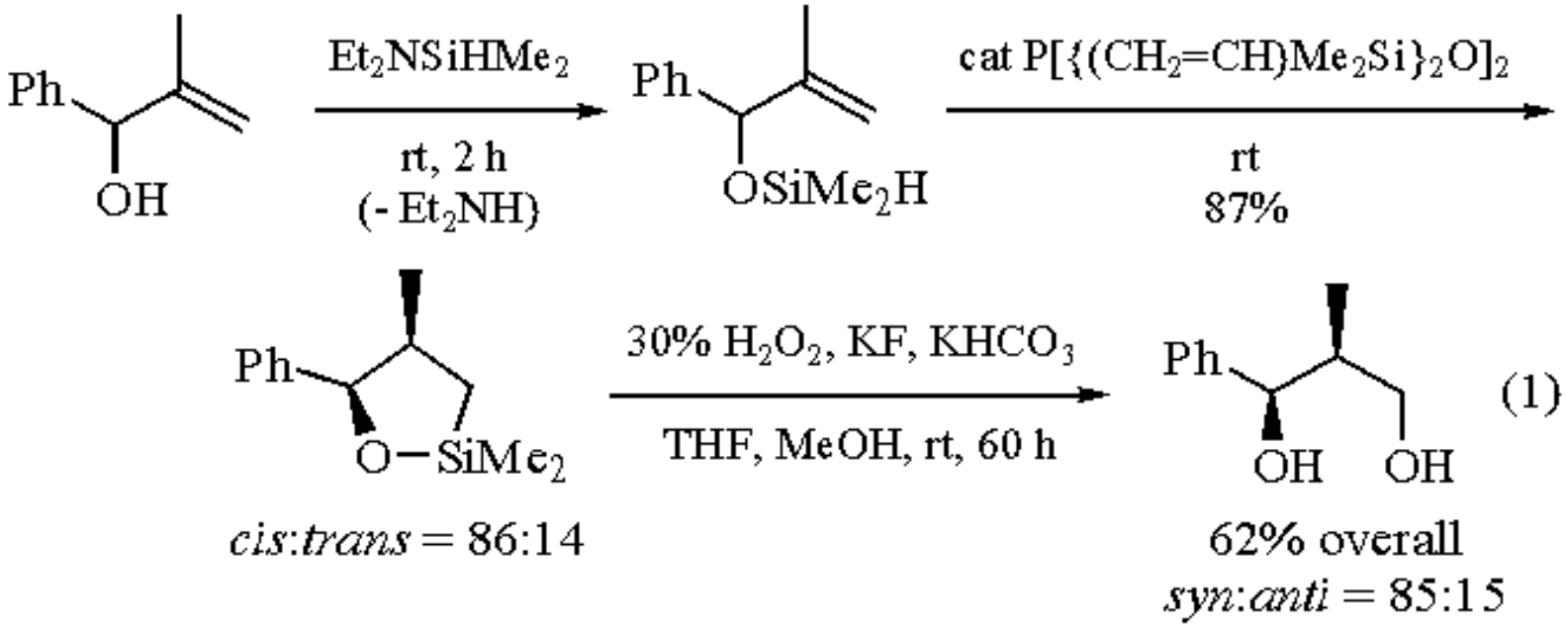

Hydrosilation Agent.

Another application of this difunctional hydrosilane is in the nickel-catalyzed hydrosilation of 1,7-octadiyne, which affords a 1,2-dialkylidenecyclohexane with a (*Z*)-vinylsilane moiety. This exocyclic silyl diene is treated with an allyl alcohol to give a silicon-tethered triene that undergoes intramolecular Diels-Alder reaction and subsequent oxidative cleavage of the silicon-carbon bond to afford a bicyclic diol (eq 2).[2]

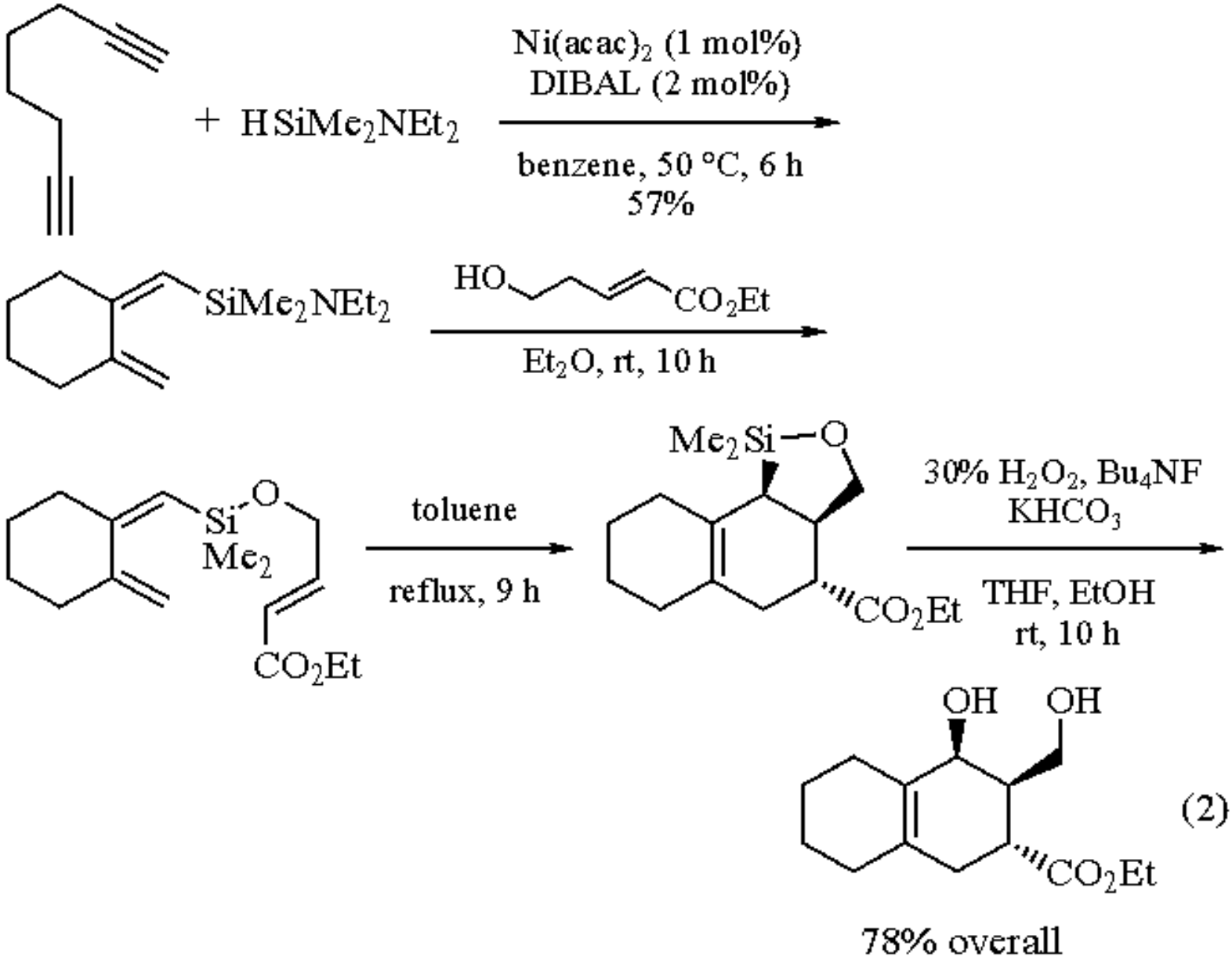

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N,N-Diethylaminosulfur Trifluoride[1]

Et_2NSF_3

[38078-09-0] · $C_4H_{10}F_3NS$ · *N,N*-Diethylaminosulfur Trifluoride · (MW 161.18)

(mild reagent for converting primary, secondary, tertiary, allylic, and benzylic alcohols to the corresponding fluorides,[1] aldehydes and ketones to difluorides,[1a,15,19] carboxylic acids to acyl fluorides,[22] and sulfoxides to α-fluoro sulfides[23])

Alternate Name: DAST.

Physical Data: bp 30-32 °C/3 mmHg; *d* 1.220 g cm^{-3}.

Solubility: sol ethereal, chlorinated, and hydrocarbon solvents; reacts violently with water and rapidly with hydroxylic solvents.

Form Supplied in: amber yellow oil; widely available.

Purification: discolored (brown) samples give increasingly lower yields of fluorinated products. Freshly distilled oil is satisfactory for use.

Handling, Storage, and Precautions: can be stored for extended periods of time in the freezer under inert atmosphere. Use in a fume hood.

Fluorodehydroxylation of Alcohols.

DAST, like several other variants of dialkylaminotrifluorosulfuranes, converts primary, secondary, tertiary, allylic, and benzylic alcohols to monofluorides.[1] The reaction conditions are mild (temperature as low as -78 to 0 °C for reactive substrates), and a variety of functionalities such as acetonides, isolated double/triple bonds, esters, ethers, amides, and unactivated halides are tolerated (eqs 1-3).[1b,8-10]

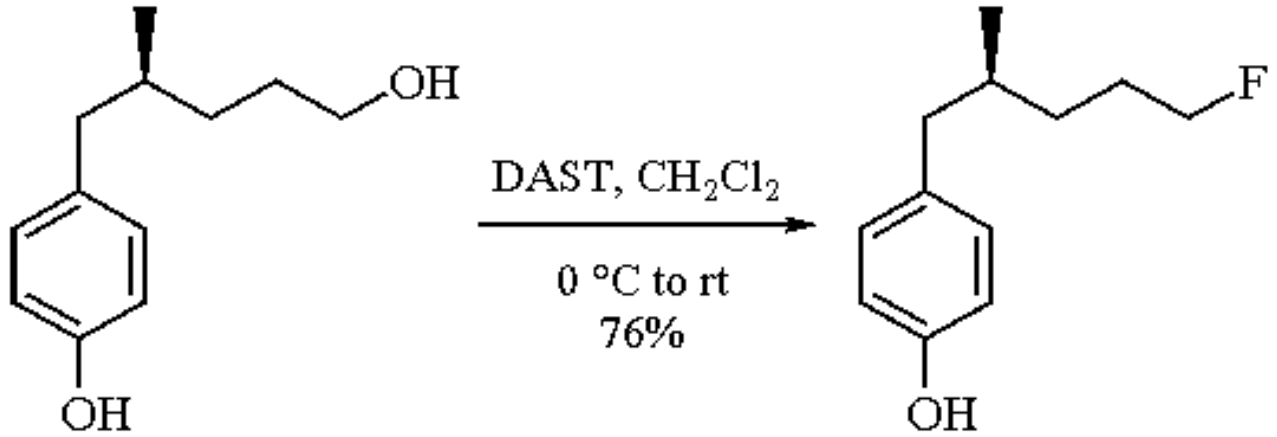

(1)

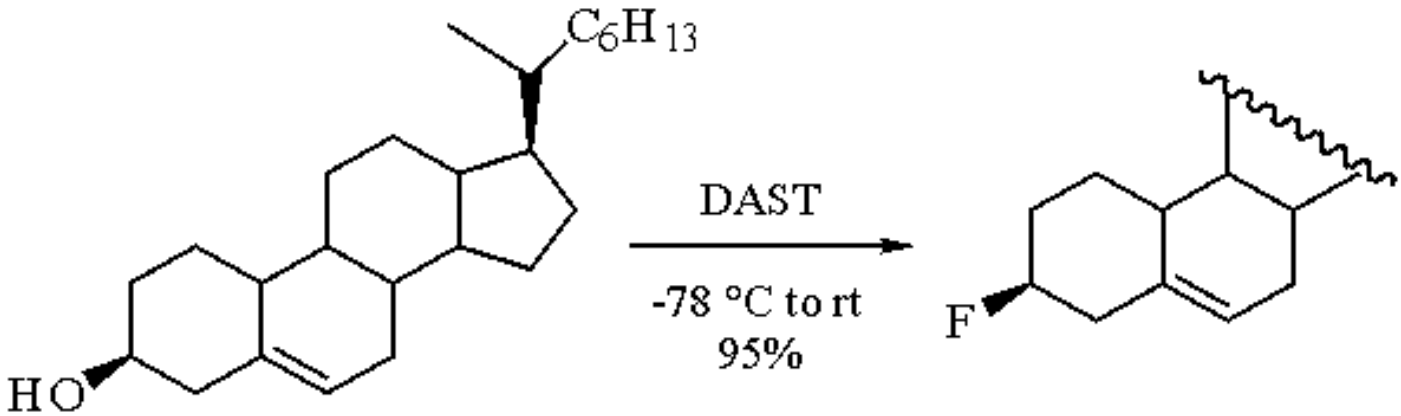

(2)

(3)

The solvents usually employed are dichloromethane, chloroform, carbon tetrachloride, fluorotrichloromethane, ether, THF, benzene, and toluene. Generally, DAST is superior to classical fluorinating agents such as ***Sulfur Tetrafluoride*** in that the latter requires much higher temperatures (typically 100 °C) and gives undesired side products. With DAST, rearrangements are sometimes observed, albeit to a lesser extent (eq 4).[1a,2,7] Thus β-elimination,[1a] ether formation,[3] Friedel-Crafts alkylation,[4] and skeletal rearrangements involving norbornyl cations[5] have been reported. The DAST reaction with isobutyl alcohol yields a mixture of 49% isobutyl fluoride and 21% of *t*-butyl fluoride.[1a] Other functionalities can interfere with the normal course of reaction. A case in point is a pinacol rearrangement with concomitant ring contraction (eq 5).[2a]

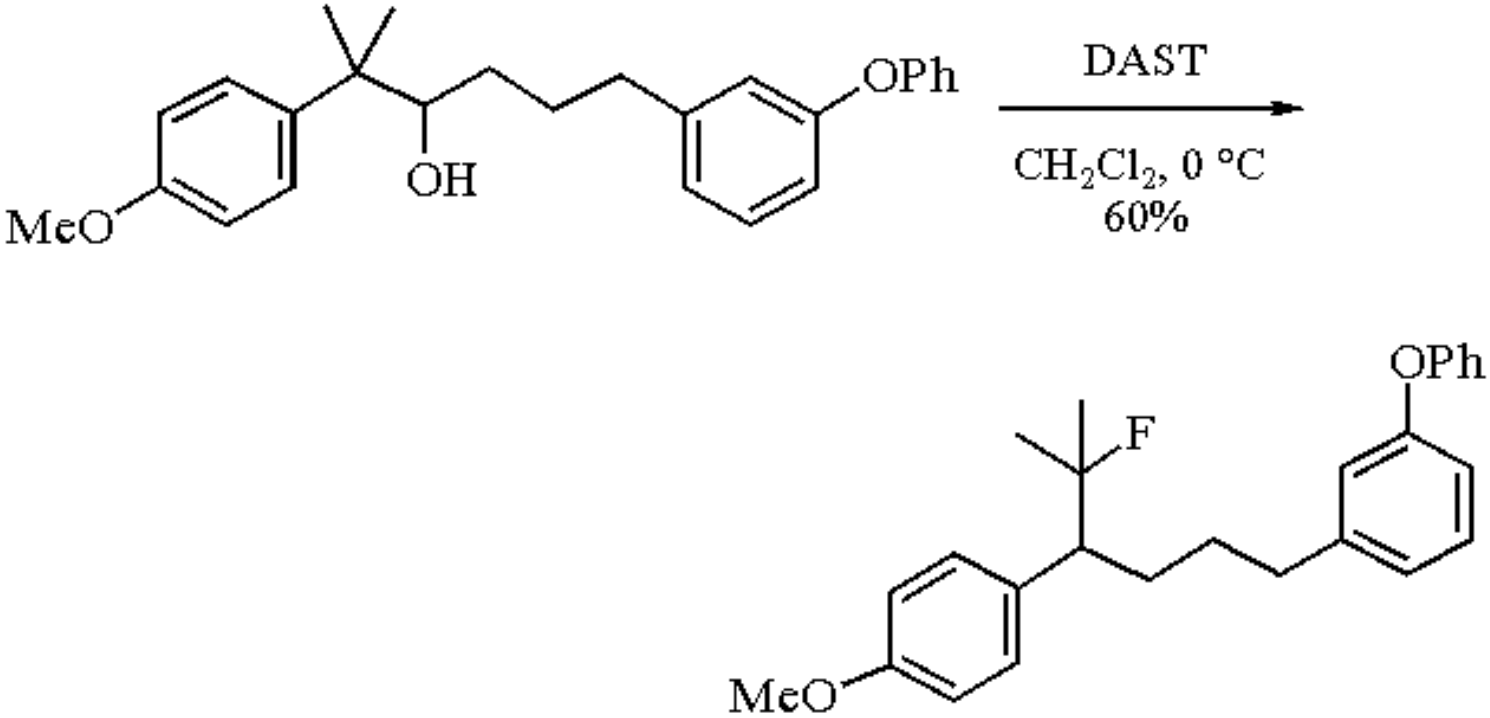

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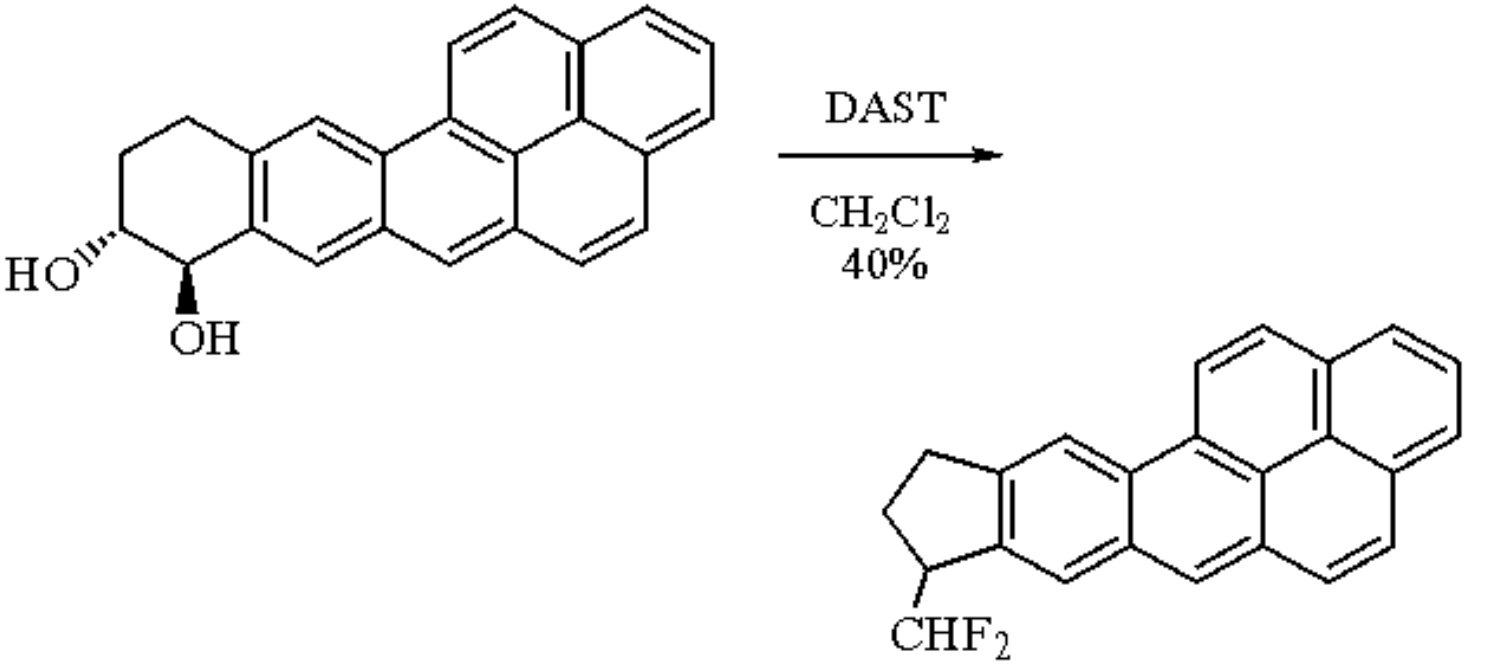

(5)

S_N2' rearrangement may occur on reacting DAST with allylic alcohols (eq 6).[6]

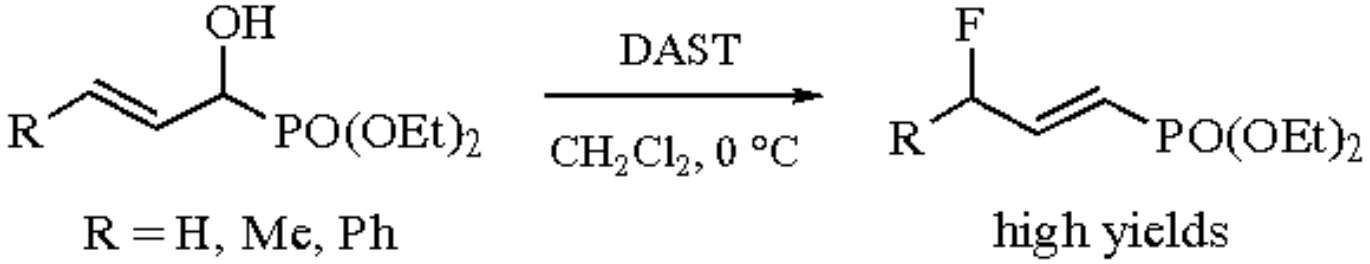

(6)

Highly varied stereochemical outcomes have been obtained in the reactions of DAST with secondary alcohols. Thus,

although products of partial or complete racemization through ionic or ion-pair mechanisms[1a] have not been widely observed, the usual steric course is complete inversion or complete retention at the reaction center. An example is the formation of (-)-2-fluorooctane (97.6% optical purity) from (+)-*S*-2-octanol.[30] On the other hand, a mixture of products of inverted and retained stereochemistry are obtained in the reaction of DAST with some protected *myo*-inositol derivatives (eq 7).[11] Interestingly, in unprotected or minimally protected sugars,[12a,b] and inositols,[12c,d] where more than two hydroxy groups are present, only one or two hydroxy groups react regio- and stereoselectively (eq 8).[12d]

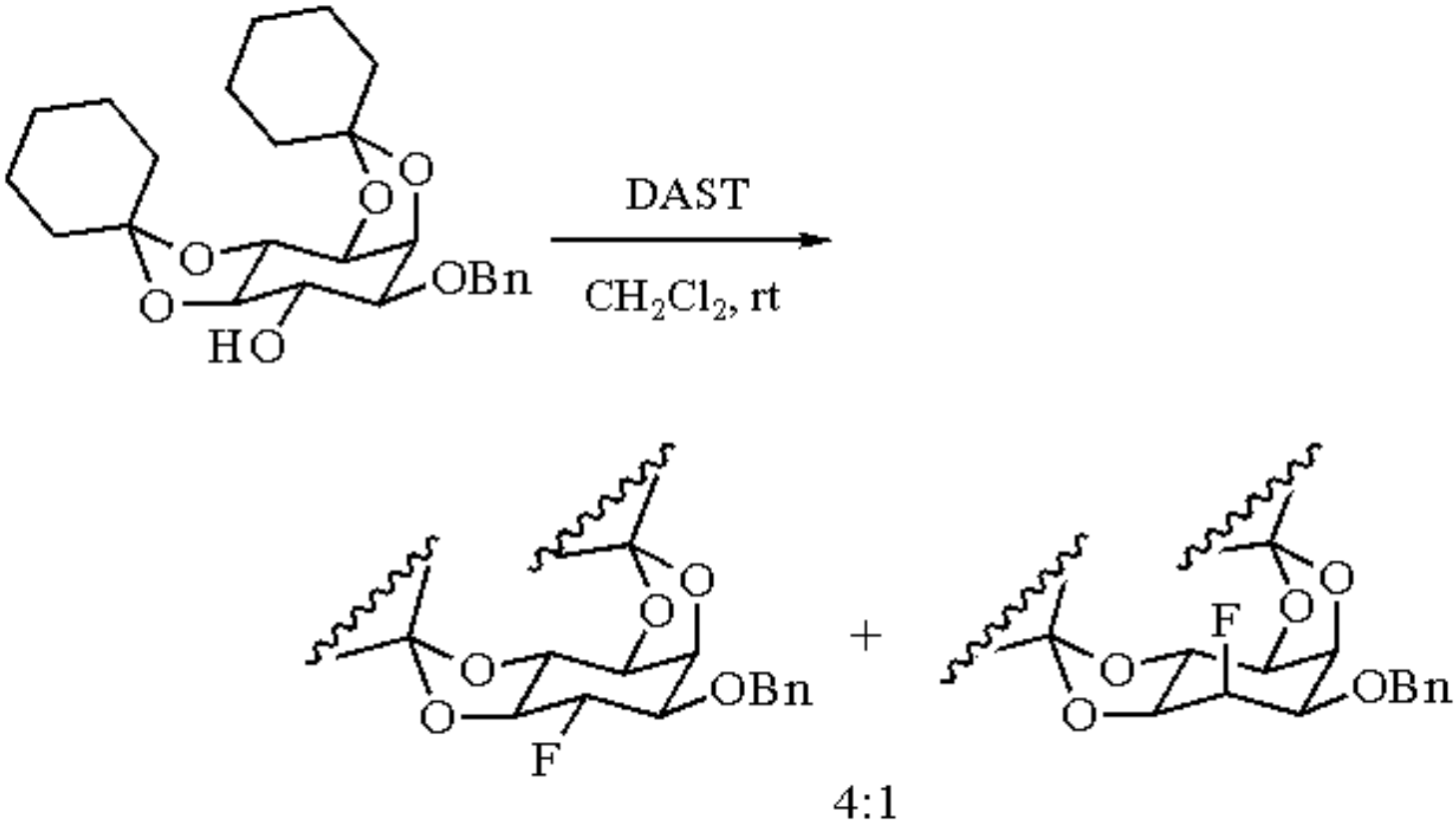

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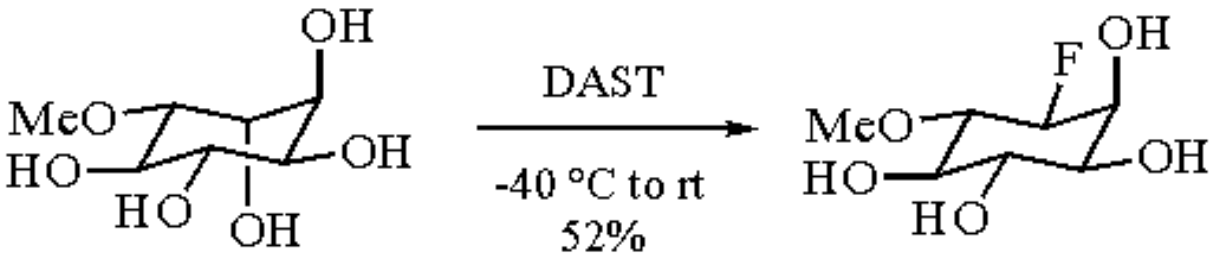

(8)

Several synthetically useful transformations involving neighboring group participation exist.[13] An example is the reaction of DAST with *N,N*-dibenzyl-L-serine benzyl ester (eq 9).[13b]

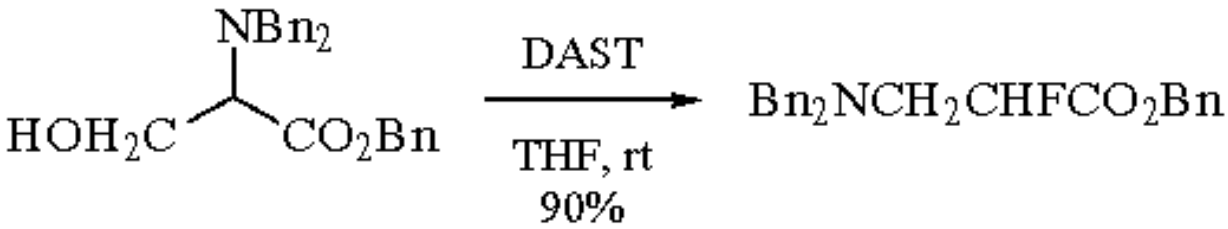

(9)

Geminal Difluorination of Aldehydes and Ketones.

The carbonyl group of aldehydes and ketones can be converted to a 1,1-difluoro group in moderate to high yields.[1a,8,14] The reaction conditions are mild (rt to 80 °C). The solvents generally used are dichloromethane and chloroform. Functional groups compatible with the fluorination of alcohols are also tolerated in the 1,1-difluorination of aldehydes and ketones (see above). An aldehyde carbonyl reacts much faster than a ketone carbonyl and selective difluorination of keto aldehydes at the aldehyde carbonyl has been reported.[14] The general order of reactivity is alcohols > aldehydes > ketones. A variety of aliphatic,[15] aromatic,[1a] and heterocyclic[16] aldehydes have been converted to 1,1-difluorinated compounds (eqs 10-12).[14b,18,19]

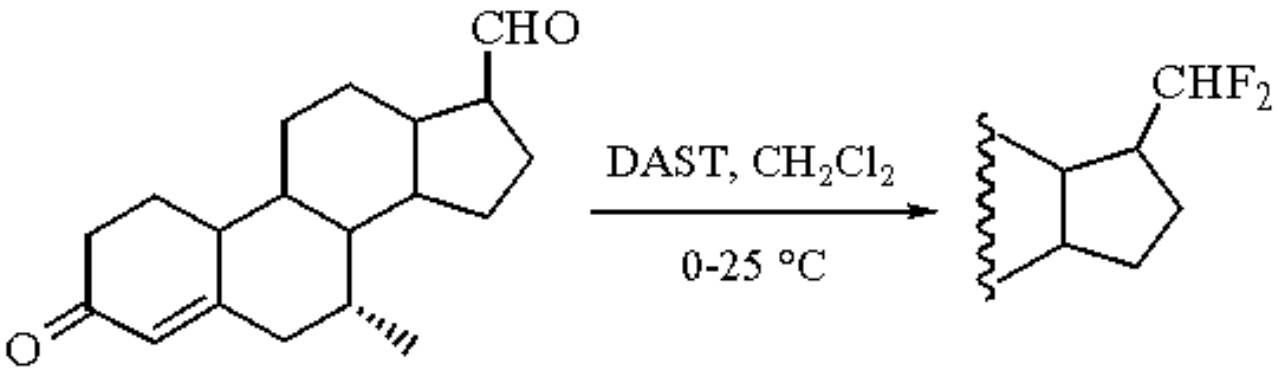

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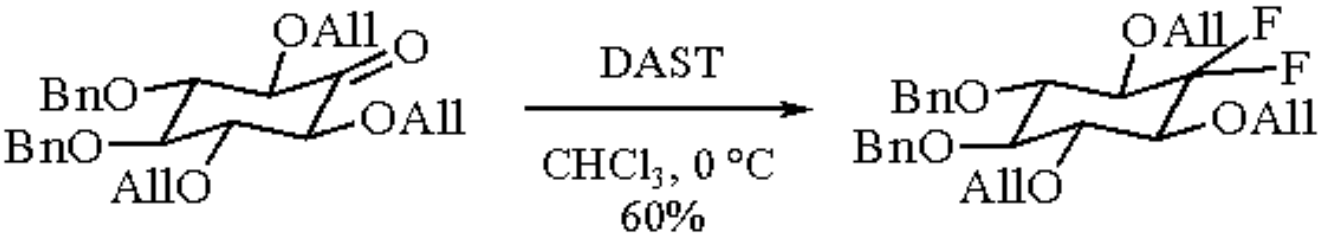

(11)

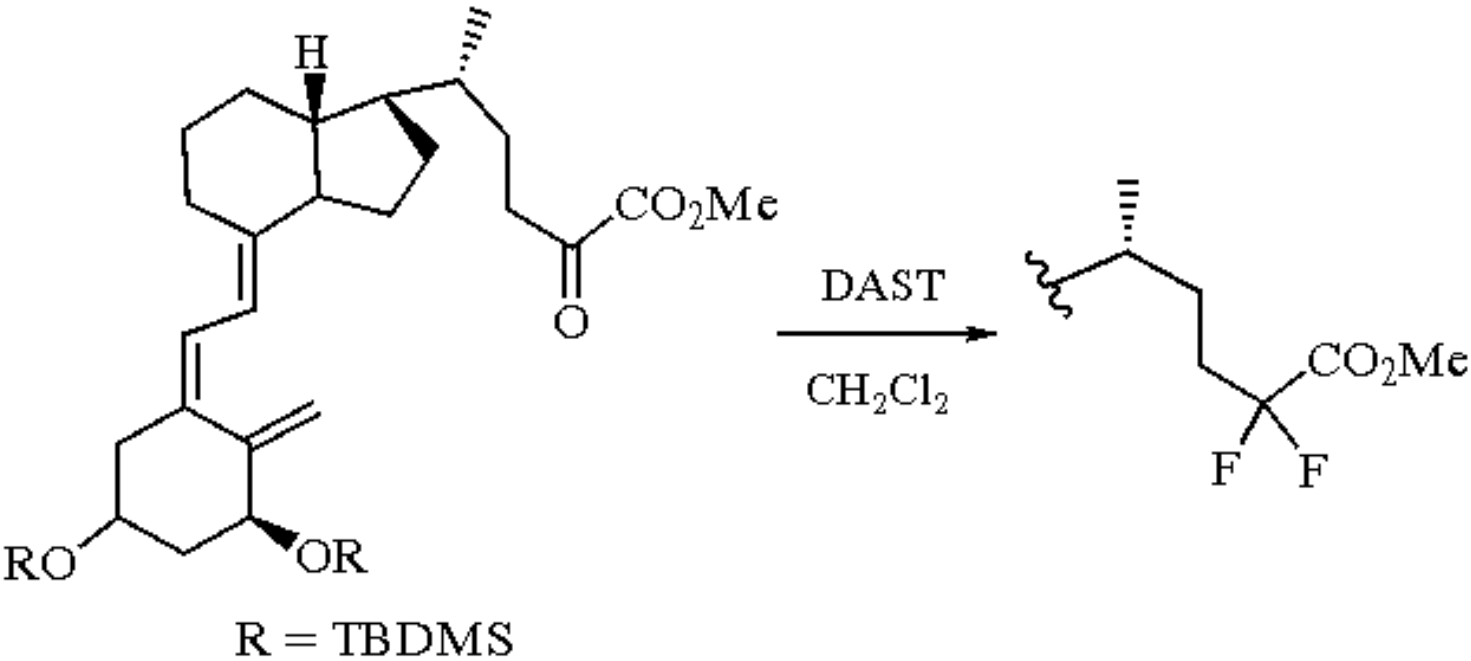

(12)

While the reactivity of ketones is similar to aldehydes in scope, vinyl fluoride formation is a complication and

sometimes DAST, in conjunction with fuming ***Sulfuric Acid*** in glyme,[17a,b] or a mixture of ***Lithium Chloride*** and ***Copper(II) Chloride***,[17b] is used for the preparation of vinyl fluorides (eq 13).

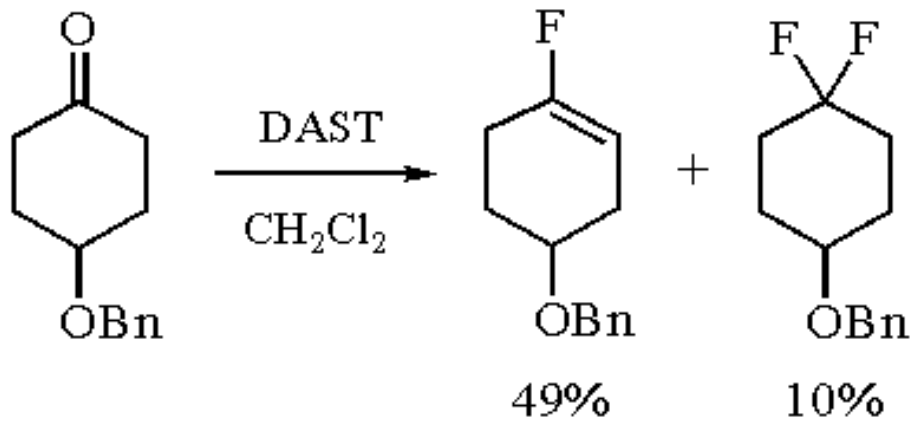

(13)

β-Diketones and β-keto esters are oxidatively fluorinated with DAST to furnish α,β-difluoro-α,β-unsaturated ketones and esters, respectively (eq 14).[20]

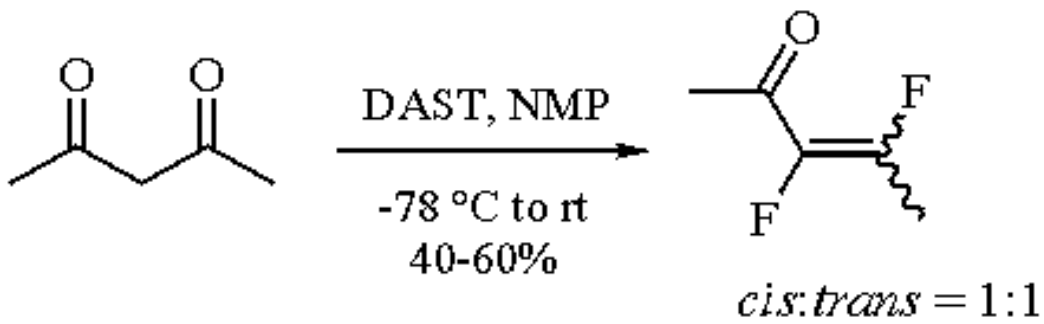

(14)

Reaction with Epoxides.

The reactivity of DAST with epoxides varies with structure. Thus cyclopentene oxide and cyclohexene oxide give a mixture of 1,1-difluoro and bis(α-fluoro) ethers (eq 15).[21] A stereospecific synthesis of *meso*- or (±)-difluorides has been accomplished in two steps using, respectively, *cis*- or *trans*-epoxides as starting materials (eq 16).[22]

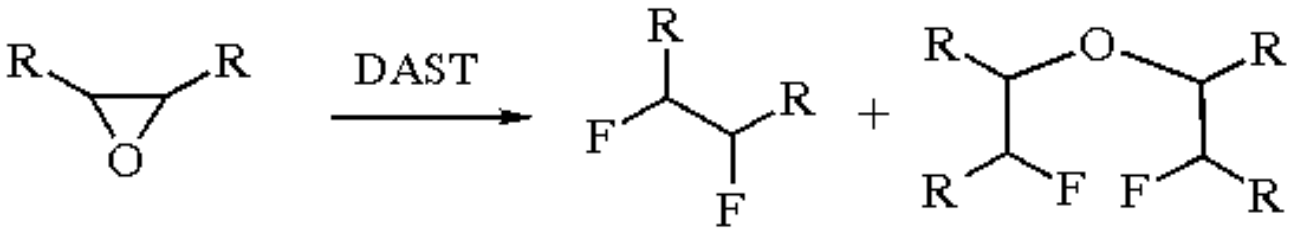

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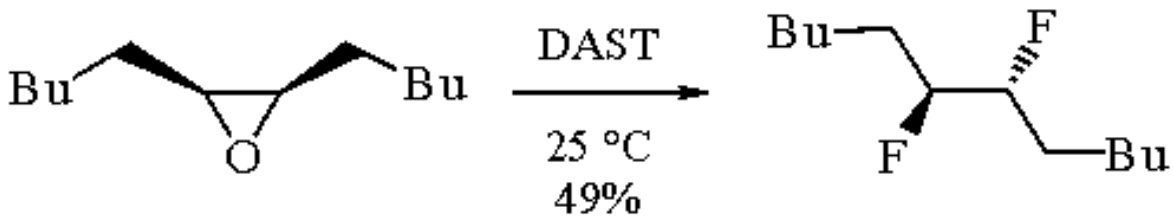

(16)

Reaction with Organic Acids.

Acyl fluorides can be prepared by the reaction of DAST with carboxylic acids in good to excellent yields.[23] α-Hydroxy acids give α-fluoroacyl fluorides which hydrolyze on workup to form α-fluoro acids.[24] Sulfur tetrafluoride, on the other hand, converts the carboxylic group into a trifluoromethyl group.[21]

Reaction with Halides and Sulfonates.

Reactive halides such as iodides, allylic, and benzylic halides, and chlorides of organic acids (sulfinic, sulfonic, and phosphonic) react with DAST to form the corresponding fluorides.[1a]

Reaction with Sulfoxides.

DAST reacts with α-hydrogen containing dialkyl and aralkyl sulfoxides to form α-fluoroalkyl sulfides in high yields (eq 17).[25] This reaction can be extended to less reactive sulfoxides by catalysis with certain Lewis acids, e.g. ***Antimony(III) Chloride*** (eq 18)[26] and ***Zinc Iodide***.[27]

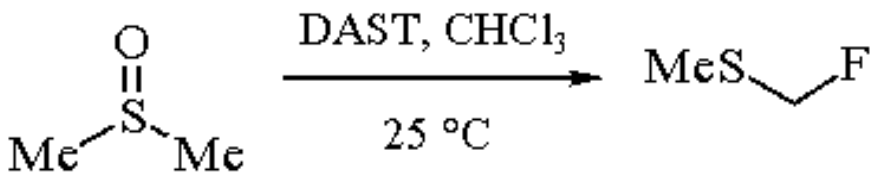

(17)

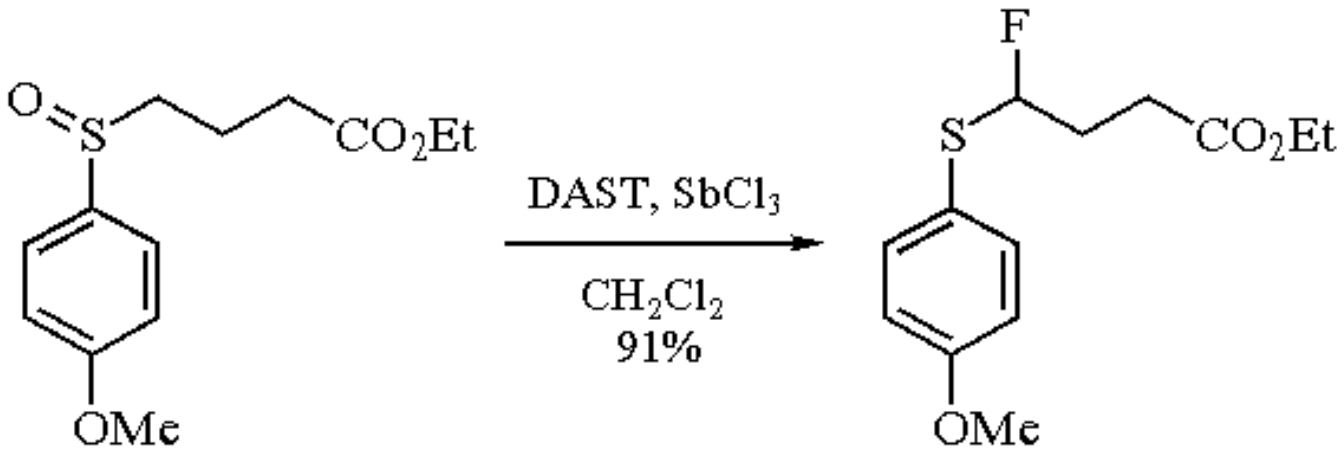

(18)

Miscellaneous Reactions.

Lactones containing α-hydrogen or fluorine do not react with DAST. However, α-hydroxy lactones undergo normal fluorodehydroxylation along with geminal difluorination at the lactone carbonyl.[28] Glycosyl fluorides can be obtained in high yield, and in a stereospecific manner, either by reacting DAST with hemithioacetals in the presence of ***N-Bromosuccinimide*** or, more simply, hemiacetals.[29b] An interesting fluorination of a phenyl ring of *N*-benzylphenylhydroxylamine has been reported (eq 19).[30]

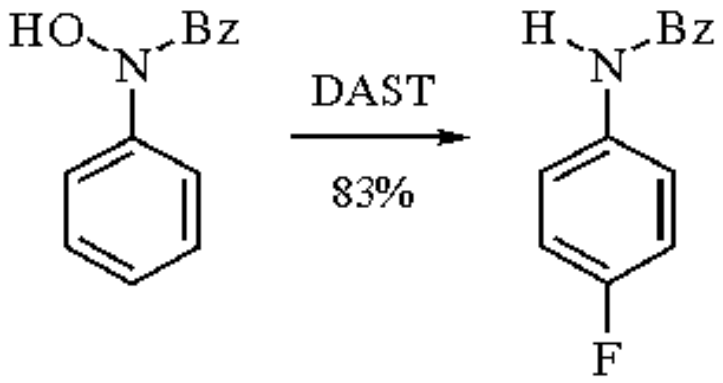

(19)

An attempt to convert the C-7 hydroxy group of 7-*epi*-taxol to a fluoride failed. Instead, a high yield of a cyclopropanated product with A-ring contraction was obtained (eq 20). A cyclopropane intermediate corner-protonated at C-19 was postulated to explain this anomalous transformation.[31]

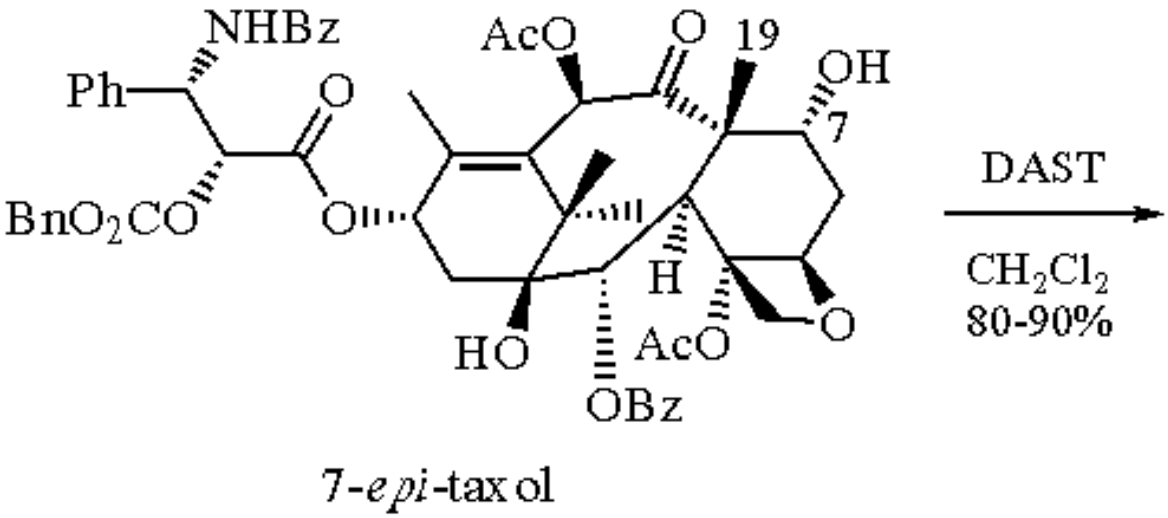

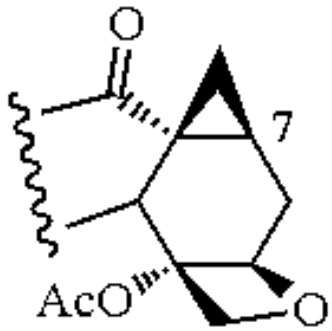

(20)

Related Reagents.

Pyridinium Poly(hydrogen fluoride); ***Sulfur Tetrafluoride***.

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Diethyl Azodicarboxylate[1]

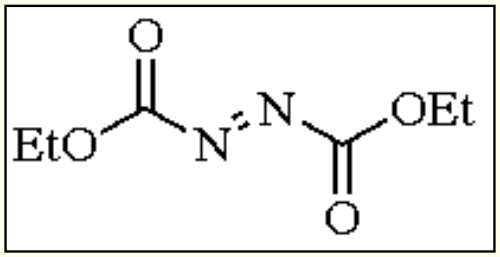

[1972-28-7] · $C_6H_{10}N_2O_4$ · Diethyl Azodicarboxylate · (MW 174.16)

(functional group oxidations;[5] dealkylation of amines;[16] enophile;[24] dienophile[33])

Alternate Names: diethyl azidoformate; DEAD; DAD.[2]

Physical Data: bp 108-110 °C/15 mmHg; bp 211 °C/760 mmHg; fp 110 °C, *d* 1.11 g cm^{-3}.

Solubility: sol CH_2Cl_2, Et_2O, toluene.

Form Supplied in: orange liquid; 90% (technical grade) and 95% purity are commonly available, as is a 40% solution in toluene.

Preparative Method: although widely available, diethyl azodicarboxylate can be readily prepared from ethyl chloroformate and hydrazine, followed by oxidation of the resulting diethyl hydrazodicarboxylate.[3]

Purification: in most cases commercial samples are used without purification. Distillation is possible, but *not recommended*.

Handling, Storage, and Precautions: flammable; may produce toxic combustion byproducts. Heat and light sensitive; should be stored in dark containers under refrigerated conditions. These containers should also be vented periodically to reduce pressure. DAD has been reported to occasionally decompose violently when heated.[3a,4] Use in a fume hood.

Introduction.

See ***Triphenylphosphine-Diethyl Azodicarboxylate*** for reactions involving the use of the combination of PPh_3 and DAD.

Functional Group Oxidations by Dehydrogenation.

The strong electron withdrawing character of diethyl azodicarboxylate makes it suitable for certain types of oxidations. In general, diethyl hydrazocarboxylate is formed as a product of any oxidation. Primary and secondary alcohols are oxidized to aldehydes and ketones, respectively, although application of this method has been limited.[5] Thiols, similarly, are oxidized to disulfides. Unsymmetrical disulfides are also available by a variation of this method.[6] The oxidation of formamides to isocyanates has been accomplished at high temperatures with DAD, although the yields are frequently low and the method does not appear to be general.[7]

Arylhydroxylamines are readily converted into nitroso compounds with DAD at 0 °C (eq 1).[8] One example of the conversion of an *N*,*N*-dimethylhydrazone to a nitrile has been reported.[9] Sulfur-containing amino acids like methionine and *S*-ethylcysteine can be oxidized to their sulfoxides in virtually quantitative yields, although another reaction pathway occurs with most other thioethers.[10] Thioethers and ethers usually react with DAD to yield α-hydrazo derivatives by hydrogen abstraction.[11] The initial ether/DAD adducts can be formed thermally at 100 °C[12] or photochemically at much lower temperatures.[13]

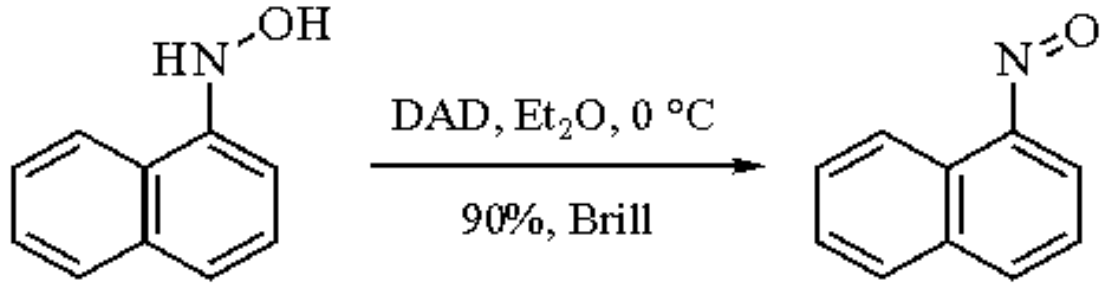

(1)

The oxidation of propargylic hydrazine derivatives with DAD to the corresponding propargylic diazenes (with subsequent spontaneous loss of N_2) forms the basis of a powerful, yet mild, allene synthesis (eq 2).[14]

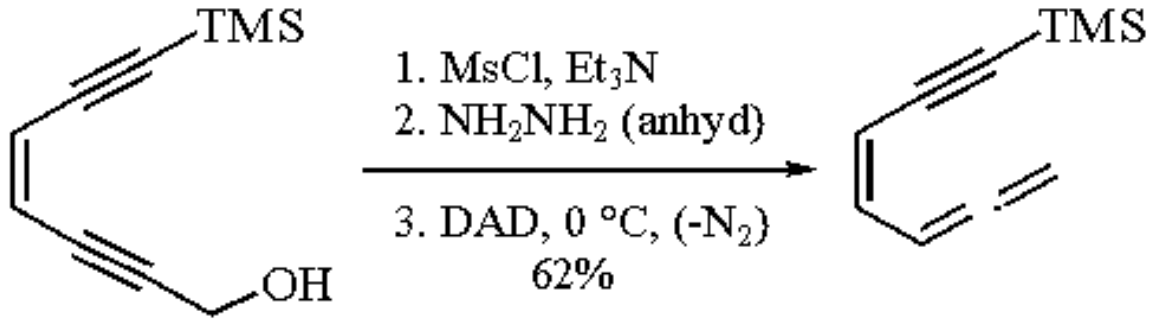

(2)

Dealkylation of Amines.

Treatment of a secondary or tertiary amine with diethyl azodicarboxylate in nonpolar solvents followed by acidic hydrolysis leads to the formation of monodealkylated amines.[15] The mechanism of this reaction is believed to involve the formation of a triaza adduct (by Michael addition) followed by a two-step ylide rearrangement yielding an alkyl-substituted hydrazocarboxylate.[12a] Research on unsymmetrically substituted amines suggests that benzyl groups are more easily removed than alkyl groups; methyl groups are the hardest to remove except in cyclic amines like *N*-methylpiperidine (eq 3).[16] The *N*-dealkylation of imines has also been reported.[17]

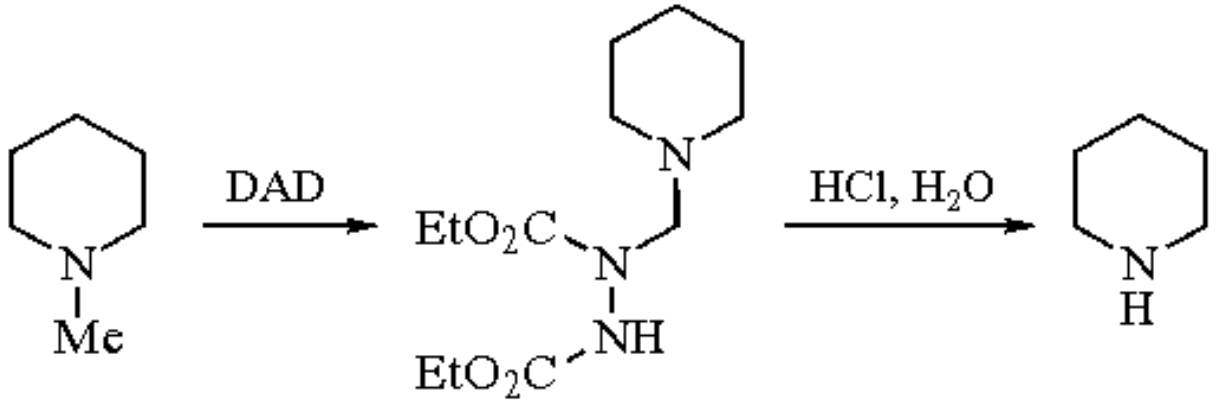

(3)

Purine Synthesis.

Aminopyrimidines and aminouracil derivatives can be converted into purines with diethyl azodicarboxylate in a number of closely related synthetic methods. Treatment of compound (**1**) with an aldehyde leads to the formation of imine (**2**), which is converted to purine (**3**) with DAD (eq 4).[18] A number of researchers have applied variations of this approach.[19]

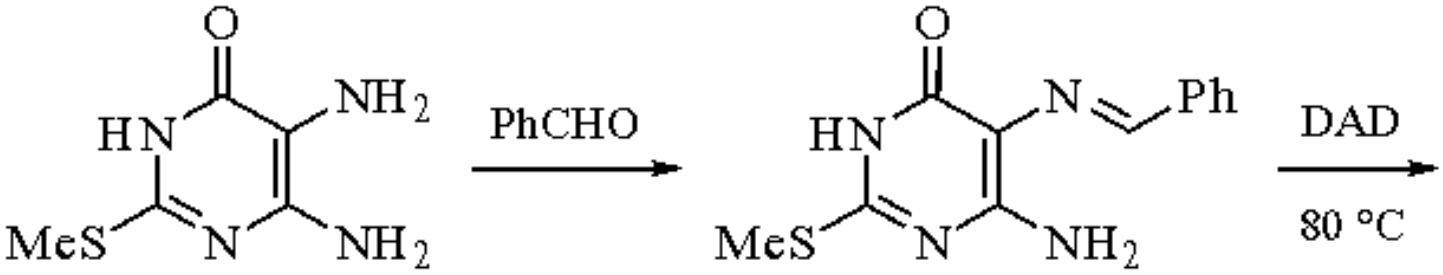

(1) (2)

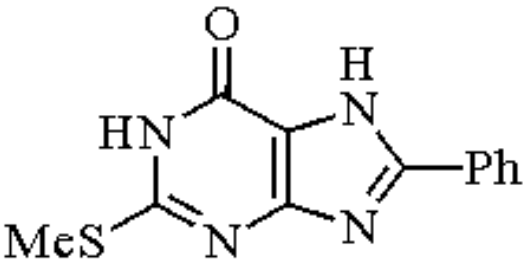

(4)

(3)

Treatment of 6-aminouracils[20] or 6-aminopyrimidines[21] (unsubstituted at the 5-position) with DAD leads to the initial formation of hydrazino Michael adducts. Treatment of these adducts with excess DAD leads to cyclization (eq 5).

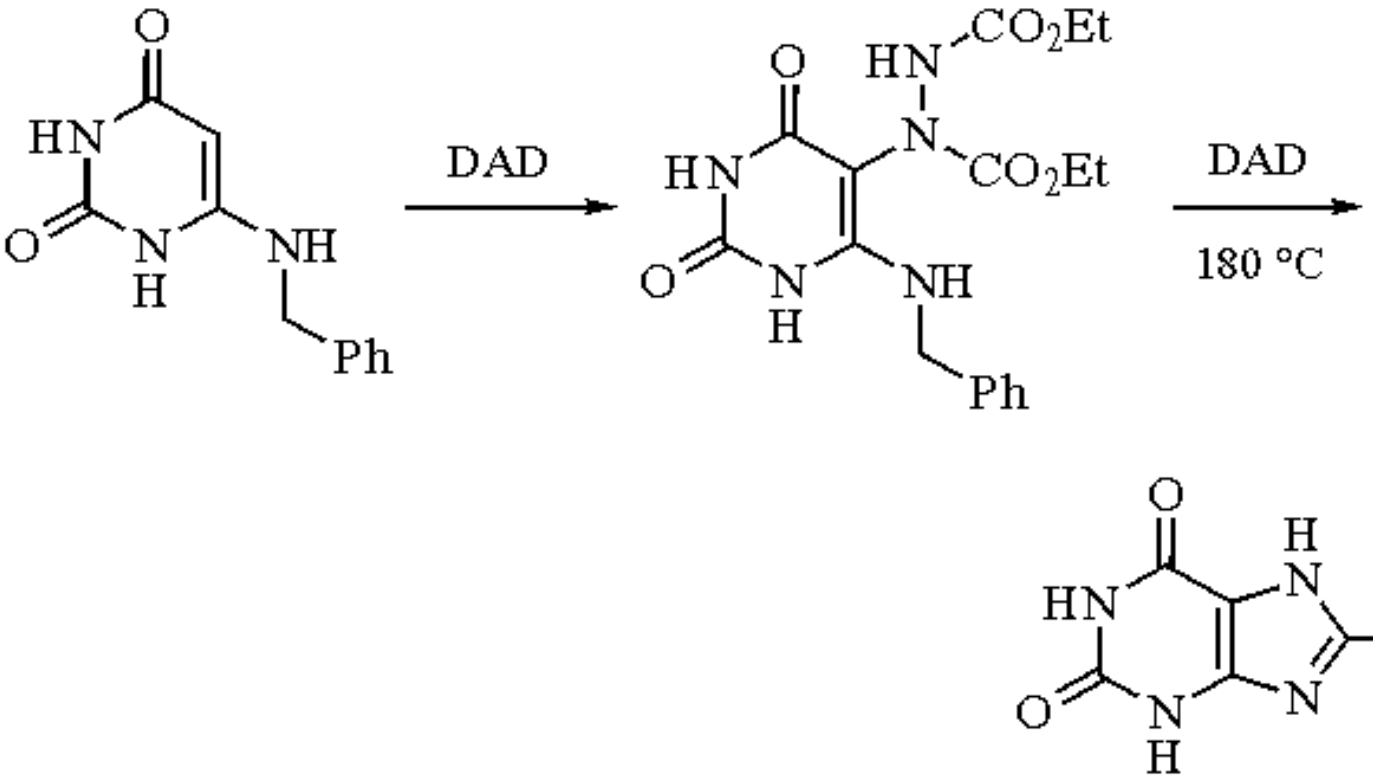

(5)

This methodology has been applied to the synthesis of the antibiotic fervenulin[22] and 8-dimethylaminotheophylline.[23] In general, high temperatures (>100 °C) are required to complete the cyclization.

Pericyclic Reactions.

In general, α-carboxyazo compounds participate in a number of pericyclic processes as noted below.

Ene Reactions.

Diethyl azodicarboxylate reacts with most simple alkenes possessing an allyl hydrogen to yield the corresponding ene products, allylic hydrazocarboxylates.[24] The uncatalyzed reaction takes place at moderate temperatures (80 °C) and bis-adducts can be formed if excess DAD is used.[25] The use of ***Tin(IV) Chloride*** catalyzes the reaction, allowing for rapid reaction at -60 °C.[26] This reaction proceeds with a surprising degree of selectivity for (*E*)-alkene geometry (eq 6). A particularly useful application of the ene reaction with DAD is in the synthesis of allyl amines, which are readily available by reduction of the initial adducts with Li/NH_3.[27]

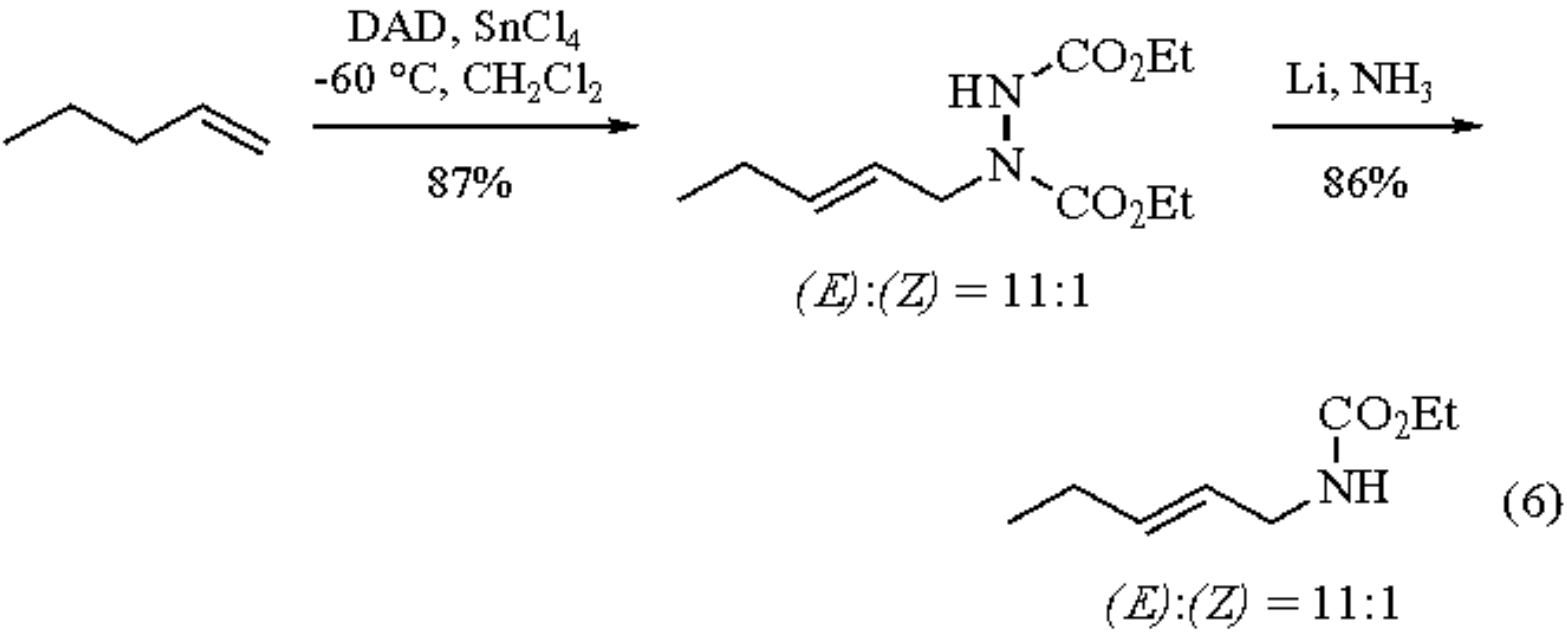

Cycloheptatriene reacts with DAD to afford exclusively ene products,[28] as do the enols of some triazene derivatives.[29] Allenes with alkyl substituents react with DAD to yield ene products in most cases (eq 7).[30] Ene reactions with DAD have also been found to be a useful way of cleaving allyl ethers.[31]

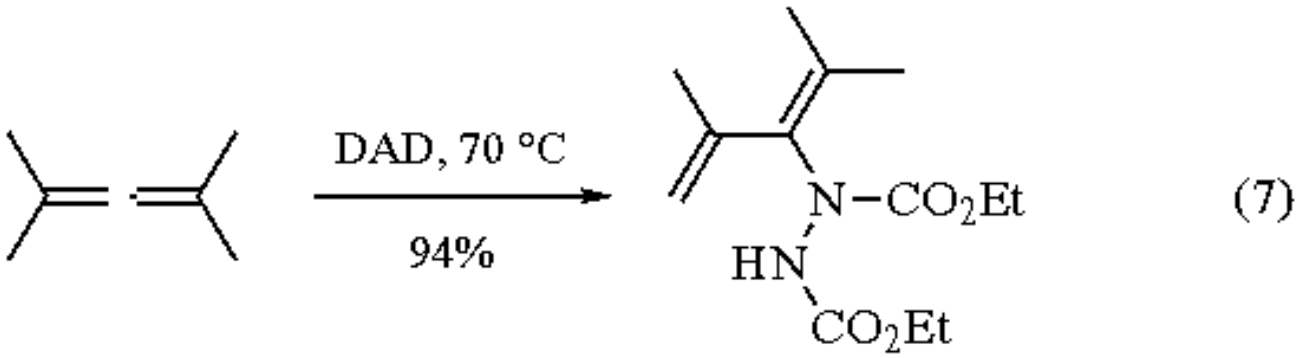

Diels-Alder [4 + 2] Cycloadditions.

Except as noted below, diethyl azodicarboxylate reacts with conjugated dienes to yield [4 + 2] cycloadducts.[32] When the diene moiety is a vinyl aromatic, cycloaddition with DAD is a powerful route for the preparation of annulated tetrahydropyridazine derivatives.[33] Thus the indole derivative (**4**) reacts with DAD at rt to afford cycloadduct (**5**) (eq 8).[34]

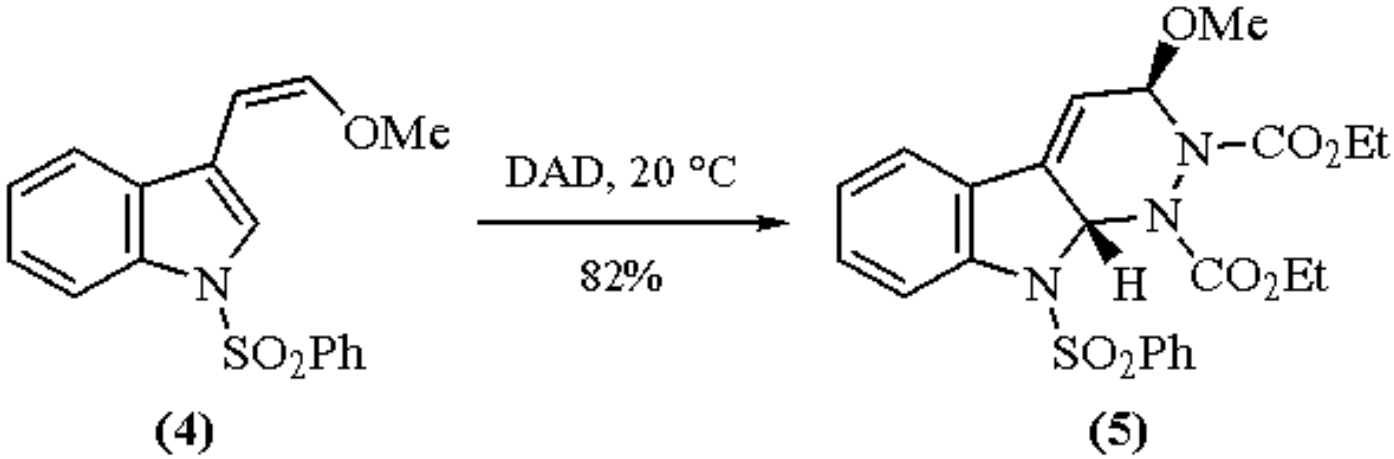

The reaction of vinylfurans with DAD usually affords intractable mixtures;[33b,e] however, furan itself undergoes cycloaddition readily, provided suitable reaction conditions[35] are employed to avoid decomposition of the reactive products.[36] Oxazole derivatives readily participate in [4 + 2] cycloadditions with DAD.[37] An asymmetric Diels-Alder reaction between DAD and pyridazin-3-ones facilitated by ***Baker's Yeast*** has been reported with ee's in the range of 9.1-62.7%.[38] The reactions of a number of acyclic heterodienes with DAD have also been reported recently, including 2-aza-1,3-dienes,[39] α,β-unsaturated thioketones,[40] and 1-thia-3-aza-1,3-dienes.[41] The quinodimethane derivatives of a number of heterocycles have been used in cycloadditions with DAD (eq 9).[42]

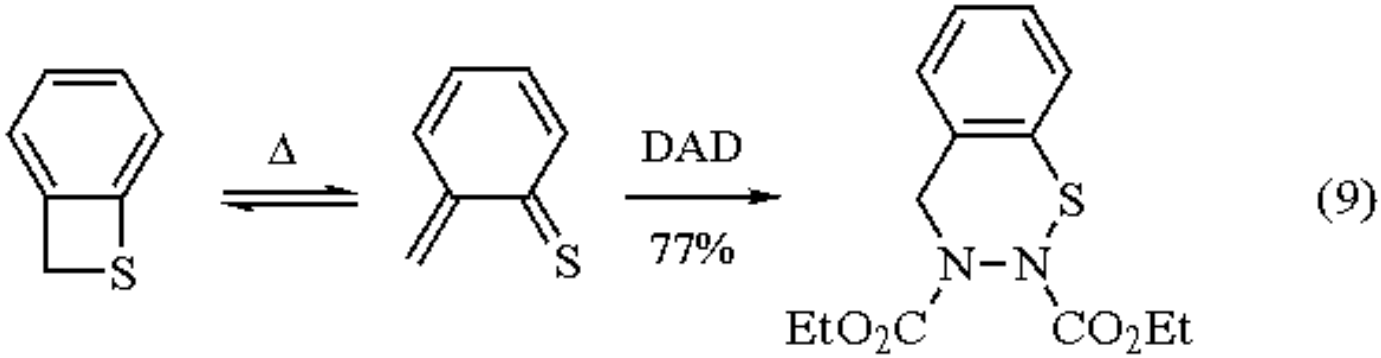

Competition Between Ene and Diels-Alder Reactions.

One area of considerable research centers on the reactivity of diethyl azodicarboxylate with conjugated dienes, systems in which two pericyclic reaction pathways are possible: Diels-Alder and ene. Although a number of researchers have investigated this area, no clear explanation for the preference of one pathway over another has emerged.[43] In most cases, one reaction course seems to be strongly predominant. At this time, only generalizations are possible.

Acyclic 1,3-dienes, for example, in which alkyl groups are present at the terminus of the diene system, tend to give ene products with DAD, while those with internal alkyl substituents yield [4 + 2] adducts. 2,3-Dimethylbutadiene therefore reacts with DAD to give the cycloadduct in 94% yield, while 2,5-dimethyl-2,4-hexadiene gives only ene products.[44,55] In cases where mixed substitution is present, predictive methods fail completely.[46]

Reactivities among cyclic dienes are equally complicated. Cyclopentadiene gives exclusively [4 + 2] adducts.[47,48] 1,3-Cyclohexadiene, however, has been reported to give solely ene products,[49] but careful reexamination of this reaction reveals that 5-15% yields of [4 + 2] cycloadducts can be obtained.[50] The reaction can be optimized to yield exclusively

cycloadducts by altering experimental conditions.[43,51] In steroidal systems, dienes in internal rings tend to undergo ene reactions,[52] while dienes located in the terminal ring give mixtures where cycloadditions are the predominant pathways (eq 10).[53] In cholesterol derivatives, reduction of the ene adducts with Li/$EtNH_2$ is a convenient way to isomerize the diene system (eq 11).[54] It has been reported that treatment with DAD will aromatize certain cyclohexadiene systems.[44,55]

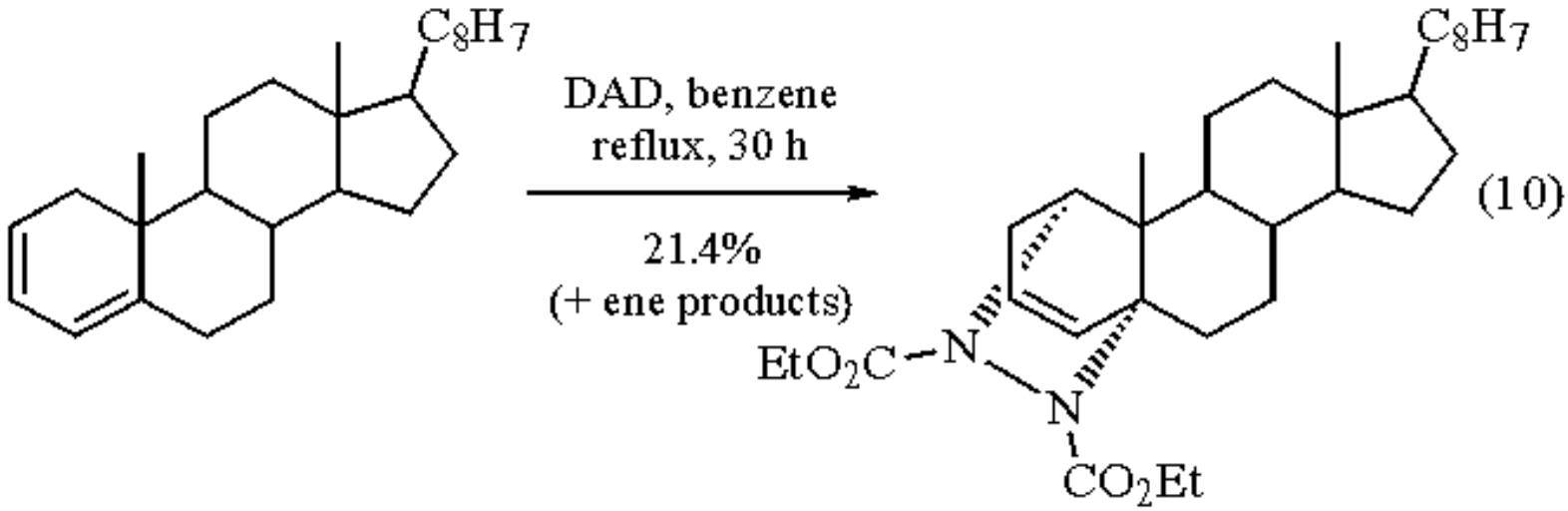

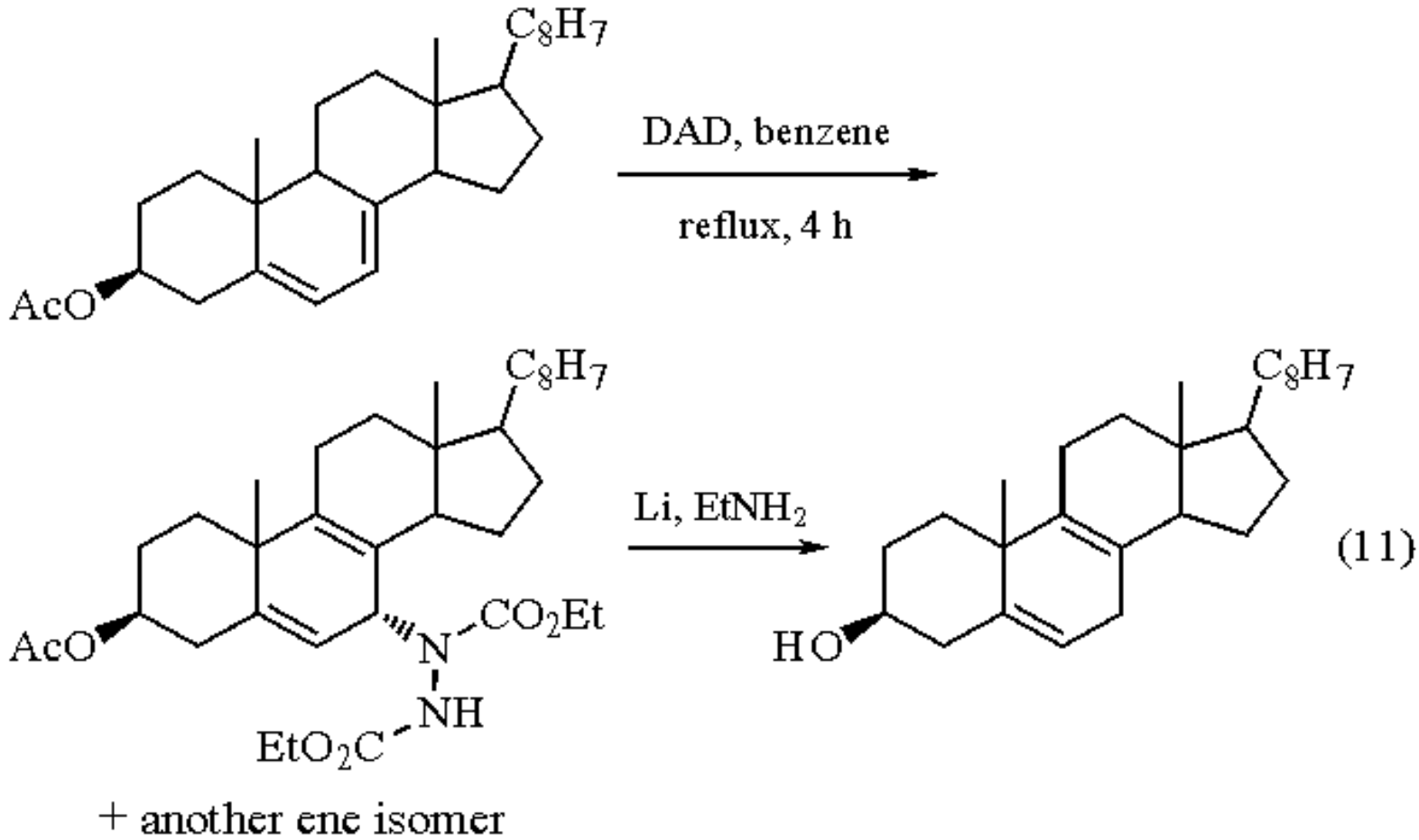

Other Cycloadditions.

Diethyl azodicarboxylate has seen little application to other types of pericyclic reactions. DAD has been reported to undergo [2 + 2][56] cycloadditions with tetramethoxyallene.[57] Two reports of [8 + 2] cycloadditions involving DAD have emerged recently, one involving 7-alkylidene-1,3,5-cyclooctatrienes[58] and the other 3-methoxy-3a-methyl-3a*H*-indene.[59] Indolizine, which is known to undergo [8 + 2] reactions with electron deficient alkenes,[60] reacts with DAD exclusively in Michael fashion.[61] A photochemically induced 1,3-dipolar cycloaddition involving DAD has been reported.[62]

Similar Reagents.

In most of the reactions involving diethyl azodicarboxylate, two closely related compounds can be employed instead. In many cases, 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) (**6**) and ***4-Phenyl-1,2,4-triazoline-3,5-dione*** (PTAD) (**7**) exhibit greater reactivity than DAD.[15,30a,37b,63]

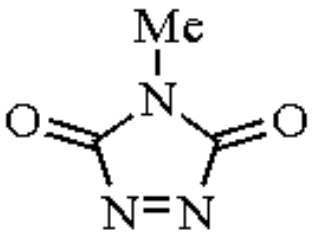

(6)

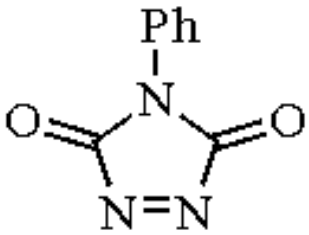

(7)

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N,N-Diethylbenzeneselenenamide[1]

PhSe-NR$_2$

(R = Et)

[57584-86-8] · $C_{10}H_{15}NSe$ · *N,N*-Diethylbenzeneselenenamide · (MW 228.22) (R = Me)

[57584-85-7] · $C_8H_{11}NSe$ · *N,N*-Dimethylbenzeneselenenamide · (MW 200.16) (NR_2 = morpholino)

[82737-08-4] · $C_{10}H_{13}NOSe$ · *N*-Phenylselenomorphine · (MW 242.24)

(reagent for α-selenenylation of aldehydes[2] and β-dicarbonyl compounds;[3] areneselenenamides are electrophilic selenium agents for enamines,[4] silyl enol ethers,[4] and α,β-unsaturated carbonyl compounds,[2] and have a more basic character than arenesulfenamides[5])

Alternate Name: *N*-phenylseleno-*N,N*-diethylamine.

Physical Data: bp 75 °C/0.1 mmHg.

Solubility: sol aprotic solvents; hydrolyzed in water; reacts with alcohols.

Form Supplied in: pale yellow oil, often with diphenyl diselenide as impurity.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$)[6] 7.56 (m, 2H) 7.2 (m, 3H) 3.0 (q, *J* = 7 Hz, 4H) 1.2 (t, *J* = 7 Hz, 6H). ^{13}C NMR[7] 131.0, 128.5, 126.9, 53.8, 14.6, 3.0.

Preparative Methods: from ***Benzeneselenenyl Chloride*** and diethylamine (eq 1).[3] ***Benzeneselenenyl Bromide***, formed from ***Diphenyl Diselenide*** and ***Bromine***, can also be used.[6] The more stable morpholino analog is obtained by the same procedure.[4,9] Optically active areneselenenamides have been prepared from chiral amines.[10,11] Selenenamides are also obtained from *N*-(trimethylsilyl)dialkylamines (eq 2)[7a,12] and used without purification.[7a]

$$\mathrm{PhSeCl} \xrightarrow[\text{hexane, 50 °C}]{\text{2 equiv } Et_2NH} \underset{59\%}{\mathrm{PhSeNEt_2}} + \overset{+}{Et_2NH_2}\ Cl^- \qquad (1)$$

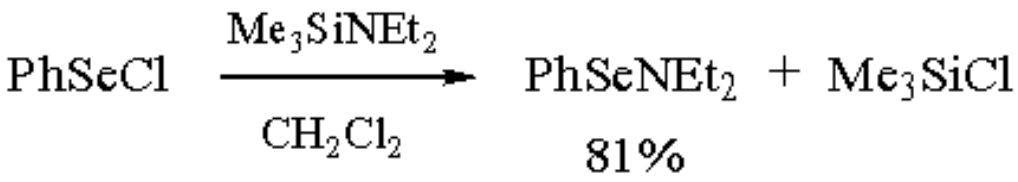

(2)

Handling, Storage, and Precautions: can be stored for several weeks below 0 °C in the absence of moisture; like its morpholino analog *N*-phenylselenomorpholine,[8] it can be prepared just before use. Use in a fume hood.

α-Selenenylation of Carbonyl Compounds.

$PhSeNEt_2$,[2] like its morpholino analog,[4,8] reacts with aldehydes to give α-phenylseleno aldehydes (eq 3). Linear aldehydes react very quickly (5 min). The reaction has been used in natural products synthesis.[6,9,13] With the morpholino analog, (phenylseleno)acetaldehyde gives a bis(phenylseleno)enamine, which is hydrolyzed to bis(phenylseleno)acetaldehyde; this is then converted into tris(phenylseleno)acetaldehyde (eq 4).[4a,b] $PhSeNEt_2$[3] and *N*-phenylselenomorpholine[8] react also with 1,3-dicarbonyl compounds (eqs 5 and 6).

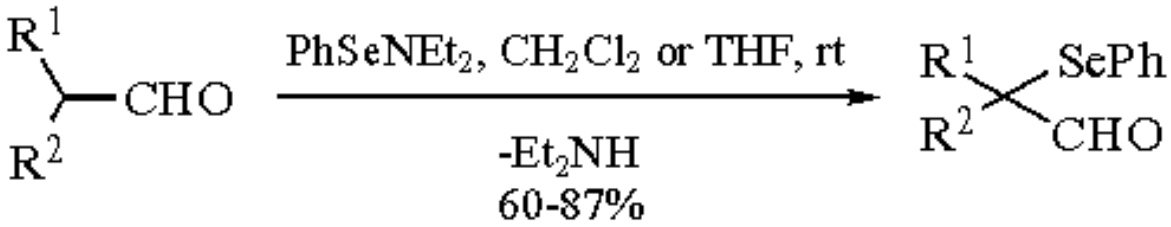

(3)

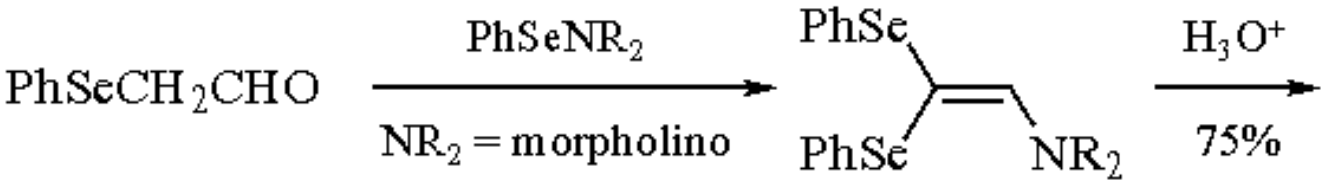

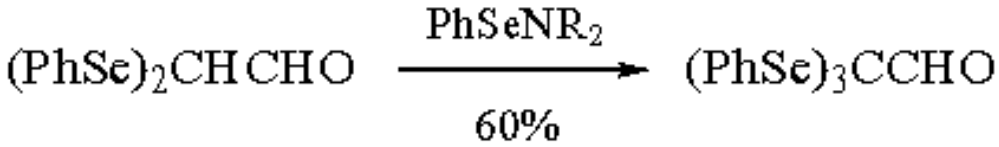

(4)

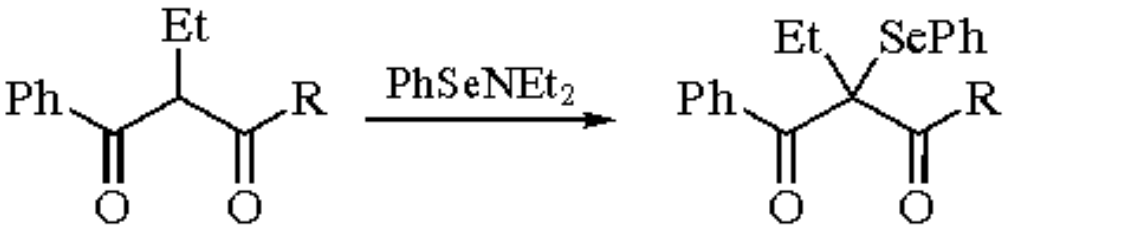

(5)

R = H, 80%; OMe, 92%

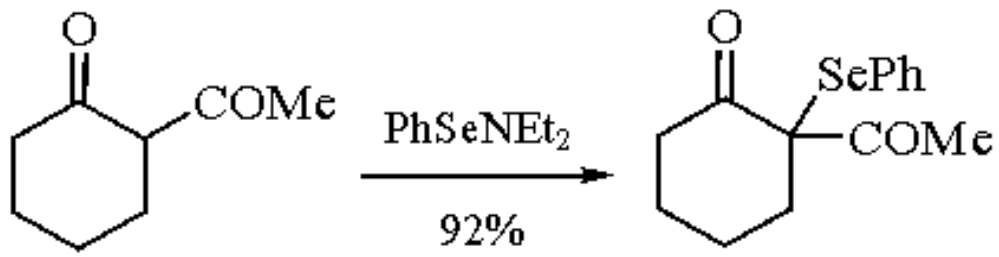

(6)

Using $PhSeNMe_2$, a reverse Claisen reaction sometimes occurs.[3] Ketones and selenenamides lead to mixtures. Chiral selenenamides and 4-alkylcyclohexanones produce α-phenylselenocyclohexanones in refluxing solvent (THF, benzene) in poor yields (20-52%) and modest enantiomeric excess.[10] 2-Phenyl-2-(*p*-chlorophenylseleno)propionaldehyde is prepared from 2-phenylpropionaldehyde and the *p*-chlorobenzeneselenenamide derived from *S*-methyl prolinate, in optically pure form.[11] α-Oxo esters react also, under the same conditions (eq 7).[4b]

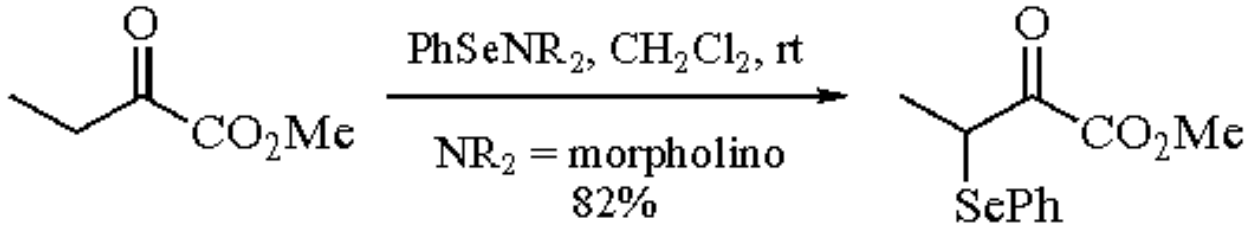

(7)

Reactions with Enamines and Silyl Enol Ethers.

Selenenamides add to enamines with elimination of an amine (eqs 4 and 8).[4b] Silyl enol ethers give α-phenylseleno ketones (eq 9)[4b] and conjugated dienoxysilanes allow access to γ-phenylseleno-α,β-unsaturated carbonyl compounds (eq 10).[4b]

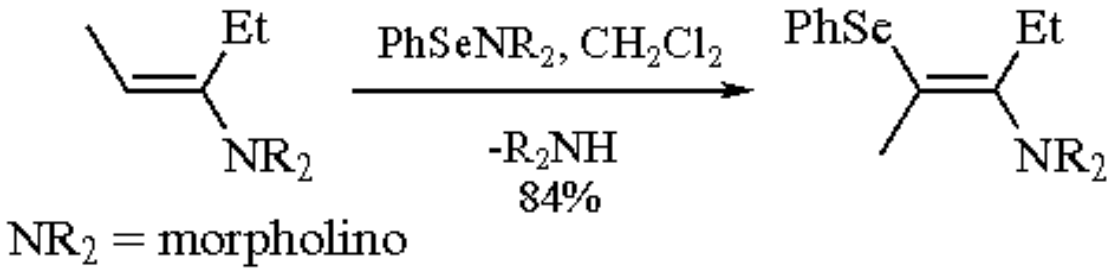

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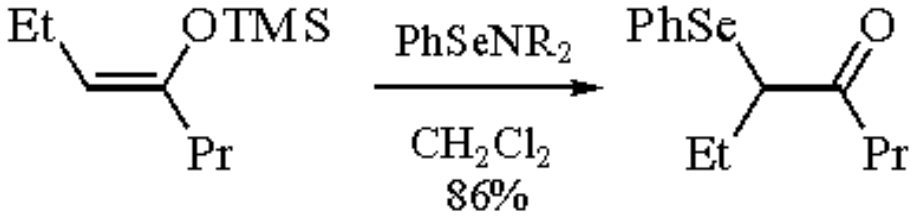

(9)

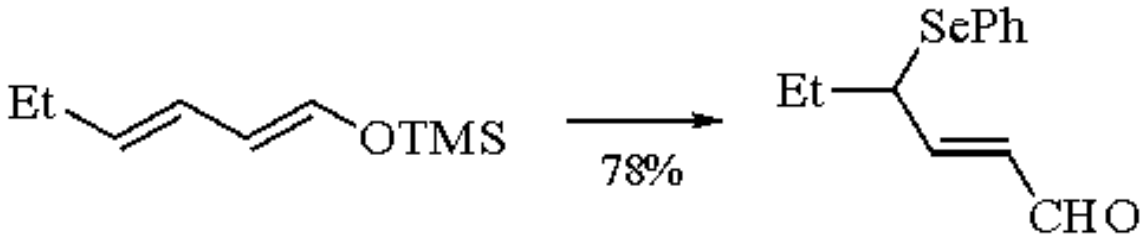

(10)

Additions to Electron-Deficient Alkenes.

$PhSeNEt_2$, formed with the PhSeOH resulting from a *syn*-elimination reaction of α-phenylseleninyl ketones, adds to the newly created double bond to give α-phenylseleno enones (eq 11).[3]

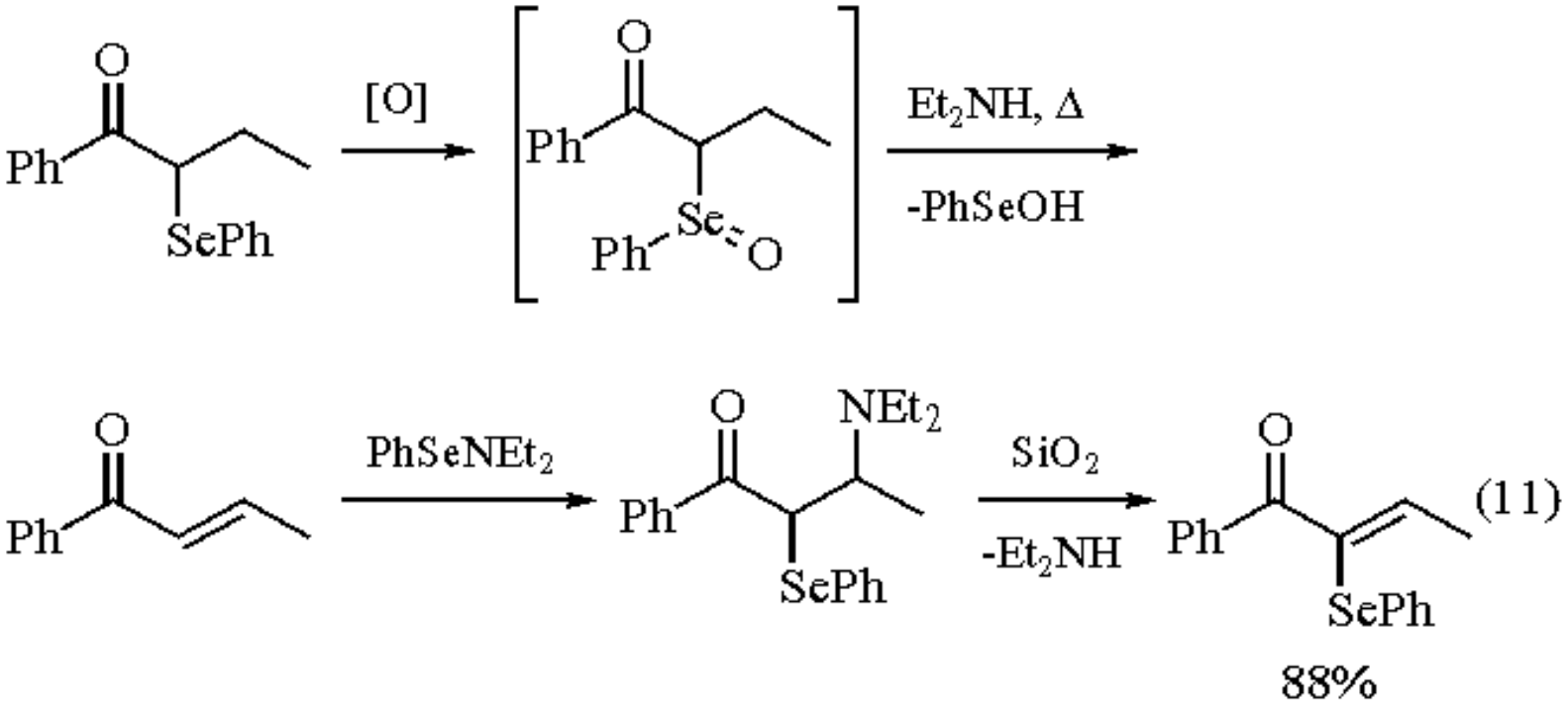

(11)

$PhSeNMe_2$ reacts also with α-alkylated enones (eq 12). The adduct is isolated and oxidized to an α-aminomethyl enone, which is the major product.[3] Selenenamides add to conjugated enals to give α-phenylseleno enals (eq 13).[4b] A demethylation occurs on a 6-methylenemisotane by treatment with *N*-phenylselenomorpholine and also when the 6-methyl-6-(phenylseleno)misotane is oxidized and treated with a secondary amine. PhSeOH, liberated during the elimination step, is transformed into a selenenamide which adds to the double bond. A retro-Mannich reaction explains the demethylation.[14]

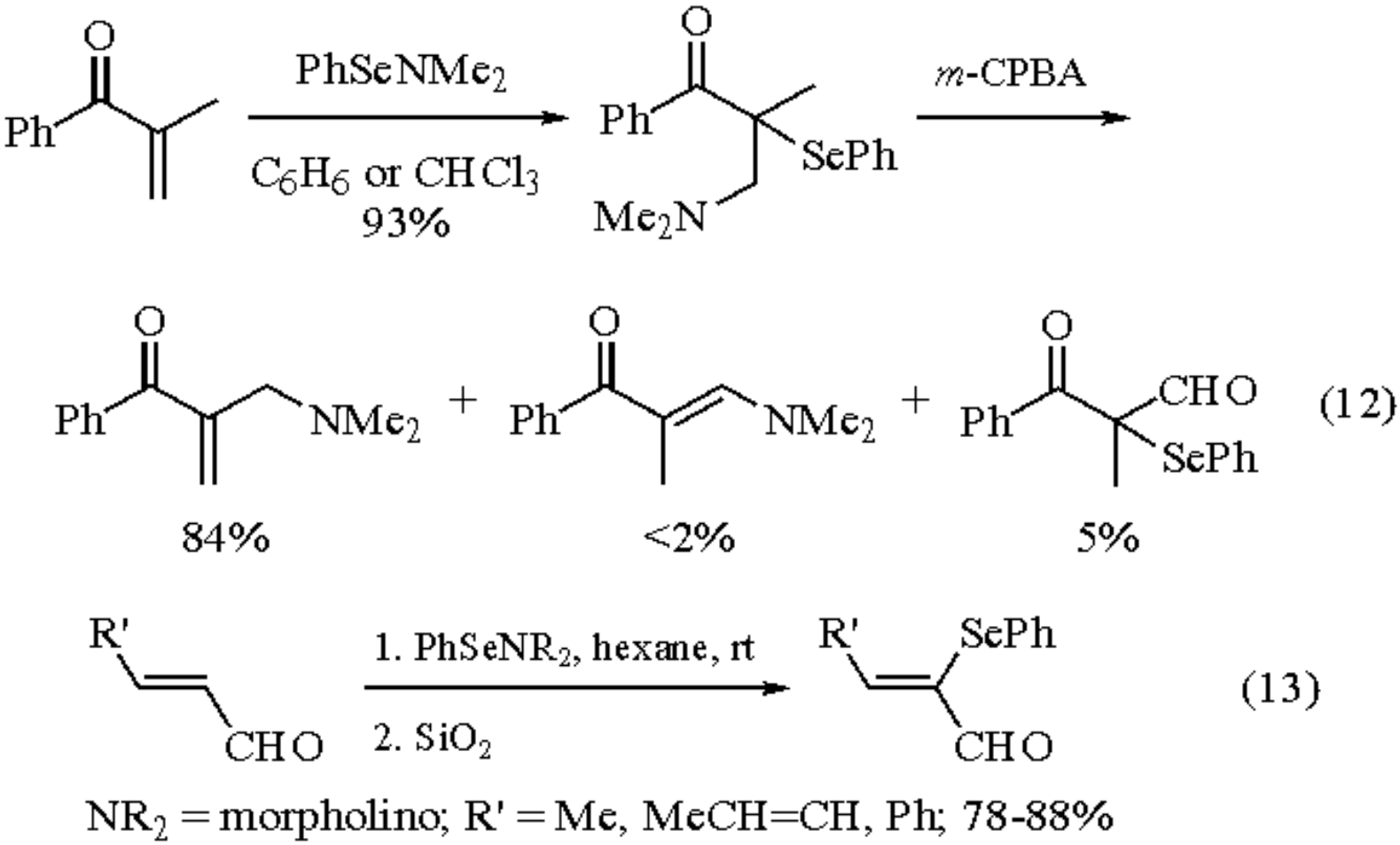

$PhSeNMe_2$ and ***Dimethyl Acetylenedicarboxylate*** give a mixture of isomers. The maleate kinetic product (**1**) partially isomerizes to the fumarate form (**2**) (eq 14).[15] The sulfenamides add only under forcing conditions.[15] Selenenamides react with butynone and ***Methyl Propiolate***.[4b]

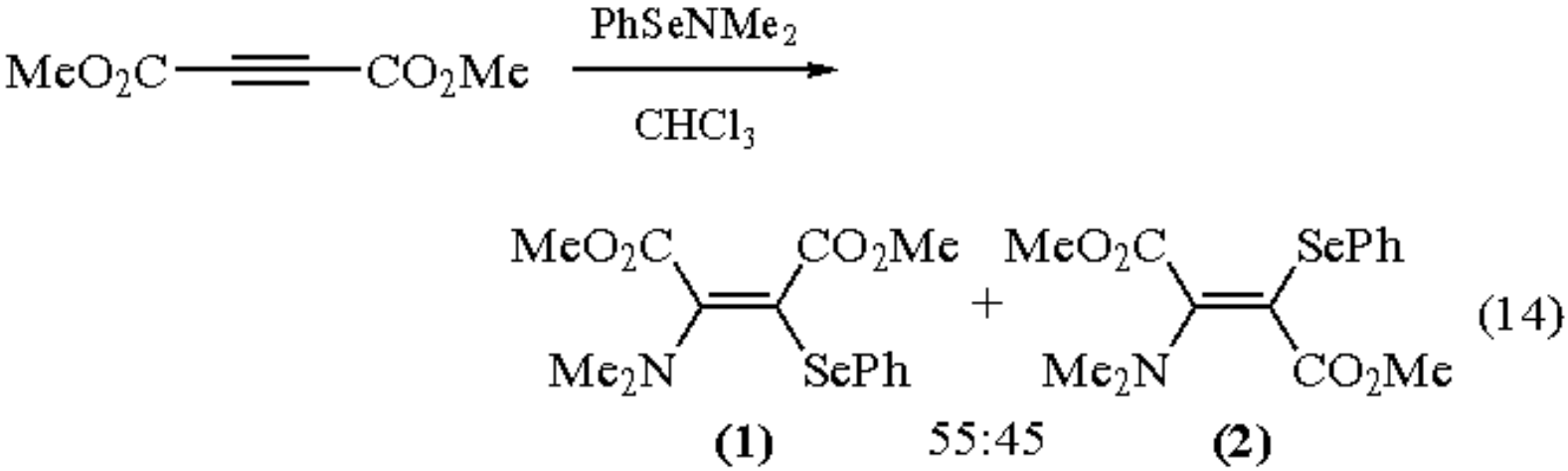

Related Reagents.

N-Phenylselenophthalimide; ***N-Phenylthiophthalimide***.

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Diethyl *N*-Benzylideneaminomethylphosphonate

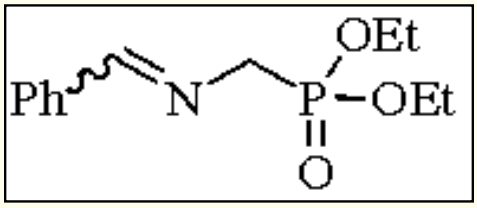

[50917-73-2] · $C_{12}H_{18}NO_3P$ · Diethyl *N*-Benzylideneaminomethylphosphonate · (MW 255.25)

(reagent for preparation of β-lactams[1] and α-aminophosphonic acids;[3] agent for quaternary carbon formation[4])

Physical Data: bp 145-149 °C/0.05 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: light yellow oil.

Analysis of Reagent Purity: readily ascertained by NMR.

Preparative Methods: 1,3,5-tribenzylhexahydro-*s*-triazine is reacted with ***Diethyl Phosphonite*** at 100 °C to yield *N*-benzylaminomethylphosphonate. *N*-Debenzylation with H_2-***Palladium on Carbon*** and subsequent Schiff base formation with PhCHO affords the title reagent in virtually quantitative yield.[1a] Alternatively, the reagent may be prepared from the *N*,*N*-bis(TMS)aminomethylphosphonate and PhCHO in the presence of a catalytic amount of ***Trimethylsilyl Trifluoromethanesulfonate***.[2] A different approach to the aminomethylphosphonate intermediate starts with conversion of *N*-hydroxymethylphthalimide to the *N*-bromomethyl compound followed by an Arbuzov reaction with ***Triethyl Phosphite***. Treatment of the resultant phthalimidomethylphosphonate with ***Hydrazine*** yields diethyl aminomethylphosphonate which is then subjected to imine formation with PhCHO.[4a]

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: stable to air and moisture. Conveniently stored under N_2 at ambient temperature or lower. Shelf life undetermined.

β-Lactams.

Diethyl *N*-benzylidineaminomethylphosphonate (**1**) has served as a starting point in three approaches to β-lactam antibiotics. Deprotonation and acylation (eq 1) yields phosphonoacetate (**2**) which is utilized in the preparation of α-thioformamido(diethylphosphono)acetates (**3**). These serve as key intermediates for further elaboration to 6-H cephalosporins (**4**) (eq 2).[1a] An attempt to extend this approach to carbapenem ring systems was unsuccessful due to the instability of later intermediates.[1b]

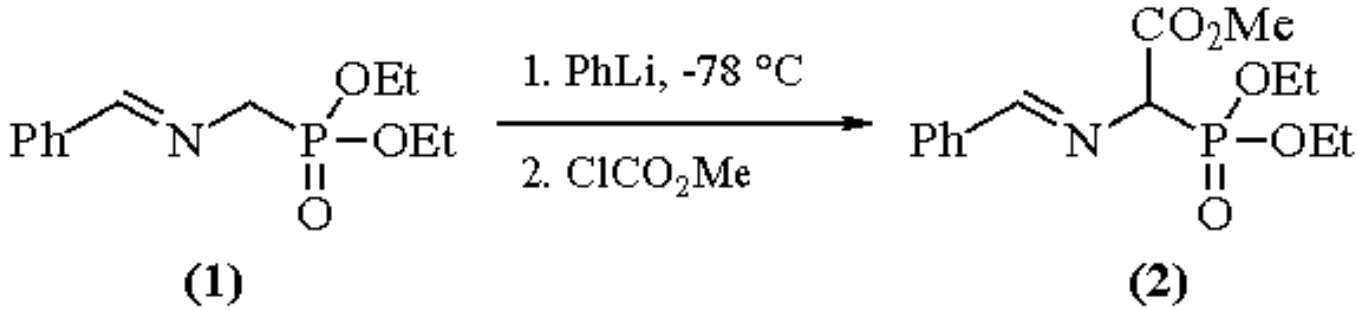

(1) (2) (1)

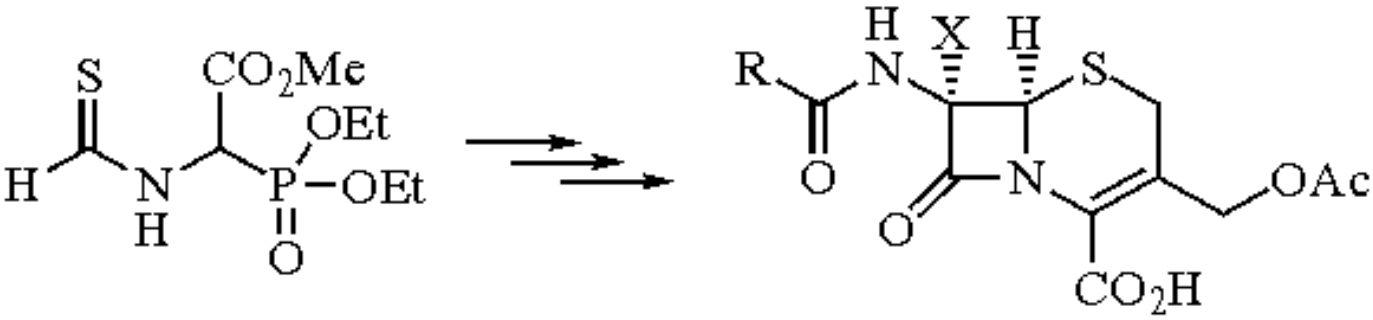

(3) (4) (2)

An example of a novel synthesis of substituted β-lactams was demonstrated by photolytic decomposition of chromium carbene complex (**5**) in the presence of (**1**) to afford the trisubstituted lactam (**6**) with a high degree of stereoselectivity and in 90% yield (eq 3).[1c]

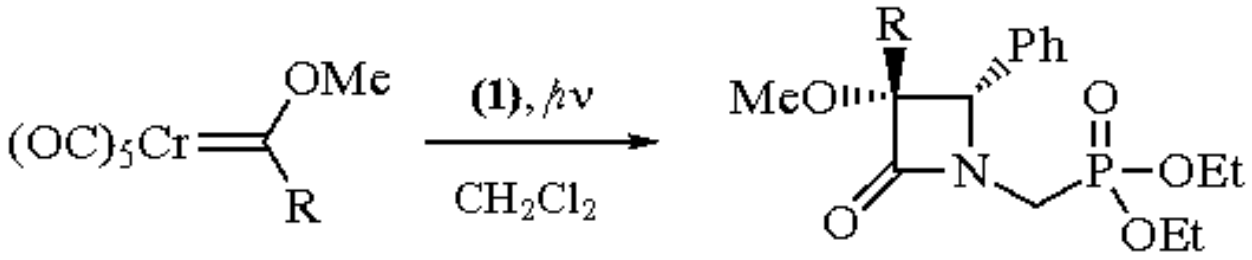

(5) (6) (3)

α-Aminophosphonic Acids.

Alkylation of the anion prepared by deprotonation of (**1**) provides, after hydrogenolysis of the benzylidene group and hydrolysis of the phosphonate esters, convenient access to α-aminophosphonic acids (**7**) (eq 4).[3a] Yields of alkylated product are generally quite high (>80%) and suitable electrophiles include primary, allylic, and benzylic halides as well as α-$BrCH_2CO_2Et$ and halomethylpyridines.[3b,3c] The 1-amino-2-arylethylphosphonic acids can be viewed as

phosphorus-based phenylalanine analogs.

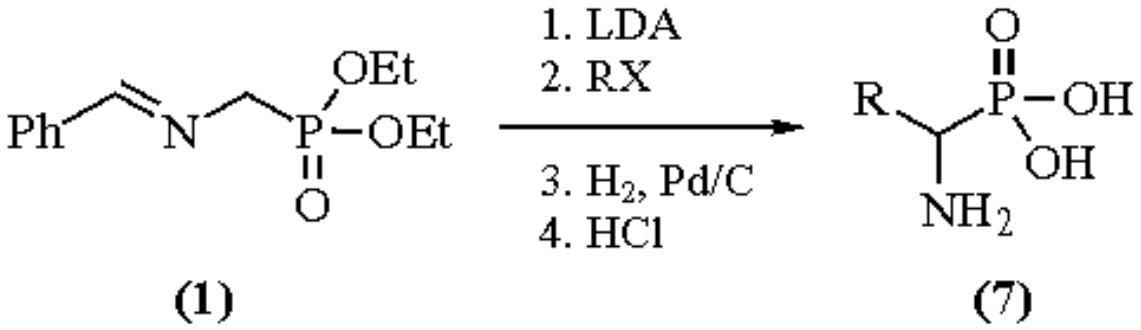

(4)

Quaternary Carbon Formation.

Probably the most innovative use of (**1**) has been in the preparation of quaternary carbon centers via geminal acylation-alkylation at a carbonyl center.[4a,4b] Lithiation of (**1**) followed by condensation with a carbonyl substrate affords, upon warming, the azadiene (**8**) (eq 5). Regioselective addition of ***n-Butyllithium*** to (**8**) generates a metalloenamine which, on alkylation followed by hydrolysis of the resultant imine, gives products of general structure (**9**) (eq 6). The entire sequence may be conveniently carried out in a single reaction vessel without isolation of intermediates with moderate to high overall yields. Judicious choice of electrophile in the alkylation may introduce functionality suitable for subsequent elaboration to 4,4-disubstituted cyclopentenones or 4,4-disubstituted cyclohexenones.[4b] This strategy has been a key feature in the syntheses of mesembrine and various Amaryllidaceae alkaloids.[4c-e]

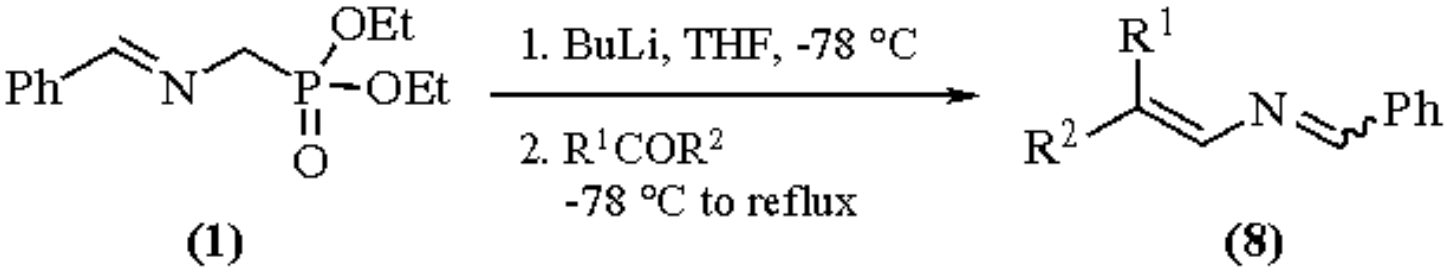

(5)

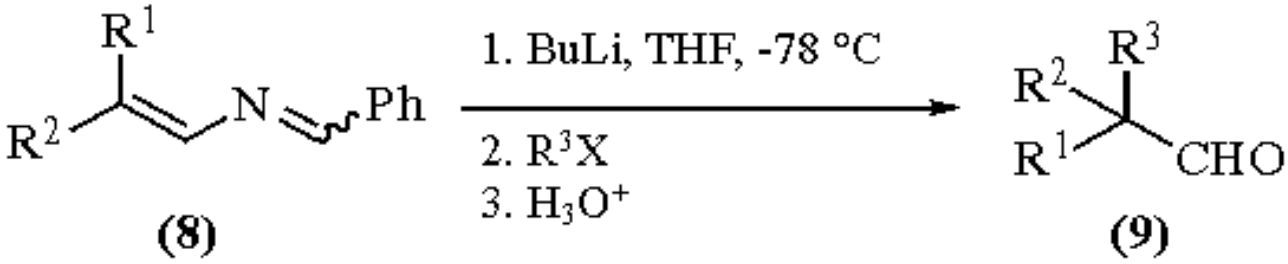

(6)

1,4-Additions.

The anion of (**1**) undergoes Michael addition to ethylidenebisphosphonate (**10**), affording functionalized *gem*-bisphosphonates (**11**) (eq 7).[5a]

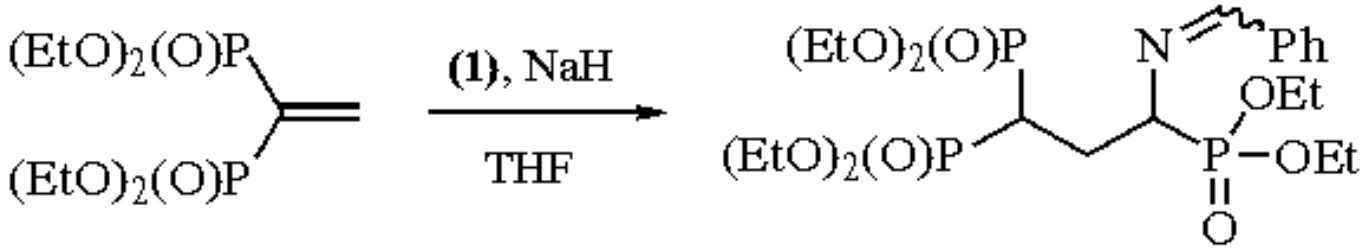

(7)

(10) **(11)**

Conjugate addition of the anion of (**1**) to acrylates affords Δ^1-pyrrolines by intramolecular cyclization via nucleophilic addition of the resultant enolate to the imine moiety (eq 8).[5b] The reaction is regioselective and stereospecific and the product distribution depends on reaction conditions and the steric nature of the substrate.

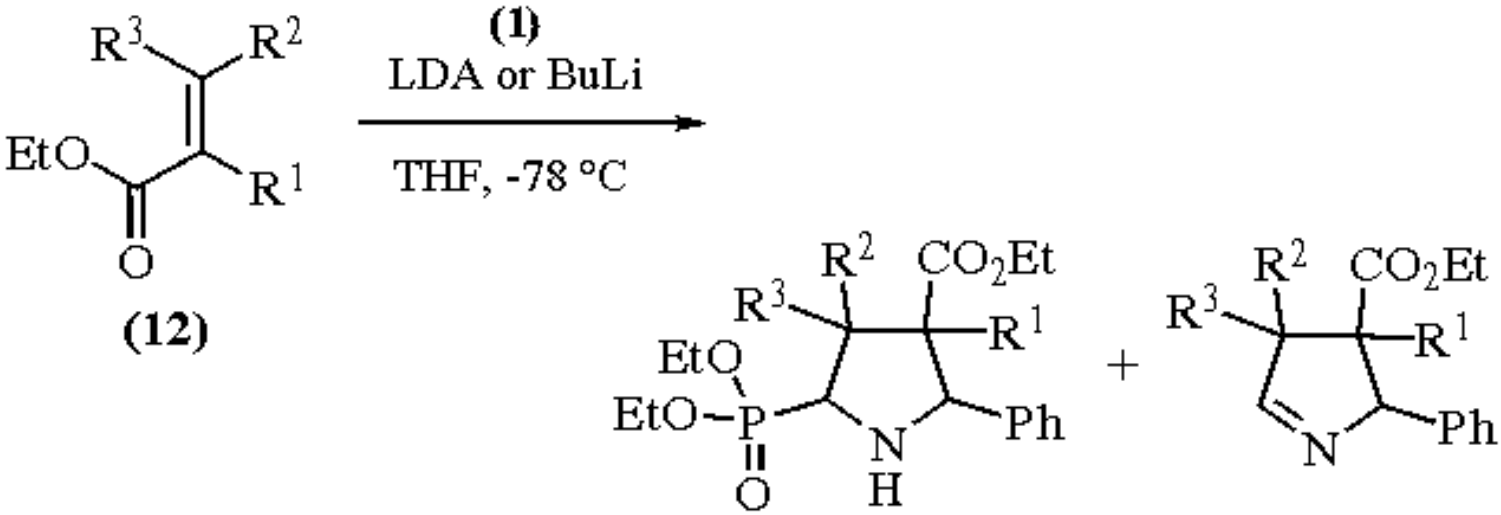

(8)

(12) **(13)** **(14)**

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Diethyl-*t*-butoxycarbonylmethylaluminum[1]

$Et_2AlCH_2CO_2$-*t*-Bu

[59211-98-2] · $C_{10}H_{21}AlO_2$ · Diethyl-*t*-butoxycarbonylmethylaluminum · (MW 200.26)

(nucleophilic reagent for epoxide opening[1,3])

Preparative Method: prepared in situ from *t*-butyl lithioacetate (Rathke's salt)[2] and ***Diethylaluminum Chloride*** in toluene at -40 °C (eq 1). Instantaneous deposition of lithium chloride is observed and the resulting suspension is used directly in reactions with epoxides.[1] Other solvents, such as THF and DME, are also used successfully.[3]

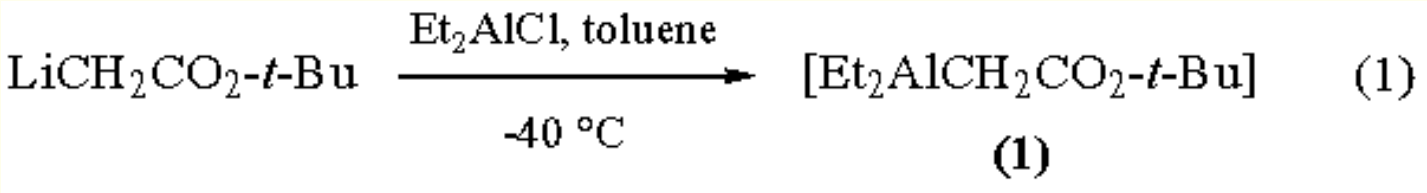

Handling, Storage, and Precautions: the reagent should be used without isolation immediately after preparation. Reactions must be performed under an inert atmosphere (N_2, Ar).

Epoxide Opening.

Reaction of diethyl-*t*-butoxycarbonylmethylaluminum with cyclohexene oxide at ambient temperature gives the *trans*-γ-hydroxy ester, which in turn can be converted into a *trans*-γ-lactone (eq 2). In contrast, the reaction of cyclohexene oxide and *t*-butyl lithioacetate gives the hydroxy ester in very poor yield (eq 3).[1]

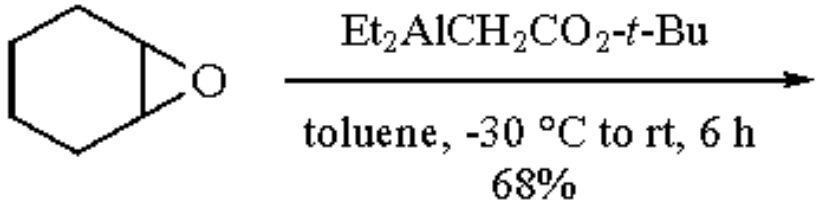

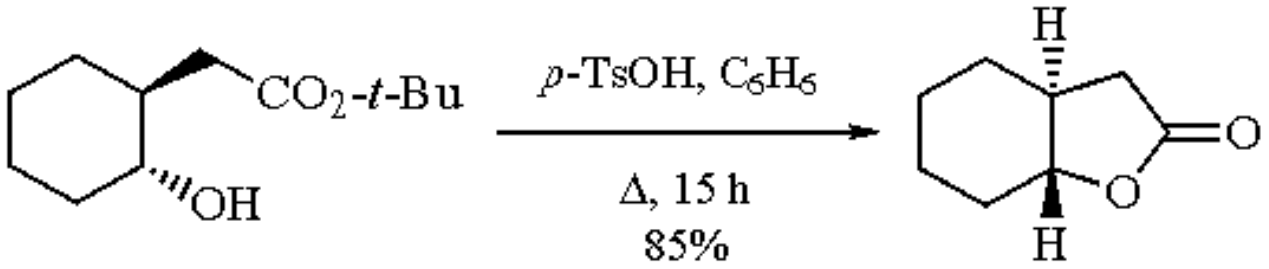

(2)

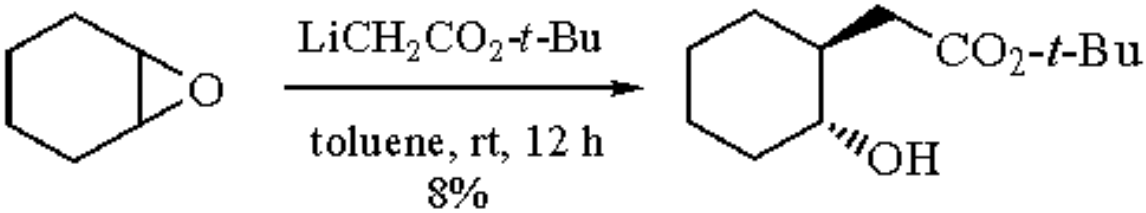

(3)

Ring opening reactions of sterically hindered epoxides, however, are not successful with this aluminum reagent in toluene (eq 4).

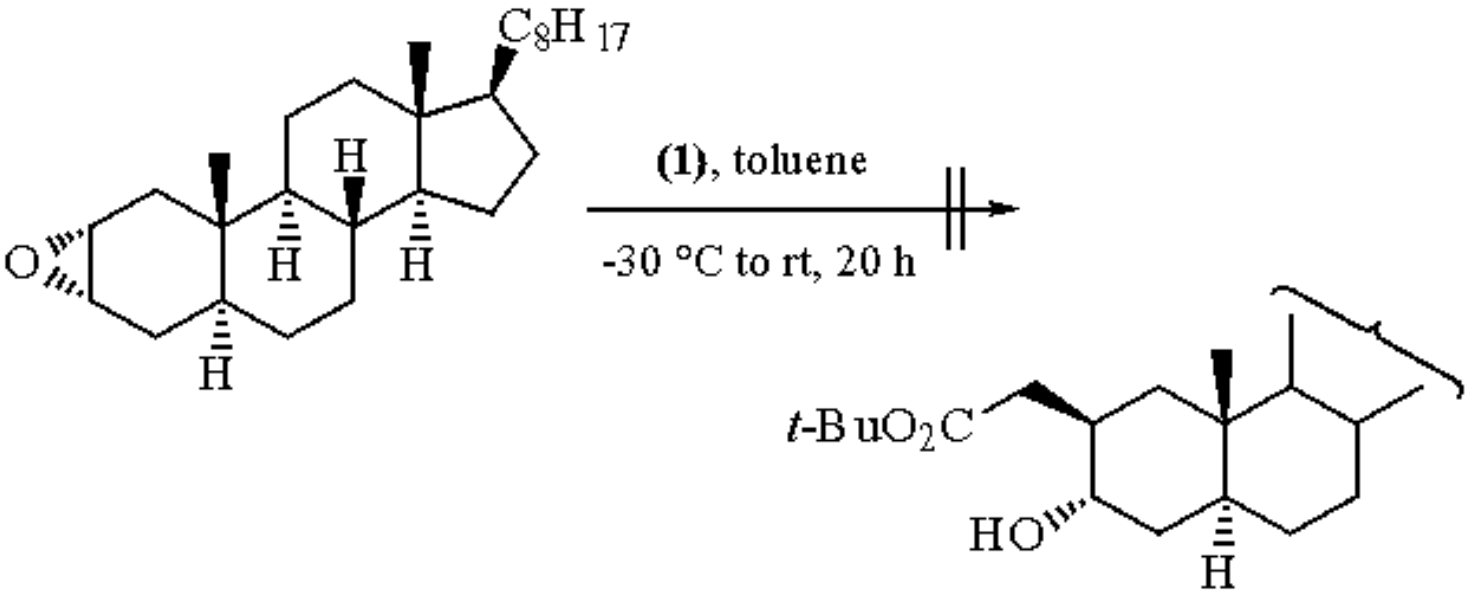

(4)

Regio- and stereospecific opening reactions of unsymmetrical epoxides may be carried out under various conditions. The reactions are much faster in THF and DME than in toluene, and the yields of hydroxy esters are also greatly improved (eqs 5 and 6).[3] Remarkably, the reactions of allylic epoxides proceed by direct S_N2 pathways (eq 5).

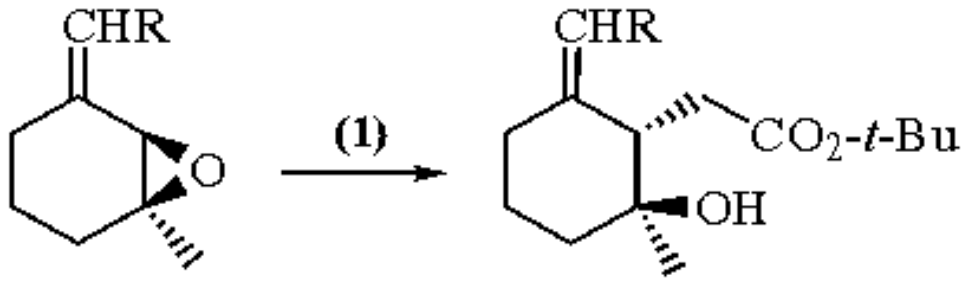

(5)

R	Conditions	Yield (%)
H	toluene, 25 °C, 2 h	24
H	THF, -55 °C, 0.5 h	94
CH_2OTBS	THF, -50 °C, 1 h	82
CH_2OTBS	DME, -50 °C, 1 h	84
CH_2OMOM	toluene, 25 °C, 2 h	25
CH_2OMOM	DME, -45 °C, 1 h	83

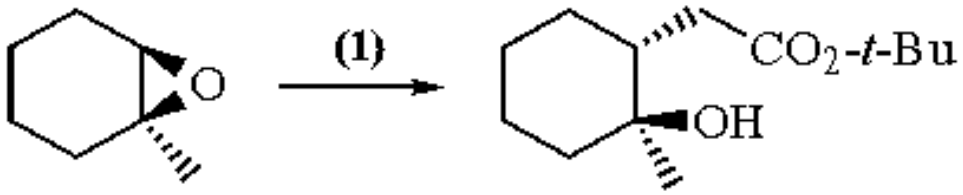

(6)

Conditions	Yield (%)
toluene, 25 °C, 8 h	5
DME, 25 °C, 4 h	45

1. Danishefsky, S. J.; Kitahara, T.; Tsai, M.-Y.; Dynak, J. *JOC* **1976**, *41*, 1669.
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Diethyl Carbonate

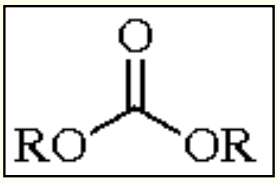

(R = Et)

[105-58-8] · $C_5H_{10}O_3$ · Diethyl Carbonate · (MW 118.13) (R = Me)

[616-38-6] · $C_3H_6O_3$ · Dimethyl Carbonate · (MW 90.08)

(*C*-alkoxycarbonylations of carbanions[2-12] and other nucleophiles;[13] synthesis of ketones[14] and tertiary alcohols;[15] allylations with allyl alkyl carbonates;[16] alkylations of nucleophilic substrates;[17-20] heterocyclic synthesis[21])

Physical Data: R = Et: bp 127 °C; *d* 0.975 g cm^{-3}. R = Me: bp 90.3 °C; *d* 1.070 g cm^{-3}.

Solubility: miscible organic alcohols, esters, ethers. R = Et: insol H_2O. R = Me: sol 13.9 g per 100 g H_2O at 20 °C.

Form Supplied in: readily available; inexpensive.

Handling, Storage, and Precautions: inhalation of the vapors of dimethyl carbonate may cause irritation.

Alkoxycarbonylations of Carbanions.

Diethyl and dimethyl carbonate are valuable reagents for the *C*-alkoxycarbonylation of enolate anions derived from active methylene compounds.[1,2] The yields, in general, are comparable to those found using other electrophilic alkoxycarbonylating agents. Various bases such as ***Sodium Hydride***, NaH-KH mixtures, metal alkoxides, and nonnucleophilic species such as ***Lithium Diisopropylamide*** at low temperature have been utilized to generate enolate anions. The latter method is particularly useful, since enolate formation is complete, and competitive condensations of the enolate anions with the substrate are avoided. Ketones[3] can readily be converted into β-keto esters and esters into malonate esters.[4] Selected examples for the conversion of a cyclic (eq 1)[3f] and an alicyclic ketone (eq 2)[3b] to the respective β-keto esters are illustrated. In the acyclic example, the kinetically formed enolate is *C*-ethoxycarbonylated.

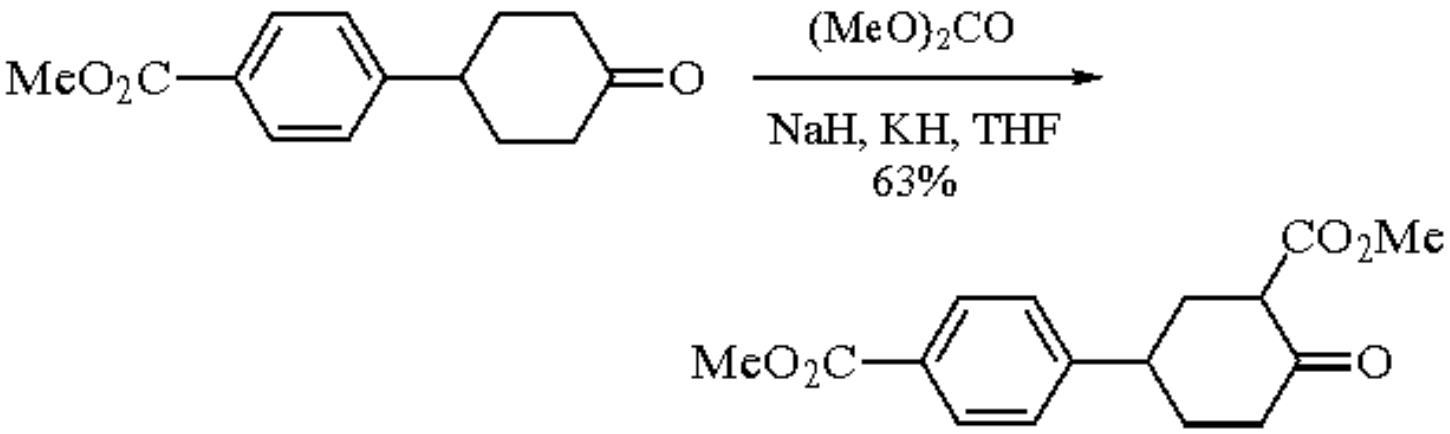

(1)

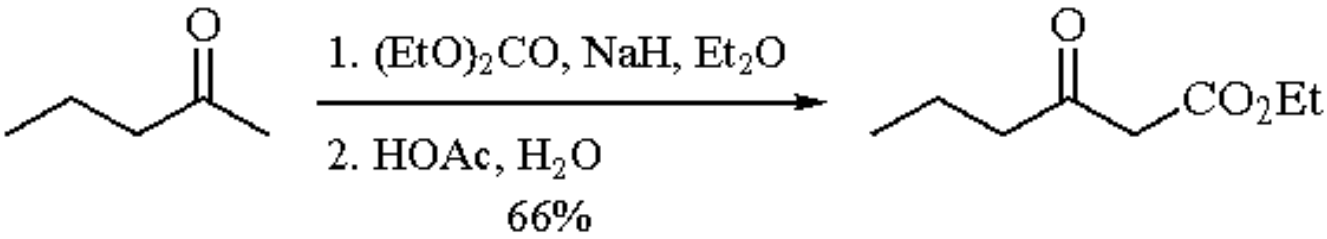

(2)

The conversion of *t*-butyl acetate to the *t*-butyl methyl malonate ester (eq 3)[4] and a *C*-methoxycarbonylation of γ-butyrolactone (eq 4) have been described.[5]

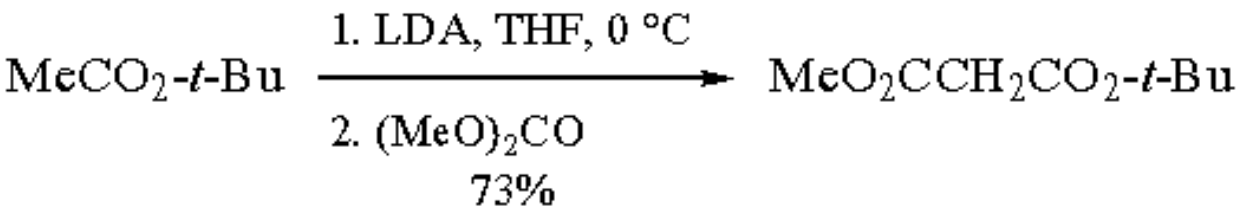

(3)

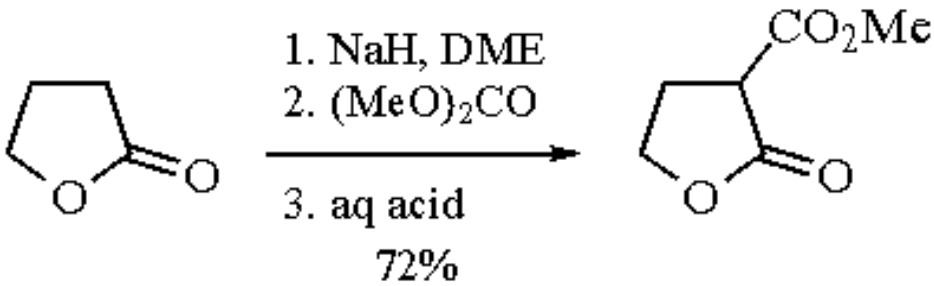

(4)

Aryl and alkyl cyanides are readily alkoxycarbonylated.[6] The α-ethoxycarbonylations of phenylacetonitrile (eq 5)[6c] and cyanopentanecarbonitrile (eq 6)[6a] are typical examples.

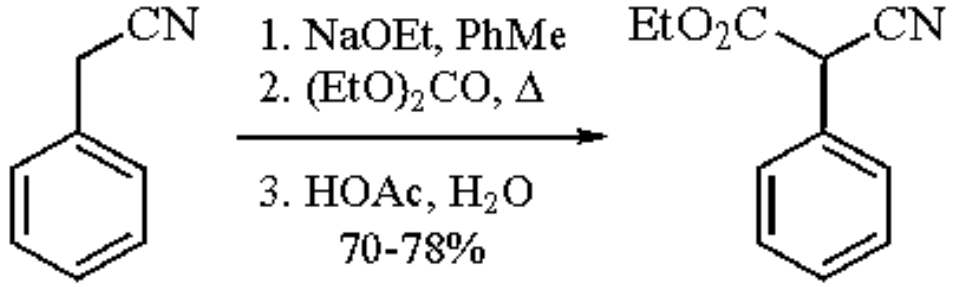

(5)

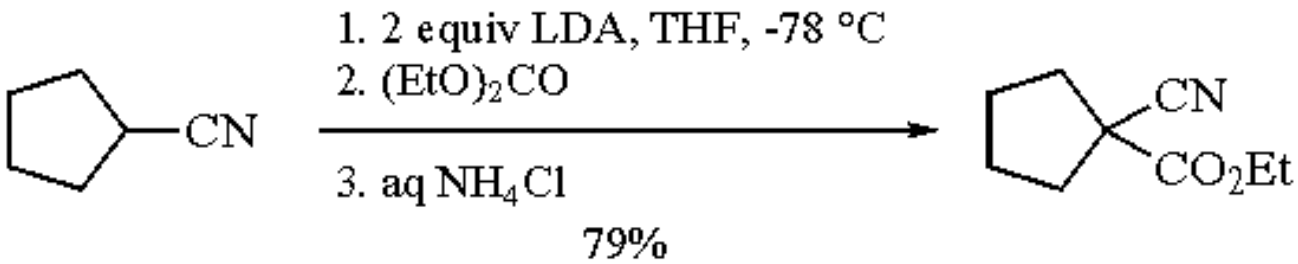

(6)

The transformations of primary nitro compounds (eq 7)[7] and isocyanides (eq 8)[8] into the α-ethoxycarbonylation products have been reported.

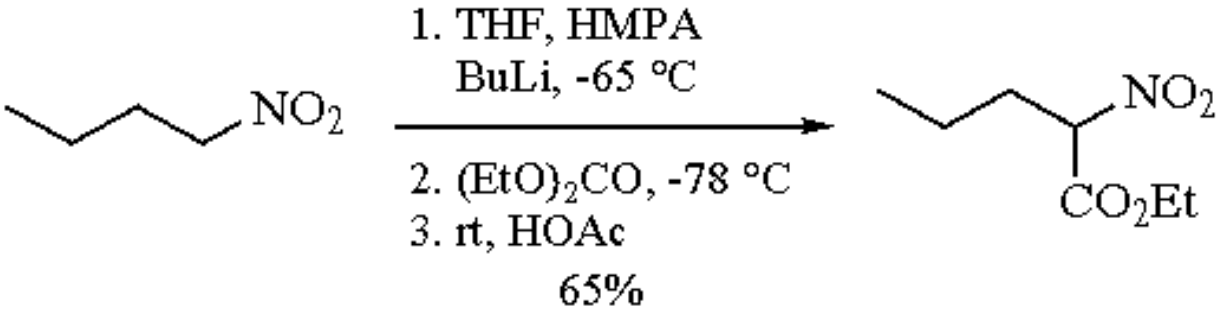

(7)

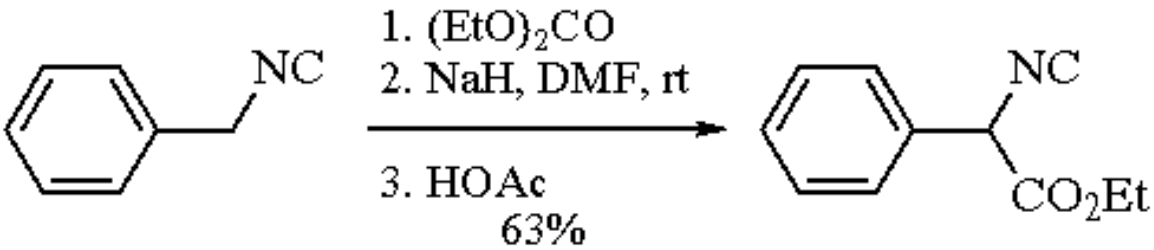

(8)

The conversion of 2,6-dimethylpyridine to ethyl 6-methylpyridine-2-acetate has been accomplished using ***Potassium Amide*** and diethyl carbonate (eq 9).[9]

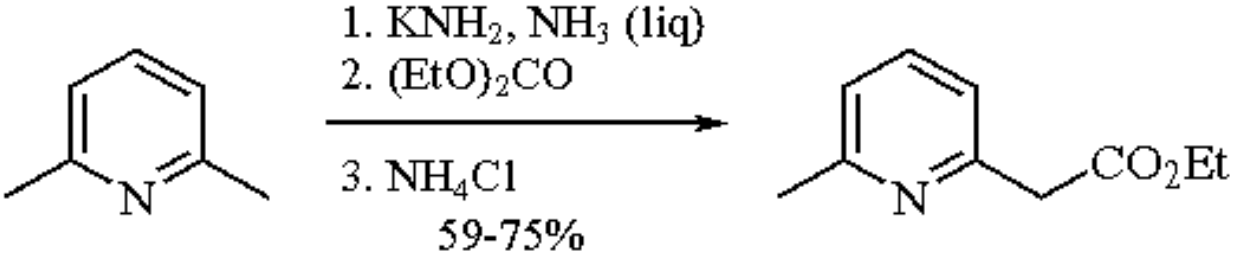

(9)

The dianions formed from cyclic or acyclic carboxylic acids on treatment with dimethyl or diethyl carbonate lead to

monoesters of malonic acid (eq 10).[10]

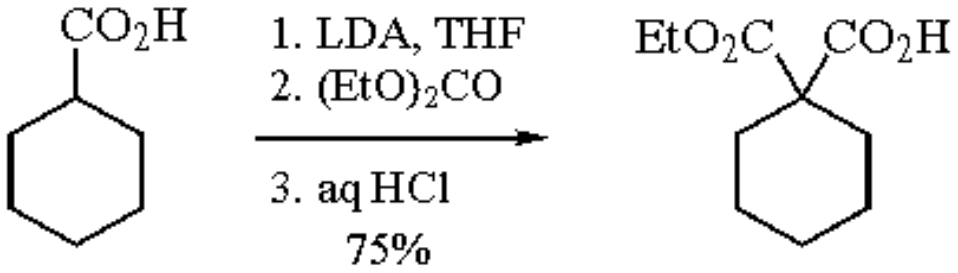

(10)

Carboxylic acid esters can be synthesized from aryl[11] or alkyl halides[11b] by treatment of the corresponding Grignard reagents with dimethyl or diethyl carbonate. For example, addition of ***Phenylmagnesium Bromide*** in THF to a THF solution of dimethyl carbonate (2.0 equiv) at 0-5 °C leads to methyl benzoate (87%).[11]

Carbanions formed via directed metalations undergo facile α-alkoxycarbonylations.[12] Lithiation of 1-(*t*-butoxycarbonyl)-1,2-dihydropyridine followed by addition of dimethyl carbonate leads to the α-methoxycarbonylated product (eq 11).[12a] The retention of configuration found in the alkoxycarbonylation of a benzyllithium analog is of interest (eq 12).[12b]

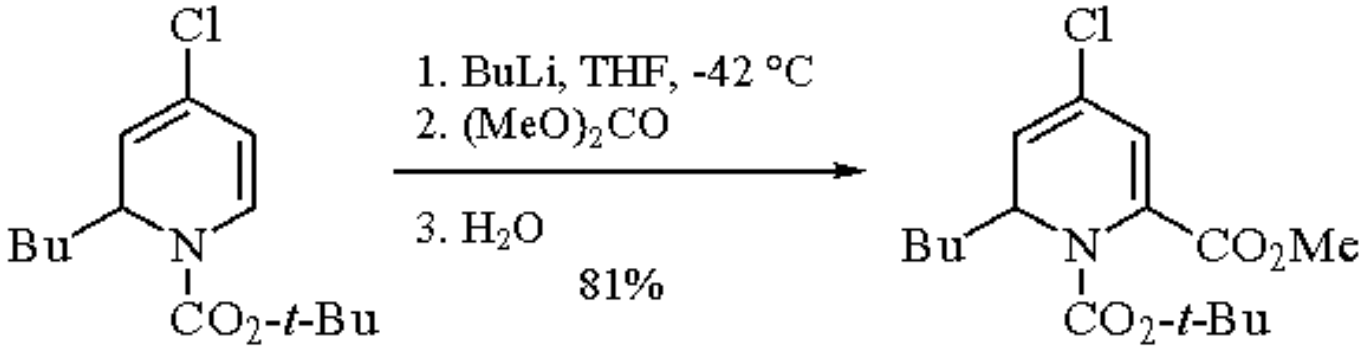

(11)

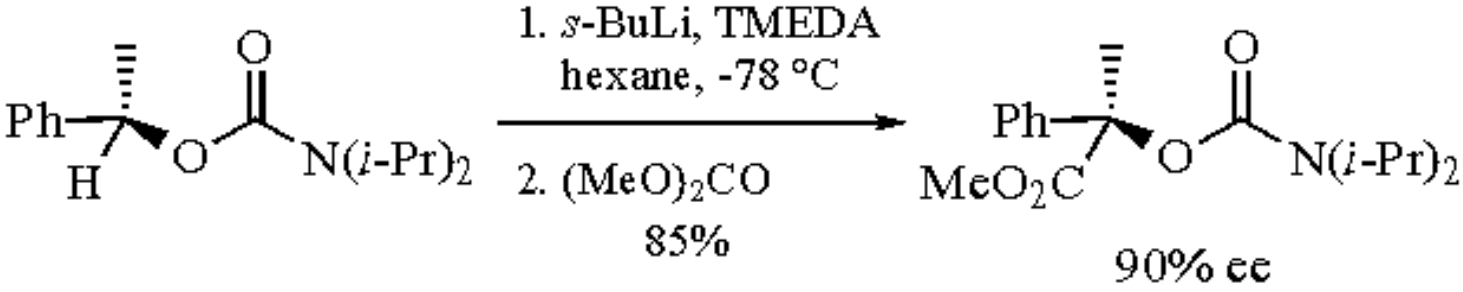

(12)

Other nucleophiles such as amines and hydrazines react with dimethyl or diethyl carbonate to yield the corresponding carbamates or carbazates. Treatment of hydrazine with diethyl carbonate leads to ethyl hydrazinecarboxylate (77-85%).[13]

Ketone Synthesis.

The synthesis of ketones can be effected by treatment of organometallics with diethyl carbonate.[14] The addition of 2 equiv of 4-chloro-3-lithiopyridine to diethyl carbonate affords bis(4-chloro-3-pyridyl) ketone (eq 13).[14c]

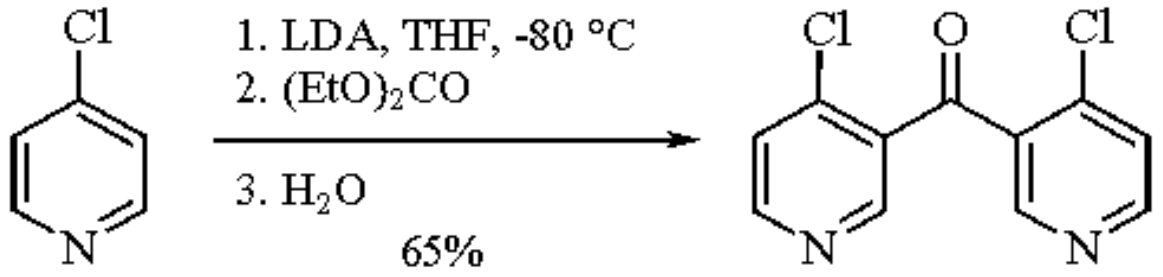

(13)

Tertiary Alcohol Synthesis.

Dimethyl or diethyl carbonate on treatment with organometallics lead to tertiary alcohols.[15]

Allylations and Alkylations.

The allylations of β-keto esters, β-diketones, malonate esters, nitriles, and nitro analogs can be accomplished under neutral conditions by use of a variety of allylic carbonates in the presence of a palladium-phosphine catalyst.[16] A typical procedure is shown (eq 14).[16a]

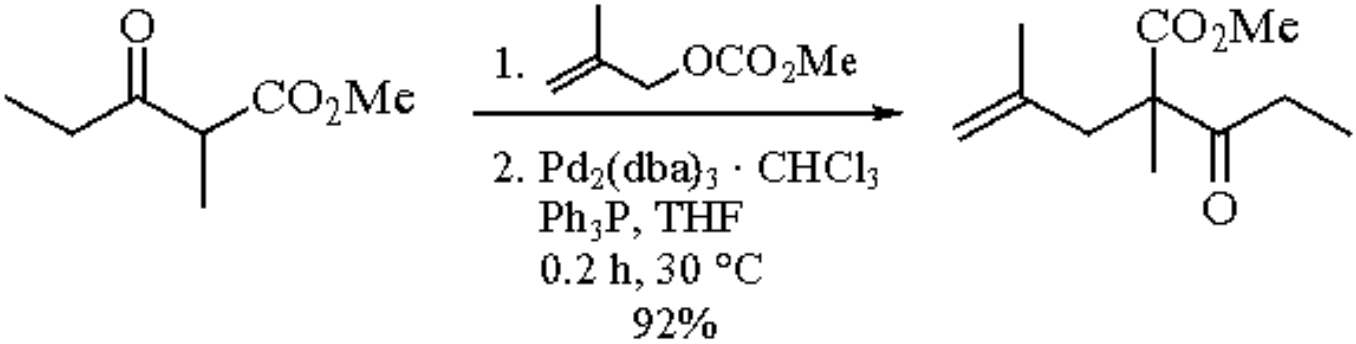

(14)

The selective mono-*N*-methylation of aromatic amines such as aniline[17] and mono-*C*-methylations of arylacetonitriles[18] by dimethyl carbonate can be performed by gas-liquid phase transfer catalysis. Dimethyl carbonate in the presence of potassium carbonate and ***18-Crown-6*** (or Aliquat 336) is useful for the *S*-methylation of alkyl or aryl thiols (eq 15), the *O*-methylation of phenols, and the *N*-methylation of imidazole.[19]

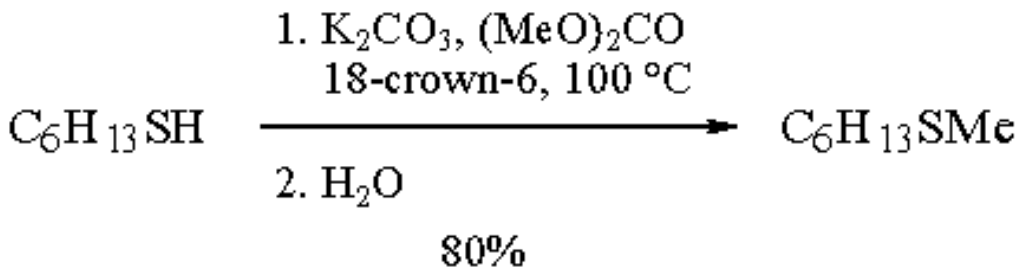

(15)

The α-methylation and α-methoxycarbonylation of primary esters has been accomplished by addition of the ester in dimethyl carbonate to a mixture of NaH in dimethyl carbonate (eq 16).[20]

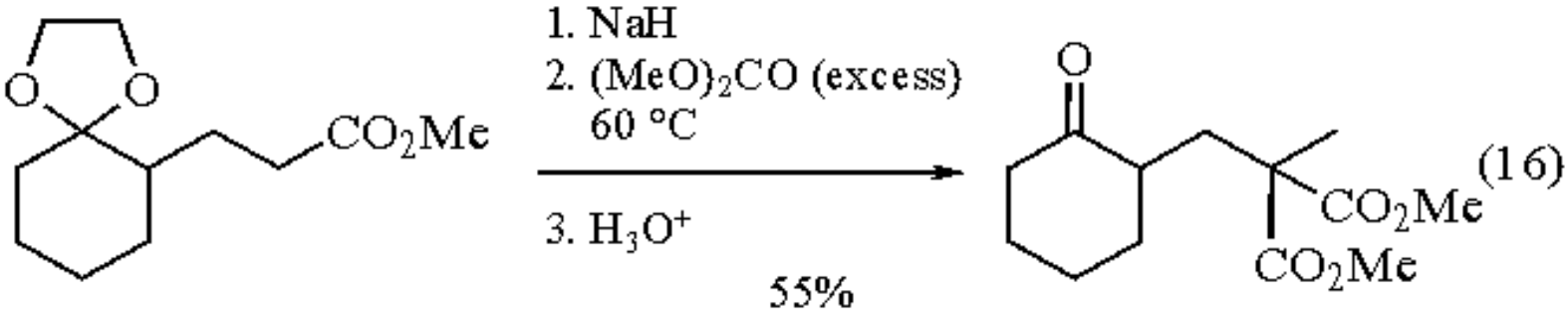

Synthesis of Heterocycles.

Many substrates react with dimethyl or diethyl carbonate to form heterocyclic compounds. Treatment of 1,2-amino alcohols with dimethyl carbonate affords 2-oxazolidinones.[21] The preparation of (*S*)-4-(phenylmethyl)-2-oxazolidinone (eq 17) is illustrative.[21c]

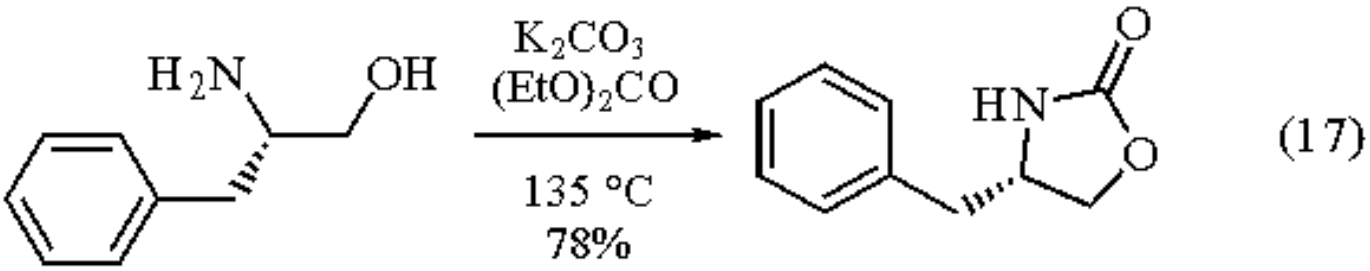

Related Reagents.

Benzyl Chloroformate; ***Carbon Dioxide***; ***Carbon Oxysulfide***; ***Di-t-butyl Dicarbonate***; ***Diethyl Oxalate***; ***Ethyl Chloroformate***; ***Methyl Magnesium Carbonate***; ***Methyl Cyanoformate***.

---

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Diethyl Chloromethylphosphonate

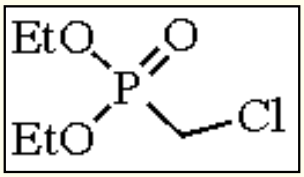

[3167-63-3] · $C_5H_{12}ClO_3P$ · Diethyl Chloromethylphosphonate · (MW 186.58)

((diethylphosphono)- or chloro(diethylphosphono)methylating agent for different functional groups; reacts mainly via the corresponding derived lithiated anion as an organometallic reagent;[1] can function as an electrophile[2])

Physical Data: bp 109-111 °C/10 mmHg; *d* 1.200 g cm^{-3}; *n*20D 1.439; δ ^{31}P 18 ppm (from 85% H_3PO_4); on a comparative scale of different phosphonates and reference compounds, the acidity of $(EtO)_2P(O)CH_2Cl$ is 1.74 pK_a units superior to that of phenylacetylene and 1 pK_a unit inferior to that of acetonitrile. Relative to other phosphonates, $(EtO)_2P(O)CH_2Cl$ is more acidic than $(EtO)_2P(O)Me$, by approximately 3 pK_a units and less acidic than $(EtO)_2P(O)CH_2Ph$ by 1.74 pK_a units.[3]

Solubility: sol THF, ether, dichloromethane, chloroform.

Form Supplied in: colorless liquid.

Preparative Methods: synthesis on a preparative scale of $(EtO)_2P(O)CH_2Cl$ and other (1-chloroalkyl)phosphonates is relatively difficult.[5-8] Ethanolysis of (chloromethyl)phosphonic dichloride is the most general and useful procedure (eq 1).[6] However, (chloromethyl)phosphonic dichloride is expensive and only commercially available in small amounts. Its preparation has been realized by reaction of ***Phosphorus(III) Chloride*** with dichloromethane in a closed metallic vessel heated at 100 °C for 24 h (eq 2).[7]

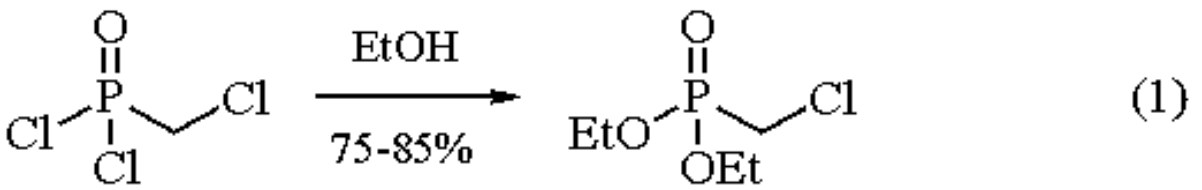

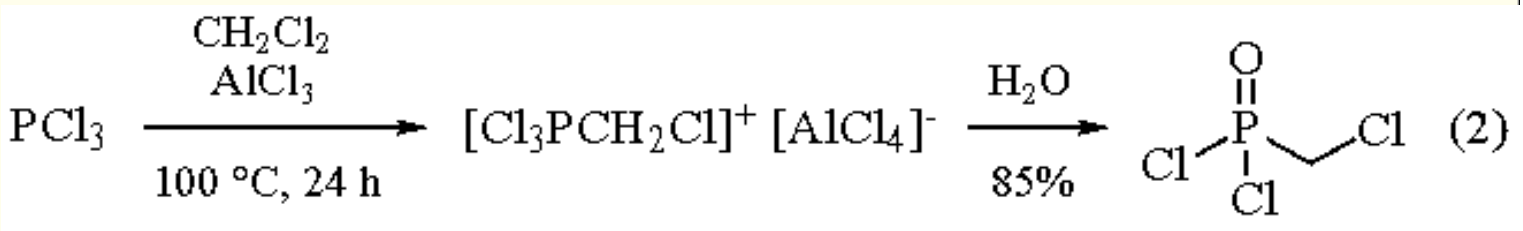

Other preparations using classical glass vessel apparatus can be used to obtain $(EtO)_2P(O)CH_2Cl$ on a small

scale (up to 10 g) from diethyl (hydroxymethyl)phosphonate (eq 3).[8]

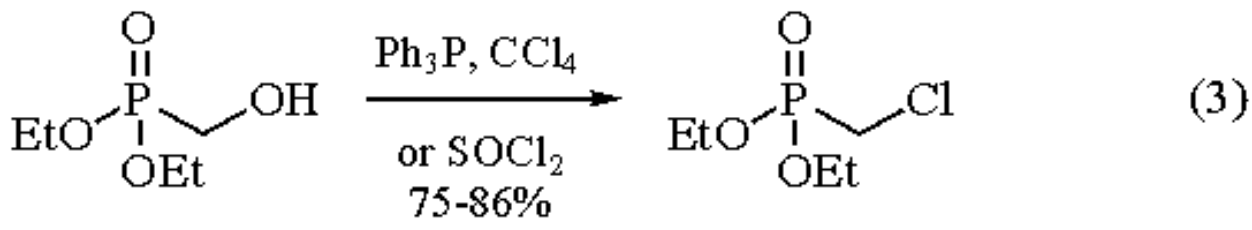

Analysis of Reagent Purity: the methyl hexyl ketone-acetone-heptane (4:1:5) system ensures effective thin-layer chromatographic separation on silufol plates of normal esters of methylphosphonic and (chloromethyl)phosphonic acids and a procedure has been developed for the identification of ^{32}P-labeled (chloromethyl)phosphonic acid esters in CCl_4 and $CHCl_3$.[4]

(Diethylphosphono)- or Chloro(diethylphosphono)methylation.

$(EtO)_2P(O)CH_2Cl$ (**1**) reacts with ***n-Butyllithium*** at low temperature in THF to give a lithiated anion which can be used as a (diethylphosphono)- or chloro(diethylphosphono)methylating agent for electrophilic compounds. As this carbanion degrades at temperatures above -30 °C to give unidentified oligomeric products,[3] it is advantageous to metalate (**1**) with an excess of ***Lithium Diisopropylamide*** (2 equiv) in THF. Under these conditions a stoichiometric amide-carbanion (1:1) association stabilizes the carbanion at 0 °C for at least 1 h (eq 4).[9]

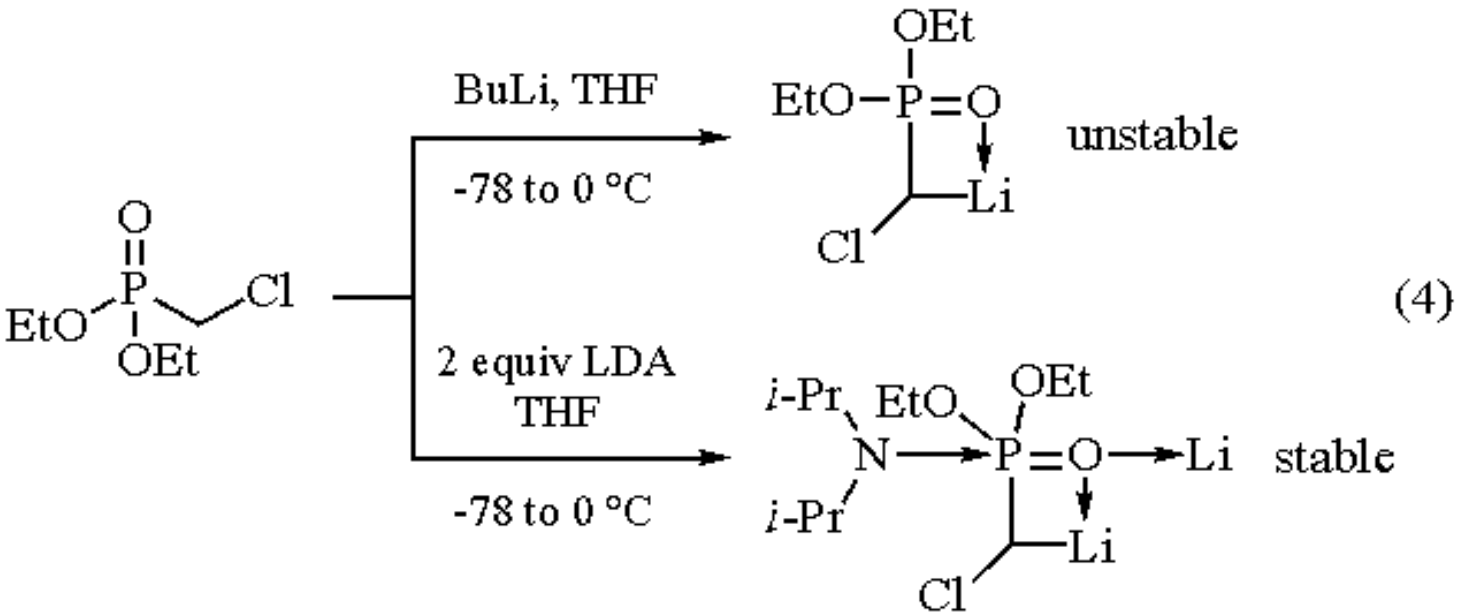

The Grignard reagent of (**1**) is known, but it has to be prepared by an exchange reaction between diethyl(iodomethy)phosphonate and isopropylmagnesium chloride. It reacts with some electrophiles such as ***Bromine***, ***Benzeneselenenyl Chloride***, and ***Benzeneselenenyl Bromide*** better than the corresponding lithiated anion (eq 5).[10]

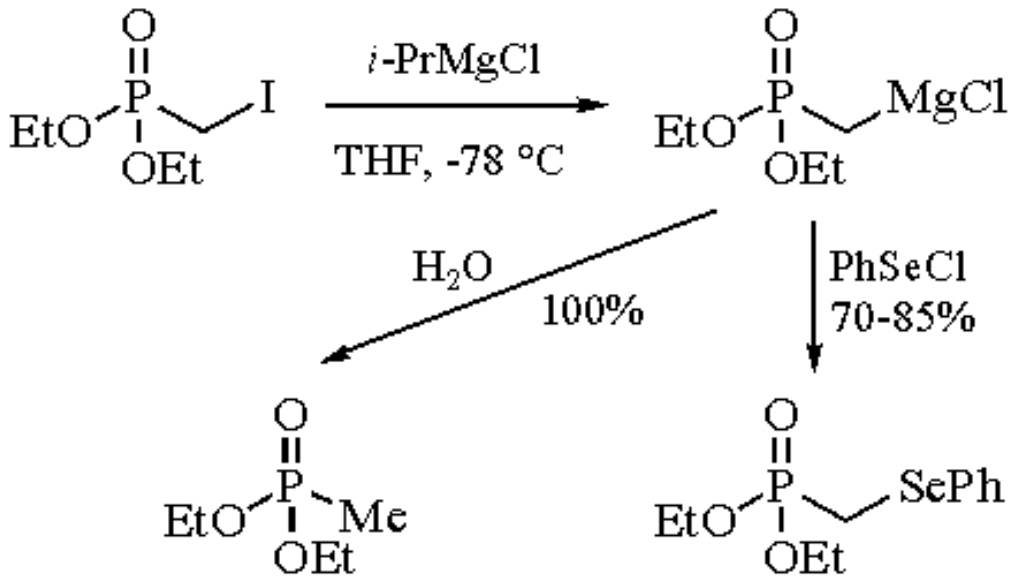

(5)

Chloro(diethylphosphono)methylation of various electrophiles such as carboxylic acid esters, diethyl carbonate, diethyl oxalate,[1] and chlorophosphates or -phosphinates[11] using the lithiated anion of (**1**) gives direct access to chloro(diethylphosphono)methyl-substituted ketones, carboxylic acid esters, and α-ketocarboxylic acid esters,[1] and chloromethylenediphosphonates or chloromethylphosphinophosphonates.[11] The reaction can be adjusted to deliver chloro(diethylphosphono)acetaldehyde (eq 6).[1]

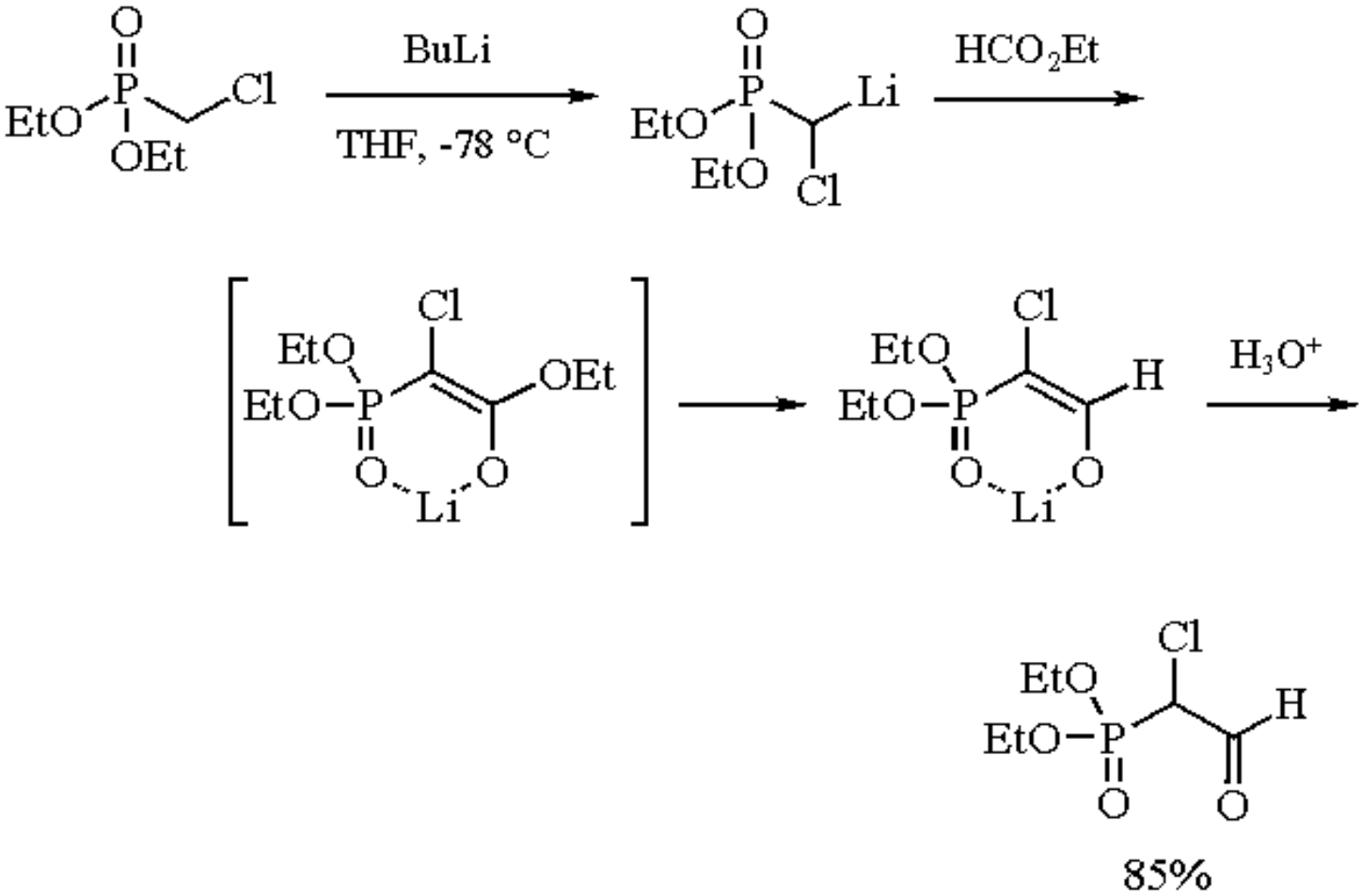

(6)

In these reactions, only the intermediate lithiated enolate prepared from ethyl carbonate[1] or ethyl chloroformate,[12] or the

intermediate lithiated anions prepared from chlorophosphates[13] or -phosphinates[14] in the presence of excess LDA, can react with aldehydes or ketones in a Horner-Emmons type reaction. The reaction leads to diethyl α-chlorinated α,β-unsaturated phosphonates when diethyl chlorophosphate is used in the initial phosphorus acyl chloride phosphonomethylation (eq 7).[13] This carbonyl alkenation reaction has been extended to the preparation of diphenyl(chlorovinyl)phosphine oxides by use of chlorodiphenylphosphine oxide as phosphonoalkylating reagent.[14] It is worth noting that (chlorovinyl)phosphonates or (chlorovinyl)phosphine oxides are obtained with predominant (*Z*) stereoselectivity.

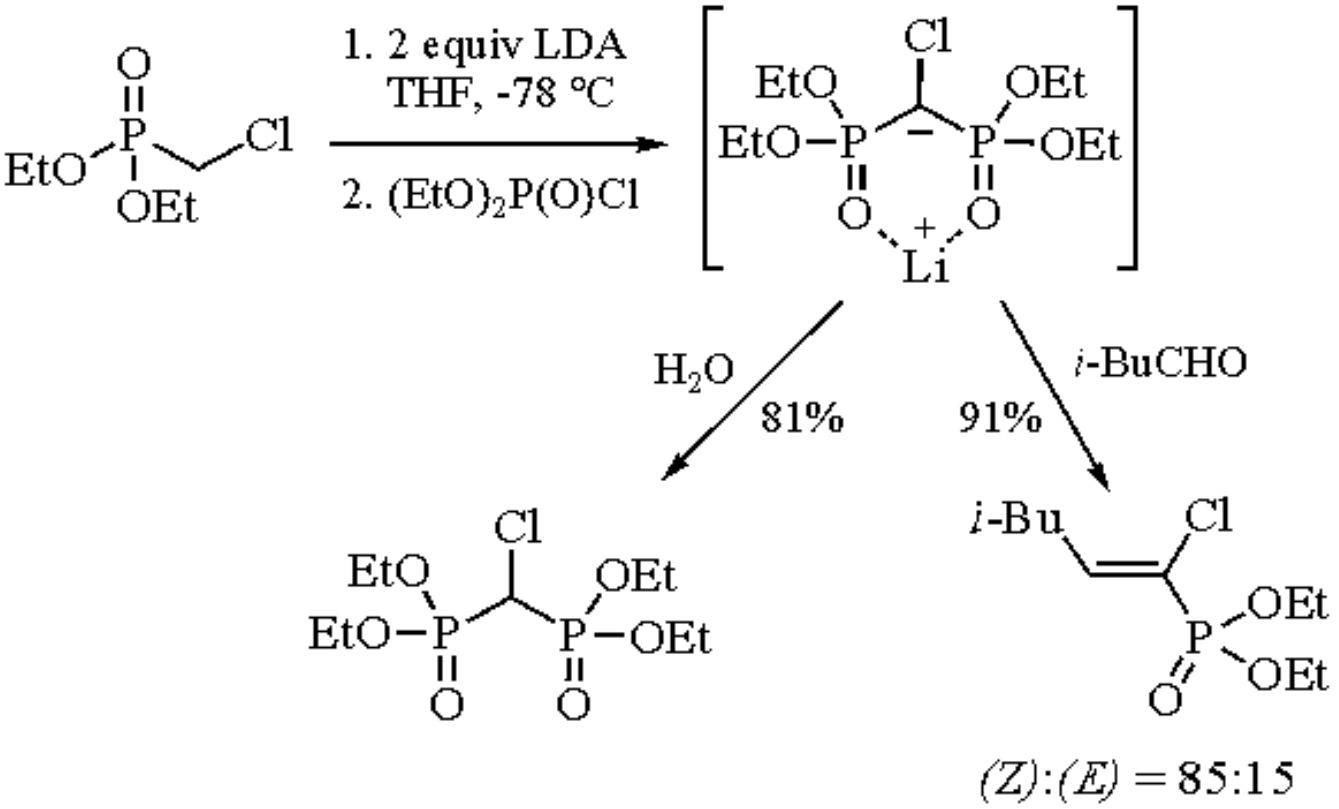

(7)

Reaction of aldehydes or ketones with the lithiated derivative of (**1**) in a mixture of THF and hexane at low temperature results in the almost immediate formation of lithiated (1-chloro-2-hydroxyalkyl)phosphonate alkoxides, which afford epoxy phosphonates on warming.[15] Under these conditions, (**1**) undergoes a Darzens-type reaction instead of a Horner-Emmons reaction. With aldehydes, this (diethylphosphono)methylation reaction can take a different course leading to (2-oxoalkyl)phosphonates, if the intermediate alkoxide anion is treated at low temperature with LDA (eq 8).[16]

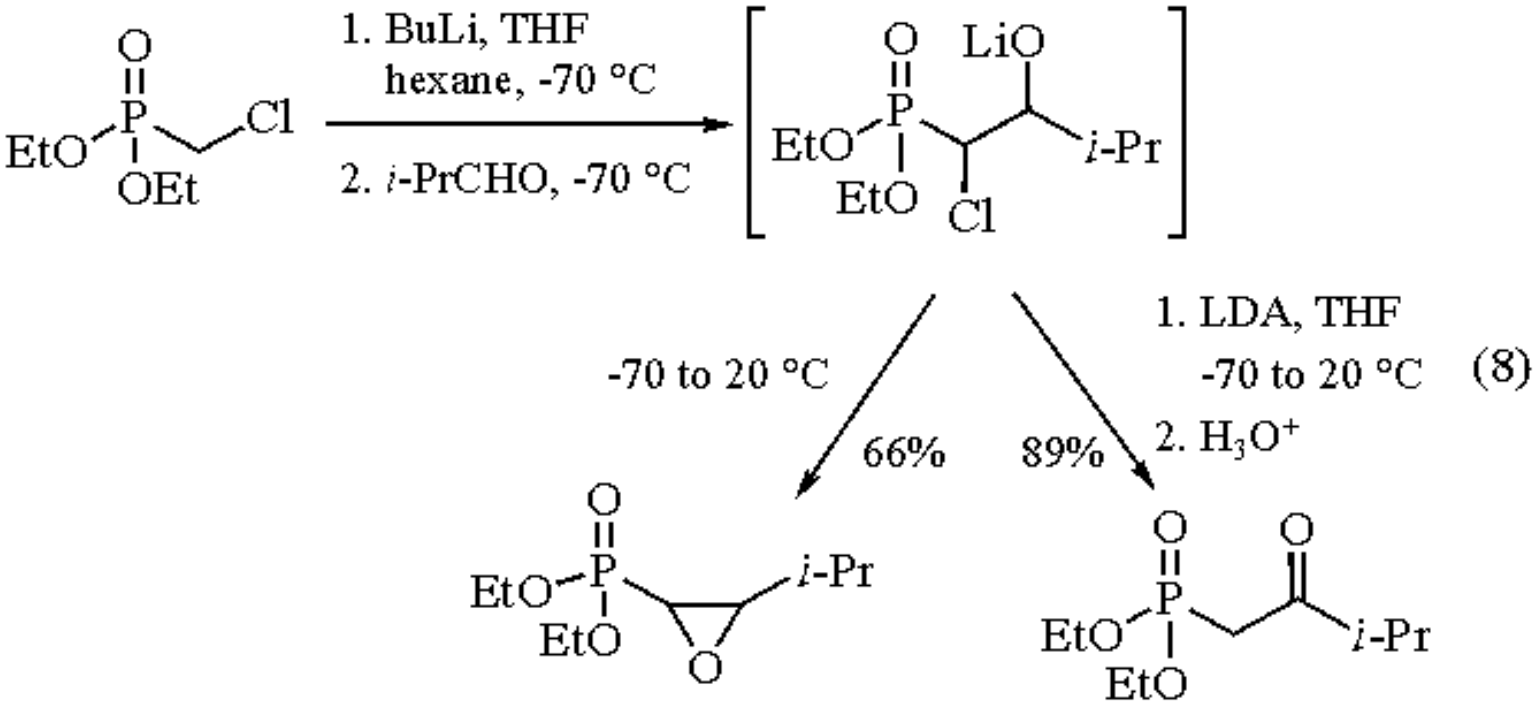

In an analogous reaction, the lithiated derivative of (**1**) reacts with aromatic imines to give aziridinylphosphonates with high stereoselectivity (eq 9).[17]

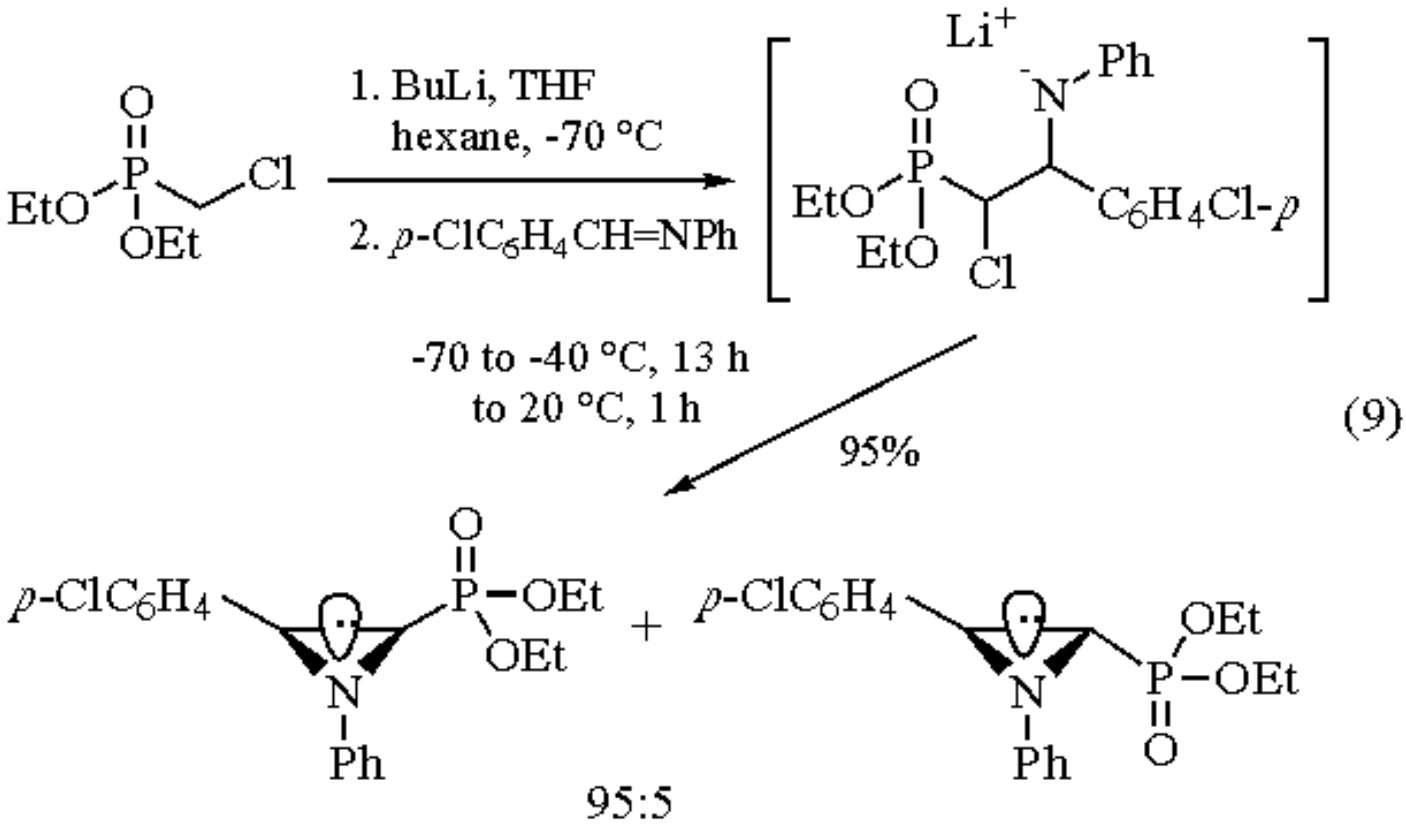

The carbanion $(EtO)_2P(O)CHClLi$ can be also carbonated,[18] chlorinated,[19] or silylated.[20] The (carboxychloromethyl)phosphonate and (dichloromethyl)phosphonate obtained serve further as reagents in Horner-Emmons alkenation reactions.[18,22-24] (Trimethylsilylchloromethyl)phosphonate can be used for the preparation of α-bromo- and α-iodophosphonates[20] and chloro(diethylphosphono)sulfine.[21]

Often these reactions can be carried out using an efficient and simple one-pot procedure. For instance, the carboxychloroalkenation takes place in two independent steps, leading to α-chloro-α,β-unsaturated acids.[18] The one-step α-chlorination or α-bromination Horner-Emmons procedure allows the preparation of dichloro-[22,23] or dibromoalkenes,[24] respectively. The method can be applied to sterically hindered cyclic ketones as an alternative to the Corey procedure,[25] with the lithium phosphate byproduct being soluble in aqueous media. It is important to note that the stabilization of the lithiated anion derived from the (dichloromethyl)phosphonate formed in situ requires the presence of the lithium salts ***Lithium Bromide*** and ***Lithium Chloride*** (eqs 10 and 11).[26]

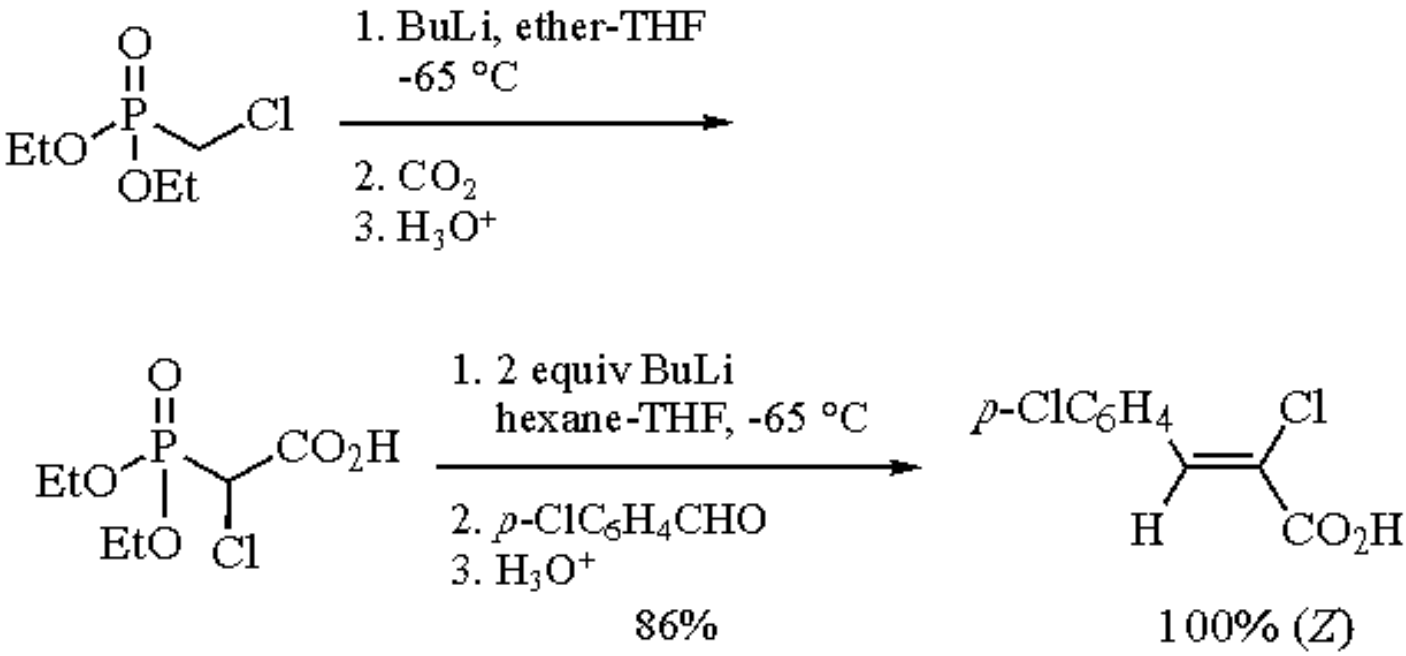

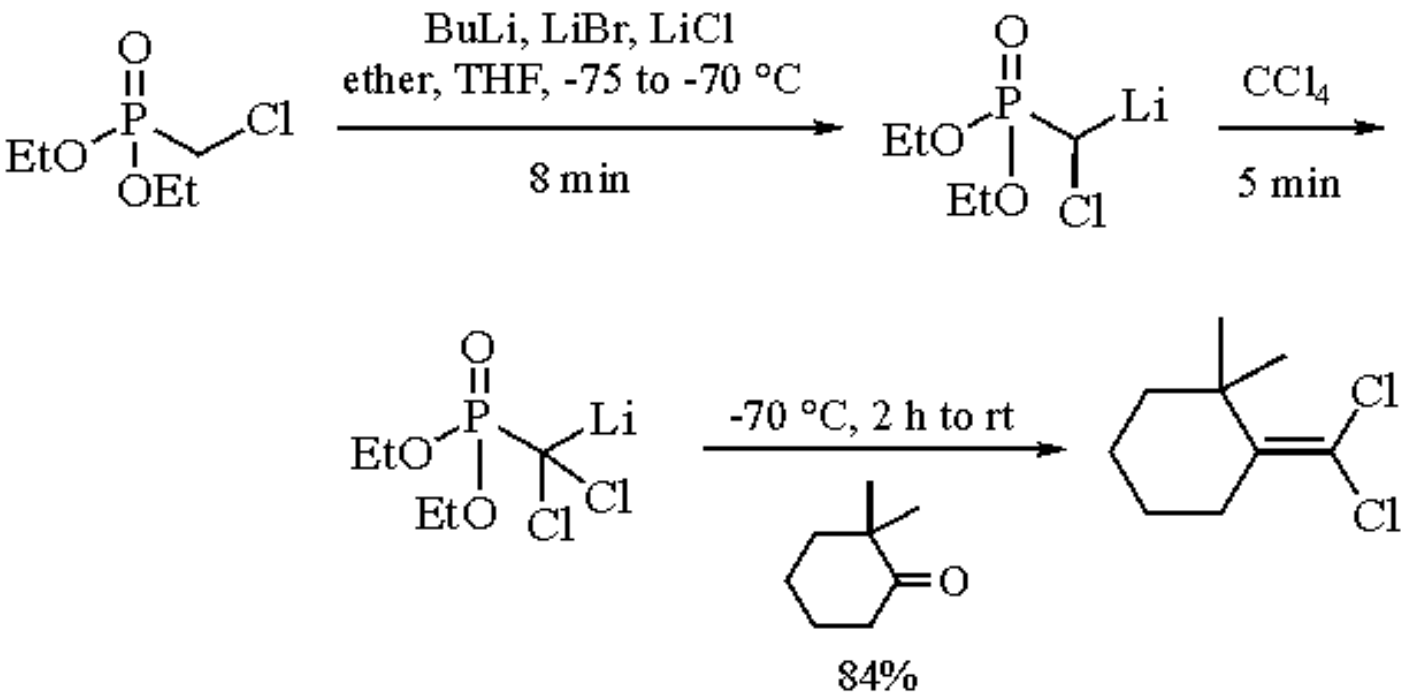

Diethyl Chloromethylphosphonate as an Electrophilic Reagent.

$(EtO)_2P(O)CH_2Cl$ can function as an electrophilic reagent to introduce a (diethylphosphono)methyl moiety to a nucleophilic substrate. The chlorine atom can be substituted by dimethyl sulfide,[27] phosphites,[28] arylcopper,[2] and phenolic compounds[29] to afford the corresponding (diethylphosphono)methylated products. For example, copper reagents prepared from aryl bromides react with (**1**) to yield diethyl (arylmethyl)phosphonates. In certain cases this method is better than the classical Michaelis-Arbuzov reaction[30] applied to arylmethyl halides because the synthesis of these last compounds by benzylic bromination is often not selective and requires a number of steps (eq 12).[2] Thiolates react with (**1**) partially by chlorine substitution and dealkylation.[31] The ethoxy group in (**1**) can also be substituted. As a specific case of the preparation of an α-functionalized chlorophosphonic acid monoester by a selective chlorination of the corresponding phosphonic acid diesters, ethyl (chloromethyl)chlorophosphonic acid ester was obtained by the reaction between (**1**) and ***Phosphorus Oxychloride*** (eq 13).[32]

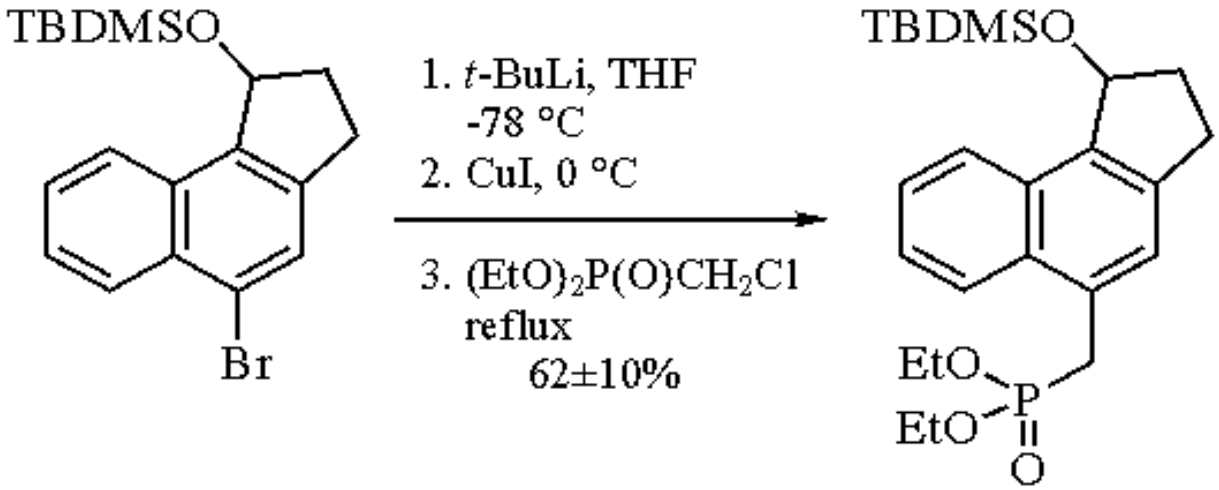

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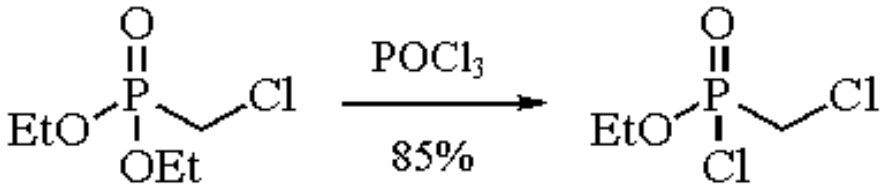

(13)

Reduction of diethyl (chloromethyl)phosphonate and other (chloroalkyl)phosphonates with different hydride reagents has been studied. Whereas ***Lithium Aluminum Hydride*** gives primary phosphines without chemoselectivity when a C-Cl bond is in an α-position to the phosphoryl group, reduction of (**1**) with AlH_3 affords (chloromethyl)phosphine with good chemoselectivity (eq 14).[33]

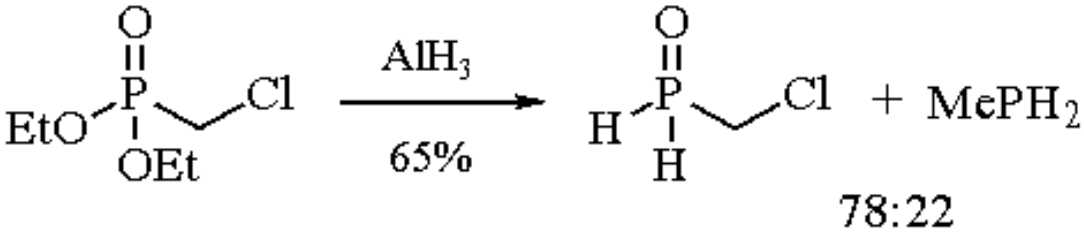

(14)

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Diethyl Chlorophosphite

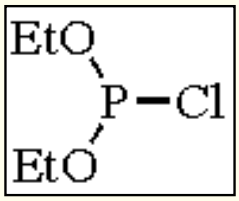

[589-57-1] · $C_4H_{10}ClO_2P$ · Diethyl Chlorophosphite · (MW 156.55)

(synthesis of allenyl phosphonates,[11] β-ketophosphonates;[8,12] phosphorylation of alcohols;[15] coupling agent[19])

Alternate Names: diethyl phosphorochloridite; diethyl chlorophosphonite; ethyl phosphorochloridite.

Physical Data: bp 153-155 °C/760 mmHg, 56-57.5 °C/30 mmHg; *d* 1.082 g cm^{-3}; fp 1 °C.

Solubility: benzene, THF, diethyl ether, methylene chloride, acetonitrile.

Form Supplied in: colorless liquid.

Preparative Methods: the reaction of ***Phosphorus(III) Chloride*** with ***Triethyl Phosphite***,[1] anhydrous ethanol,[2] or ***Sodium Ethoxide***[3] has been employed, although diethyl chlorophosphite is commercially available.

Purification: vacuum distillation.

Handling, Storage, and Precautions: the neat liquid is flammable and combustion produces toxic byproducts. Caution should be taken when handling the material due to its toxicity. Bottles of diethyl chlorophosphite should be sealed and stored under N_2 to prevent contact with moisture, which produces HCl vapor. Use in a fume hood.

General Notes.

Diethyl chlorophosphite is a reactive electrophile for the introduction of phosphorus into organic compounds. It is known to react readily with a variety of nucleophiles including amines,[4] amides,[5] alcohols (see below), and various organometallic derivatives including Grignard reagents,[6] enolates, and Reformatsky reagents.[7] Oxidation of the initial phosphorus(III) species to a phosphorus(V) species, typically from phosphite to phosphate or phosphonite to phosphonate, is accomplished with a number of reagents including air (O_2),[8] ***Iodine***,[9] ***Ozone***,[5] and ***t-Butyl Hydroperoxide***.[10]

Arbuzov-Type Rearrangements Leading to Allenyl and Allyl Phosphonates.

Reaction of diethyl chlorophosphite with propargyl alcohols in the presence of base results in the rapid formation of allenylphosphonates (eq 1).[11] This general method is believed to proceed through a cyclic transition state with rearrangement occurring at or below rt in many cases. Substitution greatly affects the rate of rearrangement. Allenylphosphonates react with a variety of nucleophiles, including alkoxides and secondary amines, to form β-ketophosphonates after hydrolysis of the intermediate enamine or enol ether (eq 2).[12]

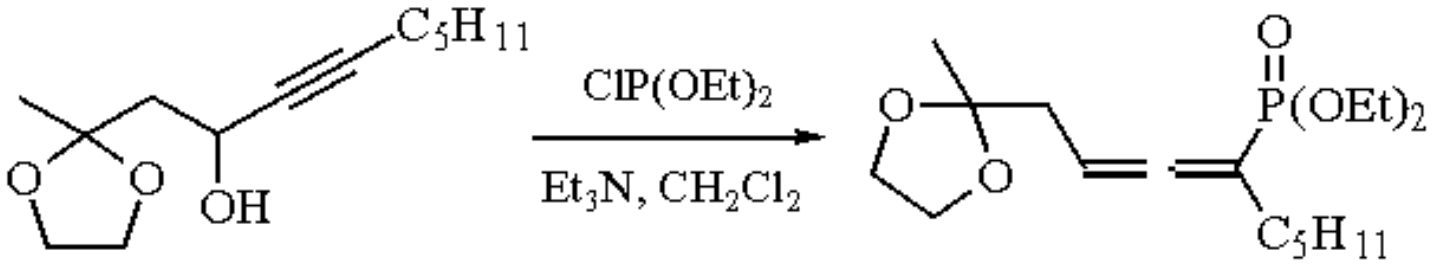

(1)

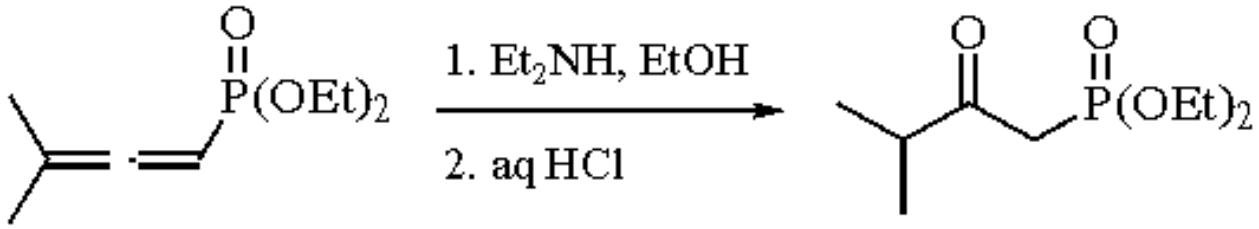

(2)

Allyl alcohols can be similarly treated to afford allylphosphonates where the selectivity in alkene geometry is dependent upon substitution (eq 3).[13] Rearrangement of the intermediate diethyl allyl phosphites takes place at 70-100 °C. A related rearrangement involves the conversion of 2,3-butadienyl phosphites (homoallenyl phosphites) to 1,3-butadienyl-2-phosphonates.

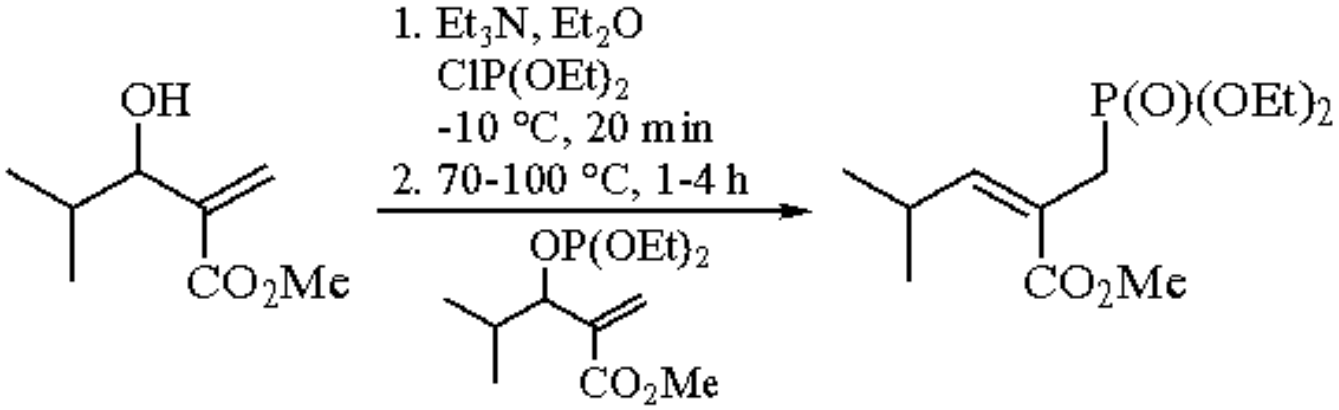

(3)

Phosphorylation of Alcohols.

Protein phosphorylation is now recognized as a critical reaction in the control of cell metabolism.[14] Diethyl chlorophosphite has been shown to be a more effective and reactive phosphorus electrophile than diphenyl

chlorophosphonate.[15] In the case of *N*-protected serine derivatives (eq 4), an excess of the phosphite is required due to the competitive reaction with the carboxylic acid.[9] Oxidation to the phosphate takes place under a variety of conditions already described.

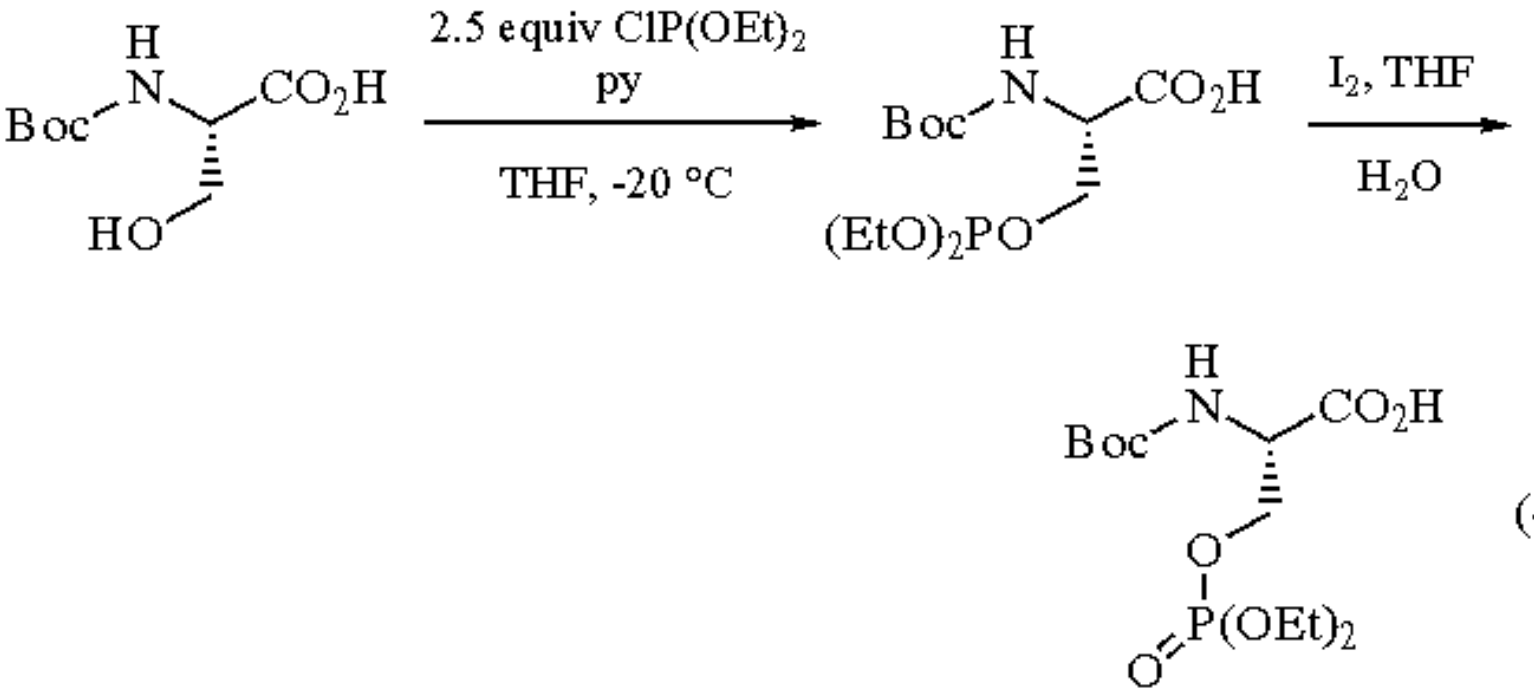

(4)

Organophosphates are also available from alcohols using diethyl chlorophosphite. In compounds containing multiple alcohol functionalities, such as derivatives of inositol (eq 5), chlorophosphites are preferred over more traditional phosphorus(V) reagents which suffer from not only lower relative reactivity, but also the tendency of the intermediate phosphate triesters to form cyclic phosphates or undergo acid-induced rearrangements.[16] Phosphate triesters can be dealkylated to the phosphates with ***Bromotrimethylsilane***.[10]

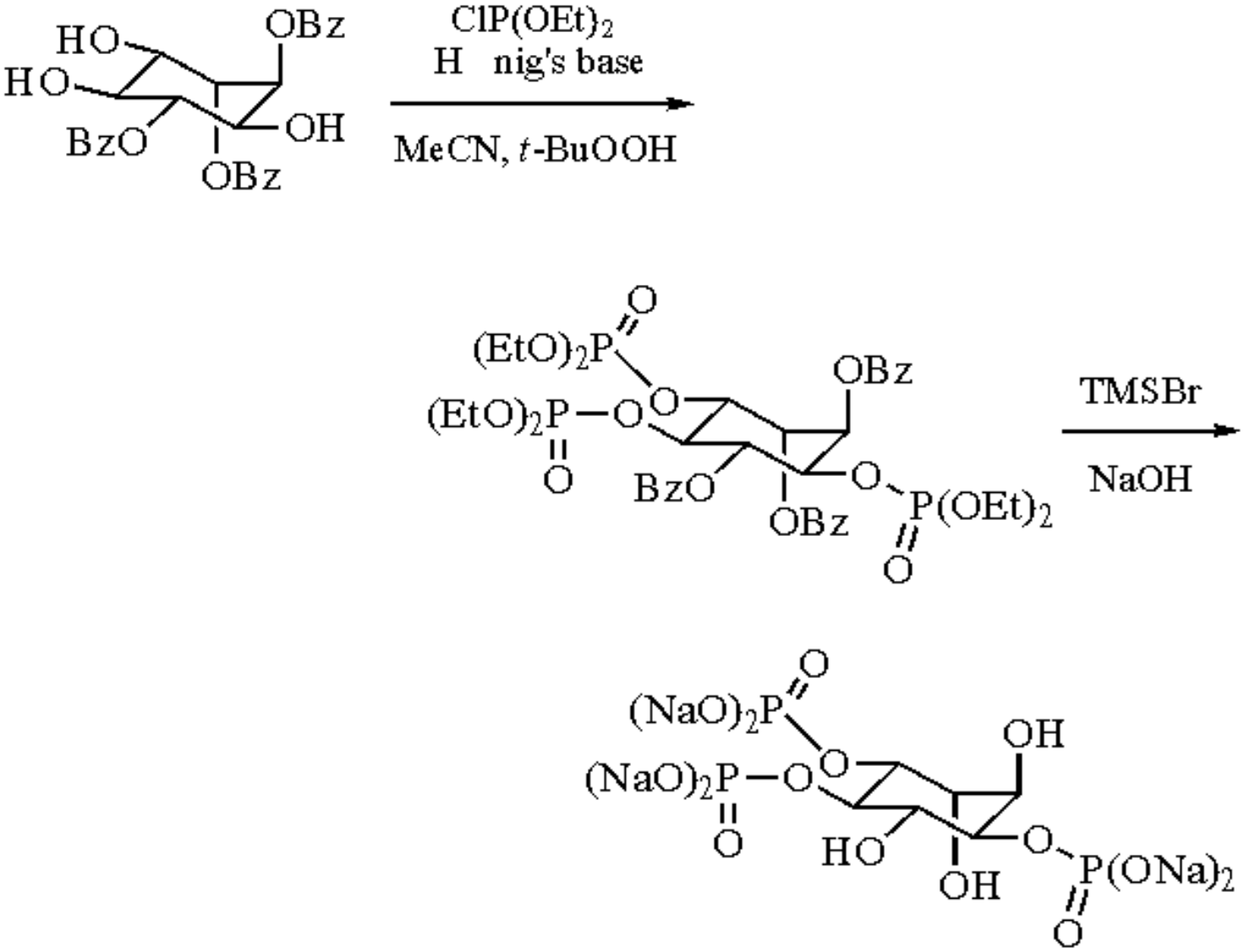

(5)

Diethyl Chlorophosphite as a Coupling Agent.

Schmidt and Martin have demonstrated the use of phosphite as a leaving group in the sialylation of sugars with catalytic ***Trimethylsilyl Trifluoromethanesulfonate***. Their procedure allows for higher yields than could be obtained using other methods for the formation of the glycosidic bond.[17] Diethyl chlorophosphite activation of amines allows for the formation of peptides.[18] In certain cases, diethyl anilinophosphite (formed by the reaction of the chlorophosphite with aniline) has also been used as the phosphite source. The researchers found that the corresponding phosphorus(V) reagents do not work as well with this coupling protocol. Reaction of 3´-(diethyl phosphonite) thymidine derivatives with a 5´-azidothymidine leads to the formation of the dinucleotide at room temperature with extrusion of N_2 (eq 6). This coupling procedure is easily accomplished and high yielding.[19]

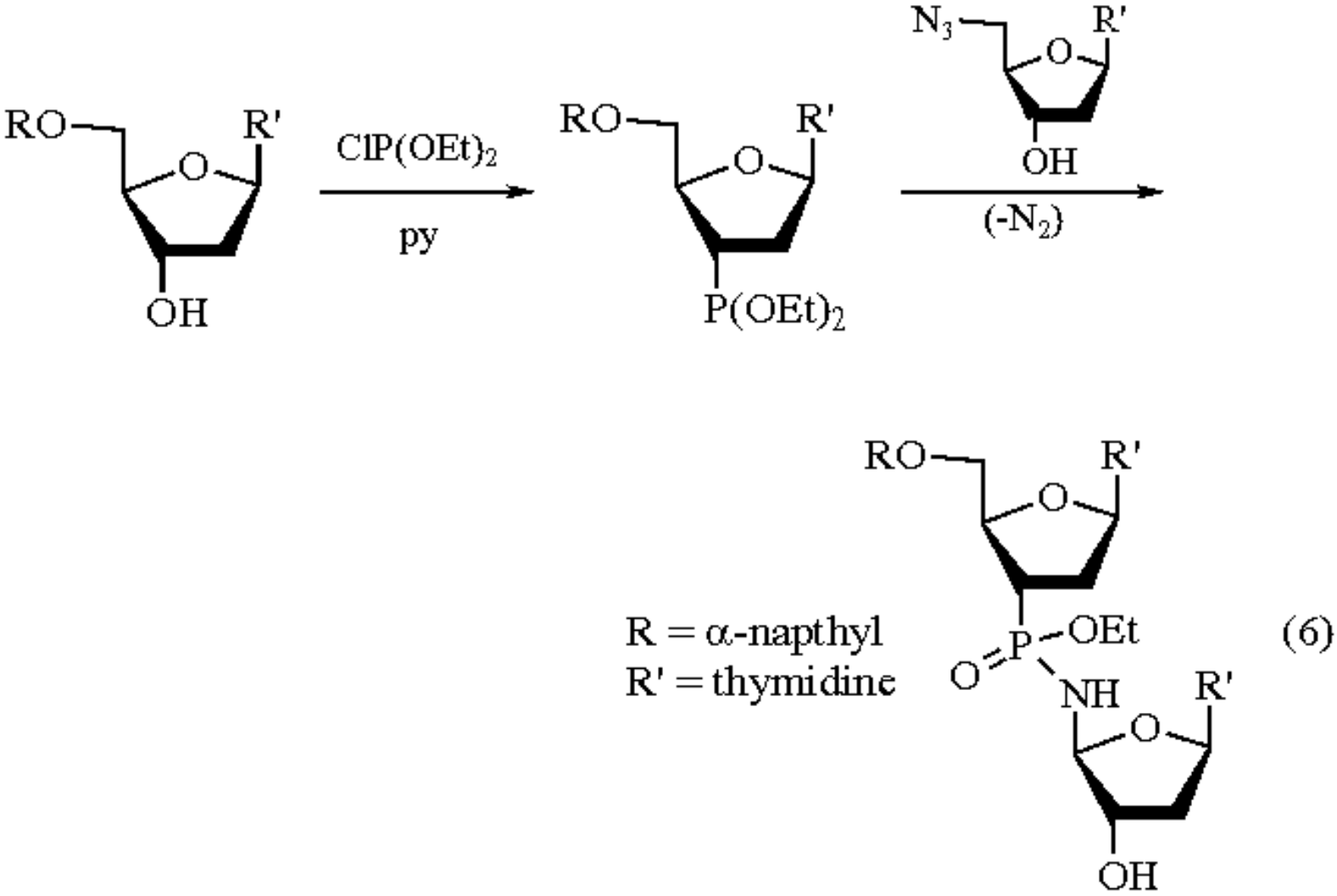

Preparation of Horner-Wadsworth-Emmons Alkenation Reagents.

Treatment of an α-hydroxy ketone with diethyl chlorophosphite in the presence of a Lewis acid results in a rapid rearrangement to the corresponding β-ketophosphonate (eq 7).[20] Treatment of an α-hydroxy ester results in the formation of an H-phosphonate diester instead of the expected rearrangement product. Horner-Wadsworth-Emmons condensation reagents[21] can also be prepared by the reaction of ketone or ester enolates with diethyl chlorophosphite followed by oxidation of the resultant phosphite (eq 8).[8] This methodology offers several advantages to the Michaelis-Arbuzov reaction,[22] including application to cyclic ketones and availability of starting materials. The competitive formation of enol phosphates by this method is not a problem as it is with phosphorylating agents.[23] Reaction of diethyl chlorophosphite with phosphoryl-stabilized anions has been reported with the products leading to 1,3-butadienylphosphonites.[24]

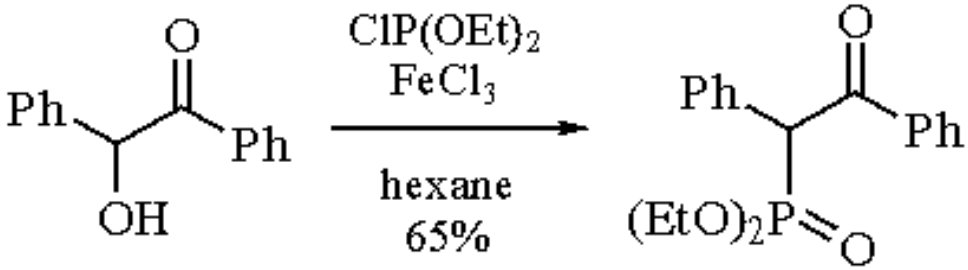

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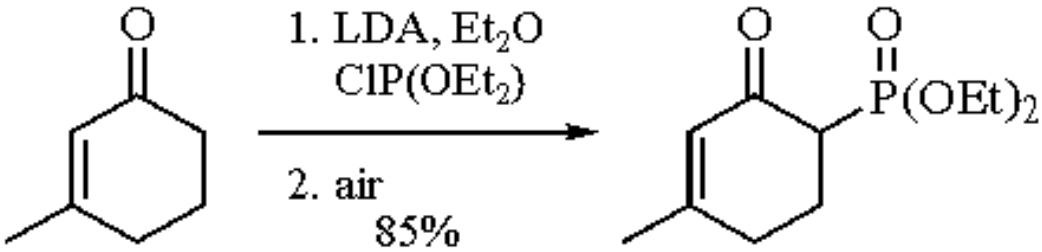

(8)

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N,N-Diethyl-2-chloro-1,1,2-trifluoroethylamine[1]

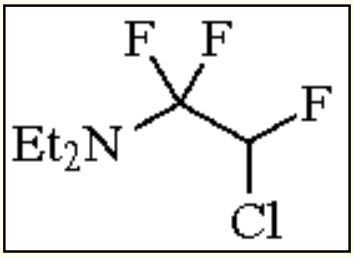

[357-83-5] · $C_6H_{11}ClF_3N$ · *N,N*-Diethyl-2-chloro-1,1,2-trifluoroethylamine · (MW 189.61)

(converts alcohols to alkyl fluorides,[2] carboxylic acids to acid fluorides;[3] used as acylating agent[4])

Alternate Names: FAR; CCT; Yarovenko's reagent.

Physical Data: bp 32-33 °C/6 mmHg; *d* 1.19 g cm^{-3}.

Solubility: sol ether, CH_2Cl_2, acetonitrile.

Preparative Method: from diethylamine and chlorofluoroethylene (87%).[5]

Form Supplied in: liquid (97%).

Handling, Storage, and Precautions: store at <0 °C. Use within 4 weeks of delivery. Fluorinating agent; handle with caution in a fume hood. Readily reacts with H_2O, alcohols, and amines.

Reactivity Pattern.

N,N-Diethyl-2-chloro-1,1,2-trifluoroethylamine, also known as Yarovenko's reagent,[6] is a relatively safe fluorinating agent that is easy to use. The reagent is tolerated by many functional groups including carbon-carbon double and triple bonds, aldehydes, ketones, esters, amides, and nitriles.[1] It is quantitatively hydrolyzed to its amide (eq 1).[2,7] This illustrates its primary reaction mode: elimination of fluorine α to nitrogen to give an iminium ion.

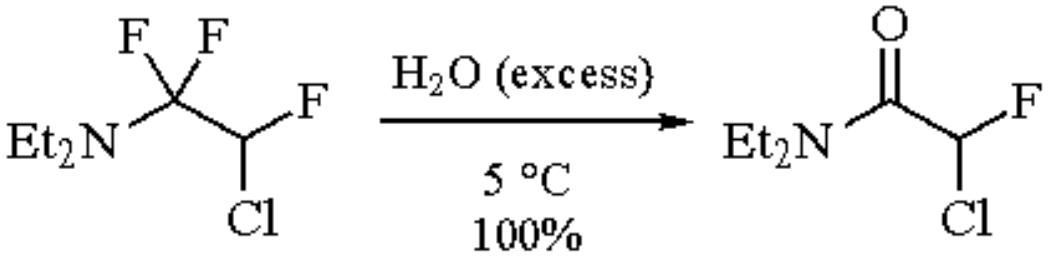

(1)

Reaction with Alcohols and Acids.

Alcohols react with FAR under mild conditions to give the corresponding fluorocarbons with inversion of stereochemistry (S_N2 process). Yields and enantioselectivities are comparable with those obtained with phenyltetrafluorophosphorane, ***N,N-Diethylaminosulfur Trifluoride*** (DAST) and ***Potassium Fluoride*** (eq 2).[2] This interconversion works well for primary, secondary, benzylic,[8] and bridgehead alcohols (eq 3),[9] but gives poor results with α- and β-hydroxy nitriles. DAST is superior in the latter application.[10] Cyclic secondary and tertiary alcohols tend to give elimination products.

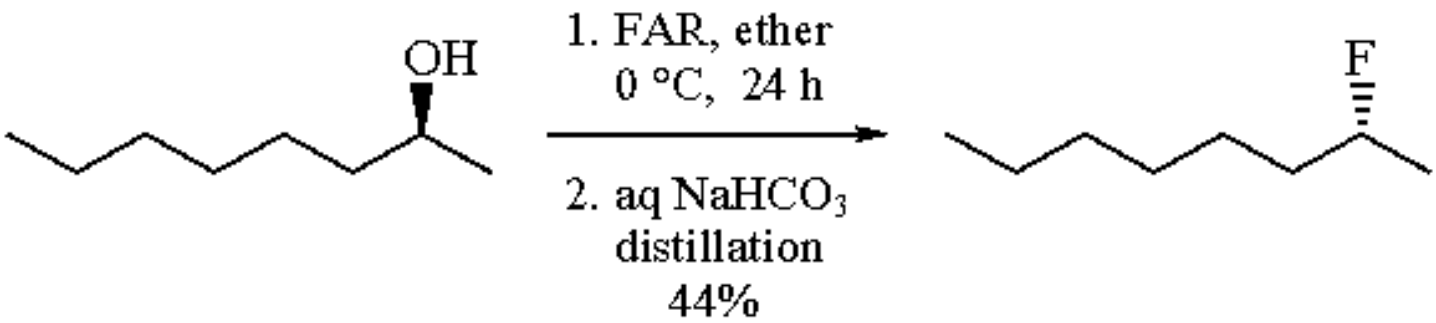

(2)

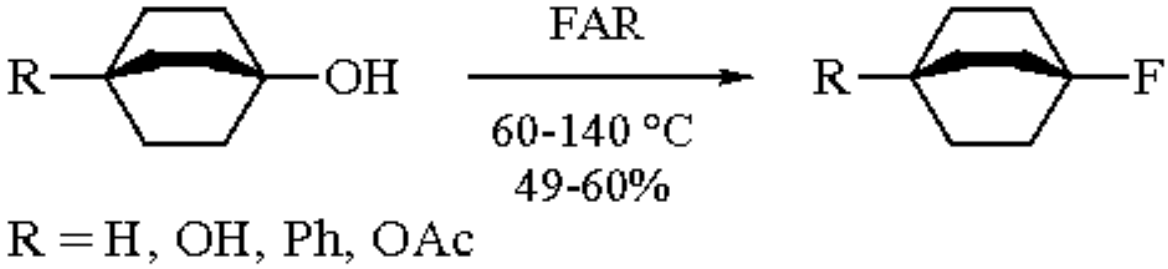

(3)

The α-hydroxycyclopropenone (**1**) reacts with FAR to give an allenic acyl fluoride that was used to synthesize allenic acid and β-keto ester derivatives (eq 4).[11]

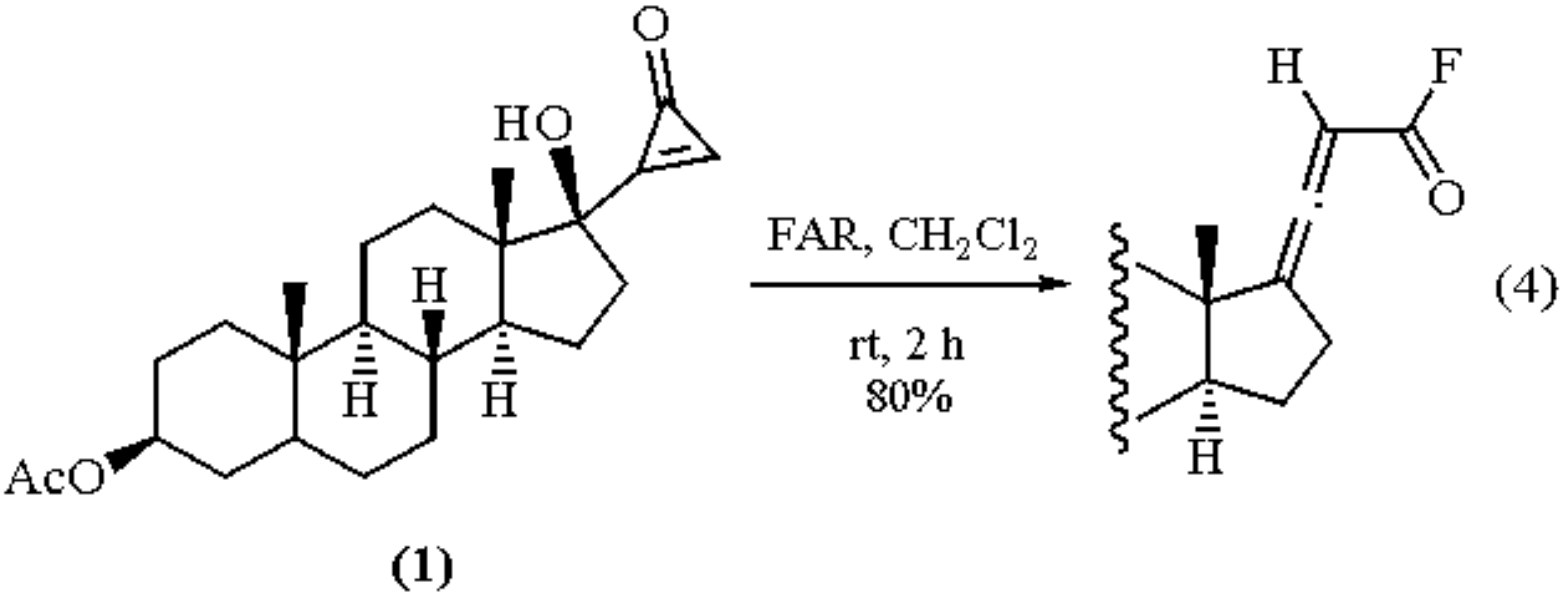

Fluorination of steroidal homoallylic alcohols with FAR gives a variety of products (cyclopropanes, B-ring expansion), depending on the conditions employed. They are thought to be derived from carbocation intermediates.[12] Fluorinated cephalosporin derivatives have been prepared as well.[13] The title reagent has also been used to prepare α-chloro-α-fluoroacetates derived from carbohydrates.[14]

Carboxylic acids can be converted to the acyl fluorides in good yields (eq 5).[6,15] Perfluoroaryl acids decarboxylate under the same conditions. FAR has been used in the synthesis of a light-stable rhodopsin.[3]

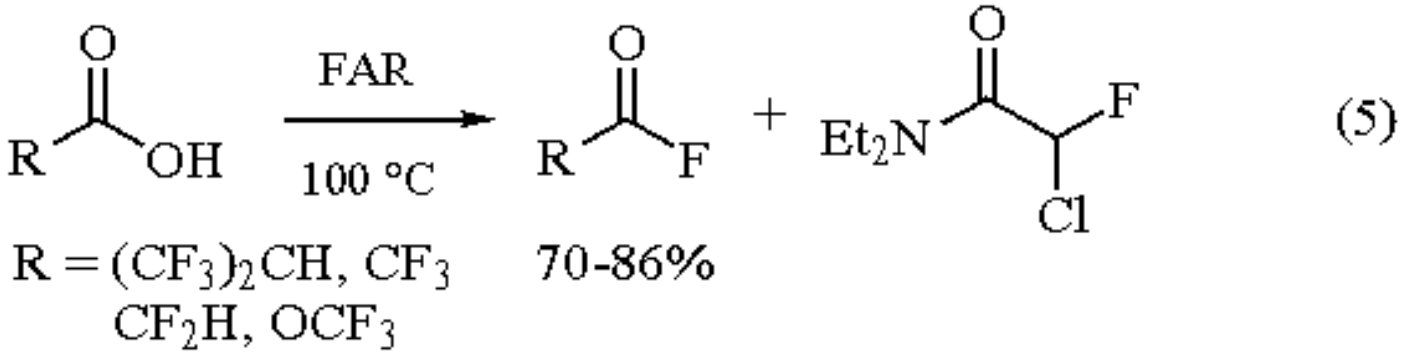

Heterocyclic Synthesis and Acylation.

Reaction of FAR with *o*-aminophenol gives the benzoxazole derivative (**2**) (eq 6). Benzimidazoles, 4-quinazolones, benzothiazoles, and 1,3-benzodioxoles have also been prepared in this manner.[16]

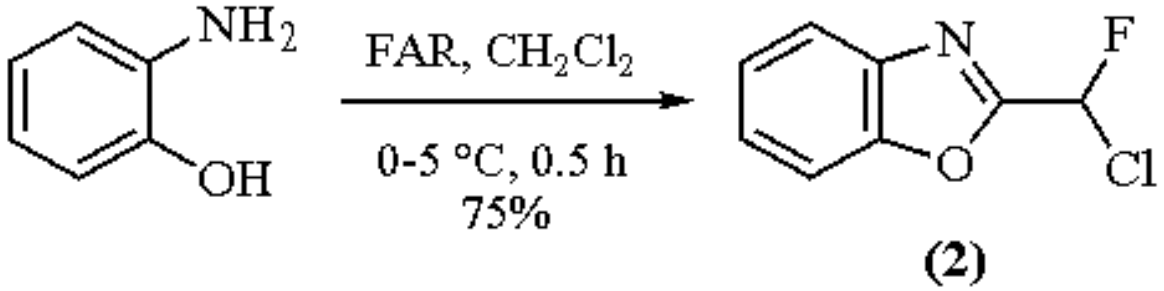

(6)

Indole has been acylated by FAR under mild conditions using a Lewis acid catalyst (eq 7). Thiophene gives 2-acylated products (52%). Electron-rich aromatics give only the *para* regioisomer (37-78%).[4]

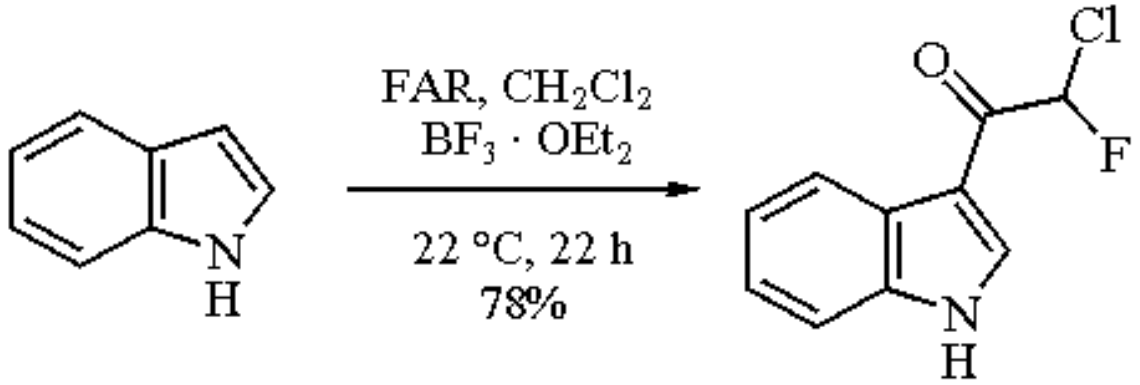

(7)

Miscellaneous Transformations.

FAR has been used in reactions with isocyanates,[17] cyanoacetic ester,[18] and organosilicon compounds[19] and to make fluoroacetic acids.[20] It has also been used to convert benzaldehydes to difluoromethylarenes.[21] A reagent that behaves much like FAR has been derived from $Et_2NCF_2CHFCF_3$ and $Et_2NCF{=}CFCF_3$.[22]

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Diethyl Cyanomethylphosphonate

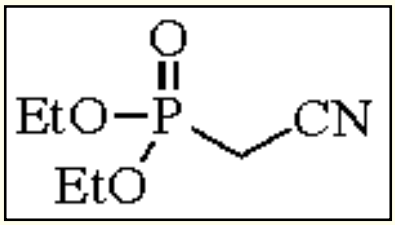

[2537-48-6] · $C_6H_{12}NO_3P$ · Diethyl Cyanomethylphosphonate · (MW 177.14)

(modified Wittig reagent, Wadsworth-Emmons modification, producing α,β-unsaturated nitriles as products from reaction with aldehydes and ketones)

Physical Data: bp 101-102 °C/0.4 mmHg; *d* 1.095 g cm^{-3}.

Solubility: sol THF, DME, methylene chloride.

Form Supplied in: oil; widely available.

Preparative Methods: prepared by the Michaelis-Arbuzov reaction[1] utilizing ***Triethyl Phosphite*** and a haloacetonitrile.[2] More recently, a preparation was reported utilizing ***Trimethyl Phosphite*** and ***Chloroacetonitrile***.[3] Thus a mixture of the two reagents was heated at 140-150 °C for 18 h under nitrogen to give a 75% yield of the closely related dimethyl cyanomethylphosphonate. Alternatively, ***Acetonitrile*** is treated with 2 equiv of ***Lithium Diisopropylamide*** in THF at -78 °C followed by diethyl chlorophosphate (***Diethyl Phosphorochloridate***) to provide a 47% yield of diethyl cyanomethylphosphonate.[4]

Handling, Storage, and Precautions: corrosive.

Modified Wittig Reagent.

The most common use of the reagent is the preparation of α,β-unsaturated nitriles from ketones or aldehydes. The stereochemistry of the α,β-unsaturated nitriles is variable, depending on the substrate[5] and the reaction conditions.[6] Pasto reported a (*Z*)-favored alkenation on 3-hydroxy-3-methylbutanal (eq 1).[7] In contrast, Paquette reported the alkenation shown in eq 2 where the (*E*)-isomer predominates.[8]

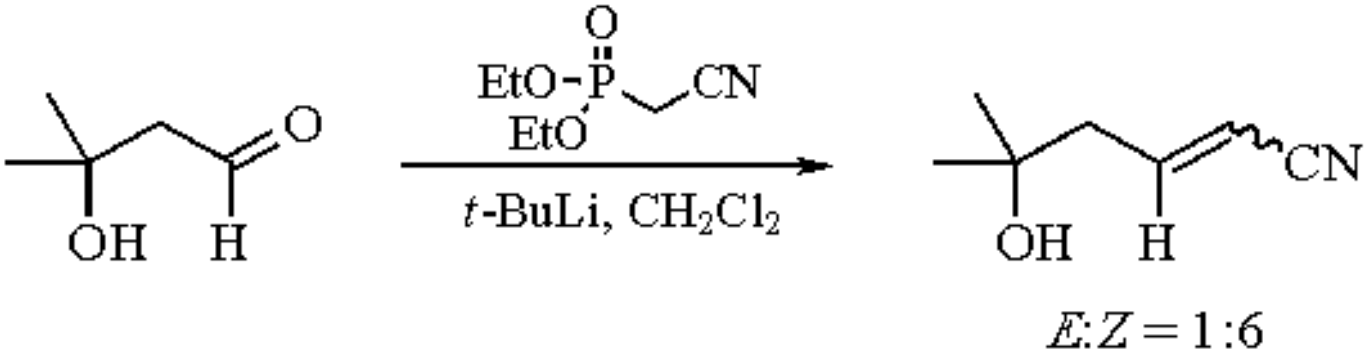

(1)

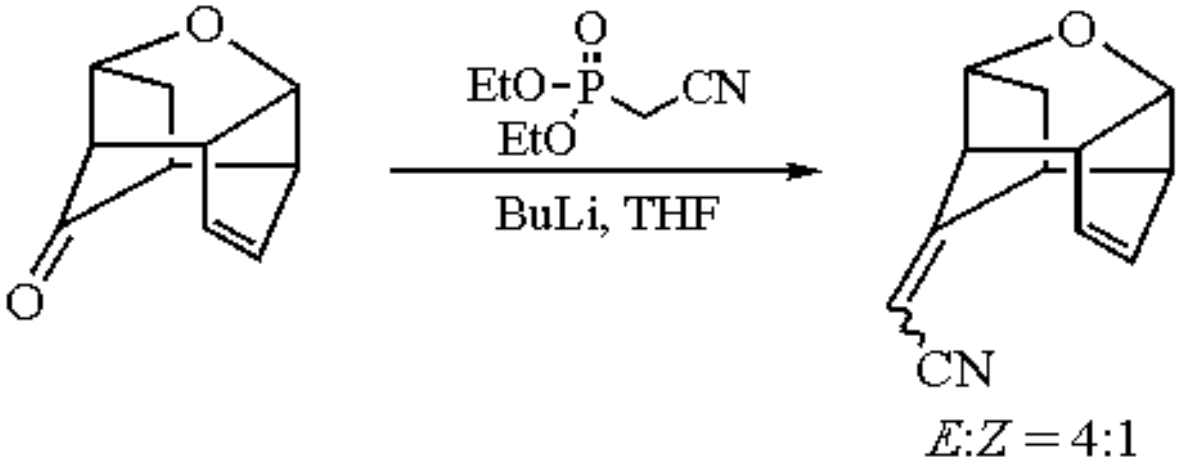

(2)

Sodium Hydride in THF or DME is the most popular base-solvent combination used to effect the Horner-Emmons reaction with diethyl cyanomethylphosphonate. Other useful but less popular conditions include: phase transfer,[9] polymer bound diethyl cyanomethylphosphonate,[10] and electrochemical methods.[11] A vast array of other reaction conditions have been reported in the literature.[12]

Other Uses.

Cyano-substituted cyclopropanes can be prepared by the reaction between diethyl cyanomethylphosphonate and epoxides (eq 3).[2]

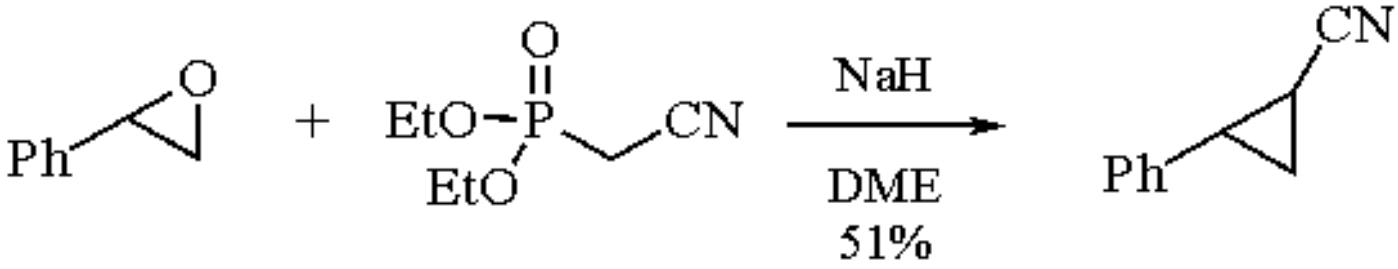

(3)

Diethyl cyanomethylphosphonate anions react with aryl iodides in the presence of copper(I) to give α-arylated alkanenitriles (eq 4).[13]

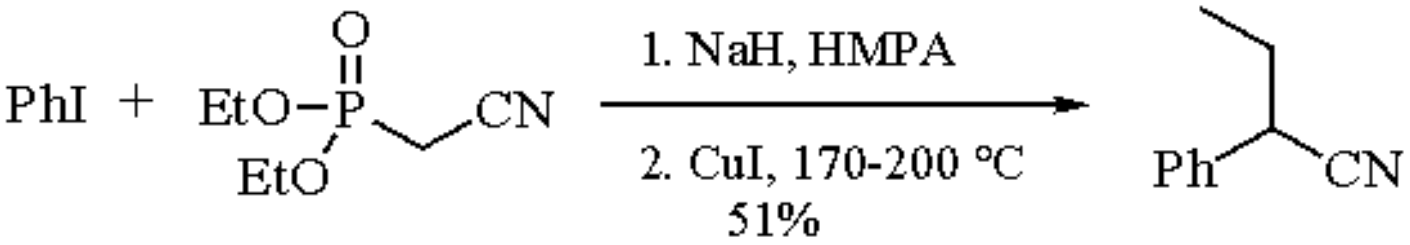

(4)

Nitrones react with diethyl cyanomethylphosphonate to yield aziridines (eq 5).[14]

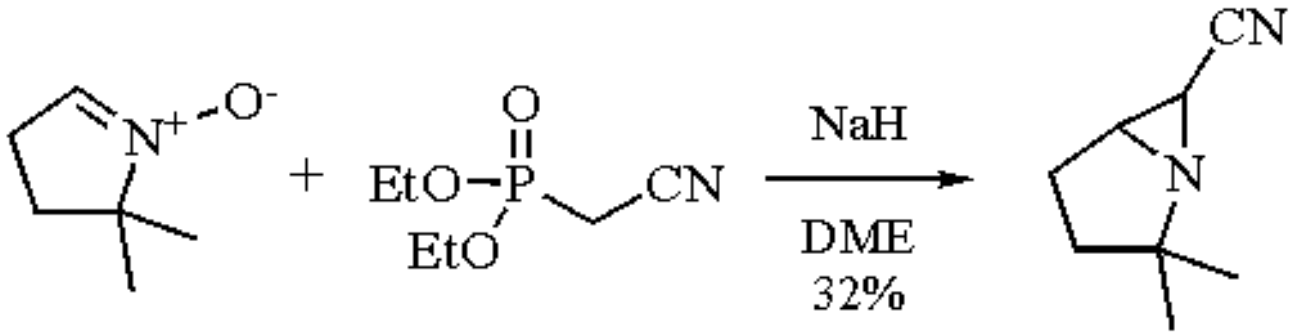

(5)

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Brad DeHoff

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Diethyl β-(Cyclohexylimino)ethylphosphonate

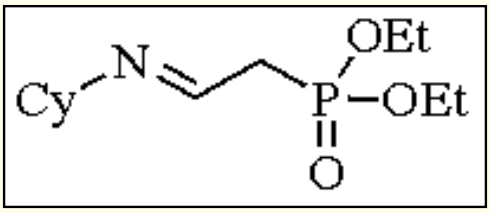

[20061-84-1] · $C_{12}H_{24}NO_3P$ · Diethyl β-(Cyclohexylimino)ethylphosphonate · (MW 261.30)

(reagent for formylalkenation at carbonyl centers[1])

Physical Data: mp 58-61 °C; bp 151-152 °C/0.04 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: crystalline solid.

Analysis of Reagent Purity: readily ascertained by NMR.

Preparative Methods: $(EtO)_2CHCH_2P(O)(OEt)_2$ is prepared by reaction of ***Triethyl Phosphite*** with $BrCH_2CH(OEt)_2$. Acetal hydrolysis affords diethyl formylmethylphosphonate, which is combined with an equimolar quantity of cyclohexylamine in MeOH. The product is isolated by fractional distillation in the presence of K_2CO_3, to prevent acid-catalyzed dimerization, and at reduced pressure, followed by crystallization from cold pentane.[1b] Yields are 65-75%. A modified procedure for imine formation uses MeCN as solvent with isolation of product from Et_2O at -40 °C to afford white crystalline material in 70% yield.[3]

Purification: distillation at reduced pressure. Crystallization from pentane at 0 °C.

Handling, Storage, and Precautions: crystalline material is stable for several months when stored under anhydrous conditions at 0 °C.

Homologation Reactions.

Diethyl β-(cyclohexylimino)ethylphosphonate (**1**) is an excellent reagent for the conversion of aldehydes and ketones to the corresponding α,β-unsaturated aldehydes.[1a,1c,1d] Anion generation is accomplished by treatment of (**1**) with 1

equiv of a strong base and a solution of the carbonyl substrate is added slowly to maintain a temperature <=5 °C. Warming to ambient temperature yields an unsaturated aldimine which is promptly hydrolyzed under biphasic conditions (aqueous ***Oxalic Acid*** or a pH 4 acetate buffer solution), thereby affording an α,β-unsaturated aldehyde of general structure (**2**) (eq 1).

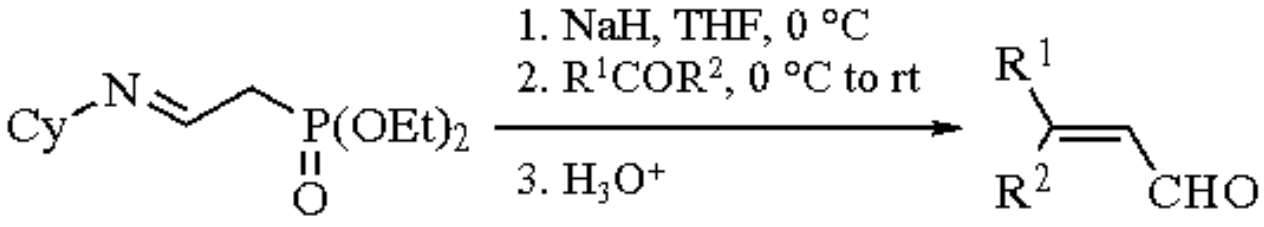

(1) (2) (1)

Attributes of this Horner-Wadsworth-Emmons reaction include (1) its simplicity in operation, (2) the generally high yields of products, (3) the fact that $Ph_3P{=}CHCHO$ and $(EtO)_2P(O)CH_2CH(OEt)_2$ do not react with ketones, and (4) the stereoselectivity for the formation of the (*E*)-alkene. A limitation is the slow reaction of the anion of (**1**) with an ester group or a free hydroxy group. Consequently, these functionalities should be masked if the substrate carbonyl is slow to react.

During spectral studies on all-*trans*-geranylgeraniol, (**1**) was utilized in the preparation of the 4´-normethyl analog by reaction with trienal (**3**) to provide *trans*-enal (**4**) in 33% yield (eq 2).[2]

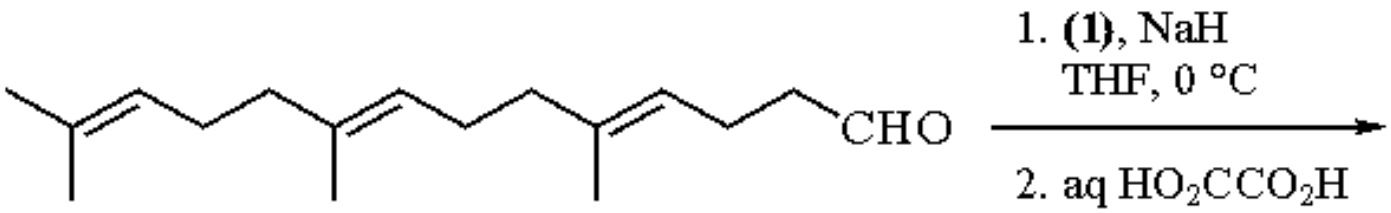

(3)

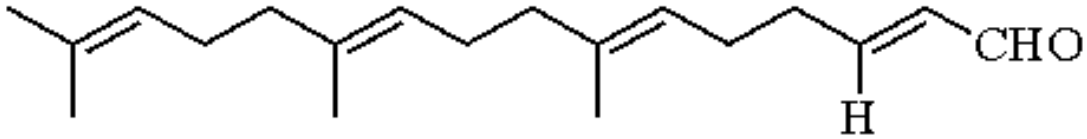

(2)

(4)

Homologation of the cyclopropanecarbaldehyde (**5**) yielded enal (**6**) in 68% yield (eq 3).[3] Conversion of (**6**) to the corresponding tosylhydrazone and subsequent pyrolysis provided a carbene-based approach to $C_{12}H_{12}$ species.

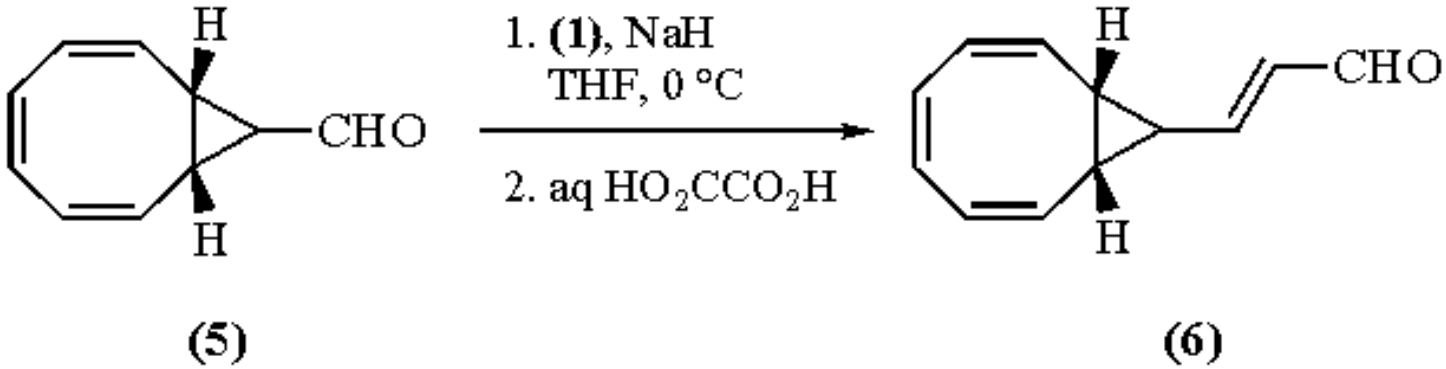

(3)

Also described was the preparation of deuterated (**1**) (eq 4). Spectroscopic studies estimated 90% deuteration at the carbon adjacent to phosphorus in a distribution of 67% d_2, 28% d_1, and 5% d_0.

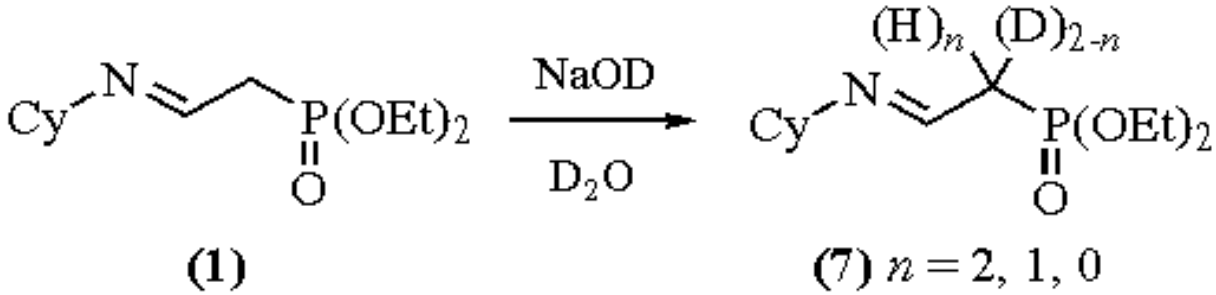

(4)

Synthetic investigations towards preparation of stable thromboxane A_2 analogs saw attempts at homologation of [3.3.1] and [3.2.1] bicyclic ketones (eqs 5 and 6).[4] While reaction of (**1**) with bicyclo[3.3.1]nonanone (**8**) yields the desired product only in low yield, the corresponding bicyclo[3.2.1]octanone (**10**) affords product in 40% yield.

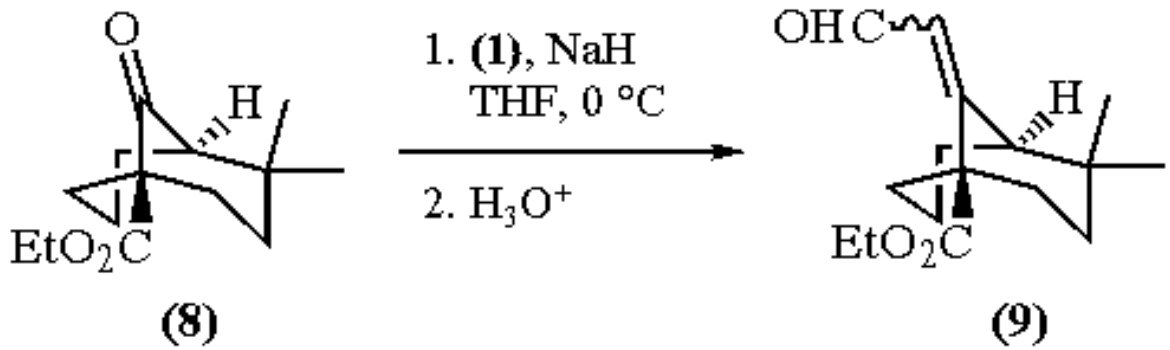

(5)

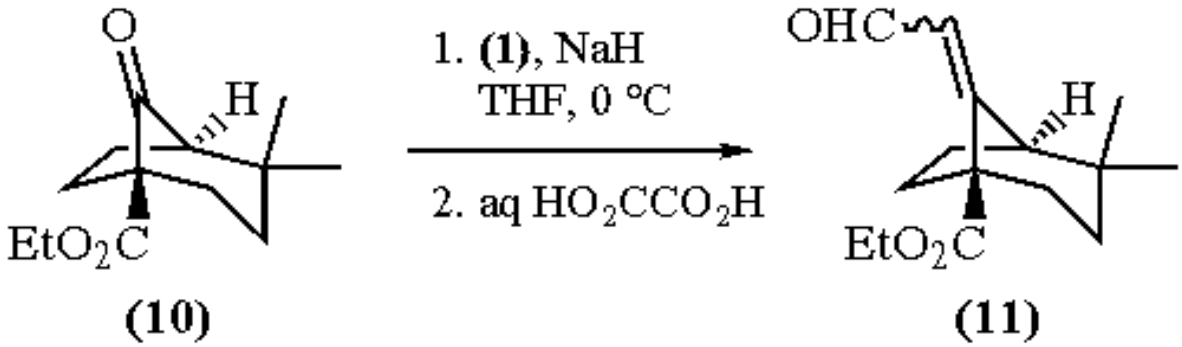

(6)

Application to the two-carbon extension of heteroaromatic aldehydes has met with limited success. Condensation of

the anion of (**1**) with 2-thiophenecarbaldehyde affords 3-(2-thienyl)propenal in 80% yield (eq 7).[5] However, treatment of 2-methyl-3-(pyrrol-2-yl)propenal (**14**) with the phosphonate anion produces the homologous dienal (**15**) in low yield (eq 8).[6]

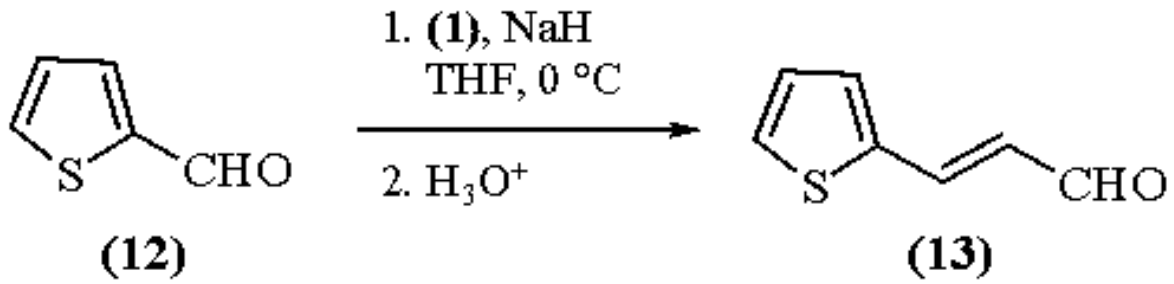

(7)

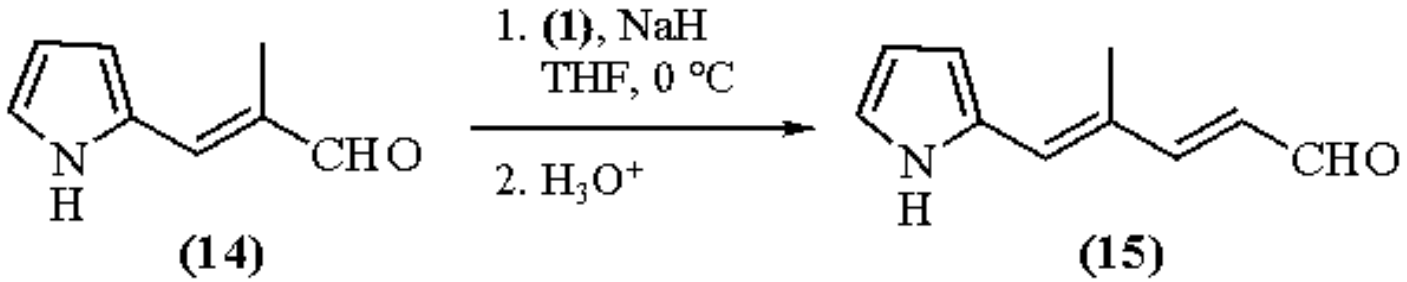

(8)

The facile synthesis of dienes was demonstrated in an approach to the galanthan alkaloid ring system.[7] Condensation of (**1**) with 2-carboxybenzaldehyde provides the substituted cinnamaldehyde (**17**) in 50% yield after esterification (eq 9). Peterson alkenation provides diene (**18**); this can be elaborated to triene (**19**) (eq 10) which undergoes intramolecular cycloaddition upon heating.

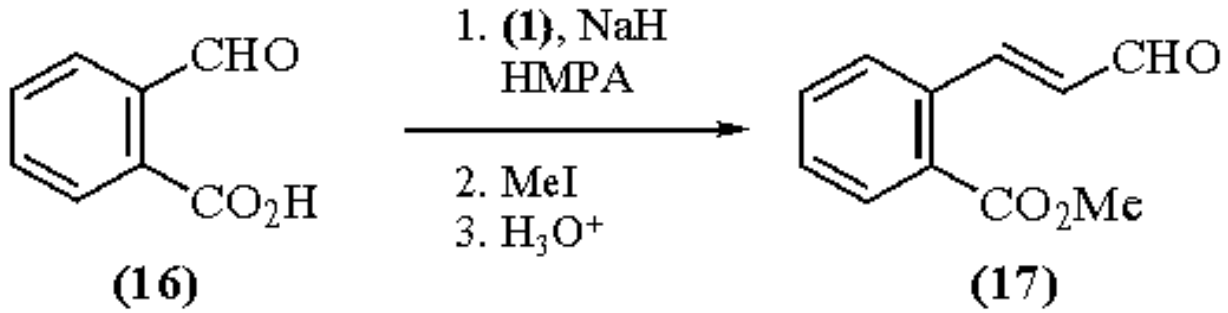

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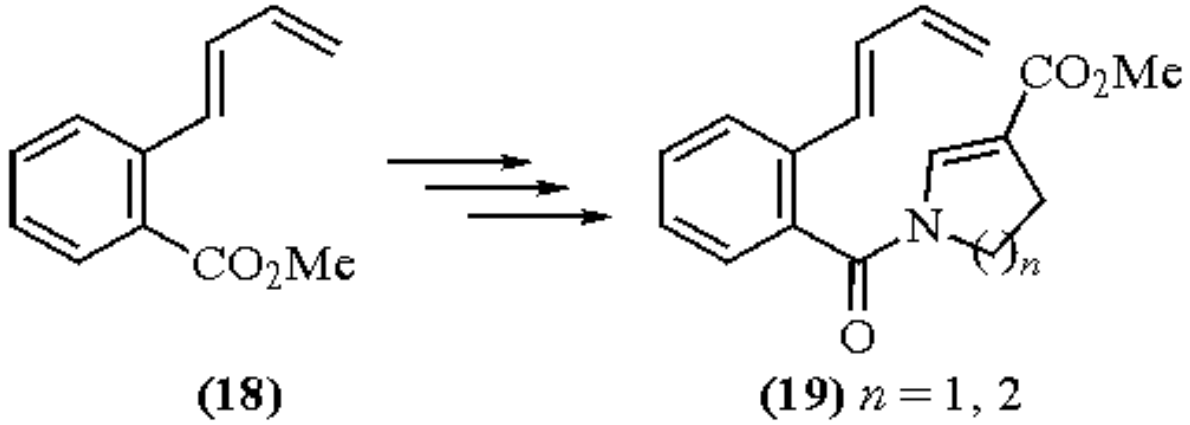

(10)

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Diethyl Diazomethylphosphonate[1]

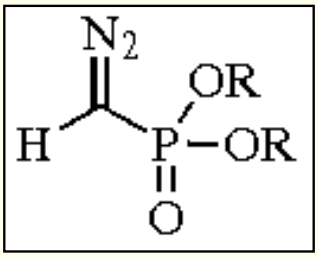

(R = Et)

[25411-73-8] · $C_5H_{11}N_2O_3P$ · Diethyl Diazomethylphosphonate · (MW 178.13) (R = Me)

[27491-70-9] · $C_3H_7N_2O_3P$ · Dimethyl Diazomethylphosphonate · (MW 152.09)

(nucleophilic diazo species for the preparation of substituted diazophosphonates,[3,4] β-ketophosphonates,[5] alkynes,[6-8] electron-rich alkenes,[9] various cyclopropane derivatives,[10-12] and five-membered rings[13,14])

Alternate Name: DAMP.

Physical Data: yellow liquid, bp 51 °C/0.1 mmHg; 86-88 °C/0.2 mmHg.

Solubility: sol organic solvents.

Preparative Method: by diazotization of diethyl or dimethyl (aminomethyl)phosphonate using ***Sodium Nitrite*** under acidic conditions.[2]

Handling, Storage, and Precautions: should be stored under an inert atmosphere at 4 °C, and handled as any other diazo compound; *all distillations should be carried out behind a blast shield.*

Introduction.

The corresponding dimethyl ester, dimethyl diazomethylphosphonate, is also widely used; this entry discusses both reagents. The acronym DAMP is used for both the ethyl and methyl derivatives.

Preparation of Diazophosphonates.

Diethyl diazomethylphosphonate is readily lithiated (***n-Butyllithium***, THF, -100 °C) and the resulting lithio derivative can be acylated (***Phenacyl Bromide***, 33%) (eq 1) or silylated (poor yield).[3] The corresponding silver derivative, formed

by treatment with ***Silver(I) Oxide***, can be alkylated with reactive allylic halides.[3] α-Diazo-β-hydroxyphosphonates result when the lithio derivative is treated with aryl aldehydes; alternatively, these can be prepared by direct reaction of DAMP with aldehydes in the presence of ***Triethylamine*** (eq 2).[4]

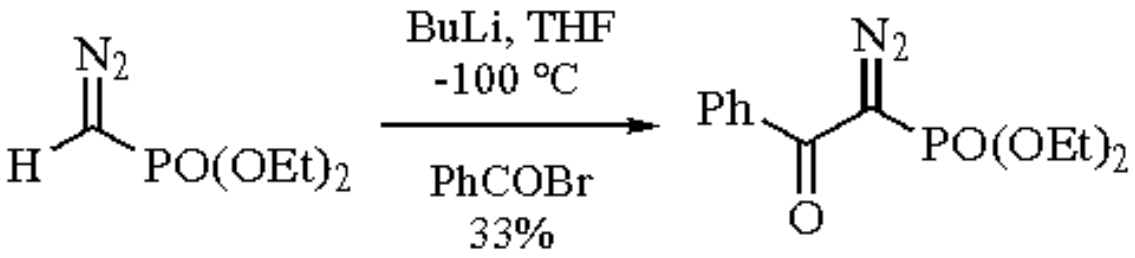

(1)

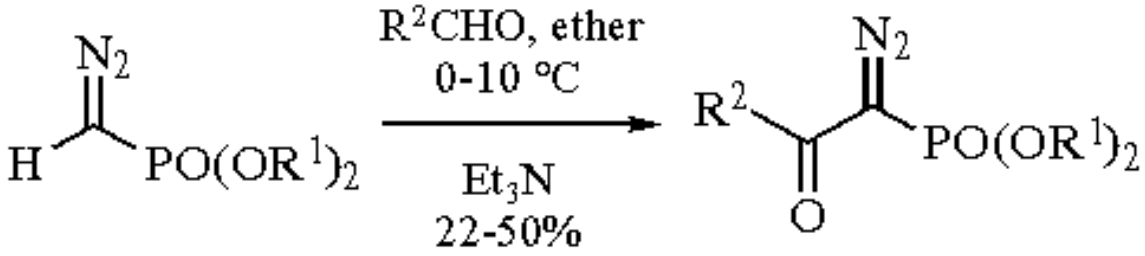

(2)

Preparation of β-Ketophosphonates.

In the presence of ***Tin(II) Chloride***, DAMP adds to aldehydes to give β-ketophosphonates in reasonable yield (eq 3).[5]

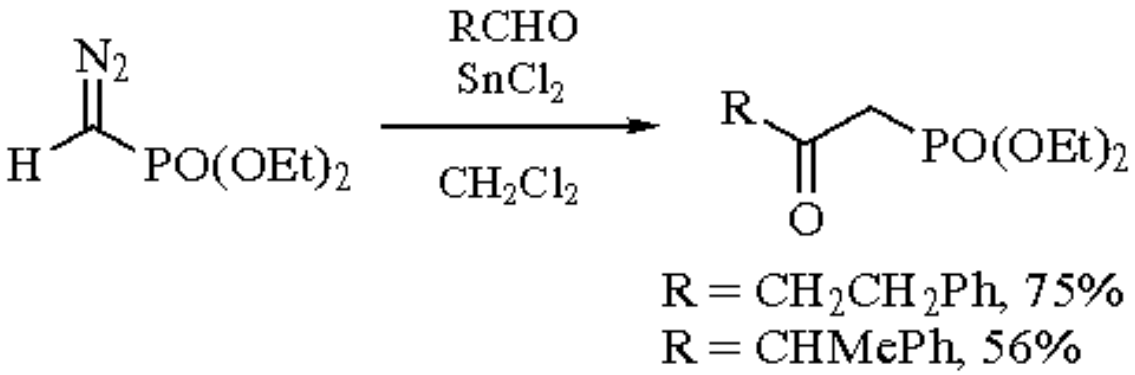

(3)

Preparation of Alkynes.

Diaryl ketones are converted into alkynes by reaction of the lithium (or potassium) salt of DAMP. The reaction presumably involves a Horner-Wadsworth-Emmons-like elimination to give the diazoalkene, followed by aryl migration with loss of nitrogen (eq 4)[6] (see also ***Diazo(trimethylsilyl)methyllithium***).

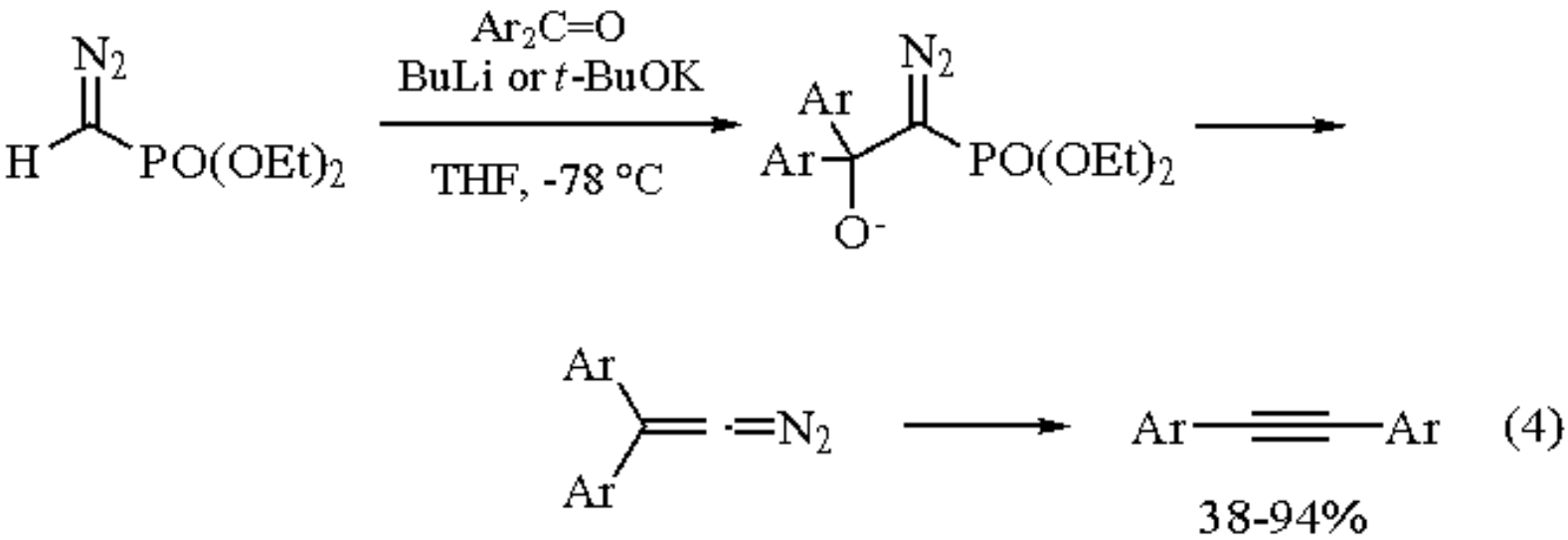

Aldehydes react to give the homologous terminal alkyne by a similar mechanism involving hydrogen migration. The reaction appears to be quite general and has been applied to complex aldehydes for natural product synthesis (eqs 5 and 6).[7,8]

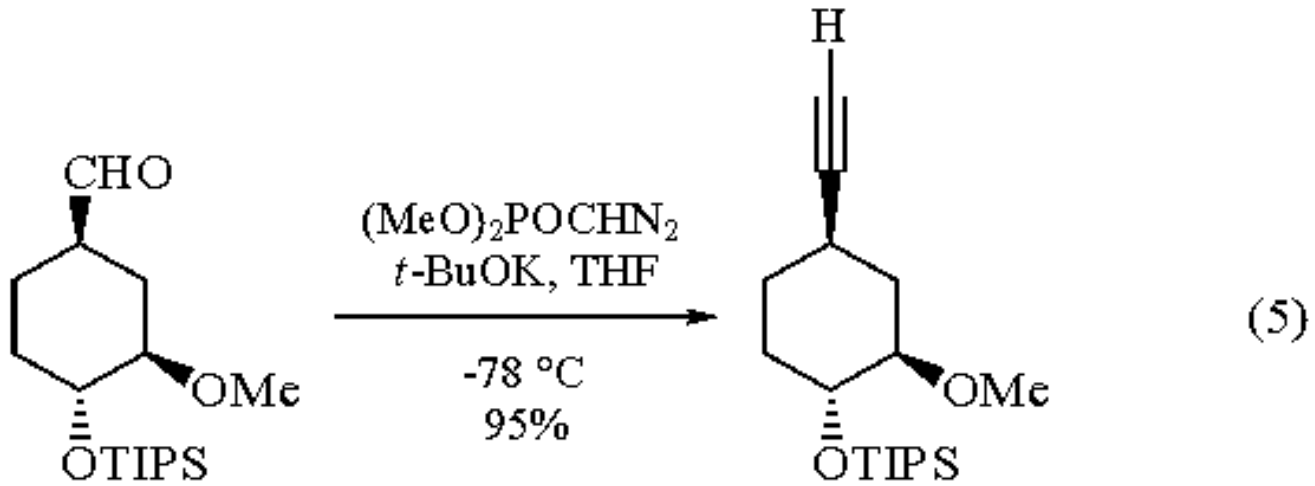

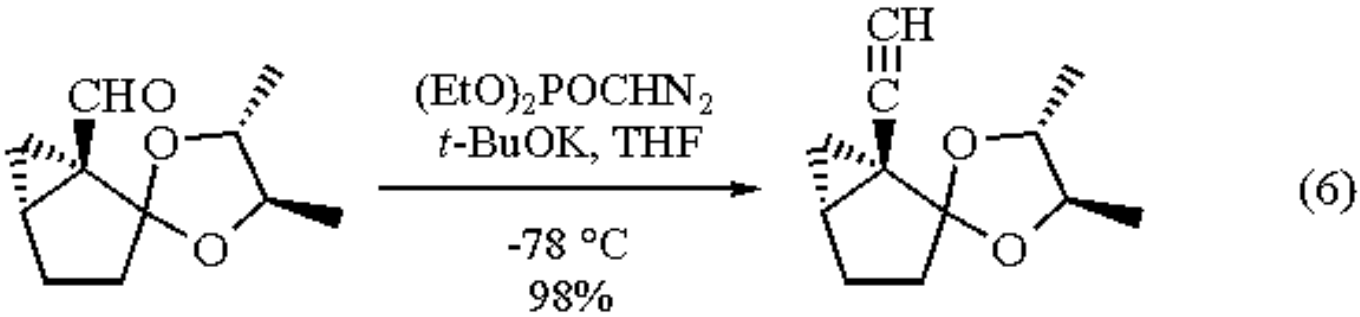

Preparation of Electron-Rich Alkenes.

Both acyclic and cyclic ketones are homologated to enol ethers or enamines by reaction with DAMP/***Potassium t-Butoxide*** followed by an alcohol or secondary amine (eqs 7 and 8).[9] The reaction presumably involves a diazoalkene intermediate, but, because alkyl groups migrate poorly, an alkyne is not formed; instead, reaction with the nucleophile occurs.

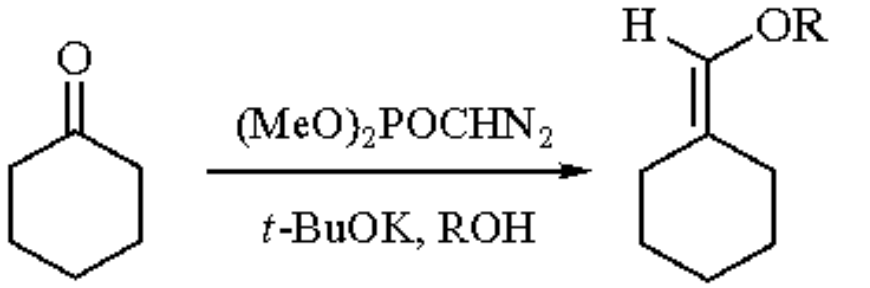

(7)

R = Me, 58%
R = *t*-Bu, 56%

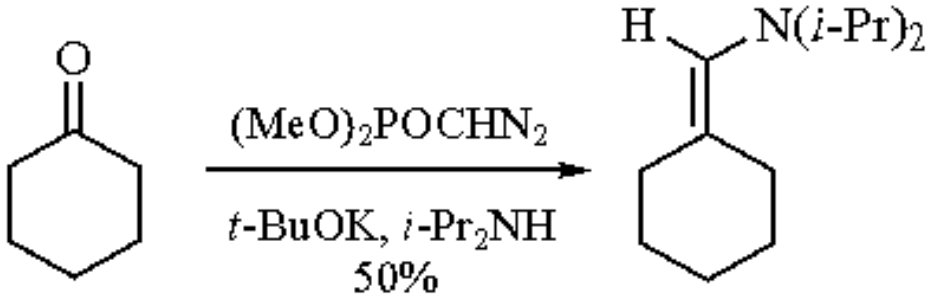

(8)

Preparation of Cyclopropanes.

When the above reactions of ketones are carried out in the presence of alkenes, alkylidenecyclopropanes are formed in good yield by addition to the alkylidenecarbene (eq 9).[10]

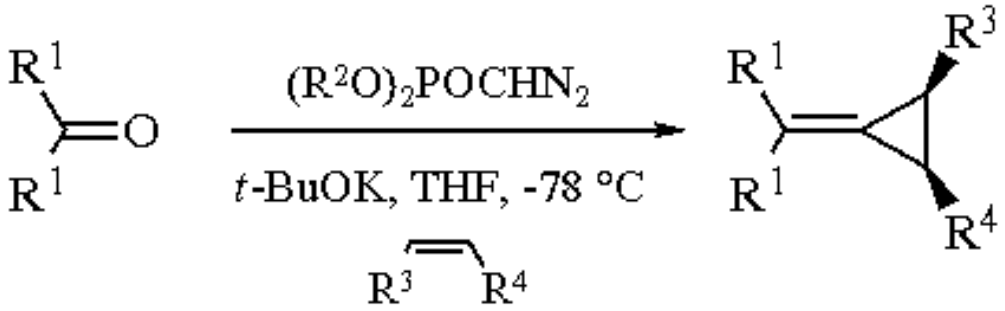

(9)

$R^1 = Me$, $R^3R^4 = (CH_2)_4$, 58%
$R^1 = R^3 = Me$, $R^4 = i\text{-Pr}$, 45%
$R^1R^1 = R^3\ R^4 = (CH_2)_4$, 70%

The reaction has been extended to α-phenylseleno ketones; in this case the resulting phenylseleno-substituted alkylidenecyclopropanes undergo rearrangement to vinylcyclopropanes.[2c,11]

An alternative route to alkylidenecyclopropanes involves ***Copper*** powder or ***Copper(I) Trifluoromethanesulfonate*** catalyzed reaction of the alkene with DAMP to give cyclopropylphosphonates, followed by Horner-Wadsworth-

Emmons reaction with an aldehyde or ketone (eq 10).[2a,12]

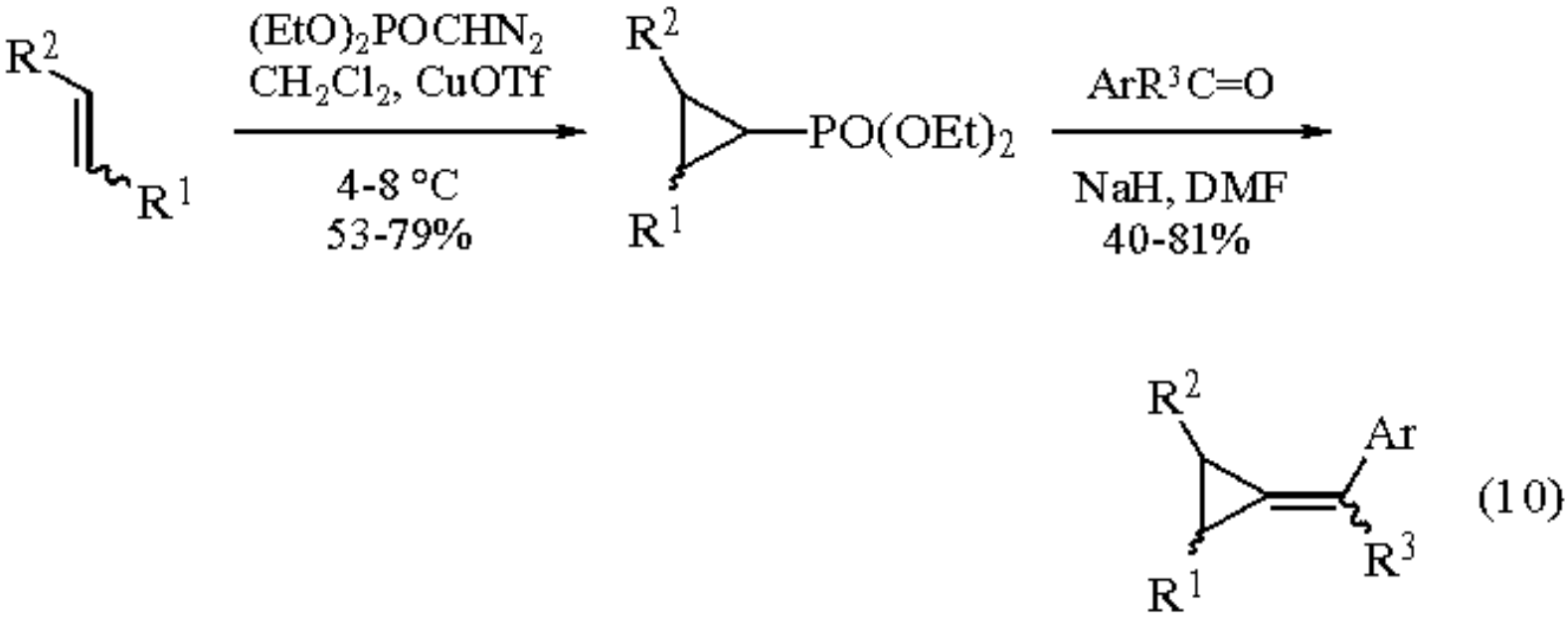

Preparation of Five-Membered Rings.

The alkylidenecarbenes generated from diazoalkenes (resulting from reaction of ketones with DAMP) undergo intramolecular C-H insertion reactions to give cyclopentenes (eq 11)[13] and dihydrofurans, and hence furans (eq 12).[14]

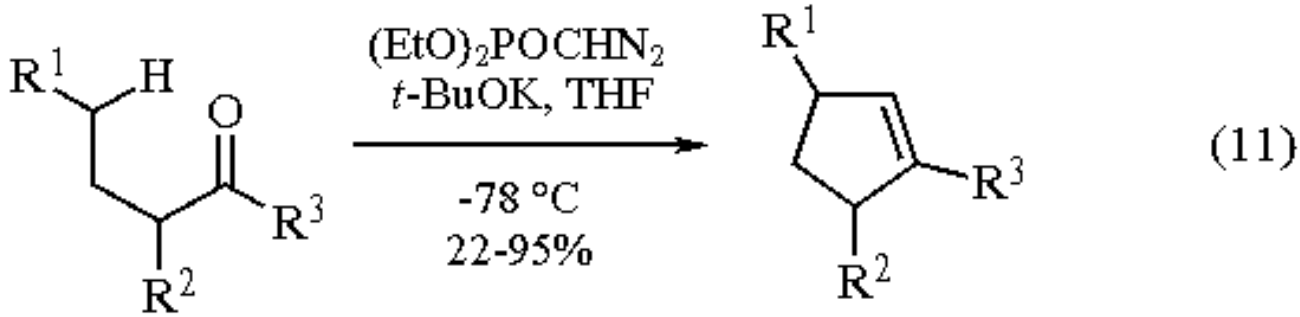

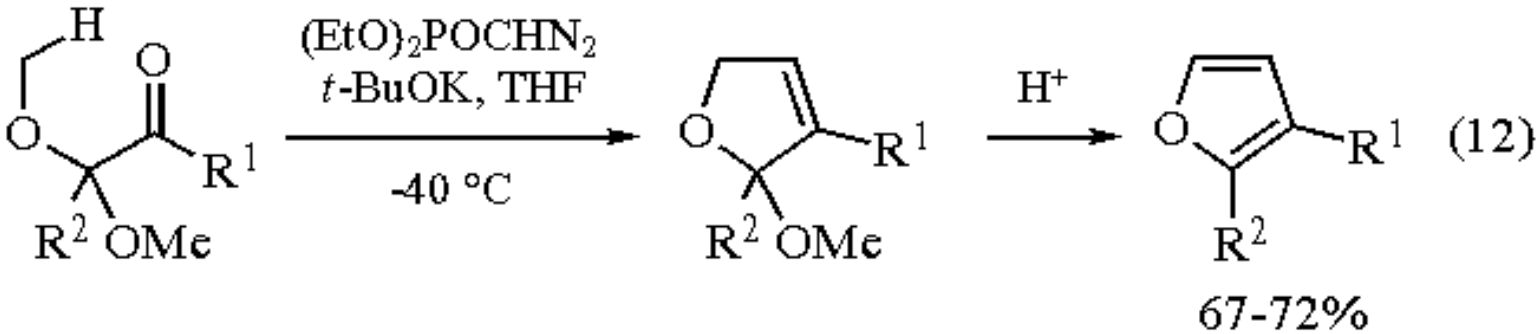

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Diethyl Dibromomalonate[1]

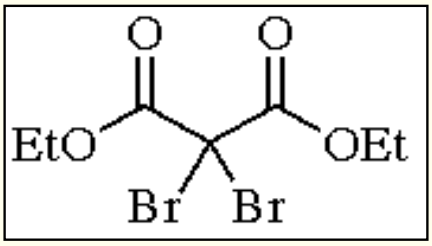

[631-22-1] · $C_7H_{10}Br_2O_4$ · Diethyl Dibromomalonate · (MW 317.96)

(used for selective bromination of polyunsaturated ester enolates;[1,3] converts alkenes into cyclopropanes in the presence of suitable heavy metal reagents[4-6])

Alternate Name: ethyl dibromomalonate.

Physical Data: bp 108-110 °C/4 mmHg.

Solubility: sol benzene, CCl_4, DMSO, THF.

Form Supplied in: commercially available in 98% purity as a liquid.

Analysis of Reagent Purity: NMR, combustion analysis.

Preparative Method: prepared in 95% yield by reaction of diethyl malonate with bromine.[1,2]

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: lachrymator; light sensitive. Store in the dark under nitrogen. This toxic reagent should be handled in a fume hood.

Enolate Bromination.

Esters can be selectively α-brominated by reaction of this reagent with the lithium enolate at -78 °C (eqs 1 and 2). The esters can then be converted to the corresponding carboxylic acids.[1,3] This bromination can be carried out on substrates bearing remote alkenic functionality. Bromination of the lithium enolate in eq 1 using Br_2 at -78 °C gave a poor yield of α-brominated ester.

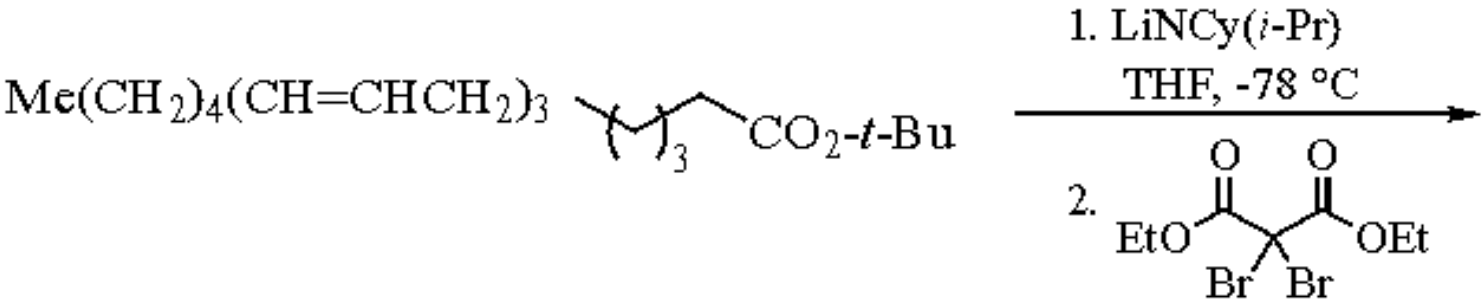

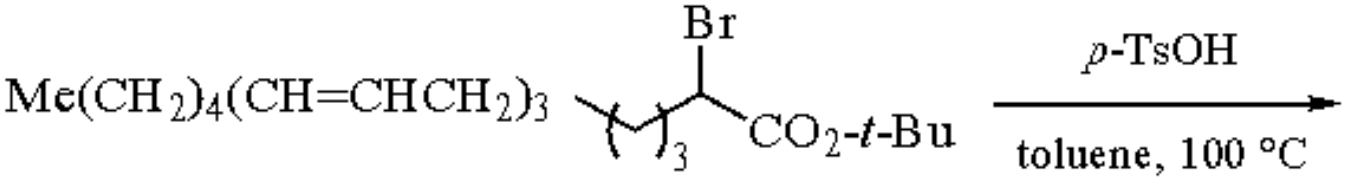

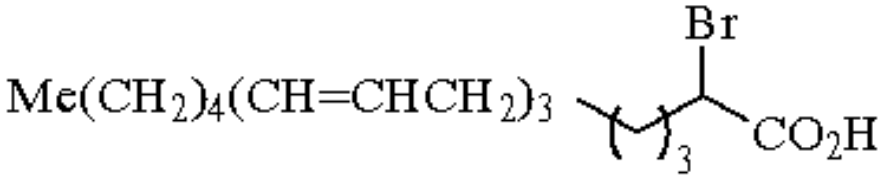

(1)

27%

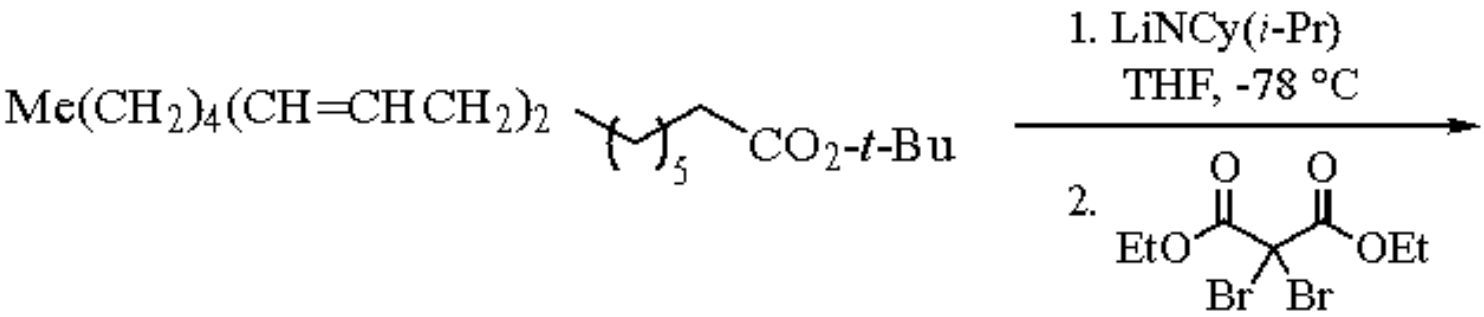

70%

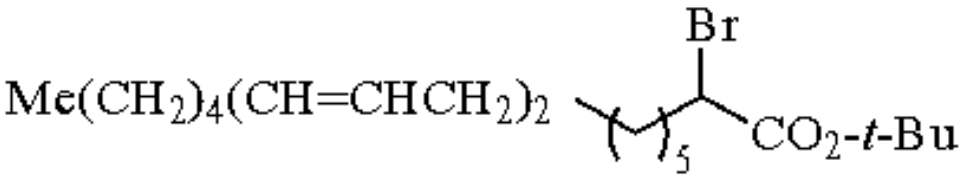

(2)

Synthesis of Cyclopropanes.

Alkenes can be cyclopropanated in a nonstereospecific fashion by treatment with diethyl dibromomalonate in the presence of ***Copper*** powder or ***Copper(I) Bromide***.[4] Higher yields are obtained when this reaction is run in DMSO (eq 3). The yield of cyclopropane product is highly dependent on the amount of copper used. Tetraethyl ethylenetetracarboxylate is commonly observed as a side-product in this transformation.

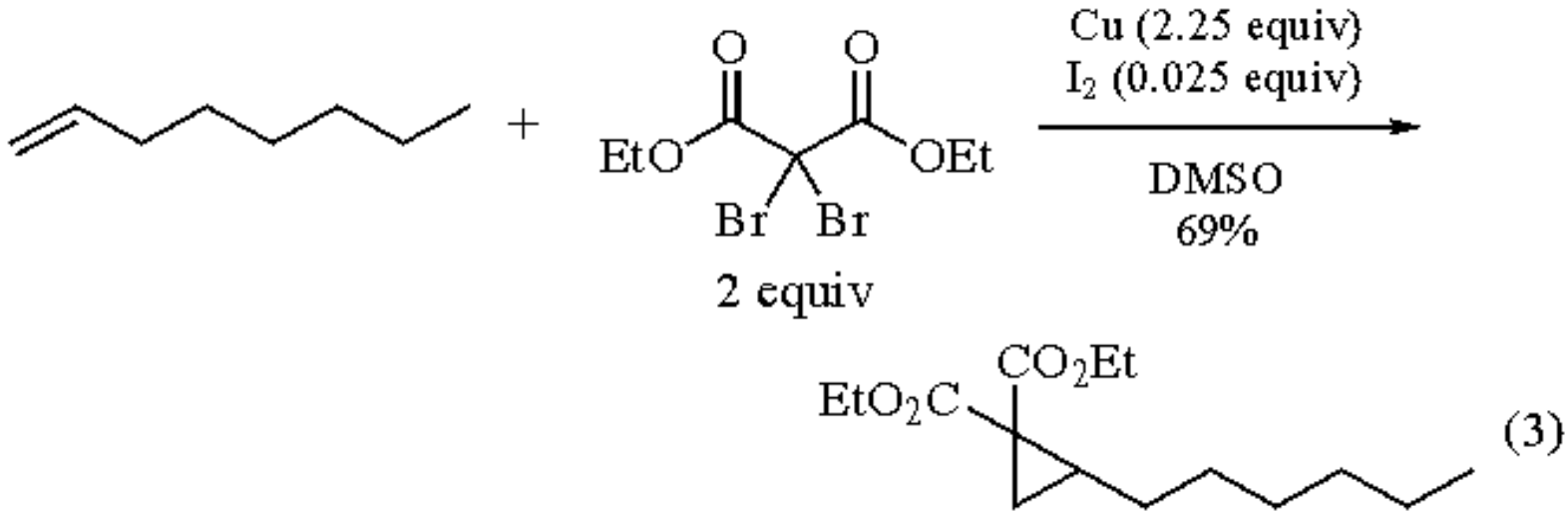

Nonstereospecific cyclopropanation of Michael acceptors can be accomplished by use of this reagent in combination with ***Tri-n-butylstibine*** (eq 4)[5] or indium.[6] Carbonyl groups can also react with diethyl dibromomalonate in the presence of tri-*n*-butylstibine to form alkenes.[7]

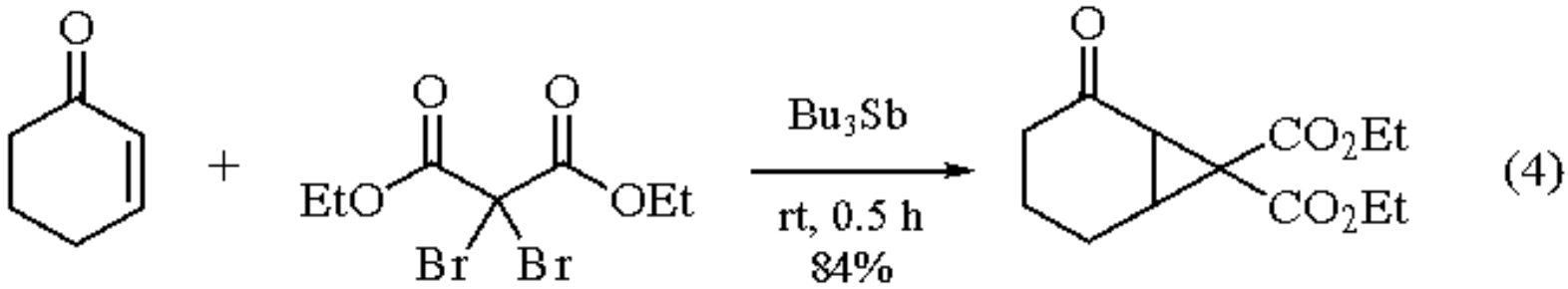

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Diethyl Dichloromethylphosphonate

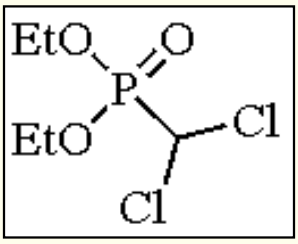

[3167-62-2] · $C_5H_{11}Cl_2O_3P$ · Diethyl Dichloromethylphosphonate · (MW 221.02)

(Horner-Emmons reagent for the synthesis of 1,1-dichloro-1-alkenes; precursor for dichloromethylphosphine)

Physical Data: bp 133 °C/10 mmHg;[1] 66 °C/0.02 mmHg;[2] *d* 1.26 g cm^{-3}; *n*25D 1.4529.

Solubility: very sol most organic solvents (ether, THF, CH_2Cl_2, hexane).

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$) δ (ppm): 1.39 (t, CH_3), 4.32 (quint, CH_2O), 5.65 (d, $^2J_{HP}$ = 2.0 Hz, CH); ^{31}P NMR ($CDCl_3$) δ (ppm): 11.10.

Form Supplied in: not commercially available.

Preparative Methods: obtained on a large scale through the Kinnear and Perren reaction of ***Phosphorus(III) Chloride*** and ***Chloroform*** in the presence of ***Aluminum Chloride***, and subsequent treatment with a large excess of EtOH (eq 1).[3,4]

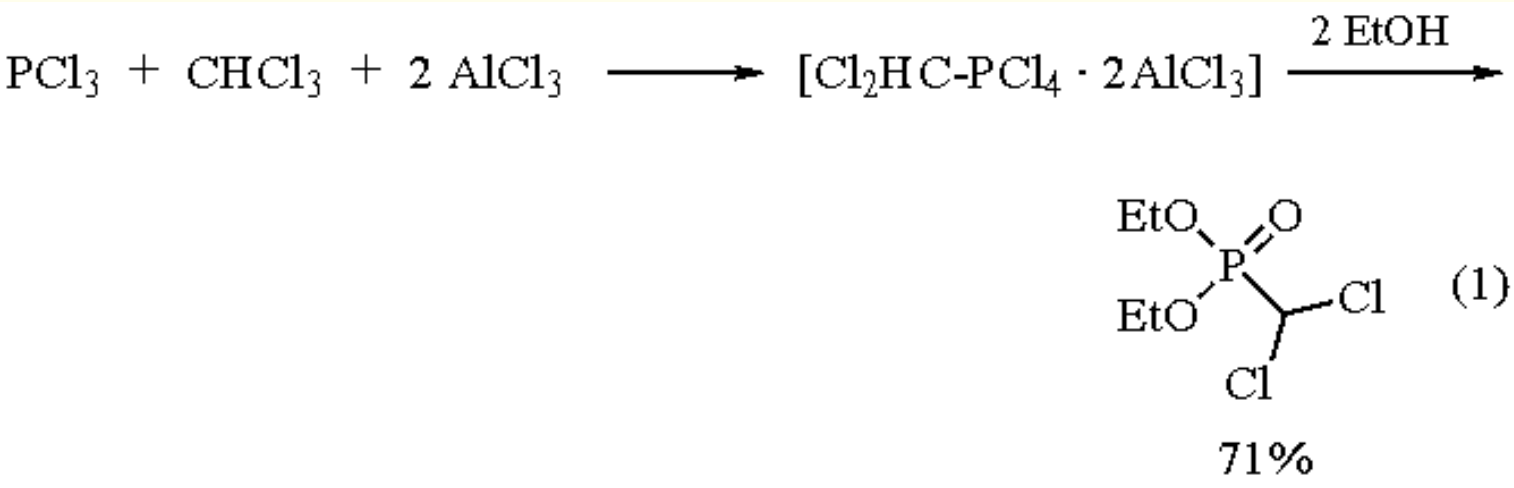

(1)

On a laboratory scale, the preferred synthesis employs the commericially available diethyl trichloromethylphosphonate: this is partially reduced by means of ***n-Butyllithium*** (eq 2)[2] or by α-lithiochloromethylphosphonate in the presence of lithium salts (eq 3).[5] The resulting phosphonate carbanion is stabilized at low temperature by lithium salts and can be protonated in acidic medium or used in situ for further reactions.

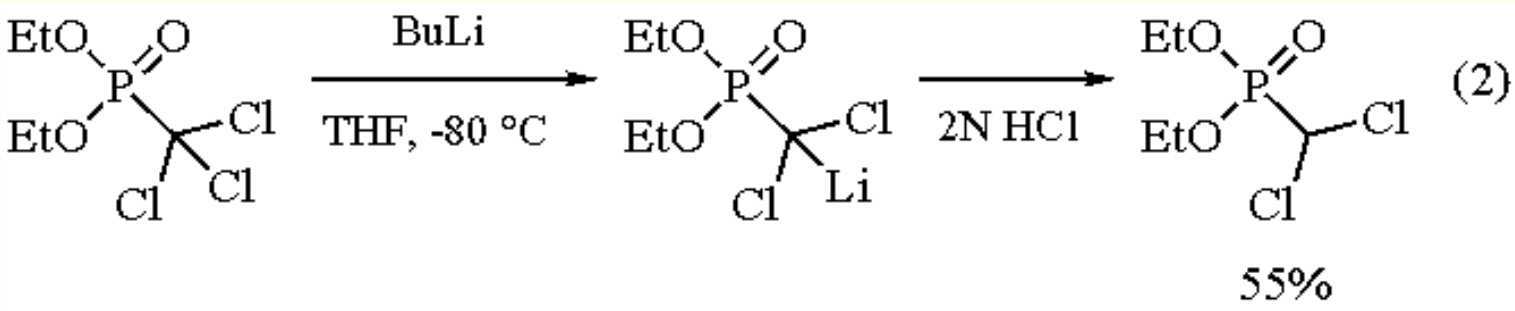

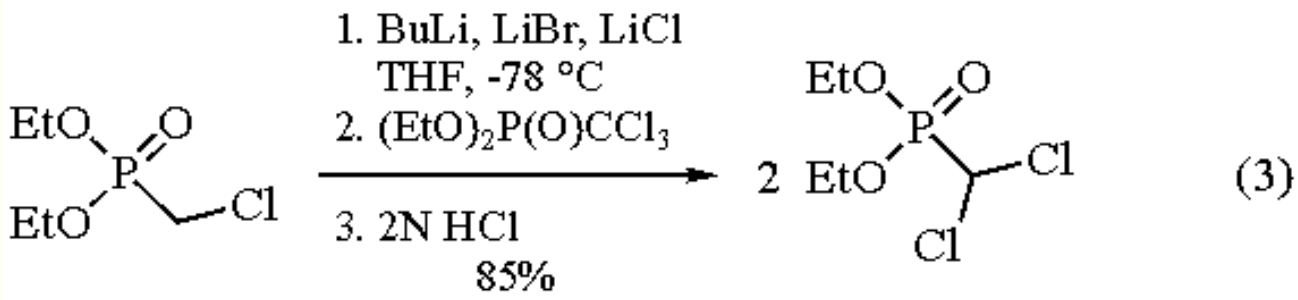

A few other methods for the reduction of trichloromethylphosphonate have been reported. These include an electrochemical approach (85%)[7] and the reaction of trivalent phosphorus reagents, such as ***Triethyl Phosphite*** (65%)[1] and ***Hexamethylphosphorous Triamide*** (72%)[8] with trichloromethylphosphonate. Diethyl dichloromethylphosphonate is also obtained by chlorination of the chloromethylphosphonate with CCl_4 or of the methylphosphonate with ***Benzenesulfonyl Chloride*** in the presence of bases (*n*-BuLi or ***Lithium Diisopropylamide***).[6]

Purification: distillation.

Handling, Storage, and Precautions: stable compound; must be stored in the absence of moisture.

Preparation of 1,1-Dichloro-1-alkenes.

This involves a Horner-Emmons reaction between $(EtO)_2P(O)CCl_2Li$ and various carbonyl compounds. This method is suitable for the preparation of large quantities of 1,1-dichloro-1-alkenes (up to 1 mol) in moderate to good yields (eq 4).[2,9,10]

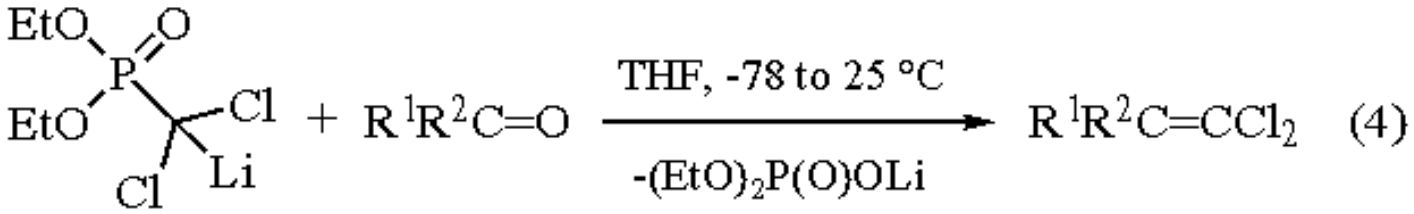

The reaction takes place smoothly and cleanly with aldehydes or ketones, even in the case of hindered carbonyl derivatives, such as adamantanone (to give **1**) or camphor (to give **2**), of enolizable ketones, and of α,β-unsaturated aldehydes and ketones.

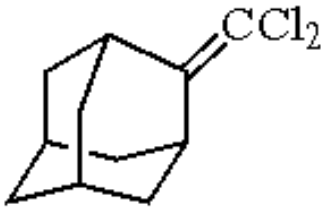

(1)

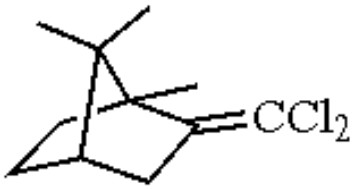

(2)

It has been applied to the synthesis of chrysanthemic[11] and pyrethric esters (e.g. **3**), their nitrogen analogs (e.g. **4**),[12] and prostacyclin analogs (e.g. **5**).[13]

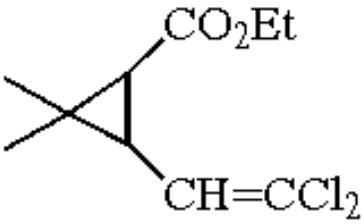

(3)

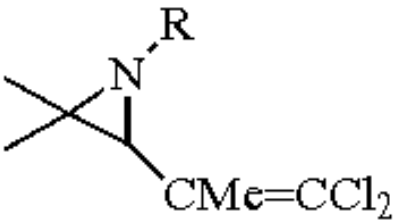

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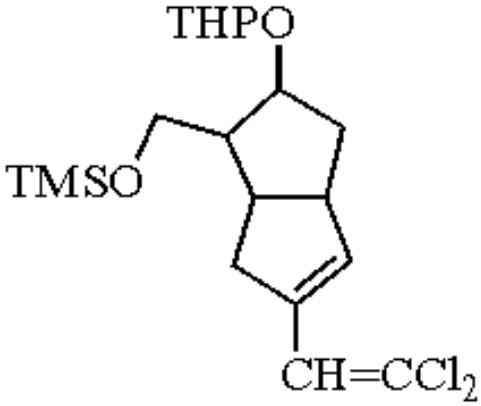

(5)

The Horner-Emmons reaction has also been tested on the phosphonate carbanion generated under electrochemical conditions. Yields are limited by side reactions, even in conditions optimized for the purpose of synthesis (see Le Menn et al.[7] and references therein). Further treatment of the *gem*-dichloroalkenes $RCH{=}CCl_2$ with butyllithium in ether or THF at a suitable temperature affords the corresponding alkynyllithium derivatives, which can be hydrolyzed or alkylated to give terminal and internal alkynes, respectively (eq 5).[13-15]

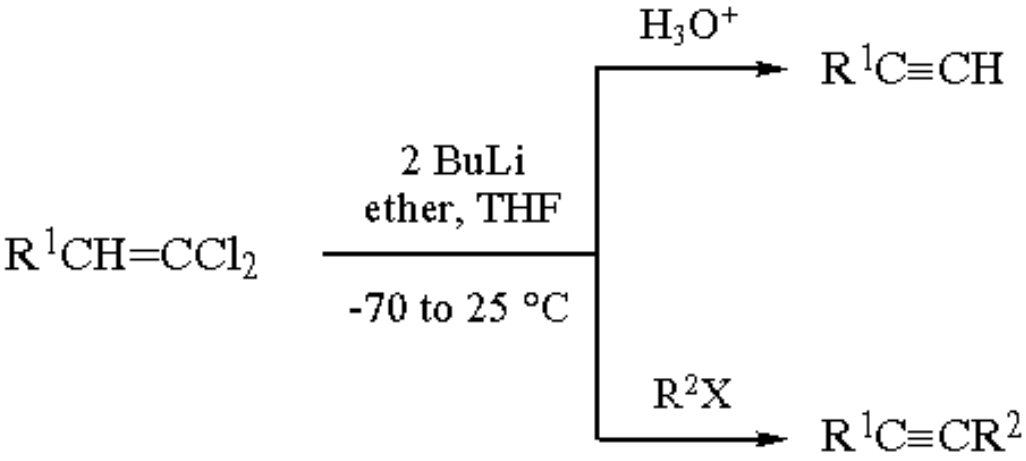

(5)

Preparation of Dichloromethylphosphine.

H_2PCHCl_2 has been prepared by reduction of diethyl dichloromethylphosphonate. The best results are obtained with ***Dichloroalane*** as reducing agent (eq 6).[16] The half-life of the dichloromethylphosphine is 6 h at rt in THF solution.

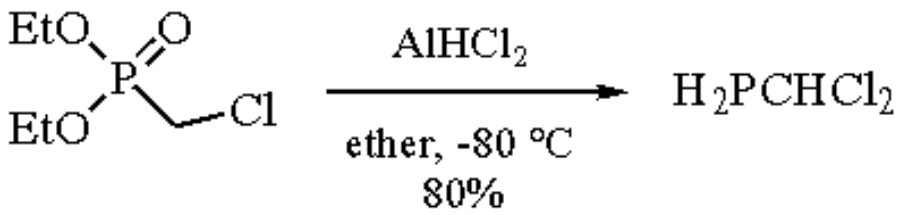

(6)

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Diethyl Difluoromethylphosphonate

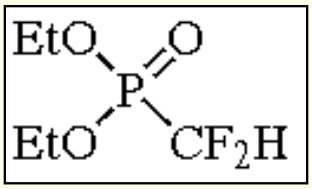

[1478-53-1] · $C_5H_{11}F_2O_3P$ · Diethyl Difluoromethylphosphonate · (MW 188.11)

(precursor for the introduction of $(EtO)_2P(O)CF_2$- and $=CF_2$ groups into organic compounds)

Preparative Methods: prepared by the reaction of sodium diethyl phosphite with ***Chlorodifluoromethane*** in hexane (49% yield)[1] or in THF (77% yield);[2] or generated in situ from diethyl bromodifluoromethylphosphonate and BuLi.[3]

Reaction with Carbonyl Compounds.

Deprotonation of diethyl difluoromethylphosphonate with ***Lithium Diisopropylamide*** at -78 °C gives the carbanion (eq 1) which is only stable at or below -78 °C.[2] Reaction of the carbanion with aldehydes and ketones at -78 °C, followed by decomposition (heating THF solution) of the intermediate, gives the corresponding 1,1-difluoroalkenes (eq 2).[2,4] The intermediate can be trapped by electrophiles, such as proton[2,5] and acid chlorides,[6] to form the corresponding phosphonates.

$$(EtO)_2P(O)CF_2H + LDA \xrightarrow[-78\ °C]{} [(EtO)_2P(O)CF_2Li] \qquad (1)$$

$$[(EtO)_2P(O)CF_2Li] \xrightarrow[-78\ °C]{RCOR'} [(EtO)_2P(O)CF_2C(OLi)RR'] \qquad (2)$$

$$[(EtO)_2P(O)CF_2C(OLi)RR'] \nearrow RR'C{=}CF_2$$

$$[(EtO)_2P(O)CF_2C(OLi)RR'] \xrightarrow{E^+} (EtO)_2P(O)CF_2C(OE)RR'$$

$$E = H,\ Ac$$

Reaction with Alkyl and Allyl Halides and Alkyl Triflates.

The carbanion of diethyl difluoromethylphosphonate also reacts with alkyl halides,[2,7,8] alkyl triflates,[9] oxalate,[10] and allyl bromide[2] to form the corresponding 1,1-difluoro phosphonates (eq 3).

$$[(EtO)_2P(O)CF_2Li] + RX \longrightarrow (EtO)_2P(O)CF_2R \qquad (3)$$

$$R = \text{alkyl, allyl; } X = I, Br, Tf$$

Reaction with Other Electrophiles.

The carbanion of diethyl difluoromethylphosphonate can be trapped with ***Chlorotrimethylsilane*** or trialkylchlorostannanes to produce the corresponding trimethylsilylated and trialkyltin-substituted 1,1-difluoro phosphonates (eq 4).[2]

$$[(EtO)_2P(O)CF_2Li] + R_3MCl \longrightarrow (EtO)_2P(O)CF_2MR_3 \qquad (4)$$

$$R = \text{alkyl; } M = Si, Sn$$

The carbanion also reacts with diethyl chlorophosphate or benzoyl chloride to give the corresponding α,α-difluoro bisphosphonate and β-ketophosphonate, respectively (eq 5).[2,11,12] Treatment of the carbanion of diethyl difluoromethylphosphonate with ***Carbon Dioxide*** at -78 °C leads to the formation of the carboxylic acid (eq 6). The thiocarboxylic acid is formed by a similar reaction of the carbanion with ***Carbon Oxysulfide*** (eq 6).[13] The carbanion reacts in a 1,4 addition with 4-chloro-β-nitrostyrene to give the nitro phosphonate (eq 7).[14]

$$[(EtO)_2P(O)CF_2Li] + RCl \longrightarrow (EtO)_2P(O)CF_2R \qquad (5)$$

$$R = (EtO)_2P(O), PhCO$$

$$[(EtO)_2P(O)CF_2Li] \xrightarrow[2.\ H^+]{1.\ COY} (EtO)_2P(O)CF_2C(O)YH \qquad (6)$$

$$Y = O, S$$

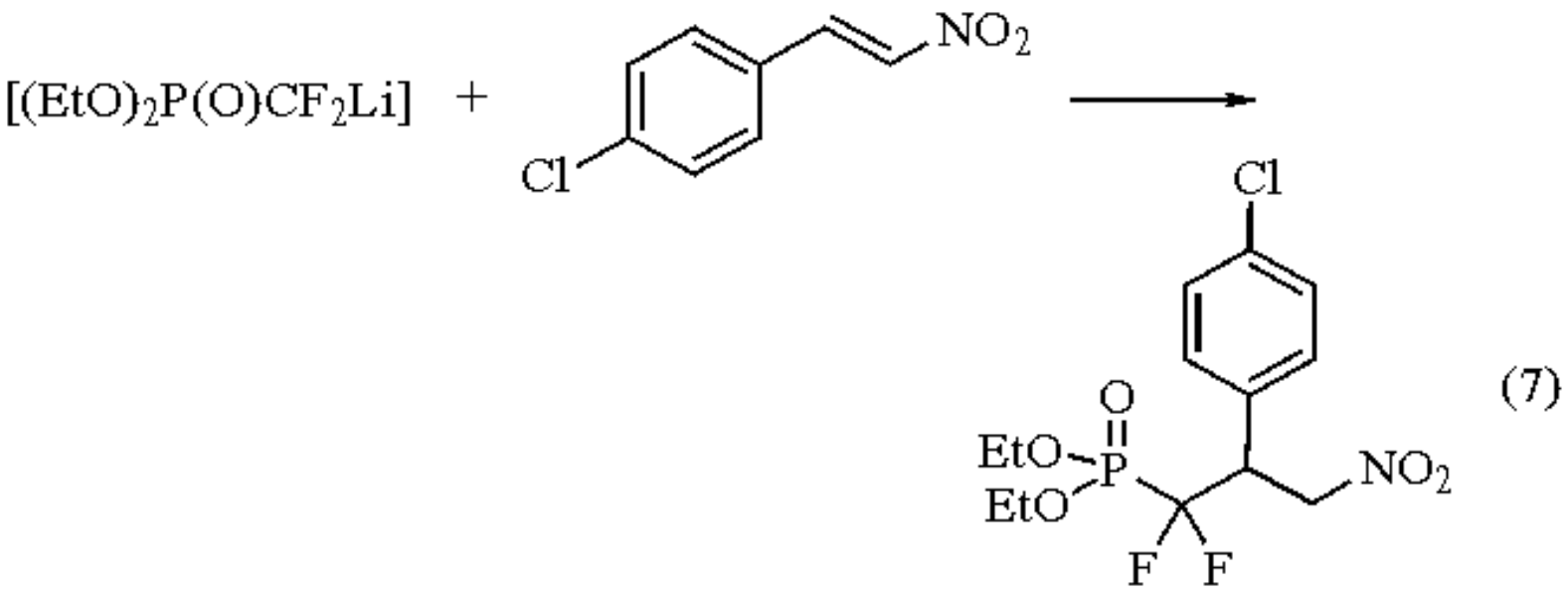

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Diethyl[dimethyl(phenyl)silyl]aluminum

$PhMe_2SiAlEt_2$

[86014-18-8] · $C_{12}H_{21}AlSi$ · Diethyl[dimethyl(phenyl)silyl]aluminum · (MW 220.36)

(can silylaluminate terminal alkynes;[1] can cross couple with alkenyl, allyl, and aryl phosphates;[3] can deoxygenate epoxides[5])

Physical Data: see ***Diethylaluminum Chloride*** and ***Dimethylphenylsilyllithium***.

Solubility: commonly prepared and used in THF-hexane.

Preparative Method: prepared in situ by adding $PhMe_2SiLi$ in THF to a hexane solution of Et_2AlCl at 0 °C.[1]

Handling, Storage, and Precautions: see ***Diethylaluminum Chloride*** and ***Dimethylphenylsilyllithium***.

Silylalumination of Alkynes and Alkenes.

The reagent adds to 1-alkynes in a regio- and stereoselective (*cis* addition) manner. Transition metal catalysts alter the regioselectivity (eq 1).[1]

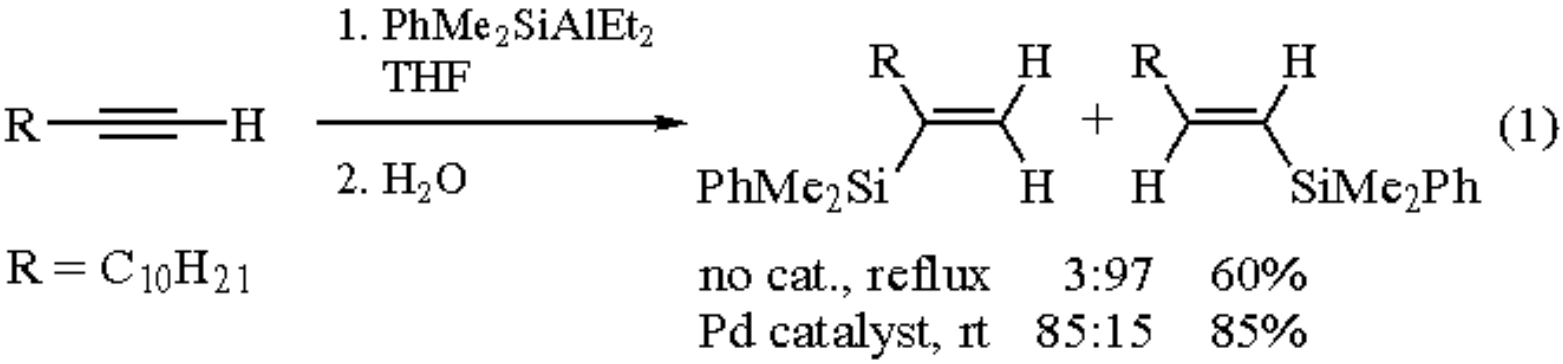

In addition reactions with allenes, $PhMe_2SiAlEt_2$ gives, albeit in low yield, allylsilanes as the major product, while contrasting regioselectivity is observed in the Cu-catalyzed silylmagnesiation by a related silylmagnesium reagent, $PhMe_2SiMgMe$ (eq 2).[2]

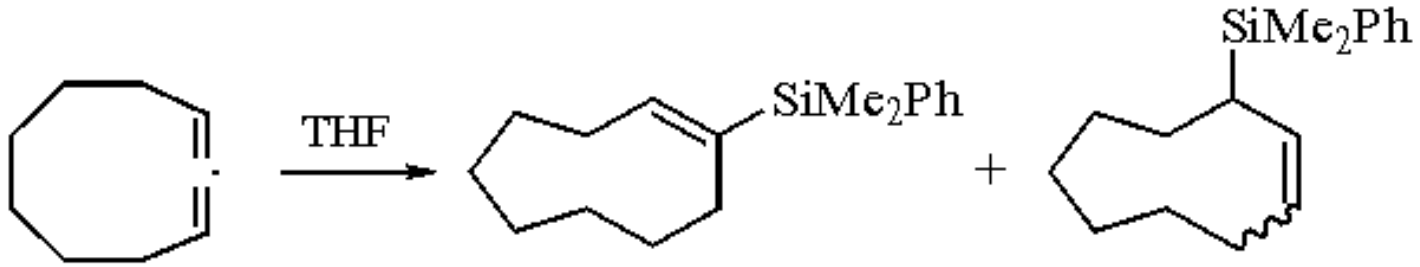

(2)

$PhMe_2SiAlEt_2$, cat. $PdCl_2(P(o\text{-Tol})_3)_2$, rt	10:90	36%
$PhMe_2SiMgMe$, cat. CuI, 0 °C	>95:<5	74%

Coupling with Allylic and Enol Phosphates.

The reagent converts allylic phosphates into allylsilanes (eq 3).[3] Reaction with (2-vinyl-1,1-cyclopropanedicarboxylate gives the 1,7-homoconjugate addition product (eq 4).[4] In the presence of a Pd catalyst, $PhMe_2SiAlEt_2$ converts enol phosphates into vinylsilanes (eq 5).[3] Higher yields are usually obtained with $PhMe_2SiMgMe$.

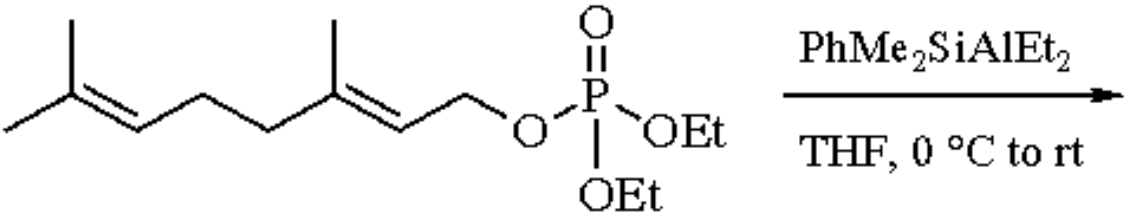

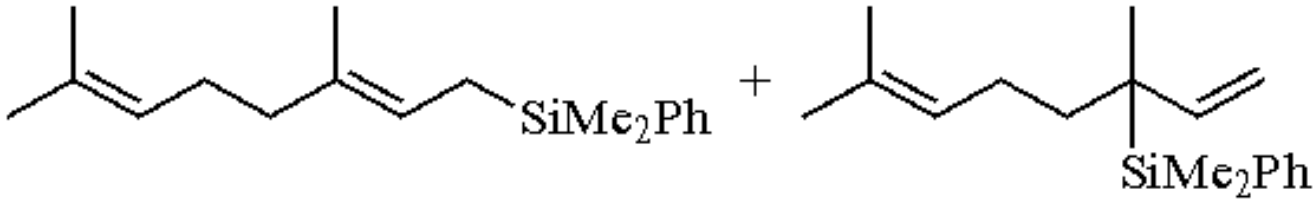

(3)

70% 15%

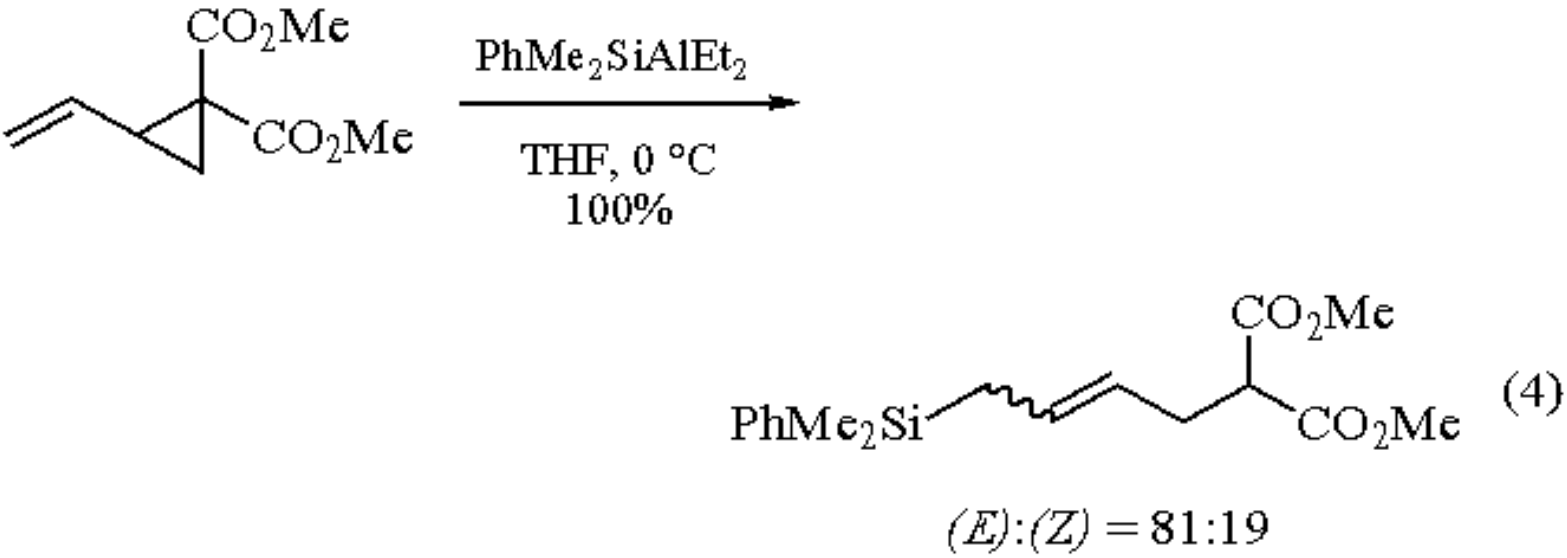

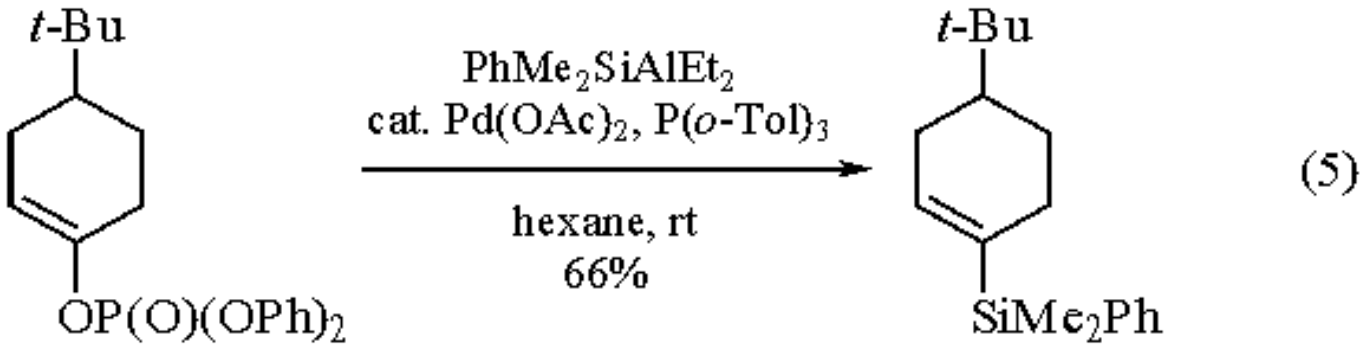

Deoxygenation of Epoxides.

The reagent deoxygenates epoxides in a stereospecific manner, although the reaction is limited to aryl-substituted epoxides (eq 6). A related reagent, [*n*-$Bu_3SnAlMe_3$]$^-Li^+$, has broader applicability.[5]

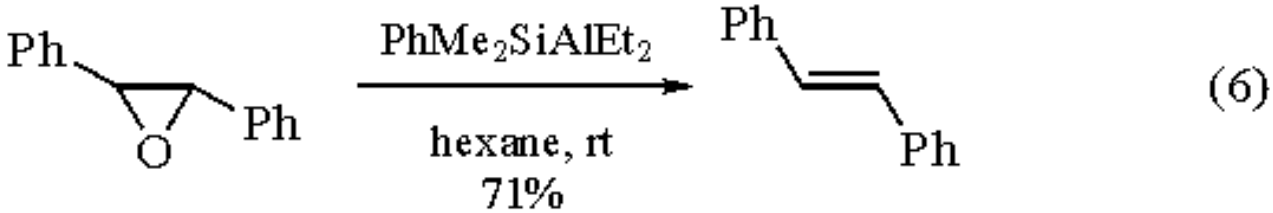

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Keisuke Suzuki & Tetsuya Nagasawa

Diethyl Ethoxymagnesiomalonate[1]

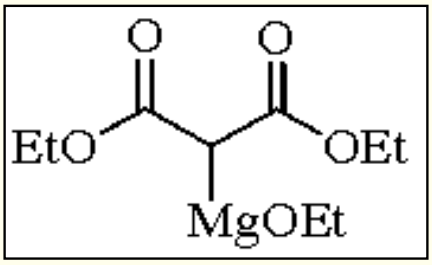

[35227-78-2] · $C_9H_{16}MgO_5$ · Diethyl Ethoxymagnesiomalonate · (MW 228.53)

(synthesis of acyl malonates[1] or methyl ketones[2])

Preparative Methods: prepared from ***Diethyl Malonate***, ***Magnesium***, ethanol, and a catalytic amount of CCl_4, as described in several procedures.[1,2a]

Handling, Storage, and Precautions: typically prepared and used immediately as a solution in solvents such as ether or benzene. The reagent is moisture sensitive; best yields are obtained when the reagent is used under anhydrous conditions.

Use in Synthesis.

Diethyl ethoxymagnesiomalonate (**1**) can be acylated with many activated carboxylic acid derivatives and alkyl chloroformates. It is soluble in aprotic solvents such as ether and benzene, and undergoes exclusive *C*-acylation.[3] A number of acylmalonates have been prepared from (**1**) including tris(ethoxycarbonyl)methane,[1a] diethyl benzoylmalonate,[1b] diethyl phenylacetylmalonate,[1c] and diethyl cyclopropylmalonate.[1d]

Several hydroxycoumarin analogs have been prepared by the addition of (**1**) to salicylic acid derivatives (eq 1).[4] A similar protocol has been utilized in the preparation of hydroxybutenolides.[5]

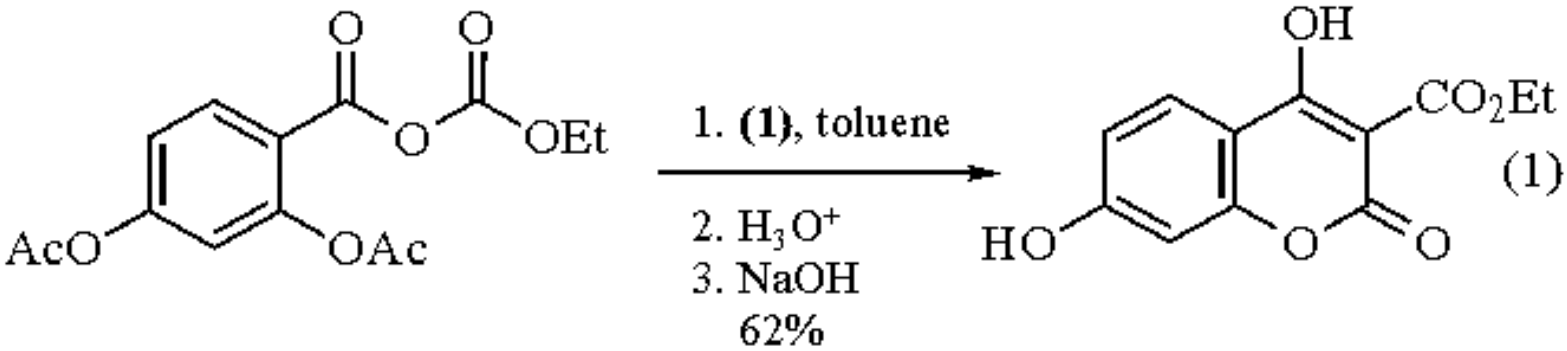

Methyl ketones can be conveniently obtained from the acylmalonate intermediate following a more vigorous hydrolysis (eq 2).[2b] Substituted acetophenones have also been prepared in this manner.[2]

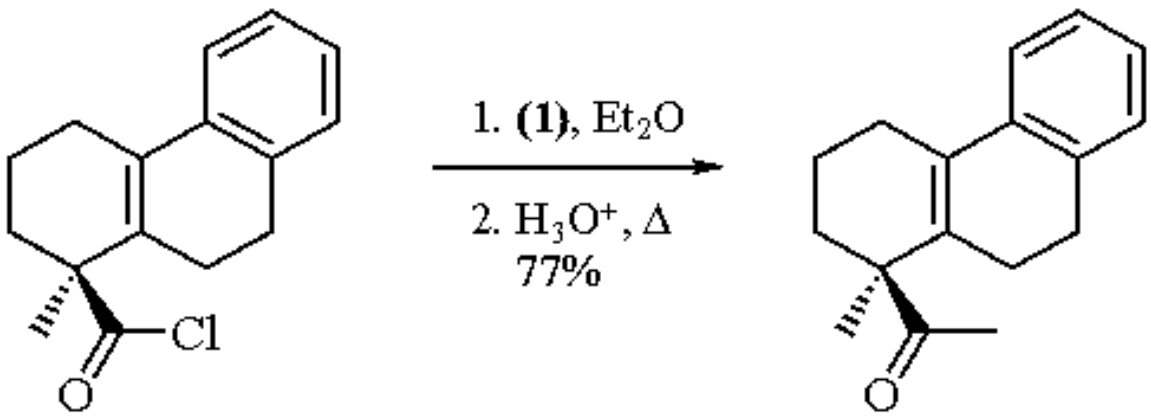

(2)

Methanetricarboxylic esters are generally prepared by the reaction of (**1**) with an alkyl chloroformate.[6] Thus ***Triethyl Methanetricarboxylate*** is obtained in high yield from (**1**) and ***Ethyl Chloroformate*** (eq 3).[1a]

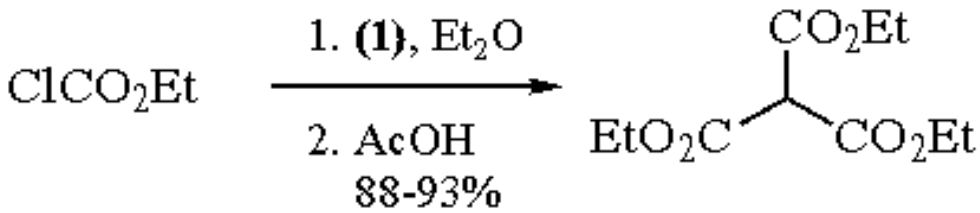

(3)

The magnesium enolate of diethyl malonate can also be generated and acylated with acid chlorides under milder conditions in a single step. Complexation of the malonate with $MgCl_2$ increases the acidity to a degree such that tertiary amines can be employed for deprotonation.[7] A number of acylmalonates can be conveniently prepared (eq 4), with optimal yields obtained using ***Triethylamine*** (2 equiv).

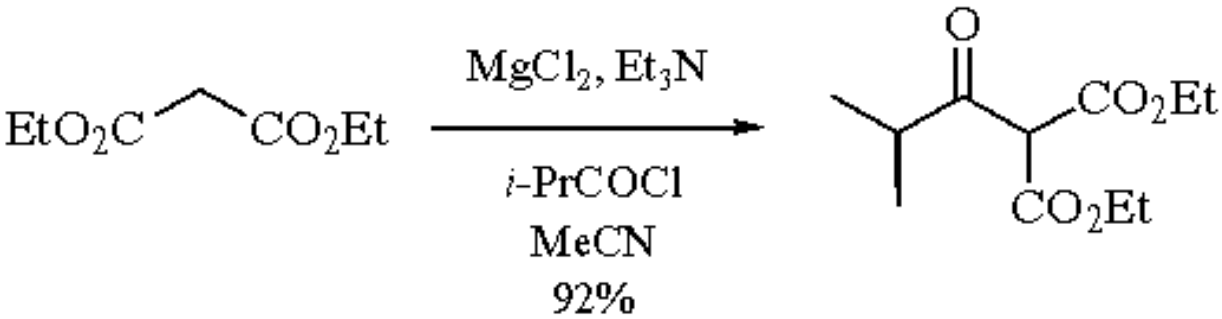

(4)

Other workers have extended this procedure to an efficient preparation of methyl ketones following bis-dealkoxycarbonylation of the intermediate acylmalonate.[8] The Michael addition of diethyl malonate to α,β-unsaturated ketones and aldehydes under these conditions has also been examined (eq 5).[9] ***Magnesium Oxide*** is also an effective base for the acylation of diethyl malonate, generating acyl malonates in moderate yields.[10]

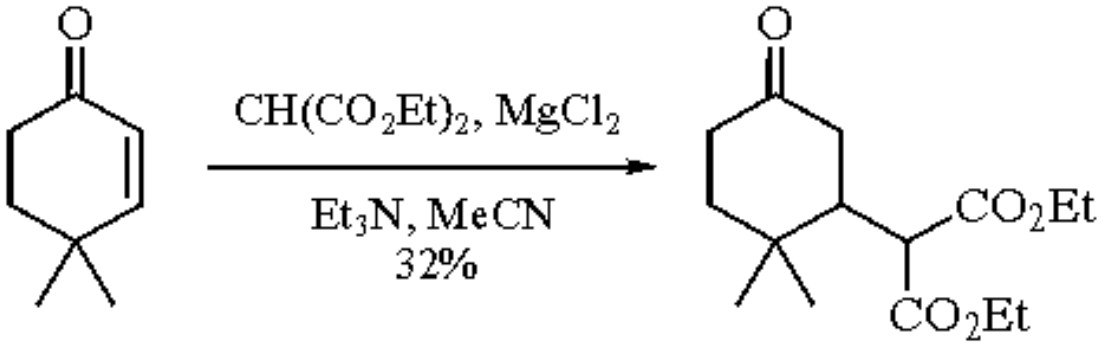

(5)

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Diethyl Malonate***; ***Ethyl 3,3-Diethoxyacrylate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Magnesium Methoxide***; ***Malonic Acid***; ***Triethyl Methanetricarboxylate***.

---

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Diethyl Ethoxymethylenemalonate

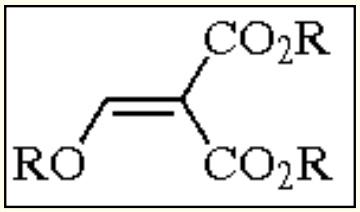

(R = Et)

[87-13-8] · $C_{10}H_{16}O_5$ · Diethyl Ethoxymethylenemalonate · (MW 216.23) (R = Me)

[22398-14-7] · $C_7H_{10}O_5$ · Dimethyl Methoxymethylenemalonate · (MW 174.15)

(push-pull alkene;[1] 1,4-addition-elimination (Ad_N-E);[2] quinoline derivatives;[3] 1,4-addition;[4] [3 + 2] cycloadditions;[5] Diels-Alder reaction;[6] protecting group for amino sugars[7] and amino acids;[8] oxo-Meldrum's acid[9])

Physical Data: R = Et: bp 108-110 °C/0.25 mmHg; *d* 1.070 g cm^{-3}. R = Me:[2h] mp 44-45 °C; bp 106 °C/0.7 mmHg.

Solubility: sol ethanol and diethyl ether.

Form Supplied in: clear liquid; widely available.

Analysis of Reagent Purity: *n*20D = 1.4612-1.4623.

Preparative Method: prepared by heating ***Triethyl Orthoformate***, ***Diethyl Malonate***, ***Acetic Anhydride***, and catalytic amounts of ***Zinc Chloride***.[10]

Purification: fractional vacuum distillation.

The ethoxy group of diethyl ethoxymethylenemalonate or dimethyl methoxymethylenemalonate can be substituted by various nucleophiles in an Ad_N-E mechanism. Malonates (eq 1),[2c,e,g,h] Grignard reagents,[2i] enolates,[2b] quaternary salts of heterocyclic bases containing an active methylene group,[2a,f] amines,[2d,k] hydrazines,[11] etc., can be used as nucleophiles in this way. In contrast, only 1,4-addition is observed with organometallic compounds at low temperature (eq 2)[4a-c] or in the oxymercuration-demercuration reaction (eq 3).[4d,12]

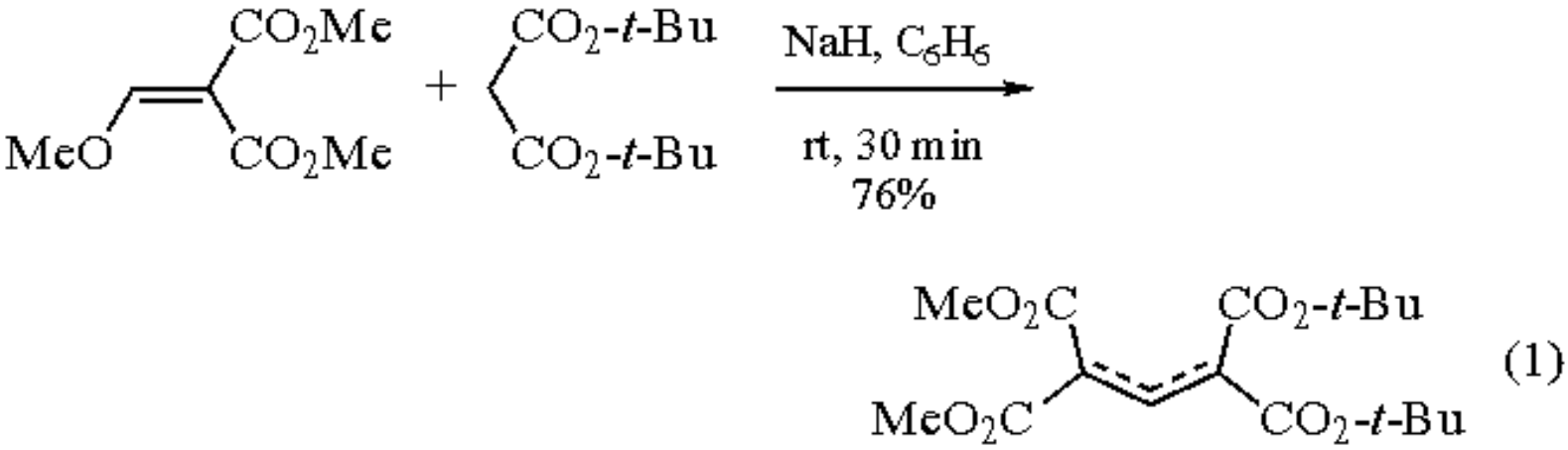

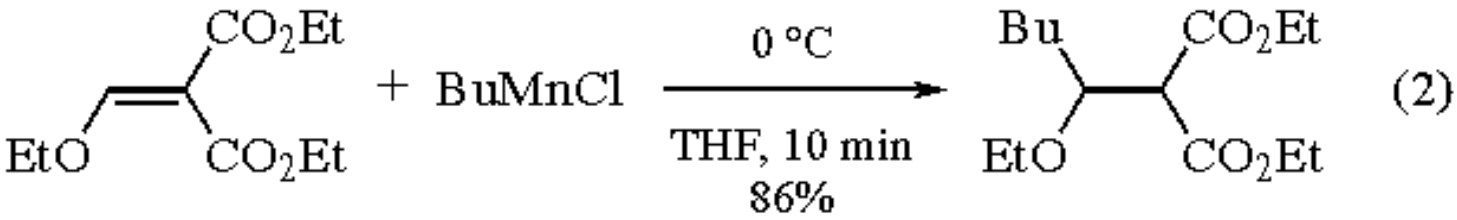

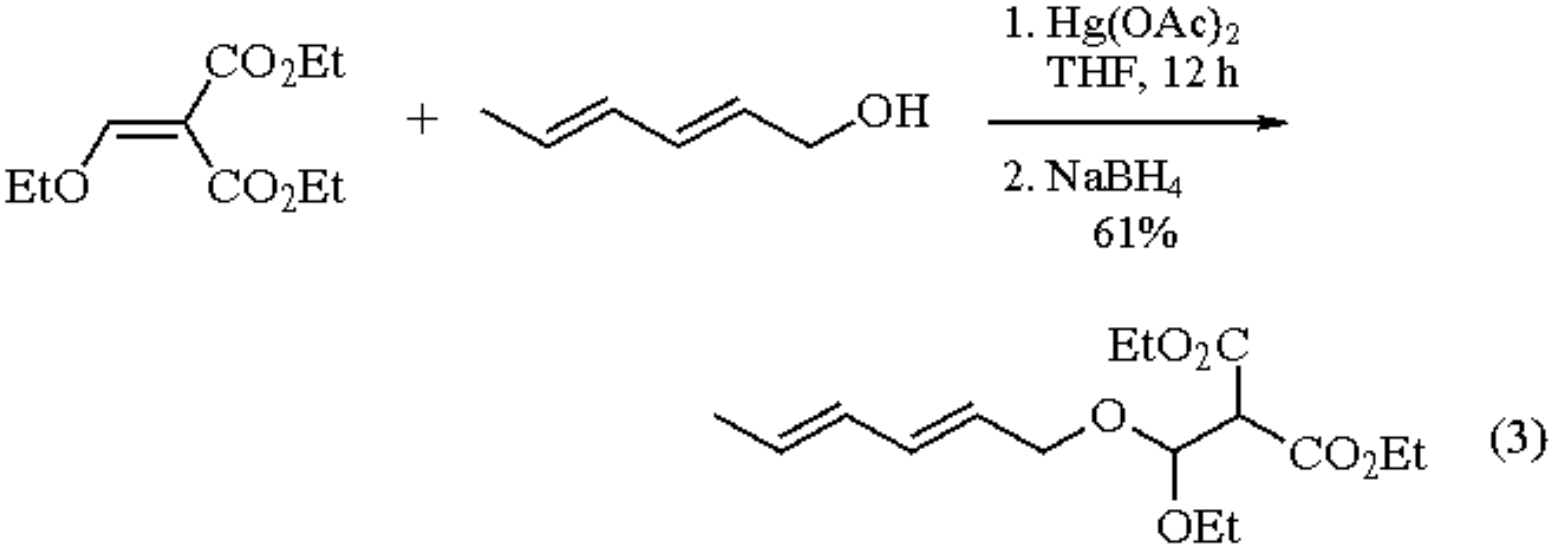

Quinoline derivatives are prepared in a sequential substitution-cyclization process (eq 4).[3] In similar reactions, various heterocycles such as 1,8-naphthyridines, 2*H*-pyrido[1,2-*a*]pyrimidin-4-ones,[3d,e] pyrazolinones,[11,13] pyrones,[2b,c] xanthyrones,[2e,h] guanidine derivatives,[14] pyrroles,[15] 1,2,4-triazoles,[16] 3-oxo-1,2,6-thiadiazine 1,1-dioxides,[17] 8-oxoimidazo[1,2-*a*]pyridiumides,[2a] 3*H*-pyrrolo[1,2-*a*]indol-3-one derivatives,[18] and 1*H*-1,4-benzodiazepines[19] can be obtained.

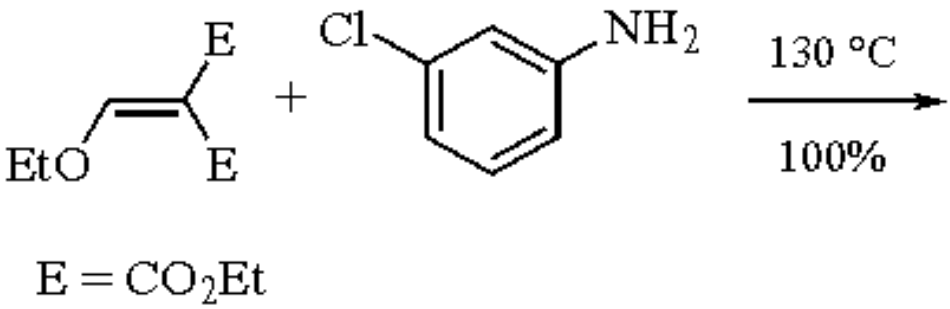

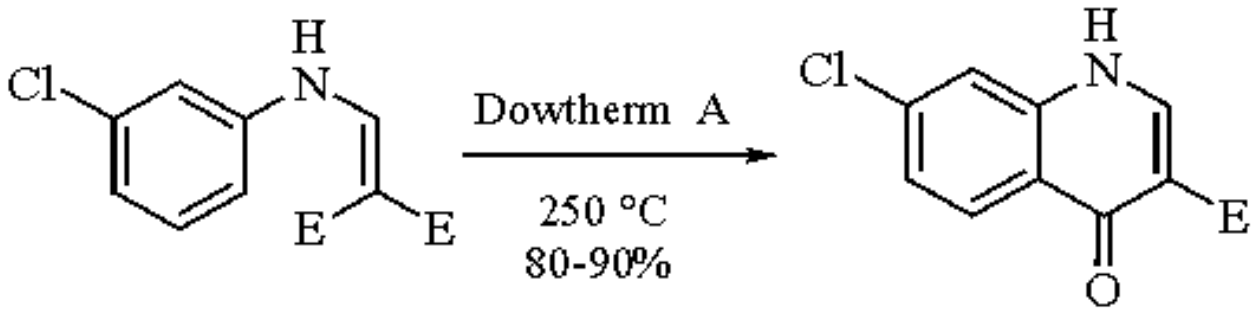

(4)

Cyclopentenones are formed in [3 + 2] cycloadditions of dimethyl methoxymethylenemalonate and cyclopropenone acetals (eq 5).[5b,e] Similarly, reaction with benzonitrilium isopropylide, which is generated in situ by a photoinduced cleavage of the corresponding azirine, leads to pyrrolines,[5f] and reaction with diazo compounds to pyrazolines.[5a,c,d,20]

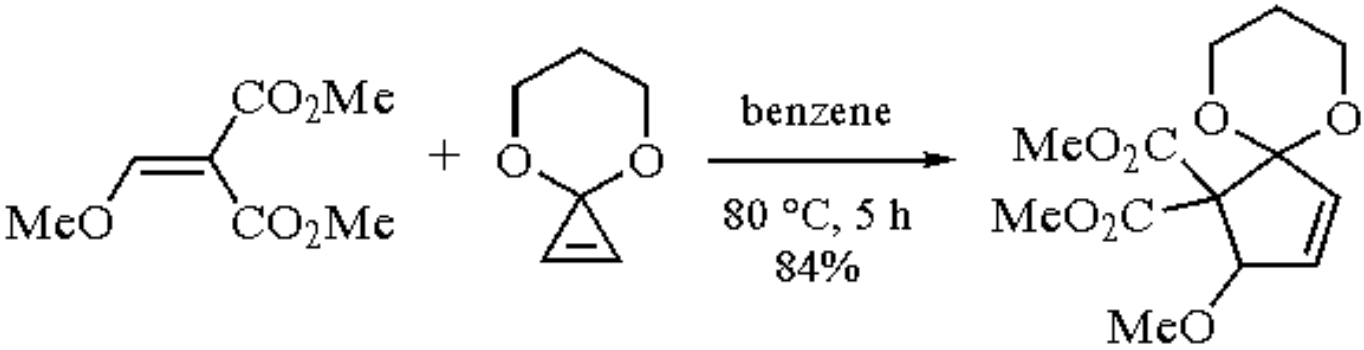

(5)

Diethyl ethoxymethylenemalonate is also used for the protection of the amino group of amino sugars and amino acids. The *N*-protecting group of amino acids can be removed using ***Bromine*** in chloroform.[8] Elimination of the 2,2-diacylvinyl group of amino sugars has been described using ***Chlorine***, ***Ammonia***, or Amberlite IRA-400 (HO^-) resin.[7]

β-Ribofuranosylmalonates can be synthesized stereoselectively through high-pressure Diels-Alder reaction of furan with dimethyl acetoxymethylenemalonate.[6] The unstable diethyl methylenemalonate is obtained from diethyl ethoxymethylenemalonate by catalytic reduction and elimination of ethanol.[21] Ozonolysis of methoxymethylene-Meldrum's acids[22] yields oxo-Meldrum's acids after workup with ***Phosphorus(III) Chloride***.[9]

Related Reagents.

Diethyl Malonate; ***3-Ethoxyacrolein***; ***3-Ethoxyacrylonitrile***; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethyleneacetoacetate***; ***Ethyl Ethoxymethylenecyanoacetate***; ***Ethyl Hydroxymethyleneacetate, Sodium Salt***.

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Diethyl Ethylidenemalonate

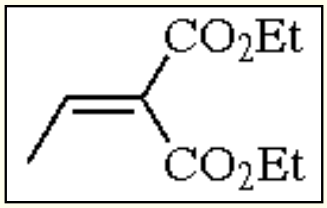

[1462-12-0] · $C_9H_{14}O_4$ · Diethyl Ethylidenemalonate · (MW 186.21)

(2,4-dienoates;[1] Michael acceptor; 1,4-addition;[2] [3 + 2] cycloaddition;[3] cyclopropanes;[4] cyclopentenes[5])

Physical Data: bp 115-118 °C/17 mmHg; *d* 1.019 g cm^{-3}.

Solubility: sol ethanol and diethyl ether.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: *n*20D = 1.4420.

Preparative Method: obtained by heating paraldehyde, ***Acetic Anhydride***, and ***Diethyl Malonate***.[6]

Purification: fractional vacuum distillation.

Handling, Storage, and Precautions: store at 5 °C. Use in a fume hood.

The reaction of diethyl ethylidenemalonate with benzaldehyde derivatives in the presence of methanolic ***Benzyltrimethylammonium Hydroxide*** (Triton B)[1b] or ***Tetramethylammonium Hydroxide***[1e] yields methyl (2*E*,4*E*)-dienoates (eq 1).[1] The reagent is used for the synthesis of cannabinoids.[1a,c]

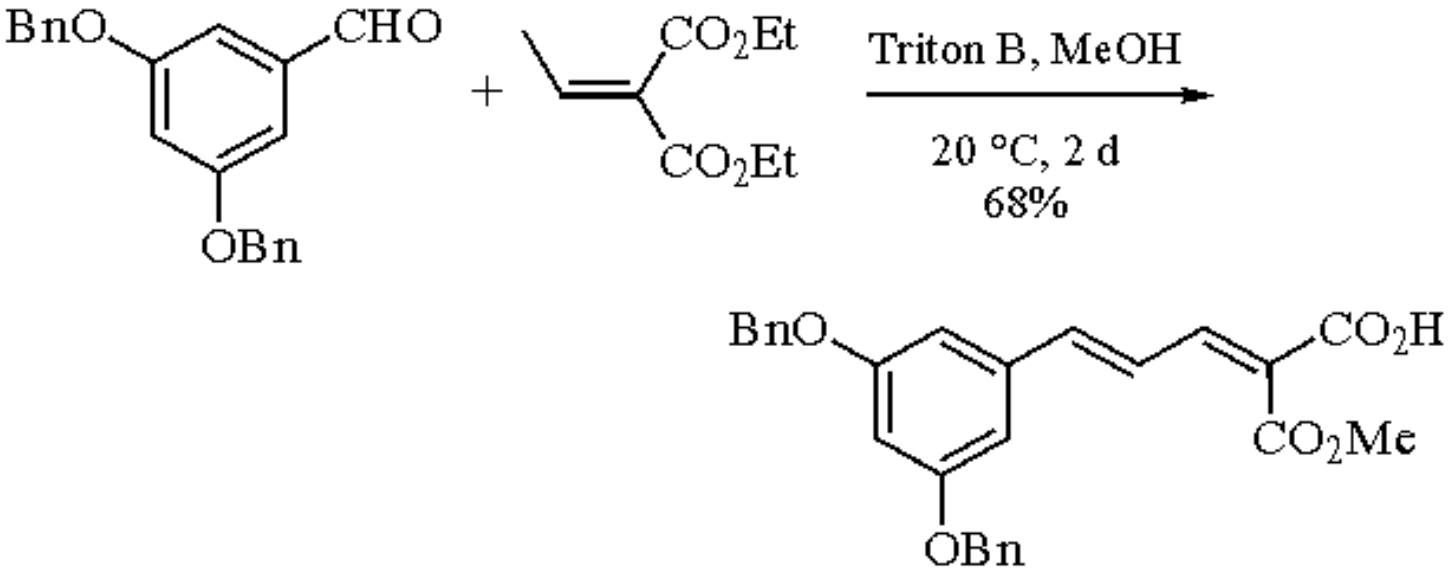

(1)

Diethyl ethylidenemalonate reacts as a Michael acceptor with nucleophiles such as enolates,[2d,p] germanium-masked dienolates,[2c] acyl anions (thiazolium salt catalyzed; eq 2),[2k] organometallic compounds (Li,[2m] Mg,[2q] Mn,[2e] Cu,[2a] Zn[2n,o]), activated nitriles (ruthenium catalyzed),[2f] and lithium trialkylalkynylborates.[2i,l]

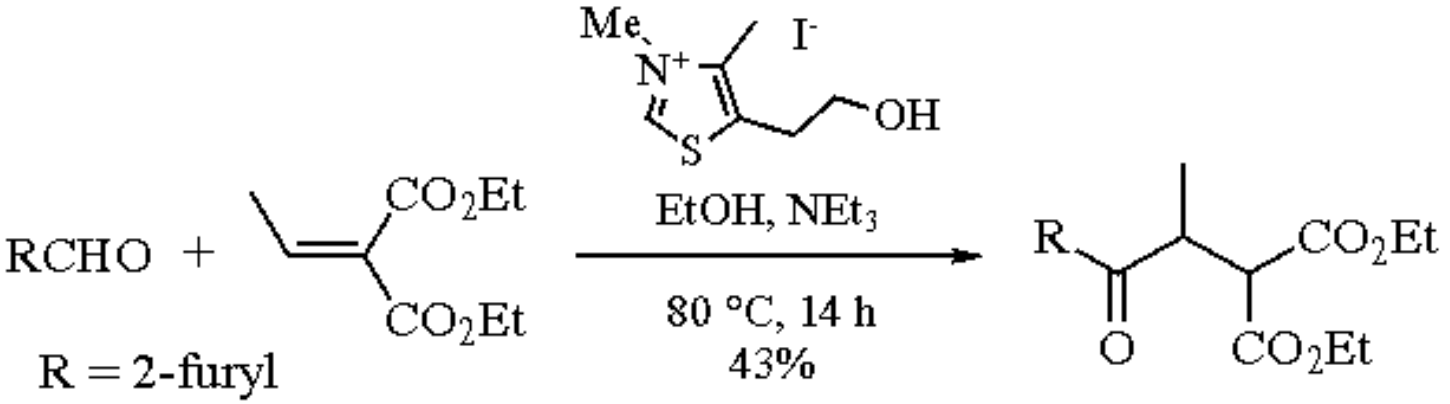

(2)

The 1,4-addition of crotylorganometallics of B, Ti, Zr, and Sn produces the *anti* adduct predominantly (eq 3).[2g,h]

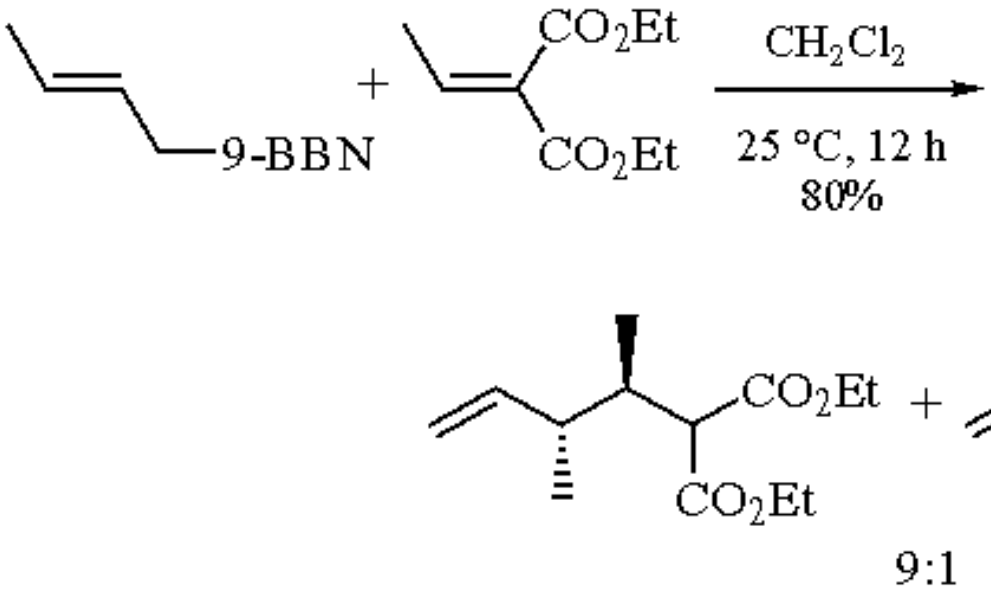

(3)

Radicals such as the cyclohexyl radical, formed in situ by photolysis of the dicarbonyl(η^5-cyclopentadienyl)iron dimer in the presence of cyclohexyl iodide, can be trapped by diethyl ethylidenemalonate to give the 1,4-addition products (eq 4).[2b]

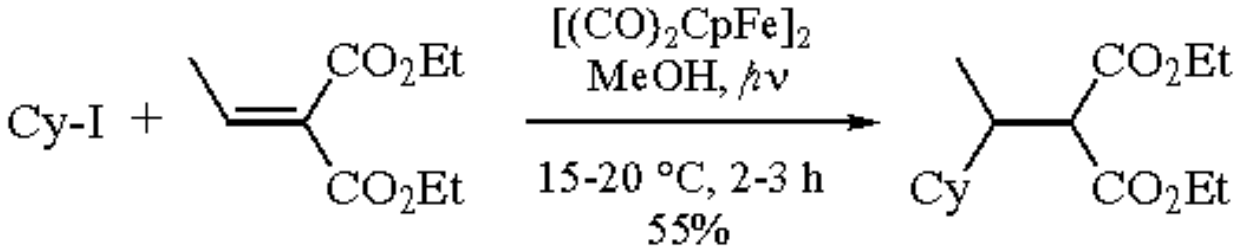

(4)

Cyclopentenones are formed in a [3 + 2] cycloaddition with cyclopropenone acetals (see ***Diethyl Ethoxymethylenemalonate***).[3] The double bond of diethyl ethylidenemalonate can be cyclopropanated in high yield with ***Bromoform*** and ***Sodium Hydroxide*** in the presence of benzyltriethylammonium chloride (**2**) (eq 5).[4] Cyclopentene derivatives can be obtained in moderate yields by treatment of diethyl ethylidenemalonate with propargyl bromides and zinc in THF at low temperature (eq 6).[5]

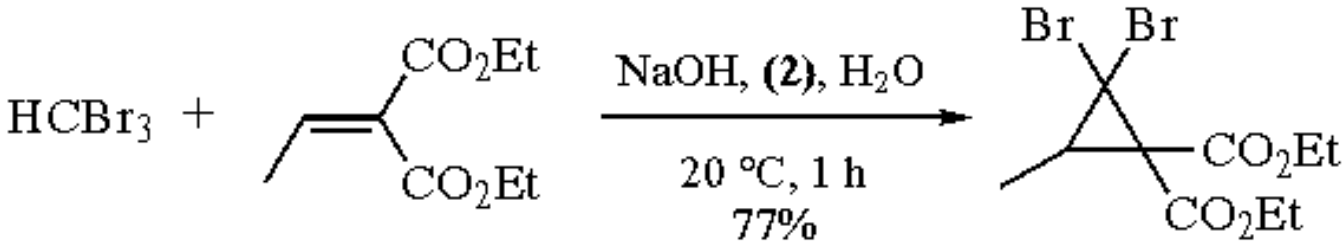

(5)

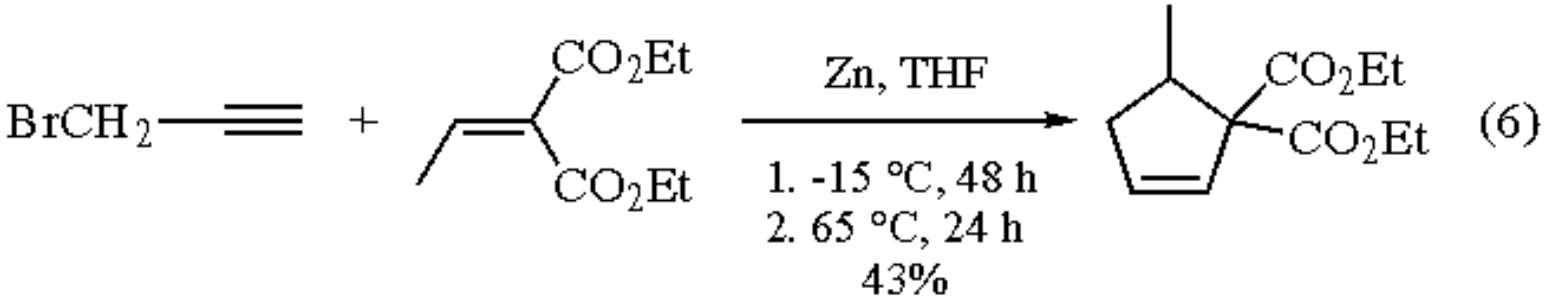

Dialkyl benzylidenemalonates obtained by Knoevenagel reaction[7] of dialkyl malonates and benzaldehyde are useful substrates for the synthesis of dialkyl mesoxalates by ozonolysis.[8]

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***Diethyl Malonate***; ***Diethyl Methylenemalonate***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***; ***Methyl 6-Oxo-1-cyclohexenecarboxylate***.

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Diethyl(1,1,2,3,3,3-hexafluoropropyl)amine[1]

$Et_2NCF_2CHFCF_3$

[309-88-6] · $C_7H_{11}F_6N$ · Diethyl(1,1,2,3,3,3-hexafluoropropyl)amine · (MW 223.16)

(conversion of the hydroxy group of alcohols to the fluoro group; preparation of 2,3,3,3-tetrafluoropropionate esters and other fluorine-containing carbonyl compounds)

Alternate Names: PPDA; Ishikawa reagent.

Physical Data: bp 56-57 °C/58 mmHg, 51 °C/40 mmHg.

Solubility: sol diethyl ether.

Analysis of Reagent Purity: ^{19}F NMR (see Takaoka et al.).[2]

Preparative Methods: diethyl(1,1,2,3,3,3-hexafluoropropyl)amine, commonly called the perfluoropropene-diethylamine adduct (PPDA) or the Ishikawa reagent, is readily prepared in yields of 72-89% by reaction of hexafluoropropene (F-propene) with diethylamine in diethyl ether solution (eq 1).[2,3] The reaction is conducted in a glass pressure vessel cooled to -70 °C and liquefied F-propene is added to the amine-ether solution. The mixture is brought to rt overnight and worked up. The resulting product is a 3:1 molar mixture of the fluoroalkylamine and the (*E*)-fluoroenamine (established by ^{19}F NMR), bp 56-57 °C/58 mmHg. When prepared by bubbling F-propene into Et_2NH-Et_2O at 0-5 °C, the reagent with molar ratio 1:1, bp 51 °C/40 mmHg, is obtained.[3] The reagent may be used directly, without distillation.

$$Et_2NH + CF_2{=}CFCF_3 \longrightarrow Et_2NCF{=}CFCF_3 + Et_2NCF_2CFHCF_3 \quad (1)$$

Handling, Storage, and Precautions: after distillation, the oil may be stored in a tightly stoppered vessel at or below rt. Only a slight discoloration is observed after six months. The reagent should be handled in a fume hood.

Conversion of Alcohols to Alkyl Fluorides.

The typical reaction of this reagent is the one-step conversion of alcohols to the corresponding fluoro compounds with concomitant formation of tetrafluorodiethylpropionamide (eq 2).[2] Similarly, acyl fluorides are readily obtained from carboxylic acids (eq 3).[2] The reaction is markedly enhanced when ***Sodium Fluoride*** is added as a scavenger for the liberated

HF.[3] The pure (*E*)-fluoroenamine, prepared by another route, shows no fluorinating ability.

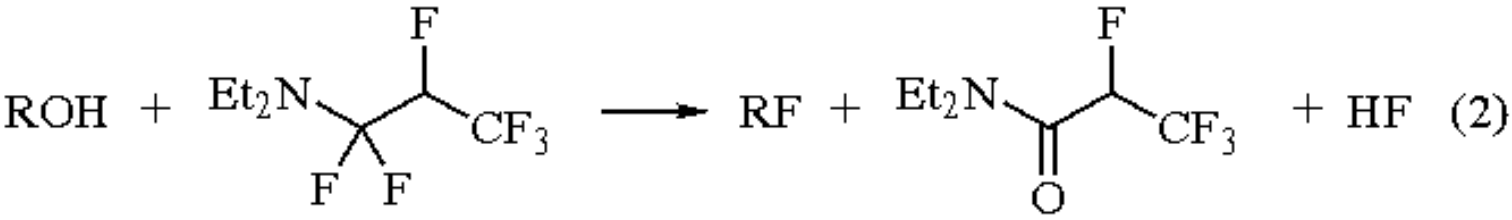

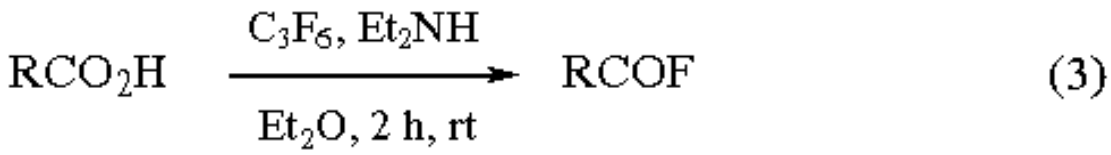

Primary alcohols react with the reagent at rt with diethyl ether as solvent during 6-20 h to give the corresponding alkyl fluorides in yields of 50-89%.[2,4,5] With benzyl alcohol, a 25% yield of dibenzyl ether is also obtained.[2] Secondary and tertiary alcohols give generally good yields of fluoride (55-80%), but significant amounts of alkenes and dialkyl ethers (formed via carbocation intermediates) are also isolated. Thus 2-octanol affords 62% 2-fluorooctane and 25% of a mixture of *trans*-2-octene, *cis*-2-octene, and 1-octene (4:3:1). In MeCN as solvent the yield of alkene exceeds 50%. While cholesterol in CH_2Cl_2 at 0-5 °C gives 83% of fluoride, borneol forms a rearranged fluoride and camphene. Notably, *t*-butyl alcohol in CCl_4 yields 78% of *t*-butyl fluoride and 9% of isobutene. 1-Adamantanol in THF gives 81% of 1-fluoroadamantane (eq 4).[2] Several mechanisms, involving S_N1 and S_N2 processes, have been proposed to account for the observed products (eq 5).[2]

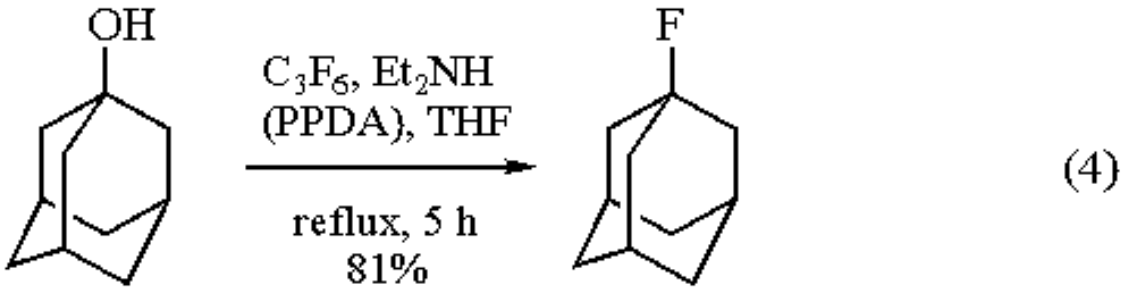

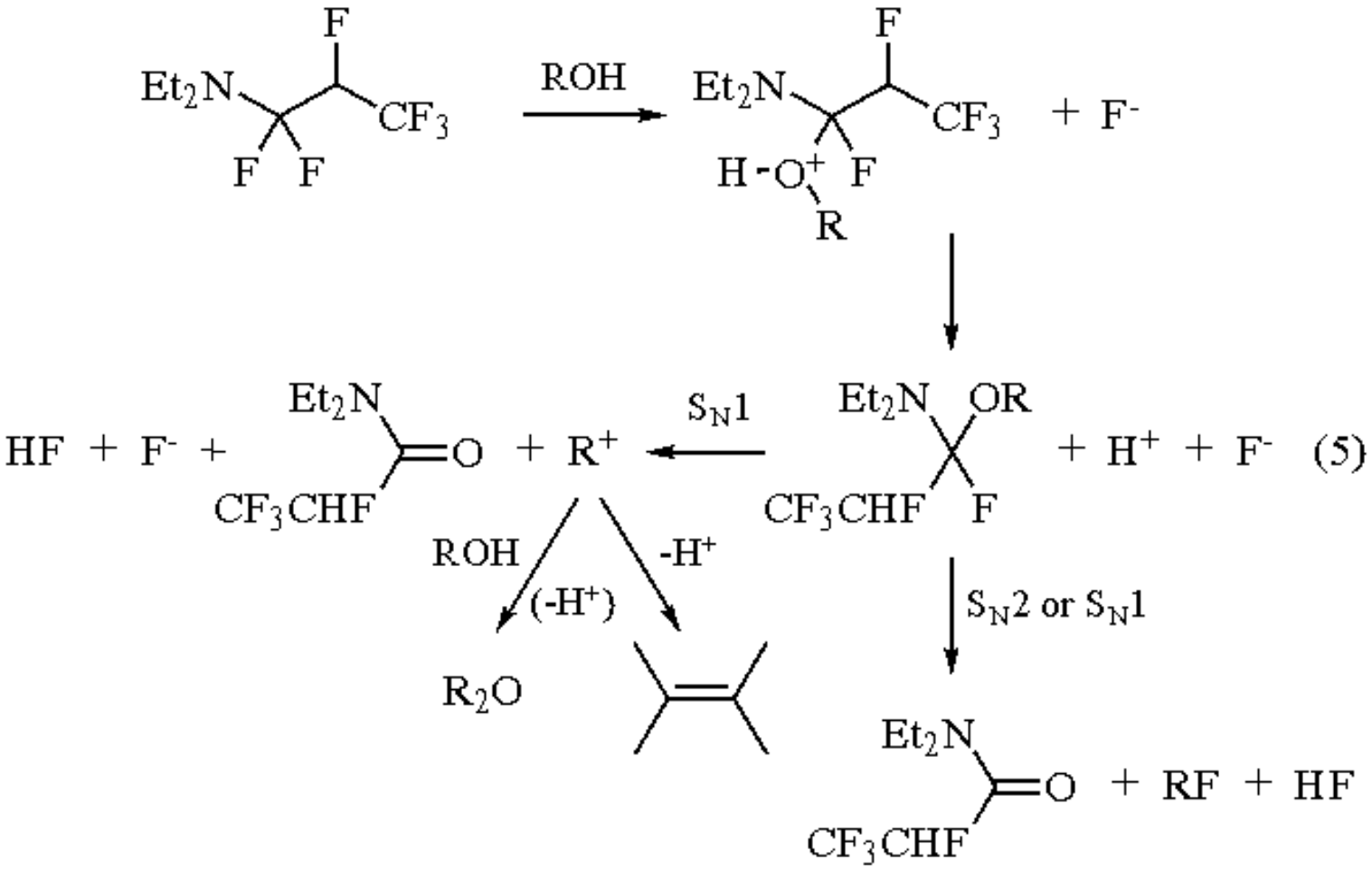

Aliphatic bromo- and chloro-substituted alcohols react with PPDA to give 40-70% yields of the corresponding fluorides.[4] However, cyclic halogenated alcohols provide very little fluoride but, primarily, tetrafluoropropionate esters. Thus 3-bromoborneol affords the fluoro ester in 65% (eq 6). A suggested mechanism for this side reaction involves the formation of an aminoacetal which undergoes fragmentation with HF (eq 7).[4]

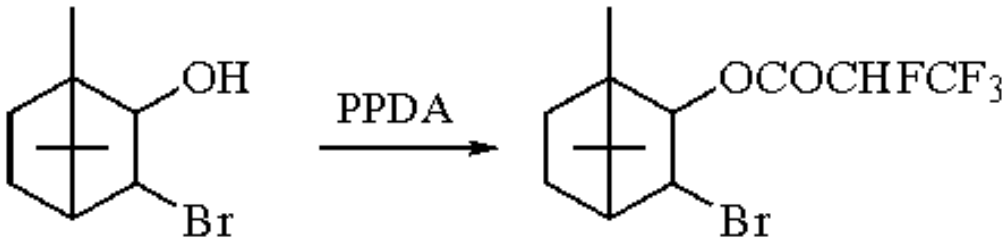

(6)

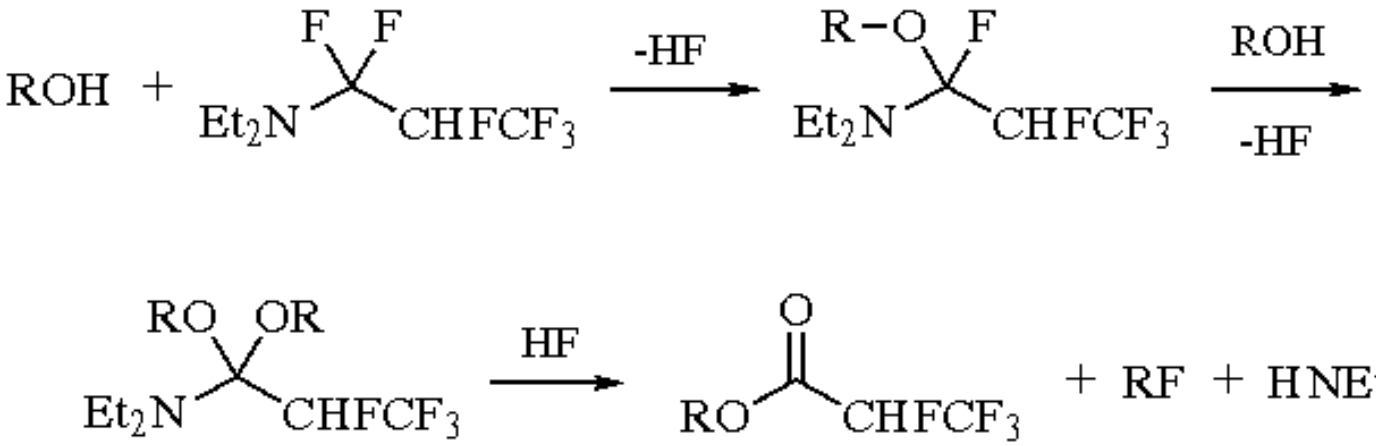

α,β-Unsaturated alcohols do not give the corresponding fluorides with PPDA because undesirable reactions, such as isomerization, cyclization, and dehydration, may occur in the presence of the HF produced by fluorination. In order to obviate these side reactions, ***Diisopropylethylamine*** is added to neutralize the HF. Under these conditions, geraniol is converted into geranyl 2,3,3,3-tetrafluoropropionate in 41% yield (eq 8). No fluoride is isolated.[6]

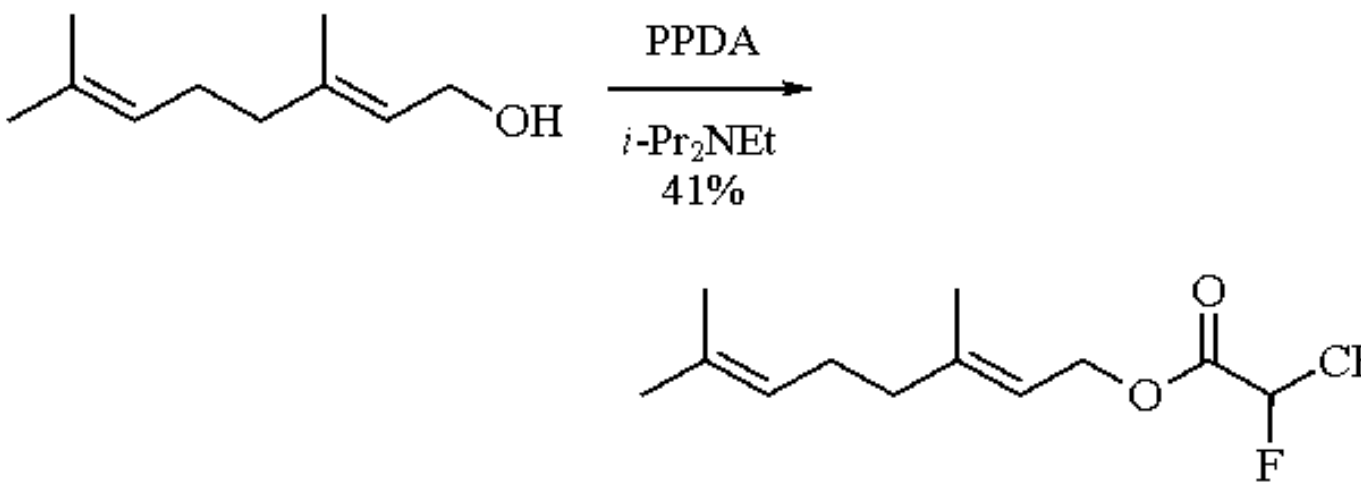

Long-chain alcohols provide fluorides and esters on treatment with PPDA.[7] For example, lauryl alcohol forms $Me(CH_2)_{10}CH_2F$ (45%) and $Me(CH_2)_{10}CH_2O_2CCHFCF_3$ (22%). 1,2-Diols yield dioxolanes and 1,3-diols give dioxanes on reaction with PPDA.[8] The use of THF, instead of Et_2O or CH_2Cl_2, is essential to mitigate side reactions. Eq 9 illustrates the reaction with 1,3-propanediol. Monoesters of ethylene glycol and PPDA provide a mixture of fluoro ester and diester (eq 10).[9] α-Hydroxy carboxylic acids, such as mandelic acid,[10] and esters[11,12] are readily fluorinated in 50-70% yields to the α-fluoro carboxylates. The reaction proceeds with inversion of configuration, as evidenced by the conversion of (*R*)-(-)-mandelic acid ethyl ester to (*S*)-(+)-2-fluoro-2-phenyl acetate with 74% ee.

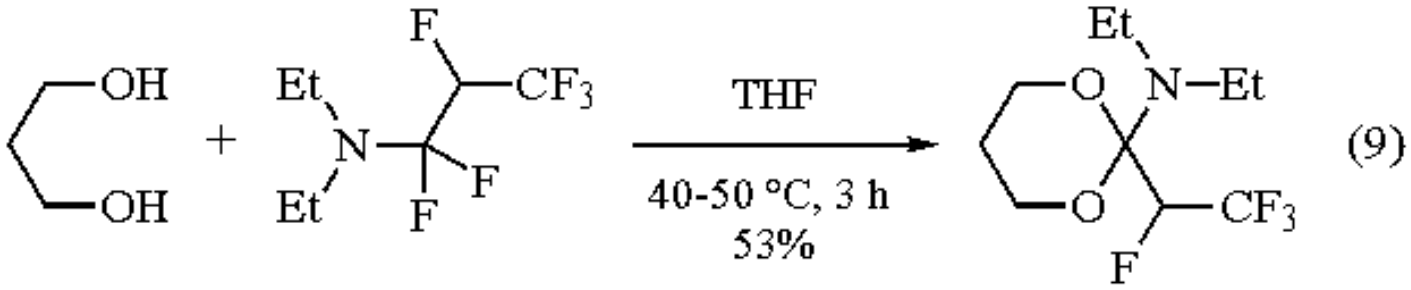

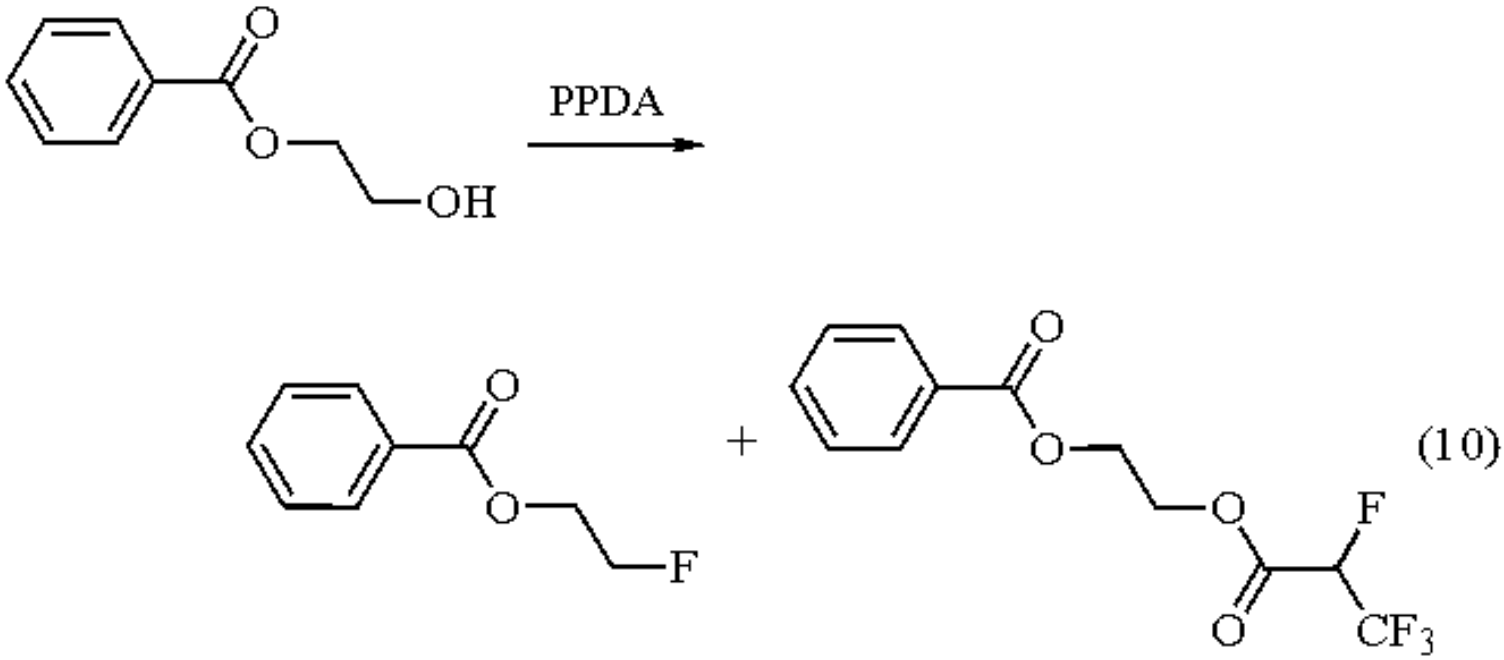

Miscellaneous Applications.

The tetrafluoropropionamide obtained by hydrolysis of PPDA reacts with ArMgX to yield $ArCOCHFCF_3$ and, subsequently, $ArCOCHFCO_2R$.[13] PPDA serves as a useful dehydrating agent for the synthesis of alkynic ketones from β-diketones in the presence of freeze-dried ***Potassium Fluoride*** in MeCN.[14] Monofluorocarboxylic acids are prepared using PPDA, directly from hydroxy esters, or indirectly from monofluorinated alkylbenzenes, followed by oxidation of the phenyl ring to -CO_2H.[15] PPDA and ureas form an intermediate which undergoes cyclization in ROH to yield 6-alkoxy-1-alkylfluorocytosines.[1] *o*-Bifunctional benzenes give heterocycles on reaction with PPDA.[1]

Related Reagents.

N,N-Diethyl-2-chloro-1,1,2-trifluoroethylamine.

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1. While there has been no comprehensive review of this reagent, a reasonably good summary is: Takaoka, A.; Iwakiri, H.; Fujiwara, N.; Ishikawa, N. *Nippon Kagaku Kaishi* **1985**, 2161 (*CA* **1987**, *107*, 58 961h). An excellent introduction can be found in Ref. 2.
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14. Kitazume, T.; Ishikawa, N. *CL* **1980**, 1327.
15. O'Hagan, D. *JFC* **1989**, *43*, 371.

Robert Filler

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Diethyl Isocyanomethylphosphonate

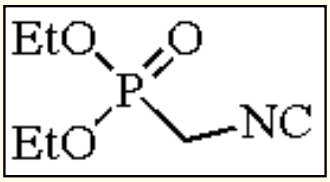

[41003-94-5] · $C_6H_{12}NO_3P$ · Diethyl Isocyanomethylphosphonate · (MW 177.14)

(reagent for the elongation of aldehydes and ketones with a one-carbon unit;[1] connective reagent;[2,3] *N,P*-acetals;[3] reagent for the conversion of nitroalkenes into 2-pyrrolephosphonates[4])

Physical Data: bp 90 °C/0.2 mmHg.

Form Supplied in: commercially available as a nearly odorless, colorless liquid.

Analysis of Reagent Purity: IR (neat) 2140 (N=C), 1300-1250 (P=O), 1040-1010 cm^{-1} (P-O); ^1H NMR (CCl_4) δ 3.9 (d, J_{H-P} = 16 Hz, CH_2).

Preparative Method: by dehydration of *N*-(diethoxyphosphorylmethyl)formamide.[5]

Handling, Storage, and Precautions: can be stored for long periods of time at 0 °C or below.

Introduction.

Diethyl isocyanomethylphosphonate (**1**), a reagent developed in 1973 by Schöllkopf et al.,[5] belongs to the category of (hetero)-substituted derivatives of methyl isocyanide, which includes ***p-Tolylsulfonylmethyl Isocyanide*** (TosMIC), ***p-Tolylthiomethyl Isocyanide***, ***Methyl N-(p-Tolylsulfonylmethyl)thiobenzimidate*** (a TosMIC derivative), and ***Ethyl Isocyanoacetate***. Aldehydes and ketones are the main substrates in the reactions of (**1**), which result in the formation of three different types of products, wherein the phosphonate group may or may not be retained.

Horner-Wadsworth-Emmons Reactions.

Horner-Wadsworth-Emmons (HWE) type reactions of (**1**) with aldehydes and ketones provide vinyl isocyanides,[1] which have been used as intermediates in the synthesis of erbstatin (eq 1)[1a,b] and of homologous aldehydes (eq 2).[1c,d]

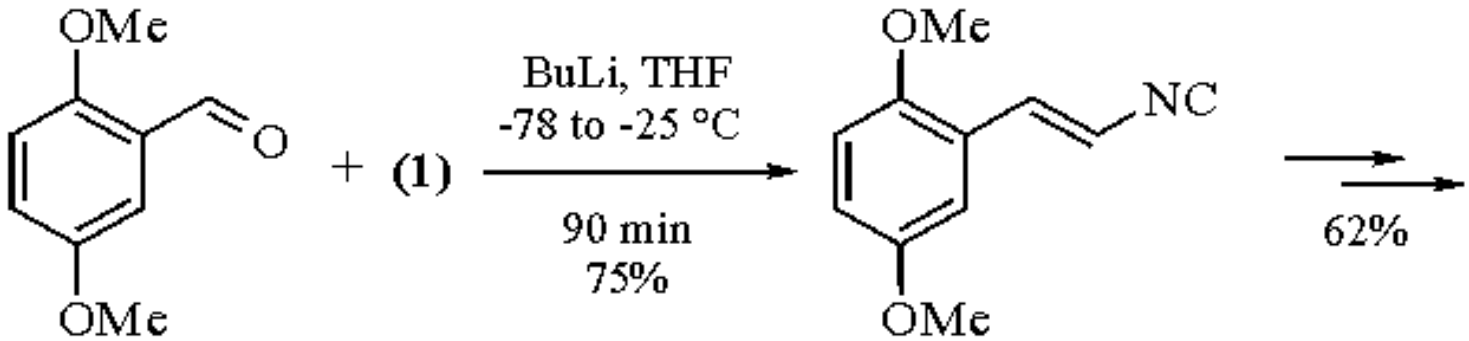

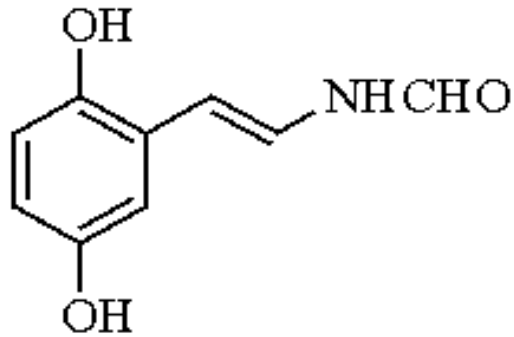

Erbstatin (1)

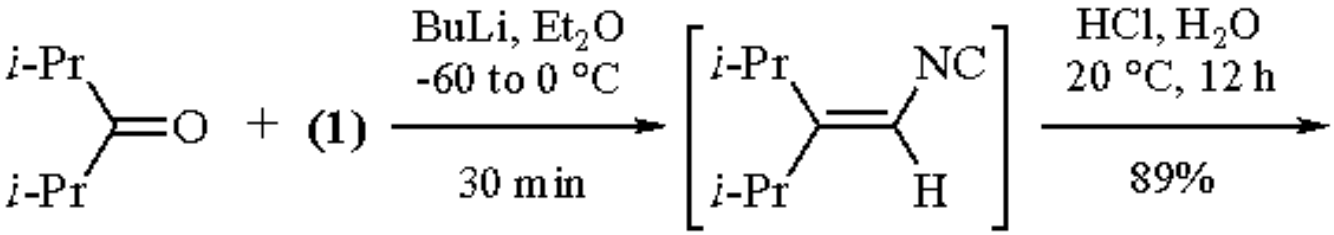

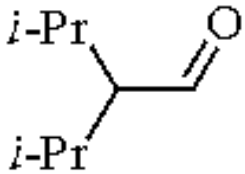

(2)

Knoevenagel Condensation Products.

A method has been developed, which avoids the HWE reaction of (**1**) (eqs 1 and 2), to prepare (formal) Knoevenagel products (**2**) by elimination of water (eq 3).[3a] Compound (**2**) has been converted into progesterone by reduction of the C17-C20 double bond, followed by C20 methylation and acid hydrolysis of $(EtO)_2P(O)CR(Me)NC$(R = 3-methoxyandrosta-3,5-dien-17-yl) (*N*,*P*-acetal behavior; eq 3).[3a] In these processes, (**1**) is used as a connective reagent to form a CO bridge between Me and a 17-steroidal group, as in eq 3. Partial hydrolysis of disubstituted derivatives of (**1**) $[(EtO)_2P(O)CR^1R^2NC]$ provides α-aminomethylphosphonic acids (esters).

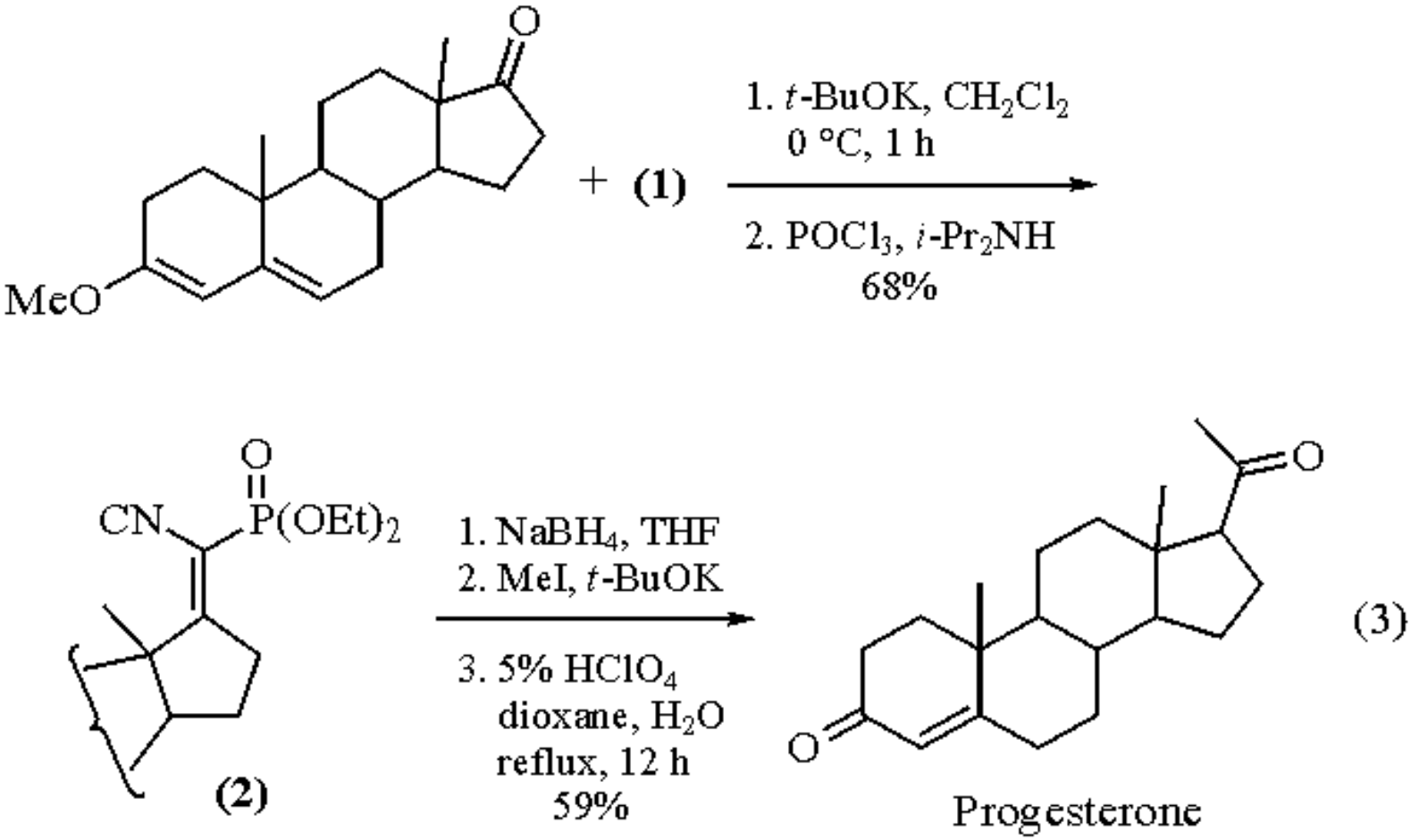

The HWE reaction of Knoevenagel products (**2**) with aldehydes, followed by acid hydrolysis to Δ^{16}-steroids, provides another example of the use of (**1**) as a connective reagent (eq 4).[2]

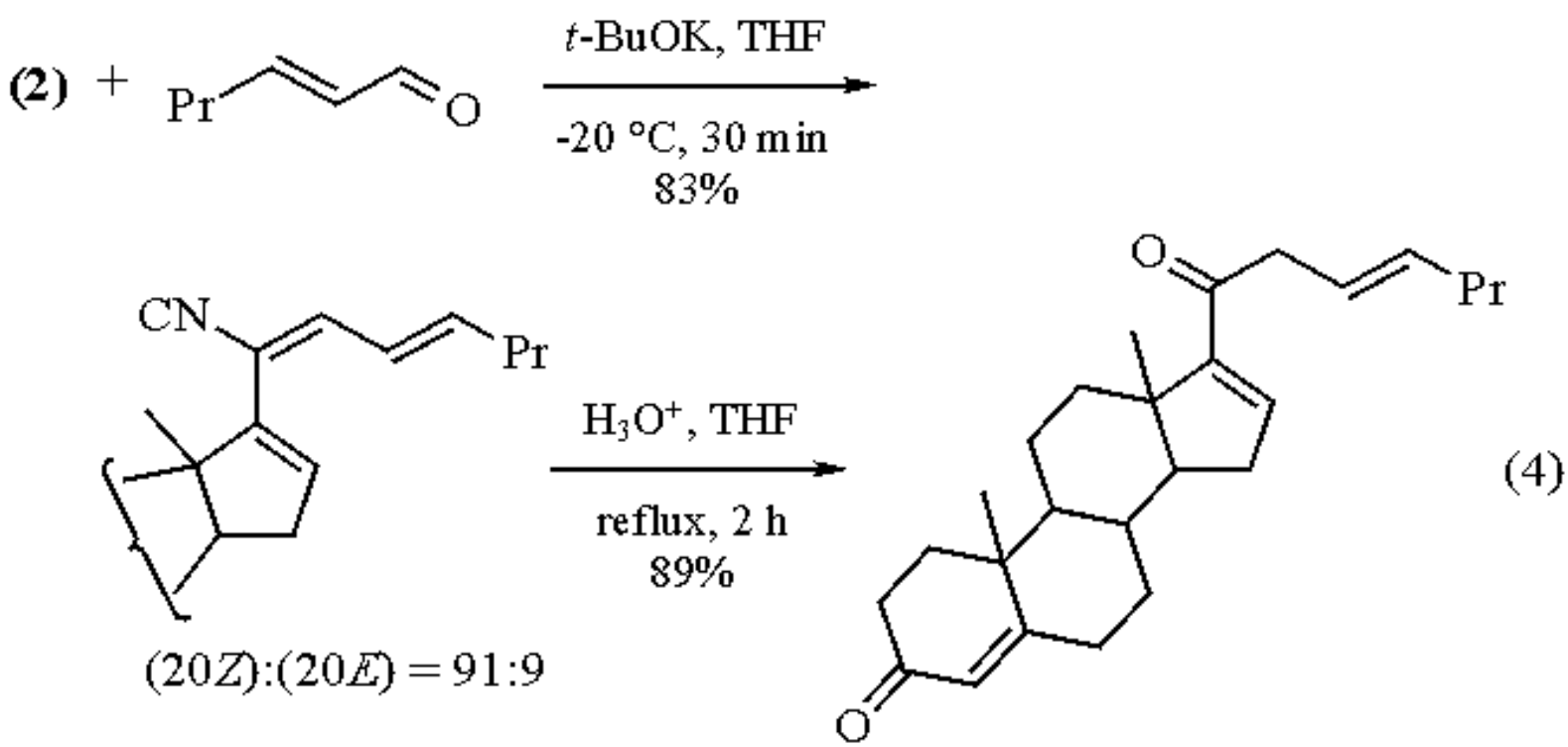

Oxazolines and Derivatives.

The first part of eq 3 (i.e. the formation of **2**) proceeds via oxazolines (**3**) (eq 5), which have been hydrolyzed to α-amino-β-hydroxyalkylphosphonic acids,[6a] and which have been subjected to base-induced electrocyclic ring opening to the formamide precursors (**4**) of isocyanides of type (**2**).[6a]

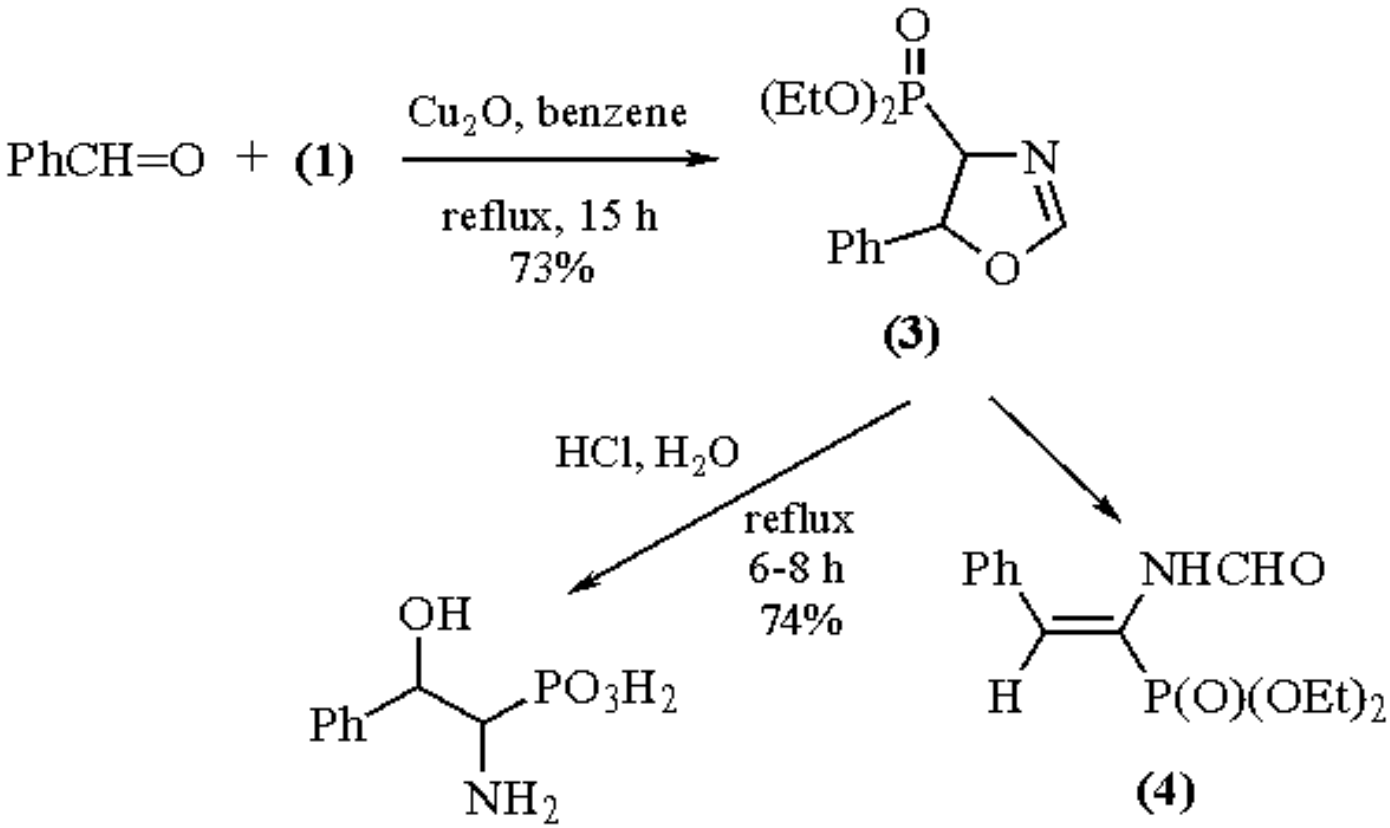

(5)

The reaction to give compounds of type (**3**) has been carried out with high asymmetric induction (>98%) using a chiral ferrocenylphosphine-gold complex as catalyst.[6b,c]

Miscellaneous.

(**1**) has been used in Passerini-type reactions,[7] and in a recent synthesis of pyrroles from nitroalkenes (eq 6).[4]

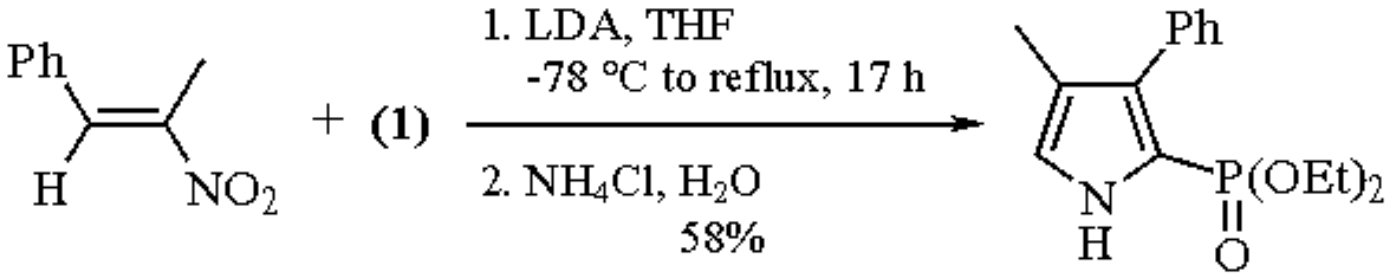

(6)

Several derivatives of (**1**) have also been used as reagents. For example, $(EtO)_2P(O)CR^1R^2NC$: (i) R^1 = H, R^2 = Me in the synthesis of corticosteroids;[8] (ii) R^1 = H, R^2 = Cl in the synthesis of indisodine;[9] (iii) R^1 = H, R^2 = S-aryl in the

synthesis of ketene *N*,*S*-acetals.[10]

---

1. Leading refs: (a) Burke, T. R., Jr. *OPP* **1991**, *23*, 127. (b) Stoelwinder, J.; van Leusen, A. M. *S* **1990**, 568. (c) Moskal, J.; van Leusen, A. M. *RTC* **1987**, *106*, 137. (d) Rachon, J. *C* **1982**, *36*, 462. (e) Hoppe, I.; Schöllkopf, U. *LA* **1984**, 600.
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Diethyl Malonate[1]

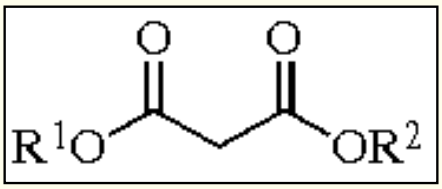

(**1**; $R^1 = R^2 = Et$)

[105-53-3] · $C_7H_{12}O_4$ · Diethyl Malonate · (MW 160.17) (**2**; $R^1 = R^2 = Me$)

[108-59-8] · $C_5H_8O_4$ · Dimethyl Malonate · (MW 132.12) (**3**; $R^1 = R^2 = t$-Bu)

[541-16-2] · $C_{11}H_{20}O_4$ · Diethyl Malonate · (MW 216.28) (**4**; $R^1 = t$-Bu, $R^2 = Me$)

[42726-73-8] · $C_8H_{14}O_4$ · *t*-Butyl Methyl Malonate · (MW 174.20) (**5**; $R^1 = t$-Bu, $R^2 = Et$)

[32864-38-3] · $C_9H_{16}O_4$ · *t*-Butyl Ethyl Malonate · (MW 188.22) (**6**; $R^1 = R^2 = Bn$)

[15014-25-2] · $C_{17}H_{16}O_4$ · Dibenzyl Malonate · (MW 284.31) (**7**; $R^1 = Bn$, $R^2 = Me$)

[52267-39-7] · $C_{11}H_{12}O_4$ · Benzyl Methyl Malonate · (MW 208.21) (**8**; $R^1 = Bn$, $R^2 = Et$)

[42998-51-6] · $C_{12}H_{14}O_4$ · Benzyl Ethyl Malonate · (MW 222.24)

(two- or three-carbon nucleophiles in enolate or enol alkylation, conjugate addition, and various condensation reactions[1])

Physical Data: (**1**) mp -50 °C; bp 199 °C; d^{20} 1.055 g cm^{-3}; n_D^{20} 1.4143; dipole moment 1.57 D. (**2**) mp -62 °C; bp 181 °C; d^{20} 1.154 g cm^{-3}; n_D^{20} 1.4140; dipole moment 2.39 D. (**3**) bp 112-115 °C/31 mmHg; d^{20} 0.965 g cm^{-3}. (**4**) bp 80 °C/11 mmHg; d^{20} 1.030 g cm^{-3}. (**5**) bp 83-85/8 mmHg; d^{20} 1.001 g cm^{-3}. (**6**) bp 188 °C/0.2 mmHg; d^{20} 1.158 g cm^{-3}. (**7**) bp 125 °C/0.5 mmHg; d^{20} 1.150 g cm^{-3}. (**8**) bp 138-139 °C; d^{20} 1.087 g cm^{-3}.

Solubility: (**1**) and (**2**) sparingly sol water; miscible in all proportions with ether and alcohol.

Form Supplied in: dimethyl and diethyl malonates are colorless liquids with a minimum assay of 99% (GC) which are widely available.

Preparative Methods: dibenzyl malonate is prepared by refluxing malonic acid with benzyl alcohol with

catalytic amount of sulfuric acid.[2] Di-*t*-butyl malonate is usually obtained from malonic acid and isobutene with catalytic amount of sulfuric acid.[3] *t*-Butyl methyl and *t*-butyl ethyl malonates can be obtained through reaction of methyl and ethyl malonyl chlorides with *t*-butyl alcohol, e.g. over activated alumina as a catalyst.[4a] Unsymmetrical methyl, ethyl, and benzyl malonates may be prepared by reaction of the corresponding monoalkyl malonates with alkyl chloroformates.[4b]

Handling, Storage, and Precautions: no specific health hazard if handled with the usual precaution.

Introduction.

The principal synthetic utility of the malonate esters may be summarized as follows:[1]

- 1) the acidity of the methylene group (pK_a &AApprox; 13) is such that metal salts can be easily formed with the metal alkoxides. The resulting carbanions undergo acylation, alkylation,[5] aldol,[6] and Michael reactions;[7]
- 2) the possibility of hydrolyzing and subsequently decarboxylating only one of the ester functions;
- 3) the usual reactions of the ester functions.

In many syntheses reported in the literature, malonates react at both the methylene group and the ester functions, which make them very useful reagents, especially in the formation of heterocycles.

The main feature of di-*t*-butyl, dibenzyl, and the *t*-butyl and benzyl alkyl malonates is that the *t*-butyl ester and benzyl ester groups can easily be cleaved by hydrolysis/decarboxylation or by hydrogenolysis/decarboxylation, respectively. Selective removal of *t*-butyl and benzyl esters may also be accomplished with ***Iodotrimethylsilane***.[8] Cleavage and decarboxylation of dimethyl, diethyl, and unsymmetrical methyl and ethyl malonates can be effected by S_N2 attack on the methyl or ethyl ester carbon with strong nucleophilic anions such as chloride, iodide, cyanide, alkylthiolates, and phenylselenate.[9]

Acylation.

Acylation of diethyl malonate followed by partial hydrolysis and decarboxylation is one of the methods used for synthesizing β-keto esters.[10] Nevertheless, further malonate derivatives such as Meldrum's acid (***2,2-Dimethyl-1,3-dioxane-4,6-dione***),[11a] and mixed malonates such as *t*-butyl ethyl malonate[11b] or potassium ethyl malonate,[11c] can also be advantageously used. The latter allows the synthesis of β-keto esters in high purity without the partial hydrolysis step so that they can be used without isolation in subsequent transformations to, for example, quinolone moieties (eq 1).[11c]

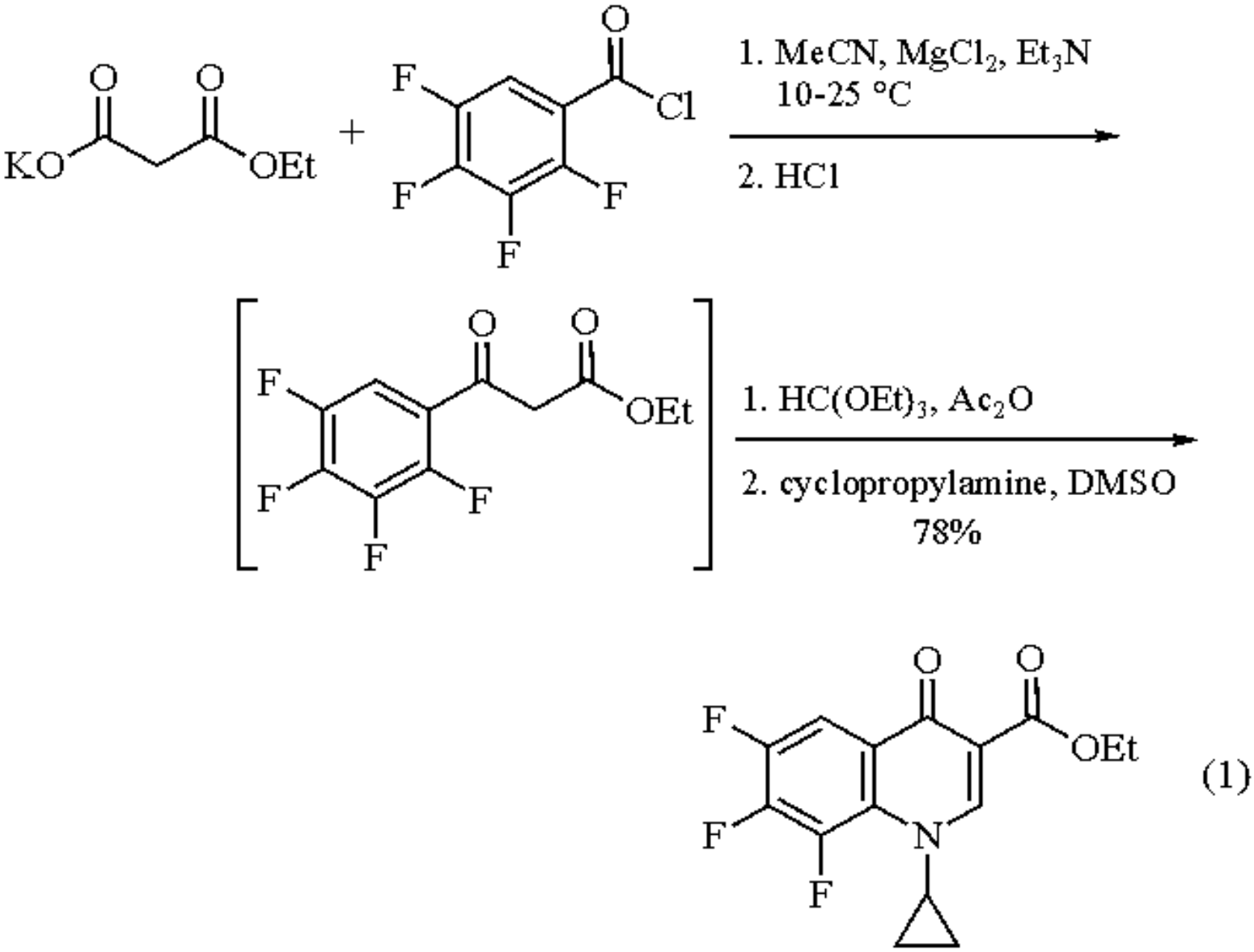

Acylation of dibenzyl malonate[12a] or di-*t*-butyl malonate[12b] followed by hydrogenolysis/decarboxylation (eq 2) or hydrolysis/decarboxylation (eq 3) of the acylmalonates yields methyl ketones.

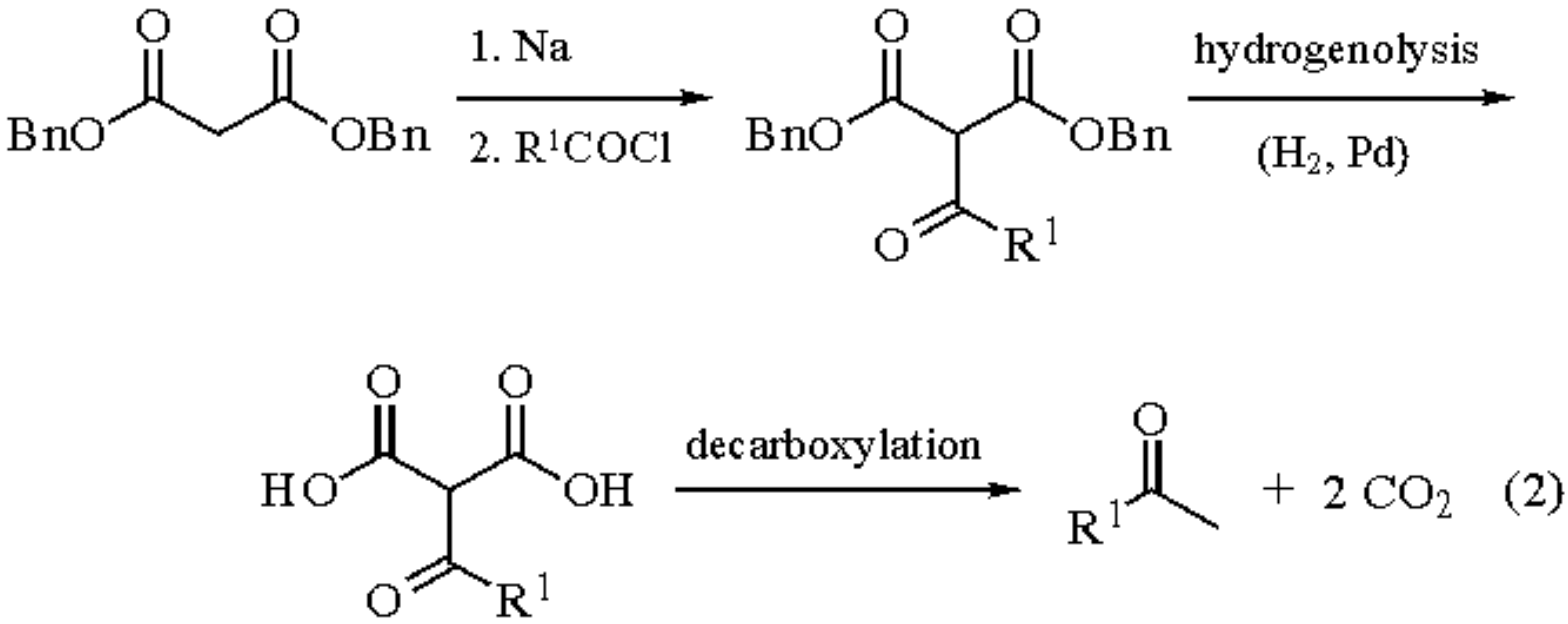

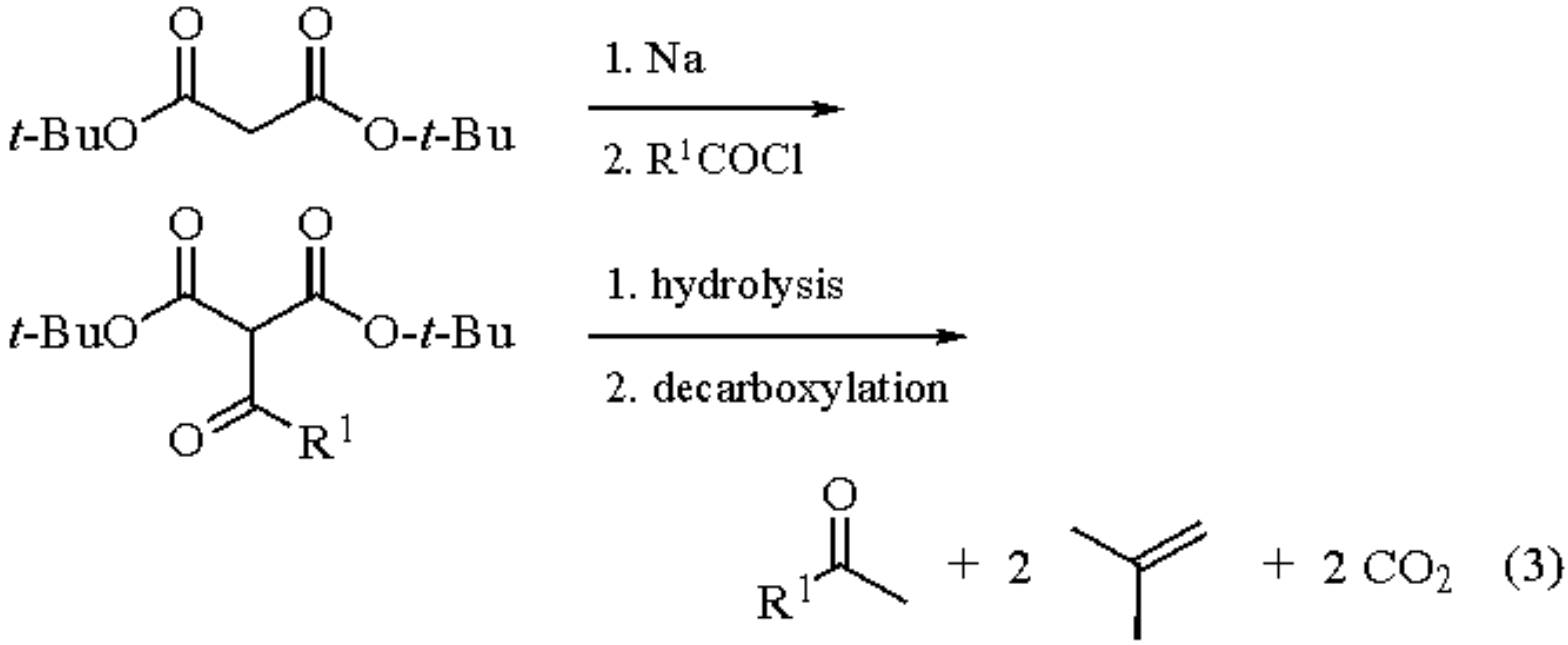

A similar synthesis of methyl 7-(2-hydroxy-5-oxo-1-cyclopentenyl)heptanoate has been reported (eq 4).[13] Condensation of orthoformates with malonates affords alkoxymethylene malonates which are widely used for heterocyclic synthesis.

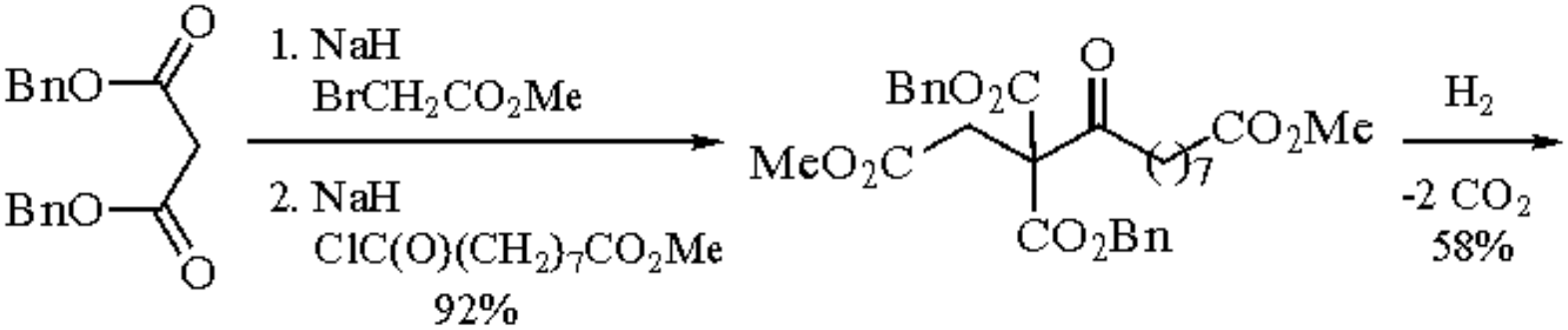

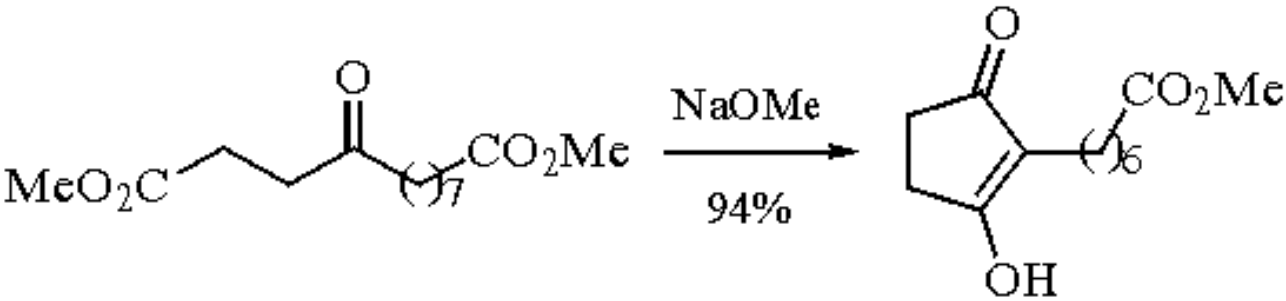

(4)

Alkylation.

[1,5] Both α-hydrogens can be replaced by alkyl substituents (eq 5).[14]

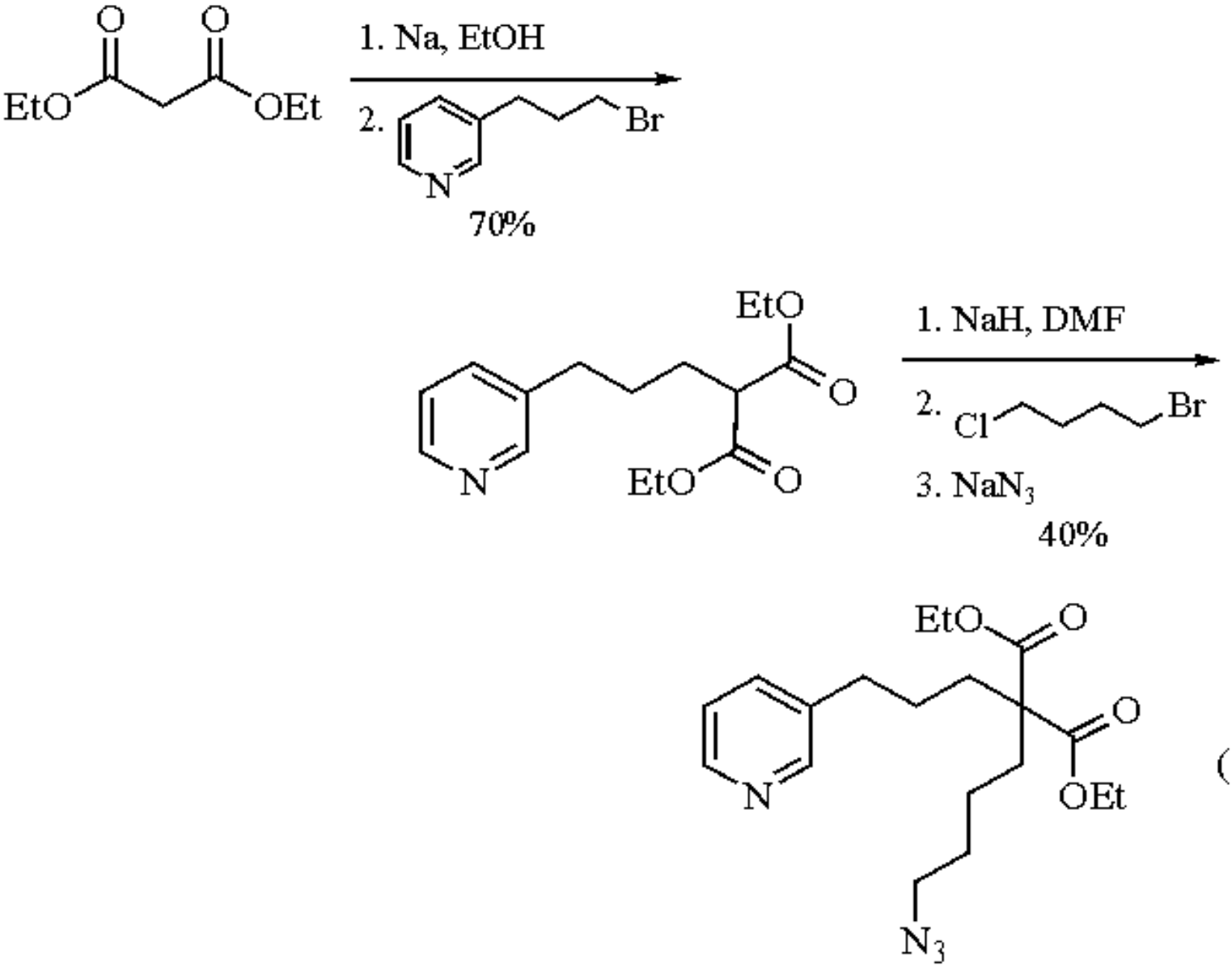

(5)

Mono- and dialkyl malonates can be further modified by partial hydrolysis and decarboxylation of an ester function,[9,14] or by reduction of both ester functions with ***Lithium Aluminum Hydride*** to give 2-substituted 1,3-propanediols (eq 6).[15] A useful synthesis of primary α-methylene alcohols involves $LiAlH_4$ reduction of the sodium salts formed from α-alkyl malonates (eq 7).[16] Cyclocondensation with *N*-ethylaniline affords a 4-hydroxy carbostyril (eq 8).[17]

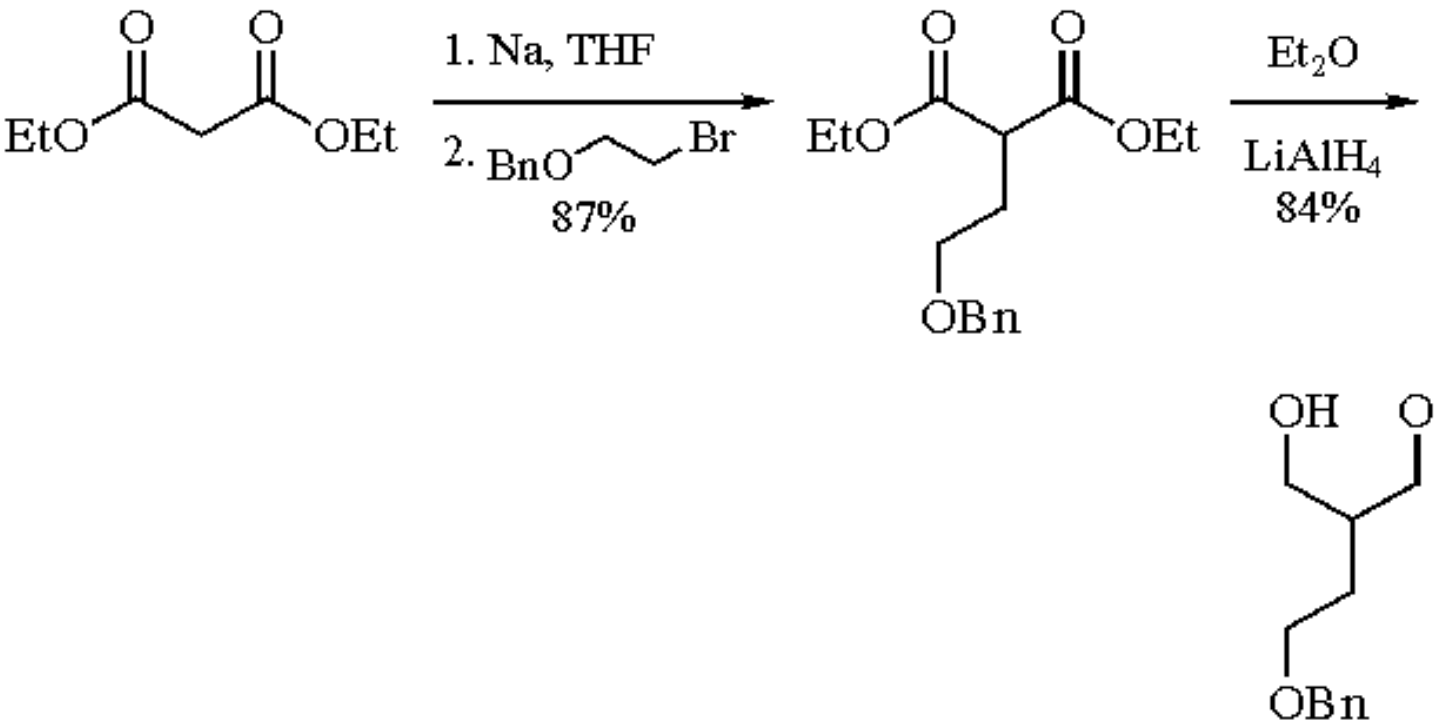

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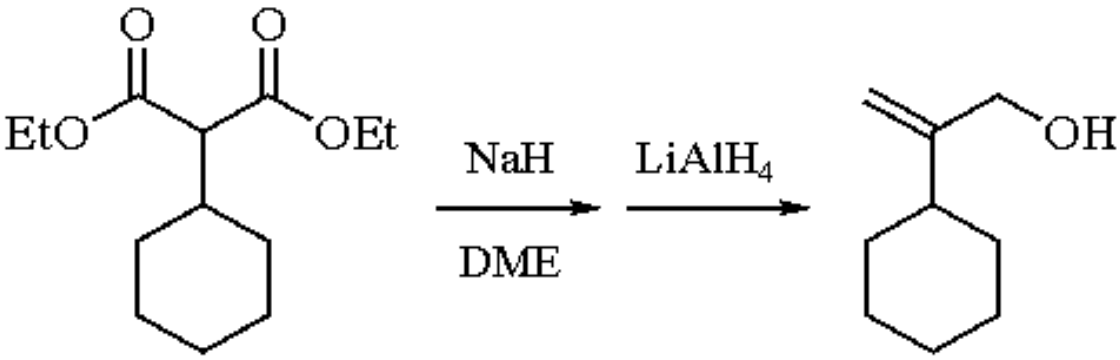

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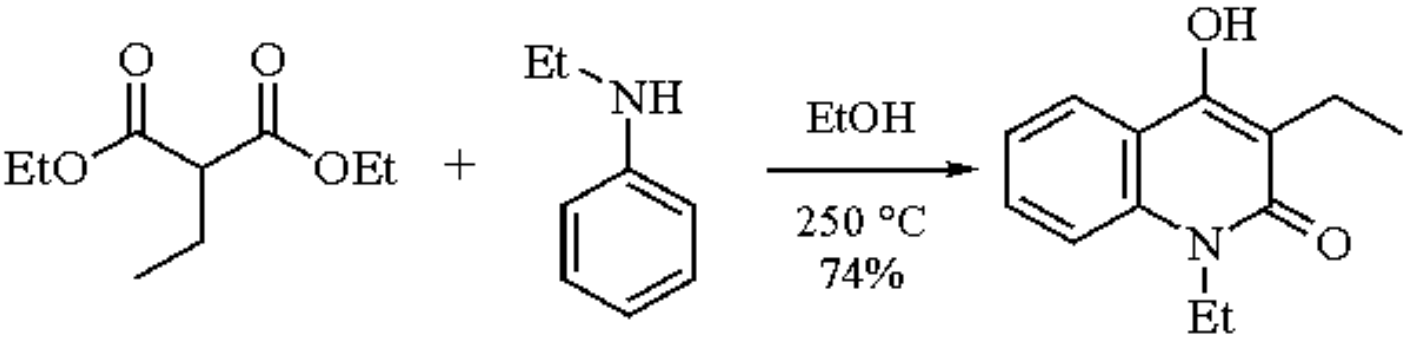

(8)

α,α-Dialkylation of malonates with dihaloalkanes and intramolecular α-alkylation with α-(o-haloalkyl)malonates provides effective approaches for construction of carbocyclic rings containing 3-21 carbon atoms.[18] Alkylation of sodio diethyl malonate with chiral 2,3-epoxybutane affords enantiomerically pure (>99% ee) *cis*-β,γ-dimethyl-γ-butyrolactone (eq 9).[19] Although α-alkylation of malonate carbanions with tertiary alkyl halides cannot usually be effected in practically useful yields owing to competing elimination, *t*-butylation of diethyl malonate could be accomplished in 56% yield under Lewis acidic conditions (BF_3, CS_2/$ClCH_2CH_2Cl$, Δ, 18 h), presumably via an S_N1-type mechanism involving the *t*-butyl carbenium ion (eq 10).[20]

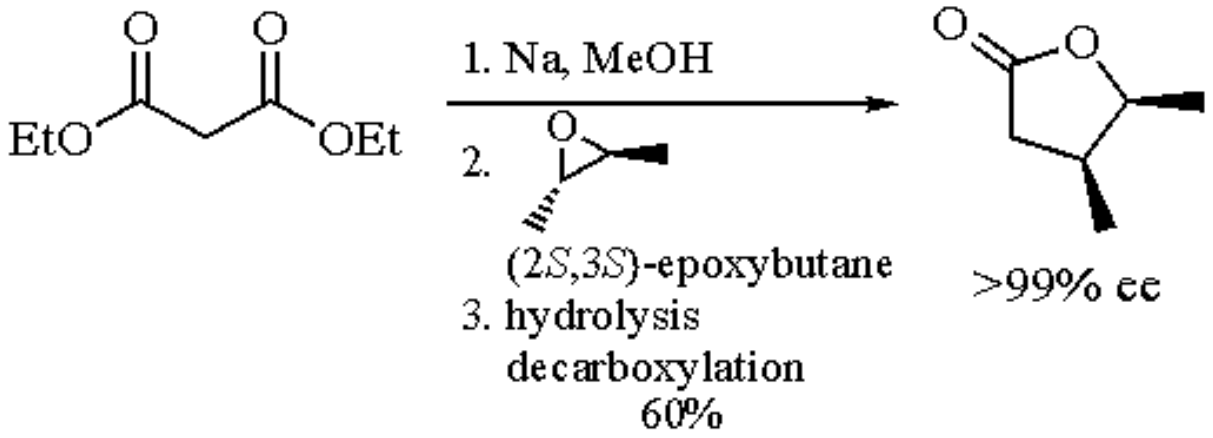

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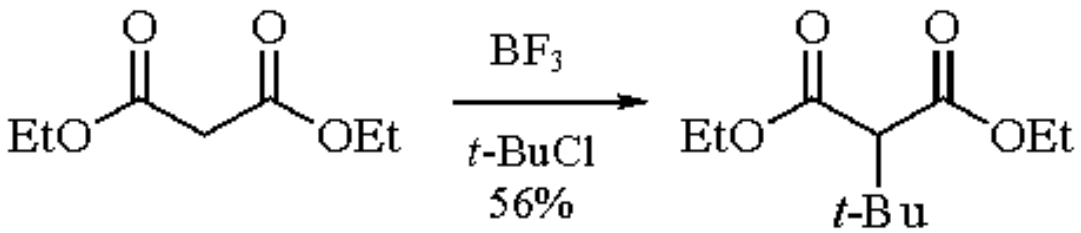

(10)

An important advance in the potential applications of malonate chemistry is the development of efficient procedures for α-allylation of malonate anions with allylic esters and lactones as well as vinyl epoxides (e.g. cyclopentadiene monoepoxide) by means of Pd^0 catalysts (eq 11).[21,22]

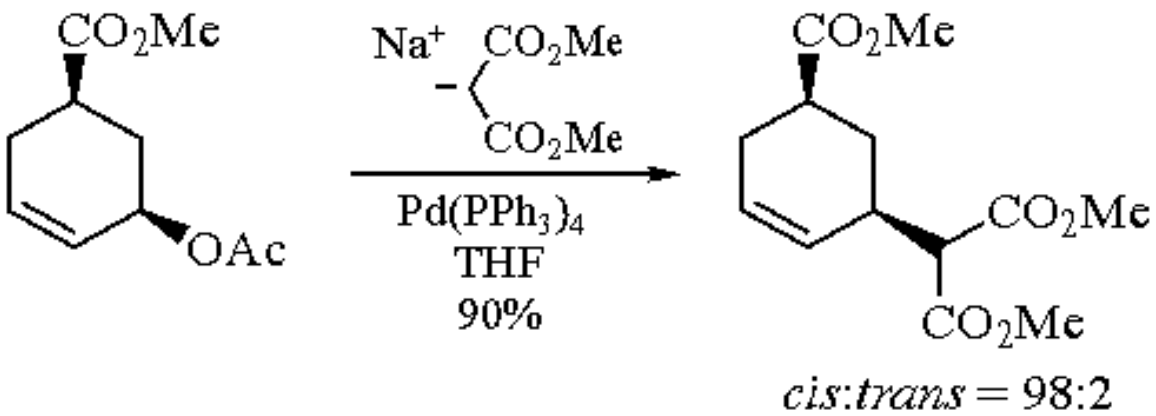

(11)

Less economically attractive, but still quite useful, are the allyl coupling reactions that occur between π-allylpalladium complexes and malonate anions. The former Pd^0-catalyzed allylations usually occur with retention of the C-O bond stereochemistry as a consequence of the two configurational inversions which occur during the formation of the π-allylpalladium intermediate and its subsequent displacement by the malonate group. It should be noted that mixtures of allylic isomers are often formed from unsymmetrical allylic esters owing to malonate attack at both C-1 and C-3 of the π-allylpalladium intermediate.

α-Alkylation of malonate esters by monosubstituted alkenes and isobutene occurs in the simultaneous presence of ***Manganese(III) Acetate*** (limiting stoichiometric oxidant) and catalytic amounts of ***Copper(II) Acetate***. The resulting α-alkenylmalonates (40-70% based on Mn^{III}) undergo hydrolysis and decarboxylation to γ,δ-unsaturated carboxylic acids.[23] α-Arylation of α-alkylmalonate diesters may be accomplished by means of coupling reactions with aryllead triacetates [$ArPb(OAc)_3$].[24] However, the unsubstituted parent malonates do not undergo arylation under the same

conditions.

Knoevenagel Reactions.

Such reactions[6] with aldehydes or ketones are frequently followed by cyclocondensation at one of the ester functions (eq 12).[25] When reacted with acetaldehyde, diethyl ethylidenemalonate is obtained which in turn can be ozonolyzed to diethyl oxomalonate (eq 13), a versatile reagent for organic synthesis.[26]

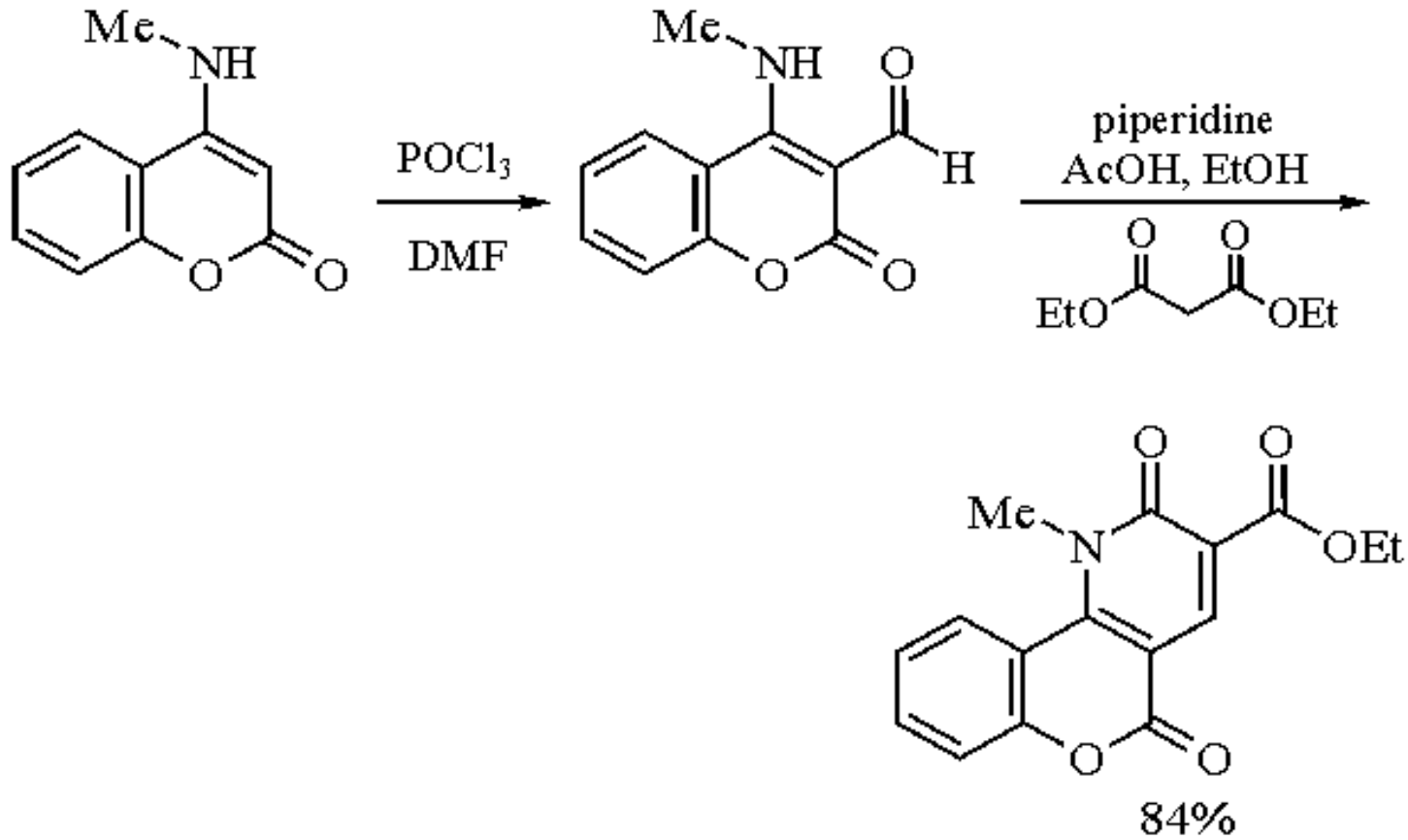

(12)

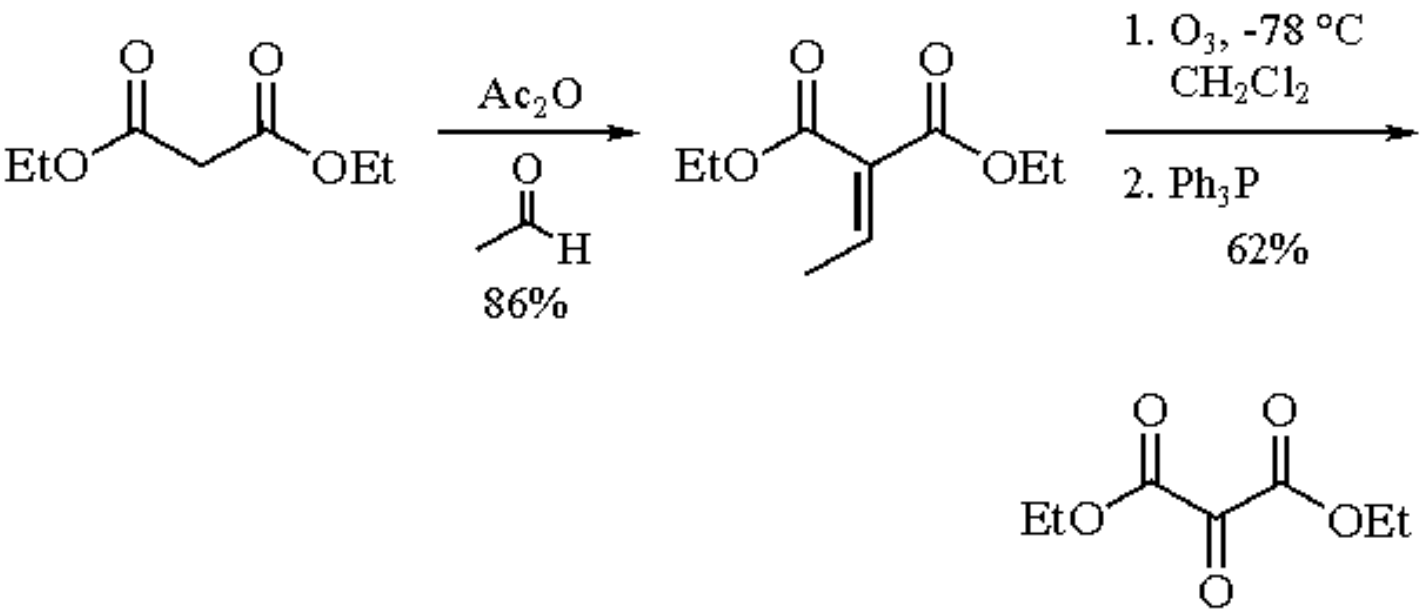

(13)

Michael Reaction.

The Michael addition[7] to activated double bonds such as those of α,β-unsaturated carbonyl compounds is frequently described in the literature. Followed by a ring-closing Claisen condensation and a subsequent decarboxylation, this sequence leads to the formation of 1,3-cyclohexanedione derivatives (eq 14).[27] They can further be aromatized to substituted resorcinols,[28] reduced to 5-substituted 2-cyclohexenones,[29] or involved in cyclocondensation reactions.[27]

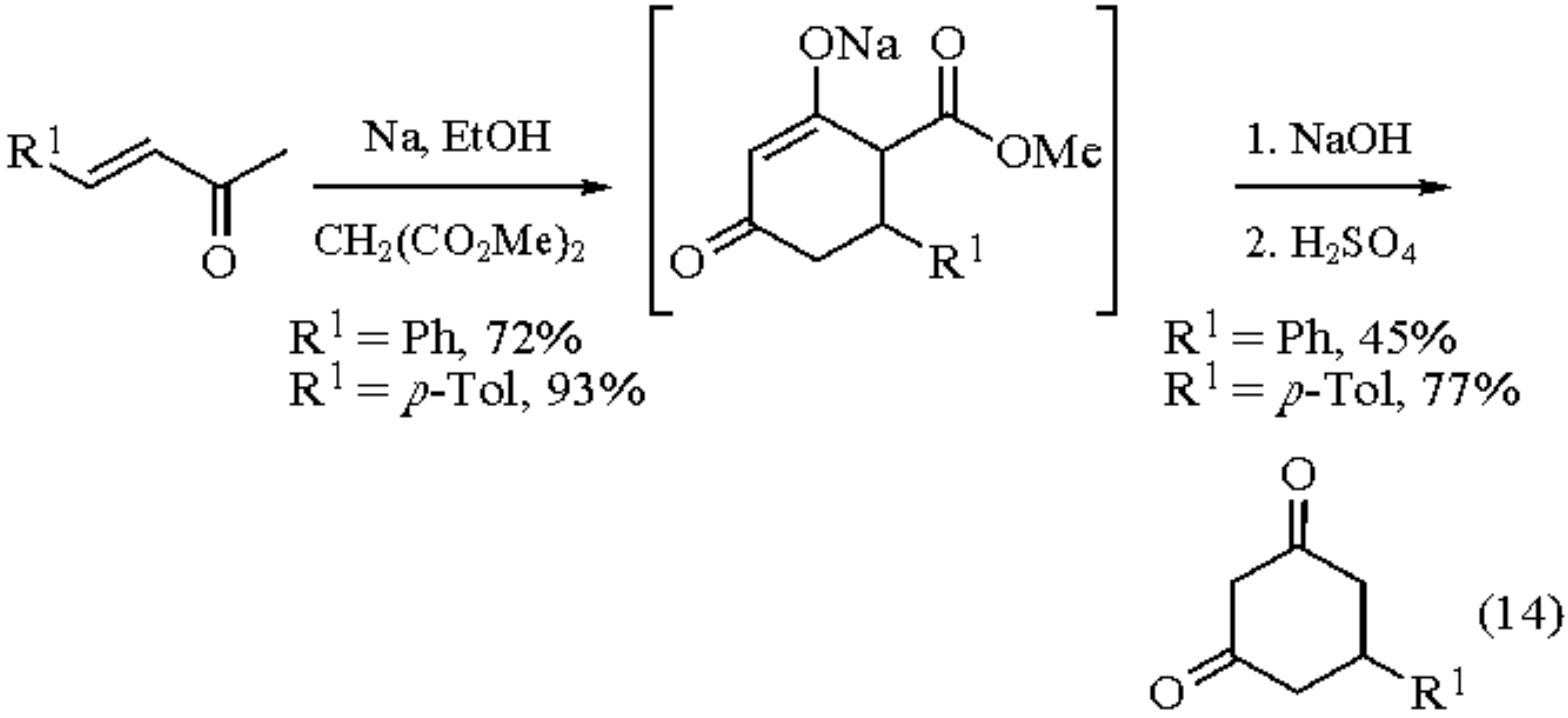

In the case of β,β-bis(trifluoromethyl)acrylic esters as starting material, an anti-Michael addition followed by a fluoride elimination has been reported (eq 15).[30]

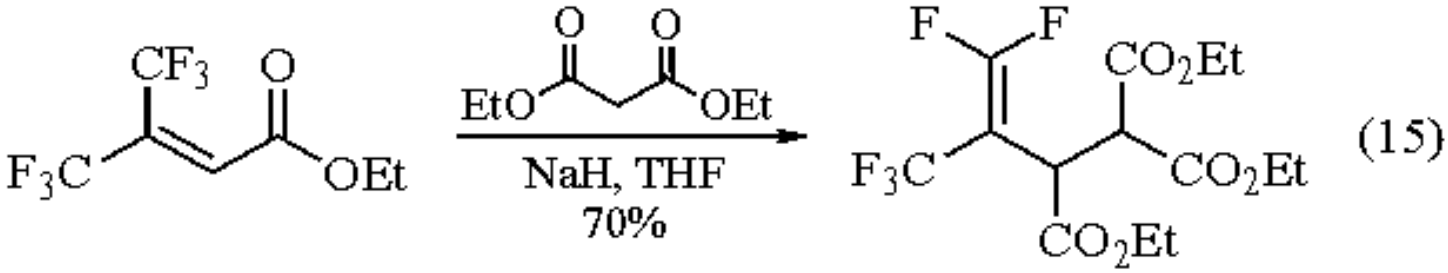

Other Reactions.

A further reaction at the central methylene group is nitrosation with ***Sodium Nitrite***, giving oximinomalonates which are subsequently reduced to the corresponding 2-aminomalonates (eq 16).[31]

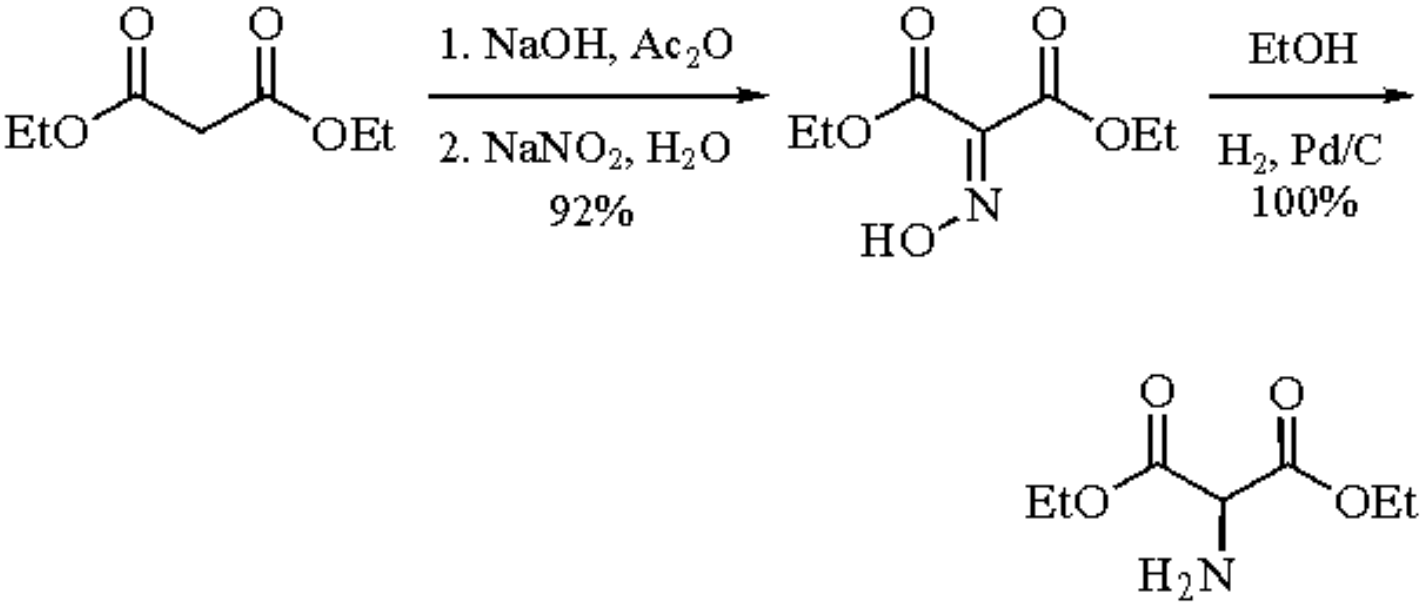

(16)

Usual reactions at the ester functions include, for example, transesterification to mixed malonates like benzyl ethyl malonate[2] or base-catalyzed cyclocondensation with ureas, thioureas, guanidines, or amidines yielding the corresponding 2-substituted pyrimidines.[32]

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Diethyl Ethoxymethylenemalonate***; ***Diethyl Ethylidenemalonate***; ***Diethyl Methylenemalonate***; ***Diethyl Oxomalonate***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***; ***Diethyl Ethoxymagnesiomalonate***; ***Ethyl Malonate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Manganese(III) Acetate***; ***Tetrakis(triphenylphosphine)palladium(0)***.

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Diethyl Methoxymethylphosphonate

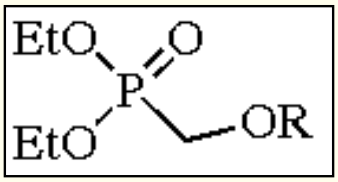

(**1a**; R = Me)

[332806-04-5] · $C_6H_{15}O_4P$ · Diethyl Methoxymethylphosphonate · (MW 182.16) (**1b**; R = $MeOCH_2CH_2$)

[70080-14-7] · $C_8H_{19}O_5P$ · Diethyl Methoxyethoxymethylphosphonate · (MW 226.21) (**1c**; R = THP)

[71855-51-3] · $C_{10}H_{21}O_5P$ · Diethyl Tetrahydropyranyloxymethylphosphonate · (MW 252.25) (**1d**; R = TBDMS)

[71855-52-4] · $C_{11}H_{27}O_4PSi$ · Diethyl (*t*-Butyldimethylsilyl)oxymethylphosphonate · (MW 282.39) (**1e**; R = $TMSCH_2CH_2$)

[90490-19-0] · $C_{10}H_{25}O_4PSi$ · Diethyl (Trimethylsilyl)ethoxymethylphosphonate · (MW 268.36)

(Horner-Emmons reagents for carbonyl homologation;[1-4] preparation of vinyl ethers[1-4] and ketene *O,S*-thioacetals[5])

Physical Data: (**1a**): bp 65-67 °C/0.1 mmHg;[6] n_D^{20} 1.4250. (**1b**): bp 105 °C/0.8 mmHg.[1] (**1c**): bp 105 °C/0.1 mmHg.[1] (**1d**): bp 85 °C/0.1 mmHg.[1] (**1e**): bp 80-82 °C/0.05 mmHg.[7]

Solubility: sol organic solvents (THF, diglyme, ether, ethyl acetate, DMF); low sol water.

Analysis of Reagent Purity: the phosphonates are isolable and can be fully characterized by standard analytical and spectroscopic techniques.[1,6,7] (**1a**) ^{31}P NMR (C_6D_6) δ -22 ppm.[8]

Preparative Methods: phosphonates (**1a**) (85%),[1] (**1b**) (74%),[1] and (**1e**) (82%)[7] are readily prepared by the Michaelis-Arbuzov reaction of ***Chloromethyl Methyl Ether***, ***2-Methoxyethoxymethyl Chloride*** (MEMCl), and ***2-(Trimethylsilyl)ethoxymethyl Chloride*** (SEMCl), respectively, with ***Triethyl Phosphite***. Reagents (**1c**) (82%) and (**1d**) (45%) are prepared from $HOCH_2PO(OEt)_2$ and ***3,4-Dihydro-2H-pyran***/***Phosphorus Oxychloride*** or ***t-Butyldimethylchlorosilane***/***Imidazole*** respectively.[1]

Handling, Storage, and Precautions: dialkyl phosphonates are irritants and their chloromethyl ether precursors are highly toxic carcinogens (or cancer suspect agents). Organolithium reagents and the other bases employed for the conversions of (**1**) are caustic and some are potentially pyrophoric. Proper handling

and special safety practices information should be obtained from the supplier and individuals should thoroughly familiarize themselves with these techniques prior to using these reagents.

Vinyl Ethers from the Horner-Emmons Alkenation.[9]

Dialkyl alkoxymethylphosphonates such as (**1**) are α-deprotonated at low temperatures (e.g. -60 °C) with strong base (***Lithium Diisopropylamide***,[10] ***n-Butyllithium***/***Potassium t-Butoxide***[5]), and the reaction of the resulting anion (Kluge reagent)[1] with aldehydes and ketones gives 1,2-adducts which undergo thermal elimination (M = Li, THF, reflux, aryl derivatives (2-4 h), aliphatic (16-72 h)).[1] Alternatively, these intermediates can be quenched to give isolable α-alkoxy-β-hydroxyalkylphosphonates which, after treatment with *t*-BuOK, undergo a more facile elimination (THF, reflux, 5 min). Polyunsaturated aldehydes are converted to polyenyl ethers using (**1a**) in 40-50% with high (*E*) stereoselectivities.[3] The MEM derivative (**1b**) is a more effective reagent for this process,[1b] while (**1d**) is ineffective because of the lability of the silyl group with respect to rearrangement.[1a] Kluge employed (**1c**) for the homologation of an intermediate ketone in his approach to the construction of the ajmaline nucleus (eq 1).[2] Heathcock also found the reagent effective for the homologation of mesityl oxide (eq 2, ca. 90% nonconjugated isomer),[4] a useful intermediate in the stereoselective synthesis of the C-1 to C-7 moiety of erythronolide A.

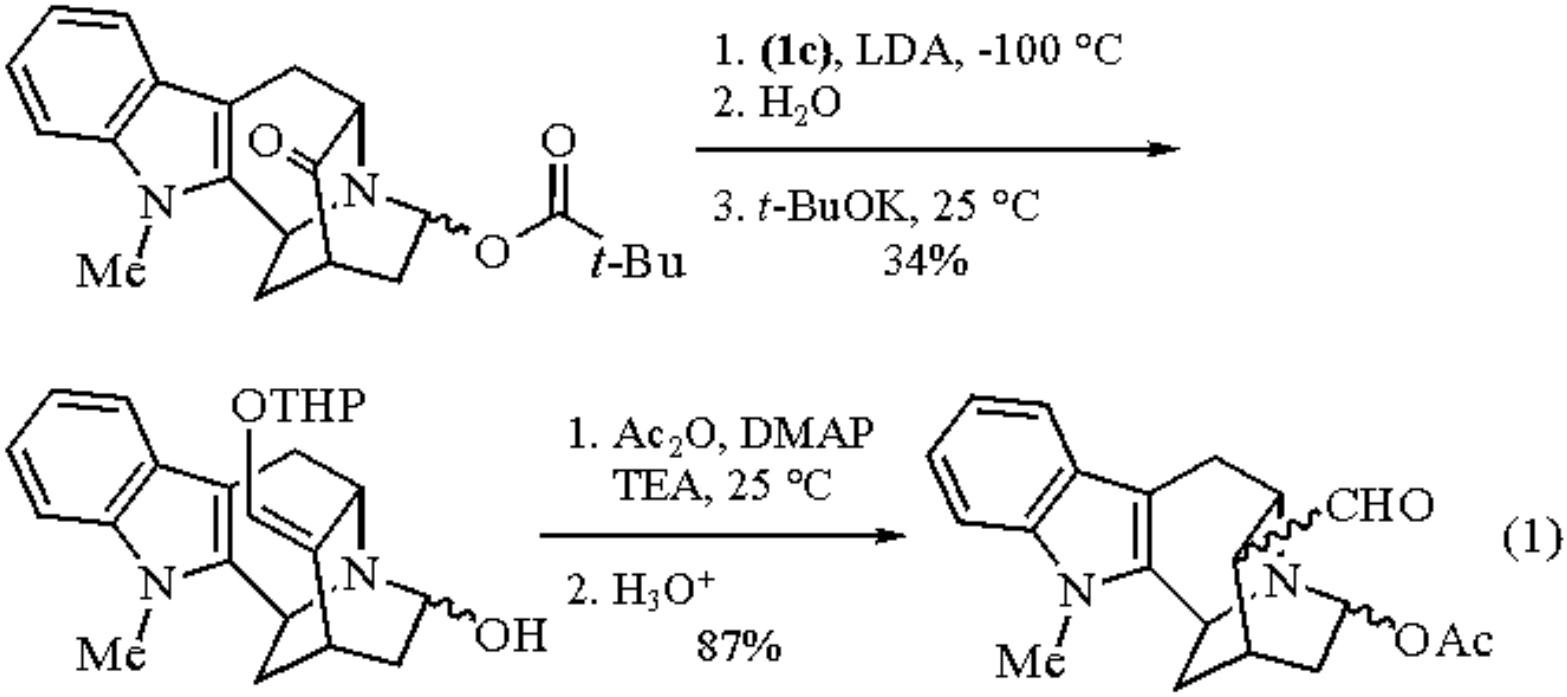

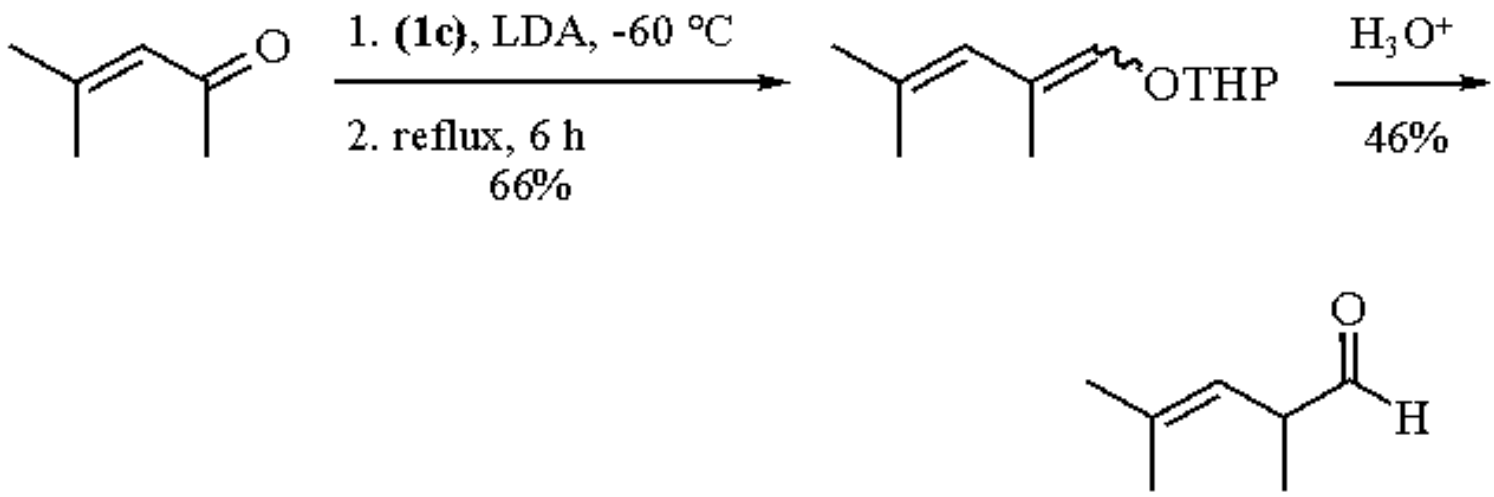

(2)

The reagents have not always been successful and several examples include the attempted homologation of thienocyclohexanones,[11] bicyclic ketones,[12,13] amides,[14] and penicillanic acid derivatives.[15] However, some polycyclic systems are effectively homologated employing (**1**) (50-60%),[16] but for others,[12] ***Methoxymethylenetriphenylphosphorane*** may be better. The sequential α-alkylation of (**1e**) (***s-Butyllithium***, RX) has been used to prepare branched α-hydroxyalkylphosphonates.[7] Related α-alkylated derivatives of (**1**) have been investigated as alkenating agents with mixed results.[17]

Ketene *O,S*-Thioacetals from (1).

An extension of these processes has been effectively employed for the synthesis of ketene *O,S*-thioacetals.[5c] Deprotonation of (**1a**) with LiBu/*t*-BuOK followed by sulfuridation and methylation produces the corresponding *O,S*-thioacetals of formylphosphonates.[5] These are lithiated with ***t-Butyllithium*** at -78 °C and condensed with aldehydes and ketones to afford ketene *O,S*-thioacetals in ca. 80% yield as essentially 1:1 (*E*)/(*Z*) mixtures (eq 3).

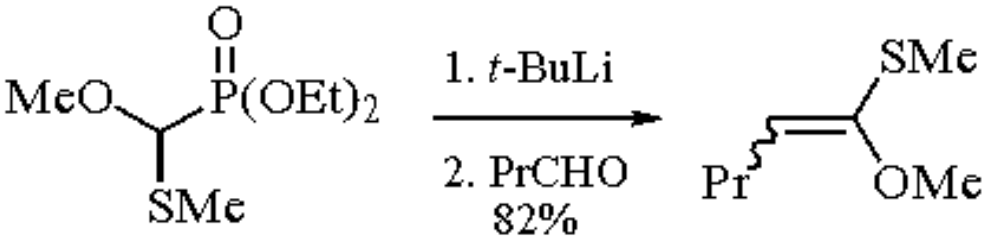

(3)

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Diethyl Methylenemalonate[1]

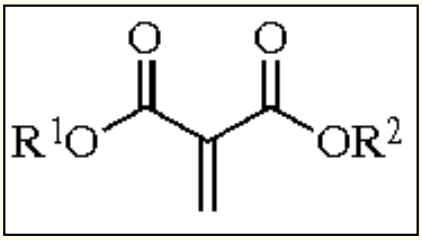

(**1**; R^1 = Et, R^2 = Et)

[3377-20-6] · $C_8H_{12}O_4$ · Diethyl Methylenemalonate · (MW 172.18) (**2**; R^1 = Me, R^2 = Me)

[3377-21-7] · $C_6H_8O_4$ · Dimethyl Methylenemalonate · (MW 144.13) (**3**; R^1 = $-CH_2CH{=}CH_2$, R^2 = $-CH_2CH{=}CH_2$)

[3377-22-8] · $C_{10}H_{12}O_4$ · Diallyl Methylenemalonate · (MW 196.20) (**4**; R^1 = *t*-Bu, R^2 = *t*-Bu)

[86633-09-2] · $C_{12}H_{20}O_4$ · Diethyl Methylenemalonate · (MW 228.29) (**5**; R^1 = Et, R^2 = $-CH_2C$&tbond;CH)

[116280-21-8] · $C_9H_{10}O_4$ · Ethyl 2-Propynyl Methylenemalonate · (MW 182.18) (**6**; R^1 = Et, R^2 = $-CH_2CO_2Et$)

[116280-23-0] · $C_{10}H_{14}O_6$ · Ethoxycarbonylmethyl Ethyl Methylenemalonate · (MW 230.22)

(Michael acceptor; Diels-Alder dienophile; polymerizes by an anionic mechanism)

Alternate Name: diethyl methylidenemalonate.

Physical Data: bp:[1a] (**1**) 60-61 °C/0.25 mmHg; (**2**) 80-82 °C/6 mmHg; (**3**) 67-68 °C/0.3 mmHg; (**4**) 67 °C/0.1 mmHg;[2] (**5**) 65-67 °C/0.3 mmHg; (**6**) 98-99 °C/0.1 mmHg.

Solubility: freely sol diethyl ether, dichloromethane, chloroform, methanol; solvent should be dry and free of nucleophile to avoid polymerization.

Form Supplied in: the diethyl ester analog is commercially available as its Diels-Alder adduct with anthracene. The reagent can be deprotected by a retro Diels-Alder reaction (see eq 1).[1a]

Analysis of Reagent Purity: GC analysis.[1a]

Preparative Methods: the classical method of preparation is a Knoevenagel condensation between ***Formaldehyde*** and ***Diethyl Malonate*** in glacial acetic acid catalyzed by ***Copper(II) Acetate*** and potassium acetate.[3] The diethyl methylenemalonate obtained polymerizes spontaneously to form a wax during the workup. The monomer can be recovered from the wax by thermal depolymerization under vacuum. Unlike other analogs, the sterically hindered

di-*t*-butyl ester does not polymerize under these conditions, and it can be isolated directly from the condensation mixture by vacuum distillation.[2] More recently, anthracene was introduced to trap the formed alkene in situ (eq 1).[1a] The Diels-Alder adduct obtained in this one-pot procedure is stable and can be purified by recrystallization. After purification, a retro Diels-Alder reaction in a high boiling fraction of mineral oil at 200-250 °C under strictly anhydrous conditions followed by vacuum distillation regenerates the methylenemalonate.

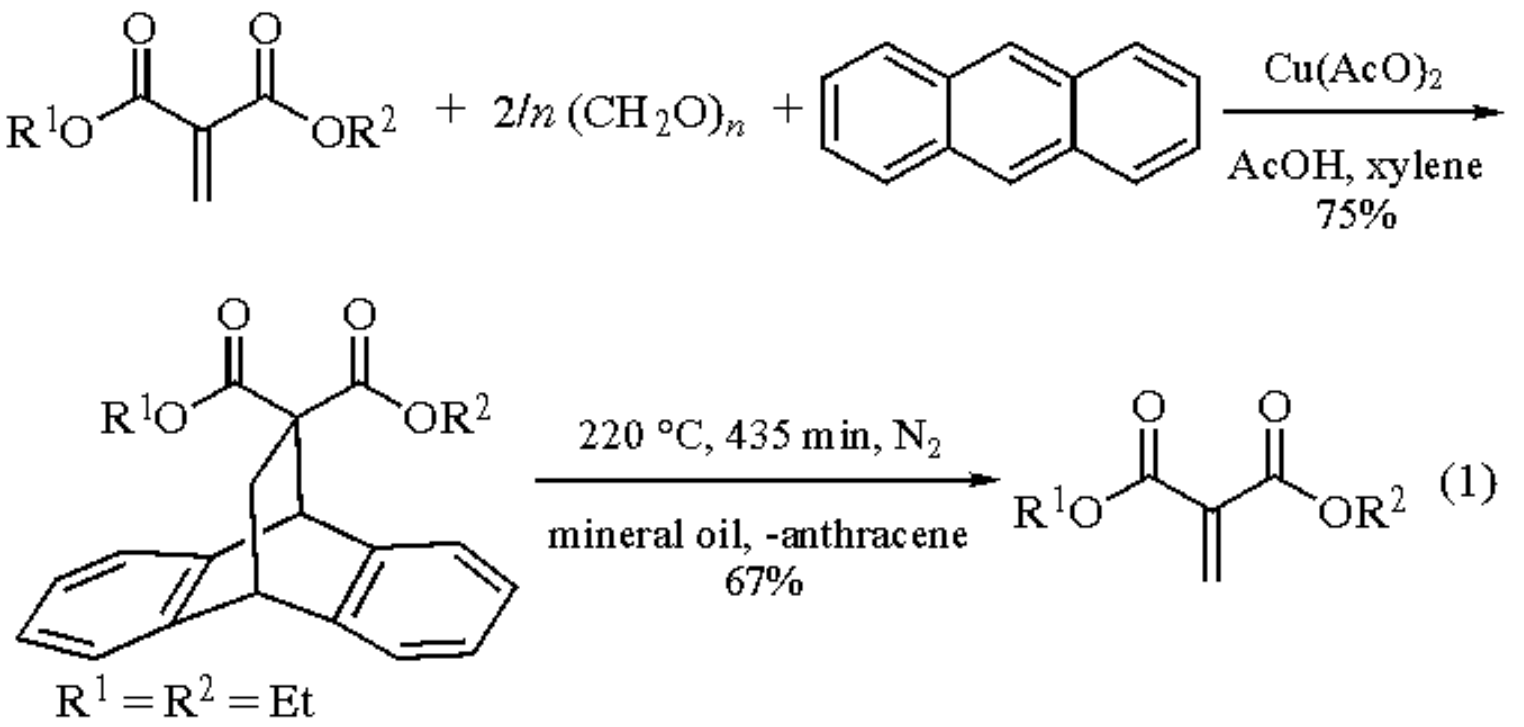

This latter method is of more practical use and affords a wide array of analogs of high purity with improved shelf stability compared to material obtained by other methods. It was used on a semimicro scale for the synthesis of the carbon-14 labeled diethyl methylenemalonate starting with carbon-14 paraformaldehyde.[4] Moreover, this strategy allows easy access to nonsymmetric and functionalized ester analogs by partial hydrolysis of the symmetric adduct with ***Potassium Hydroxide*** and subsequent alkylation of the resulting salt in DMF, as exemplified for the ethyl propargyl analog in eq 2.

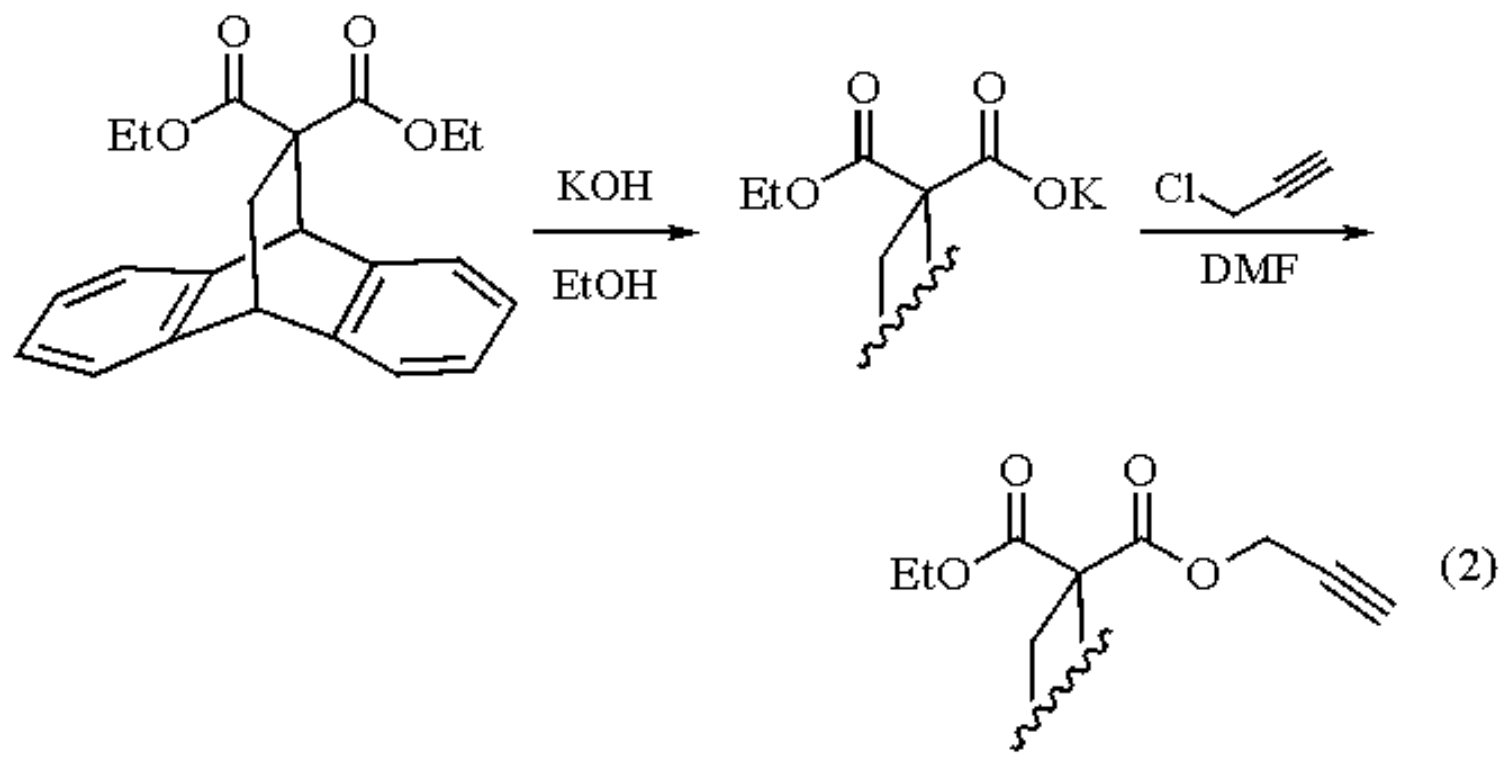

Handling, Storage, and Precautions: as methylenemalonate is very prone to anionic polymerization initiated even by water itself, it should be stored under dry inert gas in the cold. For a very long period it can be stored under SO_2 in a sealed glass container. Any glassware intended to be in contact with the reagent should be acid-washed and oven-dried and the solvent used should be dry. Due to its alkylating property, great care should be taken in handling the reagent and any contact should be avoided.

Introduction.

Only a few examples of the use of methylenemalonate esters can be found in the literature to date.

Radical Reactions.

An addition reaction of cycloalkyl radicals to diethyl methylenemalonate has been reported,[5,6] and a radical addition-cyclization reaction was described with diethyl α-(4-chlorobenzyl)malonyl radical (eq 3).[7]

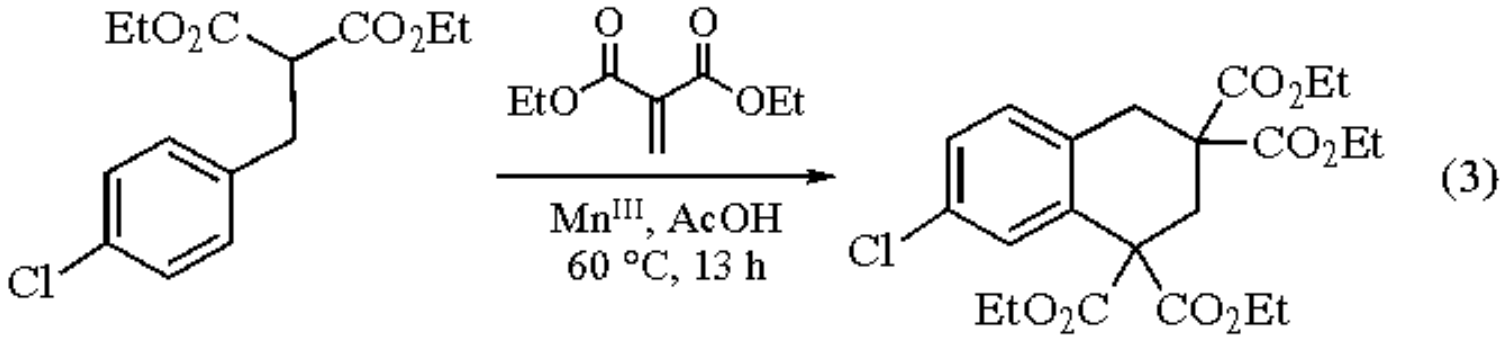

Michael Reactions.

As electrophilic alkenes, methylenemalonates are Michael acceptors and the resulting adducts are monoalkylated malonates, suitable for further elongation of the carbon chain (eq 4).[8]

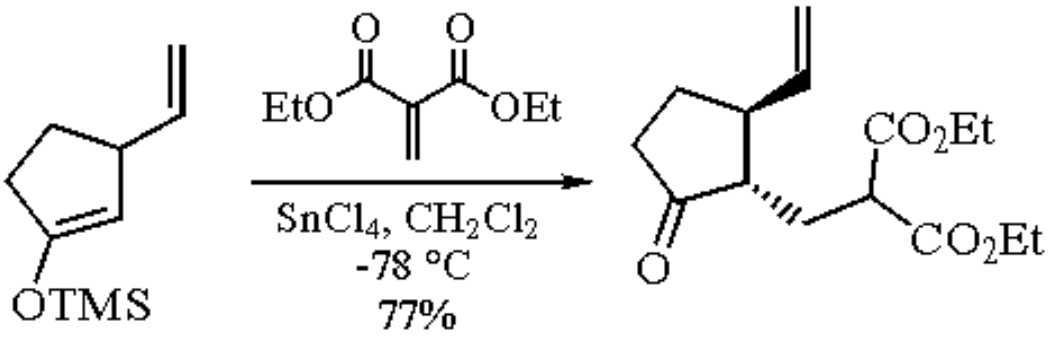

(4)

Reaction with the potassium salt of 2-nitropropane yields in one pot the corresponding *gem*-dimethylcyclopropane (eq 5).[9]

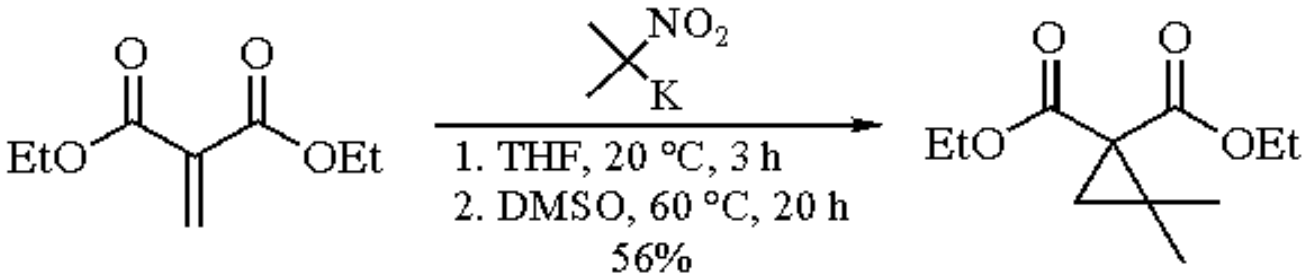

(5)

Epoxidation.

The reactivity of methylenemalonate toward epoxidation by peracid is somewhat surprising[10] (Prilezhaev reaction): even though the widely accepted rule is that reactivity parallels electron density, methylenemalonate esters afford fair yields of the oxirane upon treatment with ***m-Chloroperbenzoic Acid*** in dichloromethane, while alkyl acrylate and maleic acid do not react at all. Further, under the same conditions, allyl methyl methylenemalonate yields chemoselectively the product of epoxidation of the malonic double bond (eq 6).

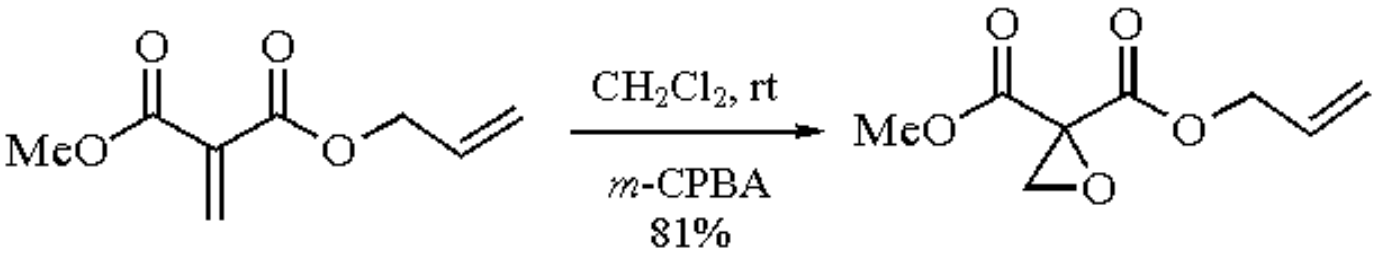

(6)

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***Diethyl Ethylidenemalonate***; ***Diethyl Malonate***; ***Formaldehyde***; ***N-(Methylthiomethyl)piperidine***.

1. (a) De Keyser, J.-L.; De Cock, Ch. J. C.; Poupaert, J. H.; Dumont, P. *JOC* **1988**, *53*, 4859. (b) *FF* **1972**, *3*, 96; **1990**, *15*, 100; **1992**, *16*, 13.
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N,N-Diethyl-*N*-methyl-*N*-(methylsulfonyl)ammonium Fluorosulfate[1]

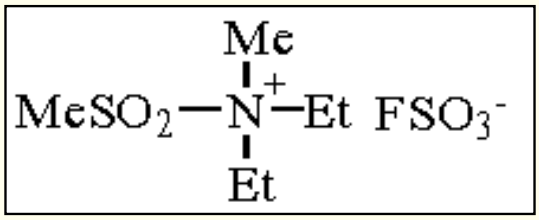

[55791-04-3] · $C_6H_{16}FNO_5S_2$ · *N,N*-Diethyl-*N*-methyl-*N*-(methylsulfonyl)ammonium Fluorosulfate · (MW 265.32)

(reagent for converting, under mild conditions, alcohols into methanesulfonate (mesylate) esters, and primary and secondary amines into methanesulfonamides[1,2])

Alternate Name: easy mesyl.

Physical Data: mp ~115 °C (dec).[2]

Solubility: sol dry MeCN (solutions decompose over a few hours at rt).[2]

Form Supplied in: not commercially available.

Preparative Method: reaction of $MeSO_2NEt_2$ with excess neat $MeOSO_2F$ at 50 °C for 72 h.[2]

Analysis of Reagent Purity: ^{1}H NMR (CD_3CN) δ: 1.40 (t, 6H), 3.11 (s, 3H), 3.60 (q, 4H), 3.70 (s, 3H).[2]

Handling, Storage, and Precautions: hygroscopic; hydrolyzed by moist air (products corrosive); stable indefinitely in a sealed ampoule at rt.

Mesylating Agent.

N,N-Diethyl-*N*-methyl-*N*-(methylsulfonyl)ammonium fluorosulfate[2]), and related compounds of the general structure $MeSO_2{+}NR^1R^2R^3$ X^- (X = FSO_3 or CF_3SO_3), are effective reagents for formation, under very mild conditions, of mesylates (from alcohols) and methanesulfonamides (from amines).[2] Good to excellent yields are obtained with easy mesyl plus a weakly basic tertiary amine (usually a catalytic amount) such as pyridine or dimethylaminoacetonitrile (DMAA) at temperatures ranging from -70 °C to rt, e.g. (-)-menthol (1 mmol), DMAA (10 µL) in CH_2Cl_2 (15 mL) at 0 °C on mixing with easy mesyl (1.2 mmol) in MeCN (1 mL) followed by workup after 10 min gave clean (-)-menthyl

mesylate (99%).[2] With relatively hindered alcohols (borneol, 5α-cholestan-3α-ol) the product may show contamination with the mesylmesylate ester ($ROSO_2CH_2SO_2Me$), the formation of which is (a) minimized by the use of (i) weak bases (py or DMAA as opposed to Et_3N or *N*-ethylmorpholine) and (ii) low concentrations of the amine, and (b) maximized by (i) strong bases and (ii) premixing of easy mesyl and the base.[2,3] Related *N*-methylsulfonylammonium salts also yield mesylates; $MeSO_2{+}NMe_3\ FSO_3^-$ is more readily prepared (85% yield in 1 h at rt) but is less soluble in MeCN and sometimes gives a poorer yield of the mesylate (35% vs. 80% of cyclohexyl mesylate under one set of conditions). In a set of comparison experiments[3] with 5α-cholestan-3β-ol (0 °C, excess py, 30 s) the yields with ***Methanesulfonyl Chloride***, ***Methanesulfonic Anhydride***, and $MeSO_2{+}NMe_3\ FSO_3^-$ were, respectively, <1%, 60%, and >98%. The cyclic sulfonylammonium salt prepared by *N*-methylation of *N*-methylpropanesultam with $MeOSO_2F$ is used in the preparation of 3-(trimethylammonio)-1-propanesulfonate esters ([3]betylates).[4]

Easy mesyl has proved useful in the preparation of fragile mesylates (e.g. *t*-BuOMs[2]), especially for immediate further transformation (eqs 1 and 2);[5,6] use of $MeSO_2Cl$ in these cases gave inferior results.

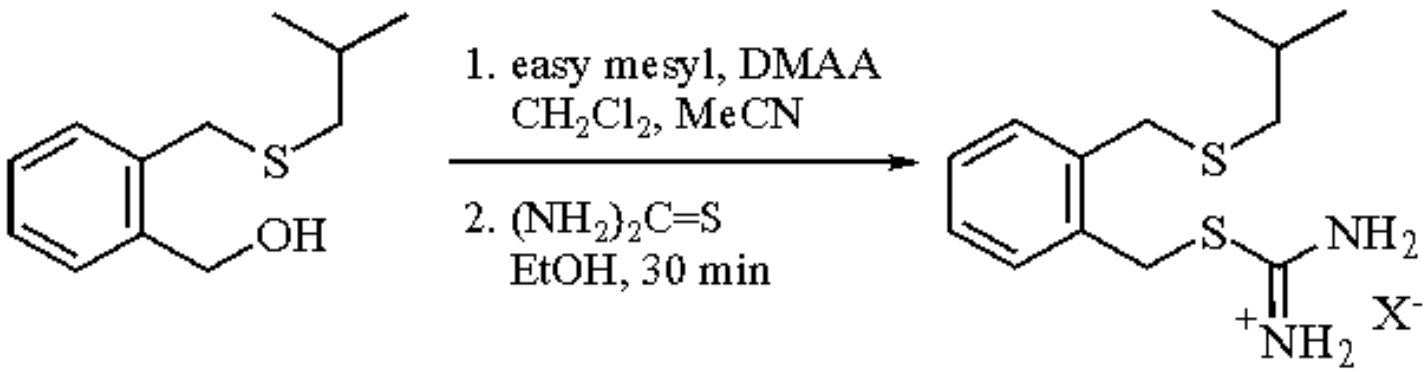

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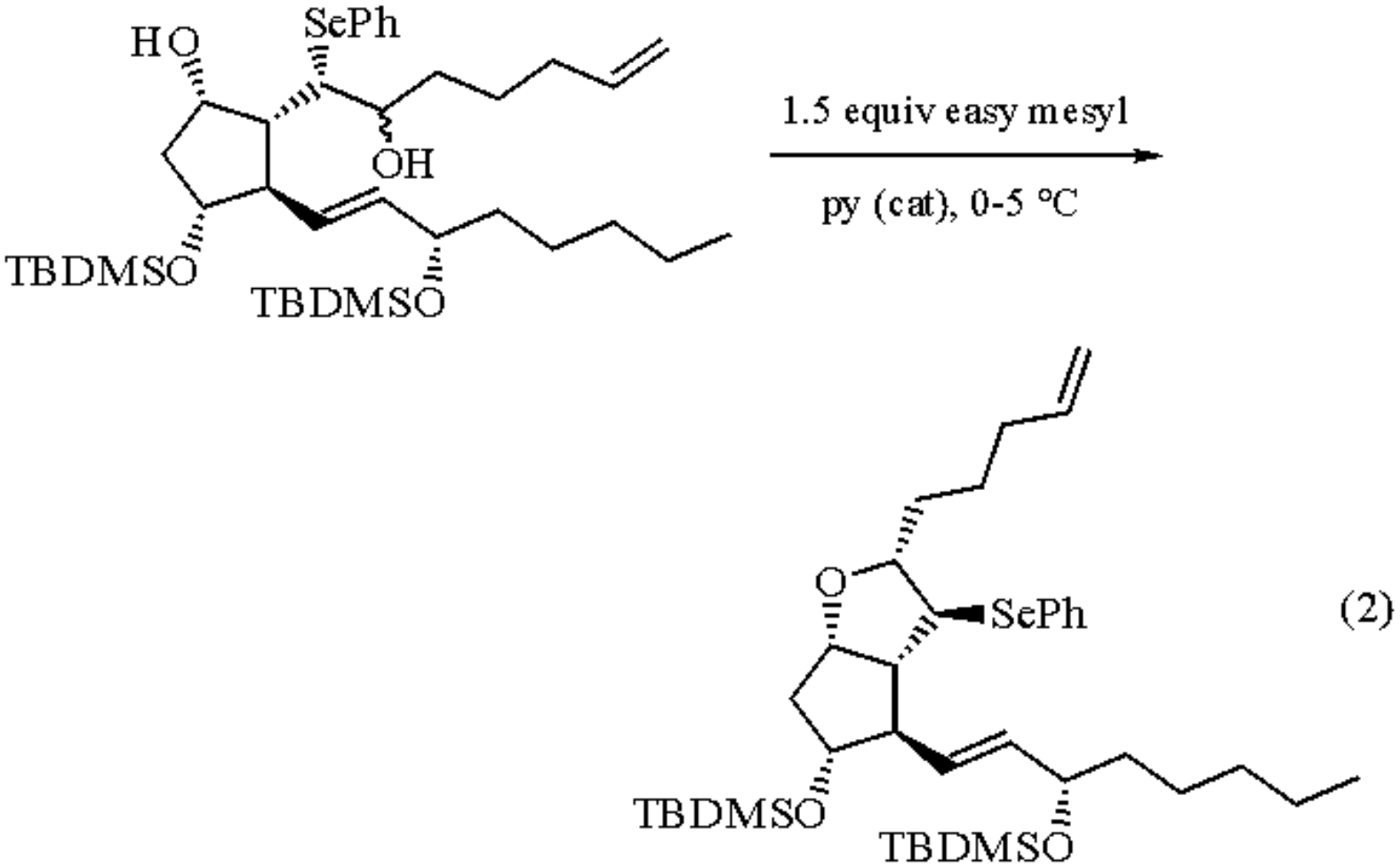

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1. Fieser, M.; Fieser, L. F. *FF* **1977**, *6*, 190.
2. King, J. F.; du Manoir, J. R. *JACS* **1975**, *97*, 2566.
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Diethyl Methylsulfinylmethylphosphonate

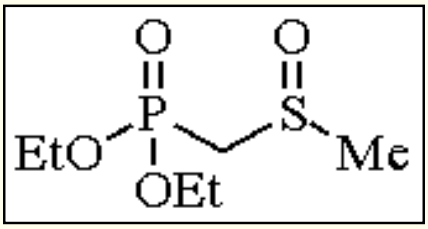

[50746-61-7] · $C_6H_{15}O_4PS$ · Diethyl Methylsulfinylmethylphosphonate · (MW 214.22)

(used for the preparation of vinyl sulfoxides and *O,S*-acetals of formyl phosphonates)

*Physical Data: n*20D = 1.4766;[1] disproportionates before boiling.

Solubility: sol acetone, CH_2Cl_2, MeOH, THF.

Preparative Methods: diethyl methylsulfinylmethylphosphonate can be obtained by controlled oxidation of ***Diethyl Methylthiomethylphosphonate***, as shown in eq 1.[1-4] The procedure using Br_2/aq. $NaHCO_3/CH_2Cl_2$ is notable because use of $H_2{}^{18}O$ allows for the preparation of ^{18}O sulfoxides.[2]

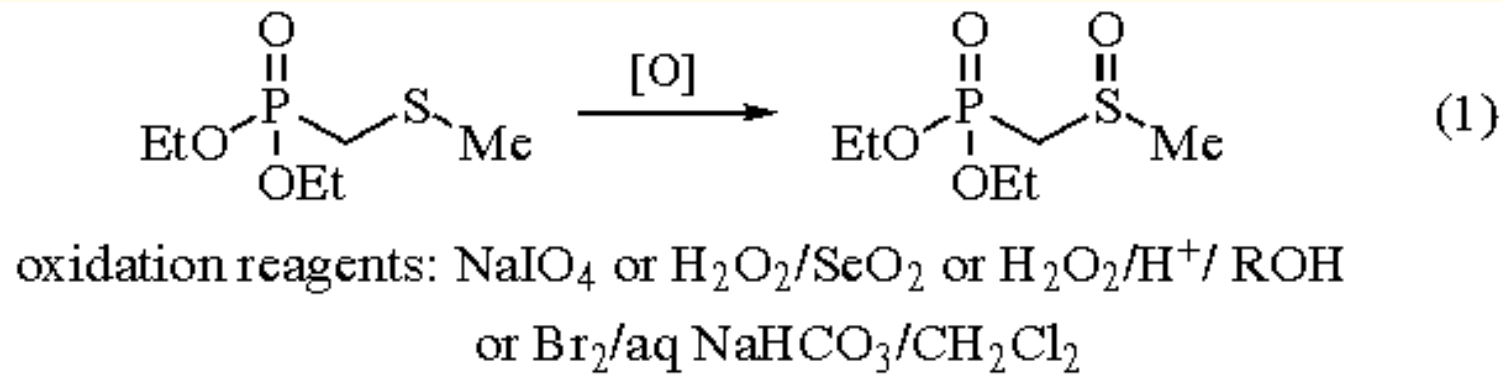

Handling, Storage, and Precautions: Diethyl methylsulfinylmethylphosphonate is reasonably stable for storage. Reactions involving this reagent are best conducted under anhydrous conditions, under nitrogen, in a well ventilated fume hood.

Reactions.

The sulfinylmethylphosphonate can be metalated with ***n-Butyllithium*** in THF and then reacted with a variety of aldehydes and ketones to form vinyl sulfoxides via the Horner-Emmons reaction (eq 2).[5] Alternatively, the reaction can be conducted under phase transfer conditions, and is then specific for aromatic aldehydes.[6] Initially a tetraalkylammonium salt was used as catalyst, but it was discovered that the phosphonate could function as its own phase transfer catalyst.[7] Subsequent reports showed that it can function generally as a phase transfer catalyst, for example in the alkylation of benzyl methyl ketone with butyl bromide.[8]

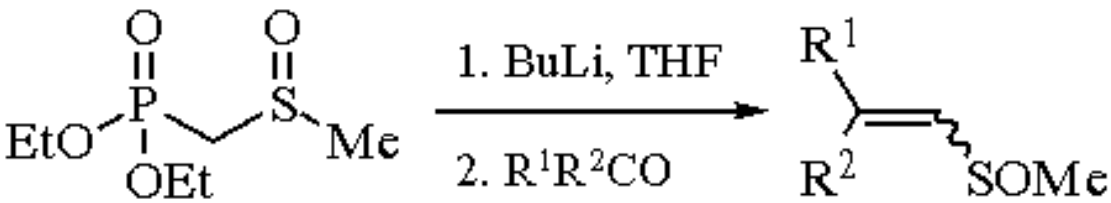

(2)

$R^1 = H$, $R^2 = Ph$, 70%, $(E):(Z) = 1:1$
$R^1 = R^2 = -(CH_2)_{4-6}$, 70-80%

Diethyl methylsulfinylmethylphosphonate undergoes the Pummerer reaction, resulting in oxidation of the α-carbon with concomitant reduction of the sulfoxide to a sulfide (eq 3).[9-12] Limited success in the transfer of chirality from sulfur to carbon has been achieved.[11]

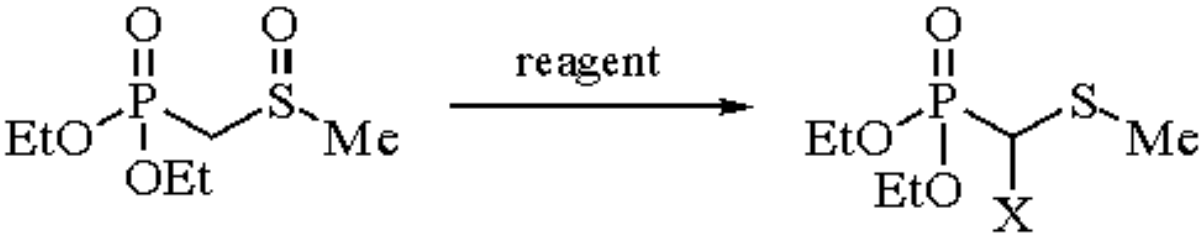

(3)

Reagent	X
I_2, ROH, R = Me, Et	OR
$(RCO)_2O$, R = Me, *t*-Bu, Ph, CF_3	OCOR
PhCOCl	Cl

If the Pummerer reaction is conducted in an aromatic solvent, Freidel-Craft products are produced (eq 4).[12,13] In a similar manner, treatment of Pummerer products with alkenes gives ene style products (eq 5).[14]

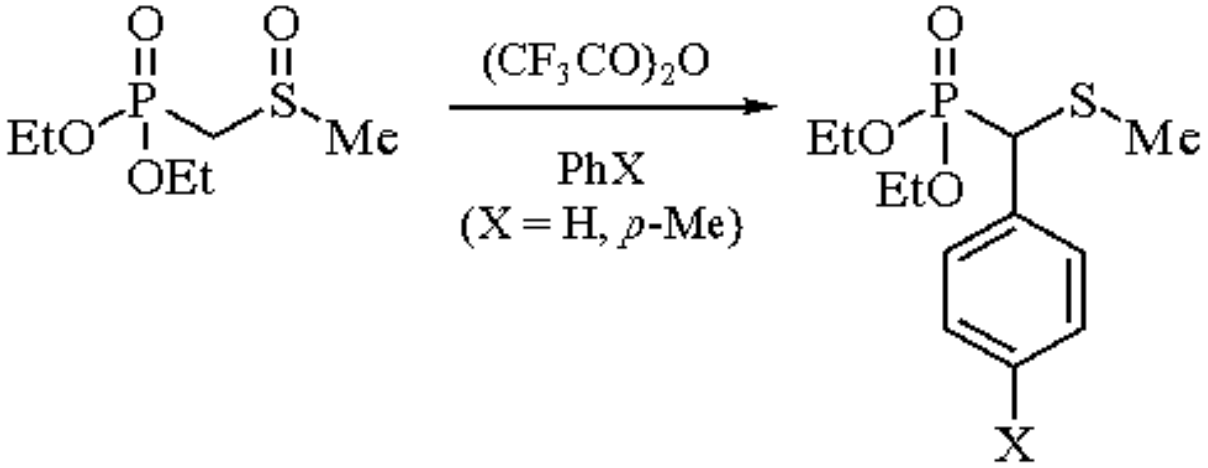

(4)

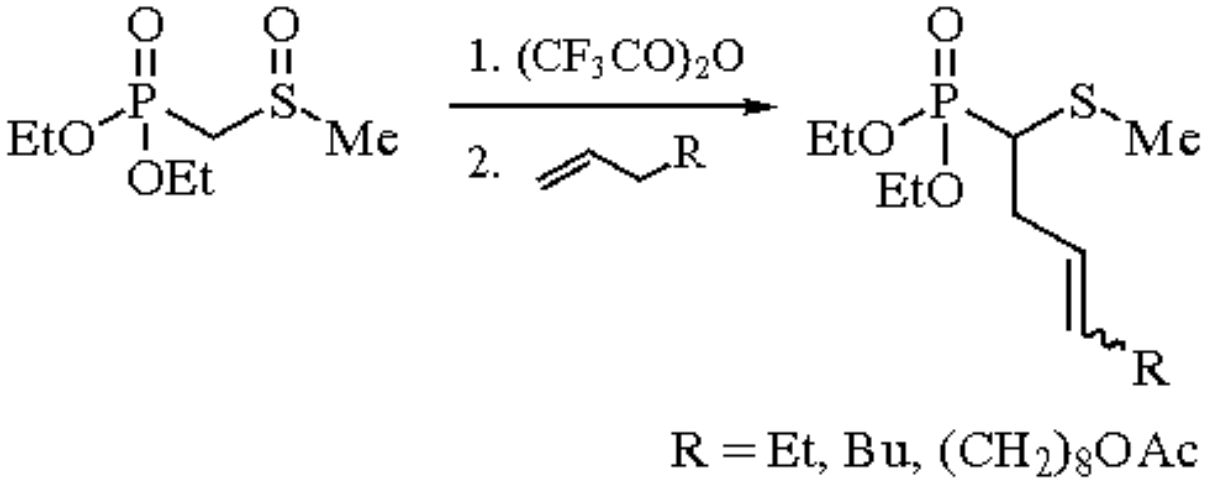

(5)

R = Et, Bu, $(CH_2)_8OAc$

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Diethyl Methylsulfonylmethylphosphonate

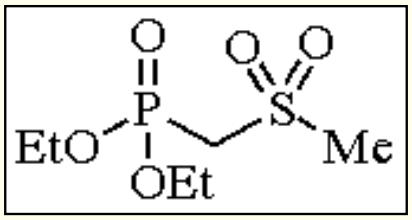

[40137-11-9] · $C_6H_{15}O_5PS$ · Diethyl Methylsulfonylmethylphosphonate · (MW 230.22)

(used for the preparation of synthetically versatile vinyl sulfones from aldehydes and ketones)

Physical Data: mp 96 °C.[1]

Solubility: sol acetone, CH_2Cl_2, DME, THF.

Preparative Methods: conveniently prepared by oxidation of ***Diethyl Methylthiomethylphosphonate*** (eq 1). Both inorganic oxidants (e.g. ***Potassium Permanganate*** in water[1,2] or ***Hydrogen Peroxide/Selenium(IV) Oxide***[4]) and organic oxidants (e.g. ***Peracetic Acid*** in ether[3] or ***m-Chloroperbenzoic Acid*** in CH_2Cl_2[5]) have been used to accomplish this transformation.

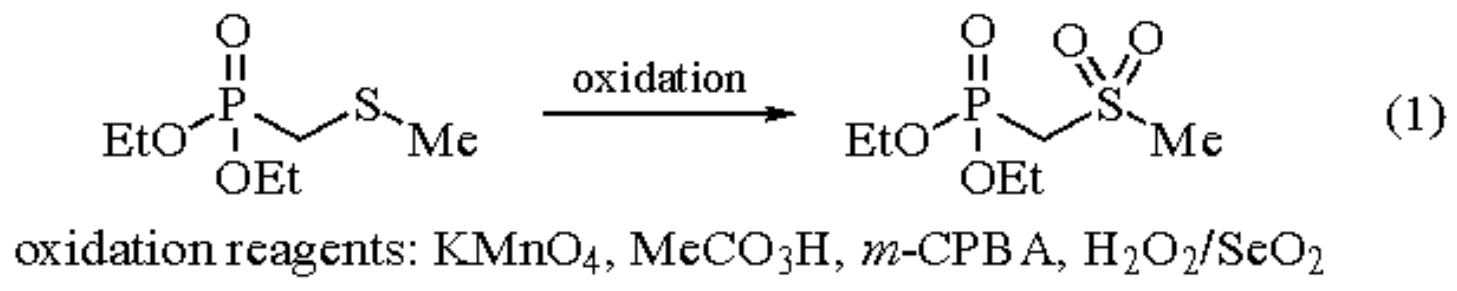

Handling, Storage, and Precautions: diethyl methylsulfonylmethylphosphonate is reasonably stable for storage. Reactions involving this reagent are best conducted under anhydrous conditions, under nitrogen, in a well ventilated fume hood.

Reactions.

Diethyl methylsulfonylmethylphosphonate has been extensively used for the preparation of synthetically useful vinyl sulfones from aldehydes and ketones via the Horner-Emmons reaction. This generally involves treatment of the phosphonate with a base (a wide variety of bases and solvents have been employed) followed by quenching with a carbonyl compound, resulting in the (often) stereoselective formation of vinyl sulfones.

Sodium Hydride, ***Sodium Methoxide***, or ***n-Butyllithium*** are commonly used to generate the phosphonate anion, which can be reacted with aryl and aliphatic aldehydes to give alkylidine sulfones (eq 2).[1-3] Enals,[6] ketones,[7] and heterocyclic aldehydes[8] also participate in this reaction, giving the corresponding vinyl sulfones.

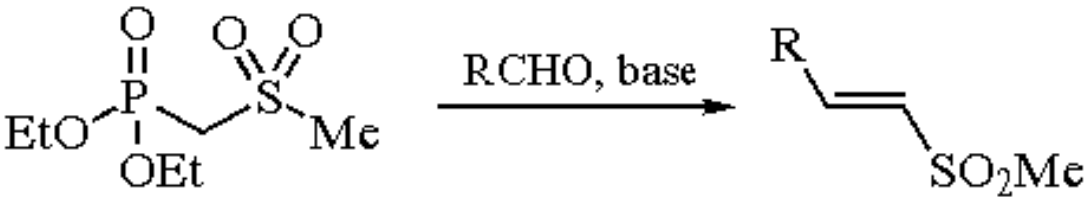

(2)

R = alkyl, aryl, heteroaryl, alkenyl
base = NaH, NaOMe, NaOEt, BuLi

Even the sterically hindered C-17β steroidal aldehyde reacts readily with the phosphonate anion to furnish the vinyl sulfone in excellent yield (eq 3).[8]

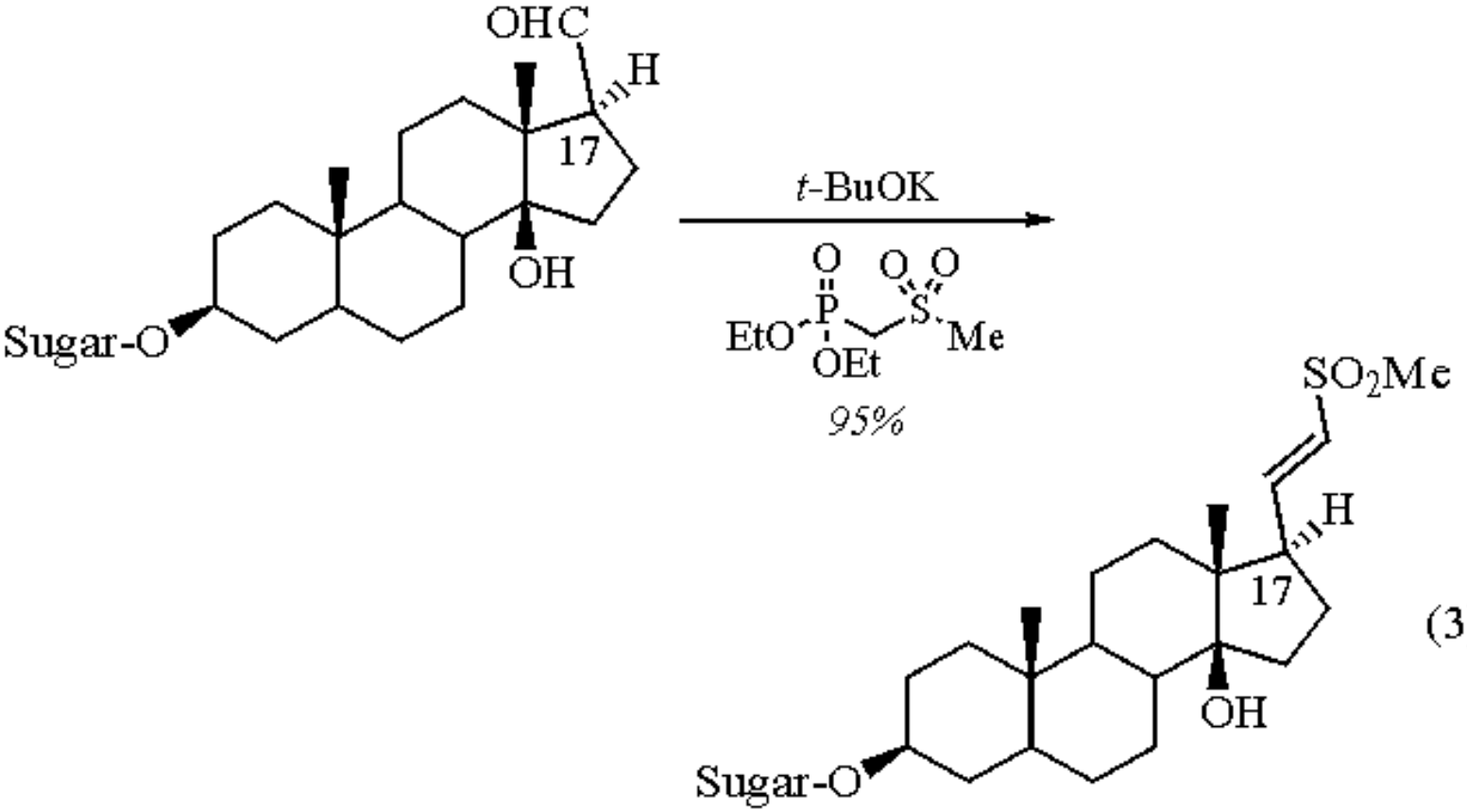

(3)

Mikolajczyk et al. have shown that the reaction can be carried out under phase transfer conditions, catalyzed by quaternary ammonium salts.[9] This reaction was found to be specific for aromatic aldehydes, and fails for enolizable aldehydes and ketones. Among the several quaternary ammonium salts investigated, ***Benzyltriethylammonium Chloride*** (TEBA) gave the best yields and was also totally stereoselective in that only (*E*)-sulfones were produced (eq 4).

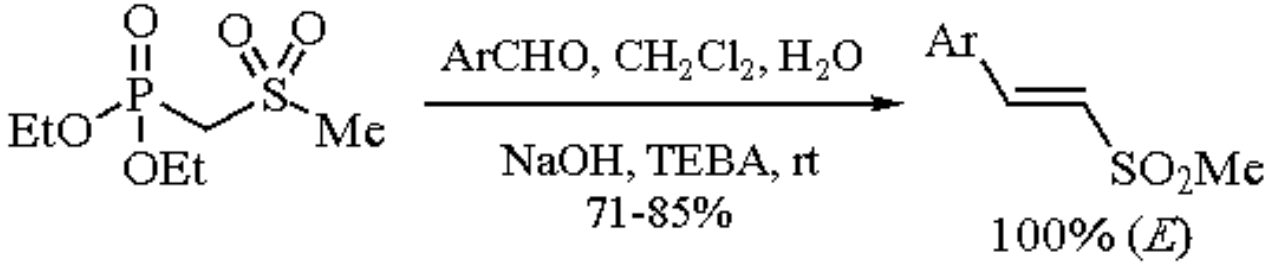

(4)

Reaction of diethyl methylsulfonylmethylphosphonate anion with enolizable ketones is often problematic and leads to unsatisfactory yields of vinyl sulfones. Fillion and co-workers have shown that the yields are improved when the reaction is conducted under sonication conditions (eq 5).[10]

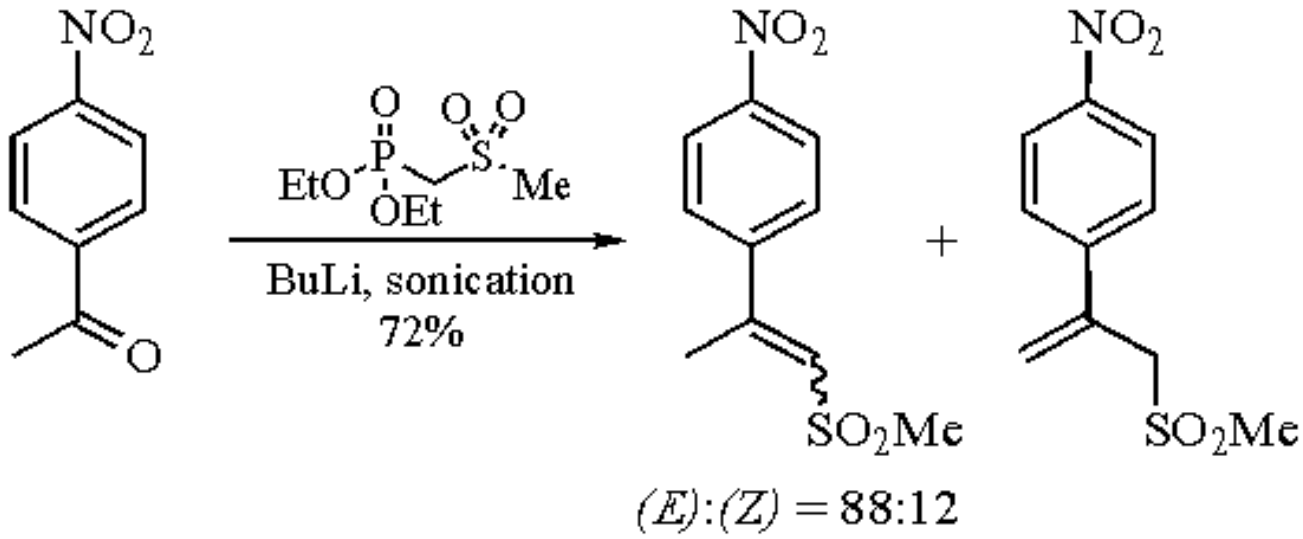

(5)

Certain ketones readily undergo the reaction, including the sensitive β-lactam dione shown in eq 6.[11]

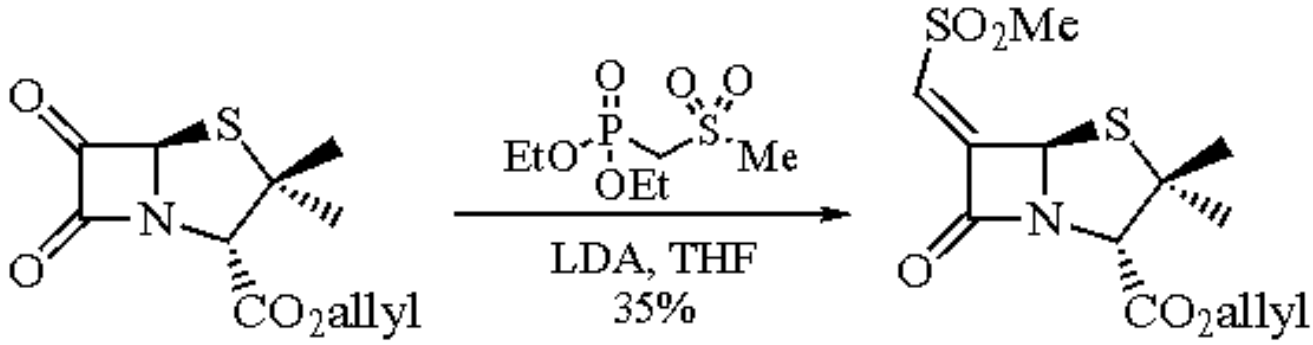

(6)

The direct synthesis of allenyl sulfones was simply accomplished by the reaction of the sulfonylphosphonate anion with ketenes (eq 7).[12] The yields of this reaction are also improved under sonication conditions.[13]

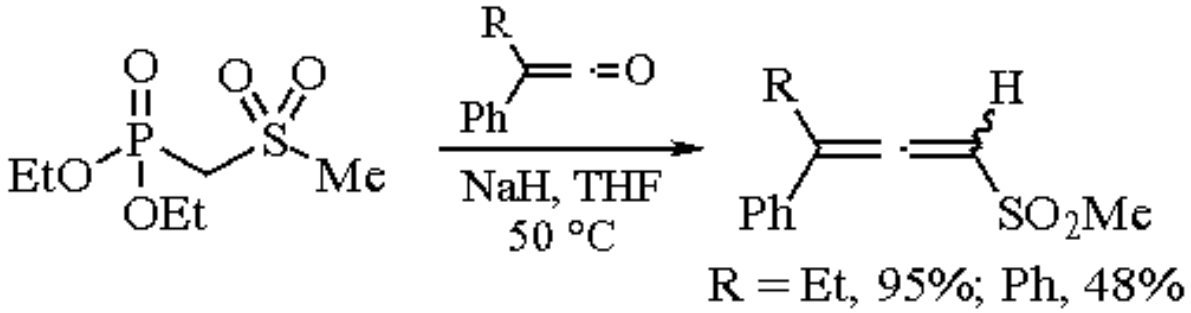

(7)

Minami et al. have shown that diethyl methylsulfonylmethylphosphonate readily undergoes the Knoevenagel reaction, resulting in the formation of 1,1-phosphonosulfonoalkenes.[14] A typical example is the condensation of the phosphonate with cinnamaldehyde in the presence of piperidine. The initially formed aldol eliminates water when treated with catalytic ***p-Toluenesulfonic Acid***, furnishing the (*E*,*E*)-isomer of 1,3-butadienylsulfonylphosphonate in excellent yield (eq 8).

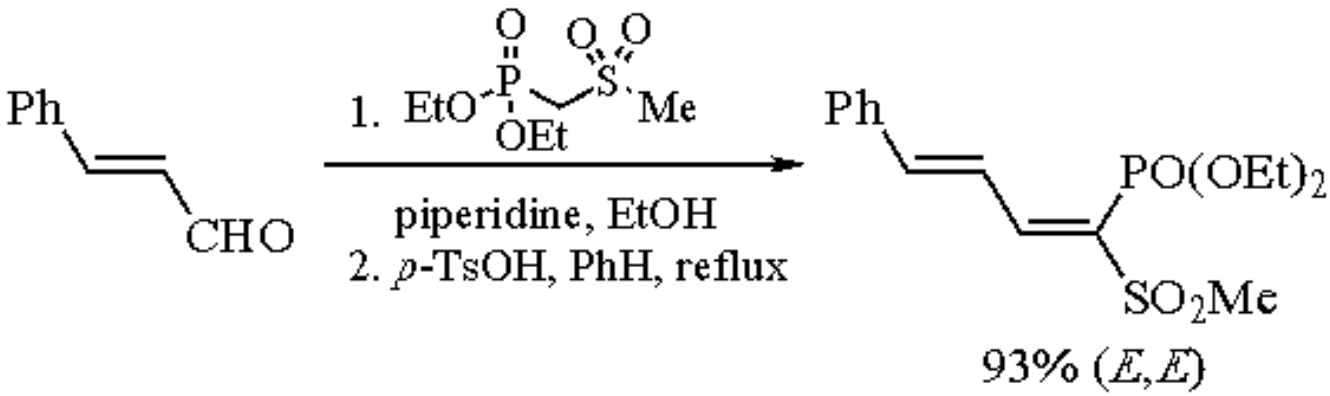

(8)

A similar sequence with formaldehyde constitutes an efficient synthesis of the simplest member of the family (eq 9).[15]

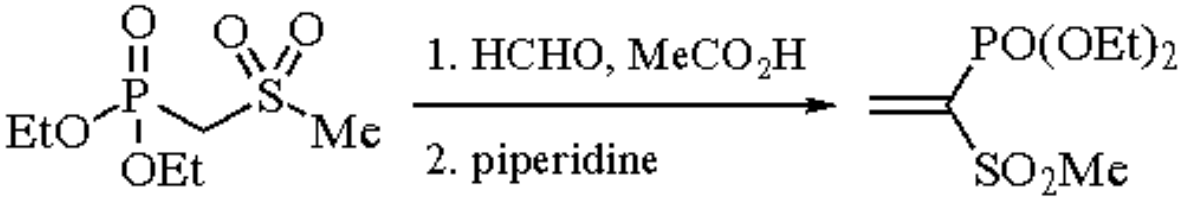

(9)

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Diethyl Methylthiomethylphosphonate

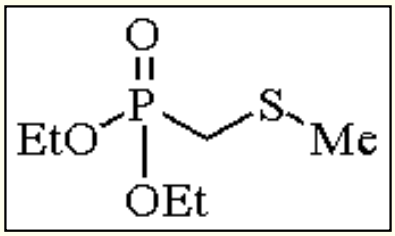

[28460-01-7] · $C_6H_{15}O_3PS$ · Diethyl Methylthiomethylphosphonate · (MW 198.22)

(used for the conversion of aldehydes and ketones to vinyl sulfides, which can be hydrolyzed to yield homologated aldehydes and ketones)

Physical Data: bp 70-72 °C/0.2 mmHg,[1] *d* 1.465 g cm^{-3}.[2]

Solubility: sol acetone, CH_2Cl_2, THF.

Form Supplied in: neat liquid.

Preparative Methods: although the reagent has recently become commercially available, a number of methods are available for its preparation.

The Arbuzov reaction between methylthiomethyl chloride and ***Triethyl Phosphite*** (no solvent, 110 °C for 6 h) gives good yields of diethyl methylthiomethylphosphonate (eq 1).[1,3]

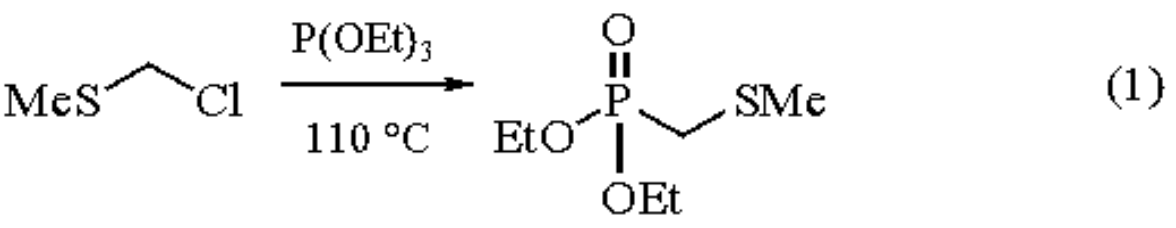

Another convenient preparation involves a nucleophilic displacement reaction between dialkyl chloromethylphosphonates and alkanethiolates (eq 2).[4]

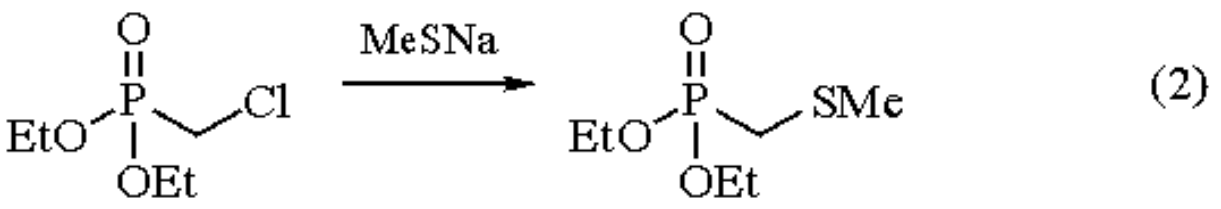

Metalated diethyl methylphosphonate reacts with elemental ***Sulfur*** to give isolable α-phosphorylthiols in high yields.[2] Alkylation with ***Iodomethane*** under phase transfer conditions gives the desired reagent (eq 3).

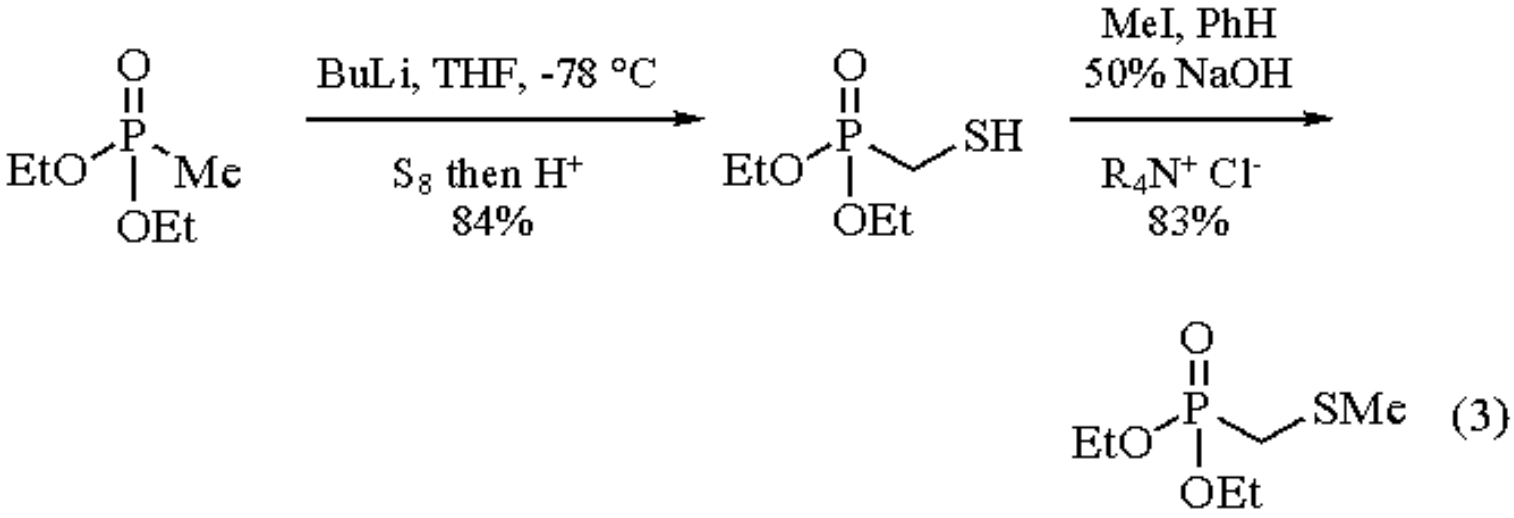

Handling, Storage, and Precautions: diethyl methylthiomethylphosphonate has a stench and is an irritant, but is reasonably stable for storage. Reactions involving this reagent are best conducted under anhydrous conditions, under nitrogen, in a well ventilated fume hood.

Reactions.

The chief utility of diethyl methylthiomethylphosphonate lies in the synthesis of vinyl sulfides from carbonyl compounds such as aldehydes or ketones via the Horner-Emmons reaction. These vinyl sulfides are stable, easily handled intermediates which upon hydrolysis furnish homologated aldehydes or ketones. Green initially showed that such a procedure was viable for the synthesis of homologous aldehydes.[1] Corey's more practical adaptation extended Green's original procedure to the synthesis of homologous ketones.[5] Thus diethyl methylthiomethylphosphonate can be metalated and alkylated with MeI to give diethyl (1-methylthio)ethylphosphonate, which can itself be metalated at -70 °C in THF with ***n-Butyllithium*** to give a lithio derivative which reacts with aldehydes or ketones. The initially formed adduct eliminates phosphonate to give vinyl sulfides (eq 4). It should be noted that the reaction often fails with readily enolizable ketones. The vinyl sulfides thus produced are easily hydrolyzed using ***Mercury(II) Chloride*** in aqueous acetonitrile to give good yields of homologated aldehydes and ketones.

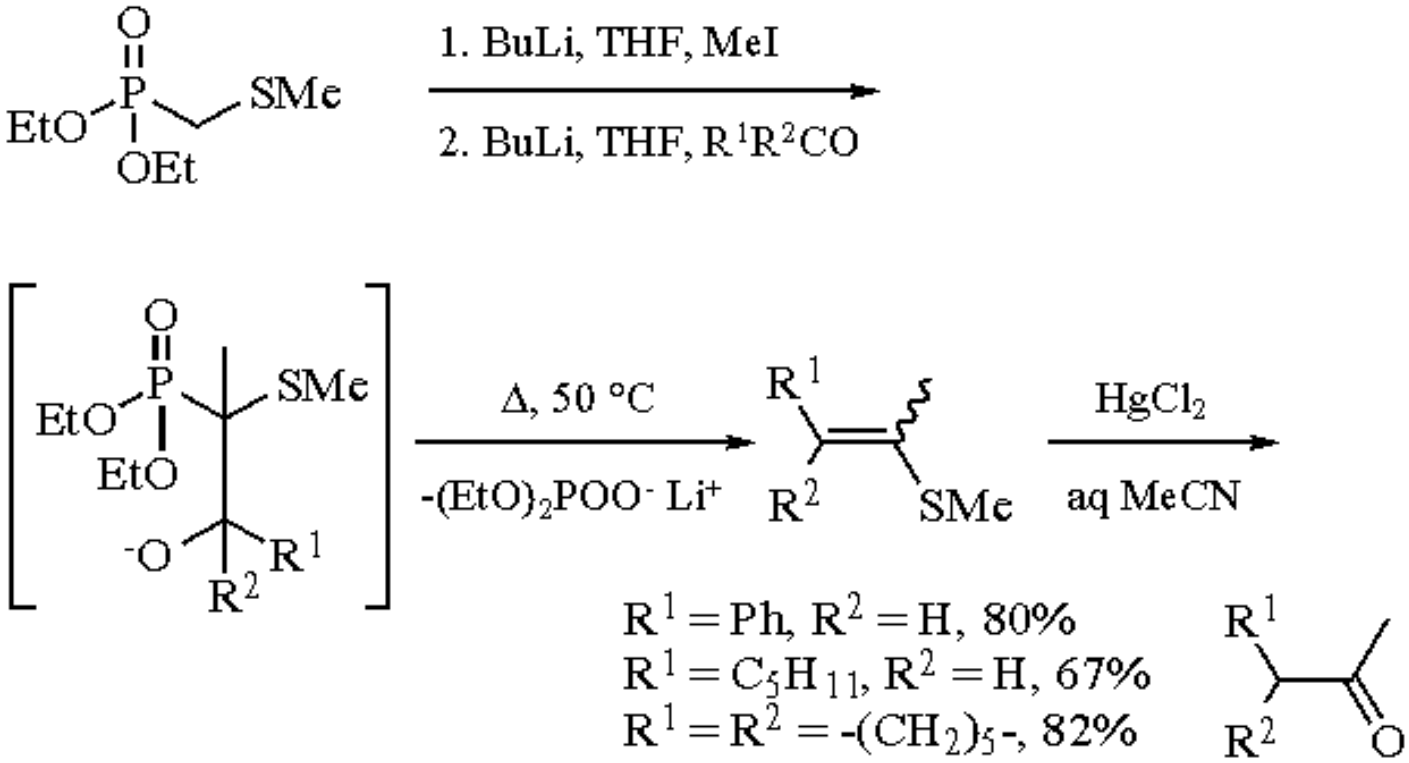

(4)

The reaction can be conducted so that water is lost instead of phosphonate, leading to the synthesis of phosphonovinyl sulfides.[6] Thus treatment of lithiated diethyl methylthiomethylphosphonate with benzaldehyde furnishes an adduct which can be isolated. Conversion of the hydroxy moiety to chloride followed by β-elimination gives phosphonovinyl sulfides. Phosphonovinyl sulfides can be oxidized to phosphonovinyl sulfoxides or sulfones, which are powerful Michael acceptors (eq 5).

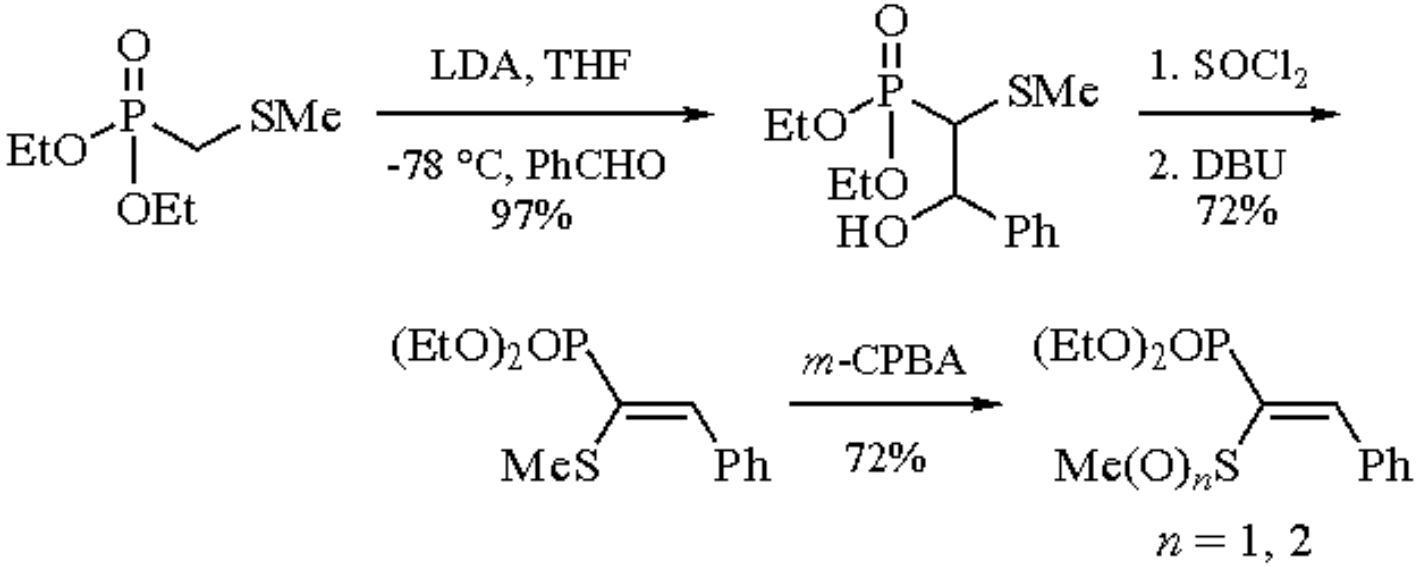

(5)

Lithiated diethyl methylthiomethylphosphonate can also react with ***Carbon Dioxide***, which upon acidification provides diethyl α-(methylthio)phosphonoacetic acid.[7] This bifunctional reagent can undergo inter- or intramolecular Horner-Emmons reactions, furnishing α-methylthio-α,β-unsaturated carboxylic acids or γ- and δ-lactones (eq 6).

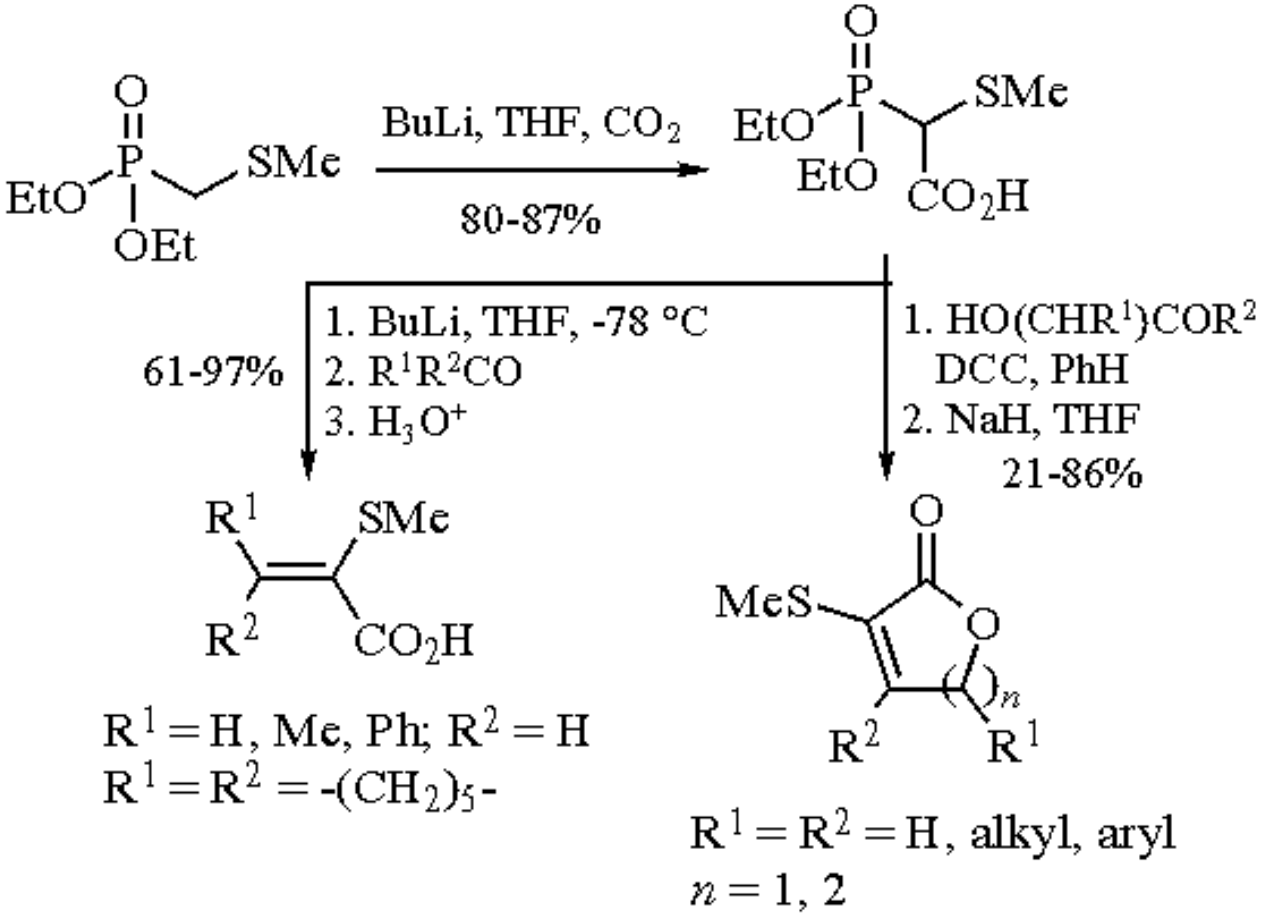

(6)

The reaction of lithiated diethyl methylthiomethylphosphonate with ketones has achieved only limited success. For example, reaction with a β-lactam dione stops at the stage of addition (eq 7) and, unlike lithiated ***Diethyl Methylsulfonylmethylphosphonate***, does not eliminate to give the corresponding vinyl sulfide.[8]

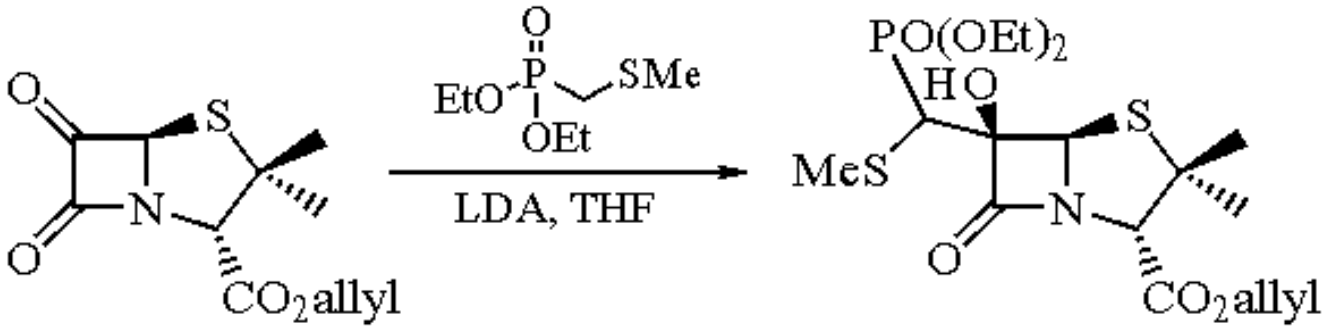

(7)

Mikolajczyk et al. examined the reaction between lithiated diethyl methylthiomethylphosphonate and an α,β-unsaturated ketone and found that the initially formed 1,2-addition product does not eliminate phosphonate, but rearranges to the more stable 1,4-addition product (eq 8).[9] The detailed mechanism of this rerrangement has not been investigated.

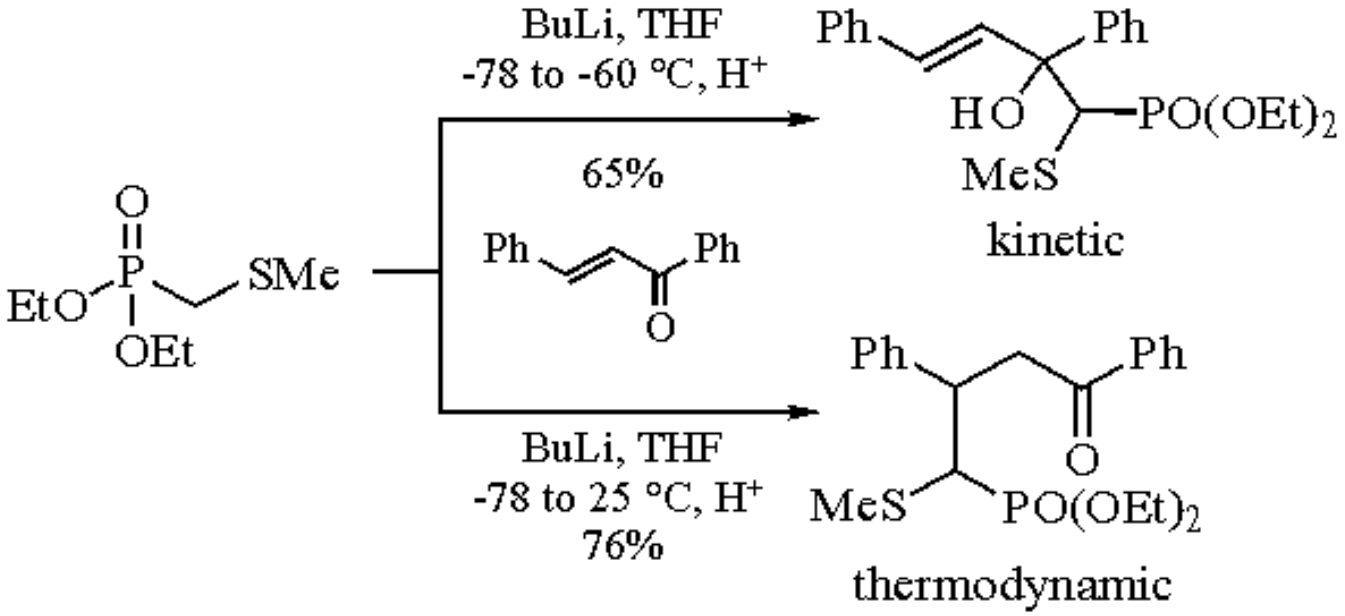

(8)

Lithiated diethyl methylthiomethylphosphonate can react with a wide variety of electrophiles to furnish a variety of α-substituted derivatives which are otherwise difficult to obtain. For example, reaction of lithiated diethyl methylthiomethylphosphonate with dialkyl disulfides to give *S*,*S*-acetals proceeds in good yields (eq 9).[10] Similarly, reaction with ***Chlorotrimethylsilane*** gives diethyl methylthio(trimethylsilyl)methylphosphonate, which after metalation undergoes a highly stereoselective Peterson alkenation with aldehydes to give (*E*)-vinylphosphonates in good yields (eq 9).[11] Zwanenberg and co-workers demonstrated that the isolation of the moisture sensitive diethyl methylthio(trimethylsilyl)methylphosphonate was not necessary in certain cases, and in one pot lithiated and treated with ***Sulfur Dioxide*** to produce very reactive sulfines (eq 10).[12]

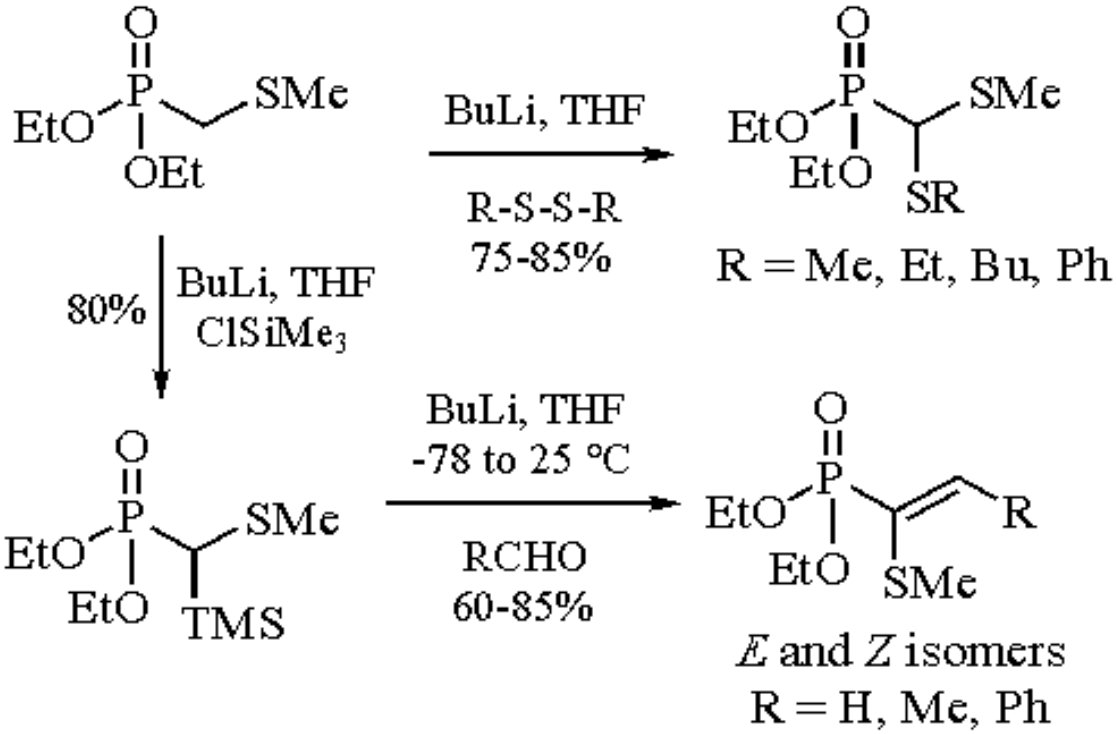

(9)

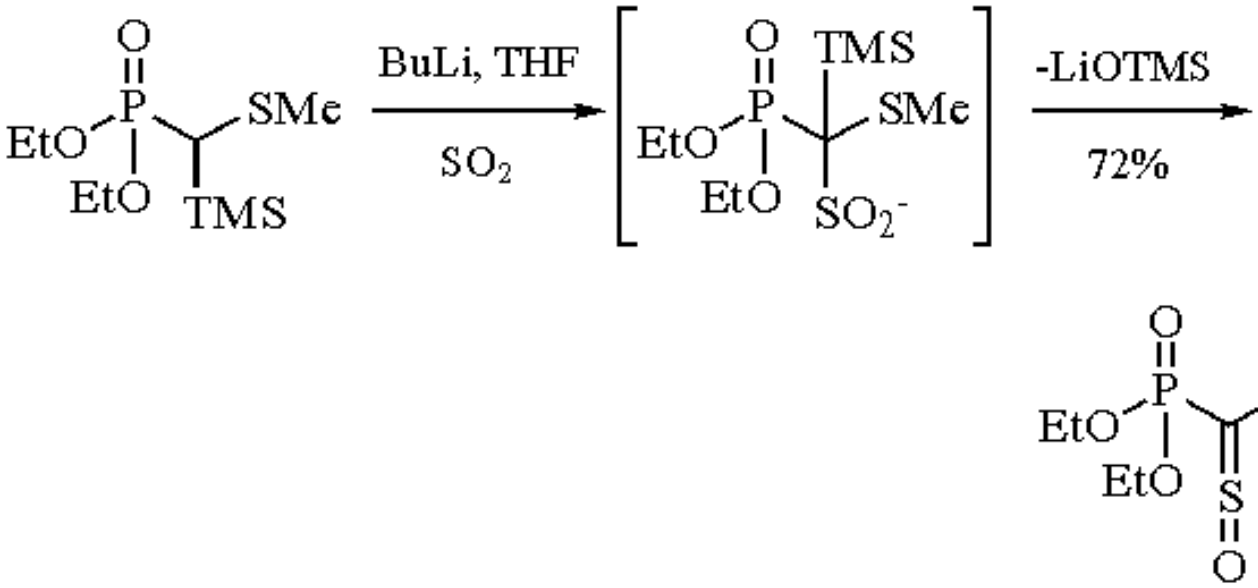

(10)

The sulfur atom in diethyl methylthiomethylphosphonate can be easily oxidized to either the sulfoxide or the sulfone, depending upon the choice of oxidant.[13] Other more unconventional oxidations of diethyl methylthiomethylphosphonate include facile anodic oxidation in NaOMe/MeOH (saturated with CO_2) to give the *O*,*S*-acetal of diethoxyphosphinylformaldehyde (eq 11).[14]

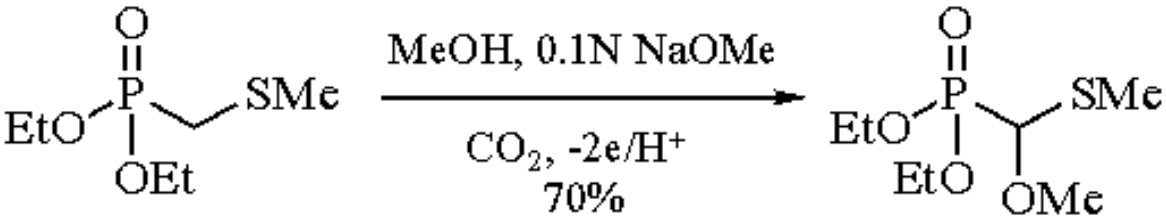

(11)

α-Chlorination of diethyl methylthiomethylphosphonate has been accomplished by lithiation followed by reaction with ***N-Chlorosuccinimide*** (NCS) as shown in eq 12.[15] The diethyl chloro(methylthio)methylphosphonate so obtained undergoes a facile Friedel-Crafts reaction with aromatic compounds, giving diethyl 1-arylmethylthiomethylphosphonates in excellent yields.

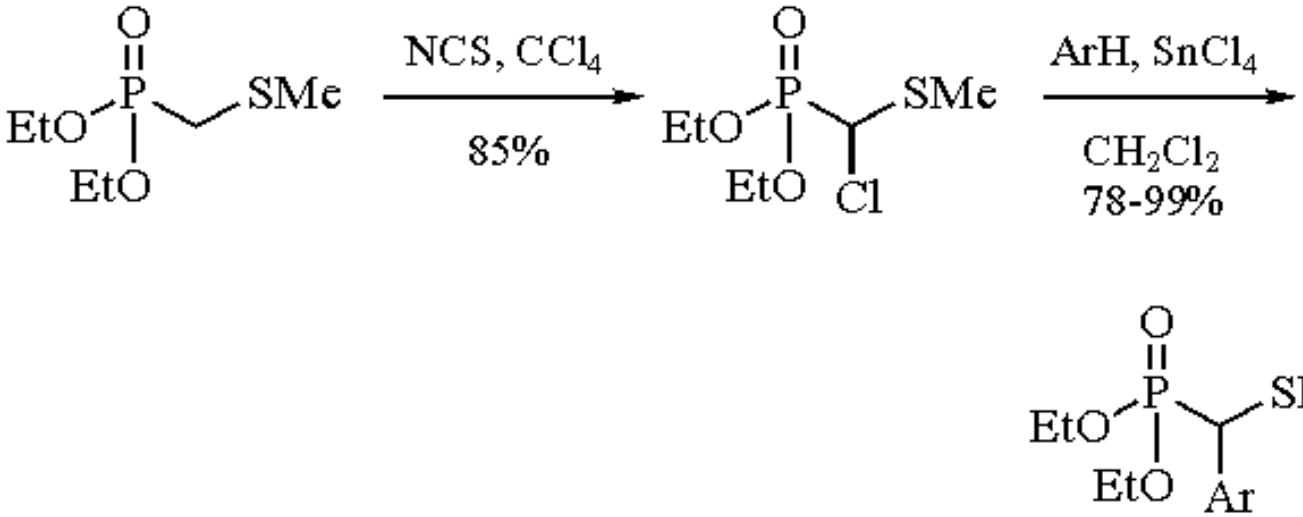

(12)

Kondo et al. have prepared sulfur ylides from diethyl methylthiomethylphosphonate by reaction with MeI/$AgClO_4$ to give a

sulfonium salt, which when treated with ***Sodium Hydride*** gave an ylide (eq 13).[16] The ylide reacts with benzaldehyde to give vinylidene sulfonium salts.

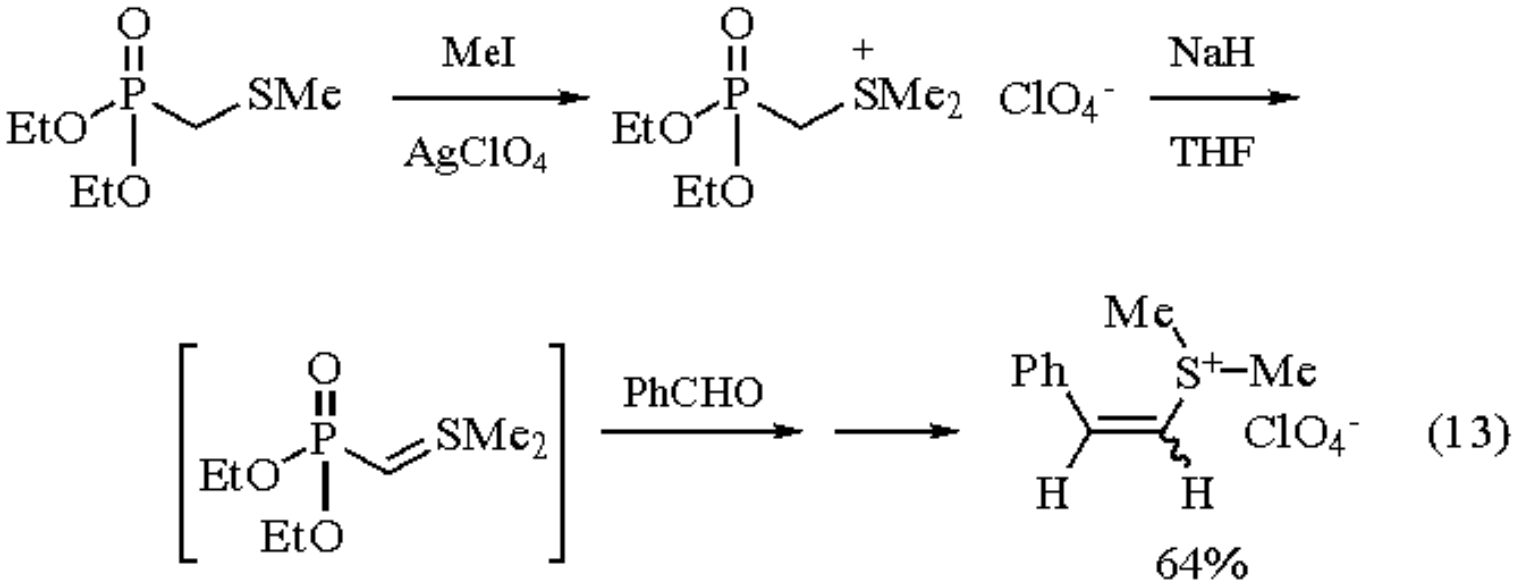

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Diethyl Morpholinomethylphosphonate

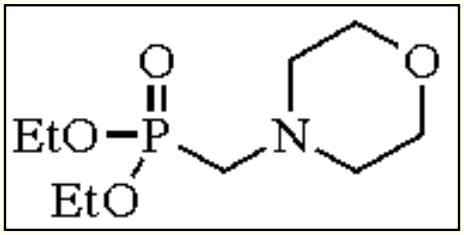

[27353-29-3] · $C_9H_{20}NO_4P$ · Diethyl Morpholinomethylphosphonate · (MW 237.24)

(for spiroannulation at carbonyl centers;[2] formyl anion equivalent[3])

Physical Data: bp 137 °C/3 mmHg.

Solubility: sol most organic solvents.

Analysis of Reagent Purity: readily ascertained by NMR.

Preparative Method: by the addition of ***Formaldehyde*** to a stirred mixture of equimolar quantities of ***Morpholine*** and ***Diethyl Phosphonite***. Vacuum distillation affords pure product in 92% yield.[1]

Purification: distillation at reduced pressure.

Amino Phosphonic Acid Esters.

During investigations on the synthesis of substituted α-amino phosphonic esters, the title compound (**3**) was obtained in high yield, exemplifying the generality of the synthetic route presented for the preparation of α-aminophosphonates (eq 1).[1]

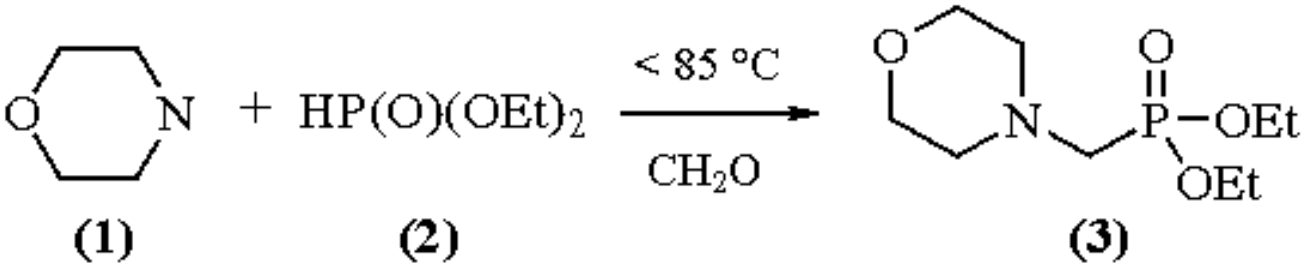

(1)

Quaternary Carbon Formation.

The utility of (**3**) for quaternization by geminal alkylation at a carbonyl center has been demonstrated.[2] Anion formation and Horner-Emmons reaction with a ketone afforded the morpholine enamine of the homologous aldehyde (eq 2), which was shown to undergo Michael addition to methyl vinyl ketone. Subsequent acid hydrolysis of the resultant imine was accompanied by intramolecular aldol condensation and dehydration, thereby resulting in the formation of 4,4-disubstituted 2-cyclohexenones (eq 3).

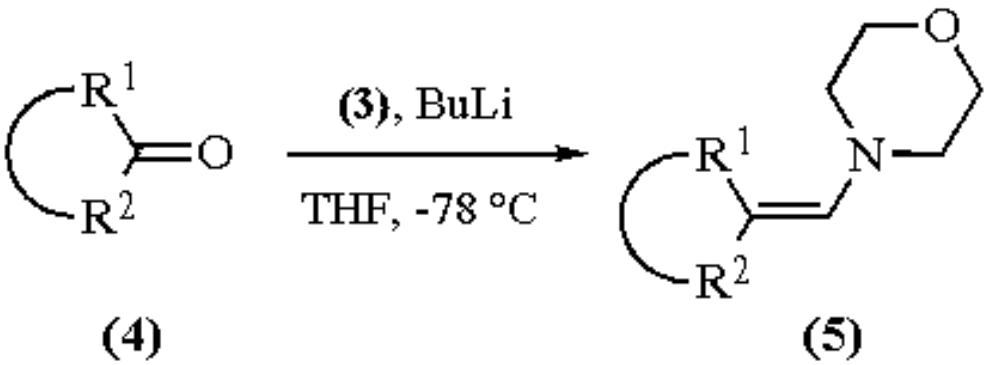

(2)

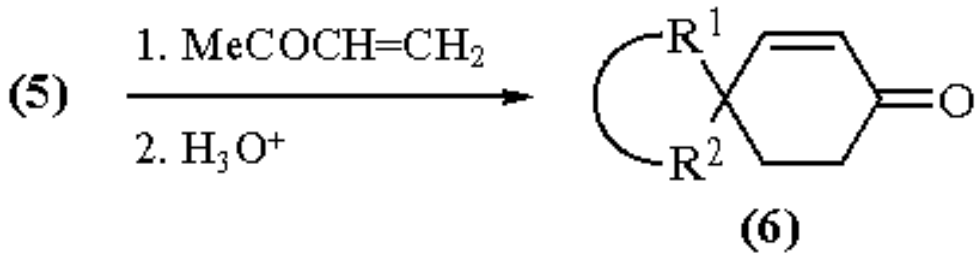

(3)

This procedure was shown to be applicable to acyclic, cyclic, aromatic, and α,β-unsaturated ketones. Use of cyclic ketones illustrated the facile production of spirocyclic ring systems. For substrates possessing conformational constraints, a reasonable degree of stereoselectivity was observed (eq 4).

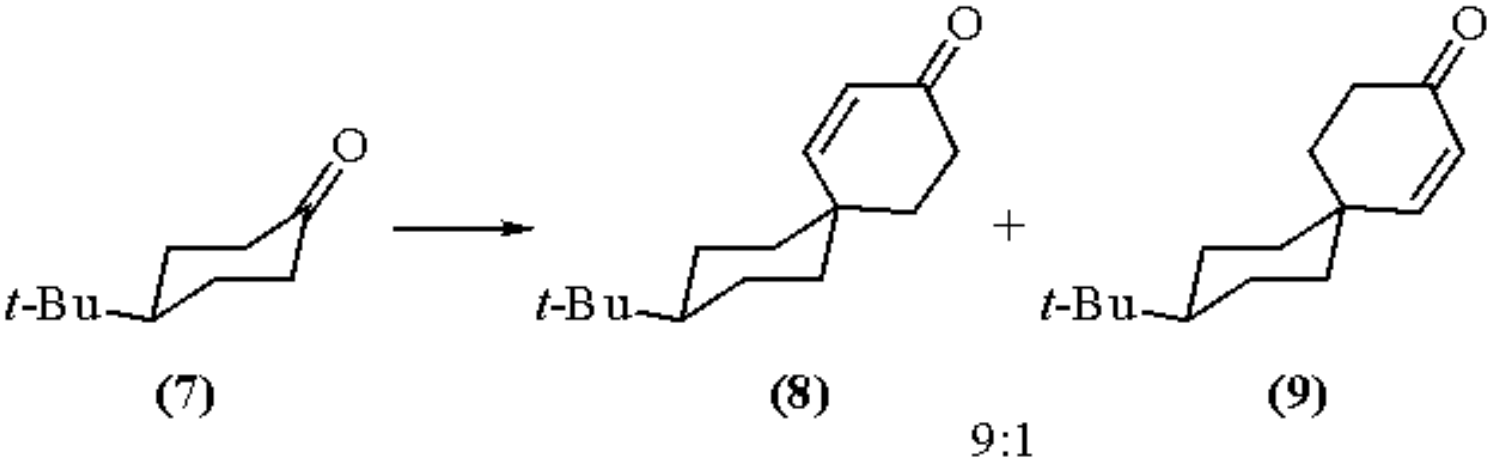

(4)

Enamine Synthesis.

Other investigations on enamine synthesis using reagent (**3**) provided an interesting but conflicting result.[3] Addition of the phosphonate anion of (**3**) to a carbonyl substrate resulted only in isolation of the α-morpholino-β-hydroxyphosphonate addition product (**10**) (eq 5). Elimination to form the enamine could not be induced even upon

treatment of (**10**) with KH. On this basis the authors suggested that the mechanism of the reaction may not be as straightforward as originally thought.

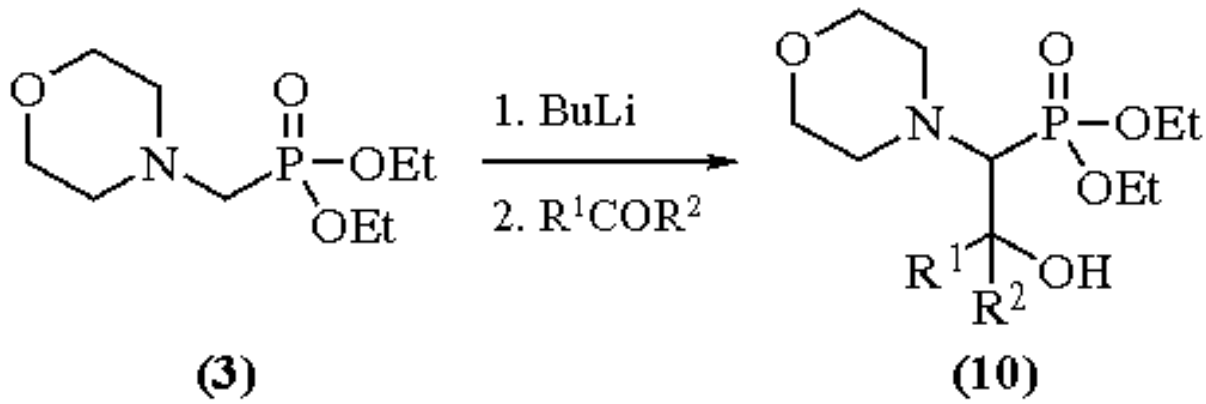

(5)

Miscellaneous.

An attempt at using the morpholinophosphonate in the preparation of sulfides by displacement of the diethyl phosphinate moiety with a thiolate anion resulted instead in the mono-dealkylation of the reagent (eq 6).[4]

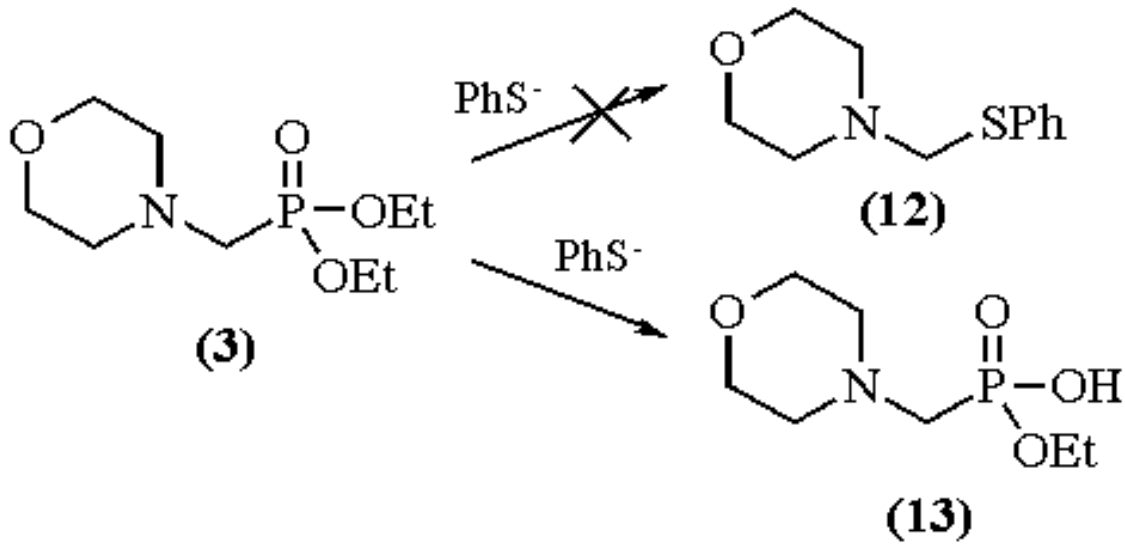

(6)

Oxidation of (**3**) with excess mercury(II) ion afforded the corresponding lactam but only in 7% yield (eq 7).[5] Based on literature precedent and experimental investigations, the transformation was proposed to occur via an intermediate iminium ion with internal participation of the phosphonate oxygen.[5]

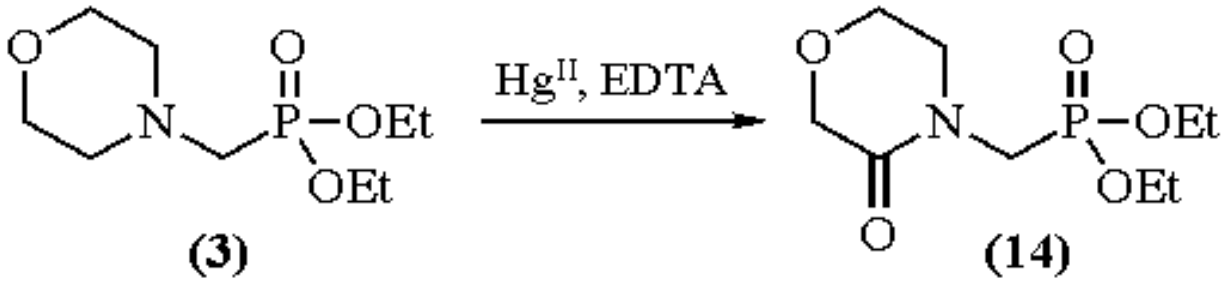

(7)

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Diethyl Oxalate

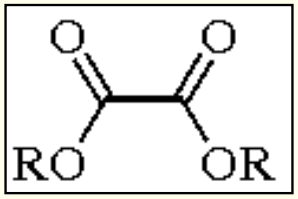

(**1**; R = Et)

[95-92-1] · $C_6H_{10}O_4$ · Diethyl Oxalate · (MW 146.14) (**2**; R = Me)

[553-90-2] · $C_4H_6O_4$ · Dimethyl Oxalate · (MW 118.09) (**3**; R = Pr)

[615-98-5] · $C_8H_{14}O_4$ · Dipropyl Oxalate · (MW 174.20) (**4**; R = Bu)

[2050-60-4] · $C_{10}H_{18}O_4$ · Dibutyl Oxalate · (MW 202.25) (**5**; R = *t*-Bu)

[691-64-5] · $C_{10}H_{18}O_4$ · Di-*t*-butyl Oxalate · (MW 202.25) (**6**; R = CH_2CH_2Cl)

[7208-92-6] · $C_6H_8Cl_2O_4$ · Bis(2-chloroethyl) Oxalate · (MW 215.03) (**7**; R = $CH_2CH{=}CH_2$)

[615-99-6] · $C_8H_{10}O_4$ · Diallyl Oxalate · (MW 170.16) (**8**; R = CH_2C&tbond;CH)

[71573-77-8] · $C_8H_6O_4$ · Di-2-propynyl Oxalate · (MW 166.13) (**9**; R = CH_2Ph)

[7579-36-4] · $C_{16}H_{14}O_4$ · Dibenzyl Oxalate · (MW 270.28)

(one- or two-carbon electrophile in acylation,[1,2] two-carbon electrophile for heterocycle synthesis;[3] activating group for α-keto ester preparation;[4] activating group for regioselective alkylation;[5] activating group for diazo ketone preparation[6])

Physical Data: (**1**): mp -40 °C; bp 185 °C; *d* 1.077 g cm^{-3}. (**2**): mp 53.3 °C; bp 164 °C. (**3**): mp -44 °C; bp 212-217 °C; *d* 1.019 g cm^{-3}. (**4**): mp -30 °C; bp 242 °C; *d* 0.987 g cm^{-3}. (**5**): mp 71 °C. (**6**): mp 39-40 °C. (**7**): bp 215 °C; *d* 1.158 g cm^{-3}. (**8**): mp 97-98 °C. (**9**): mp 80 °C.

Solubility: completely sol ether, alcohol and acetone; slightly sol hot water. The solubility of dimethyl oxalate is similar, except that it is more soluble in water. The solubilities of the other esters are similar in organic solvents, but they are insoluble in water.

Form Supplied in: the diethyl and dimethyl esters are readily available commercially in ca. 98% purity.

Preparative Methods: dimethyl oxalate;[7] di-*t*-butyl oxalate;[8] others.[9]

Handling, Storage, and Precautions: diethyl oxalate is harmful if swallowed and is irritating to the eyes. Care should be taken not to inhale the vapor. It is sensitive to moisture. It should be disposed of by burning in an approved incinerator. Dimethyl oxalate has similar properties to the diethyl ester and is harmful by inhalation and through skin. It should be disposed of by burning in an approved incinerator. Little is known about the other esters, which have been much less used. These reagents should be handled in a fume hood.

Esters of Oxalic Acid.

The diethyl ester has been most commonly used in synthesis, but the methyl ester would appear to serve equally well. Other esters may have specific applications.[10]

Electrophile in Acylation Reactions.

Ketone enolates add to one ester group of diethyl oxalate with the loss of ethanol to give the α,γ-diketo ester. The diketo ester can be converted to the β-keto ester by pyrolytic loss of CO. Both steps are exemplified in the synthesis of pimelic acid (eq 1).[11] The α,γ-diketo ester is enantiotopically reduced by ***Baker's Yeast*** to give a diastereomeric mixture of α-hydroxy-γ-keto esters which on Clemmensen reduction gives the α-hydroxy ester as a single enantiomer (eq 1).[12] *Proteus vulgaris* reduces α-keto acids to the corresponding (*R*)-α-hydroxy acids.[13]

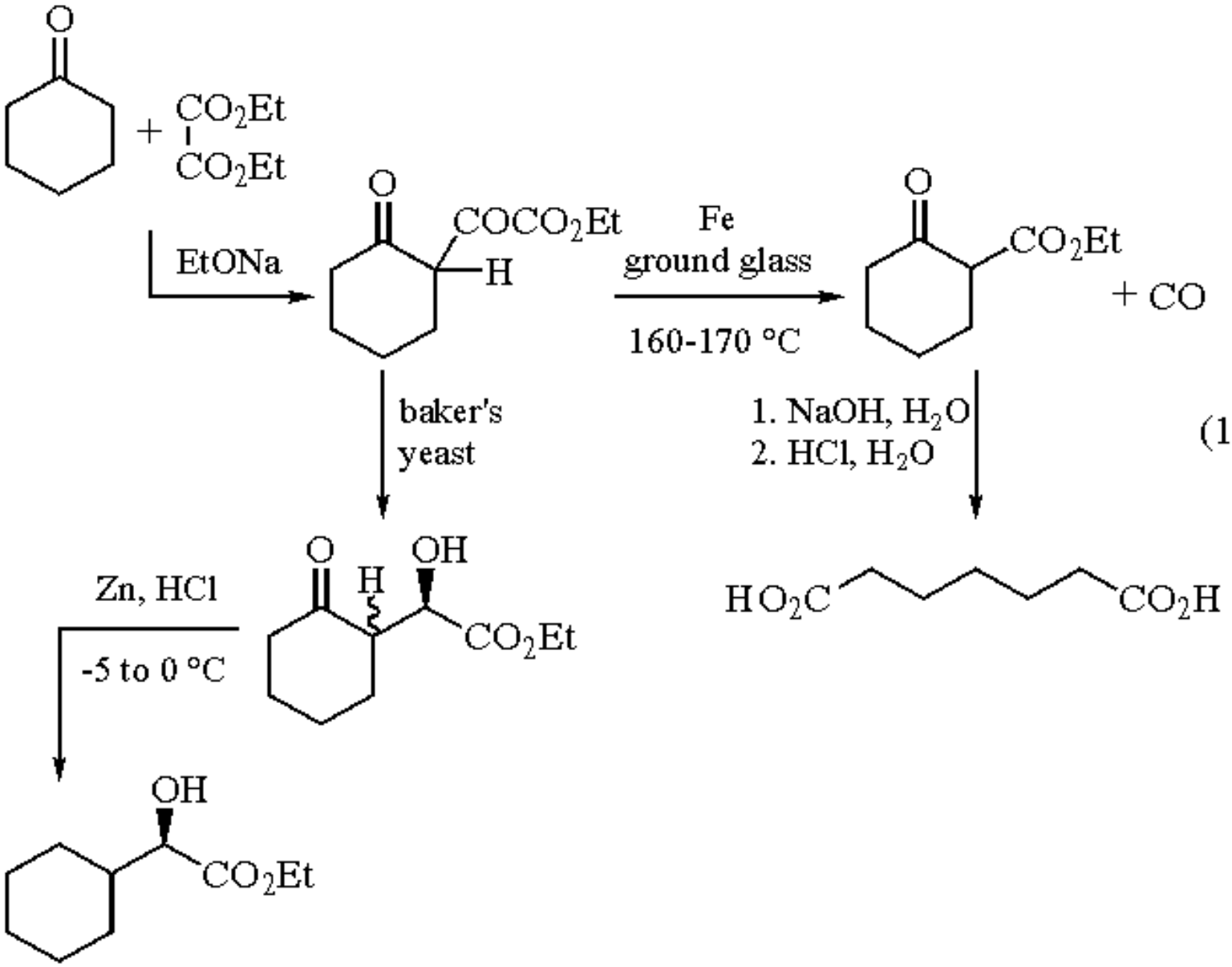

Diethyl oxalate acylates diethyl succinate in the presence of ***Sodium Ethoxide***, and the resulting triester can be hydrolyzed to α-ketoglutaric acid with the loss of CO_2 (eq 2).[14]

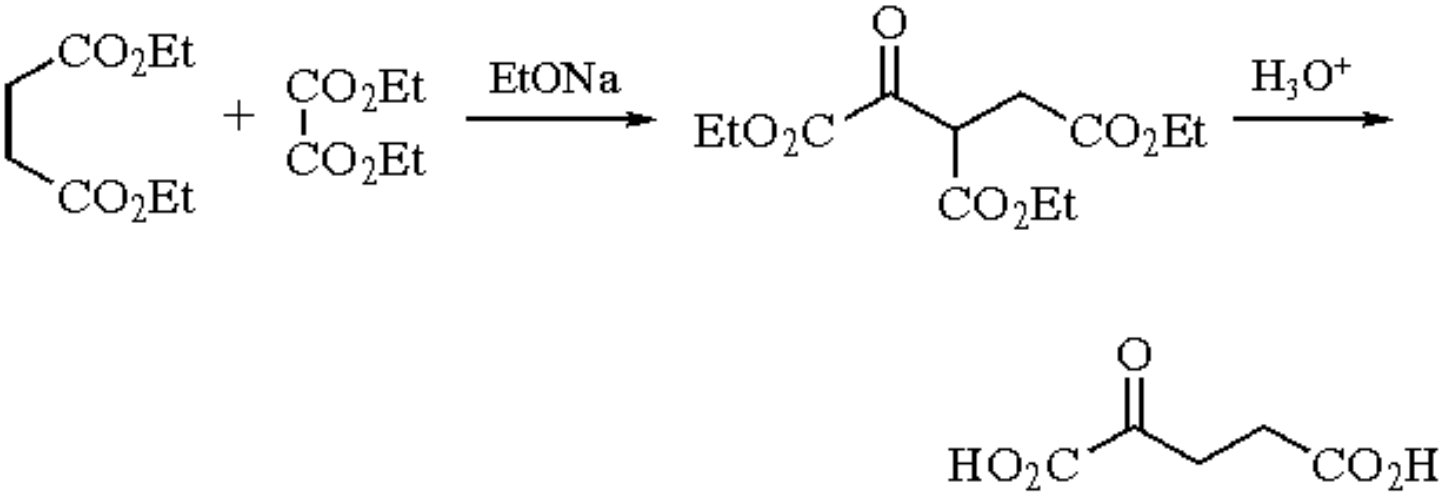

Dimethyl oxalate acylates 3-substituted dimethyl glutarates in the presence of ***Sodium Methoxide*** to give substituted cyclopentadienes (eq 3).[15] α,β-Unsaturated esters are acylated in the same way to give dimers. These are in equilibrium with the corresponding monomer and react with dimethyl malonate under basic conditions to give hydroxycyclopentenones (eq 4).[16]

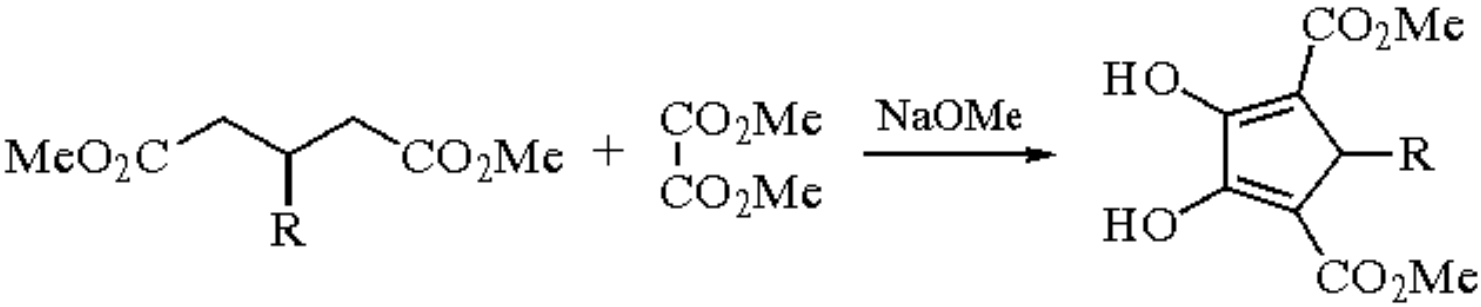

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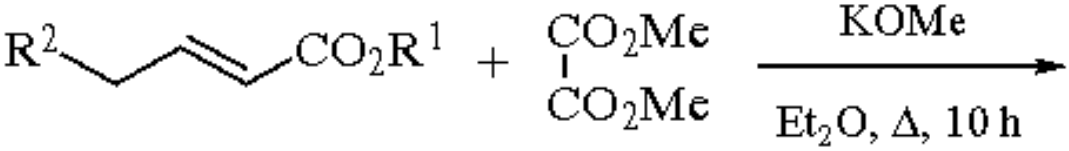

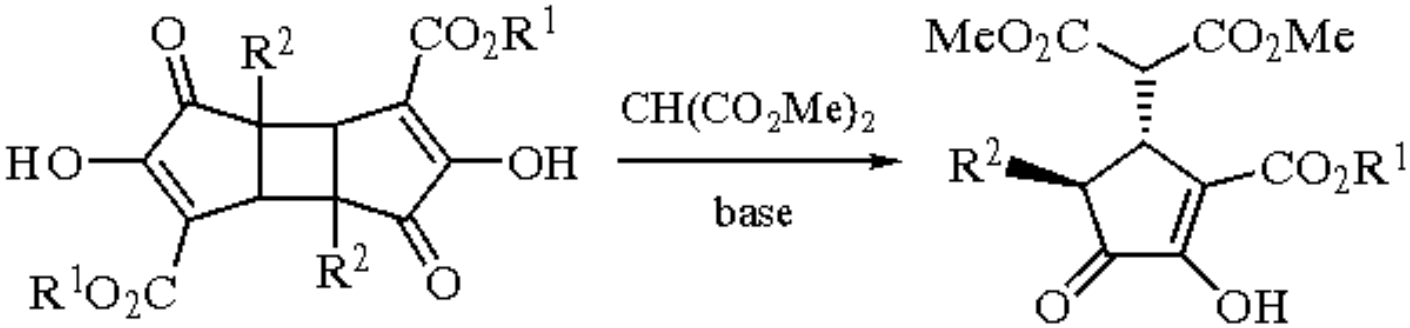

(4)

Organometallic reagents react with diethyl oxalate in THF to give α-keto esters,[17-19] usually in high yield (eq 5). The reaction was successful with a lithiated indole derivative (eq 6).[20]

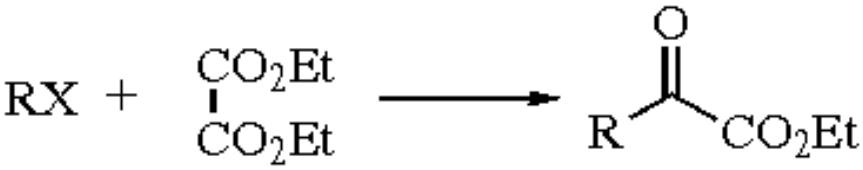

(5)

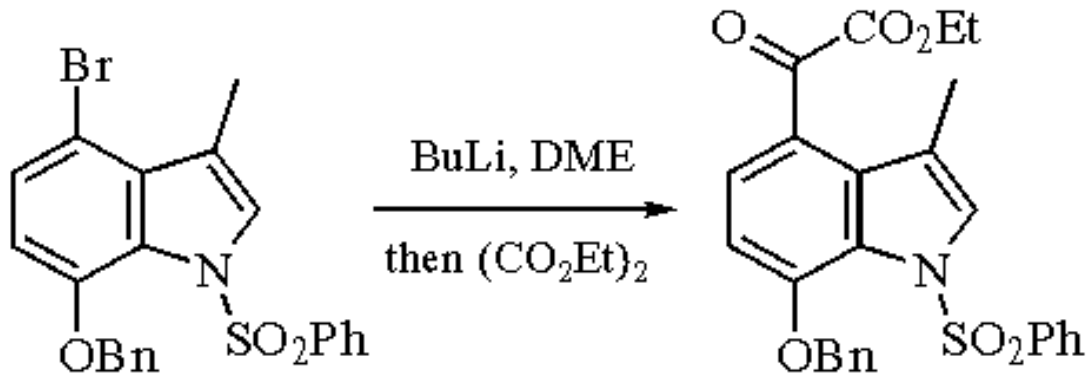

(6)

Rambaud and co-workers obtained a range of β,γ-unsaturated α-keto esters by modification of this method (eq 7).[10,13]

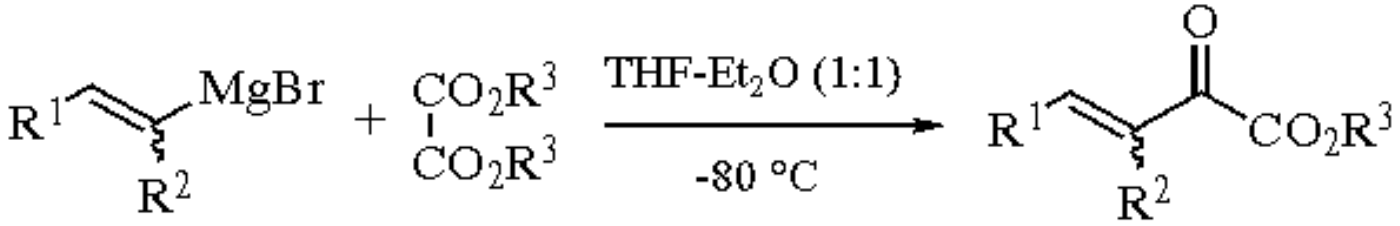

(7)

Benzyl chromium tricarbonyl complexes can be acylated with diethyl oxalate in the presence of ***Potassium t-Butoxide*** and the resulting potassium enolate can be hydrolyzed with water or trapped with ***t-Butyldimethylchlorosilane*** (eq 8).[21]

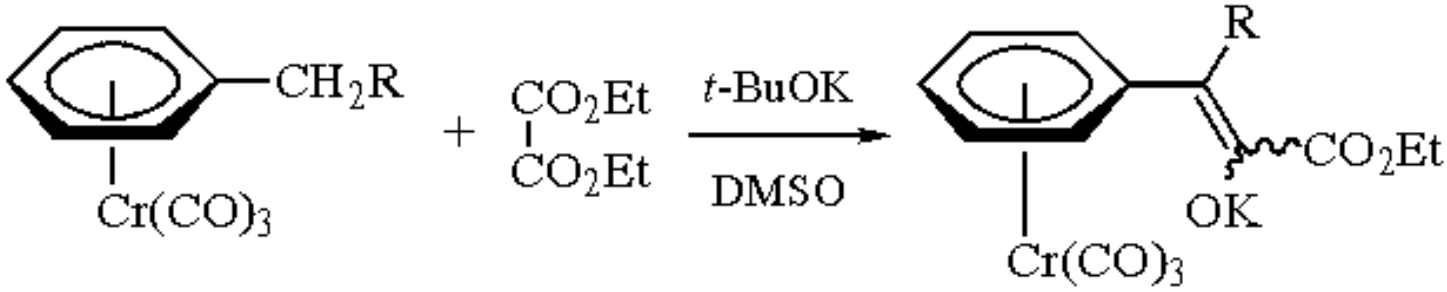

(8)

Preparation of Heterocycles.

Urea condenses with diethyl oxalate in the presence of sodium methoxide to give, after neutralization, parabanic acid (eq 9).[3]

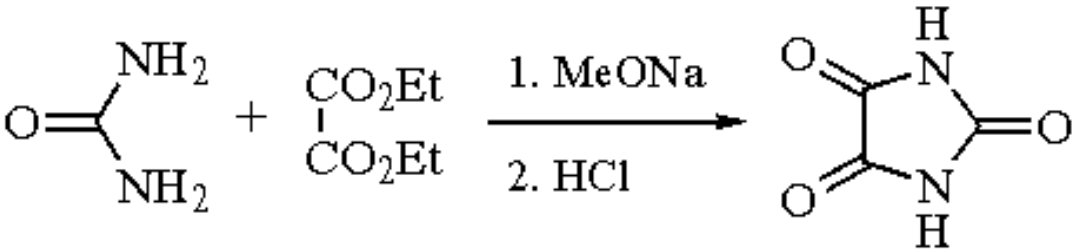

(9)

o-Nitrotoluene adds to diethyl oxalate in the presence of potassium ethoxide to give the enolate which on hydrogenation gives ethyl 2-indoylcarboxylate (eq 10).[22]

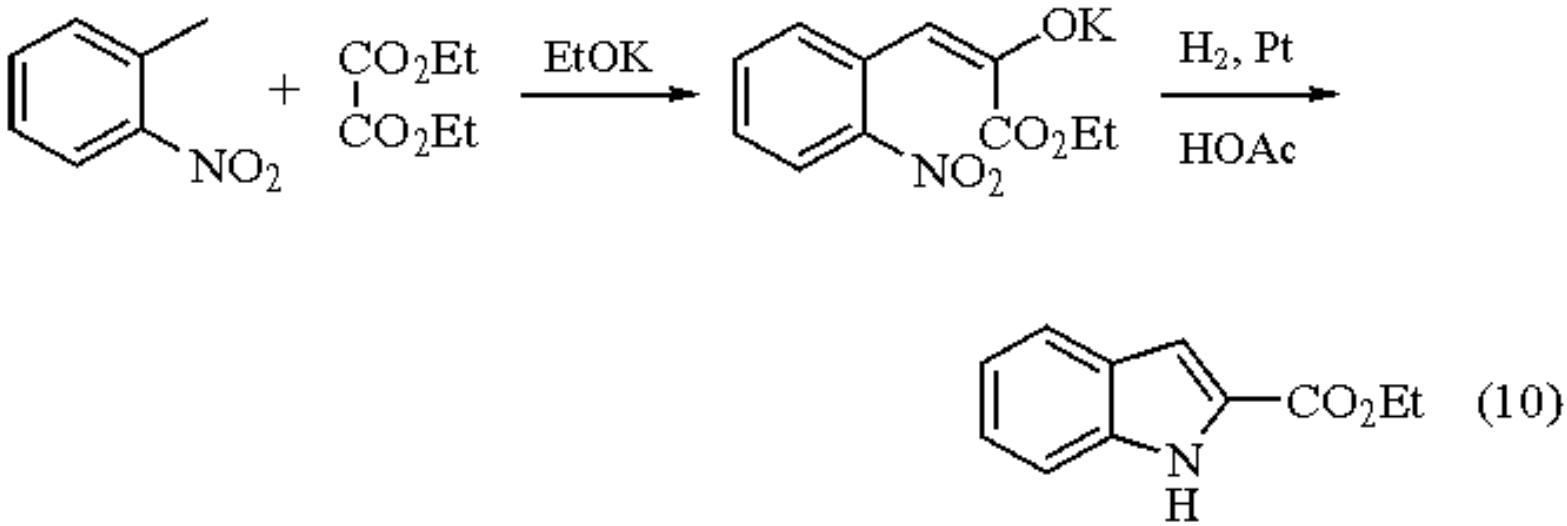

When the formimidate group is available to the enolate at the adacent *ortho* position, then a 4-nitroindole is obtained (eq 11).[23]

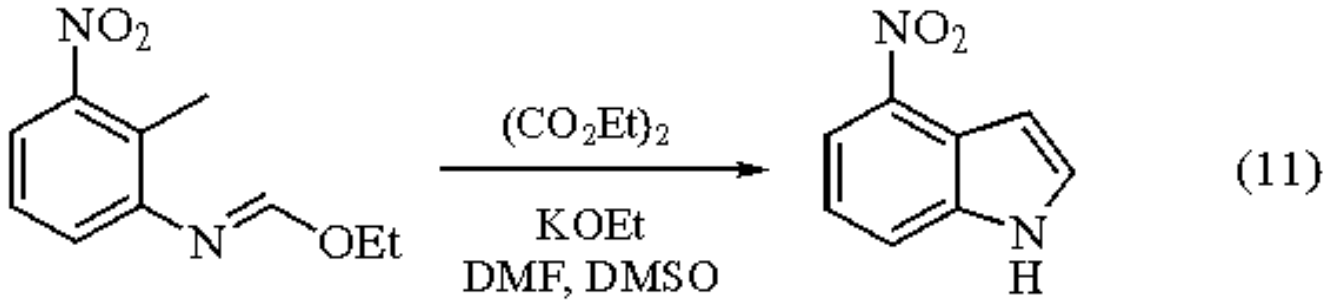

Naphthalene-1,8-diamine reacts on heating with diethyl oxalate to give a pyrimidine derivative (eq 12).[24]

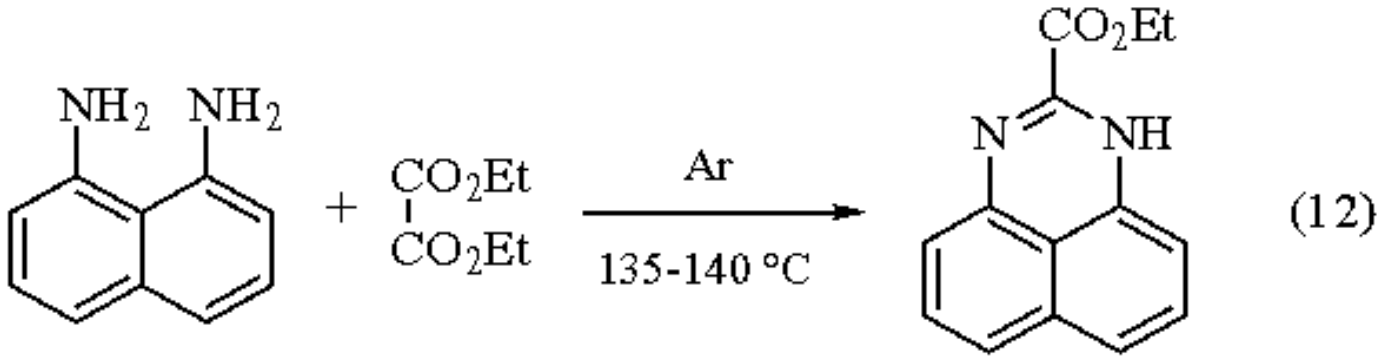

Activating Group in the Preparation of α,β-Unsaturated Ketones.

Ksander and McMurry[4] developed a sequence in which a methyl ketone is acylated by diethyl oxalate and the resulting α,γ-diketo ester acts as a nucleophile on treatment with an aldehyde. The resulting diketo lactone is pyrolyzed with the loss of CO and CO_2 to give the α,β-unsaturated ketone (eq 13).

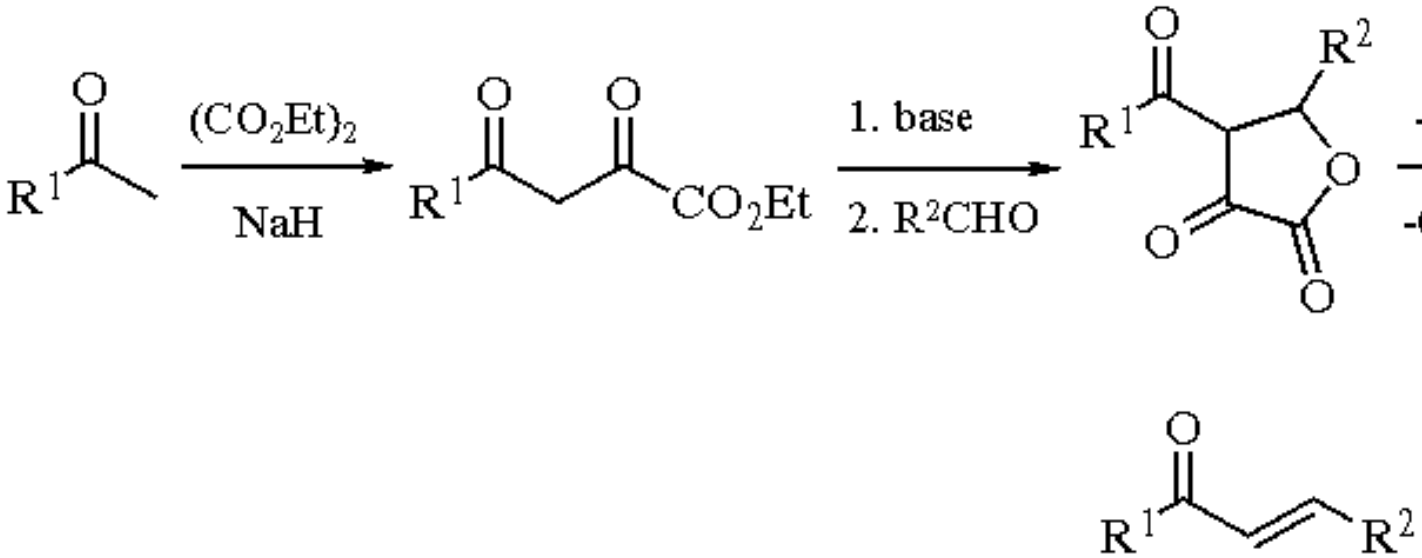

(13)

Activating Group for Regiospecific Alkylation.

An enol ester has been introduced as a directing group for alkylations, particularly in steroids, by acylation with diethyl oxalate. Methylation can be directed to C-2 rather than C-4 by this procedure, and the directing group is readily removed (eq 14).[5,25,26]

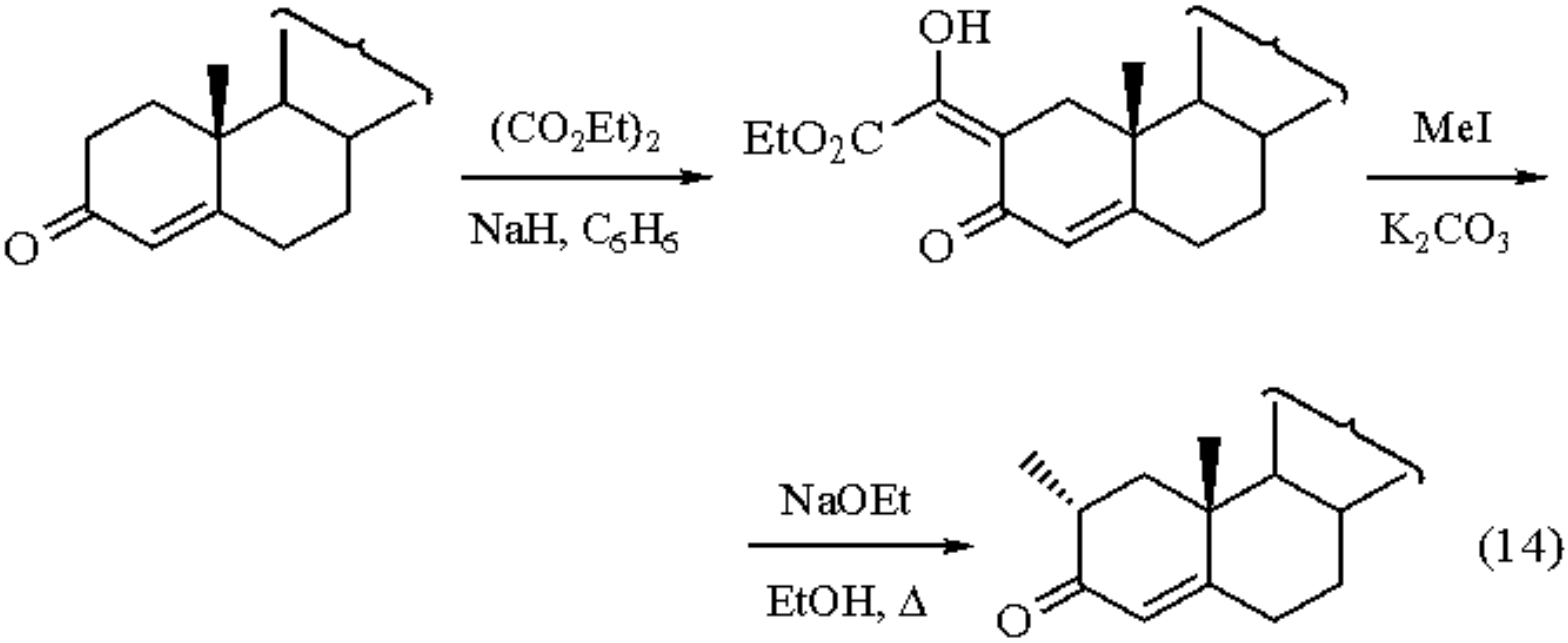

(14)

Activating Group for the Preparation of Diazo Ketones.

Acylation of a methyl ketone with diethyl oxalate in the presence of sodium ethoxide gives the sodium enolate which on treatment with ***p-Toluenesulfonyl Azide*** gives the corresponding diazomethyl ketone (eq 15).[6]

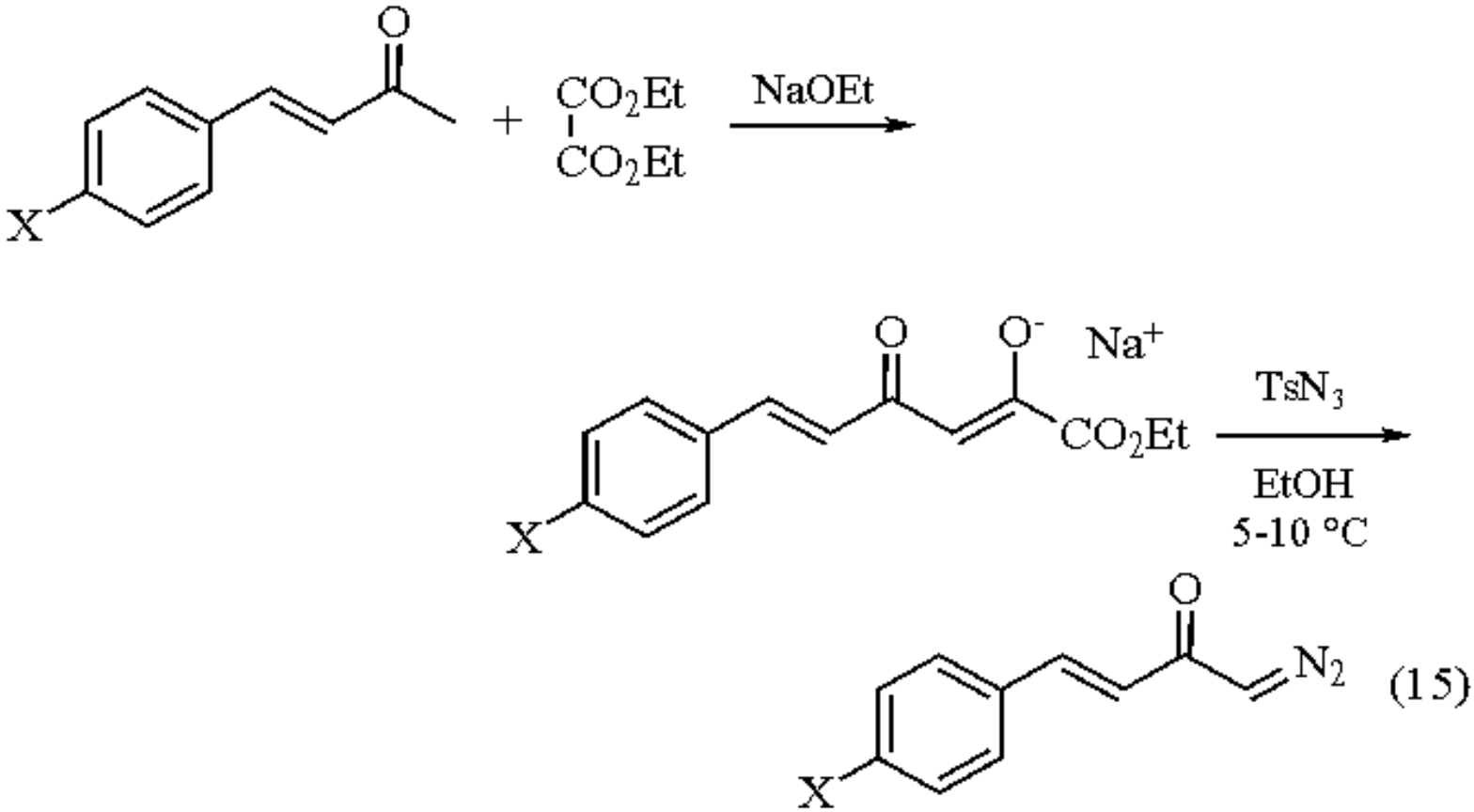

(15)

Related Reagents.

Carbon Dioxide; ***Diethyl Carbonate***; ***Methyl Magnesium Carbonate***; ***Methyl Chlorooxalate***; ***Methyl Cyanoformate***; ***Oxalic Acid***; ***Oxalyl Chloride***.

---

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Diethyl Oxomalonate

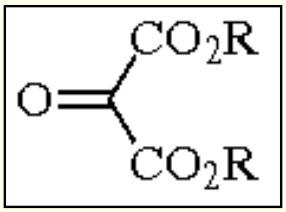

(R = Et)

[609-09-6] · $C_7H_{10}O_5$ · Diethyl Oxomalonate · (MW 174.15) (R = Me)

[3298-40-6] · $C_5H_6O_5$ · Dimethyl Oxomalonate · (MW 146.10)

(electron-deficient heterodienophile; Diels-Alder reaction;[1-4] heterodipolarophile; [3 + 2] cycloaddition;[5] 1,3-diyl trapping agent;[6] 1,4-dipolar cycloaddition;[7] [2 + 2] cycloaddition;[8] enophile; ene reaction;[9,10] electrophilic addition;[11-17] Wittig reactions;[18-22] condensation with amines;[23] Pictet-Spengler reactions[24])

Physical Data: bp 95-98 °C/12 mmHg; *d* 1.144 g cm^{-3}.

Solubility: sol ethanol and diethyl ether.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: *n*20D 1.425.

Preparative Methods: diethyl oxomalonate can be prepared by bromination of ***Diethyl Malonate*** to the dibromomalonic ester, exchange of one bromine atom for acetate and α-elimination of acetyl bromide.[25] Alternatively, diethyl malonate is condensed with benzaldehyde to afford the Knoevenagel product which is cleaved by ozonolysis.[26]

Purification: fractional vacuum distillation.

Handling, Storage, and Precautions: diethyl oxomalonate is stable for at least 6 months if stored in the refrigerator.

Diethyl oxomalonate (**1**) undergoes Diels-Alder reactions as an electron-poor heterodienophile.[1a] Thus reactions with electron-rich butadienes furnish the *gem*-diesters (**2**)[1] (eq 1), which can be converted to the monoacid (**3**) by decarboxylation[1d] or to the unsaturated δ-valerolactones (**4**) either by a Curtius degradation sequence[1b,c] or ***Cerium(IV) Ammonium Nitrate*** (CAN) oxidation (Scheme 1).[7]

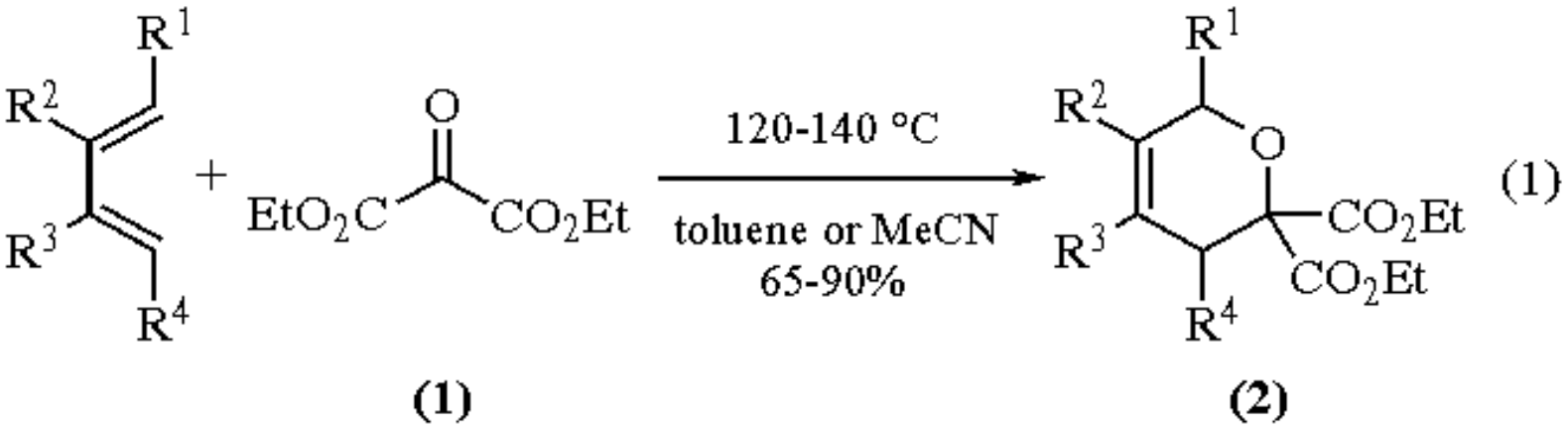

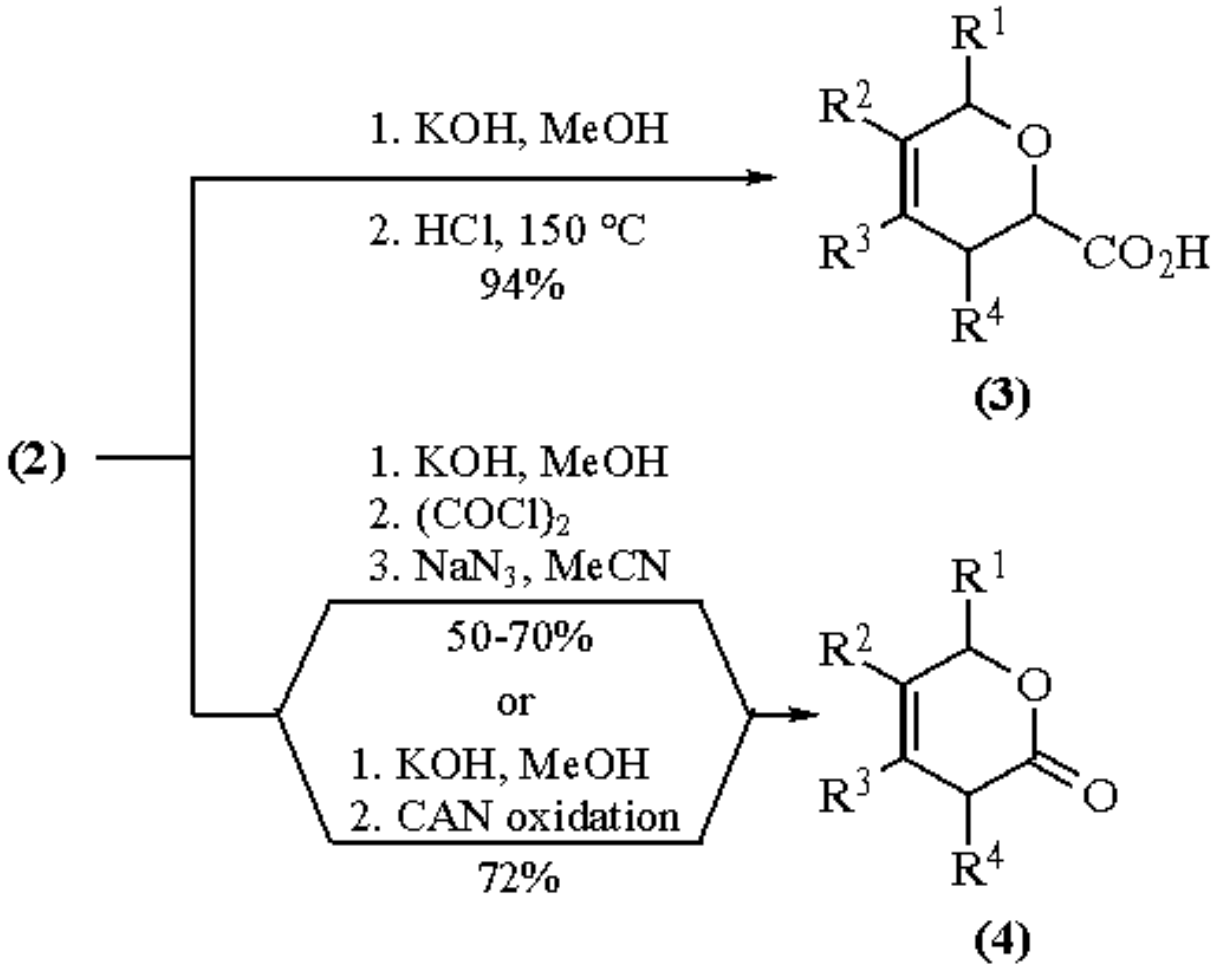

Scheme 1

The reaction is run either at elevated temperature (120-140 °C, MeCN or toluene),[1b-d] under high pressure conditions (10 kbar)[1e,f] or under Lewis acid catalysis.[1a] Chiral Lewis acids have also been applied, but gave only very modest enantioselectivities (<15% ee).[2]

Azadienes (**5**) undergo hetero Diels-Alder reactions with diethyl oxomalonate (**1**) in THF at 80 °C (eq 2).[3] 2,3-Dihydropyran-4-ones (**6**) are formed in the reaction with Danishefsky's diene (**7**) under Lewis acid catalysis at ambient temperature (eq 3).[4]

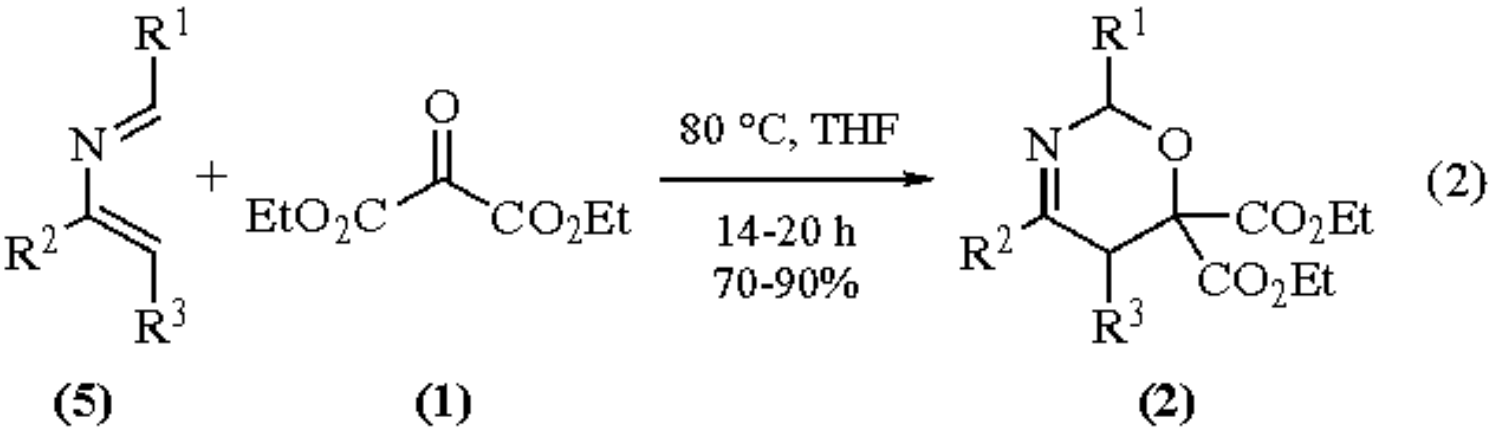

(5) (1) (2)

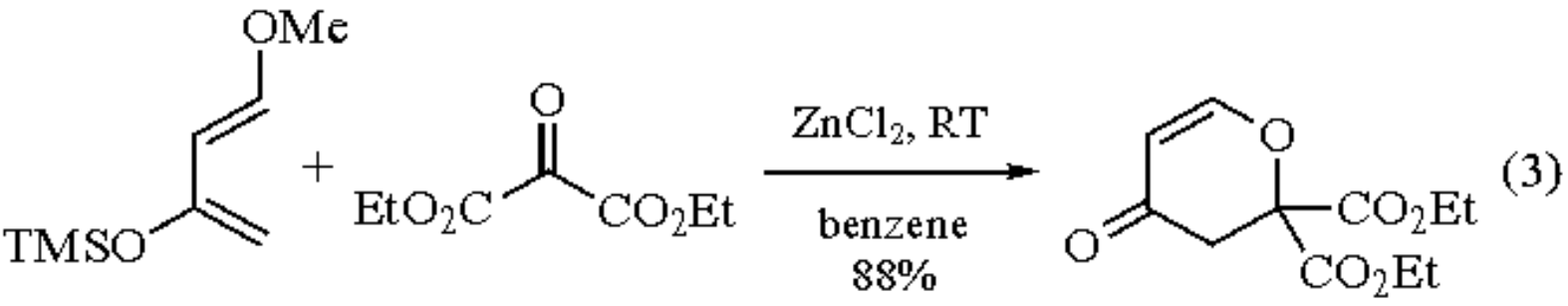

(7) (1) (6)

Reagent (**1**) has been used in [3 + 2] dipolar cycloadditions as a heterodipolarophile.[5] *N*-(Silylmethyl)-substituted ketene *N*,*S*-acetals (**8**) are converted to the 1,3-dipolar reagent (**9**) with ***Cesium Fluoride*** in MeCN, which undergoes the cycloaddition with (**1**) to afford the alkylideneoxazolidines (**10**) in modest yield, but with complete regioselectivity (eq 4).

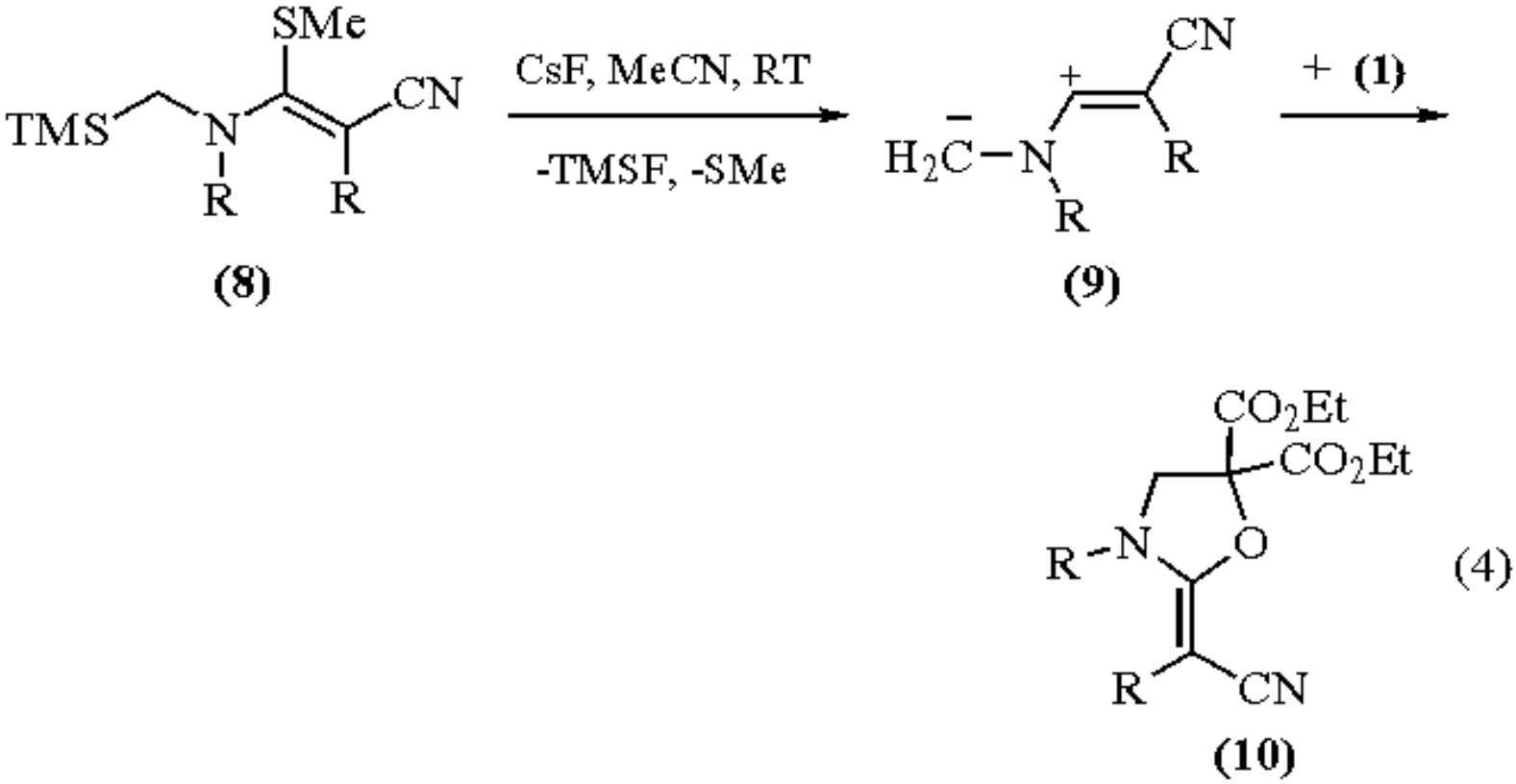

Diethyl oxomalonate has been shown to be reactive towards 1,3-diyls.[6] Heating the diazene (**11**) produces the 2-alkylidene-1,3-diyl (**12**), which is trapped in situ by (**1**) to form the fused cycloadduct (**13**) as a sole isomer in good yield (eq 5). Other diyls, however, give mixtures of isomers.

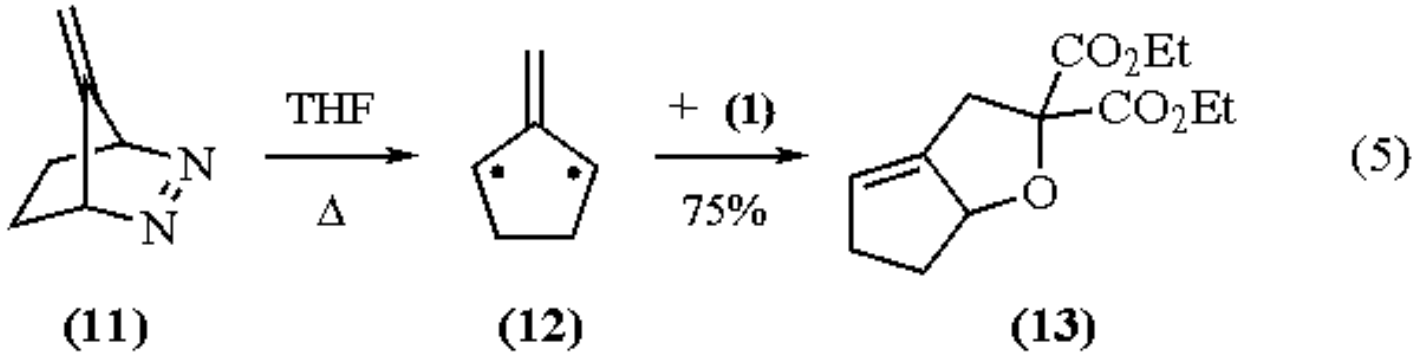

An example of a 1,4-dipolar cycloaddition of (**1**) with 6-oxo-3,6-dihydro-1-pyrimidinium-4-olate (**14**) has been described which leads to diazabicyclo[2.2.2]octanediones (**15**) (eq 6).[7]

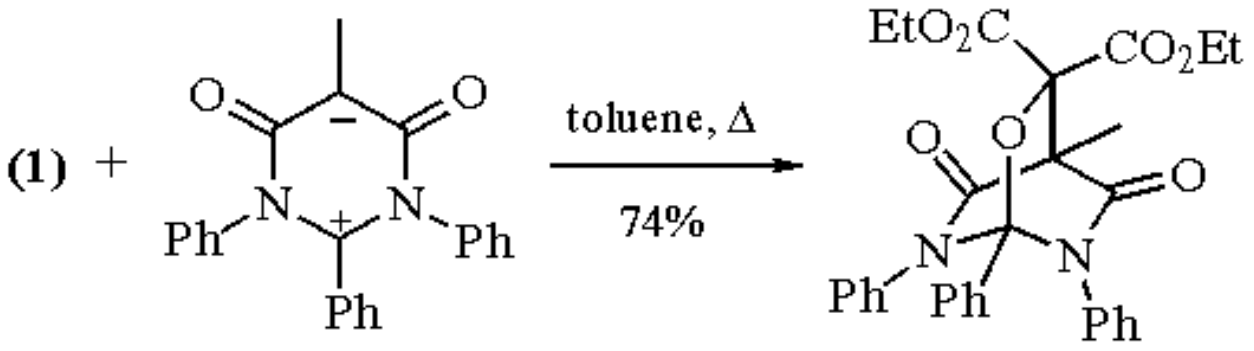

(14) (15)

[2 + 2] Cycloadditions of (**1**) and electron-rich alkenes like 1,1-dimethoxy-2-propene (**16**) have also been investigated.[8] Oxetanes (**17**) are formed in good yield with complete regioselectivity in a thermal reaction (eq 7). Under photochemical conditions, addition does not take place.

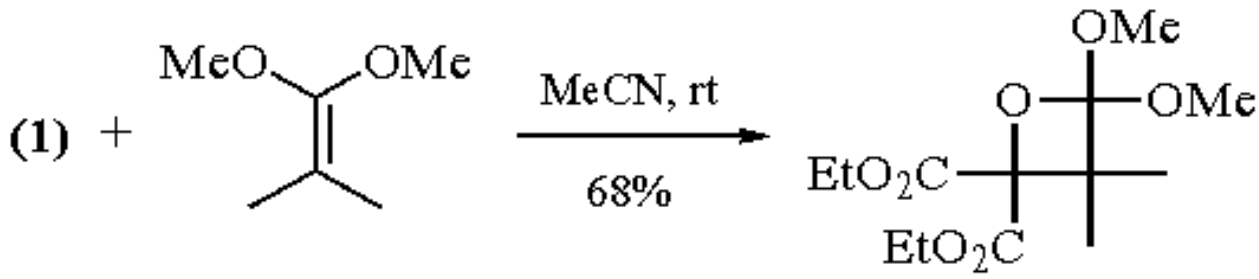

(16) (17)

Diethyl oxomalonate reacts with alkenes that have an allylic hydrogen atom in an ene reaction (eq 8).[9] The reaction is run either thermally or under Lewis acid catalysis. Occasionally the ene reaction is followed by a cyclization to form a tetrahydrofuran diester (**18**), which can be converted to the butyrolactone (**19**) by CAN oxidation (eq 8).[10]

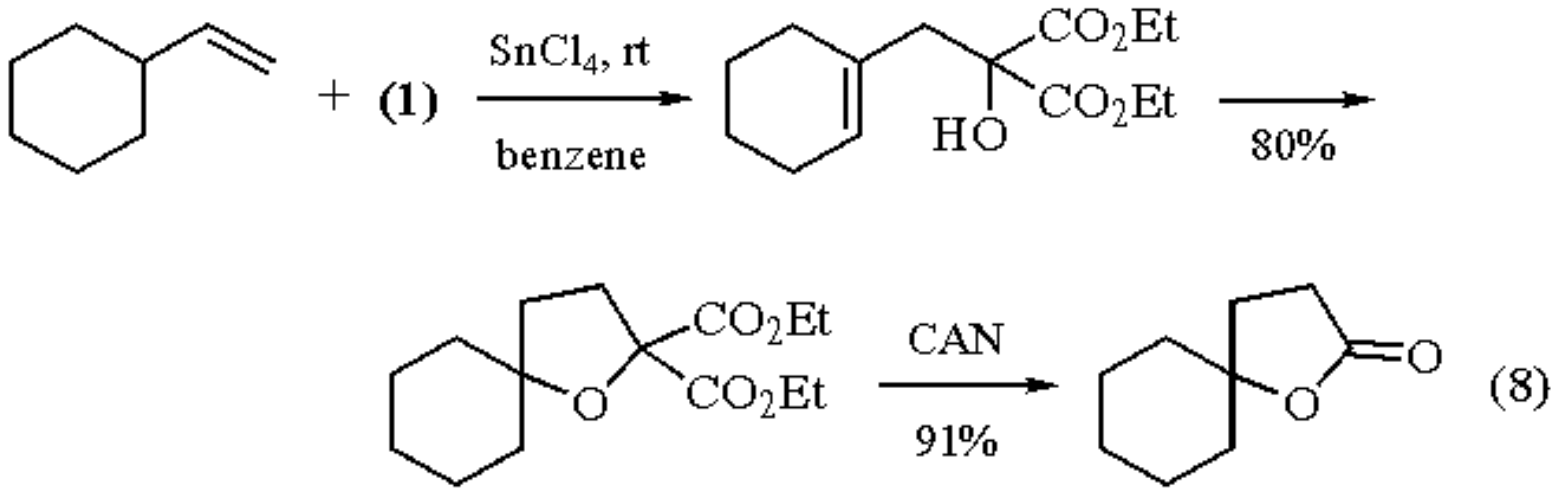

(18) (19)

Due to the adjacent ester groups, (**1**) is a highly reactive carbonyl compound which reacts with a variety of nucleophiles. Thus benzoxazinones (**20**) are formed in the reaction with aminophenols (eq 9).[11] Similarly, 6-

ethoxycarbonyl-7-oxopyrazinothiadiazines (**21**) are accessible by the reaction of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**22**) with diethyl oxomalonate (eq 10).[12]

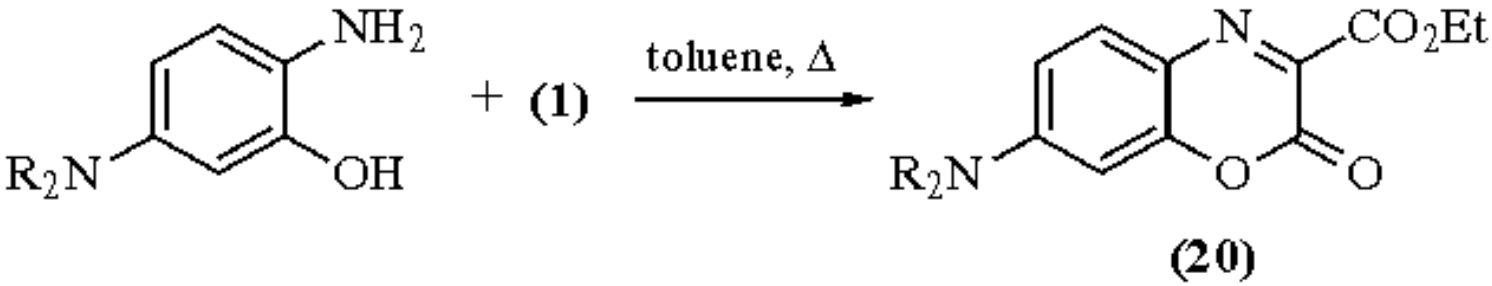

(9)

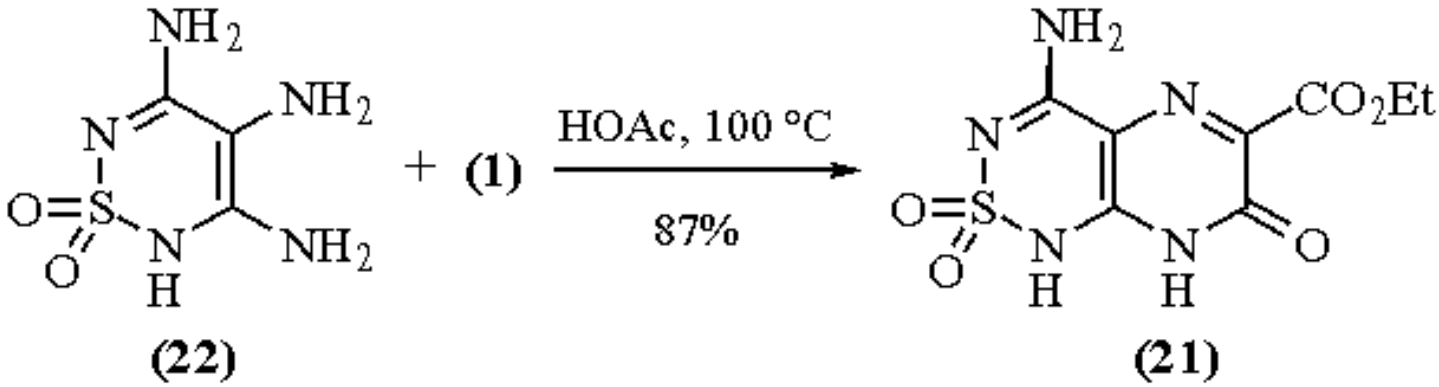

(10)

Enamines (**23**) react with diethyl oxomalonate to furnish aldol products which can be dehydrated and cyclized to the butenolides (**24**) by acid catalysis (eq 11).[13] *N*-Methylindole (**25**) smoothly adds to (**1**) to afford 3-indolylhydroxymalonate (**26**) (eq 12).[14] In the presence of ***Ethylaluminum Dichloride*** a second addition takes place and the 3,3´-bisindolyl derivative (**27**) is formed (eq 12).

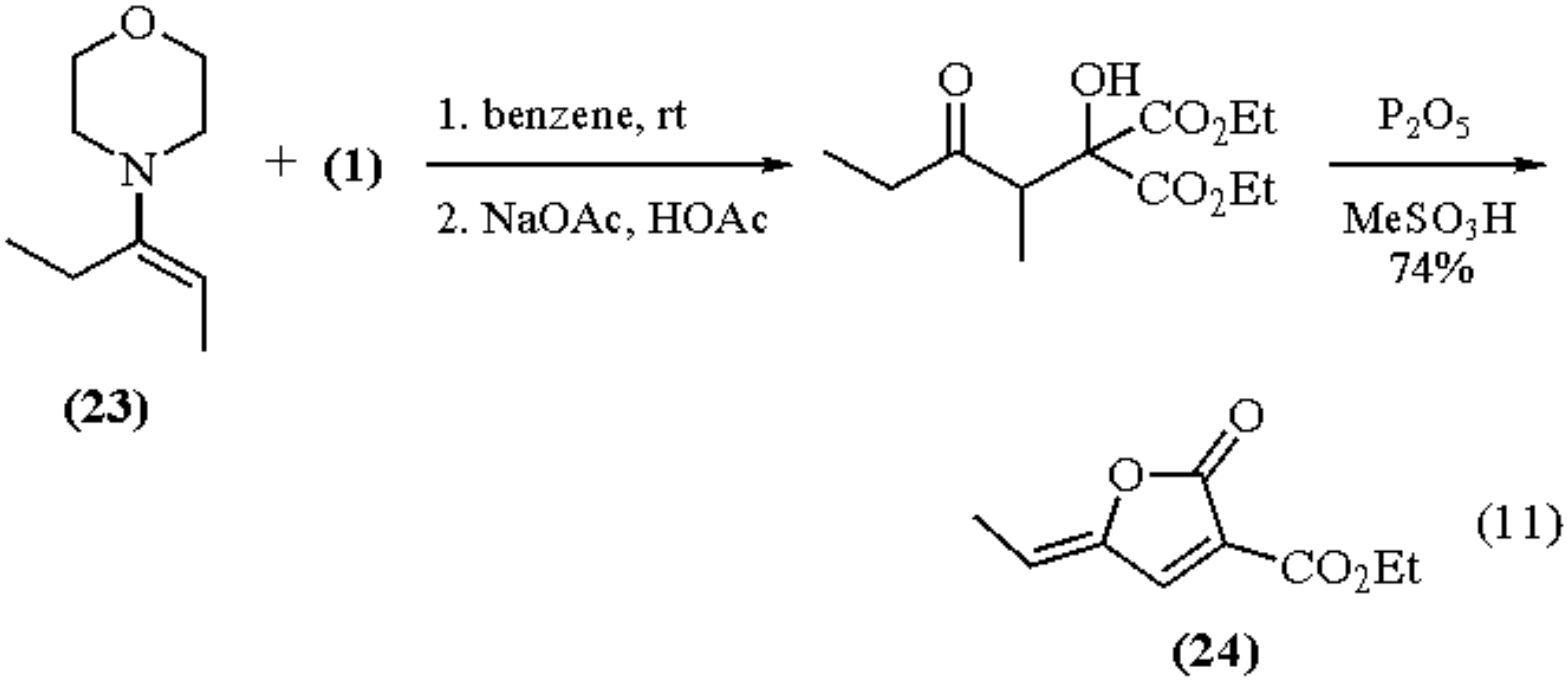

(11)

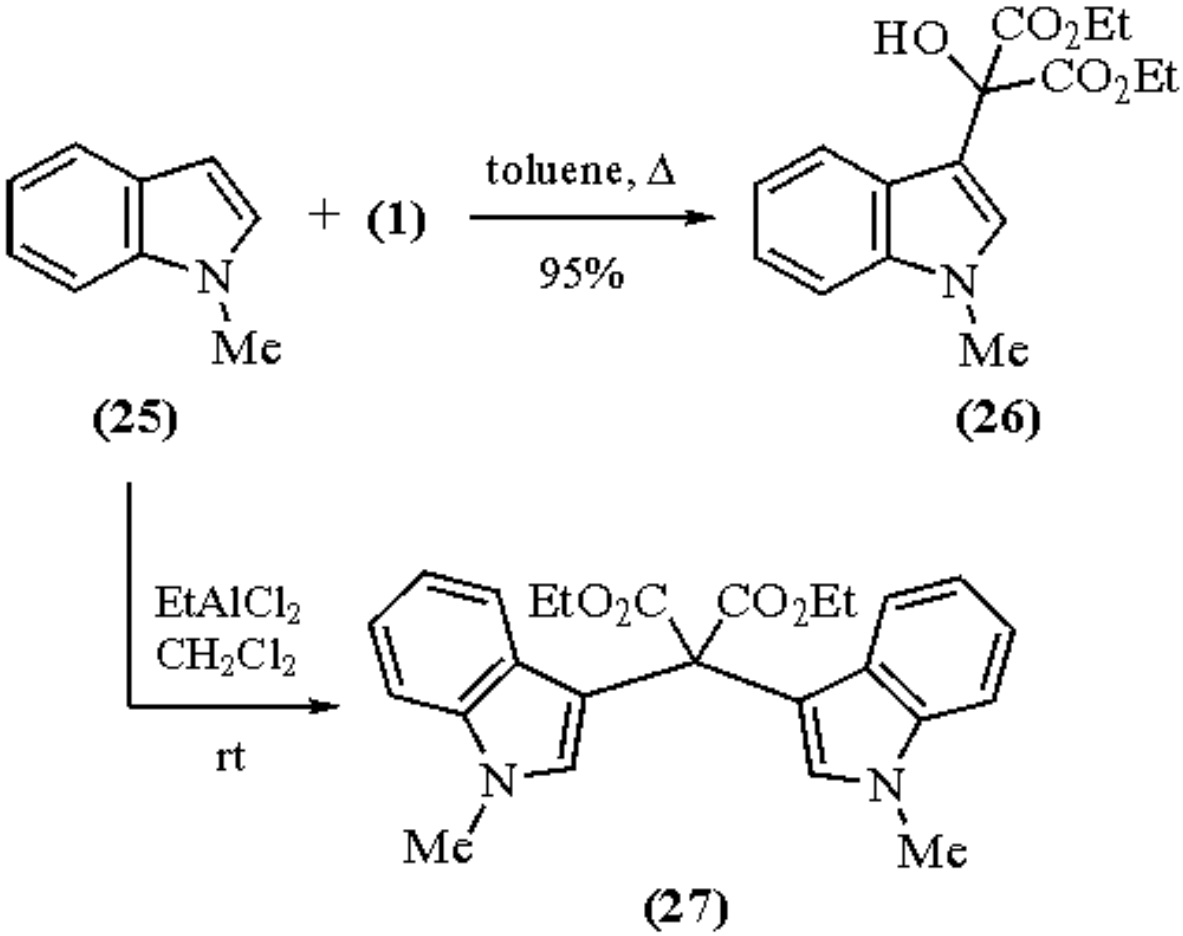

(12)

The high-pressure addition of 2,5-dialkylfurans (**28**) to (**1**) very selectively affords the addition product (**29**) (eq 13).[15] No double addition is observed. The reaction has been shown to proceed through a [1,5]-suprafacial shift of the diethyl oxomalonate moiety.

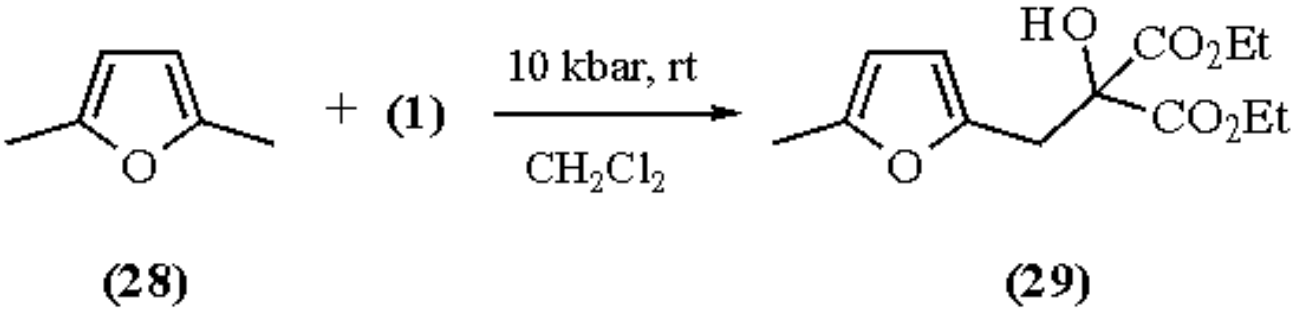

(13)

Diethyl trimethylsilyl phosphite (**30**) adds to diethyl oxomalonate in a redox process to yield α-hydroxyphosphonic ester (**31**) (eq 14).[16] Only very electron-poor ketones display such a reactivity towards trimethylsilyloxyphosphorus(III) derivatives.

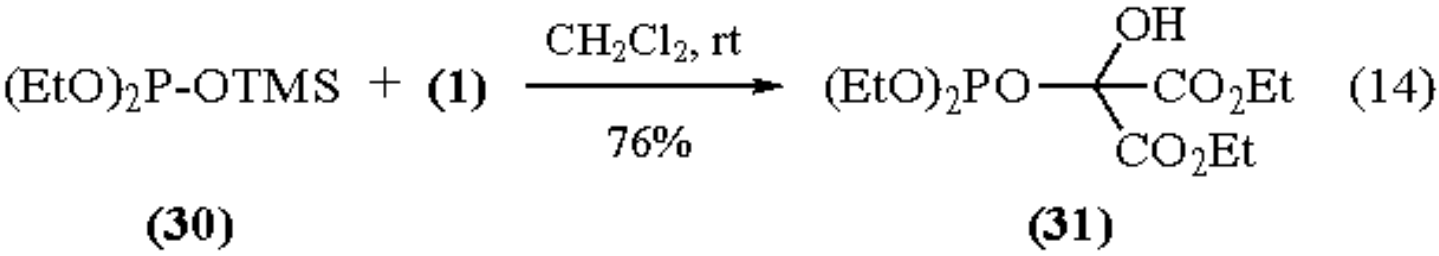

Even aromatic compounds are sufficiently reactive to add to (**1**). The reaction of *p*-xylene (**32**) with (**1**) is promoted by ***Tin(IV) Chloride*** at ambient temperature (eq 15).[17]

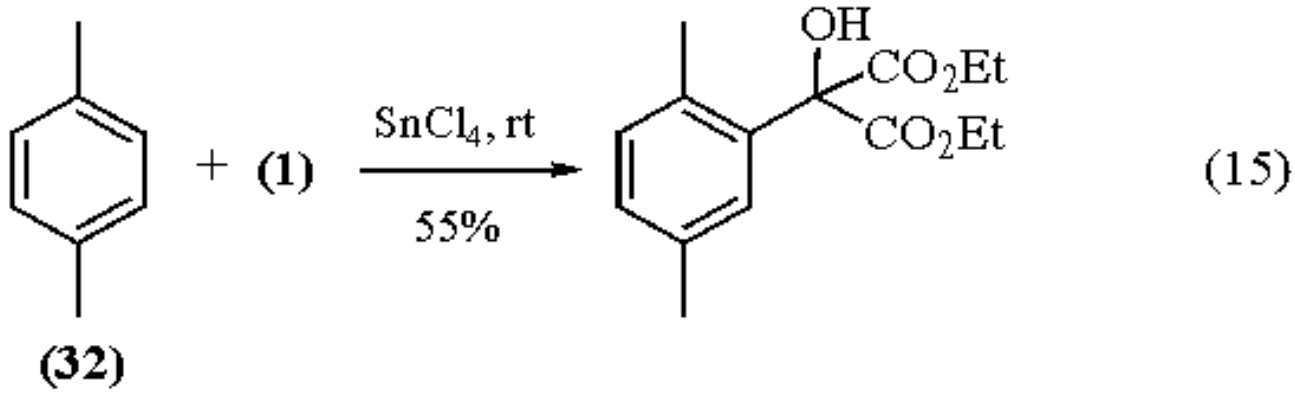

Diethyl oxomalonate has frequently been used in Wittig reactions. Thus the phosphorus ylide (**33**) of a cephalosporin derivative is smoothly converted to the unsaturated diester (**34**) (eq 16).[18] The ylide (**35**) of a dithioacetal furnishes the ketene dithioacetal (**36**) (eq 17).[19] An imino-Wittig-type reaction has been used for the construction of the side chain of the mycosporins.[20] The iminophosphorane (**37**), obtained by a Staudinger reduction of the corresponding azide, is condensed with (**1**); the resulting imine (**38**) is reduced in situ with ***Sodium Cyanoborohydride*** (eq 18).

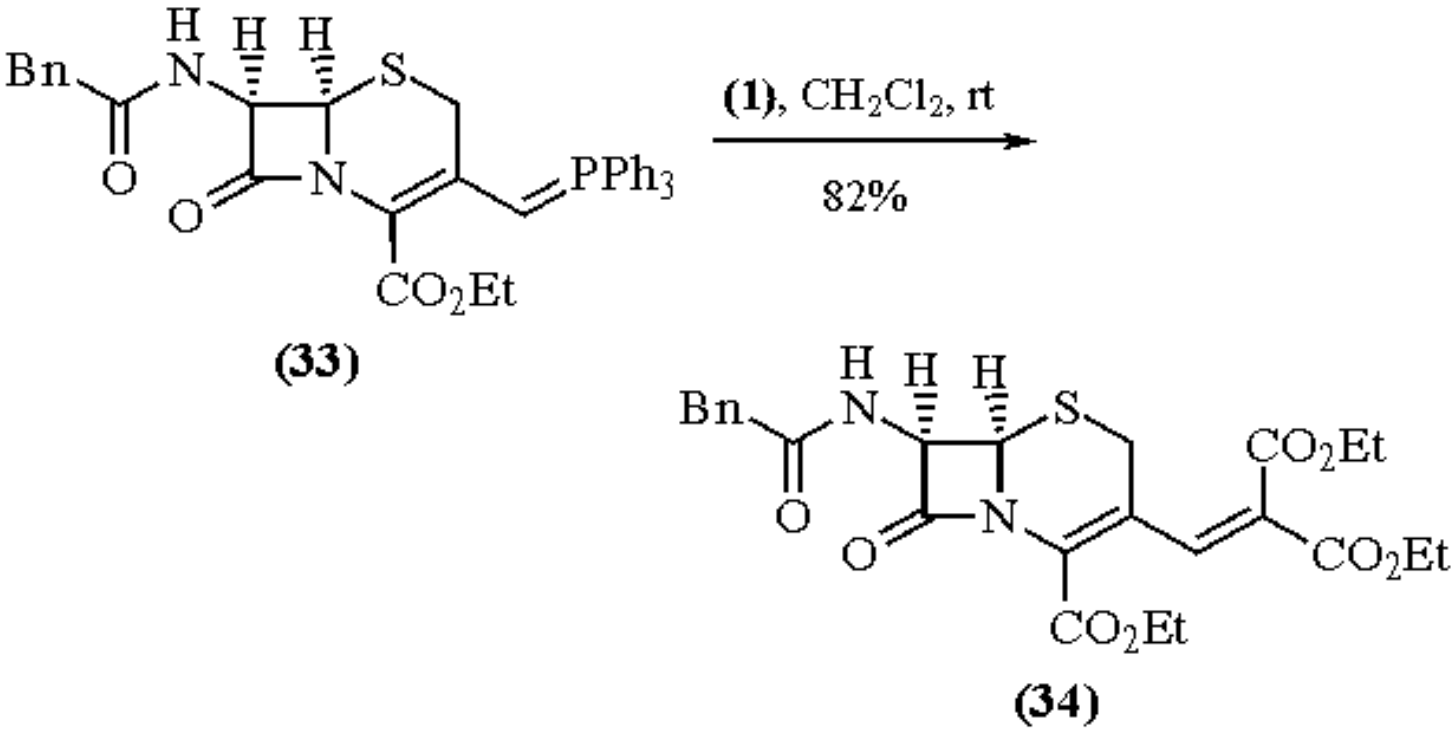

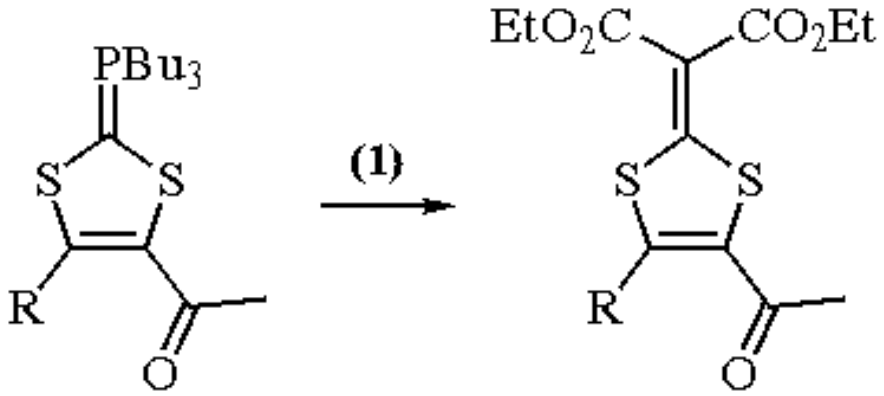

(35) (36) (17)

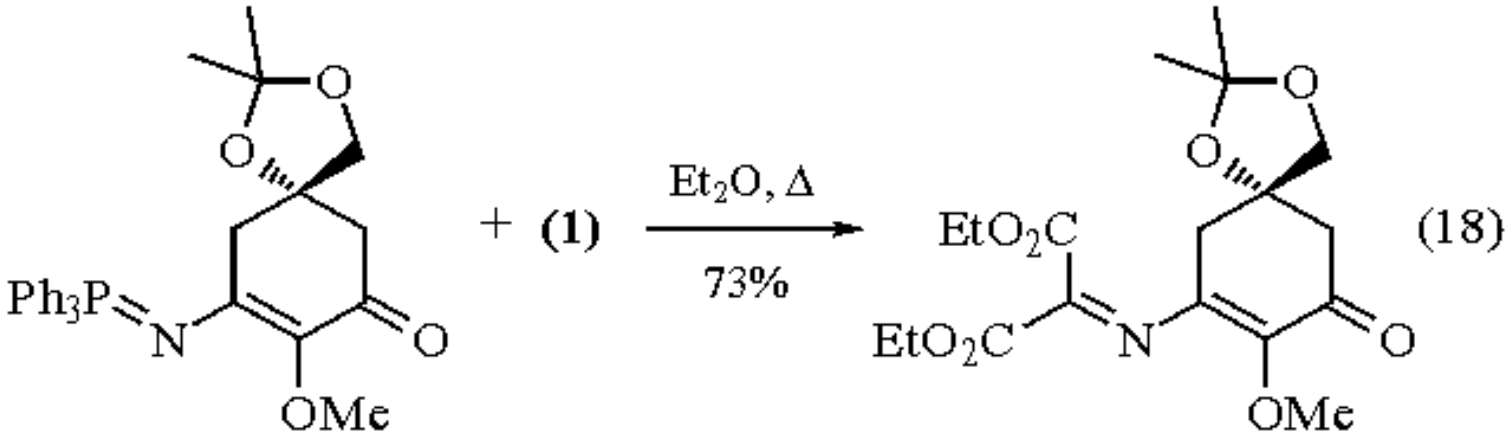

(37) (38) (18)

Reagent (**1**) has also been applied to a phospha-Wittig reaction with (**39**) to yield the phospha-alkene complex (**40**) (eq 19).[21] These complexes have been shown to take part in [2 + 2] processes with enol ethers, enamines, and ethoxyacetylene to give phosphetanes.[22]

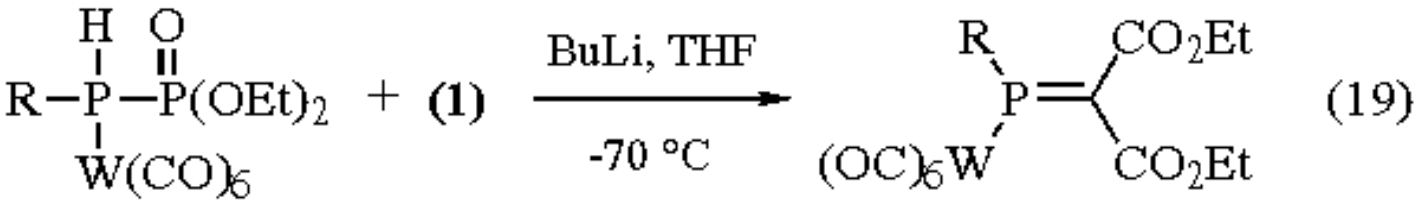

(39) (40) (19)

Amines can easily be condensed with diethyl oxomalonate by heating at reflux with water removal (Dean-Stark trap). The imines (**41**) undergo electrophilic cyclization with an internal electron-rich double bond under Lewis acid or ***Trimethylsilyl Trifluoromethanesulfonate*** catalysis to produce various nitrogen heterocycles, including piperidines, octahydroisoquinolines, azepines, and pyrrolidines (eq 20).[23] Depending on the reaction conditions *cis*-lactones (**42**) are formed in a second step very selectively (eq 20).

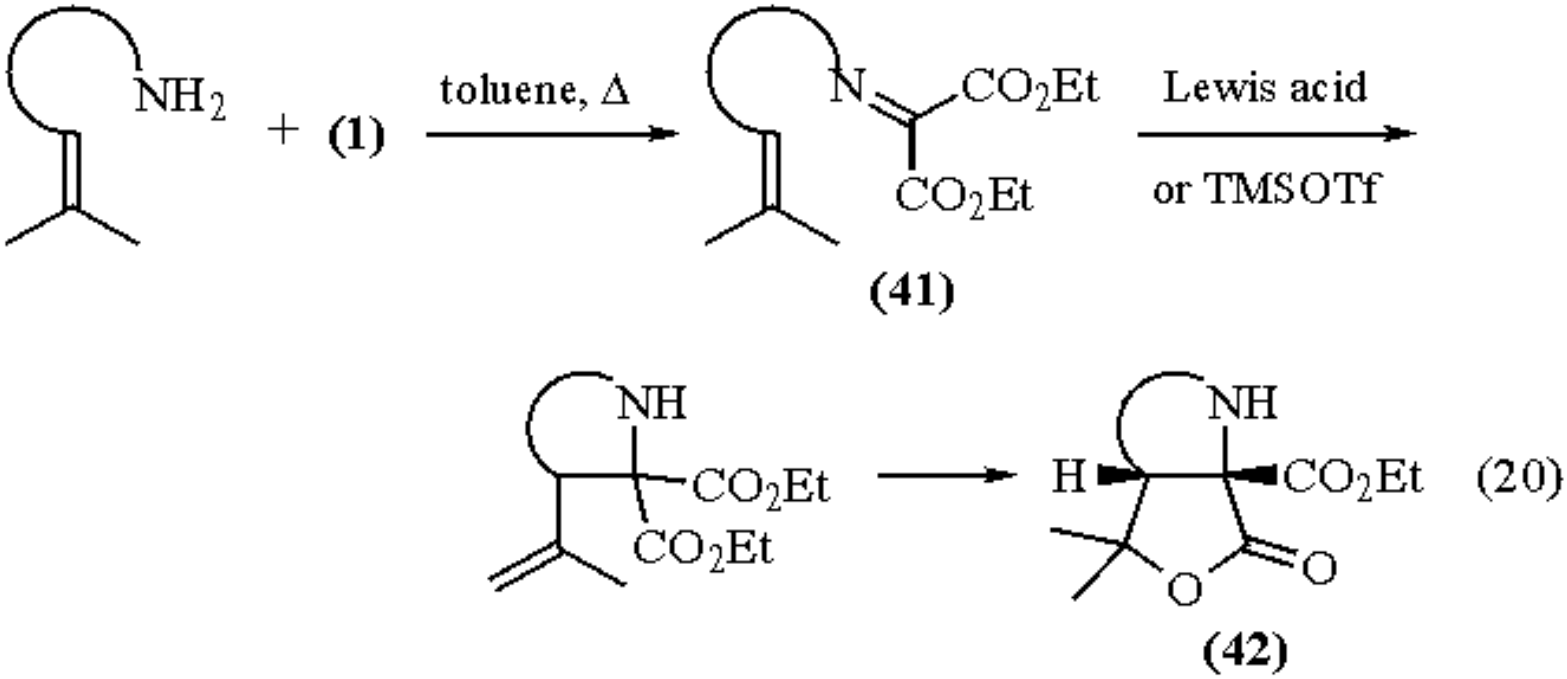

Reagent (**1**) has also been used in Pictet-Spengler reactions of tryptamine-2-carboxylic acids (**43**) (eq 21).[24] The reaction is run in refluxing benzene/dioxane/trifluoroacetic acid solution with water removal (Dean-Stark trap). Rearrangement of the initially produced iminium ion gives rise to the 1,2,3,4-tetrahydro-β-carbolin (**44**).

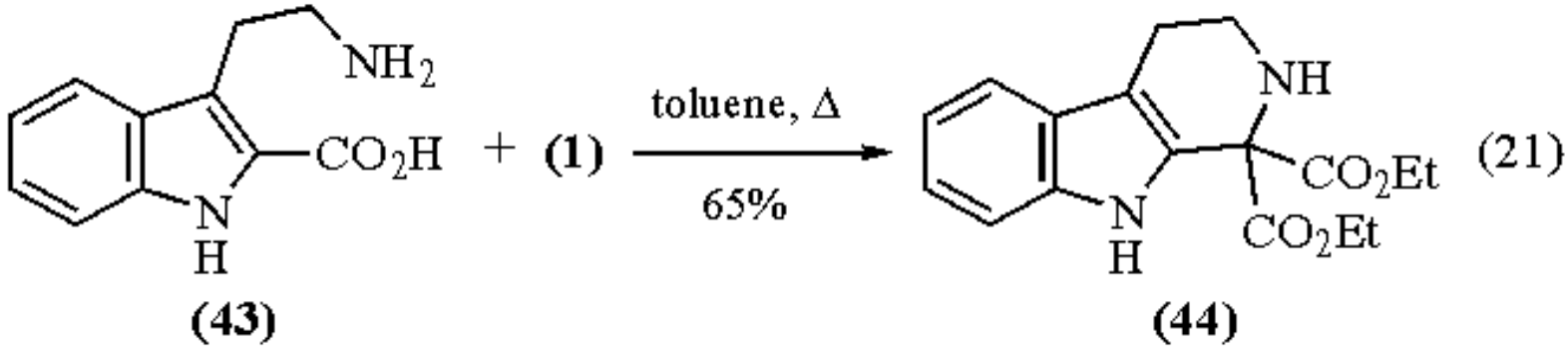

In addition to the transformations of diethyl oxomalonate described above, several achiral and chiral dialkyl oxomalonates, such as dimethyl oxomalonate,[27-40] have been used in related reactions. The esters are best prepared by ozonolysis of the Knoevenagel products of benzaldehyde and the corresponding dialkyl malonates.[23,26]

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Diethyl 2-Pentenedioate

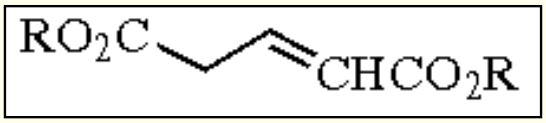

(R = Et)

[2049-67-4] · $C_9H_{14}O_4$ · Diethyl 2-Pentenedioate · (MW 186.21) (*E*)-(R = Et)

[73178-43-5] (R = Me)

[5164-76-1] · $C_7H_{10}O_4$ · Dimethyl 2-Pentenedioate · (MW 158.15) (*E*)-(R = Me)

[41527-39-3]

(effects annulations that involve the reagent's alkenic group,[1] and annulations in which the reagent functions as a bis-nucleophile[2])

Alternate Name: diethyl glutaconate.

Physical Data: diethyl: bp 236-238 °C, 125 °C/12 mmHg; *d* 1.053 g cm^{-3}.

Solubility: sol DME, DMSO, MeOH, HOAc.

Form Supplied in: the diethyl ester is more readily available commercially. It is supplied as a liquid (*E*)/(*Z*) mixture in 98% purity.

Analysis of Reagent Purity: diethyl: ^{1}H NMR.[3]

Purification: vacuum distillation.

Annulations Involving the Reagent's Alkenic Bond.

A number of applications of this reagent require the central, alkenic carbon to serve as one point of attachment in annulation processes. Eq 1[4] demonstrates a straightforward conjugate addition-intramolecular Friedel-Crafts acylation tandem, whereas a conceptually if not mechanistically related electrochemical process is shown in eq 2.[5]

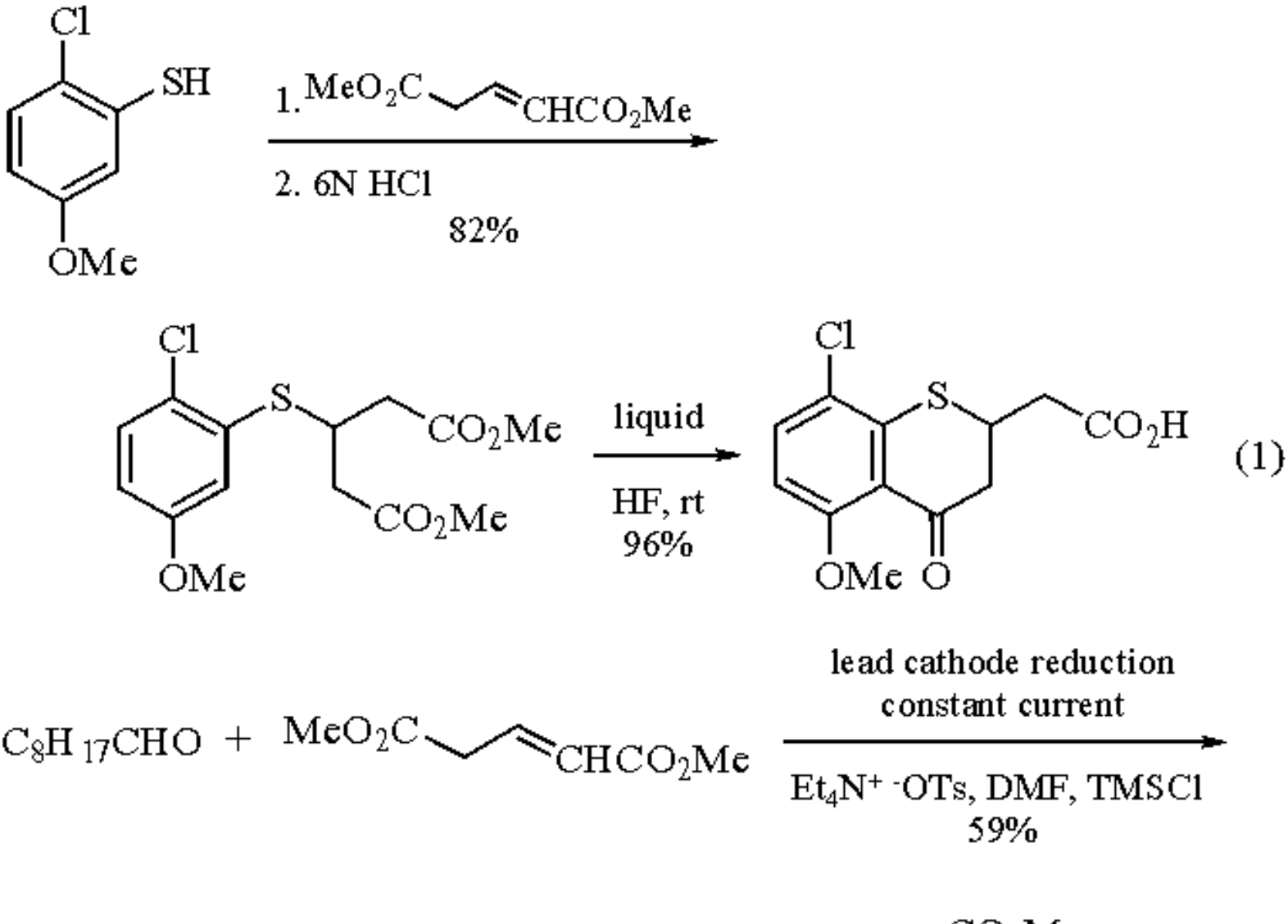

An additional transformation of this type in which the reagent provides both conjugate addition and nucleophilic reaction sites for ring formation is shown in eq 3.[1]

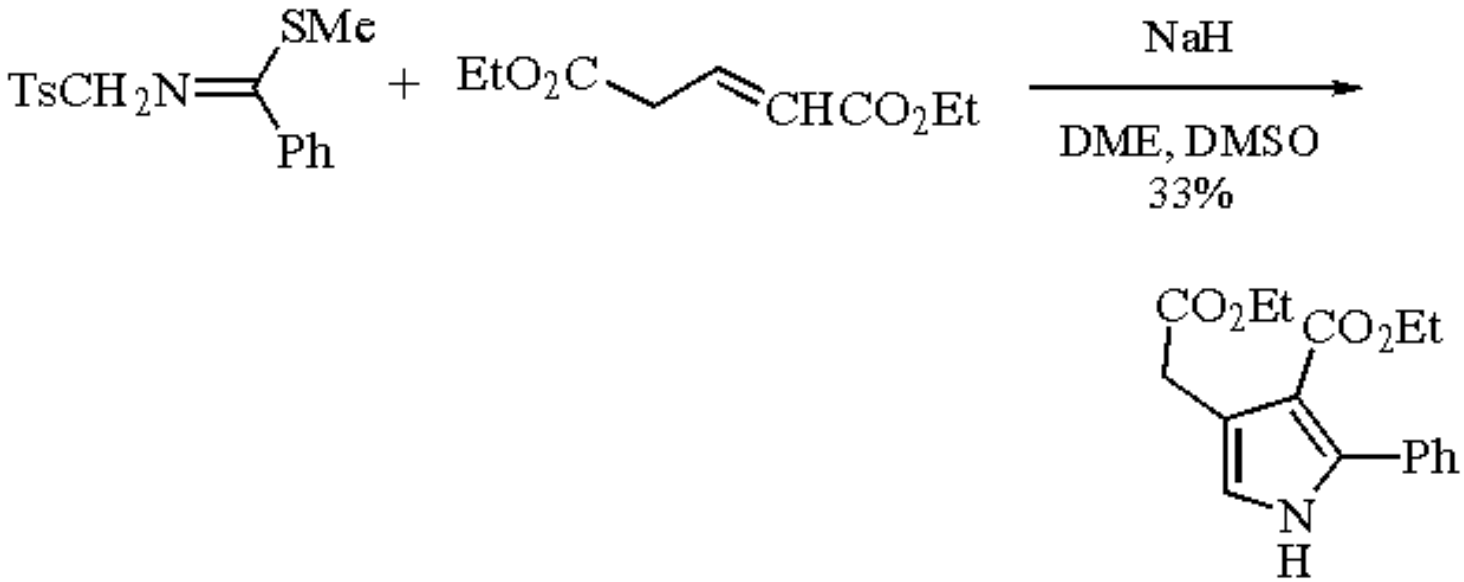

(3)

Annulations without Reaction at an Alkenic Site.

Processes that append a five-carbon unit derived from the reagent without the attachment of substituents at the reagent's central carbon are also known. In eq 4,[6] eq 5,[7] and eq 6[2] the reagent acts as a bis-nucleophile in ring-forming processes.

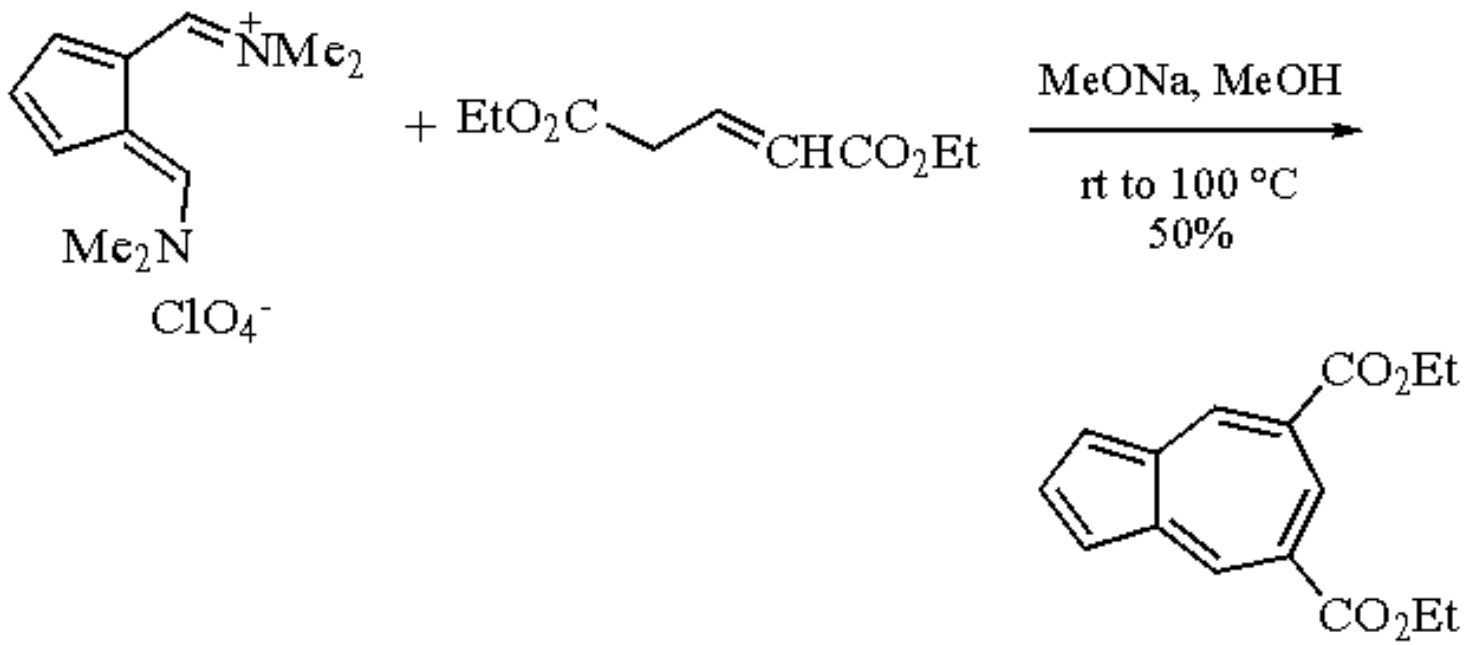

(4)

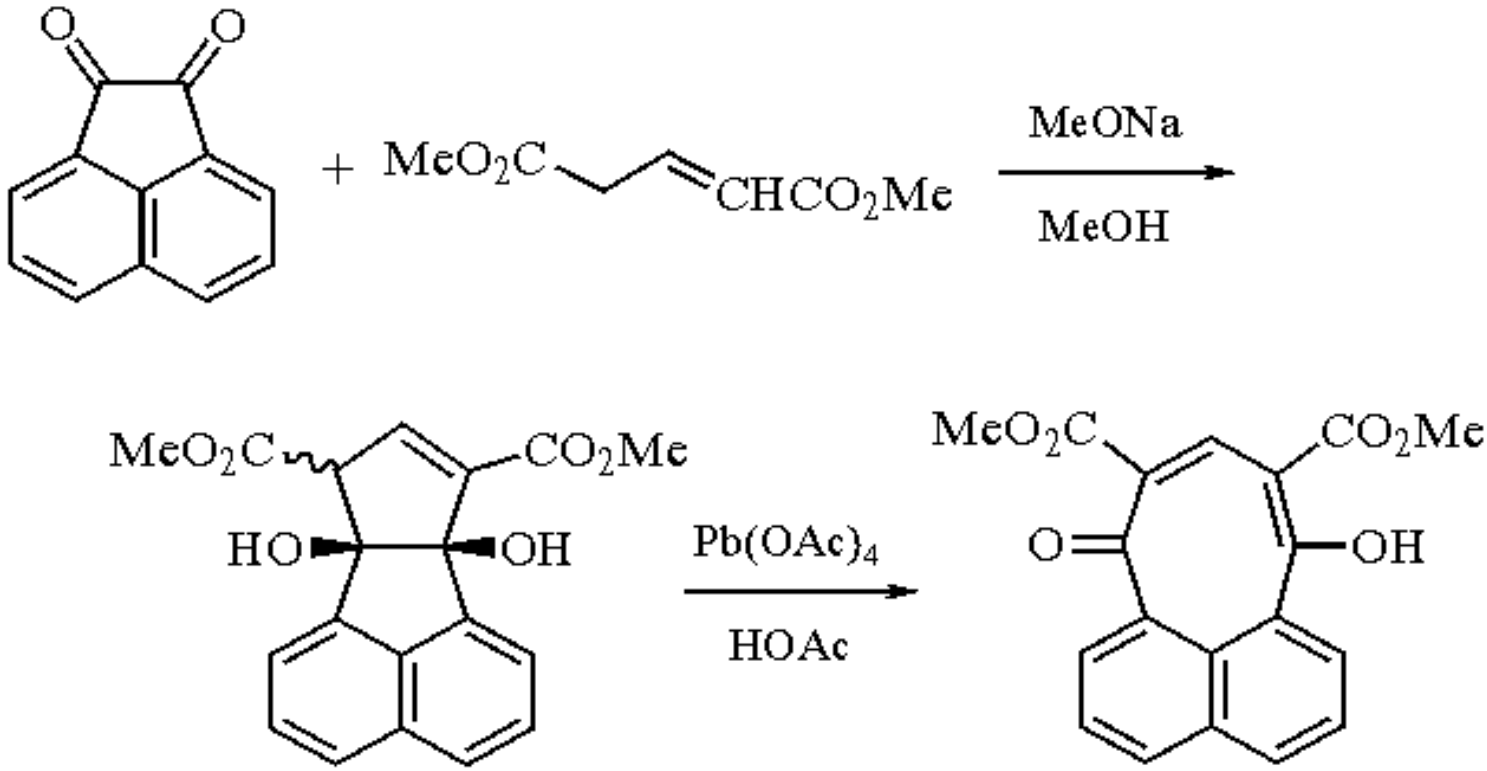

(5)

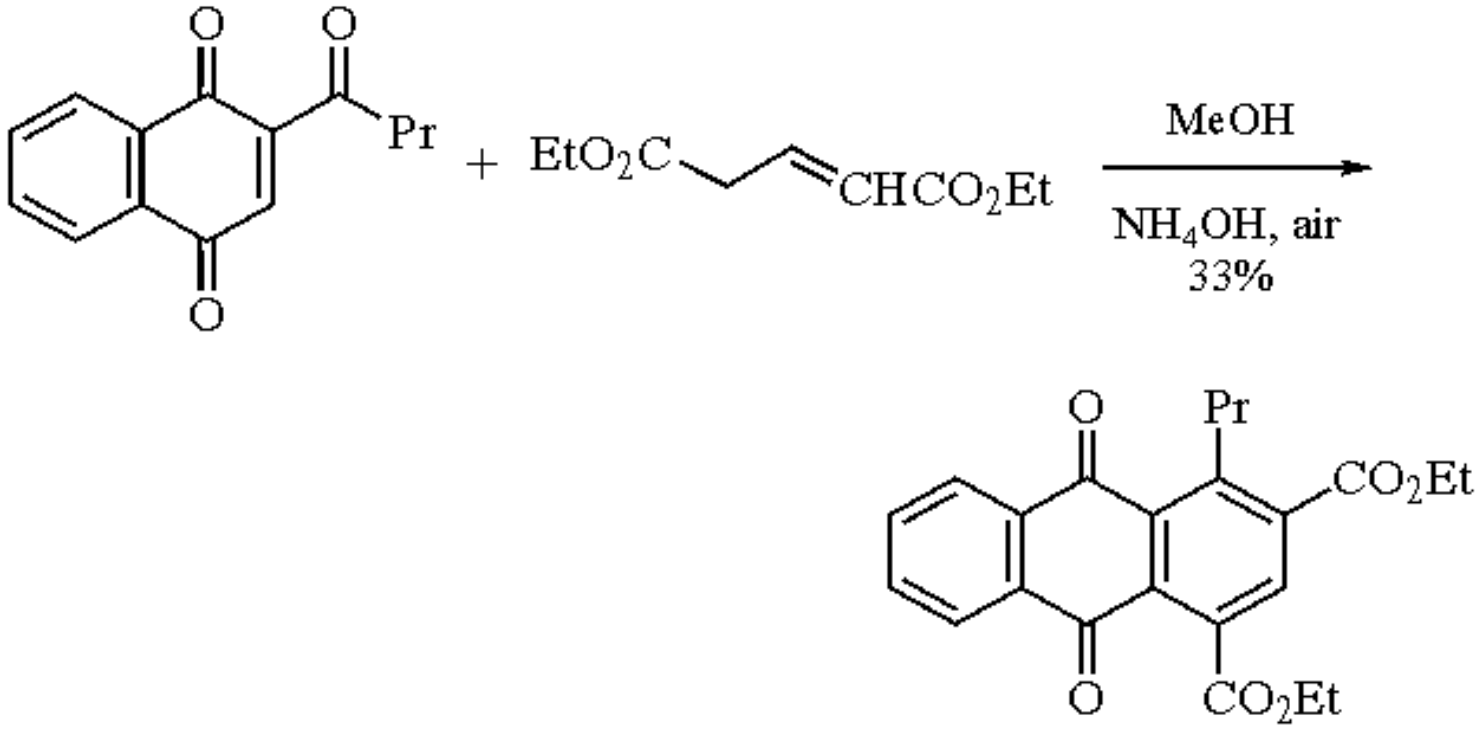

(6)

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Diethyl Phenyl Orthoformate[1]

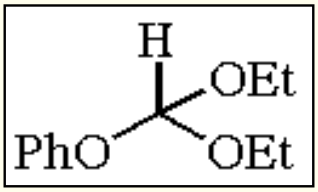

[14444-77-0] · $C_{11}H_{16}O_3$ · Diethyl Phenyl Orthoformate · (MW 196.25)

(mixed orthoformate which undergoes monosubstitution with Grignard reagents and other organometallic reagents to give diethyl acetals)

Alternate Name: diethoxy(phenoxy)methane.

Physical Data: bp 112 °C/13 mmHg; *n*20D 1.4799; *d* 1.016 g cm^{-3}

Solubility: insol cold H_2O; sol most organic solvents.

Analysis of Reagent Purity: ^1H NMR.[2]

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: store in absence of water. Possibility of hydrolysis and disproportionation.[2] Irritates eyes, skin, and lungs. Use in a fume hood.

Diethoxymethylation.

The reagent reacts with various nucleophiles, especially Grignard reagents (RMgX) under mild conditions, and gives good yields of the homologous aldehyde diethyl acetals (eq 1).[3]

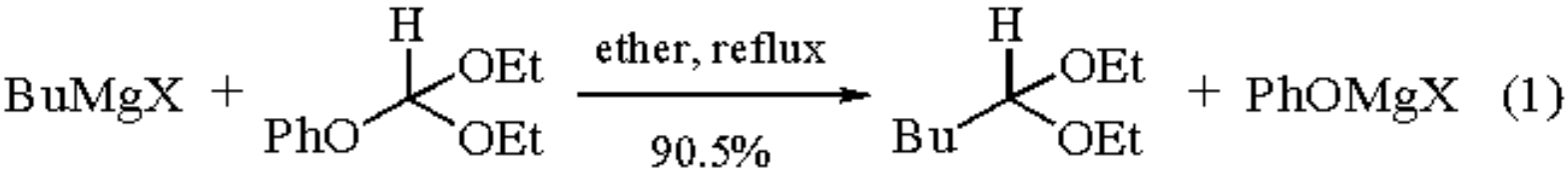

Owing to the lack of reviews, the scope of the reaction is best shown by grouping the possible Grignard reagents: alkyl-MgX;[3-5] alkenyl-MgX (other than allyl);[6] allyl-MgX (allyl rearrangements possible);[4,7] vinyl-MgX;[4] cycloalkadienylmethyl-MgX;[8] alkynyl- or alkynylalkyl-MgX (an important group);[4,9] aryl-MgX;[3,10] 1-phenyl-1-

ethyl-MgX;[11] 3-quinolizidinemethyl-MgX;[12] bullvalenyl-MgX;[13] arylsulfonylchloromethyl-MgX;[14] Bu_3Sn-MgX (important source of various organotin reagents);[15] *t*-butylMgX does not react.[4] Propargylorgano-Al, -Mg, and -Zn derivatives (propargyl-allene rearrangements) react analogously,[16] as do some cyclic organolithium compounds,[17] a dilithiocarborane,[18] some organozinc ester enolates,[4] and cyclohexanone magnesium enolate.[4]

Related Reagents.

Simple orthoformates like ***Triethyl Orthoformate*** react analogously,[19] but yields are generally low. Ethyl diphenyl orthoformate reacts with 2 equiv of ***Phenylmagnesium Bromide*** to give ethylbenzhydryl ether in 87% yield.[3]

See also ***Carbon Monoxide***; ***N,N-Dimethylformamide***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***Triethyl Orthoformate***.

---

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Heinrich Kuhlmann

Diethyl Phenylsulfinylmethylphosphonate

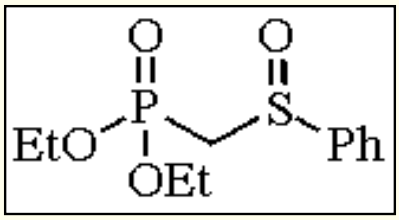

[65915-25-5] · $C_{11}H_{17}O_4PS$ · Diethyl Phenylsulfinylmethylphosphonate · (MW 276.29)

(used for the preparation of vinyl sulfoxides and *O,S*-acetals of formyl phosphonates)

*Physical Data: n*20D = 1.5236.[1]

Solubility: sol acetone, MeOH, CH_2Cl_2, THF.

Preparative Method: most conveniently prepared by controlled oxidation of ***Diethyl Phenylthiomethylphosphonate*** (eq 1).[1-3]

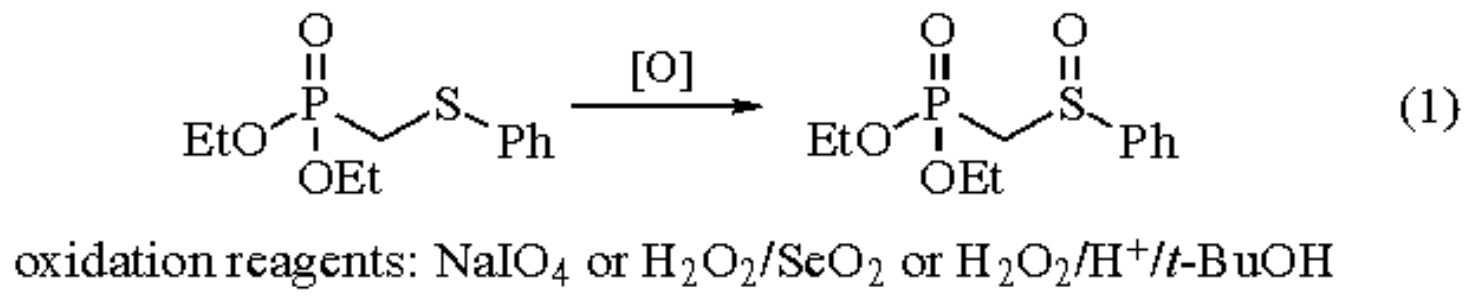

Handling, Storage, and Precautions: diethyl phenylsulfinylmethylphosphonate is reasonably stable for storage. Reactions involving this reagent are best conducted under anhydrous conditions, under nitrogen, in a well ventilated fume hood.

Reactions.

The applications of diethyl phenylsulfinylmethylphosphonate center on its ability to undergo Horner-Emmons and Pummerer reactions.

In the Horner-Emmons reaction, the sulfinylphosphonate can be metalated with ***n-Butyllithium*** in THF and then reacted with aldehydes or ketones to form vinyl sulfoxides. For example, this sequence, followed by intramolecular Michael addition, has been used to synthesize chroman sulfoxide, an important intermediate in the synthesis of α-tocopherol (eq 2).[4] Modest transfer of chirality from the sulfoxide to the bicyclic product has been observed in this

reaction.

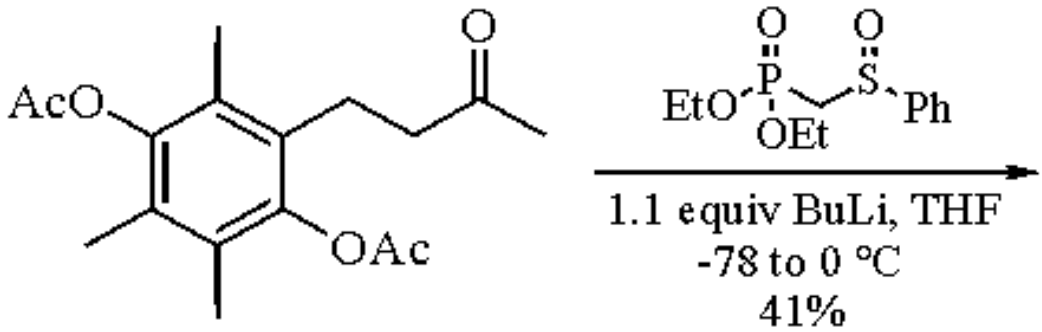

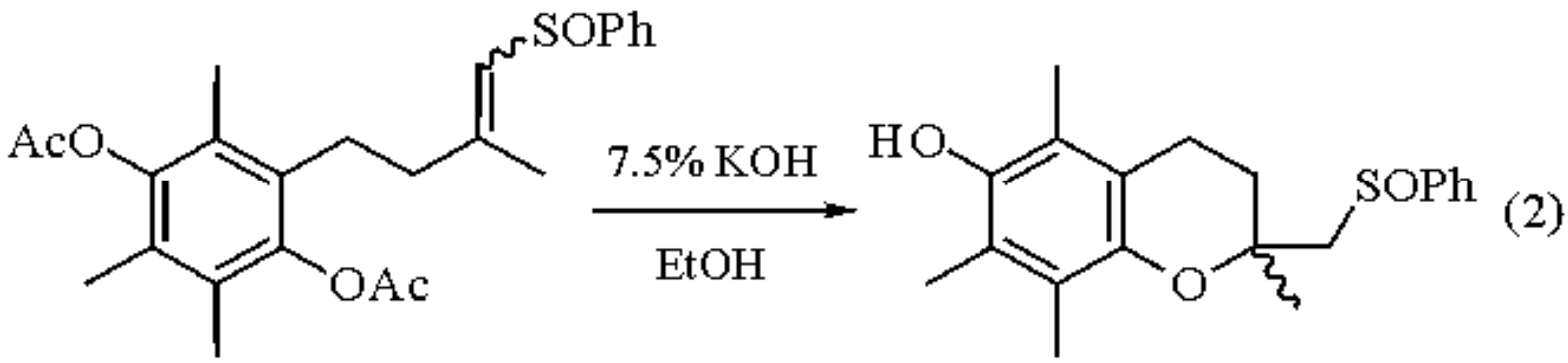

$(E):(Z) = 1:1$

Alternatively, the reaction can be conducted under phase transfer conditions, and is then specific for aromatic aldehydes (eq 3).[5] Initially a tetraalkylammonium salt was used as catalyst, but it was discovered that the phosphonate could function as its own phase transfer catalyst (eq 3).[6] Subsequent reports showed that it can function generally as a phase transfer catalyst, for example in the alkylation of benzyl methyl ketone with butyl bromide.[7]

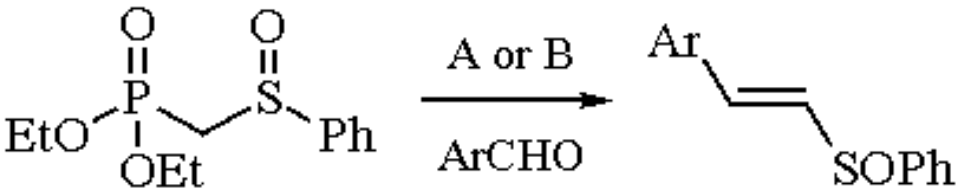

A: CH_2Cl_2, 50% aq NaOH — 53%, $(E):(Z) = 82:18$

B: CH_2Cl_2, 50% aq NaOH, $Et_3N^+Bn\ Cl^-$ — 48-57%

Diethyl phenylsulfinylmethylphosphonate undergoes the Pummerer reaction under a variety of conditions, resulting in oxidation of the α-carbon with concomitant reduction of the sulfoxide to a sulfide (eq 4).[8-11] Limited success in the transfer of chirality from sulfur to carbon has been achieved.[10]

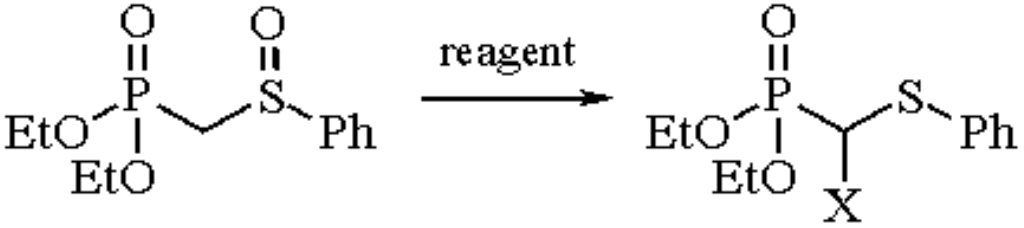

(4)

Reagent	X
I_2, ROH (R = Me, Et)	RO
$(RCO)_2O$ (R = Me, *t*-Bu, Ph, CF_3)	RCO_2
PhCOCl	Cl

If the Pummerer reaction is conducted in an aromatic solvent, Freidel-Crafts products are produced (eq 5).[11]

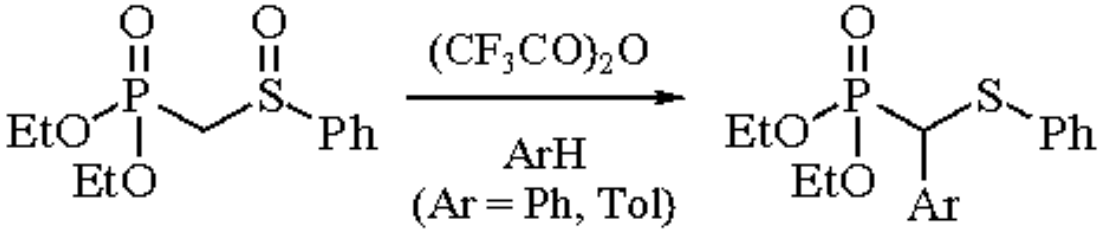

(5)

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Diethyl Phenylthiomethylphosphonate

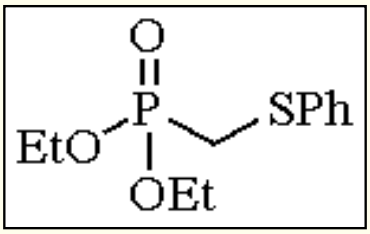

[38066-16-9] · $C_{11}H_{17}O_3PS$ · Diethyl Phenylthiomethylphosphonate · (MW 260.29)

(used for the conversion of aldehydes and ketones to vinyl sulfides, which can be hydrolyzed to yield homologated aldehydes and ketones)

Physical Data: bp 145-150 °C/0.5 mmHg.[1]

Solubility: sol CH_2Cl_2, THF, MeOH.

Form Supplied in: neat liquid.

Preparative Methods: although the reagent is commercially available, there are a number of methods available for its preparation.

The Arbuzov reaction between phenylthiomethyl chloride (***Chloromethyl Phenyl Sulfide***) and ***Triethyl Phosphite*** is the most commonly used method of preparation (eq 1).[2,3]

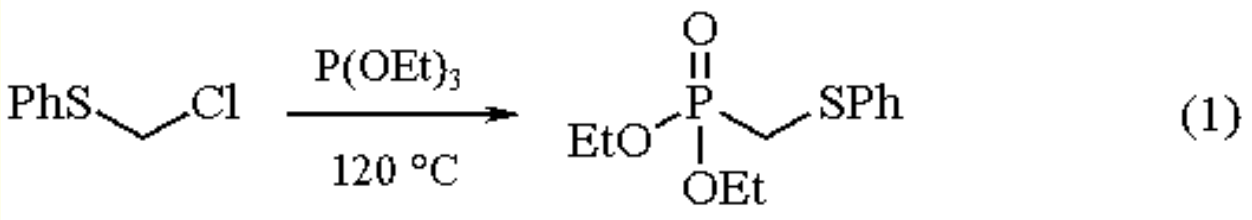

A useful alternative to the Arbuzov reaction is the Michaelis-Becker reaction between phenylthiomethyl chloride and sodium diethyl phosphite (eq 2).[3]

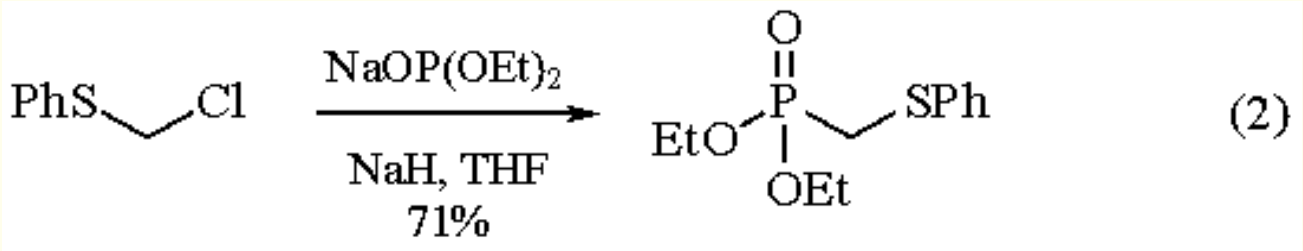

An umpolung version of the Michaelis-Becker reaction involves the treatment of ***Diethyl Phosphorochloridate*** with lithiated methyl phenyl sulfide (eq 3).[1]

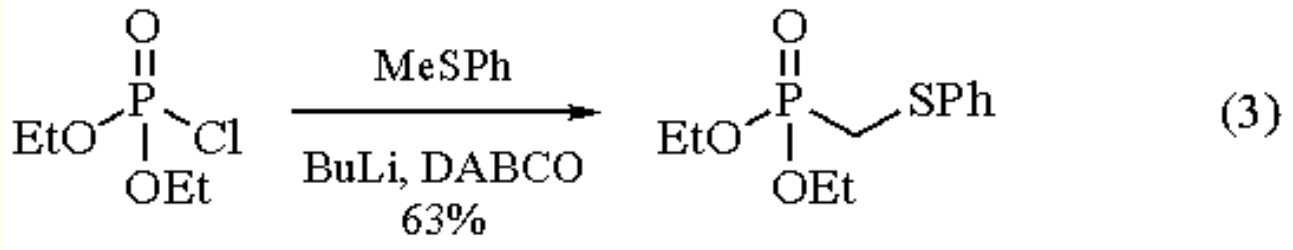

Moderate yields have been obtained in the Mitsunobu coupling of diethyl 1-hydroxyalkylphosphonates and thiophenol (eq 4).[4]

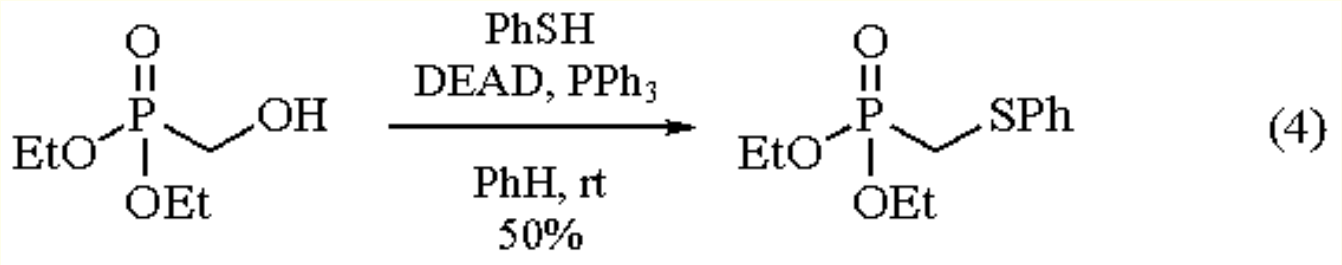

Handling, Storage, and Precautions: has a stench and is an irritant, but is reasonably stable for storage. Reactions involving this reagent are best conducted under anhydrous conditions, under nitrogen, in a well ventilated fume hood.

Reactions.

In general, anions generated from diethyl phenylthiomethylphosphonate can be alkylated or reacted with aldehydes or ketones to make vinyl sulfides or vinylphosphonates. We shall consider only selected examples here because most of the reactions of diethyl phenylthiomethylphosphonate are strictly analogous to those of ***Diethyl Methylthiomethylphosphonate*** and the reader is referred to that entry.

The reaction of metalated diethyl phenylthiomethylphosphonate with ketones to give vinyl sulfides often proceeds in excellent yields (eq 5).[5]

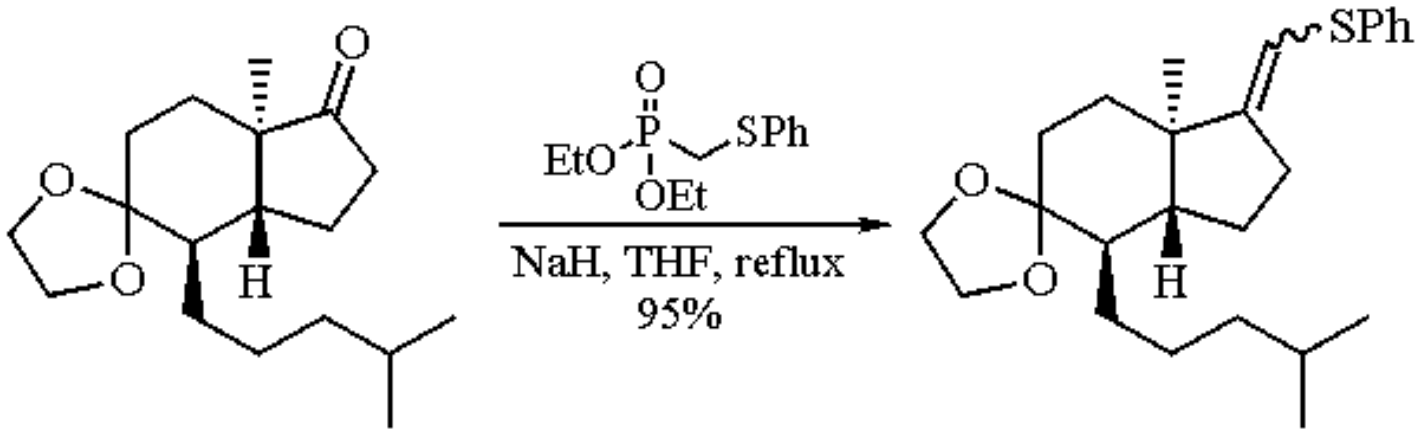

(5)

The reaction of lithiated diethyl phenylthiomethylphosphonate with aryl nitriles to give ketimines, followed by hydrolysis, provides a simple route to synthetically useful β-keto sulfides (eq 6).[6] Alternatively, the anion can be quenched with ***Carbon Dioxide*** to furnish α-phenylthiodiethylphosphonocarboxylic acids (eq 6).[7]

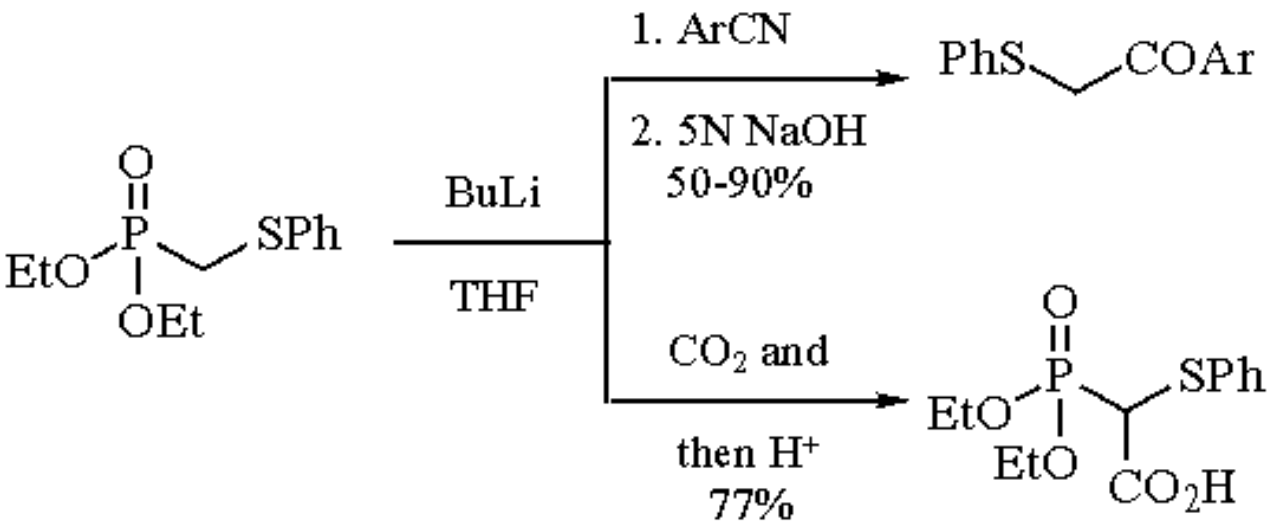

(6)

Reaction of the lithiated reagent with alkyl halides, followed by oxidation to a sulfoxide and elimination, constitutes an efficient synthesis of predominately *trans*-vinylphosphonates (eq 7).[8]

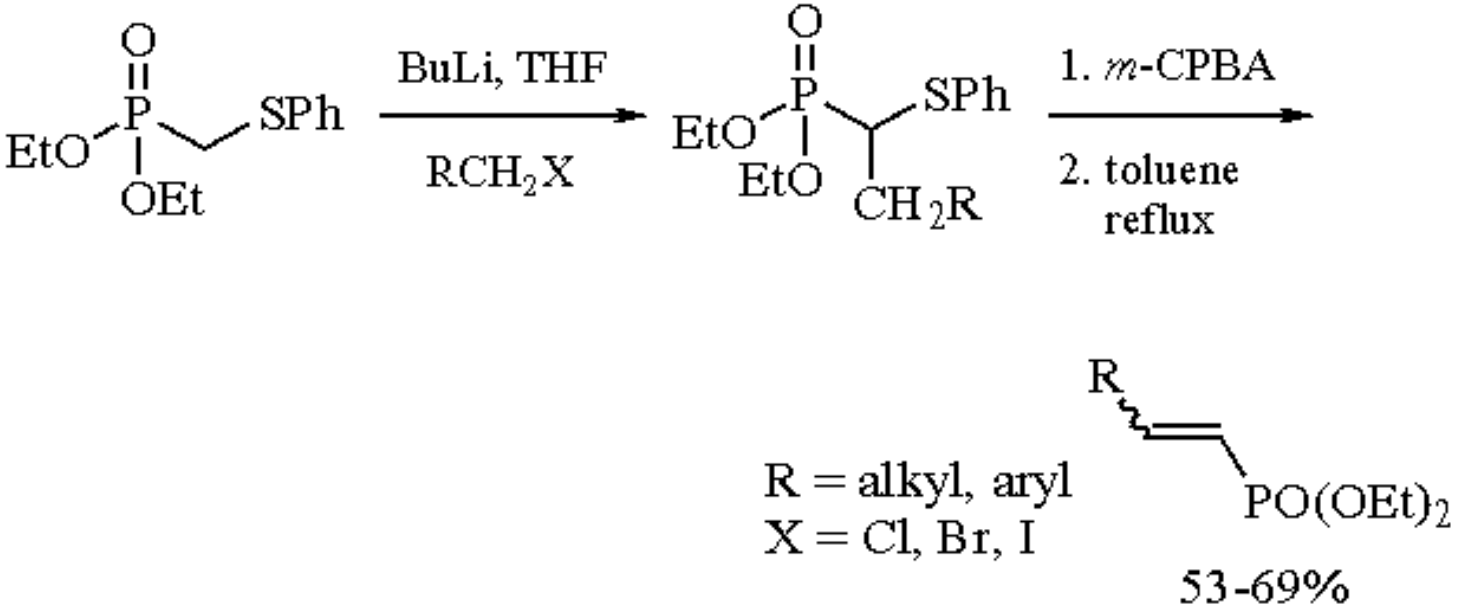

(7)

Treatment of the reagent with ***N-Chlorosuccinimide*** gives diethyl α-chlorophenylthiomethylphosphonate,[3,9] which can be reacted with alcohols to furnish *O,S*-acetals or metalated and reacted with aldehydes and ketones in the usual way to furnish 1-chloro-1-phenylthioalkenes (eq 8).[9] Initial oxidation to the sulfone followed by metalation and condensation with aromatic aldehydes furnishes 1-chloro-1-phenylsulfonylalkenes (eq 8).[10]

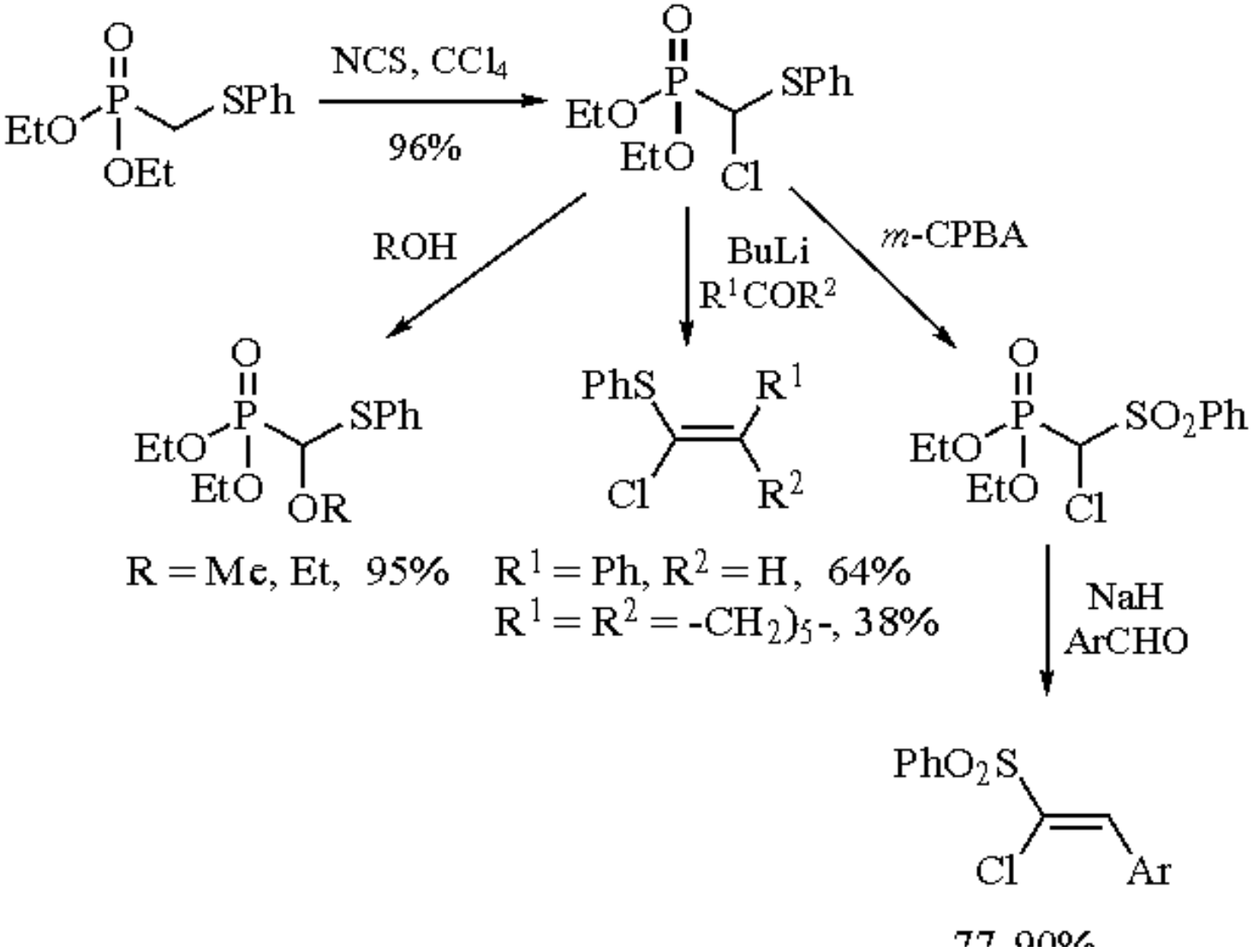

(8)

77-90%

Controlled oxidation of the reagent to give ***Diethyl Phenylsulfinylmethylphosphonate*** is discussed separately under the section for that reagent.

---

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Diethyl Phosphonite

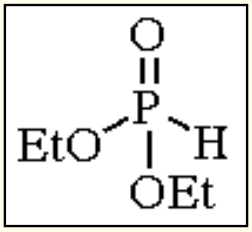

[762-04-9] · $C_4H_{11}O_3P$ · Diethyl Phosphonite · (MW 138.10)

(weak acid whose anion can function as a nucleophile at phosphorus, engaging in S_N2 displacement reactions and carbonyl additions; can hydrophosphonylate imines, ketenes, and enamines; can phosphonylate vinyl and aryl halides with Pd^0 catalysis; can function as an amine-protecting group[1])

Alternate Names: diethyl phosphite; DEP.

Physical Data: bp 50-51 °C/2 mmHg; *d* 1.072 g cm^{-3}.

Solubility: sol water, THF, alcohol.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: should be stored in absence of moisture and freshly distilled before use if any suspicion exists regarding purity.

Nucleophilic Displacement.

The anion of DEP can be formed using strong bases (i.e. alkali metals, alkoxides, or hydrides) and can undergo a variety of displacement reactions which are generally known as Michaelis-Becker reactions.[1] The mechanism of these reactions is viewed as proceeding via classical S_N2 attack by phosphorus on the electrophilic center.[2] A variety of phosphonates have been prepared by this method (eqs 1 and 2).[3,4]

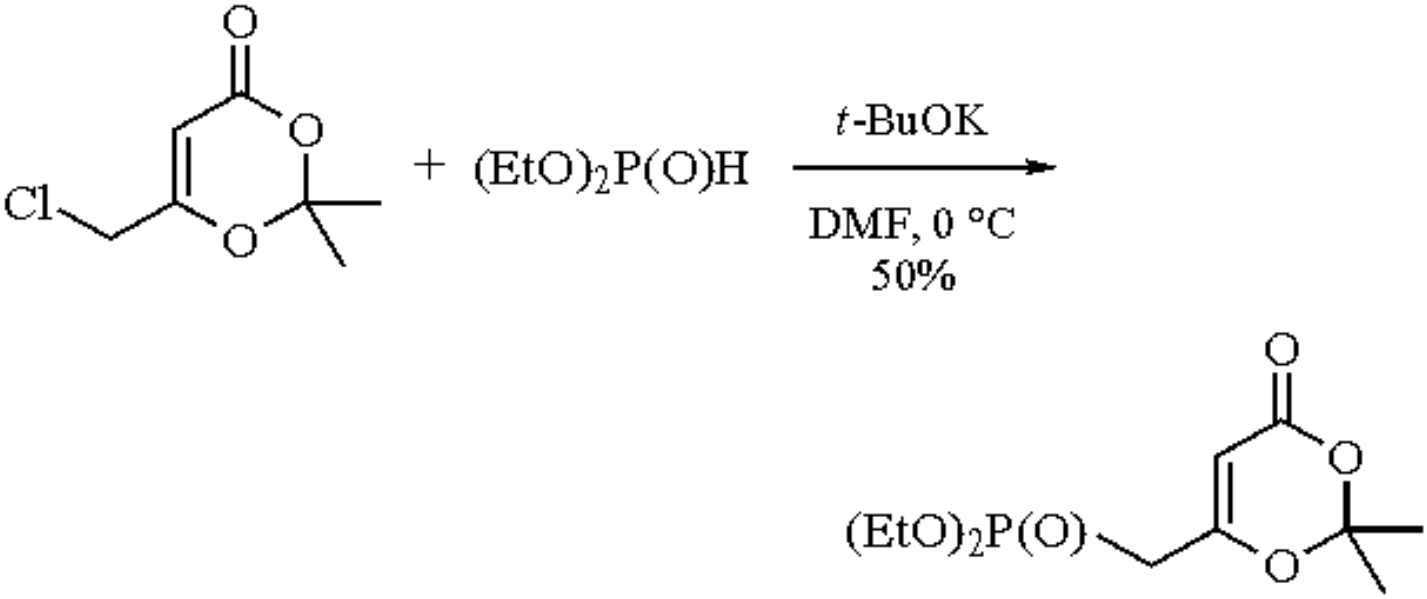

(1)

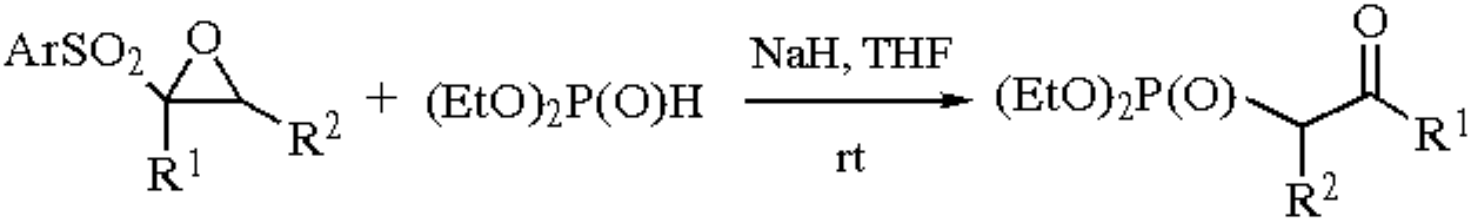

(2)

R^1, R^2, Yield (%) = Me, H, 70; C_3H_7, H, 90; C_5H_{11}, H, 87; CH_2=CHMe, H, 82; Me, Me, 60; Me, Ph, 75; Et, Ph, 78

As with trialkyl phosphites, reaction of DEP anion with α-halo ketones results in Perkov-type products produced from phosphorus attack at the carbonyl carbon rather than that bearing the halide (eq 3).[5]

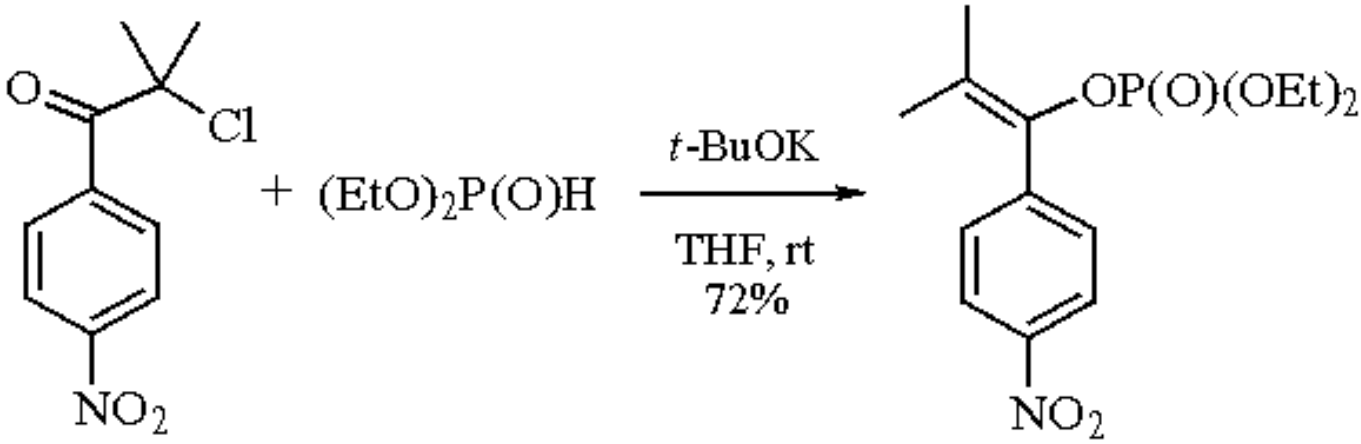

(3)

Reaction of the anion with α-halo esters[6] or α-halo phosphonates[7] is reported to proceed cleanly with simple displacement of the halogen.

Reactions with Multiple Bond Systems.

In addition to displacement reactions, the anion of DEP can add to a carbonyl carbon, forming the corresponding α-hydroxy phosphonate. This reaction, known as the Pudovik reaction, has been shown to be catalytic in the amount of phosphite salt necessary to promote the reaction.[8] Typically, a small amount of alkoxide is added to the reaction mixture (eqs 4 and 5).[9,10]

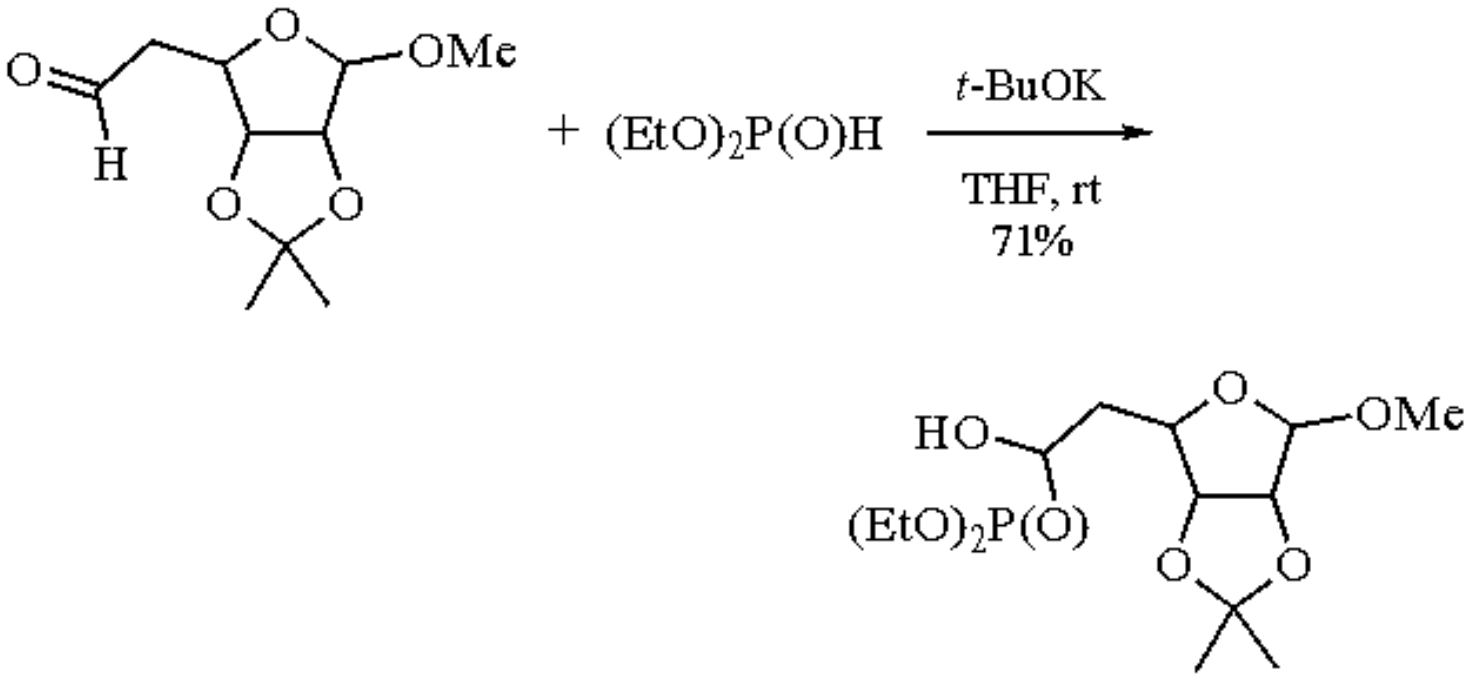

(4)

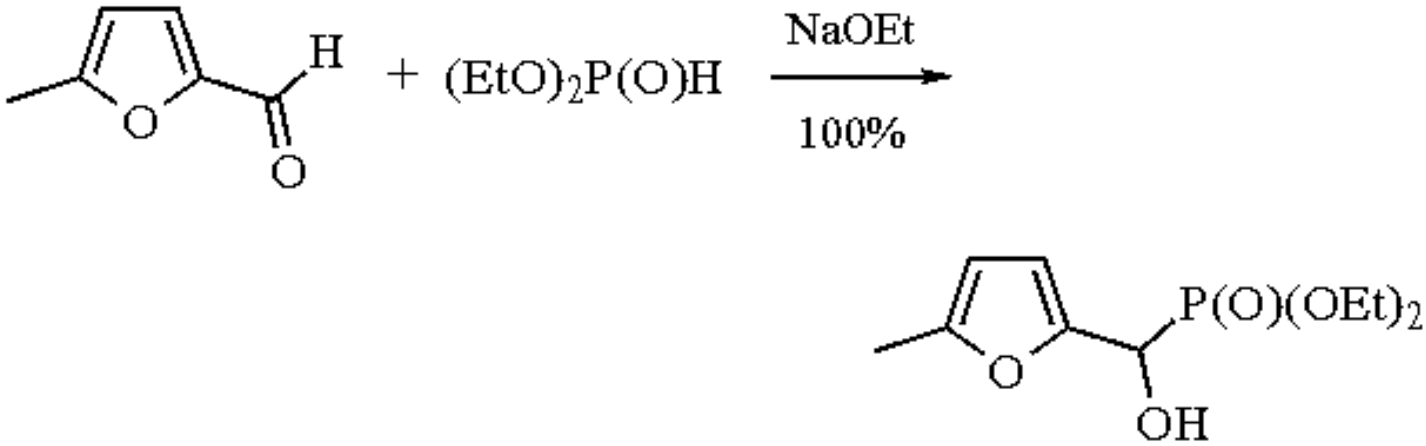

(5)

It has been shown that the rate of the reaction increases in a manner directly proportional to the solvating power of the medium.[11] Other approaches which have been successfully employed to promote the Pudovik reaction with aldehydes or ketones include (a) neutral amine bases (eq 6),[12] (b) chiral amine bases where asymmetric induction resulted,[13] (c) phase-transfer catalysis,[14] (d) solid phase basic catalysis with alumina,[15] and (e) solid phase basic catalysis with fluoride salts (eq 7).[16]

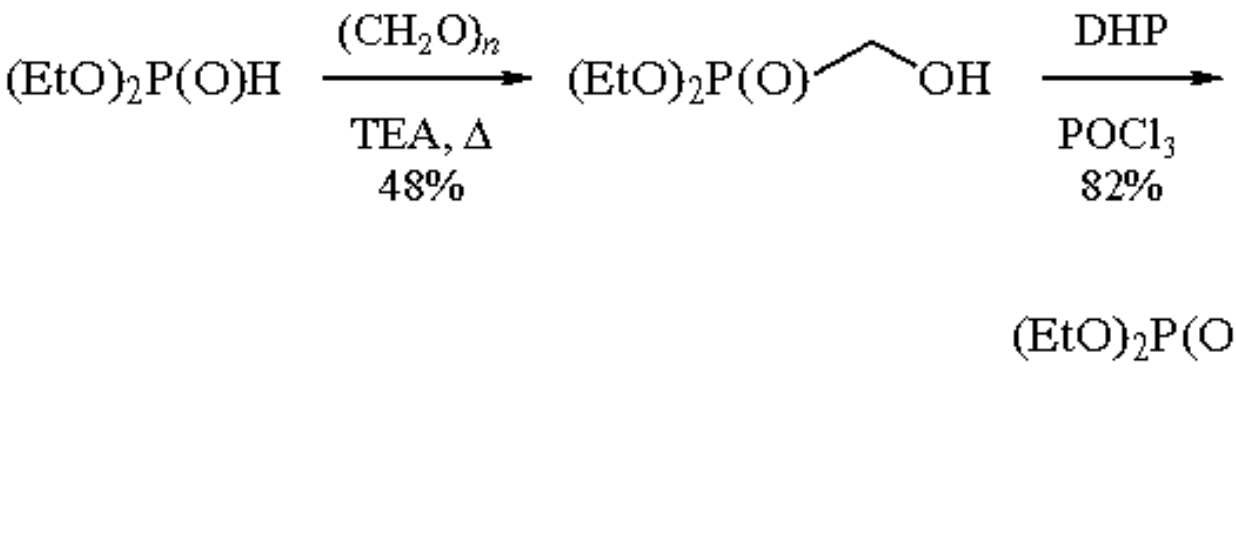

(6)

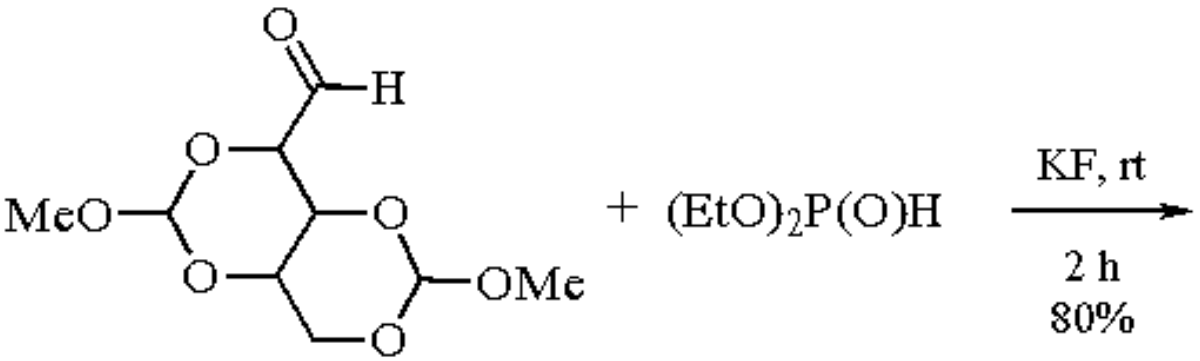

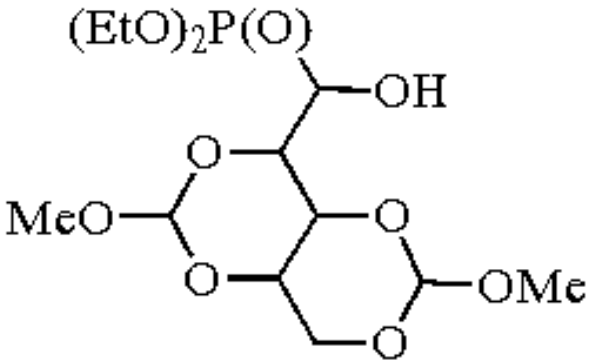

(7)

In addition to carbonyl systems, DEP adds to imines (eq 8),[17] ketene acetals (*O*,*N*-;*S*,*N*-;*N*,*N*-) (eq 9),[18] and enamines (eq 10).[19]

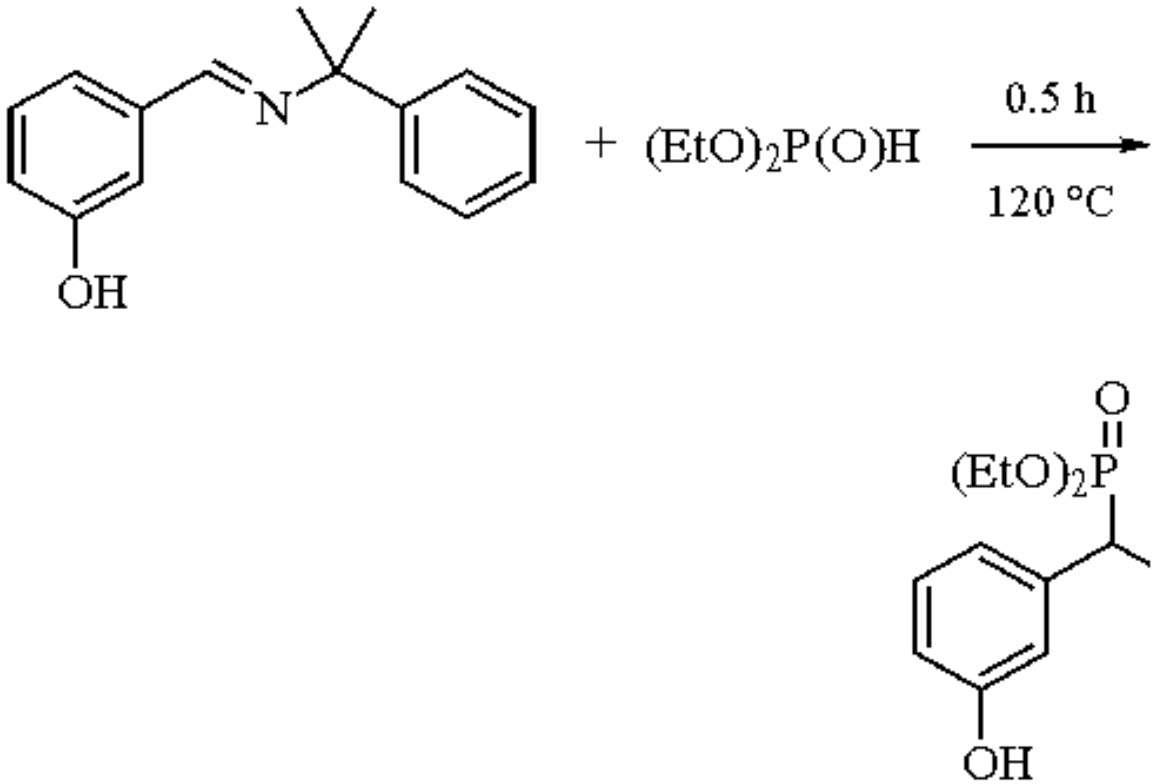

(8)

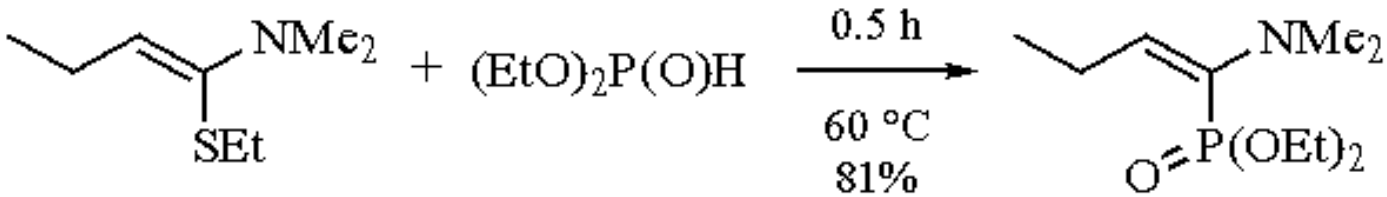

(9)

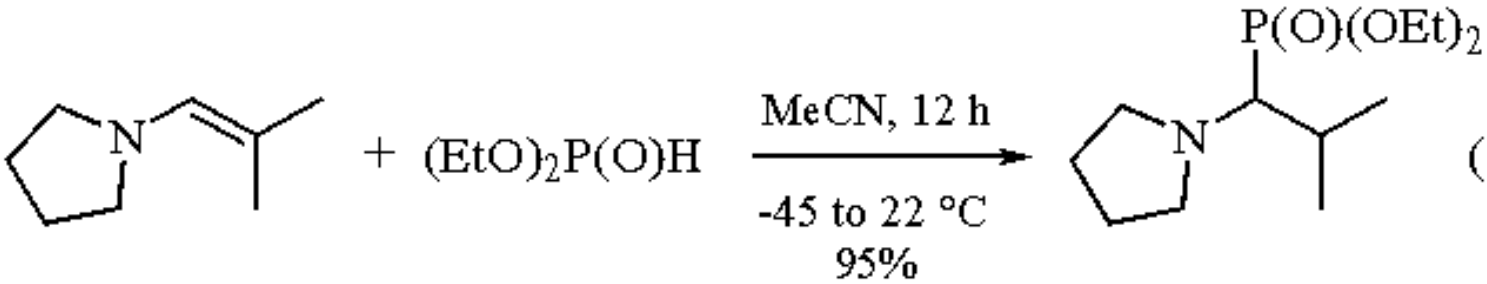

(10)

Another aspect of multiple bond addition by DEP is conjugate addition to α,β-unsaturated esters,[20] amides,[21] and nitriles[20] via the sodium salt and the addition to nitroalkenes in the presence or absence of neutral amine bases.[22] With α,β-unsaturated ketones and aldehydes, product mixtures arise, resulting from competing 1,2- vs.1,4-addition and can be influenced by factors such as steric hindrance and reaction temperature.

Palladium-Catalyzed Phosphonylation.

Complexes of palladium(0) have been used to catalyze the addition of DEP to aryl (eq 11)[23] and vinyl (eq 12)[24] halides. As is typical, the bromo and iodo compounds were significantly more reactive than the chloro. For the arylation reactions, good yields were obtained irrespective of substitution. In the case of the vinylation reactions, addition occurs stereospecifically.

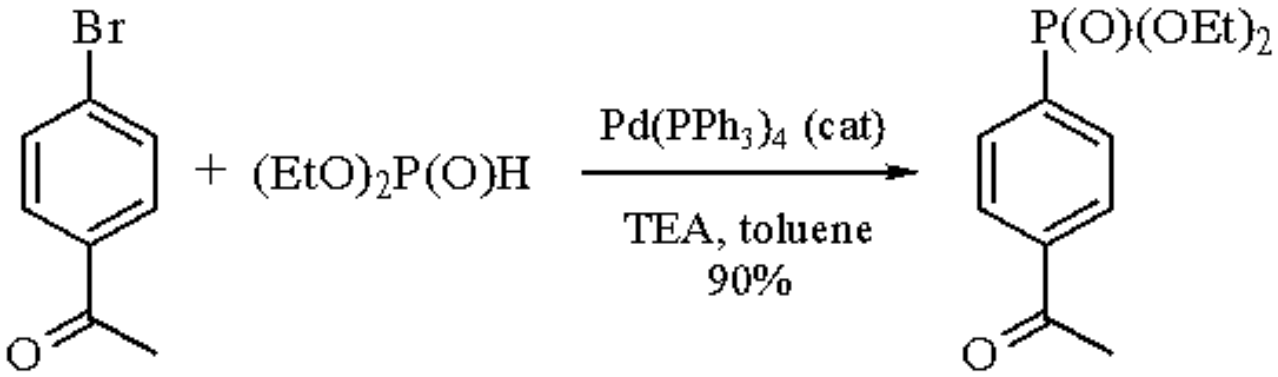

(11)

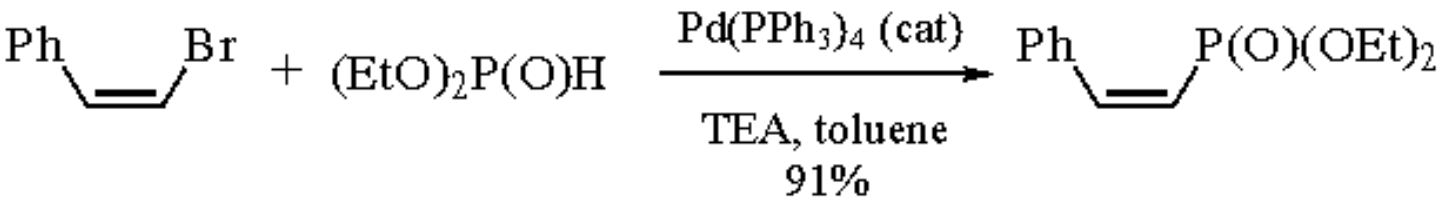

(12)

Amine Protecting Group.

The use of DEP in peptide synthesis has found successful application as both an amine protecting group and carboxylic acid activating group.[25] Interestingly, the amine protection aspect of its use has been exploited in other areas of organic synthesis (eq 13).[26]

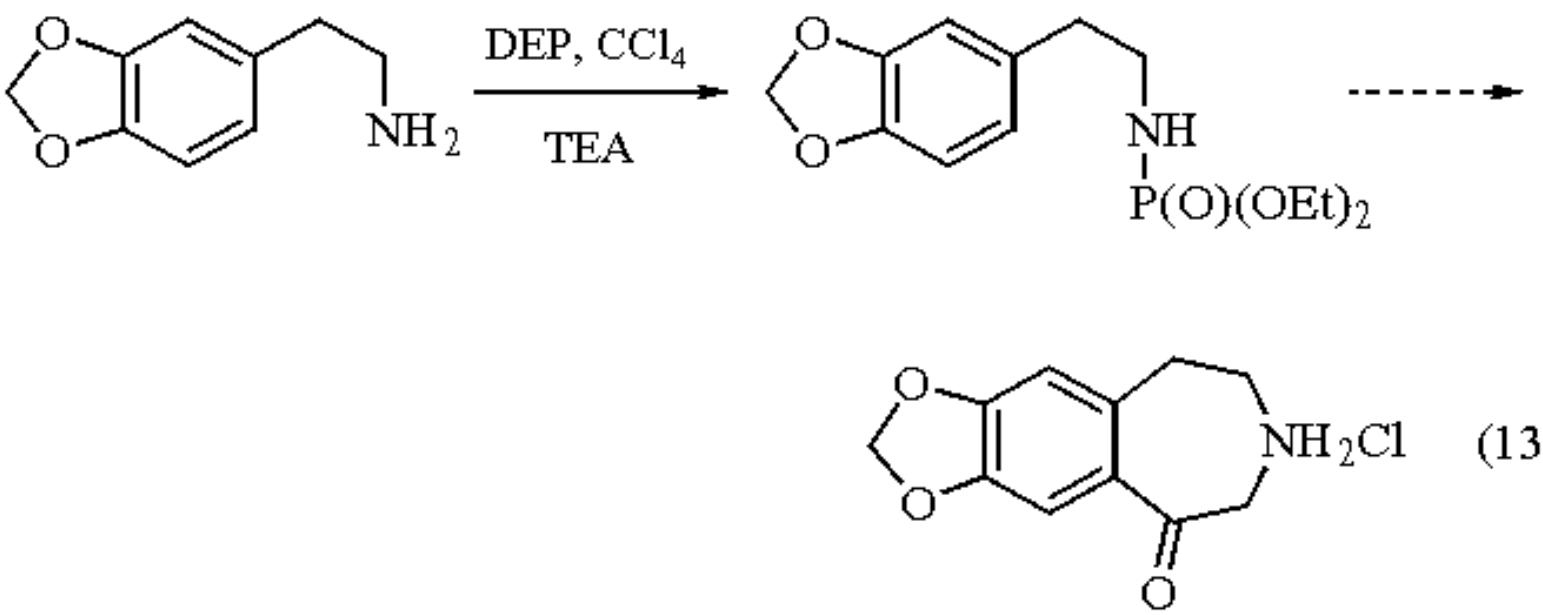

(13)

Radical Reactions.

The photostimulation of aryl iodides in the presence of DEP as its sodium or potassium salt presents a highly efficient approach to prepare diethyl arylphosphonate esters.[27] This reaction has been explored mechanistically and is believed to be operating via a radical chain S_N1 mechanism. With diiodo, iodobromo and iodochloro (except *meta*) arenes, bis substitution occurs. Other radical reactions which involve DEP include use as a hydrogen atom source in radical

deoxygenations[28] and radical additions to terpenes.[29]

Specialized Reactions.

DEP is known to react with diazo compounds, in the presence of copper(II) salts, to form diethyl phosphonates.[30] The reaction is sensitive to stoichiometry and has been largely applied with α-diazo esters and 2-diazo-1,3-diketones (eq 14).[30]

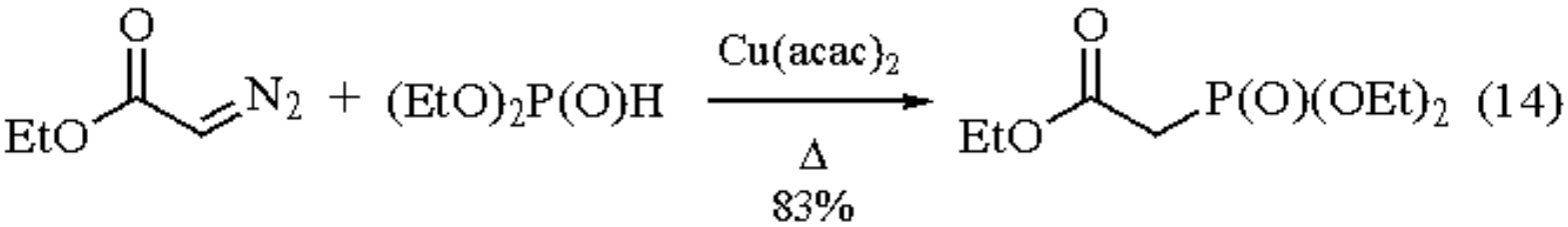

A reagent prepared from the sodium salt of DEP and ***Tellurium*** metal (either catalytic or stoichiometric) is useful for the deoxygenation of terminal epoxides to the corresponding alkenes.[31] The deoxygenation occurs on nonterminal epoxides but is significantly slower and therefore allows for selective reaction to take place.

Phosphate esters can be prepared from reacting triflates with potassium DEP.[32] The reactivity follows the order aryl > cyclohexenyl > cyclopropyl > alkyl.

When *gem*-dibromocyclopropanes or *gem*-dibromoalkenes are reacted with DEP (neat) in the presence of ***Triethylamine***, high yields (90%) of the monobromo compounds are obtained.[33] This method contrasts with other approaches generally involving the use of metallic reagents.

---

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Kenneth Green

American Cyanamid Co., Pearl River, NY, USA

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Diethyl Phosphorobromidate[1]

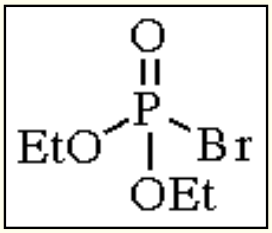

[51761-27-4] · $C_4H_{10}BrO_3P$ · Diethyl Phosphorobromidate · (MW 217.00)

(β-lactam formation; peptide synthesis; formation of trifluoroacetyl bromide)

Alternate Names: diethoxyphosphorus oxybromide; diethyl bromophosphate.[1]

Physical Data: bp 75 °C/1.5 mmHg, bp 58-59 °C/0.25 mmHg.

Solubility: sol CH_2Cl_2, Et_2O, toluene.

Preparative Methods: prepared in good yield from the reaction between ***N-Bromosuccinimide*** and diethyl hydrogen phosphite,[1] or from the bromination of ***Triethyl Phosphite*** with ***Bromine*** at -30 °C to -25 °C.[2] It can also be prepared in almost quantitative yield by reacting diethyl hydrogen phosphite with ***Chlorotrimethylsilane*** followed by bromine at -78 °C.[3]

Purification: distilled under reduced pressure.[1]

Handling, Storage, and Precautions: highly toxic, corrosive, and a lachrymator. It should be used in a fume hood. It is highly moisture sensitive and undergoes thermal decomposition. It generates toxic byproducts when decomposition occurs. Should be stored under nitrogen in a cool dry place.

Formation of β-Lactams from β-Amino Acids.

Diethyl phosphorobromidate is a very effective condensing reagent for the formation of β-lactams from β-amino acids.[4] This methodology works well for *N*-substituted β-amino acids, which cyclize to the corresponding β-lactams in moderate to high yield (eq 1). In the case of *N*-unsubstituted β-amino acids, the β-lactam formation does not give good results. This methodology allows the products to be easily isolated by simple aqueous work-up.

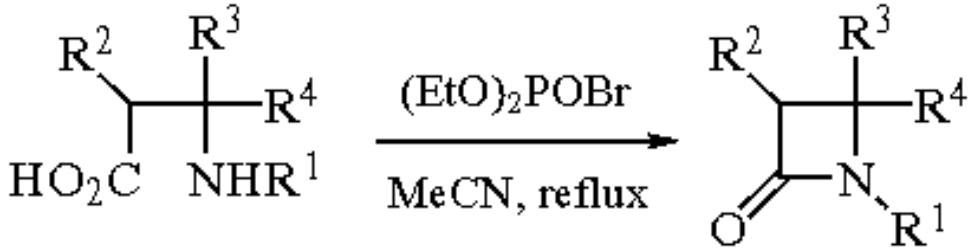

(1)

$R^1 = Bn, i\text{-}Pr;\ R^2 = H, Me;\ R^3 = H, Me, Ph, CO_2Me;\ R^4 = H, Me$

Peptide Formation.

A number of organophosphorus compounds, such as ***Diphenyl Phosphorazidate*** and ***Diethyl Phosphorocyanidate***, have been used for peptide synthesis. The expense and rather limited availability of these reagents prevents their general laboratory use. Diethyl phosphorobromidate has been shown to be a useful and inexpensive reagent for the synthesis of amides and, in particular, racemization-free peptide synthesis.[2] It forms reactive diethylphosphoric-carboxylic mixed anhydride intermediates with carboxylic acids (eq 2). These reactive intermediates are susceptible to nucleophilic attack at the carbonyl carbon. Diethyl phosphorobromidate is particularly effective for coupling sterically hindered α,α-disubstituted amino acids, while most of the usual coupling methods are of limited value for incorporating these amino acids into peptides.

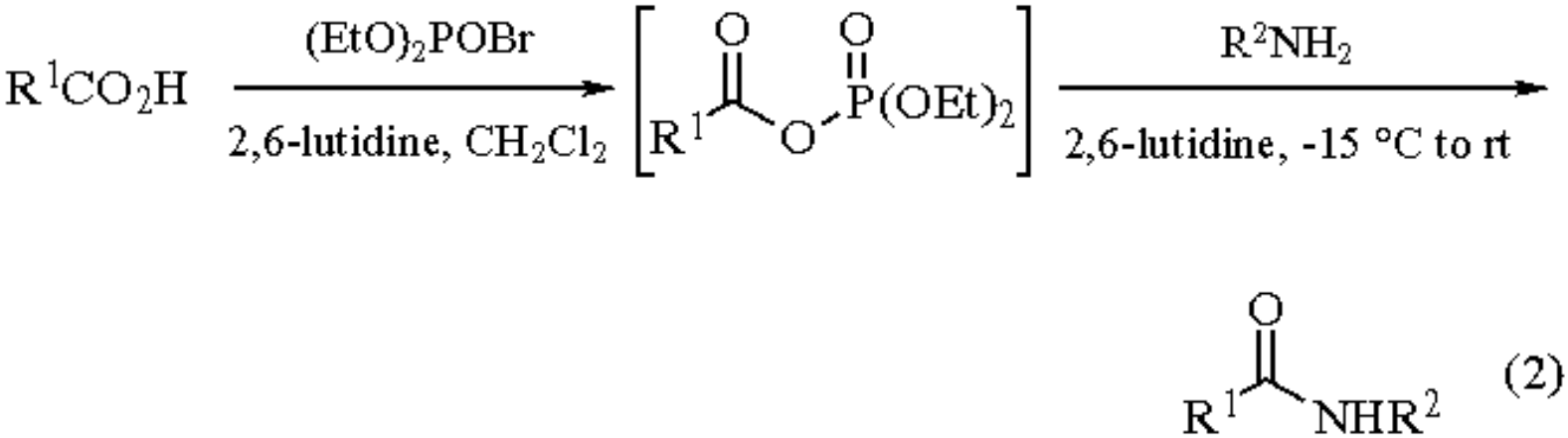

(2)

Trifluoroacetyl Bromide.[3]

Diethyl phosphorobromidate reacts with ***Trifluoroacetic Anhydride*** at ambient temperature in the presence of catalytic amounts of ***N-Methylimidazole*** to yield quantitative amounts of trifluoroacetyl bromide and diethylphosphoric-trifluoroacetyl mixed anhydride (eq 3). These can be readily separated.[3]

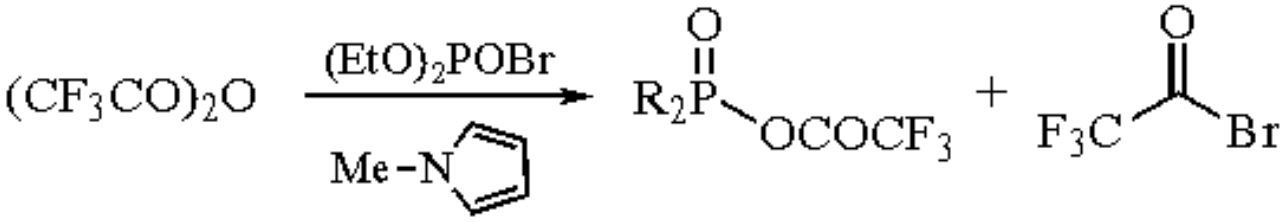

(3)

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Yi-Yin Ku

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Diethyl Phosphorochloridate[1]

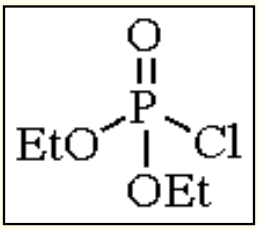

[814-49-3] · $C_4H_{10}ClO_3P$ · Diethyl Phosphorochloridate · (MW 172.55)

(highly electrophilic phosphorylating reagent easily installed on anionic carbon,[2] oxygen,[3] nitrogen,[4] and sulfur;[5] ketones are converted to enol phosphates which can be reduced to alkenes[6] or alkanes,[7] or coupled with organometallic reagents to form substituted alkenes;[8] enol phosphates can be tranformed into β-keto phosphonates,[9] useful for Horner-Emmons homologation, or into terminal alkynes;[10] used to convert carboxylic acids to other carboxylic derivatives[11])

Alternate Name: diethyl chlorophosphate.

Physical Data: bp 60 °C/2 mmHg; *d* 1.194 g cm^{-3}.

Handling, Storage, and Precautions: highly toxic, corrosive. Use in a fume hood.

Phosphorylation.

Diethyl phosphorochloridate is highly electrophilic and can be cleanly reacted at an anionic center provided that prior metalation is regio- and chemoselective. For example, phenols,[12] thiophenols,[5] and anilines[4] can be phosphorylated under basic conditions (eq 1). The phosphorylated compound can be isolated, or treated further with bases, resulting in orthometalation followed by a facile 1,3-phosphorus migration from the heteroatom to carbon. If carbon phosphorylation is desired, simply treating thiophenol with 2 equiv of ***n-Butyllithium*** followed by diethyl phosphorochloridate gave a moderate yield (58%).[5]

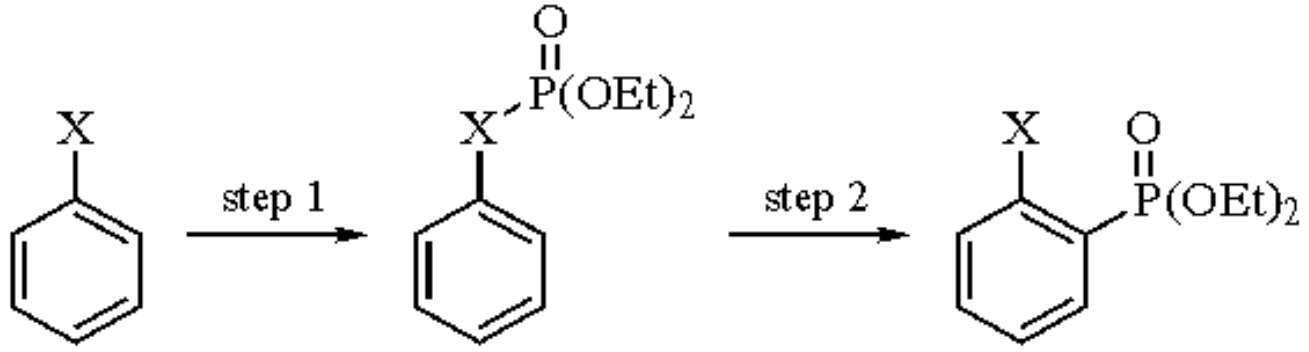

(1)

(1) **(2)** **(3)**

X	Step 1 (% yield **(2)**)	Step 2 (% yield **(3)**)
OH	NaH, THF; $(EtO)_2P(O)Cl$ (50-85%)	LDA, THF -78 °C to rt (90%)
SH	NaH, THF, rt; $(EtO)_2P(O)Cl$ (63%)	LDA, THF -78 to 0 °C (16%)
HNMe	$(EtO)_2P(O)Cl$, Et_3N, THF (97%)	LDA, THF -78 to rt (63%)

Synthetic preparation of oligonucleotides in a cost-efficient manner can be complicated by low chemoselectivity during phosphorylation, suggesting the need for prior nitrogen protection. It has been determined that despite the higher acidity of guanosine and thymidine over a hydroxy, addition of 1 equiv of the phosphorylating agent provided only the phosphates (eq 2).[3] Adenosine and cytidine bases were compatible as well.

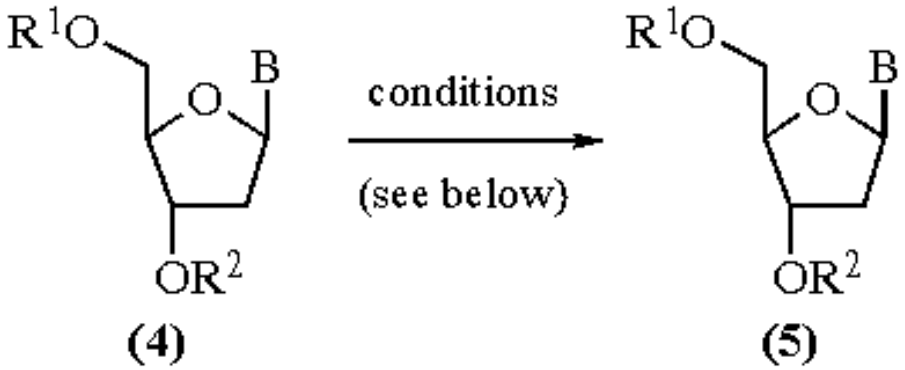

(2)

(4) R1	(4) R2	(4) B	Conditions	(5) R1	(5) R2	% Yield
TBS	H	guanosine	*t*-BuMgCl (2 equiv) THF, rt (EtO)$_2$P(O)Cl	TBS	P(O)(OEt)$_2$	94
H	TBS	thymidine	*t*-BuLi, (2 equiv) THF, -50 °C (EtO)$_2$P(O)Cl	P(O)(OEt)$_2$	H	85

Phosphorylation of substituted 1,4-dihydropyridine dianions occurred selectively (eq 3).[2b] Other reports documented selective phosphorylation at C-5 of thiophenes[2a] and the *ortho* position of various substituted benzenes.[13] It has been noted that certain heterocycles demonstrated alternative pathways, such as nucleophilic attack at carbon rather than phosphorus (eq 4).[14]

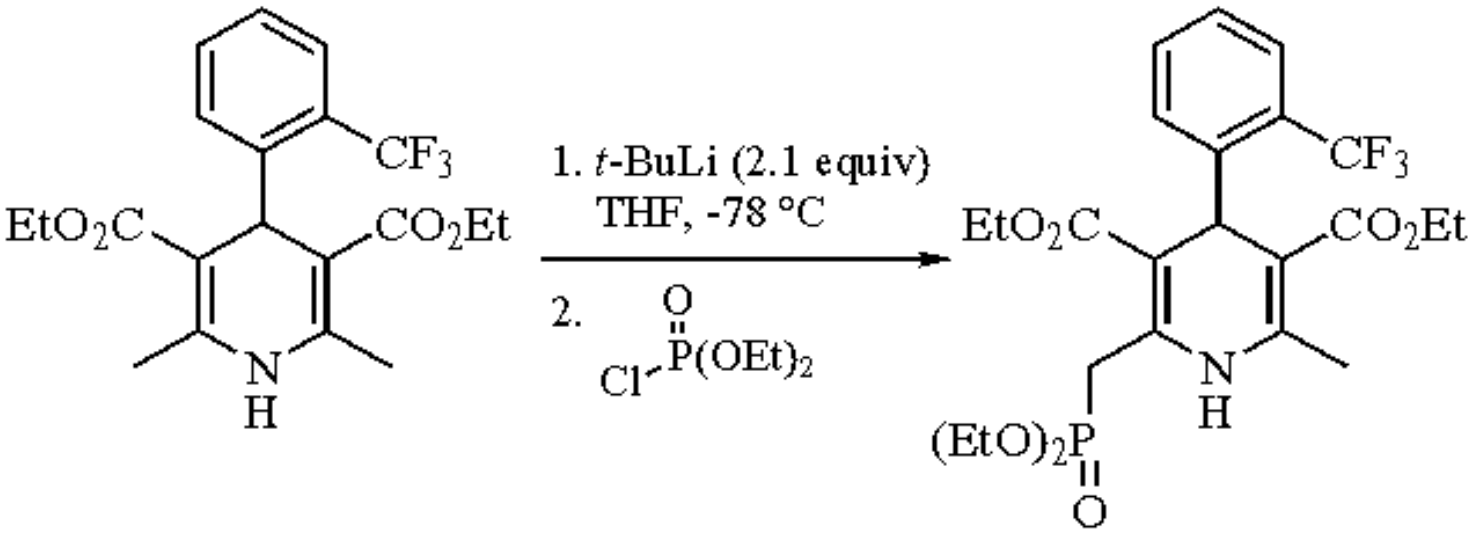

(3)

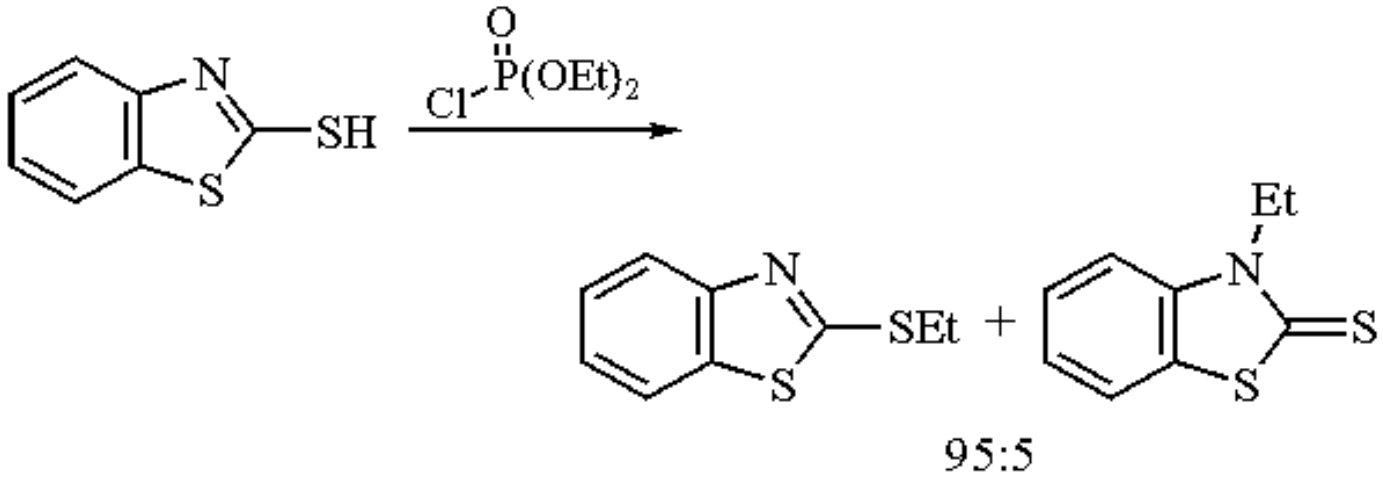

(4)

Trapping of ester, lactone, or ketone enolates results in rapid *O*-phosphorylation, thus providing the enol phosphate (eq 5).[9] Further treatment with base resulted in facile rearrangement to the β-ketophosphonate (eq 5).[15] However, regioisomeric β-ketophosphonates can often be observed from a regiochemically pure enol phosphate (eq 6).[9a] Since the classical Arbuzov reaction is limited to primary alkyl iodides (competing Perkov reaction is known with secondary halides), an alternative method was sought. Installation of an alkene blocking group sufficed (eq 7).[9a] Dienol phosphates have also been prepared and the authors note that ***Lithium 2,2,6,6-Tetramethylpiperidide*** was the preferred base for regiochemical control.[16]

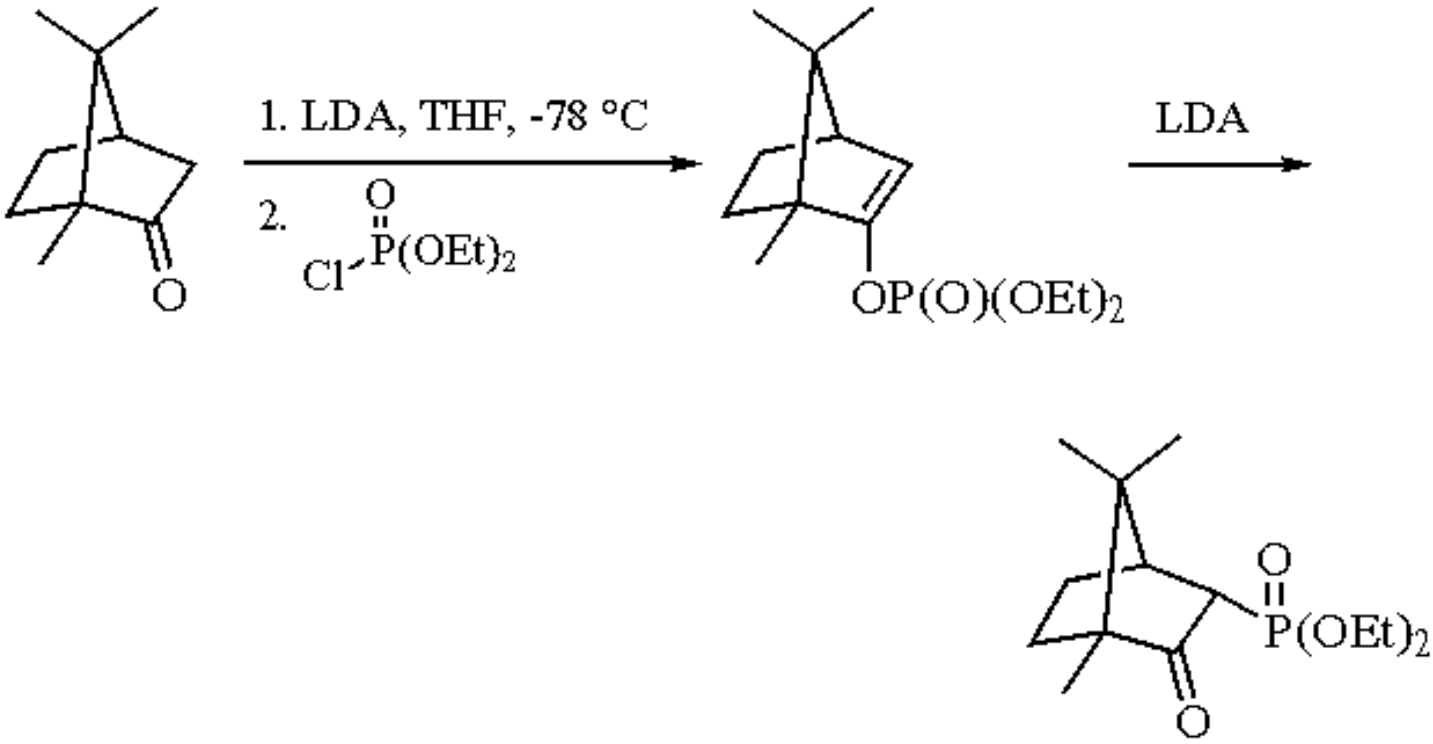

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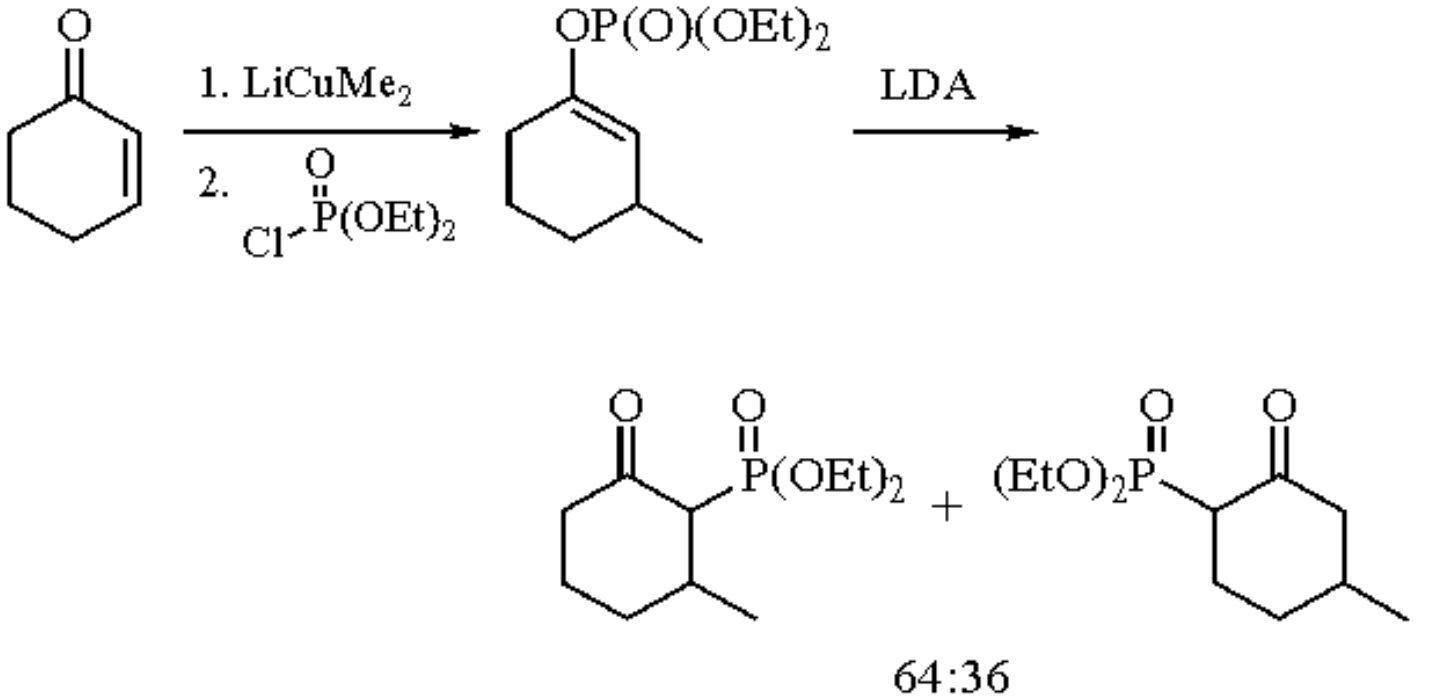

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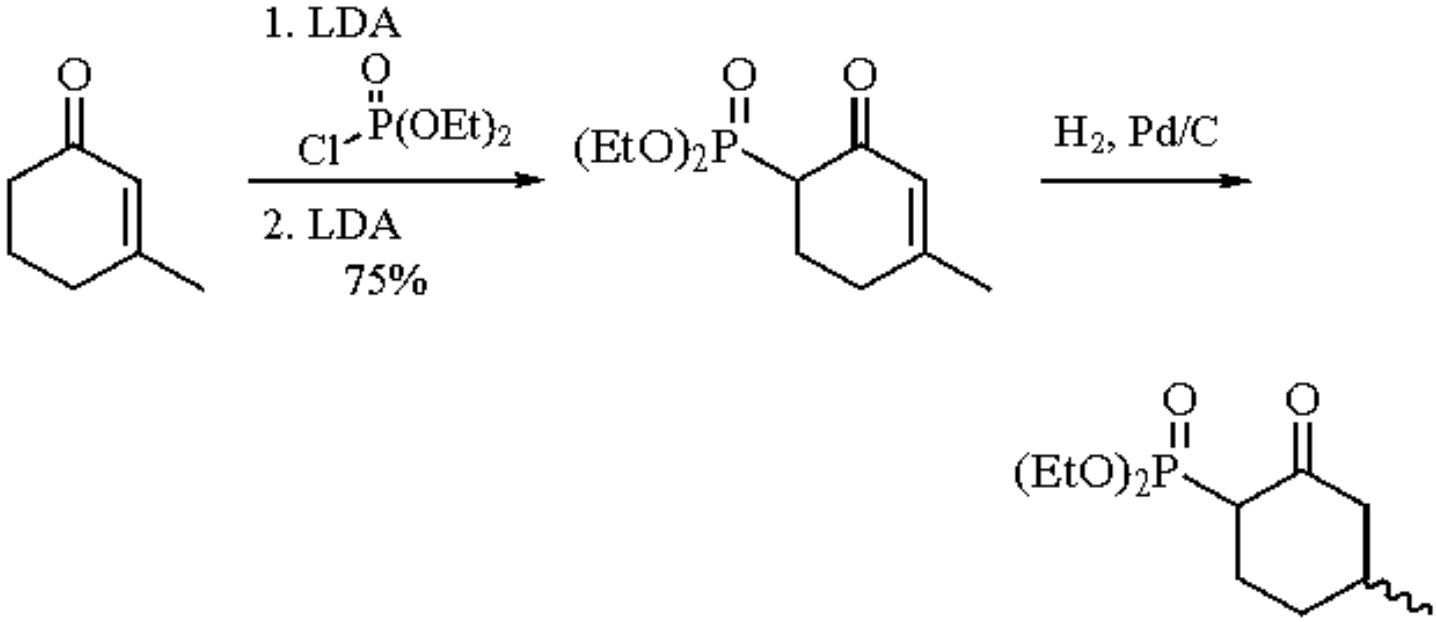

(7)

β-Ketophosphonates are valuable intermediates in the realm of Horner-Emmons alkenation methodology. Acyclic variants are difficult to obtain from enol phosphates due to competing alkyne and allene formation. One solution utilized the dianion derived from α-bromo ketones and trapping with diethyl phosphorochloridate;[17] however, only moderate yields of β-keto phosphonates were reported. The most efficient procedure utilizes the anion derived from dialkyl methylphosphonate, addition to an aldehyde, followed by oxidation (eq 8).[18]

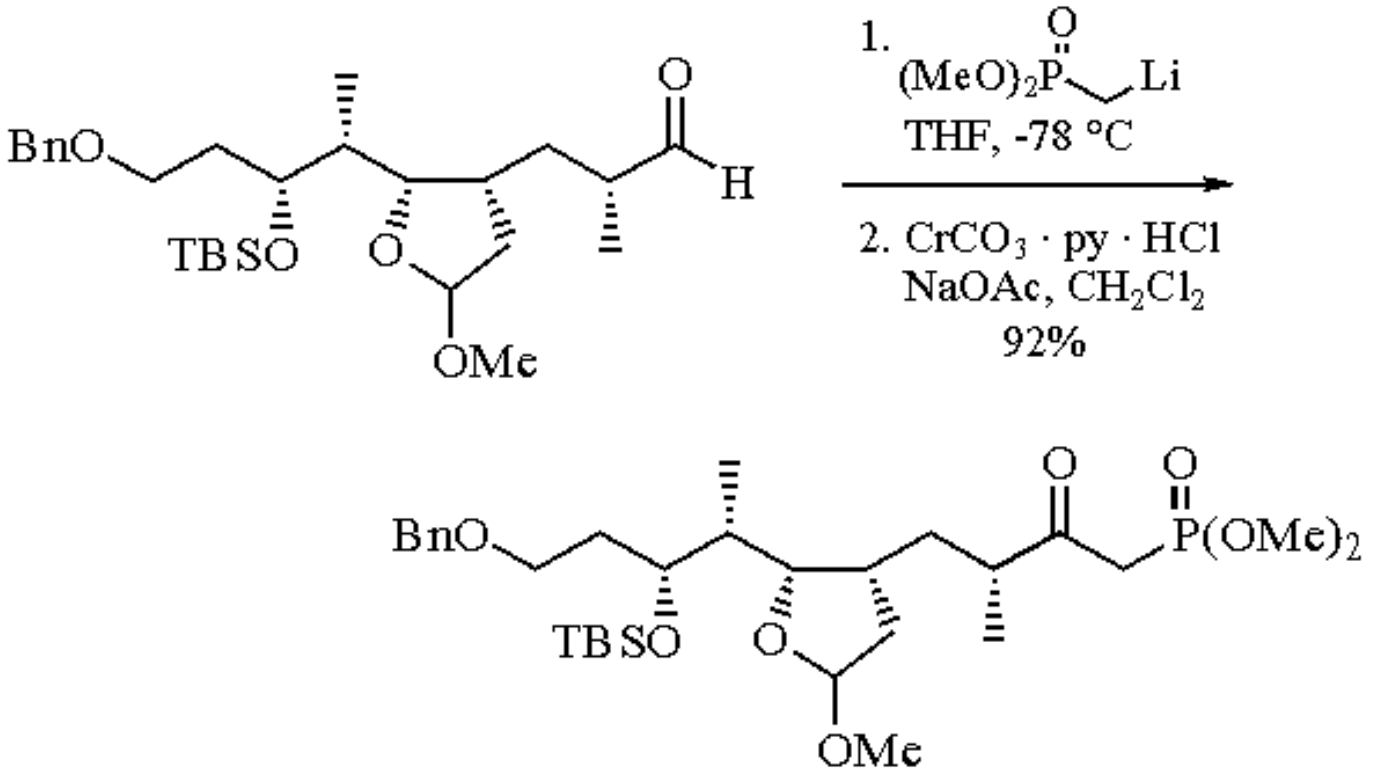

(8)

Interconversion of Carboxylic Acid Derivatives.

Diethyl phosphorochloridate is useful for activation of carboxylic acids toward nucleophilic attack. Subsequent treatment of the phosphate ester with thallium sulfides produced thiol esters.[19] Variations[11] on this theme included prior formation of a heterocyclic phosphonate followed by treatment with alcohols, amines, or thiols, thus providing a racemization-free method to prepare esters, amides, and thiol esters, respectively (eq 9).[11b]

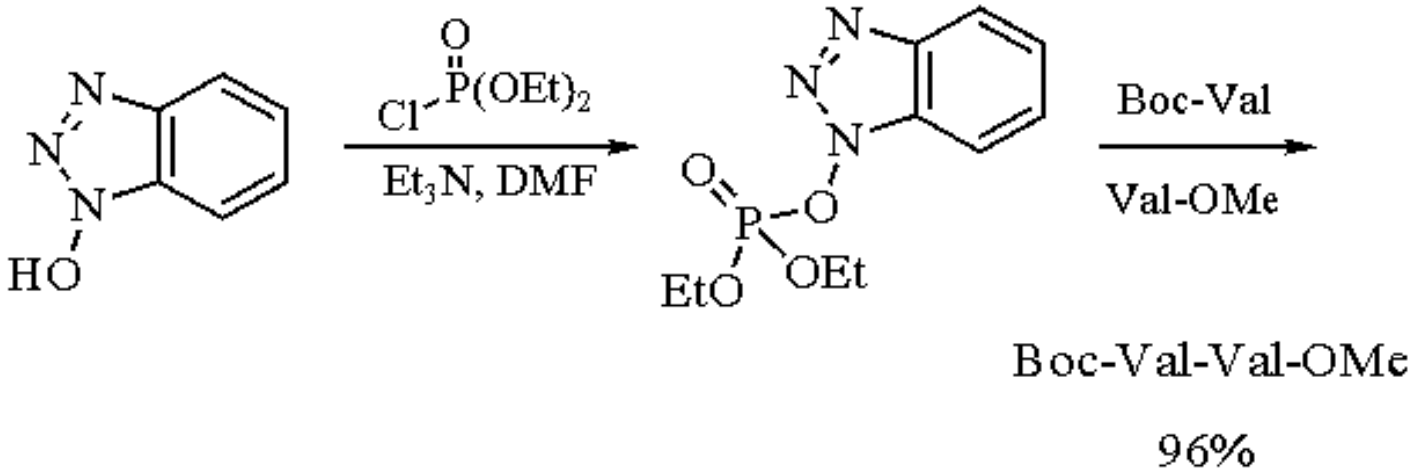

(9)

Amines can be readily transformed to an alcohol surrogate (eq 10)[20] and phenols to anilines.[21]

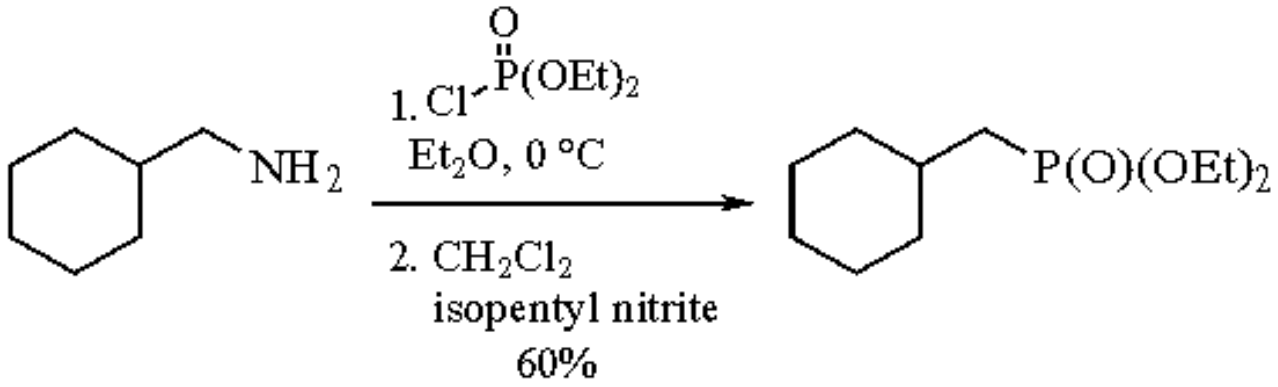

(10)

Deoxygenation of Phenols and Ketones.

Excision of oxygen from a molecule is often encountered in a synthetic sequence. Phenols are readily deoxygenated by formation of the phosphate followed by reduction under dissolving metal conditions.[22] It has been noted that the Birch conditions result in low yields, whereas an alternative method utilizing activated ***Titanium*** metal is superior (eq 11).[23] Under this protocol, enol phosphates are efficiently reduced as well.[6b] Conversion of an enone to a regiochemically defined alkene was accomplished via 1,4-reduction, enolate trapping, and reduction of the trapped enol phosphate (eq 12).[6a] Enol phosphates can be fully reduced to alkanes by hydrogenation of palladium catalysts[7] or converted to vinyl iodides when treated with ***Iodotrimethylsilane***.[24]

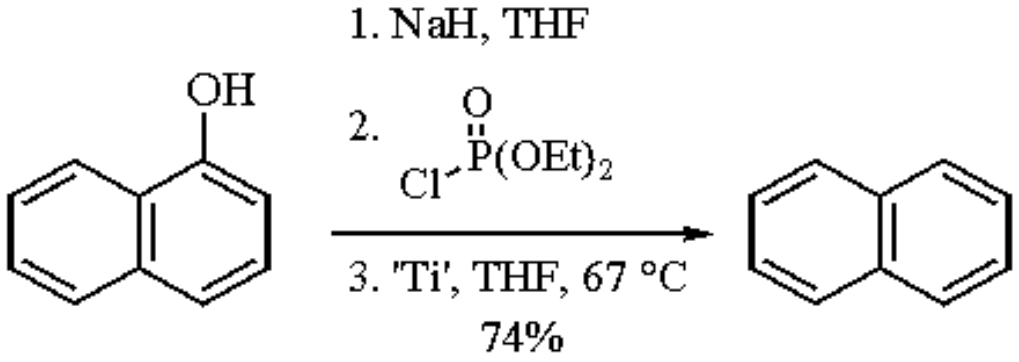

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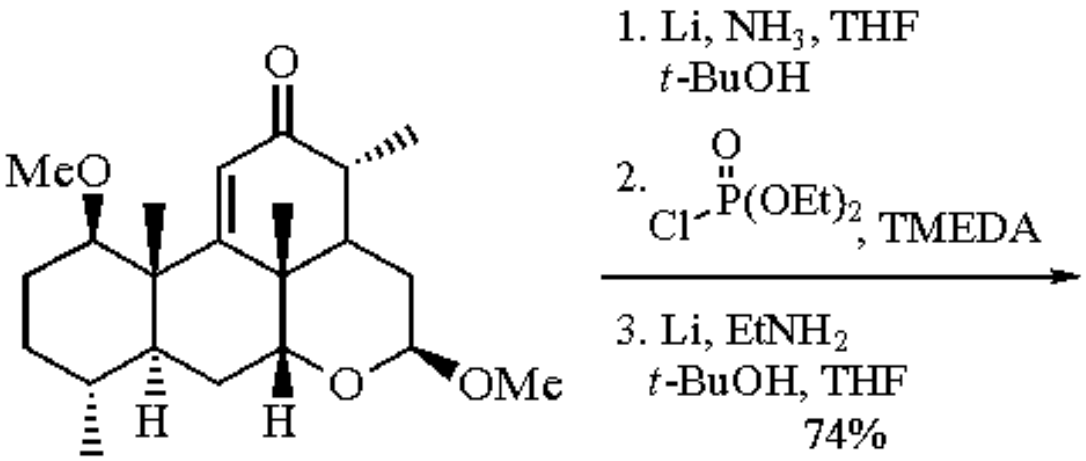

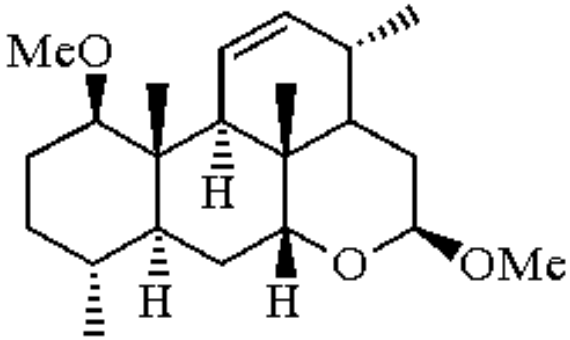

(12)

Synthesis of Alkenes and Alkynes.

Enol phosphates are smoothly transformed into substituted alkenes when treated with organometallic reagents. If the enol phosphate was derived from a β-keto ester, cuprate reagents are generally reactive enough to encourage conjugate addition-phosphate elimination (eq 13).[25] In the event that this coupling fails, the combination of Pd^0 and ***Trimethylaluminum*** results in regio- and stereospecific methylation.[8b] Substrates lacking an ester moiety on the enol phosphate can be alkylated with Grignard reagents under nickel catalysis (eq 14).[8a]

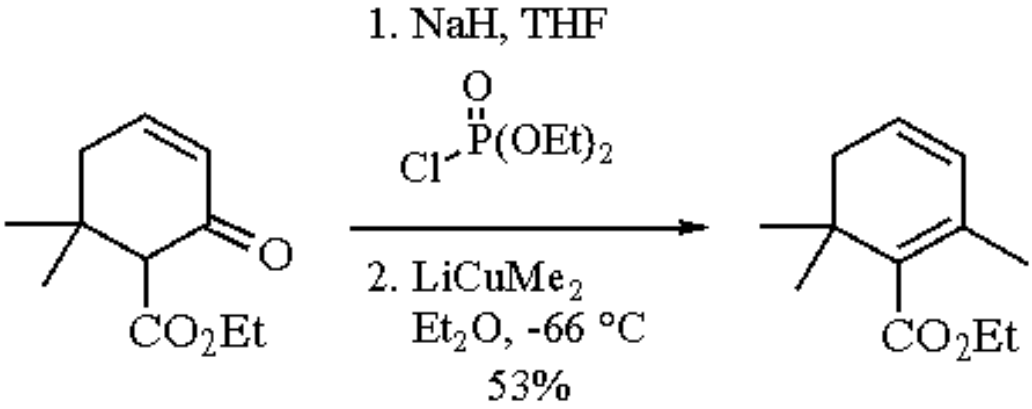

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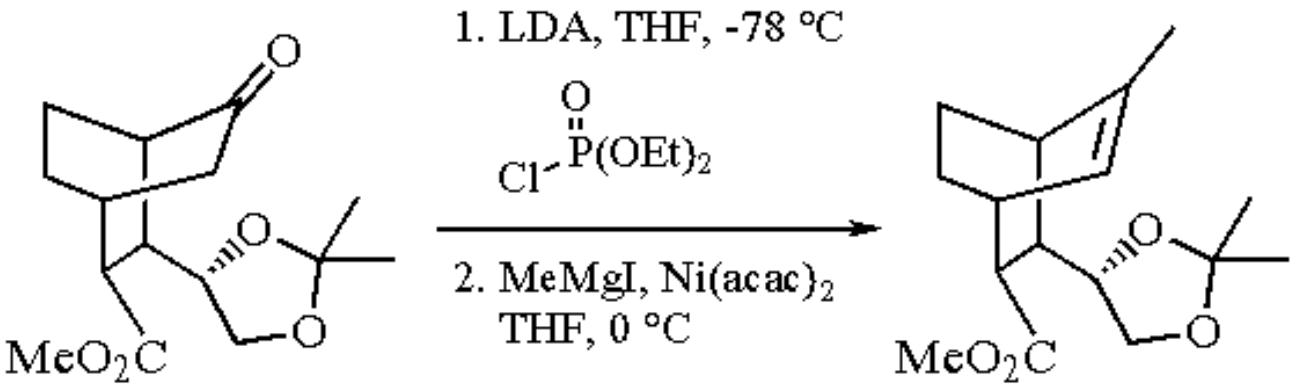

(14)

One of the most useful applications of β-keto phosphonates is the Horner-Emmons alkenation procedure (eq 15).[18] Variations of this theme have employed β-imino[26] and β-sulfonyl phosphates.[27]

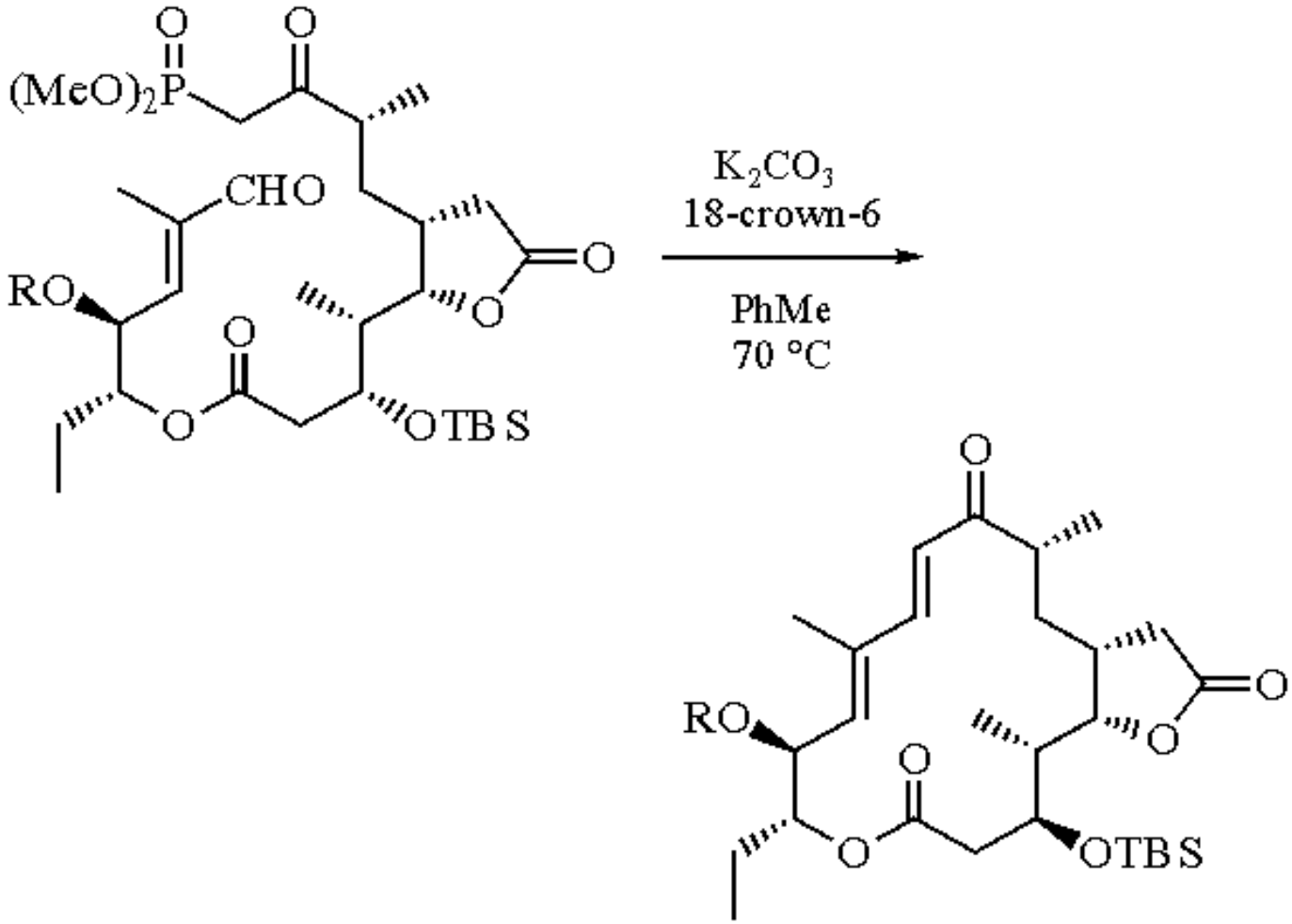

(15)

Alkynes are available from methyl ketones[10] by elimination of the enol phosphate (eq 16).[28] When the ketone contains α-branching, lithium tetramethylpiperidide has been recommended to circumvent allene formation.

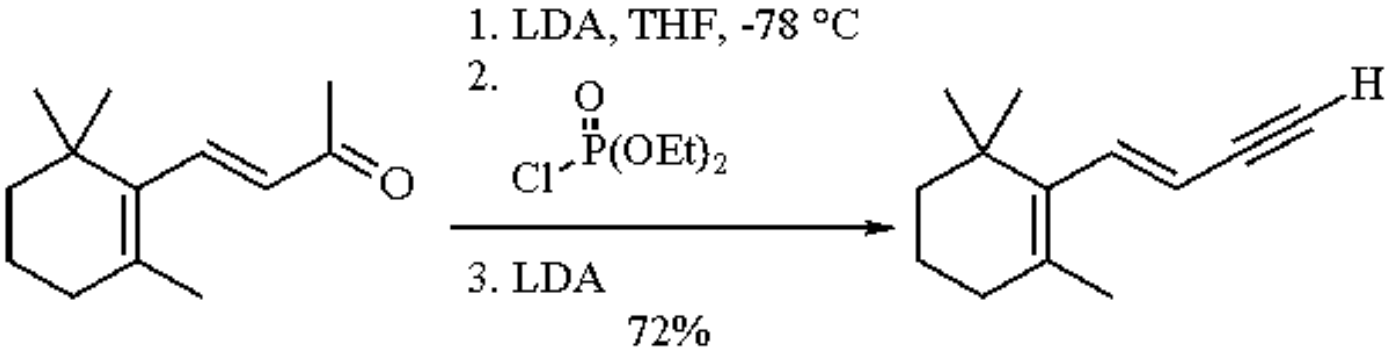

(16)

Miscellaneous.

Allylic phosphates have found applications in π-allyl palladium chemistry. It has been demonstrated that allylic phosphates undergo oxidative addition more readily than the corresponding acetate, such that chemoselectivity could be achieved when these functionalities were present in the same molecule (eq 17).[29] Finally, β-keto phosphonates were coupled with epoxides to provide useful yields of spirocyclopropanes (eq 18).[30]

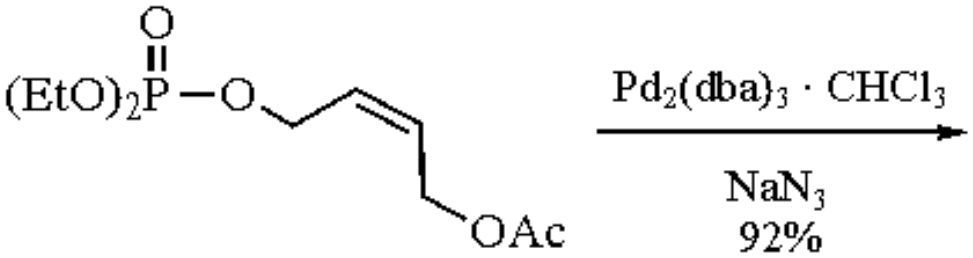

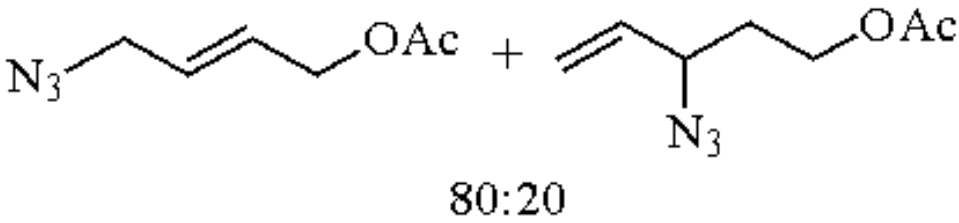

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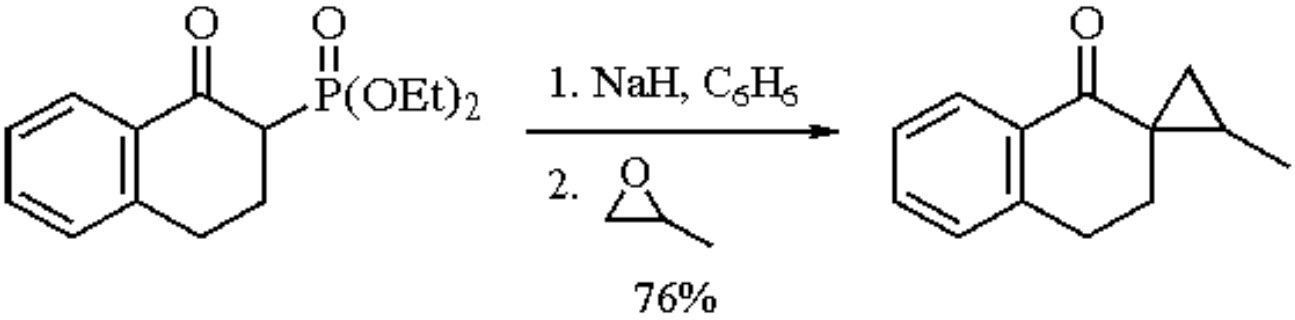

(18)

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Diethyl Phosphorocyanidate[1]

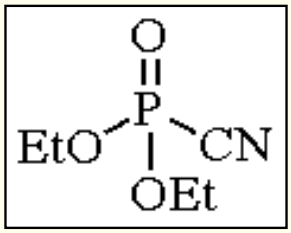

[2942-58-7] · $C_5H_{10}NO_3P$ · Diethyl Phosphorocyanidate · (MW 163.11)

(synthesis of amides,[3] esters,[2] α-aminonitriles,[12] aryl thiocyanates,[15] and cyanophosphates[17])

Alternate Names: diethyl cyanophosphonate; diethylphosphoryl cyanide; diethoxyphosphoryl cyanide; diethyl cyanophosphate; DEPC.

Physical Data: bp 93-96 °C/14 mmHg; fp 80 °C; *d* 1.075 g cm^{-3}.

Solubility: sol DMF, THF, Et_2O, toluene.

Form Supplied in: pale yellow liquid; 93% (technical grade).

Preparative Method: can be readily prepared from ***Triethyl Phosphite*** and ***Cyanogen Bromide***.[2]

Purification: in most cases, commercial samples are used without purification. However, freshly prepared DEPC contains an impurity of diethyl phosporoisocyanidate. Addition of anhydrous ***Cobalt(II) Chloride*** to a sample of crude DEPC, followed by dilution with ether forms a green precipitate which is removed by filtration; distillation of the filtrate gives pure DEPC.[2]

Handling, Storage, and Precautions: is very toxic and corrosive. It must be handled in a fume hood. The reagent is moisture sensitive and should be stored under nitrogen in a refrigerator.

Synthesis of Amides.

DEPC is an efficient and useful reagent for amide formation and is applicable to racemization-free peptide synthesis. Amides of various types can be obtained by the simple mixing of carboxylic acids and amines with DEPC in the presence of ***Triethylamine*** (eq 1).[3] Both aromatic and aliphatic acids easily react with aromatic and aliphatic amines. The reaction is rapid, clean, and usually free of contamination from side products.

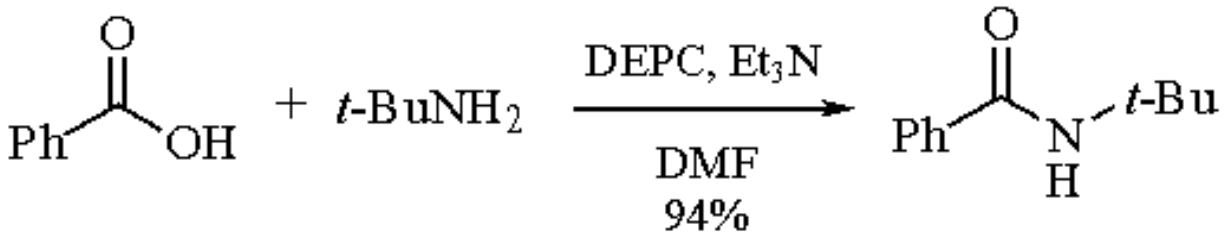

(1)

Studies of selected coupling methods for the attachment of amino acid derivatives to *cis*- and *trans*-4-aminocyclohexanecarboxylic acid have shown DEPC to be the reagent of choice as coupling agent.[4] A study directed towards racemization during peptide coupling of benzyloxycarbonyl-L-phenylalanyl-L-valine with L-proline *t*-butyl ester revealed that, among different coupling agents, DEPC coupling afforded the least racemization.[5]

Following their application as effective peptide coupling agents in the solution phase, both DEPC and ***Diphenyl Phosphorazidate*** (DPPA)[6] have been shown to be useful in solid-phase peptide synthesis.[7,8] Using these reagents, synthesis of porcine motilin, comprising 22 amino acids, was successfully achieved.[7]

Synthesis of Esters and Thioesters.

Reaction of DEPC with carboxylic acids in the presence of triethylamine gives transient acyl cyanides, which in the presence of alcohols[2] or thiols[9] results in the formation of the corresponding esters or thiolesters (eq 2).

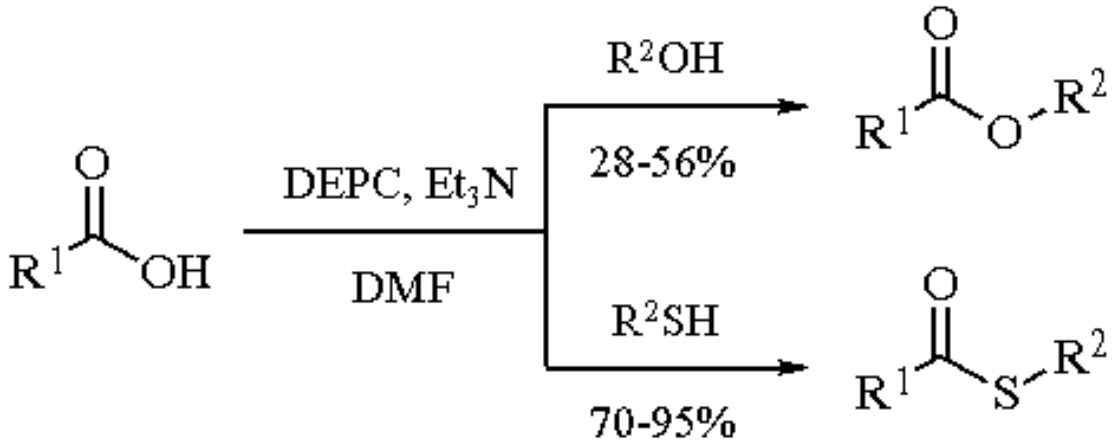

(2)

Although esterification yields are not generally satisfactory, the advantage of this method is that the reaction proceeds under mild and almost neutral conditions. The method can be efficiently applied to the synthesis of thiolesters in high yields with little racemization, as demonstrated by the formation of the ethylthiol ester of benzoyl-L-leucine.[9]

C-Acylation.

A direct *C*-acylation of active methylene compounds can be achieved using a carboxylic acid and DEPC in the presence of base under exceptionally mild conditions (eq 3).[10,11] The reactions are best carried out in DMF solution, though hexane, toluene, ether, or THF may be used. Triethylamine, ***1,8-Diazabicyclo[5.4.0]undec-7-ene***, ***N,N,N´,N´-Tetramethylethylenediamine***, ***Sodium Hydride***, or ***Potassium Carbonate*** may be used as a base.

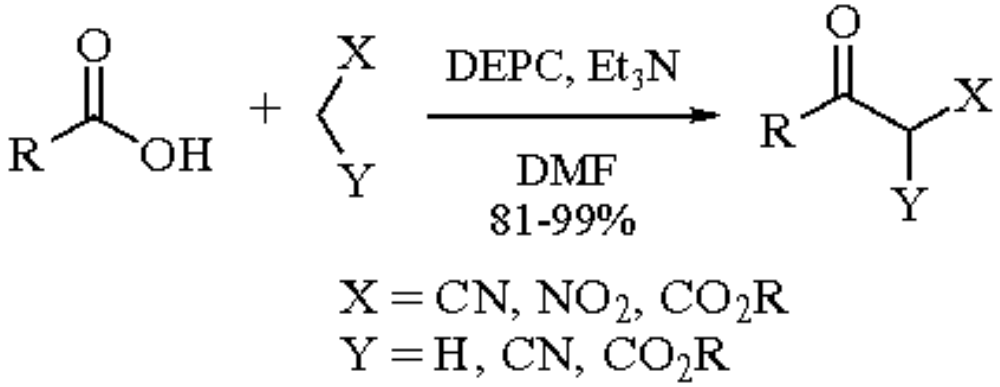

(3)

Synthesis of α-Aminonitriles.

α-Aminonitriles can be efficiently prepared from carbonyl compounds with DEPC and amines under mild conditions, in a modified Strecker synthesis.[12] Since the nitrile functionality of α-aminonitrile can be easily converted to the acid, this constitutes a convenient method for the preparation of α-amino acids. The superiority of this method over the classical Strecker synthesis of α-aminonitriles was demonstrated by the reaction of 4-cholesten-3-one (**1**) with DEPC and ***Pyrrolidine***, which afforded the α-aminonitrile (**2**) in 62% yield (eq 4). The classical Strecker conditions using a mixture of KCN and pyrrolidine hydrochloride in aqueous THF did not yield any α-aminonitriles.

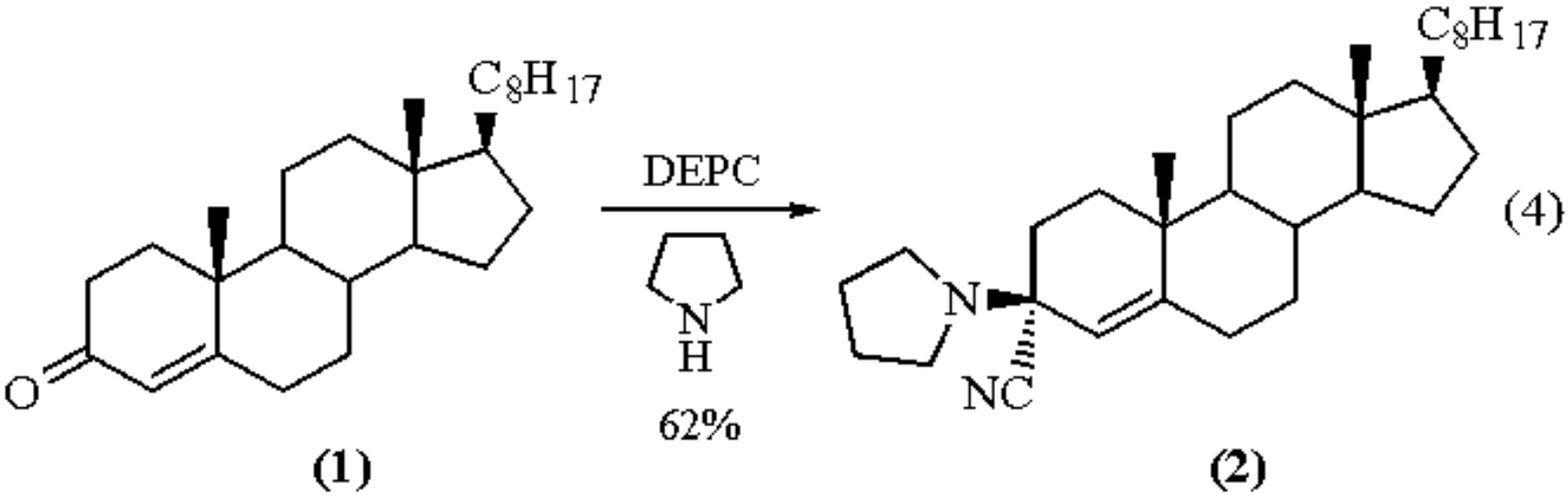

(4)

Modified Reissert-Henze Reaction.

The α-cyanation of aromatic amine oxides (Reissert-Henze reaction) is usually carried out using benzoyl chloride and potassium cyanide.[13] Alternatively, α-cyano-substituted aromatic nitrogen heterocycles can be prepared by reaction of their corresponding *N*-oxide with DEPC in the presence of triethylamine (eq 5).[14]

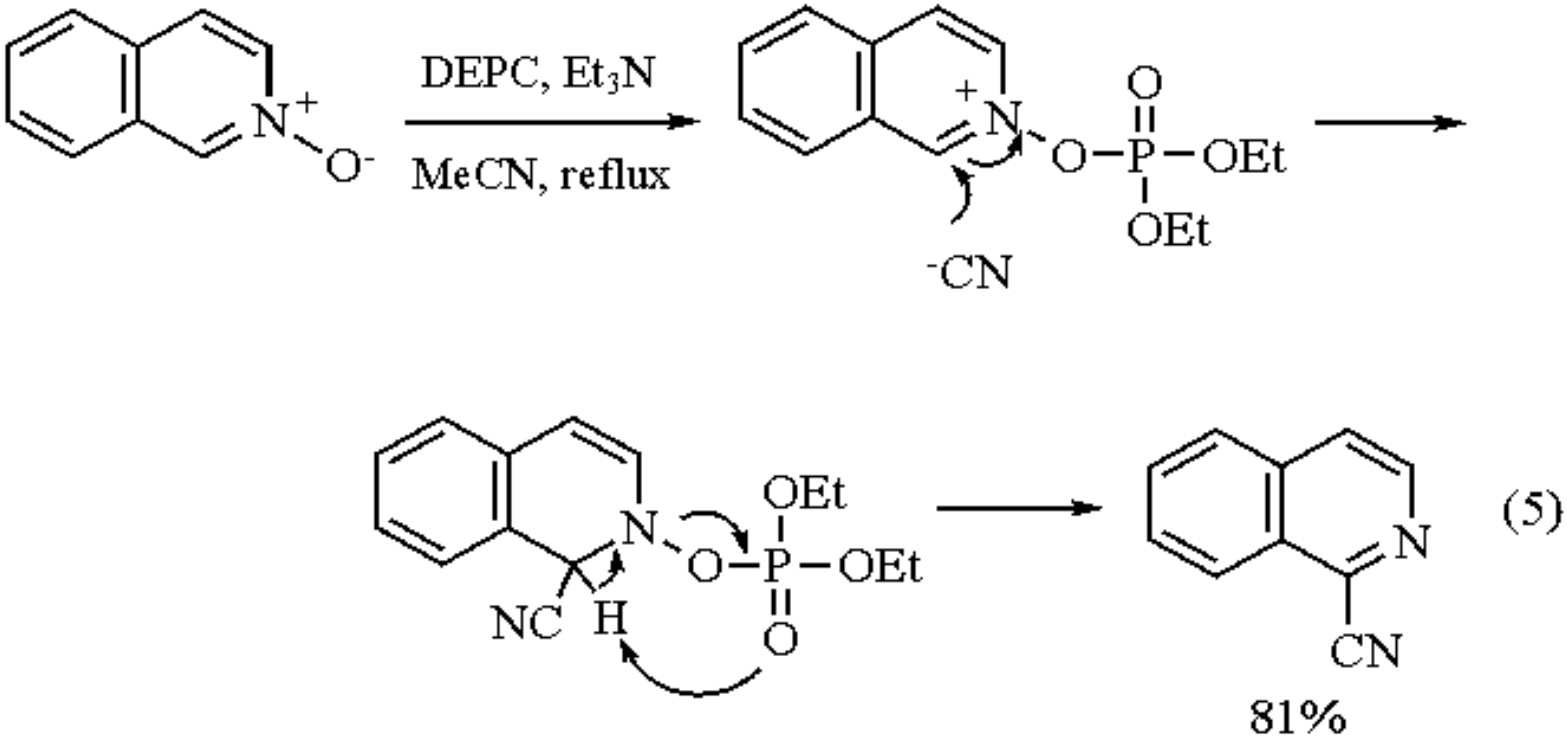

Synthesis of Aryl Thiocyanates.

Aryl thiocyanates can be prepared in one step from the sodium salt of the arylsulfinic acid by treatment with DEPC in refluxing THF. The thiocyanates are obtained in good yields and even hindered substrates like adamantane give the corresponding thiocyanate in moderate yield (eq 6).[15]

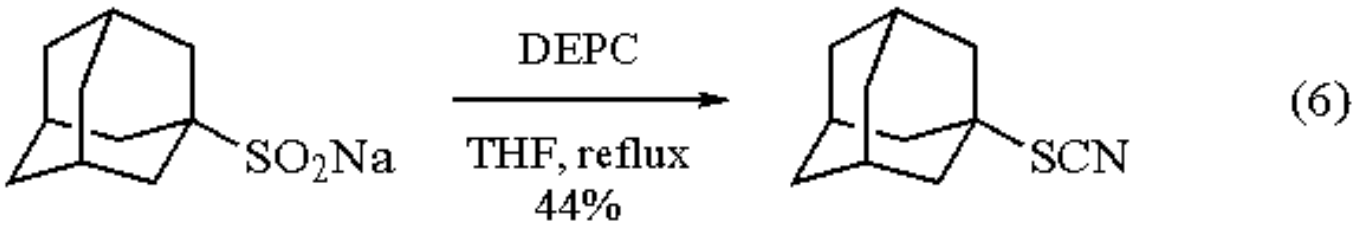

Epoxidation of Alkenes.

A mixture of DEPC and ***Hydrogen Peroxide*** smoothly epoxidizes alkenes at rt in the presence of ***2-Hydroxypyridine*** or ***1,2,4-Triazole***.[16] Methylene chloride is reported to be the solvent of choice. Various alkenes were epoxidized in 60-93% yields. *trans*-Stilbene and 1-dodecene, which are less susceptible to electrophilic attack by peroxycarboxylic acids, smoothly underwent this DEPC/H_2O_2 reaction.

Synthesis of Cyanophosphates as Versatile Intermediates.

Reaction of aldehydes or ketones with DEPC in the presence of a catalytic amount of ***Lithium Diisopropylamide*** (LDA) in THF gives cyanophosphates in high yield (eq 7).[17] Various cyclic and aromatic ketones react with DEPC to give cyanophosphates. Even conjugated or hindered ketones such as α-tetralone or benzophenone, which are known

not to give cyanohydrins under the usual reaction conditions, react smoothly with DEPC to give cyanophosphates.

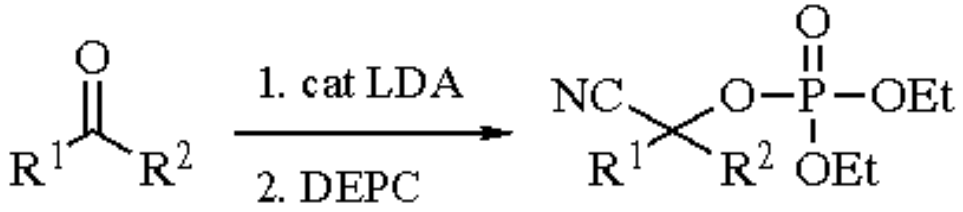

(7)

Reductive Cyanation of Ketones and Aldehydes.

Saturated and unsaturated carbonyl compounds react with DEPC and ***Lithium Cyanide*** to give intermediate cyanophosphates which can be reduced with ***Samarium(II) Iodide*** in the presence of *t*-butanol to give nitriles (eq 8).[18]

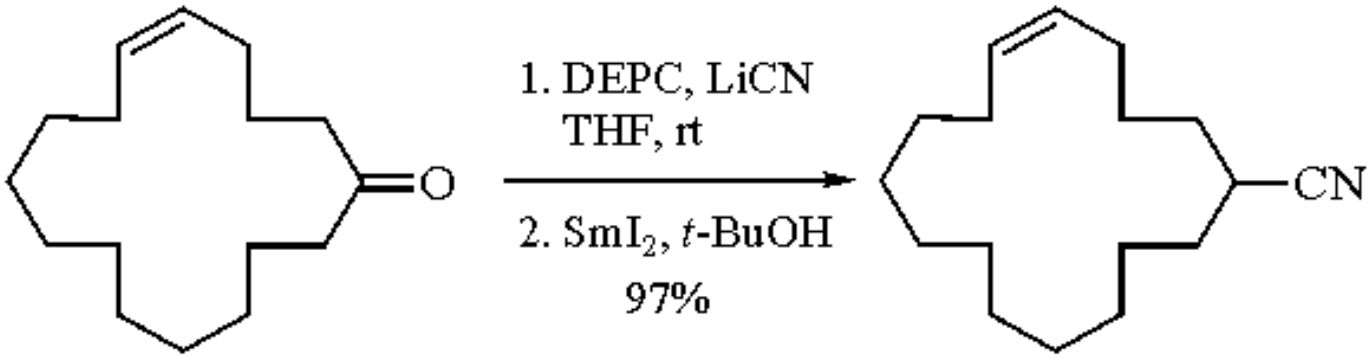

(8)

α,β-Unsaturated Nitriles.

Cyanophosphates prepared by the reaction of aromatic ketones in the presence of lithium cyanide can be readily converted into α,β-unsaturated nitriles by treatment with ***Boron Trifluoride Etherate*** at rt (eq 9).[19] This reaction was used to convert 4-isobutylacetophenone to α-cyanostyrene, which upon hydrogenation followed by hydrolysis gives ibuprofen in 70% overall yield (eq 10).[19a]

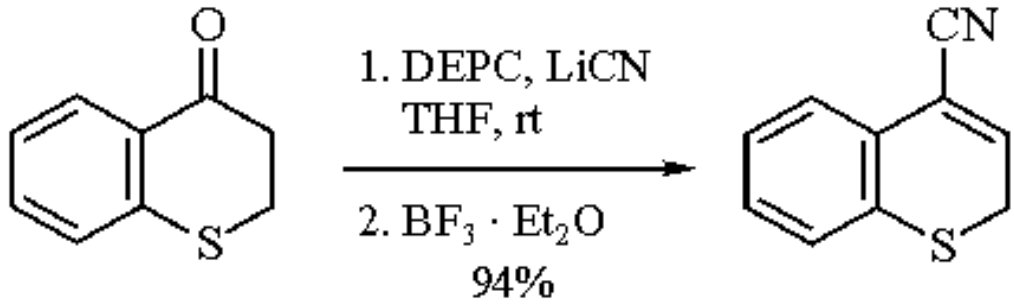

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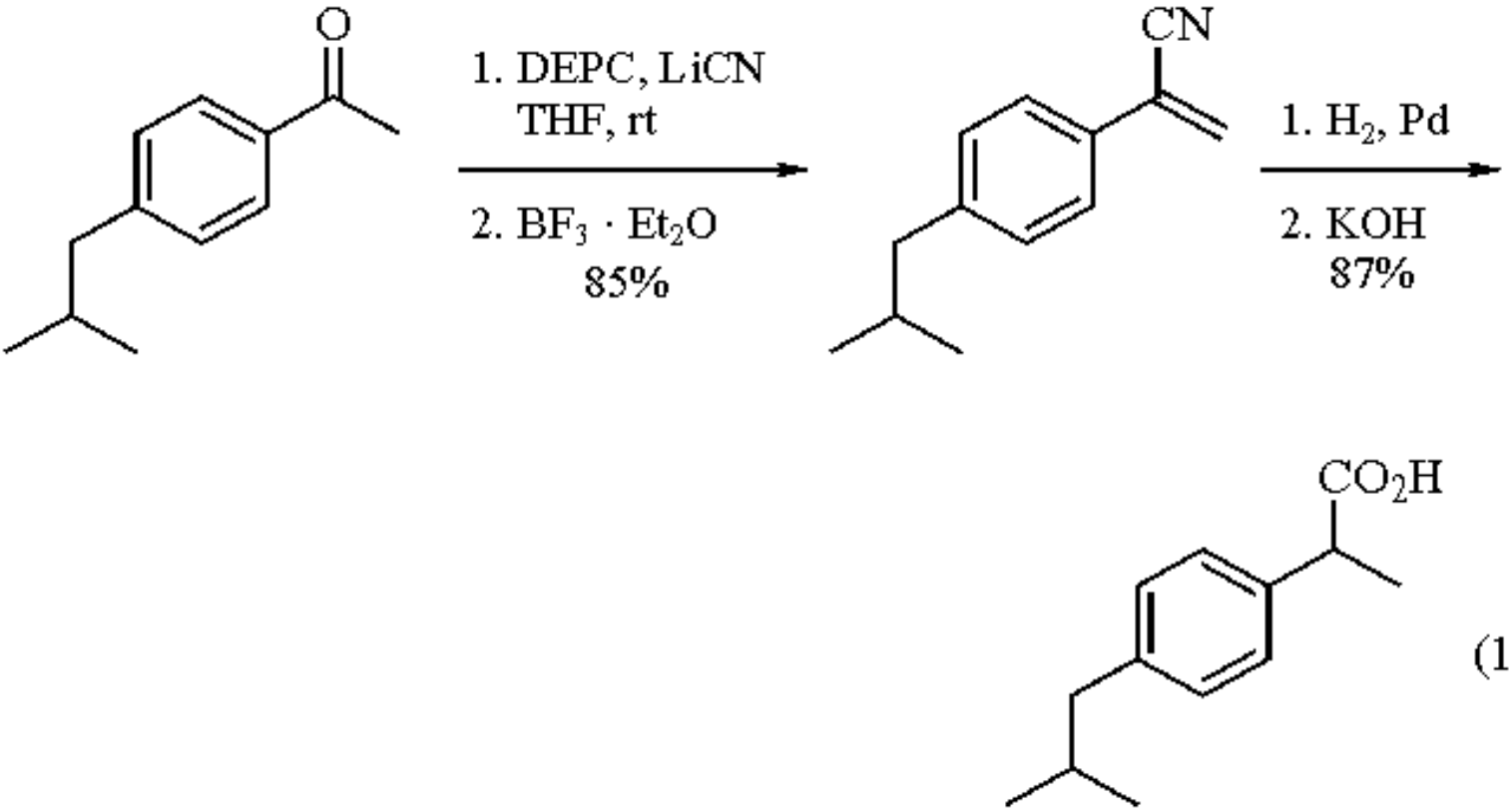

(10)

Deoxygenation of α,β-Unsaturated Ketones.

Cyanophosphates, prepared from α,β-unsaturated ketones or aromatic ketones by treatment with DEPC and lithium cyanide, can be reductively cleaved with ***Lithium*** in liquid ammonia to give the corresponding methylene compounds (eq 11).[20] In the case of α,β-enones, this procedure is superior to the more commonly employed thioacetal and desulfurization deoxygenation method. This method for α,β-enones is simple and the products are obtained in excellent yields without isomerization or reduction of the double bond.

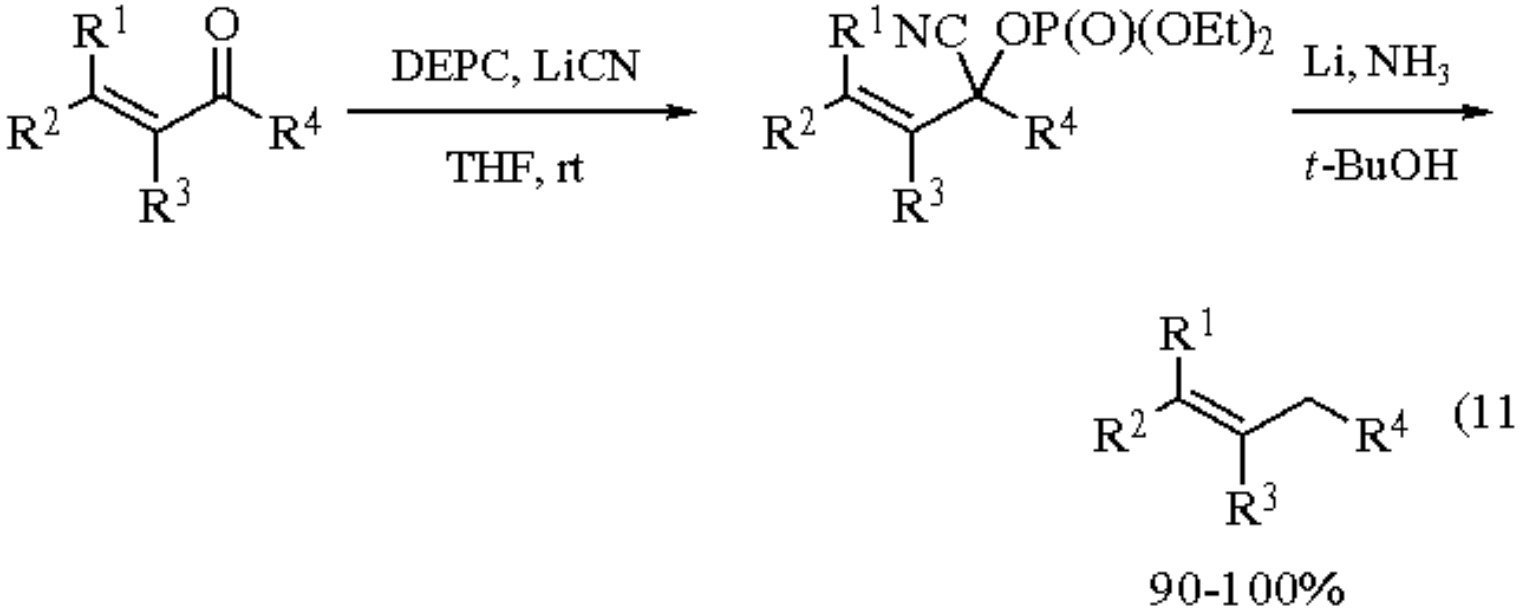

(11)

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N,N-Diethyl-1-propynylamine[1]

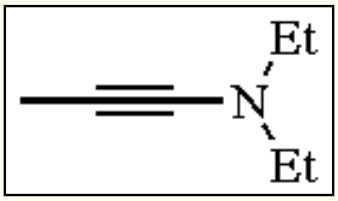

[4231-35-0] · $C_7H_{13}N$ · *N,N*-Diethyl-1-propynylamine · (MW 111.19)

(for dehydrations;[1b,2] synthesis of amino-furans[3] and -amides,[4] cyclobutadienes,[5] cyclobutenes,[6] cyclobutanones,[7] vinylogous amides[8])

Alternate Names: 1-(*N,N*-diethylamino)propyne; DAP.

Physical Data: colorless liquid; amine odor; bp 130-132 °C.

Solubility: sol MeCN, THF, CH_2Cl_2, toluene, ether, CCl_4.

Preparative Methods: from commercially available 1-diethylamino-2-propyne,[9,10] *N,N*-diethylpropanamide,[11,12] miscellaneous methods.[1d]

Purification: by distillation under reduced pressure (bp 80-85 °C/100 mmHg).

Handling, Storage, and Precautions: reacts with H_2O, CO_2; slowly oxidizes in air/UV light. This reagent should be used in a fume hood.

Addition Reactions.

N,N-Diethyl-1-propynylamine (**1**) participates in many types of reactions with alkynes, alkenes, dienes, benzynes, and 1,3-dipoles, giving products that arise either by concerted or polar processes involving zwitterionic intermediates.[1] Much of its chemistry may be explained by considering its resonance structures.

(1)

Reaction of (**1**) with electron-deficient alkenes such as α,β-unsaturated sulfones (eq 1),[7] α,β-unsaturated nitriles (α-chloroacrylonitrile,[13] 1-cyanocyclopentene[6]), and trifluorochloroethylene[14] gives cyclobutenes such as (**2**), (**3**), and (**4**) that can be converted into cyclobutanones.

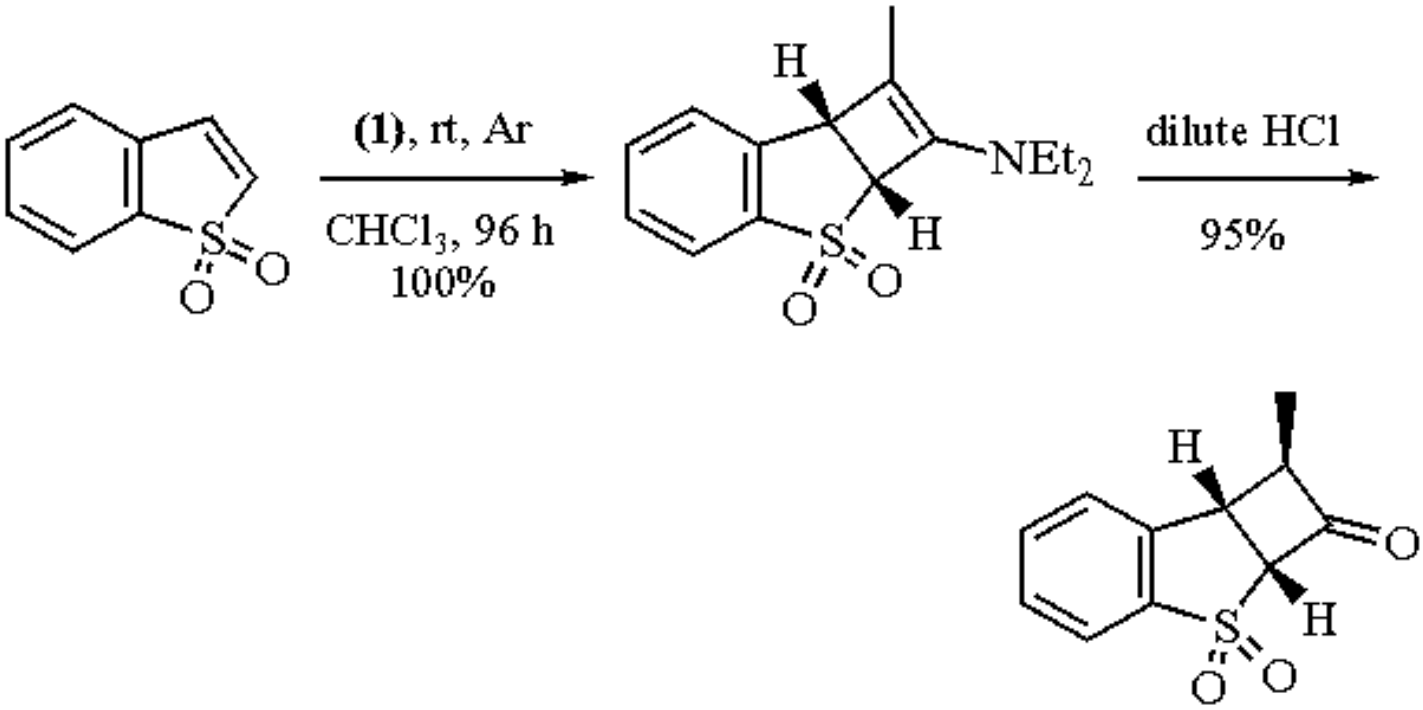

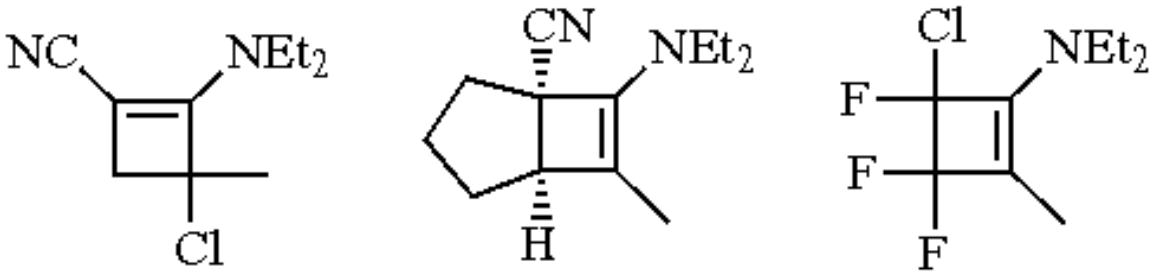

(2) 75% **(3)** 75% **(4)** 76%

In reactions with 1-alkynyl sulfones, the intermediate cyclobutadienes can be trapped as metal complexes or as Diels-Alder adducts (eq 2).[5]

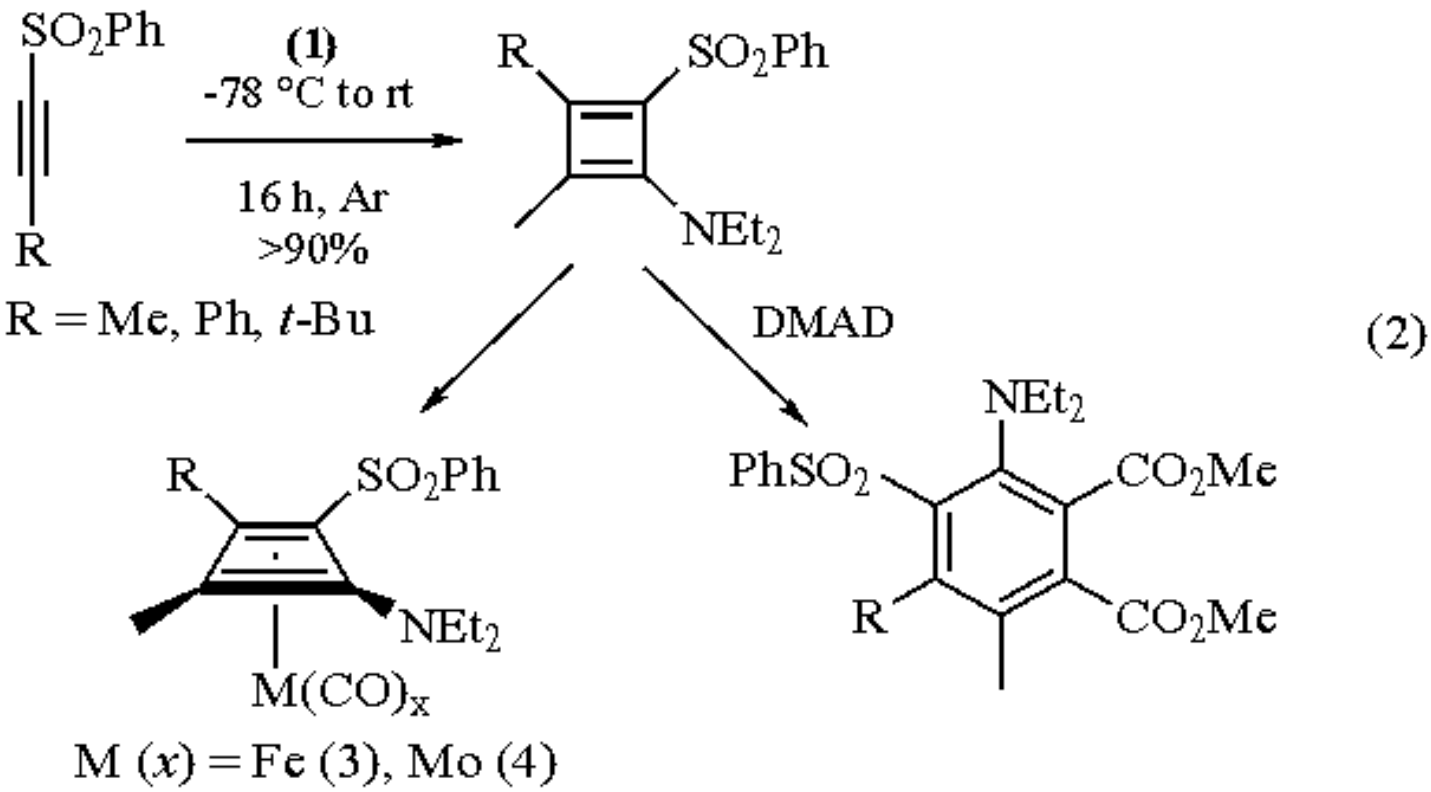

A [2 + 2] reaction with a sulfene gives thiete 1,1-dioxide (**5**).[15] Michael addition of (**1**) to electrophilic isoxazoles yields bicyclic adducts.[16]

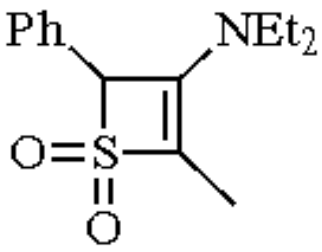

(5) 79%

1,3-Oxazin-6-ones and (**1**) provide pyridine derivatives by an inverse electron demand [4 + 2] cycloaddition-elimination reaction sequence (eq 3).[17] Fused-bicyclic oxazinones behave similarly and have been converted into thienopyridines,[18] quinolones,[19] and quinolines.[19] Pyridazinecarboxylates are converted either into 2-aminopyridines or into aniline derivatives with (**1**), depending on pyridazine ring carboxylate substitution patterns.[20] 2-Substituted pyrimidines and (**1**) give azetodiazocines by a series of reactions that include a formal [4 + 2] cycloaddition, 1,3-sigmatropic shift, [2 + 2] cycloaddition, and isomerization.[21]

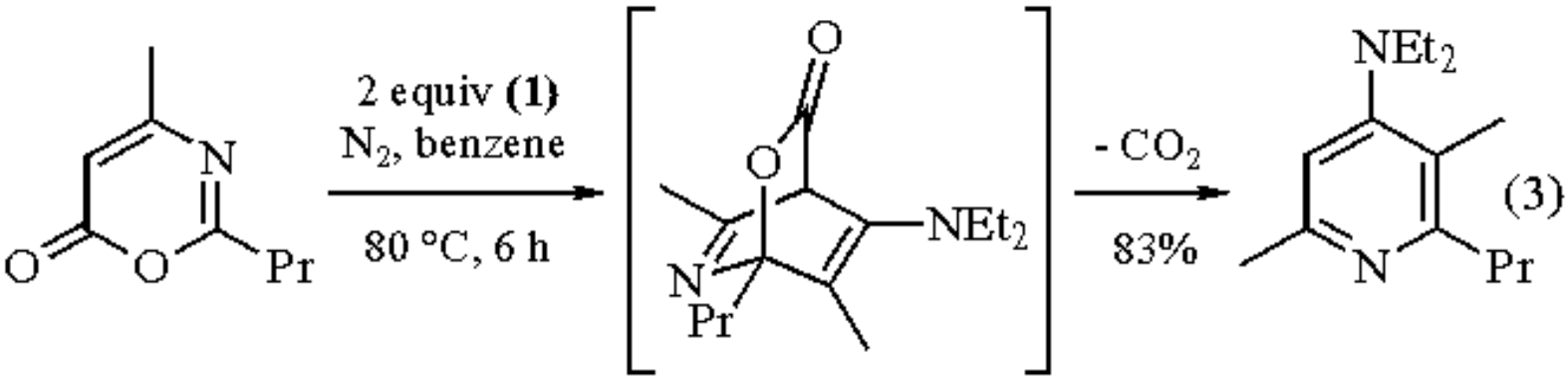

Ring Interconversions and Expansions.

N,*N*-Diethyl-1-propynylamine has been used to convert heterocyclic systems into other heterocyclic or carbocyclic systems. Reactions occur by addition-elimination (eq 4)[22] and dipolar addition (eq 5)[23a] pathways.

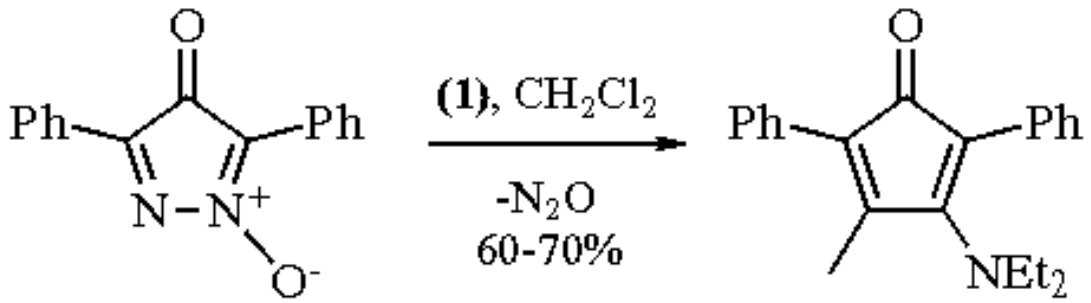

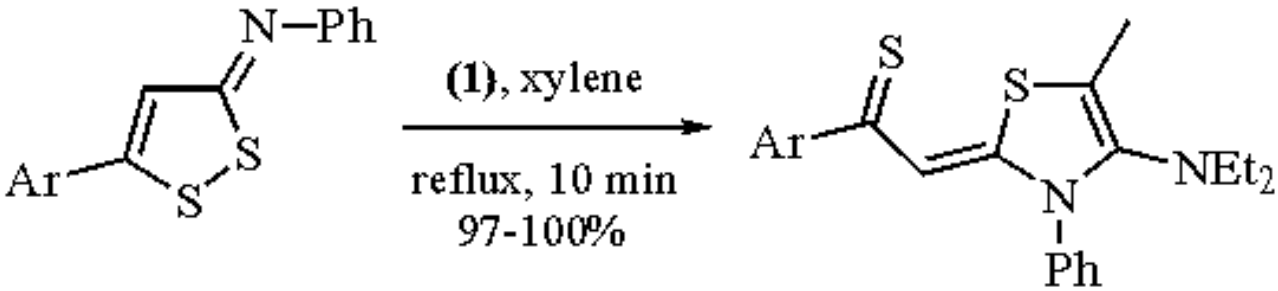

6-Oxo-1,3,4-oxadiazines are readily converted into substituted 2-pyrones (eq 6).[24] Likewise, pyridines are derived from pyrimidines[25] and 1,2,3-triazines.[26] Oxathiadiazines give 1,2,6-thiadiazines on addition of (**1**).[27]

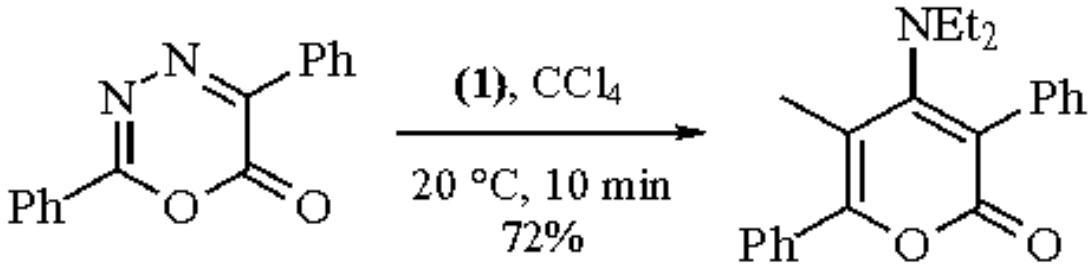

Many ring expansions have been reported with (**1**). They generally proceed through dipolar addition mechanisms. Depending on their substitution patterns, 1,2-diacylcyclopropenes give either aminofurans (eq 7) or

aminocyclopentadienes.[3]

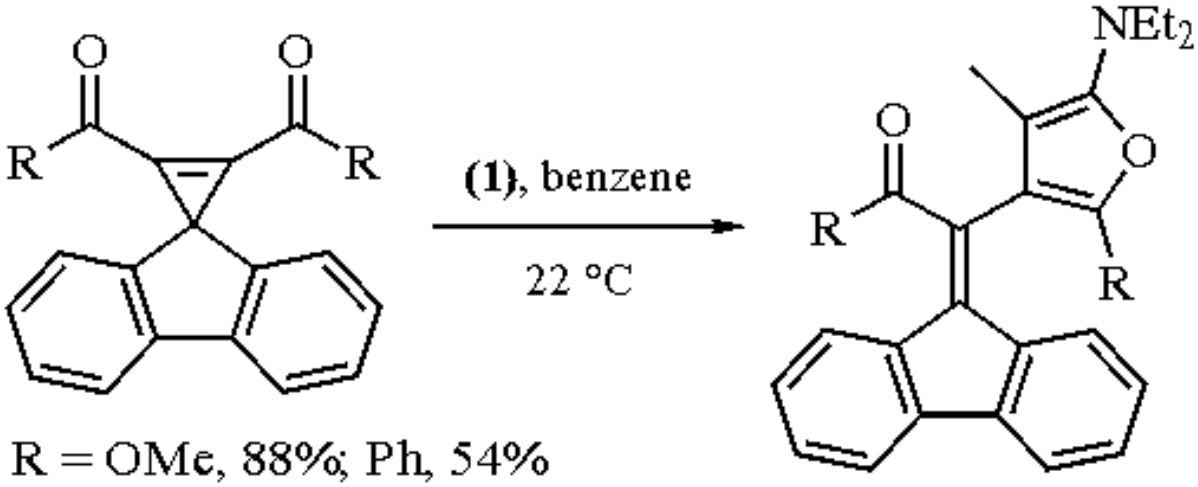

(7)

Thiophosphonic acid anhydrides and (**1**) give thiaphosphorinanes (eq 8).[28] Thioazetidinones give 1,3-thiazines[29] and 1,2-dithioles give thiopyrans on reaction with (**1**).[23]

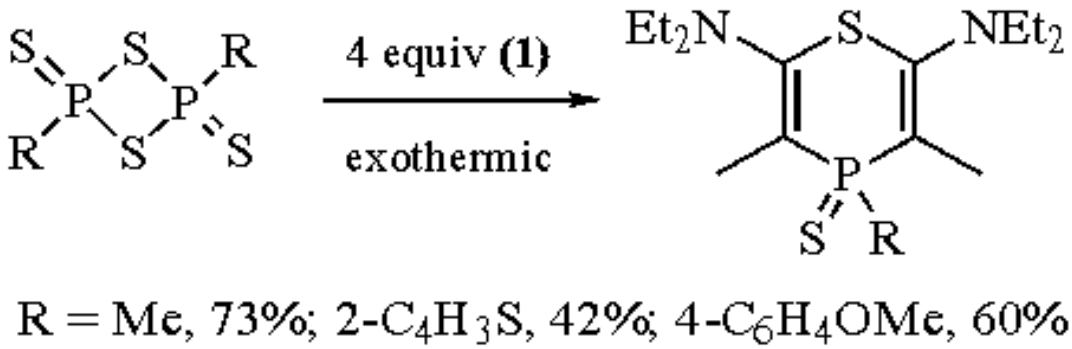

(8)

Oxazolidinones and dioxolanones react with (**1**) via 1,7-dipolar intermediates to produce oxazepinones (eq 9) and dioxepinones.[30]

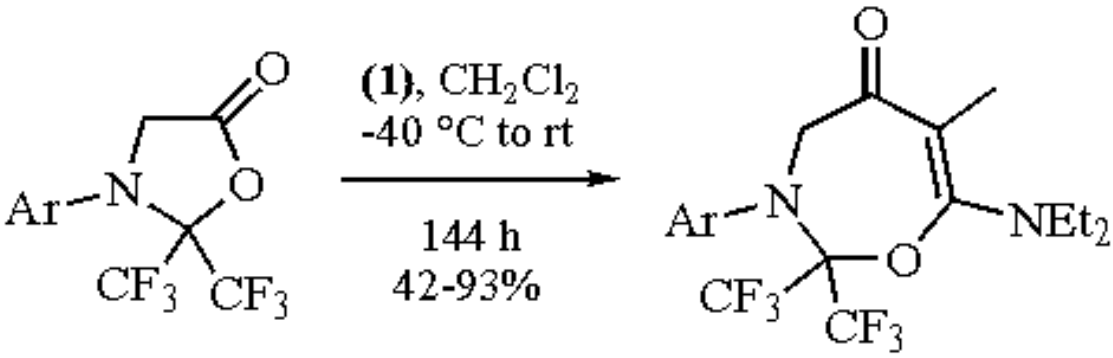

(9)

Acylation Reactions.

N,*N*-Diethyl-1-propynylamine reacts with carbonyl and carboxyl groups to give acylated products. The reaction pathway (stepwise or cycloaddition) depends upon substitution patterns and solvent polarity.[1] α,β-Epoxy ketones and (**1**) give vinylogous epoxy amides (eq 10).[8] Alkyl and aryl dithioaryl esters form (*E*)-α,β-unsaturated thioamides on

reaction with (**1**) (eq 11).[31] Acyclic and cyclic trithiocarbonates, as well as thiazolthiones, provide similar derivatives in good yields.[31-33]

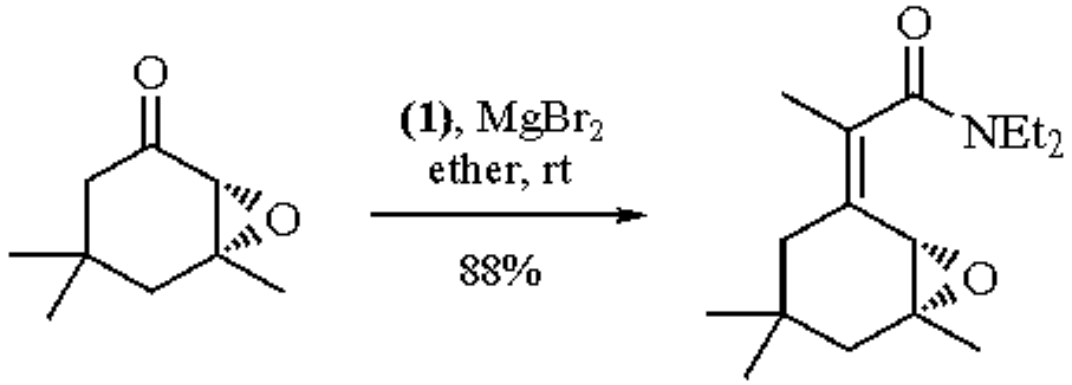

(10)

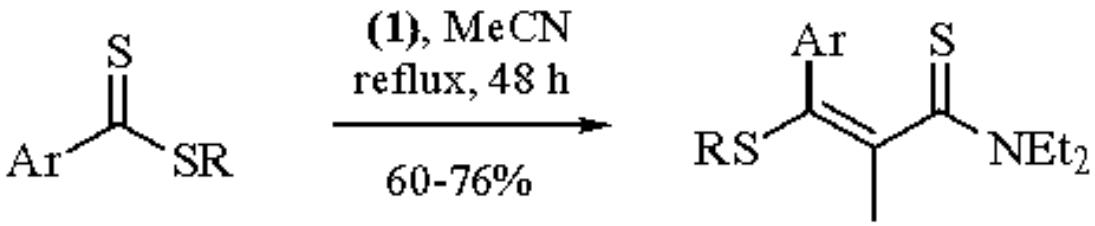

(11)

Ar = Ph, 4-MeC$_6$H$_4$
R = Me, Ph

Acylation of *N*-acylhydroxylamines by (**1**) provides an entry to α-aminoamides after deprotection (eq 12).[4] Betaines also react with (**1**) to give triazinediones[34] and pyrimidines.[35]

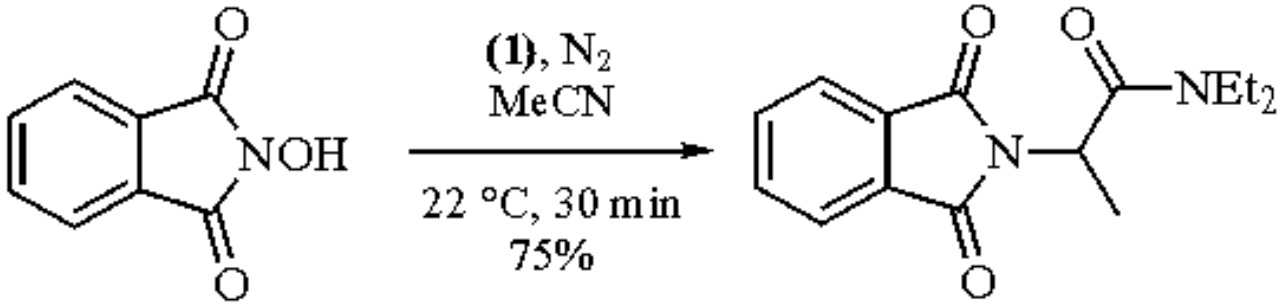

(12)

Acylations also occur with metal-coordinated thioaldehydes and thioketones to yield thioacrylamides[36] and with *N*-acyl-*S*-alkyl(aryl)thiobenzimidates to give *N*-acylaza-1,3-butadienes.[37]

Reactions with Isocyanates and Ketenes.

Products derived from reactions of isocyanates or ketenes with (**1**) depend strongly on the electrophile structure. Cycloaddition occurs by oxygen attack on an intermediate ketiminium salt, followed by ring opening.[1] Ketene and (**1**) give an allenecarboxamide (eq 13).[38] With silicon-substituted ketenes, silylalkyne (**6**) is produced via silicon migration from an initially formed allenecarboxamide.[39] Similarly, CO_2 yields allene dicarboxamide (**7**) in a reaction with 2 equiv of (**1**).[40] Isothiocyanates and (**1**) give α-sulfinylamidines via ring-opening of intermediate 1,2-dihydro-1,2-

thiazetes.[41]

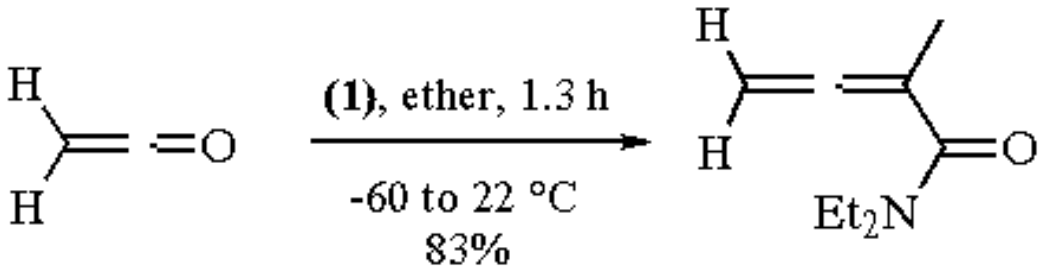

(13)

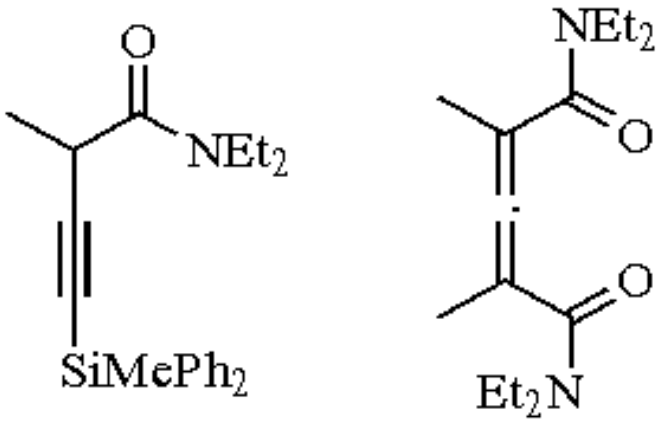

(6) 83% (7) 100%

Dehydrations.

The title reagent has been used for carboxyl activation in the conversion of acids to anhydrides[2] (ynamines are faster than carbodiimides or ***Ethoxyacetylene***),[1c] acids and amines to amides,[2] benzaldoximes to benzonitriles,[42] and in peptide synthesis.[43] Heterocyclic systems have been prepared by cyclizing *o*-diheteroaromatics, β-amino alcohols, and 1,2-diamines with (**1**).[44]

Miscellaneous Transformations.

Arenesulfenyl chlorides add to (**1**) to give (*E*)- and (*Z*)-2-arylthio-1-chloro-*N*,*N*-diethylenamines that can be cyclized to benzothiophenes with ***Zinc Chloride***.[45] Phosphinous halides add to *N*,*N*-diethyl-l-butynylamine to give phosphirenes.[46]

---

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Diethyl Succinate

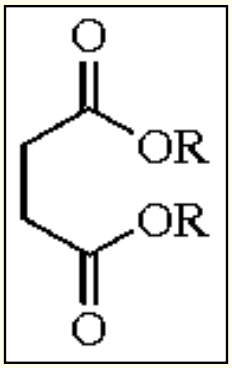

(**1**; R = Et)

[123-25-1] · $C_8H_{14}O_4$ · Diethyl Succinate · (MW 174.20) (**2**; R = Me)

[106-65-0] · $C_6H_{10}O_4$ · Dimethyl Succinate · (MW 146.14) (**3**; = R = *i*-Pr)

[924-88-9] · $C_{10}H_{18}O_4$ · Diisopropyl Succinate · (MW 202.25) (**4**; R = (-)-menthyl)

[34212-59-4] · $C_{24}H_{42}O_4$ · Dimenthyl Succinate · (MW 394.59)

(acyloin condensation,[1] self-condensation,[2] Stobbe condensation,[3] and various enolate reactions)

Physical Data: (**1**): mp 18-19 °C; bp 217.7 °C; *d* 1.047 g cm^{-3}. (**2**): mp -20 °C; bp 200 °C; *d* 1.117 g cm^{-3}. (**3**): bp 247 °C; *d* 0.99 g cm^{-3}. (**4**): mp 62-64 °C; bp 200-205 °C/2 mmHg.

Solubility: sol H_2O (19.2 g L^{-1} at 20 °C).

Acyloin Condensation.[1]

A simplification and improvement of the acyloin condensation of diethyl succinate (**1**) to give 1,2-bis(trimethylsilyloxy)cyclobutene has been reported (eq 1).[4]

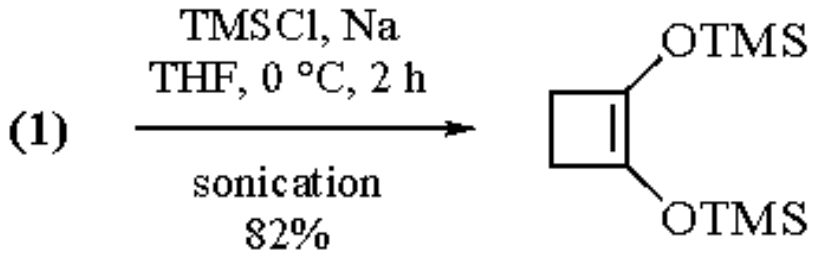

(1)

Self-Condensation.

Diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate can be prepared by the self-condensation of (**1**) in the presence of a strong base catalyst (eq 2).[2]

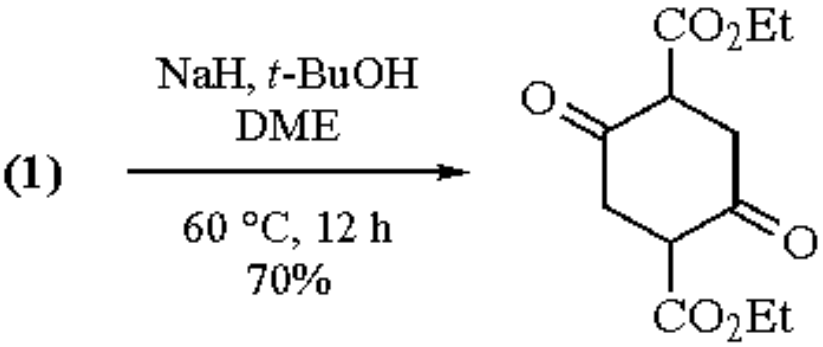

(2)

Stobbe Condensation.[3]

The succinates react with ketones (eq 3)[5] or aldehydes (eq 4)[6] in the presence of ***Sodium Hydride*** or alkoxides to form monoesters of α-alkylidene succinic acids. The Stobbe condensation products are important synthetic intermediates which have been used in the preparation of various natural products such as lignan isolariciresinol, cordigerine, and hinokinin.[7]

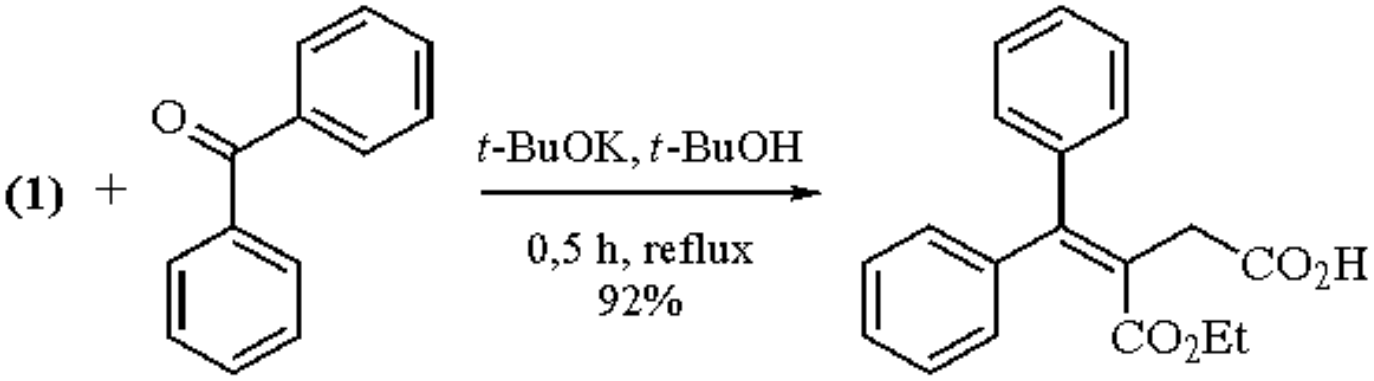

(3)

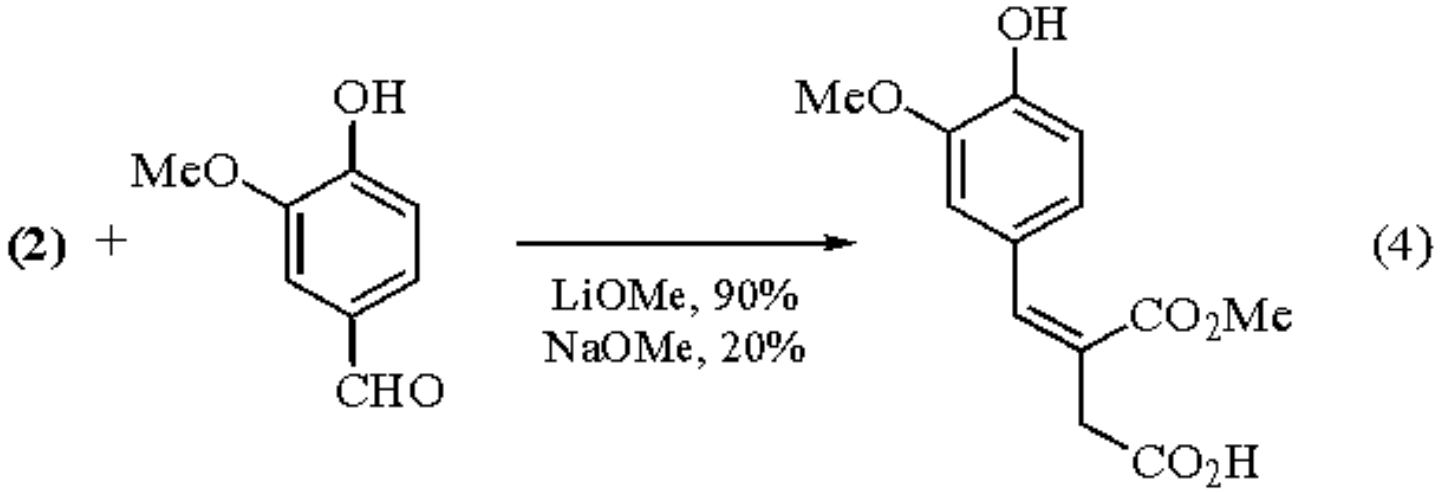

Metal enolates of (**1**) also react with various esters (eqs 5 and 6).[8,9]

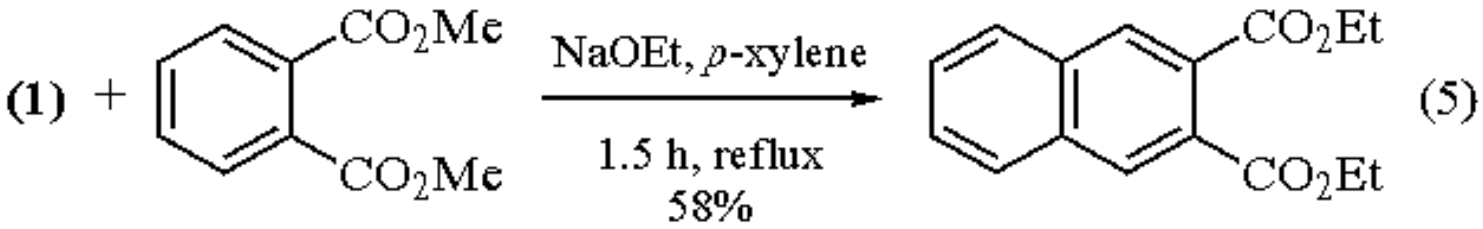

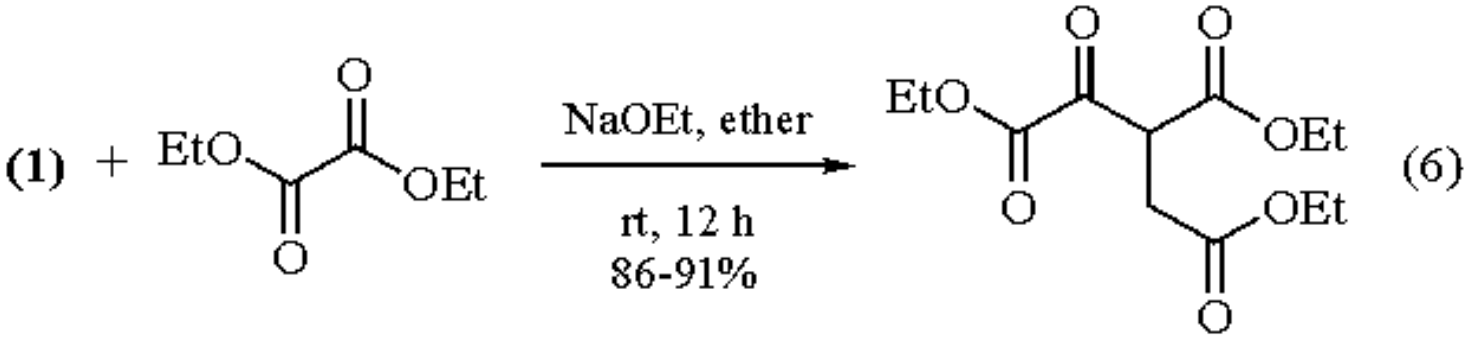

Diethyl Dilithiosuccinate.

This reagent (**5**) is readily prepared[10] by treatment of (**1**) with ***Lithium Diisopropylamide*** (2 equiv) at -78 °C in THF (eq 7). The dianion can be isolated and trapped to give the bis-silylated product (eq 8).[10] Interestingly, using only 1 equiv of LDA also gave the same compound as the major product (45%) together with unreacted (**1**) (30%) and only a small amount of the monosilylated product (5%), suggesting that the di-enolate (**5**) is preferentially formed in the reaction.

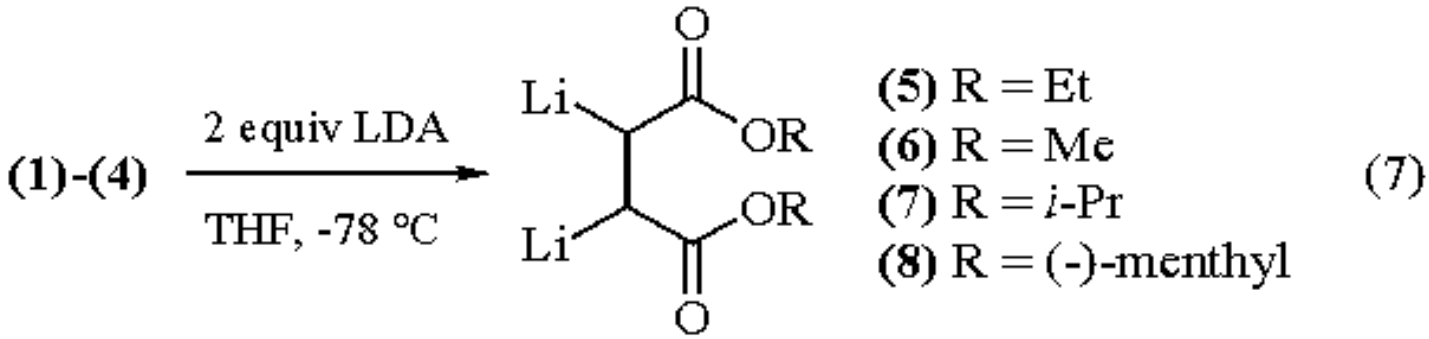

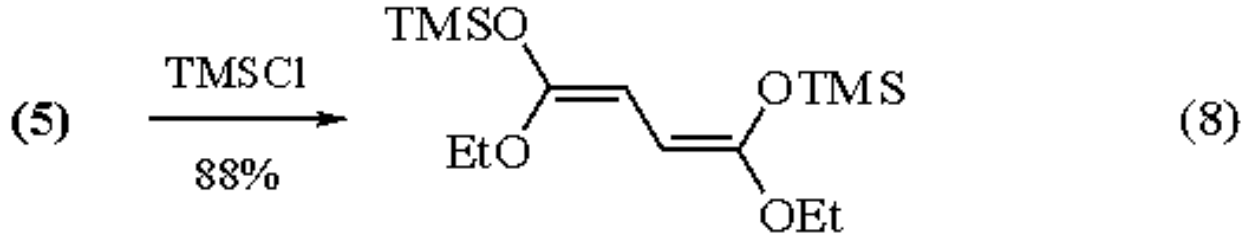

mixture of isomers

γ-Butyrolactone Synthesis.

The di-enolate (**5**) reacts with aldehydes and ketones (eq 9)[11] and α-keto esters (eq 10)[12] to give γ-butyrolactones in good yields. These types of lactones are useful intermediates in the synthesis of cyclopentenones.[13]

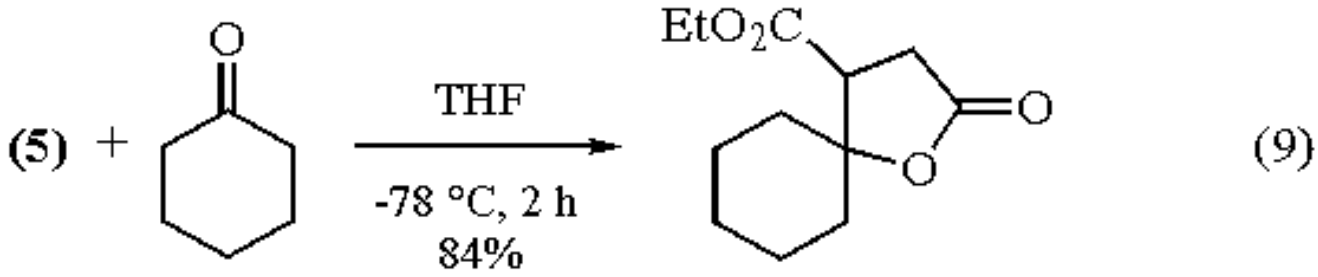

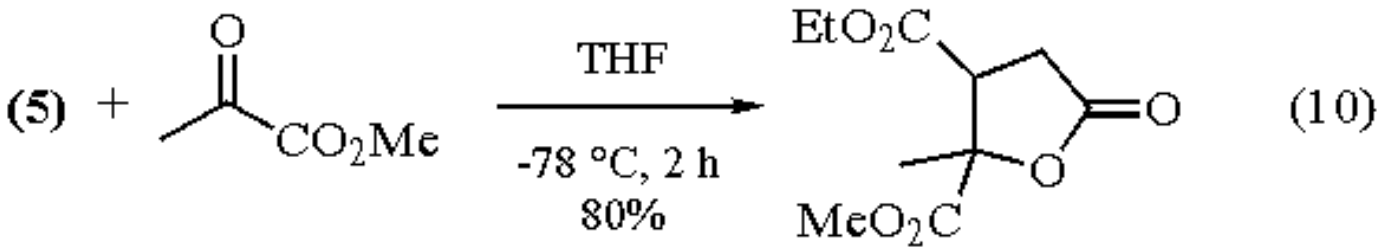

cis:*trans* = 2:1

Alkylation.

The dianion (**5**) can be mono- or dialkylated with reactive halides in good yields in the presence of ***Hexamethylphosphoric Triamide***.[10,11] Successive alkylation of (**5**) with ***Benzyl Bromide*** and ***Iodomethane*** gave the

mixed alkylated product in 60% yield (eq 11).[10]

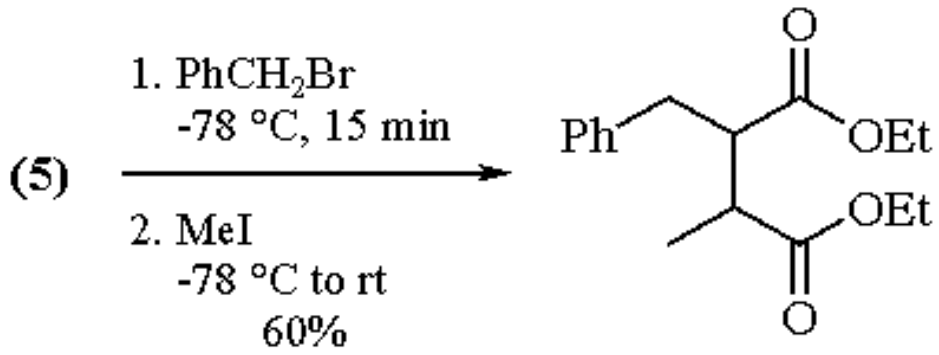

(11)

Carbocyclization.

Alkylation of the dianion (**6**) with dihalides provides a facile method for the preparation of carbocycles.[14] The reaction has been successfully applied to the synthesis of a natural propellane, modhephene (eq 12).[15]

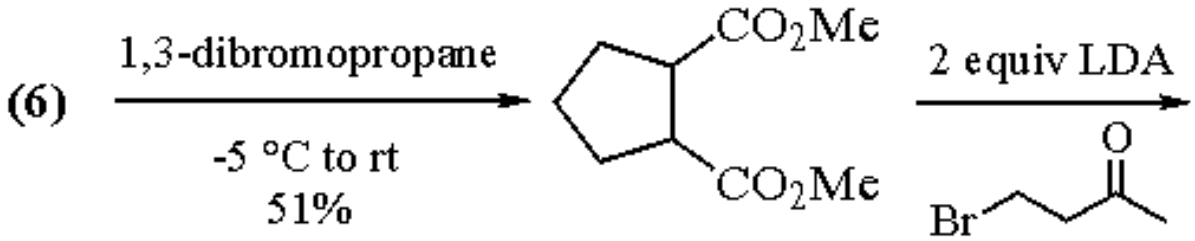

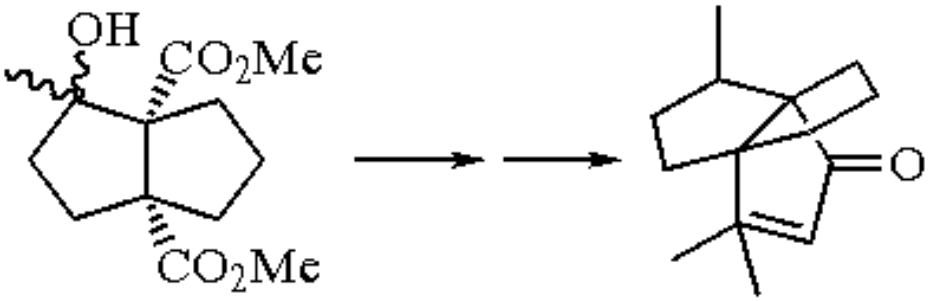

(12)

Modhephene

An efficient asymmetric carbocyclization to give three- to six-membered ring compounds can be achieved using the dianion of chiral dimenthyl succinate (**8**) (eq 13).[16]

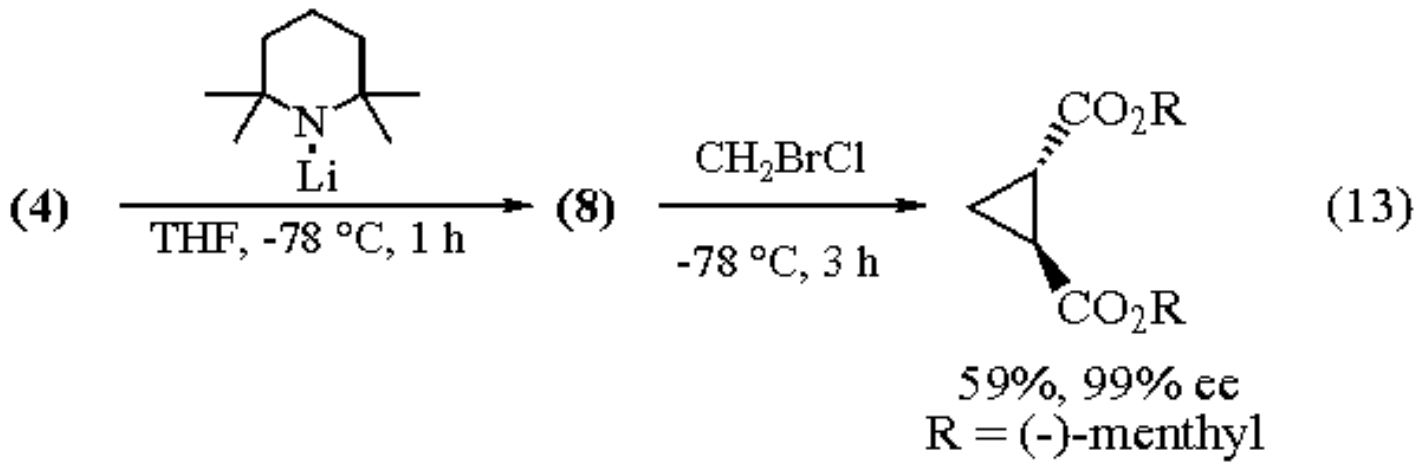

Direct condensation of dianion (**7**) with 2-(bromomethyl)acrylate provides a one-pot preparation of cyclopentanones (eq 14).[17] The use of the diisopropyl ester in this reaction is superior to diethyl or dibenzyl derivatives, both of which gave lower yields of the coupling products.

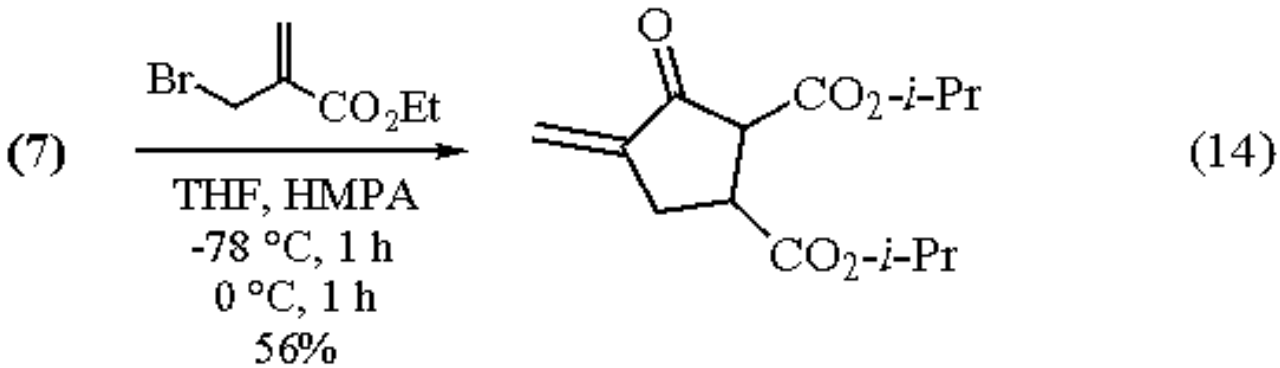

Related Reagents.

N-Chlorosuccinimide; ***2,5-Dihydro-2,5-dimethoxyfuran***; ***2,5-Dimethoxytetrahydrofuran***; ***Succindialdehyde***; ***Succinic Anhydride***; ***Succinimide***.

---

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Diethyl(tributylstannyl)aluminum

n-$Bu_3SnAlEt_2$

[92074-24-3] · $C_{16}H_{37}AlSn$ · Diethyl(tributylstannyl)aluminum · (MW 375.15)

(in the presence of $Pd(PPh_3)_4$ or CuCN catalyst, is a reagent for synthesis of allylstannanes or vinylstannanes from allylic acetates or alkynes; mediates Reformatsky reactions)

Physical Data: see entries for ***Diethylaluminum Chloride*** and ***Tri-n-butylstannyllithium***.

Solubility: sol THF.

Preparative Methods: Et_2AlCl (hexane, toluene, or THF solution, 1.0 equiv) is added to n-Bu_3SnLi[1] (1.0 equiv) derived from ***n-Butyllithium*** (3.0 equiv) and anhydrous ***Tin(II) Chloride*** (1.0 equiv) in THF at 0 °C. The mixture is stirred for 20 min at 0 °C and the reagent is used directly for further reactions.

Synthesis of Allylstannanes.

Addition of the reagent (**1**) to allylic acetates or allylic phosphates in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** catalyst affords allylstannanes (eqs 1-3).[2,3] The reagent reacts with the less substituted carbon of allylic substrates to form allylstannanes with inversion of configuration. Reaction of the crude products, generated from allylic acetates and (**1**), with aldehydes catalyzed by ***Boron Trifluoride Etherate*** provides homoallylic alcohols.[3] The allylic phosphate protocol does not require the extra Lewis acid since the aluminum phosphate serves as a Lewis acid. Alternatively, the presence of an equimolar amount of aldehyde in the reaction system results in the direct formation of homoallylic alcohols (eq 4).[2] n-$Bu_3SnAlEt_2$ and a Pd^0 complex catalyze the intramolecular reductive coupling of allyl acetates with vinyl and aryl bromides (eq 5).[4]

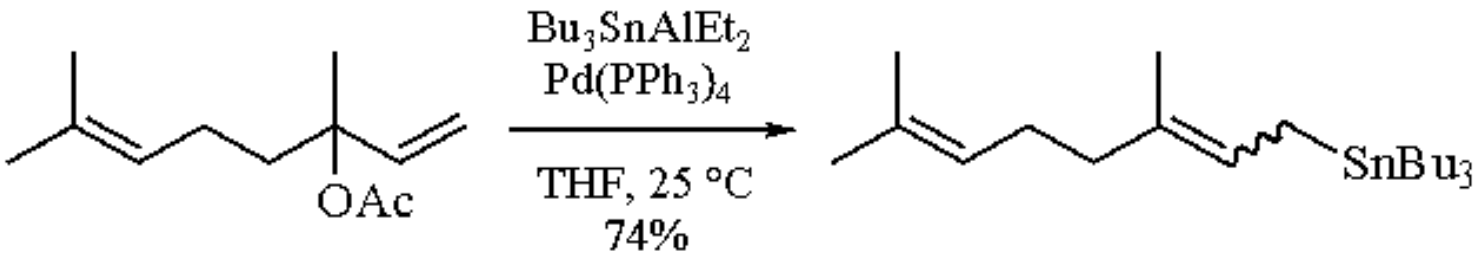

(1)

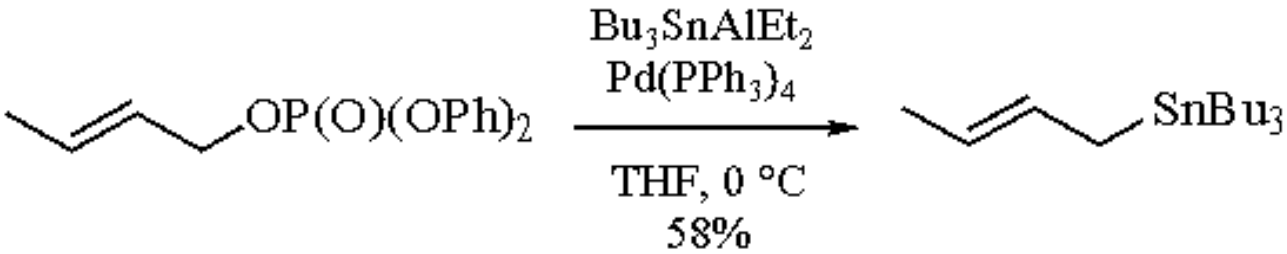

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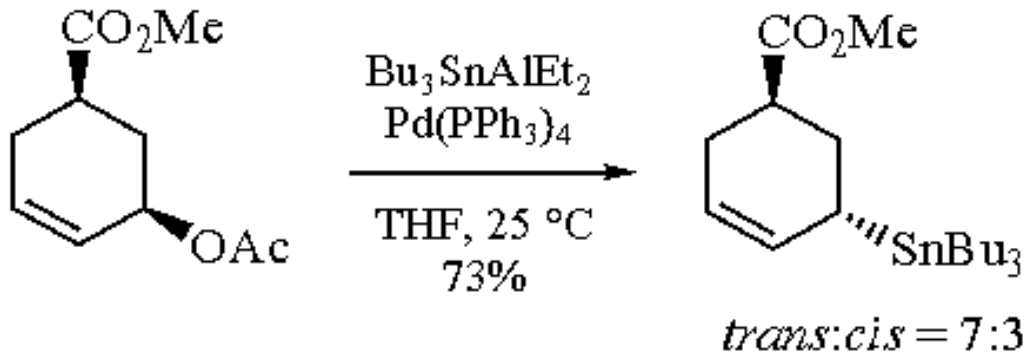

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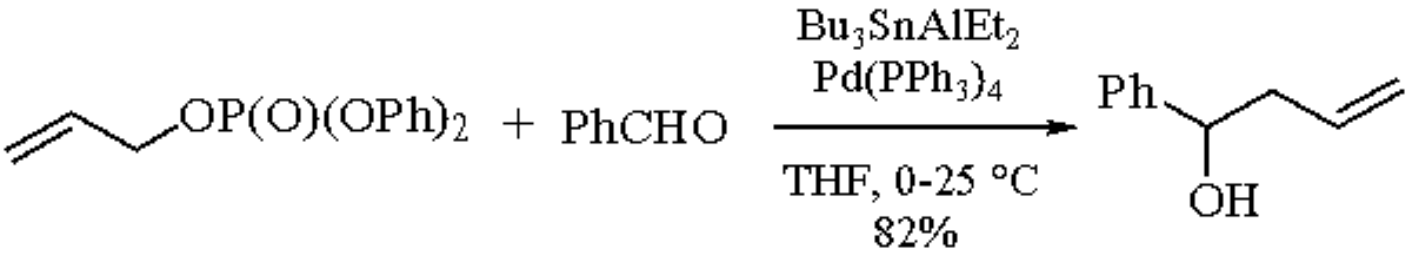

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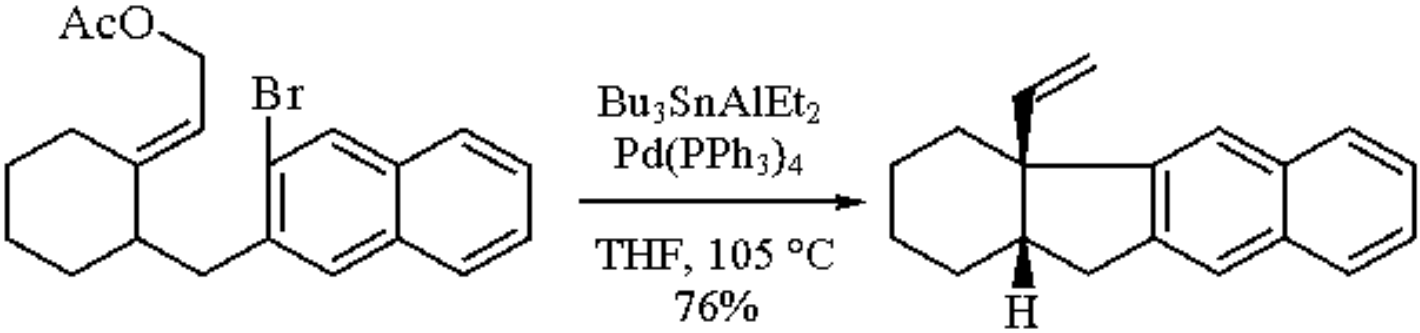

(5)

Stannylalumination of Alkynes.

Reaction of 1-alkynes with (**1**) in the presence of ***Copper(I) Cyanide*** catalyst provides a mixture of (*E*)-1-tributylstannyl-1-alkenes and their regioisomers in good yield (eq 6).[5] The intermediate adducts undergo electrophilic substitution reactions to provide alkenylstannanes. The kinetically favored regioisomer is the 1-stannylalkene, whereas the thermodynamically favored regioisomer is the 2-stannyl derivative.[1d,6] This reaction has been applied to functionalized alkynes,[7a] enynes,[7b] and allenes.[8] Stannylalumination of propargyl or homopropargyl acetals affords vinylstannanes (eq 7).[7a] Reaction of 5-hydroxy-1,2-pentadiene with (**1**) gives 5-hydroxy-2-tributylstannyl-1-pentene in the presence of a Co catalyst (eq 8).[8]

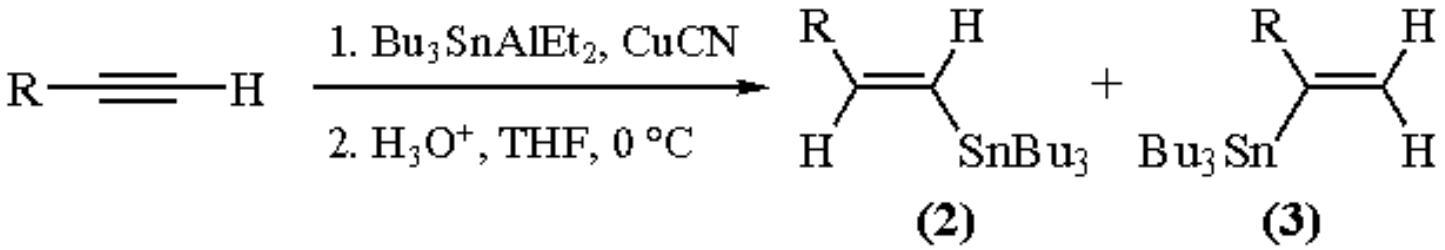

(6)

R = $PhCH_2OCH_2CH_2$, 86%, **(2)**:**(3)** = 81:19
R = Ph, 88%, **(2)**:**(3)** = 79:21
R = $C_{10}H_{21}$, 87%, **(2)**:**(3)** = 38:62

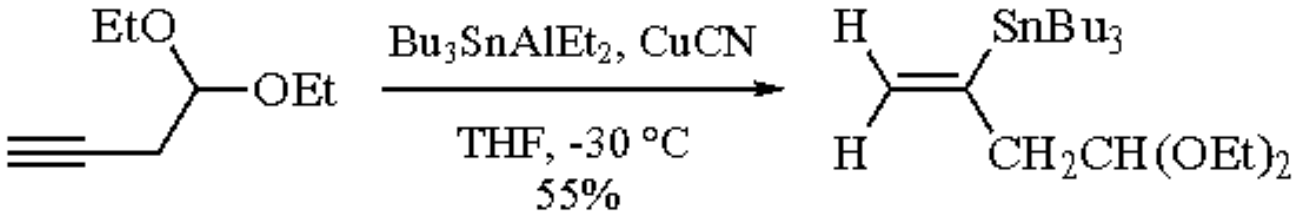

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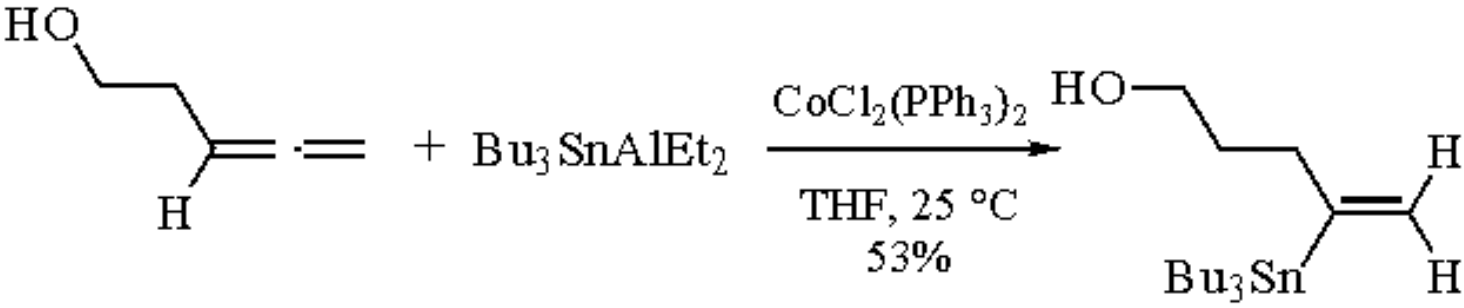

(8)

Reformatsky-Type Reaction.[9]

Treatment of α-bromo carbonyl compounds with the reagent affords aluminum enolates which react with ketones or aldehydes to give β-hydroxy carbonyl compounds in good yields (eq 9). Yields are generally improved by addition of catalytic amounts of $Pd(PPh_3)_4$. Treatment of a mixture of 2-bromo-2-methylcyclohexanone and benzaldehyde with the reagent provides the expected β-hydroxy ketone (eq 10). Reaction of methyl γ-bromocrotonate gives α-adducts exclusively (eq 11). $Bu_3PbAlEt_2$ can be used in the same way.[9]

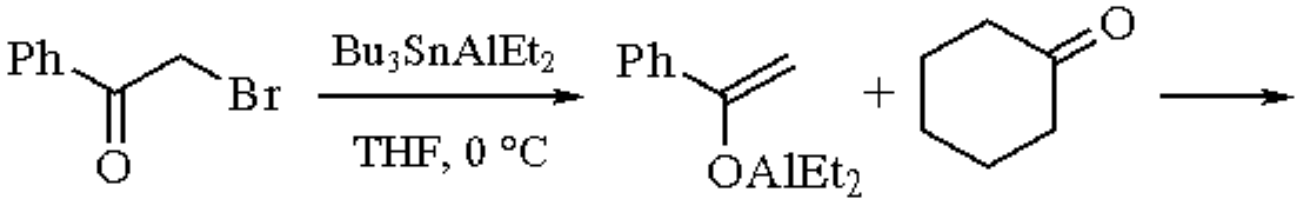

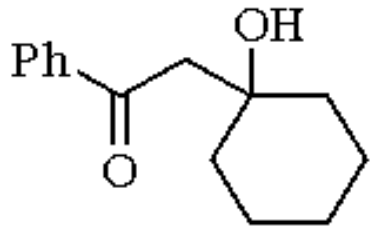

(9)

76%

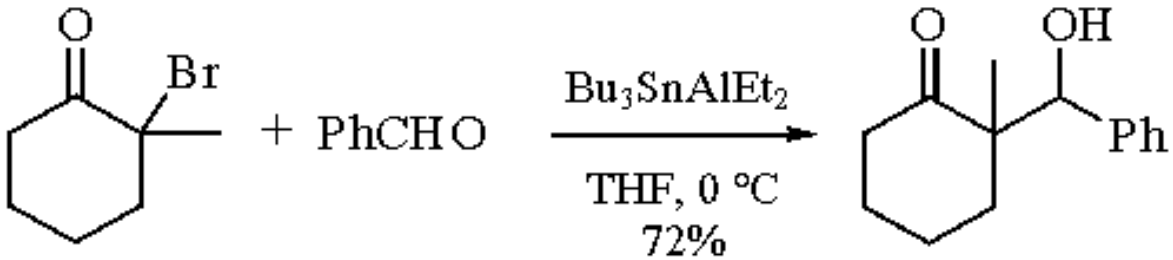

(10)

erythro:*threo* = 42:58

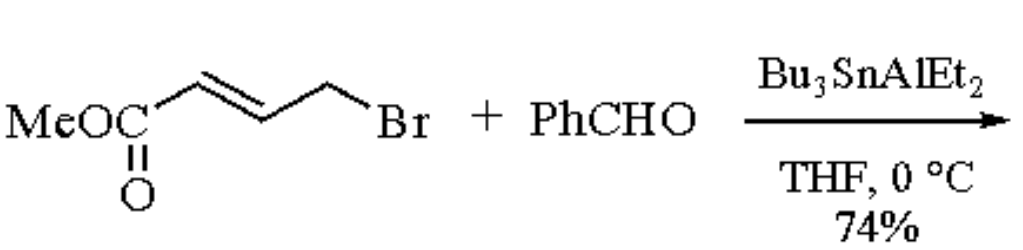

(11)

erythro:*threo* = 54:46

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Diethyl Trimethylsilyl Phosphite[1]

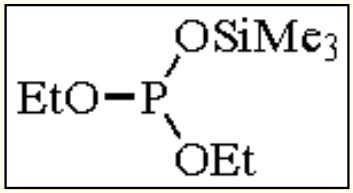

[122289-10-5] · $C_7H_{19}O_3PSi$ · Diethyl Trimethylsilyl Phosphite · (MW 210.32)

(nucleophilic, trivalent phosphorus reagent capable of forming a diethyl phosphonate derivative by displacement reaction or silylphosphonylation of multiple bond functionalities such as aldehydes and ketones, both saturated and unsaturated[1d])

Alternate Name: DTP.

Physical Data: bp 63-65 °C/15 mmHg.

Preparative Methods: generally prepared by reacting the sodium salt of ***Diethyl Phosphonite*** with ***Chlorotrimethylsilane*** in ether.[1a] Alternatively, the reagent has been prepared by reacting diethyl phosphonite with chlorotrimethylsilane in ether/TEA.[1b]

Handling, Storage, and Precautions: is susceptible to hydrolysis and should be prepared immediately prior to use. The salts generated during preparation of the compound are typically removed by filtration and the solution of DTP used without further purification or simply evaporated and the crude material used without purification.

Carbonyl Addition.

The 1,2-addition of DTP to carbonyl moieties is known as the Abramov reaction. Several reports of this smooth addition reaction have been published. Representative examples are given in Table 1. The initially formed diethyl α-trimethylsiloxyphosphonates are typically isolated via distillation and result from intramolecular transfer of silicon (eq 1).[1b]

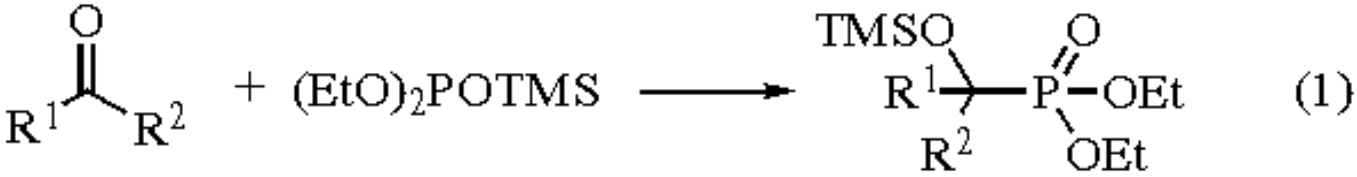

(1)

Table 1 Reactions of DTP With Saturated Carbonyl Substrates

Carbonyl	Yield (%)	Conditions
MeCHO[2]	72	3 h, 20 °C
PhCHO[2]	66	1.5 h, 50 °C
EtCOMe[3]	55	1.5 h, 120 °C
Cyclopentanone[3]	52	1.5 h, 20 °C
Cl_3CCHO[4]	92	- 20 °C
CF_3COCF_3[5]	95	- 25 °C
PhCOMe[1b]	73	3 h, 110 °C
MeCOMe[1b]	63	3 h, 110 °C
Cyclohexanone[1b]	91	3 h, 110 °C

A convenient method to prepare ketones (eq 2)[6] and α-hydroxy ketones (eq 3)[7] has been developed using these 1,2-carbonyl addition products.

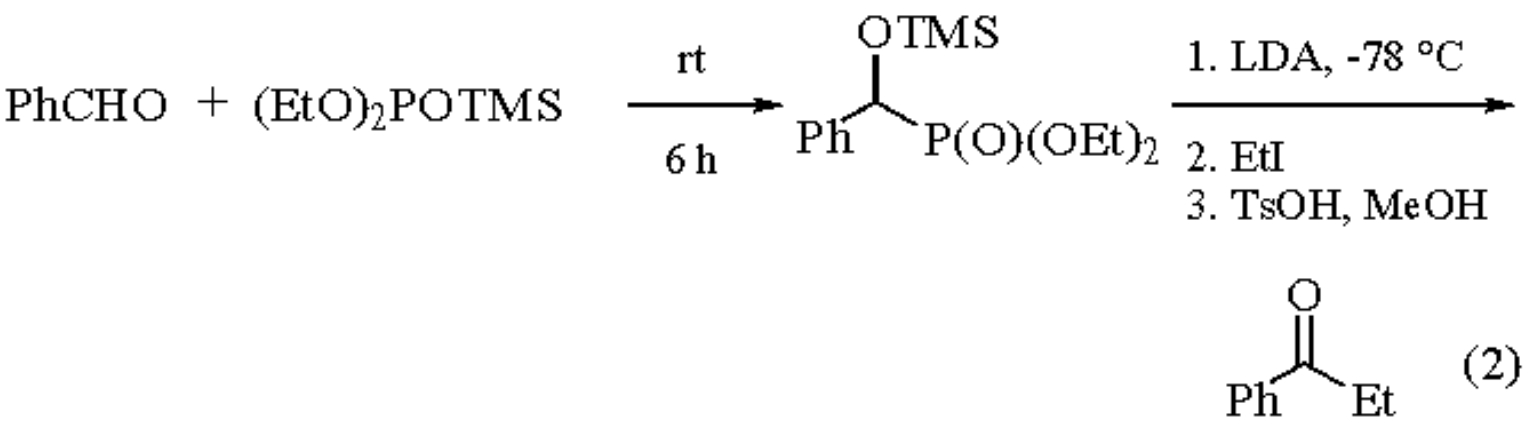

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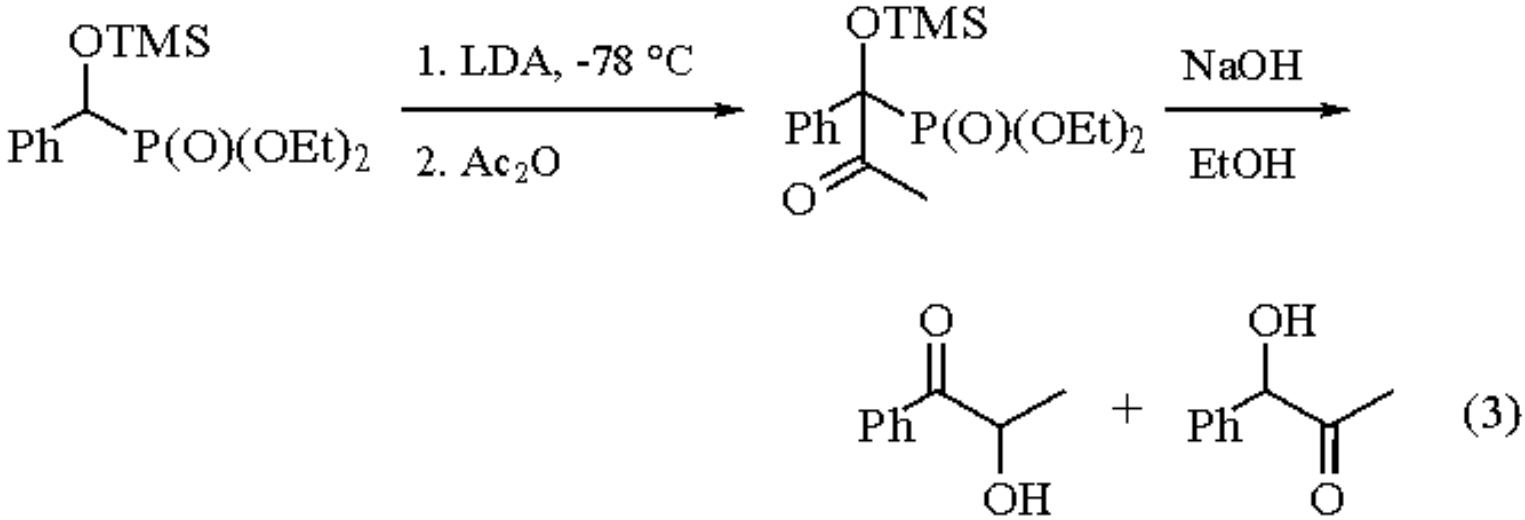

Conjugate Additions.

The reaction of DTP with α,β-unsaturated aldehydes, ketones, esters, and nitriles has been reported by several workers.[8] In general, reactions with α,β-unsaturated aldehydes occur at rt via a 1,2-addition mode. With ***Methyl Vinyl Ketone***, addition requires heating and occurs in a 1,4-manner. However, 1,2-addition products begin to compete as the steric bulk of the β-carbon increases. To circumvent the forcing conditions required for additions to α,β-unsaturated esters and ketones, a method involving Lewis acid catalysts has been developed using diethyl phosphonite and ***Trimethylaluminum***.[9]

Ketene and β-Dicarbonyl.

The reaction of DTP with ketene is exothermic and requires cooling. The resultant [1-(trimethylsiloxy)vinyl]phosphonate can be isolated by distillation (eq 4).[3a,8b]

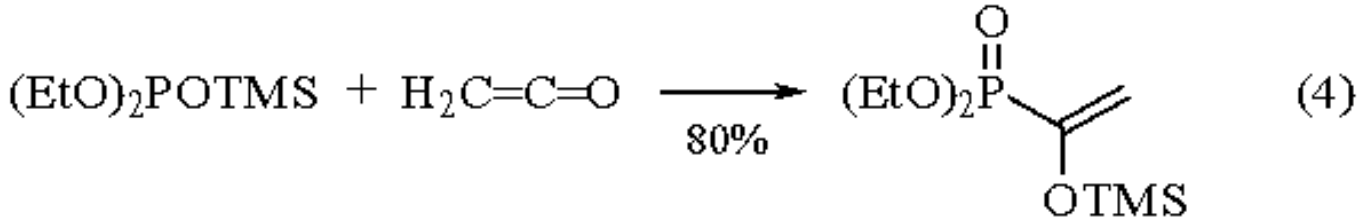

With β-dicarbonyl reaction partners, the reaction course is dependent upon the dicarbonyl component. For ***Ethyl Acetoacetate***, an exothermic reaction occurs upon addition of the ester to DTP and the predicted 1,2-addition product is isolated after distillation (eq 5).[8c]

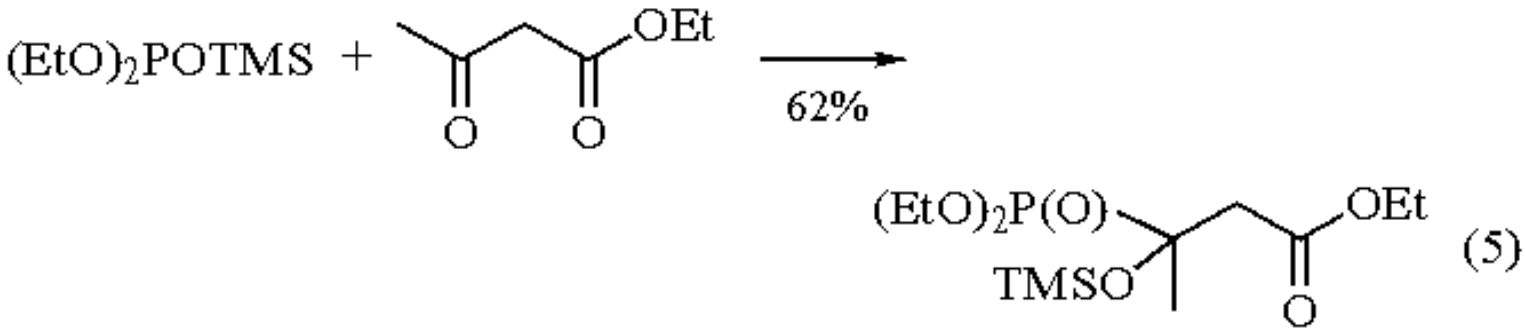

For ***2,4-Pentanedione***, multiple products as well as the 1,2-addition product are formed, resulting from competing reactions such as (a) silylation of the enol form of the dione, (b) addition of a second molecule of DTP to the 1,2-addition product, forming an oxaphospholane upon cyclization and loss of methoxytrimethylsilane.[10] In the case of ethyl phenylglyoxylate, rearrangement of the initial 1,2-addition product occurs by transfer of the diethyl phosphonate to produce the diethyl phosphate product (eq 6).[11]

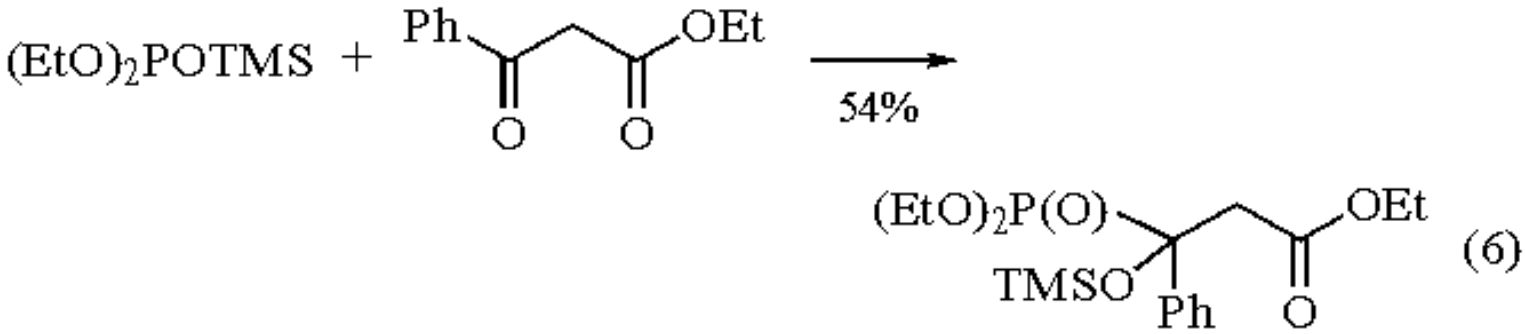

With phenylglyoxylonitrile, an exothermic reaction occurs with DTP to provide a mixture of the phosphonate 1,2-addition product and phosphate rearrangement product. Finally, with α-ketophosphonates such as diethyl acetylphosphonate, straightforward 1,2-addition occurs to provide the bis-phosphonate (eq 7).[12]

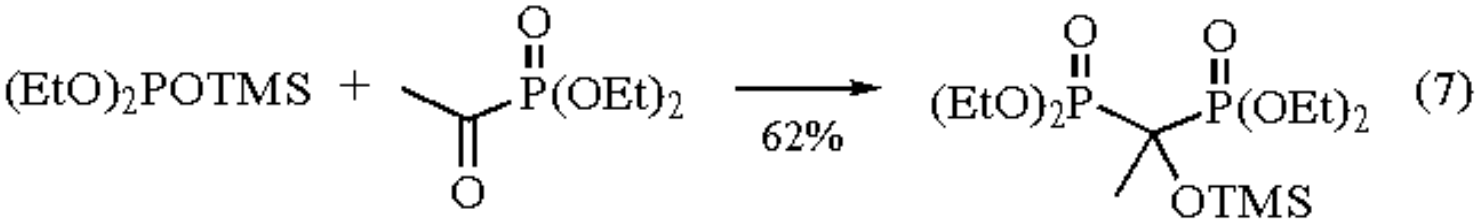

Epoxides.

The addition of DTP to epoxides is reported to occur most effectively under Lewis acid (***Zinc Iodide***, ***Iron(III) Chloride***, ***Tin(II) Chloride***, ***Tin(IV) Chloride***) or basic (***n-Butyllithium***) catalysis. Reaction generally occurs at moderate temperatures (55 °C), undergoing exclusive ring opening at the terminal carbon.[13] This method has been used to prepare fructophosphonic acids (eq 8).[14]

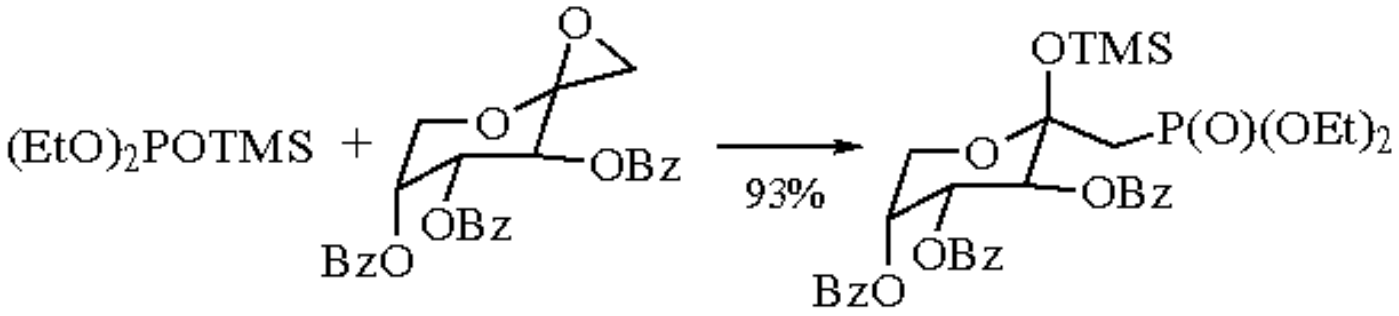

(8)

1. (a) Liotta, D.; Sunay, U.; Ginsberg, S. *JOC* **1982**, *47*, 2227. (b) Creary, X.; Geiger, C. C.; Hilton, K. *JACS* **1983**, *105*, 2851. (c) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *JACS* **1978**, *100*, 3467. (d) For an excellent review of the chemistry of phosphorus reagents, see: Engel, R. *Synthesis of Carbon-Phosphorus Bonds*; CRC: Boca Raton, FL, 1988.
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8. (a) Esters: Okamoto, Y.; Sakurai, H. *S* **1982**, 497. (b) Aldehydes, ketones, esters, nitriles: Novikova, Z. S.; Mashoshima, S. N.; Sapozhnikova, T. A.; Lutsenko, I. F. *JGU* **1971**, *41*, 2655. (c) Aldehydes, ketones: see Ref 1c. (d) Cyclic ketones: Liotta, D.; Sunay, U.; Ginsberg, S. *JOC* **1982**, *47*, 2227.
9. Green, K. *TL* **1989**, *30*, 4807.
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11. Konovalova, I. V.; Burnaeva, L. A.; Saifullina, N. Sh; Pudovik, A. N. *JGU* **1976**, *46*, 17.
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Diethylzinc[1]

Et_2Zn

[557-20-0] · $C_4H_{10}Zn$ · Diethylzinc · (MW 123.50)

(useful organometallic reagent for organic synthesis;[1] polymerization catalyst)

Physical Data: mp -28 °C; bp 118 °C; bp 27 °C/30 mmHg; *d* 1.187 g cm^{-3}.

Solubility: sol most organic solvents; reacts with acidic hydrogens; pyrophoric; reacts violently with water.

Form Supplied in: colorless liquid; available as 1.0 M solution in hexanes and 1.1 M solution in toluene, or neat in a metal cylinder.

Analysis of Reagent Purity: can be titrated by iodometric methods[4] or by complexometry.[5]

Preparative Methods: prepared by the reaction of ***Zinc/Copper Couple*** with ***Ethyl Iodide*** followed by distillation (81-84%).[2] It can also be prepared via a B/Zn exchange reaction.[3]

Handling, Storage, and Precautions: highly flammable liquid; spontaneous ignition in air; reacts violently with water. Should be kept under an inert atmosphere.[6] Neat diethylzinc is best destroyed by first diluting with THF, followed by slow addition of ethanol at 0 °C.

Addition to Carbonyl Compounds.

Diethylzinc, like other dialkylzincs, reacts only slowly with carbonyl compounds. ***Carbon Dioxide*** can be used as protecting gas for reactions performed with diethylzinc and the formation of a zinc propionate is observed only under a high pressure of CO_2 and at higher temperatures.[7] Whereas the reaction of ***Acetaldehyde*** with neat diethylzinc is complete within a few hours, the reaction with higher homologs requires several days.[8] Higher diorganozinc derivatives do not add to aldehydes in solution. The addition of magnesium salts to diethylzinc considerably accelerates the addition to the carbonyl group (eq 1).[9] Similarly, the addition of a tetraalkylammonium chloride or of a catalytic amount of ***N,N,N´,N´-Tetramethylethylenediamine*** accelerates the addition reaction and limits the formation of reduction product.[10]

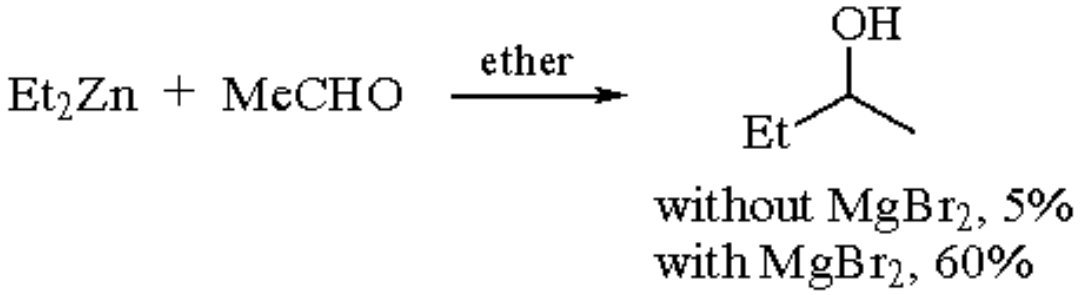

(1)

Neat diethylzinc does not add to ketones and its reaction with benzophenone produces only diphenylmethanol.[11] As in the case of aldehydes, the addition of diethylzinc is accelerated by the presence of magnesium salts.[9] With 1,2-diketones, diethylzinc undergoes an addition in the reverse way to the carbonyl group, producing an α-alkoxy ketone (eq 2).[12] A similar reaction with α-diimines leads to zincated enamines which can be converted to indolizidines after the addition of an aldehyde and heating (eq 3).[13]

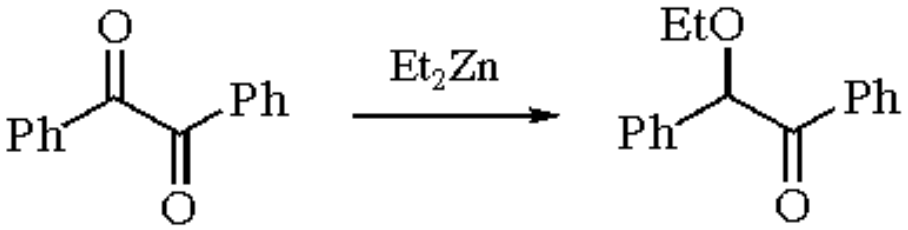

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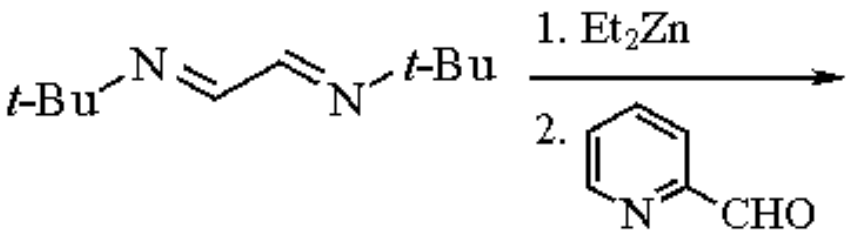

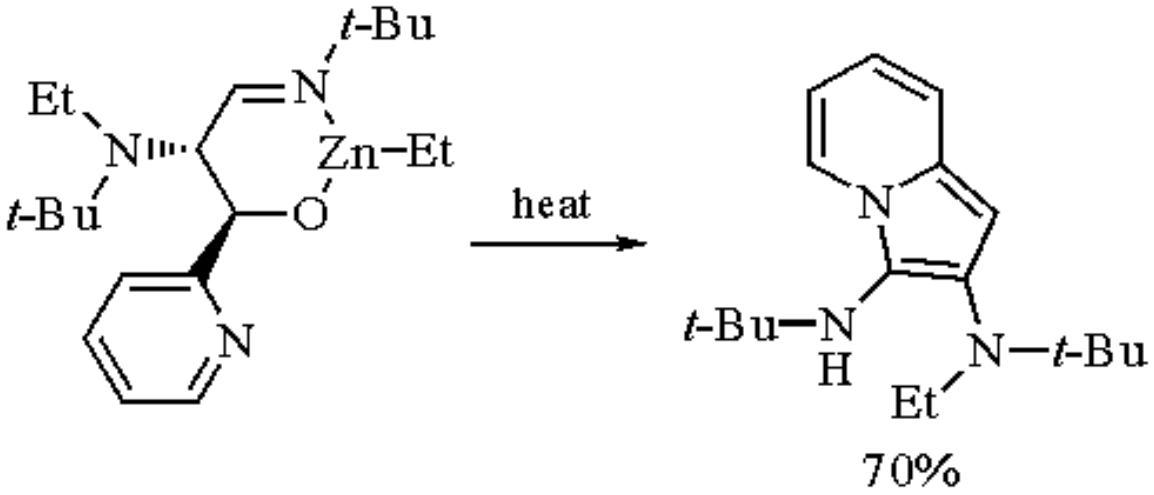

(3)

The presence of a heteroatom at the α-position to the carbonyl group accelerates the addition and diethylzinc adds to the aldehyde (**1**) via a chelate controlled transition state producing the alcohol (**2**), which was further converted to *exo*-brevicomin (eq 4).[14] The addition of diethylzinc to (-)-menthyl phenylglyoxylate gives, after saponification, an α-hydroxy acid with a good diastereoselectivity (eq 5).[15] The low reactivity of diethylzinc with aldehydes has been

advantageously exploited by performing the addition reaction in the presence of a chiral catalyst.[16]

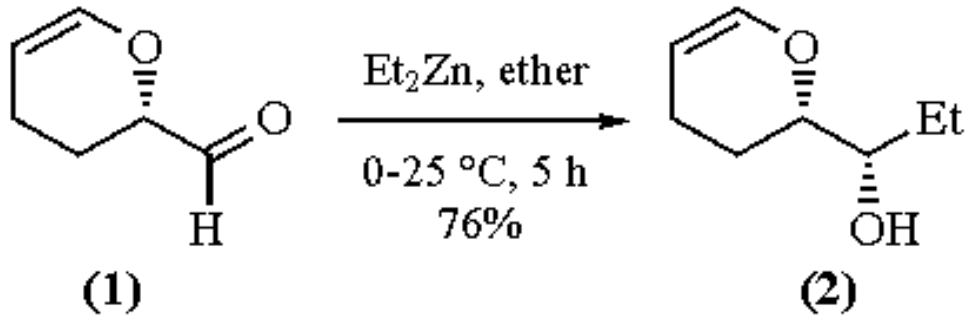

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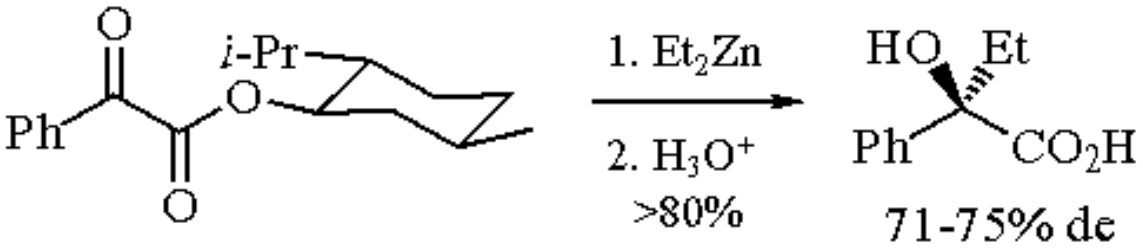

(5)

Mukaiyama showed that the chiral proline derivative (**3**) catalyzes the addition of diethylzinc to benzaldehyde, unfortunately without any asymmetric induction.[17] Oguni found a few years later that (*S*)-leucinol (**4**) also catalyzes the reactions and the same addition proceeds with 48% ee.[18] Since this discovery, a variety of amino alcohols were found to catalyze the addition of diethylzinc to aldehydes with high enantioselectivity (up to 99% ee).[16,19-34] (-)-3-*Exo*-(dimethylamino)isoborneol, (-)-DAIB (**5**), has a particularly high catalytic activity. In the presence of 2 mol % of this catalyst, the addition of diethylzinc to benzaldehyde in toluene is complete within 6 h at 0 °C (98% ee).[20] This catalyst is effective for aromatic aldehydes but gives lower enantioselectivities with aliphatic aldehydes. A series of readily available pyrrolidinylmethanols (**6**), derived from proline, give excellent results both with aliphatic and aromatic aldehydes (eq 6).[21] Remarkably, chiral quaternary ammonium salts such as (**7**) catalyze in the solid state the addition of benzaldehyde to diethylzinc with a good enantioselectivity (eq 7).[22] Chiral metal complexes can also be used as catalysts, and the reaction of diethylzinc with aldehydes in the presence of a chiral oxazoborolidine produces ethylated secondary alcohols in 52-95% ee.[23]

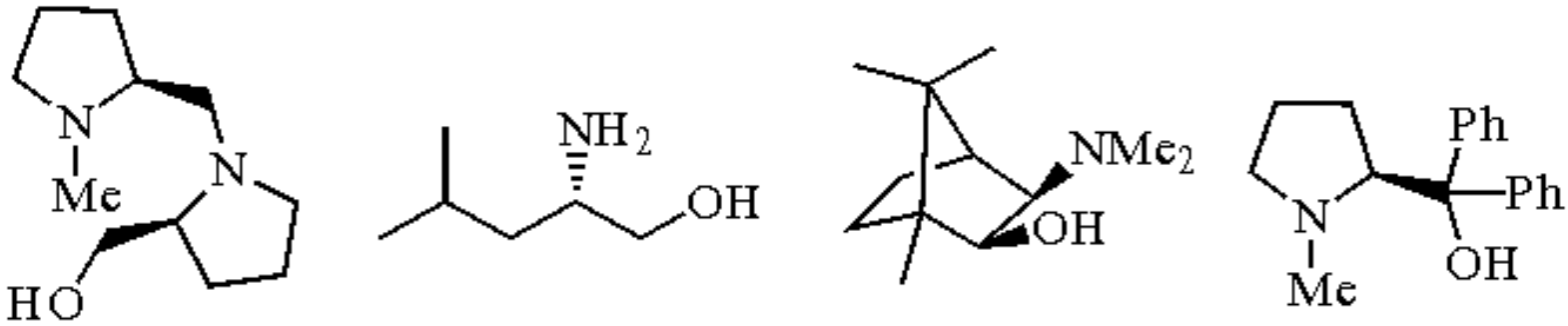

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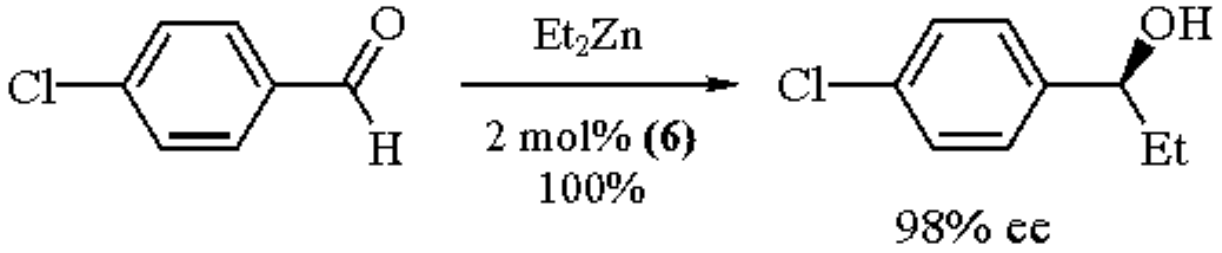

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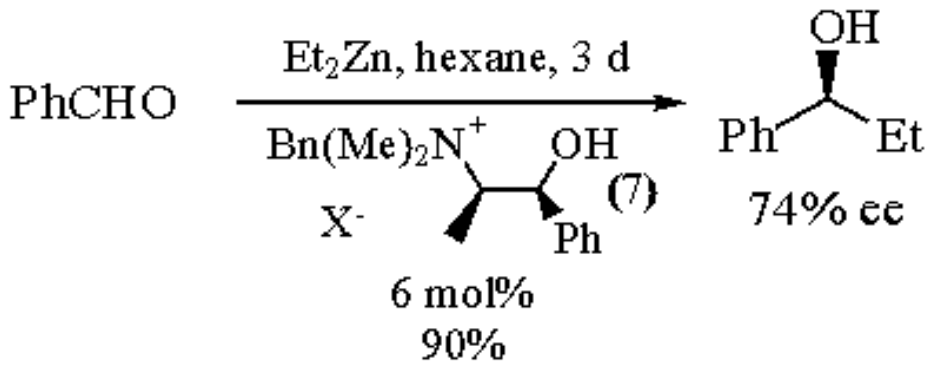

(7)

Very active titanium catalysts (**8**) and (**9**) have been developed respectively by Yoshioka and Ohno,[24] and Seebach.[25] Their high catalytic activity allows the extension to the enantioselective addition of higher dialkylzincs (eq 8)[25] and to both functionalized aldehydes and dialkylzincs (eqs 9-11).[26,27] The excellent functional group tolerance allows the use of many functionalized aldehydes.

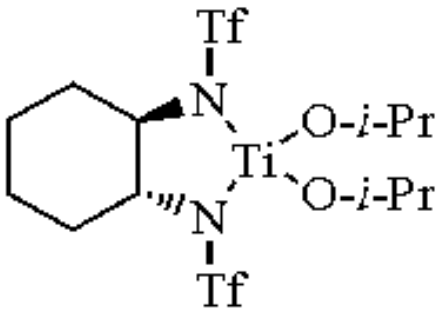

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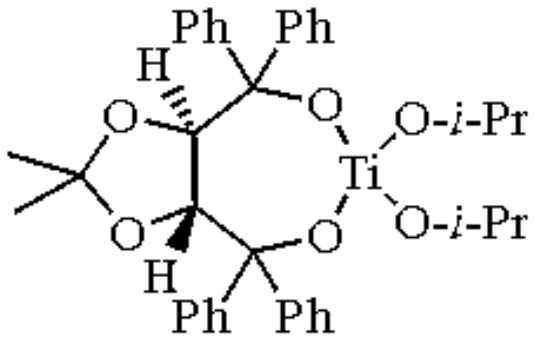

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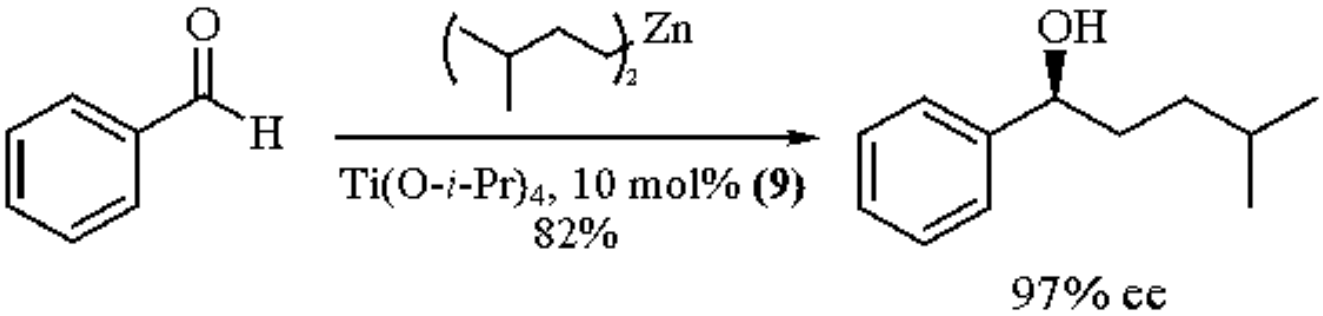

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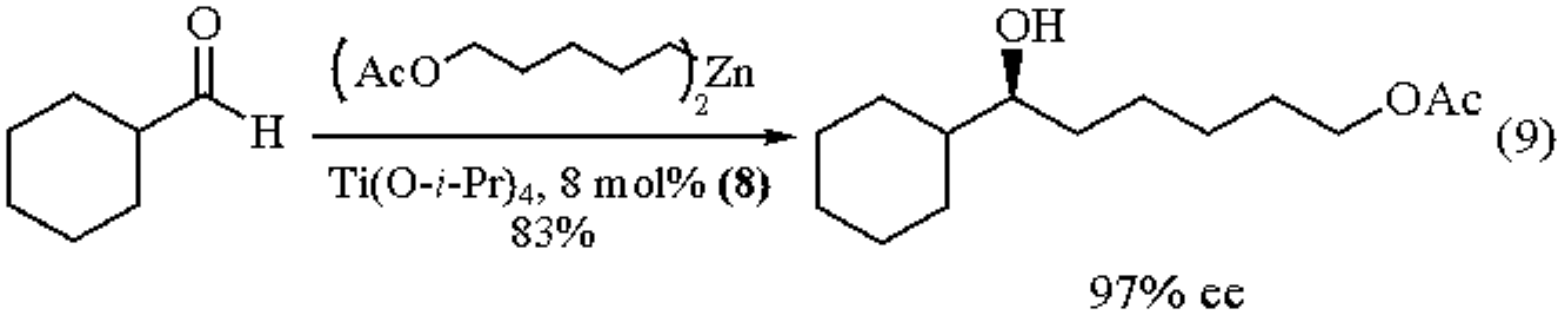

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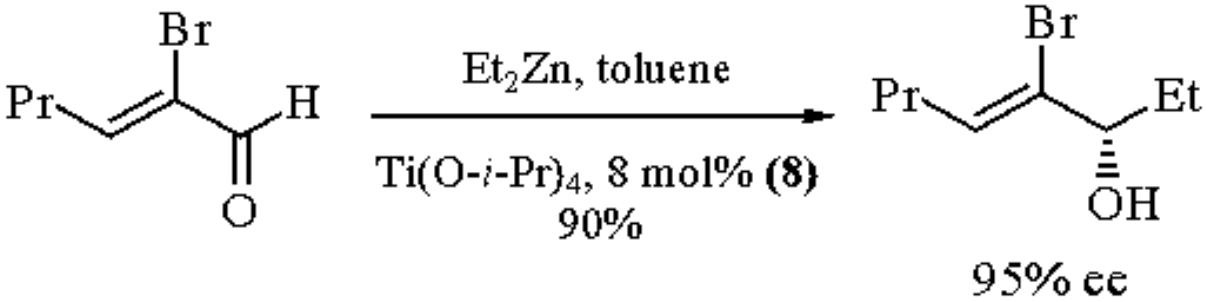

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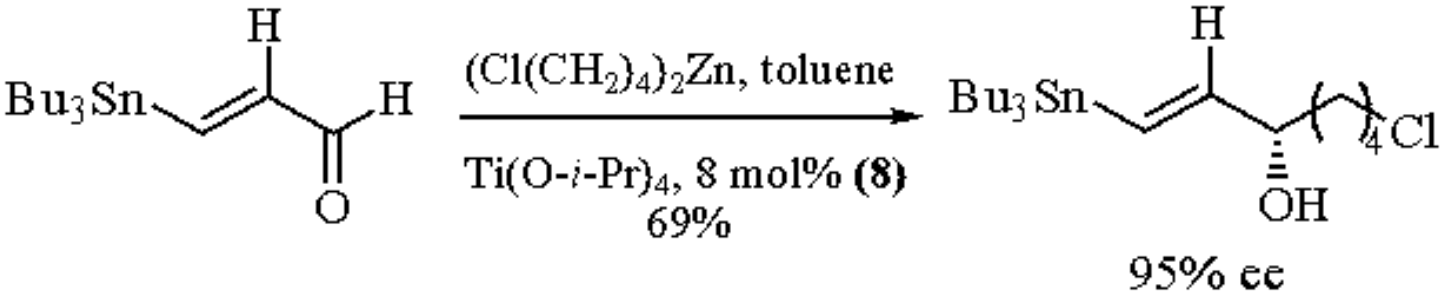

(11)

A new method for the enantioselective synthesis of lactones is based on the enantioselective addition of 3- or 4-formyl esters in the presence of catalytic amounts of the amino alcohol (**10**) (eq 12).[28] γ-Hydroxy ketones can be prepared enantioselectively by the addition of diethylzinc to the ketoaldehyde (**11**) (eq 13).[29] Optically active hydroxy aldehydes are obtained with high enantioselectivity by the addition of diethylzinc to monoprotected dialdehydes (eq 14).[30] A variety of other functionalized aldehydes have been ethylated under similar conditions (eqs 15 and 16).[31]

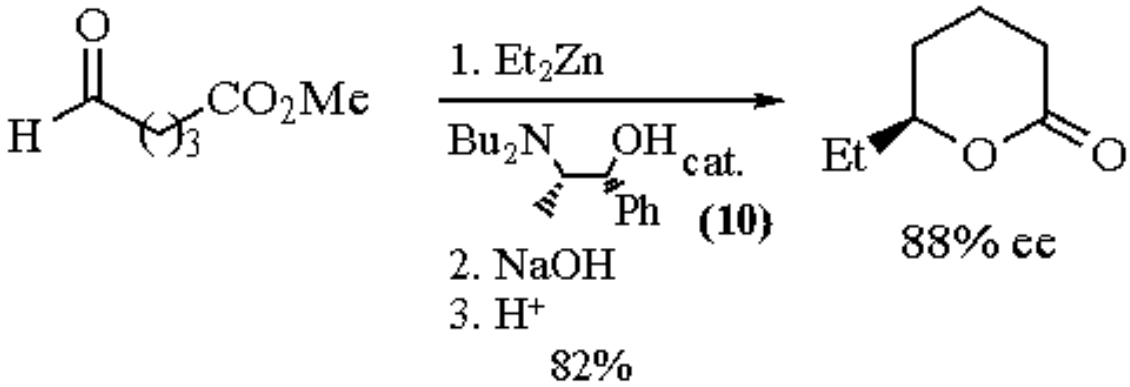

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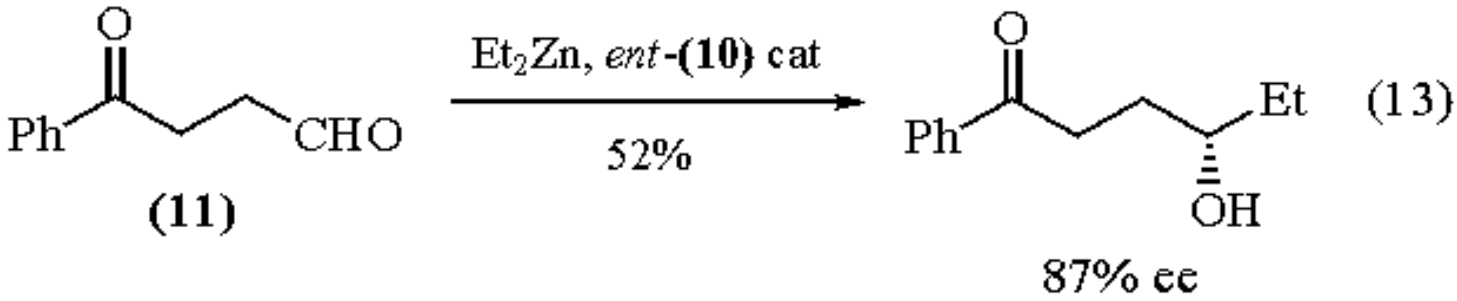

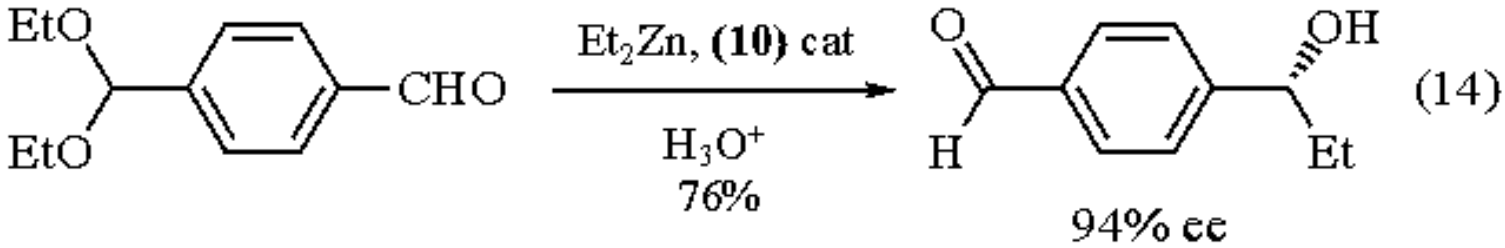

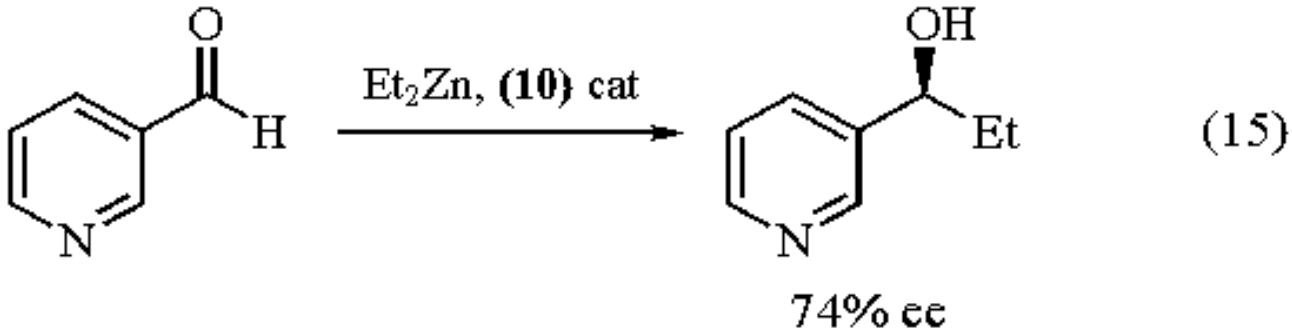

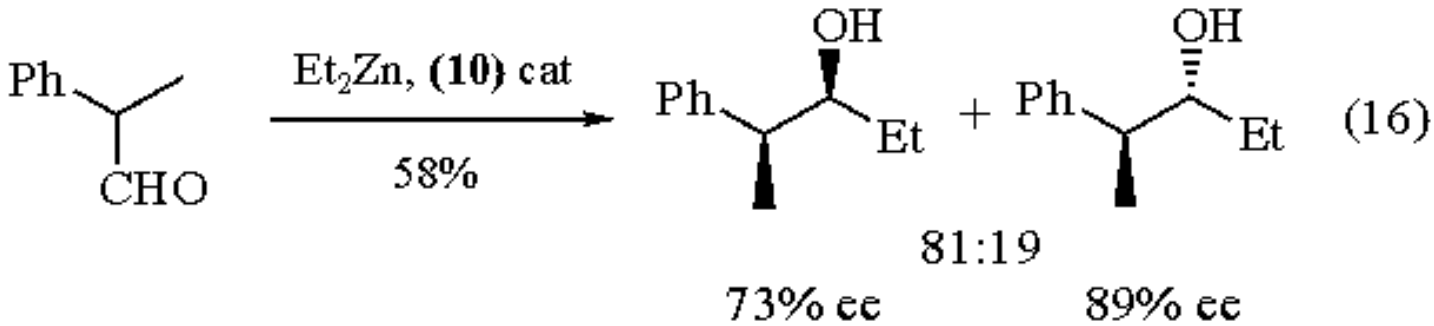

The addition of diethylzinc to activated imines such as *N*-diphenylphosphinoylimines of type (**12**) proceeds in good yields and excellent enantioselectivity, allowing the synthesis of enantiomerically enriched secondary amines (eq 17).[32a] An enantioselective ethylation on *N*-(amidobenzyl)benzotriazoles catalyzed by chiral amino alcohols is also possible.[32b]

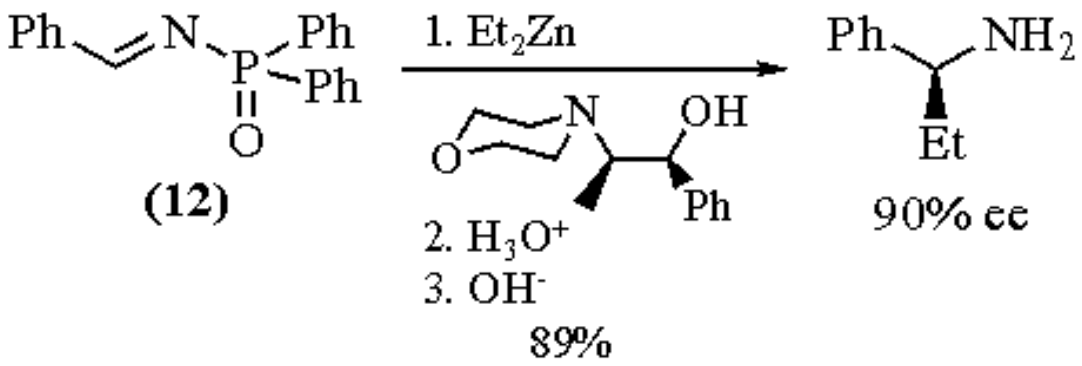

(17)

Polymer-bound chiral catalysts[33] and chiral catalysts supported an silica gel and alumina[34] have been successfully employed for the enantioselective addition of diethylzinc to aldehydes. Little success was obtained in the addition of diethylzinc to esters or lactones. However, the addition to ***Diethyl Oxalate*** produces ethyl 2-ethyl-2-hydroxybutanoate in 75% yield.[9] The reaction with acid chlorides[1,35] or anhydrides[1,36] proceeds in some cases satisfactorily;[35,36] however, Pd^0 [37] or Cu^I [26,38] catalysis gives more predictable results and allows the extension of the reaction to higher functionalized homologs (eq 18).[26,38]

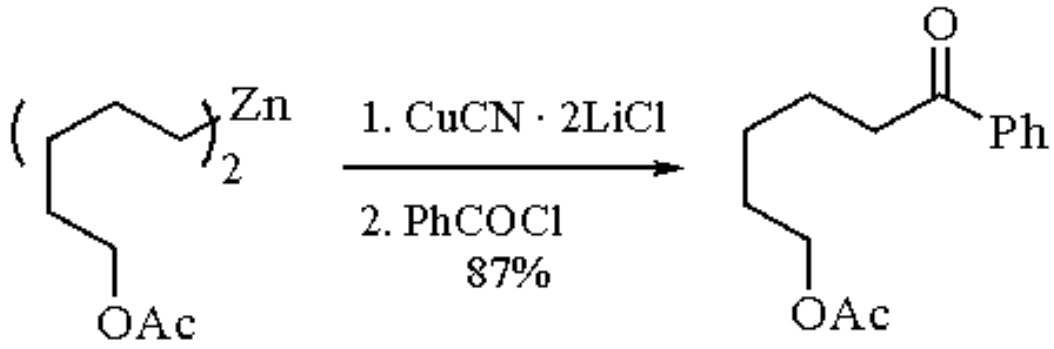

(18)

Addition of Diethylzinc to Double or Triple Bonds.

Diethylzinc, like higher homologs, is able to add to activated alkynes such as propiolic esters in the presence of a THF soluble copper salt such as CuCN.2LiCl (eq 19).[26] Less reactive alkynes such as 1-(methylthio)-1-hexyne or phenylacetylene also react with the reagent EtCu(CN)ZnEt.2LiCl, leading stereospecifically to the *syn* adducts (eq 20).[39] Diethylzinc can be added to unfunctionalized alkynes in the presence of $ZrCp_2I_2$.[40] In the case of terminal alkynes, the addition shows a low regioselectivity, producing a mixture of alkenylzinc species (eq 21).[40] Remarkably, the addition to internal alkynes proceeds well, leading after iodolysis to tetrasubstituted alkenyl iodides (eq 22).[40] The addition to alkenes is more difficult. However, the intramolecular carbozincation of alkenes mediated by a palladium or nickel catalysis is possible (eq 23).[41] The role of diethylzinc in this reaction is to transmetalate the palladium(II) intermediate back to an organozinc reagent and to generate the Pd^0 catalyst. This Pd catalysis can also be used for an efficient generation of primary alkylzinc iodides (eq 24).[41] In the absence of palladium salts, the iodine-exchange reaction requires a temperature of 50 °C.[26,27b] This I/Zn exchange reaction constitutes a unique method for preparing functionalized dialkylzincs (eq 25).[26] The Michael addition of diethylzinc to α,β-unsaturated ketones proceeds well in the presence of a nickel catalyst. In the presence of a chiral nickel catalyst, good to excellent enantioselectivities are observed (eq 26).[42]

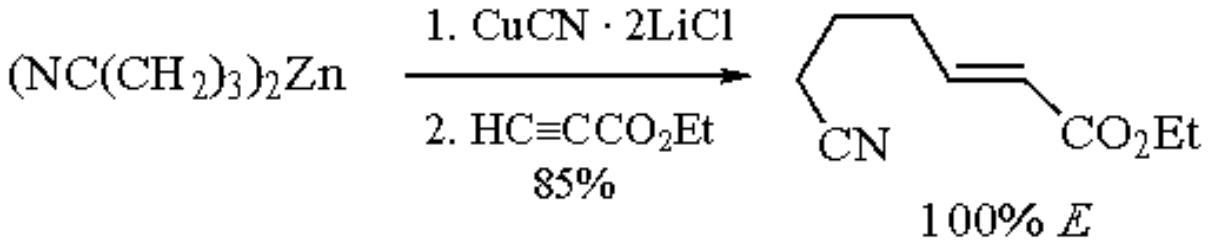
(NC(CH2)3)2Zn
1. CuCN · 2LiCl
2. HC≡CCO2Et
85%
CN
CO2Et
100% E

(19)

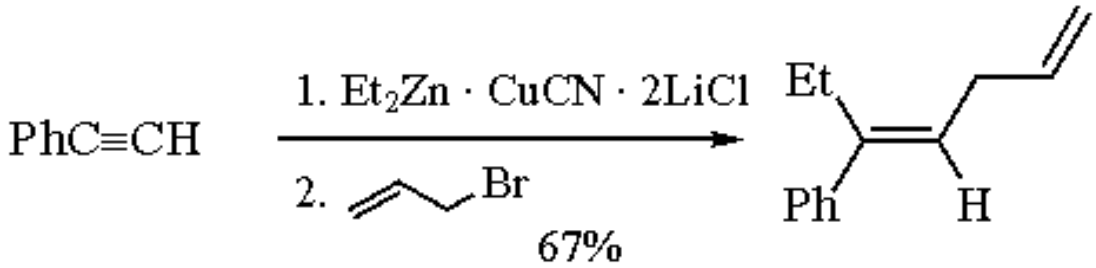
PhC≡CH
1. Et2Zn · CuCN · 2LiCl
2.
Br
67%
Et
Ph
H

(20)

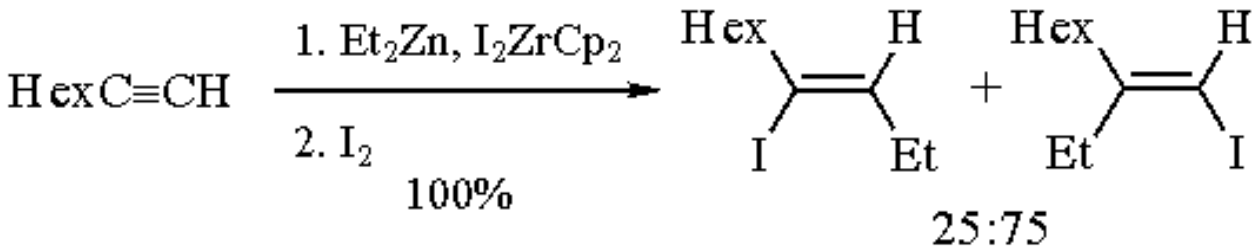
HexC≡CH
1. Et2Zn, I2ZrCp2
2. I2
100%
Hex
H
I
Et
+
Hex
H
Et
I
25:75

(21)

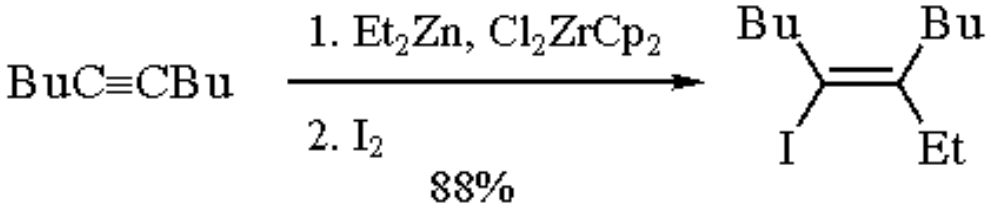
BuC≡CBu
1. Et2Zn, Cl2ZrCp2
2. I2
88%
Bu
Bu
I
Et

(22)

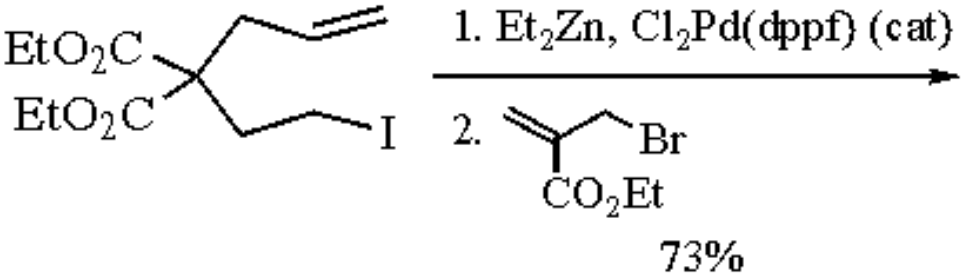
EtO2C
EtO2C
I
1. Et2Zn, Cl2Pd(dppf) (cat)
2.
Br
CO2Et
73%

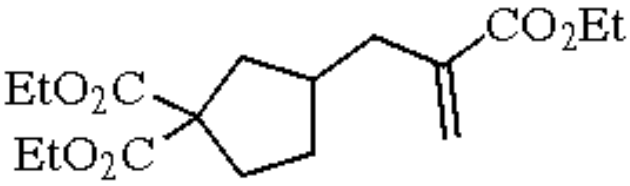
CO2Et
EtO2C
EtO2C

(23)

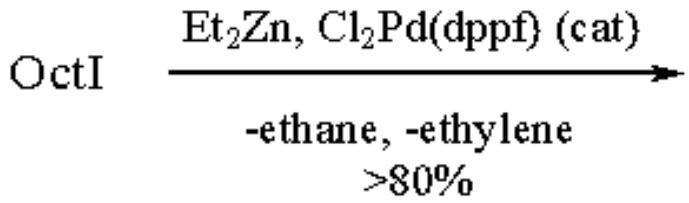

(24)

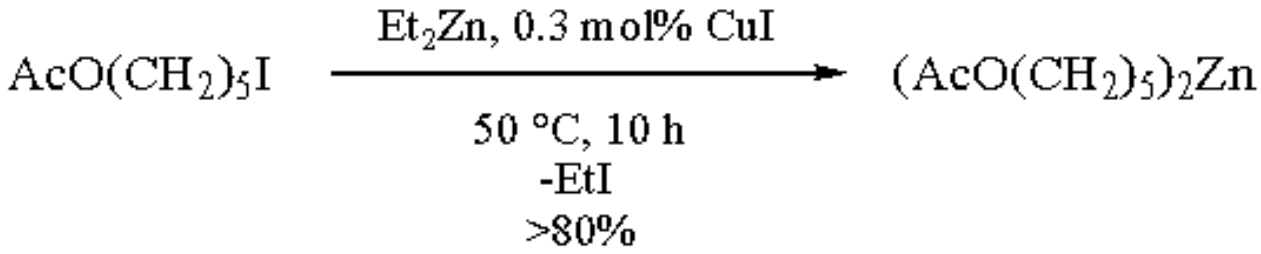

(25)

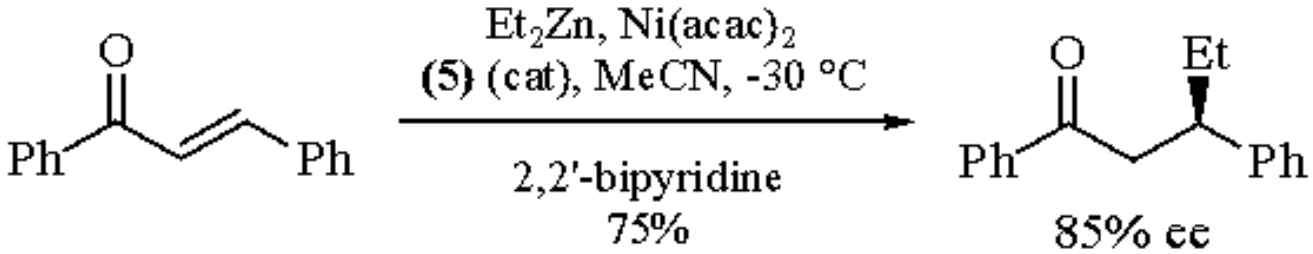

(26)

Cyclopropanation.

The reaction of diethylzinc with ***Diiodomethane*** rapidly produces ICH_2ZnEt (see ***Ethyliodomethylzinc*** and ***Iodomethylzinc Iodide***).[1,43] A further exchange can occur, leading to $(ICH_2)_2Zn$.[43] Both of these iodomethylzinc derivatives are excellent cyclopropanation reagents, and their generation with diethylzinc (Furukawa method) allows convenient cyclopropanation reactions (eq 27).[44]

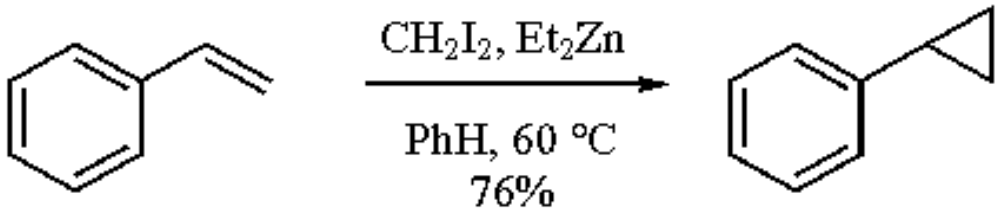

(27)

The reaction gives especially good results with electron-rich alkenes (eq 28).[45] The cyclopropanation was originally performed under the strict absence of oxygen. It was later found that the presence of air accelerates the reaction and improves the yields (eq 29).[1,46] An extension of the cyclopropanation using higher 1,1-diiodoalkanes is possible, and leads preferentially to the *syn* products (eqs 30 and 31).[47] An *anti* stereoselectivity is observed with allylic alcohols (eq 32).[47] Benzene and polynuclear aromatic compounds are cyclopropanated by ***1,1-Diiodoethane*** and diethylzinc in moderate yields (eq 33).[48] Highly diastereoselective cyclopropanations can be performed with chiral allylic and homoallylic alcohols and acetal derivatives (eq 34).[49] The cyclopropanation of silylated ketene acetals using ***Bromoform*** and diethylzinc allows the generation of polyfunctional zinc carbenoids and the performance of intramolecular cyclopropanations (eq 35).[50]

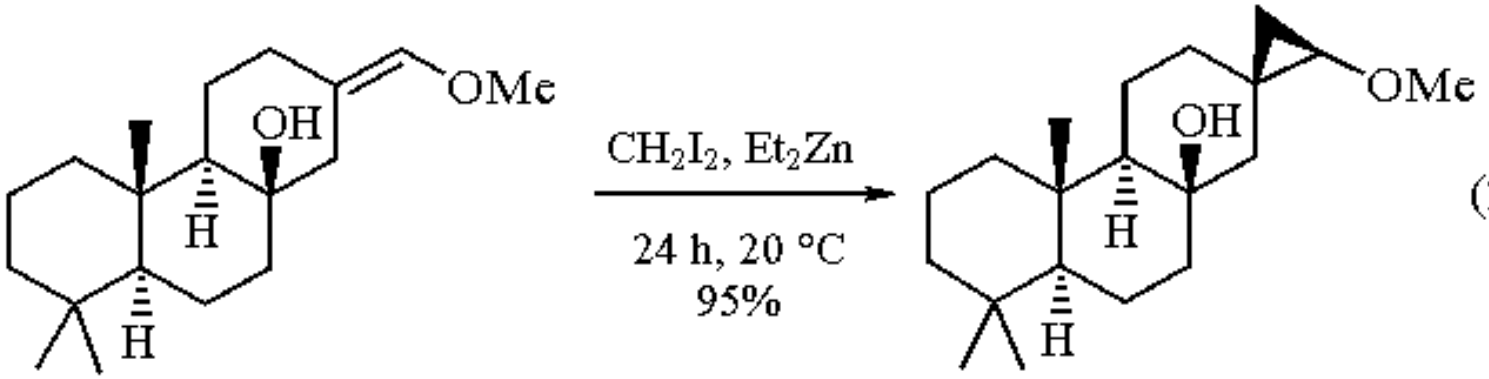

(28)

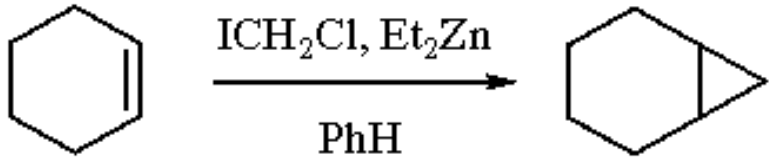

(29)

without air, 60 °C, 11 h 79%
with air, 40 °C, 1 h 91%

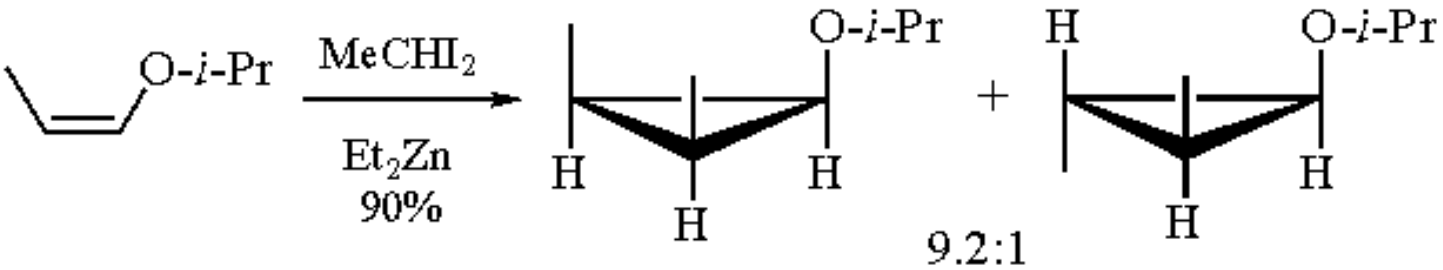

(30)

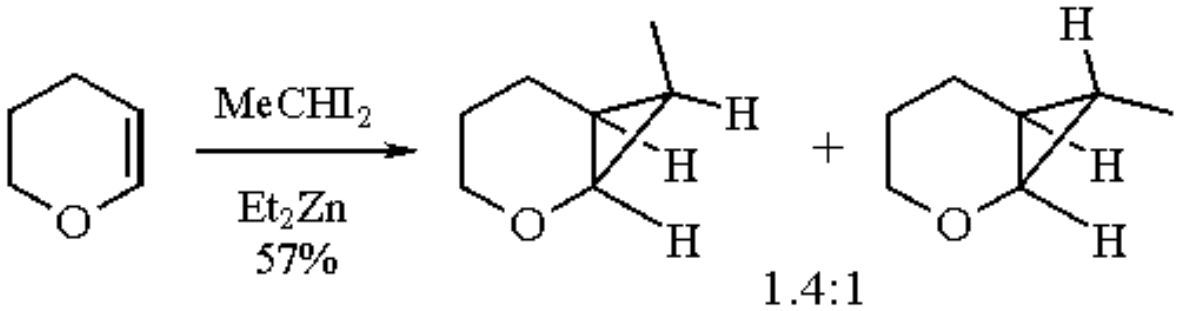

(31)

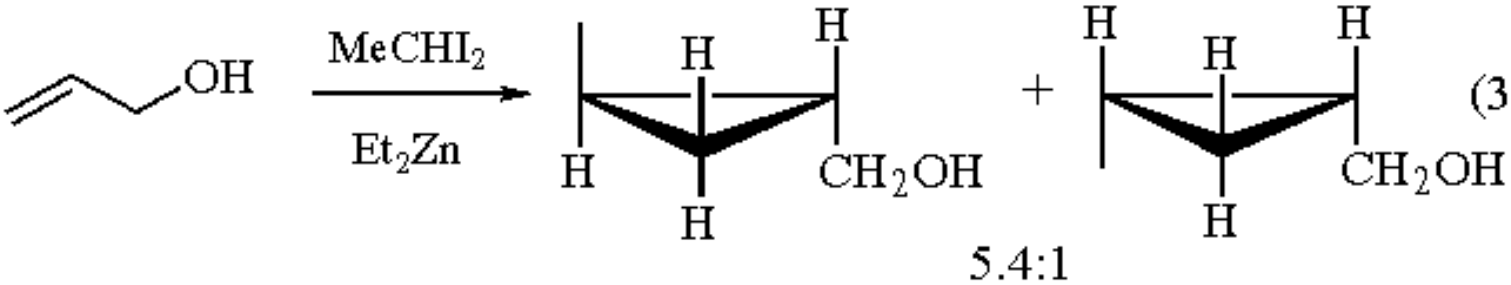

(32)

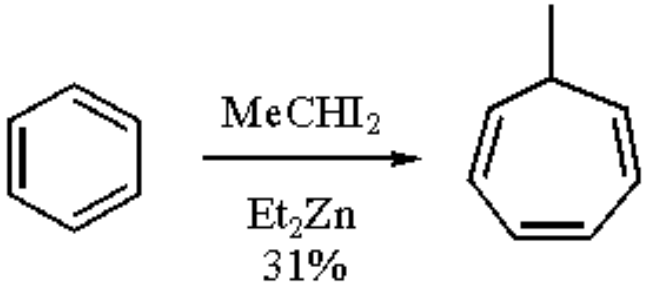

(33)

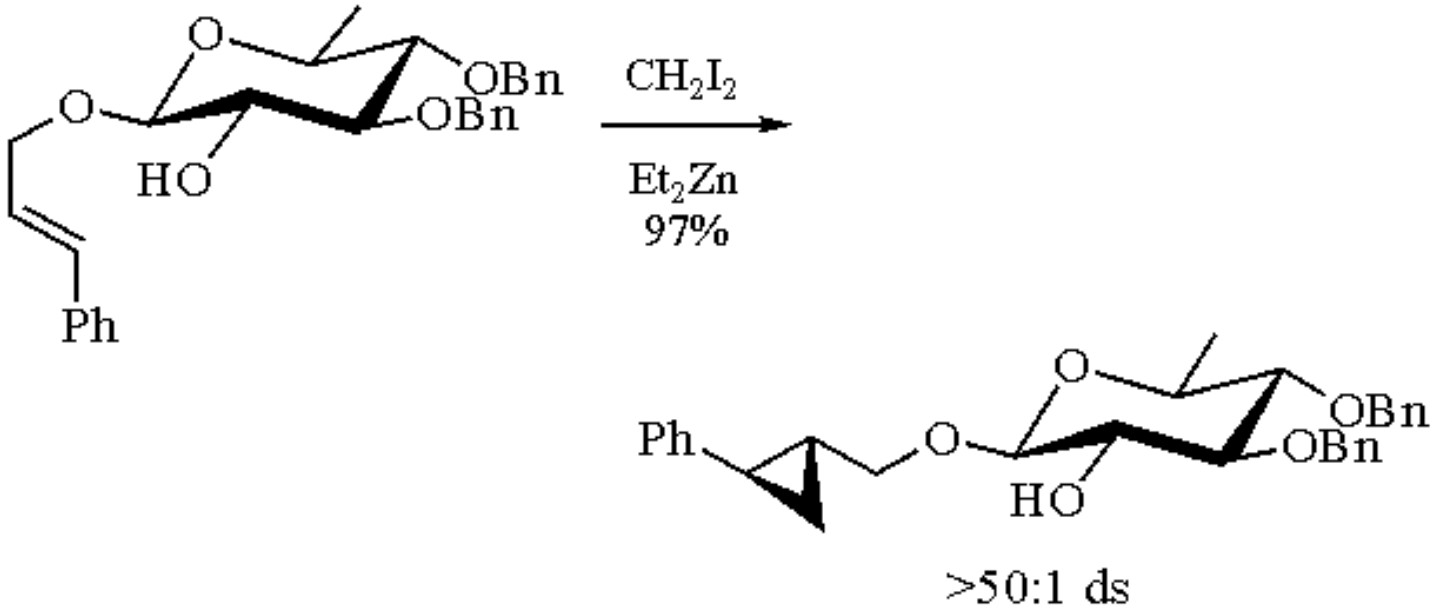

(34)

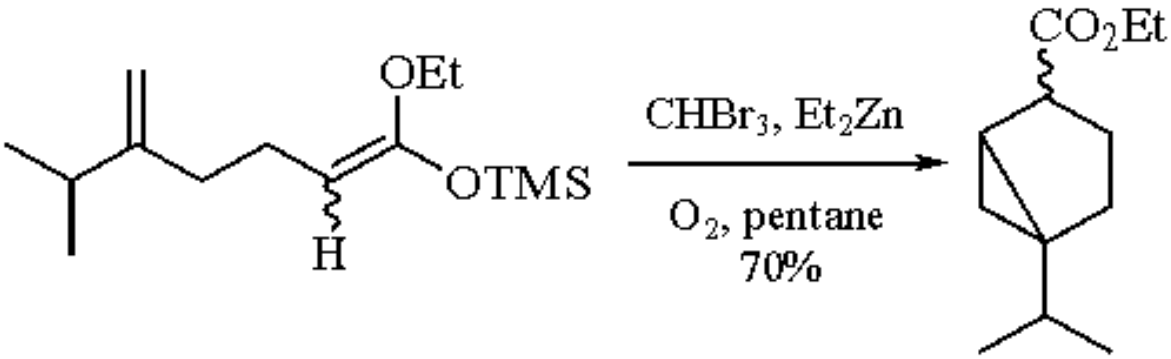

(35)

Miscellaneous Reactions.

Diethylzinc undergoes a variety of substitution reactions with tertiary halides.[51] The elimination of HX is an important side reaction. By treating dithioacetals with ***Diiodomethane*** and diethylzinc, vinyl sulfides are obtained in satisfactory yields.[52] A direct treatment of diethylzinc with a dithioacetal produces the substitution product.[53] Ketocarbenoids have also been generated from α,α-dibromo ketones (eq 36).[54] Finally, diethylzinc has been used to prepare zinc enolates (eq 37)[55] or mixed lithium-zinc enolates (eq 38).[56]

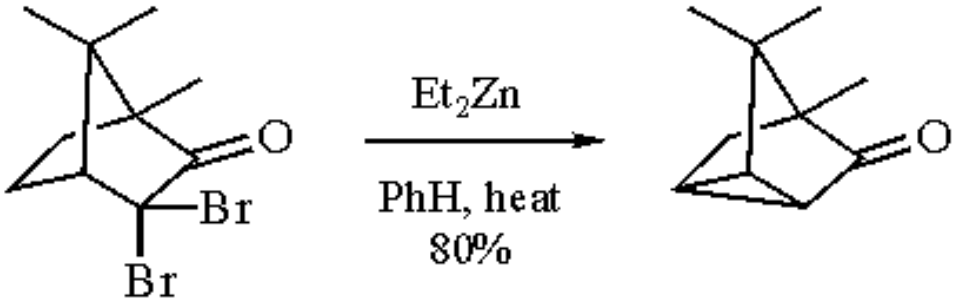

(36)

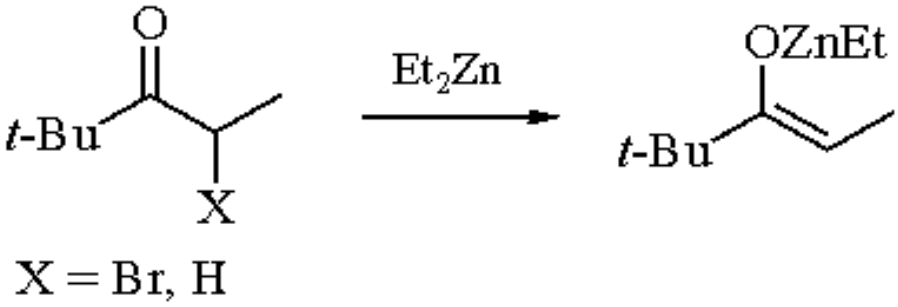

(37)

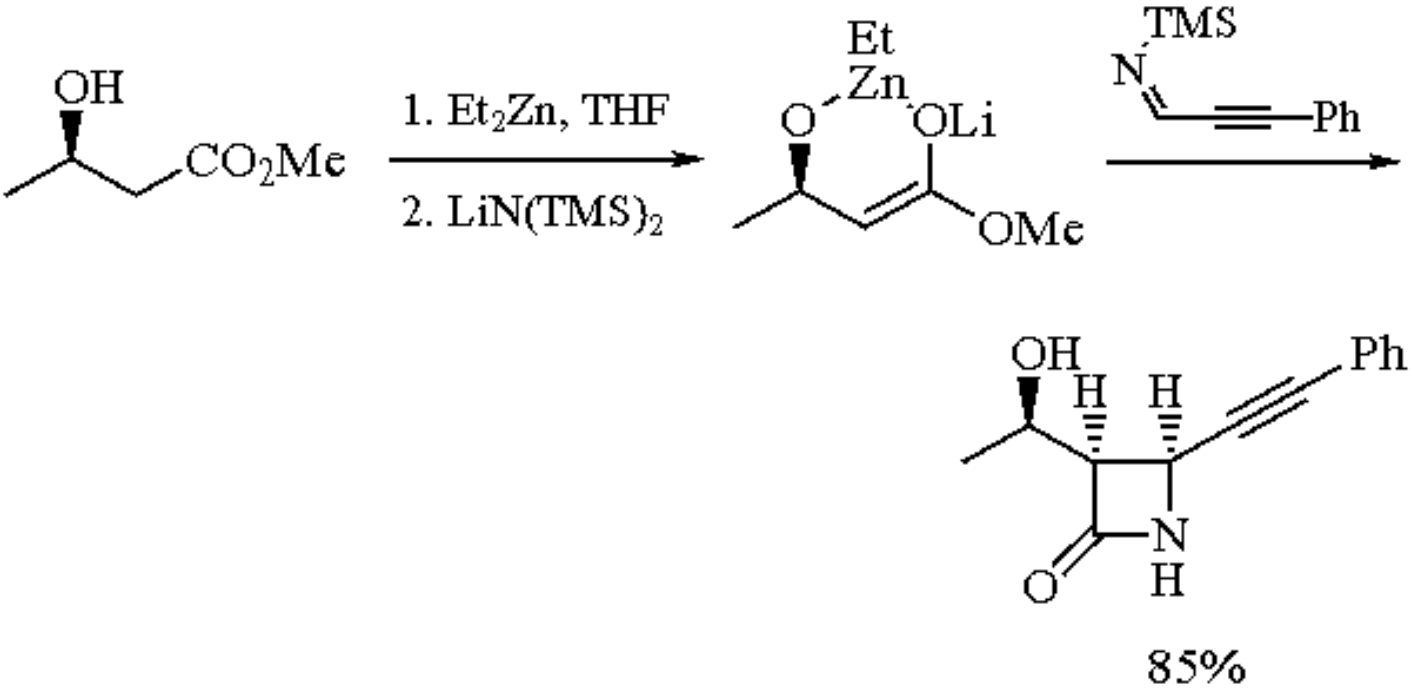

(38)

Related Reagents.

Diethylzinc-Bromoform-Oxygen; ***Diethylzinc-Iodoform***.

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Diethylzinc-Bromoform-Oxygen

Et_2Zn-$CHBr_3$-O_2

(Et_2Zn)

[557-20-0] · $C_4H_{10}Zn$ · Diethylzinc-Bromoform-Oxygen · (MW 123.50) ($CHBr_3$)

[75-25-2] · $CHBr_3$ · Diethylzinc-Bromoform-Oxygen · (MW 252.73)

(cyclopropanation reagent[1])

Preparative Method: the reaction of bromoform with diethylzinc generates dibromomethylzinc bromide in situ.[1]

Handling, Storage, and Precautions: the reagent cannot be stored and should be used directly after its preparation.

Cyclopropanation Reactions.

The treatment of ***Diethylzinc*** and ***Bromoform*** with an alkene in the presence of ***Oxygen*** produces monobromocyclopropanes in good yields (eq 1).[1] Low yields are obtained if no oxygen is passed through the reaction mixture. The cyclopropanation of *cis*-cyclooctene (see ***Iodomethylzinc Iodide***) and *cis*-2-butene give *syn*-bromocyclopropanes with high stereoselectivity (eqs 2 and 3).[1] Styrene was found to inhibit the cyclopropanation, suggesting a radical reaction. A related system can also be used to perform a ring expansion of alkylbenzenes (eq 4).[1] The reaction is possible with ***Diethylzinc-Iodoform***, leading to ethylated cycloheptatrienes.[2] A novel cyclopropanation is observed by reacting bromoform and diethylzinc with ketene acetals, leading to spiro- and bicyclic esters in good yields (eqs 5 and 6).[3] If no allylic hydrogen or unsaturation is present in the molecule, a different reaction is observed (eq 7).[3] The new cyclopropanation procedure has been applied in a synthesis of (±)-sabinene (**1**) (eq 8).[3]

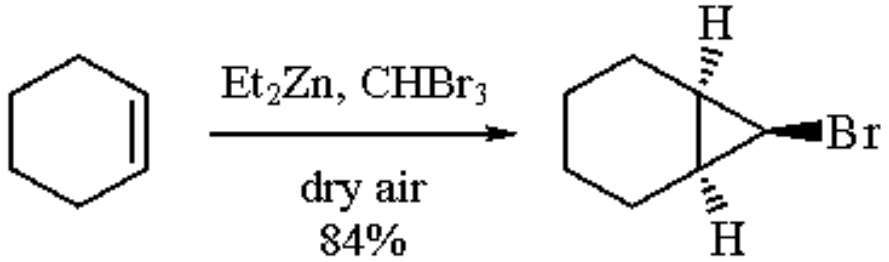

(1)

syn:*anti* = 1.9

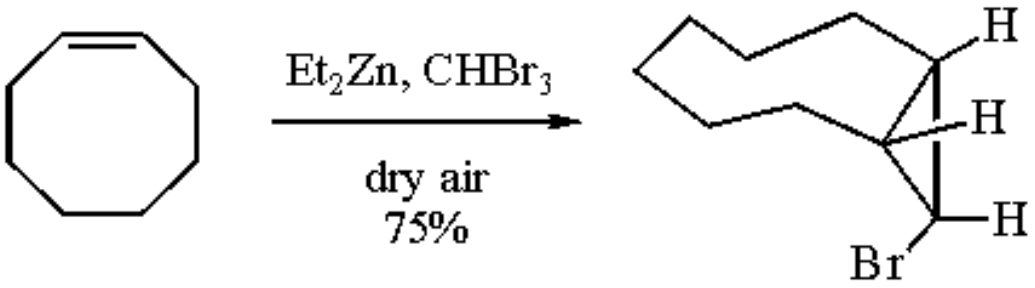

(2)

syn:*anti* = 7.1

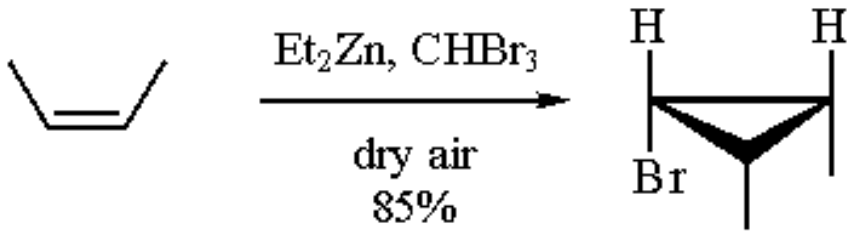

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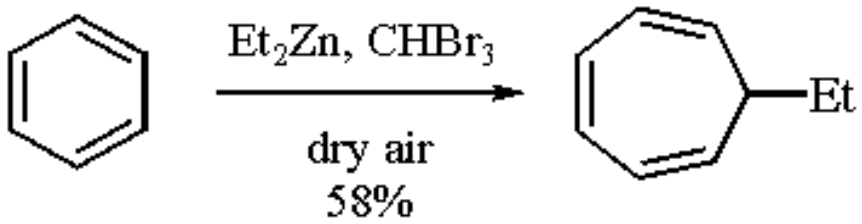

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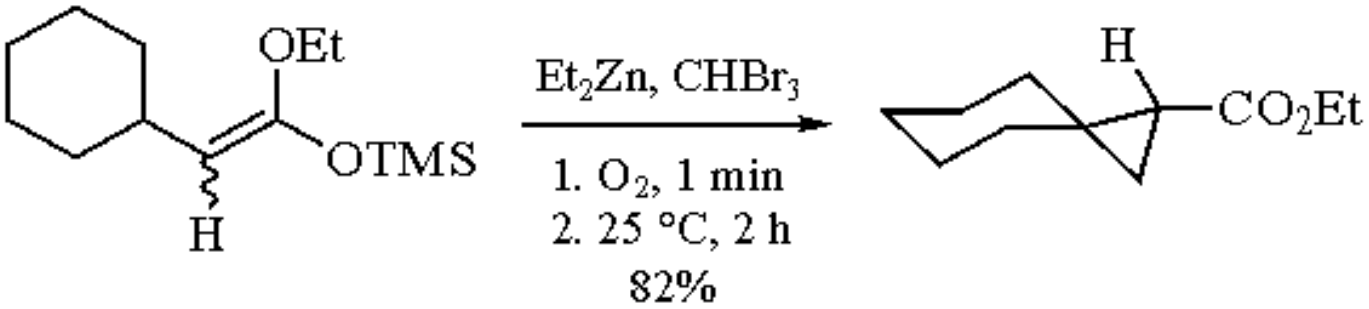

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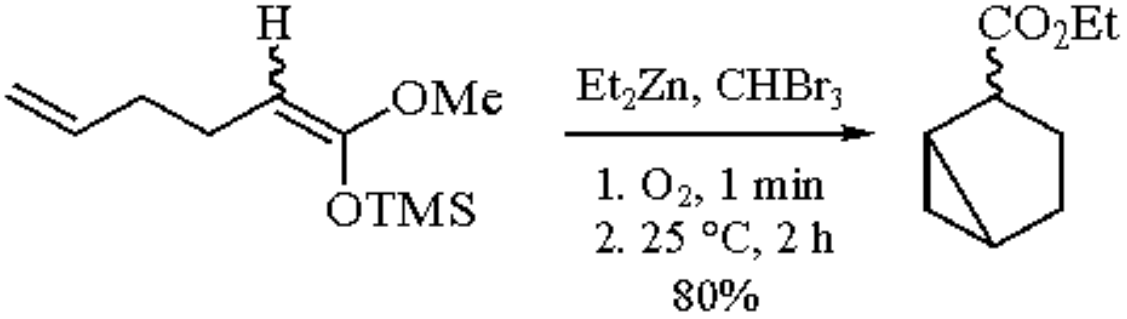

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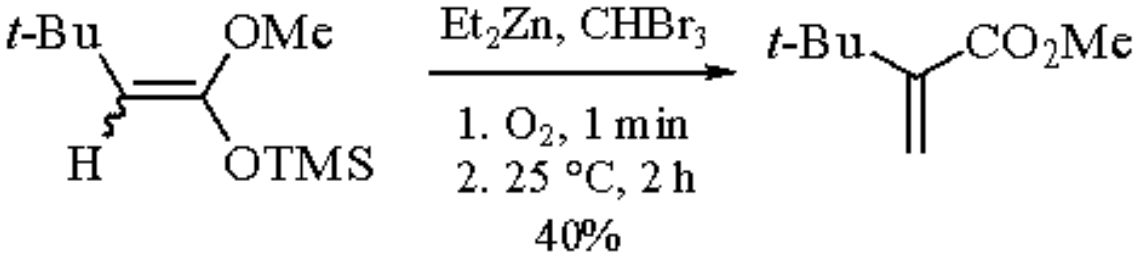

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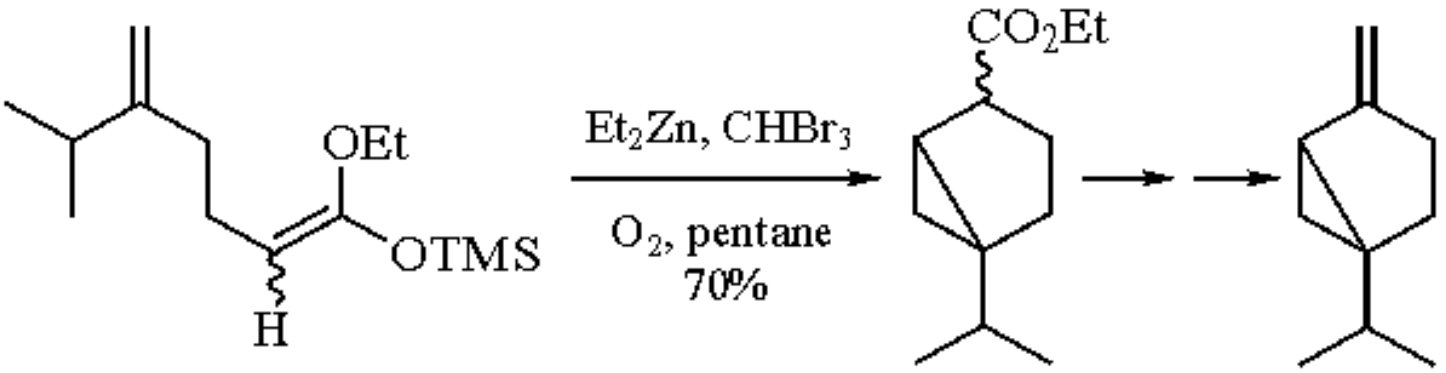

(8)

(1)

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Diethylzinc-Iodoform

Et_2Zn-CHI_3

(Et_2Zn)

[557-20-0] · $C_4H_{10}Zn$ · Diethylzinc-Iodoform · (MW 123.50) (CHI_3)

[75-47-8] · CHI_3 · Diethylzinc-Iodoform · (MW 393.73)

(combination reagent for monoiodocarbene formation and cyclopropanation)

Physical Data: Et_2Zn: mp -28 °C; bp 117 °C; *d* 1.205 g cm^{-3}. CHI_3: mp 120-123 °C; *d* 4.008 g cm^{-3}.

Solubility: sol alkene substrates.

Preparative Method: prepared in situ by addition of iodoform to a mixture of alkene and diethylzinc.

Handling, Storage, and Precautions: diethylzinc is pyrophoric and moisture sensitive. Iodoform is toxic and an irritant.

General Discussion.

The reaction of cyclohexene with the monoiodocarbene generated from the action of ***Diethylzinc*** on ***Iodoform*** in light petroleum produced a mixture of stereoisomeric monoiodocyclopropanes. The yield was only 10% for this reaction.[1] It was later found that the reaction was highly dependent on the concentration of the alkene and the temperature. If the reaction was performed with the alkene as the solvent and the temperature lowered to 0 °C, it produced a 70% yield of a mixture of cyclopropyl iodides (eq 1).[2] The lowered yield and altered ratio of *syn*:*anti* isomers was attributed to the thermal instability of the *syn* isomer. The reaction of *n*-butyl vinyl ether resulted only in the formation of polymeric material. None of the cyclopropyl derivative was observed.

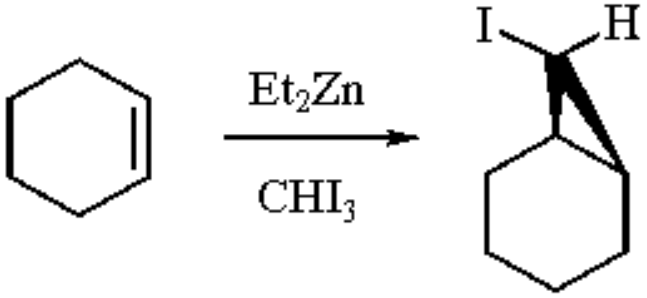

(1)

light petroleum, 10%, *syn*:*anti* = 0.5
50 °C, neat alkene, 50%, *syn*:*anti* = 45:55
0 °C, neat alkene, 70%, *syn*:*anti* = 66:34

The reaction of diethylzinc and iodoform in benzene produces ethylcycloheptatriene in 48% yield (eq 2). The reaction is believed to proceed via the tropylium cation, which undergoes subsequent transformation to the ethyl substituted product by further reaction with ***Ethylzinc Iodide***. If toluene was used in place of benzene, a mixture of the three regioisomeric cycloheptatrienes was formed.[3]

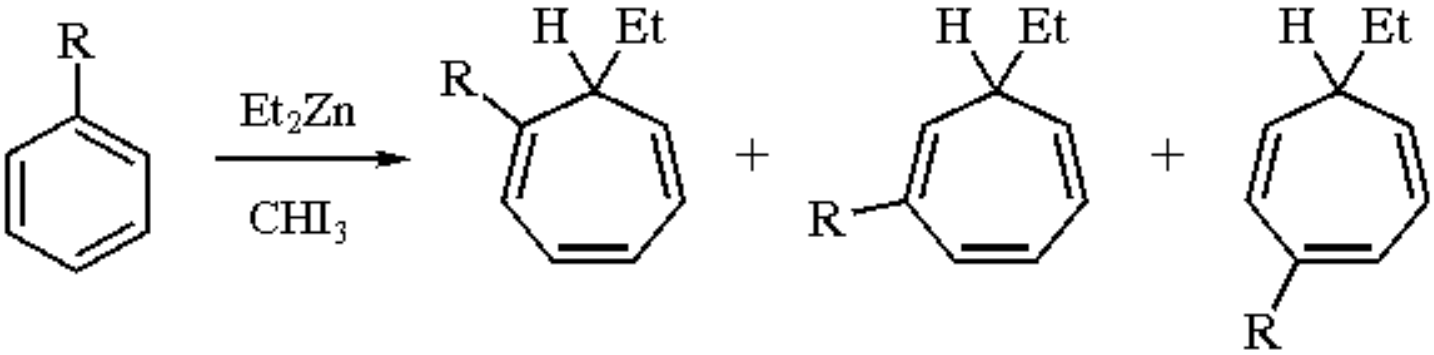

(2)

R = H, 48%
R = Me, 60%, 57:22:21

An investigation of the stereoselectivity of the iodocyclopropanation process has shown that for cycloalkenes the ratio of *syn*:*anti* isomers increases as the ring size increases. For cyclopentene, only the *anti* isomer was obtained due to decomposition of the *syn* isomer. Cyclohexene produces a 0.63:1.0 *syn*:*anti* ratio in 40% yield. The *syn*-iodocyclopropane predominates in a ratio of 3.8:1 for the reaction with cycloheptene. Only the *syn* compound was produced with cyclooctene, but the yield was only 18% (eq 3). The photolysis of iodoform in the presence of cyclooctene provides the same compound in 72% yield. Cyclodecene and cyclododecene also afford only the *syn* adducts.[4]

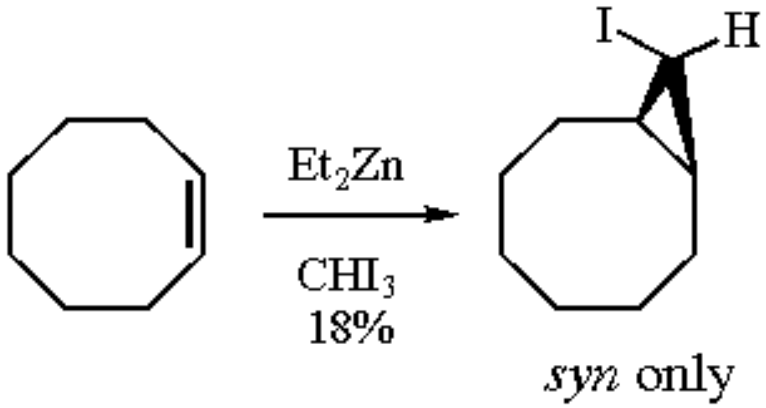

(3)

For the acyclic diene *cis*-2-butene, the stereochemical integrity of the methyl groups was maintained in the final iodocyclopropane (eq 4). In this case, only the *syn* product was formed.

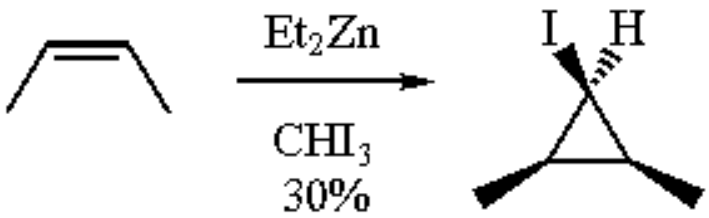

(4)

Related Reagents.

Dibenzenechromium.

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4. Dehmlow, E. V.; Stütten, J. *TL* **1991**, *32*, 6105.

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Difluoramine

NHF_2

[10405-27-3] · F_2HN · Difluoramine · (MW 53.01)

(reagent for introducing difluoroamine groups into organic molecules;[1-3] synthesis of diazirines;[4] deamination of primary amines[5])

Alternate Name: fluoroimide.

Physical Data: bp -23 °C.

Preparative Methods: difluoramine can be generated from tetrafluorohydrazine, which is made by reaction of NF_3 with various metals at 375 °C.[6] Conversion into difluoramine is accomplished by heating tetrafluorohydrazine with ***Thiophenol*** in an evacuated bulb.[7] Difluoramine is also generated by heating *N*,*N*-difluorourea with conc. ***Sulfuric Acid***.[8]

Handling, Storage, and Precautions: is shock sensitive. Reactions should be carried out in a fume hood.

Synthesis of Diazirines.

The reaction of *t*-octylazomethine or *t*-butylazomethine with difluoramine has been shown to give diazirine (eq 1).[4] Other substituted imines produce substituted diazirines, α-fluoroazo compounds, or α-fluoroalkylidene hydrazines in relative yields dependent upon the structure of the imine (eq 2).[9]

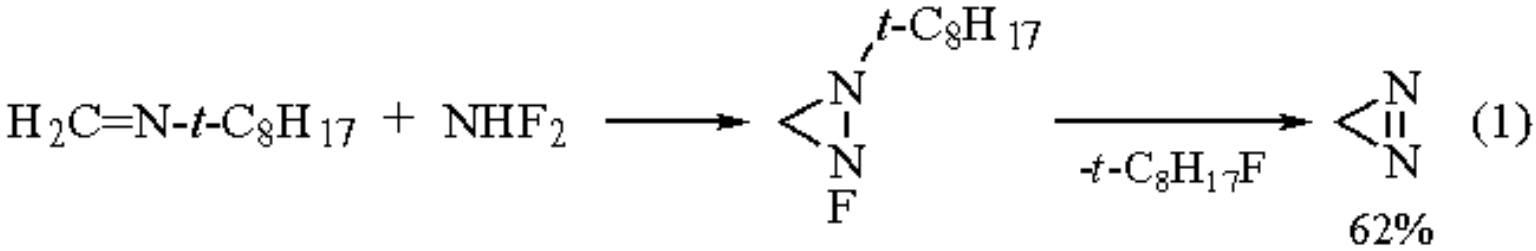

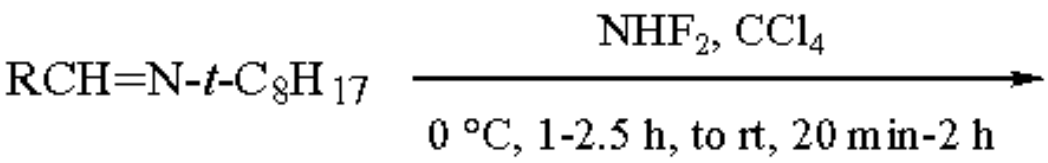

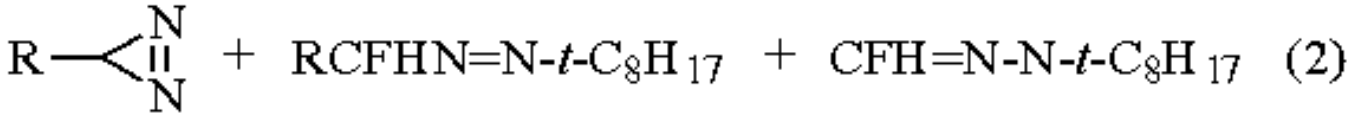

R = Me	37%	40%	-
R = Ph	-	-	62%

Reactions of Carbonyl Compounds with Difluoramine.

Difluoramine reacts with aldehydes and ketones to give α-difluoroamino alcohols of varying stability (eq 3).[1] Aliphatic ketones and aldehydes react with difluoramine in H_2SO_4 or oleum with replacement of the carbonyl by two difluoroamino groups (eq 4).[2]

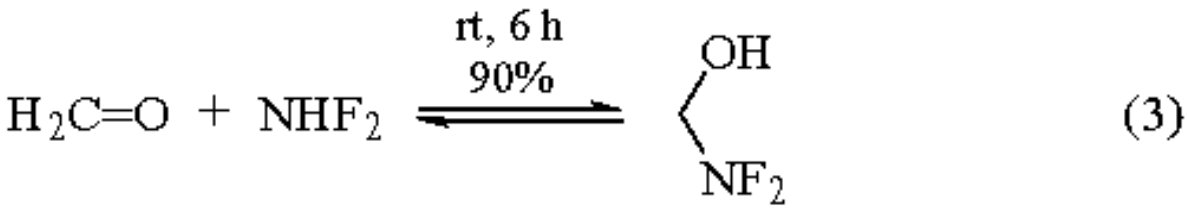

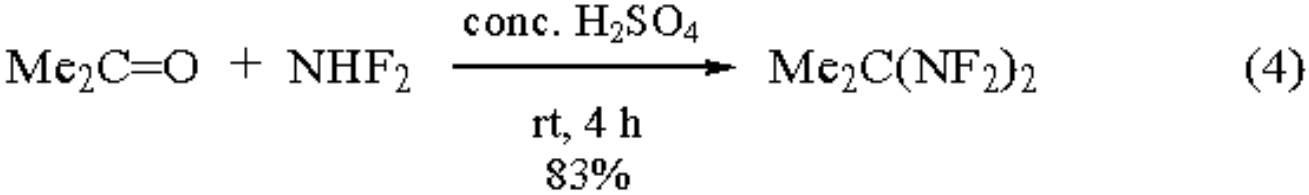

Carbocation precursors in the γ-position cyclize to give difluoroamino substituted lactones (eq 5) and tetrahydrofurans.[2] Michael addition of difluoramine takes place with α,β-unsaturated carbonyl compounds (eq 6).

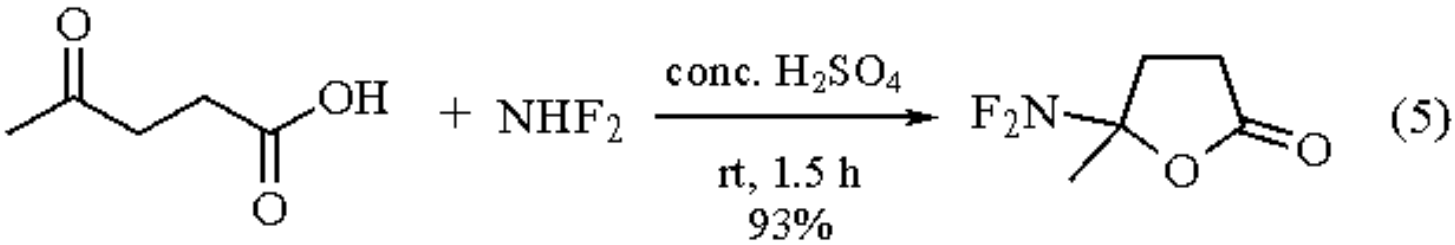

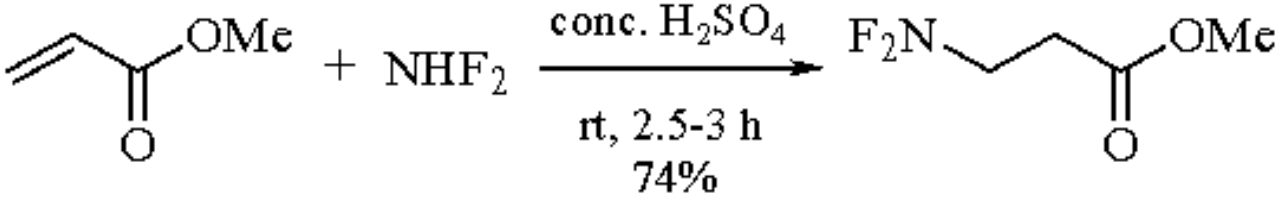

(6)

Difluoramine undergoes reaction with α-hydroxy ketones and 1,2-diketones in fuming H_2SO_4 to form 4-difluoroamino or 4,5-bis(difluoroamino) substituted 1,3-dioxa-2-thiolane 2,2-dioxides, respectively (eq 7).[8] Difluoramine is generated in situ by the interaction of *N*,*N*-difluorourea with concentrated H_2SO_4 in these reactions. Difluoramine reacts vigorously with acetone phenylhydrazone to give *N*-fluorodimethylketimine (eq 8).[10]

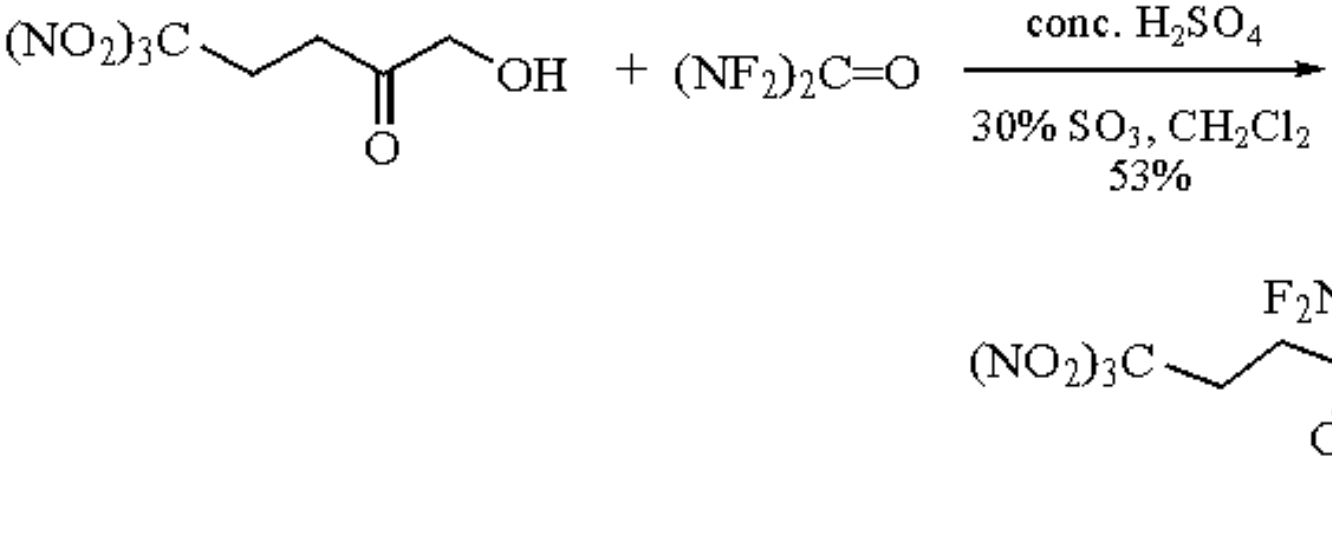

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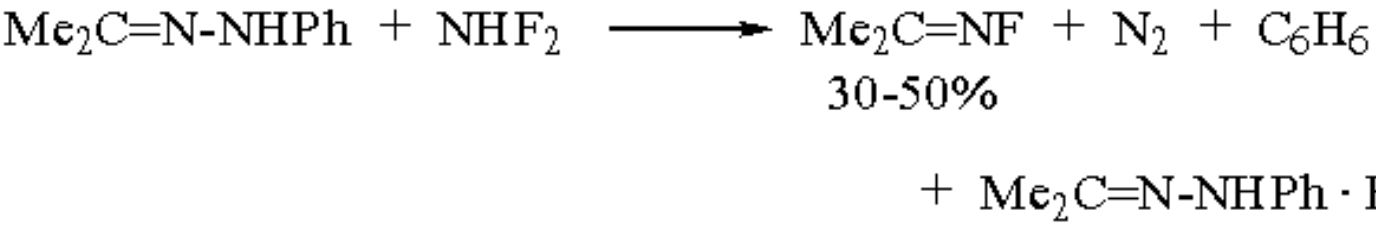

$+ Me_2C{=}N\text{-}NHPh \cdot HF$ (8)

Reaction of Alkynes with Difluoramine.

The reaction of 3-hexyne with difluoroamine, catalyzed by the ***Boron Trifluoride*** complex of ***Phosphoric Acid***, gives 3-hexanone, 3,3-bis(difluoroamino)hexane, 3-difluoroamino-3-fluorohexane, and *N*-(α-difluoroaminopropyl)propionamide in various yields.[11]

Alkylation of Difluoramine.

Difluoramine can be alkylated with an alkyl halide, alcohol, alkene, or ether to yield difluoroamino substituted alkanes.[3] Ether derivatives require no catalysis; with alkenes the boron trifluoride complex of phosphoric acid or H_2SO_4 is used (eq 9). Yields are sensitive to time and temperature and range from 50-60 % for the alkene reactions to quantitative for the ethers.

$$Me_2C{=}CH_2 + NHF_2 \xrightarrow{96\%\ H_2SO_4} Me_3CNF_2 \qquad (9)$$

Deamination of Primary Amines.

Difluoramine converts primary amines to alkanes (eq 10). Secondary amines, such as aziridine, azetidine, and dibenzylamine, react with difluoramine to yield, respectively, ethylene (eq 11), cyclopropane, and bibenzyl by releasing nitrogen and coupling the remaining fragments.[5,12]

$$BuNH_2 + NHF_2 \xrightarrow[61\%]{rt} BuNH_3^+F^- + N_2 + C_4H_{10} \qquad (10)$$

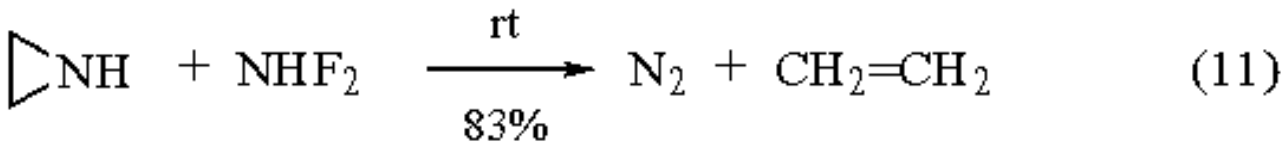

Reaction of *C*-Nitroso Compounds with Difluoramine.

The reaction of difluoramine with *C*-nitroso compounds affords *N*-substituted *N*´-fluorodiimide *N*-oxides (eq 12); *N*-aryl substituted *N*´-fluorodiimide *N*-oxides can be converted to azoxy compounds with Grignard reagents (eq 12).[13]

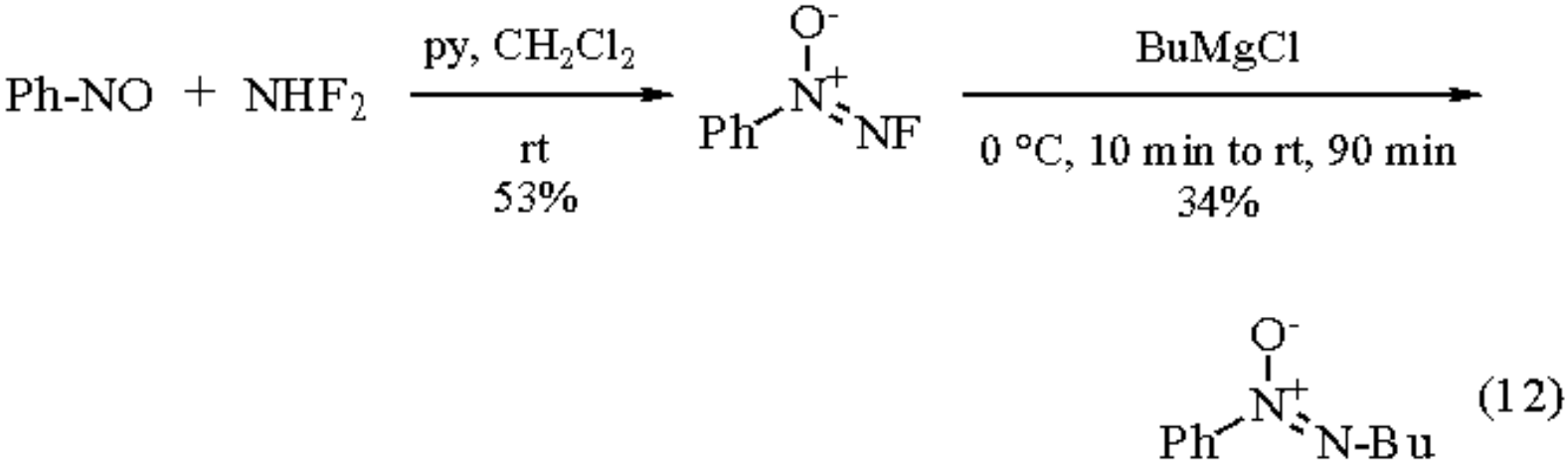

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Difluoromethylenetriphenylphosphorane[1]

$Ph_3P{=}CF_2$

[33558-14-4] · $C_{19}H_{15}F_2P$ · Difluoromethylenetriphenylphosphorane · (MW 312.30)

(utilized for the introduction of $=CF_2$ into organic compounds)

Alternate Name: triphenylphosphonium difluoromethylide *[34034-84-9]*.

Preparative Methods: prepared in situ by the reaction of lithium or ***Sodium Chlorodifluoroacetate*** with ***Triphenylphosphine***[2-6] (or, analogously, with ***Tri-n-butylphosphine***[7,8]); by the reaction of ***Dibromodifluoromethane*** with 2 equiv of tertiary phosphines;[6,9] or by the dehalogenation of bromodifluoromethyltriphenylphosphonium bromide with tertiary phosphines[9] or metals.[10]

Reactions with Carbonyl Compounds.

Treatment of sodium or lithium chlorodifluoroacetate and triphenylphosphine with aldehydes or perfluoroalkyl aryl ketones gives the corresponding 1,1-difluoroalkenes in 52-78% yields (eq 1).[1-6,11] Monoglyme (MG), diglyme (DG), and triglyme (TG) have been employed as solvents in the above reaction. In DMF, DMSO, dimethylacetamide, tetramethylurea, and *N*-methyl-2-pyrrolidone, reaction of sodium chlorodifluoroacetate and tributylphosphine with ketones bearing α-protons affords the corresponding 1,1-difluoroalkenes in 35-46% yields.[7,8] However, Burton reported that less than 10% of 1,1-difluoroalkenes were obtained from the reaction of sodium chlorodifluoroacetate and tributylphosphine with non-activated ketones[9] and a different type of reaction was observed with activated ketones.[12]

$$Ph_3P + ClCF_2CO_2Na + R^1C(O)R^2 \xrightarrow{100\ ^\circ C} R^1R^2C{=}CF_2 \qquad (1)$$

Difluoromethylenation of aldehydes and ketones has also been accomplished in 81-87% yields by the reaction with dibromodifluoromethane and 2 equiv of triphenylphosphine[6] or ***Hexamethylphosphorous Triamide***[9] in DG, TG, and DMF solvents (eq 2). Alternatively, bromodifluoromethyltriphenylphosphonium bromide or bromodifluoromethyltris(dimethylamino)phosphonium bromide,[10] generated from dibromodifluoromethane and triphenylphosphine or tris(dimethylamino)phosphine, can be treated with carbonyl compounds and 1 equiv of the corresponding phosphine[1] or metals (Zn, Cd, and Hg)[10] to obtain 1,1-difluoroalkenes (eq 3).

$$2\,R^1{}_3P + CF_2Br_2 + R^2C(O)R^3 \xrightarrow{70\ ^\circ C} R^2R^3C{=}CF_2 \qquad (2)$$

$$[R^1{}_3PCF_2Br]^+ Br^- + R^1{}_3P \text{ (or metals)} \xrightarrow{R^2C(O)R^3} R^2R^3C{=}CF_2 \quad (3)$$

$R^1 = Ph_3P, (Me_2N)_3P$
$R^2, R^3 = H$, alkyl, aryl
metals = Zn, Cd, Hg

---

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1,3-Dihydrobenzo[*c*]thiophene 2,2-Dioxide

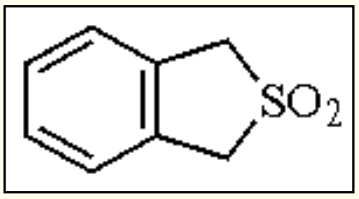

[2471-91-2] · $C_8H_8O_2S$ · 1,3-Dihydrobenzo[*c*]thiophene 2,2-Dioxide · (MW 168.21)

(a source of *o*-quinodimethanes[1] that are useful diene intermediates in Diels-Alder reactions; a source of benzocyclobutene)

Physical Data: mp 150-151 °C.

Solubility: sol EtOH, $CHCl_3$, C_6H_6, boiling water; slightly sol Et_2O.

Preparative Methods: by oxidation of 1,3-dihydrobenzo[*c*]thiophene;[2] from ***α,α´-Dibromo-o-xylene***, rongalite (***Sodium Hydroxymethanesulfinate***, $HOCH_2SO_2Na.2H_2O$), and ***Sulfur Dioxide***.[3]

Purification: recrystallization (H_2O; H_2O-EtOH; CH_2Cl_2-petroleum ether; $CHCl_3$-C_6H_6; C_6H_6-petroleum ether).

Handling, Storage, and Precautions: unstable to alkali and concentrated H_2SO_4.

Source of *o*-Quinodimethane.

Since Cava and Deana proposed and trapped *o*-quinodimethane as an intermediate in the thermal conversion of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide to benzocyclobutene and 1,2,5,6-dibenzocyclooctadiene,[2a] its synthetic utility as a diene in Diels-Alder reactions has been investigated extensively. Its isomer, the sultine 1,4-dihydro-2,3-benzoxathiin 3-oxide, also is a precursor of *o*-quinodimethane, and is especially useful because it decomposes at a lower temperature (80 °C) than does the sulfone.[3,4]

Substitution of the sulfone via its anion occurs readily,[5] thus providing a convenient source for a variety of *o*-quinodimethane diene components. Both intermolecular (eq 1)[6] and intramolecular (eqs 2-5)[5] Diels-Alder reactions of *o*-quinodimethanes have been achieved via thermolysis of the sulfone either in a high boiling solvent or by passing a solution in an inert solvent through a hot (300 °C) quartz tube.[5b] In one case (eq 6) the cycloaddition occurs across a carbonyl group instead of a vinyl group.[5c] Steroidal systems have been accessed through intramolecular cyclizations (eq 2)[5b,d,e] Benzocyclobutenes are obtained from benzo[*c*]thiophene sulfones,[7] and these occasionally are used as sources of *o*-quinodimethanes. 1-Aryl[8] and 1-alkoxy, hydroxy, thioalkyl, and amino[9] derivatives of 1,3-dehydrobenzo[*c*]thiophene

2,2-dioxide are obtained by cyclization reactions and not from the parent compound. Other 1- and 1,3-substituted sulfones are obtained by rhodium(II)-catalyzed cyclization of α-diazo-β-arylmethanesulfonyl esters.[10] Chiral 1-alkoxy-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides lead to asymmetric induction in the Diels-Alder reaction via the chiral substituent of the *o*-quinodimethane.[9a-c]

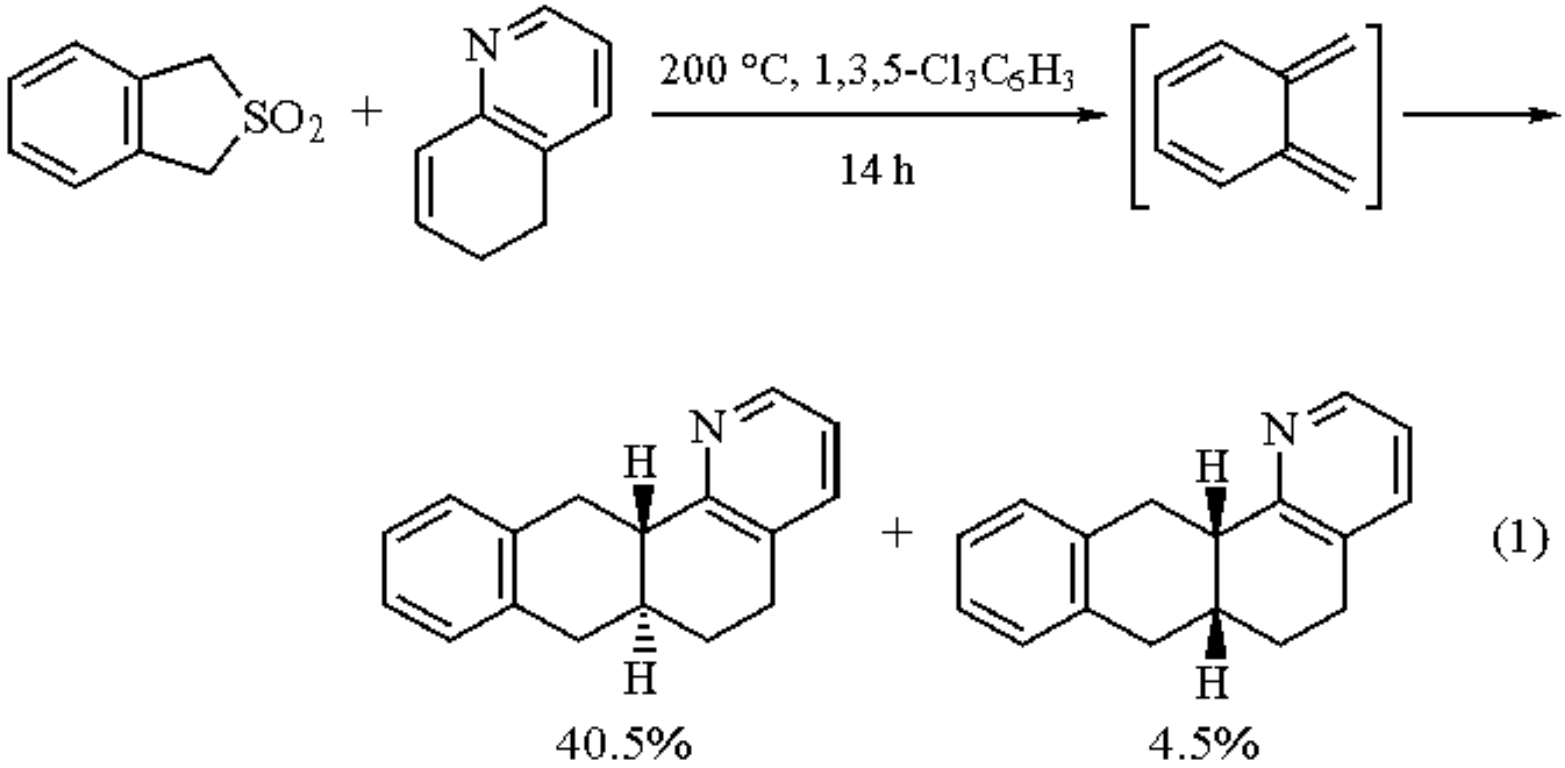

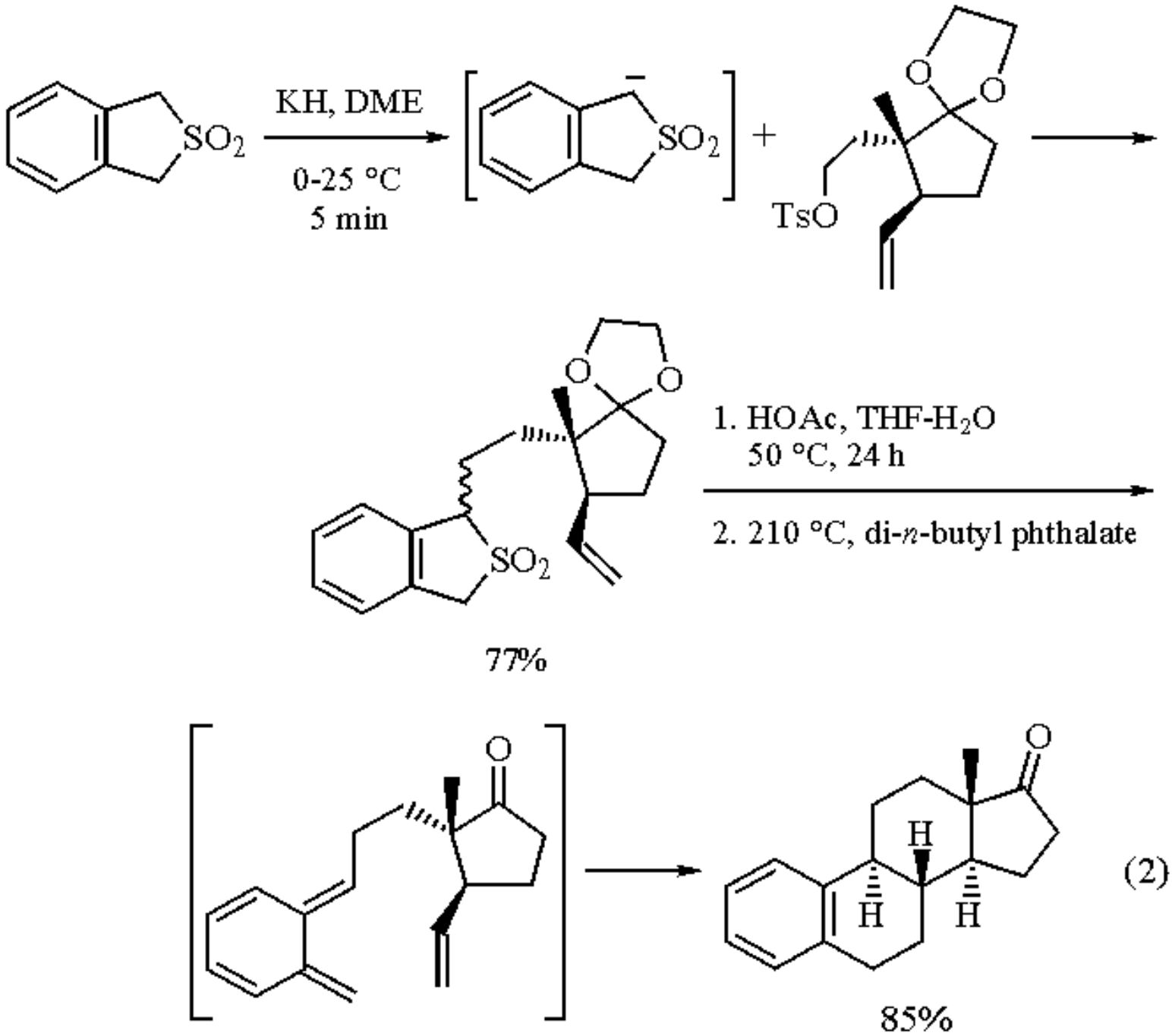
KH, DME
0-25 °C
5 min
TsO
1. HOAc, THF-H2O
50 °C, 24 h
2. 210 °C, di-n-butyl phthalate
77%
85%

(2)

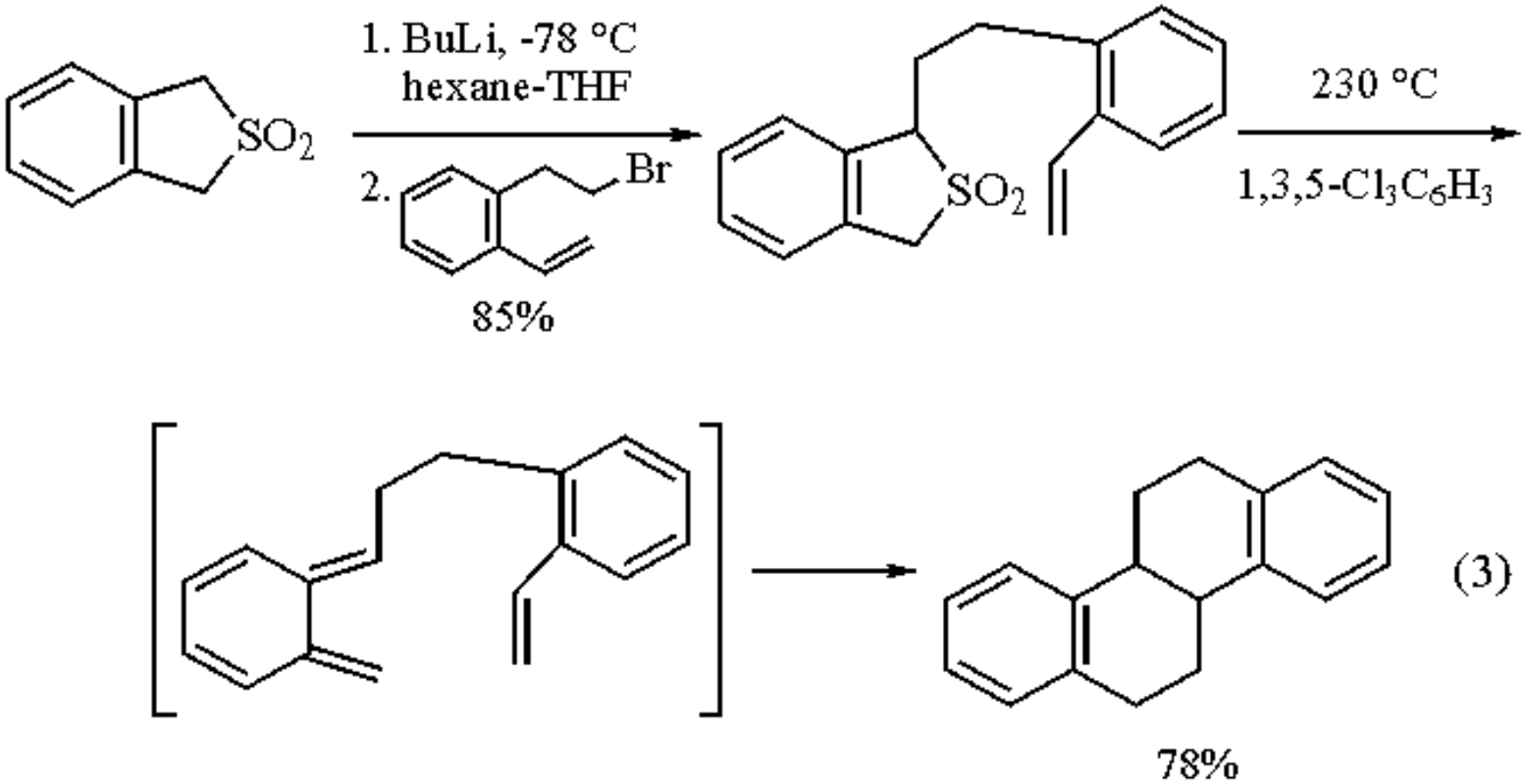
1. BuLi, -78 °C
hexane-THF
2.
Br
85%
SO2
230 °C
1,3,5-Cl3C6H3
78%

(3)

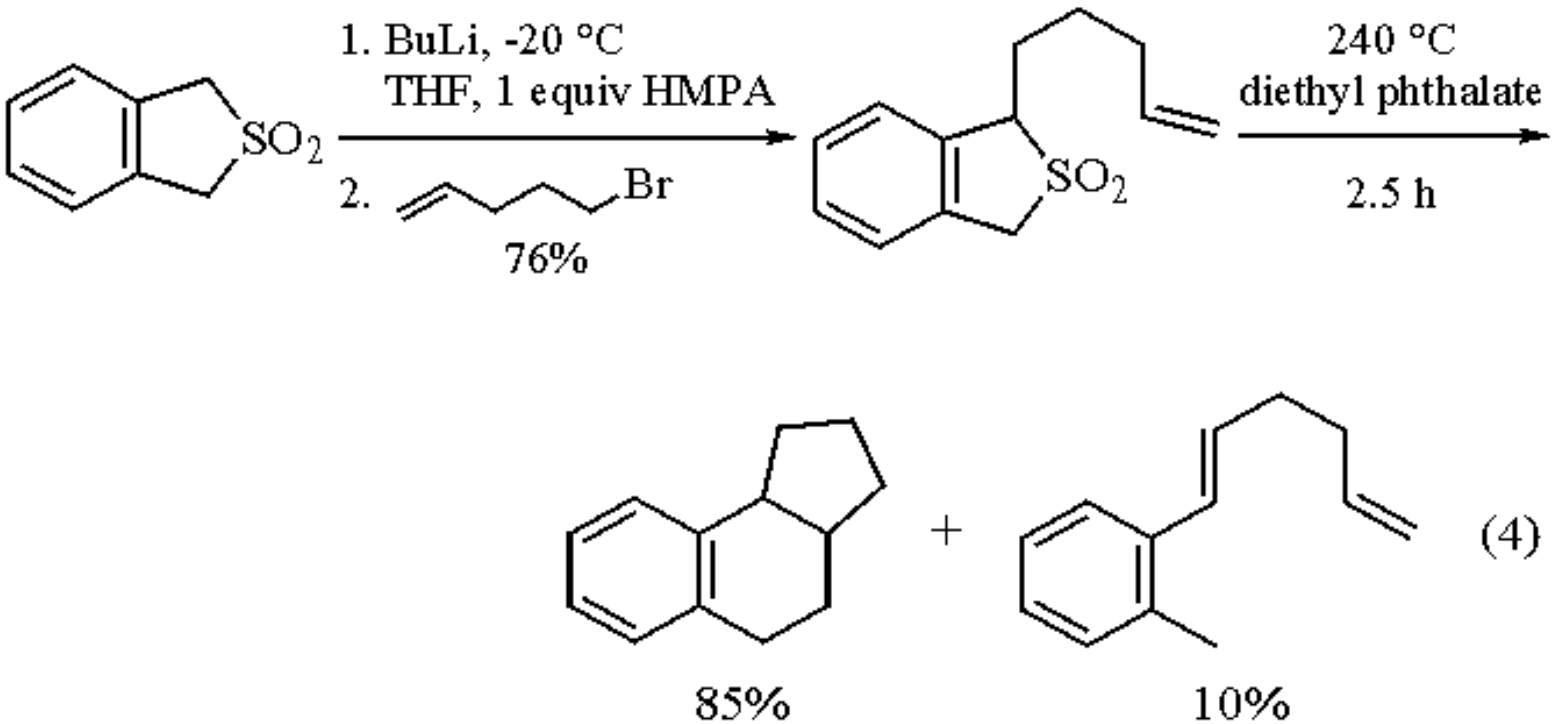
1. BuLi, -20 °C
THF, 1 equiv HMPA
2.
Br
76%
SO2
240 °C
diethyl phthalate
2.5 h
85%
10%

(4)

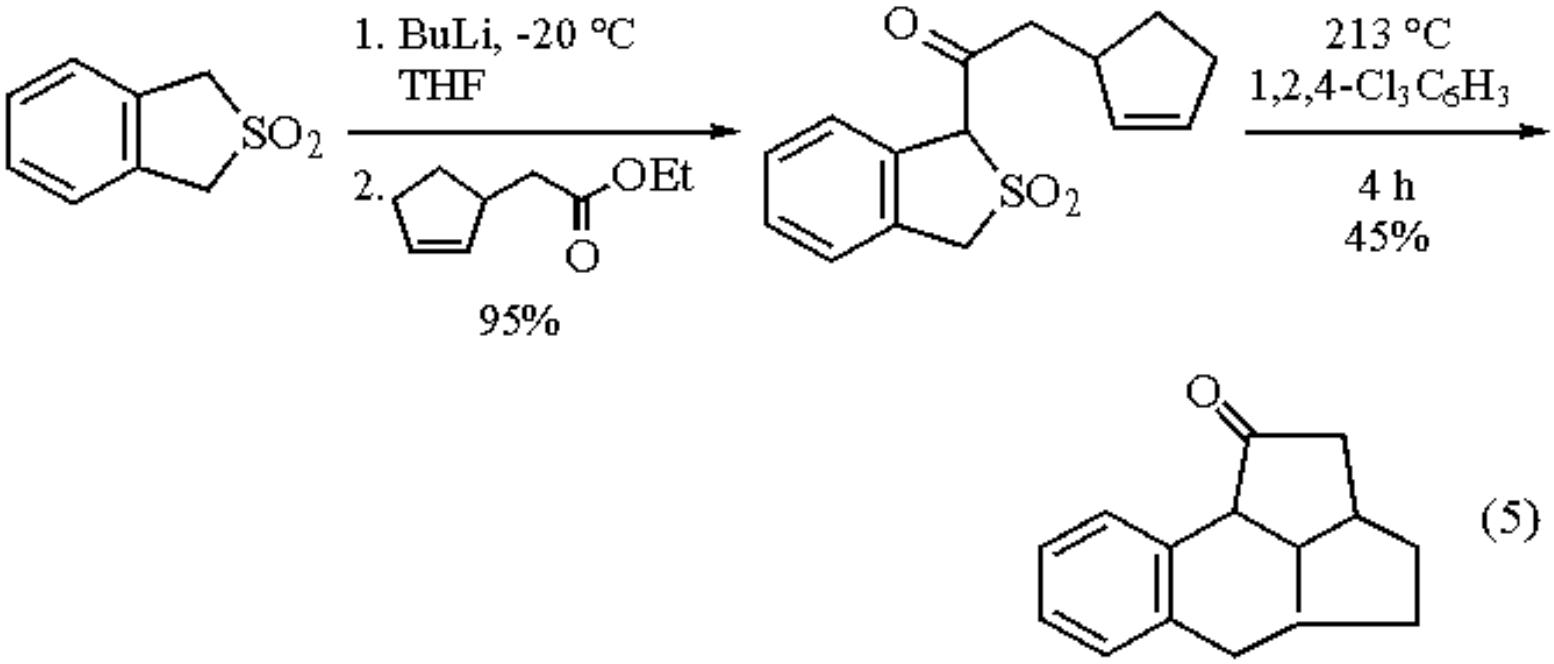

(5)

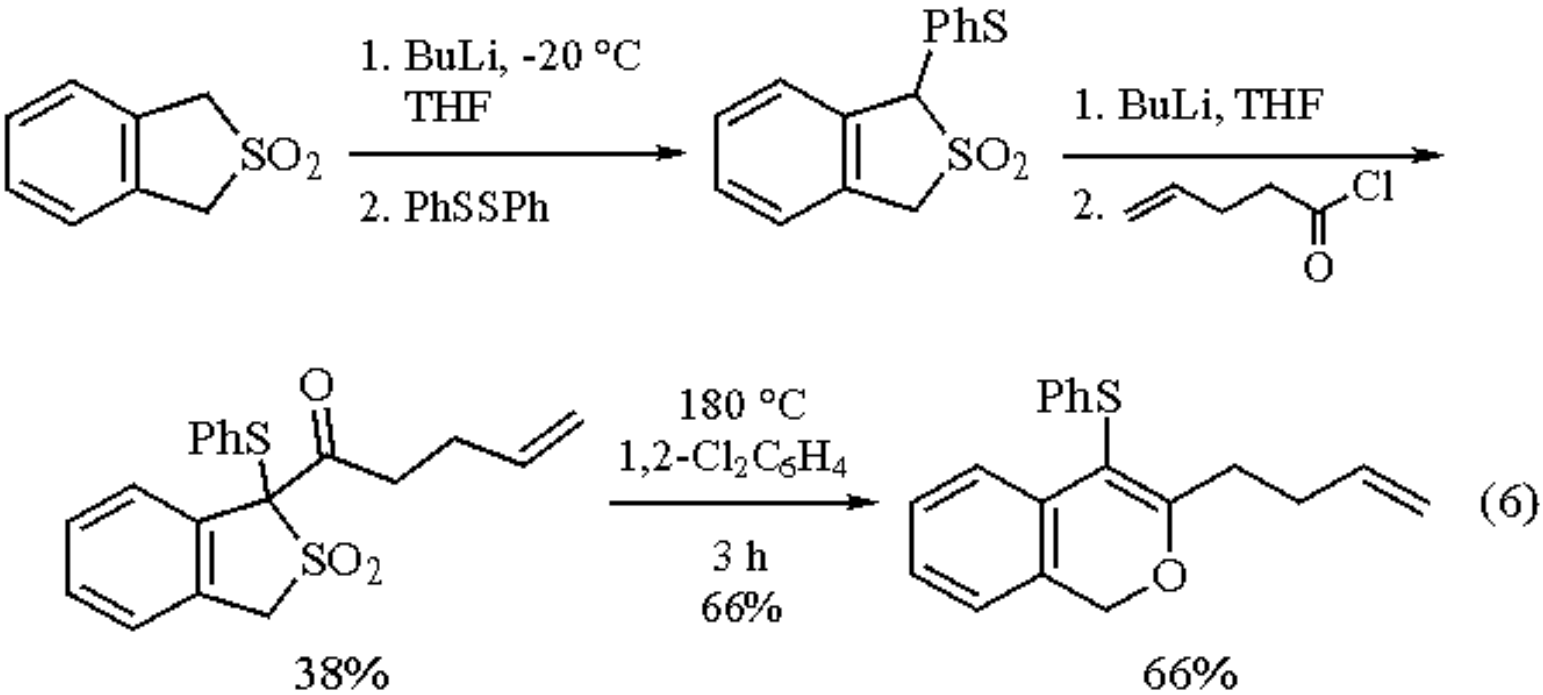

(6)

Miscellaneous.

The nitrated product, 4-nitro-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide, gives 3-nitro-1,2-dimethylbenzene on treatment with ***Raney Nickel***.[11] Light-catalyzed bromination of the parent sulfone yields 1,3-dibromo-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide from which isothianaphthene 2,2-dioxide can be generated and trapped by dienophiles (eq 7).[12]

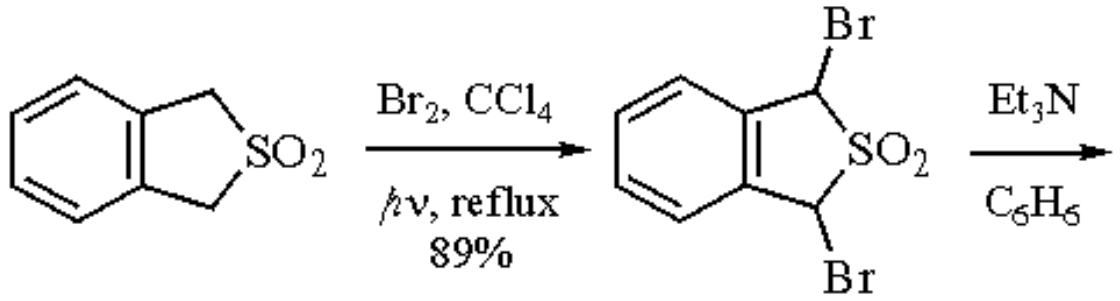

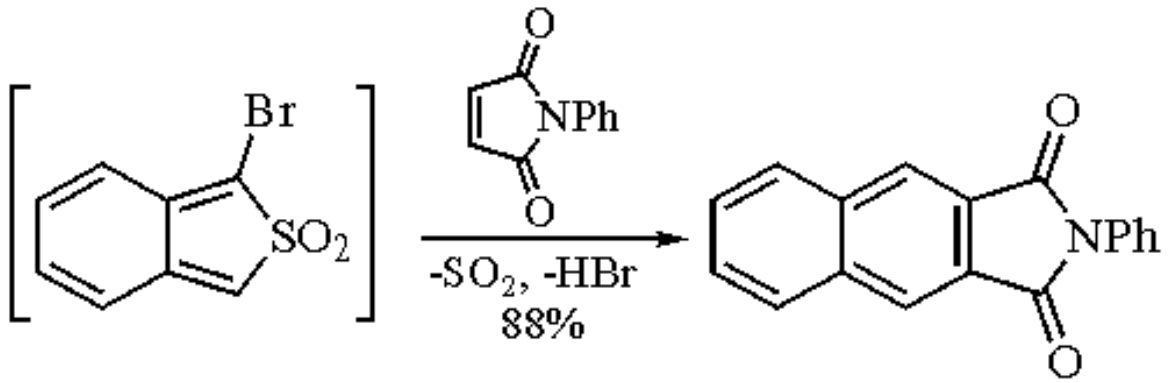

(7)

Related Reagents.

α,α´-***Dibromo-o-xylene***.

---

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2,5-Dihydro-2,5-dimethoxyfuran

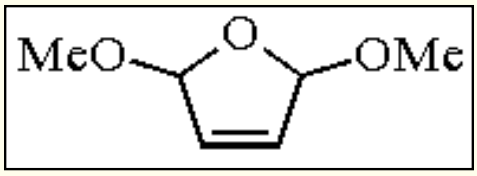

[332-77-4] · $C_6H_{10}O_3$ · 2,5-Dihydro-2,5-dimethoxyfuran · (MW 130.14)

(masked 1,4-dialdehyde; convenient for the synthesis of substituted furans and tetrahydrofurans)

Physical Data: colorless liquid; bp 160-162 °C; *d* 1.0730 g cm^{-3}.

Solubility: practically insol H_2O; sol MeOH, Et_2O, THF.

Form Supplied in: commercially available as a mixture of *cis* and *trans* isomers.

Preparative Method: electrolytic methoxylation of ***Furan***.[1]

Handling, Storage, and Precautions: flammable liquid; must be stored in a cool, ventilated place. Noxious by inhalation, ingestion, or contact with skin. Use in a fume hood.

2-Substituted Furans.

2,5-Dihydro-2,5-dimethoxyfuran (**1**) reacts with 1,3-dicarbonyl compounds in the presence of Lewis acids to give 2-substituted furans after elimination of MeOH (eq 1).[2]

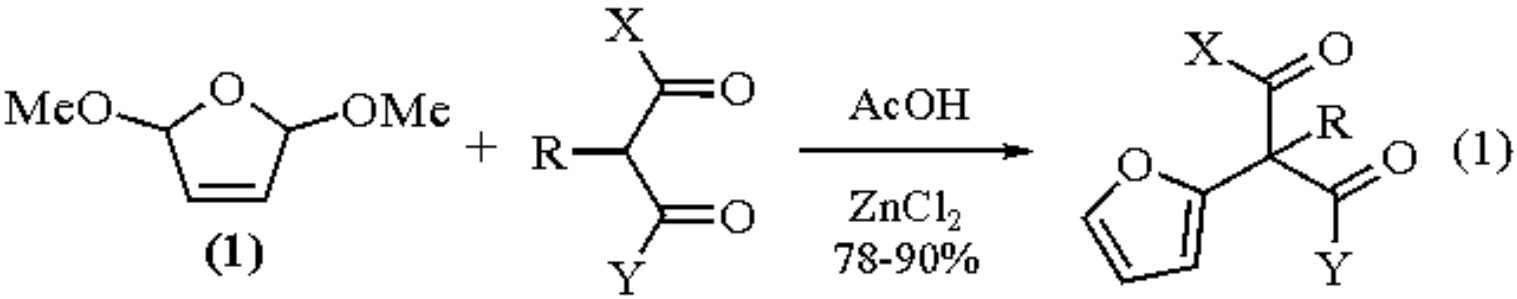

X = Me, OEt; Y = Me, OEt

In the same manner, ***Chlorodiphenylphosphine*** affords furan-2-phosphine oxide,[3] in contrast to ***Cyanotrimethylsilane*** which leads to 2-cyano-5-methoxydihydrofuran.[4]

Reaction of the Double Bond.

Photocycloadditions of (**1**) to anisole,[5] triazolo[4,3-*b*]pyridazine,[6] or ***Maleic Anhydride***[7] give 2,3,4,5-tetrasubstituted furans. 1,3-Dipolar cycloaddition can be performed with nitrones[8] and nitrile oxides.[9] The thermal [4 + 2] reaction between (**1**) and ***Cyclopentadiene*** proceeds in good yield.[10] Permanganate oxidation of the isomer mixture of (**1**) affords exclusively the diol from the *cis* isomer (eq 2).[11]

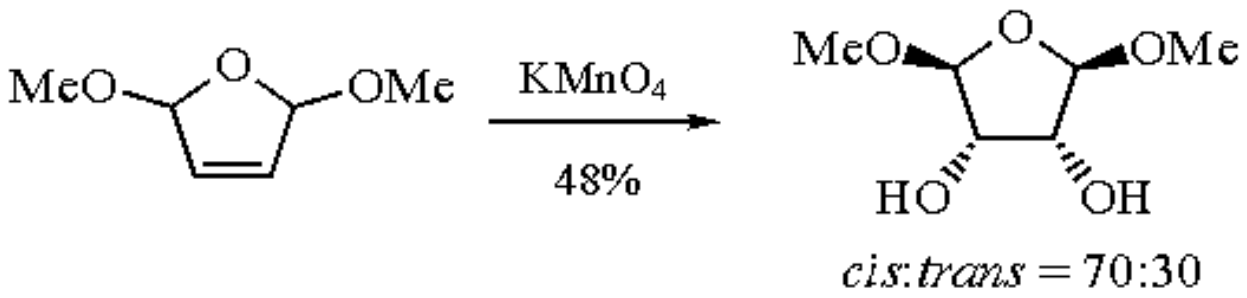

(2)

Ozonolysis of (**1**) followed by reduction leads to a monoprotected glyoxal useful for reactions with stabilized phosphoranes (eq 3).[12]

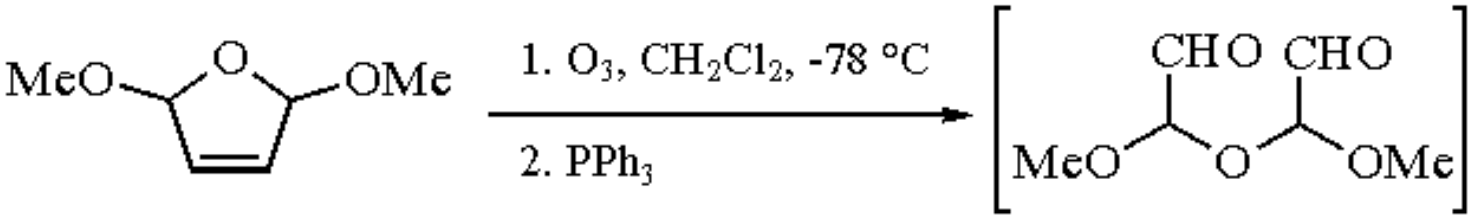

(3)

γ-Aldehydo esters are obtained from (**1**) by double bond migration mediated by a ruthenium hydride complex (eq 4),[13] or by treatment with ***Iodotrimethylsilane*** (in lower yield).[14]

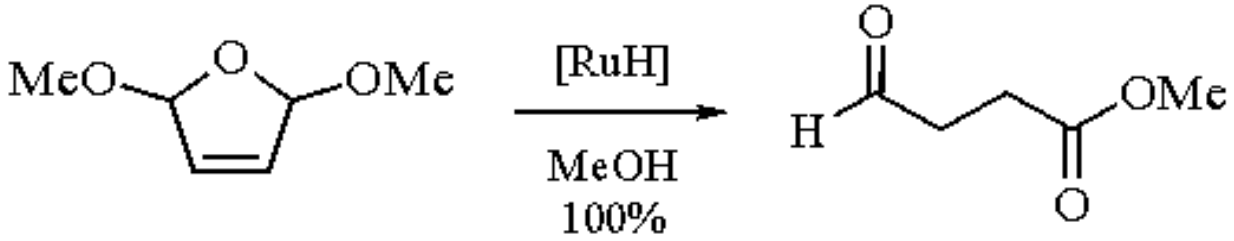

(4)

Related Reagents.

α,β-***Butenolide***; ***2,5-Dimethoxytetrahydrofuran***; ***Furan***; ***Glyoxal***; ***Succindialdehyde***; ***2-Trimethylsilyloxyfuran***.

---

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1,2-Dihydro-4,6-dimethyl-2-thioxo-3-pyridinecarbonitrile

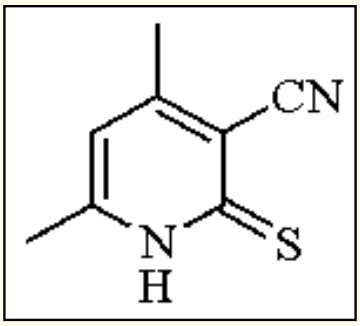

[54585-47-6] · $C_8H_8N_2S$ · 1,2-Dihydro-4,6-dimethyl-2-thioxo-3-pyridinecarbonitrile · (MW 164.22)

(for access to the corresponding disulfide for use in synthesis of esters, lactones, and amides from carboxylic acids)

Physical Data: mp 250-264 °C (dec).

Solubility: sparingly sol toluene and CH_2Cl_2.

Form Supplied in: crystalline solid.

Preparative Method: the reagent (**1**) is prepared in essentially quantitative yield by reaction of 2-cyanothioacetamide with ***2,4-Pentanedione***.[1] The corresponding disulfide (**2**) [bis(3-cyano-4,6-dimethylpyridinyl) disulfide] is prepared by oxidation of (**1**) with ***Iodine*** under basic conditions.[2]

Handling, Storage, and Precautions: the reagent should be treated as a potential irritant.

The principal synthetic application of the reagent (**1**) is as a source of the corresponding symmetrical disulfide (**2**) (eq 1).[2] The disulfide (**2**) is used to effect esterifications (eqs 2-4)[3,4] and amidations (eqs 5 and 6)[5,6] (see also ***2,2´-Dipyridyl Disulfide***).

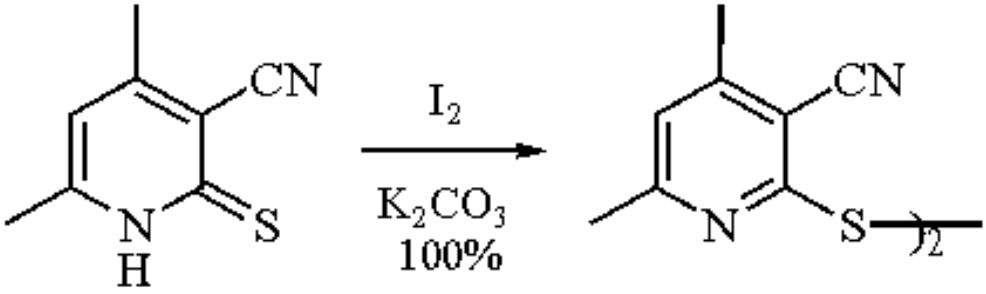
CN
I2
K2CO3
100%
CN
N
H
S
N
S
2

(1)

(1) **(2)**

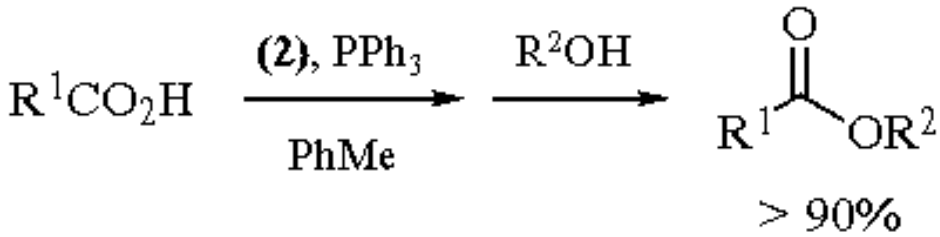
R1CO2H
(2), PPh3
PhMe
R2OH
O
R1
OR2
> 90%

(2)

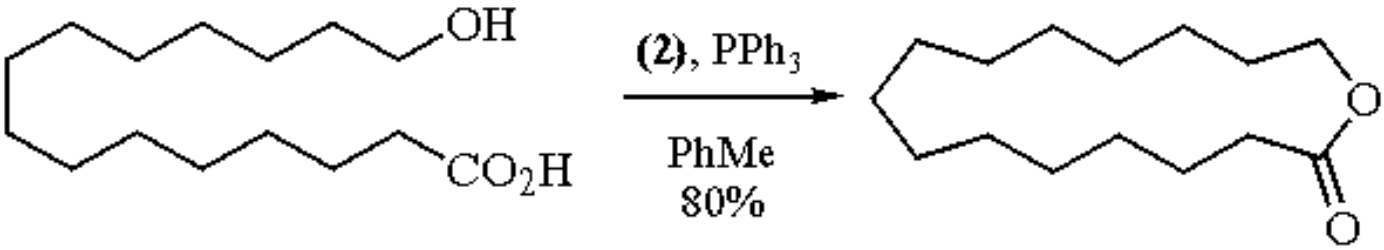
OH
CO2H
(2), PPh3
PhMe
80%
O
O

(3)

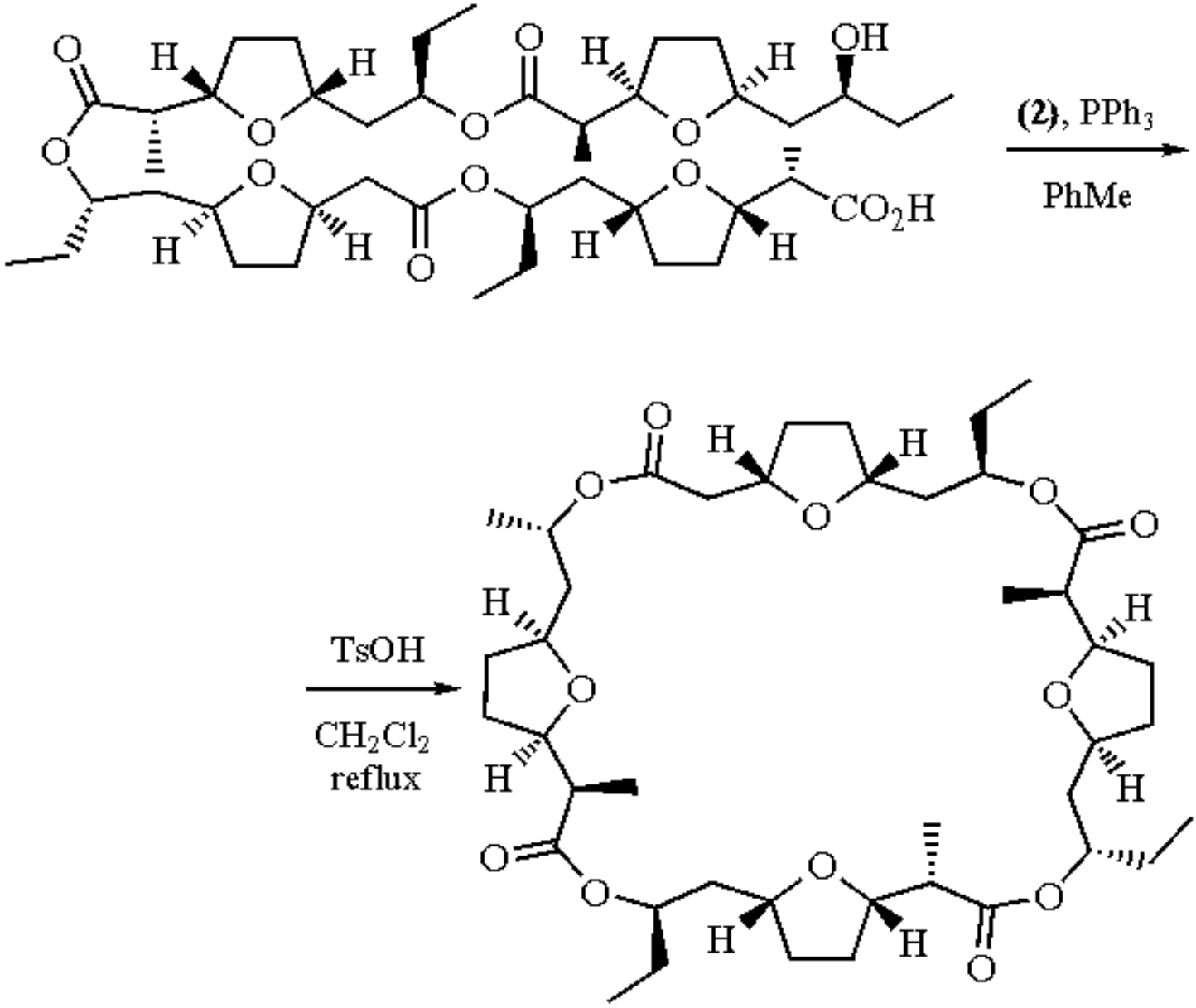

(4)

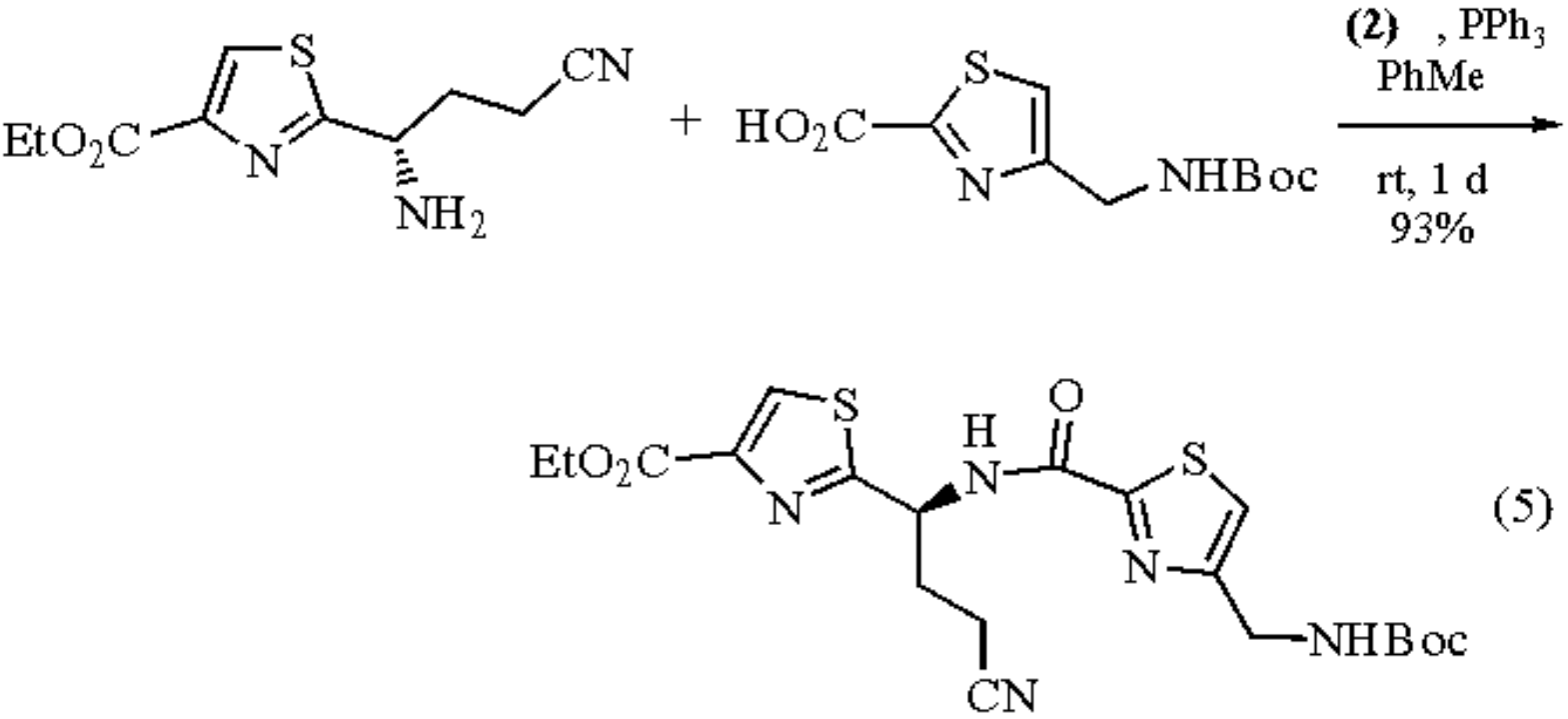
(2) , PPh3
PhMe
rt, 1 d
93%
(5)

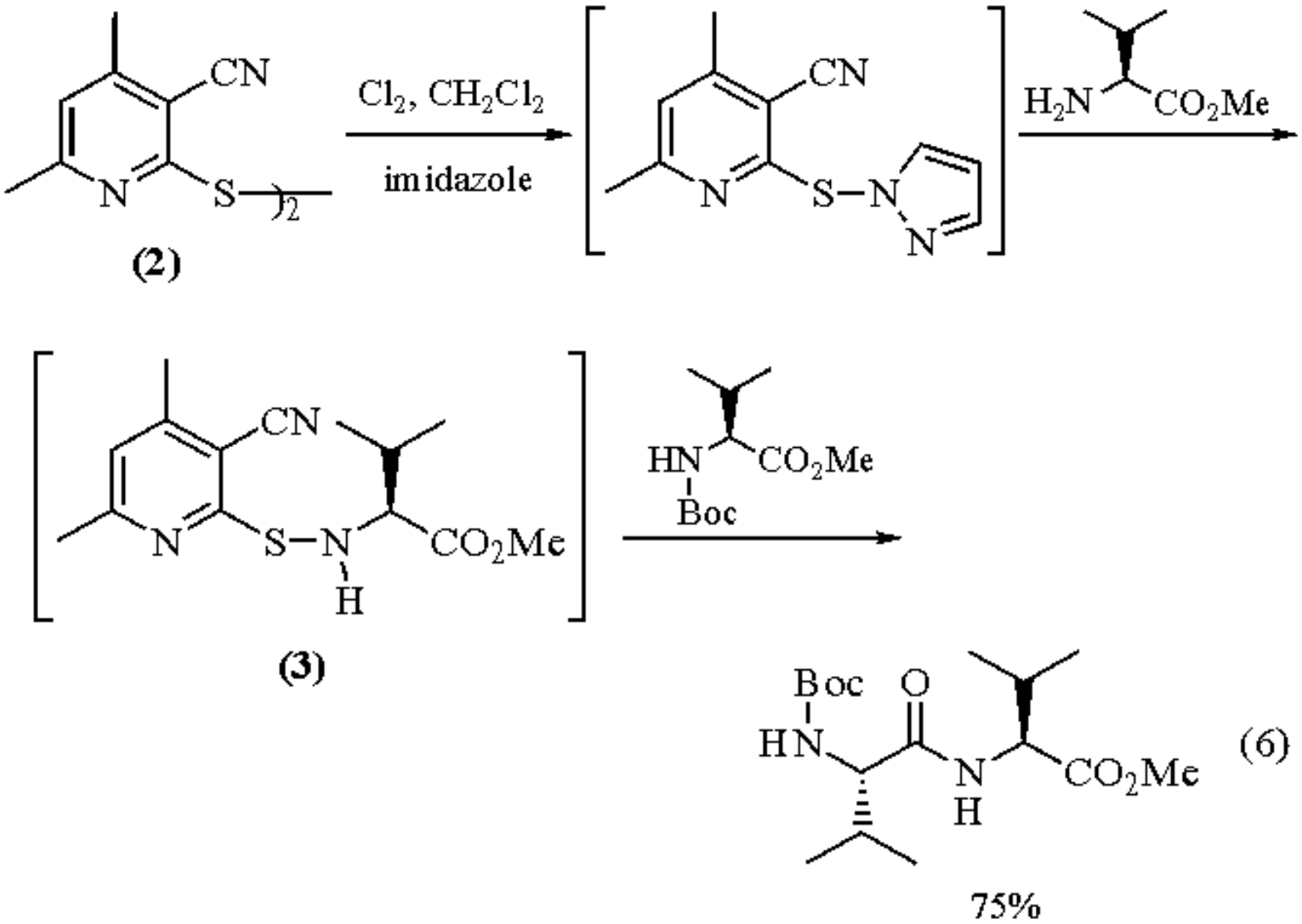
Cl2, CH2Cl2
imidazole
(2)
(3)
75%
(6)

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5. Schmidt, U.; Schefenacker, K. *LA* **1985**, 1254.
6. Schmidt, U.; Potzolli, B. *LA* **1987**, 935.

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Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone[1]

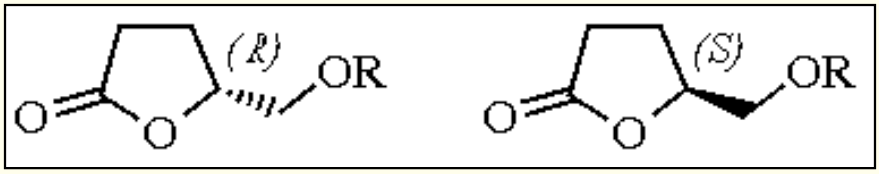

(*R*)-(-)-(**1**; R = H)

[52813-63-5] · $C_5H_8O_3$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 116.12) (*S*)-(+)-(**2**; R = H)

[32780-06-6] · $C_5H_8O_3$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 116.12) (*R*)-(-)-(**3**; R = Bn)

[77697-15-5] · $C_{12}H_{14}O_3$ · Dihydro-5-(benzyloxymethyl)-2(3*H*)-furanone · (MW 206.24) (*S*)-(+)-(**4**; R = Bn)

[32780-08-8] · $C_{12}H_{14}O_3$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 206.24) (*R*)-(-)-(**5**; R = Tr)

[78158-90-4] · $C_{24}H_{22}O_3$ · Dihydro-5-(trityloxymethyl)-2(3*H*)-furanone · (MW 358.42) (*S*)-(+)-(**6**; R = Tr)

[73968-62-4] · $C_{24}H_{22}O_3$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 358.42) (*R*)-(-)-(**7**; R = TBDMS)

[130767-09-8] · $C_{11}H_{22}O_3Si$ · Dihydro-5-(*t*-butyldimethylsilyloxymethyl)-2(3*H*)-furanone · (MW 230.38) (*S*)-(+)-(**8**; R = TBDMS)

[62396-80-9] · $C_{11}H_{22}O_3Si$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 230.38) (*R*)-(-)-(**9**; R = TBDPS)

[128075-94-5] · $C_{21}H_{26}O_3Si$ · Dihydro-5-(*t*-butyldiphenylsilyloxymethyl)-2(3*H*)-furanone · (MW 354.52) (*S*)-(+)-(**10**; R = TBDPS)

[102717-29-3] · $C_{21}H_{26}O_3Si$ · Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone · (MW 354.52) (*R*)-(-)-(**11**; R = Ts)

[58879-33-7] · $C_{12}H_{14}O_5S$ · Dihydro-5-(tosyloxymethyl)-2(3*H*)-furanone · (MW 270.30) (*S*)-(+)-(**12**; R = Ts)

[58879-34-8] · $C_{12}H_{14}O_5S$ · Dihydro-5-(tosyloxymethyl)-2(3*H*)-furanone · (MW 270.30)

(versatile chiral building blocks used in the synthesis of a wide variety of natural products[1a-d] and other biologically important molecules,[2] including anti-HIV dideoxynucleosides;[1e,f] also useful for preparing optically active ligands[3])

Alternate Names: (*R*)- and (*S*)-γ-hydroxymethyl-γ-butyrolactones; 5-oxotetrahydrofuran-2-methanol; 5-hydroxymethylpentanolide.

Physical Data: (**1**) bp 101-102 °C/0.048 mmHg;[4,5] (**2**) bp 122-130 °C/0.6 mmHg;[5,6] (**3**) bp 160-170 °C/0.4-0.6 mmHg;[7] (**4**) bp 160-164 °C/0.02 mmHg; 152-160 °C/0.04 mmHg;[8,9] (**5**) mp 153-154 °C;[10] (**6**) mp 153-154 °C;[10] (**7**)-;[11] (**8**) bp 88-92 °C/0.05 mmHg;[12] (**9**) mp 72-73 °C;[13] (**10**) mp 75-76 °C;[14] (**11**) mp 84.5-86 °C;[15,16] (**12**) mp 85-87 °C.[15,17]

Preparative Methods: both enantiomers of dihydro-5-(hydroxymethyl)-2(3*H*)-furanone and their trityl derivatives are commercially available but expensive. The simplest and by far most popular method for preparing (*S*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**2**)[1e,f] consists of enantiospecific deamination of L-glutamic acid[5] and subsequent selective reduction[15] of the resulting carboxylic acid (**13**) (eq 1). Purification of the intermediate acid (**13**) by crystallization[5] and not by distillation[18] is recommended in order to secure an excellent optical yield (>98% ee). Likewise, (*R*)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**1**) (>98% ee) can be obtained from D-glutamic acid.[5] As the latter is considerably more expensive than its natural antipode, an appealing option is to convert the (*S*)-lactone into its enantiomer (eq 2).[17] Also available and equally useful is an inversion route to (*R*)-dihydro-5-(trityloxymethyl)-2(3*H*)-furanone (**5**) by way of the Mitsunobu reaction (eq 3).[10]

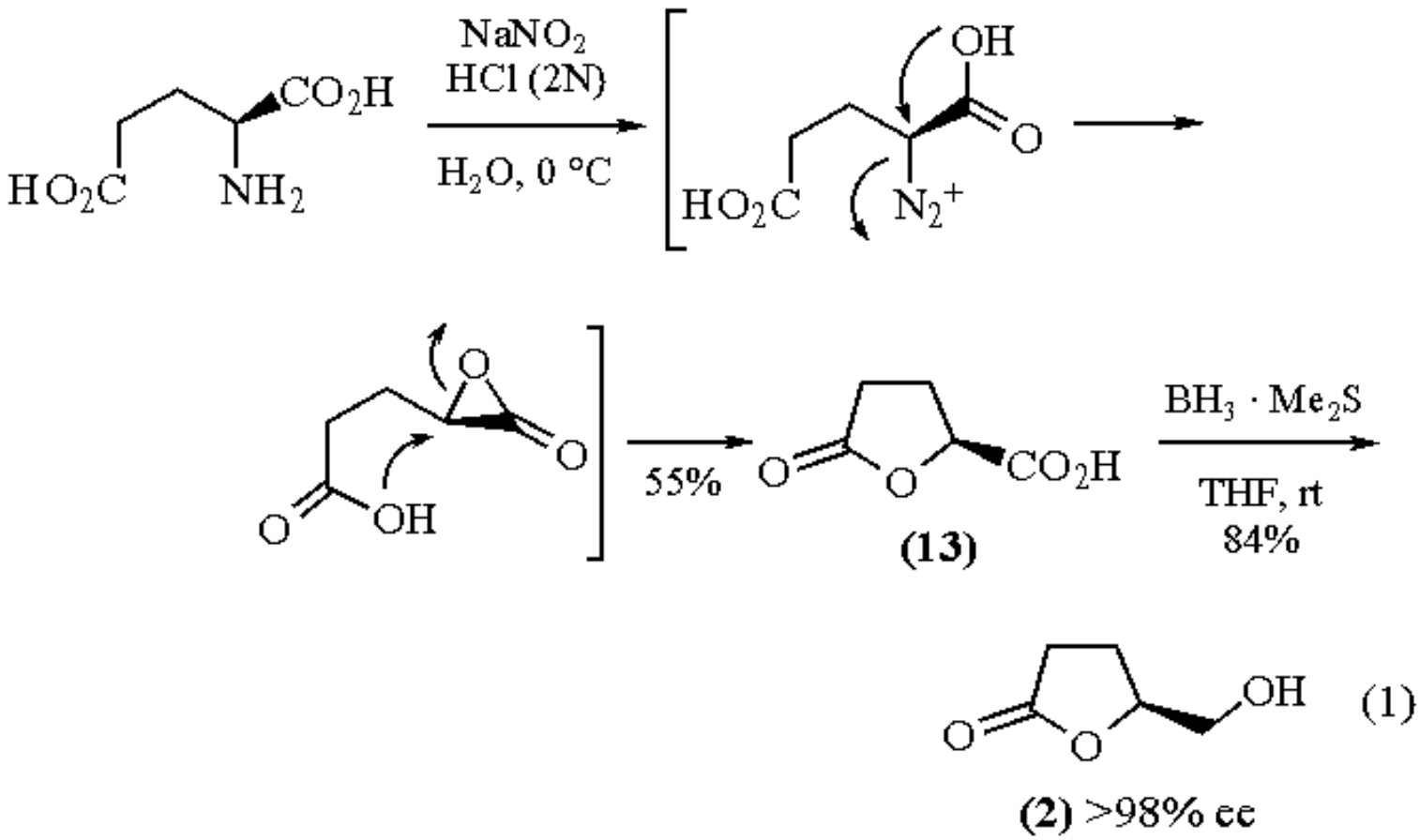

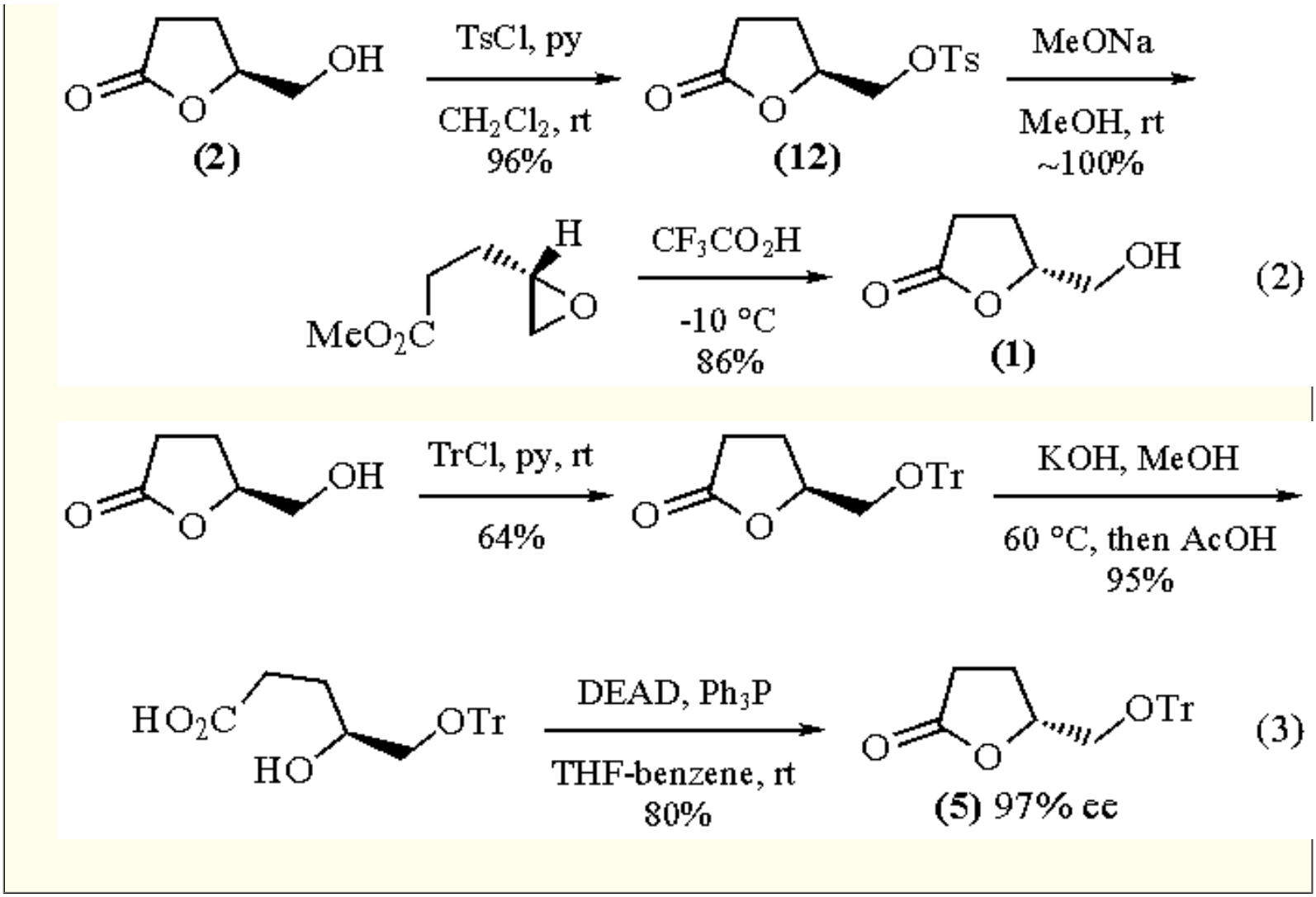

Synthetic Applications.

(*S*)-Dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**2**) was first described in 1971 as an intermediate in the synthesis of D-ribose from L-glutamic acid.[19] Since then, this lactone and its (*R*)-enantiomer[4] have found widespread use as chirons for constructing a rich variety of natural products ranging from simple pheromones[16,20] to complex macrocycles[1b,21] and ionophore antibiotics.[22] The chemical manipulation of these chirons often involves lactone cleavage at an early stage,[3,21,23] as illustrated by the preparation of suitable intermediates for the synthesis of the *Vespa orientalis* pheromone (*R*)-δ-*n*-hexadecanolactone (**14**) (eq 4),[6] the antiviral fungal metabolite brefeldin A (**15**) (eq 5),[24] and (7aα)-*epi*-hemibrevetoxin B (**16**) (eq 6).[9]

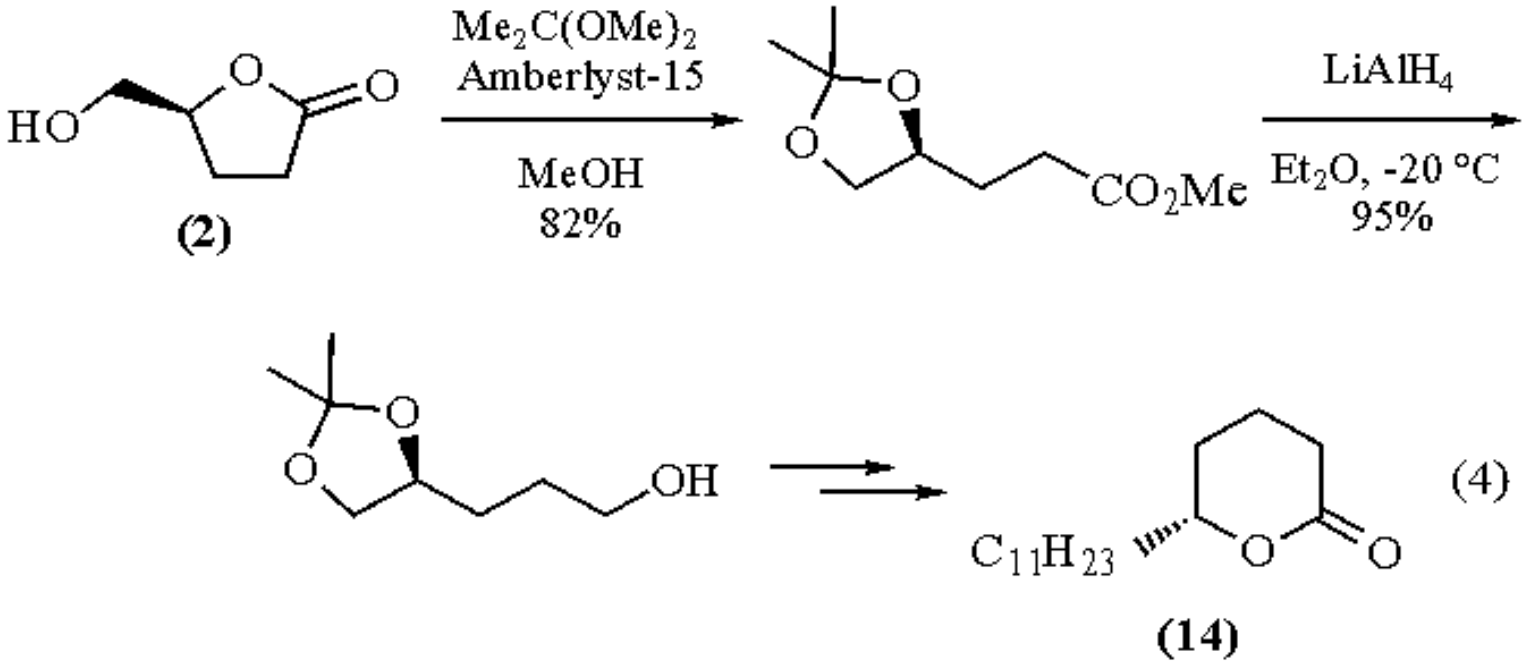
HO
O
O
(2)
Me2C(OMe)2
Amberlyst-15
MeOH
82%
O
O
CO2Me
LiAlH4
Et2O, -20 °C
95%
O
O
OH
C11H23
O
O
(14)

(4)

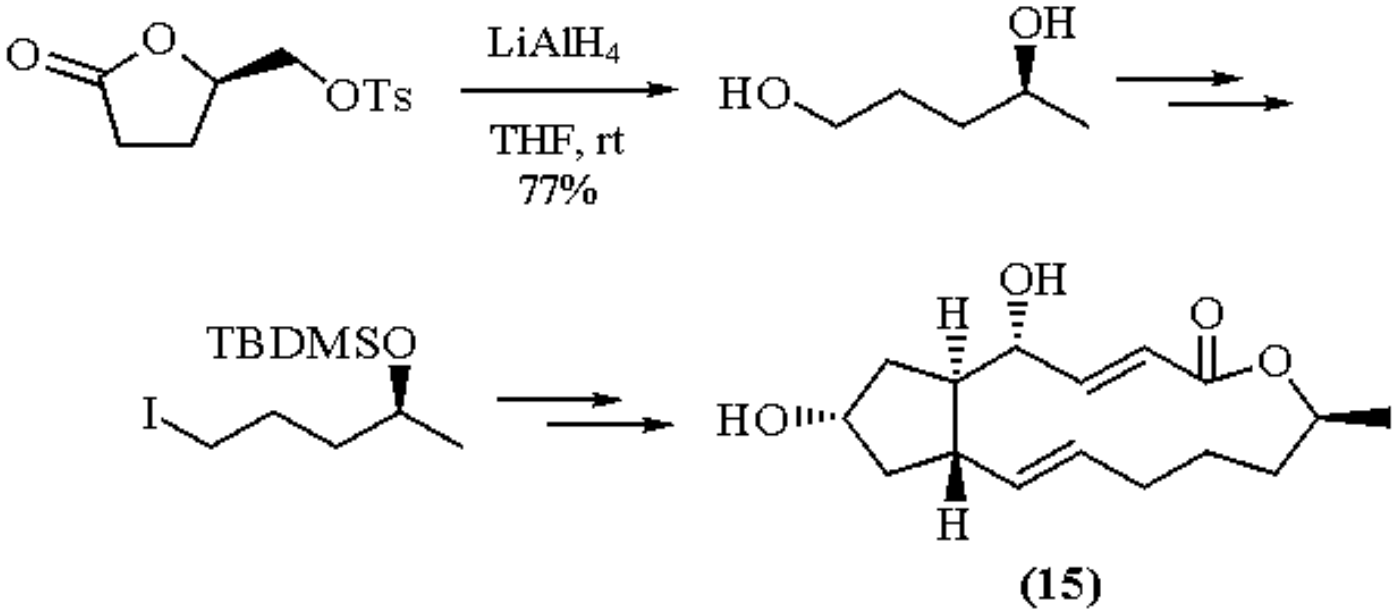
O
O
OTs
LiAlH4
THF, rt
77%
OH
HO
TBDMSO
I
OH
H
O
O
HO
H

(15)

(5)

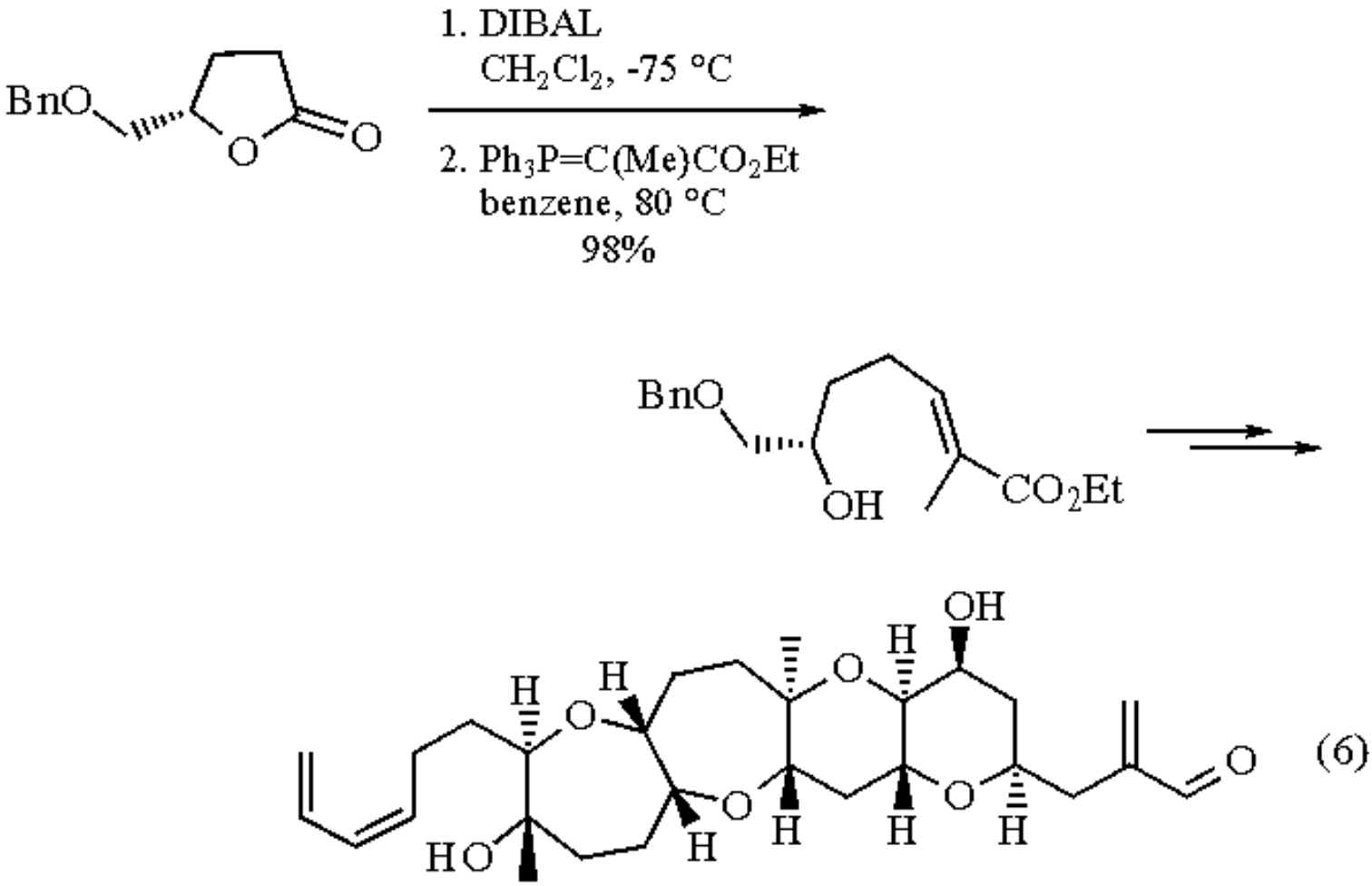

(16)

Optically active γ-alkyl-γ-butyrolactones are readily available from the tosylates through a one-pot reductive procedure[25a] or by alkylative side-chain elongation with the appropriate organocuprate (eq 7).[15]

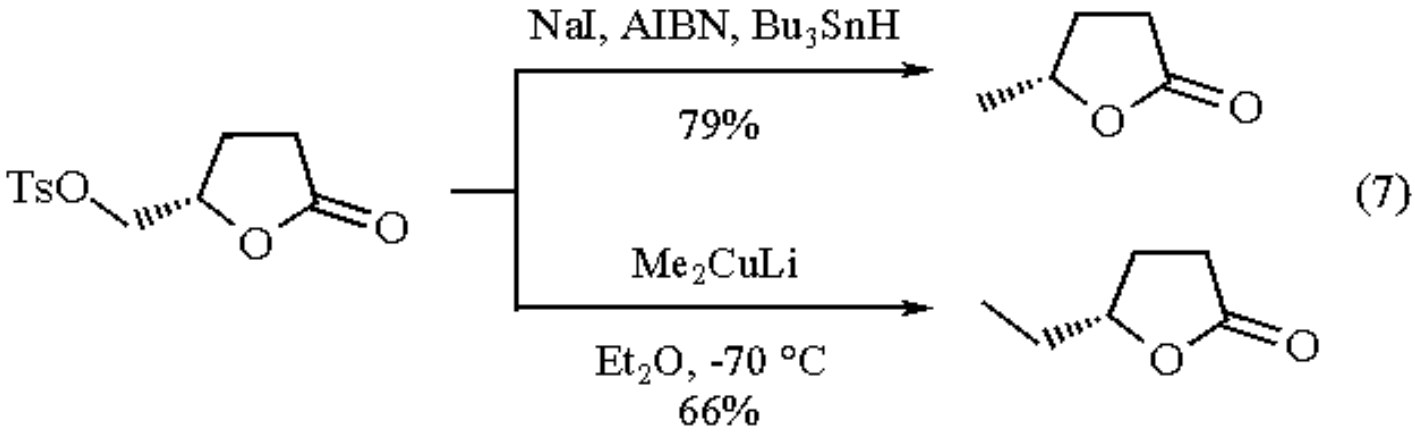

Protection of the alcohol moiety with a bulky group, such as trityl or *t*-butyldiphenylsilyl (TBDPS), shields the *syn* face of the lactone, thereby forcing incoming reagents to attack *anti* to the side chain.[26,2c] This scenario has been heavily exploited for the stereocontrolled introduction of one or two ring substituents through alkylation[2c,26-29] or aldolization.[30] For instance, sequential dialkylation of (*S*)-dihydro-5-(trityloxymethyl)-2(3*H*)-furanone provides products of high diastereomeric purity which can be transformed into β,β-disubstituted γ-butyrolactones (eq 8).[26] Various optically active lactones with predetermined substitution patterns, available in a similar way, have been utilized as key intermediates in the synthesis of

indole alkaloids,[27] lignans,[1d,9] β-lactams,[31] and other natural products.[1a,32]

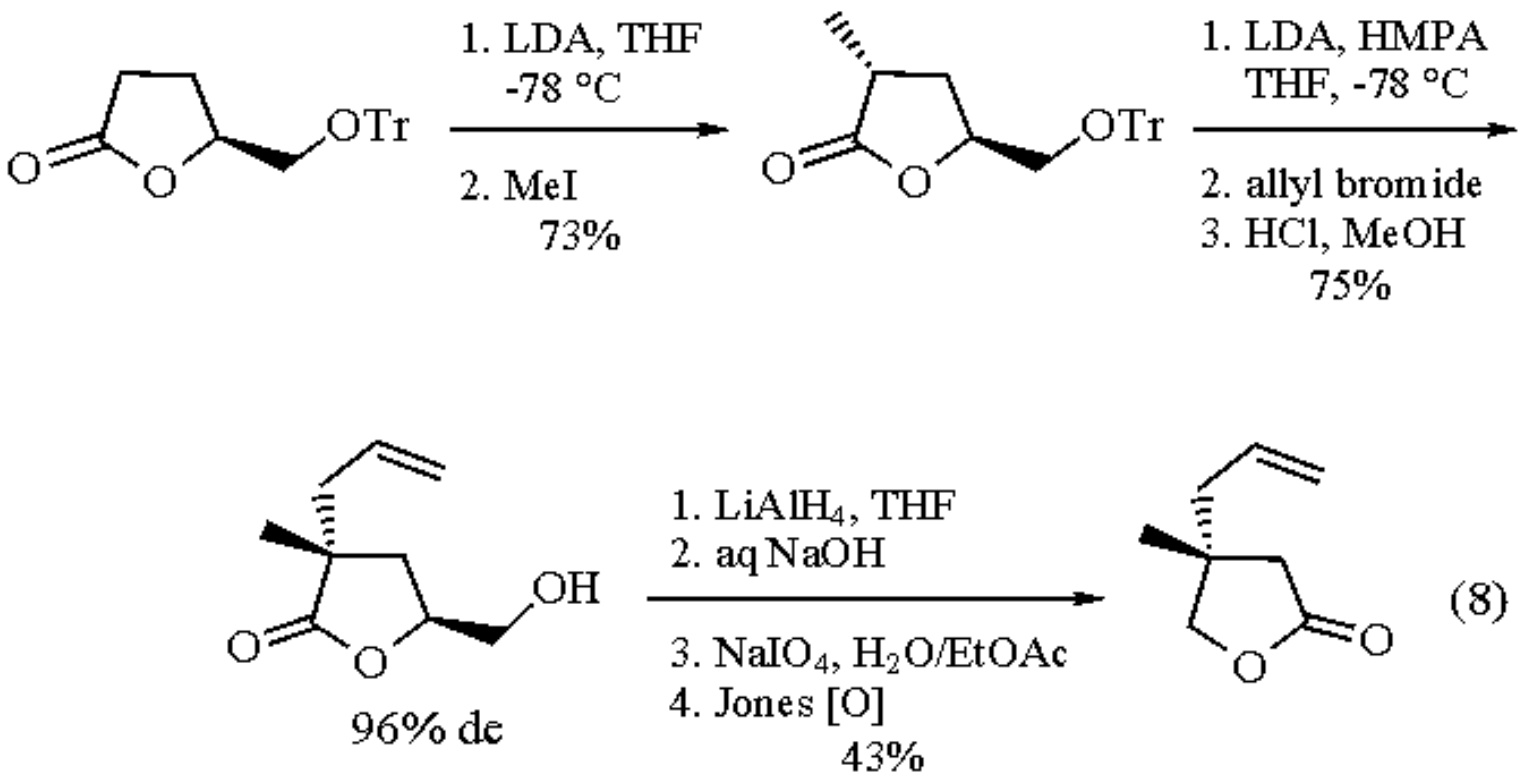

The initial *trans*-alkylated lactones can be easily epimerized in situ by enolization and protonation from the less hindered face[29] using *t*-butyl bromide as the proton source (eq 9).[2b] Further handling of the so-formed *cis* isomers allows for the total synthesis of dihydromevinolin (**17**) and several analogs of import as cholesterol lowering agents.[2b]

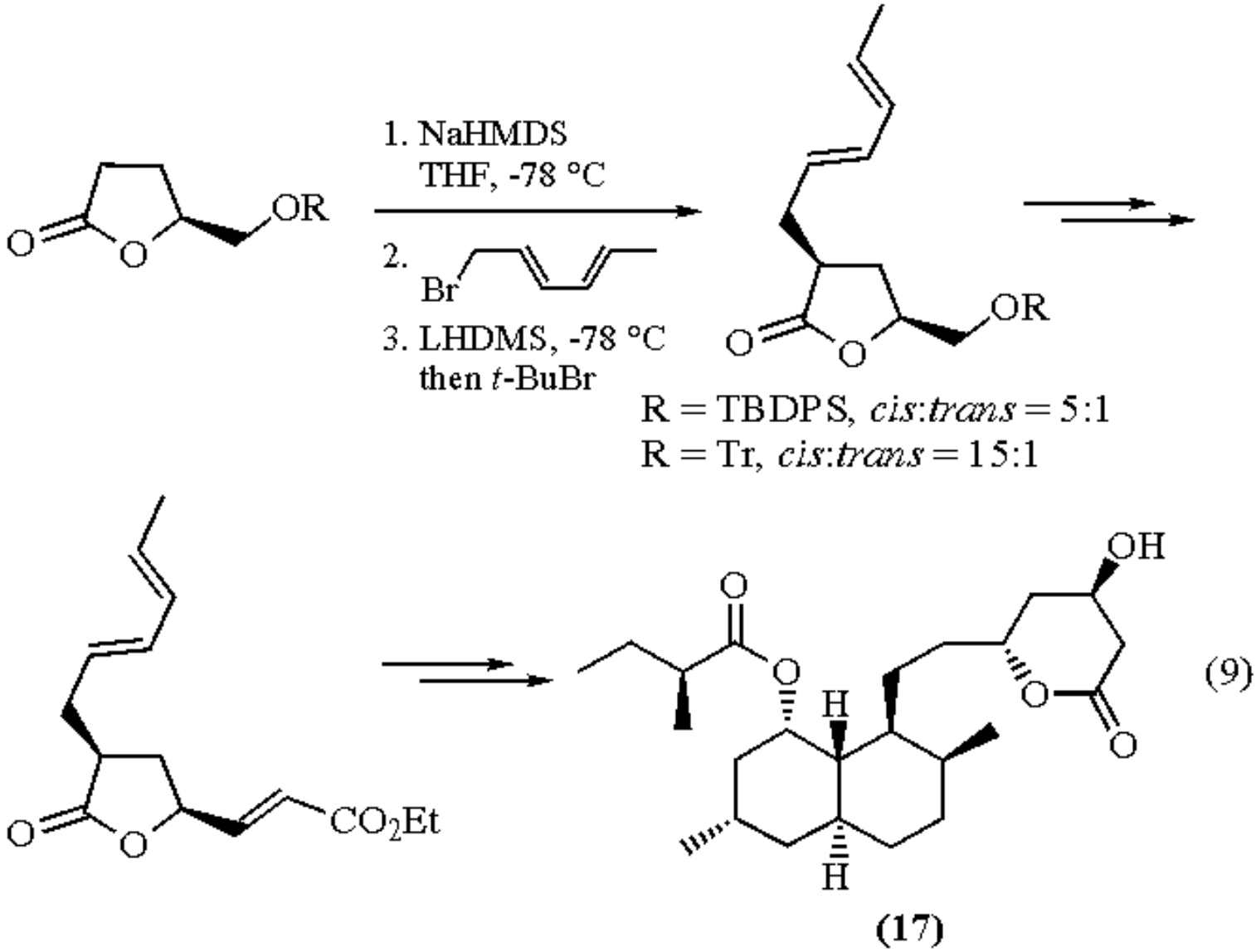

Stereoselective *trans* α-hydroxylation of (*S*)-dihydro-5-(*t*-butyldiphenylsiloxymethyl)-2(3*H*)-furanone can be realized in good yield by enolization and reaction with the ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** complex (MoOPH) (eq 10).[33] Appropriate manipulation of the resulting *trans*-hydroxylactone provides 1,3-polyols[1b] typified by (**18**),[33a] as well as tetrahydropyran (**19**) which is a key intermediate in mevinic acid syntheses.[33b]

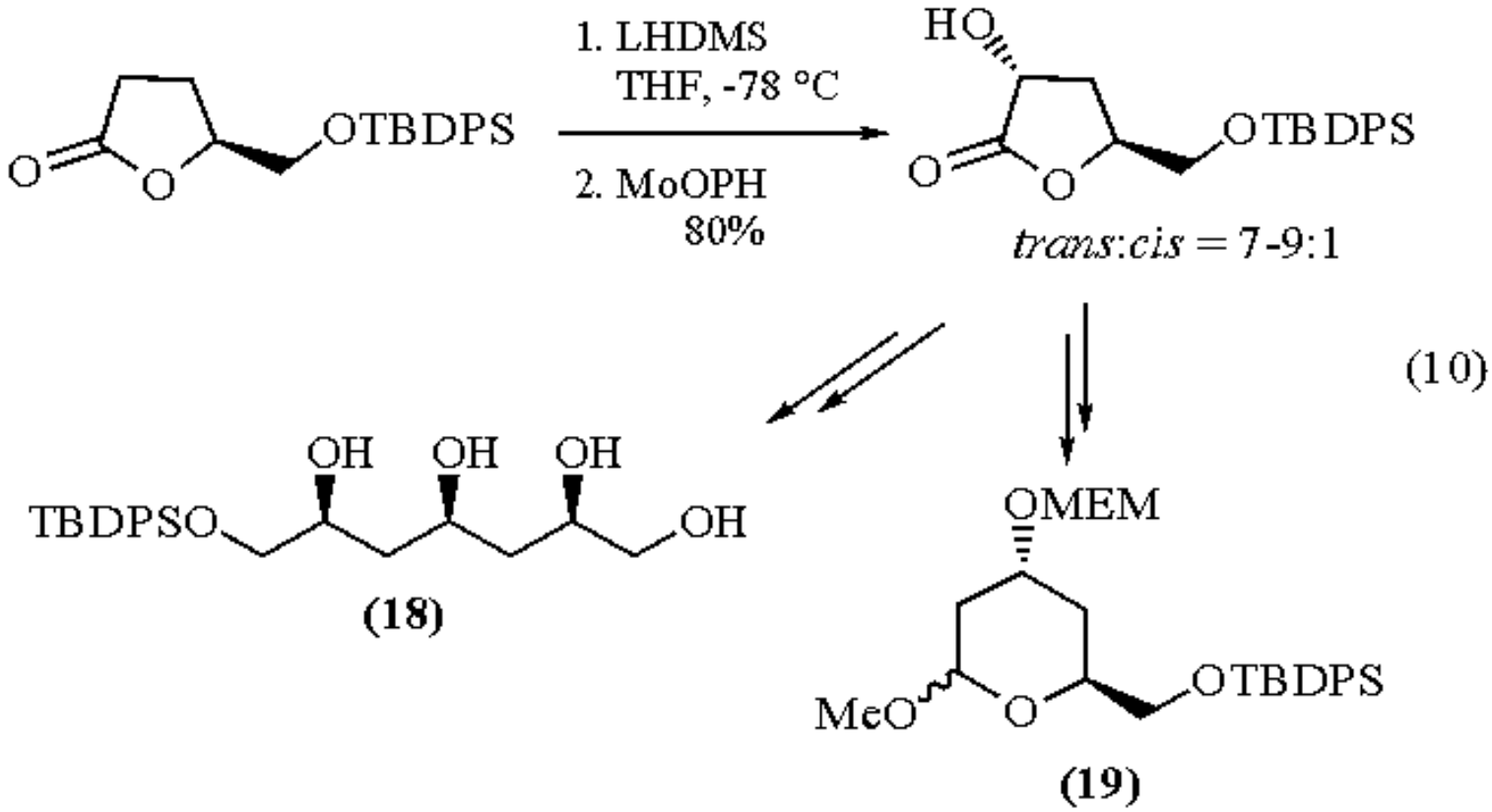

Owing to the urgent need of new drugs for the treatment of AIDS, many methods for converting the title lactones into antiviral dideoxynucleosides have been devised within the past few years.[1e,f,12,34] A viable synthesis of the potent anti-HIV agent 3´-deoxy-2´,3´-dehydrothymidine (d4T, **21**) relies on *trans* selective sulfenylation of the lactone-derived silyl ketene acetal (**20**) with *N*-(phenylthio)-ε-caprolactam (eq 11).[35] In comparable fashion, (**21**) and related nucleosides have been prepared through selenenylation of (**20**).[36]

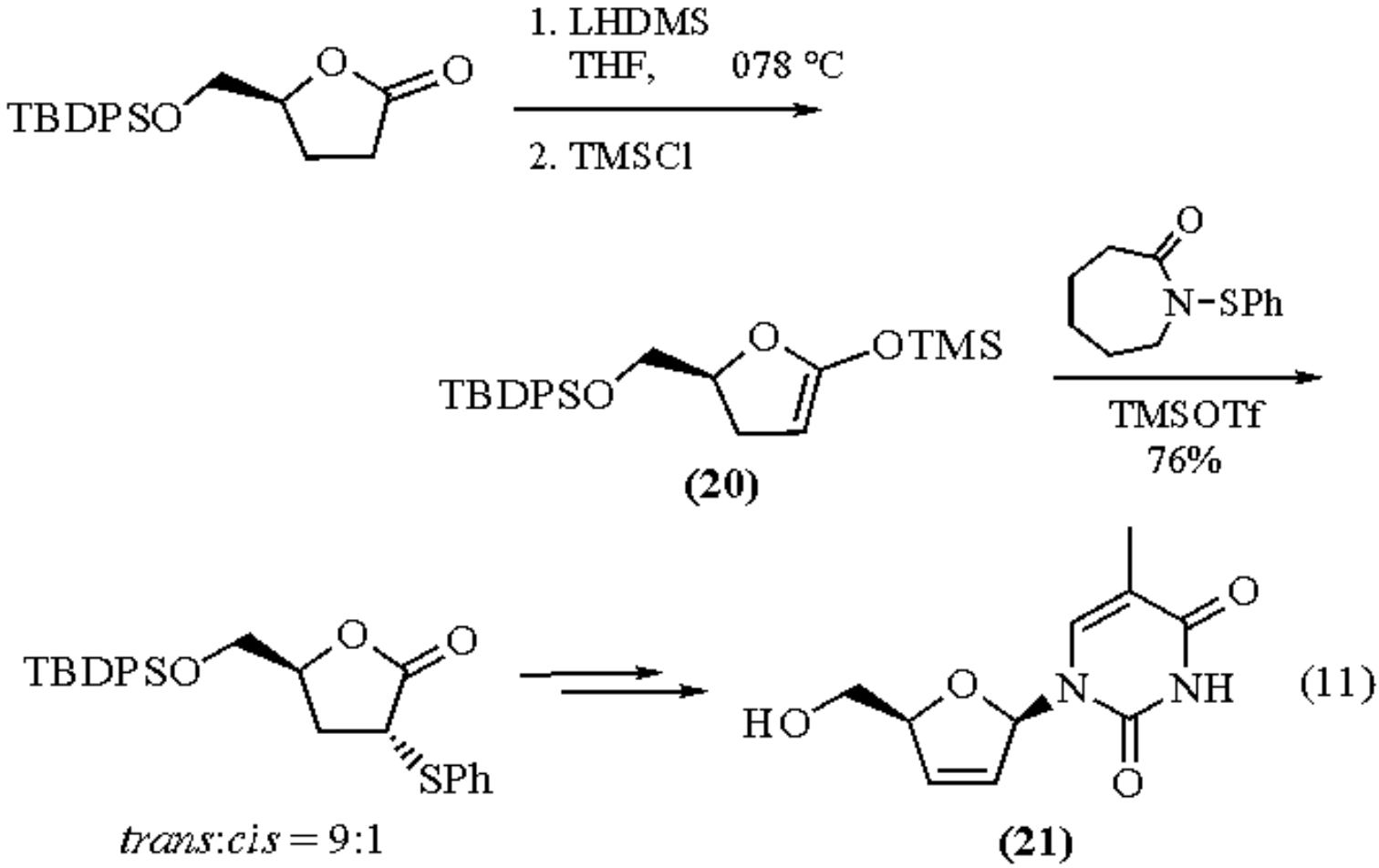

Related Chirons.

The commercially available (*R*)-(-)- and (*S*)-(+)-enantiomers of 5-hydroxymethyl-2(5*H*)-furanone (**22** and *ent*-**22**) and their various protected derivatives have also been extensively used in the synthesis of natural products,[1b -d,37,38] nucleosides,[1e,f] and other bioactive substances.[39,40] A cost-effective, versatile route to these chirons[14,37,40b] is illustrated by the preparation of (**22**) (eq 12).[38]

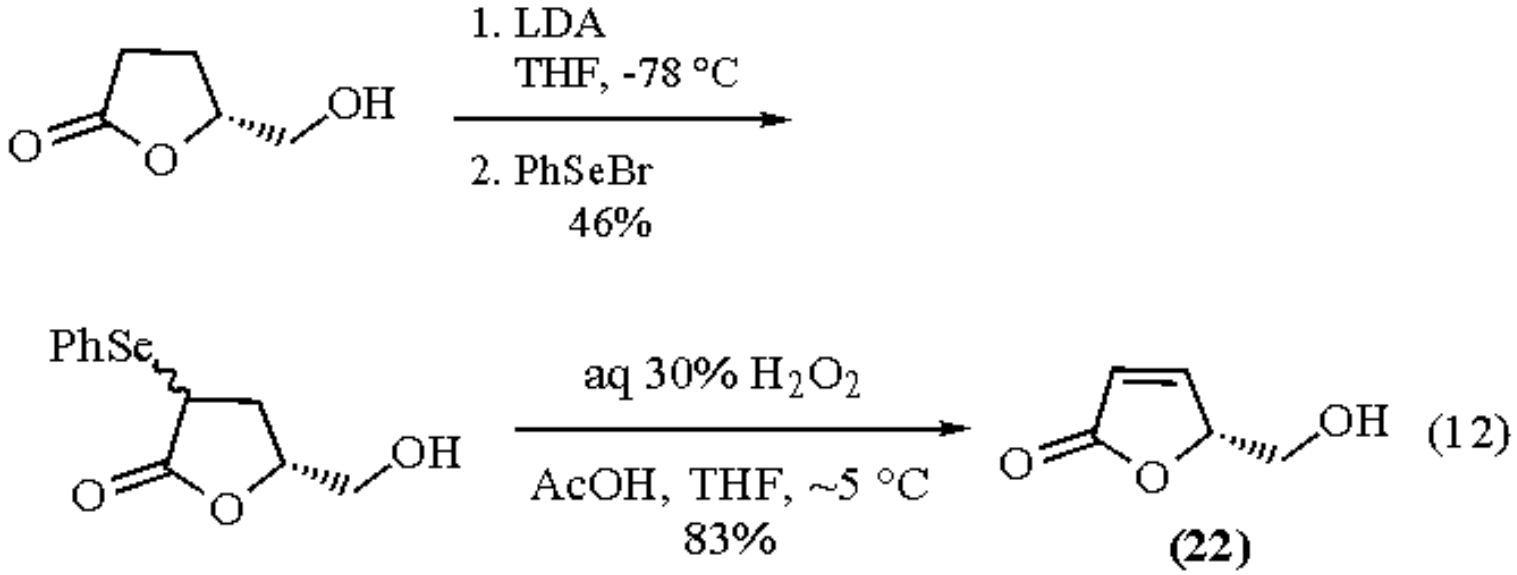

Related Reagents.

α,β-***Butenolide***; γ-***Butyrolactone***; ***(R)-Pantolactone***; β-***Propiolactone***; ***2-Trimethylsilyloxyfuran***; β-***Vinyl***-α,β-***butenolide***.

---

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(2*S*)-(+)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine[1]

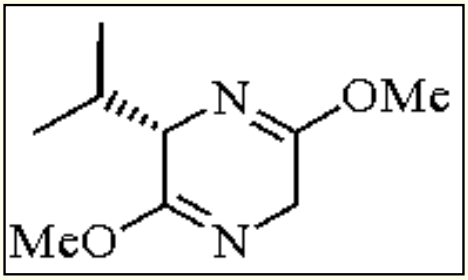

[78342-42-4] · $C_9H_{16}N_2O_2$ · (2*S*)-(+)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine · (MW 184.24)

(Schöllkopf-Hartwig bislactim ether reagent for asymmetric synthesis of amino acids by reaction of the metalated reagent with alkyl halides,[2] aldehydes,[3] ketones,[4] epoxides,[5] and enones,[6] and subsequent hydrolysis of the resulting bislactim ether adduct)

Physical Data: bp 103-104 °C/15 mmHg; *d* 1.03 g cm^{-3}; [α]20D -109 (*c* = 1, EtOH).

Solubility: sol ether, THF, *n*-hexane.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: NMR.[2]

Purification: distillation.

Handling, Storage, and Precautions: store refrigerated.

Bislactim Ether Method.

The commercially available bislactim ethers of cyclo(L- and D-Val-Gly) and cyclo(L- and D-Val-Ala)[7] are very versatile reagents for the preparation of nonproteinogenic amino acids in high yields and with excellent enantioselectivities (typically >95%).[1]

Reactions of the Lithiated Bislactim Ether.

The procedure involves metalation with ***n-Butyllithium*** in THF at -70 °C and reaction of the resulting azaenolate with alkyl halides (eq 1).[2] The latter enters with high diasteroselectivity *trans* to the isopropyl group. The alkylation products

are hydrolyzed under mild acidic conditions to give the desired amino acid ester and the chiral auxiliary L-Val-OMe, which can be separated by distillation or chromatography (eq 1). As well as reacting with primary and secondary alkyl halides and sulfonates,[8] the lithiated bislactim ether reacts in good yields and with high *trans* diastereoselectivities (in general >95%) with a variety of other electrophiles such as ketones,[9] acyl chlorides,[10] thioketones,[11] epoxides,[5] α,β-unsaturated esters,[12] and arene-manganese tricarbonyl complexes.[13]

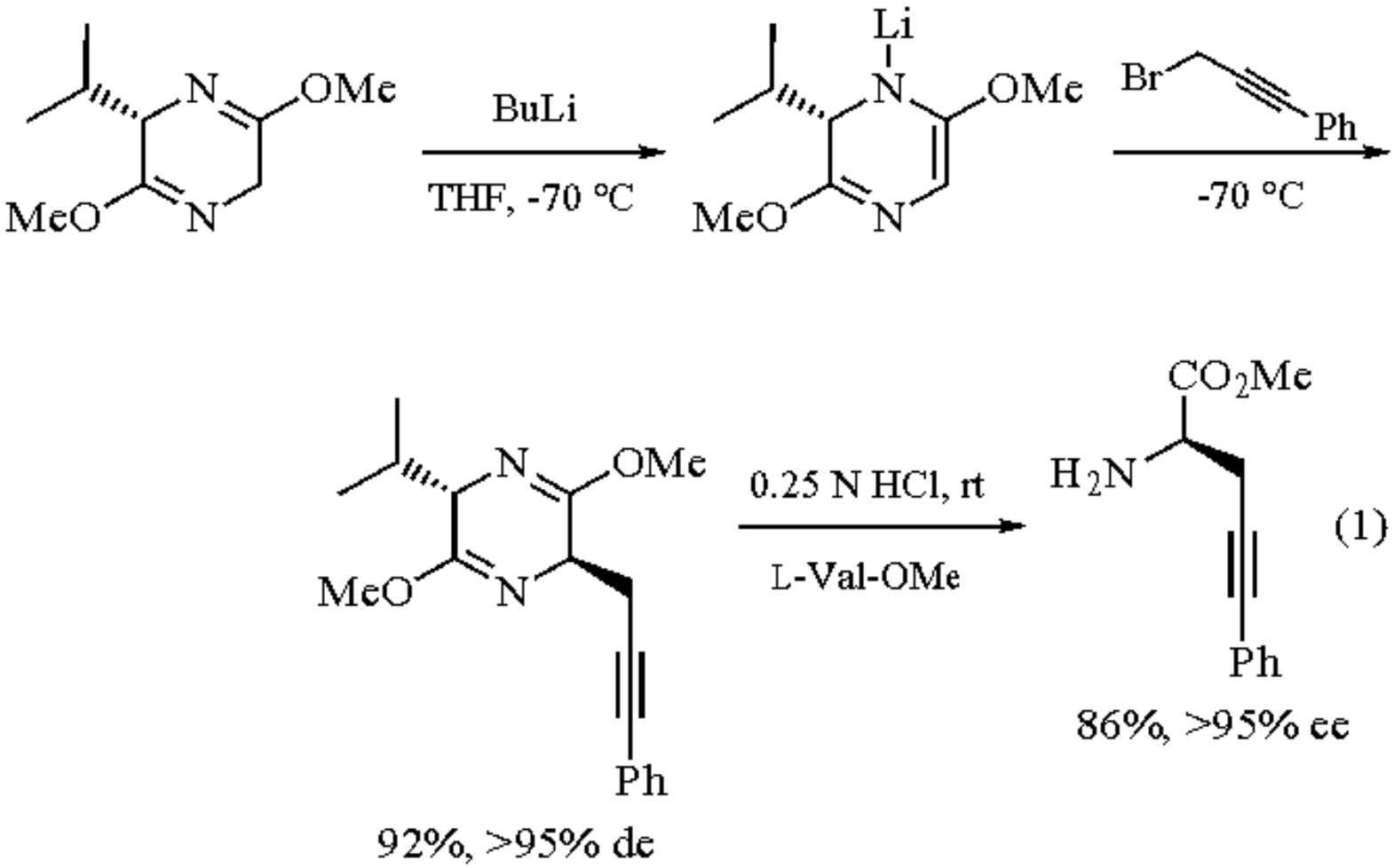

Reaction of the Titanated Bislactim Ether.

The titanium derivative of the bislactim ether of cyclo(L-Val-Gly) reacts with alkyl aldehydes,[3] aryl aldehydes,[14] and α,β-unsaturated aldehydes[15] highly diastereoselectively to give almost exclusively the *syn* addition products (eq 2). Hydrolysis with dilute ***Trifluoroacetic Acid***[3c] affords (2*R*, 3*S*)-β-hydroxy-α-amino acid methyl esters. α-Amino-γ-nitro amino acids can be obtained by 1,4-addition of the titanated bislactim ether to nitroalkenes and subsequent hydrolysis of the adduct.[16]

(2S)-(+)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine

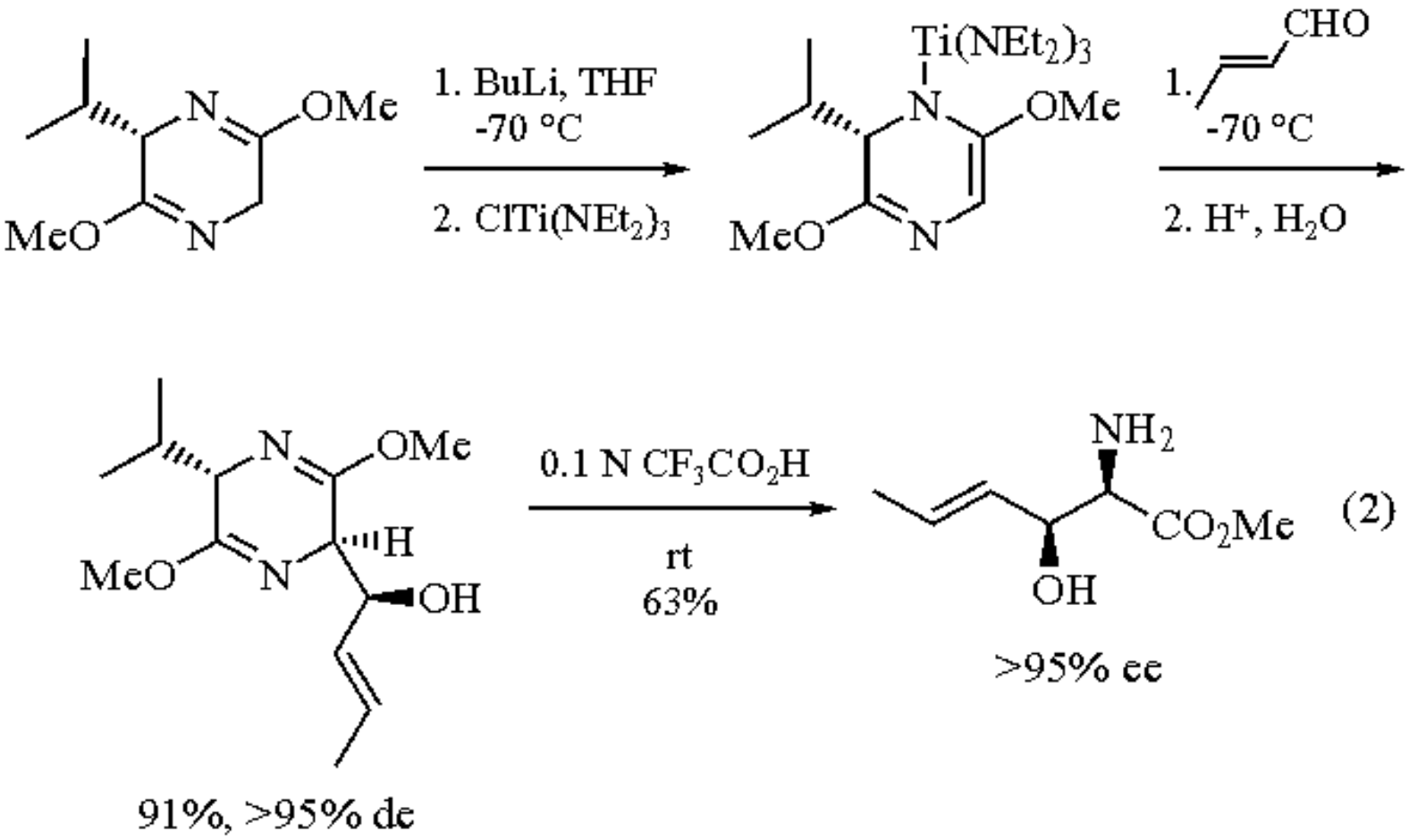

Reactions of the Bislactim Ether Cuprate.

The lithiated bislactim ether can be converted to an azaenolate cuprate by treatment with CuBr.SMe_2 (see ***Copper(I) Bromide***).[6] Conjugate addition of the cuprate to enones (eq 3)[6] and dienones,[17] or alkylation[6] with base labile electrophiles like ethyl 3-bromopropionate, proceeds with high *trans* diastereoselectivity. Hydrolysis of the Michael adducts and subsequent protection afford (2*R*,3*R*)-*N*-Boc-δ-oxo-α-amino acid methyl esters (eq 3).

(2S)-(+)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine

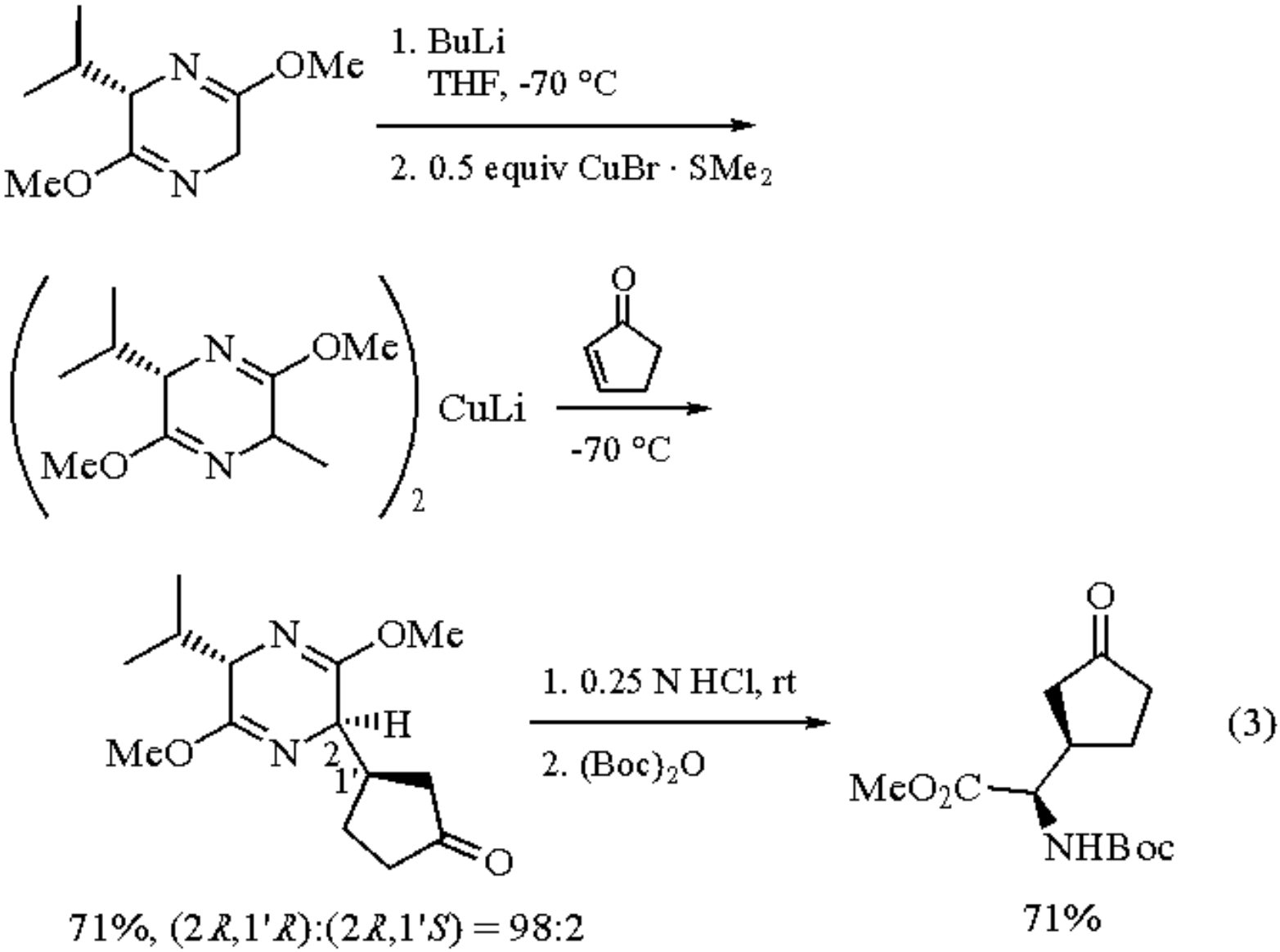

Reactions of the Bislactim Ether Carbene.

Diazotization of the lithiated bislactim ether generates an electrophilic carbene species, which reacts in good yields and with high diastereomeric excess (<95%) with alkenes[18] and aryl alkynes[19] (eq 4) to give spirocyclopropanes and spirocyclopropenes, respectively. Hydrolysis of the latter affords the novel (*R*)-1-amino-2-arylcyclopropene-1-carboxylic acids.[19]

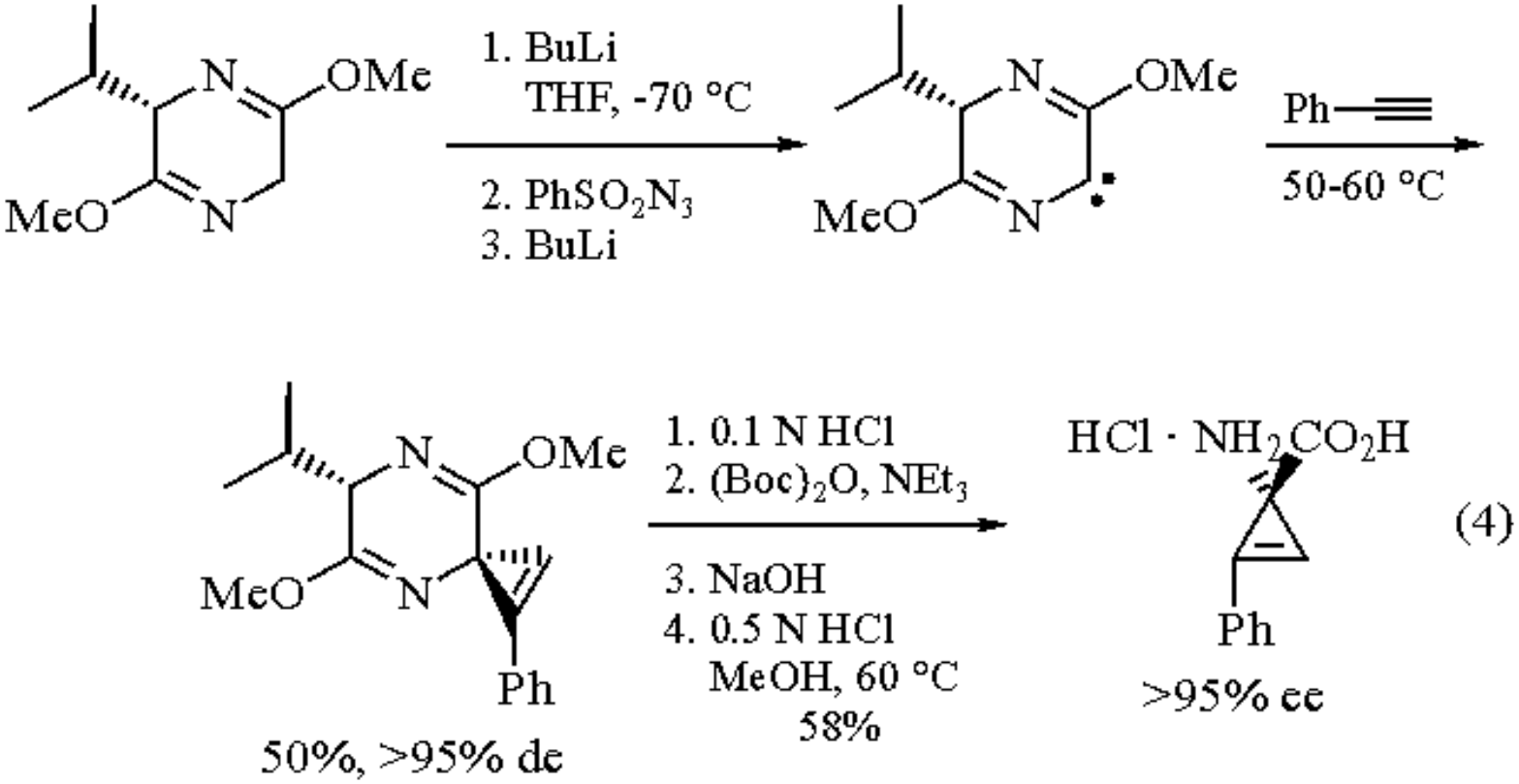

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***.

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3,4-Dihydro-2*H*-pyran[1]

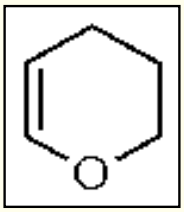

[110-87-2] · C_5H_8O · 3,4-Dihydro-2*H*-pyran · (MW 84.12)

(widely used OH-protecting reagent;[1] applicable to alkanols, phenols, thiols; stable at high pH; labile at low pH; generally resistant to nucleophiles and organometallic reagents; resistant to hydride reductions; labile under Lewis acidic conditions)

Physical Data: mp -70 °C; bp 86 °C; fp -15 °C; *d* 0.922 g cm^{-3}.

Solubility: sol water, ethanol.

Handling, Storage, and Precautions: it has been reported that the tetrahydropyranyl (THP) ethers form sensitive organic peroxides when in contact with peroxy reagents. Violent explosions have occurred during purification of these compounds. Precautions normally sufficient in isolation of such products have failed to destroy the sensitive components.[2]

Tetrahydropyranylation of Alcohols.

Protection of alcohol functionality as the THP ether is an often-utilized tool in organic synthesis. It must be noted that the reaction of a chiral alcohol with dihydropyran introduces an additional asymmetric center and hence a diastereomeric mixture is obtained (eq 1). This can lead to difficulties with purification, assignment of spectral features, etc., but does not prevent successful implementation.[3]

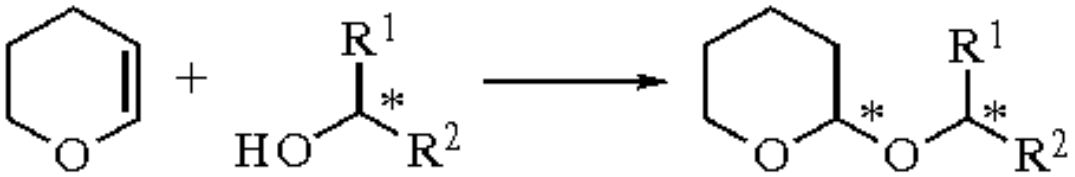

(1)

A variety of reaction conditions for the synthesis of THP derivatives, the majority acidic, have been proposed in the literature (eq 2). The techniques have been highly optimized and increasingly mild conditions have been developed. Mineral acids have classically been used to effect the reaction.[4] Products have been obtained in 20-93% yields using these methods. However, the use of mineral acids is clearly limiting with respect to substrates containing sensitive

functionality. Nevertheless, many applications in steroid[5] and saccharide[6] chemistry are possible using this technology. Significantly, tetrahydropyranyl ethers are not known to migrate in 1,2-diol systems.

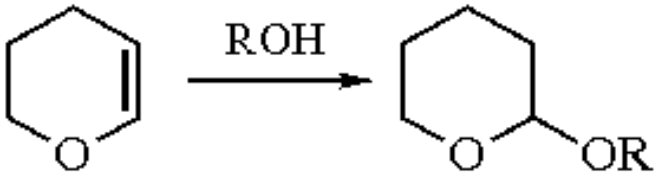

≡ R-OTHP (2)

The standard acid catalyst for effecting tetrahydropyranylation of alcohols has become ***p-Toluenesulfonic Acid***. Reaction of even tertiary alcohols with excess dihydropyran is usually complete in 0.5-1 h at rt, although sometimes reflux temperatures are required. Yields range from 60 to 84% for tertiary alcohols.[7] Catalysis by *p*-TsOH can give very high yields, depending on conditions and choice of solvent: *p*-TsOH (dioxane, 20 °C, 5 min, 71-97%).[8]

Tetrahydropyranylation of primary and secondary alcohols can give high yields under mild and neutral conditions using ***Iodotrimethylsilane*** (25 °C, 30 min, 80-95%). Workup is particularly convenient, consisting of evaporation of volatiles and chromatography when required. Tertiary alcohols, however, yield the corresponding iodide rather than the THP ether.[9]

Reaction using ***Boron Trifluoride Etherate*** (Et_2O-petroleum ether, 25 °C, 47-76%) gives moderate yields with evaporation of volatiles being the only workup required.[10]

Pyridinium p-Toluenesulfonate (25 °C, 4 h, 94-100%) is a mild and efficient catalyst, particularly applicable to the protection of highly acid sensitive alcohols. Yields were markedly superior to procedures employing $BF_3.Et_2O$, *p*-TsOH, and ***Hydrogen Chloride***.[11]

Tetrahydropyranylation of tertiary alcohols, while more difficult owing to the hindered nature of the substrates or competitive elimination, can be carried out using dihydropyran and ***Triphenylphosphine Hydrobromide*** (25 °C, 6-24 h, 80-96%).[12] The method is applicable to even very sensitive substrates such as mevalonolactone (eq 3).

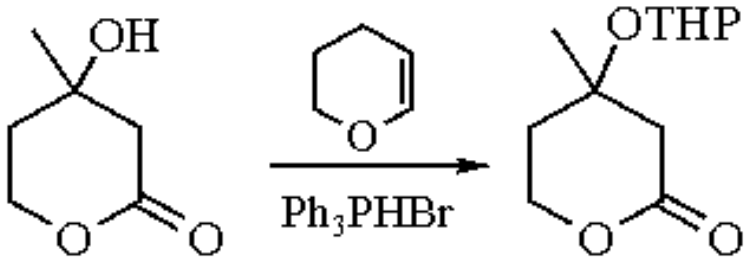

(3)

Tetrahydropyranylation of alcohols can be carried out under very mild conditions in the presence of bis(trimethylsilyl) sulfate (0 °C, 1 h, 89-100%). No rearrangement is observed even with tertiary allylic alcohols.[13]

Protocols have been developed which utilize an insoluble solid catalyst in combination with dihydropyran to effect the protection of alcohols as their corresponding THP ethers. These procedures are advantageous in that the catalyst may be recovered by simple filtration and the products isolated by evaporation of volatiles. In many cases the catalyst can be reused without regeneration. Reaction of alcohols with dihydropyran in the presence of Amberlyst H-15 (25 °C, 1 h, 90-98%) yields THP derivatives. Alternatively, a solution of dihydropyran and the alcohol may be passed slowly through a column of silica overlaid with Amberlyst H-15 to yield the THP ethers directly (73-97%).[14] The acidic clay

Montmorillonite K10 (25 °C, 15-30 min, 63-95%) is similarly applicable.[15] Reillex® 425 resin (86 °C, 1.5 h, 84-98%)[16] is applicable with the advantage that it does not promote the sometimes troublesome polymerization of dihydropyran.[17] Polymeric derivatives of pyridinium *p*-toluenesulfonate are also effective. Poly(4-vinylpyridinium *p*-toluenesulfonate) and poly(2-vinylpyridinium *p*-toluenesulfonate) catalysts yield tetrahydropyranyl derivatives of primary, secondary, and tertiary alcohols (24 °C, 3-8 h, 72-95%).[18]

Cleavage of Tetrahydropyranyl Derivatives.

Deprotection of THP ethers has been carried out using ***Acetic Acid*** (H_2O-THF (3:3:2), 50 °C, 5 h, 97%),[19] HOAc (H_2O-THF (2:1:as required), 47 °C, 4 h, 82%),[20] HOAc (THF-H_2O (4:2:1), 45 °C, 3.5 h),[21] aqueous ***Oxalic Acid*** (MeOH, 50-90 °C, 1-2 h),[22] *p*-TsOH (MeOH, 25 °C, 1 h, 94%),[23] pyridinium *p*-toluenesulfonate (EtOH, 55 °C, 3 h, 98-100%),[24] bis(trimethylsilyl) sulfate (MeOH, 25 °C, 10-90 min, 93-100%).[13] Cleavage with Amberlyst H-15 (MeOH, 45 °C, 0.5-2 h, 93-98%)[25] is advantageous in that the acid catalyst can be recovered by filtration and no aqueous workup is required. Organotin phosphate condensates are effective in the selective cleavage of THP ethers (MeOH, reflux, 2 h, 80-90%) in the presence of MEM ethers, MOM ethers, and 1,3-dioxolanes.[26] The catalyst is insoluble in the reaction medium and can be reused repeatedly.

Selective cleavage of THP ethers in the presence of *t*-butyldimethylsilyl ethers can be accomplished by treatment with mild Lewis acids: ***Dimethylaluminum Chloride*** (-25 °C to 25 °C, 1 h, 98%) or ***Methylaluminum Dichloride*** (-25 °C, 0.5 h, 90%).[27] Selective cleavage of THP ethers of primary, secondary, and tertiary alcohols can be carried out in the presence of *t*-butyldimethylsilyl, acetyl, mesyl, and methoxymethyl ethers, in the presence of thiostannane catalysts: $Me_2Sn(SMe)_2$-$BF_3.Et_2O$ (-20 °C or 0 °C, 3-25 h, 80-97%).[28]

Tetrahydropyranylation of Thiols.

Tetrahydropyranyl derivatives of thiols have been utilized for the masking of this functional group (eq 4).

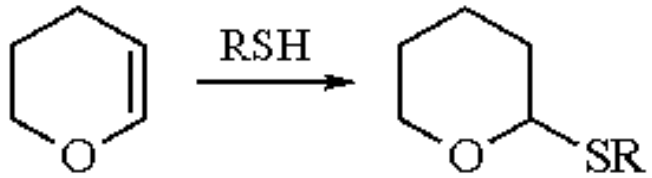

≡ R-STHP (4)

Thiols react with dihydropyran in the presence of $BF_3.Et_2O$ (0 °C, 0.5 h, 25 °C, 1 h) to yield (*S*)-2-tetrahydropyranyl hemithioacetals in satisfactory yields.[29] In contrast to *O*-tetrahydropyranyl ethers, an *S*-tetrahydropyranyl ether is stable to 4 N HCl-MeOH.[30] Deprotection is conveniently accomplished with ***Silver(I) Nitrate*** (0 °C, 10 min)[31] or ***Hydrogen Bromide-Trifluoroacetic Acid*** (90 min)[32] in quantitative yields. Oxidation to disulfides can be carried out with ***Iodine***[33] or ***Thiocyanogen***.[34]

Tetrahydropyranylation of Amides.

Aromatic amides, alkyl amides, ureas, sulfonamides, and imides undergo reaction with dihydropyran-***Hydrogen Chloride*** (benzene, reflux, 2 h, 22-73%), yielding the expected adducts.[35]

Tetrahydropyranylation of Amines.

Purines react with dihydropyran in the presence of a catalytic amount of *p*-TsOH to give the 9-tetrahydro-2-pyranyl derivatives (50-87%) (eq 5).[36]

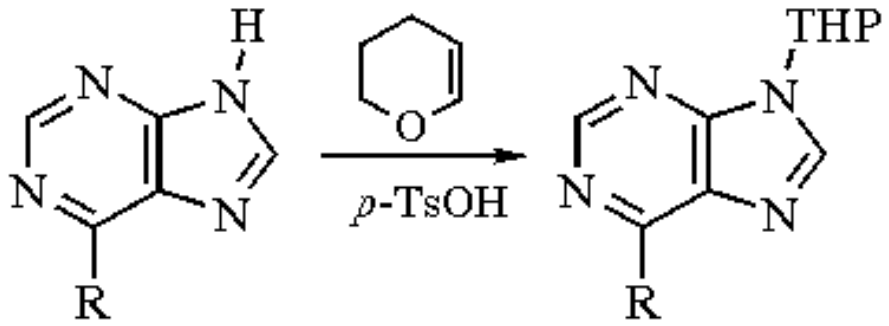

(5)

Functional Group Manipulation of Tetrahydropyranyl Derivatives.

While tetrahydropyranyl derivatives are often utilized as masked equivalents of alcohols, etc., it is possible to perform functional group manipulation on such species. In these cases the tetrahydropyranyl derivatization serves to activate the alcohol rather than protect it.

Conversion of alcohols to their corresponding alkyl halides can be accomplished in two steps by conversion to the THP ethers followed by treatment with ***Triphenylphosphine-Carbon Tetrabromide*** (23 °C, 24 h, 62-87%).[37] In the case of tertiary substrates, 15-25% elimination is observed. Similarly rapid conversion of tetrahydropyranyl derivatives to their corresponding bromides or iodides can be carried out with 1,2-bis(diphenylphosphino)ethane tetrahalides (0.1-4 h, 0 °C to 23 °C, 81-96%).[38] Methyl esters and *t*-butyldimethylsilyl ethers and alkenes are unreactive under these reaction conditions. Direct conversion of alcohol tetrahydropyranyl ethers to bromides, chlorides, trifluoroacetates, methyl ethers, or nitriles can be effected with ***Triphenylphosphine Dibromide*** (25 °C, 30 min, 43-89%).[39] Tetrahydropyranyl ethers may be converted to benzyl ethers, MEM ethers, benzoates, or tosylates by reaction with the appropriate electrophile in the presence of $Bu_3SnSMe\text{-}BF_3.EtO_2$ (0 °C, 7-70 h, 75-78%). Oxidation of the intermediate alkoxystannane with ***Pyridinium Chlorochromate*** yields aldehydes (83%).[40]

Ring Opening Reactions of Dihydropyran.

Treatment of dihydropyran with *n*-pentylsodium,[41] or ***n-Butyllithium***[42] yields *trans*-1-hydroxy-4-nonene (73%) (eq 6).

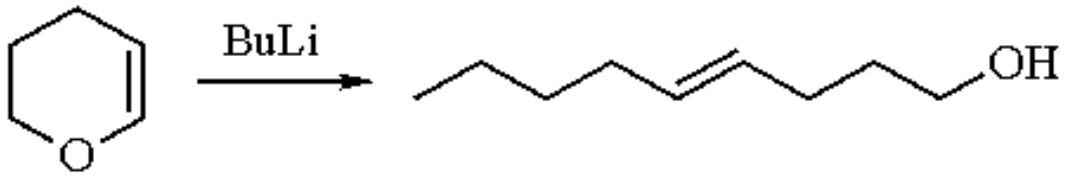

(6)

Cleavage of dihydropyran with HCl(aq) (30 min, 25 °C) constitutes a convenient preparation of 5-hydroxypentanal (eq 7).[43]

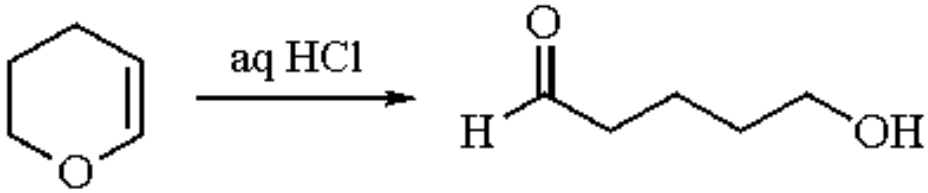

(7)

Tetrahydropyranyl ethers are unstable to reduction with ***Lithium Aluminum Hydride-Aluminum Chloride*** (eq 8). Cleavage occurs in the tetrahydropyranyl ring or exocyclicly.[44] The reaction is seldom useful synthetically since the two modes are competitive. In marked contrast, tetrahydropyranyl derivatives of thiols are cleaved selectively at the ring carbon-oxygen bond, giving hydroxyalkyl thioethers (58-82%) (eq 9).[45]

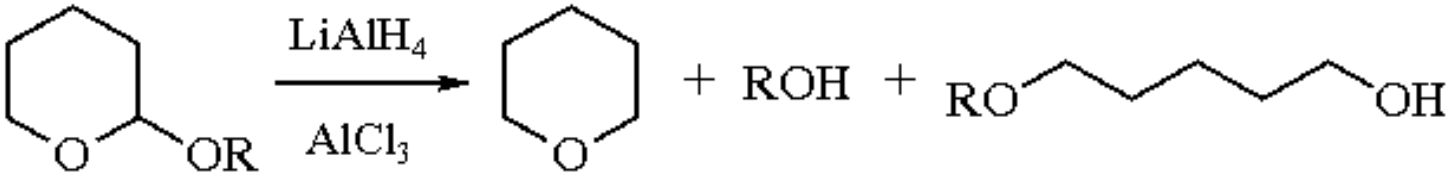

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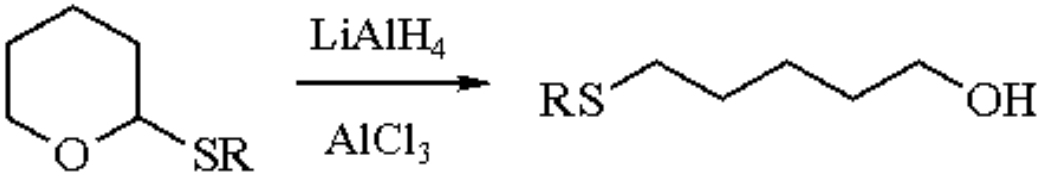

(9)

Tetrahydropyranyl derivatives of amines are hydrogenolized by $LiAlH_4$ in the absence of any Lewis acid (eq 10).[46]

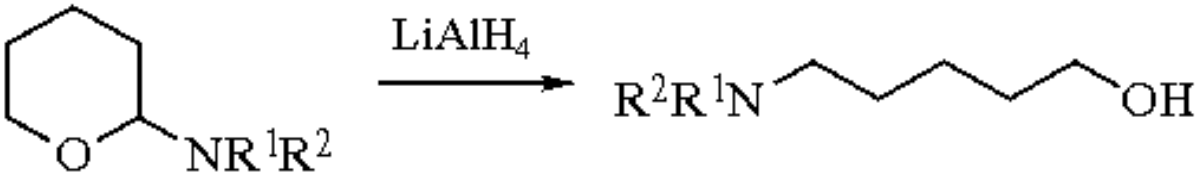

(10)

Dihydropyran is a convenient starting material for the preparation of (*E*)-4-hexen-1-ol, in three steps (eq 11).[47]

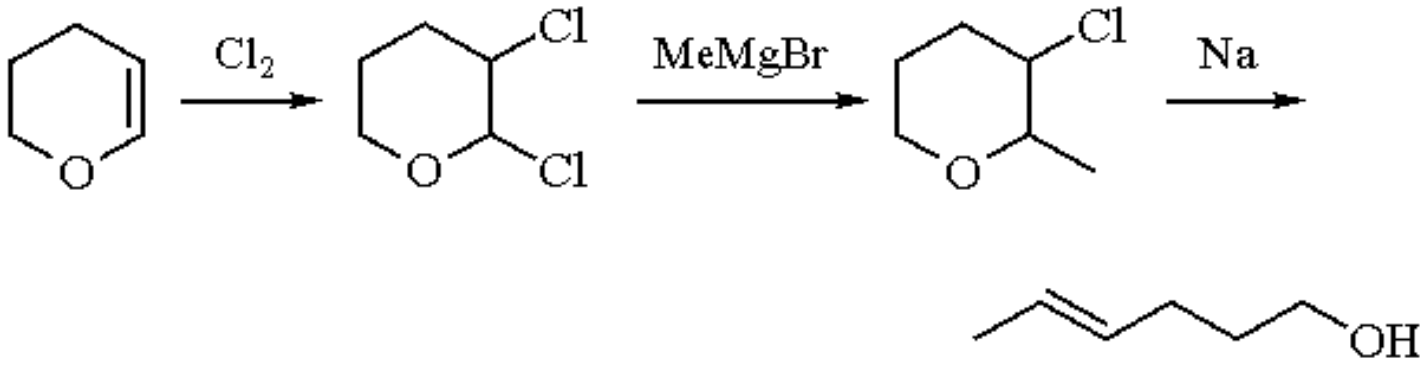

(11)

Anion Chemistry.

Dihydropyran and derivatives can be quantitatively deprotonated with ***t-Butyllithium*** (-78 °C to 5 °C, 0.5 h, THF) (eq 12). The resulting anion reacts with electrophiles such as ketones and alkyl halides in good yields. Cuprates derived from this anion add smoothly in conjugate fashion to α,β-enones in excellent (91%) yields (eq 13).[48]

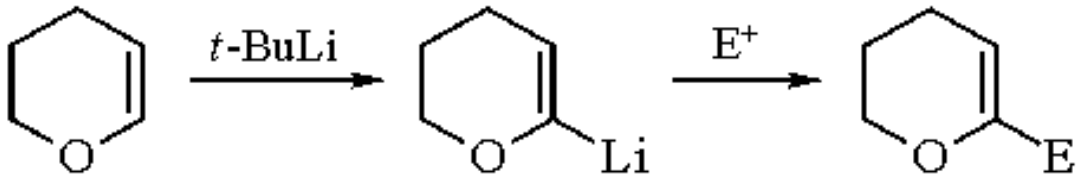

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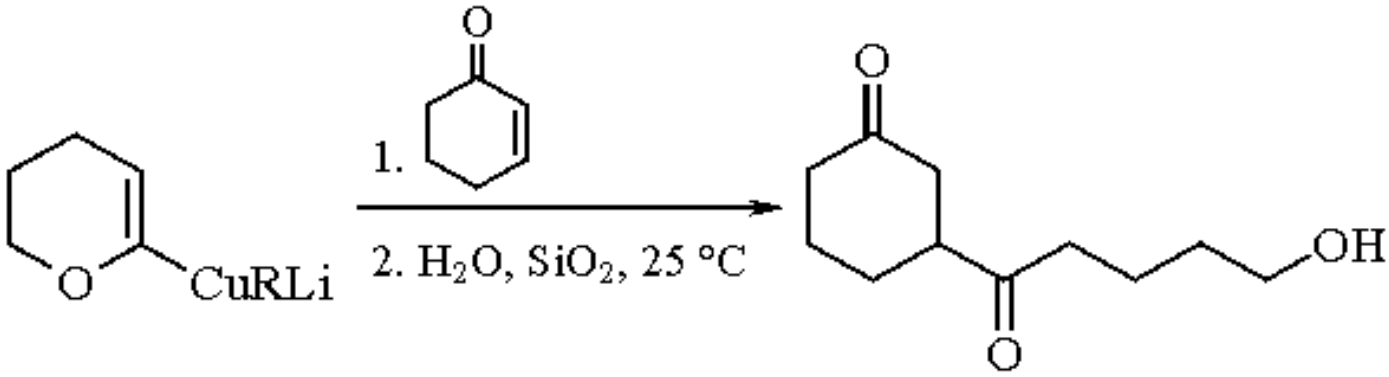

(13)

Electrophilic Addition to Dihydropyran.

Electrophilic addition of acetals and orthoesters to dihydropyran occurs in the presence of mild catalyst systems such as ***Chlorotrimethylsilane-Tin(II) Chloride*** (0 °C, 2 h, 55-84%) (eq 14).[49] The synthetic utility of the reaction is however limited by the lack of stereocontrol.

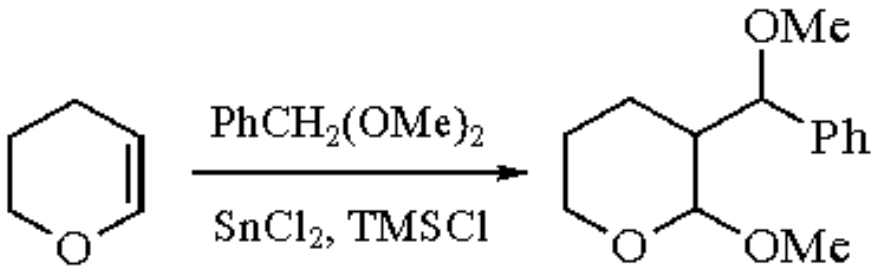

(14)

Specific Applications.

The THP protecting group has been widely applied in the field of organic synthesis and no attempt can be made to comprehensively review its use in these pages. However, several specific applications may be of interest.

Introduction of the *trans*-CH=CHCH$_2$OH moiety may be conveniently accomplished using a mixed Gilman cuprate reagent bearing a terminal THP-protected ether (eq 15).[50] The transformation is of considerable utility in several fields of synthesis, including prostaglandin chemistry.

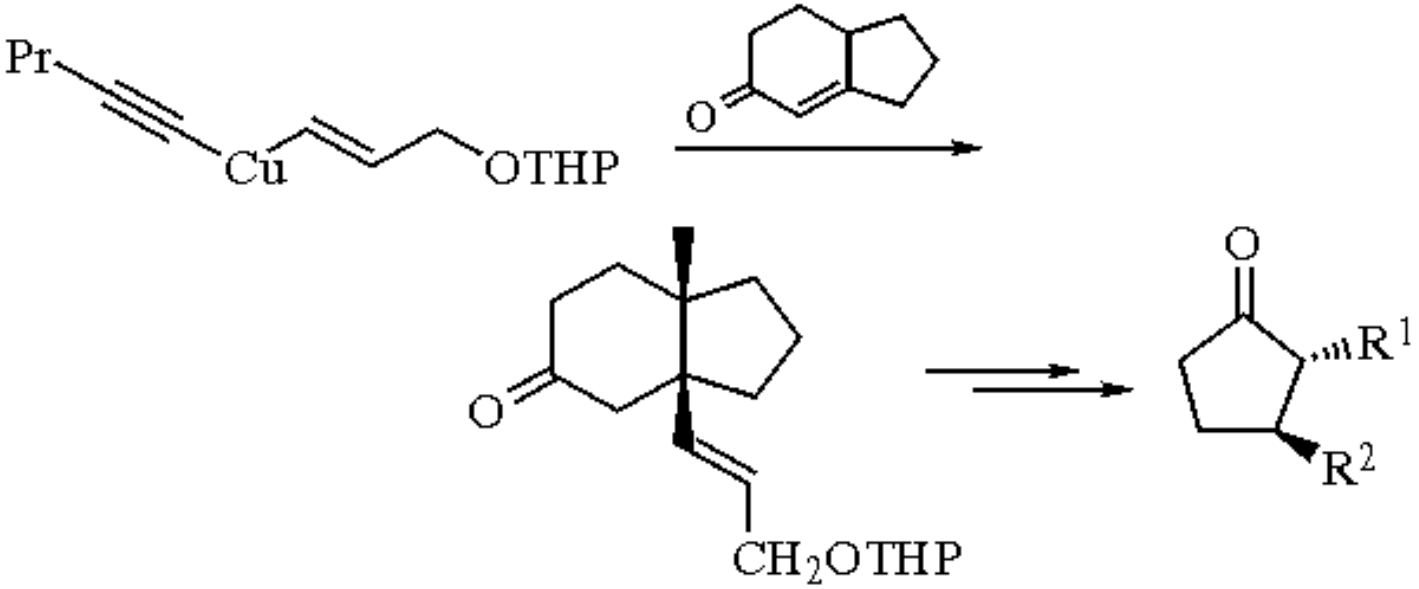

(15)

The tetrahydropyranyl derivative of propargyl alcohol, tetrahydro-2-(2-propynyloxy)-2*H*-pyran, can be converted to methyl 4-hydroxy-2-butynoate in four steps.[51] Diethyl [(2-tetrahydropyranyloxy)methyl]phosphonate is a convenient Wadsworth-Emmons reagent.[52] Tetrahydropyranyl esters of α-bromo acids can be used in the Reformatsky reaction for the preparation of β-hydroxy acids.[53] Elimination of a tetrahydropyranyloxy moiety from butyne-1,4-diols with lithium hydride constitutes an efficient method for the synthesis of allenic alcohols.[54]

Related Reagents.

2-Chloroethyl Chloromethyl Ether; ***Dimethoxymethane***; ***Ethyl Vinyl Ether***; ***p-Methoxybenzyl Chloride***; ***(p-Methoxybenzyloxy)methyl Chloride***; ***2-Methoxyethoxymethyl Chloride***.

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3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one

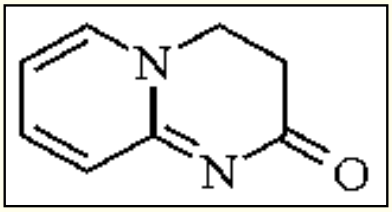

[5439-14-5] · $C_8H_8N_2O$ · 3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one · (MW 148.16)

(synthesis of esters and amides from carboxylic acids; glycosylation)

Physical Data: mp 155-156 °C; mp (HCl salt) 284-285.5 °C (dec); mp (HBr salt) 299-300 °C (dec); mp (HI salt) 263-264 °C (dec).

Solubility: sol MeOH, EtOH, H_2O.

Form Supplied in: both the free base and salts are obtained as colorless solids.

Analysis of Reagent Purity: the reagent has a betaine-like structure and behaves as a salt in terms of the reagent's solubility. The literature reports various melting points values for both the anhydrous and hydrated forms of the reagent but the conditions used to determine melting point have been shown to be critical and care must be exercised if this property is to be used as a measure of reagent purity.[1]

Preparative Methods: is prepared by reaction of 2-aminopyridine with either ***Acrylic Acid*** itself or an equivalent (2-bromo- or 2-iodopropionic acid, ***Methyl Acrylate***, ethyl 2-bromopropionate, β-***Propiolactone***).[1,2]

Purification: the free base and salts are readily recrystallized from MeOH-Et_2O.[1]

Handling, Storage, and Precautions: the reagent may be dried over P_2O_5 in vacuo (135 °C/17 mmHg).

Introduction.

The principal synthetic application of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**1**) is an acid scavenger; it is an example of a proton sponge (see ***1,8-Bis(dimethylamino)naphthalene***). The reagent has been used in the esterification and amination of alkyl and aryl carboxylic acids and also in glycosylation of 2-amino-2-deoxy sugars.

Synthesis of Esters from Carboxylic Acids.[3]

Esterification (eq 1) proceeds by activation of the carboxyl component using a 2-halopyridinium salt (**2**; X = Cl, Y = I or X = F, Y = OTs) and (**1**) (2.4 equiv) in the presence of an alcohol. The best solvents for this process are CH_2Cl_2 or MeCN, but a range of other solvents may also be used.

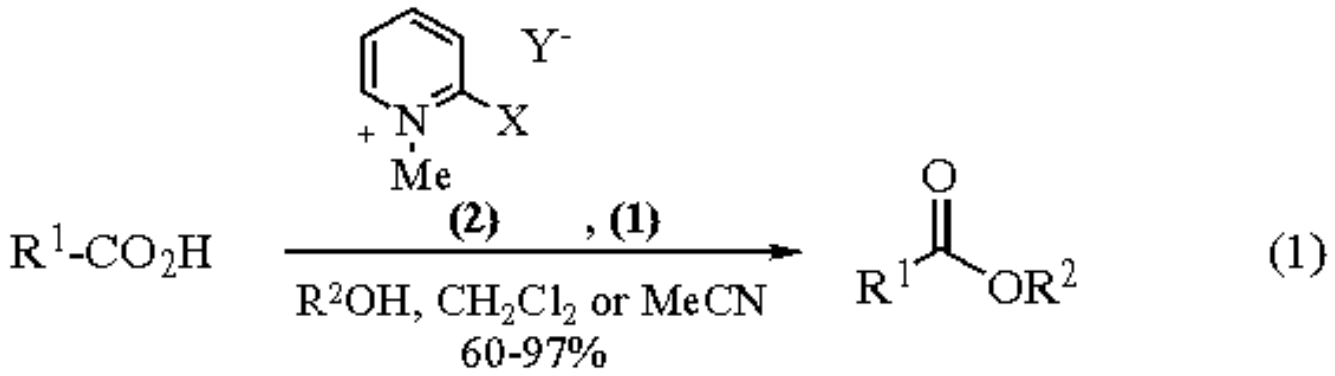

Synthesis of Amides from Carboxylic Acids.[4]

In the corresponding amidation process (eq 2) there is a requirement for the addition of 1 equiv of a tertiary amine (***Tri-n-butylamine***) to ensure efficient utilization of the amine component (R^2R^3NH). Once again, carboxyl activation is achieved using a 2-halopyridinium salt (**2**) but, unlike the esterification reaction, amidation is best carried out as a two-step one-pot process.

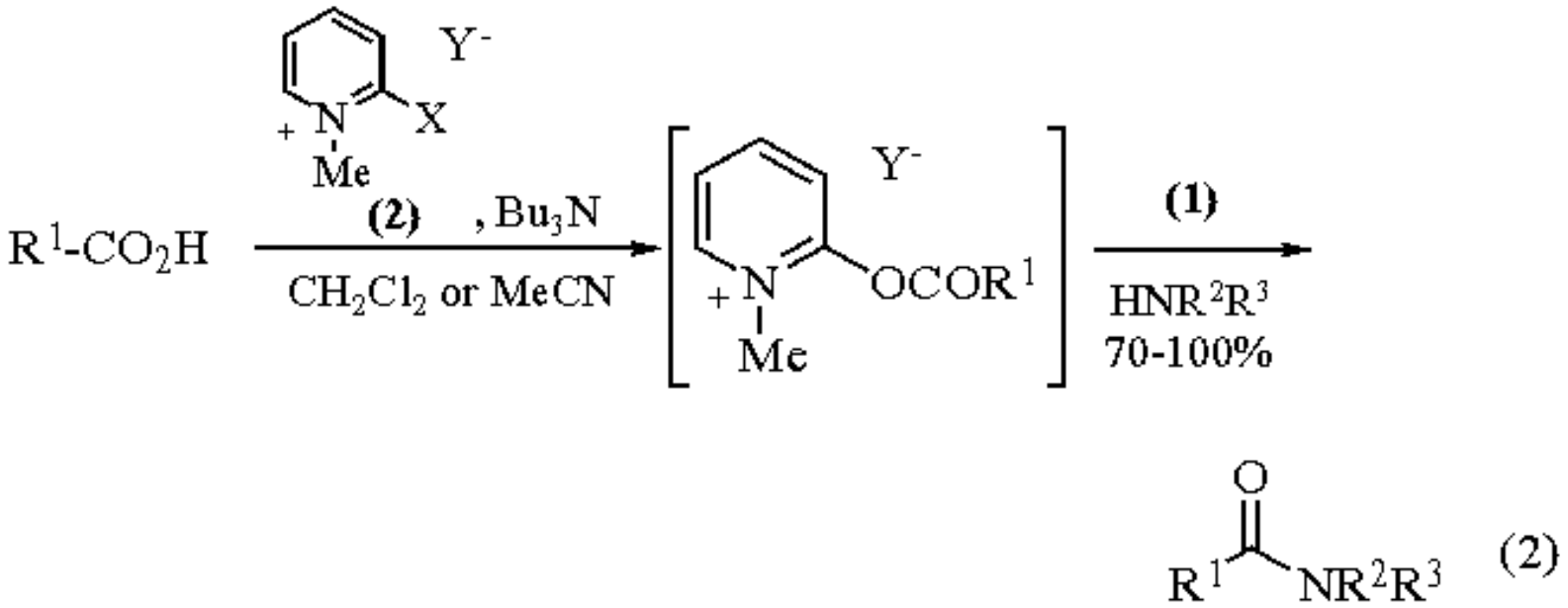

Yields for both the esterification (eq 1) and amidation (eq 2) reactions are generally high, but the advantages associated with use of (**1**) over other reagents for these types of transformation have yet to be clearly defined.

Glycosylation.[5]

3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one has been used in conjunction with ***Silver(I) Trifluoromethanesulfonate*** as a reagent combination to mediate the glycosylation of *N*-protected 2-amino-2-deoxy sugars using a glycosyl bromide as the glycosyl donor (eq 3).

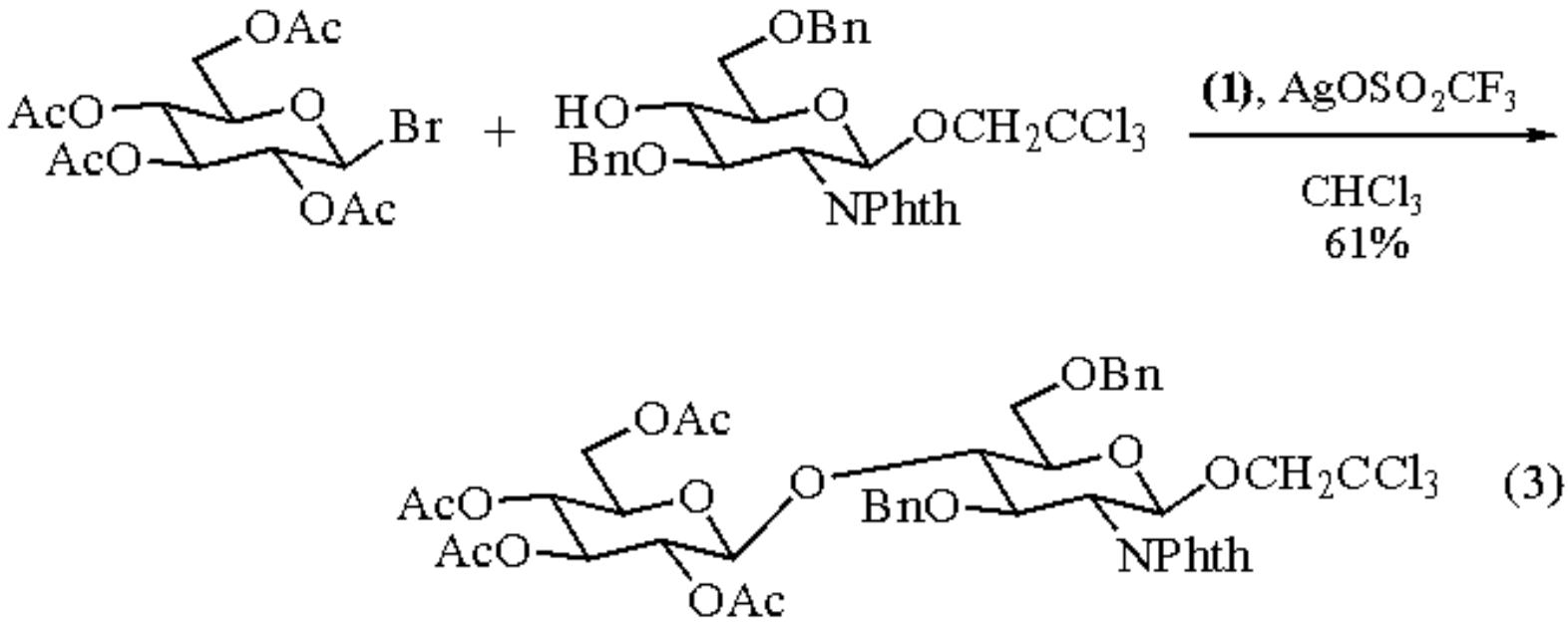

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Dihydroquinidine Acetate[1]

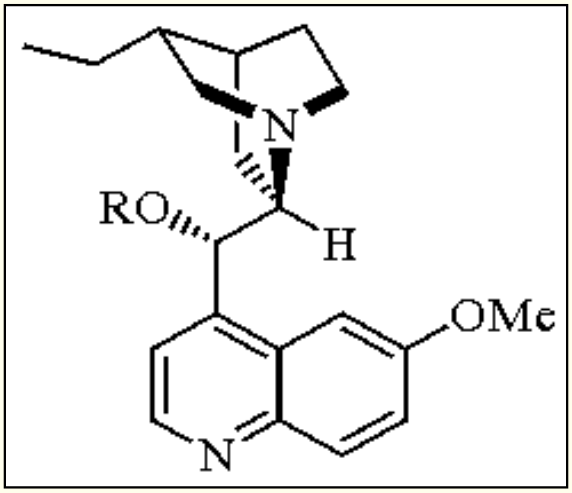

(R = Ac)

[72989-10-7] · $C_{22}H_{28}N_2O_3$ · Dihydroquinidine Acetate · (MW 368.47) (R = *p*-$ClC_6H_4C(O)$-)

[113162-02-0] · $C_{27}H_{29}ClN_2O_3$ · Dihydroquinidine *p*-Chlorobenzoate · (MW 464.99) (R = H)

[1435-55-8] · $C_{20}H_{26}N_2O_2$ · Dihydroquinidine · (MW 326.44)

(asymmetric dihydroxylation;[2] conjugate additions;[3] carbonyl additions[3])

Alternate Name: DHQD-Ac.

Physical Data: *p*-$ClC_6H_4C(O)$-: mp 102-105 °C; $[\alpha]_D$ -73° (*c* = 1, EtOH).

Solubility: *p*-$ClC_6H_4C(O)$-: sol CH_2Cl_2, Et_2O, EtOH, EtOAc.

Form Supplied in: the *p*-chlorobenzoate is available as a white foam.

Preparative Methods: the acetate is prepared from dihydroquinidine[4] and the *p*-chlorobenzoate is commercially available. The phthalazine-derived bis(dihydroquinidine) ligand is commercially available.[5] A formulation of the standard reactants for the asymmetric dihydroxylation (AD-mix-β) on the small scale has been developed and is commercially available.[6] AD-mix-β (1 kg) consists of potassium osmate (0.52 g), the phthalazine-derived ligand (5.52 g), $K_3Fe(CN)_6$ (700 g), and powdered K_2CO_3 (294 g).

Purification: the recovery of dihydroquinidine *p*-chlorobenzoate after a dihydroxylation reaction is accomplished in the following manner:[7] the crude dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) is dissolved in ether, cooled to 0 °C, and HCl gas is bubbled into the solution until a pH of 1-2 is obtained using wet pH paper. The pale yellow precipitate of the hydrochloride salt is collected by filtration and dried under high vacuum (0.01

mmHg). The free base is liberated by suspending the salt in EtOAc, cooling the heterogeneous mixture to 0 °C, and adding 28% NH_4OH (or 15% NaOH) until a pH = 11 is obtained. After separation, the aqueous layer is extracted with portions of EtOAc, the combined organic layers are dried over Na_2SO_4, and the solvent removed in vacuo to give the pure DHQD-CLB as a white foam.

Handling, Storage, and Precautions: toxic; use in a fume hood.

Chiral Ligand for the Asymmetric Dihydroxylation of Alkenes.

Dihydroquinidine acetate (DHQD-Ac) was found to be one of the first efficient cinchona-derived chiral ligands for the asymmetric dihydroxylation reaction of substituted alkenes.[8] For example, styrene could be dihydroxylated in 61% ee (62% yield) using a mixture of 1.1 equiv of DHQD-Ac and 1.1 equiv of ***Osmium Tetroxide*** in toluene. An osmium-catalyzed asymmetric process, in which the co-oxidant is ***N-Methylmorpholine N-Oxide*** (NMO) and the chiral ligand is DHQD-CLB, was described later.[9] The other enantiomer of the diol could also be obtained by using the analogous dihydroquinine ester (***Dihydroquinine Acetate***), which acts as a pseudoenantiomer of the dihydroquinidine ester. Significant increases in the level of asymmetric induction of the dihydroxylation were later observed if the re-oxidant NMO was replaced by potassium hexacyanoferrate(III) ($K_3Fe(CN)_6$) (eq 1).[10]

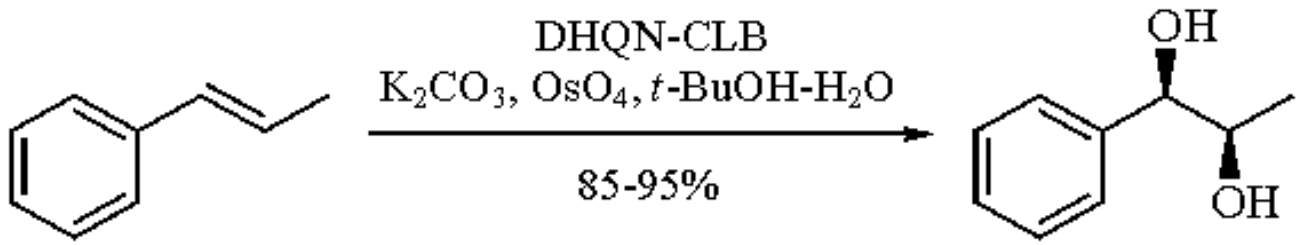

(1)

NMO (slow addition)	86% ee
NMO (no slow addition)	65% ee
$K_3Fe(CN)_6$	91% ee

The nature of the group attached to the 9-*O* position of dihydroquinidine was found to have a profound impact on the level of stereochemical induction in these reactions and a variety of new ligands have been developed (see **1**-**5**).[11]

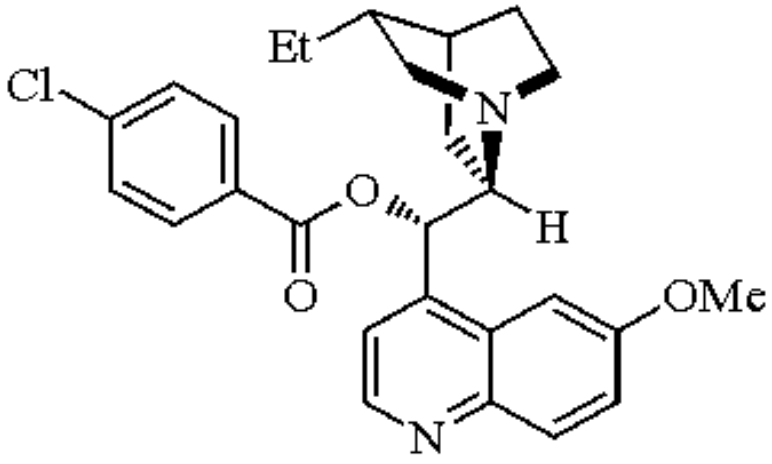

(1)
DHQD-CLB

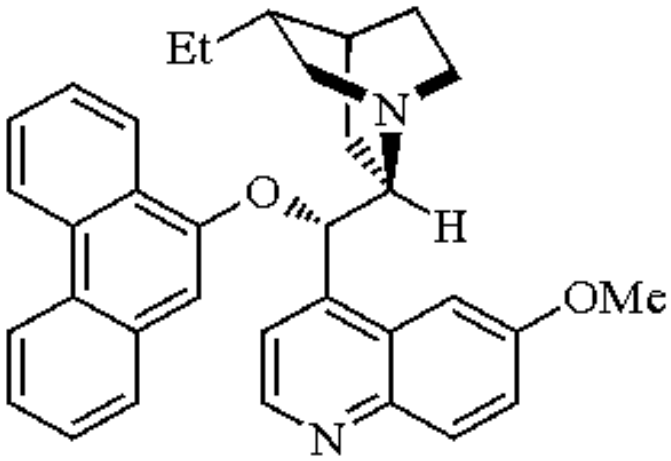

(2)
DHQD-PHN

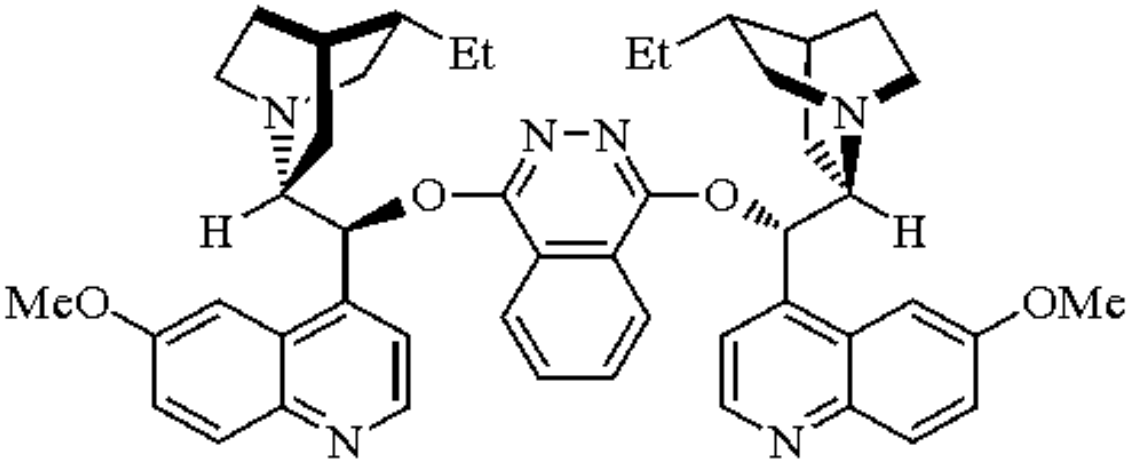

(3)
$(DHQD)_2$-PHAL
ligand used in AD-mix-β

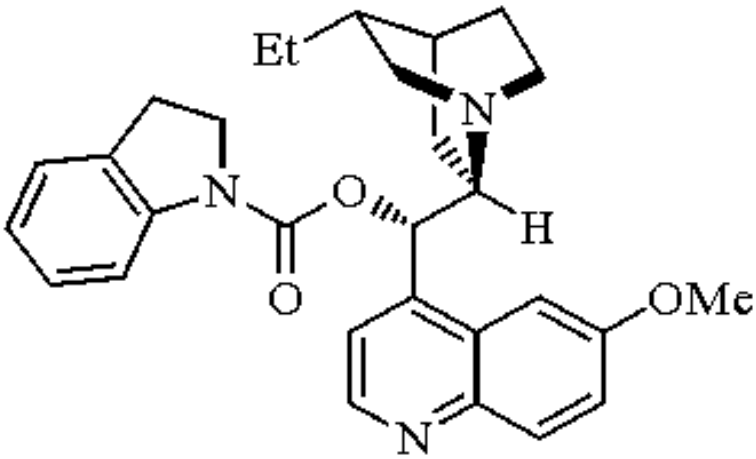

(4)

(4)
DHQD-IND

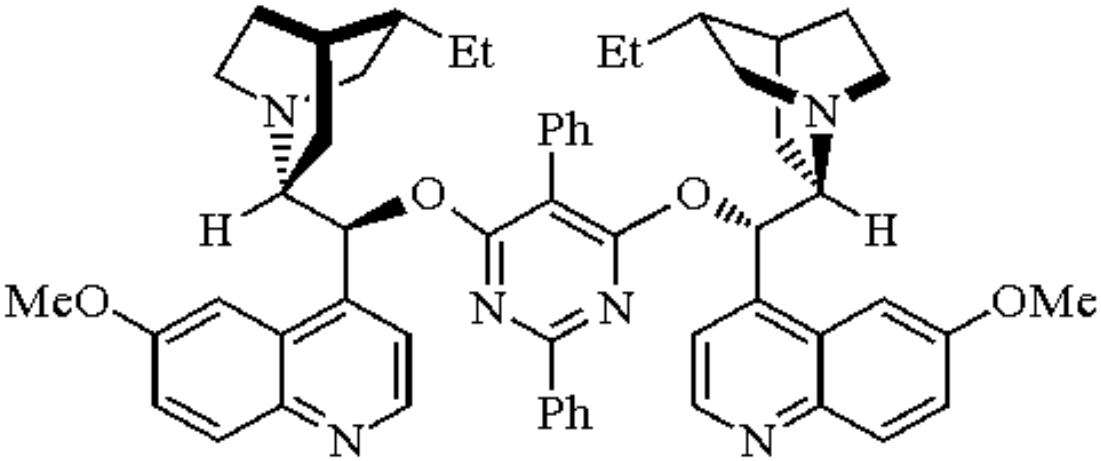

(5)
$(DHQD)_2$-PYR

The phthalazide bis(cinchona) derivatives [$(DHQD)_2$-PHAL][5,6,12] are the best ligands for the asymmetric dihydroxylation of *trans*, 1,1-disubstituted,[13] and trisubstituted alkenes, enol ethers,[14] α,β-unsaturated ketones,[15] and α,β- and β,γ-unsaturated esters,[16] whereas the DHQD-IND ligand[17] turns out to be superior for *cis*-alkenes (Table 1). The bis(cinchona) alkaloid-substituted pyrimidine ligand was found to be the best for monosubstituted terminal alkenes.[18] The addition of ***Methanesulfonamide*** to enhance the rate of osmate(VI) ester hydrolysis is recommended for all nonterminal alkenes.

Table 1 Alkenes Dihydroxylated using DHQD Ligands

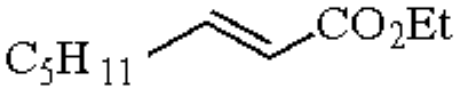 (DHQD)$_2$-PHAL 99% ee	(DHQD)$_2$-PHAL 97% ee	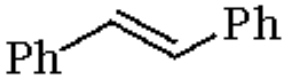 (DHQD)$_2$-PHAL >99.5% ee
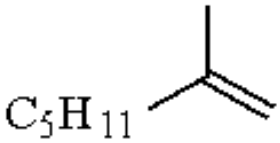 (DHQD)$_2$-PHAL 78% ee	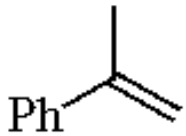 (DHQD)$_2$-PHAL 94% ee	(DHQD)$_2$-PHAL 97% ee
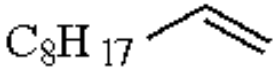 (DHQD)$_2$-PHAL 84% ee (DHQD)$_2$-PYR 89% ee	(DHQD)$_2$-PHAL 77% ee	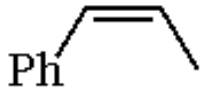 DHQD-IND 72% ee
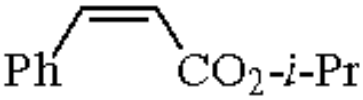 DHQD-IND 80% ee	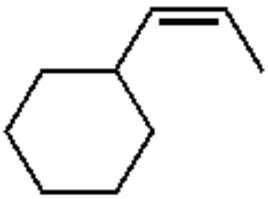 DHQD-IND 56% ee	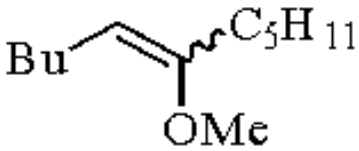 (DHQD)2-PHAL 95% ee
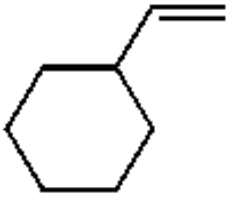 (DHQD)$_2$-PHAL 88% ee (DHQD)$_2$-PYR 96% ee	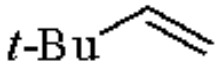 (DHQD)$_2$-PHAL 64% ee (DHQD)$_2$-PYR 92% ee	

Asymmetric dihydroxylation of substituted aryl allyl ethers also proceeds with high enantioselectivities (89-95% ee) providing that there are no *ortho* substituents on the aryl group.[19] Dienes,[20] polyenes,[21] and enynes[22] can also be regioselectively dihydroxylated (eqs 2-5). In some cases, such as in the asymmetric dihydroxylation of α,β- and β,γ-unsaturated amides,[23] the amount of ligand and potassium osmate in the AD-mix content has to be increased fivefold to achieve good catalytic turnover rates.

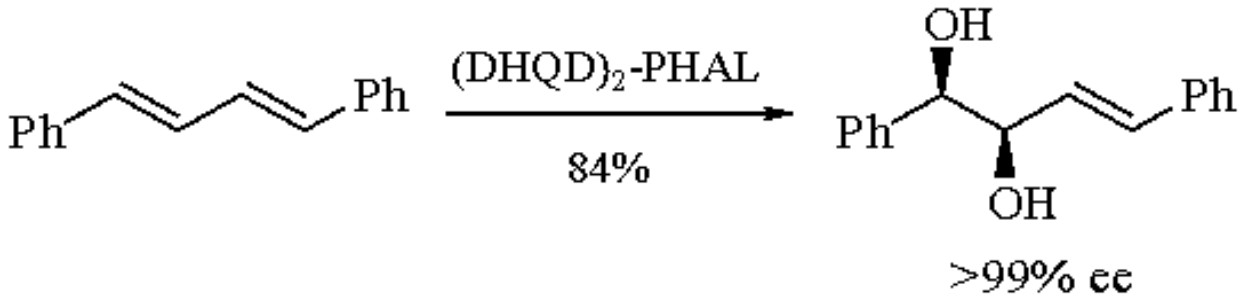

(2)

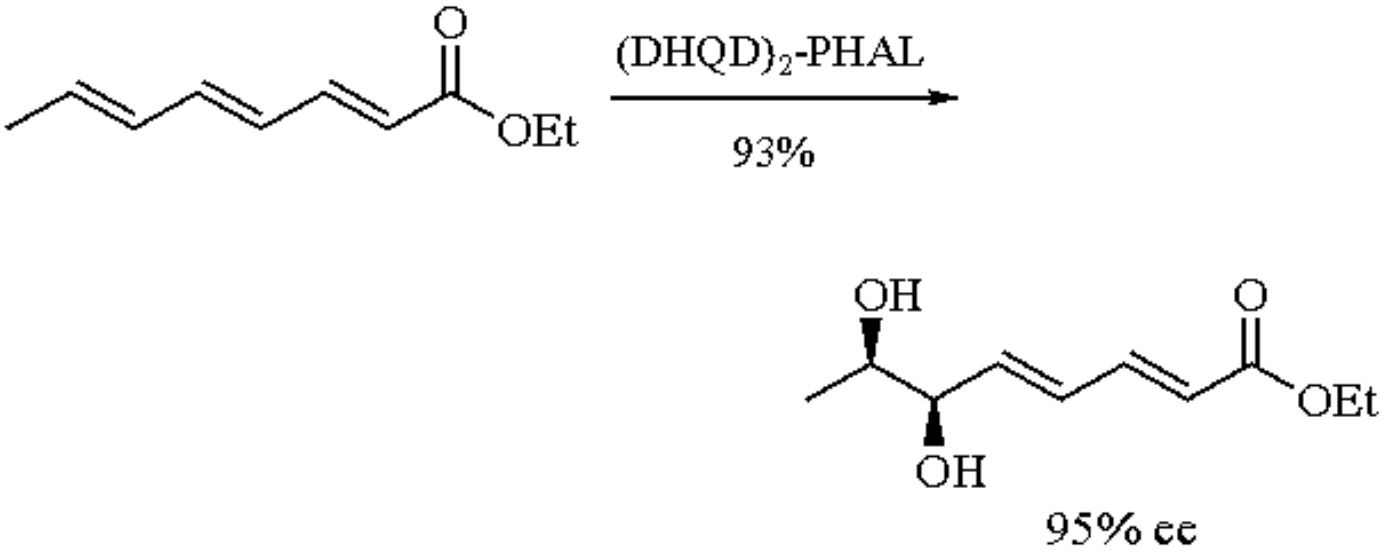

(3)

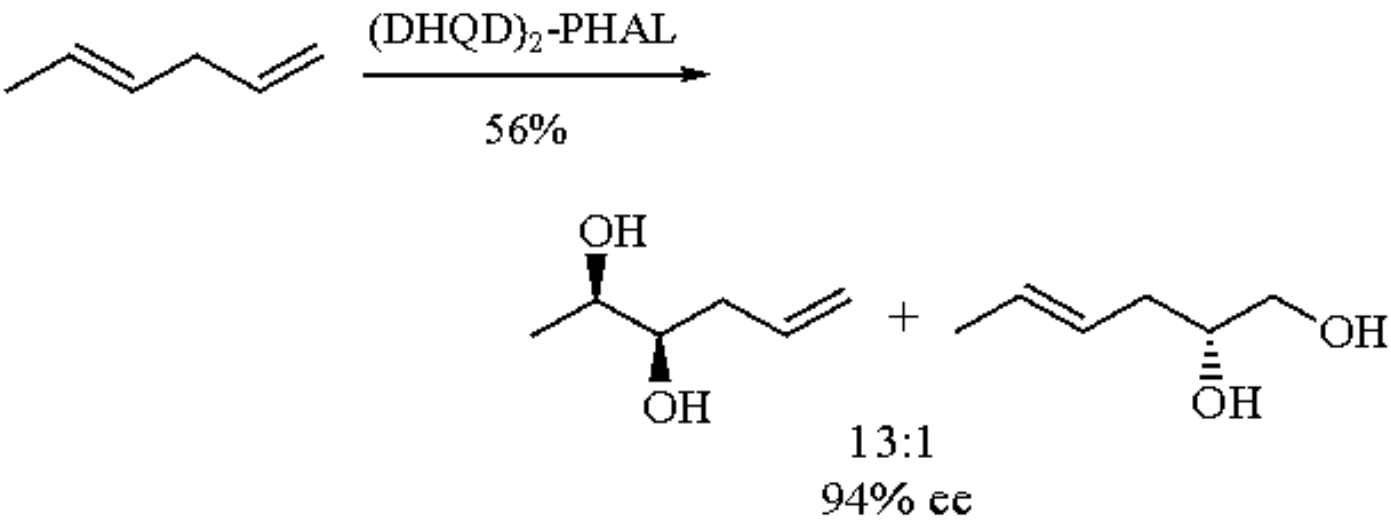

(4)

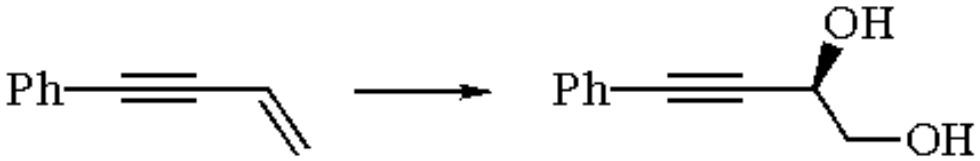

(5)

$(DHQD)_2$-PHAL 73% ee
DHQD-PHN 53% ee

The prediction of the absolute stereochemistry of the predominant enantiomer obtained is provided by the model shown in Scheme 1.

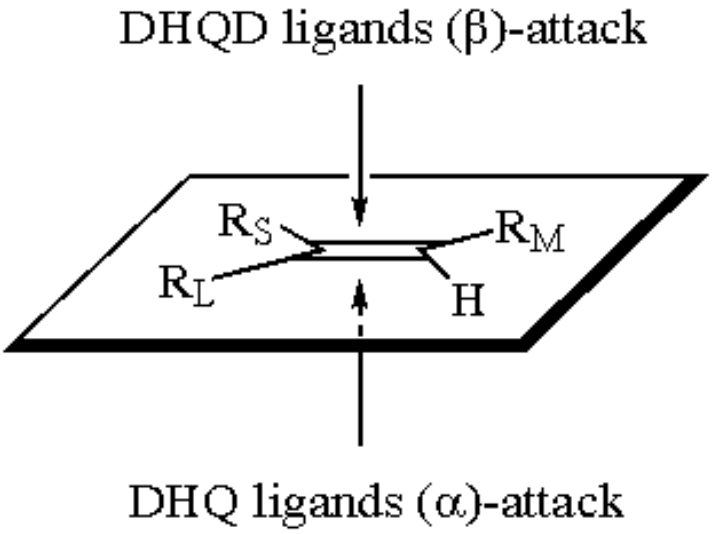

Scheme 1

By employing polymer-bound alkaloid derivatives, heterogeneous catalytic asymmetric dihydroxylation has been achieved with good to excellent enantioselectivities in the dihydroxylation of *trans*-stilbene.[24] These polymers can be recovered and reused while both the yields and the optical purities of diols were maintained.

Double Diastereoselection in the Dihydroxylation Reaction.

The dihydroxylation reaction of chiral nonracemic substrates using the cinchona-derived ligand leads to a matched and mismatched pair (eq 6).[25] Kinetic resolution of several racemic secondary alcohols has also been examined.[26]

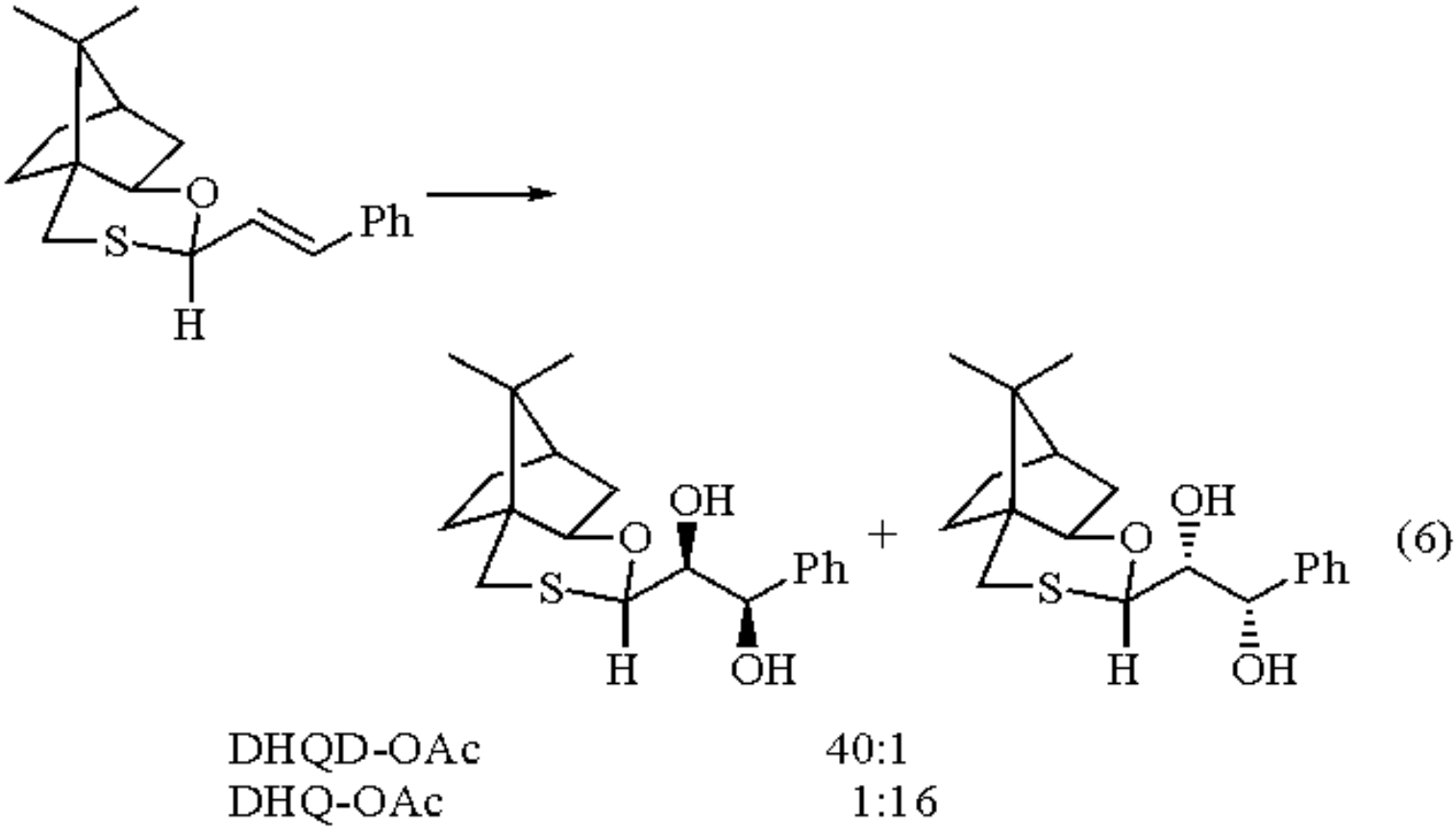

Additional examples of asymmetric dihydroxylation are provided under the entry for ***Dihydroquinine Acetate***.

Chiral Ligand for other Stereoselective Reactions.[1]

The effect of the addition of dihydroquinidine-derived alkaloids on the product enantioselectivity has also been investigated in the addition reaction of ***Diethylzinc*** to aldehydes,[27] in the addition of aromatic thiols to conjugated cycloalkenones,[28] and in the heterogeneous hydrohalogenation of α,α-dichlorobenzazepinone-2.[29] In these cases, the dihydroquinidine derivatives were not the optimal ligands.

---

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2. (a) Lohray, B. B. *TA* **1992**, *3*, 1317. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *CRV* **1994**, *94*, 2483.
3. Blaser, H.-U. *CRV* **1992**, *92*, 935.
4. (a) Rabe, P.; Huntenburg, W.; Schultze, A.; Volger, G. *CB* **1931**, *64*, 2487. (b) Hesse, O. *LA* **1882**, *214*, 1. (c) Hesse, O. *LA* **1887**, *241*, 255.
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13. Wang, Z.-M.; Sharpless, K. B. *SL* **1993**, 603.
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17. Wang, L.; Sharpless, K. B. *JACS* **1992**, *114*, 7568.
18. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *JOC* **1993**, *58*, 3785.
19. Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *TL* **1993**, *34*, 2267.
20. Xu, D.; Crispino, G. A.; Sharpless, K. B. *JACS* **1992**, *114*, 7570.
21. Crispino, G. A.; Sharpless, K. B. *TL* **1992**, *33*, 4273.
22. Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *TL* **1992**, *33*, 3833.
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Dihydroquinine Acetate[1]

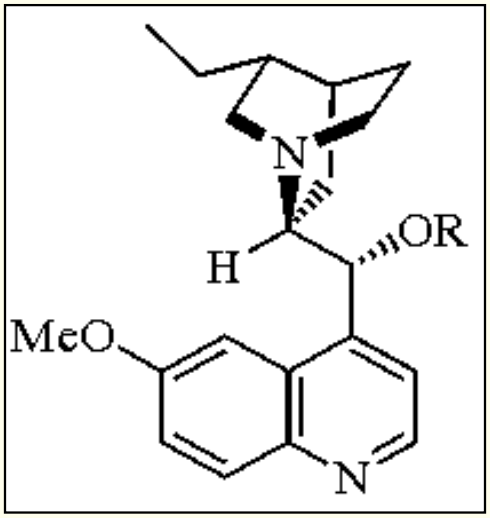

(R = Ac)

[75917-54-3] · $C_{22}H_{28}N_2O_3$ · Dihydroquinine Acetate · (MW 368.47) (R = *p*-$ClC_6H_4C(O)$-)

[113162-88-9] · $C_{27}H_{29}ClN_2O_3$ · Dihydroquinine *p*-Chlorobenzoate · (MW 464.99) (R = H)

[522-66-7] · $C_{20}H_{26}N_2O_2$ · Dihydroquinine · (MW 326.44)

(asymmetric dihydroxylation;[2] conjugate additions;[3] carbonyl additions[3])

Alternate Name: DHQ-Ac.

Physical Data: *p*-$ClC_6H_4C(O)$-: mp 130-133 °C; $[\alpha]_D$ +150° (*c* = 1, EtOH).

Solubility: *p*-$ClC_6H_4C(O)$-: sol CH_2Cl_2, Et_2O, EtOH, EtOAc.

Form Supplied in: the *p*-chlorobenzoate is available as a white foam.

Preparative Methods: the acetate is prepared from dihydroquinine[4] and the *p*-chlorobenzoate is commercially available. The phthalazine-derived bis(dihydroquinine) ligand is commercially available.[5] A formulation of the standard reactants for the asymmetric dihydroxylation (AD-mix-α) on the small scale has been developed and is commercially available.[6] AD-mix-α (1 kg) consists of potassium osmate (0.52 g), the phthalazine-derived ligand (5.52 g), $K_3Fe(CN)_6$ (700 g), and powdered K_2CO_3 (294 g).

Purification: dihydroquinine *p*-chlorobenzoate is recovered after a dihydroxylation reaction using the same method as that described for ***Dihydroquinidine Acetate***.

Handling, Storage, and Precautions: toxic; use in a fume hood.

Chiral Ligand for the Asymmetric Dihydroxylation of Alkenes.

Dihydroquinine-derived chiral ligands have been used as pseudoenantiomers of the dihydroquinidine analog in the catalytic asymmetric dihydroxylation of alkenes. In general, the enantioselectivities with these ligands are as good as or slightly lower than those obtained with the dihydroquinidine ligand. For example, styrene could be dihydroxylated in 62% ee using a mixture of dihydroquinidine *p*-chlorobenzoate (DHQD-CLB, 0.13 equiv), ***Osmium Tetroxide*** (0.13 equiv), and ***N-Methylmorpholine N-Oxide***, whereas the analogous reaction with dihydroquinine *p*-chlorobenzoate produced the diol of opposite absolute stereochemistry in 54% ee.[7]

As in the dihydroquinidine series, the phthalazide cinchona derivative [$(DHQ)_2$-PHAL] (**1**)[6] is the best ligand for the asymmetric dihydroxylation of terminal, *trans*, 1,1-disubstituted, and trisubstituted alkenes, and enol ether,[8] whereas the DHQ-IND ligand (**2**)[9] turns out to be superior for *cis*-alkenes (Table 1). The addition of ***Methanesulfonamide*** to enhance the rate of osmate(VI) ester hydrolysis is recommended for all nonterminal alkenes.

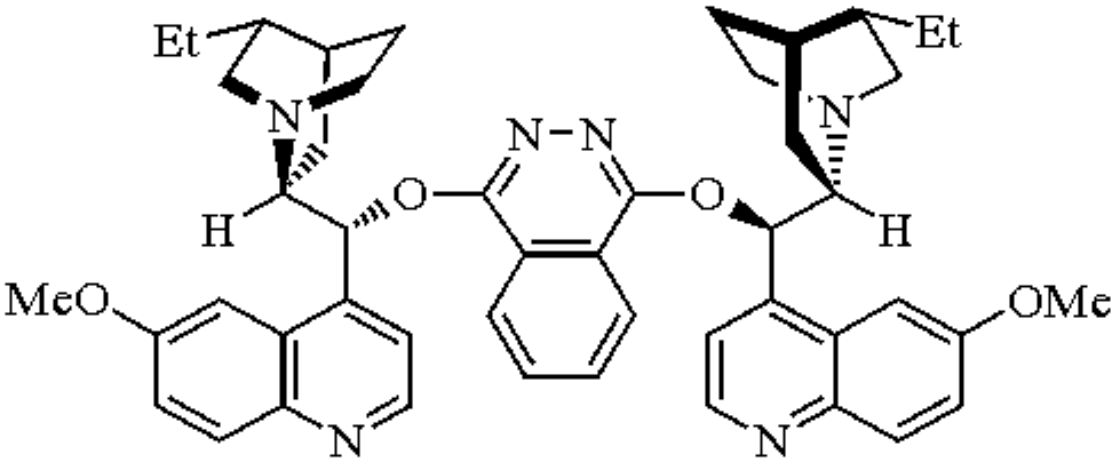

(1)
$(DHQ)_2$-PHAL
(ligand used in AD-mix-α)

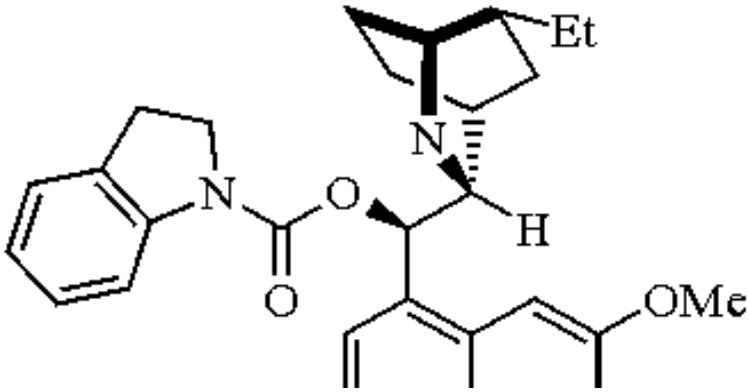

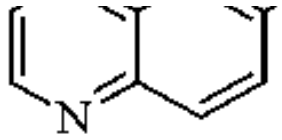

(2)
DHQ-IND

Table 1 Alkenes Dihydroxylated using DHQ Ligands

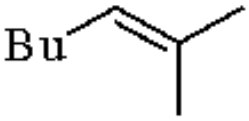	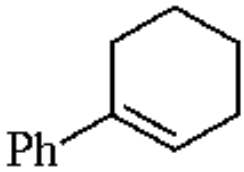	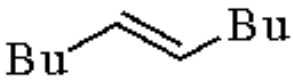
$(DHQD)_2$-PHAL 98% ee $(DHQ)_2$-PHAL 95% ee	$(DHQD)_2$-PHAL 99% ee $(DHQ)_2$-PHAL 97% ee	$(DHQD)_2$-PHAL 97% ee $(DHQ)_2$-PHAL 93% ee
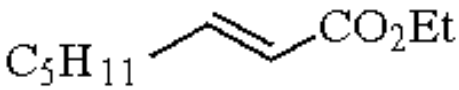	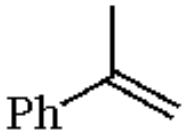	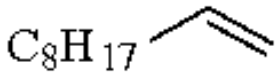
$(DHQD)_2$-PHAL 99% ee $(DHQ)_2$-PHAL 96% ee	$(DHQD)_2$-PHAL 94% ee $(DHQ)_2$-PHAL 93% ee	$(DHQD)_2$-PHAL 84% ee $(DHQ)_2$-PHAL 80% ee
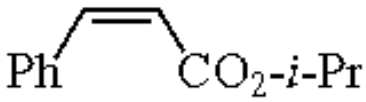	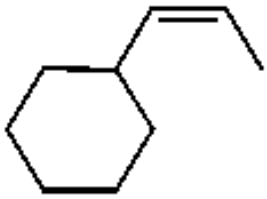	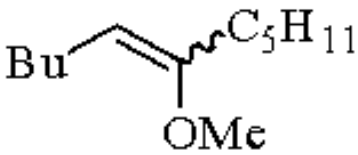
DHQD-IND 80% ee DHQ-IND 72% ee	DHQD-IND 56% ee DHQ-IND 44% ee	$(DHQD)_2$-PHAL 95% ee $(DHQ)_2$-PHAL 96% ee

For additional examples of regioselective asymmetric dihydroxylations, see ***Dihydroquinidine Acetate***.

Double Diastereoselection in the Dihydroxylation Reaction.

The dihydroxylation reaction of chiral nonracemic substrates using the cinchona-derived ligand leads to a matched and mismatched pair.[10] The dihydroquinine-derived ligand was found to be superior to its pseudoenantiomer in the dihydroxylation of carbohydrate derivatives (eq 1).[11]

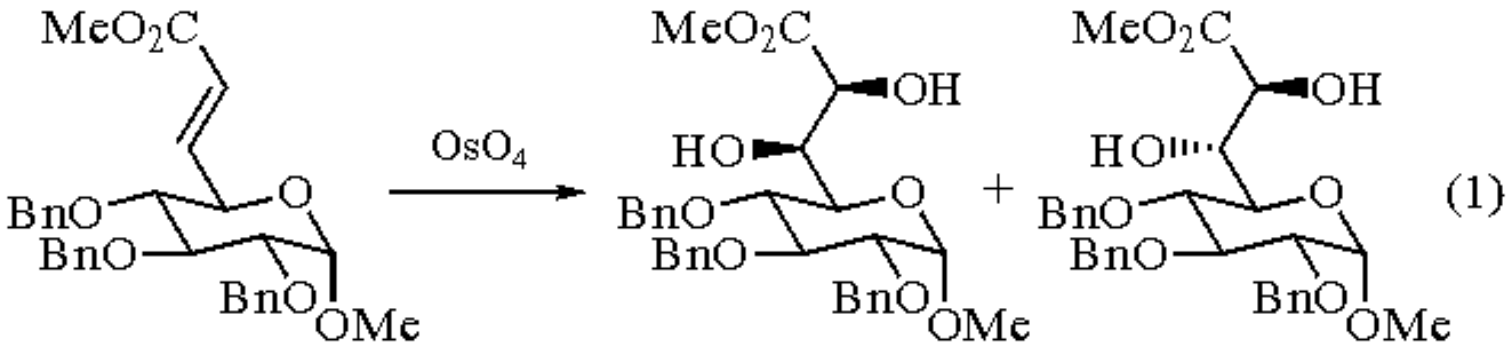

DHQH-CLB	1.3:1
DHQ-CLB	20.5:1
No ligand	10.3:1

For additional examples and an extensive discussion on the use of these ligands in asymmetric dihydroxylation reactions, see ***Dihydroquinidine Acetate***.

Chiral Ligand for Other Stereoselective Reactions.

The effect of the addition of dihydroquinine-derived alkaloids on the product enantioselectivity has also been investigated in the addition reaction of ***Diethylzinc*** to aldehydes,[12] in the addition of aromatic thiols to conjugated cycloalkenones,[13] and in the heterogeneous hydrohalogenation of α,α-dichlorobenzazepinone-2.[14]

---

1. Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
2. (a) Lohray, B. B. *TA* **1992**, *3*, 1317. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *CRV* **1994**, *94*, 2483.
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4. (a) Rabe, P.; Huntenburg, W.; Schultze, A.; Volger, G. *CB* **1931**, *64B*, 2487. (b) Hesse, O. *LA* **1882**, *214*, 1. (c) Hesse, O. *LA* **1887**, *241*, 255.
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Dihydridotetrakis(triphenylphosphine)ruthenium(II)

$(Ph_3P)_4RuH_2$

[19529-00-1] · $C_{72}H_{62}P_4Ru$ · Dihydridotetrakis(triphenylphosphine)ruthenium(II) · (MW 1152.26)

(catalyst for hydration of nitriles,[3] isomerization of alkynes,[5,6] Knoevenagel reactions and conjugate additions,[8] and transfer hydrogenation[9])

Physical Data: light yellow dimagnetic solid, mp 180 °C.

Solubility: slightly sol benzene, toluene, THF.

Preparative Methods: prepared from ***Ruthenium(III) Chloride*** or ruthenium(III) acetylacetonate by reduction with ***Triethylaluminum*** in the presence of ***Triphenylphosphine*** in THF or benzene under nitrogen at room temperature.[1] The complex can also be prepared by reaction of ***Dichlorotris(triphenylphosphine)ruthenium(II)*** with ***Sodium Borohydride*** and triphenylphosphine.[2]

Purification: recrystallization from benzene, toluene, or THF.

Handling, Storage, and Precautions: is air and light sensitive and should be stored under argon in the dark.

Amide Synthesis.

The hydration of nitriles with two equivalents of water in the presence of the title reagent (**1**) as catalyst gives the corresponding amide in good yields (eq 1).[3] This reaction has been used in the transformation of δ-ketonitriles to ene-lactams (eq 2). The ruthenium reagent also catalyzes reactions of amines with nitriles in aqueous medium at 160 °C to give amides in 75-95% yield (eq 3).[4] This process has been extended to the preparation of polyamides.

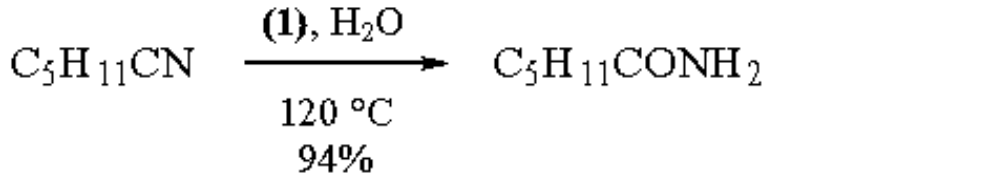

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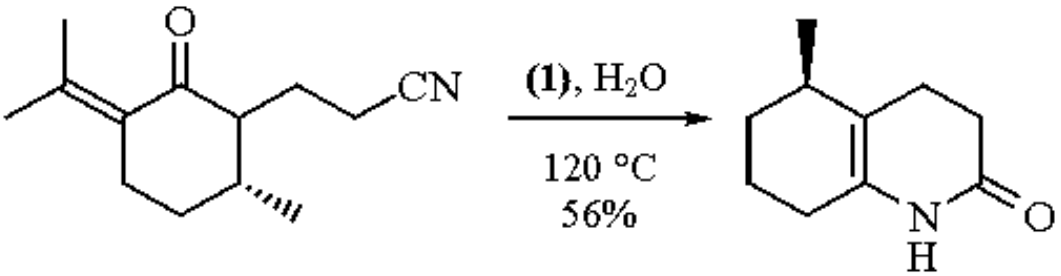

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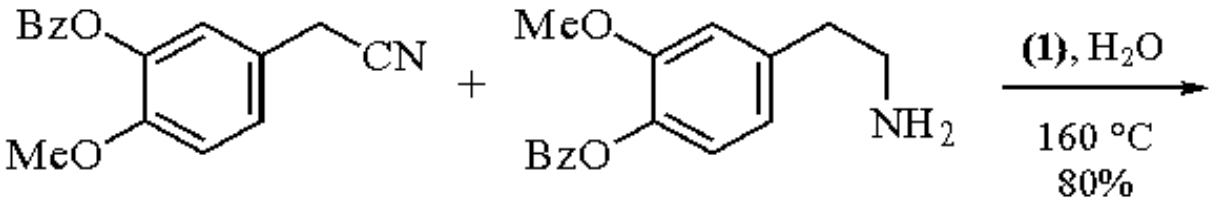

(3)

Isomerization of Alkynes to Conjugated Dienes.

(*E*,*E*)-α,β,γ,δ-Dienones can be prepared stereoselectively from their corresponding α,β-unsaturated alkynyl ketones using the title reagent (**1**) as catalyst in a single step in good yields (eq 4).[5] Other routes used to synthesize these compounds include the Horner-Wadsworth-Emmons reaction and the Knoevenagel condensation, which involve multiple steps and strong basic conditions and may provide isomeric mixtures of products. Aryl α,β-unsaturated alkynyl ketones rearrange more readily than alkyl α,β-unsaturated alkynyl ketones. Similarly, α,β-unsaturated alkynyl esters rearrange stereoselectively to the corresponding (2*E*,4*E*)-dienoic esters in the presence of (**1**) (eq 5).[6] Inclusion of ***Tri-n-butylphosphine*** improves the yield of the reaction. This transformation has been extended to the preparation of o-alkoxy-(2*E*,4*E*)-dienoates, o-oxo-(2*E*,4*E*)-dienoates, and δ-oxo-α,β,γ,δ-dienones.[7]

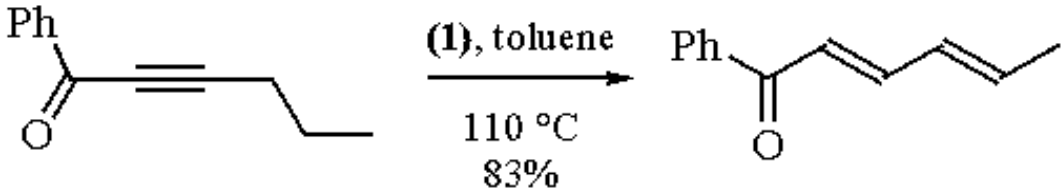

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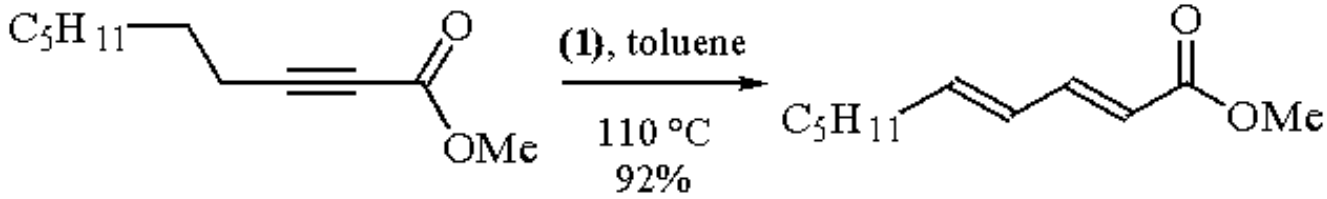

(5)

Aldol and Michael Reactions of Activated Nitriles.[8]

Nitriles react with aldehydes or ketones in the presence of (**1**) to give the corresponding α,β-unsaturated nitriles (eq 6). Michael addition of nitriles to α,β-unsaturated carbonyl compounds proceeds smoothly in the presence of (**1**) at rt under neutral conditions with high diastereoselectivity (eq 7). None of the corresponding aldol products is formed in the reaction.

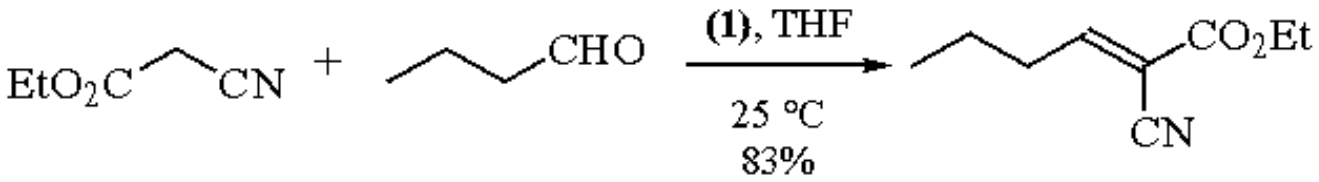

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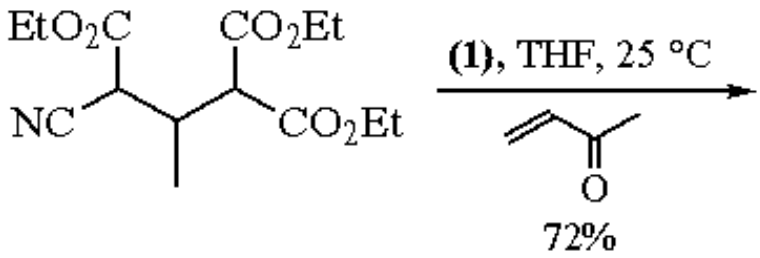

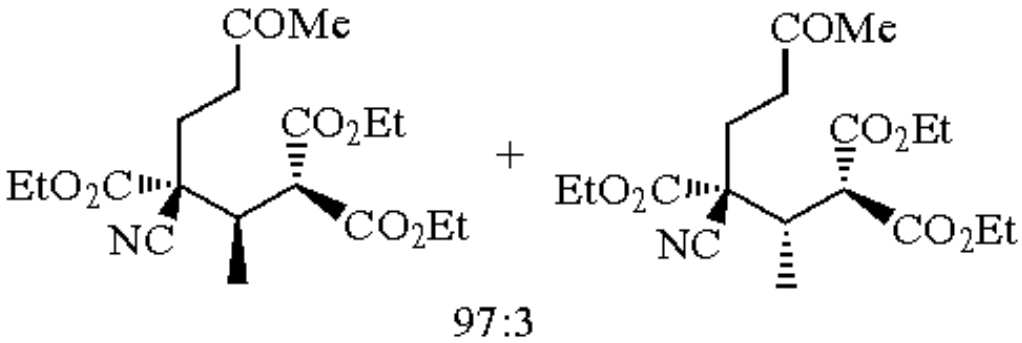

(7)

Transfer Hydrogenation of Aldehydes and Ketones.[9]

The title reagent (**1**) has been used as a catalyst in the transfer of hydrogen from alcohols, such as isopropanol, cyclohexanol, and benzyl alcohol, and ethers, such as 2,5-dihydrofuran, to aldehydes and ketones in excellent yields (eq 8).

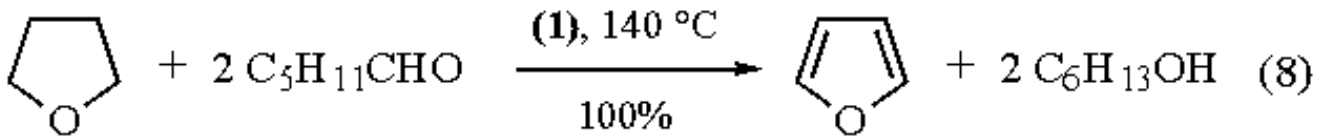

(8)

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5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4*H*)-oxazine[1]

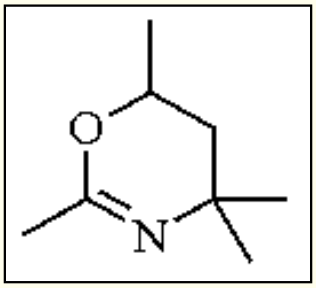

[26939-18-4] · $C_8H_{15}NO$ · 5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4*H*)-oxazine · (MW 141.21)

(α-carbanion serves as acetate or acetaldehyde enolate equivalent for synthesis of α,β-unsaturated aldehydes, aliphatic aldehydes, α-amino ketones, unsymmetrical ketones, and substituted carboxylic acids)

Physical Data: bp 47-49 °C/17 mmHg.

Preparative Method: prepared by the acid-catalyzed condensation of ***Acetonitrile*** and 2-methyl-2,4-pentanediol in 65% yield (eq 1).[2]

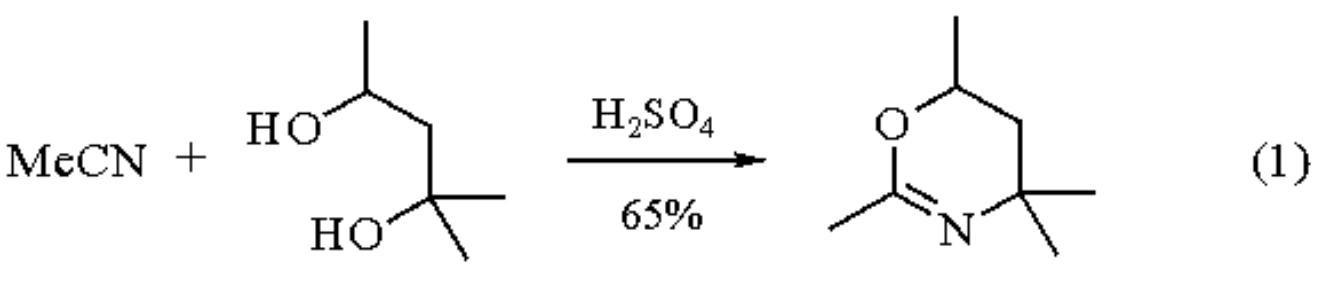

Handling, Storage, and Precautions: no special precautions required; this reagent can be stored for months at rt under an inert atmosphere.

Synthetic Utility.

The lithio anion, or the potassio anion generated using ***Potassium-Graphite***,[3] of this reagent can be alkylated with a variety of electrophiles to form α-substituted oxazines.[2] Reduction of the oxazine with ***Sodium Borohydride*** followed by hydrolysis with ***Oxalic Acid*** affords the corresponding aldehyde. However, the oxazine could not be hydrolyzed by this procedure when the electrophile was a nitrile or ester.[4] Thus aliphatic aldehydes can be readily prepared via this protocol (isolation of the intermediates is not necessary) (eq 2, Table 1).[2,5] By substituting $NaBD_4$ or $NaBT_4$ for $NaBH_4$ in the reduction, the corresponding C_1 deuterated and tritiated aldehydes are obtained.[6]

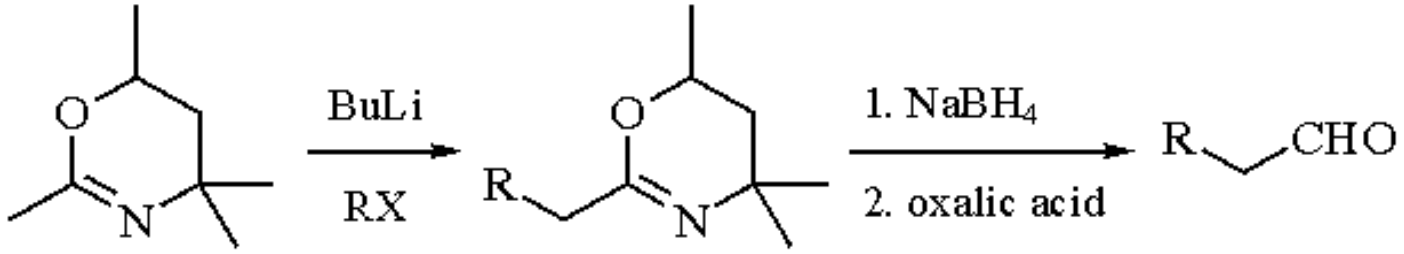

(2)

Table 1 Aldehydes via Eq 2

Electrophile	Aldehyde	Yield (%)
		65
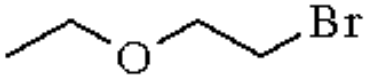		54
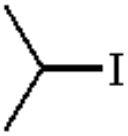	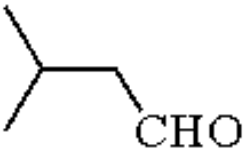	47

Retreatment of the initially alkylated oxazine with ***t-Butyllithium*** and alkylation with a second electrophile forms, after reduction and hydrolysis, α,α-disubstituted aldehydes. Cycloalkanecarbaldehydes are produced by α,α-dialkylation with 1,*n*-dihalides (eq 3).[2,7]

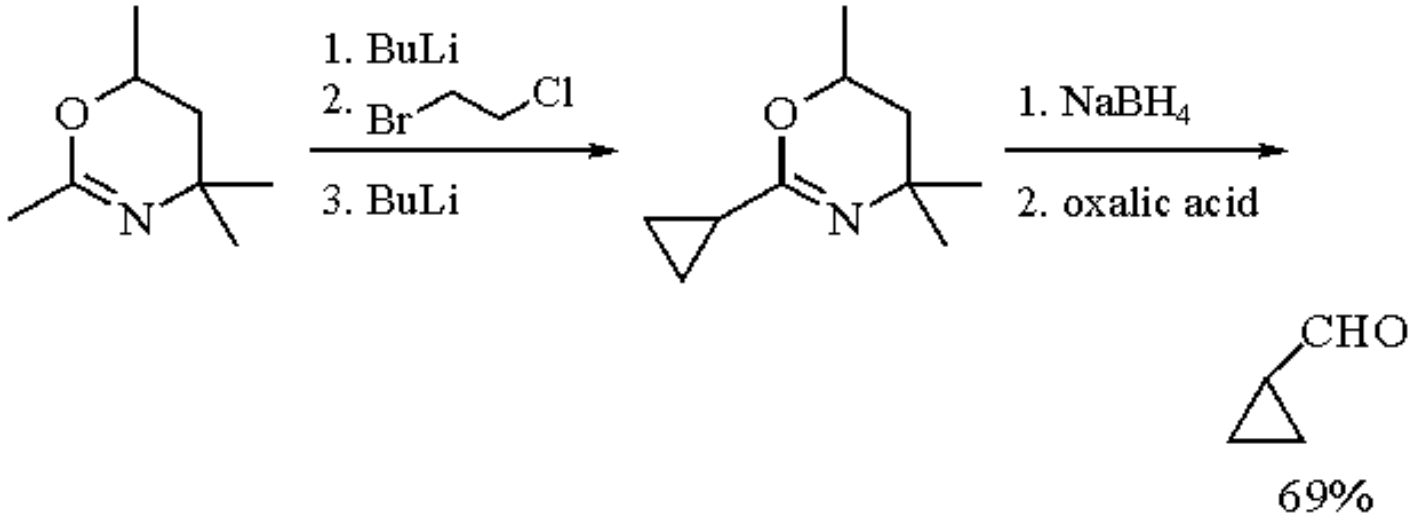

(3)

Acid-catalyzed hydrolysis of the oxazine allows for the formation of functionalized carboxylic acids (eq 4).[8]

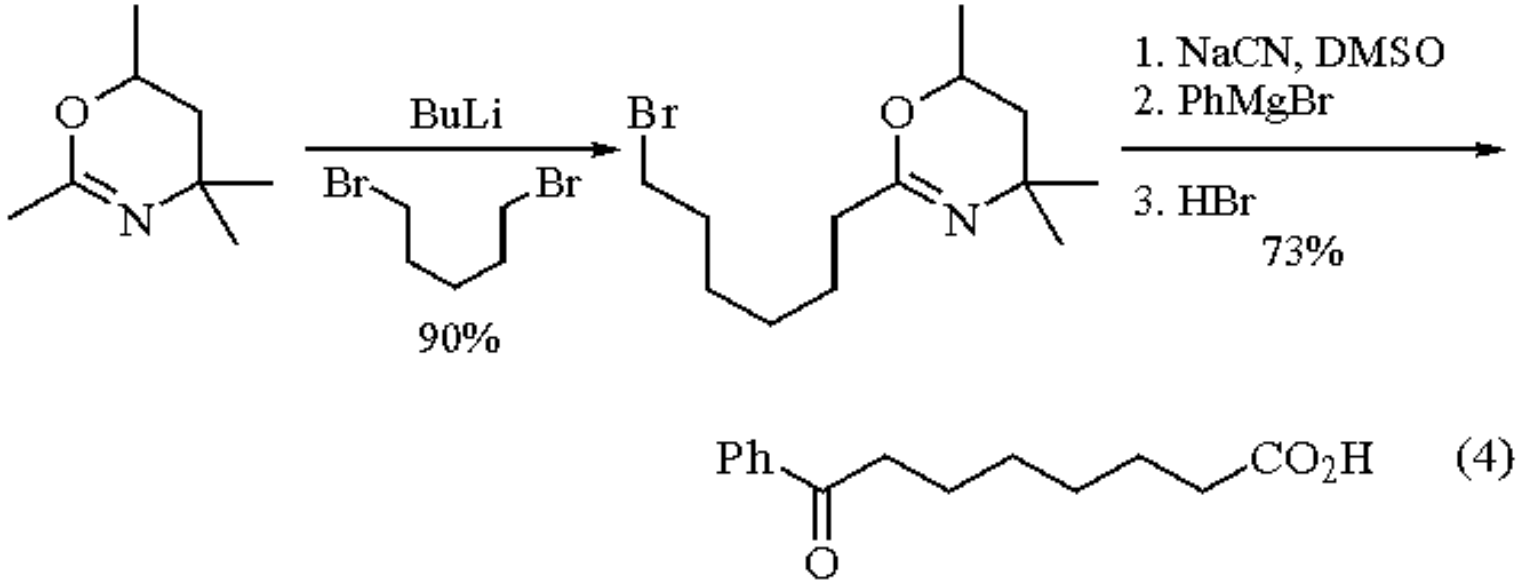

The *N*-methyloxazinium salts formed by alkylation of the dihydro oxazines with ***Iodomethane*** undergo Grignard addition to the iminium double bond. Aqueous hydrolysis affords unsymmetrical ketones (eq 5).[9]

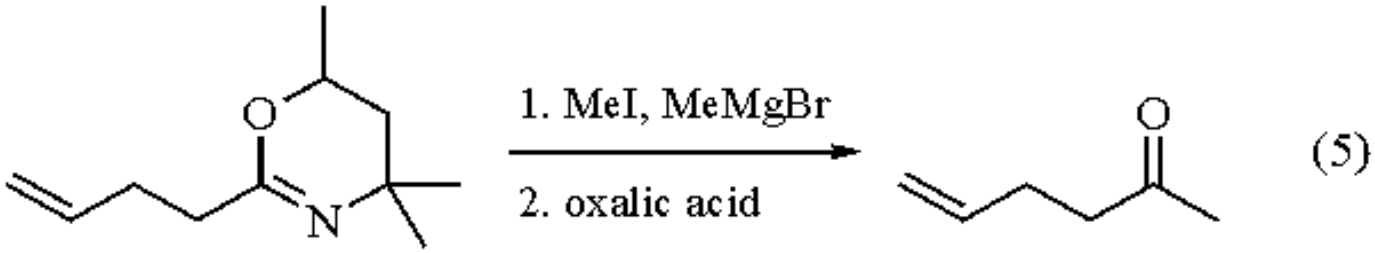

The lithio anion of the title reagent adds in a 1,2-fashion to carbonyl compounds. Reduction of the oxazine followed by hydrolysis and dehydration affords the α,β-unsaturated aldehydes (eq 6).[2,10]

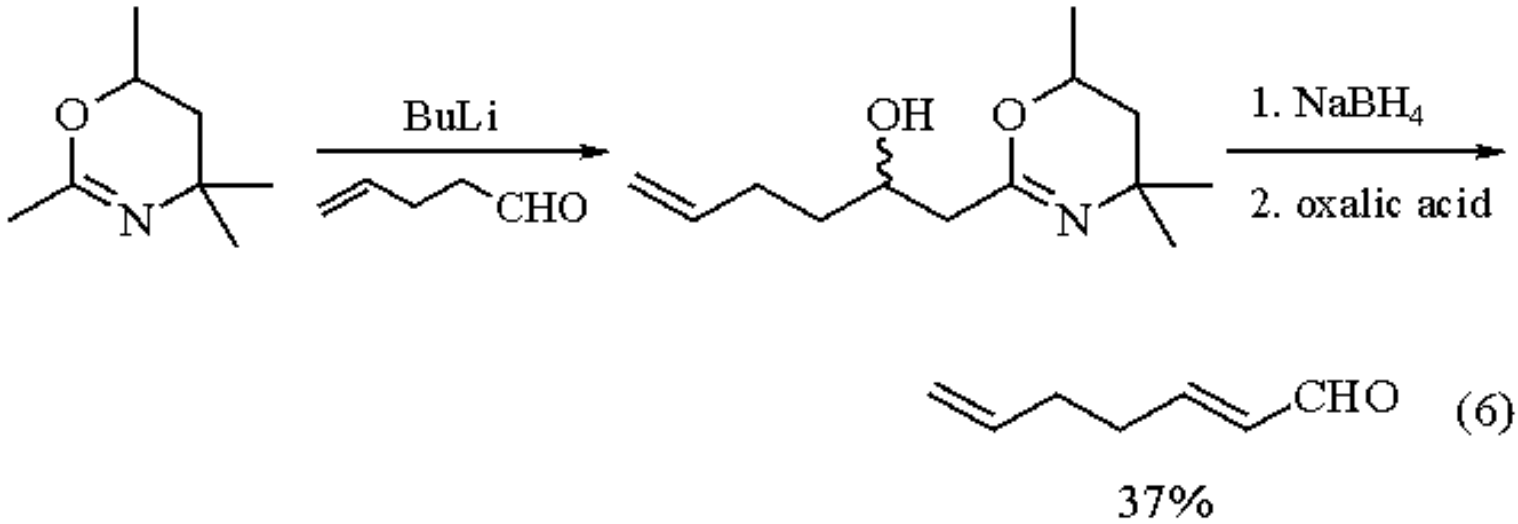

Improved (*E*)/(*Z*) ratios can be obtained by using oxazine phosphonates (**1**)[11] and phosphonium ylides (**2**)[11] and Peterson-type α-trimethylsilyl oxazines (**3**) and (**4**).[12]

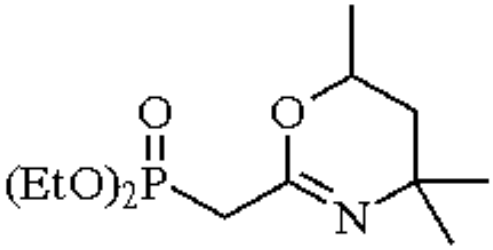

(1)

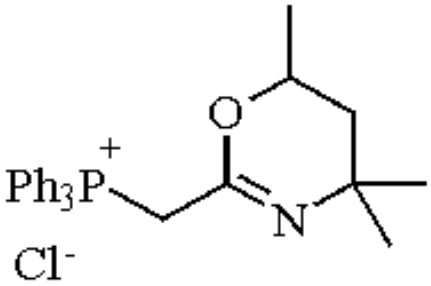

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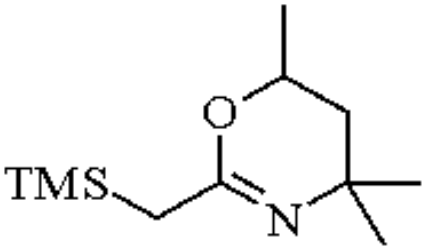

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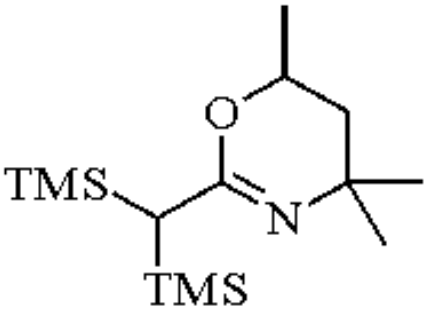

(4)

The title reagent can also be used as a precursor to α-amino ketones.[13] In addition, the *N*-oxide of the title reagent cycloadds with dipolarophiles in 1,3-dipolar cycloadditions.[14]

Related Reagents.

Acetaldehyde N-t-Butylimine; ***Dilithioacetate***; ***Ethyl Lithioacetate***; ***(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline***; ***2-Methylbenzothiazole***; ***2-Methyl-2-thiazoline***; ***2,4,4-Trimethyl-2-oxazoline***.

---

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10. (a) Whittaker, M.; McArthur, C. R.; Leznoff, C. C. *CJC* **1985**, *63*, 2844. (b) Meyers, A. I.; Nabeya, A.; Adickes, H. W.; Fitzpatrick, J. M.; Malone, G. R.; Politzer, I. R. *JACS* **1969**, *91*, 764. (c) Meyers, A. I.; Collington, E. W. *T* **1971**, *27*, 5979.
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13. Talaty, E. R.; Bengtsson, K. C.; Pankow, L. M. *SC* **1980**, *10*, 99.
14. Ashburn, S. P.; Coates, R. M. *JOC* **1984**, *49*, 3127.

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Dihydroxy(phenyl)borane[1]

$PhB(OH)_2$

[98-80-6] · $C_6H_7BO_2$ · Dihydroxy(phenyl)borane · (MW 121.93) (anhydride)

[3262-89-3] · $C_{18}H_{15}B_3O_3$ · Dihydroxy(phenyl)borane Anhydride · (MW 311.74)

(protective group for diols,[1c] template for C-C bond formation; phenylating agent;[2] catalyst for hydroalumination;[3] chromatography agent[1c])

Alternate Name: phenylboric acid.

Physical Data: mp 216 °C (anhyd); dipole moment 1.72 D (dioxane); pK_a 8.86 (25 °C, H_2O).

Solubility: sol H_2O 2.5%, benzene 1.75%, xylene 1.2%, ether 30.2%, methanol 178%.

Form Supplied in: white solid, widely available; contains varying amounts of the anhydride.

Preparative Method: from ***Phenylmagnesium Bromide*** and ***Trimethyl Borate***.[1d]

Purification: crystallization from H_2O.

Handling, Storage, and Precautions: readily forms trimeric anhydride upon standing or heating (eq 1); moderately toxic by ingestion; mildly toxic by skin contact.[4]

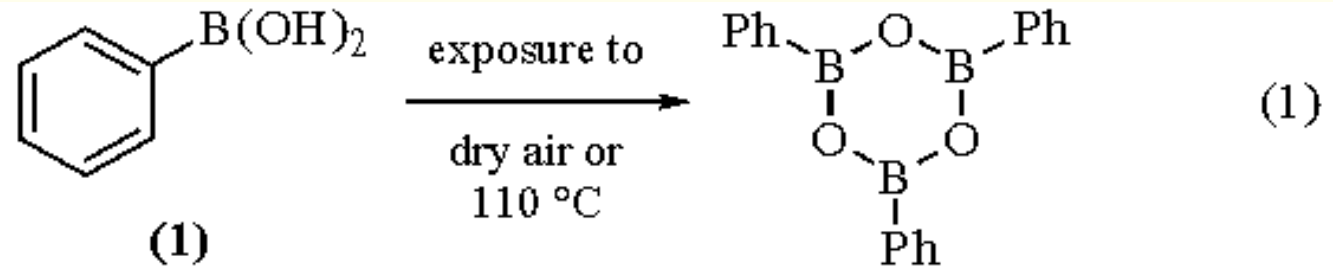

Reactions with Diols, Amino Alcohols, Diamines, Hydroxy Acids, and Catechols.[1c]

Most of the chemistry of dihydroxy(phenyl)borane (**1**) centers around its ready formation of cyclic boronate esters (eq 2). With diols the ease of formation follows the order $n = 3 > 2 > 4$. *cis*-Cycloalkene-1,2-diols readily form the cyclic boronates, whereas the *trans*-diols react with 2 equiv of (**1**) (eq 3) or form polymeric diesters. This latter feature has been used to separate *cis*/*trans* mixtures of polyols by distillation of the butylboronates or by crystallization of the phenylboronates. In the total synthesis of anthracyclines, the desired 7,9-*cis*-diol relationship was established by reaction of (**1**) with a *cis*/*trans* mixture of an early intermediate, which gave the *cis*-boronate exclusively (eq 4).[5]

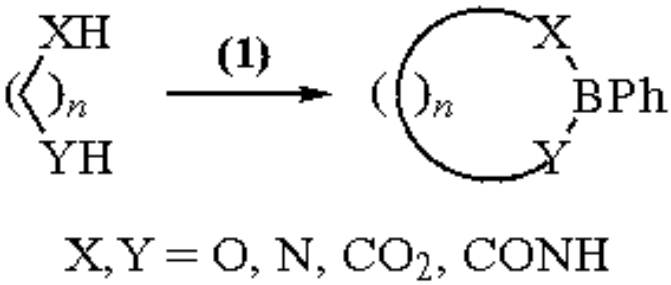

(2)

X,Y = O, N, CO_2, CONH

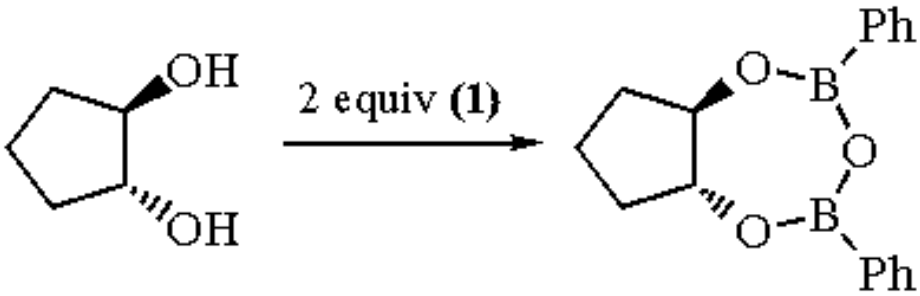

(3)

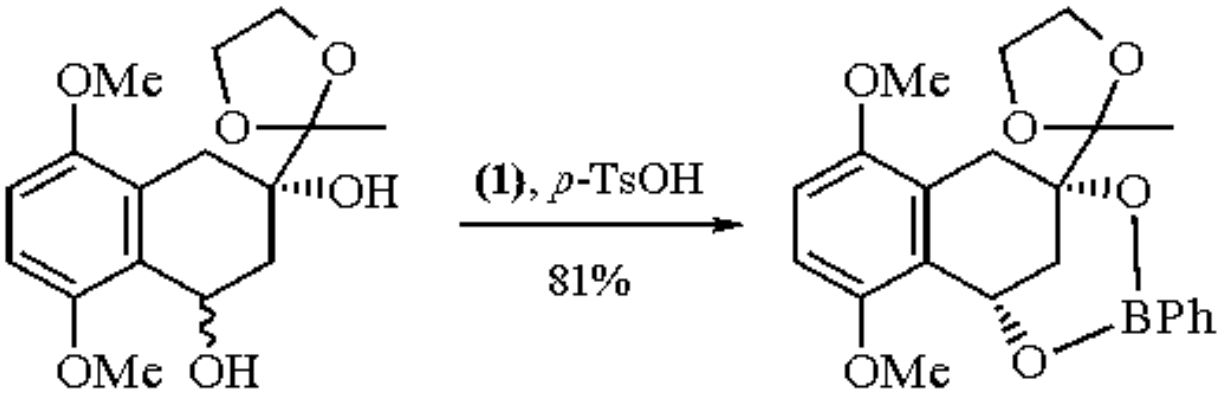

(4)

Catalytic osmylation of alkenes in the presence of (**1**) immediately gives the cyclic boronates. In this way a bisboronate with host properties was prepared (eq 5).[6]

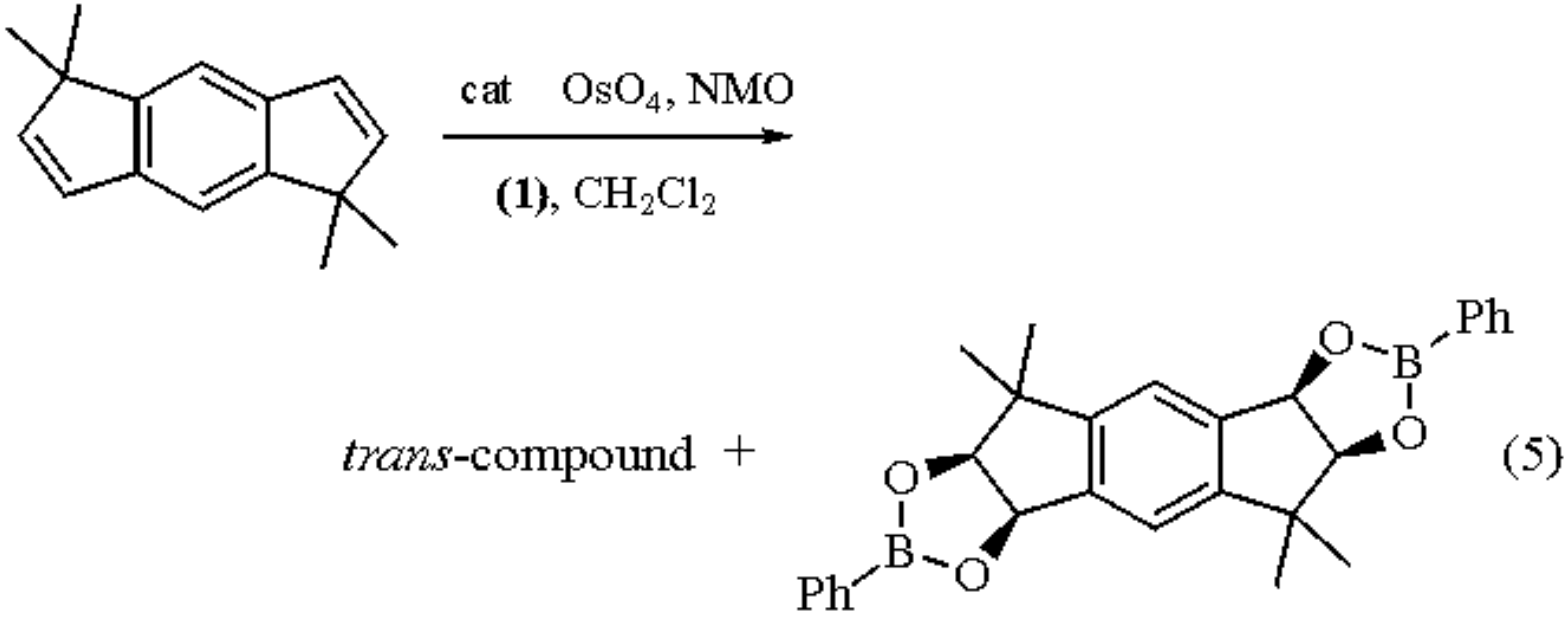

In alkaline aqueous solutions, (**1**) forms stable anionic adducts with diols (eq 6).[7] A large variety of anionic ligands has been prepared through the condensation of (**1**) with 3 equiv of pyrazole under basic conditions.[8]

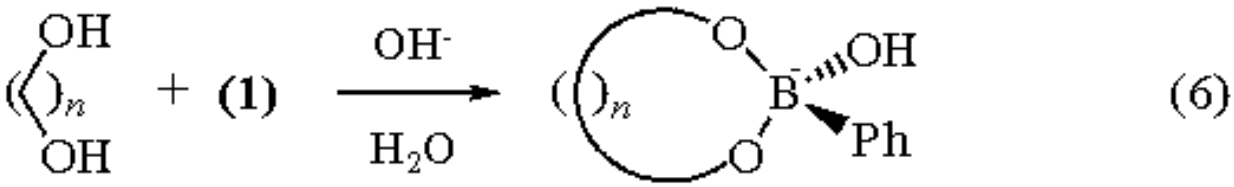

Azeotropic reflux is the most frequently used method of preparation of cyclic boronate esters; simple heating in polar solvents like acetone, pyridine, DMF, or even 2-methoxyethanol can be used with polar diols. Most cyclic boronates can be hydrolyzed easily by adding water to their solutions in organic solvents. In more reluctant cases, alkaline or acidic solutions or aqueous ***Hydrogen Peroxide*** have been used. In the latter case, (**1**) is concomitantly oxidized to phenol.[9] If the use of water is precluded, exchange with ***Ethylene Glycol*** or more particularly ***1,3-Propanediol*** followed by removal of the volatile adduct offers a useful alternative.

Protective Group.

Due to its easy attachment and removal, (**1**) is ideally suited as protective group for diols, particularly carbohydrates[1c] and nucleosides.[10] The phenylboronate protective group is compatible with the following reaction types, mostly on hydroxy groups: acylation, sulfonation, methylation (***Diazomethane-Boron Trifluoride***), phosphorylation, tritylation, silylation, bromination (***Bromoform-Triphenylphosphine***), reaction with ***Phenyl Isocyanate***, nucleophilic substitution, and Swern oxidation.[1c]

Chromatographic Separations.

Cyclic esters of polyols, amino alcohols, or catechols with either (**1**) or dihydroxy(butyl)borane have been used for gas chromatographic analysis, particularly for the measurement of drugs in biological fluids.[1c,11] Addition of (**1**) to eluents for paper chromatography[1c] or TLC[12] leads to a much increased separation of polyols that differ mainly in relative

configuration but are very similar in polarity, such as carbohydrates and glycosides. An affinity gel or HPLC stationary phase suited for the separation of carbohydrates, glycosides, nucleosides, and enzymes can be prepared by covalent attachment of (**1**) to a solid support like agarose, polyacrylamide, polystyrene, or silica. Many of these are commercially available.[13]

Template for C-C Bond Formations.

Dihydroxy(phenyl)borane is ideally suited as a template, serving to facilitate and direct reactions between two oxygen-containing substrates. Hydroxyalkylation of phenols with aldehydes, in the presence of 1 equiv of (**1**), gave the *ortho* products exclusively via the cyclic boronate esters (eq 7).[14] Pyrolysis of the same esters resulted in formation of *ortho*-quinone methides (**2**) which could be trapped in the usual way (eq 7).[15] Condensation of (**1**) with benzoin gave the dioxaborole, which by virtue of its enforced *cis* configuration could be easily photocyclized (eq 8). The product gave 9,10-phenanthrenequinone upon hydrolysis with base in the presence of air.[16] The dioxaboroles obtained from azeotropic reflux of acyloins and (**1**) undergo aldol condensation with aldehydes to give α,β-dihydroxy ketones after hydrolytic workup (eq 9).[17] The parent compound polymerizes when treated with catalytic amounts of ***Zinc Chloride*** and a starter aldehyde (eq 10).[18]

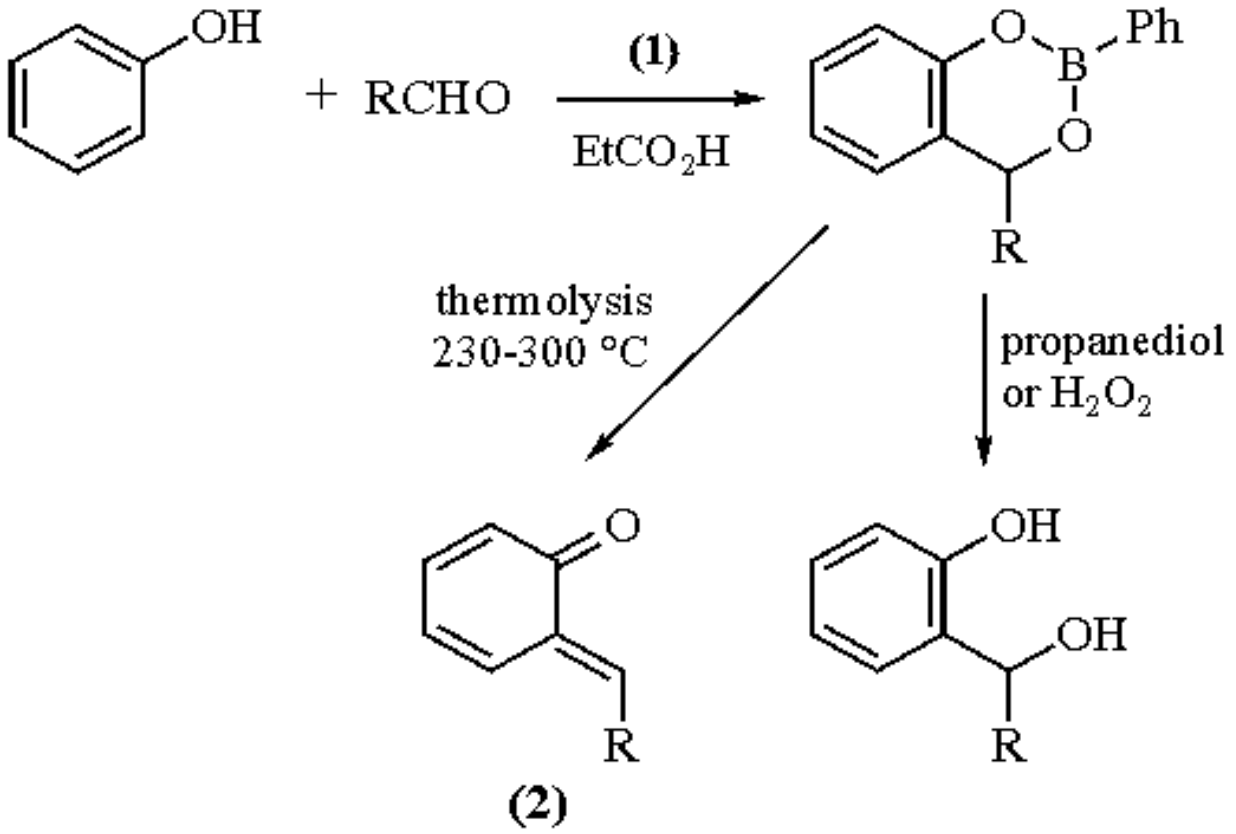

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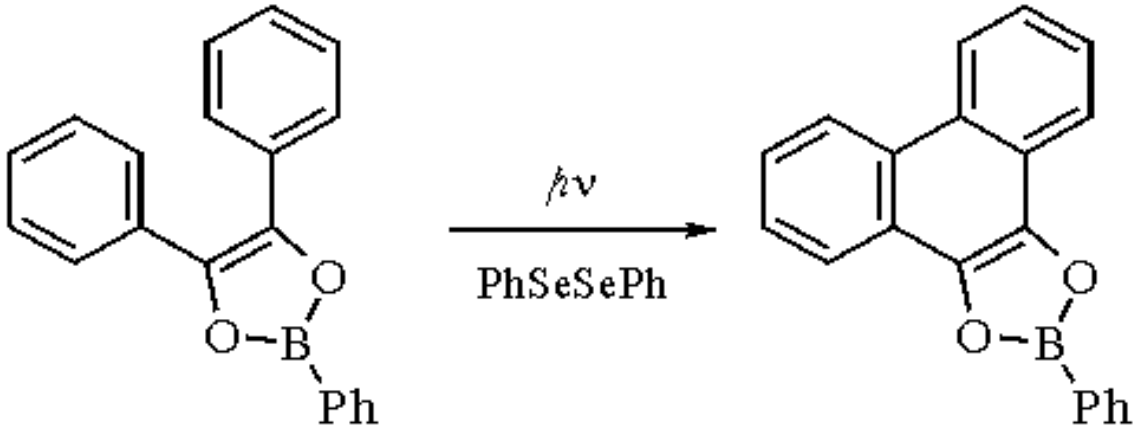

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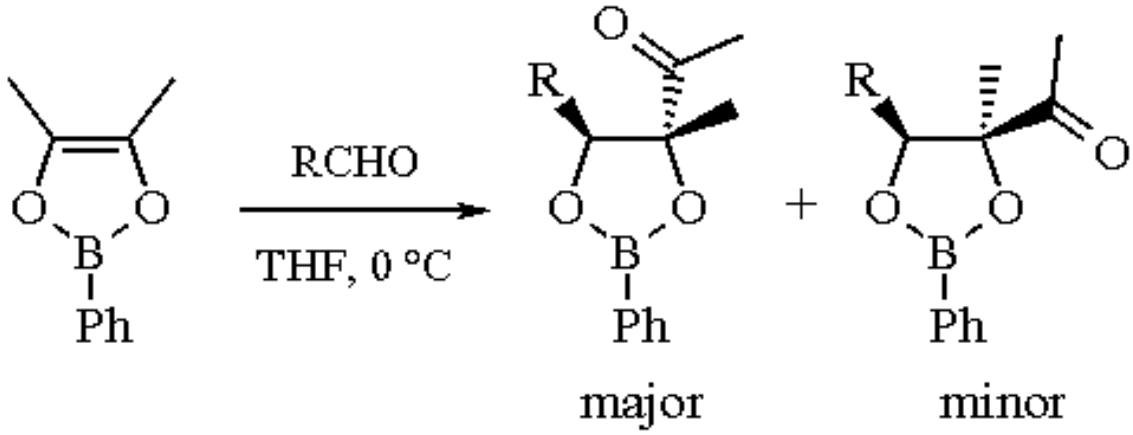

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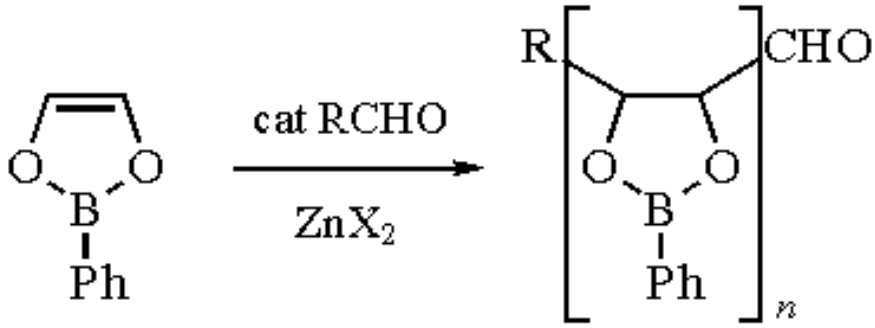

(10)

Suzuki and Heck Reactions.

Cross-coupling reactions of (**1**) with Ar-X (X = Br, I, OTf) (eq 11),[2] heteroaryl-X (X = Cl, Br, I, or OTf),[19] and vinyl-X (X = Br,[20] OTf[21]) are catalyzed by several Pd compounds in the presence of base. The reaction can be performed in two-phase or aqueous solvents.[22] Because of the ready availability and stability of (**1**) this method has superseded earlier approaches using Grignard reagents and organostannanes. If the Suzuki reaction is performed in the presence of CO, diaryl ketones, biaryls, or arylcarboxylic acids may be obtained, depending on the conditions.[23]

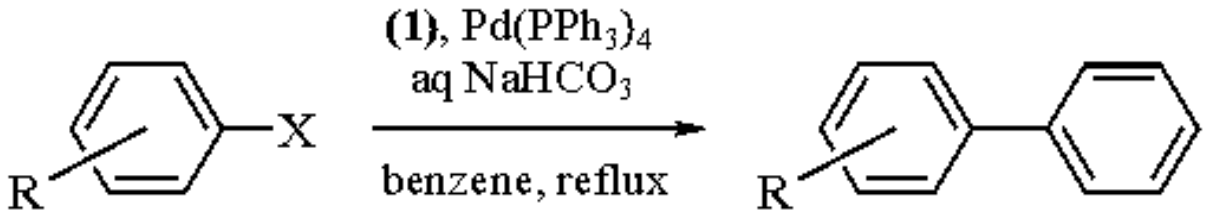

(11)

Heck reactions of (**1**) with styrene (eq 12) and ***Acrylic Acid*** have been reported.[24]

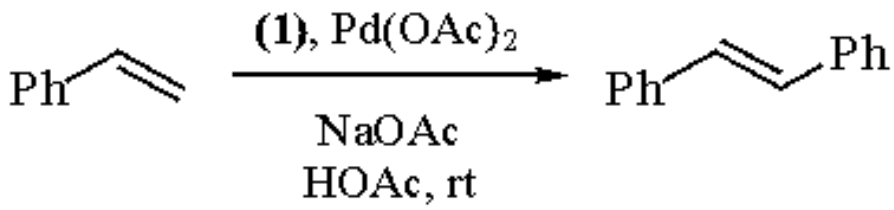

(12)

Hydroalumination.

The hydroalumination of alkenes with ***Dichloroalane*** is catalyzed by (**1**) (eq 13).[3]

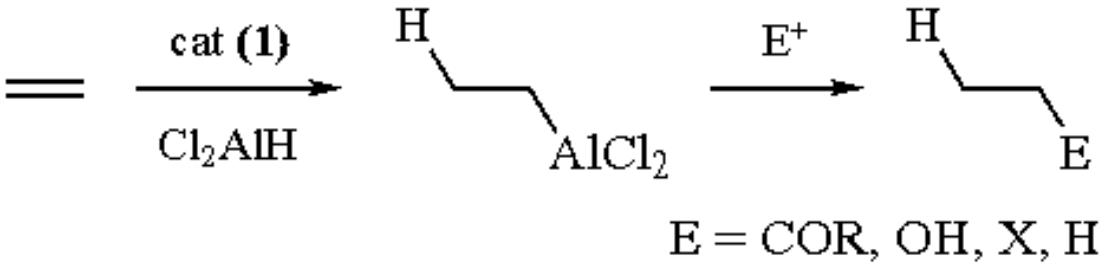

(13)

Asymmetric Synthesis.

Homologation of the boronate ester of (+)-pinanediol with ***Dichloromethyllithium***, followed by alkylation with ***Methylmagnesium Bromide***, proceeds with 97% diastereoselectivity (eq 14).[25] The sequence was repeated and the product oxidized with $NaBO_3$ to give (2*S*,3*S*)-3-phenyl-2-butanol in high optical purity. Treatment of several chiral boronate esters with ***Potassium Hydride*** gave chiral dialkoxymonoalkylborohydrides, which were used for the asymmetric reduction of ketones with moderate enantioselectivity.[26]

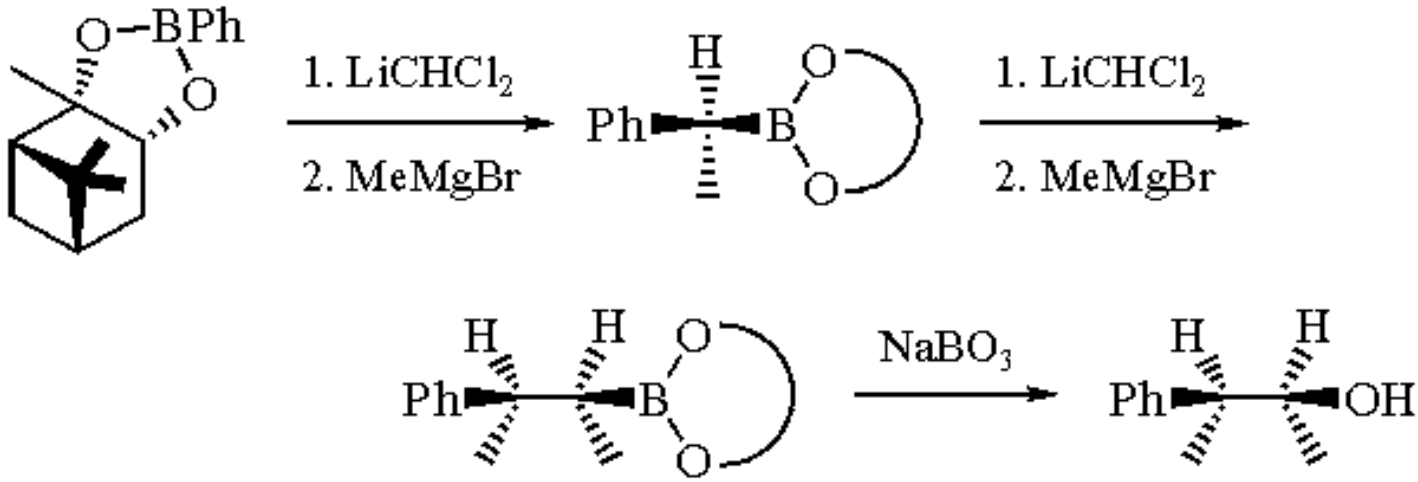

(14)

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Diimide[1]

HN=NH

(*cis*)

[15626-42-3] · H_2N_2 · Diimide · (MW 30.03) (*trans*)

[15626-43-4]

(mild, noncatalytic reducing agent for the *syn* reduction of C=C and C&tbond;C bonds; does not react with O-O, N-O, or other easily reduced single bonds, or with C=O, C=N, or aromatic π-bonds)

Alternate Name: diazene.

Form Supplied in: generated in situ.

Preparative Methods: the most widely used methods involve the Cu^I-catalyzed ***Oxygen*** or ***Hydrogen Peroxide*** oxidation of hydrazine, and the acid-catalyzed decarboxylation of ***Potassium Azodicarboxylate***.

Introduction.

The reduction of C-C π-bonds in the presence of various N-N-containing compounds ultimately capable of producing diimide dates back to 1905;[2] however, it was not until the early 1960s that the role of *cis*-diimide (diazene) was recognized.[3-6] The results of stereochemical studies[7] and theoretical calculations[8] indicate that *cis*-diimide is the active reducing agent, and that the reduction occurs via a concerted, symmetry allowed transfer of the hydrogen atoms of *cis*-diimide to the C=C or C&tbond;C bond, as illustrated in eq 1. In competition with the reduction of C-C π-systems, diimide undergoes a more facile disproportionation reaction to produce nitrogen and hydrazine[9] which requires the use of considerable excesses of the diimide precursor.

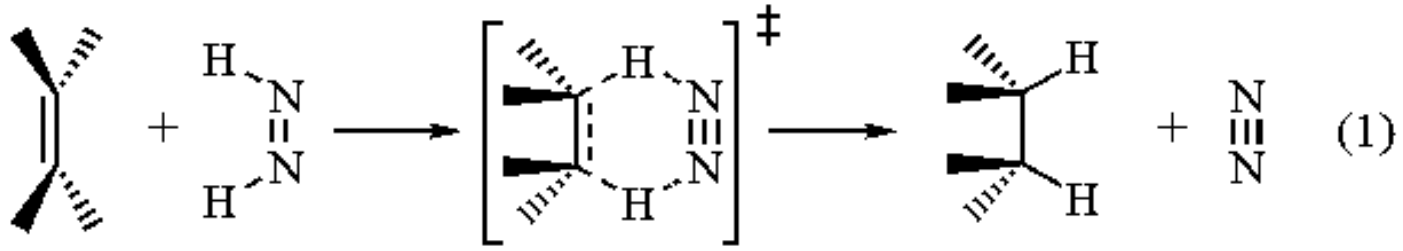

An important feature of the reduction of C-C π-systems is that many highly reactive functional groups can be present which would not survive under other chemical reducing or catalytic hydrogenation conditions. Such functional groups include allylic and benzylic derivatives, halides, sulfur-containing systems, O-O and N-O containing systems, and complex

bioorganic molecules. Examples of the latter systems are shown in eqs 2 and 3.[10,11]

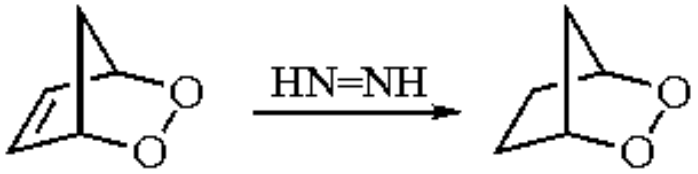

(2)

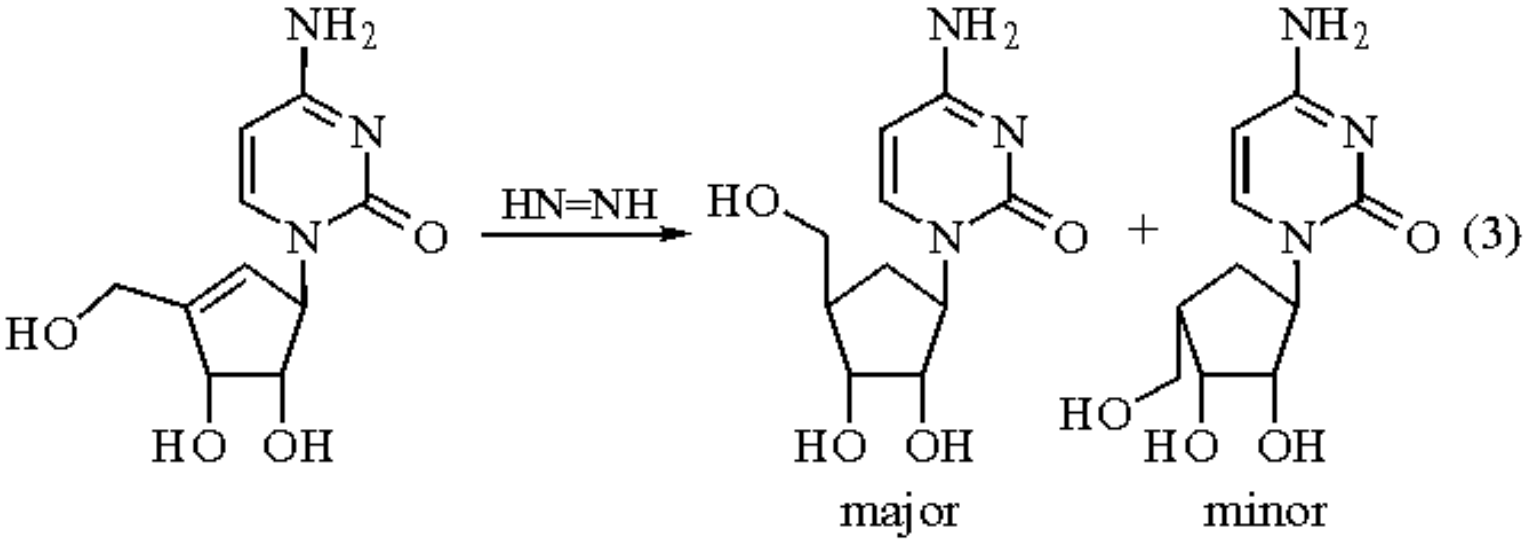

(3)

Relative Reactivity Toward Reduction by Diimide.

Carbon-carbon triple bonds, in general, are more reactive than double bonds toward reduction by diimide.[7,12] The relative reactivity of double bonds toward reduction decreases as the degree of alkyl substitution on the double bond increases,[12] and increases with increasing strain (see Table 1).[12] 1,3-Dienes are more reactive than monoenes, with the degree of substitution affecting the relative reactivity as observed with alkenes.[13] Examples of intramolecular selectivity are illustrated in eqs 4-6.[14-16]

Table 1 Relative Reactivities of Substituted Alkenes and 1,3-Dienes Toward Reduction by Diimide

Substrate	k_{rel}[12]
Cyclohexene	1.00
1-Pentene	20.2
trans-2-Pentene	2.59
cis-2-Pentene	2.65
2-Methyl-1-pentene	2.04
2-Methyl-2-butene	0.28
2,3-Dimethyl-2-butene	0.50
Bicyclo[2.2.1]heptene	450.0
Bicyclo[2.2.2]octene	29.0
1,3-Cyclohexadiene	47.0

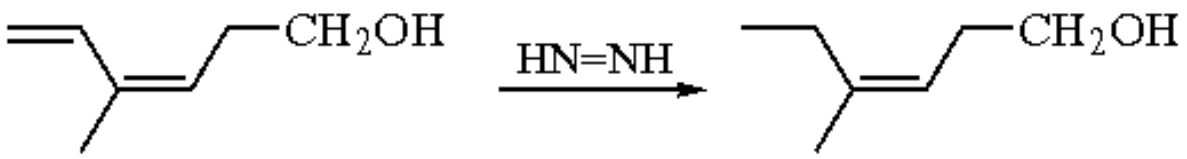

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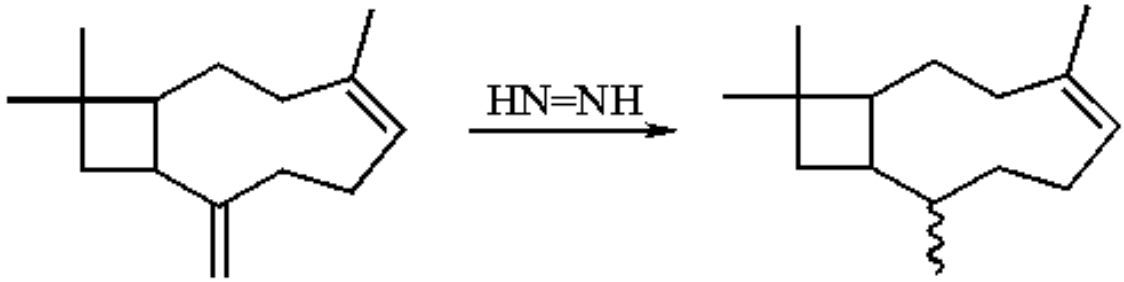

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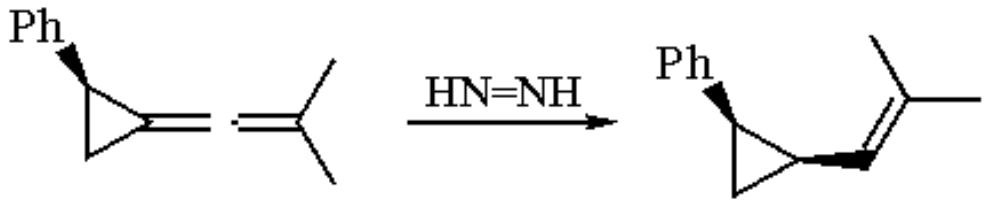

(6)

Electronegatively substituted double bonds (e.g. α,β-unsaturated carboxylic acids) are more reactive toward reduction by diimide than are alkyl- or electron donating-substituted π-systems. (The attempted reduction of α,β-unsaturated aldehydes,

ketones, and esters generally results in the formation of products deriving from the reaction of the carbonyl compound with hydrazine, which is formed by the disproportionation of the diimide.)

Facial Selectivity of Reduction.

The results of experimental and theoretical studies suggest that the transition state for diimide reduction lies very early along the reaction coordinate with the *cis*-diimide approaching the less sterically hindered face of the π-system (eq 6).

Electronic factors also play a role in determining the chemoselectivity of reduction by diimide; this is illustrated in eq 7, in which *anti-exo* reduction occurs preferentially to *syn-exo* reduction.[17]

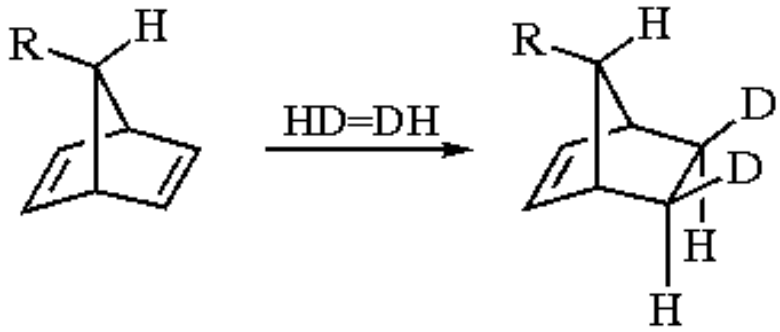

(7)

$R = OH, O_2CMe, OCMe_3$

Methods of Generation of Diimide.

Numerous methods have been discovered for the generation of diimide.[1a] Of these, only two processes find wide use: firstly, the air (oxygen) or ***Hydrogen Peroxide*** oxidation of hydrazine in the presence of copper(I) and a catalytic amount of a carboxylic acid (eq 8) (the carboxylic acid apparently being required to catalyze the isomerization of *trans*- to *cis*-diimide); secondly, the reaction of ***Potassium Azodicarboxylate*** with a carboxylic acid in aprotic solvents (eq 9).[18] The azodicarboxylate salt is formed by the reaction of ***Potassium Hydroxide*** with azodicarboxamide (commercially available). The latter procedure is especially useful for the position-specific and stereochemically controlled incorporation of deuterium or tritium into organic systems. An example is shown in eq 10, illustrating both the facial and stereoselectivity of the reaction.[19]

$$N_2H_4 \xrightarrow[Cu^I,\ RCO_2H]{O_2 \text{ or } H_2O_2} HN{=}NH \qquad (8)$$

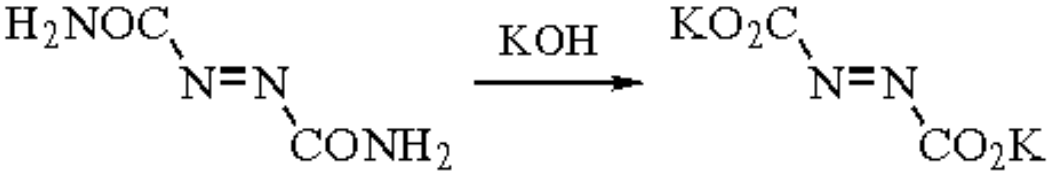

HN=NH (9)

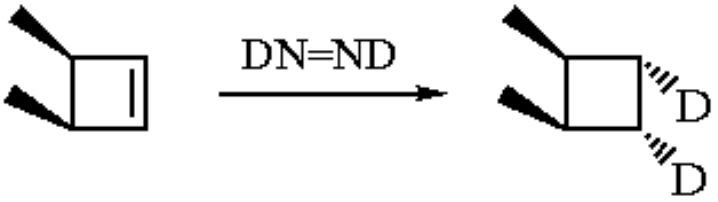

(10)

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Diiminosuccinonitrile[1]

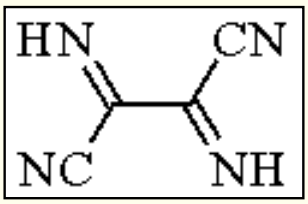

[28321-79-1] · $C_4H_2N_4$ · Diiminosuccinonitrile · (MW 106.09)

(adds to electron-rich alkenes to give dicyanotetrahydropyrazines;[2] reacts with ketones to yield dicyanoisoimidazoles[3])

Alternate Name: DISN.

Physical Data: mp 165-166 °C (dec); sublimes at 100 °C/1 mmHg; heat of combustion 5.09 kcal g^{-1};[4] dipole moment 1.59 D.

Solubility: (25 °C, g 100 mL^{-1}): acetone (21), THF (21), MeCN (18), DMAc (5.9), ether (1.5); insol benzene and hydrocarbons.

Preparative Method: a solution of dry ***Triethylamine*** (1.5 mL) in CH_2Cl_2 (15 mL) is added dropwise over 45 min to a solution of ***Hydrogen Cyanide*** (20 g, 0.74 mol) and cyanogen (17.4 g, 0.34 mol) in CH_2Cl_2 (120 mL) at -45 to -40 °C; the reaction is mildly exothermic and DISN precipitates as the triethylamine is added; after 30 min the product is collected while still cold and washed with CH_2Cl_2 and ether to give 33.6 g (95%) of DISN as a fine tan powder of sufficient purity for synthetic use.[4]

Purification: dissolve in hot ethyl acetate with Darco treatment, evaporate the solution to a slush, suction filter, and wash the solid with ether and dry in inert atmosphere; an air-stable white crystalline solid is obtained.

Handling, Storage, and Precautions: oral toxicity is ALD 90 mg/kg in rat; causes severe irritation on contact with rabbit eyes and permanent damage is prevented only by immediate flushing with water; causes mild skin and nose irritation; use only in a fume hood or in very well-ventilated areas with adequate protection (it produces HCN when wet or in contact with hydroxylic solvents); slowly discolors on exposure to light, and decomposes in water ($t_{1/2}$ about 2 weeks at ambient conditions).

Heterocycle Synthesis.

DISN is similar in reactivity to benzoyl cyanide in reactions with alcohols and aromatic amines. Dimethyloxaldiimidate is formed when DISN is treated with methanol under acid or base catalysis (eq 1).[3] Depending on the conditions, from neutral, to an equivalent amount of acid, to strong acidic medium, the reaction between DISN and *o*-phenylenediamine can afford three different products (eq 2).[3] DISN also has the same reactivity toward ***Diaminomaleonitrile*** (eq 3), although only one example is shown here.[5]

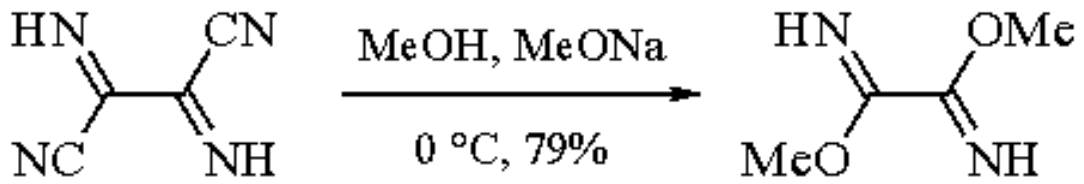

(1)

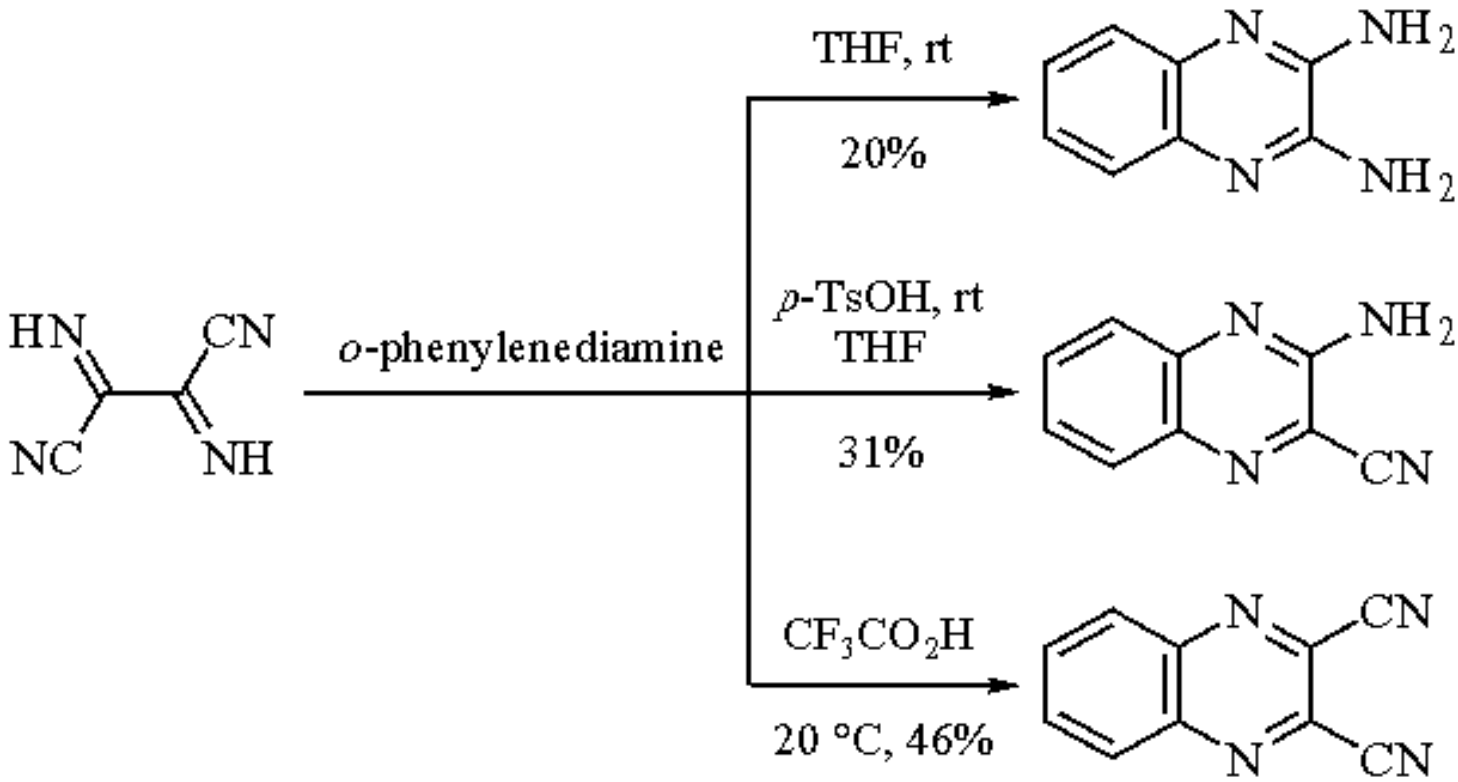

(2)

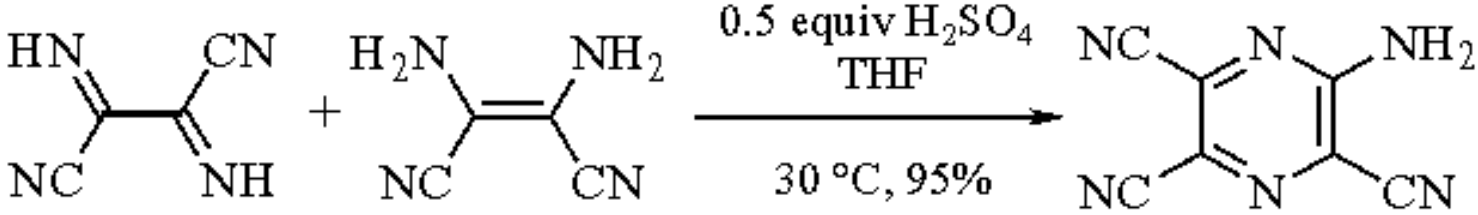

(3)

Oxalyl cyanide can be isolated from controlled hydrolysis of DISN (eq 4).[3]

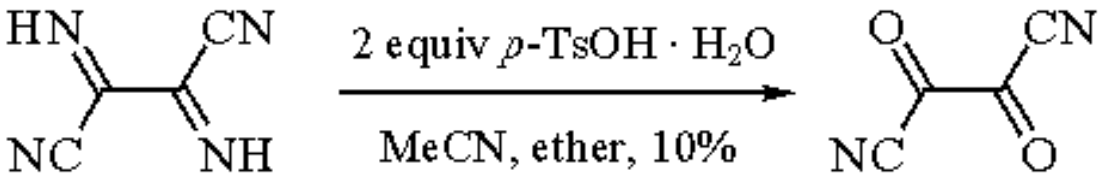

(4)

DISN undergoes [4 + 2] cycloadditions with electron-rich alkenes (eq 5).[2a]

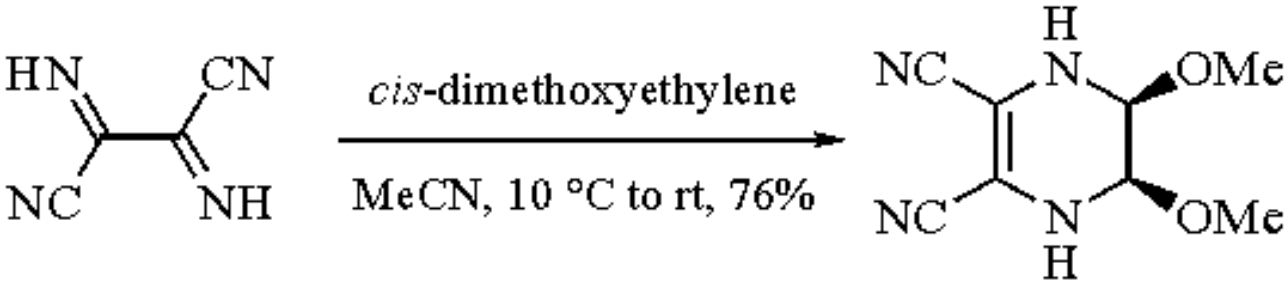

(5)

2,2-Dimethyl-4,5-dicyanoisoimidazole is formed in high yield by the addition of DISN to ***2,2-Dimethoxypropane*** under acidic conditions (eq 6).[3]

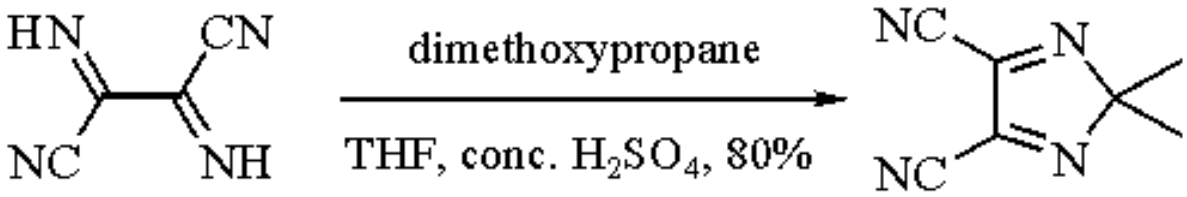

(6)

DISN reacts with ***Sulfur Dichloride*** or seleninyl chloride in methylene chloride to give dicyano-1,2,5-thiadiazole[3] or dicyano-1,2,5-selenadiazole (eqs 7 and 8).[6]

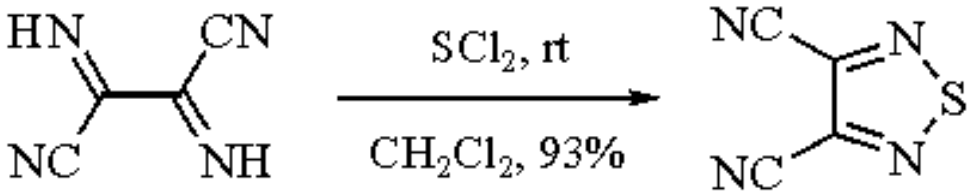

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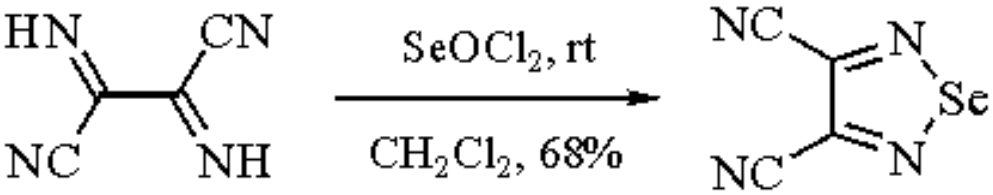

(8)

Trifluoroacetic Anhydride reacts with DISN to yield 4,5-dicyano-2-hydroxy-2-trifluoromethyl-2*H*-imidazole (eq 9).[7]

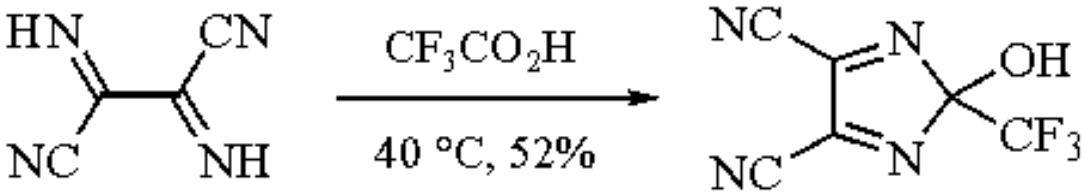

(9)

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1. Begland, R. W.; Cairncross, A.; Donald, D. S.; Hartter, D. R.; Sheppard, W. A.; Webster, O. W. *JACS* **1971**, *93*,

4955.
2. (a) Fukunaga, T.; Begland, R. W. *JOC* **1984**, *49*, 813. (b) Fukunaga, T. *JACS* **1972**, *94*, 3242.
3. Begland, R. W.; Hartter, D. R. *JOC* **1972**, *37*, 4136.
4. Webster, O. W.; Hartter, D. R.; Begland, R. W.; Sheppard, W. A.; Cairncross, A. *JOC* **1972**, *37*, 4133.
5. Begland, R. W.; Hartter, D. R.; Donald, D. S.; Cairncross, A.; Sheppard, W. A. *JOC* **1974**, *39*, 1235.
6. Roesky, H. W.; Gries, T.; Hofmann, H.; Schimkowiak, J.; Jones, P. G.; Meyer-Bäse, K.; Sheldrick, G. M. *CB* **1986**, *119*, 366.
7. Roesky, H. W.; Sundermeyer, J. *CB* **1991**, *124*, 366.

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1,3-Diiodo-5,5-dimethylhydantoin

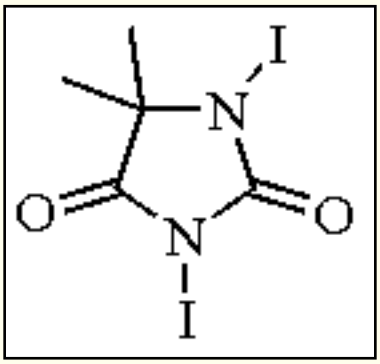

[2232-12-4] · $C_5H_6I_2N_2O_2$ · 1,3-Diiodo-5,5-dimethylhydantoin · (MW 379.92)

(electrophilic iodination)

Alternate Name: DIH.

Solubility: sol acetone; slightly sol CH_2Cl_2.

Preparative Method: by reaction of ***Iodine Monochloride*** (0.11 mol) with 5,5-dimethylhydantoin (0.05 mol) and ***Sodium Hydroxide*** (0.1 mol) in ice-water at 0 °C;[1] the product is used without further purification.

Handling, Storage, and Precautions: store under nitrogen at 0 °C and protect from light and moisture to avoid decomposition; irritating solid; avoid inhalation of the powder.

DIH has been used for the same electrophilic iodination of many organic compounds for which ***N-Iodosuccinimide*** is used. The advantages of DIH include its high iodine content, satisfactory stability, and its economical preparation (which does not require expensive silver salts), whereas its disadvantages include its limited solubility. In the few reported examples, DIH has been found to achieve the electrophilic iodination of organic compounds with results comparable to or better than those obtained using *N*-iodosuccinimide. These applications have included the electrophilic iodination of electron-rich arenes using DIH in acetone and the preparation of α-iodo ketones by reaction of enol acetates with DIH in dioxane at 90 °C.[1] In addition, DIH has been used for the preparation of 1,2-dioxetanes by iodohydroperoxylation of alkenes and for the cleavage of dithiane protecting groups.[2,3]

1. Orazi, O. O.; Corral, R. A.; Bertorello, H. E. *JOC* **1965**, *30*, 1101.
2. Kopecky, K. R.; Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J.-Y. *CJC* **1975**, *53*, 1103.
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Diiododimethylsilane

Me_2SiI_2

[15576-81-5] · $C_2H_6I_2Si$ · Diiododimethylsilane · (MW 311.96)

(reducing agent; preparation of *N*-(iododimethylsilyl)trialkylphosphinimines, bis(2,2´-bipyridine) complexes of silicon, di-μ-iodo-bis(tetracarbonyltungsten); chemistry of 7-silanorbornadienes and dimethylsilylene)

Alternate Name: dimethylsilyl diiodide.

Physical Data: bp 170 °C; *d* 2.203 g cm^{-3}.

Solubility: sol most organic solvents.

Preparative Method: 8.2 g (21 mmol) of ***Boron Triiodide*** and 7.4 g (57 mmol) of ***Dichlorodimethylsilane*** are refluxed for 3 days at 120 °C; the crude product is then isolated by adding ***Copper*** powder until the color disappears followed by fractional distillation in a spinning band column apparatus (65% yield).[1]

Handling, Storage, and Precautions: reacts vigorously with water, but without spattering; highly toxic, flammable liquid; use in a fume hood.

Reduction of α-Aryl Alkanols.

This reaction can be accomplished in CH_2Cl_2 at rt with 1 equiv of diiododimethylsilane (eq 1).[2]

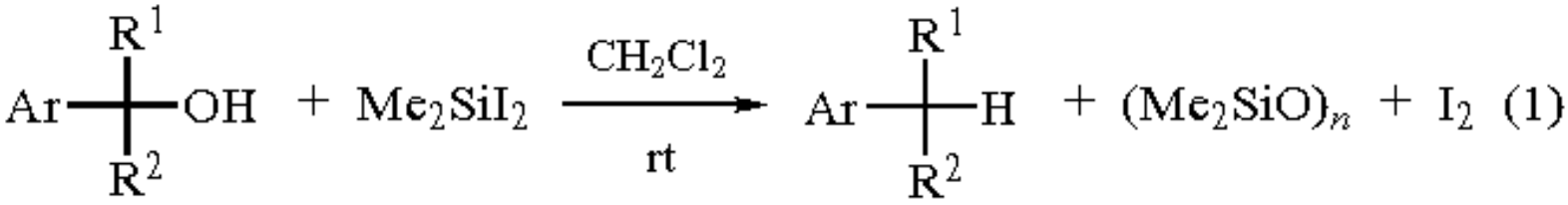

Ar	R^1	R^2	Yield (%)
Ph	Ph	Ph	94
Ph	Ph	Me	100
Ph	Me	Me	50
Ph	Ph	H	100
Ph	PhCO	H	45

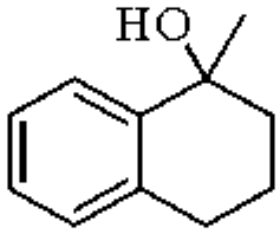

72

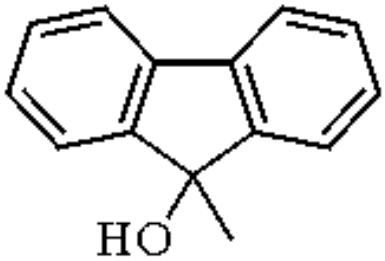

79

The reaction is far milder and more effective than comparative reductions of alcohols with ***Aluminum Chloride***-palladium and ***Lithium-Ammonia***. This method also permits reduction in the presence of other functional groups. A neighboring β-keto group, for example, is not reduced by diiododimethylsilane. The reaction is rapid, and reduction occurs best with secondary and tertiary α-aryl alkanols to give the corresponding alkanes in good yields.

Reductive Condensation of Ketones.

Diiododimethylsilane reacts with various ketones in the presence of ***Zinc*** to give the corresponding reductive condensation products in good yield (eq 2).[3]

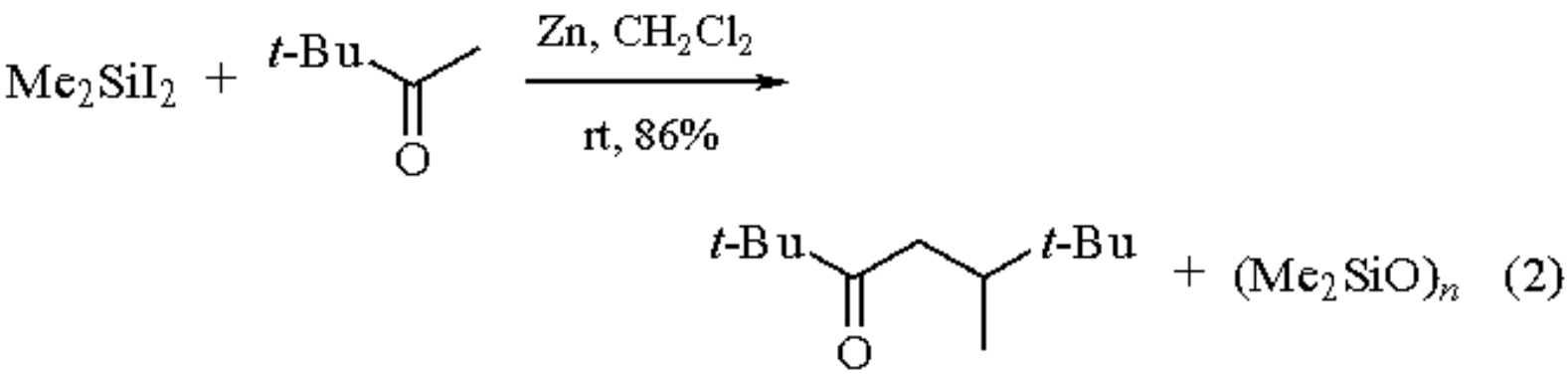

Reductive condensation products have been obtained from this reaction for *t*-BuCOMe, MeCOMe, EtCOEt, and cyclohexanone. The reaction of Me_2SiI_2 with Ph_2CO in the presence of zinc gave benzopinacolone.

Preparation of *N*-(Iododimethylsilyl)trialkylphosphinimines.

N-(Iododimethylsilyl)trialkylphosphinimines are accessible by transsilylation of the corresponding *N*-trimethylsilyl compounds or by the reaction of bis(trialkylphosphinimino)dimethylsilane with diiododimethylsilane (eq 3).[4]

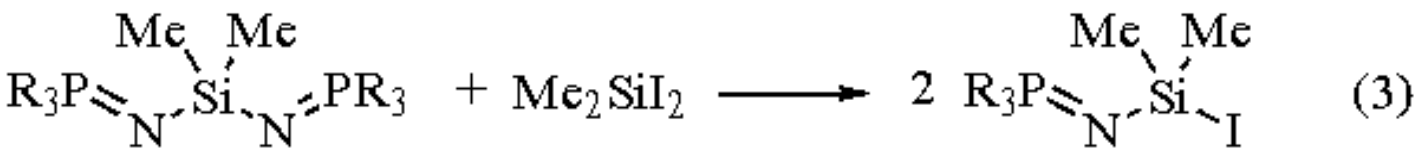

In a subsequent reaction, most of the compounds undergo dimerization to form dicationic four-membered systems (eq 4). Only compounds with bulky groups at the phosphorus atom are stable as monomers.

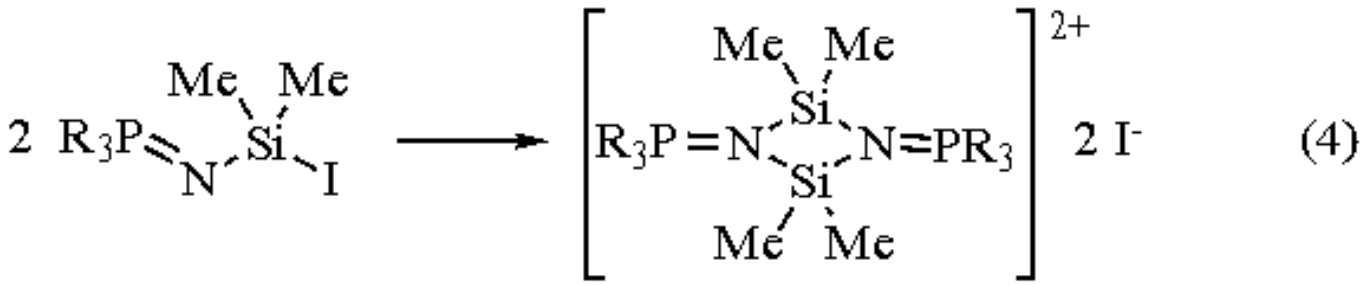

Preparation of Bis(2,2´-bipyridine) Complexes of Silicon.

A bis(2,2´-bipyridine) complex of silicon was synthesized by the direct reaction of 2,2´-bipyridine with diiododimethylsilane in chloroform (eq 5).[5] An ionic compound is formed. In solution it contains the *cis*-octahedral $[SiMe_2(bipy)]^{2+}$ cation (**1**).

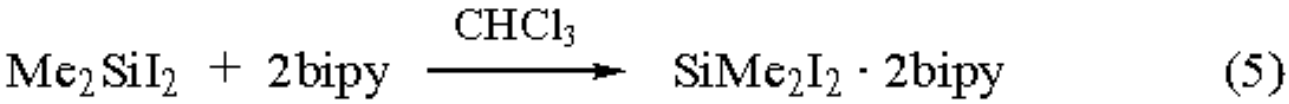

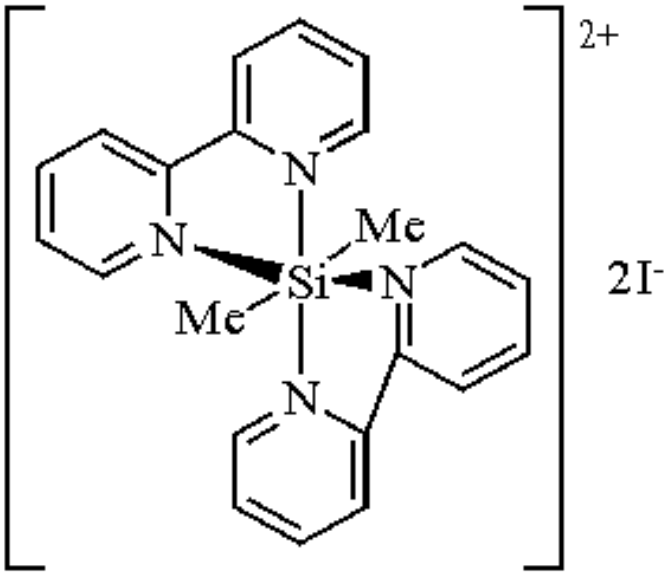

(1)

Preparation of Di-μ-iodobis(tetracarbonyltungsten).

Hexacarbonyltungsten reacts with diiododimethylsilane to give $[(CO)_4WI]_2$ (eq 6).[6] The dinuclear complex (**2**) is diamagnetic. The iodine atoms serve as bridging ligands between metal atoms.

$$W(CO)_6 \xrightarrow[h\nu]{Me_2SiI_2} [(CO)_4WI]_2 \qquad (6)$$

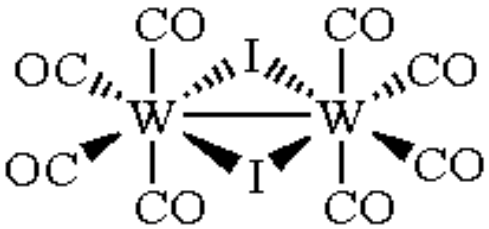

(2)

Chemistry of 7-Silanorbornadienes and Dimethylsilylene, Me_2Si.

7-Silanorbornadienes react rapidly with halogens at -20 °C to +20 °C to yield Me_2SiX_2 (X = Cl, Br, I) and the naphthalene or benzene derivatives (eq 7).[7]

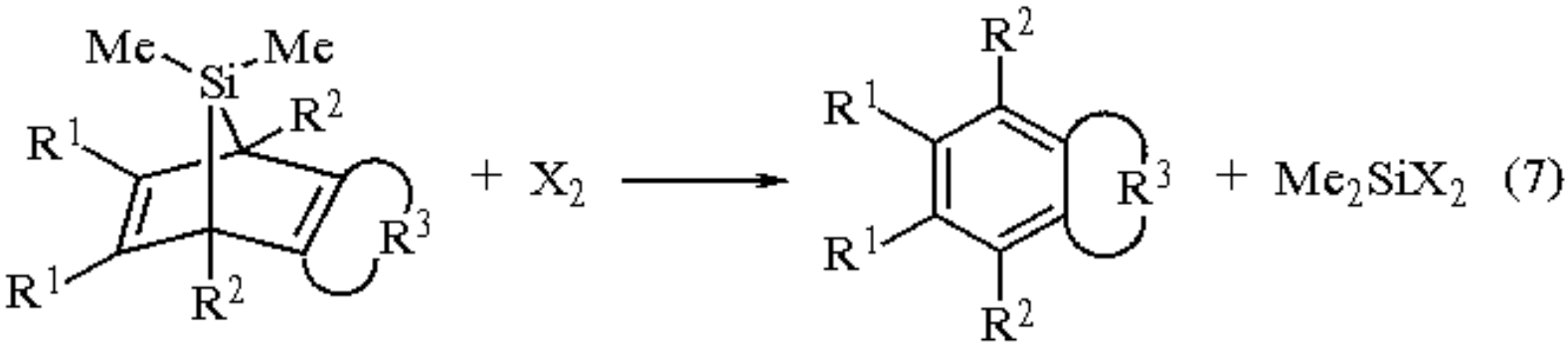

R^1	R^2	R^3
H	H	benzo
H	Ph	cycloocteno
Ph	Me	cycloocteno
Ph	Ph	benzo

Halogen can be abstracted from the C-Hal bond in benzyl iodide (or bromide), leading to Me_2SiX_2 and toluene (eq 8).[7]

$$2\ PhCH_2X \xrightarrow[X = Br,\ I]{Me_2Si} 2\ PhMe + Me_2SiX_2 \qquad (8)$$

High-Purity Alkali Metal Halides.

Alkali metal halides are refined by reaction in the gas phase with alkyl-, aryl-, or alkoxyhalosilanes.[8] This brings about an exchange between the Si-bound halogen and the anion of the contaminant, while the C-containing radical has a reducing effect. Diiododimethylsilane is used to purify ***Sodium Iodide*** in this manner.

Related Reagents.

Diiodosilane.

---

1. Wolfsberger, W.; Schmidbaur, H. *JOM* **1971**, *28*, 301.
2. Ando, W.; Ikeno, M. *TL* **1979**, 4941.
3. Ando, W.; Ikeno, M. *CL* **1980**, 1255.
4. Wolfsberger, W. *JOM* **1979**, *173*, 277.
5. Kummer, D.; Gaisser, K. E.; Seshadri, T. *CB* **1977**, *110*, 1950.
6. Schmid, G.; Boese, R.; Welz, E. *CB* **1975**, *108*, 260.

7. Appler, H.; Neumann, W. P. *JOM* **1986**, *314*, 247.
8. Lebl, M. *CA* **1972**, *77*, 37 185e.

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1,1-Diiodoethane

$MeCHI_2$

[594-02-5] · $C_2H_4I_2$ · 1,1-Diiodoethane · (MW 281.86)

(reagent for methylcyclopropanation of alkenes and ethylidenation of carbonyl compounds)

Alternate Name: ethylidene iodide.

Physical Data: bp 179-180 °C; *d* 2.84 g cm^{-3}.

Solubility: sol most organic solvents.

Preparative Methods: mix 39.6 g (0.40 mol) of 1,1-dichloroethane, 187 g (1.2 mol) of ethyl iodide, and 2.0 g of ***Aluminum Chloride*** and heat on a steam bath for 3 h; wash the mixture with H_2O and then $NaHSO_3$, and dry over $MgSO_4$; distillation provides 67.3 g (60%) of the product boiling at 75-76 °C/25 mmHg.[1] An alternative procedure utilizes the reaction of ***Iodine***, ***Triethylamine***, and the hydrazone of ***Acetaldehyde***: from 1 mol of acetaldehyde, 95 g (34% from acetaldehyde) of 1,1-diiodoethane can be isolated; this procedure is a little more involved, but provides a viable alternative if 1,1-dichloroethane is not available.[2]

Handling, Storage, and Precautions: corrosive and irritant; emits toxic fumes if heated to decomposition or comes in contact with acids. Use in a fume hood; store over copper powder and protect from light.

Methylcyclopropanation of Alkenes.

Various reagents will react with 1,1-diiodoethane to effect the methylcyclopropanation of alkenes. These reagents include ***Diethylzinc***,[3] ***Ethylzinc Iodide***,[4] ***Copper*** powder,[5] ***Zinc/Copper Couple***,[4] ***Zinc/Silver Couple***,[4] trialkylaluminum reagents,[6] and ***Samarium(0)***.[7] For simple alkenes, the diethylzinc (eq 1) and trialkylaluminum methods (eq 2) appear to be the ones of choice. The various zinc couples and copper powder provided lower yields of methylcyclopropane products. For cyclohexene (eq 1), diethylzinc afforded predominantly the *endo*-isomer.[3] The use of copper powder gave the *exo*-isomer as the major product.[5]

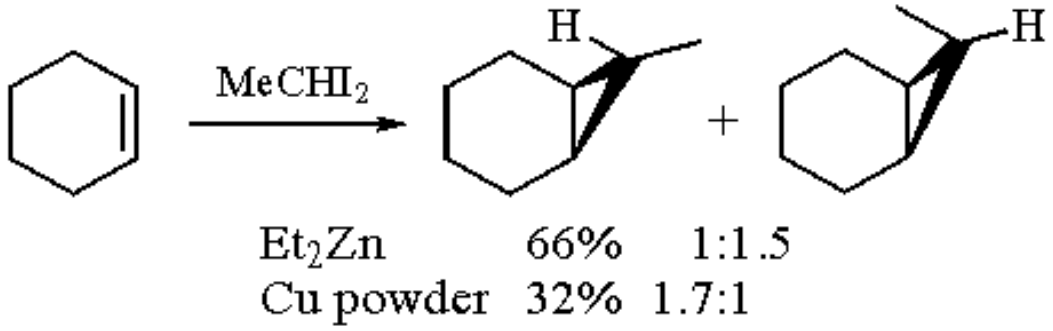

(1)

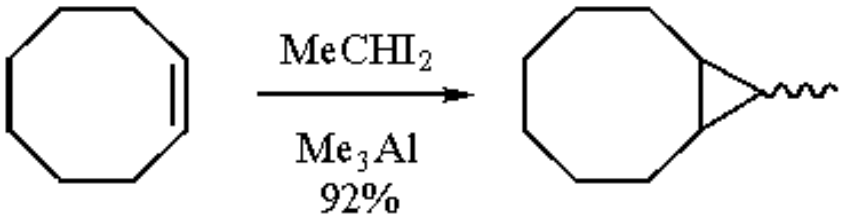

(2)

Reactive alkenes, such as enol ethers, can be methylcyclopropanated effectively using Zn/Cu couple. Trimethylsilyloxycyclohexene (eq 3) produces a 3.1:1.0 mixture of isomers, with the *exo*-isomer being the major product.[8] The reaction of 1-methoxy-1,4-cyclohexadiene was regioselective as well as stereoselective, yielding exclusively the *endo*-isomer (eq 4).[9] A cyclohexenediol bis-silyl ether has been methylcyclopropanated using either diethylzinc or Zn/Cu couple.[10] A ketene acetal was cyclopropanated using the diethylzinc procedure.[11]

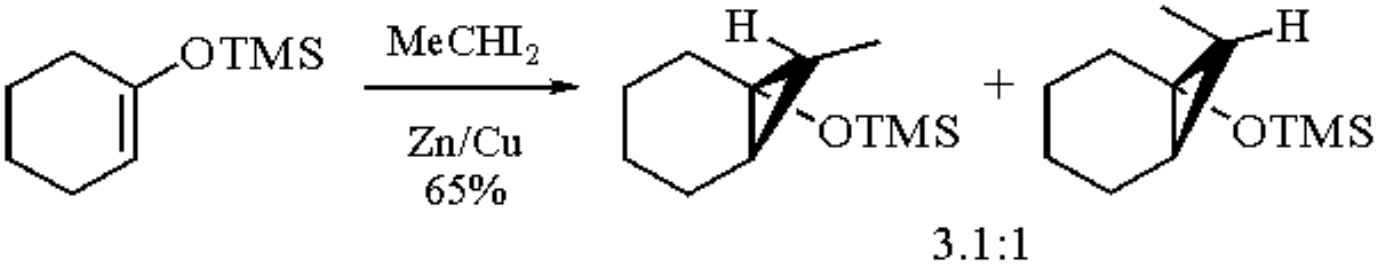

(3)

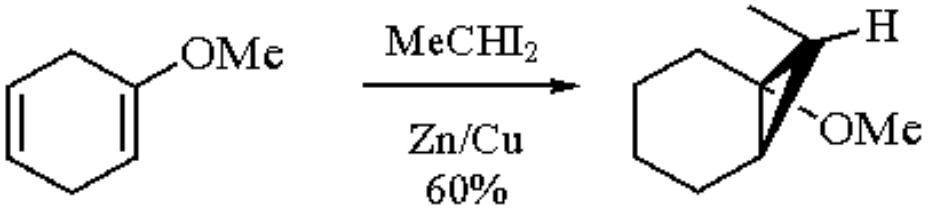

(4)

Allylic alcohols may be methylcyclopropanated using a number of different conditions. In Table 1 are shown the results for some cyclic allylic alcohols under different reaction conditions.[3b,4a,4b,7] For 2-cyclopenten-1-ol and 2-cyclohexen-1-ol, the yields as well as the ratios of the isomeric products formed were found to be very similar for different zinc reagents. The samarium-promoted reaction for cyclohexenol provided the cyclopropane with a higher *exo*:*endo* diastereoselectivity (83:17).[7]

Table 1 Comparison of Methylcyclopropanations of Cyclic Allylic Alcohols with 1,1-Diiodoethane

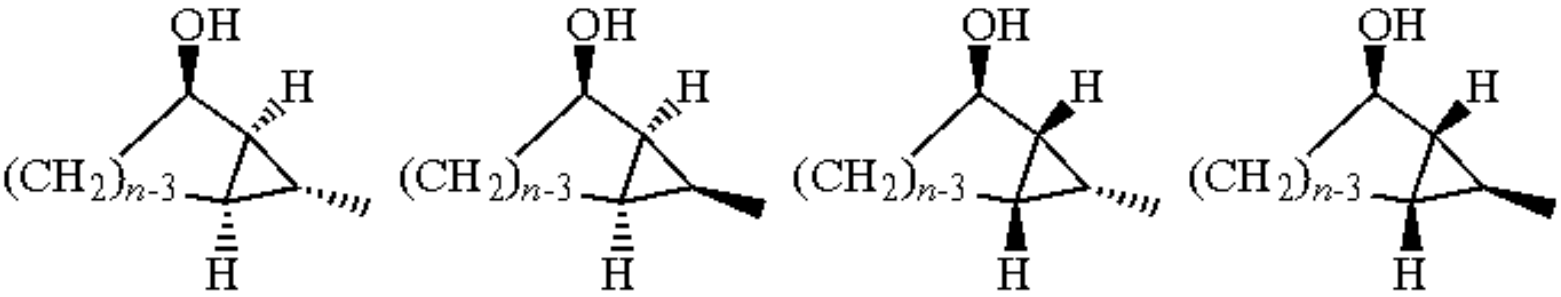

(1) **(2)** **(3)** **(4)**

n	Reagent	Yield (%)	Ratio of products (**1**:**2**:**3**:**4**)
5	Zn(Cu) (30 mesh)	62[4a]	78:22:0:0
	Zn(Ag) (30 mesh)	78[4a]	76:24:0:0
	Zn-CuCl (dust)	71[4a]	76:24:0:0
	EtZnI	67[4a]	73:27:0:0
	Et_2Zn	60[4b]	76:24:0:0
6	Zn-CuCl	84[4b]	72:28:0:0
	Et_2Zn	60[3b]	63:37:0:0
	Sm(Hg)	100[7]	83:17:0:0
7	Zn-CuCl	74[4b]	59:19:20:2
	Et_2Zn	72[4b]	49:20:21:10
8	Zn-CuCl	88[4b]	0:0:72:28
	Et_2Zn	76[3b]	0:0:71:29

Substrate: 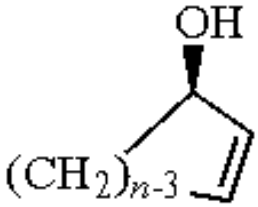

The allylic alcohols derived from the bislactim ether of cyclo(-L-Val-Gly-) have been methylcyclopropanated (eq 5) using the diethylzinc method in good yields with good diastereoselectivities.[12]

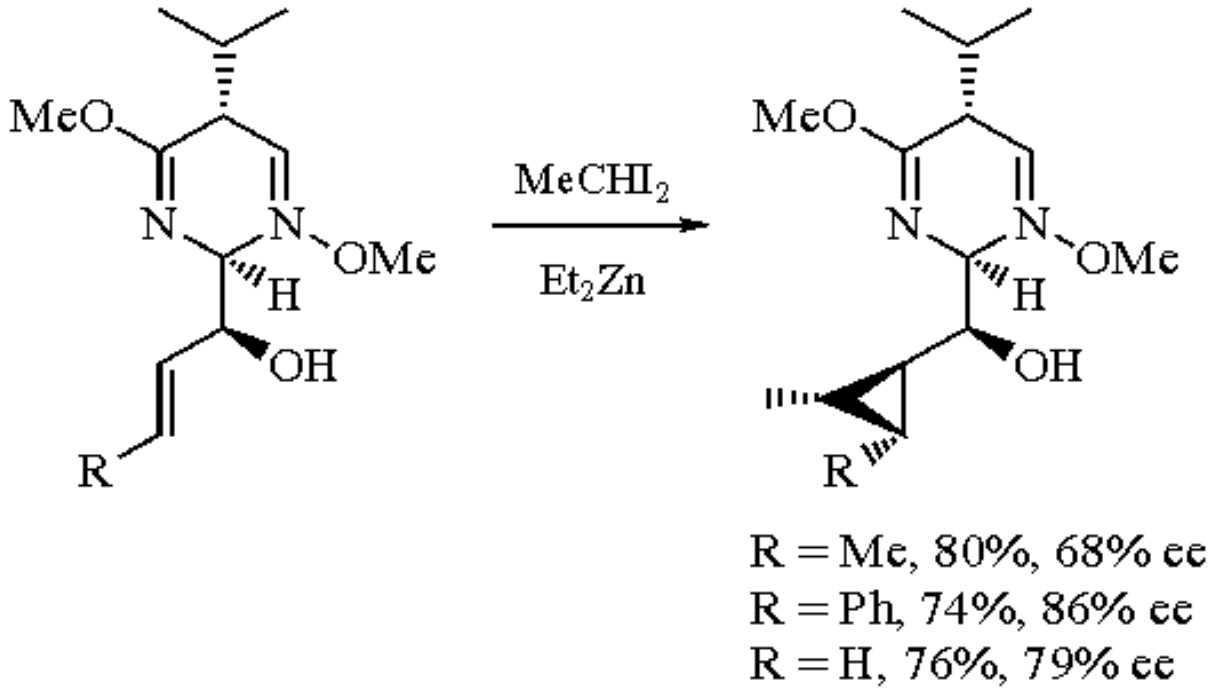

(5)

(*E*)-Ethylidenation of Aldehydes.

The reduction of 1,1-diiodoethane by ***Chromium(II) Chloride*** produces a *gem*-dichromium reagent which will react with aldehydes, selectively affording (*E*)-alkenes in excellent yield. The reaction conditions also work well for enolizable ketones. The reaction of α-tetralone produced the alkene in 85% yield as a 16:84 mixture of (*E*):(*Z*) isomers, respectively.[13] The lactol (eq 6) on reaction with $CrCl_2$ and 1,1-diiodoethane delivered the alkene with >95:5 (*E*):(*Z*) selectivity.[14] The corresponding reactions with the ethylidene triphenyl- or triethylphosphorane were less selective.

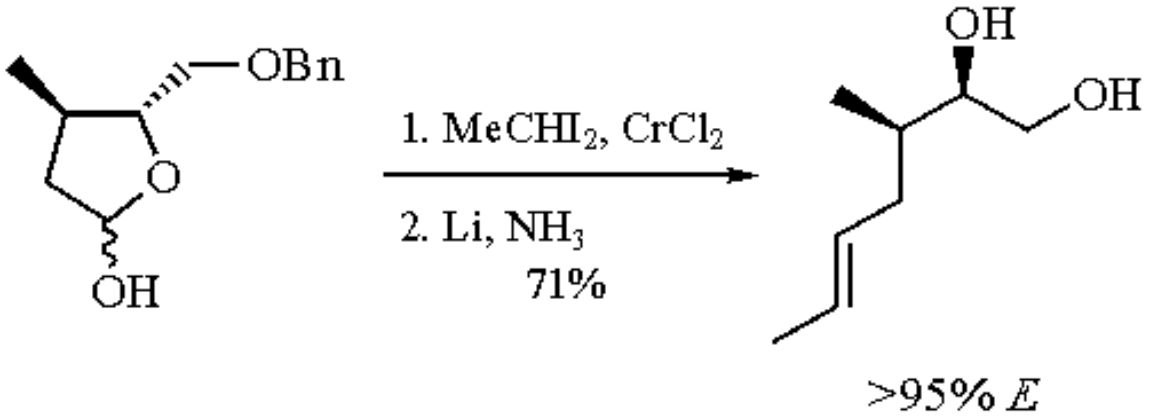

(6)

The α-alkoxyaldehyde (eq 7) was ethylidenated in excellent yield under these conditions. Again, the reaction was highly (*E*) selective (>99%); more importantly, no epimerization was observed.[15]

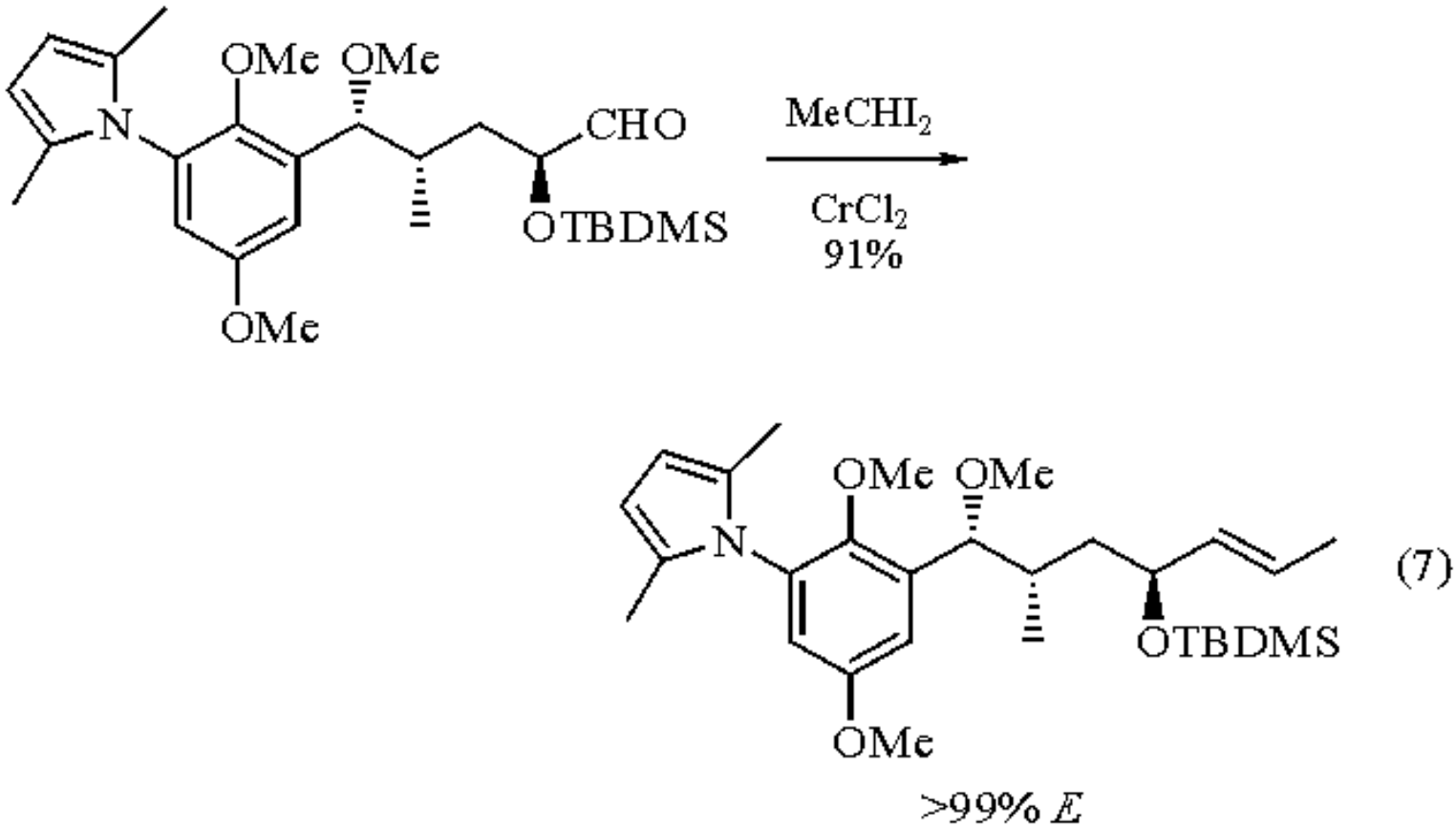

A deuterated vinylcyclobutane (eq 8) was synthesized using 1,1-diiodoethane-1-*d*. The (*E*):(*Z*) ratio in this case was 19.5:1. The deuterated reagent was prepared using the hydrazone method. The reaction was accompanied by a small amount of epimerization (1.7%).[16]

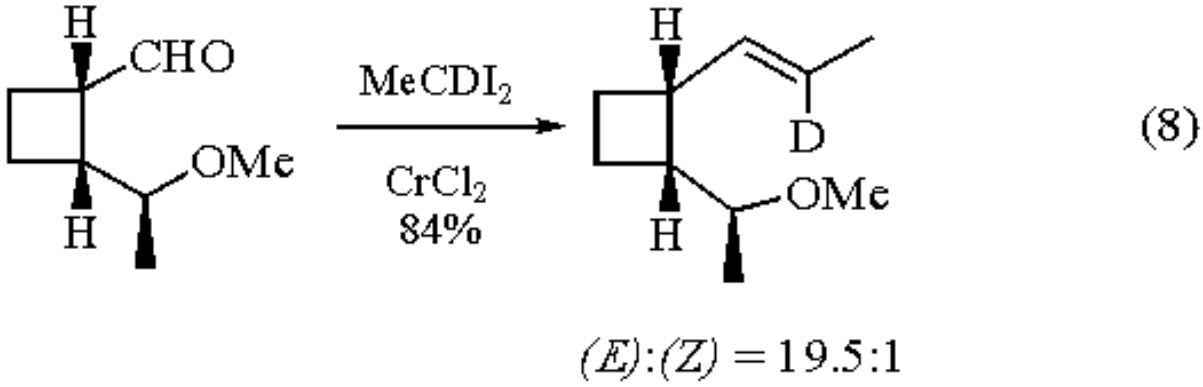

Miscellaneous.

1,1-Diiodoethane has been used to prepare ethylidene ditriflate by reaction with ***Silver(I) Trifluoromethanesulfonate***.[17] It has also been utilized to prepare 1,1-bis(bistrifluoromethyl)phosphano)ethane[18] and octacarbonyl (μ-ethylidene)diiron.[19]

Related Reagents.

1,2-Dibromoethane; ***Diiodomethane***; ***1,3-Diiodopropane***.

1. Letsinger, R. L.; Kammeyer, C. W. *JACS* **1951**, *73*, 4476.
2. Friedrich, E. C.; Falling, S. N.; Lyons, D. E. *SC* **1975**, *5*, 33.
3. (a) Nishimura, J.; Kawabata, N.; Furukawa, J. *T* **1969**, *25*, 2647. (b) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *JOC* **1977**, *42*, 3031.
4. (a) Friedrich, E. C.; Biresaw, G. *JOC* **1982**, *47*, 1615. (b) Friedrich, E. C.; Biresaw, G. *JOC* **1982**, *47*, 2426.
5. Kawabata, N.; Yamagishi, N.; Yamashita, S. *BCJ* **1977**, *50*, 466.
6. Maruoka, K.; Fukutani, Y.; Yamamoto, H. *JOC* **1985**, *50*, 4412.
7. Molander, G. A.; Etter, J. B. *JOC* **1987**, *52*, 3942.
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9. Hoberg, J. O.; Larsen, R. D.; Jennings, P. W. *OM* **1990**, *9*, 1334.
10. Lewicka-Piekut, S.; Okamura, W. H. *SC* **1980**, *10*, 415.
11. Rousseau, G.; Slougui, N. *TL* **1983**, *24*, 1251.
12. Groth, U.; Schöllkopf, U.; Tiller, T. *LA* **1991**, 857.
13. Okazoe, T.; Takai, K.; Utimoto, K. *JACS* **1987**, *109*, 951.
14. McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *TL* **1989**, *30*, 7029.
15. Baker, R.; Castro, J. L. *JCS(P1)* **1990**, 47.
16. Getty, S. J.; Berson, J. A. *JACS* **1991**, *113*, 4607.
17. Bullock, R. M.; Hembre, R. T.; Norton, J. R. *JACS* **1988**, *110*, 7868.
18. Phillips, I. G.; Ball, R. G.; Cavell, R. G. *IC* **1988**, *27*, 4038.
19. Sumner, C. E.; Collier, J. A.; Pettit, R. *OM* **1982**, *1*, 1350.

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Diiodomethane

CH_2I_2

[75-11-6] · CH_2I_2 · Diiodomethane · (MW 267.84)

(precursor to methylene transfer reagents: in combination with various metals or alkyl metals, generates carbenoids which cyclopropanate alkenes[1] or methylenate carbonyls;[2] precursor to ICH_2Met and I_2CHMet nucleophiles;[3] participates in radical-mediated couplings[4])

Alternate Name: methylene iodide.

Physical Data: mp 6 °C; bp 181 °C; *d* 3.325 g cm^{-3}.

Solubility: slightly sol H_2O; sol Et_2O, $CHCl_3$, EtOH, hexane, etc.

Form Supplied in: pale yellow liquid; crystallizes as pale yellow needles or plates; typically stabilized with copper powder.

Purification: fractional distillation from CaH_2 generally provides reagent of sufficient purity for typical uses.

Handling, Storage, and Precautions: store over copper powder to inhibit radical-induced decomposition; protect from light; incompatible with many metals (Al, Mg, Na, etc.) and strong bases; mildly corrosive; toxicity presumed to be on par with CH_2Cl_2, i.e. moderately toxic, mutagenic; use in a fume hood.

Methylenations.

A wide variety of carbonyl methylenating reagents utilize CH_2I_2 as the carbon source. Several of these have proven to be useful alternatives to the Wittig reaction.[5] Cainelli and co-workers found that treatment of CH_2I_2 with 2 equiv of ***Magnesium Amalgam*** in the presence of ketones affords alkenes in good yields (eq 1).[6] The intermediate in these reactions is presumed to be $CH_2(MgI)_2$, and the reaction works well with ketones and aldehydes of variable structure. This reagent is particularly useful for the formation of dideuterated terminal alkenes (using CD_2I_2, eq 2),[7] since methylenation using deuterated Wittig reagents is often accompanied by various degrees of scrambling of the deuterium label.[8]

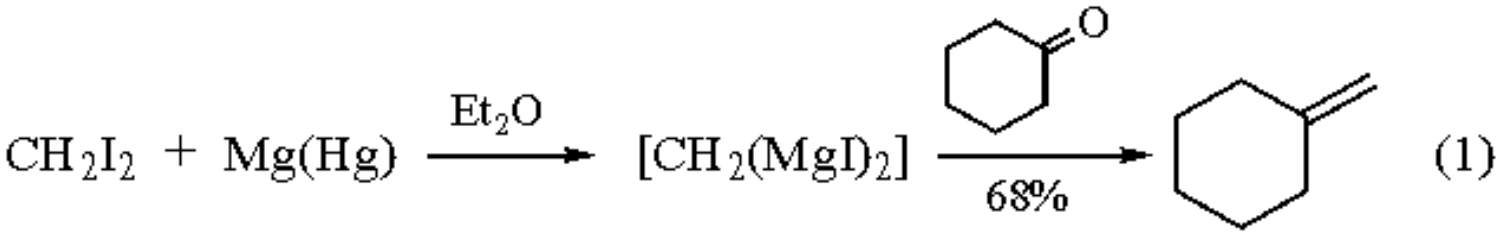

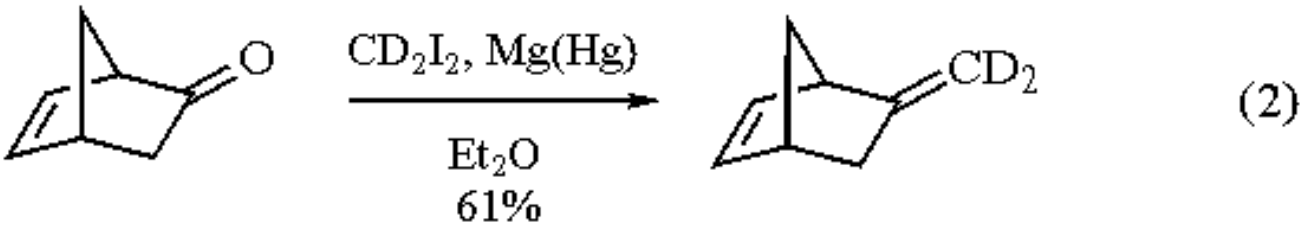

Chromium(II) also mediates the alkenation of aldehydes by geminal diiodides (eq 3).[9] This transformation presumably proceeds via a 1,1-bis[chromium(III)] species, and works best with substituted diiodides. Generally, high levels of (*E*) selectivity are obtained.

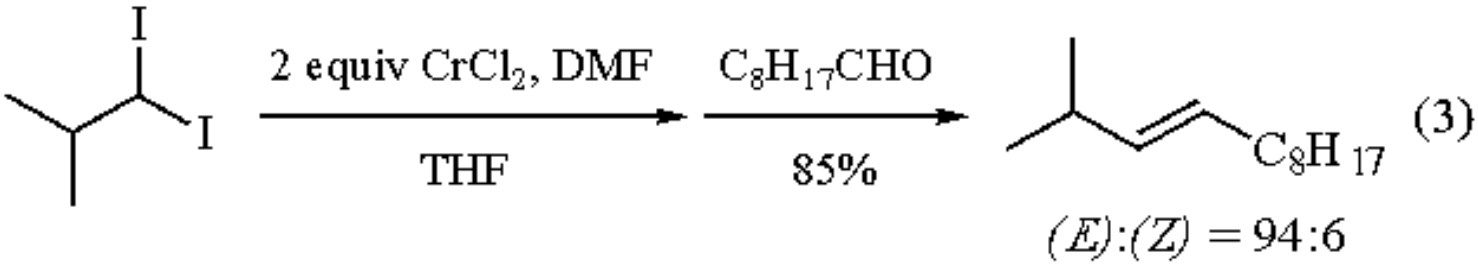

Certain methylenating reagents utilize CH_2I_2 in combination with 2 equiv of ***Zinc*** and a Lewis acid.[2,10,11] A Lewis acid is not essential for this transformation,[11] but greatly accelerates the reaction and improves selectivity and yields. The most commonly used Lewis acids include ***Trimethylaluminum***,[2,10a] ***Titanium Tetraisopropoxide***,[10a] ***Titanium(IV) Chloride***,[10b,10c] ***Dichlorobis(cyclopentadienyl)zirconium***,[10d] and ***Dichlorobis(cyclopentadienyl)titanium***.[10e] Of a variety of Lewis acids and dihalomethanes examined, Takai and co-workers found that $CH_2I_2/Zn/Me_3Al$ and $CH_2Br_2/Zn/TiCl_4$ afforded the best results.[10f] Substrates for these reactions can vary from simple ketones such as acetophenone (eq 4)[2] to complex steroidal ketones.[10b] Chemoselective methylenation of an aldehyde in the presence of a ketone can also be achieved (eq 5).[10a] Other unsaturated functionalities also react with these reagents. For example, the Eisch reagent[10e] $[CH_2(ZnI)_2/Cp_2TiCl_2]$ has been shown to react with benzonitrile to afford, after hydrolysis, acetophenone (eq 6).

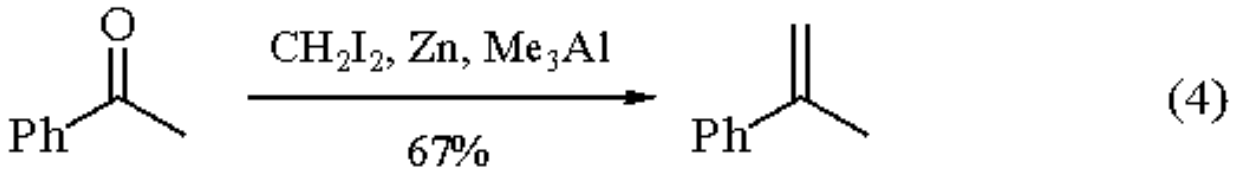

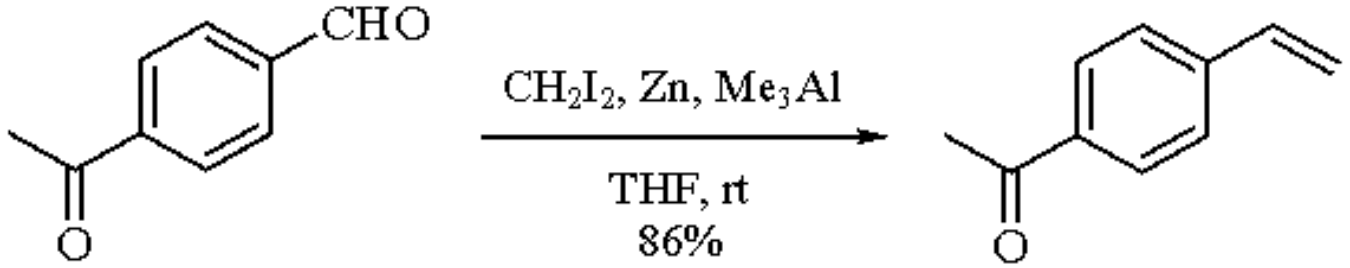

(5)

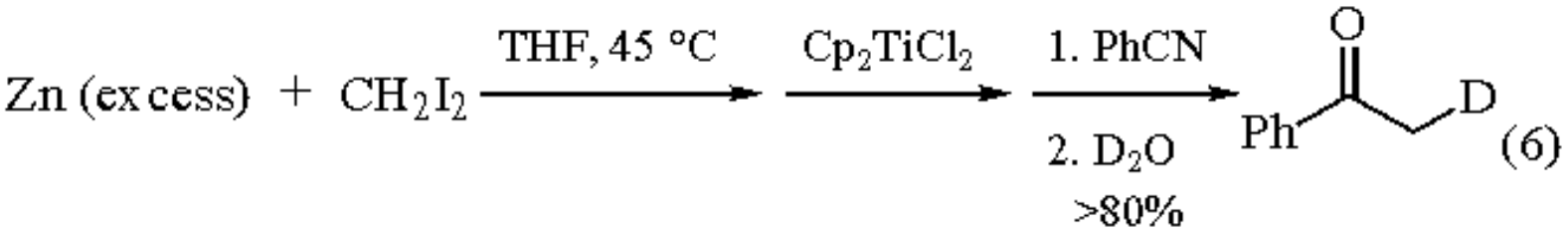

(6)

Cyclopropanations.

A variety of metallic species mediate the cyclopropanation of alkenes in the presence of CH_2I_2 (vide infra). A much simpler procedure is the photolysis of CH_2I_2 in the presence of alkenes.[12] Although this method was initially reported to give a mixture of products in poor yields,[12a] the addition of iodine scavengers and acid scavengers to the reaction medium results in clean, high-yielding reactions.[12b-d] Sterically hindered alkanes are cyclopropanated much more readily than with metal-based reagents (eq 7), and double bond geometry is generally retained (eq 8). Remarkably, products arising from C-H bond insertion are not observed, ruling out the formation of free carbene in these reactions. The iodomethyl cation (ICH_2^+) has been proposed as an intermediate in these reactions.[12c,12d]

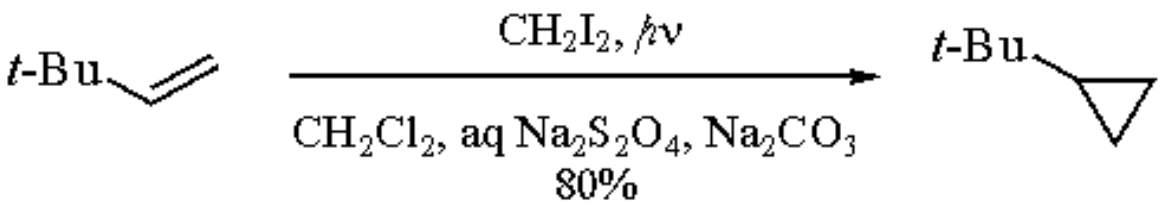

(7)

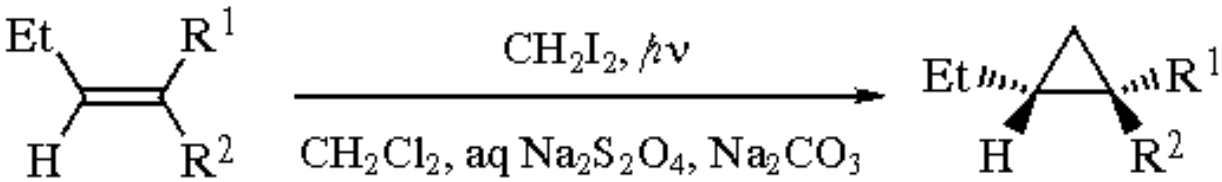

(8)

$R^1 = Et, R^2 = H$; 75%
$R^1 = H, R^2 = Et$; 76%

Perhaps the most common use of CH_2I_2 in organic synthesis is in metal-mediated cyclopropanations. Foremost among these are zinc-mediated cyclopropanations (Simmons-Smith reaction).[1,13] This is a widely utilized and versatile transformation. Treatment of CH_2I_2 and an alkene with ***Zinc/Copper Couple*** in refluxing Et_2O affords the corresponding cyclopropane, generally in good yield (eq 9).[14] The source of the zinc is crucial to the success of the

reaction, and several reliable protocols exist.[15] The use of ***Diethylzinc*** place of the Zn/Cu couple generates a similar reagent;[16] this modification has several advantages, including the option of using noncoordinating solvents. In many cases, the use of ***Chloroiodomethane***/Et_2Zn in place of CH_2I_2/Et_2Zn is desirable, as the former is more reactive.[17] Regardless of the method of reagent generation, the stereochemical course of the reaction is strongly influenced by proximal oxygen substituents (eq 10), and several effective chiral auxiliaries have been developed.[18]

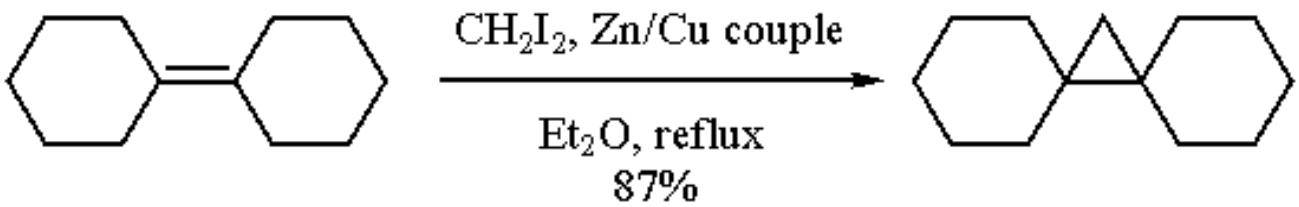

(9)

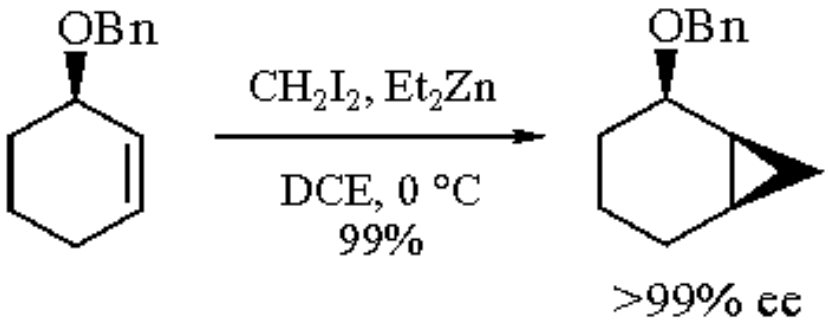

(10)

Similarly, treatment of CH_2I_2 with a trialkylaluminum reagent (e.g. ***Triisobutylaluminum***) in the presence of alkenes also affords cyclopropanes.[19] This reagent system exhibits a reactivity pattern complementary to the zinc- and samarium-based systems, reacting preferentially with isolated alkenes rather than with allylic alcohols (eq 11).[19a]

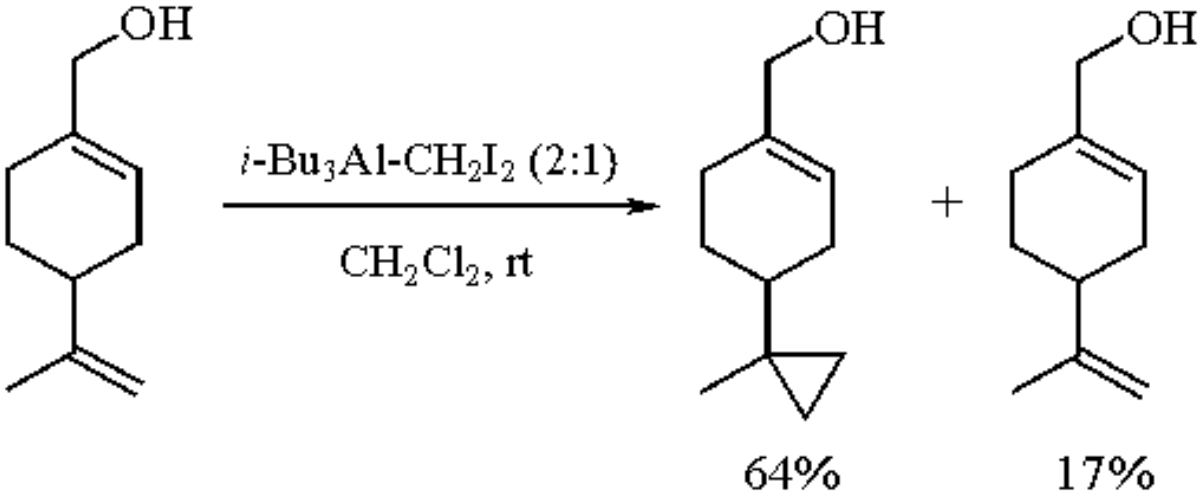

(11)

A very versatile reagent for the cyclopropanation of alkenes is derived from CH_2I_2 and Sm(Hg) or ***Samarium(II) Iodide***.[20] These reagents react well with allylic alcohols (eq 12)[20a,b] and enolates (eq 13),[20d] and are subject to the same hydroxy-directing effects[20a,b,f,g] as the zinc-based reagents (vide supra). In fact, an oxygen substituent is required for cyclopropanation to occur.[20b] A diastereoselective cyclopropanation utilizing a chiral acetal as a chiral auxiliary has also recently been reported (eq 14).[20g] The substitution of $ClCH_2I$ for CH_2I_2 in these reactions often results in higher yields.[20b] Interestingly, a comparison of the response of the CH_2I_2/Sm(Hg) and CH_2I_2/SmI_2 reagents towards various allylic alcohols showed little or no difference in either reactivity, chemoselectivity, or stereoselectivity.[20b]

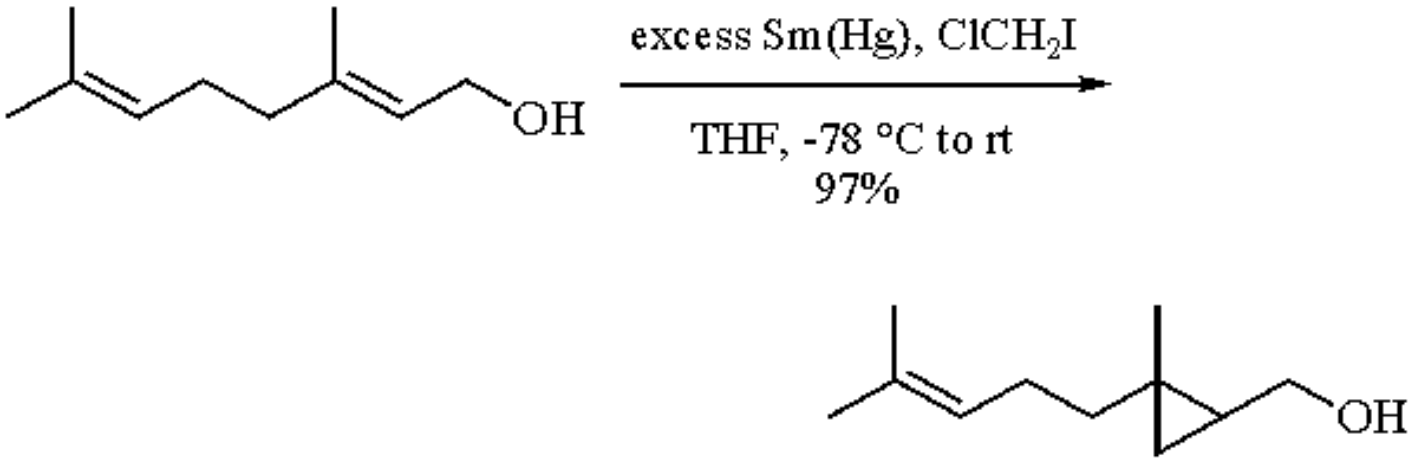

(12)

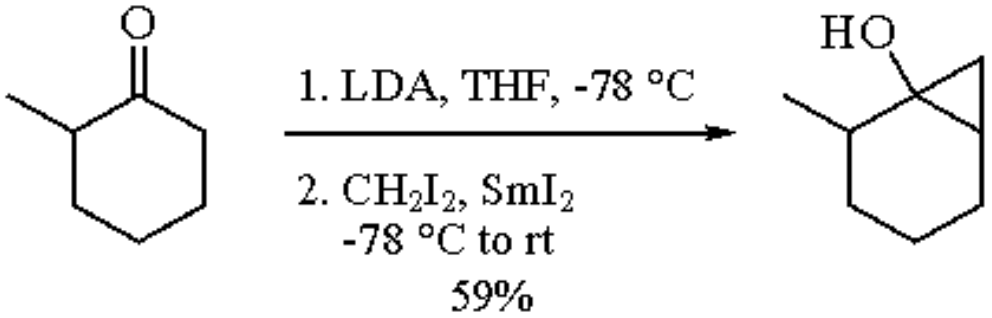

(13)

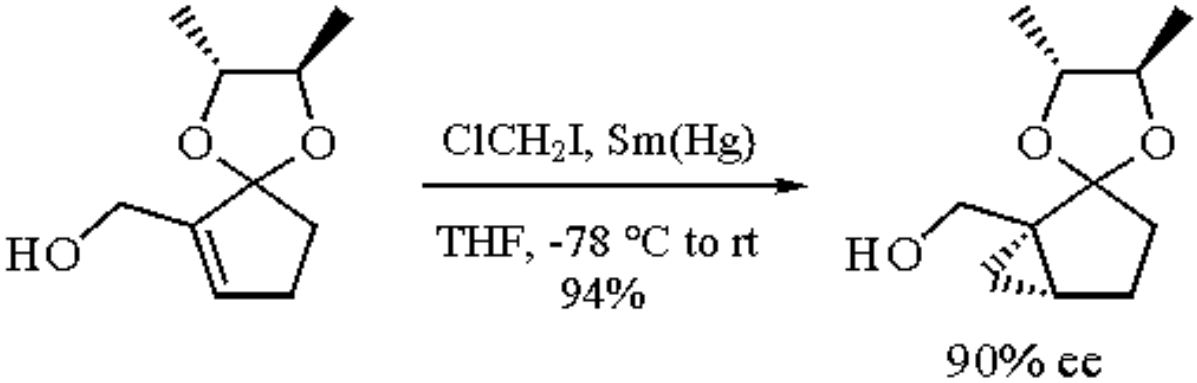

(14)

Nucleophilic Additions of ICH_2.

Halomethyllithium reagents are generally unstable except at very low temperatures (<-90 °C),[21] but the use of additives such as ***Lithium Bromide*** results in greater stability, particularly for ***Chloromethyllithium*** and ***Bromomethyllithium***.[21c,22] The utility of ICH_2Li is still limited, however.[23] Fortunately, an alternative method for the generation of an iodomethyl nucleophile has been developed which utilizes ***Samarium(0)*** as the metal.[3,20c] Aldehydes, ketones, and enones all participate well in this reaction, and yields range from moderate to excellent (eq 15). In the illustrated example, the alkene is not cyclopropanated, consistent with the observation that tertiary allylic alcohols react sluggishly with samarium carbenoids.[20b]

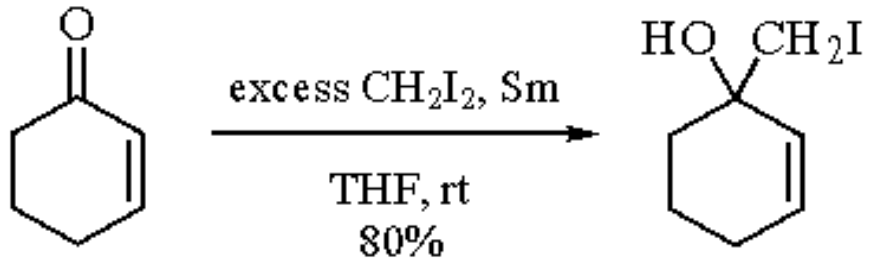

(15)

The replacement of an allylic alcohol oxygen by CH_2I has also been achieved by the use of aluminum reagents.[24] The combination of ***Triethylaluminum***, Et_2AlCl, and Et_2AlOEt mediates this reaction (eq 16).

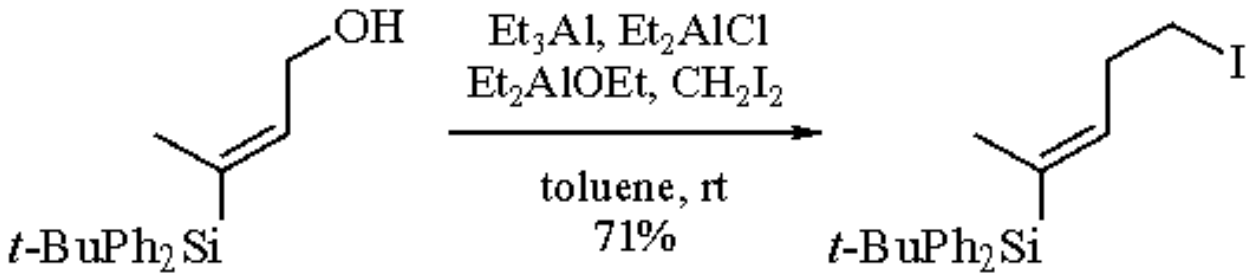

(16)

Nucleophilic Additions of I_2CH.

Deprotonation of CH_2I_2 by base affords I_2CHMet derivatives which are more stable than the corresponding ICH_2Met species and react well with a variety of electrophiles.[25] Among the bases used successfully are Cy_2NLi,[25a] ***Sodium Hexamethyldisilazide*** (NaHMDS),[25b] ***Lithium Hexamethyldisilazide*** (LiHMDS),[25b] and ***Lithium Diisopropylamide*** (LDA).[25c] I_2CHLi reacts well with aldehydes (eq 17),[25a] and also with silacyclobutanes, affording 2-iodosilacyclopentanes after ring enlargement of the intermediate five-coordinate siliconate (eq 18).[25c] I_2CHNa has been shown to react with electrophiles such as ***Chlorotrimethylsilane***, ***Ethyl Iodide***, and ***Allyl Iodide***.[25b]

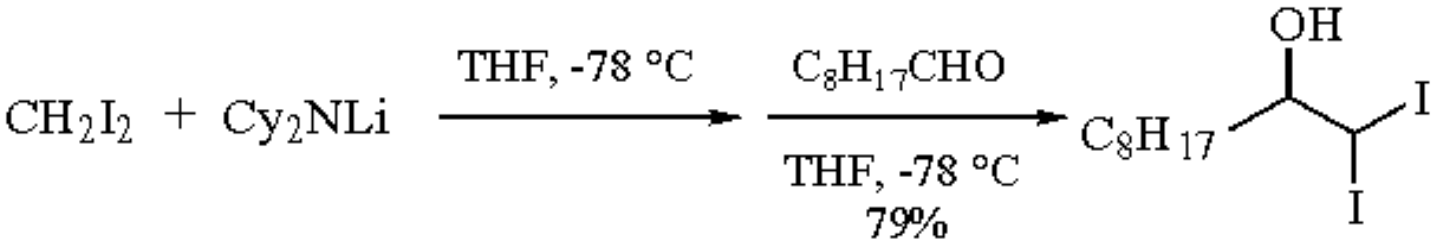

(17)

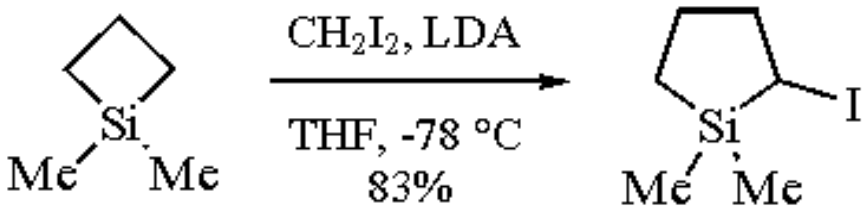

(18)

A convenient synthesis of vinyl iodides using I_2CHLi has been reported by Julia and co-workers.[25b] Treatment of CH_2I_2 with LiHMDS followed by the addition of a lithiated sulfone affords vinyl iodides after aqueous workup. The selectivity is generally low, however (eq 19).

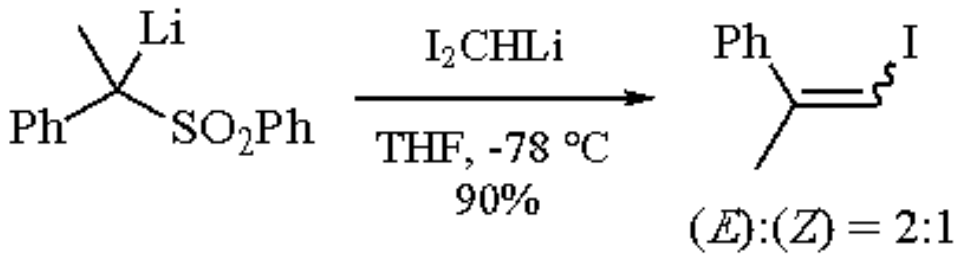

(19)

Radical Additions Utilizing CH_2I_2.

The radical addition of the ICH_2 fragment to α,β-unsaturated ketones mediated by ***Triethylborane*** provides a route to γ-iodo ketones (eq 20).[4] The intermediate boron enolates can be either hydrolyzed or alkylated in some cases.[4] Vinylsilacyclobutanes are also alkylated by the putative ICH_2 radical, affording highly functionalized silylcyclobutane derivatives (eq 21).[26]

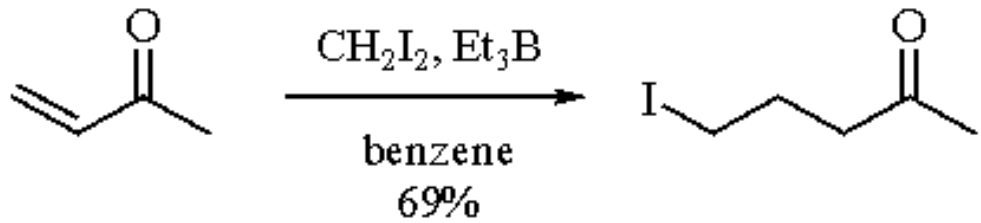

(20)

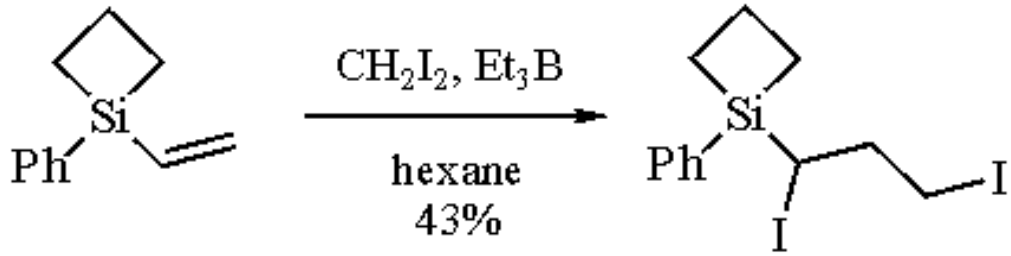

(21)

Alkylation Reactions.

CH_2I_2 has seen limited use as an alkylating reagent, since heterodihalomethanes such as $ClCH_2I$ and $ClCH_2Br$ are preferred for these reactions.[27,28] CH_2I_2 has been used for alkylative cyclizations, however. A recent interesting application is the formation of 2-imino-1,3-dithiazetidines from thioureas (eq 22).[29a] Mixtures of isomers are obtained unless one of the urea nitrogen atoms is deactivated as a sulfonamide, amide, or carbamate. In addition, diamines are known to react with CH_2I_2: slow addition of the diamine to a solution of CH_2I_2 is necessary to obtain good yields (eq 23).[29b]

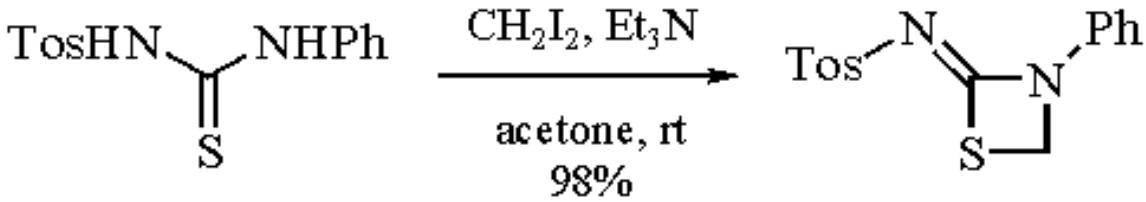

(22)

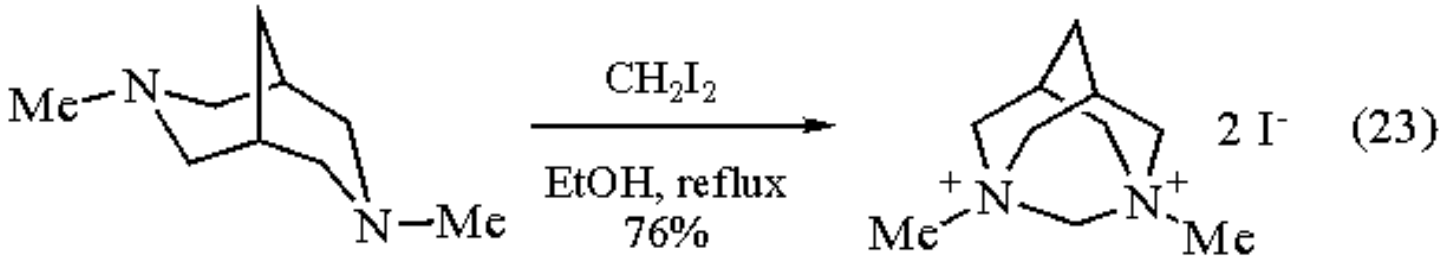

In a mechanistically distinct but related example, dithianes are produced by the Pt-catalyzed coupling of CH_2I_2 with thiols (eq 24).[30]

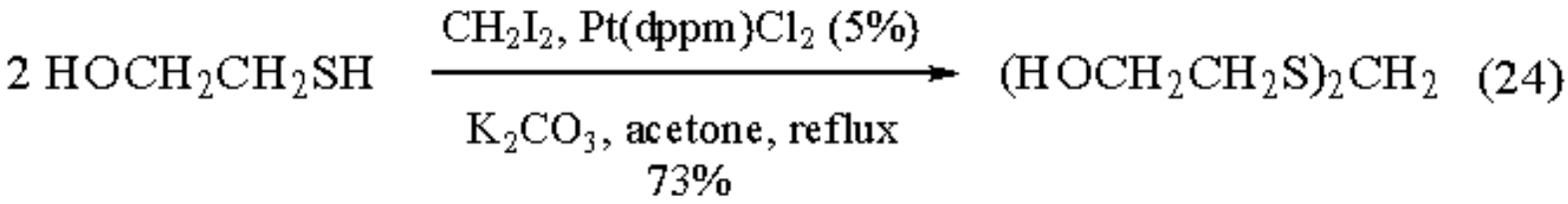

Other Uses.

Several other transformations also utilize CH_2I_2. For example, heating CH_2I_2 with 2 equiv of ***Tin(II) Bromide*** and a catalytic amount of ***Triethylamine*** affords a di-tin compound[31a] which can be exhaustively methylated to afford bis(trimethylstannyl)methane (eq 25).[31b] In addition, a convenient procedure for the in situ preparation of the valuable reagent SmI_2 involves simply treating Sm powder with CH_2I_2 in THF.[32]

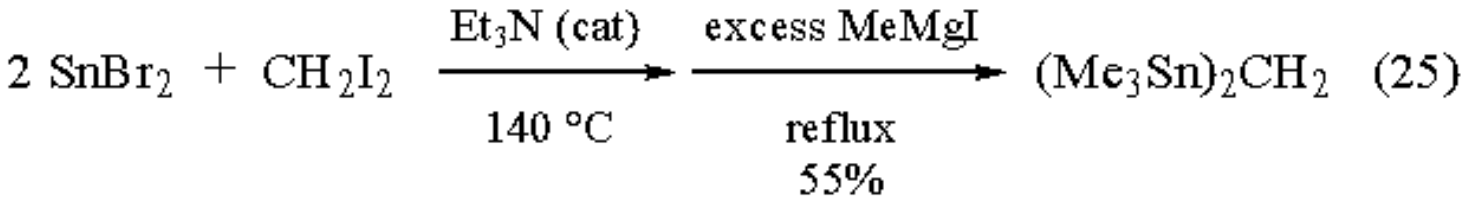

Related Reagents.

Chloroiodomethane; ***Dibromomethane***; ***1,1-Diiodoethane***; ***Diiodomethane-Zinc-Titanium(IV) Chloride***; ***Iodomethylzinc Iodide***.

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James P. Edwards

Diiodomethane-Zinc-Titanium(IV) Chloride

CH_2I_2-Zn-$TiCl_4$

(CH_2I_2)

[75-11-6] · CH_2I_2 · Diiodomethane-Zinc-Titanium(IV) Chloride · (MW 267.84) (Zn)

[7440-66-6] · Zn · Diiodomethane-Zinc-Titanium(IV) Chloride · (MW 65.37) ($TiCl_4$)

[7550-45-0] · Cl_4Ti · Diiodomethane-Zinc-Titanium(IV) Chloride · (MW 189.71) (Ti(O-*i*-Pr)$_4$)

[546-68-9] · $C_{12}H_{28}O_4Ti$ · Diiodomethane-Zinc-Titanium Tetraisopropoxide · (MW 284.26)

(reagent combination for methylenation of aldehydes and ketones)

Physical Data: CH_2I_2: mp 6 °C; bp 181 °C; *d* 3.325 g cm^{-3}. Zn: mp 419.5 °C; *d* 7.140 g cm^{-3}. $TiCl_4$: mp -24 °C; bp 136.4 °C; *d* 1.730 g cm^{-3}. Ti(O-*i*-Pr)$_4$: mp 20 °C; bp 58 °C/1 mmHg; *d* 0.955 g cm^{-3}.

Solubility: sol THF.

Preparative Methods: prepared in situ.

Handling, Storage, and Precautions: CH_2I_2 is corrosive and is light sensitive; it is usually stabilized with a small amount of copper. $TiCl_4$ is highly toxic and extremely moisture sensitive. Ti(O-*i*-Pr)$_4$ is an irritant and is flammable. Zn is a moisture-sensitive, flammable solid.

General Discussion.

The reagent prepared by the combination of ***Diiodomethane***, ***Zinc***, and ***Titanium(IV) Chloride*** is very effective at converting enolizable aldehydes and ketones into their methylene derivatives (eq 1).[1] The reaction many times provides improved yields over the conventional ***Methylenetriphenylphosphorane***. The β-acetoxy ketone was transformed into the alkene (eq 1) in 73% yield with minimal side reactions. The standard Wittig conditions produced only a 39% yield of the desired methylenated product along with a number of other side products derived from elimination reactions.[2]

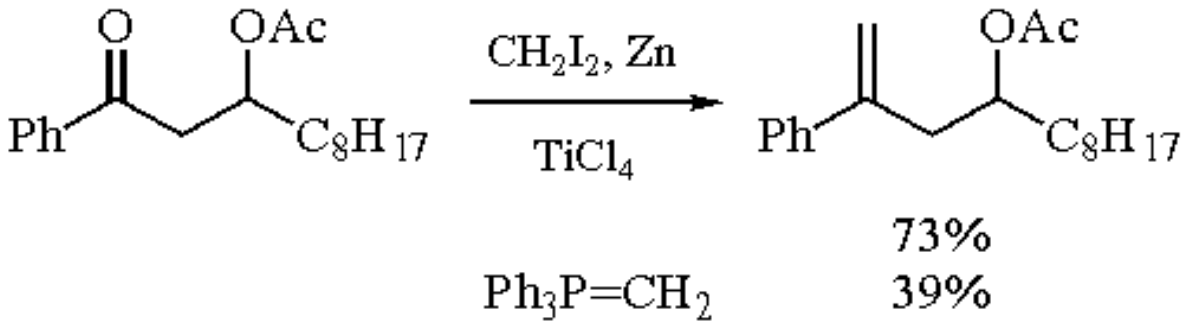

(1)

In the case of α-tetralone, the CH_2I_2 reagent combination was superior to the ***Dibromomethane-Zinc-Titanium(IV) Chloride*** reagent. The former conditions deliver the product in 88% yield, while the latter set produces only an 11% yield of alkene (eq 2).[2]

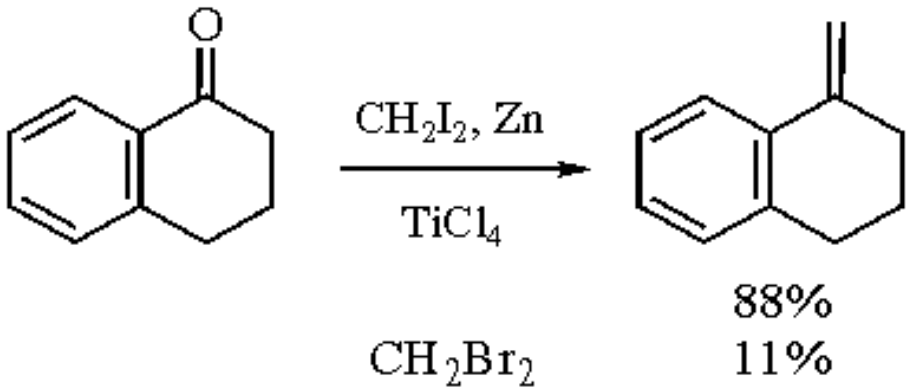

(2)

By the appropriate choice of reaction conditions, chemoselective methylenations can be performed. One can chemoselectively convert an aldehyde into the methylene derivative in the presence of a ketone (eq 3). This requires that the reagent's reactivity be moderated slightly by using ***Titanium Tetraisopropoxide*** in place of $TiCl_4$. The reagent prepared from $TiCl_4$ is too reactive to offer any appreciable levels of selectivity. Alternatively, a ketone may be methylenated selectively in the presence of an aldehyde if the keto-aldehyde is first pretreated with ***Titanium Tetrakis(diethylamide)*** (eq 4). The ketones still require the $TiCl_4$ prepared reagent.[3]

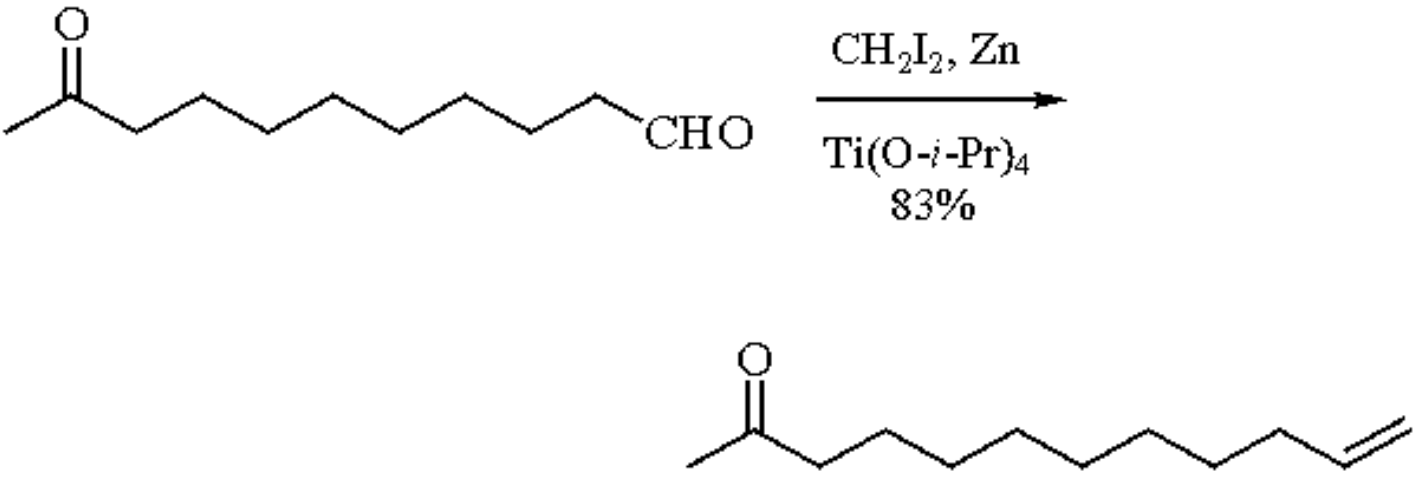

(3)

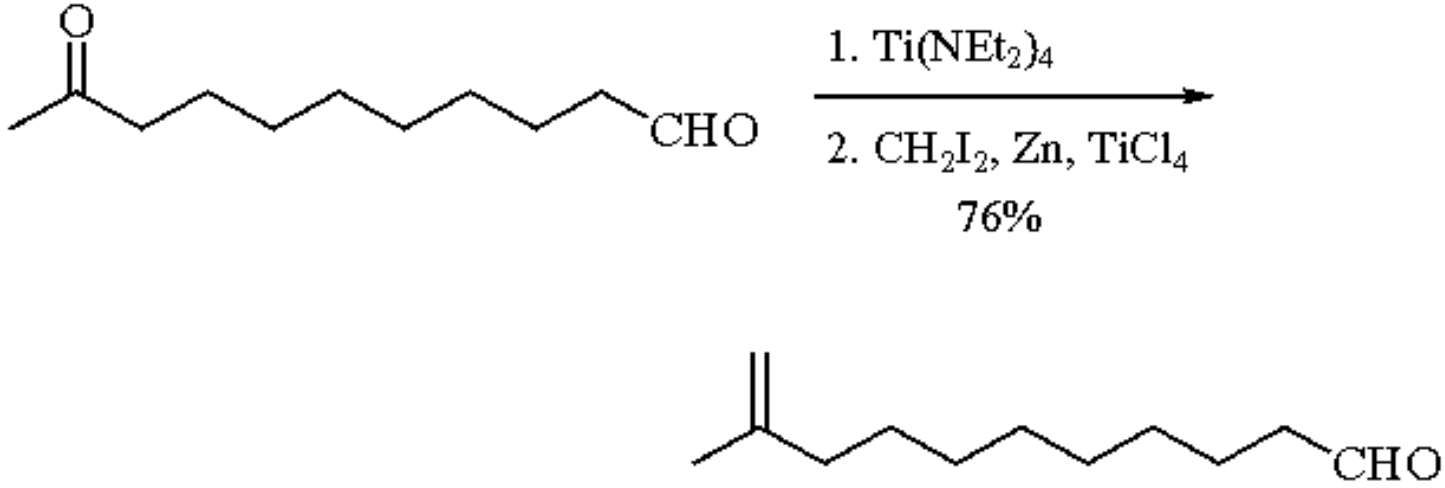

(4)

A number of optically active α-amino ketones have been converted to allylic amines using this reagent (eq 5). The yields were moderate and the enantiomeric excesses generally were very high (>98%). The one exception was the α-phenylglycine-derived ketone which provided the alkene in only 48% ee.[4]

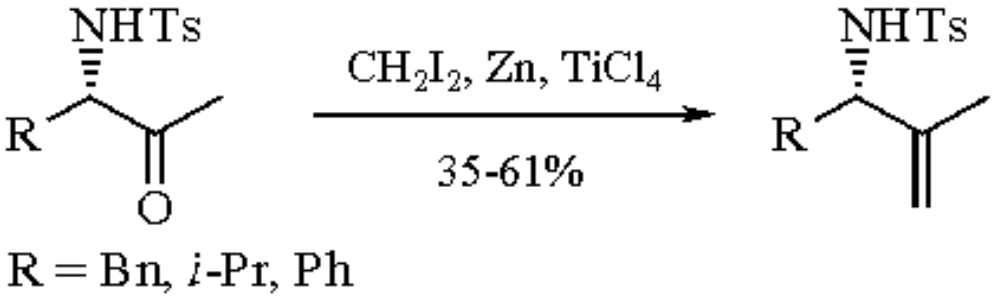

(5)

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Diiodo(methyl)bis(triphenylphosphine)rhodium(III)[1]

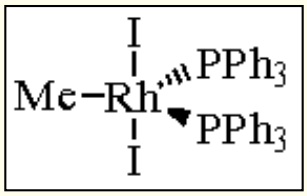

[47829-28-7] · $C_{37}H_{33}I_2P_2Rh$ · Diiodo(methyl)bis(triphenylphosphine)rhodium(III) · (MW 896.35)

(used in cross-coupling of organomercurials with alkyl halides[2])

Physical Data: mp 170 °C (dec); ^{1}H NMR (CD_2Cl_2) δ 2.8 (dt, *J* = 2.9, 5.3 Hz, C*H*$_3$), 7.39 (m, $H_{m,p}$ of Ph), 7.63 (m, H_o of Ph); λ_{max} (log ε in CH_2Cl_2) 250 (sh), 340 (3.71), 500 (sh), 610 (2.31); *d* 1.67 g cm^{-3}.

Solubility: sparingly sol benzene and chloroform; sol CH_2Cl_2 and nitromethane; insol acetone or petroleum.

Form Supplied in: dark green crystalline solid.

Preparative Methods: ***Chlorotris(triphenylphosphine)rhodium(I)*** (1.0 g, 1.08 mmol) is allowed to stir in ***Iodomethane*** (20 mL) for 1 h; excess solvent is removed in vacuo and the resulting mass extracted with acetone; recrystallization from benzene affords green crystals of $MeRhI_2(PPh_3)_2.C_6H_6$;[1] an alternate method of preparing uncomplexed $MeRhI_2(PPh_3)_2$ involves addition of iodomethane in dichloromethane to $(Ph_3P)_3Rh^+HC(SO_2CF_3)_2^-$.[2]

Handling, Storage, and Precautions: the dry solid is moderately air-stable but rapidly air-oxidizes in solution.

Methylation of Organomercurials.[3]

The stoichiometric cross-coupling of organomercurials with alkyl halides proceeds in moderate to excellent yields using $MeRhI_2(PPh_3)_2$. Optimal conditions for cross-coupling alkenylmercurials include addition of excess ***Lithium Chloride***, using HMPA as solvent, and running the reaction at 70 °C for 24 h. Indeed, addition of $MeRhI_2(PPh_3)_2$ to styrylmercury(II) chloride under these conditions affords propenylbenzene in excellent yield (eq 1). Only small amounts of product formed, however, in reactions where the rhodium complex was prepared in situ with subsequent attempts at cross-coupling.

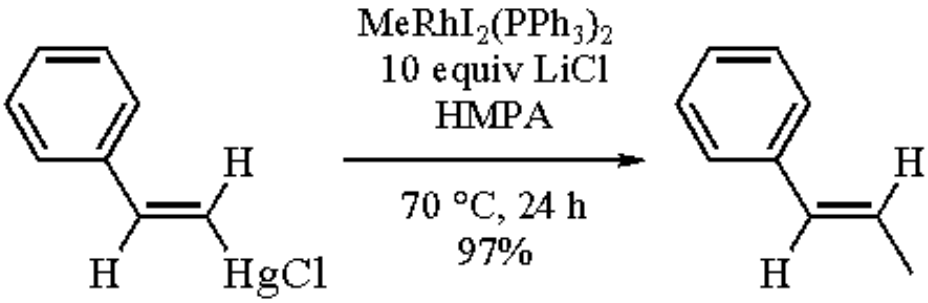

(1)

Dialkynylmercury compounds transmetalate with $MeRhI_2(PPh_3)_2$ to give products with complete methylation of both organic moieties

(eq 2). Attempted methylation of *n*-decylmercury(II) chloride gives only *n*-decane, 1-decene, and other isomeric decenes. Methylation of benzylmercury(II) chloride and α-chloromercurioacetophenone has also failed.

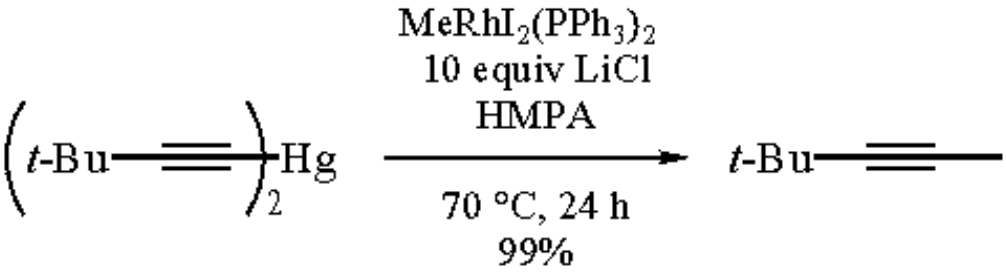

(2)

Arylmercurials react with $MeRhI_2(PPh_3)_2$ in the presence of excess iodomethane to give the corresponding methyl-substituted arenes (eqs 3 and 4). This reaction is general for arylmercurials containing electron donating and withdrawing groups, as well as heterocyclic organomercurial derivatives.

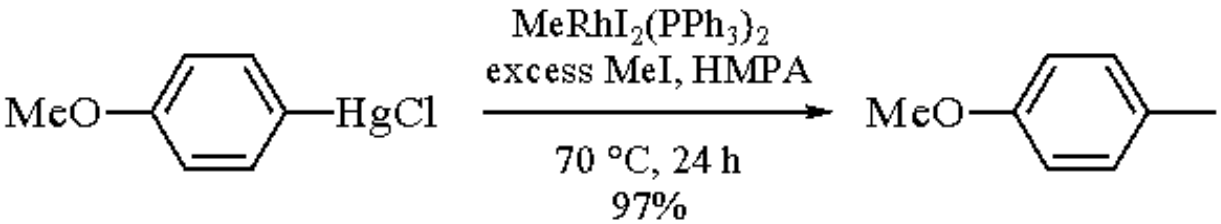

(3)

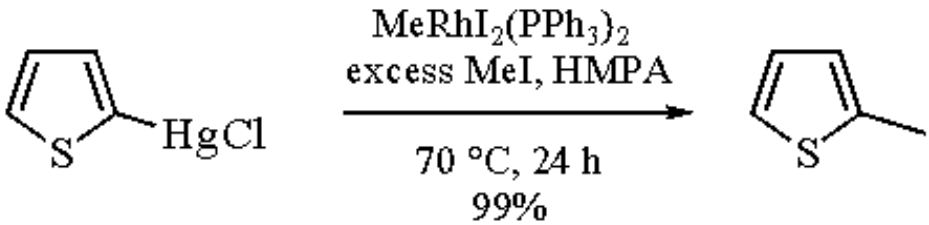

(4)

Unfortunately, attempts to catalyze the methylation of alkenylmercurials using $MeRhI_2(PPh_3)_2$ afford significant amounts of dimerized product.[4] Better yields of cross-coupling products are obtained in catalyzed reactions of dialkynylmercurials (ca. 60%). This catalyst system is also effective for the cross-coupling of arylmercurials with alkenyl halides.

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1,3-Diiodopropane

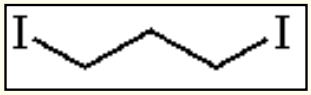

[627-31-6] · $C_3H_6I_2$ · 1,3-Diiodopropane · (MW 295.89)

(electrophilic trimethylene synthon)

Physical Data: bp 111-113 °C/31 mmHg; *d* 2.576 g cm^{-3}.

Form Supplied in: light brown liquid stabilized with copper.

Handling, Storage, and Precautions: light sensitive; must be stored in the dark. Use in a fume hood.

Ring Forming Reactions.

Stepwise ring closure using 1,3-diiodopropane as an electrophile is an important method for the construction of four- to six-membered rings. The ketimine (**1**) is converted into (**2**) (a pivotal intermediate for preparation of clinically useful antihypertensive eburnane alkaloids) by treatment with 1,3-diiodopropane in the presence of ***Diisopropylethylamine*** in acetonitrile under an inert atmosphere. The presence of oxygen leads to the formation of the corresponding 1-hydroxy derivative, presumably via a radical chain oxidation process initiated by iodine generated by the thermal decomposition of 1,3-diiodopropane (eq 1).[1]

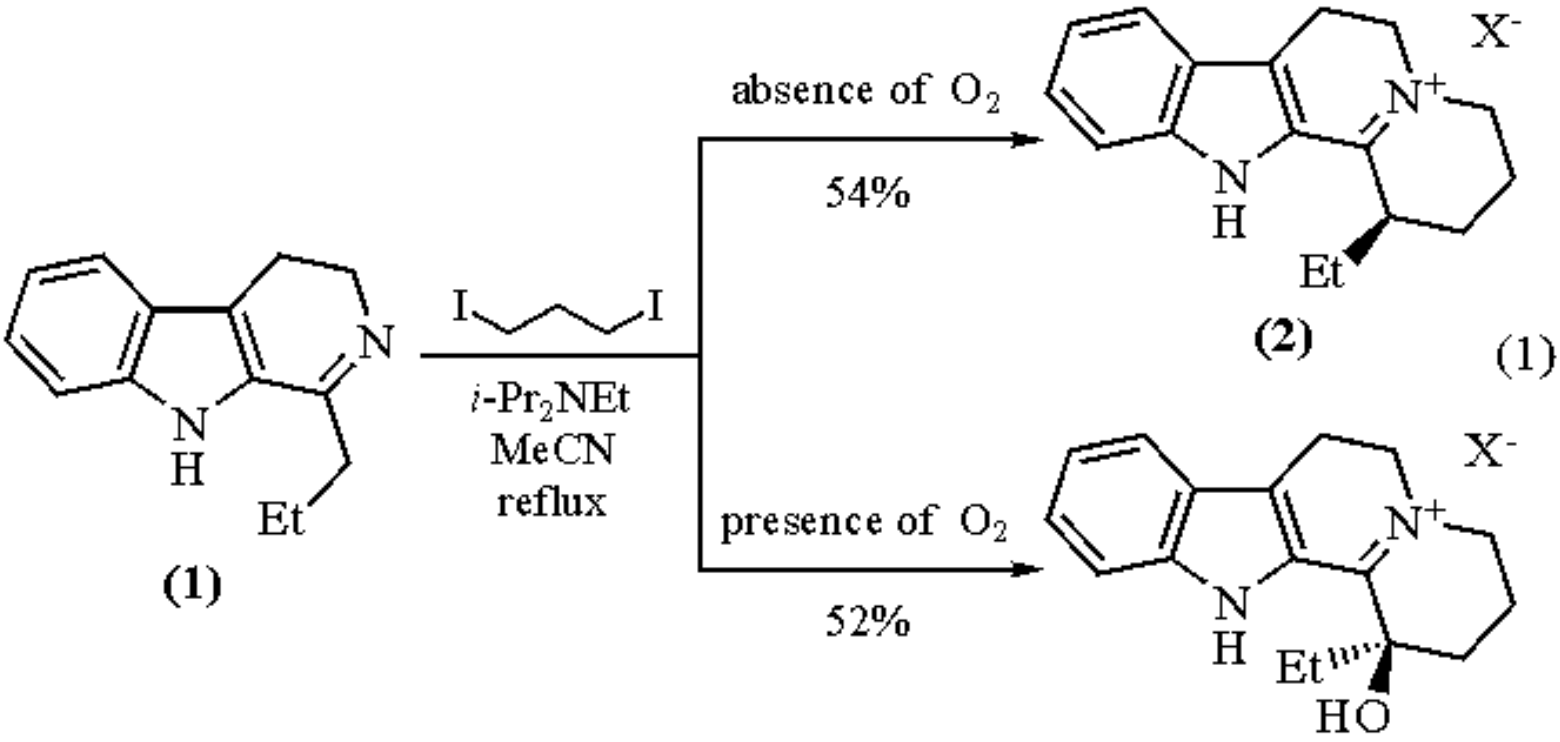

A chiral α-sulfinyl ketimine anion undergoes annulation with 1,3-diiodopropane to give a cyclic β-sulfinyl enamine which is a precursor for various indolizidine alkaloids (eq 2).[2]

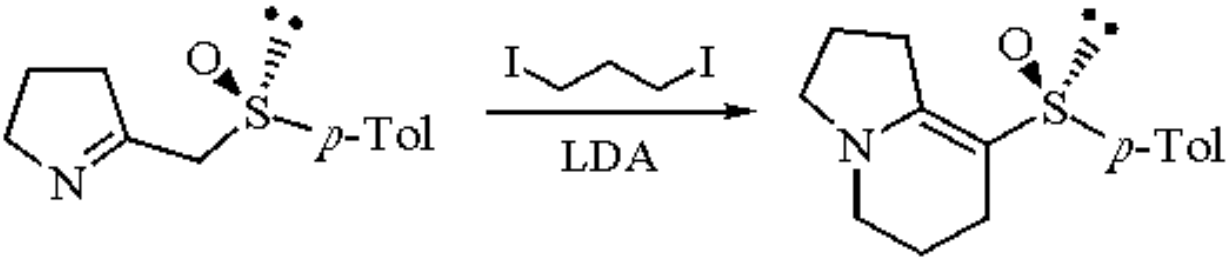

The α,α´-dianion generated by treatment of (*p*-tolylsulfinyl)acetone with 2.2 equiv of ***Lithium Diisopropylamide*** (LDA) reacts with 1,3-diiodopropane to afford the α´-substituted product (**3**), which is intramolecularly cyclized with LDA to give 2-(p-tolylsulfinyl)cyclohexanone (eq 3).[3]

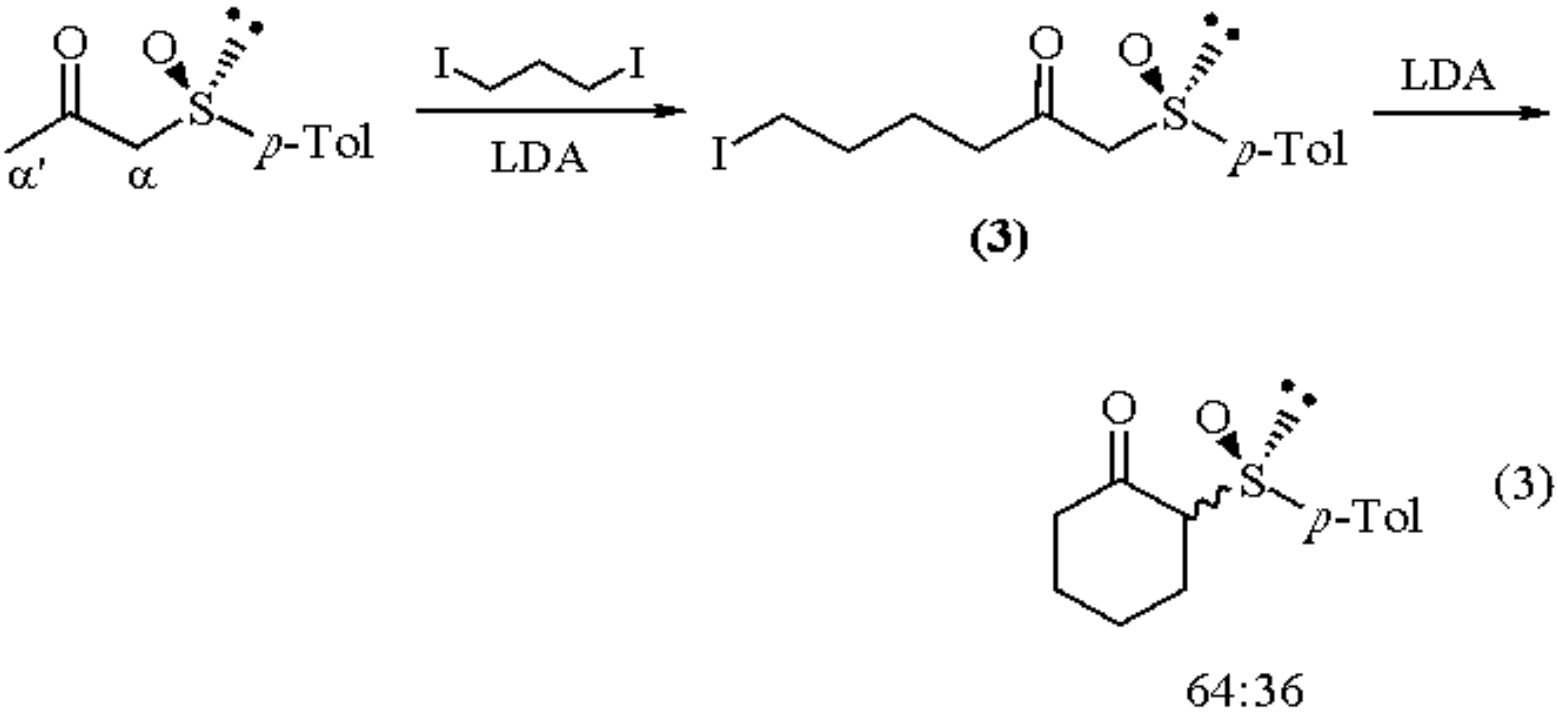

Treatment of 2,5-dihydrothiophene 1,1-dioxide with 2 equiv of ***Lithium Hexamethyldisilazide*** and 1,3-diiodopropane affords the fused bicyclic sulfone (eq 4).[4] On the other hand, 2-trimethylsilyl-2,5-dihydrothiophene 1,1-dioxide gives the spiro sulfone on treatment with ***n-Butyllithium*** and 1,3-diiodopropane in the presence of ***Hexamethylphosphoric Triamide*** (HMPA) (eq 5).[5]

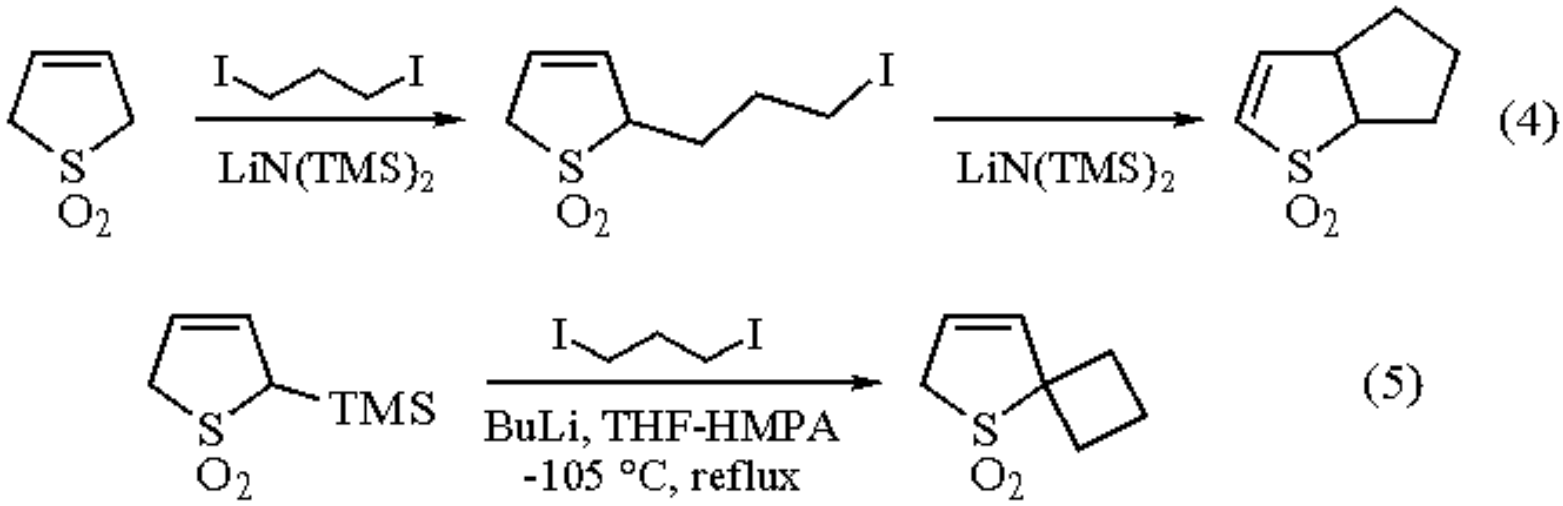

Copper Isocyanide Mediated Annulation with α,β-Unsaturated Esters.

1,3-Diiodopropane reacts with α,β-unsaturated esters to give cyclopentanecarboxylates in the presence of copper isocyanide (eq 6).[6,7] The intermediacy of a 3-iodopropylcopper isocyanide complex is proposed; 1,3-dibromopropane and 1,3-dichloropropane give much inferior yields. Diethyl fumarate and diethyl maleate both afford trans-1,2-dicarbethoxycyclopentane, presumably because diethyl maleate is converted to diethyl fumarate prior to the cyclization and/or because *cis*-1,2-diethoxycarbonylcyclopentane, once formed, isomerizes to the *trans* isomer under the conditions

(eq 7).

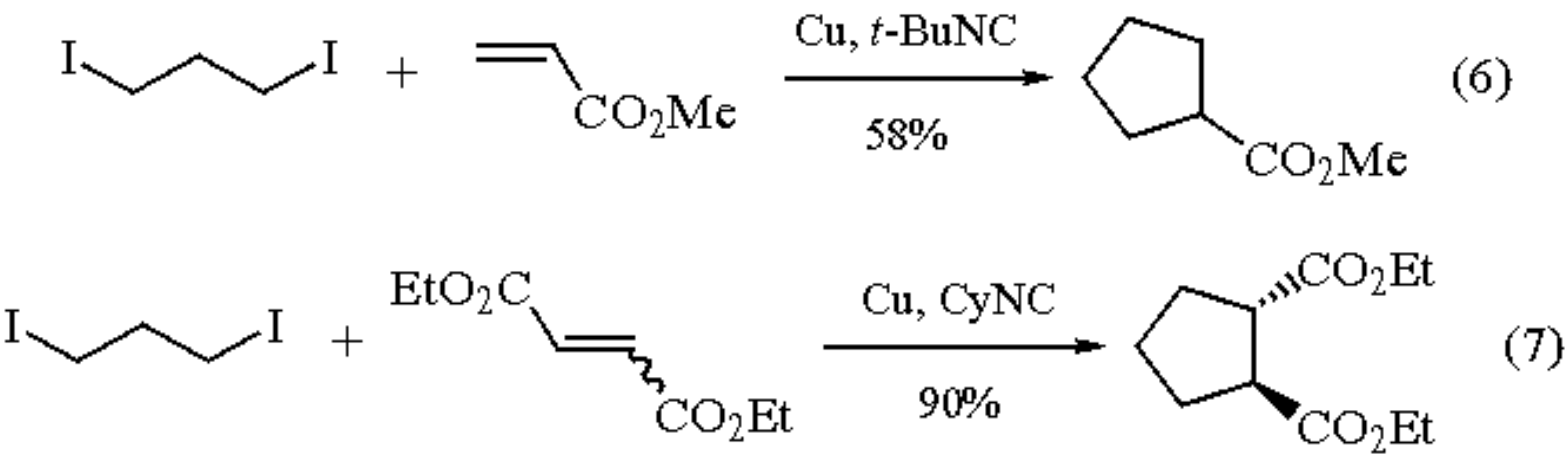

Reaction with Heteroatom Nucleophiles.

1,3-Diiodopropane reacts with 2 equiv of heteroatom nucleophiles, i.e. carboxylates or amines, to give trimethylene-linked dimers. For example, the ammonium salt of monobenzyl tartaric acid is alkylated by 0.5 equiv of 1,3-diiodopropane to give (**4**), which is used as a ligand for titanium in a complex for asymmetric epoxidation of allylic alcohols (eq 8).[8] A C_2 symmetric dimer of (1*R*,2*S*)-(-)-ephedrine is also prepared by alkylation with 1,3-diiodopropane and used as an asymmetric catalyst for addition of ***Diethylzinc*** to aldehydes (eq 9).[9]

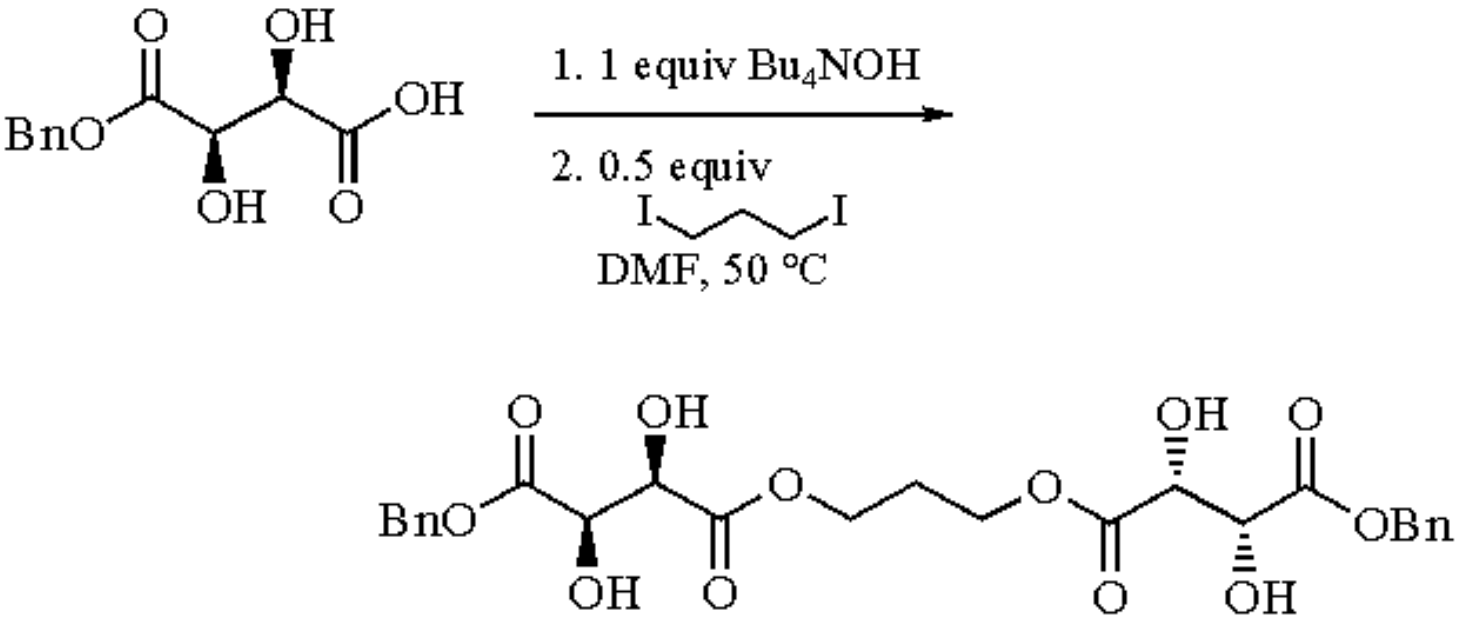

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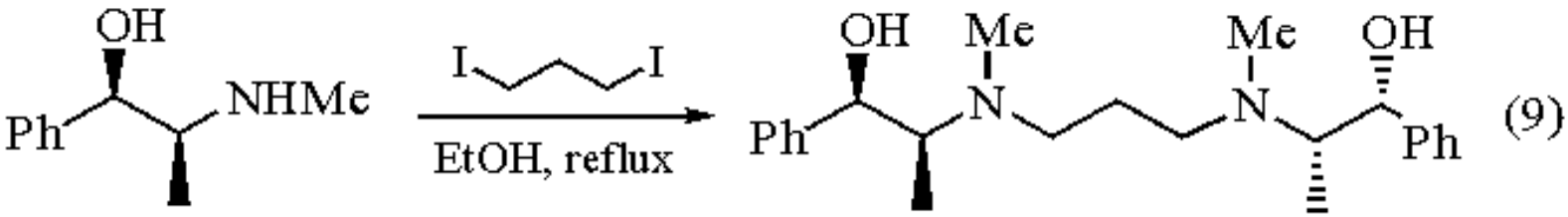

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Diiodosilane

H_2SiI_2

[13760-02-6] · H_2I_2Si · Diiodosilane · (MW 283.91)

(strong, oxophilic Lewis acid, converts alcohols, ethers, and acetals to iodoalkanes;[1,3] converts carboxylic acid derivatives to acyl iodides;[2] mild reducing agent[3])

Alternate Name: DIS.

Physical Data: colorless liquid; mp -1 °C; bp 149.5 °C; bp 58 °C/25 mmHg; bp 0 °C/3.8 mmHg; fp 38 °C; *d* 2.7943 g cm^{-3}.

Solubility: highly sol hydrocarbons and chlorinated solvents; reacts with oxygen- and nitrogen-containing solvents.

Form Supplied in: pale yellow liquid packed under nitrogen in ampules.

Preparative Method: phenylsilane and iodine are mixed in a 1:1 molar ratio without solvent at -20 °C in the presence of catalytic amounts of ethyl acetate; fractional distillation removes volatile side products (benzene and HI) and affords the reagent in the form of a colorless oil.

Handling, Storage, and Precautions: is sensitive to moisture; handle and store under nitrogen; stabilized by metallic copper; refrigeration and absence of light recommended for storage over long periods of time.

Introduction.

All transformations described below are conveniently carried out in either chloroform or dichloromethane at temperatures between -40 and 50 °C. Aqueous work-up with sodium hydrogencarbonate (in which all silicon compounds, including excess reagent, form insoluble polymers) is applicable in most cases. Water-sensitive products are isolated by direct fractional distillation of the reaction mixture.

Diiodosilane (DIS) exhibits properties and reactivities that are either similar or complementary to those of ***Iodotrimethylsilane*** (TMSI). These reagents share two dominant characteristics: both are strong, hard, oxophilic Lewis acids and effective sources of nucleophilic, soft iodide ions. The differences between them arise from the facts that DIS is a stronger Lewis acid than TMSI, it is less sensitive to steric effects, and it can also behave as a hydridic reducing agent.

Conversion of Alcohols and Ethers to Iodoalkanes.[1]

Although both TMSI and DIS react with alcohols and alkyl ethers to produce the corresponding iodoalkanes (with inversion of configuration at carbon), they exhibit complementary selectivities. While TMSI reacts with primary oxygen functions more readily than with secondary ones, DIS exhibits the opposite preference, reacting with secondary alcohols and ethers faster than with the primary functions. As illustrated by the case of butane-1,3-diol (eq 1), this preference of DIS is applicable for regioselective transformations of polyols.

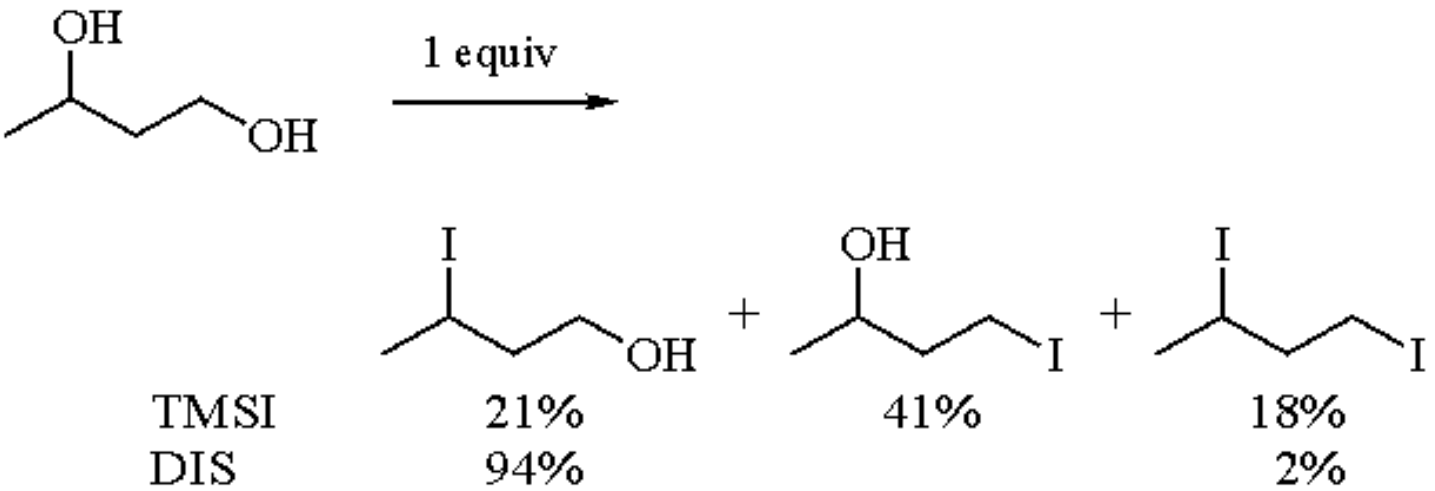

Synthesis of Acyl Iodides.[2]

Various carboxylic acid derivatives, including carboxylic acids, esters, lactones, anhydrides, and acyl chlorides are converted by DIS to acyl iodides. These transformations are accelerated by ***Iodine***. These reactions, when followed by addition of an appropriate alcohol, represent an overall esterification or transesterification method which is particularly useful for sterically hindered and/or poorly nucleophilic alcohols. In the absence of iodine, DIS reacts with carboxylic acids and esters, much as does TMSI, to form the corresponding silyl carboxylates as the final product. Lactones react with DIS to produce either silyl o-iodocarboxylates or o-iodoacyl iodides (eq 2), depending on the reaction conditions. The reaction between DIS and 1 equiv of a carboxylic anhydride affords, in the presence of iodine, 2 equiv of acyl iodide.

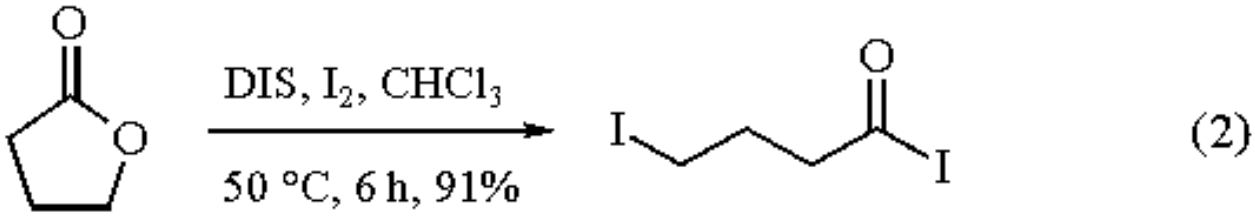

Deprotection of Acetals.[3]

At low temperatures (-42 °C) and short reaction times (few minutes), DIS (5-10 mol %) catalyzes clean deprotection of various acetals, affording the parent ketones and aldehydes with no apparent reduction of the latter (eq 3). These reactions proceed much more rapidly with DIS than with TMSI, probably due to the higher Lewis acidity and lower steric demands of DIS relative to TMSI. The reactivity difference between the two reagents is particularly apparent with

sterically congested acetals, e.g. 4,5-dimethyldioxolane. While these compounds react with TMSI quite sluggishly, their reactions with DIS proceed almost as rapidly as observed with sterically nonhindered acetals.

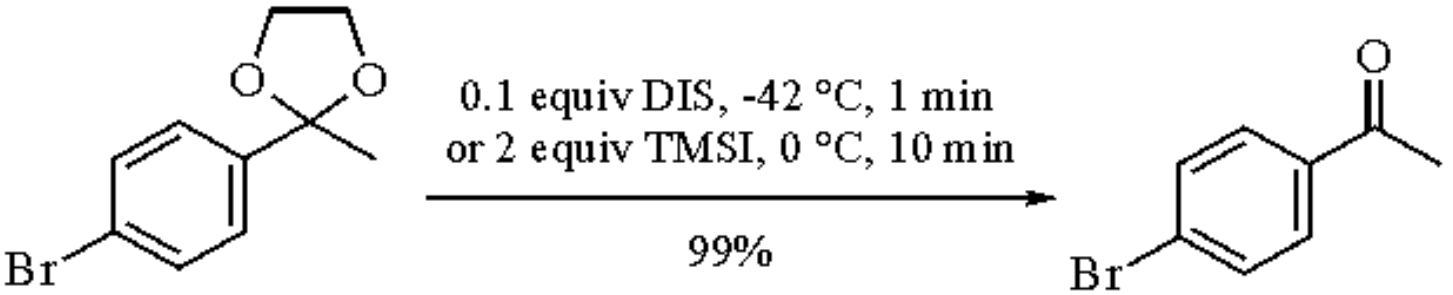

(3)

Reductive Cleavage of Acetals to Iodoalkanes.[3]

At temperatures above 0 °C, DIS effectively reduces acetals as well as unprotected ketones and aldehydes to iodoalkanes (eqs 3-6). Reaction rates are highly dependent on the substrate, with the following tendencies:

- 1)Aromatic acetals are generally more reactive than their aliphatic counterparts.
- 2)Acetals are rapidly reduced to the corresponding iodoalkanes, while free aldehydes, and particularly ketones, are essentially inert under the reaction conditions (but can be significantly activated by catalytic amounts of iodine).
- 3)Dimethyl acetals form the parent ketones preferentially, while all other acetals, including diethyl acetals and dioxolanes, are reduced to iodoalkanes.

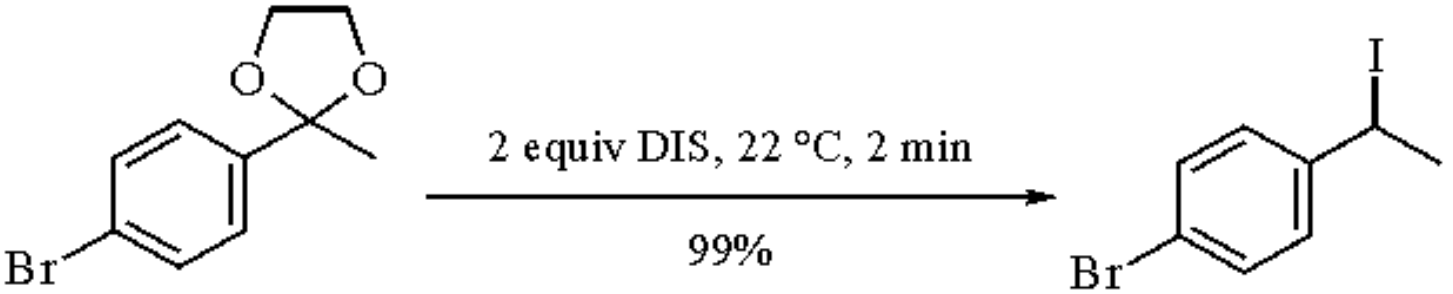

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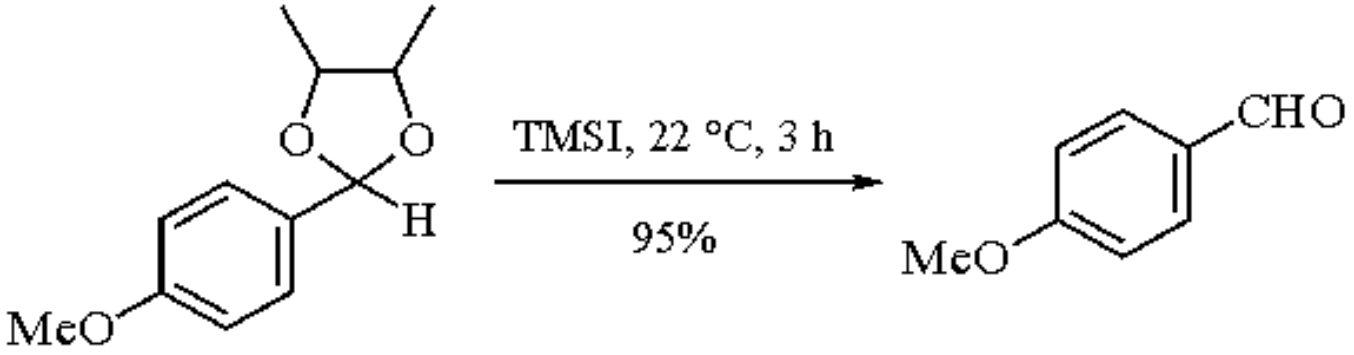

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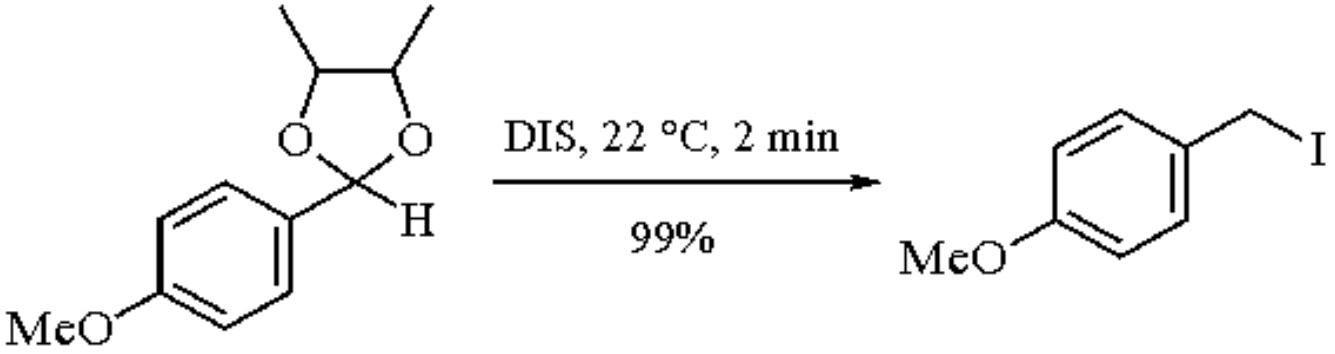

(6)

This reactivity pattern represents inversion of the normal order of reactivity of protected and unprotected carbonyl compounds. In polyfunctional molecules containing both free and protected carbonyls, acetals are chemoselectively reduced by DIS to iodoalkanes in preference to unprotected ketones and aldehydes (eqs 7 and 8).[4]

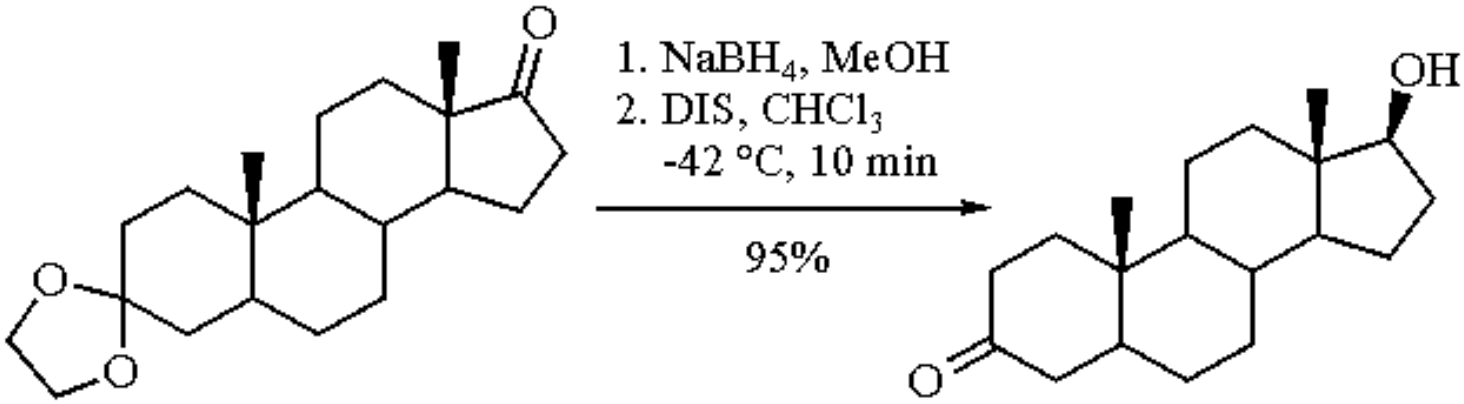

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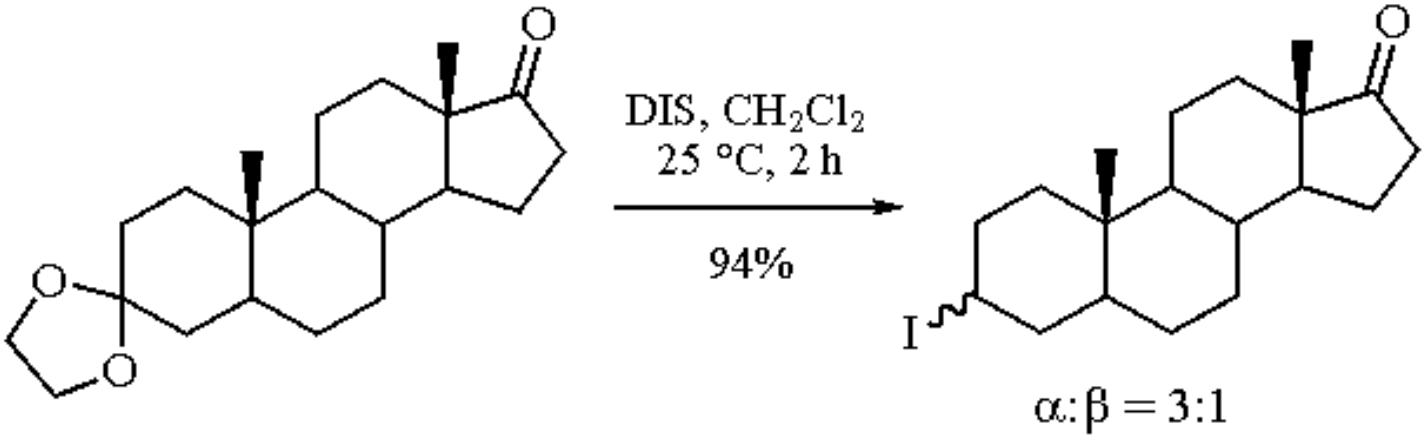

(8)

The reaction of DIS with tetrahydropyranyl (THP) derivatives can be controlled by the amount of reagent used (eqs 9 and 10).[3] While 1 equiv of DIS yields 2-iodo-THP exclusively, excess reagent produces 1,5-diiodopentane.

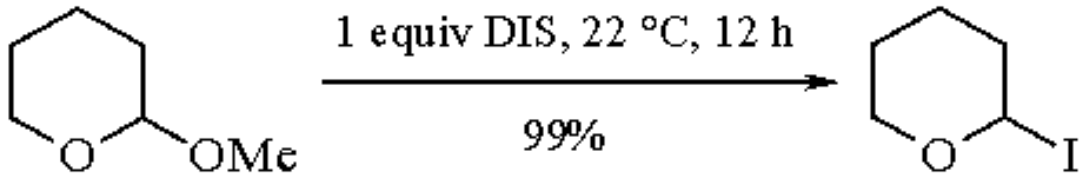

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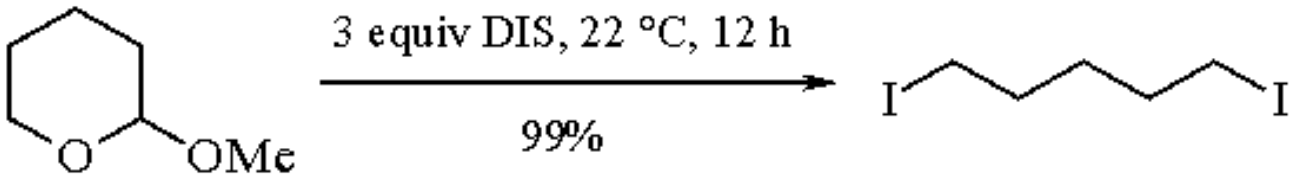

(10)

Dehalogenation of α-Halo Ketones.[5]

α-Halo ketones react readily with DIS between 0 °C and rt to produce the parent ketones. Reactions are faster with DIS than with TMSI but the same order of substrate reactivity, i.e. primary > secondary > tertiary halides, is observed with both reagents. The same transformation can be achieved with phenylsilane (the precursor of DIS) and catalytic amounts of iodine.

Miscellaneous.

Cyclopropyl ketones react with either DIS or TMSI to produce γ-iodo ketones. Again, reaction occurs much faster with DIS than with TMSI (eq 11). Sulfoxides are reduced readily with both reagents to sulfides. Phosphine oxides may be reduced to phosphines provided that an iodine scavenger is present.

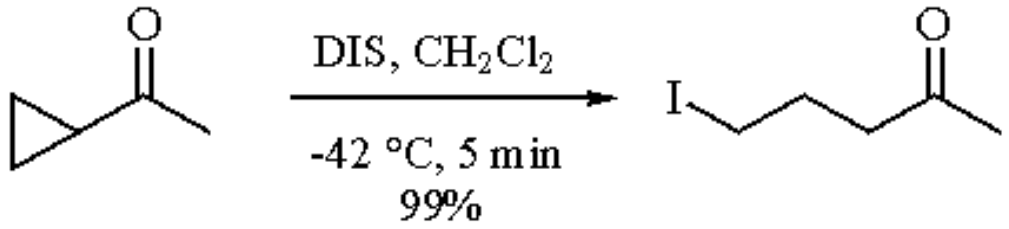

(11)

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Diisobutylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide

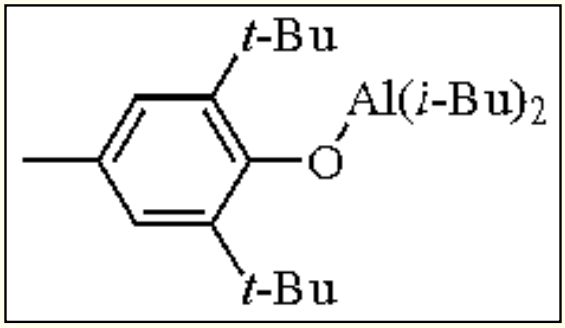

[56252-56-3] · $C_{23}H_{41}AlO$ · Diisobutylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide · (MW 360.62)

(selective reducing agent for enones,[4] particularly prostaglandins,[1,3] β-keto esters,[5] and epoxides;[6] hydroalumination agent;[7] polymerization catalyst[8])

Solubility: sol toluene, CH_2Cl_2, hexane.

Form Supplied in: prepared from commercially available reagents and used in situ.

Preparative Method: prepared by reaction of ***Diisobutylaluminum Hydride*** with 2,6-di-*t*-butyl-4-methylphenol in toluene at 0 °C for 1 h.[1,2]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable; use in a fume hood and protect from oxygen and moisture; solution is stable at 0 °C for several weeks.

Selective Reduction of Enones.

One of the most crucial problems in prostaglandin syntheses is the stereoselective reduction of the C_{15} keto group to the desired (15*S*)-alcohol. The title compound has been devised as the key reagent for a simple and practical solution to this problem.[1] Thus a prostaglandin intermediate is reduced to dihydroxylactone with 92% stereoselectivity (eq 1). In marked contrast, the acetate of the prostaglandin intermediate is reduced without any stereoselectivity, thereby implying the importance of the coordination of the bulky aluminum reagent with the 11-hydroxy group. This reagent has been successfully used for stereoselective reduction of several other prostaglandin intermediates.[3]

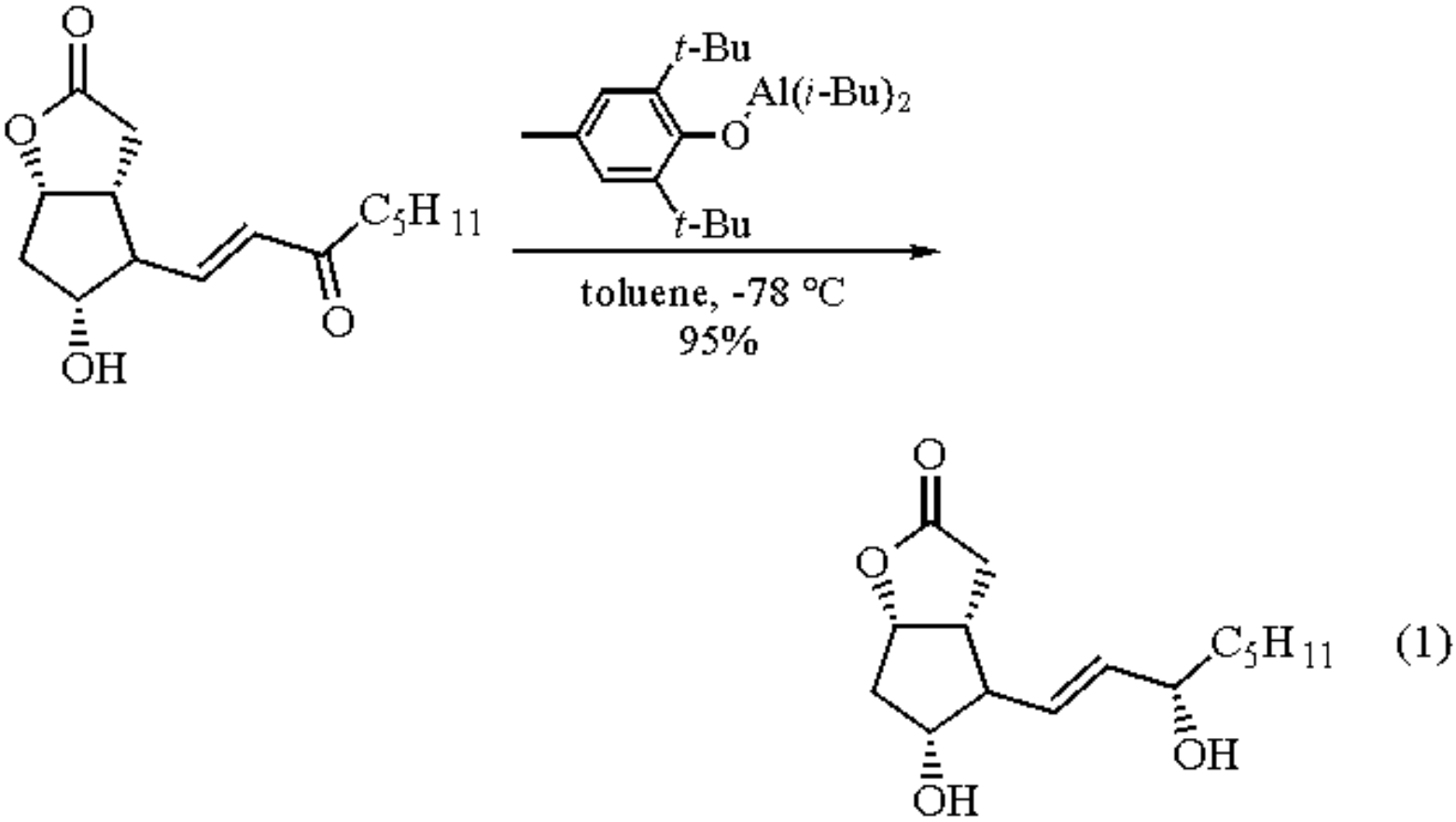

This reducing agent has also been used to reduce an oxodienelactone to a dienol as a key step in the synthesis of the lichen macrolide (+)-aspicilin (eq 2).[4] Dihydroxylation of the dienol with ***Osmium Tetroxide*** and pyridine followed by ***Hydrogen Sulfide*** reduction gave the macrolide in 40% yield.

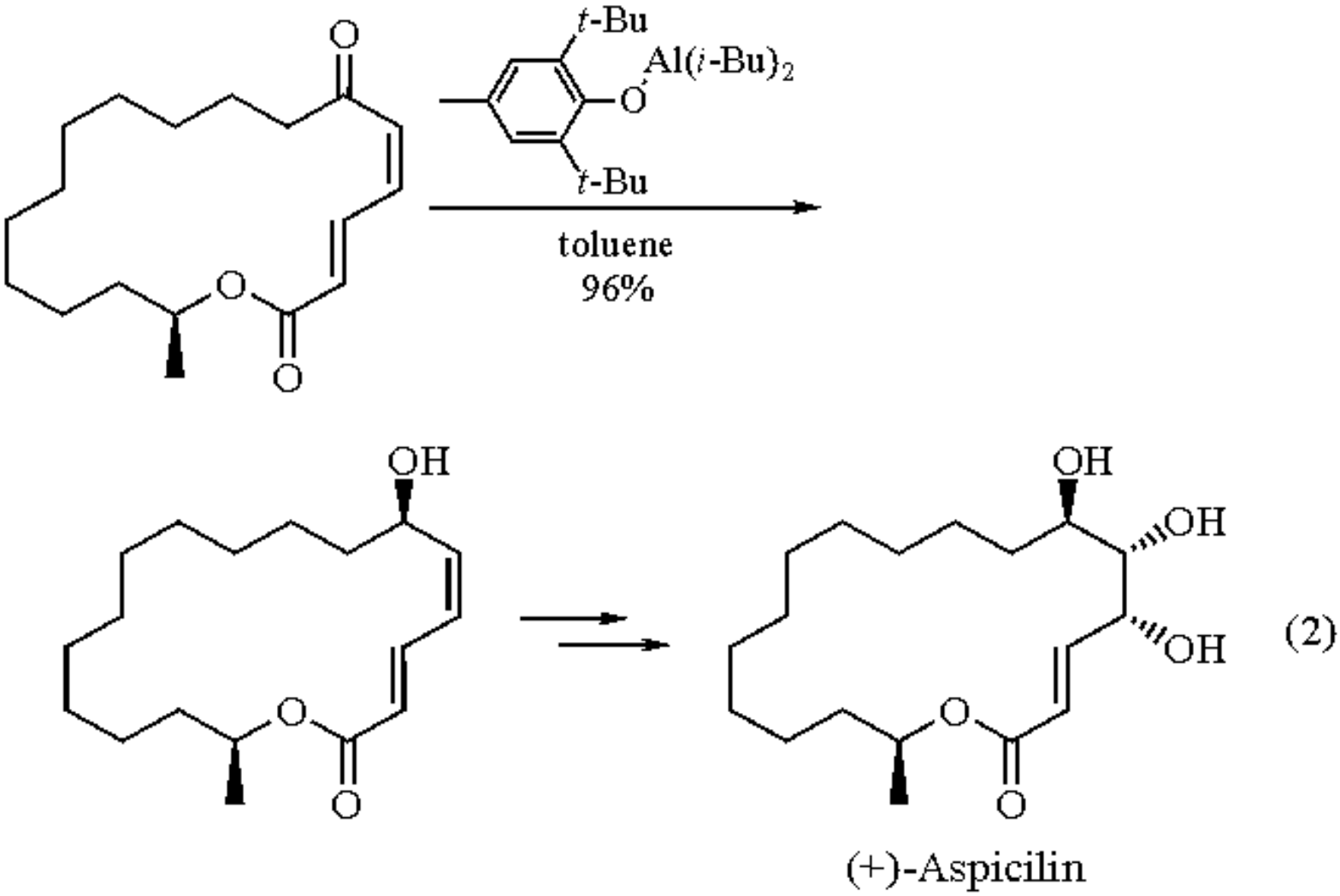

Diastereoselective Reduction of β-Keto Esters.

Reduction of β-keto esters of the chiral α-naphthylborneol is stereoselective because one face of the carbonyl group is blocked by the naphthyl group (eq 3).[5]

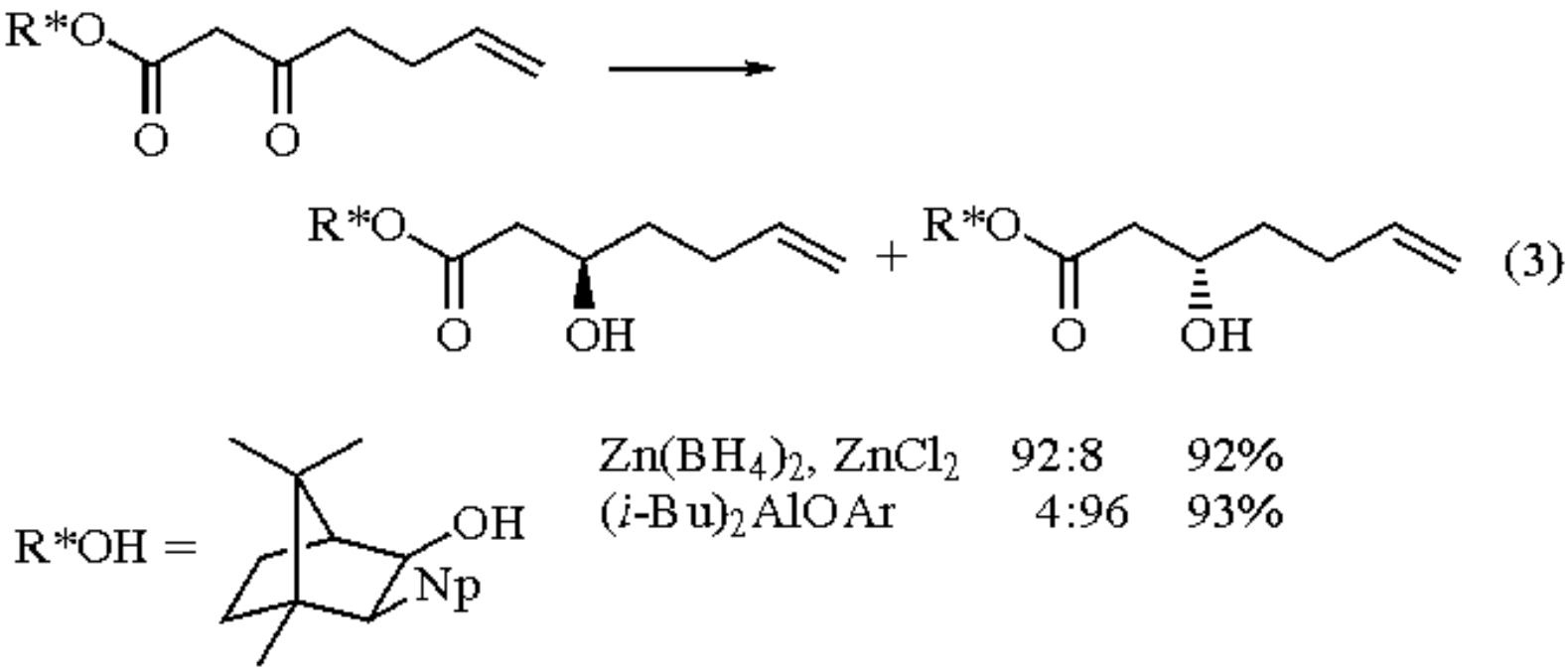

Selective Reduction of Epoxides.

The regioselective reduction of methylenecycloalkane oxides has been studied with a variety of reducing agents. Among these, the title reducing agent and its analogs (diisobutylaluminum 2,4,6-tri-*t*-butylphenoxide and diisobutylaluminum 4-bromo-2,6-di-*t*-butylphenoxide) were found to be most satisfactory, giving the desired less-substituted alcohols with good selectivity (eqs 4-6).[6]

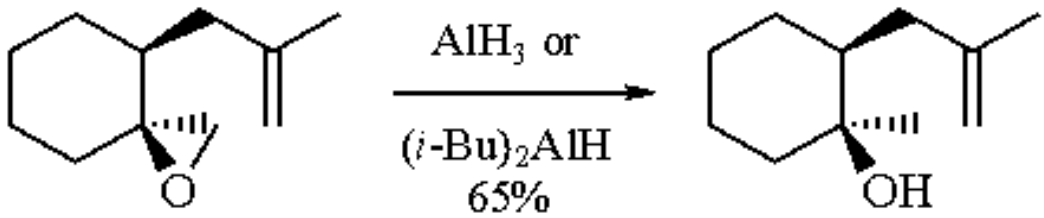

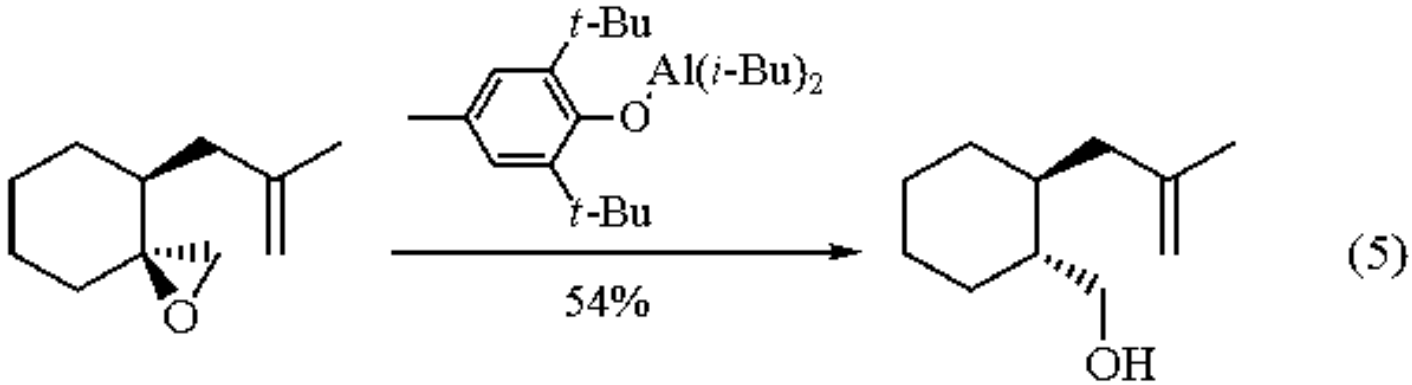

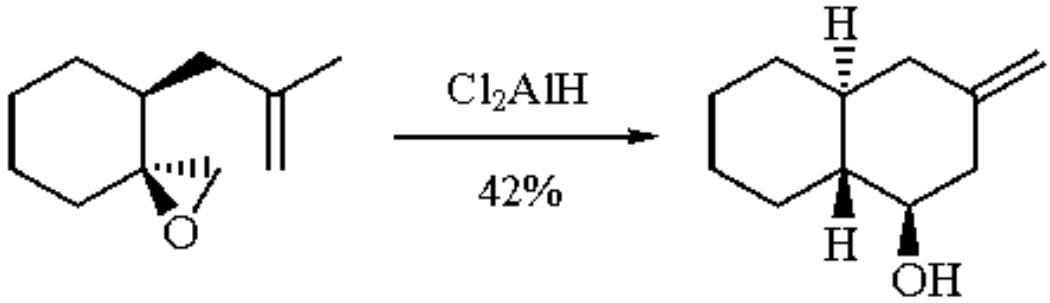

(6)

Hydroalumination.

The hydroalumination of alkenes with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide is carried out in the presence of ***Dichlorobis(cyclopentadienyl)zirconium*** and ***Diisobutylaluminum Hydride*** as catalysts.[7]

Polymerization.

The combination of ***Lithium*** and diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide was found to be effective as an initiator for several types of polymerization of methyl methacrylate at elevated temperature.[8]

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Diisobutylaluminum Hydride[1]

***i*-Bu$_2$AlH**

[1191-15-7] · $C_8H_{19}Al$ · Diisobutylaluminum Hydride · (MW 142.22)

(reducing agent for many functional groups; opens epoxides; hydroaluminates alkynes and alkenes)

Alternate Names: DIBAL; DIBAL-H; DIBAH.

Physical Data: mp -80 to -70 °C; bp 116-118 °C/1 mmHg; *d* 0.798 g cm^{-3}; fp -18 °C.

Solubility: sol pentane, hexane, heptane, cyclohexane, benzene, toluene, xylenes, ether, dichloromethane, THF.

Form Supplied in: can be purchased as a neat liquid or as 1.0 and 1.5 M solutions in cyclohexane, CH_2Cl_2, heptane, hexanes, THF, and toluene.

Handling, Storage, and Precautions: neat liquid is pyrophoric; solutions react very vigorously with air and with H_2O, and related compounds, giving rise to fire hazards; use in a fume hood, in the absence of oxygen and moisture (see ***Lithium Aluminum Hydride*** for additional precautions); THF solutions should only be used below 70 °C, as above that temperature ether cleavage is problematic.

Reduction of Functional Groups.[2]

Diisobutylaluminum hydride has several acronyms: DIBAH, DIBAL-H, and DIBAL. For the purpose of this article, DIBAL will be used.

In general, aldehydes, ketones, acids, esters, and acid chlorides are all reduced to the corresponding alcohols by this reagent. Alkyl halides are unreactive towards DIBAL. Amides are reduced to amines, while nitriles afford aldehydes upon hydrolysis of an intermediate imine. Isocyanates are also reduced to the corresponding imines. Nitro compounds are reduced to hydroxylamines. Disulfides are reduced to thiols, while sulfides, sulfones, and sulfonic acids are unreactive in toluene at 0 °C. Tosylates are converted quantitatively to the corresponding alkanes. Cyclic imides can be reduced to carbinol lactams.

Comparable stereochemistry[2] is observed in the reduction of ketones with DIBAL, ***Aluminum Hydride***, and ***Lithium Aluminum Hydride***. Excellent 1,3-asymmetric induction is possible with DIBAL (eq 1); however, this is strongly solvent dependent.[3a]

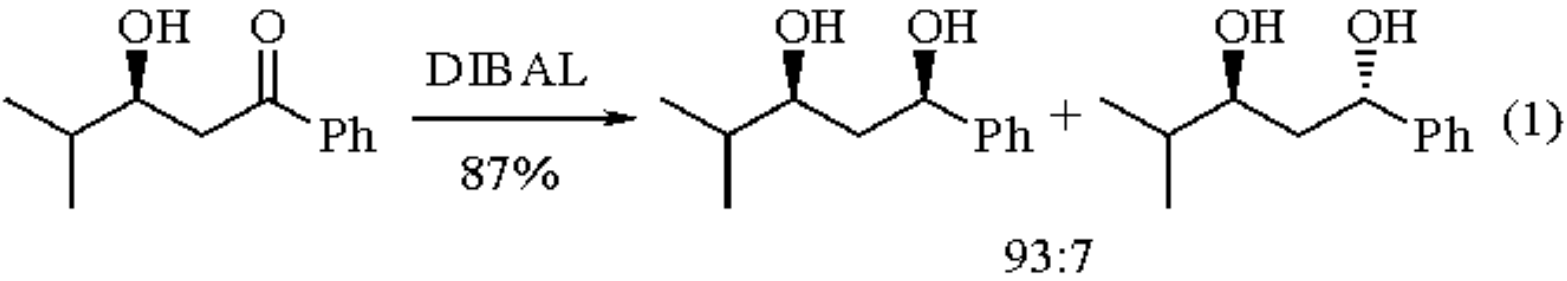

In addition to the hydroxy directing group, amines and amides also showed excellent 1,3-asymmetric induction.[3b] In conjunction with chiral additives, DIBAL can reduce ketones with moderate to good enantioselectivity (eq 2).[4] The use of the Lewis acid ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD) along with DIBAL allows discrimination between carbonyl groups (eq 3).[5,6]

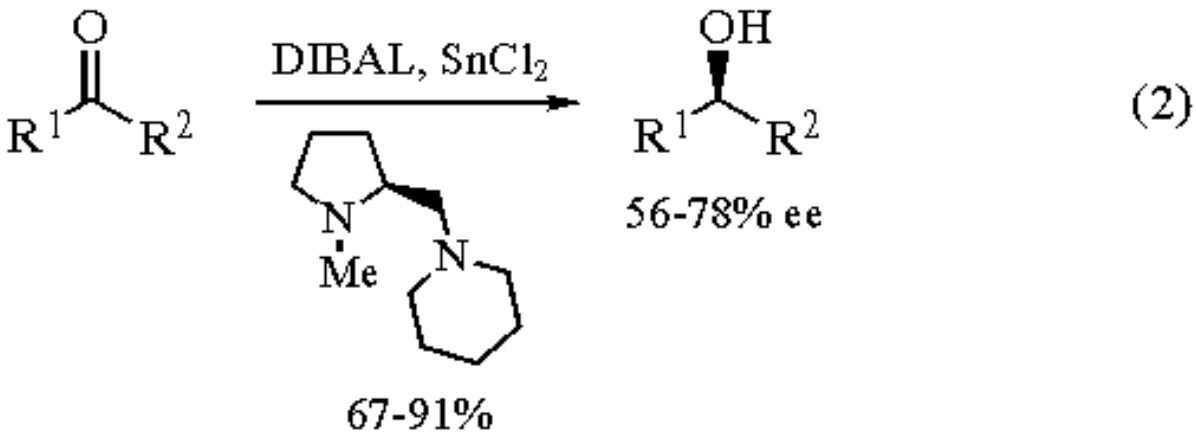

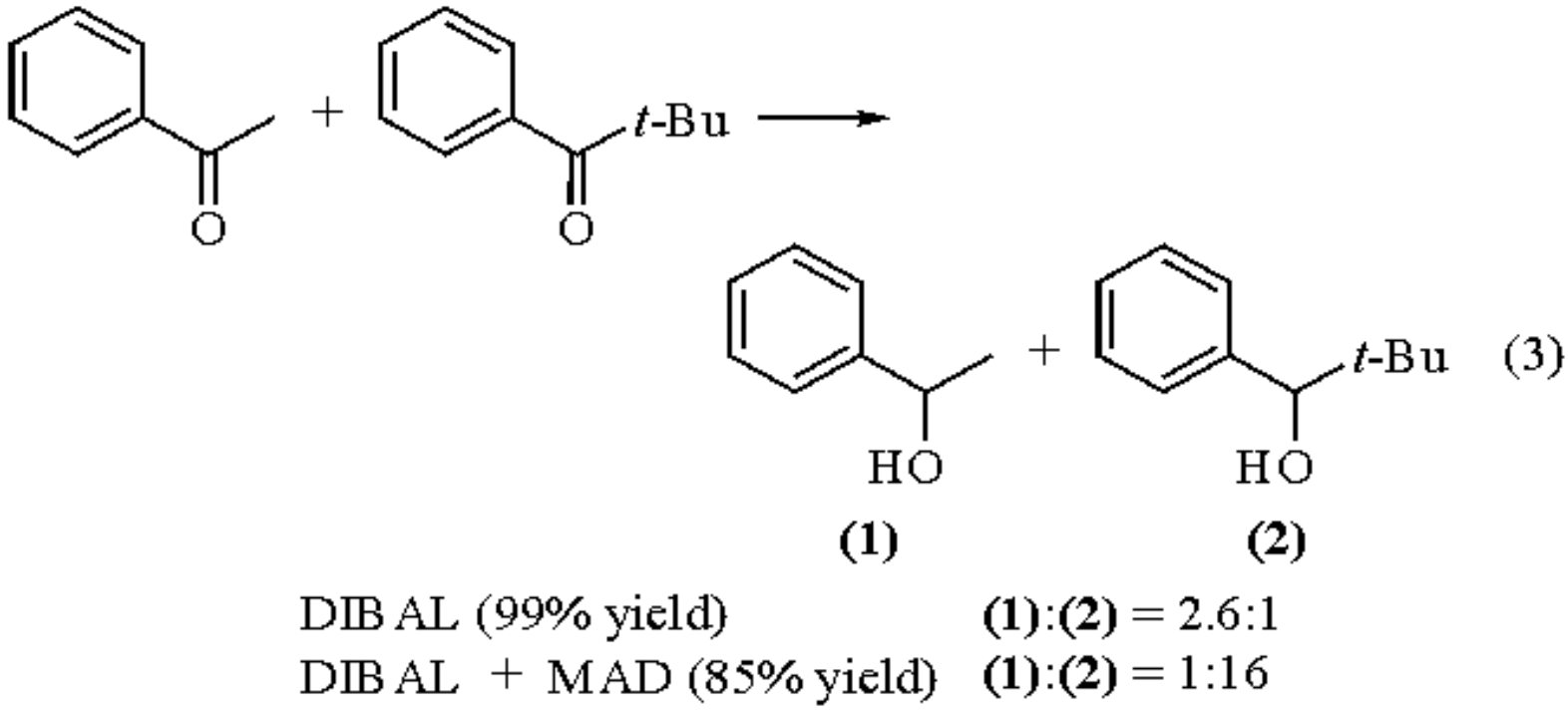

Reduction of α-halo ketones to the carbonyl compounds can be accomplished with DIBAL in the presence of ***Tin(II) Chloride*** and ***N,N,N´,N´-Tetramethylethylenediamine*** (eqs 4 and 5).[7] Under these conditions, vicinal dibromides are converted to the corresponding alkenes.

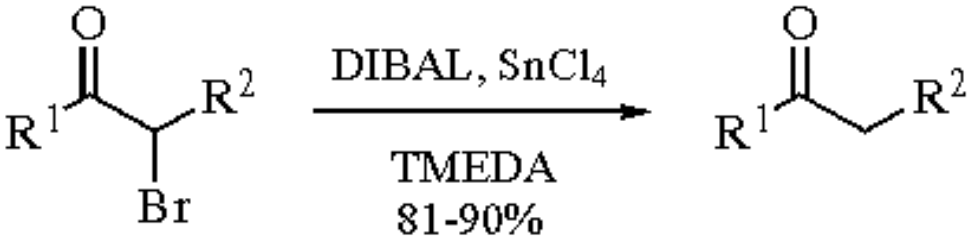

(4)

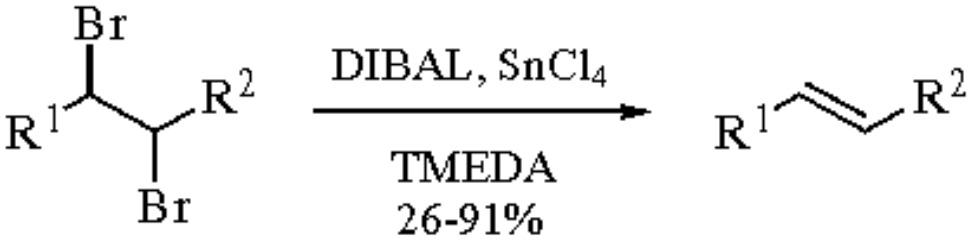

(5)

DIBAL is the reagent of choice (see also ***Aluminum Hydride***) for the reduction of α,β-unsaturated ketones to the corresponding allylic alcohols (eq 6).[8a] A reagent derived from DIBAL and ***Methylcopper*** in HMPA alters the regiochemistry such that 1,4-reduction results (eq 7).[8b] Reductions of chiral β-keto sulfoxides occur with high diastereoselectivity.[9] The choice of reduction conditions makes it possible to obtain both epimers at the carbinol carbon (eqs 8 and 9).

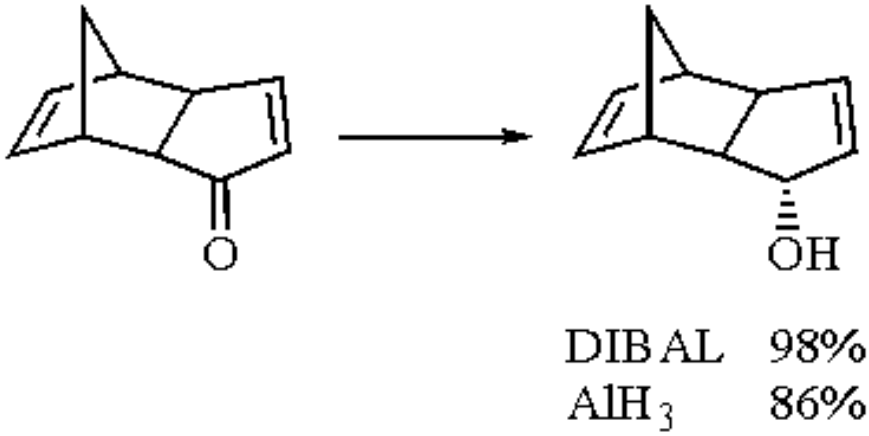

(6)

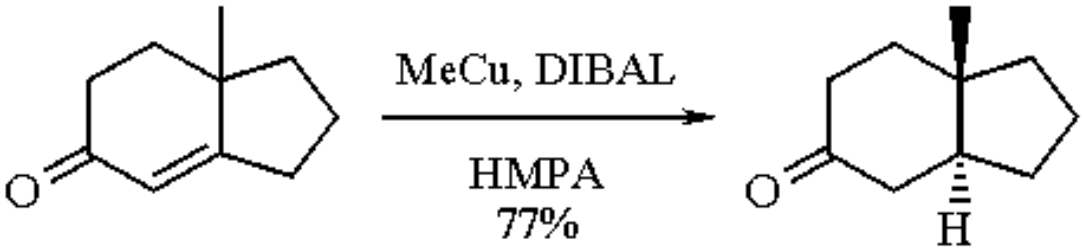

(7)

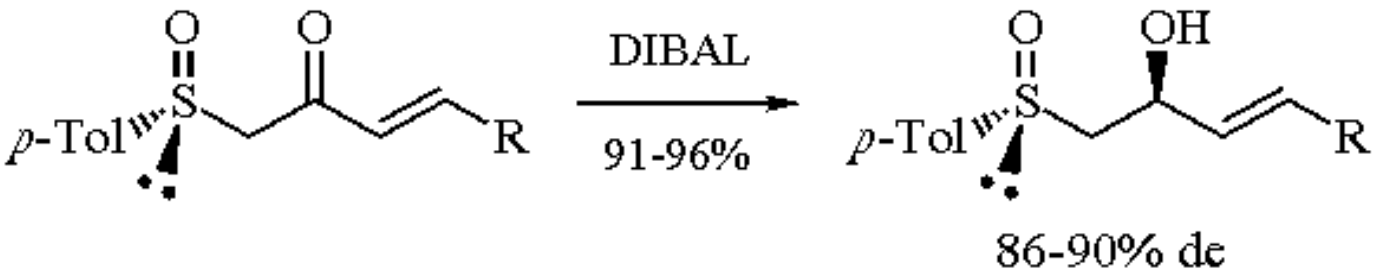

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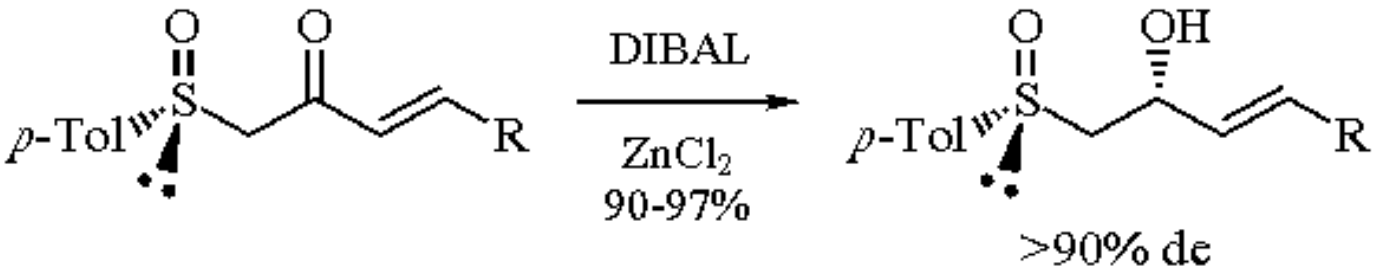

(9)

In conjuction with ***Triethylaluminum***, DIBAL has been used to mediate a reductive pinacol rearrangement[10] with enantiocontrol, as shown in eq 10.[22]

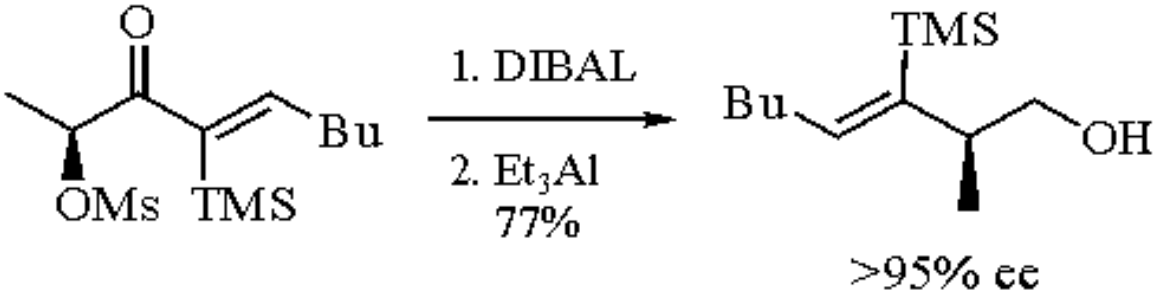

(10)

DIBAL is an excellent reagent for the reduction of α,β-unsaturated esters to allylic alcohols without complications from 1,4-addition (eq 11).[11]

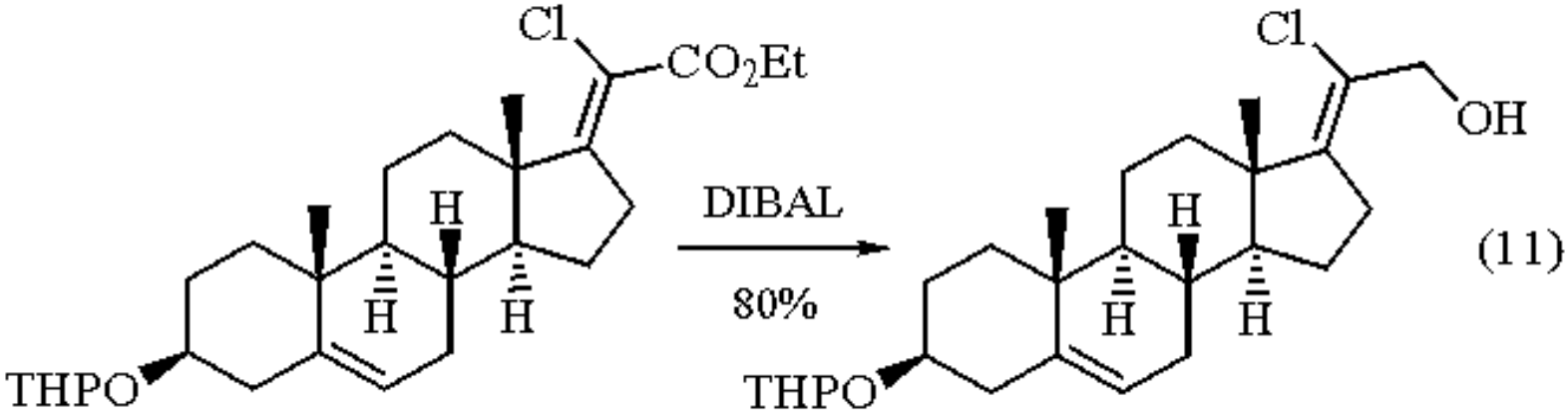

(11)

Due to its Lewis acidity, DIBAL can be used in the reductive cleavage of acetals (see also ***Aluminum Hydride***). Chiral acetates are reduced with enantioselectivity (eq 12).[12] Oxidation of the intermediate alcohol followed by β-elimination gives an optically active alcohol, resulting in a net enantioselective reduction of the corresponding ketone.

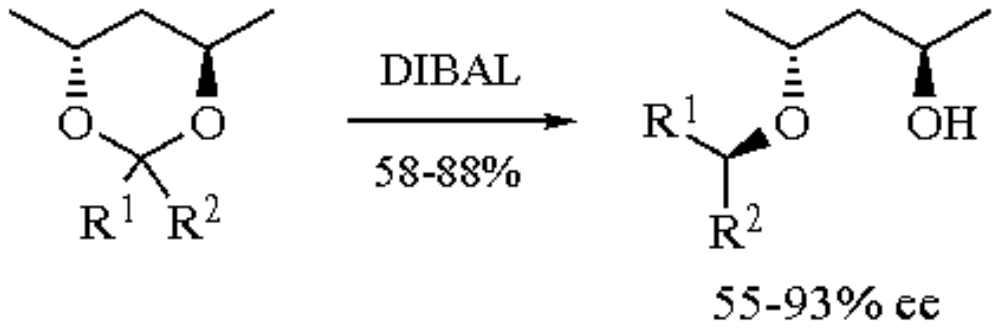

(12)

At low temperatures DIBAL converts esters to the corresponding aldehydes (eq 13)[13] and lactones to lactols (eq 14).[14] DIBAL reduction of α,β-unsaturated γ-lactones followed by an acidic work-up transforms the intermediate lactol to the furan (eq 15).[15] The reduction of nitriles can lead to aldehydes after hydrolysis of an intermediate imine (eq 16).[16] However, cyclic imines can be produced if a ***Sodium Fluoride*** work-up follows the reduction of halonitriles (eq 17).[17] Furthermore, imines can be reduced with excellent stereocontrol (eq 18).[18]

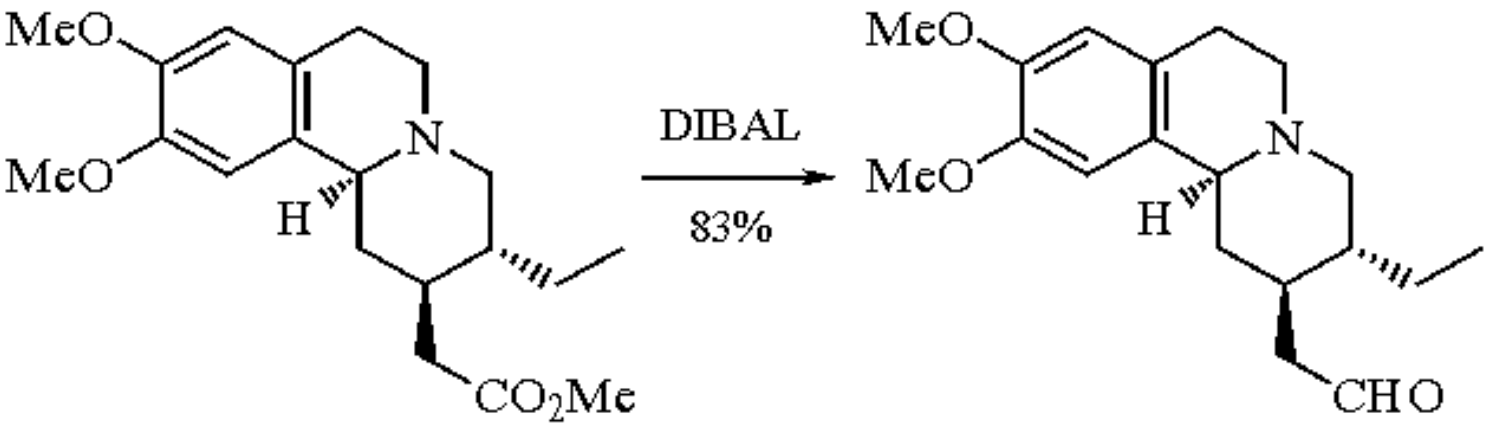

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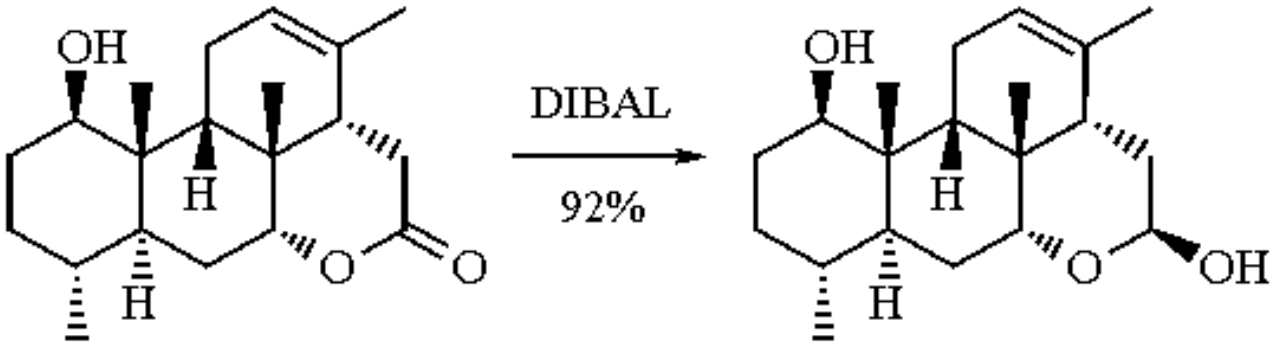

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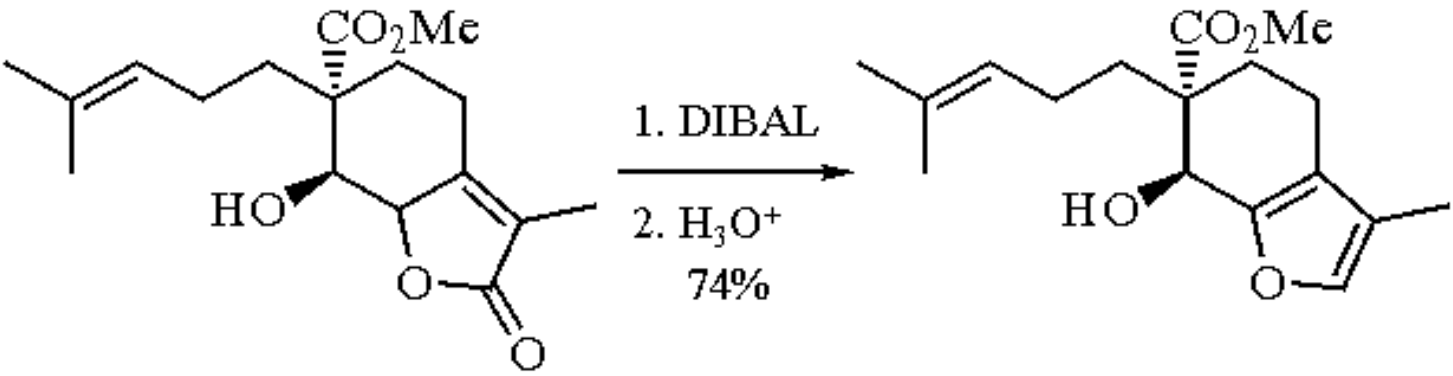

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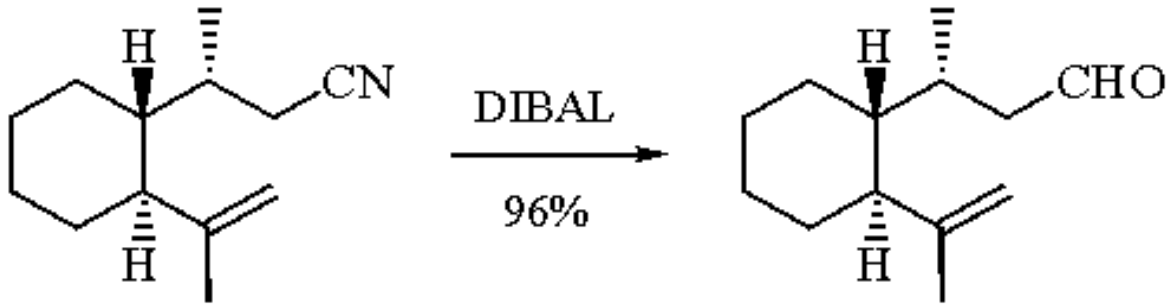

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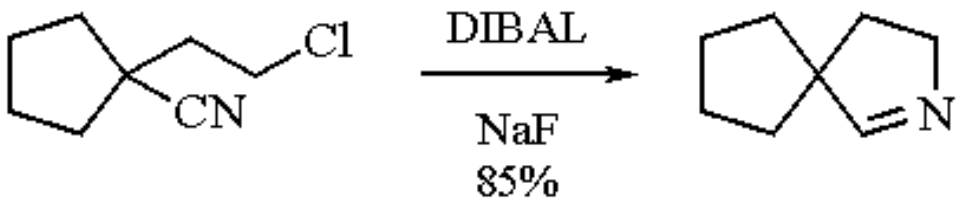

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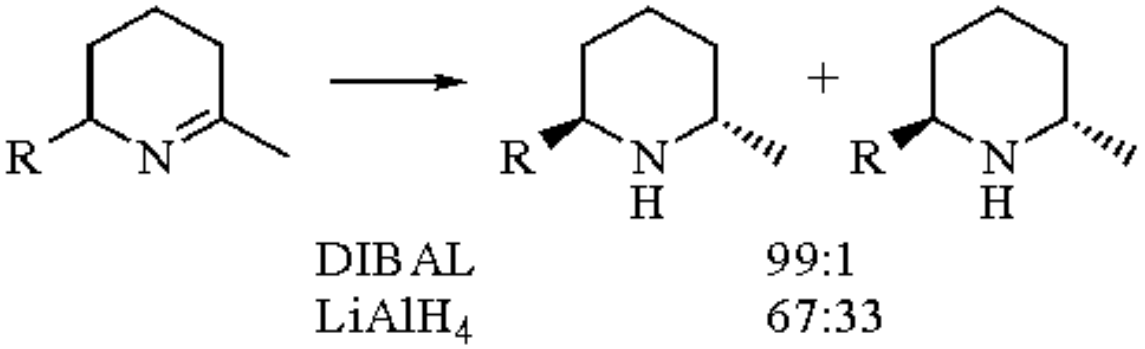

(18)

DIBAL can also be used for the reductive cleavage of cyclic aminals and amidines (eq 19).[19] Oximes can be reduced to amines. Due to the Lewis acidity of DIBAL, however, rearranged products are obtained (eq 20).[20] This chemistry was used to prepare the alkaloid pumiliotoxin C via the Beckmann rearrangement/alkylation sequence shown in eq 21.[21]

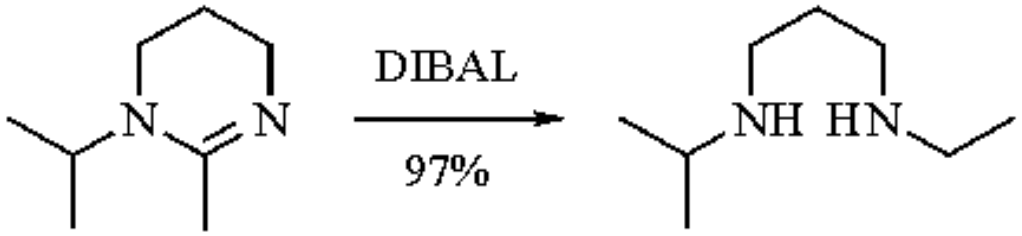

(19)

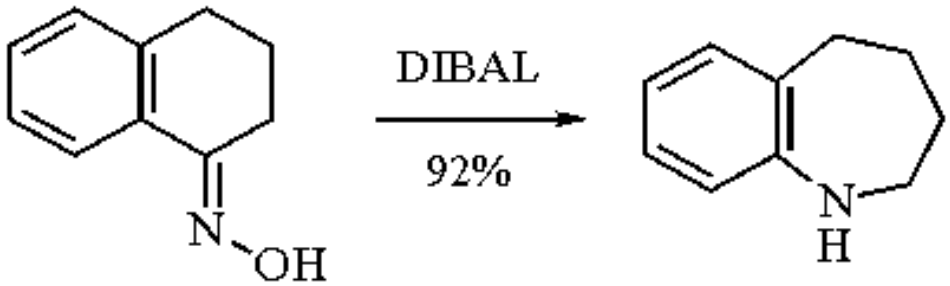

(20)

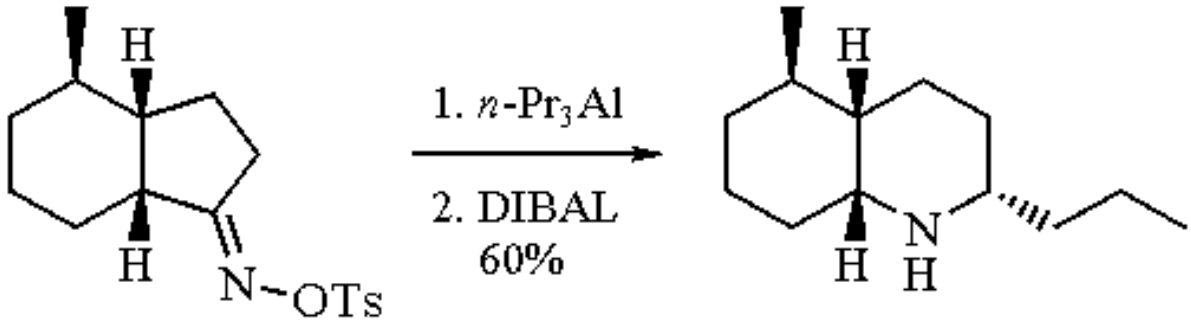

(21)

While sulfones are unreactive with DIBAL at 0 °C in toluene,[2] reduction to the corresponding sulfide has been accomplished at higher temperatures.[22] This reaction can be accomplished with ***Lithium Aluminum Hydride***, but fewer equivalents are required and yields are better using DIBAL (eq 22).

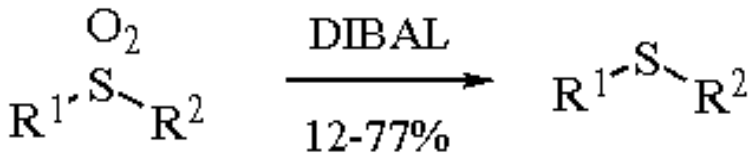

(22)

The reagent combination of DIBAL and ***n-Butyllithium***, which is most likely lithium diisobutylbutylaluminum hydride, has also been used as a reducing agent.[23]

Epoxide Ring Opening.

As a result of its Lewis acidity, several reaction pathways are followed in the reductive ring opening of epoxides by DIBAL. Attack at the more hindered carbon via carbenium ion-like intermediates (see also ***Aluminum Hydride***) or S_N2' type reactions, are both known with vinyl epoxides. These modes stand in contrast to results with $LiAlH_4$ (eqs 23-25).[24]

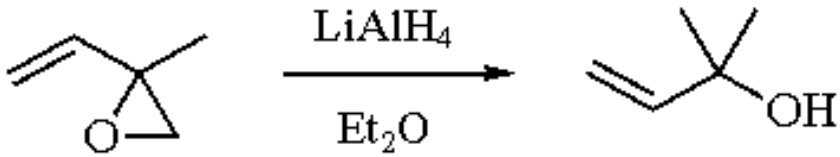

(23)

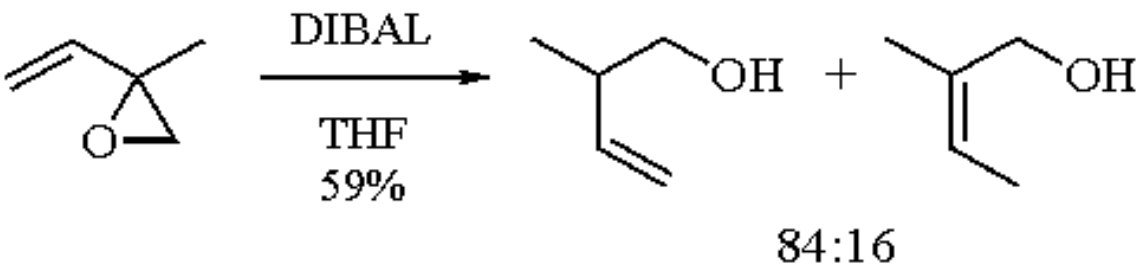

(24)

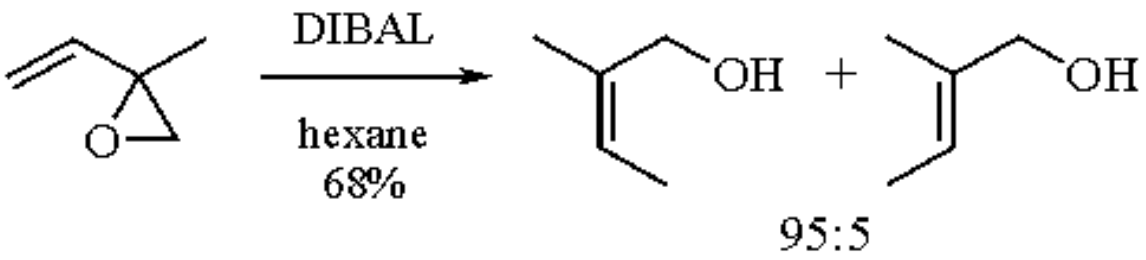

(25)

Hydroalumination Reactions.

DIBAL reacts with alkynes and alkenes to give hydroalumination products. *Syn* additions are usually observed; however, under appropriate conditions, equilibration to give a net *anti* addition is possible.[25] If the substrate has both an alkene and an alkyne group, then chemoselectivity for the alkyne is observed (eq 26).[26]

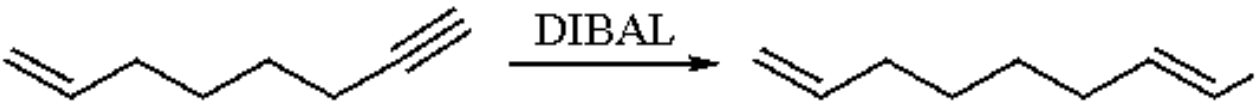

(26)

The intermediate alkenylalane can be used in several ways. If a protiolytic work-up is used, then formation of the corresponding (*Z*)-alkene is observed (eq 27).[27] Treatment of the alkenylalane with ***Methyllithium*** affords an ate complex which is nucleophilic and reacts with a variety of electrophiles, e.g. alkyl halides, CO_2, MeI, epoxides, tosylates, aldehydes, and ketones (eq 28).[1c,1h,26]

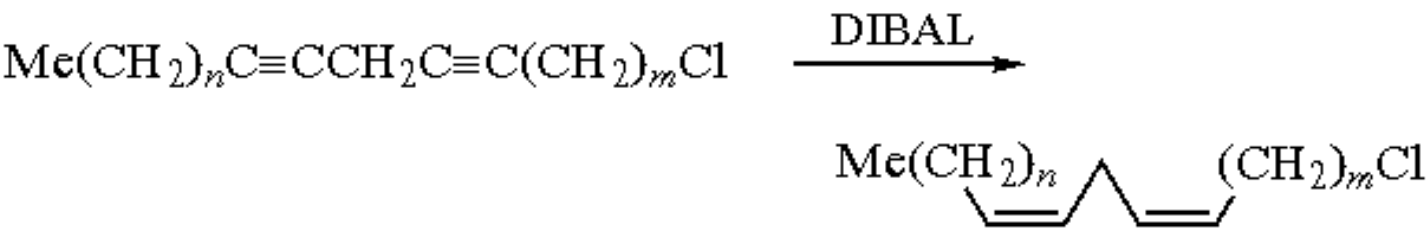

(27)

n	*m*	
5	6	82%
3	8	94%
2	9	87%

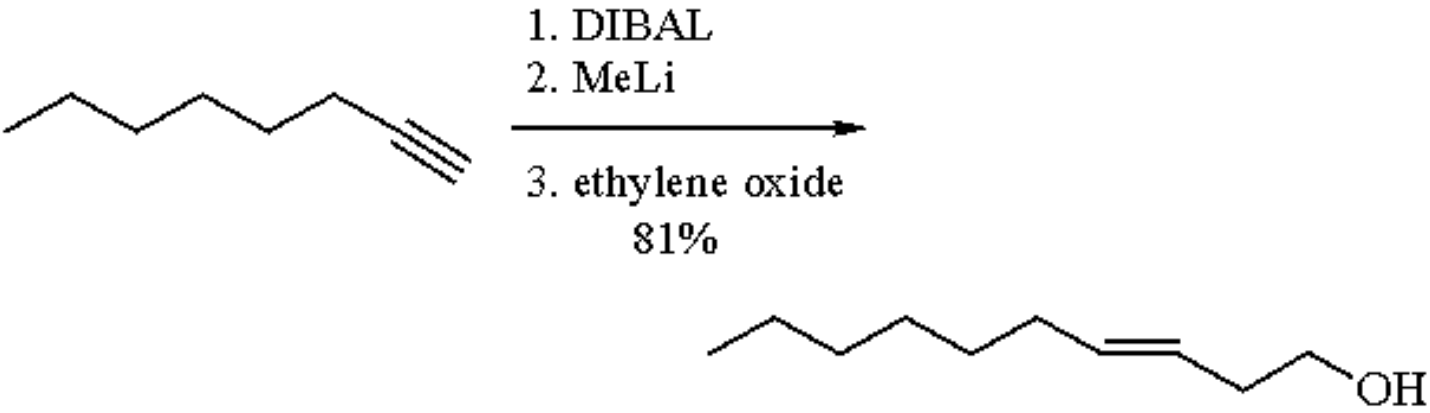

(28)

Hydroalumination of a terminal alkene followed by treatment of the intermediate alane with oxygen gives a primary alcohol (eq 29).[28]

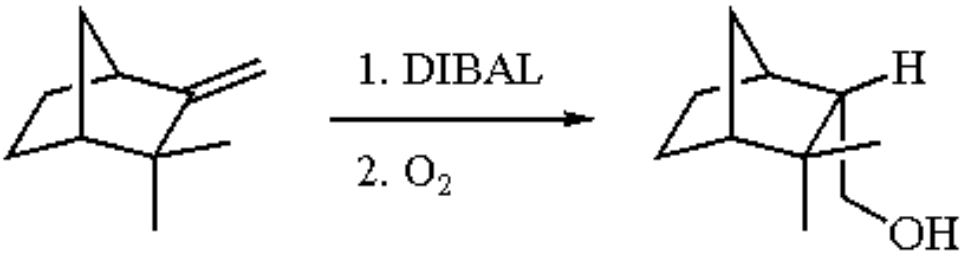

(29)

Alkenylalanes can dimerize to afford 1,3-butadienes (eq 30),[29] and can be cyclopropanated under Simmons-Smith conditions to give cyclopropylalanes (eq 31),[30] which can be used for further chemistry.

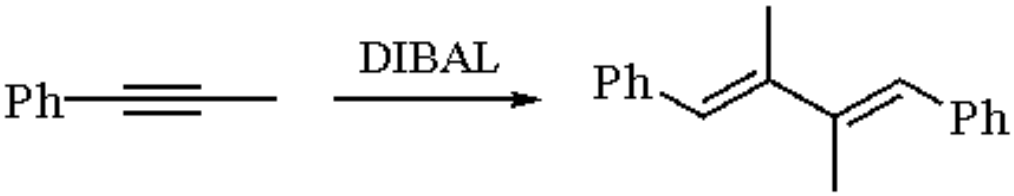

(30)

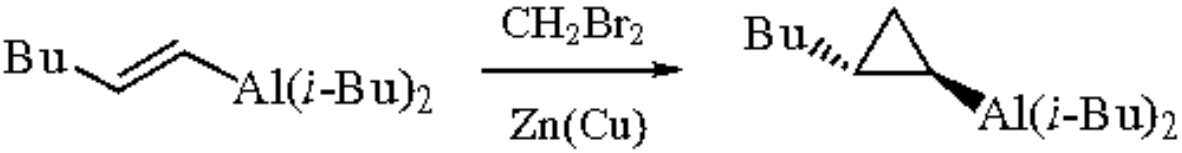

(31)

Alkenylalanes can also be transmetalated (eq 32),[31] or coupled with vinyl halides via palladium catalysis (eq 33).[32]

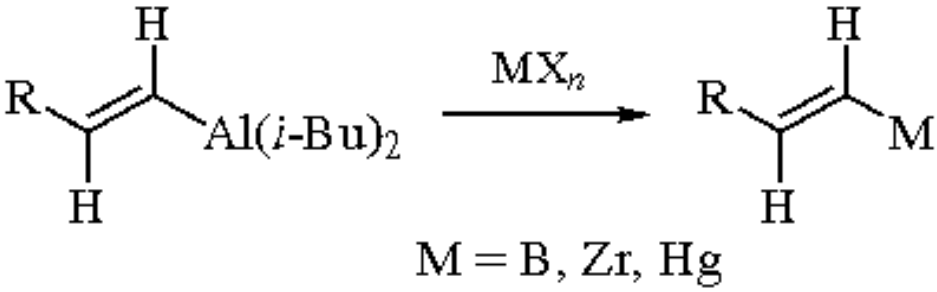

(32)

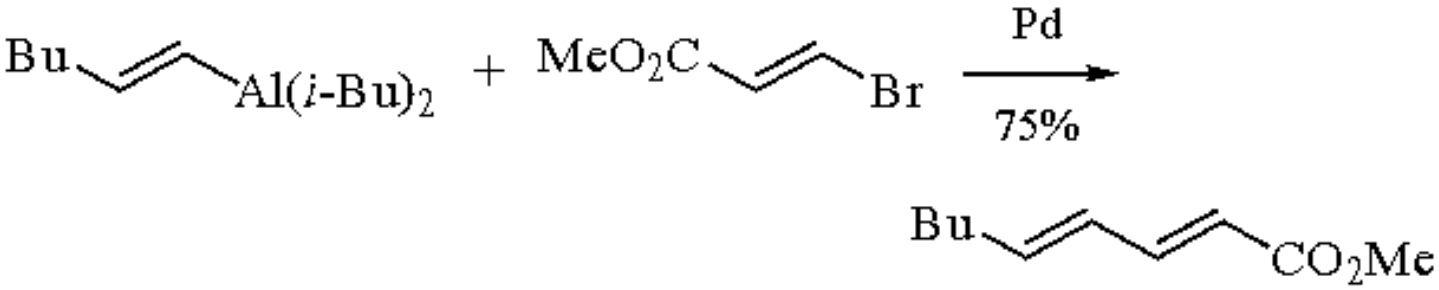

(33)

Addition of DIBAL to allenes has been observed to occur at the more highly substituted double bond (eq 34).[33]

(34)

$R^1 = C_7H_{15}$; $R^2 = H$ (88%), TMS (74%)

The conversion of unconjugated enynes to cyclic compounds has also been accomplished using DIBAL (eq 35).[34]

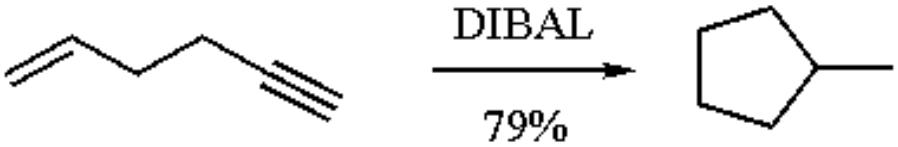

(35)

Related hydroalumination reactions have been reported using ***Lithium Aluminum Hydride***.

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Diisobutylaluminum Phenoxide[1]

***i*-Bu$_2$AlOPh**

[4165-53-1] · $C_{14}H_{23}AlO$ · Diisobutylaluminum Phenoxide · (MW 234.32)

(base for aldol condensation of methyl ketones[2])

Solubility: sol toluene and THF.

Preparative Method: prepared in situ by careful addition of ***Diisobutylaluminum Hydride*** to a THF solution of 1 equiv of phenol.[2]

Handling, Storage, and Precautions: solutions are moisture and air sensitive and should be prepared and handled under an inert atmosphere; use in a fume hood.

Aldol Condensations.

Diisobutylaluminum phenoxide has been used as a base in conjunction with ***Pyridine*** for effecting regiospecific aldol condensations of methyl ketones via the corresponding kinetic aluminum enolates. As an intermolecular example, the condensation of 2-octanone gave a mixture of isomeric 9-methylpentadecenones in good yield (eq 1).[2]

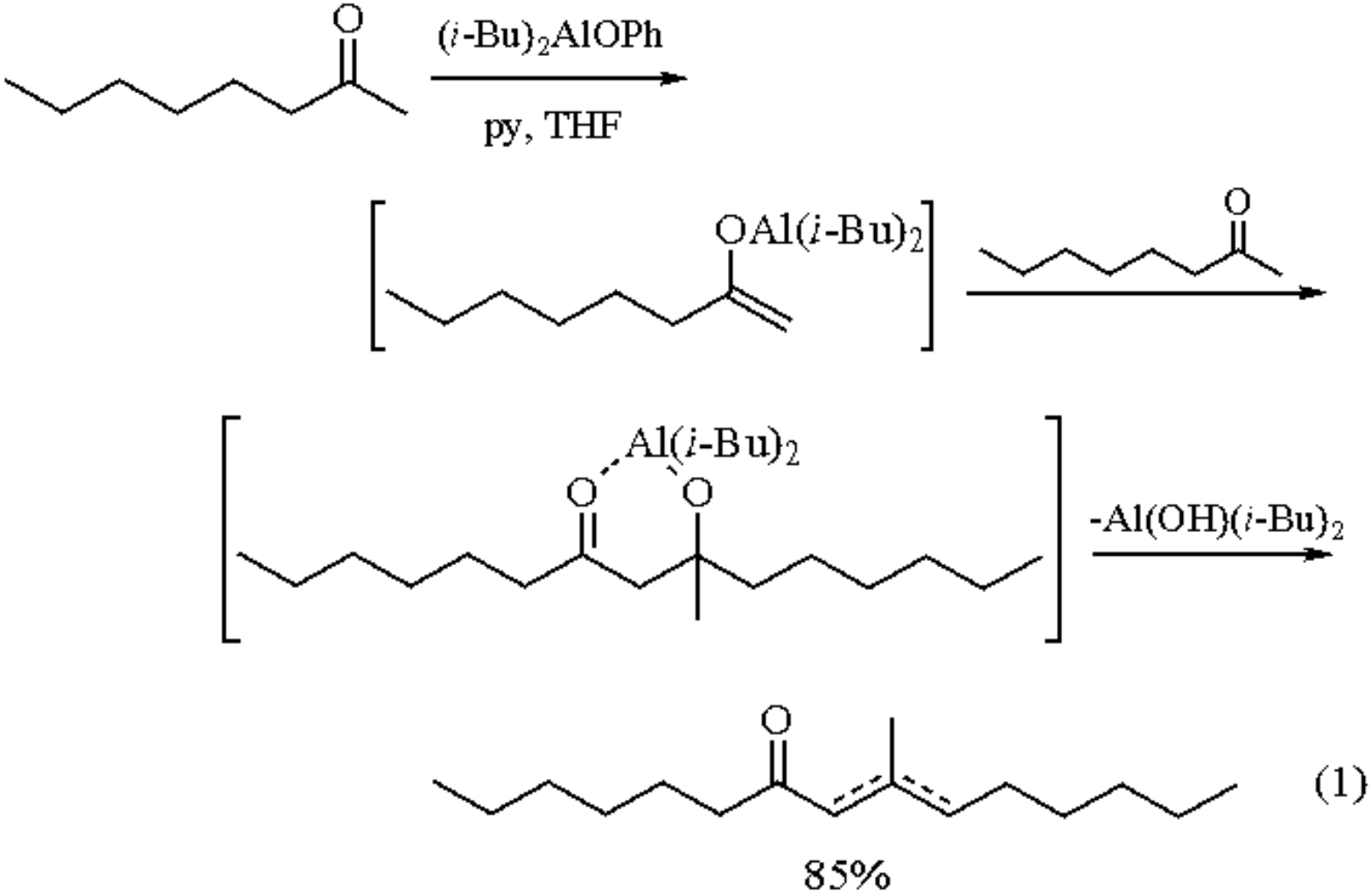

The intramolecular aldol condensation of 2,15-hexadecanedione, which required the use of the reagent in large excess, gave a mixture of isomeric 3-methylcyclopentadecenones (eq 2).[3] Subsequent hydrogenation over ***Palladium on Carbon*** gave (±)-muscone in good overall yield, compared to earlier efforts using the corresponding magnesium enolate.[4]

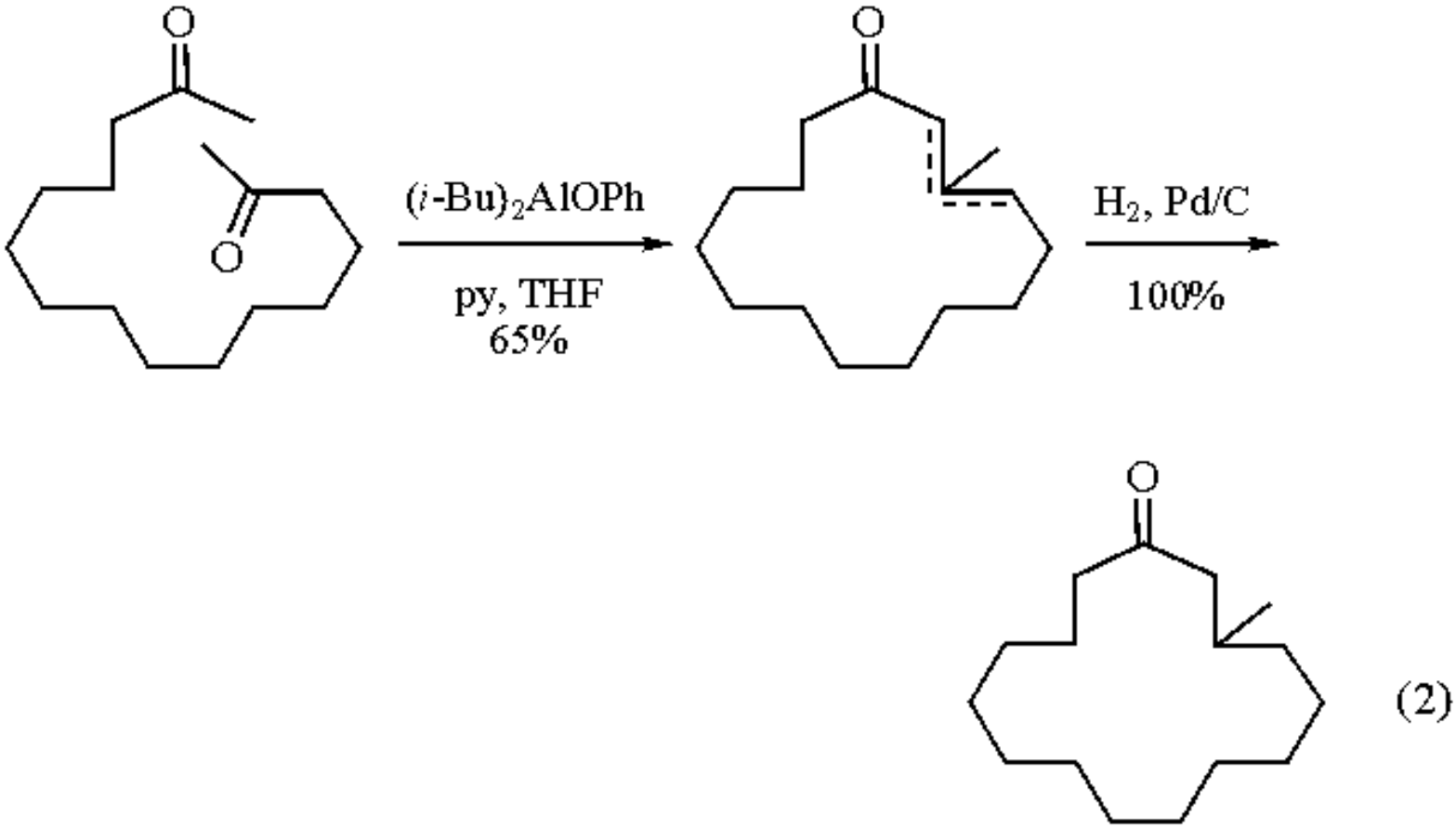

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Diisobutylaluminum Phenyl Selenide

***i*-Bu$_2$AlSePh**

[85028-55-3] · $C_{14}H_{23}AlSe$ · Diisobutylaluminum Phenyl Selenide · (MW 297.28)

(phenylselenylation agent for Beckmann rearrangement of oxime sulfonates,[1,2] acetal cleavage,[4,5] and epoxide opening[6])

Solubility: sol toluene, CH_2Cl_2, hexane.

Form Supplied in: prepared in situ from commercially available reagents.

Preparative Methods: by addition of ***Diphenyl Diselenide*** (1 equiv) to a 1 M hexane solution of ***Diisobutylaluminum Hydride*** (2 equiv) in CH_2Cl_2 at 0 °C for 30 min.[1]

Handling, Storage, and Precautions: use in a fume hood; the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture; the solution should be used as prepared for best results.

Imino Selenoether Synthesis.

Treatment of cyclododecanone and acetophenone oxime methanesulfonates with diisobutylaluminum phenyl selenide (1.1 equiv) in hexane/CH_2Cl_2 at 0 °C for 30 min provides the corresponding imino selenoethers in good yields via organoaluminum-promoted Beckmann rearrangement of oxime sulfonates and subsequent trapping of the intermediary iminocarbocation by phenyl selenide (eqs 1 and 2).[1,2] Dimethylaluminum methyl selenide is also employable for this transformation.[3]

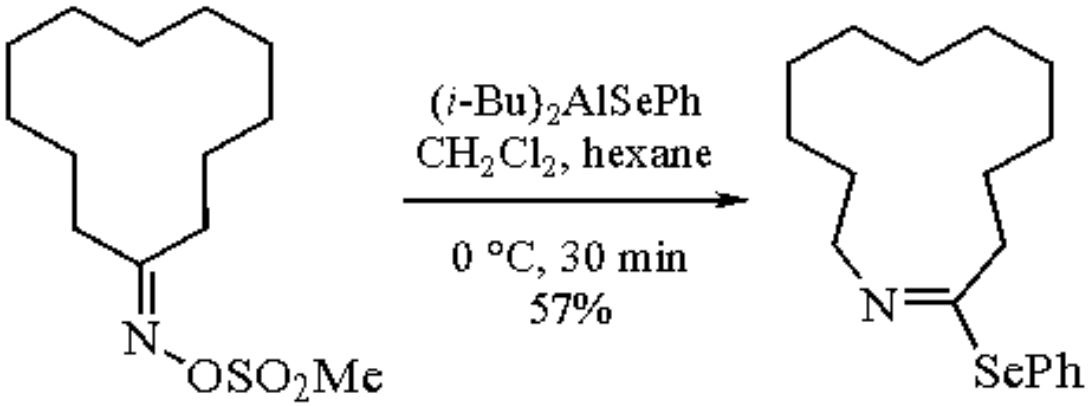

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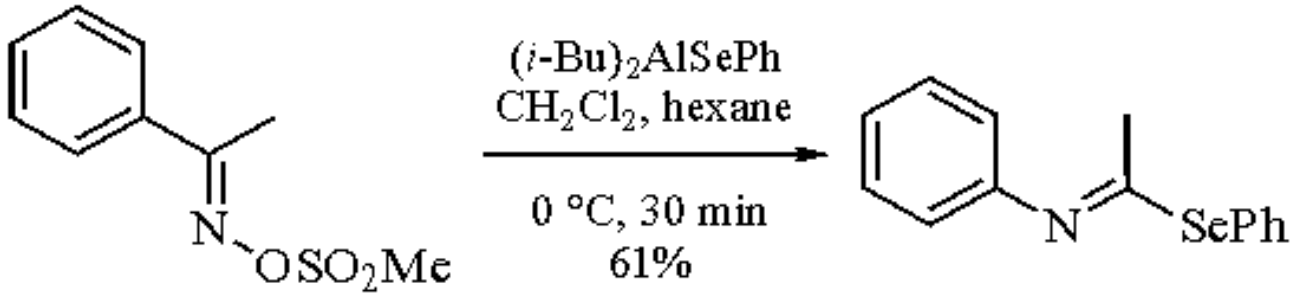

(2)

Monoselenoacetal Synthesis.

A new method for preparation of monoselenoacetals has been developed which involves the reaction of acetals with diisobutylaluminum phenyl selenide.[4] When ***Dimethoxymethane*** was treated with diisobutylaluminum phenyl selenide (1 equiv) in hexane/toluene at 40 °C for 5 h, methoxy(phenylseleno)methane was formed in 98% yield (eq 3). Diethylaluminum ethyl selenide is also employable as a selenolate agent. Alkyl methoxymethyl ethers are transformed to the alkyl phenylselenomethyl ethers with high selectivity under similar reaction conditions (eq 4). Diselenoacetals are accessible with excess amounts of diisobutylaluminum phenyl selenide (eq 5).

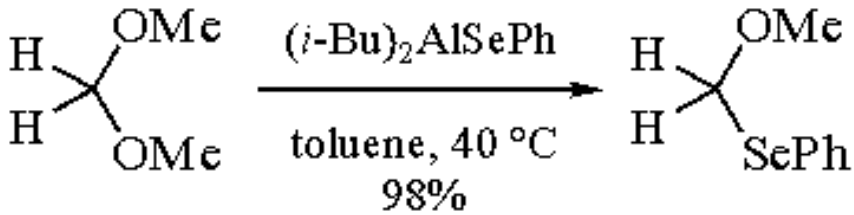

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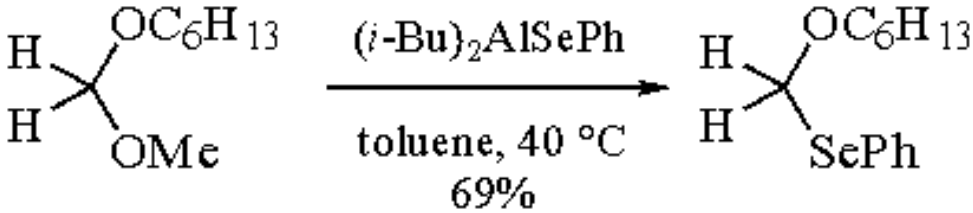

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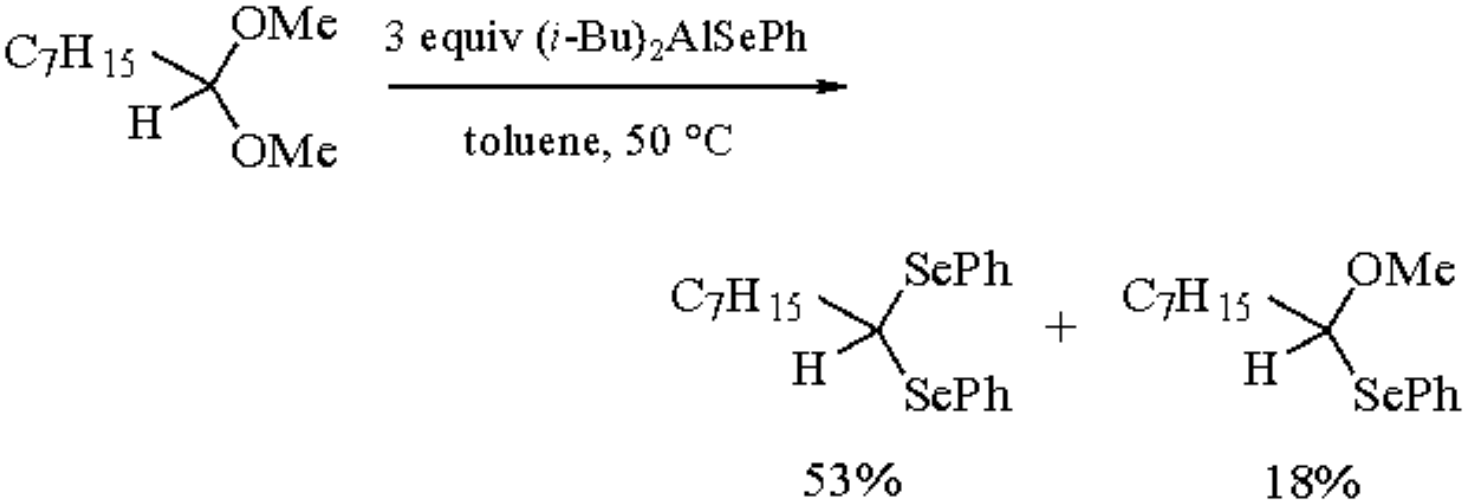

(5)

1-Methoxy-1-(phenylseleno)ethane, prepared in this way, generates the 1-methoxyethyl radical upon treatment with

catalytic ***Azobisisobutyronitrile*** and ***Tri-n-butylstannane*** in benzene at 80 °C for 2 h, and this radical adds to methyl acrylate to furnish a Michael adduct in good yield (eq 6).[5]

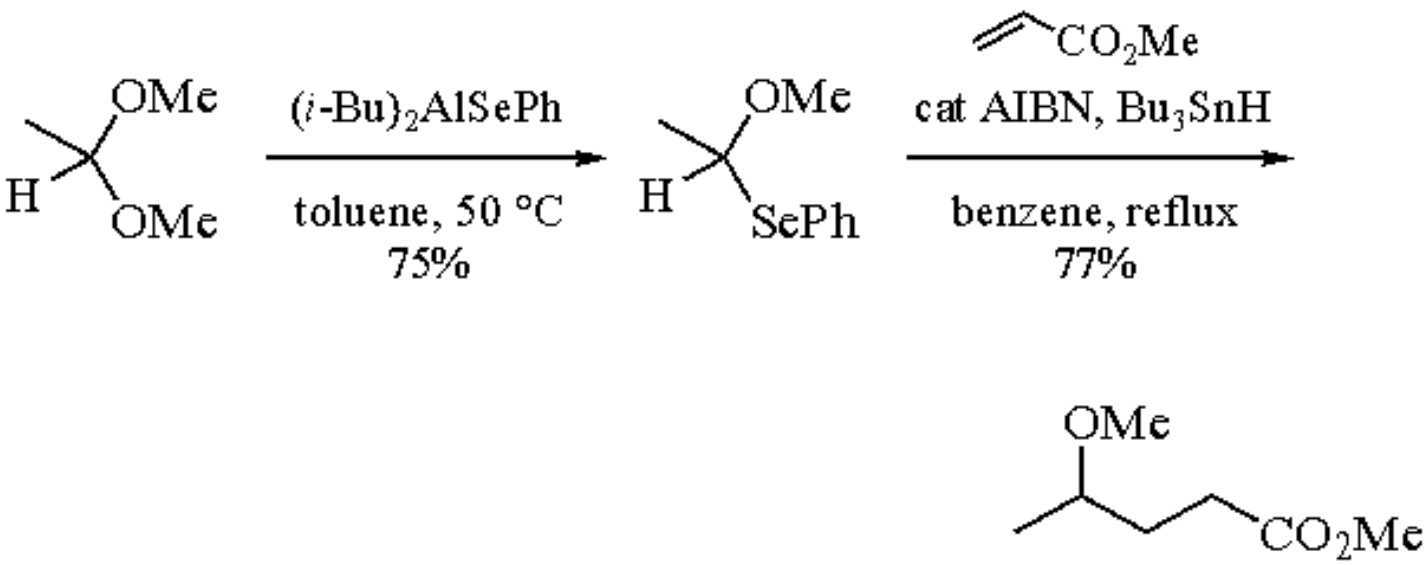

(6)

Contra-*trans*-Diaxial Opening of Epoxides.

Treatment of an α,β-epoxy alcohol with NaSePh affords the 1,3-diol exclusively in 90% yield. However, use of diisobutylaluminum phenyl selenide in CH_2Cl_2 at 0 °C to rt exhibits the opposite regioselectivity, furnishing the 1,2-diol as a major product (eq 7).[6] When diisobutylaluminum phenyl selenide is combined with ***Titanium Tetraisopropoxide*** as a cocatalyst, the selectivity of epoxide opening is considerably lowered. ***Dimethylaluminum Methylselenolate*** was less selective for this transformation, giving two isomeric diols in a 1:2 ratio. This tendency is also observed with the epoxy *t*-butyldimethylsilyl ether substrate (eq 8).

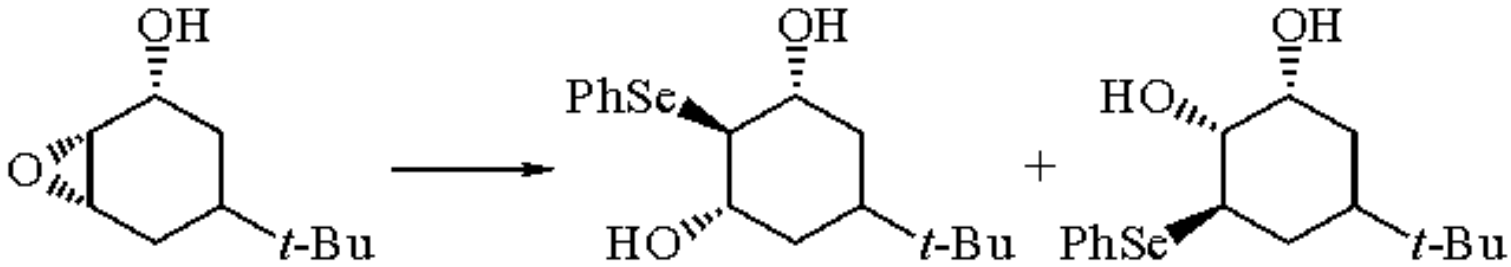

(7)

PhSeNa	100:0	90%
(*i*-Bu)$_2$AlSePh	20:80	80%

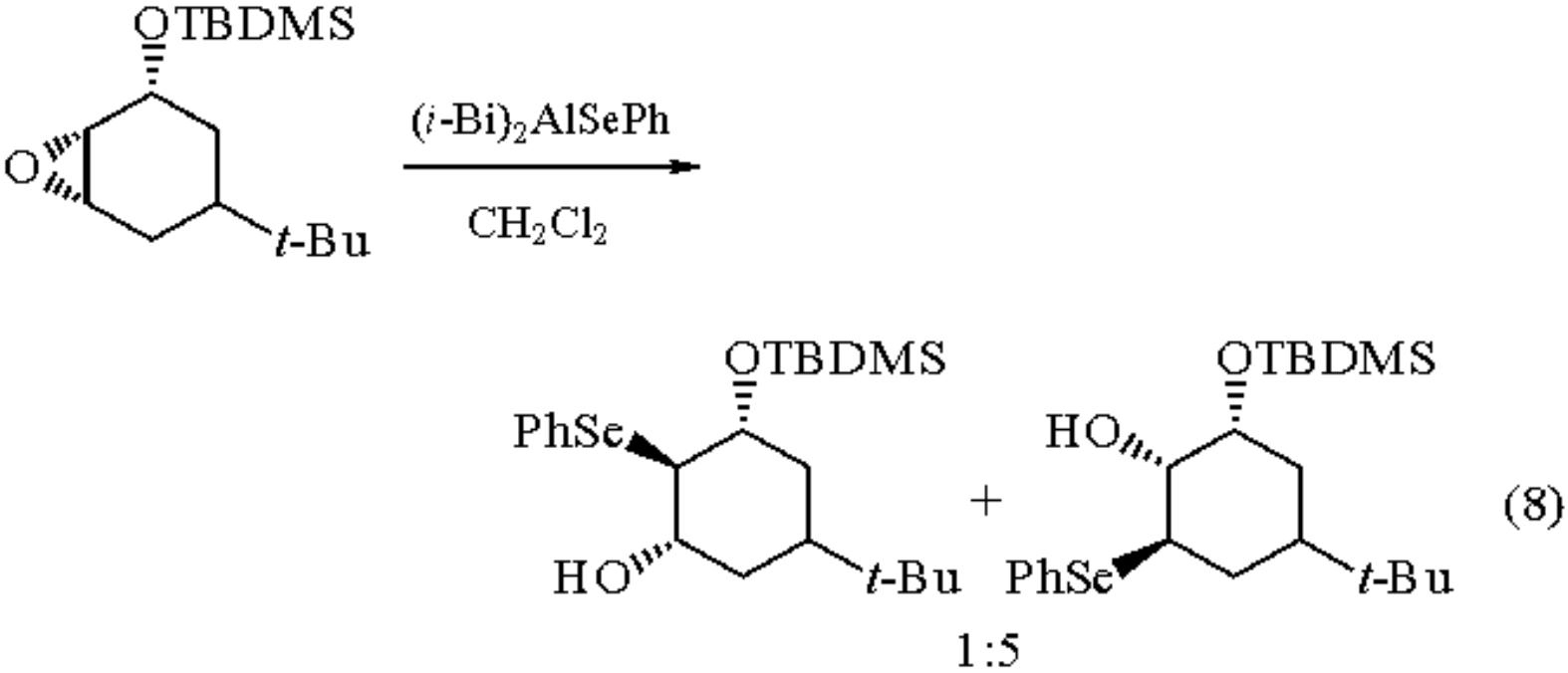

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Diisopinocampheylborane

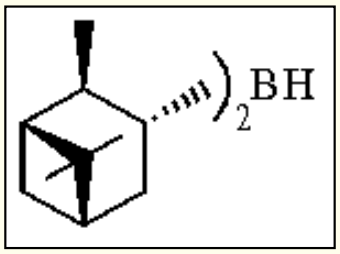

(+)

[21947-87-5] · $C_{20}H_{35}B$ · Diisopinocampheylborane · (MW 286.31) (-)

[21932-54-7]

(chiral hydroborating reagent for asymmetric hydroboration of *cis*-alkenes to provide access to optically active secondary alcohols;[1] precursor for the preparation of a large number of chiral reagents for asymmetric synthesis.[1])

Alternate Name: Ipc_2BH.

Physical Data: white crystalline dimer.

Solubility: sparingly sol THF.

Analysis of Reagent Purity: active hydride is determined by hydrolysis of an aliquot and measuring the hydrogen evolved according to the standard procedure;[2] enantiomeric purity is determined by measuring the rotation of the α-pinene liberated in its reaction with 0.5 equiv of ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA)[3] or reaction with aldehydes.[4]

Preparative Method: (+)-diisopinocampheylborane is prepared in high enantiomeric purity and good yield (Table 1) by hydroboration of commercially available (-)-α-pinene (of low enantiomeric purity) with ***Borane-Dimethyl Sulfide*** (BMS) complex, carried out by mixing the two reagents to make a solution of known molarity in THF at 0 °C or rt (eq 1); the mixture is left without stirring at 0 °C for ~12 h for the development of crystals (the slow crystallization facilitates the incorporation of the major diastereomer in the crystalline product, leaving the undesired isomer in solution); the supernatant solution is decanted using a double-ended needle; the crystalline lumps are broken and washed with diethyl ether and dried under vacuum (~12 mmHg) at rt.[3,4]

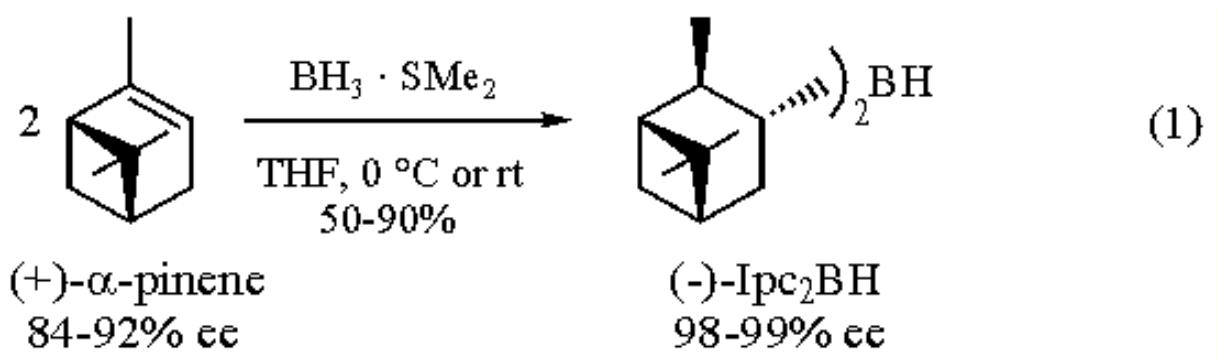

Table 1 Synthesis of Diisopinocampheylborane (Ipc_2BH) of High Optical Purity via Selective Single Crystallization in THF (Optimized Conditions)

(+)-a-Pinene % ee	Molar ratio[a]	Molarity M (in borane)	Temp (°C)	Isolated (% yield)	(-)-Ipc_2BH % ee[b]
92.0	2.3:1	1	0	70 75	>99
91	2.5:1	1.25	20 25[c]	>90	>99
84	2:1	1	0	50 60	98.3

[a] Molar ratio of a-pinene to BMS. [b] Based on measuring the rotation of the (+)-a-pinene obtained from (-)-Ipc_2BH. [c] At times, Ipc_2BH starts precipitating immediately; in such cases the reaction mixture should be redissolved at 50 55 °C, followed by slow recrystallization.[4]

Handling, Storage, and Precautions: air sensitive, reacting instantaneously with protic solvents to liberate hydrogen; must be handled under an inert atmosphere (N_2 or Ar); can be stored at 0 °C under inert atmosphere for several months without loss of hydride activity.[4]

Asymmetric Hydroboration.

Brown and Zweifel originally carried out the hydroboration of α-pinene to study the sensitivity of the α-pinene structure towards rearrangement. Surprisingly, the hydroboration reaction proceeded without rearrangement and stopped at the dialkylborane (R_2BH) stage.[5] This important reaction (reported in 1961) thus gave birth to a unique reagent, diisopinocampheylborane (Ipc_2BH). The failure of this reagent to hydroborate a third molecule of α-pinene suggested the possibility of its application in asymmetric hydroboration of less sterically hindered alkenes.

The first substrate which was asymmetrically hydroborated using Ipc_2BH was *cis*-2-butene, and the enantiomeric purity of the product 2-butanol (87% ee) obtained in this preliminary experiment was spectacular (eq 2), since Ipc_2BH was made from α-pinene of low optical purity.[5] This reaction represents the first nonenzymatic asymmetric synthesis for achieving high enantioselectivity. Its discovery marked the beginning of a new era of practical asymmetric synthesis obtained via reagent control.[1,5]

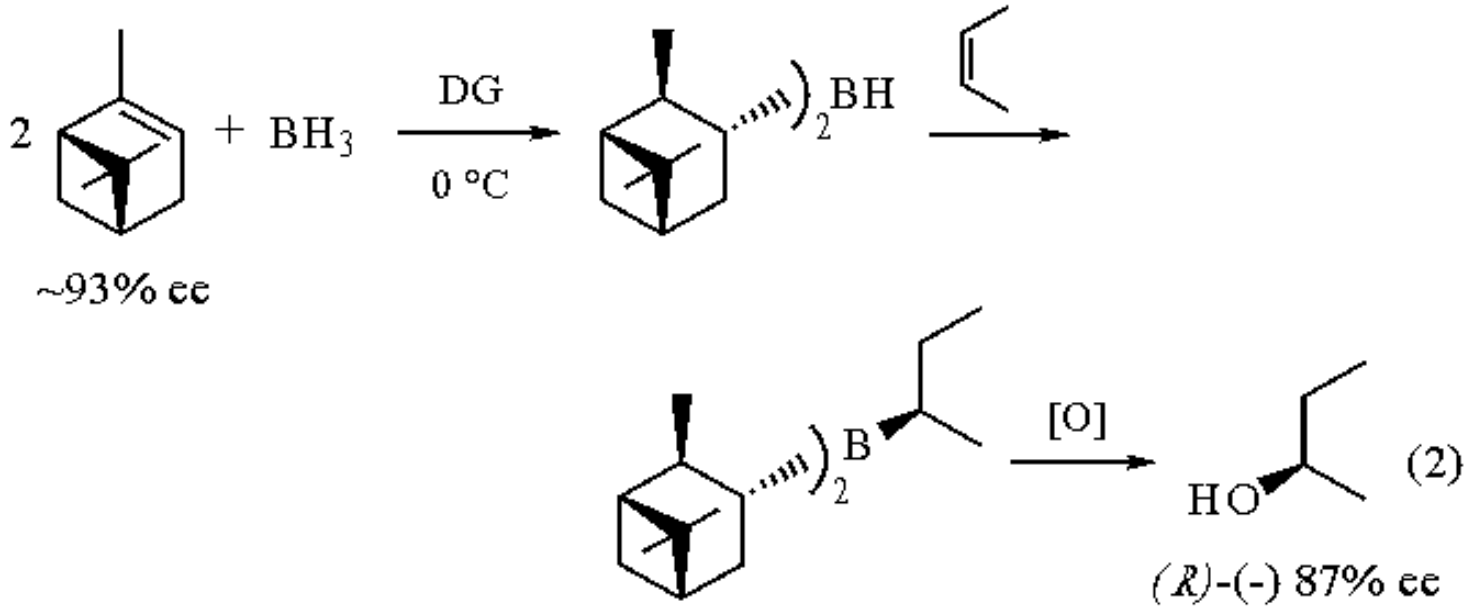

Later, Brown and co-workers developed the method described above for the preparation of enantiomerically pure Ipc_2BH (>99% ee)[3,4] and applied the reagent in the asymmetric hydroboration of prochiral alkenes. Oxidation of the trialkylboranes provided optically active alcohols. In the case of *cis*-alkenes, secondary alcohols were obtained in excellent enantiomeric purity (Figure 1). The reaction is general for most types of *cis*-alkene, e.g. *cis*-2-butene forms (*R*)-2-butanol in 98.4% ee, and *cis*-3-hexene is converted to (*R*)-3-hexanol in 93% ee. However, the reagent is somewhat limited in reactions with unsymmetrical alkenes; e.g. *cis*-4-methyl-2-pentene yields 4-methyl-2-pentanol with 96% regioselectivity but only 76% ee (Figure 1).[6]

Asymmetric hydroborations of heterocyclic alkenes are highly regio- and enantioselective. For example, hydroboration of 2,3-dihydrofuran with Ipc_2BH followed by oxidation provides 3-hydroxyfuran in 83% ee, which can be upgraded to essentially the enantiomerically pure form (>99% ee) (Figure 2).[7]

Applications.

The ability of Ipc_2BH to hydroborate *cis*-alkenes has been elegantly applied to the preparation of key intermediates which have been utilized in syntheses of valuable target molecules.[1a] For example, asymmetric hydroboration-oxidation of 5-methylcyclopentadiene to the corresponding optically active alcohol has been applied in the synthesis of loganin (eq 3).[8a] In another example, a prostaglandin precursor was obtained by the asymmetric hydroboration-oxidation reaction of methyl cyclopentadiene-5-acetate (eq 4).[8b] Ipc_2BH has also been used in the preparation of $PGF_{2\alpha}$.[9]

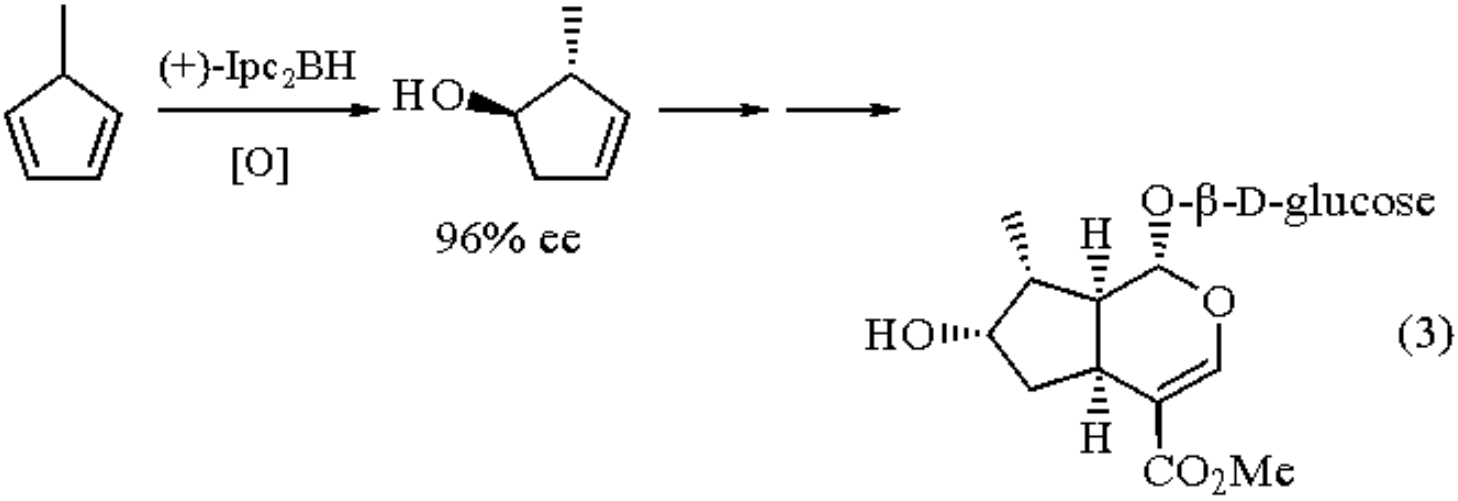

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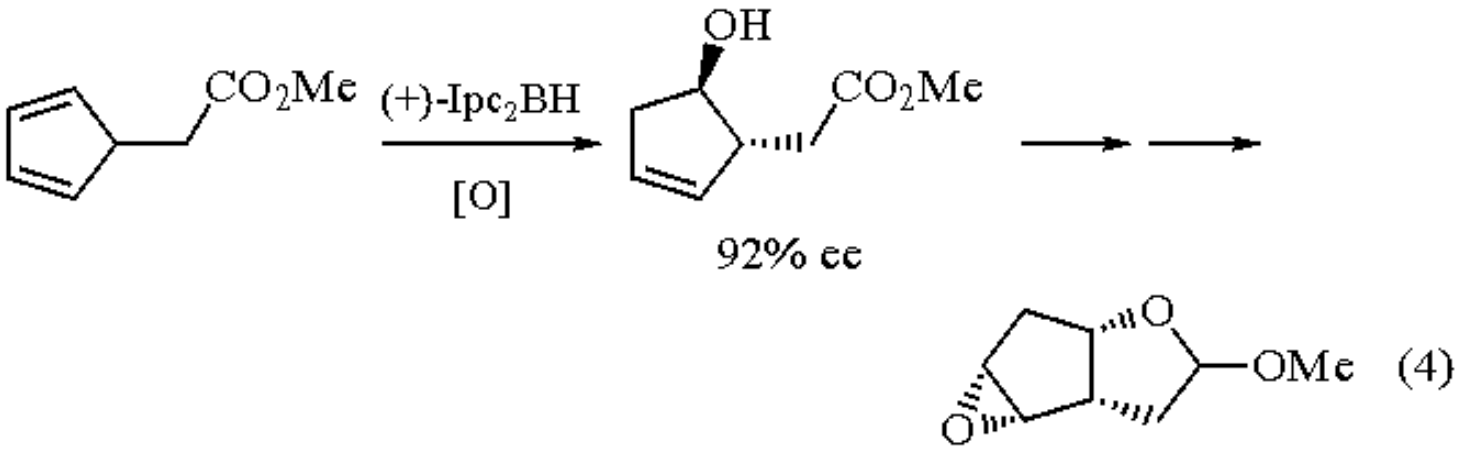

(4)

Both the enantiomers of Ipc_2BH have been elegantly applied in the asymmetric hydroboration of safranol isoprenyl methyl ether for the synthesis of carotenoids (3*R*,3´*R*)-, (3*S*,3´*S*)-, and (3R,3´S;*meso*)-zeaxanthins (eq 5).[10] (3*S*,5*R*,3´*S*,5´*R*)-Capsorubin, a carotenoid found in the red paprika *Capsicum annuum*, was synthesized via a key step involving asymmetric hydroboration of the unsaturated acetal followed by an aldol condensation (eq 6).[11] Asymmetric hydroboration using Ipc_2BH was also applied in the stereocontrolled synthesis of a linearly fused triquinane, (+)-hirsutic acid (eq 7).[12]

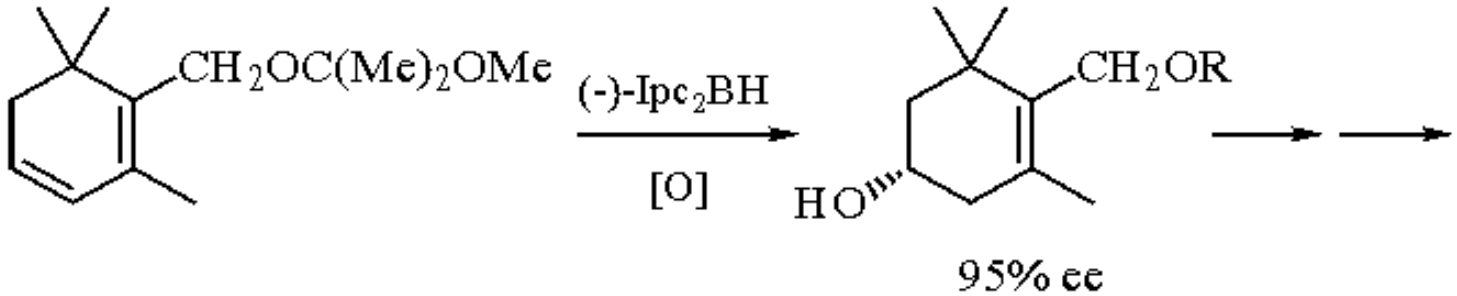

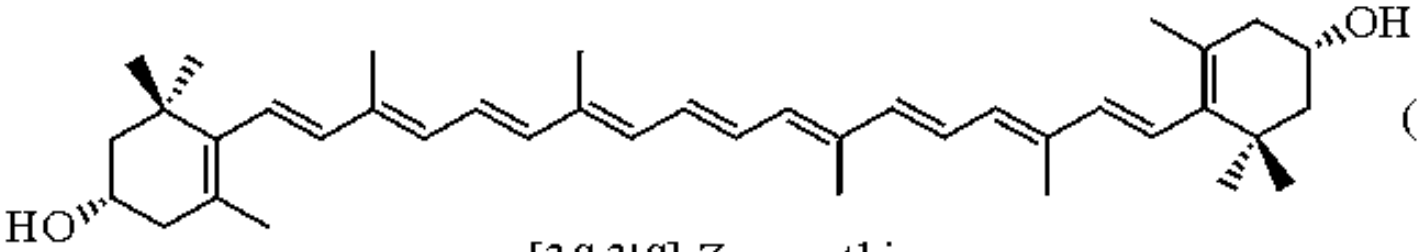

(5)

[3*S*,3'*S*]-Zeaxanthin

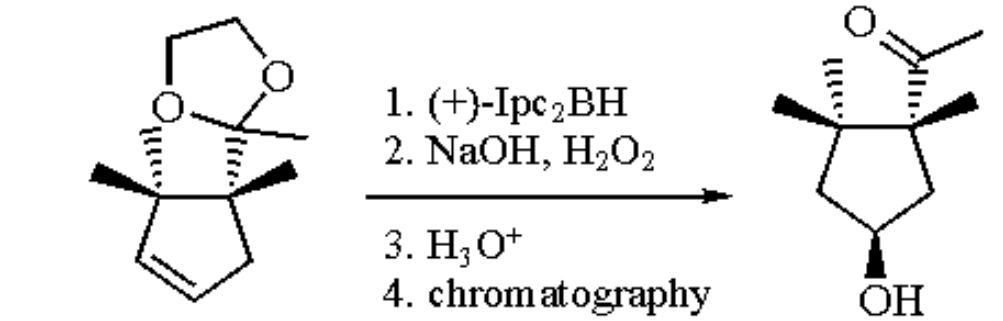

from (+)-camphor

>99% ee

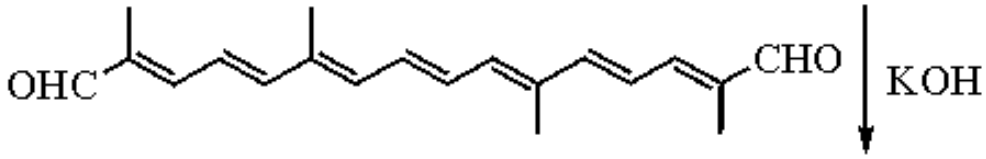

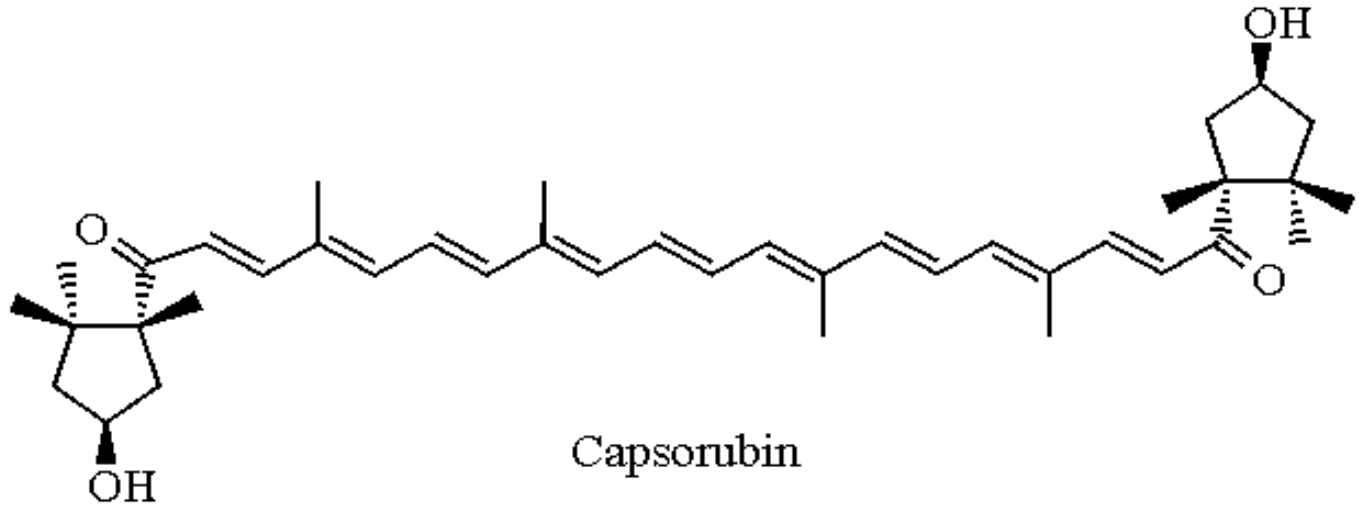

(6)

Capsorubin

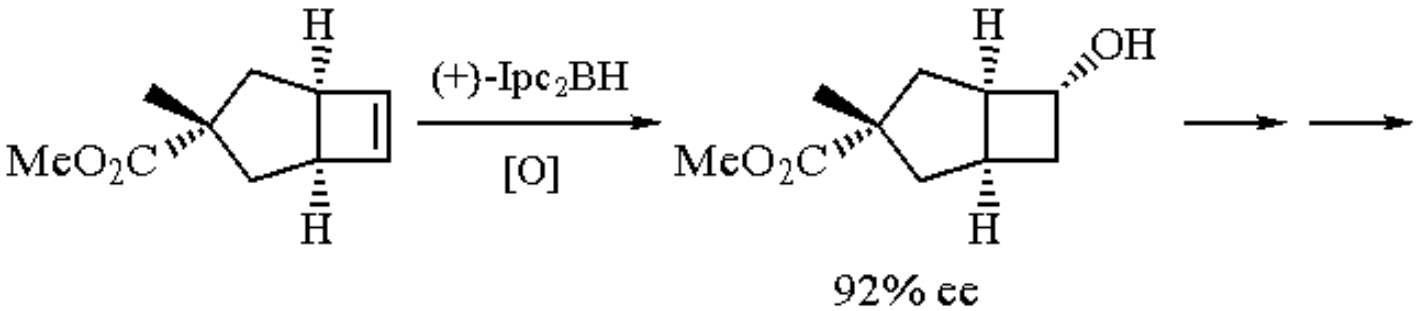

92% ee

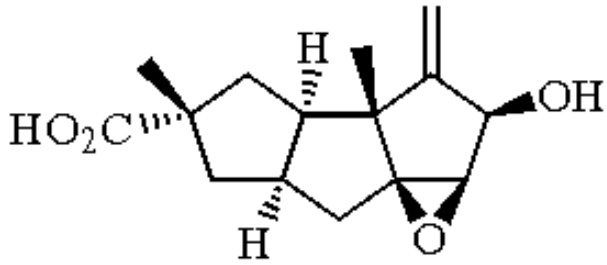

(7)

(+)-Hirsutic acid

Diisopinocampheylborane is not an effective asymmetric hydroborating agent for 2-substituted 1-alkenes. High selectivities have, however, been achieved where one of the substituents is very bulky. This aspect has been elegantly demonstrated by the synthesis of both enantiomers of a precursor of tylonolide, the aglycone of tylosin, which is one of the members of the polyoxomacrolide antibiotics. In both cases the isomeric ratio was at least 50:1 (eqs 8 and 9).[13]

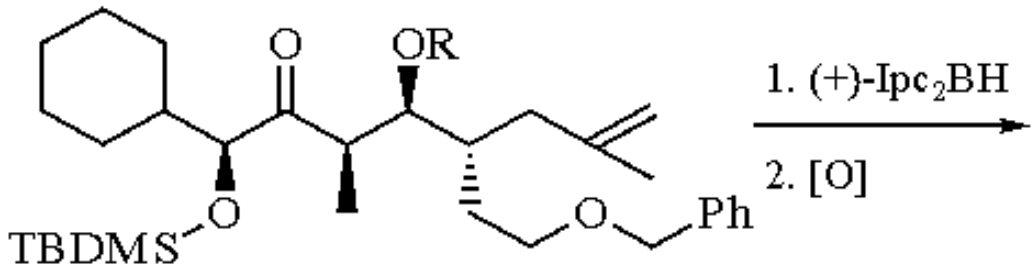

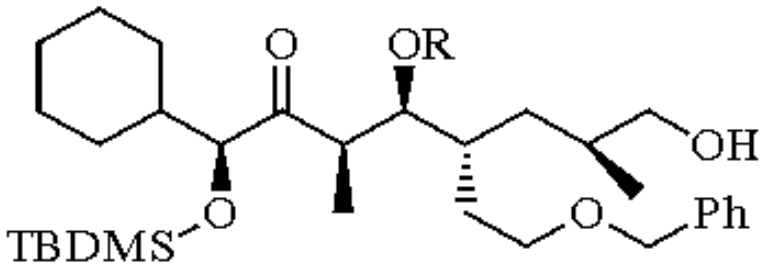

(8)

99% ee

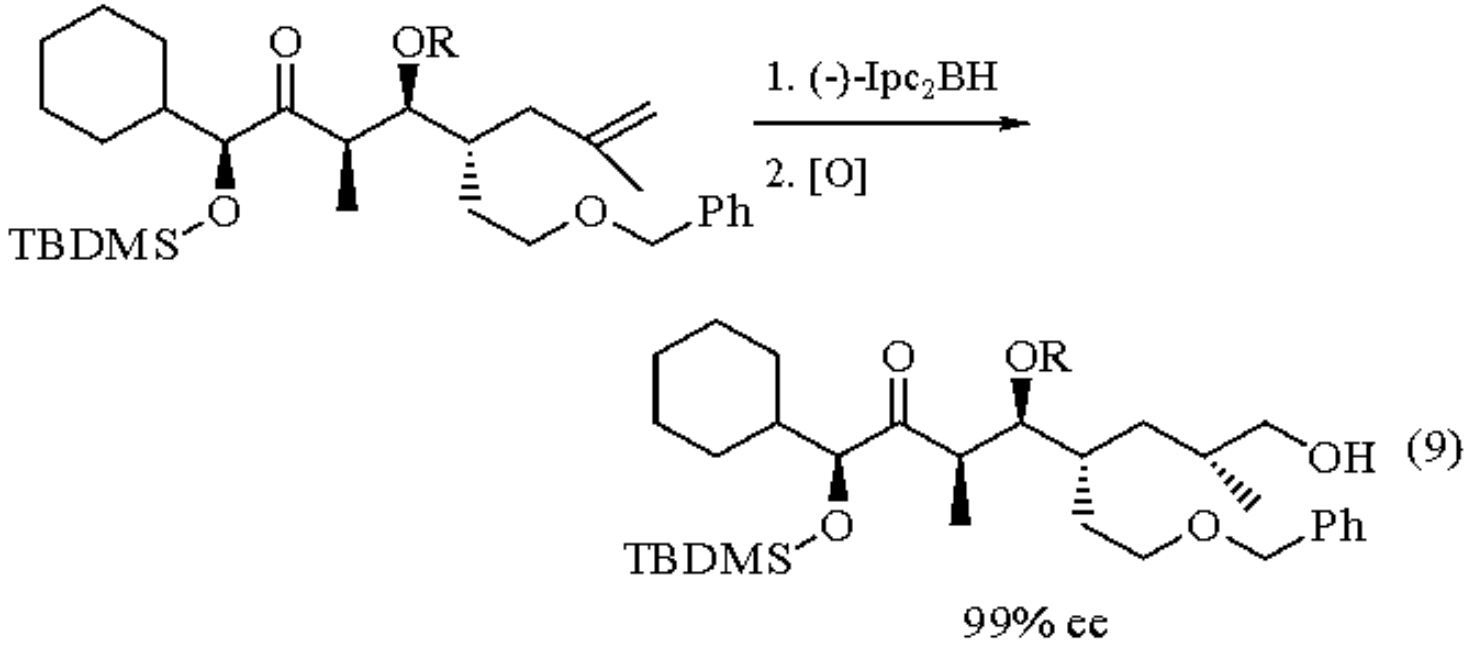

Application of Various Chiral Reagents Derived from Ipc_2BH.

Diisopinocampheylborane does not normally yield satisfactory ee's in hydroboration reactions of 1,1-disubstituted alkenes, *trans*-alkenes, or trisubstituted alkenes. This problem has been partially solved by the introduction of ***Monoisopinocampheylborane***, $IpcBH_2$, which is derived from Ipc_2BH. $IpcBH_2$ handles *trans*-alkenes and trisubstituted alkenes effectively, since it is of lower steric requirement than Ipc_2BH (Table 2). Moreover, $IpcBH_2$ and Ipc_2BH provide an entry into the synthesis of a large variety of optically active borinate and boronate esters. These esters have been successfully converted into α-chiral aldehydes, acids, amines, α-chiral *cis*- and *trans*-alkenes, α-chiral alkynes, β-chiral esters, ketones,[1] etc.

Table 2 Asymmetric Hydroboration of Alkenes with Ipc_2BH and $IpcBH_2$

		% ee of alcohol	
Class[a]	Alkene	Ipc_2BH	$IpcBH_2$
I	2-Methyl-1-alkenes	~20	~1
II	*cis*-Alkenes	³ 99	~25
III	*trans*-Alkenes	~20	70 90[b]
IV	Trisubstituted alkenes	~20	60 ³ 99[b]

[a] Steric requirement increases from class I to class IV. [b] The ee of initial product can be upgraded to 99% ee via crystallization.

Other reagents which have been derived from Ipc_2BH include ***Diisopinocampheylboron Trifluoromethanesulfonate*** (Ipc_2BOTf),[14] ***B-Methoxydiisopinocampheylborane*** (Ipc_2BOMe), and ***(+)-B-Chlorodiisopinocampheylborane*** and its bromo- and iodo analogs (Scheme 1).[1] Ipc_2BOTf and Ipc_2BOMe reagents are used in stereoselective C-C bond forming reactions (aldol condensation and allylboration); Ipc_2BCl (DIP-chloride™) is used for asymmetric reduction of prochiral ketones, and Ipc_2BX(X = Br or I) for enantioselective opening of *meso*-epoxides to nonracemic halohydrins. Numerous applications of all these reagents have been reviewed in detail.[1]

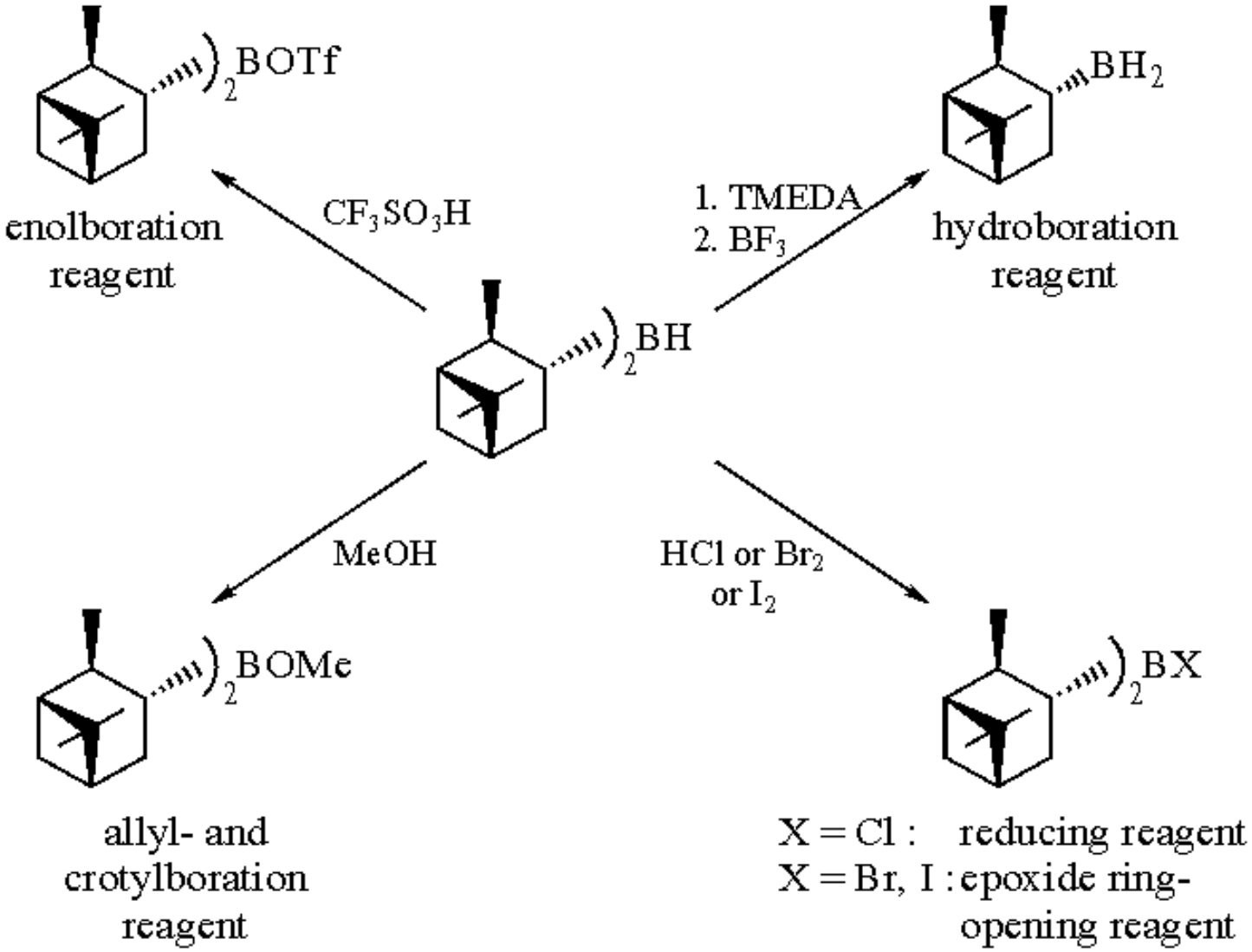

Scheme 1

Related Reagents.

(+)-B-Chlorodiisopinocampheylborane; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***Dilongifolylborane***; ***(R,R)-2,5-Dimethylborolane***; ***B-Methoxydiisopinocampheylborane***; ***Monoisopinocampheylborane***.

---

1. For some excellent reviews on synthetic applications of diisopinocampheylborane and related reagents, see: (a) Brown, H. C.; Ramachandran, P. V. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 2, in press. (b) Brown, H. C.; Ramachandran, P. V. *PAC* **1991**, *63*, 307. (c) Brown, H. C.; Singaram, B. *ACR* **1988**, *21*, 287. (d) Srebnik, M.; Ramachandran, P. V. *Aldrichim. Acta* **1987**, *20*, 9. (e) Matteson, D. S. *S* **1986**, 973.

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Diisopinocampheylboron Trifluoromethanesulfonate

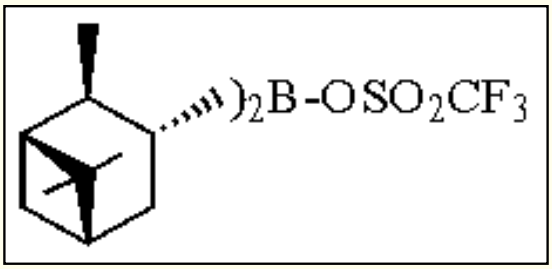

(+)

[108266-89-3] · $C_{21}H_{34}BF_3O_3S$ · Diisopinocampheylboron Trifluoromethanesulfonate · (MW 434.36) (-)

[108161-70-2]

(enolboration reagent for enantio- and diastereoselective aldol condensation of oxazolines[1] and ketones;[2] also used for Ireland-Claisen rearrangement[3])

Alternate Name: diisopinocampheylboron triflate; Ipc_2BOTf.

Physical Data: colorless, viscous oil; bp <=150 °C/0.01 mmHg (bulb-to-bulb distillation); (-)Ipc_2BOTf $[\alpha]_D$ -43.5° (*c* = 30.4, hexane); ^{11}B NMR (hexane) broad singlet at δ = 60 ppm (with reference to $BF_3.OEt_2$).

Solubility: highly sol in both polar and nonpolar aprotic solvents, e.g. diethyl ether, THF, dichloromethane, pentane, hexane, etc.

Preparative Methods: the (+) enantiomer of the reagent (first reported in 1981)[1] is prepared from commercially available (-)-α-pinene (~87% ee) by hydroboration with ***Borane-Dimethyl Sulfide*** in THF at 0 °C, which generates ***Diisopinocampheylborane***, (+)-Ipc_2BH, in more than 99% ee.[4] The crystalline Ipc_2BH is isolated and treated with ***Trifluoromethanesulfonic Acid*** at 0 °C either in dichloromethane[5a] or hexane.[5b] The reagent develops color in dichloromethane. However, it has been prepared in hexane as a clear and colorless solution which separates from an immiscible colored lower layer. In calculating the molarity of the reagent solution, a 60-70% conversion to triflate is assumed.[2] The reagent is usually prepared in situ from Ipc_2BH, and then its aldol reaction is carried out in the same flask by sequential addition of the required reagents[5,11] (procedure A).[6] Alternatively, the enantiomerically pure reagent can be conveniently prepared by treatment of commercially available (-)- or ***(+)-B-Chlorodiisopinocampheylborane*** (DIP-Cl™) with triflic acid at 0 °C in hexane (Scheme 1).[7] This method (procedure B) generates Ipc_2BOTf instantaneously in almost quantitative yield. The reagent generated by procedure B can be utilized for aldol reaction in the same manner as described for procedure A.

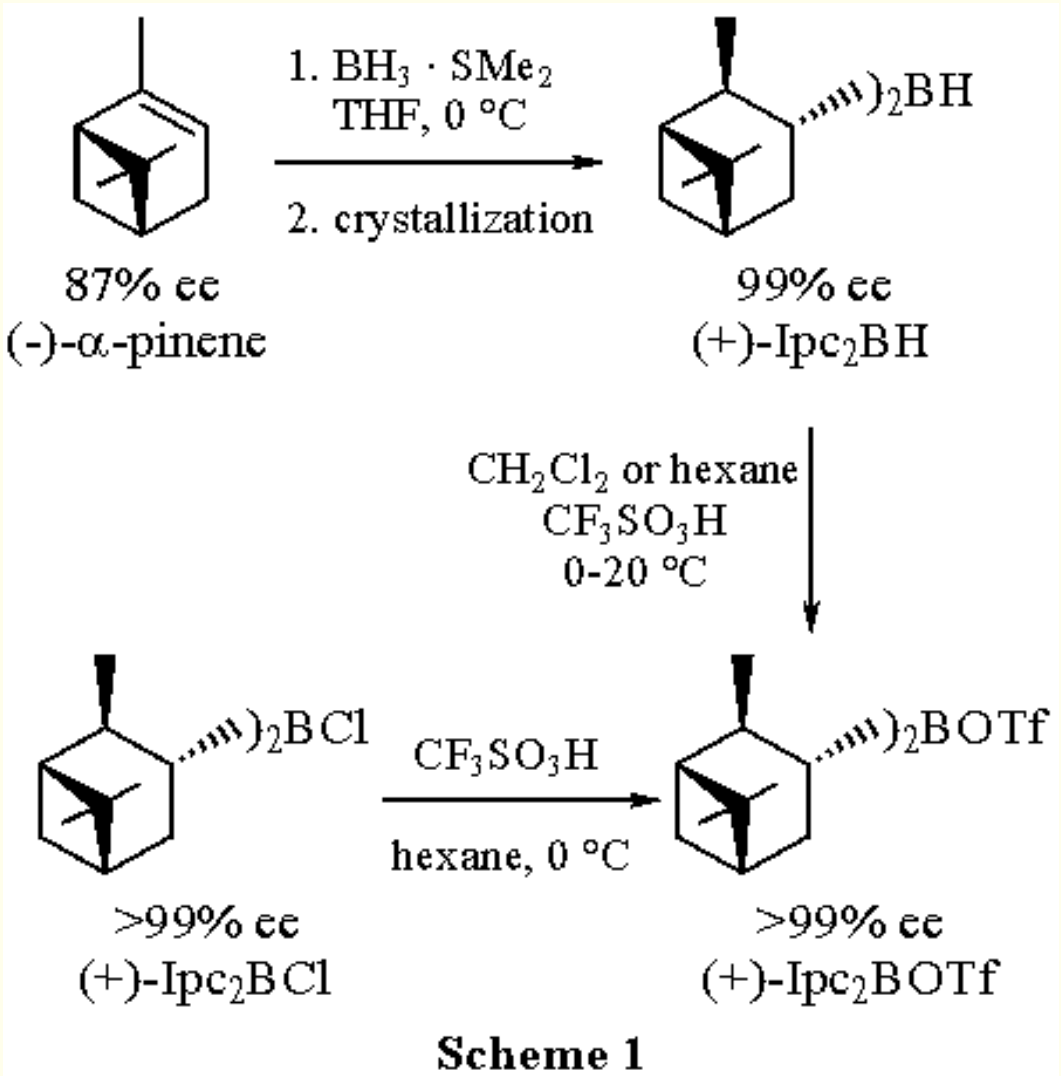

Scheme 1

Handling, Storage, and Precautions: air sensitive; reacts instantaneously with protic solvents to liberate triflic acid; should be freshly prepared prior to use; the freshly prepared reagent turns from pale yellow to clear red upon standing. All transformations involving this reagent should be carried out under N_2 using standard techniques for air sensitive reagents; use in a fume hood.

Boron Azaenolates from Oxazolines.

The reagent is useful for asymmetric aldol condensations of achiral oxazolines. Treatment of 2-ethyl-4-dimethyl-2-oxazoline with Ipc_2BOTf in the presence of a tertiary amine furnishes a boron azaenolate. Without isolation, treatment with an aldehyde in ether at -78 °C provides an alkylated oxazoline, which is hydrolyzed and converted to β-hydroxy ester via treatment with ***Diazomethane***. Although the yields for the four-step sequence are only moderate, the *anti* selectivities of the hydroxy acids are excellent with enantioselectivities of 77-85% ee (eq 1).[1]

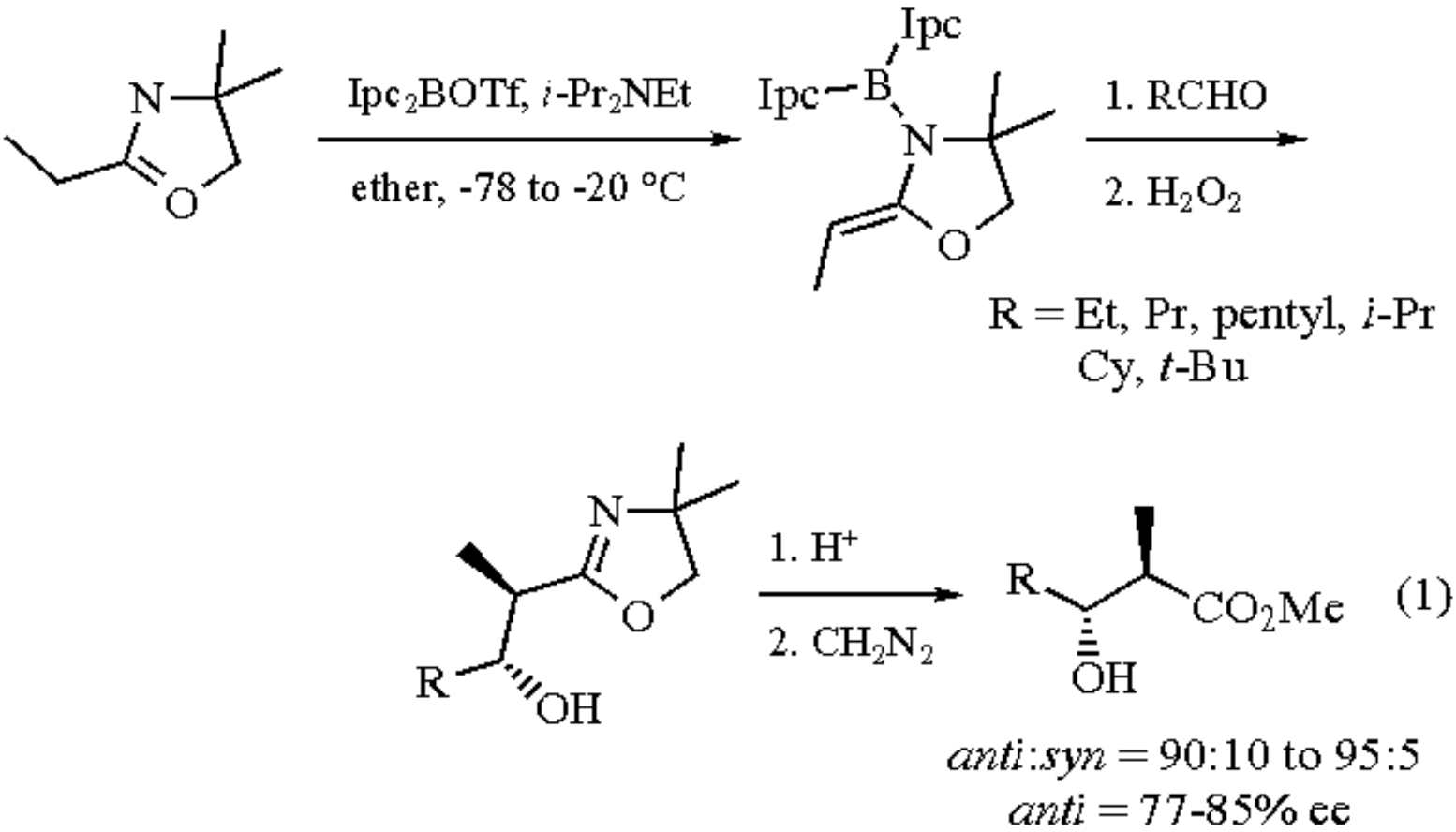

Boron Enolates from Ketones.

Boron enolates are highly versatile intermediates in organic synthesis.[8] Their high reactivity and stereoselectivity are often utilized for aldol condensation reactions.[9,10] The reagent has been elegantly applied for regio- and stereoselective enolboration of ketones and subsequent enantio- and diastereoselective aldol reactions with aldehydes.[11] For example, the aldol reaction between ethyl ketones and aldehydes using the (+) or (-) reagent in the presence of a tertiary amine in dichloromethane gives (via the desired (*Z*)-enolborinate) *syn*-α-methyl-β-hydroxy ketones in good enantiomeric excess (66-93% ee) and with high diastereoselectivity (&egt;95%) (eq 2). In contrast, the *anti* selectivity of the aldol product derived from diethyl ketone via formation of the (*E*)-enolate, derived from Ipc_2BCl (DIP-Cl™) with ***Methacrolein***, proceeds with negligible enantioselectivity.[11a] However, use of both the triflate and the chloride reagents in the aldol reaction of methyl ketones with aldehydes have been reported to give β-hydroxy ketones in moderate enantiomeric excess (53-78% ee) with a reversal in the enantioface selectivity of the aldehyde compared to the corresponding ethyl ketone *syn*-aldol. This variable selectivity is interpreted as evidence for the participation of competing chair and boat transition states.[11]

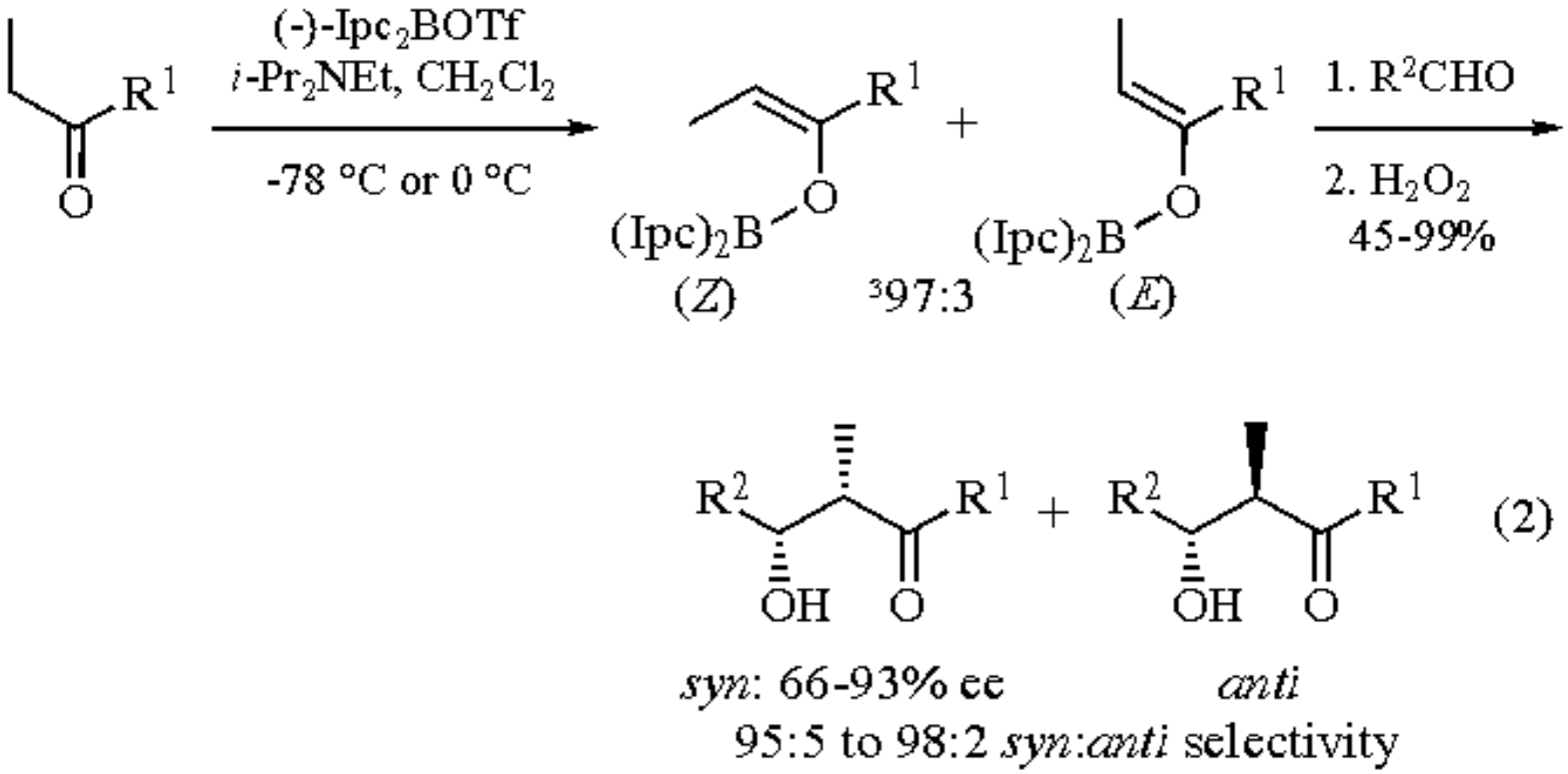

(2)

The aldol methodology mediated by Ipc_2BOTf was successfully applied to a macrolide antibiotic synthesis. Paterson reported a convenient asymmetric synthesis of a C_{19}-C_{27} segment of rifamycin S used in the Kishi synthesis, based on ethyl ketone aldol reactions mediated by optically pure reagent.[12a] He also reported the novel aldol approach to the synthesis of an enantiomerically pure C_7-C_{15} segment of tirandamycin A.[12b] This was prepared via enolboration of the (*R*)-ethyl ketone by (-)-Ipc_2BOTf in the presence of a tertiary amine. Addition of aldehyde to the corresponding enolborinate, followed by oxidative workup and chromatographic purification, led to the two separated *syn*-aldol isomers (8:1 ratio with 63% combined yield) with no *anti*-aldol product detected by HPLC. The major 1,2-*syn*-3,4-*syn* diastereomer is reported to be enantiomerically pure. Moreover, it was observed that enantiomeric excess of the major aldol isomer is significantly enhanced relative to the starting ketone. The corresponding aldol product is reduced to the 1,3-diol (eq 3) and subsequently converted to the enantiomerically pure C_7-C_{15} segment of tirandamycin A via pyranone synthesis.[12b]

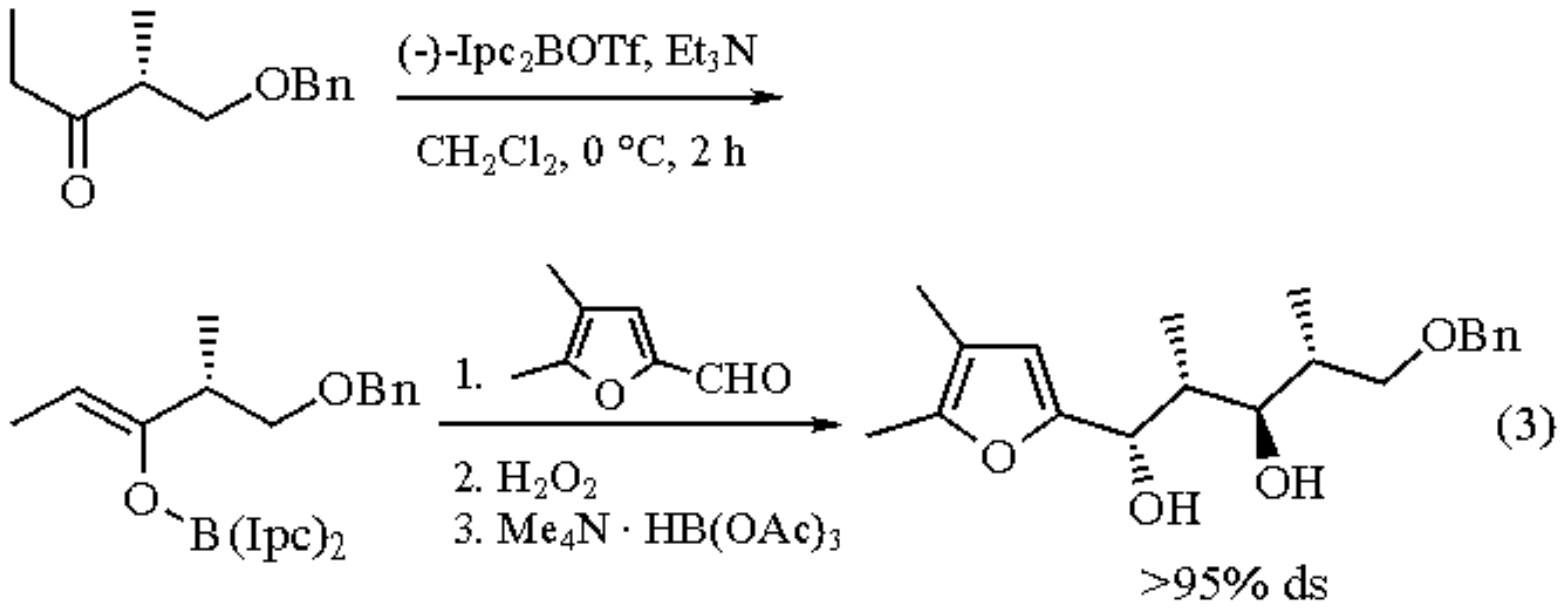

Dihydropyrones are valuable intermediates for the synthesis of a variety of substituted tetrahydropyran rings. Recently, stereoselective aldol reactions of β-chlorovinyl ketones using the dienol boronate derivative derived from chiral Ipc_2BOTf was utilized for enantioselective formation of dihydropyrones. No detectable racemization was reported on the cyclization step (eq 4).[12c]

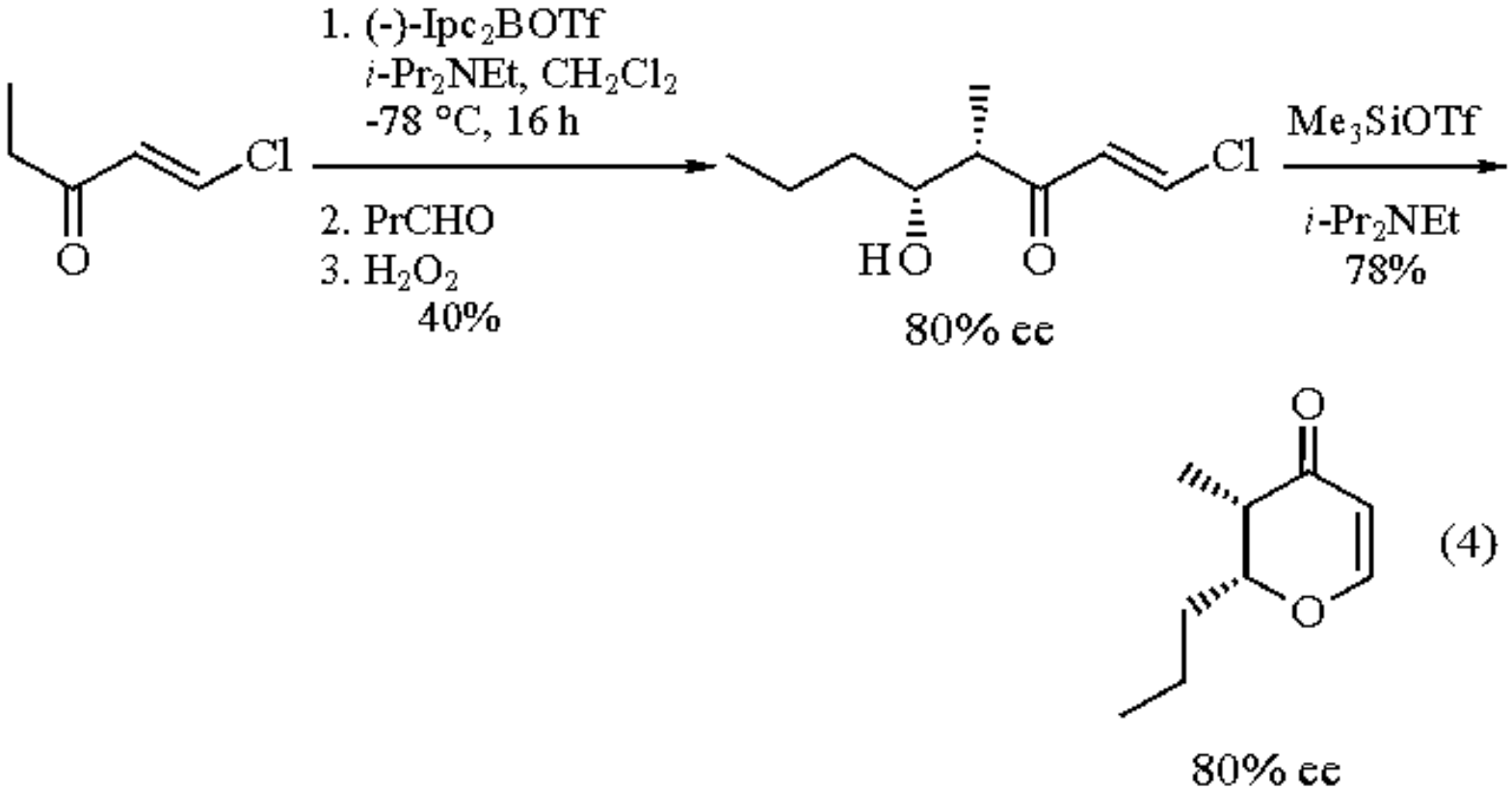

Ireland-Claisen Rearrangement.

Oh et al. recently reported the Ireland-Claisen rearrangement of a variety of *O*-protected 2-butenyl glycolates via chelated boron and tin triflates to give, after esterification, methyl 2-methoxy/benzyloxy-3-methyl-4-pentenoates.[3] In

reactions using Ipc_2BOTf, diastereoselection as high as 99.5% was reported. The diastereoselection obtained in reactions using ***Tin(II) Trifluoromethanesulfonate***, ***Zinc Trifluoromethanesulfonate***, and ***Di-n-butylboryl Trifluoromethanesulfonate*** was far lower than in reactions with Ipc_2BOTf. Moreover, the rate of rearrangement with boron enolates was found to be higher than the rates of rearrangement of the silyl ketene acetals or lithium enolate. As anticipated the *cis*-alkene gives better diastereoselectivity than the *trans* isomer (eq 5). With this high diastereoselection obtained using Ipc_2BOTf, it is surprising that the enantioselectivity of this reaction is only 0-10% ee.[3]

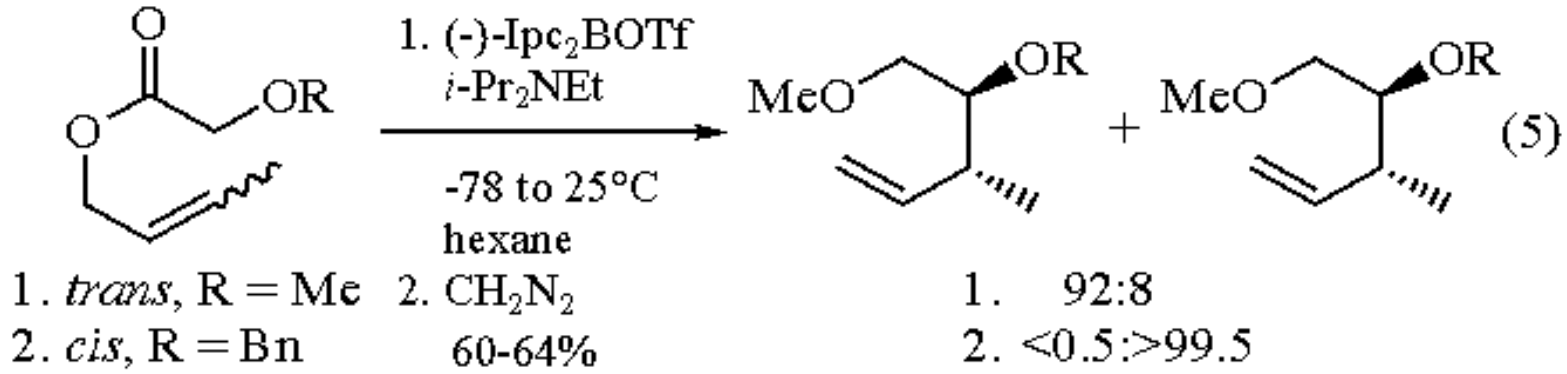

Related Reagents.

(+)-B-Chlorodiisopinocampheylborane; ***Diisopinocampheylborane***; ***(R,R)-2,5-Dimethylborolane***.

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6. Purification of Ipc_2BOTf by distillation is unnecessary and probably inadvisable as optimum results are obtained with freshly prepared undistilled reagent.[2]
7. Dhar, R. K.; Brown, H. C.; unpublished results.
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9. For an examination of the effect of leaving group (X) on the stereoselective enolboration of ketones with various R_2BX reagents (X = OTf, OMs, Cl, Br, I), see: (a) Brown, H. C.; Ganesan, K.; Dhar, R. K. *JOC* **1993**, *58*, 147. (b) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *JACS* **1989**, *111*, 3441. (c) Goodman, J. M.; Paterson, I. *TL* **1992**, 7223.
10. Selective *trans* deprotonation of the ketone-L_2BOTf complex leads to formation of (*Z*)-enolborinate; see: Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *JACS* **1981**, *103*, 3099. An alternative explanation for L_2BCl to (*E*)-enol borinate and L_2BOTf to (*Z*)-enol borinate has been proposed by Corey and Kim; see: Corey, E. J.; Kim, S. S. *JACS* **1990**, *112*, 4976.
11. (a) Paterson, I.; Goodman, J. M. *TL* **1989**, *30*, 997. (b) Paterson, I.; Goodman, J. M.; Isaka, M. *TL* **1989**, *30*, 7121. (c) Paterson, I.; McClure, C. K. *TL* **1987**, *28*, 1229.
12. (a) Paterson, I.; McClure, C. K.; Schumann, R. C. *TL* **1989**, *30*, 1293. (b) Paterson, I.; Lister, M. A.; Ryan, G. R. *TL*

1991, *32*, 1749. (c) Paterson, I.; Osborne, S. *TL* **1990**, *31*, 2213.

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(*R**,*R**)-α-(2,6-Diisopropoxybenzoyloxy)-5-oxo-1,3,2-dioxaborolane-4-acetic Acid[1]

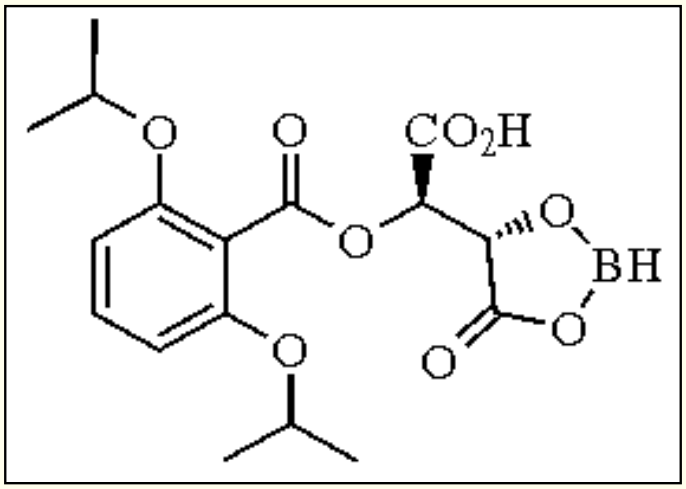

(*R*,*R*)

[131703-55-4] · $C_{17}H_{21}BO_9$ · (*R**,*R**)-α-(2,6-Diisopropoxybenzoyloxy)-5-oxo-1,3,2-dioxaborolane-4-acetic Acid · (MW 380.16) (*S*,*S*)

[131703-56-5]

(chiral Lewis acid catalyst for Diels-Alder,[1,2] aldol-type,[3] allylation,[4] and hetero Diels-Alder[5] reactions)

Solubility: sol dichloromethane, propionitrile, THF.

Form Supplied in: the acyloxyborane.THF complex is available as a 0.1-0.2 M solution in dichloromethane or propionitrile.

Analysis of Reagent Purity: ^{1}H NMR (CD_2Cl_2, -95 °C, 500 MHz) δ 1.07-1.13 (m, 6H, 2CH_3), 1.24 (br, 6H, 2CH_3), 4.50 (br, 2H, 2$(CH_3)_2$C*H*), 4.70-4.92 (m, 1H, $CHCO_2B$), 5.45-5.72 (m, 1H, C*H*CO_2H), 6.48 (br, 2H, 2*m*-H), 7.21 (br, 1H, *p*-H).

Preparative Methods: to a solution of (*R*,*R*)- or (*S*,*S*)-mono-(2,6-diisopropoxybenzoyl)tartaric acid (74 mg, 0.2 mmol) in dry dichloromethane or propionitrile (1 mL) is added BH_3.THF (0.189 mL of 1.06 M solution in THF, 0.2 mmol) at 0 °C under an argon atmosphere. The reaction mixture is stirred for 1 h at 0 °C to produce the chiral acyloxyborane. Only 2 equiv of hydrogen gas should evolve under these reaction conditions (0 °C). See also Furuta.[1]

Handling, Storage, and Precautions: the acyloxyborane solution should be flushed with Ar and stored

tightly sealed (to preclude contact with oxygen and moisture) below 0 °C. Use in a fume hood.

Acyloxyborane as an Activating Device for Carboxylic Acids.[2a]

The reduction of carboxylic acids by borane is an important procedure in organic synthesis. The remarkable reactivity of borane towards carboxylic acids over esters is characteristic of this reagent. Such selectivity is rarely seen with other hydride reagents.

The rapid reaction between carboxylic acids and borane is related to the electrophilicity of the latter. The carbonyl group of the initially formed acyloxyborane intermediate, which is essentially a mixed anhydride, is activated by the Lewis acidity of the trivalent boron atom. Addition of 1/3 equiv of the ***Borane-Tetrahydrofuran*** complex to acrylic acid in dichloromethane followed by addition of a diene at low temperature results in the formation of Diels-Alder adducts in good yield (eq 1). Further, the reaction is successful even with a catalytic amount of borane.

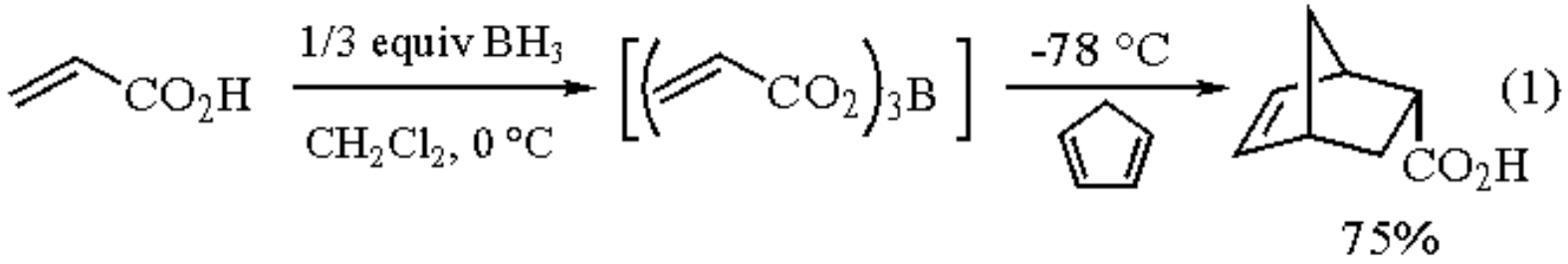

Asymmetric Diels-Alder Reaction of Unsaturated Carboxylic Acids.[2a]

A chiral acyloxyborane (CAB) complex (**1**) prepared from mono(2,6-dimethoxybenzoyl)tartaric acid and 1 equiv of borane is an excellent catalyst for the Diels-Alder reaction of α,β-unsaturated carboxylic acids and dienes. In the CAB-catalyzed Diels-Alder reaction, adducts are formed in a highly diastereo- and enantioselective manner under mild reaction conditions (eq 2). The reaction is catalytic: 10 mol % of catalyst is sufficient for efficient conversion, and the chiral auxiliary can be recovered and reused.

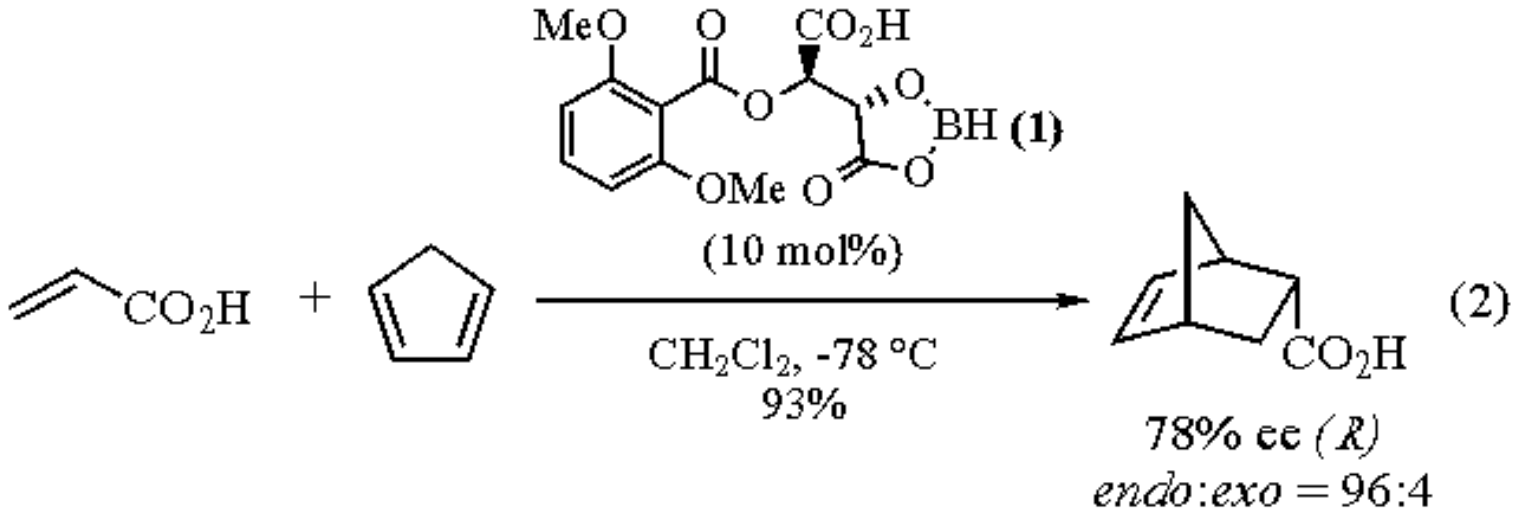

Asymmetric Diels-Alder Reaction of Unsaturated Aldehydes.[1,2b-e]

The boron atom of acyloxyborane is activated by the electron-withdrawing acyloxy groups, and consequently acyloxyborane derivatives are sufficiently Lewis acidic to catalyze certain reactions. Thus, asymmetric Diels-Alder reactions of α,β-enals with dienes using (**1**) as a Lewis acid catalyst have been developed. For example, the reaction of cyclopentadiene and methacrolein gives the adduct in 85% yield (*endo*:*exo* = 11:89) and 96% ee (major *exo* isomer) (eq 3). Some additional examples are listed in Figure 1. The α-substituent on the dienophile increases the enantioselectivity, while β-substitution dramatically decreases the selectivity. In the case of a substrate having substituents in both α- and β-positions, high enantioselectivity is observed; thus the α-substituent effect overcomes that of the β-substituent.

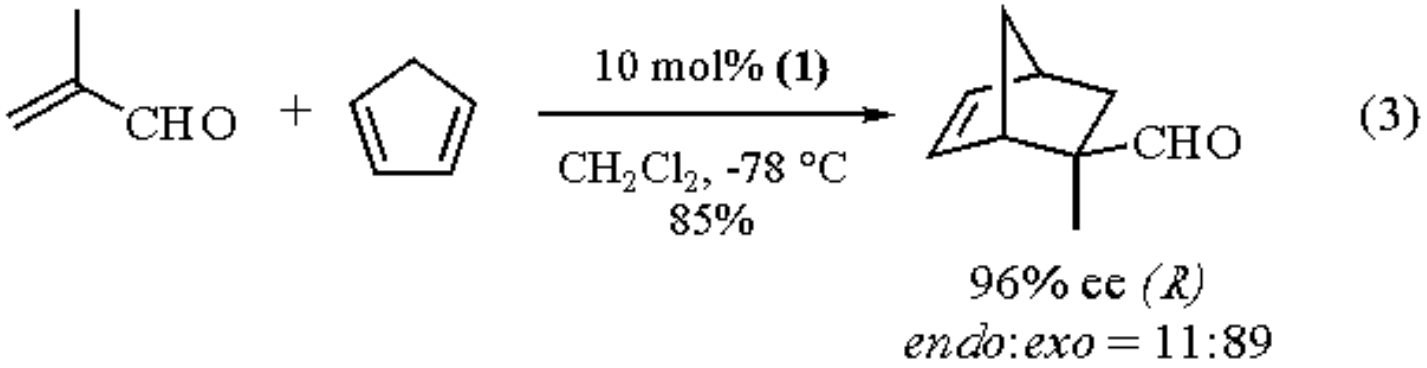

The intramolecular Diels-Alder reaction of 2-methyl-(*E*,*E*)-2,7,9-decatrienal with CAB catalysis proceeds with high diastereo- and enantioselectivities.[2c]

Asymmetric Aldol-Type Reaction.[3]

CAB complex (**2**) is an excellent catalyst for the Mukaiyama condensation of simple achiral enol silyl ethers of ketones with various aldehydes. The CAB-catalyzed aldol process allows the formation of adducts in a highly diastereo- and enantioselective manner (up to 96% ee) under mild reaction conditions (eqs 4 and 5). The reactions are catalytic: 20

mol % of catalyst is sufficient for efficient conversion, and the chiral auxiliary can be recovered and reused.

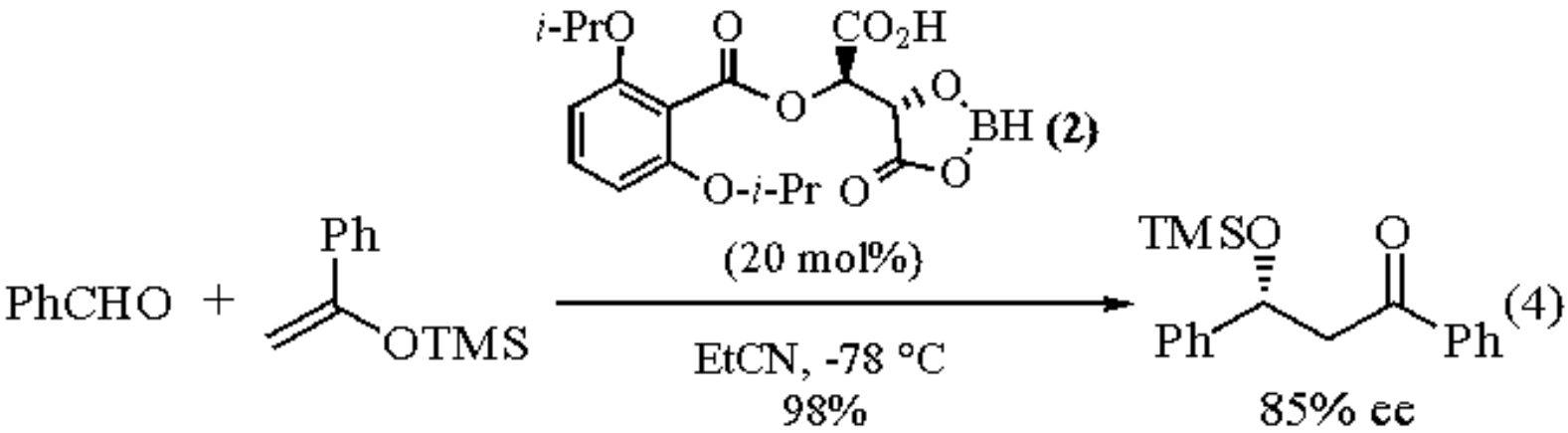

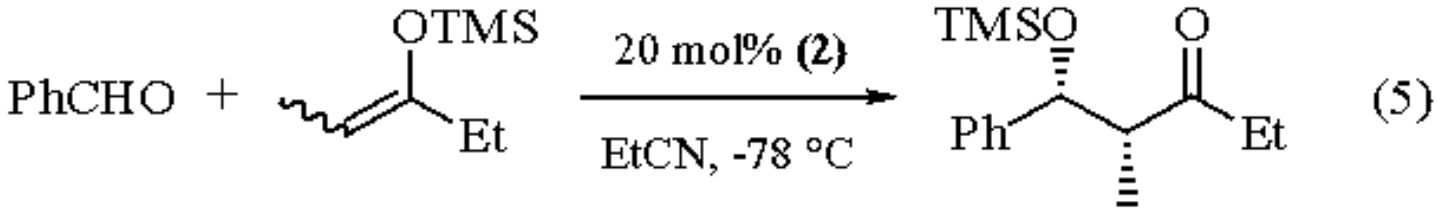

$(E):(Z) = 4:1$ 96%, 96% ee, $syn:anti = 94:6$
$(E):(Z) = 1:49$ 97%, 96% ee, $syn:anti = 93:7$

Almost perfect asymmetric induction is achieved in the *syn* adducts, reaching 96% ee, although a slight reduction in both the enantio- and diastereoselectivities is observed in the reactions with saturated aldehydes. It is noteworthy that, regardless of the stereochemistry of the starting enol silyl ethers, the CAB-catalyzed reaction is highly selective for *syn* adducts. The high *syn* selectivity and the independence of selectivity on the stereochemistry of silyl ethers in the CAB-catalyzed reactions are fully consistent with Noyori's ***Trimethylsilyl Trifluoromethanesulfonate***-catalyzed aldol reactions of acetals,[6] and thus may reflect the acyclic extended transition state mechanism postulated in the latter reactions (Figure 2). Judging from the product configurations, the CAB catalyst (from natural tartaric acid) should effectively cover the *si*-face of carbonyl following its coordination and the selective approach of nucleophiles from the *re*-face should result.

A catalytic asymmetric aldol-type reaction of ketene silyl acetals with achiral aldehydes also proceeds with the CAB catalyst (**2**), which can furnish *syn*-β-hydroxy esters with high enantioselectivity (eq 6).

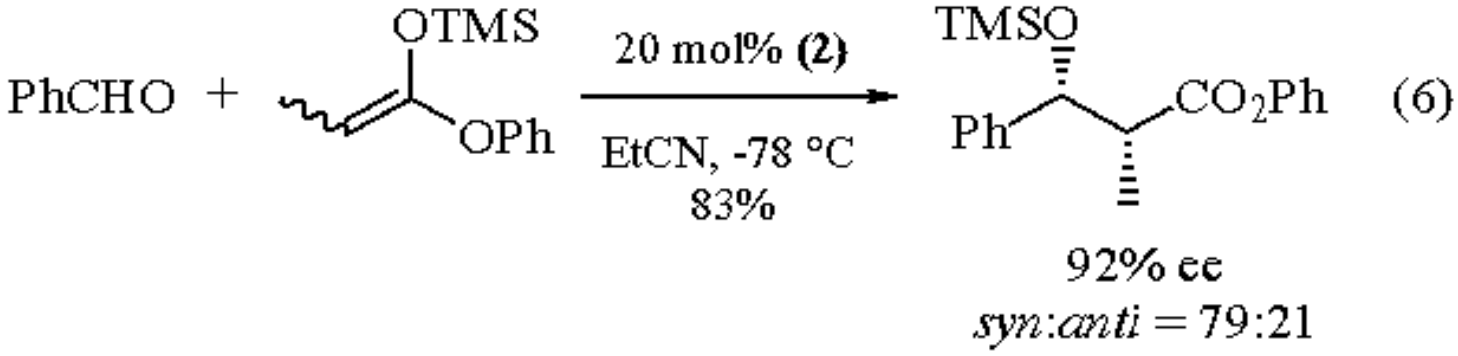

This reaction is sensitive to the substituents of the starting ketene acetals. The use of ketene silyl acetals from phenyl

esters leads to good diastereo- and enantioselectivities with excellent chemical yields.

Analogous with the previous results of enol silyl ethers of ketones, nonsubstituted ketene silyl acetals are found to exhibit lower levels of stereoregulation, while the propionate-derived ketene silyl acetals display a high level of asymmetric induction. The reactions with aliphatic aldehydes, however, resulted in a slight reduction in optical and chemical yields. With phenyl ester-derived ketene silyl acetals, *syn* adducts predominate, but the selectivities are moderate in most cases in comparison with the reactions of ketone-derived silyl enol ethers. Exceptions are α,β-unsaturated aldehydes, which revealed excellent diastereo- and enantioselectivities. The observed *syn* selectivity and *re*-face attack of nucleophiles on the carbonyl carbon of aldehydes are consistent with the aforementioned aldol reactions of ketone-derived enol silyl ethers.

Asymmetric Allylation (Sakurai-Hosomi Allylation).[4]

Condensation of achiral aldehydes with allylsilanes promoted by CAB catalyst (**2**) (20 mol %) at -78 °C in propionitrile produces homoallylic alcohols with excellent enantioselectivity (eq 7).

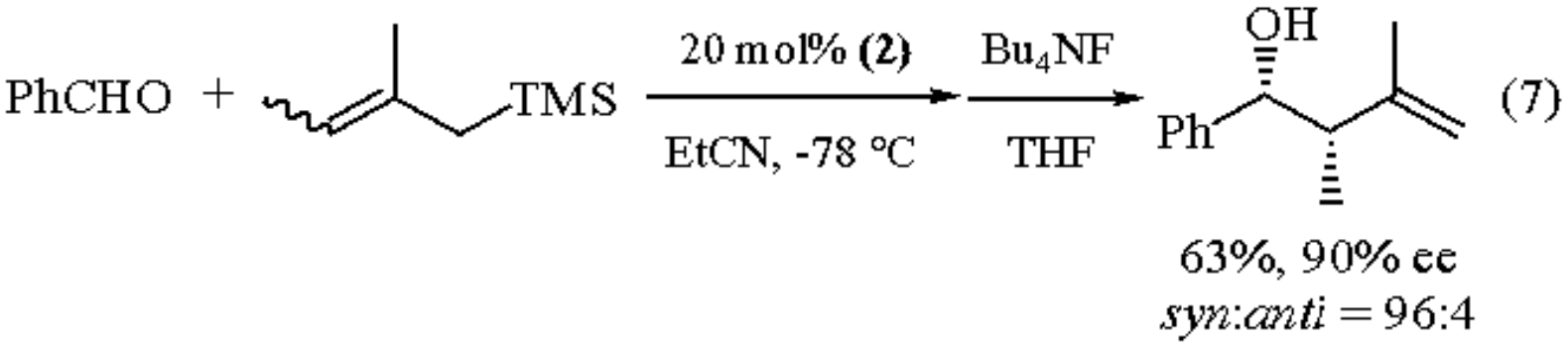

Alkyl substitution at the alkene of the allylsilanes increases the reactivity, permitting lower reaction temperature and improved asymmetric induction. γ-Alkylated allylsilanes exhibit excellent diastereo- and enantioselectivities, affording *syn* homoallylic alcohols with high enantiomeric purity. The *syn* selectivity of these reactions is independent of the allylsilane stereochemistry. Thus regardless of the geometry of the starting allylsilane, the predominant isomer in this reaction has *syn* configuration. The observed preference for relative and absolute configurations for the adduct alcohols derived from reaction catalyzed by the (2*R*,3*R*)-ligand-borane reagent can be rationalized on the basis of an extended transition state model similar to that for the CAB-catalyzed aldol reaction (see Figure 2).

Allystannanes are more nucleophilic than allylsilanes. Addition of achiral allylstannanes to achiral aldehydes in the presence of (**1**) (20 mol %) and ***Trifluoroacetic Anhydride*** (40 mol %) also affords homoallylic alcohols with high diastereo- and enantioselectivities (eq 8).

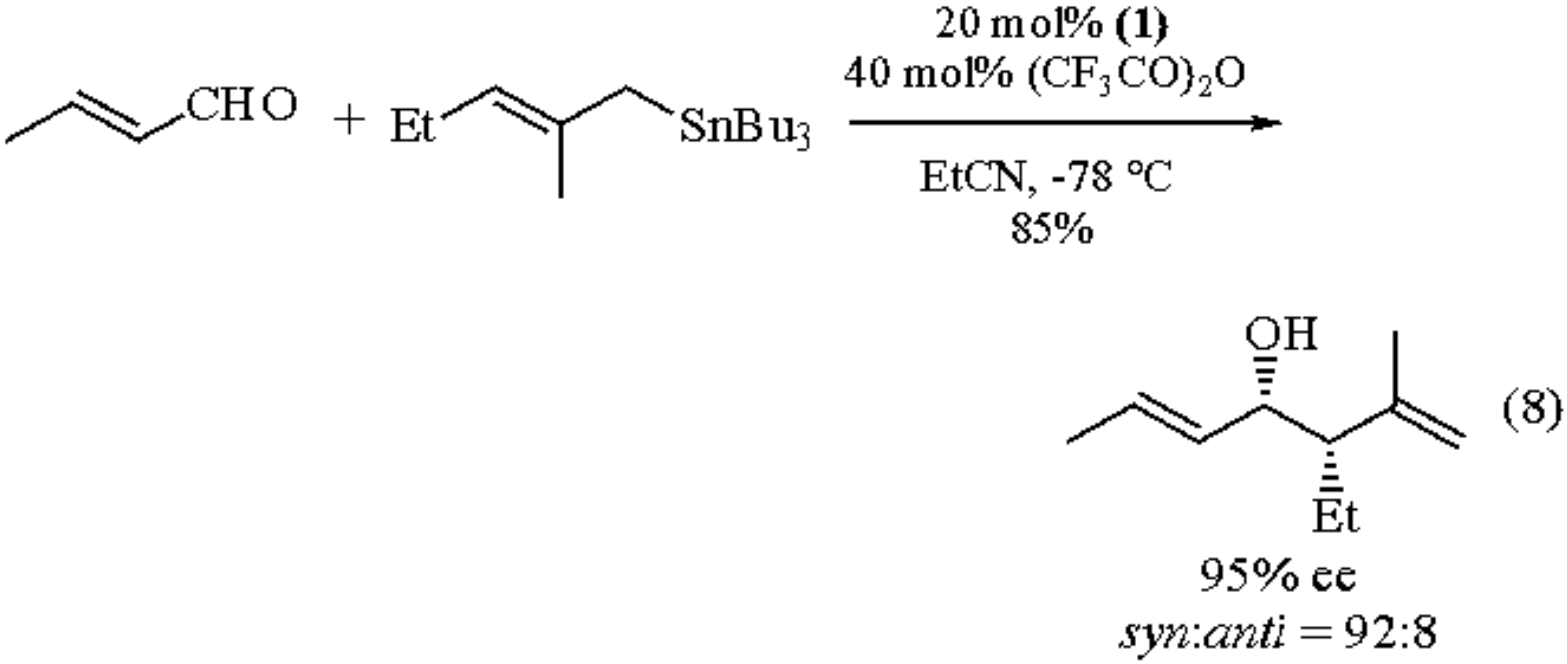

Asymmetric Hetero Diels-Alder Reaction.[5]

In contrast to the CAB catalyst (**2**; R = H) which is stable and both air and moisture sensitive, the *B*-alkylated CAB catalyst (**3**; R = Ph or alkyl) is stable and can be stored in a closed container at rt. A solution of the CAB (**3**; R = Ph) catalyzes Diels-Alder, aldol, and Sakurai-Hosomi reactions. Although the asymmetric inductions achieved by these complexes are slightly less efficient than that of the corresponding hydride-type catalyst, the CAB catalyst (**3**; R = Ph) is shown to be an excellent system for hetero Diels-Alder reactions.

The *B*-alkylated CAB catalyst (**3**) is easily prepared in situ by mixing a 1:1 molar ratio of tartaric acid derivative and phenylboronic acid in dry propionitrile at room temperature for 0.5 h. The hetero Diels-Alder reaction of aldehydes with Danishefsky dienes is promoted by 20 mol % of this catalyst solution at -78 °C for several hours to produce dihydropyranone derivatives of high optical purity (eq 9).

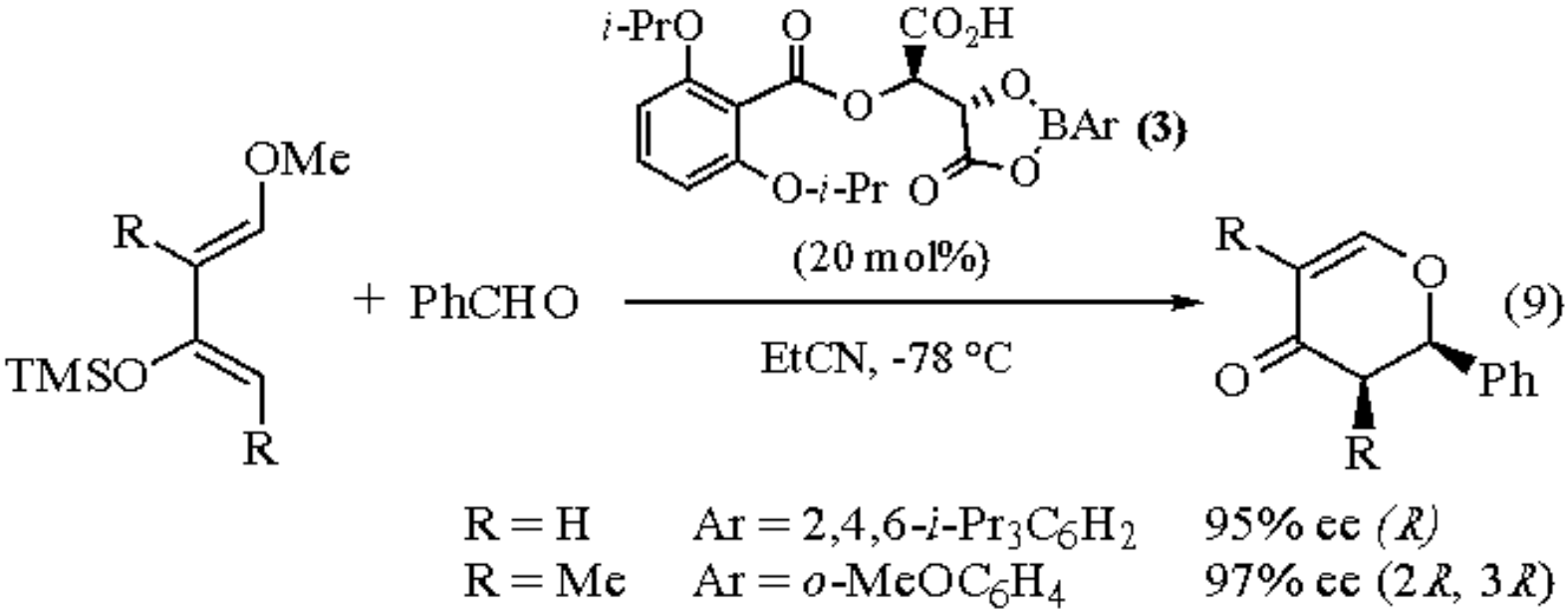

1. Furuta, K.; Gao, Q.; Yamamoto, H. *OS* **1995**, *72*, 86.
2. (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *JACS* **1988**, *110*, 6254. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *JOC* **1989**, *54*, 1481. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H. *TL* **1989**, *30*, 7231. (d) Ishihara, K.; Gao, Q.; Yamamoto, H. *JOC* **1993**, *58*, 6917. (e) Ishihara, K.; Gao, Q.; Yamamoto, H. *JACS* **1993**, *115*, 10412.
3. (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *JACS* **1991**, *113*, 1041. (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *SL* **1991**, 439. (c) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *BCJ* **1993**, *66*, 3483.
4. (a) Furuta, K.; Mouri, M.; Yamamoto, H. *SL* **1991**, 561. (b) Marshall, J. A.; Tang, Y. *SL* **1992**, 653. (c) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *JACS* **1993**, *115*, 11490.
5. (a) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *JOC* **1992**, *57*, 1951. (b) Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *T* **1994**, *50*, 979.
6. Noyori, R.; Murata, S.; Suzuki, M. *T* **1981**, *37*, 3899.

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(Diisopropoxymethylsilyl)methylmagnesium Chloride

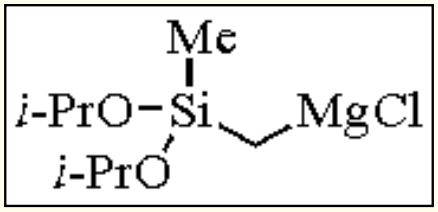

[85719-58-0] · $C_8H_{19}ClMgO_2Si$ · (Diisopropoxymethylsilyl)methylmagnesium Chloride · (MW 235.08)

(a nucleophilic hydroxymethylating agent for organic halides, in combination with metal-catalyzed coupling reaction followed by oxidative cleavage of the silicon-carbon bonds)

Solubility: sol THF.

Preparative Method: prepared under nitrogen by reaction of commercially available chloromethyl(diisopropoxy)methylsilane *[2212-08-0]* with ***Magnesium*** in THF, using essentially the same method as that described for the preparation of the monoisopropoxy analog (see ***(Chloromethyl)isopropoxydimethylsilane***).

Analysis of Reagent Purity: the yield of the reagent is usually >90%, but may be titrated before use by one of the standard methods.

Handling, Storage, and Precautions: can be stored under nitrogen at rt for at least two days without loss of activity.

Nucleophilic Hydroxymethylating Agent.

The Grignard reagent serves as a versatile nucleophilic hydroxymethyl anion equivalent in combination with the ***Hydrogen Peroxide*** oxidation of the silicon-carbon bond (eq 1).[1,2] The primary products, $(i\text{-PrO})_2MeSiCH_2E$, are stable to weakly basic and acidic aqueous workup and silica gel chromatography. The method is suitable for the nucleophilic hydroxymethylation of halides via a transition metal-catalyzed cross-coupling reaction, but works poorly with carbonyl groups because of the formation of complex mixtures in the first step. When transition metal catalysts such as copper, nickel, or palladium are used, care should be taken to remove them before the oxidation, otherwise vigorous decomposition of hydrogen peroxide may occur.

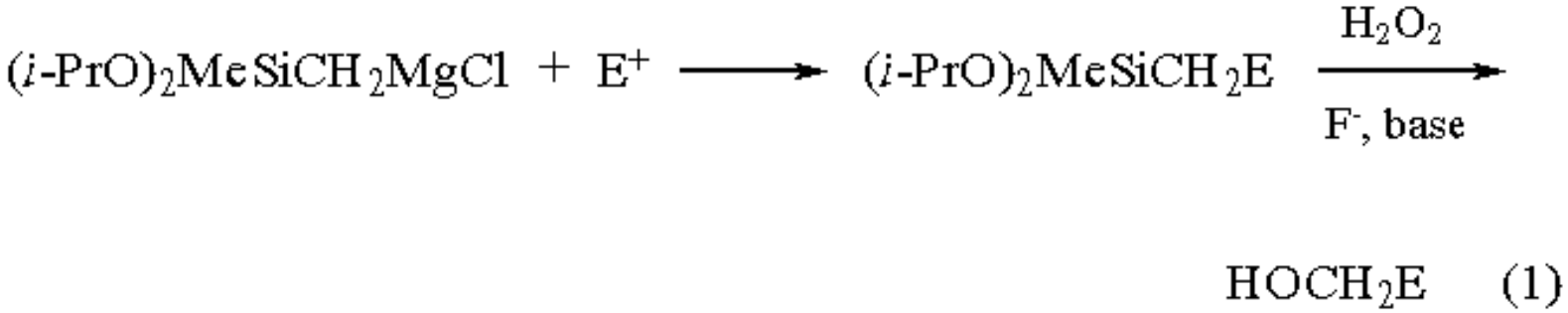

Allylic halides, such as geranyl and neryl chlorides (eq 2), are hydroxymethylated without loss of regio- and stereochemistry.[2] This method, among others, has been reported to be successfully used for the nucleophilic hydroxymethylation of a 2,3-epoxyalkyl bromide (eq 3).[3] The hydroxymethylation of alkenyl and aryl halides can be attained via a nickel- or palladium-catalyzed cross-coupling reaction with the Grignard or zinc reagent, followed by hydrogen peroxide oxidation (eqs 4 and 5).[2] An enol phosphate can also be hydroxymethylated via the nickel-catalyzed cross-coupling (eq 6).[2] Since the enol phosphate is readily available from ketone, this transformation provides a novel method for the regioselective dehydration-hydroxymethylation of ketones.

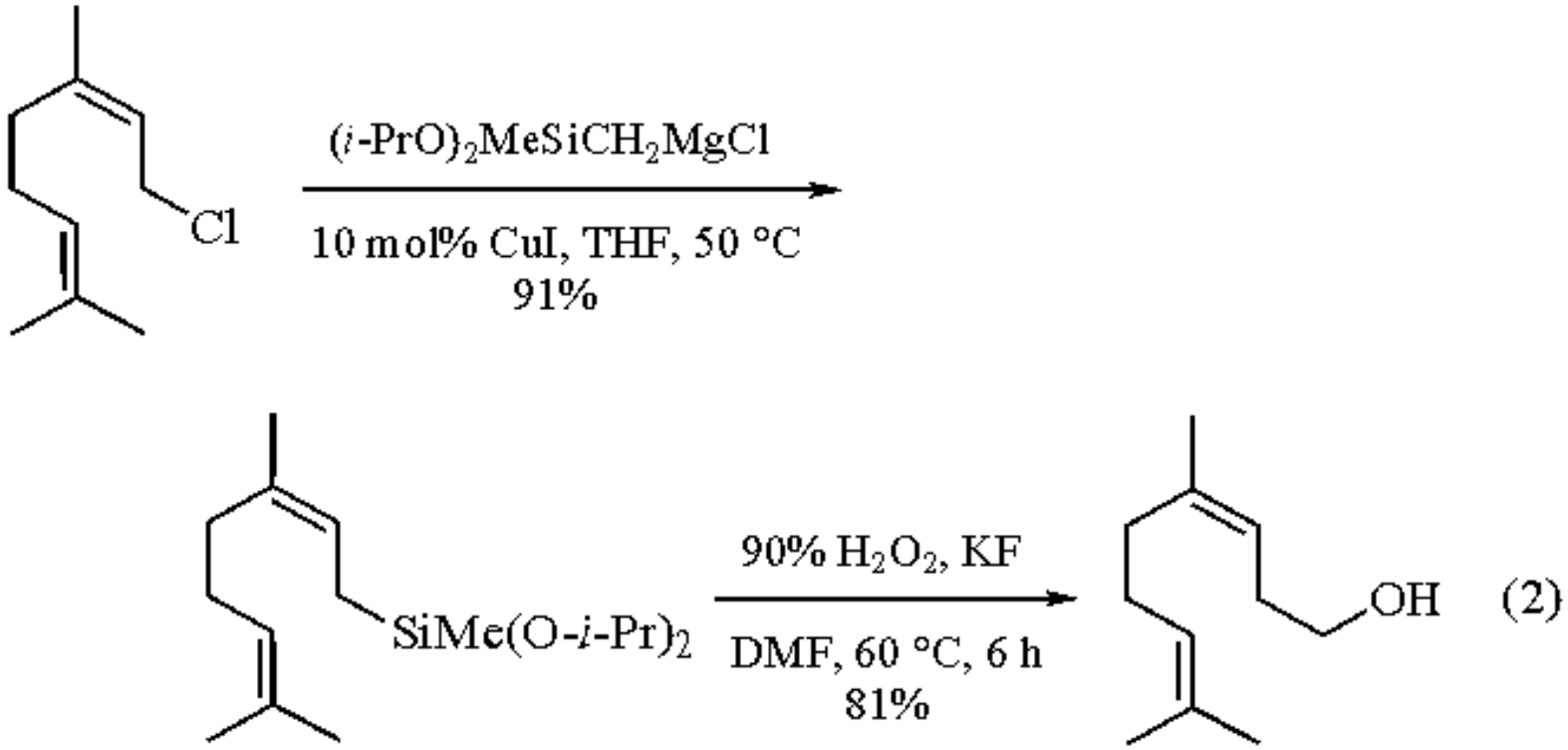

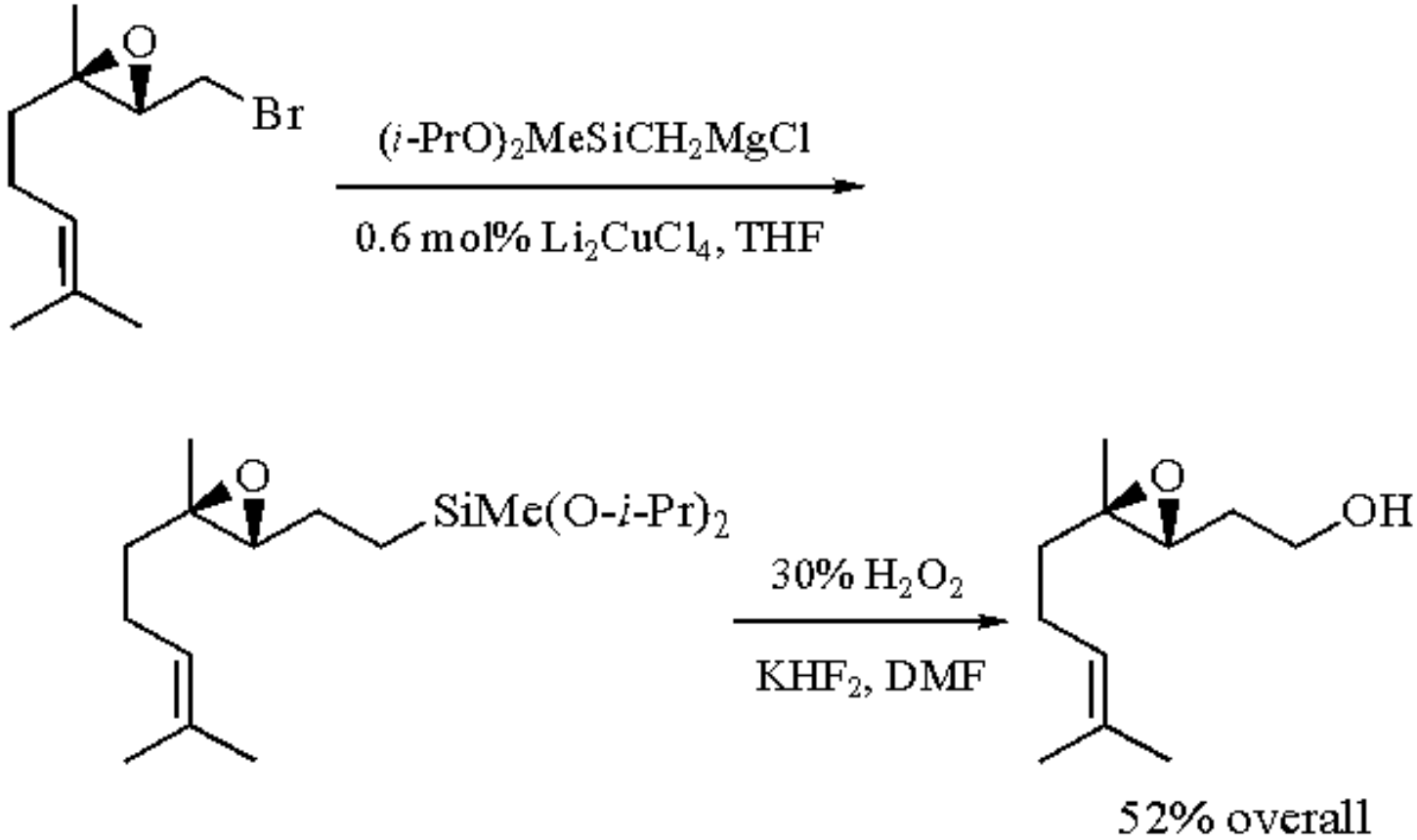
O
Br
(i-PrO)2MeSiCH2MgCl
0.6 mol% Li2CuCl4, THF
O
SiMe(O-i-Pr)2
30% H2O2
KHF2, DMF
O
OH
52% overall

(3)

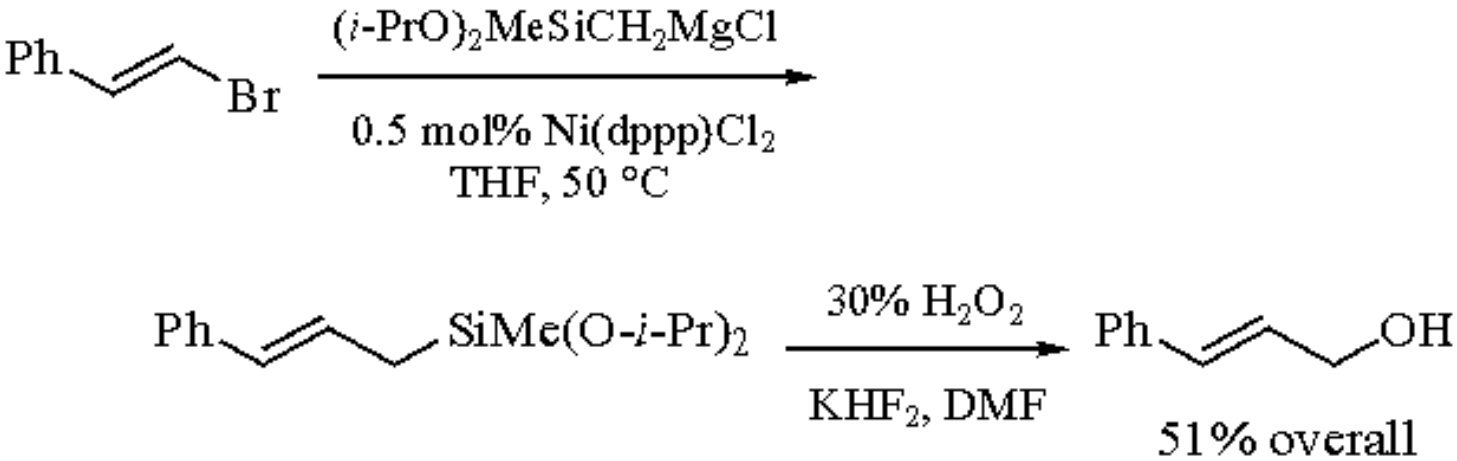
Ph
Br
(i-PrO)2MeSiCH2MgCl
0.5 mol% Ni(dppp)Cl2
THF, 50 °C
Ph
SiMe(O-i-Pr)2
30% H2O2
KHF2, DMF
Ph
OH
51% overall

(4)

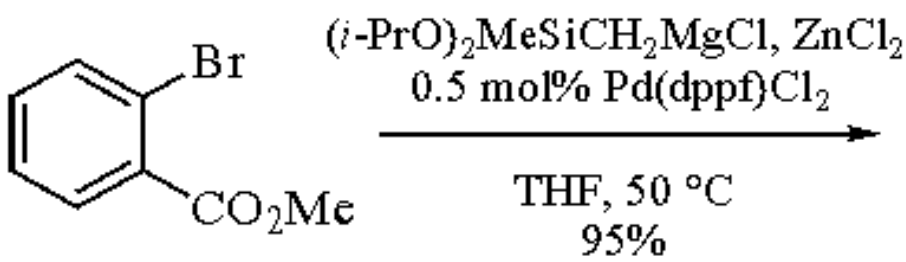

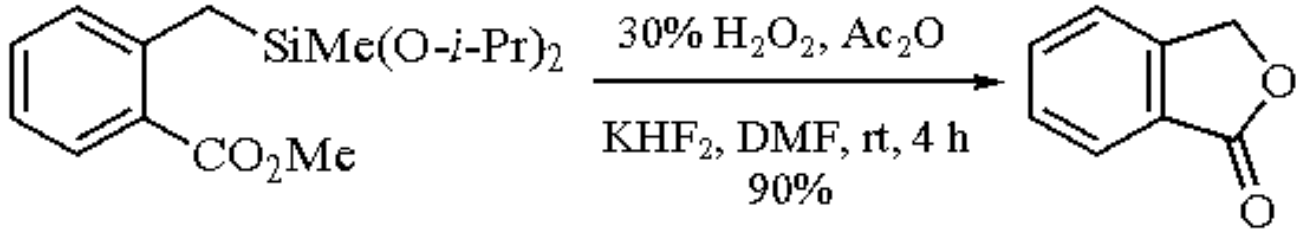

(5)

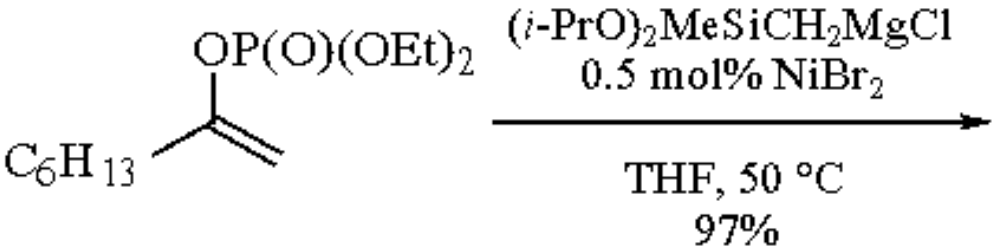

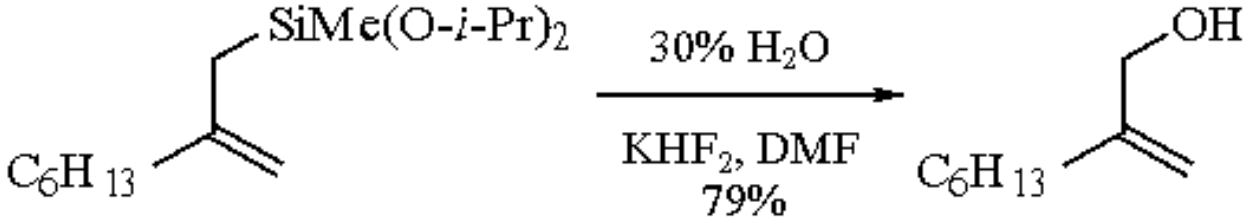

(6)

Related Reagents.

The transformations described here may also be carried out with the monoisopropoxy analog of this reagent (see ***(Chloromethyl)isopropoxydimethylsilane***). See also ***t-Butoxymethyllithium***; ***3-(1-Ethoxyethoxy)propyllithium***; ***Trimethylsilylmethyllithium***; ***Trimethylsilylmethylmagnesium Chloride***; and ***(Triphenylstannylmethyl)lithium***.

---

1. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *OS* **1990**, *69*, 96.
2. Tamao, K.; Ishida, N.; Kumada, M. *JOC* **1983**, *48*, 2120.
3. Tius, M. A.; Fauq, A. *JACS* **1986**, *108*, 6389.

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Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate[1,2]

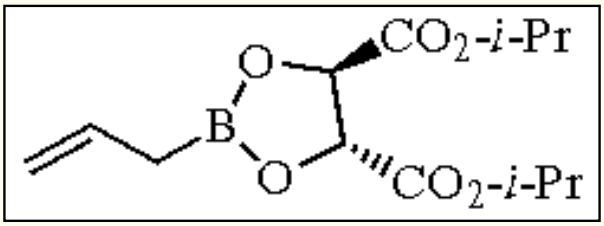

L-(*R*,*R*)

[99417-55-7] · $C_{13}H_{21}BO_6$ · Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate · (MW 284.12) D-(*S*,*S*)

[99493-25-1]

(reagent for the asymmetric allylboration of aldehydes to produce homoallylic alcohols[2])

Alternate Name: tartrate allylboronate.

Physical Data: bp 88-90 °C/0.03 mmHg.

Solubility: sol toluene, THF, ether, CH_2Cl_2.

Analysis of Reagent Purity: ^{11}B NMR (δ 35, $CDCl_3$); capillary GC;[2c] solutions are easily standardized via reaction of an aliquot with cyclohexanecarbaldehyde.[2c]

Preparative Method: prepared by the reaction of ***Triisopropyl Borate*** and ***Allylmagnesium Bromide*** in Et_2O followed by an acidic extractive workup and direct esterification with diisopropyl tartrate (DIPT) (eq 1).[2c]

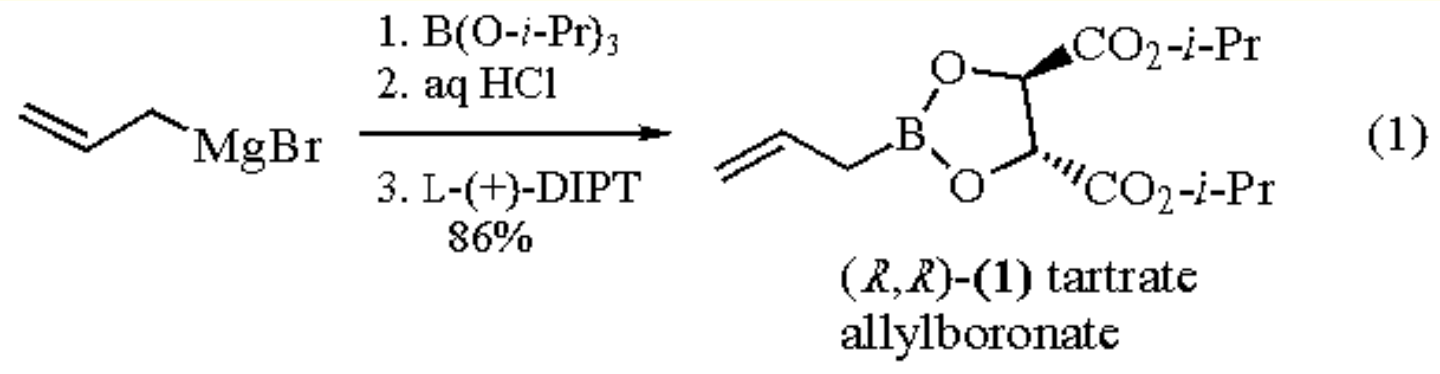

Handling, Storage, and Precautions: allylboronates are typically handled as a solution in toluene (0.5-1.0 M) and transferred by syringe under an inert atmosphere. The reagent, stored neat or as a solution in toluene over 4Å molecular sieves under an argon atmosphere in a refrigerator (-20 °C), is stable for several months. In the presence of water, (**1**) rapidly hydrolyzes to DIPT and the achiral allylboronic acid.

Reactions with Achiral Aldehydes.

The reaction of tartrate allylboronates with achiral aldehydes proceeds with moderate to excellent enantioselectivity (60-92% ee) and high yield (80-90%). Simple aliphatic aldehydes give good enantioselectivities (decanal 86% ee, CyCHO 87% ee, eq 2),[2] while β-alkoxy and conjugated aldehydes give diminished selectivities (60-80% ee) (eq 3).[3] The enantioselectivity is highly temperature and solvent dependent. Best results for reactions with the vast majority of aldehydes are obtained in toluene at -78 °C.[2c] 4Å molecular sieves are included to ensure that the reaction is anhydrous. Other tartrate esters (e.g. diethyl tartrate) may also be used without loss of enantioselectivity.

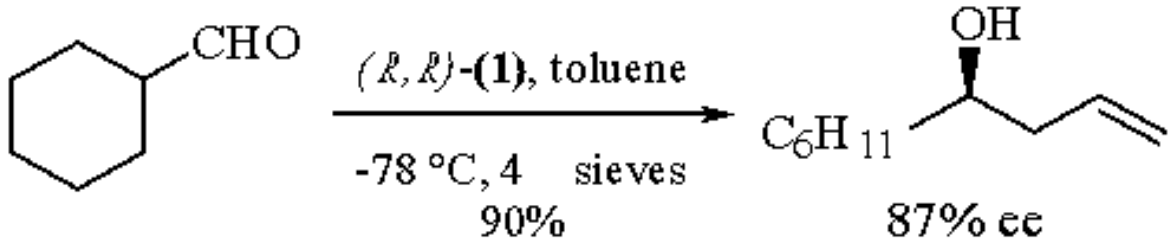

(2)

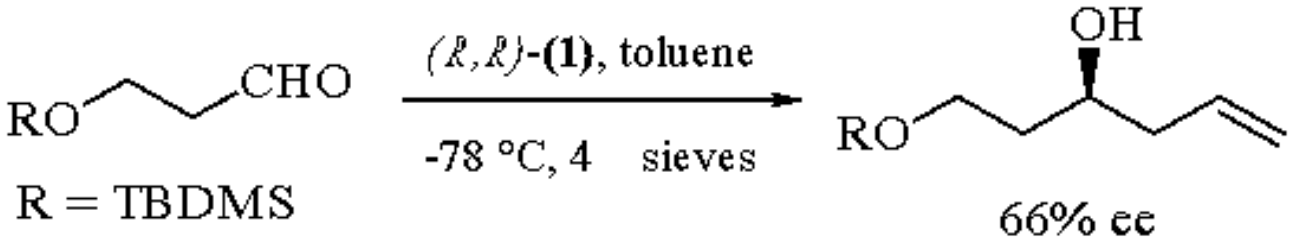

(3)

An allylboronate reagent with a conformationally rigid tartramide auxiliary was designed to improve the enantioselectivity of the reactions with achiral aldehydes.[4] The *N,N´*-dibenzyl-*N,N´*-ethylenetartramide modified allylboronate (**2**) (R = CH_2Ph) is considerably more enantioselective than (**1**) (CyCHO, 97% ee) but has very poor solubility in toluene at -78 °C. Consequently, reactions of (**2**) often require up to 48 h. *N,N´*-Bistrifluoroethyl-*N,N´*-ethylenetartramide modified allylboronate (**3**) (R = CH_2CF_3) is much more soluble at -78 °C than the dibenzyl derivative and therefore reacts with aldehydes much more efficiently (CyCHO, -78 °C, THF, 5 h, 91%, 94% ee).[5]

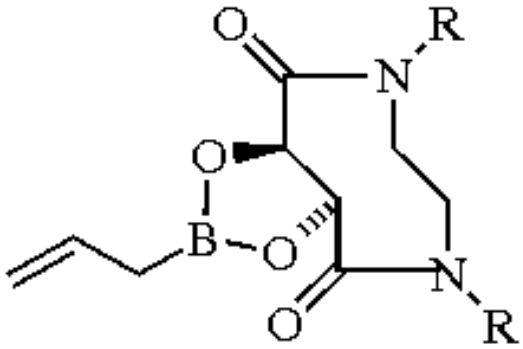

(2) R = CH_2Ph
(3) R = CH_2CF_3

The poor results obtained with various unsaturated aldehydes have been overcome by conversion of these substrates to the corresponding metal carbonyl complexes.[6,7] For example, allylboration of 2-decynal proceeds with 72% ee, while that of its cobalt complex proceeds with excellent enantioselection (eqs 4 and 5).[6]

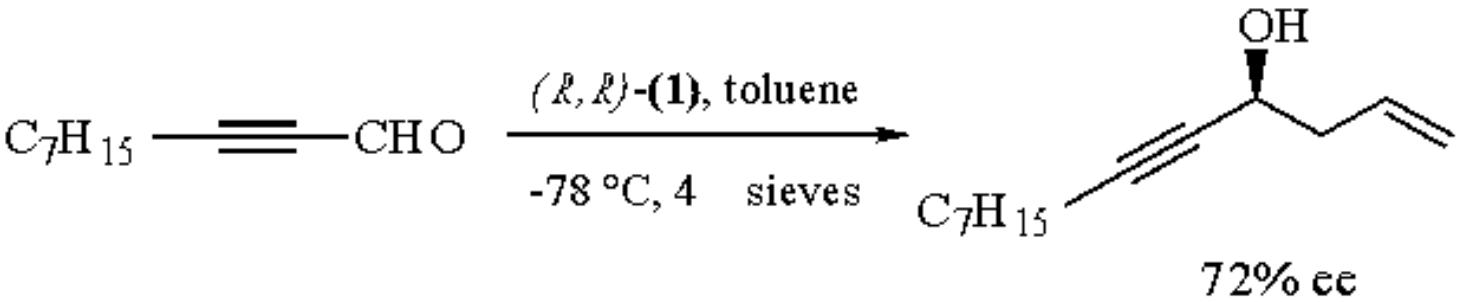

(4)

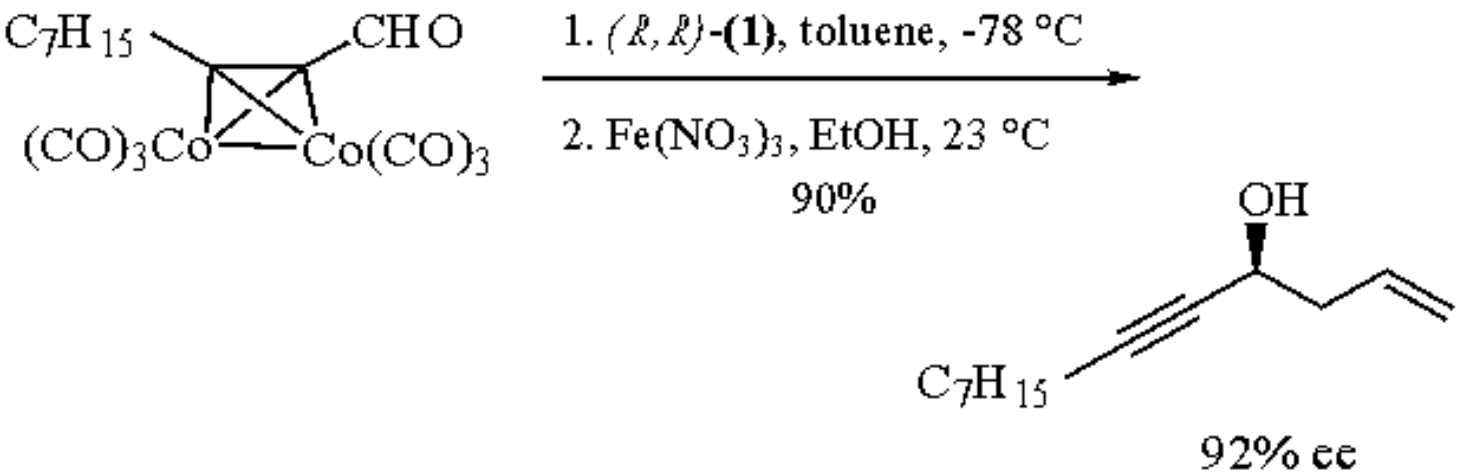

(5)

A second example of the allylboration of a metal carbonyl containing substrate is a highly group- and face-selective allylboration of a *meso* iron-diene dialdehyde complex (eq 6).[7] Efficient kinetic resolutions of racemic diene aldehyde-$Fe(CO)_3$ complexes have also been demonstrated.[7]

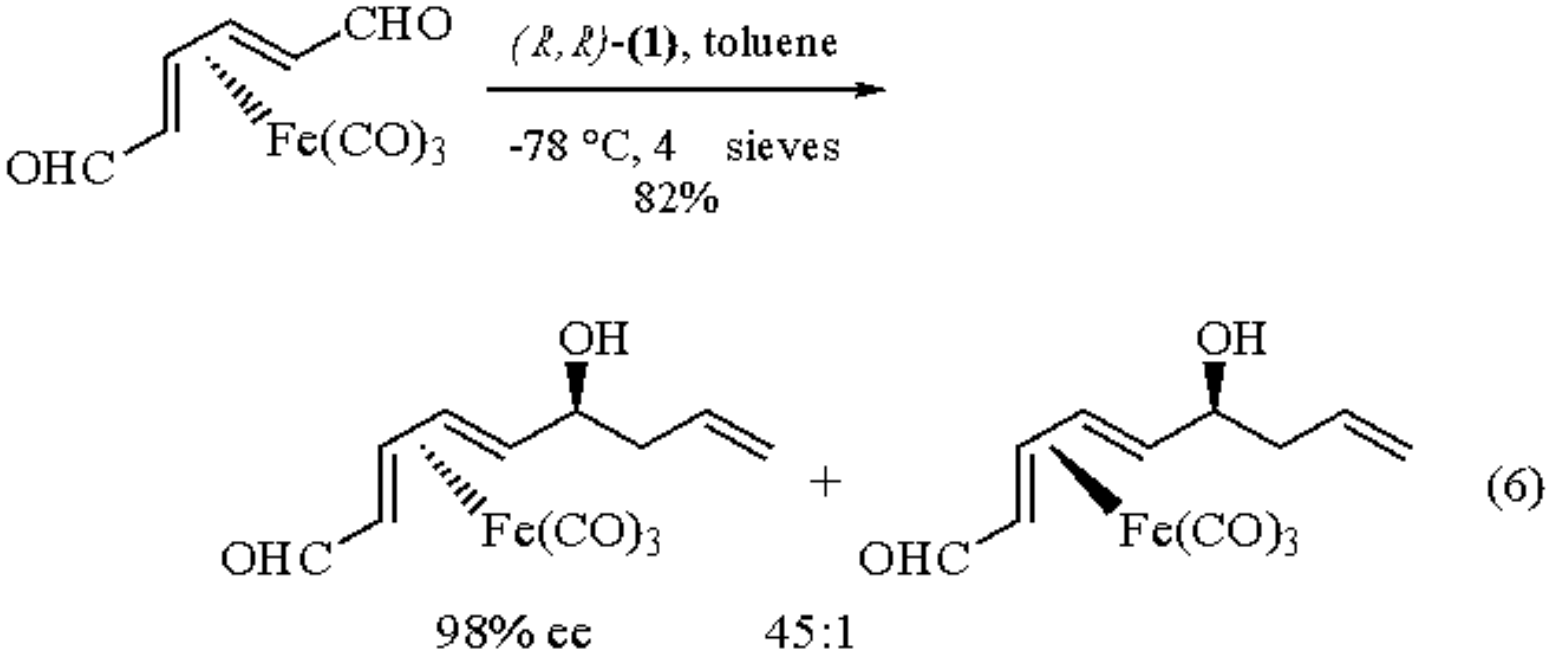

Reactions with Chiral Aldehydes.[1,8]

The tartrate allylboronates have been shown to serve as highly useful chiral acetate enolate equivalents in the reactions with α-chiral aldehydes. The diastereoselectivities obtained are good to excellent, depending on whether the reaction is a matched or mismatched case (eqs 7 and 8).[3] These reagents have been applied to several complex problems in natural product synthesis.[8,9] As shown in eq 8, the diastereoselection is significantly improved by using the rigid tartramide reagent (**3**).[5]

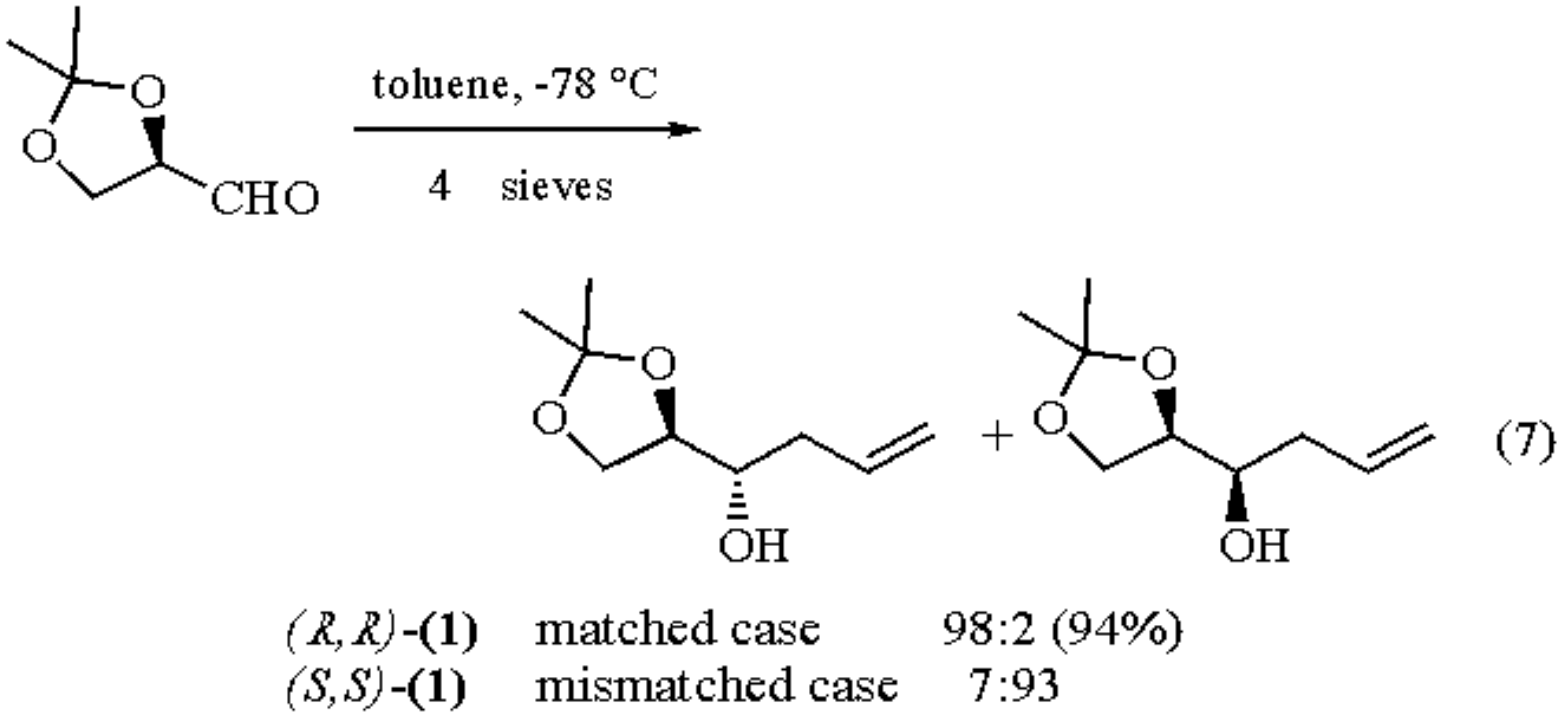

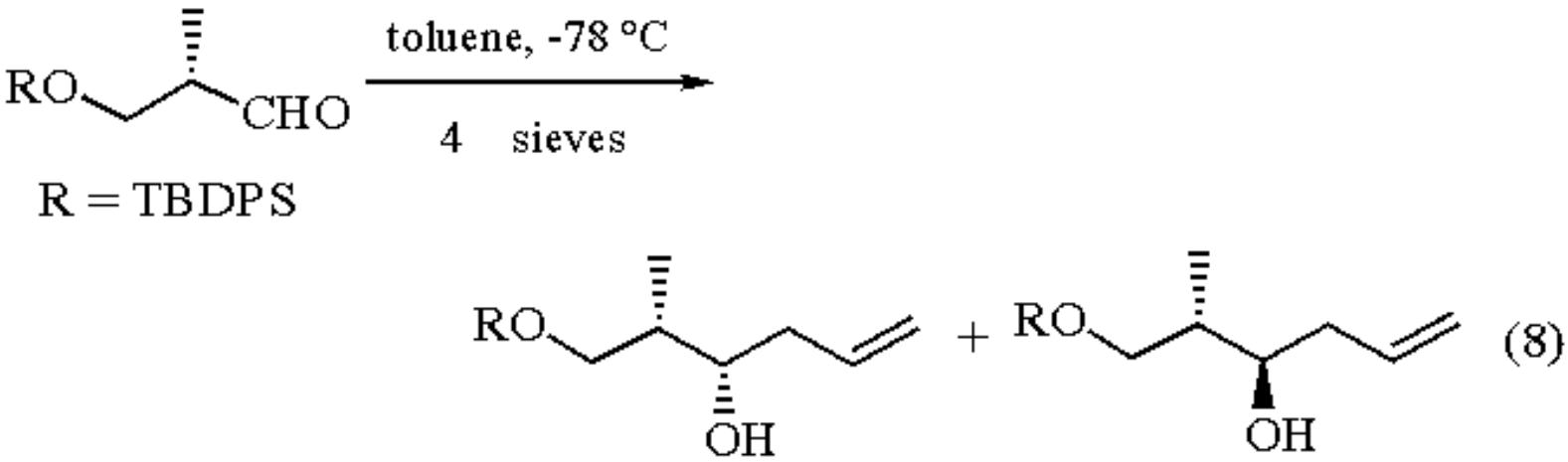

(R, R)-**(1)**	matched case	79:21 (72%)
(S,S)-**(1)**	mismatched case	13:87
(R, R)-**(3)**		8:92 (82%)
(S,S)-**(3)**		3:97

The tartrate-derived allylboronate reagents in the best cases compare favorably with other allylboration reagents in their reactions with both achiral and chiral aldehydes (e.g. ***B-Allyldiisopinocampheylborane***; β-allyl-2-(trimethylsilyl)borolane; 2,5-dimethyl-β-allylborolane; 1,2-diamino-1,2-diphenylethane modified allylboranes). The advantage of the tartrate-modified allylboronate reagent rests with its ease of preparation and its capability of prolonged storage without noticeable deterioration.

Related Allylboronate Reagents.

A stereoselective synthesis of *anti* 1,2-diols has been achieved by using a DIPT-modified (*E*)-γ-[(cyclohexyloxy)dimethylsilyl]allylboronate reagent.[10] This reagent is best applied in double asymmetric reactions with chiral aldehydes such as D-glyceraldehyde acetonide (eq 9).

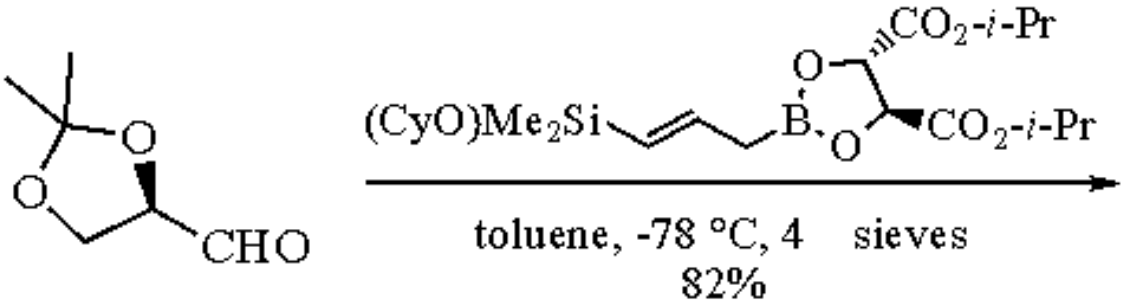

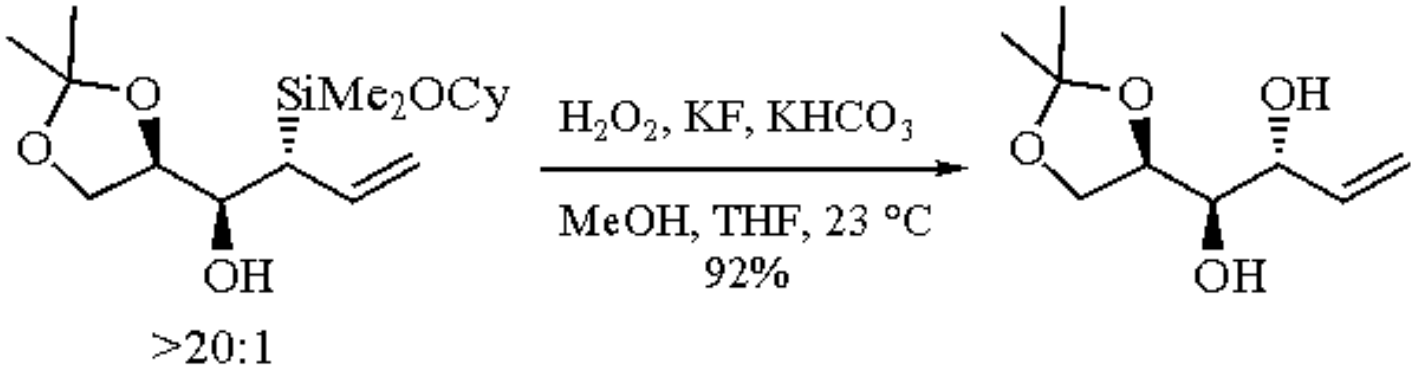

(9)

A chiral allylic alcohol β-carbanion equivalent has also been developed which utilizes a DIPT-modified (*E*)-γ-(dimethylphenylsilyl)allylboronate reagent.[10] This method involves treating the product homoallylic alcohol with ***Dimethyldioxirane*** and subjecting the derived epoxide to an acid-catalyzed Peterson elimination. This sequence has been applied in the synthesis of the trioxadecalin ring system of the mycalamides (eq 10).[11]

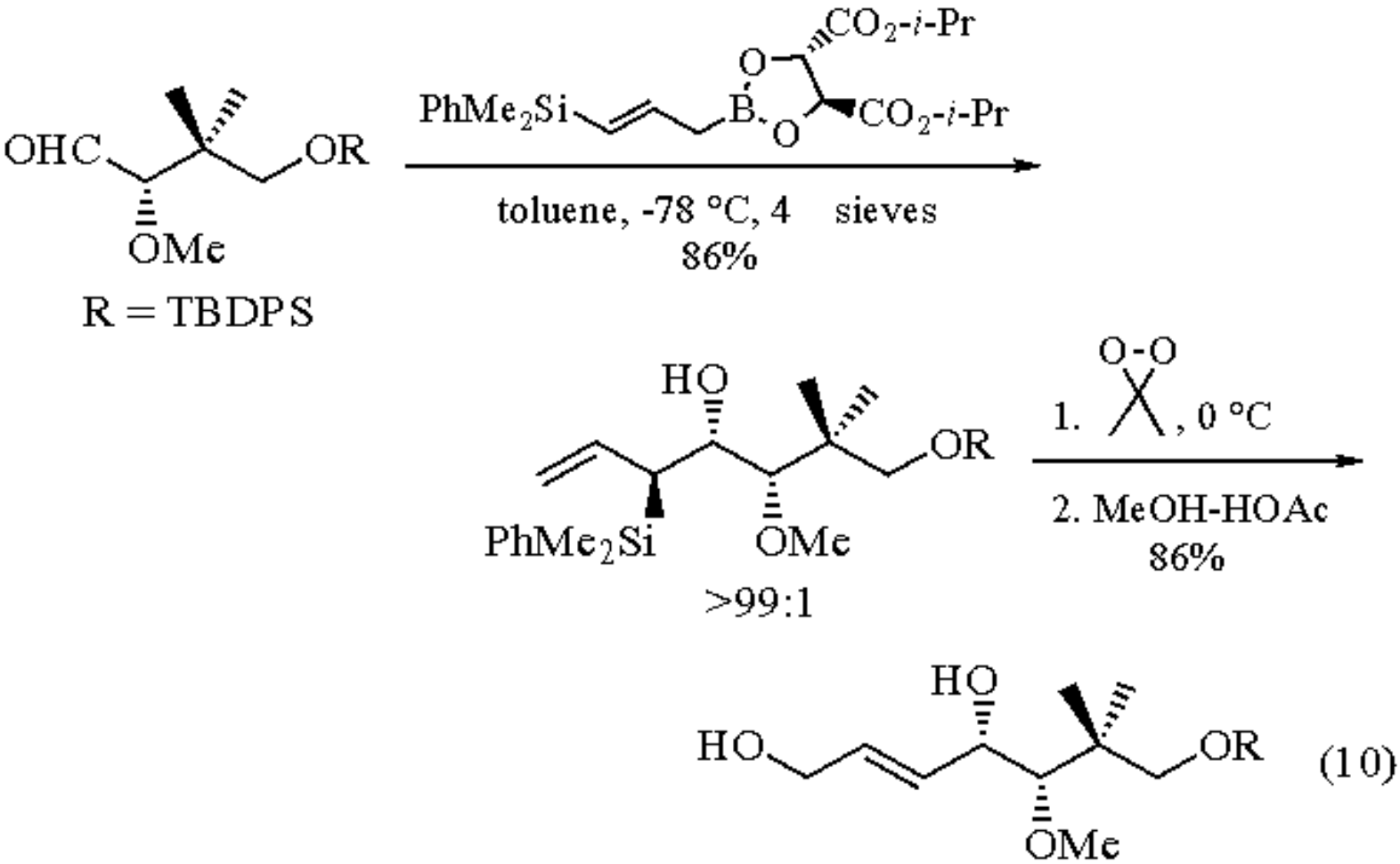

(10)

Highly stereoselective introduction of a β,β-dimethylhomoallylic alcohol subunit was also accomplished in this synthesis by using a DIPT-modified prenylboronate (eq 11).[11]

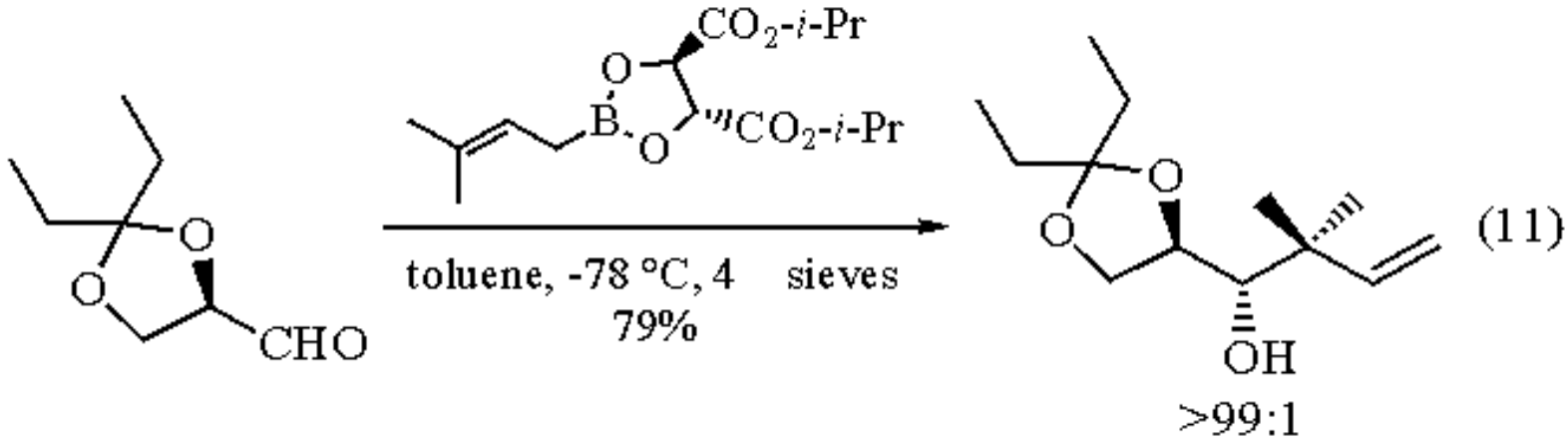

(11)

All the reagents discussed above are readily prepared using techniques described for the preparation of the tartrate-modified crotylboronates, and can be handled in a similar manner.

Related Reagents.

B-Allyldiisopinocampheylborane; ***(E)-1-(N,N-Diisopropylcarbamoyloxy)crotyllithium***.

1. Roush, W. R. *COS* **1991**, *2*, 1.
2. (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *JACS* **1985**, *107*, 8186. (b) Roush, W. R; Banfi, L.; Park, J. C.; Hoong, L. K. *TL* **1989**, *30*, 6457. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *JOC* **1990**, *55*, 4109.
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Diisopropylamine

***i*-Pr$_2$NH**

[108-18-9] · $C_6H_{15}N$ · Diisopropylamine · (MW 101.19)

(strong hindered base capable of catalyzing asymmetric protonation in photodeconjugation of α,β-unsaturated esters;[1] deracemizes amino acids;[2] forms quinquevalent cyclic phosphoranes with triflic anhydride;[3] useful reagent in isocyanate synthesis;[4] promotes thermal rearrangements of cyclopropylimines to pyrroles;[5] in combination with HF, stereoselectively opens epoxides to *trans*-fluorohydrins[6])

Physical Data: mp -61 °C; bp 83-84 °C; *d* 0.7178 g cm^{-3}; *n*20D 1.3915; p$K_a^{H_2O}$ 11.13; pK_a^{THF} 35.7.

Solubility: very sparingly sol H_2O; sol most organic solvents.

Form Supplied in: neat colorless liquid; widely available.

Purification: can be dried over and distilled from fresh potassium hydroxide immediately before use.

Handling, Storage, and Precautions: highly flammable, corrosive liquid with a strong ammonia-like smell; irritating to eyes, respiratory system, and skin; use in a fume hood.

Diastereo- and Enantioselective Protonations.

Photodeconjugation of acyclic α,β-unsaturated esters, containing at least one hydrogen in the γ-position, is a useful synthetic method for preparation of their thermodynamically less stable β,γ-unsaturated isomers in high yield.[7] It was proposed[7b,7e] that this process proceeded via photoenolization involving a pseudocyclic transition state, since cyclic esters were found to be completely inert to photochemical deconjugation.[7b,7e,8] If the starting α,β-unsaturated ester is α-substituted, and either a chiral amino alcohol is added to the reaction mixture,[9] or the ester group contains a chiral alcohol moiety,[1] then photodeconjugation leads to enantio- or diastereoselective protonation, respectively.

In the latter case, diastereoselectivity of the protonation of the new asymmetric center is enhanced in the presence of 0.1 equiv of diisopropylamine in hexane at -40 to -70 °C (eq 1).[1] Methanol, diethylamine, dibutylamine, *N*-ethylbenzylamine, (+)- and (-)-ephedrine, (+)-*O*-methylephedrine, and *N*-(2-hydroxy- and 2-methoxyethyl)benzylamines proved to be less effective additives, while dicyclohexylamine gave similar diastereoisomeric excess (de).

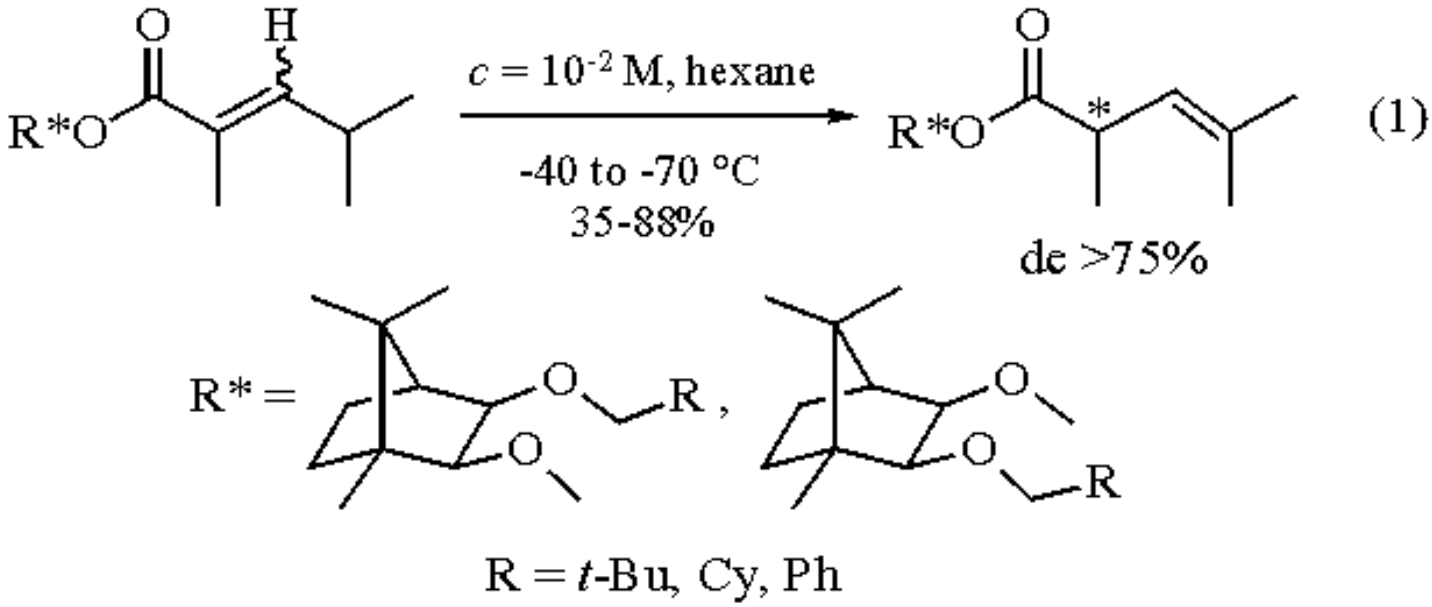

Deracemization of *N*-benzylidene methyl esters of racemic amino acids by a lithium amide, followed by asymmetric protonation by a chiral acid, yields optically active amino acids.[10] The enantiomeric excess (ee) and yield are increased by an amine exchange involving diisopropylamine after the metalation step by ***Lithium Hexamethyldisilazide*** (LHMDS) and prior to the asymmetric protonation by means of ***(2R,3R)-Dipivaloyltartaric Acid*** (DPTA) (eq 2).[2] By this method, the asymmetric induction exceeds or equals that obtained in the classical procedure using ***Lithium Diisopropylamide*** as the base, and the yield is somewhat higher. Use of other amines (e.g. ethylamine, ***Piperidine***, chiral *N*-ethyl-α-methylbenzylamine), but not triethylamine, may enhance the asymmetric induction more than does diisopropylamine.

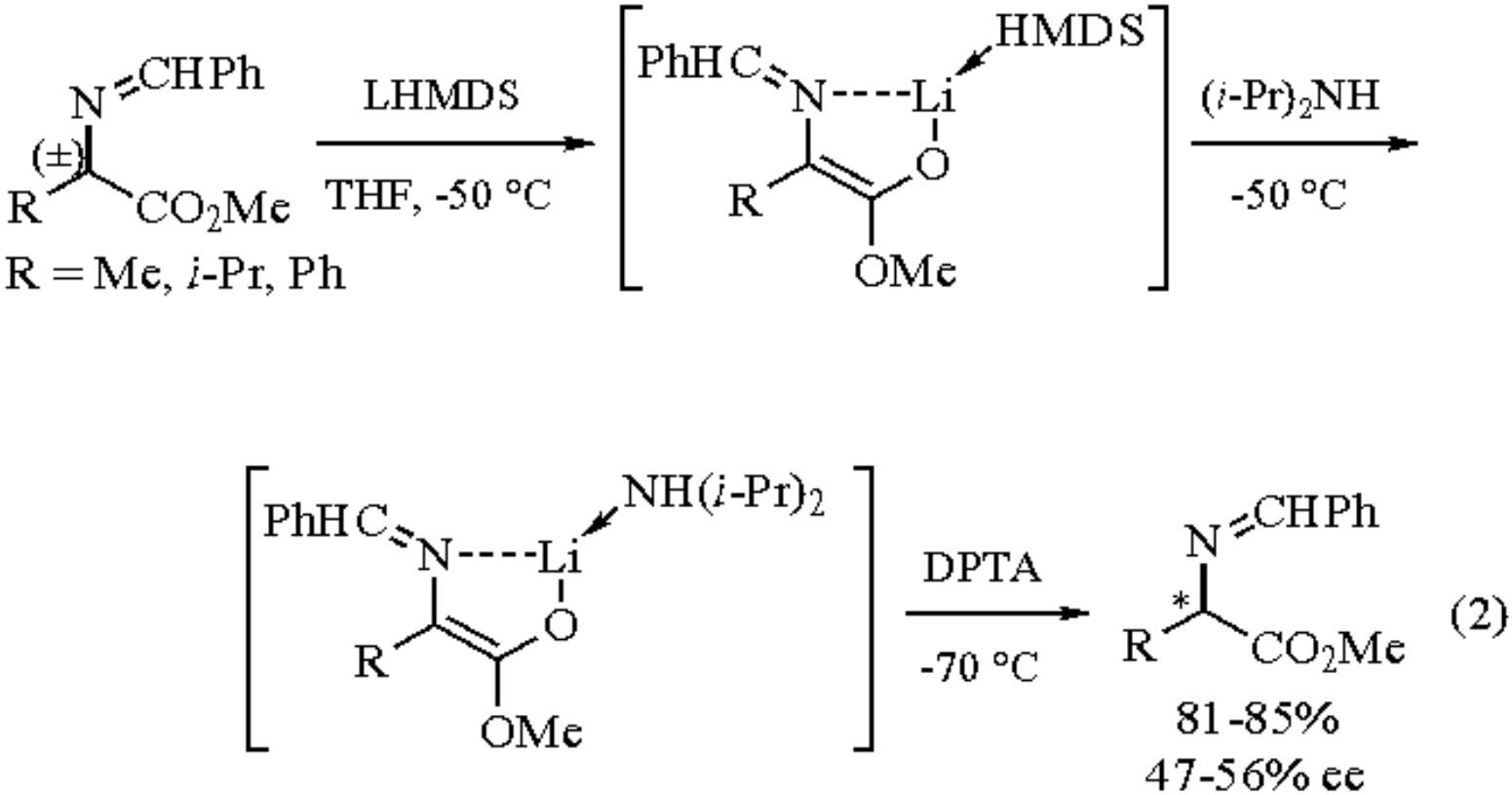

Synthesis of Cyclic Phosphoranes.

Quinquevalent cyclic phosphoranes can be prepared[3] in good yields from readily available phosphine oxides by treatment with ***Trifluoromethanesulfonic Anhydride*** in dichloromethane at 0 °C, followed by an ether solution of diisopropylamine (2 equiv) and 1,2-diols or catechols at -78 °C (eq 3). Earlier, five-coordinate phosphoranes were prepared from tetravalent phosphorus compounds. Diisopropylammonium triflate can be readily precipitated by the addition of ether to the reaction mixture. This method could not be extended to cyclic phosphonates and phosphinates.

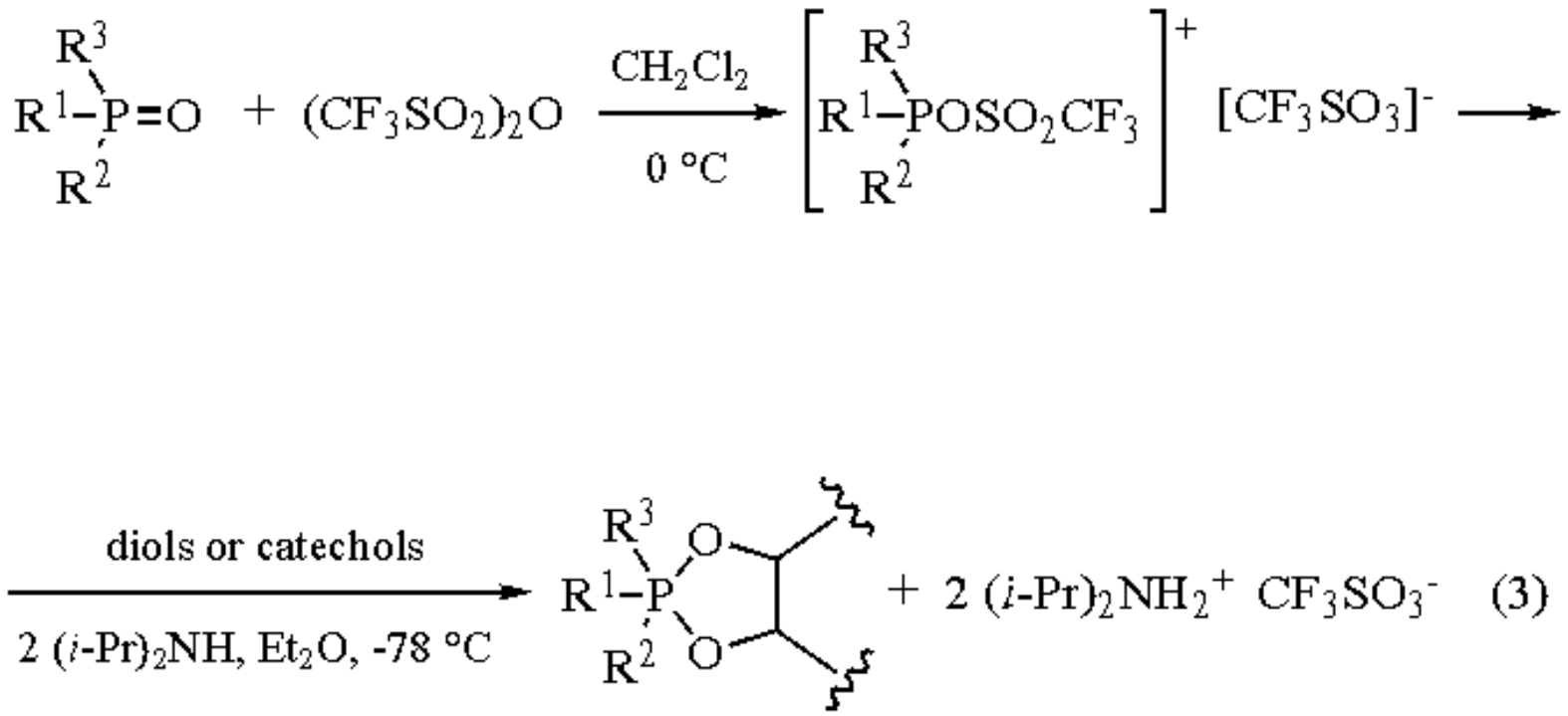

Isocyanate Synthesis.

General methods[11] for the preparation of isocyanates include the dehydration of formamides by ***Phosgene***,[12] diphosgene,[13] and ***Phosphorus Oxychloride***[14] in combination usually with tertiary amines. The replacement of ***Triethylamine*** by diisopropylamine enhances the average yields of the phosphoryl chloride method to the levels of the phosgene or diphosgene procedures.[4] In addition, the isocyanates are often obtained in higher purity. Less bulky secondary amines, e.g. diethylamine, do not give any trace of the isocyanate. Phosphoryl chloride (1.1 equiv) is added dropwise to a dichloromethane solution of formamide and diisopropylamine (2.7 equiv) at 0 °C. In the case of simple alkylformamides, e.g. methyl *N*-formylaminoacetate, formamide is added to a mixture of phosphoryl chloride and diisopropylamine.

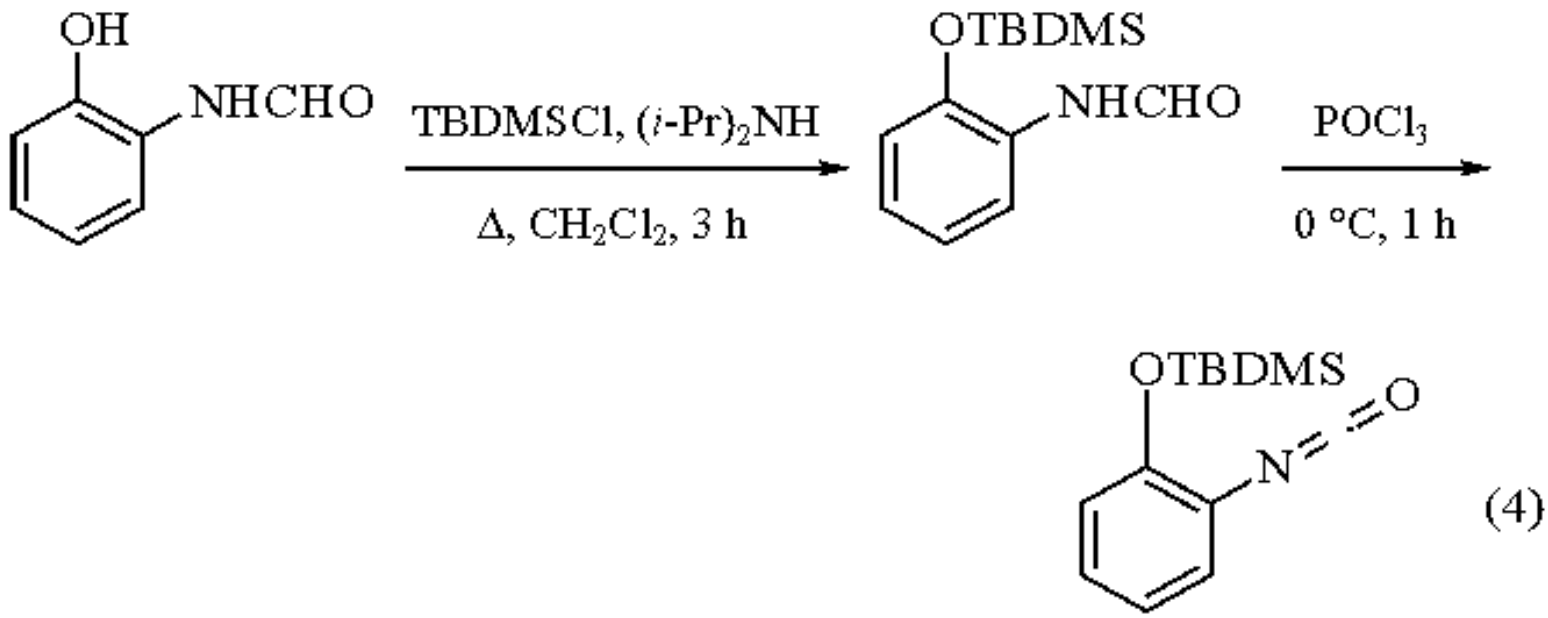

This method is considerably milder than the diphosgene method. It gives ferrocenylalkyl isocyanates in fair yields, whereas diphosgene/triethylamine fails to give isocyanates or leads to a mixture of isocyanate and cyanide. Chiral isocyanates derived from amino acids yield racemic isocyanates. With diisopropylamine, a combination of *O*-silylation and dehydration affords a one-pot preparation of the 2-siloxyphenyl isocyanate (eq 4).

Synthesis of *N*-Alkyl-2-chloropyrroles.

The thermolysis of *N*-*t*-alkyl-2,2-dichlorocyclopropylimines in *N*-methylpyrrolidine (NMP) gives 3-chloropyrroles in high yields via fission of the 1,3-bond (eq 5).[4] When Lewis bases in ethyl phenyl ether are added, thermal ring opening via 1,2-bond cleavage is favored, yielding 2-chloro isomers (eq 5). Among the bases studied, diisopropylamine guided this reaction path most effectively;[4] CaO and K_2CO_3 also facilitated this rearrangement, but to a lesser extent than diisopropylamine. In contrast to other cyclopropylimines, the ring transformation was not effected by NH_4Cl or HBr additives.[4,15]

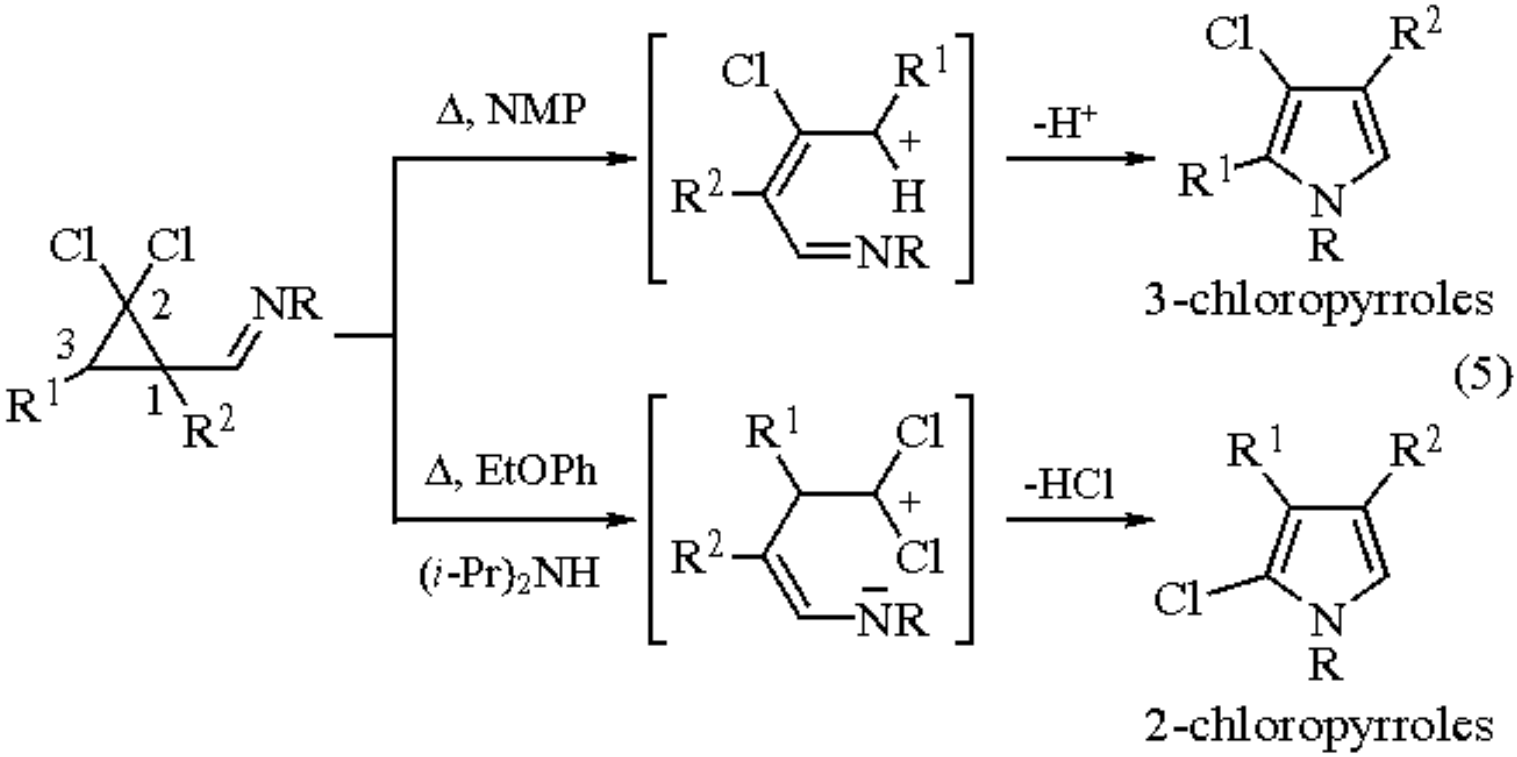

Synthesis of Fluorohydrins.

The addition of ***Hydrogen Fluoride*** to an oxirane is a synthetic method for the preparation of fluorohydrins.[16] Diisopropylamine trihydrofluoride (Jullien's reagent[6]), prepared by lyophilization of a solution of a 1:3 mol ratio of diisopropylamine and 48% aqueous HF solution in a Nalgene polyethylene bottle,[17] serves as an attenuated source of HF. It stereospecifically converts epoxides into *trans*-fluorohydrins (eq 6).

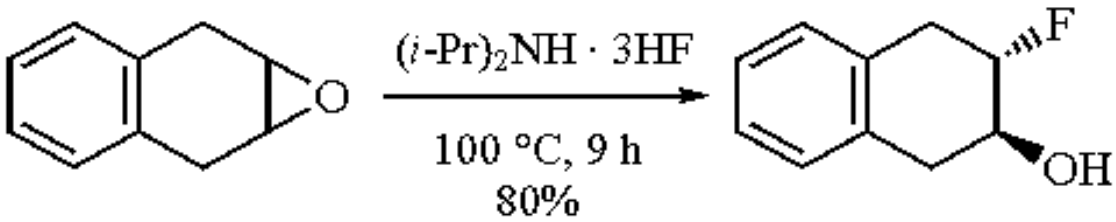

(6)

During the regioselective opening of epoxides, diisopropylamine trihydrofluoride initially donates a fluoride ion, and then HF donates a proton. Jullien's reagent can be stored in a desiccator at rt for periods longer than 6 months without noticeable decomposition,[17] and can be used at 78-150 °C (typically at 110 °C) in an excess of 1.5-5 equiv for up to 30 h.[6,17,18,19] Olah's reagent, ***Pyridinium Poly(hydrogen fluoride)***,[20] employed below -5 °C for 15 min, gives somewhat lower yields of fluorohydrins with decreased regioselectivity (eq 7).

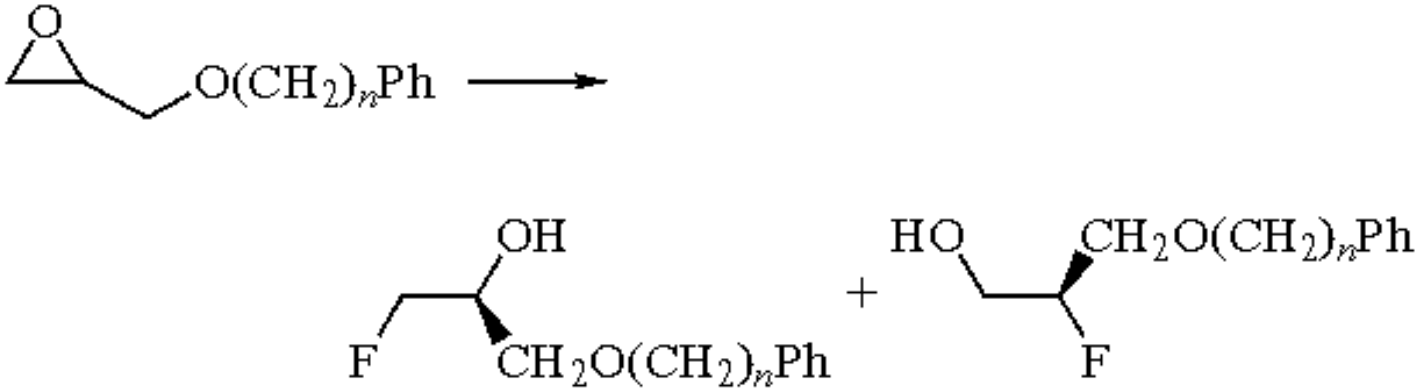

(7)

Jullien's reagent	$n = 1$, 110 °C	15:1	75%
	$n = 2$, 110 °C	6:1	81%
Olah's reagent	$n = 1$, -5 °C	1.1:1	60%
	$n = 2$, -5 °C	1:4	68%

The regioselective ring opening of epoxides by Jullien's reagent is governed primarily by steric factors.[17] *trans*-Epoxides afford a mixture of *erythro* isomers, while *cis*-epoxides yield *threo* isomers (eqs 8 and 9).[6a]

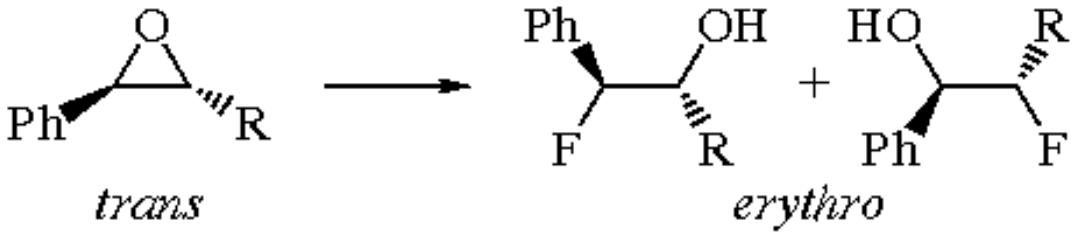

(8)

R = Me	74%	9%
R = Ph	62%	

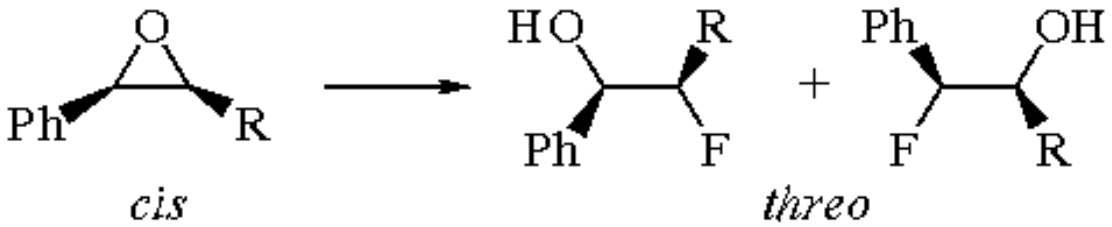

(9)

R = Me	76%	9%
R = Ph	75%	

Other di- and trialkylamine trihydrofluorides[6a,6b] and diisopropylamine dihydrofluoride[6a] afford lower yields; use of HF in polar basic solvents, KF_2, or boron trifluoride etherate with or without HF frequently results in polymerization or rearrangement of the products.[16]

---

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(*E*)-1-(*N,N*-Diisopropylcarbamoyloxy)crotyllithium[1a,1b]

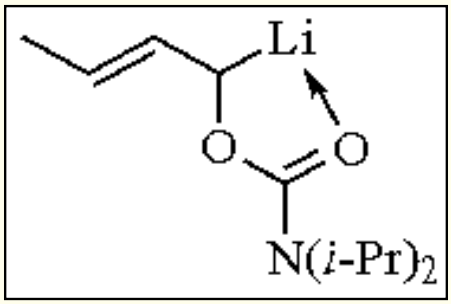

[81725-22-6] · $C_{11}H_{20}LiNO_2$ · (*E*)-1-(*N*,*N*-Diisopropylcarbamoyloxy)crotyllithium · (MW 205.23)

(homoenolate reagent for the stereoselective introduction of the butyric acid β-enolate synthon onto aldehydes and ketones;[1,2a,2b] prototype of several analogous reagents)

Preparative Method: prepared in situ from (*E*)-2-butenyl *N*,*N*-diisopropylcarbamate[3a,3b] by deprotonation at -78 °C with ***n-Butyllithium*** in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) in ether or hexane (eq 1).

Handling, Storage, and Precautions: must be prepared and handled under inert gas (Ar or N_2) to exclude oxygen and moisture;[3a] solutions in ether decompose slowly above -60 °C.

Diastereoselective Homoaldol Reaction.[1]

The lithium-TMEDA complex adds γ-selectively to aldehydes and ketones[3] to give *anti*-(*Z*)-4-hydroxy-1-(*N*,*N*-diisopropylcarbamoyloxy)-1-alkenes as a consequence of the intervention of a five-membered chelate (eq 1). The stereoselectivity is enhanced to >97% ds by in situ metal exchange with ***Titanium Tetraisopropoxide***.[4-6] The pure (*E*)-carbamate (>97%)[3] must be used for achieving high stereoselectivities.[5b,6] 2-Enals react with clean 1,2-regioselectivity.[4,7]

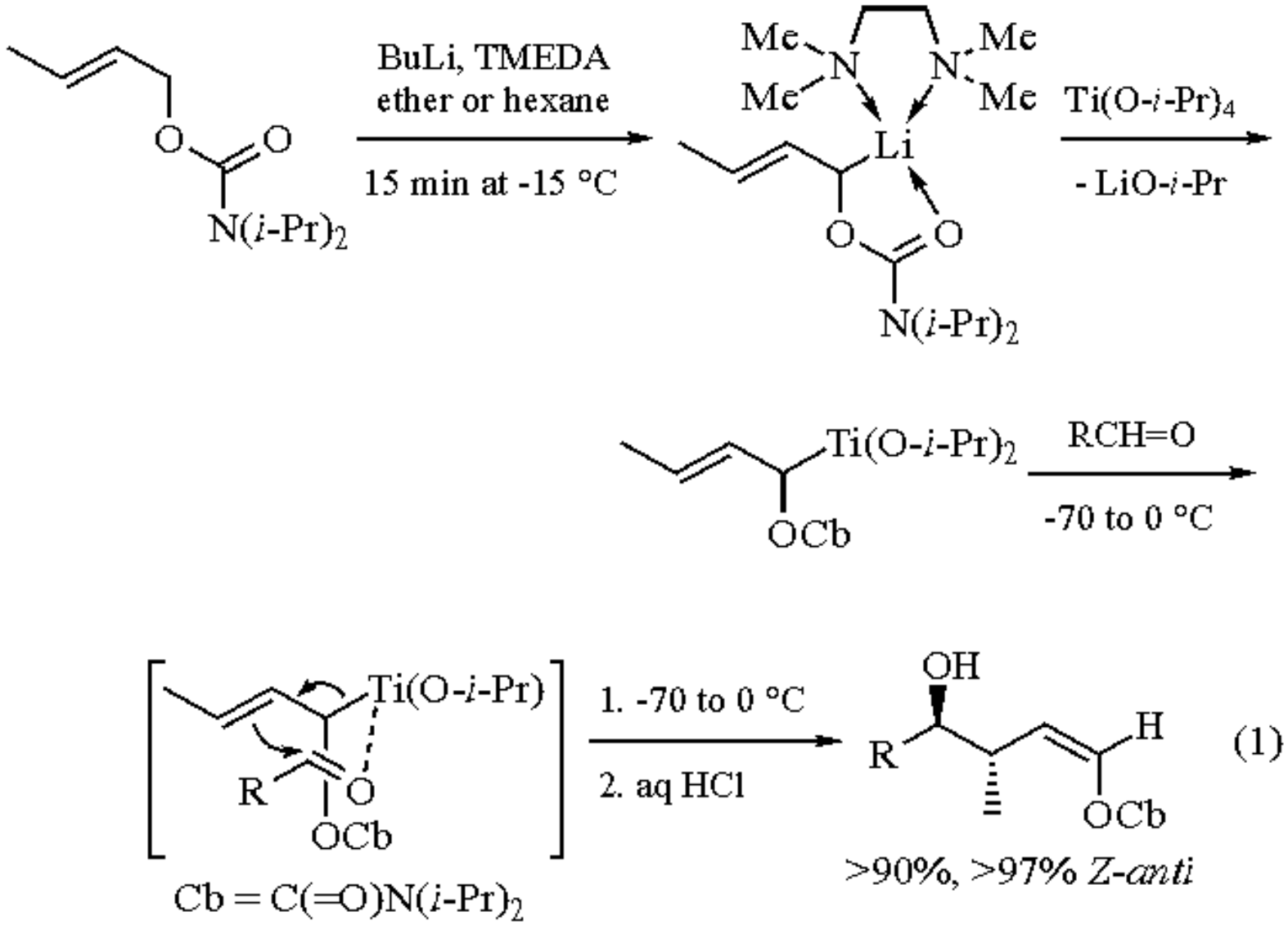

Enantiopure aldehydes furnish 1:1 diastereomeric mixtures due to the reagent-controlled chirality transfer[5b,5c] and the configurational stability[8] of the racemic titanium intermediate (eq 2). The enantiomerically enriched reagent is also available (see ***(-)-Sparteine***).[9] The *O*-(4-hydroxy-1-alkenyl) carbamates were converted by hydroxy-directed epoxidation via stable *O*-(1,2-epoxy-4-hydroxyalkyl) carbamates[5b,10] to methyl 3-deoxy-3-*C*-methylhexofuranosides (eqs 3 and 4)[5b,5c] and to 2-heterosubstituted γ-lactones.[10b]

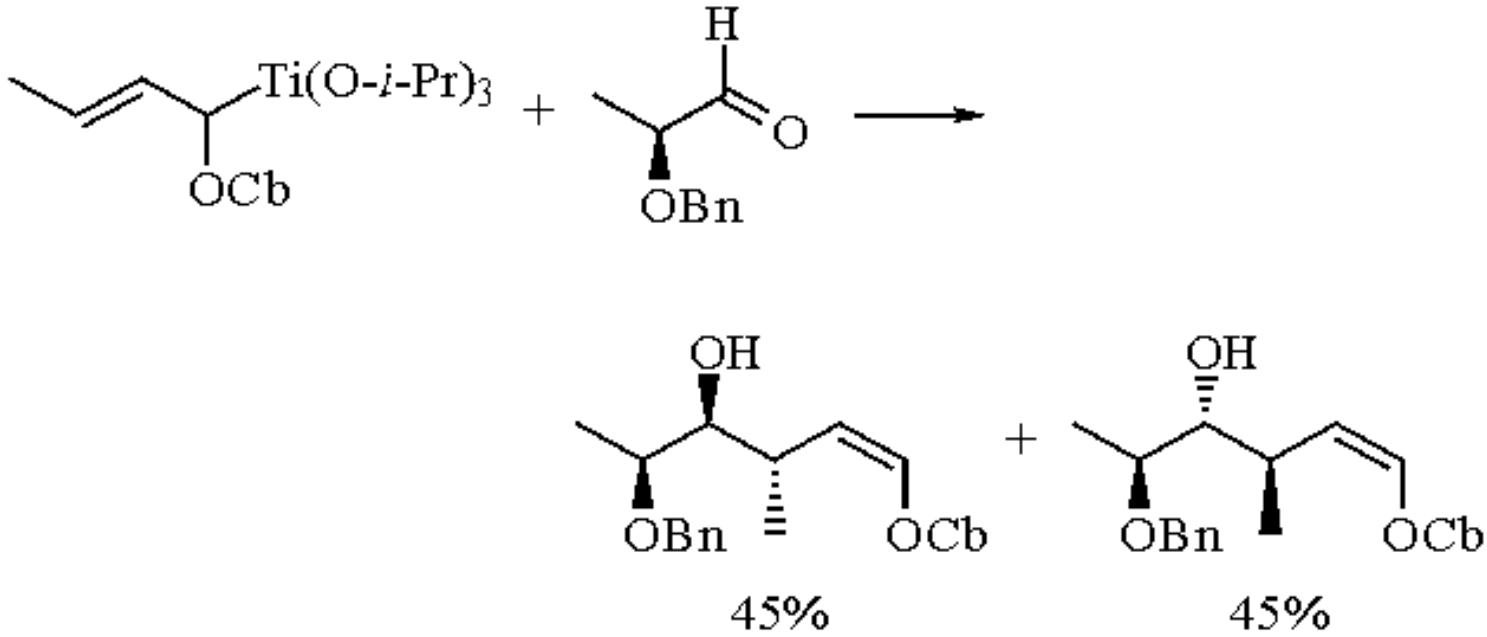

$OCb = OC(=O)N(i\text{-}Pr)_2$

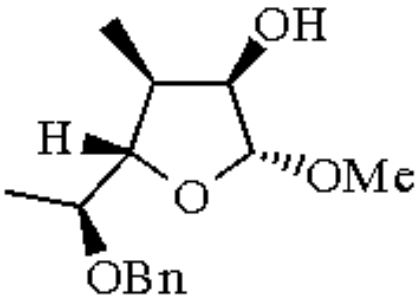

(3)

(E)-1-(N,N-Diisopropylcarbamoyloxy)crotyllithium

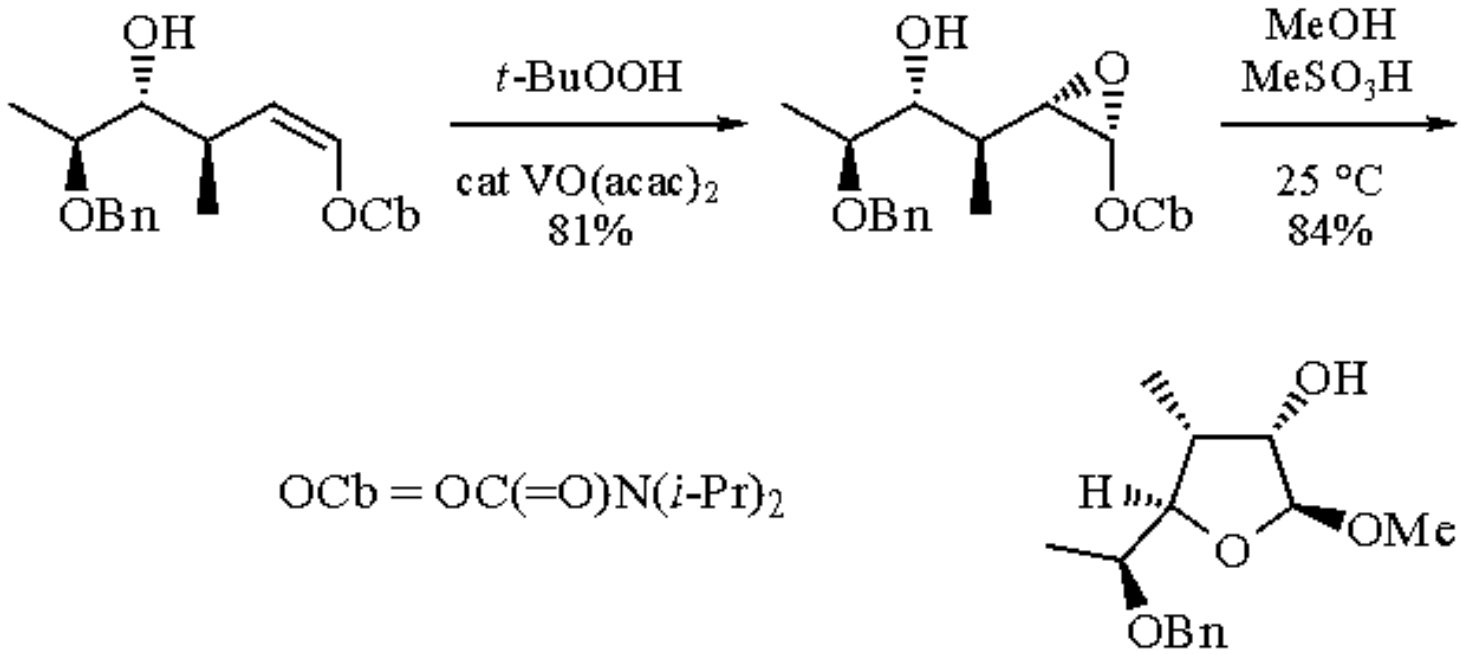

(4)

The mercury(II) salt-catalyzed methanolysis furnishes 2-methoxytetrahydrofurans, which can be oxidized to *trans*-3,4-disubstituted γ-lactones (eq 5).[3a,5a] 1,4-Alkanediols are accessible by a hydroboration sequence.[11]

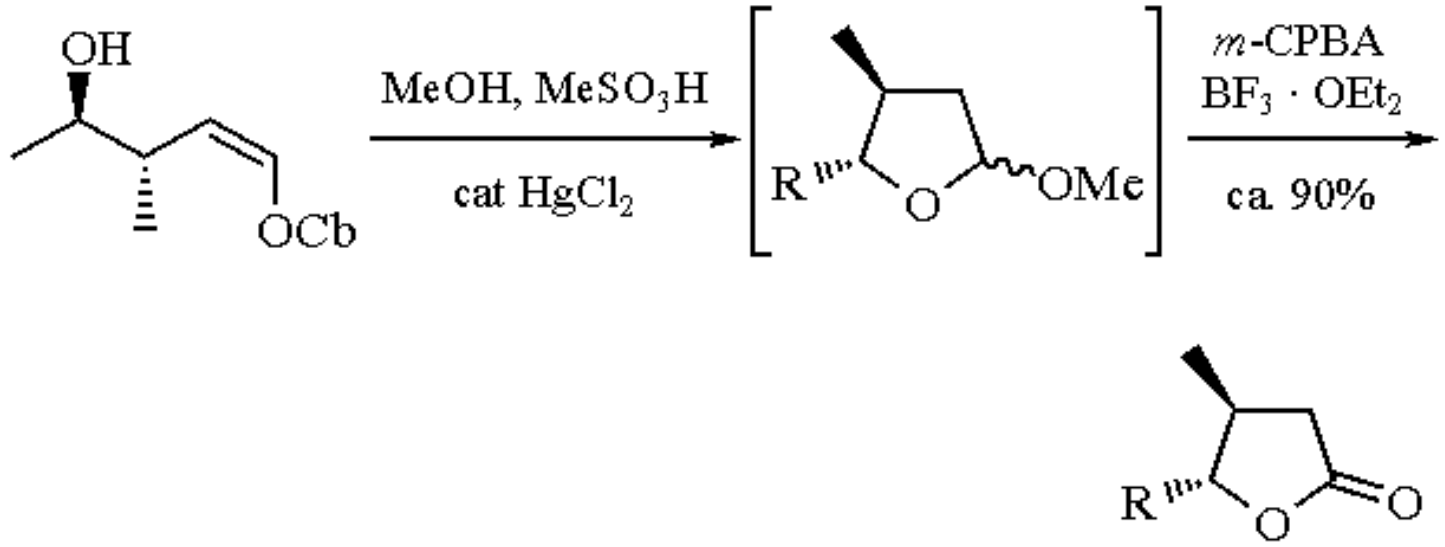

(5)

The enol carbamates can be used for further C-C coupling reactions. The Lewis acid-catalyzed condensation with carbonyl compounds leads to stereochemically homogeneous tetrahydrofuran-3-carbaldehydes.[12] Both the acidic vinylic proton[6,13] and the carbamate group in enol carbamates undergo stereospecific substitution reactions.[6,13a] The racemic reagent has also been applied in the total synthesis of rifamycin S intermediates[14] and of doubly *C*-branched sugar analogs.[7]

Alkylation does not offer useful levels of regioselectivity.[3a] The reaction with *p*-toluenesulfonyl fluoride yields (*E*)-1-(*N*,*N*-diisopropylcarbamoyloxy)-1-(4-methylphenylsulfonyl)-2-butene,[15] which is a useful reagent for nucleophilic crotonoylation.[15b] (*Z*)-1-(*N*,*N*-Diisopropylcarbamoyloxy)butenyllithium reacts, after metal exchange by diisobutylaluminum methanesulfonate, with modest *syn*-(*E*) diastereoselectivity.[16]

Related Reagents.

Up to three alkyl groups, aryl groups, and several types of hetero substitutents in the allyl moiety are permitted in 1-lithio-2-alkenyl carbamates.[1a,3a] The addition of 1-(1-cyclopentenyl)-1-(*N*,*N*-diisopropylcarbamoyloxy)methyllithium[11] or of 3-(dimethylphenylsilyl)-1-(*N*,*N*-diisopropylcarbamoyloxy)-2-propenyllithium[17] to (*S*)-2-aminoalkanals was utilized to prepare several dipeptide isosteres. A higher analog was used in the total synthesis of (±)-anisomelic acid.[18] The homoaldol adducts from 1-(*N*,*N*-diisopropylcarbamoyloxy)-3-(trimethylsilyl)-2-propenyllithium offer a flexible and highly diastereoselective access to all four possible geometric isomers of 1,3-alkadienyl carbamates.[19] Enantiomerically enriched 1,3-disubstituted 1-lithio-2-alkenyl carbamates, such as (1*S*,2*E*)- or (1*R*,2*Z*)-1-(*N*,*N*-diisopropylcarbamoyloxy)-1-methyl-2-butenyllithium[20] are configurationally stable below -70 °C in ether or hexane and are prepared by deprotonation of the nonracemic carbamate esters[21] (see also ***(-)-Sparteine***). Trapping these by trialkylstannyl chlorides proceeds with $S_{E'}$ *anti* stereochemistry[22] to provide enantiomerically enriched (*Z*)-1-methyl-3-trialkylstannyl-1-butenyl *N*,*N*-diisopropylcarbamates, which are valuable chiral homoenolate reagents.[23]

Alternative reagents for some of the transformations described above include (*E*)-1-methoxycrotylboronates[24] and (1-alkoxycrotyl)tributylstannanes.[25]

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Diisopropyl 2-Crotyl-1,3,2-dioxaborolane-4,5-dicarboxylate[1,2]

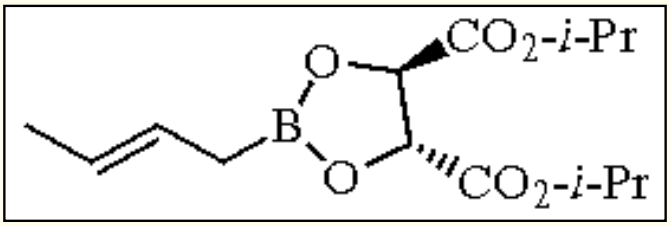

(**1**) L-(*R*,*R*)-tartrate (*E*)-crotyl

[99745-86-5] · $C_{14}H_{23}BO_6$ · Diisopropyl 2-Crotyl-1,3,2-dioxaborolane-4,5-dicarboxylate · (MW 298.14) D-(*S*,*S*), (*Z*)

[99687-40-8] L-(*R*,*R*), (*Z*)

[106357-20-4] (**2**) D-(*S*,*S*), (*E*)

[106357-33-9]

(reagents for the asymmetric crotylboration of aldehydes to produce either *syn* or *anti* β-methylhomoallylic alcohols)[2]

Physical Data: bp 80 °C/0.1 mmHg.

Solubility: sol toluene, THF, ether, or CH_2Cl_2.

Analysis of Reagent Purity: ^{11}B NMR, data for (*E*)-crotyl: (δ 34.8, C_6D_6);[2b] the purity of the reagent is best determined by capillary GC;[2b] solutions of the reagent can be standardized using cyclohexanecarbaldehyde.[2b]

Preparative Method: prepared by treatment of (*E*)- or (*Z*)-crotylpotassium with ***Triisopropyl Borate*** followed by acidic extractive workup and direct esterification with diisopropyl tartrate (DIPT) (eqs 1 and 2).[2]

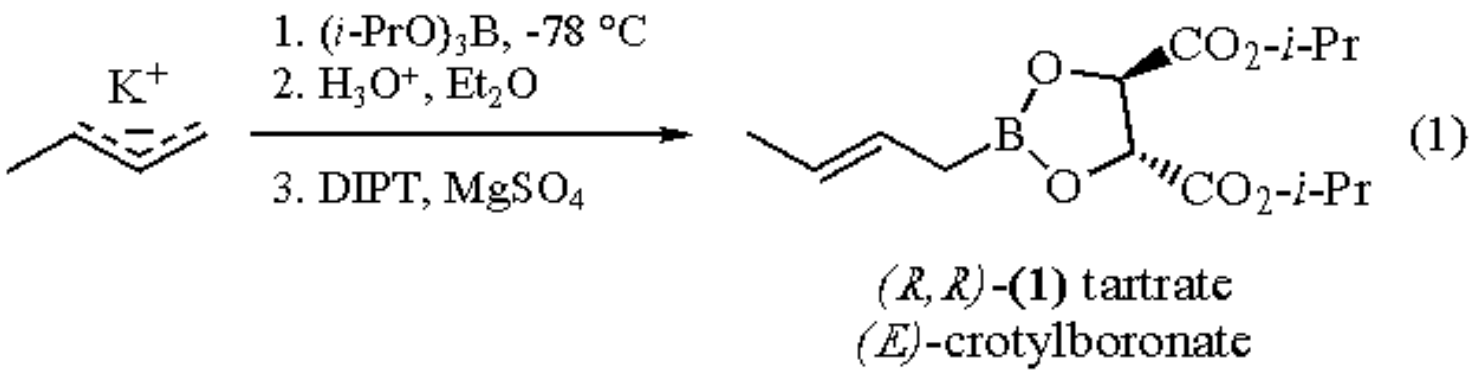

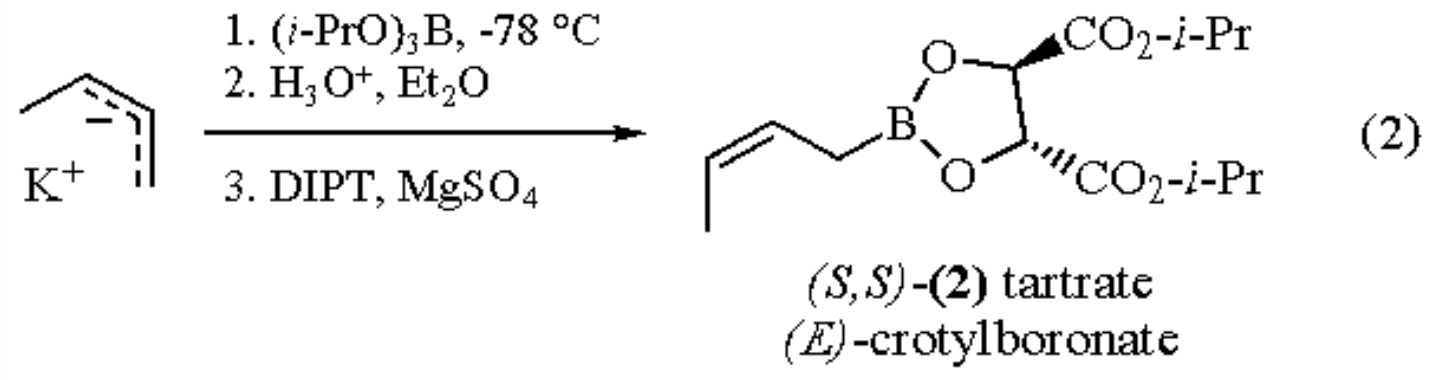

Handling, Storage, and Precautions: typically the reagents are handled as solutions in toluene (0.5-1M) and transferred by syringe under an inert atmosphere; stored neat or as a solution in toluene over 4Å molecular sieves under an argon atmosphere in a refrigerator (-20 °C), the reagent is stable for many months. In the presence of water, (**1**) rapidly hydrolyzes to achiral crotylboronic acid, the presence of which leads to reduced enantioselectivity in reactions with aldehydes.

Reactions with Achiral Aldehydes.

The tartrate ester modified (*E*)- and (*Z*)-crotylboronates undergo rapid additions to aldehydes at -78 °C. The enantioselectivities obtained for aliphatic linear or α-monobranched aldehydes range from 72 to 91% ee.[2] When cyclohexanecarbaldehyde is treated with the (*E*)-crotylboronate reagent at -95 °C in toluene, the homoallylic alcohol is obtained in 98% yield and 91% ee (eq 3). The (*Z*)-crotylboronate reagent gives slightly lower selectivity (83% ee, eq 4). The *anti*:*syn*/*syn*:*anti* ratios obtained are also excellent for this reagent (typically greater than 98:2 and 2:98 for (**1**) and (**2**), respectively).

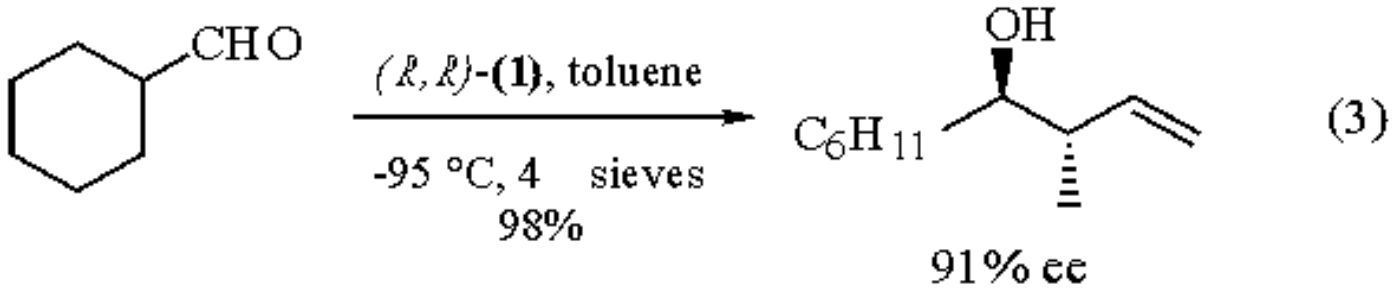

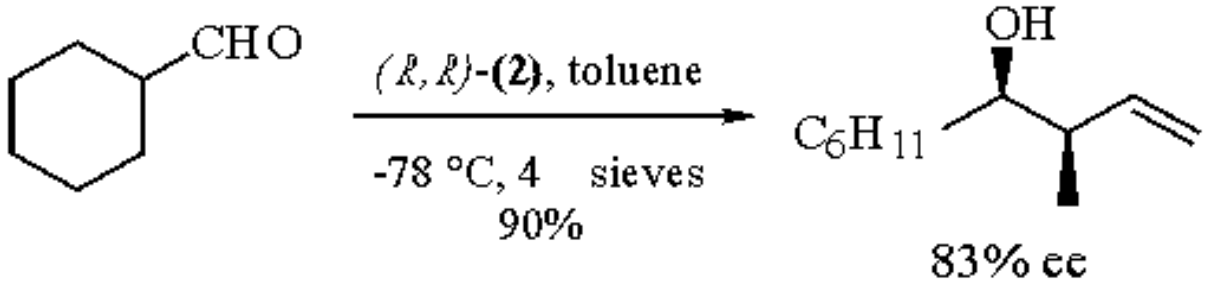

(4)

As with the corresponding allylboronate, the enantioselectivity of reactions with β-alkoxy and conjugated aldehydes are lower (55-74% ee). In the case of benzaldehyde (91%, 66% ee), selectivity can be improved by the use of the derived chromium tricarbonyl complex. The homoallylic alcohol is obtained after oxidative decomplexation in high yield and 92% enantiomeric purity (eq 5).[3]

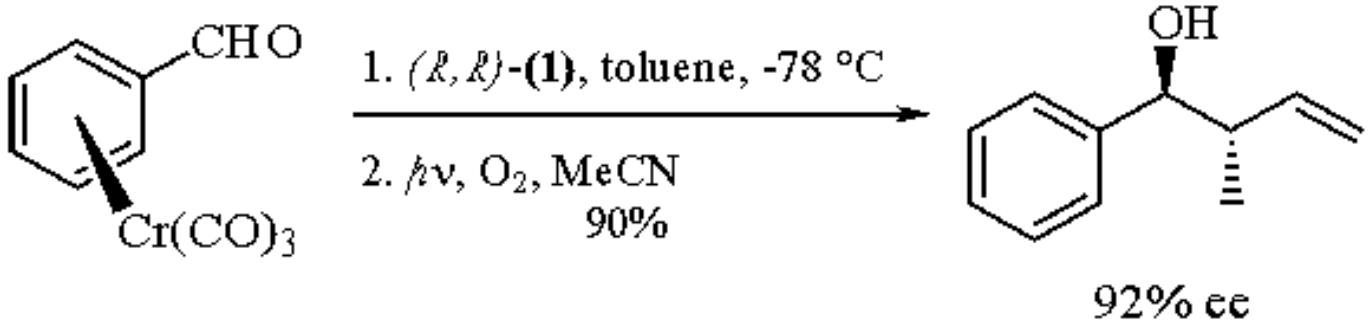

(5)

Reactions with Chiral Aldehydes.

Addition of the (*E*)- or (*Z*)-crotylboronate reagent to optically active β-alkoxy-α-methylpropionaldehydes gives the corresponding polypropionate structures with good to excellent diastereoselection (eqs 6 and 7).[4] Three of the four stereochemical triads can be prepared in high yield with useful levels of selectivity. The all-*syn* stereoisomer of eq 7 is best prepared using other methods, such as the crotyltin methodology developed by Keck and co-workers.[5] The polypropionate structures with 1,3-*anti* relationships between branching methyl groups are prepared with excellent diastereoselection (via matched double asymmetric reactions). Those with a 1,3-*syn* relationship are more difficult to prepare. The relative diastereoselectivity of the reaction of α-methyl chiral aldehydes with (*E*)- and (*Z*)-crotylboronates can be predicted by use of the *gauche* pentane model.[6]

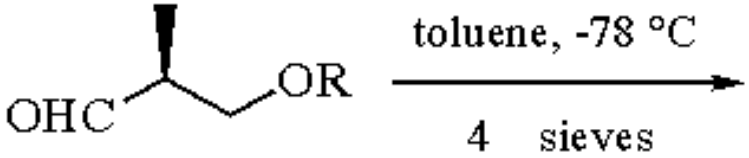

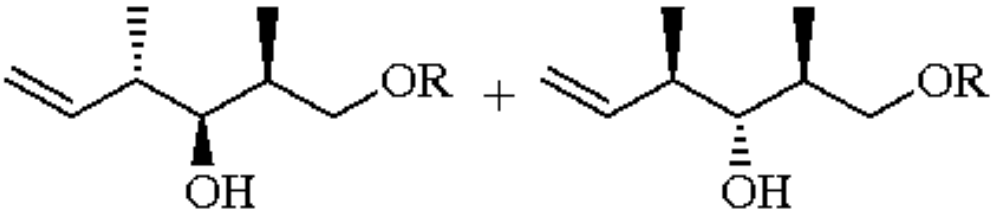

(6)

R = TBDMS, *(R,R)*-**(1)**	97:3	80%
R = TBDPS, *(S,S)*-**(1)**	10:90	77%

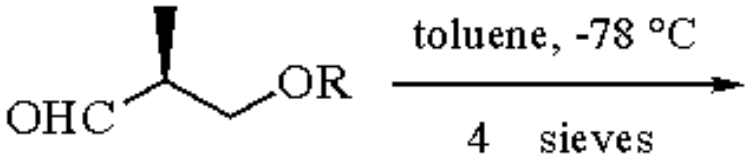

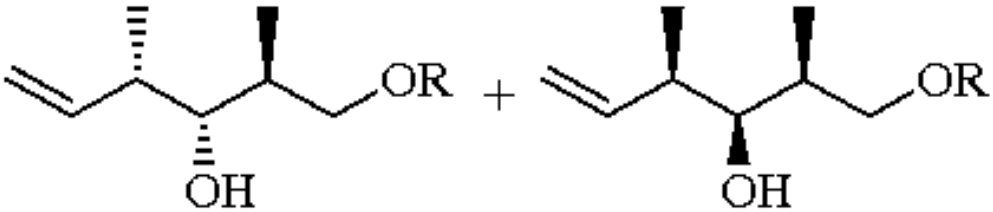

(7)

R = TBDMS, *(R,R)*-**(2)**	98:2	71%
R = TBDPS, *(S,S)*-**(2)**	27:73	

Both (*E*)- and (*Z*)-crotylboronates have been used in several applications in natural product synthesis.[4b,7] One application of both the allylboronate and (*E*)-crotylboronate reagents is found in the synthesis of the C(19)-C(29) segment of rifamycin S. The desired stereochemistry at C(25)-C(26) of the rifamycin ansa chain is set with excellent stereocontrol (>95:5) and high yield (87%) (eq 8).[4b,7a]

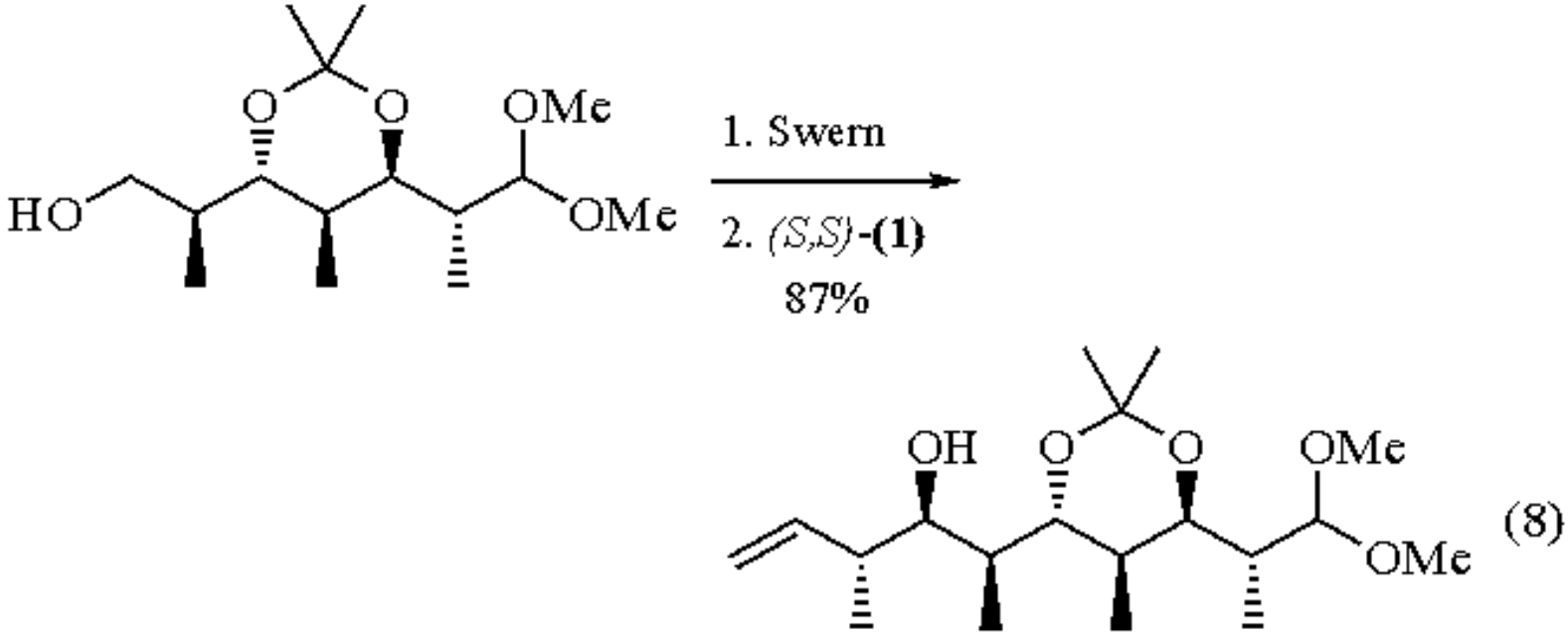

The (*E*)- and (*Z*)-crotylboronates provide selectivity in the best cases comparable to that obtained with other crotylboration procedures. Combining ease of preparation, stability, and selectivity the tartrate-modified (*E*)- and (*Z*)-crotylboronates are highly useful propionate enolate equivalents.

Related Reagents.

B-Allyldiisocaranylborane; ***B-Crotyldiisopinocampheylborane***; ***(R,R)-2,5-Dimethylborolane***.

---

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Diisopropylethylamine

***i*-Pr$_2$NEt**

[7087-68-5] · $C_8H_{19}N$ · Diisopropylethylamine · (MW 129.24)

(hindered non-nucleophilic amine base used in alkylations, selective generation of enolates, aldol-like reactions, and eliminations)

Alternate Names: DIPEA; DIEA; Hünig's base.

Physical Data: bp 127 °C; *d* 0.742 g cm^{-3}.

Solubility: sol most organic solvents.

Handling, Storage, and Precautions: corrosive and flammable liquid; flush containers with nitrogen or argon to prevent exposure to carbon dioxide; vapors are harmful; avoid absorption through the skin; use in a fume hood.

Metal-Catalyzed Couplings.

DIPEA can be used as a base in the palladium(0)-catalyzed alkoxycarbonylation of both allyl phosphates and acetates.[1] Treatment of diethyl (*E*)-2-hexenyl phosphate with ***Tris(dibenzylideneacetone)dipalladium*** and ***Triphenylphosphine*** in the presence of 1 equiv of DIPEA in ethanol under 30 atm CO pressure leads to an 84:16 mixture of *trans*- and *cis*-ethyl heptenoates in 88% yield (eq 1). The base used neutralizes the phosphoric acid generated. Without DIPEA, the alkyl ester is not produced. Allyl acetates behave in a similar manner (eq 2). Use of other tertiary bases, such as triethylamine, leads to lower yields of products.

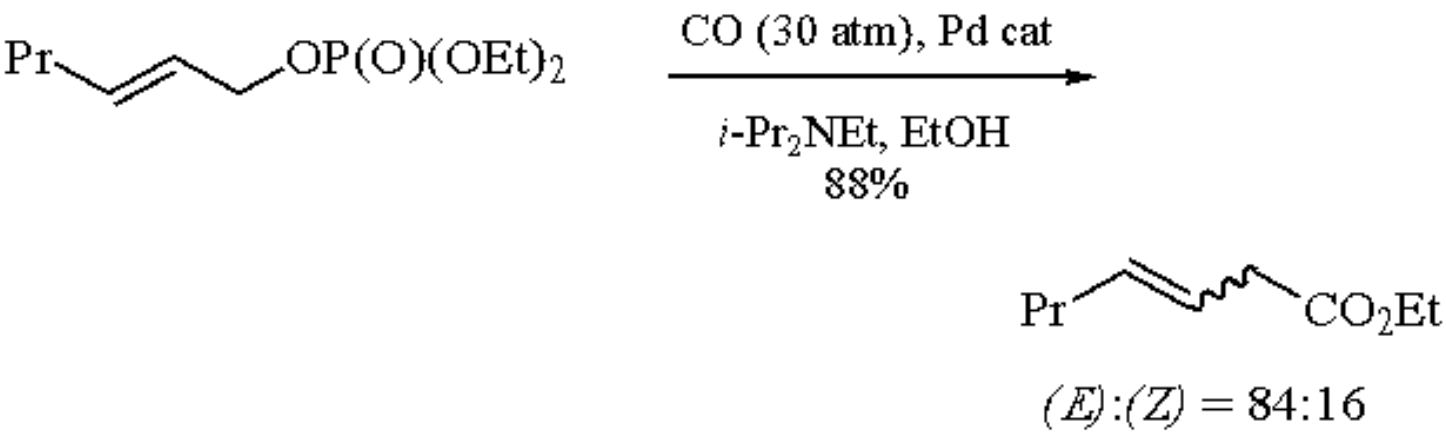

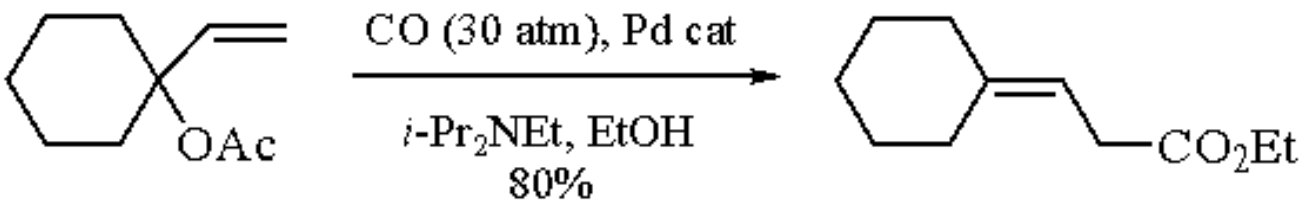

(2)

In an asymmetric variation of the Heck reaction,[2] the sterically demanding DIPEA is used in combination with (*R*)-***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl*** ((*R*)-BINAP) for generating enantiomerically enriched 2-aryl-2,3-dihydrofurans from aryl triflates.[3] However, in a comparison study, the base ***1,8-Bis(dimethylamino)naphthalene*** (proton sponge) was found to be superior in regards to enantiomeric purity for the arylation reaction (eq 3).[4,5]

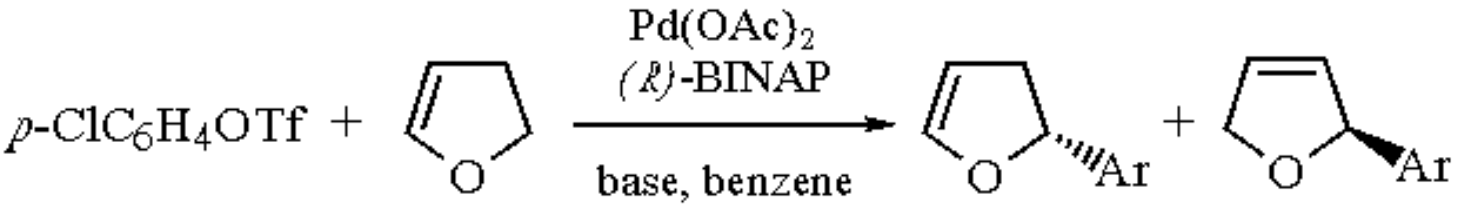

(3)

base	% ee (yield)	% ee (yield)
DIPEA	82 (92)	60 (8)
Et_3N	75 (98)	9 (2)
proton sponge	96 (71)	17 (29)

Selective Enolate Formation.

This base, in combination with boryl triflates, is widely applied in the enolate generation of ketones for use in directed cross-aldol reactions.[6] Reaction of 4-methyl-2-pentanone with DIPEA and ***Di-n-butylboryl Trifluoromethanesulfonate*** in ether at -78 °C produces the unisolated boron enolate. Subsequent treatment with hexanal yields the cross-aldol product in 70% yield as the sole regioisomer (eq 4).[7] Reaction takes place at the methyl group of the ketone, while none of the ketone or aldehyde self-condensation products are observed. In a complementary fashion, substitution of ***2,6-Lutidine*** for DIPEA and ***9-Borabicyclononyl Trifluoromethanesulfonate*** (9-BBN triflate) for di-*n*-butylboryl triflate yields the opposite regioisomer as the sole product (eq 4).[8]

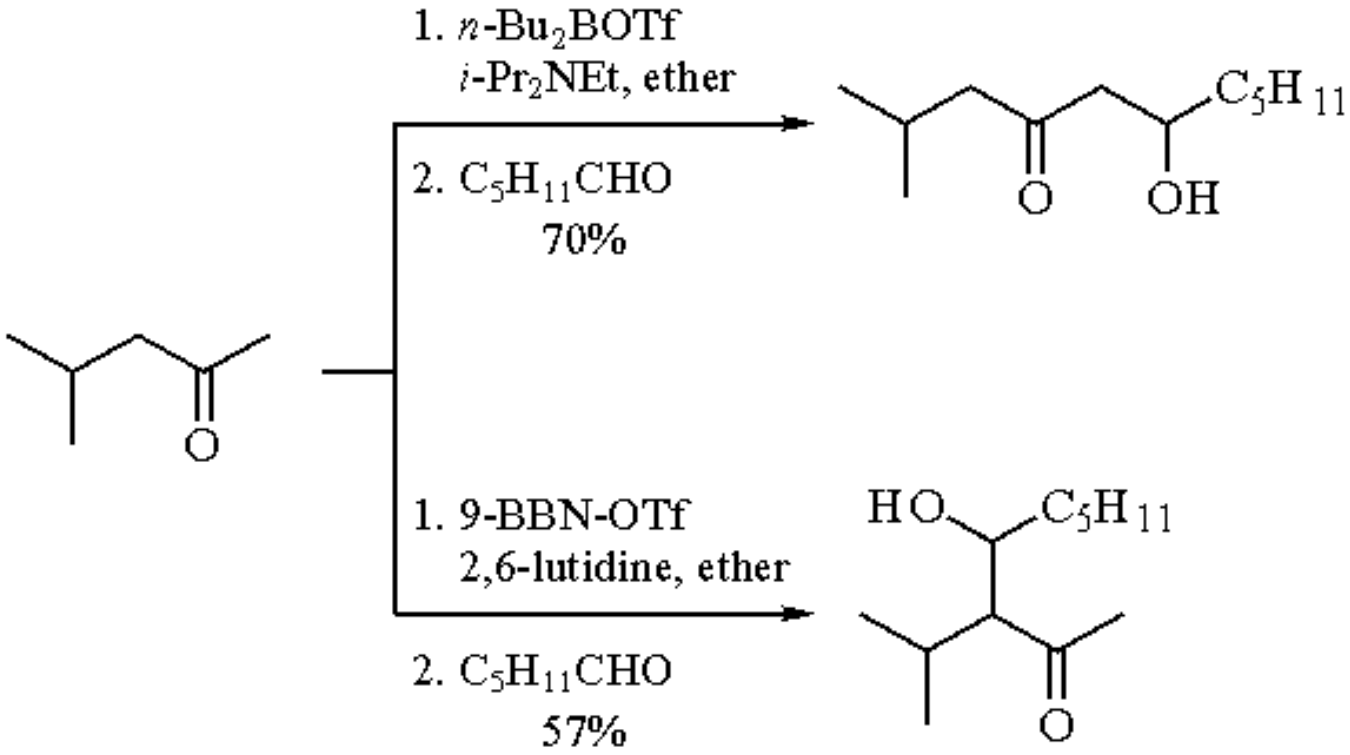

(4)

Proper choice of boron reagent, reaction solvent, and tertiary amine base influences the enolate geometry of ketones[9] and esters.[10] The use of dialkylboron triflates or dialkylboron halides, such as *B*-chloro-9-BBN, with DIPEA in ether at -78 °C favors the (*Z*)-enol borinates of ketones, while the more sterically demanding dialkylboron halides, such as dicyclohexylboron chloride (Chx_2BCl), with ***Triethylamine*** favor the (*E*)-enol borinates (eq 5).[9a,9b]

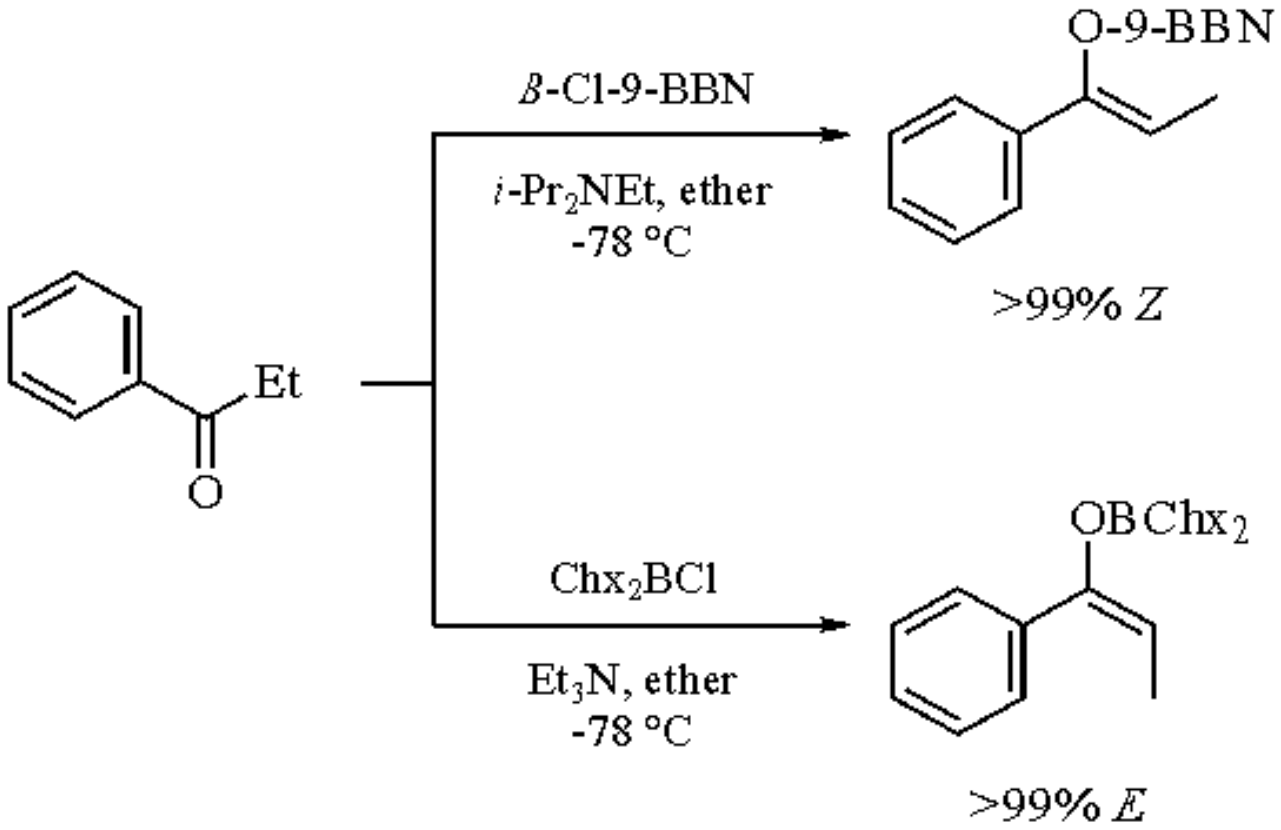

(5)

Similar complementary methodologies exist for generating both the (*E*) and (*Z*) boron enolates of esters. The

combination of chiral nonracemic bromoborane (**1**) and DIPEA in CH_2Cl_2 selectively converts *trans*-crotyl propionate into the (*E*)-boron enolate (**2**), which subsequently undergoes a highly enantioselective and diastereoselective Ireland-Claisen rearrangement to generate the *threo* product (**3**) in 75% yield and >97% ee. In comparison, use of triethylamine in a solvent mixture of toluene and hexane leads to a 90:10 mixture of (*Z*)- and (*E*)-boron enolates (**4**), which rearranges to generate the *erythro* product (**5**) as the major isomer in 65% yield and high enantiomeric excess (eq 6).[10a,11]

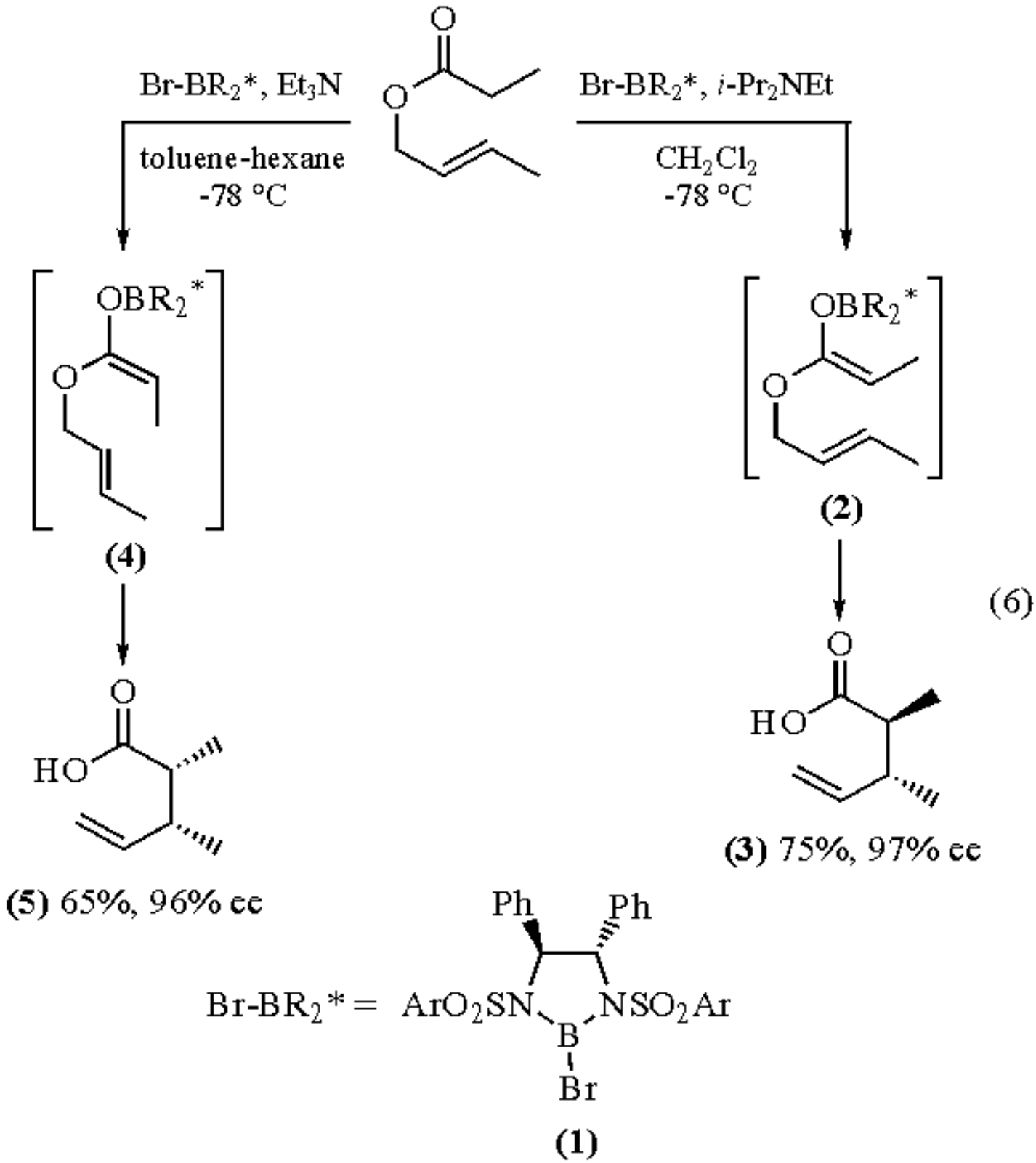

(6)

The stereoselective generation of silylketene acetals from alkyl esters and ***Triethylsilyl Perchlorate***[12] is quite effective

using DIPEA as the base at -70 °C in a 1:1 solvent mixture of CH_2Cl_2 and CCl_4 (see ***2,2,6,6-Tetramethylpiperidine***).

Phenols and enols can be *O*-methylated in moderate to good yields using ***Trimethylsilyldiazomethane*** with DIPEA in methanol-acetonitrile.[13]

Thioesters[10c,10d] and oxazolidones[14] can also be selectively converted into dialkylboryl enolates using DIPEA as base and the appropriate boron triflates. The thioester enolates readily react with imines to generate β-amino thioesters (eq 7),[10e] whereas the oxazolidone boron enolates can undergo alkylation with acetoxyazetidinones (eq 8).[14] *S*-*t*-Butyl bromothioacetate undergoes a highly stereospecific Darzens condensation with substituted benzaldehydes using ***Dicyclopentylboryl Trifluoromethanesulfonate*** and DIPEA at -78 °C to afford the *trans*-glycidic ester (eq 9).[15]

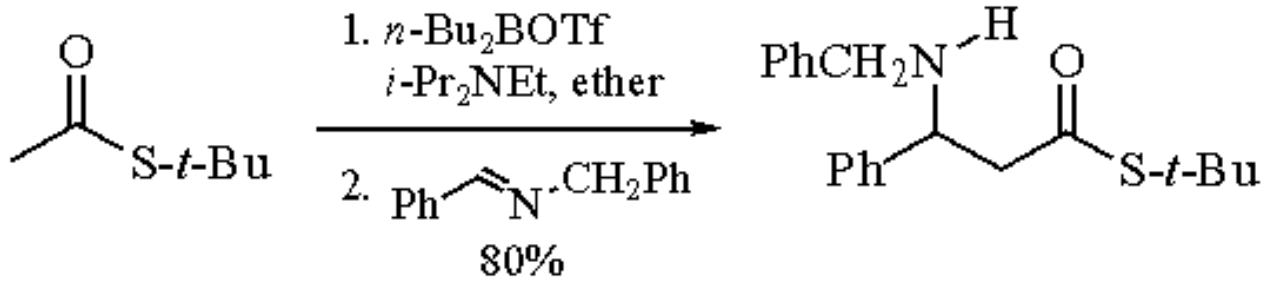

(7)

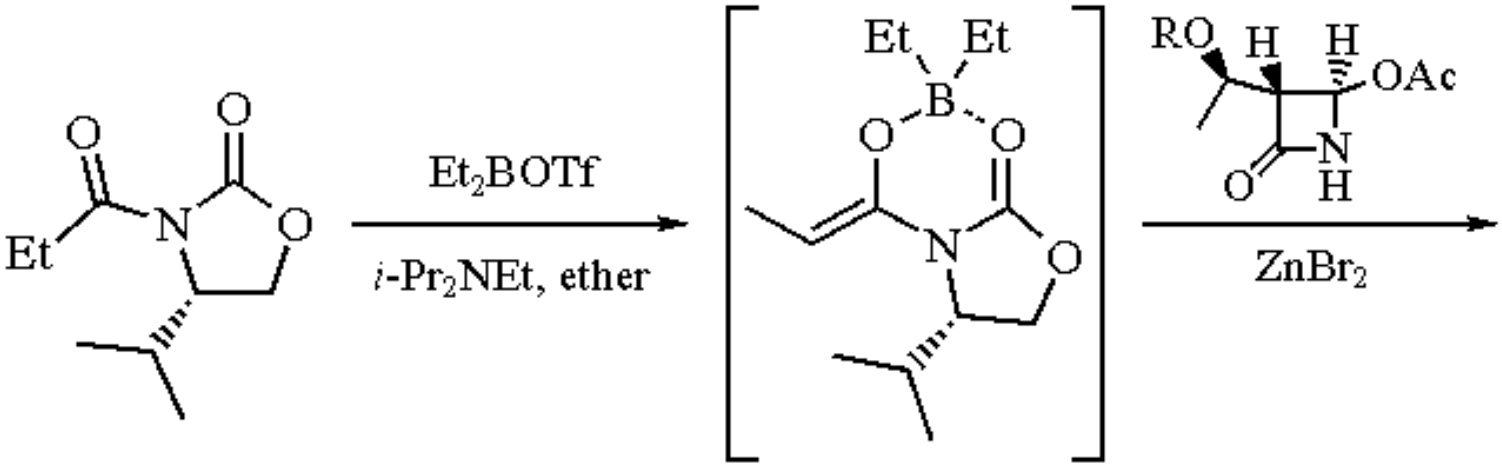

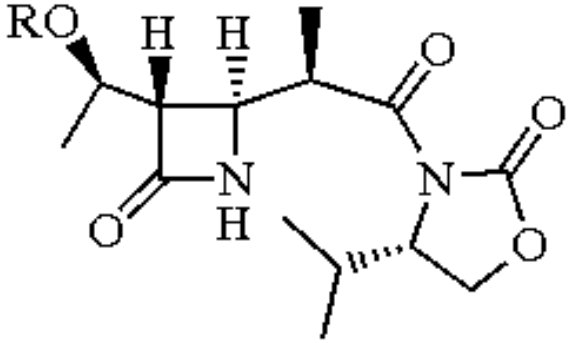

(8)

73%, β:α = >99:1

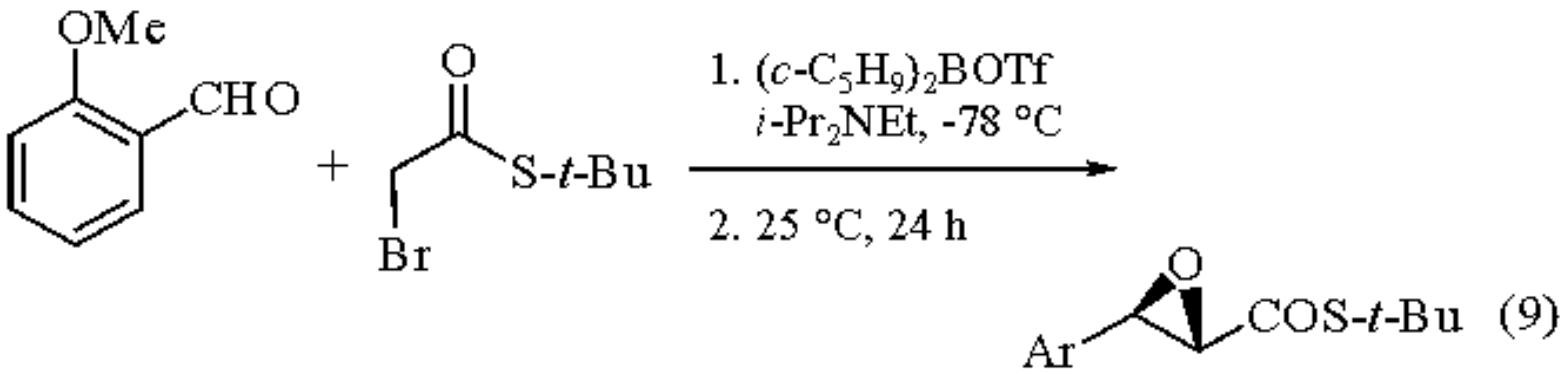

Aldol-like reactions between aldehydes and nitriles,[16] alkylpyridines,[17] 2-methyloxazoles, 2-methylthiazoles,[18] glycolates, and thioglycolates[19] are possible in the presence of boryl triflates and DIPEA. Methyl-*O*-allyl glycolate tin(II) (or boron) enolates, prepared easily using DIPEA as base, undergo Wittig rearrangement to afford α-hydroxy esters with a high degree of diastereoselectivity (eq 10).[20]

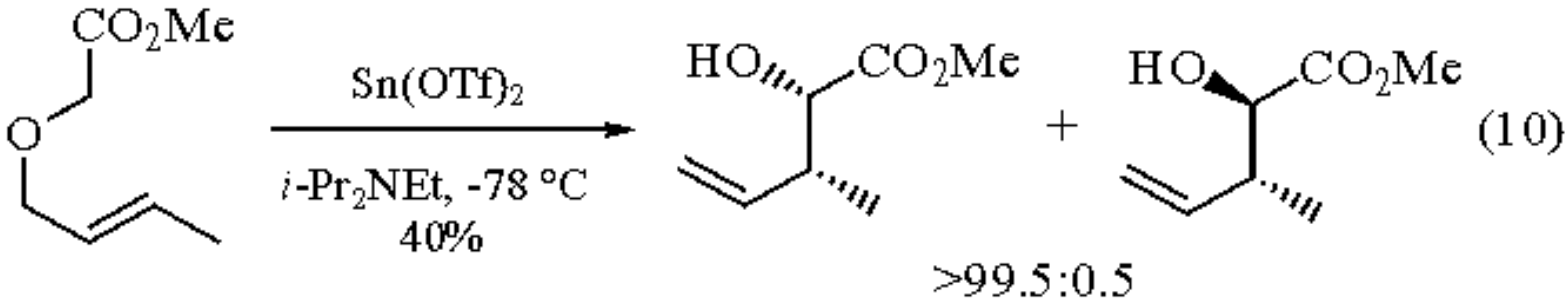

Diisopropylethylamine also finds application in the preparation of titanium enolates from esters,[21] aryl ketones,[22] and oxazolidones.[23]

Base-Promoted Alkylation.

This sterically hindered amine is widely used in organic synthesis as a proton scavenger. Its lack of quaternization makes it an excellent choice of a base for use with very reactive alkylating agents.[24] In the field of protecting group chemistry, DIPEA is a particularly useful base for protection of alcohols as substituted ethers.[25] For example, the tertiary alcohol of mevalonic lactone can be protected as the *p*-methoxybenzyloxymethyl ether using an excess of DIPEA and 3 equiv of *p*-methoxybenzyl chloromethyl ether (eq 11).[26]

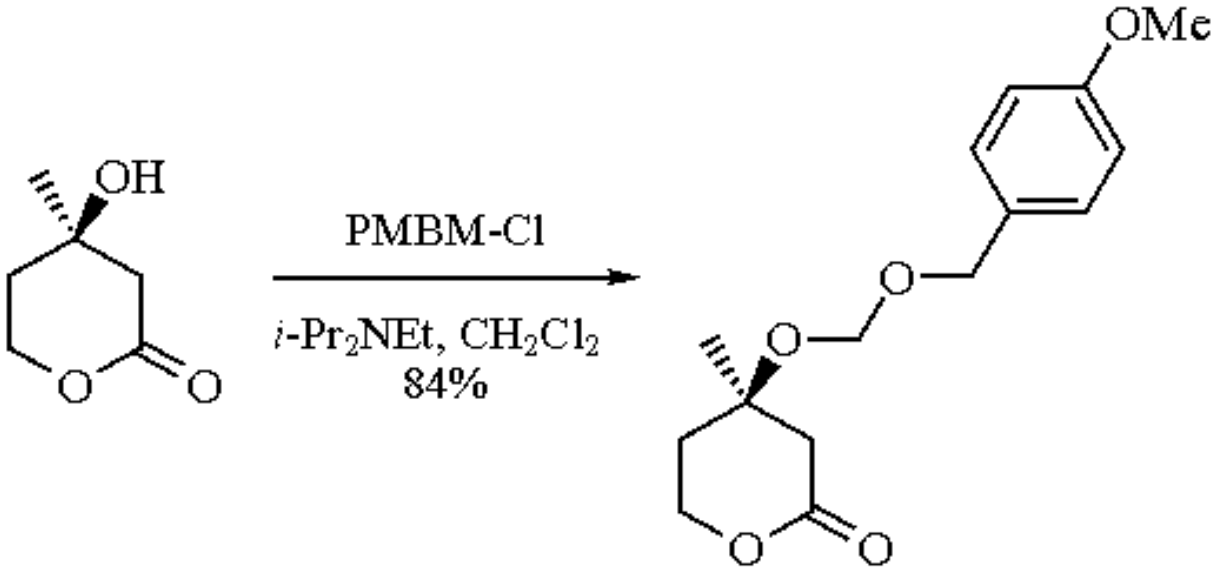

(11)

2,4-Disubstituted oxazolones are alkylated in high yields using alkyl halides with DIPEA as a base in DMF (eq 12).[27] DIPEA can be used together with ***Triethyloxonium Tetrafluoroborate*** for the esterification of sterically hindered carboxylic acids.[28]

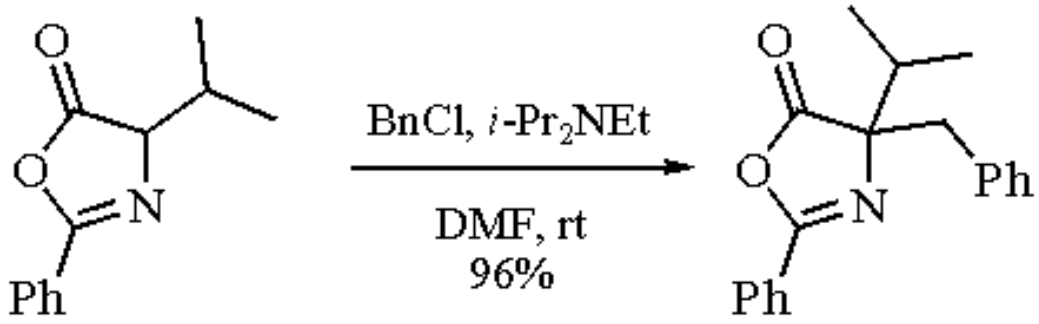

(12)

The alkylsulfination of diacetone-D-glucose with sulfinyl chlorides and DIPEA in toluene at -78 °C produces the (*S*)-sulfinates as the major products. Simply changing the base from DIPEA to pyridine and the solvent from toluene to THF results in a remarkable stereochemical reversal, affording the (*R*)-sulfinates as the major products (eq 13).[29]

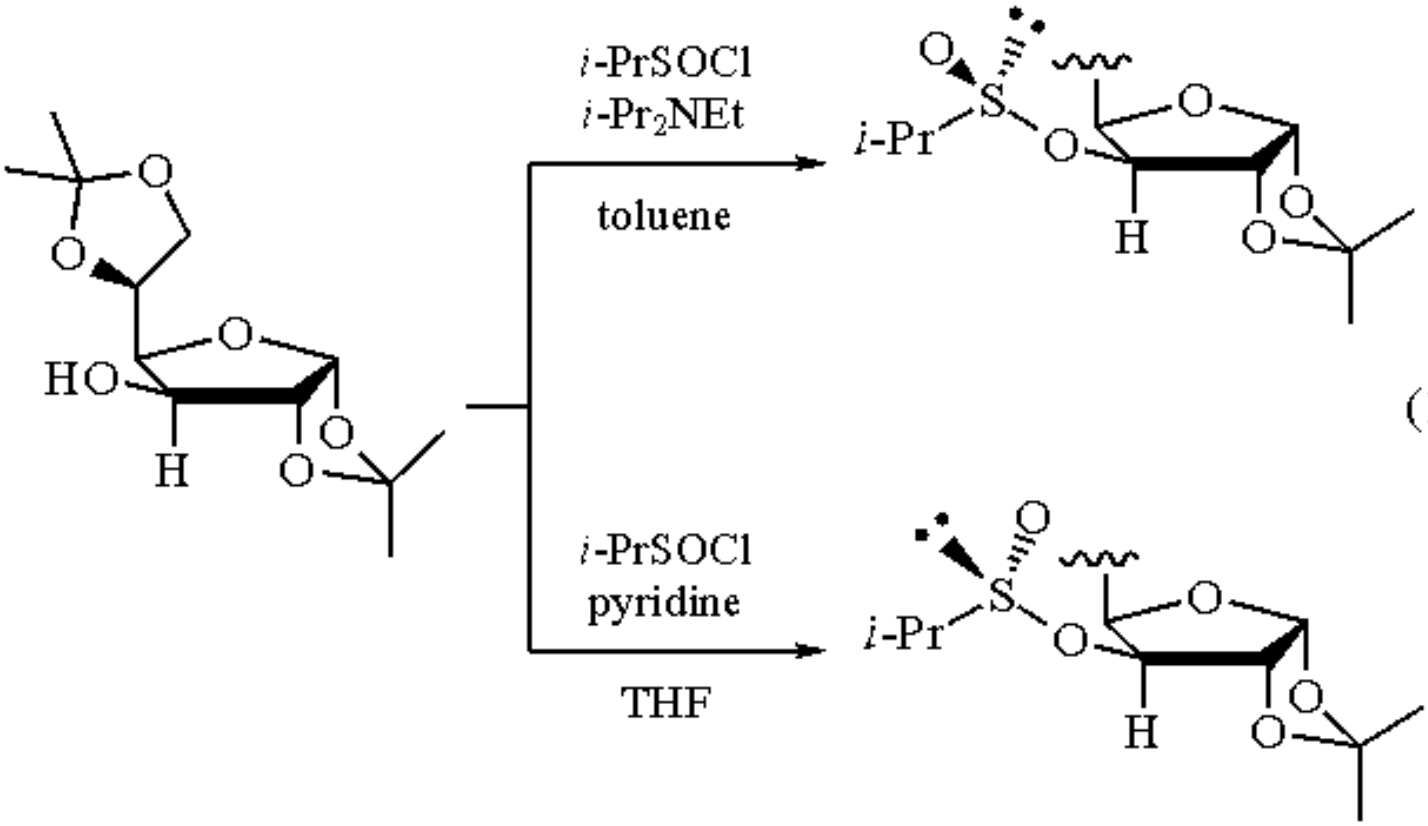

(13)

The alkylation of protected uracils with alkyl halides using DIPEA in DMF or acetonitrile furnishes the alkylated uracils in good to moderate yields (eq 14). The alkylations involving ribofuranosyl bromides furnish the β-isomers as the sole products.[30]

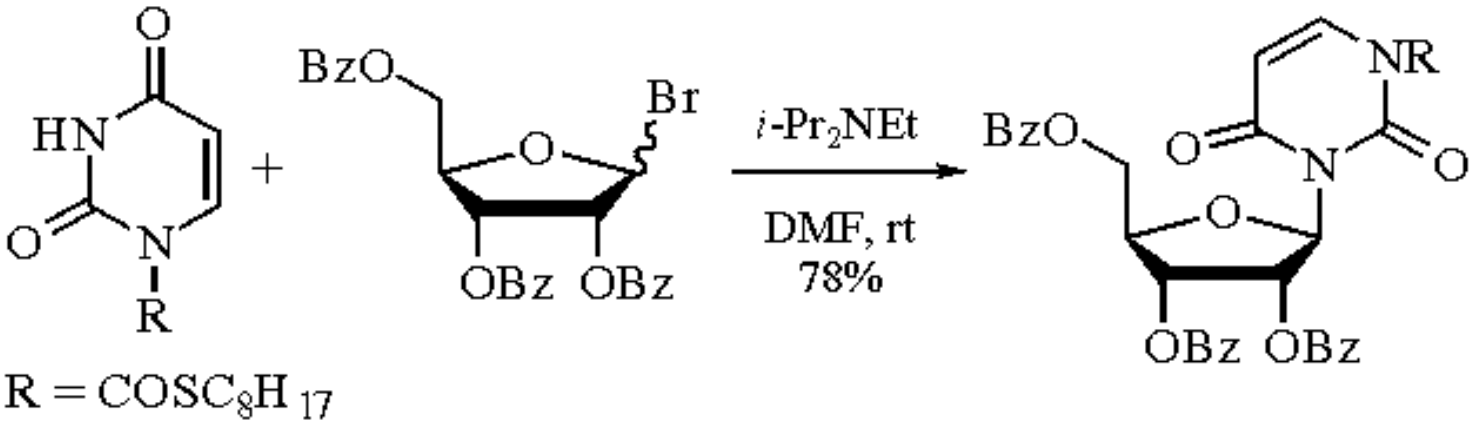

(14)

Exposure of hydroxyl vinyl ethers to ***Trifluoromethanesulfonic Anhydride*** and DIPEA in CH_2Cl_2 at -78 °C results in a stereospecific cyclization to afford cyclic hemiacetals in near quantitative yield (eq 15).[31]

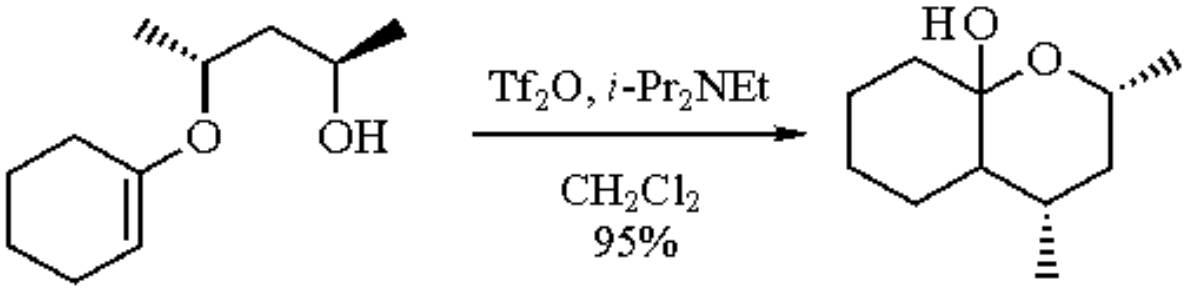

(15)

Addition of DIPEA to a mixture of phenylsulfenyl chloride and an unsaturated alcohol or carboxylic acid results in high yields of cyclic ethers or lactones, respectively.[32] The presumed mechanism involves the intermediacy of an episulfonium ion (eq 16).

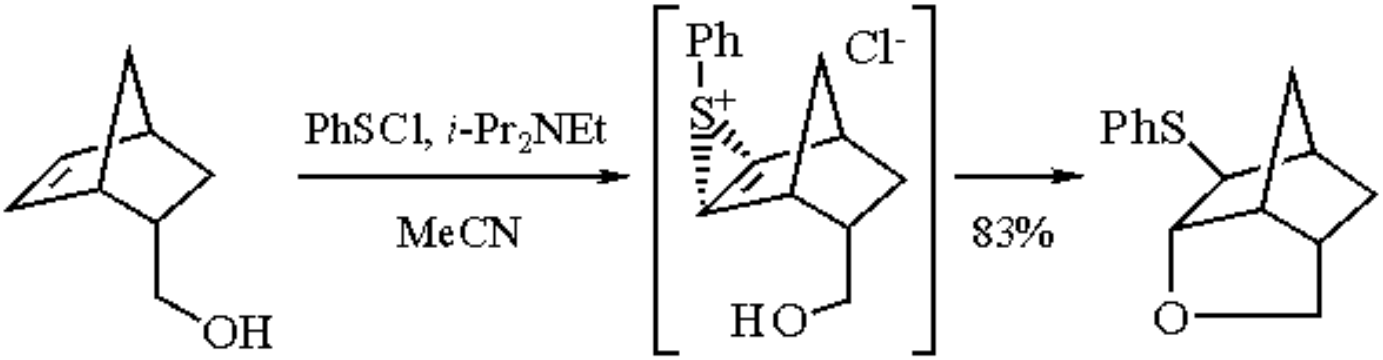

(16)

Eliminations.

The eliminative deoxygenation of acetals into enol ethers is accomplished using ***Trimethylsilyl Trifluoromethanesulfonate*** and a slight excess of DIPEA (eq 17);[33] similarly, treatment of 2-alkyloxazolidines with ***Chlorotrimethylsilane*** and DIPEA leads to *N*-(trimethylsilyloxyalkyl)enamines (eq 18).[34] Thioacetals follow similar chemistry to furnish vinyl sulfides.[35] Deoxygenation of sulfoxides with DIPEA and ***Iodotrimethylsilane*** produces vinyl sulfides.[36]

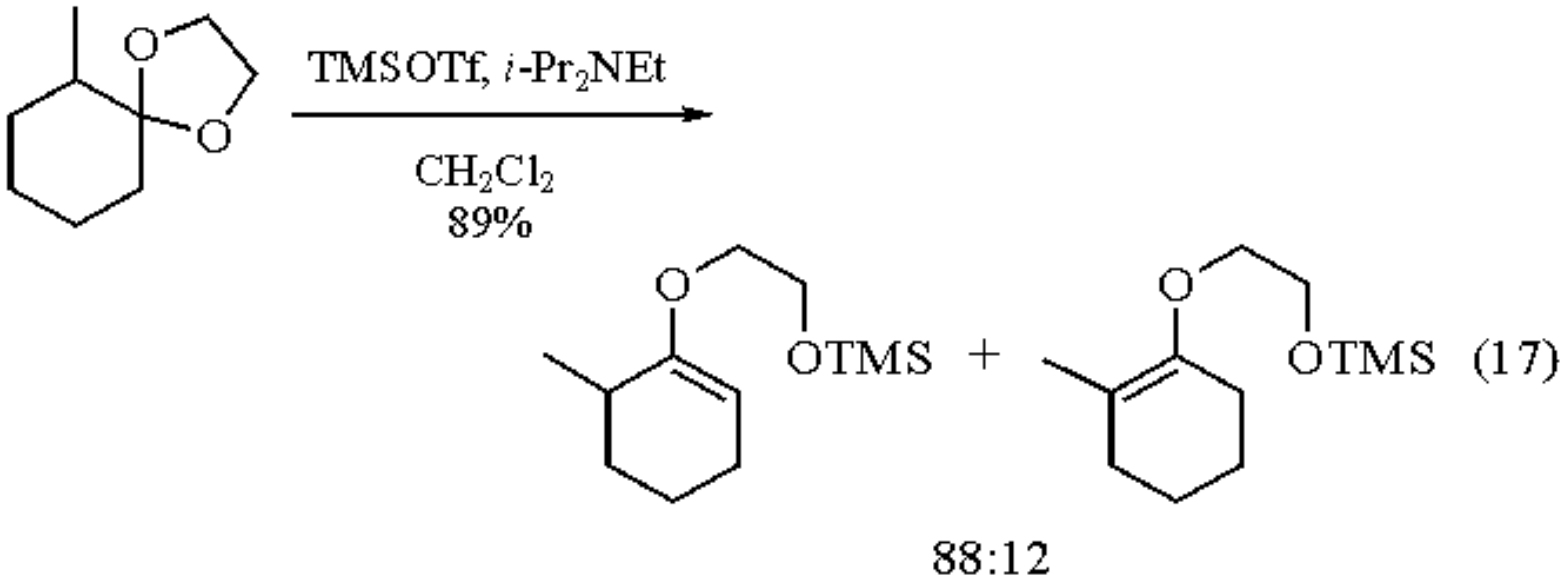

(17)

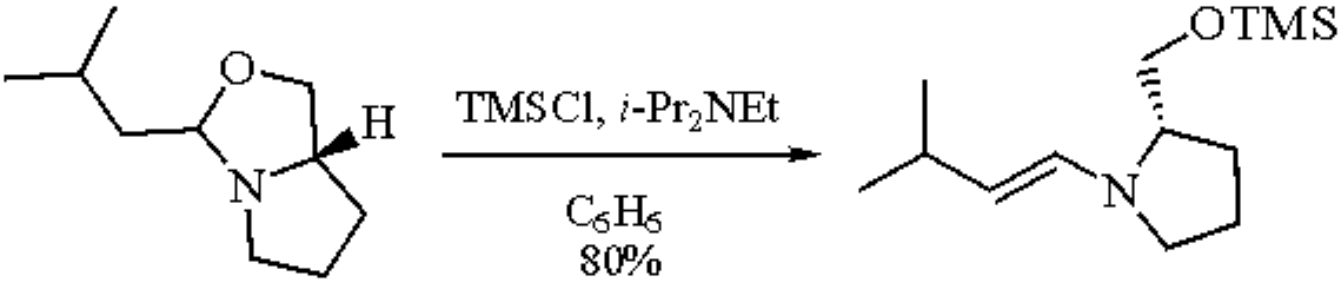

(18)

Peptide Couplings.

Diisopropylethylamine, as well as triethylamine, *N*-methylmorpholine, and other tertiary amines, find utility in the coupling of amino acids to prepare peptides.[37] The basicity and steric nature of the tertiary amine utilized during the coupling reaction influences the degree of racemization.[38]

Minor dipeptide impurities, which sometimes are difficult to remove, can form during the *N*-acylation of amino acids. Acylation of alanine using benzoyl chloride and aqueous NaOH yields *N*-benzoylalanine (60%), which contains about 1.2% of the dipeptide impurity. Use of DIPEA nearly eliminates the impurity and results in a 72% yield of *N*-acylated product.[39]

The coupling of *N*-methylated amino acids is sometimes problematic. However, the combination of 3 equiv of DIPEA and 1 equiv of bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP) in CH_2Cl_2 results in good yields of desired dipeptides. Methyl *N*-methylvalinate successfully couples with other amino acids using these reaction conditions. Epimerization during the coupling is not observed (eq 19).[40]

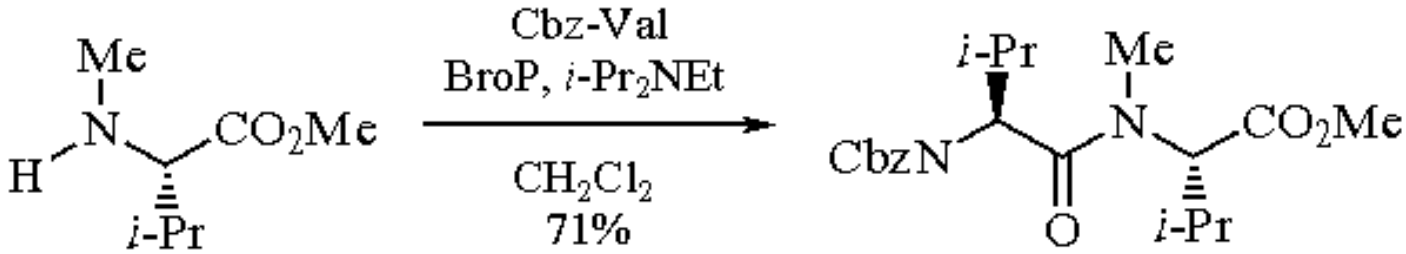

(19)

Related Reagents.

Lithium Chloride-Diisopropylethylamine.

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9-*O*-(1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane, Potassium Salt

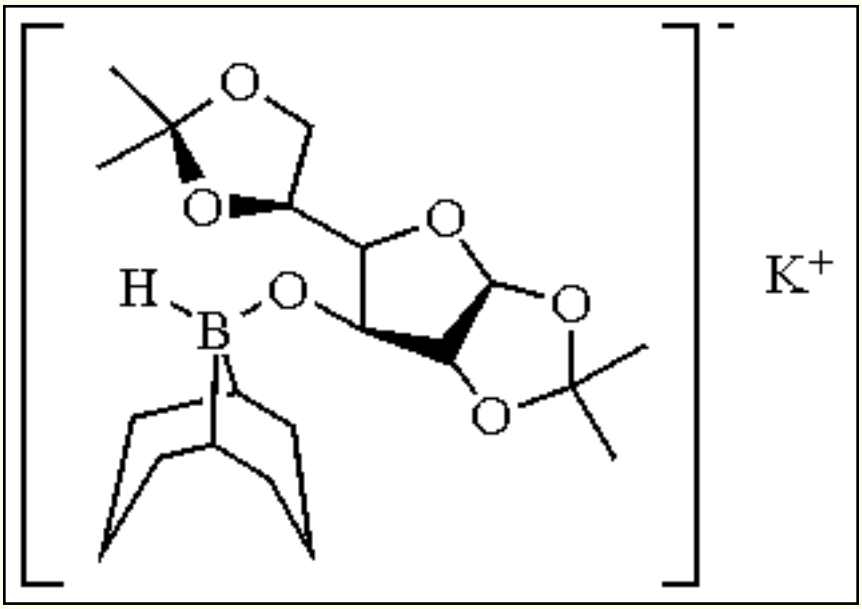

[101696-41-7] · $C_{20}H_{34}BKO_6$ · 9-*O*-(1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane, Potassium Salt · (MW 420.40)

(chiral borohydride reagent for enantioselective reduction of ketones[1])

Alternate Names: K-glucoride; K 9-*O*-DIPGF-9-BBNH.

Solubility: usually prepared and stored in THF solution.[1]

Analysis of Reagent Purity: ^{11}B NMR (δ 1.33, br s) and strong absorption at 2038 cm^{-1} in the IR spectrum (B-H str); stoichiometric ratio of K:B:H as 1:1:1 by analysis.[1]

Preparative Method: 9-BBN, by reaction with the chiral alcohol 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (DPGF) (both commercially available), is transformed into the borinic ester 9-*O*-DIPGF-9-BBN which, by treatment with a modest excess (1.1-1.5 equiv) of

potassium hydride, is completely transformed within 2 h into K-glucoride.[1]

Handling, Storage, and Precautions: K-glucoride is relatively stable toward disproportionation at rt, especially when the THF solution is stored over excess potassium hydride under a positive pressure of nitrogen.[1]

Enantioselective and Diastereoselective Reduction of Carbonyl Compounds.

K-Glucoride is the first example of a well-defined chiral borohydride reagent containing a monosaccharide as chiral auxiliary;[2] moreover, it has only one hydride per reagent molecule.[1a] K-Glucoride allows the reduction of various ketones[1a-c] to the corresponding alcohols in THF, even at -78 °C; it was first used for hindered alkyl phenyl ketones (like pivalophenone)[1a] and it gave considerably higher enantioselectivity than Noyori's BINAL-H reagent (see ***Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl***).[1a] Reduction of unhindered aliphatic ketones (like 2-butanone) with the same reagent gave only very low optical yields; for such compounds the lithium hydrido-9-BBN-nopol benzyl ether adduct (NB-Enantride™)[1a] is much more favorable. On the other hand, the reduction of pinacolone, which is relatively hindered, gave a reasonable enantioselectivity (70%), while NB-Enantride gave only 2%. A significant effect of reaction temperature on optical induction was demonstrated for propiophenone,[1c] with ee's varying from 92% at -78 °C to 76% at 0 °C. It is noteworthy that the alcohols obtained were always enriched in the (*R*) enantiomer.

Prochiral ketones bearing various functionalities near the carbonyl group can be reduced by K-glucoride; for example very good optical yields can be obtained in the reduction of α-keto esters[3a] to the corresponding α-hydroxy esters. The ee's obtained are always close to 100%, even with relatively hindered derivatives. Moreover, all of the α-hydroxy esters obtained were enriched in the (*S*) enantiomer. In contrast, *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (Alpine-borane®)[3a] usually gave lower optical yields and very slow reactions with relatively hindered compounds; in this case the absolute configuration of product depends on the starting α-keto ester. While α-hydroxy esters can be obtained with high ee by reduction with K-glucoride, the same procedure gave only poor results in the asymmetric reduction of β-keto esters.[3a]

Secondary or tertiary β-amino alcohols can be obtained by reduction of α-amino ketones with K-glucoride;[3b] best results were obtained starting from aromatic α-amino ketones (44-73% ee), while aliphatic amino ketones gave only low enantioselectivity (9-33% ee). Interestingly, the amino alcohols obtained are enriched in the (*S*) enantiomer and the enantioselectivity increases with the bulkiness of the substituents on the amino group.

α,β-Alkynic ketones can be reduced to the corresponding (*R*)-alkanols with K-glucoride;[3c] ee's are good with compounds bearing an internal triple bond (61-87%), while they drop with terminal alkynes (in this case the (*S*) configuration is preferred). K-glucoride can also be used for the diastereoselective reduction of chiral racemic cyclic and bicyclic ketones to give the less stable alcohol with excellent diastereoselectivity.[1c]

Other Reductions.

There is an example of a reduction (resolution) of racemic 1,2-epoxyalkanes to give the corresponding (*R*)-2-alkanols with moderate ee (up to 43.3%).[4]

The enantioselective synthesis of optically active secondary amines via asymmetric reduction of prochiral ketimines was studied by screening various chiral hydrides.[5a,b] In this case, K-glucoride gave only disappointing results and was inferior to other reagents. Better results were obtained in the asymmetric reduction of prochiral *N*-diphenylphosphinylimines to chiral *N*-(diphenylphosphinyl)amines (eq 1),[5c] which can then be readily converted into optically active primary amines. For this reaction the stereochemical course depends dramatically on the relative bulkiness of the groups R^1 and R^2. The reaction conditions for reduction of C=N double bonds are the same as used for ketones, but the high reactivity of diphenylphosphinylimines dramatically reduces the reaction time.

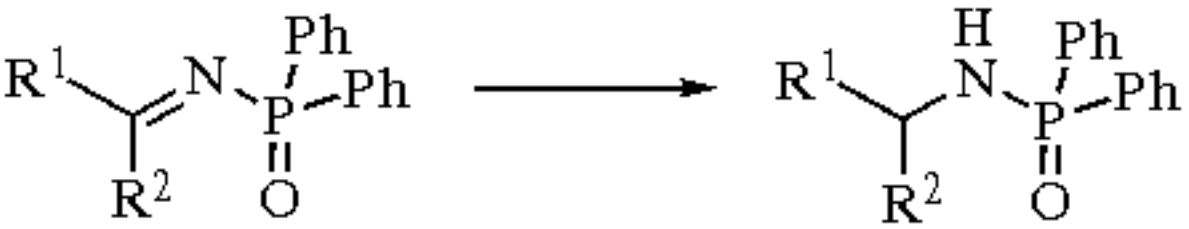

(1)

Finally, K-glucoride can also be used for the enantioselective reduction with moderate ee (52%) of 1-substituted 2-methylisoquinolinium salts, which are employed in the preparation of 1-substituted 2-methyltetrahydroisoquinoline alkaloids.[5d]

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Han, C. K. *Bull. Korean Chem. Soc.* **1991**, *12*, 565.

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Diisopropylsilyl Bis(trifluoromethanesulfonate)

$$i\text{-}Pr_2Si(OSO_2CF_3)_2$$

[85272-30-6] · $C_8H_{14}F_6O_6S_2Si$ · Diisopropylsilyl Bis(trifluoromethanesulfonate) · (MW 412.39)

(bifunctional silyl protecting group for 1,2-, 1,3-, and 1,4-diols)

Physical Data: bp 85-86 °C/2 mmHg; *d* 1.396 g cm^{-3}; fp 110 °C.

Preparative Method: conveniently prepared by the slow addition of 2 equiv of ***Trifluoromethanesulfonic Acid*** to a stirring mixture of ***Chlorodiisopropylsilane***, followed by direct distillation of the product from the reaction flask to yield the product as a pale yellow oil.[1]

Handling, Storage, and Precautions: store in the refrigerator under an inert atmosphere of argon or nitrogen. Special care should be used when handling since diisopropysilyl bis(trifluoromethanesulfonate) has been classified as a corrosive.

The use of silyl protecting groups in organic synthesis has been limited to monofunctional silicon compounds. Their use has been enhanced by the fact that they may be put on and removed under mild conditions. Diisopropylsilyl bis(trifluoromethanesulfonate) and its analog, ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***, go one step further in protecting group technology. The two electrophilic sites on silicon allow for the simultaneous protection of 1,2-, 1,3-, and 1,4-diols, and in some cases form a rigid system which allows for asymmetric stereocontrol in subsequent organic transformations.[1]

Polyfunctional silicon protecting groups have been employed by researchers before the use of silicon ditriflates. Trost and co-workers found in the development of methodology towards the synthesis of erythronolide A that ***Di-t-butyldichlorosilane*** was relatively unreactive under standard silylation conditions and required forcing conditions (65-95 °C, ***1-Hydroxybenzotriazole***, MeCN, or DMF) for its employment.[2] These two factors make dichlorosilanes limited in their applicability. Silicon ditriflates will react readily with many diols in the presence of 3 equiv of ***2,6-Lutidine*** in chloroform at temperatures ranging from 0-25 °C. The generality of this polyfunctional protecting group is illustrated by the formation of the silyl-protected diols (**1**), (**2**), and (**3**).

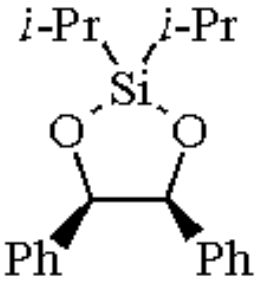

(1) 83%

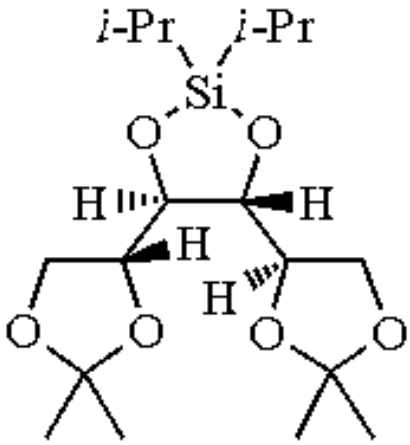

(2) 88%

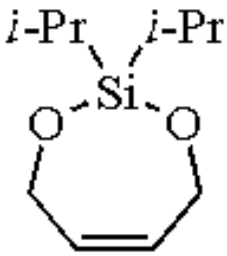

(3) quant

Corey and Link utilized diisopropylsilyl bis(trifluoromethanesulfonate) as a silylating agent for catechols in the first enantioselective synthesis of pure (*R*)- or (*S*)-isoproterenol (eq 1).[3]

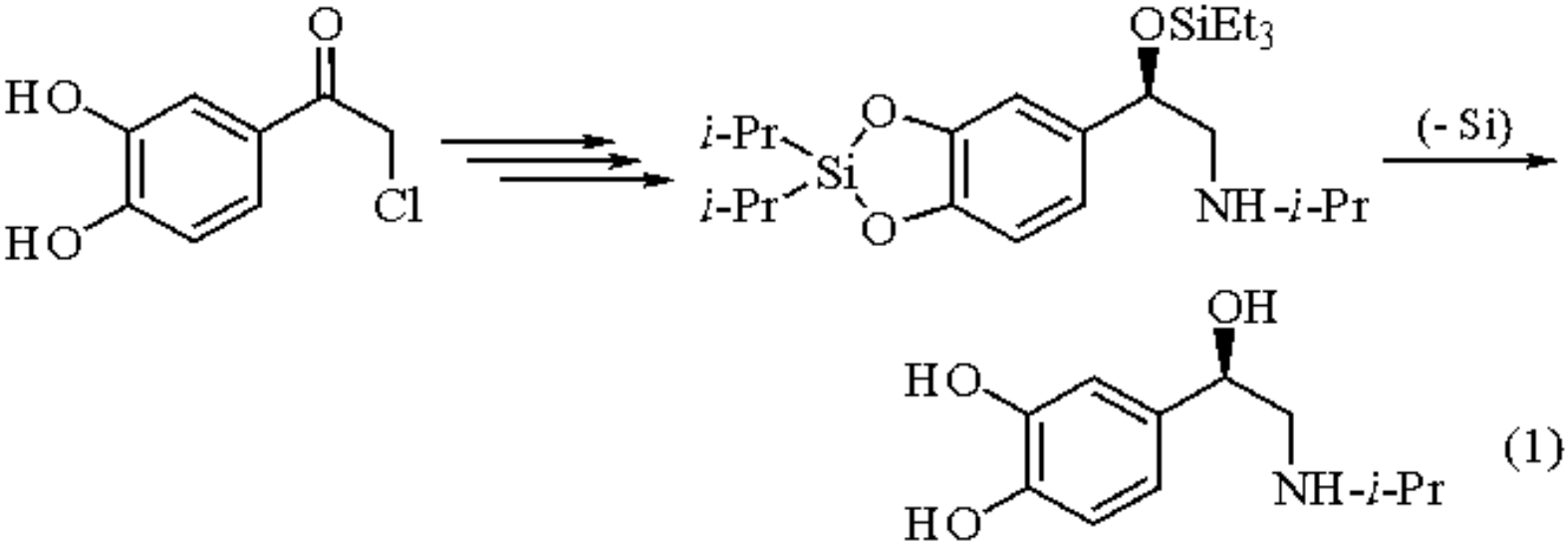

(1)

Related Reagents.

Di-t-butyldichlorosilane; ***Di-t-butylmethylsilyl Trifluoromethanesulfonate***; ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***; ***Dichlorodimethylsilane***; ***Dichlorodiisopropylsilane***.

---

1. Corey, E. J.; Hopkins, P. B. *TL* **1982**, *23*, 4871.
2. Trost, B. M.; Caldwell, C. G. *TL* **1981**, *22*, 4999.
3. Corey, E. J.; Link, J. O. *TL* **1990**, *31*, 601.

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Dichlorodiisopropylsilane

***i*-Pr$_2$SiCl$_2$**

[7751-38-4] · $C_6H_{14}Cl_2Si$ · Dichlorodiisopropylsilane · (MW 185.17)

(nucleoside 3´,5´-hydroxy protection; component in Peterson alkenation reaction)

Physical Data: bp 50-55 °C/5 mmHg.[1,2]

Solubility: sol most organic solvents.

Preparative Method: conveniently prepared by the reaction of diisopropylsilane in carbon tetrachloride with ***Palladium(II) Chloride*** at 140 °C for 8 h in a steel bomb. Washing the residue with ether and removing the ether by rotary evaporation yields the product which is purified by distillation to yield a clear colorless oil.

Handling, Storage, and Precautions: special care should be used when handling since the reagent is corrosive.

Nucleoside-protecting Group.

The use of silicon groups as protection for hydroxy groups has been widely exploited.[3] One potentially useful way to protect a nucleoside is by using a protecting group which spans the 3´- and 5´-hydroxy groups. One of the useful groups which can be used as a bifunctional protecting group in nucleosides is the diisopropylsilyl group. Reaction of the nucleoside with dichlorodiisopropylsilane and ***Imidazole*** in DMF gives the protected nucleoside (eq 1).[4] This method has not been widely used; the more common 3´,5´-hydroxy-bridging protecting group is a tetraisopropyldisiloxy group.[5]

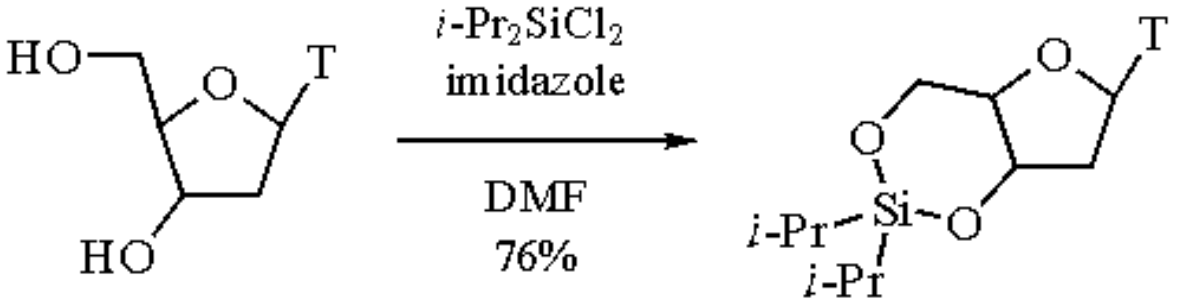

(1)

Nucleosides are generally linked together through phosphate linkages. Studies are being directed toward synthesizing alternative linkages that will impart different solubilities to oligonucleotides. A diisopropylsilyl protecting group has

also been used as a phosphate linker isostere (eq 2).[1]

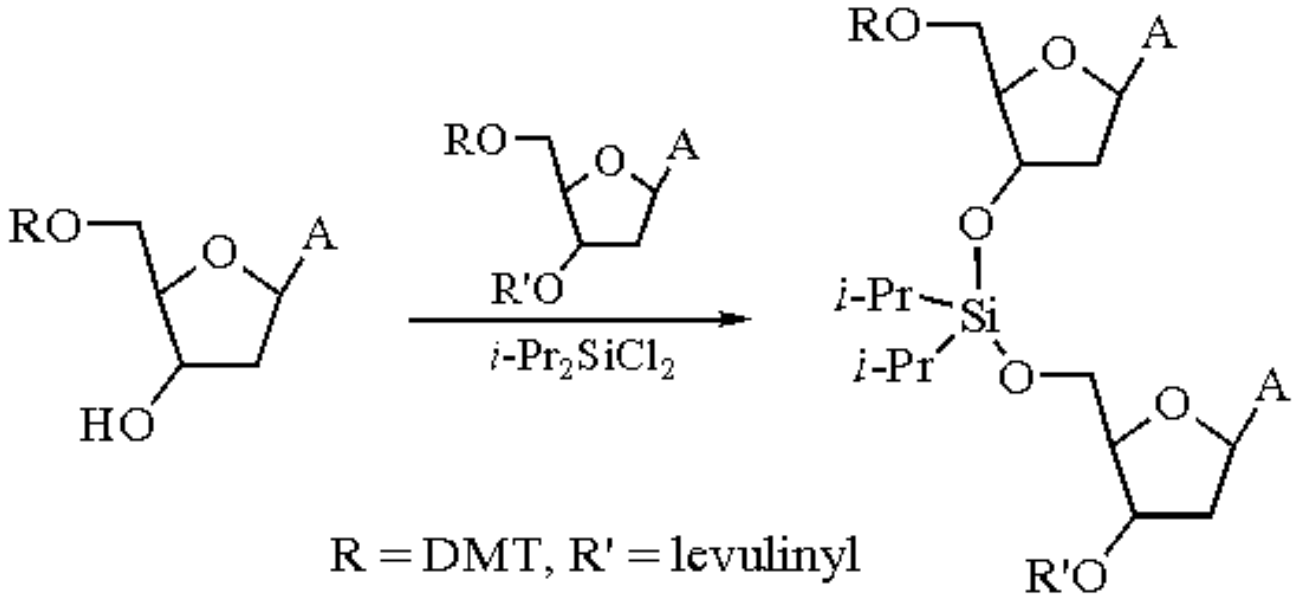

(2)

A diisopropylsilyl group has also been used as a linker in a radical cyclization reaction to form eight-membered rings (eq 3).[6]

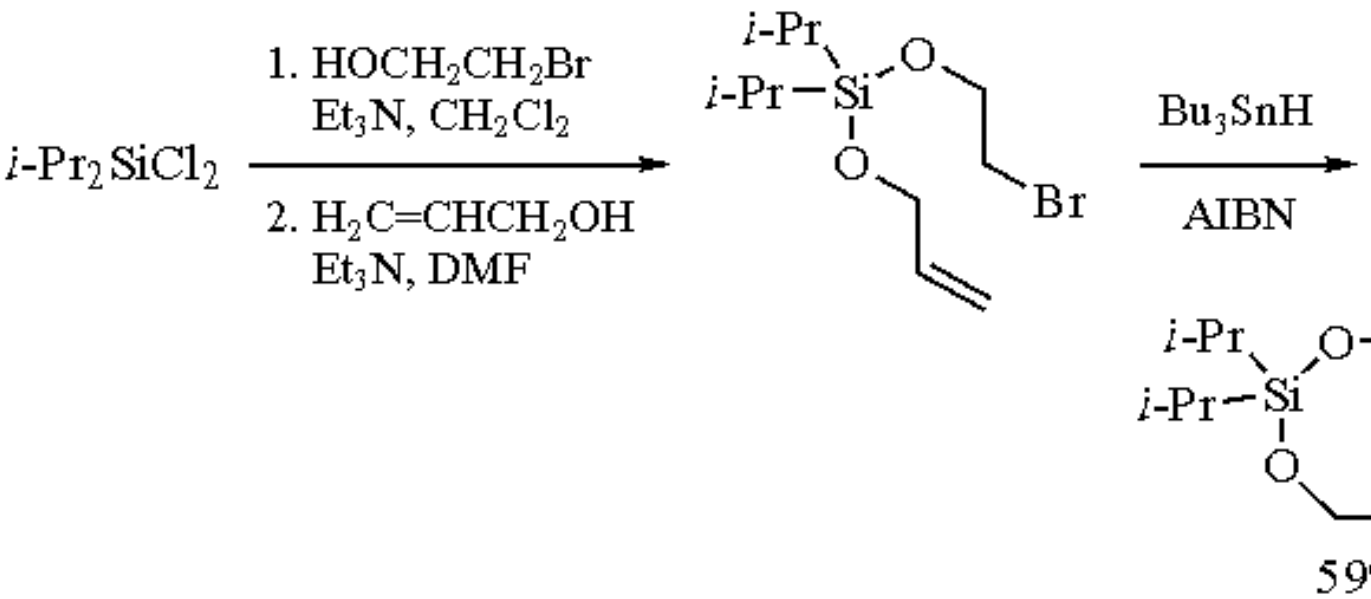

(3)

Modified Peterson Alkenation.

The Peterson alkenation is a useful method for the alkenation of carbonyl compounds. Dichlorodiisopropylsilane has been used in a Peterson alkenation modification (eq 4).[7]

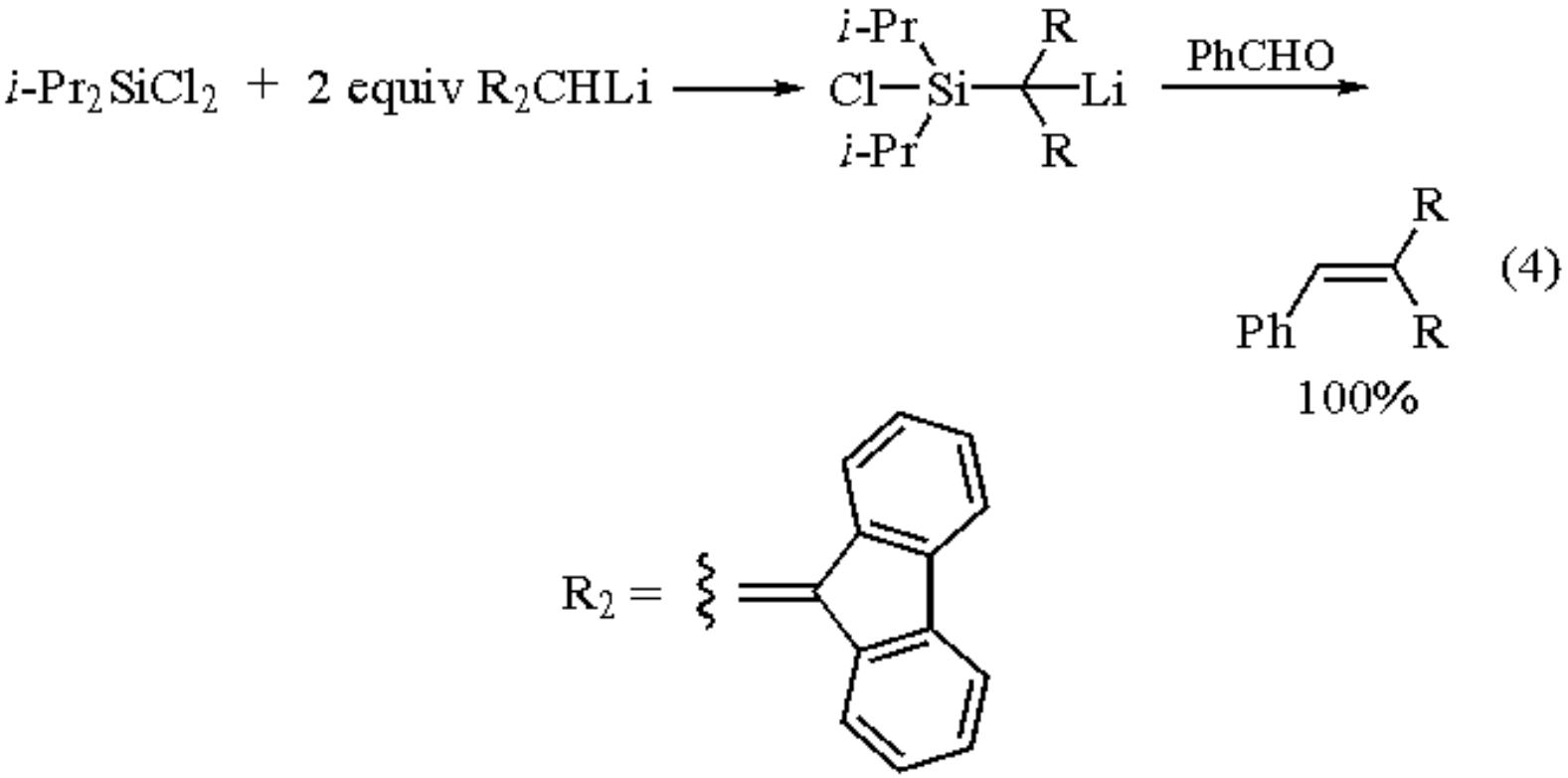

Related Reagents.

Di-t-butyldichlorosilane; ***Di-t-butylmethylsilyl Trifluoromethanesulfonate***; ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)***; ***Dichlorodimethylsilane***; ***Diisopropylsilyl Bis(trifluoromethanesulfonate)***.

---

1. Cormier, J. F.; Ogilvie, K. K. *Nucleic Acid Res.* **1988**, *16*, 4583.
2. Hurd, C. D.; Yarnall, W. A. *JACS* **1949**, *71*, 755.
3. For reviews on silylations see: (a) Klebe, J. F. *ACR* **1970**, *3*, 299. (b) Cooper, B. E. *CI(L)* **1978**, 794.
4. Furusawa, K.; Katsura, T. *TL* **1985**, *26*, 887.
5. Markiewicz, W. T. *JCR(S)* **1979**, 24.
6. Hutchinson, J. H.; Daynard, T. S.; Gilliard, J. W. *TL* **1991**, *32*, 573.
7. Couret, C.; Escudie, J.; Delpon-Lacaze, G.; Satge, J *JOM* **1992**, *440*, 233.

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Diketene[1]

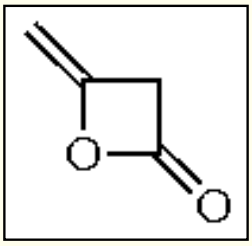

[674-82-8] · $C_4H_4O_2$ · Diketene · (MW 84.07)

(acetoacetylation reagent; acetylketene equivalent for heterocyclic synthesis)

Alternate Name: 4-methyleneoxetan-2-one.

Physical Data: mp -7.5 °C; bp 69-70 °C/100 mmHg; *d* 1.090 g cm^{-3}.

Solubility: sol most organic solvents; immiscible H_2O, hexane.

Form Supplied in: neat liquid.

Analysis of Reagent Purity: IR (2150 cm^{-1}), NMR.

Preparative Method: via dimerization of ketene.[2]

Purification: vacuum distillation.

Handling, Storage, and Precautions: lachrymator; best stored as a solid (refrigerated) in plastic containers; avoid contamination; prepare for exothermic reactions. Handle in a fume hood.

Acetoacetylation Reagent.

Diketene is most commonly used as a reagent for the acetoacetylation of nucleophiles, including alcohols, phenols, amines, anilines, thiols, and carbanions. ***4-Dimethylaminopyridine***[3] and tertiary amines are often the catalysts of choice, but sodium acetate, sulfuric acid, and a variety of other catalysts can also be used (eq 1). Amines can usually be acetoacetylated at 0-20 °C without any catalyst.

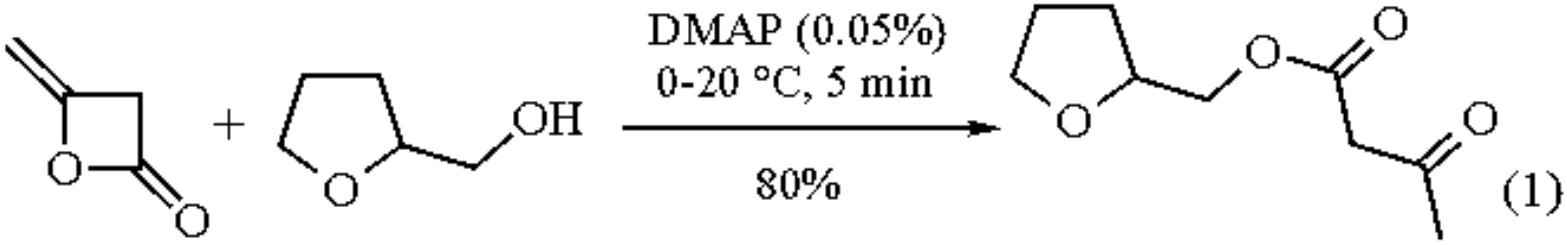

Alternate reagents for acetoacetylation include *t*-butyl acetoacetate[4] and ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one*** (the diketene-acetone adduct). Both are prepared from diketene and are less reactive but easier to handle.

Acetoacetate esters are versatile synthetic intermediates; their chemistry is more thoroughly described elsewhere.[1a,b] Acetoacetate esters can be converted into γ,δ-unsaturated ketones (via Carroll rearrangement, eq 2),[5] into a variety of heterocycles via diazotization/cyclization (eq 3)[6] or the Hantzsch pyridine synthesis (eq 4),[7] or in the direct synthesis of other heterocycles, as discussed below.

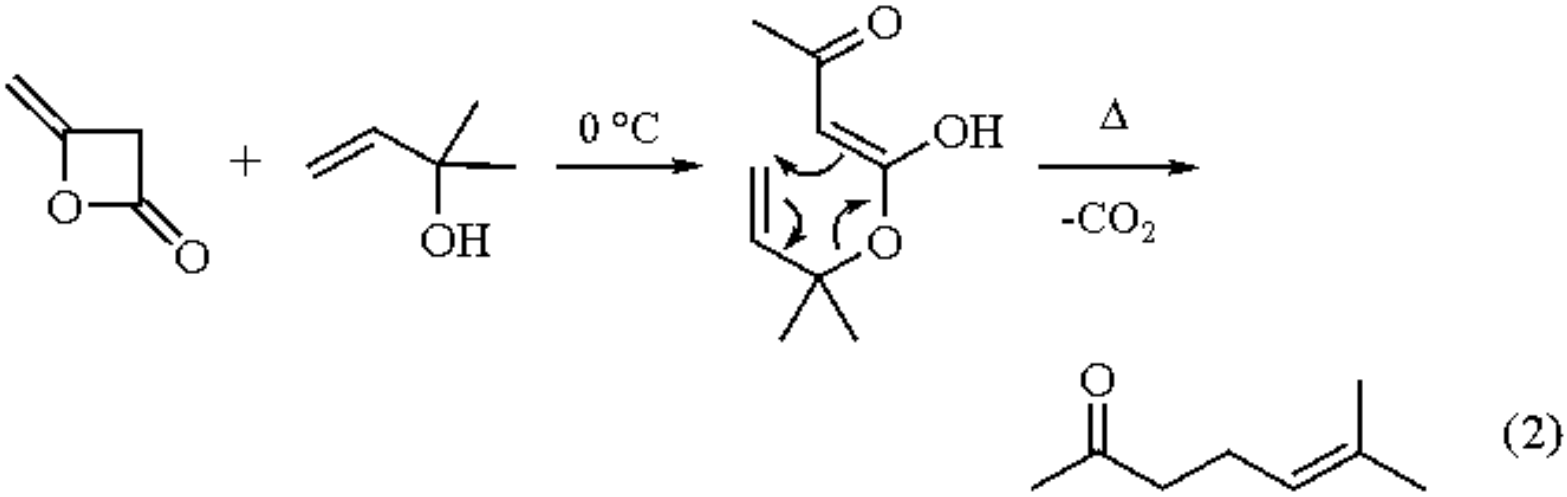

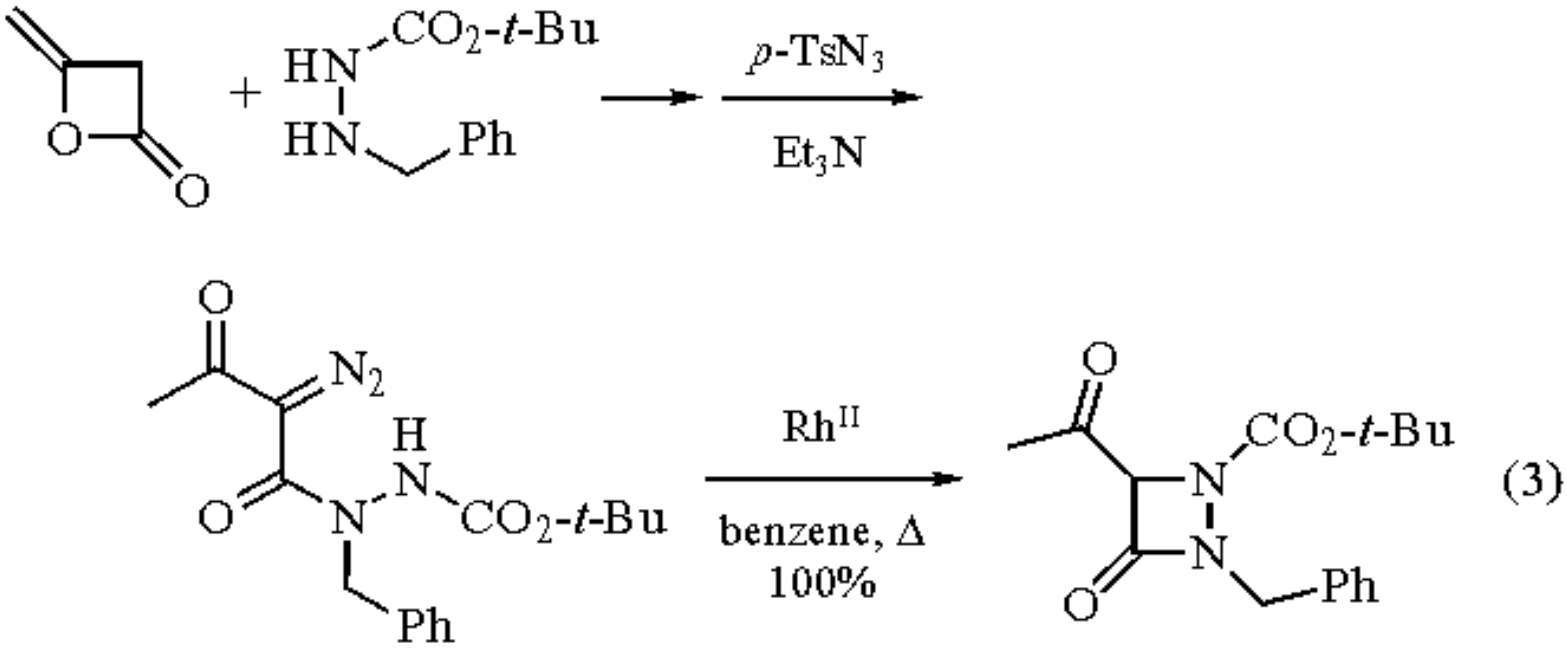

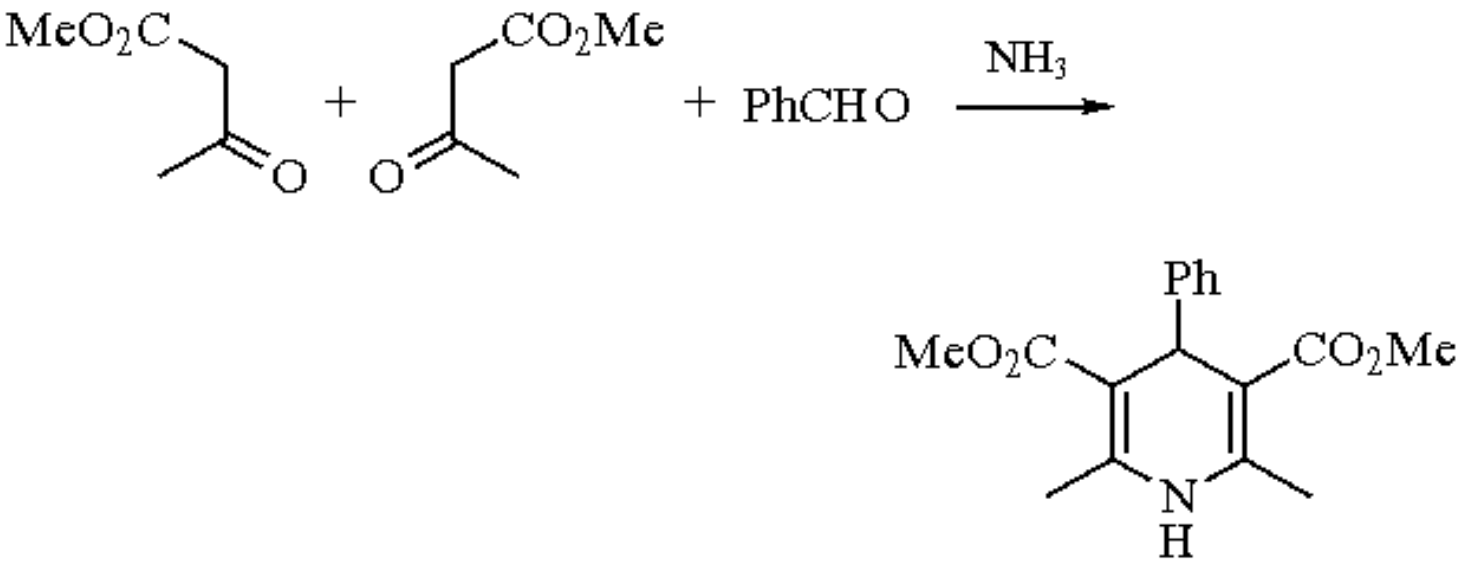

(4)

Preparation of Ketene.

Diketene is a convenient laboratory source of ketene. The dimer can be cracked at temperatures above 500 °C in a hot tube with a glowing filament (eq 5) to provide two molecules of ketene, free from the methylketene contaminant which is observed during the preparation of ketene by pyrolysis of acetone.[8]

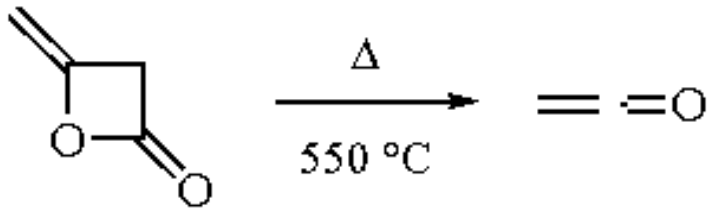

(5)

Malonic Anhydride.

The ozonolysis of diketene provides malonic anhydride, which can be trapped with nucleophiles at low temperatures to afford malonate half-esters (eq 6).[9]

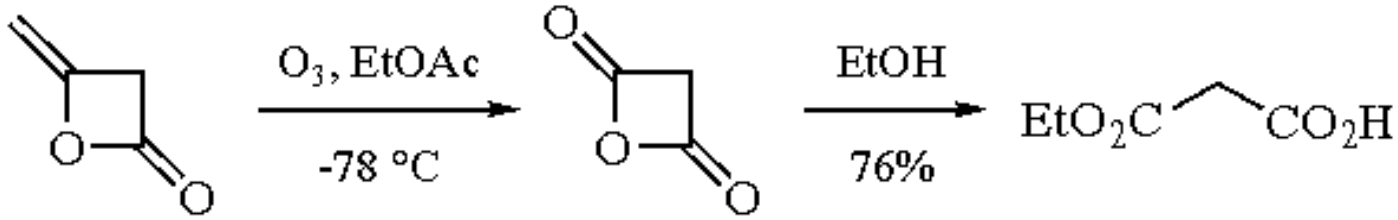

(6)

Preparation of 3-Methylenepropanoic Acids.

Grignard reagents, in the presence of specific transition metal catalysts, react with diketene to afford 3-substituted 3-butenoic acids (eq 7).[10] The process has been optimized for large-scale synthesis of 3-aryl-3-butenoic acids.[11]

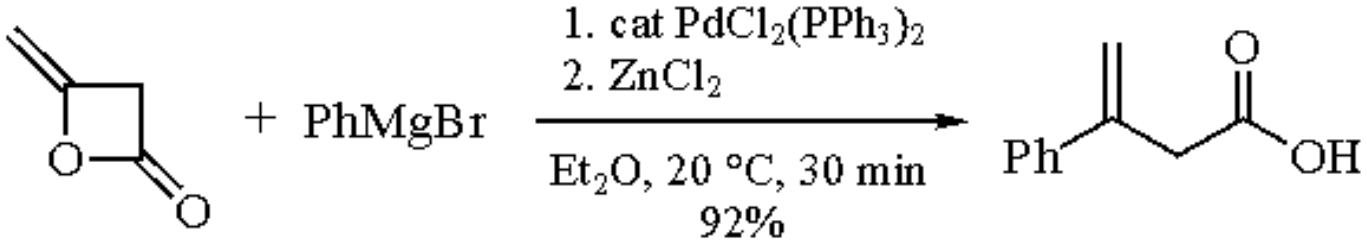

Acetoacetate Dianion Equivalent.

In the presence of ***Titanium(IV) Chloride***, diketene reacts with aldehydes in a ring opening/condensation sequence to provide 4-substituted acetoacetate esters without the need for dianion formation (eq 8).[12] Reaction with ketones requires the use of the corresponding acetals.[13]

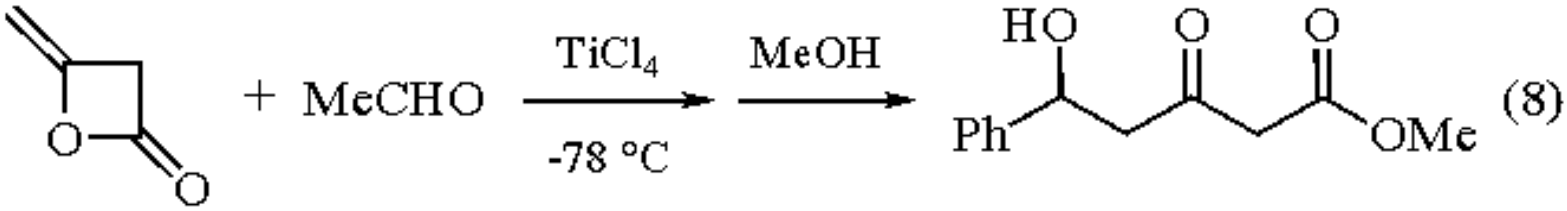

Halogenated Acetones and Acetoacetic Acid Derivatives.

Diketene reacts with hydrogen chloride or chlorine to afford acetoacetyl chloride and 4-chloroacetoacetyl chloride, respectively.[14] These compounds can be further chlorinated, initially at C-2, to provide other chlorinated materials (eq 9). This work is thoroughly described in the patent literature.[1a] Workup with alcohols provides chloroacetoacetate esters, while hydrolysis and decarboxylation can be used to prepare substituted acetone derivatives.[15]

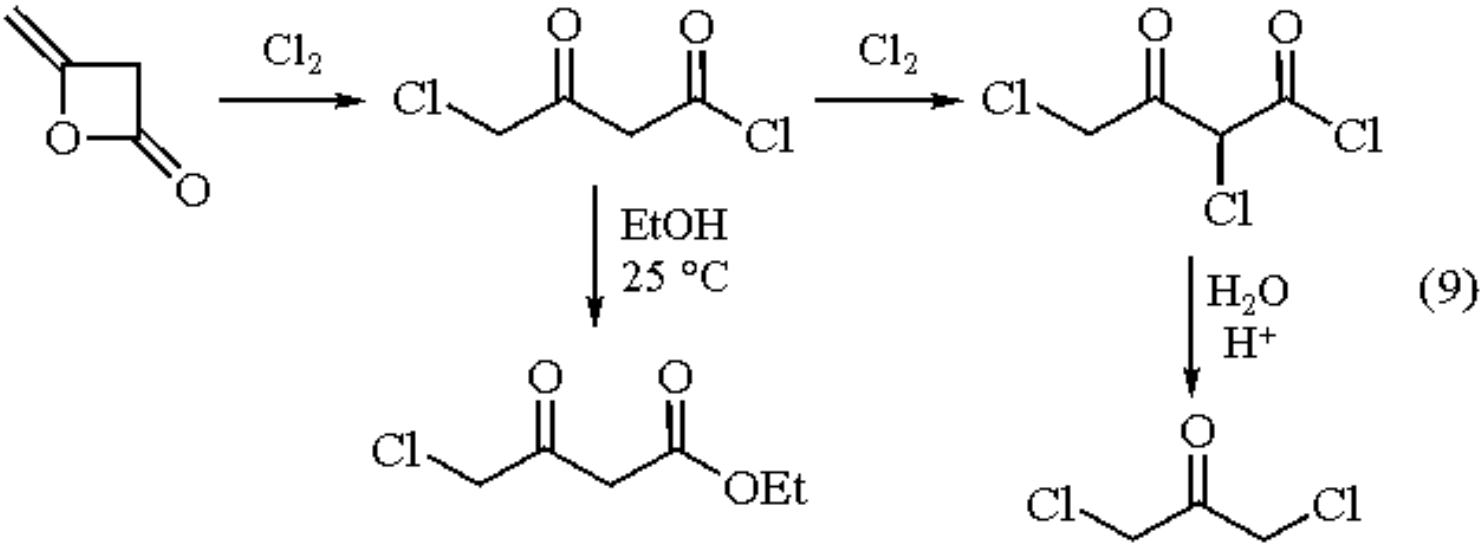

Acetone Enolate Equivalent.

The careful hydrolysis of diketene with sodium hydroxide provides sodium acetoacetate which reacts with

electrophiles at C-2 to form unstable β-keto acids; these decarboxylate on workup to provide substituted acetone derivatives (eq 10).[16]

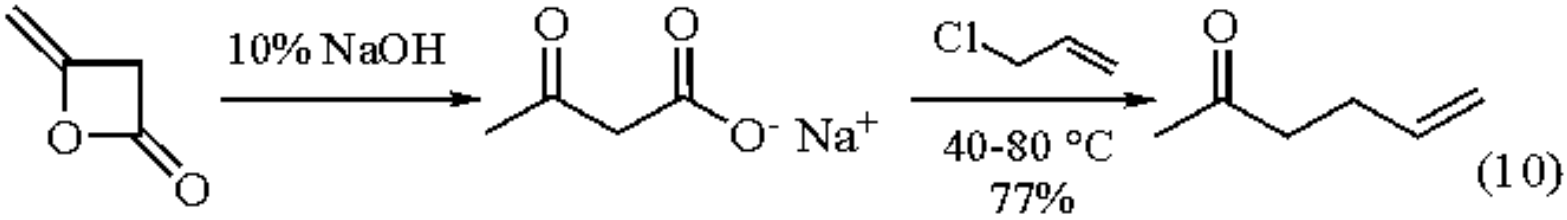

β-Butyrolactone.

β-Butyrolactone, which is a valuable reagent for the preparation of β-hydroxybutyric acid derivatives and polymers, is easily prepared by reduction of diketene over ruthenium (eq 11).[17] Enantioselective reduction processes have been developed.[18] *Caution*: β-butyrolactone is a known carcinogen.

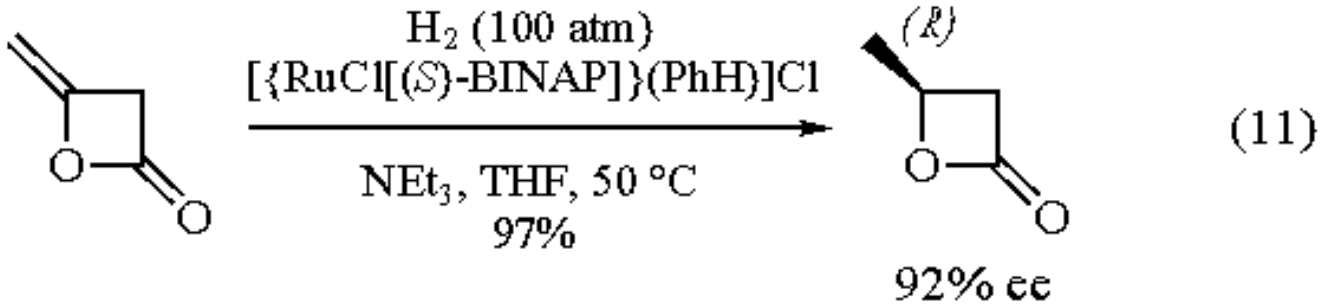

4-Substituted Acetoacetic Acid Derivatives: Radical, Carbene, and [2 + 2] Photocycloaddition.

Radical and carbene additions, and photochemical [2 + 2] reactions of diketene, all involve the exocyclic methylene group of the diketene molecule. Carbene[19] and nitrene[20] additions (eq 12), as well as photocycloaddition (eq 13),[21] give spirocyclobutyrolactones. Ring opening these spirocyclic butyrolactones provides a synthesis of 4-substituted acetoacetates.

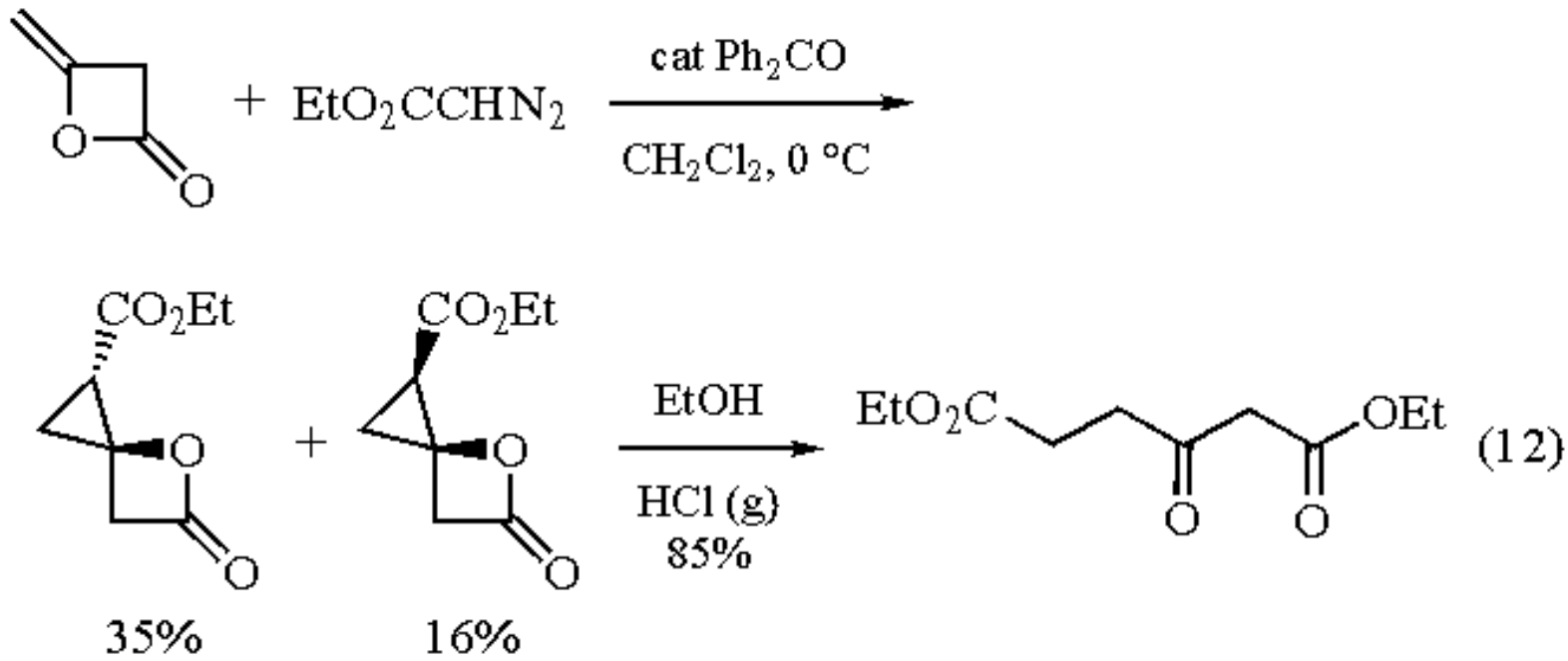

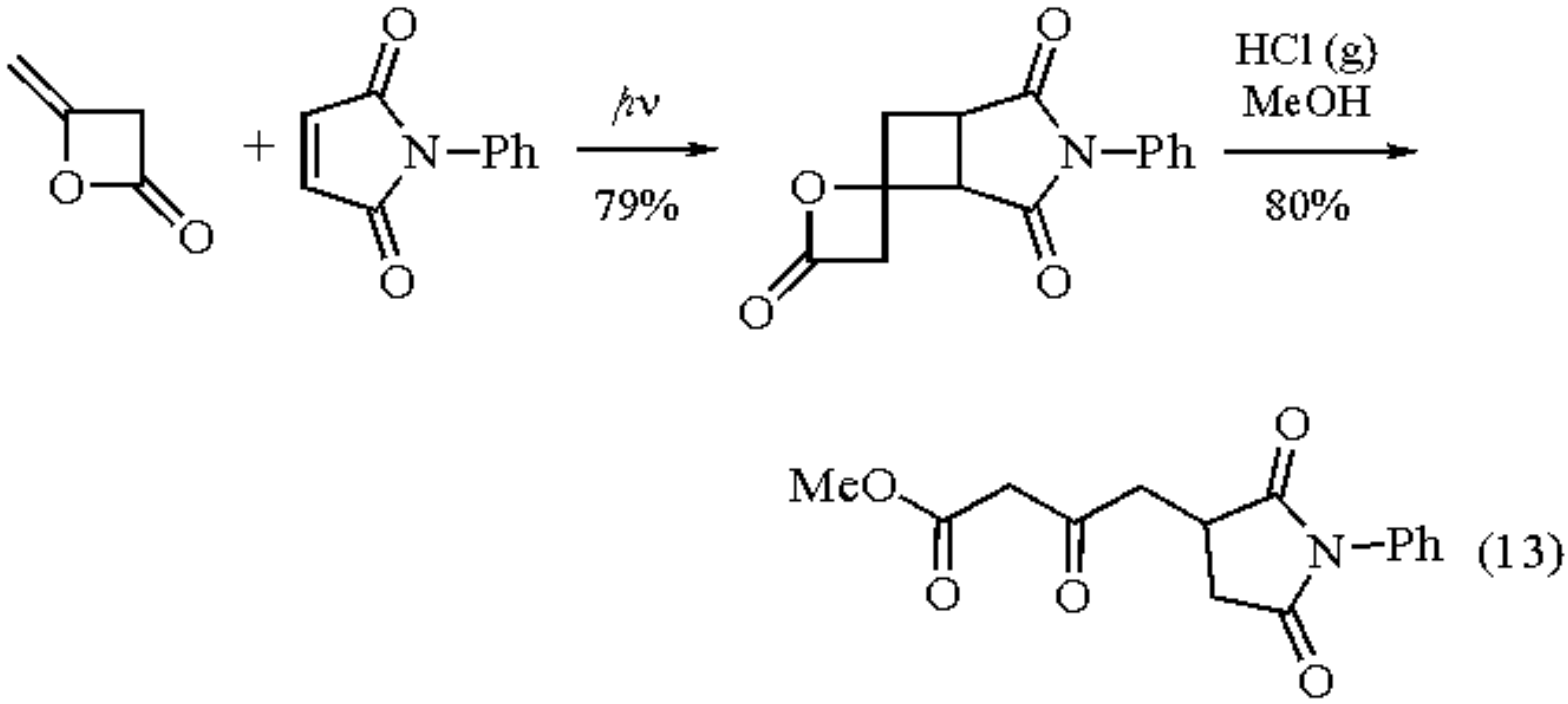

Likewise, radical addition to the double bond of diketene provides routes to substituted β-lactones and acetoacetic acid derivatives (eq 14).[22]

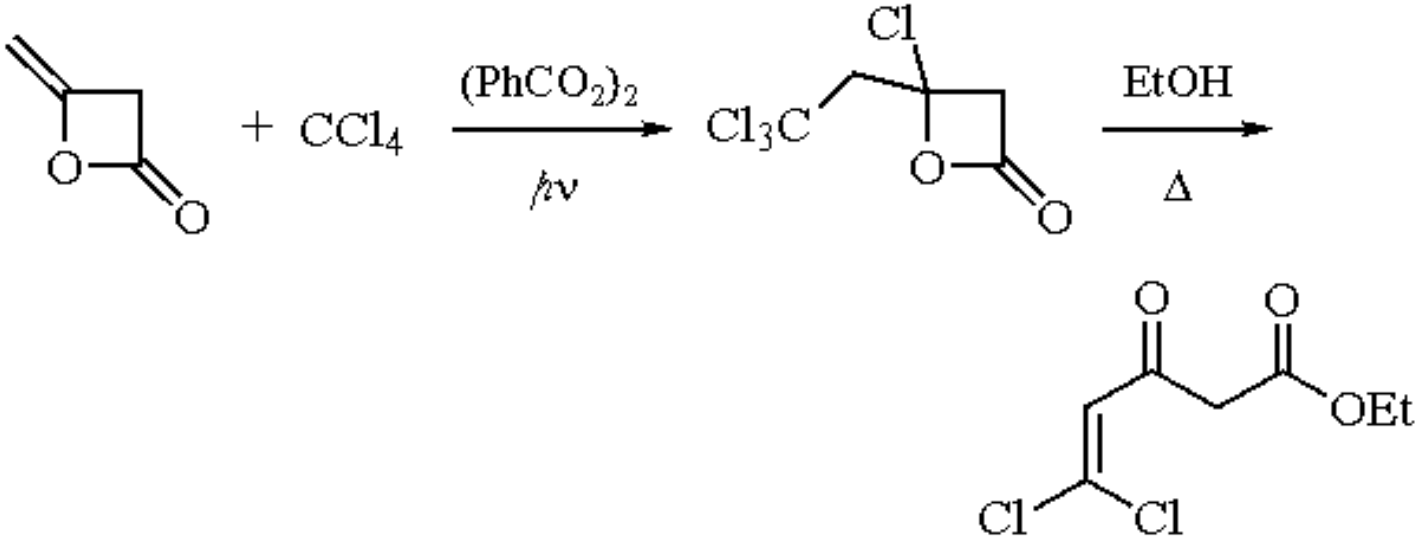

(14)

Preparation of Heterocycles.

Diketene is used extensively for the preparation of heterocycles. The products can often be predicted by viewing diketene as an acetylketene equivalent. A leading example is provided for each of several types of heterocyclization; many other substrates react analogously. The reader is referred to more detailed reviews for further discussion.[1,23]

Pyrone and Pyridone Formation via Acetoacetylation of an Active Methylene Group: Dehydroacetic Acid.

The fungicide dehydroacetic acid is prepared via the base-catalyzed dimerization of diketene (eq 15),[1a,24] which is based upon the acetoacetylation of the activated methylene group of a ring-opened diketene molecule. Other 4-pyrones are similarly formed when diketene reacts with compounds containing active methylene groups.[25]

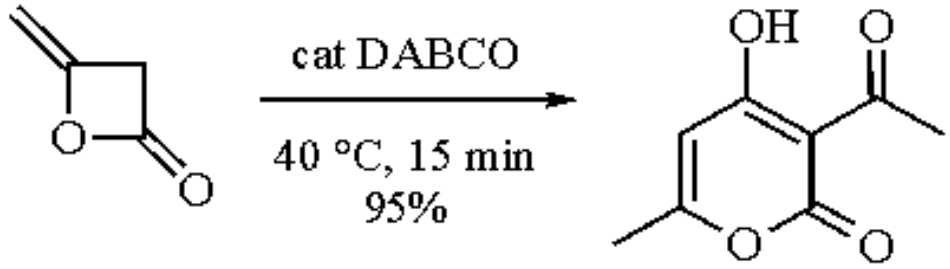

(15)

Likewise, diketene reacts with simple enamines to afford pyrones (eq 16).[26] Enamides, however, more commonly provide pyridones upon treatment with diketene (eq 17).[27] Because of the multiple functional groups normally present during heterocyclic synthesis with diketene, several different products can often be produced, depending on the reaction conditions.

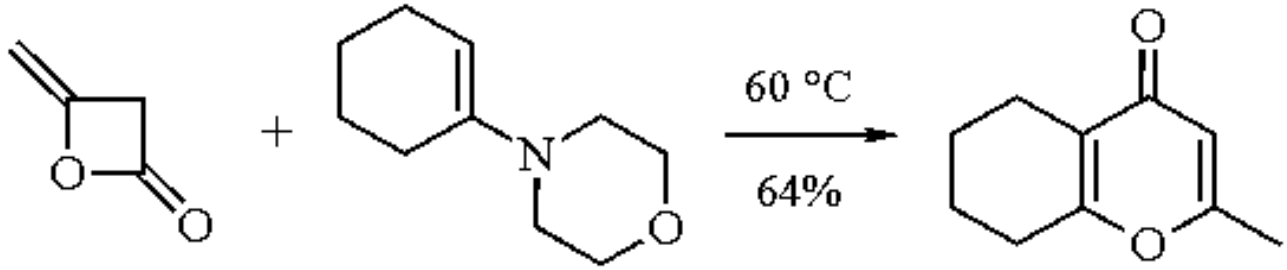

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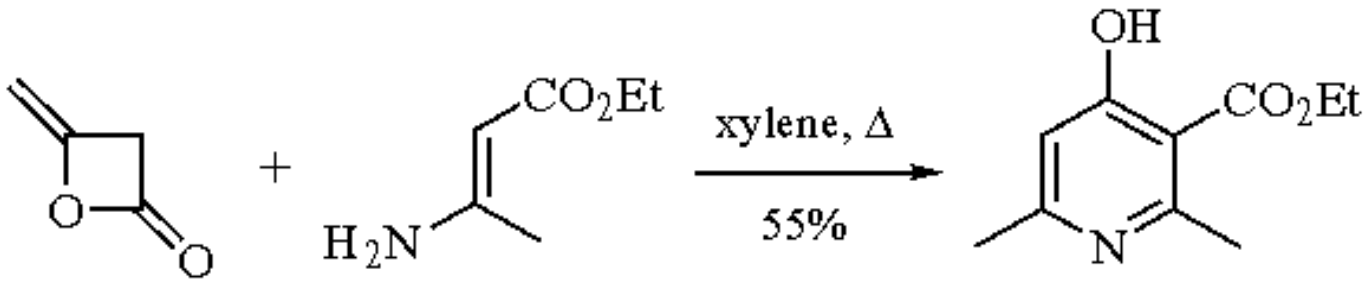

(17)

6-Methyluracil.

The reaction of diketene with urea to afford 6-methyluracil (eq 18) is one of the classic heterocyclic syntheses which utilizes diketene;[28] many analogous heterocycles can be prepared by reaction of bisnucleophilic species with diketene.

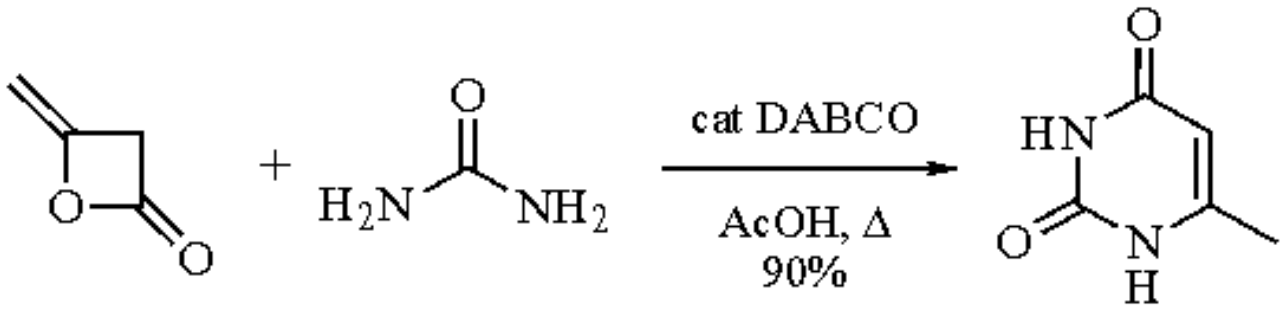

(18)

Preparation of Furanones (Butenolides) and Pyrrolidinones.

Diketene acetoacetylates α-hydroxy ketones[29] and α-hydroxy acids,[30] and α-amino ketones[31] and acids,[32] which undergo intramolecular condensation to afford five-membered heterocycles as shown (eqs 19 and 20).

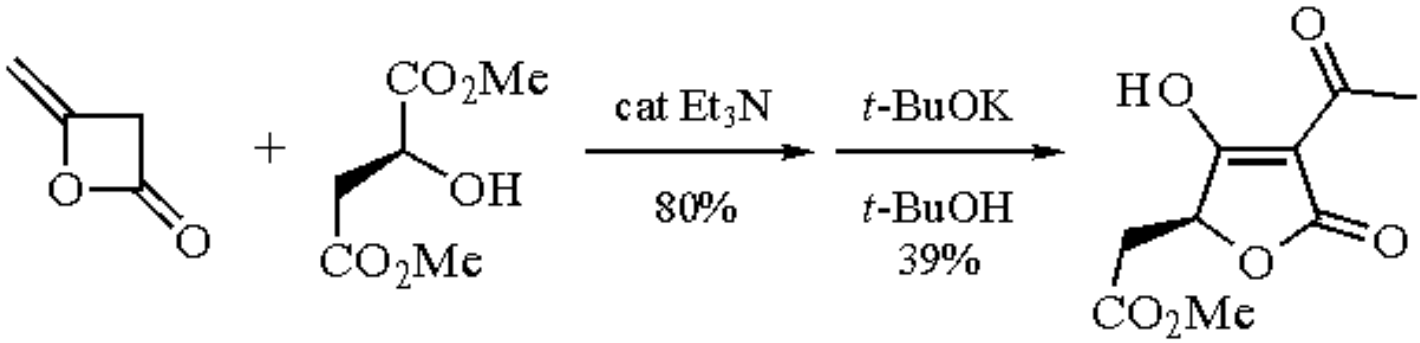

(19)

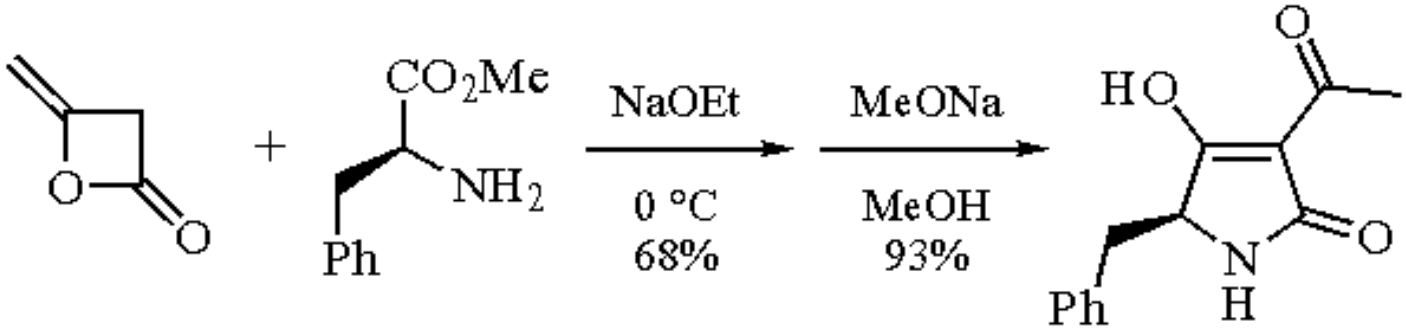

(20)

β-Lactams.

The imidazole-promoted reaction of imines with diketene can be used to prepare β-lactams (eq 21).[33]

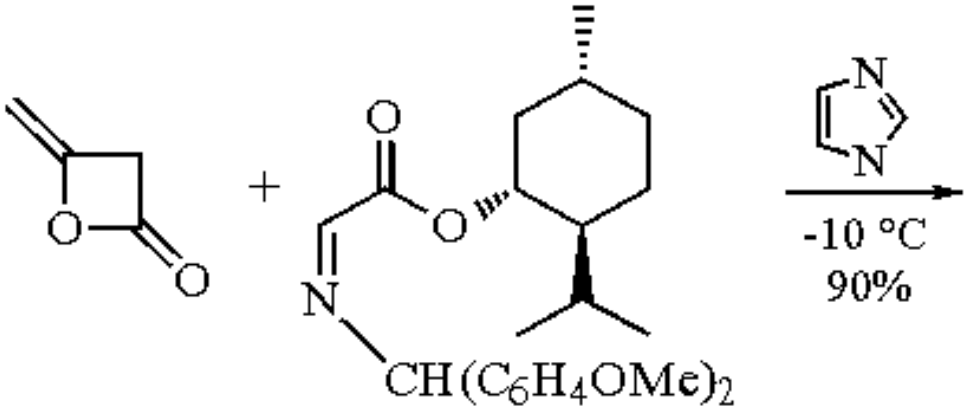

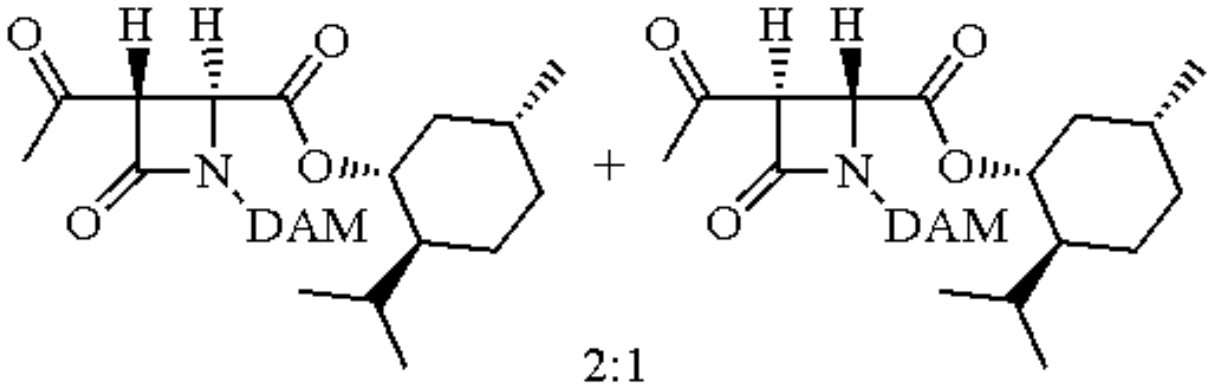

(21)

Related Reagents.

Acetoacetic Acid; ***Ethyl Acetoacetate***; ***Ethyl 4-Chloroacetoacetate***; ***Methyl Dilithioacetoacetate***; β-***Methyl***-β-***propiolactone***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

---

1. (a) Clemens, R. J. *CRV* **1986**, *86*, 241. (b) Clemens, R. J.; Witzeman, J. S. In *Acetic Acid and Derivatives*; Dekker: 1993; p 173. (c) Boese, A. B., Jr. *Ind. Eng. Chem.* **1940**, *32*, 16. (d) Bormann, D. *MOC* **1968**, *7*, 53.
2. William, J. W.; Krynitsky, J. A. *OSC* **1955**, *3*, 508.
3. Nudelman, A.; Kelner, R.; Broida, N.; Gottlieb, H. E. *S* **1989**, 387.
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Robert J. Clemens

Dilithioacetate[1]

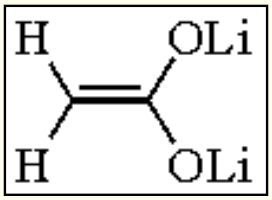

[31509-80-5] · $C_2H_2Li_2O_2$ · Dilithioacetate · (MW 71.92)

(metalated species used to elaborate or functionally substitute the α-carbon of carboxylic acids;[3] useful for highly substituted examples;[4] possible alternatives for the malonic ester synthesis and the Haller-Bauer, Reformatsky,[23] and Wittig[28] reactions)

Physical Data: colorless solid.

Solubility: slightly sol THF; reacts with H_2O, air (O_2, CO_2), and protic solvents. Ethylene glycol-based solvents may react with lithium amides from which the dianions are formed. Dianions derived from disubstituted acetic acids are soluble in THF; less sol other ether solvents. Most carboxylate dianions are stable up to the boiling point of THF.

Formation and Reactivity.

The metalation of carboxylic acids is a general phenomenon and many aliphatic, alicyclic, araliphatic, and functionally substituted acetic acids have been used in various applications.[1] The intermediate carboxylate dianions are commonly generated by one of four methods: (1) a carboxylic acid and 2 equiv of lithium (sodium) naphthalenide[2] or preferably (2) 2 equiv of LDA;[3] (3) a carboxylate salt and 1 equiv of LDA;[4] (4) a metathetical reaction of a dilithium carboxylate dianion and a metal halide. The more traditional method of reacting 2 equiv of a Grignard reagent with carboxylic acids (Ivanov reagents[1e]) is restricted to examples in which the carboxylate α-protons are relatively acidic, principally arylacetates (pK_a <= 22).[5]

Accordingly, carboxylate dianions have been formed (method 3) from ***Lithium Diisopropylamide*** and Li, Na, K, Ca, Mg, and Zn carboxylates. Metathesis of dilithium dianions with ***Copper(I) Iodide***, ***Zinc Chloride***, and several other metal halides produced carboxylate dianions with more selective reactivity.[6-8] Monosubstituted acetic acids yield dilithium or lithium-sodium dianions with limited solubilities, presumably due to polymeric aggregation of the metalated species.[9,10] HMPA has been recommended as cosolvent.[9] Monosubstituted acetic acids with bulky substituents (Ph, *t*-Bu) and disubstituted acetic acids form soluble (THF) dianions. Glycol ether solvents may react with LDA and THF is preferred.[11,12] LDA is preferred as base[1c] and, although more hindered bases[13] may be necessary for special applications, amines from less hindered lithium amides can react competitively with some electrophiles (TMSCl).[11] The lithium amide of hexamethyldisilazane is not sufficiently basic (pK_a &egt; 26 (THF))[14] for general use

(LDA, pK_a &egt; 36 (THF)).[15] In examples where the carboxylate dianion is soluble, as little as 3 mol % of the amine can be used for metalation (eq 1).[1c] The latter is a useful variation for reactions with highly reactive electrophiles where diisopropylamine might compete for electrophiles (acylation).[16]

$$Me_2CHCO_2Na + LDA \xrightarrow[25\text{-}30\ ^\circ C]{BuLi} i\text{-}Pr_2NH + [Me_2CCO_2]^{2-}\ Li^+Na^+ \quad (1)$$

Unsaturated carboxylic acids as their Cu dianions react selectively at the γ-rather than the α-position with allyl bromide and vinylic epoxides[6,7] The reaction occurs by an S_N2' process and the yields and selectivity are impaired with substituted allyl bromides. Other electrophiles react poorly; however, unsaturated ketones react with the Cu dianion of acetic acid[8] predominantly by 1,2-addition.

LDA or LTBA metalation of Zn or Mg carboxylates offers considerable promise because they are soluble.[17,18] Small, aliphatic carboxylic acids, aromatic, and arylacetic acids form crystalline zinc carboxylates as their TMEDA complexes which are soluble in THF and hot toluene (eq 2). Butyric acid and larger aliphatic zinc carboxylates are soluble in hot toluene without TMEDA. The lithium amide displaces TMEDA as ligand on metalation and an additional equivalent abstracts the α-protons (eq 3). Reaction with carbonyl compounds provides adducts in yields equivalent to the Reformatsky reaction (eq 4). This metalated species is especially useful for acetic and propionic acids. Unlike alkali metal dianions, alkylation is not selective and disubstituted products are formed except when activating substituents are present (R = Ph). Like *t*-butylacetate anion,[19,20] alkylation of acetic acid dianion (**1**) (R = H) fails in the absence of dipolar solvents.

$$RCH_2CO_2H + ZnO + TMEDA \xrightarrow[90\text{-}95\%]{\Delta,\ toluene} [RCHCO_2]_2Zn \cdot TMEDA \quad (2)$$

$$[RCHCO_2]_2Zn \cdot TMEDA + 4\,LTBA \longrightarrow [(RCHCO_2)_2Zn\,(NH\text{-}t\text{-}Bu)_2]^{4-}\ 4Li^+ \quad (3)$$

R = Me, H

(1)

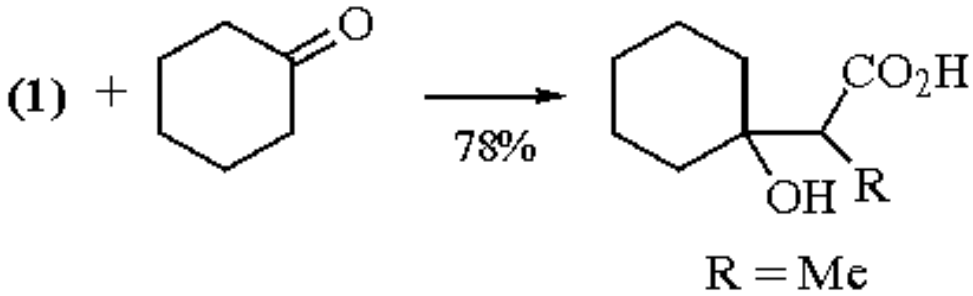

(4)

Reactions with Electrophiles.

Carboxylate dianions have been treated with many electrophiles,[1] but reactions with alkyl halides and carbonyl compounds have been used most widely. Most common carboxylate dianions have been reported to react successfully except acetic acid and cyclopropanecarboxylic acids where carboxyl derivatives must be used with few exceptions.[21] Carboxylate dianions are especially useful where forcing conditions are required, as in reactions with epoxides,[22] or in reactions with carbonyl substrates where hydrolysis of a carboxyl derivative causes product degradation.[23] Carbonyl addition is sensitive to steric effects, but steric hindrance must be severe to prevent adduct formation (eq 5).[23] The adduct may cyclize spontaneously on isolation, forming a β-lactone in highly constrained examples.[23b]

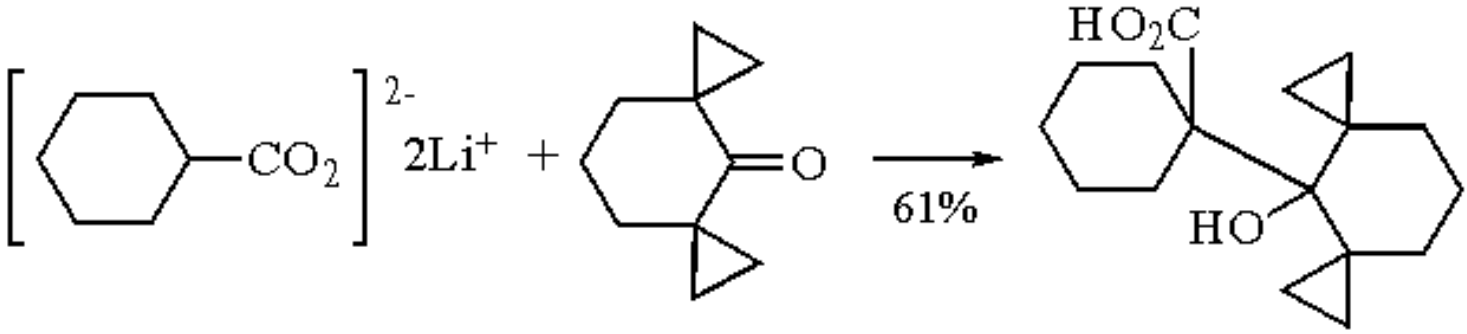

(5)

A *C*-silylated analog, the trimethylsilylacetic acid dianion (**2**), forms carbonyl adducts which undergo spontaneous Peterson elimination (eq 6).[24] Mixtures of (*E*) and (*Z*) products are obtained. The limited accessibility of (**2**) has been overcome by use of a softer, *C*-silylating reagent (eq 7)[25]

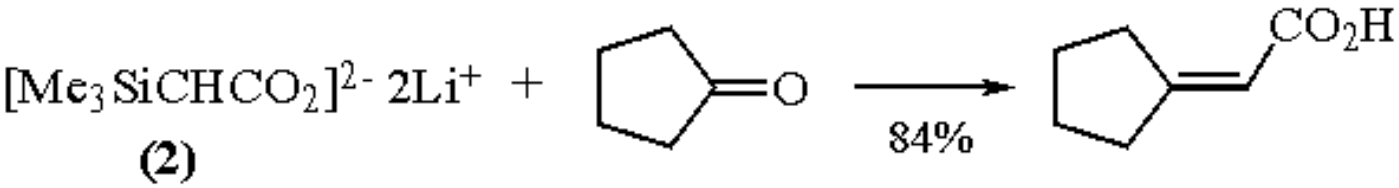

(6)

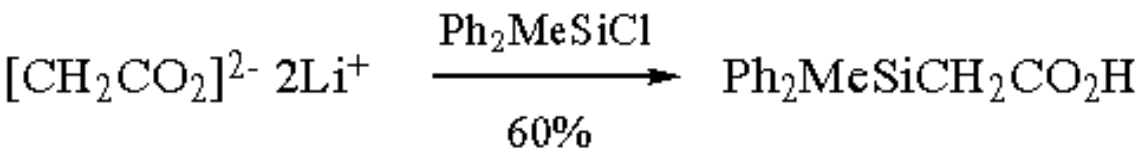

(7)

Unsaturated carboxylate dianions have been used to demonstrate the reversibility of carbonyl addition. The α:γ ratio of adducts depends on the metal ion, temperature, solvent polarity, time, and steric effects (eqs 8 and 9).[26] Reaction with

aldehydes gives *threo* products predominantly, and the *threo*:*erythro* ratio can reach 49:1 if the substituents are sufficiently large and thermodynamic conditions are used (eq 10).[27] The major *threo* isomer (**5**) can produce either *trans* (**8**) or *cis* (**9**) alkene in many cases (eqs 11 and 12). Formation of β-lactone (**7**) is a general reaction[28] and *cis* elimination of carbon dioxide makes this sequence a useful alternative to the Wittig reaction.[28] Use of DMF acetals or DEAD effects an *anti* elimination through a charged intermediate and produces (*Z*)-alkene (**9**).[29] Lactones (**7**) can be alkylated stereospecifically (eq 13) if the lactone is sufficiently stable.[30,31] Combination of these procedures allows substantial control to be exercised over syntheses of di- and trisubstituted alkenes.

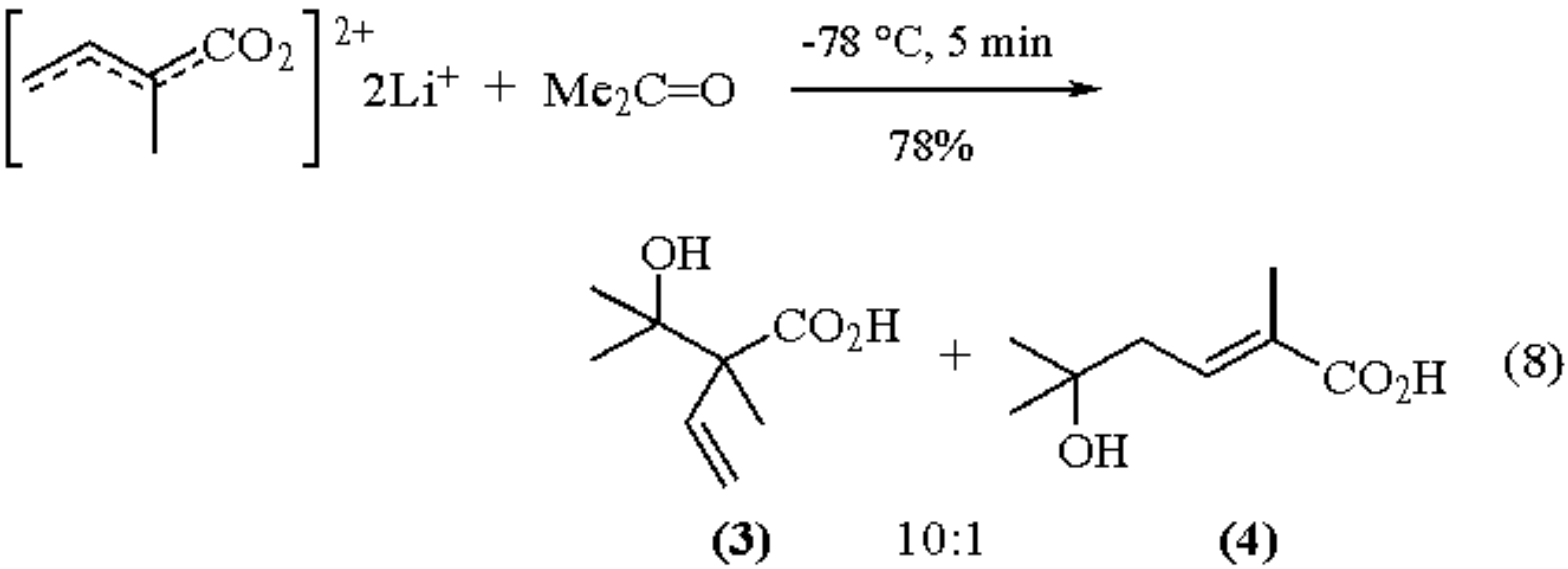

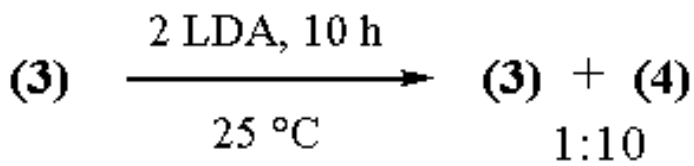

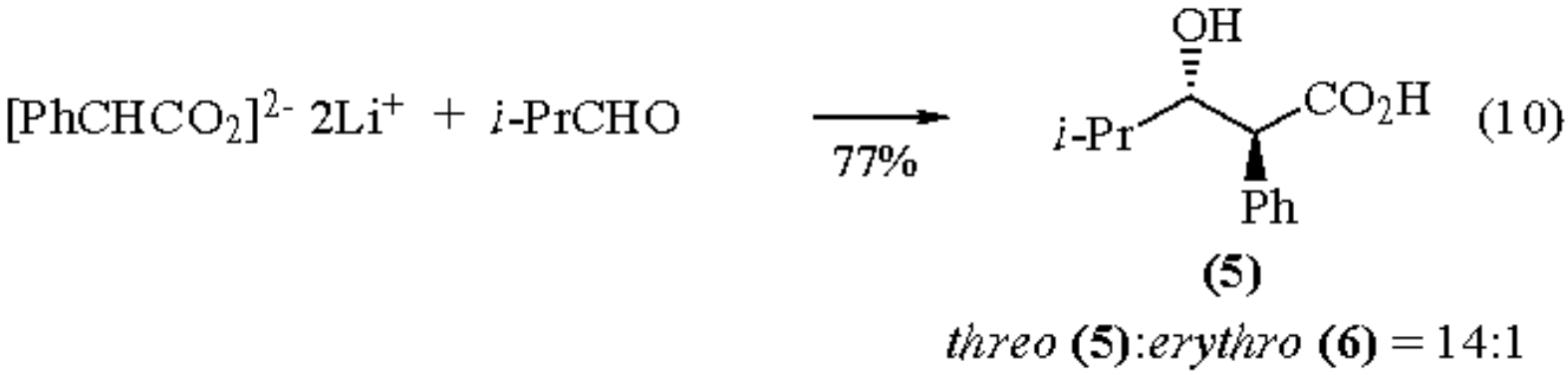

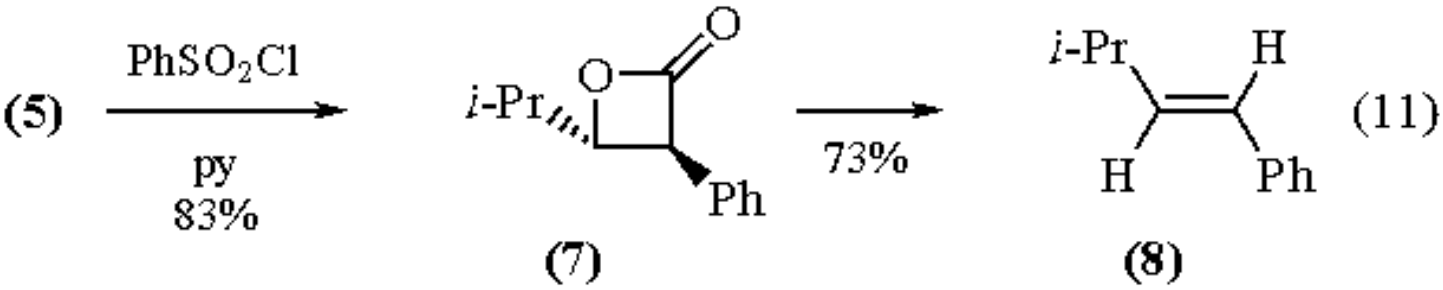

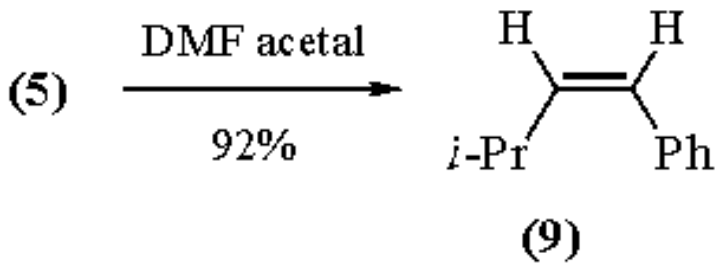

(12)

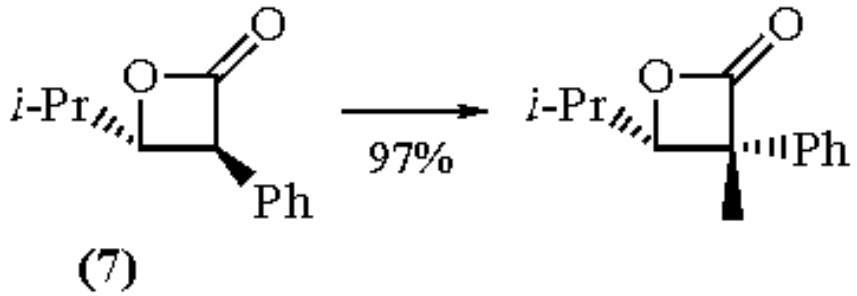

(13)

Alkylation of carboxylate dianions in which one cation is lithium and the other an alkali metal is a simple synthetic operation.[1] Many primary and secondary halides (tosylates) have been used and success is independent of the leaving group and the order of introduction of the substituents.[1c] Further, successful reaction does not depend on obtaining a homogeneous solution of the dianion. Simple functionally substituted (ethers, double bonds, acetals, carboxylates) alkylating agents can be accommodated. Alkyl halides sensitive to elimination proceed normally unless steric hindrance in the dianion is extreme.[4] The stability of carboxylate dianions is important in uses with epoxides[22] or acylaziridines[32] where extended reaction times or forcing conditions may be necessary (eq 14). The scale and low temperatures are not important requirements. The production of the hypolipidemic agent gemfibrozil uses typical reaction conditions (eq 15).[1 7,33]

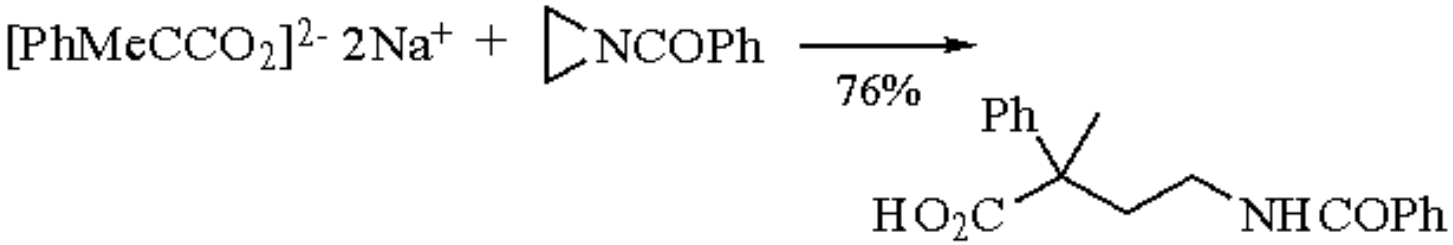

(14)

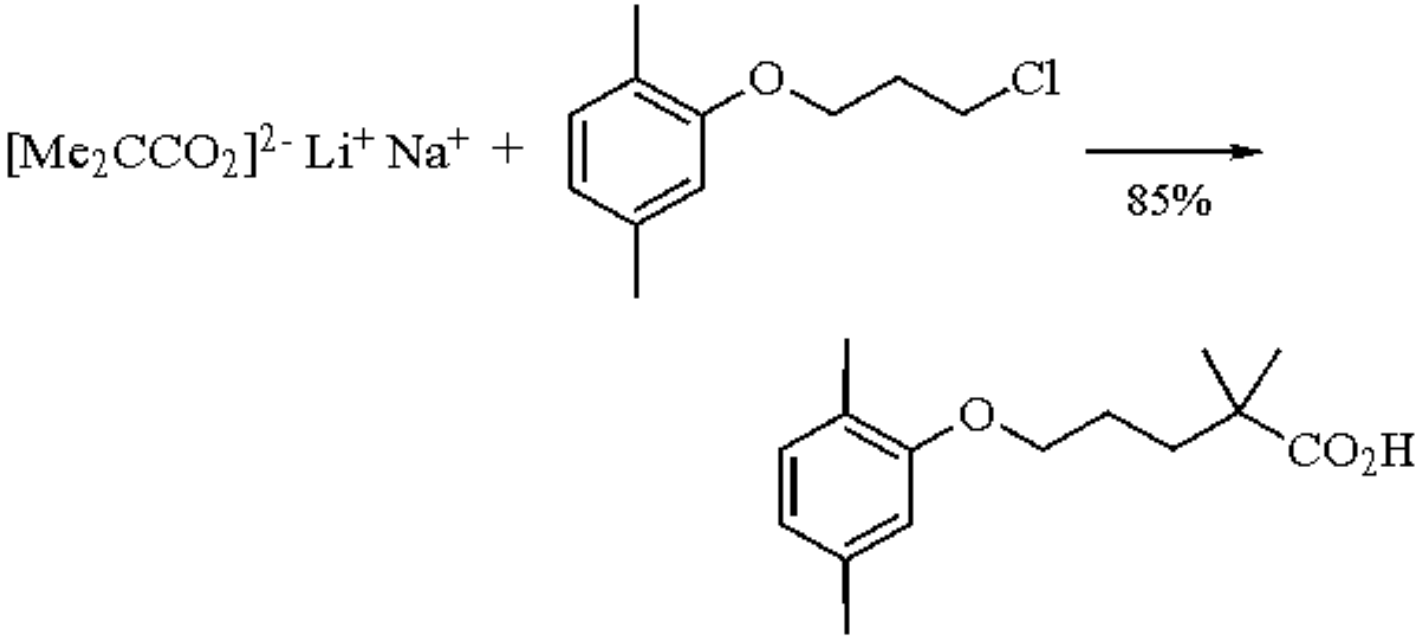

(15)

Chiral Syntheses.

Asymmetric syntheses with carboxylate dianions requires a chiral amide that can also act as a chiral auxiliary by remaining associated with the dianion without being covalently bonded to it. Carbonyl addition gave as much as 85% ee in a carefully chosen model (eq 16).[34] Alkylation is much less stereospecific than carbonyl addition and it proved to be much less selective in the formation of a chiral product (eq 17).[35]

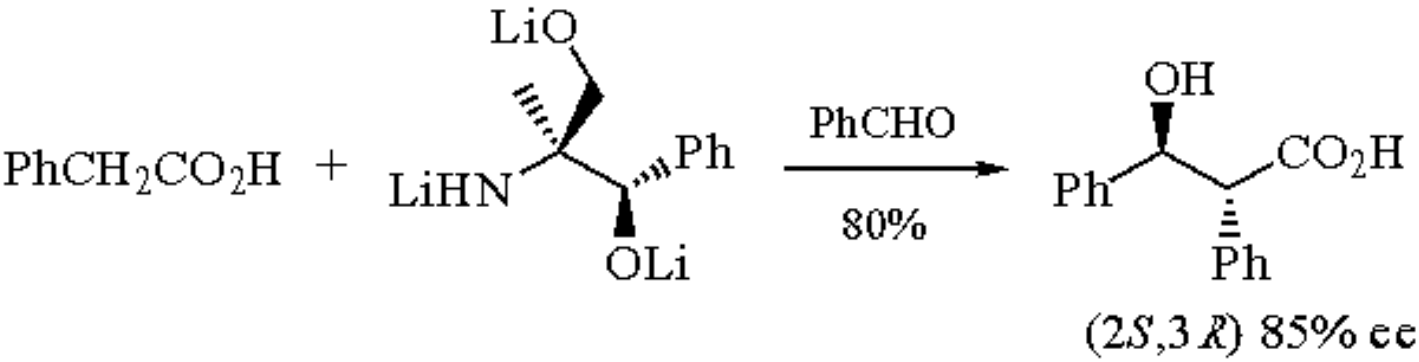

(16)

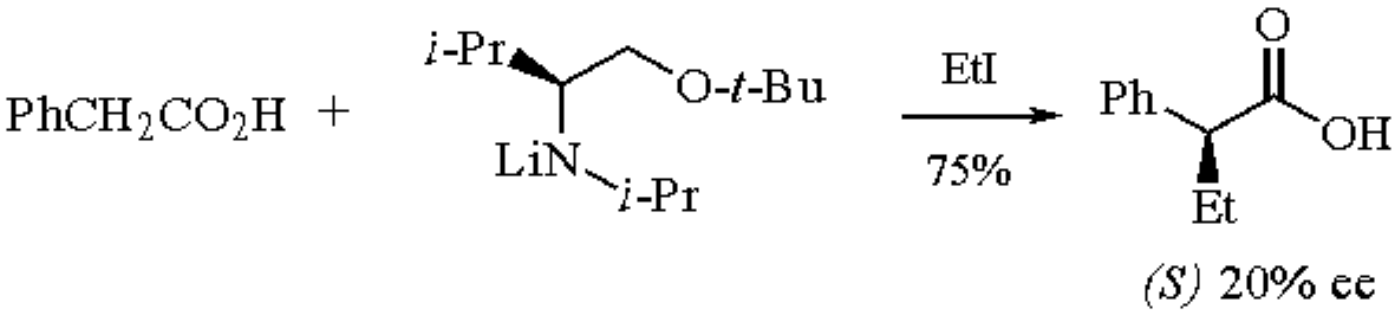

(17)

Related Reagents.

t-Butyl α-Lithiobis(trimethylsilyl)acetate; ***t-Butyl α-Lithioisobutyrate***; ***t-Butyl Trimethylsilylacetate***; ***2,6-Dimethylphenyl Propionate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl Trimethylsilylacetate***; ***2-Methyl-2-(trimethylsilyloxy)-3-pentanone***; ***Trimethylsilylacetic Acid***.

---

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1,4-Dilithiobutane[1]

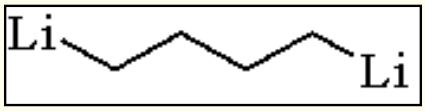

[2123-72-0] · $C_4H_8Li_2$ · 1,4-Dilithiobutane · (MW 69.99)

(converts various functional groups into cyclopentanes and synthetic metallacyclopentane intermediates; useful synthon for preparing α,o-bifunctional compounds; precursor of other organobimetallic reagents)

Alternate Name: 1,4-butanediyldilithium.

Solubility: sol ether, THF, hydrocarbons.

Form Supplied in: generally prepared in ether and used in solutions which range from 0.5 to 1.2 M.

Analysis of Reagent Purity: titration;[2,3] ^{1}H NMR: α-CH_2 signals at δ -0.8 to -1.1 ppm;[4] quenching with chlorotrimethylsilane;[2,3,5] GLC.[6]

Preparative Method: see ***1,5-Dilithiopentane***.

Handling, Storage, and Precautions: solutions are highly flammable and must be stored and handled in the absence of proton sources, carbon acids, and oxygen. Flasks and Schlenk tubes should be flushed with dry Ar or N_2. At -20 °C, ether solutions have a useful life of 1 to 4 months.[5,7] At higher temperature (~30 °C), organolithiums react readily with ethers.[8]

Structure.

MO calculations suggest for 1,4-dilithiobutane a doubly bridged structure which is 34.6 kcal mol^{-1} more stable than the extended form (eq 1).[9] That structure, along with others,[1a] would be responsible for the relative stability of the reagent.

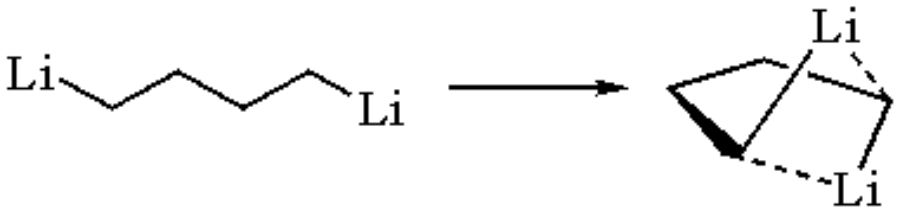

(1)

Synthetic Applications.

Organolithium and organomagnesium bifunctional compounds usually react with various carbon electrophiles and metal halides in a comparable manner, whether as such or as biscuprates, and are often used interchangeably. However, because of a generally more convenient method of preparation, di-Grignard reagents are more widely used in organic synthesis (see ***1,4-Bis(bromomagnesio)butane*** and ***1,5-Bis(bromomagnesio)pentane***).

Cyclopentane Derivatives.

1,4-Butanediyldilithium can directly lead to cyclopentane derivatives by consecutive additions to dielectrophiles such as esters, lactones, and anhydrides, to give 1-substituted cyclopentanols. This annulation strategy has been successfully used for the synthesis of spiro compounds. Thus a spirobutenolide is readily prepared from 1-ethoxy-2,5-dihydrofuran-2-one and 1,4-dilithiobutane (eq 2).[10]

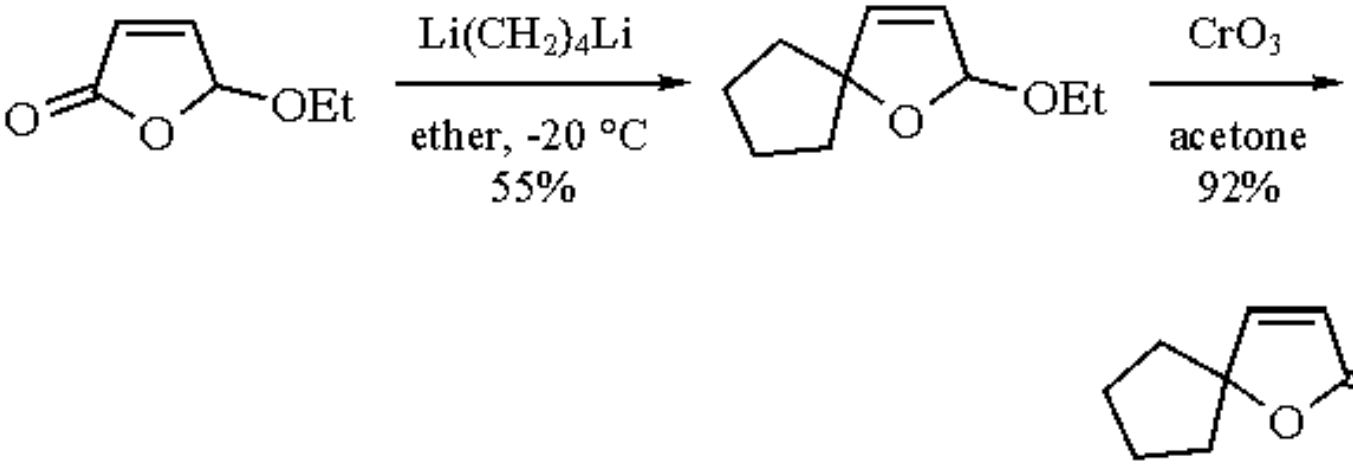

(2)

Organobiscuprates.[11]

1,4-Dilithiobutane, as organobiscuprate, reacts directly with ***Carbon Monoxide*** to give cyclopentanone, but yields are low (eq 3).[12] For the formation of cycloalkanones, the reaction between a metallacycle and carbon monoxide is much more efficient (see eq 5, below).

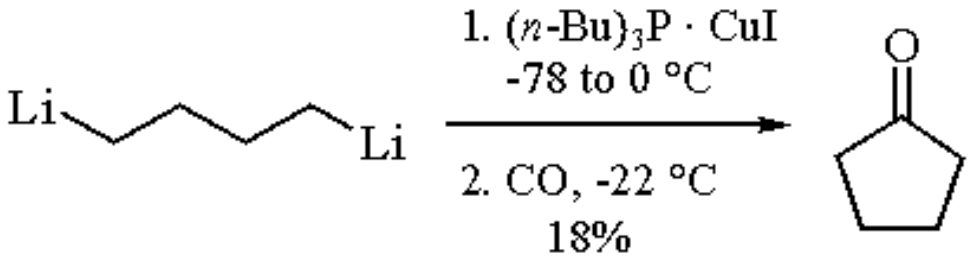

(3)

In presence of ***Phenylthiocopper(I)*** (2 equiv),[13] 1,4-dilithiobutane affords the corresponding organobis(heterocuprate), as formulated in eq 4, which reacts with β-bromocyclopent-2-en-1-one, 3-chlorocyclohex-2-en-1-one, and 3-chloro-5,5-dimethylcyclohex-2-en-1-one to form spiro[4.4]nonan-2-one, spiro[4.5]decan-7-one, and 9,9-dimethylspiro[4.5]decan-7-one (eq 4), respectively, in excellent yields.[14] This annulation methodology was applied to 3-bromo-2-methylcyclopent-2-en-1-one and 3-chloro-2-methylcyclohex-2-en-1-one to form 1-methylspiro[4.4]nonan-2-one and 6-methylspiro[4.5]decan-7-one with similar results.

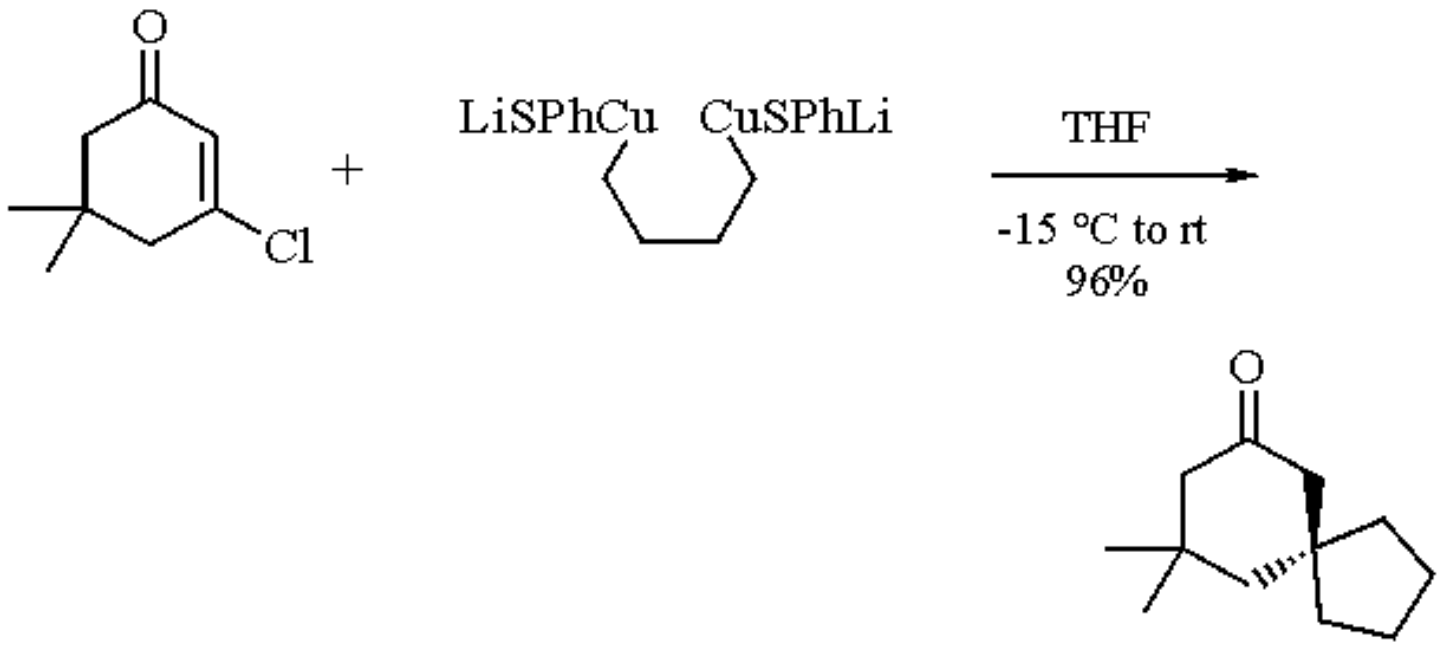

(4)

Metallacyclopentanes.[15]

The synthesis of various metallacyclopentanes starting with metal halides constitutes an important and useful application of 1,4-dilithiobutanes.[16] These metallacycles readily produce cyclopentanones via carbonylation. The formation of hexahydroindan-3-one illustrates such an approach (eq 5).[5]

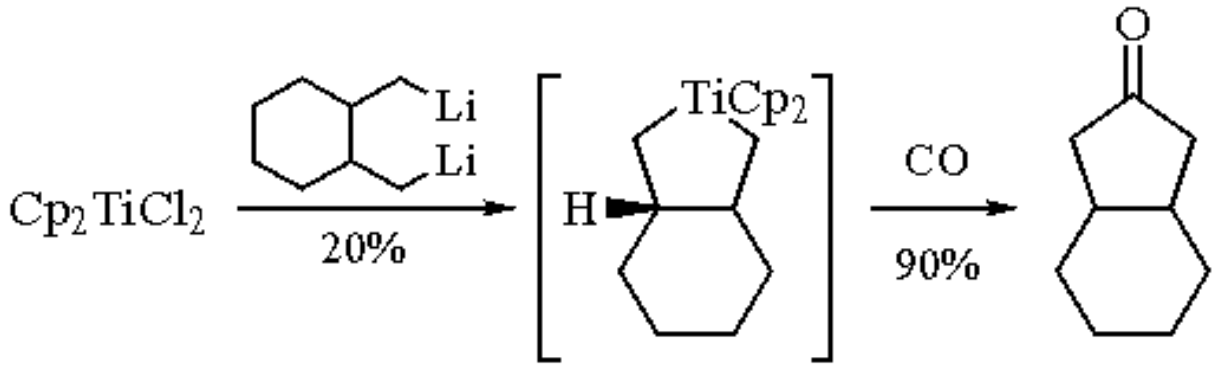

(5)

The reaction of 1,4-dilithiobutane with ***Chlorotriphenylsilane*** provides, as major product, the corresponding silacyclopentane rather than the expected 1,4-bis(triphenylsilyl)butane (eq 6).[17]

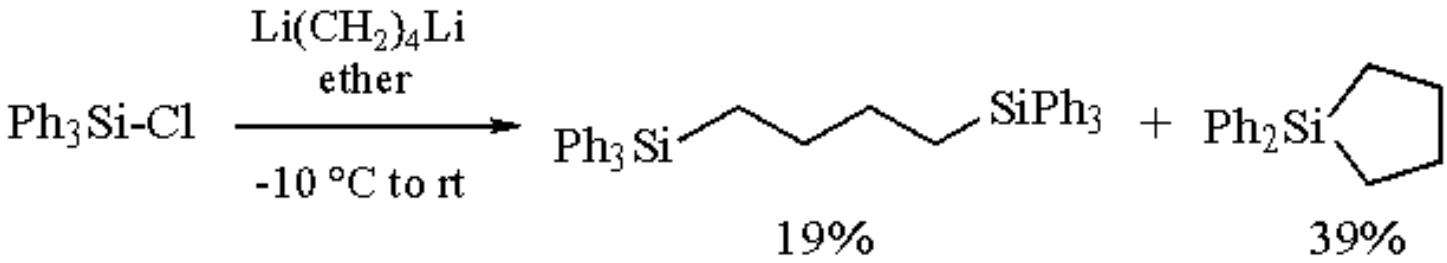

(6)

α,ο-Bifunctional Compounds.

1,4-Dilithiobutane has also been used for the preparation of α,ο-bifunctional compounds such as 1,6-hexanedioic acid and 1,6-hexanedial (see ***1,5-Dilithiopentane***). This procedure is typified by the transformation of 1,10-phenanthroline to 1,4-bis(1,10-phenanthrolinyl)butane, which was further transformed to a molecular trefoil knot (eq 7).[18]

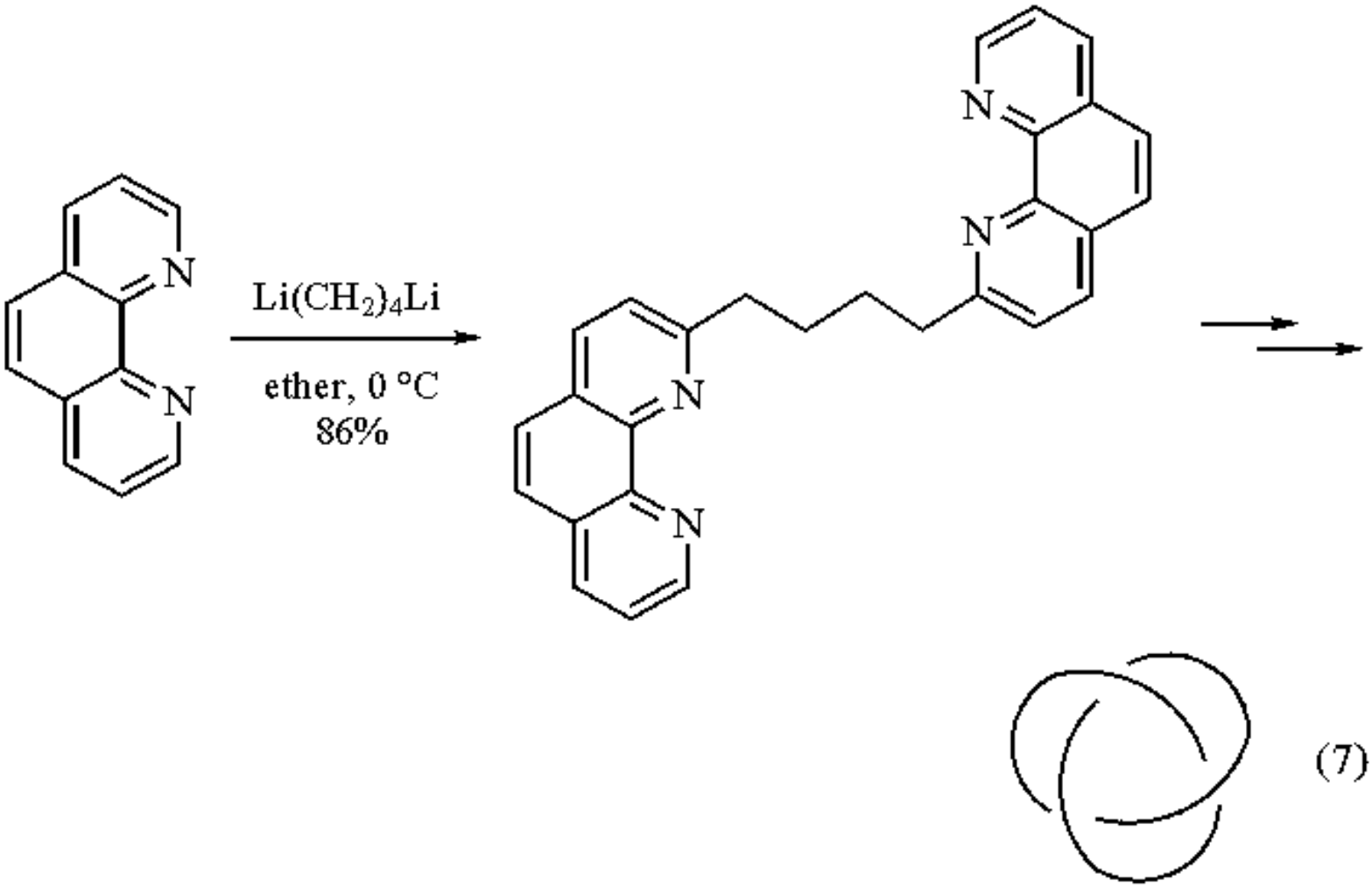

(7)

Organocopper/Zinc Reagents.[19]

1,4-Heterobimetallic reagents of zinc and copper were prepared by reaction of 1,4-diiodobutane with ***Zinc*** dust in THF and subsequent transmetalation with CuCN.2LiCl (see ***Copper(I) Cyanide***) (eq 8). This reagent, which contains two different metals, undergoes selective coupling with electrophiles (E^1) such as aldehydes, iodoalkynes, enones, and nitroalkenes, leading to a monocoupled zinc and copper organometallic compound. Exposure of this intermediate to a second electrophile (E^2) provides the corresponding polyfunctional compound. The second electrophile may be ***Allyl Bromide***, 3-iodocyclohex-2-en-1-one, ***Chlorotrimethylstannane***, or benzaldehyde.[20] Less than 5% of symmetrical dicoupling adducts are observed as byproducts.

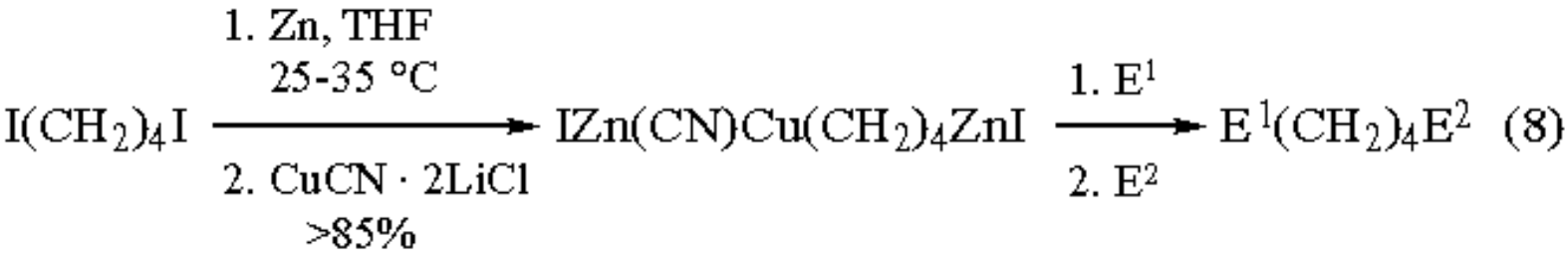

A typical example of this type of coupling involves the use of this reagent with cyclohex-2-en-1-one (E^1) and α-(bromomethyl)acrylate (E^2) (eq 9).

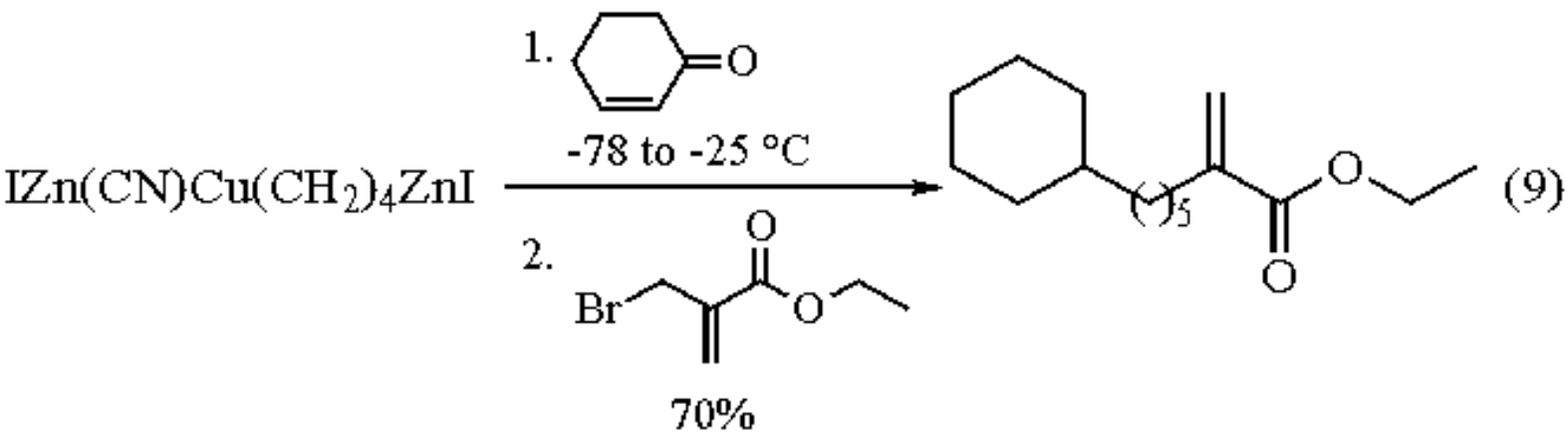

Related Reagents.

The quaternization methodology based on organobis(heterocuprates) is fairly general. Thus spiroannulation can be achieved with a variety of unsaturated organodilithio reagents such as 1,4-dilithiopent-4-ene (eq 10), 1-lithio-2-(2-lithiophenyl)ethane (eq 11), and 2,2´-dilithiobiphenyl (eq 12) providing, respectively, 1-methylenespiro[4.5]decan-7-one, spiro[cyclohexane-1,1´-indan]-3-one, and spiro[cyclohexane-1,9´-fluoren]-3-one.[12]

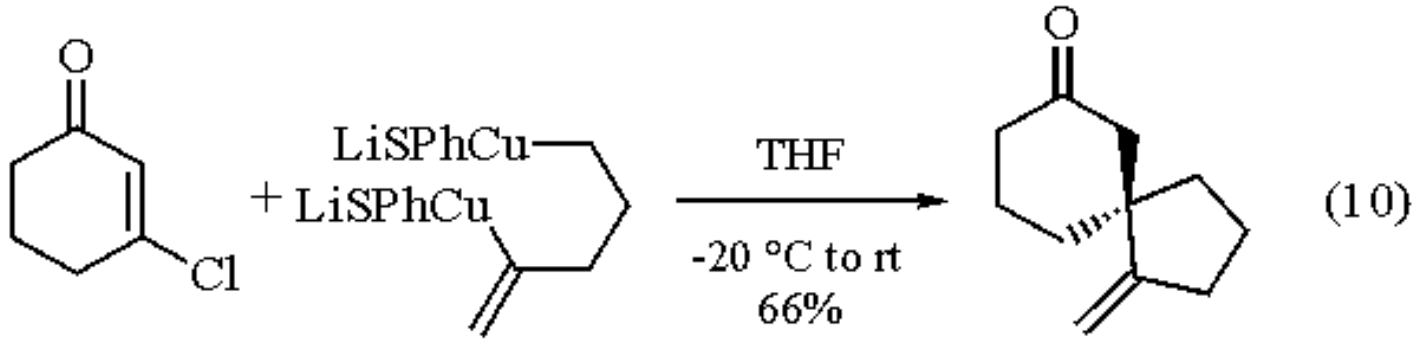

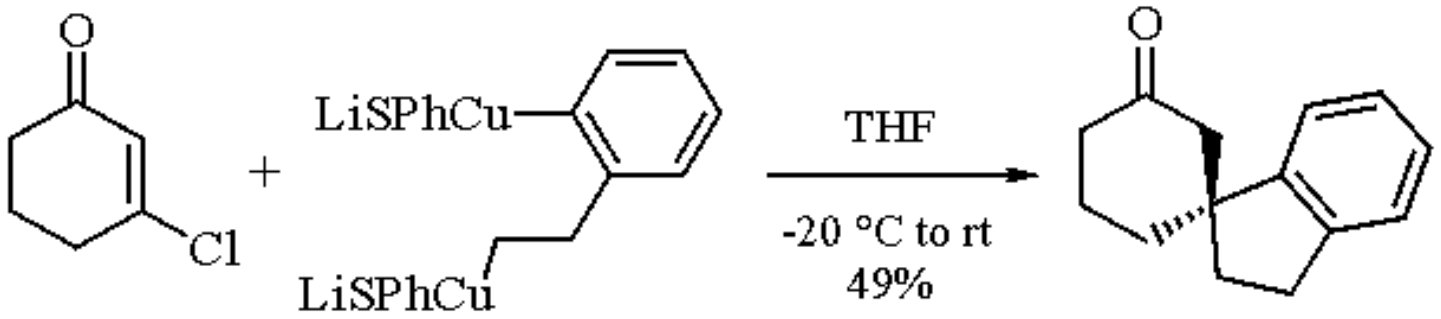

(11)

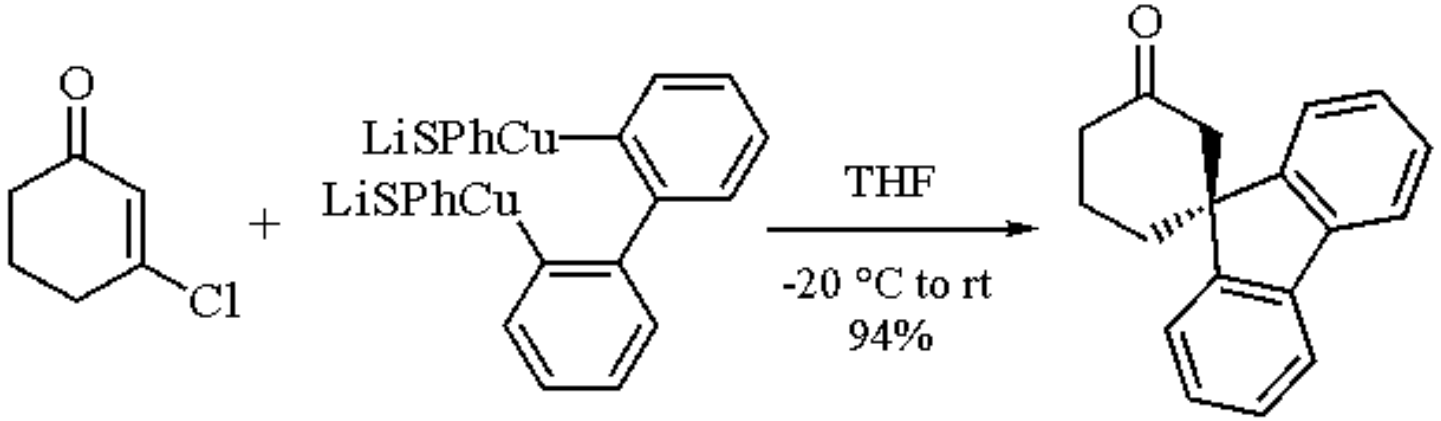

(12)

See also ***1,4-Bis(bromomagnesio)butane***, ***1,5-Bis(bromomagnesio)pentane***, and ***1,5-Dilithiopentane***.

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Lithium α-Lithiomethanenitronate[1]

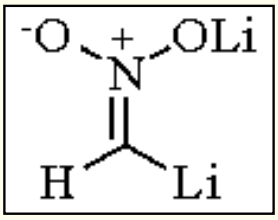

[-] · $CHLi_2NO_2$ · Lithium α-Lithiomethanenitronate · (MW 72.91)

(highly nucleophilic derivatives of nitromethane and of other primary nitroalkanes[2] for alkylation,[2-6] hydroxyalkylation,[2,5,7-12] and acylation[2,5,8,13])

Preparative Methods: the reagent may be generated in THF solution.[4,10,12] A solution of the nitroalkane in THF is treated with ~2 equiv ***n-Butyllithium*** or ***Lithium Diisopropylamide*** at temperatures between -75 and -95 °C; the yields of the subsequent reactions are higher when the double lithiation is carried out in the presence of the cosolvent HMPA or, preferably, of the nonmutagenic ***N,N´-Dimethylpropyleneurea*** (DMPU).[14] The solutions are usually bright yellow and are stable for a few hours at temperatures below about -50 °C; evaporation of the solvents at low temperature leads to residues which decompose spontaneously.

Reactivity of Doubly Lithiated Nitroalkanes (1).

While nitronates (**2**) are readily generated from nitroalkanes (**3**) (pK_a &AApprox; 10), their C-nucleophilicity is generally poor.[1,15,16] Alkylations of (**2**) with alkyl halides occur preferentially on oxygen, but the addition to aldehydes and ketones is highly reversible; the acylation is only possible with acylimidazolines or other special reagents.[1,17] The most useful reaction of (**2**) is their Michael addition to α,β-unsaturated carbonyl compounds. There have been several preparative improvements in recent decades: the use of silyl nitronates (see ***Trimethylsilyl Methanenitronate***), employment of new catalyst systems such as Al_2O_3 and ***Potassium Fluoride***,[15] application of high pressure,[18] and the use of dilithio derivatives (**1**). They are highly nucleophilic and react at carbon irreversibly with all electrophiles tested, including alkyl halides,[2-6] aldehydes and ketones,[2,5,7-12] acid chlorides,[2,5,8,13] and halogens such as bromine:[19] with α,β-enals[5] and α,β-enones[8] they add in a 1,2- not in a 1,4-fashion. The structure of reagents (**1**) is unknown; thus in the formulae used here they are shown with the lithium at carbon, since this is where reactions with electrophiles occur.

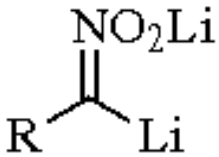

(1)

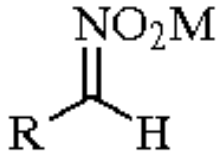

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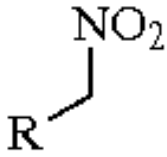

(3)

Applications of Simple Dilithionitronates (1) in Synthesis.

Some products from reactions of the lithiated lithionitronates with electrophiles are shown in the accompaning equations. Thus nitropropane can be hexylated to give 3-nitrononane (**4**) in 50% yield (eq 1).[3,4] Nitropropane was also added to cyclohexenone to yield (52%) the unsaturated nitro alcohol (**5**), a type of compound not available by any other nitroaldol-forming method (eq 2).[8]

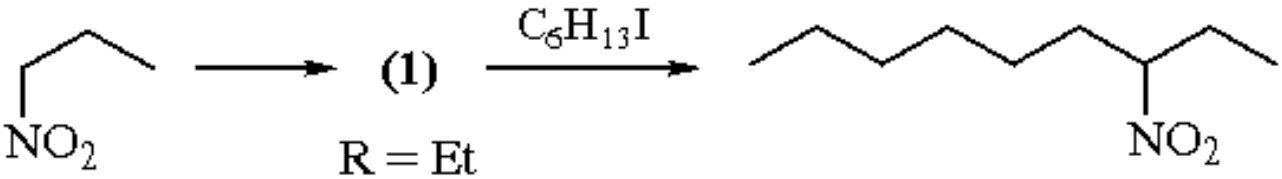

(4)

(1)

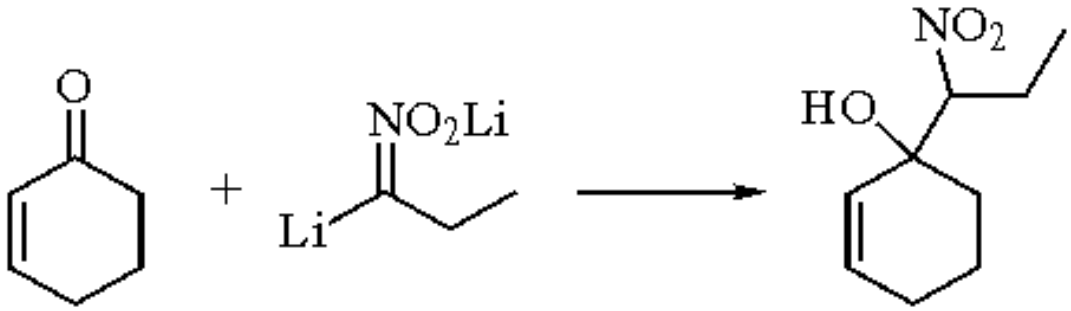

(5)

(2)

The 1,4-adduct of BuLi to 1-nitro-1-butene can be further lithiated in situ to form a doubly lithiated reagent (**6**) which is acylated by methyl 2-methylpropanoate, with formation after aqueous workup of the nitro ketone (**7**) in an overall yield of 30% (eq 3).[8] An application of nitroalkane *C*-acylation[2,5,8,13] to the synthesis of *rac*-amino acids is exemplified with the aminoheptanoic ester (**8**), prepared in two steps (50% yield)[13] from nitrohexane and methyl chlorocarbonate (eq 4).

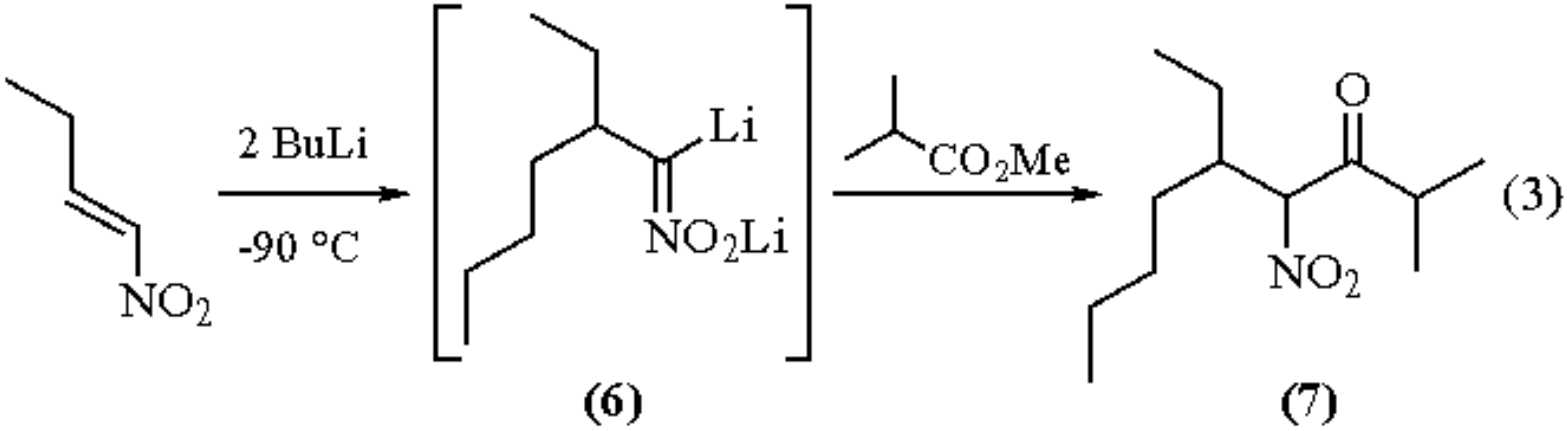

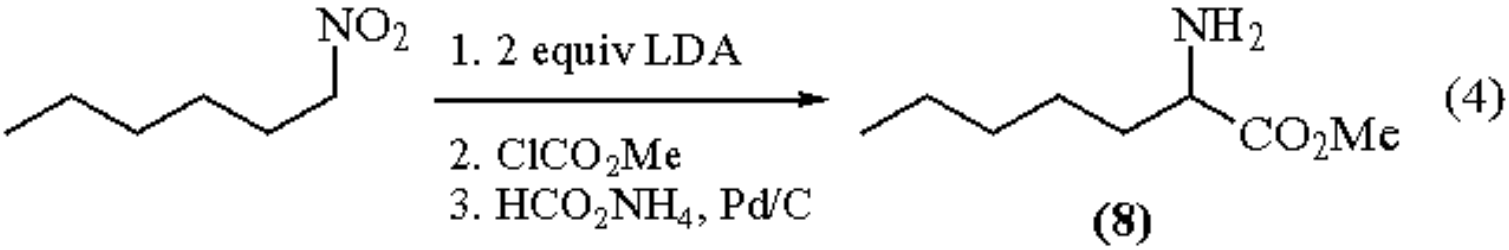

Dilithionitronates Bearing Additional Functional Groups.

The doubly lithiated nitroalkanes can also be generated from precursors containing additional functional groups. For instance, 1-nitro-2-propene gives a reagent (**9**), which was added to benzophenone to give the otherwise not accessible nitroaldol adduct (**10**) in 53% yield (eq 5).[8] More surprising is the fact that nitroalkanes with β-leaving groups, such as trifluoronitroethane,[11,12] can also be doubly lithiated to give rather stable reagents of type (**11**). These may be used for the reactions with various electrophiles mentioned above. Thus the trifluoromethyl-substituted nitroaldol (**12**) with a tertiary hydroxy group could be prepared in 60% yield (eq 6).[12] *Retro*-nitroaldol cleavage occurs readily during bulb-to-bulb distillation (90 °C/10 mmHg).

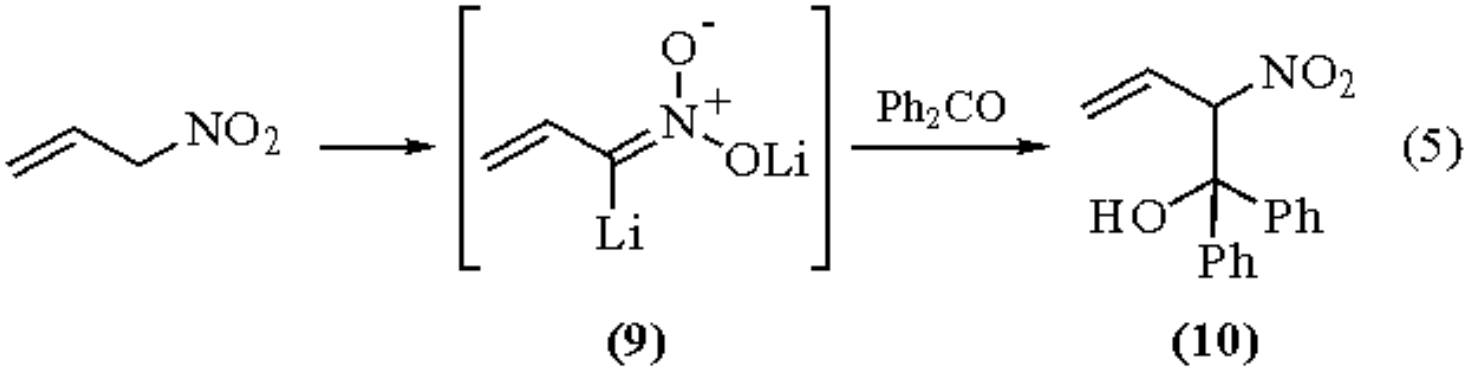

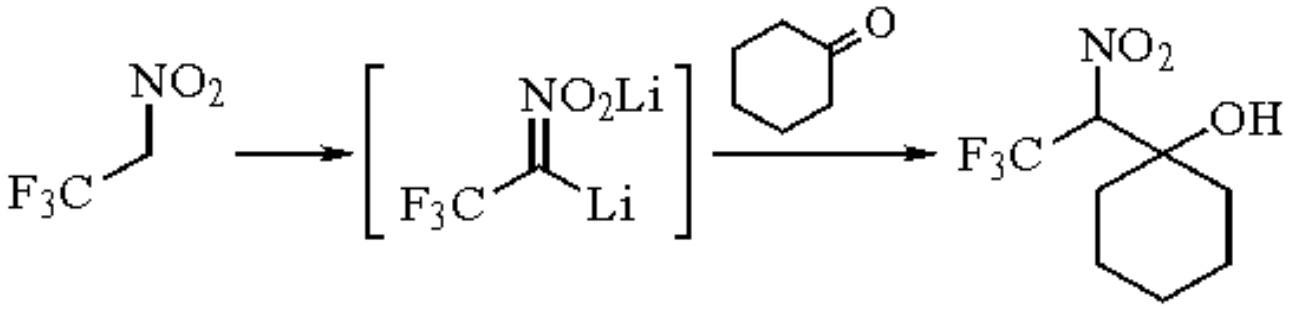

(6)

(11) **(12)**

Nitroaldol additions of doubly lithiated alkoxyl-substituted nitroalkanes can be highly diastereoselective, as demonstrated by the addition of THP-protected 2-nitroethanol to cyclohexanecarbaldehyde to form (**13**) (64%) (eq 7).[5] Another example is the preferential formation of the (*S*,*S*)-diastereoisomer (**14**) in the allylation of a glyceraldehyde-derived nitro compound (68% yield; dr = 82:18) (eq 8).[6]

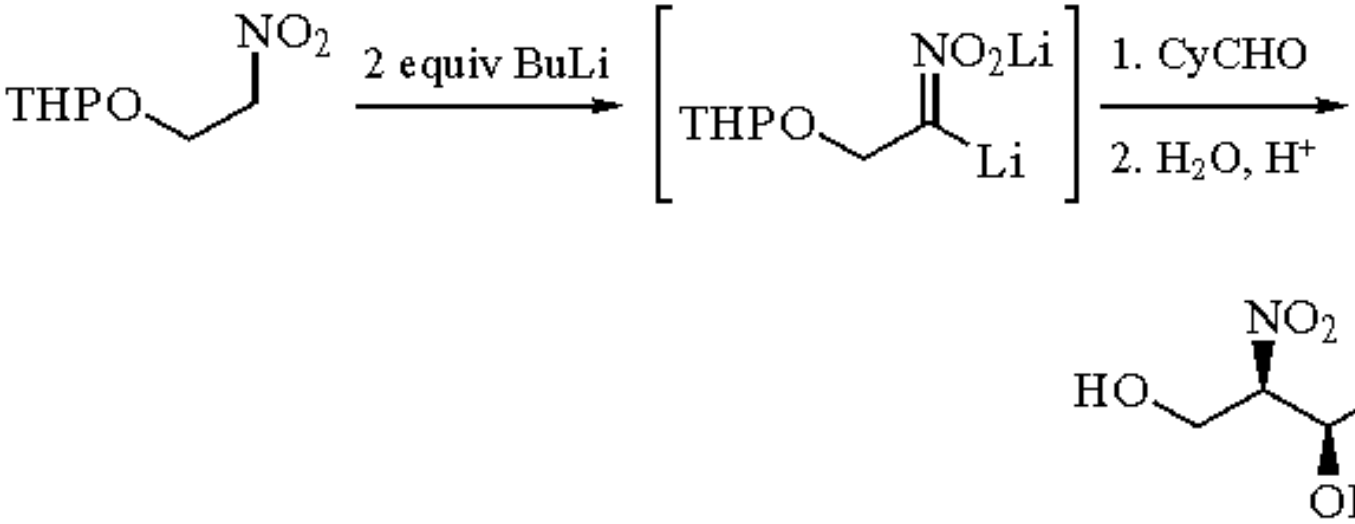

(7)

(13) >95% *syn*

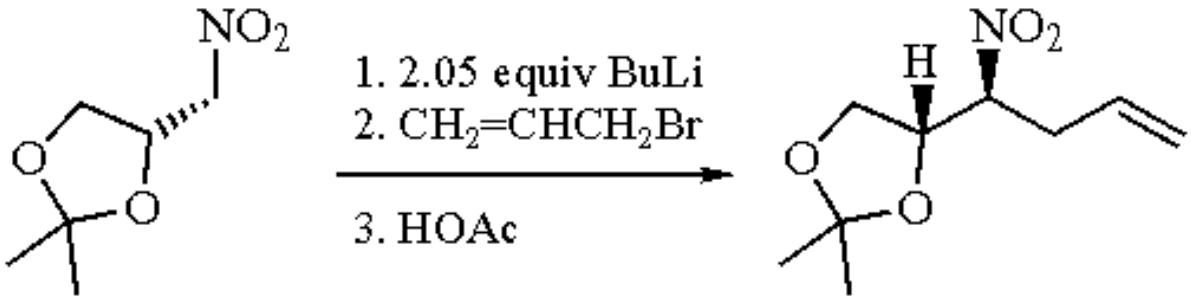

(8)

(14) *(S,S)*

Related Reagents.

O,O-Dilithio-1-nitropropene; ***Nitroethane***; ***Nitromethane***.

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O,O-Dilithio-1-nitropropene[1]

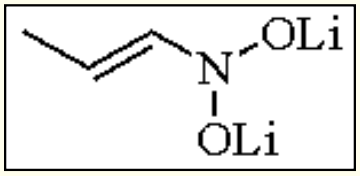

[-] · $C_3H_5Li_2NO_2$ · *O,O*-Dilithio-1-nitropropene · (MW 100.96)

(reacts with electrophiles at the β-position; electrophiles may be alkyl halides, aldehydes, ketones, α,β-unsaturated aldehydes and ketones, esters, and nitroalkenes[1-10])

Alternate Name: N,N-[bis(lithioxy)]-1-propenylamine.

Preparative Methods: generated by α,β-double deprotonation of nitroalkanes with BuLi or LDA.

Generation of Reagents (1) from Suitable Nitroalkanes.

Treatment of nitroalkanes with excess strong base may lead to α,α- or α,β-double deprotonation (eq 1). With simple nitroalkanes (**2**) (R = H or alkyl) the isomeric dilithio derivatives (**1**) and (**3**) can be generated selectively by reversing the mode of addition of the reagents. The lithium lithionitronate (**3**) is formed when 2 equiv ***n-Butyllithium*** are added to a solution of the nitroalkane in THF/HMPA or ***N,N´-Dimethylpropyleneurea*** (DMPU) at -90 °C,[6,11] while the bis(lithioxy)enamine (**1**) is generated when the nitroalkane is added to the solution of 2 equiv BuLi under otherwise identical conditions (eq 2).[10] With nitroalkanes (**4**) bearing an additional acidifying group R^2 in the β-position, such as vinyl[4] or aryl[2,3,5] or methoxycarbonyl,[3,6,7] the base (BuLi[2-5] or ***Lithium Diisopropylamide***[3,6,7]) can be added to the nitroalkane solution for the α,β-double deprotonation. If there is just one α-nitro CH proton in (**4**) (R^1 &neq; H), only α,β-deprotonation can occur; in this case, 1 equiv of BuLi is used for the first deprotonation, followed by 1 equiv of ***t-Butyllithium*** for the second deprotonation.[8,9] In Table 1 the conditions for different nitroalkanes are listed. The solutions of reagents (**1**) are all colored from light yellow to deep red; they are stable for some hours at temperatures below -50 °C. The structure of reagents (**1**) is unknown; thus in the formulae used herein they are shown with both lithiums at oxygen, because of the known affinity of lithium for oxygen.

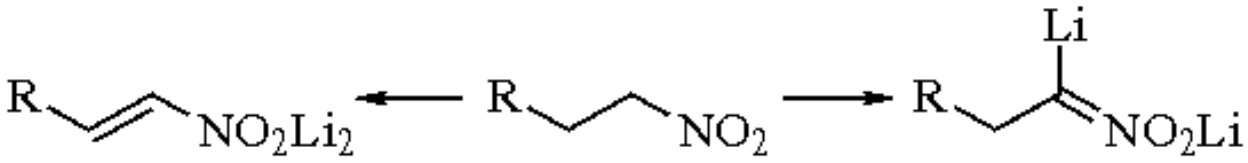

(1) (2) (3) (1)

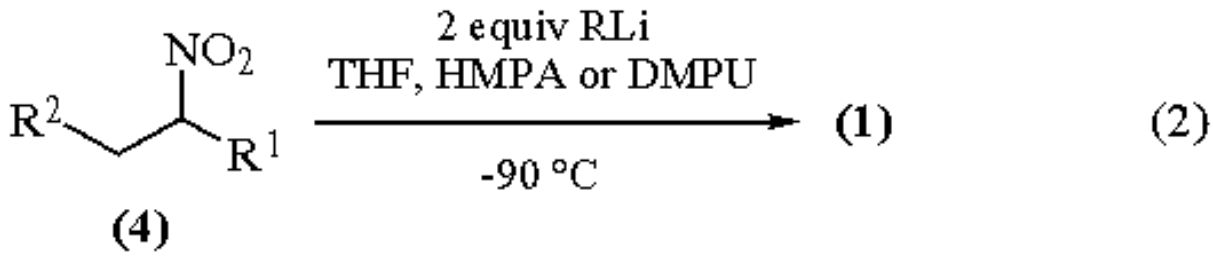

Table 1 Conditions for Generation of Dianion Derivatives

Substitution pattern of nitroethane moiety (4) R^1	R^2	Conditions for a,b-double deprotonation
H	H or alkyl	inverse addition of nitroalkane to 2 equiv BuLi
H	vinyl or aryl	2 equiv BuLi added
H	CO_2Me	2 equiv LDA added
alkyl or	H $(CH_2)_n$	1 equiv BuLi, then 1 equiv *t*-BuLi

Reactions of α,β-Doubly Deprotonated Nitroalkanes with Electrophiles.

The chemistry of doubly lithiated methyl 3-nitropropanoate (**1**) (R = CO_2Me) is covered in the article on ***Methyl 3-Nitropropanoate***. The reagents (**1**) are formally enamines with two LiO substituents on nitrogen; they are *much* more reactive nucleophiles than normal enamines and have been called super-enamines.[2] These reagents are also, formally, doubly reduced nitroalkenes (other reagents are formally doubly reduced unsaturated carbonyl compounds;[1c,1d,12] we have occasionally called such systems LUMO-filled π-systems[1c]). As outlined in eq 3, they provide nucleophilic reactivity in the β-position of a nitro group. Nitroalkenes, on the other hand, are highly reactive electrophiles, so that the reactivity of the dilithio derivatives (**1**) constitutes an umpolung[13] of nitroalkene reactivity (eq 3).

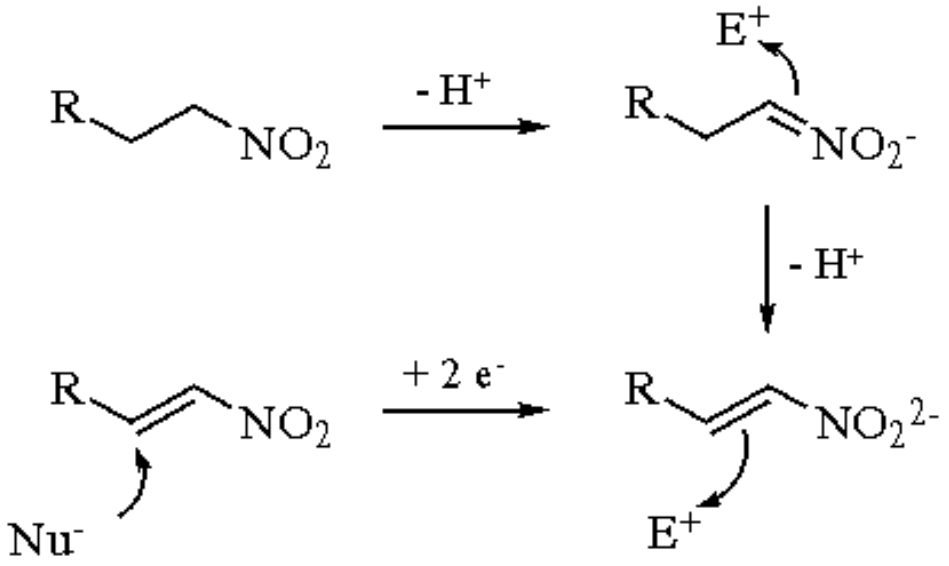

(3)

An example of the preparation of a homo-nitroaldol from a simple nitropropane is shown in eq 4.[10] The nitroalcohol (**5**) is isolated in 77% yield, with essentially no isomeric ordinary nitroaldol being formed; the diastereomer ratio (dr) is poor (2.6:1).

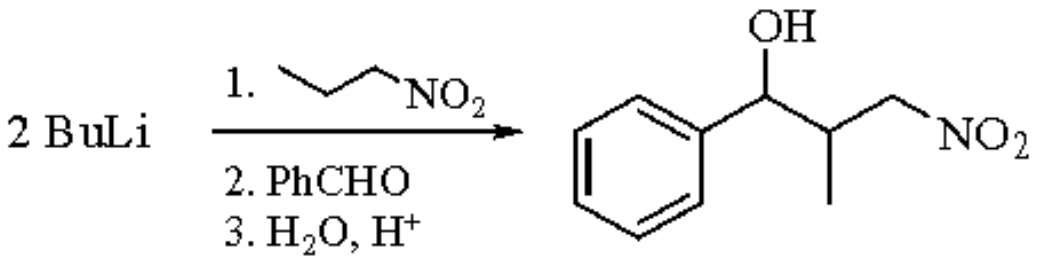

(4)

(5)

More complex nitroalcohols of this type are produced when nitrocyclopentane and nitrocyclohexane are doubly lithiated and added to benzaldehydes to give (**6**) (40% yield, dr = 4:1) and (**7**) (32% yield, dr > 20:1),[8] or when 1,1,1-trifluoro-2-nitropropane is employed (see (**8**) in eq 5) (20% yield, dr = 3:1).[9] A special demonstration of the reactivity umpolung is the preparation of an unsymmetrical 2,3-diaryl-1,4-dinitrobutane (**9**) from 2-phenylnitroethane and a 2-arylnitroethylene (65% yield) (eq 6).[5]

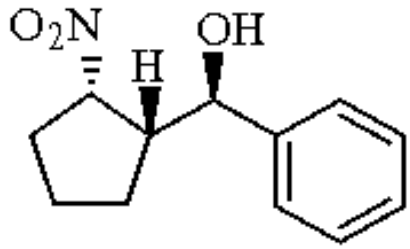

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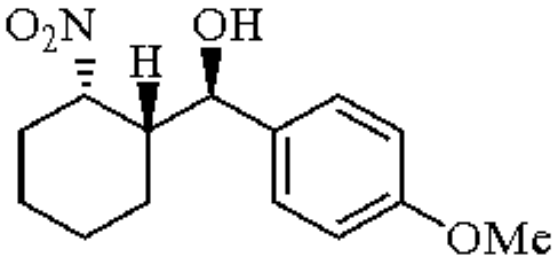

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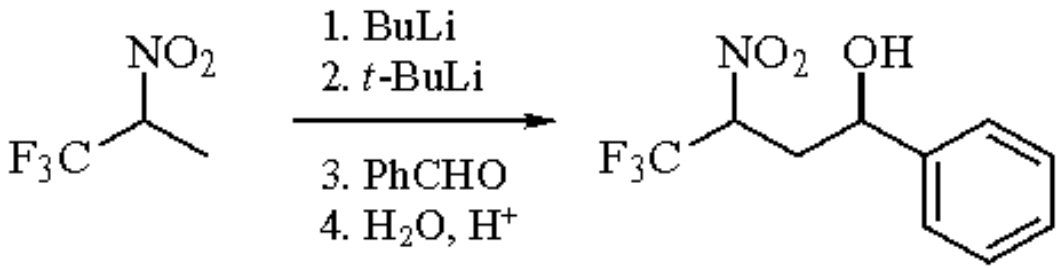

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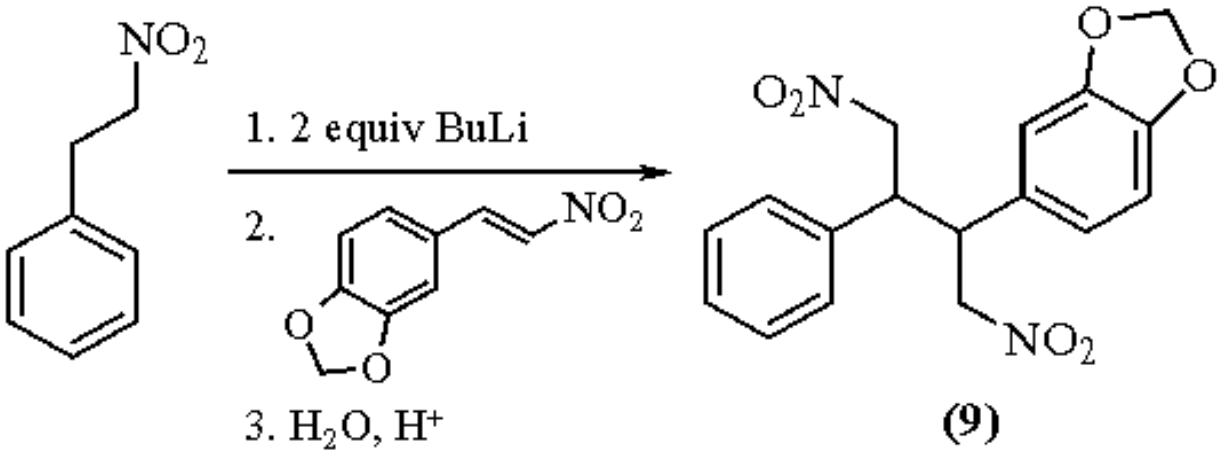

(6)

(9)

Finally, in eq 7 the reactivity of the butadiene derivative (**10**) is outlined; from the bright red solutions of this reagent and electrophiles the isomeric 2-vinylnitroalkanes and 1-nitro-2-alkenes are obtained in varying ratios.[4] Remarkably, only the regioisomer resulting from reaction at the 4-position is formed in the Michael addition to cyclic (five- through seven-membered ring) and open-chain α,β-enones.[4,14] The product (**11**), isolated in ~50% yield with cyclohexenone, has been converted to the 1,7-dicarbonyl derivative (**12**) by Nef reaction[4,14] carried out under the McMurry conditions.[15]

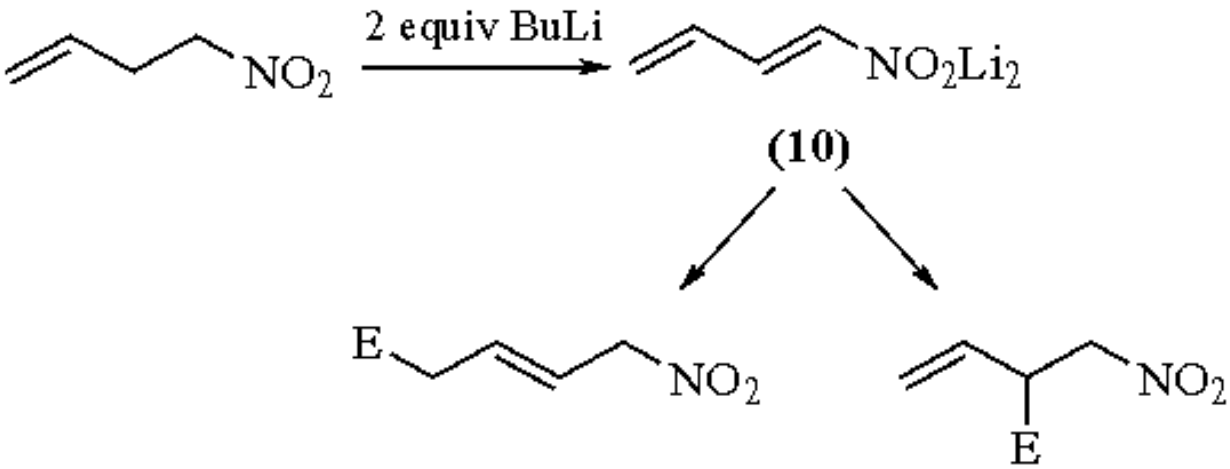

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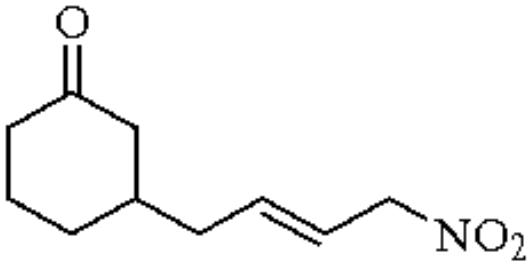

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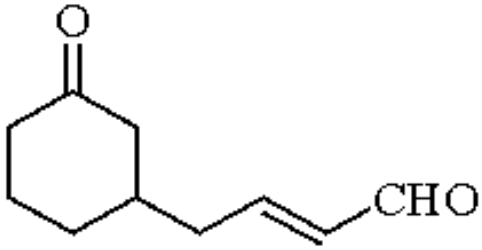

(12)

Related Reagents.

Lithium α-Lithiomethanenitronate; ***Methyl 4-Nitrobutanoate***; ***Methyl 3-Nitropropanoate***; ***Nitroethane***.

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1. (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. C. *C* **1979**, *33*, 1. (b) Döpp, D.; Döpp, H. *MOC* **1990**, *E14b*, 780. (c) Seebach, D. Pohmakotr, M. *T* **1981**, *37*, 4047. (d) Thompson, C. M.; Green, D. L. C. *T* **1991**, *47*, 4223. (e) Ono, N. In *Nitro Chemistry*; Feuer, H.; Nielsen A. T., Eds.; VCH: New York, 1990; Chapter 1. (f) Wade, P. A.; Giuliano, R. M. In *Nitro Chemistry*; Feuer, H.; Nielsen, A. T., Eds.; VCH: New York, 1990; Chapter 2.
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13. Seebach, D. *AG(E)* **1979**, *18*, 239.
14. For further examples and details, see: Henning, R. Dissertation, Universität Giessen, 1978.
15. Ho, T. L.; Wong, C. M. *S* **1974**, 196.

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1,5-Dilithiopentane[1]

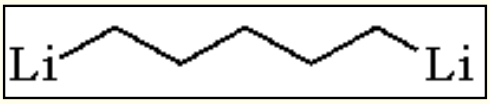

[2223-58-7] · $C_5H_{10}Li_2$ · 1,5-Dilithiopentane · (MW 84.02)

(constructing block agent: transformations of carboxyl groups and metal halides into cyclohexane and metallacyclohexane synthetic intermediates, and α,o-bifunctional compounds; in presence of Cu^I ion, the reagent is transformed into an organobiscuprate)

Alternate Name: 1,5-pentanediyldilithium.

Solubility: sol ether, THF, hydrocarbons.

Form Supplied in: prepared in ether and used in solutions which usually range from 0.5 to 1.2 M.

Analysis of Reagent Purity: titration;[2] ^{1}H NMR α-CH_2 signal δ -0.81 (t, *J* = 9 Hz);[3] quenching with chlorotrimethylsilane;[3,4] GLC.[5]

Preparative Methods: was first prepared by direct reaction of 1,5-dibromopentane with ***Lithium*** metal at 0 °C in anhydrous ether.[4,8] This method was later improved by using lithium metal (4 equiv) containing 1% Na with 1,5-dichloropentane (1 equiv).[5] The optimum procedure[9] uses a 12.5% excess of lithium and maintains the temperature at 0 °C (eq 1). Yields up to 90% can be obtained by this method, which may also serve to prepare lower analogs.

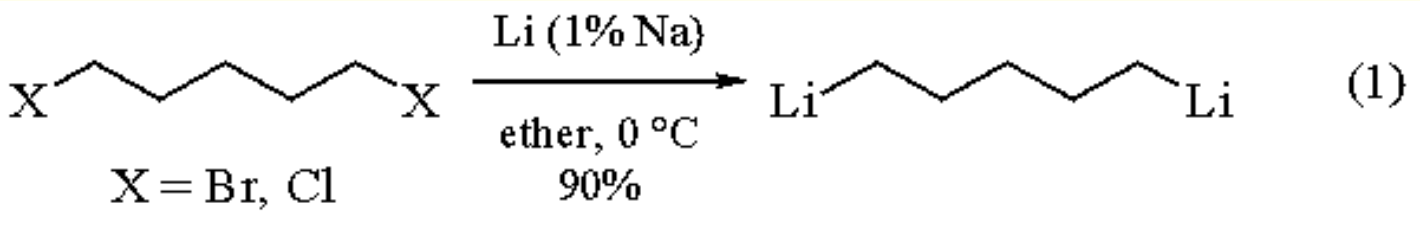

The Barbier procedure, under ultrasonic irradiation, may also be used. In a particular case, 1,5-dibromopentane (2 equiv), methyl *R*(-)-2-methyloctanoate (1 equiv) and lithium (8 equiv) were reacted in THF at -25 °C for 25 min (see eq 3).[10]

1,5-Dilithiopentane can also be prepared by lithium-iodine exchange between ***t-Butyllithium*** and 1,5-diiodopentane (eq 2).[3] This method requires a temperature of -78 °C and 4 equiv of *t*-BuLi.[2] The excess of reagent is important, as a stoichiometric amount leads to the corresponding cycloalkane almost quantitatively.

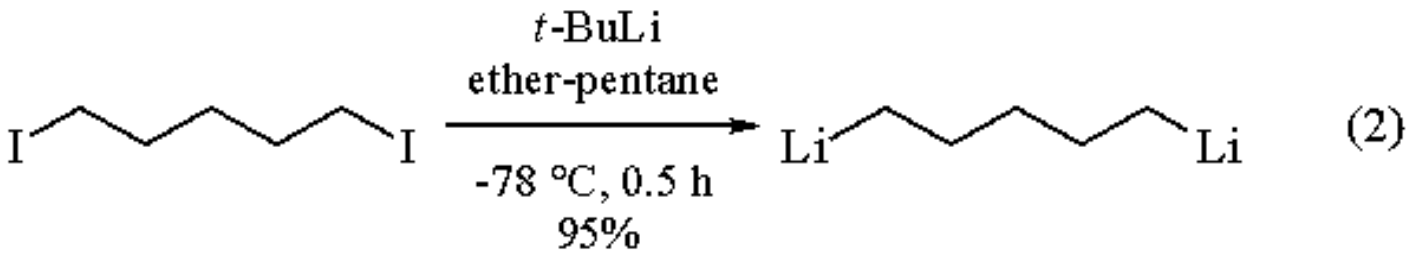

The procedure also generates, in excellent yields, lithio compounds from homoallylic-type iodides. Alkyl bromides and secondary iodides may also be used, but yields are lower.

Handling, Storage, and Precautions: solutions are highly flammable; must be stored and handled in the absence of proton sources, carbon acids, and oxygen. Flasks and Schlenk tubes should be flushed with dry Ar or N_2. At -20 °C, ether solutions have a useful life of one to four months.[5,6] At higher temperature (~30 °C), organolithiums react readily with ethers.[7]

Synthetic Applications.

1,5-Dilithiopentane converts various electrophiles and bis(electrophiles) into cyclohexane and spirobicyclic compounds. It is also useful for the preparation of α,o-bifunctional compounds and other organobimetallic reagents.

Cyclohexane Derivatives.

1,5-Dilithiopentane reacts as a bis(nucleophile) with geminal bis(electrophile), providing cyclohexane derivatives, as is exemplified in eq 3, with a chiral ester as substrate.[10]

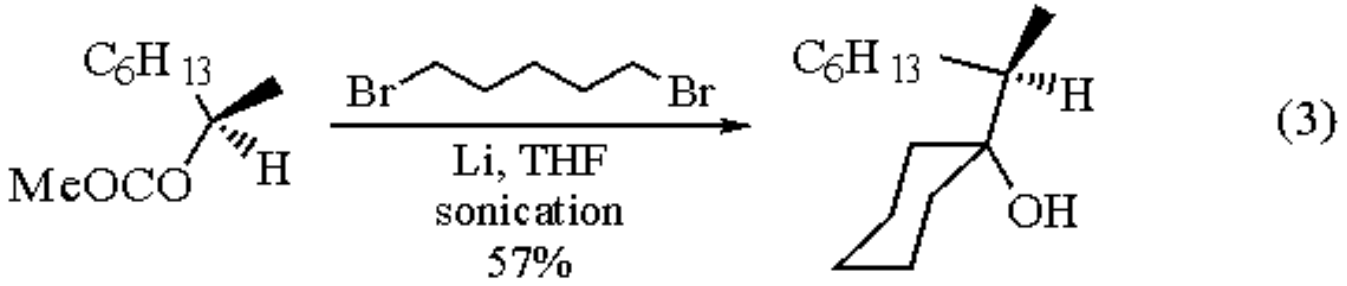

Cyclohexanone can also be prepared in modest yield from 1,5-dilithiopentane and ***Carbon Monoxide***.[11]

Unlike smaller rings, six-membered metallacycles are not available through cycloaddition reactions. They are formed by the reaction of metal dihalides with appropriate organobismetallic reagents such as 1,5-dilithiopentane.[12] The deuterated 1,5-dilithiopentane in eq 4 was used in a mechanistic study of the thermal decomposition of metallacycles.[13]

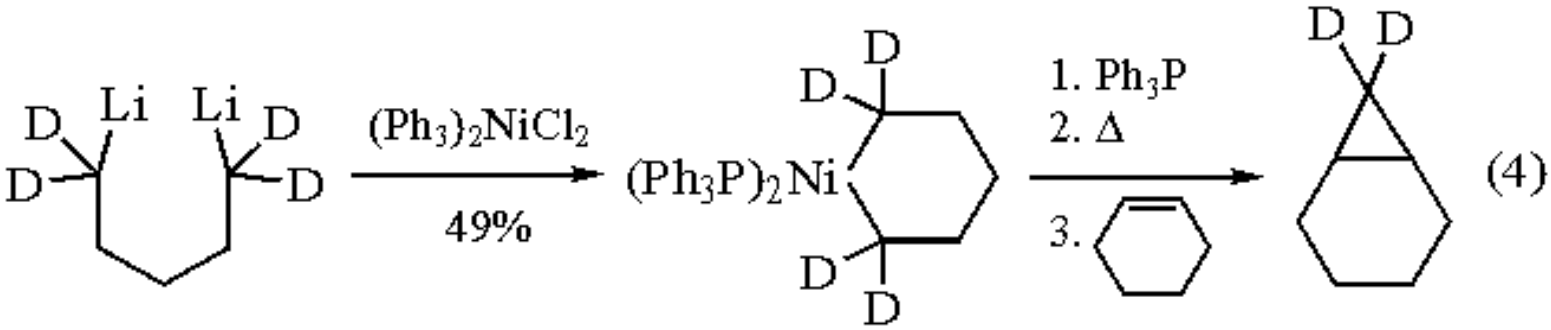

α,o-Bifunctional Compounds.

1,5-Dilithiopentane reacts readily with ***Chlorotrimethylsilane*** to produce 1,5-bis(trimethylsilyl)pentane. This reaction has been used to titrate the reagent (eq 5).[3,4] 1,5-Bis(trimethylstannyl)pentane was produced in a like manner (80%) from ***Chlorotrimethylstannane***.[3]

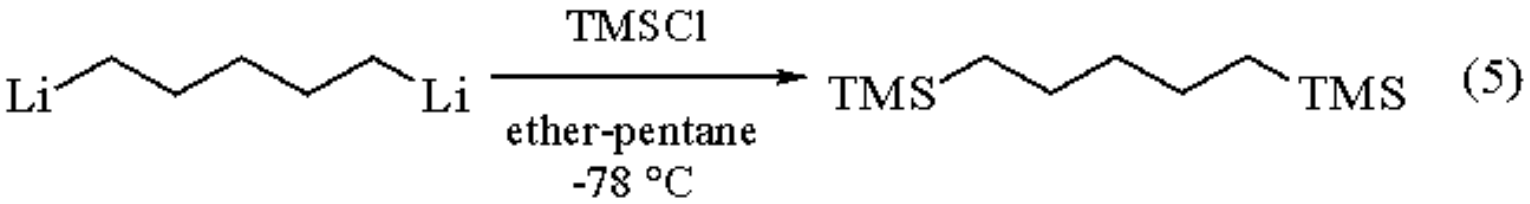

1,5-Dilithiopentane is less prone to cyclization than 1,4-dilithiobutane, as is shown by the reactions of the two compounds with ***Chlorotriphenylsilane***.[14] Thus 1,5-dilithiopentane gives mainly (75%) 1,5-bis(triphenylsilyl)pentane (eq 6) while the parent compound, under the same conditions, furnishes 1,4-bis(triphenylsilyl)butane in only 19%, the main product of the reaction being the cyclic product 1,1-diphenyl-1-silacyclopentane (see also ***1,4-Dilithiobutane***).

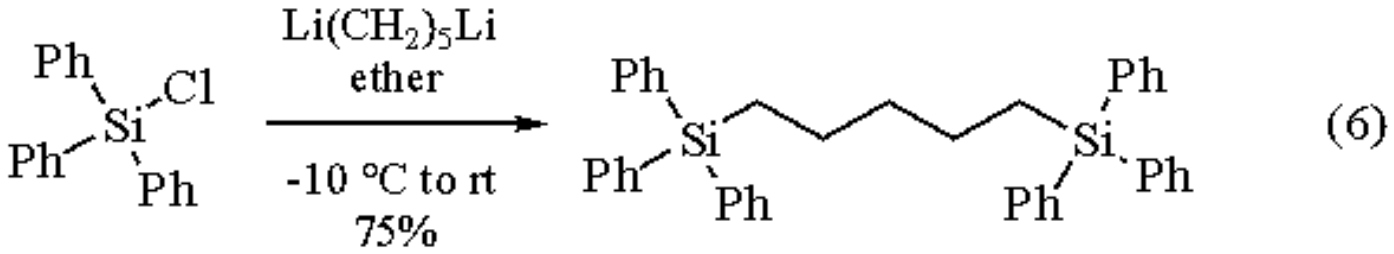

α,o-Diketones can be easily produced by the reaction of an organobiscuprate with an acyl chloride.[15] Thus 1,5-dilithiopentane, in the presence of ***Phenylthiocopper(I)***,[16] reacts with benzoyl chloride to give 1,7-diphenylheptane-1,7-dione (eq 7).[17]

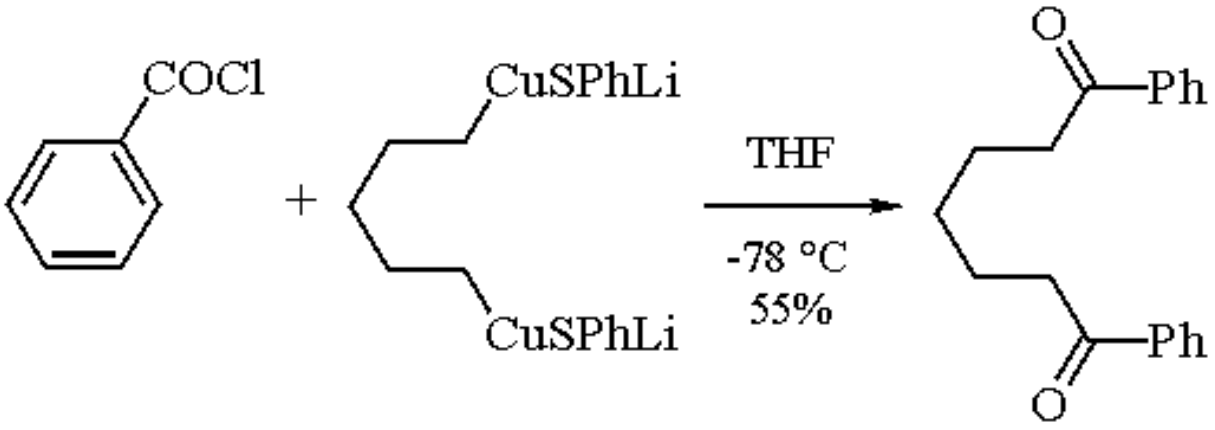

(7)

The yield of open chain products resulting from the addition of 1,*n*-dilithioalkane to at least 2 equiv of substrate may be optimized by performing the reaction in dilute solution.[18]

Heterobimetallic zinc and copper reagents have been prepared from 1,5-diiodopentane.[19] The interesting point with this reagent is that the two organometallic moieties have quite different reactivities. It is thus possible to prepare bis(functionalized) compounds by successively reacting the reagent with two different electrophiles. Very good yields (60-80%) have been obtained with various substrates (eq 8) (see also ***1,4-Dilithiobutane***).

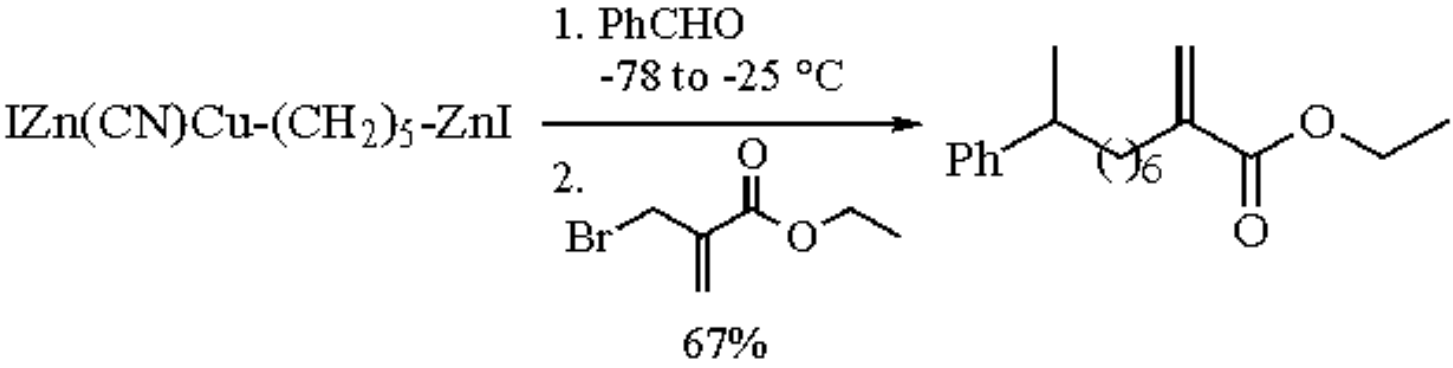

(8)

Spiroannulation.

The first published reaction of 1,5-dilithiopentane involved a cyclization. Thus the preparation of 6-silaspiro[5.5]undecane was realized from 1,5-dilithiopentane and 1,1-dichloro-1-silacyclohexane (eq 9).[8]

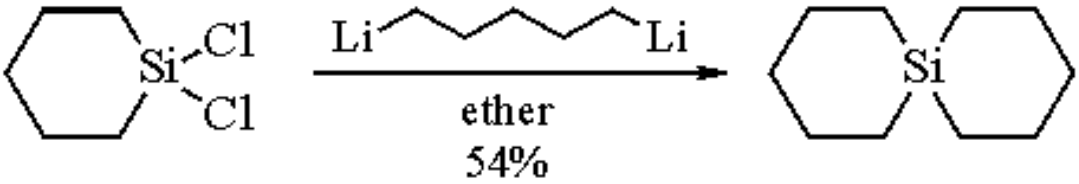

(9)

1,5-Dilithiopentane and parent dilithio compounds such as 1-lithio-3-(2-lithiophenyl)propane and 1,5-dilithiohex-5-ene can also be used in their bis(heterocuprate) form. In this manner, various spiroketones have been obtained in good to excellent yields.[6,15] For example, spiro[5.5]undecan-2-one was synthesized with a 74% yield from 3-chlorocyclohex-2-en-1-one and the bis(heterocuprate) prepared by adding, at -78 °C, a THF solution of 1,5-dilithiopentane to phenylthiocopper, also in THF (eq 10) (see also ***1,4-Dilithiobutane***).

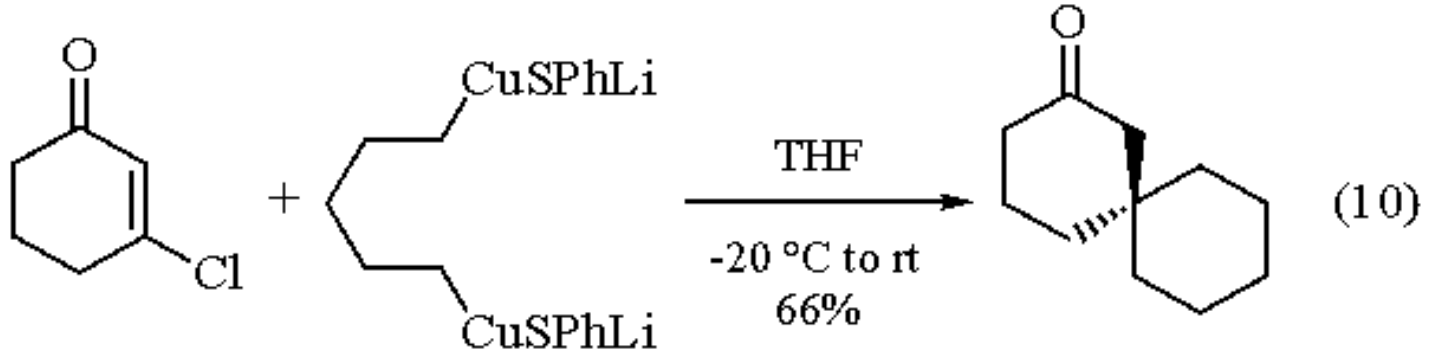

The direct and stereoselective synthesis of a known key intermediate of the sesquiterpenes β-vetivane, hinesol, and epihinesol was achieved using this methodology.[20] The desired *cis* stereochemistry was obtained, as expected, based on related work (eq 11).[21]

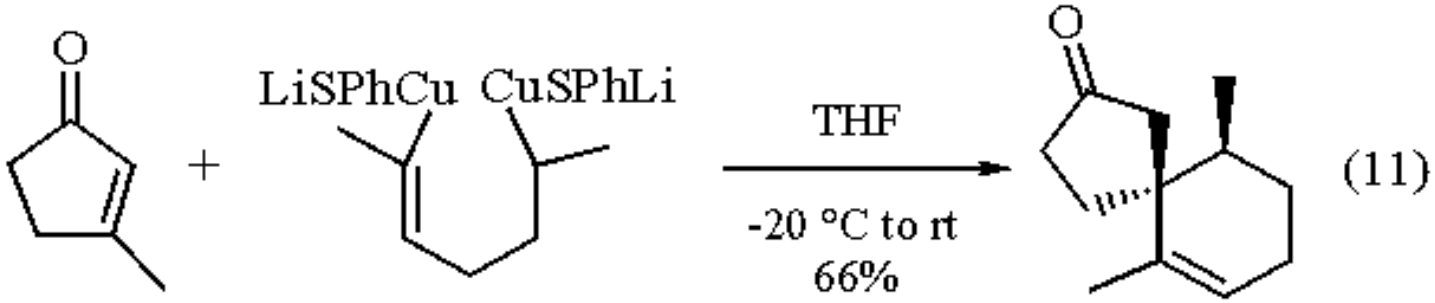

Related Reagents.

1,4-Bis(bromomagnesio)butane; ***1,5-Bis(bromomagnesio)pentane***; ***1,4-Dilithiobutane***.

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1,3-Dilithiopropyne[1]

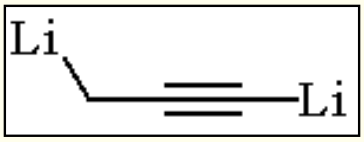

[58335-31-2] · $C_3H_2Li_2$ · 1,3-Dilithiopropyne · (MW 51.93)

(anionic propargyl coupling reagent[2,3])

Preparative Methods: from allene via dilithiation;[3,4] from propyne via dilithiation;[2,5,6] from 1-bromopropyne via polylithiation.[7]

Handling, Storage, and Precautions: solutions of the reagent are stable at 20 °C and should be handled in the usual way (argon).

Propargylation.

The introduction of a propargylic group as a nucleophile formally requires the protection of the terminal alkyne, e.g. as the trialkylsilylated derivative.[8] An efficient alternative is provided by 1,3-dilithiopropyne, readily available via dilithiation of either propyne or ***Allene***.[2-6] In particular, the dilithio derivative circumvents the general problem of propargyl and allenyl metal derivatives which equilibrate in solution and often give mixtures of alkenes and alkynes on reaction with electrophiles.[9,10]

As a rule, 1,3-dilithiopropyne, originating from propyne, reacts preferentially at the 3-position with various electrophiles, including ***Chlorotrimethylsilane***, epoxides, and alkyl halides (eq 1).[2,5] Poor regiochemical control has been reported when allyl halides are involved.[11] Reaction with carbonyl derivatives leads to the β-alkynyl alcohol (eq 2).[12]

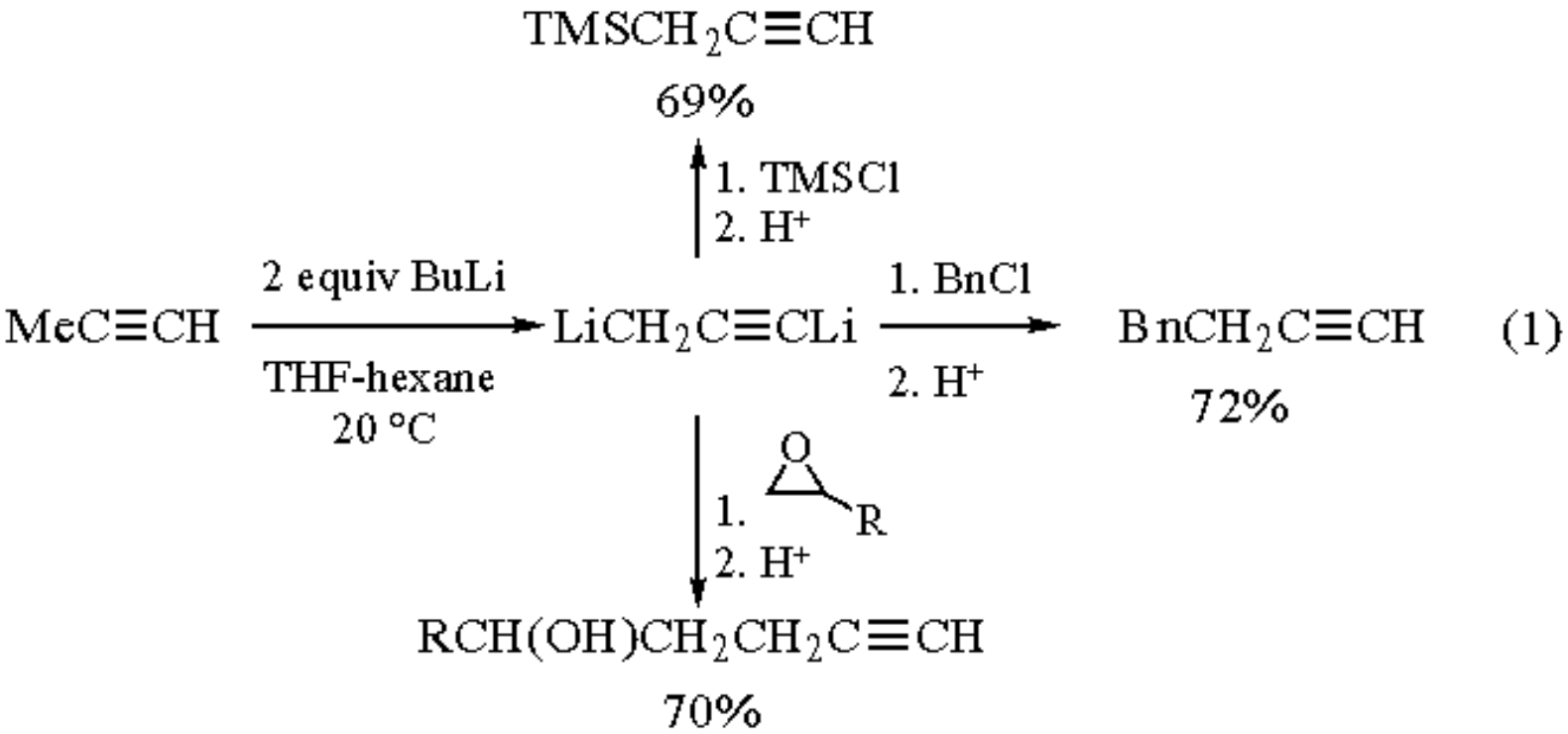

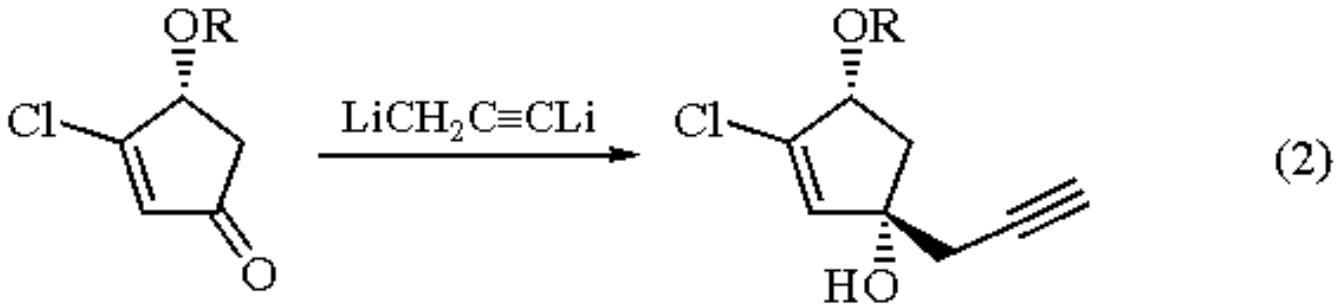

The reagent also undergoes efficient sequential 1,3-dialkylation. After introduction of the first group at the 3-position, subsequent reaction with a variety of electrophiles (***Iodine***, ***Formaldehyde***, RX, epoxide) occurs at the terminal alkynic position (eq 3).[2,6] Dilithio derivatives of 3-substituted propyne also react preferentially at the propargylic carbon site with electrophiles.[5,7,11,13]

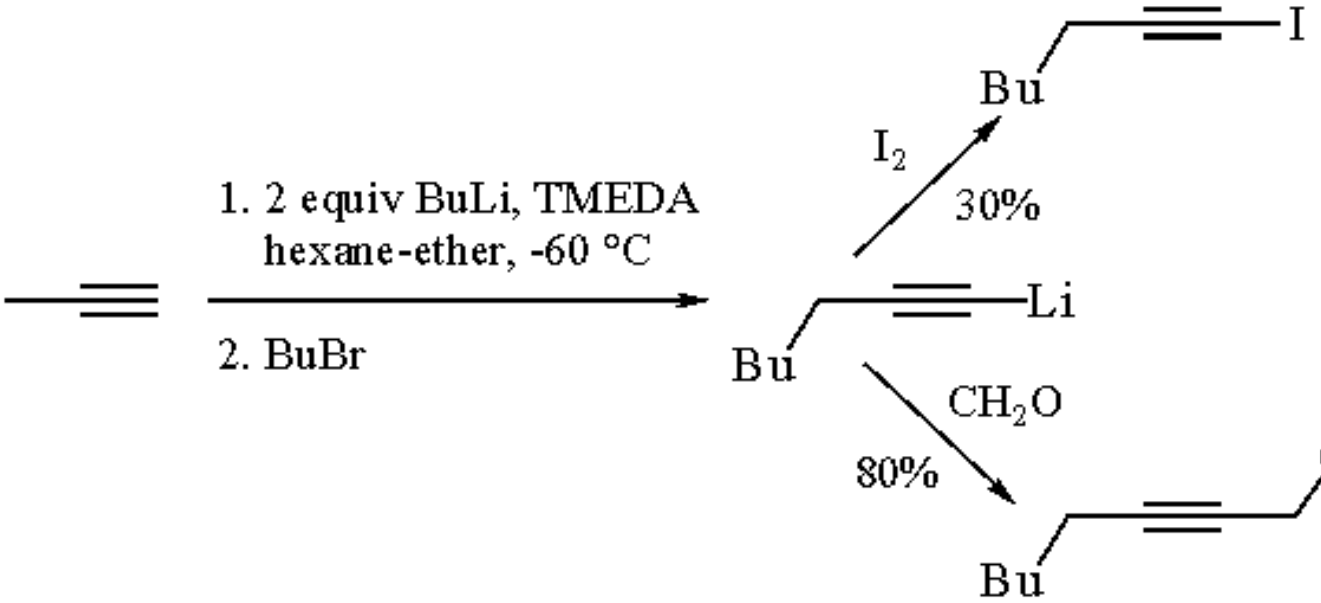

(3)

Controlled lithiation of allene produces an active species which also behaves as a propargyl dianion.[14] The presence of hexane was found necessary to obtain pure alkynic derivatives upon alkylation with alkyl halides, including allylic ones (eq 4).[3,15] In the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** or in THF, a 1:3 ratio of allenic/alkynic derivatives results.[3]

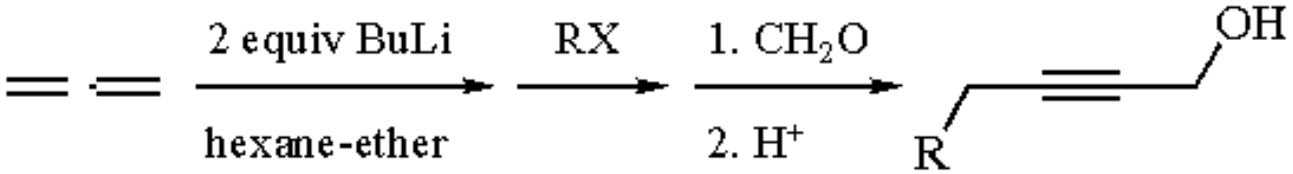

(4)

The dilithio derivative, obtained from allene at -55 °C with 2 equiv of ***n-Butyllithium*** in THF, reacts with the lithium salt of carboxylic acids, leading to conjugated allenyl ketones (eq 5).[16,17]

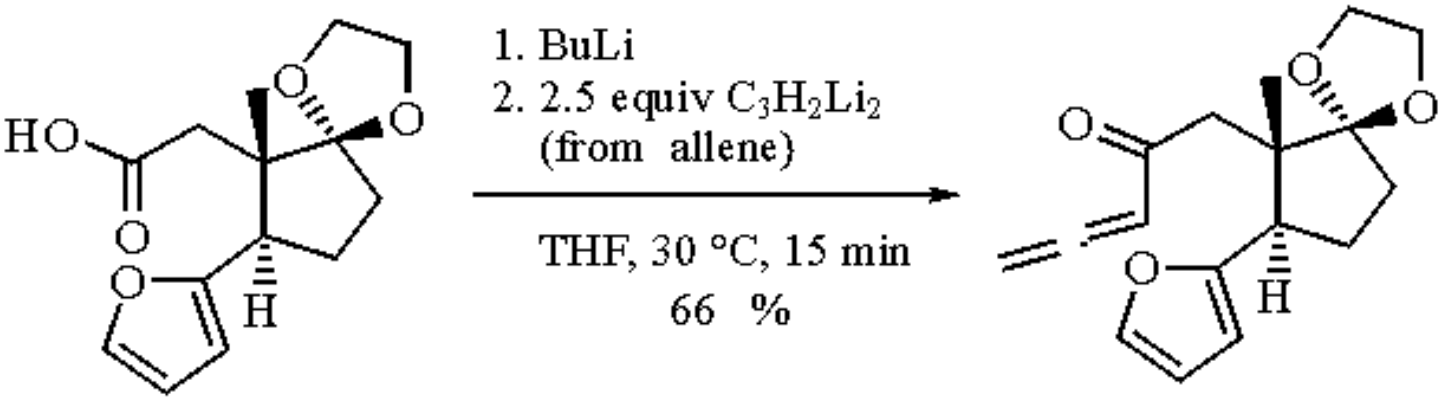

(5)

The general reactivity of 1,3-dilithiopropyne is in line with the propargylide structure.[18] An acetylide structure with a bridging lithium has been calculated for $C_3H_2Li_2$.[19,20]

Related Reactions.

High regiocontrol in favor of propargyl products is also shown by the dilithium reagents prepared from phenyl propargyl sulfide[11] (eq 6) and selenide.[21]

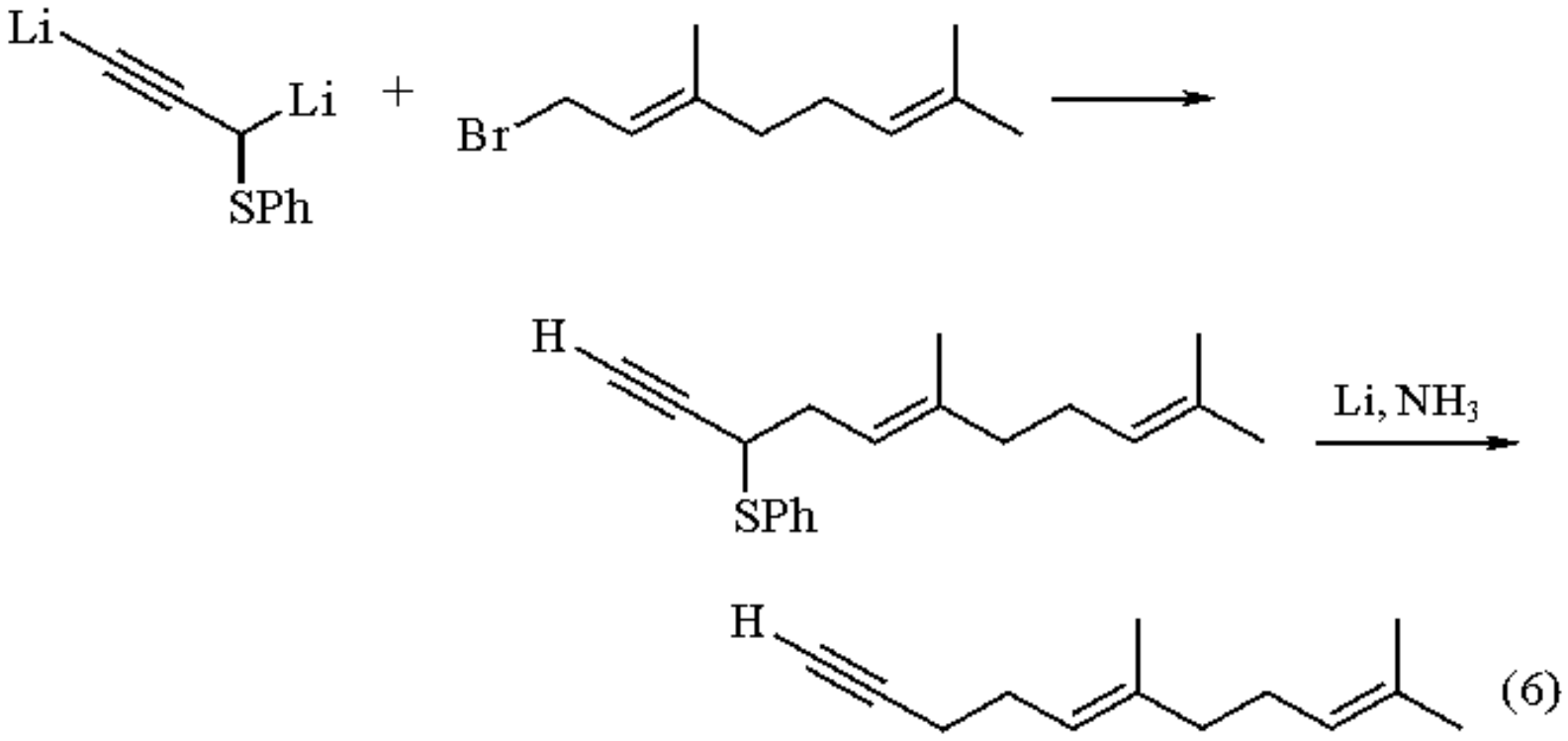

Related Reagents.

Allenyllithium; ***3-Lithio-1-triisopropylsilyl-1-propyne***; ***1-Lithio-3-trimethylsilyl-1-propyne***; ***Propynyllithium***; ***Propynylmagnesium Bromide***.

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Dilithium Acetylide[1]

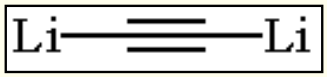

[1070-75-3] · C_2Li_2 · Dilithium Acetylide · (MW 37.90)

(as dianion and as bistrimethylsilyl derivative finds use in the synthesis of variously substituted alkynes,[7] alkenes,[5] γ-diketones,[4] etc.; preferred over its sodium counterpart in reactions with enolizable carbonyls)

Alternate Name: dilithioacetylene.

Physical Data: white crystalline solid; *d* 1.65 g cm^{-3}.

Solubility: insol; used as suspension in THF, Et_2O, liq NH_3, or a hydrocarbon.

Form Supplied in: freshly prepared sample is recommended for good results, although commercially available.

Preparative Methods: from ***Acetylene***:[2] THF (250 mL) is added to ***n-Butyllithium*** (2.0 mol) in ether (1250 mL) maintained at -20 °C and dry acetylene gas bubbled through the solution for 2-3 h to obtain a copious white precipitate. The resulting mixture is boiled under reflux for 12 h to ensure disproportionation of any ***Lithium Acetylide***.

From ***Trichloroethylene***:[3] to 100 mL of 1:1 mixture of anhydrous ether and THF is added 0.6 mol BuLi, cooled to -78 °C, and 0.2 mol ***Trichloroethylene*** in 50 mL of ether is added dropwise over 20 min. The mixture is stirred for 2 h at rt, by which time the flask is full of white solid.

Trichloroethylene as a source is claimed to yield superior results in obtaining dilithioacetylene, as shown by silylating the dianion.

Handling, Storage, and Precautions: highly moisture sensitive; very short exposure to air under good ventilation allowed. Use of freshly prepared solution advised. Use in a fume hood.

γ-Diketone Synthesis.[4]

This is a convenient reagent for preparing synthetically useful γ-diketones not generally accessible by other methods. Dilithium acetylide adds to two moles of aldehyde to give alkynic glycols, which upon catalytic reduction followed by oxidation using Sarett's procedure give 1,4-diketones in moderate to good yields (eq 1).

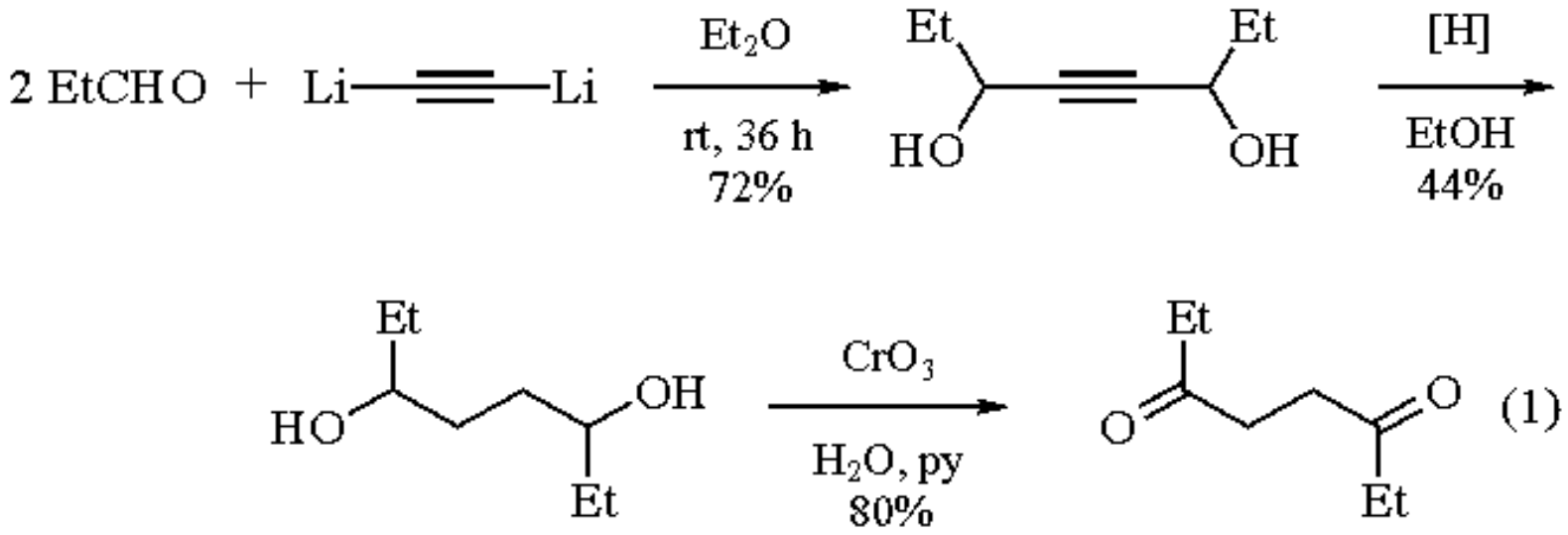

This approach to γ-diketones is superior to the complementary bis-dithiane route, especially with secondary and tertiary aldehydes.

Substituted Alkenes.[5]

Dilithioacetylene with trialkylboranes gives dilithium ethynylbis(trialkylborates), which on treatment with ***Iodine*** followed by hydrolysis or oxidation give alkenes or ketones. Alkenes thus obtained are a mixture of (*E*) and (*Z*) isomers. However, an alternate methodology using equimolar amounts of ***Cyanogen Bromide*** and ***Sodium Methoxide*** to treat the borate offers a convenient route to obtain (*E*)-alkenes exclusively. If 3 equivs of BrCN to 1 equiv of NaOMe are used, tri- and tetrasubstituted alkenes are formed (eq 2).

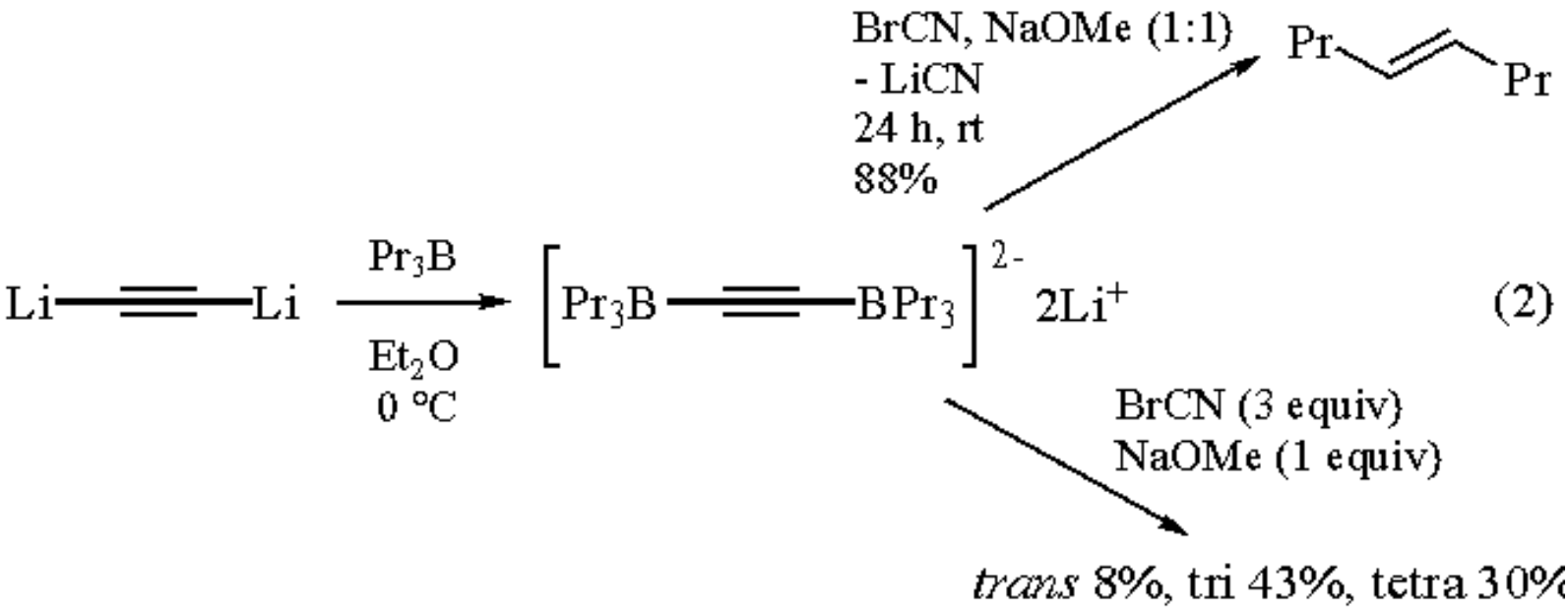

The yield for the disubstituted alkene drops considerably if the R group is not primary.

Arylpropargyl Amines.[6]

Therapeutically useful aryl propargylamines are obtainable in virtually quantitative yield by the reaction of dilithium acetylide with *N*-(methoxymethyl)aniline (eq 3). The product propargyl aniline can be further transformed by the same approach to symmetric and unsymmetric aryl diamines. This method is superior to the traditional *N*-alkylation method or the Mannich reaction in terms of yields and simplicity.

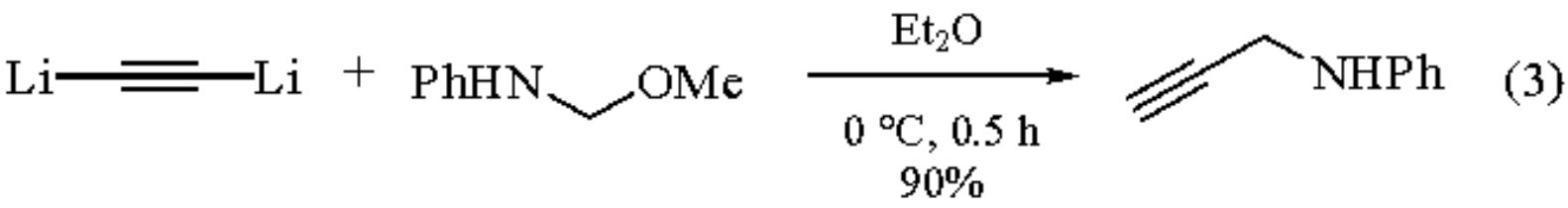

Bistrimethylsilylacetylene.[7]

Although alkynide anions are excellent nucleophiles and readily undergo acylation and alkylation with appropriate electrophiles, reactions with tertiary alkyl halides are not synthetically useful because of the competing elimination reaction. However, tertiary alkylation of alkynic carbon is possible via bis-silylalkynes under Lewis acid catalysis in high yields (eq 4).

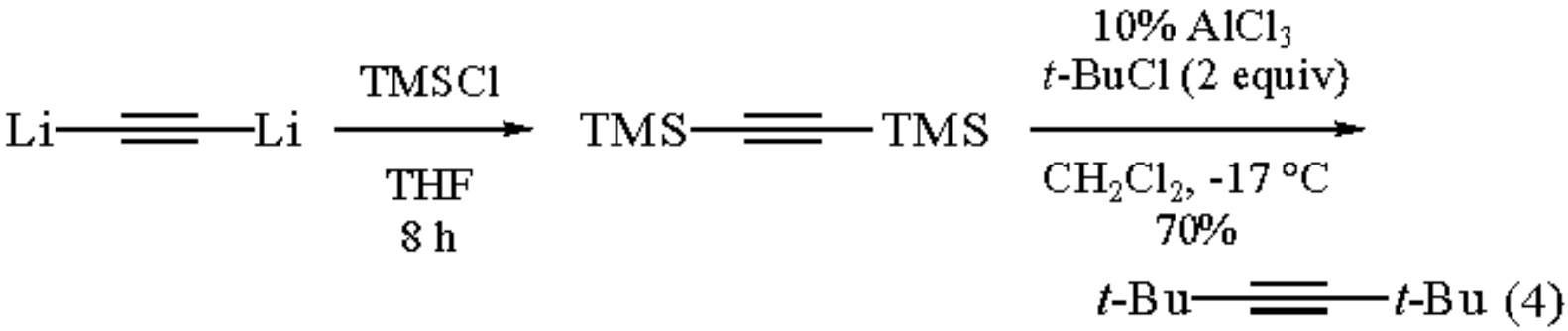

Bis(1-adamantyl)acetylene is also prepared by this route. This reaction fails with primary or secondary alkyl halides.

Bis(trimethylsilyl)acetylene finds use, inter alia, as a dienophile,[8] and in making iodoethynyltrimethylsilane[9] which, with arylcopper reagents, is used to make arylalkynes.[10]

Related Reagents.

Acetylene; ***Bis(trimethylsilyl)acetylene***; ***Ethynyldimethylaluminum***; ***Ethynylmagnesium Bromide***; ***Lithium Acetylide***; ***Tri-n-butylstannylacetylene***; ***Trimethylsilylacetylene***.

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Dilithium Cyanobis(dimethylphenylsilyl)cuprate

$(Me_2PhSi)_2Cu(CN)Li_2$

[110769-32-9] · $C_{17}H_{22}CuLi_2NSi_2$ · Dilithium Cyanobis(dimethylphenylsilyl)cuprate · (MW 373.97)

(higher-order copper reagent for transfer of a dimethylphenylsilyl group to enones, allenes, alkynes, epoxides, and alkyl halides)

Physical Data: relatively stable reagent at rt; usually prepared in situ at 0 °C.

Solubility: sol THF (-78 °C and above).

Preparative Methods: prepared[1] by adding 0.5 equiv of dry ***Copper(I) Cyanide*** to dimethylphenylsilyllithium in THF (eq 1), which in turn is generated from ***Chlorodimethylphenylsilane*** and ***Lithium*** metal. Analogous bis(trimethylsilyl)cyanocuprates are prepared in a similar manner.

$$2\ Me_2PhSi\text{-}Li \xrightarrow[\text{THF, 0 °C}]{\text{CuCN}} \underset{\textbf{(1)}}{(Me_2PhSi)_2Cu(CN)Li_2} \qquad (1)$$

Handling, Storage, and Precautions: cannot be stored or isolated. Care must be taken to avoid oxygen and moisture in the reaction system. Use in a fume hood.

Structure and Properties of the Reagent.

Low-temperature ^{29}Si, ^{13}C, and ^{1}H NMR spectroscopic techniques have been used to probe the nature of these higher-order cuprates.[2] These studies showed conclusively the facile dissociation-reassociation of ligands on copper. In the presence of ***Methyllithium***, dimethylphenylsilyllithium, and copper(I) cyanide, a mixed metallocuprate is formed (eq 2). The metallocuprate (**2**) preferentially transfers the dimethylphenylsilyl group to enones and 1-alkynes.

$$(Me_2PhSi)_2Cu(CN)Li_2 + MeLi \rightleftharpoons \underset{\textbf{(2)}}{(Me_2PhSi)(Me)Cu(CN)Li_2} \qquad (2)$$

Conjugate Additions to Enones.

In general, the reactivities of lower-order and higher-order cyano silylcuprates are very similar toward α,β-unsaturated ketones in ether (eq 3).[2] In some cases, as with alkynic esters, a higher-order reagent gives higher yields and greater stereoselectivity at -78 °C. When the bis(trimethylsilyl)cyanocuprate (**3**) was added to ethyl 2-butynoate, a high yield of only the (*E*)-isomer was obtained (eq 4).[3]

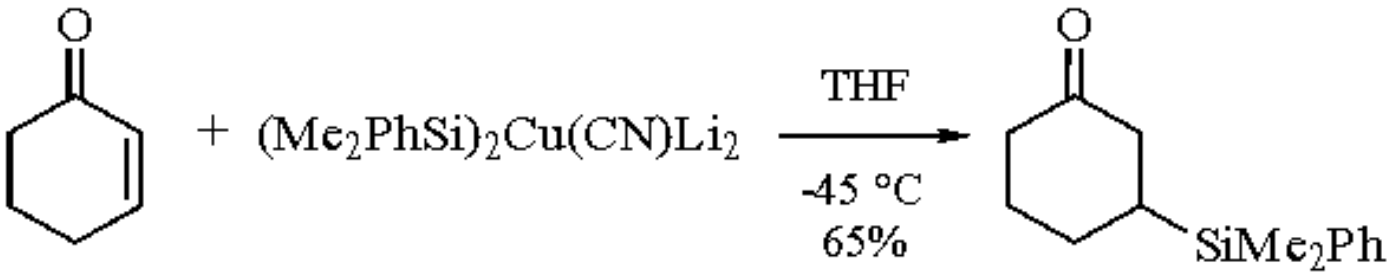

(3)

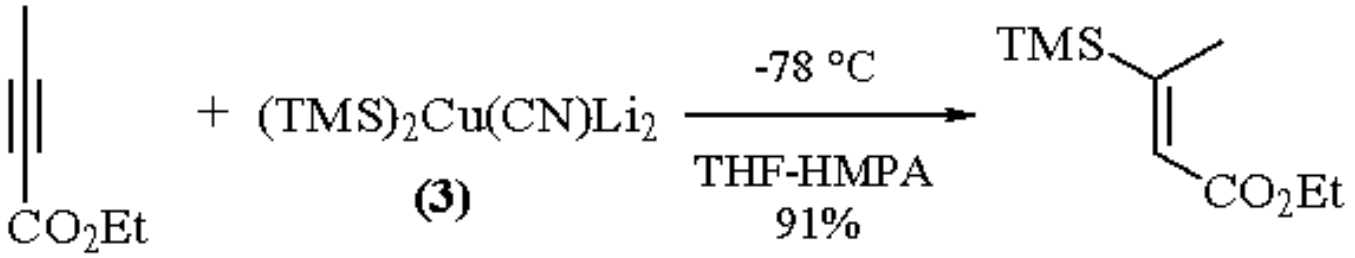

(4)

With cyclohexenone, the corresponding lower-order cuprate gave a 58% product yield and, in the case of eq 4, a mixture of (*E*/*Z*) adducts was observed with the corresponding lower-order cuprate. Interestingly, the mixed (dimethylphenylsilyl)(methyl)cyanocuprate (**2**) gave the highest yield (94%) of adduct with cyclohexenone.

Silylcupration of Alkynes.

Higher-order silyl cuprates such as (**1**) add regioselectively to terminal alkynes in a *cis* fashion, and the intermediate vinylcopper species (**4**) may be trapped with electrophiles to give 2,2-disubstituted vinylsilanes (**5**) (eq 5).[1,2] Corresponding reactions with the lower-order cuprate of reagent (**1**) give low yields of regioisomeric vinylsilanes upon protonation.[4]

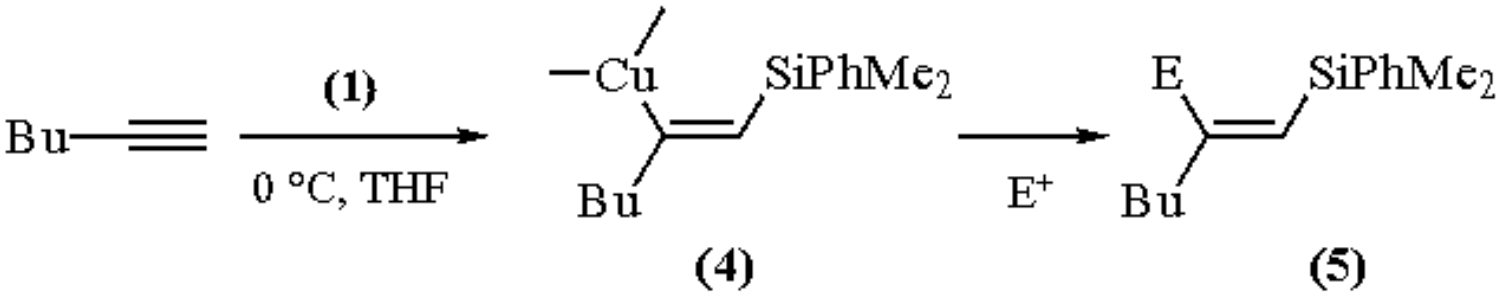

(5)

Typical electrophiles (E^+) that have been employed are ammonium chloride for protonation (94% yield), ***Iodomethane*** (71%), cyclohexenone (54%), and ***Propylene Oxide*** (89%). An example of trapping a vinylcopper species with an ethyl

acrylate precursor is shown in eq 6 for the synthesis of the vinylsilane (**6**).[4,5]

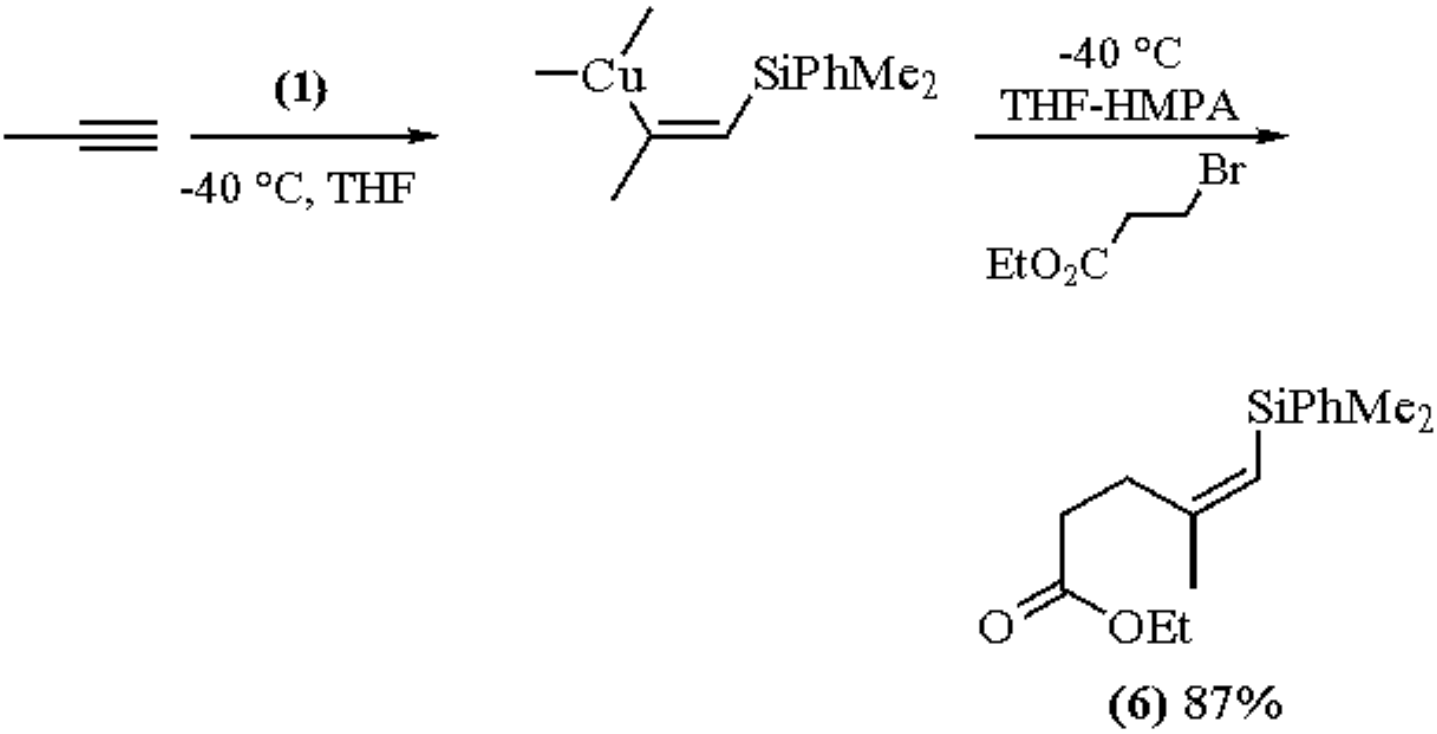

Silylcupration of Allenes.

As a type of activated alkene, allenes undergo silylcupration with reagent (**1**) to give either vinyl- or allylsilanes.[6] Simple alkylallenes react quickly at -78 °C to give allylsilanes cleanly (eq 7). In this case the silyl group is transferred to the less substituted carbon of the allene.

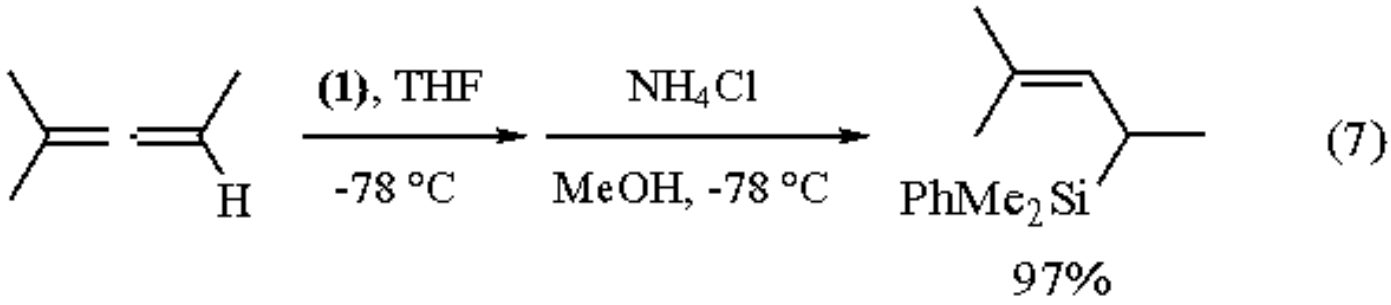

With allene itself or terminal allenes the regioselectivity is reversed and vinylsilanes are the major products.[7,8] In these cases an intermediate allylcuprate (**7**) is generated which can be quenched with electrophiles such as ***Chlorine***, ***Acetyl Chloride***, or a proton to give products (**8**), (**9**), and (**10**), respectively (eq 8).

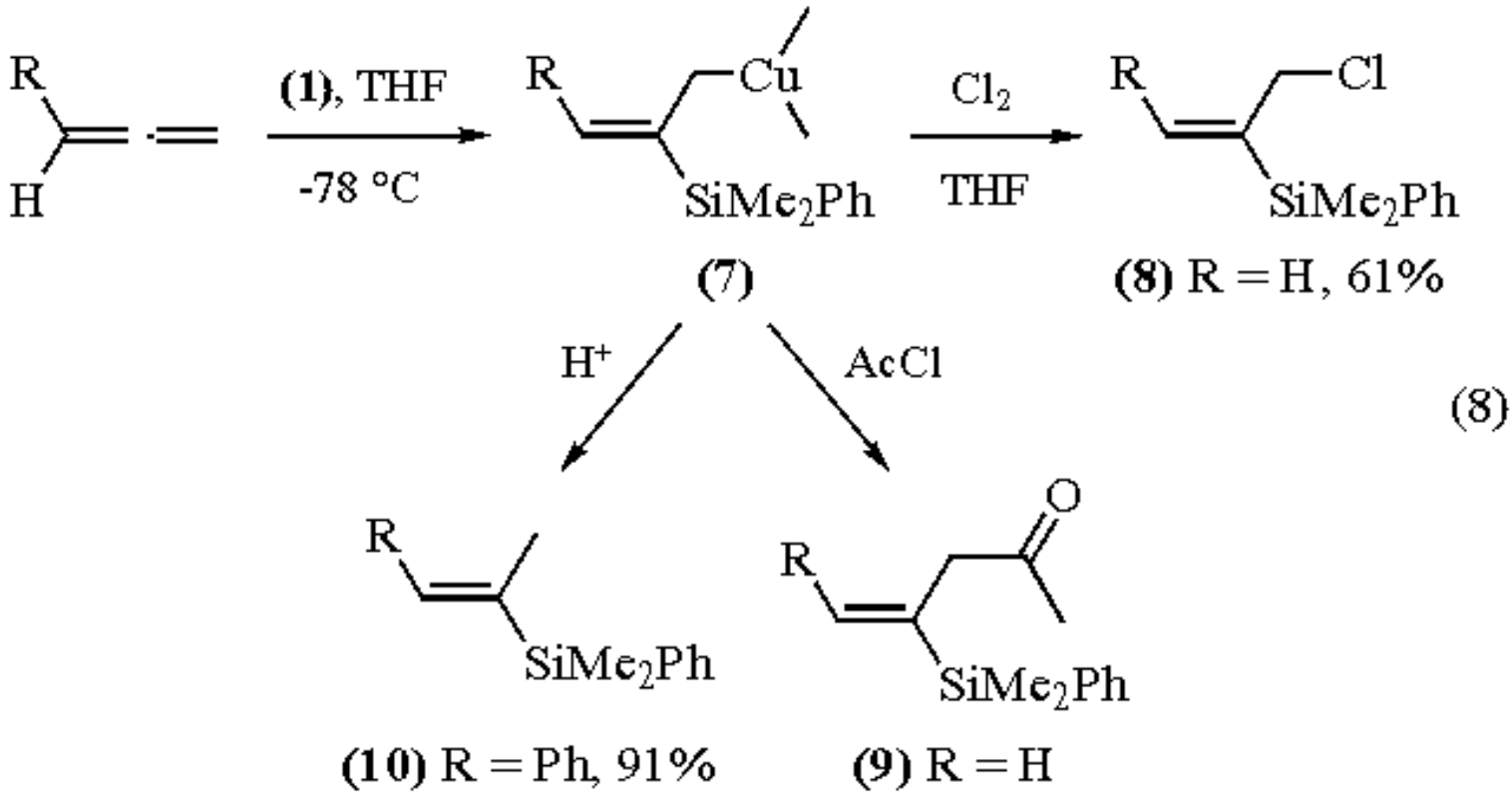

(8)

Intermediate (**7**) (R = H) behaves abnormally when reacted with cyclohexenone and iodine. In the former case, 1,2-addition, and not conjugate addition, prevails; in the latter case, an unusual rearrangement occurs to form the 2-iodoallylsilane (**11**) (eq 9).

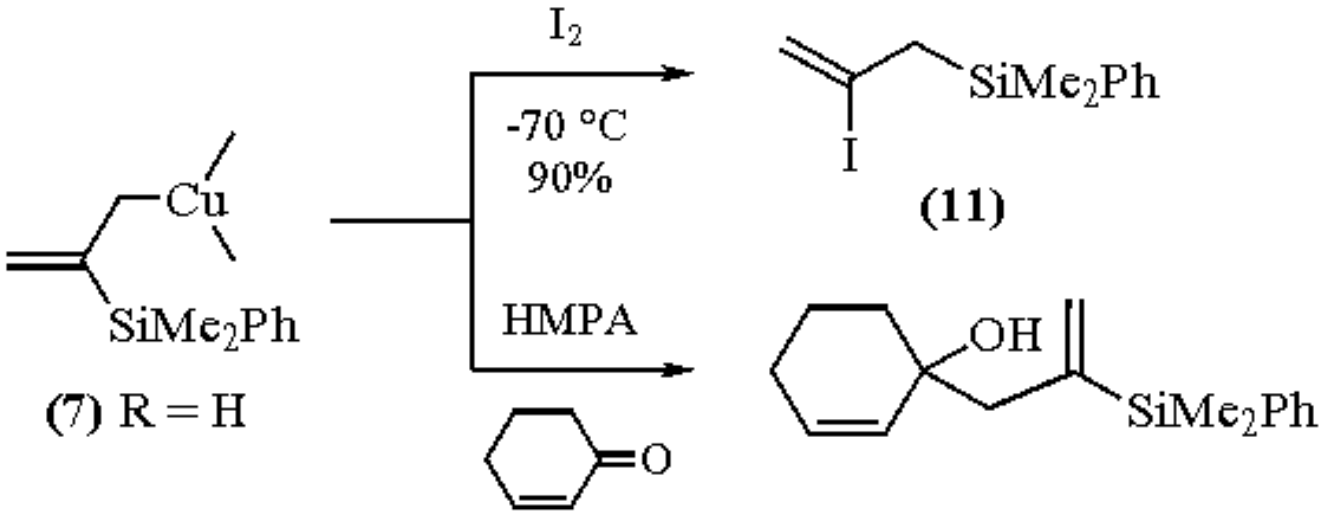

(9)

Previously, the reactions of reagents (**1**) and (**3**) with 3,3-dimethylallene were reported to give the allylsilane adduct (**12**) initially which, upon trapping with cyclohexenone and acetyl chloride, produced the expected adducts (**13**) and (**14**), respectively (eq 10).[9]

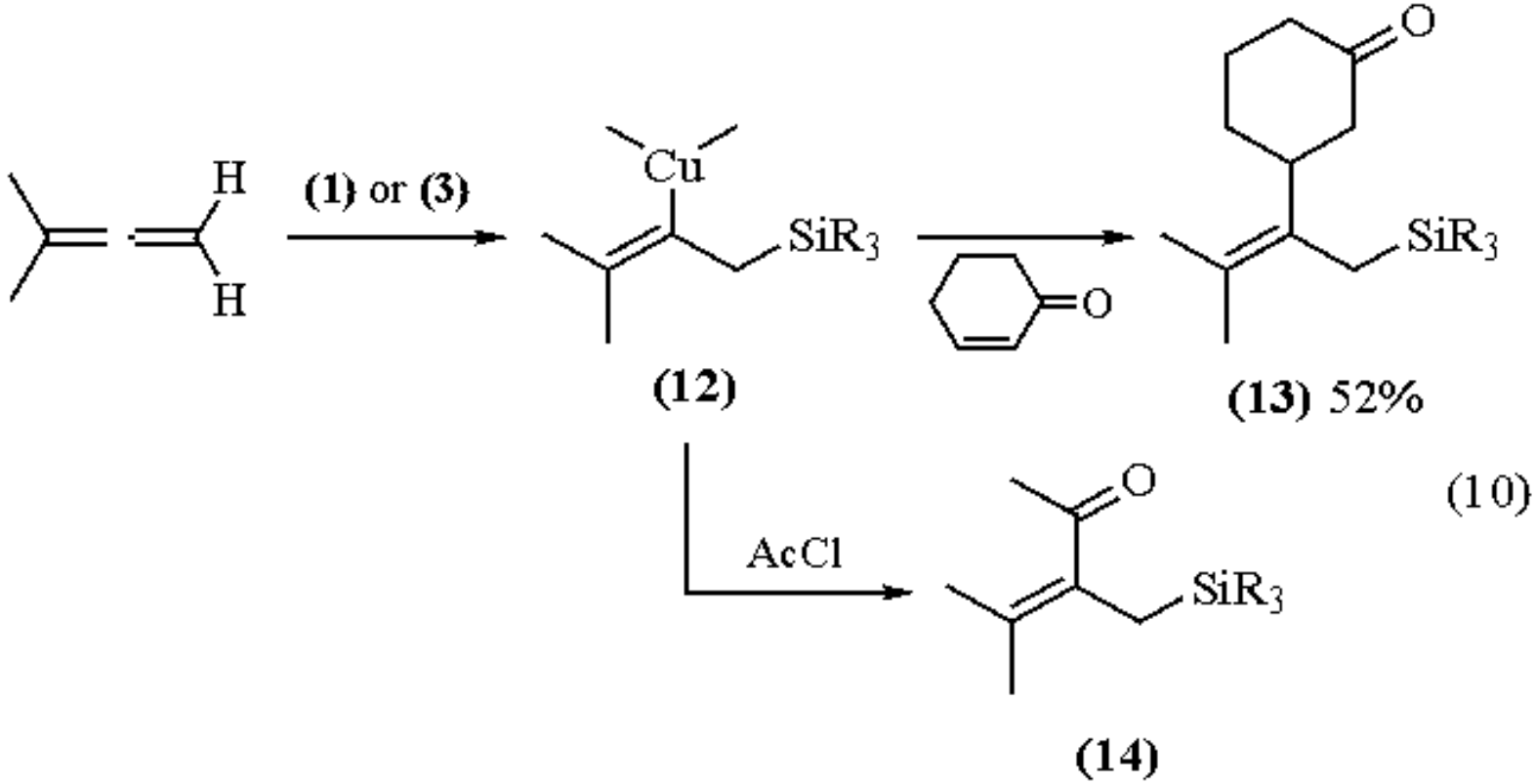

(10)

Silylcuprations of Strained Alkenes.

The reactions between oxabicyclo[3.2.1]octenones and reagent (**1**) and its lower-order analog have been studied.[10] Silylcupration of 8-oxabicyclo[3.2.1]oct-6-en-3-one (**15**) with (**1**) is rapid and is followed by a slower step involving trapping onto the carbonyl group at C-3 to give a ring-closed cyclobutanol product (**16**) along with some of the protonated ketone (**17**) (eq 11).

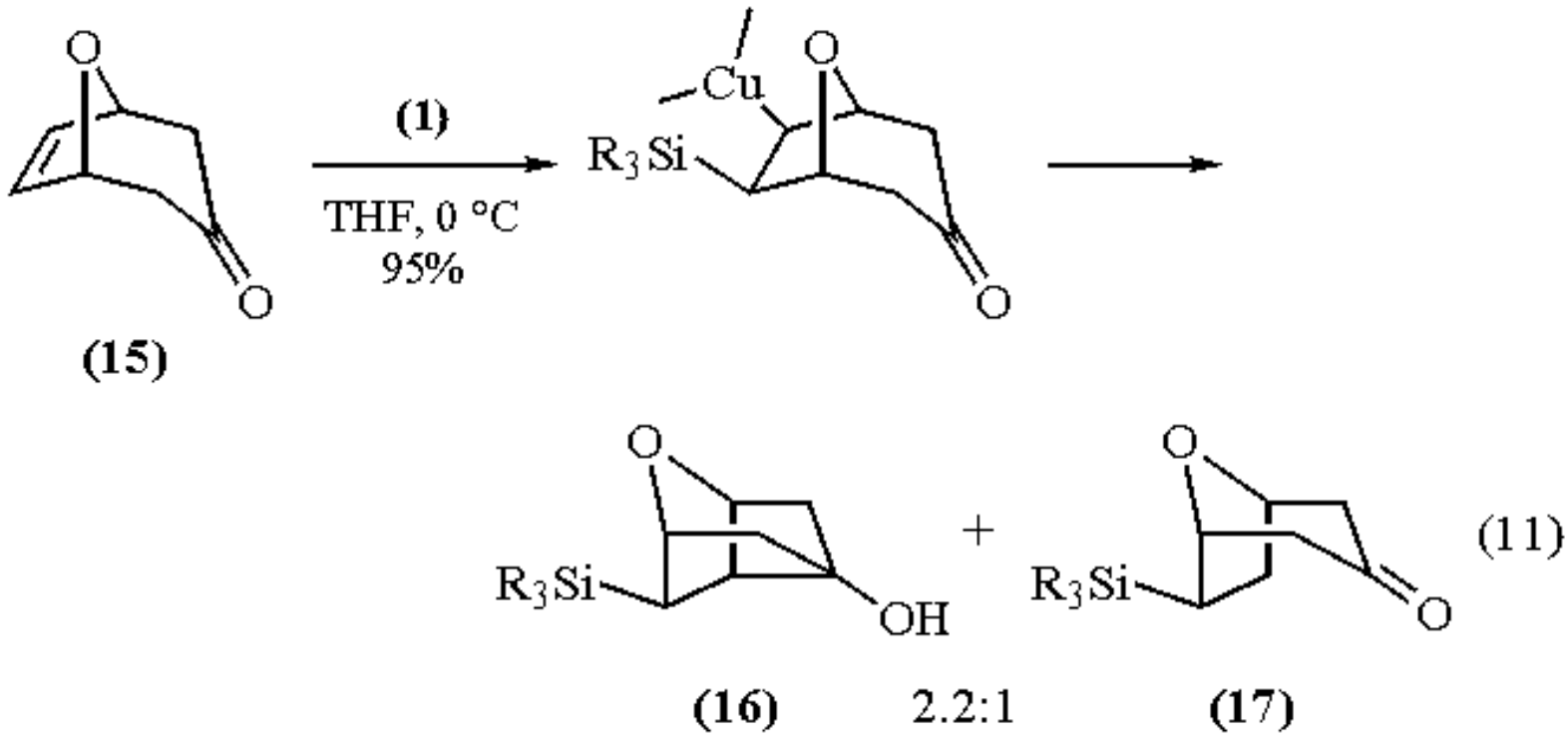

(11)

Silylcupration of α-methyl substituted derivatives of (**15**) produced intermediates (**18**) which undergo such slow ring closure onto the ketone that (**18**) could be trapped with electrophiles (MeI or H^+). In an unusual oxidation process, treatment of intermediate (**18**) (R^1 = R^2 = Me) with dry silica gel produced the β-hydroxysilane (**19**) in quantitative yield (eq 12). Product (**19**) easily undergoes a base-catalyzed Peterson alkenation to the starting alkene.

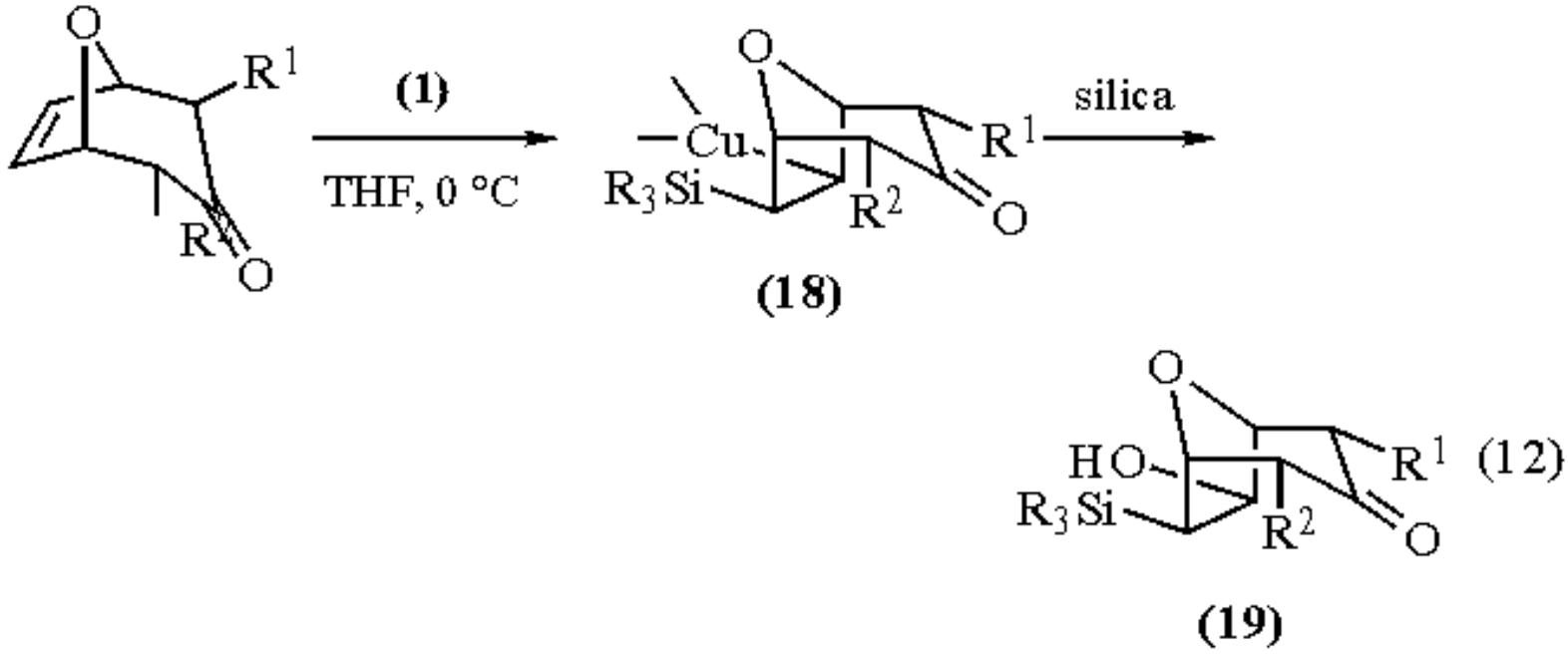

In summary, the higher-order silyl cuprates (**1**) and (**3**) tend to be more reactive and more nucleophilic than their lower-order counterparts in silylcuprations and S_N2-like displacements. Both classes of reagents are fairly stable up to ambient temperatures.

Related Reagents.

Dimethylphenylsilyllithium; ***Dimethylphenylsilyl(methyl)magnesium***; ***Lithium Cyano(dimethylphenylsilyl)cuprate***.

---

1. Fleming, I.; Roessler, F. *CC* **1980**, 276.
2. Sharma, S.; Oehlschlager, A. C. *JOC* **1991**, *56*, 770.
3. Audia, J. E.; Marshall, J. A. *SC* **1983**, *13*, 531.
4. Hoeman, M. Ph.D. Thesis, The University of Michigan, 1993.
5. Fleming, I.; Newton, T. W.; Roessler, F. *JCS(P1)* **1981**, 2527.
6. Fleming, I.; Pulido, F. J. *CC* **1986**, 1010.
7. Singh, S. M.; Oehlschlager, A. C. *CJC* **1991**, *69*, 1872.
8. Fleming, I.; Rowley, M. *T* **1989**, *45*, 413.
9. Cuadrado, P.; González, A. M.; Pulido, F. J.; Fleming, I. *TL* **1988**, *29*, 1825.
10. Lautens, M.; Belter, R. K.; Lough, A. J. *JOC* **1992**, *57*, 422.

Joseph P. Marino & David P. Holub

Dilithium Pentamethyltricuprate[1]

$Li_2Cu_3Me_5$

[61701-36-8] · $C_5H_{15}Cu_3Li_2$ · Dilithium Pentamethyltricuprate · (MW 279.69)

(highly regiospecific organometallic methylating agent for conjugate addition to enones[2] and enals,[3,4] and for displacement of allylic acetates,[5] carbamates,[5] and lactones[6])

Solubility: sol diethyl ether to -78 °C.

Analysis of Reagent Purity: low temperature NMR spectroscopy in ether indicates a reagent of discrete Me(5):Cu(3) stoichiometry as a structurally complex aggregate.[7]

Preparative Method: to ***Copper(I) Iodide*** (2.0 mmol) in 5.0 mL ether at -78 °C is added a 0.95 M solution of ***Methyllithium*** (3.3 mmol). Insoluble MeCu is initially produced with 1 equiv of MeLi:CuI; subsequent addition of MeLi dissolves most MeCu; a small amount of MeCu remains after complete addition.

Handling, Storage, and Precautions: use immediately following preparation, in a fume hood.

α,β-Unsaturated Ketones.

$Li_2Cu_3Me_5$, formed as an aggregate in ether when the MeLi:MeCu ratio is at least 0.66:1, is a more highly regiospecific conjugate methylating agent for α,β-unsaturated ketones than ***Lithium Dimethylcuprate*** or ***Dilithium Trimethylcuprate***. Rates of reaction for $Li_2Cu_3Me_5$ with enones are comparable to $LiCuMe_2$ and Li_2CuMe_3, even in hindered systems (eq 1).[2]

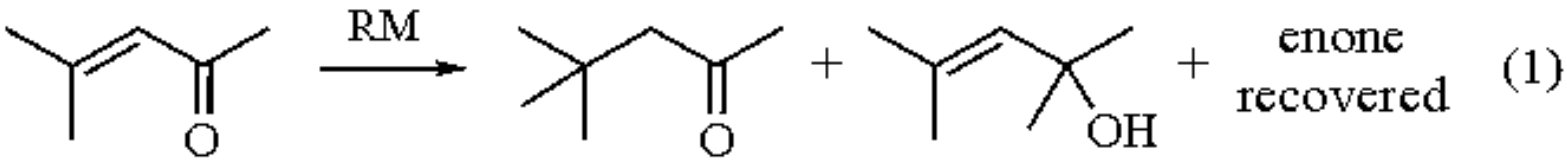

RM =		
	$LiCuMe_2$	82: 1:17
	Li_2CuMe_3	19:79:2
	$Li_2Cu_3Me_5$	96: 0:4

α,β-Unsaturated Aldehydes.

$Li_2Cu_3Me_5$ is more effective than $LiCuMe_2$ for the conjugate methylation of enals (eq 2). The use of ether-pentane as solvent was found to increase the ratio of 1,4-methylation to 1,2-methylation by $Li_2Cu_3Me_5$ (eq 3).[3,4]

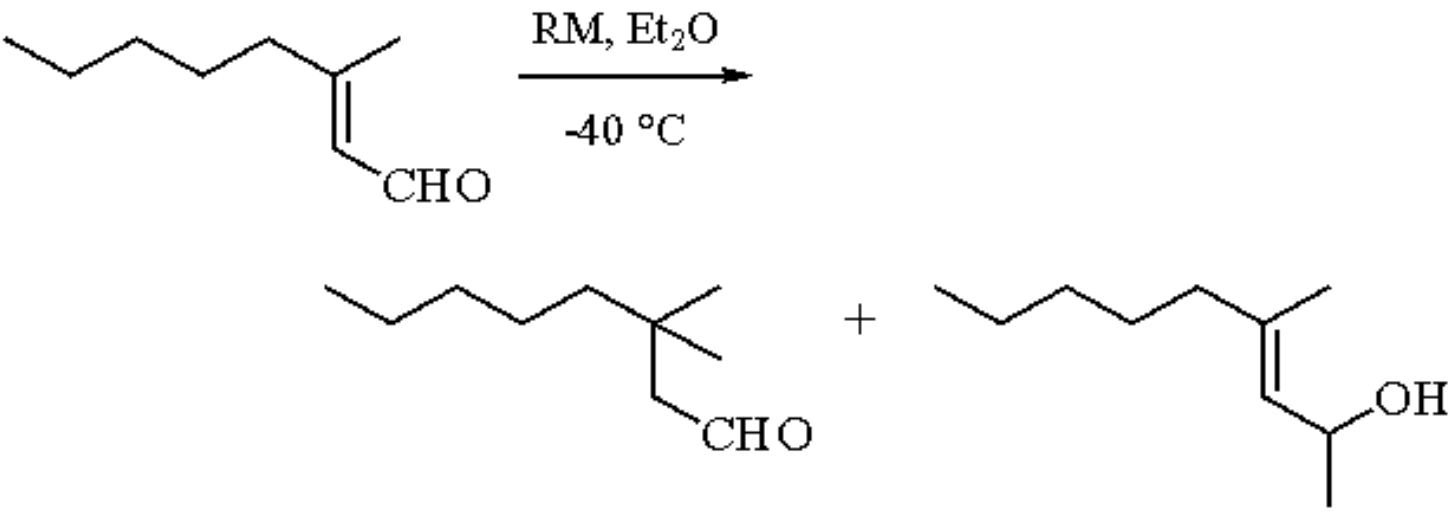

(2)

RM =			
	$LiCuMe_2$	91.5:8.5	90%
	$Li_2Cu_3Me_5$	>99.5:<0.5	90%

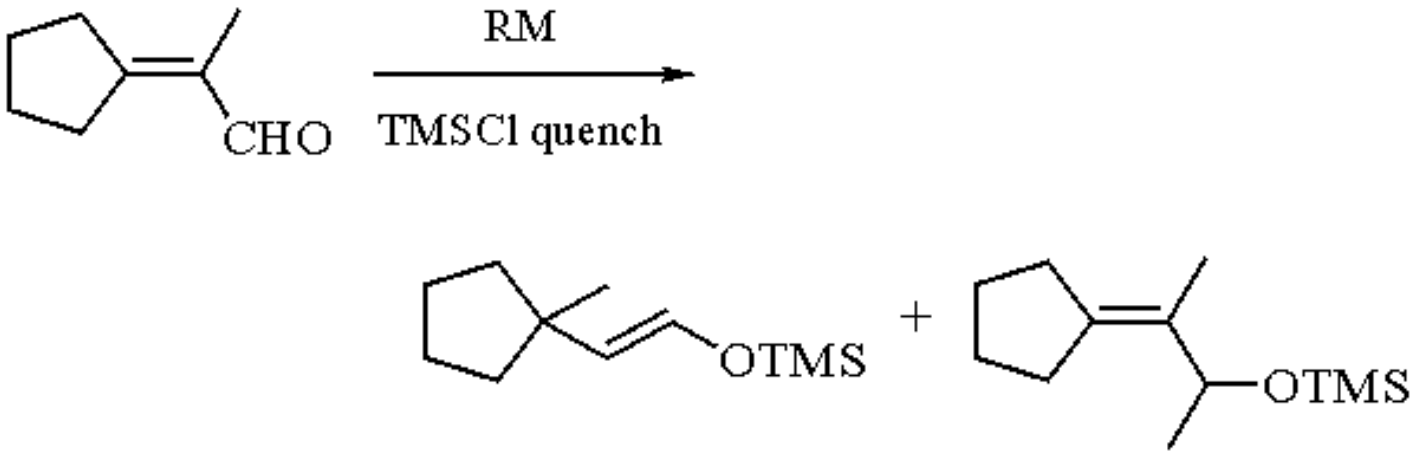

(3)

RM =		
	$LiCuMe_2$ (Et_2O, 86%)	36.0:64.0
	$Li_2Cu_3Me_5$ (Et_2O, 85%)	77.5:22.5
	$Li_2Cu_3Me_5$ (Et_2O-pentane, 88%)	95.1:4.9

Allylic Acetates, Carbamates, and Lactones.

The addition of $Li_2Cu_3Me_5$ to allylic carbamates results in exclusively *syn*,δ-methylation, while $LiCuMe_2$ exhibits depressed regio- and stereochemical control (eq 4). The methylation of allylic acetates occurs with similar regio- and stereospecificity using either $LiCuMe_2$ or $Li_2Cu_3Me_5$; however, the displacement of allylic acetates with Li_2CuMe_3 or

$LiCuMe_2$ generally proceeds with less regio- and stereospecificity than the displacement of the corresponding allylic carbamates (eq 4).[5]

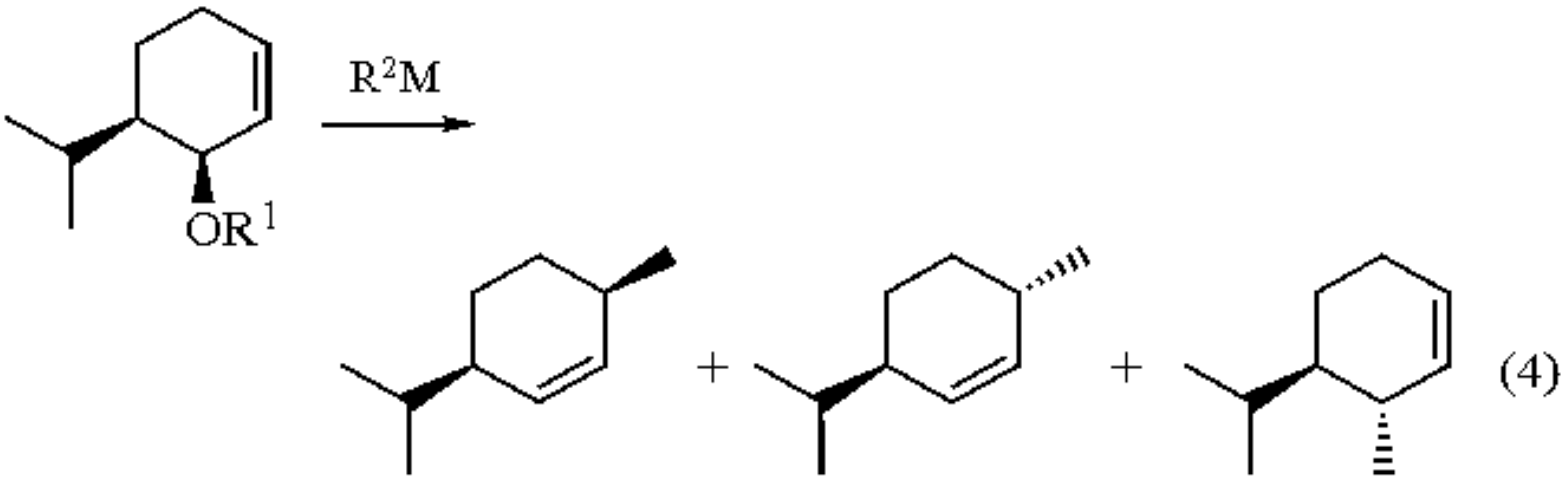

a) $R^1 = CONHPh$

$R^2M = LiCuMe_2$	(79%)	57:27:16
$Li_2Cu_3Me_5$	(92%)	>99:<1:0

b) $R^1 = COMe$

$R^2M = LiCuMe_2$	(89%)	0:65:35
$Li_2Cu_3Me_5$	(87%)	<1:66:33

A detailed study of the methylation of various gibberellin allylic lactones by $Li_2Cu_3Me_5$, $(LiCuMe_2)_2$ and $(LiCu_2Me_3)_2$ revealed the following trends (eq 5): (1) attack at the tertiary position C-10 is possible only by an S_N2' pathway; (2) attack at the secondary carbon C-2 is the most favored reaction, whether by S_N2 or S_N2' attack; and (3) the usual S_N2' *anti* displacement[8] by organocuprates can be suppressed and S_N2' *syn* attack at C-2 can be induced by increasing the steric bulk surrounding C-3. Under these steric constraints, S_N2' *syn* attack at a secondary site is a more favorable reaction than S_N2 displacement at the tertiary carbon C-10.[6]

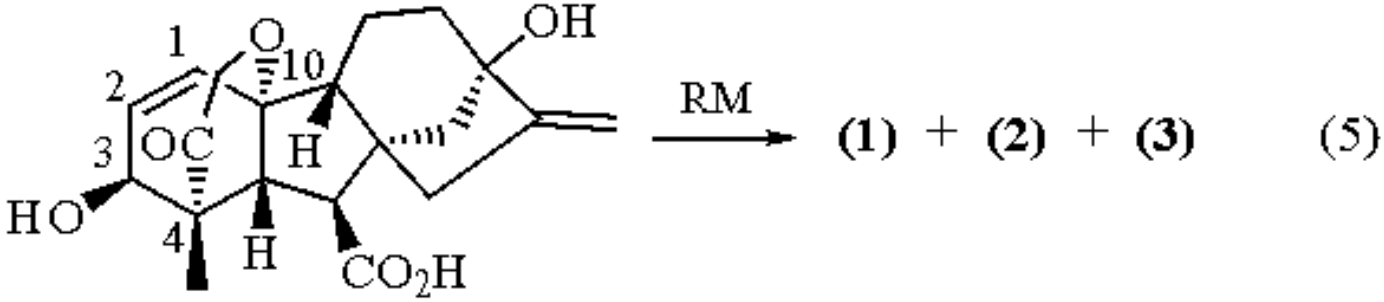

	(1):(2):(3)
RM = $Li_2Cu_3Me_5$	5:80 :14
$(LiCuMe_2)_2$	0:95 :5
$(LiCu_2Me_3)_2$	21:47 :0

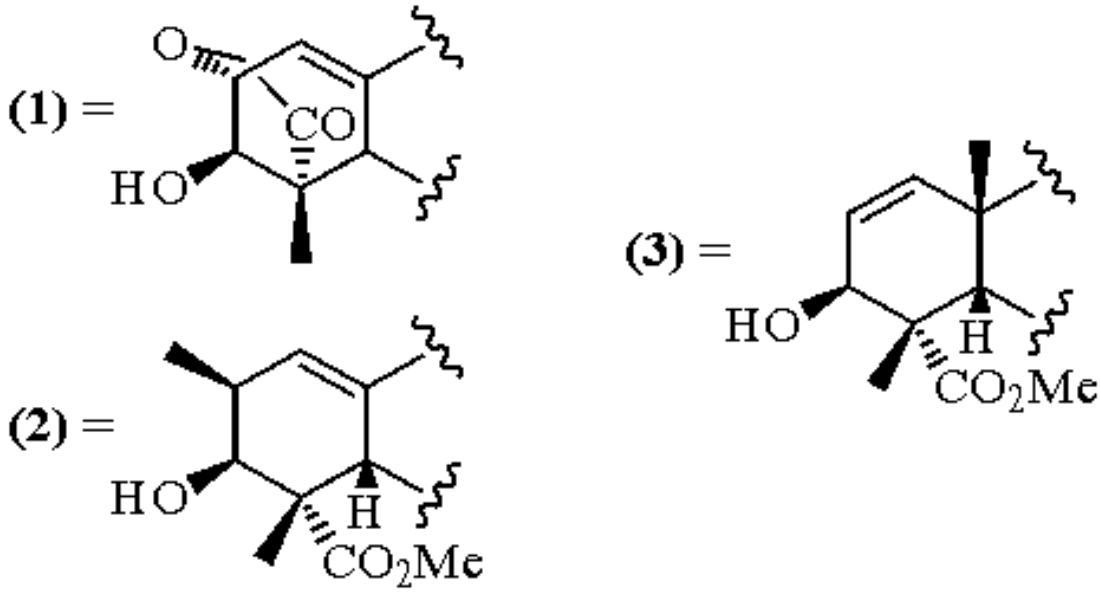

Related Reagents.

Dilithium Trimethylcuprate; ***Lithium Dimethylcuprate***.

---

1. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *T* **1984**, *40*, 5005.
2. Ashby, E. C.; Lin, J. J.; Watkins, J. J. *JOC* **1977**, *42*, 1099.
3. Clive, D. L. J.; Farina, V.; Beaulieu, P. *CC* **1981**, 643.
4. Clive, D. L. J.; Farina, V.; Beaulieu, P. L. *JOC* **1982**, *47*, 2572.
5. Gallina, C. *TL* **1982**, *23*, 3093.
6. Beale, M. H. *JCS(P1)* **1985**, 1151.
7. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *JACS* **1985**, *107*, 3197.
8. Corey, E. J.; Boaz, N. W. *TL* **1984**, *25*, 3063.

Dilithium Tetrabromonickelate(II)

Li_2NiBr_4

[13826-95-4] · Br_4Li_2Ni · Dilithium Tetrabromonickelate(II) · (MW 392.19)

(source of soft nucleophilic bromide, reacting with epoxides[1] and functionalized aziridines[2] regiospecifically)

Solubility: sol THF.

Form Supplied in: prepared from commercially available LiBr and $NiBr_2$.

Preparative Method: anhydrous ***Lithium Bromide*** (6.96 g, 0.08 mol) and ***Nickel(II) Bromide*** (8.72 g, 0.04 mol) are stirred in dry THF (95 mL) at 25 °C. After 48 h, the stirring is stopped and undissolved solids are allowed to settle. The resulting clear dark blue solution is about 0.4M in Li_2NiBr_4. In reactions, 1.6 equiv of the reagent are typically added per equiv of substrate and allowed to stir at the requisite temperature until completion.[1,3]

Handling, Storage, and Precautions: the reagent should be generated in a dry, inert atmosphere and used directly.

Bromohydrins.

Dilithium tetrabromonickelate was initially developed as a source of soft bromide for use in reactions with epoxides.[1a] It was reasoned that tetrabromonickelate as a source of bromide, along with the presence of a hard but mild electrophile (Li^+), would facilitate ring opening in the presence of other acid sensitive groups. Examples below show that epoxides undergo regioselective ring opening to give bromohydrins in which the bromine adds preferentially to the less-hindered position of the epoxide (eqs 1 and 2).

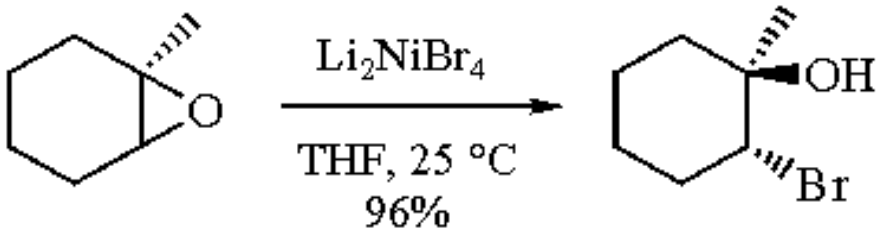

(1)

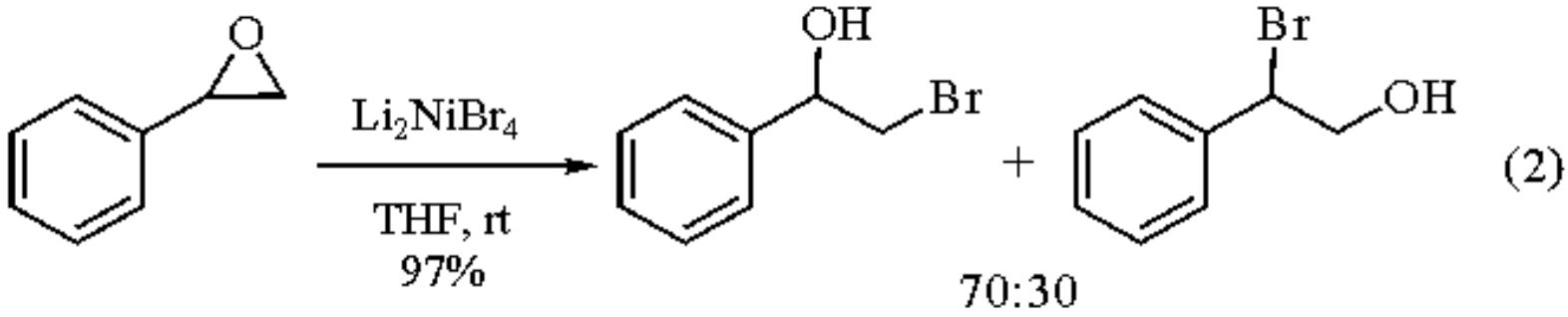

In certain acid or base sensitive compounds, other methods, such as the use of alkali metal salts in the presence of dipolar aprotic solvents, are clearly not satisfactory, in that the resultant bromide ion is somewhat hard and can thus function as a base as well as a nucleophile. The consequences of this are seen in eq 3, where cyclization of the product occurs when LiBr in DMF is used, as opposed to clean epoxide opening without secondary cyclization with Li_2NiBr_4/THF.

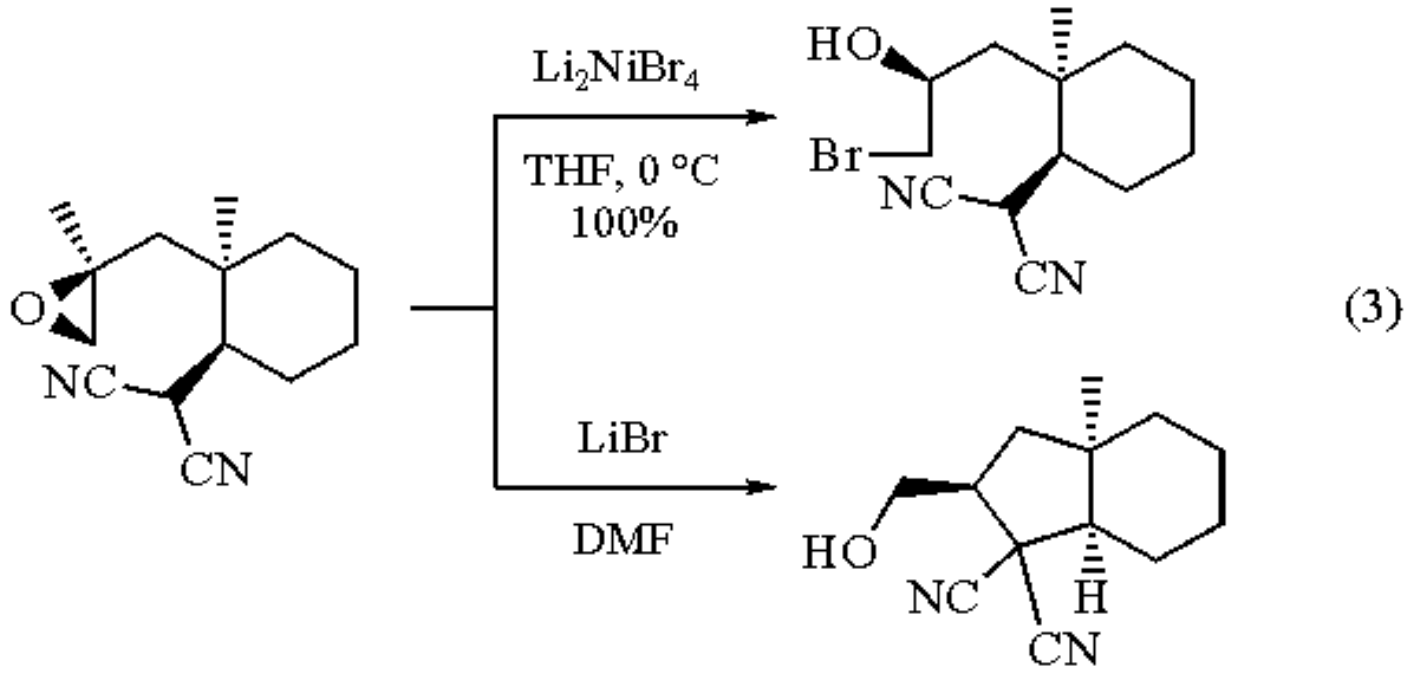

In a synthetic route to α-enol aldehydes, reaction of α-cyano-α-hydroxymethyl epoxides with Li_2NiBr_4, followed by treatment of the mixture of the two intermediate compounds with pyridine/THF, led to the desired aldehyde (eq 4).[3]

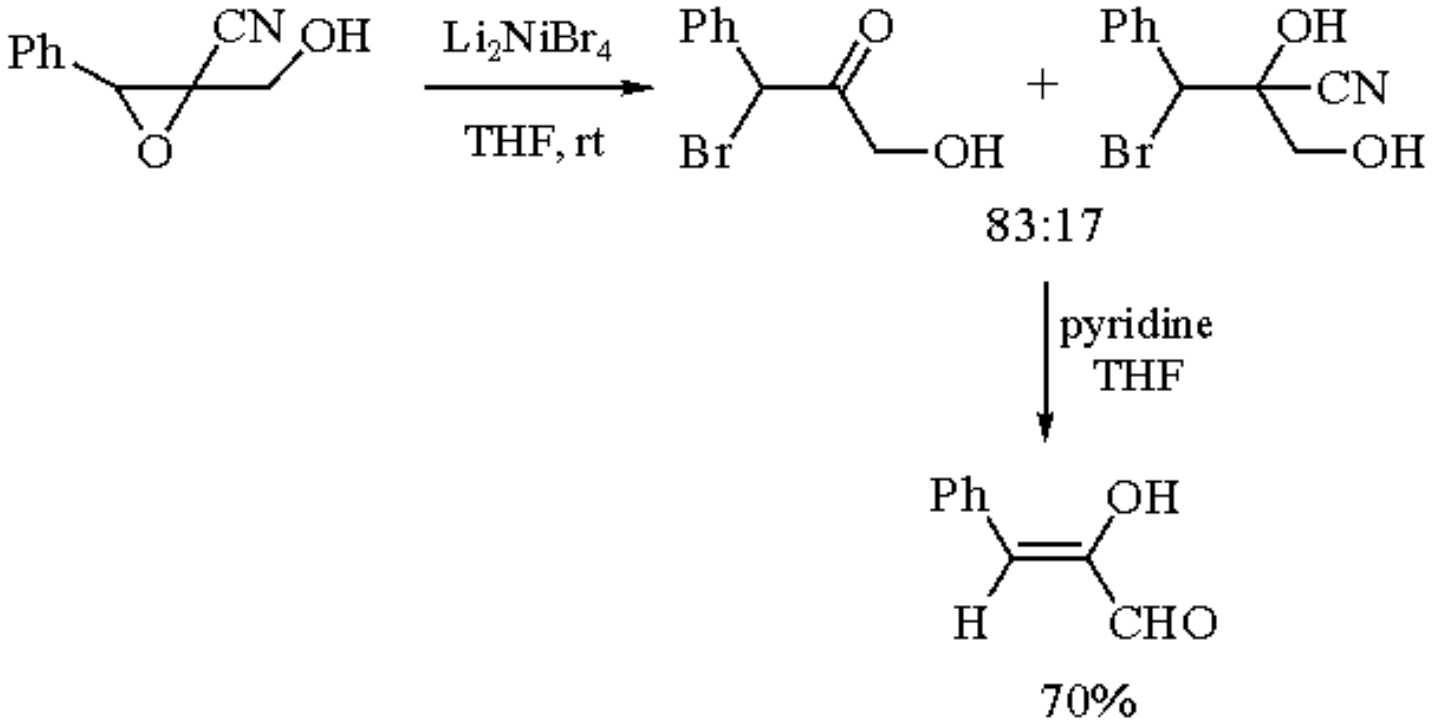

(4)

Aziridine Opening.

Suitably protected and functionalized chiral bis-aziridines, prepared from D-mannitol, were allowed to react with Li_2NiBr_4 in THF. Depending on the protecting group, either chiral polysubstituted piperidines or bis-α-bromoamines were formed (eq 5).[2]

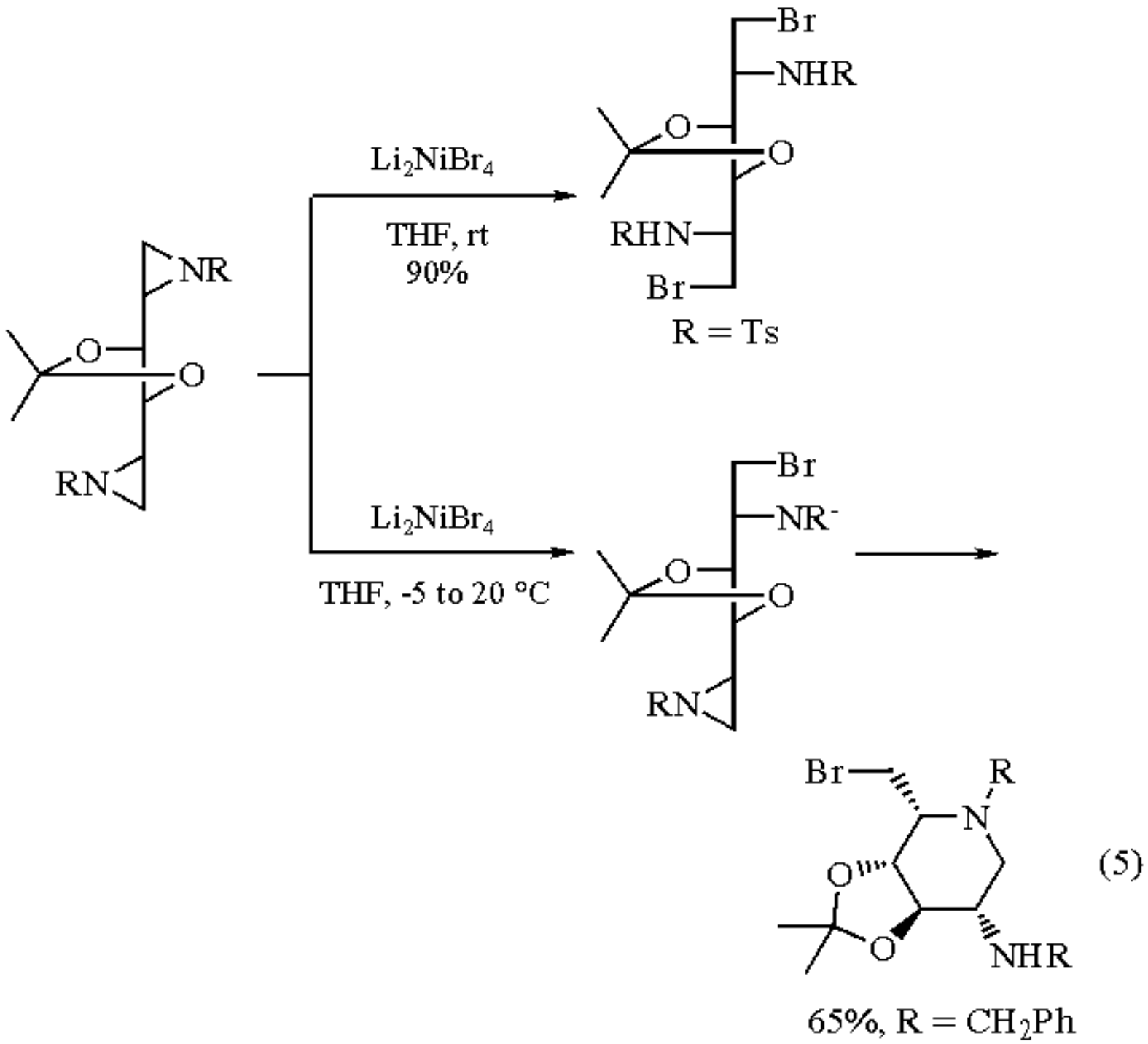

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1. (a) Dawe, R. D.; Molinski, T. F.; Turner, J. V. *TL* **1984**, *25*, 2061. (b) Pansegrau, P. D.; Anderson, K. S.; Widlanski, T.; Ream, J. E.; Sammons, R. D.; Sikorski, J. A.; Knowles, J. R. *TL* **1991**, *32*, 2589.
2. Duréault, A.; Tranchepain, I.; Greck, C.; Depezay, J.-C. *TL* **1987**, *28*, 3341.
3. Layachi, K.; Ariès-Gautron, I.; Guerro, M.; Robert, A. *T* **1992**, *48*, 1585.

Lawrence B. Fertel

Occidental Chemical Corporation, Grand Island, NY, USA

Dilithium Tetrachlorocuprate(II)[1,2]

Li_2CuCl_4

[15489-27-7] · Cl_4CuLi_2 · Dilithium Tetrachlorocuprate(II) · (MW 219.24)

(organic soluble copper catalyst[1] used in catalytic quantities to improve the efficiency of halide[2] and allylic acetate[3] displacements with Grignard reagents; it is used in stoichiometric amounts to open epoxides[4] and aziridines[5a])

Physical Data: d 0.910 g cm^{-3}.

Solubility: sol up to concentrations of 0.5 M in THF.

Form Supplied in: commercially available as a 0.1 M solution in THF.[2a]

Preparative Methods: prepared in THF solution by reaction of ***Lithium Chloride*** (0.2 mol) and ***Copper(II) Chloride*** (0.1 mol).[5b]

Handling, Storage, and Precautions: moisture and oxygen sensitive.

Introduction.

The addition of two or more equivalents of lithium chloride to copper(II) chloride will result in a dark red THF soluble solution of dilithium tetrachlorocuprate.[1,2] Dilithium tetrachlorocuprate has been used most frequently to enhance the efficiency of halide displacements with a Grignard reagent. The reagent is used catalytically in amounts less than 10 mol % and typically it will increase the displacement yield.

Halide Displacements with Grignard Reagents.

The first report describing the use of dilithium tetrachlorocuprate was by Kochi and Tamura in 1971.[2] They described the coupling of *n*-butylmagnesium bromide with *n*-hexyl bromide using Li_2CuCl_4 to afford decane in 78% yield. This report was followed by the use of more complex substrates, including Grignard reagents containing protected ethers, unsaturation, and strained rings with homoallylic halides (eqs 1-3).[6-8] It is noteworthy that displacement predominated over dehydrohalogenation in these cases.

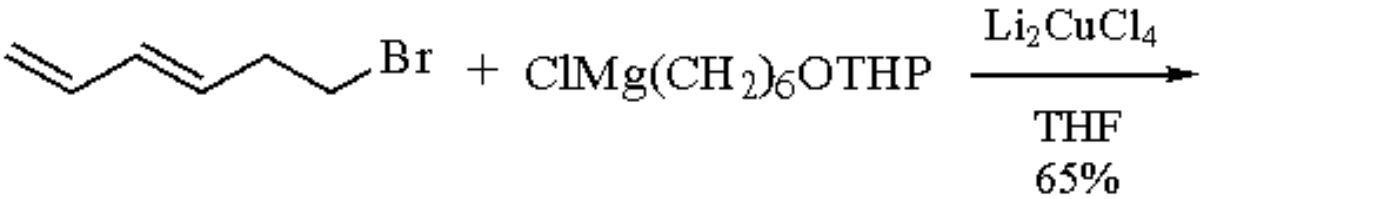

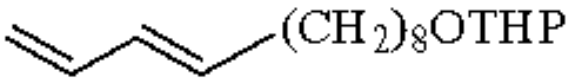

(1)

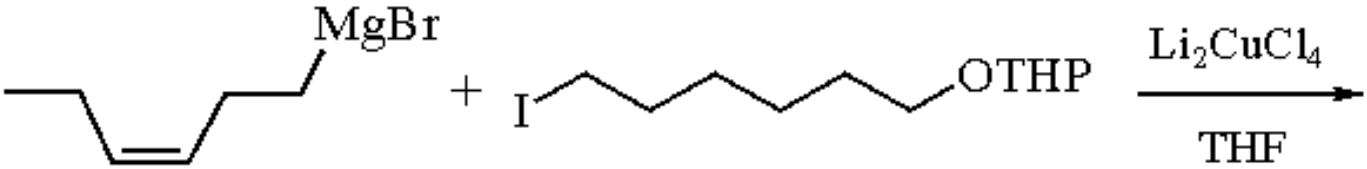

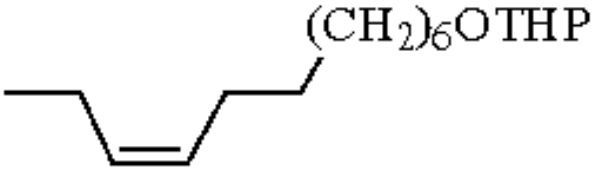

(2)

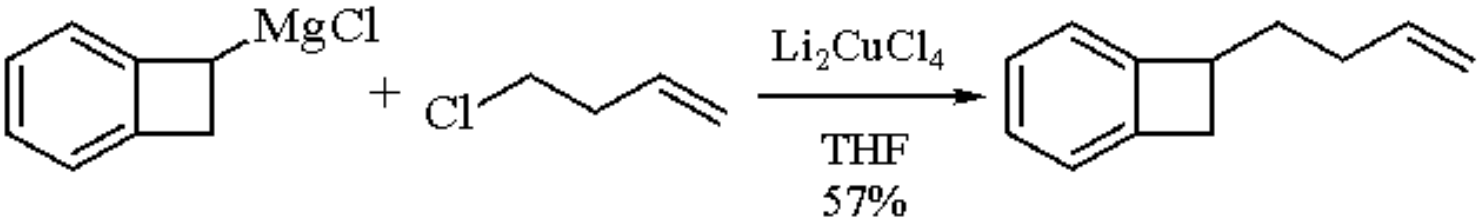

(3)

Sterically hindered Grignard reagents were coupled with toluenesulfonates to afford sterols with modified side chains (eq 4)[9] and with benzylic halides resulting in neopentyl derivatives of naphthalenes (eq 5).[10] In this example the copper catalyst reduced homodimer formation (i.e. 1,2-bisnaphthylethane formation).

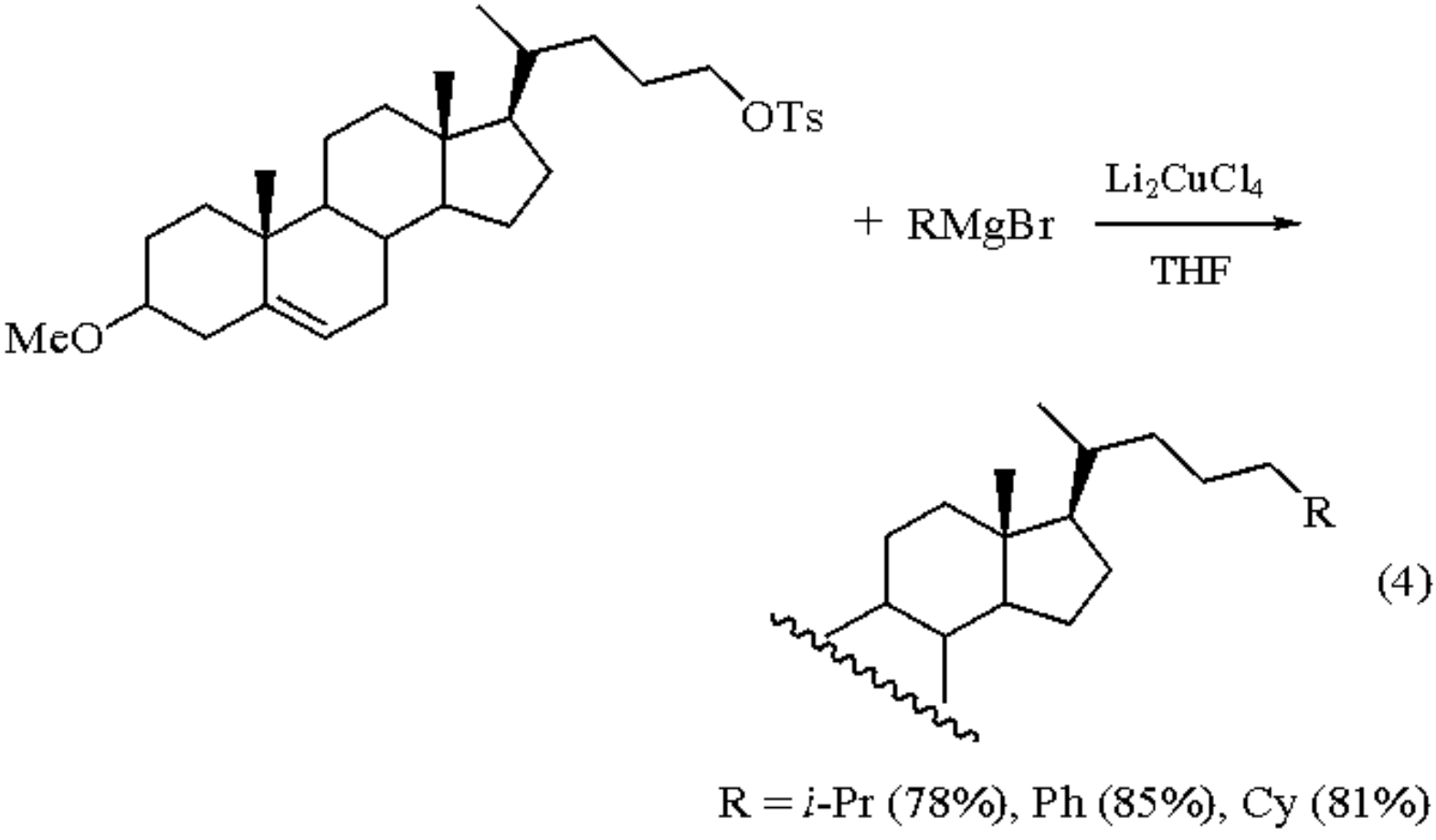

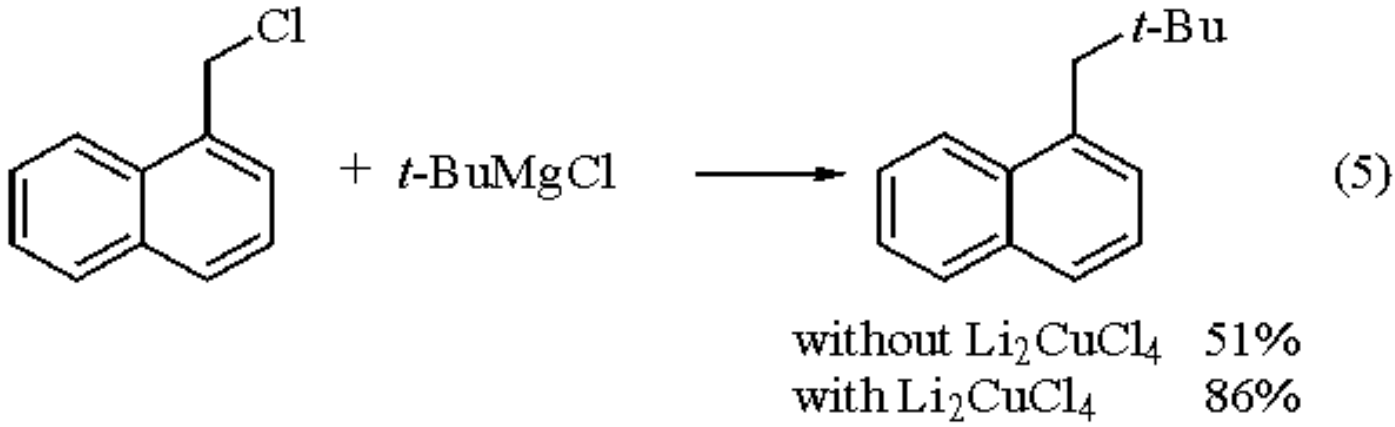

The benzylic type Grignard reagent derived from 3-chloromethylfuran would not displace an allylic halide unless dilithium tetrachlorocuprate was employed (eq 6).[11]

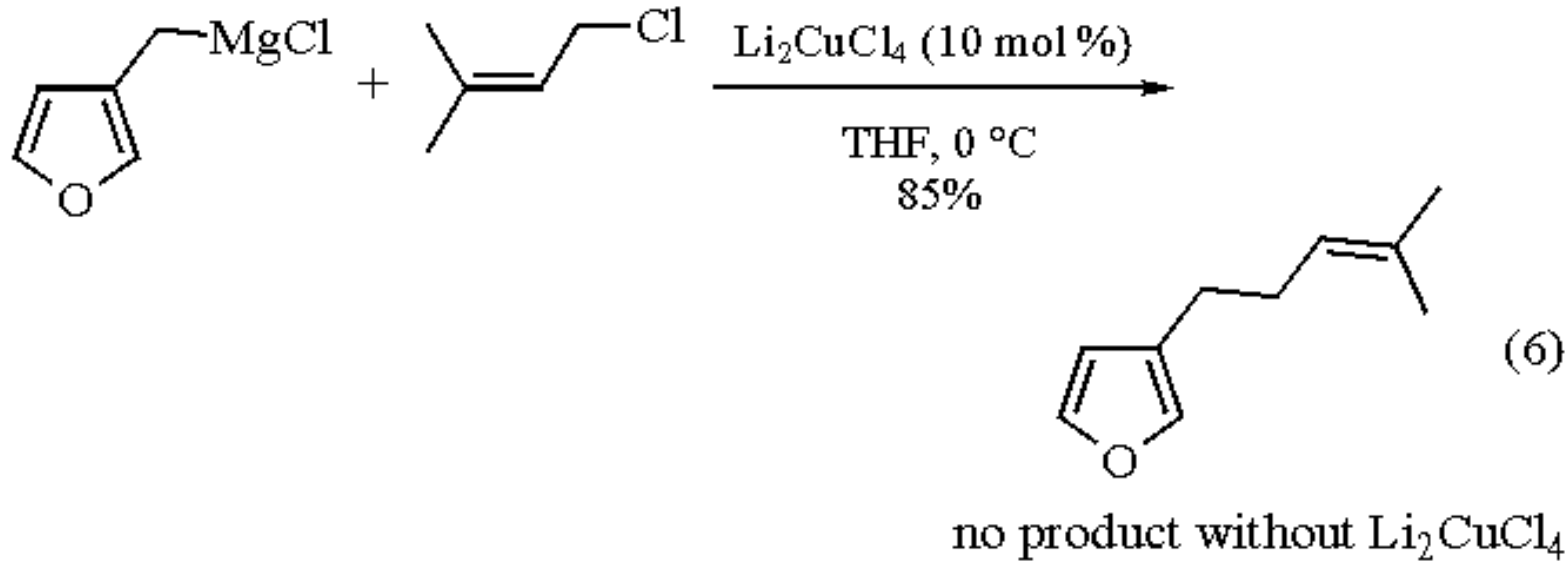

Functionalized Grignard reagents were efficiently coupled with halides containing an ester (eq 7)[12] or carboxylic acid salt (eq 8).[13] In both cases there was little reaction at the carboxyl termini. The alkenic product from eq 8 was of interest for use in ultra thin-layer photoresists. High purity alkene in which double bond isomers were not present was obtained with Li_2CuCl_4 catalysis.

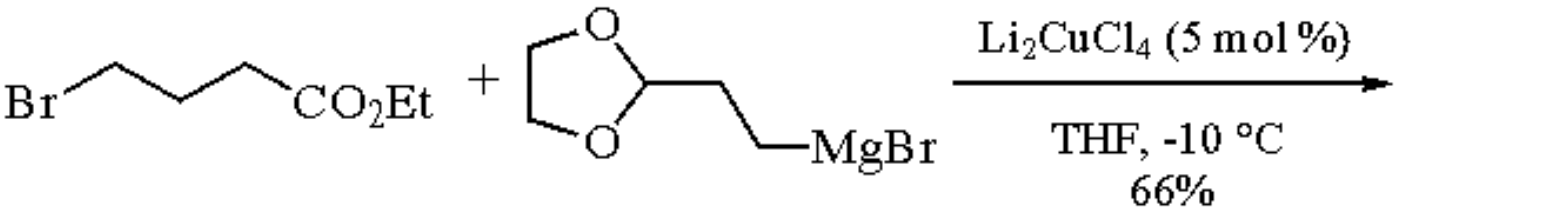

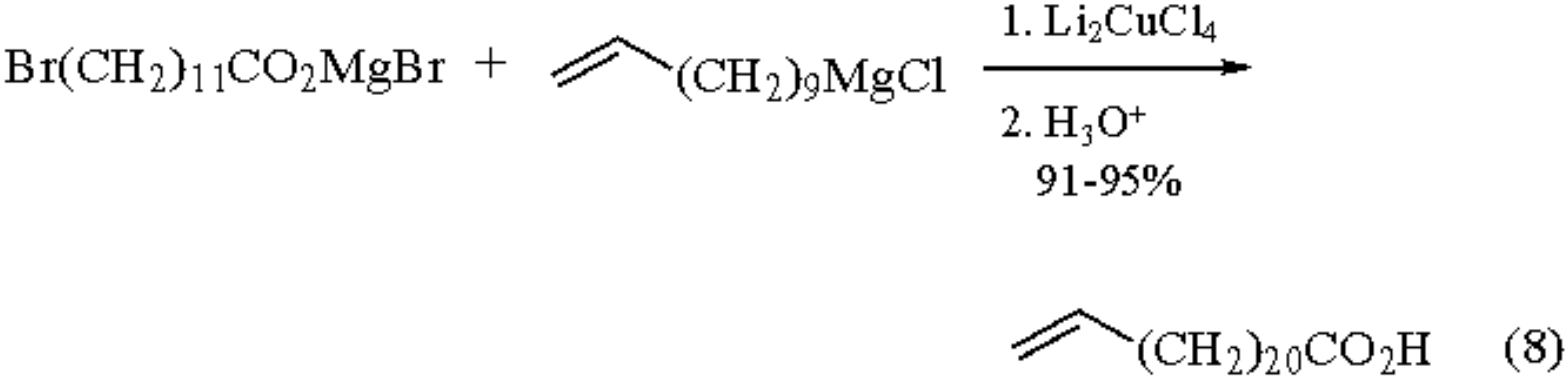

A vinylic type Grignard reagent was coupled with *n*-octyl iodide to afford 2-substituted 1,3-dienes in high yields. In this example, CuI was not an effective coupling catalyst (eq 9).[14]

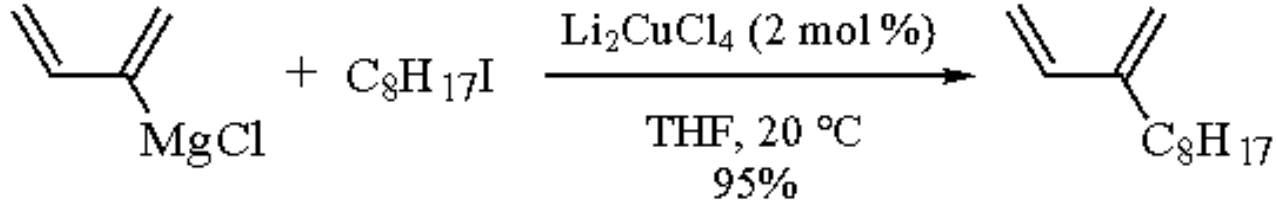

(9)

A double displacement was reported by Schlosser using 1 mol % of the copper catalyst (eq 10).[15]

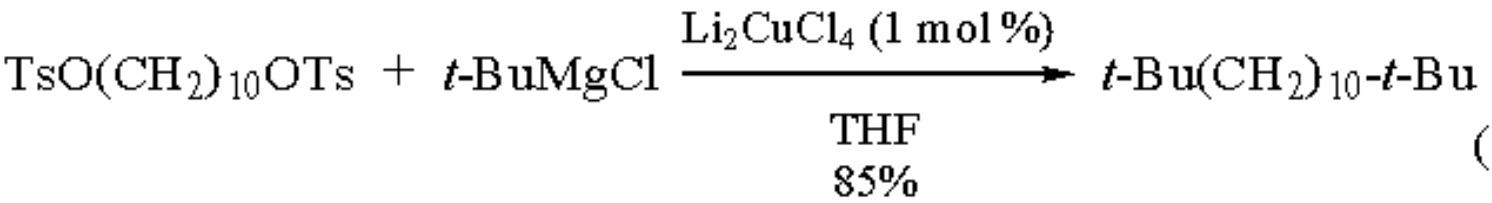

(10)

A cyclic α-halo ether was displaced with the aid of dilithium tetrachlorocuprate. The copper catalyst increased the yield and stereoselectivity for the displacement (eq 11).[16]

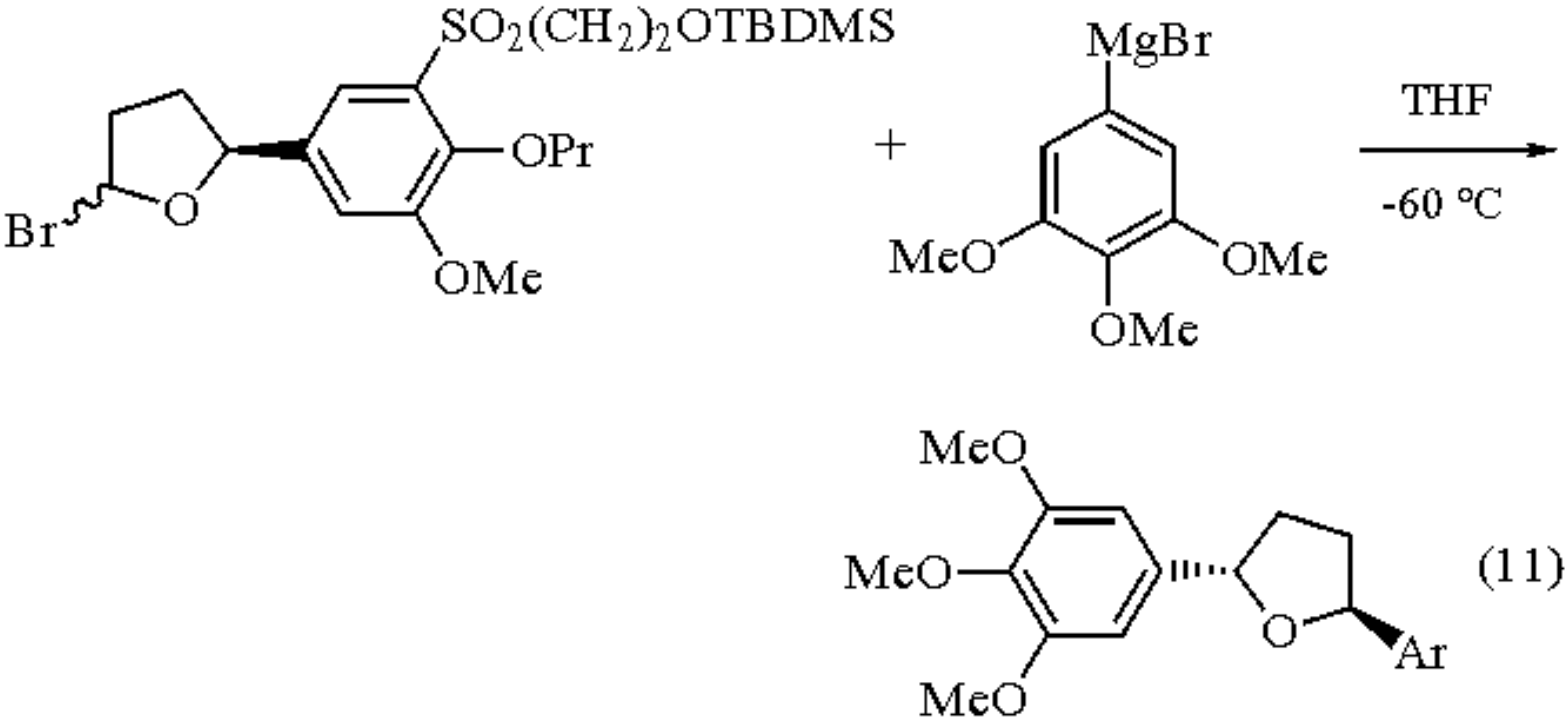

(11)

without Li_2CuCl_4	78%	*trans*:*cis* = 40:1
with Li_2CuCl_4	88%	*trans*:*cis* = 90:1

Allylic Acetate and Quaternary Ammonium Salt Displacements.

The first report using dilithium tetrachlorocuprate in allylic acetate displacements was by Schlosser in which *trans*-crotyl acetate was converted into *trans*-2-octene (eq 12).[3] The reaction was reported to be regio- and stereoselective. In

addition to the desired coupling product, the reaction also produced 10% of the carbonyl addition product 5-methyl-5-nonanol. The level of carbonyl addition product could be reduced using stoichiometric amounts of ***Copper(I) Iodide***. The coupling of a (*Z*)-trisubstituted allylic acetate also proceeded with 100% regio- and stereocontrol (eq 13).[17] In this latter example, nerol derivatives containing an allylic acetate were compared with those containing a bromide, sulfonium salt, ammonium salt, and a carbonate. The acetate was superior, both in terms of maintaining alkene geometry and regiocontrol (α- vs. γ-attack).

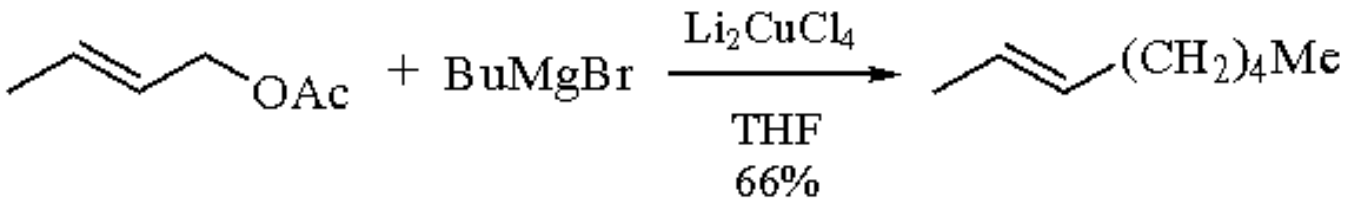

(12)

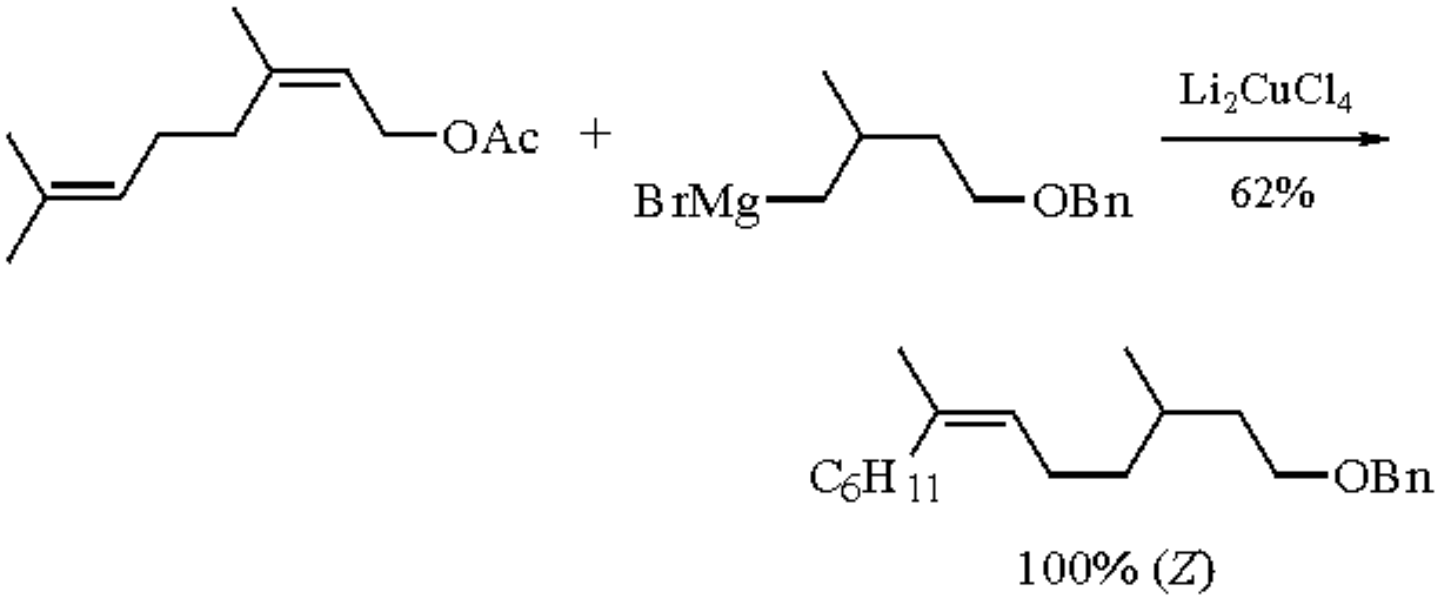

(13)

The regiocontrol was rationalized by Backvall, who observed drastic changes in regiochemistry with changes in reaction conditions. Rapid addition of the Grignard reagent resulted in α-attack (eq 14).[18] A slow Grignard addition in the presence of higher catalyst loadings (5 mol % vs. 2 mol %) completely reversed the regiochemistry of the displacement.

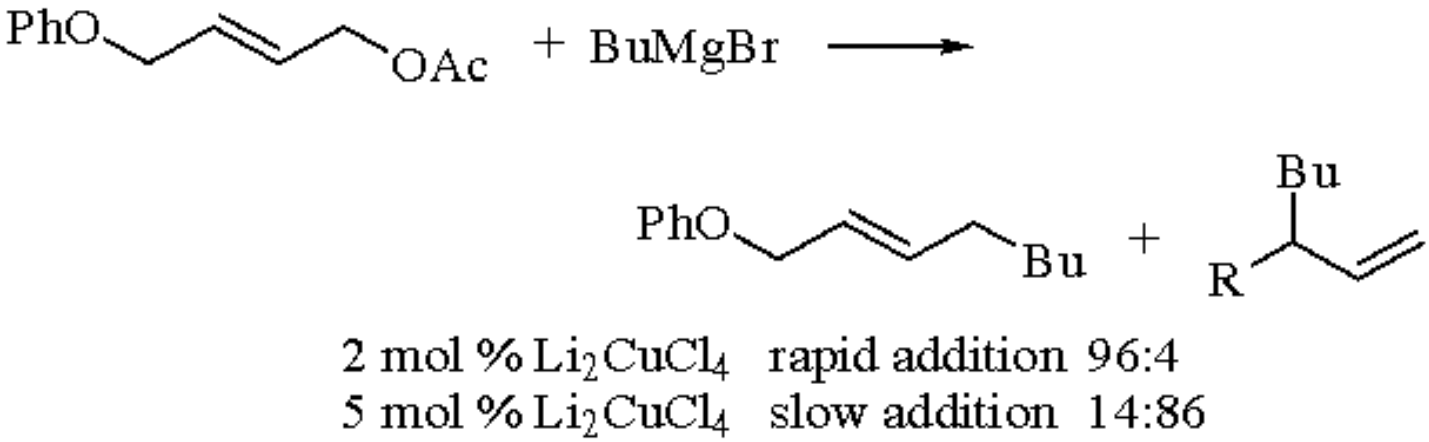

(14)

These results were explained by assuming the presence of a monoalkylcopper complex (**1**) and a dialkylcopper complex

(**2**) (eq 15). With rapid addition, there is a buildup of the dialkylcopper species which favors the α-product. Support for this was provided by reacting preformed *n*-Bu_2CuLi with the acetate to afford a 96:4 mixture of regioisomers. A slow addition, on the other hand, will result in predominant reaction via the monoalkylcopper species, which favors γ-attack.

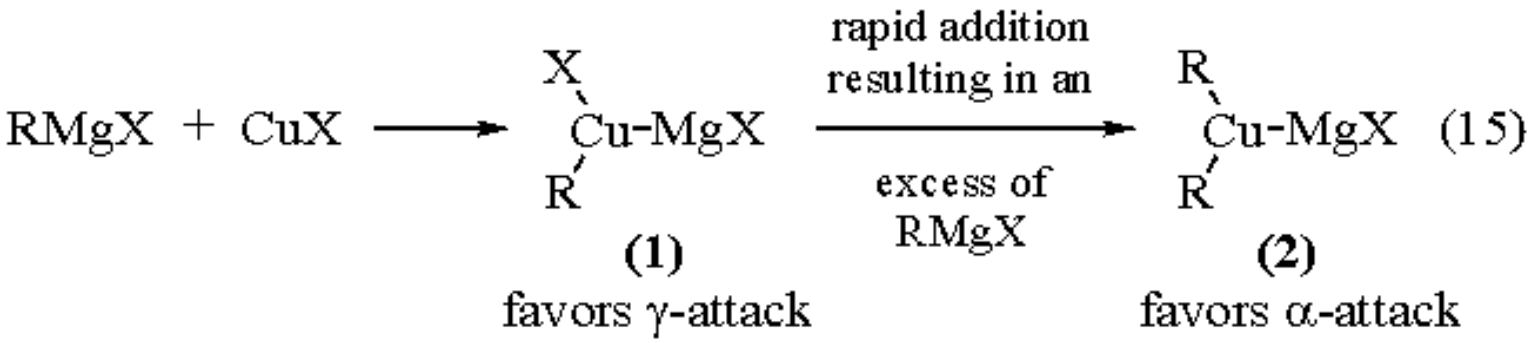

The displacement of allylic acetates was extended to diene systems. A study of all four stereoisomers of 2,4-heptadienyl acetate showed that only the (*E*,*E*) isomer was 100% stereospecific (eq 16).[19] The (2*Z*,4*E*) isomer was the least stereospecific, resulting in a 2:1 ratio of diene isomers (eq 17).

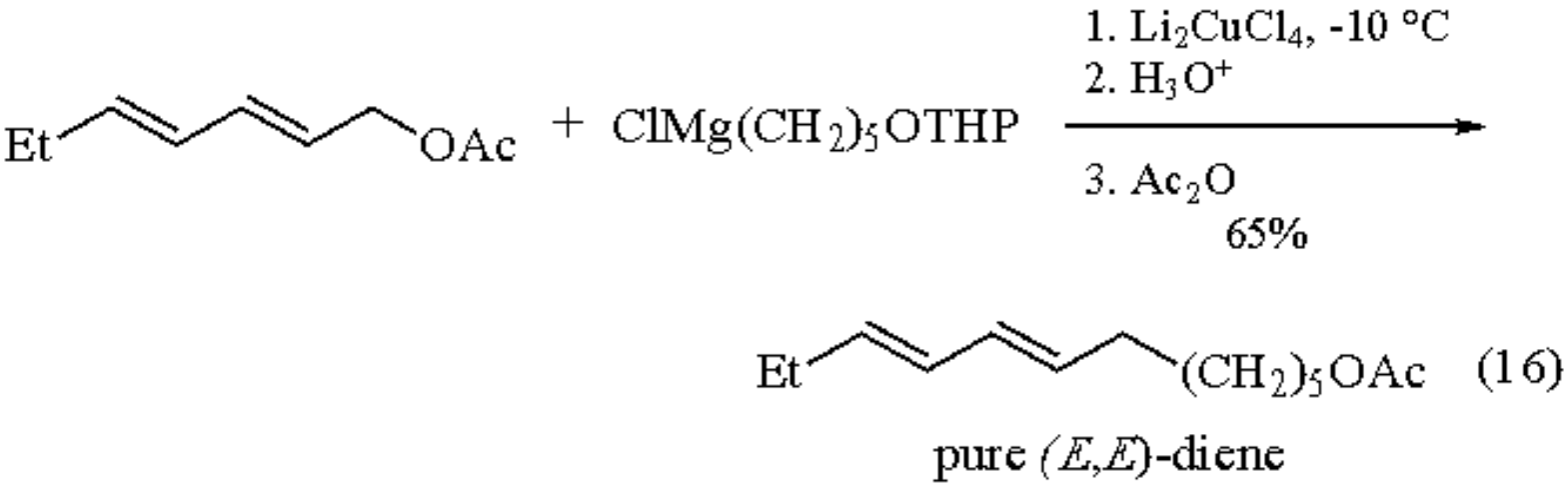

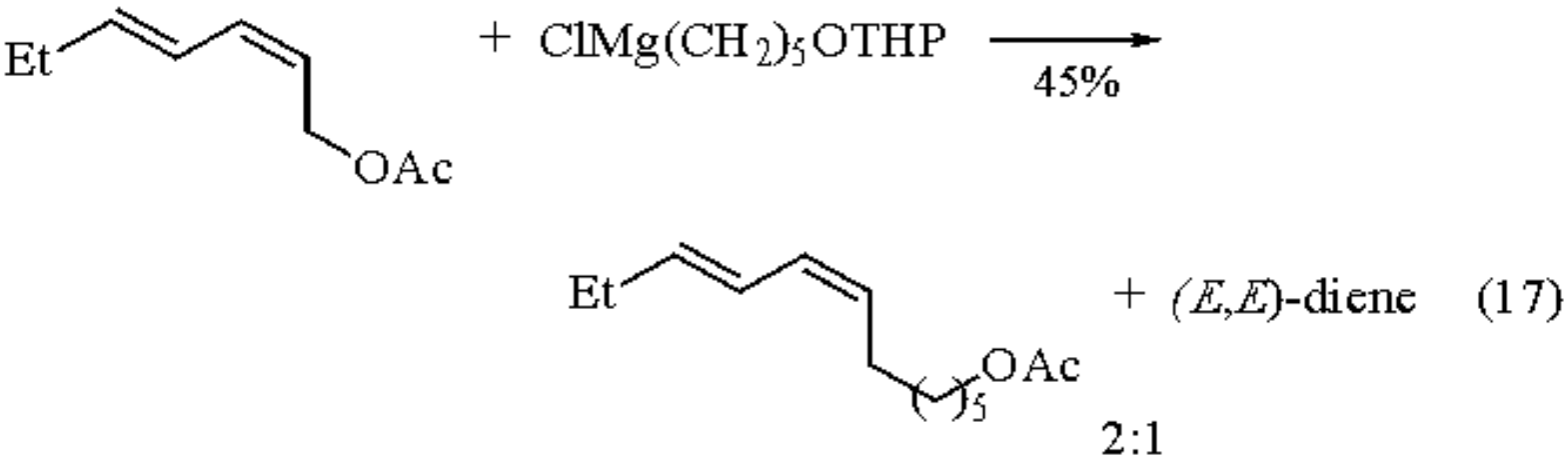

The displacement reported by Roush in which an (*E*,*E*)-diene afforded a mixture of regioisomers may have been improved using the rapid addition technique or by using a preformed copper reagent (eq 18).[20]

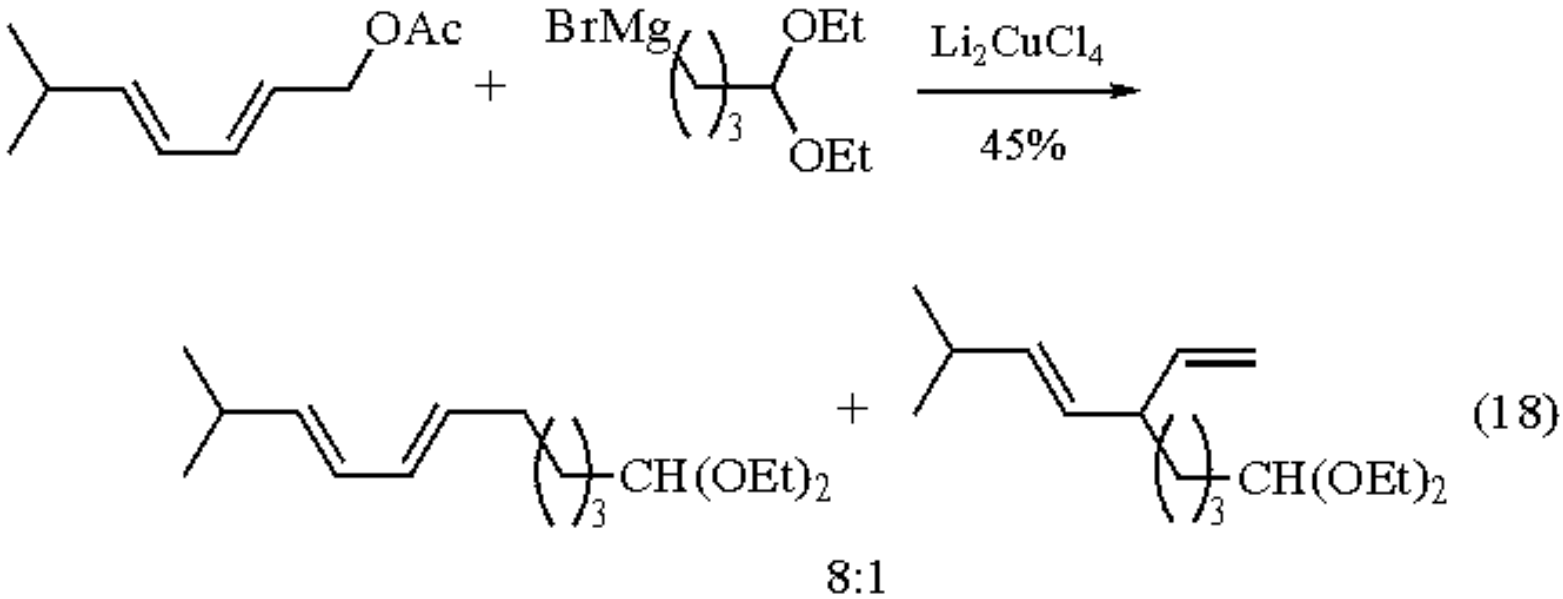

(18)

An allylic quaternary ammonium salt was also a good substrate for displacement under dilithium tetrachlorocuprate catalysis (eq 19).[21]

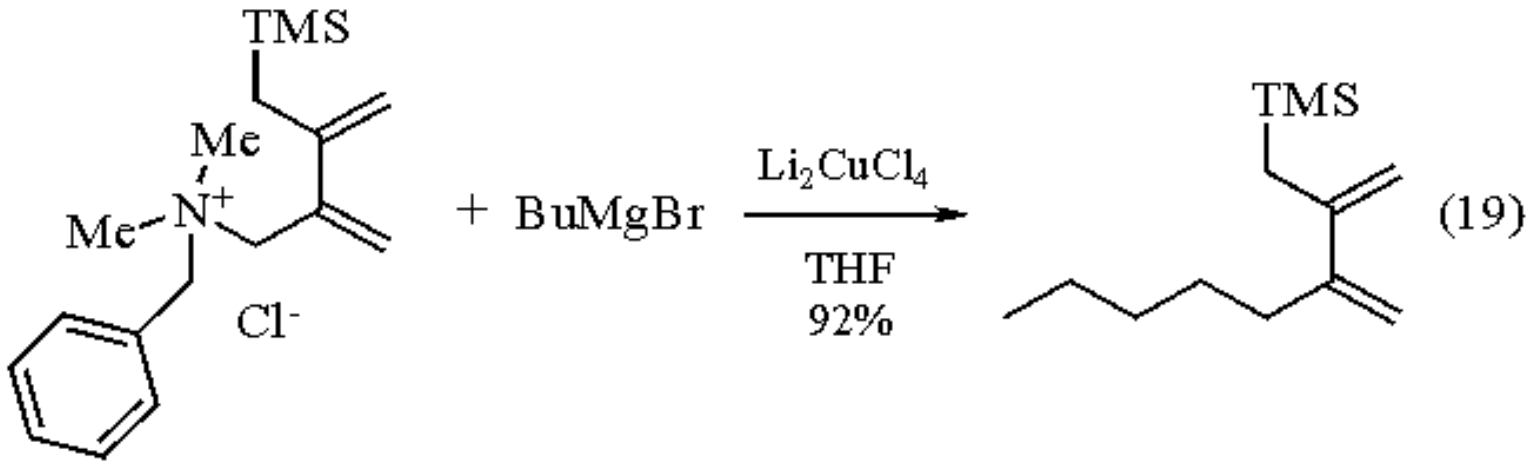

(19)

Epoxide and Aziridine Opening.

When used in excess of stoichiometric quantities, the reagent will open epoxides[4] and activated aziridines.[5a] The epoxide of cyclohexene was opened at rt to afford a *trans*-chlorohydrin in near quantitative yield (eq 20).[4] The opening usually occurs at the least hindered site; however, styrene oxide produced a mixture of chlorohydrins with the secondary chloride predominating. The opening of strained rings was extended to aziridines which are activated as the toluenesulfonamide (eq 21).[5]

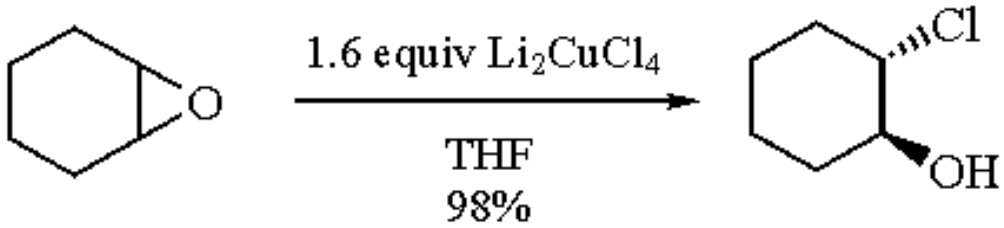

(20)

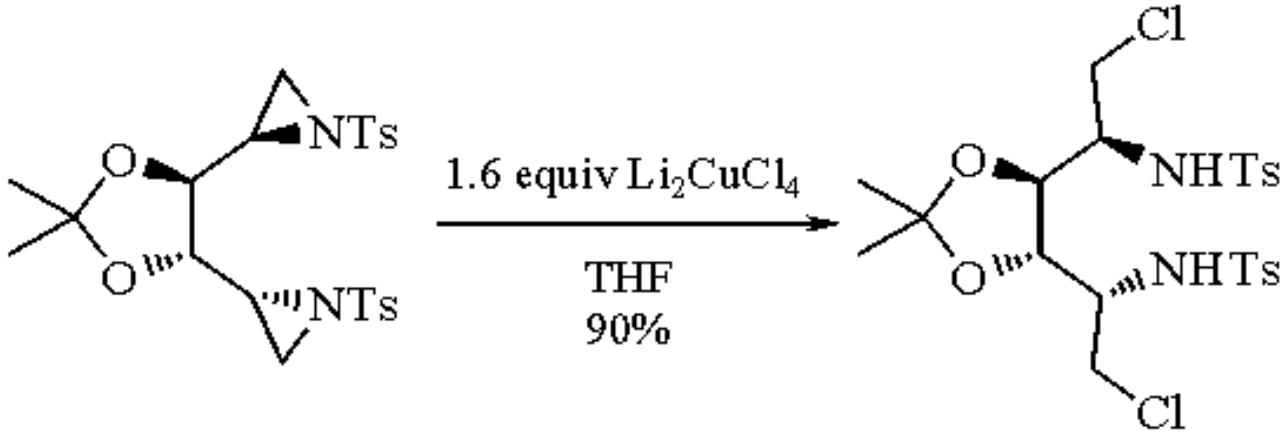

(21)

Cross-Coupling Reactions.

There are only a few reports describing the use of dilithium tetrachlorocuprate as a catalyst for coupling Grignard reagents with vinylic and aryl iodides.[14,22-24] In one report, one of two iodides was replaced using Li_2CuCl_4 (eq 22).[23] An example using a 1,3-diene indicates that palladium catalysis may be more effective for these types of transformations (eq 23).[14]

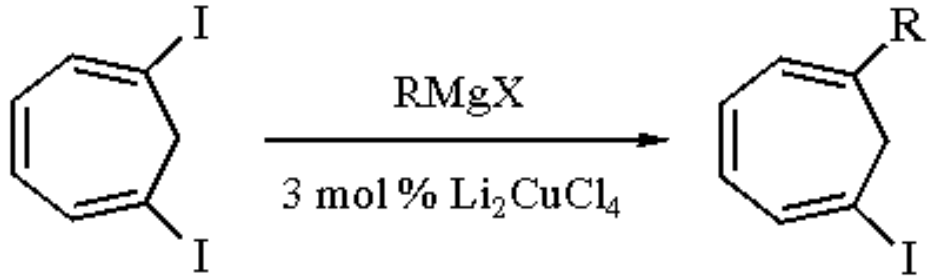

(22)

R = allyl (84%), Bu (51%)
vinyl (88%)

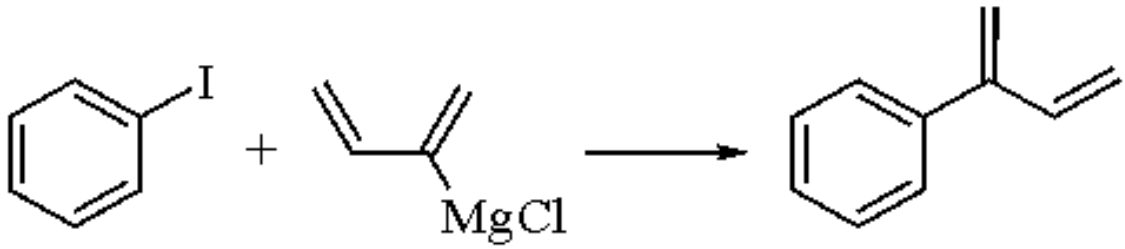

(23)

with Li_2CuCl_4 45%
with $Pd(PPh_3)_4$ 75%

There is one report in which a carbonylative cyclization was observed, presumably by intramolecular trapping of an acylmetal derivative (eq 24).[24]

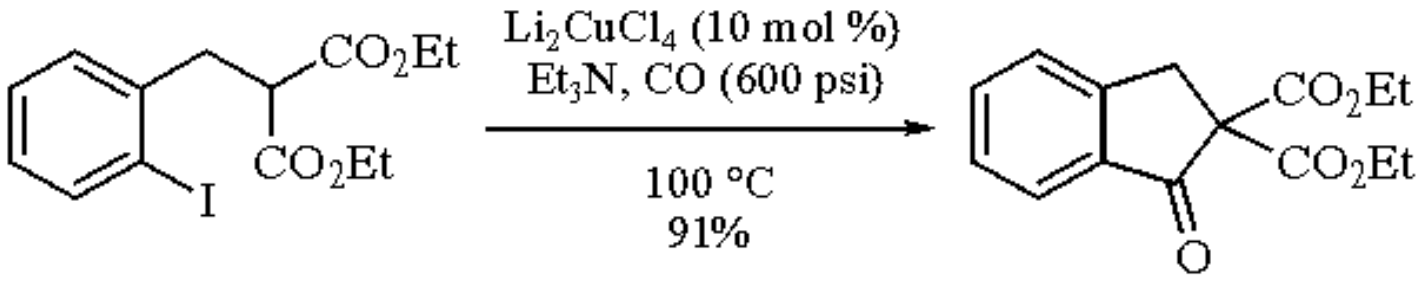

(24)

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Dilithium Tetrachloropalladate(II)[1]

Li_2PdCl_4

[15525-45-8] · Cl_4Li_2Pd · Dilithium Tetrachloropalladate(II) · (MW 262.11) (hydrate)

[123334-21-4]

(catalyst for coupling of aryl- and vinylmercurials with alkenes[2] and carbon monoxide;[3] can cyclopalladate many compounds;[4] can oxidize alkenes[5])

Solubility: sol H_2O, polar organic solvents.

Form Supplied in: commercially available as a hydrate, $Li_2PdCl_4.xH_2O$; red purple solid. *Drying:* at 100 °C and 0.1 mmHg for 24 h.

Preparative Method: very often prepared in situ from 1 equiv of ***Palladium(II) Chloride*** and 2 equiv of ***Lithium Chloride*** in the appropriate solvent (MeOH, EtOH, $MeCO_2H$, THF).

Handling, Storage, and Precautions: is hygroscopic and should be stored in the absence of moisture. Toxicity data are not available.

Coupling of Mercury Derivatives.

Various arylmercurials undergo transmetalation with Li_2PdCl_4 in methanol, ethanol, acetic acid, or THF to form arylpalladium salts. In the presence of alkenes these produce arylated alkenes (eq 1).[6] The reaction is usually stoichiometric in Li_2PdCl_4; however, a catalytic version with ***Copper(II) Chloride*** as a cooxidant has been reported.[7]

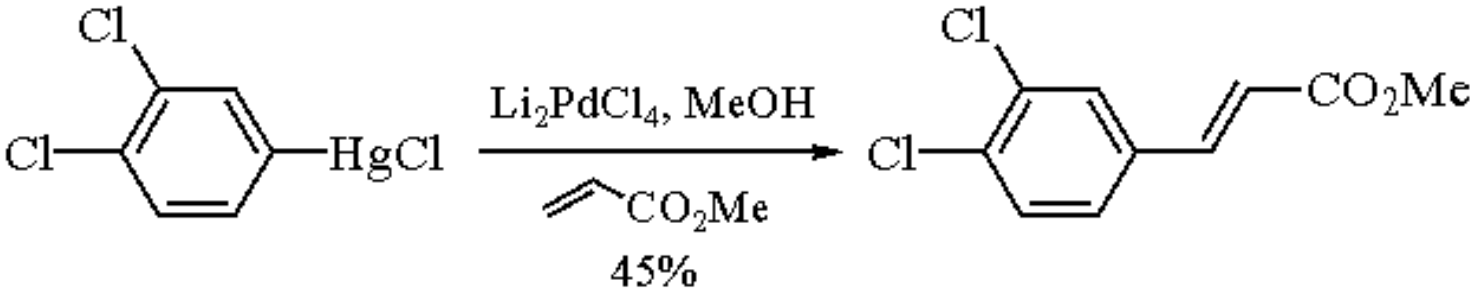

(1)

Similarly, organopalladium intermediates derived in situ from 5-mercurated pyrimidine nucleosides and Li_2PdCl_4 in

MeOH react with alkenes and disulfides to produce nucleosides substituted at the C-5 position by carbon[8] or sulfur (eq 2).[9]

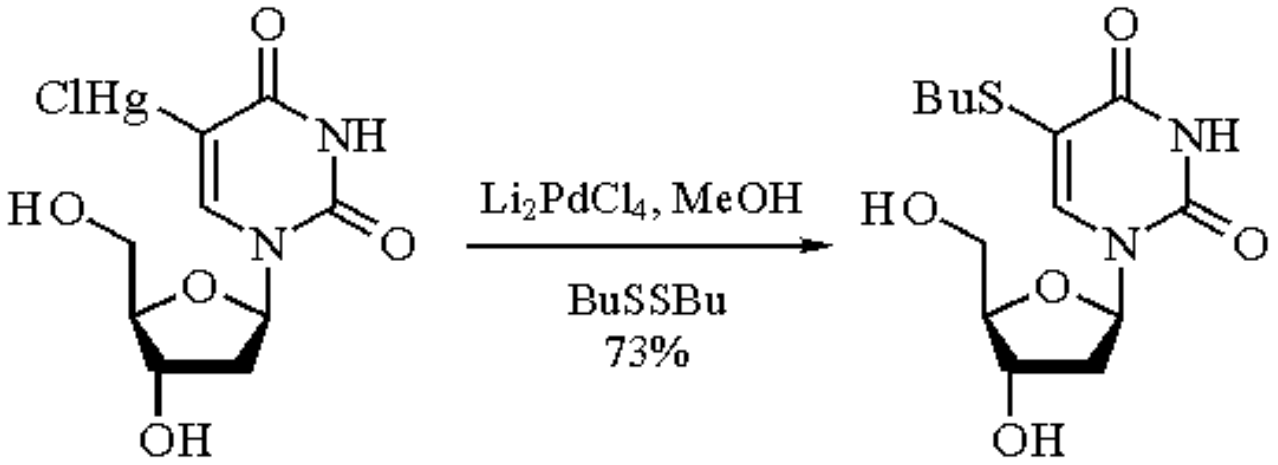

(2)

Vinylmercury(II) chlorides, acyclic alkenes, and Li_2PdCl_4 generate halide-bridged dimeric (π-allyl)palladium complexes in high yield.[10] The analogous reaction of monocyclic alkenes affords either (π-allyl)palladium complexes or 1,4-dienes, depending on the reaction conditions employed (eq 3).[2] (π-Allyl)palladium complexes can be prepared by the reaction of Li_2PdCl_4 with bicyclic alkenes,[11] dienes,[12] vinyl- and methylenecyclopropanes[13], vinyl- and methylenecyclobutanes,[14] and dienolsilyl ethers.[15] These π-allyl complexes are electrophilic in character and undergo reaction with a variety of nucleophiles.[16]

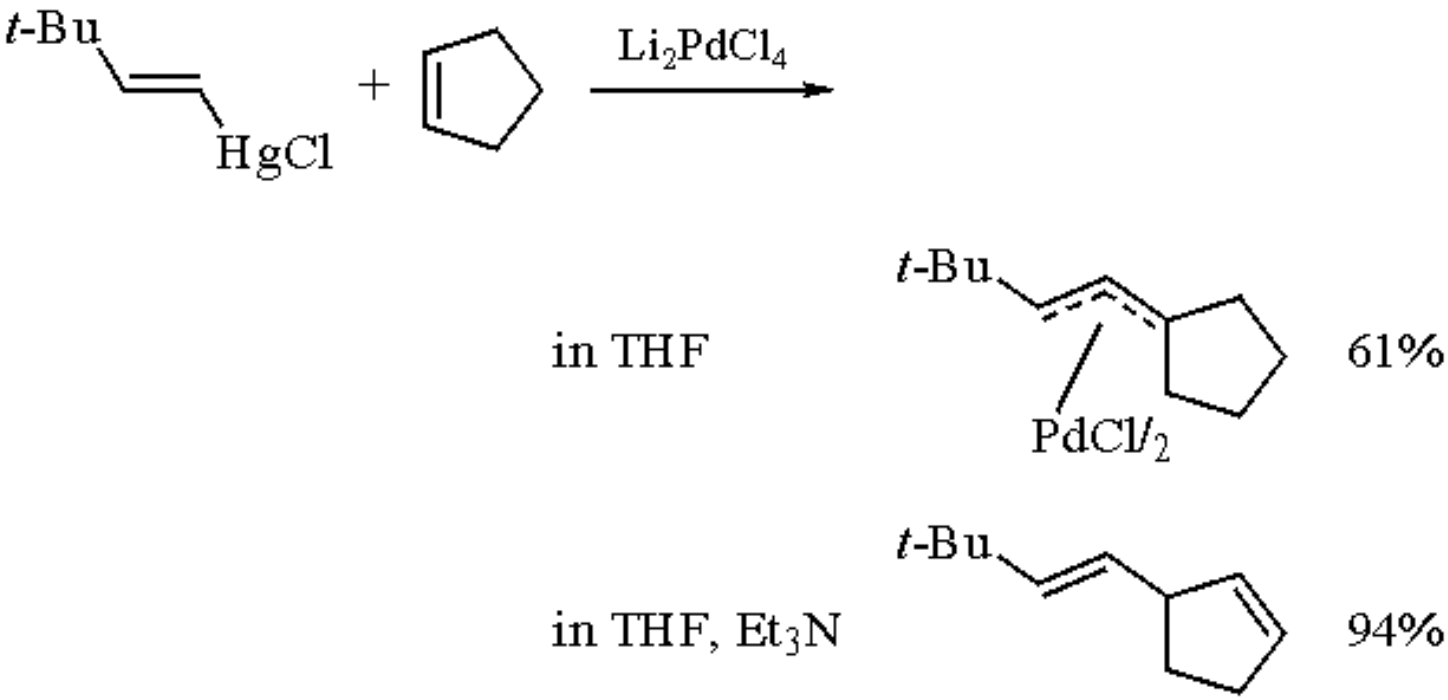

(3)

Aryl- and vinylmercurials readily react with ***Carbon Monoxide*** in the presence of Li_2PdCl_4 at atmospheric pressure. α,β-Unsaturated acids are formed in high yields in aqueous THF or acetic acid.[3] Analogous reaction in the presence of alcohols affords α,β-unsaturated esters (eq 4).[17]

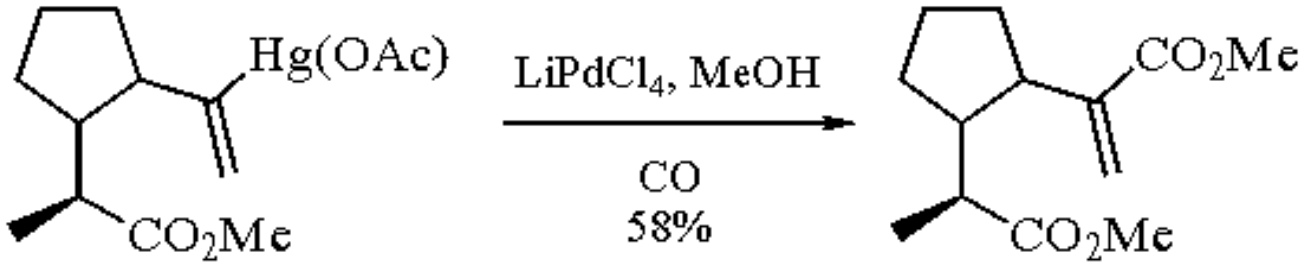

(4)

Addition of vinyl- and arylmercurials to vinyl epoxides gives allylic alcohols.[18]

Cyclopalladation.

Tertiary benzylamines,[19] benzalimines,[20] aromatic azo compounds,[21] and substituted furans[22] undergo coordination with Li_2PdCl_4, followed by electrophilic attack of the metal on the *ortho*-position of the benzene/furan ring, to give a cyclopalladated five-membered ring. Cyclopalladation reactions have been extensively reviewed.[4] The system Li_2PdCl_4/NaOAc is most commonly used, acetate acting as a base to facilitate the C-H bond cleavage. The palladation can be performed in methanol, ethanol, acetone, dioxane, and chloroform, as well as in binary water-organic mixtures. As a rule, palladation occurs at ambient temperature. However, heating is required in certain cases. These palladacycles can react with alkenes (eq 5), carbon monoxide, carbon dioxide, halogens, organolithium and Grignard reagents, acid chlorides, and alkyl chlorides.[23]

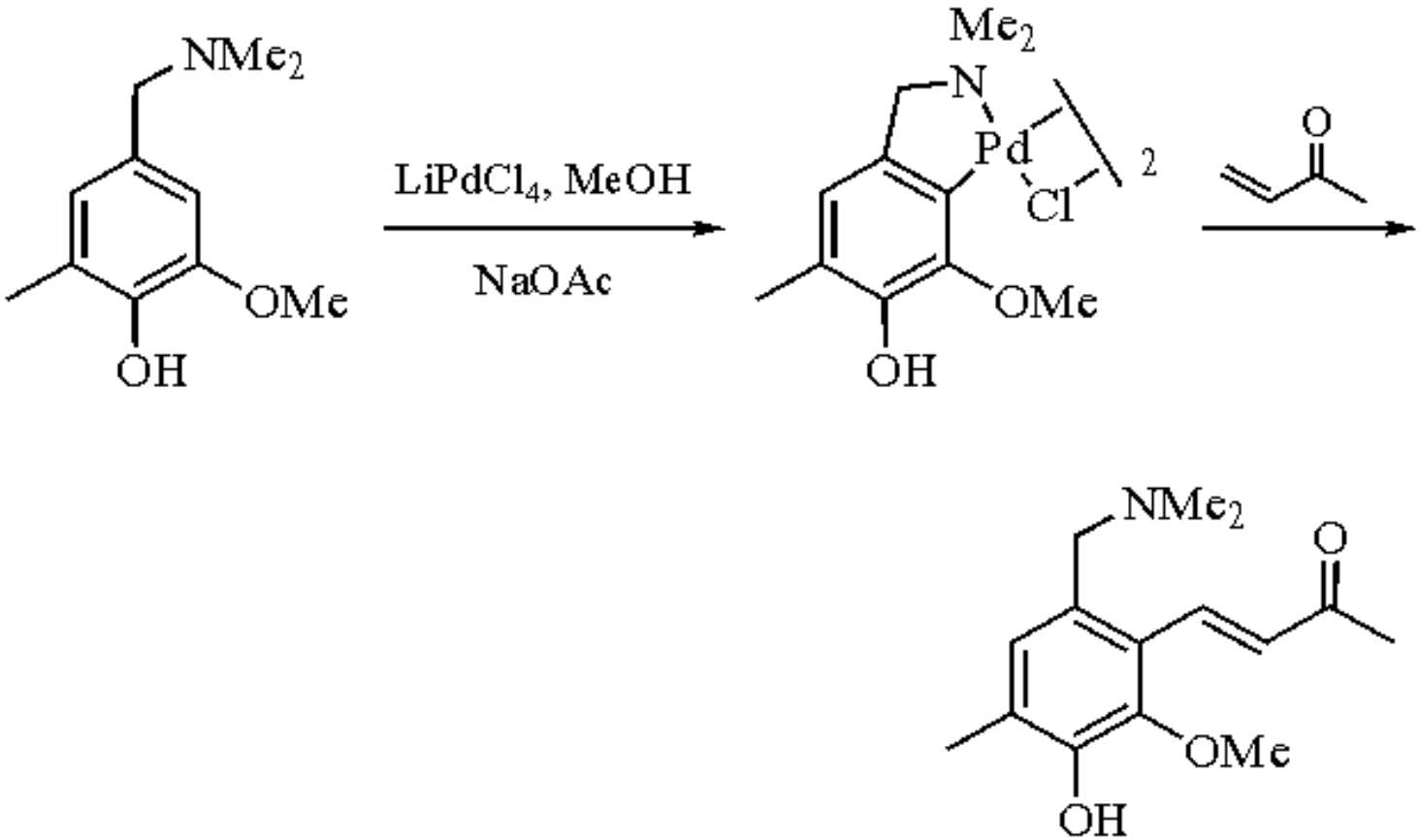

(5)

Allylic[24] and homoallylic[25] amines and sulfides undergo regiospecific carbopalladation in the presence of stabilized enolates and Li_2PdCl_4 to provide stable five-membered palladacycles (eq 6). This reaction has also been performed

intramolecularly.[26] Pd in these cycles can be replaced by carboxylate[26] (CO, MeOH), hydrogen[24] (H_2 or ***Sodium Borohydride***), or by a substituted vinyl group[26] (***Methyl Vinyl Ketone***, ***Triethylamine***).

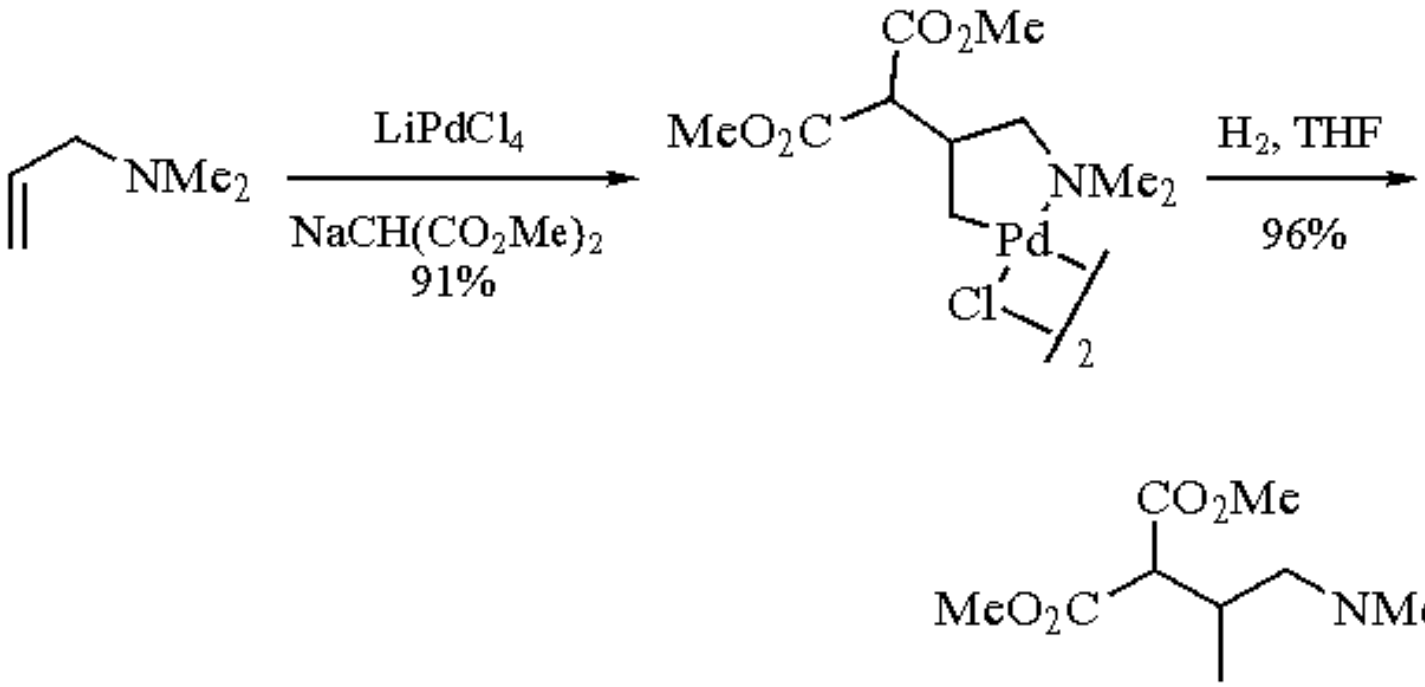

(6)

Oxidation of Alkenes.

Alkenes can be oxidized by Li_2PdCl_4 to aldehydes or ketones (Wacker reaction).[5] Because the reagent is expensive, the reaction is usually carried out with a cooxidant, most often $CuCl_2$. In the presence of alcohols, acetals and vinyl ethers may be formed (eq 7).[5b] Intramolecular versions of oxypalladation are known to produce unsaturated lactones. Carboxylic acids with $\Delta^{3,4}$, $\Delta^{4,5}$, and $\Delta^{5,6}$ unsaturation undergo this reaction in aqueous solution.[25,27,28] Cyclization of 2-hydroxychalcones gives flavones (eq 8).[29]

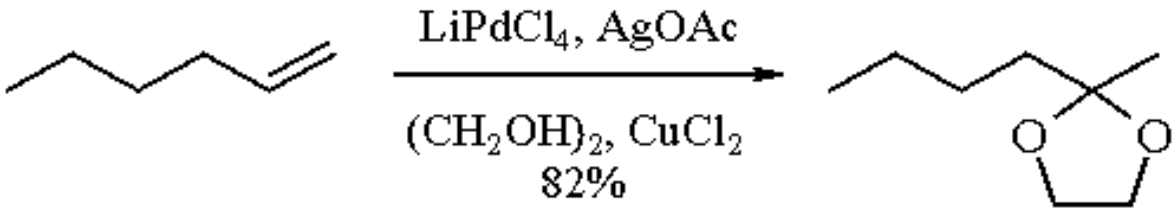

(7)

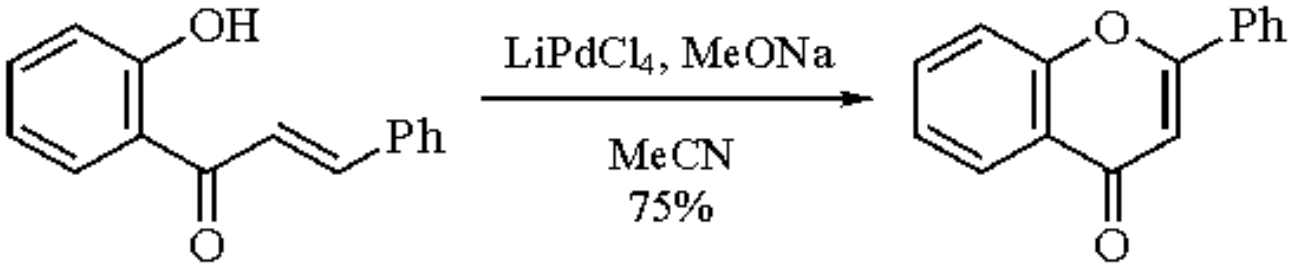

(8)

Vinylation.

N-Phenylhydroxamic acids can be vinylated in the presence of Li_2PdCl_4 to give derivatives that readily undergo [3,3]-sigmatropic rearrangement to form indoles (eq 9).[30]

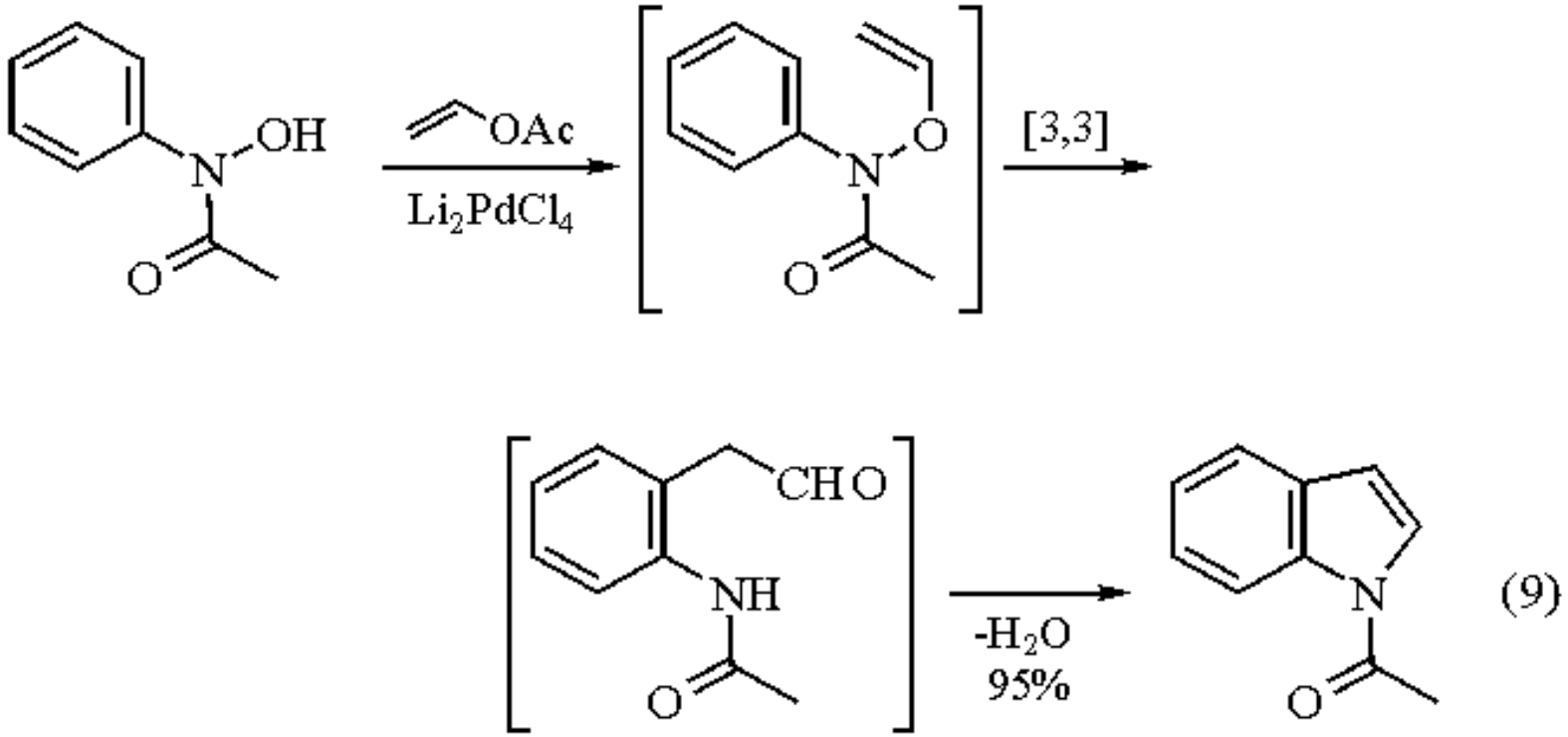

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Dilithium Tributylcuprate

Li_2CuBu_3

[61288-01-5] · $C_{12}H_{27}CuLi_2$ · Dilithium Tributylcuprate · (MW 248.77)

(organometallic butylating agent for ketones,[1] enol ethers,[2] and organomercurials[3])

Physical Data: in ether, ^1H NMR spectra have shown[4] that Li_2CuBu_3 is not an actual species, but a more complex mixture that can be more accurately represented as a BuLi to BuCu ratio. In pentane, however, Li_2CuBu_3 exists in equilibrium with BuLi and $LiCuBu_2$ (see ***Dilithium Trimethylcuprate***).

Solubility: sol ether, THF, and pentane to -80 °C.

Preparative Method: ***n-Butyllithium*** (3.3 mmol) is added to ***Copper(I) Iodide*** (1.0 mmol) in ether at -40 °C.

Handling, Storage, and Precautions: Li_2CuBu_3 should be used as soon as possible following preparation. Use in a fume hood.

Addition to Ketones and Enol Ethers.

Li_2CuBu_3 behaves similarly to Li_2CuMe_3[5] in enhancing the yield and stereoselectivity in reactions with ketones (eq 1)[2] (see ***Dilithium Trimethylcuprate***). Notable in additions to hindered ketones is a depression of carbonyl reductions with Li_2CuBu_3 compared to the alkyllithium reagent.

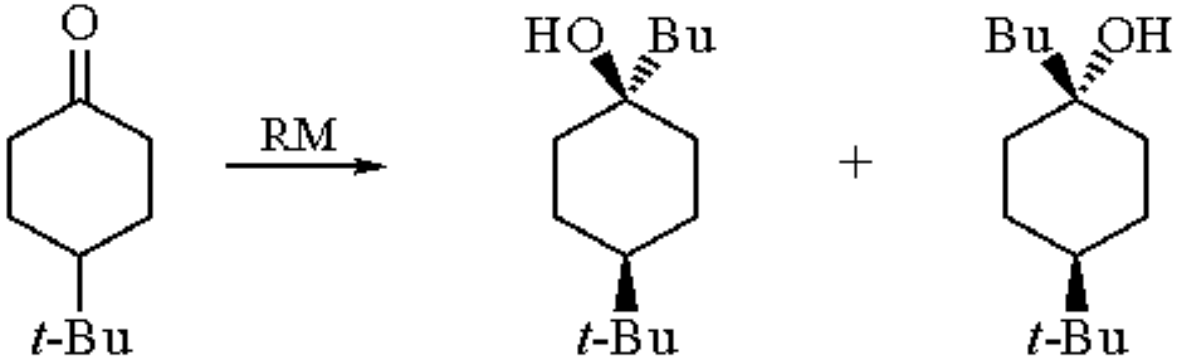

(1)

RM =	BuLi, 5 °C, 93%	73:27
	BuLi, -78 °C, 98%	86:14
	Li_2CuBu_3, -78 °C, >99%	97:3

Li_2CuBu_3 undergoes reaction with 2,3-dihydrofuran to yield 3-octen-1-ol in 75% yield.[2] The optimal conditions for reaction use 5.0 equiv of butyllithium per 1.0 equiv CuI. This result raises the possibility that the reactive agent may be a cuprate species possessing a Bu:Cu ratio that is >3 (eq 2).[4,6]

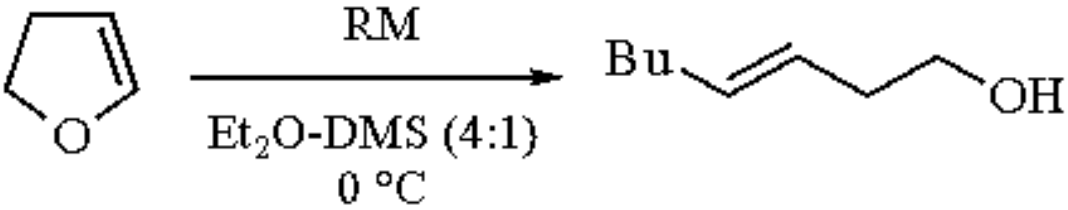

(2)

RM =	$LiCuBu_2$	15%
	Li_2CuBu_3	75%

Alkylation of Organomercurials.

Butylation of alkenyl-, phenyl-, and alkylmercurials with Li_2CuBu_3 proceeds only in moderate yield (40-60%), but nonetheless exhibits an almost tenfold enhancement in yield over that obtained with $LiCuBu_2$.[3]

---

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Dilithium Trimethylcuprate[1]

Li_2CuMe_3

[61278-42-0] · $C_3H_9CuLi_2$ · Dilithium Trimethylcuprate · (MW 122.53)

(organometallic methylating agent for ketones,[2] enones,[3,4] halides,[5] and hydrazones[6] and for cross-coupling reactions with mercury(II) chlorides[7])

Physical Data: in Et_2O, Li_2CuMe_3 exists in equilibrium with MeLi and $LiCuMe_2$.[8] In THF, however, it has been shown by ^7Li NMR that Li_2CuMe_3 is not a discrete species, but an equilibrium mixture of more complex organocuprates which may be more accurately represented as a MeLi-to-MeCu ratio.[9] In this article, Li_2CuMe_3 is employed to represent a 3:1 ratio of MeLi to CuI. It is additionally important to recognize that the varied modes of reaction of Li_2CuMe_3 suggest that different species or mechanisms of reaction may occur under specific conditions with certain reactants. In some cases the course of reaction indicates an initial metal ion-oxygen complexation followed by the addition of MeLi, while in others the reaction of a higher order cuprate appears likely.

Solubility: sol ether and THF to -100 °C.

Preparative Method: to ***Copper(I) Iodide*** (30 mmol) suspended in 100 mL anhydrous ether or THF at 0 °C is added ***Methyllithium*** (90 mmol, 2 M in THF or ether) and the light tan solution is stirred for 10 min before cooling and use.

Handling, Storage, and Precautions: Li_2CuMe_3 should be used immediately following preparation to obtain optimal yields.

Addition to Ketones.

The addition of an organolithium or Grignard reagent to an unhindered cyclohexanone generally leads to the predominant formation of the axial alcohol.[10] However, the 3:2 mixture of $LiCuMe_2$ and MeLi to form the Li_2CuMe_3 complex adds to 4-*t*-butylcyclohexanone to give 94% *trans*-4-*t*-butyl-1-methylcyclohexanol in 91% yield (eq 1).[2] Similar results have been observed with 4a-methyl-*trans*-2-decalone and 2-methylcyclohexanone (eq 2), as well as with various C(3)-substituted cyclohexanones (eq 3).[11]

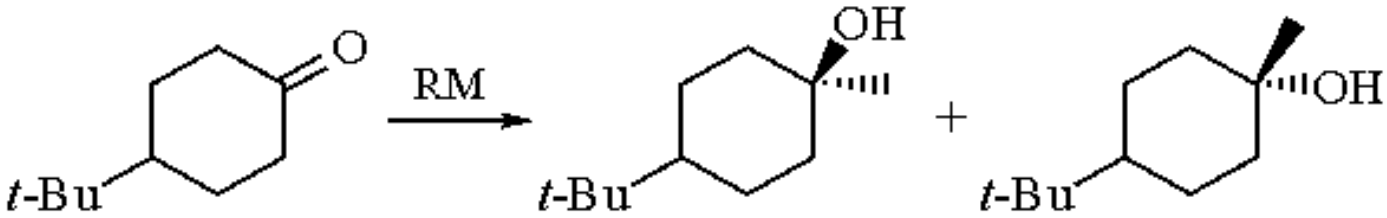

(1)

RM =	MeMgI, 5 °C	51:49
	Me_2Mg	70:30
	MeLi	65:35
	MeLi, -78 °C	79:21
	Li_2CuMe_3, -70 °C	94:6

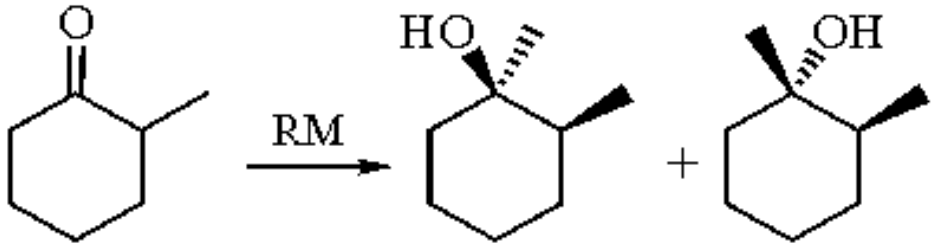

(2)

RM =	MeMgI, 0 °C	84:16
	MeLi, -78 °C	92:8
	Li_2CuMe_3, -78 °C	97:3

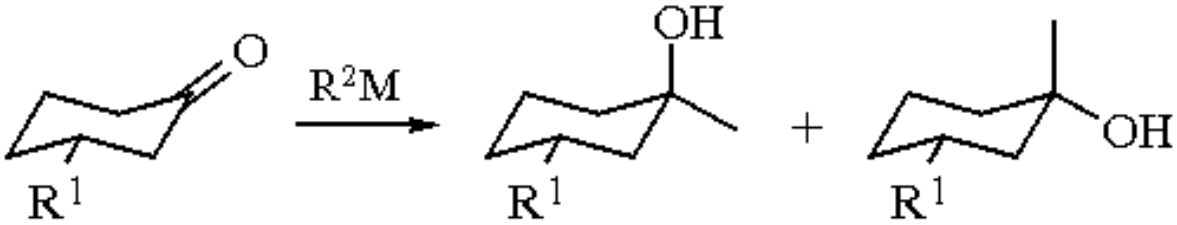

(3)

R^1	R^2M	% axial attack
TMS	MeLi, Et_2O	15
TMS	Li_2CuMe_3, Et_2O	2
t-Bu	MeLi	19
t-Bu	Li_2CuMe_3	3
H	MeLi	21
H	Li_2CuMe_3	6

Comparable stereoselectivity resulted from the slow addition of MeLi to a solution of ketone and $LiCuMe_2$ and the use of ***Lithium Perchlorate*** and ***Lithium Bromide*** in solution with MeLi.[12] These results suggest a complexation of the ketone by $LiCuMe_2$ followed by rapid addition by MeLi from the least hindered face. Interestingly, Li_2CuMe_3 showed no stereochemical advantage over MeLi in the reaction with 2-methylcyclopentanone.[2] However, methylation of racemic 2-methyl-2-phenyl-1-indanone gave addition predominantly from the least hindered face (eq 4).[13]

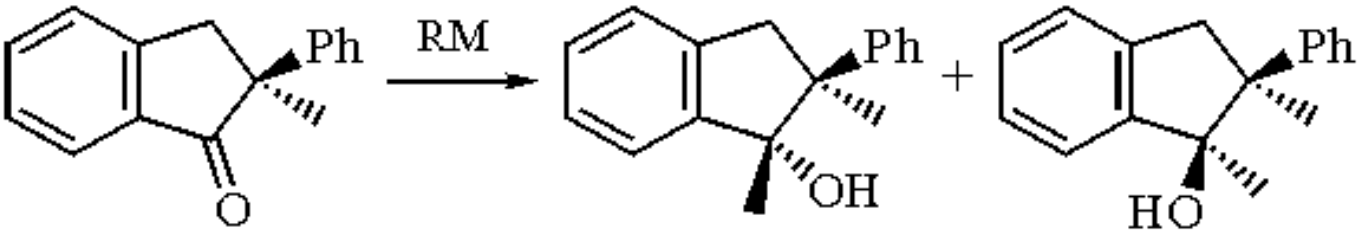

(4)

RM =	MeMgBr	78:22
	MeLi	15:85
	Li_2CuMe_3	18:82

Addition to Enones.

Li_2CuMe_3 provides exclusive 1,4-addition to α,β-unsaturated carbonyl compounds.[3,4] While the Li_2CuMe_3 complex has a similar reaction rate to $LiCuMe_2$ for conjugate addition to β-monosubstituted enones in THF, Li_2CuMe_3 yields mostly 1,2-addition for sterically hindered β-disubstituted enones. This regioselectivity is presumably due to the more rapid 1,2-addition by MeLi relative to the sterically demanding 1,4-addition by Li_2CuMe_3. The use of ether as solvent results in an increase in the overall rate of reaction at the cost of a decrease in regioselectivity. This loss of selectivity is presumably a result of 1,2-addition by MeLi (eq 5).[4]

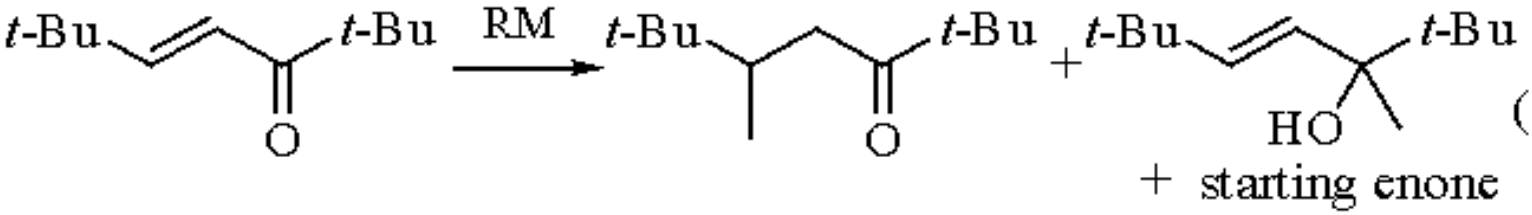

(5)

RM =	$LiCuMe_2$, THF, 3 h	95:0 :5
	Li_2CuMe_3, THF, 3 h	100:0 :0
	$LiCuMe_2$, Et_2O, 10 min	63:0 :37
	Li_2CuMe_3, Et_2O, 10 min	53:47:0

The reaction of Li_2CuMe_3 with (*Z*)-hexenolide in ether at 0 °C gave a mixture of 4-alkenoic acid and 4-methyl 5-hexenoic acid in 89% total yield (eq 6).[14]

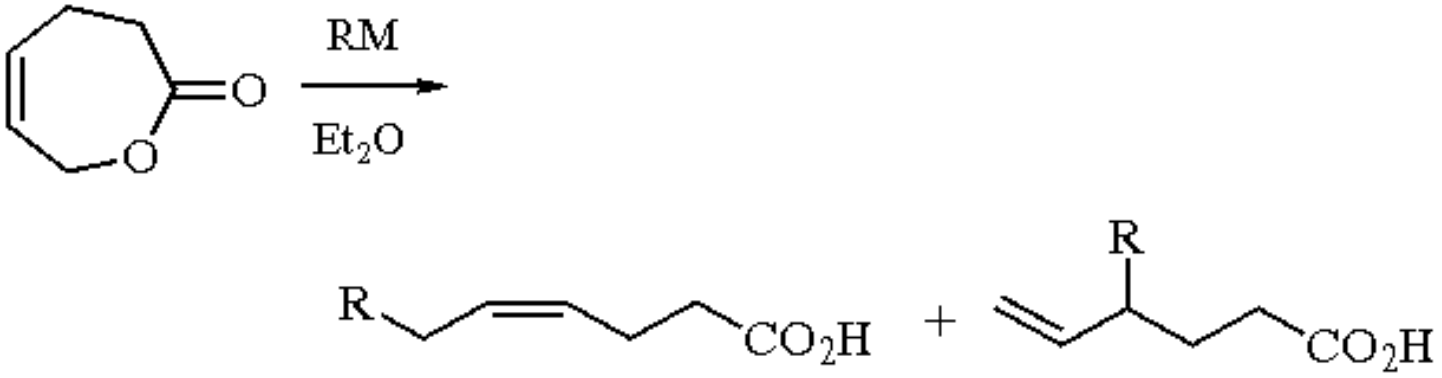

(6)

RM = $LiCuMe_2$ (92%) 88:12
Li_2CuMe_3 (89%) 85:15

Substitution of Halides.

Li_2CuMe_3 generally shows higher reactivity and enhanced yields compared with $LiCuMe_2$ and $Li_2Cu_3Me_5$ in the substitution of alkyl, allylic, vinylic, and aryl halides (eqs 7 and 8).[5]

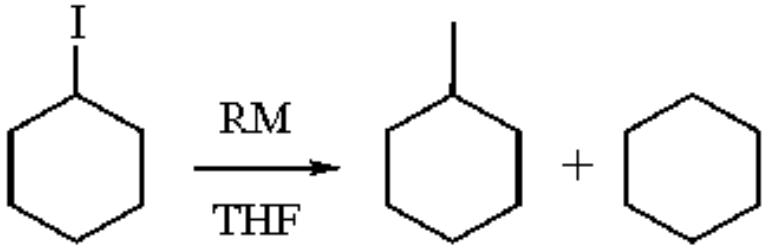

(7)

RM = $LiCuMe_2$ 21%:14%
Li_2CuMe_3 93%:5%

(8)

RM = $LiCuMe_2$ 0%
Li_2CuMe_3 quantitative

The rate of halogen reactivity was I > Br > Cl > F; THF proved to be the most efficacious solvent investigated, except for substitution of fluorine in which ether was proven to be more effective. Notable exceptions to this generally successful reaction are bromo- and chlorocyclohexane, chloro- and fluorobenzene, and *p*-chloroanisole. These compounds showed either no reaction with any cuprate investigated or halogen-metal exchange which resulted in reduction.

The reaction of 6-substituted 1-heptenes with Li_2CuMe_3 led to varied products, depending on the leaving group, implicating a complex reaction mechanism for this displacement reaction (eq 9).[15] The 6-iodo-substituted compounds produced a reaction profile of products which supports the possibility that the displacement of iodide by Li_2CuMe_3 may proceed through an electron transfer mechanism, while leaving group displacement in the other 6-substituted electrophiles occurs via an apparent S_N2 mechanism.

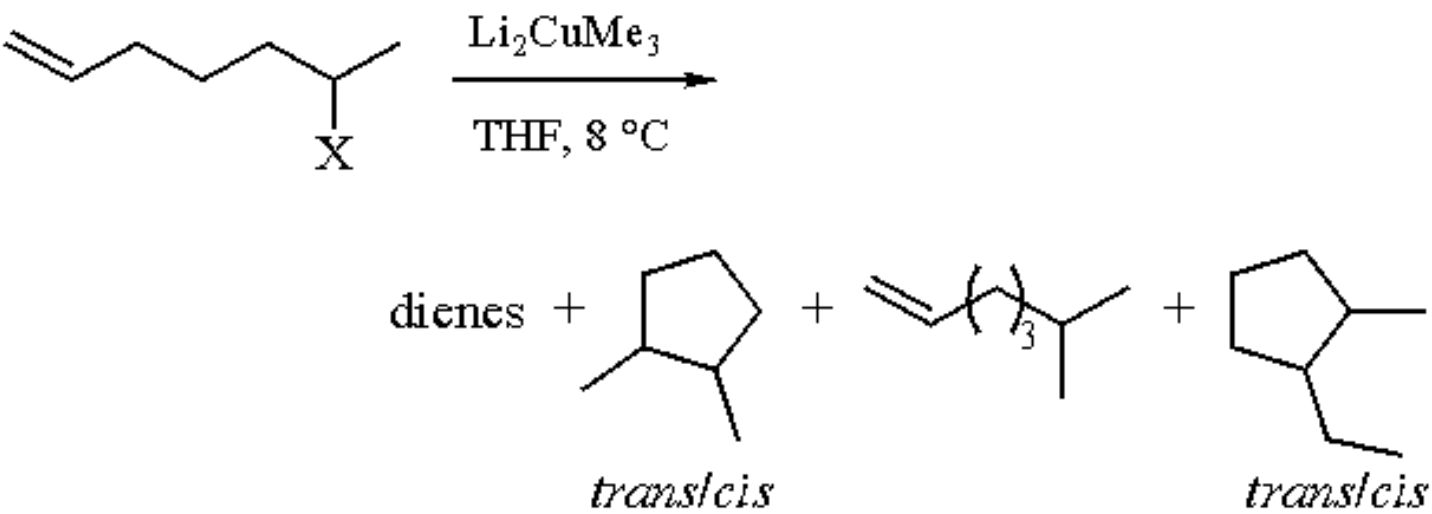

(9)

X =	OTs	5	:	0	:	20	:	0
	Cl	trace	:	0	:	0	:	0
	Br	2.6	:	9.6 (7.7)	:	64	:	0
	I	1.5	:	10.7 (1.1)	:	14	:	62 (0.22)

Boron Trifluoride Etherate catalyzes the substitution reaction of Li_2CuMe_3 with *N*-benzoyl-3-bromo-2,3-didehydrohomoserine-γ-lactone to give the 3-methylbut-2-enoic acid-γ-lactone in 78% yield (eq 10).[16]

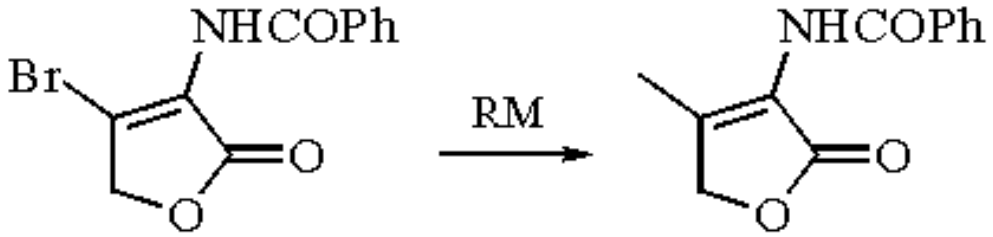

(10)

RM = $LiCuMe_2$, THF, 0 °C	26-29%
Li_2CuMe_3	intractable mixture
$MeLi + BF_3 \cdot Et_2O$ then $LiCuMe_2$	78%

Activation of C-N.

It has been shown that Li_2CuMe_3 provides a source of Cu^I which activates C-N bonds in hydrazones toward nucleophilic attack by MeLi in ether.[6] The reaction fails in THF due to the preferential complexation of Cu^I by THF. The final result is a *gem*-dialkylated product. In a subsequent publication,[17] it was shown that addition of Li_2CuMe_3 to aldehyde tosylhydrazones resulted in the formation of hindered cuprates which react smoothly with alkyl halides in the normal cuprate fashion (eq 11).

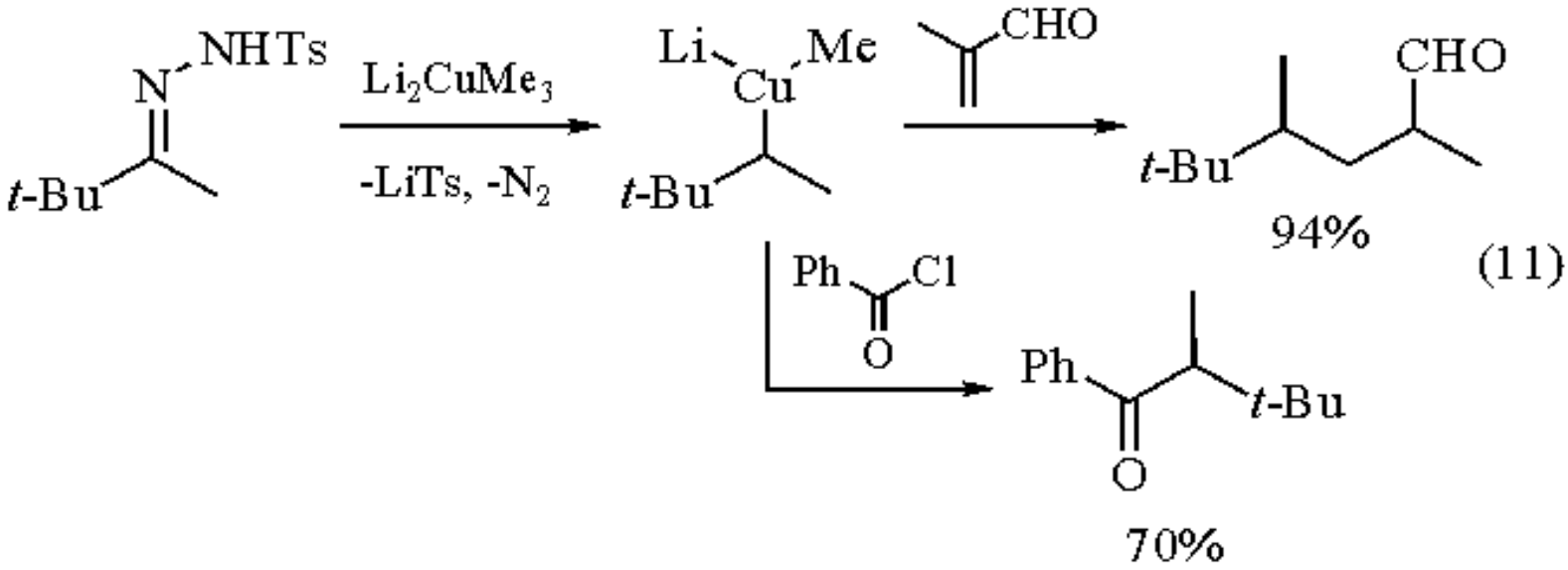

(11)

The reaction of tosylhydrazones from secondary or tertiary aldehydes give acceptable yields, while unbranched tosylhydrazones result in low yields. The reaction proceeds through an initial 1,2-addition to the C-N bond, followed by selective secondary or tertiary ligand transfer.

Cross-Coupling Reactions with Organomercurials.

The addition of 5 equiv of Li_2CuMe_3 to aryl mercury(II) chlorides in ether followed by quenching with MeLi and oxygen resulted in effective methylation (eq 12).[7,18] In addition, organomercurials produced via oxymercuration of alkenes react readily with Li_2CuMe_3 (eq 13). A compilation of all the reaction types revealed the order of reaction efficiency to be aryl- > vinyl- > primary alkyl- > secondary alkylmercurial. The reactions are proposed to proceed via an initial mercury-copper transmetalation to generate a mixed diorganocopper species which then undergoes a thermal or oxidative elimination to produce the cross-coupled product. The highly stereoselective nature of the reaction is inconsistent with a radical anion chain mechanism for the cross coupling.

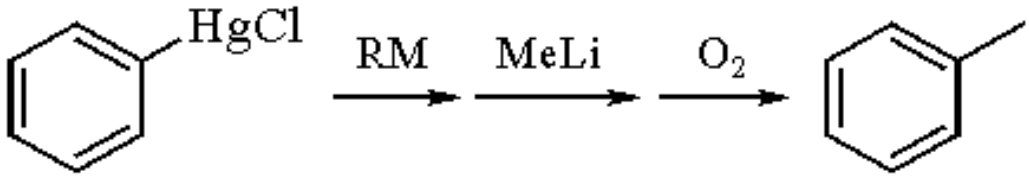

(12)

RM = $LiCuMe_2$ 76%
Li_2CuMe_3 92%

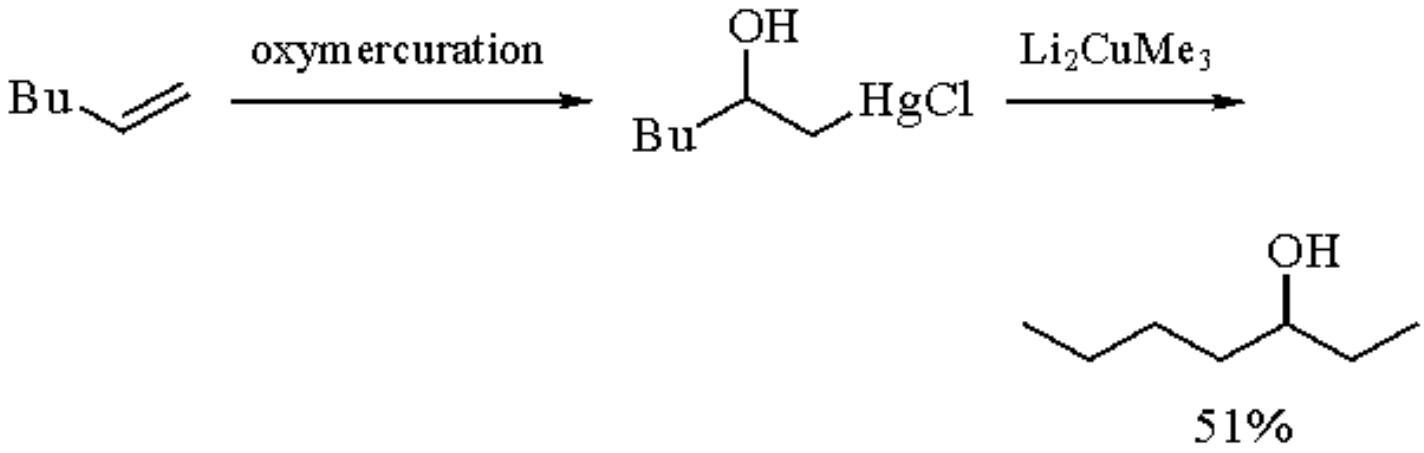

(13)

Related Reagents.

Dilithium Pentamethyltricuprate; ***Lithium Dimethylcuprate***.

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18. Larock, R. C.; Leach, D. R. *OM* **1982**, *1*, 74.

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Dilithium (Trimethylstannyl)(2-thienyl)cyanocuprate

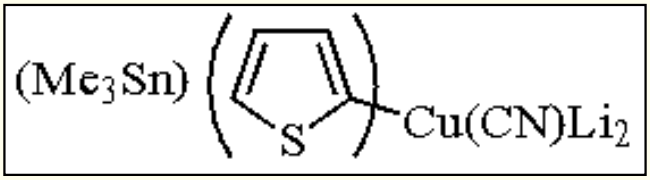

[112621-93-9] · $C_8H_{12}CuLi_2NSSn$ · Dilithium (Trimethylstannyl)(2-thienyl)cyanocuprate · (MW 350.37)

(reagent for transfer of the Me_3Sn moiety to the β-carbon of α,β-unsaturated carbonyl compounds[1,2])

Solubility: sol THF.

Preparative Method: the higher-order cuprate $(Me_3Sn)(2\text{-Th})Cu(CN)Li_2$ (**1**) (Th = thienyl) can be prepared by the treatment of a solution of ***Hexamethyldistannane*** and thiophene in dry THF with ***Methyllithium***, followed by addition of solid ***Copper(I) Cyanide*** (eq 1).[1] Although the actual structure of the reagent is not known, formula (**1**) is used for convenience and to show stoichiometry. Analogous formulations have been employed for higher-order alkylcuprates.[4] A solution of the reagent in THF is bright yellow in color.

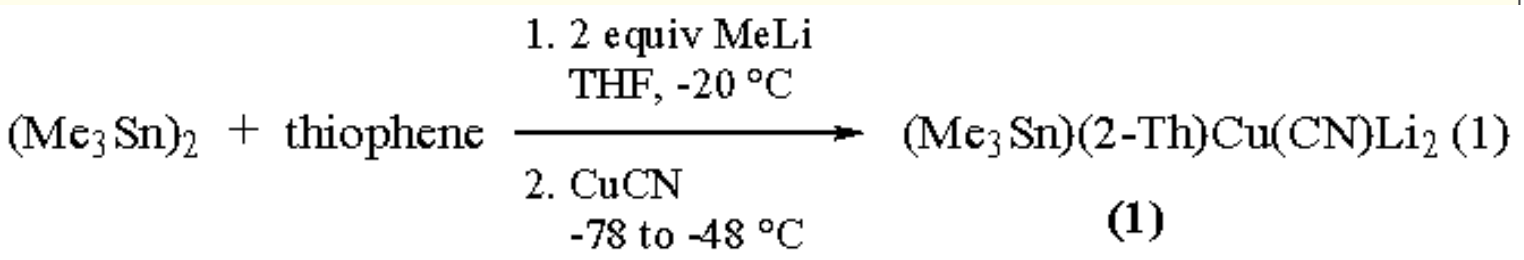

Handling, Storage, and Precautions: the reagent should be prepared using dry THF under an inert atmosphere. Since organotin[3] and cyanide compounds are toxic, work-up of reactions employing the reagent should be carried out in a fume hood.

Reaction with α,β-Unsaturated Carbonyl Compounds.

Reagent (**1**) effects efficient conjugate addition of the Me_3Sn function to α,β-unsaturated ketones, aldehydes, and esters (eqs 2 and 3).[1] In this type of reaction, (**1**) appears to be less reactive than Me_3SnLi[5,6] but more reactive than the lower-order cuprate $Me_3SnCu(SPh)Li$ (**6**) (see ***Lithium Phenylthio(trimethylstannyl)cuprate***). Thus Me_3SnLi converts (**4**) into (**5**) under conditions[5] much milder than those indicated in eq 3, while reagent (**6**) fails to react with (**4**).[6]

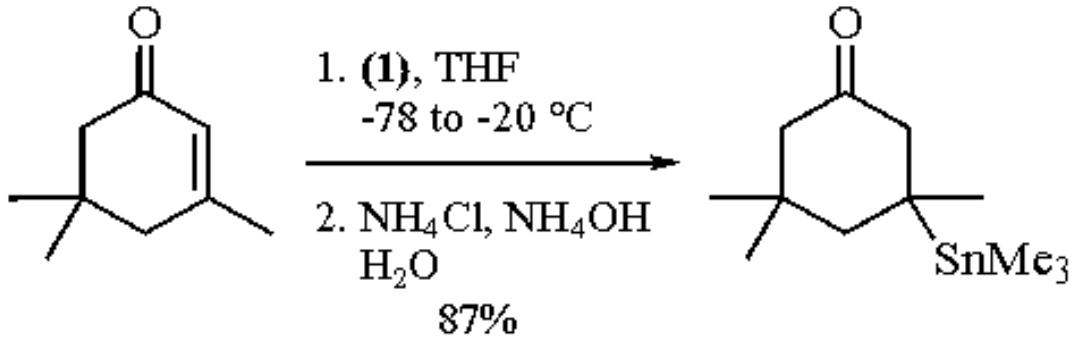

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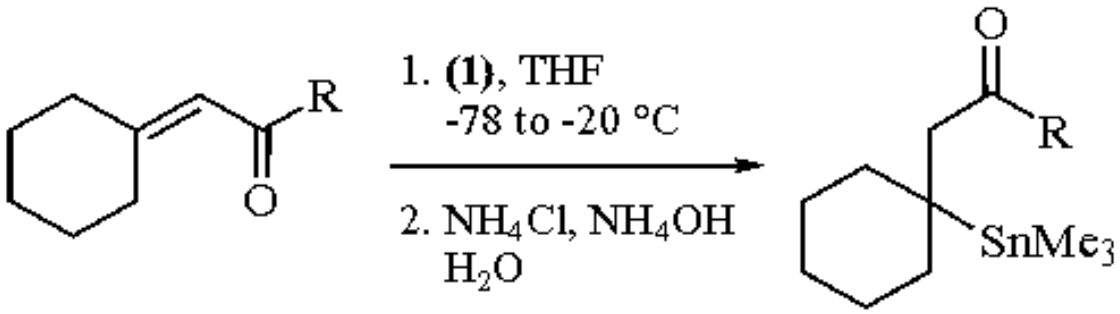

(3)

(2) R = H
(4) R = OEt

(3) R = H, 62%
(5) R = OEt, 91%

Reaction with α,β-Alkynic Esters.

Reagent (**1**) is useful for the stereoselective conversion of α,β-alkynic esters into alkyl (*Z*)-3-trimethylstannyl-2-alkenoates.[1] Although the lower-order cuprate (**6**) also effects this type of transformation,[7] reactions of (**6**) with substrates containing an ether function on the γ-carbon produce mainly the products of PhS transfer.[7] This difficulty is avoided by utilization of reagent (**1**) (eq 4).[1,8] Interestingly, the intermediate derived from the reaction of (**7**) with (**1**) can be trapped with reactive alkylating agents (eq 5).[1] An intramolecular version of this process has also been achieved (eq 6).[1]

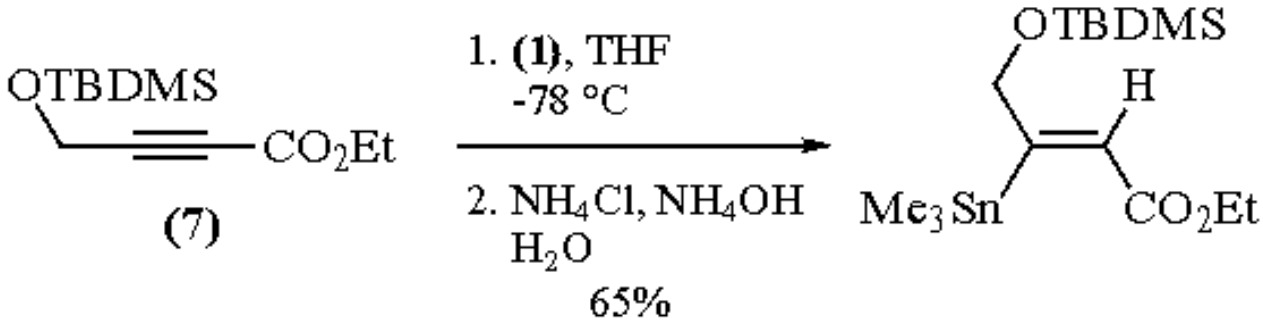

(4)

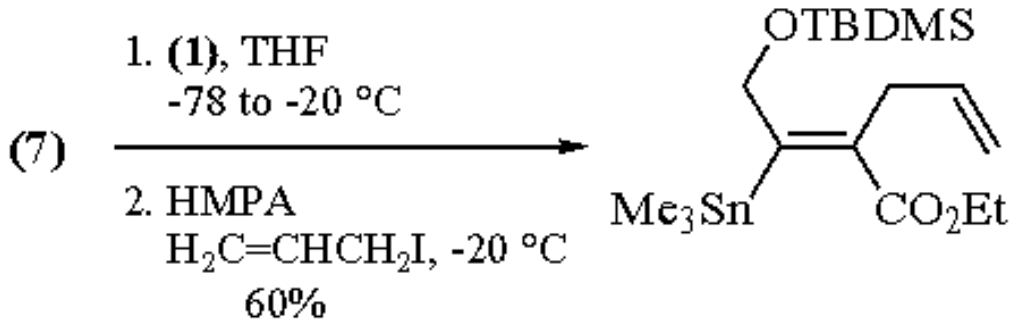

(5)

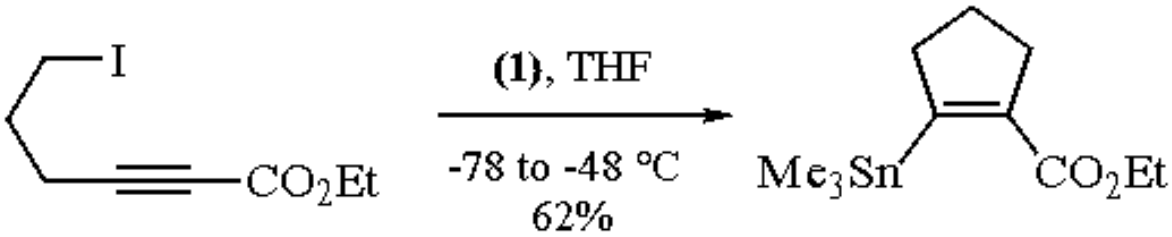

(6)

Related Reagents.

A number of higher-order mixed (trialkylstannyl)cyanocuprates related in structure to (**1**) have been reported. These reagents, which include the (trimethylstannyl)cuprates $(Me_3Sn)(R)Cu(CN)Li_2$ (**8**) (R = Me)[9] and (**9**) (R = Bu)[9,10] and the (tributylstannyl)cuprates $(Bu_3Sn)(R)Cu(CN)Li_2$ (**10**) (R = 2-Th),[2,11] (**11**) (R = Me),[12,13] and (**12**) (R = Bu),[14-16] have been prepared via a variety of interesting methods[9-14] and have been shown to be excellent sources of the Me_3Sn and Bu_3Sn moieties in reactions with an impressive array of electrophilic substrates. Representative examples are given in eqs 7-11.[9,10,13,14,16]

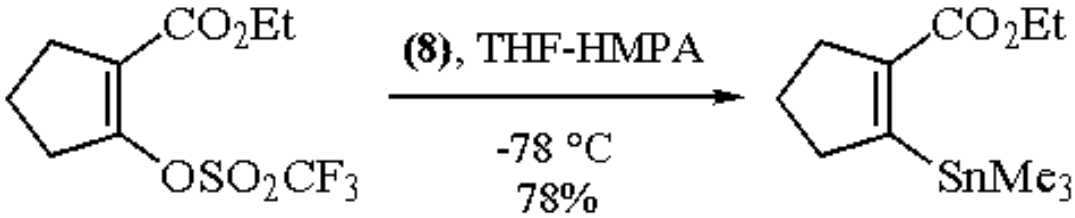

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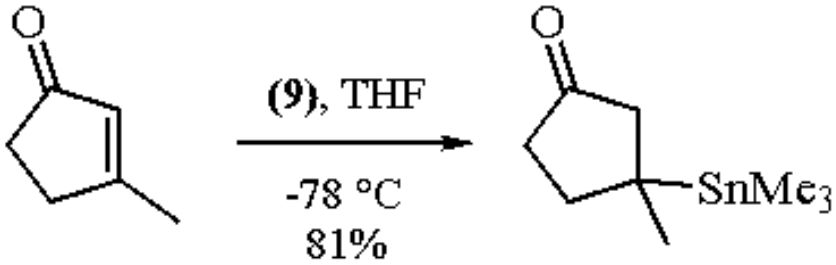

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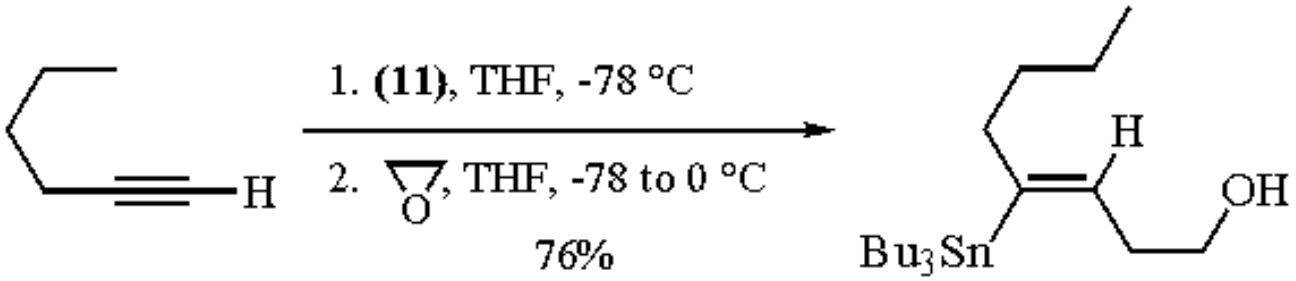

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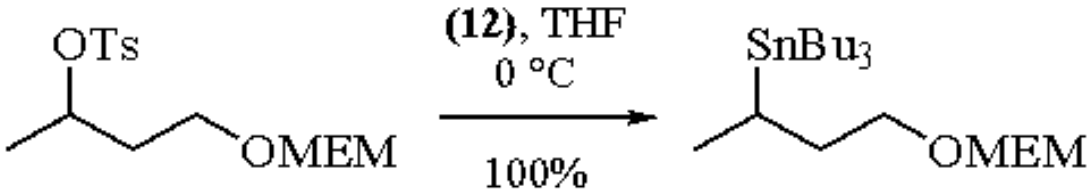

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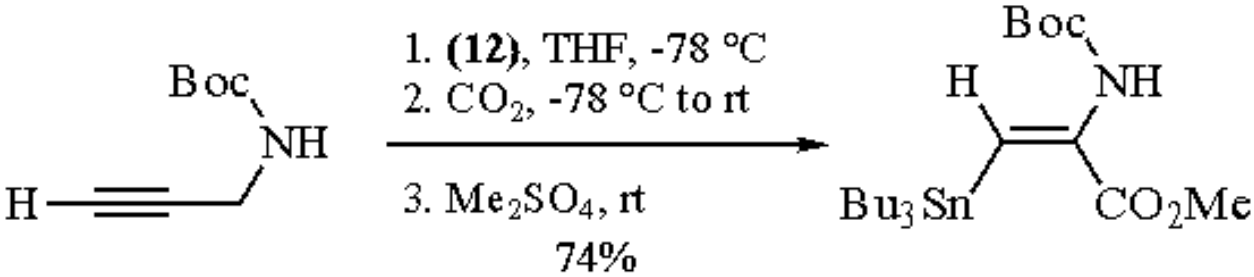

(11)

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Dilithium Tris(1-pentynyl)cuprate

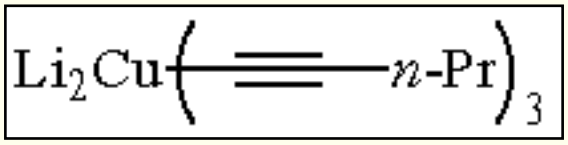

[58384-88-6] · $C_{15}H_{21}CuLi_2$ · Dilithium Tris(1-pentynyl)cuprate · (MW 278.79)

(organometallic alkynylating agent for α,β-unsaturated ketones[1] and for displacement of electrophilic amines[2])

Solubility: sol ether to -78 °C.

Preparative Method: to purified ***Copper(I) Iodide*** (10.5 mmol) suspended in ether at 0 °C is added 1-pentynyllithium (30 mmol; prepared from ***n-Butyllithium*** and 1-pentyne).[3]

Handling, Storage, and Precautions: should be used immediately following preparation.

Addition to α,β-Unsaturated Cyclic Ketones.

$Li_2Cu(1\text{-pentynyl})_3$, in ether with HMPA as cosolvent, adds regiospecifically to cyclic enones to produce 1,2-alkylation products in high (85-95%) yield (eq 1).[1] $Li_2Cu(1\text{-pentynyl})_3$, as well as other dilithium trialkynylcuprates, failed to give 1,2- or 1,4-addition products in ether alone.[3,4]

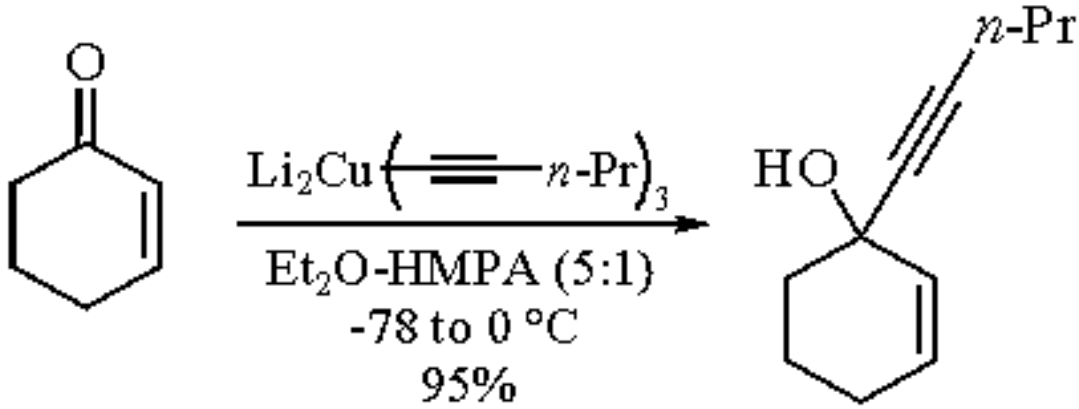

(1)

Synthesis of 1-Alkynylamines.

1-Pentynylamines are formed by displacement of electrophilic amines with $Li_2Cu(1\text{-pentynyl})_3$ in 69-87% yield (eq 2) depending on the amine substrate and the conditions used in the preparation of $Li_2Cu(1\text{-pentynyl})_3$.[2] For example, formation of $Li_2Cu(1\text{-pentynyl})_3$ from 3 equiv of 1-pentynyllithium and 1 equiv of ***Copper(I) Cyanide*** resulted in a 69% yield, while forming $Li_2Cu(1\text{-pentynyl})_3$ from 3 equiv of 1-pentynyllithium and 1 equiv of CuBr.DMS (see ***Copper(I) Bromide***) gave an 87% yield using the same electrophilic amine.

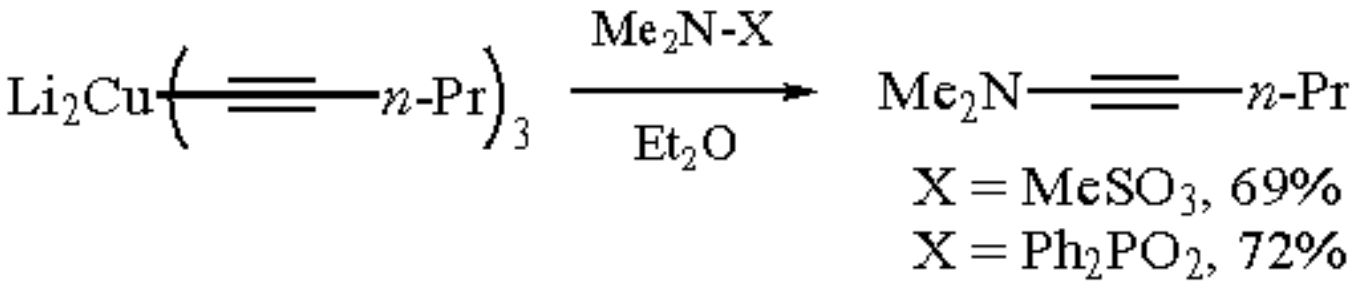

(2)

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Dilongifolylborane[1]

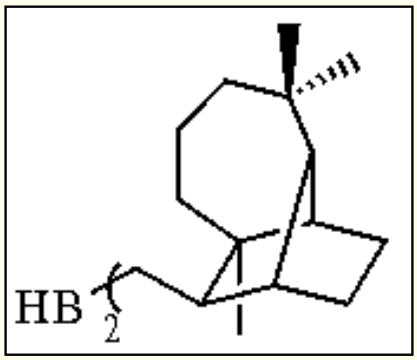

[77882-24-7] · $C_{30}H_{51}B$ · Dilongifolylborane · (MW 422.55)

(reagent for asymmetric hydroboration of prochiral alkenes[1,2])

Alternate Name: Lgf_2BH.

Physical Data: mp 160-161 °C (sealed evacuated capillary).

Solubility: sparingly sol common organic solvents, i.e. THF, CCl_4, CH_2Cl_2, $CHCl_3$. The suspended material is active.

Form Supplied in: white solid, mp 161-163 °C.

Preparative Method: although now commercially available, the reagent is readily prepared by hydroboration of (+)-longifolene with ***Borane-Dimethyl Sulfide*** ($BH_3.SMe_2$) in a 2:1 ratio (eq 1).

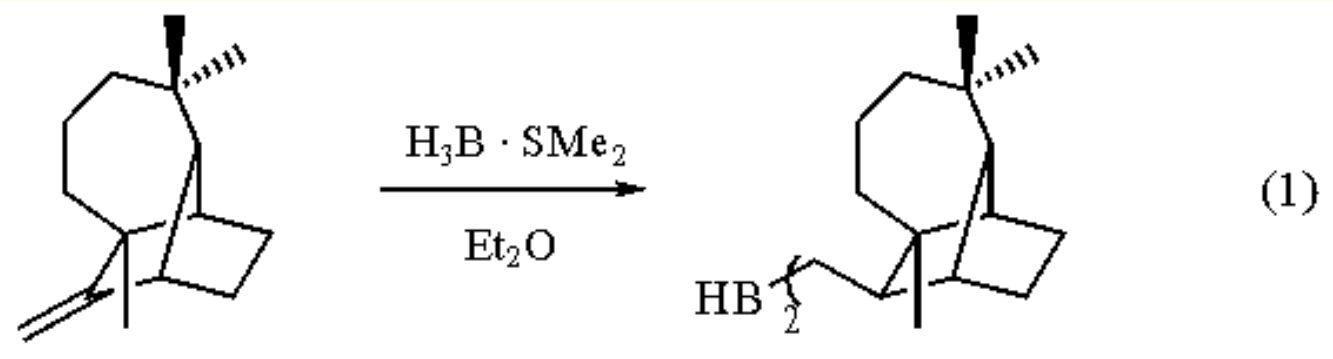

Handling, Storage, and Precautions: guidelines for handling air- and moisture-sensitive reagents should be followed.[1c] The pure reagent is described as an irritant.

Asymmetric Hydroboration.[2]

Dilongifolylborane (Lgf_2BH) is a chiral dialkylborane intermediate in steric requirement between the two widely investigated chiral organoboranes derived from α-pinene: ***Monoisopinocampheylborane*** ($IpcBH_2$)[3] and ***Diisopinocampheylborane*** (Ipc_2BH).[4]

Due to the hindered *exo* face environment of the longifolene double bond, the addition of borane proceeds exclusively from the *endo* face. Even in the presence of excess longifolene, hydroboration stops cleanly at the dialkylborane stage.

The reported levels of asymmetric induction achieved with this reagent in the hydroboration-oxidation of representative alkenes are in the range of 59-78% ee for *cis* and 45-75% ee for trisubstituted alkenes. The highest levels of asymmetric induction have been recorded for *cis*-2-butene (eq 2) and 2-methyl-2-pentene (eq 3).[2]

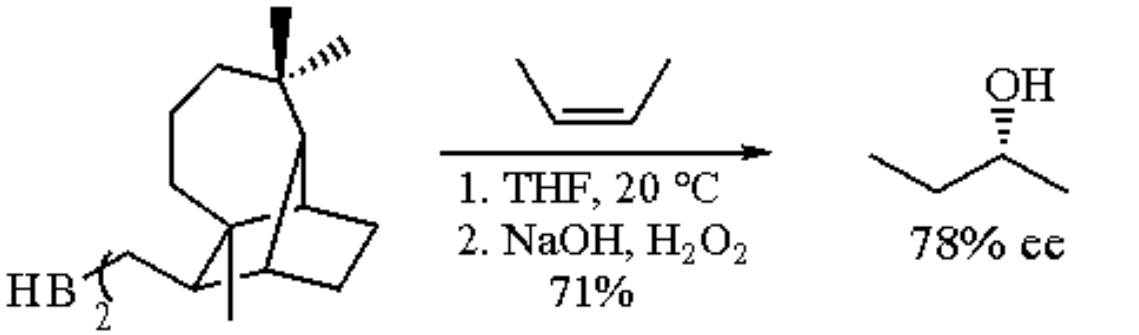

(2)

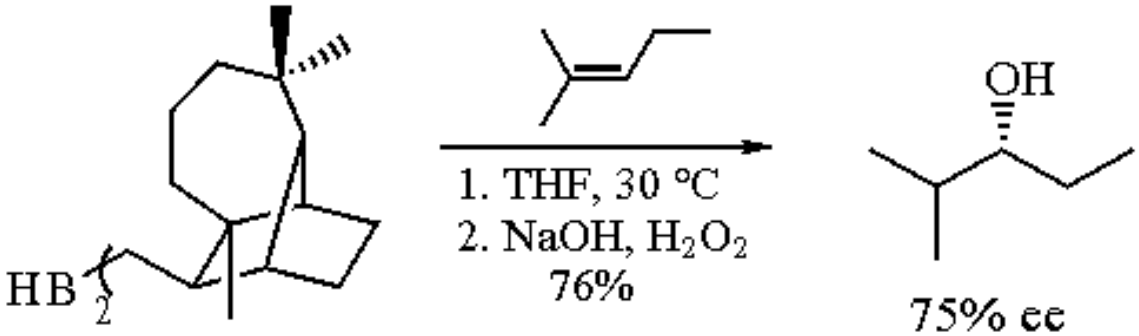

(3)

Trisubstituted alkenes such as 2,4,4-trimethyl-2-pentene and 1-phenylcyclopentene, which apparently exceed the steric requirements of Lgf_2BH, fail to react after 4 days at 35 °C.

Although the ready availability of only the (+)-longifolene enantiomer potentially limits the use of Lgf_2BH as a reagent for natural product synthesis, this form proved appropriate for the preparation of an optically enriched intermediate in a synthesis of the naturally occurring enantiomer of verrucarinic acid (eq 4).[5]

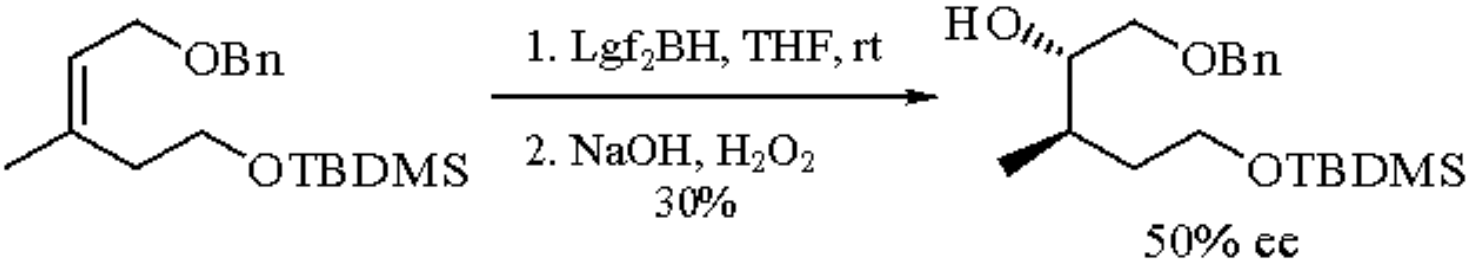

(4)

(+)-Longifolene of >99% ee can be liberated from Lgf_2BH which has been diastereomerically enriched by recrystallization from THF at 0 °C (eq 5).[6]

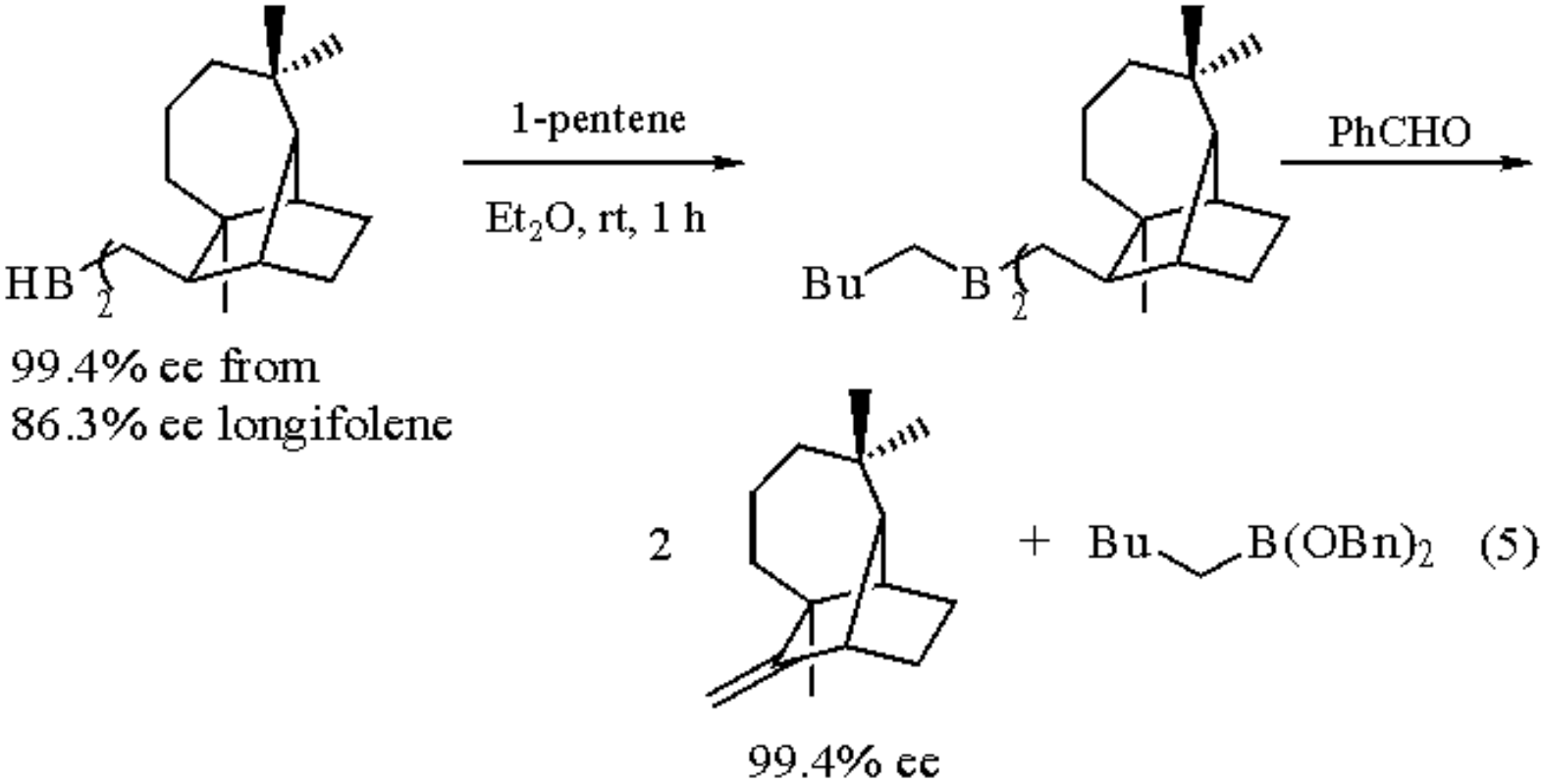

(5)

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Robert P. Short

Polaroid Corporation, Cambridge, MA, USA

Dimesitylborane[1]

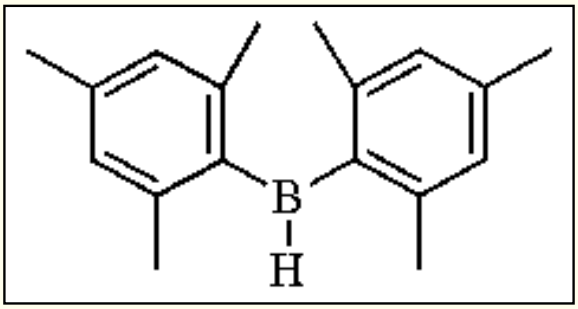

[51458-06-1] · $C_{18}H_{23}B$ · Dimesitylborane · (MW 250.19)

(very selective hydroborating reagent for alkenes and alkynes;[2] preparation of boron-stabilized alkyl and vinyl carbanions[2,3])

Alternate Names: bis(2,4,6-trimethylphenyl)borane; Mes_2BH.

Physical Data: mp 162-164 °C.

Solubility: moderate sol THF (37.5 g L^{-1}).

Form Supplied in: white solid.

Preparative Methods: from Mes_2BF and $LiAlH_4$;[1,2a] Mes_2BH_2Li (Mes_2BF + 2 LiH) and benzyl chloride[2a] or MeI;[2b] Mes_2BF and LiH.[2c]

Purification: recrystallization from 1,2-dimethoxyethane.[1,2a]

Handling, Storage, and Precautions: solid stable in air and in THF but reacts with moisture and protic solvents. Best stored under an inert atmosphere. Use in a fume hood.

Hydroboration of Alkenes.

Mes_2BH is a highly selective reagent for the hydroboration of alkenes.[2a] In general, suspensions of the reagent in THF react slowly with mono- (**1**) and 1,2-disubstituted (**2**) alkenes (8-25 h, 25-65 °C) and reactions are very sensitive to steric factors. The air-stable (and often crystalline) dimesitylboranes which result may be oxidized to alcohols with alkaline ***Hydrogen Peroxide*** (eq 1). Geminally disubstituted alkenes and cycloalkenes react very slowly with Mes_2BH.

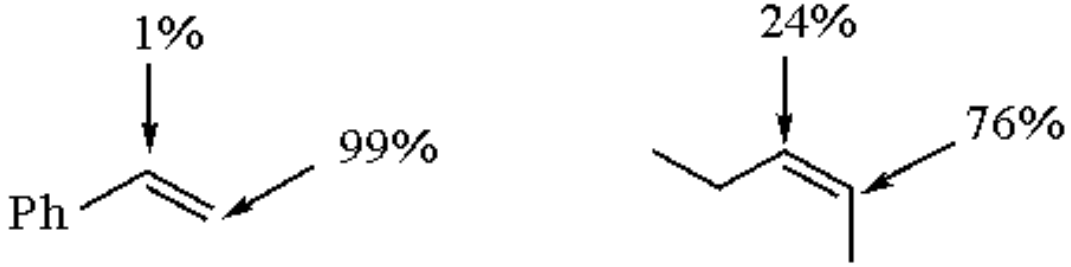

(1) (2)

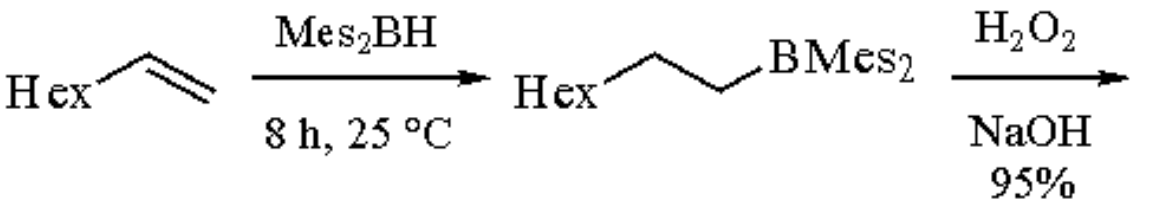

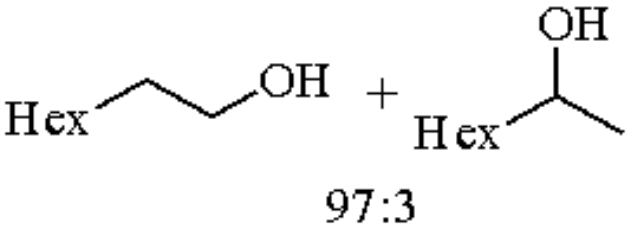

(1)

Alkyl dimesitylboranes of the type produced by these hydroboration reactions also have been found to be useful in the preparation of boron-stabilized carbanions which may be alkylated[3] (eq 2) or converted into alkenes,[4] glycols,[5] or ketones[6] upon reaction with carbonyl compounds. The bulky dimesitylboryl group not only imparts stability to its derivatives but sterically promotes the C_γ-alkylation of allylic carbanions.[7]

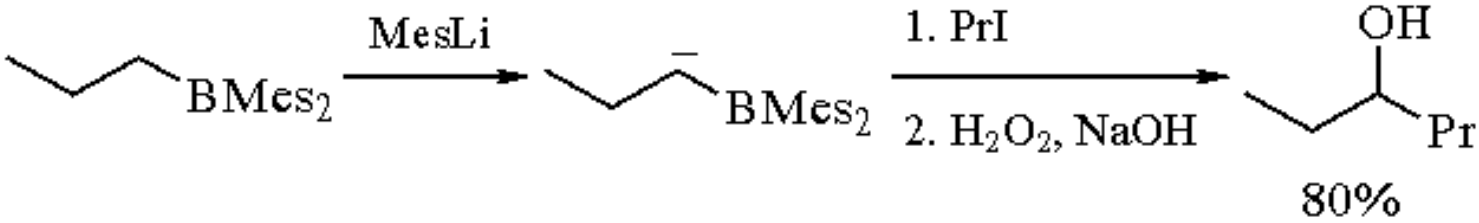

(2)

Hydroboration of Alkynes.

Generally, Mes_2BH reacts rapidly (within minutes) with alkynes, giving aldehydes and ketones upon oxidation of resulting vinylboranes (eq 3).[2a] The slow rate of reaction of Mes_2BH with cyclohexanone[2c] suggests that such relatively rapid hydroborations could be conducted in the presence of many common nonacidic functional groups. Compatability with halides,[8] phosphines, and ferrocene[9] has been demonstrated. Unprecedented regioselectivity was observed in the hydroboration-oxidation of 2-hexyne (**3**) where isomeric 2- and 3-hexanone were produced in a ratio of 90:10 (cf. 60:40 with ***Diborane*** and 78:22 with ***9-Borabicyclo[3.3.1]nonane***), making this the most selective hydroborating agent of unsymmetrical alkynes known (see also **4**).[2a]

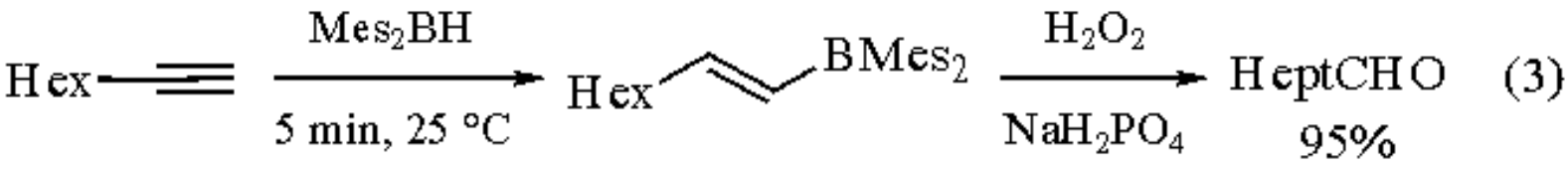

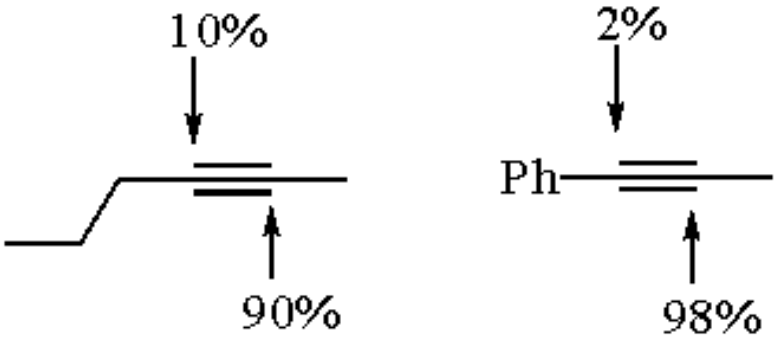

(3) **(4)**

The directing influence of silyl and stannyl groups has been used regioselectively to prepare α-metallovinylboranes which are precursors of boron-stabilized vinyl carbanions (eq 4).[2b]

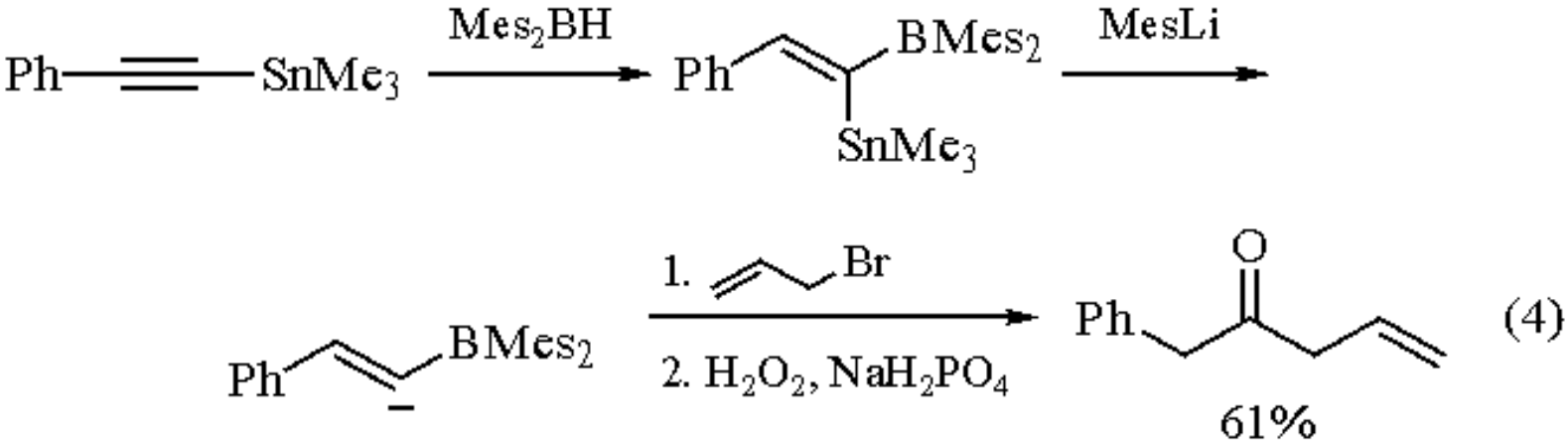

The resistance to boron ate-complex formation imparted by the mesityl groups to certain vinyl dimesitylboranes has been shown to enable metal-halogen exchange-initiated nucleophilic addition reactions to the boron-activated double bond (eq 5).[8]

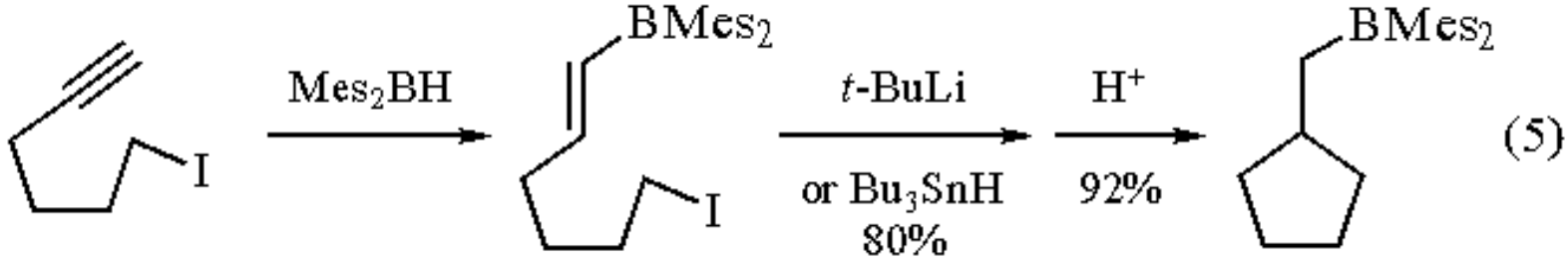

Related Reagents.

9-Borabicyclo[3.3.1]nonane; ***Borane-Dimethyl Sulfide***; ***Borane-Tetrahydrofuran***; ***Dicyclohexylborane***; ***Disiamylborane***.

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3,4-Dimethoxybenzyl Bromide

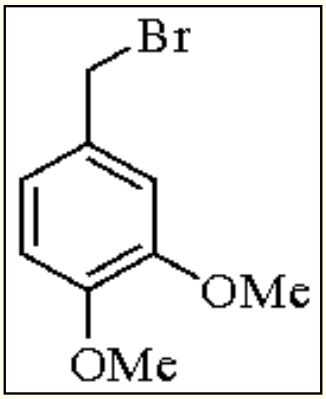

[21852-32-4] · $C_9H_{11}BrO_2$ · 3,4-Dimethoxybenzyl Bromide · (MW 231.09)

(reagent for introduction of 3,4-dimethoxybenzyl protecting group, which can be cleaved selectively under conditions of benzylic oxidation[1])

Alternate Name: DMBBr.

Physical Data: mp 52-53 °C.

Solubility: reactions are usually carried out in polar solvents such as THF or DMF.

Preparative Methods: synthesized from commercially available 3,4-dimethoxybenzyl alcohol and PBr_3[2] or HBr.[3]

Purification: recrystallization from absolute ethanol.[2]

Handling, Storage, and Precautions: the reagent is quite unstable and is best prepared fresh or stored at low temperature under nitrogen. It is a lachrymator.

3,4-Dimethoxybenzyl Ethers (DMB Ethers).

The benzyl group is a frequently used protecting group[4] in organic synthesis due to its acid and base stability, and its facile removal by catalytic hydrogenation or with sodium in liquid ammonia. The group is most commonly used to protect alcohol functions; however, it may not be generally applied to substrates which have other functional groups susceptible to the reductive conditions. To overcome this problem and generally to extend the range of protecting groups available, methoxy-substituted benzyl ethers have been prepared (e.g. the 3,4-dimethoxy[1] and 4-methoxybenzyl[5] (PMB) ethers). DMB ethers are made using the benzyl bromide (or chloride), alcohol, and base,[1] or

with base sensitive substrates using the trichloroacetimidate[6] (see ***Benzyl 2,2,2-Trichloroacetimidate***). PMB ethers can also made in similar fashion under either basic[5] or acidic[7] conditions. DMB ethers can be removed oxidatively using ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** (DDQ)[1,5] or trityl tetrafluoroborate,[5b,c,6,7a] and PMB ethers have also been cleaved with a variety of other methods.[4,8] The products obtained are the methoxy substituted benzaldehyde and the parent alcohol (eq 1), although with an allylic alcohol there is a risk of over oxidation to give the enone (eq 2).[9] Methoxybenzyl ethers with free α- or β-hydroxy groups can be converted to acid cleavable acetals with DDQ oxidation under anhydrous conditions, and further oxidized to base cleavable benzoates.[10] Simple benzyl ethers and many other protecting and functional groups remain unaffected under these conditions.[1,5]

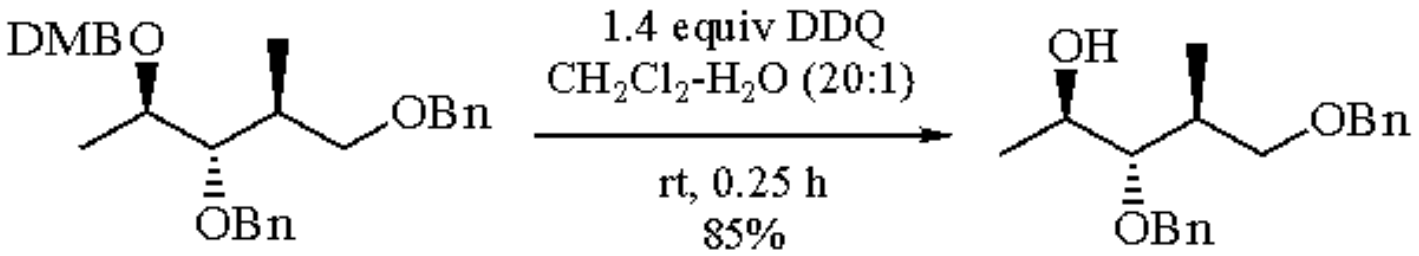

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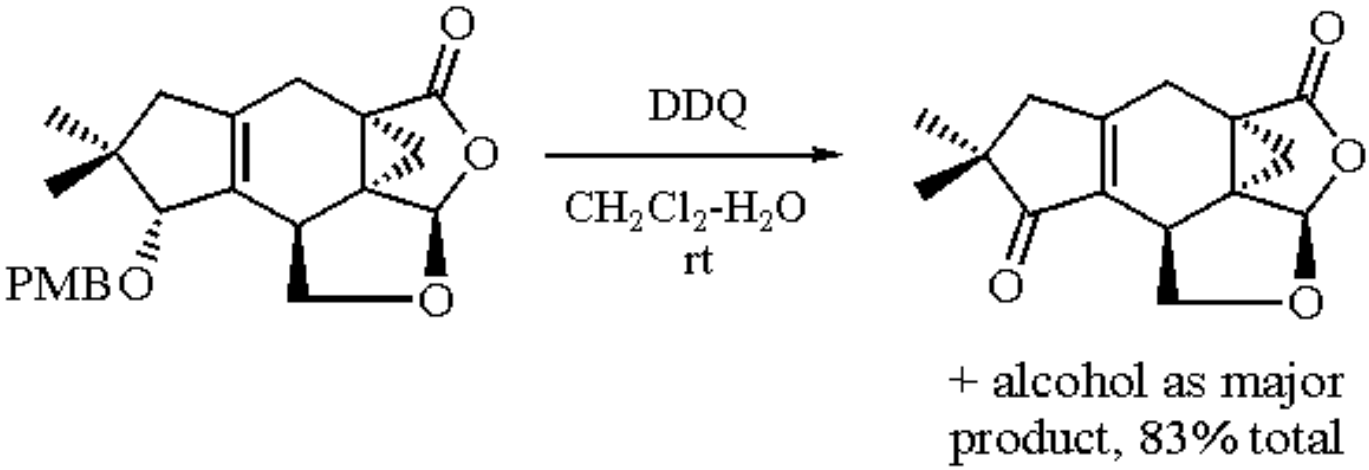

(2)

Each substituted benzyl ether has a different oxidation potential (1.45 V for the DMB-OR, and 1.78 V for the PMB-OR), so each methoxy substitution pattern results in different rates of ether cleavage.[1,11] This means that the DMB group can be removed in the presence of a PMB ether with high selectivity (eq 3).[1] It has also been shown that other methoxybenzyl ethers react at widely differing rates.[11] For example, the reaction time for the DMB ether was <20 min (86% yield of alcohol), and the 2,6-dimethoxy isomer required 27.5 h (80% yield) (eq 4).[11] Other substitution patterns give reaction times between these two extremes.

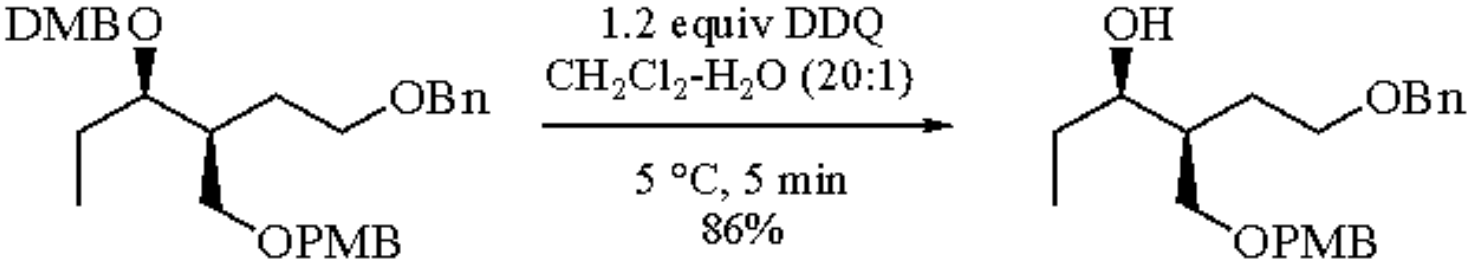

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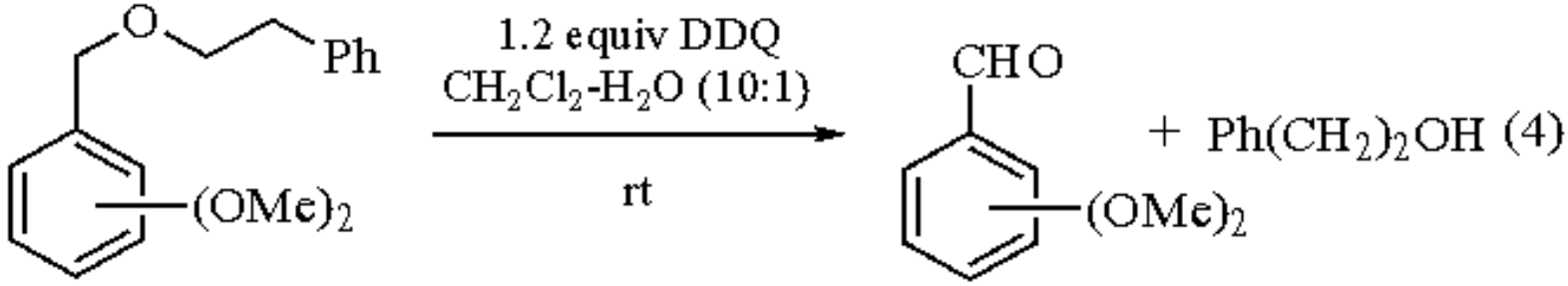

PMB and DMB ethers are less readily cleaved than simple benzyl ethers using catalytic hydrogenation.[12] W-4 ***Raney Nickel*** gave the best selectivities (eq 5), but deprotection using ***Sodium-Ammonia*** showed no discrimination at all.[12]

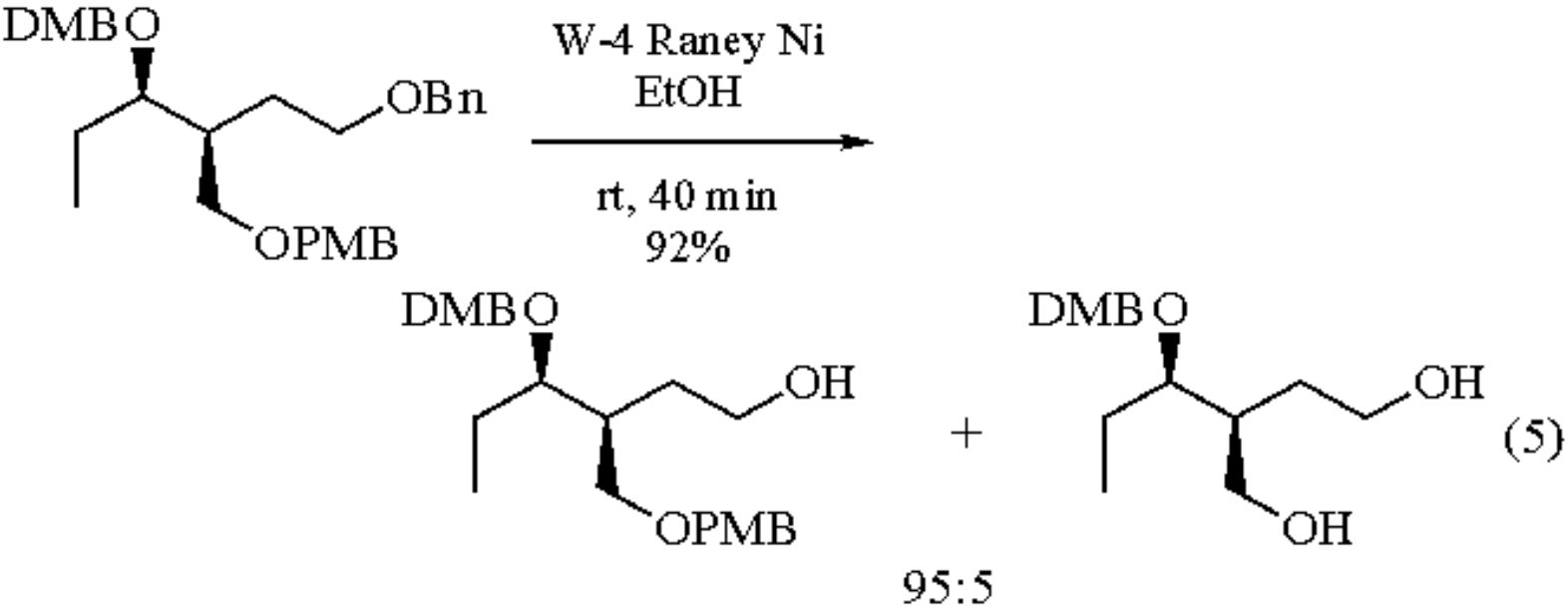

The versatility of a combination of the substituted and unsubstituted benzyl ethers as protecting groups has been shown in the multi-step syntheses of 16-membered macrolides[13] and other natural products.[14,15] The DMB group alone has also been used as an alcohol protecting group in molecules ranging from the relatively simple[16] to complex oligoribonucleotides,[6,7a] and occasionally for protection of nitrogen-containing groups.[8,17]

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3,5-Dimethoxybenzyl 4-Nitrophenyl Carbonate

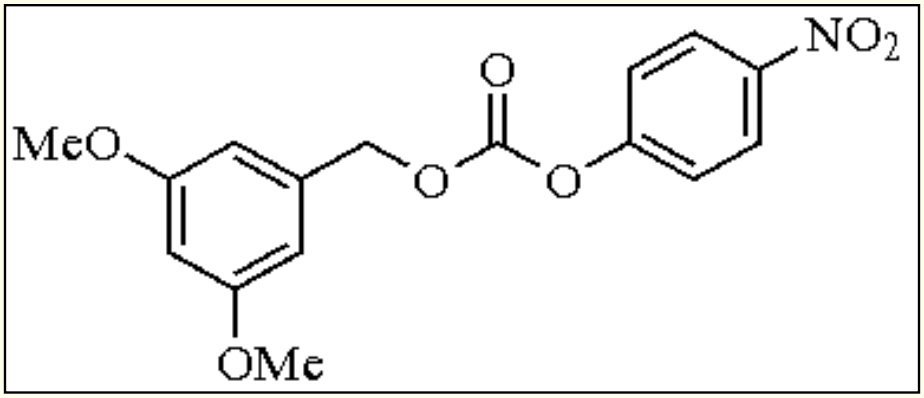

[6453-62-9] · $C_{16}H_{15}NO_7$ · 3,5-Dimethoxybenzyl 4-Nitrophenyl Carbonate · (MW 333.30)

(amino-protecting group used in peptide synthesis[1])

Physical Data: mp 114-15 °C.

Solubility: sol chloroform, THF.

Preparative Method: by reduction of 3,5-dimethoxybenzoic acid with ***Lithium Aluminum Hydride*** and then acylation of the resulting 3,5-dimethoxybenzyl alcohol with 4-nitrophenyl chloroformate.[1]

N-Protection of Amino Acids.

Reaction of amino acids with the reagent (**1**) in aqueous THF in the presence of ***Sodium Hydroxide*** affords 3,5-dimethoxybenzyloxycarbonyl derivatives in 55-76% yields (eq 1).[1] This protecting group can be cleaved by irradiation with a high-pressure mercury lamp for 1.5 h in aqueous dioxane (42-85% yields). The advantage is provided in that acidic, basic, or reductive reaction conditions can be avoided.

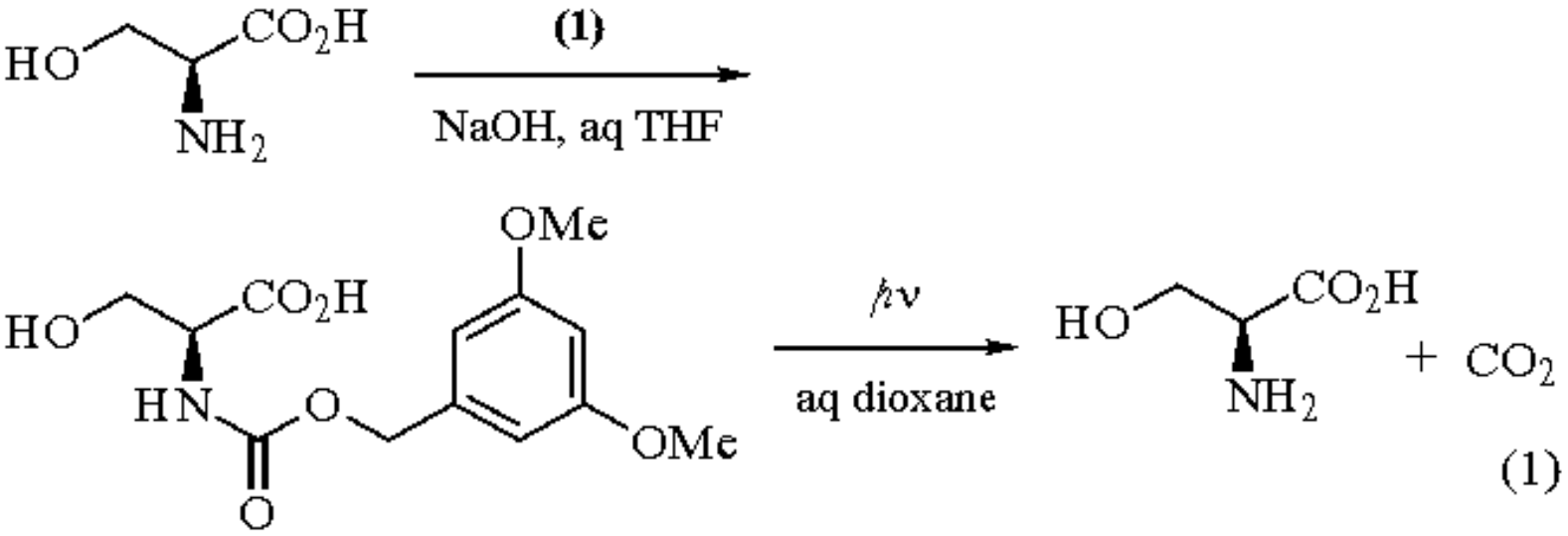

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Dimethoxycarbenium Tetrafluoroborate[1]

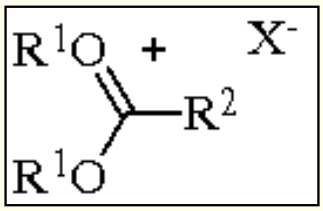

(**1**; R^1 = Me, R^2 = H, X = BF_4)

[18346-68-4] · $C_3H_7BF_4O_2$ · Dimethoxycarbenium Tetrafluoroborate · (MW 161.89) (**2**; R^1 = Me, R^2 = H, X = Br)

[70146-62-2] · $C_3H_7BrO_2$ · Dimethoxycarbenium Bromide · (MW 154.99) (**3**; R^1 = Me, R^2 = H, X = $SbCl_6$)

[27434-62-4] · $C_3H_7Cl_6O_2Sb$ · Dimethoxycarbenium Hexachloroantimonate · (MW 409.56) (**4**; R^1 = Me, R^2 = H, X = PF_6)

[50318-32-6] · $C_3H_7F_6O_2P$ · Dimethoxycarbenium Hexafluorophosphate · (MW 220.05) (**5**; R^1 = Me, R^2 = H, X = SbF_6)

[66226-85-5] · $C_3H_7F_6O_2Sb$ · Dimethoxycarbenium Hexafluoroantimonate · (MW 310.83) (**6**; R^1 = Et, R^2 = H, X = BF_4)

[1478-41-7] · $C_5H_{11}BF_4O_2$ · Diethoxycarbenium Tetrafluoroborate · (MW 189.94) (**7**; R^1 = Me, R^2 = Et, X = BF_4)

[64950-83-0] · $C_5H_{11}BF_4O_2$ · Dimethoxy(ethyl)carbenium Tetrafluoroborate · (MW 189.94) (**8**; R^1 = Et, R^2 = H, X = $SbCl_6$)

[1663-59-8] · $C_5H_{11}Cl_6O_2Sb$ · Diethoxycarbenium Hexachloroantimonate · (MW 437.61) (**9**; R^1 = Et, R^2 = H, X = PF_6)

[97632-94-5] · $C_5H_{11}F_6O_2P$ · Diethoxycarbenium Hexafluorophosphate · (MW 248.10) (**10**; R^1 = Et, R^2 = Me, X = BF_4)

[21872-75-3] · $C_6H_{13}BF_4O_2$ · Diethoxy(methyl)carbenium Tetrafluoroborate · (MW 203.97) (**11**; R^1 = allyl, R^2 = H, X = BF_4)

[18346-72-0] · $C_7H_{11}BF_4O_2$ · Diallyloxycarbenium Tetrafluoroborate · (MW 213.97) (**12**; R^1 = *n*-Pr, R^2 = H, X = BF_4)

[18346-70-8] · $C_7H_{15}BF_4O_2$ · Diisopropoxycarbenium Tetrafluoroborate · (MW 218.00) (**13**; R^1 = *i*-Pr, R^2 = H, X = BF_4)

[18346-71-9] · $C_7H_{15}BF_4O_2$ · Dipropoxycarbenium Tetrafluoroborate · (MW 218.00) (**14**; R^1 = Me, R^2 = Ph, X = BF_4)

[878-36-4] · $C_9H_{11}BF_4O_2$ · Dimethoxy(phenyl)carbenium Tetrafluoroborate · (MW 237.99) (**15**; R^1 = Et, R^2 = Ph, X = BF_4)

[70861-63-1] · $C_{11}H_{15}BF_4O_2$ · Diethoxy(phenyl)carbenium Tetrafluoroborate · (MW 266.04) (**16**; R^1 = Me, R^2 = 2,4,6-$Me_3C_6H_2$, X = BF_4)

[15655-62-6] · $C_{12}H_{17}BF_4O_2$ · Dimethoxy(mesityl)carbenium Tetrafluoroborate · (MW 280.07)

(ambident electrophiles;[1,2] alkylation of S-,[3,4] N-,[5] and O-nucleophiles;[6,7] acylation of C-nucleophiles[8])

Physical Data: mp: (**1**) 20 °C; (**4**) 72 °C; (**6**) 20 °C; (**8**) 151-152 °C; (**10**) 55 °C; (**14**) 88-90 °C; (**15**) dec; (**16**) 89-91 °C.

Solubility: freely sol liquid sulfur dioxide and arsenic trifluoride.[9b,c] When prepared in situ, halogenated solvents such as dichloromethane or 1,1,2-trichlorotrifluoroethane are most commonly used.[2,5b,6a,b,8e,f] With these solvents, however, the reagents are only slightly soluble and usually exist as a slurry at -30 °C. Refer to Olah et al.,[9a] where solubilities follow the trend phosphates > antimonates > borates.

Form Supplied in: the reagents are prepared in situ. They exist as colorless solids when isolated.[6d] Stability of the carbenium ions varies considerably, especially in the substituted analogs.[6,8e,8f]

Preparative Methods: each reagent is conveniently prepared by introduction of the desired Lewis acid such as ***Boron Trifluoride Etherate***, ***Antimony(III) Chloride***, or phosphorus pentafluoride to a cooled solution containing the appropriate orthoformate (or orthoester, R^2 &neq; H).[2] For dimethoxycarbenium bromide, the use of sulfur dioxide at -30 °C is required.[9b] For isolation techniques using a specially designed apparatus, see Pindur and Flo.[10]

Purification: since the reagents are prepared in situ, they are commonly used without further purification. When isolable, the reagents are purified by recrystallization.

Handling, Storage, and Precautions: dialkoxycarbenium salts are hygroscopic and should therefore be kept under an inert atmosphere (Ar or N_2). For optimal results, reaction vessels should be flame dried and purged with argon using anhydrous solvents in all instances.[6a] If isolable, storage in a dry box or a tightly sealed vessel under an inert atmosphere is recommended. Olah et al.[9a] describe the phosphate series to be stable under an inert atmosphere at rt without refrigeration. The borate and antimonate series are generally stable for weeks under an inert atmosphere at 0 °C. All dialkoxycarbenium salts are powerful acylating/alkylating

agents; therefore skin and eyes should be protected when handling the solutions and especially the isolated salts. Use in a fume hood.

Introduction.

Dialkoxycarbenium salts exhibit an interesting dichotomy in reactivity.[2g] These ambident electrophiles are powerful acylating and alkylating agents. The mode of reactivity can be altered depending upon the nucleophile, the reagent, the reaction temperature, the reaction time, and the solvent. Prepared in situ, these salts surpass in reactivity other common alkylating agents such as Meerwein's salt, alkyl triflates, and alkyl halides.[2,6,8] Each cationic component serves as a versatile electrophile which has proven to be an efficient formylating or alkylating reagent. All of the dialkoxycarbenium salts are accessible by judicious choice of orthoester and Lewis acid. Limitations include solubility and stability, which make the commercially available trialkyloxonium tetrafluoroborates attractive (see ***Triethyloxonium Tetrafluoroborate***, ***Trimethyloxonium Tetrafluoroborate***).[7a] However, dialkoxycarbenium salts provide a means for efficient acylation or alkylation of weak nucleophiles not accessible from their parent counterparts.

Alkylation of Sulfur Nucleophiles.

Dimethoxycarbenium tetrafluoroborate has been extensively used in the conversion of numerous thiacyclophanes to polycyclic aromatic compounds.[3c] This method efficiently transforms sulfide linkages into carbon-carbon double bonds via a Stevens rearrangement followed by an elimination step. Using this sequence, dimethyldihydropyrene[3c,d] was synthesized in five steps, two of which involved the formation of a bis(sulfonium)cyclophane intermediate with dimethoxycarbenium tetrafluoroborate (eq 1).

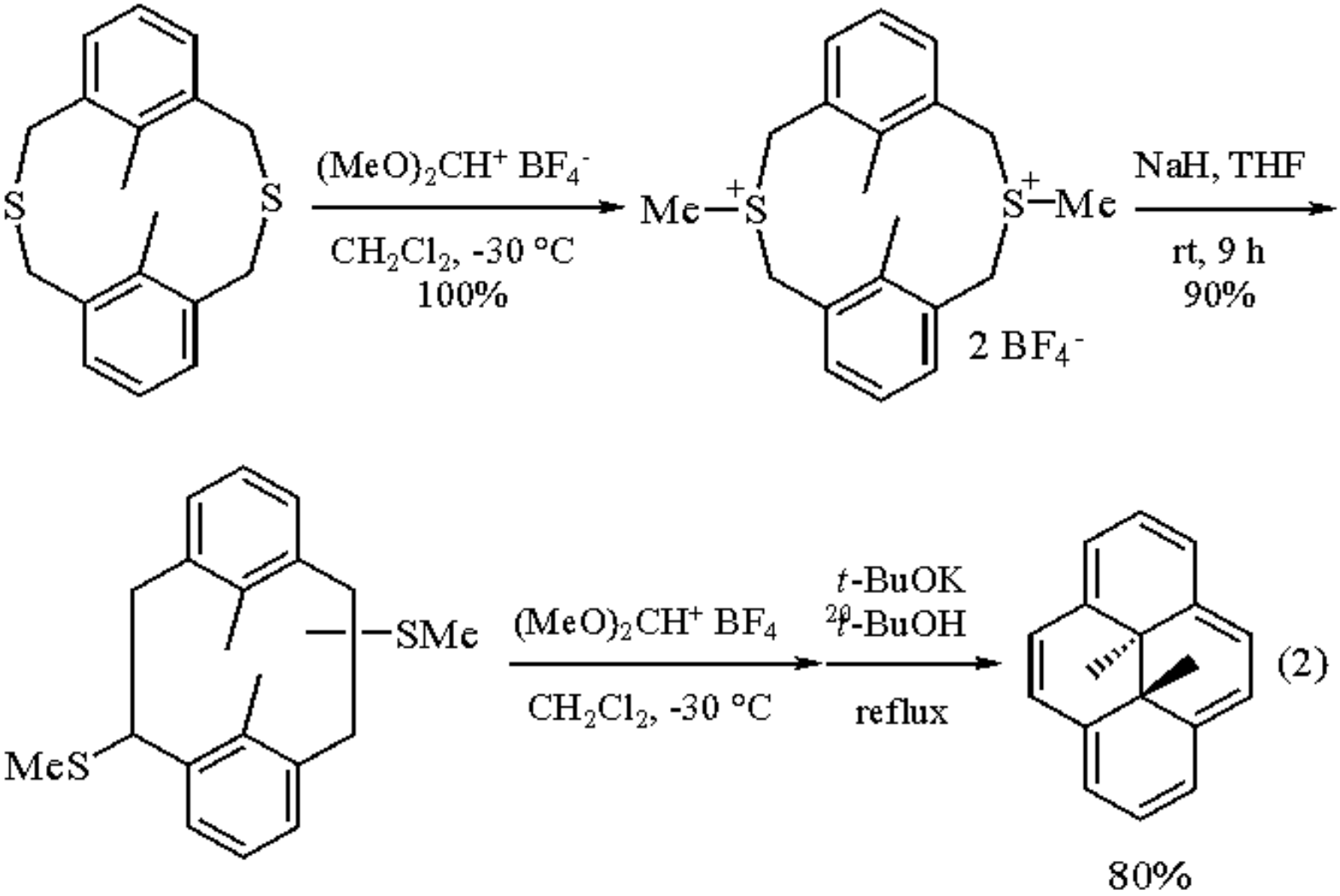

Formation of other bis(sulfonium) salts using dimethoxycarbenium tetrafluoroborate was successfully applied toward the synthesis of other pyrene derivatives such as [2.2]metaparacyclophene-1,9-diene,[3e] [7],[7.7]circulene,[3f] [2.2](2,6)pyridinophene-1,9-diene,[3g] and [2.2.2](1,3,5)cyclophane-1,9,17-triene.[3h] Another example of sulfur activation employing both dimethoxycarbenium tetrafluoroborate as well as hexafluorophosphate has been applied to the synthesis of various organic charge-transfer complexes.[4a,b] Critical for the success of these syntheses is the conversion of various thione derivatives to the corresponding selenone derivatives. Treatment of thieno[3,4-*d*]-1,3-dithiole-2-thione with dimethoxycarbenium hexafluorophosphate afforded the desired thionium hexafluorophosphate, which was subsequently transformed to the selenone analog in the presence of ***Hydrogen Selenide*** (eq 2).

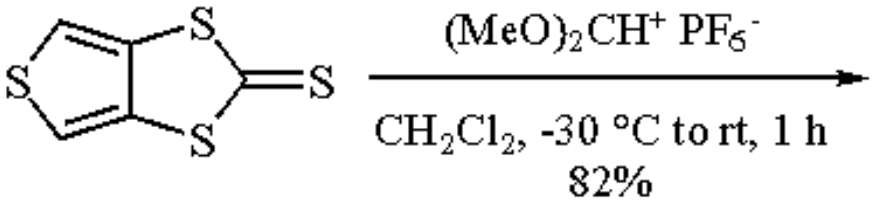

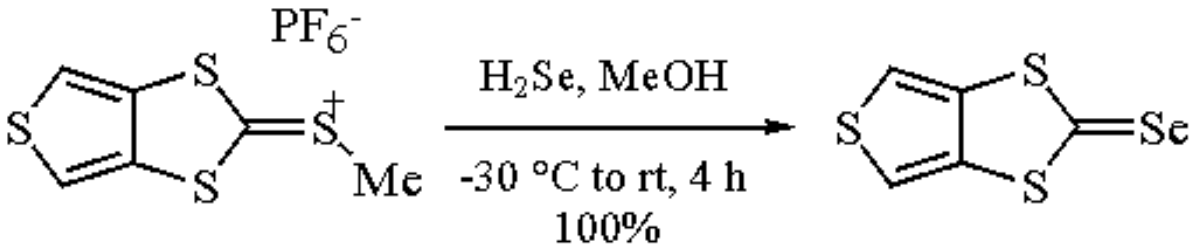

(2)

Activation of the carbon-sulfur double bond with dialkoxycarbenium salts has led to the preparative synthesis of similar analogs. Thioimidates can be prepared by the selective alkylation of thioamides using either dimethoxy- or diethoxycarbenium tetrafluoroborate (eq 3).[4c,d] The products isolated are used as key intermediates in the synthesis of β-lactams. Meerwein's salt also carries out the transformation shown in eq 3. Other examples include the formation of hexachloroantimonate salts via ethylation of dithiolodithione dimers (eq 4).[4e] Lastly, heterolysis of disulfide bonds has been achieved by treatment of a diaryl disulfide with diethoxycarbenium tetrafluoroborate (eq 5).[4f]

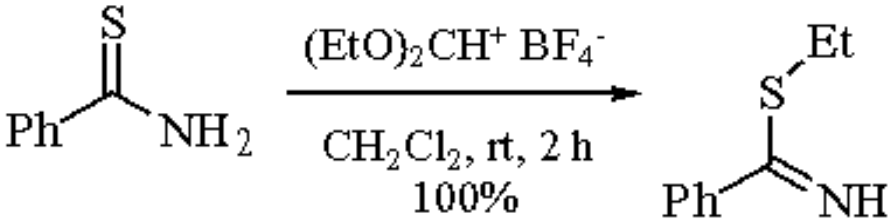

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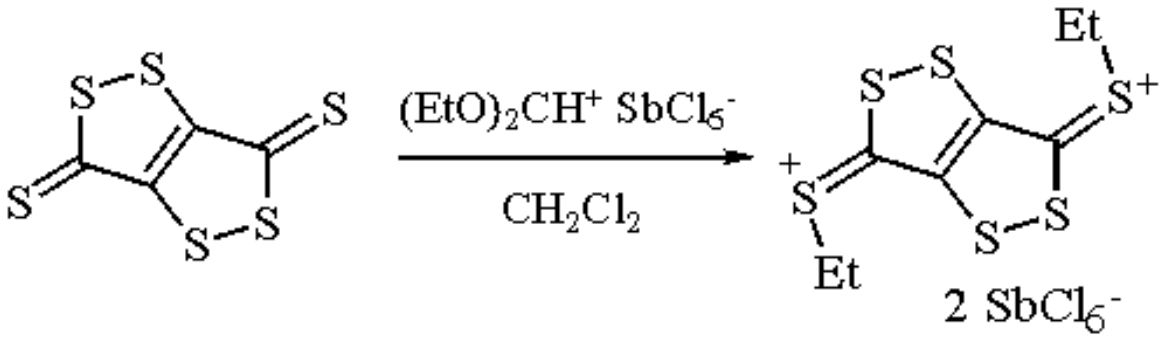

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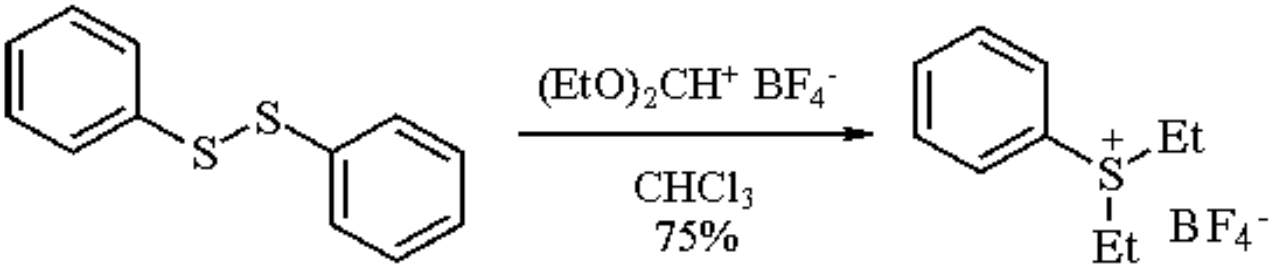

(5)

Alkylation of Nitrogen Nucleophiles.

Dialkoxycarbenium tetrafluoroborates provide an efficient means for the production of secondary amines through nitrilium salt intermediates.[5b] *N*-Alkylnitrilium salts other than *N*-methyl or *N*-ethyl are not readily accessible using the trialkyloxonium tetrafluoroborates. Treatment of a series of dialkoxycarbenium salts with benzonitrile furnished, after reductive workup, the desired substituted benzylamines (eq 6). Higher analogs such as *n*-propyl did not provide the desired *n*-propylbenzylamine but rather isopropylbenzylamine. This rearrangement does limit applications of other higher-order dialkoxycarbenium salts.

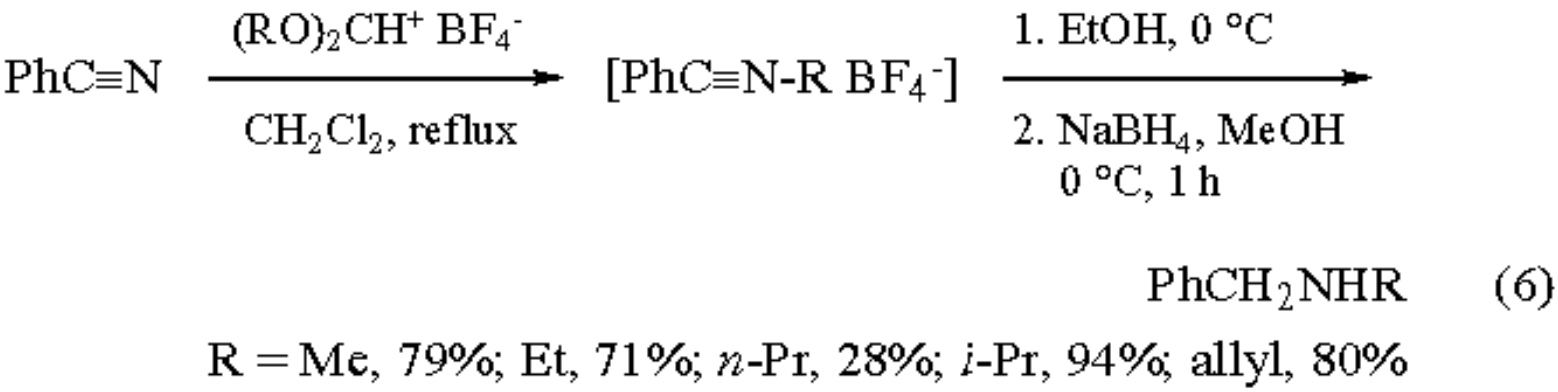

Formation of nitrilium salts has also been applied to the field of organometallic chemistry.[5c] In these examples the reductive workup of the intermediate iminoester with sodium borohydride is eliminated. Diethoxycarbenium tetrafluoroborate is used to perform two nitrogen-based alkylations (eq 7). The resulting complex is isolated and purified by recrystallization.

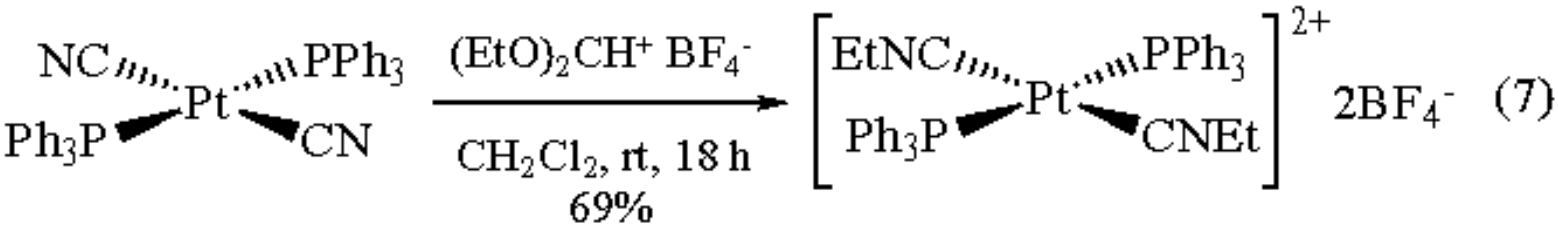

Another example of activation/reduction is illustrated in the preparation of 1-alkyl-2,1-benzisoxazoline derivatives.[5d] Treatment of 2,1-benzisoxazoles with dialkoxycarbenium hexachloroantimonate affords the desired 1-alkyl-2,1-benzisoxazolium salts, which are subsequently treated with a variety of nucleophilic reagents (eq 8). The following transformation is catalyzed by in situ preparation of either dimethoxy- or diethoxycarbenium salts as well as the related trialkyloxonium tetrafluoroborates. Nucleophilic reagents employed include Grignards, cyanides, malonates, morpholines, and other amine derivatives. The end products were obtained in good yields without appreciable amounts of ring-opened byproducts.

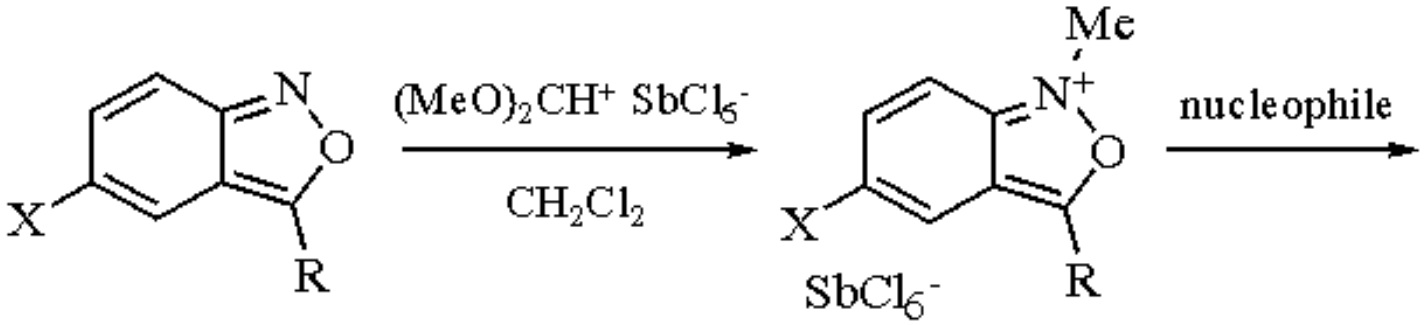

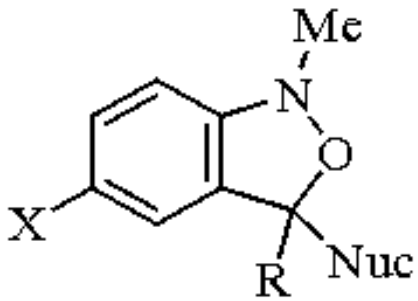

(8)

X = H; R = Me, 89%
X = Cl; R = Ph, 94%

A final example of nitrogen activation of weak organic bases is in the alkylation of *N*,*N*-disubstituted sulfonamides.[5e] The reagent of choice is dialkoxycarbenium hexachloroantimonate because sulfonamides are inert toward Meerwein's salt. Shown in eq 9 is the formation of two hexachloroantimonates from the corresponding *N*,*N*-disubstituted sulfonamides. Subsequent treatment of these salts with aqueous acid effectively cleaves the N-S bond into corresponding amine and sulfonic acid derivatives.

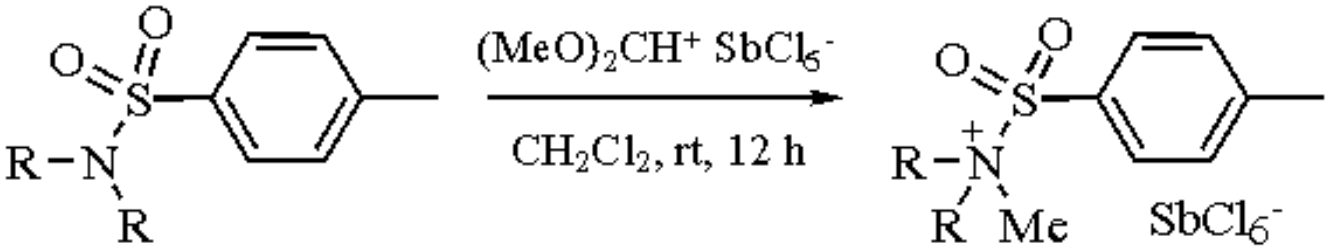

(9)

R = Me, 60%
R = -(CH2)4-, 80%

Alkylation of Oxygen Nucleophiles.

Dialkoxycarbenium hexachloroantimonates are versatile reagents in the alkylation of a variety of oxygen-containing substrates.[6a] Even weak nucleophiles which are inert to trialkyloxonium salts are cleanly and rapidly alkylated. Treatment of diethoxycarbenium hexachloroantimonate with sulfoxides (eq 10),[6a] aldehydes, ketones, esters (eq 11),[6c] and amides (eq 12)[6a] yield alkylated products which can either be isolated as antimonate salts or their subsequent transformation products.

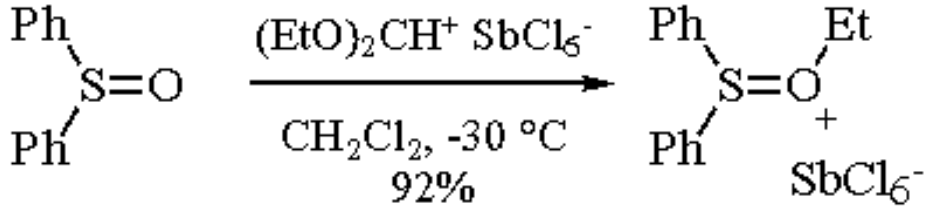

(10)

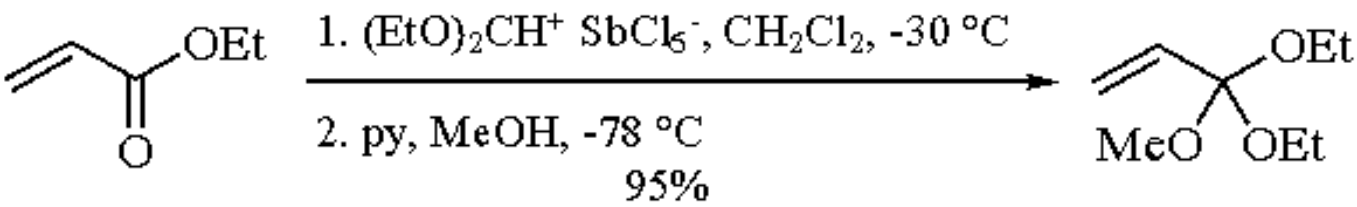

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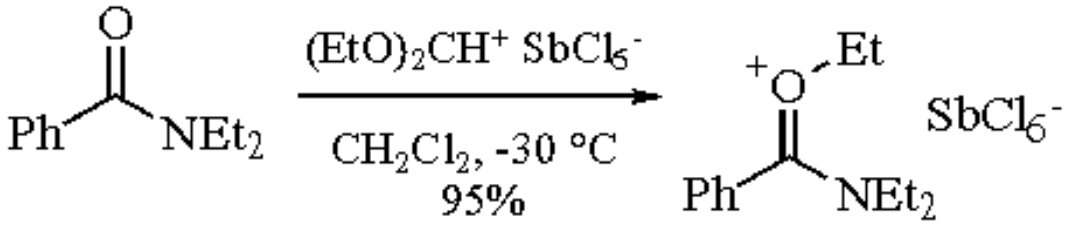

(12)

Dimethoxycarbenium tetrafluoroborates are stronger alkylating agents than their parent trialkyloxonium tetrafluoroborates. Interestingly, the preparation of methyl or ethyl Meerwein's salt can be accomplished by treatment of the appropriate dialkoxycarbenium salt with either dimethyl or diethyl ether (eq 13).[7] This procedure has been reported to yield the desired trialkyloxonium salt in very high purity.

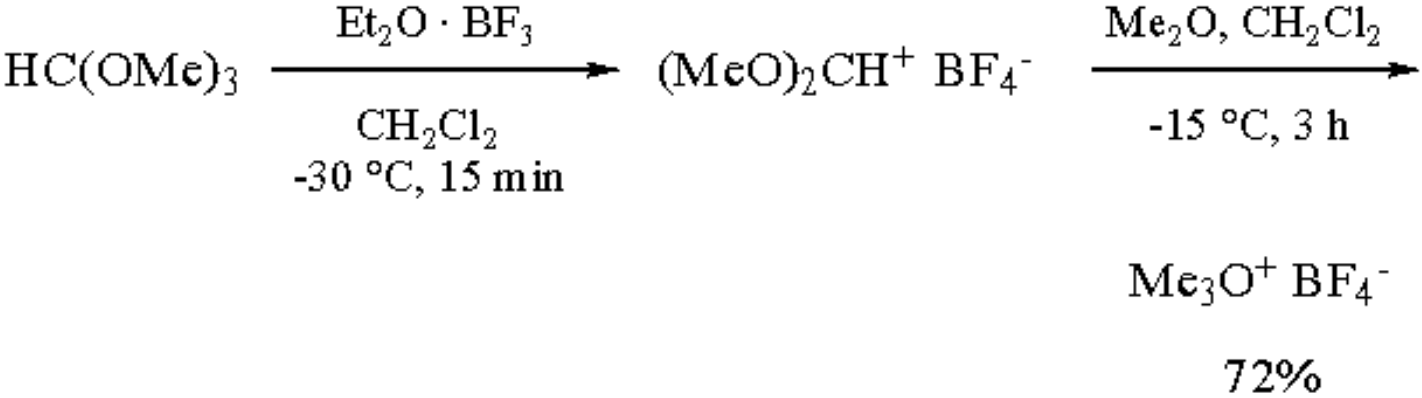

(13)

Aryl-substituted dimethoxycarbenium tetrafluoroborates, although sluggish in reactivity due to the steric conjestion about the carbenium center, will alkylate at oxygen.[6b] Treatment of 2,6-dimethyl-4-pyrone with an aryl-substituted tetrafluoroborate salt affords the desired 4-methoxy-2,6-dimethylpyrylium tetrafluoroborate in good yield (eq 14).

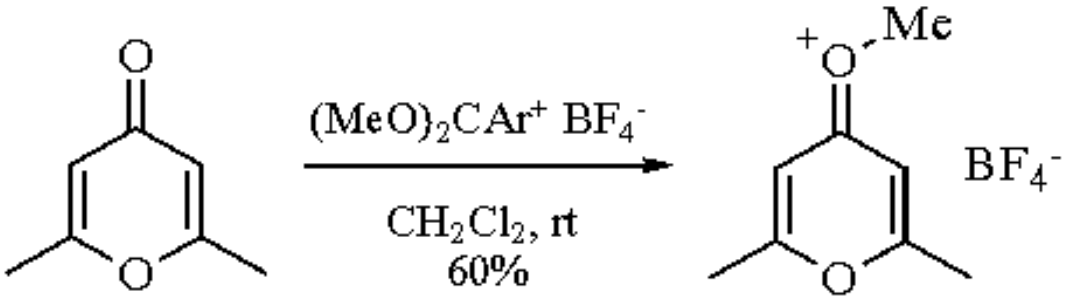

(14)

Ar = Ph or 2,4,6-$Me_3C_6H_2$

Acylation of Carbon Nucleophiles.

The foregoing examples illustrate the use of dialkoxycarbenium salts for the selective alkylation of weakly nucleophilic heteroatoms.[2g] In these examples, reaction conditions of thermodynamic control were generally employed. However, when dialkoxycarbenium salts are used under conditions of kinetic control a different type of product is obtained. Under the latter reaction conditions, carbocyclic or aromatic conjugated cyclic and acyclic ketones are converted into protected derivatives of formyl ketones.[8b] Employing diethoxycarbenium tetrafluoroborate prepared in situ with a variety of cyclic (eq 15) and acyclic (eq 16) ketones in the presence of ***Diisopropylethylamine*** at low temperatures in a methylene chloride solution affords the corresponding β-keto acetals.[8c] Other functional groups such as halide, nitrile, alkene, arene, and ester functionalities are compatible with this method. Regioselectivity is governed by steric effects; therefore reaction generally takes place at the less substituted α-position.

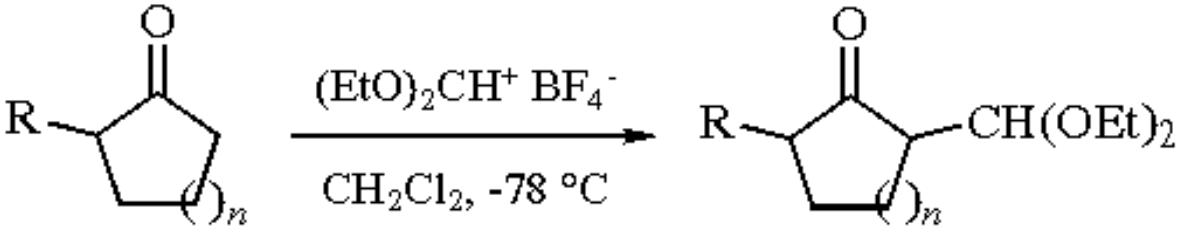

(15)

R = H	$n = 1$	45%
R = H	$n = 2$	87%
R = Me	$n = 2$	11%

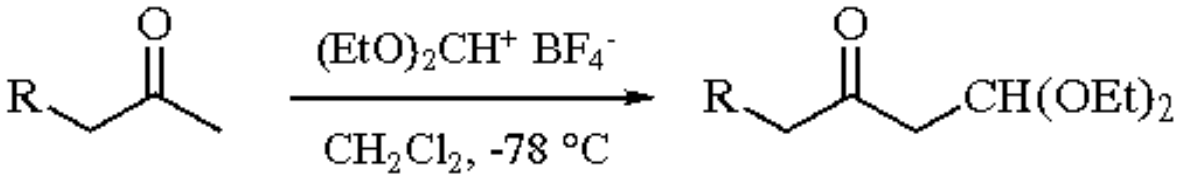

(16)

R = Me	76%
R = $Me_2C{=}CH$	58%
R = $EtO_2CCH_2CH_2$	59%

This method has been extended to the preparation of α,β-unsaturated aldehydes via β-keto acetals (eq 17)[8c] and some

aryl-substituted bicyclo[3.3.1]nonadienones through an acid-catalyzed cyclization of the α-(diethoxymethyl) ketones (eq 18).[8d]

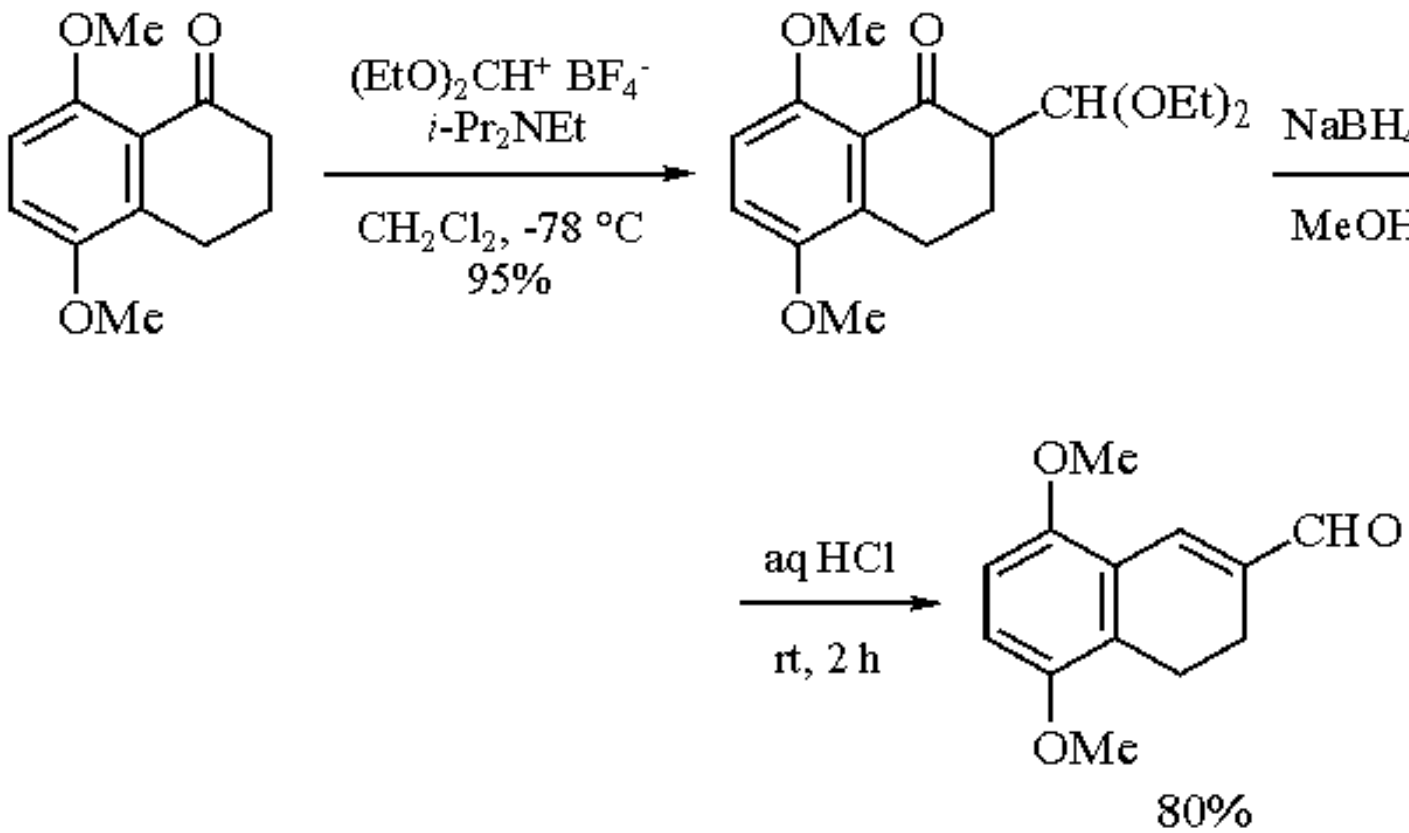

(17)

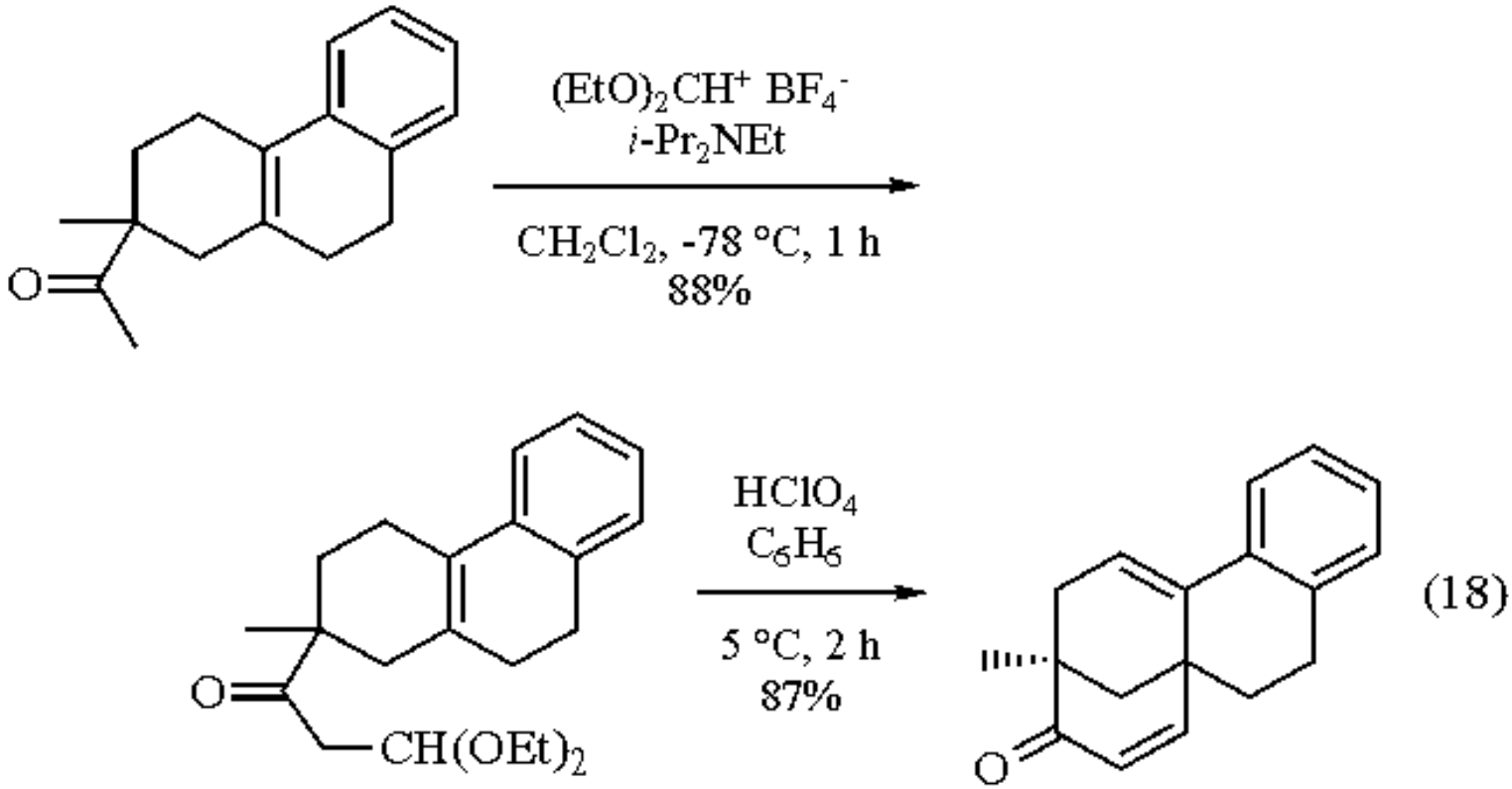

(18)

High levels of regioselectivity are observed when reactions between electron-rich heterocycles and dialkoxycarbenium tetrafluoroborates are carried out. From 2-methylindole, several 3-acylated indoles are produced without *N*-alkylation

(eq 19).[8e] Conversion to the desired aldehyde or ketone after initial acylation is observed upon aqueous workup.

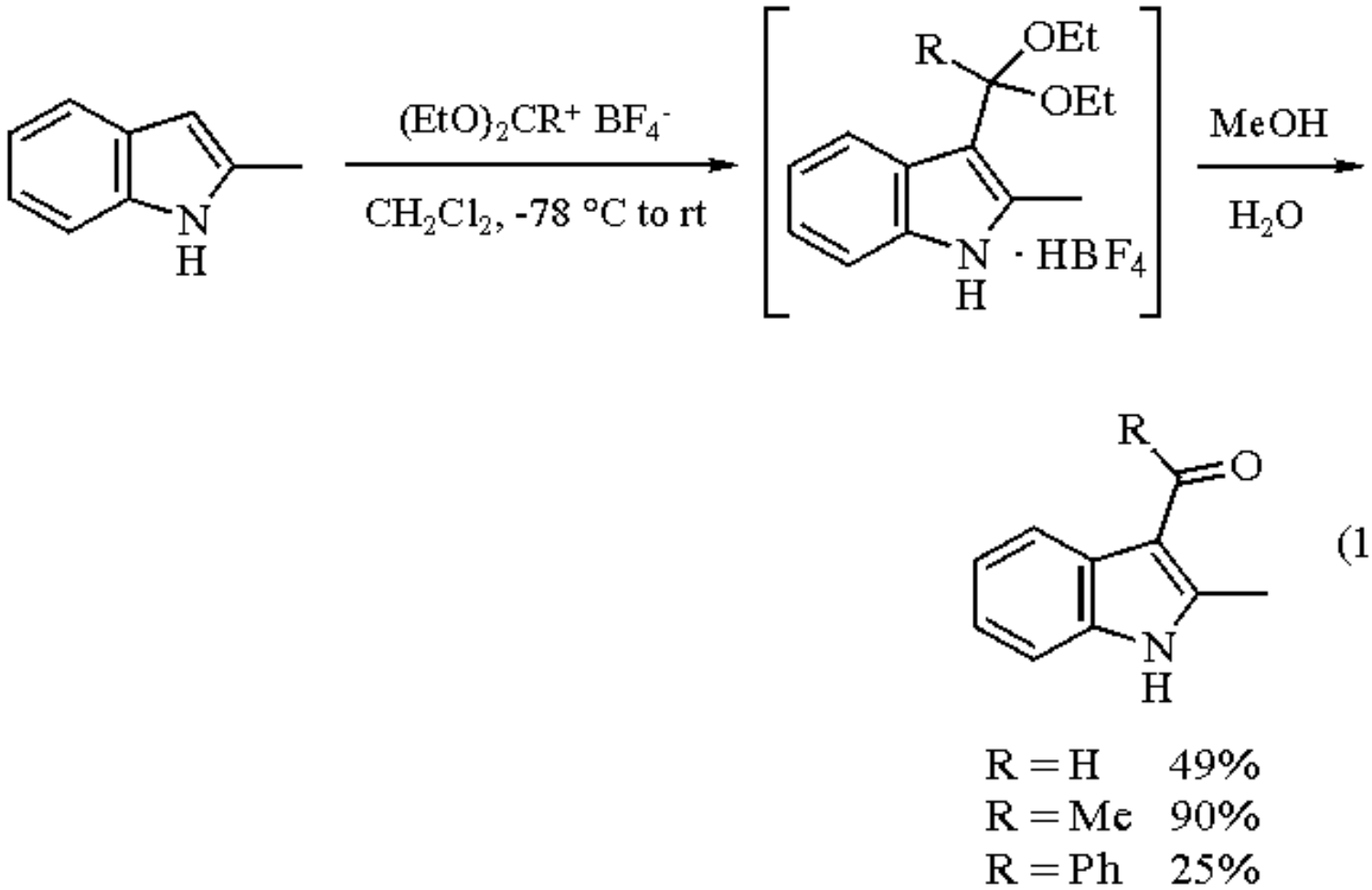

(19)

Treatment of 2,3-substituted indoles with diethoxycarbenium tetrafluoroborates results in selective acylation on the nitrogen.[8f] Interestingly, however, upon switching to the dimethoxy derivative, alkylation on nitrogen predominates even in the 2-methylindole series. As the steric size of the carbenium ion increases, for example when switching from dialkoxycarbenium salts to dialkoxyalkylcarbenium salts, one observes a shift from acylation to alkylation as well as a decrease in overall reactivity.

Another interesting variation in the electrophilic reactivity of these ambident reagents exists in the area of anionic acylations. Treatment of dimethoxycarbenium tetrafluoroborate, predominately an alkylating agent, with either lithium cyclononatetraenide[8g] or potassium cyclopentadienylirondicarbonyl[8h] results in the formation of the desired acylated derivatives.

Related Reagents.

Dimethyliodonium Hexafluoroantimonate; ***O-Methyldibenzofuranium Tetrafluoroborate***; ***Triethyl Orthoformate***; ***Triethyloxonium Tetrafluoroborate***; ***Trimethyloxonium Tetrafluoroborate***.

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1,1-Dimethoxyethane

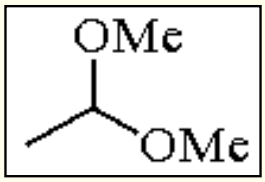

[534-15-6] · $C_4H_{10}O_2$ · 1,1-Dimethoxyethane · (MW 90.12)

(reagent for diol protection[1] and condensation reactions[8])

Alternate Name: acetaldehyde dimethyl acetal.

Physical Data: mp -113.2 °C; bp 64.5 °C; *d* 0.850 g cm^{-3}.

Solubility: sol most organic solvents.

Handling, Storage, and Precautions: flammable liquid.

Diol Protection.

1,1-Dimethoxyethane used for the protection of diols as acetals of acetaldehyde can offer advantages over the more commonly employed acetonide protection using ***2,2-Dimethoxypropane*** or ***Acetone***. The acetonides tend to prefer the formation of five-membered rings and thus offer some selectivity for 1,2-diol over 1,3-diol protection. This selectivity is switched for the *O*-ethylidene derivatives. This is believed to result from an elimination of an axial methyl group in the chair conformations of the *O*-ethylidene compounds.[1] This is illustrated in the ethylidenation (eq 1) of L-sorbose. The use of acetaldehyde for this transformation is ineffective.[2] The product of the acetonation of L-sorbose is shown for comparison purposes. Similar selectivity has been observed in the protection of steganone (eq 2).[3] Although a new stereocenter is created and there is the possibility of generating a mixture of stereoisomers, the one with the equatorial methyl group is usually preferred.

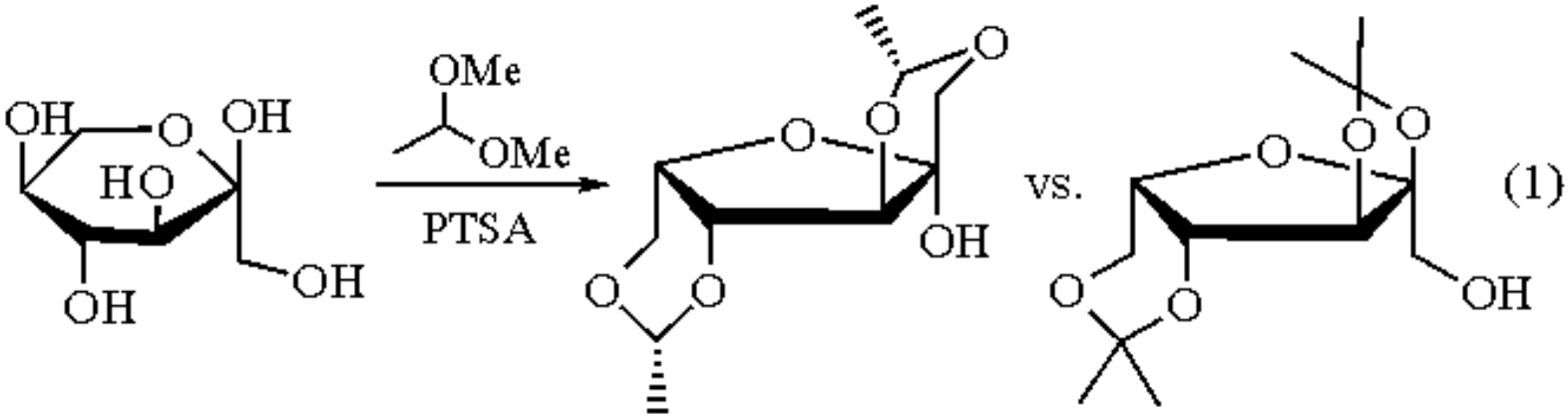

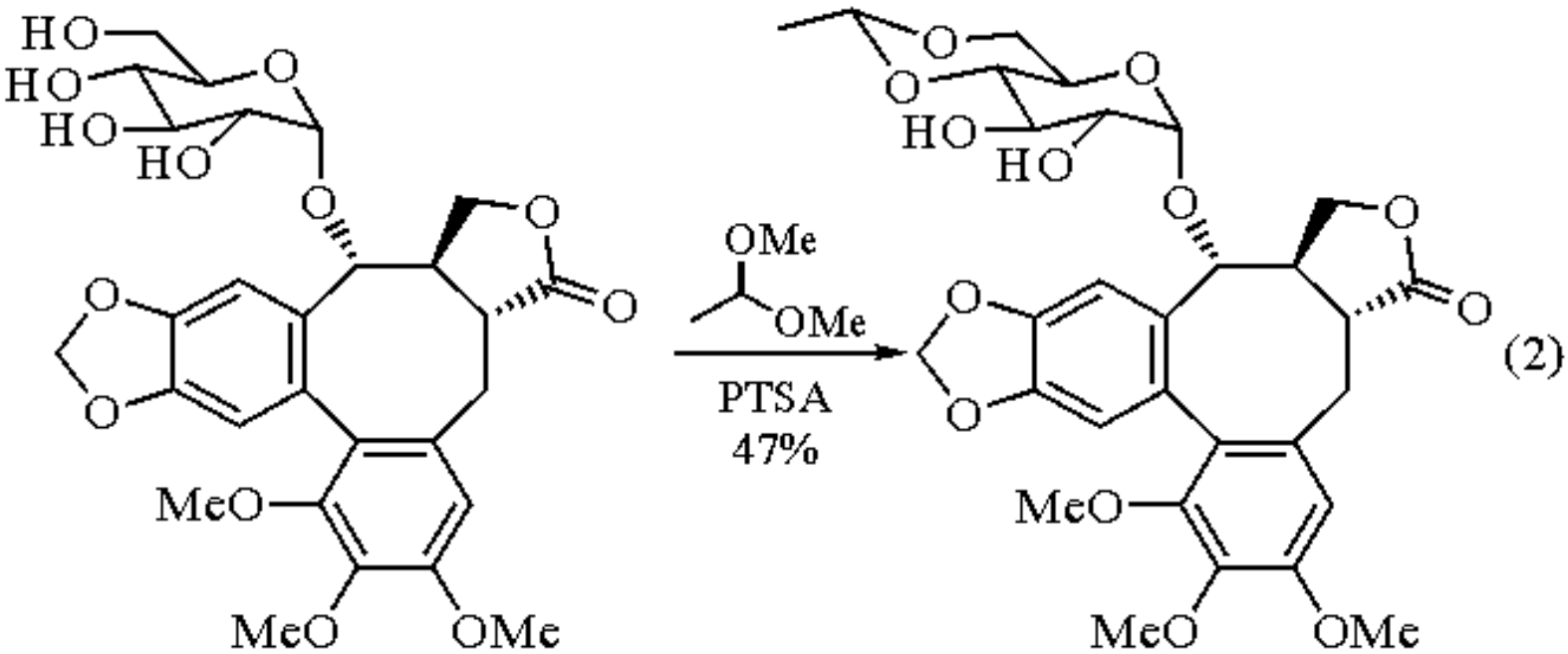

Mixed acetals of acetaldehyde can be prepared by reaction of 1,1-dimethoxyethane with another alcohol under acid catalysis. If the alcohol is a tertiary allylic one (eq 3), the mixed acetal loses methanol to form the enol ether which then undergoes a Claisen rearrangement.[4]

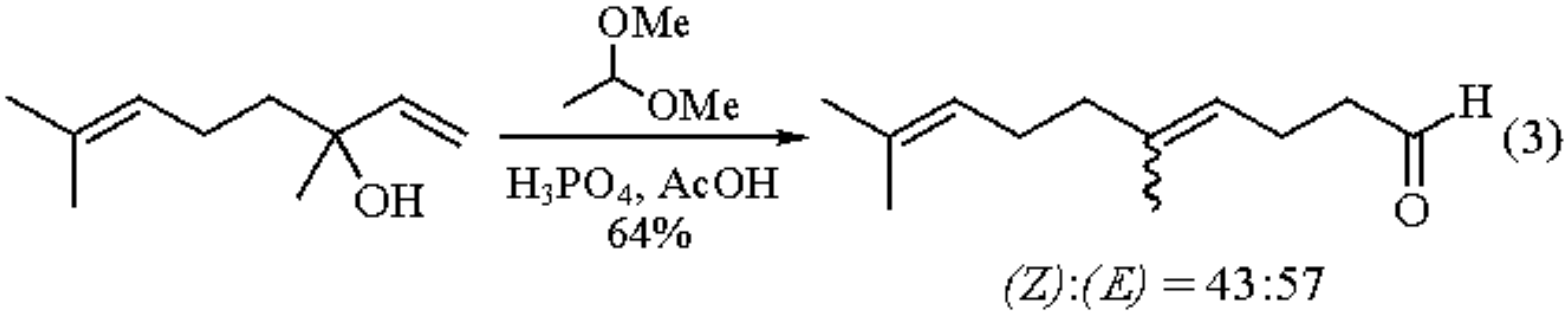

The reaction of the bis(trimethylsilyloxy)pyrimidine (eq 4) in the presence of ***Titanium(IV) Chloride*** and the acetal produces the α-methoxyethyluracil in 62% yield.[5]

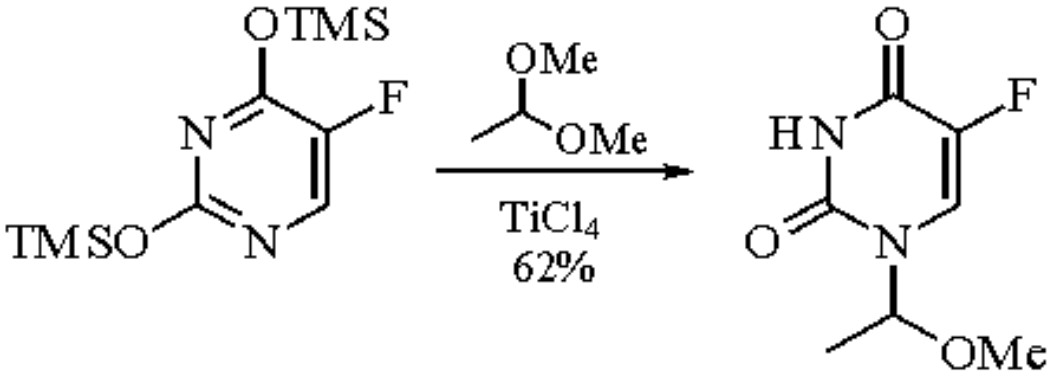

(4)

Cyanotrimethylsilane reacts with 1,1-dimethoxyethane (eq 5) to afford 2-methoxypropanenitrile in 73% yield if catalyzed by ***Boron Trifluoride Etherate***[6] and in 63% yield if catalyzed by ***Zinc Iodide***.[7]

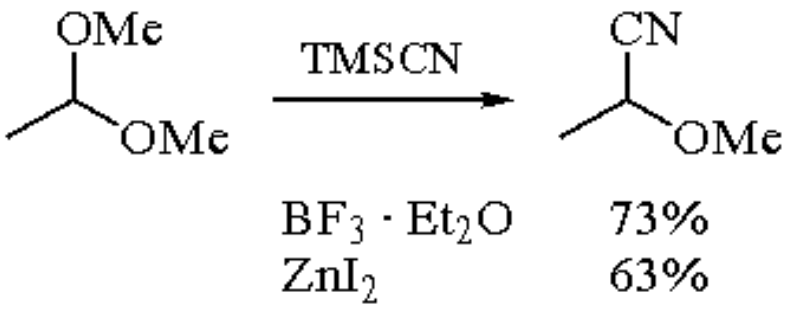

(5)

Condensation Reactions.

The dimethyl acetal of acetaldehyde serves as a useful surrogate for ***Acetaldehyde*** in a number of Lewis acid mediated condensation reactions.[8] Vinyl ethers are especially receptive partners in these reactions. Methyl vinyl ether reacts to produce the 3-methoxy acetal (eq 6) in 60% yield. This product is also accompanied by 18% of an addition product derived from further reaction of the vinyl ether with the methoxy acetal. The relative reactivity of this acetal as well as a number of other acetals has been reported.[9]

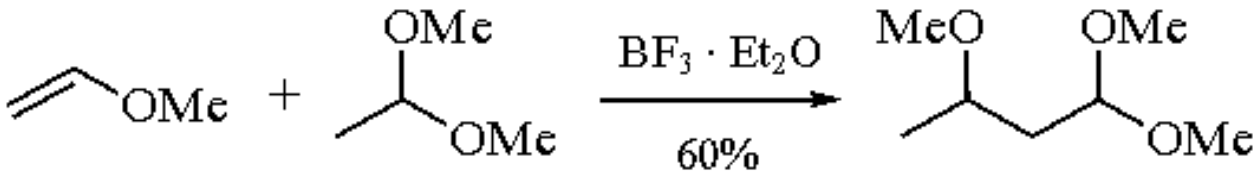

(6)

Trimethylsilyl enol ethers couple with the acetal in an aldol-type reaction to afford β-methoxy carbonyl compounds. These reactions can be effected by the use of a number of different Lewis acids. Some of the Lewis acids that have been employed are $TiCl_4$, ***Tin(IV) Chloride***, ***Zinc Bromide***, ***Triphenylmethyl Perchlorate*** or hexachloroantimonate, and ***Trimethylsilyl Trifluoromethanesulfonate***. The silyloxy diene (eq 7) on treatment with the acetal in the presence of either $SnCl_4$ or $ZnBr_2$ provides the aldol product in 62% and 63% yield, respectively.[10] The bis(thiomethyl)silyloxy diene (eq 8) when treated with trityl perchlorate condenses with 1,1-dimethoxyethane to provide the β-methoxy ketone in 61% yield.[11]

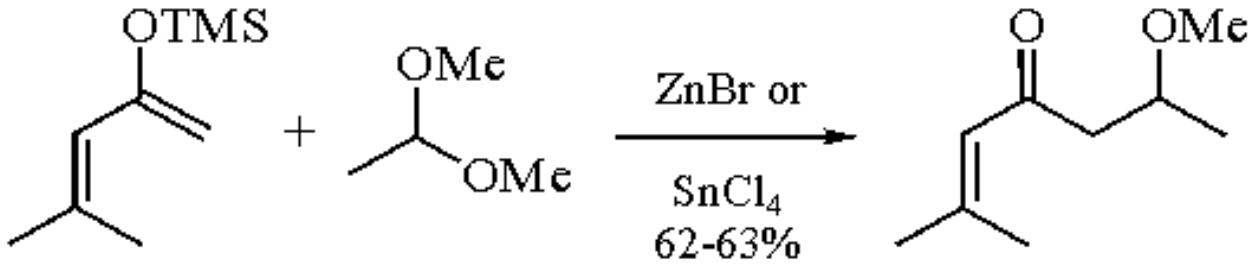

(7)

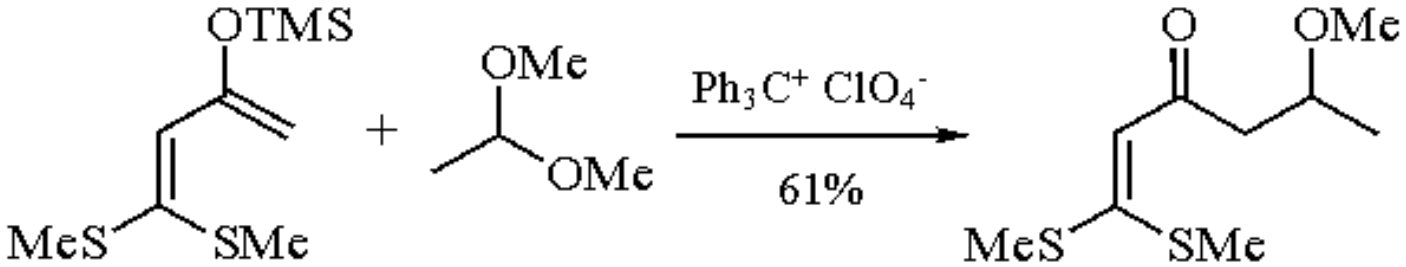

(8)

Stereoselectivity.

A $TiCl_4$-catalyzed reaction of the silyloxy diene (eq 9) with the acetal results in a 57:43 (*E*):(*Z*) mixture of products in 51% yield. These products are derived from attack at the γ-position of the carbonyl system.[12]

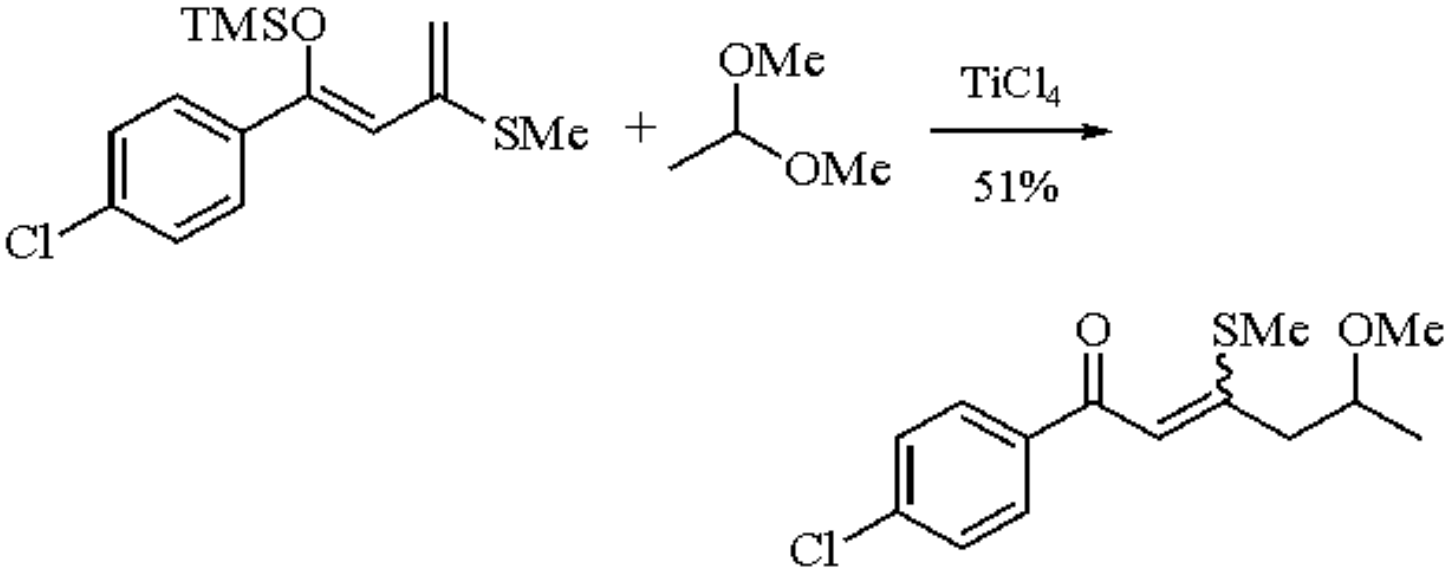

(9)

(E):*(Z)* = 57:43

The reaction of the silyl enol ether of *t*-butyl acetoacetate, trimethylsilyl triflate, and the dimethyl acetal (eq 10) affords a 1:1 mixture of stereoisomers in 90% yield.[13]

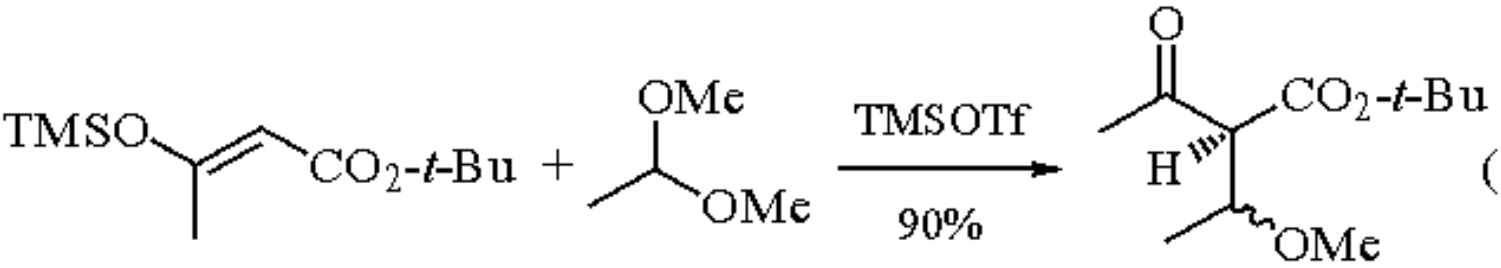

(10)

The enol ether derived from (*R*)-hexahydromandelic acid (eq 11) produces the aldol product in good yield. The products were reduced with ***Lithium Aluminum Hydride*** for the determination of the enantiomeric excesses. If the reaction is catalyzed by Me_3SiOTf, the product after reduction has an ee of 60% and an *erythro*:*threo* ratio of 9:1. Catalysis by Ph_3CSbCl_6 results in an increase in the ee to 98%, but the *erythro*:*threo* ratio drops to 4:1.[14]

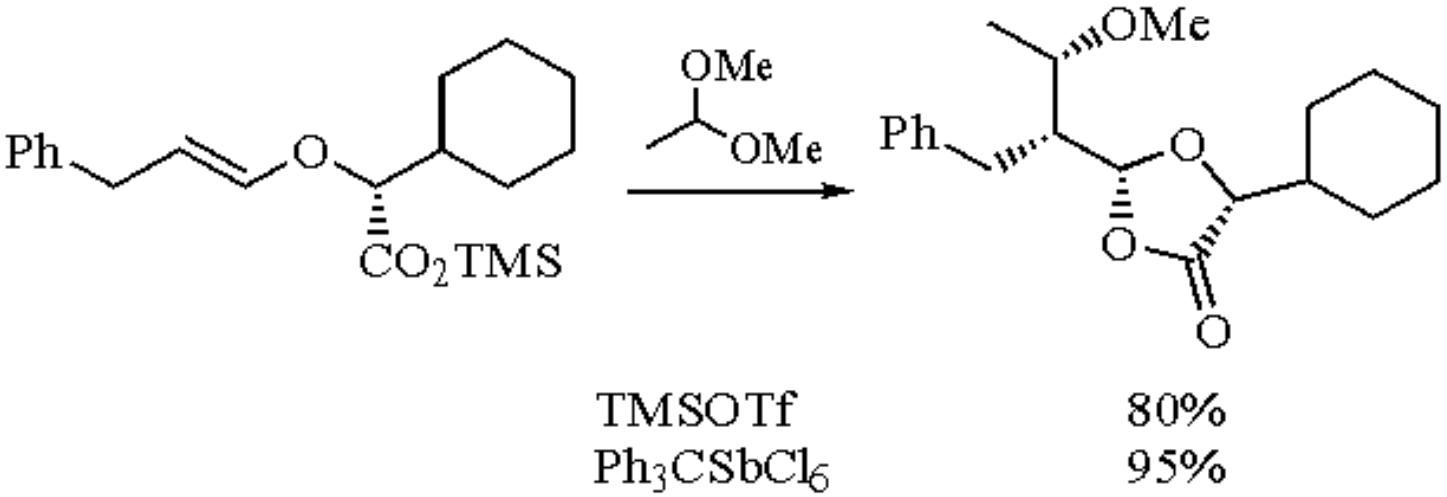

(11)

Allylic and allenic stannanes also couple with 1,1-dimethoxyethane. Treatment of the tributylallenylstannane with $TiCl_4$ and the acetal (eq 12) yields a 56:44 mixture of *threo*:*erythro* isomers in 67% yield.[15] An aqueous-mediated condensation of the cyclohexenylstannane (eq 13) furnishes an 85% yield of *erythro* and *threo* stereoisomers in a 62:38 ratio.[16]

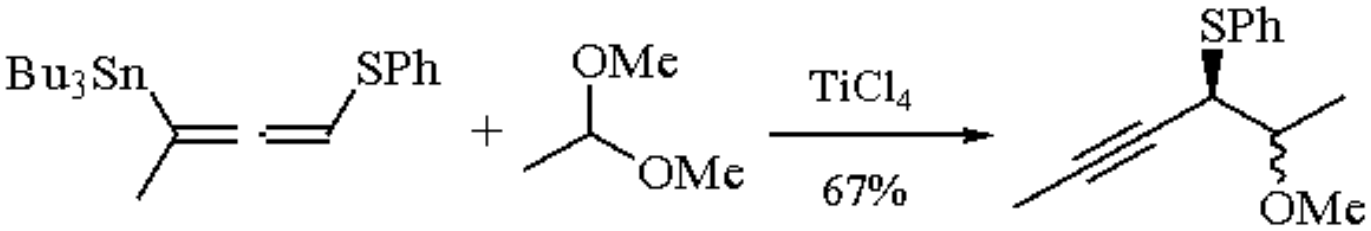

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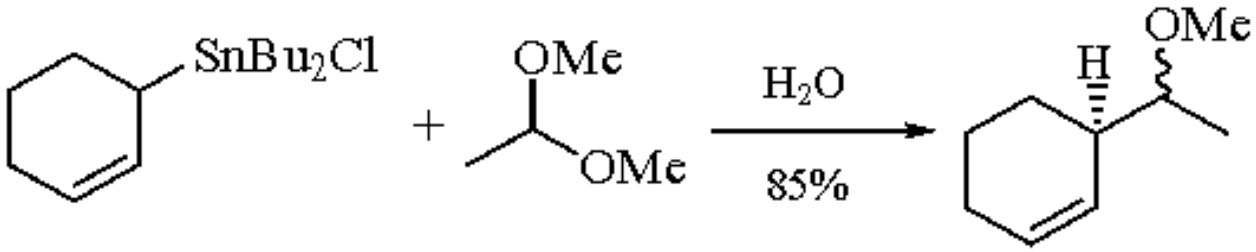

(13)

Pictet-Spengler condensations of tryptophan derivatives lead to the formation of *cis*/*trans* mixtures of tetrahydro-β-carbolines. The ratio of products depends on the nature of the substituent on the nitrogen. *N*-(Hydroxy)tryptophan ethyl ester on reaction with 1,1-dimethoxyethane (eq 14) and ***Trifluoroacetic Acid*** in CH_2Cl_2 produces a 2:1 (*cis*/*trans*) mixture of diastereomers.[17] The *N*-benzyl derivative under the same conditions gives an 84:16 (*trans*/*cis*) mixture.[18]

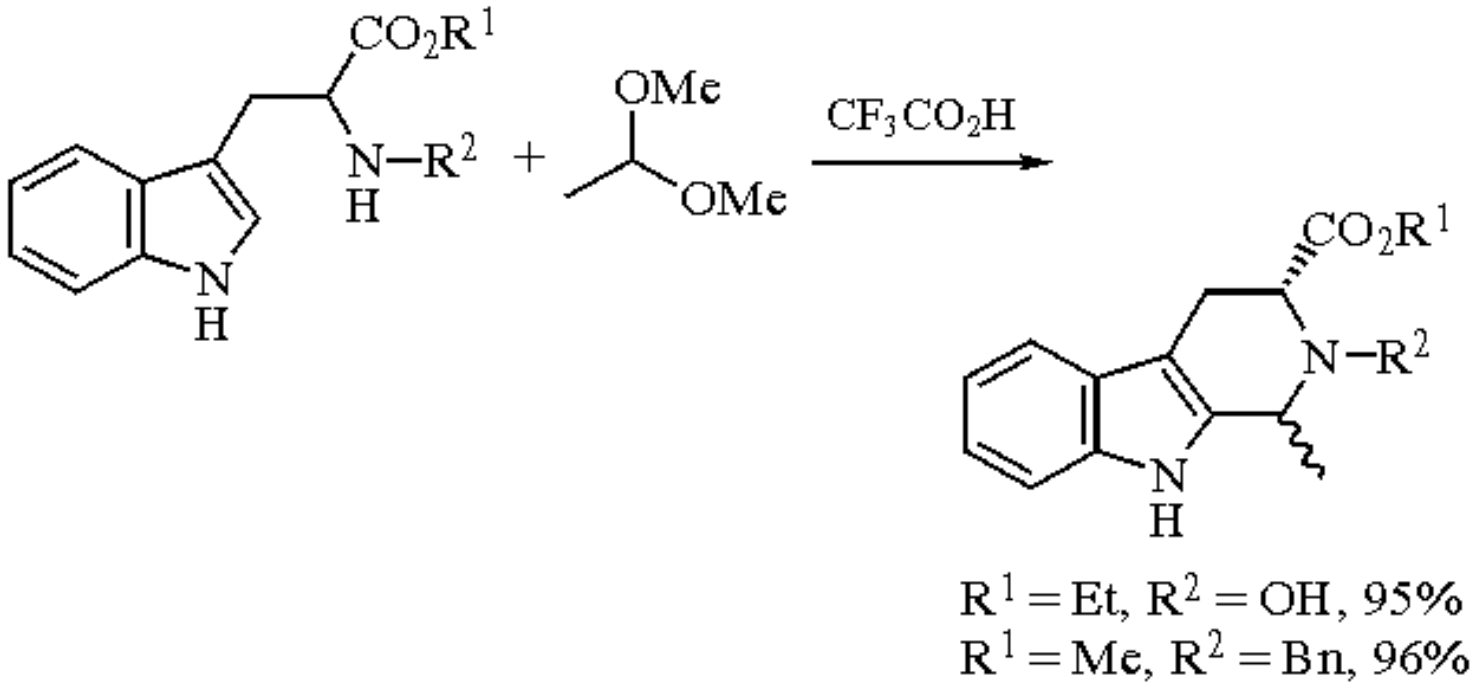

(14)

meso-Tetramethylporphyrinogen is produced in 28% yield by the reaction of pyrrole and the dimethyl acetal of acetaldehyde (eq 15) in CCl_4 in the presence of CF_3CO_2H.[19]

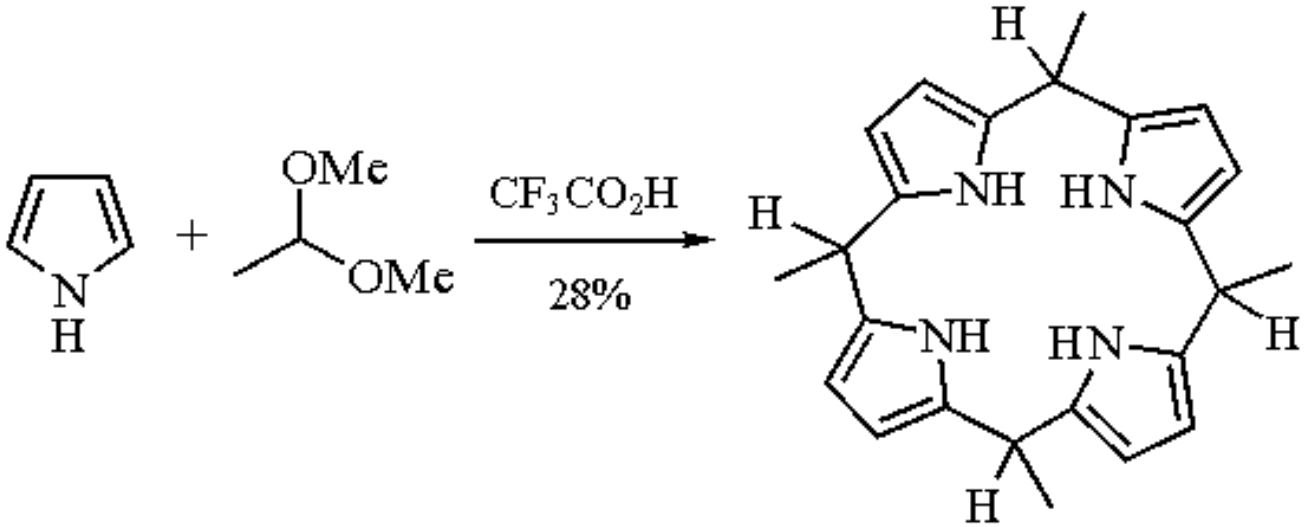

(15)

Miscellaneous.

Calculations[20] and NMR investigations[21] of the conformations of 1,1-dimethoxyethane have been reported. The acetal can be used to prepare the methoxy(phenylseleno) acetal of acetaldehyde using ***Diisobutylaluminum Phenyl Selenide***,[22] and selenoacetaldehyde employing bis(dimethylaluminum) selenide.[23]

Related Reagents.

Dimethoxymethane; ***2,2-Dimethoxypropane***; ***Triethyl Orthoformate***.

---

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Dimethoxymethane

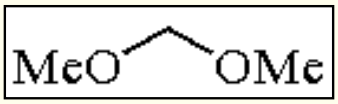

[109-87-5] · $C_3H_8O_2$ · Dimethoxymethane · (MW 76.10)

(widely used OH-protecting reagent, applicable to alkanols, phenols, and carboxylic acids; stable above pH 4; resistant to bases; resistant to nucleophiles; resistant to organometallic reagents; resistant to catalytic hydrogenation; resistant to hydride reduction; labile with Lewis acids; resistant to most oxidants; convenient reagent for the chloromethylation of arenes; applicable to the C-6 methylenation of steroids; useful solvent for the preparation of Grignard reagents and organolithium derivatives)

Physical Data: bp 41-42 °C; mp -104.8 °C; *d* 0.863 g cm^{-3}; fp -17 °C.

Solubility: sol water (24% at 16 °C), chloroform, 1,2-dichloroethane, dichloromethane, THF.

Methoxymethylation of Alcohols and Related Compounds.

Dimethoxymethane is a convenient reagent for the protection of alcohols as their methoxymethyl (MOM) ethers. The MOM protecting group is superior to such common alternatives as the tetrahydropyranyl (THP) group in that it avoids the complication of introducing additional chirality during its installation. This is particularly important when the alcohol to be protected is chiral and hence the introduction of a second asymmetric center during the protection would generate a diastereomeric mixture, complicating purification, assignment of NMR signals, etc.

The MOM protecting group has been widely applied in synthesis. Classically it has been installed under basic conditions using ***Chloromethyl Methyl Ether***.[1] Application of this procedure is therefore limited to species stable to basic conditions and nucleophiles. Additionally, the use of chloromethyl methyl ether has been sharply curtailed since it has been shown to be a potent carcinogen.[2] Conversely, dimethoxymethane is comparatively nontoxic. *O*-Methoxymethylation using dimethoxymethane under acidic conditions has greatly expanded the applicability of this protecting group. Treatment of alcohols with a large excess of dimethoxymethane, and ***Phosphorus(V) Oxide*** at rt, affords the corresponding methoxymethyl ethers (94-99%) (eq 1). In most cases, no further purification is required.[3]

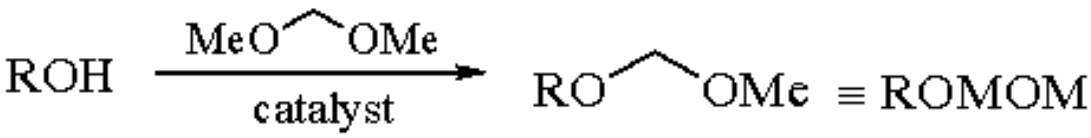

(1)

MOM ethers can be formed via acid-catalyzed acetal exchange effected with ***p-Toluenesulfonic Acid***. The reaction can be driven to completion by the removal of the methanol formed with molecular sieves or by azeotropic distillation with

methylene chloride cosolvent. This method advantageously avoids the use of the very large excesses of phosphorus pentoxide usually required, which complicates the workup of large scale preparations of alkanolic or phenolic methoxymethyl ethers. Preparation of 10-20 kg quantities of material has been demonstrated.[4]

A general methodology for the preparation of methoxymethyl derivatives, using the methoxymethyl cation generated from $Zn^0/BrCH_2CO_2Et$/dimethoxymethane, has also been described. Methoxymethyl derivatives of phenols, thiols, imides, alkyl carboxylates, aryl carboxylates, and alkynes can be prepared in good to high yields (45-88%). In addition, esterification of acid chlorides can be effected using dimethoxymethane and anhydrous ***Zinc Bromide*** (eq 2).[5]

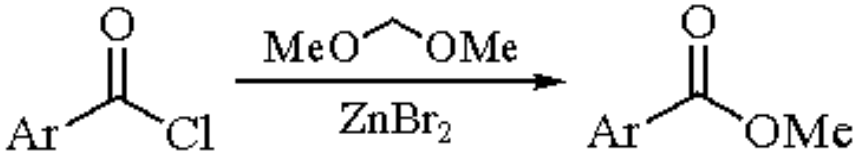

(2)

Methoxymethyl ethers of primary alcohols may be conveniently prepared, in high yields, using ***Nafion-H*** catalyst ($MeOCH_2OMe$, 41 °C, 10-24 h). Reaction of secondary alcohols requires elevated temperatures. The solid catalyst is separated by filtration and the product purified by chromatography. Tertiary alcohols yield alkenic dehydration products. Bridgehead tertiary alcohols yield methyl ethers.[6]

Iodotrimethylsilane also catalyzes the acetal exchange with dimethoxymethane to yield methoxymethyl ethers of primary and secondary alcohols under mild reaction conditions (25 °C, 1-6 h, 76-95%). In the low yielding examples (76-80%), the remaining starting materials are recovered. Tertiary alcohols yield the corresponding alkyl iodides rather than MOM ethers. The reaction can also be carried out using in situ generated iodotrimethylsilane (***Allyltrimethylsilane-Iodine***).[7]

The treatment of primary and secondary alcohols with dimethoxymethane in the presence of catalytic amounts of ***Lithium Bromide*** and *p*-toluenesulfonic acid at rt affords the corresponding dimethoxymethyl derivatives (25 °C, 15 min to 2 h, 71-100%), under particularly mild conditions. Examples include allylic, propargylic, cyclic, and neopentyl alcohols. Tertiary alcohols are not completely protected even after 24 h at reflux temperature. 1,3-Diols yield cyclic acetals.[8]

Cleavage of Methoxymethyl Derivatives.

Cleavage of methoxymethyl ethers to expose the parent alcohols is conventionally carried out under protic acid conditions: 2 N HOAc (90 °C, 40 h),[9] HCl (aq) (MeOH, 62 °C, 15 min),[10] 6 M HCl (THF-H_2O, 50-55 °C, 6-8 h),[11] CF_3CO_2H (H_2O-THF),[12] HCl (g) (MeCN).[13] Alternatively, the deprotection may be carried out using Lewis acids under anhydrous conditions: $PhSH/BF_3.Et_2O$,[14] Me_3SiCl/Et_4NBr (0 °C)[15] (selective cleavage of MOM ether in the presence of acetonide), $Me_3SiBr/n\text{-}Bu_4NBr$ (0 °C, 25 min to 12 h).[16] Selective cleavage of MOM esters in the presence of MOM ethers under mild conditions can be effected with Bu_3SiBr (trace MeOH).[17] More recently, nonacidic and aprotic conditions for the cleavage of MOM ethers have been developed. The reaction has been carried out with very high yields: Me_2BBr (-78 °C, 1 h, 90-93%).[18] Similarly, MOM ethers of 1,2- or 1,3-diols are cleaved in high yields under mild conditions using $(i\text{-PrS})_2BBr$ (-78 °C). Protic or Lewis acids yield cyclic diol formals with these substrates.[19] Activation of MOM ethers via hydride abstraction to facilitate cleavage can be effected with $TrBF_4$ (25 °C).[20]

Chloromethylation of Arenes.

Dimethoxymethane reacts under Friedel-Crafts conditions to accomplish the chloromethylation of aryls. Chloromethylation of thioanisole using dimethoxymethane/$AlCl_3$ affords *p*-methylthiobenzyl chloride (74%), contaminated with a trace of *o*-methylthiobenzyl chloride (150:1) (eq 3).[21]

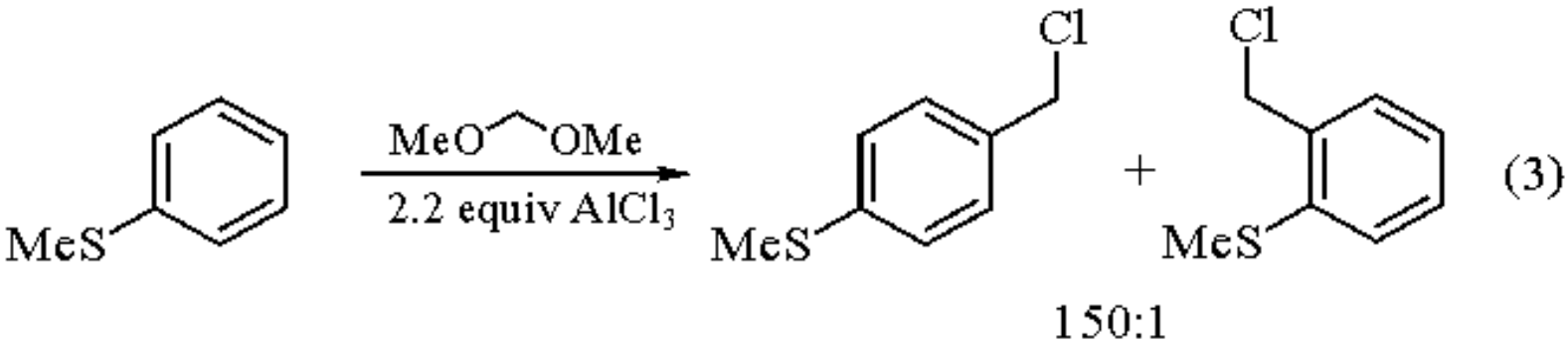

Alternative procedures employing chloromethyl methyl ether in acetic acid[22] or aqueous formaldehyde and hydrochloric acid[23] show inferior selectivity and yield. Similarly, *p*-nitrophenol can be chloromethylated (69%) using dimethoxymethane and HCl (eq 4).[24]

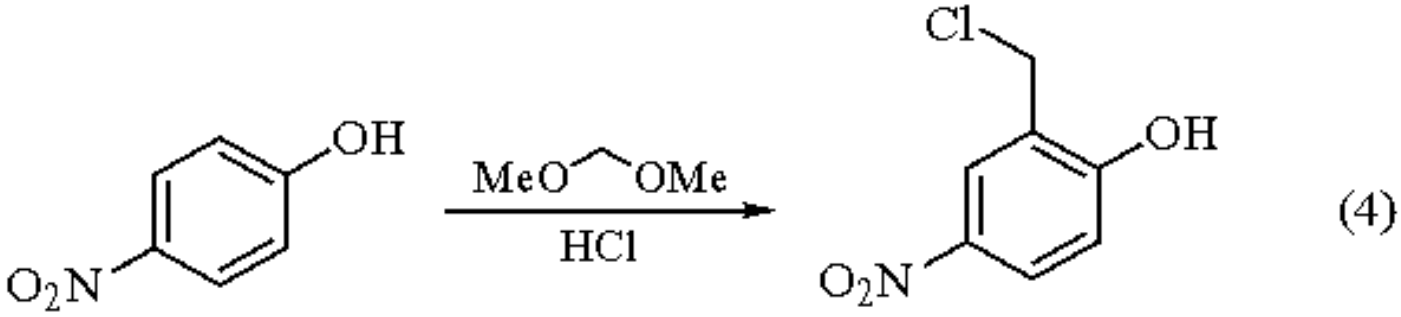

6-Methylenation of 3-Oxo-Δ^4-steroids.

A simple, single step, 6-methylenation of 3-oxo-Δ^4-steroids using dimethoxymethane has been described (eq 5). The protocol replaces a multi-step series of reactions.

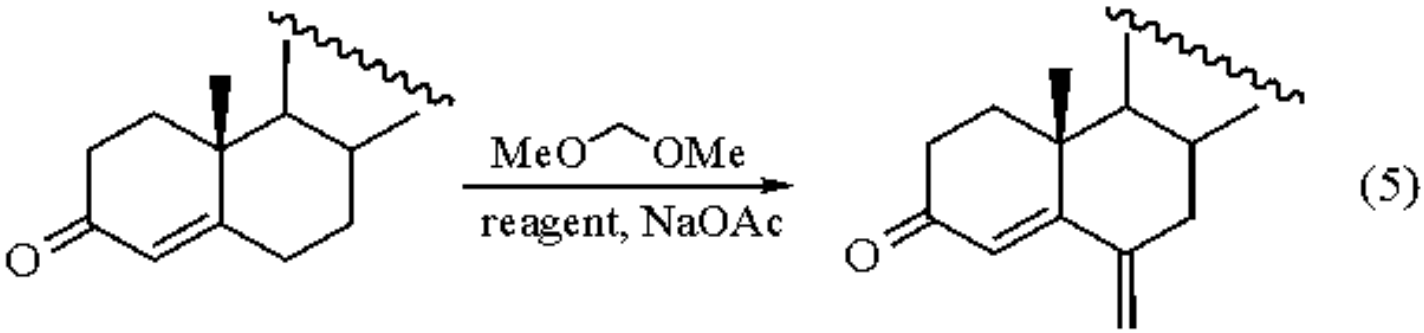

A number of Lewis or protic acids are effective: $POCl_3$, *p*-TsOH, H_2SO_4, $HClO_4$, HX, Amberlyst H-15, P_4O_{10}/silica

gel, PCl_5, $EtOP(O)Cl_2$. Of these, ***Phosphorus Oxychloride*** is the most suitable. The reaction can also be carried out using diethoxyethane and other formaldehyde acetals. Of these, diethoxymethane and dimethoxymethane yield superior results.[25]

Solvent for Preparation of Grignard and Organolithium Reagents.

Dimethoxymethane has been utilized as a solvent for the preparation of Grignard reagents from chloromethyl methyl ether (eq 6). While the reaction can be carried out in more common solvents, such as THF, dimethoxymethane is the solvent of choice owing to enhanced stability of the Grignard reagent in this medium.[26]

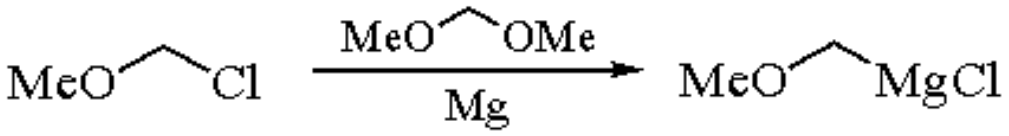

(6)

Methoxymethyllithium can be prepared from chloromethyl methyl ether in dimethoxymethane solvent (eq 7).[27] The reaction is unsuccessful in more common solvents, such as diethyl ether or THF.

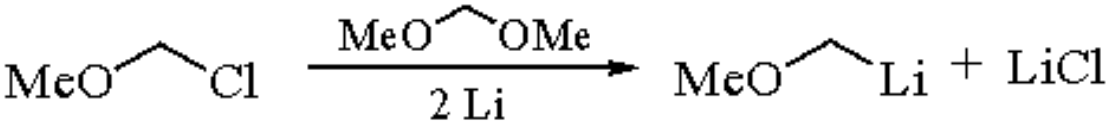

(7)

Related Reagents.

Chloromethyl Methyl Ether.

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2,2-Dimethoxypropane

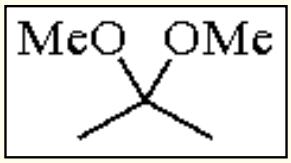

[77-76-9] · $C_5H_{12}O_2$ · 2,2-Dimethoxypropane · (MW 104.15)

(reagent used in the preparation of acetals,[1,2] acetonides,[3] isopropylidene derivatives of sugars[4-6] and nucleosides,[7] methyl esters of amino acids,[8] and enol ethers;[9] undergoes the aldol condensation with enol silyl ethers;[10] used in the preparation of hypophosphite esters[11] and dimethylboronate esters[12])

Physical Data: bp 83 °C; *d* 0.847 g cm^{-3}.

Form Supplied in: liquid; widely available.

Handling, Storage, and Precautions: flammable liquid; irritant.

Formation of Acetals.

The reagent can be used to prepare a variety of acetals via transacetalization. This involves interchanging the alkoxy or ketone groups in an acidic medium. Both symmetrical [$R^1R^2C(OR^3)_2$] and mixed [$R^1R^2C(OR^3)OR^4$] acetals can be obtained, depending upon the choice of conditions.[1]

The three equilibria shown in eqs 1-3 are established when 2,2-dimethoxypropane, an alcohol, and a catalytic amount of acid are mixed. Distillation of the methanol formed shifts the equilibrium far in the direction of the new acetals. Methanol and 2,2-dimethoxypropane form a binary azeotrope; however, this can be broken by the addition of a hydrocarbon solvent such as hexane or benzene.

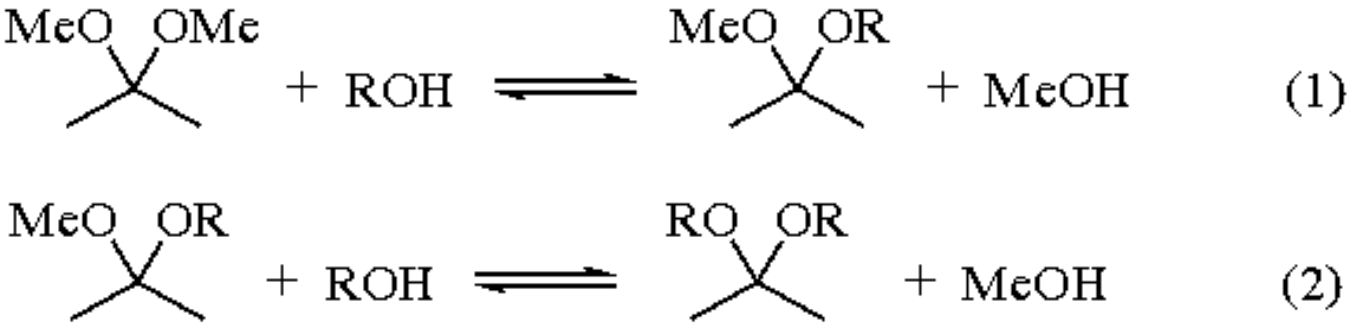

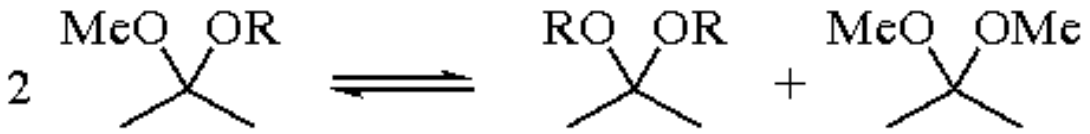

(3)

Methyl acetals of other ketones can be obtained by acidifying a mixture of the ketone, methanol, and 2,2-dimethoxypropane and removing the acetone formed by distillation. In this case, the function of the 2,2-dimethoxypropane is to react with the water formed to give methanol and acetone (eqs 4 and 5). This is evidenced by the fact that the reaction is very slow in the absence of alcohol or water, but fast when methanol is present. The rate of the reaction is also directly related to the alcohol concentration.[1]

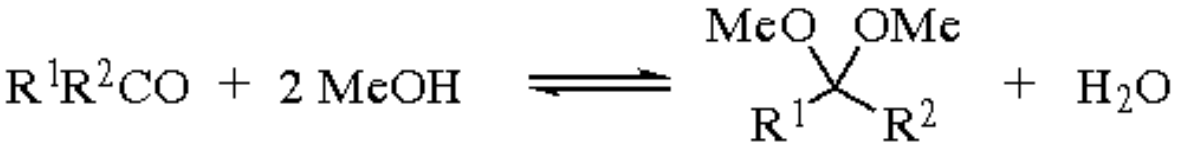

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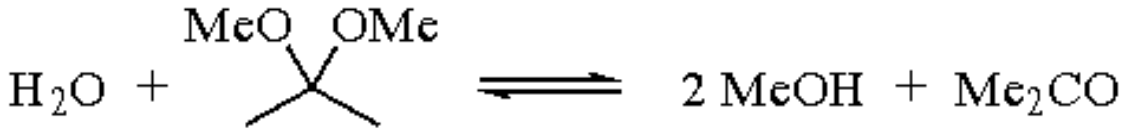

(5)

One undesirable side reaction is the formation of enol ethers via the acid-catalyzed loss of one molecule of alcohol from the acetal. This occurs even at relatively low temperatures (50 °C). In order to suppress this reaction, the procedure was modified to include a neutralization with base prior to workup.

A recent example of the use of 2,2-dimethoxypropane in the above capacity involves the reaction of an aldehyde or ketone with ***o-Nitrobenzyl Alcohol*** to afford the bis-*o*-nitrobenzyl acetal derivative.[2] This protecting group has the advantage that it is photoremovable in high yield by irradiation at 350 nm.

Acetonide Formation.

The reagent has been used to great advantage as a protecting group for the labile dihydroxyacetone side chain of the corticosteroids. Cyclic acetal formation between the 17α,21-diol grouping of the prednisolone side chain and 2,2-dimethoxypropane in an acid-catalyzed exchange reaction gives 17α,21-isopropylidenedioxypregnane in good yield (eq 6).[3]

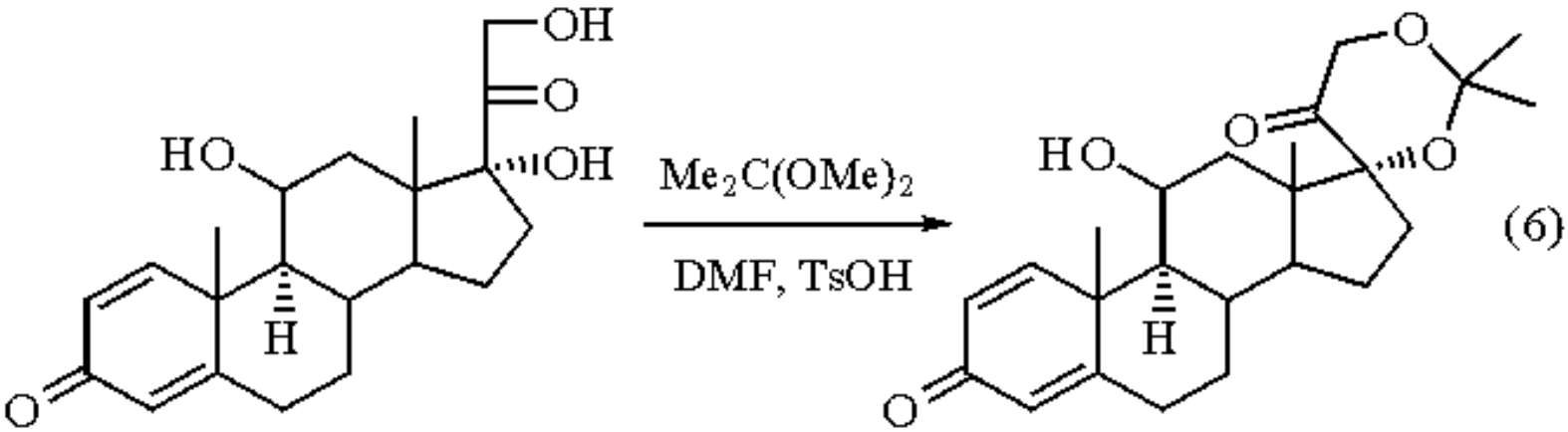

(6)

The base stability of the isopropylidenedioxy function makes it useful for the preparation of C-21 modified cortical hormones whose formation requires strongly basic conditions. The acetonide is easily cleaved with aqueous acetic or formic acid in the presence of heat.

Isopropylidene Derivatives of Sugars and Nucleosides.

A mixture of 2,2-dimethoxypropane, DMF, and a catalytic amount of ***p-Toluenesulfonic Acid*** constitutes an efficient acetonating agent capable of protecting vicinal, *trans*-diequatorial hydroxy groups and of forming *N*-acetyl-2,2-dimethyloxazolidines from vicinal hydroxy and acetamido groups.[4] Reaction of methyl α-D-glucopyranoside under the above conditions gives recovered starting material, methyl 4,6-*O*-isopropylidene-α-D-glucoside, and a trace amount of the diisopropylidene glucoside (eq 7). Similarly, deoxyinosamine, upon treatment with the same reagent mixture, affords as the major product the diisopropylidene derivative (eq 8).

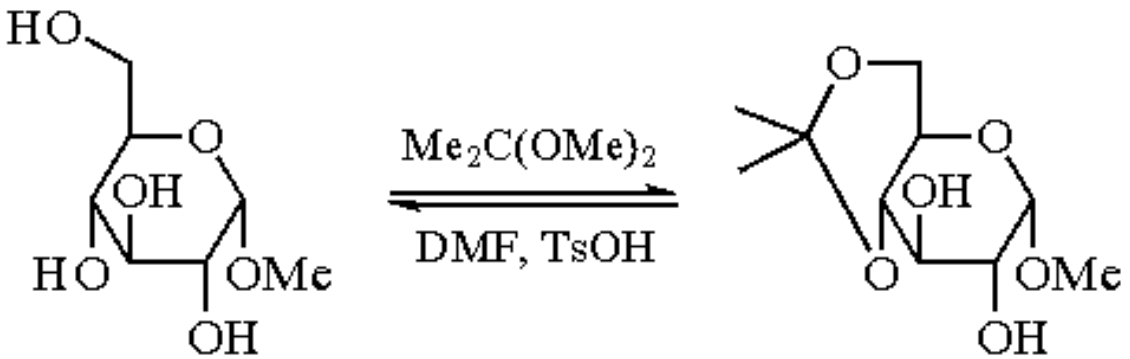

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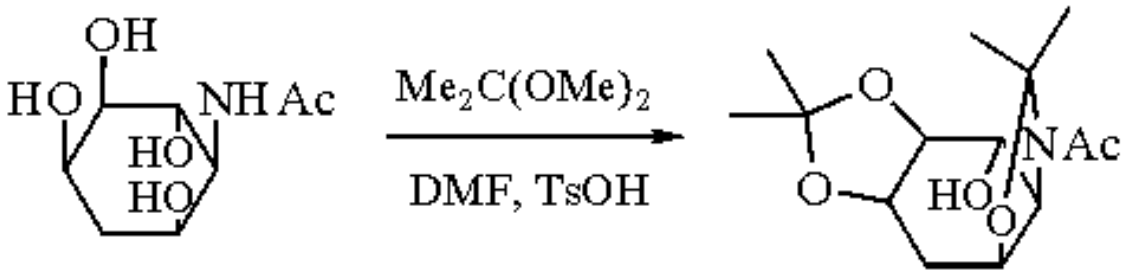

(8)

A further improvement to the existing procedure involves the substitution of ***Tin(II) Chloride*** for the *p*-toluenesulfonic acid and 1,2-dimethoxyethane for DMF.[5a] Studies involving D-mannitol have shown that the tin(II) chloride does not act as a Lewis acid catalyst or as a source of HCl (by reaction with the hydroxy groups) since the use of zinc chloride under identical conditions gives no reaction. In this particular case, it was subsequently demonstrated that no catalyst is required and that isopropylidenation occurs under completely neutral conditions, presumably via acetal exchange.[5b] Tin(II) chloride has been used to catalyze isopropylidene formation in other carbohydrate systems.[6]

The ability of 2,2-dimethoxypropane to act as a water scavenger has resulted in its use (in conjunction with acetone and an acid catalyst) in the protection of the 2´,3´-hydroxy groups of purine and pyrimidine nucleosides.[7] Here again, the formation of acetone and methanol serves to drive the equilibrium towards the product.

Esterification of Amino Acids.

Methyl ester hydrochlorides of amino acids have been prepared in which 2,2-dimethoxypropane has been used as the source of the methoxy group, the reaction solvent, and the reagent for the removal of the water formed by virtue of the hydrolysis of the acetal to methanol and acetone.[8a] This procedure has also been used to prepare the methyl esters of fatty acids.[8b]

Enol Ethers.

Treatment of testosterone acetate with 2,2-dimethoxypropane/DMF/TsOH converts this material into the enol ether (eq 9).[9] In this case, enol ether formation is attributed to loss of water directly from the unsaturated hemiacetal.

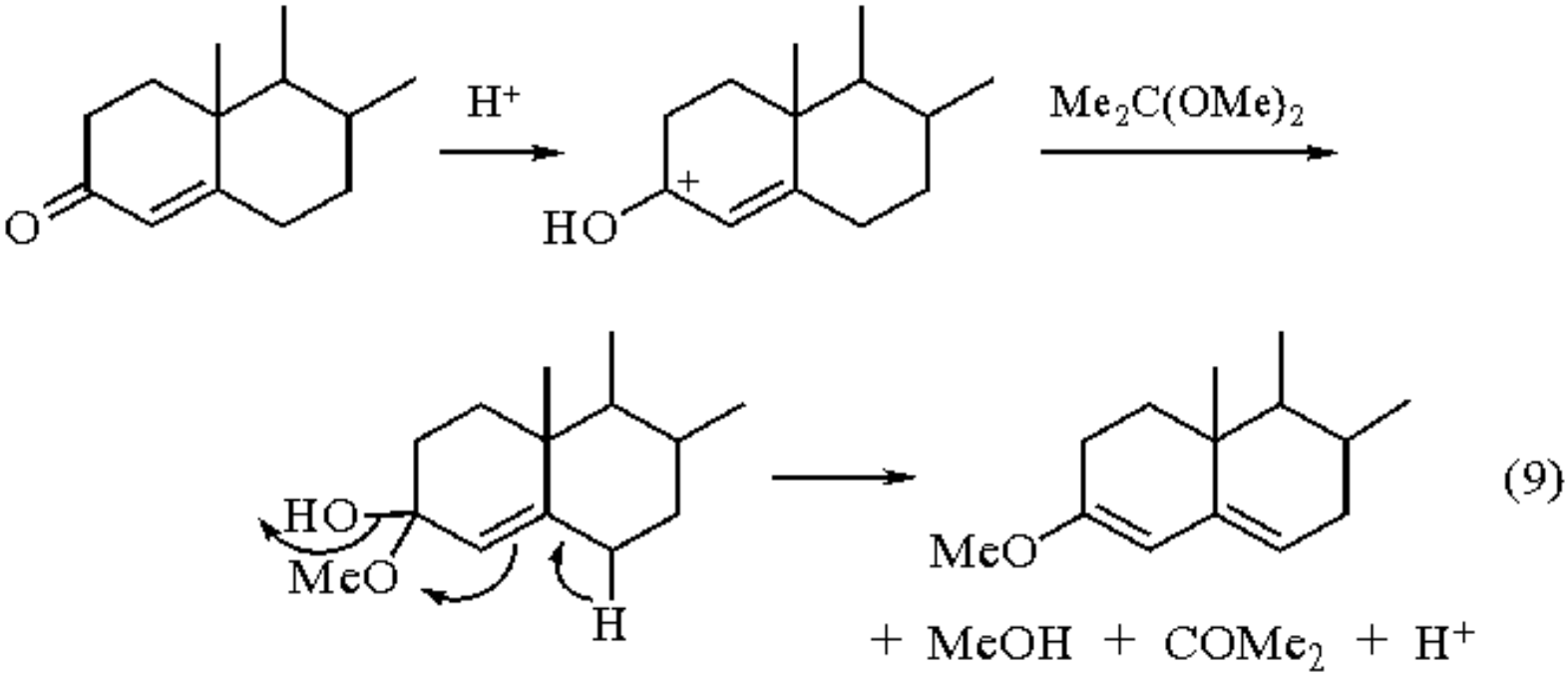

(9)

Aldol Condensation with Enol Silyl Ethers.

The first example of an aldol condensation between an unactivated enolate and an electrophilically activated carbonyl substrate was accomplished using enol silyl ethers and acetals or orthoesters in conjunction with a catalytic amount of ***Trimethylsilyl Trifluoromethanesulfonate***. The reaction proceeds very readily at -78 °C and affords the *erythro*-aldol product with high stereoselectivity.[10] The use of 2,2-dimethoxypropane in this reaction affords β-methoxy ketones (eq 10).

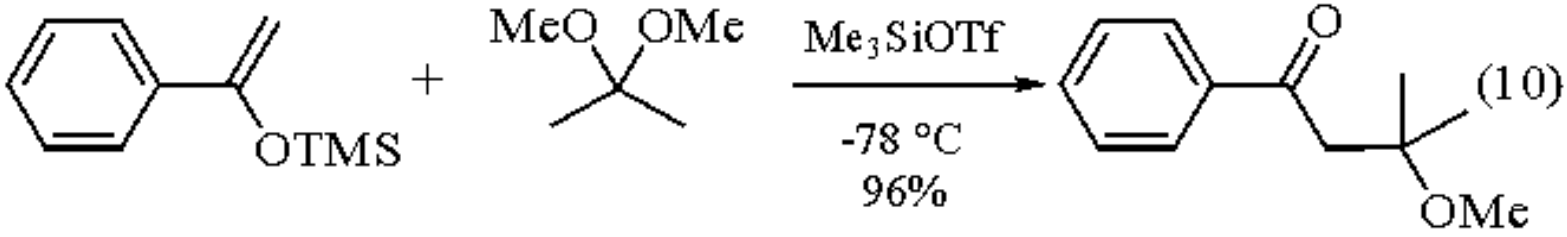

(10)

Hypophosphite Esters.

Methyl hypophosphite has been prepared by the reaction between ***Hypophosphorous Acid*** and 2,2-dimethoxypropane (eq 11).[11] However, the product reacts further with the acetone formed to give 1-hydroxy-1,1-dimethylmethylphosphinate (eq 12).

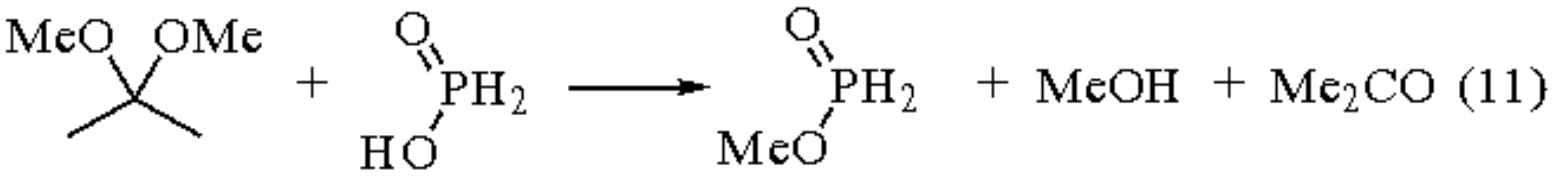

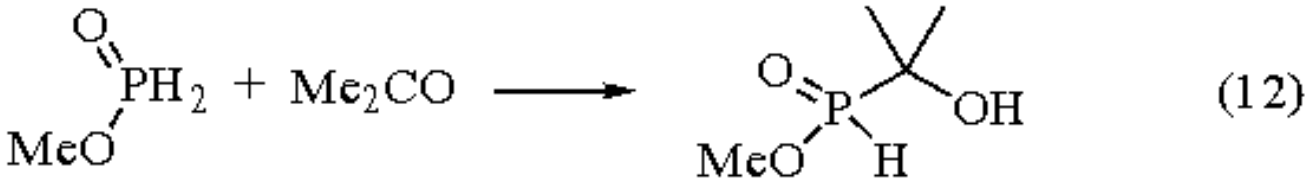

Dimethyl Boronate Esters.

Dimethyl esters of arylboronic acids have been prepared by heating a mixture of the acid, 2,2-dimethoxypropane, and ***Zinc Chloride*** (catalyst).[12]

---

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5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene

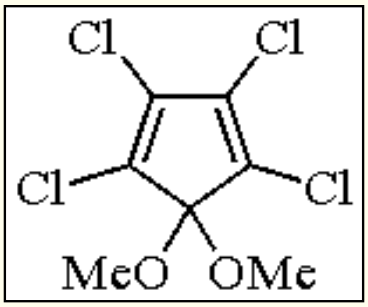

[2207-27-4] · $C_7H_6Cl_4O_2$ · 5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene · (MW 263.94)

(Diels-Alder diene;[1] steroid synthesis;[2] cyclopentanones;[3] norbornadienone[4])

Physical Data: yellow liquid with sweet odor; bp 108-110 °C/11 mmHg; d_4^{20} 1.50 g cm^{-3}.

Preparative Method: dechlorination of hexachlorocyclopentadiene in methanolic potassium hydroxide solution (eq 1).[5]

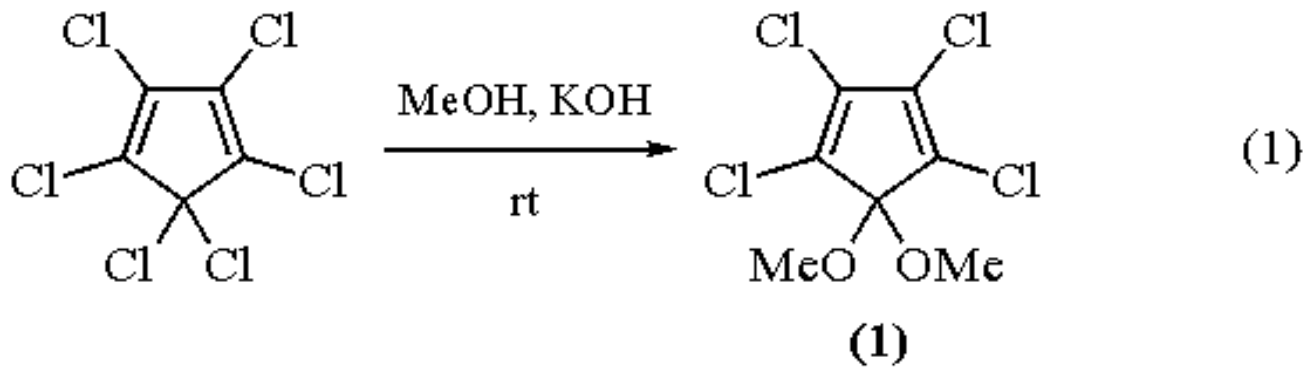

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: do not inhale the vapor; can cause dizziness. This reagent should only be used in a fume hood.

5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (**1**) is an excellent diene for Diels-Alder reactions. It undergoes cycloaddition reactions with ***Ethylene*** and subsequent reductive dechlorinations using Na/*t*-BuOH/THF to give 7,7-dimethoxynorbornene (eq 2).

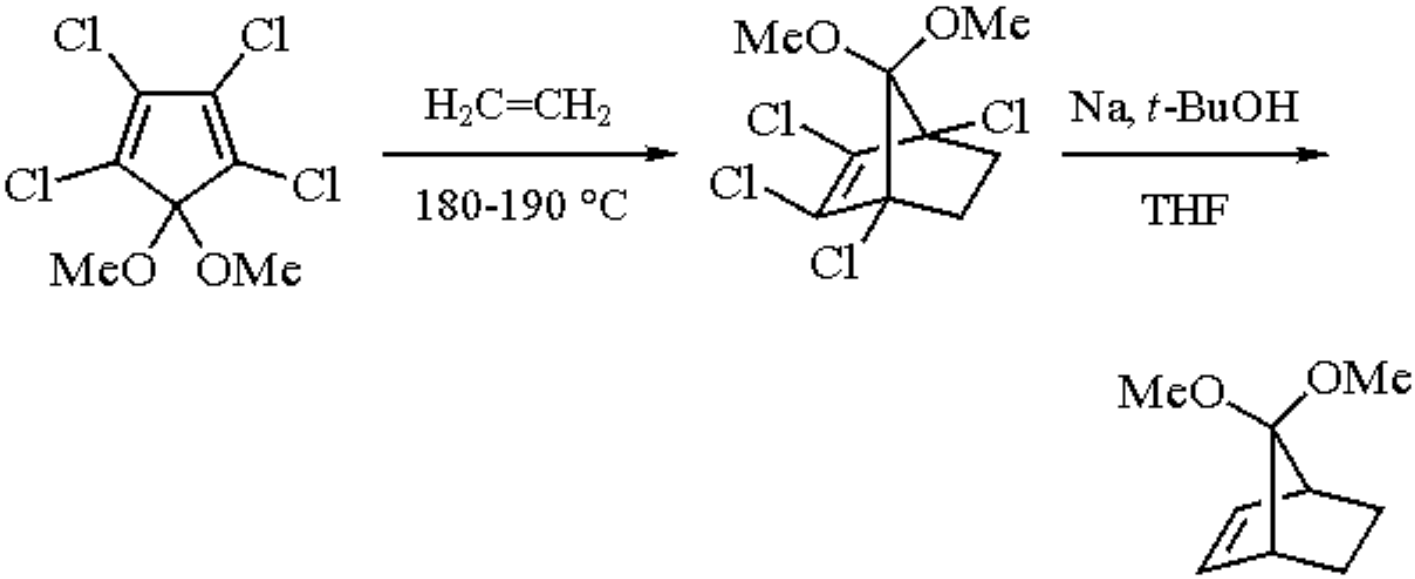

(2)

A wide range of alkenes undergo [4 + 2] cycloaddition reactions with (**1**). The adducts can be used in the preparation of cyclopentane moieties. Reductive dechlorination of adducts followed by ***Potassium Permanganate*** oxidation yields cyclopentanone units (eq 3).

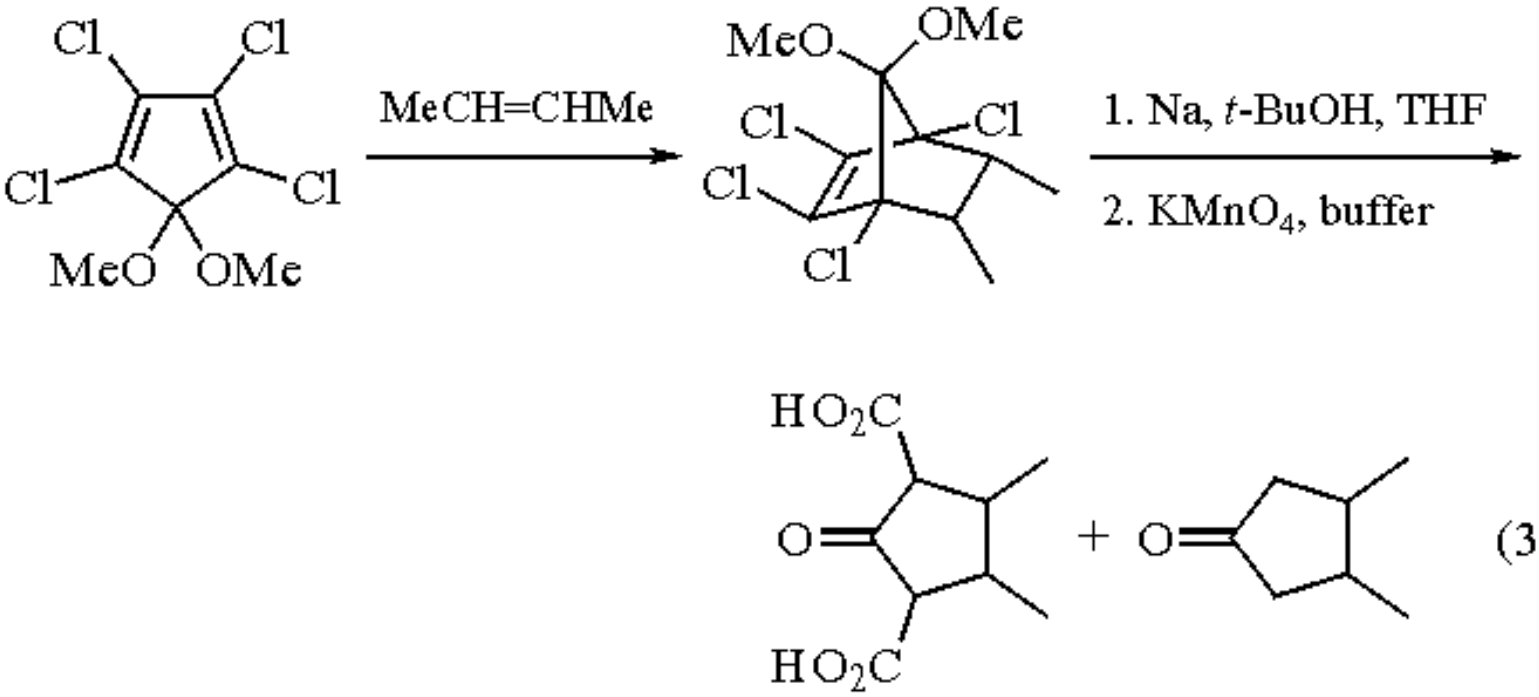

(3)

The bicyclic enone (**2**), which is useful for steroid synthesis, can be synthesized by Diels-Alder reaction with (**1**), followed by three subsequent steps. When (**2**) is treated with ***Vinylmagnesium Bromide*** followed by ***Potassium Hydride***, (**3**) is obtained, which can be converted to steroids (eq 4).

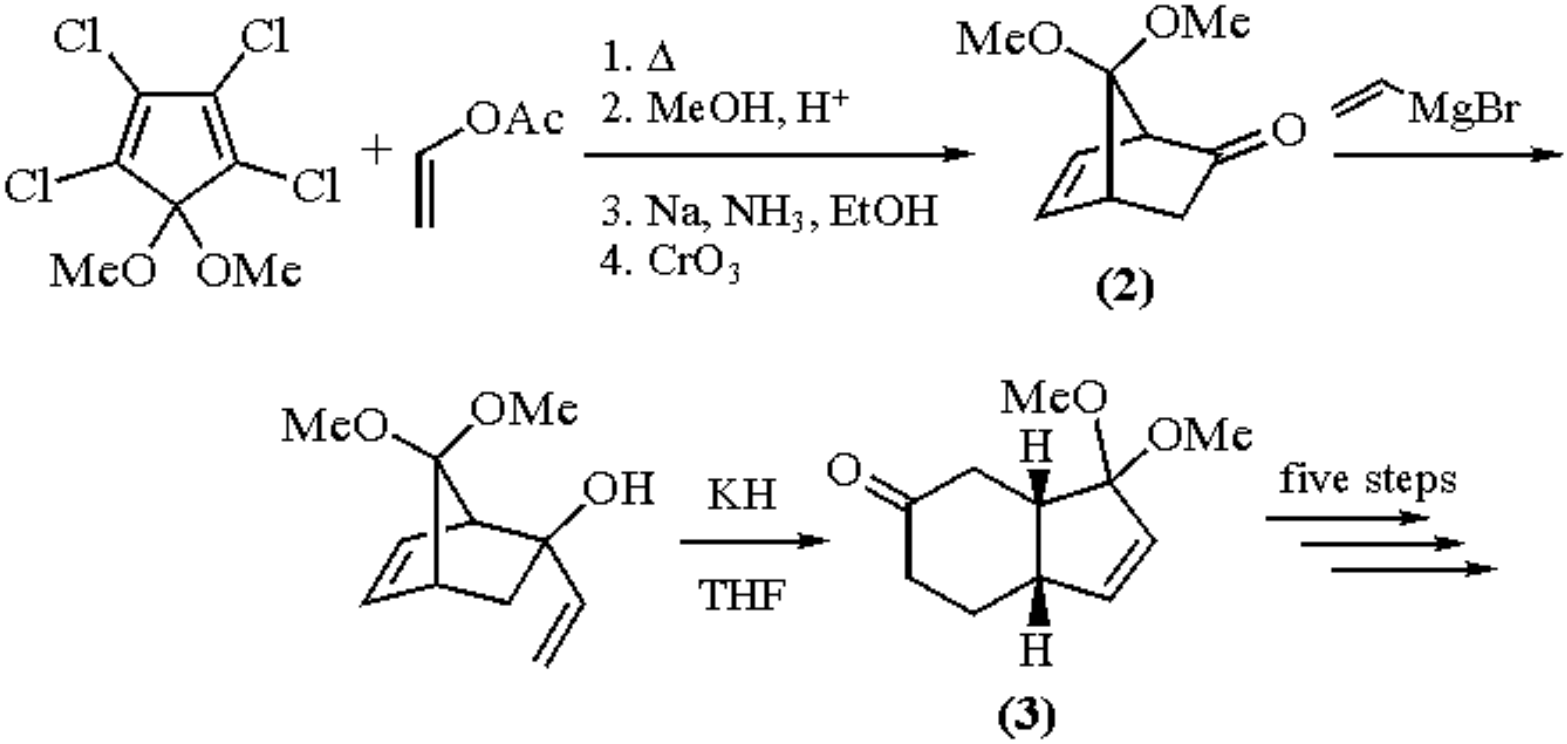

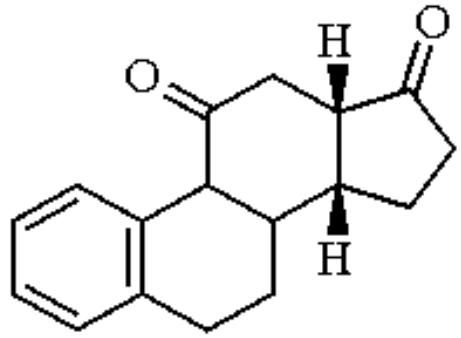

(4)

The reaction of (**1**) with cyclic dienophiles can be used in the preparation of *cis*-fused bicyclo[4.*n*.0]dienes (eq 5).

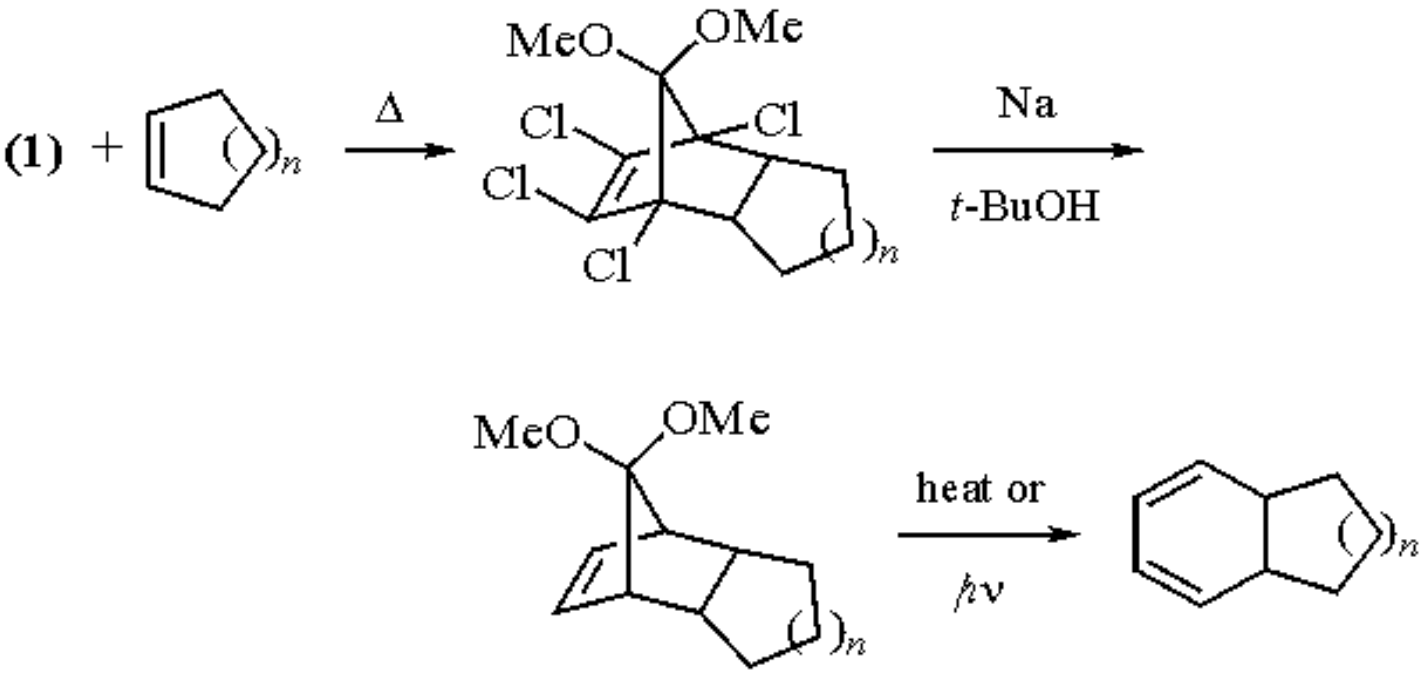

(5)

Diels-Alder reactions of (**1**) with 3,3-dimethylcyclopropene followed by reductive dechlorination and acidic hydrolysis gives 7,7-dimethylcycloheptatriene (eq 6).

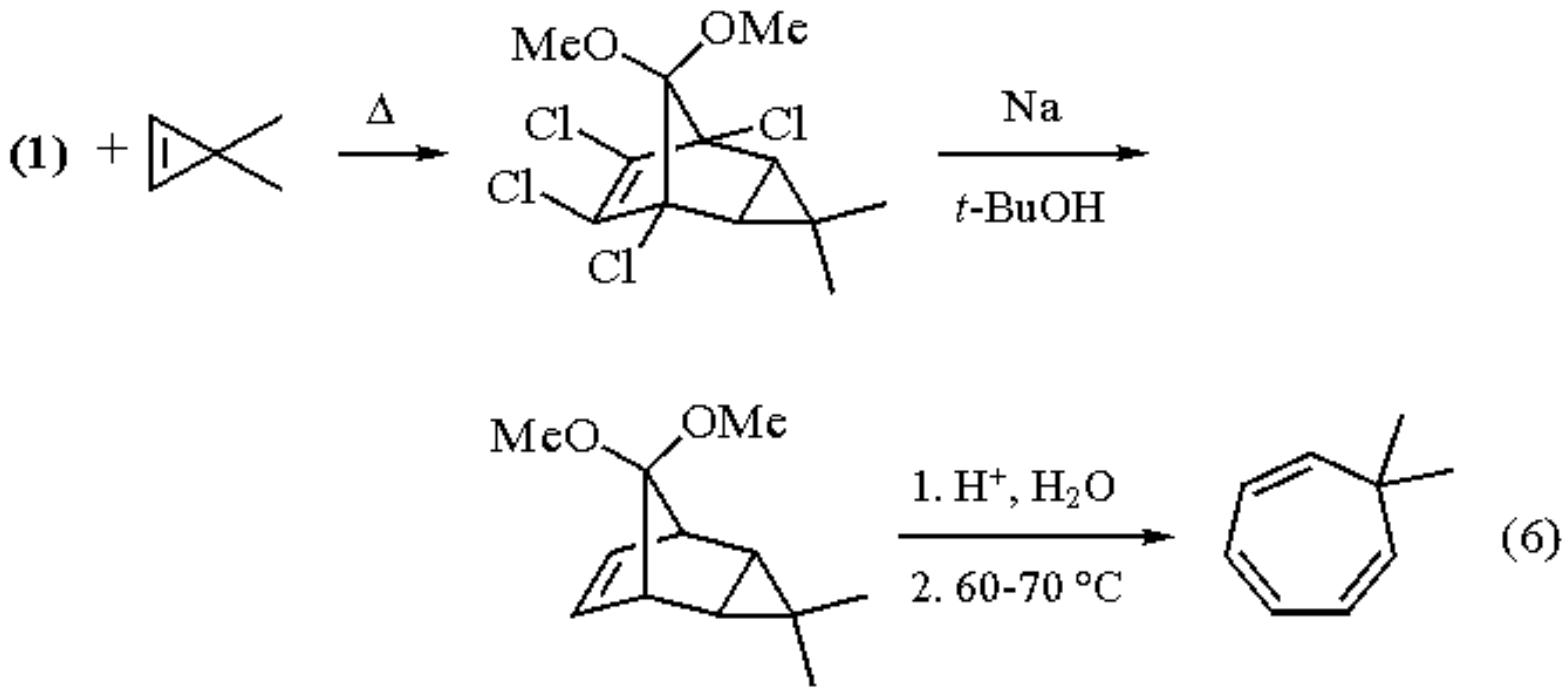

Norbornadienone can be synthesized from (**1**). Diels-Alder reaction of (**1**) with 1,2-dibromoethylene followed by a sequence of steps gives norbornadienone (eq 7).

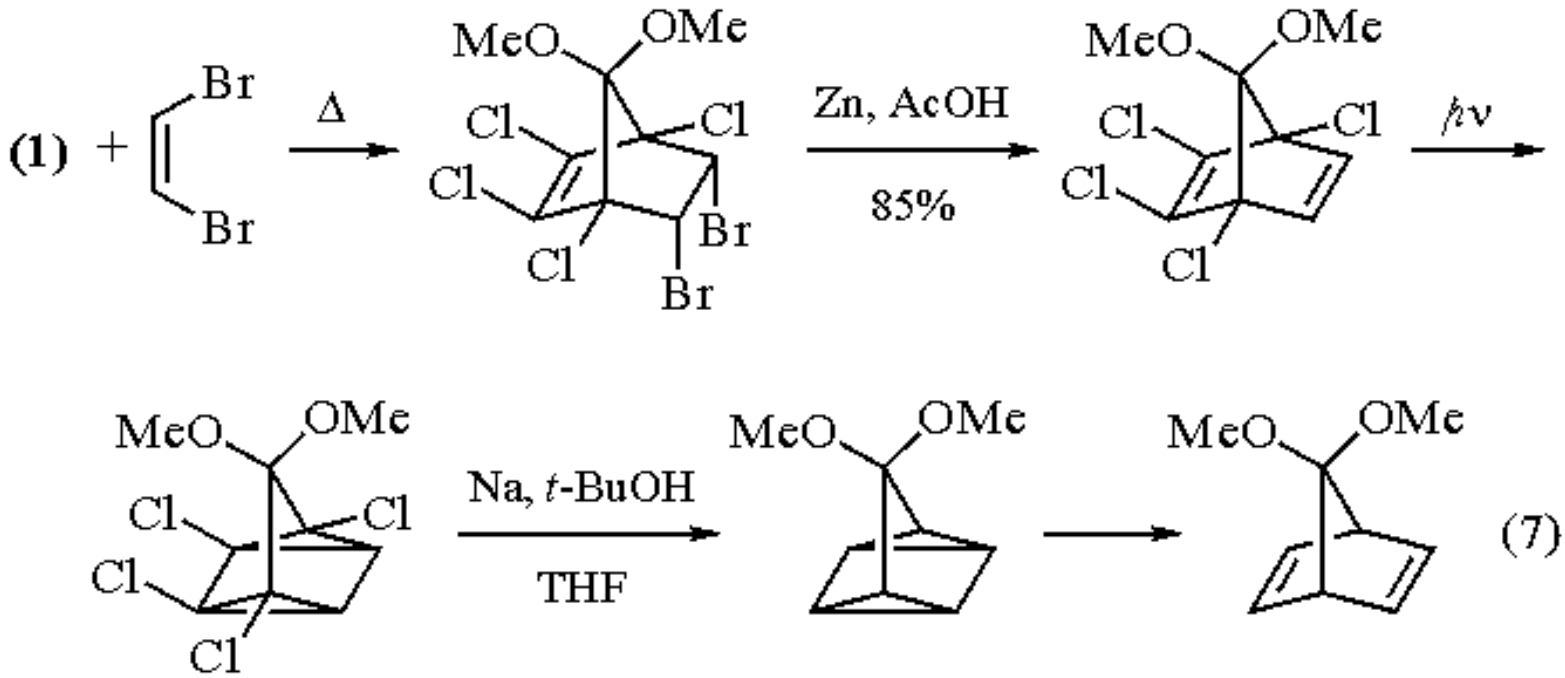

Highly complex molecules like hexacyclo[6.5.1.0.^{2,7}.0.^{4,9}.0^{10,14}]tetradeca-5,12-diene can be synthesized by Diels-Alder reaction with (**1**) (eq 8).

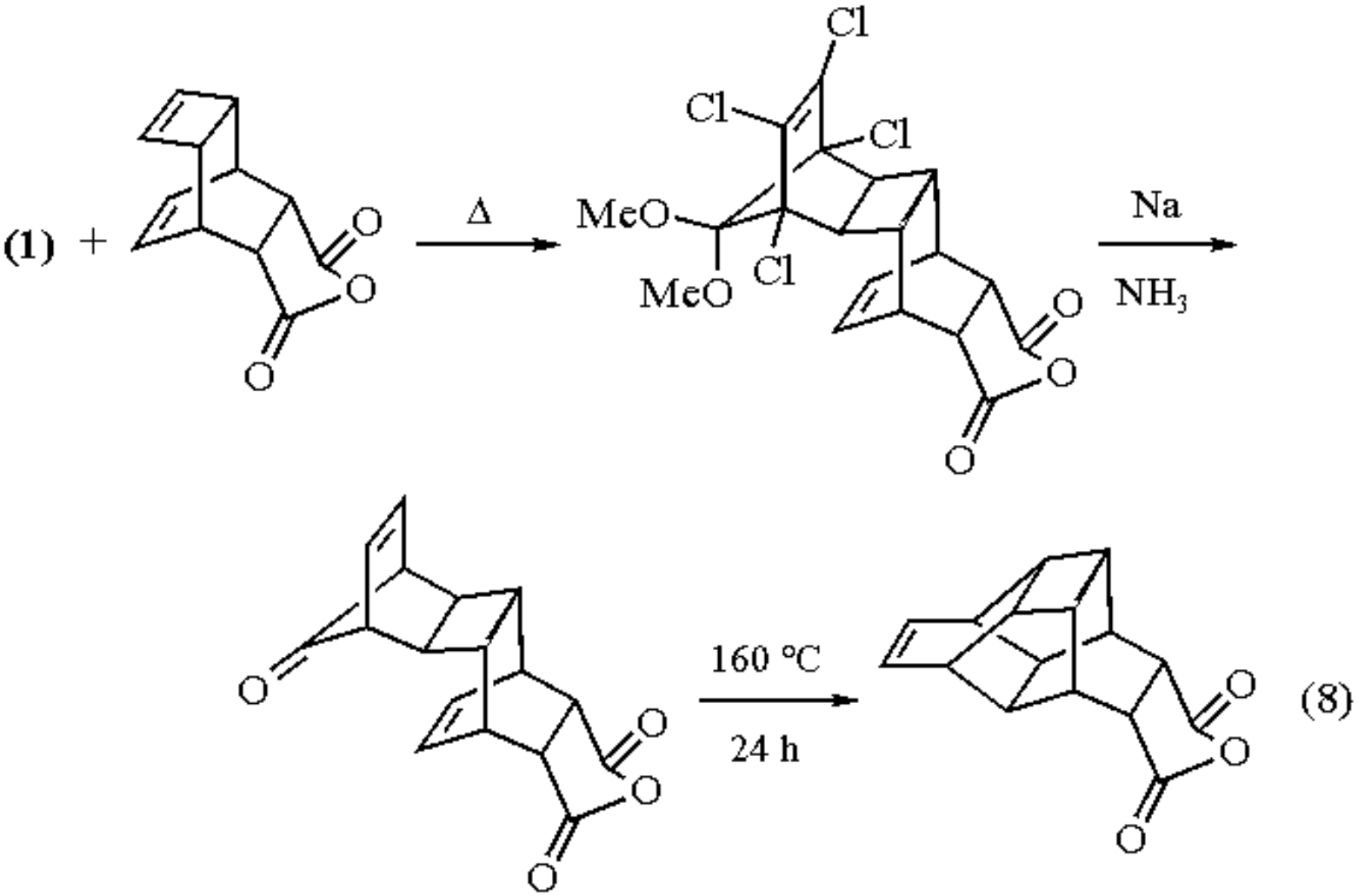

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2,5-Dimethoxytetrahydrofuran

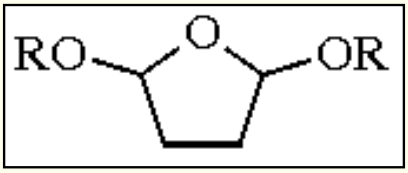

(R = Me)

[696-59-3] · $C_6H_{12}O_3$ · 2,5-Dimethoxytetrahydrofuran · (MW 132.16) (R = Et)

[3320-90-9] · $C_8H_{16}O_3$ · 2,5-Diethoxytetrahydrofuran · (MW 160.21)

(1,4-butanedial equivalents; useful for constructing heterocycles; the methoxy derivative is more commonly used)

Alternate Name: DMTHF.

Physical Data: R = Me: bp 145-147 °C; *d* 1.020 g cm^{-3}. R = Et: bp 167-174 °C; *d* 0.967 g cm^{-3}.

Solubility: practically insol H_2O; sol MeOH, Et_2O, THF.

Form Supplied in: colorless liquids; commercially available as a mixture of *cis* and *trans* isomers.

Preparative Method: by catalytic hydrogenation of 2,5-dialkoxy-2,5-dihydrofurans.[1]

Handling, Storage, and Precautions: flammable liquids; must be stored in a cool ventilated place. Noxious by inhalation, ingestion, or by contact with skin. Use in a fume hood.

Synthesis of Pyrroles, Pyrrolidines, Carbazoles, and Dihydropyridazines.

2,5-Dimethoxytetrahydrofuran[1] is a stable compound which liberates 1,4-butanedial (***Succindialdehyde***) in acid medium. The latter reacts with primary amines and hydrazines to give pyrrole derivatives according to the Paal-Knorr reaction of 1,4-dicarbonyl compounds (eq 1).[2]

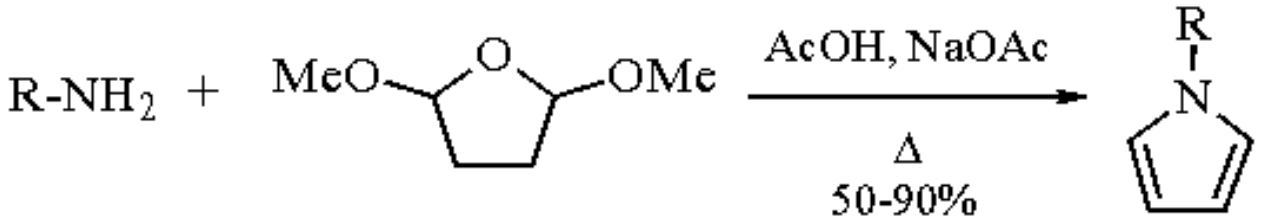

(1)

Thus a large variety of polyfunctionalized aliphatic, aromatic, or heterocyclic derivatives bearing a primary amine function give pyrroles by heating in acetic acid[3] in the presence of DMTHF. Interestingly, the same reaction performed in refluxing benzene affords 9-substituted carbazoles[4] in a one-pot synthesis (eq 2).

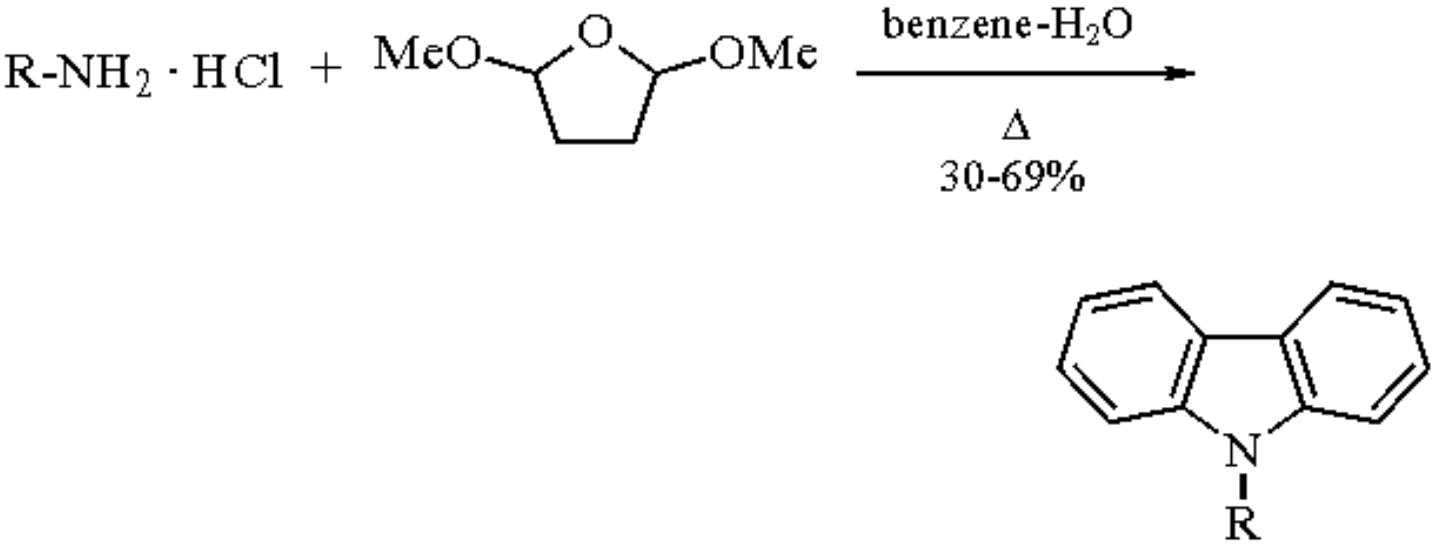

(2)

When the reaction with unsubstituted hydrazines is conducted in a saturated solution of HCl in ethanol, formation of either pyrrole (X = NO_2) or dihydropyridazine (X = H) (eq 3) occurs.[5] A mixture of both heterocyclic compounds[6] has also been observed.

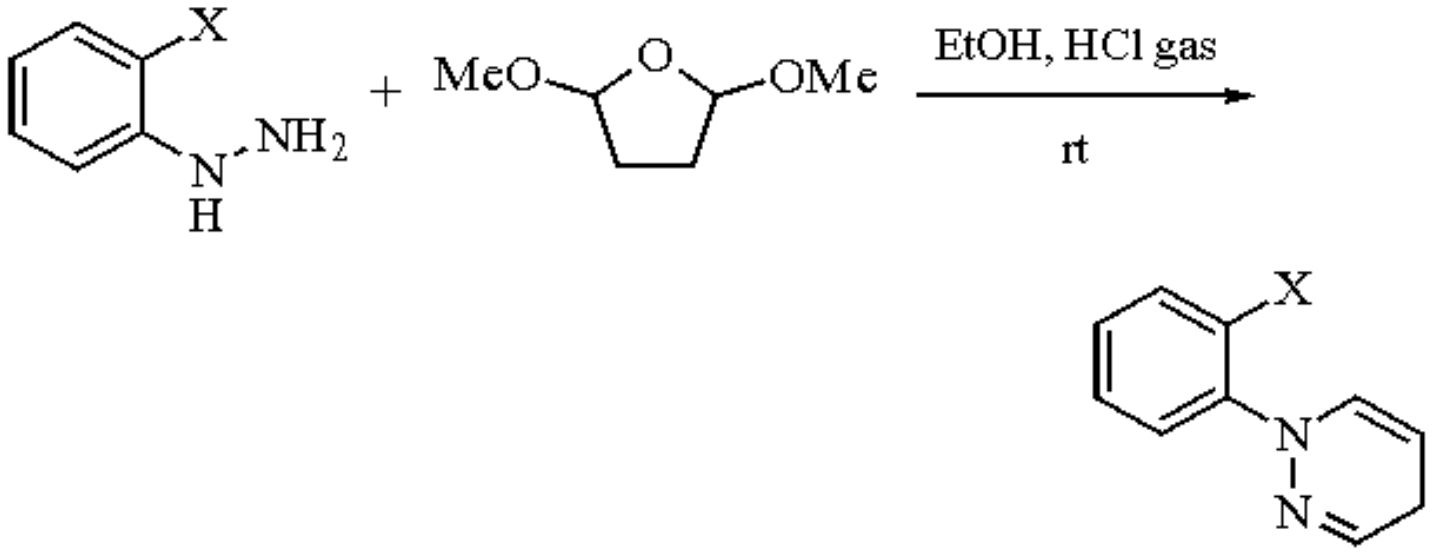

(3)

The Robinson-Schopf condensation of DMTHF with *R*-(-)-phenylglycinol in the presence of ***Potassium Cyanide*** affords 2-cyano-5-oxazolopyrrolidine (eq 4).[7] This synthon constitutes the basis of a general method for the synthesis of

enantiomerically pure pyrrolidine[8] and pyrrolizidine[9] alkaloids.

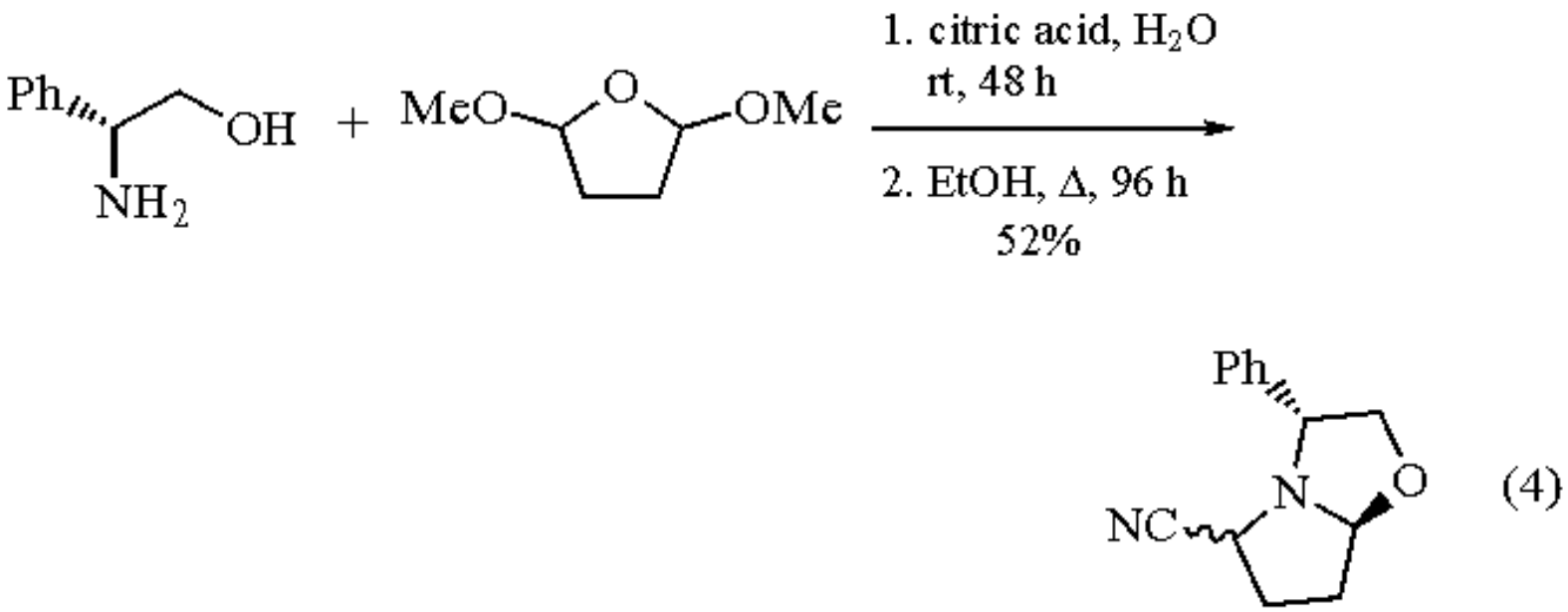

Substituted Furans.

Either 2- or 2,5-substituted tetrahydrofuran derivatives can be formed by nucleophilic addition of benzotriazole,[10] ***Chlorodiphenylphosphine***,[11] silyl ethers,[12] or ***Cyanotrimethylsilane***[13] (eq 5). However, halotrimethylsilanes induce acetal cleavage to give 1,4-dihalo-1,4-dimethoxybutane and not 2,5-dibromotetrahydrofuran (eq 6).[14]

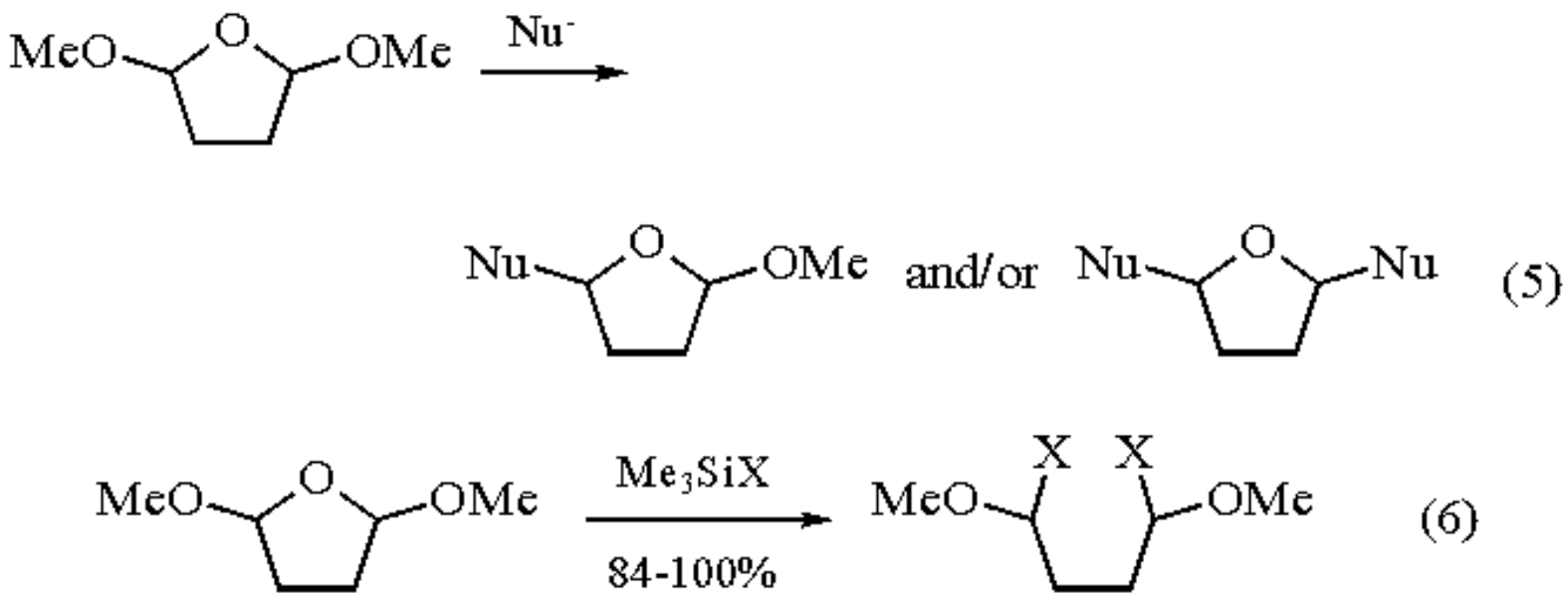

Acyclic Derivatives.

DMTHF also reacts as a dialdehyde in the presence of acid, without recyclization to a five-membered ring system. Thus condensation with dithiols affords bisdithioacetals,[15] reaction with β-naphthol leads to dibenzoxanthene derivatives (eq 7),[16] and aldolization reaction with aromatic aldehydes gives diaryl-2,3-diformylbutadienes.[17]

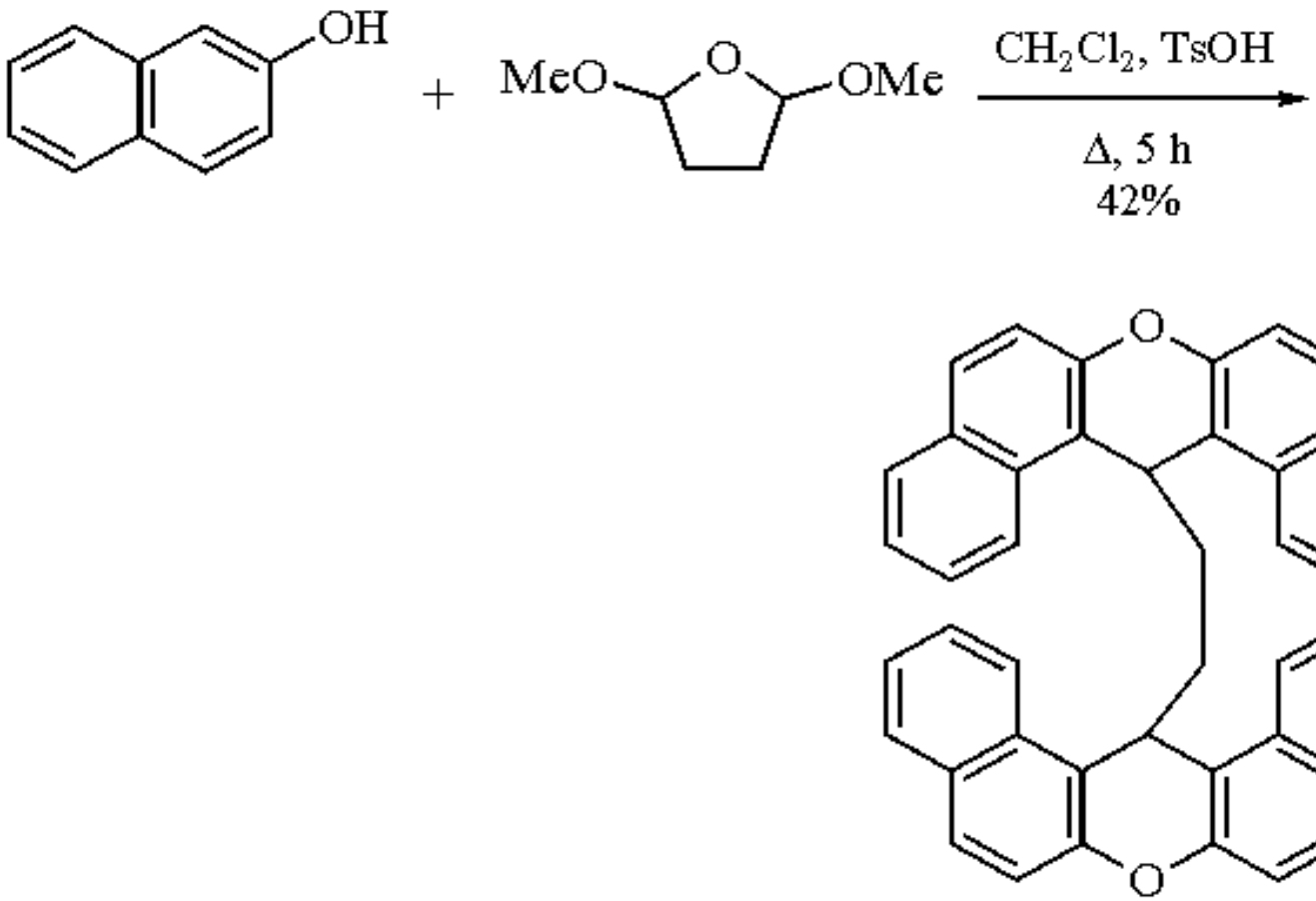

(7)

Related Reagents.

2,5-Dihydro-2,5-dimethoxyfuran; ***Furan***; ***Glutaraldehyde***; ***Succindialdehyde***; ***2-Trimethylsilyloxyfuran***.

---

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1,1-Dimethoxy-3-trimethylsilyloxy-1,3-butadiene

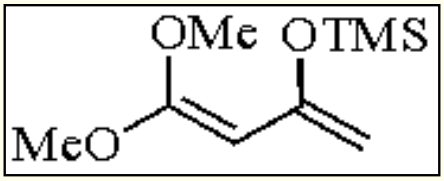

[61539-61-5] · $C_9H_{18}O_3Si$ · 1,1-Dimethoxy-3-trimethylsilyloxy-1,3-butadiene · (MW 202.32)

(diene in Diels-Alder reactions)

Physical Data: bp 84-87 °C/10 mmHg; *n*23D 1.4640.

Analysis of Reagent Purity: ^{1}H NMR (60 MHz, neat) δ 4.39 (s, 1 H), 4.07 (d, *J* = 1.0 Hz, 1 H), 3.99 (d, *J* = 1.0 Hz, 1 H), 3.61 (s, 3 H), 3.52 (s, 3 H), 0.14 (s, 9 H); IR (film) 1657, 1272, 1251, 850 cm^{-1}.

Preparative Method: enol silylation of 4,4-dimethoxy-3-buten-2-one, which is prepared from 4,4-dichloro-3-buten-2-one.[1]

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; should be handled in a well-ventilated fume hood.

Diels-Alder Reactions.

This diene is more powerful than Danishefsky's diene in Diels-Alder reactions with electron-deficient dienophiles.[2] The enhanced nucleophilic character of the diene apparently overrides the steric difficulties associated with the (*Z*)-methoxy group.

There are many examples of Diels-Alder reactions of the diene with quinones as the dienophile.[1a,3] While halogen substituents on the quinone have been used to direct the regiochemistry of the addition, haloquinones are not always easy to prepare. Sulfinylquinones are a convenient alternative (eq 1).[3d]

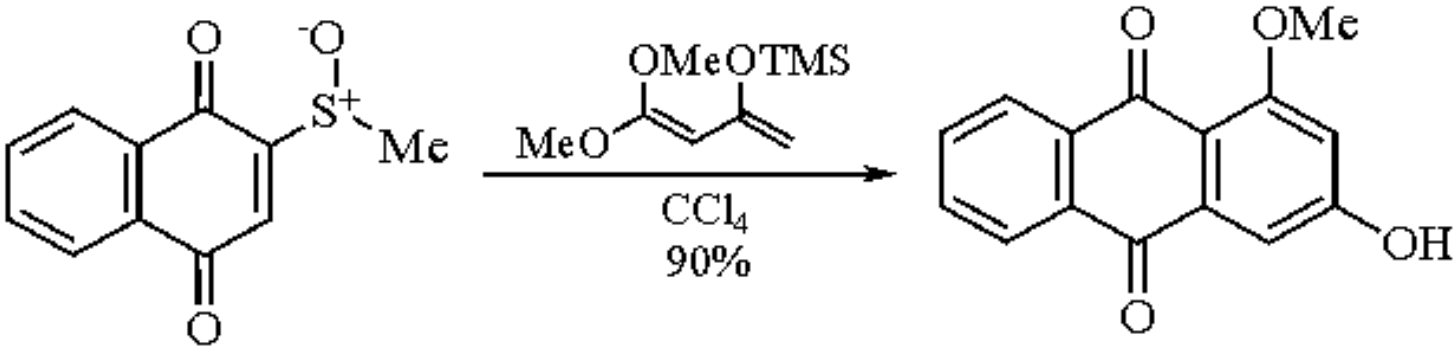

(1)

The Diels-Alder reaction with methyl *trans*-β-nitroacrylate, an alkyne equivalent, allows access to substitution patterns that are otherwise difficult to synthesize (eq 2).[4] Comparison of eq 2 with the corresponding reaction using methyl propiolate (eq 3) indicates that this represents an umpolung of Diels-Alder reactivity.[2] When the alkyne is substituted as shown in eq 4, more drastic conditions are necessary (xylene, 140 °C, 18 h).[5] Allenes have also been used in Diels-Alder reactions with the diene.[1b,2,6]

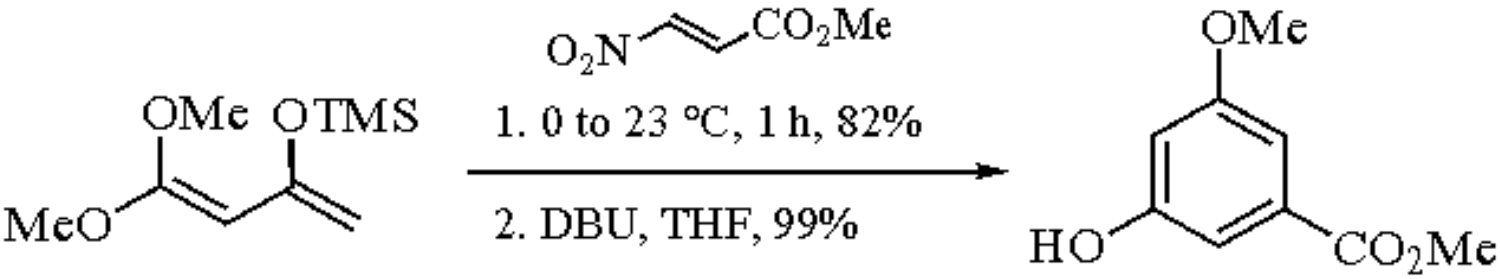

(2)

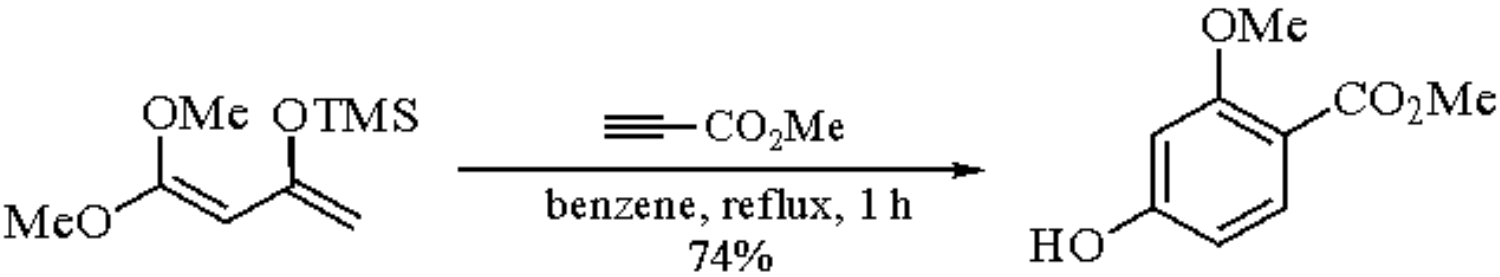

(3)

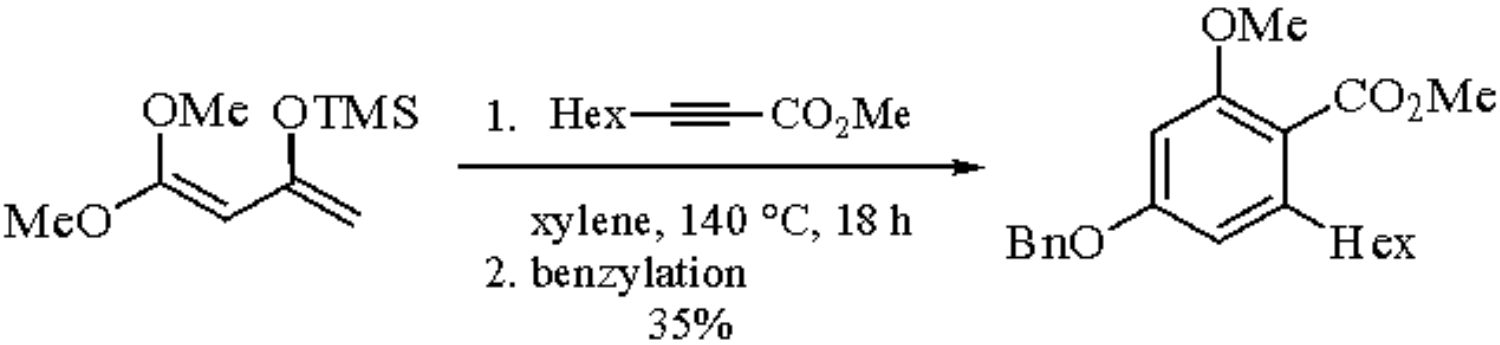

(4)

The key step in one approach to the natural product griseofulvin and its analogs involves a Diels-Alder reaction with the diene.[7] For example, a tetrasubstituted dienophile was used to form three contiguous quaternary centers in the cycloaddition step shown in eq 5.[7d]

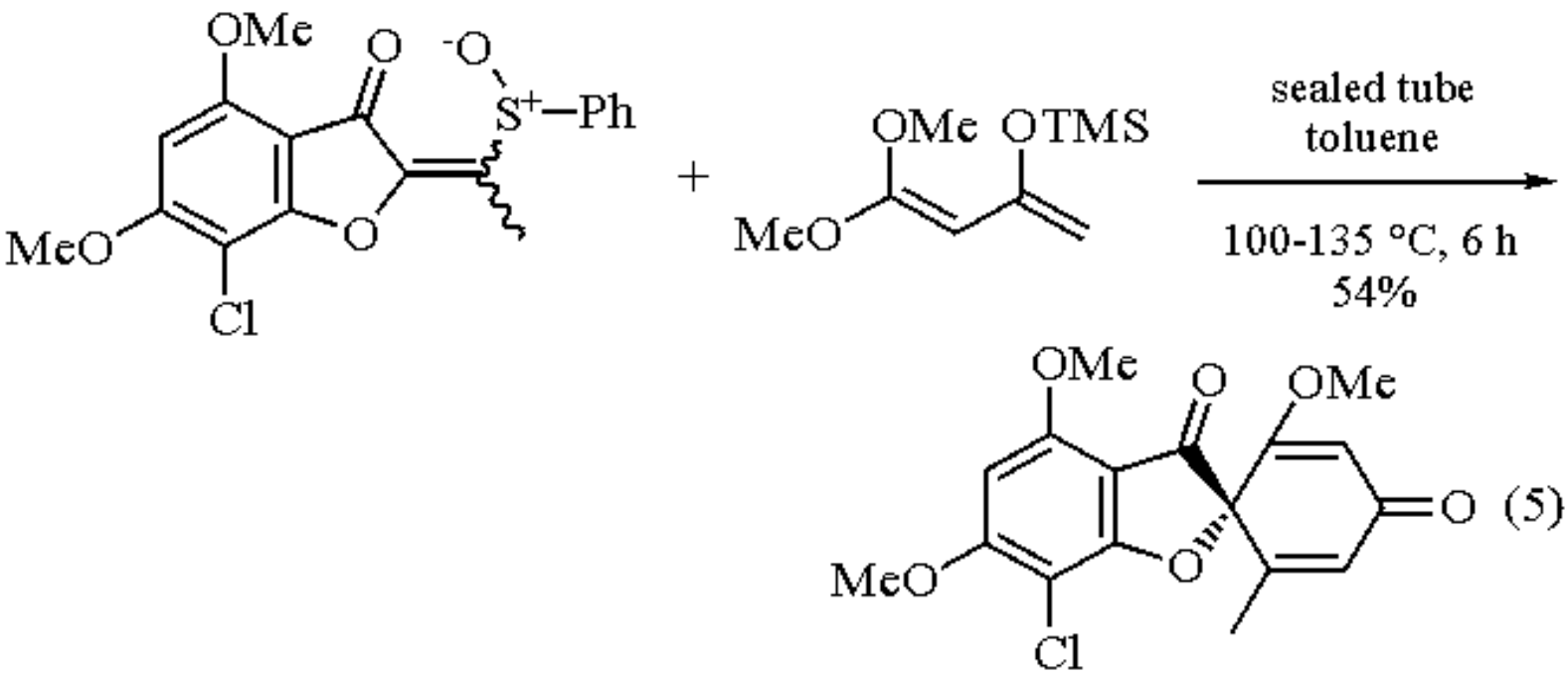

(5)

Seven-membered carbocycles such as heptafulvenes[8] and tropones[9] (eq 6) have been successfully prepared by Diels-Alder reactions of the diene with triafulvenes or cyclopropenes, respectively.

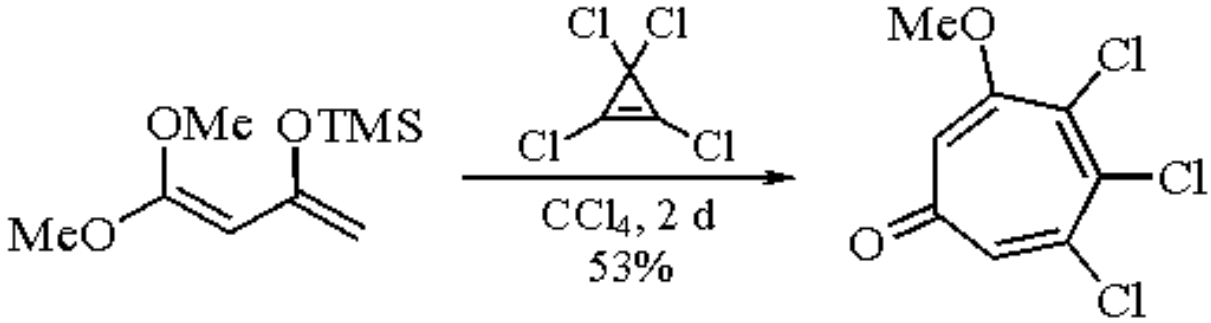

(6)

Hetero Diels-Alder Reactions.

Carbonyl compounds and the diene react in the presence of the mild Lewis acid $Eu(fod)_3$ (eq 7)[10] or ***Zinc Chloride***[11] as catalysts to give dihydropyrones in high yields. Under similar conditions, transoid dienes such as 1,1,4-trimethoxybutadiene or 1,1-dimethoxybutadiene undergo polymerization. The higher reactivity of the diene has been ascribed to its preference for the cisoid conformation.[11]

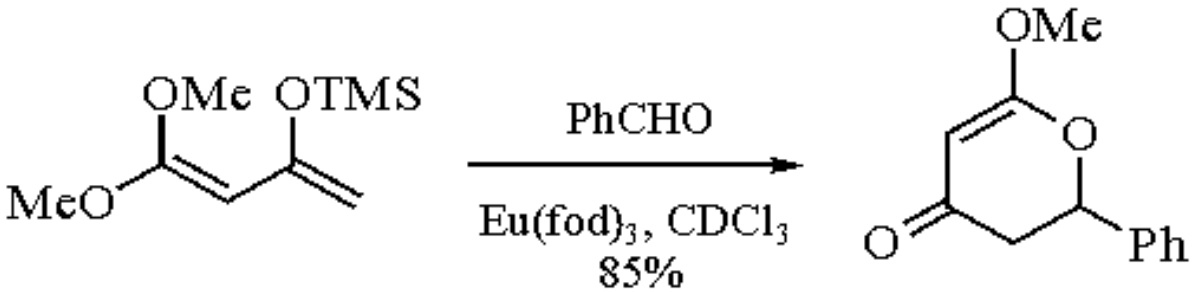

(7)

Related Reagents.

1,3-Dimethoxy-1-trimethylsilyloxy-1,3-butadiene; ***1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene***.

---

1. (a) Banville, J.; Brassard, P. *JCS(P1)* **1976**, 1852. (b) Fink, M.; Gaier, H.; Gerlach, H. *HCA* **1982**, *65*, 2563.
2. Danishefsky, S.; Singh, R. K.; Gammill, R. B. *JOC* **1978**, *43*, 379.
3. (a) Botha, M. E.; Giles, R. G. F.; Yorke, S. C. *JCS(P1)* **1991**, 85. (b) Giles, R. G. F.; Green, I. R.; Niven, M. L.; Yorke, S. C. *JCS(P1)* **1988**, 2459. (c) Potts, K. T.; Bhattacharjee, D.; Walsh, E. B. *JOC* **1986**, *51*, 2011. (d) Kraus, G. A.; Woo, S. H. *JOC* **1986**, *51*, 114. (e) Brisson, C.; Brassard, P. *JOC* **1981**, *46*, 1810. (f) Giles, R. G. F.; Yorke, S. C.; Green, I. R.; Hugo, V. I. *CC* **1984**, *8*, 554. (g) Grandmaison, J. L.; Brassard, P. *T* **1977**, *33*, 2047.
4. Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *JACS* **1978**, *100*, 2918.
5. Danishefsky, S.; Etheredge, S. J. *JOC* **1979**, *44*, 4716.
6. Yoshida, M.; Harada, N.; Nakamura, H.; Kanematsu, K. *TL* **1988**, *29*, 6129.
7. (a) Ko, B. S.; Oritani, T.; Yamashita, K. *Han'guk Nonghwa Hakhoechi* **1992**, *35*, 395 (*CA* **1993**, *118*, 212 734x). (b) Ko, B. S.; Oritani, T.; Yamashita, K. *ABC* **1990**, *54*, 2199. (c) Tomozane, H.; Takeuchi, Y.; Choshi, T.; Kishida, S.; Yamato, M. *CPB* **1990**, *38*, 925. (d) Danishefsky, S.; Walker, F. J. *JACS* **1979**, *101*, 7018. (e) Danishefsky, S.; Etheredge, S. J. *JOC* **1978**, *43*, 4604.
8. Eicher, T.; Abel, M. *S* **1987**, *6*, 542.
9. Banwell, M. G.; Knight, J. H. *CC* **1987**, *14*, 1082.
10. (a) Castellino, S.; Sims, J. J. *TL* **1984**, *25*, 2307. (b) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *JOC* **1984**, *49*, 392. (c) Danishefsky, S.; Langer, M. E. *JOC* **1985**, *50*, 3672 (footnote 15 therein).
11. Van Balen, H. C. J. G.; Broekhuis, A. A.; Scheeren, J. W.; Nivard, R. J. F. *RTC* **1979**, *98*, 36.

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1,3-Dimethoxy-1-trimethylsilyloxy-1,3-butadiene

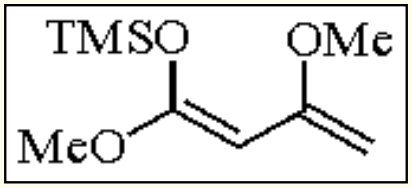

[106875-55-2] · $C_9H_{18}O_3Si$ · 1,3-Dimethoxy-1-trimethylsilyloxy-1,3-butadiene · (MW 202.32) (*E*)

[74272-66-5] (*Z*)

[90857-62-8]

(diene in Diels-Alder reactions; nucleophile)

Physical Data: bp 54 °C/0.5 mmHg.

Analysis of Reagent Purity: IR (film) 1660, 1270, 1255, 845 cm^{-1}; ^1H NMR (199.5 MHz, $CDCl_3$) δ 4.32 (d, *J* = 1 Hz, 1 H), 4.00 (dd, 2 H), 3.53 (d, 6 H), 0.28 (s, 9 H); ^{13}C NMR (50.10 MHz, $CDCl_3$) δ 157.9, 89.6, 77.8, 74.9, 54.1, 53.1, -0.6. The stereochemistry of the diene has been determined to be (*Z*) by NOE experiments.[1]

Preparative Method: enol silylation of methyl (*E*)-3-methoxy-2-butenoate, which is prepared from methyl acetoacetate and trimethyl orthoformate.[2]

Purification: the diene should be distilled at the lowest possible temperature to avoid intramolecular silyl migration which occurs above 80 °C.

Handling, Storage, and Precautions: stable in an inert atmosphere under anhydrous conditions when stored at 5 °C for several months. Use in a fume hood.

Diels-Alder Reactions.

Diels-Alder reactions of quinones with a variety of polarized dienes is an efficient method for the synthesis of highly substituted anthraquinones. The regioselectivity of the reaction is controlled by hydroxy,[3] halo (eq 1),[4] and sulfonyl[5] directing groups on the dienophile. In most cases, methanol is lost in preference to TMSOH during aromatization.[6]

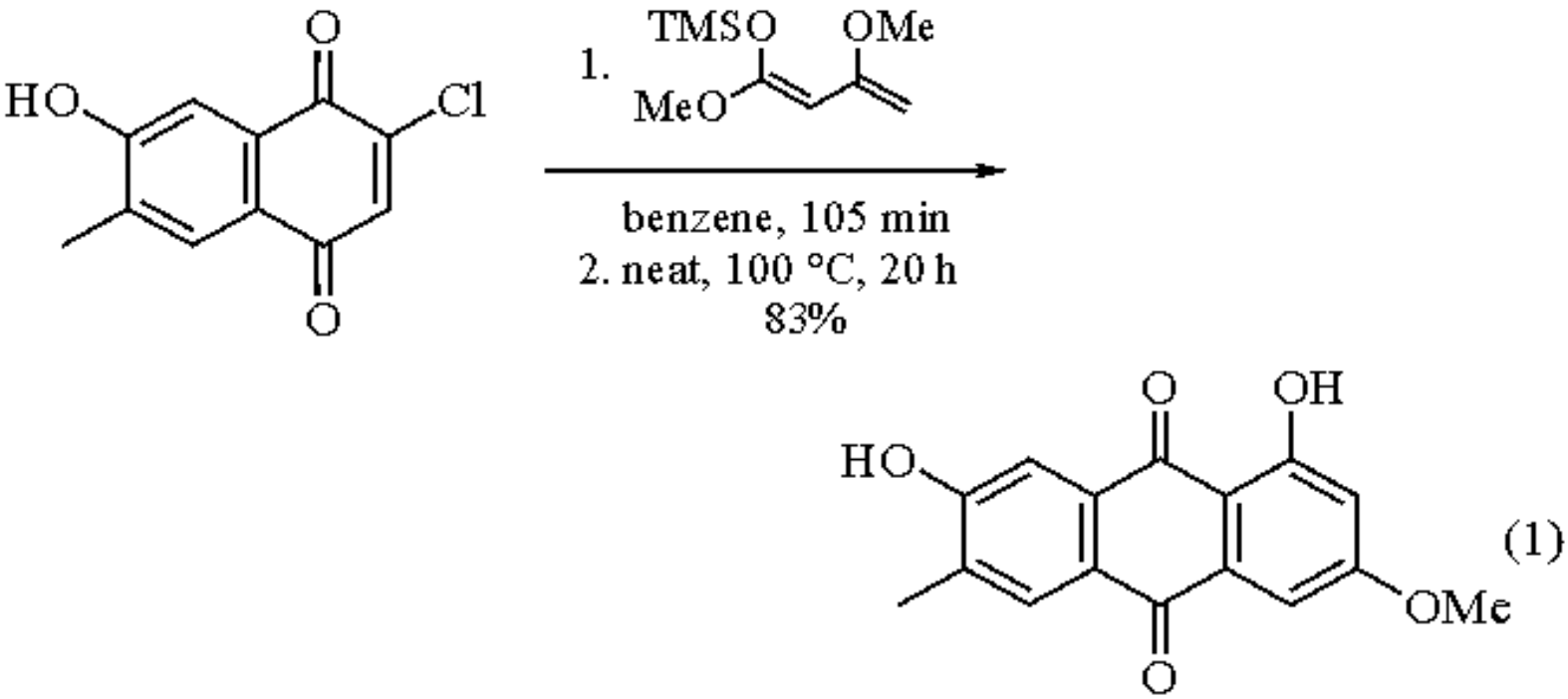

(1)

In the presence of Lewis acids the diene condenses with aldehydes and unactivated ketones in a regiospecific manner to provide δ-lactones in good yield.[7] The diene has also been used to trap photochemically generated thioformaldeyde.[8] While $Eu(hfc)_3$[7] and oxovanadium(IV) complex[9] catalysts have been reported to induce asymmetry in cycloadditions with Danishefsky's diene, zero or very poor optical yields have been obtained with this diene under the same conditions. This suggests that substituents at the 1-position of the diene make a critical contribution to the asymmetric induction.[7,9]

Diastereoselective hetero Diels-Alder reactions have been successful in $Eu(hfc)_3$ catalyzed condensations of the diene with α-alkoxy[7,10] and α-amino aldehydes (eq 2).[11] Cycloaddition with α-alkoxy imines requires a strong Lewis acid such as ***Diethylaluminum Chloride*** to ensure rapid reaction and to suppress polymerization of the diene.[12] The degree of diastereoselectivity is dependent on the alkyl side chain and the alkoxy or amine protecting group. Amino acid esters have been used as chiral auxiliary groups in reactions of the diene and imines with $EtAlCl_2$ as catalyst (eq 3).[13]

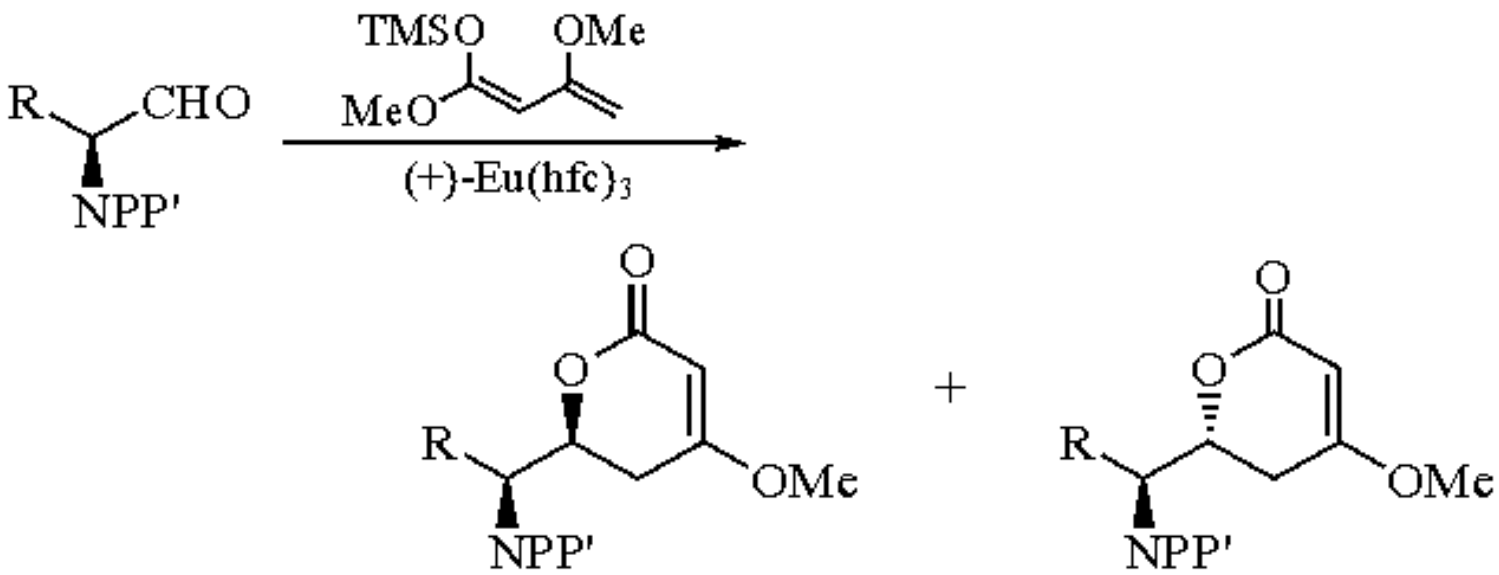

(2)

R = *i*-Pr, P = Boc, P' = H; 80%	95:5	chelation
R = *i*-Bu, P = P' = Bn; 87%	<1:>99	nonchelation

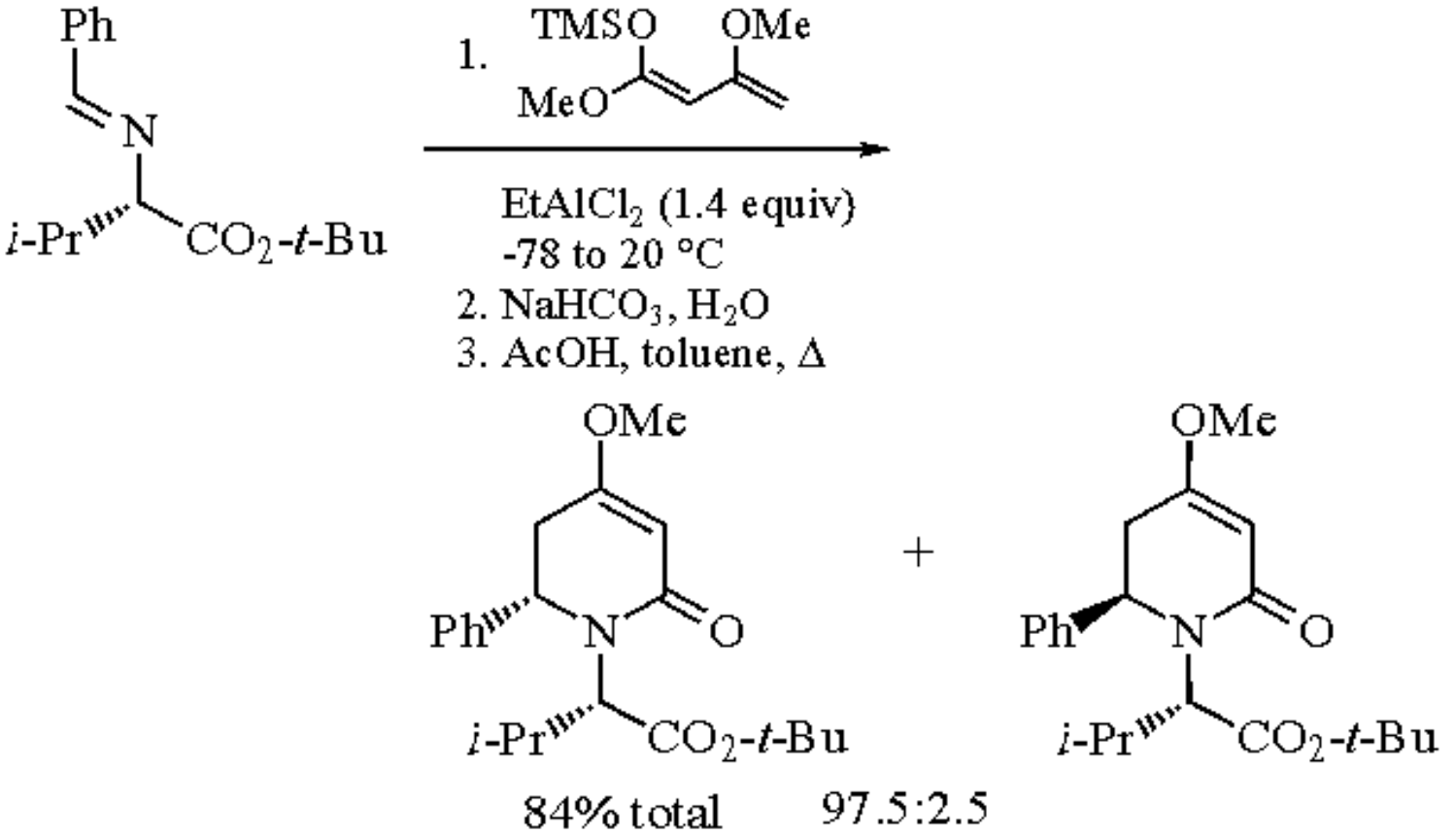

(3)

84% total 97.5:2.5

Alkylation.

Nucleophilic attack by the diene on 2,3,5-tri-*O*-benzyl-D-ribofuranosyl acetate in the presence of ***Trimethylsilyl Trifluoromethanesulfonate*** occurs at the carbonyl carbon of the 2-benzyloxy group instead of at the C-1 carbon of the in situ generated oxonium ion (eq 4).[14]

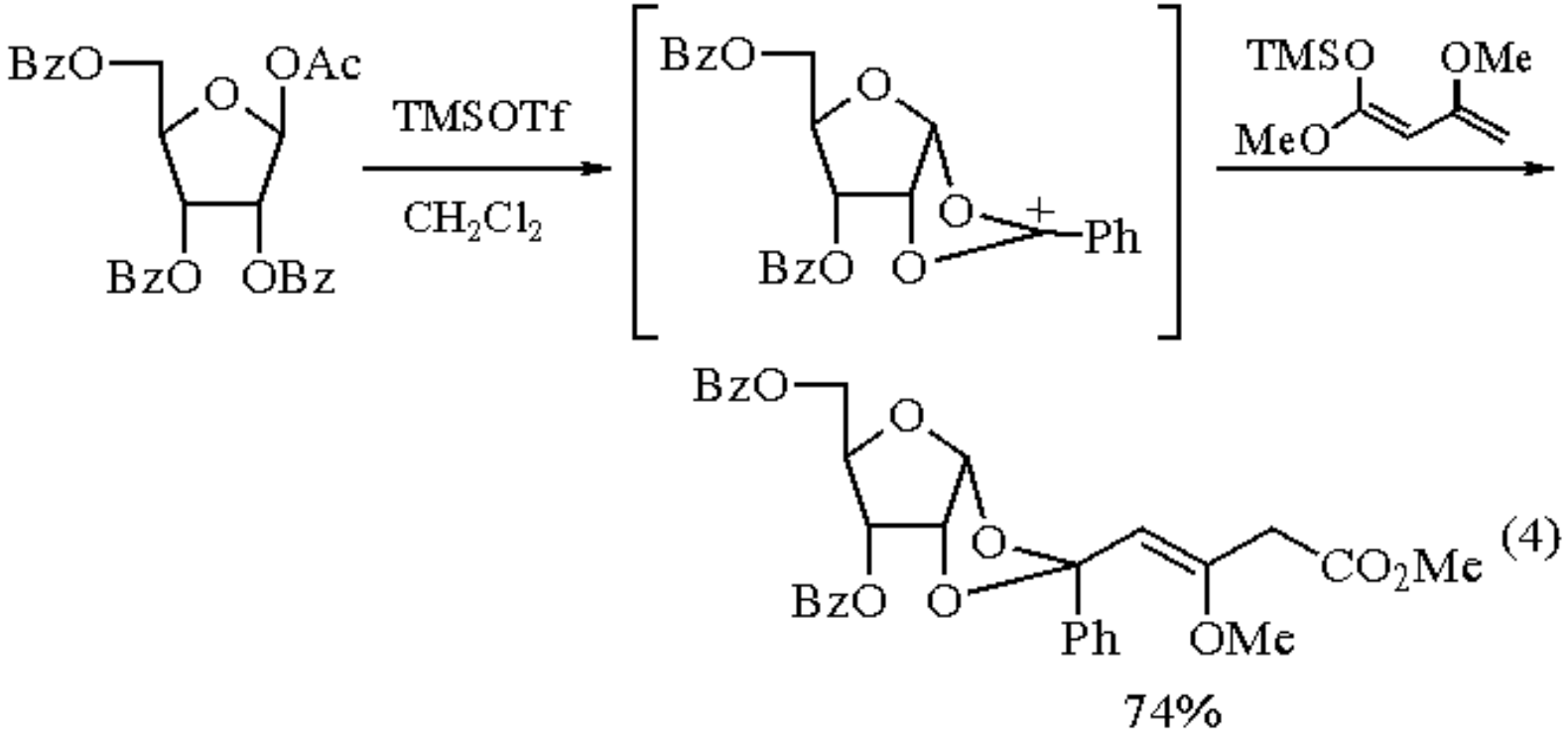

Related Reagents.

1,1-Dimethoxy-3-trimethylsilyloxy-1,3-butadiene; ***1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene***.

---

1. Bell, S. H.; Cameron, D. W.; Feutrill, G. I.; Skelton, B. W.; White, A. H. *TL* **1985**, *26*, 6519.
2. (a) Savard, J.; Brassard, P. *TL* **1979**, *51*, 4911. (b) Savard, J.; Brassard, P. *T* **1984**, *40*, 3455. (c) Midland, M. M.; Koops, R. W. *JOC* **1990**, *55*, 5058.
3. Cameron, D. W.; De Bruyn, P. J. *TL* **1992**, *33*, 5593.
4. Brisson, C.; Brassard, P. *JOC* **1981**, *46*, 1810.
5. (a) Iwao, M.; Kuraishi, T. *BCJ* **1987**, *60*, 4051. (b) Watanabe, M.; Tsukazaki, M.; Hamada, Y.; Iwao, M.; Furukawa, S. *CPB* **1989**, *37*, 2948.
6. Examples where the methyl ether is the major product: (a) Coleman, R. S.; Grant, E. B. *JOC* **1991**, *56*, 1357. (b) Paquet, J.; Brassard, P. *CJC* **1989**, *67*, 1354.
7. Midland, M. M.; Graham, R. S. *JACS* **1984**, *106*, 4294.
8. Ward, D. E.; Gai, Y.; Zoghaib, W. M. *CJC* **1991**, *69*, 1487.
9. Togni, A. *OM* **1990**, *9*, 3106.
10. Midland, M. M.; Koops, R. W. *JOC* **1990**, *55*, 5058.
11. (a) Midland, M. M.; Afonso, M. M. *JACS* **1989**, *111*, 4368. (b) Midland, M. M.; Koops, R. W. *JOC* **1990**, *55*, 4647.
12. Midland, M. M.; Koops, R. W. *JOC* **1992**, *57*, 1158.
13. Waldmann, H.; Braun, M.; Dräger, M. *TA* **1991**, *2*, 1231.
14. (a) Yokoyama, Y. S.; Inoue, T.; Kuwajima, I. *BCJ* **1984**, *57*, 553. (b) Yokoyama, Y. S.; Elmoghayar, M. R. H.; Kuwajima, I. *TL* **1982**, *23*, 2673.

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1,2-Dimethoxyvinyllithium[1]

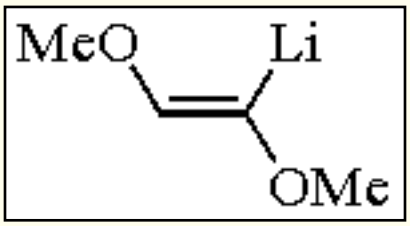

[59648-89-4] · $C_4H_7LiO_2$ · 1,2-Dimethoxyvinyllithium · (MW 94.04)

(reacts with aldehydes and ketones to form allylic alcohols;[1] the functionally equivalent reagent, 2-lithio-1,4-dioxene, reacts with aldehydes, ketones, and methyl halides[2,3] to form allylic alcohols and methylated alkenes)

Form Supplied in: prepared in situ and used directly.

Preparative Method: prepared in situ under nitrogen by the reaction of 1,2-dimethoxyvinyl bromide in anhydrous ether at -70 °C with ***n-Butyllithium*** in hexane. 1,2-Dimethoxyvinyl bromide is obtained from the reaction at 0 °C of aqueous ***Glyoxal*** in methanol (2 equiv)/dichloromethane with ***Hydrogen Bromide*** gas, followed by dehydrohalogenation with sodium *t*-butoxide (1 equiv).[1]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (N_2 or Ar) to exclude oxygen and moisture.

Additions to Aldehydes and Ketones.

1,2-Dimethoxyvinyllithium adds to aldehydes and ketones to yield allylic alcohols. The alcohols, when dissolved in THF and 6 N hydrochloric acid, rearrange to α-methoxy-α,β-unsaturated aldehydes.[1] With aromatic aldehydes, α-methoxycinnamaldehydes are obtained in isolated yields of 51-76% (eq 1). Cyclohexanone is converted to the unsaturated aldehyde in 86% yield (eq 2).

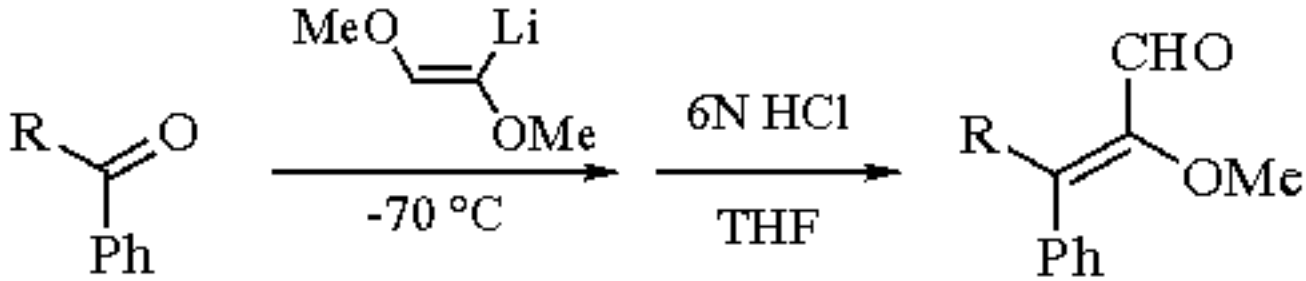

(1)

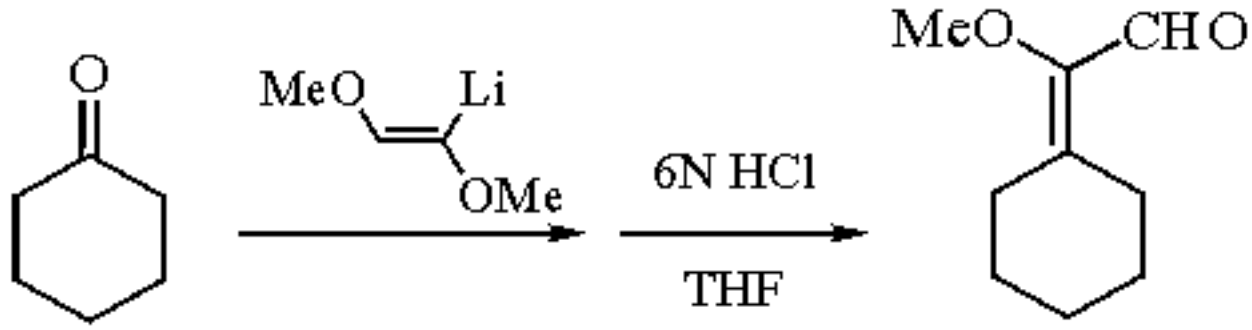

(2)

Pentacarbonyl [(*Z*)-1,2-dimethoxyvinyl]carbene complexes can be prepared by the addition of the reagent to ***Hexacarbonylchromium*** and ***Hexacarbonyltungsten*** followed by protonation or alkylation, respectively.[4] Synthesis of simple aldehydes from 1,2-dimethoxyvinyllithium and trialkylboranes has been reported.[5]

Functionally Equivalent Reagents.

2-Lithio-1,4-dioxene is prepared by the addition of ***n-Butyllithium*** in hexane to 1,4-dioxene cooled in an ice/water bath[2] or by the addition of ***t-Butyllithium*** to the dioxene.[2,3] The reagent has been identified by its ^{13}C NMR spectrum[2] and is stable even at rt. Addition of the reagent to aldehydes and ketones yields secondary and tertiary allylic alcohols (eq 3), which can be converted into α-hydroxy ketones,[3] α,α´-dihydroxy ketones,[3] and 2-oxaalkanal 1-dithioacetals.[5] 2-Lithio-1,4-dioxene may also be methylated.[2]

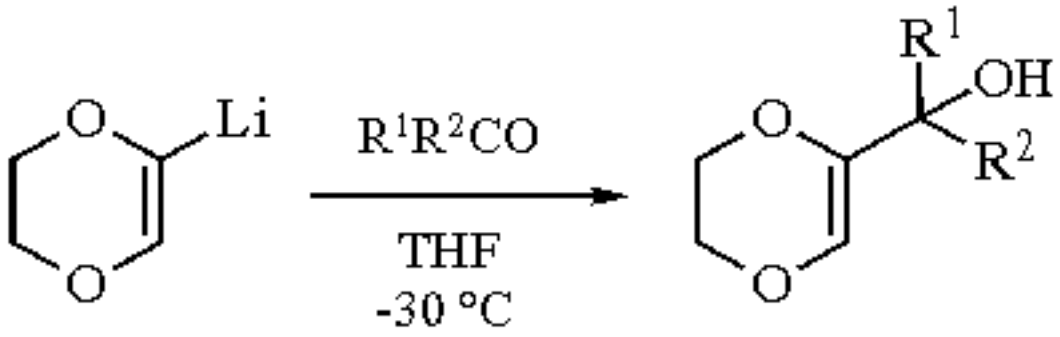

(3)

4-Lithio-2,2-dimethyl-1,3-dioxole, prepared as in eq 4, reacts with aldehydes and ketones to form allylic alcohols, which subsequently afford α-keto aldehydes.[6,7]

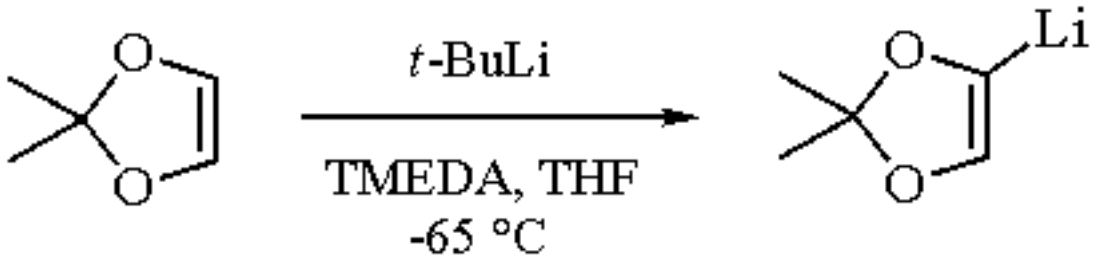

(4)

Related Reagents.

1-Ethoxyvinyllithium; ***1-Methoxyallenyllithium***; ***1-Methoxyvinyllithium***.

---

1. Skold, C. N. *SC* **1976**, *6*, 119.
2. Saylor, R. W.; Sebastian, J. F. *SC* **1982**, *12*, 579.
3. Fetizon, M.; Goulaouic, P.; Hanna, I. *TL* **1985**, *26*, 4925.
4. Dötz, K. H.; Kuhn, W.; Thewalt, U. *CB* **1985**, *118*, 1126.
5. Koshino, J.; Sugawara, T.; Yogo, T.; Suzuki, A. *SC* **1983**, *13*, 1149.
6. Fetizon, M.; Goulaouic, P.; Hanna, I. *S* **1987**, *503*.
7. Flynn, D. L.; Mitscher, L. A.; Veysoglu, T.; Wielogorski, Z. *H* **1982**, *18*, 83.

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N,N-Dimethylacetamide Dimethyl Acetal[1]

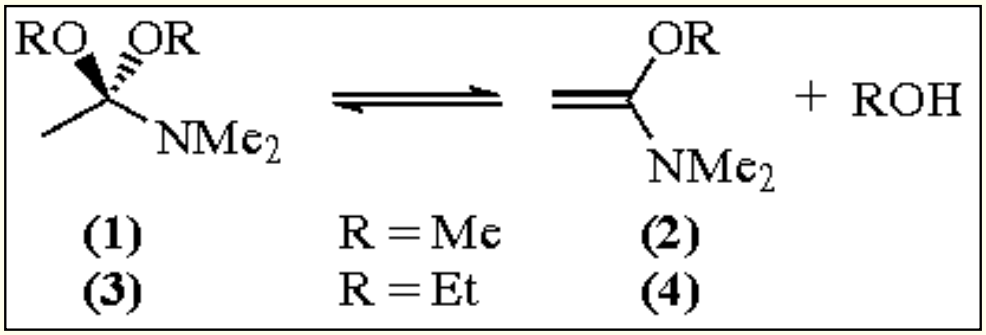

(**1**; R = Me)

[18871-66-4] · $C_6H_{15}NO_2$ · *N,N*-Dimethylacetamide Dimethyl Acetal · (MW 133.19) (**2**; R = Me)

[867-89-0] · $C_5H_{11}NO$ · *N,N*-Dimethylacetamide Dimethyl Acetal · (MW 101.15) (**3**; R = Et)

[19429-85-7] · $C_8H_{19}NO_2$ · *N,N*-Dimethylacetamide Diethyl Acetal · (MW 161.24) (**4**; R = Et)

[816-65-9] · $C_6H_{13}NO$ · *N,N*-Dimethylacetamide Dimethyl Acetal · (MW 115.17)

(Eschenmoser-Claisen rearrangements;[2] monoacylation of diols;[3] triazine synthesis[4])

Physical Data: mixture of (**1**) and (**2**) bp 105-110 °C; *d* 0.911 g cm^{-3}. Mixture of (**3**) and (**4**) bp 126-129 °C. (**2**) bp 104-105 °C. (**4**) bp 126 °C.

Solubility: sol benzene, toluene, xylene, DMF, chloroform.

Form Supplied in: amide acetal (**1**) is commercially available, usually as a mixture of (**1**) and (**2**). The commercial mixture is 85-95% pure; methanol (5-10%) may be present as a stabilizer.

Preparative Methods: O-methylation of *N,N*-dimethylacetamide with ***Dimethyl Sulfate*** (or diethyl sulfate), followed by reaction with ***Sodium Methoxide*** (or ethoxide). Fractional distillation affords mixtures of (**1**) and (**2**) (or **3** and **4**). Treatment with calcium metal and redistillation gives the ketene *O,N*-acetals (**2**) (58%) (or **4**; 74%).[5]

Introduction.

Amide acetal reagent (**1**) is in equilibrium with its enamine (eq 1).[5] The stabilized carbenium ion, which is an intermediate in this equilibrium, adds to nucleophiles under neutral conditions.

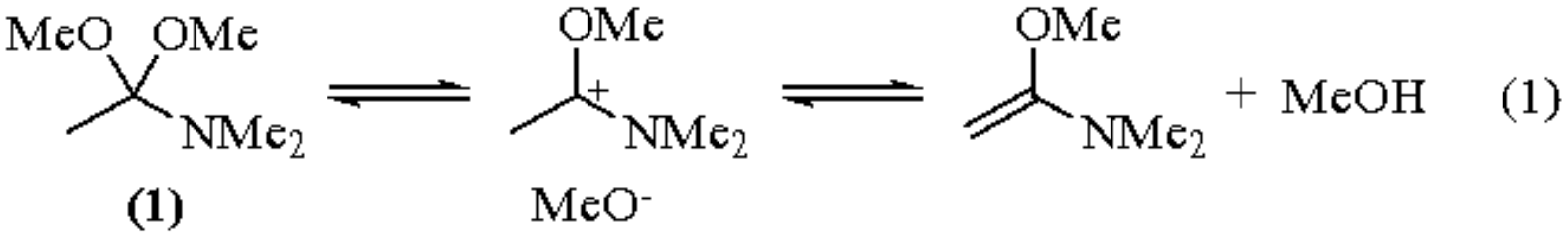

Eschenmoser-Claisen Rearrangement.

Condensation of (**1**) with allylic alcohols followed by loss of a second equivalent of methanol gives ketene *N,O*-acetals, which undergo 3,3-sigmatropic rearrangement to afford γ,δ-unsaturated amides (eq 2).

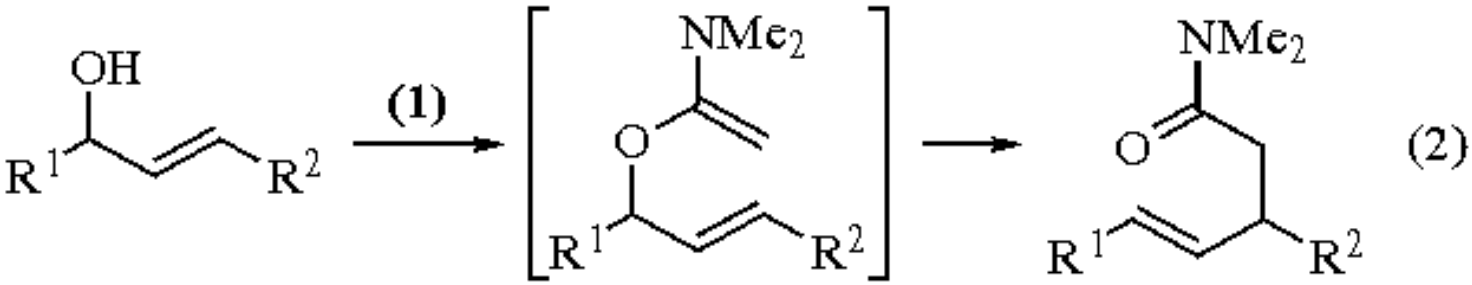

In a general procedure, the allylic alcohol and dimethylacetamide dimethyl acetal are heated at reflux in a high boiling solvent such as xylene or DMF with simultaneous distillation of methanol. Other suitable solvents include diglyme, dioxane, toluene, and benzene. Several papers indicate that the Eschenmoser-Claisen reaction proceeds at lower temperatures with higher yields and shorter reaction times than the classical Claisen and the orthoester Claisen rearrangements.[6] However, it suffers the disadvantage that the product is a disubstituted amide, a functional group which is not always easily converted to other groups.[7] Several examples of transformations of disubstituted amides to other functional groups are included in the discussion below.

Eschenmoser and co-workers demonstrated that the amide acetal rearrangement of cyclohexenols is stereospecific, i.e. the *cis*-4-substituted cyclohexenol gives a single stereoisomer of the cyclohexeneacetamide product (eq 3), whereas the *trans*-cyclohexenol affords its stereoisomer (eq 4).[8]

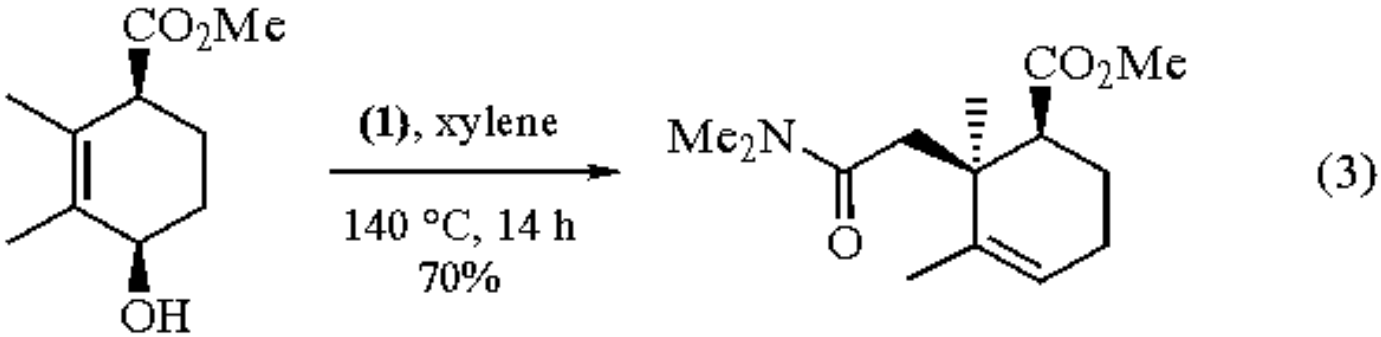

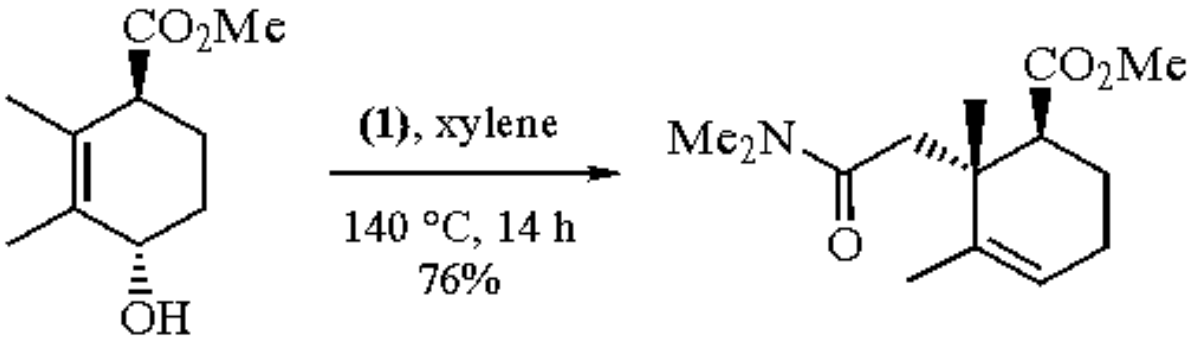

(4)

Benzyl alcohols rearrange to *o*-methylbenzeneacetamides (eq 5).

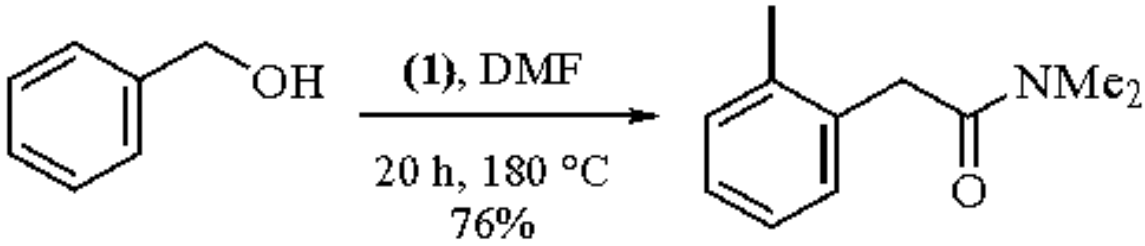

(5)

The amide acetal rearrangement, like the Claisen rearrangement, generally proceeds through a chairlike transition state with all substituents in equatorial positions, an arrangement which leads to *trans* geometry of the double bond in the product and chirality transfer (eq 6).[9]

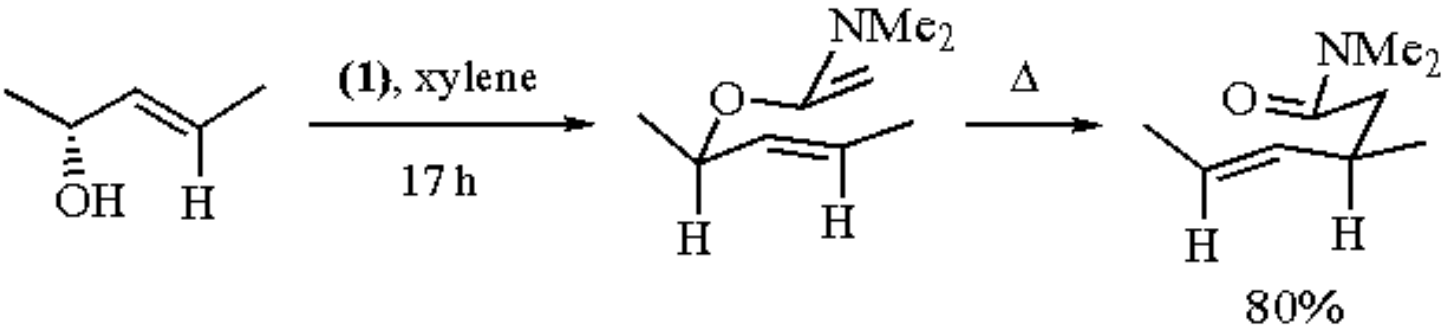

(6)

The products of the Eschenmoser-Claisen rearrangement with 3-(trimethylsilyl)allyl alcohols (eq 7) undergo protonolysis and desilylation with ***Hydrogen Fluoride*** to give β,γ-unsaturated amides which can be converted into the corresponding esters.[10]

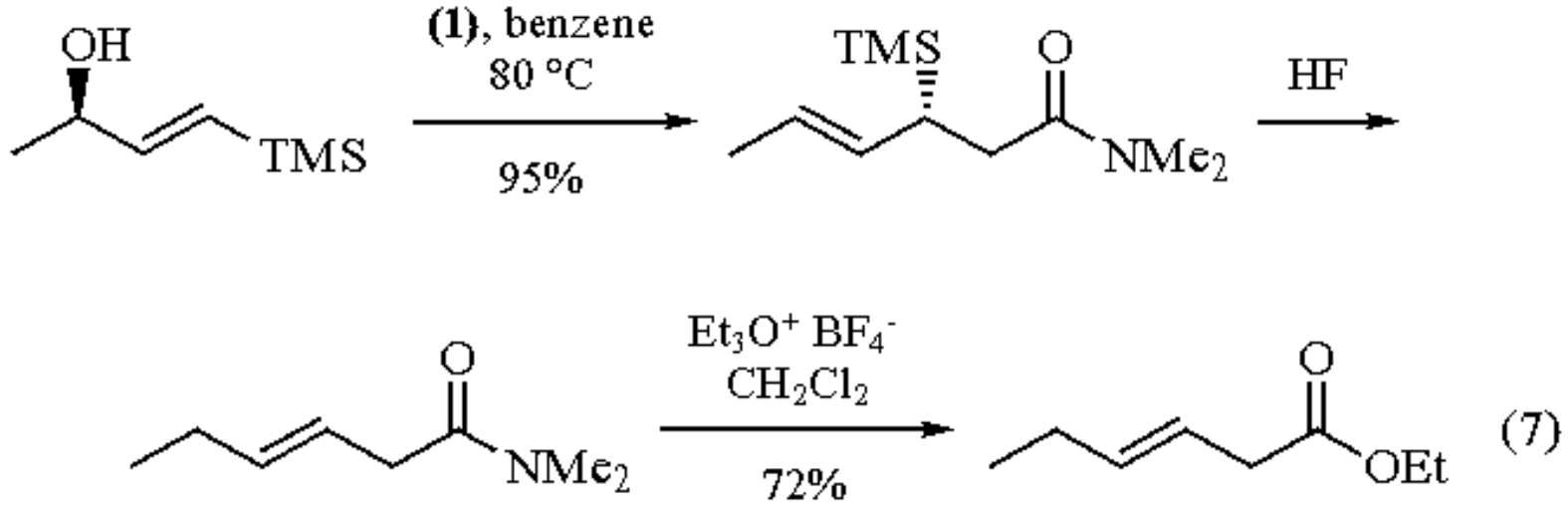

The Eschenmoser-Claisen method was used for the rearrangement of an allyl alcohol bearing two organometallic groups because of its nearly neutral conditions (eq 8). The product, obtained in 74% yield with 90% chirality transfer, was reduced with ***Lithium Triethylborohydride*** to the primary homoallylic alcohol.[11]

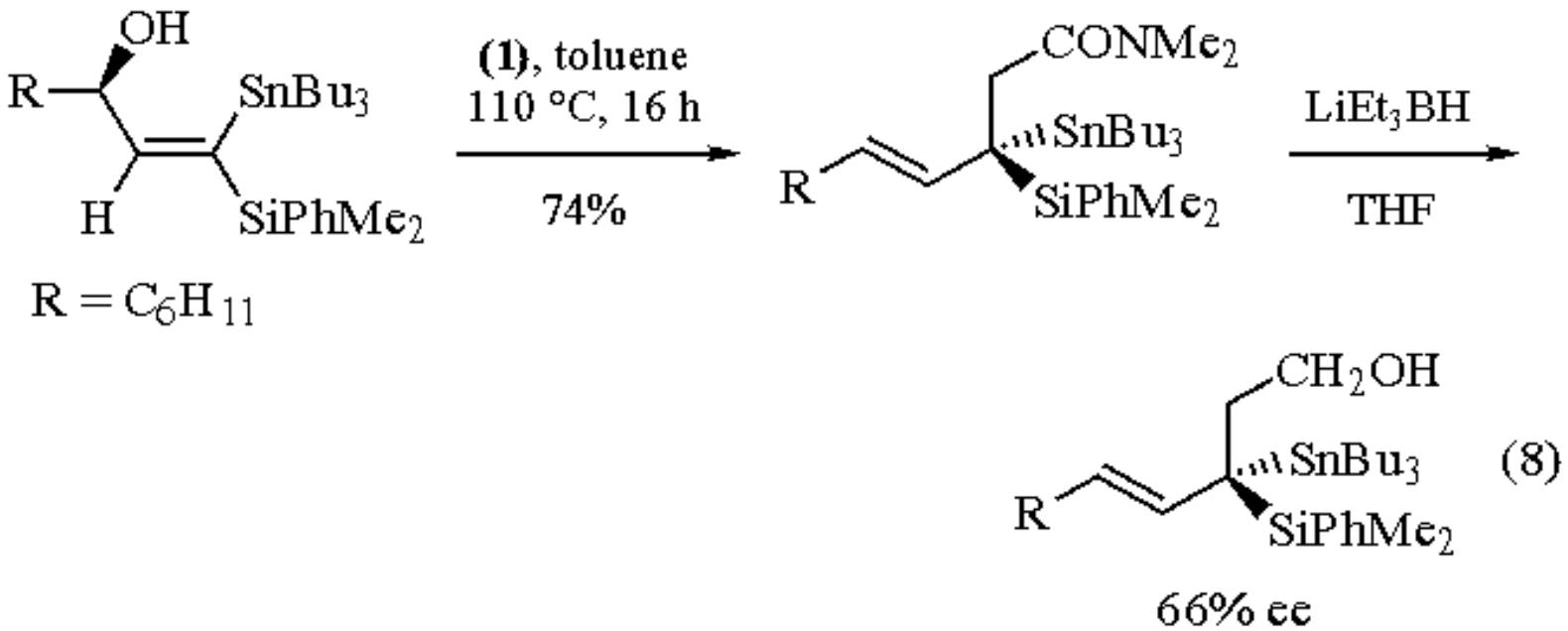

Parker and co-workers found that terminal propargyl alcohols condense with dimethylacetamide diethyl acetal (**3**) to form an intermediate which undergoes amine migration. This enamine subsequently rearranges through an orthoester Claisen rearrangement (eq 9).[12] A side product is the enol ether, which is formed from the enol derived from the enamine. Hydrolysis of the products gives a γ-keto ester.

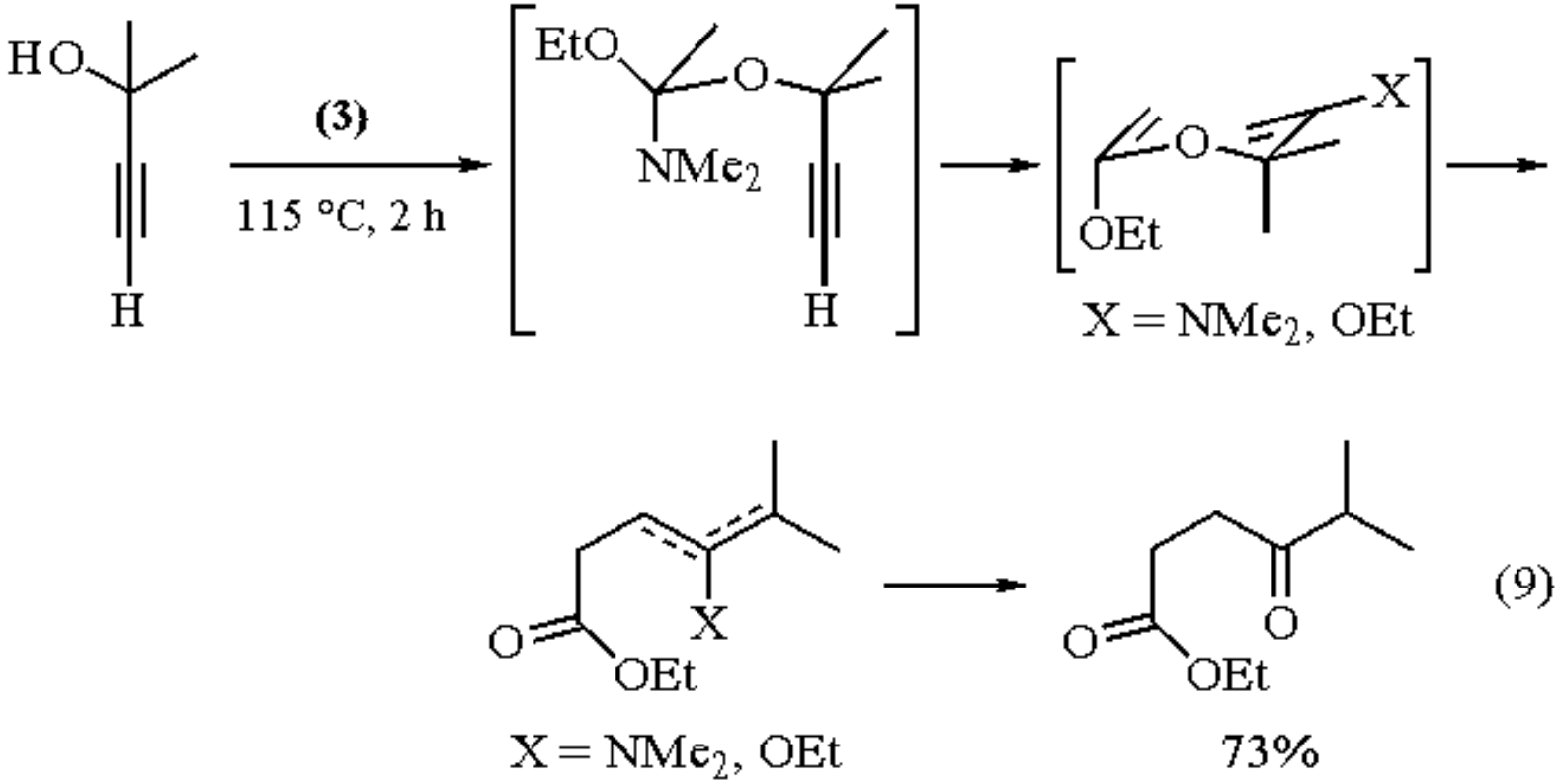

(9)

Substituted propargyl alcohols undergo the simple Claisen-type rearrangement to give allenic amides (eq 10).

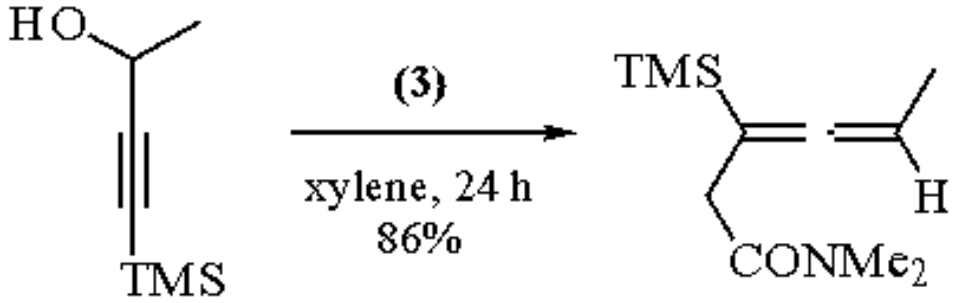

(10)

Amide acetal Claisen rearrangements have been used in the synthesis of *C*-glycopyranosides,[6] pyranosides,[13] sugars,[14,15] and indole alkaloids.[7,16] In Corey's synthesis of thromboxane B_2, an amide product is transformed to a lactone by iodolactonization followed by deiodination with ***Tri-n-butylstannane*** (eq 11).[14]

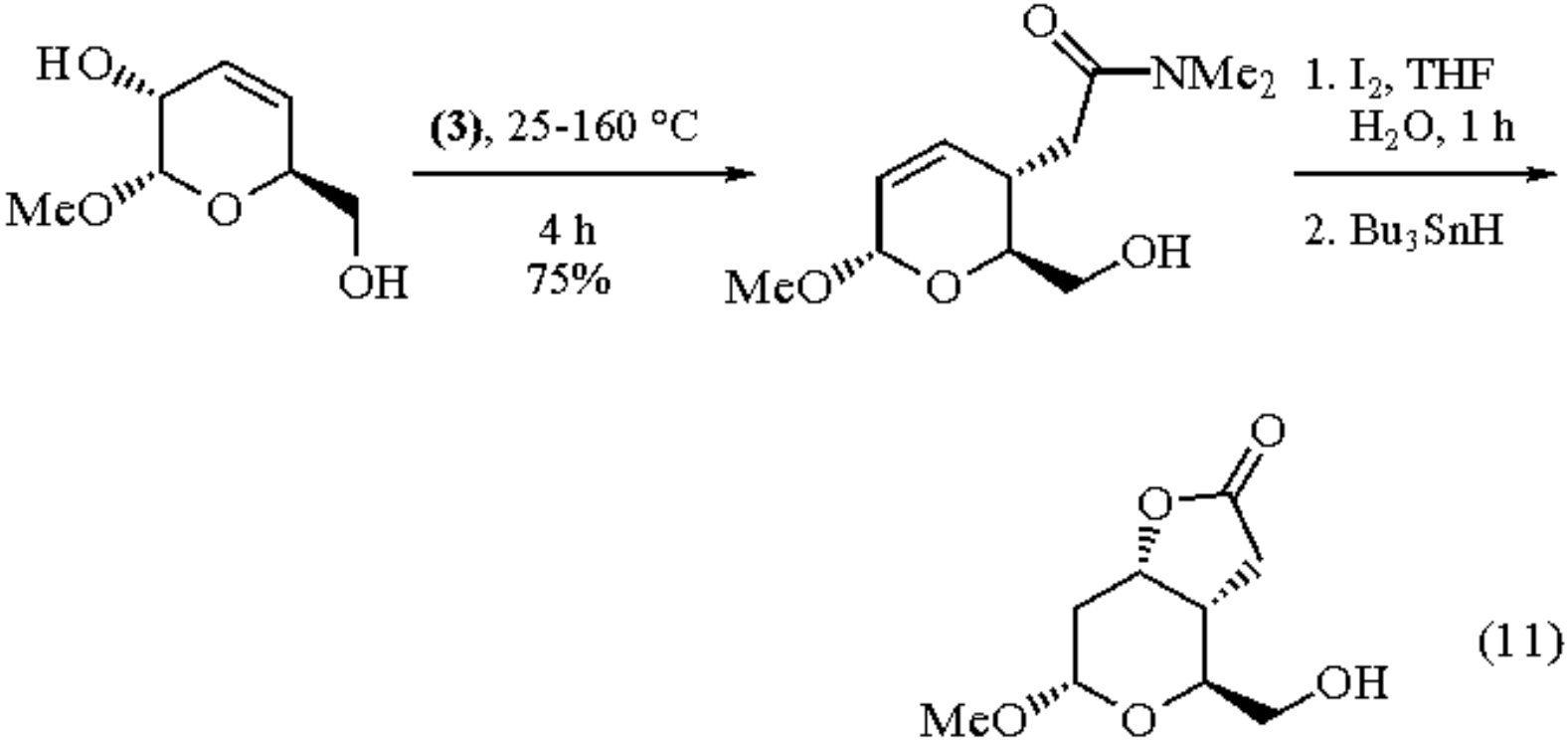

(11)

Monoacylation of Diols.

Vicinal diols form (dimethylamino)ethylidene acetals, which can be cleaved with aqueous acetic acid to give monoacylated products.[3] In unsymmetrical diols, the less hindered hydroxy group is selectively protected. For example, with this method 1,2-*O*-isopropylidene-α-D-glucofuranose is selectively acylated at the C-6 hydroxy group.

Heterocycle Synthesis.

N,*N*-Dimethylaminomethylenehydrazones are formed by addition of this reagent to α-ketohydrazones.[4] Subsequent heating with ammonium acetate in acetic acid causes cyclization to give 1,2,4-triazines (eq 12).

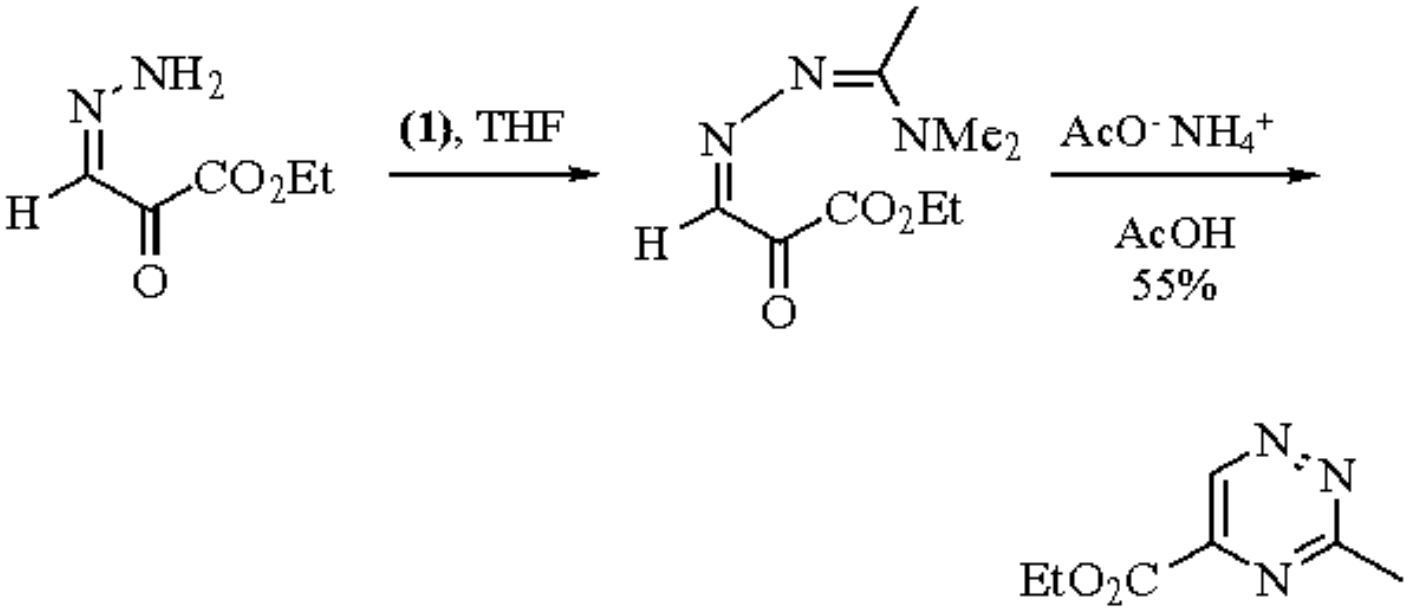

(12)

1,2,4-Triazoles and 1,2,4-oxadiazoles can be synthesized in high yields in a two-step procedure with this reagent. First the dimethyl acetal condenses with an amide to give an *N*-acylamidine. Subsequently, reaction with acetic acid and hydrazine gives triazoles, whereas addition of hydroxylamines gives oxadiazoles (eq 13).[17]

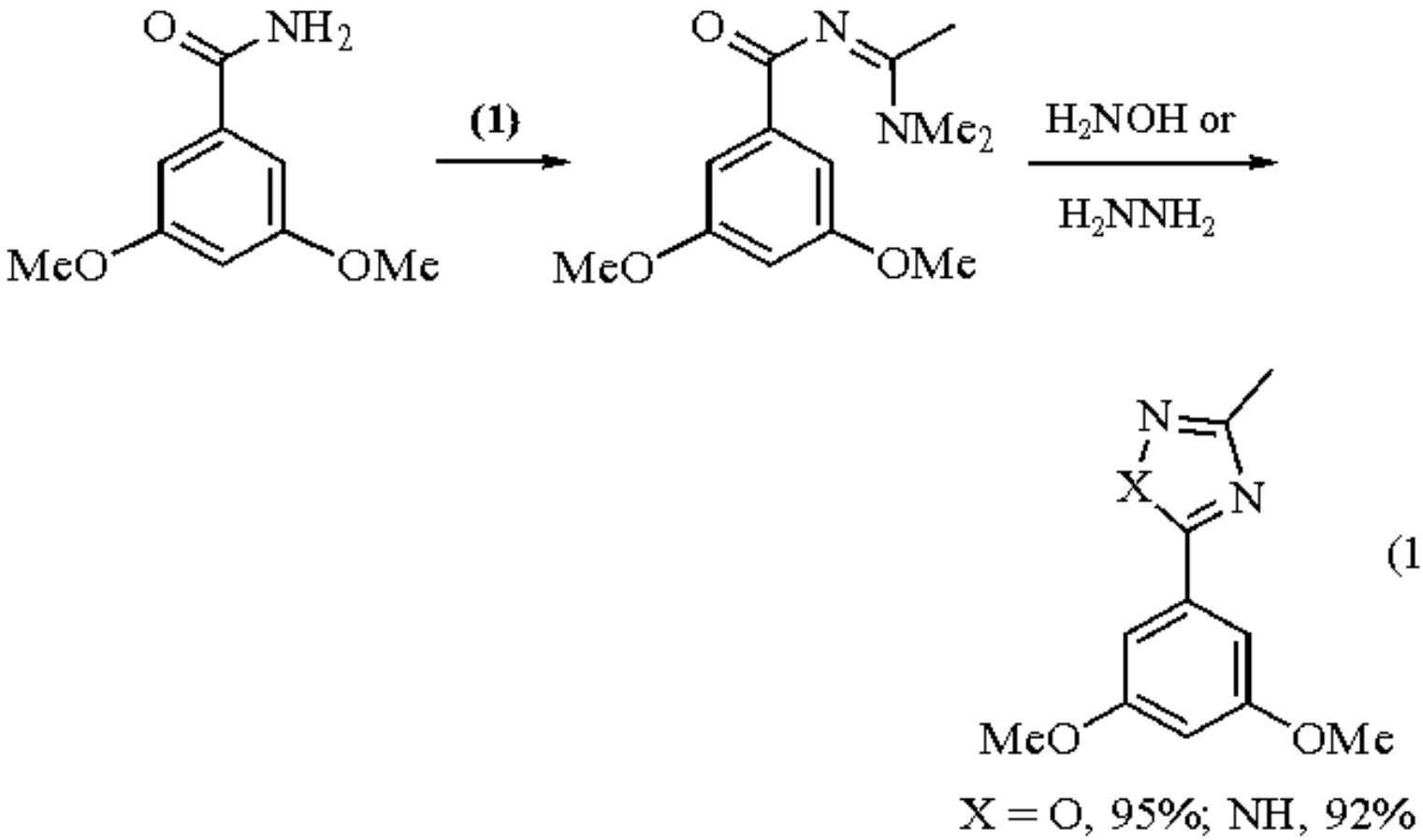

(13)

Another method for the synthesis of 1,2,4-oxadiazoles is condensation of the amide acetal with an amidoxime (eq 14).[18] Fused amino pyridines have been formed through the cyclocondensation of an amide acetal with an amino ketone.[19]

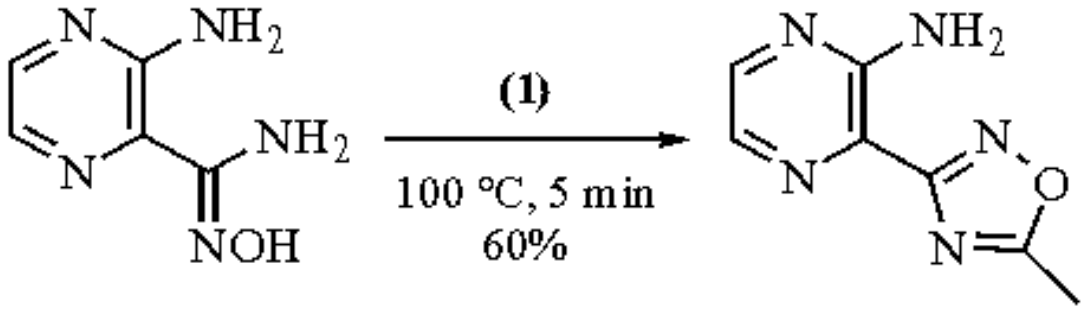

(14)

Related Reagents.

Diketene; ***N,N-Dimethylformamide Diethyl Acetal***; ***N,N-Dimethylpropionamide Dimethyl Acetal***; ***Dimethyl Sulfate***; ***Ethyl 3,3-Diethoxyacrylate***; ***Ethyl Vinyl Ether***; ***2-Methoxy-1,3-butadiene***; ***Triethyl Orthoacetate***.

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Kathlyn A. Parker & Lynn Resnick

Dimethyl 1,3-Acetonedicarboxylate[1]

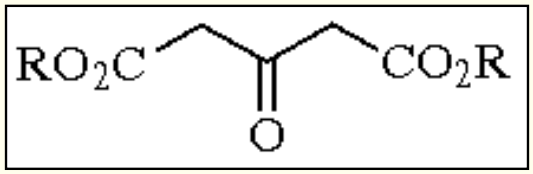

(**1**; R = Me)

[1830-54-2] · $C_7H_{10}O_5$ · Dimethyl 1,3-Acetonedicarboxylate · (MW 174.15) (**2**; R = Et)

[105-50-0] · $C_9H_{14}O_5$ · Diethyl 1,3-Acetonedicarboxylate · (MW 202.21) (**3**; R = H)

[542-05-2] · $C_5H_6O_5$ · 1,3-Acetonedicarboxylic Acid · (MW 146.10)

(acidic β-keto esters, which undergo 2:1 condensations with α-dicarbonyl compounds to form bicyclo[3.3.0]octane-3,7-diones;[1-6] Robinson-Schöpf condensation to form piperidones;[7] α,α- and α,α´-dialkylation with 1,*n*-dibromoalkanes; aldol and Claisen condensations with 1,3-dicarbonyl compounds;[13] various heterocyclizations with nitriles and aldehydes;[16] α,α´-aldol annulations with 1,2-enedials, producing tropone derivatives[20 -22])

Physical Data: (**1**) bp 150 °C/25 mmHg; *d* 1.185 g cm^{-3}. (**2**) bp 250 °C/760 mmHg; bp 140 °C/12 mmHg; *d* 1.113 g cm^{-3}. (**3**) decomposes upon heating.

Solubility: sol ethanol, methanol.

Form Supplied in: colorless liquid.

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: can be stored in the refrigerator. Does not appear to be toxic.

Dimethyl and diethyl 1,3-acetonedicarboxylates (**1** and **2**) have been extensively used in the Weiss-Cook condensation reaction with various 1,2-dicarbonyl compounds, either at acidic or alkaline pH to form *cis*-bicyclo[3.3.0]octane-3,7-dione derivatives, as well as [*n*.3.3]propellanes in a single step (eqs 1 -4).[1 -6] These tetraesters are isolated in the *anti* bisenol form. They have been employed in the synthesis of several natural and nonnatural products.[1,2]

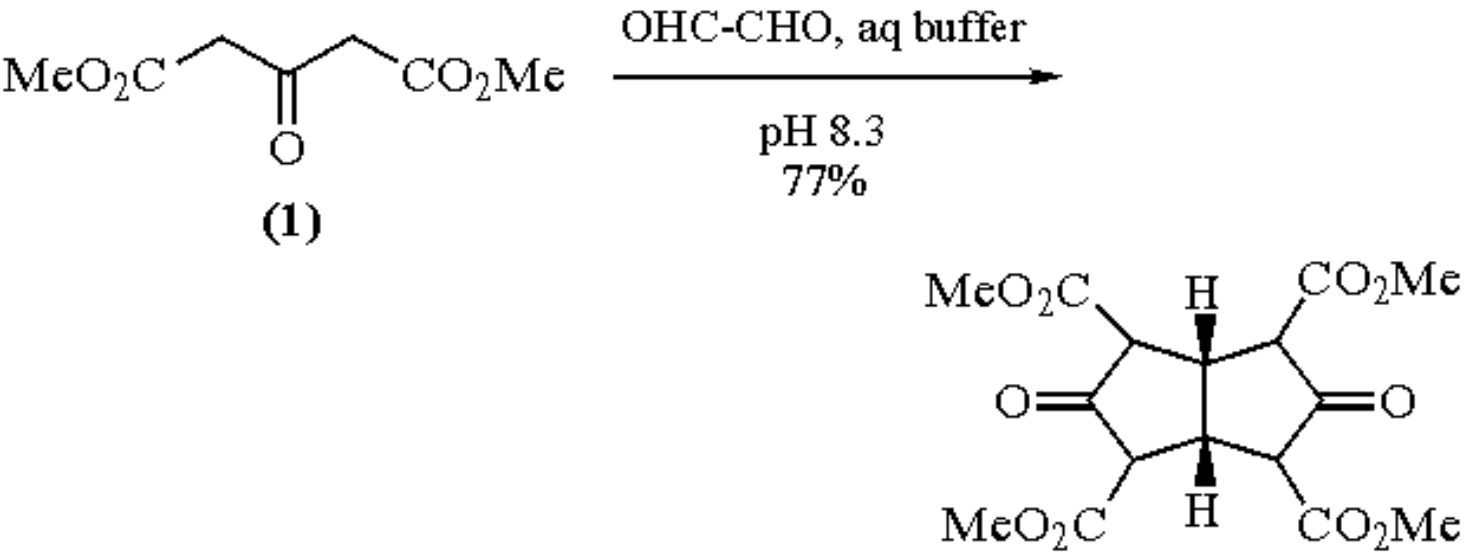
MeO2C
CO2Me
O
(1)
OHC-CHO, aq buffer
pH 8.3
77%
MeO2C
H
CO2Me
O
O
MeO2C
H
CO2Me
(1)

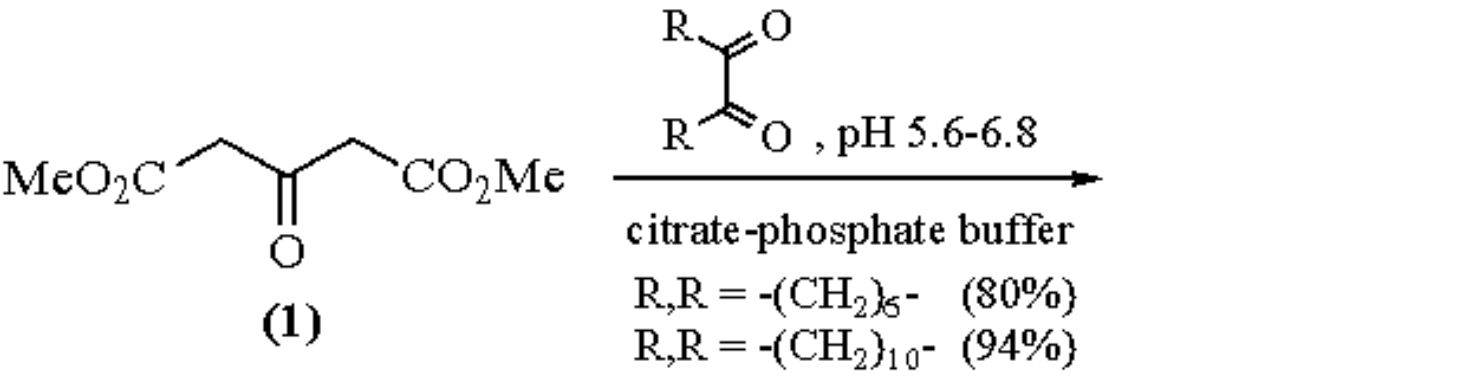
MeO2C
CO2Me
O
(1)
R
O
R
O
, pH 5.6-6.8
citrate-phosphate buffer
R,R = -(CH2)5- (80%)
R,R = -(CH2)10- (94%)
MeO2C
R
CO2Me
O
O
MeO2C
R
CO2Me
(2)

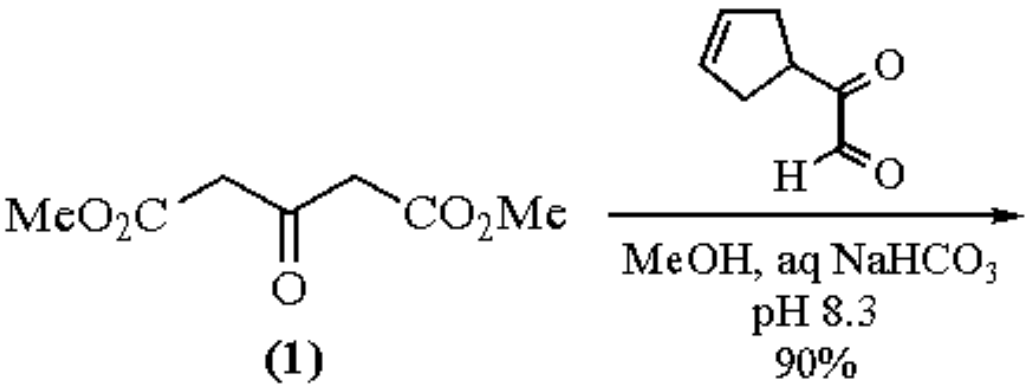

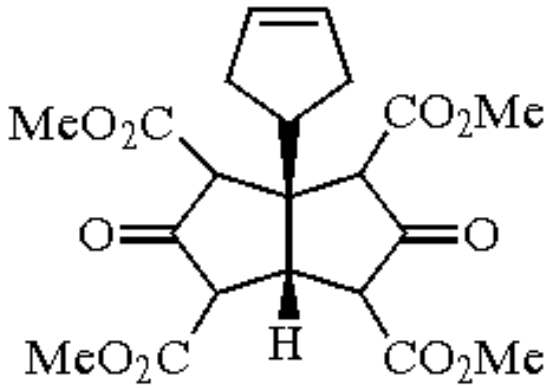

(3)

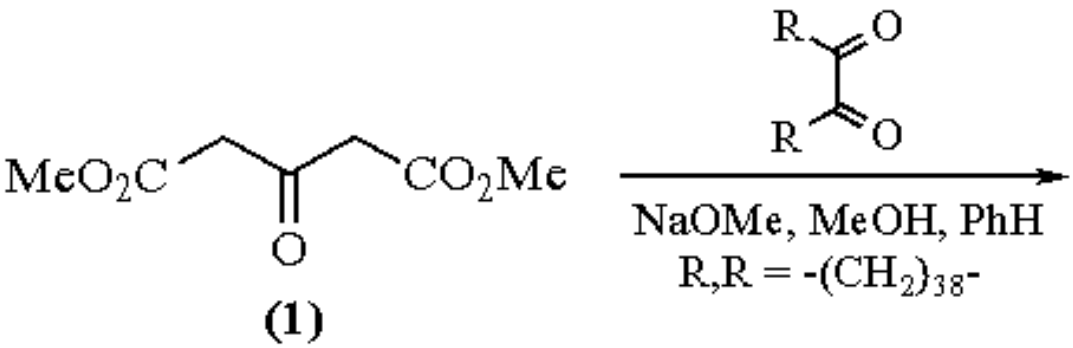

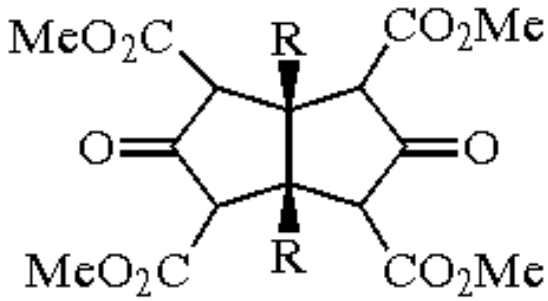

(4)

The diacid (**3**) undergoes the Robinson-Schöpf condensation with β-ethoxyglutaraldehyde and ammonium chloride to produce 7-ethoxy-9-azabicyclo[3.3.1]nonan-3-one (eq 5).[7]

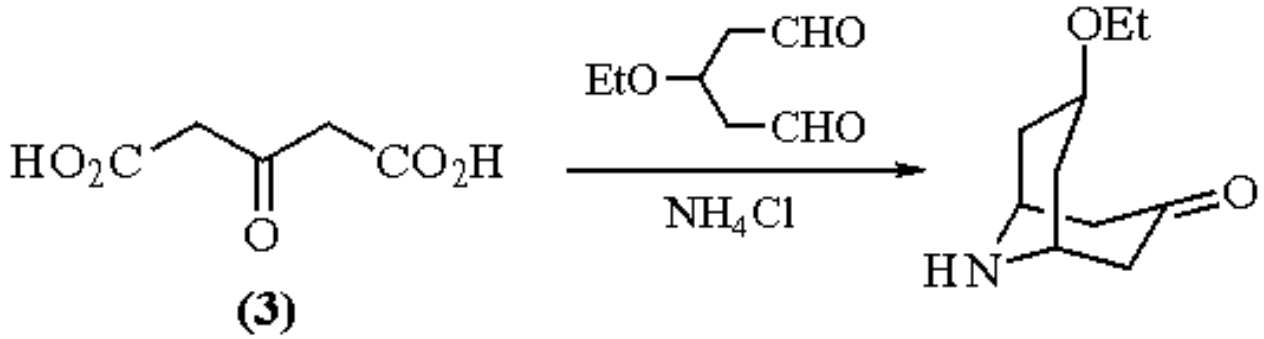

(5)

Dimethyl 1,3-acetonedicarboxylate (**1**), upon heating with acenaphthenequinone in the presence of glycine (catalyst) in norbornadiene as the solvent, affords dimethyl 7,10-fluoranthenedicarboxylate, a key intermediate in the synthesis of corannulene (eq 6).[8] Diethyl 1,3-acetonedicarboxylate (**2**) in the presence of ***Manganese(III) Acetate*** in acetic acid adds to the exocyclic enol lactone to provide an oxaspirolactone (eq 7).[9] Condensation of (**1**) (excess) with 1,3-cyclohexanedione in citrate phosphate buffer at pH 6.8 affords 5,6,7,8-tetrahydro-5-oxocoumarin-4-ylacetate (eq 8)[10] in good yield.

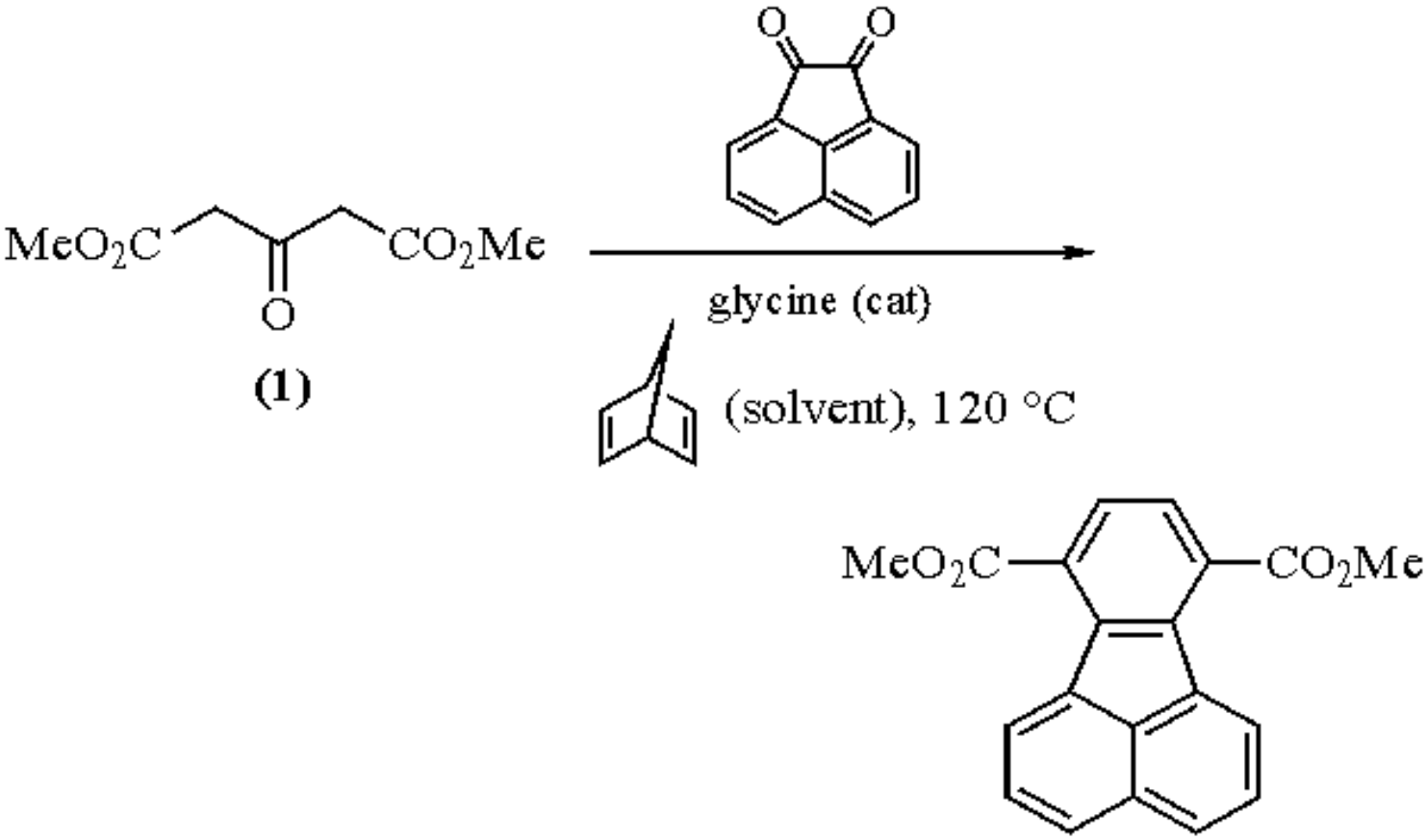

(6)

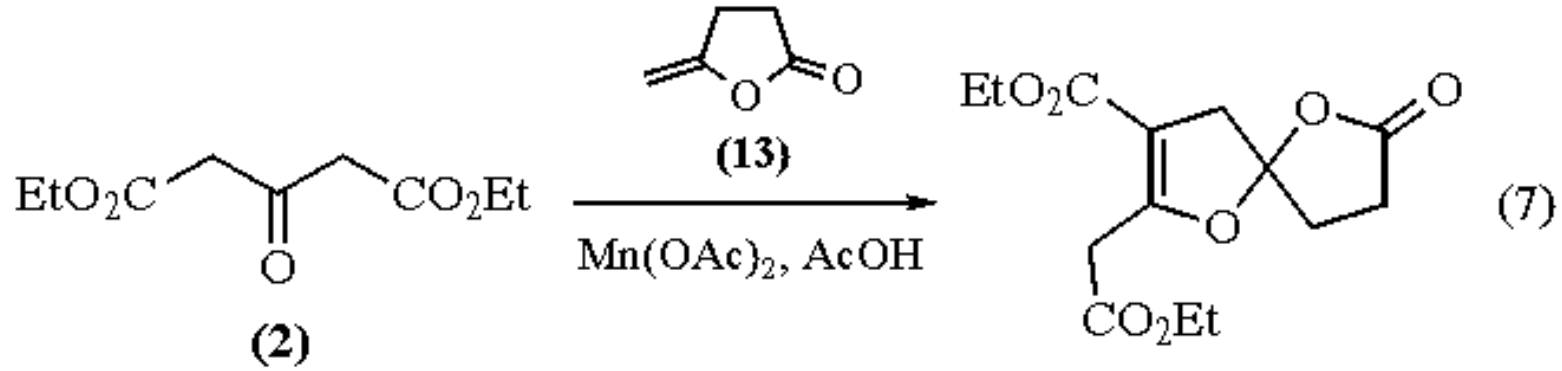

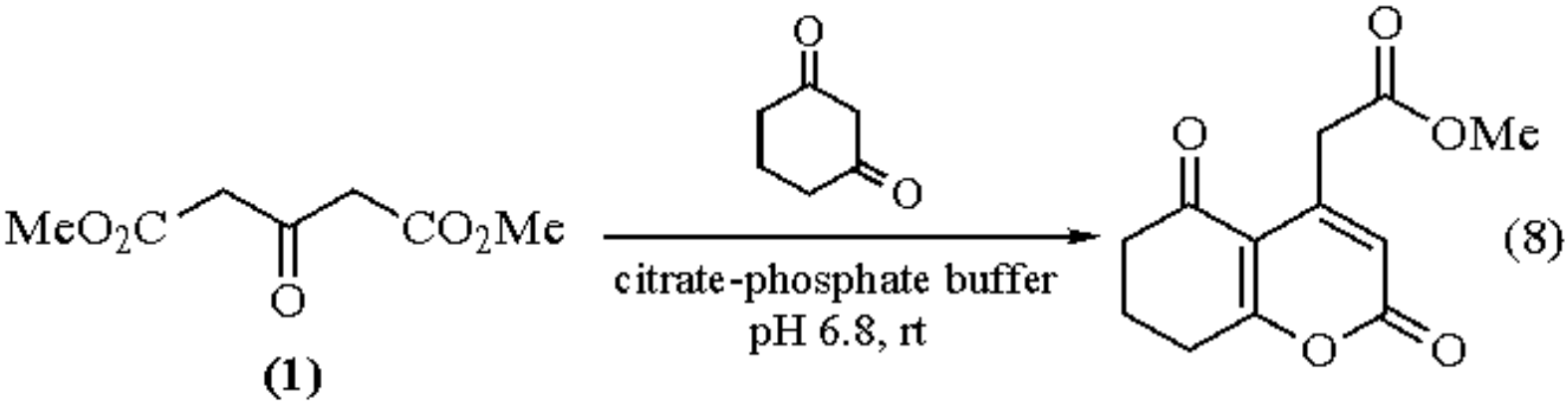

Alkylation of (**2**) with 1,3-dibromopropane and ***1,4-Dibromobutane***, individually, provides the cyclohexanone and cyclopentyl bis-esters, respectively (eqs 9 and 10).[11]

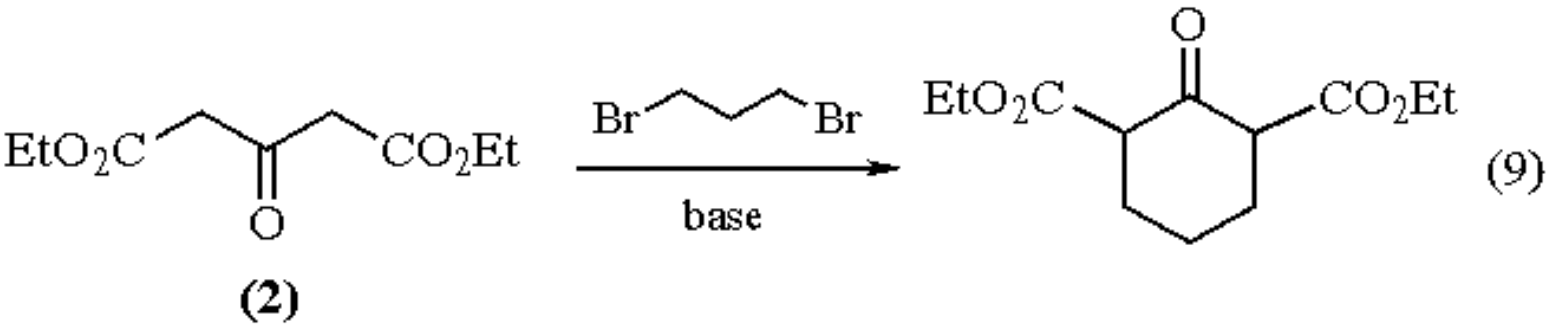

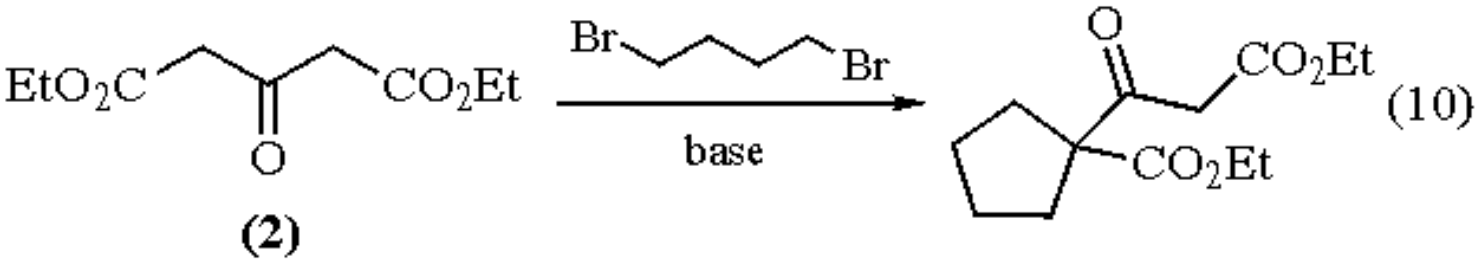

Reaction of (**1**) with α,α´-***Dibromo-o-xylene*** under phase-transfer conditions yields bicyclo[4.4.1]undecan-11-one (eq 11).[12] The related naphthyl derivatives have also been prepared.

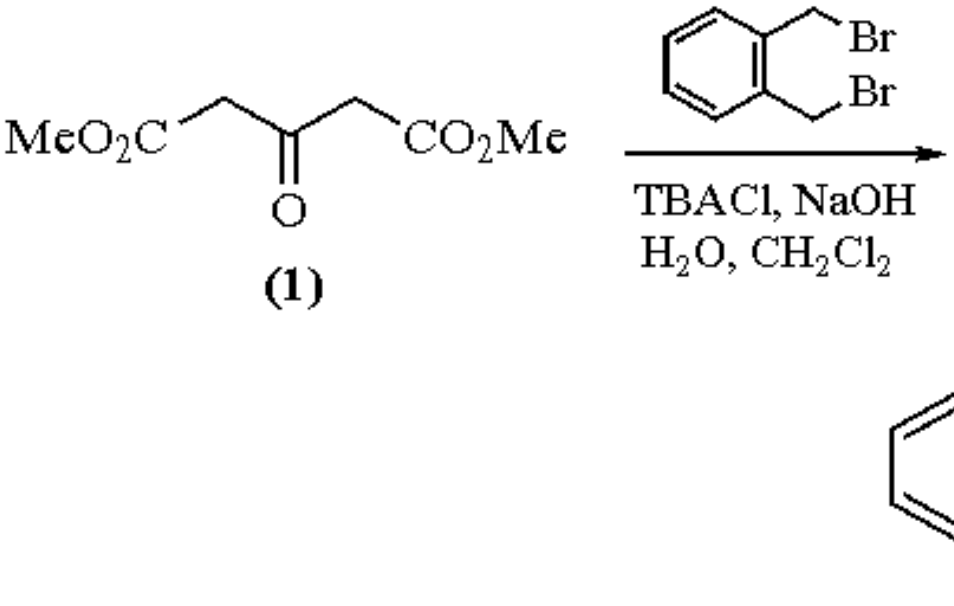

(11)

Condensation of (**2**) with ***Diethyl Malonate*** in the presence of ***Sodium Ethoxide*** gives diethyl 2,4,6-trihydroxybenzene-1,3-dicarboxylate (eq 12),[13] while condensation of either (**1**) or (**2**) with an aldehyde and an amine in a 1:2:1 ratio provides the corresponding piperidones (eq 13).[14]

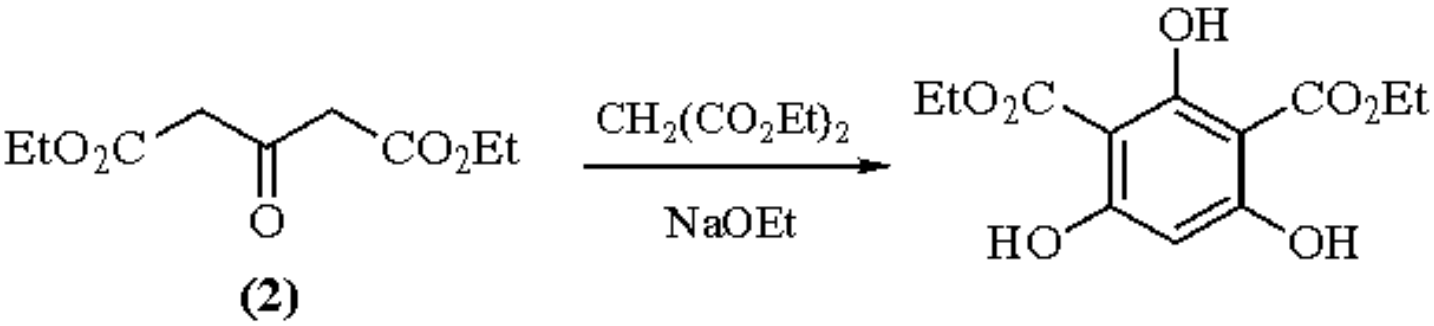

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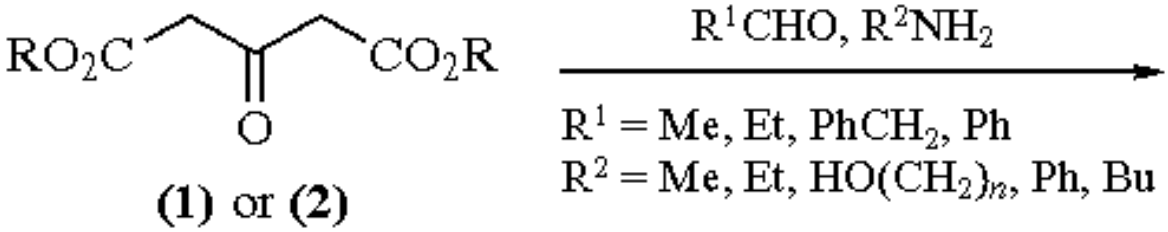

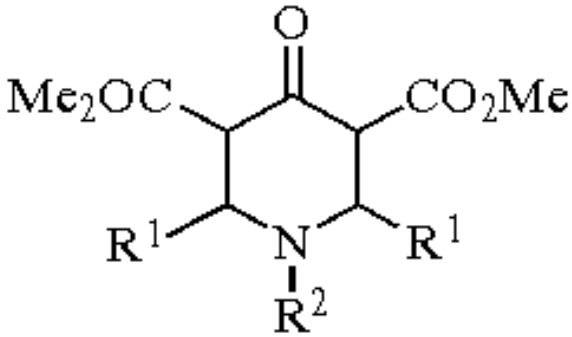

(13)

Condensation of (**3**) with 3,4-dihydro-β-carboline in aqueous methanol gives an amino acid intermediate which after esterification and treatment with aqueous ammonia cyclizes to the keto lactam illustrated in eq 14.[15]

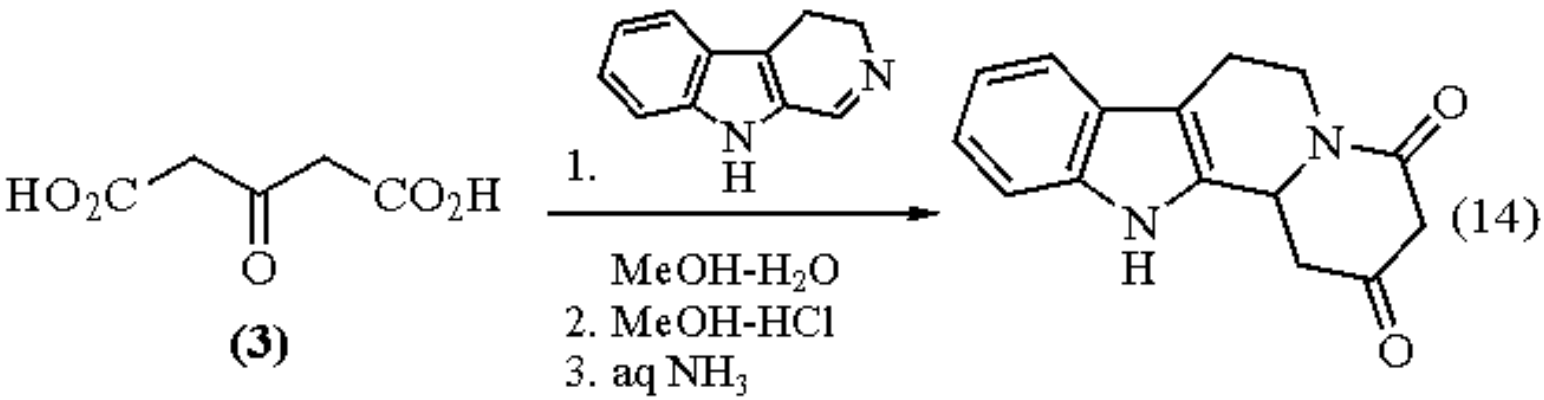

Reaction of (**1**) with trifluoroacetonitrile in the presence of ***Potassium t-Butoxide*** in THF produces methyl 4,6-dihydroxy-2-trifluoromethyl-3-pyridinecarboxylate (eq 15).[16]

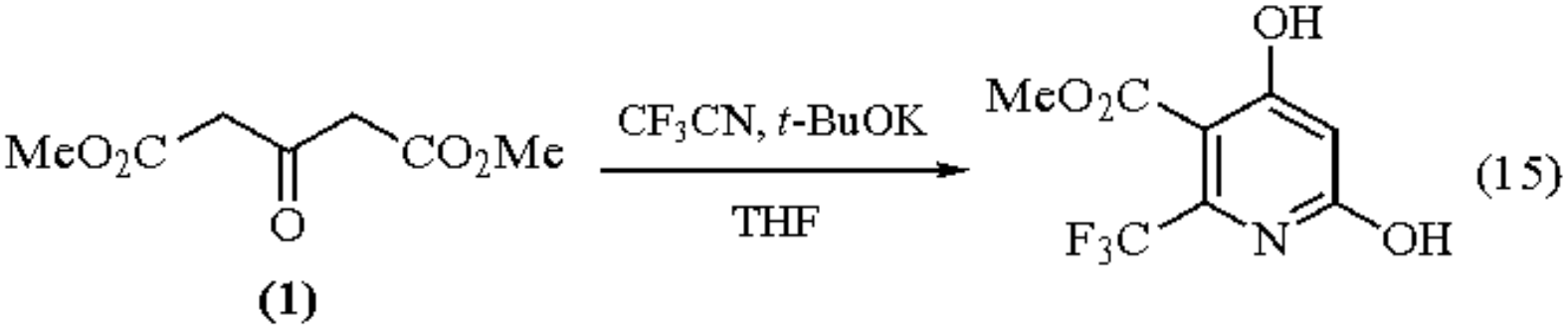

Reaction of (**2**) with ***Malononitrile*** and ***Sulfur*** in the presence of diethylamine as a catalyst affords ethyl 2-amino-3-cyano-5-(ethoxycarbonyl)thiophene-4-acetate (eq 16).[17] Diester (**1**) undergoes condensation with salicylaldehyde derivatives in the presence of piperidine to form the corresponding bis-coumarins represented in eq 17.[18] Condensation of (**2**) with *N*-methylaminoacetaldehyde at pH 9-10 produces ethyl 3-(ethoxycarbonyl)-1-methylpyrrole-2-acetate and 3-(ethoxycarbonyl)-1-methylpyrrole-2-acetic acid (eq 18).[19]

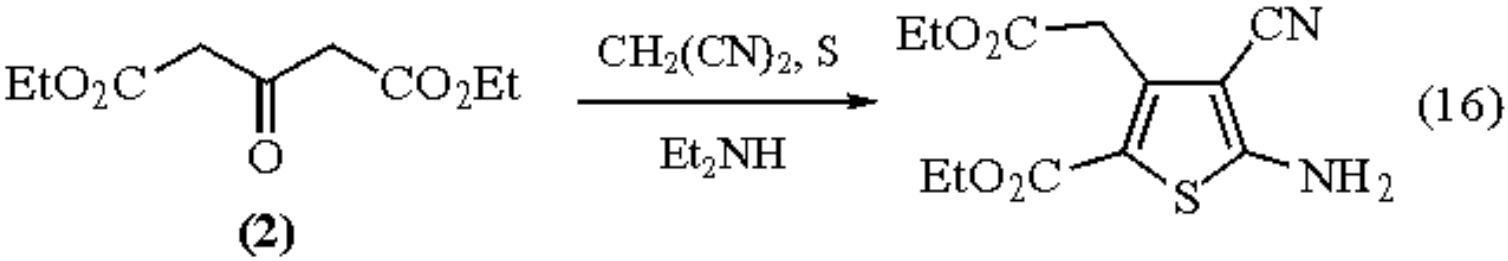

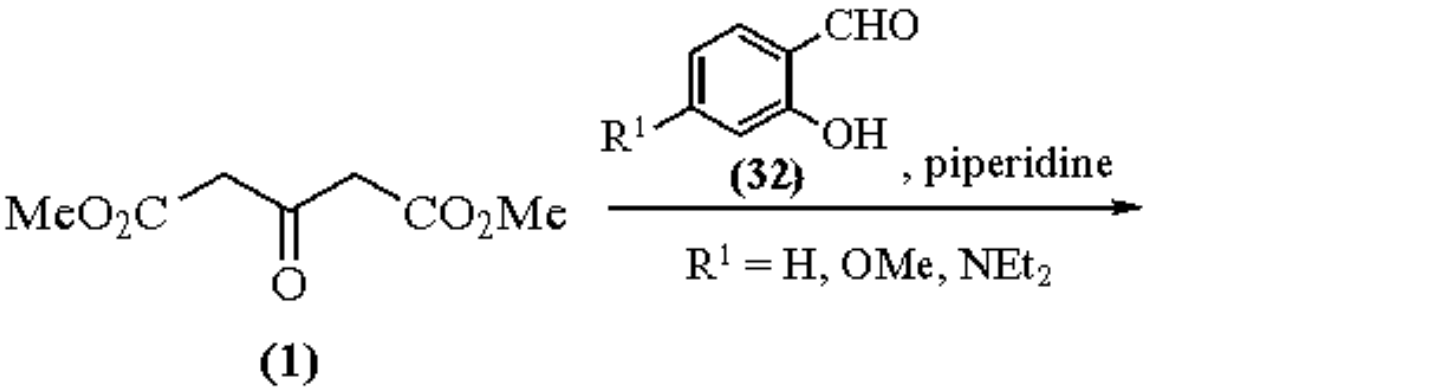

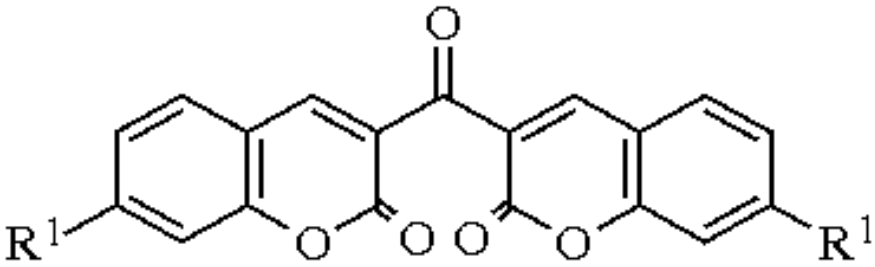

(17)

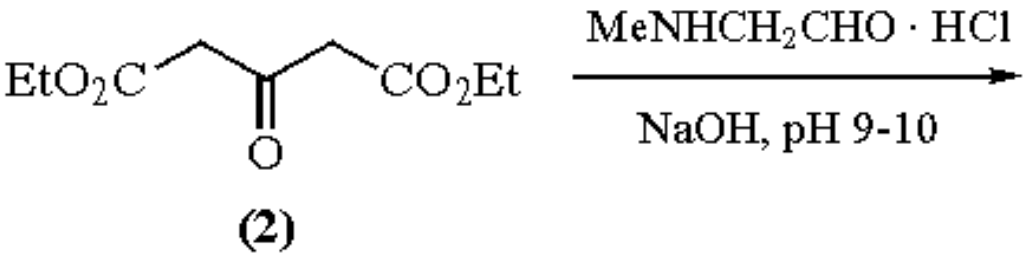

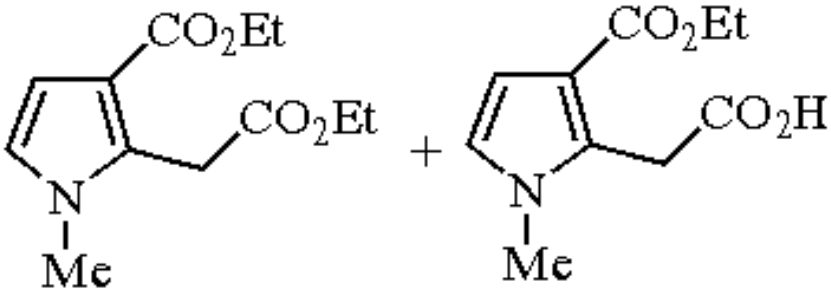

(18)

Diester (**1**) undergoes condensation with pyrrole-, *N*-methylindole- and 2,3-indenedicarbaldehydes to provide tropone derivatives (eqs 19-21).[20-22]

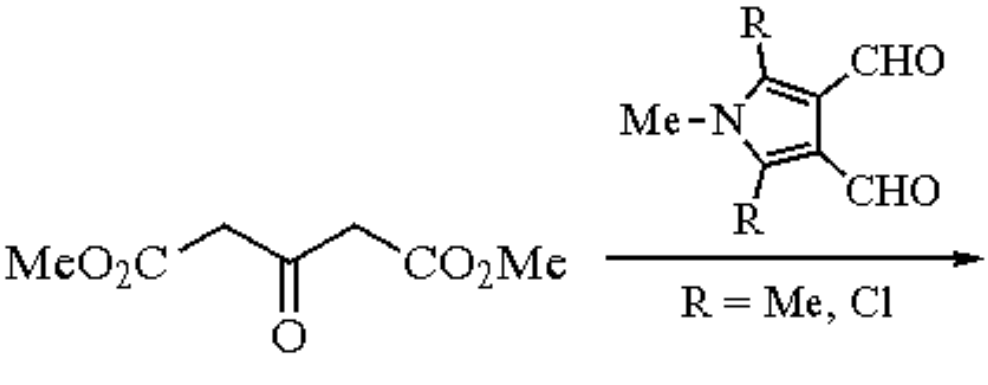
R
CHO
Me-N
CHO
R
MeO2C
CO2Me
O
R = Me, Cl

(1)

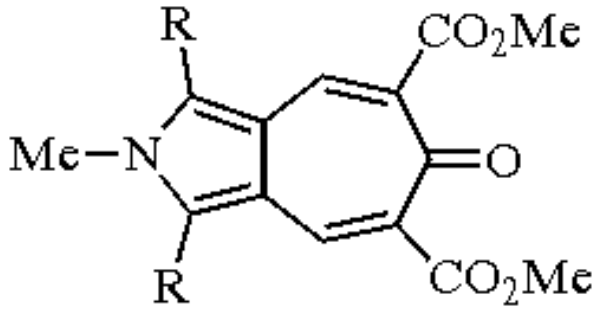
R
CO2Me
Me-N
O
R
CO2Me

(19)

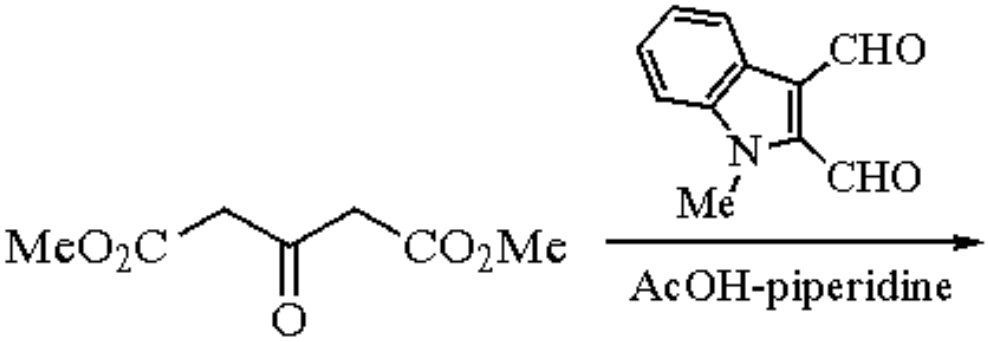
CHO
N
CHO
Me
MeO2C
CO2Me
O
AcOH-piperidine

(1)

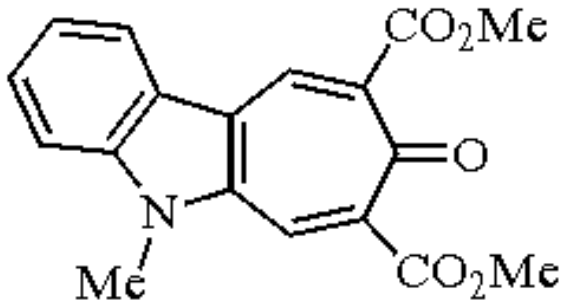
CO2Me
O
N
Me
CO2Me

(20)

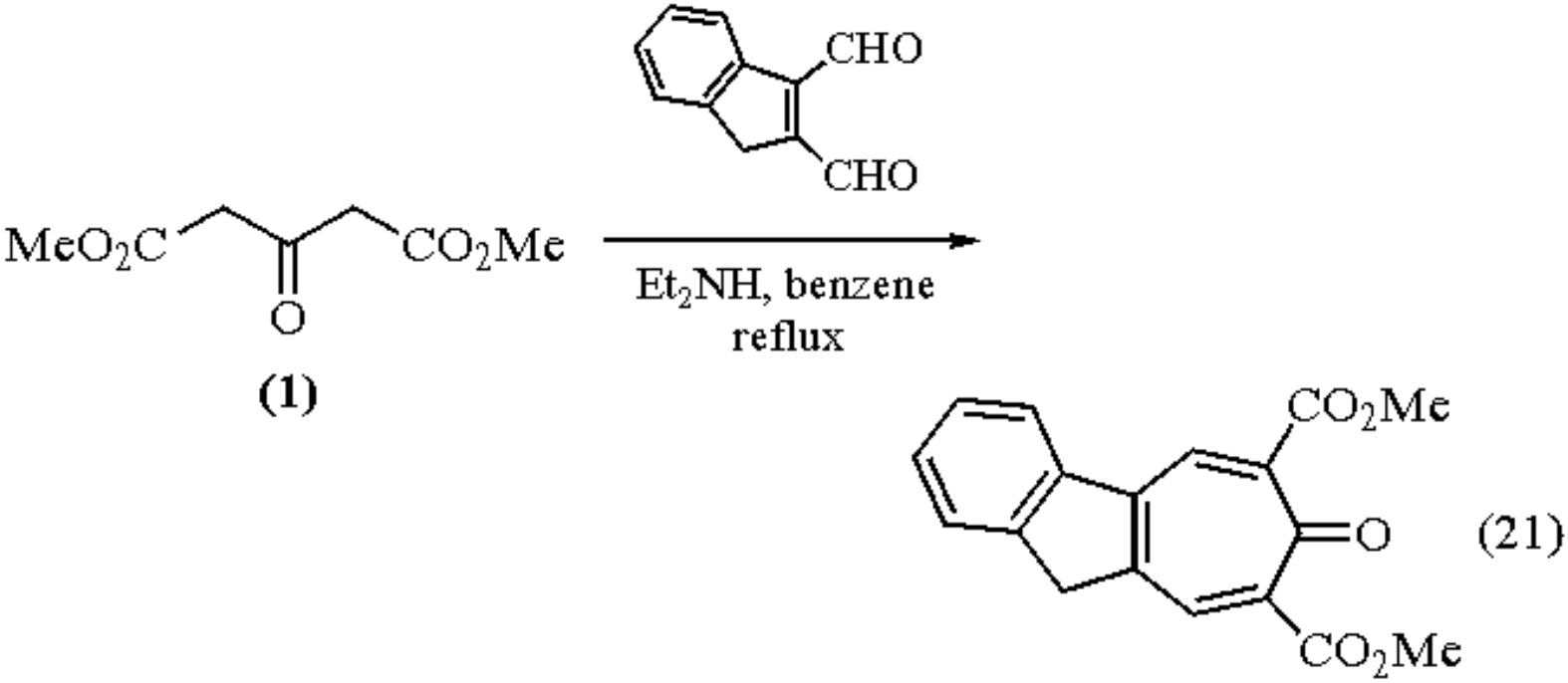

Reaction of (**1**) with activated ***Zinc*** in the presence of aniline in acetic acid affords the corresponding secondary amine depicted in eq 22.[23]

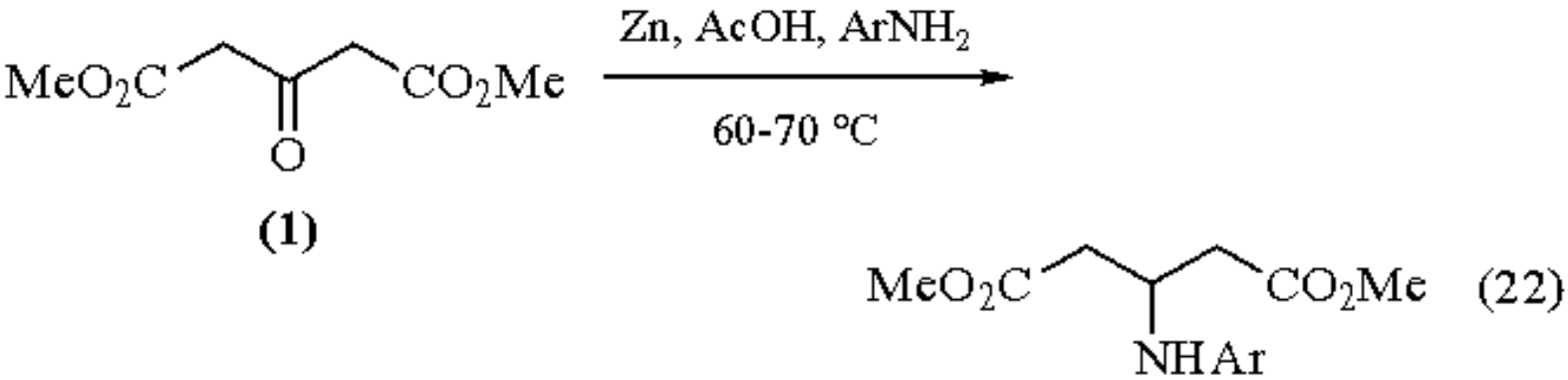

Related Reagents.

Acetoacetic Acid; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***Ethyl Acetoacetate***; ***Methyl Dilithioacetoacetate***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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Dimethyl Acetylenedicarboxylate

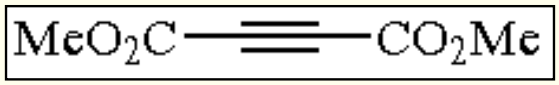

[762-42-5] · $C_6H_6O_4$ · Dimethyl Acetylenedicarboxylate · (MW 142.11)

(an electron deficient symmetrical alkynic diester useful as a dienophile and dipolarophile in cycloaddition reactions;[1] can undergo [2 + 2] cycloaddition;[2] Michael acceptor;[3] synthesis of phthalic acid derivatives[4] and heteroaromatics[5])

Alternate Name: DMAD.

Physical Data: bp 195-198 °C; bp 98 °C/20 mmHg; *d* 1.1564 g cm^{-3}.

Solubility: sol common organic solvents, e.g. diethyl ether, ethyl alcohol, carbon tetrachloride.

Form Supplied in: commercially available liquid.

Handling, Storage, and Precautions: lachrymator and vesicant; avoid inhalation and contact with skin or eyes. Use in a fume hood.

As a Dienophile in the Diels-Alder Cycloaddition.

DMAD is a ubiquitous dienophile capable of facile cycloadditions with a wide variety of dienes. Much effort has been devoted to the development of dienes which retain additional functionality in the Diels-Alder adduct. New dienes are often reacted with DMAD in order to test their efficacy as a diene in the Diels-Alder reaction.[6] DMAD is a liquid with a high boiling point and can be used as the Diels-Alder solvent. The number of possible stereoisomers is limited. Due to the symmetry of DMAD there are no regio or *endo*/*exo* isomers with respect to the dienophile. For this reason, DMAD is not useful for determining any regioselective biases of a diene. The triple bond gives rise to a double bond in which the product methyl esters are necessarily *cis*. A maximum of two stereoisomers are possible only if the two faces of the diene are either electronically[7] or sterically[8] nonequivalent, otherwise one isomer is produced. The two esters make the triple bond electron poor, and therefore well suited for normal electron demand Diels-Alder cycloadditions. A comparison of relative Diels-Alder reaction rates of common dienophiles, including DMAD, has been performed.[9]

Diels-Alder adducts from DMAD are 1,4-cyclohexadienes, which are prone to aromatization. In fact, the Diels-Alder/aromatization sequence constitutes a powerful protocol for the synthesis of phthalate derivatives (see below). Aromatization is facile when loss of a small molecule is possible. In many cases a benzenoid compound, not the initial Diels-Alder adduct, is directly isolated. Loss of an alcohol is common (eq 1).[10]

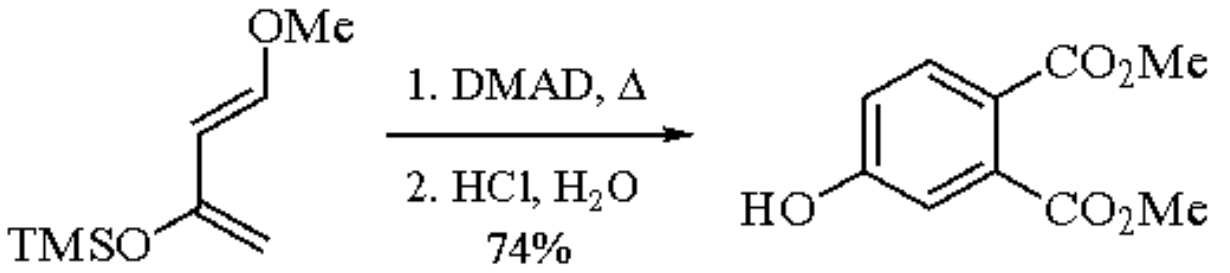

(1)

If loss of a small molecule is not possible, the diene adduct can be treated with oxidizing agents such as ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone***.[11] In the case of cyclic dienes, the initial adduct can undergo a retro-Diels-Alder reaction, extruding carbon dioxide,[12] carbon monoxide,[13] or ethylene[14] to produce aromatic products (eqs 2-4).

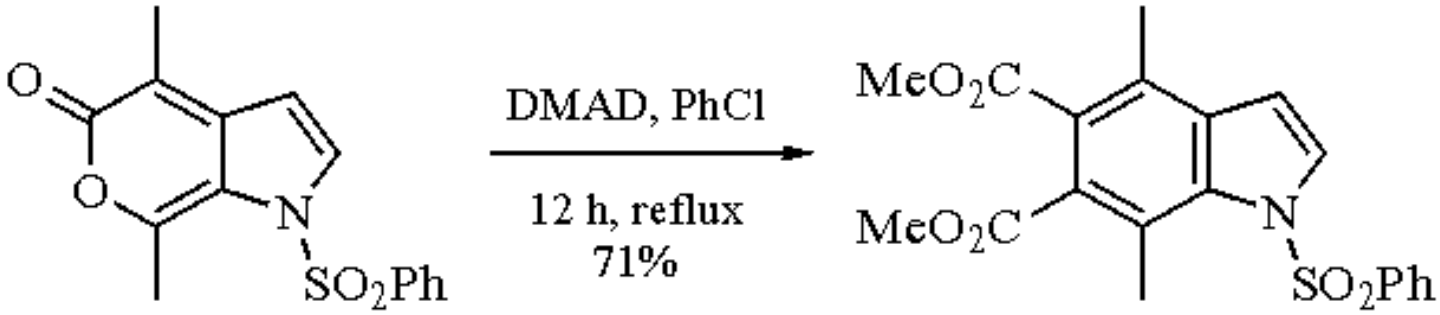

(2)

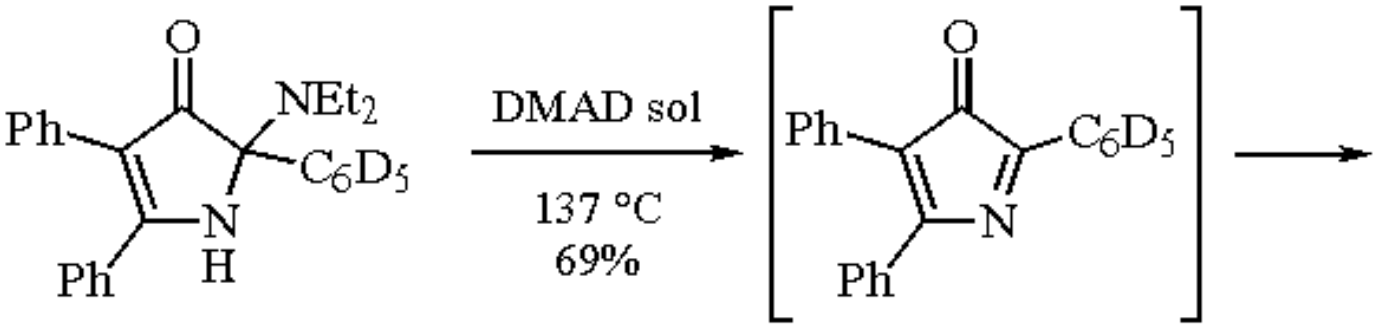

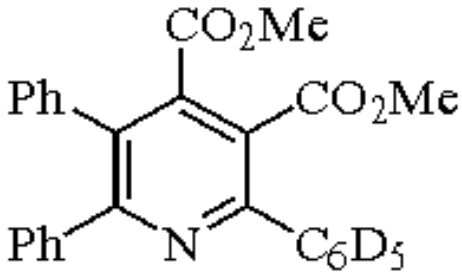

(3)

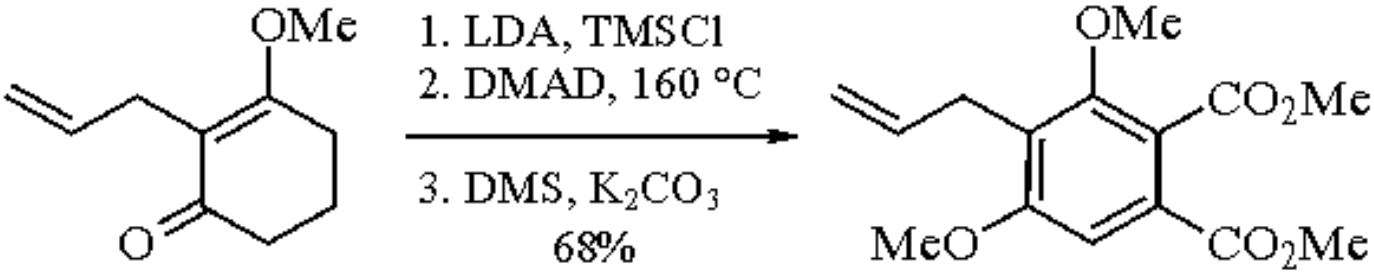

(4)

Adducts possessing a [2.2.1] ring system, obtained from five-membered cyclic dienes such as furans[15] and pyrroles,[16] may fragment to gain aromaticity. DMAD has been exceedingly useful for the synthesis of a number of heteroaromatics such as indoles[17] and furans.[18] Electron deficient alkynes are well suited for the synthesis of pyrimidines from 1,3-diazabutadienes (eq 5).[19]

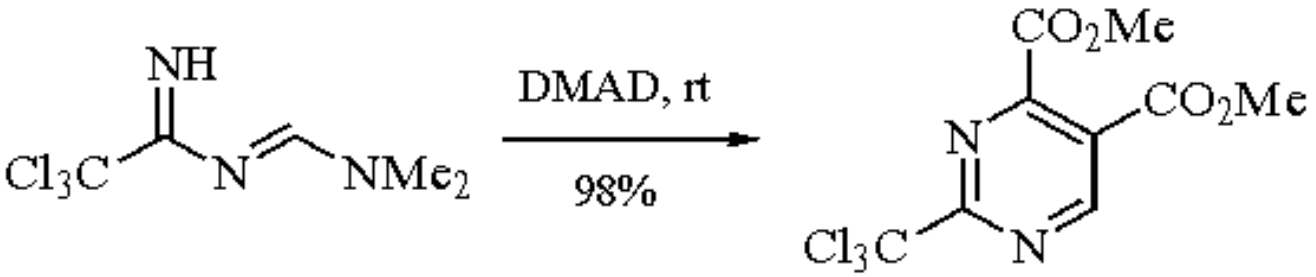

(5)

The cycloaddition of DMAD with anthracene[20] has been used for the synthesis of an interesting new iodate phosphorolytic agent.[21] DMAD has been used extensively in the development of *o*-quinodimethane equivalents (eq 6).[22]

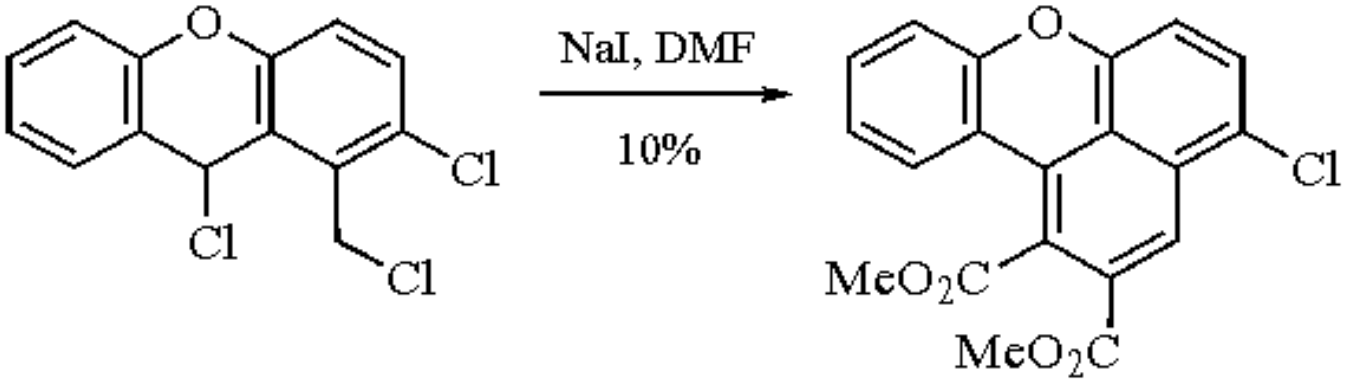

(6)

Examples of higher order cycloadditions with DMAD are abundant. Extended conjugated cycloalkenes such as heptafulvene,[23] fulvenes,[24] azulenes,[25] and indolizines[26] have furnished higher order cycloadducts on treatment with DMAD.

As a Dipolarophile.

Not surprisingly, DMAD also undergoes cycloadditions with 1,3-dipoles. Cycloadditions with common 1,3-dipoles such as azides,[27] diazo alkanes,[28] nitrile imines,[29] nitrile ylides,[30] nitrile oxides,[31] azomethine imines,[32] azoxy compounds,[33] azomethine ylides,[34] and nitrones[35] have been reported. As in the case of the Diels-Alder reaction, the number of stereoisomers obtained is limited (see above). When the faces of the dipole are not equivalent, DMAD can add stereoselectively.[36] Two recent synthetically interesting examples of cycloaddition of DMAD with carbonyl ylides[37] and azomethine ylides[38] are illustrated (eqs 7 and 8).

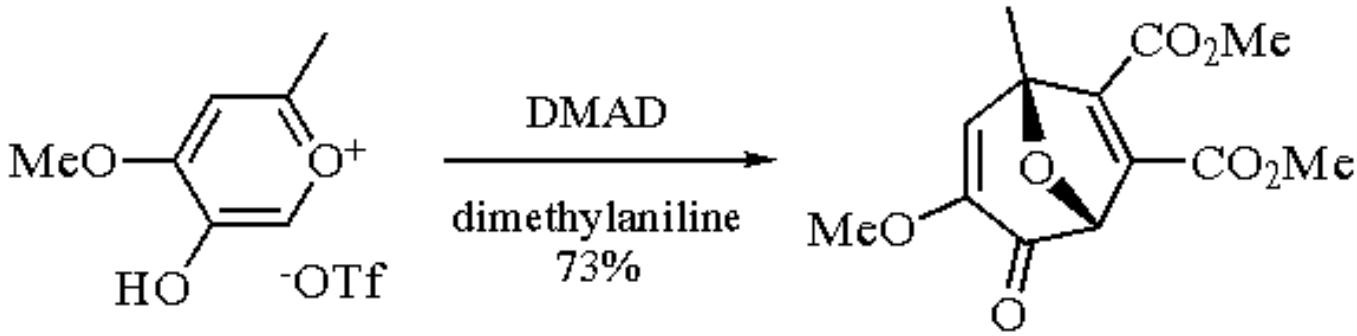

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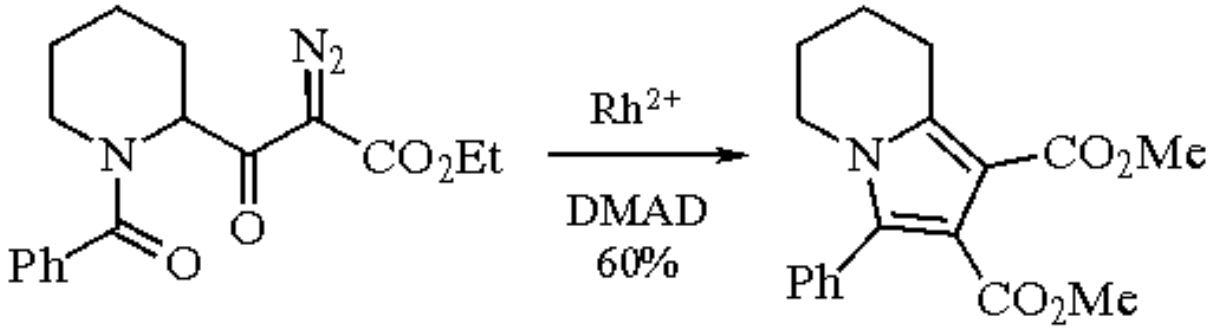

(8)

Due to the unsaturation remaining in the [3 + 2] adducts obtained with DMAD, aromatization and sigmatropic rearrangements are common. Adducts from α-diazo ketones tend to undergo 1,5-acyl sigmatropic rearrangements (eq 9).[39]

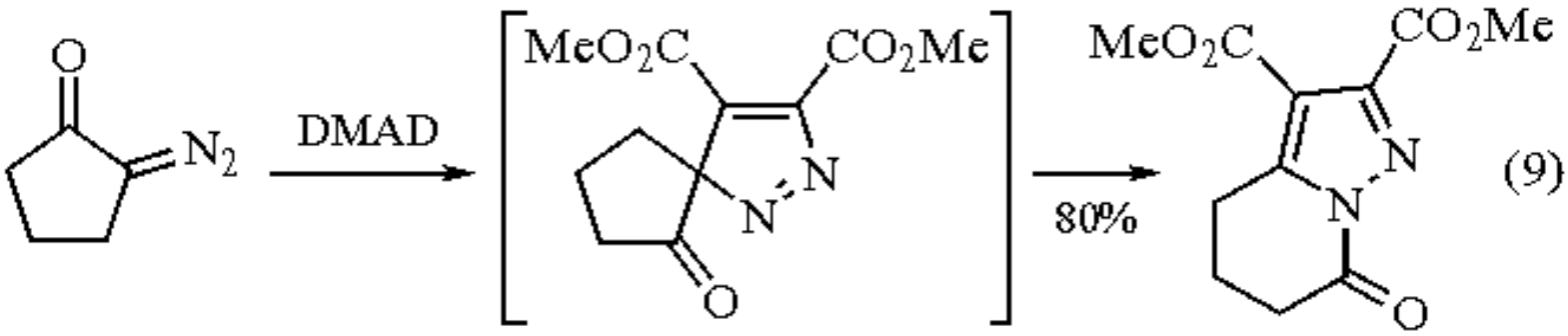

(9)

Simple fragmentations of the [3 + 2] adducts are also common. Reaction of DMAD with quinoxaline 4-oxide gives a pyrrole compound (eq 10).[40] The initial [3 + 2] adduct fragments and incorporates a second molecule of DMAD.

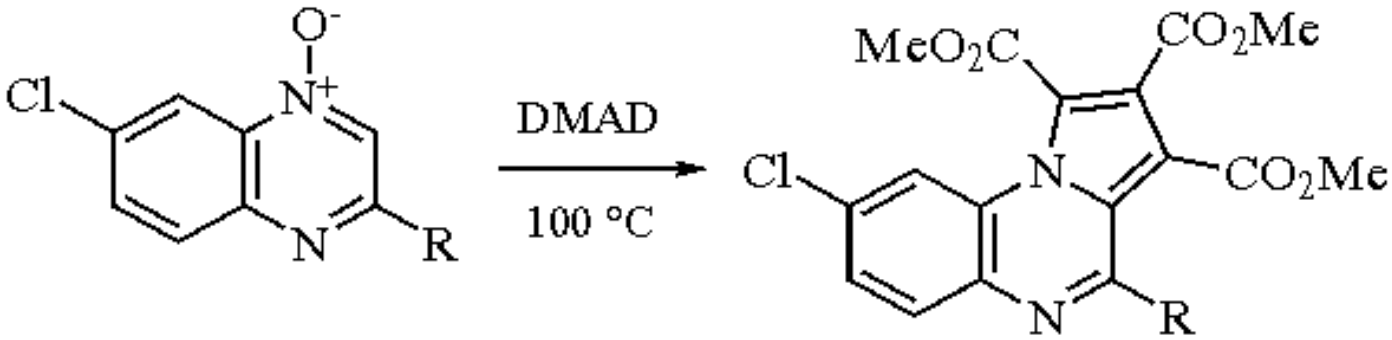

(10)

Cyclization with extended dipoles is known. Benzothiazole undergoes Michael addition with DMAD to form a 1,4-

dipole intermediate which subsequently cyclizes with a second molecule of DMAD (eq 11).[41] 1,4-Thiazepines have been constructed via cyclization of DMAD with a 1,5-dipole (eq 12).[42]

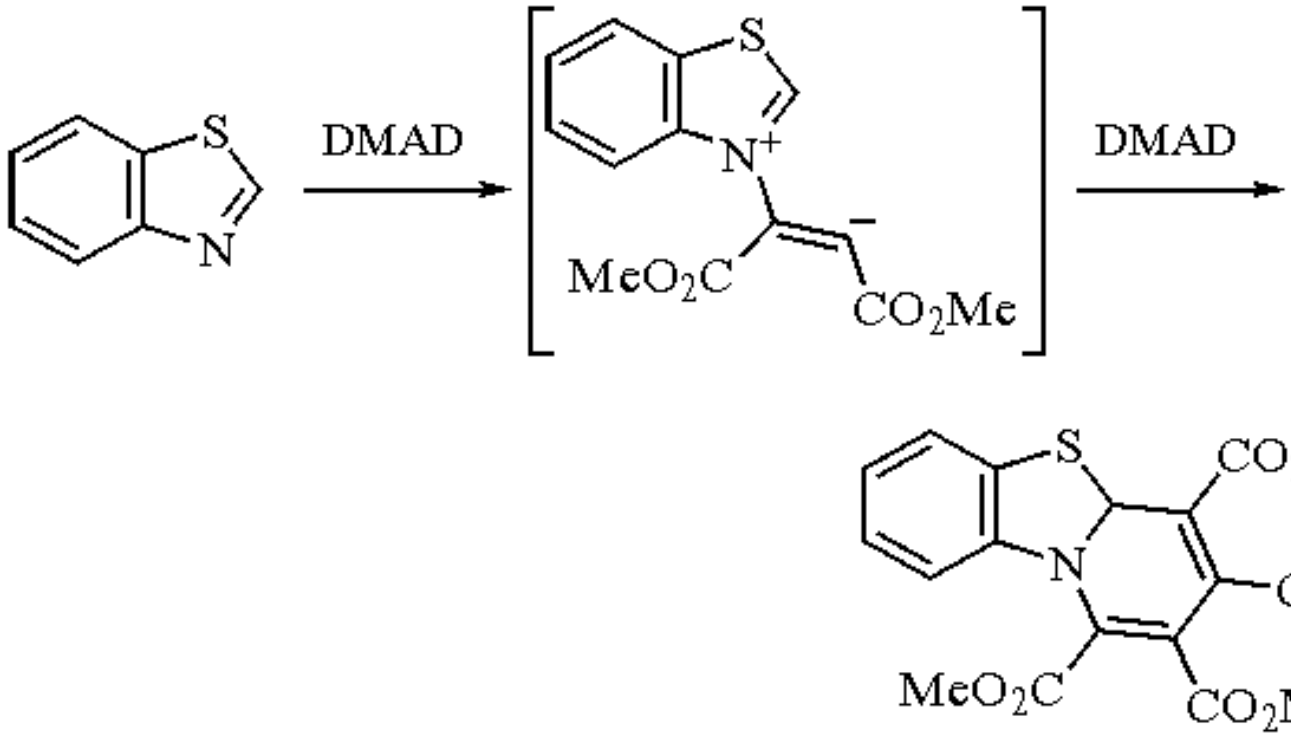

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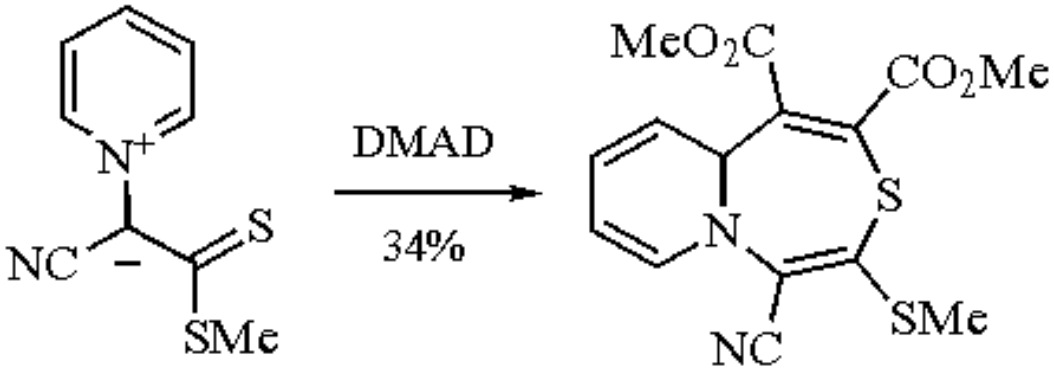

(12)

[2 + 2] Cycloaddition.

DMAD readily undergoes [2 + 2] cycloadditions with enamines, often at ambient temperatures, to form cyclobutene compounds.[43] In many cases these compounds are not isolated and tend to fragment to form 1,3-dienamines.[44] When the enamine is cyclic the ring is enlarged by two carbon atoms (eq 13).[45] This chemistry has successfully been carried out on a range of enamine substrates including indoles,[46] quinolines,[47] and vinylogous imides (enamino lactams).[48] The cycloaddition with enamines is compatible with a wide range of functionalities (eq 14).[49]

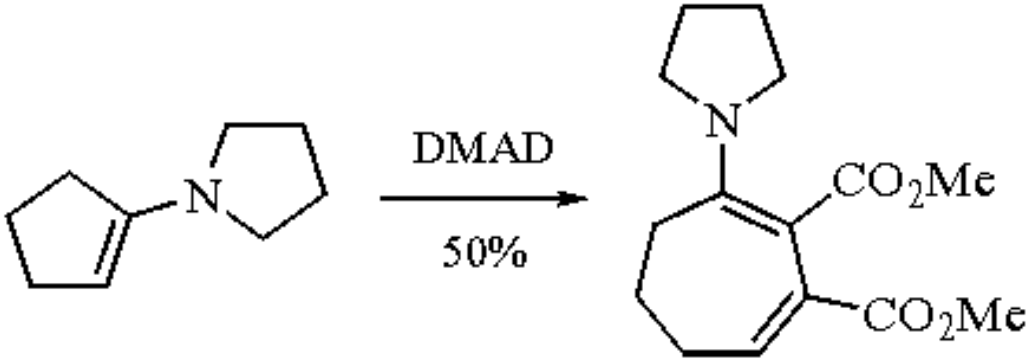

(13)

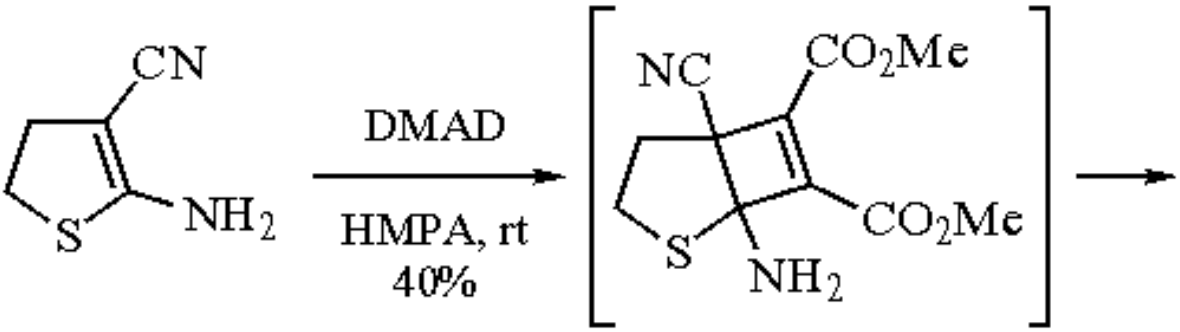

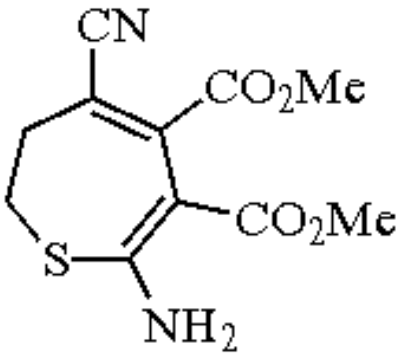

(14)

1,1-Dimethoxyalkenes,[50] enol ethers,[51] and silyl enol ethers[52] undergo Lewis acid mediated [2 + 2] cycloaddition with DMAD to afford cyclobutene compounds. In the case of silyl enol ethers the [2 + 2] adducts can generate fragmentation products analogous to the enamine substrates. The common isolation of simple Michael adducts and strong solvent dependency on yield is solid evidence for a stepwise mechanism involving dipolar intermediates.[53]

As a Michael Acceptor.

A wide variety of nucleophiles undergo 1,4-addition with DMAD. There are examples where carbon,[54] oxygen,[55] nitrogen,[56] and halogen[57] nucleophiles undergo simple Michael addition, thus making DMAD useful for the synthesis of a great number of substituted alkenes. A predominance of the (*Z*)-isomer (methyl esters *trans*) is most common.[58] Frequently, the initial Michael adducts cyclize; this presents a facile route to heterocycles and especially heteroaromatics. With amine nucleophiles the resultant enamines (or vinylogous urethanes) often cyclize onto nearby electrophilic centers. The process is especially efficient when a five- or six-membered ring can be formed. Thus vinylogous amides yield pyridines on treatment with DMAD, whereas α-amino ketones give pyrroles (eqs 15 and 16).[59]

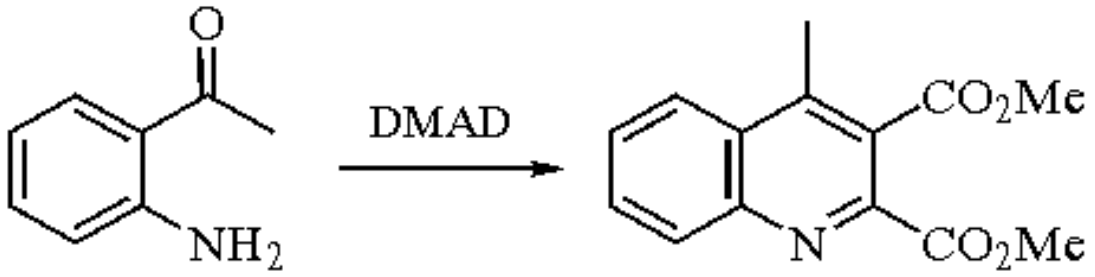

(15)

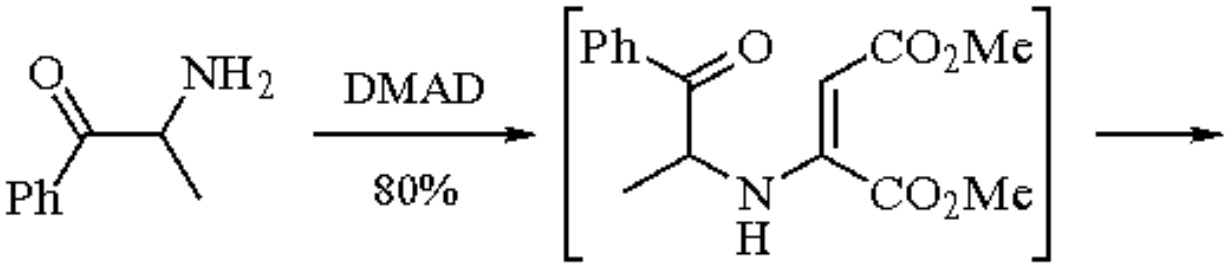

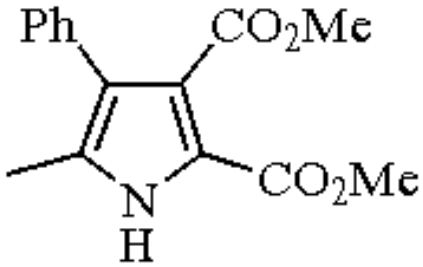

(16)

Alternatively, a nearby nucleophile in the Michael adduct may attack the ester moiety of DMAD. This process is facile when five- or six-membered rings can be formed (eq 17).[60]

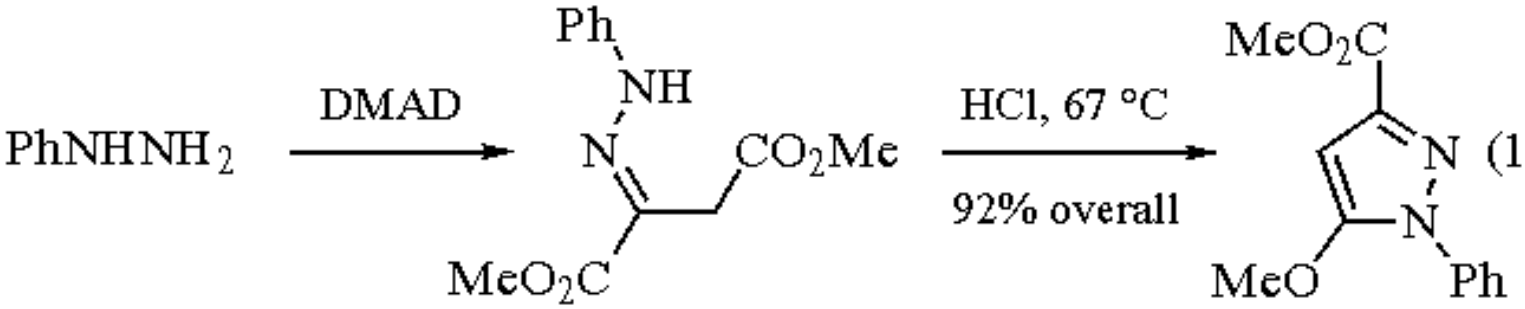

(17)

If there are no proton sources to quench the enolate formed by the Michael addition, cyclization onto a nearby electrophilic center is possible. Thus treatment of the benzyl anion of 5-pyrimidinecarboxylate with DMAD affords a quinazoline (eq 18).[61]

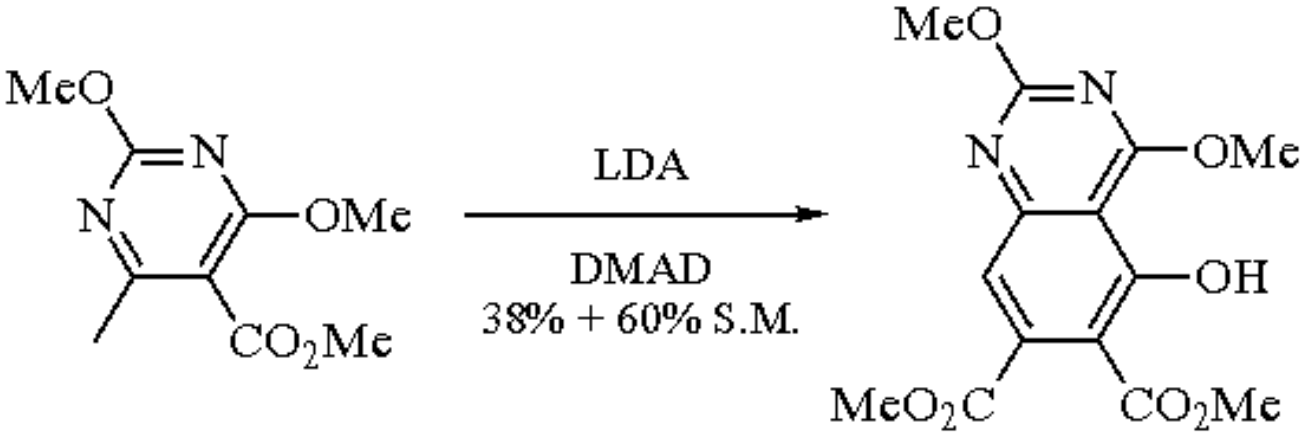

(18)

Alternatively, the enolate could undergo another Michael addition, incorporating a second molecule of DMAD which then cyclizes (see dipolar reactions, eq 11). DMAD reacts with *p*-toluenethiosulfonate at rt to form tetramethyl thiophenetetracarboxylate in good yield (eq 19).[62] Interestingly, phenylacetylene, diphenylacetylene, or 3-phenyl-2-propynoate did not give any thiophenes. Apparently only alkynes with two electron-withdrawing groups will work.

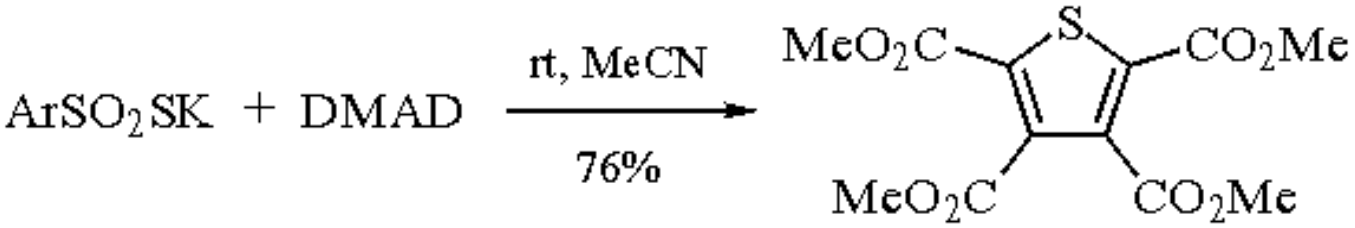

(19)

1,4-Addition of radicals to DMAD are also known.[63] Michael addition of the *t*-butoxy radical,[64] selenyl radicals,[65] and the isopropyl radical[66] (eq 20) have recently been studied.

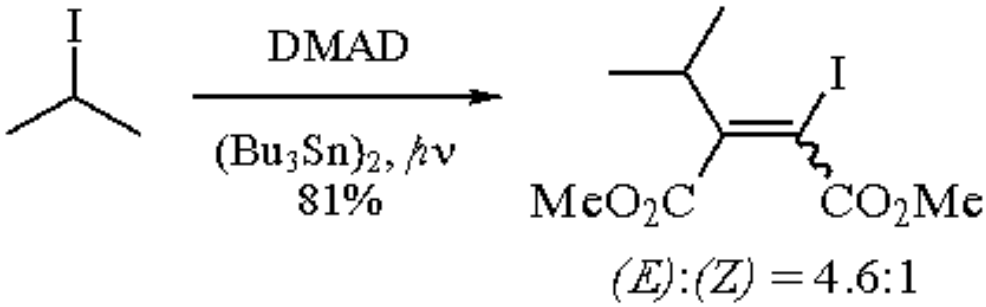

(20)

DMAD has been used in a palladium-catalyzed annulation with aryl halides.[67]

Related Reagents.

Methyl Propiolate.

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John E. Stelmach & Jeffrey D. Winkler

(α,α-Dimethylallyl)trimethylsilane[1]

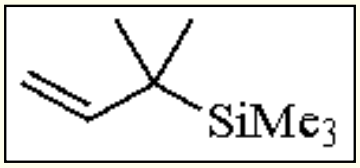

[67707-64-6] · $C_8H_{18}Si$ · (α,α-Dimethylallyl)trimethylsilane · (MW 142.32)

(regiospecific prenylation of acetals;[2] precursor of substituted tetrahydrofurans via reactions with carbonyl compounds[2])

Solubility: sol common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: treatment of ***Trichlorosilane*** with 3-methylbut-2-en-1-ylmagnesium chloride followed by ***Methylmagnesium Bromide*** (2 equiv) provides (α,α-dimethylallyl)dimethylsilane (bp 108 °C) in 76% yield with 99% isomeric purity. The hydrosilane is converted to the ethoxysilane quantitatively by the reaction with ethanol catalyzed by ***Hydrogen Hexachloroplatinate(IV)***, and then fluorinated in situ with ***Tetrafluoroboric Acid*** to give the fluorosilane in 87% yield. The latter is methylated with a small excess of ***Methyllithium*** to give (α,α-dimethylallyl)trimethylsilane in 96% yield.[2] Alternatively, (α,α-dimethylallyl)trimethylsilane can be prepared from 3-methylbut-1-yn-3-ol in six steps.[3]

Purification: distillation.

Handling, Storage, and Precautions: can be stored in a glass bottle.

Prenylation of Acetals.

(α,α-Dimethylallyl)trimethylsilane reacts with acetals in the presence of a Lewis acid to give the corresponding homoallyl alcohols with complete regioselectivity (eqs 1 and 2). The reaction with carbonyl compounds often leads to the formation of tetrahydrofuran derivatives (eq 3), presumably through the formation of chloride.[2]

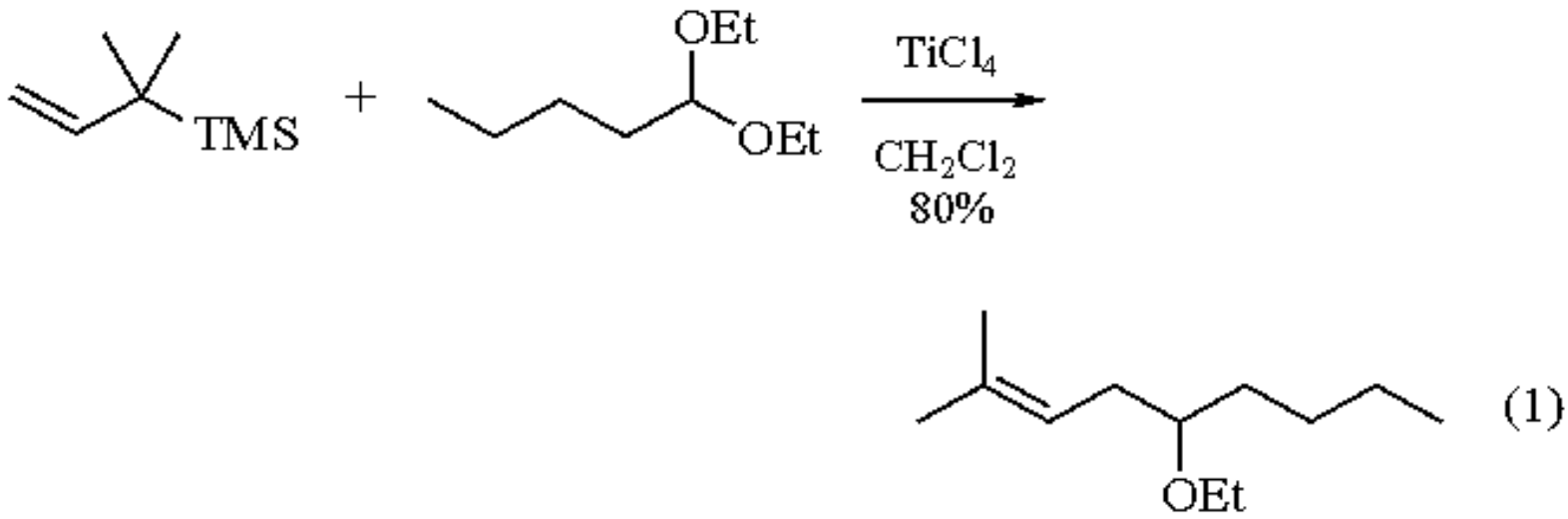

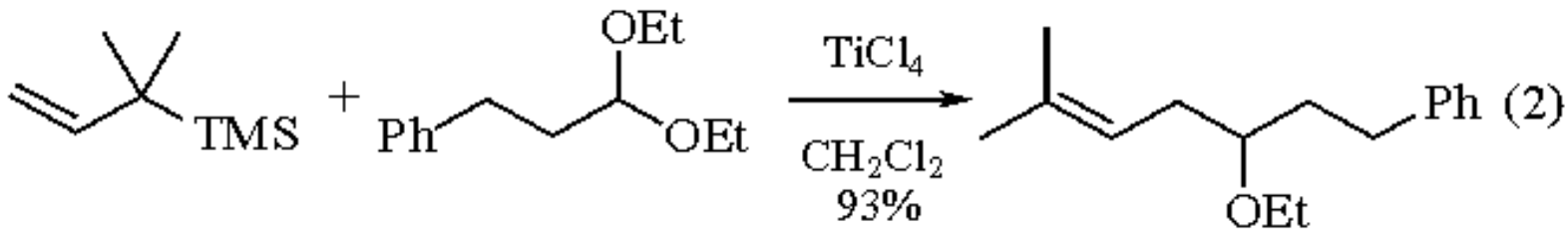

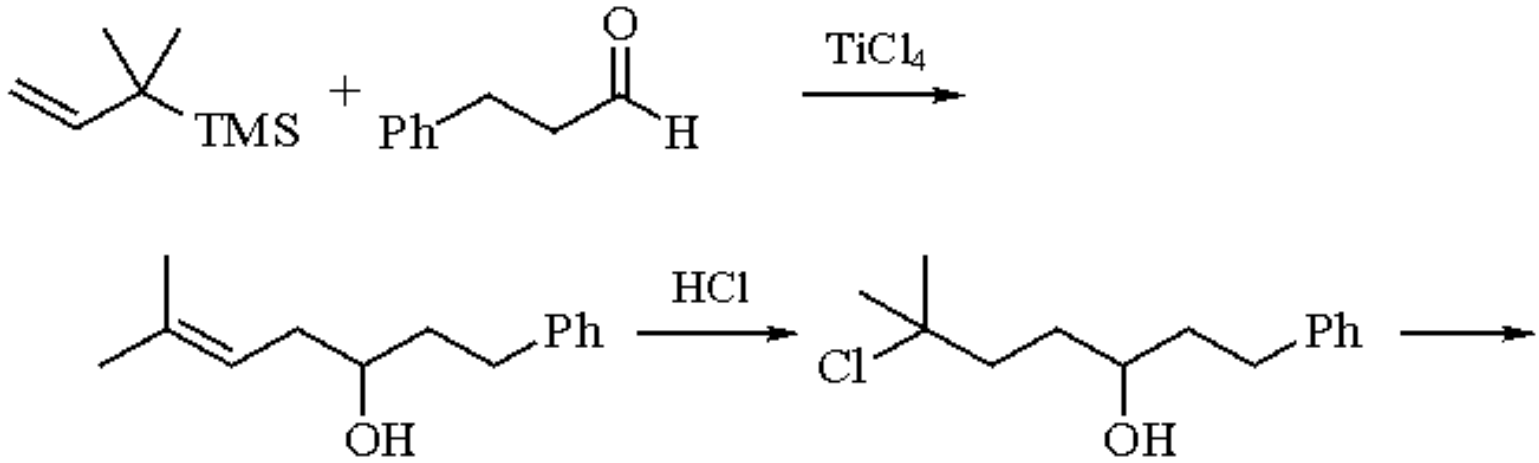

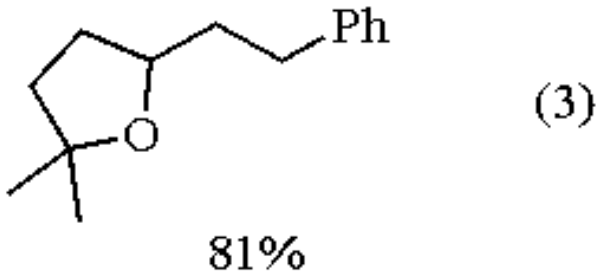

Cycloaddition with Silyl Shift.

The reaction of (α,α-dimethylallyl)trimethylsilane with ***4-Phenyl-1,2,4-triazoline-3,5-dione*** gives a cycloaddition

product where the trimethylsilyl group undergoes a 1,2-shift (eq 4).[4]

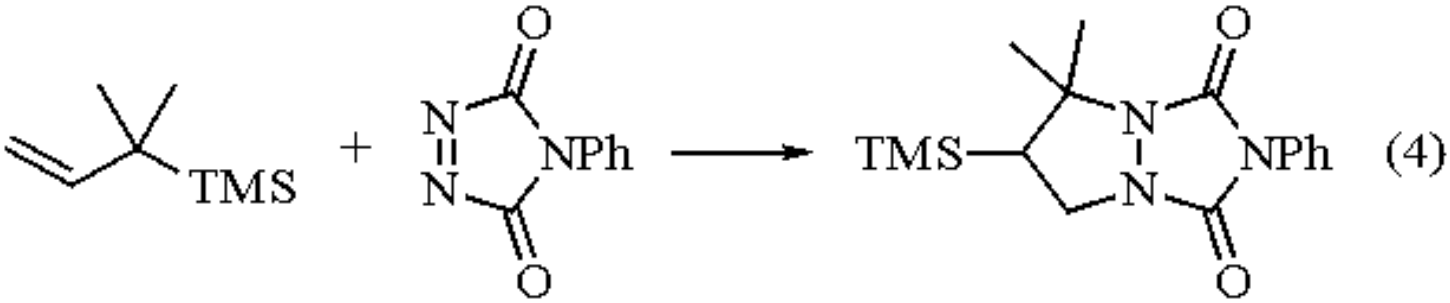

Photochemical Prenylation.

Photolysis of (α,α-dimethylallyl)trimethylsilane in the presence of 1-methyl-2-phenyl-1-pyrrolinium perchlorate leads to the formation of a (3,3-dimethylprop-2-en-1-yl)pyrrolidine as the sole regioisomer (eq 5).[5]

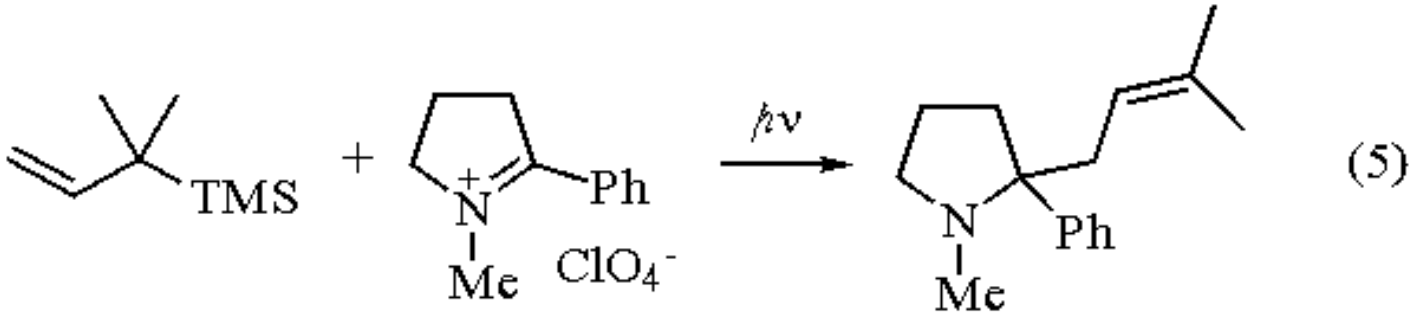

Isomerization.

(α,α-Dimethylallyl)trimethylsilane can undergo isomerization to (γ,γ-dimethylallyl)trimethylsilane with fluoride ion catalysis.[6]

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Dimethylaluminum Amide

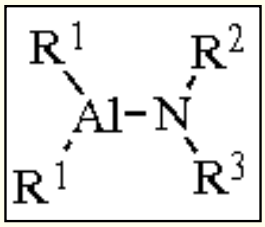

(R^1 = Me, R^2 = H, R^3 = H)

[24758-44-9] · C_2H_8AlN · Dimethylaluminum Amide · (MW 73.07) (R^1 = Me, R^2 = Me, R^3 = Me)

[7398-63-2] · $C_4H_{12}AlN$ · Dimethylaluminum Dimethylamide · (MW 101.13) (R^1 = Me, R^2 = Et, R^3 = Et)

[51706-28-6] · $C_6H_{16}AlN$ · Dimethylaluminum Diethylamide · (MW 129.18) (R^1 = Et, R^2 = Me, R^3 = Me)

[13154-82-0] · $C_6H_{16}AlN$ · Diethylaluminum Dimethylamide · (MW 129.18) (R^1 = Et, R^2,R^3 = -$CMe_2(CH_2)_3CMe_2$-)

[54159-47-6] · $C_{13}H_{28}AlN$ · Diethylaluminum 2,2,6,6-Tetramethylpiperidide · (MW 225.35)

(mild, nonbasic amine transfer reagents, compatible with many functional groups[1])

Physical Data: dialkylaluminum amides[2] are commonly prepared in situ. Dimethylaluminum amide exists as a six-membered ring trimer in the solid state.[2c]

Solubility: sol dichloromethane, benzene, toluene, xylene.

Preparative Methods: dialkylaluminum amides are conveniently prepared in situ from the appropriate trialkylaluminum and amine[3] or amine hydrochloride.[4]

Handling, Storage, and Precautions: dialkylaluminum amides are hydrolytically unstable. 1 M stock solutions can be prepared and stored in the freezer, although best results are usually obtained with freshly prepared reagents.[3,5]

Preparation of Dialkylaluminum Amides.

Although in early studies dialkylaluminum amides were isolated,[6] in practice the reagents are either made in situ from

primary and secondary amines or ammonia and a trialkylaluminum, or stock solutions are prepared and stored.[3,5] Diethylaluminum amides often show reduced reactivity compared to dimethylaluminum amides,[3] which are less reactive than dialkylhaloaluminum-amine complexes.[4b,6d,7] Dialkylaluminum amides that have been used in organic synthesis include dimethylaluminum amide, dimethylaluminum anilide, dimethylaluminum *o*-bromoanilide, dimethylaluminum 2-(diethylamino)ethylamide, dimethylaluminum *N*-methoxy-*N*-methylamide, diethylaluminum diethylamide, diethylaluminum *n*-propylamide, diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP), diethylaluminum *N*-methylanilide, and dimethylaluminum *N*-methyl-*N*-trimethylsilylamide.

Conversion of Esters to Amides.

The reaction of dimethylaluminum amides with a variety of esters to produce amides in high yields has been widely used (eq 1).[1,3]

$$Me_2AlNR^1R^2 + R^3CO_2R^4 \xrightarrow[25\text{-}41\ ^\circ C]{CH_2Cl_2} R^3CONR^1R^2 \qquad (1)$$

$$R^1, R^2 = H, \text{alkyl, aryl}$$

In general, aminolysis of esters requires high temperatures and/or long reaction times,[8] and the strong alkali metal catalysts sometimes used[9] are often not compatible with sensitive functionality. The use of dimethylaluminum amides has the advantages of low temperatures and moderate reaction times. The aluminum amides are conveniently prepared in situ and appear to be mild, nonbasic reagents, compatible with many functional groups. The isolation of the product is simple, since hydrolysis of the aluminum reagents and products affords only methane and acid-soluble aluminum salts. For example, this procedure has been used to prepare the oxindole portion of gelsemine (eq 2).[10]

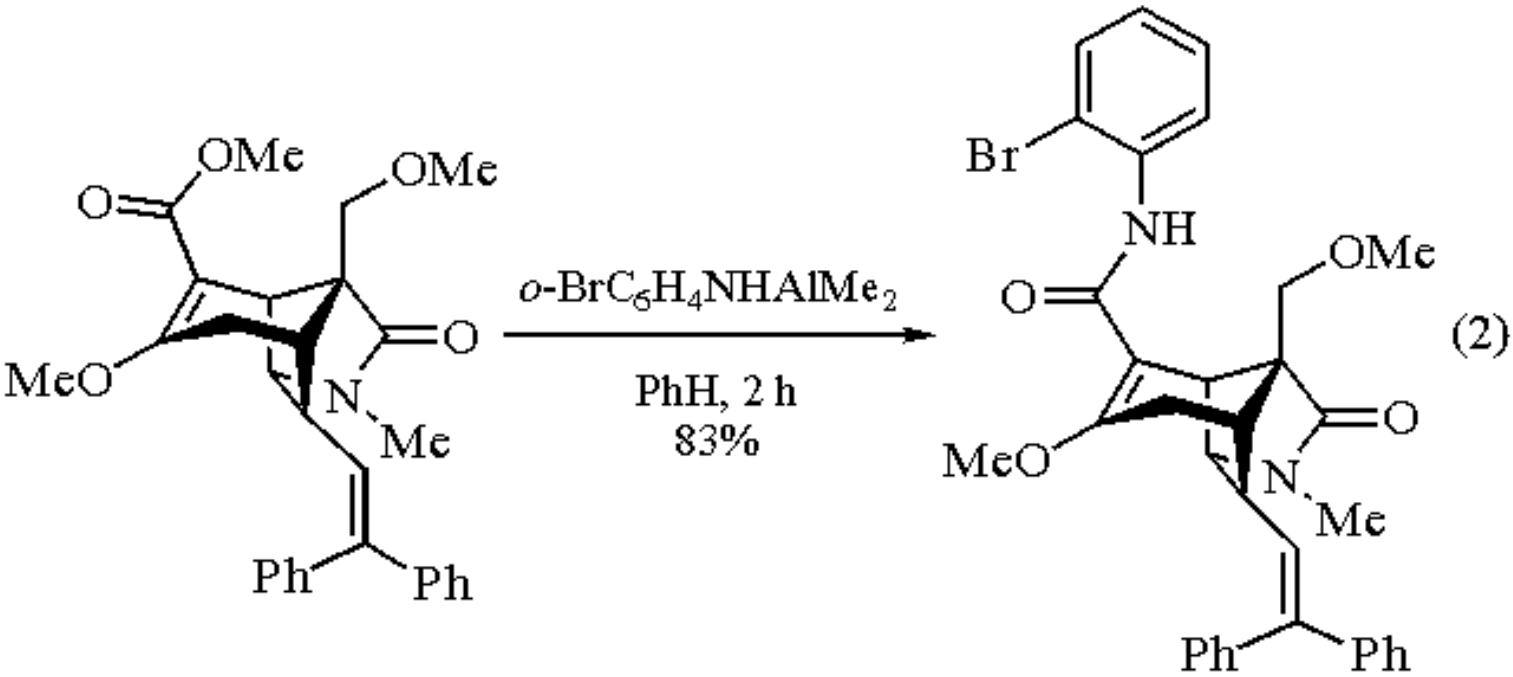

This method has also been used to prepare *N*-substituted 4-(1*H*-imidazol-2-yl)benzamides from the corresponding

methyl ester and *N*-substituted amine in the presence of ***Trimethylaluminum*** (eq 3).[11]

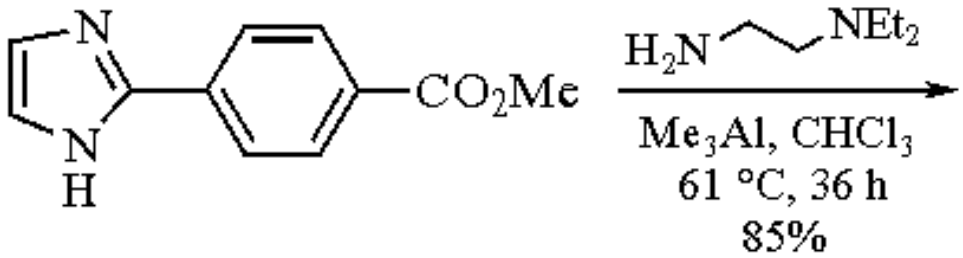

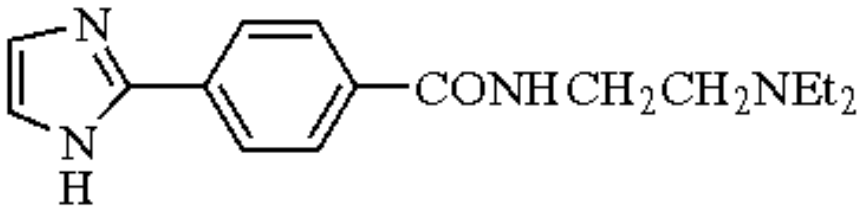

(3)

Lactones undergo acyl-oxygen bond cleavage when treated with dialkylaluminum amides to produce hydroxy amides upon hydrolysis.[3,6a] A hindered lactone was converted to the corresponding hydroxy amide upon treatment with dimethylaluminum amide (eq 4). Sodium amide in liquid ammonia was unsuccessful at performing the same transformation.[3]

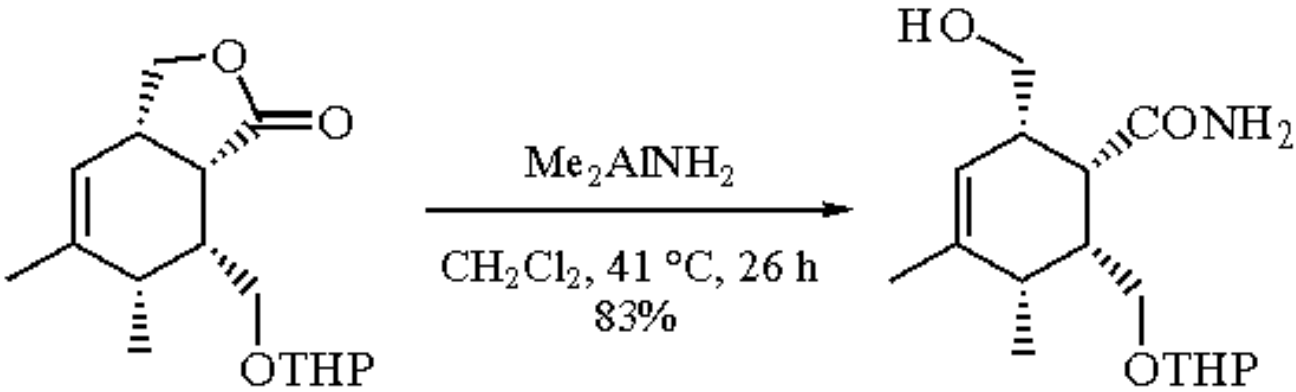

(4)

The aluminum amide reagent derived from *N,O*-dimethylhydroxylamine (see also ***N,O-Dimethylhydroxylamine***) was used to achieve lactone ring-opening in the total syntheses of (+)-actinobolin and (-)-bactobolin (eq 5).[12]

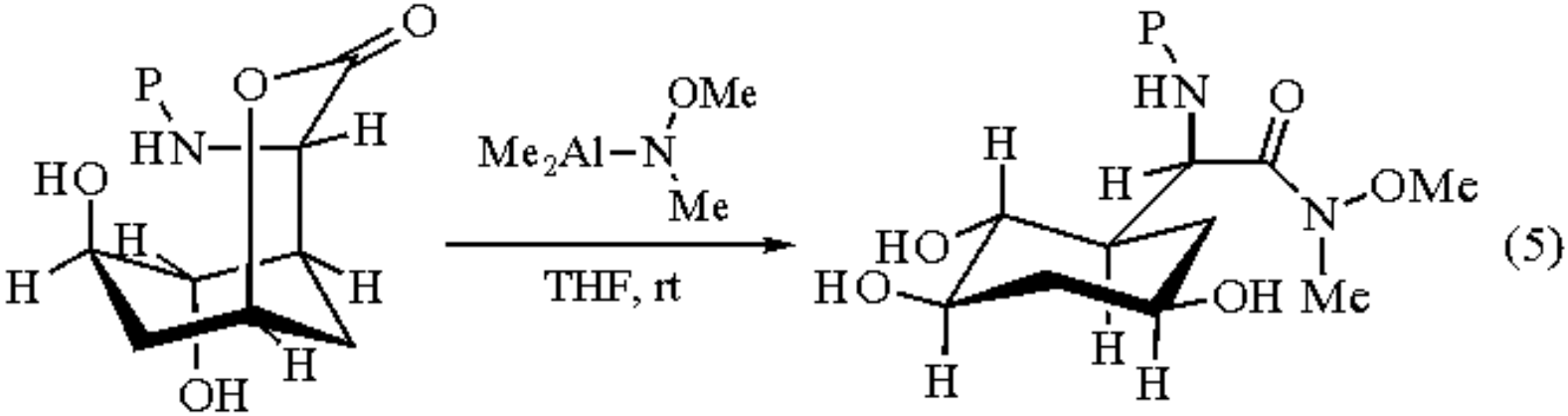

P = *p*-$MeC_6H_4CH_2SO_2$-

An alternative procedure involves the use of ***Dimethylaluminum Chloride***-amine complexes in the same transformations. These reagents, prepared from the reactions of trimethylaluminum with conveniently handled, readily available amine hydrochloride salts, provide efficient means for the aminolysis of esters (eq 6).[4,13]

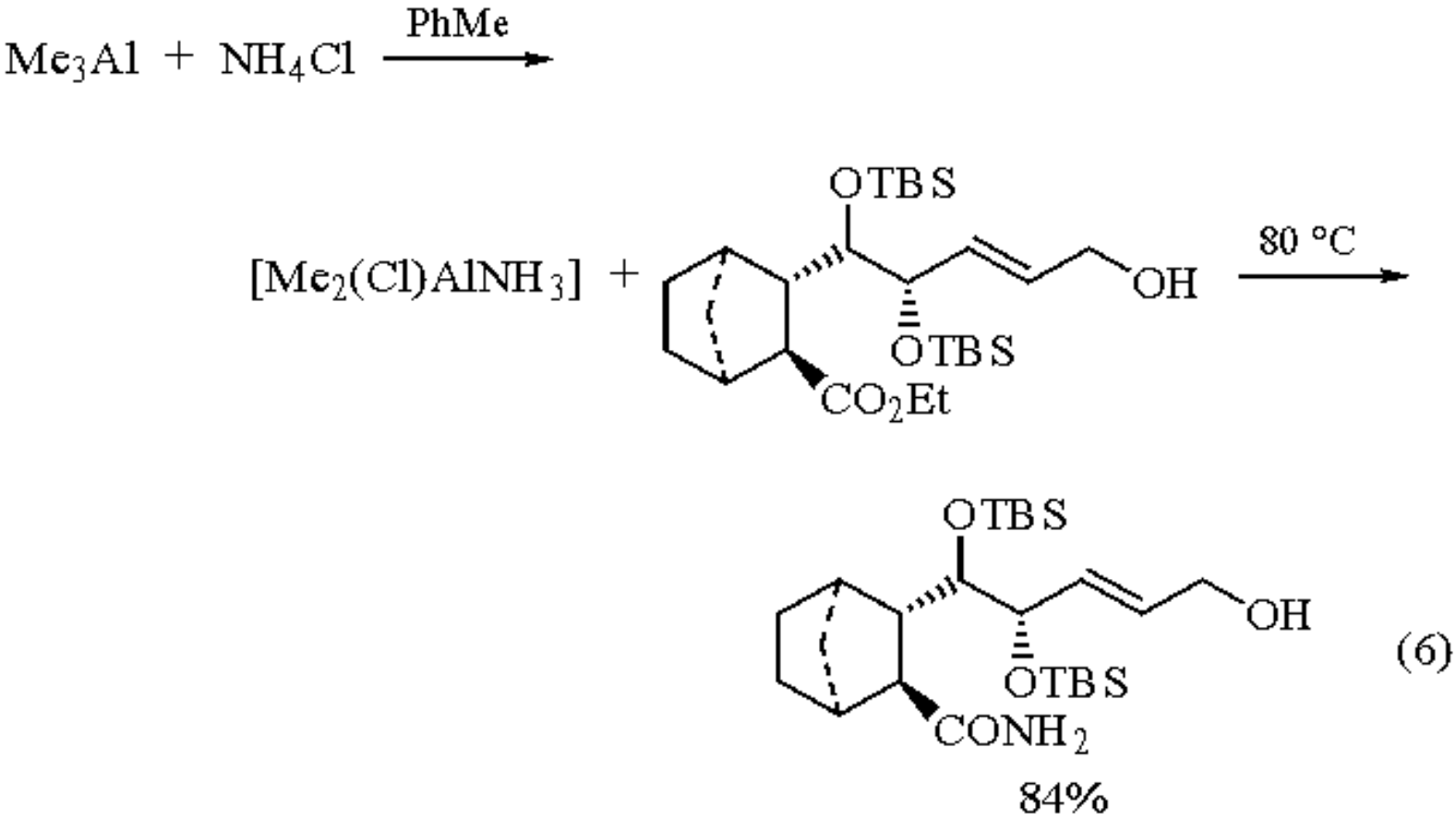

The use of these alternative aluminum reagents avoids the necessity of having to condense and measure volatile low molecular weight amines and ammonia. In a diastereospecific synthesis of the C-20-C-34 segment of the immunosuppressant FK-506, a lactone is converted to the hydroxy amide when subjected to the complex from trimethylaluminum and ***N,O-Dimethylhydroxylamine*** hydrochloride (eq 7).[14]

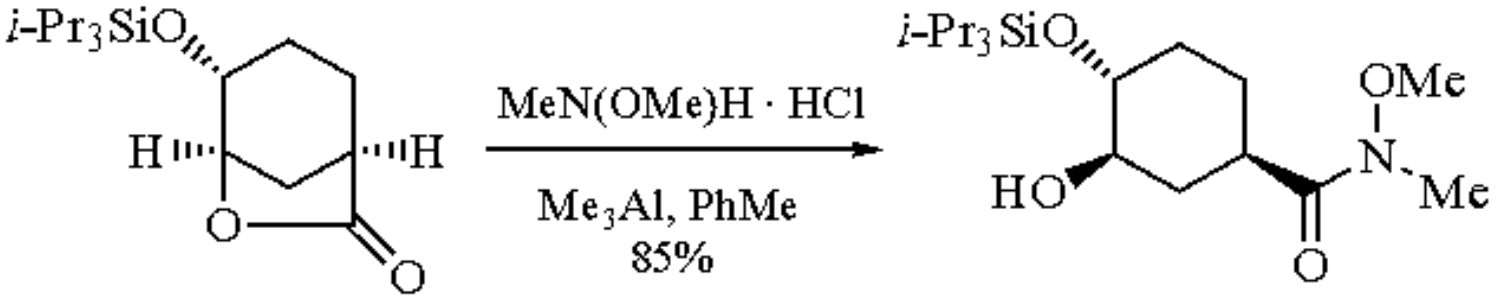

(7)

This type of reaction can also be done intramolecularly, affording lactams (eq 8).[15] β-Lactams can also be synthesized, as in Woodward's synthesis of cephalosporin C (eq 9).[16]

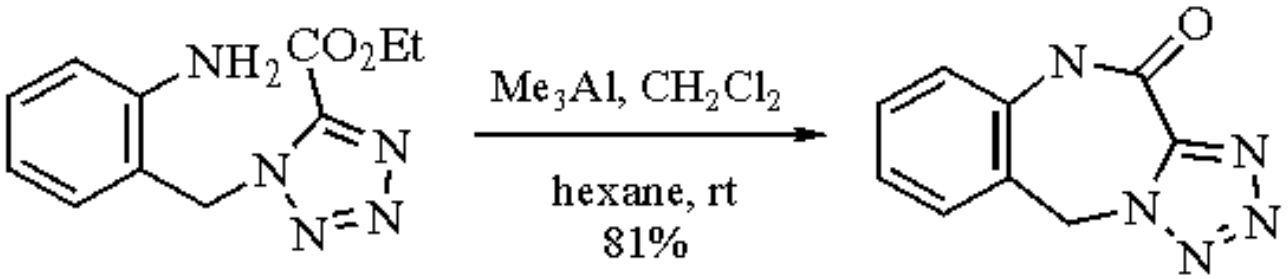

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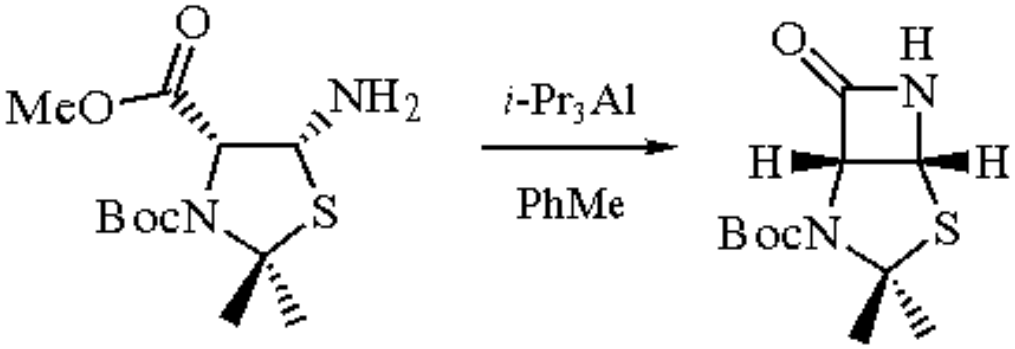

(9)

Bifunctional units such as 1,2-diaminoethane are effectively coupled with trimethylaluminum to produce reagents that can be treated with esters to give 2-imidazolines and benzimidazoles directly (eq 10).[17]

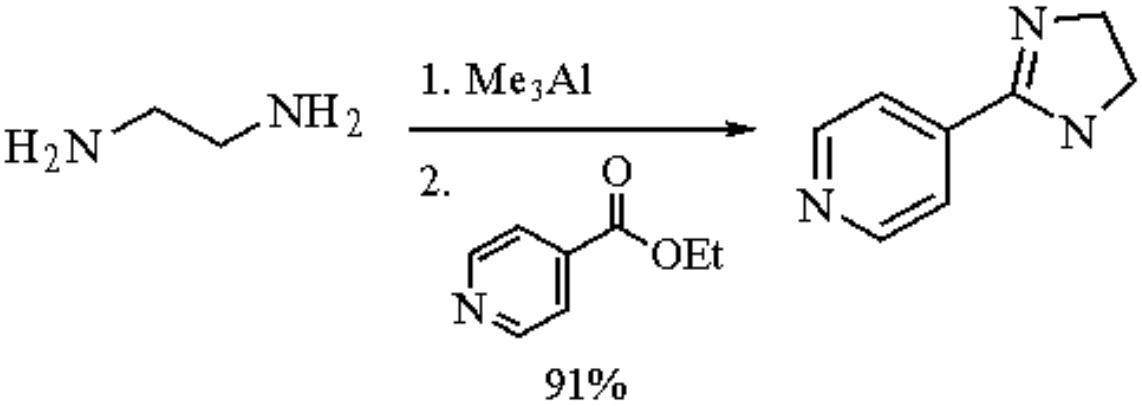

(10)

Transaminations can also be achieved using dialkylaluminum amides. For example, Schreiber used dimethylaluminum *N*-methoxy-*N*-methylamide to convert an oxazolidone auxiliary to the *N*-methyl-*N*-methoxy amide (eq 11).[18] This transformation gives a key intermediate corresponding to the C-22-C-28 segment of rapamycin in a form suitable for

alkylative coupling.

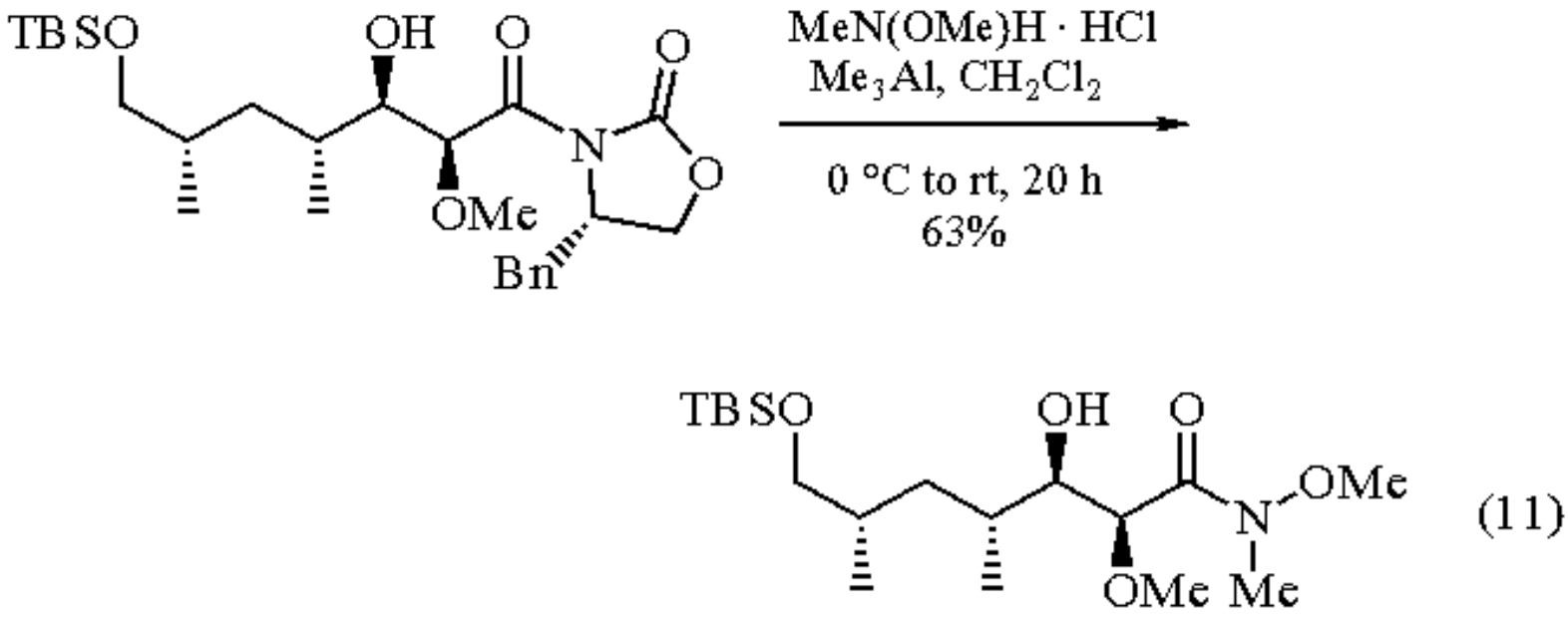

Conversion of Esters to Nitriles.

Esters are converted to nitriles in a one-pot procedure when heated with 2 equiv of dimethylaluminum amide in refluxing xylene (eq 12).[5] This reaction, which is thought to proceed through a carboxamide or aluminum derivative of a carboxamide as an intermediate, is the first direct conversion of an ester to a nitrile.

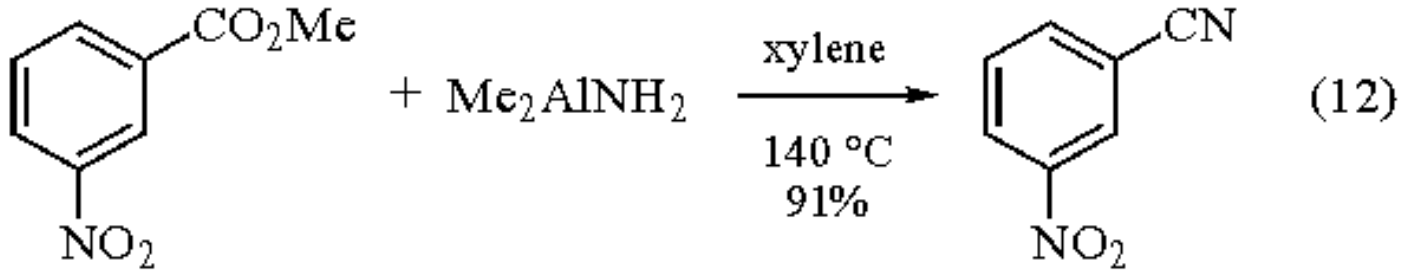

In studies toward the total synthesis of tetronomycin, Yoshii and co-workers used this procedure to directly convert a lactone to a hydroxy nitrile (eq 13).[19]

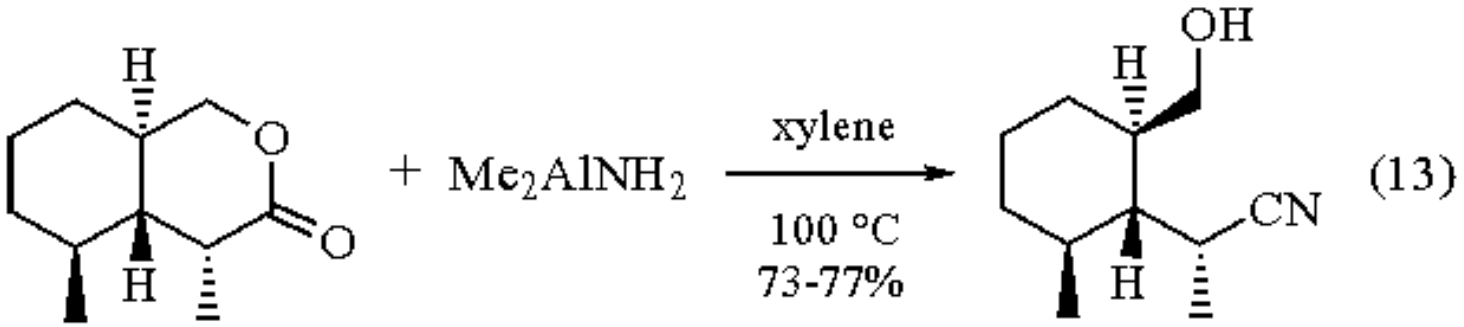

Conversion of Nitriles to Amidines.

Often methods used for amidine synthesis are moderate to poor yielding, multistep processes.[20] In early studies, dimeric aluminum amidine derivatives resulting from the addition of diethylaluminum dimethylamide to benzonitriles were isolated for spectroscopic study,[6b,c] but the synthetic scope of the reaction in preparing amidines was not demonstrated. However, it was recently found that the addition of a dimethylchloroaluminum-amine complex[4] to a nitrile produces the corresponding amidine directly (eq 14).[7]

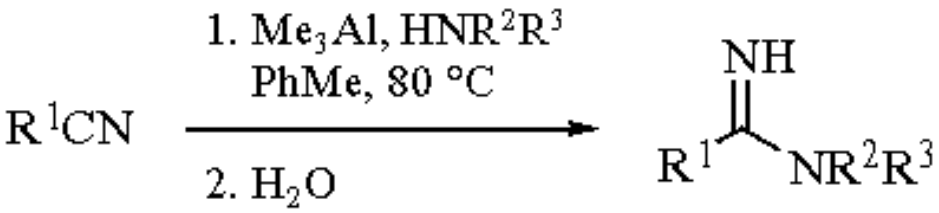

(14)

Dialkylaluminum amides react sluggishly with nitriles compared to the corresponding dialkylchloroaluminum-amine complexes.[4b,6d,7] Alkyl, benzyl, and aryl amidines are prepared in high yield (78-96%) from the corresponding nitriles using this method. Mono- and disubstituted amidines are obtained from *N*-substituted amine complexes. This transformation can also be achieved intramolecularly. By generating the dimethylchloroaluminum-amine complex in situ from 6-aminocapronitrile hydrochloride and trimethylaluminum, caprolactamidine was prepared (eq 15).

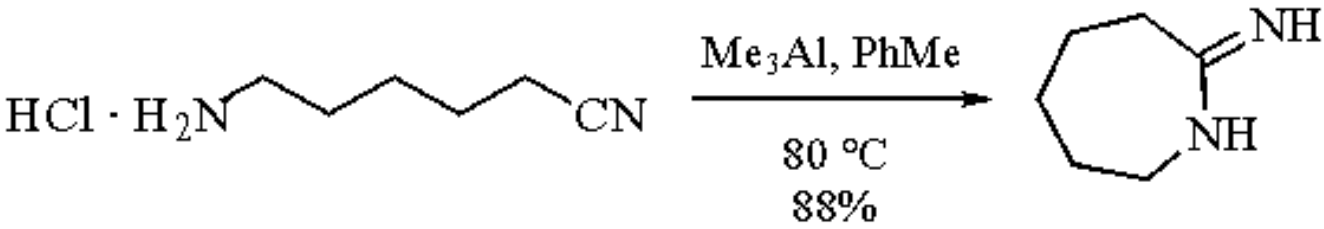

(15)

Additionally, guanidines can be prepared from the corresponding *N*-substituted cyanamide (eq 16).[7]

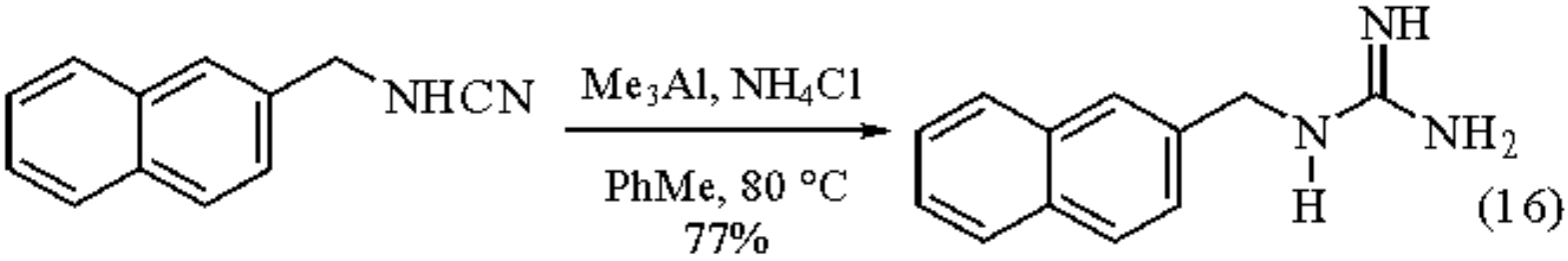

(16)

Epoxide and Oxetane Cleavage.

Diethylaluminum amides react stoichiometrically with epoxides at rt to give, after hydrolysis, β-amino alcohols in good yield (eq 17).[21] The classical method of reacting epoxides directly with amines is limited by the poor reactivity of nonnucleophilic or bulky amines and the high temperatures often necessary. This procedure avoids these problems.

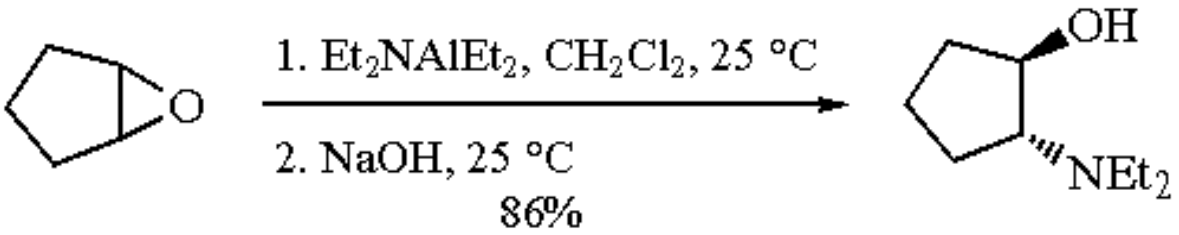

(17)

The reaction of 1-hexene oxide with diethylaluminum diethylamide occurs exclusively at the terminal carbon (eq 18). In contrast, the reaction of isoprene oxide with diethylaluminum *n*-propylamide gives a mixture of products in which the tertiary carbinyl amine predominates (eq 19). This can be compared to the direct reaction of isoprene oxide with *n*-propylamine, which gives the tertiary allylic alcohol.[22]

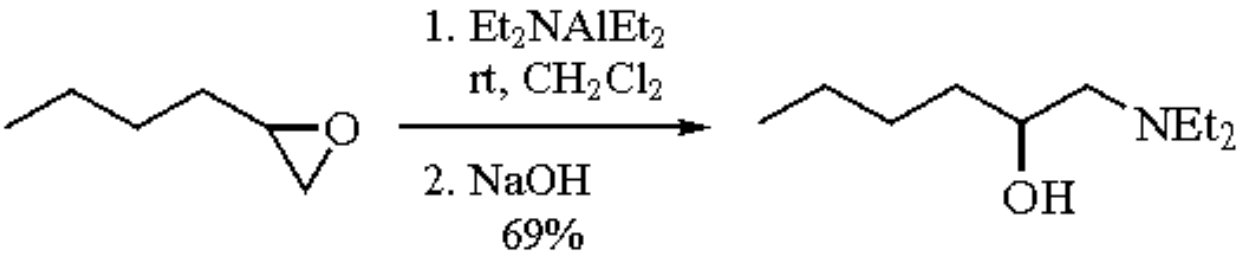

(18)

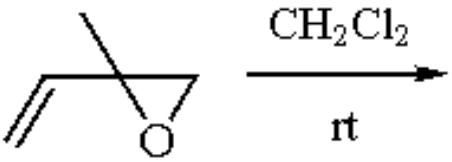

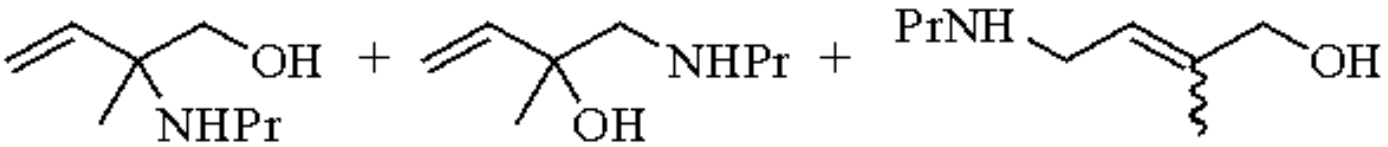

(19)

$Et_2NAlNHPr$	72:17:11
$PrNH_2$	0:100:0

Epoxides can be converted to allylic alcohols using ***Diethylaluminum 2,2,6,6-Tetramethylpiperidide*** (DATMP),[23] which is readily prepared from diethylaluminum chloride and the corresponding lithium amide.[24] On reaction with DATMP in benzene, (*E*)-cyclododecene oxide is converted quantitatively in 1 h at 0 °C into (*E*)-2-cyclododecen-1-ol (eq 20).[23] In contrast, under the same reaction conditions, the (*Z*)-isomer affords only 8% of the alcohol. DATMP seems virtually unreactive toward all *cis*-2,3-disubstituted epoxides.

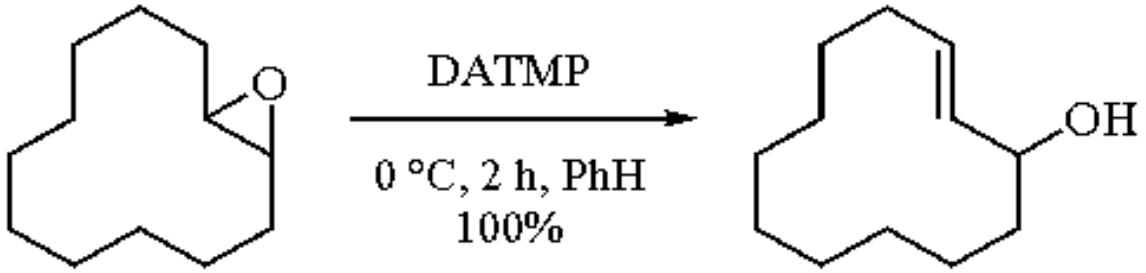

(20)

DATMP is very reactive towards 2,2,3-trisubstituted epoxides (eqs 21 and 22).[24] The observed selectivity is consistent with a cyclic *syn*-elimination mechanism, in which the organoaluminum compound adds to the epoxide preferentially on the same side as hydrogen at C-3. The proton required for elimination is supplied by the alkyl group on C-2 which is *cis* to the hydrogen atom on C-3.[23] The resulting double bond generally prefers the (*E*) configuration.

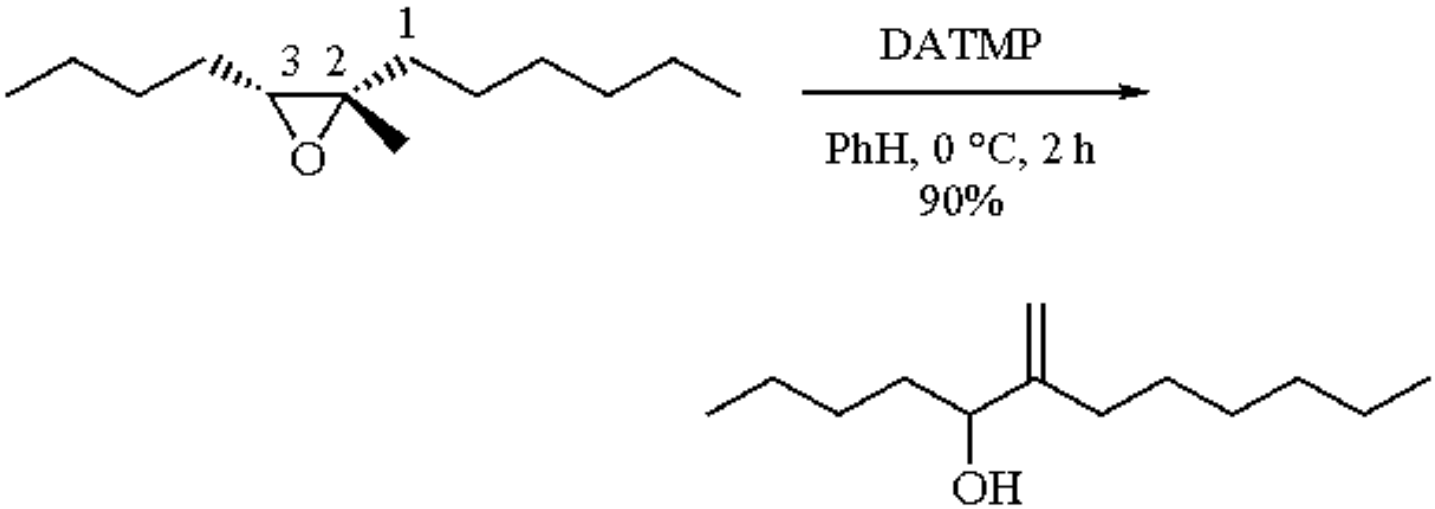

(21)

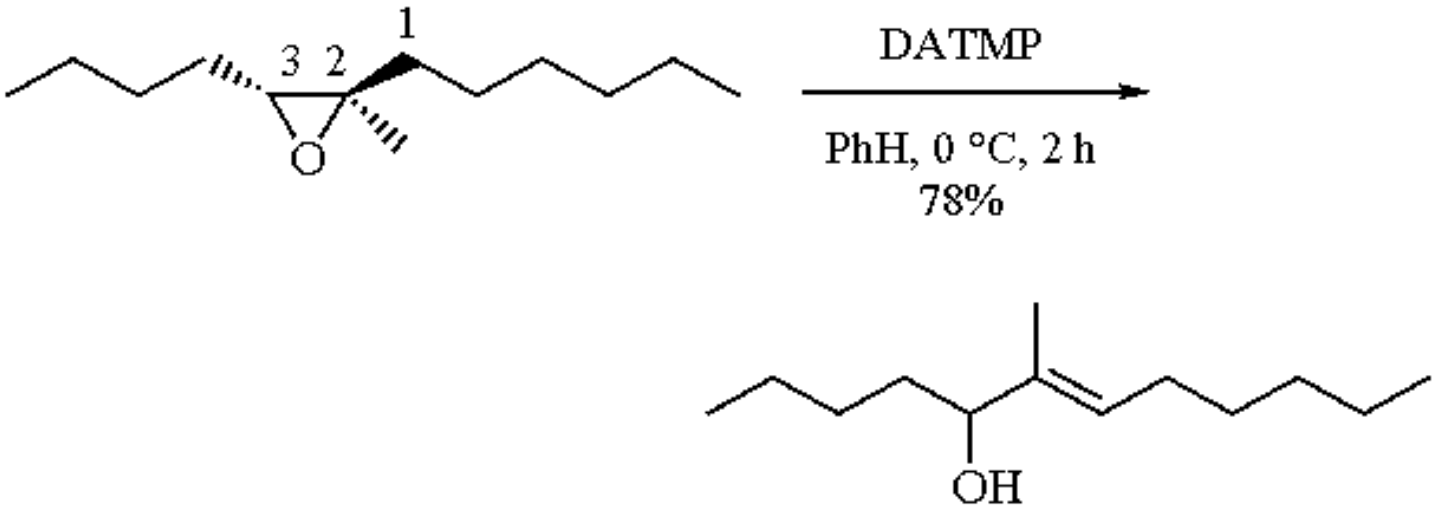

(22)

Similarly, homoallylic alcohols can be made by rearrangement of oxetane rings using an organoaluminum amide. Reaction of oxetanes with diethylaluminum methylanilide in boiling benzene gives the corresponding homoallylic alcohols in high yields (eqs 23 and 24).[25] Again the (*E*) configuration of the product is preferred.

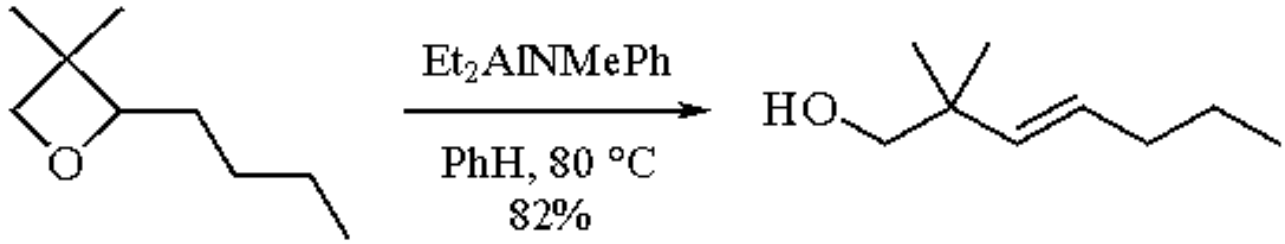

(23)

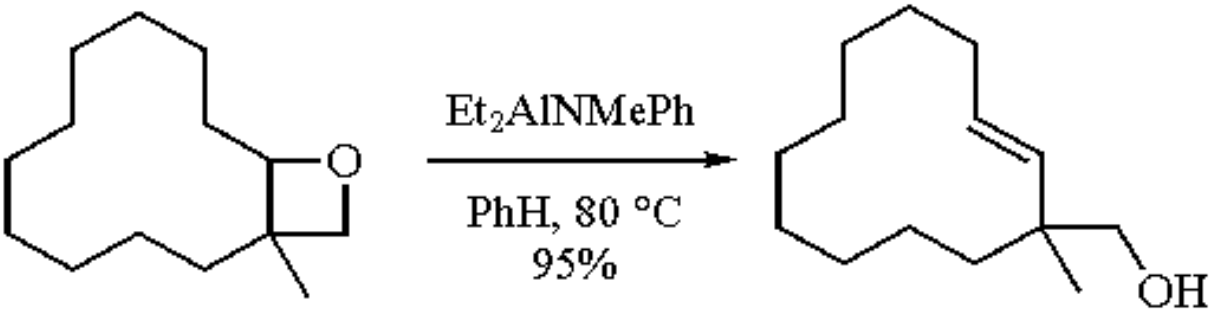

(24)

Substitution of Allylic Phosphates.

Nucleophilic substitution of allylic phosphates can be accomplished using dialkylaluminum amides. For example, the reaction of *cis*- or *trans*-5-isopropenyl-2-methyl-2-cyclohexenyl diethyl phosphate with dimethylaluminum phenylamide results in the corresponding allylic amines (eq 25).[26] Substitution occurs with predominant inversion of configuration.[27]

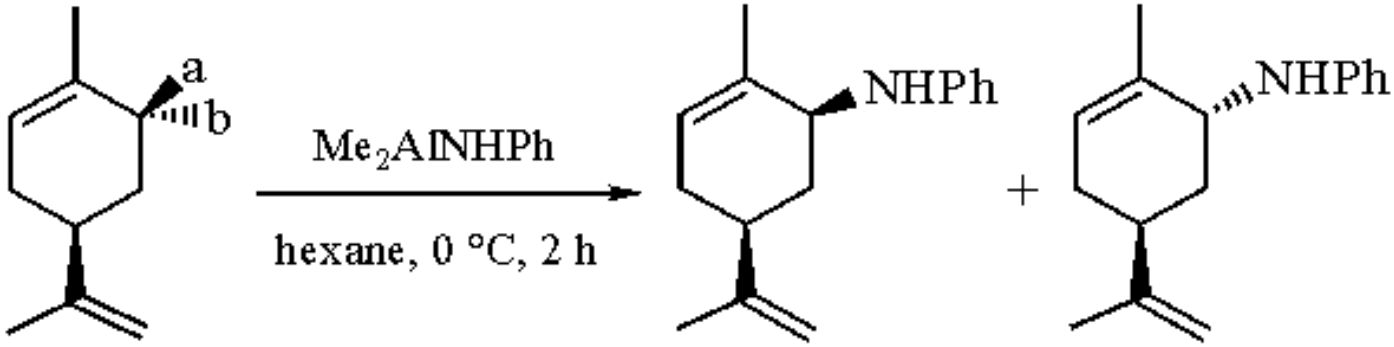

(25)

	yield (%)	*cis*:*trans*
a = OPO(OEt)$_2$, b = H	70	12:88
a = H, b = OPO(OEt)$_2$	87	99:1

Conversion of Ketones to *N*-Methyl Imines.

N-Methyl imines[28] can be formed from the reaction between ketones and (trimethylsilyl)(dimethylalumino)methylamine (eq 26).[29] Imine yields are fair using this method. The aluminum reagent is prepared by treating the corresponding trimethylsilylalkylamine with trimethylaluminum in benzene.

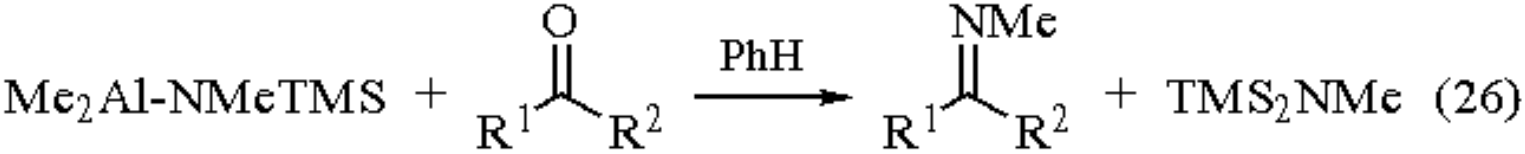

R^1	R^2	Temp (°C)	Yield (%)
Ph	Me	rt	14
t-Bu	Me	rt	38
i-Pr	*i*-Pr	80	65
Ph	Ph	80	<42

---

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Dimethylaluminum Chloride[1]

Me_2AlCl

[1184-58-3] · C_2H_6AlCl · Dimethylaluminum Chloride · (MW 92.51)

(strong Lewis acid that can also act as a proton scavenger; reacts with HX to give methane and MeAlClX)

Alternate Name: chlorodimethylaluminum.

Physical Data: mp -21 °C; bp 126-127 °C; *d* 0.996 g cm^{-3}.

Solubility: sol most organic solvents; stable in alkanes or arenes.

Form Supplied in: commercially available neat or as solutions in hexane or toluene.

Analysis of Reagent Purity: solutions are reasonably stable but may be titrated before use by one of the standard methods.[1e]

Handling, Storage, and Precautions: must be transferred under inert gas (Ar or N_2) to exclude oxygen and water. Use in a fume hood.

Introduction.

The general properties of alkylaluminum halides as Lewis acids are discussed in the entry for ***Ethylaluminum Dichloride***. Dialkylaluminum halides are less acidic than alkylaluminum dihalides. Me_2AlCl is more expensive than ***Diethylaluminum Chloride***, but the methyl group of Me_2AlCl is much less nucleophilic than the ethyl group of Et_2AlCl. Much higher yields will generally be obtained by use of Me_2AlCl in the ene reactions of carbonyl compounds. In other cases, such as the Diels-Alder reactions of α,β-unsaturated esters, comparable yields will be obtained with either Lewis acid.

Catalysis of Diels-Alder Reactions.

Me_2AlCl has been used as a Lewis acid catalyst for inter- and intramolecular Diels-Alder reactions with a wide variety of dienophiles. High diastereoselectivity is obtained from chiral α,β-unsaturated *N*-acyloxazolidinones with more than 1 equiv of Me_2AlCl.[2] Use of Me_2AlCl as a catalyst affords high yields in inter- and intramolecular Diels-Alder reactions of α,β-unsaturated ketones (eq 1),[3,4] and intramolecular Diels-Alder reactions of α,β-unsaturated

aldehydes.[4,5] Me_2AlCl-catalyzed Diels-Alder reactions of α,β-unsaturated *N*-acylsultams (eq 2)[6] and 1-mesityl-2,2,2-trifluoroethyl acrylate (eq 3)[7] proceed in high yield with excellent asymmetric induction. Methylaluminum sesquichloride, prepared from Me_2AlCl and ***Methylaluminum Dichloride***, catalyzes an intramolecular Diels-Alder reaction with an aldehyde as the dienophile to afford a dihydropyran.[8]

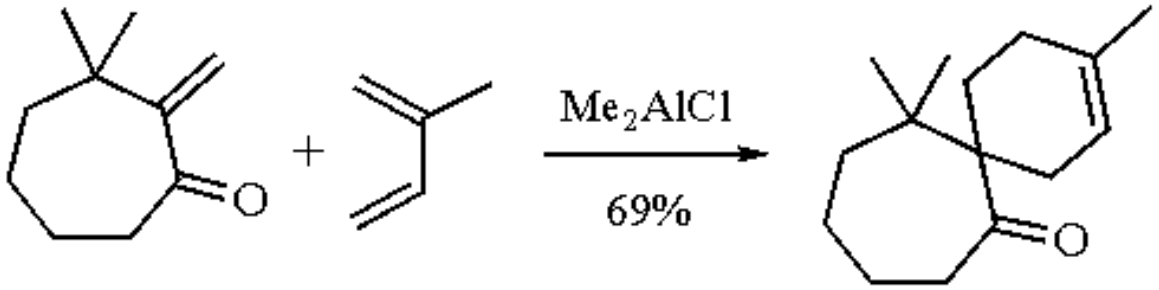

(1)

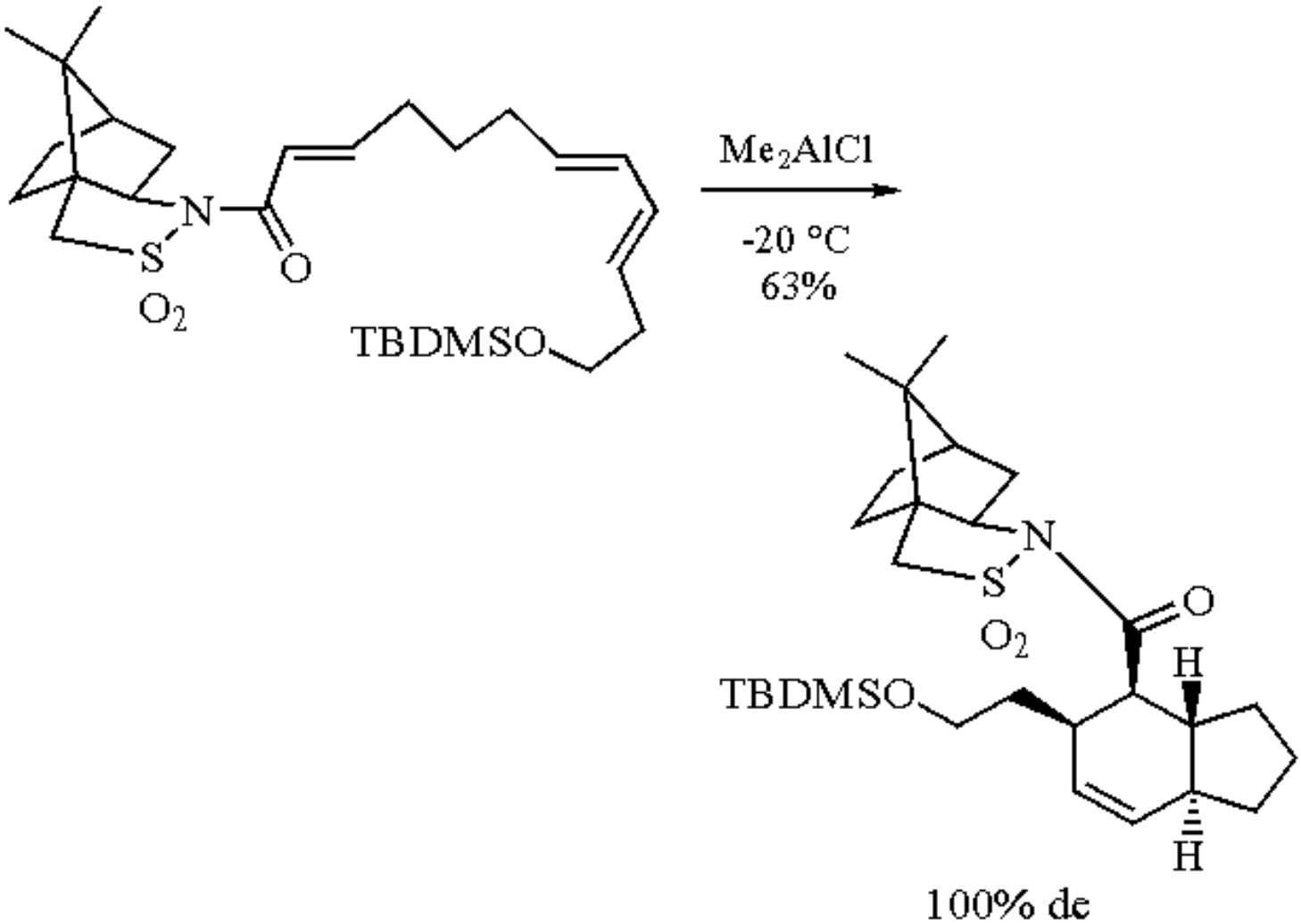

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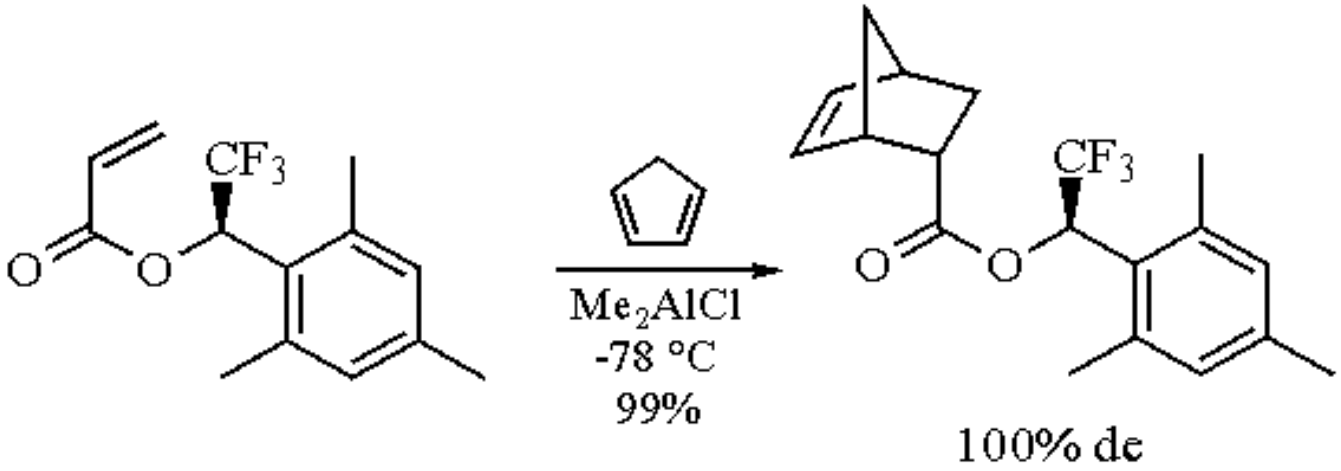

(3)

Catalysis of Ene Reactions.[9]

A wide variety of Lewis acids will catalyze the ene reactions of formaldehyde with electron-rich alkenes. Electron-deficient aldehydes, such as chloral and glyoxylate esters, also undergo ene reactions with a variety of Lewis acid catalysts. Ene reactions of aliphatic and aromatic aldehydes with alkenes that can form a tertiary cation, and of formaldehyde with mono- and 1,2-disubstituted alkenes, are best carried out with 1 or more equiv of Me_2AlCl. The alcohol-Me_2AlCl complex produced in the ene reaction decomposes rapidly to give methane and a nonbasic aluminum alkoxide that does not react further (eq 4). This prevents solvolysis of the alcohol-Lewis acid complex or protonation of double bonds. Good to excellent yields of ene adducts are obtained from aliphatic and aromatic aldehydes and 1,1-di- and trisubstituted alkenes. ***Formaldehyde*** is more versatile and gives good yields of ene adducts with all classes of alkenes.[10] When less than 1 equiv of Me_2AlCl is used, γ-chloro alcohols are formed, resulting from the stereospecifically *cis* addition of the hydroxymethyl and chloride groups to the double bond (eq 5). The chloro alcohols are converted to ene-type adducts in the presence of excess Me_2AlCl. Formaldehyde undergoes Me_2AlCl-induced reactions with terminal alkynes to give a 2:3 mixture of the ene adduct allenic alcohol and the (*Z*)-3-chloro allylic alcohol in 50-75% yield (eq 6).[11]

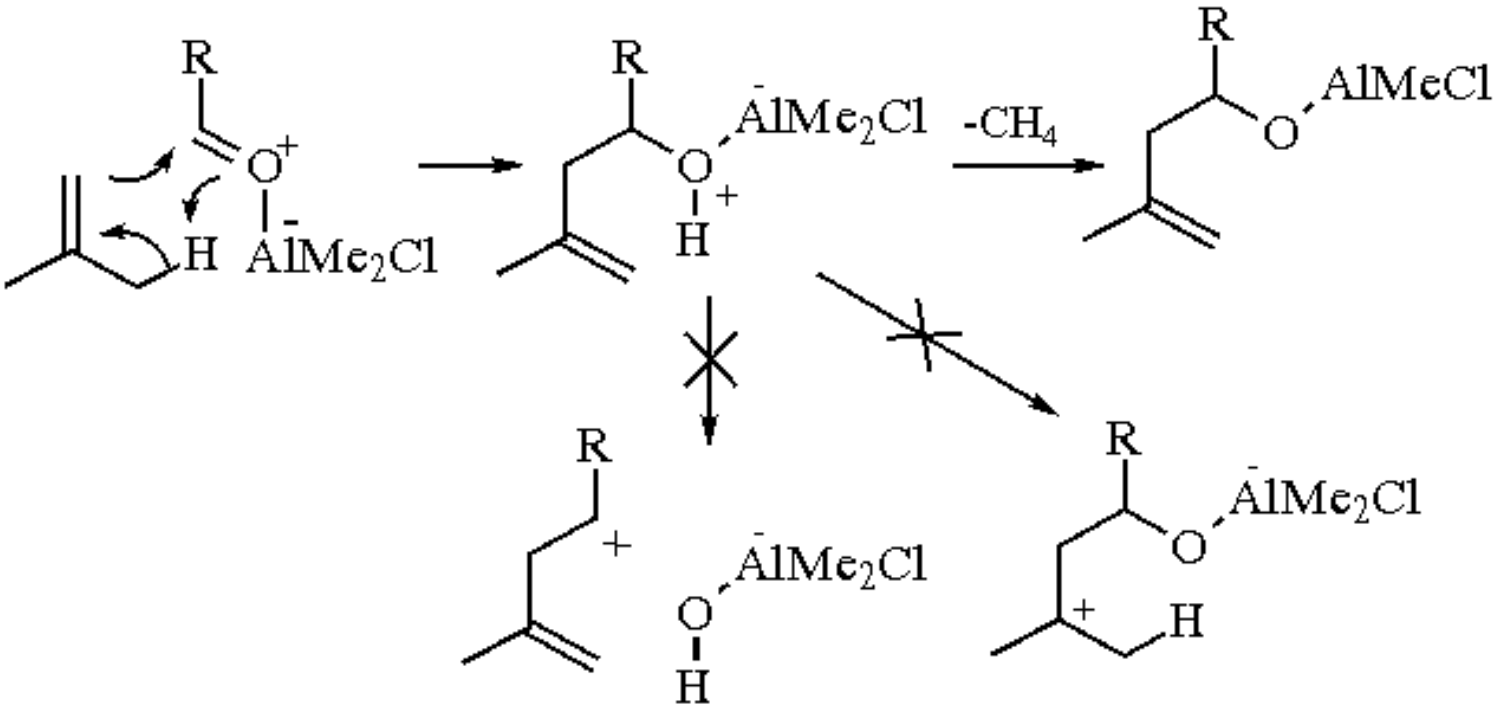

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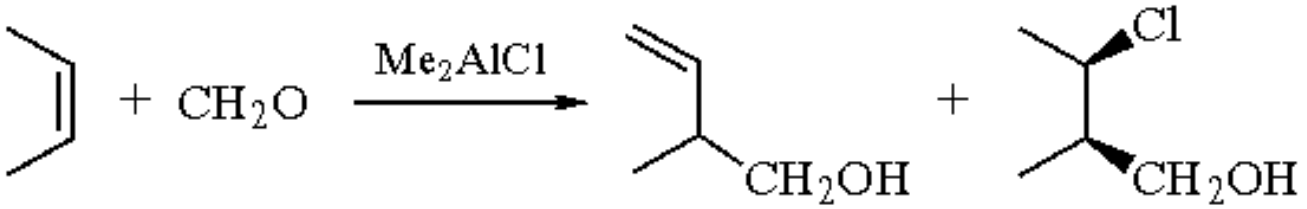

(5)

1 equiv	20%	39%
1.5 equiv	73%	2%

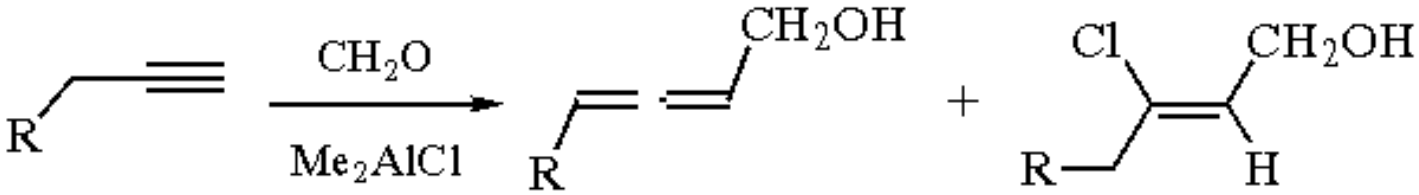

(6)

Me_2AlCl catalyzes the ene reactions of a variety of aldehydes with (*Z*)-3β-acetoxy-5,17(20)-pregnadiene at -78 °C.[12] The stereoselectivity with aliphatic aldehydes is >10:1 in favor of the 22α-isomer, while aromatic aldehydes produce predominantly the 22β-isomer (eq 7). Me_2AlCl is also the Lewis acid of choice for ene reactions of α-halo aldehydes (eq 8).[13] Ene reactions of vinyl sulfides to produce enol silyl ethers are also catalyzed by Me_2AlCl (eq 9).[14]

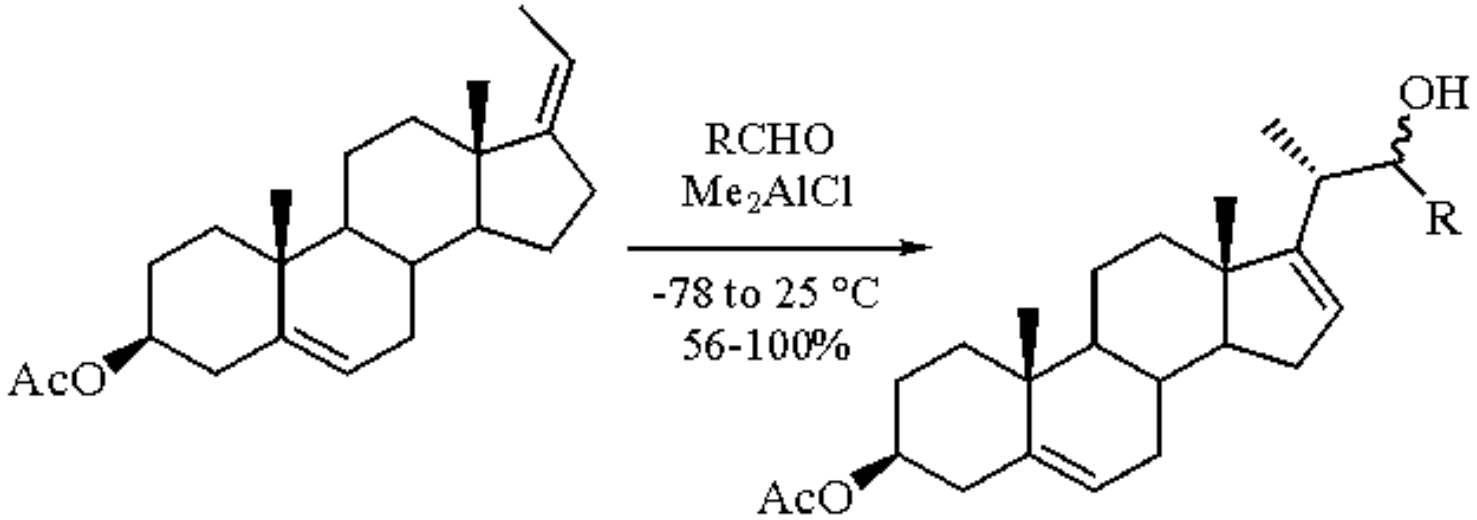

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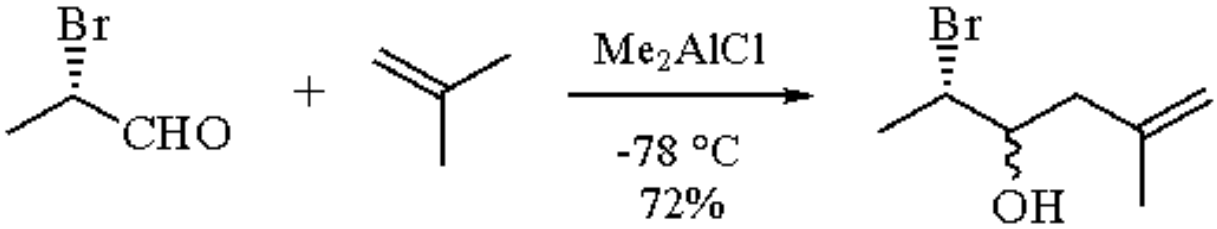

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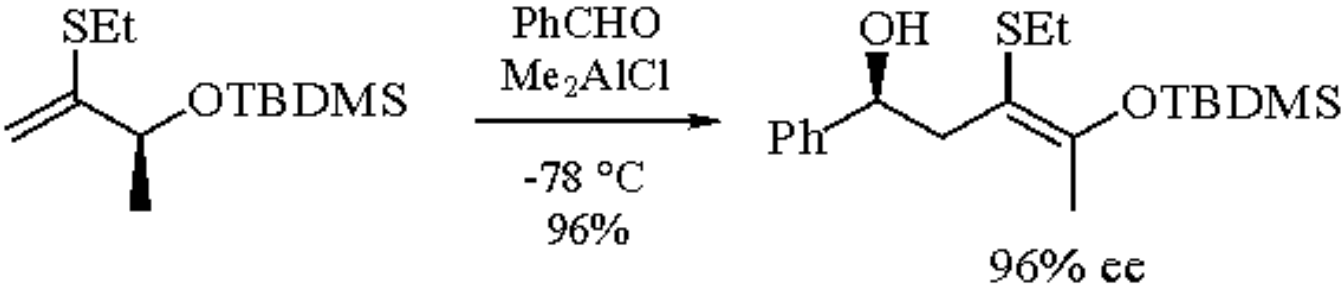

(9)

Type-I intramolecular ene reactions of aldehydes, such as citronellal, that contain electron-rich trisubstituted double bonds proceed readily thermally or with a variety of Lewis acids. Intramolecular ene reactions with less nucleophilic 1,2-disubstituted double bonds proceed efficiently with Me_2AlCl as the Lewis acid catalyst (eqs 10 and 11).[15,16]

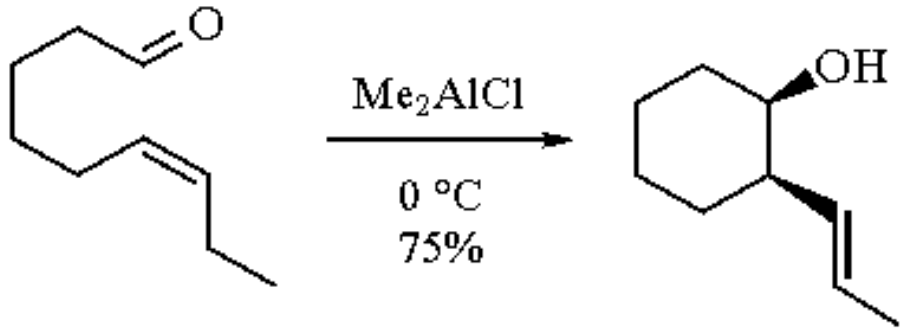

(10)

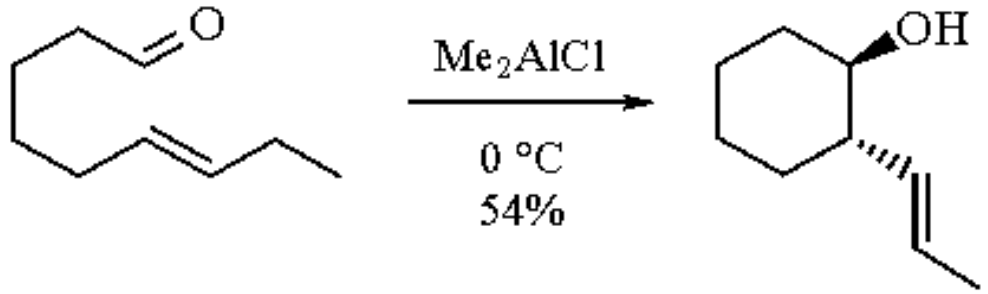

(11)

Type-II intramolecular ene reactions of aldehydes and ketones proceed readily with Me_2AlCl as the Lewis acid.[17-19] Unsaturated aldehydes and ketones can be generated in situ by Me_2AlCl-catalyzed reaction of ***Acrolein*** and ***Methyl Vinyl Ketone*** with alkylidenecycloalkanes at low temperatures (eq 12).[17] The monocyclic aldehyde reacts further under these conditions. The monocyclic ketone can be isolated at low temperature but undergoes a second ene reaction at rt to give the bicyclic alcohol. β-Keto esters form tertiary alcohols in intramolecular ene reactions. The products are stable because they are converted to the aluminum alkoxide (eq 13).[18] Intramolecular Me_2AlCl-catalyzed ene reactions have been used for the preparation of the bicyclic mevinolin ring system (eq 14).[19]

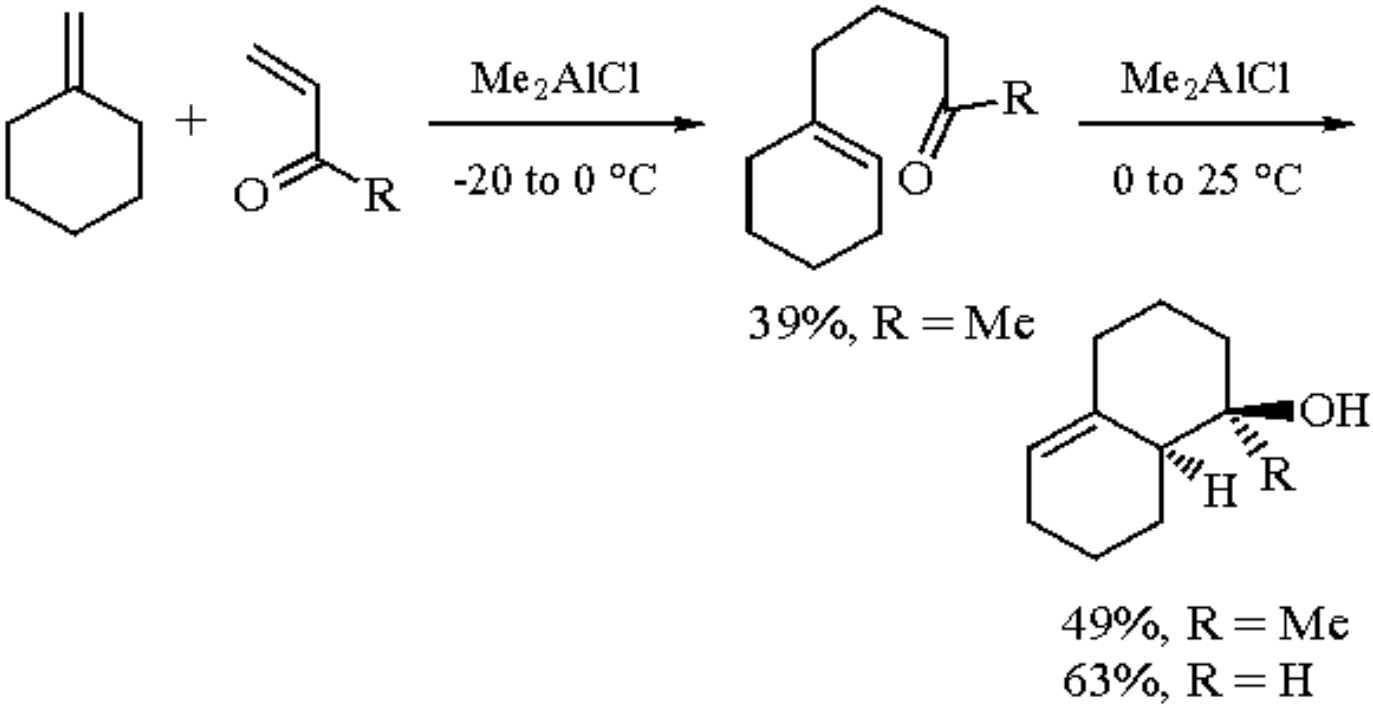

(12)

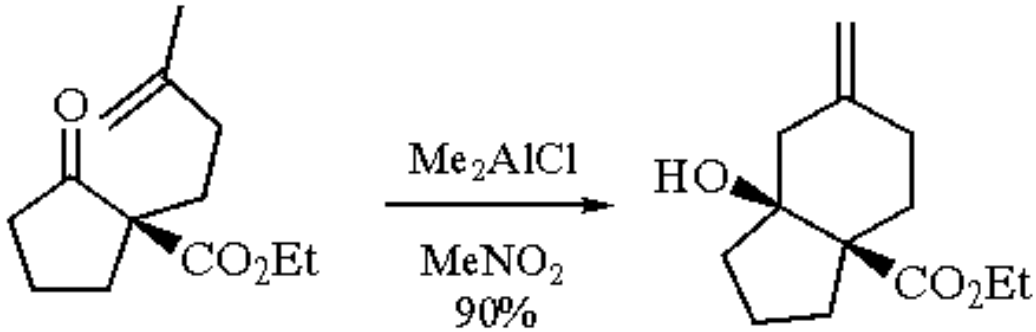

(13)

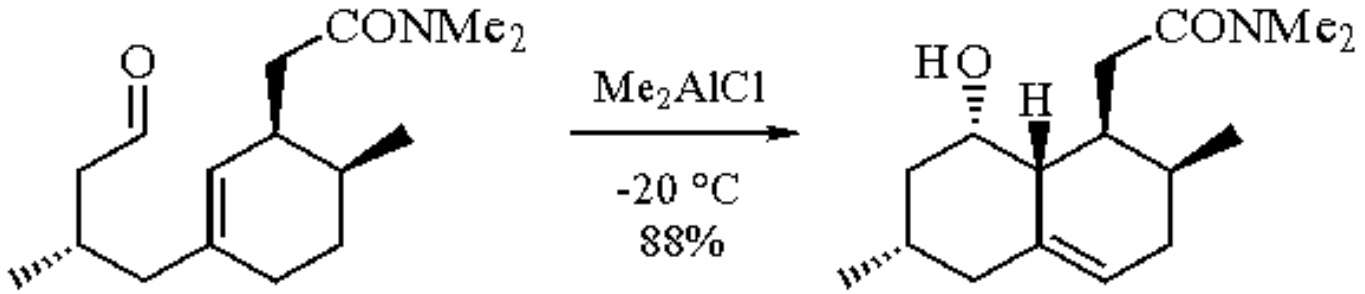

(14)

Generation of Electrophilic Cations.

Me_2AlCl in dichloromethane cleaves THP ethers without deprotecting *t*-butyldimethylsilyl ethers.[20] Azido enol silyl ethers undergo Me_2AlCl-catalyzed reactions with ***Allyltributylstannane*** and enol ethers, giving conjugate addition-type products that are isolated as the silyl enol ethers (eq 15).[21] Me_2AlCl will open norbornane epoxide to the rearranged chlorohydrin.[22]

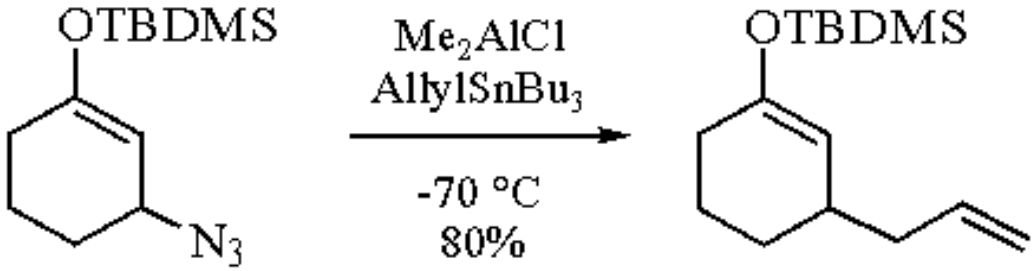

(15)

Formation and Reaction of Aluminum Enolates.

Aluminum enolates prepared from esters react with imines to give a β-lactam resulting from aldol-type addition followed by ring closure (eq 16).[23]

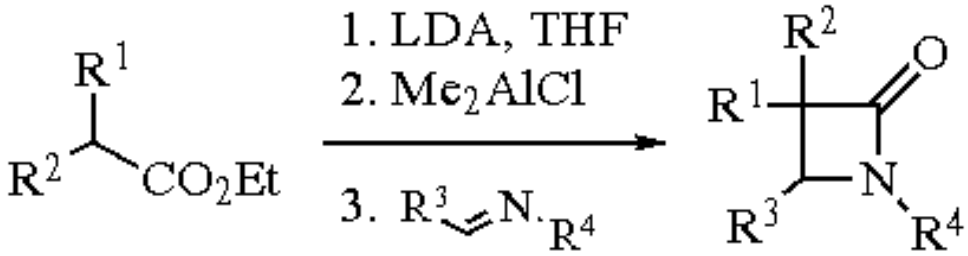

(16)

Formation and Reaction of Alkynylaluminum Reagents.

Lithium acetylides react with Me_2AlCl to give dimethylaluminum acetylides that react analogously to the more commonly used diethylaluminum acetylides (see ***Diethylaluminum Ethoxyacetylide***). Addition of the aluminum acetylide to propiolactone results in an S_N2 reaction to give an alkynic acid (eq 17).[24]

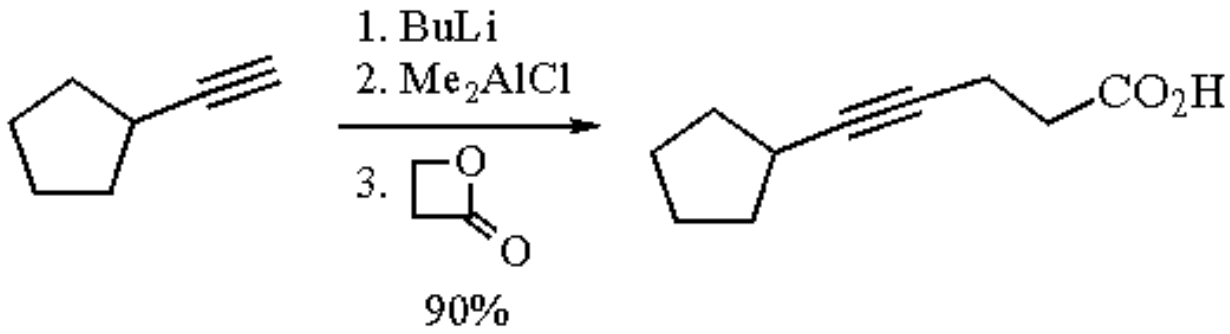

(17)

Reaction as a Nucleophile.

Me_2AlCl will react analogously to MeMgBr and transfer a methyl group to many nucleophiles. Since ***Methylmagnesium Bromide*** and ***Methyllithium*** are readily available, use of Me_2AlCl to deliver a methyl group is needed only when the stereochemistry of addition is an important issue. High levels of asymmetric induction are obtained in the conjugate addition of Me_2AlCl to unsaturated acyloxazolidinones with carbohydrate-derived chiral auxiliaries (eq 18).[25] Me_2AlCl differs from higher dialkylaluminum chlorides in that methyl addition is a radical process that requires photochemical or radical initiation. Me_2AlCl will convert acid chlorides to methyl ketones.[26]

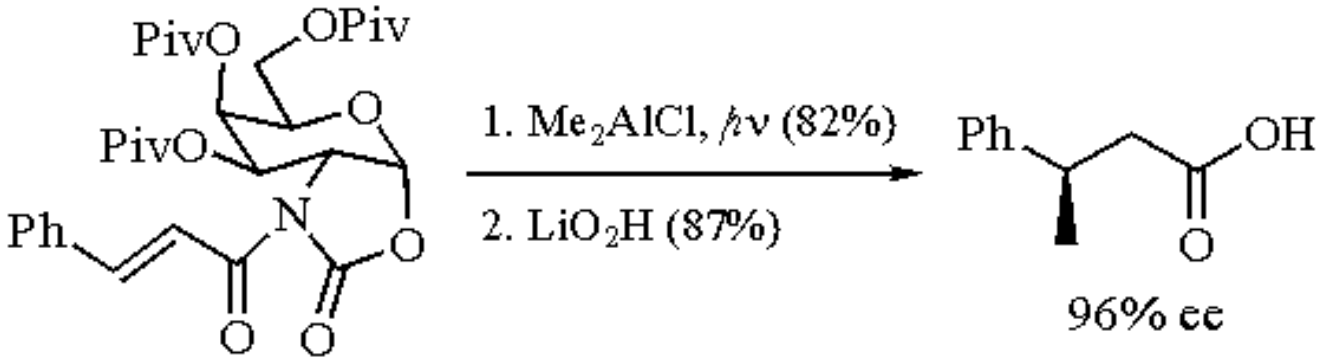

(18)

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Dimethylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide

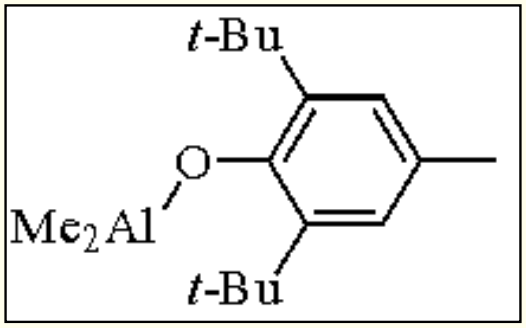

[86803-85-2] · $C_{17}H_{29}AlO$ · Dimethylaluminum 2,6-Di-*t*-butyl-4-methylphenoxide · (MW 276.44)

(designer Lewis acid for amphiphilic alkylation,[1] amphiphilic reduction,[2] stereoselective Diels-Alder reaction;[3] oxidative methylation[4])

Alternate Name: DAD.

Solubility: sol CH_2Cl_2, toluene, hexane.

Preparative Method: by reaction of a 1-2 M hexane solution of ***Trimethylaluminum*** with 1 equiv of 2,6-di-*t*-butyl-4-methylphenol in toluene or CH_2Cl_2 at room temperature for 1 h.[1,2]

Handling, Storage, and Precautions: the concentrated reagent and solutions are highly flammable and must be handled in the absence of oxygen and moisture. Solutions should be used as prepared for best results.

Amphiphilic Alkylation.

DAD is a bulky, oxygenophilic organoaluminum reagent which, like ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD), has been utilized for stereoselective activation of carbonyl groups. The combination of DAD with Grignard reagents or organolithium reagents generates an amphiphilic alkylation system which reacts with substituted cyclohexanones to afford equatorial alcohols, frequently the minor product with other organometallics (eq 1).[1] In general, MAD gives more reliable results in this amphiphilic alkylation than DAD (eq 2).

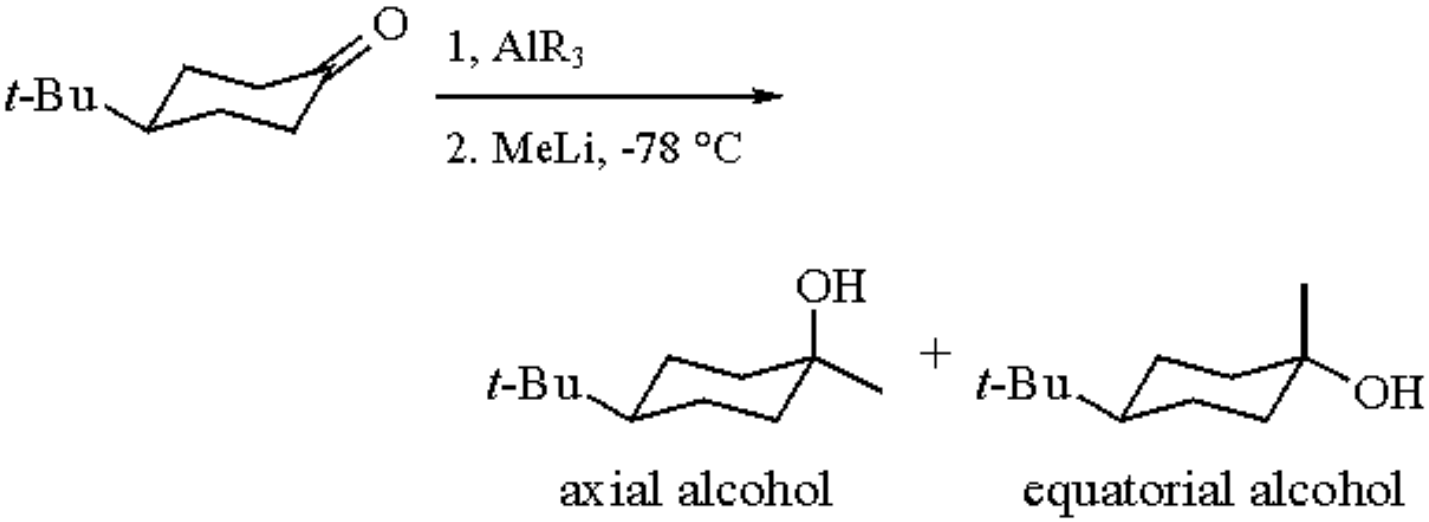

Al reagent:	none	79:21	
	Me_3Al	76:24	
	i-Bu_3Al	64:36	
	Me_2AlOPh	72:28	
	DAD	5:95	81%
	MAD	1:99	84%

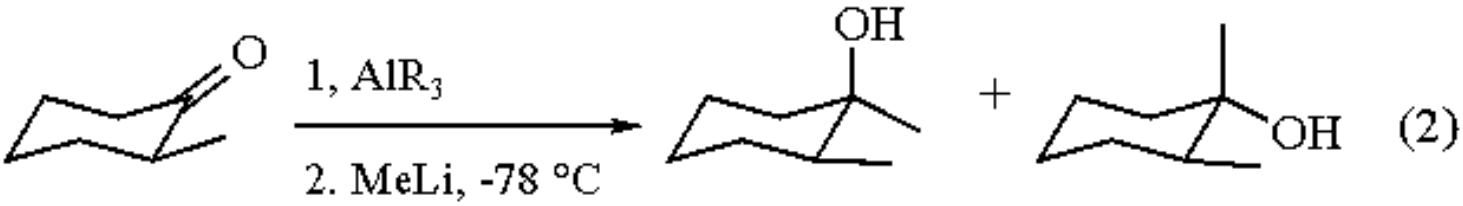

Al reagent:	none		92:8
	DAD	80%	58:42
	MAD	84%	14:86

Amphiphilic Reduction.

When a bulky nucleophile such as ***t-Butylmagnesium Chloride*** is employed for the amphiphilic reaction system using DAD, substituted cyclohexanones afford equatorial alcohols almost exclusively as reduction products with high selectivity (eq 3).[2]

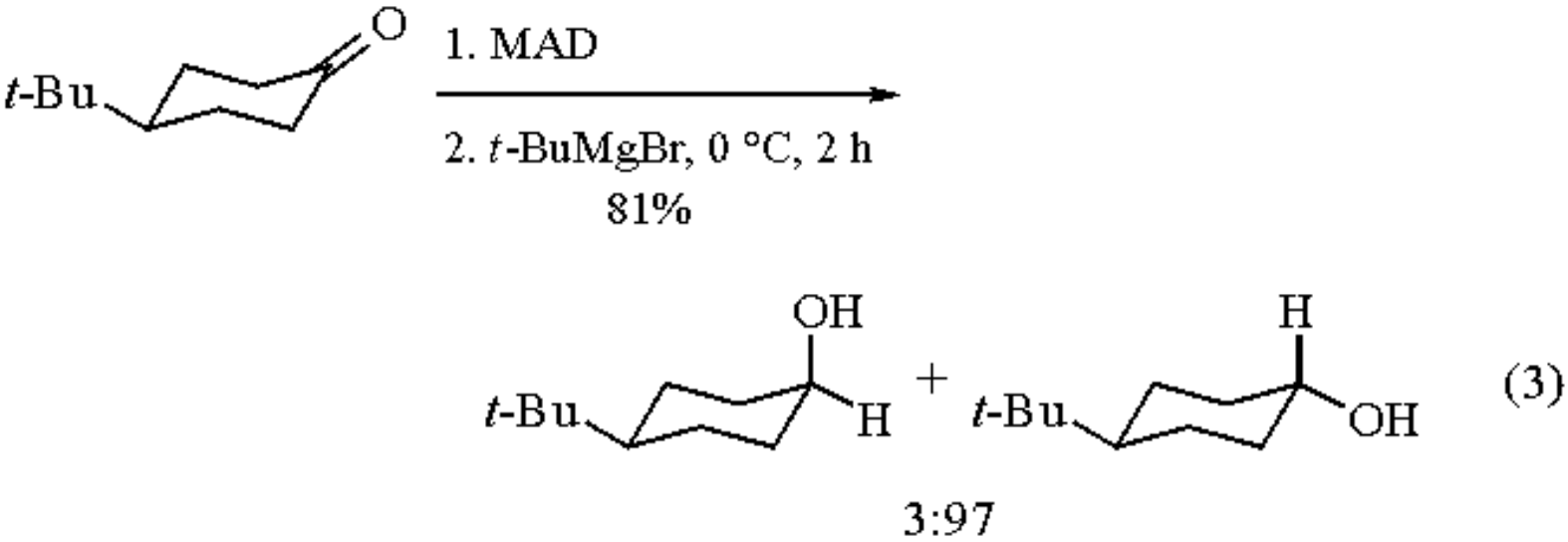

Stereoselective Diels-Alder Reaction.

The steric effect of DAD on the stereoselectivity in Diels-Alder reactions of cyclic dienes and α,β-unsaturated aldehydes has been studied.[3] For example, the ***Boron Trifluoride Etherate*** catalyzed Diels-Alder reaction of cyclopentadiene with acrolein gives a mixture of *endo*- and *exo*-adducts in a ratio of 9:1. The *endo* selectivity is improved by use of trimethylaluminum. Introduction of a more bulky 2,6-di-*t*-butyl-4-methylphenoxy group on aluminum by use of DAD results in a further enhancement in *endo* selectivity (eq 4). However, use of the even more hindered MAD catalyst lowers the *endo* selectivity.

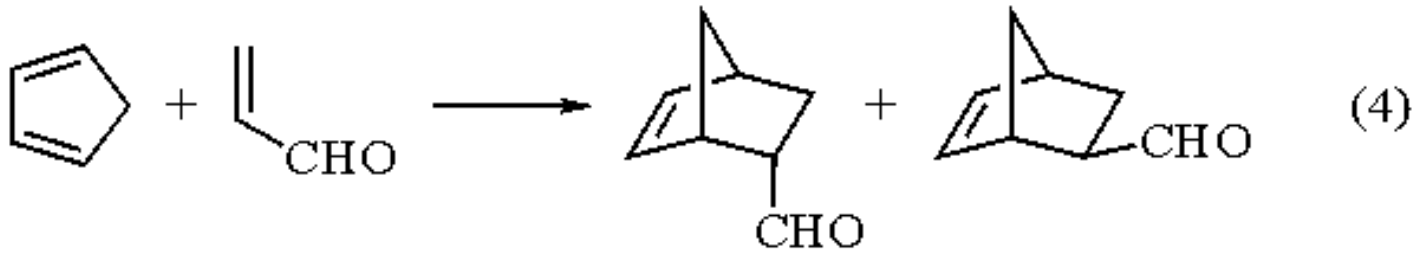

$BF_3 \cdot OEt_2$	9:1	46%
Me_3Al	24:5	57%
DAD	32:1	52%
MAD	12:1	56%

In contrast, both DAD and MAD enhance *exo* selectivity in the Diels-Alder reaction of cyclopentadiene with methacrolein. This is due to steric repulsion between the bulky catalyst and cyclopentadiene, rather than an electronic effect involving the carbonyl group of the dienophile, as observed in the cycloaddition with acrolein (eq 5).

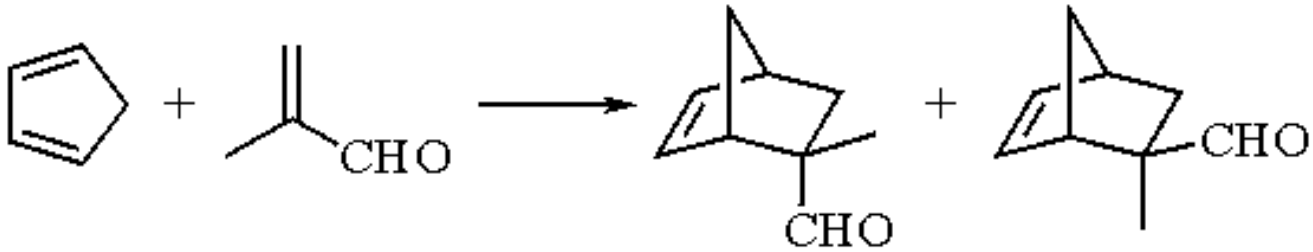

(5)

heat	1:5	
Me_3Al	1:15	64%
DAD	1:24	67%
MAD	1:48	76%

Oxidative Methylation.

A novel and direct transformation of aromatic aldehydes to the corresponding methyl ketones has been accomplished using a DAD/ether complex in toluene at rt (eq 6).[4]

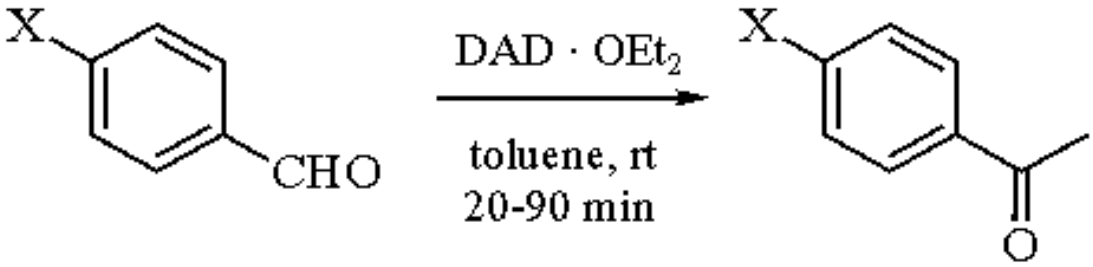

(6)

X = H	100%
X = Me	100%
X = Cl	100%
X = NO_2	84%

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4. (a) Power, M. B.; Barron, A. R. *TL* **1990**, *31*, 323. (b) Power, M. B.; Barron, A. R. *Polyhedron* **1990**, *9*, 233.

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Dimethylaluminum Iodide

Me_2AlI

[2938-72-9] · C_2H_6AlI · Dimethylaluminum Iodide · (MW 183.96)

(methylating agent; catalyst)

Alternate Name: dimethyliodoaluminum.

Physical Data: bp 111 °C/50 mmHg.[1]

Solubility: sol toluene, benzene.

Form Supplied in: must be prepared.[2]

Handling, Storage, and Precautions: although little is reported in general compilations of safety, normal precautions should prevail. Assume that this reagent behaves like ***Diethylaluminum Iodide***: moisture-sensitive and pyrophoric. Reacts with water to form an explosive and flammable gas. Extremely harmful if vapors are inhaled. The reagent is absorbed through skin. Wear gloves. Corrosive. Air-sensitive; must be stored under inert atmosphere. Use in a fume hood.

Alkylating Agent: Addition to a Carbonyl Group.

When Me_2AlI is used to deliver a methyl group to a carbonyl, there appears to be a powerful solvent effect that directs attack on cyclohexanones (eq 1).[2] Although the reaction specificity is notable, the reaction is of minimal value because most starting material is recovered, often in the range of 90%.

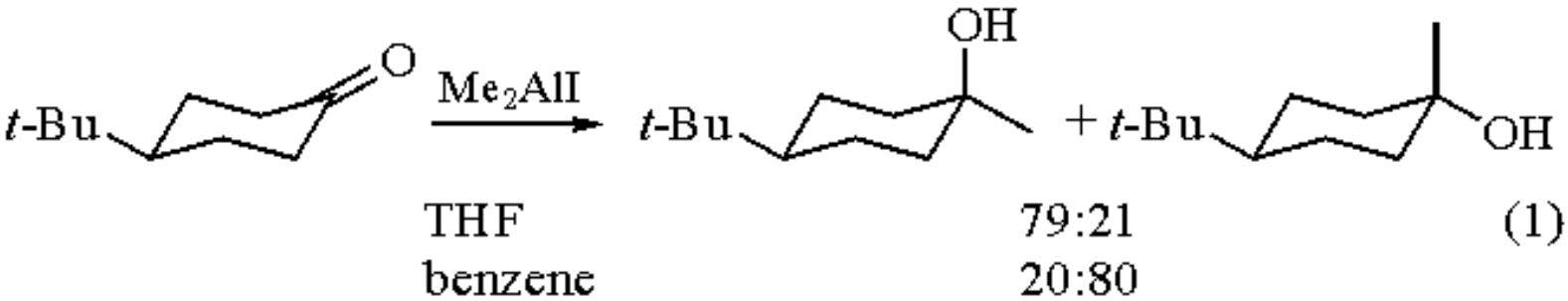

A preference was also noted for 1,4-attack over 1,2-attack (eq 2). As comparison, reaction with ***Trimethylaluminum*** gave exclusive 1,2-attack.

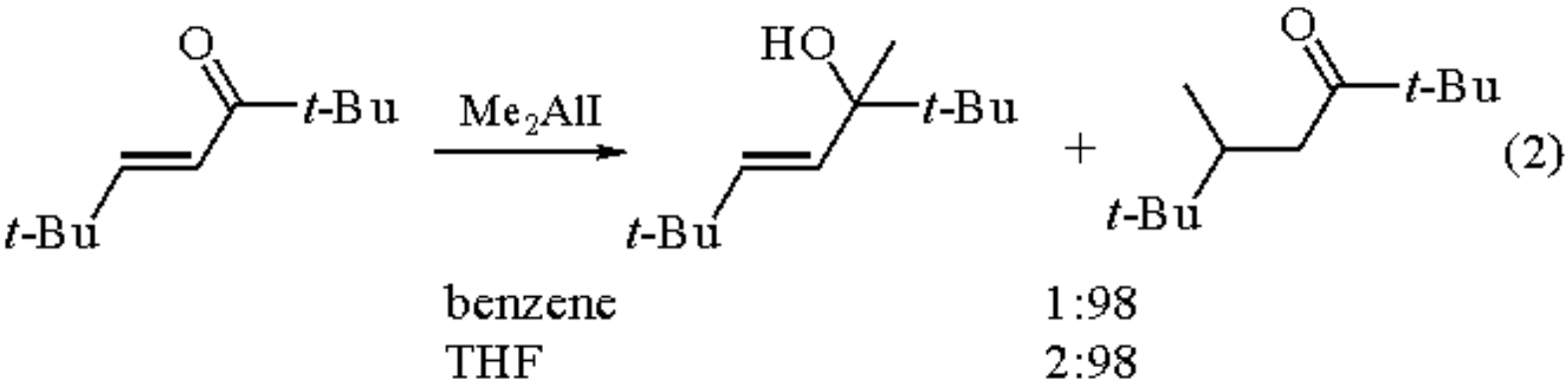

Related Reagents.

Diethylaluminum Chloride; ***Diethylaluminum Iodide***; ***Ethylaluminum Dichloride***; ***Methylaluminum Dichloride***.

---

1. Grosse, A. V.; Mavity, J. M. *JOC* **1940**, *5*, 106.
2. Ashby, E. C.; Noding, S. A. *JOC* **1979**, *44*, 4792.

Bradford P. Mundy

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Dimethylaluminum Methylselenolate[1]

$Me_2AlSeMe$

[67132-62-1] · C_3H_9AlSe · Dimethylaluminum Methylselenolate · (MW 151.04)

(preparation of methyl selenoesters; aldol condensation of enones)

Solubility: reaction are typically run in toluene.

Preparative Methods: conveniently prepared by heating a toluene solution of ***Trimethylaluminum*** with powdered ***Selenium*** for 2 h at reflux.[2] The yellow-colored supernatant was transferred to a septum-capped argon-filled Erlenmeyer flask.

Handling, Storage, and Precautions: the reagent was found to retain its activity for approximately one month at rt. Selenium reagents are toxic and should be handled with caution, in a fume hood.

Methyl Selenoesters.

Methyl and ethyl carboxylates and lactones are converted into methyl selenoesters in almost quantitative yields (eq 1).[2,3] While δ-valerolactone and *trans*-2-hydroxycyclohexane acetic acid γ-lactone were converted cleanly to hydroxy selenoesters, γ-butyrolactone was recovered unchanged. Acetals and isolated double bonds were not affected. Thionoesters are also converted to thionoselenoesters in similar yields.[4,5]

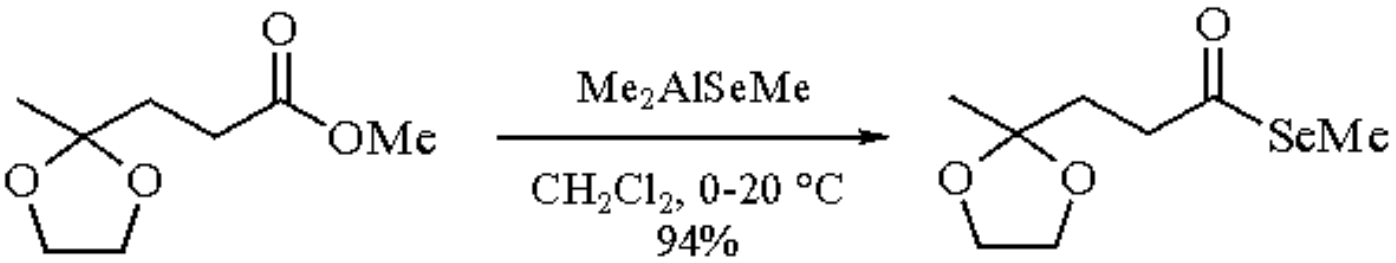

(1)

Methyl *cis*- and *trans*-cyclohexanedicarboxylates are converted to the corresponding selenoesters without enolization (eq 2).[6] The conversion seems to be sensitive to steric factors, allowing selective transformation of one ester group in the presence of others (eqs 3 and 4).[6] *t*-Butyl and trimethylsilyl esters are unreactive.

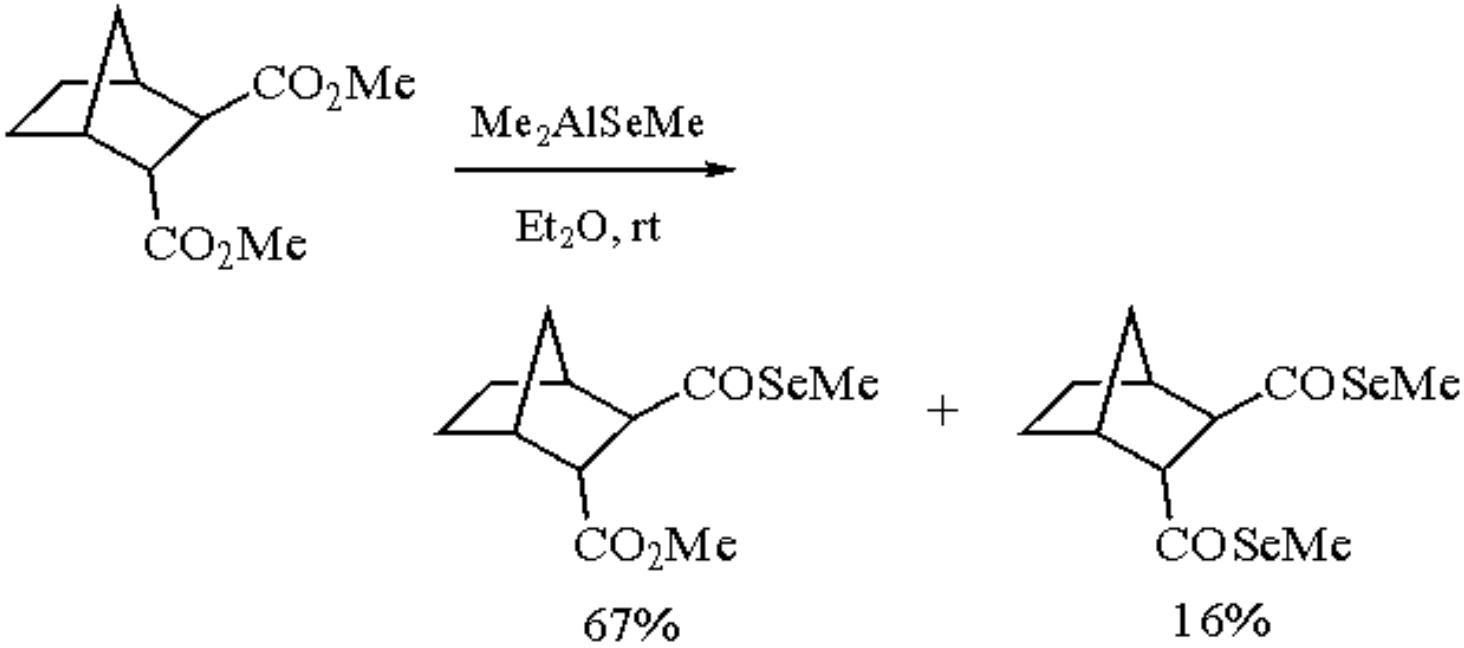

(2)

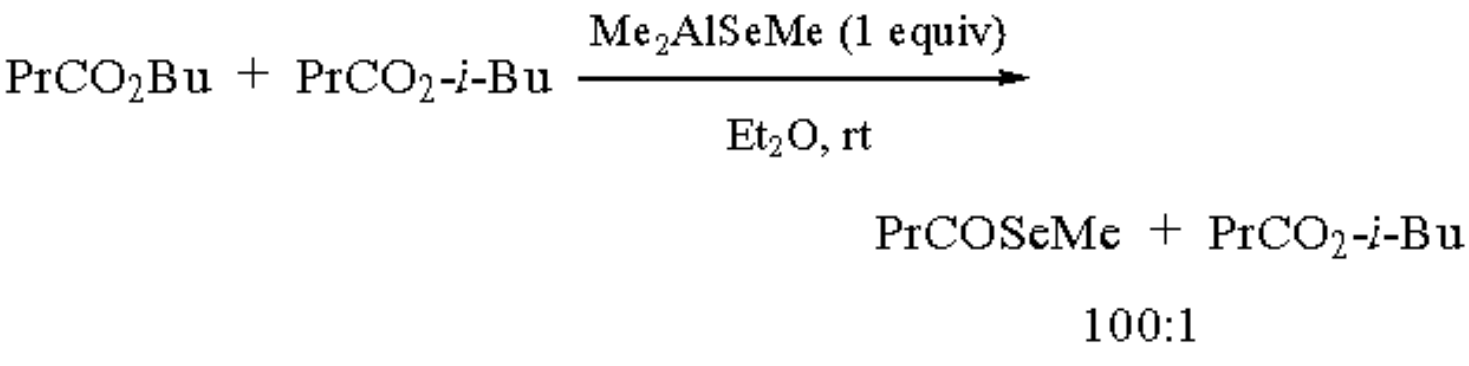

(3)

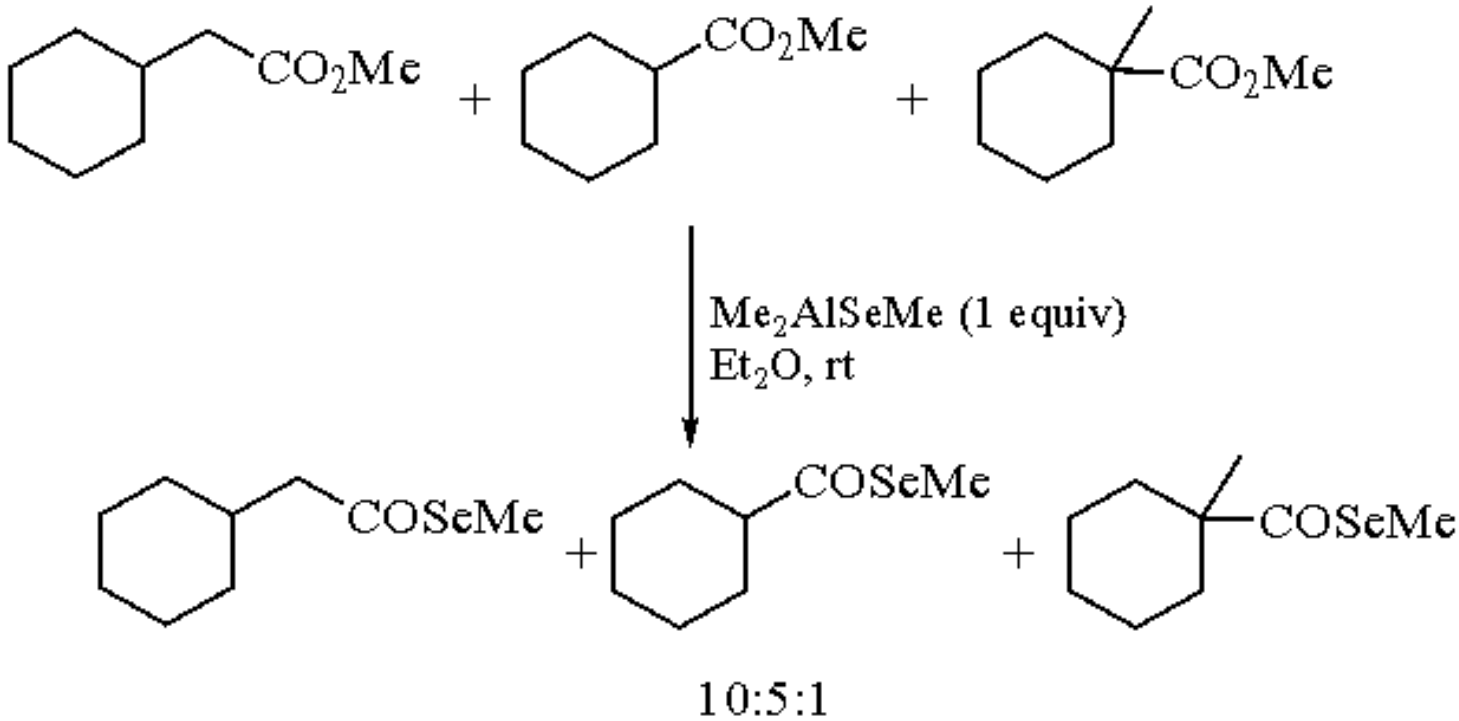

(4)

Selenoesters react with various nucleophiles to afford acids (water), esters (alcohols), and amides (amines).[3] Ketones,

including enones, were prepared in excellent yields from selenoesters and organocuprates.[6,7] Selenoesters gave slightly higher yields compared to corresponding acid chlorides.[7] While organomanganese and organoboronates were also effective, organocadmium and organomercury compounds were not effective.

Selenoesters afford 2-unsubstituted oxazoles upon reaction with various isocyanides in the presence of copper(I) salts and ***Triethylamine*** or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.[3] They are also mild acyl electrophiles in Friedel-Crafts reactions with ***Copper(I) Trifluoromethanesulfonate*** as catalyst (eq 5).[3] Benzene was not acylated and toluene was acylated in low yield.

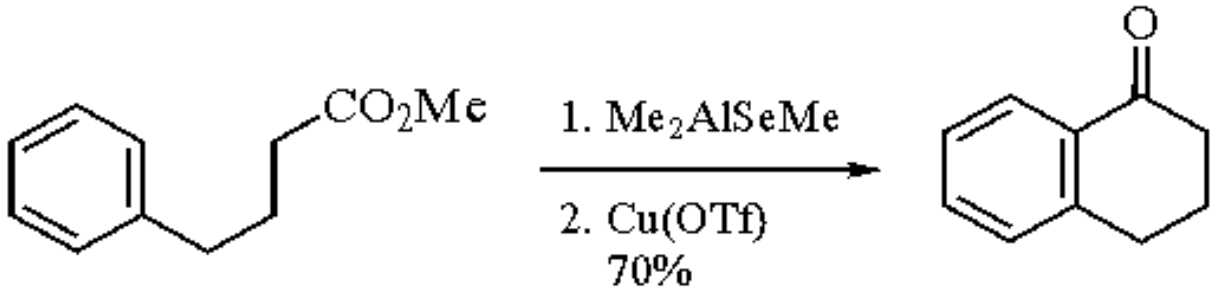

(5)

Aldol Condensation of Enones.

This reagent adds methylselenol to enones in 1,4-fashion. The intermediate, an aluminum enolate, undergoes aldol condensation with aldehydes (see ***Diethylaluminum Thiophenoxide***) (eq 6).[8,9] This reagent also converts δ-alkylidene-δ-lactones to 1,3-cyclohexanediones, probably via an aluminum enolate.[10]

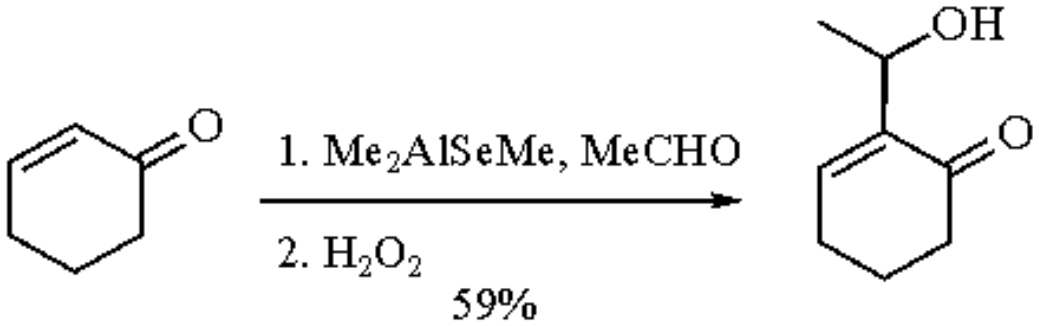

(6)

Beckmann Rearrangement.

Beckmann rearrangements of cyclododecanone and acetophenone oxime mesylates have been accomplished to afford an imino selenoether with 2 equiv of the title reagent (eq 7).[11]

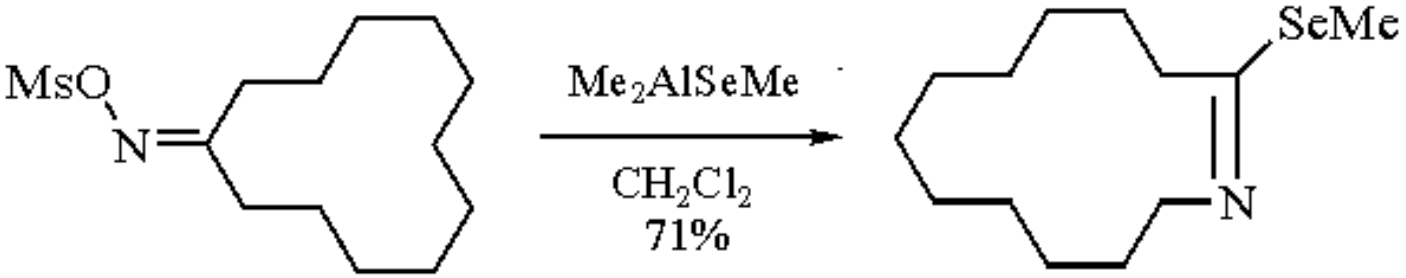

(7)

This reagent can also open up oxiranes in preference to selenoester formation.[2,3]

---

1. Fieser, M. *FF* **1980**, *8*, 182; **1986**, *12*, 197.
2. Kozikowski, A. P.; Ames, A. *JOC* **1978**, *43*, 2735.
3. Kozikowski, A. P.; Ames, A. *T* **1985**, *41*, 4821.
4. Khalid, M.; Ripoll, J.-L.; Vallee, Y. *CC* **1991**, 964.
5. Lemarié, M.; Valleé, Y.; Worrell, M. *TL* **1992**, *33*, 6131.
6. Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *TL* **1983**, *24*, 4355.
7. Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *TL* **1983**, *24*, 4359.
8. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *BCJ* **1981**, *54*, 274.
9. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *TL* **1980**, *21*, 361.
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11. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *JACS* **1983**, *105*, 2831.

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Dimethylaluminum Trifluoromethanesulfonate

Me_2AlOTf

[107259-64-3] · $C_3H_6AlF_3O_3S$ · Dimethylaluminum Trifluoromethanesulfonate · (MW 206.12)

(Lewis acid[1-3])

Solubility: sol dichloromethane, hexane.

Preparative Methods: to a solution of ***Trimethylaluminum*** in dichloromethane at -78 °C was added 1 equiv of ***Trifluoromethanesulfonic Acid***. The resulting mixture was stirred at -78 °C for 30 min and 0 °C for 30 min under N_2.[1]

Handling, Storage, and Precautions: generated in situ and used directly.

Dimethylaluminum trifluoromethanesulfonate is used as a Lewis acid for alkenic cyclizations (eq 1),[1] cationic rearrangements (eq 2),[2] and epoxide-initiated cation-alkene cyclizations (eq 3).[3]

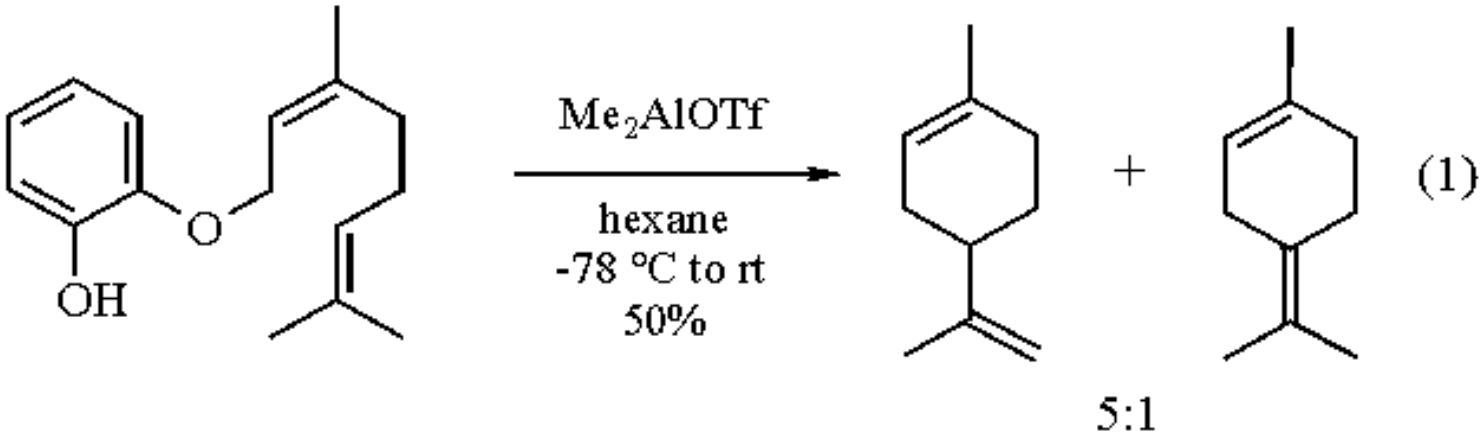

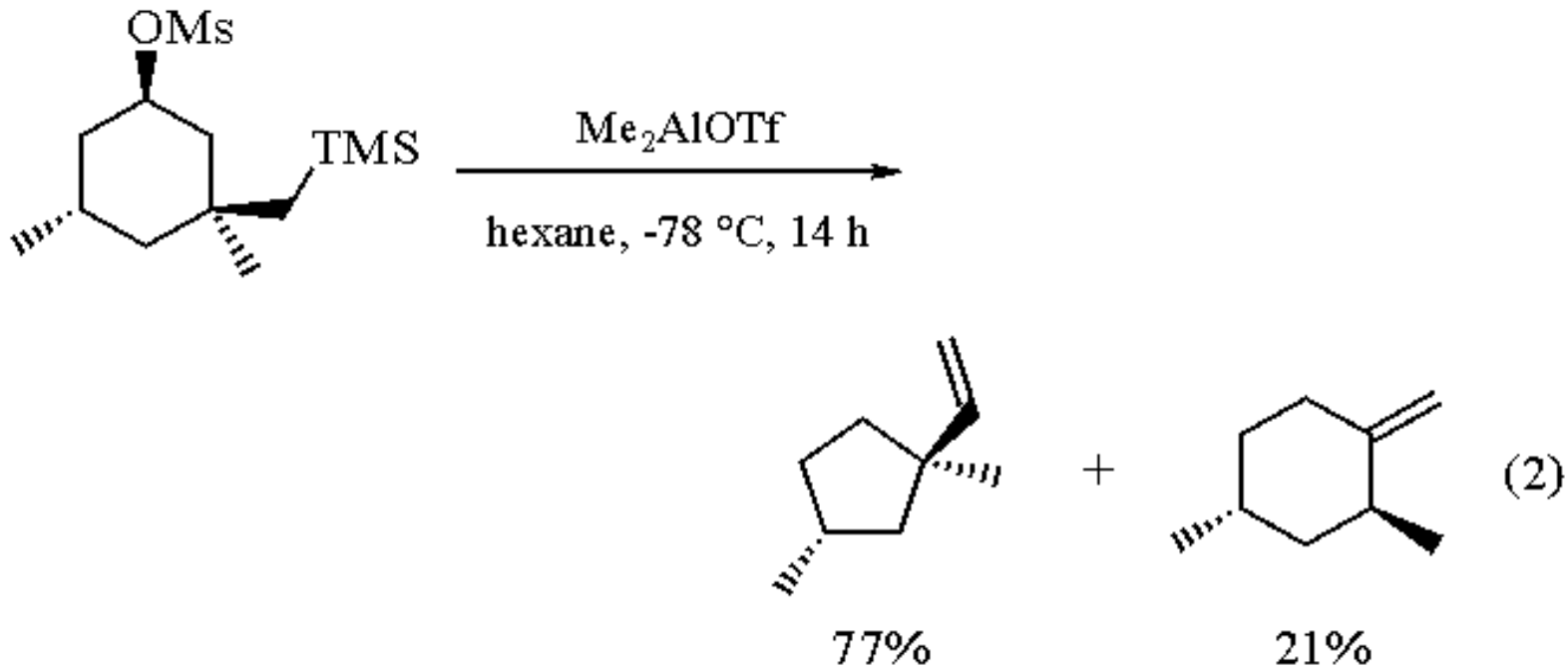

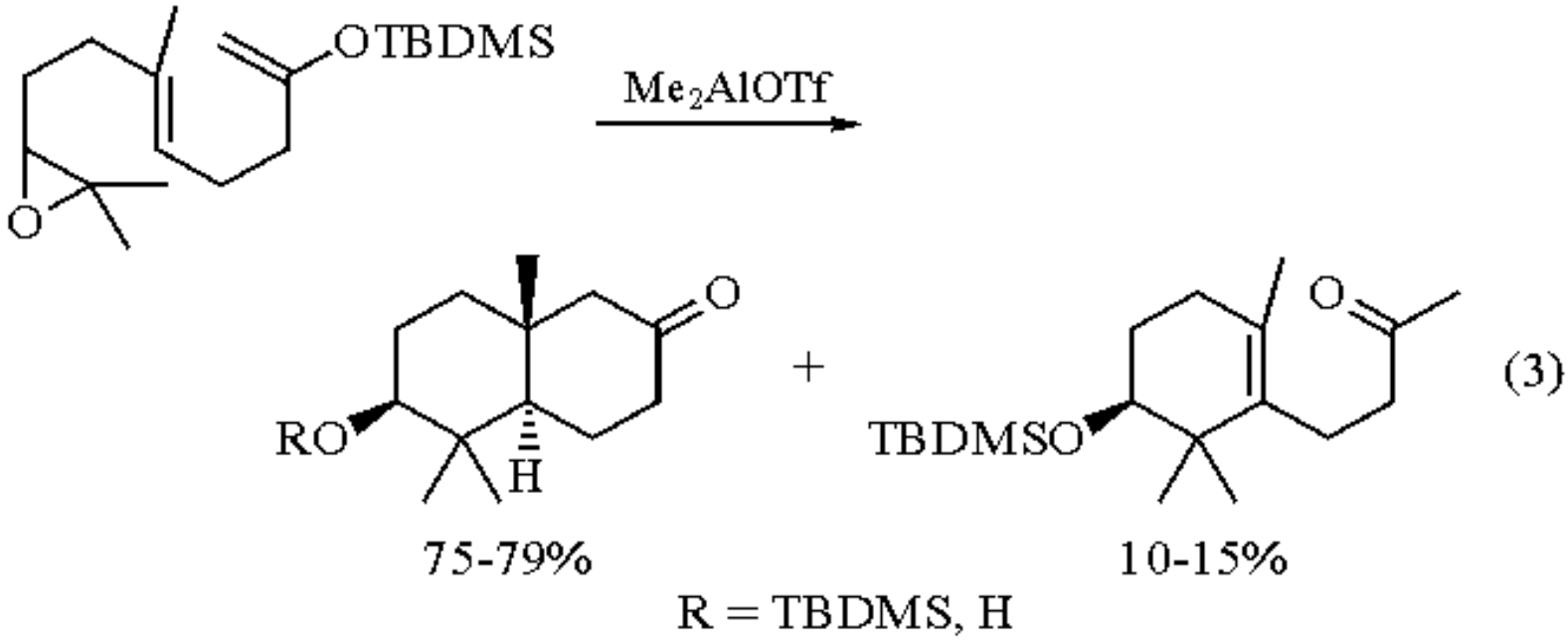

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1. Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *T* **1986**, *42*, 2193.
2. Tanino, K.; Hatanaka, Y.; Kuwajima, I. *CL* **1987**, 385.
3. Corey, E. J.; Sodeoka, M. *TL* **1991**, *32*, 7005.

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Tokyo Institute of Technology, Japan

4-(Dimethylamino)benzaldehyde[1]

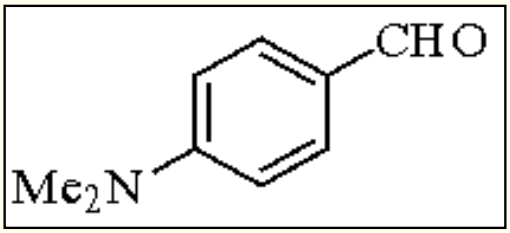

[28602-27-9] · $C_9H_{11}NO$ · 4-(Dimethylamino)benzaldehyde · (MW 149.19)

(preparation of aldehydes from Grignard reagents;[2] color test reagent for pyrroles,[3] primary amines,[4] and hydrazines[5])

Physical Data: mp 74 °C; bp 176-177 °C/17 mmHg.

Form Supplied in: light yellow solid.

Handling, Storage, and Precautions: upon exposure to light, solid will turn pink.

Formylation Reagent.

The reagent reacts with Grignard reagents to give *p*-dimethylaminophenyl carbinols, which upon treatment with diazonium salts undergo cleavage to the aldehyde (eq 1).[2b] Use of diazotized sulfanilic acid at pH 5-6 (0-5 °C) as the cleaving agent is advantageous, as the ether-insoluble methyl orange byproduct is readily separated from the aldehyde. Yields for both steps are generally moderate, being 50-75% for the Grignard addition, and 60-82% for the cleavage reaction.[2a] This method purportedly is advantageous to ethoxymethyleneaniline or ethyl orthoformate in that it provides aldehydes of high purity directly from the ether extracts, and works equally well for the synthesis of aliphatic or aromatic aldehydes (as does the alternative reagent ***Pentacarbonyliron***[6]).

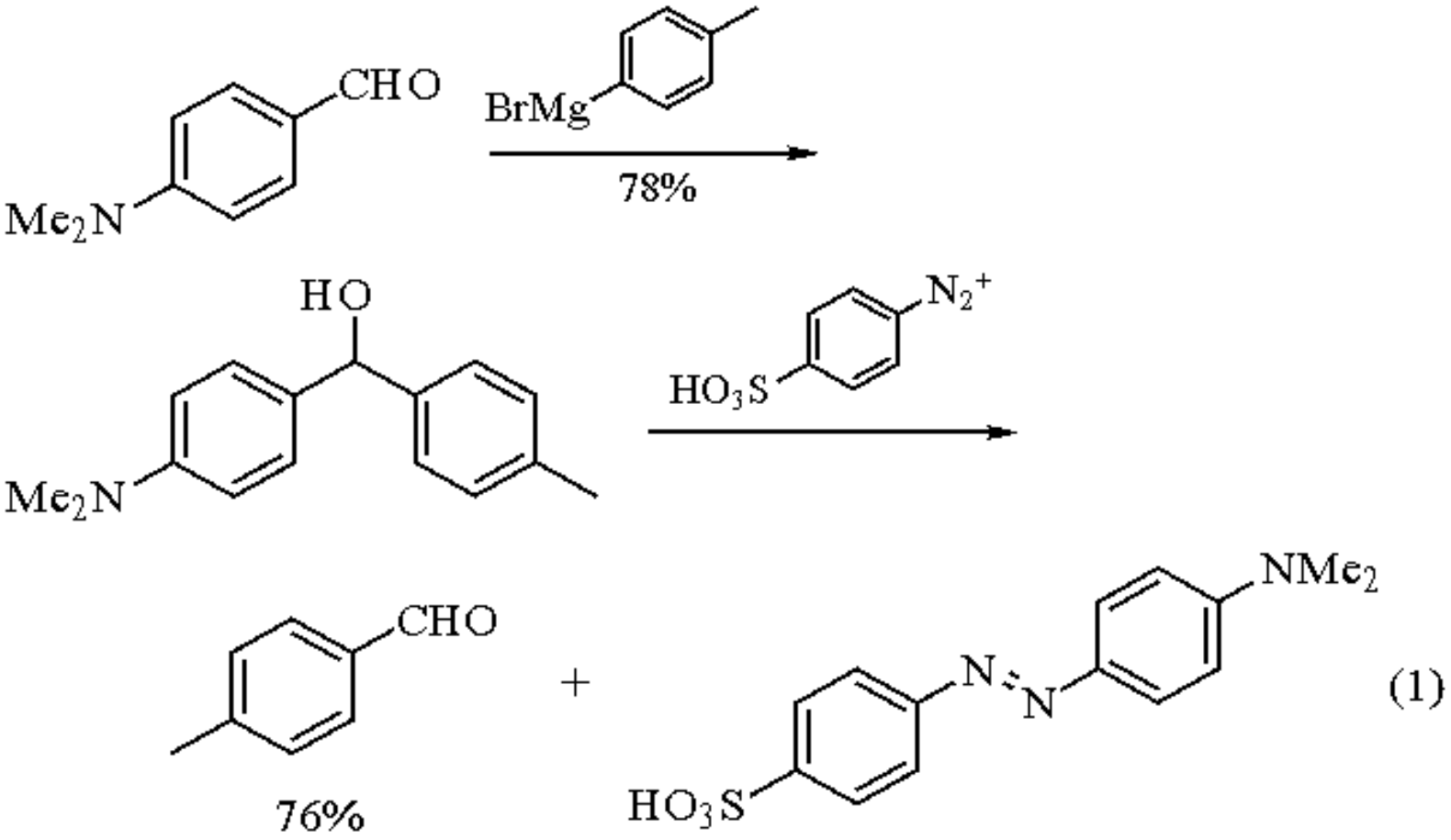

Related Reagents.

N,N-Dimethylformamide; ***N-Ethoxymethyleneaniline***; ***N-Methyl-N-(2-pyridyl)formamide***.

---

1. (a) Carnduff, J. *QR* **1966**, *20*, 169. (b) Roger, R.; Neilson, D. G. *CRV* **1961**, *61*, 179. (c) Kharasch, M. S., Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*, Prentice Hall: Engelwood Cliffs, NJ, 1954.
2. (a) Stiles, M.; Sisti, A. J. *JOC* **1960**, *25*, 1691. (b) Sisti, A.; Burgmaster, J.; Fudim, M. *JOC* **1962**, *27*, 279. (c) Sisti, A. J. *OSC* **1973**, *5*, 46.
3. Feigl, F. *Spot Tests*; Elsevier: Amsterdam, 1954; Vol. 2, p 198.
4. Schreiber, J.; Witkop, B. *JACS* **1964**, *86*, 2441.
5. Feigl, F. *Spot Tests*; Elsevier: Amsterdam, 1954; Vol. 2, p 219.
6. Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *BCJ* **1982**, *55*, 1663.

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2-(Dimethylamino)-3-butenenitrile[1]

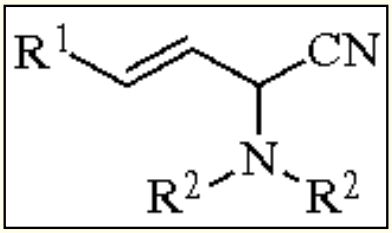

(**1**; R^1 = H, R^2 = Me, Me)

[96840-18-5] · $C_6H_{10}N_2$ · 2-(Dimethylamino)-3-butenenitrile · (MW 110.18) (**2**; R^1 = H, R^2 = $(CH_2)_4$)

[96840-19-6] · $C_8H_{12}N_2$ · 2-(1-Pyrrolidino)-3-butenenitrile · (MW 136.20) (**3**; R^1 = H, R^2 = $(CH_2)_5$)

[96840-20-9] · $C_9H_{14}N_2$ · 2-(1-Piperidino)-3-butenenitrile · (MW 150.25) (**4**; R^1 = R^2 = Me, Me)

[74603-42-2] · $C_7H_{12}N_2$ · 2-(Dimethylamino)-3-pentenenitrile · (MW 124.21) (**5**; R^1 = Me, R^2 = Et, Et)

[81540-41-2] · $C_9H_{16}N_2$ · 2-(Diethylamino)-3-pentenenitrile · (MW 152.27) (**6**; R^1 = Me, R^2 = $(CH_2)_4$)

[74603-43-3] · $C_9H_{14}N_2$ · 2-(1-Pyrrolidino)-3-butenenitrile · (MW 150.25) (*E*)-(**7**; R^1 = Me, R^2 = $(CH_2)_4$)

[101132-09-6] · $C_9H_{14}N_2$ · 2-(Dimethylamino)-3-butenenitrile · (MW 150.25) (*E*)-(**8**; R^1 = Me, R^2 = $(CH_2)_5$)

[101132-11-0] · $C_{10}H_{16}N_2$ · 2-(Piperidino)-3-pentenenitrile · (MW 164.28)

(lithiation gives ambident anions for nucleophilic acylation (acrolein C-1 anion) and for use as ester homoenolate equivalents; synthesis of α-cyano enamines, α´-hydroxy-α,β-enones, γ-lactones, and, by Grignard alkylation, allylic amines)

Physical Data: (**3**) bp 94 °C/10 mmHg; *d* 0.981 g cm^{-3}. (**4**) bp 64-65 °C/10.5 mmHg; *d* 0.876 g cm^{-3}. (**7**) bp 51 °C/0.015 mmHg. (**8**) bp 55 °C/0.015 mmHg.

Metalation.

Deprotonation of either β,γ- or α,β-unsaturated α-(dialkylamino)nitriles with ***Lithium Diisopropylamide*** or ***n-Butyllithium*** at low temperatures generates ambident nitrile-stabilized carbanions.[2-6]

Alkylation.

Alkylation of the nitrile-stabilized carbanions from β,γ- and α,β-unsaturated α-(dialkylamino)nitriles with various electrophiles occurs regioselectively at the γ-position to give α-cyano enamines (α-amino acrylonitriles) (eq 1).[2-6] Substitution at the β-position of these substrates does not change the regioselectivity for γ-alkylation; however, a combination of increased steric hindrance at the β-position *and* diminished size of the α-dialkylamino group leads to mixtures of α- and γ-alkylation products (eq 1; $NR^1R^2 = NMe_2$).[6] In contrast, the β,γ-unsaturated α-(morpholino)nitriles show high α-regioselectivity in alkylations.[7]

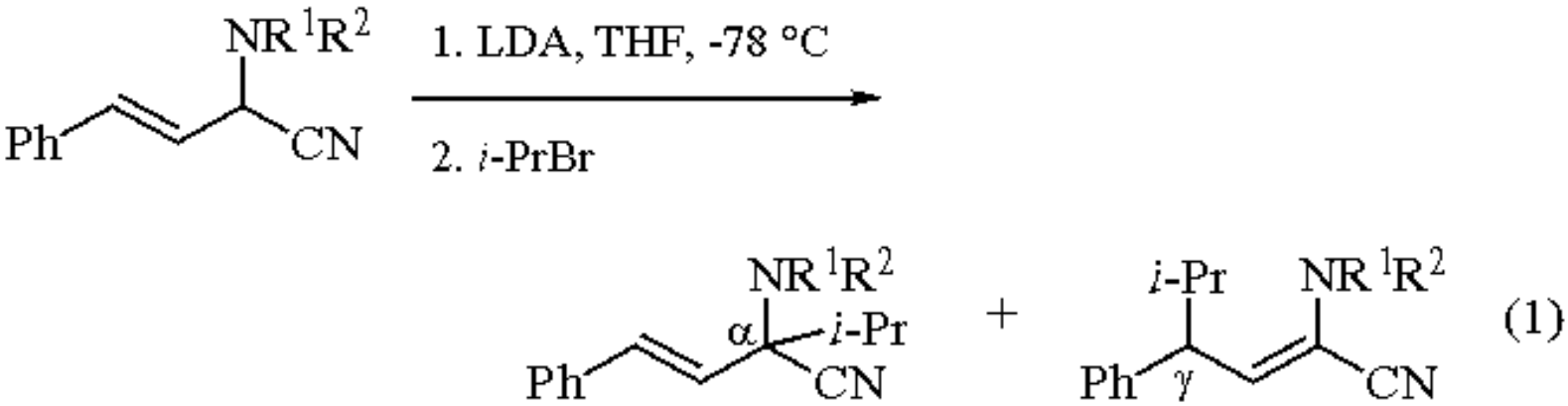

$R^1, R^2 = Me$, 75%, α:γ = 27:73; $R^1 = Me$, $R^2 = Cy$, 64%, α:γ = 0:100

Addition of the nitrile-stabilized anions derived from these unsaturated α-(dialkylamino)nitriles to aromatic[3,4,6] and aliphatic[4] aldehydes occurs at the γ-carbon. However, the corresponding reaction with ketones provides either the kinetic α-alkylation product or the thermodynamic γ-alkylation product depending on conditions. In the former case, hydrolysis of the α-adducts affords α´-hydroxy-α,β-unsaturated ketones (eq 2),[5] whereas in the latter case, hydrolysis of the δ-hydroxy-α-cyano enamines gives rise to γ-lactones (eq 3).[3-5] The addition of an equivalent of anhydrous ***Zinc Chloride*** to these reactions reduces competing aldol condensations.[5] The reaction of the anions of unsaturated α-(dialkylamino)nitriles with α,β-unsaturated ketones generally results in alkylation at the γ-carbon of the nitrile and 1,4-addition to the α,β-unsaturated ketone. With β-substituents on the α,β-unsaturated ketone the kinetic 1,2-γ-product is favored at low temperatures and the thermodynamic 1,4-γ-product is formed at 25 °C.[2]

2-(Dimethylamino)-3-butenenitrile

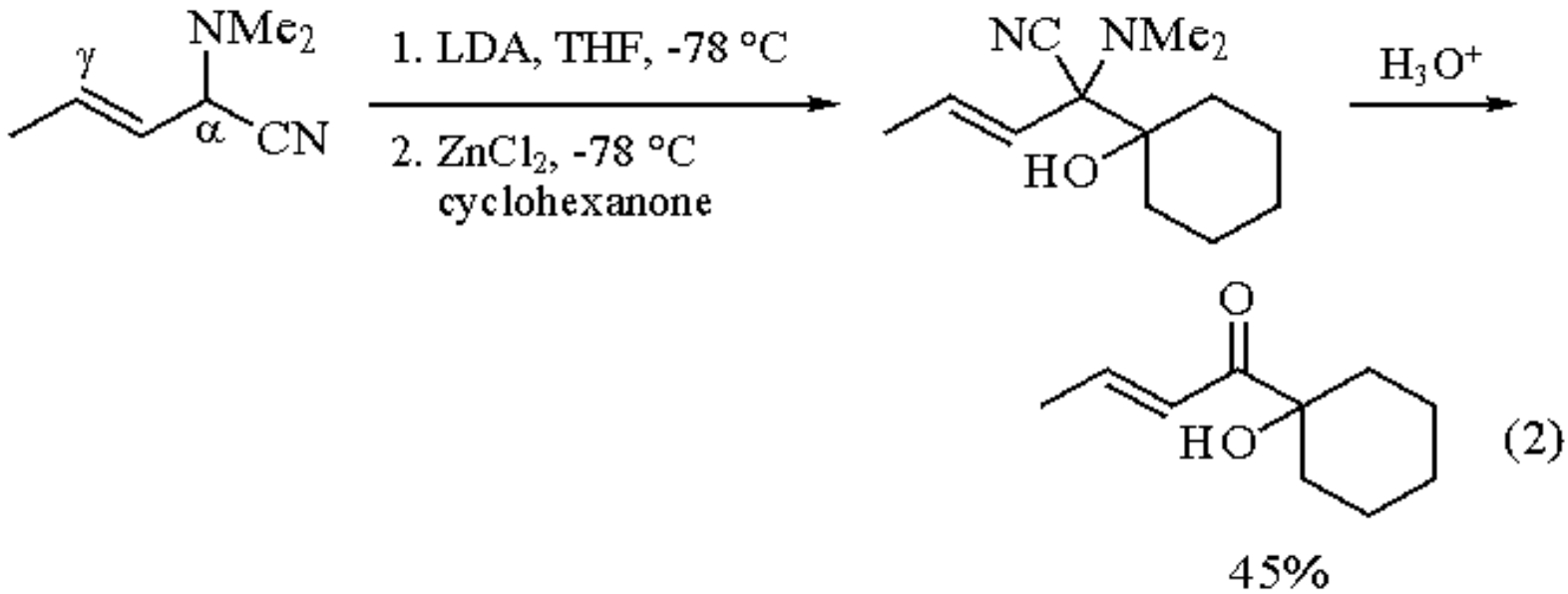

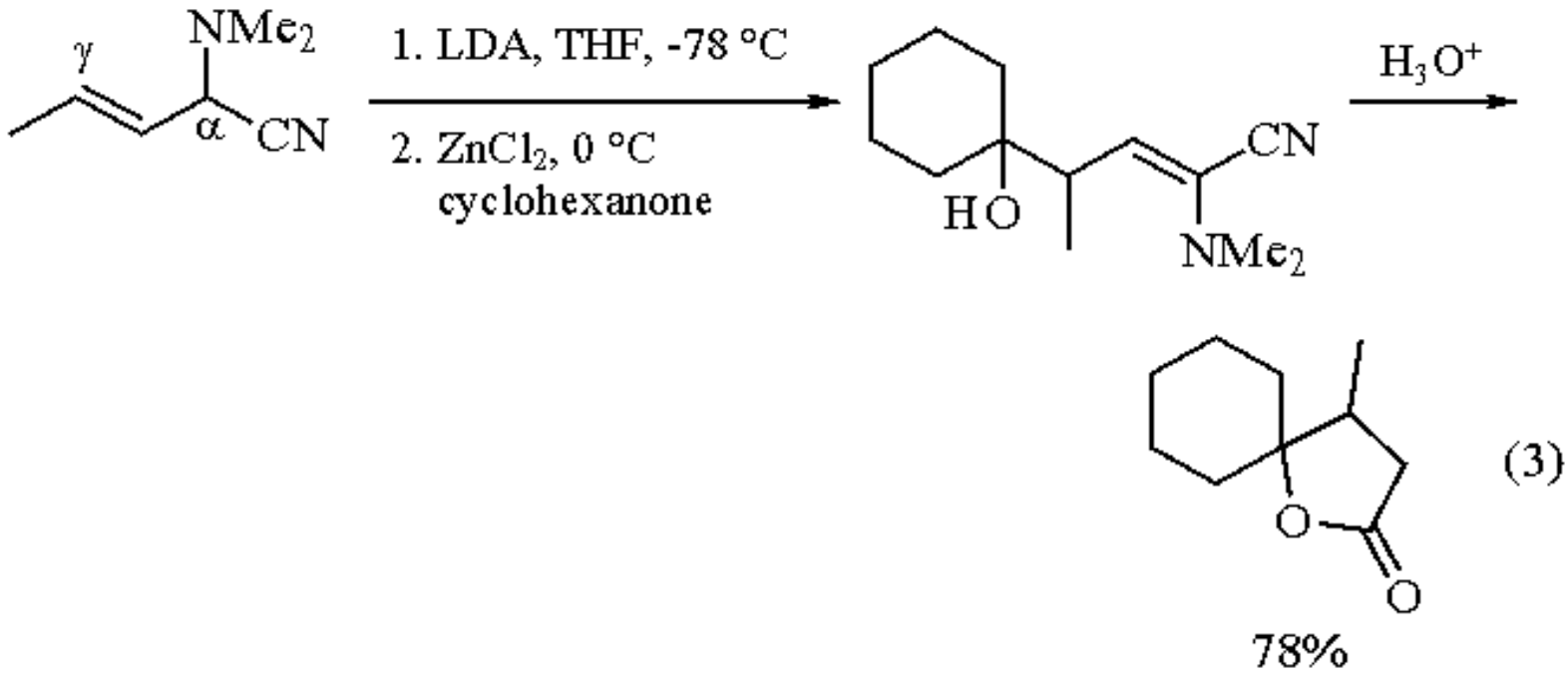

Cyano Group Substitution by Grignard Reagents (Bruylant's Reaction).

The reaction of primary and secondary aliphatic, aromatic, or vinylic Grignard reagents with α-dialkylamino-β,γ-unsaturated nitriles leads to α-substituted allylic amines (eq 4).[8]

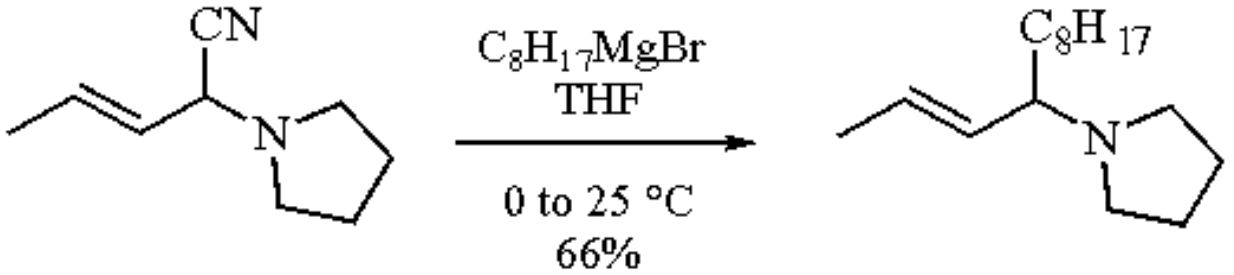

(4)

Related Reagents.

2-(t-Butylamino)-3-methyl-2-butenenitrile; ***1,3-Dibutoxy-1-lithio-1-propene***; ***1-Ethoxy-1-(trimethylsilyloxy)cyclopropane***; ***1-Methoxyallenyllithium***; ***(E)-3-Methylthio-2-propenyl p-Tolyl Sulfone***.

---

1. Albright, J. D. *T* **1983**, *39*, 3207.
2. Lesur, B.; Toye, J.; Chantrenne, M.; Ghosez, L. *TL* **1979**, 2835.
3. Costisella, B.; Gross, H. *T* **1982**, *38*, 139 (*CA* **1982**, *97*, 55 908k).
4. Costisella, B.; Gross, H.; Schick, H. *T* **1984**, *40*, 733 (*CA* **1984**, *101*, 54 818v).
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6. Ahlbrecht, H.; Vonderheid, C. *S* **1975**, 512 (*CA* **1975**, *83*, 206 350m)
7. Takahashi, K.; Honma, A.; Ogura, K.; Iida, H. *CL* **1982**, 1263.
8. Ahlbrecht, H.; Dollinger, H. *S* **1985**, 743.

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4-Dimethylamino-3-butyn-2-one

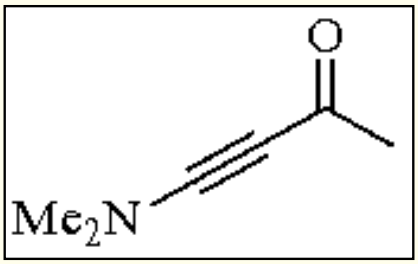

[20568-22-3] · C_6H_9NO · 4-Dimethylamino-3-butyn-2-one · (MW 111.14)

(activates carboxylic acids)

Physical Data: bp 40 °C/10^{-4} mmHg.

Solubility: sol THF.

Preparative Methods: bromination of 4-(dimethylamino)but-3-en-2-one leads essentially in quantitative yield to the hydrobromide which is treated with ***Triethylamine***. Further treatment with ***Potassium t-Butoxide*** leads to the title reagent.[1,2]

Purification: distillation at 40 °C/10^{-4} mmHg.

Handling, Storage, and Precautions: thermally unstable and is best stored at below -50 °C if kept for a prolonged period.

Introduction.

4-Dimethylamino-3-butyn-2-one is used to prepare activated enol esters,[3] which are then reacted further. Aryl carboxylic acids, e.g. benzoic acid, undergo addition to 4-dimethylamino-3-butyn-2-one in THF at -60 °C in the presence of methanol, ethanol, 2-propanol, or *t*-butyl alcohol to give the enol ester (**1**) in high yield (eq 1).

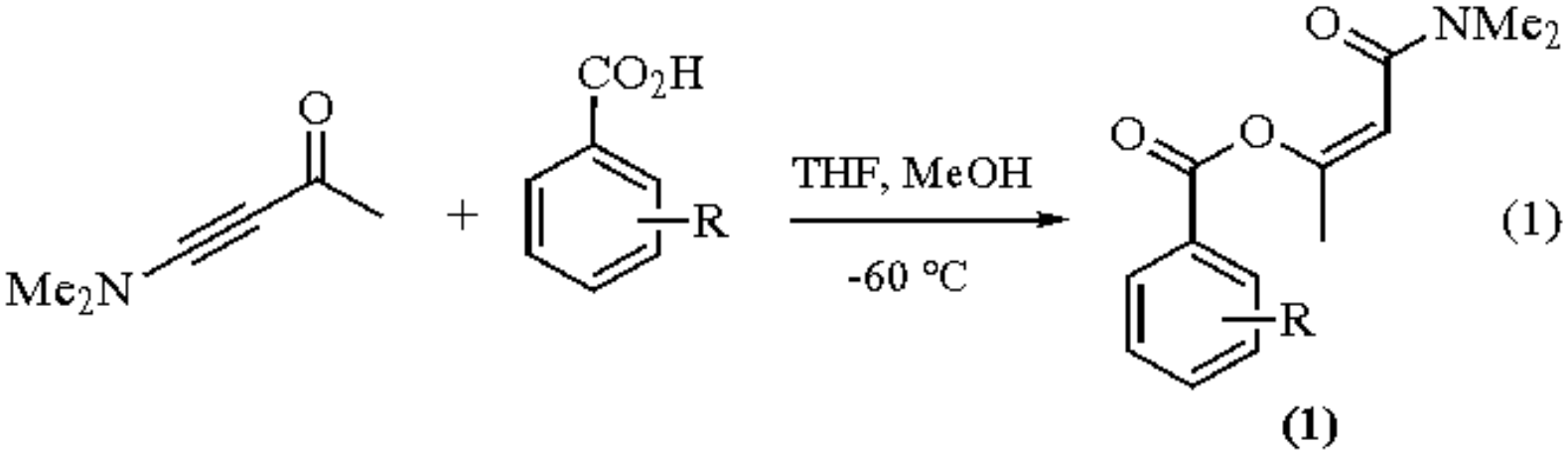

No competing addition of alcohols is observed under these conditions. A diverse range of other carboxylic acids, including those incorporating phenolic, amino and thiol functions have been utilised in this reaction where only products of type (**1**) are seen.

Synthesis of Thiol and Selenol Esters.

Reaction of enol esters with Li, Na, and K salts of primary, secondary, and tertiary thiolates and enolates occurs at 0 °C to give the corresponding thiol and selenol esters (**2**) and (**3**), respectively, in good yields (eq 2).[3]

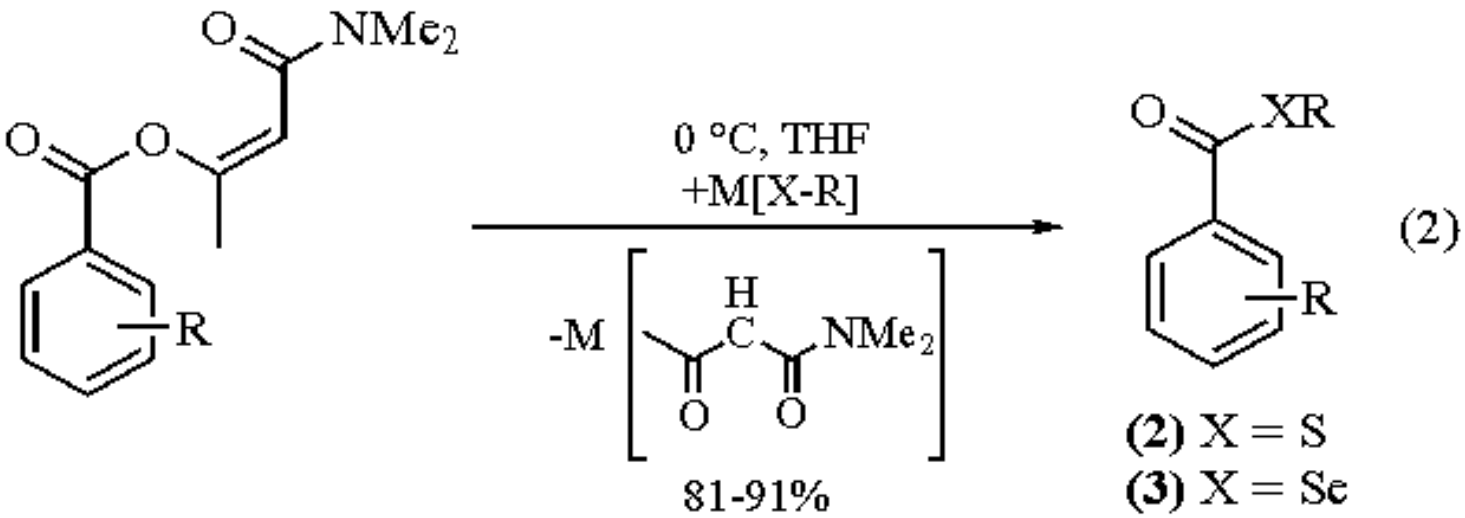

Synthesis of Carboxylic Acid Esters.

Alcohols react with (**1**) in the presence of protic or Lewis acids to give esters (eq 3);[5] this esterification procedure has also been applied to the generation of large ring lactones (eq 4).[4]

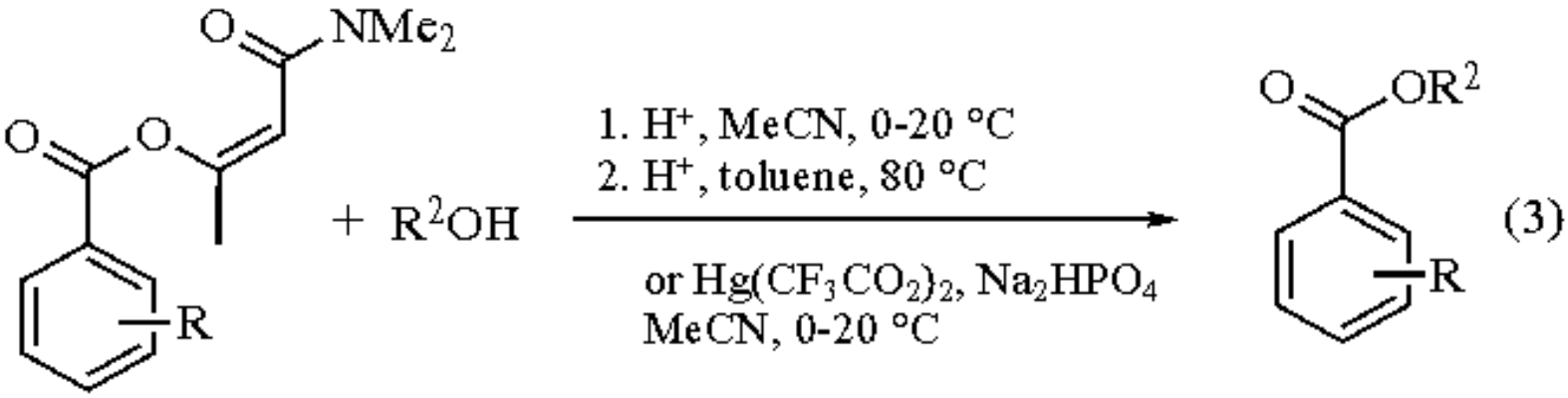

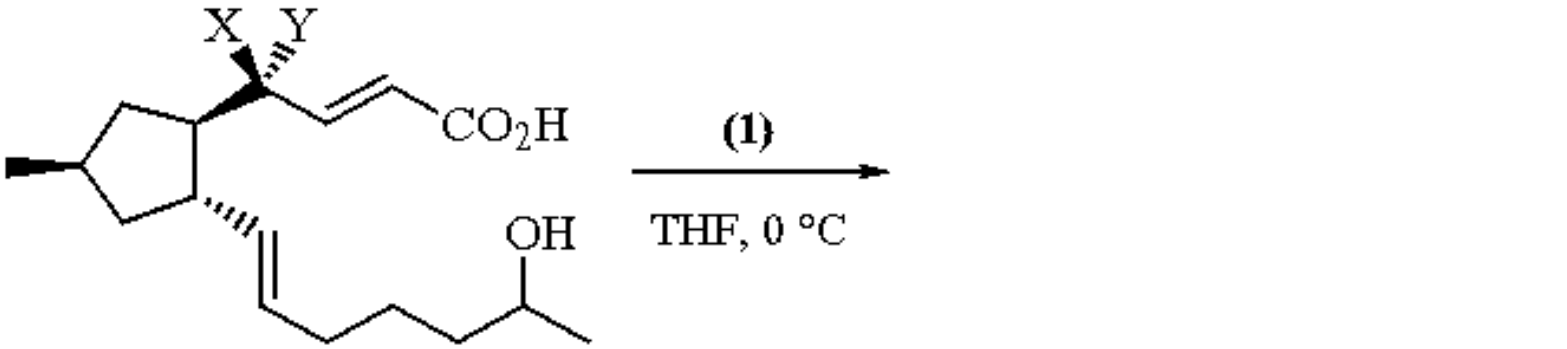

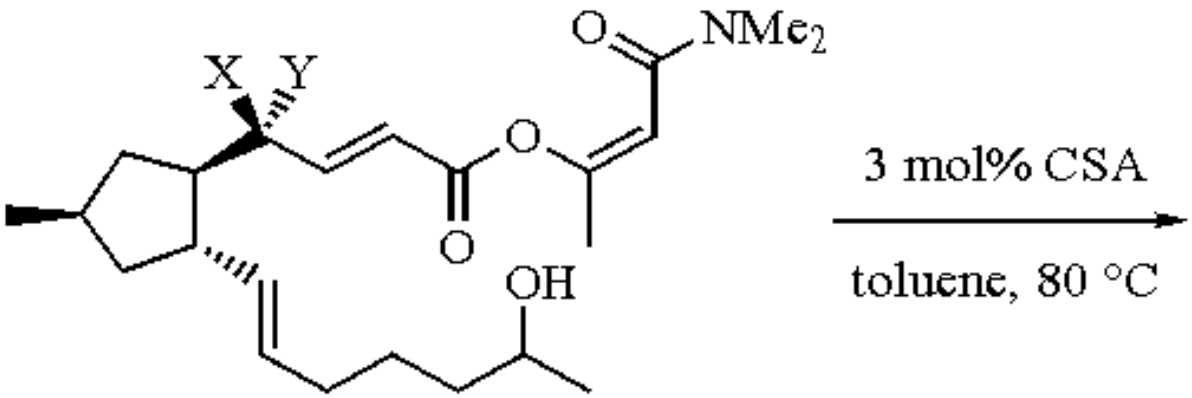

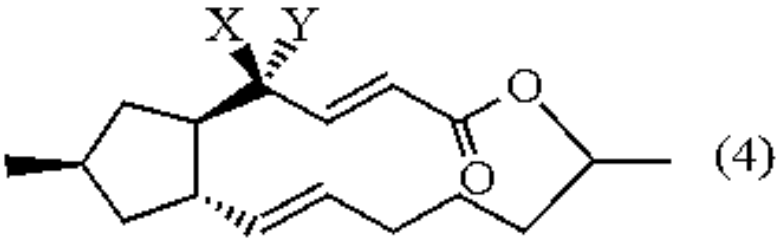

X = H, Y = MEMO; Y = H, X = MEMO

Synthesis of Amide and Peptide Linkages.

Enol ester (**1**) reacts with amines to give amides (eq 5).[6] 4-Dimethylamino-3-butyn-2-one can also be used to achieve carboxyl activation of *N*-protected amino acids suitable for further coupling reactions with carboxyl-protected amino acids to give peptides.[7,8] The amount of racemization observed in this process is low. Serine, tyrosine, 4-hydroxyproline, cysteine, and histidine can be linked to form a dipeptide without protection of the second functional

group (OH, SH, NH).

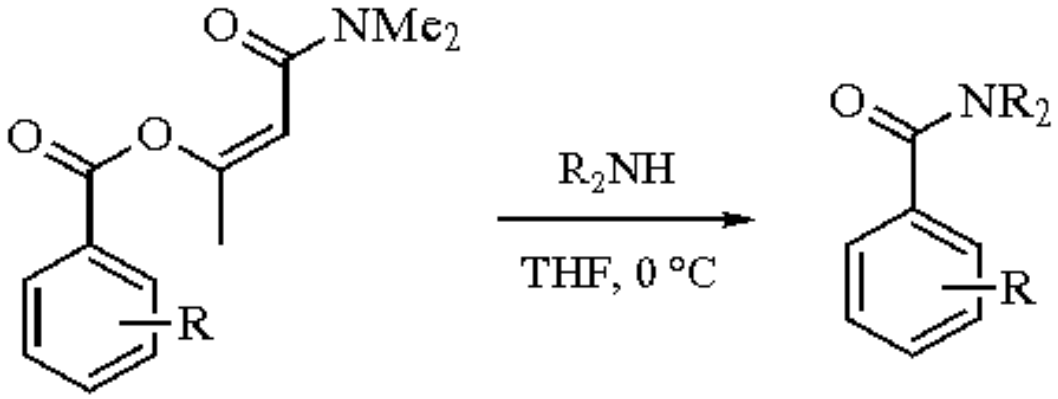

(5)

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(*R*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine

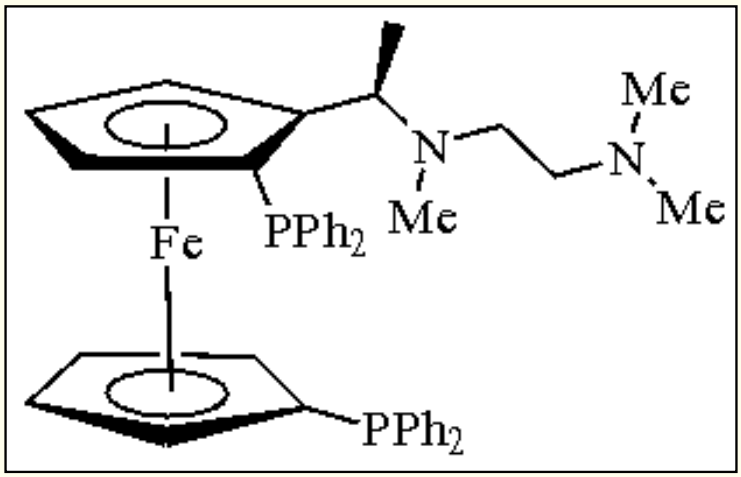

[119477-31-5] · $C_{41}H_{43}FeN_2P_2$ · (*R*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine · (MW 682.62)

(chiral ligand for asymmetric synthesis;[1] gold(I)-catalyzed asymmetric aldol reaction;[2] silver(I)-catalyzed asymmetric aldol reaction;[3] enantioselective synthesis of β-hydroxy-α-aminophosphonates;[4] asymmetric allylic alkylation;[5] asymmetric allylic aminations;[6] asymmetric hydrogenations;[7] asymmetric [3 + 2] cycloaddition reactions[8])

Physical Data: viscous liquid, [α]25D +313° (*c* = 0.3, $CHCl_3$).

Solubility: sol dichloromethane, 1,2-dichloroethane, toluene, diethyl ether.

Preparative Methods: can be prepared[9] in two steps from commercially available (-)-(*R*)-*N*,*N*-dimethyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine.

Handling, Storage, and Precautions: although air stable at rt, storage under anhydrous conditions under an inert atmosphere is recommended both to prevent the slow air oxidation of the phosphorus(III) ligating groups and absorption of atmospheric moisture.

Chiral Ferrocenylamine Ligands.

Chiral ferrocenylamine ligands typified by the title reagent (**1**) have played a key role in the development of both

methodology and ligand design[10] for asymmetric synthesis, particularly for the enantioselective formation of C-C bonds using catalytic quantities of chiral transition-metal catalysts. In the following discussion, both (**1**) and close analogs will be discussed and compared because small structural modifications of the alkyl side-chain of (**1**) can lead to significant increases in stereoselectivity.[11]

Gold(I)-Catalyzed Aldol Reaction.

In 1986 an elegant enantioselective and diastereoselective synthesis of dihydrooxazolines was reported, using the aldol reaction of an aldehyde with an α-isocyanoacetate ester (formally a Knoevenagel reaction) using a cationic gold(I) complex of (**1**) (eq 1).[2]

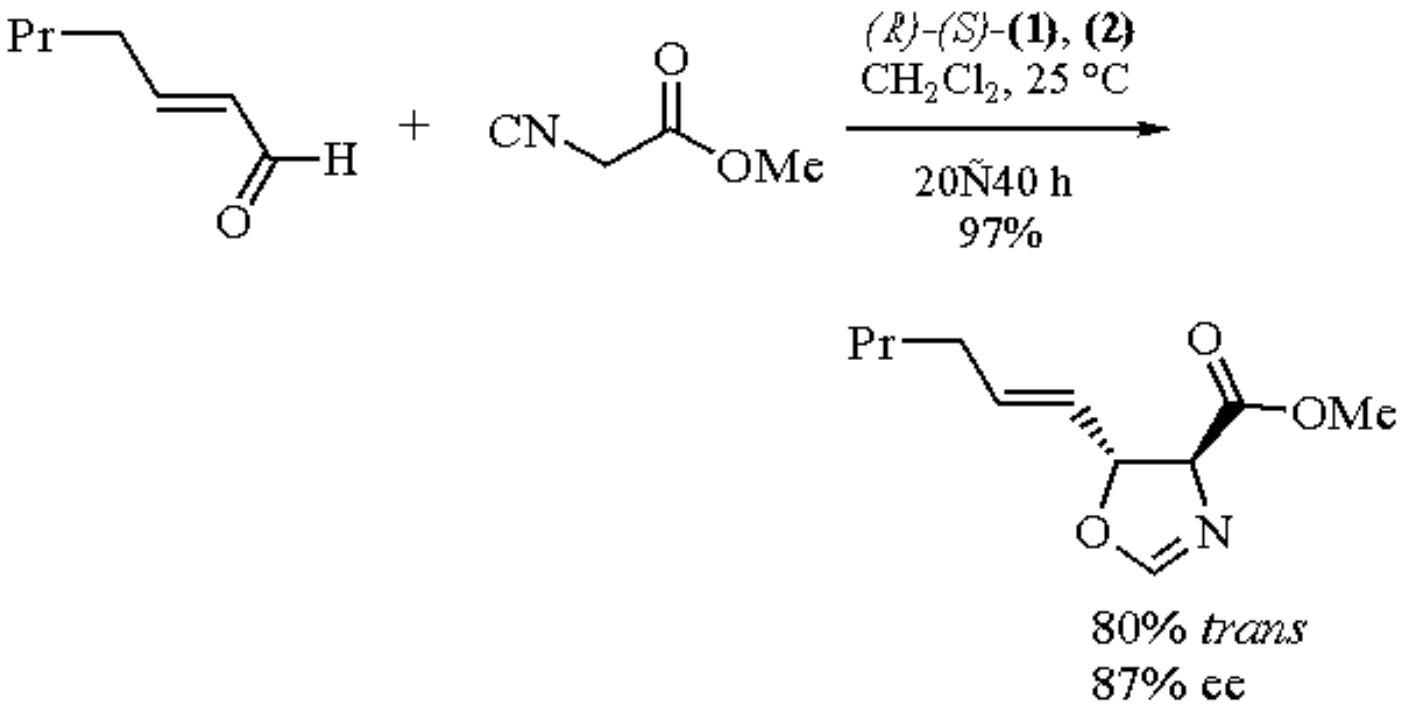

(1)

The gold(I) complex is prepared in situ by the reaction of (**1**) with bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**2**),[12] typically in anhydrous dichloromethane. The dihydrooxazolines obtained provide a ready access to enantiomerically pure β-hydroxy-α-amino acid derivatives. High diastereo- and enantioselectivity are generally maintained with a wide variety of substituted aldehydes,[2,13,14] and α-isocyanoacetate esters.[15-17] *N*,*N*-Dimethyl-α-isocyanoacetamides[18] and α-keto esters[19] have been substituted for the α-isocyanoacetate ester and aldehyde component, respectively, sometimes with improved stereoselectivity. The effect of both the central and planar chirality of (**1**) on the diastereo- and enantioselectivity of the gold(I)-catalyzed aldol reaction has been studied.[20] The modification of the terminal dialkylamino group of (**1**) can lead to improvements in the stereoselectivity of the reaction, which in certain cases can be dramatic (eq 2).[11,21] The utility of the gold(I)-catalyzed aldol reaction in the synthesis of natural products has been demonstrated.[22,23] The gold(I)-catalyzed reaction of an α-isocyanomethylphosphonate ester with an aldehyde provides an enantioselective synthesis of β-hydroxy-α-aminophosphonic acid derivatives.[24-26]

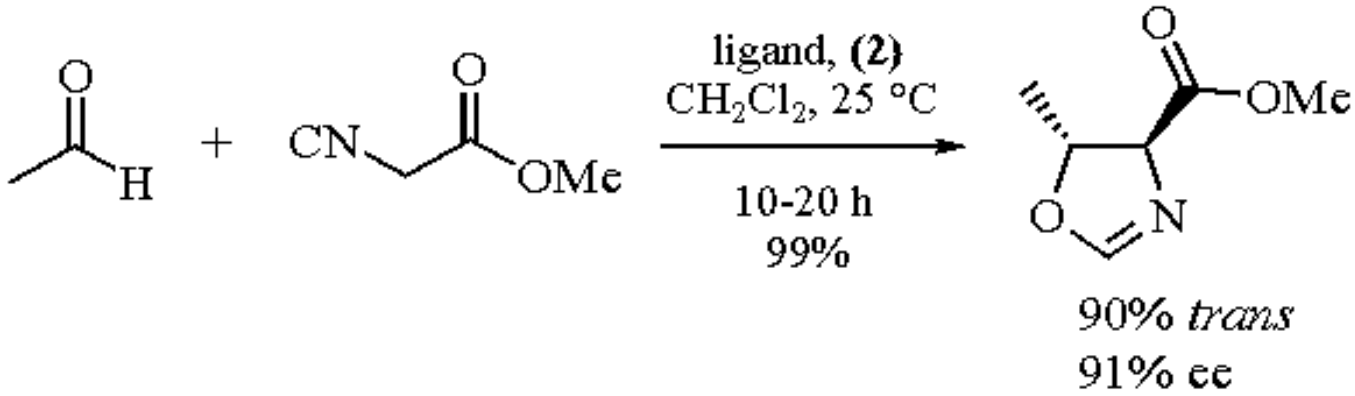

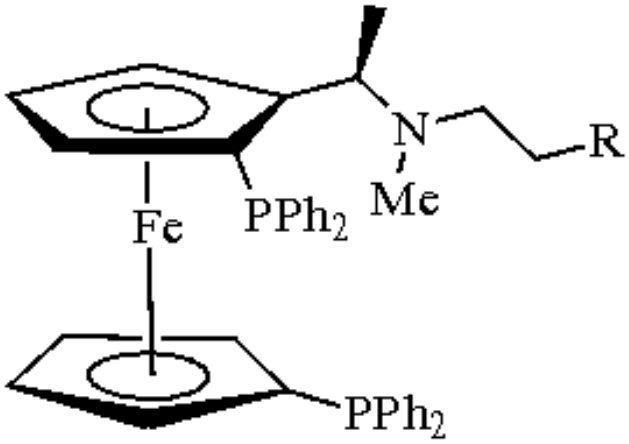

Ligand	R	% *trans*	% ee	% Yield
(R)-*(S)*-**(1)**	NMe_2	78	37	94
(R)-*(S)*-**(3)**	NEt_2	84	72	100
(R)-*(S)*-**(4)**	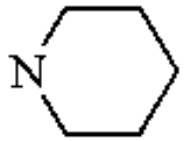	85	85	100
(R)-*(S)*-**(5)**	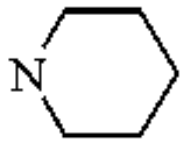	89	89	99

Silver(I)-Catalyzed Aldol Reaction.

In 1991 the silver(I)-catalyzed aldol reaction of an aldehyde with an α-isocyanoacetate ester was reported, analogous to the above mentioned gold(I)-catalyzed reaction.[3] The catalyst was prepared in situ from (**2**) and ***Silver(I) Perchlorate***. The stereoselectivity of the silver(I)-catalyzed reaction was shown to be temperature dependent, which was attributed to the variation of the degree of metal coordination with temperature. Slow addition of the α-isocyanoacetate ester to a mixture of the aldehyde and catalyst, which favored the preferred tricoordinate Ag^{I}, gave high diastereo- and enantioselectivity (eq 3).

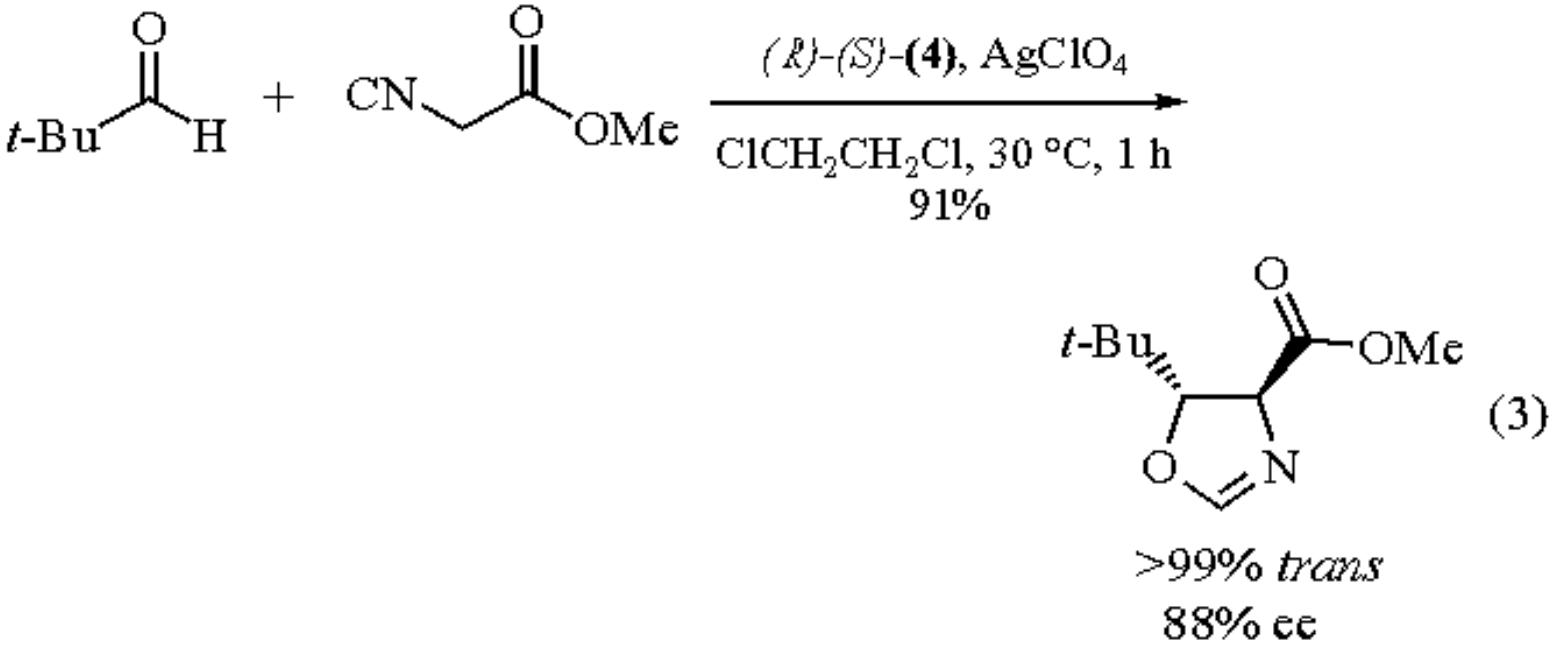

Earlier workers reported the silver(I)-catalyzed reaction of an aldehyde with ***p-Tolylsulfonylmethyl Isocyanide*** (eq 4).[27] The (*R*)-(*R*)-dihydrooxazolines formed can be reduced with ***Lithium Aluminum Hydride*** to provide a facile route to α-alkyl-β-(*N*-methylamino)ethanols in good to excellent yield.

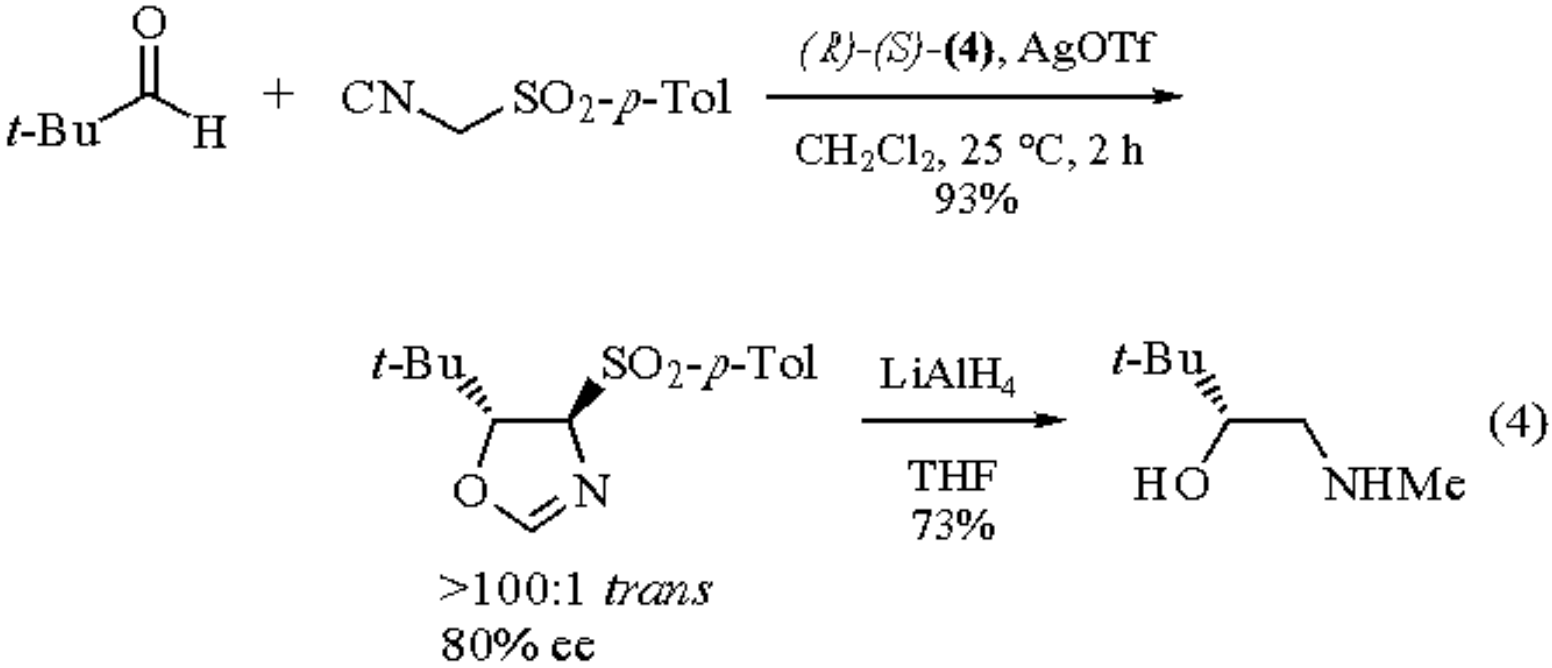

Asymmetric Allylations.

The asymmetric allylation of β-diketones with π-allyl Pd^{II} complexes using the chiral ligand (**1**) was reported to proceed with low stereoselectivity.[5] Modification of the alkyl side-chain of (**1**) led to significant improvements in enantioselectivity (eq 5).[5,28-31]

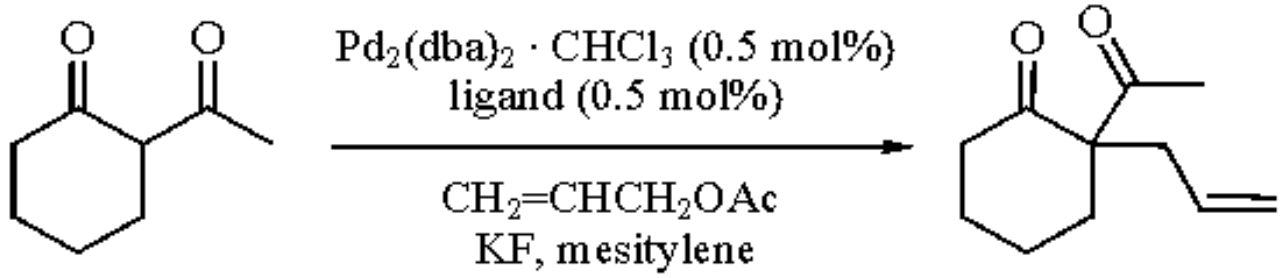

(5)

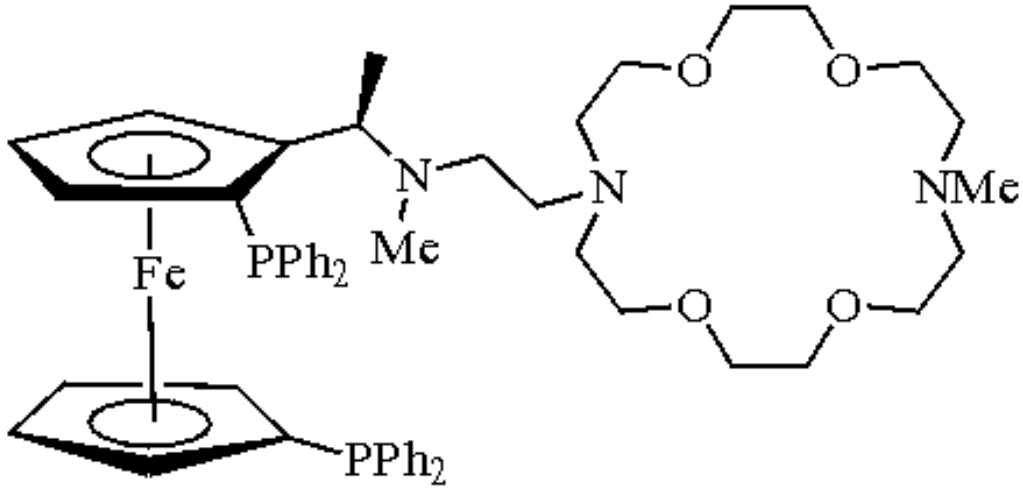

(6)

Ligand	Yield (%)	ee *(R)* (%)
(1)	57	22
(6)	92	75

The in situ formed Pd^{II} catalyst system prepared with the hydroxyalkyl-substituted ferrocenylamine (**7**) led to the opposite absolute configuration at the carbon stereocenter (eq 6).[28] A similar inversion of stereochemistry is observed with ferrocenylamine ligands containing a free hydroxyl substituent in the gold(I)-catalyzed aldol reaction.[21b] Although asymmetric allylic aminations can be achieved using the chiral ligand (**7**), significantly improved enantioselectivity is obtained with the bis(hydroxyalkyl)-substituted ligand (**8**) (eq 7).[6]

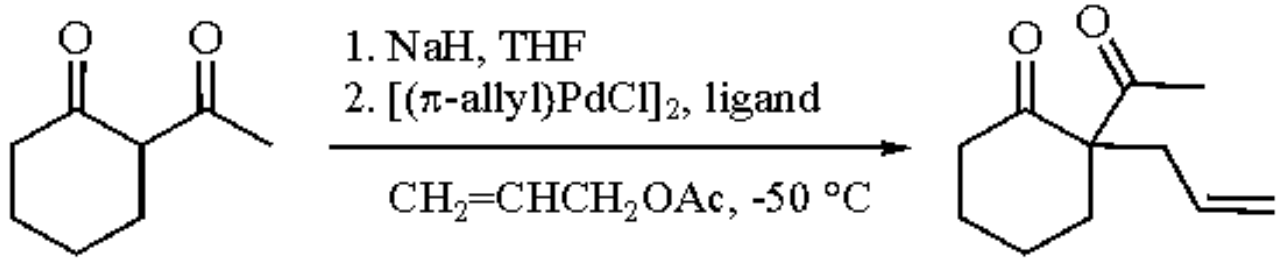

(6)

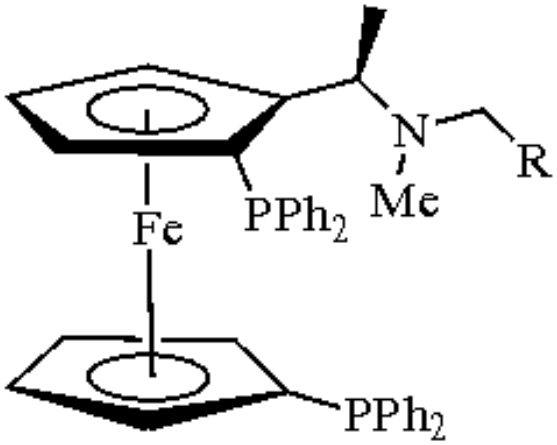

Ligand	Yield (%)	ee *(S)* (%)
(7)	100	73
(8)	55	49

(7) R = CH_2CH_2OH
(8) R = $CH(CH_2OH)_2$

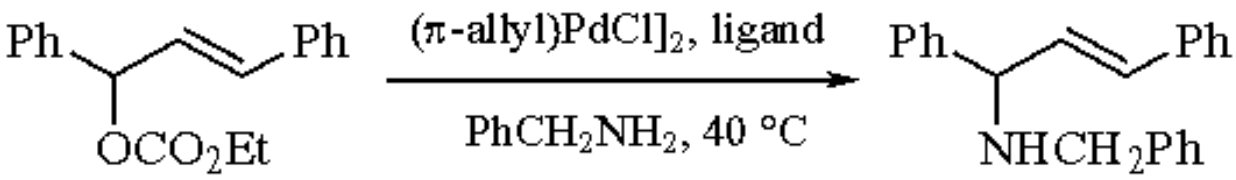

(7)

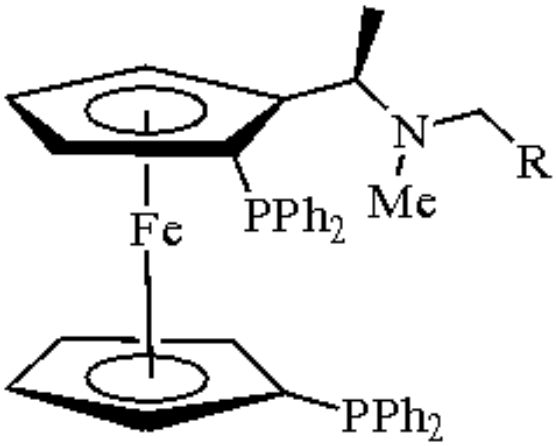

Ligand	Yield (%)	ee *(R)* (%)
(7)	80	79.3
(8)	93	97

(7) R = CH_2CH_2OH
(8) R = $CH(CH_2OH)_2$

(R)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(S)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine

An interesting intramolecular variation of this reaction provides oxazolidones, which may be hydrolyzed to synthetically useful optically active 2-amino-3-butenols (eq 8).[32] The absolute stereochemistry of the stereocenter formed is dependent upon the geometry about the double bond of the 2-butenylene dicarbamate substrate. A related Pd^{II}-promoted [3 + 2] cycloaddition of an activated alkene with a 2-(sulfonylmethyl)-2-propenyl carbonate, using the bis(hydroxyalkyl)-substituted ligand (**8**), gave methylenecyclopentane derivatives with high asymmetric induction.[8]

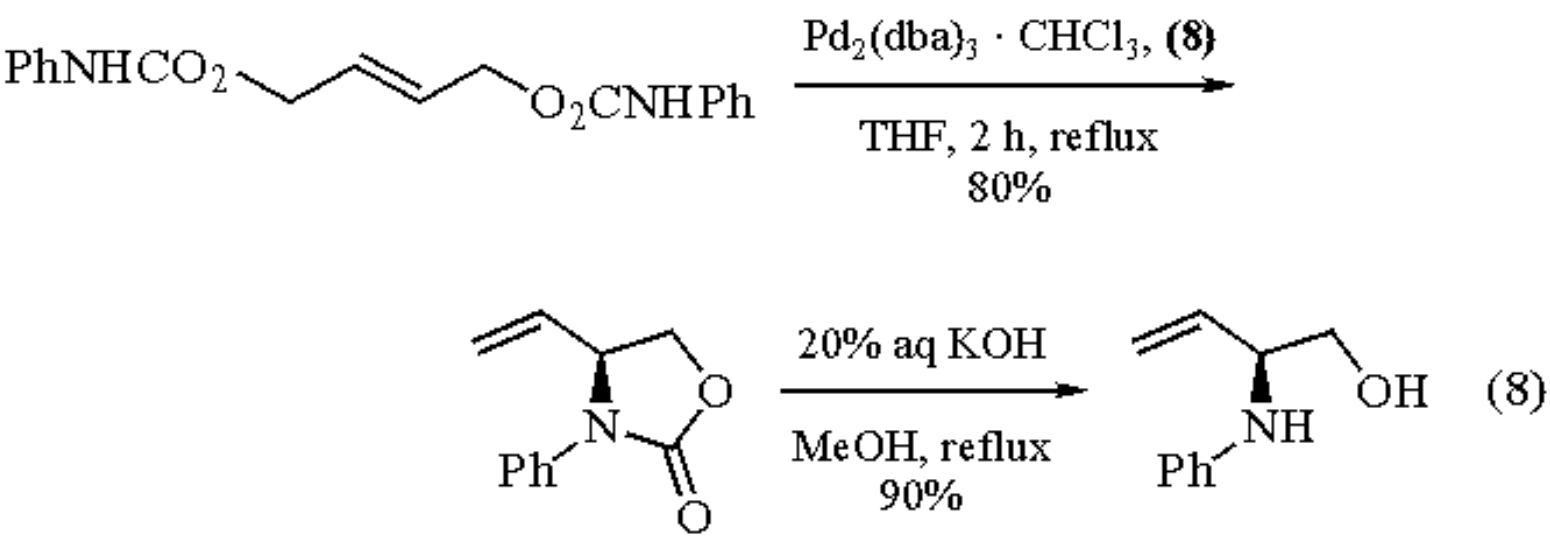

Asymmetric Hydrogenations.

Catalytic asymmetric hydrogenations of β-disubstituted-α-phenylacrylic acids have been achieved using the Rh^{I} complex of (**4**) (eq 9).[7,33] Asymmetric hydrogenation of unsymmetrically substituted trisubstituted acrylic acids leads to the formation of two stereocenters in high ee.[7] The variation of the terminal dialkylamino substituents has little effect on enantioselectivity.[33] A study of a Ru^{II} complex of (**1**) was reported as a model for understanding the stereoselective transition state of asymmetric hydrogenations.[34]

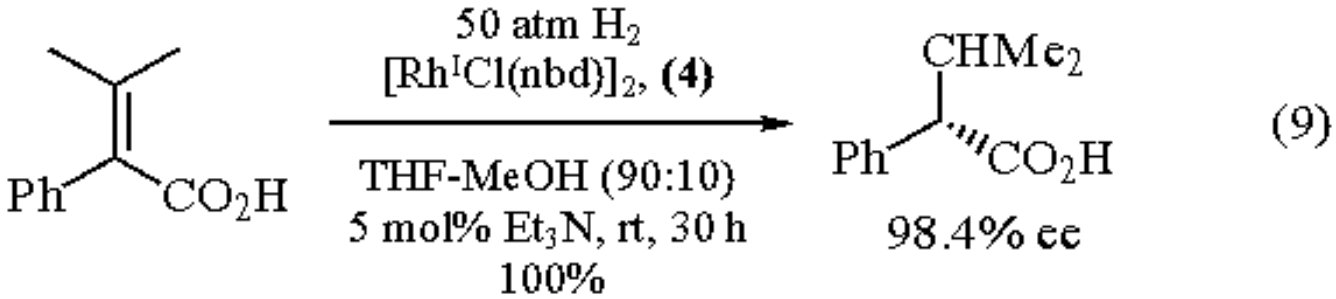

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21. (a) Hayashi, T.; Yamazaki *JOM* **1991**, *413*, 295. (b) Pastor, S. D.; Togni, A. *HCA* **1991**, *74*, 905.
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26. For a more detailed discussion, see Bis(cyclohexyl isocyanide)gold(I) Tetrafluoroborate-(*R*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine.
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Stephen D. Pastor

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(2-Dimethylaminoethyl)triphenylphosphonium Bromide

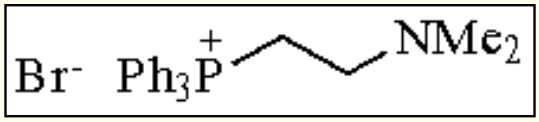

[21331-80-6] · $C_{22}H_{25}BrNP$ · (2-Dimethylaminoethyl)triphenylphosphonium Bromide · (MW 414.33)

(precursor to dimethylaminoethylidenetriphenylphosphorane, which condenses with aldehydes and ketones to give allylic amines[1])

Physical Data: mp 201 °C.

Form Supplied in: white solid; widely commercially available.

Preparative Methods: this reagent and analogous *N*,*N*-dialkylaminoethyltriphenylphosphonium bromides are prepared by condensation of the corresponding β-amino alcohols with ***Triphenylphosphine*** in the presence of ***Hydrogen Bromide***.[1]

Purification: recrystallization from acetic acid-chloroform.

Handling, Storage, and Precautions: should be dried in vacuo for best results.

Reaction with Aldehydes and Ketones.

The ylide derived from deprotonation of (2-dimethylaminoethyl)triphenylphosphonium bromide with ***n-Butyllithium*** reacts with a wide variety of aldehydes and ketones in a modified Wittig reaction to yield the homologated unsaturated amine (eq 1).

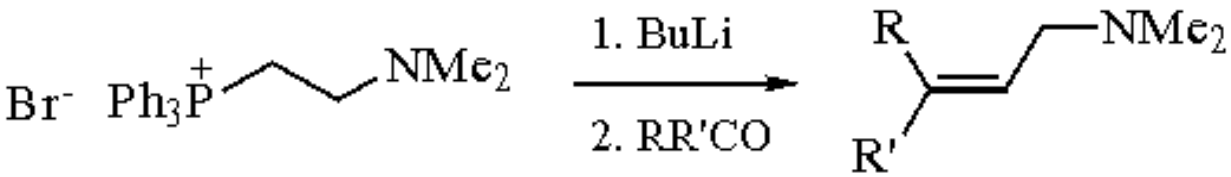

(1)

The stereoselectivity of this reaction with aromatic aldehydes has been investigated and conditions have been described for the selective formation of either alkene isomer (eqs 2 and 3).[1,2]

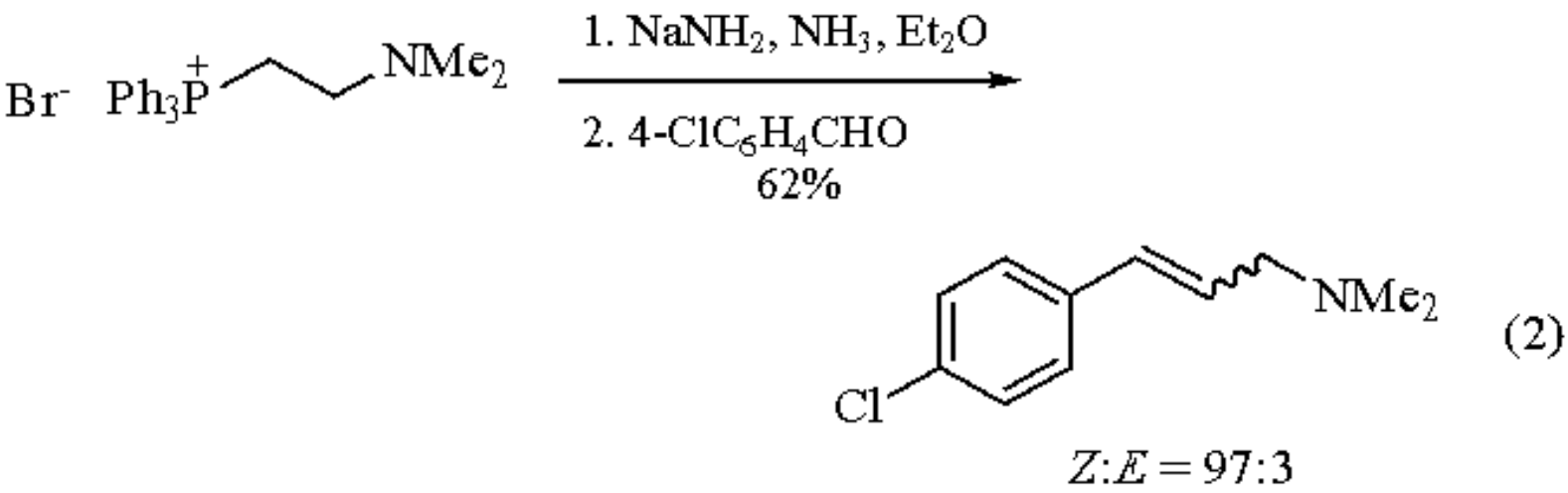

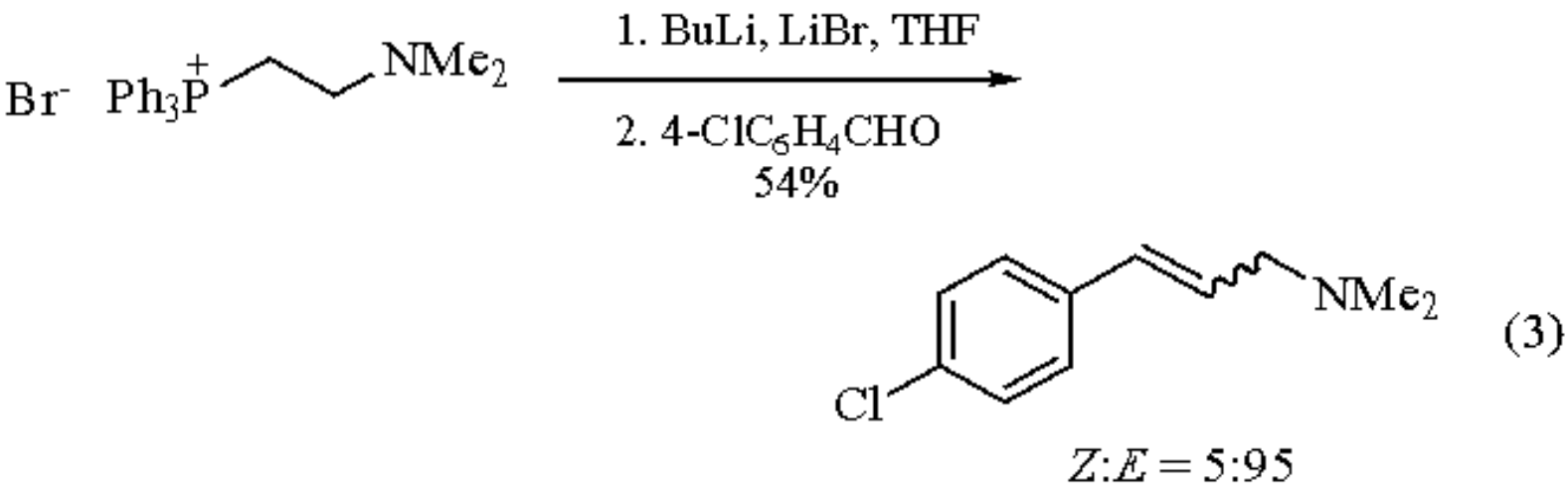

The ylide reacts readily with both unactivated and hindered ketones to give products such as (**1**)-(**3**) and, in the case of unsymmetrical ketones, can show impressive levels of stereoselectivity.[1,3,4]

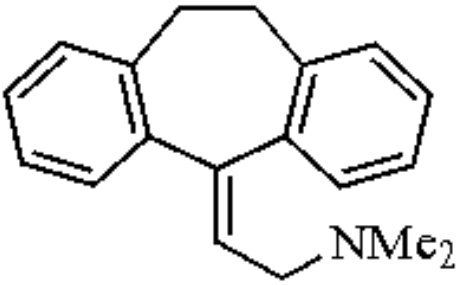

(1)

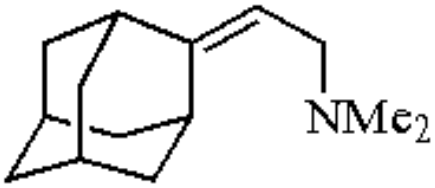

(2)

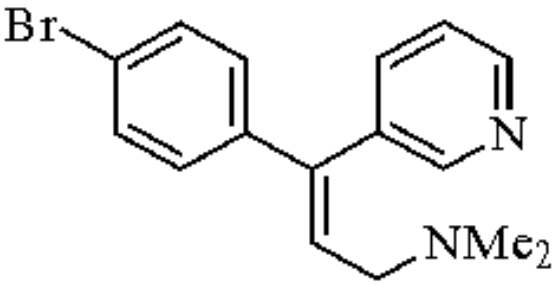

(3)

Related Reagents.

Attempts to extend this reaction by using the analogous ylide generated from (2-methylaminoethyl)triphenylphosphonium bromide (**4**) are plagued by low chemical yields.[1] In contrast, treatment of the phosphonium salt (**4**) with two equivalents of BuLi generates the dianion that reacts with aldehydes to give the

secondary allylic amines in high chemical yields with a modest preference for the (*E*) alkene isomer.[5]

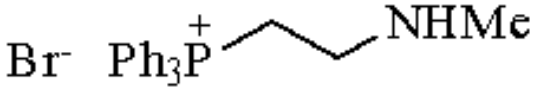

(4)

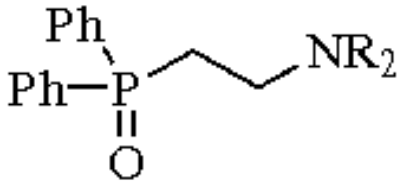

(5)

The phosphine oxide (**5**) has also been developed for the stereoselective synthesis of allylic amines.[6] Condensation of the lithium anion of this reagent with ketones gives an equal mixture of the *syn* and *anti* addition products which can typically be separated by chromatography or distillation. The individual diastereomers are then subjected to a *syn* elimination protocol to provide the individual (*E*) and (*Z*) allylic amines in good overall chemical yields.

---

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6-Dimethylaminofulvene[1]

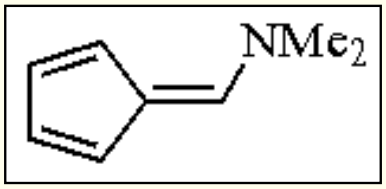

[696-68-4] · $C_8H_{11}N$ · 6-Dimethylaminofulvene · (MW 121.18)

(synthesis of azulenes[2])

Physical Data: mp 67-68 °C.

Form Supplied in: yellow crystals; commercially available.

Preparative Methods: may be conveniently prepared by the reaction of cyclopentadienylsodium with ***N,N-Dimethylformamide-Dimethyl Sulfate***.[3,4] Alternatively, cyclopentadiene has been condensed with ***N,N-Dimethylformamide Diethyl Acetal***.[5,6]

Purification: recrystallization from petroleum ether or cyclohexane.

Handling, Storage, and Precautions: should be protected from light during storage.

Synthesis of Azulenes.

6-Dimethylaminofulvene undergoes [6 + 4] cycloadditions with thiophene 1,1-dioxides (**1**) to yield substituted azulenes (**3**). The reaction is believed to proceed via the indicated intermediate (**2**), although it has not been directly observed. Subsequent extrusion of sulfur dioxide and elimination of dimethylamine yields the azulene product (eq 1). 3,4-Dichlorothiophene 1,1-dioxide is significantly more reactive than the unsubstituted heterocycle.[7,8] Azulenes have also been obtained in low yield from related reactions of 6-dimethylaminofulvene with 5-alkoxycarbonyl-2-pyrones.[9]

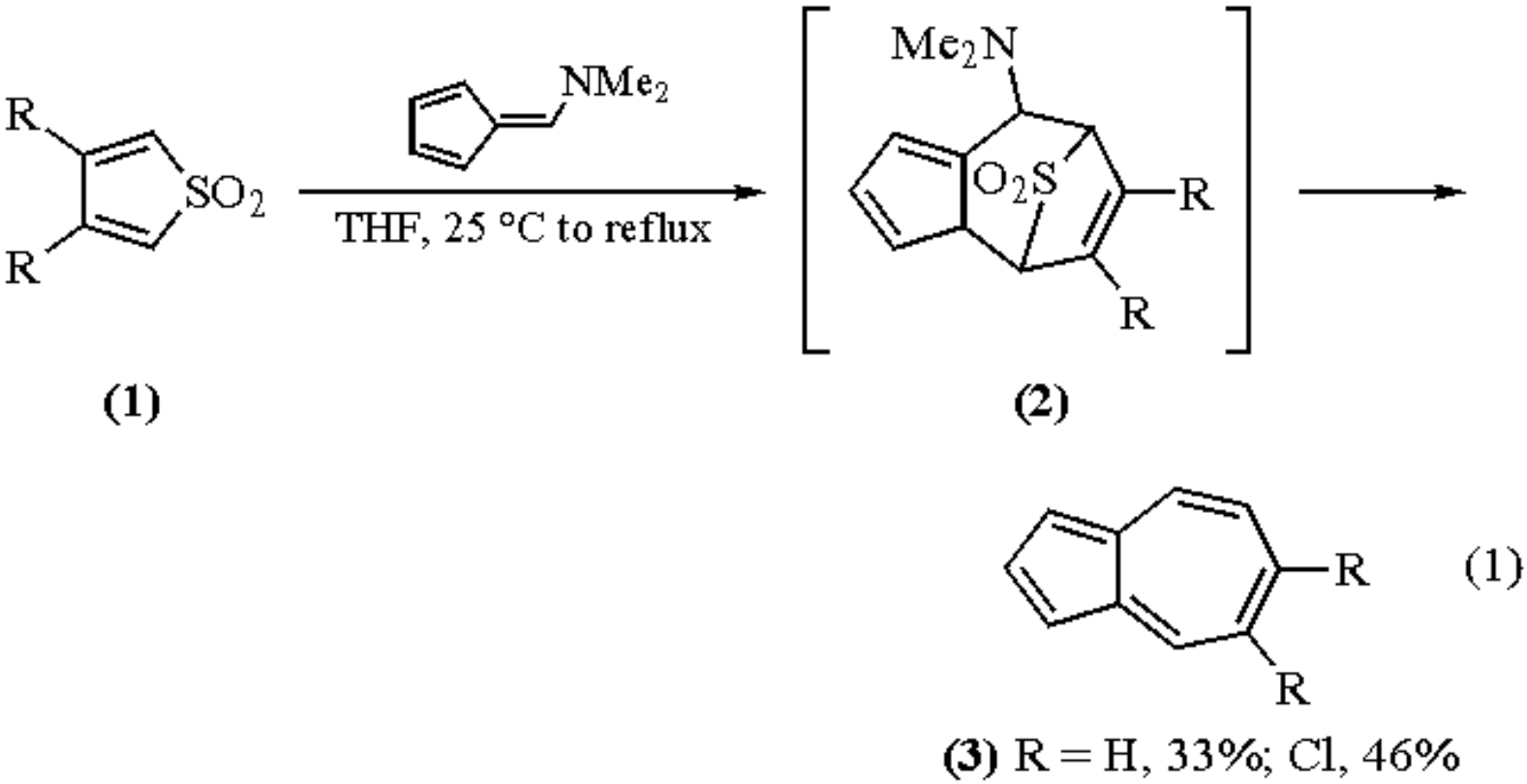

6-Dimethylaminofulvene has been used in short synthetic routes to the hydroazulene sesquiterpene degradation products guaiazulene and chamazulene. The [6 + 4] cycloaddition reaction of 6-dimethylaminofulvene with 2-ethyl-5-methylthiophene 1,1-dioxide (**4**) produced a mixture of regioisomers favoring the desired product (eq 2). The major isomer (**5**) was converted into chamazulene in two additional steps.[2]

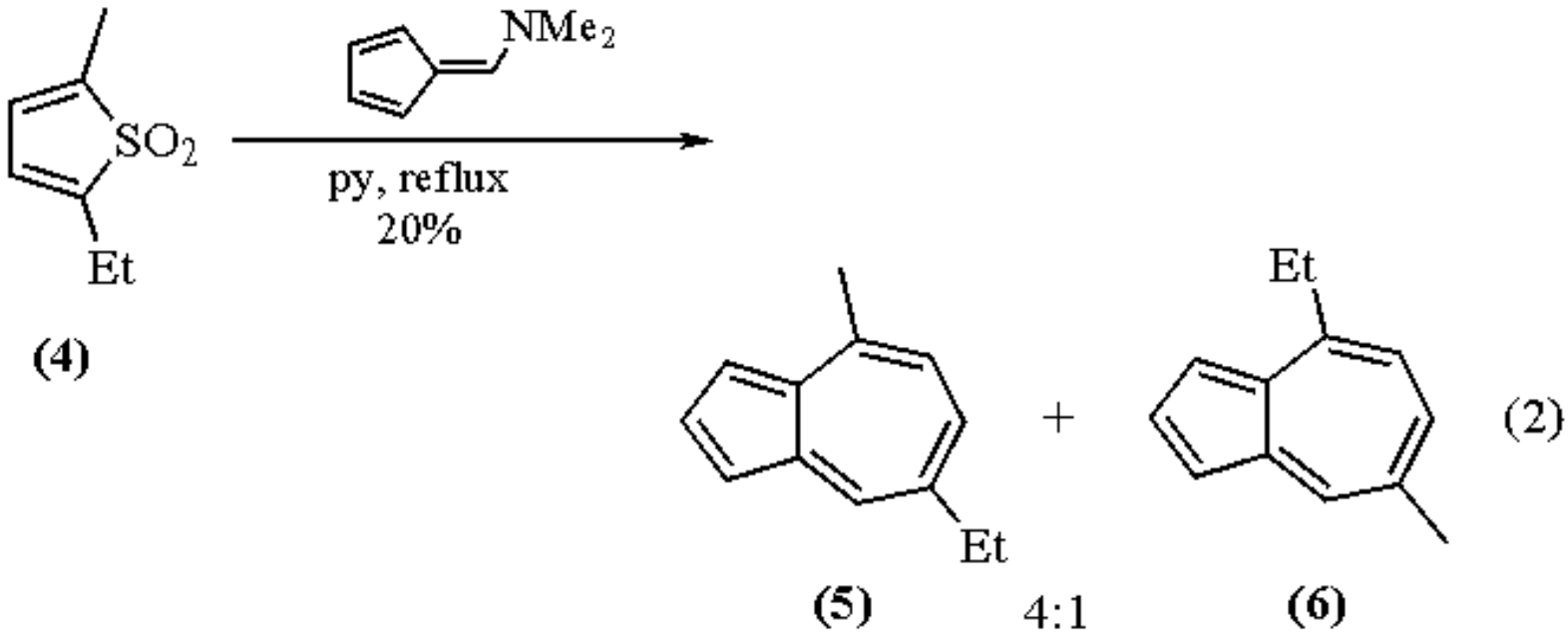

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[[[(Dimethylamino)methylene]amino]methylene]dimethylammonium Chloride[1]

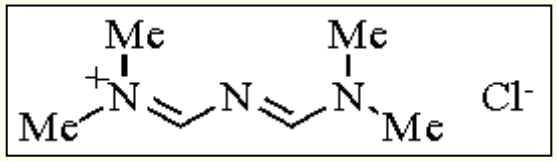

[20353-93-9] · $C_6H_{14}ClN_3$ · [[[(Dimethylamino)methylene]amino]methylene]dimethylammonium Chloride · (MW 163.65)

(β-dimethylaminomethylenating agent for ketones and amines;[2] yields enamino derivatives of esters and lactones;[3] converts Grignard reagents to aldehydes[4])

Alternate Name: Gold's reagent.

Physical Data: mp 100-102 °C.

Solubility: sol water, chloroform; insol nonpolar organic solvents.

Form Supplied in: tan to dark brown solid; commercially available.

Preparative Methods: [5] a 1 L, one-necked, round-bottomed flask is equipped with a Claisen adapter, mechanical stirrer, reflux condenser, and mineral oil bubbler. The flask is charged with cyanuric chloride (73.8 g, 0.4 mol) (*Caution*: cyanuric chloride is a lachrymator and causes burns on contact with the skin), ***N,N-Dimethylformamide*** (175.4 g, 2.4 mol) and 1,4-dioxane (100 mL). The resulting solution is stirred and heated at 85 °C for 2-3 h while a considerable amount of carbon dioxide is evolved. When gas evolution is minimal, the reaction mixture is allowed to cool to room temperature; the product rapidly solidifies (eq 1). The flask which contains the solid product is connected to an isopropyl alcohol/dry ice trap and the solvent is removed by evacuating the system to approximately 0.05 mmHg. The crude product weighs 186-187 g (95% yield). Another method of isolating the product is by rapid filtration and washing with acetone.

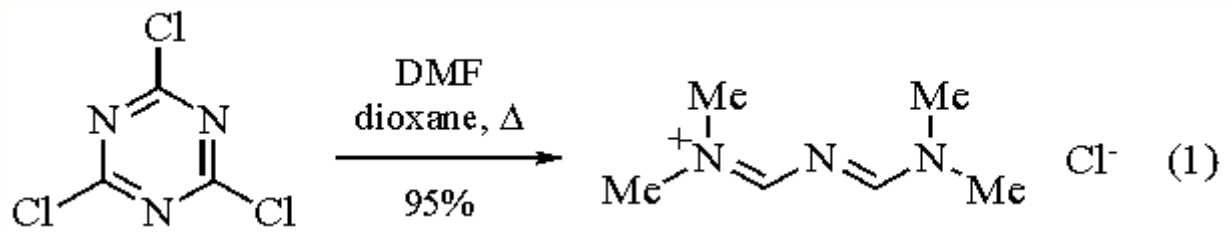

(1)

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.27 (s, 6H, two CH_3), 3.43 (s, 6H, two CH_3), 9.57 (s, 2H, -CH=N).

Handling, Storage, and Precautions: Gold's reagent is very hygroscopic and should be handled under a moisture-free environment. If kept dry, it has a substantial

shelf-life. Store in desiccator over anhydrous calcium sulfate.

Reaction with Mononucleophiles.

Gold's reagent (GR) is a general β-dimethylaminomethylenating agent which reacts successfully with anions derived from ketones (eq 2)[2] to produce enaminones, and with amides (eq 3)[2] to produce acylamidines. The stoichiometry of the reactions involves using 1 equiv of Gold's reagent and 1 equiv of base which was prepared by a reaction of the appropriate alcohol with sodium metal.

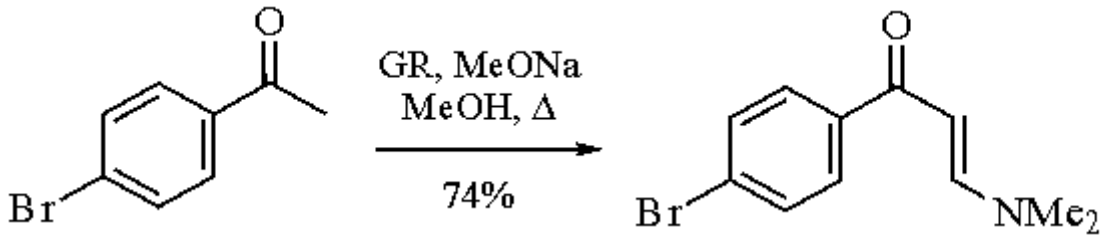

(2)

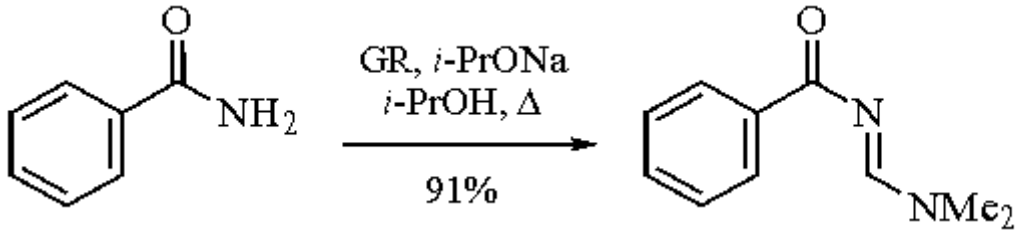

(3)

Gold's reagent also reacts with amines (eq 4)[2] to produce amidines. This reaction has been utilized in the preparation of a chiral formamidine from L-valinol *t*-butyl ether. Reports of the use of this chiral auxiliary in the asymmetric syntheses of indole,[6,7] isoquinoline,[8-10] and pyrrolidine[11] alkaloids have appeared.

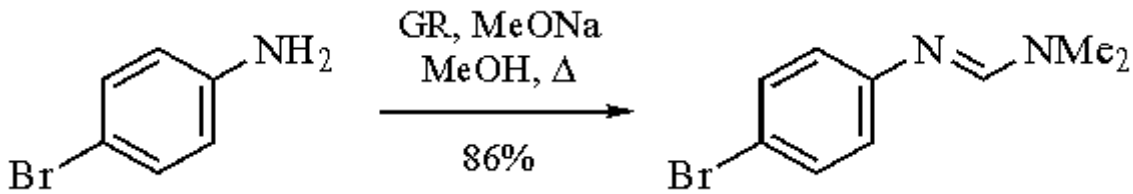

(4)

The reaction with anions derived from unsymmetrical ketones (eq 5)[12] proceeds with complete regioselectivity to produce the least substituted enaminone. Use of other similar reagents result in mixtures.[13]

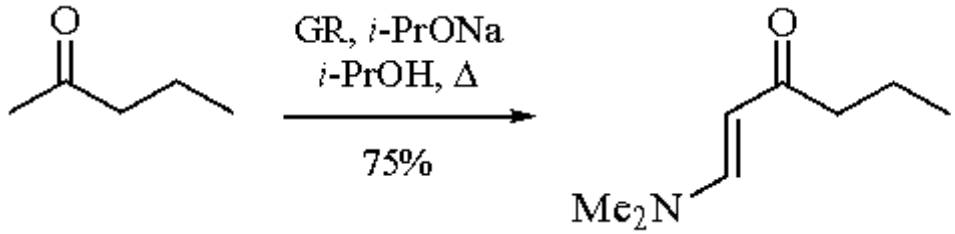

(5)

The reaction with anions derived from esters (eq 6) and lactones (eq 7)[3] also result in β-dimethylaminomethylenation. These reactions are interesting in that enamino lactones can be converted to α-methylene lactones.[14,15]

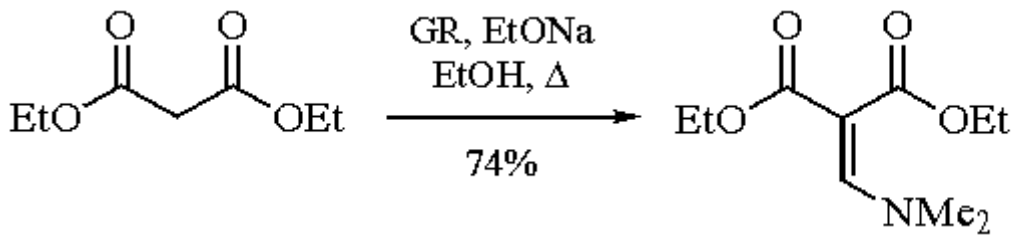

(6)

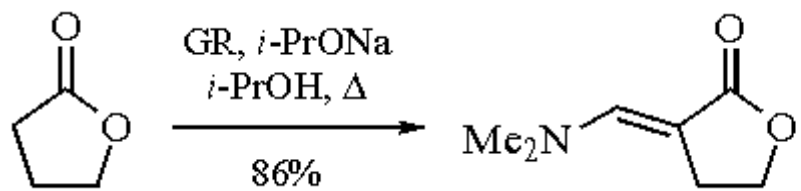

(7)

Reaction of Gold's reagent with the anion of *o,p*-nitrotoluenes (eq 8)[3] results in the formation of phenyl enamines. It has been shown that *o*-nitrophenyl enamines can be converted to indoles.[16]

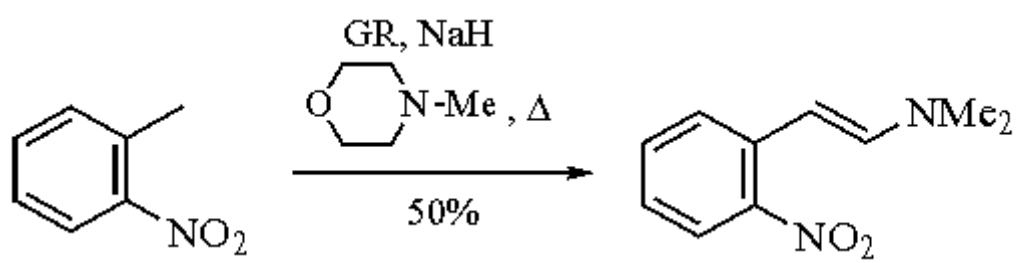

(8)

Other effective β-dimethylaminomethylenating agents include the formamide acetals,[17] some of which are also commercially available. They are, however, expensive, moisture and heat sensitive, and require potent, mutagenic alkylating agents for their preparation. Under some circumstances they also necessitate high reaction temperatures and long reaction times. Alternatively, Gold's reagent is prepared in a single step, and in nearly quantitative yield, without purification, from inexpensive raw materials. The reaction of Gold's reagent with an amine or other substrate can be carried out at relatively low temperatures (65-90 °C) and moderate reaction times (12-24 h).

Reaction with Grignard Reagents.

The reaction of Gold's reagent with Grignard reagents (eq 9)[4] produced one-carbon homologated aldehydes upon acid hydrolysis of the intermediates. This is general for aromatic, benzylic, and aliphatic Grignard reagents. This is an advantage over a method using 2-oxazolines,[18] which only works for aromatic and benzylic Grignard reagents. Another reagent used in formylating Grignard reagents is ***N-Methyl-N-(2-pyridyl)formamide***,[19] which was developed by Meyers. This reagent, however, is somewhat expensive and is prepared in two steps in 80% overall yield and usually involves recovery of a byproduct.

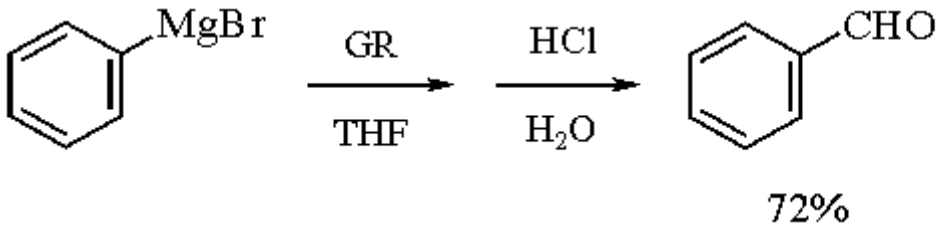

(9)

Reaction with Dinucleophiles.

The reaction of Gold's reagent with 1,2- and 1,3-dinucleophiles incorporates a CH=N-CH unit into a ring. Upon reaction with ***Phenylhydrazine*** (eq 10) and ***Guanidine*** (eq 11),[20] the corresponding triazole and triazine are produced. The mechanism can be viewed as the two nucleophilic sites displacing the two dimethylamino groups. In the reaction with 2-(cyanomethyl)pyrrole (eq 12),[21] a 6-azaindolizine is formed. An alternative mechanism for cyclization was postulated involving a [1,5]-sigmatropic hydrogen shift followed by a 6π-electrocyclic ring closure.

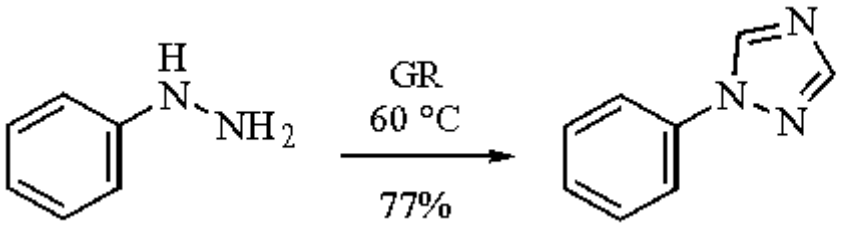

(10)

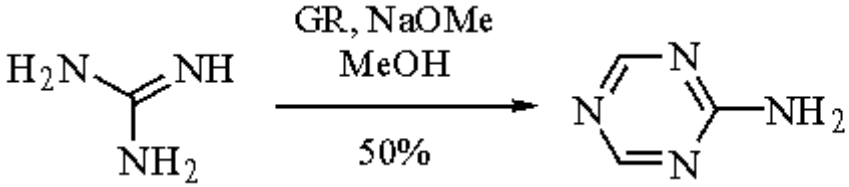

(11)

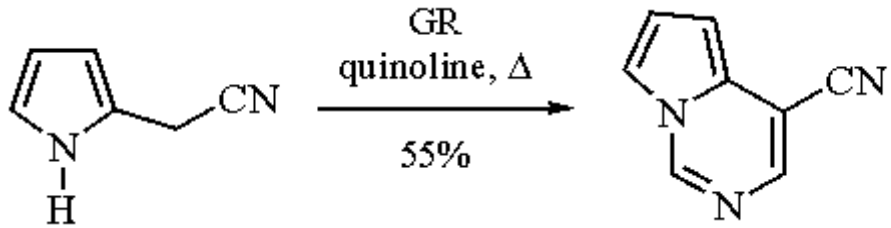

(12)

Gold's reagent also reacts with 1,4- and 1,5-dinucleophiles. In the reaction with *o*-aminophenols (eq 13) and *o*-hydroxyacetophenones (eq 14),[22] it serves as a one-atom linchpin to form the corresponding oxazoles and pyranones. Gold's reagent reacts initially to form a β-dimethylaminomethylene derivative, which undergoes intramolecular cyclization to form the fused ring. In the case of anthranilic acid (eq 15),[23] Gold's reagent serves as a two-atom linchpin. The resulting azalactone reacts with *N*,*N*-dimethylformamidine, which is produced in the initial reaction with Gold's reagent. The final product is a quinazolinone.

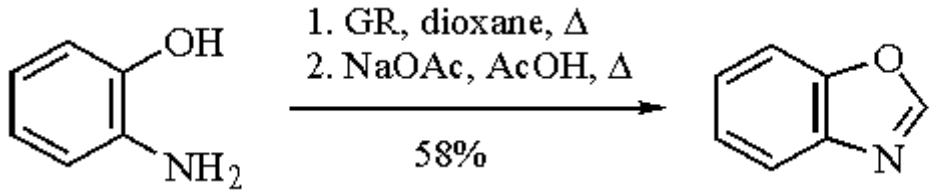

(13)

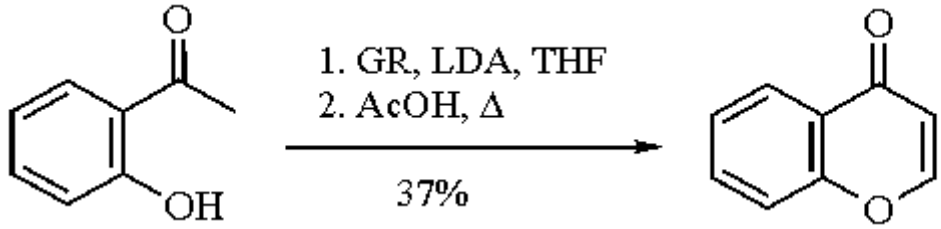

(14)

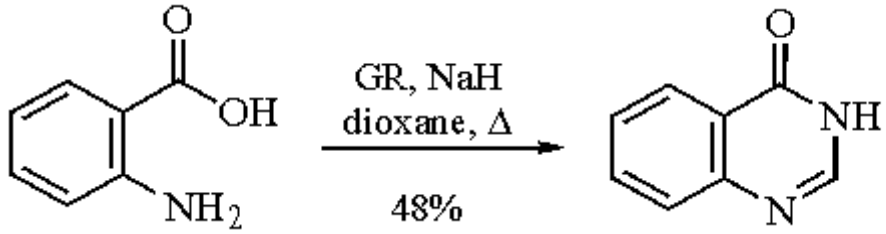

(15)

There are other reagents such as DMF acetals[24] and ***Dimethylchloromethyleneammonium Chloride***[25] which (in some cases) accomplish similar functions. Gold's reagent has some distinct advantages over these compounds. It is a well defined, stable, and preformed salt which reacts cleanly with a variety of nucleophiles under basic conditions with significant regioselective control. It is also an efficient, economical and clean alternative to analogous reagents.

Related Reagents.

t-Butoxybis(dimethylamino)methane; ***N,N-Dimethylformamide Diethyl Acetal***; ***N-Formylpiperidine***; ***N-Methylformanilide***.

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Dimethylaminomethyllithium

Me_2NCH_2Li

[26285-58-5] · C_3H_8LiN · Dimethylaminomethyllithium · (MW 65.06)

(agent for nucleophilic dialkylaminomethylation; regioselective preparation of 2-dialkylamino alcohols)

Physical Data: the X-ray structure of the ether-complexed dimer of *N*,*N*-dimethylaminobenzyllithium[1a] and its structure in solution (^{1}H, ^{13}C NMR)[1b] have been reported. The pK_a of its potassium salt has been determined to be 41.1.[1c]

Solubility: sol THF and ether.

Form Supplied in: prepared in situ by the methods described below and used directly.

Handling, Storage, and Precautions: must be prepared and handled under inert gas (Ar) to exclude oxygen and moisture.

General Discussion.

The direct preparation of *N*,*N*-dialkylaminomethyllithium (**2**) by deprotonation of tertiary aliphatic methylamines (**1**) with alkyllithium bases is normally not possible. Thus dimethyldodecylamine is deprotonated by ***t-Butyllithium*** only to the extent of 7%.[2a] The slow deprotonation rate of (**1**) and the thermal instability of (**2**) prevent further enrichment in (**2**). To solve this problem, acceleration of metalation by activation of the base or the amine has been used.

With the stronger basic system ***s-Butyllithium*/*Potassium t-Butoxide*** the direct preparation of the potassium salts (**4**) from (**1**) is possible when excess amine is used as solvent (e.g. ***Triethylamine***, *N*-methylpiperidine, *N*-methylpyrrolidine) (eq 1).[2b] The potassium salts can be alkylated but are strongly basic. Enolizable carbonyl compounds are only deprotonated. When the potassium salts are treated with ***Lithium Bromide*** in ether, the more nucleophilic lithium salts (**2**) are formed and hydroxyalkylation to give 2-amino alcohols (**3**) is possible even with acidic carbonyl compounds such as cyclohexenone.

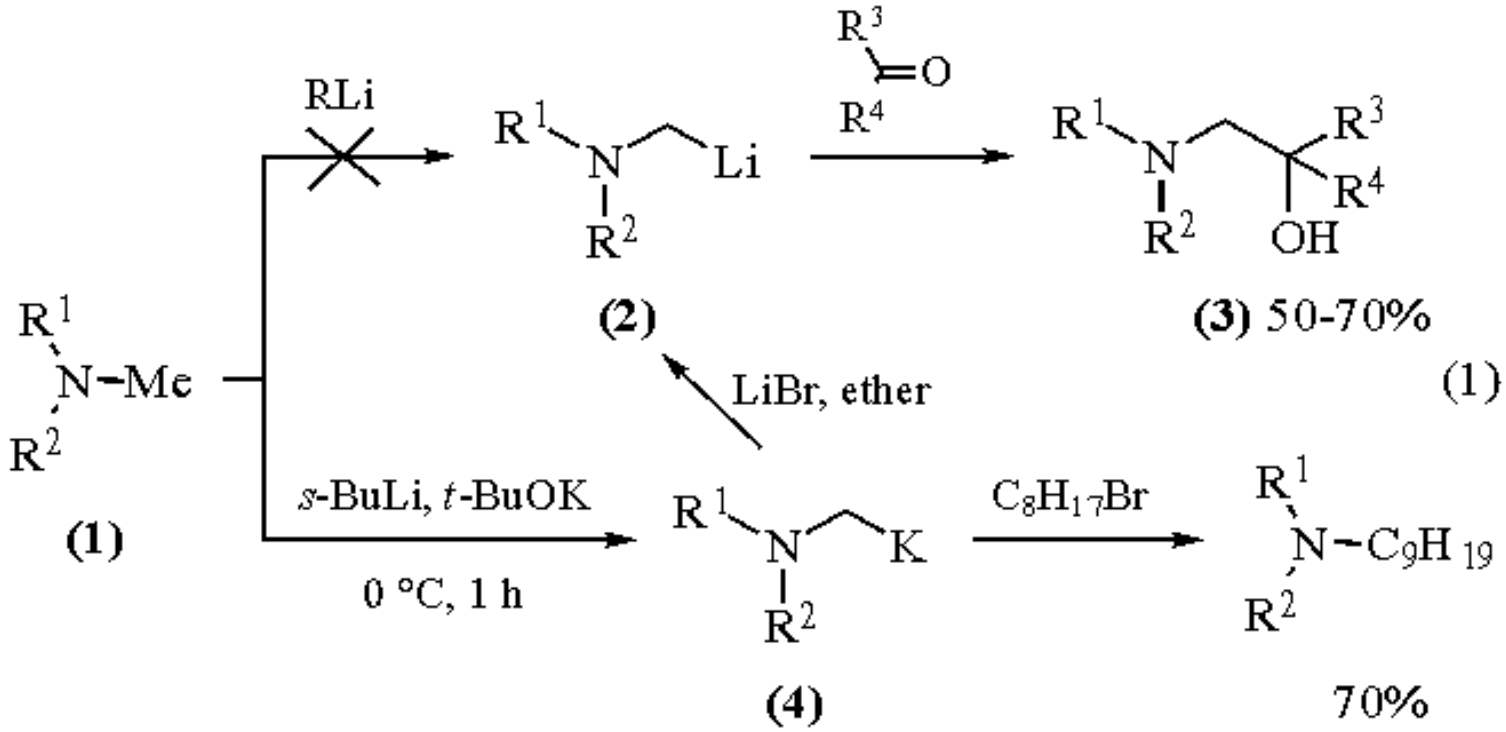

The easiest way to activate the amines consists of complexation with ***Boron Trifluoride*** prior to metalation to give, after deprotonation with *s*-butyllithium, a sort of dipole-stabilized[3] anion (**6**), as demonstrated for *N*-methylpyrrolidine and *N*-methylpiperidine.[4] After quenching with benzaldehyde, benzophenone, or cyclohexanone the corresponding 2-amino alcohols (**3**) have been obtained in good yields (eq 2). Alkylation with ***Iodomethane*** (51%), oxidation with ***Iodine*** to give the 1,2-diamine (65%), and acylation with benzonitrile (50%) or ***Methyl Acrylate*** (69%) are also reported.

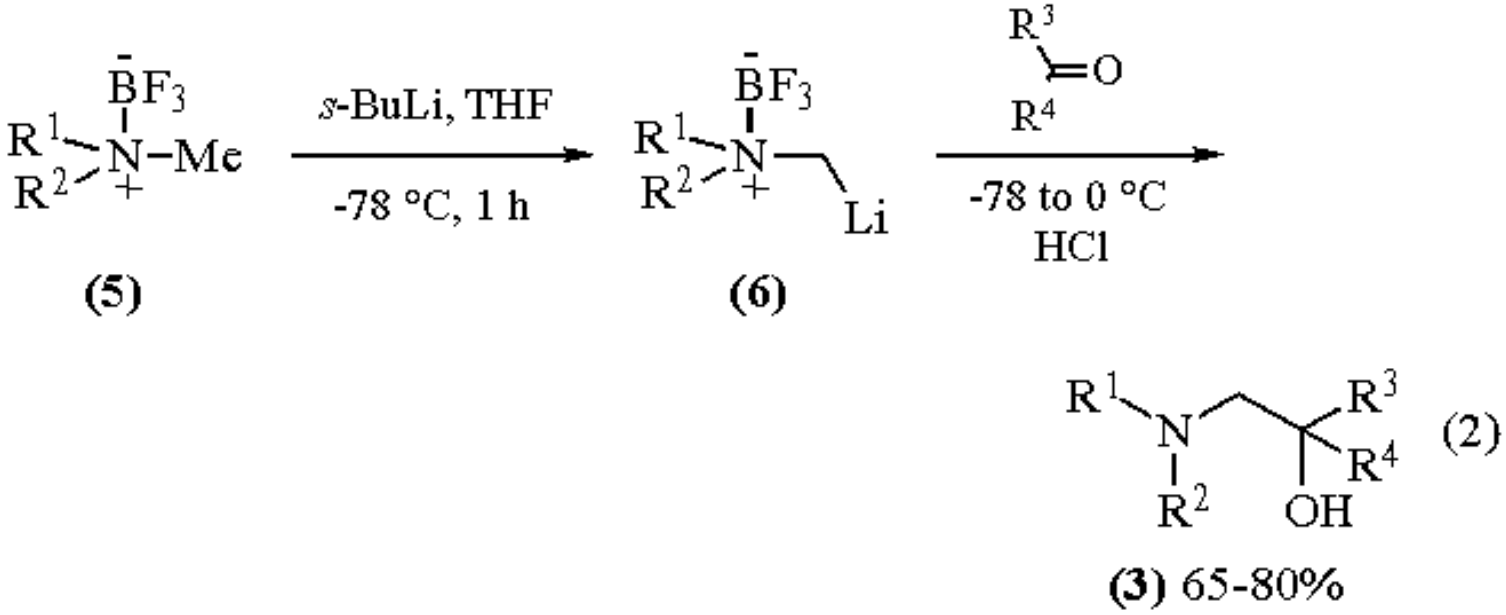

To avoid the difficulties of direct deprotonation, the very fast method of tin-lithium exchange can be used. From α-stannylated amines (**7**) the α-lithioamines (**2**) are available immediately with ***n-Butyllithium*** in hexane (e.g. trimethylamine, *N*-methylpiperidine, *N*,*N*-dimethylaniline, *N*-methyldiphenylamine) and can be trapped with benzaldehyde to give the amino alcohols (**8**) in high yields (eq 3).[5] The only exception observed has been with *N*-lithiomethylmorpholine, which decomposed rapidly.

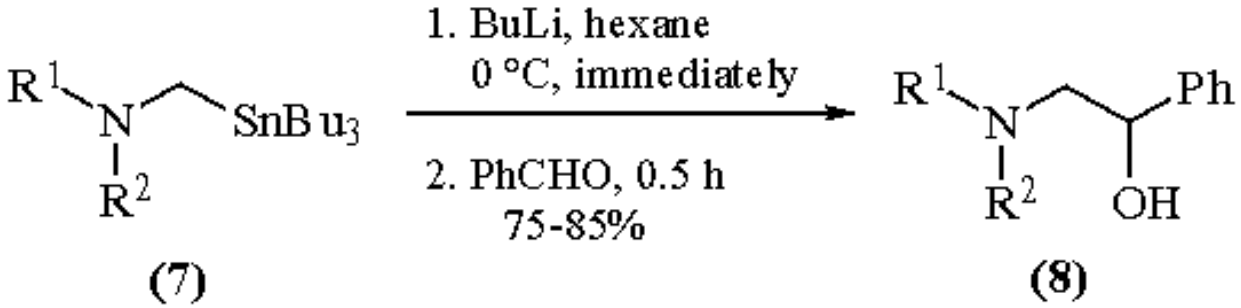

(3)

The method has been extended to other *N*-methylamines, of which *N*-benzyldimethylamine is the most interesting, since after electrophilic reaction the benzyl group can be removed reductively to give formally the product of α-lithiodimethylamine. After reaction at -65 °C with ***Chlorotrimethylsilane***, the silylated amine is obtained in 87% yield. However, after warming to rt for 1 h, only the product of a Wittig rearrangement is found.[6] For comparison of the three methods see Table 1.

Table 1 Comparison of Preparation of 2-Amino Alcohols (**3**) by the Different Methods Described

R^1	R^2	R^3	R^4	Eq	Yield (%)
$(CH_2)_5$		H	Ph	(1)	73
$(CH_2)_5$		H	Ph	(2)	79
$(CH_2)_5$		H	Ph	(3)	85
$(CH_2)_5$		H	*t*-Bu	(1)	41
$(CH_2)_5$		H	*i*-Pr	(1)	62
$(CH_2)_5$		$(CH_2)_5$		(1)	50
$(CH_2)_5$		$(CH_2)_5$		(2)	68
$(CH_2)_5$		$(CH_2)_3(CH)_2$		(1)	50
$(CH_2)_4$		H	Ph	(1)	68
$(CH_2)_4$		H	Ph	(2)	68
$(CH_2)_4$		Ph	Ph	(2)	65
Me	Me	H	Ph	(1)	68
Me	Me	H	Ph	(3)	81
Me	Ph	H	Ph	(3)	81

Some further synthetic applications are given in eqs 4 and 5.[7,8]

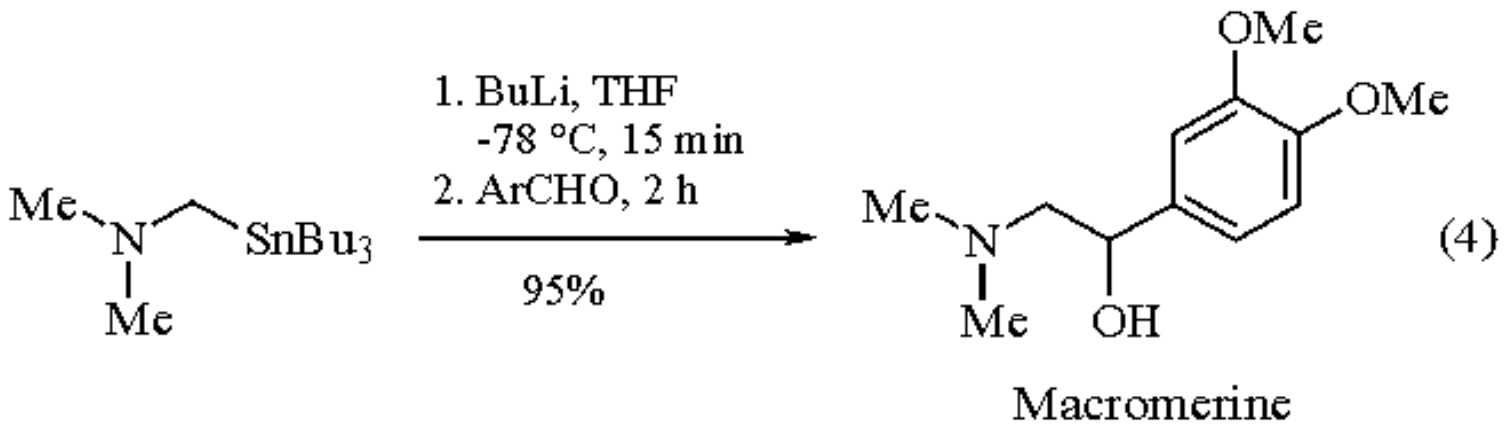

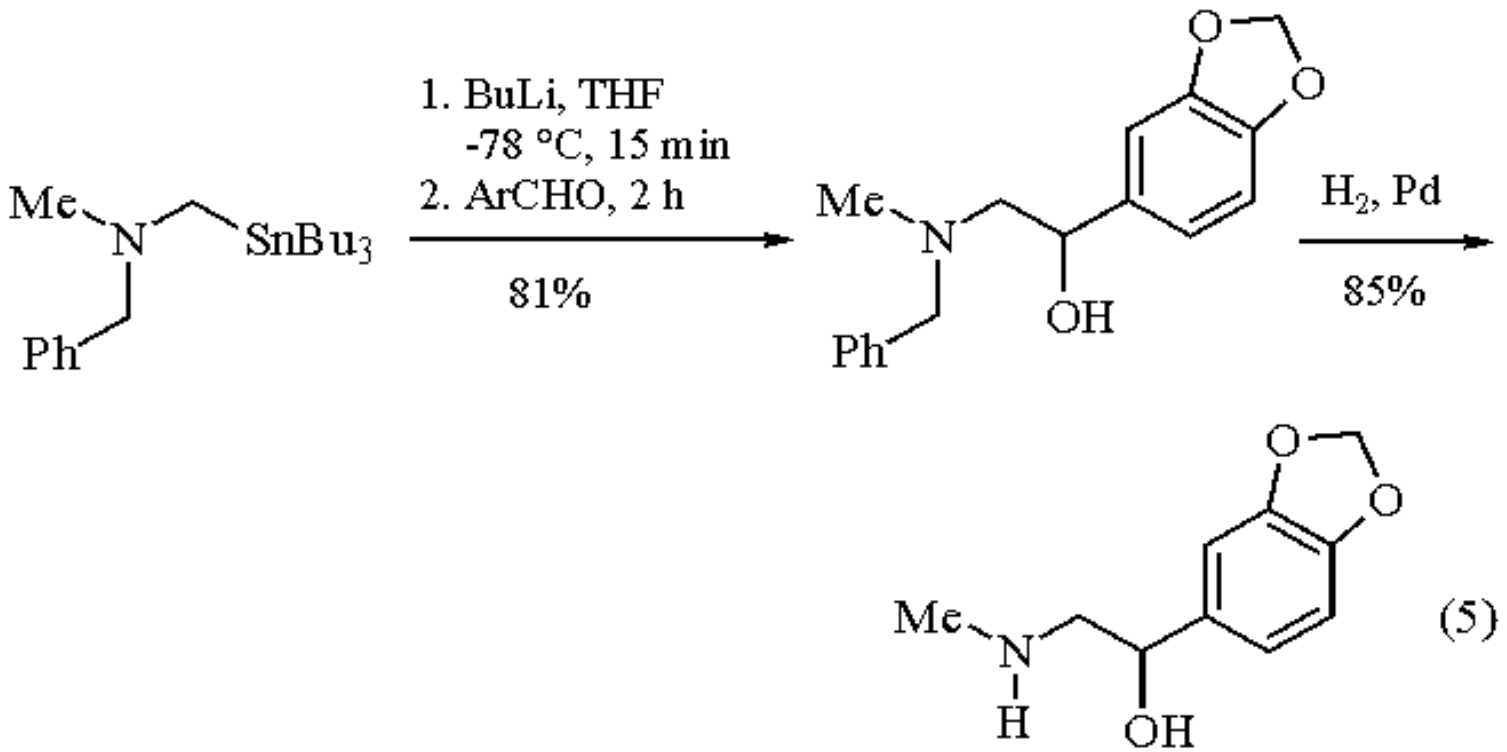

The α-stannylated amines (**7**) are best prepared by addition of ***Tri-n-butylstannyllithium*** to *S,N*-acetals (50-75%)[5,6] or tributylstannylmagnesium chloride to *O,N*-acetals (65-89%)[7] or immonium salts (75-89%).[8]

Another way to accelerate metalation is through intramolecular complexation:[9] ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA)[10] or ***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine*** (PMDTA)[11] can be deprotonated at the methyl group with alkyllithiums in alkanes to give the corresponding aminoalkyllithiums; the latter can be trapped with ***Chlorotrimethylstannane*** or benzaldehyde. Lithiated PMDTA has been characterized by NMR methods and shown to be monomeric in solution.[12]

All reactions described so far are restricted to the generation of dialkylaminomethyllithiums and failed to generate homologous dialkylaminoalkyllithiums. This limitation can be overcome by acceleration of the tin-lithium exchange reaction by built-in complexing ligands, as for the generation of lithiated and configurationally stable aziridine reagents.[13] The method has been exploited for the preparation of enantiomerically enriched aminoalkyllithium compounds to study their configurational stability (eq 6).[14]

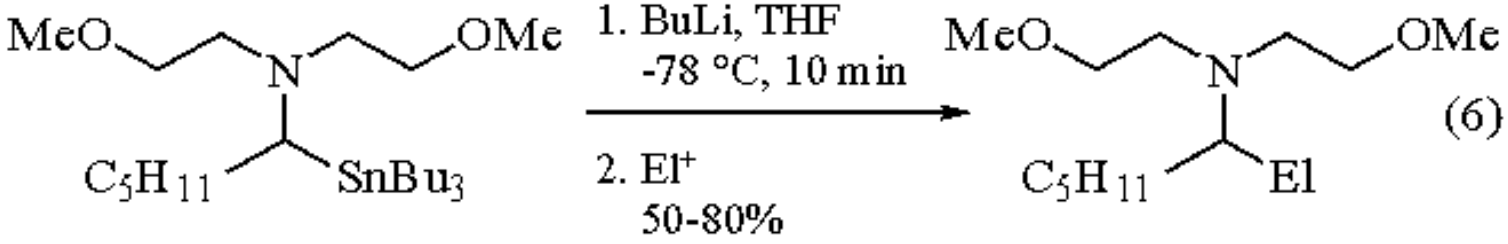

More generally, secondary and even tertiary dialkylaminoalkyllithium reagents can be generated by reductive metalation of *S*,*N*-acetals with ***Lithium 4,4´-Di-t-butylbiphenylide*** (LiDBB) (eq 7).[15]

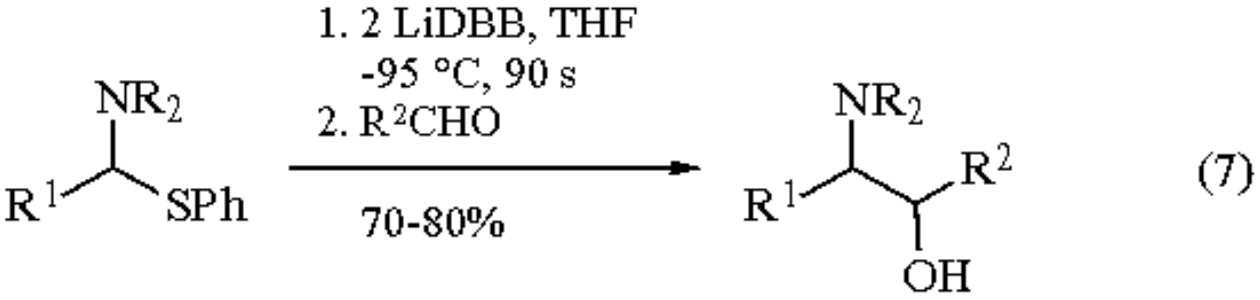

Related Reagents.

N-t-Butoxycarbonyl-N-methylaminomethyllithium; ***N´-t-Butyl-N-methyl-N-trimethylsilylmethylformamidine***; ***N-Nitrosodimethylamine***.

---

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(Dimethylamino)methyl Methyl Ether[1]

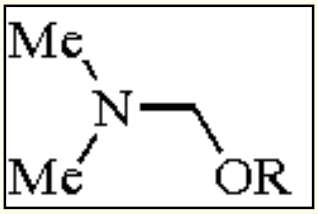

(**1**; R = Me)

[62393-45-7] · $C_4H_{11}NO$ · (Dimethylamino)methyl Methyl Ether · (MW 89.14) (**2**; R = Bu)

[56275-84-4] · $C_7H_{17}NO$ · Butyl (Dimethylamino)methyl Ether · (MW 131.22)

(precursor for *N*,*N*-dimethyl(methylene)ammonium salts;[2,3] useful for the in situ dimethylaminomethylation of silyl enol ethers to produce β-(*N*,*N*-dimethylamino) ketones (Mannich bases)[4,5])

Physical Data: (**1**) bp 67 °C/760 mmHg; (**2**) bp 128 °C/756 mmHg.

Solubility: sol H_2O, acetonitrile.

Preparative Methods: amino ethers (**1**)[3] and (**2**)[6] are prepared from a mixture of dimethylamine (0.5 mol), alcohol (1 mol), and ***Potassium Carbonate*** (0.6 mol) at 0 °C. ***Paraformaldehyde*** is added after a few min, and the mixture is stirred overnight at room temperature. The product is purified by filtration followed by distillation to give a colorless liquid.

Handling, Storage, and Precautions: handle with gloves in a well-ventilated fume hood. Incompatible with acids and acid chlorides. Readily decomposes in water in the presence of acid.

General Discussion.

The mechanism of the acid-catalyzed hydrolysis of (**2**), which involves the formation of an iminium intermediate, has been studied in detail.[6] *N*,*N*-Dimethyl(methylene)ammonium salts are readily obtained by the reaction of (**1**) with acid halides (eq 1) or ***Methyltrichlorosilane*** (eq 2).[3] The latter method may be used in situ for dimethylaminomethylation of silyl enol ethers to give β-(*N*,*N*-dimethylamino) ketones in good yield (eq 3).[4]

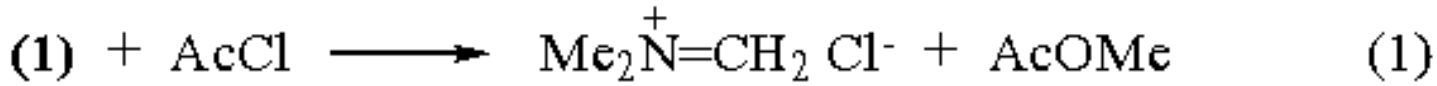

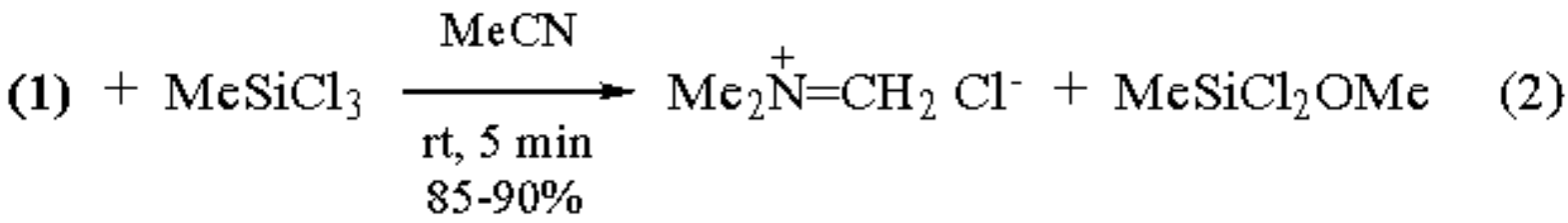

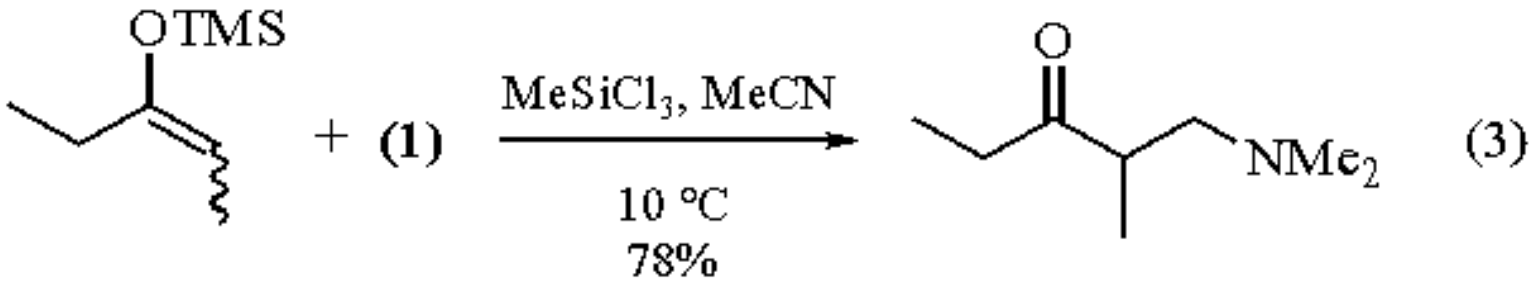

In a similar manner, (**2**) reacts with silyl enol ethers in the presence of either ***Iodotrimethylsilane*** or ***Trimethylsilyl Trifluoromethanesulfonate*** to provide the Mannich reaction product (eq 4).[5] However, in the reaction of (**2**) with ***Chlorotrimethylsilane*** the effective intermediate is believed to be an oxonium salt as there is no evidence of the formation of an iminium salt. It is interesting to note that the use of ***Bis(dimethylamino)methane*** in the place of (**2**) in the above reaction does not proceed smoothly.

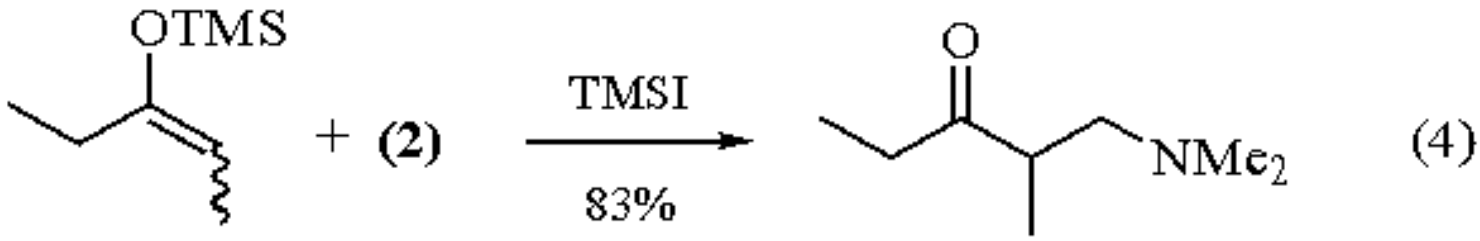

Terminal alkynes have also been converted in excellent yields into Mannich bases by reaction with (**2**) instead of formaldehyde and dimethylamine (eq 5).[7]

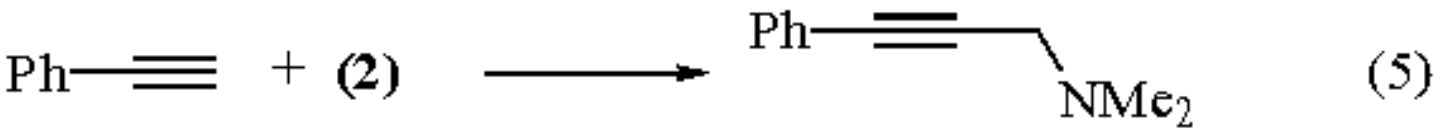

Related Reagents.

Bis(dimethylamino)methane; ***t-Butoxybis(dimethylamino)methane***; ***Dimethyl(methylene)ammonium Iodide***; ***Formaldehyde-Dimethylamine***; ***(Methoxymethyl)bis(trimethylsilyl)amine***; ***N-(Methylthiomethyl)piperidine***.

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(2-Dimethylaminomethylphenyl)phenylsilane

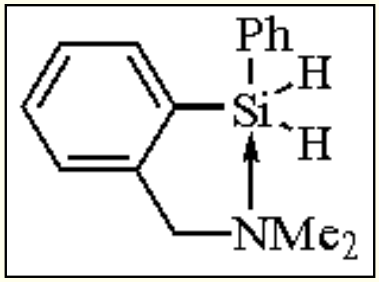

[129552-42-7] · $C_{15}H_{19}NSi$ · (2-Dimethylaminomethylphenyl)phenylsilane · (MW 241.41)

(hydrosilylating agent; selective reducing agent for carbonyls, acyl chlorides, carboxylic acids, and heterocumulenes under neutral conditions)

Physical Data: bp 115 °C/0.05 mmHg.

Solubility: sol ether, THF, alkanes, aromatics, chlorinated solvents.

Preparative Methods: to 67 g (0.5 mol) of *N*,*N*-dimethylbenzylamine in 300 mL of anhydrous ether are added dropwise under nitrogen 200 mL (0.5 mol) of ***n-Butyllithium*** (2.5 M in hexane). After being stirred for 48 h at 25 °C, the yellow suspension is transferred into a dropping funnel and added at 0 °C to 54 g (0.5 mol) of phenylsilane in 200 mL of ether. The mixture is stirred for 16 h, then filtered over celite. Solvents are removed under vacuum, and the residue is diluted in pentane, filtered again and fractionally distilled to give 82 g (68%) of 2-(dimethylaminomethylphenyl)phenylsilane (**1**).[1]

Related aminoarylsilanes are similarly prepared[2] from 1-(dimethylaminomethyl)naphthalene and 1-(dimethylamino)naphthalene, giving [8-(dimethylaminomethyl)-1-naphthyl]phenylsilane (**2**) and [8-(dimethylamino-1-naphthyl]phenylsilane (**3**), respectively.

General Discussion.

The reducing properties of silicon hydrides are enhanced by intramolecular pentacoordination.[1,3] Solvolysis is observed with alcohols and phenols, and addition to carbonyls occurs without the requirement of external catalysts. Some previous reports concerned the reduction of aroyl chlorides to aldehydes using organosilanes under catalytic conditions with Pd/C[4] or tributyltin hydride with catalytic Pd^0,[5] but incompatible functional groups on the substrate must be avoided. Such problems are overcome with organosilicon hydrides activated by intramolecular coordination of an aminoaryl group. These reagents react with acyl chlorides in carbon tetrachloride, affording chlorosilanes and aldehydes (eq 1).[6] The reactions are fast and quantitative. The aldehydes are either isolated by direct distillation from

the crude product mixture, or trapped after filtration over wet silica. The organosilanes can be recycled after separation and treatment with ***Lithium Aluminum Hydride***. Halogen, methoxy, and nitroaryl substituents, heteroaryl groups, and alkenes remain unchanged. The method is also suitable for the conversion of dicarboxylic acid chlorides into dialdehydes.

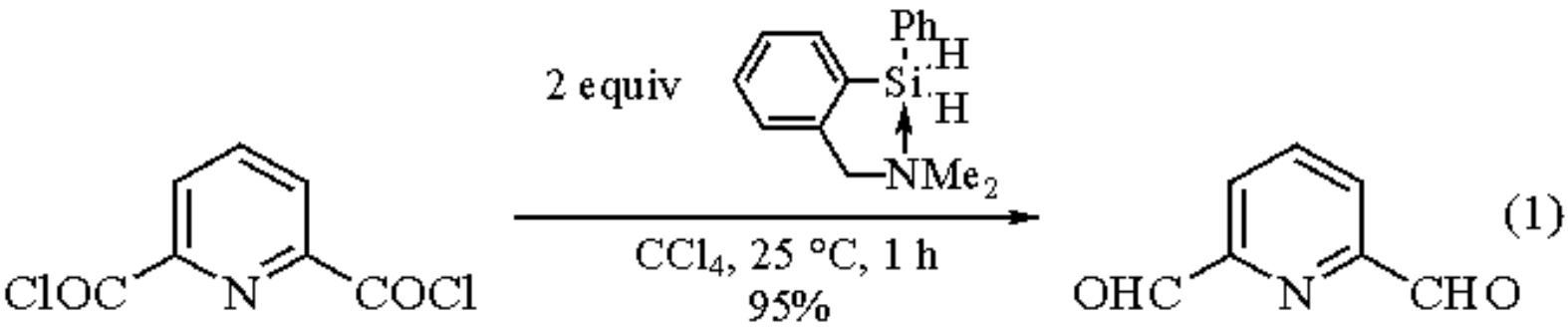

Hydrosilylation of isocyanates and isothiocyanates (eq 2) is readily achieved under mild conditions. Treatment of the adducts through the one-pot addition of acyl chlorides gives *N*-acylformamides and *N*-acylthioformamides.[7] *N,N´*-Dialkyl *C*-acylamidines result from the acylation[8] of *C*-silylamidines, obtained (eq 3) by hydrosilylation of alkylcarbodiimides with (**2**).

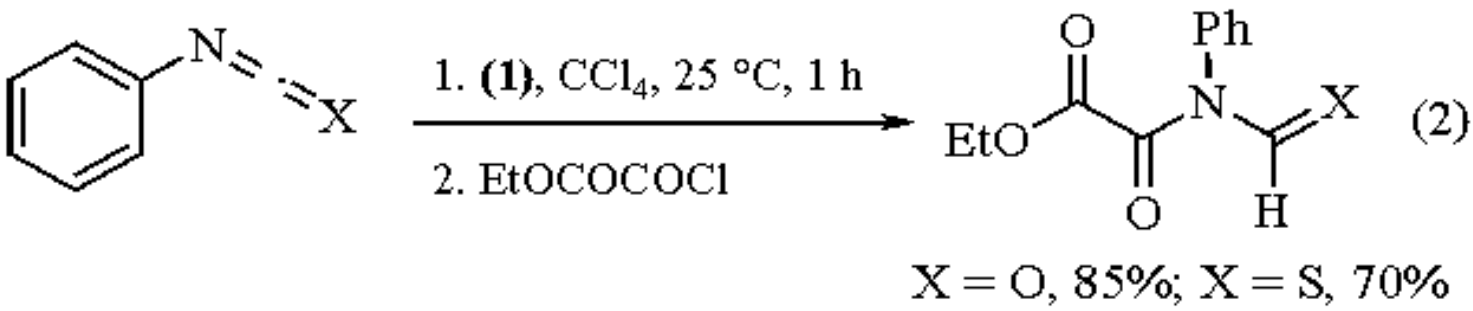

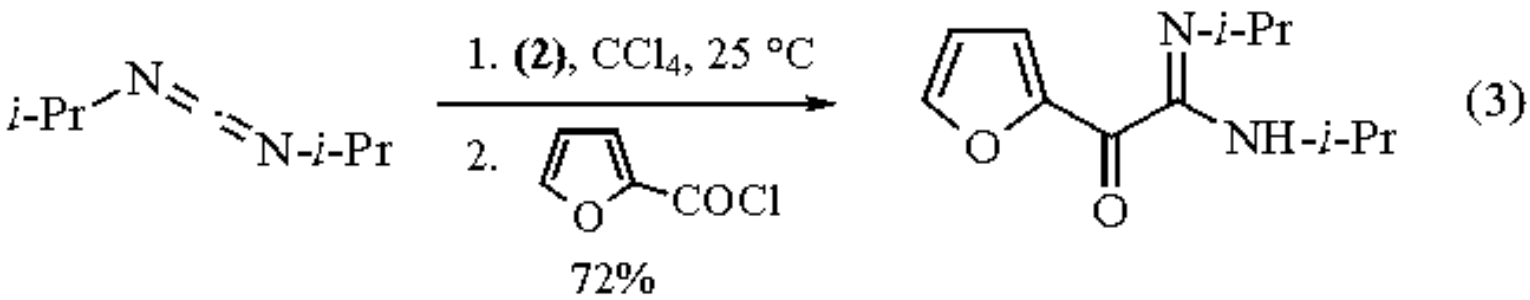

Pentacoordinated hydrosilanes react with excess aryl isocyanates to give isocyanurates.[9] Carboxylic acids are directly reduced to aldehydes in a one-pot process[10] through the thermal decomposition of pentacoordinated silyl carboxylates (eq 4). The aldehydes are extracted from the crude product mixture by distillation, or separated from the trisiloxane by column chromatography over Florisil. The reaction is selective, since fluoro, nitro, cyano, methoxy and heteroaryl substituents do not react with the silane. The present method also permits the reduction of α,β-unsaturated acids. The efficiency follows the order (**2**) > (**1**) > (**3**).

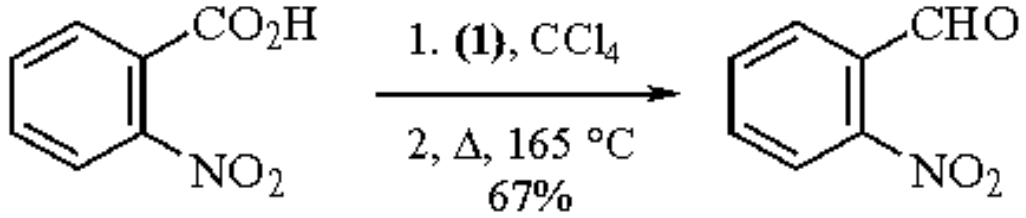

(4)

Related Reagents.

Triethylsilane; ***Triethylsilane-Trifluoroacetic Acid***.

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1-(*N,N*-Dimethylamino)-2-methyl-1-propene

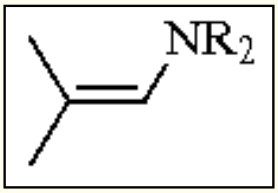

(**1**; R = Me)

[6906-32-7] · $C_6H_{13}N$ · 1-(*N,N*-Dimethylamino)-2-methyl-1-propene · (MW 99.20) (**2**; R,R = $-(CH_2)_4-$)

[2403-57-8] · $C_8H_{15}N$ · 1-Pyrrolidino-2-methyl-1-propene · (MW 125.24) (**3**; R,R = $-(CH_2)_2O(CH_2)_2-$)

[2403-55-6] · $C_8H_{15}NO$ · 1-Morpholino-2-methyl-1-propene · (MW 141.24) (**4**; R,R = $-(CH_2)_5-$)

[673-33-6] · $C_9H_{17}N$ · 1-Piperidino-2-methyl-1-propene · (MW 139.27) (**5**; R,R = $-(CH_2)_6-$)

[94167-75-6] · $C_{10}H_{19}N$ · 1-Perhydroazepino-2-methyl-1-propene · (MW 153.30)

(either the enamine nitrogen or its β-carbon atom is nucleophilic, undergoing substitution or conjugate addition;[1] can take part in 1,2- or 1,4-cycloaddition[1])

Physical Data: (**1**) bp 89-90 °C; *n*20D 1.4221; $IR_{C=C}$ 1680 cm^{-1}. (**2**) bp 50 °C/14 mmHg; *n*20D 1.4739; $IR_{C=C}$ 1674 cm^{-1}. (**3**) bp 59-60 °C/17 mmHg; *n*20D 1.4676; $IR_{C=C}$ 1675 cm^{-1}. (**4**) bp 65-67 °C/12 mmHg; *n*20D 1.4676; $IR_{C=C}$ 1675 cm^{-1}. (**5**) bp 85-86 °C/12 mmHg; *n*20D 1.4845; $IR_{C=C}$ 1667.

Preparative Methods: the usual method of preparation for these enamines is the condensation of a secondary amine with isobutyraldehyde (2-methylpropanal) (eq 1).[2]

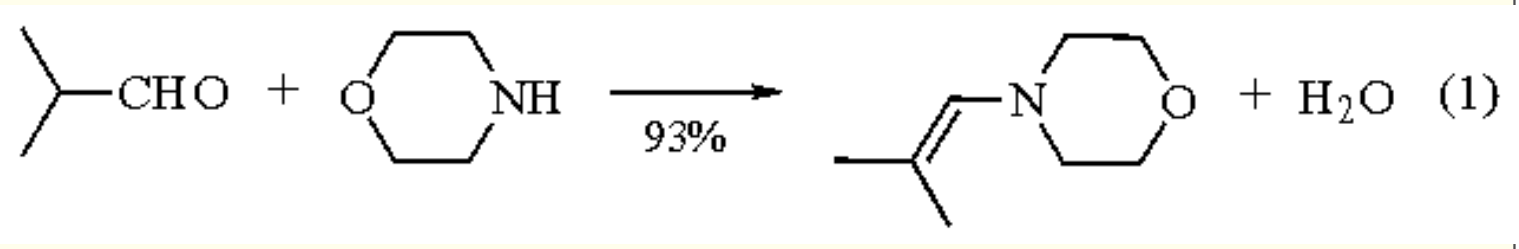

Handling, Storage, and Precautions: colorless liquid; readily reacts with water or atmospheric oxygen. Should be stored under dry nitrogen.

Alkylation.

Enamines derived from β-disubstituted aldehydes are alkylated on nitrogen by alkyl halides. Activated alkyl halides provide easier access to *C*-alkylated products, but the increased activity also results in greater amounts of dialkylation products. Allyl, benzyl, and propargyl halides give *C*-alkylated products with these enamines. However, in some cases (e.g. crotyl bromide, eq 2),[3] *N*-alkylation may occur initially, followed by isomerization to the *C*-alkyl isomer (e.g. via [3,3]-sigmatropic rearrangement). High dielectric solvents favor *C*-alkylation in these reactions. Ternary iminium ions can alkylate acyclic enamines (eq 3).[4]

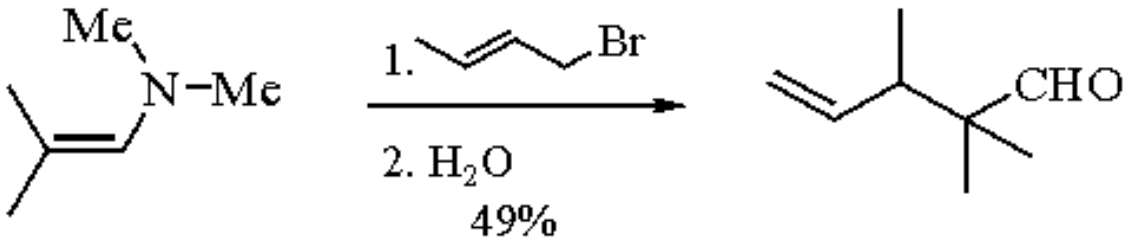

(2)

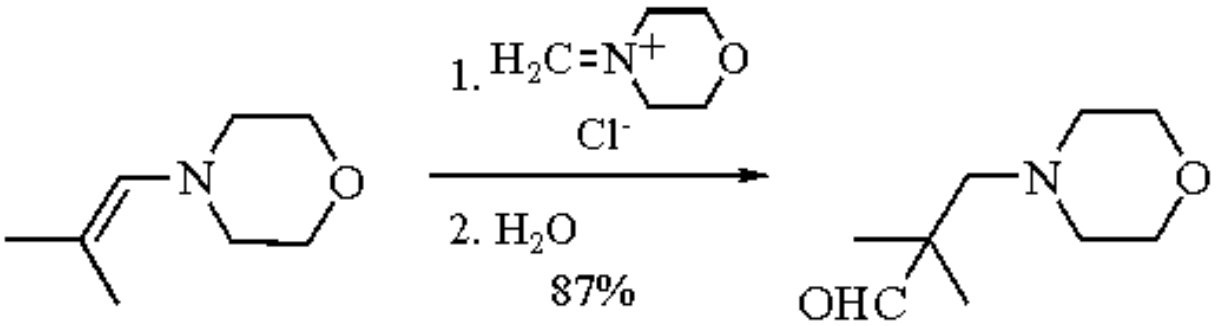

(3)

Acylation.

Addition of ***Acetyl Chloride*** to the morpholine enamine of isobutyraldehyde gives normal *C*-acylation which upon hydrolysis produces a keto aldehyde (eq 4).[5]

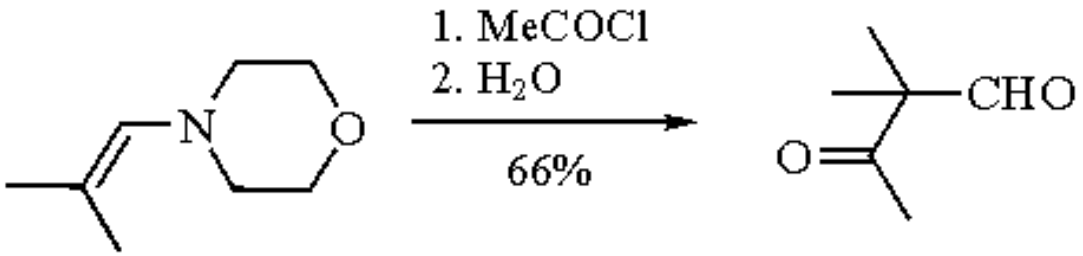

(4)

Cycloaddition.

The initial product formed when an electrophilic alkene such as ***Methyl Vinyl Ketone*** is allowed to react with an acyclic enamine is a dihydropyran (eq 5).[6]

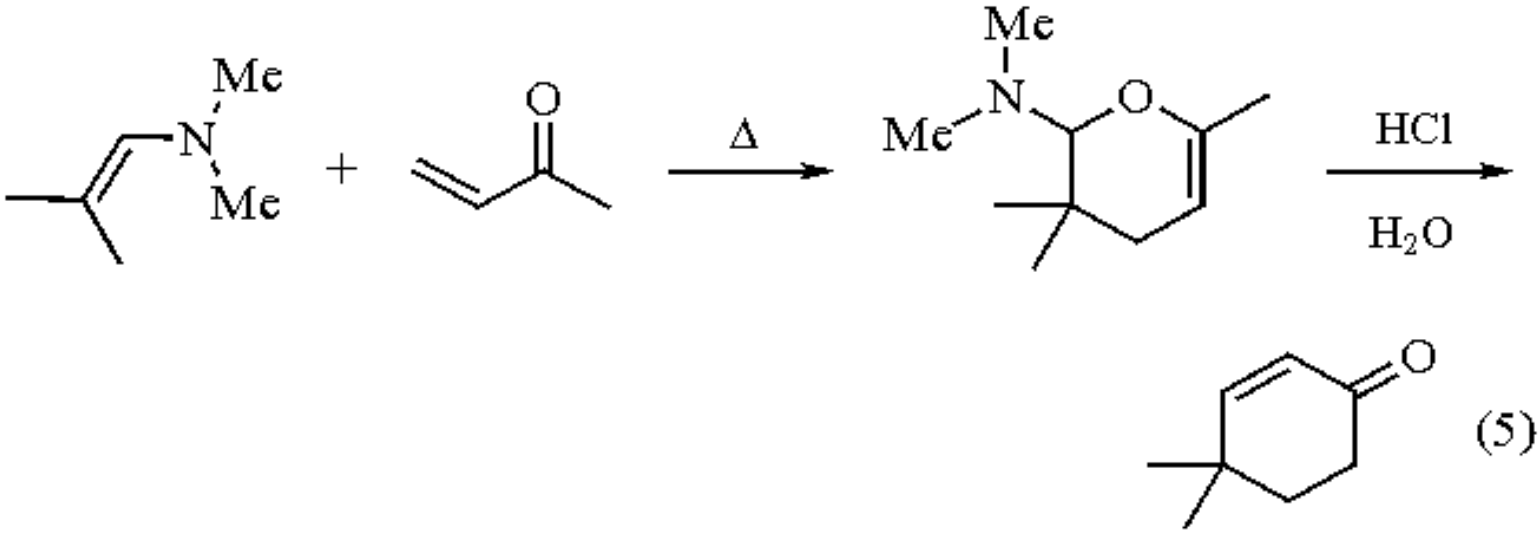

[2 + 2] Cycloaddition takes place to form thermally stable cyclobutane products when acyclic enamines with no β-hydrogens are treated with dimethylketene,[7] ***Methyl Acrylate***,[2b] fumaronitrile,[2c] and ***Dimethyl Fumarate*** or diethyl fumarate.[2c,8] The thermal and the photochemical fumarate reactions give different stereoisomeric products (eqs 6 and 7).[8]

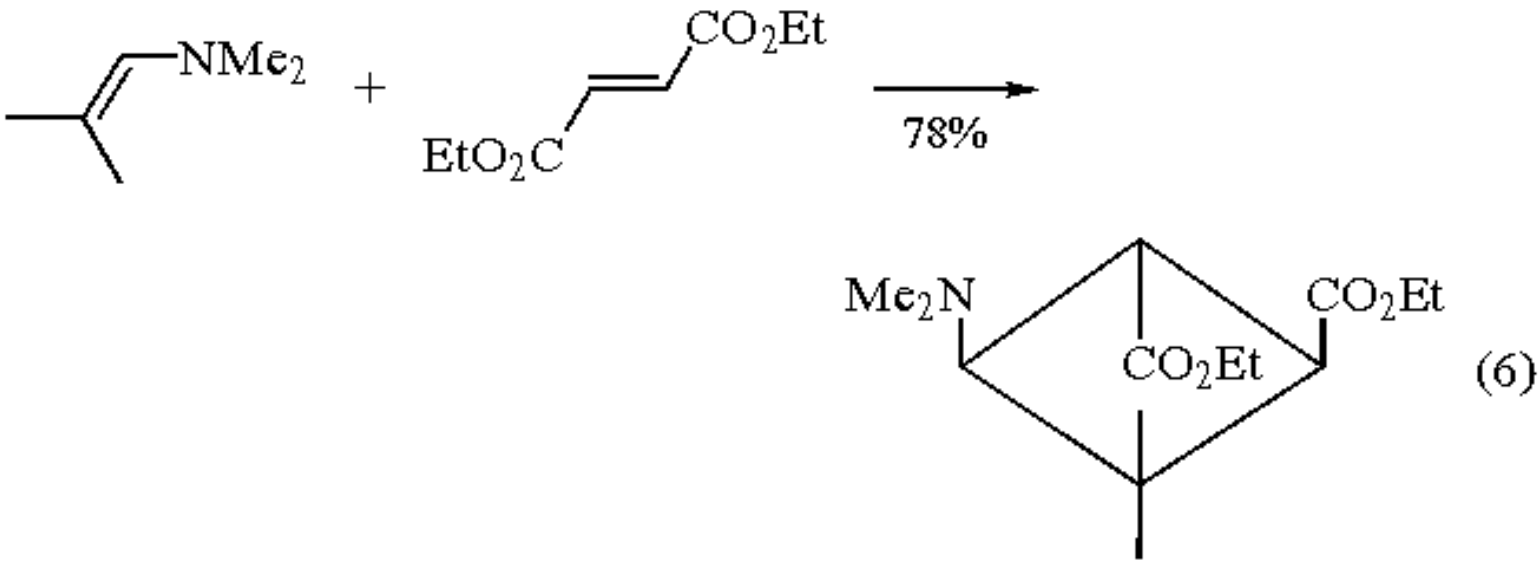

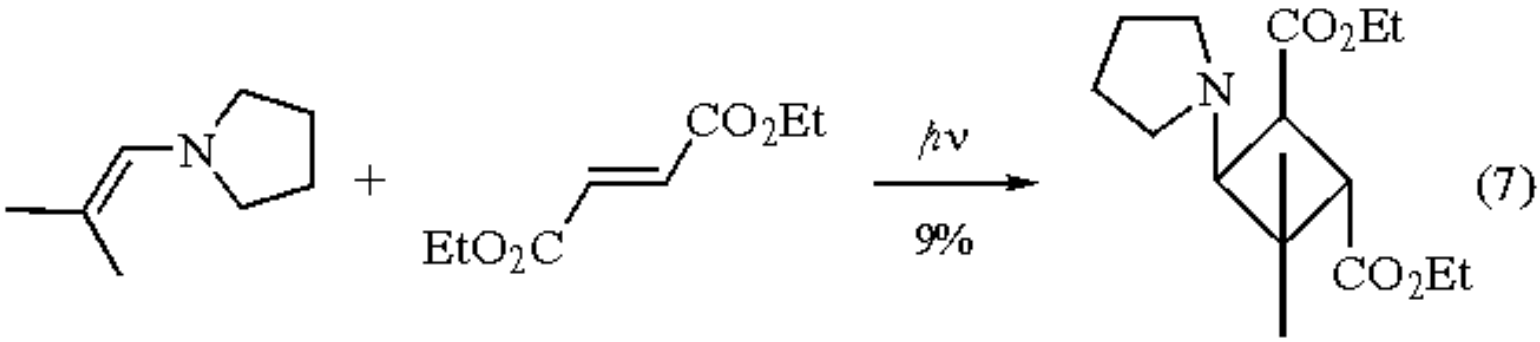

Acid-catalyzed hydrolysis effects aldol cyclization to give 4,4-dimethyl-2-cyclohexenone.[6b]

Related Reagents.

Crotyl Chloride; ***Methyl Acrylate***; ***Methyl Vinyl Ketone***; ***Morpholine***; ***Piperidine***; ***Pyrrolidine***; ***1-Pyrrolidino-1-cyclohexene***; ***1-Pyrrolidino-1-cyclopentene***.

---

1. (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *JACS* **1963**, *85*, 207. (b) Szmuszkovicz, J. *Advances in Organic Chemistry: Methods and Results*; Interscience: New York, 1964; Vol. 4, p 1 (c) Kuehne, M. E. *S* **1970**, 510. (d) Dyke, S. F. *The Chemistry of Enamines*; Cambridge University Press: London, 1973. (e) Hickmott, P. W. *T* **1982**, *38*, 1975, 3363. (f) Pitacco, G.; Valentin, E. *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Wiley: New York, 1982; Part 1, p 623. (g) Granik, V. G. *RCR* **1984**, *53*, 383. (h) *Enamines: Synthesis, Structure, and Reactions*, 2nd ed.; Cook, A. G., Ed.; Dekker: New York, 1988.
2. (a) Benzing, E. *AG* **1959**, *71*, 521. (b) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. *JOC* **1961**, *26*, 625. (c) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. *JOC* **1964**, *29*, 801.
3. Brannock, K. C.; Burpitt, R. D. *JOC* **1961**, *26*, 3576.
4. Böhme, H.; Osmers, K.; Wagner, P. *TL* **1972**, 2785.
5. Inukai, T.; Yoshizawa, R. *JOC* **1967**, *32*, 404.
6. (a) Fleming, I.; Karger, M. H. *JCS(C)* **1967**, 226. (b) Chan, Y.; Epstein, W. W. *OSC* **1988**, *6*, 496.
7. Hasek, R. H.; Martin, J. C. *JOC* **1963**, *28*, 1468.
8. Lewis, F. D.; Ho, T.-I.; DeVoe, R. J. *JOC* **1980**, *45*, 5283.

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1-(Dimethylamino)-2-nitroethylene[1]

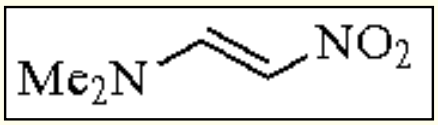

[1190-92-7] · $C_4H_8N_2O_2$ · 1-(Dimethylamino)-2-nitroethylene · (MW 116.14)

(synthetic reagent for nitroalkenes and nitroaromatics;[1] can undergo addition-elimination reaction with nucleophiles;[1] can effect inverse electron demand Diels-Alder reaction[2])

Physical Data: mp 104 °C.

Solubility: sol alcohols, ethers, chloroform, acetone; slightly sol *n*-hexane.

Preparative Methods: by reaction of ***N,N-Dimethylformamide Diethyl Acetal*** (85% yield)[3] or ***N,N-Dimethylformamide-Dimethyl Sulfate*** complex (60%)[4] with ***Nitromethane***; condensation of ***Triethyl Orthoformate*** with $MeNO_2$ in the presence of DMF (52%),[5] or addition-elimination reaction of ***1-Nitro-2-phenylthioethylene*** with Me_2NH (74%).[6]

Preparation of Nitroalkenes.

1-Dimethylamino-2-nitroethylene can be converted into synthetically useful nitroalkenes by addition-elimination reactions with nucleophiles such as organometallic reagents (eq 1),[7] enolates (eq 2),[8] indoles (eq 3),[9] polyalkoxybenzenes (eq 4),[9] a certain pyrimidine derivative (eq 5),[10] and the anion of fluorene (eq 6).[11]

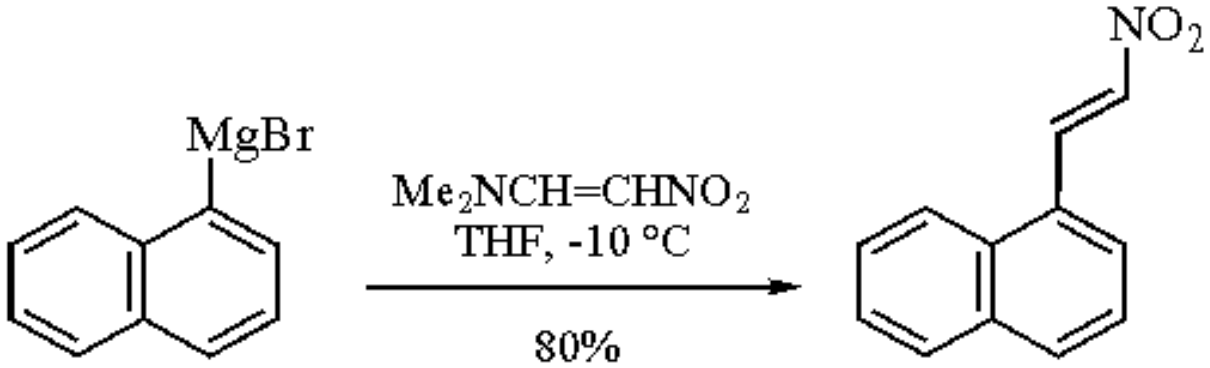

(1)

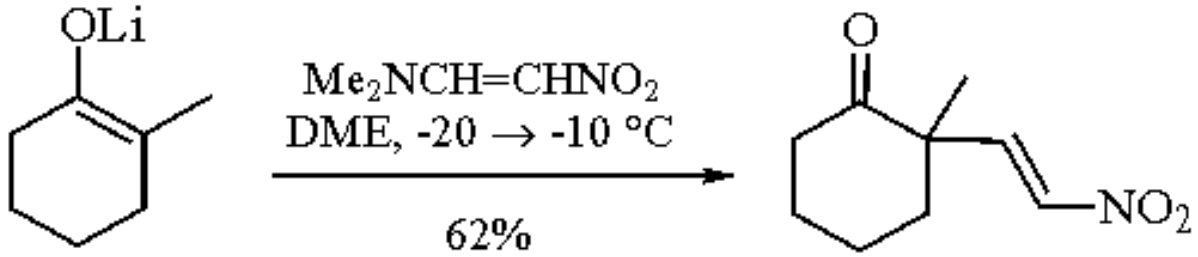
OLi
Me2NCH=CHNO2
DME, -20 → -10 °C
62%
O
NO2

(2)

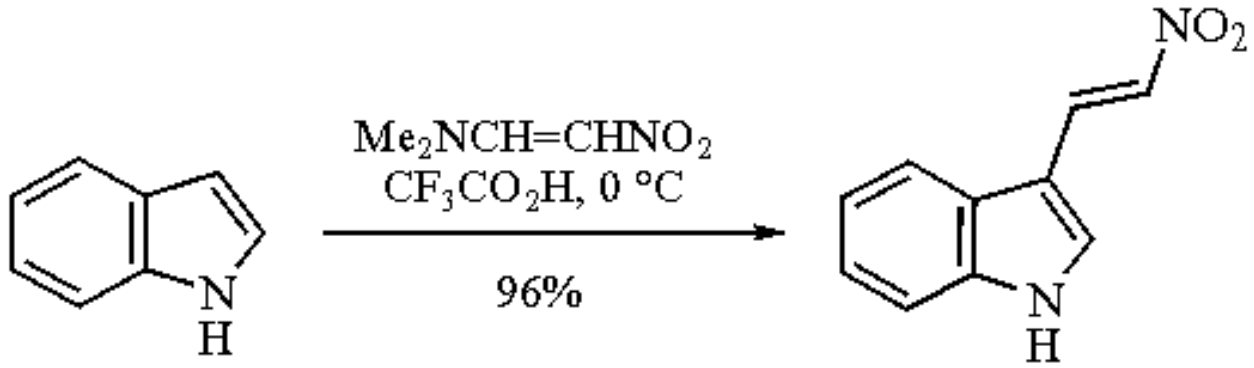
Me2NCH=CHNO2
CF3CO2H, 0 °C
96%
N
H
NO2

(3)

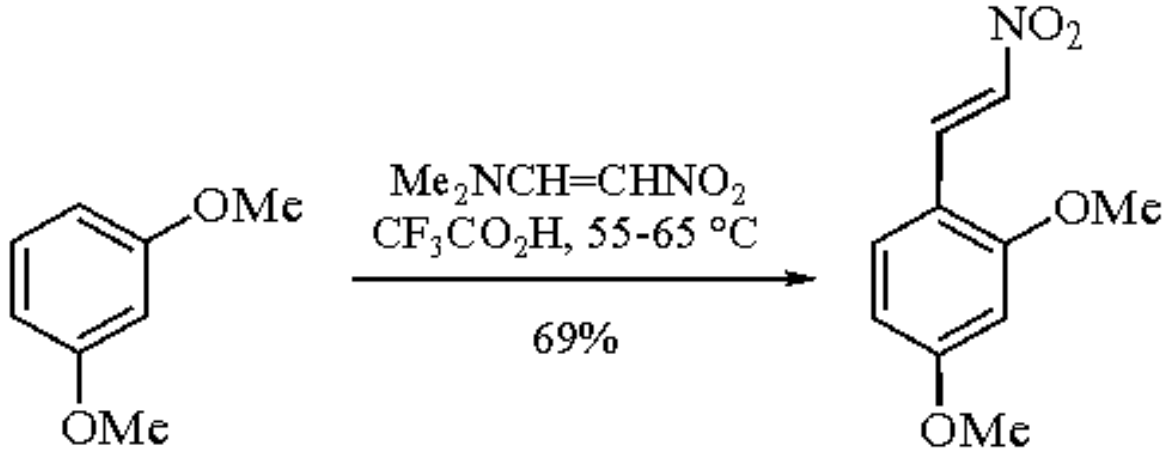
OMe
OMe
Me2NCH=CHNO2
CF3CO2H, 55-65 °C
69%
NO2
OMe
OMe

(4)

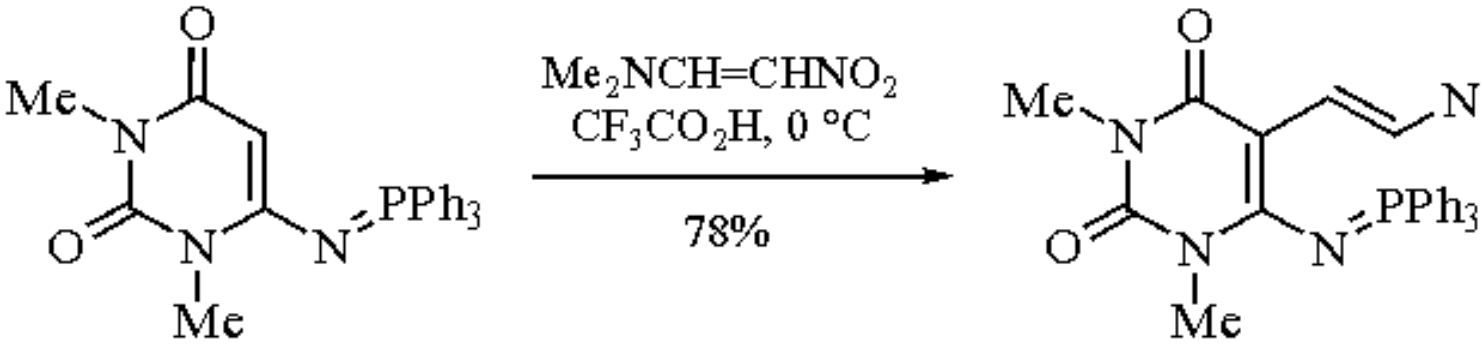
O
Me
N
O
N
Me
N
PPh3
Me2NCH=CHNO2
CF3CO2H, 0 °C
78%
O
Me
N
O
N
Me
N
PPh3
NO2

(5)

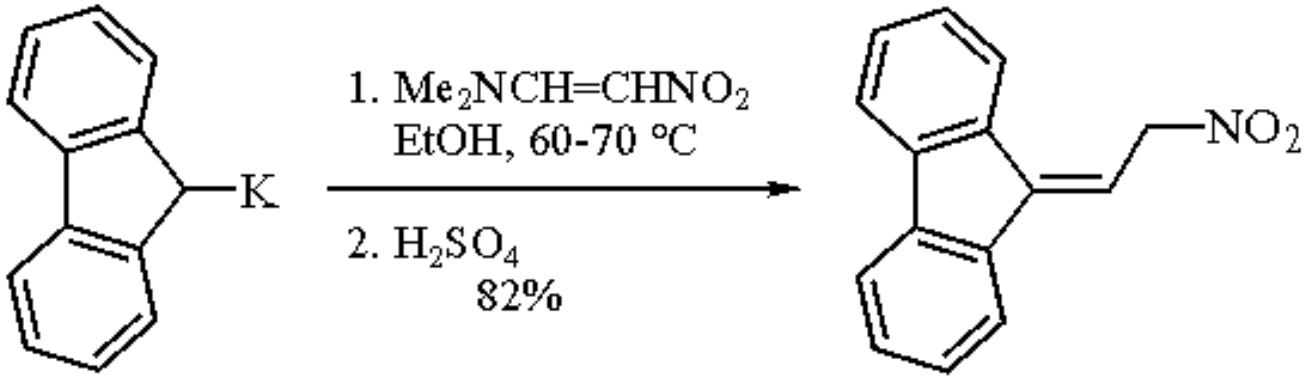

(6)

Preparation of Nitroaromatics.

Certain nitroalkene intermediates formed by addition-elimination reaction with active methylene compounds further undergo ring closure to produce nitroaromatics (eqs 7-9).[12-14]

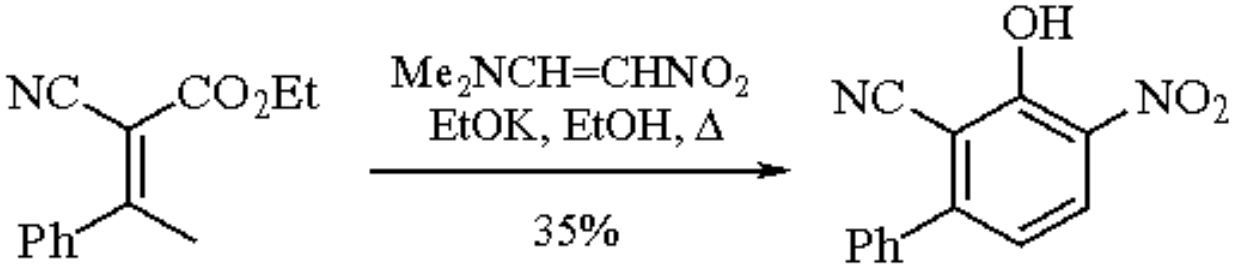

(7)

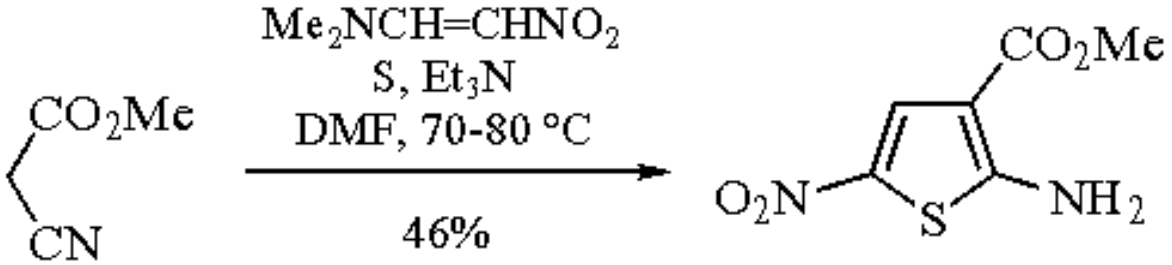

(8)

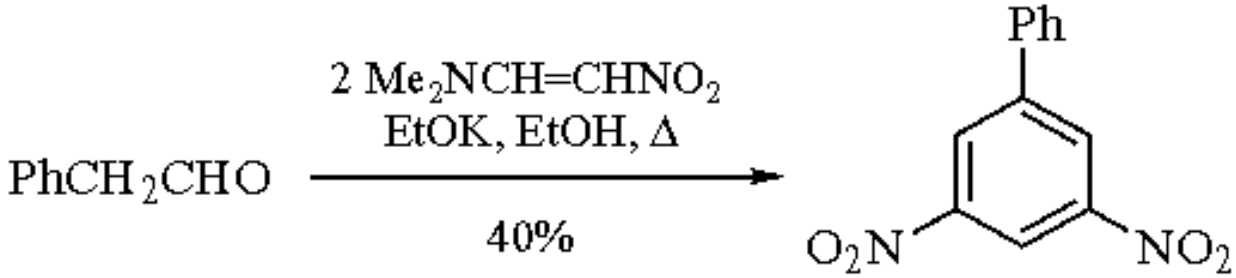

(9)

3-Aryl-1,2,4,5-tetrazines react with 1-dimethylamino-2-nitroethylene by an inverse electron demand Diels-Alder reaction to give 3-aryl-5-nitropyridazines (eq 10).[2]

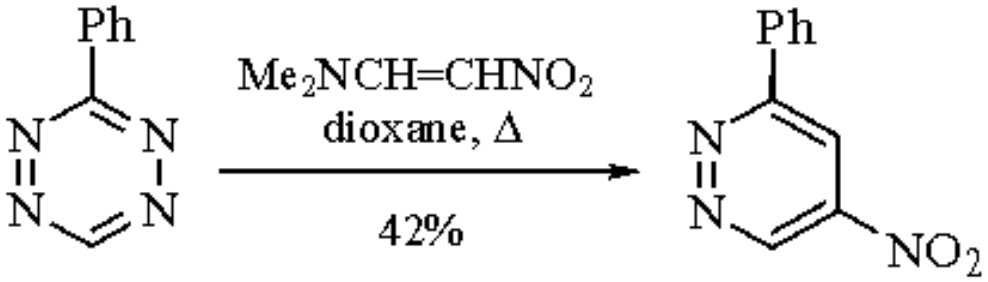

(10)

Related Reagents.

1-Nitro-2-phenylsulfonylethylene; ***1-Nitro-2-phenylthioethylene***.

---

1. (a) Rajappa, S. *T* **1981**, *37*, 1453. (b) Barrett, A. G. M.; Graboski, G. G. *CRV* **1986**, *86*, 751.
2. Marcelis, A. T. M.; van der Plas, H. C. *H* **1985**, *23*, 683.
3. Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *LA* **1961**, *641*, 1.
4. Severin, T.; Brück, B. *CB* **1965**, *98*, 3847.
5. Faulques, M.; Rene, L.; Royer, R. *S* **1982**, 260.
6. Kamimura, A.; Ono, N. *S* **1988**, 921.
7. Severin, T.; Scheel, D.; Adhikary, P. *CB* **1969**, *102*, 2966.
8. (a) Node, M.; Nagasawa, H.; Naniwa, Y.; Fuji, K. *S* **1987**, 729. (b) Lerche, H.; König, D.; Severin, T. *CB* **1974**, *107*, 1509.
9. (a) Büchi, G.; Mak, C.-P. *JOC* **1977**, *42*, 1784. (b) Somei, M.; Sato, H.; Komura, N.; Kaneko, C. *H* **1985**, *23*, 1101.
10. Molina, P.; Vilaplana, M. J. *S* **1990**, 474.
11. Severin, T.; Schnabel, I. *CB* **1969**, *102*, 1707.
12. Severin, T.; Brück, B.; Adhikary, P. *CB* **1966**, *99*, 3097.
13. Schäfer, H.; Gewald, K. *ZC* **1983**, *23*, 179.
14. Severin, T.; Adhikary, P.; Dehmel, E.; Eberhard, I. *CB* **1971**, *104*, 2856.

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4-Dimethylaminopyridine[1]

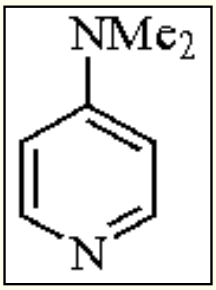

[1122-58-3] · $C_7H_{10}N_2$ · 4-Dimethylaminopyridine · (MW 122.19)

(catalyst for acylation of alcohols or amines,[1-11] especially for acylations of tertiary or hindered alcohols or phenols[12] and for macrolactonizations;[13-15] catalyst for direct esterification of carboxylic acids and alcohols in the presence of dicyclohexylcarbodiimide (Steglich-Hassner esterification);[5] catalyst for silylation or tritylation of alcohols,[9,10] and for the Dakin-West reaction[20])

Alternate Name: DMAP.

Physical Data: colorless solid; mp 108-110 °C; pK_a 9.7.

Solubility: sol MeOH, $CHCl_3$, CH_2Cl_2, acetone, THF, pyridine, HOAc, EtOAc; partly sol cold hexane or water.

Form Supplied in: colorless solid; commercially available.

Preparative Methods: prepared by heating 4-pyridone with HMPA at 220 °C, or from a number of 4-substituted (Cl, OPh, SO_3H, $OSiMe_3$) pyridines by heating with DMA.[2] Prepared commercially from the 4-pyridylpyridinium salt (obtained from pyridine and $SOCl_2$) by heating with DMF at 155 °C.[1,2]

Purification: can be recrystallized from EtOAc.

Handling, Storage, and Precautions: skin irritant; corrosive, toxic solid.

Acylation of Alcohols.

Several 4-aminopyridines speed up esterification of hindered alcohols with acid anhydrides by as much as 10 000 fold; of these, DMAP is the most commonly used but 4-pyrrolidinopyridine (PPY) and 4-tetramethylguanidinopyridine are somewhat more effective.[11] DMAP is usually employed in 0.05-0.2 mol equiv amounts.

DMAP catalyzes the acetylation of hindered 11β- or 12α-hydroxy steroids. The alkynic tertiary alcohol acetal in eq 1 is acetylated at rt within 20 min in the presence of excess DMAP.[3]

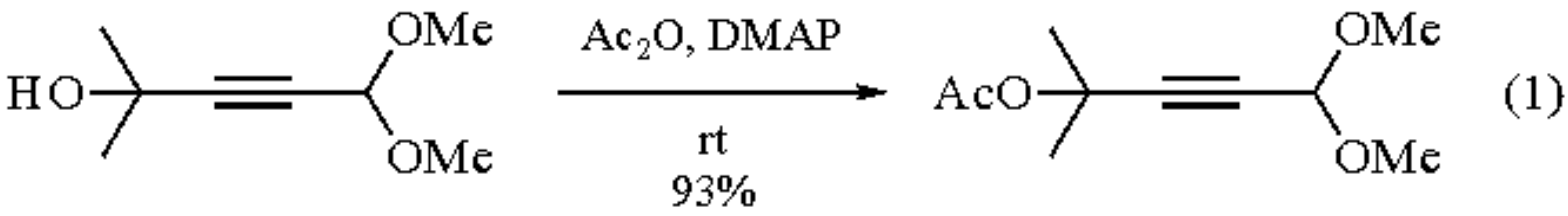

Esterifications mediated by ***2-Chloro-1-methylpyridinium Iodide*** also benefit from the presence of DMAP.[22]

DMAP acts as an efficient acyl transfer agent, so that alcohols resistant to acetylation by ***Acetic Anhydride-Pyridine*** usually react well in the presence of DMAP.[4a] Sterically hindered phenols can be converted into salicylaldehydes via a benzofurandione prepared by DMAP catalysis (eq 2).[4b]

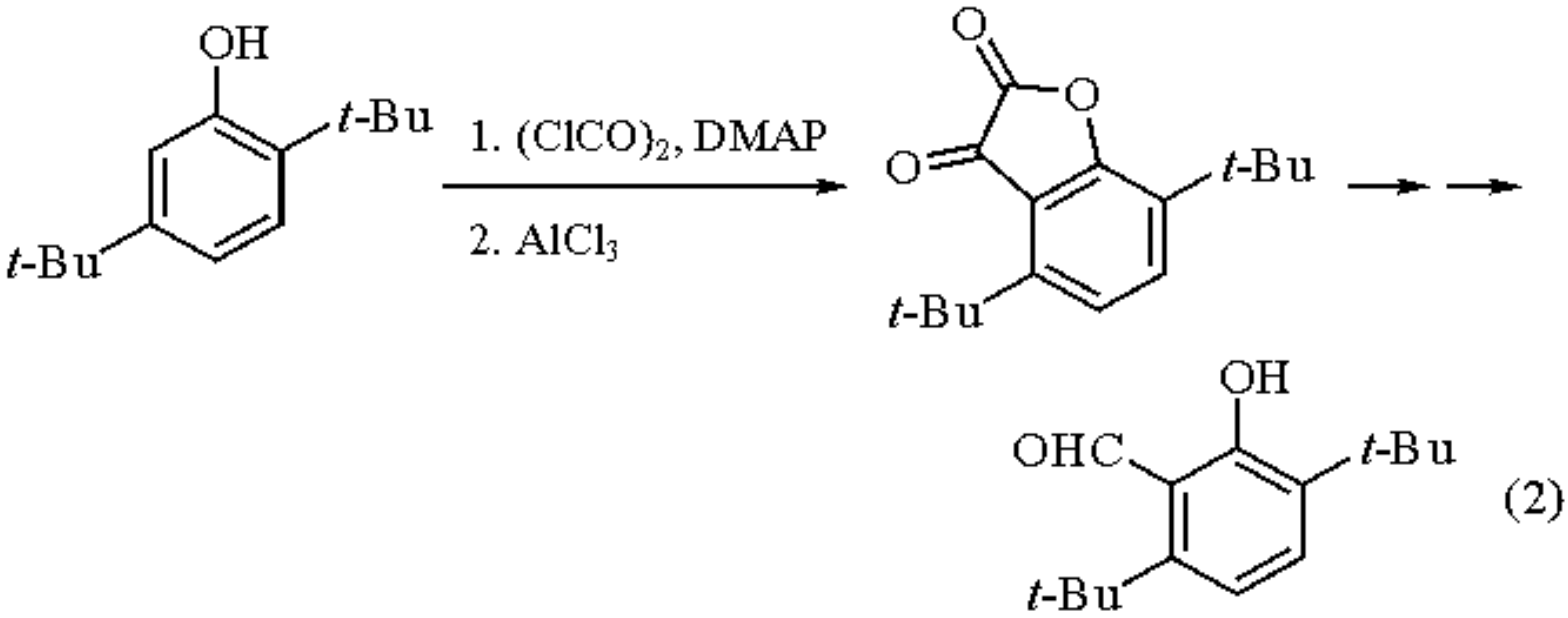

Direct Esterification of Alcohols and Carboxylic Acids.

Instead of using acid anhydrides for the esterification of alcohols, it is possible to carry out the reaction in one pot at rt by employing a carboxylic acid, an alcohol, ***1,3-Dicyclohexylcarbodiimide***, and DMAP.[5,6] In this manner, *N*-protected amino acids and even hindered carboxylic acids can be directly esterified at rt using DCC and DMAP or 4-pyrrolidinopyridine (eq 3).[5]

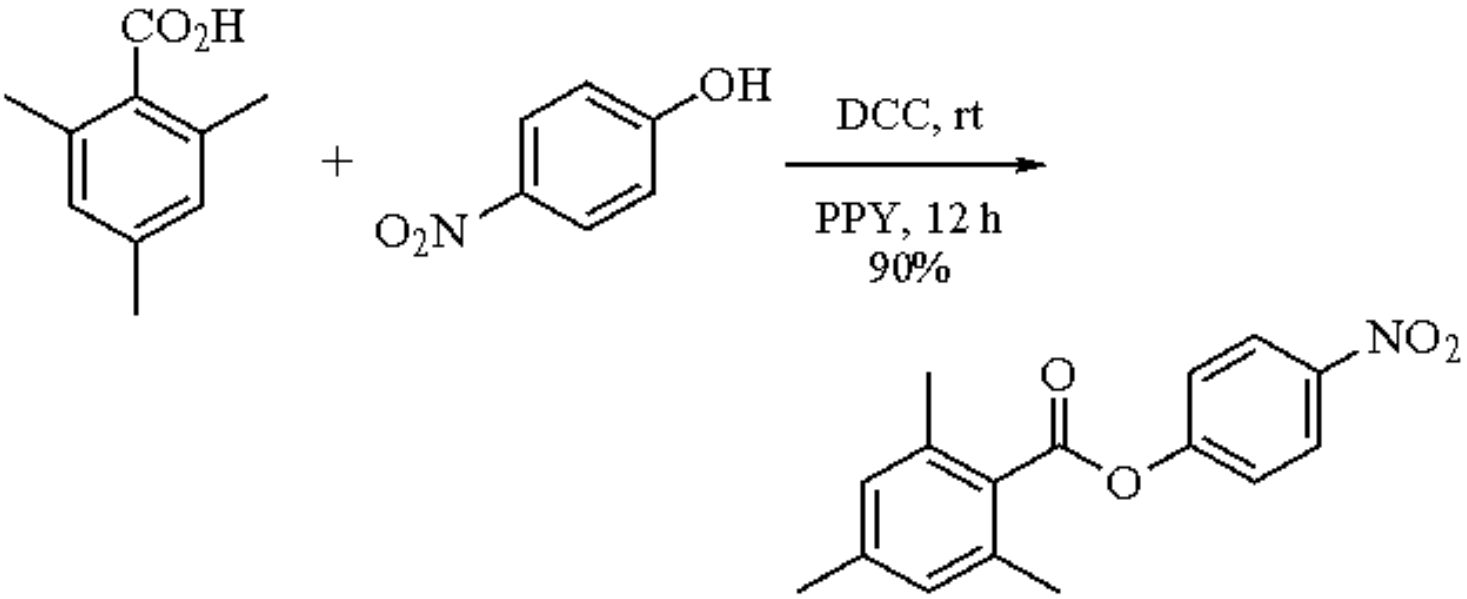

(3)

DCC-DMAP has been used in the synthesis of depsipeptides.[6b] Macrocyclic lactones have been prepared by cyclization of hydroxy carboxylic acids with DCC-DMAP. The presence of salts of DMAP,[13a] such as its trifluoroacetate, is beneficial in such cyclizations, as shown for the synthesis of a (9*S*)-dihydroerythronolide.[13b] Other macrolactonizations have been achieved using ***2,4,6-Trichlorobenzoyl Chloride*** and DMAP in ***Triethylamine*** at rt[14] or ***Di-2-pyridyl Carbonate*** (6 equiv) with 2 equiv of DMAP at 73 °C.[15]

Acylation of Amines.

Acylation of amines is also faster in the presence of DMAP,[7] as is acylation of indoles,[8a] phosphorylation of amines or hydrazines,[2,8] and conversion of carboxylic acids into anilides by means of ***Phenyl Isocyanate***.[1] β-Lactam formation from β-amino acids has been carried out with DCC-DMAP, but epimerization occurs.[8b]

Silylation, Tritylation, and Sulfinylation of Alcohols.

Tritylation, including selective tritylation of a primary alcohol in the presence of a secondary one,[9] silylation of tertiary alcohols, selective silylation to *t*-butyldimethylsilyl ethers,[6] and sulfonylation or sulfinylation[10] of alcohols proceed more readily in the presence of DMAP. Silylation of β-hydroxy ketones with ***Chlorodiisopropylsilane*** in the presence of DMAP followed by treatment with a Lewis acid gives diols (eq 4).[16]

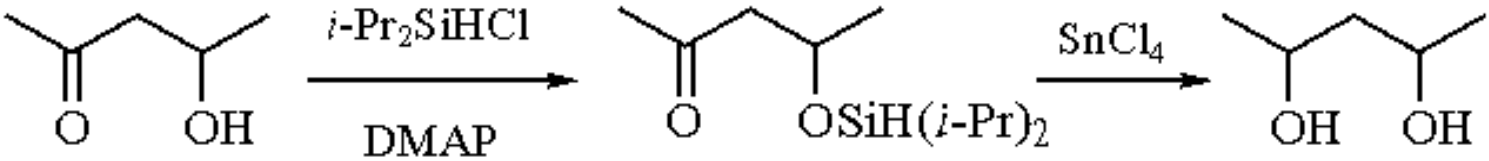

(4)

Miscellaneous Reactions.

Alcohols, including tertiary ones, can be converted to their acetoacetates by reaction with ***Diketene*** in the presence of DMAP at rt.[17] Decarboxylation of β-keto esters has been carried out at pH 5-7 using 1 equiv of DMAP in refluxing wet

toluene (eq 5).[18]

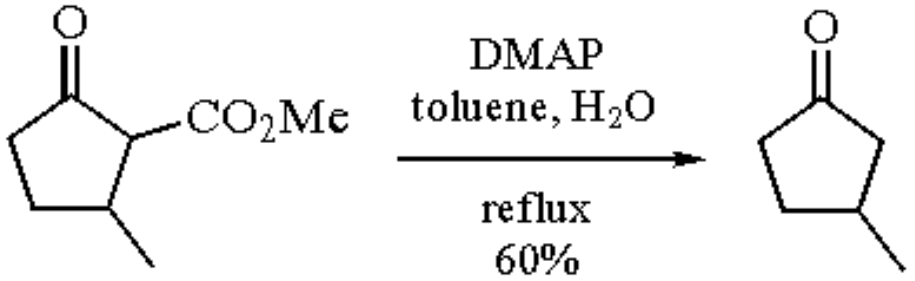

(5)

Elimination of water from a *t*-alcohol in a β-hydroxy aldehyde was carried out using an excess of ***Methanesulfonyl Chloride***-DMAP-H_2O at 25 °C.[23]

Glycosidic or allylic alcohols (even when *s*-) can be converted in a 80-95% yield to alkyl chlorides by means of ***p-Toluenesulfonyl Chloride***-DMAP. Simply primary alcohols react slower and secondary ones are converted to tosylates.[24]

Aldehydes and some ketones can be converted to enol acetates by heating in the presence of TEA, Ac_2O, and DMAP.[2] DMAP catalyzes condensation of malonic acid monoesters with unsaturated aldehydes at 60 °C to afford dienoic esters (eq 6).[19]

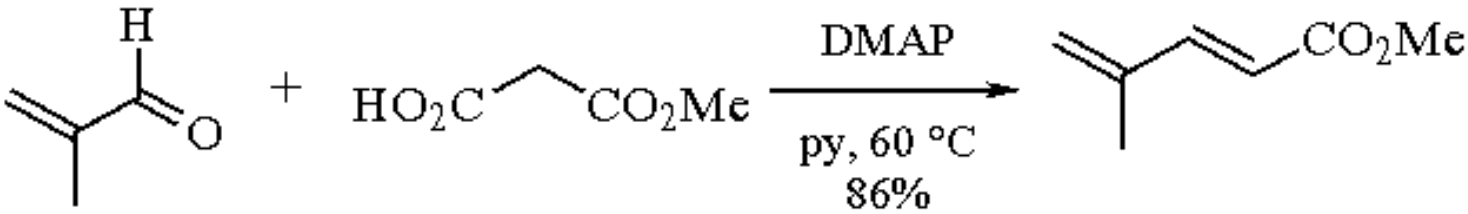

(6)

The conversion of α-amino acids into α-amino ketones by means of acid anhydrides (Dakin-West reaction)[20] also proceeds faster in the presence of DMAP (eq 7).

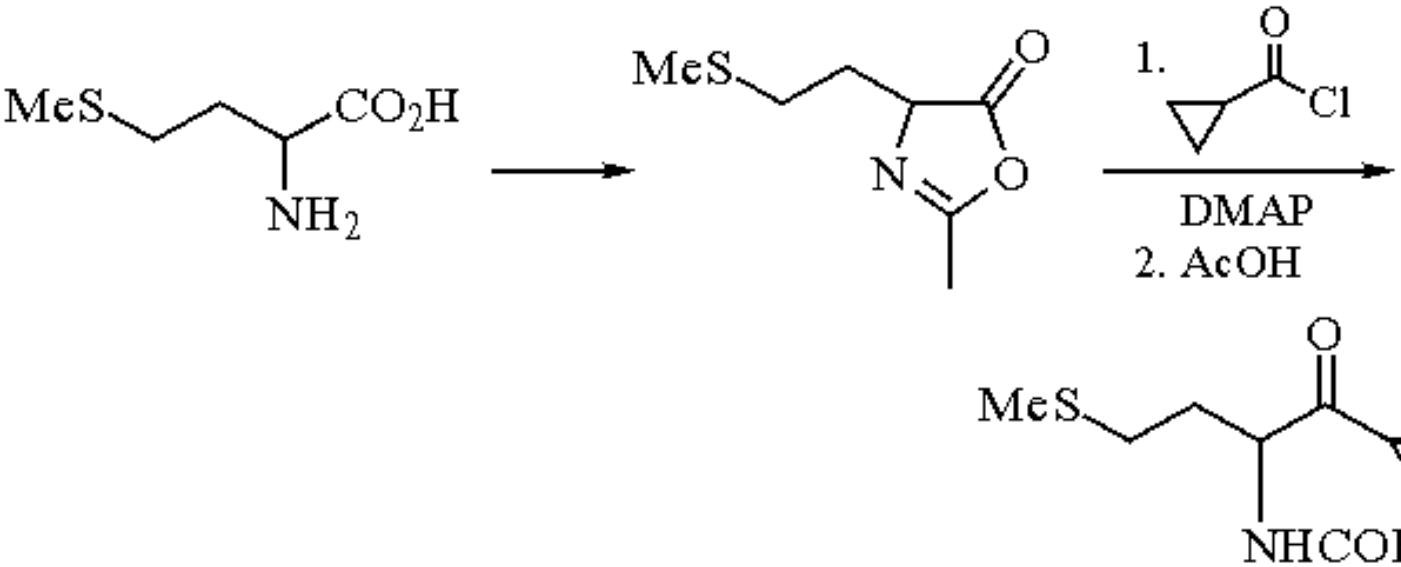

(7)

Ketoximes can be converted to nitrimines which react with Ac_2O-DMAP to provide alkynes (eq 8).[21]

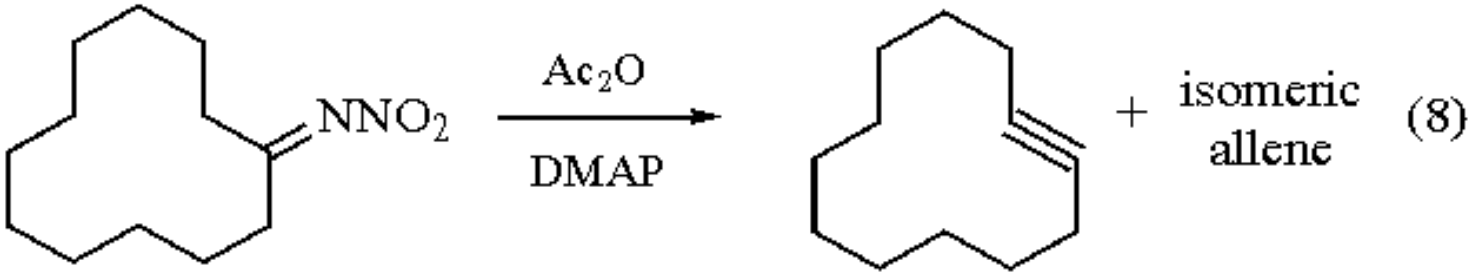

For the catalysis by DMAP of the *t*-butoxylcarbonylation of alcohols, amides, carbamates, NH-pyrroles, etc., see ***Di-t-butyl Dicarbonate***.

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Alfred Hassner

4-(Dimethylamino)pyridinium Chlorochromate

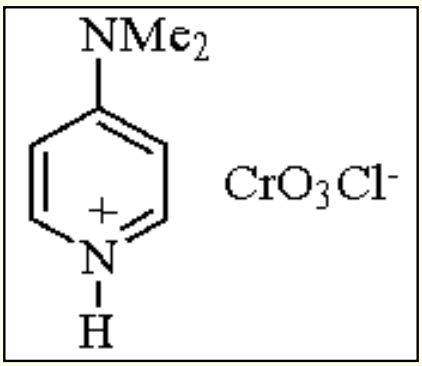

[81121-61-1] · $C_7H_{11}ClCrN_2O_3$ · 4-(Dimethylamino)pyridinium Chlorochromate · (MW 258.65)

(mild chromium oxidant, selective for the oxidation of benzylic, allylic, and sterically hindered alcohols to the corresponding aldehydes or ketones)

Alternate Name: DMAPCC.

Physical Data: mp 92-94 °C.

Solubility: sol H_2O; sl sol dichloromethane, chloroform.

Form Supplied in: yellow powder; commercially available.

Analysis of Reagent Purity: elemental analysis.

Preparative Method: by addition of ***4-Dimethylaminopyridine*** to a cooled solution of ***Chromium(VI) Oxide*** oxide in aqueous HCl.[1]

Handling, Storage, and Precautions: nonhygroscopic, shelf stable at rt indefinitely; slightly light sensitive over a period of days; preferably should be stored for long periods in a brown glass container. Treat as a typical chromium(VI)-amine reagent: oxidizer and cancer suspect agent. The reagent is most conveniently used as a suspension in CH_2Cl_2 or $CHCl_3$.

Selective Oxidant for Benzylic and Allylic Alcohols.

DMAPCC was developed in an investigation of the effects of varying the amine ligand on chlorochromate oxidations

of alcohols.[1] Compared to other pyridinium ligands, the (dimethylamino)pyridinium species oxidizes primary alcohols only very slowly. For example, when *n*-heptanol is treated with 4.0 equiv of DMAPCC in dichloromethane for 4 h, 94% of the starting alcohol is recovered (5% oxidation to heptanal).

In contrast to these results, DMAPCC is a useful reagent for the oxidation of allylic and benzylic alcohols to the corresponding aldehydes or ketones (eqs 1-3).[1] Like ***Pyridinium Chlorochromate***, the reagent is acidic enough to isomerize initially formed (*Z*)-unsaturated aldehydes to the corresponding (*E*)-isomers (eq 4). The benzylic selectivity is illustrated in the oxidation of 3-[4-(hydroxymethyl)phenyl]propanol using DMAPCC (eq 5). Treatment of this diol with excess reagent affords the benzaldehyde derivative in 62% yield. Less than 2% dialdehyde is obtained under these conditions. In contrast, oxidation of this diol using PCC under analogous conditions affords a mixture of mono- and dialdehyde in 45% and 32% yield, respectively.[1]

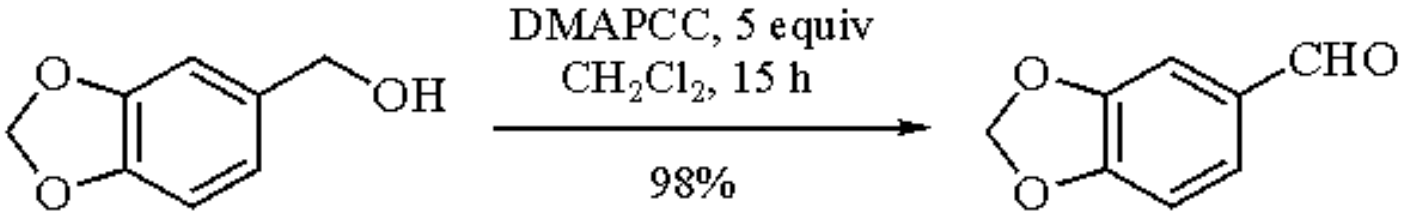

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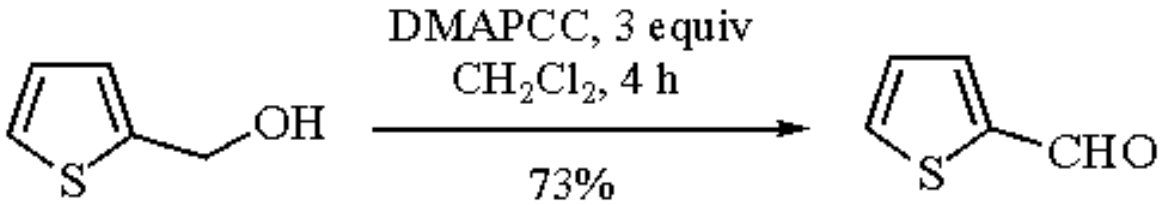

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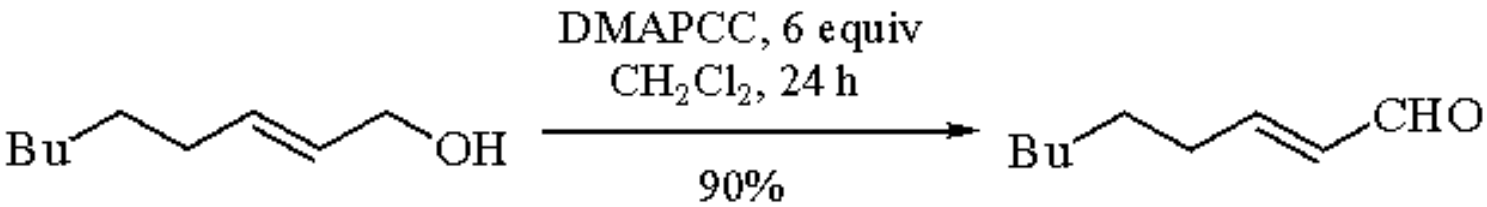

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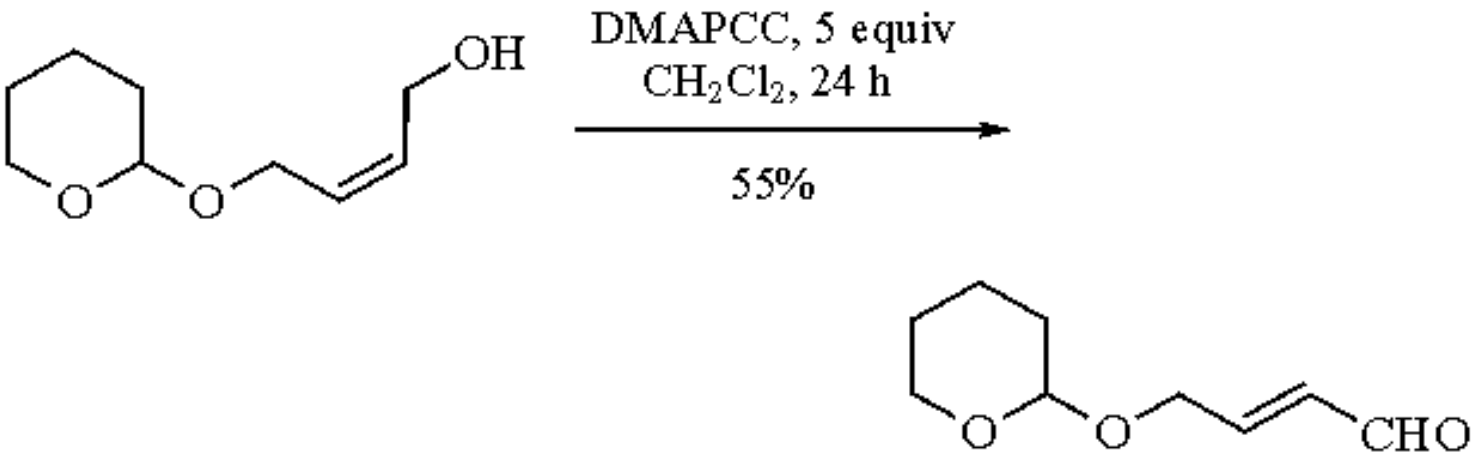

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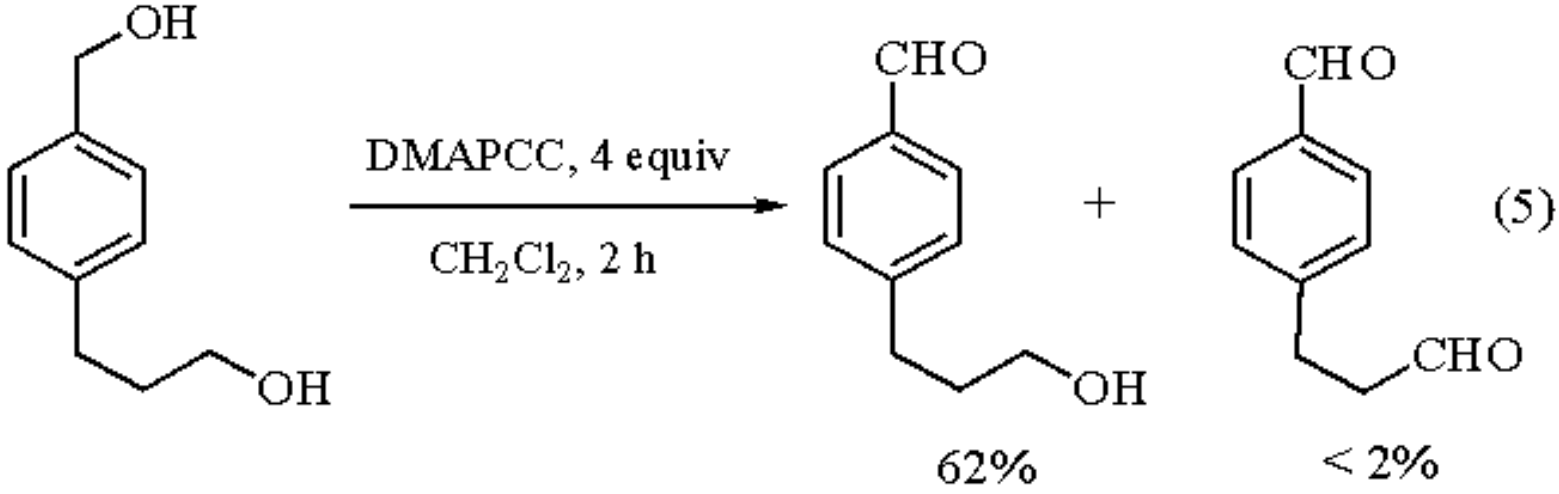

Other Selective Oxidations of Alcohol Functions.

In the attempted selective oxidation of the reduction product of andrenosterone with 3 equiv of DMAPCC under normal conditions, 11-oxotestosterone was obtained in 49% yield (eq 6). Less than 3% andrenosterone was obtained under these conditions.[1] Similarly, treatment of the triol in eq 7 with 4 equiv of the reagent for 3 h affords the more hindered monoketone in 36% yield.[2] Allowing the reaction to proceed for 22 h affords the tricarbonyl compound in 23% yield. It is likely that these observed selectivities are due to differential breakdown of the initially formed, more sterically hindered, secondary chromate ester.

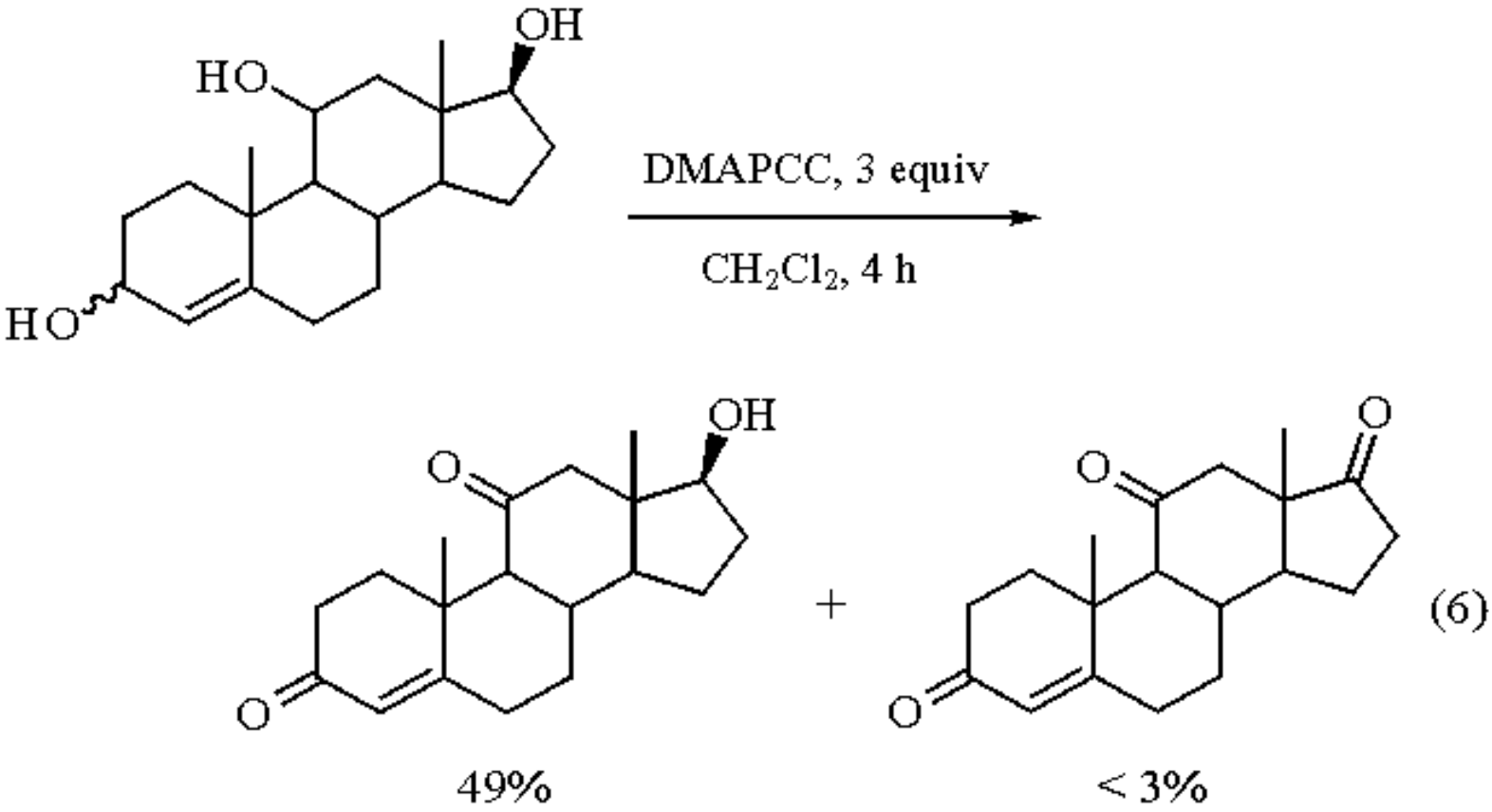

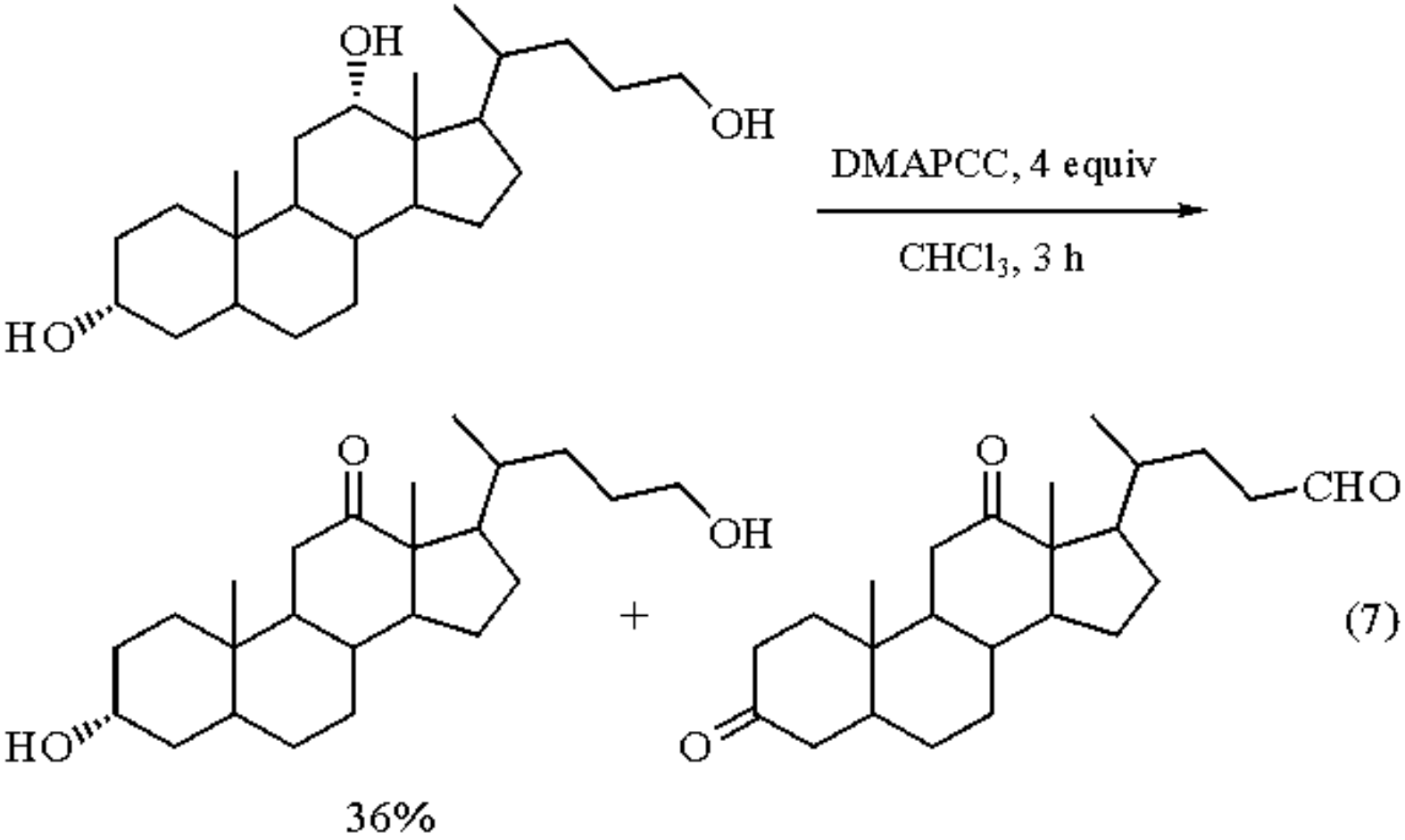

(7)

Limitations.

As with most amine-modified chromium(VI) reagents, attempted oxidations of unprotonated basic nitrogen-containing molecules with DMAPCC are generally unsuccessful.[3] In the attempted oxidation of 2-pyridylcarbinol with this reagent, no aldehyde is observed, nor can starting alcohol be recovered from the reaction mixture. 4-(Dimethylamino)pyridine is the only organic product isolated from the reaction.[3]

Alternative Reagents for Related Selective Oxidations.

Manganese Dioxide has been widely used for the selective oxidations of allylic and benzylic alcohols; however, the reagent is most effective when freshly prepared, large excesses of the reagent must be used, and long reaction times are generally necessary for successful oxidations.[4] ***Barium Manganate*** has also proved to be an effective reagent for similar oxidations.[5] A number of amine-modified chromium(VI) reagents have also been reported to display allylic and benzylic oxidation selectivity.[3]

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4-(Dimethylamino)pyridinium Chlorosulfite Chloride

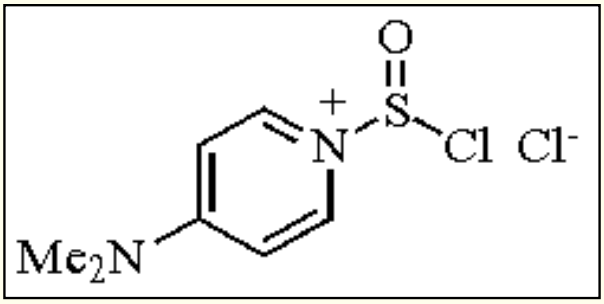

[86128-91-8] · $C_7H_{10}Cl_2N_2OS$ · 4-(Dimethylamino)pyridinium Chlorosulfite Chloride · (MW 241.16)

(synthesis of esters and amides from carboxylic acids; dehydration of aldoximes; synthesis of chlorosilanes)

Physical Data: mp 155-157 °C.

Solubility: sol CH_2Cl_2.

Preparative Methods: generated by reaction of ***4-Dimethylaminopyridine*** with ***Thionyl Chloride*** in CH_2Cl_2 at -20 °C and isolated as a solid. The reagent is most commonly prepared and used in situ.[1]

Purification: need not be isolated; no methods have been described for its purification.

Handling, Storage, and Precautions: must be assumed to be moisture sensitive; precautions should be taken in accordance with those advised for both DMAP and $SOCl_2$.

Carboxyl Activation: Synthesis of Esters and Amides from Carboxylic Acids.

4-(Dimethylamino)pyridinium chlorosulfite chloride is more reactive than either ***Thionyl Chloride*** or thionyl chloride/pyridine for carboxyl activation. Aliphatic and aromatic, as well as amino acids (in racemic form), undergo activation (via the acyl halide) and subsequent esterification by reaction with an alcohol at -20 °C (eq 1).[1] The esterification step requires the addition of a second equivalent of DMAP and this method has been applied to a range of functionalized carboxylic acids.

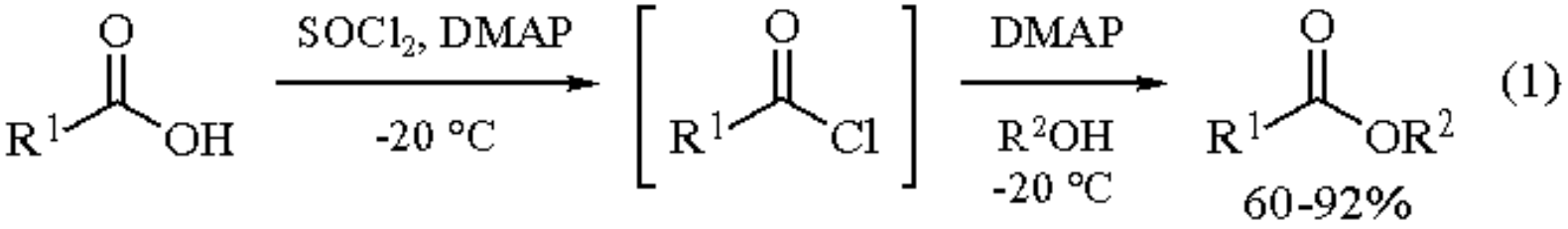

High yields of esters are obtained from both acid-sensitive (cyanoacetic acid) and base-sensitive carboxylic acids (3-phenylpropionic acid and trichloroacetic acid) and, in these latter cases, use of 4-(dimethylamino)pyridinium chlorosulfite chloride is much more effective than use of thionyl chloride alone. The esterification process has been claimed to be independent of the steric environment of the carboxyl function, though this reagent may be of more limited value with heavily substituted benzoic acids.[2]

Carboxyl activation, in the presence of a primary amine, leads to the corresponding amide in excellent yield (eq 2).[3] In both the esterification and amidation processes and the oxime dehydration reaction discussed below, recovery of DMAP is straightforward.

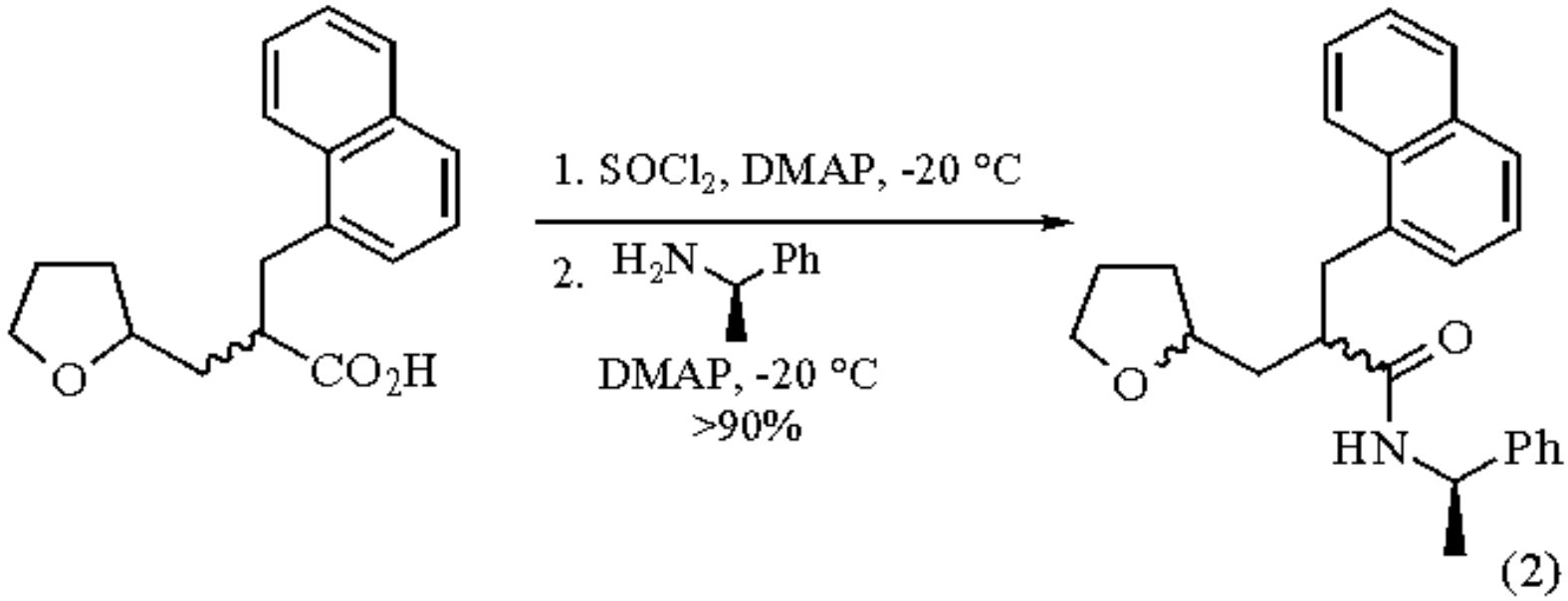

Dehydration of Aldoximes.

A range of alkyl, aryl, and heteroaryl aldoximes undergo smooth dehydration with 4-(dimethylamino)pyridinium chlorosulfite chloride at -10 to +10 °C to give the corresponding nitriles in 70-100% yield (eq 3).[4]

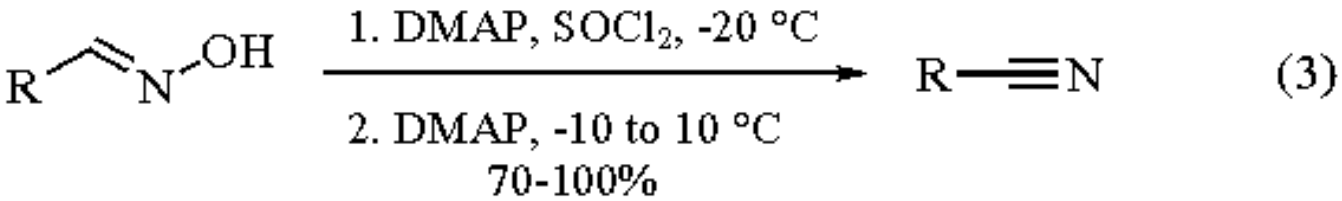

Synthesis of Chlorosilanes.

t-Butyldiphenylsilanol has been converted to the corresponding chlorosilane in quantitative yield using 4-(dimethylamino)pyridinium chlorosulfite chloride (eq 4).[5] The use of oxalyl chloride/DMAP (see ***Oxalyl Chloride***) is also highly effective for this transformation, but a number of other reagents (concentrated HCl; MeCOCl; $SOCl_2$; *o*-phenylene cyclohexylphosphorochlorimidate/SO_2Cl_2) either fail completely or give inferior yields of product.

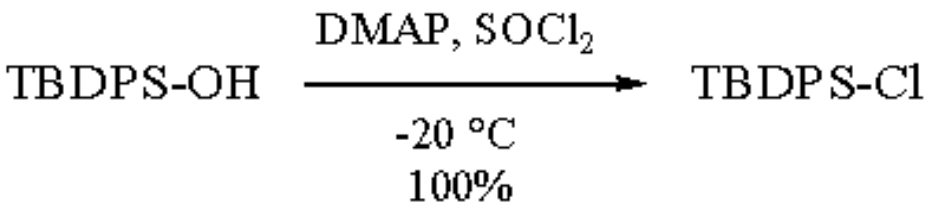

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(4*R*,5*R*)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane-Titanium(IV) Chloride

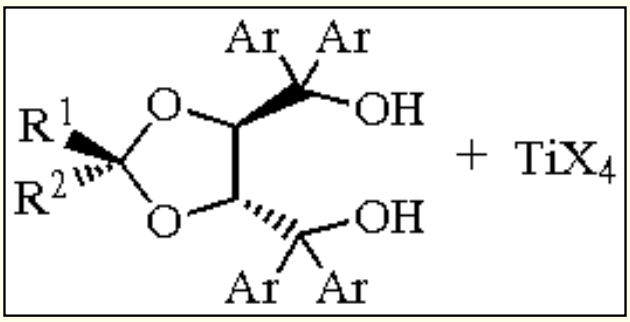

(R^1 = Me, R^2 = Me, Ar = Ph)

[93379-49-8] · $C_{31}H_{30}O_4$ · (4*R*,5*R*)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane · (MW 466.61) (R^1 = mesityl, R^2 = H, Ar = Ph)

[114026-75-4] · $C_{38}H_{36}O_4$ · (4*R*,5*R*)-2-Mesityl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane · (MW 556.74) (R^1 = Me, R^2 = Me, Ar = 1-naphthyl)

[137536-94-8] · $C_{47}H_{38}O_4$ · (4*R*,5*R*)-2,2-Dimethyl-4,5-bis(hydroxydi-1-naphthylmethyl)-1,3-dioxolane · (MW 666.85) (R^1 = *t*-Bu, R^2 = H, Ar = Ph)

[114026-72-1] · $C_{33}H_{34}O_4$ · (4*R*,5*R*)-2,*t*-Butyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane · (MW 494.67) (R^1 = Ph, R^2 = Me, Ar = Ph)

[109306-21-0] · $C_{36}H_{32}O_4$ · (4*R*,5*R*)-2-Methyl-2-phenyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane · (MW 528.65) (R^1 = Et, R^2 = Et, Ar = 3,5-$Me_2C_6H_3$)

[138710-29-9] · $C_{41}H_{50}O_4$ · (4*R*,5*R*)-2,2-Diethyl-4,5-bis(hydroxydi-3,5-xylylmethyl)-1,3-dioxolane · (MW 606.91)

(chiral alkyltitanium reagent for asymmetric alkylation reaction;[1] chiral Lewis acid for asymmetric Diels-Alder reaction, [2 + 2] cycloaddition reaction, and intramolecular ene reaction;[2] reagent for asymmetric hydrocyanation of aldehydes and for kinetic resolution of α-aryl carboxylic acid derivatives[2])

Preparative Methods: chiral titanates are usually prepared by mixing dichlorodiisopropoxytitanium and a chiral 1,4-diol in toluene. Other solvents such as ether and dichloromethane can also be employed. The alcohol exchange reaction takes place immediately at rt. Wherever necessary, liberated isopropyl alcohol is

removed by azeotropic removal with toluene.[3] The chiral 1,4-diols are prepared from dimethyl (or diethyl) tartrate by a two-step procedure comprising acetalization followed by the addition of an aryl Grignard reagent.[4,5]

Handling, Storage, and Precautions: chiral titanates are usually prepared just before use under argon atmosphere. Care should be taken to avoid moisture, especially when a catalytic amount of the reagent is used.

Chiral Alkylating Reagent.

The chiral methyltitanium reagent prepared from (**1**) and ***Methyllithium*** or methyl Grignard reagent adds to various aldehydes with moderate to good enantioselectivity (eq 1).[6] Furthermore, the ate complex prepared from the chiral tetraalkoxytitanium (**2**) and methyllithium adds to aromatic aldehydes with more than 90% ee (eq 2).[7] The chiral allyltitanium reagent (**3**) having a cyclopentadienyl group on titanium adds to various aldehydes to give the corresponding allylated products with high optical purity (eq 3).[8]

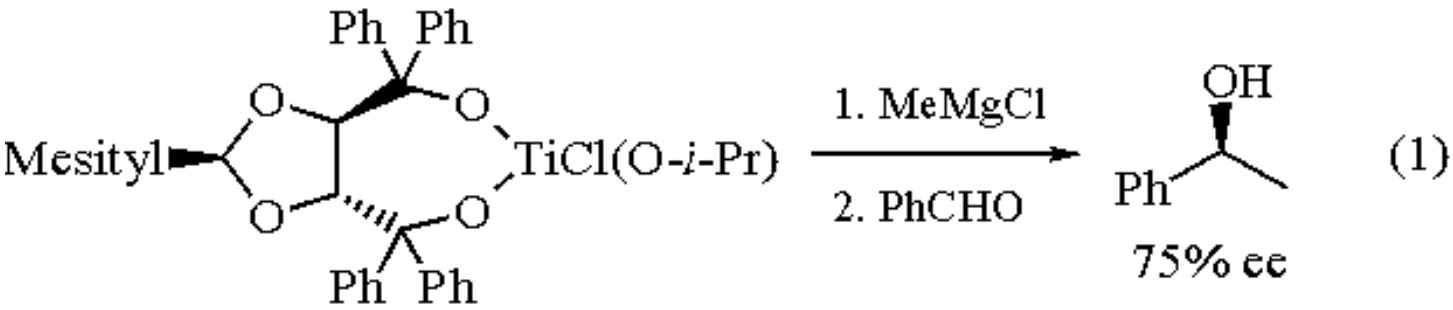

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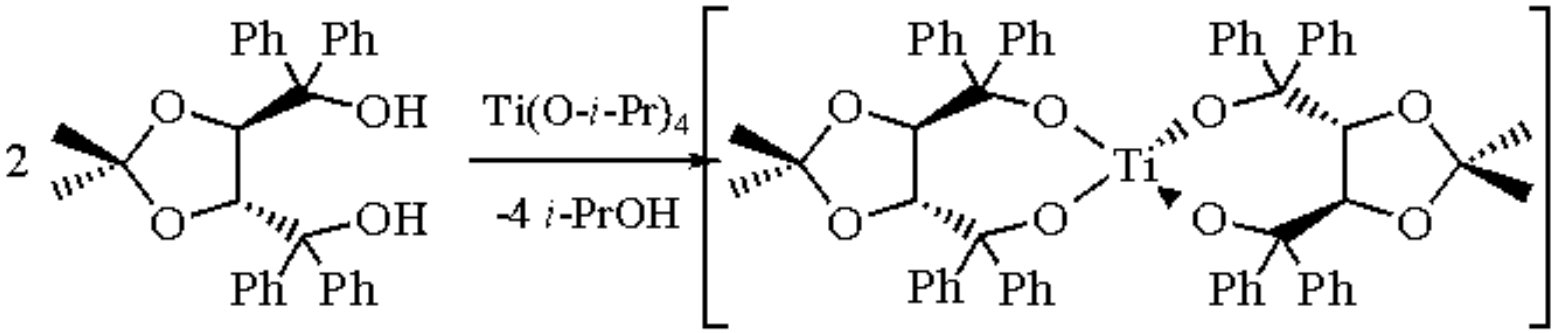

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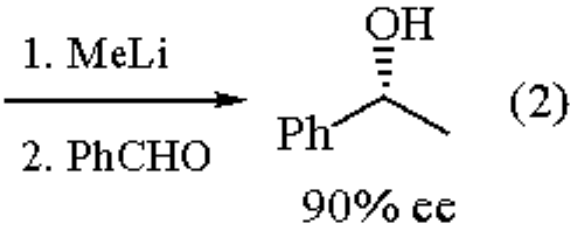

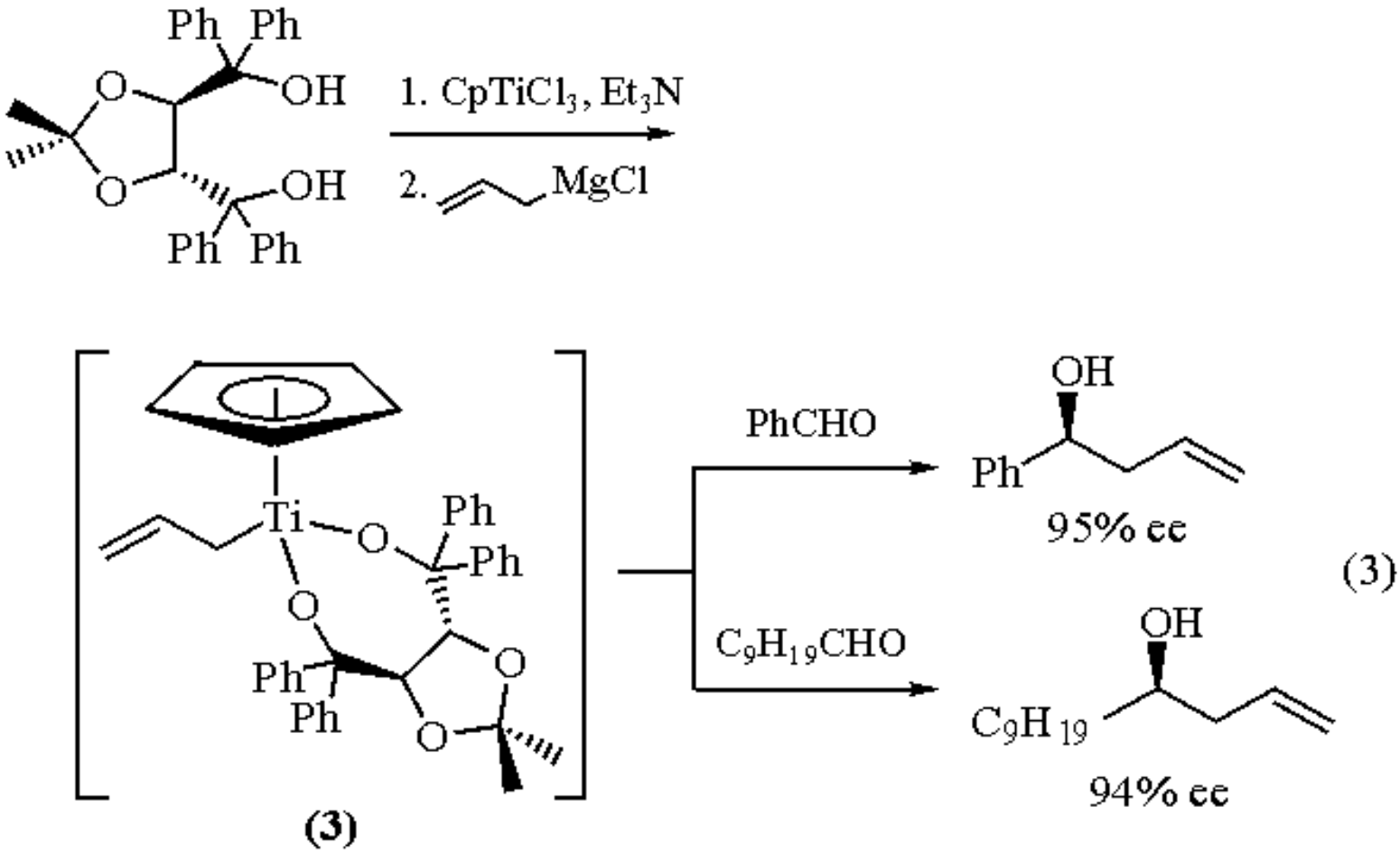

Chiral titanates can be employed as catalysts for the alkylation of aldehydes using dialkylzinc reagents. For example, by the use of a catalytic amount of the chiral titanium reagent (**4**), addition of ***Diethylzinc*** to various aldehydes occurs with high enantioselectivity in the presence of ***Titanium Tetraisopropoxide*** (eq 4).[9] Furthermore, by using the chiral tetraalkoxytitanium (**2**), the alkylation reaction can be carried out in ether, which enables the use of various dialkylzinc reagents prepared in situ from the corresponding Grignard reagents and ***Zinc Chloride*** (eq 5).[10]

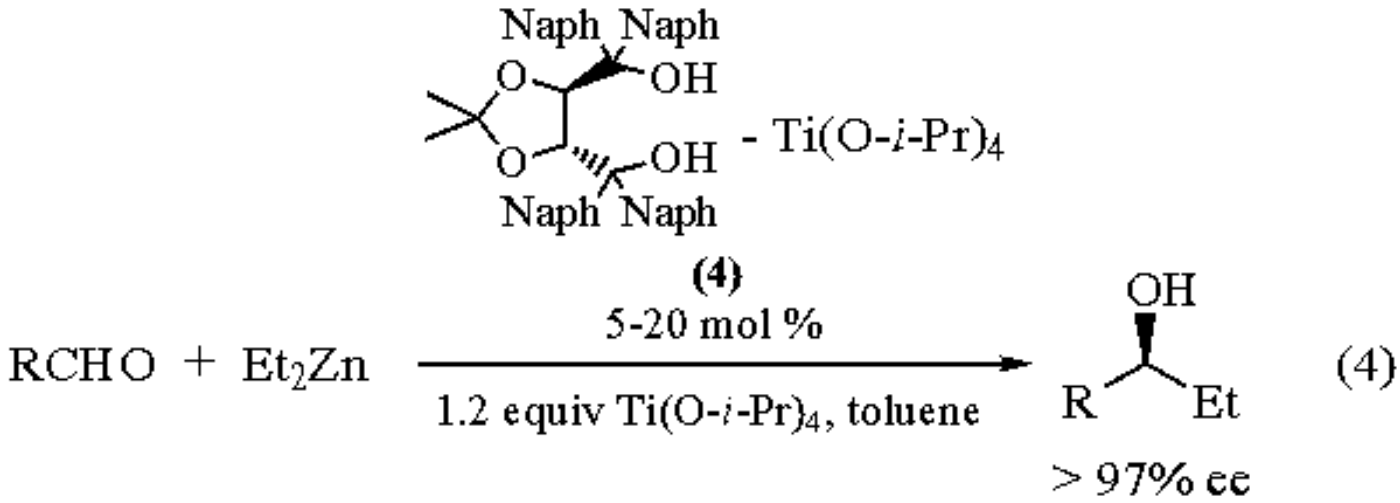

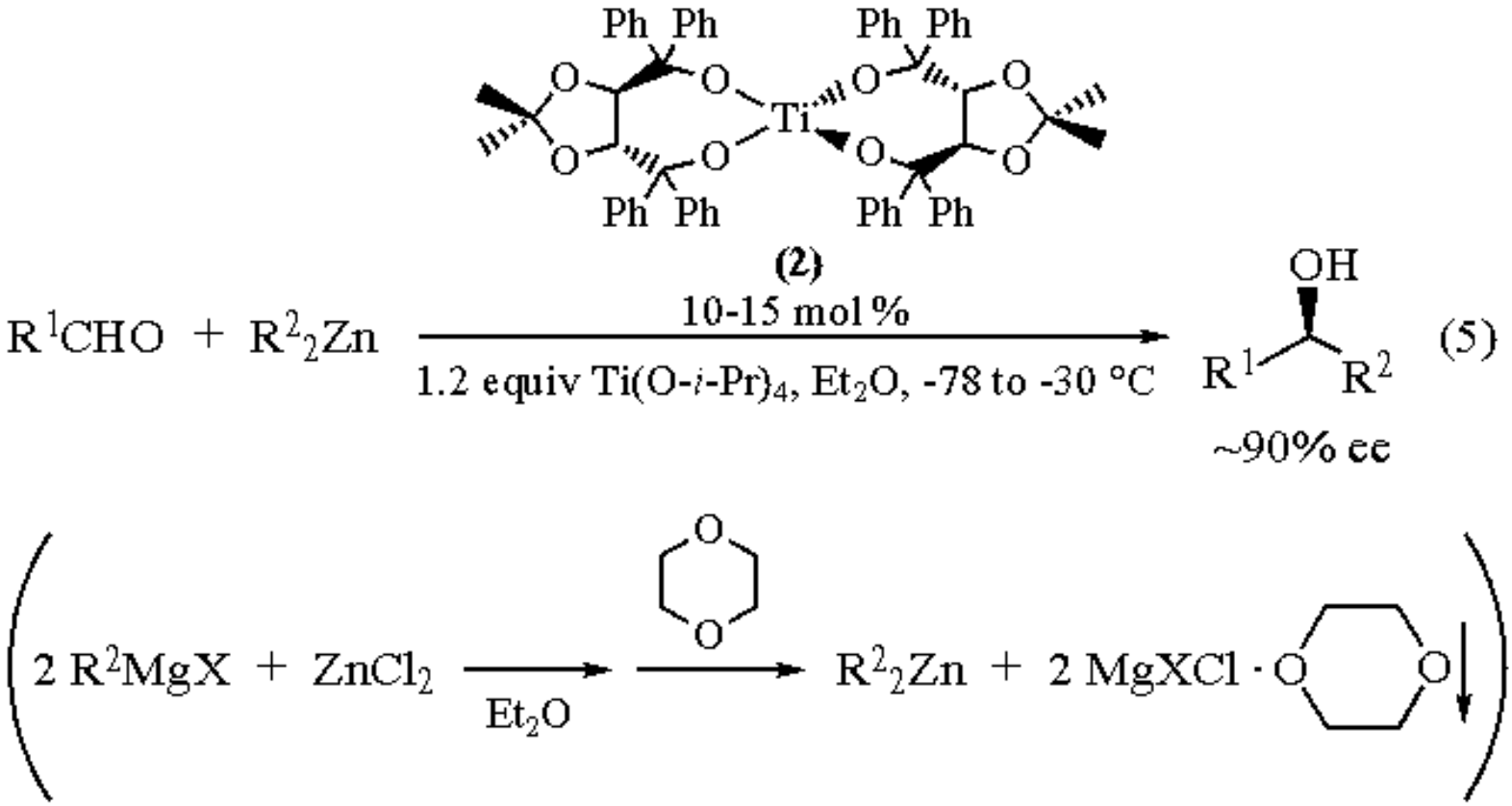

Chiral Lewis Acid.

These chiral titanium reagents are widely used as chiral Lewis acid catalysts. The Diels-Alder reaction of methyl acrylate and cyclopentadiene affords the *endo* adduct in moderate enantioselectivity when a stoichiometric amount of the chiral titanium reagent (**5**) is employed (eq 6).[6] Use of 3-(2-alkenoyl)-1,3-oxazolidin-2-ones as dienophiles greatly improves the optical purity of the cycloadduct when the 2-phenyl-2-methyl-1,3-dioxolane derivative (**6**) is used as a chiral ligand. Most importantly, the reaction proceeds with the same high enantioselectivity for the combination of various dienophiles and dienes even when 5-10 mol % of the chiral titanium reagent is employed in the presence of molecular sieves 4A (eqs 7 and 8).[11]

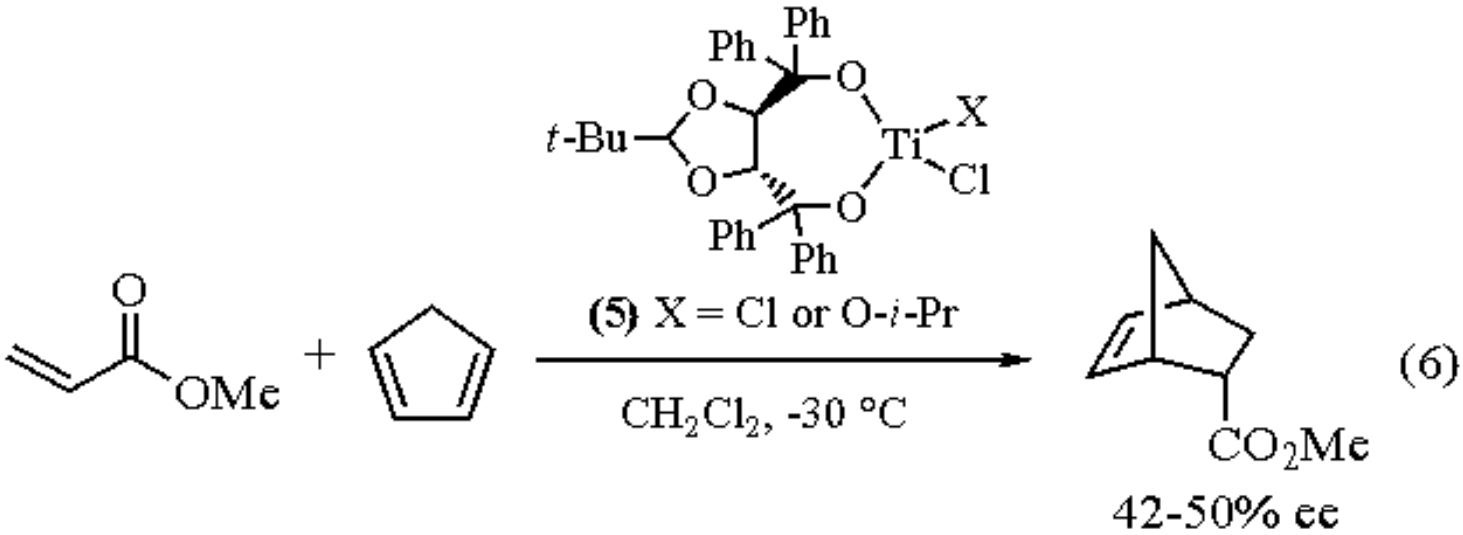

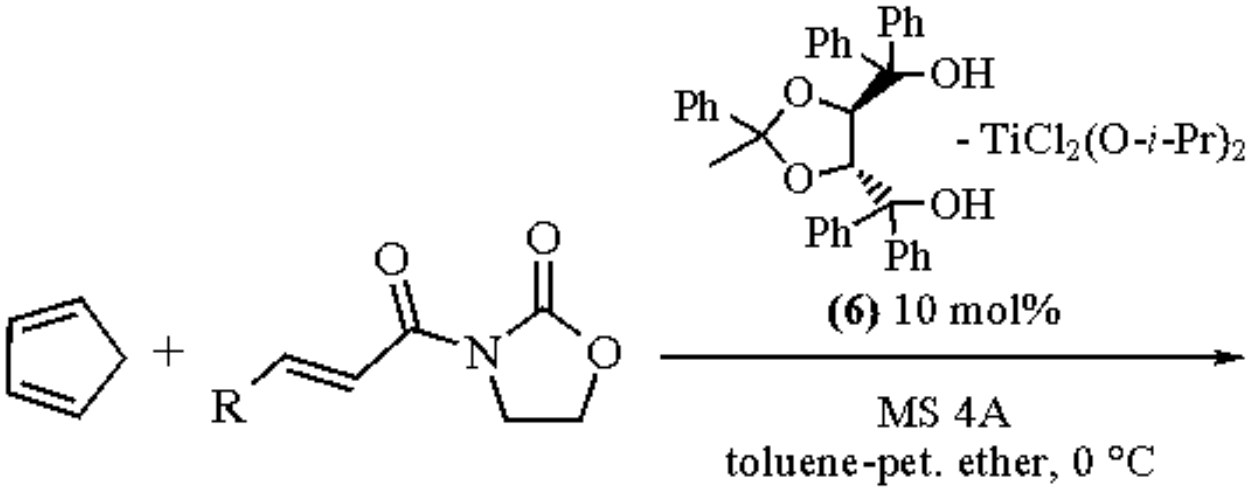
Ph
Ph
OH
Ph
O
O
- TiCl2(O-i-Pr)2
OH
Ph
Ph
(6) 10 mol%
O
O
N
O
R
MS 4A
toluene-pet. ether, 0 °C

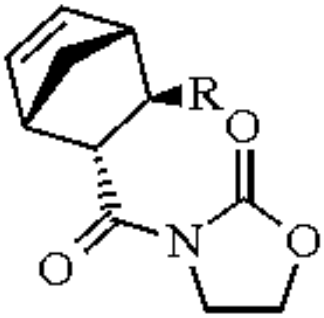
R
O
N
O
O

(7)

80-94% ee

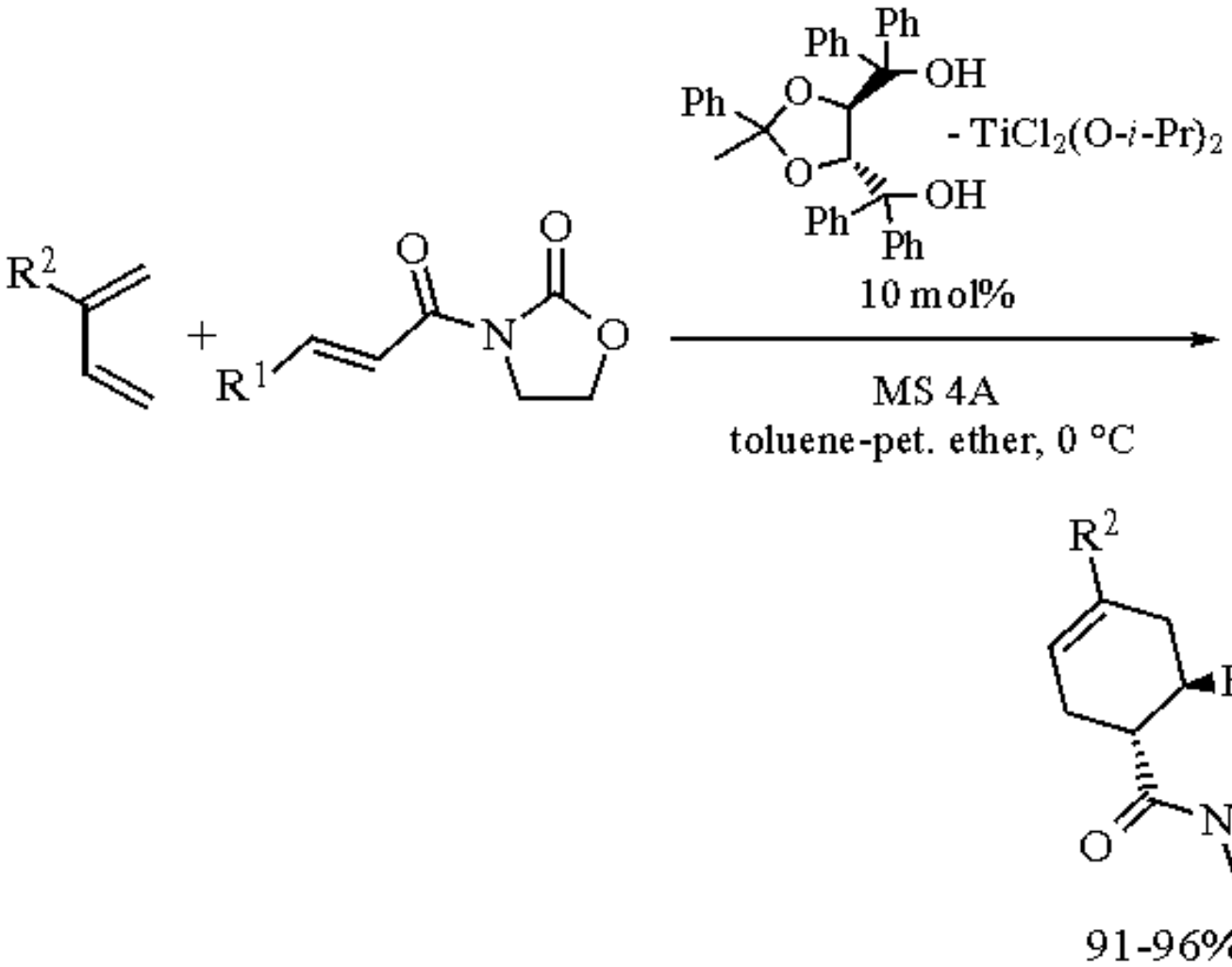

(8)

The origin of the high enantioselectivity is found to lie in an attractive π-π interaction between the aryl group of the diol moiety and the dienophiles. Replacement of the phenyl group by a 3,5-dimethylphenyl group (as shown in **7**), which has higher π-basicity than a phenyl group, affords improved enantioselectivities in some cases (eq 9).[12]

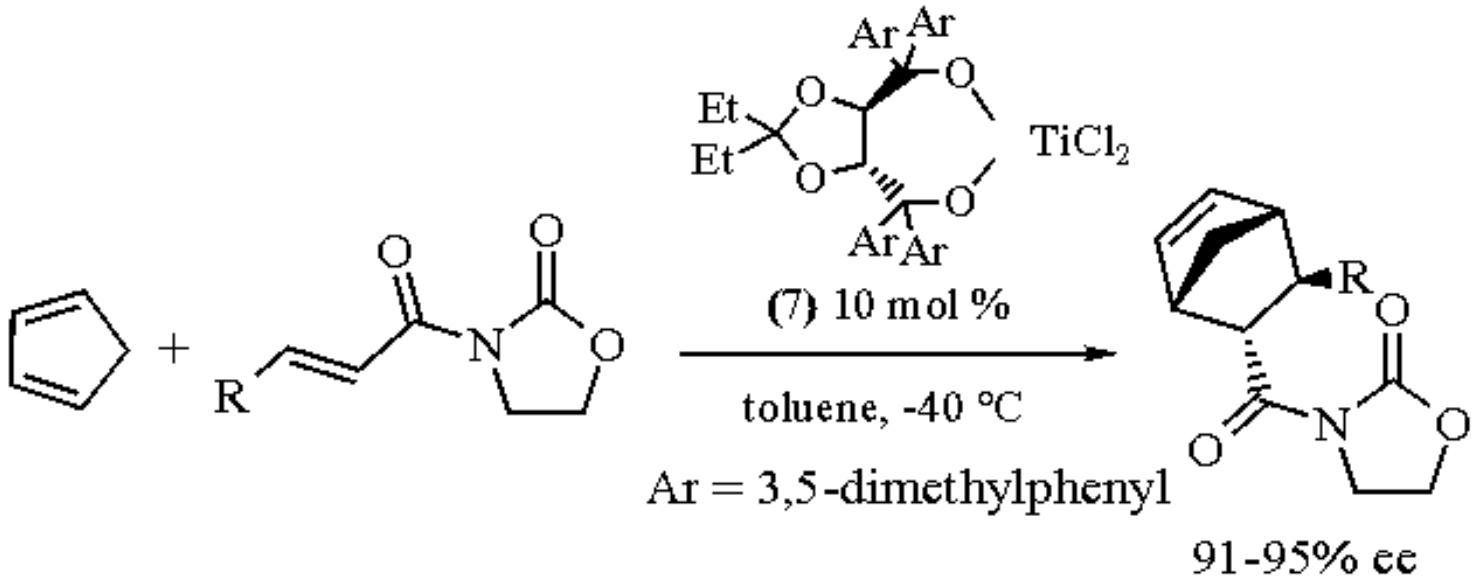

(9)

The chiral titanium reagent (**6**) also catalyzes the [2 + 2] cycloaddition reaction of 1,3-oxazolidin-2-one derivatives of

α,β-unsaturated carboxylic acids and ketene dithioacetals in the presence of MS 4A to give cyclobutanone dithioacetal derivatives with high optical purity (eq 10).[13] Vinyl sulfides, alkynyl sulfides, and 1,2-propadienyl sulfides can also be employed in this reaction to give the corresponding cyclobutanes, cyclobutenes and methylenecyclobutane derivatives with high optical purity (eqs 11 and 12).[13-15]

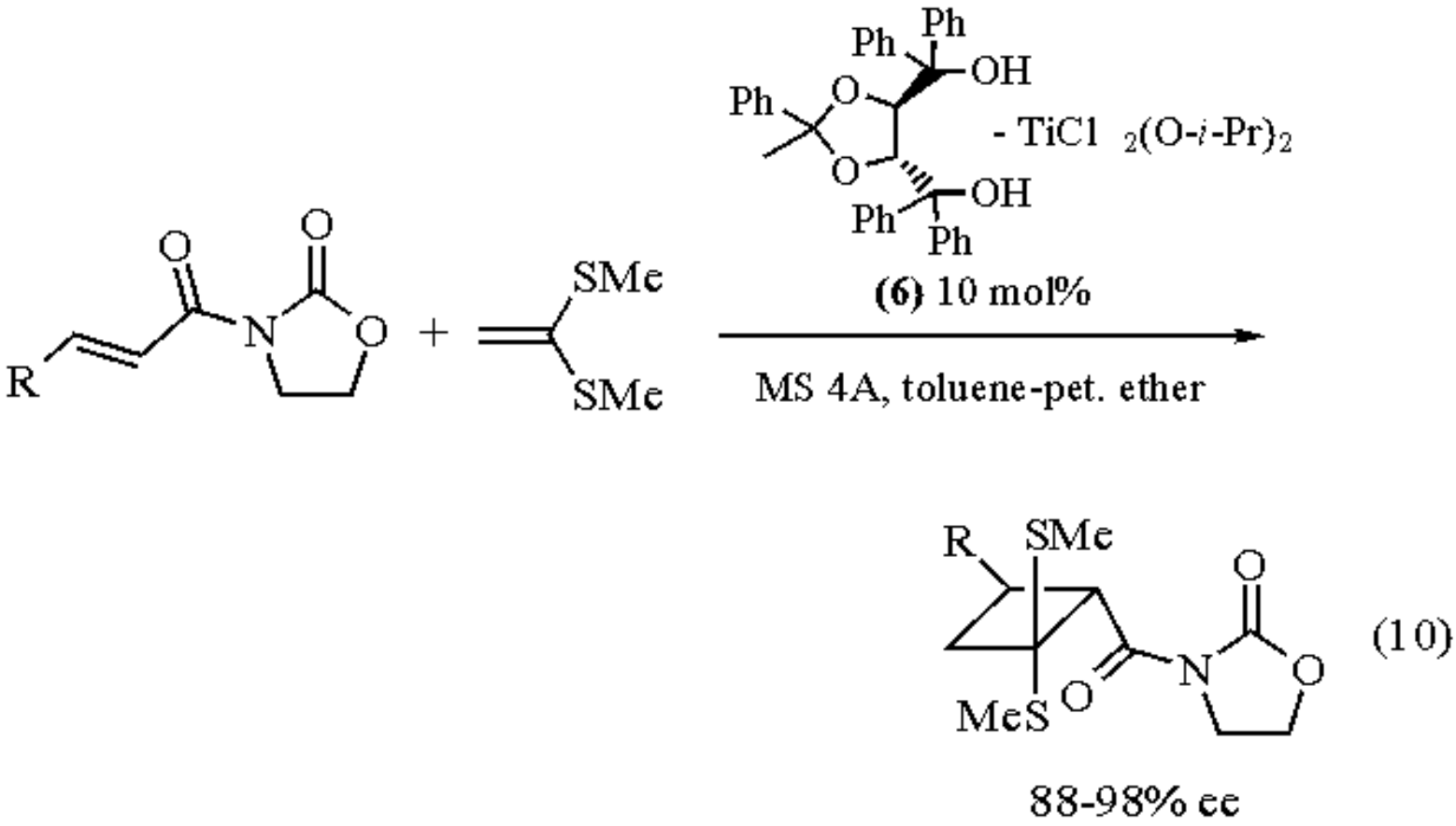

(10)

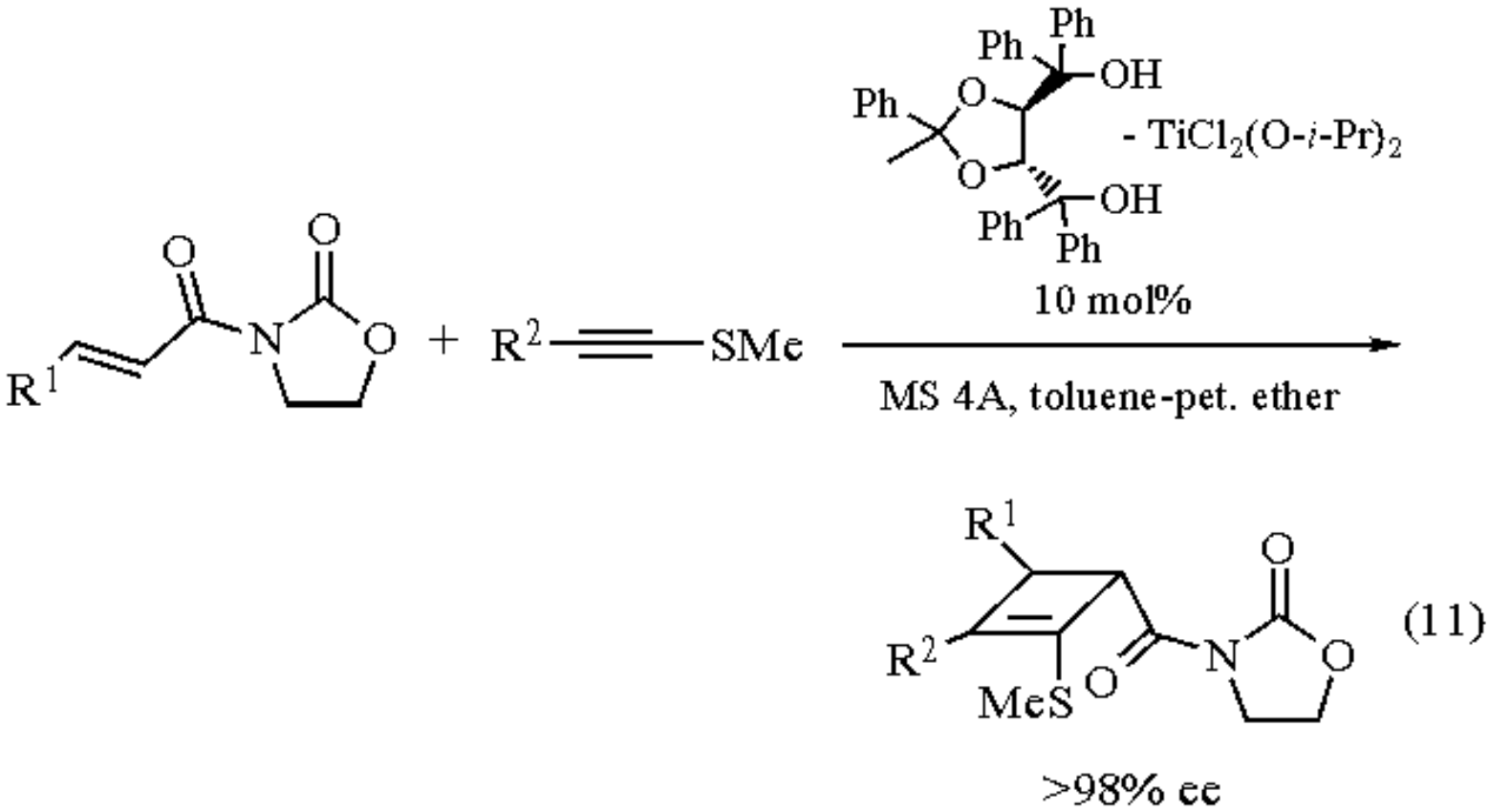

(11)

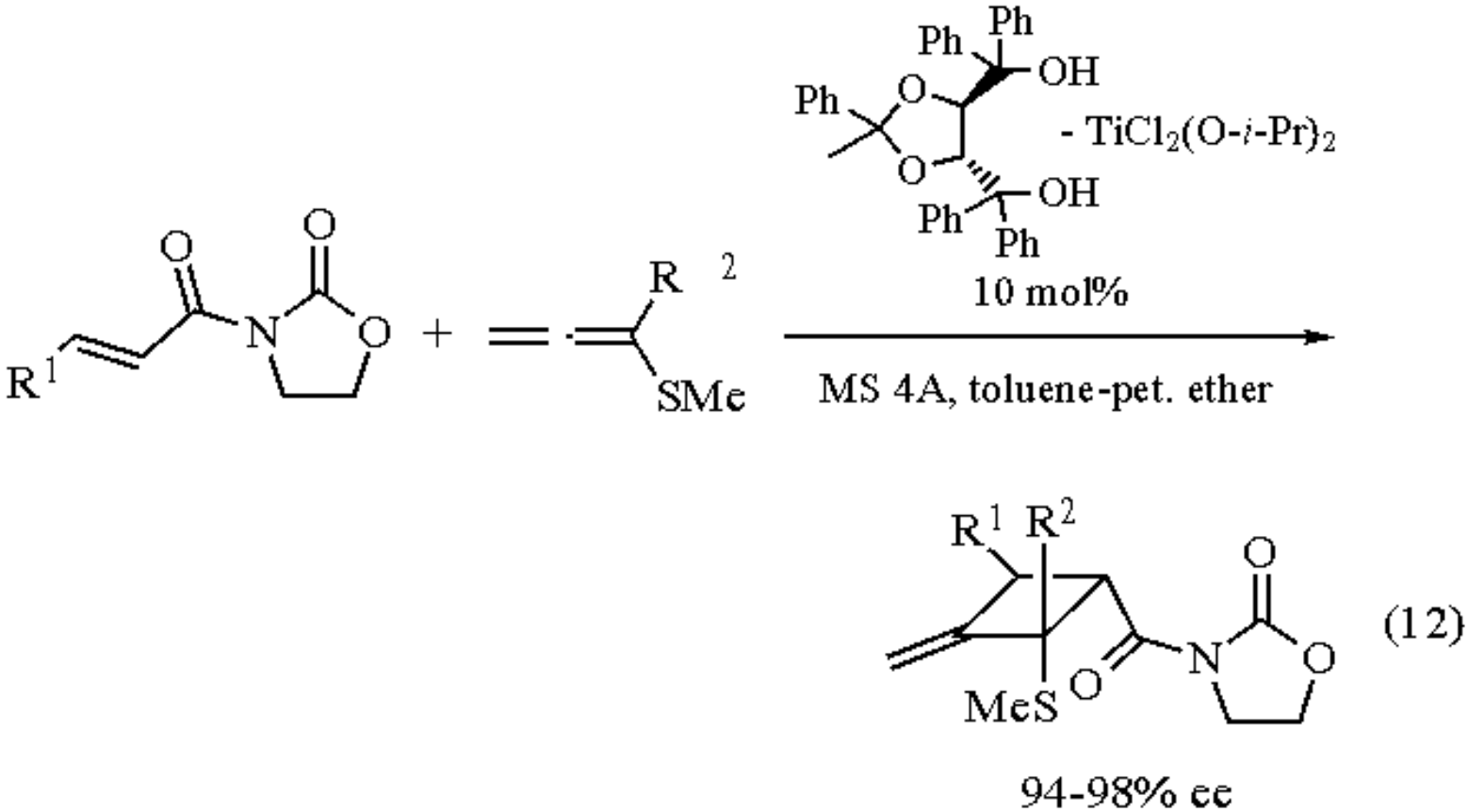

(12)

By using a stoichiometric amount of the chiral titanium reagent prepared by mixing chiral diol, ***Titanium(IV) Chloride***, and titanium tetraisopropoxide, the asymmetric [2 + 2] cycloaddition reaction of 1,4-benzoquinones and styrenes gives the corresponding cyclobutane derivatives with high optical purity. These rearrange to 2,3-dihydrobenzofuran

derivatives on mild acid treatment (eq 13).[16]

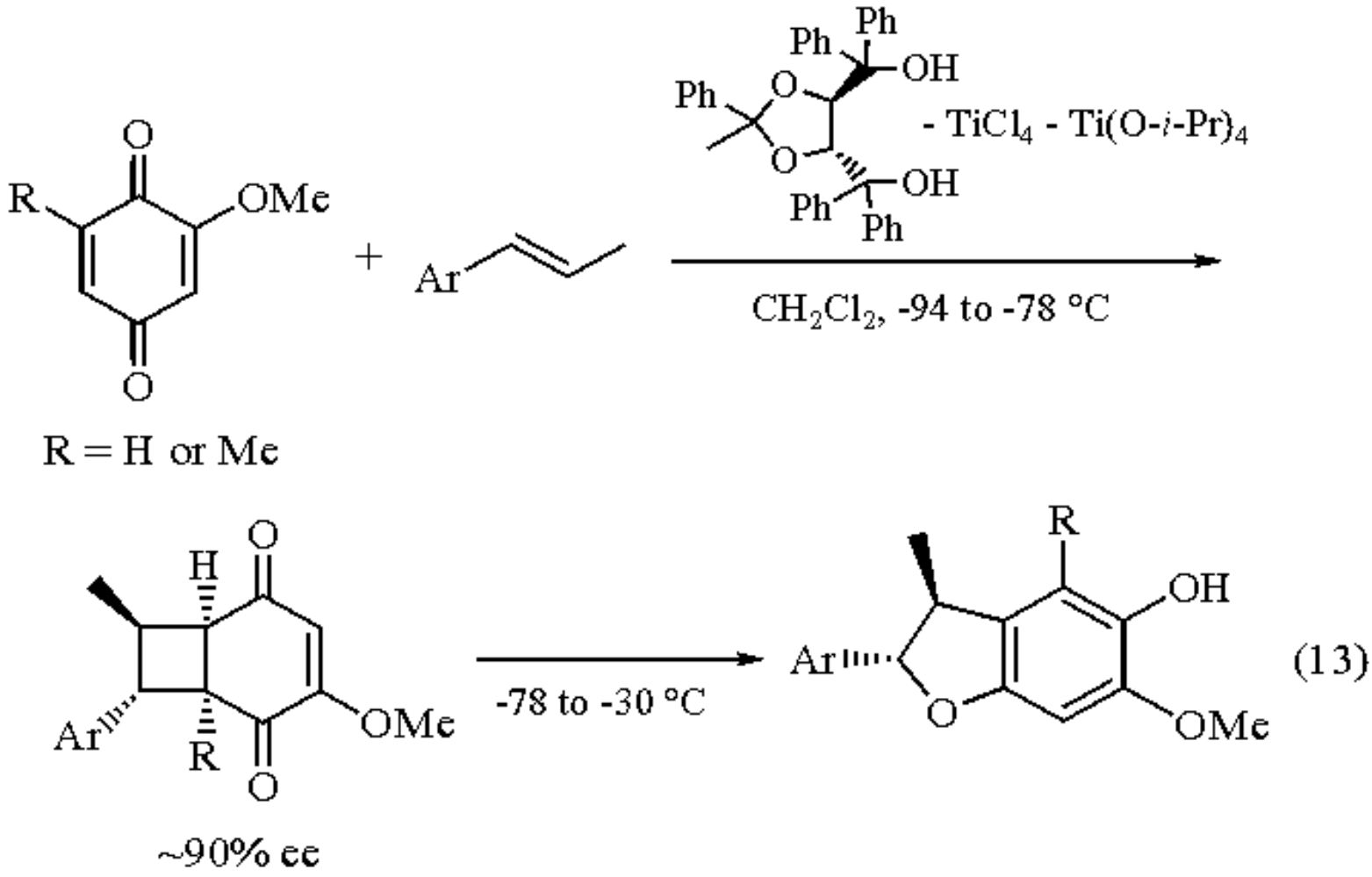

The asymmetric intramolecular ene reaction of 1,3-oxazolidin-2-one derivatives of a diene carboxylic acid is also promoted by a stoichiometric amount of the chiral titanium reagent (**6**) to give cyclopentane or cyclohexane derivatives with high optical purity (eq 14).[17]

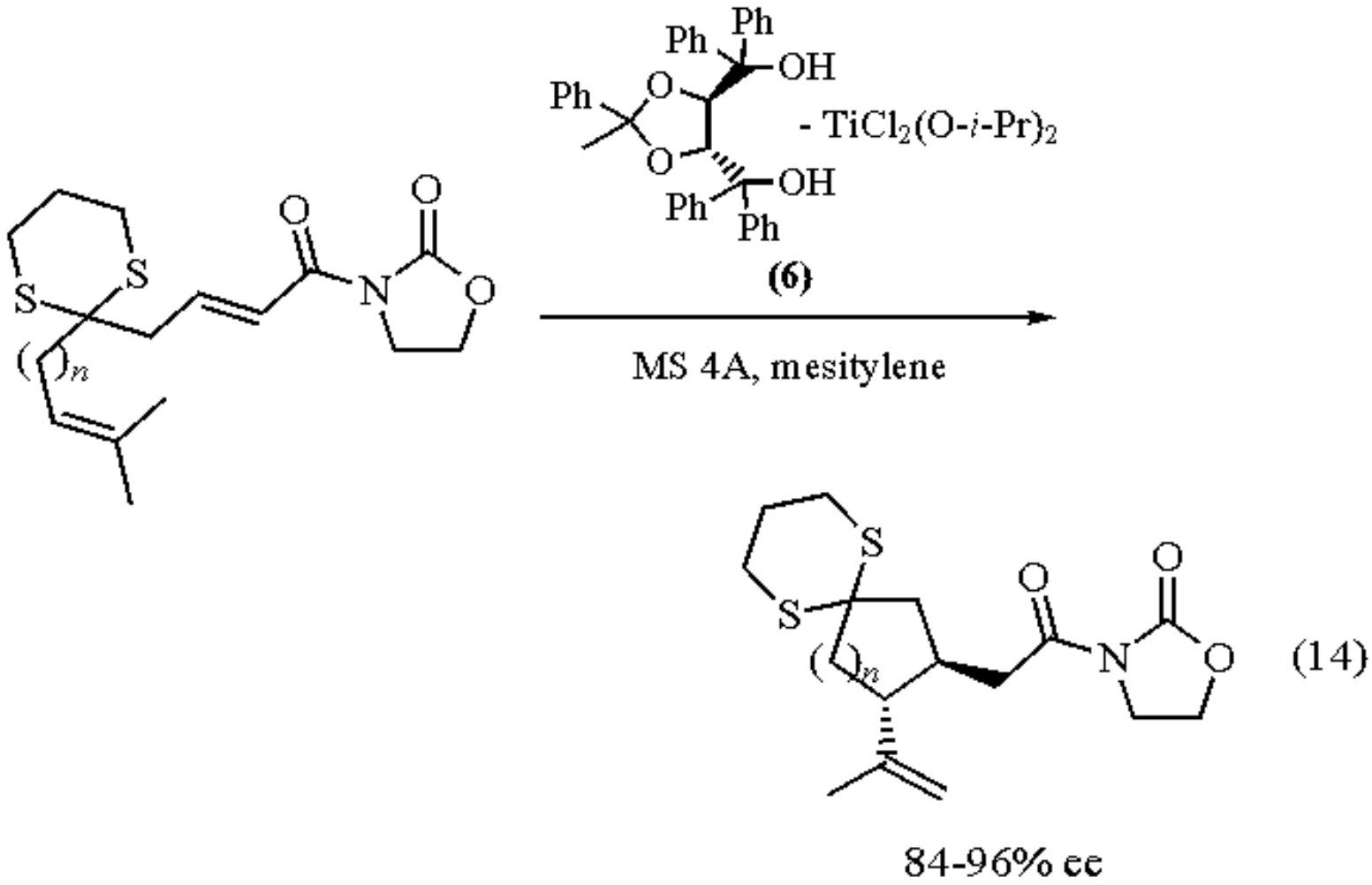

Other Reactions.

Chiral titanates can be employed in several other asymmetric reactions. For example, the chiral titanate (**6**) promotes hydrocyanation of aryl aldehydes by ***Cyanotrimethylsilane*** at low temperature (-65 °C) to give the corresponding cyanohydrins with high optical purity (eq 15).[18] Alkyl aldehydes are also converted into their cyanohydrins in high optical purity by employing the chiral titanium dicyanide species prepared in situ from the chiral titanate (**6**) and TMSCN at rt (eq 16).[18]

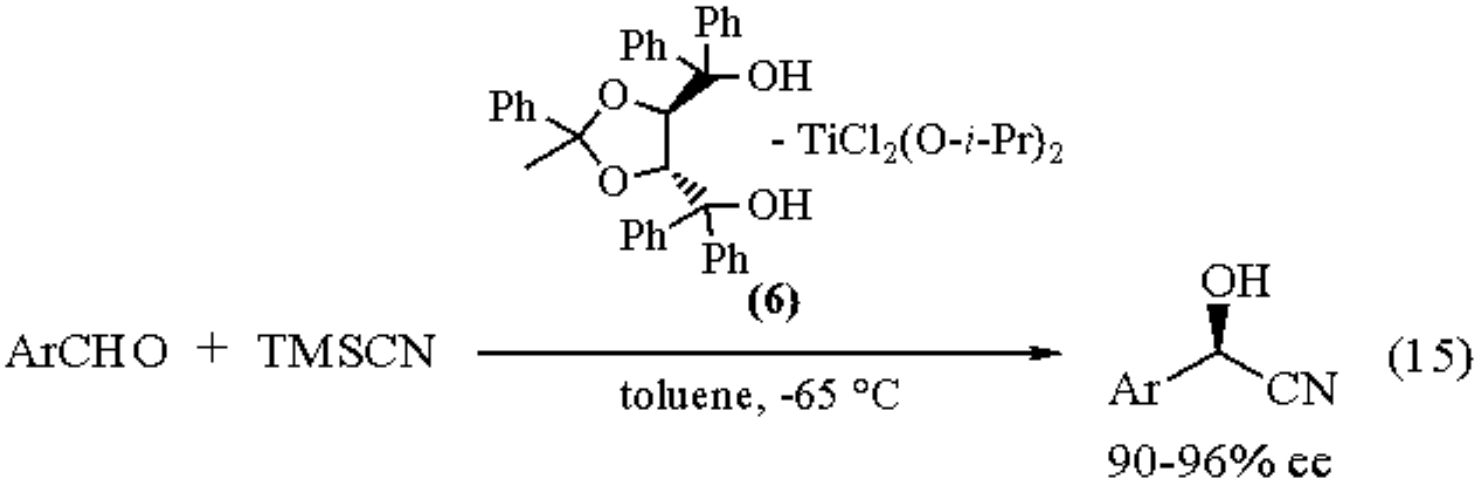

(4R,5R)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane-Titanium(IV) Chloride

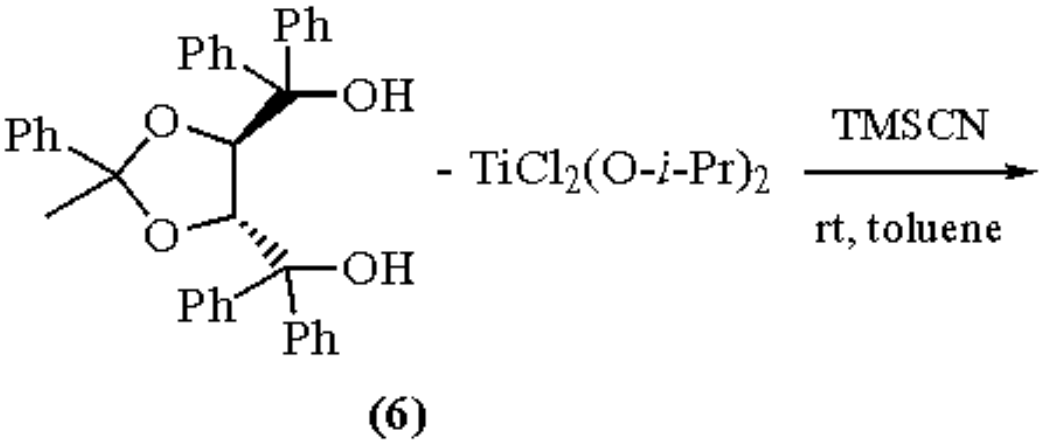

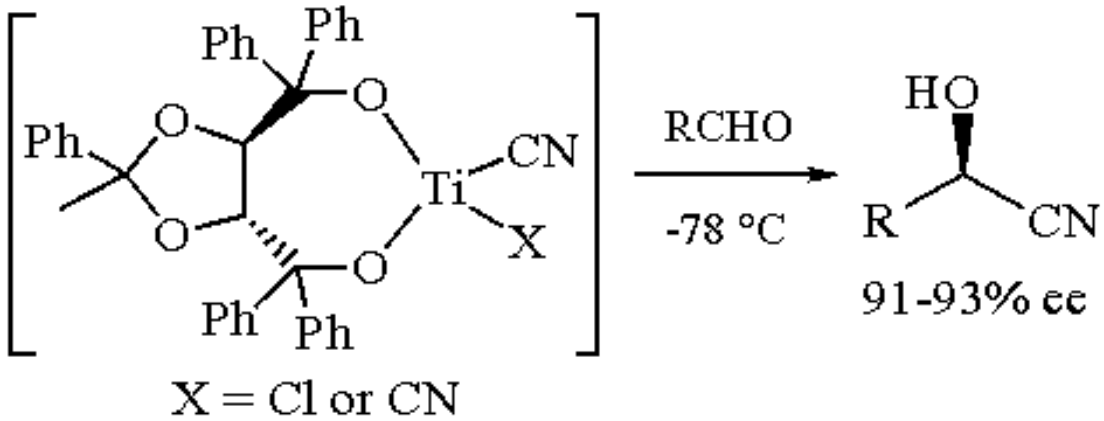

(16)

In the presence of a catalytic amount of the chiral titanium reagent (**8**) prepared from titanium tetraisopropoxide and the (*R*)-1,4-diol, kinetic resolution of *S*-(2-pyridyl) thioesters of α-aryl carboxylic acids is achieved with high relative rate of both the enantiomers to give the (*R*)-isopropyl esters with high optical purity (eq 17).[19]

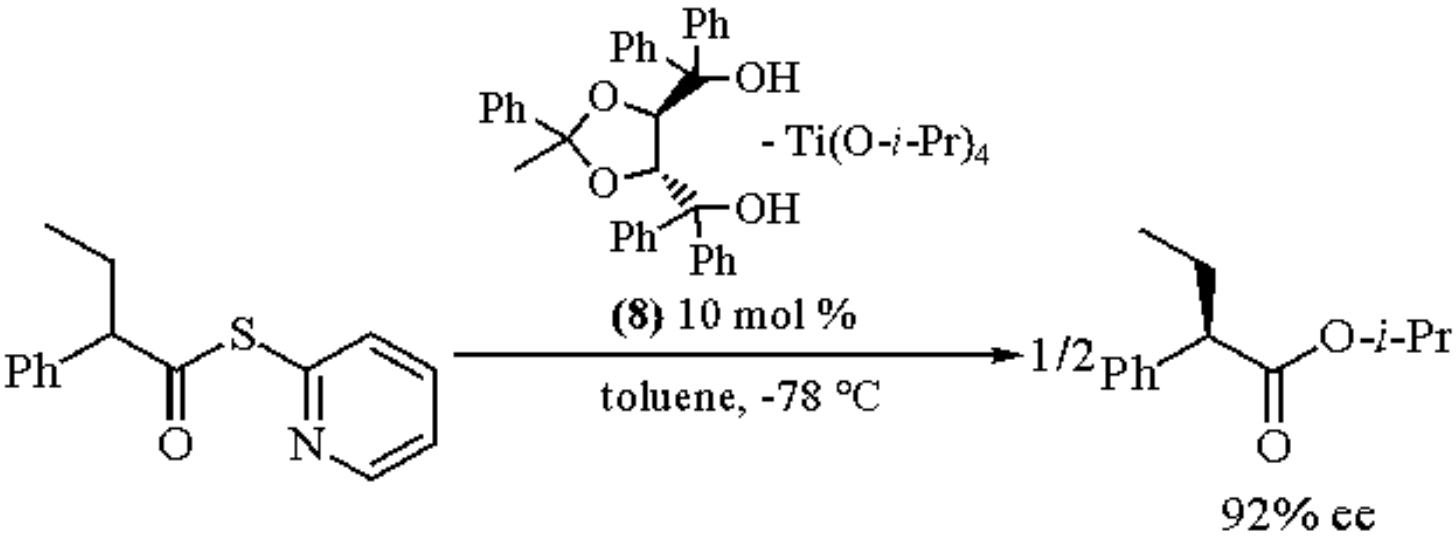

(17)

The enantioselective iodolactonization of α-hydroxy carboxylic acid derivatives is achieved by using a stoichiometric amount of the chiral titanium reagent (**8**) (eq 18).[20]

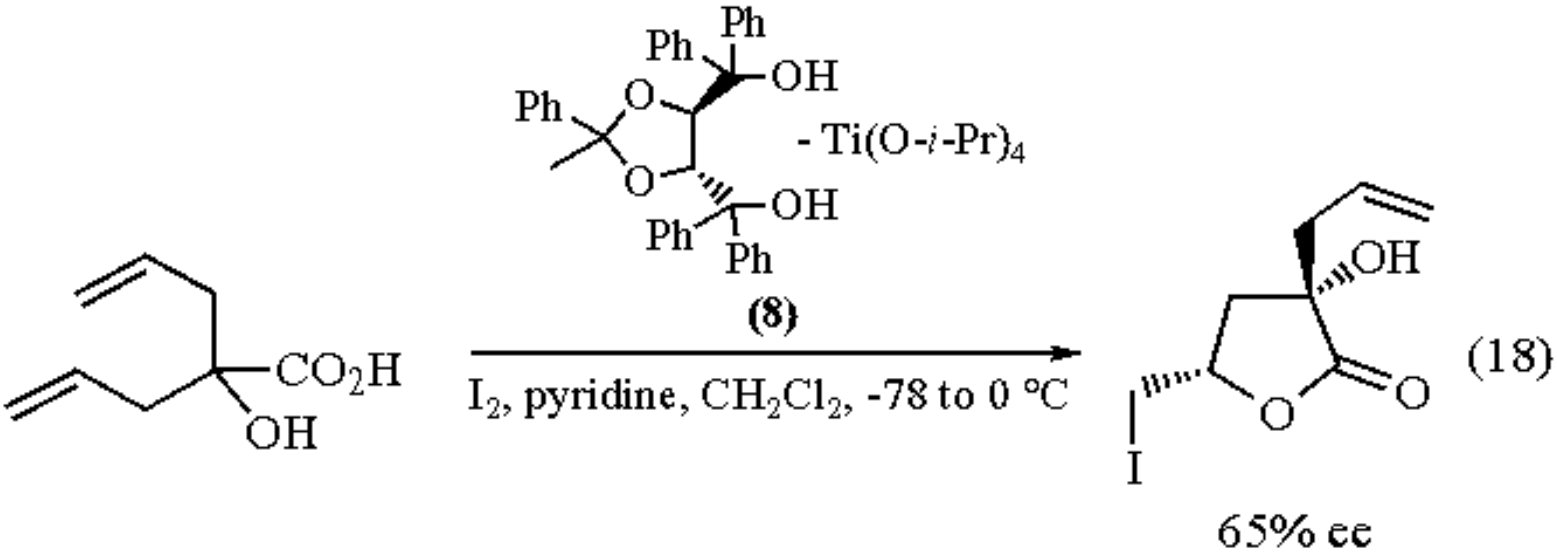

Related Reagents.

Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O^{α},O$^{α´}$]titanium; ***Dichlorotitanium Diisopropoxide***; ***2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide***.

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The University of Tokyo, Japan

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N-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium Hexafluorophosphate *N*-Oxide

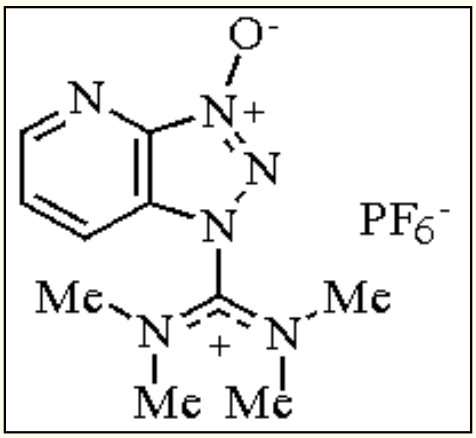

[148893-10-1] · $C_{10}H_{15}F_6N_6OP$ · *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium Hexafluorophosphate *N*-Oxide · (MW 380.28)

(coupling reagent for peptide synthesis[1-4])

Alternate Name: HATU.

Physical Data: mp: sample decomposes at temperatures above 180 °C.

Solubility: sol DMF (0.6 mol L^{-1}).

Form Supplied in: white solid; commercially available.

Purification: by crystallization from a mixture of MeCN and CH_2Cl_2.

Handling, Storage, and Precautions: is very stable, not hygroscopic, and can be stored indefinitely at 0 °C. HATU solutions in DMF (0.5 M) can be stored in an inert atmosphere for weeks (after 4 weeks, purity is 85 %). Syntheses of peptides carried out with freshly prepared and 3-week old solutions show crude products of similar quality.[5] Violent decomposition can occur when dried at elevated temperature.

General Considerations.

HATU is the 7-azabenzotriazolyl analog of ***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate*** (HBTU).[6] X-ray structure determinations of both HATU and HBTU have revealed that the solid-state structures differ from the formulations commonly presented in the literature.[7] The solid-state structure is not the *N,N,N´,N´*-tetramethyluronium salt but rather the guanidinium *N*-oxide.

HATU and its pyrrolidinium derivative, 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide (HAPyU), have been used as condensing reagents for the preparation of peptides by both solution and solid-phase techniques.[1-3] In solution, reaction of α-amino protected amino acids or dipeptides with equimolar amounts of α-carboxyl protected amino acid hydrochlorides or amino amides, and base (2 equiv) [***Diisopropylethylamine*** (DIPEA), *N*-methylmorpholine (NMM), ***2,4,6-Collidine***, or ***1,8-Bis(dimethylamino)naphthalene*** (Proton Sponge, PS)] in DMF proceeds cleanly, yielding the corresponding peptides in good yields. The level of epimerization in HATU-mediated couplings was reduced compared to HBTU-promoted acylations (eq 1) (Table 1).[1,4,8]

$$RCO_2H + R'NH_2 \xrightarrow[\text{DIPEA}]{\text{HATU}} RCONHR' \qquad (1)$$

Table 1 Racemization during HATU/HBTU Couplings in Solution

Entry	RCOOH	R¢NH$_2$ or R¢NH$_2$·HCl	Conditions	DL-isomer (%)
1	Z Phg OH	H Val OMe·HCl	HATU, PS- (3 equiv), 7 h	<1 2
2	Z Phg OH	H Val OMe·HCl	HBTU, PS- (3 equiv), 7 h	4.0
3	Bn Val OH	H Val OMe·HCl	HATU, NMM- (3 equiv), 3 h	28.3
4	Bn Val OH	H Val OMe·HCl	HBTU, NMM- (3 equiv), 3.5 h	46.8
5	Z Phe Val OH	H Val OMe·HCl	HATU, DIPEA- (3 equiv), 3.5 h	<1 2
6	Z Phe Val OH	H Val OMe·HCl	HBTU, DIPEA- (3 equiv), 4 h	4.1
7	Z Gly Phe OH	H Pro NH$_2$	HATU, DIPEA- (2 equiv)	1.6

							(2 equiv)	
8	Z	Gly	Phe	OH	H	Pro	NH_2	HATU, collidine-(2 equiv)	0.8
9	Z	Gly	Phe	OH	H	Pro	NH_2	HBTU, DIPEA-(2 equiv)	3.9
10	Z	Gly	Phe	OH	H	Pro	NH_2	HAPyU, DIPEA-(2 equiv)	1.3
11	Z	Gly	Phe	OH	H	Pro	NH_2	HAPyU, collidine-(2 equiv)	0.8
12	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HATU, DIPEA-(2 equiv), 3 h	4.0
13	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HBTU, DIPEA-(2 equiv), 3 h	17
14	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HATU, collidine-(2 equiv), 3 h	<0.1
15	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HBTU, collidine-(2 equiv), 3 h	12
16	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HAPyU, DIPEA-(2 equiv), 3 h	5.0
17	Fmoc	Phe	Ser-(*t*-Bu)	OH	H	Pro	NH_2	HAPyU, collidine-(2 equiv), 3 h	<0.1

The results, collected in Table 1, clearly indicated that (i) HATU is superior to HBTU (entries 1 vs. 2, 3 vs. 4, 5 vs. 6, 7 vs. 9, and 12 vs. 13); (ii) HAPyU is similar to HATU, although in some cases HAPyU can give slightly better results (entries 7 vs. 10); and (iii) the use of collidine considerably reduces the level of epimerization (entries 7 vs. 8, 12 vs. 14, 13 vs. 15, and 16 vs. 17).

HATU activation has been adapted for automated stepwise solid-phase peptide synthesis for both fluorenylmethyloxycarbonyl (Fmoc) and *t*-butyloxycarbonyl (Boc) strategies. For the former, the fragment 65-74 (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2) of the acyl carrier protein was chosen as a model to compare the performance of HATU and HBTU. Results from these studies indicated that uronium salt coupling is superior to carbodiimide and pentafluorophenyl ester-mediated methods, and the aza derivatives are more efficient than HBTU.[3]

HATU has shown special utility for the synthesis of peptides containing hindered amino acids. Thus the solid-phase assembly of the model pentapeptide H-Tyr-Aib-Aib-Phe-Leu-NH_2 was compared via three different coupling methods, HATU, HBTU, and Fmoc-amino acid fluorides, the last named being known as one of the most efficient reagents for

couplings involving consecutive Aib units.[9] After 2 h coupling using 4 equiv of both Fmoc-Aib-OH and Fmoc-Tyr(*t*-Bu)-OH, as well as HXTU plus 8 equiv of DIPEA (all remaining couplings were carried out for 30 min), the pentapeptide was obtained with a purity of 94% for the HATU synthesis, and only 43% for HBTU. The synthesis conducted under similar conditions with Fmoc-Aib-F gave a purity of 96%, indicating that the reactivity of HATU is much closer to that of fluorides than to that of HBTU.[3]

The use of HATU for the solid-phase coupling of *N*-methyl amino acids has also been shown to be beneficial if compared with HBTU, as found during the syntheses of fragments of cyclosporin (CsA): H-Val-MeLeu-Ala-NH_2 (HATU, >99%; HBTU, 87%);[10] H-MeLeu-MeLeu-Ala-NH_2 (HATU, >99% HBTU, 34%);[10] H-D-Ala-MeLeu-MeLeu-MeVal-Phe-Val-OH (HATU, 85%; HBTU, 8%).[3]

Various protected peptide segments have been coupled by solid-phase techniques using HATU-mediated coupling methods.[11] Thus the synthesis of the *N*-terminal domain of γ-zein protein has been reported in good yield by eight successive segment couplings of the same protected hexapeptide to give the desired sequence using HATU and ***3-Hydroxy-3H-1,2,3-triazolo[4,5-b]pyridine*** (HOAt) in the presence of DIPEA.[12]

Less racemization is observed for solid-phase segment condensations in the presence of HATU relative to HBTU. The coupling of Fmoc-Phe-Ser(*t*-Bu)-OH onto H-Pro-resin was accompanied by 5% and 15% racemization, respectively, with HATU and HBTU in the presence of DIPEA. Replacement of DIPEA with collidine reduced the racemization level to 3%, confirming the effects observed for coupling reactions carried out in solution.[4]

HATU and HAPyU have been used for the cyclization of linear peptides in both solution and solid-phase modes. Cyclization in solution with HAPyU of a linear hexapeptide constructed exclusively from L-amino acids gave a better yield and less racemization at the *C*-terminal residue compared to other uronium or phosphonium salts.[13] HATU has also been shown to be the method of choice for cyclizations conducted while the peptide still remains anchored to the polymeric support. In the preparation of a library of 1296 cyclic pentapeptides, cyclization was complete after 1 h as judged by the ninhydrin test.[14]

In the absence of the carboxylic component, HATU, as is the case for HBTU, reacts with amino groups leading to the formation of tetramethylguanidinium derivatives.[5,15] In syntheses conducted in solution, an excess of either HATU or amino component should be avoided. In both solution and solid-phase strategies, the order of addition of reagents is critical. HATU should be delivered to the carboxylic component for preactivation prior to addition of the amine.

In addition, formation of the guanidinium derivative can also occur during slow reactions, such as the preparation of cyclic peptides, where both amino and carboxylic components are of necessity present together in equimolar amounts. An excess of the uronium salt can block the amino group.[16] For the synthesis of cyclic peptides, the phosphonium derivatives 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) and 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (AOP), which are also commercially available, may be more useful.

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Dimethyl Bis(methylthio)methylphosphonate[1]

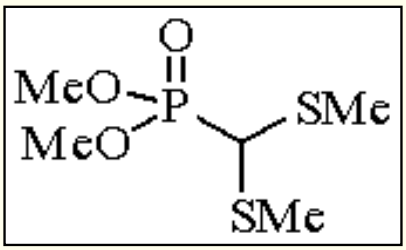

[61779-87-1] · $C_5H_{13}O_3PS_2$ · Dimethyl Bis(methylthio)methylphosphonate · (MW 216.29)

(treatment with base gives a carbanion that reacts with aldehydes and ketones[1-5])

Alternate Name: O,O-dimethyl formylphosphonate *S,S*-dimethyl thioacetal.

Physical Data: bp 72 °C/0.05 mmHg.

Solubility: sol THF, DME.

Form Supplied in: not commercially available.

Preparative Methods: $(MeO)_2P(O)CH(SMe)_2$[6] and related *S,S*-thioacetals of formylphosphonates[6,7] are readily prepared in high yields by the Arbuzov reaction of trialkyl phosphites with chloro dithioacetals (eq 1).[1,8] Other syntheses of thiophosphonates are known.[9]

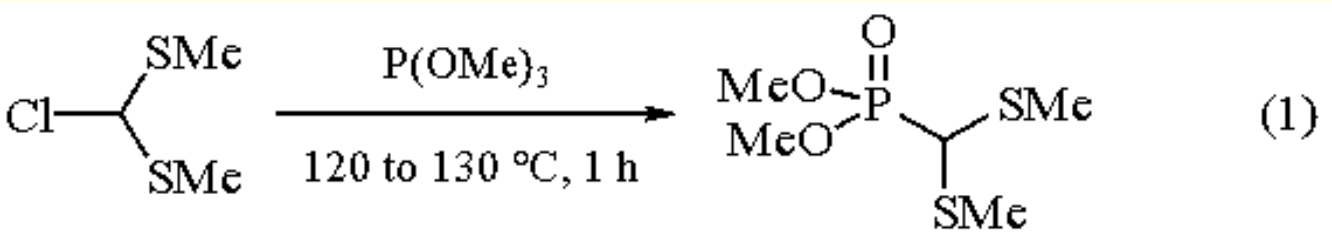

Reactions with Aldehydes and Ketones.

The carbanion derived from the treatment of $(MeO)_2P(O)CH(SMe)_2$ with a base reacts with cyclic and acyclic, aliphatic and aromatic aldehydes and ketones in a Horner-Wadsworth-Emmons reaction to give ketene *S,S*-thioacetals in high yields[1-5] (eq 2[2,3]). The carbanion is generated using either ***n-Butyllithium*** in THF at -78 °C[2,3] or, less commonly, ***Sodium Hydride*** in DME.[2] Alternatively, with aromatic aldehydes the reaction may be performed under two-phase

conditions using ***Benzyltriethylammonium Chloride*** (TEBA) as a phase-transfer catalyst.[2]

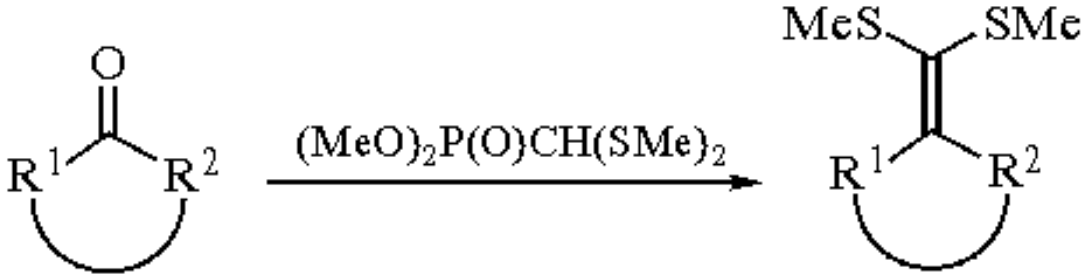

(2)

Product	Conditions	Yield (%)	Ref
$H_2C{=}CH(SMe)_2$	BuLi, THF, -78 °C	96	2
$Me_2C{=}CH(SMe)_2$	BuLi, THF, -78 °C	80	2
$PhHC{=}CH(SMe)_2$	BuLi, THF, -78 °C	90	2
	NaH, DME	75	
	50% NaOH, THF, 5% TEBA	88	
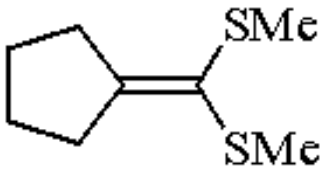	BuLi, THF, -78 °C	82	2
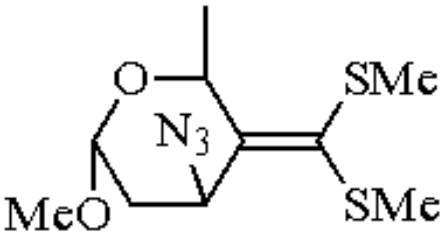	BuLi, THF, -78 °C	60	3

Ketene *S*,*S*-thioacetals are key synthetic intermediates, susceptible to nucleophilic and electrophilic attack.[1,2b,10] Hydrolysis and alcoholysis of ketene *S*,*S*-thioacetals yields carboxylic acids and esters, respectively. Other transformations of ketene *S*,*S*-thioacetals allow homologation of the precursor carbonyl compound and polyfunctional ketene *S*,*S*-thioacetals provide access to heterocycles (e.g. eq 3).[11]

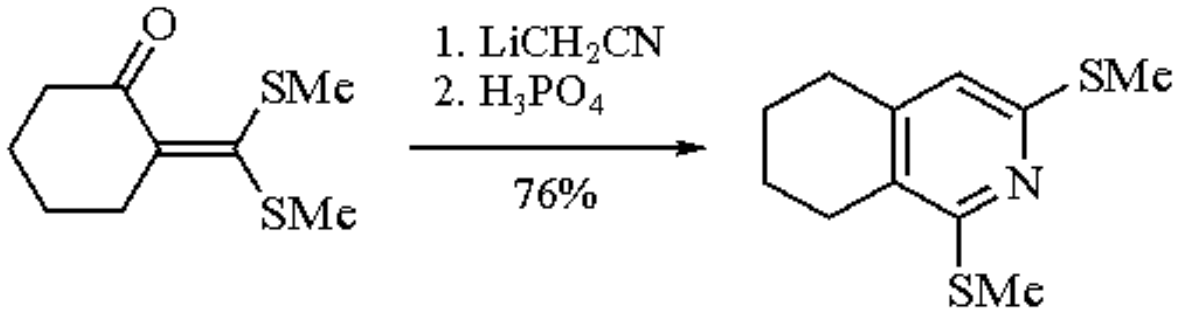

(3)

Alternative methods for the preparation of ketene *S*,*S*-thioacetals from carbonyl compounds include the Wittig reaction with phosphite ylides and the Peterson reaction with lithium derivatives of trimethylsilyl dithioacetals (eq 4).[1] The Wittig preparation is limited to aldehydes and is further restricted by the availability of the phosphite ylides. Also,

whereas the phosphate ester byproduct of the Horner-Wadsworth-Emmons reaction is water soluble and therefore easily separated from the ketene *S,S*-thioacetal, the phosphine oxide byproduct of the Wittig reaction is usually of a solubility similar to the product. The Peterson alkenation is a general synthesis, but suffers long reaction times and low yields with sterically hindered ketones.

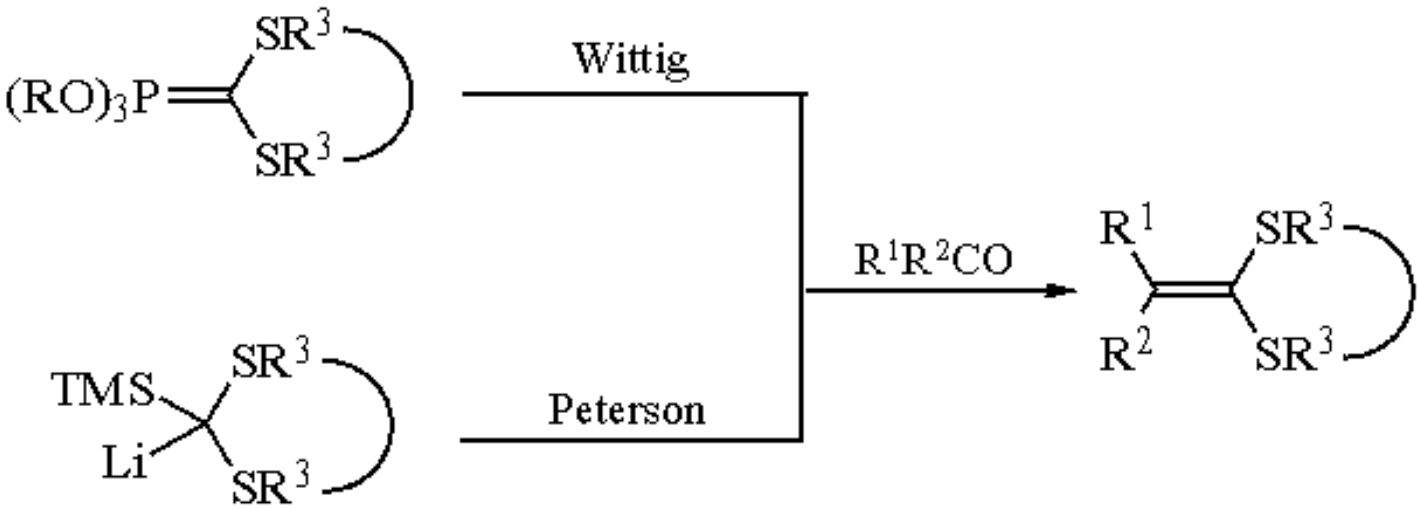

(4)

Related Systems.

The carbanions of related *S,S*-thioacetals of formylphosphonates also react with aldehydes and ketones, including α,β-unsaturated aldehydes and ketones, to give the corresponding ketene *S,S*-thioacetals[2,4,5,12] (e.g. eq 5[2,12]). Horner-Wadsworth-Emmons reactions of carbonyl compounds with *O,S*-thioacetals of formylphosphonates[2a,5] [e.g. $(MeO)_2P(O)CH(SMe)OMe$] and mono(thio)phosphonates[4,13] [e.g. $(MeO)_2P(O)CH_2SMe$] are also known.

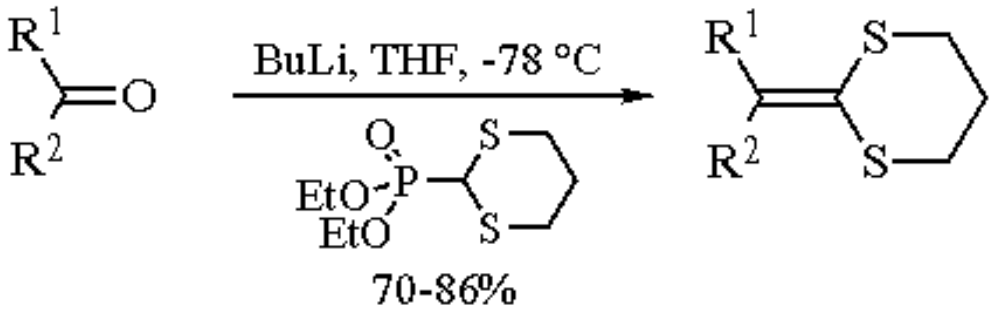

(5)

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(*R,R*)-2,5-Dimethylborolane[1]

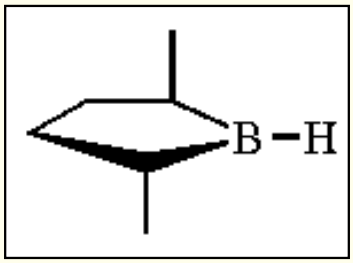

[97011-90-0] · $C_6H_{13}B$ · (*R,R*)-2,5-Dimethylborolane · (MW 96.00)

(reagent for asymmetric hydroboration;[2] also used as an auxiliary for asymmetric ketone reduction,[3] aldol,[4] and crotylboration[5] reactions; derived reagents are used in double asymmetric syntheses[6])

Physical Data: the most stable precursor is a complex with (*S*)-(+)-prolinol: mp 225-226 °C; [α]21D +23.2° (*c* 1.28, $CHCl_3$).

Solubility: sol pentane, Et_2O, THF.

Analysis of Reagent Purity: optical purity is assayed by oxidation (NaOMe, H_2O_2) to give 2,5-hexanediol, which has a maximum published rotation $[\alpha]^{23}_D$ -35.6° (*c* 8.29, $CHCl_3$). Derivitization of the diol as the bis-MTPA ester followed by HPLC analysis gives the relative amounts of (*R,R*)-, (*R,S*)-, and (*S,S*)-diols present.

Preparative Methods: a ca. 1:1 mixture of *cis*- and *trans*-*B*-methoxy-2,5-dimethylborolanes is first obtained by reaction of the Grignard reagent derived from 2,5-dibromohexane with diethylaminodichloroborane, followed by acidic methanolysis (eq 1).[2]

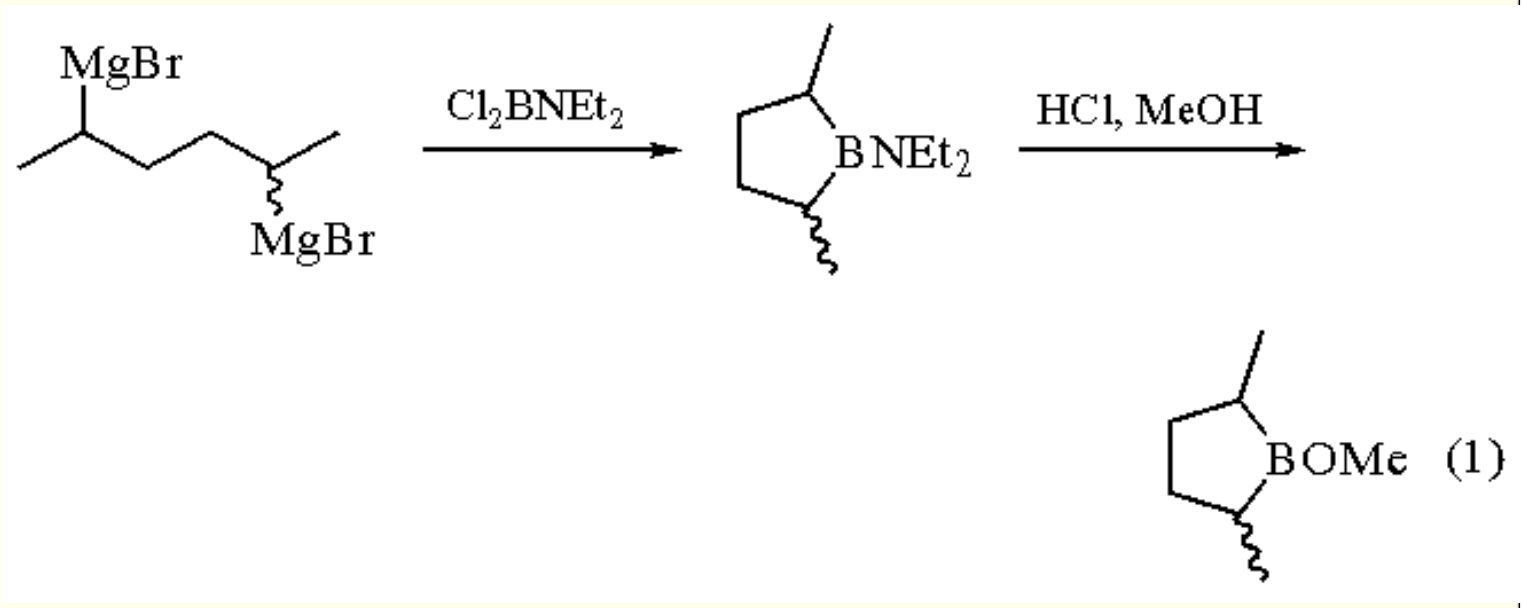

The *cis* isomer is then selectively complexed with *N,N*-dimethylaminoethanol, and the resolvable *trans* isomer is isolated by vacuum transfer (eq 2).

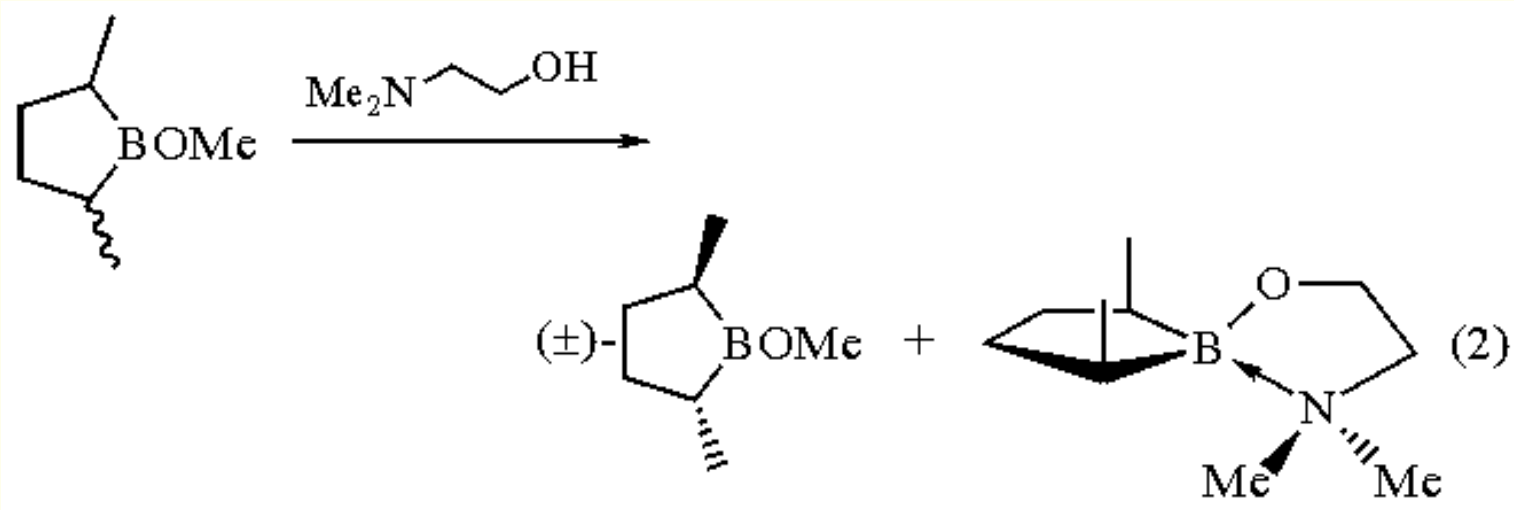

Reagent (**1**) is obtained by treatment of the racemic *trans* isomer with 0.45 equiv of (*S*)-prolinol, followed by vacuum transfer of the volatile fraction containing mostly (*S,S*)-2,5-dimethyl-*B*-methoxyborolane (eq 3). Through similar manipulation, (**2**) is obtained (eq 4).

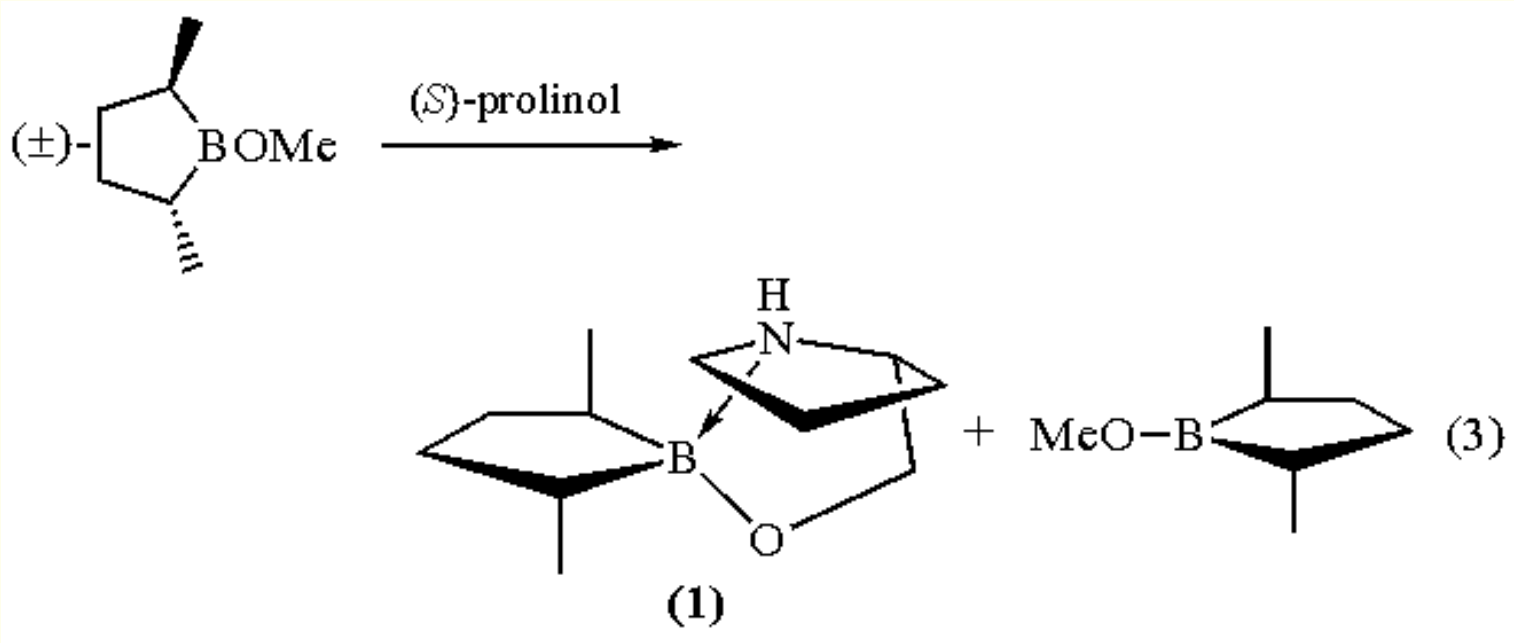

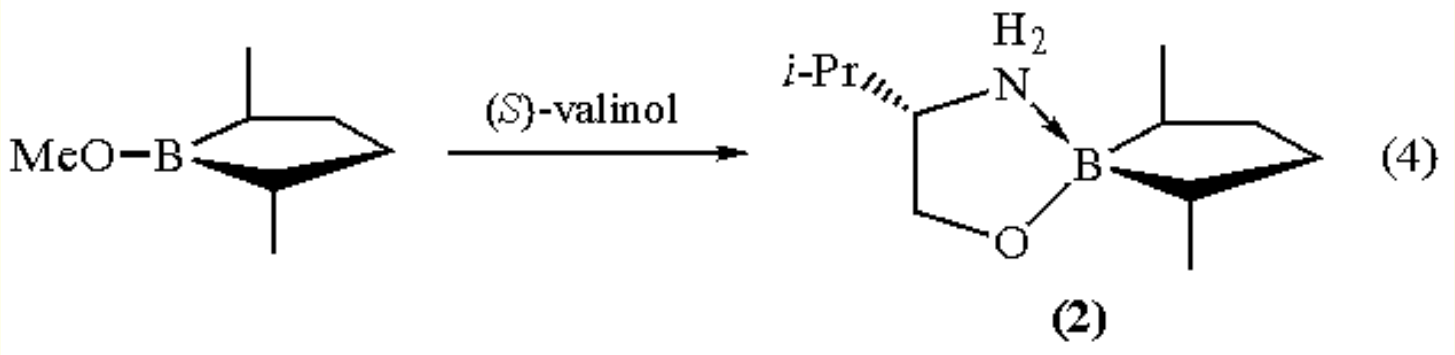

Handling, Storage, and Precautions: (*R,R*)-2,5-dimethylborolane is stored as an air- and moisture-stable

complex (**1**) with (*S*)-(+)-prolinol. The (*S*,*S*)-isomer is stored as a stable complex with either (*R*)-(-)-prolinol or as a complex (**2**) with (*S*)-(+)-valinol, which is more readily available. The reagent and many of its derivatives are extremely air- and moisture-sensitive, and may ignite when exposed to air. Precautions for the handling of such materials should be rigorously followed.[7]

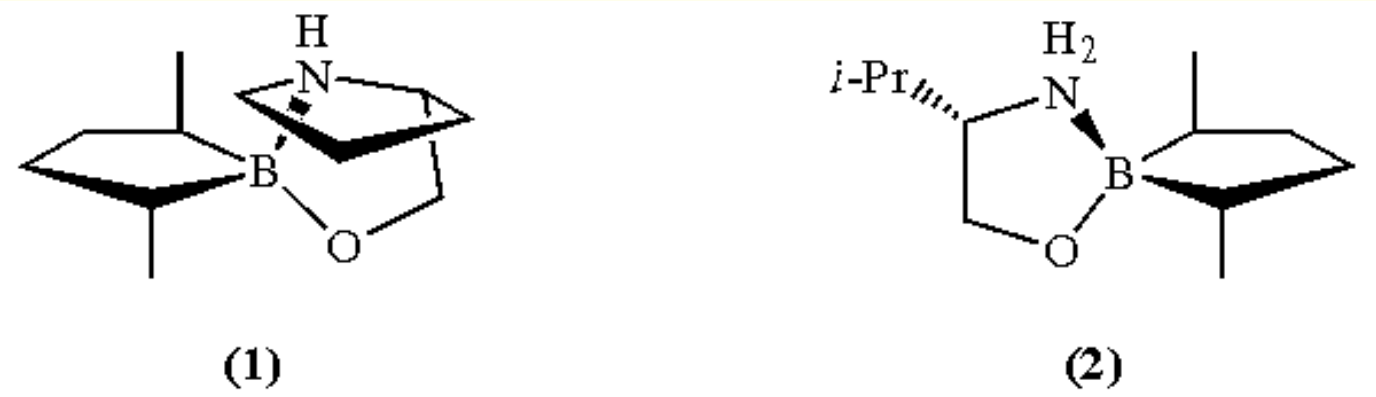

Asymmetric Hydroboration.[2]

For reaction with a prochiral alkene, (*R*,*R*)-2,5-dimethyl-*B*-methoxyborolane is liberated from (**1**) and a standard solution of the corresponding lithium dihydridoborate in ether is prepared (eq 5). Hydroboration is effected by addition of ***Iodomethane*** to the solution of dihydridoborate and alkene (eq 6). After oxidation, chiral secondary alcohols of high enantiomeric purity and predictable configuration are obtained from *cis*, *trans*, and trisubstituted alkenes. As is the case with other known asymmetric hydroborating agents,[8] 2-methyl-1-alkenes react with low asymmetric induction.

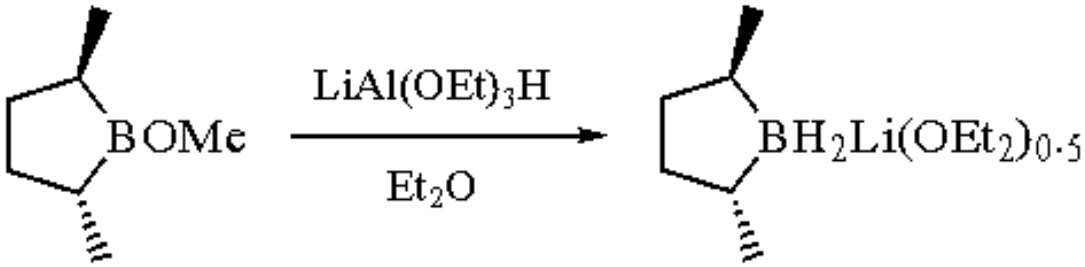

(5)

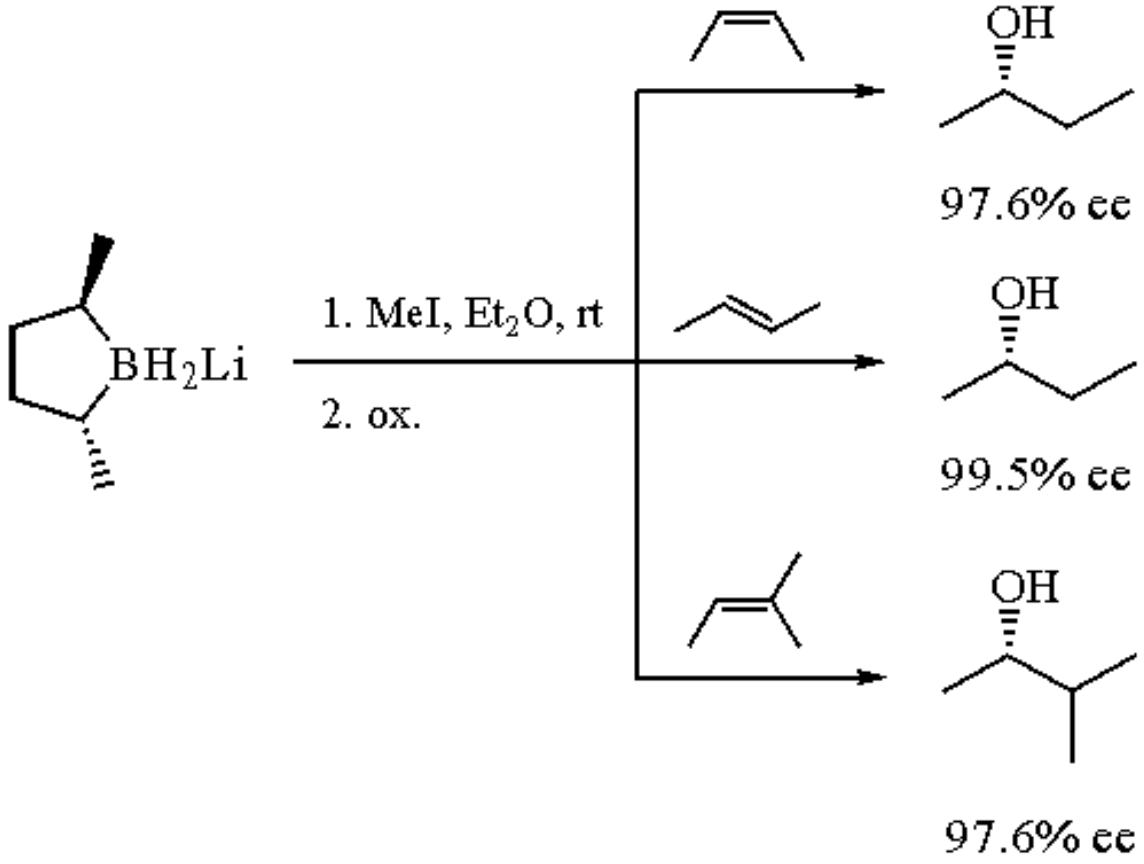

(6)

Asymmetric Reduction of Ketones.[3a,b]

A reagent system consisting of (*R*,*R*)-2,5-dimethylborolane (1.0 equiv) and the corresponding borolanyl mesylate (0.2 equiv) reduces a variety of prochiral ketones with asymmetric induction in the range of 80-100% ee. The reagent system is prepared in situ by addition of 1.4 equiv of ***Methanesulfonic Acid*** to a solution of the lithium dihydridoborate, prepared as in eq 5 above (eq 7).

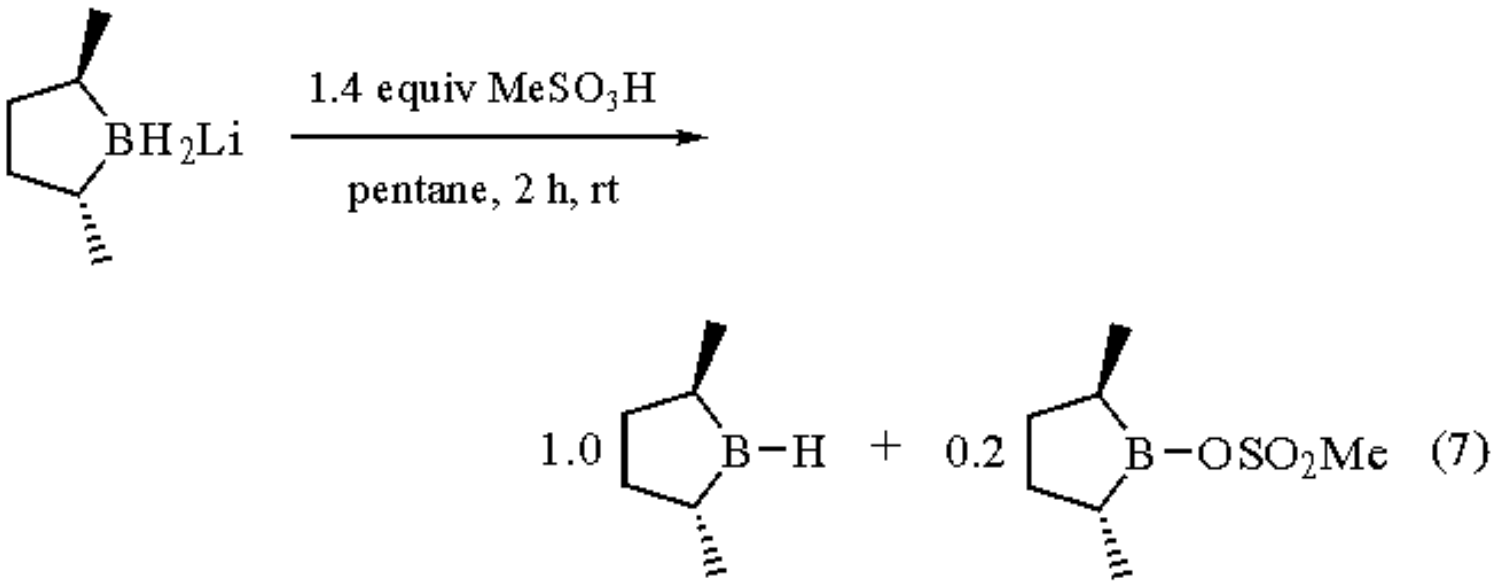

(7)

Kinetic and molecular modeling studies support the view that asymmetric ketone reduction proceeds through reaction of the borolane with a complex formed by coordination of the borolanyl mesylate *syn* to the smaller alkyl group (R^1) of the

ketone (eq 8).[3b] After reaction is complete, the chiral borolane moiety is recovered as a crystalline complex with 2-amino-2-methyl-1-propanol (eq 9).

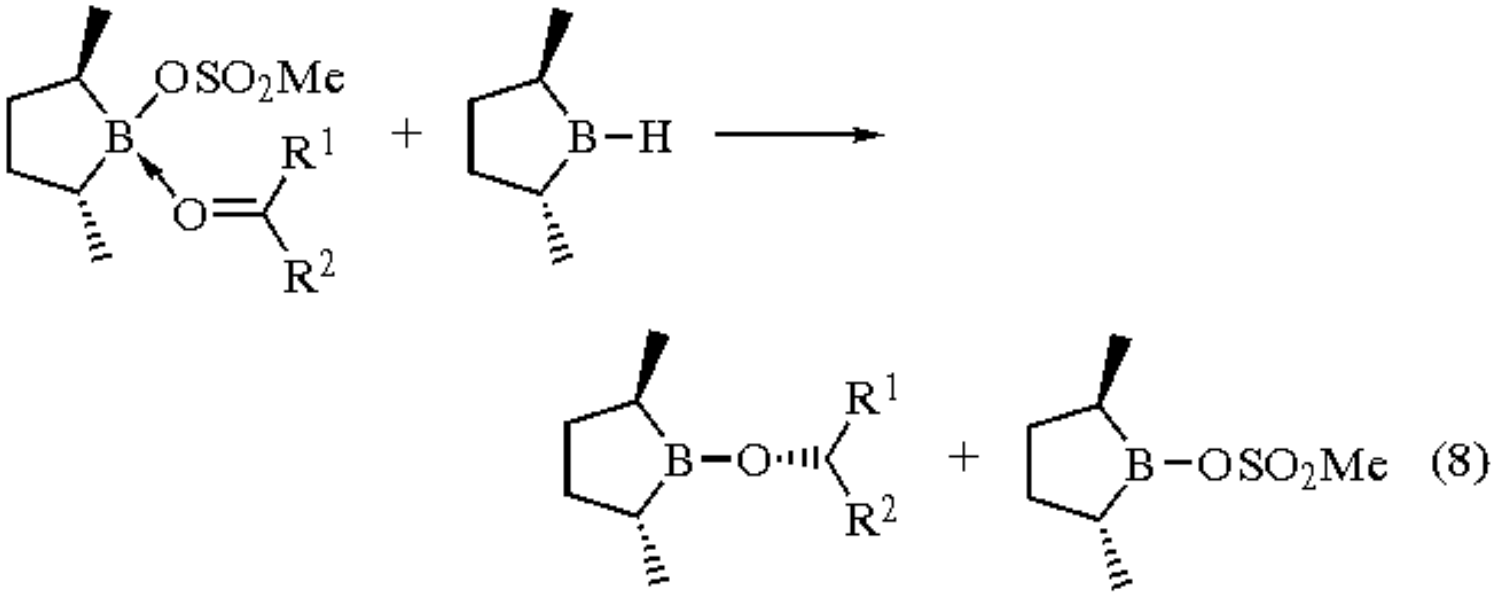

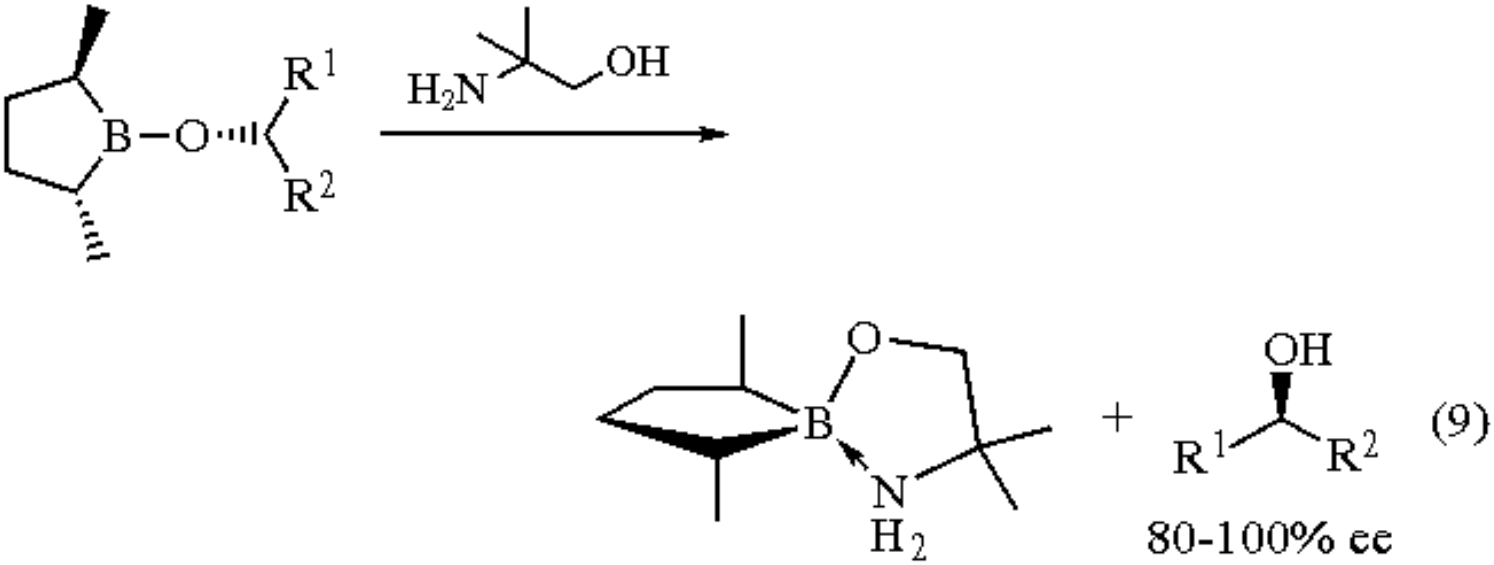

Asymmetric Aldol Reactions.[4]

For use in asymmetric aldol reactions, the dihydridoborate (eq 5) is converted to the borolanyl triflate (eq 10). The derived boron enolates of 1,1-diethylpropyl propanethioate (R = Me) and ethanethioate (R = H) react with representative aldehydes to give β-hydroxythioates with good to excellent enantioselectivity (eq 11). In the propanethioate series (R = Me), the observed 2,3-*anti* selectivity (*anti*:*syn* &egt; 30:1) is related to the preponderance of *E*(O)-geometry in the enolate.[9] The 1,1-diethylpropyl group of the thioate was selected to maximize the *E*(O):*Z*(O) ratio. Due to their intrinsically high enantioselectivity, the above enolates undergo highly diastereoselective aldol reactions with chiral aldehydes.[10] These double asymmetric[6] reactions have been employed in natural product syntheses.[11]

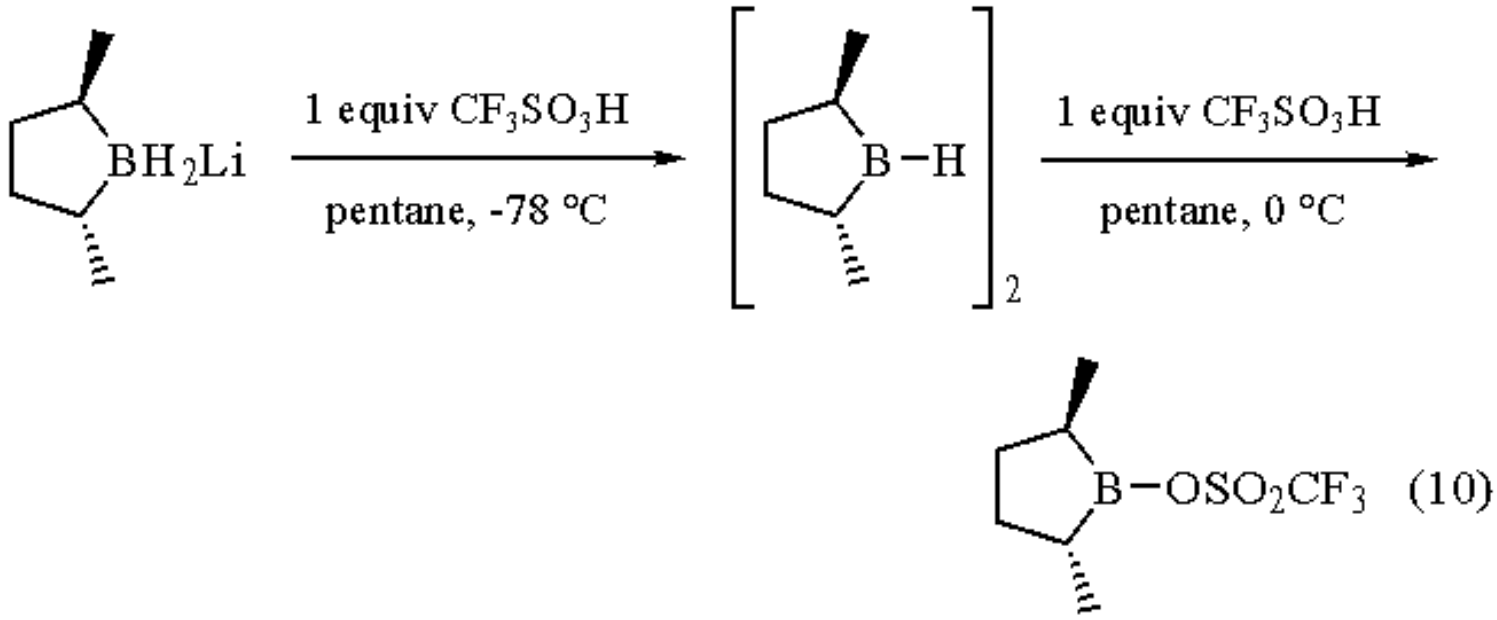

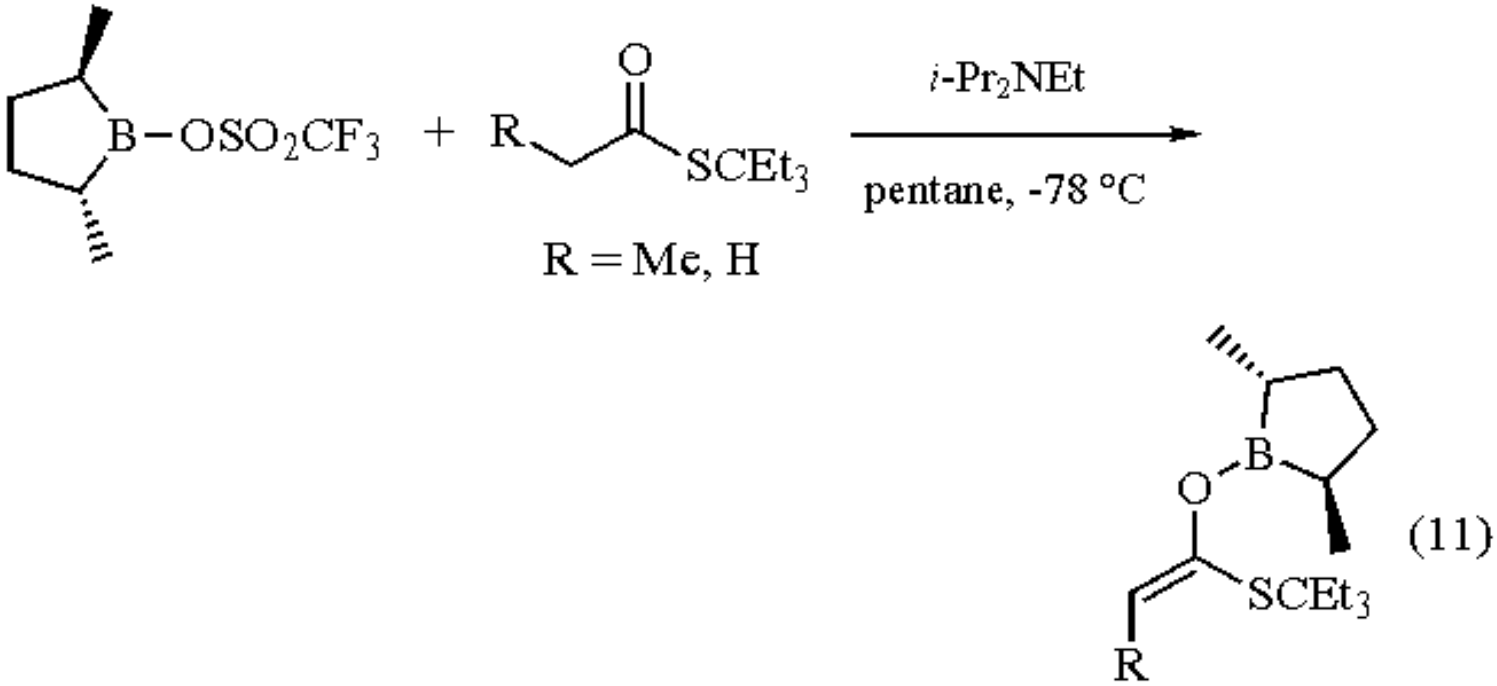

The borolanyl triflate (eq 10) has also been employed to form the chiral boron enolates of methyl ketones which have additional chiral centers present in their carbon framework. Reaction of these enolates with chiral aldehydes constitutes a triple asymmetric synthesis, in which the approximate multiplicativity of the three diastereofacial selectivities appears to be valid.[12]

Asymmetric Crotylboration.[5]

Reagents for crotylboration are prepared from 2,5-dimethyl-*B*-methoxyborolane (eq 5) by addition of (*Z*)- or (*E*)-crotylpotassium under standard conditions. Reactions with representative achiral aldehydes are 93-96% diastereoselective and 86-97% enantioselective for the major diastereomer (eqs 12 and 13). Results with chiral aldehydes conform to the rule of double asymmetric synthesis.[6]

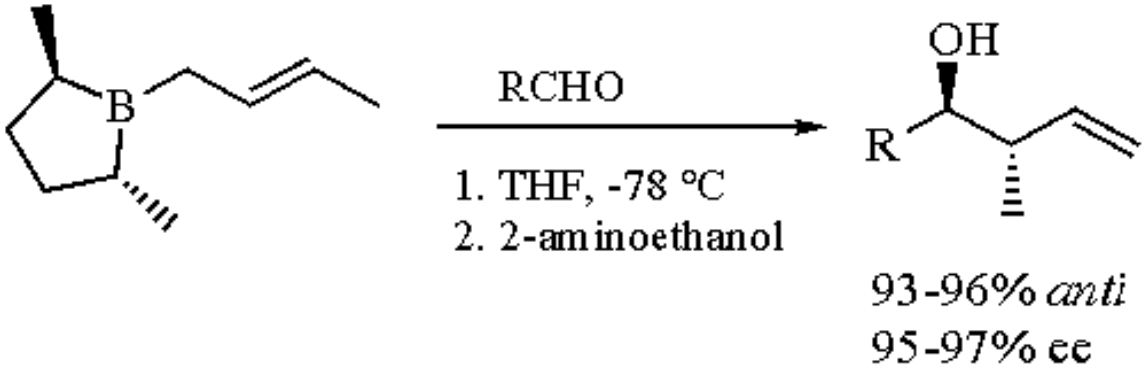

(12)

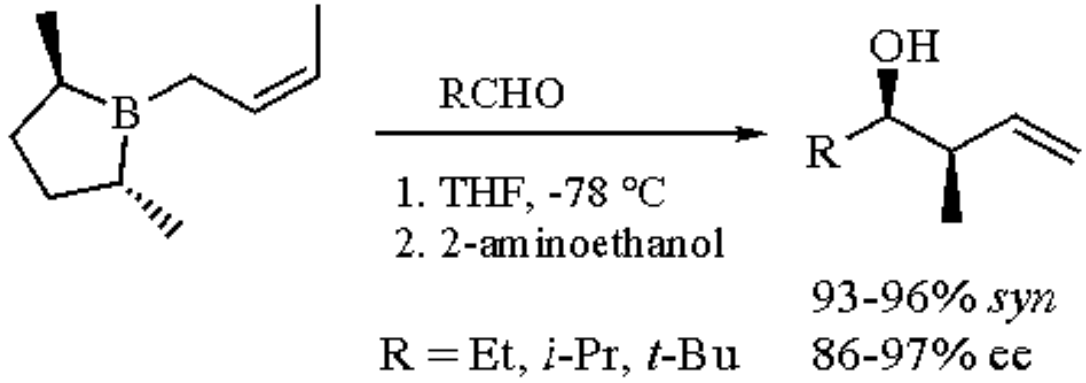

(13)

Related Reagents.

Diisopinocampheylborane; ***Dilongifolylborane***; ***Monoisopinocampheylborane***.

---

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Robert P. Short

Dimethyl 3-Bromo-2-ethoxy-1-propenylphosphonate[1]

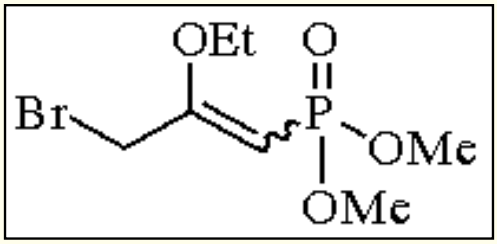

[73542-48-0] · $C_7H_{14}BrO_4P$ · Dimethyl 3-Bromo-2-ethoxy-1-propenylphosphonate · (MW 273.08) (*E*)

[87278-14-6] (*Z*)

[119226-85-6]

(reagent for effecting cyclopentenone annulations[2,3])

Physical Data: colorless liquid; distillation temperature (bulb-to-bulb) 110 °C/0.05 mmHg.

Solubility: sol THF, $CHCl_3$, EtOAc, and other common organic solvents.

Preparative Method: is readily prepared in two steps from the commerically available keto phosphonate (**1**).[2b] Reaction of (**1**) with ***Triethyl Orthoformate*** in the presence of $FeCl_3.6H_2O$, followed by allylic bromination of the resultant enol ether (**2**), provides the title reagent (**3**) in 71% overall yield (eq 1).

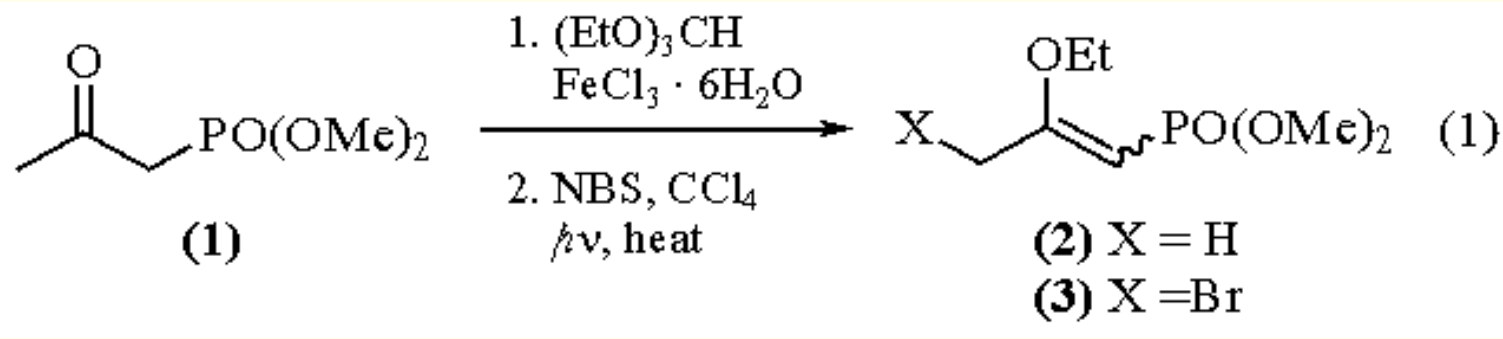

Handling, Storage, and Precautions: should be used shortly after its preparation and should be handled only in a well-ventilated fume hood.

Cyclopentenone Annulations.

The use of (**3**) for the synthesis of 2-cyclopentenones involves three steps, as shown in general terms in eq 2. Alkylation of carbonyl substrates (**4**) with reagent (**3**),[4] followed by mild acid hydrolysis of the resultant products (**5**), affords the diketo phosphonates (**6**). Subjection of the latter substances to intramolecular Horner-Emmons processes[5] provides the annulation products (**7**).

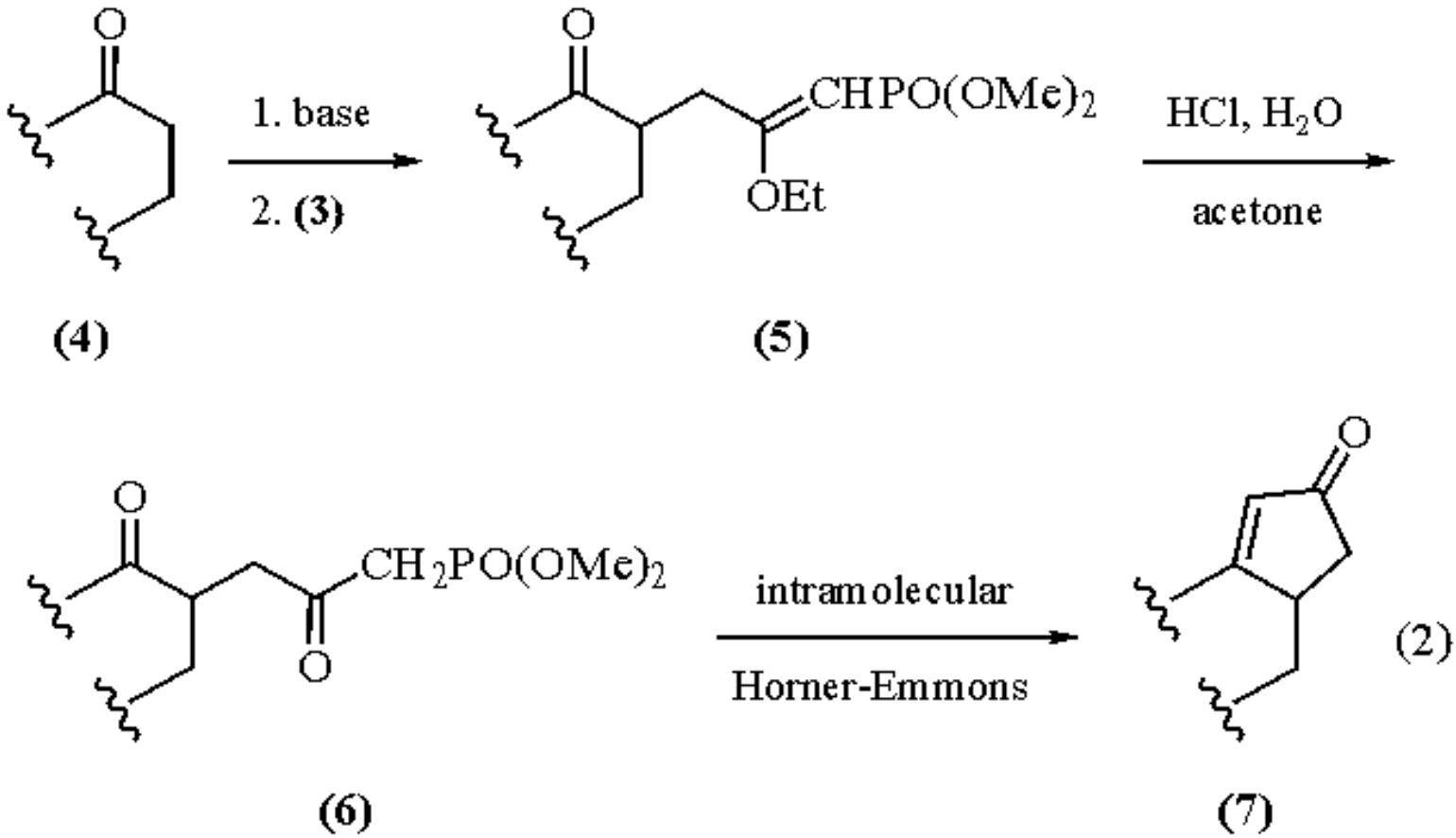

A variety of functionalized ketones have been alkylated successfully with reagent (**3**).[2,6-10] In those cases in which this process is sluggish or inefficient, the use of the iodo reagent (**8**) is beneficial.[11-14]

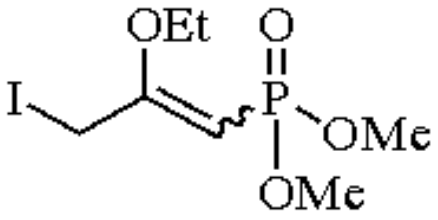

(**8**)

Conversion of (**5**) into (**6**) (eq 2) is typically accomplished by treatment of (**5**) with dilute aqueous HCl in acetone at rt.[2,6-14] Under these conditions, groups that are potentially acid sensitive (acetals,[2,8] esters,[2,10,11] conjugated diene system[12]) are (normally) stable, although cleavage of a primary TBDMS ether has been noted.[13]

The intramolecular Horner-Emmons reaction (eq 2) has been effected via a variety of procedures, including the use of ***Sodium Hydride*** in DME,[2,6,13-18] THF,[8,15] or DMF[11] at various temperatures, ***Potassium Carbonate*** in the presence of

18-Crown-6 in benzene[7,9] or toluene,[19] phase-transfer conditions employing ***Tetra-n-butylammonium Hydroxide***-water in benzene[20] or toluene,[10] and $MeSOCH_2Na$ in THF.[12] While the use of NaH as base is usually satisfactory, this protocol fails to convert (**9**) into bicyclo[3.3.0]oct-1-en-3-one (**10**).[16] This transformation is readily achieved, however, as shown in eq 3.[20]

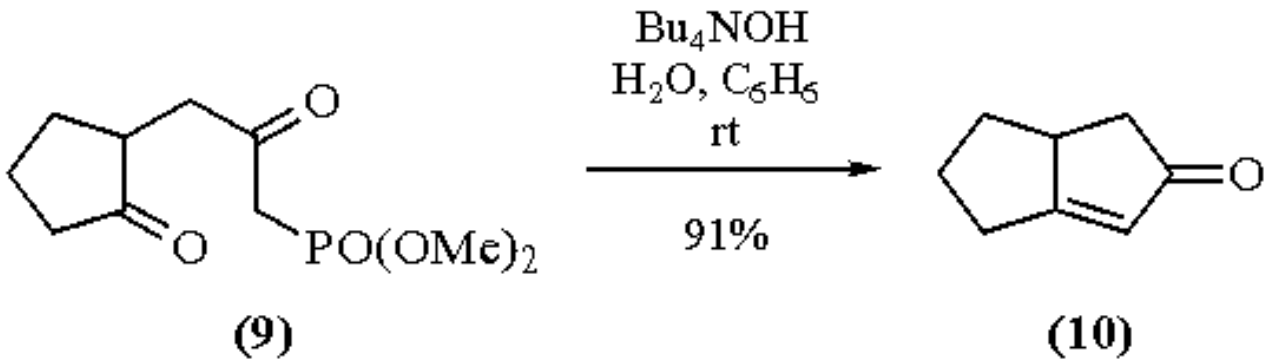

(3)

Compared with other procedures for effecting cyclopentenone annulations,[3] the method under discussion (eq 2) has several advantages. The overall process is convergent in nature, is generally efficient, and, importantly, the final step (internal Horner-Emmons reaction) can be achieved under conditions that do not isomerize the initially formed product (**7**). The synthetic utility of this method is illustrated by the examples given in eqs 4 and 5.[9,14]

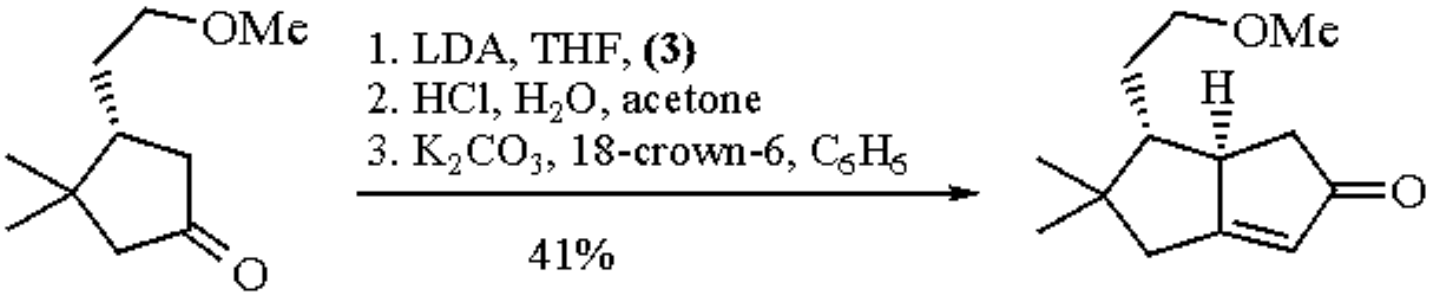

(4)

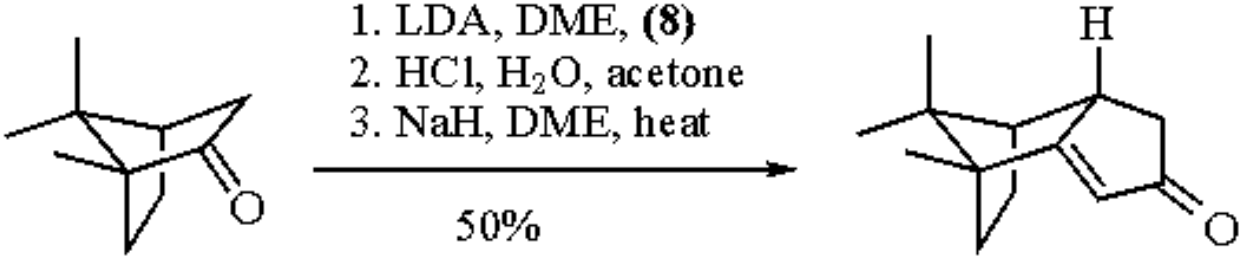

(5)

Related Reagents.

Allyl Chloride; ***2,3-Dichloropropene***; ***Methallyl Chloride***.

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4. For the overall conversion of (**4**) into diketo phosphonates structurally related to (**6**), employing diethyl 3-bromo-1-propenylphosphonate and diethyl 3-iodo-1-propynylphosphonate as the initial alkylating agents, see Poss, A. J.; Smyth, M. S. *SC* **1987**, *17*, 1735 and Poss, A. J.; Belter, R. K. *JOC* **1987**, *52*, 4810.
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Dimethyl Bromomalonate

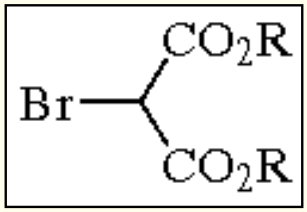

(**1**; R = Me)

[868-26-8] · $C_5H_7BrO_4$ · Dimethyl Bromomalonate · (MW 211.02) (**2**; R = Et)

[685-87-0] · $C_7H_{11}BrO_4$ · Diethyl Bromomalonate · (MW 239.08) (**3**; R = *t*-Bu)

[15960-79-9] · $C_{11}H_{19}BrO_4$ · Di-*t*-Butyl Bromomalonate · (MW 295.20)

(cyclopropanation of Michael acceptors;[1,2] synthesis of vinylogous urethanes from thioamides via the Eschenmoser sulfide contraction[3-5])

Physical Data: (**1**) bp 112.5-113 °C/15 mmHg.[6] (**2**) bp 150-152 °C/25 mmHg.[6] (**3**) bp 120-125 °C/11 mmHg.[7]

Form Supplied in: (**1**) technical grade, ~90% purity; (**2**) technical grade, 85-95% purity, contains varying amounts of diethyl malonate and diethyl dibromomalonate.

Analysis of Reagent Purity: (**1**) ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, s), 4.87 (1H, s);[8] (**2**) ^{1}H NMR (CCl_4) δ 1.34 (6H, t, *J* = 7 Hz), 4.28 (4H, q, *J* = 7 Hz), 4.72 (1H, s); IR (CCl_4) 1750 cm^{-1}; (**3**) ^{1}H NMR ($CDCl_3$) δ 1.45 (18H, s), 4.6 (1H, s);[9] ^{13}C NMR ($CDCl_3$) δ 27.4, 45.4, 83.5, 163.3;[9] IR (KBr) 1756 cm^{-1};[9] IR (CCl_4) 1765, 1740 cm^{-1};[10] IR (film) 1735 cm^{-1}.[4]

Preparative Methods: (**1**): by treatment of ***Malonic Acid*** with ***Bromine*** in diethyl ether followed by esterification with HCl in methanol;[11] by electrolytic bromination of dimethyl malonate with ***Magnesium Bromide*** or ***Copper(II) Bromide*** and ***Sodium Methoxide*** in acetonitrile-water at 2-3 °C.[12] (**2**): by light-induced bromination of ***Diethyl Malonate*** with bromine in carbon tetrachloride;[13] by treatment of diethyl malonate with bromotrichloromethane and ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** in benzene at 0 °C.[14] (**3**): by bromination of ***Malonic Acid*** with bromine in diethyl ether at rt followed by sulfuric acid catalyzed esterification with ***Isobutene*** in diethyl ether at rt;[7] by bromination of di-*t*-butyl malonate with bromine and ***Calcium Carbonate*** in chloroform at rt followed by reflux;[7] by lithiation of di-*t*-butyl malonate with ***n-Butyllithium*** in THF at -78 °C followed by addition of bromine and allowing reaction to warm to rt;[10] by lithiation of di-*t*-butyl malonate with *n*-butyllithium in THF at -78 °C, addition of ***Chlorotrimethylsilane***, warming to rt, and treatment of the resulting trimethylsilyl ketene acetal solution with bromine in carbon

tetrachloride.[4]

Cyclopropanation.

Bromomalonates react with Michael acceptors (α,β-unsaturated aldehydes, ketones, esters, and nitriles) under basic conditions to yield cyclopropane-1,1-dicarboxylic esters (eqs 1 and 2). Sodium[1,15] or potassium alkoxides,[10] ***1,1,3,3-Tetramethylguanidine***,[10] ***Potassium Carbonate***,[16] ***Diisopropylethylamine***,[2] and ***Cesium Fluoride*** or ***Potassium Fluoride***[17] have been used as bases in this reaction.

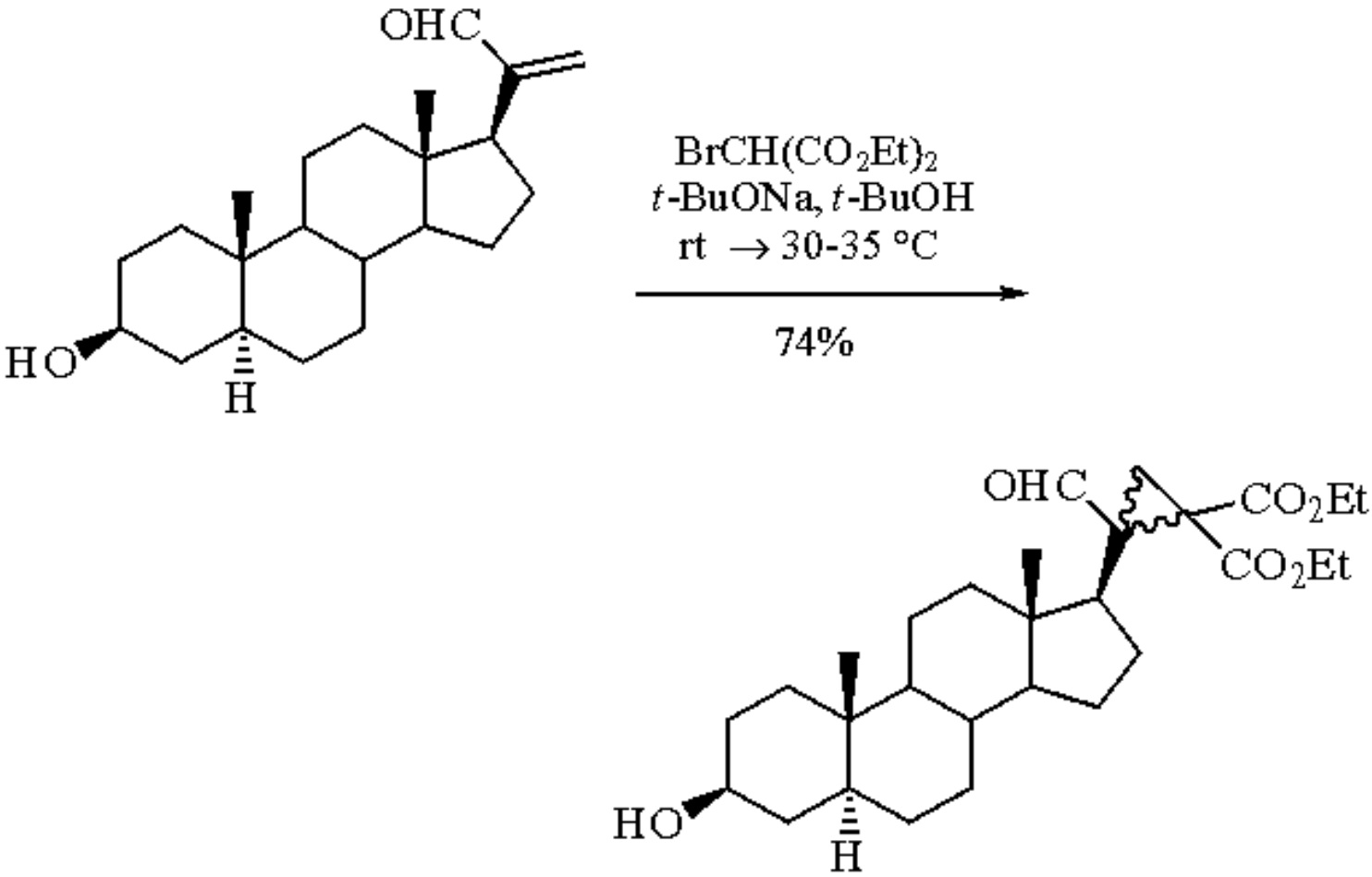

(1)

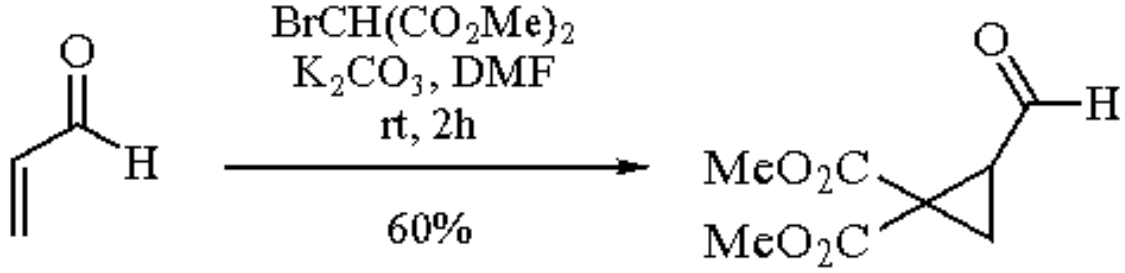

(2)

Eschenmoser Sulfide Contraction.

Thioamides react with bromomalonates under mild conditions to give vinylogous urethanes (eq 3).[3,4,5] In some cases, the addition of a phosphine is unnecessary because the intermediates spontaneously extrude sulfur.[3,5] The Battersby group has made extensive use of this process, followed by ester hydrolysis and decarboxylation, as a method for introduction of a methyl group in studies of vitamin B_{12} biosynthesis.[4,18] Use of 2-^{13}C labeled di-*t*-butyl bromomalonate (prepared from $^{13}CH_3CO_2H$) allows introduction of a ^{13}C-labeled methyl group.[18d]

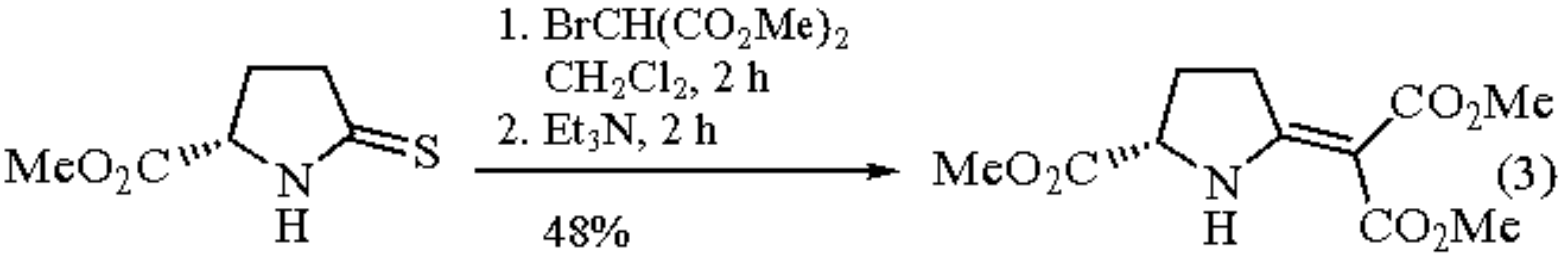

N-, *O*-, and *S*-Alkylation.

Amino-, aryloxy-, and thiomalonates can be prepared by alkylation of amines,[7,8,11,19] phenols,[6,20] and thiols,[21] respectively, with bromomalonates (eq 4).

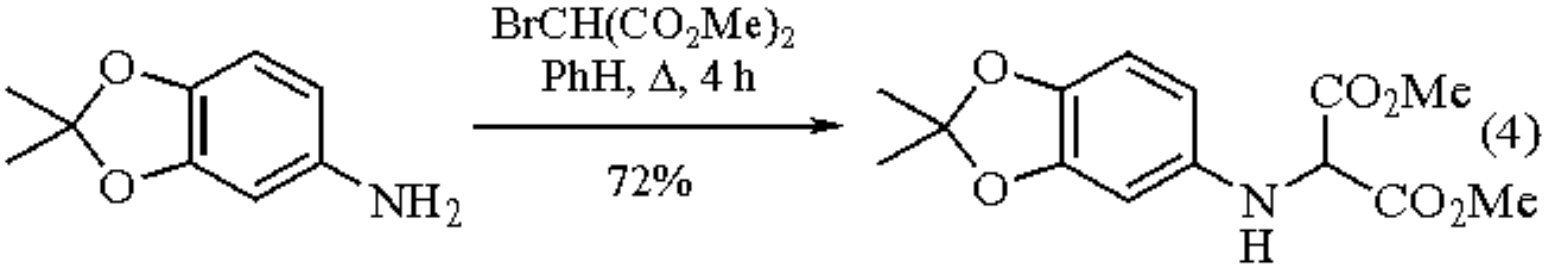

Other Applications.

Mn^{III}-promoted radical additions of dimethyl bromomalonate to alkenes give (β-bromoalkyl)malonates (eq 5).[22] A Wittig-type alkenation of aldehydes can be accomplished with ***Tri-n-butylstibine*** and bromomalonates (eq 6).[23] Bromomalonates can also serve as oxidizing agents, probably by acting as Br^+ donors (eq 7).[24]

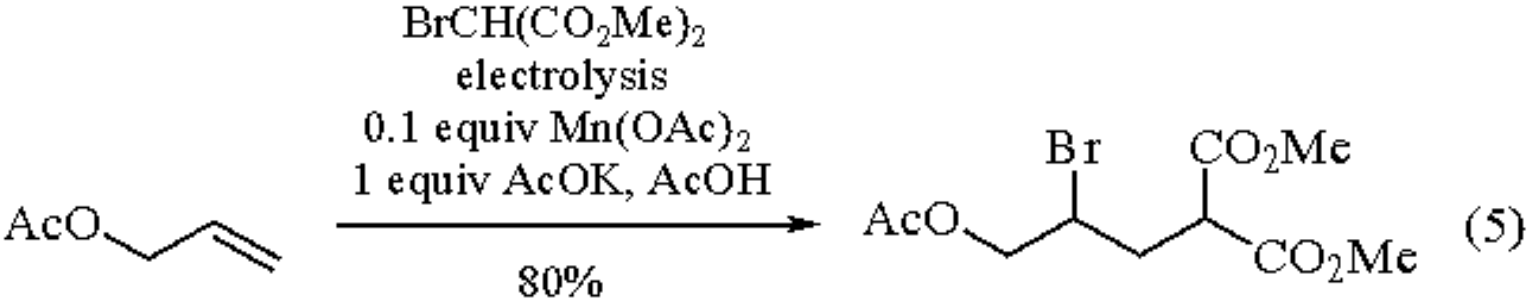

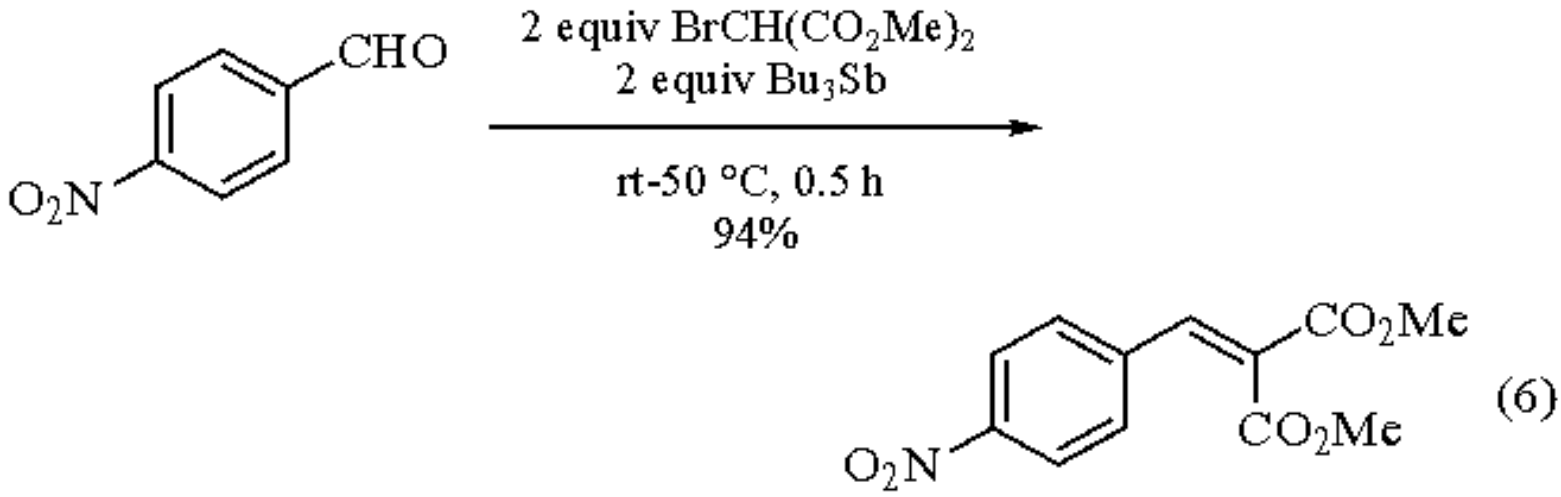

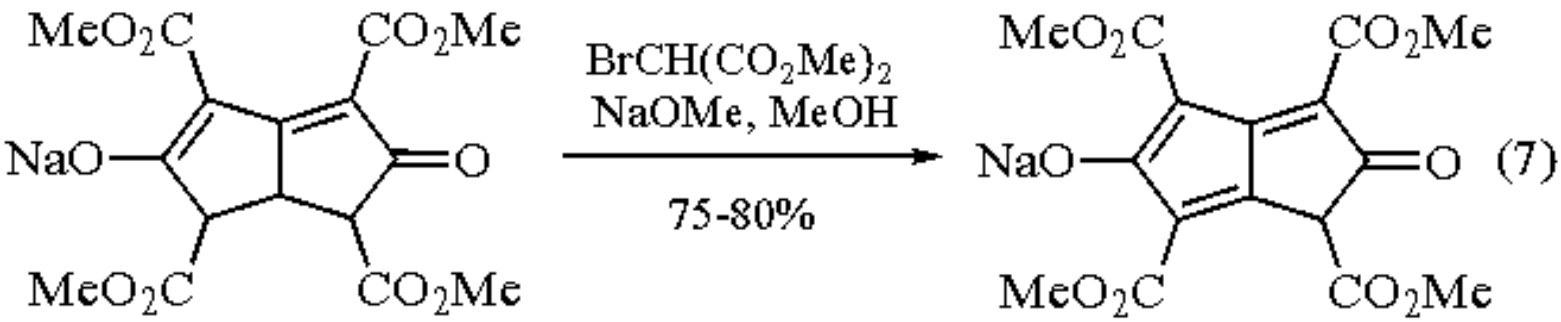

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Dimethylbromomethyleneammonium Bromide

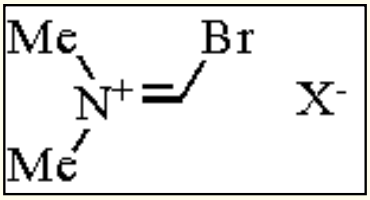

(**1**; X = Br)

[24774-61-6] · $C_3H_7Br_2N$ · Dimethylbromomethyleneammonium Bromide · (MW 216.91) (**2**; X = $POBr_2$)

[-] · $C_3H_7Br_3NOP$ · Dimethylbromomethyleneammonium Dibromophosphate · (MW 343.77)

(conversion of primary, secondary, and tertiary aliphatic alcohols,[1] including those in sugars and nucleosides,[2] into the corresponding bromides; preparation of β-bromovinyl aldehydes,[3] and β-bromo-α,β-unsaturated ketones[4])

Physical Data: (**1**) mp 156-158 °C.

Form Supplied in: prepared in situ.

Preparative Methods: reagent (**1**) can be prepared by dropwise addition of ***Thionyl Bromide*** to DMF in a chlorinated solvent; after the addition is complete, the mixture is heated at 40 °C to remove any remaining sulfur dioxide (eq 1).[1]

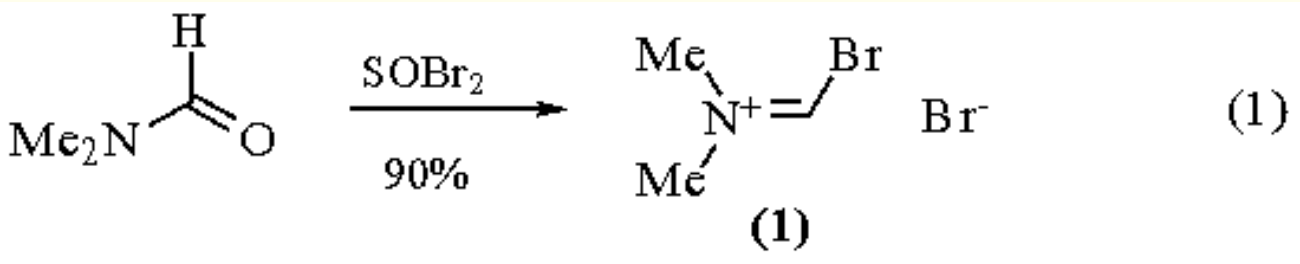

An alternative preparation of this reagent from ***Triphenylphosphine***, ***Bromine***, and ***N,N-Dimethylformamide*** is claimed to be easier to perform.[1] A third route involves passing gaseous ***Hydrogen Bromide*** through a solution of ***Dimethylchloromethyleneammonium Chloride***.[1,2]

Reagent (**2**) can be prepared by adding ***Phosphorus(III) Bromide*** slowly to DMF in chloroform.[2] Reagent (**2**) is more reactive than the bromide salt (**1**), which has been accounted for by a rapid exchange of the bromide and dibromophosphate anions (eq 2).

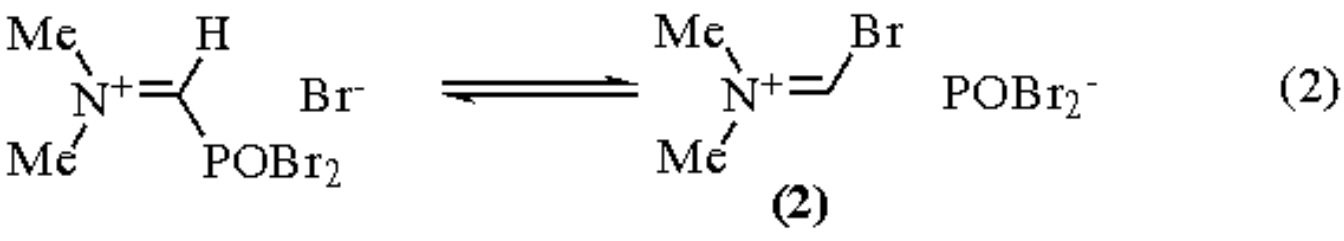

Handling, Storage, and Precautions: the reagents are corrosive, air-sensitive, and lachrymatory, and must be treated with caution. Avoid skin contact. Reagents (**1**) and (**2**) must be generated prior to the reaction under anhydrous conditions. An explosion of a flask containing a β-bromovinyl aldehyde has been reported.[5] Use in a fume hood.

Conversion of Alcohols into Bromides.

Alcohols have been converted into the corresponding bromides in high yields using reagent (**1**) (eq 3).[1] Hydroxy groups of nucleosides are converted into bromides using similar conditions.[3] Thus, yields (%) for the following compounds were obtained: R^1/R^2 = $Me(CH_2)_3CH_2/H$ (89); $CyCH_2$ (82); PrMeCH (83); Et_2CH (82).

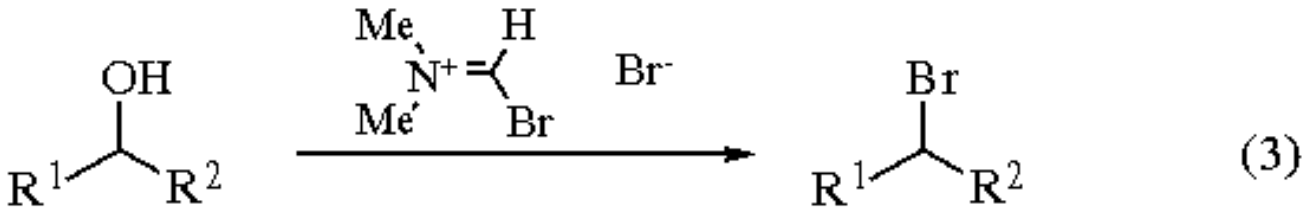

The reagent derived from DMF-***Triphenylphosphine Dibromide*** converts primary alcohols into bromides, but converts secondary alcohols into formate esters. Where primary and secondary alcohol functions are present, they are respectively converted into bromide and formate (eq 4).[4]

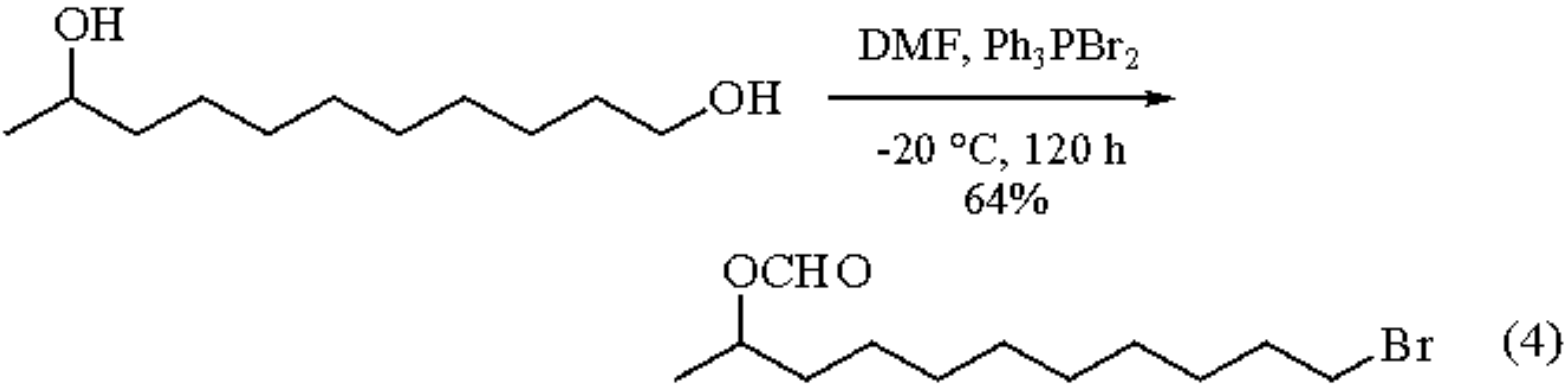

Reaction with 1,3-Diketones.

Mewshaw[5] reported that cyclic 1,3-diketones can be converted into β-bromo-α,β-unsaturated ketones in high yields

using reagent (**1**) (eq 5). The corresponding β-chloro-α,β-unsaturated ketones have been synthesized using dimethylchloromethyleneammonium chloride. Complexes derived from DMF and ***Phosphorus Oxychloride*** can give bis(β-chlorovinyl aldehydes) (eq 6).[6]

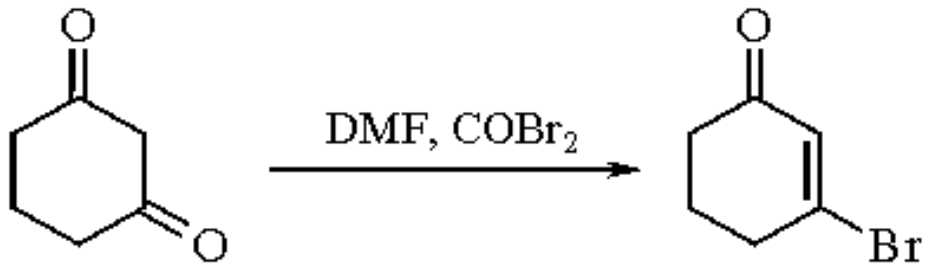

(5)

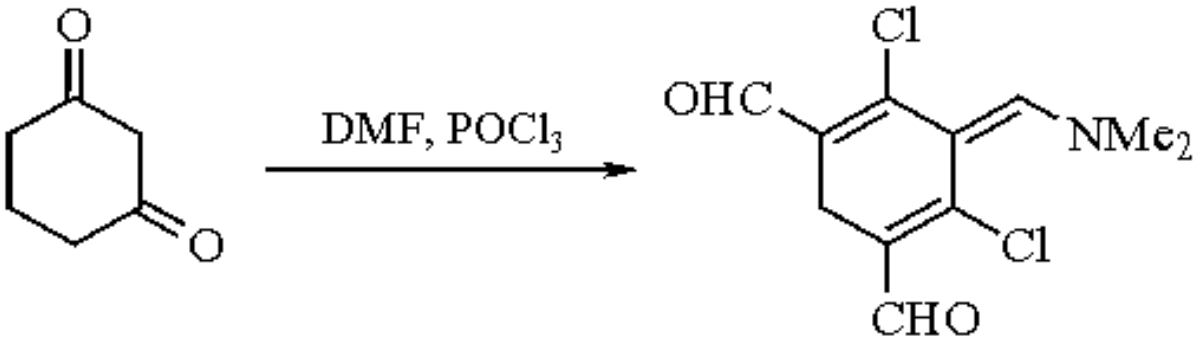

(6)

Preparation of β-Bromovinyl Aldehydes.

Reagents (**1**) and (**2**) react with methyl or methylene ketones to give β-bromovinyl aldehydes (β-BVAs) (eq 7).[2,7,8] Steroidal systems containing a ketone function also undergo this reaction.[9]

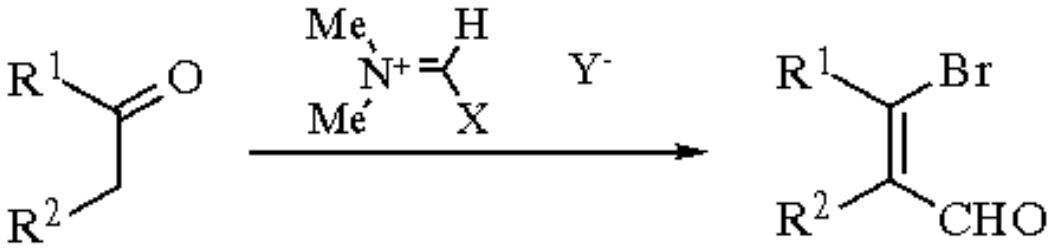

(7)

$$X = Y = Br;\ X = Br,\ Y = POBr_2$$

β-BVAs have been used as synthetic intermediates. The bromide group is easily displaced[7,9,11] and the aldehyde group is readily converted into other functionalities (eqs 8 and 9).[7,10-12] β-BVAs have not received the same level of attention as β-chlorovinyl aldehydes,[6,10,13] probably owing to the comparative instability of the former compounds.

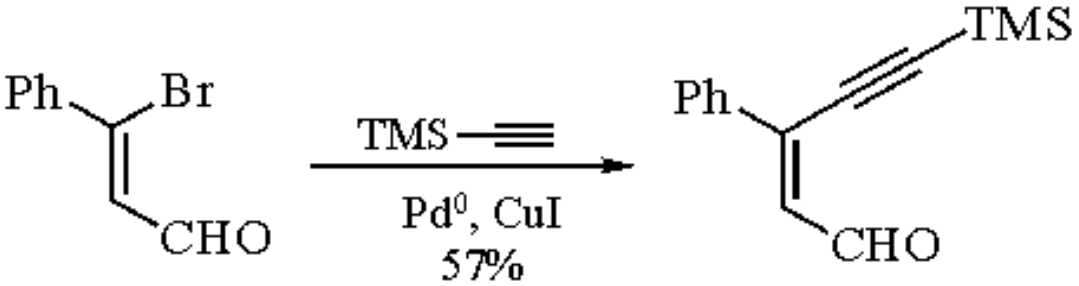

(8)

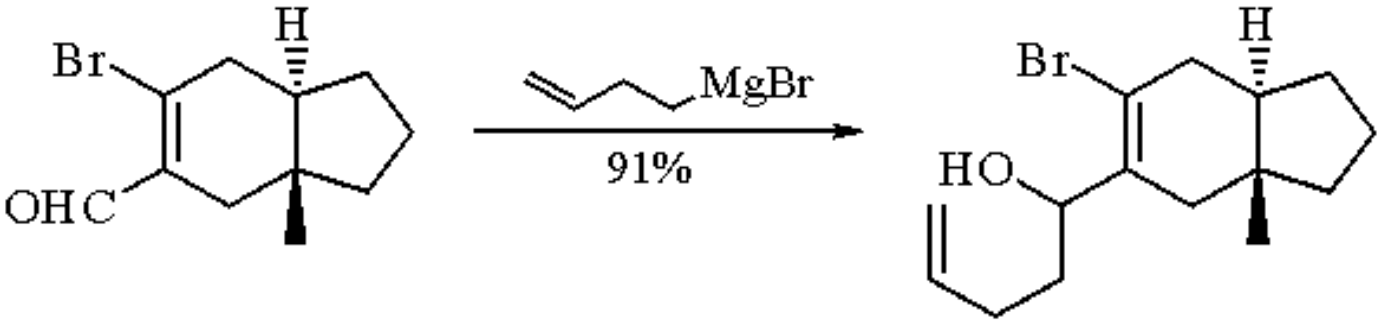

(9)

Related Reagents.

Dimethylchloromethyleneammonium Chloride; ***N,N-Dimethylformamide***; ***Phosphorus(III) Bromide***.

---

1. (a) Hepburn, D. R.; Hudson, H. R. *JCS(P1)* **1976**, 754; (a) Hepburn, D. R.; Hudson, H. R. *CL(L)* **1974**, 664.
2. Arnold, Z.; Holy, A. *CCC* **1961**, *26*, 3059.
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University of Sheffield, UK

(*S*)-*N,N*-Dimethyl-*N´*-(1-*t*-butoxy-3-methyl-2-butyl)formamidine[1,2]

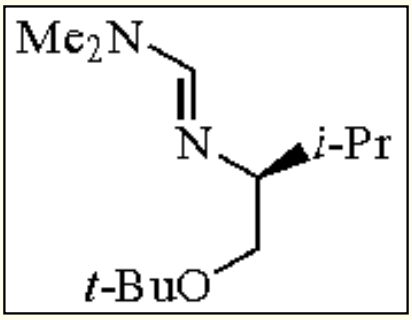

(*E*)-(*S*)

[114318-94-4] · $C_{12}H_{26}N_2O$ · (*S*)-*N,N*-Dimethyl-*N´*-(1-*t*-butoxy-3-methyl-2-butyl)formamidine · (MW 214.40)
(*S*)

[66919-83-3] (*R*)

[90482-06-7]

(chiral auxiliary for derivatization, directed lithiation, and asymmetric alkylation adjacent to nitrogen of benzylic or allylic secondary amines by formamidine exchange, metalation, alkylation, and hydrolysis[1,2])

Physical Data: bp 55-65 °C/0.05 mmHg; $[\alpha]_D$ -59.6° (*c* 3.5, EtOH).[2]

Preparative Methods: easily prepared from (*S*)-valinol in a high yielding four-step procedure (eq 1).[2] Other chiral formamidines can be prepared and used successfully in the methodology outlined here (eq 2).[2,3]

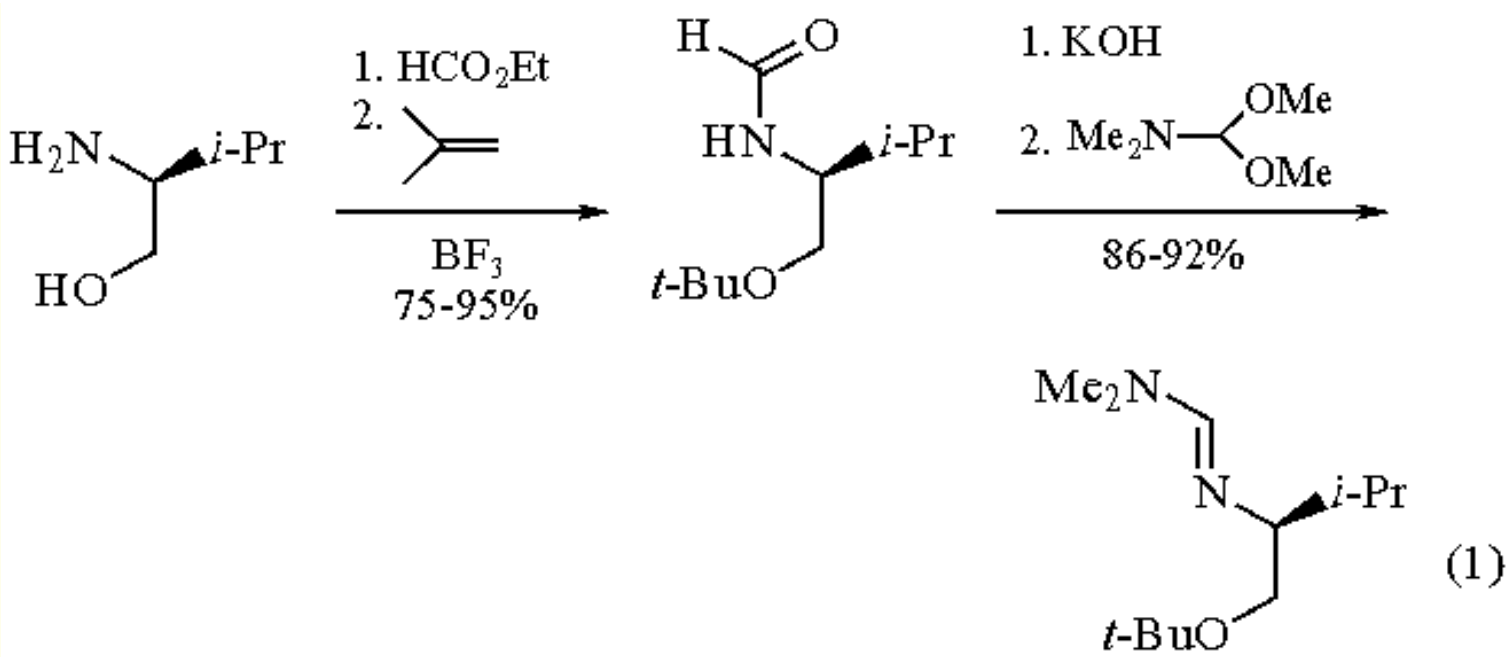

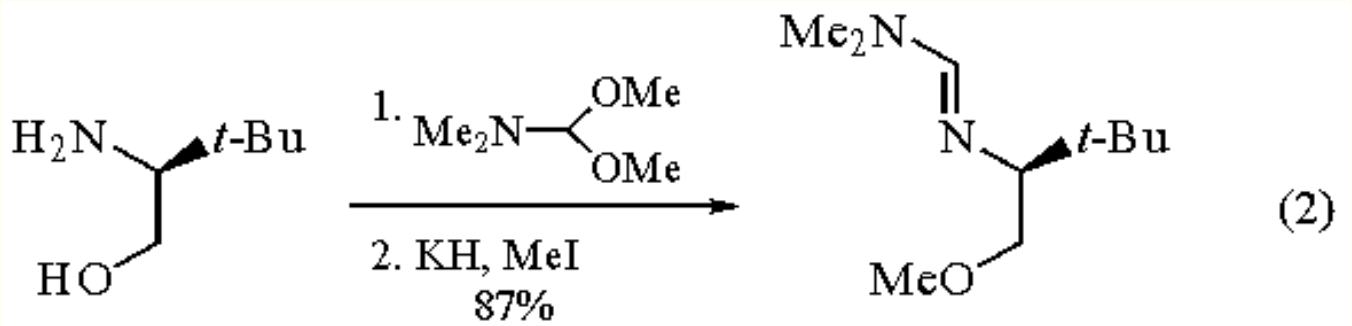

Handling, Storage, and Precautions: store under argon at rt; use in a fume hood.

Introduction.

In the equations, VBE will be used to depict the valinol *t*-butyl ether portion of the formamidine, while the *t*-leucinol methyl ether portion will be abbreviated LME.

Upon heating the title formamidine with a secondary amine, dimethylamine is extruded, affording a chiral formamidine derivative of the original amine (eq 3).[4a]

(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine

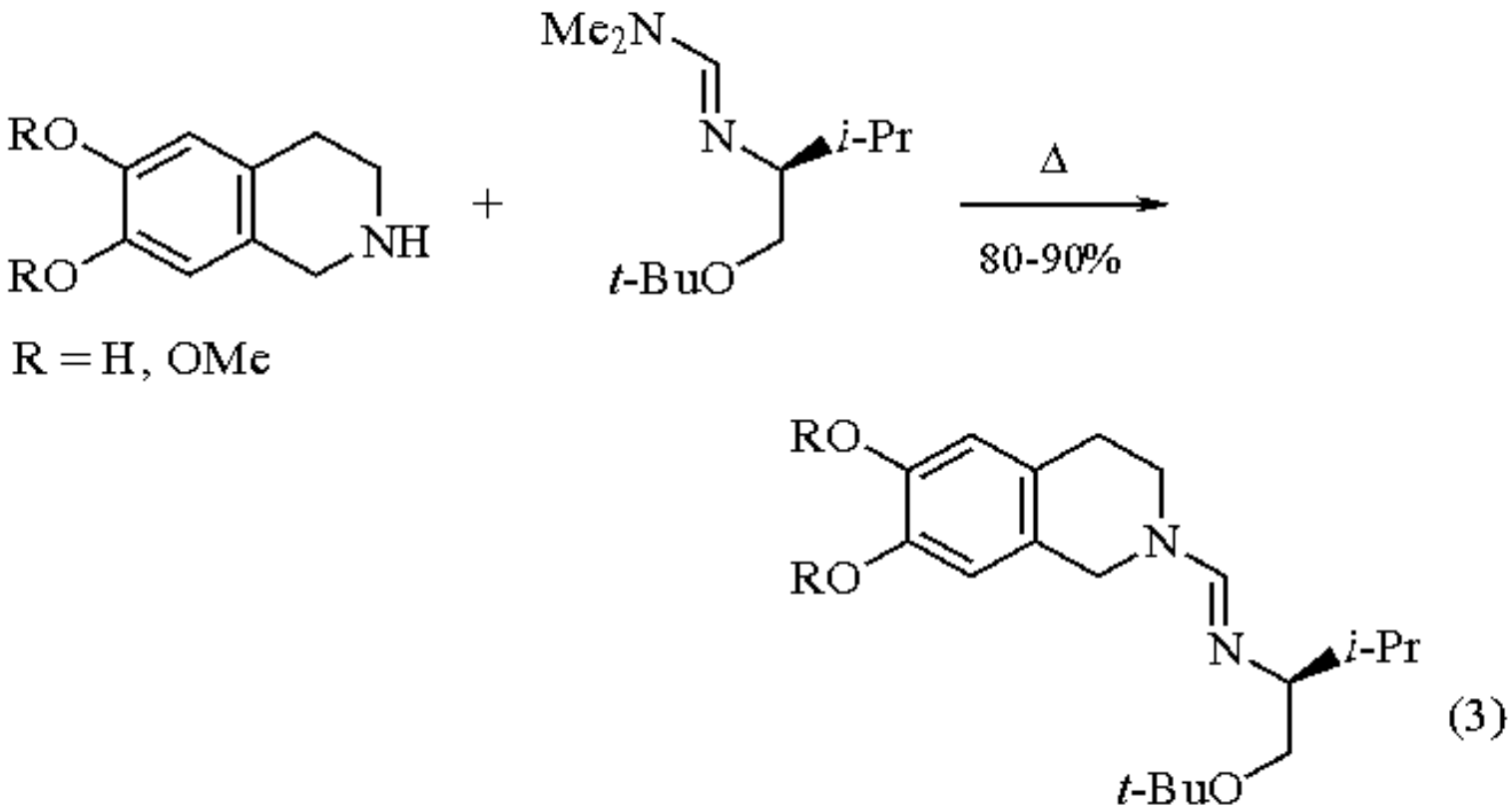

Deprotonation and alkylation followed by formamidine removal allows entry to a host of isoquinoline alkaloids (eq 4).[3b,4]

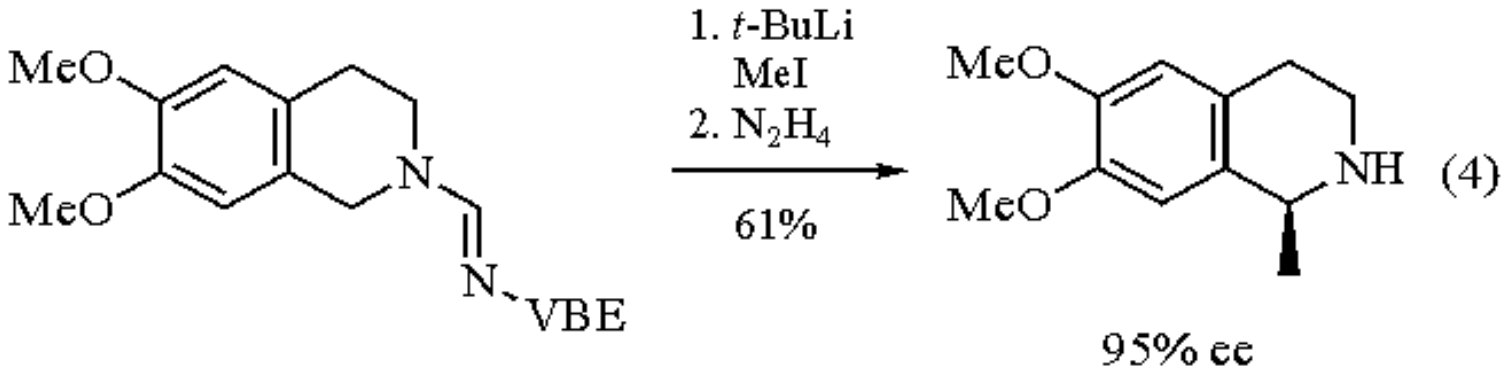

This protocol has also been an avenue to a variety of indole alkaloids (eq 5).[5]

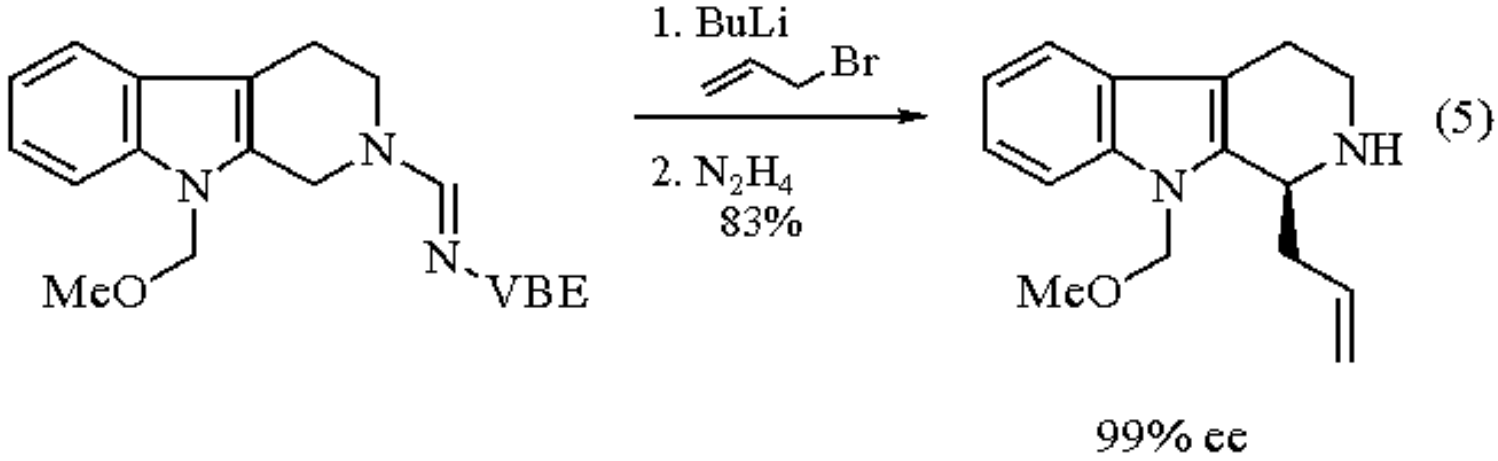

(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine

Chiral 1-alkyl-2-benzazepines can be formed by utilization of the same method (eq 6).[3a]

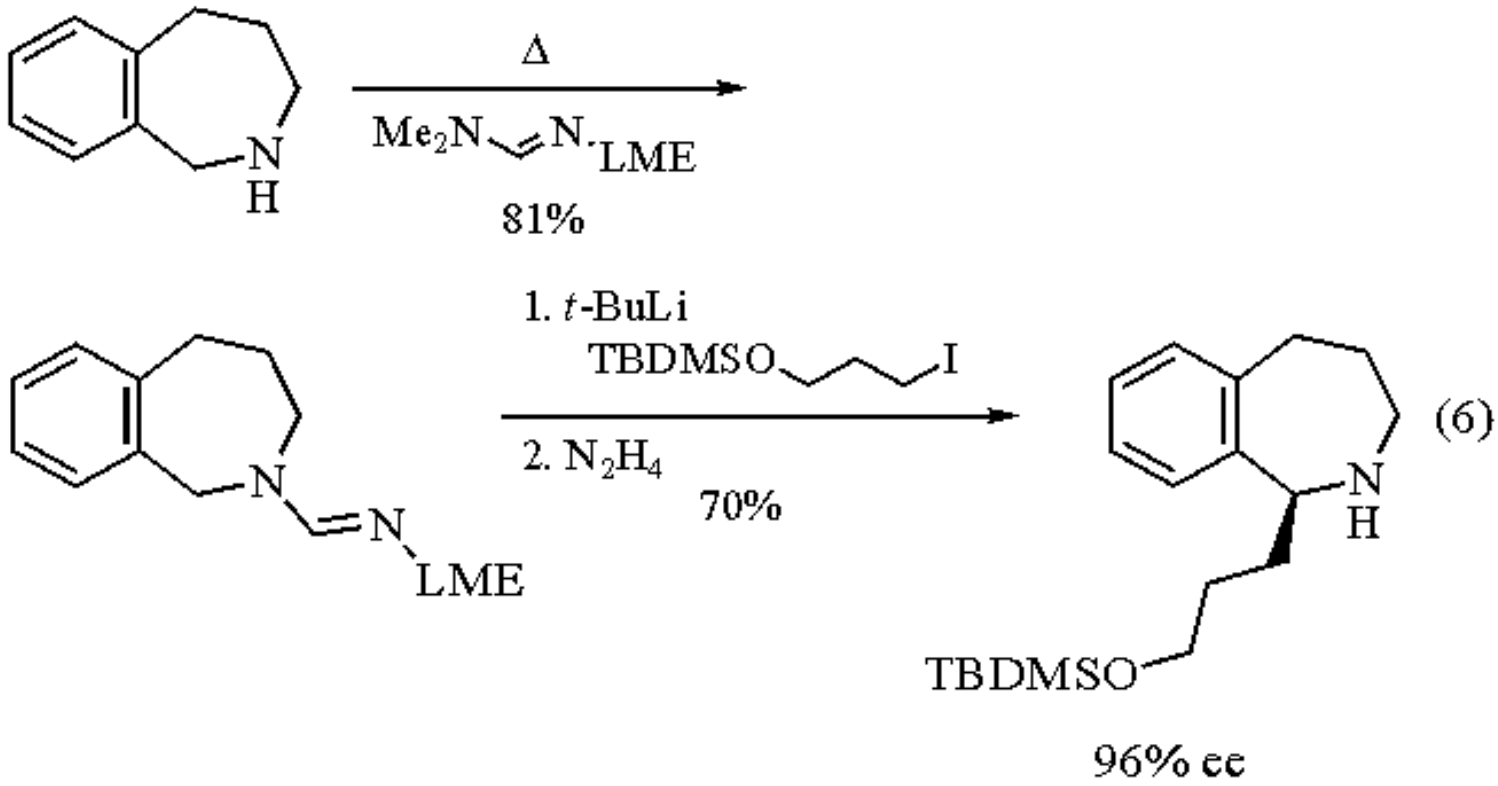

This strategy also works well for the asymmetric alkylation of 3-pyrrolines (eq 7)[6] and tetrahydropyridines (eq 8).[7]

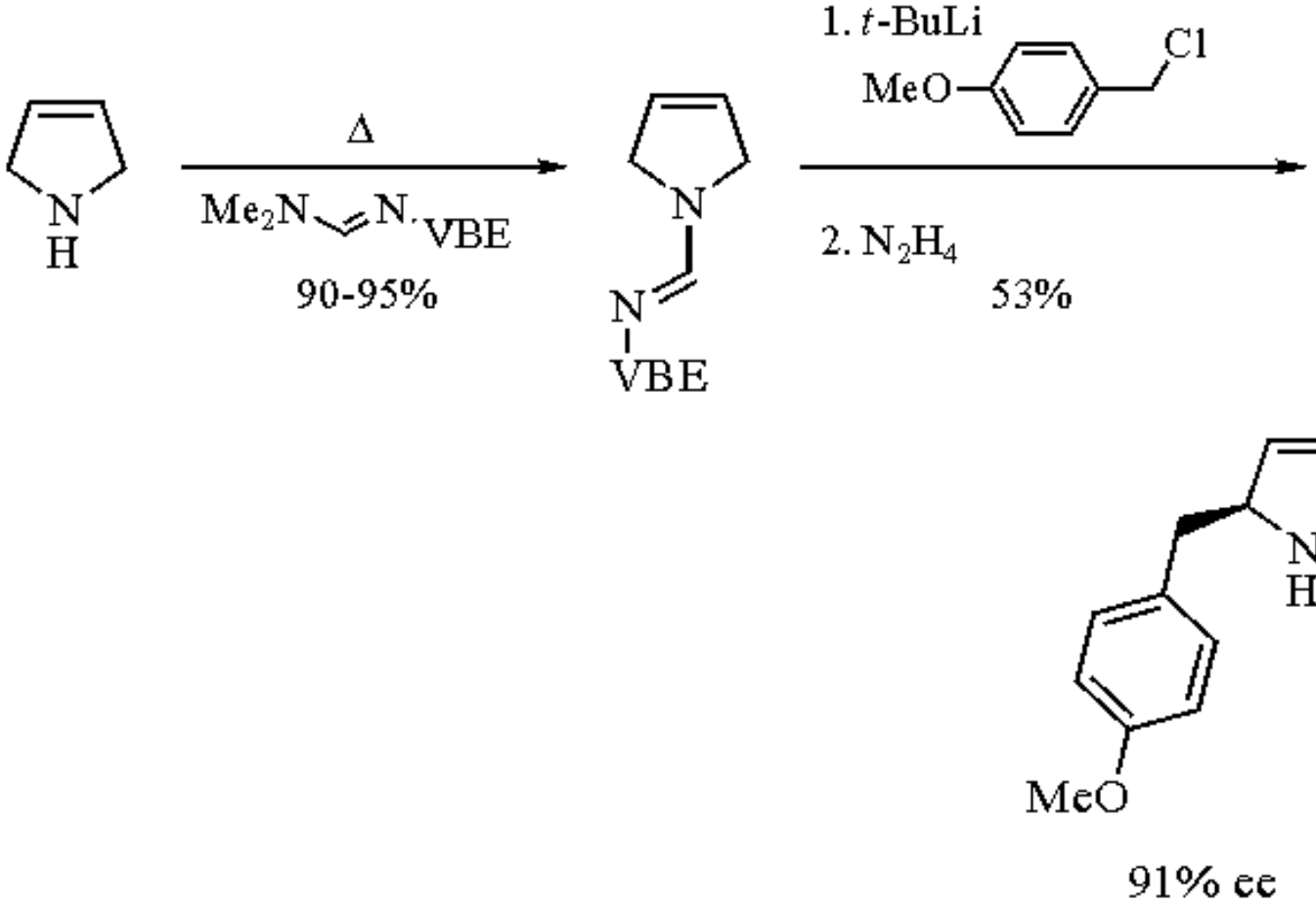

(7)

(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine

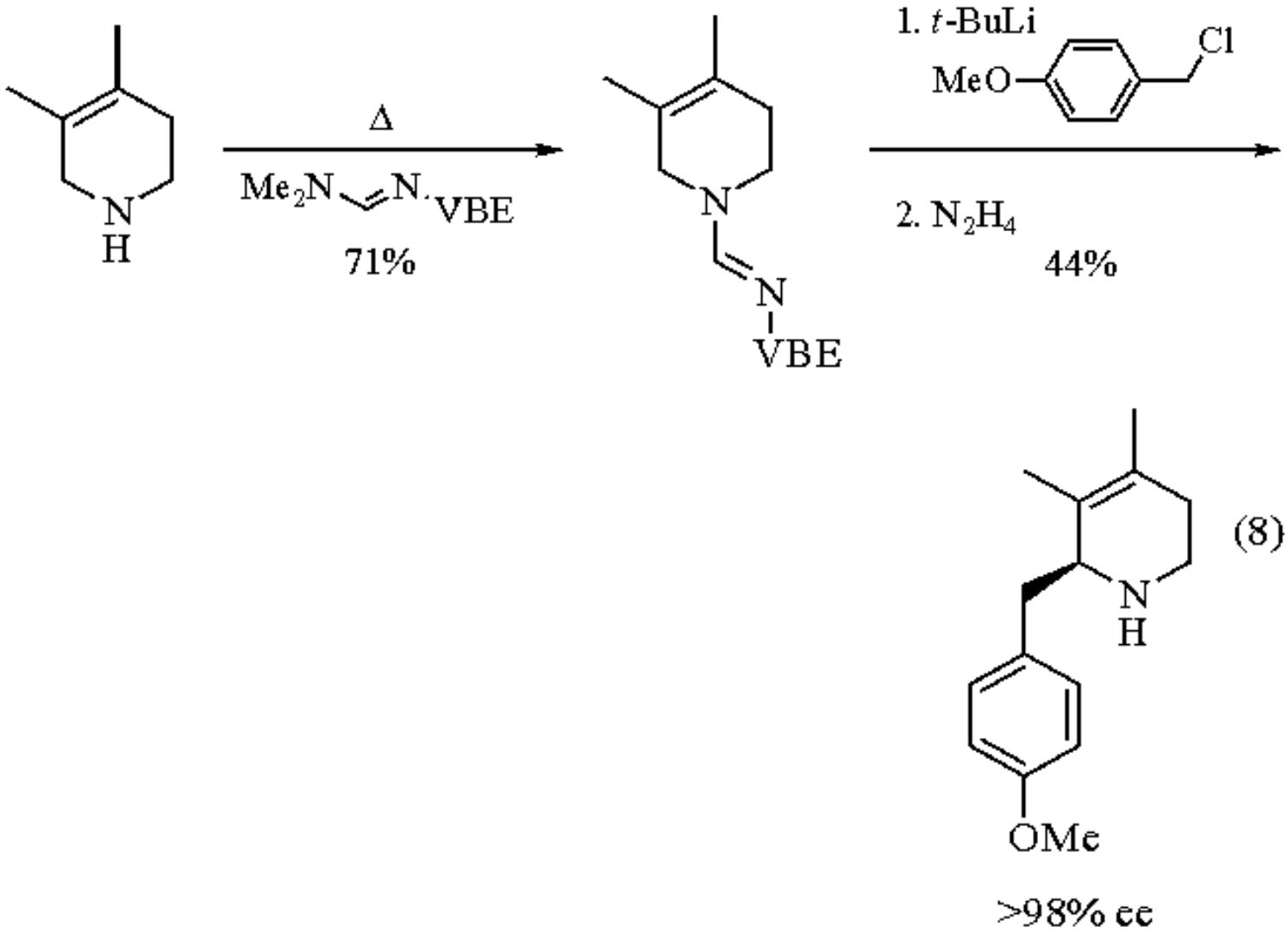

The mechanistic process of these asymmetric alkylations and the configurational stability of the chiral lithioformamidines have been investigated.[8] A limitation of this strategy is that saturated, cyclic, secondary amines (e.g. pyrrolidines and piperidines) cannot be successfully alkylated in an asymmetric fashion.

Related Reagents.

N-t-Butoxycarbonyl-N-methylaminomethyllithium; ***N´-t-Butyl-N,N-dimethylformamidine***; ***N´-t-Butyl-N-methyl-N-trimethylsilylmethylformamidine***; ***N,N-Dimethylformamide Diethyl Acetal***; ***(R)-Methyl 2-t-Butyl-3(2H)-oxazolecarboxylate***; ***N-Nitrosodimethylamine***.

---

1. (a) Meyers, A. I. *T* **1992**, *48*, 2589. (b) Meyers, A. I.; Highsmith, T. K. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1990. (c) Meyers, A. I. *Aldrichim. Acta* **1985**, *18*, 59. (d) Meyers, A. I. *H* **1984**, *21*, 360.
2. (a) Dickman, D. A.; Boes, M.; Meyers, A. I. *OSC* **1993**, *8*, 204. (b) Meyers, A. I.; Boes, M.; Dickman, D. A. *OSC* **1993**, *8*, 573.
3. (a) Meyers, A. I.; Hutchings, R. H. *T* **1993**, *49*, 1807. (b) Meyers, A. I.; Elworthy, T. R. *JOC* **1992**, *57*, 4732.
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J. W.; Meyers, A. I. *JOC* **1991**, *56*, 6873. (e) Meyers, A. I.; Sielecki, T. M. *JACS* **1991**, *113*, 2789. (f) Gottlieb, L.; Meyers, A. I. *JOC* **1990**, *55*, 5659. (g) Meyers, A. I.; Guiles, J. *H* **1989**, *28*, 295.
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3,3-Dimethyl-1-butynylcopper(I)

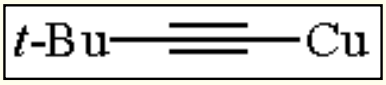

[40575-23-3] · C_6H_9Cu · 3,3-Dimethyl-1-butynylcopper(I) · (MW 144.70)

(used in preparation of mixed cuprates; acts as weak nucleophile)

Alternate Names: *t*-butylethynylcopper(I); copper(I) *t*-butylacetylide.

Physical Data: orange solid; mp 80-150 °C (dec).

Solubility: sol ether, saturated hydrocarbons.

Preparative Methods: most conveniently prepared in situ by treatment of 3,3-dimethyl-1-butyne with ***n-Butyllithium***, followed by addition of ***Copper(I) Iodide*** or the $Me_2S.CuBr$ complex (see ***Copper(I) Bromide***).[1,2] 3,3-Dimethyl-1-butynylcopper(I) (**1**) can be isolated as a solid by addition of 3,3-dimethyl-1-butyne to a premixed solution of ***Copper(II) Sulfate*** and ***Hydroxylamine*** hydrochloride in aqueous ammonia. The aqueous layer is decanted and the precipitate is extracted with pentane. After workup, (**1**) is collected upon concentration of the solvent. Alternatively, (**1**) has been prepared by photoreduction of ***Copper(II) Acetylacetonate*** in the presence of 3,3-dimethyl-1-butyne.[3]

Handling, Storage, and Precautions: air and moisture sensitive. Use in a fume hood.

Weak Nucleophile.

Alkynyl organocopper reagents are weak nucleophiles; however, (**1**) will react with pivaloyl chloride to give 2,2,6,6-tetramethyl-4-heptyn-3-one (**2**) in 69% yield (eq 1).[4] The more reactive higher-order cuprate (**3**), formed from (**1**) and 2 equiv of lithium *t*-butylacetylide, transfers a *t*-butylacetylene group to phosphonoamine (**4**), affording alkynylamine (**5**) in 60% yield (eq 2).[5]

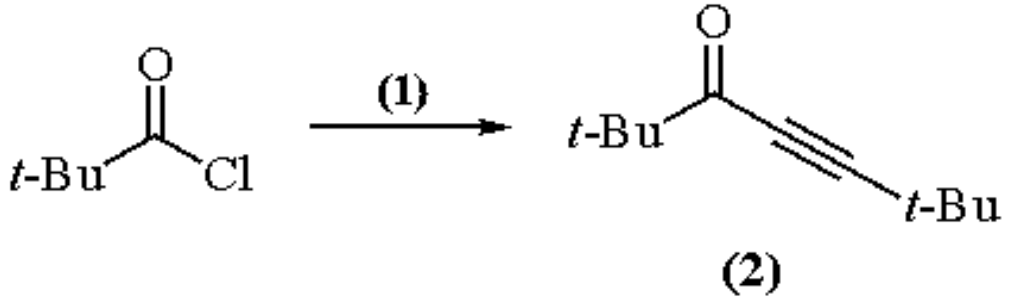

(1)

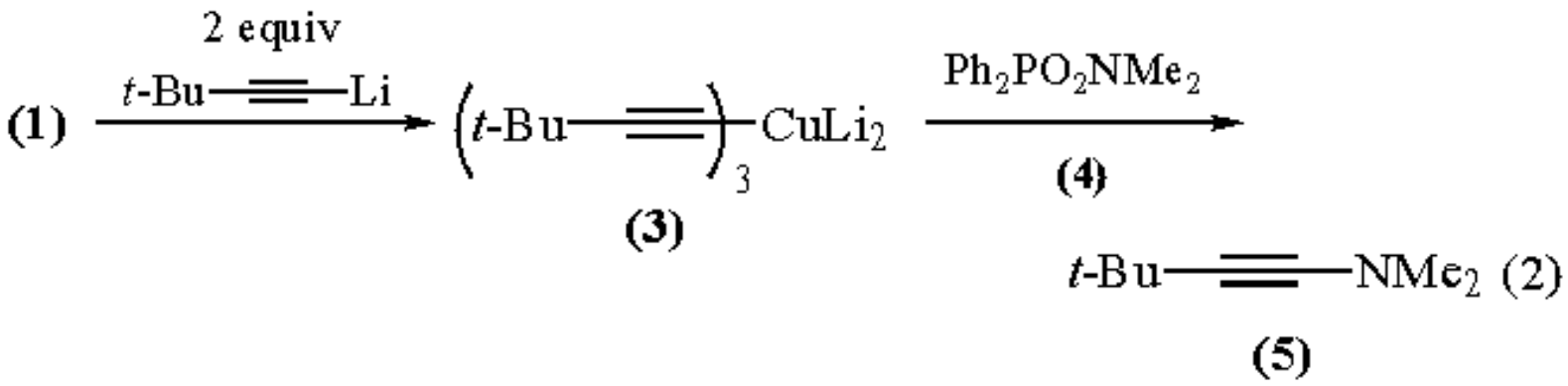

Other attempts at electrophilic transfer of a *t*-butylacetylene group are not as successful. Treatment of (**1**) with ***Cyanogen Bromide*** does not produce the desired nitrile (**6**); instead, bis-alkyne (**7**) is the only product isolated (eq 3).[6] The cuprate prepared from (**1**) and butylmagnesium bromide reacts slowly with benzoyl chloride, affording only a moderate yield (28%) of ketone (**8**) (eq 4).[7]

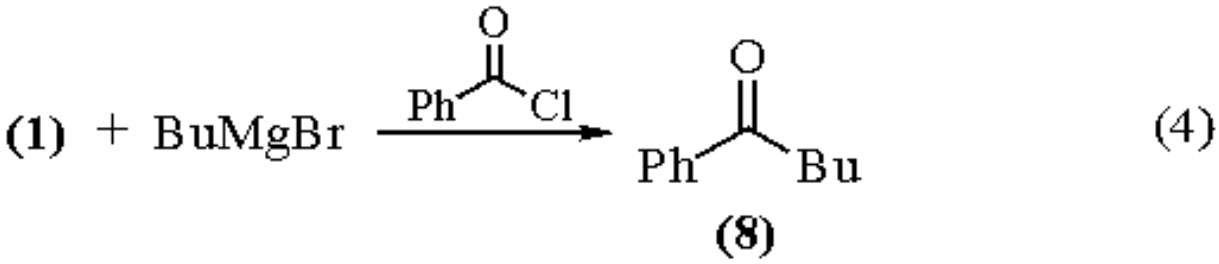

Mixed Organocuprates.

The title reagent is most commonly used for the in situ preparation of mixed cuprates. Alkynes bind tightly to copper, allowing selective transfer of a synthetically valuable primary, secondary, or vinylogous lithium reagent.[1,8] The *t*-butylacetylene ligand offers several advantages, including good solubility in ether and THF, thermal stability allowing reactions to be run at 0 °C, and volatile, easily removed byproducts. The first examples demonstrated the transfer of methyl and vinyl substituents to isophorone (**9**) (eq 5).[1] More complex groups include the α-acrolein anion equivalent (**12**), which adds in 1,4-fashion to enones in excellent yields (eq 6).[9,10]

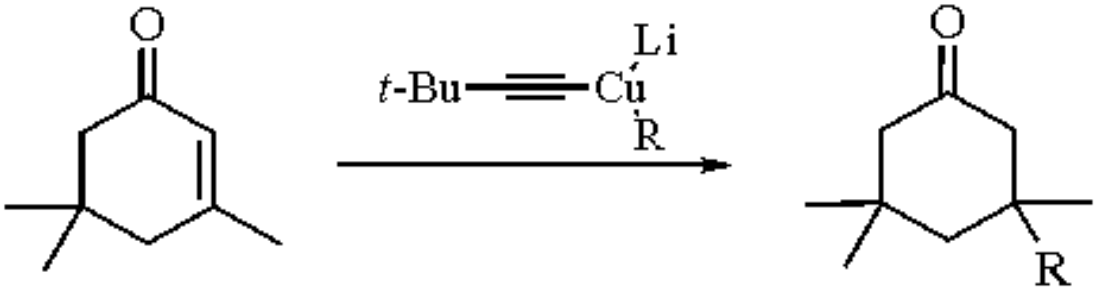

(5)

(9)

(10) R = Me, 76%
(11) R = vinyl, 52%

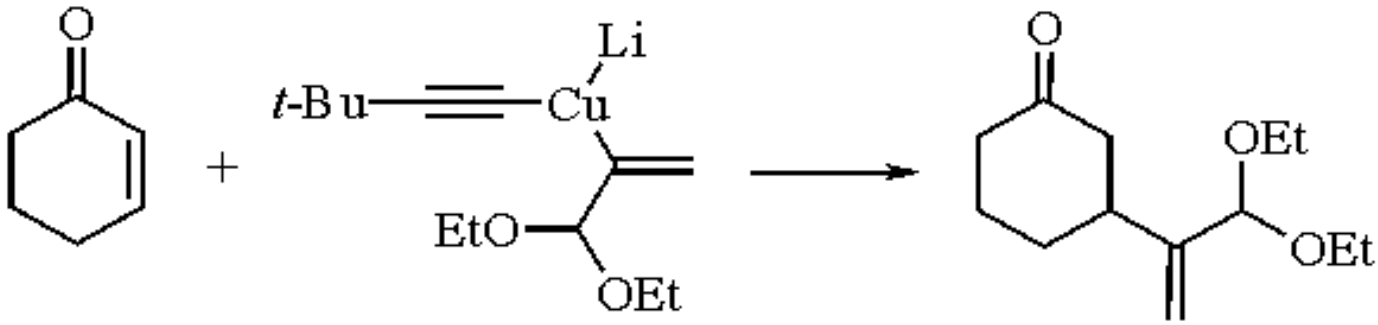

(6)

(12) **(13)**

Mixed cuprates derived from (**1**) have been used in natural product total synthesis. 1,4-Addition of the cyclopropylcuprate (**14**) to 2-cyclohexen-1-one provided adducts (**15**) and (**16**) in a 3.1:1 ratio in 45% yield (eq 7). The *threo* adduct (**15**) can then be converted to (±)-*threo*-juvabione (**17**) in several steps.[11] The 1-heptenyl cuprate (**19**) reacts with primary iodide (**18**) to give alkene (**20**), with complete retention of the *cis* stereochemistry, in 36% yield with a 25% recovery of (**18**). Intermediate (**20**) can then be taken forward in a synthesis of LTB_4 (**21**) (eq 8).[12]

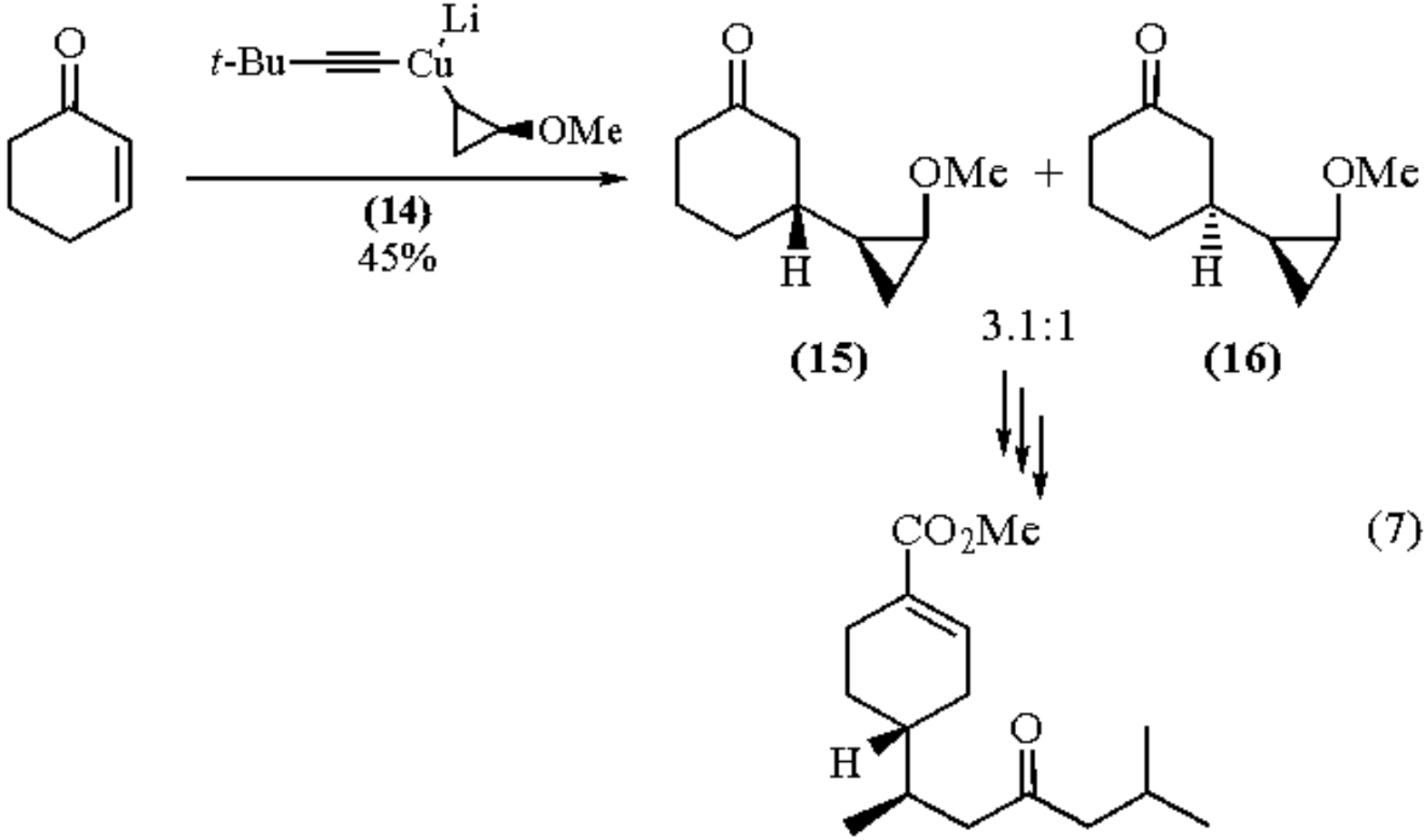

(17) (±)-*threo*-Juvabione

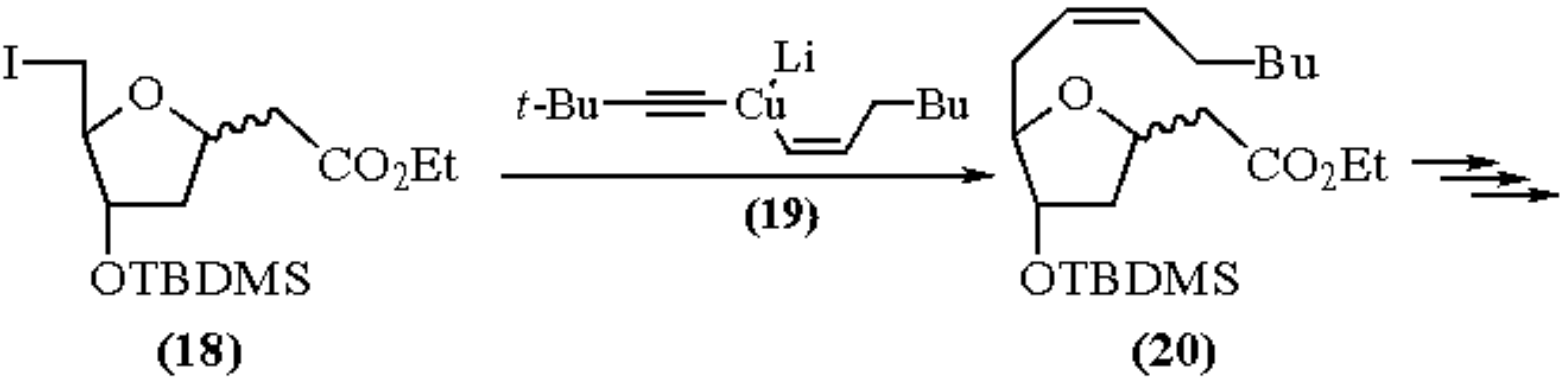

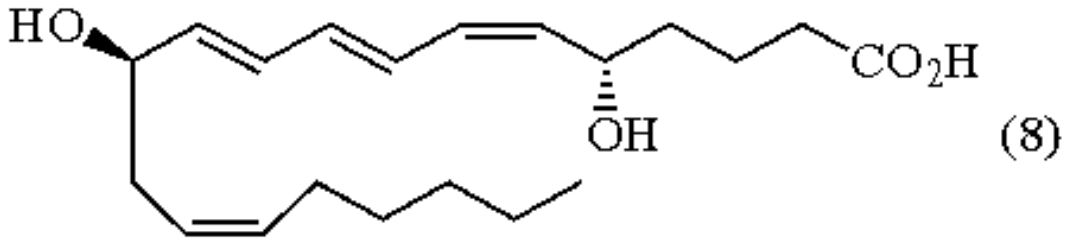

(21) LTB_4

Related Reagents.

Lithium (3,3-Dimethyl-1-butynyl)methylcuprate; ***Lithium (3,3-Dimethyl-1-butynyl)vinylcuprate***; ***Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate***; ***(3-Methoxy-3-methyl-1-butynyl)copper(I)***; ***3-Methyl-3-buten-1-ynylcopper(I)***.

---

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Matthew E. Voss

The Du Pont Merck Pharmaceutical Company, Wilmington, DE, USA

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Dimethylcarbamoyl Chloride

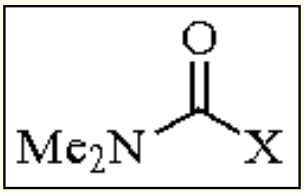

(**1**; X = Cl)

[79-44-7] · C_3H_6ClNO · Dimethylcarbamoyl Chloride · (MW 107.55) (**2**; X = F)

[431-14-1] · C_3H_6FNO · Dimethylcarbamoyl Fluoride · (MW 91.10)

(convenient source of the dimethylaminocarbonyl unit; introduction of carbamates as directing groups)

Alternate Names: DMC-Cl; dimethylcarbamic chloride; dimethylcarbamyl chloride; *N,N*-dimethylaminocarbonyl chloride.

Physical Data: (**1**) bp 165-167 °C; bp 55-57 °C/11 mmHg; *d* 1.678 g cm^{-3}. (**2**) bp 54-56 °C/51 mmHg.

Form Supplied in: both halides are colorless liquids; the chloride is widely available; the fluoride is not commercially available.

Handling, Storage, and Precautions: the liquid chloride decomposes on exposure to moist air or water and is usually kept under argon or nitrogen. Distillation at reduced pressure is recommended to prevent decomposition. It is a powerful lachrymator and a confirmed carcinogen and mutagen. Extreme care should be taken to avoid inhalation or skin contact. When heated to decomposition, toxic fumes containing CO, HCl, and NO_x are emitted. Use in a fume hood.

Source of the Dimethylaminocarbonyl Unit.

The chemistry of dimethylcarbamoyl chloride (DMC-Cl) parallels that of acid chlorides in that the chloride can be replaced by other nucleophiles.[1,2] However, these reactions are generally not as facile as their acid halide counterparts. Some reactions proceed via a trace equilibrium component, the more reactive dimethylaminoacylium ion (Me_2+N=C=O Cl^-). As a consequence, DMC-Cl is both less reactive and less selective than acid halides when reacted with substrates containing more than one nucleophilic site.[3,4] Reaction of DMC-Cl with alcohols (phenols), amines, and thiols affords the respective carbamates, ureas, and thiocarbamates (eq 1), which classically exhibit significant bioactivities.[5] Thus many important pharmaceuticals and especially agricultural biocides contain the DMC unit.[5,6] In these acylations, pyridine often is the preferred acid scavenger.[7] Like acid chlorides, DMC-Cl activates imine functions

in the synthesis of heterocycles (eq 2).[8]

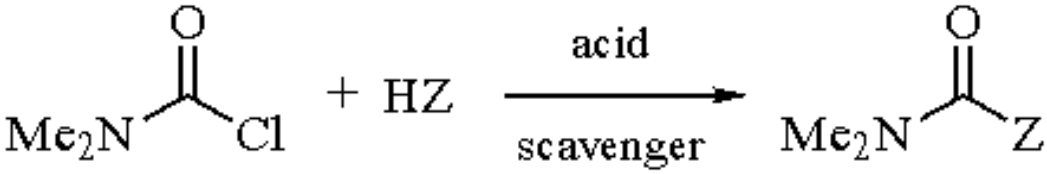

(1)

Z = OR, OAr, NR_2, SR, etc.

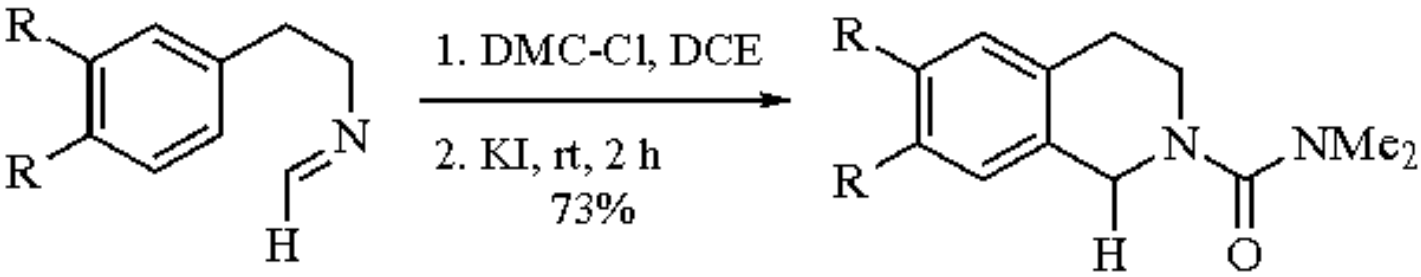

(2)

R = OMe

Dimethylamides are available by heating DMC-Cl with alkali carboxylates.[9] Presumably an intermediate carbamic carboxylic anhydride loses CO_2. Aryl carboxamides also have been made from DMC-Cl by Friedel-Crafts acylation of arenes.[10] By including a hydrolysis step, this is a general route to aromatic carboxylic acids. Alkynylamides are available by a palladium-catalyzed condensation of terminal alkynes with DMC-Cl (eq 3).[11] Conjugated aldehydes react with carbamoyl chlorides to form dienyl carbamates (eq 4), which have been used as dienes in the Diels-Alder reaction.[4,12] After formation of the Diels-Alder adduct, the carbamate can be converted to the allylic alcohol by ***Lithium Aluminum Hydride*** reduction.[12]

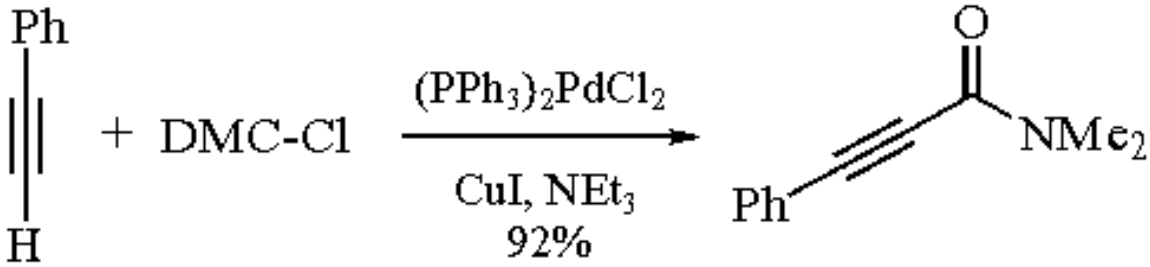

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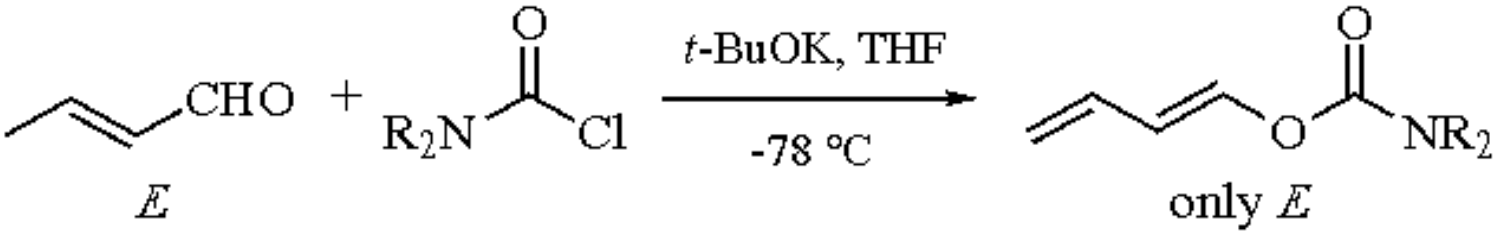

(4)

Eliminations.

The reagent also has been used to dehydrate primary amides to nitriles.[13] Tetramethylformamidinium chloride is

formed by the condensation of DMF with DMC-Cl.[14] This is the key intermediate in the synthesis of ***Tris(dimethylamino)methane***,[15] a reagent used to introduce enamine functions in compounds containing activated methylene groups (eq 5).[16]

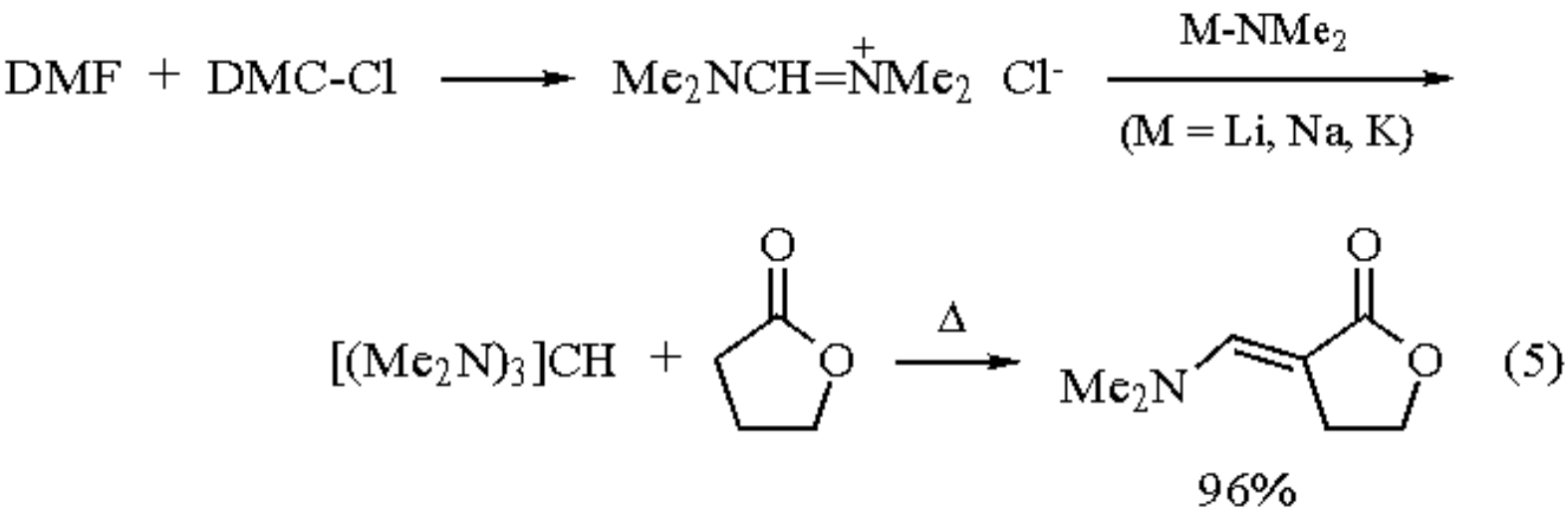

Carbamates as Directing Groups.

Deprotonation of aryl and many heteroaromatic carbamates with RLi/TMEDA occurs regioselectively at the *ortho* site. Subsequent treatment of the lithiated intermediates with electrophiles has yielded an enormous variety of *ortho*-substituted products in excellent yield (eq 6).[17] In an extension of this reaction the product is treated with a Grignard reagent in the presence of Ni^0 catalyst to replace the carbamate function. This latter reaction also works well without the prior *ortho* substitution step (eq 7).[18] Allylic and benzylic carbamates undergo similar substitution (eq 8)[19] and α-lithiation of *O*-vinyl carbamates recently has been demonstrated (eq 9).[20] In these processes, *N*,*N*-diethyl- and *N*,*N*-diisopropylcarbamates generally react more cleanly (also, in eq 8, the ratio of α to γ products is 5:95 with the NEt_2 reactant).[17-20] With lithioallyl *N*,*N*-diisopropylcarbamates, regio- and stereoselective homoaldol type additions have even been achieved via titanates.[19]

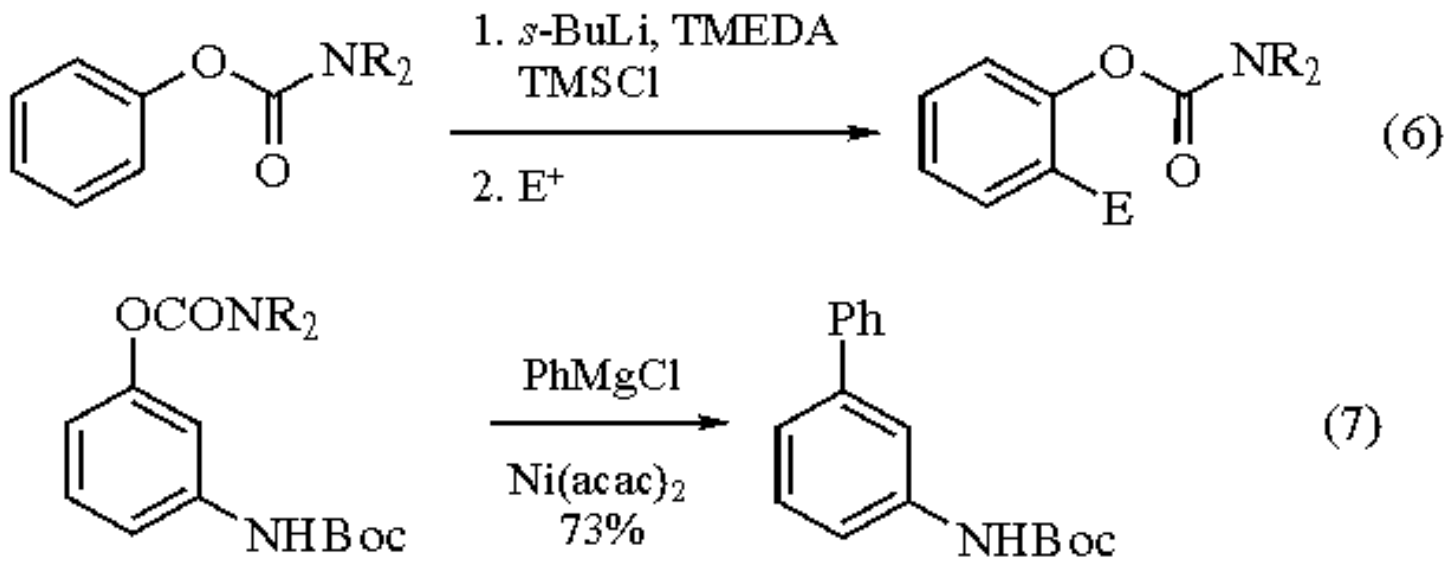

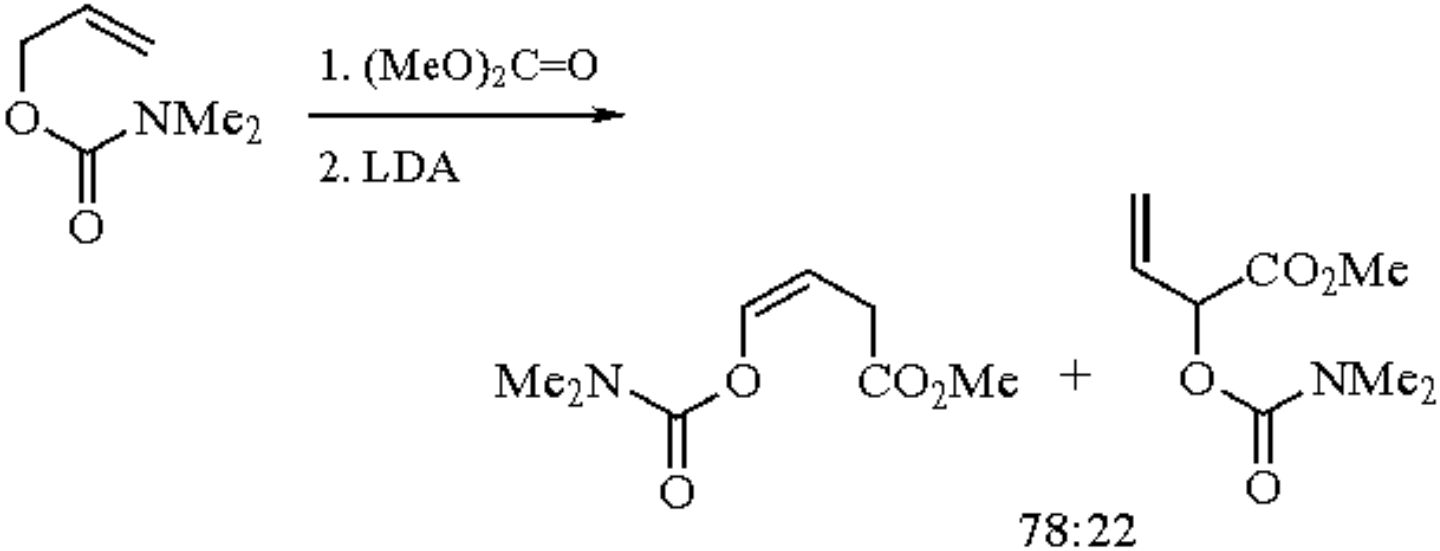

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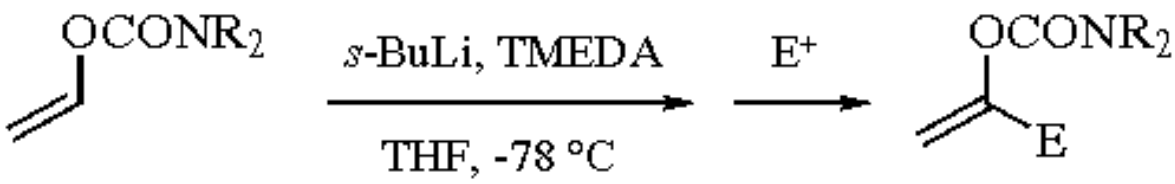

(9)

The DMC-Cl derived carbamates of cyclic allylic and homoallylic alcohols are epoxidized with ***m-Chloroperbenzoic Acid*** with high *syn* stereoselectivity (eq 10).[21] The carbamate function has also been used to direct the stereochemical course of Grignard additions to ketones by a chelation control mechanism (eq 11).[12] In the reaction depicted the diastereofacial selectivity is 100%; the product (R^2 = -$(CH_2)_2CH{=}CMe_2$) is an intermediate on the route[12] to the sesquiterpene hernandulcin, which is over 1000 times sweeter than sucrose.[22]

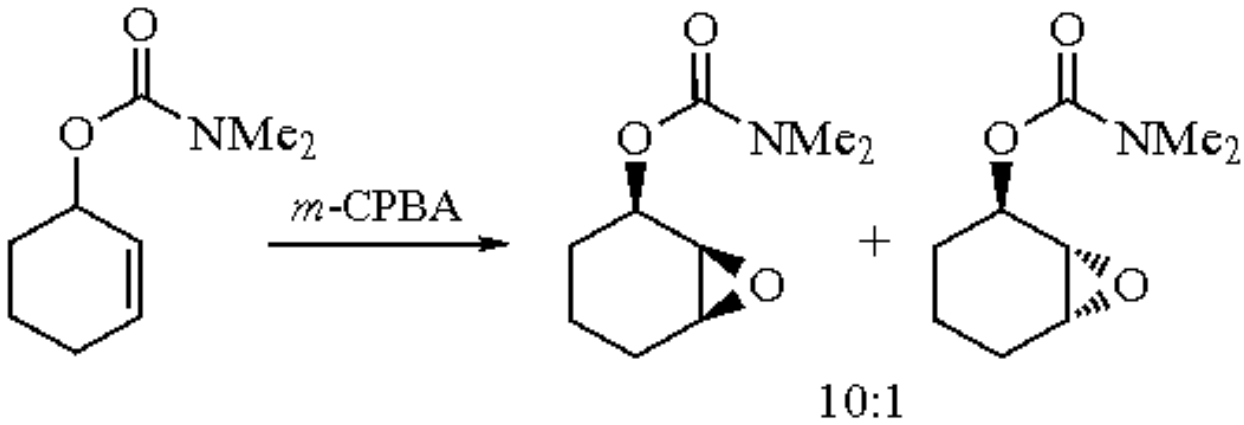

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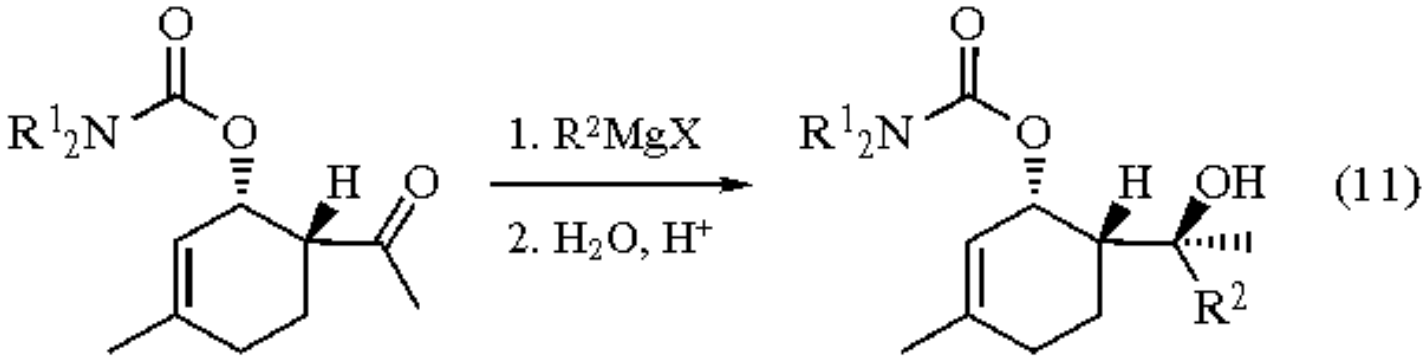

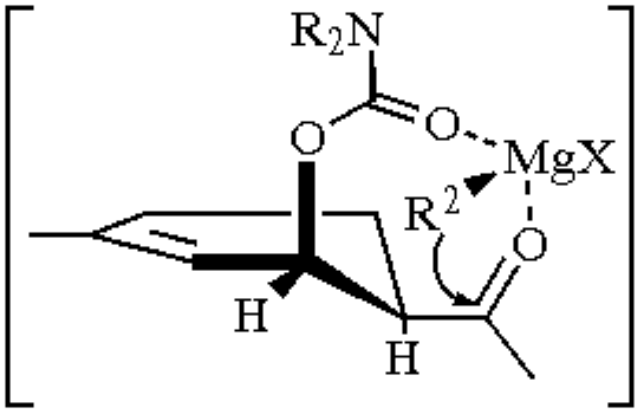

Dimethylcarbamoyl Fluoride.

The reagent is prepared directly from DMC-Cl by halide exchange; IR (CCl_4) 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (s). While an equilibrium process is involved, the thermodynamics overwhelmingly favor the acyl fluoride. Many fluoride sources have been utilized.[23] However, in the most efficient preparation (95% yield), DMC-Cl is stirred neat with ***Potassium Fluoride*** activated by 4 mol % ***18-Crown-6*** at rt (reaction monitored by IR).[24] Alternatively, an acetonitrile suspension of DMC-Cl and KF-CaF_2 is stirred at 50 °C for 24 h.[25]

There normally is little advantage in using DMC-F in place of the chloride as an acylating agent. An exception is the reaction of trimethylsilyl (TMS) protected anions which undergo electrophilic carbodesilyations in the presence of a catalytic amount of naked F^-. This scheme has been used to stereospecifically convert enol silyl ethers to vinyl carbamates (eq 12).[26] The *O*-acylation is catalyzed by $PhCH_2$+NBu_3 F^- (BTAF) and has been performed with enol silyl ethers from aldehydes and aliphatic, aromatic, and conjugated ketones.[26] A similar process has been utilized to obtain the hindered pyrazolecarboxylic acid from 1-methylpyrazole (eq 13).[27] The greater acidity of HC(5) accounts for the success of the first step of this synthesis (for H/D exchange in NaOMe/MeOD at 139 °C, the relative rate constants (k_2´) are HC(3) = 1, HC(4) = 2, HC(5) = 1500).[28]

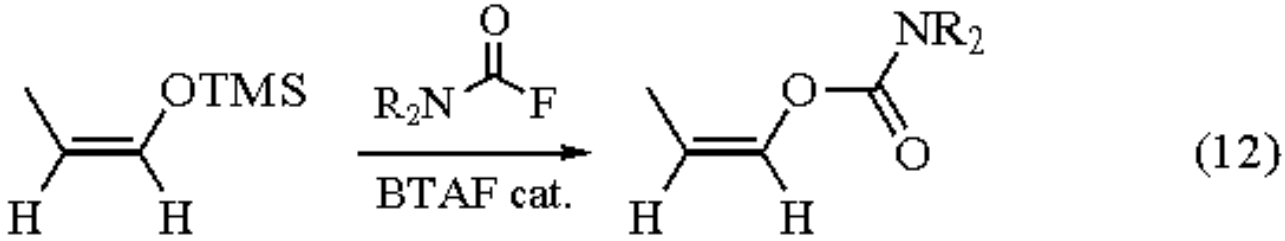

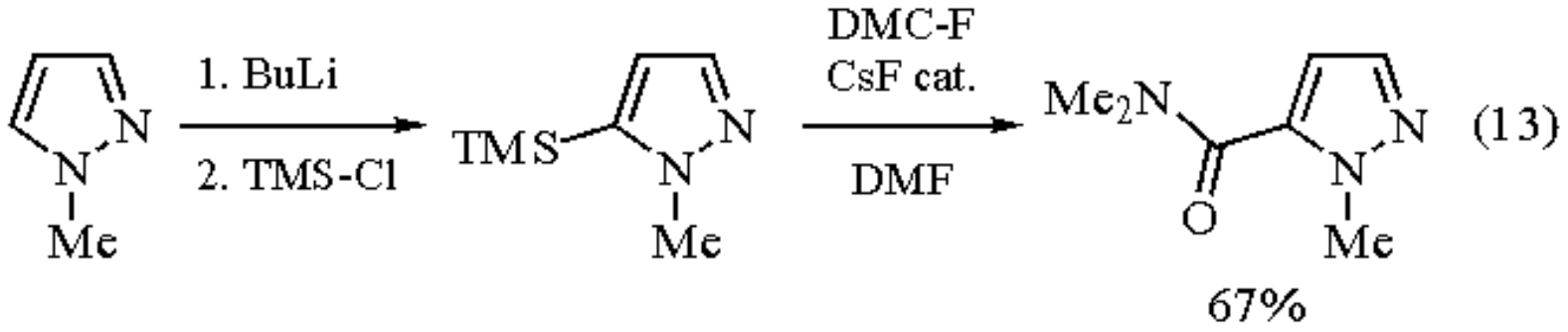

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Dimethylchloromethyleneammonium Chloride

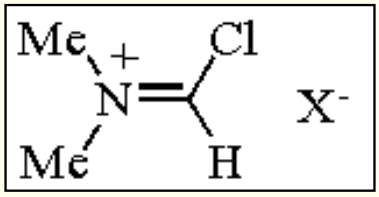

(**1**; X = Cl)

[3724-43-4] · $C_3H_7Cl_2N$ · Dimethylchloromethyleneammonium Chloride · (MW 128.01) (**2**; X = PO_2Cl_2)

[21382-90-1] · $C_3H_7Cl_3NO_2P$ · Dimethylchloromethyleneammonium Dichlorophosphate · (MW 226.43)

(formylation of arenes,[1-3] heterocycles,[1-3] and alkenes;[2,3] conversion of alcohols into chlorides,[4] and carboxylic acids into acid chlorides;[5] preparation of β-chlorovinyl aldehydes,[3,6] cyclic β-chloro-α,β-unsaturated ketones,[7] and the conversion of acyclic precursors into ring systems[8])

Alternate Names: Vilsmeier reagent; Arnold's reagent.

Physical Data: (**1**) mp 132 °C (dec).

Solubility: fairly sol polar solvents.

Form Supplied in: the chloride (**1**) is a white hygroscopic powder and is commercially available. The dichlorophosphate (**2**) is made in situ.

Preparative Methods: ***Thionyl Chloride***,[4b] ***Oxalyl Chloride***,[5] or ***Phosgene*** is added slowly to ***N,N-Dimethylformamide***, with cooling, to give the chloride (**1**) (eq 1). A solvent (typically dichloromethane,[5] chloroform, or 1,1,2-trichloroethylene)[9] may be used, and is advisable for large scale preparations.

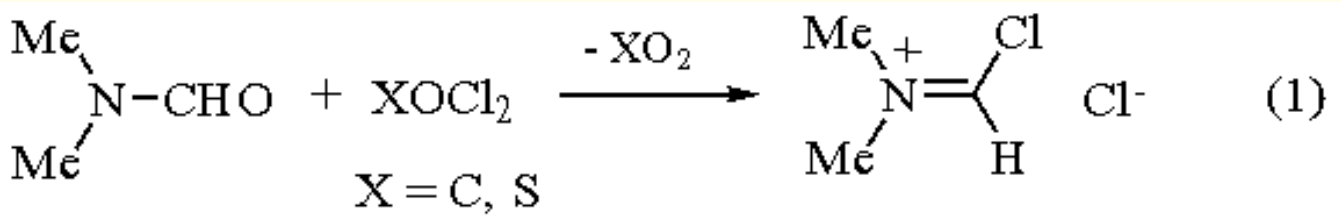

The most commonly used Vilsmeier reagent is that formed by adding ***Phosphorus Oxychloride*** to DMF, to give dimethylchloromethyleneammonium dichlorophosphate (**2**).[9] Reagent (**2**) is more reactive than reagent (**1**). Recent reports suggest that DMF-***Pyrophosphoryl Chloride*** ($P_2O_3Cl_4$) gives an even more reactive iminium intermediate (eq 2) than either salt (**1**) or salt (**2**).[10]

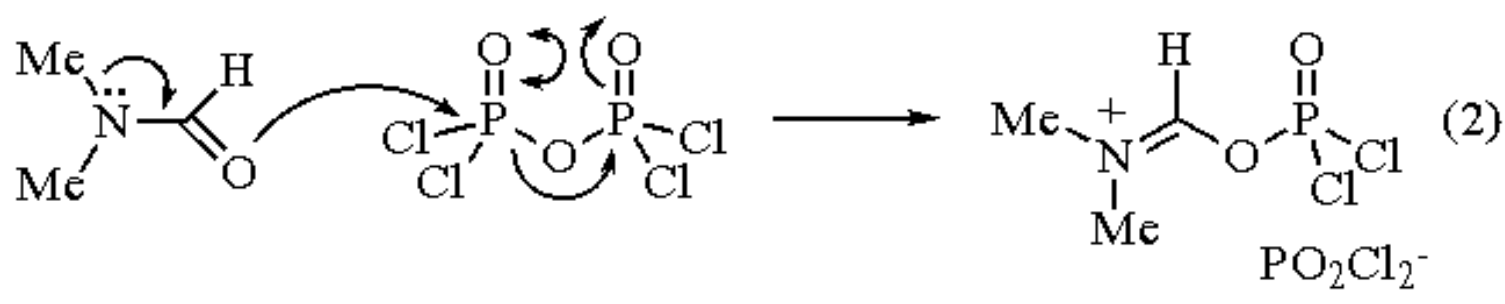

Handling, Storage, and Precautions: the chloride (**1**) is hygroscopic. DMF is an irritant and is harmful by skin absorption. The halogenating agents (thionyl chloride, phosgene, phosphorus oxychloride, etc.) are all corrosive and lachrymatory. Use in a fume hood.

Conversion of Alcohols into Chlorides.

Reagent (**1**) has been used to convert alcohols into chlorides in moderate to high yields.[4] An alternative Vilsmeier reagent derived from *N*,*N*-diphenylbenzamide-oxalyl chloride has been used for the same transformation. Sensitive groups, such as acetals, are not affected by the reaction conditions (eq 3) and the yields are high.[11]

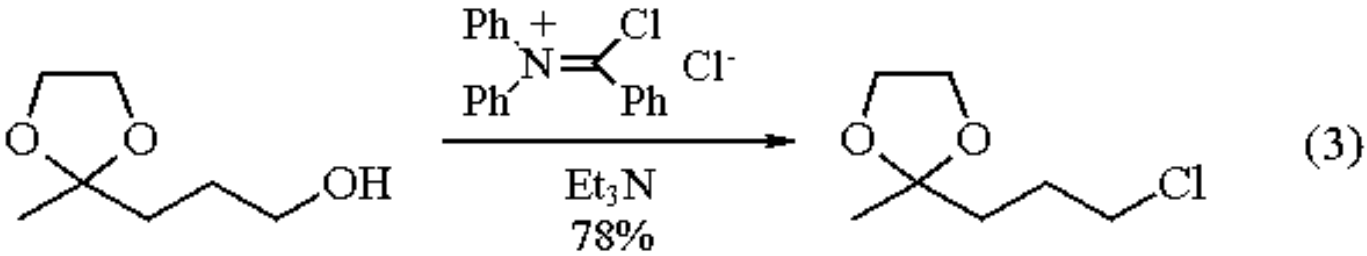

Conversion of Carboxylic Acids to Acid Chlorides.

Reagent (**1**) has been used to convert a wide variety of carboxylic acids into acid chlorides.[5] A catalytic quantity of DMF may be used; thus isobutyric acid is converted into isobutyroyl chloride (89%) upon treatment with DMF (3 mol %) and phosgene.[5c]

Formylation of Arenes and Heterocyclic Systems.

Reagent (**2**) is the most commonly used Vilsmeier reagent for formylation of arenes and heterocycles. The subject has been extensively reviewed.[1-3] The formylation process is general for all activated aromatic systems (e.g. pyrene, anthracene, azulene, ferrocene, and *N*,*N*-dimethylaniline)[12a] and electron-rich heterocyclic systems (e.g. thiophenes, indoles,[12b] furans, and pyrroles (eq 4)).[12c] Formylations continue to be regularly reported in the literature.[13] However, simple aromatic hydrocarbons such as benzene and toluene do not react with Vilsmeier reagents, although the adduct formed from DMF-***Trifluoroacetic Anhydride*** has been used to formylate some unactivated aromatic hydrocarbons, e.g. naphthalene (50%) and 1,3,5-trimethylbenzene (60%).[14] DMF-$P_2O_3Cl_4$ has been reported to be a good formylating agent.[10] The time and temperature of the reaction, and the stoichiometry of the reagent, can be crucial to the outcome of

the reaction.

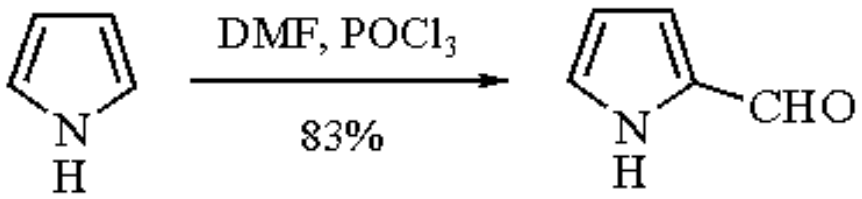

(4)

Formylation of Alkenes.

Activated alkenes, e.g. styrene, undergo formylation by DMF-$POCl_3$, usually giving α,β-unsaturated aldehydes in high yields.[3,15] 1-Aryl-1,3-butadienes are similarly formylated.[16] Simple alkenes can give complex products as a result of a series of reactions. Thus isobutene affords a trimethinium salt after repeated iminoalkylation (eq 5).[17] However, by using *N*-formylmorpholine (NFM)-$POCl_3$, alkenes have been successfully monoformylated (eqs 6 and 7).[18]

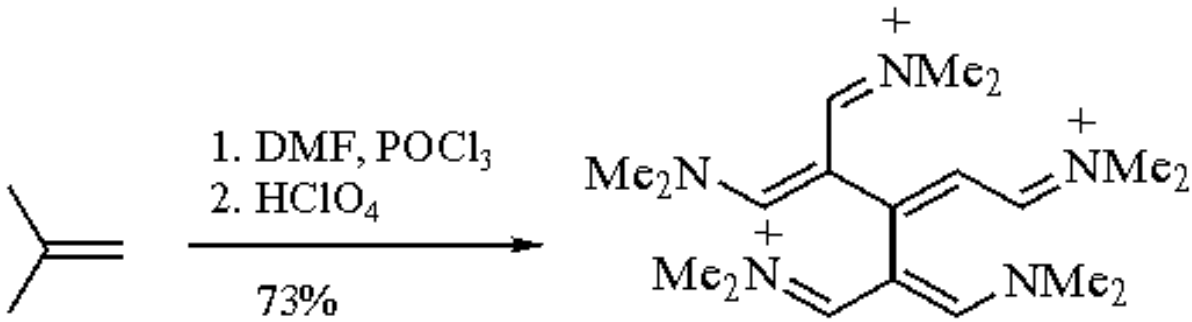

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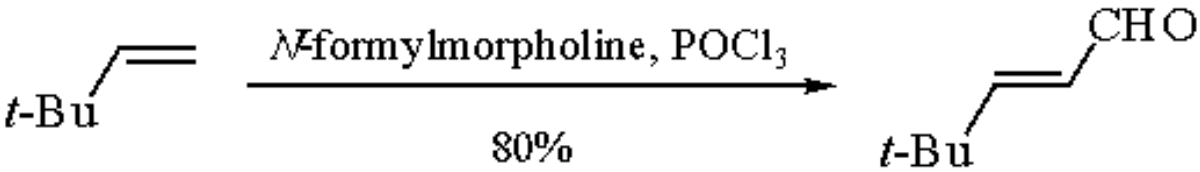

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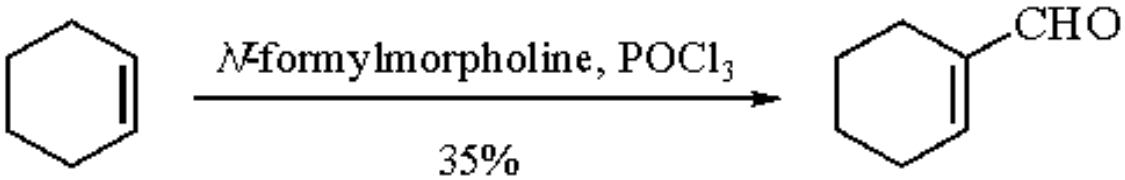

(7)

Depending upon the reaction conditions and the structure of the alkene, isomerization of the carbon-carbon double bond may occur prior to formylation (eq 8).[19]

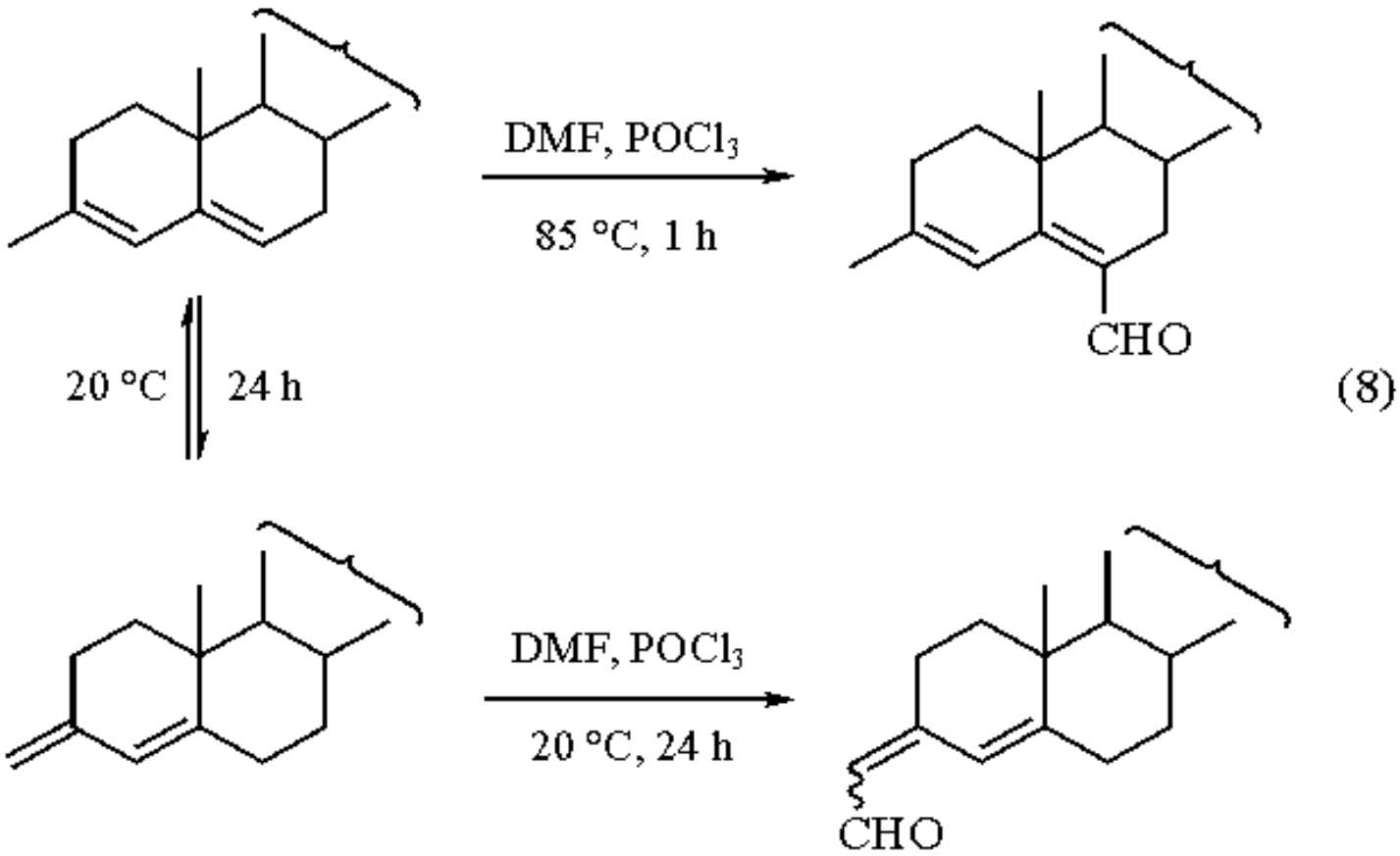

Silyl enol ethers react with DMF-$POCl_3$ to give α-formyl carboxylic esters.[20]

Reaction of Carbonyl Compounds with DMF-$POCl_3$.

This subject has been extensively reviewed.[21] Methyl and methylene ketones are the most studied classes of compound; they afford β-chlorovinyl aldehydes (β-CVAs) when allowed to react with DMF-$POCl_3$ (eq 9). Acyclic, cyclic, heterocyclic, and benzo-fused ketones all give β-CVAs, which have proved to be useful intermediates in organic synthesis.[3] The chlorine atom is readily displaced by nucleophiles and the aldehyde can then be transformed by means of condensations, reaction with Grignard reagents, or Wittig reagents. Condensations involving the aldehyde group, followed by base-catalyzed cyclization, allows the formation of a wide variety of heterocycles, e.g. thiophenes, isoxazoles (eq 10), pyrimidines (eq 10), and pyrazoles.[3,22] More than 50 different ring systems have been synthesized using Vilsmeier methodology.[22]

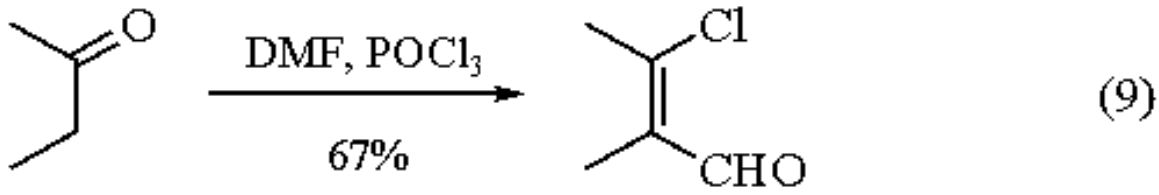

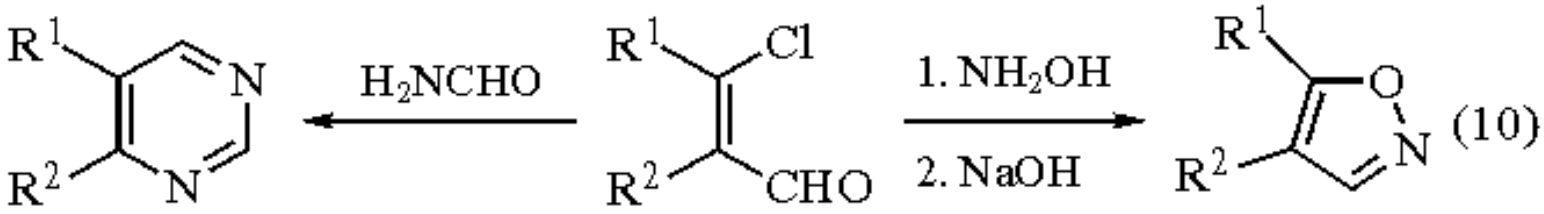

β-CVAs can be hydrogenated to give saturated aldehydes, allowing the introduction of an aldehyde β with respect to the original ketone function (eq 11).[23]

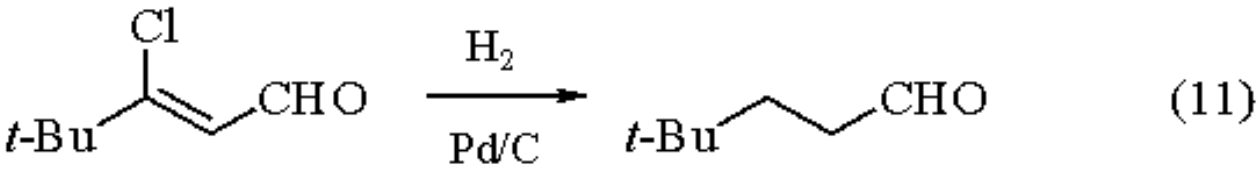

β-CVAs have been used as dienophiles in Diels-Alder reactions.[24] Treatment of β-CVAs with strong aqueous base affords alkynes.[25] The chlorine atom can be removed using ***Zinc*** in ethanol,[26a] or hydrogen over ***Palladium on Carbon*** in the presence of ***Triethylamine***,[26b] giving α,β-unsaturated aldehydes.

Reaction of 1,3-Diketones.

Salt (**1**) reacts with cyclic 1,3-diketones, giving β-chloro-α,β-unsaturated ketones.[7] Cyclic 1,3-diketones can give bis-β-CVAs upon treatment with reagent (**2**).[27] 2,4-Pentanedione gave 2,4-dichlorobenzaldehyde on reaction with DMF-$POCl_3$ (eq 12),[28] and 2,4-dichloro-1,3-benzene dicarbaldehyde on reaction with the adduct from NFM-$POCl_3$ (eq 13).[27b]

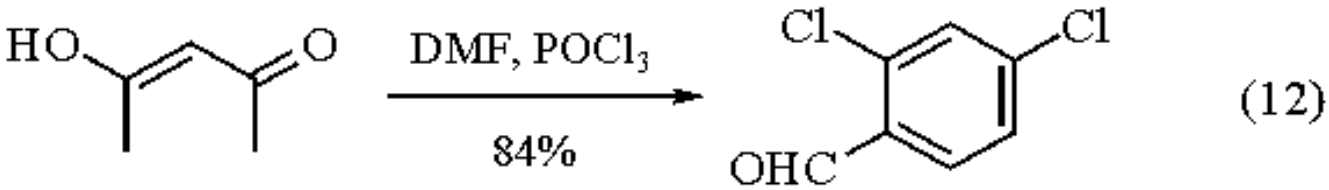

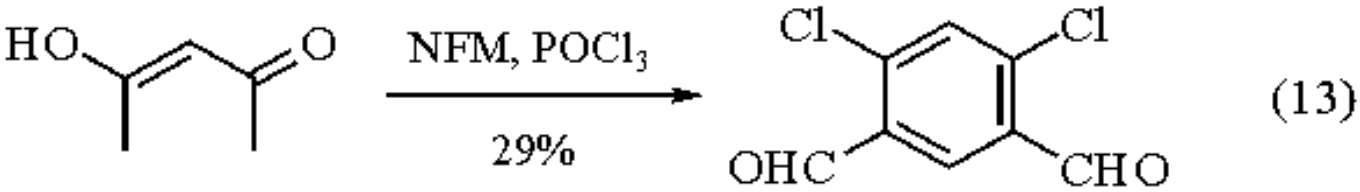

Epoxidation of Alkenes.

When reagent (**1**) is treated with ***Hydrogen Peroxide*** the reagent (**3**) is formed, which is capable of epoxidizing alkenes.[29] However, the selectivity of reagent (**3**) is poor, and chlorinated products are also obtained. The yields and selectivity are improved by reacting alkenes with the intermediate (**4**), obtained from *N*-methylpyrrolidine-$POCl_3$ and H_2O_2.[30] Little chlorination of the alkene was noted and no Baeyer-Villiger products were identified from ketone-containing substrates. Acetals are not cleaved under the reaction conditions. Epoxidation occurs at the most substituted carbon-carbon double bond (eq 14).[30]

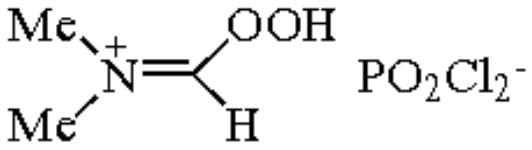

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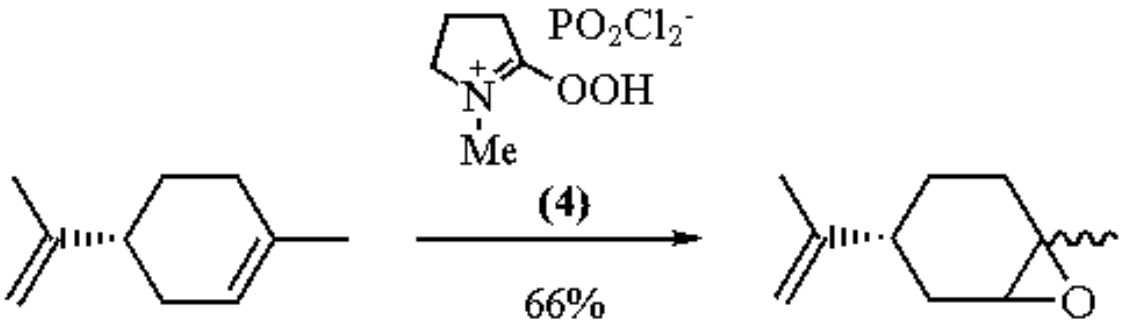

(14)

Cyclizations under Vilsmeier Conditions.

A large number of substrates undergo cyclization in the presence of DMF-$POCl_3$ and other Vilsmeier reagents.[8] The outcome of the reaction often depends upon the reaction time and temperature, and the nature of the Vilsmeier species. For example, benzylacetamides give quinolines and related systems; the nature of the product depends upon the conditions used (eq 15).[31]

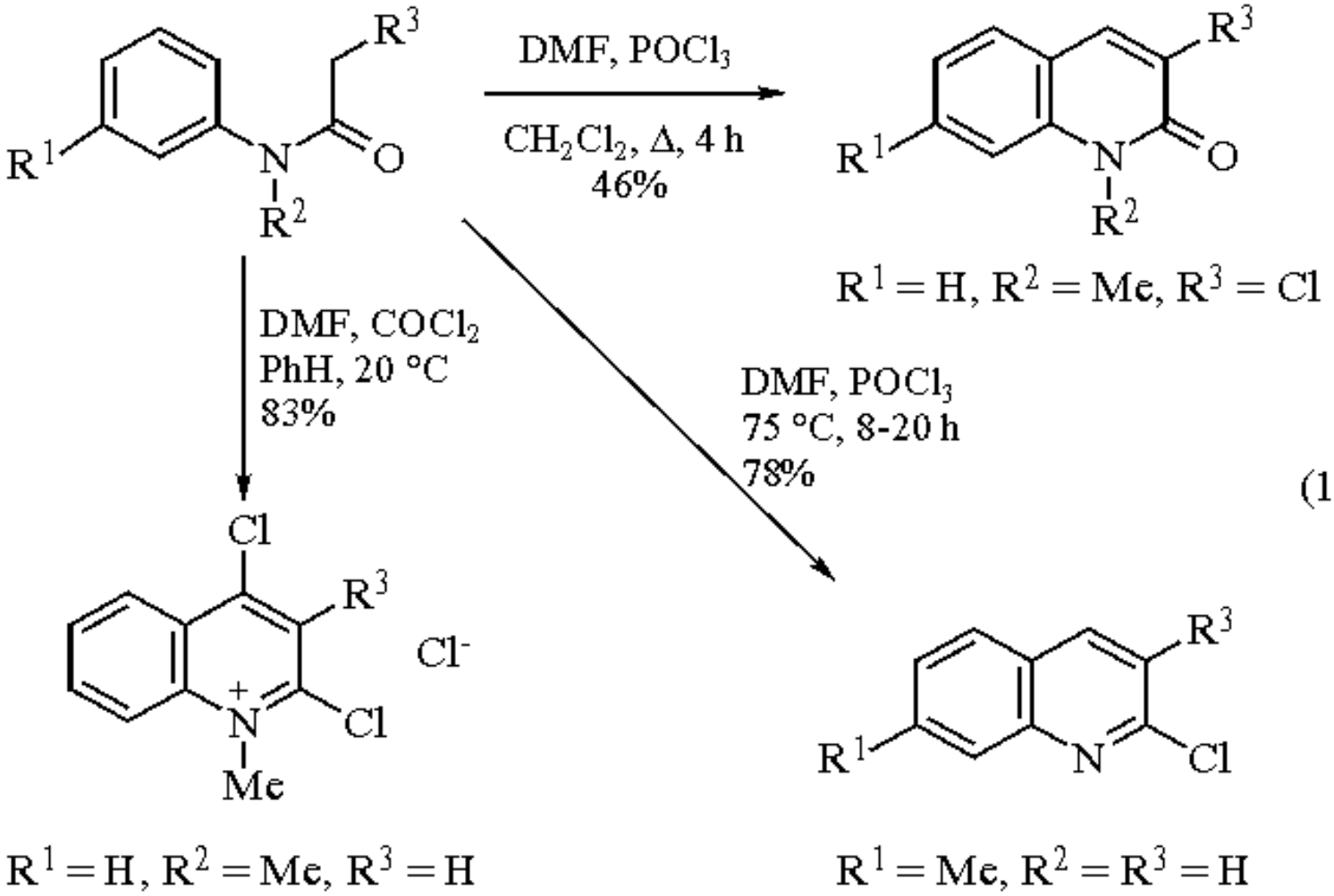

2-Hydroxyacetophenones give 3-formylchromones.[32] Aryl benzyl ketones have been converted into 2-aryl-1,3-dichloroindenes.[33] Alkylidenemalononitriles give 2-chloro-3-cyanopyridines.[34] Unsaturated alcohols may undergo dehydration prior to formylation and cyclization (eq 16).[35]

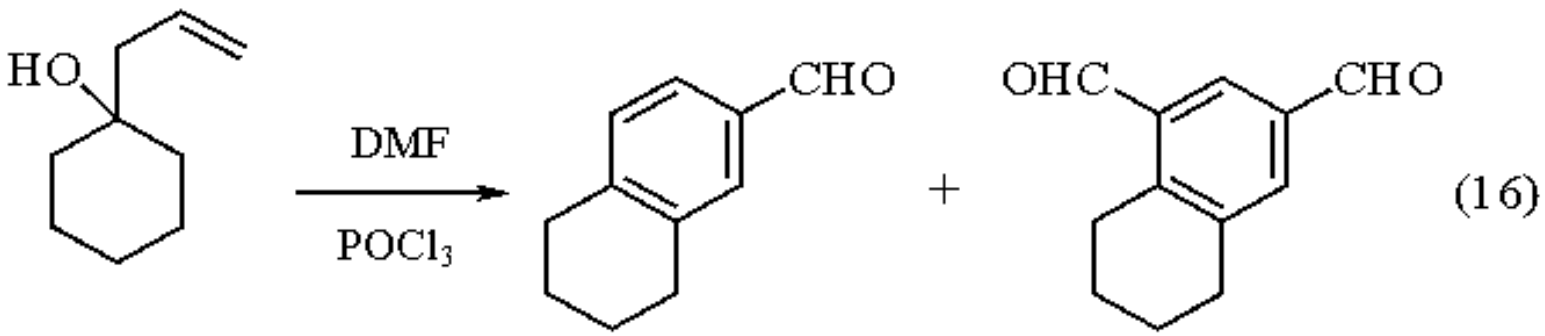

Related Reagents.

Dimethylbromomethyleneammonium Bromide; ***N,N-Dimethylformamide***; ***Formyl Chloride***; ***N-Methyl-N-phenyl(chloromethylene)ammonium Phosphorochloridate***.

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Dimethyl Chlorophosphite

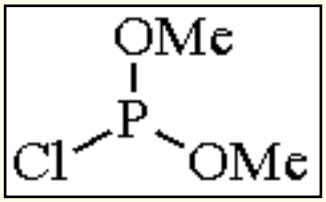

[3743-07-5] · $C_2H_6ClO_2P$ · Dimethyl Chlorophosphite · (MW 128.50)

(reactive phosphitylating agent for secondary alcohols; oxidation of the resulting phosphites provides phosphates)

Alternate Names: dimethyl phosphorochloridate; dimethyl chlorophosphonite; dimethoxychlorophosphine.

Preparative Method: obtained by reaction of ***Trimethyl Phosphite*** with ***Phosphorus(III) Chloride*** in HMPA.[1]

Inositol Phosphates.[2]

Phosphorylation of inositol derivatives is complicated by the relative unreactivity of phosphorus(V) reagents towards the secondary alcohol groups of inositol, and the tendency of the resulting phosphate triester intermediates to undergo cyclization and migration to neighboring hydroxy groups. Phosphitylation using the more reactive dimethyl chlorophosphite has avoided these problems while adding new selectivity features. For example, exhaustive phosphitylation of 1,4-dibenzoyl-*myo*-inositol (**1**) with excess dimethyl chlorophosphite[3] and ***Diisopropylethylamine*** yields the tetrakis(dimethyl phosphate) (**2a**) after ***Hydrogen Peroxide*** oxidation of the intermediate phosphite ester (eq 1).

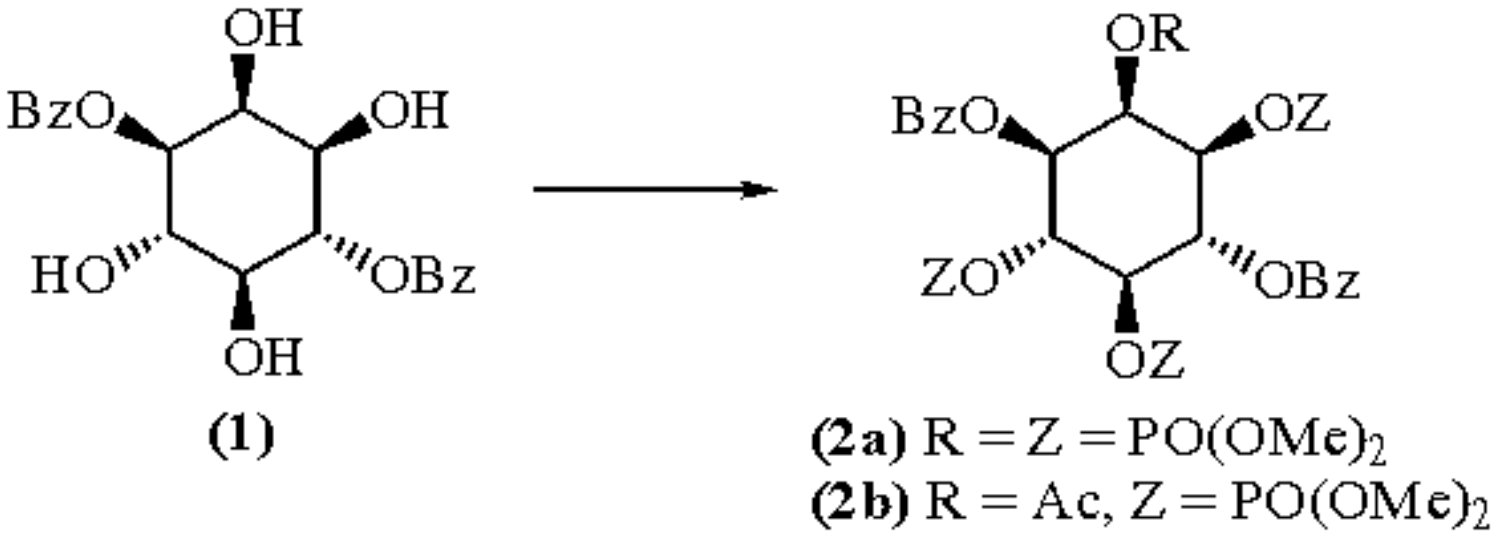

(1)

This suggests that it is possible to convert all the free hydroxy groups in any appropriately protected inositol to phosphate esters, including bisphosphorylation of a *cis*-vicinal diol. However, if less than the stoichiometric amount of dimethyl chlorophosphite (3.3 equiv) is used, partial phosphitylation of (**1**) is effected yielding the tris(dimethyl phosphate) (**2b**) after acetylation and oxidation. Only the more reactive equatorial 3-, 5-, and 6-hydroxy groups on (**1**) are phosphorylated.

The use of other phosphorus(III) reagents has recently been suggested for the synthesis of inositol phosphates. These include ***Dibenzyl N,N-Diisopropylphosphoramidite*** (**3**),[4] and *o*-xylylene *N*,*N*-diethylphosphoramidite (**4**).[5]

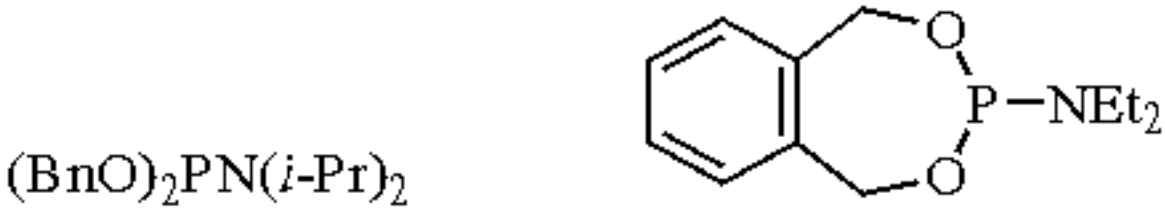

(3) (4)

The indirect method of phosphorylation using a phosphorochloridite followed by oxidation to the phosphate has also been applied in the synthesis of monophosphate esters from hindered alcohols. This has been reported using diallyl chlorophosphite, $(CH_2{=}CHCH_2O)_2PCl$,[6] and ***Diethyl Chlorophosphite***, $(EtO)_2PCl$.[7]

---

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Dimethyl Diazomalonate[1]

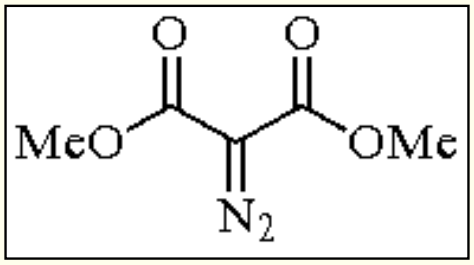

[6773-29-1] · $C_5H_6N_2O_4$ · Dimethyl Diazomalonate · (MW 158.13)

(carbene or carbenoid precursor;[1] cyclopropanation;[2] synthesis of oxazoles[3] and furans;[4] ring expansion;[5] deoxygenation of epoxides;[6] alkenation;[7] *C*-glycosidation;[8] etherification[9])

Physical Data: bp 60-61 °C/2 mmHg.

Solubility: sol ether, THF, halocarbon and hydrocarbon solvents.

Form Supplied in: not commercially available.

Preparative Methods: diazomalonates are generally prepared by diazo transfer reaction of malonates and sulfonyl azides.[10a] A recent modification employs polystyrene-supported trialkylammonium azide (generated in situ) under phase-transfer catalysis conditions and allows for facile isolation.[10b]

Handling, Storage, and Precautions: dimethyl diazomalonate has been utilized more extensively than has diethyl diazomalonate due to the explosion hazard of the latter. Nonetheless, care should be taken in preparation and handling of dimethyl diazomalonate. Storage at low temperature is recommended. The decomposition of dimethyl diazomalonate evolves nitrogen and can result in high pressures.

Cyclopropanation.

Decomposition of dimethyl diazomalonate by direct photolysis or by transition metal catalysis in the presence of alkenes leads to cyclopropanation (eq 1).[2a] The use of alkynes to trap the carbenoid species affords cyclopropenes (eq 2).[2b] Rhodium(II) acetate-catalyzed reaction with allenes allows ready access to methylenecyclopropanes, which form the basis for a methylenecyclopentane annulation protocol (eq 3).[2c]

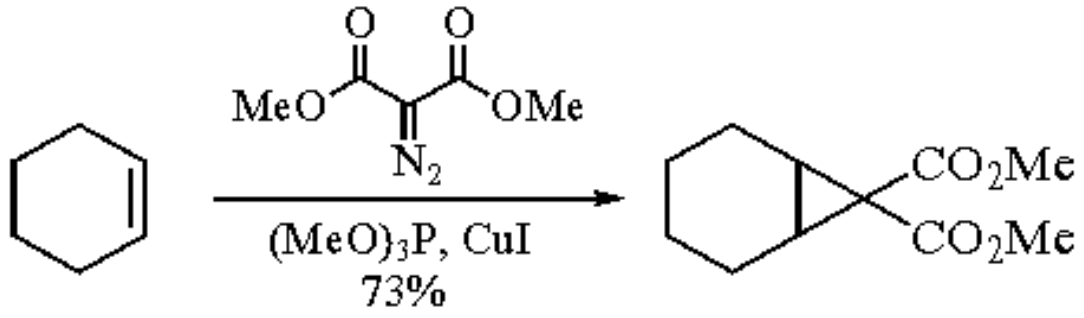

(1)

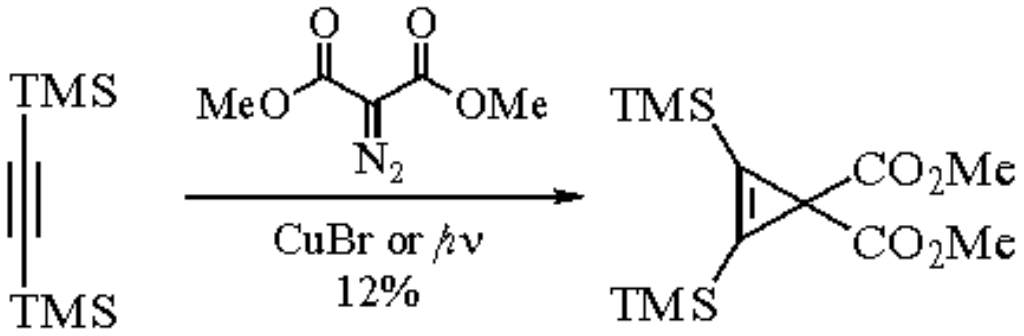

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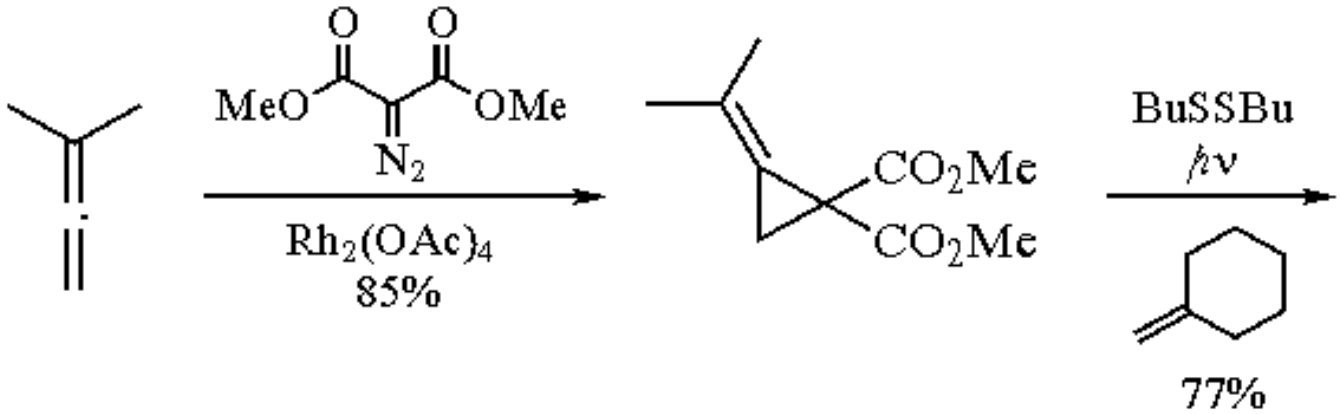

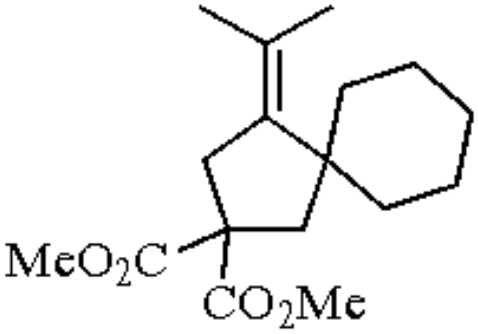

(3)

Synthesis of Oxazoles and Furans.

Dimethyl diazomalonate reacts with a variety of nitriles in the presence of rhodium(II) acetate to afford 2-substituted 5-methoxy-4-methoxycarbonyl-1,3-oxazoles (eq 4).[3] This reaction is fairly general in scope, although cyclopropanation and insertion can be competing processes.

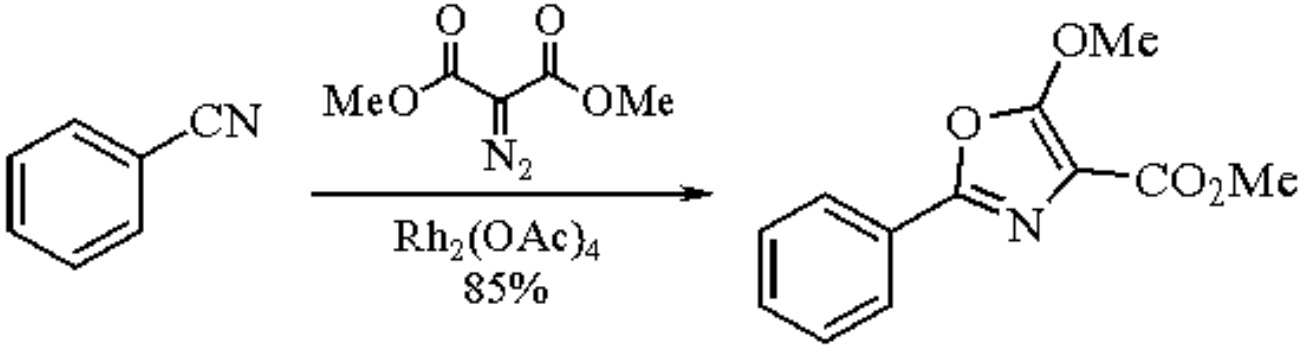

(4)

In contrast to the direct photolytic cyclopropanation of alkynes with dimethyl diazomalonate, benzophenone-sensitized photolysis in the presence of alkynes affords furans as the major products in moderate yields (eq 5).[4a]

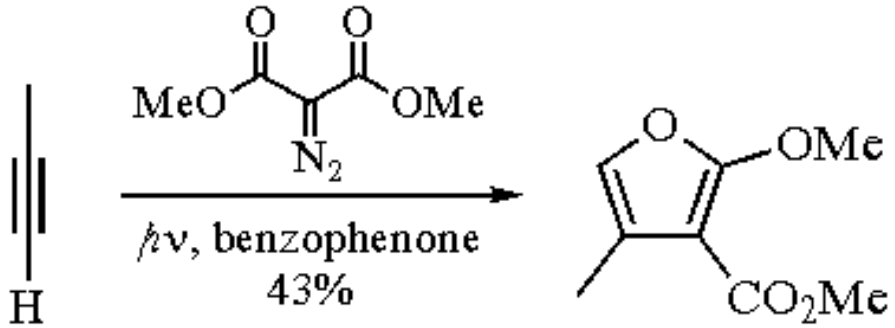

(5)

An alternative furan synthesis is based upon allylic C-H insertion upon reaction with a ketone-derived enol ether.[4b] Reduction and hydrolysis affords the furan (eq 6). With aldehyde-derived enol ethers, copper(I) induced reaction with dimethyl diazomalonate yields an alkoxycyclopropane diester, whose reduction, hydrolysis, and oxidation affords a spiro-β-methylene-γ-lactone (eq 7).

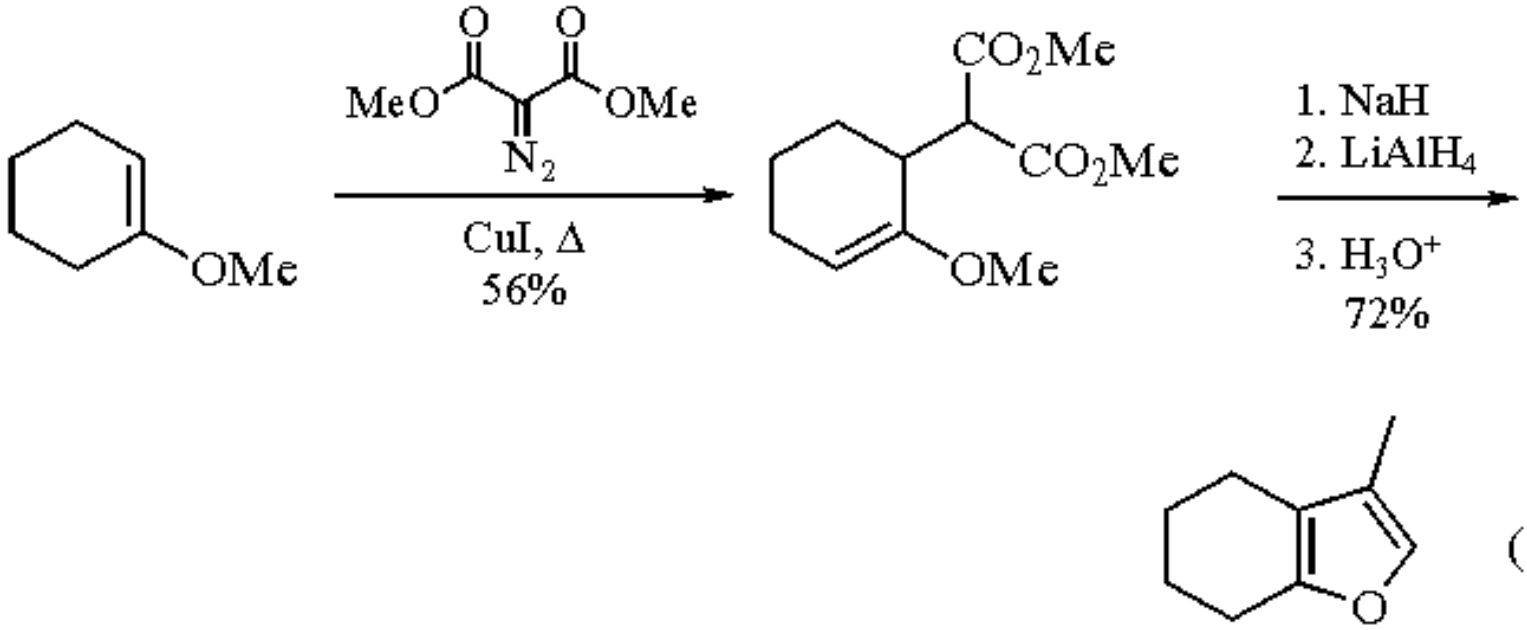

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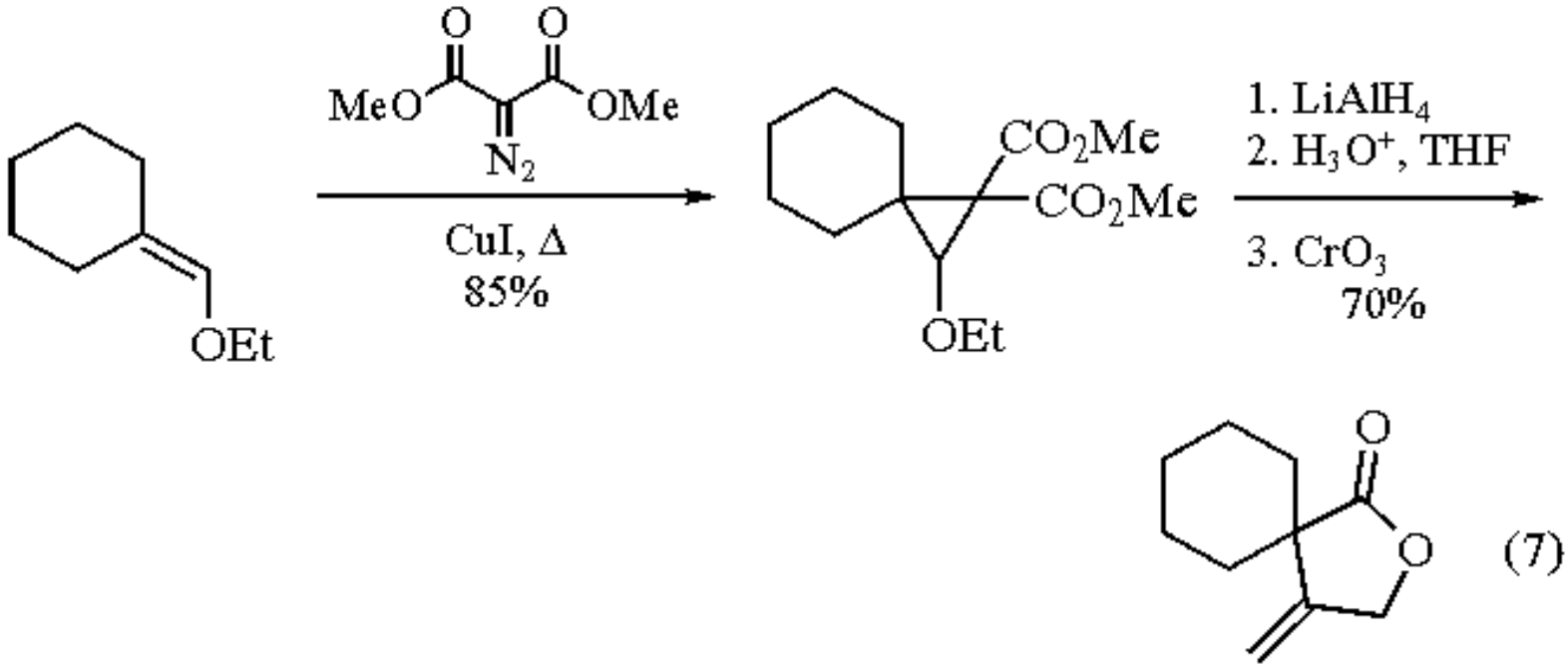

(7)

Ring Expansion.

Sulfonium ylides can be prepared from sulfides and dimethyl diazomalonate under rhodium(II) or copper catalysis. Subsequent [2,3] or [1,2] rearrangement of the ylides derived from cyclic sulfides allows for ring expansion. Examples include the synthesis of *cis*-thiacyclooctene (eq 8),[5a] dihydrothiazinones (eq 9),[5b] and homocephems (eq 10).[5c]

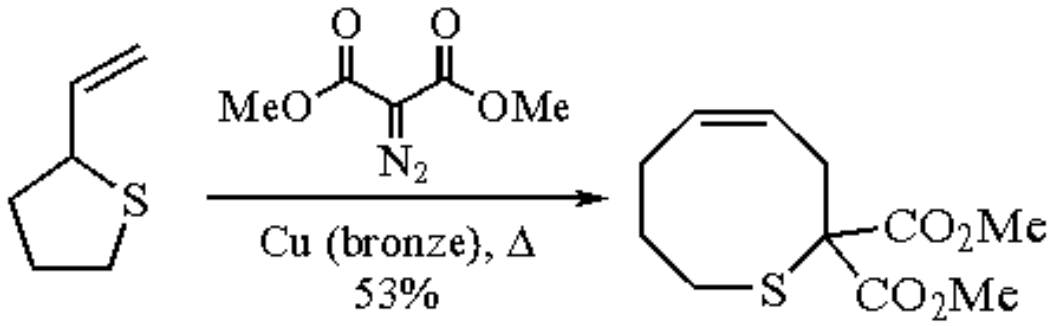

(8)

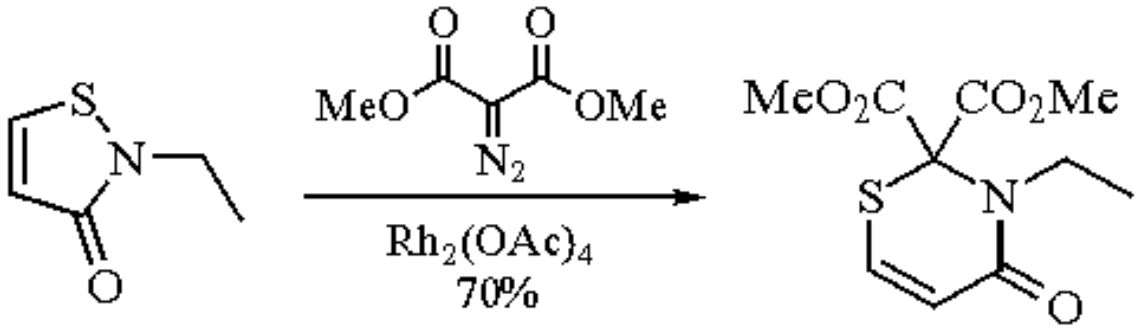

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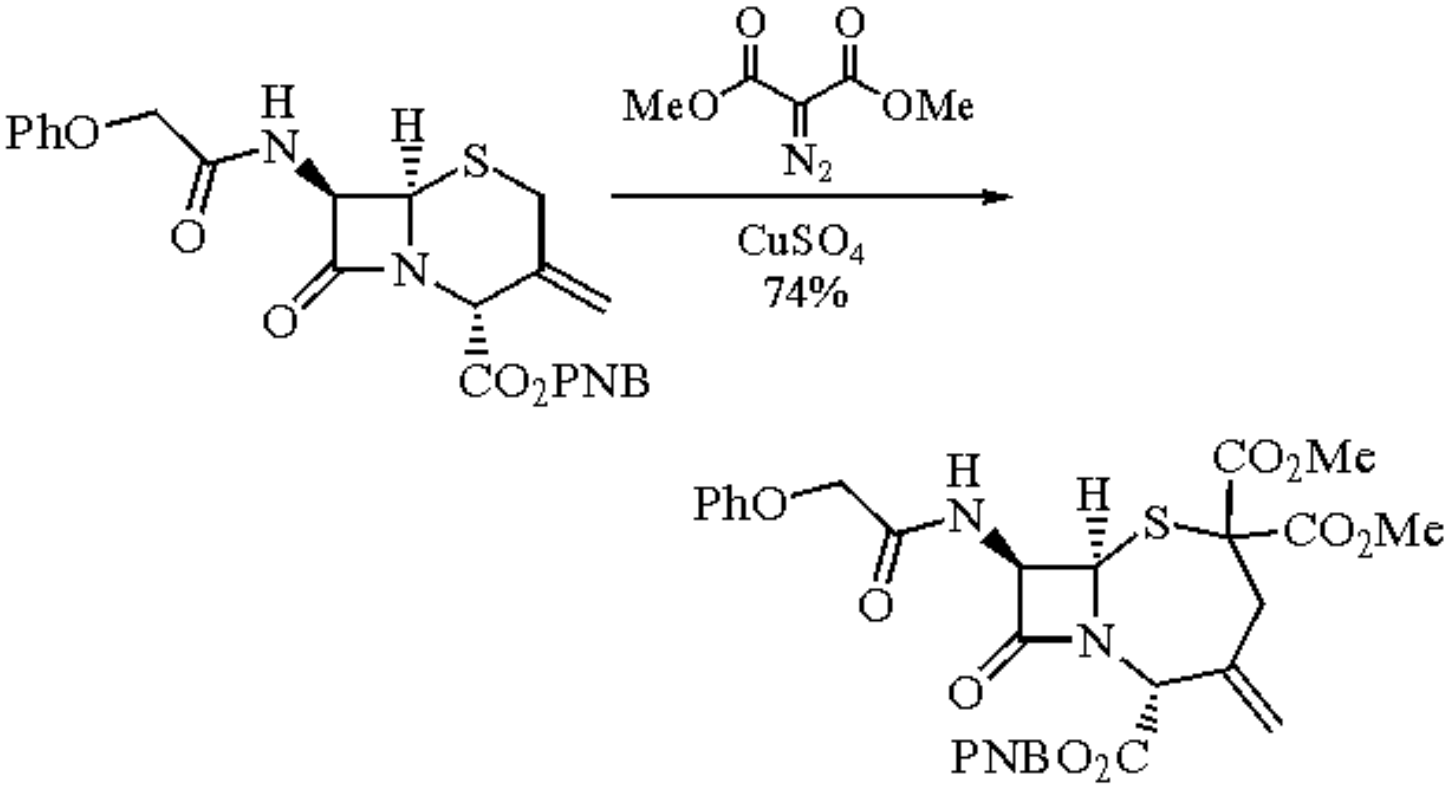

(10)

Deoxygenation of Epoxides.

In the presence of catalytic rhodium(II) acetate, dimethyl diazomalonate deoxygenates epoxides under neutral conditions (eq 11).[6] This reaction tolerates functionality such as ketones, esters, alkyl and silyl ethers and halogen substituents, although alcohols and aldehydes undergo competing insertion reactions.

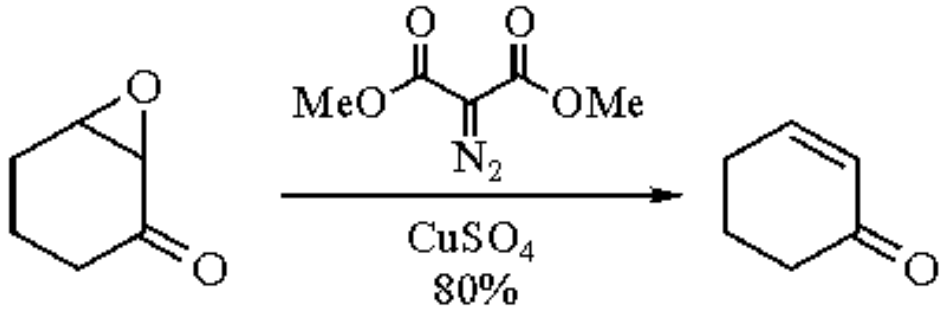

(11)

Alkenation.

Alkenation of thiolactones can be achieved by rhodium(II) acetate-catalyzed reaction with dimethyl diazomalonate (eq 12).[7a] Recently, an efficient alternative alkenation protocol has been demonstrated to be applicable to a variety of ketones and aldehydes by reaction with ***Tri-n-butylstibine*** and dimethyl diazomalonate in the presence of ***Copper(I) Bromide*** (eq 13).[7b] This process is proposed to occur via tributylstibonium bis(methoxycarbonyl)methylide.

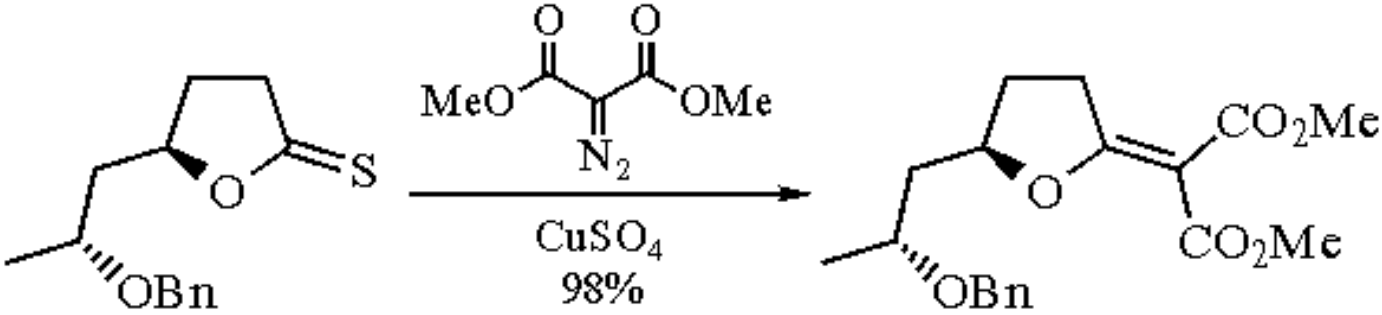

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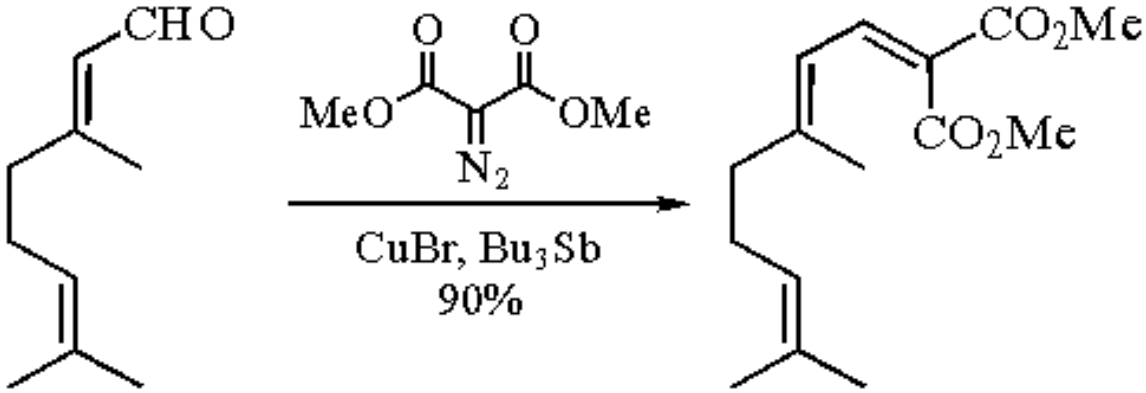

(13)

C-Glycosidation.

Reaction of phenyl thioglycosides with dimethyl diazomalonate in the presence of rhodium(II) acetate allows for the construction of *C*-glycosyl linkages in moderate yields under neutral conditions (eq 14).[8a] The methodology is applicable to both thiofuranosides and thiopyranosides. A related insertion process allows for a mild carbon extension of 4-phenylthioazetidinones (eq 15).[8b]

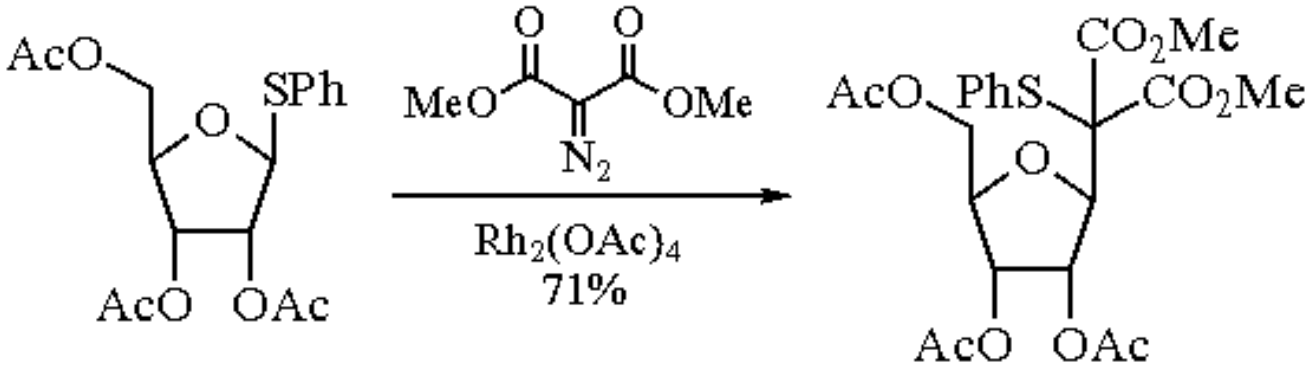

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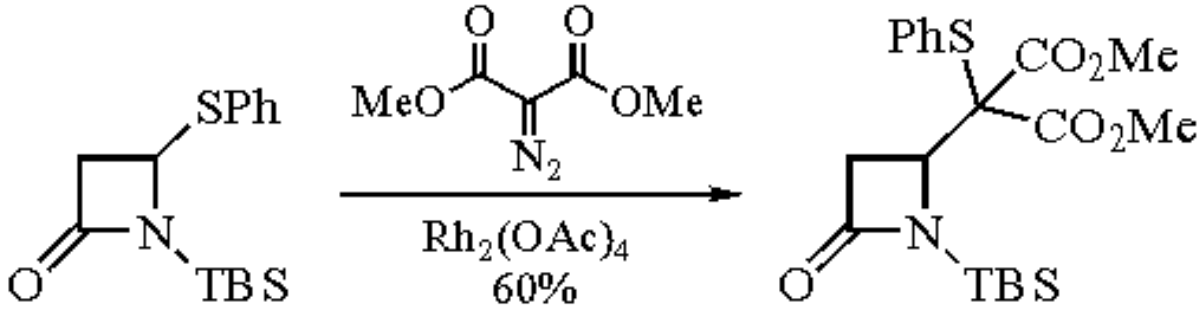

(15)

Etherification.

Rhodium(II) acetate-catalyzed O-H insertion of dimethyl diazomalonate is exceedingly facile, resulting in an efficient, neutral etherification in the presence of other sensitive functionality (eq 16).[9]

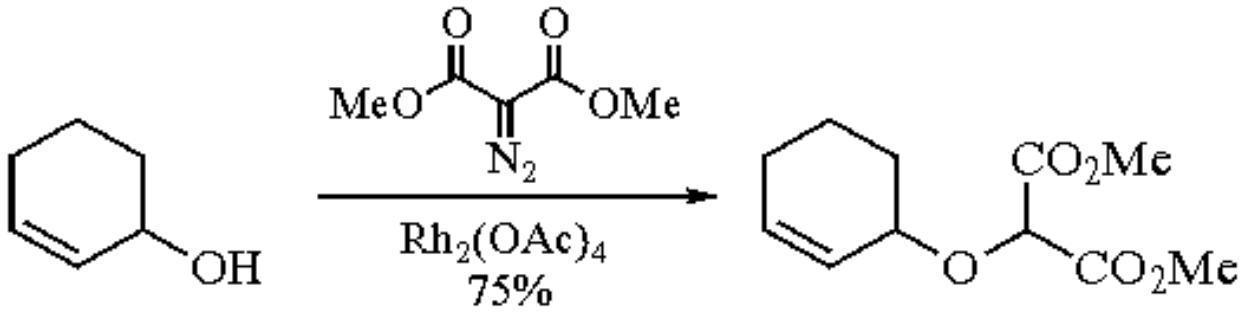

(16)

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Dimethyl Diazomethylphosphonate

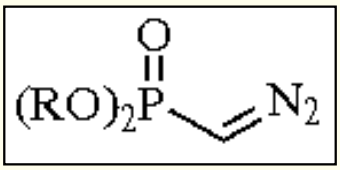

(R = Me)

[27491-70-9] · $C_3H_7N_2O_3P$ · Dimethyl Diazomethylphosphonate · (MW 150.09) (R = Et)

[25411-73-8] · $C_5H_{11}N_2O_3P$ · Diethyl Diazomethylphosphonate · (MW 178.15)

(bifunctional reagents capable of Horner-Wadsworth-Emmons and carbene chemistry;[6] conversion of aldehydes to terminal alkynes;[6a] preparation of vinyl ethers[10] and enamines;[11] cyclopropanation of alkenes;[20] cycloaddition to furnish heterocycles[21])

Alternate Name: DAMP.

Physical Data: (R = Me) bp 59 °C/0.1 mmHg; *n*25D 1.4585. (R = Et) bp 86-88 °C/0.2 mmHg; *n*25D 1.4503.

Solubility: insol H_2O; sol MeOH, THF, toluene.

Preparative Methods: for the most part, the reagents have been prepared by the method of Seyferth,[1] a convenient three-step sequence beginning with commercially available *N*-(bromomethyl)phthalimide. More recently, two alternatives have been detailed, both of which appear to offer synthetic utility.[2]

Handling, Storage, and Precautions: stable indefinitely when stored at 4 °C under argon. *Caution*: All distillations should be carried out behind a blast shield.

Preparation of Diazo Phosphonates.

Diethyl (diazomethyl)phosphonate is readily lithiated (***n-Butyllithium***, THF, -100 °C) and the resulting lithio derivative can be acylated (PhCOBr, 33%) (eq 1) or silylated (poor yield).[3] The corresponding silver derivative, formed by treatment with ***Silver(I) Oxide***, can be alkylated with reactive allylic halides.[3] α-Diazo-β-hydroxy phosphonates result when the lithio derivative is treated with aryl aldehydes; alternatively they can be prepared by direct reaction of DAMP with aldehydes in the presence of ***Triethylamine*** (eq 2).[4]

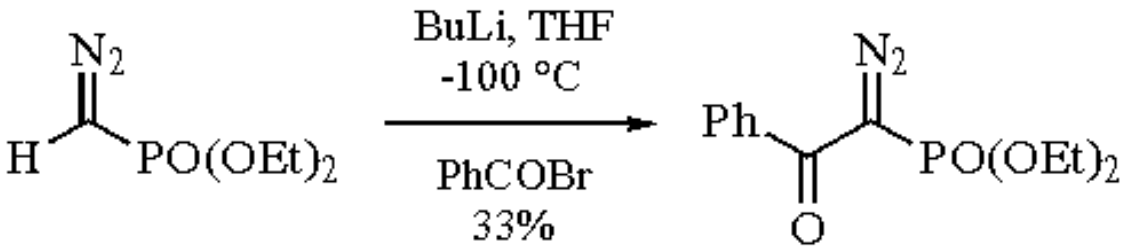

(1)

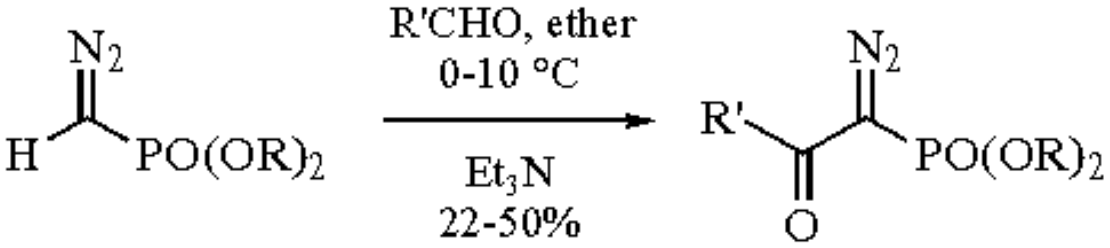

(2)

Insertion Reactions.

The reagents, with Lewis acid catalysis, insert smoothly into readily fissile bonds. Thus aldehydes are converted into β-keto phosphonates[5] on treatment with the reagents and ***Tin(II) Chloride*** (eq 3).

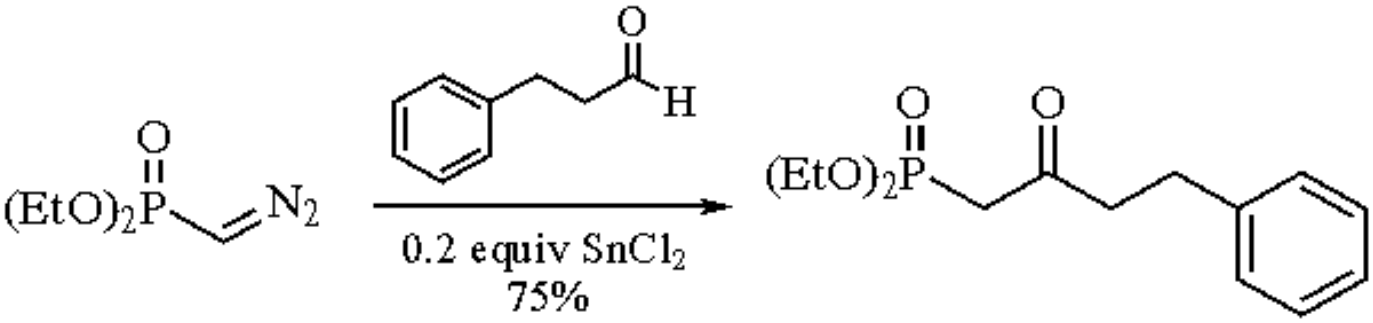

(3)

Tandem Horner-Wadsworth-Emmons Carbene Reactions.

Carbonyl groups, on treatment with the anion of the reagents, are smoothly converted into intermediate vinyl carbene species.[6,9] In the case of ketones, one of three pathways is then followed. The first is a [1,2]-aryl shift which may occur to form an internal alkyne (eq 4).[6a,7] Reports indicate that, for the most part, this shift does not occur with transfer of an alkyl group.[8] The second possibility occurs when an abstractable hydrogen is available, into which bond the carbene inserts.[9] Examples of this chemistry abound; the method is useful for furnishing vinyl ethers (eq 5),[2b,6b,10] enamines (eq 5),[6b,11] cyclic alkenes (eq 6),[9,12,13] furans,[14] and other heterocycles (eq 7).[15] A recent example describes possible limitations of this technology, however; use of ***Trimethylsilyldiazomethane*** offers some improvement.[12b] Here, the alkenation sequence is provided by a Peterson alkenation reaction. Finally, the intermediate vinylcarbene species may be intercepted by alkenes, to yield methylenecyclopropanes.[2a,16]

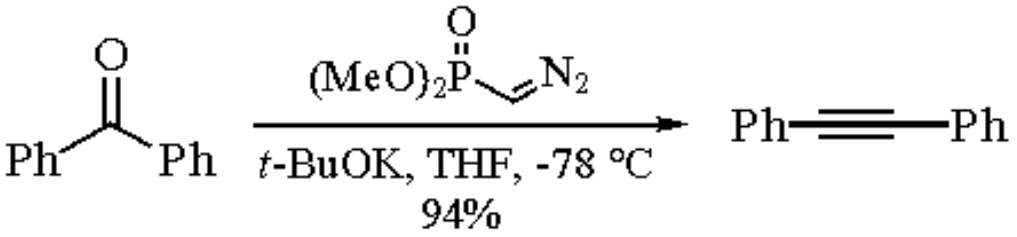

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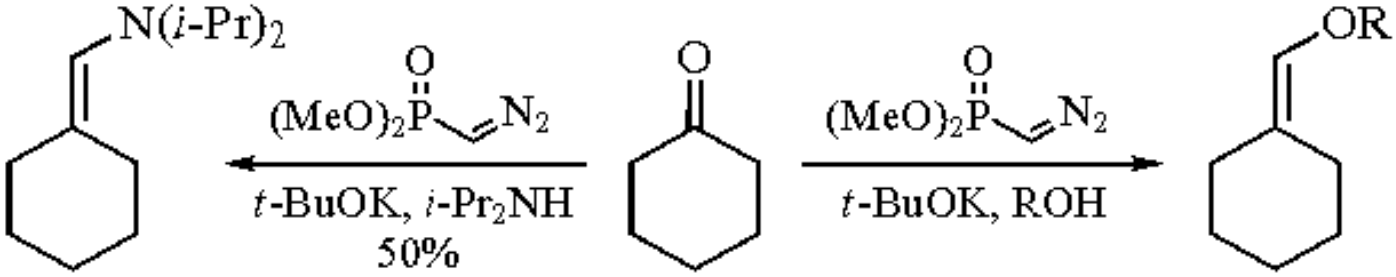

(5)

R = Me, 58%
R = *t*-Bu, 56%

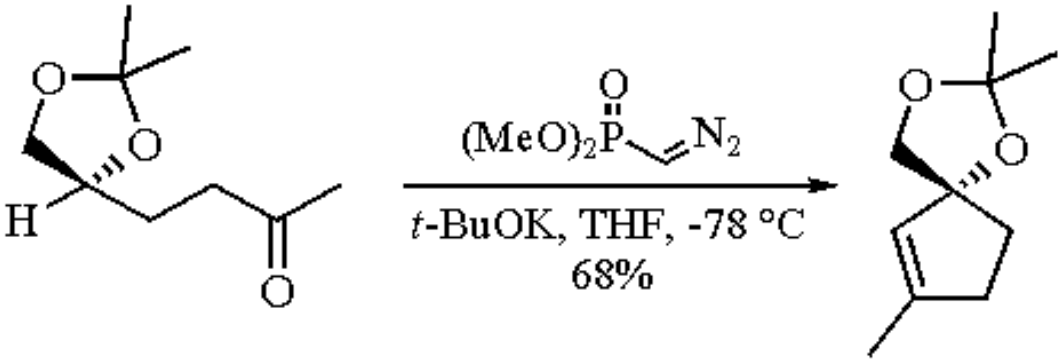

(6)

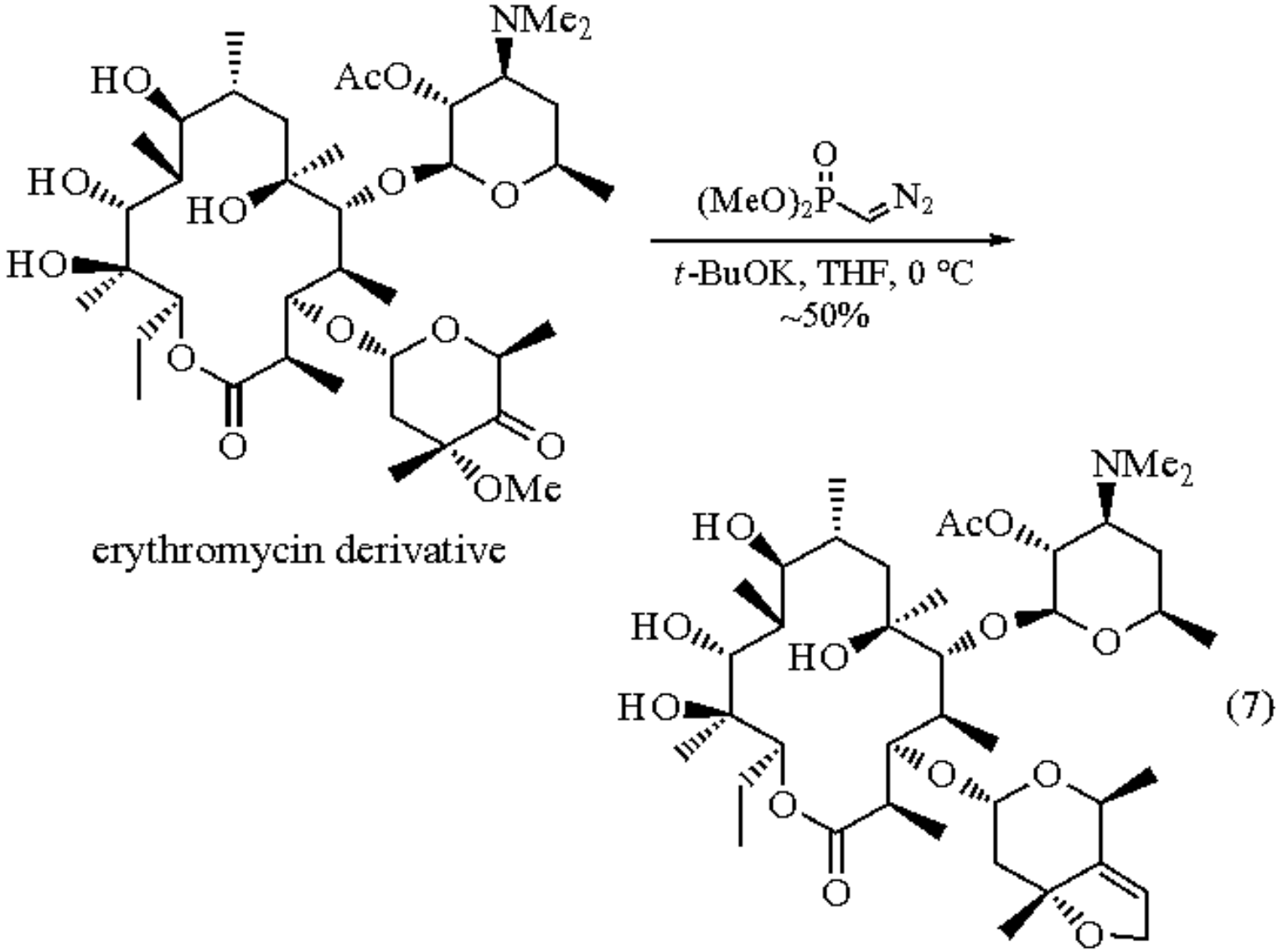

(7)

With aldehydes, treatment with dialkyl diazomethylphosphonate leads exclusively to terminal alkynes (eq 8).[2b,6a] This has proven useful, and is compatible with adjacent chirality (eqs 9 and 10).[17,18] The method provides a useful alternative to the Corey-Fuchs protocol, which could prove troublesome in some circumstances.[19]

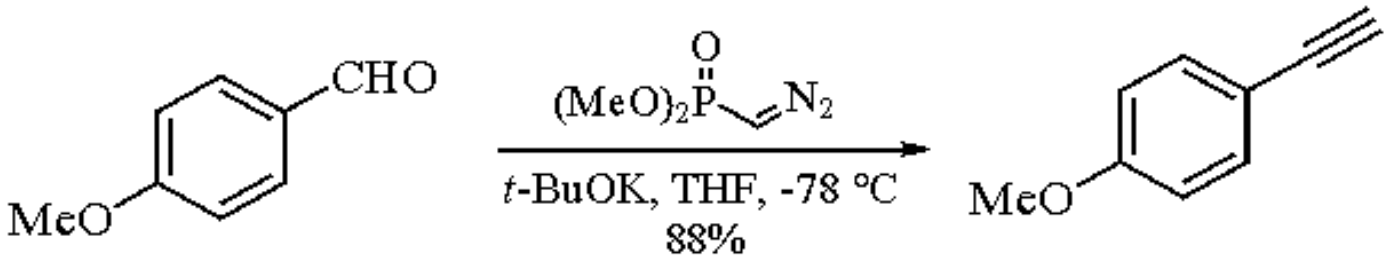

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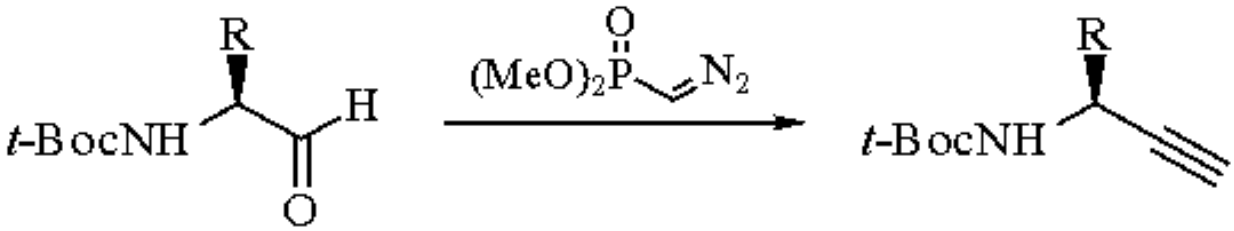

(9)

R = Me, *i*-Pr, Bn, *i*-Bu, 4-$CH_2C_6H_4OBn$, -$(CH_2)_4NHCbz$

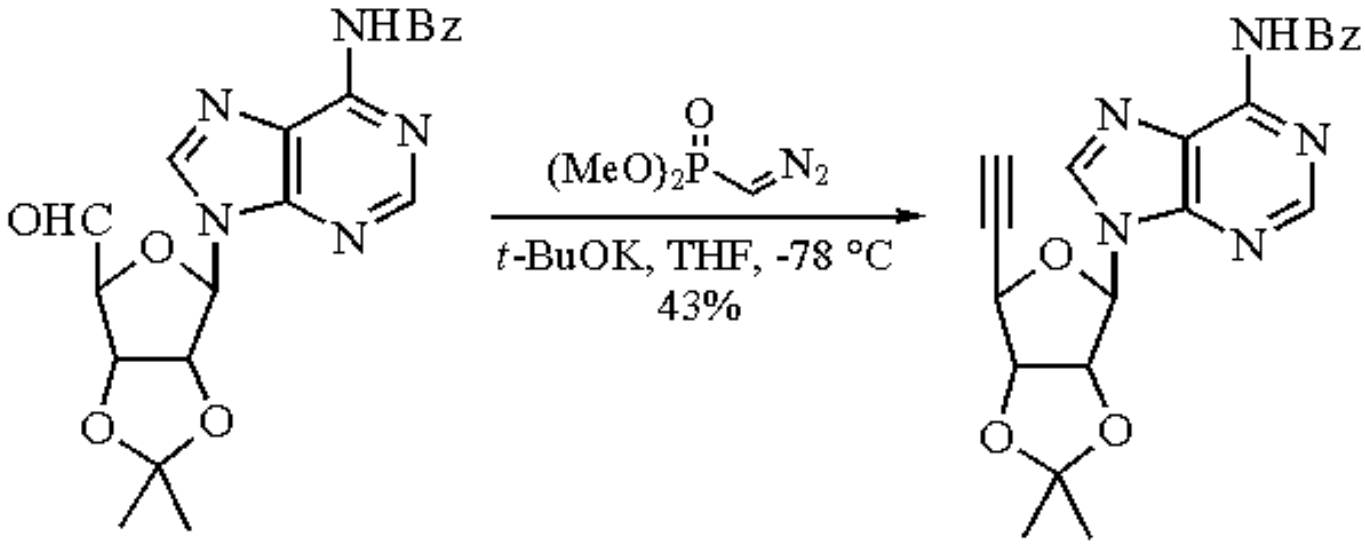

(10)

Cyclopropanation.

The reagents furnish cyclopropylphosphonates on exposure to alkenes in the presence of a metal or metal salt (eq 11).[1,20]

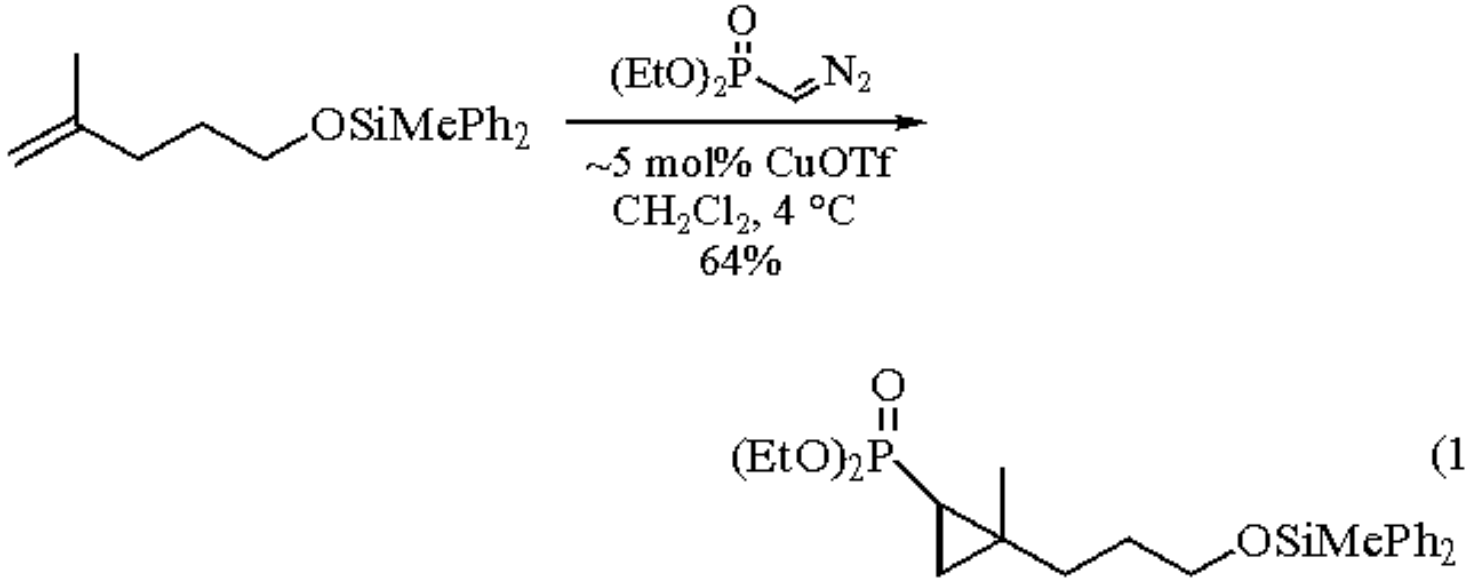

(11)

Cycloadditions.

The dipolar nature of the reagent has been exploited in the synthesis of pyrazolines,[1] 1,2,4-diazaphospholes (eq 12),[21]

dihydropyridazines,[18] pyridazines,[22] and pyrazoles.[23] On installation of a dipolarophilic group α to the diazo moiety, intramolecular cycloadditions are possible, and have been extensively investigated (eq 13).[24]

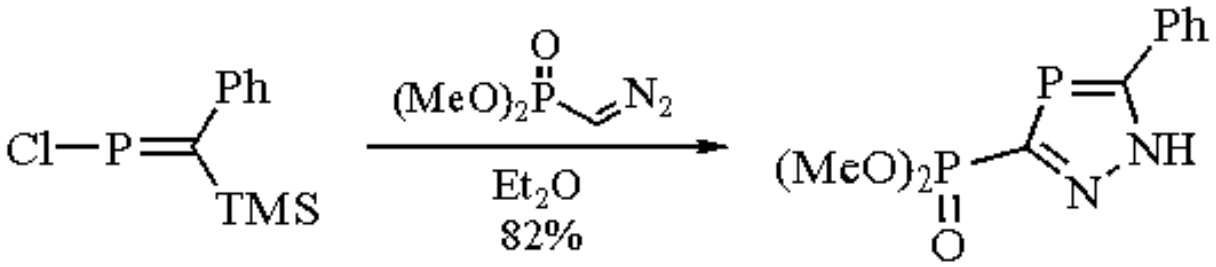

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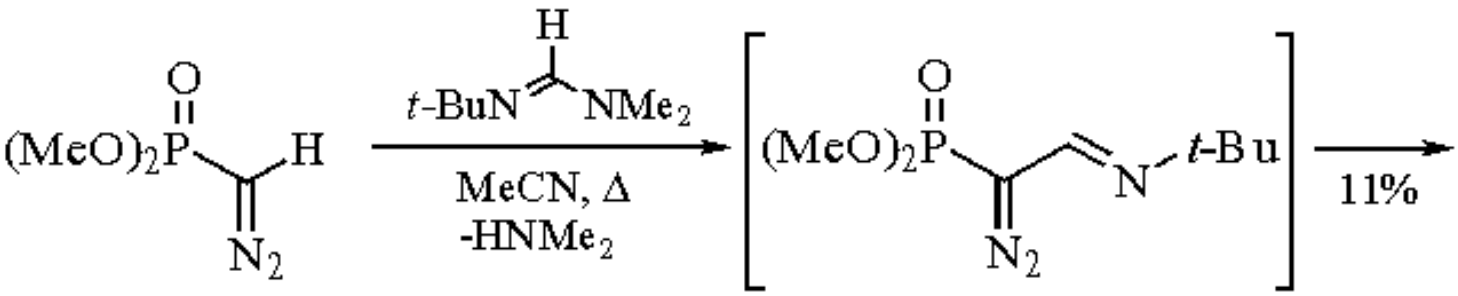

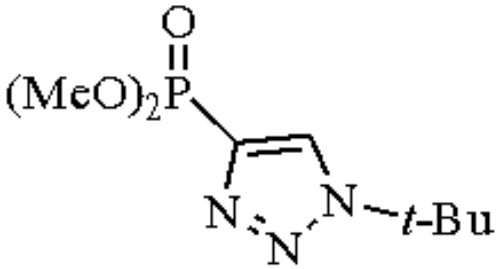

(13)

Related Reagents.

Methylenecyclopropane.

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1. Seyferth, D.; Marmor, R. S.; Hilbert, P. *JOC* **1971**, *36*, 1379.
2. (a) Lewis, R. T.; Motherwell, W. B. *T* **1992**, *48*, 1465. (b) Ohira, S. *SC* **1989**, *19*, 561.
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24. Regitz, M.; Schoder, W. *S* **1985**, 178.

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(-)-(*S*,*S*)-α,α´-Dimethyldibenzylamine

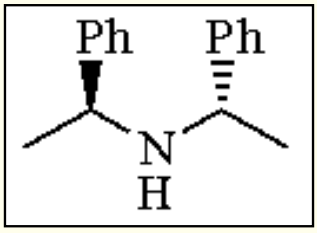

[56210-72-1] · $C_{16}H_{19}N$ · (-)-(*S*,*S*)-α,α´-Dimethyldibenzylamine · (MW 225.36)

(starting material for the formation of chiral amide reagents; useful in the stereospecific deprotonation of prochiral ketones, and as a chirality transfer agent in the reactions of prochiral enolates; stereoselective conjugate addition of organometallic reagents to unsaturated carbonyl systems[1])

Physical Data: (free base): bp 103-105 °C/0.5 mmHg;[2] $[\alpha]_D$ -157° (*c* 2.4, EtOH);[1a] -197.3° (*c* 3.65, benzene);[1b] -187.9° (*c* 6.87, benzene);[3] -171.6° (*c* 6.71, chloroform).[4] (HCl salt): mp >300 °C; $[\alpha]_D$ -84.1° (*c* 3, EtOH);[1a] -72.1° (*c* 2.94, EtOH).[1b]

Solubility: readily sol common organic solvents (ether, THF, chloroform, etc.); insol H_2O.

Form Supplied in: available commercially.

Analysis of Reagent Purity: diastereomeric purity can be assessed by the ^1H NMR chemical shift of the methyl groups,[1a] and by GC analysis.[5] Optical purity can be assessed by derivatization with (*R*)-(-)-1-(1-naphthyl)ethyl isocyanate and ^1H NMR analysis of the product.[4]

Preparative Methods: minor improvements to the original catalytic hydrogenation procedure[6] have been described (eq 1).[1a] This method provides (*S*,*S*)-(-)-(**1**) with an optical purity of only 70%. Enantiomerically pure (*S*,*S*)-(-)-(**1**) can be obtained by recrystallization of the hydrochloride salt of this enriched material from water[1b] or the benzoate salt from isopropanol.[3] A chemical reduction procedure has also been described that yields optically active (*S*,*S*)-(**1**) with 74% enantiomeric excess (eq 2).[2] A significant improvement to the former procedures is the diastereoselective hydrogenation of imines catalyzed by rhodium/chiral diphosphines, which yields (*S*,*S*)-(**1**) with an optical purity of 99.4% (eq 3).[5]

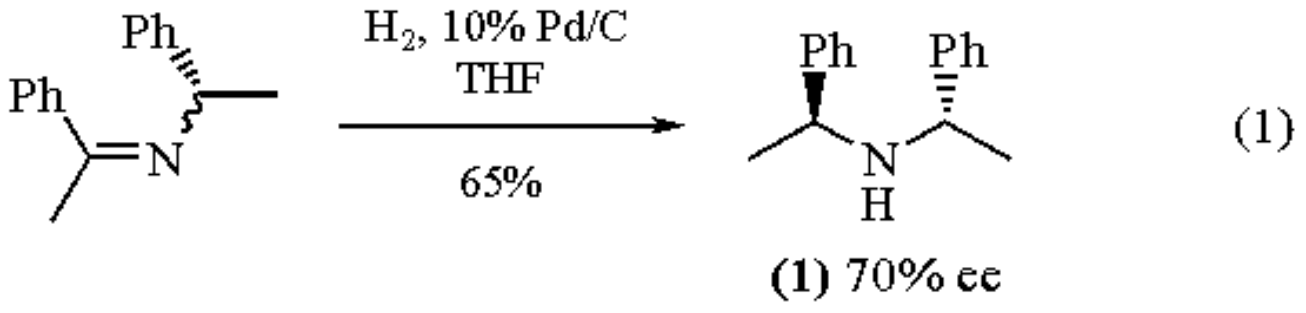

(1)

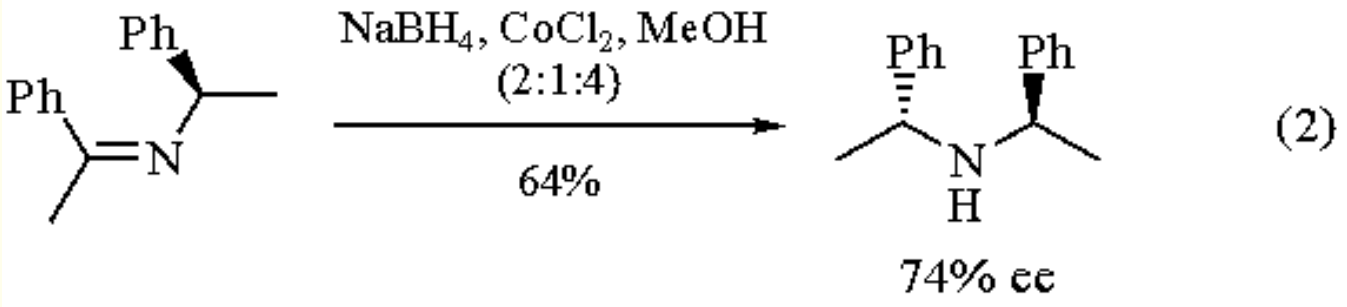

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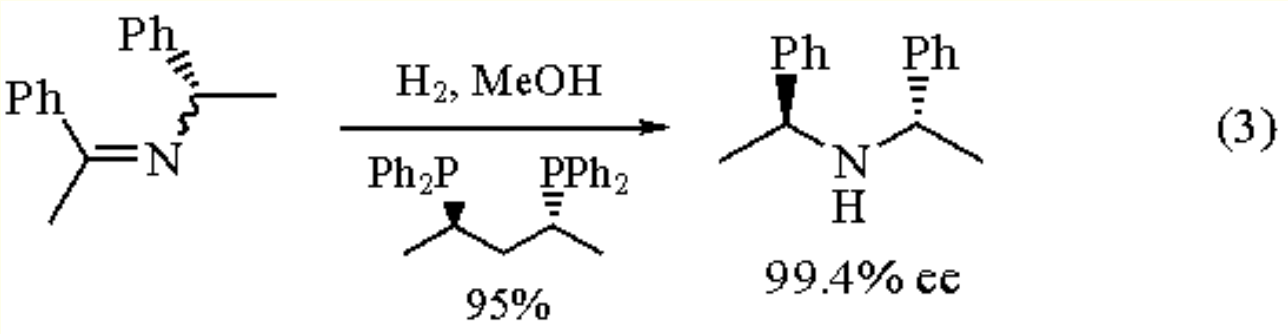

(3)

Purification: the free base can be distilled. The HCl salt can be recrystallized from water, which removes diastereomeric impurities. The benzoate salt can be recrystallized from isopropanol.

Handling, Storage, and Precautions: no special precautions have been noted in the literature. The free base is a clear distillable liquid that should be stored under an inert atmosphere to prevent air oxidation. Long term storage may lead to some coloration of the material.

Introduction.

In most cases the (*R*,*R*) and (*S*,*S*) enantiomers of (**1**) possess similar synthetic applications. References to both enantiomers have been incorporated into this article, under the heading of (*S*,*S*). The equations depict the actual enantiomer used in each publication.

Asymmetric Deprotonation/Protonation of Ketones.

Lithium amides of chiral amines have been used for performing asymmetric deprotonations of symmetrically substituted (prochiral) ketones.[7,8] The resulting optically active enols or enol derivatives (most frequently enol silanes) are highly versatile synthetic intermediates. Particularly useful for this purpose are chiral amines possessing C_2

symmetry, such as (**1**). For example, reaction of 4-*t*-butylcyclohexanone with the lithium amide of (*R*,*R*)-(**1**) (readily prepared in situ by treatment of (**1**) with ***n-Butyllithium***) is highly stereoselective; the resulting enol silyl ether possesses an 88% ee (eq 4).[9]

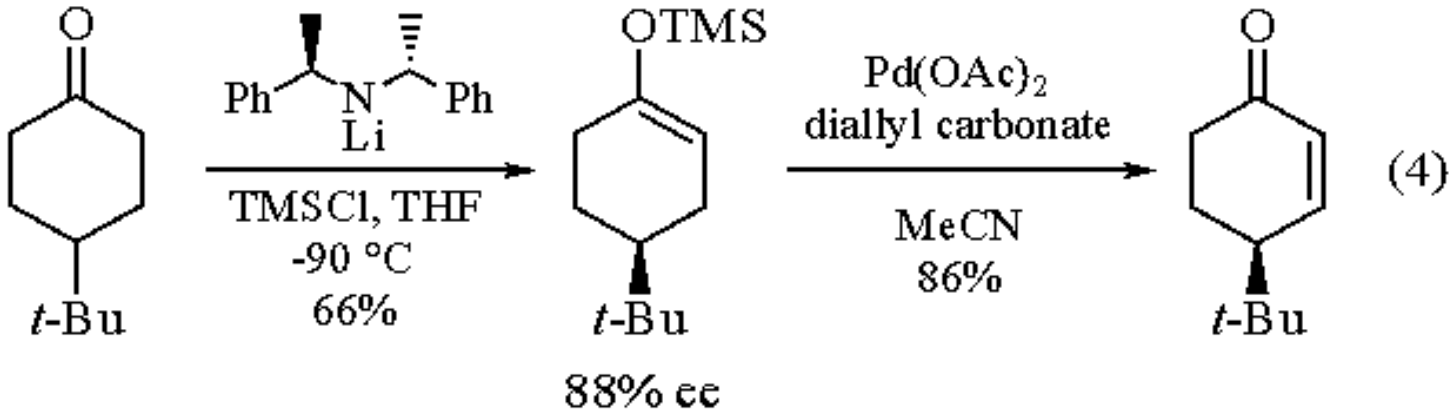

The most predictable results are obtained with conformationally rigid systems, such as those represented in eqs 5 and 6, which possess axially oriented α-protons.[10,11] This minimizes complications resulting from the presence of diastereotopic α-protons, although unexpected modes of deprotonation have been described with related chiral amides, which may involve boat conformations.[12] To prevent enolate equilibration (with the resulting loss of stereoselectivity), Corey's internal quench method for enolate trapping with silyl chlorides is frequently used.[13] The stereospecificity of this deprotonation is highly dependent on solvent and temperature conditions. Best results are obtained at -100 °C or lower temperatures, with THF as the solvent.

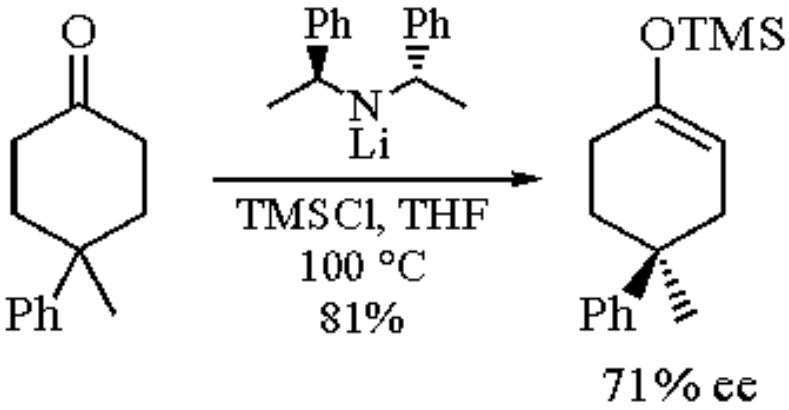

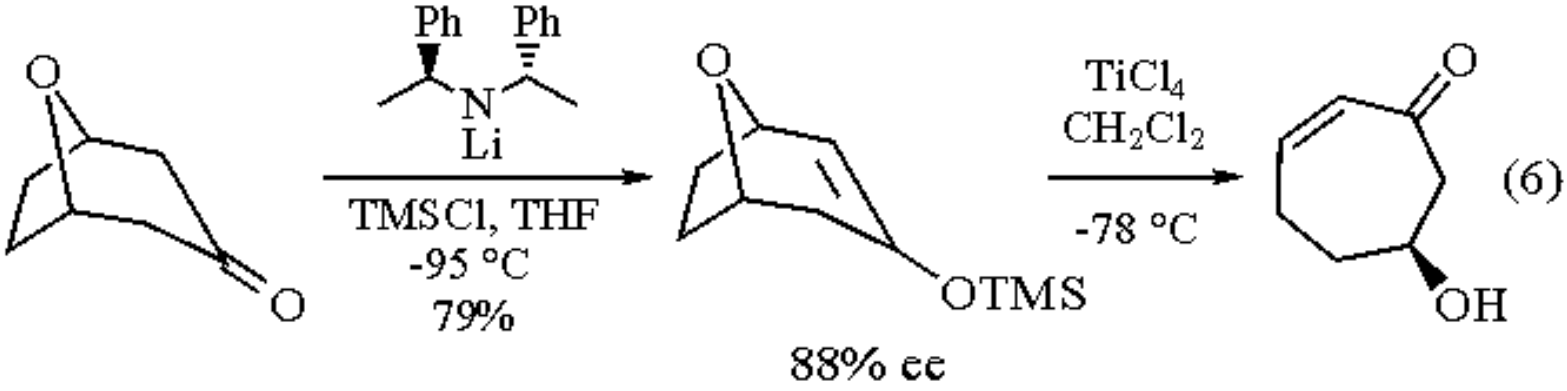

The lithium amide of (*S*,*S*)-(**1**) has been used to convert racemic α-substituted ketones into optically active ketones via

sequential deprotonation/asymmetric protonation of rigid prochiral enolates. Enantiomeric enrichment may occur during the protonation step as a result of the tight coordination between the enolate and the lithium amide in the form of diastereomeric complexes (eq 7).[14]

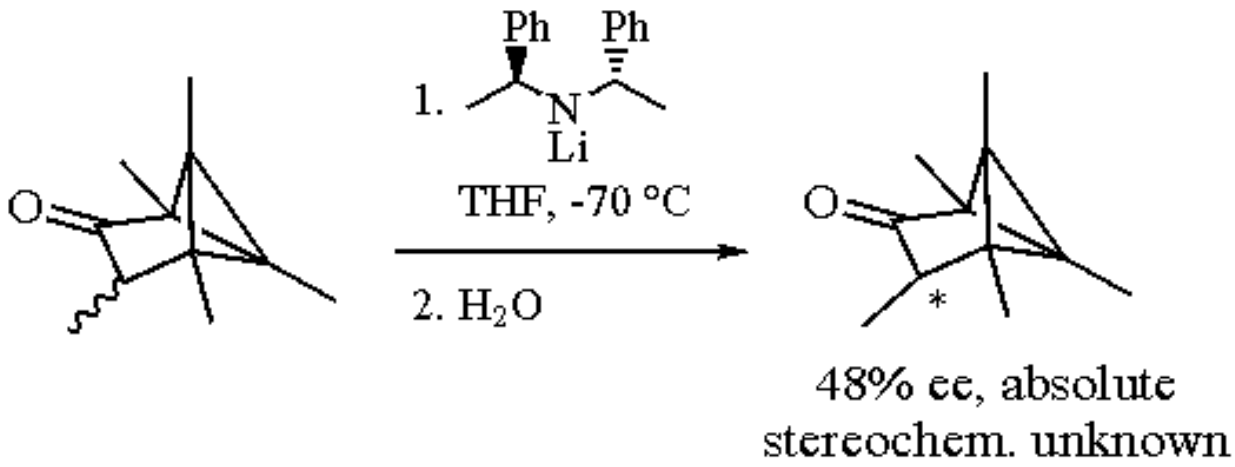

(7)

Alternatively, the enantiomeric enrichment derives from kinetic differences in the rate of deprotonation of the two ketone enantiomers (eq 8).[15] Ether is the best solvent for these reactions.

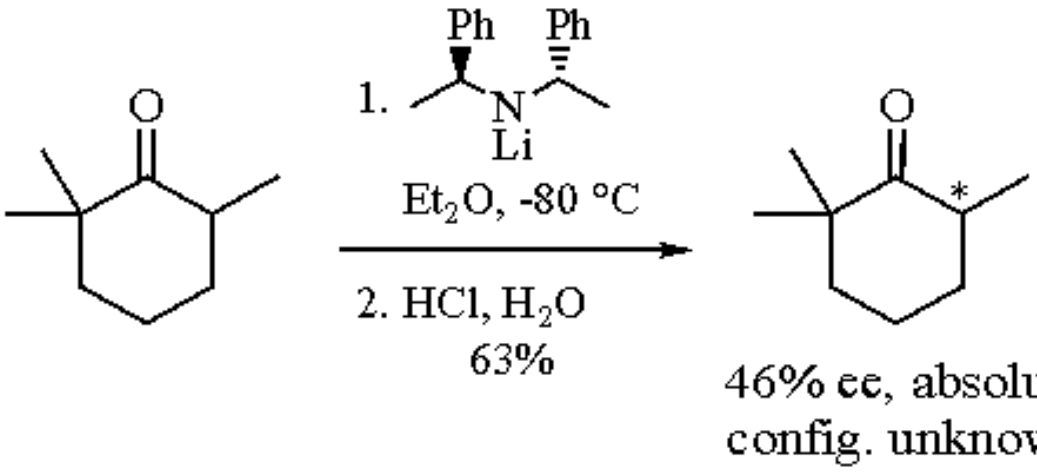

(8)

The lithium amide of (**1**) has also been used to perform the kinetic resolution of racemic lactams by selective kinetic deprotonation of one of the enantiomers, followed by reaction of the partially formed enolates with an electrophile.[16] These procedures have not proven to be particularly useful yet, since high enantiomeric purity is only achieved at low conversions of the starting materials (eq 9).[17]

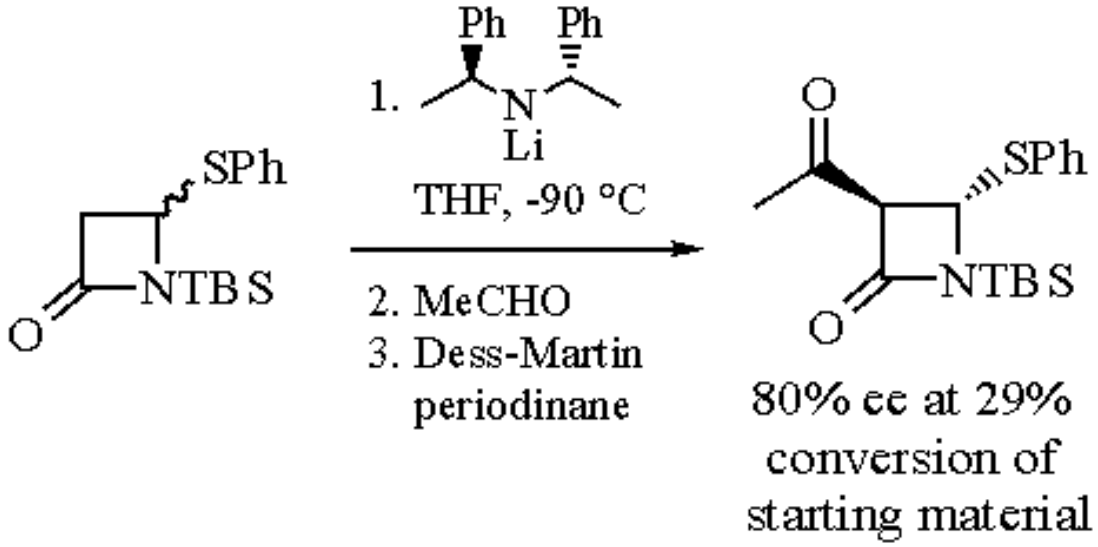

(9)

Stereoselective Alkylation of Prochiral Enolates.

A limited amount of work has demonstrated the potential use of chiral amines in inducing stereoselectivity in the alkylation/carboxylation of prochiral enolates. The selectivity of these reactions, like those described above, is highly dependent on solvent and temperature conditions. The use of ether at -196 °C provides optimal results in a particular system (eq 10).[18]

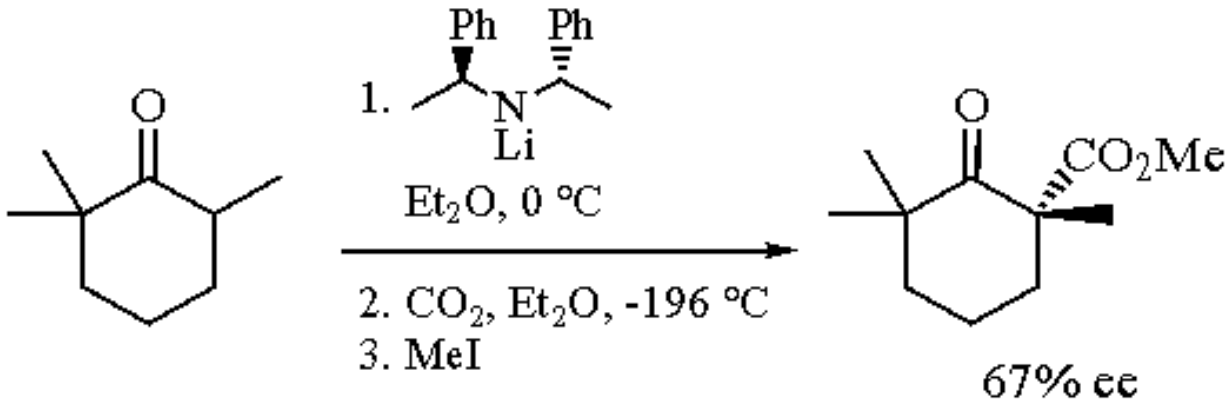

(10)

Asymmetric Induction in Organometallic Reactions.

A number of chiral amines have been used as nontransferable ligands for the enantioselective conjugate addition of organocopper reagents, with optical yields as high as 95%.[19-22] (*R*,*R*)-(**1**) has also been used for this purpose, effecting the conjugate addition of organocopper reagents to enones with moderate to high enantioselectivity (eq 11).[23,24] The use of dimethyl sulfide as the solvent for this transformation is critical, since ether solvents produce products of low optical activity.

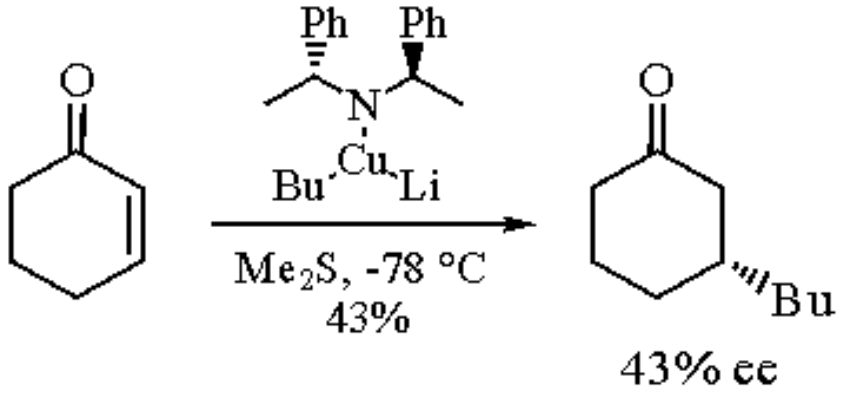

(11)

Although (**1**) itself has not been shown to be useful in the stereospecific 1,2-addition of organometallic reagents to carbonyl compounds, closely related amines, such as (*R*)-(α-methoxymethylbenzyl)-(*S*)-(α-methylbenzyl)amine, have been used to direct the addition of organolithium reagents to benzaldehyde with up to 95% stereoselectivity (eq 12).[25]

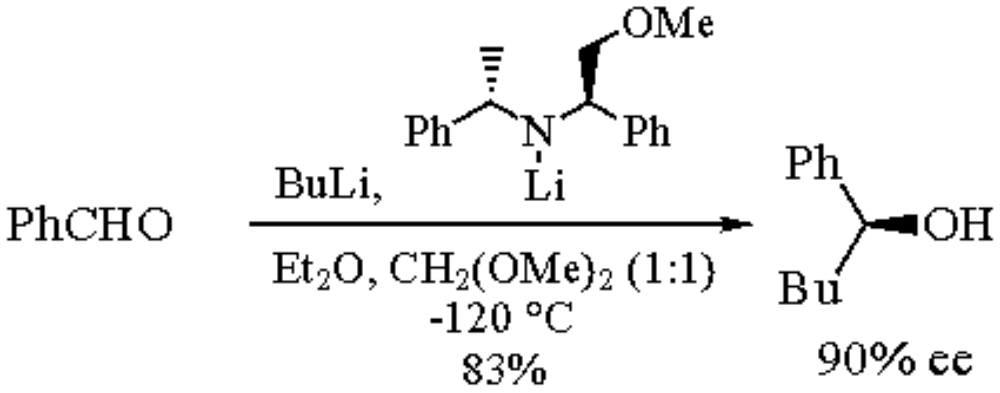

(12)

Enantioselective Conjugate Additions.

(*R*,*R*)-(**1**) has been used in the synthesis of (*R*)-β-aminobutanoic acid. The conjugate addition of the lithium amide of (*R*,*R*)-(**1**) to (*E*)-methyl crotonate proceeds with complete diastereoselectivity. Catalytic reduction of the benzyl groups results in the formal stereospecific 1,4-addition of an amino group to an unsaturated ester (eq 13).[26] Although (**1**) has not been used extensively for this type of transformation, a variety of other chiral amines have been used for similar purposes.[8,27,28]

(-)-(S,S)-alpha,alpha´-Dimethyldibenzylamine

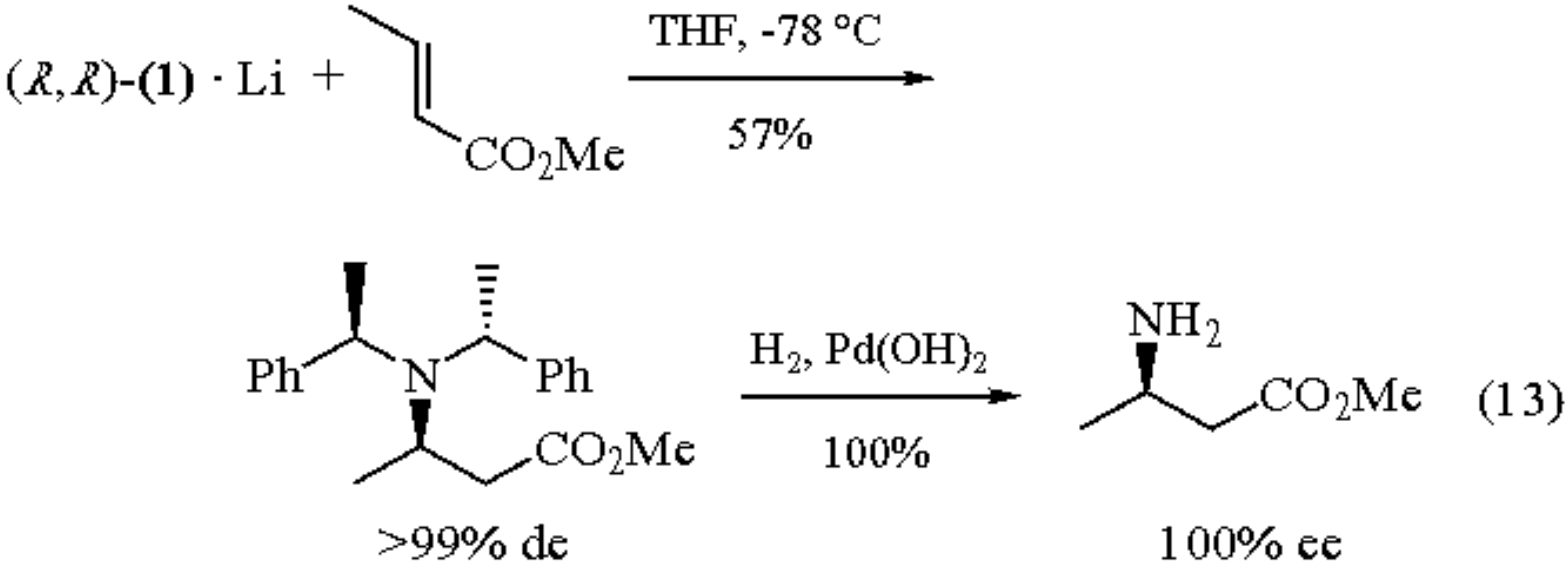

Chiral Auxiliary.

(*R*,*R*)-(**1**) has been used as a chiral auxiliary to direct the stereochemistry of addition of a nucleophile to an acrylate moiety. Almost complete stereoselectivity is achieved in the addition of cyclopentanecarboxylic acid lithium dianion to the α-substituted acrylate substrate (eq 14).[29] This methodology allows stereochemical control at the α-position of a β-amino ester and thus complements the methodology described above[26] for the stereoselective formation of β-substituted β-amino esters.

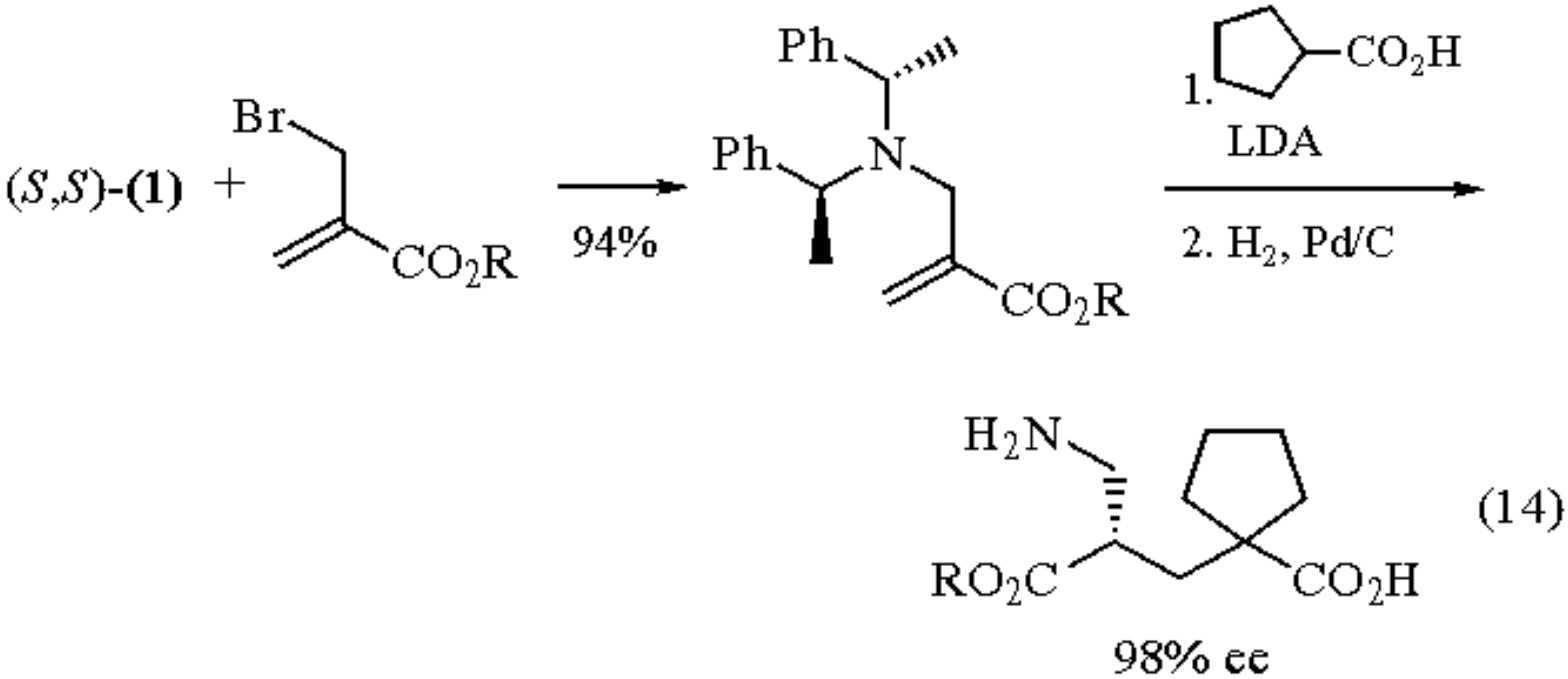

Other Enantioselective Reactions.

Enantioselective epoxide elimination by chiral bases has been demonstrated.[30] More recently, the enantioselective [2,3]-Wittig rearrangement of a 13-membered propargylic allylic ether has been performed using the lithium amide of (*R*,*R*)-

(**1**) as the base for deprotonation (eq 15).[4] For this particular substrate, THF is a better solvent than ether, although pentane produces better results in a related transformation (eq 16).[4] In fact, a change in solvent in this type of reaction has been shown to lead to a reversal of the stereoselectivity of the transformation.[4]

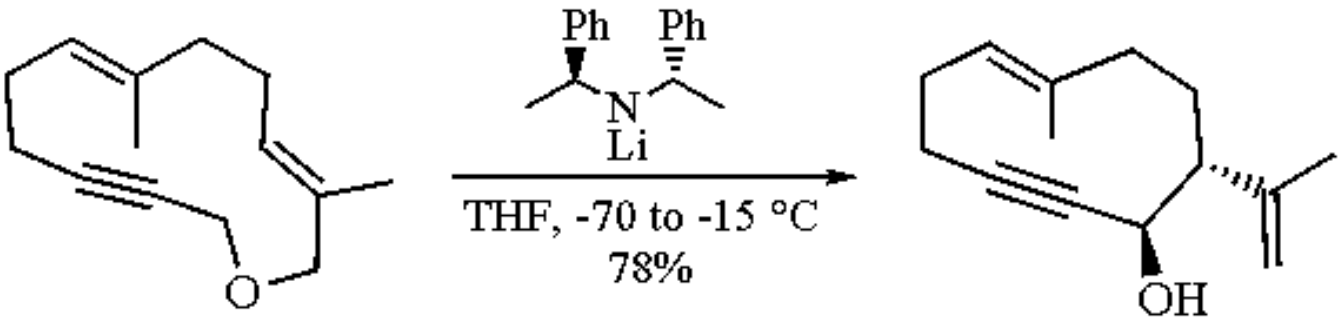

(15)

70% ee

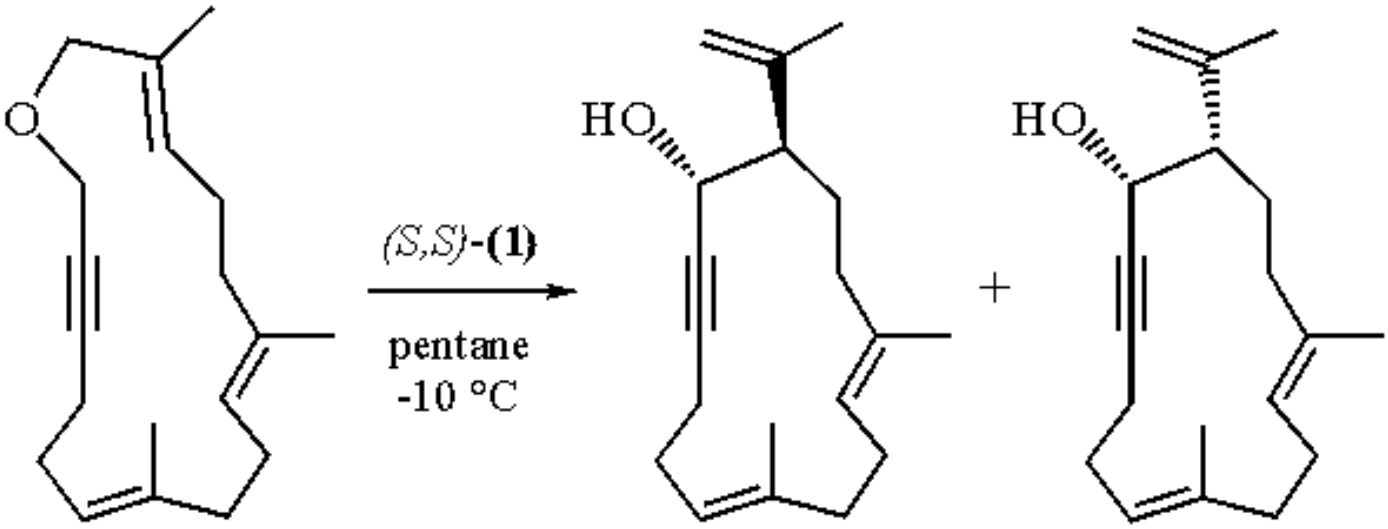

(16)

33% ee 60:40

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N,N-Dimethyl Dichlorophosphoramide

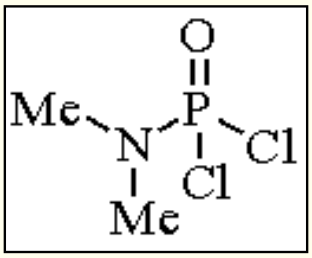

[677-43-0] · $C_2H_6Cl_2NOP$ · *N,N*-Dimethyl Dichlorophosphoramide · (MW 161.96)

(electrophilic phosphorylating reagent used to convert vicinal diols to alkenes[2,3] and to activate carboxylic acids and alcohols towards nucleophiles)

Alternate Names: (dimethylamido)phosphoryl dichloride; dimethylphosphoramidic dichloride; *N,N*-dimethylamidophosphorodichloridate.

Physical Data: bp 194-195 °C/760 mmHg; *d* 1.369 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid.

Preparative Method: obtained by treatment of ***Phosphorus Oxychloride*** with dimethylamine.[1]

Purification: fractional distillation.

Handling, Storage, and Precautions: very reactive towards water, alcohols, and amines.

Diol Elimination.

N,N-Dimethyl dichlorophosphoramide efficiently converts vicinal diols into cyclic phosphoramides. These cyclic phosphoramides, when treated with ***Lithium*** in ammonia, afford alkenes resulting primarily via *syn* elimination.[2,3] The process occurs in high yield with cyclic diols to afford *cis*-alkenes contaminated with ~10% of the *trans*-isomer (eq 1). Yields, however, are typically much lower with cyclic *trans*-diols which afford *trans*-alkenes in 10- and 12-membered rings (eq 2); for a complete discussion on alternative methods, consult Block.[4]

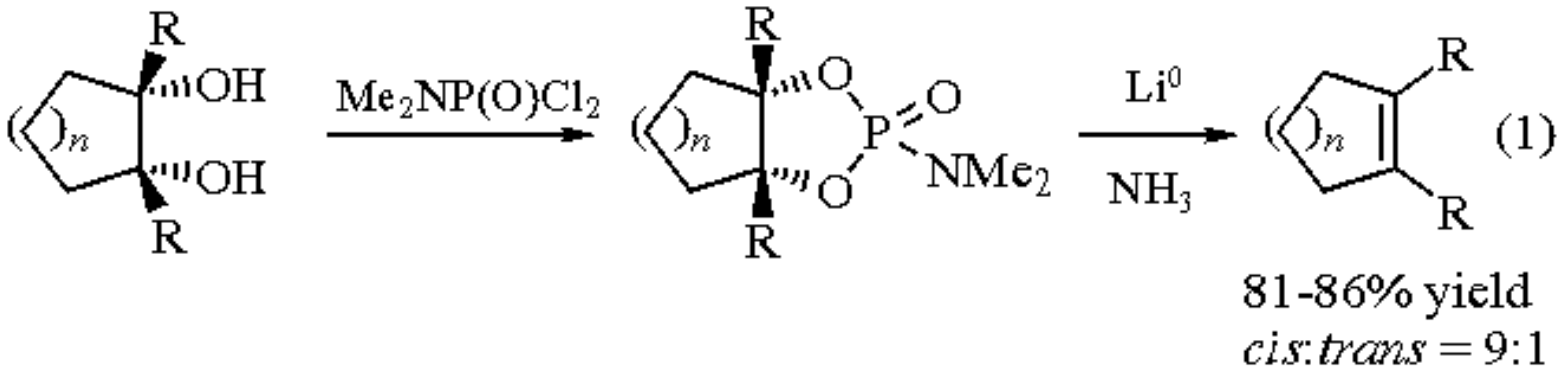

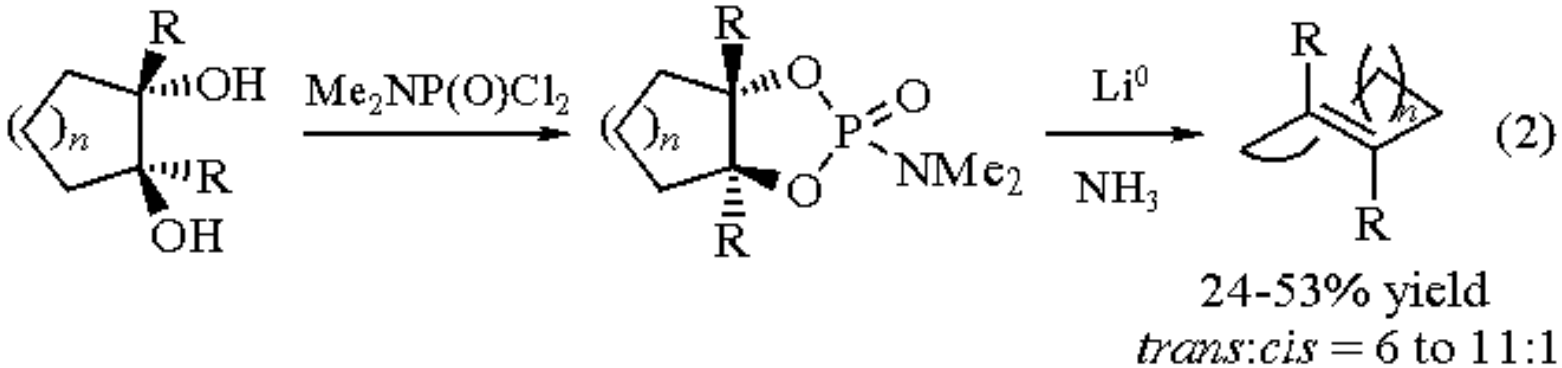

Carboxylic Acid Activation.

Dimethyl dichlorophosphoramide readily phosphorylates carboxylic acids to give a mixed anhydride which reacts at carbon with a variety of nucleophiles. Upon heating the mixed anhydride, the dimethylamino group is transferred to produce tertiary amides.[5] Alternatively, alcohols or thiols can be added to produce esters[6] or thiol esters[7] at 0-25 °C (eq 3).

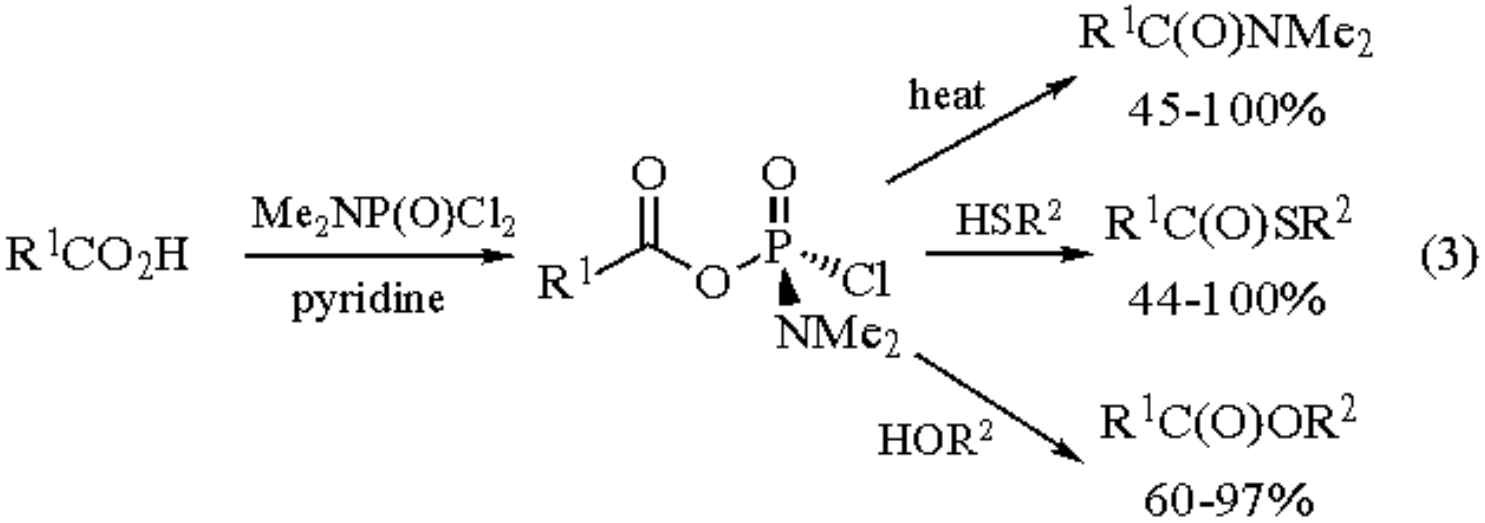

Applications of this method in the synthesis of β-lactams have been reported via the closure of β-amino alcohols[8] in high yield (eq 4) and the coupling of acetic acids with imines[9] in low to moderate yields (eq 5).

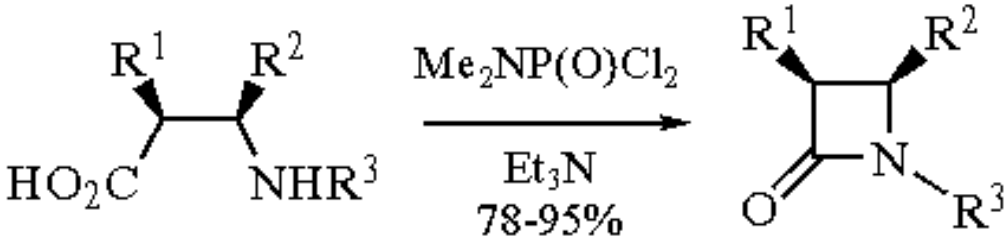

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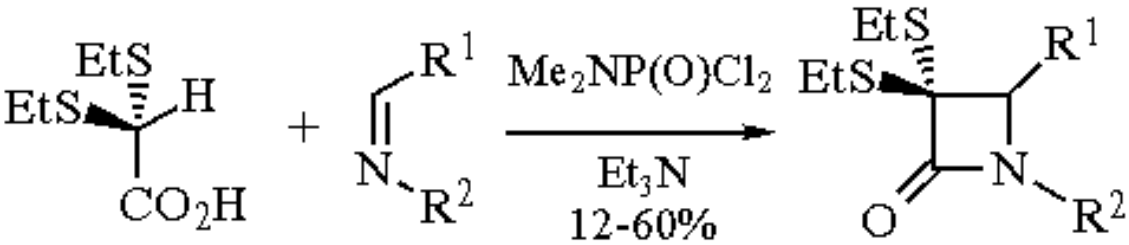

(5)

Although yields are often quite good (eqs 1-5) these methods are rarely used instead of acid chloride or ***1,3-Dicyclohexylcarbodiimide*** couplings.

Alcohol Activation.

Dimethyl dichlorophosphoramide also readily phosphorylates alcohols to produce an activated alcohol which undergoes displacement and elimination reactions. Primary, secondary, and tertiary alcohols are phosphorylated at rt. Upon heating the activated alcohol at ~80 °C for several hours, primary alcohols produce alkyl chlorides by an S_N2 process, tertiary alcohols produce alkenes by elimination (*trans* elimination is slightly more facile than *cis*), and secondary alcohols produce mixtures of alkyl chlorides and alkenes (eq 6).[10]

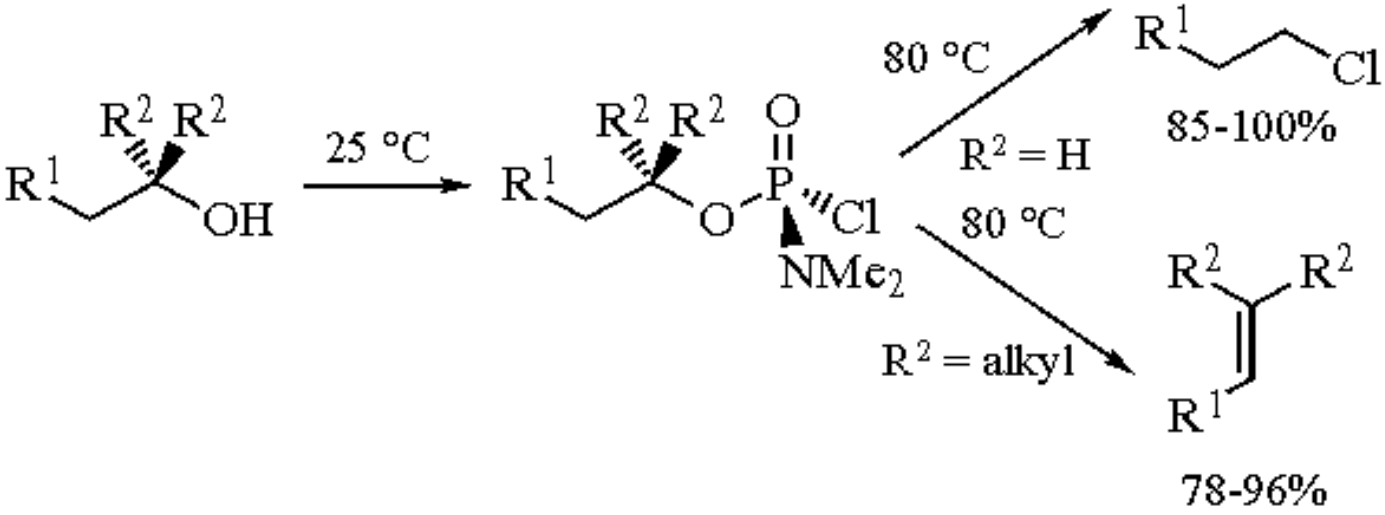

(6)

The phosphorylated alcohols may be treated at rt with dimethylamine to produce a tetramethylphosphorodiamidate derivative. These derivatives can be treated with lithium/ethylamine to reductively cleave the carbon-oxygen bond and produce deoxygenation products (eq 7).[11]

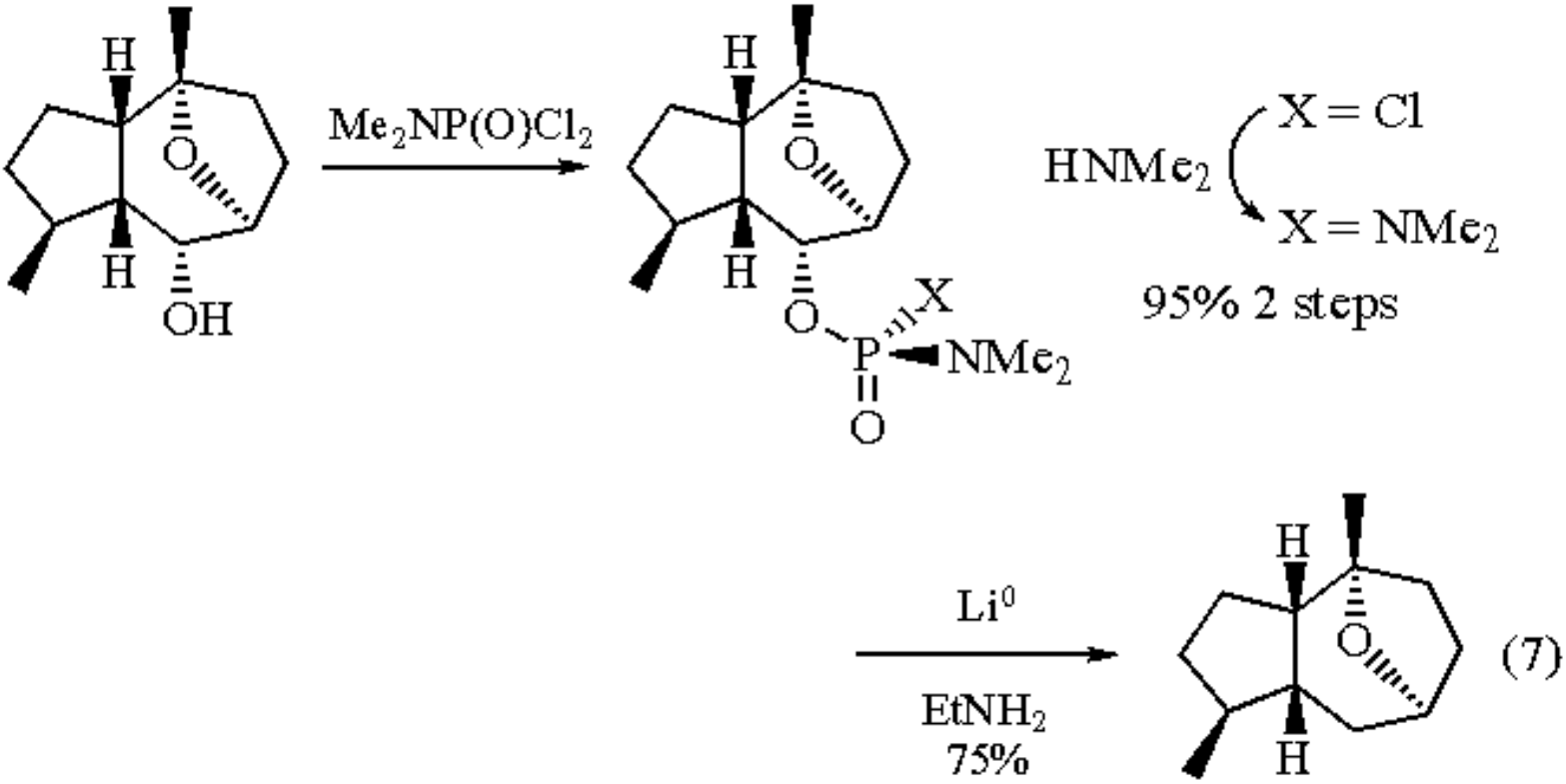

Dimethyl dichlorophosphoramide phosphorylates a broad range of alcohols, but the production of alkenes and alkyl chlorides is of somewhat limited utility since the two processes are competitive with secondary alcohols and since *trans* and *cis* eliminations occur at comparable rates. The reductive deoxygenation, on the other hand, is quite efficient with a broad range of substrates.

---

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2,2-Dimethyl-1,3-dioxane-4,6-dione[1]

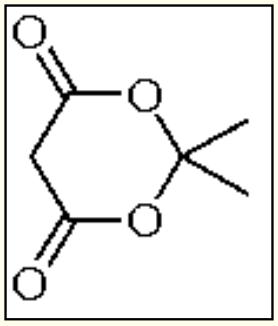

[2033-24-1] · $C_6H_8O_4$ · 2,2-Dimethyl-1,3-dioxane-4,6-dione · (MW 144.12)

(substitute for malonic esters as a two- or three-carbon nucleophile)

Alternate Name: Meldrum's acid.

Physical Data: mp 94-95 °C (dec); pK_a 4.8 in water, 7.3 in DMSO.[2]

Form Supplied in: colorless crystals; commercially available.

Purification: recrystallization from acetone and water.

Introduction.

Meldrum's acid (**1**) is not just a simple substitute for malonic esters but rather a unique reagent in its own right for the following reasons. Firstly, the acidity of Meldrum's acid is comparable to that of acetic acid,[2] and its stable enolate anion (**2**) is susceptible to the attack of various electrophiles even under nearly neutral conditions. Arnett[2a] has shown that the anomalously high acidity of (**1**) relative to dimethyl malonate and dimedone is the result of restricted rotation of the ester bonds in the bislactone structure. Subsequently, Houk[2c] and Wiberg[2d] have completed computational studies that provide an explanation of the acidity enhancement of (**1**), i.e. loss of a proton from the (*E*) rotamer (**3**) is easier than from the (*Z*) rotamer (**4**). Secondly, Meldrum's acid is susceptible to nucleophilic attack at the carbonyl groups, which results in ring cleavage, forming acetone and malonic acid derivatives (eq 1). Among the reactions of Meldrum's acid derivatives, the four described in the following sections have been the most frequently used for organic synthesis.[1b]

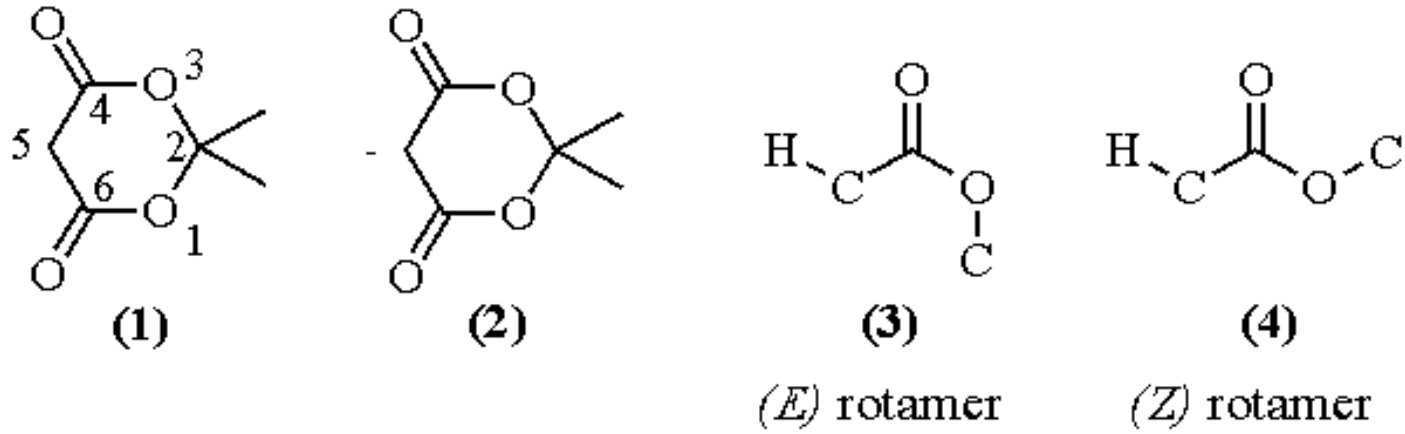

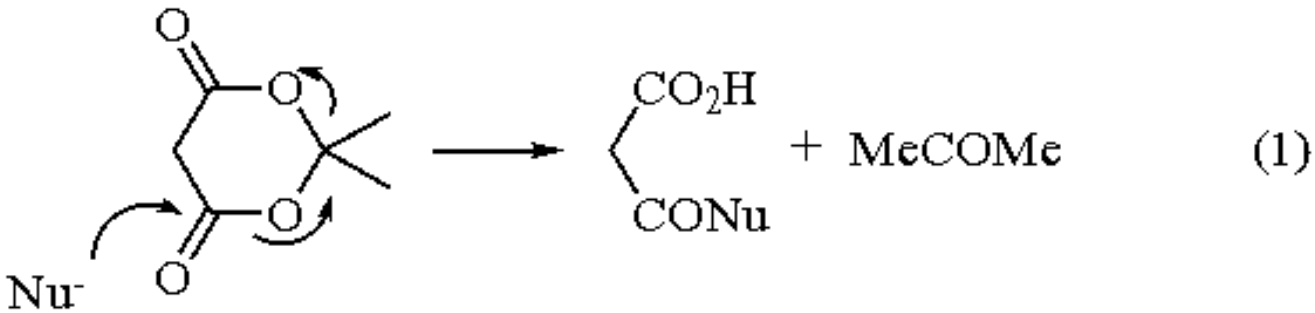

Ring Opening Reactions Initiated by Nucleophiles.

Under solvolytic conditions, Meldrum's acid derivatives generally form malonyl monoesters (eq 1). When ethanolysis is conducted in the presence of pyridine and ***Copper*** powder, subsequent decarboxylation occurs, giving monocarboxylates (eq 2)[3]. Amines cleave the dioxane ring in a similar manner, giving amides. In the reaction shown in eq 3, the 5-alkyl intermediate formed via Michael addition of (**1**) to the α,β-unsaturated ketone undergoes intramolecular attack by the amine nitrogen to form a tetrahydropyridone ring.[4] β-Keto esters can be readily prepared by the reaction of 5-acyl Meldrum's acids with alcohols (eq 4).[5] This reaction has been the most widely used application of Meldrum's acid, and it figures as a key step in many organic syntheses.[1b] Steps in the syntheses of tricyclic bimane,[6] a thiol analytical agent for proteins, and didemnin,[7] a cytotoxic cyclic peptide, are representative examples, which are illustrated in eqs 5 and 6, respectively. A chiral dienophile has been prepared by this method (eq 7).[8]

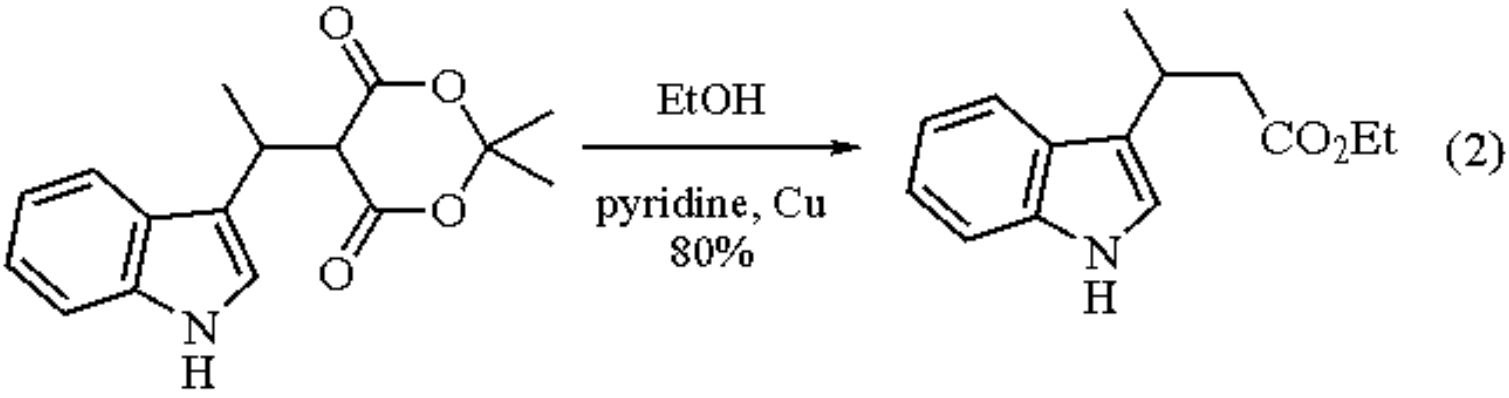

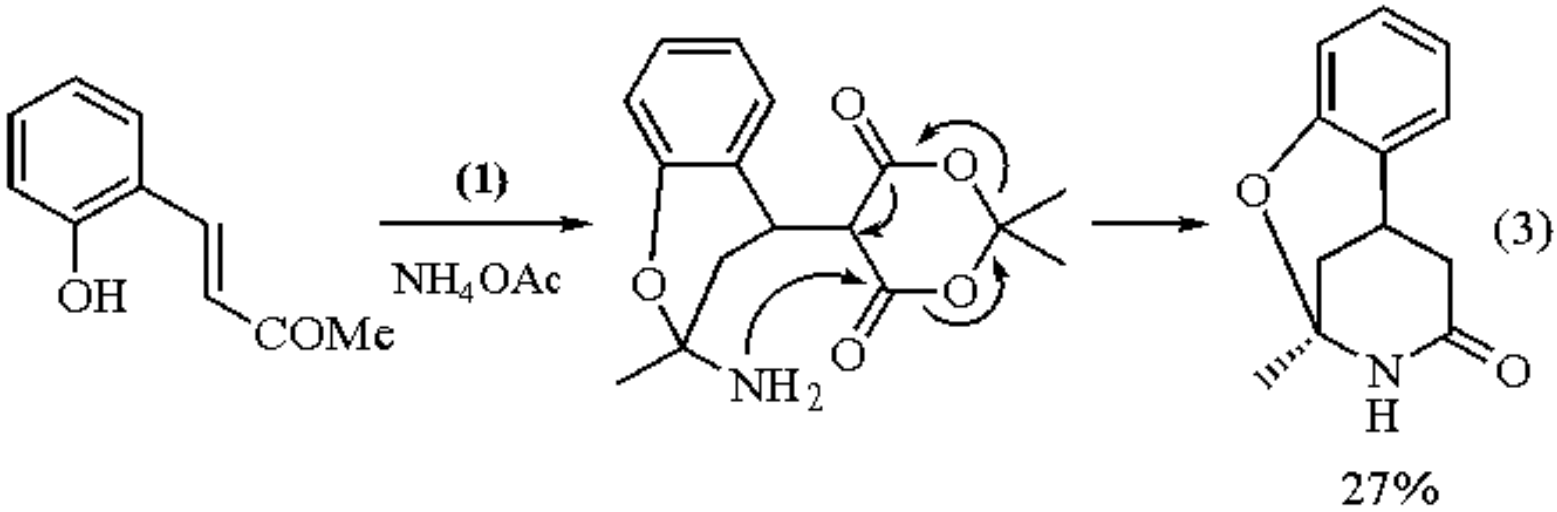
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O
27%

(3)

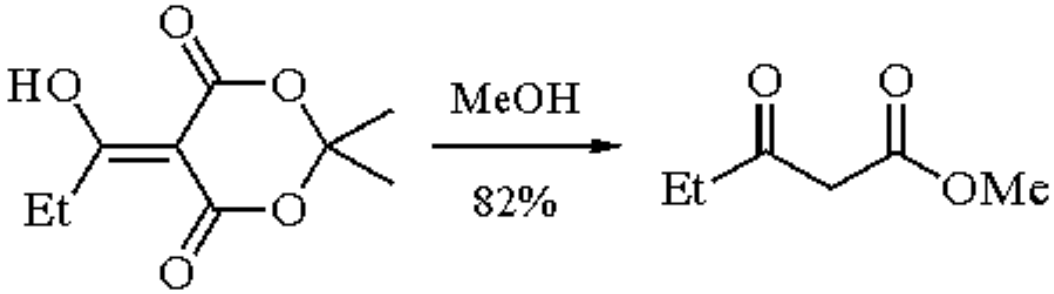
HO
O
O
O
O
Et
MeOH
82%
O
O
Et
OMe

(4)

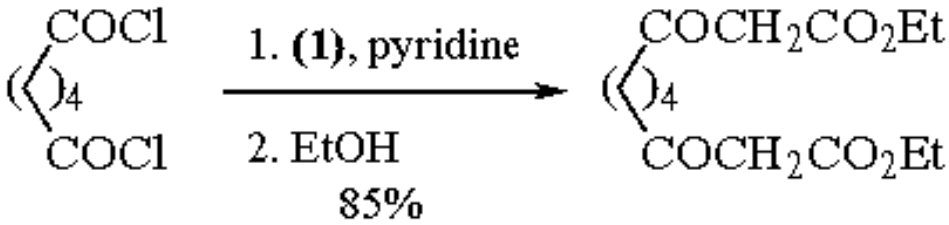
COCl
4
COCl
1. (1), pyridine
2. EtOH
85%
COCH2CO2Et
4
COCH2CO2Et

(5)

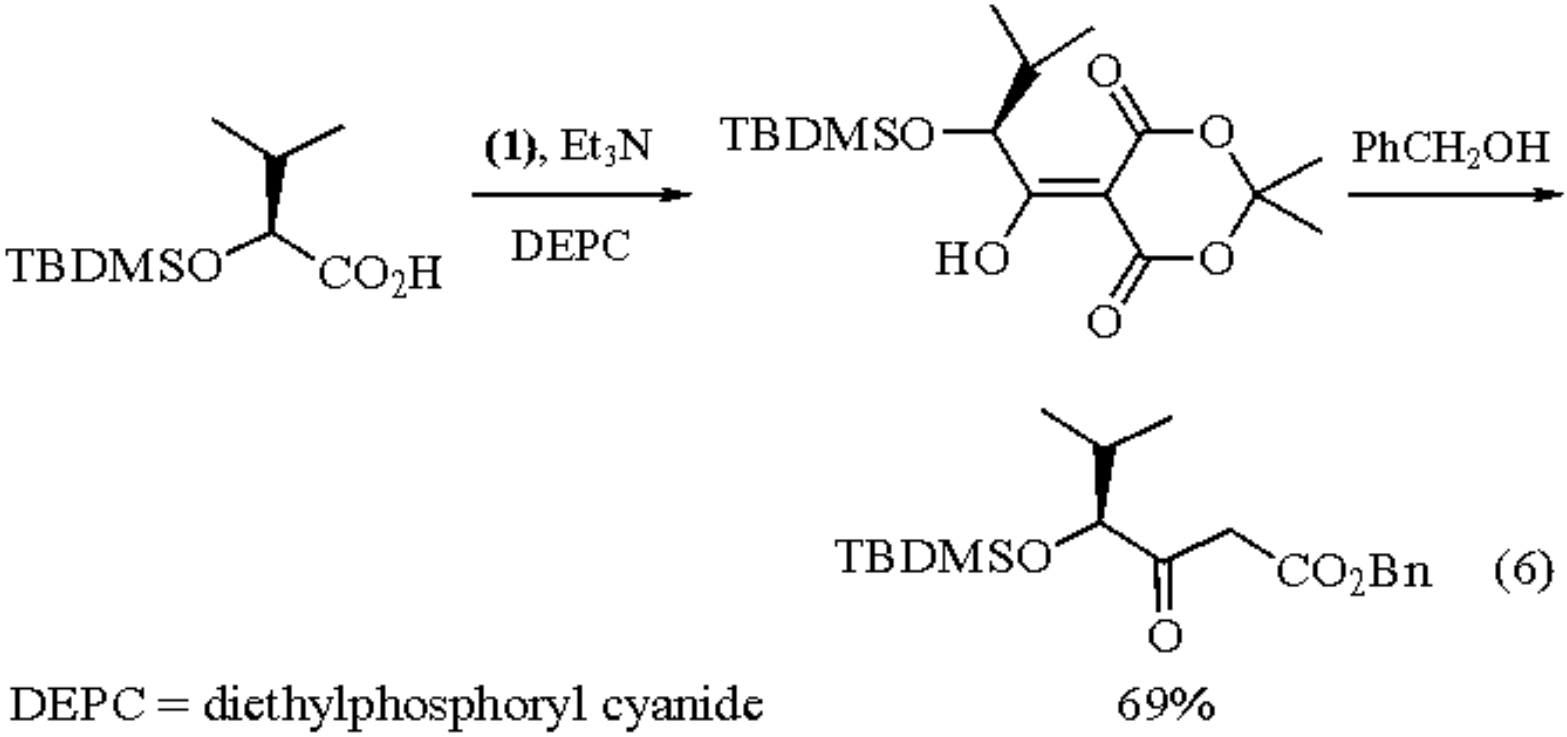

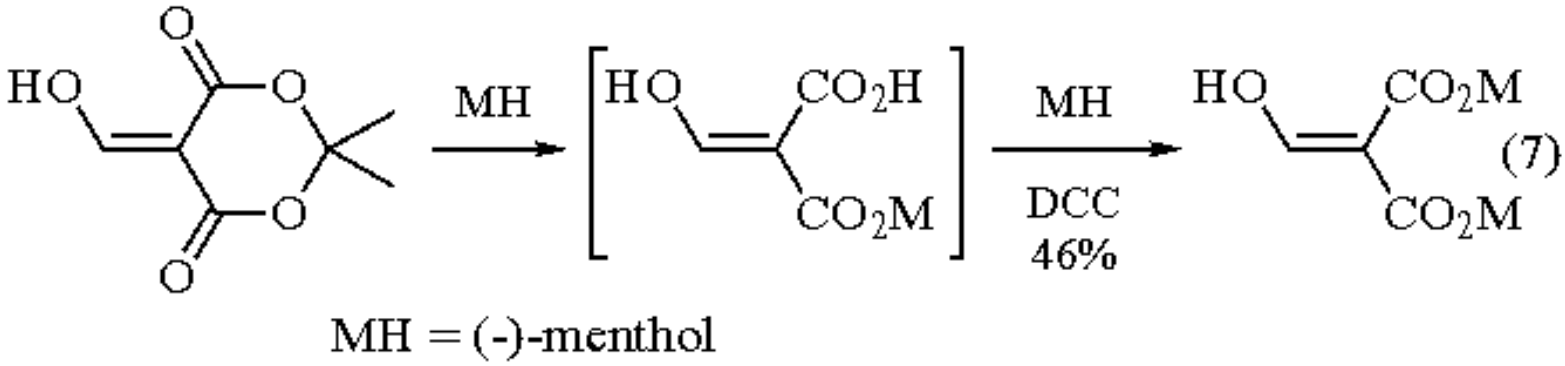

Conjugate Addition.

5-Methylene Meldrum's acids, which are easily prepared by a variety of methods[1] (in particular by the Knoevenagel reaction of (**1**) with carbonyl compounds), undergo conjugate additions with various nucleophiles, such as hydride (eq 8),[9] organometallic reagents (eq 9),[10] and phenols (eq 10).[11] Polyacylated alkenes are susceptible to conjugate addition of enolates, leading to a variety of products (eq 11).[12] Analogously, homoconjugate addition of nucleophiles to spiro-cyclopropyl derivatives takes place resulting in cyclopropyl ring opening (eq 12).[13]

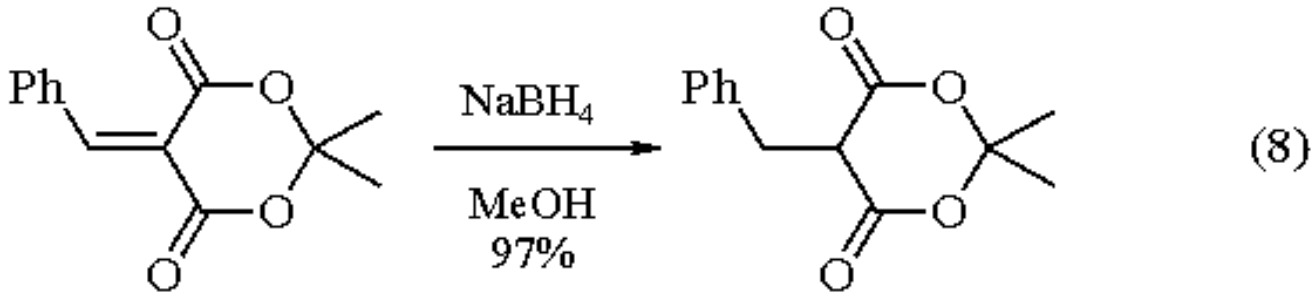

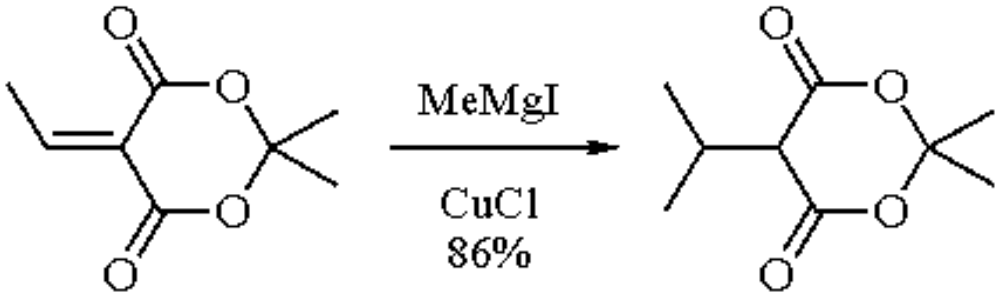
MeMgI
CuCl
86%

(9)

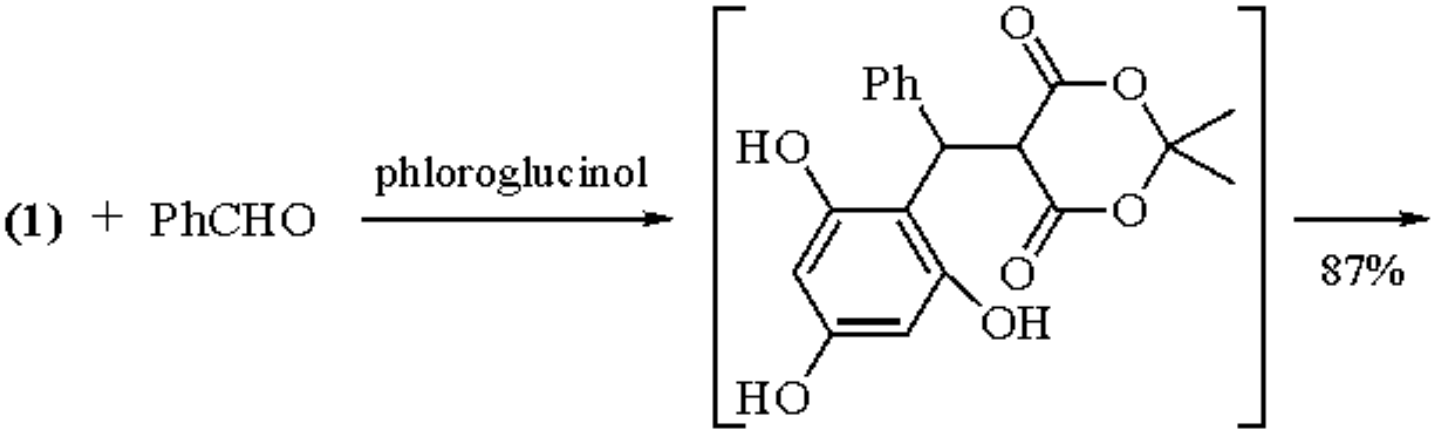
(1) + PhCHO
phloroglucinol
Ph
HO
OH
HO
87%

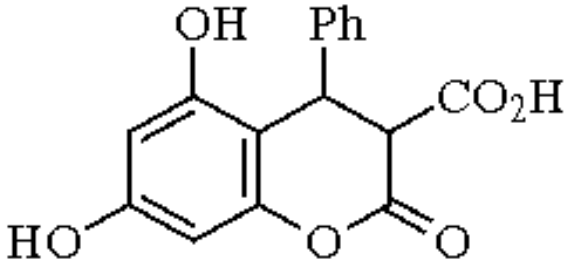
OH
Ph
CO2H
HO

(10)

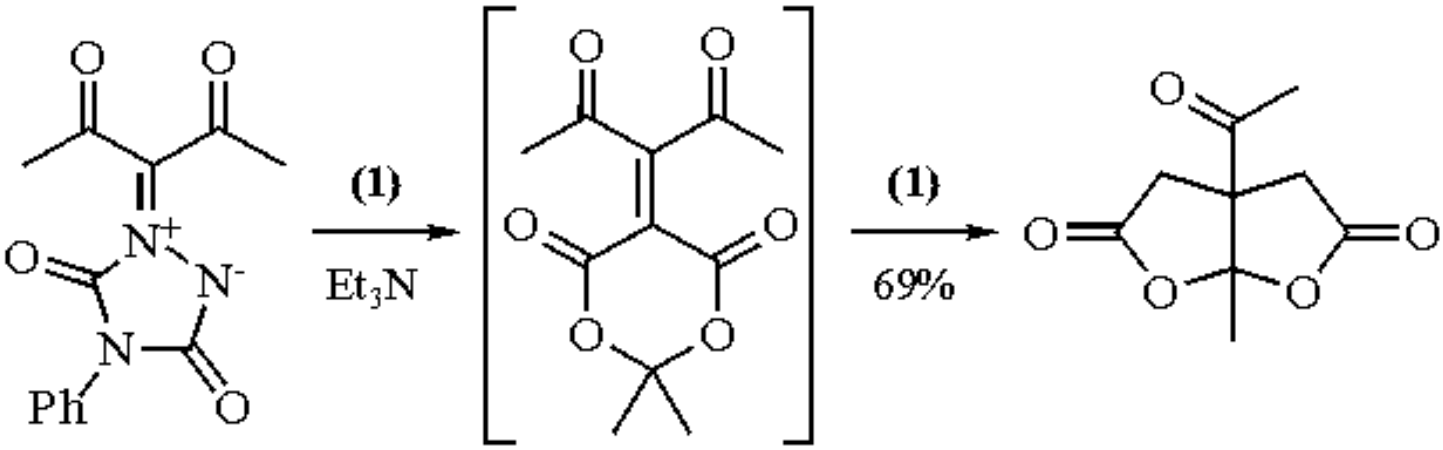
(1)
Et3N
(1)
69%
Ph

(11)

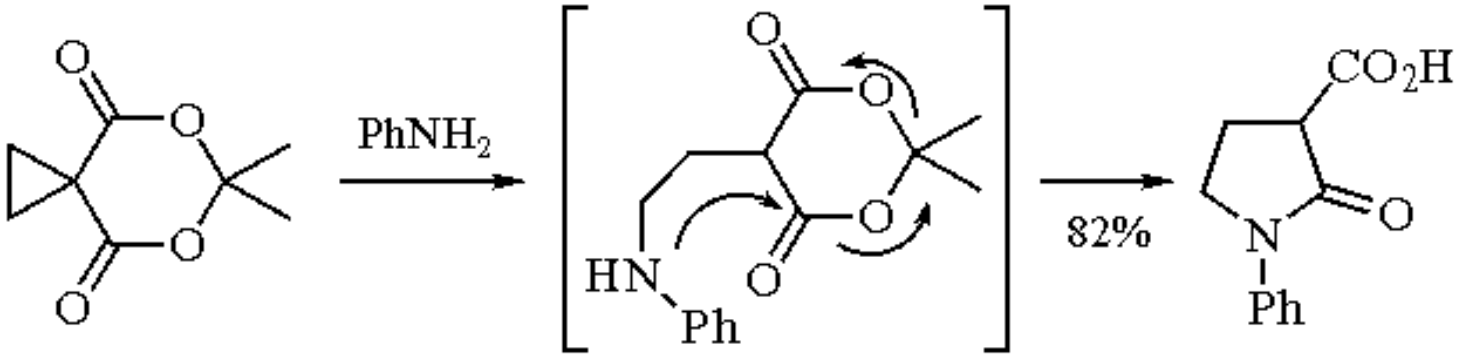

(12)

Cycloaddition.

The C=C double bond of 5-methylene Meldrum's acid is usually an active dienophile (eq 13),[14] but the derivatives also act as reactive heterodienes both in inter- (eq 14)[15] and intramolecular (eqs 15 and 16)[16,17] Diels-Alder reactions.

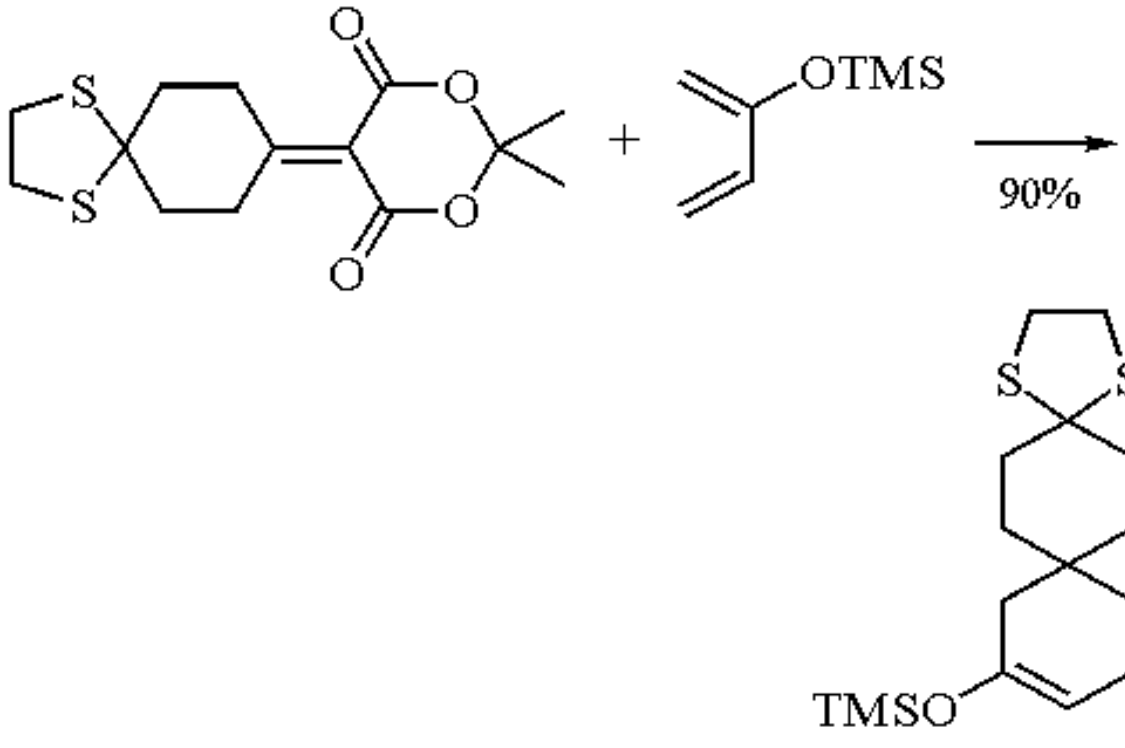

(13)

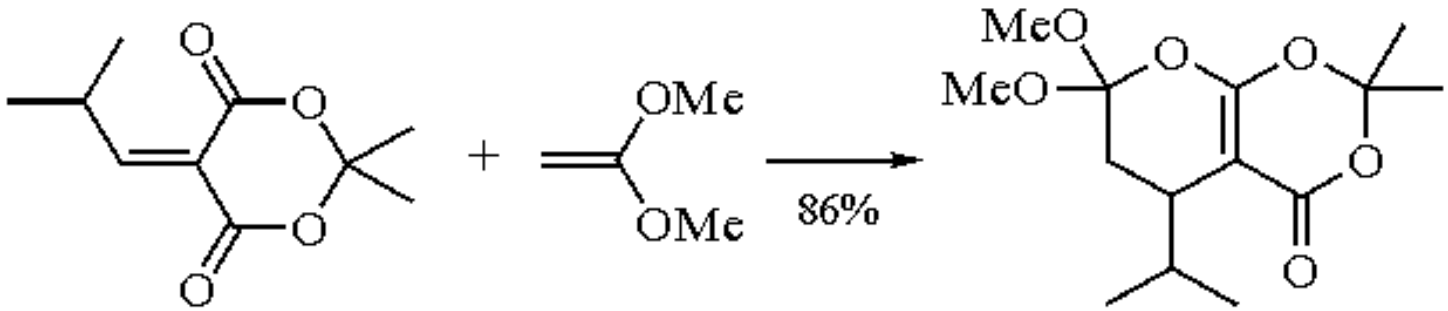

(14)

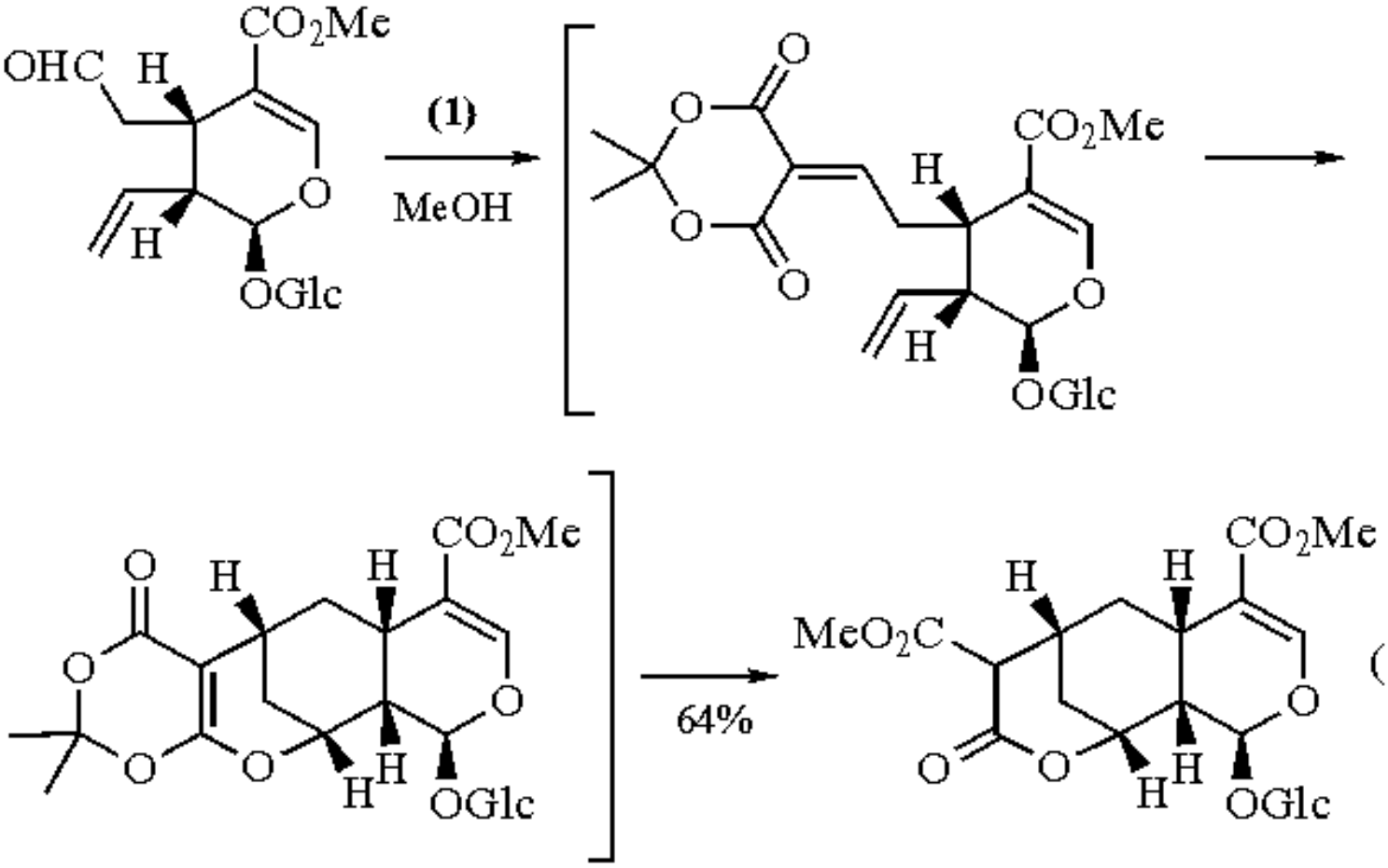
OHC
H
CO2Me
(1)
MeOH
O
H
OGlc
CO2Me
H
O
H
OGlc
64%
MeO2C
(15)

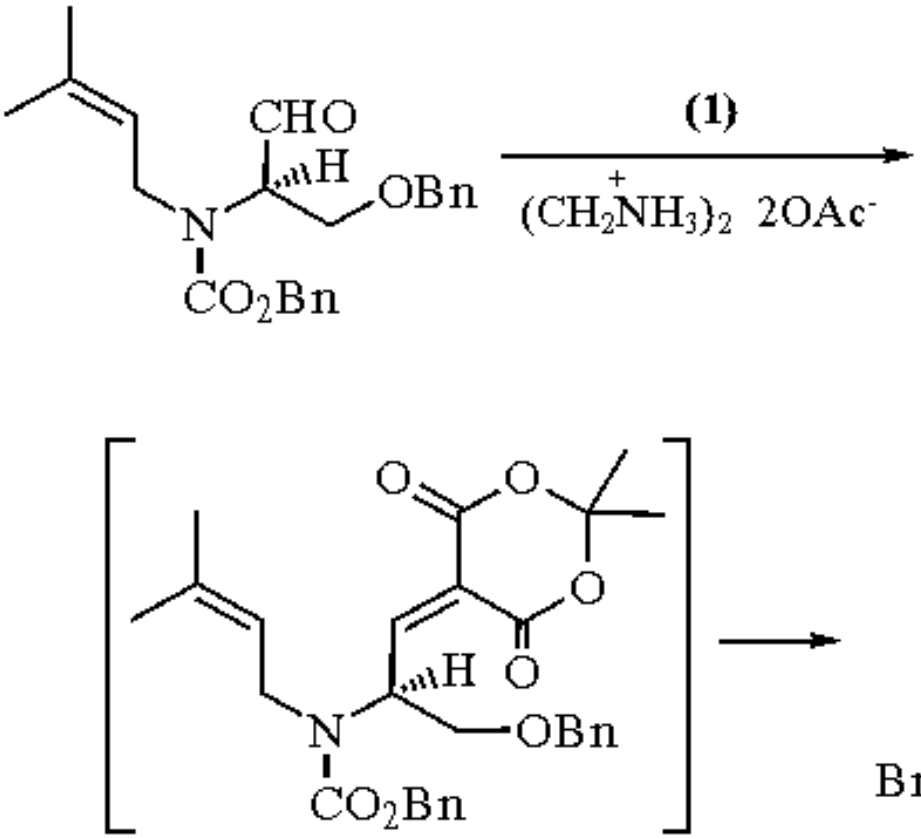
CHO
H
OBn
N
CO2Bn
(1)
(CH2NH3)2 2OAc-
H
OBn
BnO2C
(16)

Pyrolysis.

5-Methylene Meldrum's acid loses acetone and carbon dioxide at elevated temperatures giving methyleneketenes which further lose carbon monoxide thereby generating alkylidenecarbenes (eq 17).[1b] A wide variety of reactive species such as benzyne, cyclohexyne and hydroxyacetylene has been detected.[18] Various heterocycles (eq 18)[19] have been synthesized by intramolecular trapping of these chemical species.[1b]

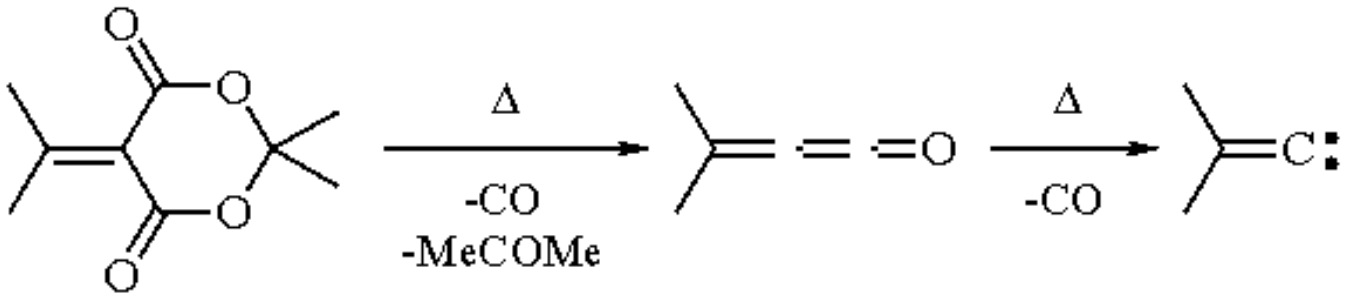

(17)

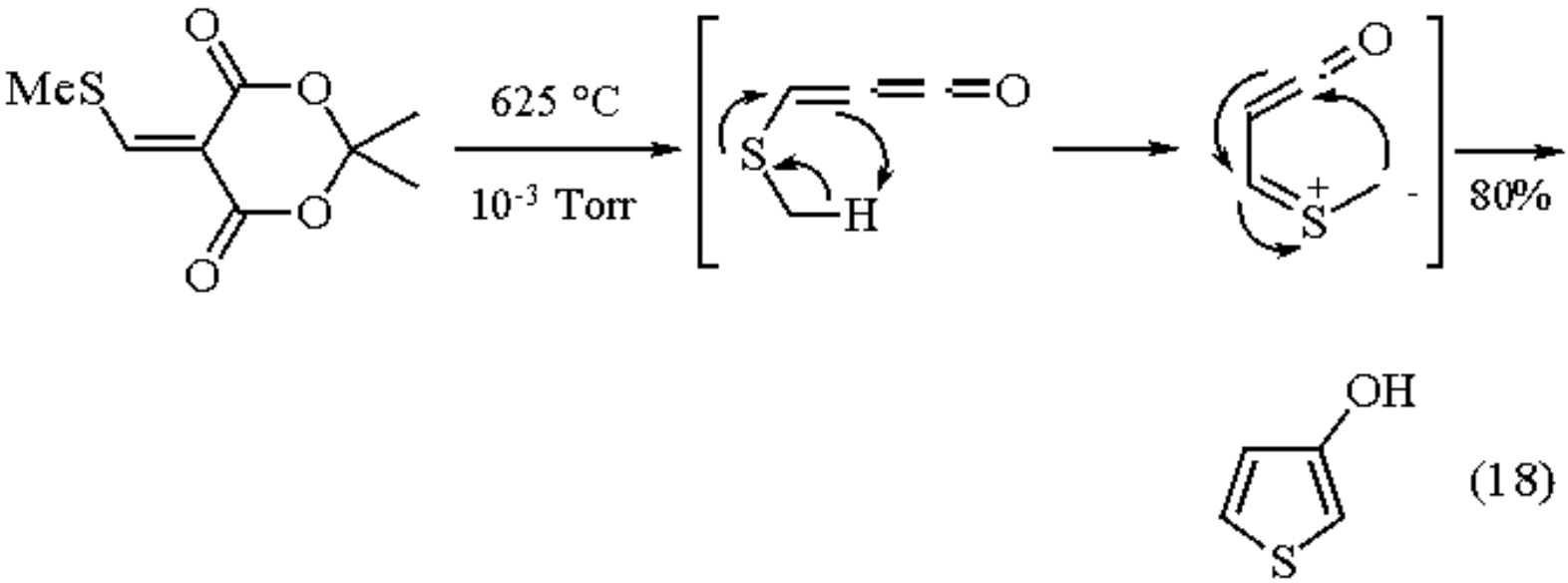

(18)

Other Applications.

Recently, the applications of Meldrum's acid have been extended to the syntheses of a macrocyclic β-keto lactone (eq 19),[20] 4-pyridyl-substituted heterocycles (eq 20),[21] and 2-substituted indoles (eq 21).[22] The structures of Meldrum acid derivatives[23] and the kinetics of nitrosation of (**1**)[24] have been studied by NMR and X-ray methods.

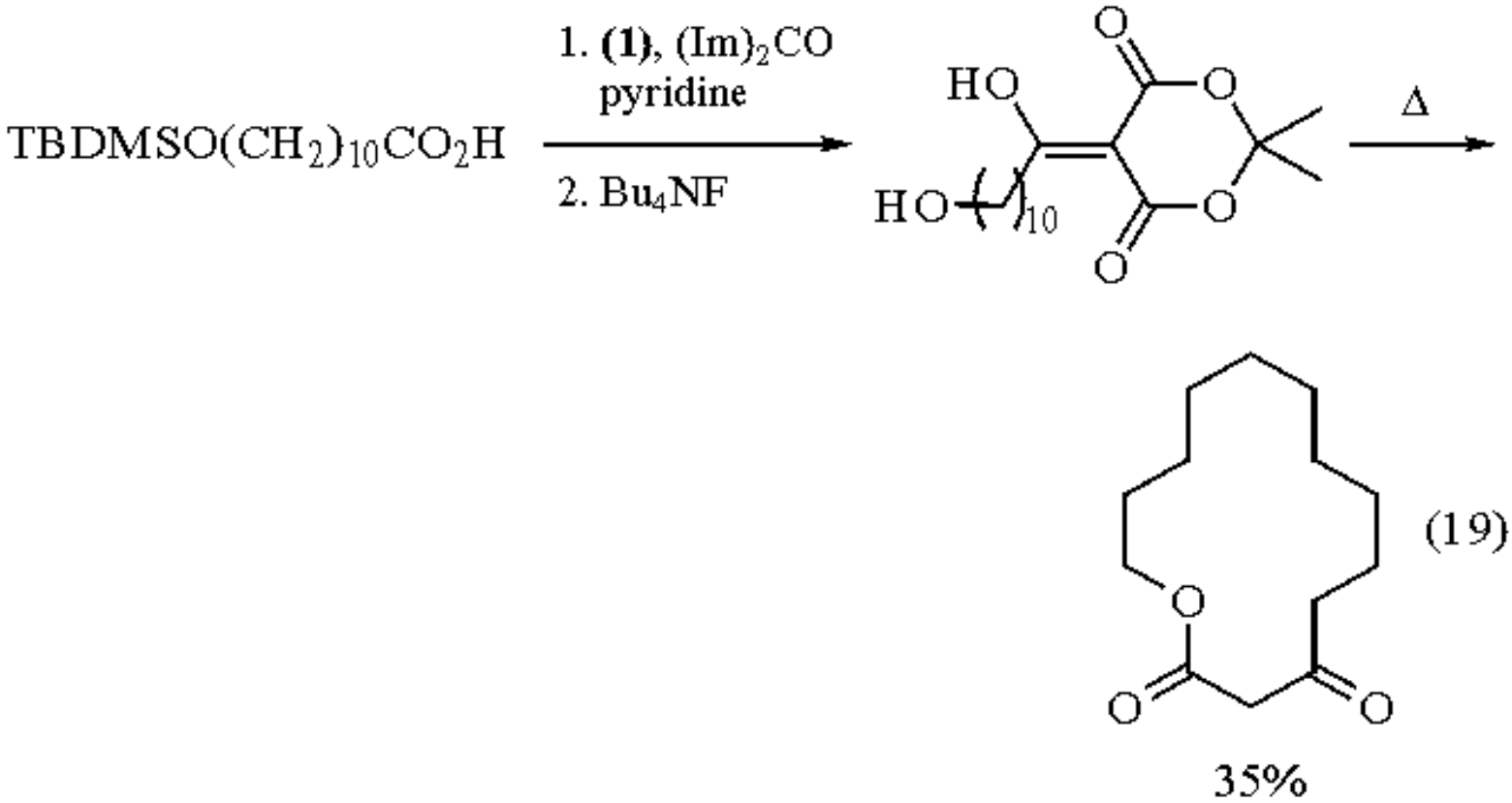
TBDMSO(CH2)10CO2H
1. (1), (Im)2CO
pyridine
2. Bu4NF
HO
HO
10
O
O
O
O
O
Δ
O
O
O
35%

(19)

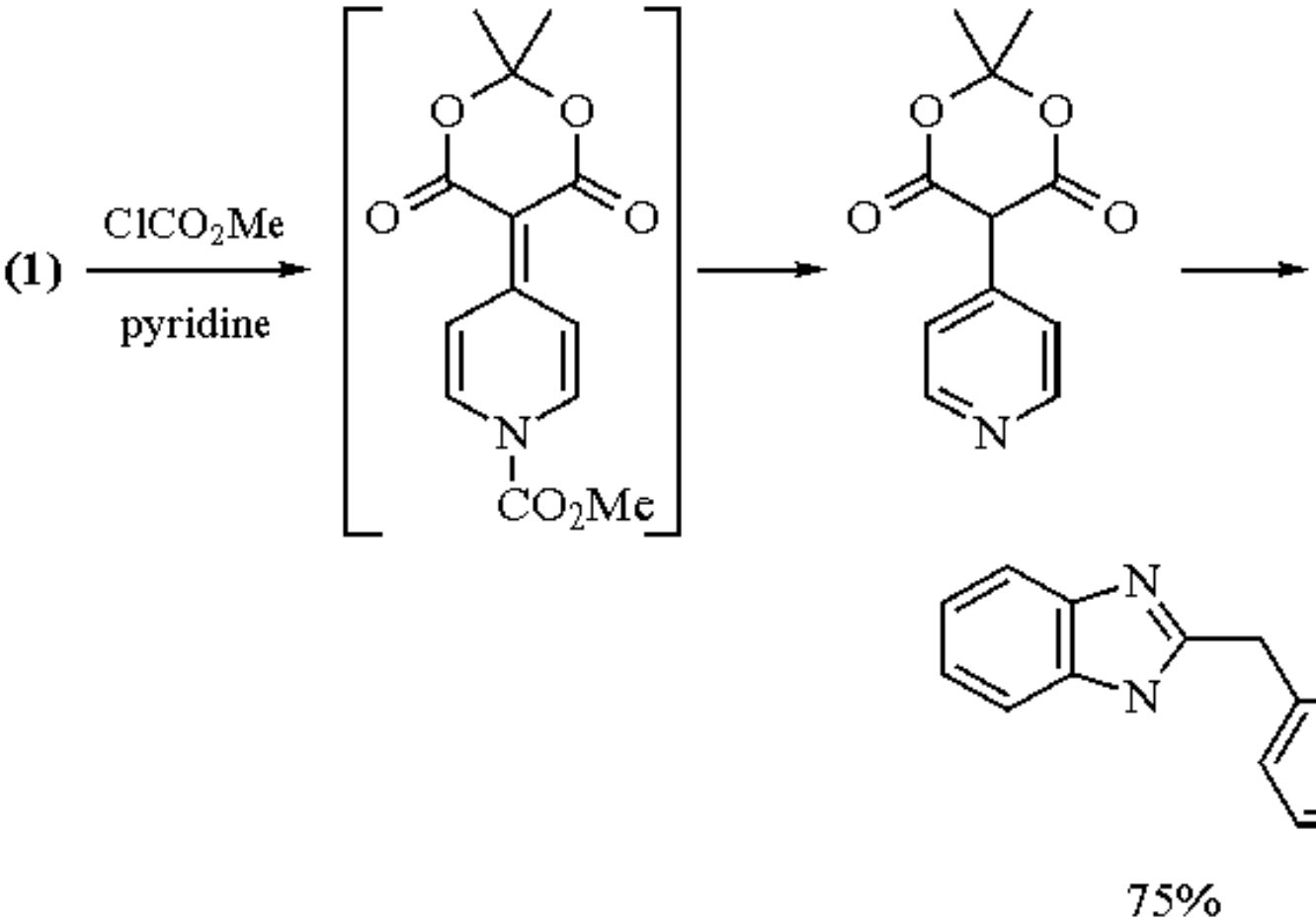
(1)
ClCO2Me
pyridine
O
O
O
O
N
CO2Me
O
O
O
O
N
N
N
N
75%

(20)

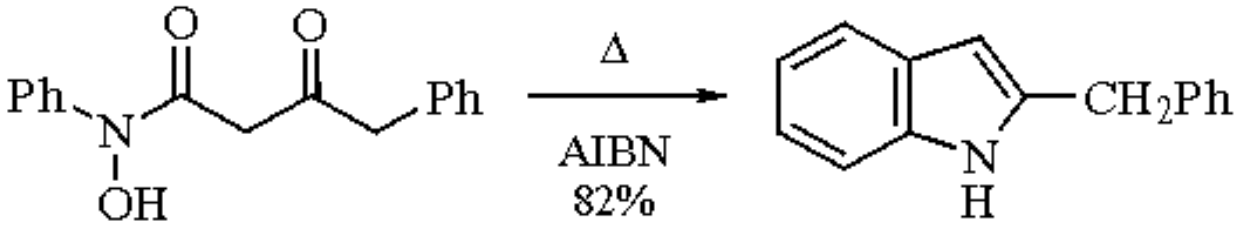

(21)

Related Reagents.

Diethyl Malonate; ***6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione***; ***Diethyl Ethoxymagnesiomalonate***; ***Ethyl Malonate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Malonic Acid***.

---

1. (a) McNab, H. *CSR* **1978**, *7*, 345. (b) Chen, B.-C. *H* **1991**, *32*, 529.
2. (a) Arnett, E. M.; Harrelson, J. A. *JACS* **1987**, *109*, 809. (b) Bausch, M. J.; Gaudalupe-Fasano, C.; Gostowski, R.; Selmarten, D.; Vaugh, A. *JOC* **1991**, *56*, 5640; cf. Bordwell, F. G. *ACR* **1988**, *21*, 456. (c) Wang, X.; Houk, K. N. *JACS* **1988**, *110*, 1870. (d) Wiberg, K. B.; Laidig, K. E. *JACS* **1988**, *110*, 1872.
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4. Svelik, J.; Goljer, I.; Turecek, F. *JCS(P1)* **1990**, 1315; cf. (a) Pettit, G. R.; Herald, D. L.; Singh, S. B.; Thornton, T. J.; Mullaney, J. T. *JACS* **1991**, *113*, 6692. (b) Patino, N.; Frérot, E.; Galeotti, N.; Poncet, J.; Coste, J.; Dufour, M.-N.; Jouin, P. *T* **1992**, *48*, 4115.
5. (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *JOC* **1978**, *43*, 2087. (b) Oikawa, Y.; Yoshioka, T.; Sugano, K.; Yonemitsu, O. *OSC* **1990**, *7*, 359.
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10. Huang, X.; Chan, C.-C.; Wu, Q.-L. *TL* **1982**, *23*, 75.
11. Nair, V. *SC* **1987**, *17*, 723.
12. Wilson, R. M.; Hengge, A. C.; Ataei, A.; Ho, D. M. *JACS* **1991**, *113*, 7240.
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14. Bell, V. L.; Holmes, A. B.; Hsu, S.-Y.; Mock, G. A.; Raphael, R. A. *JCS(P1)* **1986**, 1507.
15. Bitter, J.; Leitich, J.; Partale, H.; Polansky, O. E.; Reimer, W.; Ritter-Thomas, U.; Schlamann, B.; Stilkerieg, B. *CB* **1980**, *113*, 1020.
16. (a) Tietze, L. F.; Bärtels, C. *LA* **1991**, 155. (b) Tietze, L. F.; Beifuss, U.; Lokos, M.; Rischer, M.; Gohrt, A.; Scheldrich, G. M. *AG(E)* **1990**, *29*, 527.
17. Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *JACS* **1988**, *110*, 6467.
18. For example: (a) Tseng, J.; McKee, M. L.; Shevlin, P. B. *JACS* **1987**, *109*, 5474. (b) Wentrup, C.; Lorencak, P. *JACS* **1988**, *110*, 1880.
19. Hunter, G. A.; McNab, H. *CC* **1990**, 375.
20. Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A.; Weiler, L. *CJC* **1992**, *70*, 1427.
21. Henning, H.-G.; Stemplinger, G.; Rothe, K. *LA* **1992**, 813.
22. Hirao, K.; Mohri, K.; Yonemitsu, O.; Tabata, M.; Sohma, J. *TL* **1992**, *33*, 1459.
23. Blake, A. J.; McNab,. H.; Monahan, L. C. *JCS(P2)* **1991**, 2003.
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6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione

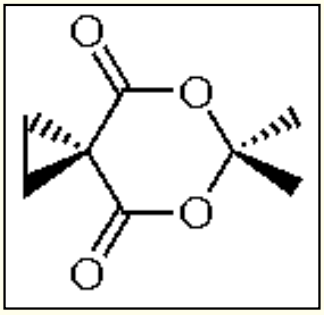

[5617-70-9] · $C_8H_{10}O_4$ · 6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione · (MW 170.18)

(reagent for electrophilic four-carbon homologation by homo-Michael reactions and for preparation of five- and six-membered heterocycles)

Physical Data: mp 58-60 °C;[1] for MS and NMR spectral data, see Maquestiau and Helferty.[2]

Solubility: sol ether, THF, DME, DMF; insol H_2O.

Preparative Method: the preparation of this compound has been described (eq 1).[1]

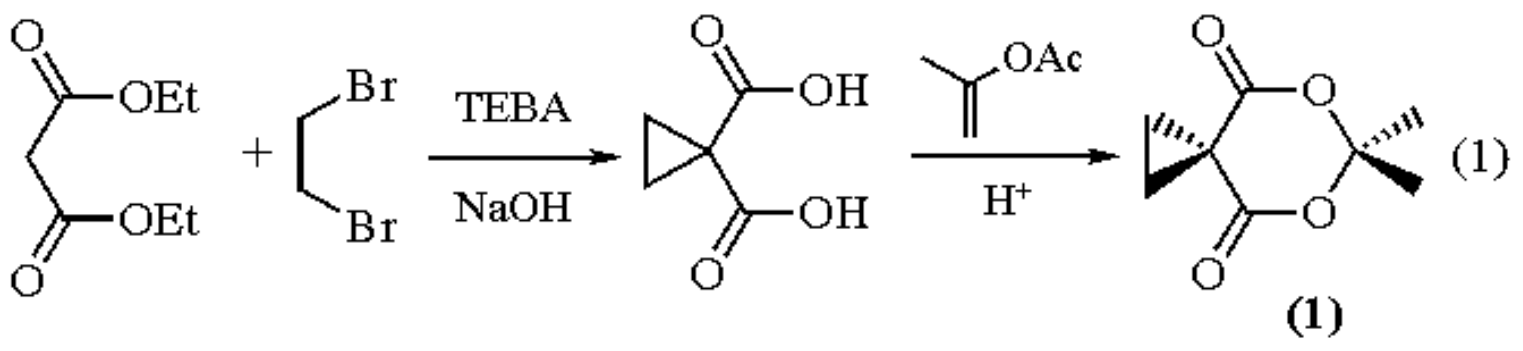

Handling, Storage, and Precautions: use in a fume hood.

Nucleophilic Ring Opening Reactions.

This derivative of Meldrum's acid (***2,2-Dimethyl-1,3-dioxane-4,6-dione***) exhibits enhanced reactivity in nucleophilic ring opening reactions compared to the corresponding diester of 1,1-cyclopropanedicarboxylate. For example, (**1**) undergoes ring opening with piperidine to give the zwitterion (**2**) (eq 2).[3] The facility of these homo-Michael reactions is attributable to the enhanced overlap of the carbonyl group double bonds with the adjacent cyclopropane ring bonds and to the stability of the

6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione

1,3-dioxane-4,6-dione anion leaving group.

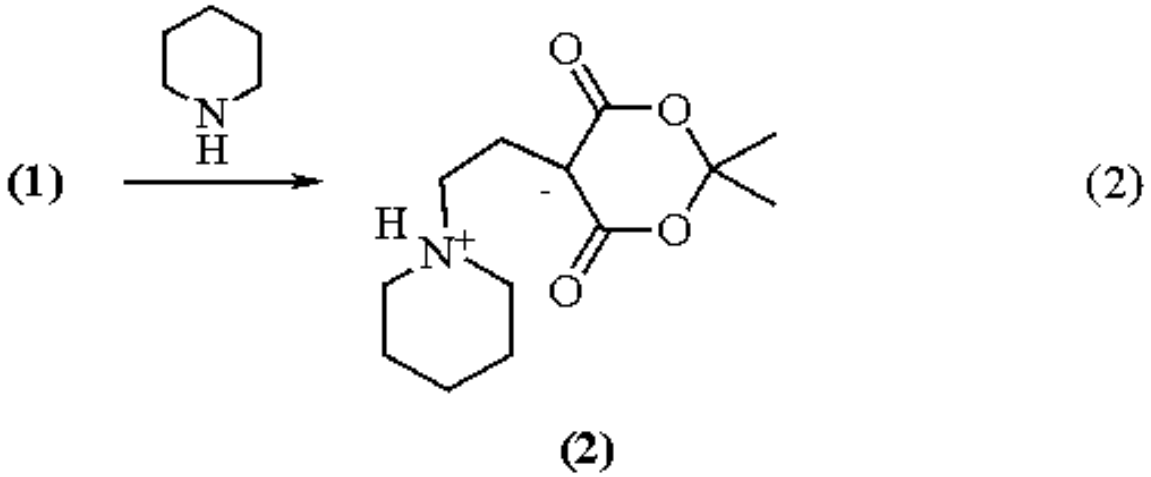

Similarly a number of carbon, sulfur, nitrogen, and oxygen nucleophiles react with this substrate under very mild conditions (eq 3).[3,4]

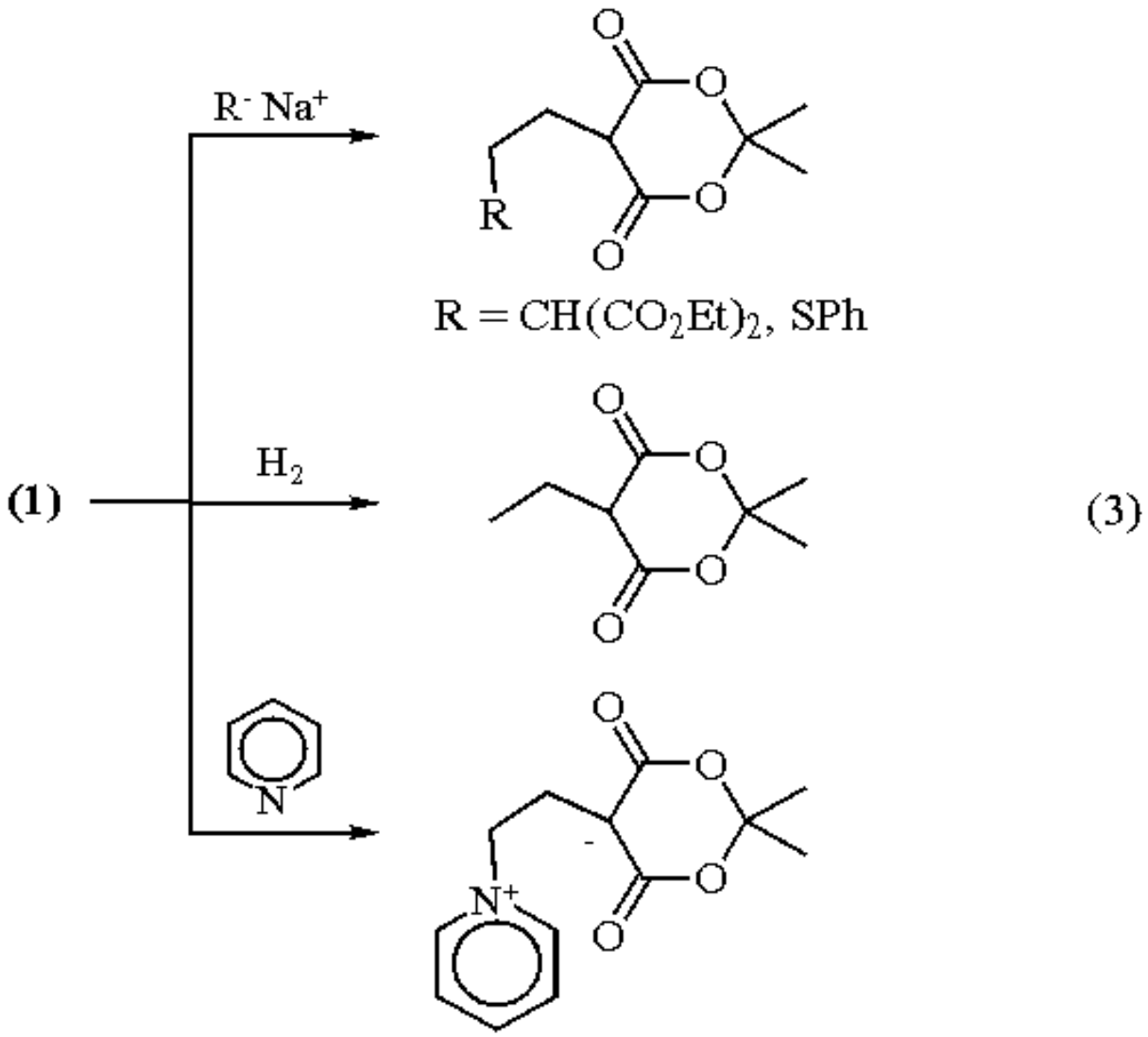

The norcarane analog of (**1**) has been prepared from bicyclo[4.1.0]heptane-7,7-dicarboxylic acid (eq 4). Hydrolytic ring

cleavage occurs in refluxing aqueous acetone with inversion of stereochemistry to give, after fragmentation of the dioxane ring and lactonization, the *trans*-fused γ-butyrolactone-α-carboxylic acid. Conversion to the α-methylene lactone is accomplished by a Mannich reaction.[5]

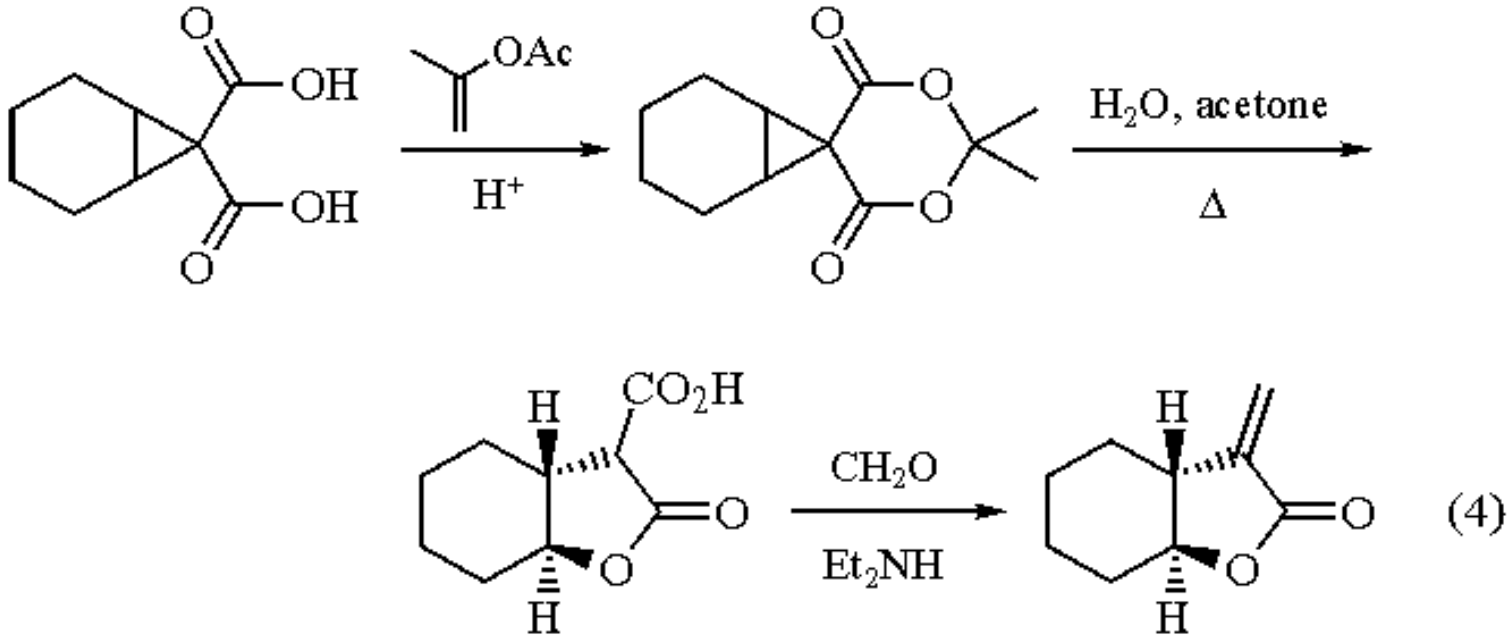

Reaction of (**1**) with aniline at rt results in opening of the cyclopropane ring and cyclization to give 2-oxo-1-phenyl-3-pyrrolidine carboxylic acid (eq 5).[3]

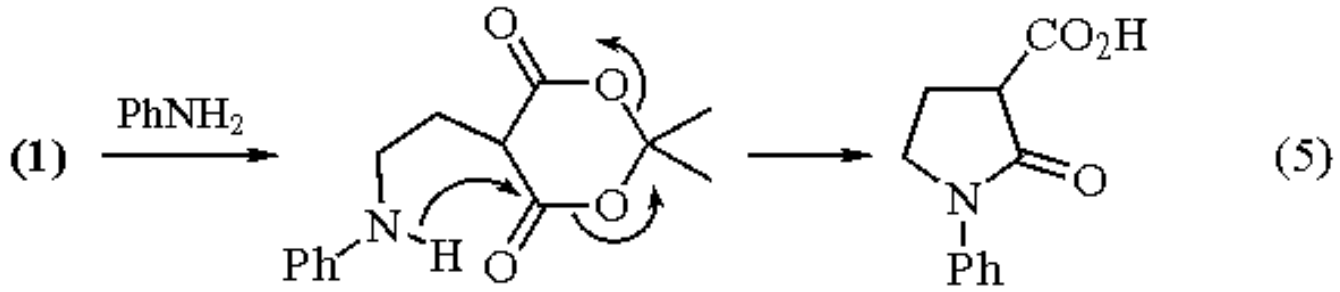

A number of amino esters,[6] pyrroles,[7] and other heterocyclic derivatives[8] have been used to effect nucleophilic ring opening of (**1**). However, due to the poor nucleophilicity of pyrrole, the reaction is carried out using ***Sodium Hydride*** as base (eq 6).

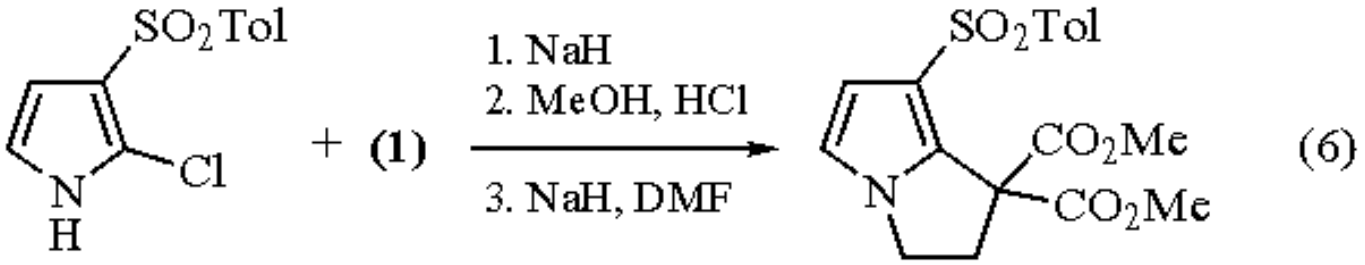

Reaction of (**1**) with alkyl- and arylhydrazines gives 1-substituted 1,4,5,6-tetrahydro-3(2*H*)-pyridazinones (eq 7).[9]

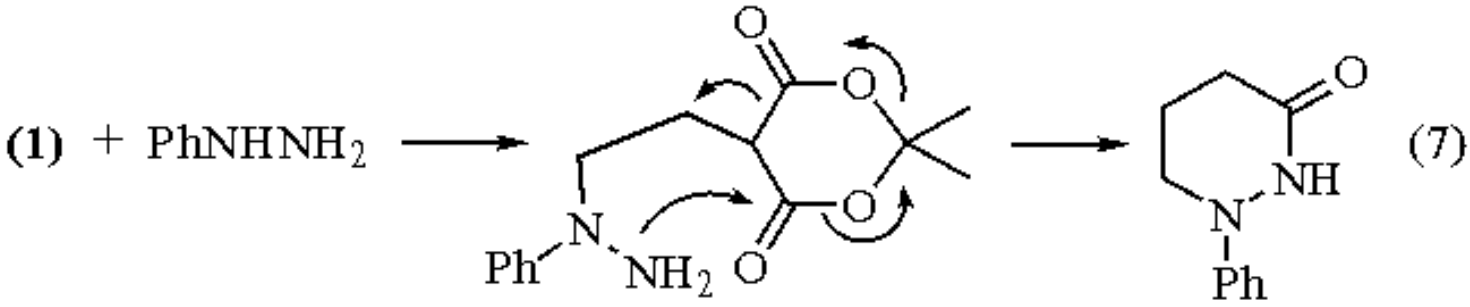

Lewis acid-catalyzed ring opening of (**1**) using ***Ethylaluminum Dichloride*** and ***Allyltrimethylsilane*** has also been reported (eq 8).[10]

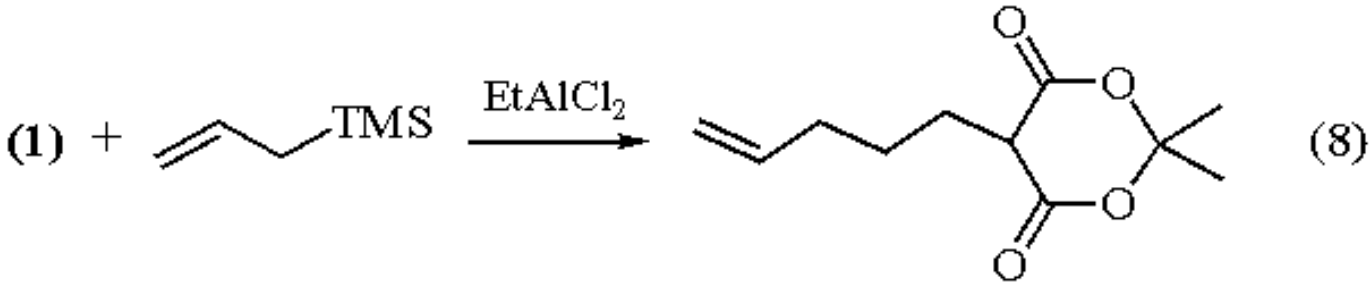

The spiro-activated vinylcyclopropane 6,6-dimethyl-1-vinyl-5,7-dioxaspiro[2.5]octane-4,8-dione reacts with nucleophiles exclusively on the cyclopropane ring position bearing the vinyl group (eq 9).[11]

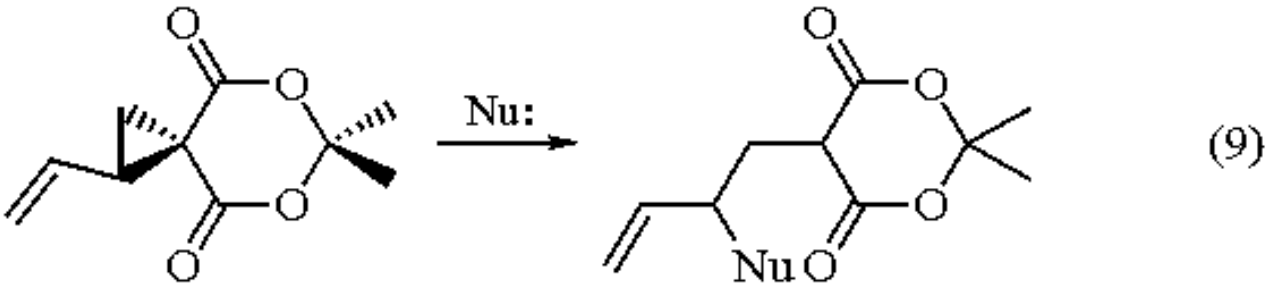

Nu: = piperidine, NaSPh, $NaCH(CO_2Me)_2$

Ketene Formation.

Pyrolysis of (**1**) at 500 °C/0.5 mmHg gives carbonylcyclopropane which dimerizes at rt or which can be trapped using aniline to give a cyclopropanecarboxamide (eq 10).[12]

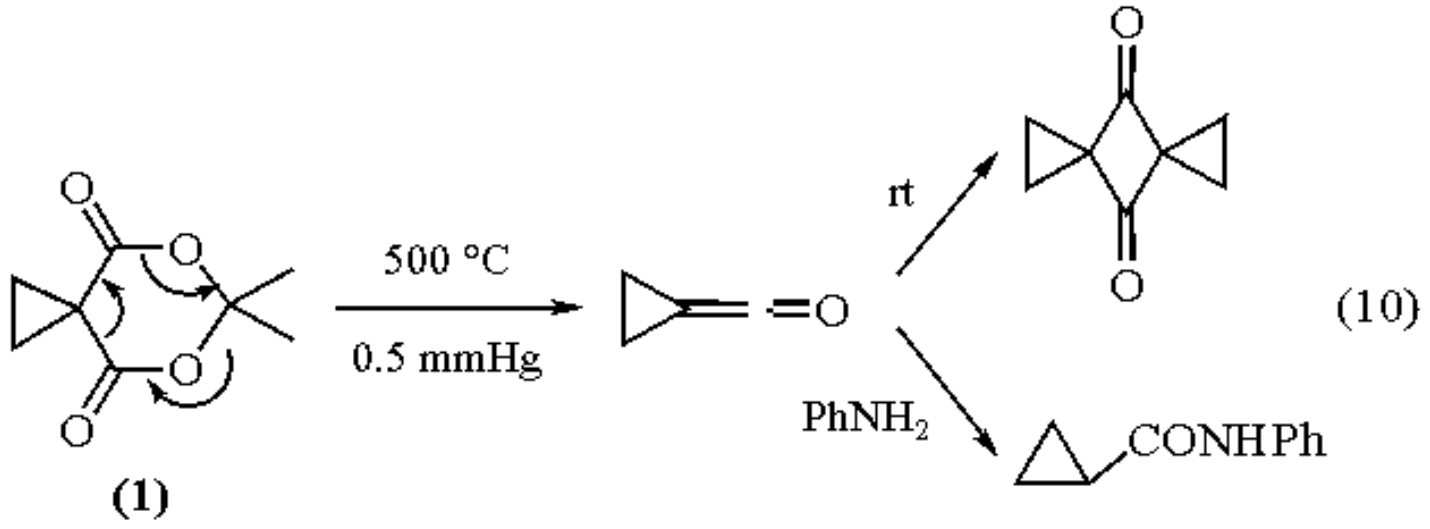

Related Reagents.

Cyclopropanone; ***Cyclopropenone 1,3-Propanediyl Acetal***; ***Diethyl Malonate***; ***Diethyl Methylenemalonate***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***; ***[1-(Ethoxycarbonyl)cyclopropyl]triphenylphosphonium Tetrafluoroborate***; ***1-Ethoxycyclopropanol***.

---

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4. Horton, M.; Pattenden, G. *JCS(P1)* **1984**, 811.
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Dimethyldioxirane[1]

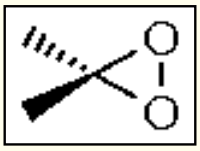

[74087-85-7] · $C_3H_6O_2$ · Dimethyldioxirane · (MW 74.09)

(selective, reactive oxidizing agent capable of epoxidation of alkenes and arenes,[11] oxyfunctionalization of alkanes,[19] and oxidation of alcohols,[23] ethers,[21] amines, imines,[32] and sulfides[35])

Alternate Name: DDO.

Physical Data: known only in the form of a dilute solution.

Solubility: sol acetone and CH_2Cl_2; sol most other organic solvents, but reacts slowly with many of them.

Form Supplied in: dilute solutions of the reagent in acetone are prepared from Oxone and acetone, as described below.

Analysis of Reagent Purity: the concentrations of the reagent can be determined by classical iodometric titration or by reaction with an excess of an organosulfide and determination of the amount of sulfoxide formed by NMR or gas chromatography.

Preparative Methods: the discovery of a convenient method for the preparation of dimethyldioxirane has stimulated important advances in oxidation technology.[1] The observation[2] that ketones enhance the decomposition of the monoperoxysulfate anion prompted mechanistic studies that implicated dioxiranes as intermediates.[3] Ultimately, these investigations led to the isolation of dilute solutions of several dioxiranes.[4] DDO is by far the most convenient of the dioxiranes to prepare and use (eq 1). Several experimental set-ups for the preparation of DDO have been described,[4-6] but reproducible generation of high concentration solutions of DDO (ca 0.1M) is aided by a well-formulated protocol.[6] The procedure involves the portionwise addition of solid Oxone (***Potassium Monoperoxysulfate***) to a vigorously stirred solution of $NaHCO_3$ in a mixture of reagent grade ***Acetone*** and distilled water at 5-10 °C. The appearance of a yellow color signals the formation of DDO, at which point the cooling bath is removed and the DDO-acetone solution is distilled into a cooled (-78 °C) receiving flask under reduced pressure (80-100 Torr). After preliminary drying over reagent grade anhydrous $MgSO_4$ in the cold, solutions of DDO are stored over molecular sieves in the freezer of a refrigerator at -10 to -20 °C. In instances where the concentration of DDO is crucial, analysis is typically based on reaction with an excess of an organosulfide monitored by NMR.[4,7,8]

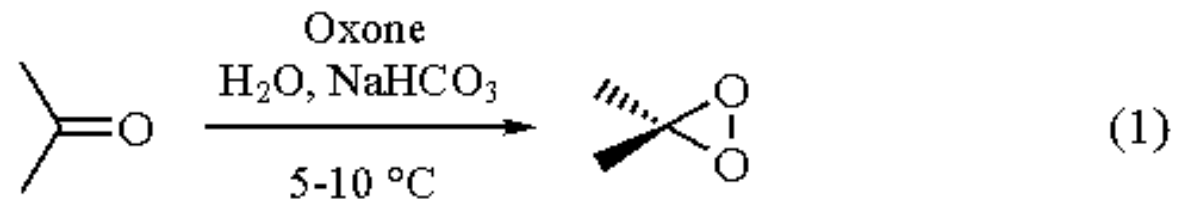

Handling, Storage, and Precautions: solutions of the reagent can be kept in the freezer of a refrigerator (-10 to -20 °C) for as long as a week. The concentration of the reagent decreases relatively slowly, provided solutions are kept from light and traces of heavy metals. These dilute solutions are not known to decompose violently, but the usual precautions for handling peroxides should be applied, including the use of a shield. All reactions should be performed in a fume hood to avoid exposure to the volatile oxidant.

Introduction.

Reactions with DDO are typically performed by adding the cold reagent solution to a cold solution of a reactant in acetone or some other solvent. CH_2Cl_2 is a convenient solvent which facilitates reaction in a number of cases. After the reactant has been consumed, as monitored by TLC, etc., the solvent and excess reagent are simply removed to provide a nearly pure product. An excess of DDO is often used to facilitate conversion, provided further oxidation is not a problem. Where the product is especially sensitive to acid, the reaction can be run in the presence of solid ***Potassium Carbonate*** as an acid scavenger and drying agent. When it is important to minimize water content, the use of powdered molecular sieves in the reaction mixture is recommended. Reactions can be run from ambient temperatures down to -78 °C.

Dimethyldioxirane is a powerful oxidant, but shows substantial selectivity in its reactions. It has been particularly valuable for the preparation of highly reactive products, since DDO can be employed under neutral, nonnucleophilic conditions which facilitate the isolation of such species. Whereas DDO performs the general conversions of more classic reagents like ***m-Chloroperbenzoic Acid***, it generates only an innocuous molecule of acetone as a byproduct. This is to be contrasted with peracids whose acidic side-products can induce rearrangements and nucleophilic attack on products. Although several other dioxiranes have been prepared, these usually offer no advantage over DDO. An important exception is ***Methyl(trifluoromethyl)dioxirane***, whose greater reactivity is advantageous in situations where DDO reacts sluggishly, as in the oxyfunctionalization of alkanes.

The need to prepare DDO solutions beforehand, the low yield of the reagent based on ***Potassium Monoperoxysulfate*** (Oxone) (ca. 5%),[6] and the inconvenience of making DDO for large-scale reactions are drawbacks that can be avoided when the product has good stability. In these instances, an in situ method for DDO oxidations is recommended.

Oxidation of Alkenes and Other Unsaturated Hydrocarbons.

The epoxidation of double bonds has been the major area for the application of DDO methodology and a wide range of alkenes are effectively converted to epoxides by solutions of DDO.[4,7] Epoxidation is stereospecific with retention of alkene stereochemistry, as shown by the reactions of geometrical isomers; for example, (*Z*)-1-phenylpropene gives the *cis*-epoxide cleanly (eq 2), whereas the (*E*) isomer yields the corresponding *trans*-epoxide. Rate studies indicate

that this reagent is electrophilic in nature and that alkyl substitution on the double bond enhances reactivity.[7] Interestingly, *cis*-disubstituted alkenes react 7-9 times faster than the *trans* isomers, an observation that has been interpreted in terms of a spiro transition state.[9]

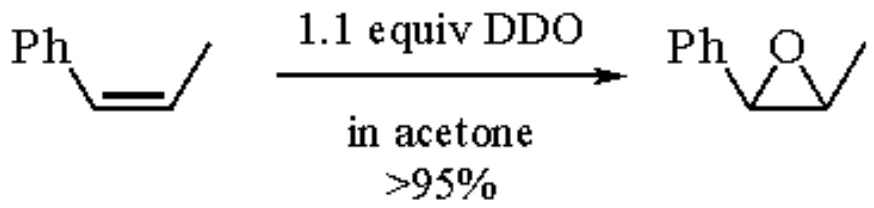

(2)

From a preparative viewpoint, the use of DDO solutions, while efficient and easy to perform, are generally not needed for simple alkenes that give stable epoxides. Rather, in situ methodology is suggested. However, the extraordinary value of isolated DDO has been amply demonstrated for the generation of unstable epoxides that would not survive most epoxidation conditions.[1] A good example of this sort of application is the epoxidation of precocenes, as exemplified in eq 3.[10] A number of impressive epoxidations have been reported for oxygen-substituted alkenes, including enol ethers, silyl enol ethers, enol carboxylates, etc.[1] Examples include a number of 1,2-anhydro derivatives of monosaccharides.[11] Steric features often result in significant stereoselection in the epoxidation, as illustrated in eq 4.[11] Conversions of alkenes with two alkoxy substituents have also been achieved (eq 5), even when the epoxides are not stable at rt.[12]

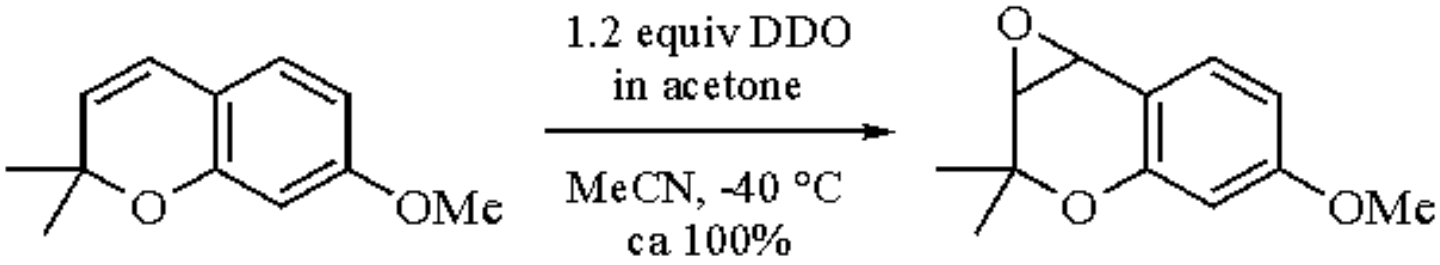

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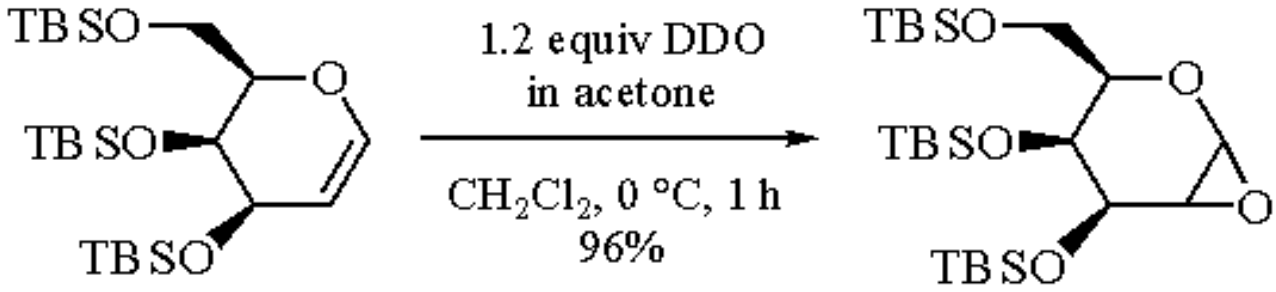

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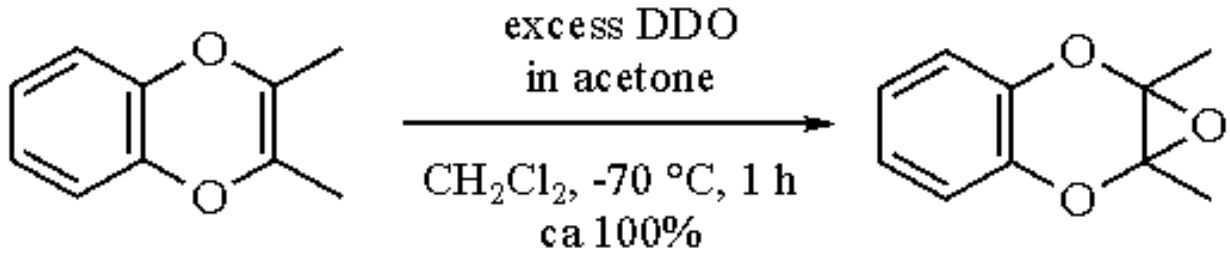

(5)

Although reactions are much slower with conjugated carbonyl compounds, DDO is still effective for the epoxidation of these electron-deficient double bonds (eq 6).[13] Alkoxy-substitution on such conjugated alkenes can also be

tolerated (eq 7).[14]

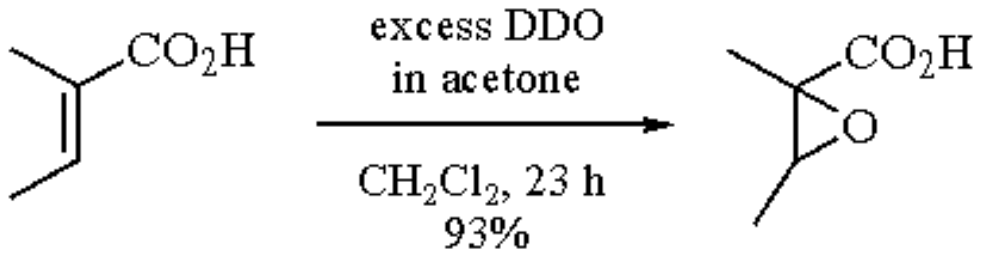

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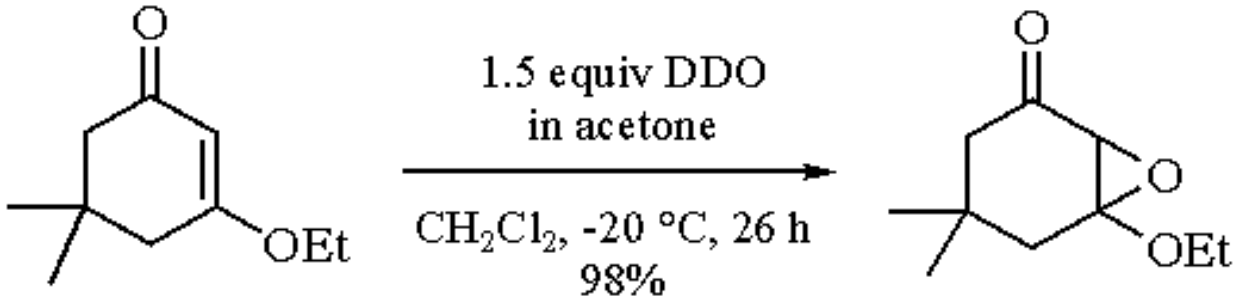

(7)

Allenes react with DDO by sequential epoxidation of the two double bonds to give the previously inaccessible, highly reactive allene diepoxides.[15] In the case of the *t*-butyl-substituted allene shown in eq 8, a single diastereomer of the diepoxide is generated, owing to steric control of the *t*-butyl group on reagent attack.

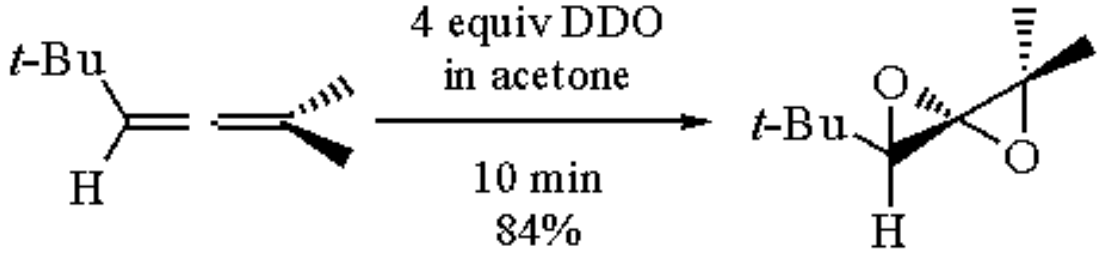

(8)

Certain polycyclic aromatic hydrocarbons can be converted to their epoxides, as typified by the reaction of phenanthrene with DDO (eq 9).[4] Aromatic heterocycles like furans and benzofurans also give epoxides, although these products are quite susceptible to rearrangement, even at subambient temperatures (eq 10).[16] The oxidation of heavily substituted phenols by DDO leads to quinones, as shown in eq 11, which illustrates the formation of an orthoquinone.[17] The corresponding hydroquinones are intermediates in these reactions, but undergo ready oxidation to the quinones.

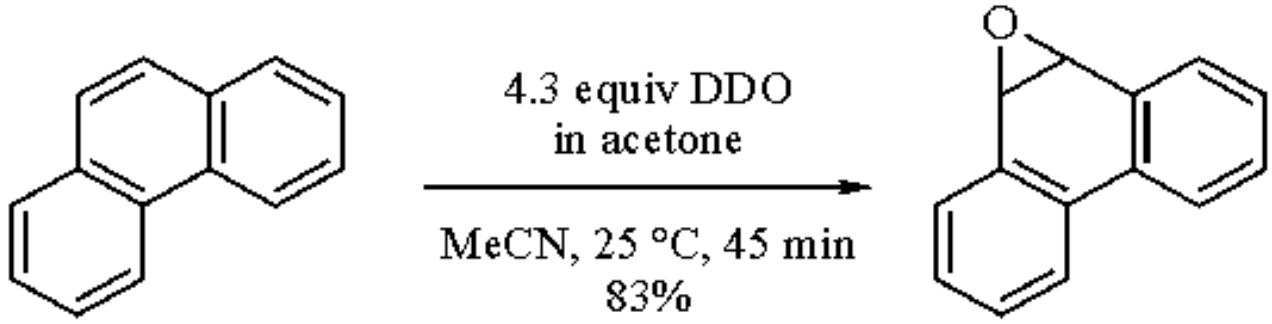

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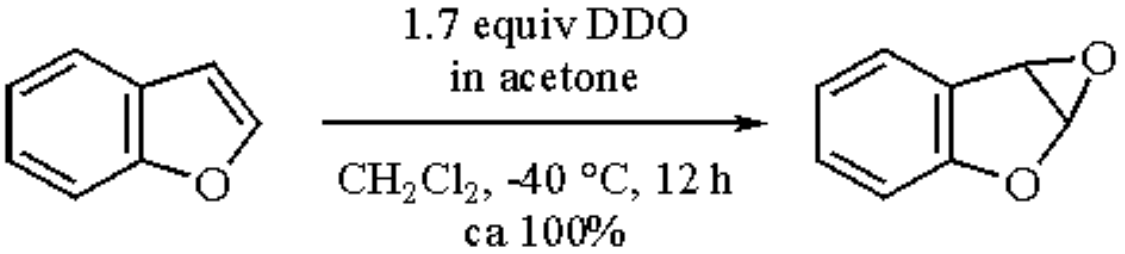

(10)

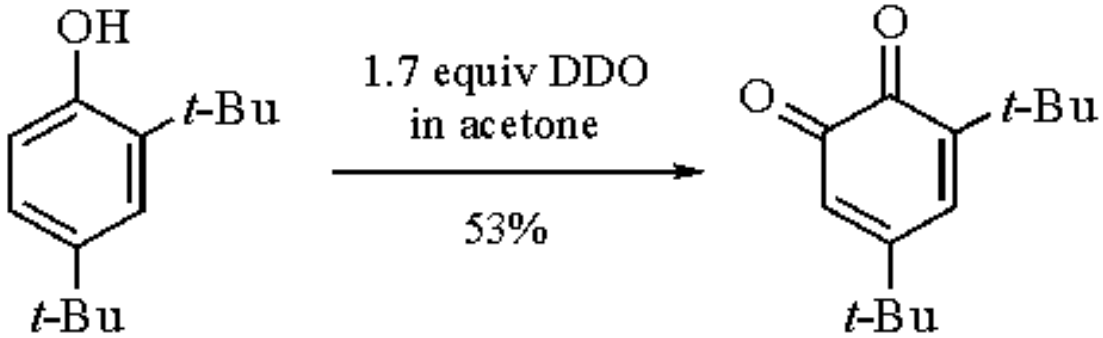

(11)

Finally, preformed lithium enolates are converted to α-hydroxy ketones by addition to a cold solution of DDO (eq 12).[18]

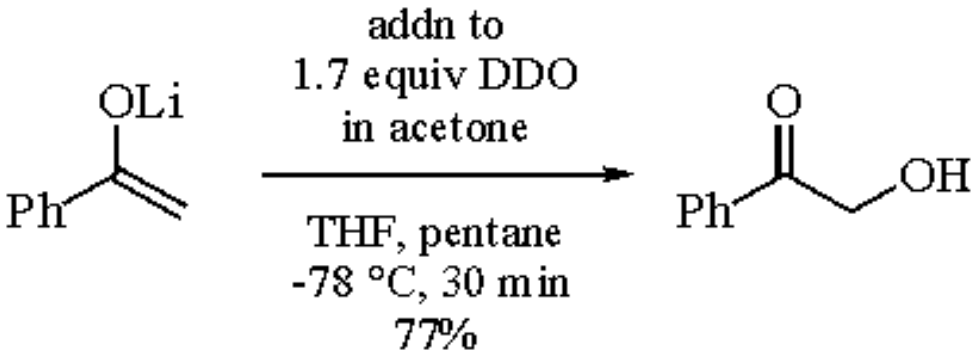

(12)

Oxidation of Saturated Hydrocarbons, Ethers, and Alcohols.

Surely the most striking reaction of dioxiranes is their ability to functionalize unactivated C-H bonds by the insertion of an oxygen atom into this σ-bond. This has opened up an important new area of oxidation chemistry.[1] While DDO has been used in a number of useful transformations outlined below, the more reactive ***Methyl(trifluoromethyl)dioxirane*** is often a better reagent for this type of conversion, despite its greater cost and difficulty of preparation.

The discrimination of DDO for tertiary > secondary > primary C-H bonds of alkanes is more pronounced than that of the *t*-butoxide radical.[19] Good yields of tertiary alcohols can be secured in favorable cases, as in the DDO oxidation of adamantane to 1-adamantanol, which occurs with only minor reaction at C-2 (eq 13). Of major significance is the observation that these reactions are stereospecific with high retention of configuration, as illustrated by the oxidation of *cis*-dimethylcyclohexane shown in eq 14; the *trans* isomer gives exclusively the diastereomeric alcohol. This and other data have been interpreted in terms of an oxenoid mechanism for the insertion into the C-H bond. Several

interesting applications in the steroid field involve significant site selectivity as well.[20] The slower reactions of DDO with hydrocarbons without tertiary hydrogens are less useful and lead to ketones owing to a rapid further oxidation of the initially formed secondary alcohol. For example, cyclododecane is converted to cyclododecanone.

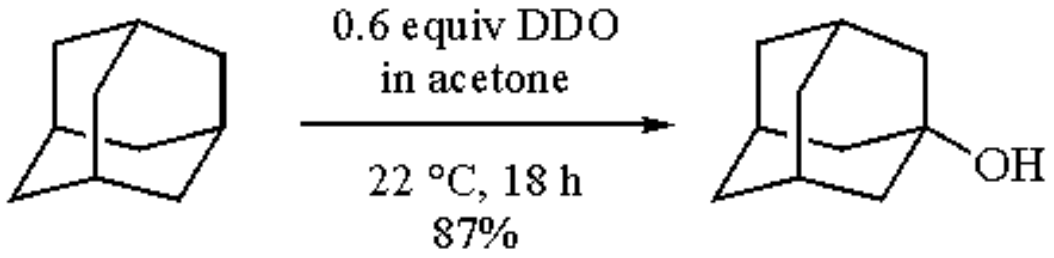

(13)

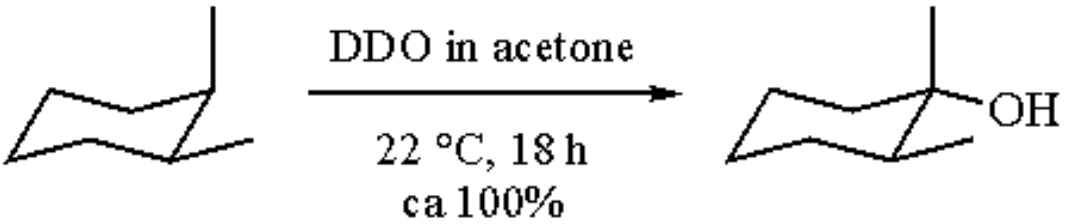

(14)

Ethers and acetals are slowly converted by DDO to carbonyl compounds. This serves as a nontraditional method for deprotection of these derivatives, an example of which is shown in eq 15.[21,22] Hemiacetals are presumed intermediates in these transformations.

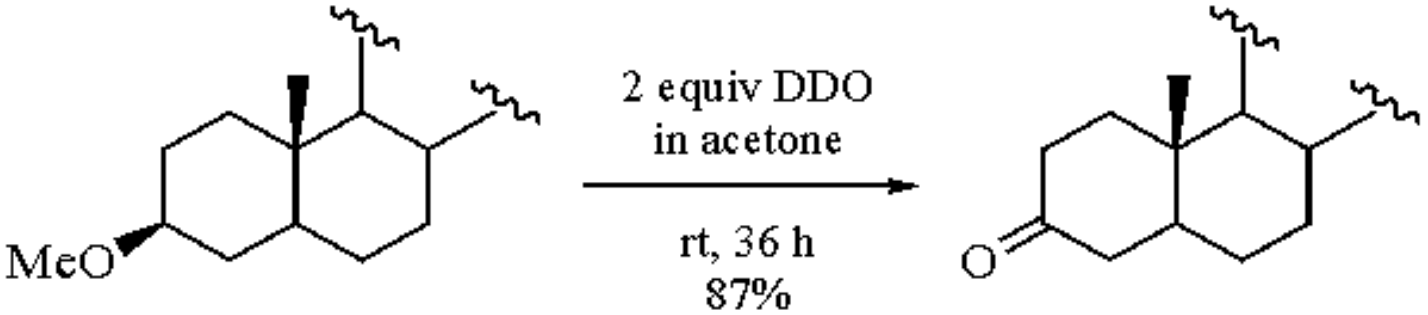

(15)

While DDO has been little used for the oxidation of simple alcohols, it has found application in useful conversions of vicinal diols. The oxidation of tertiary-secondary diols to α-hydroxy ketones occurs without the usual problem of oxidative cleavage between the two functions (eq 16).[23] DDO has also been used to convert appropriate optically active diols selectively into α-hydroxy ketones of high optical purity; for example, see eq 17.[24]

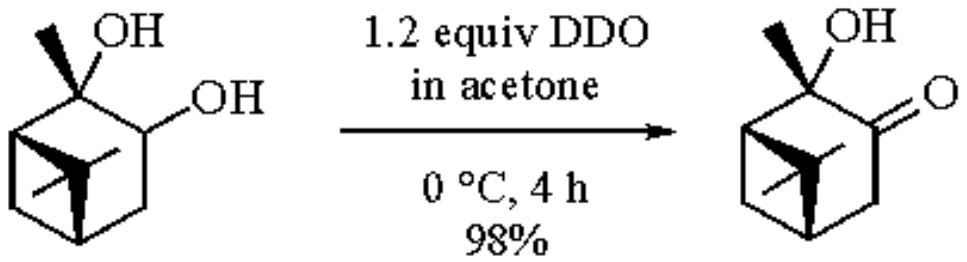

(16)

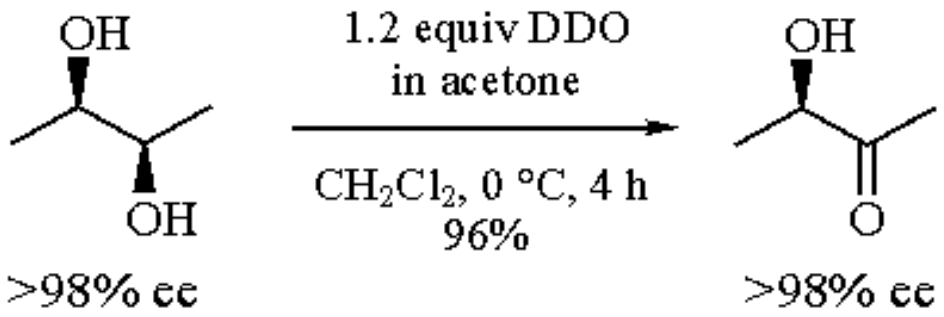

(17)

Finally, the Si-H bond of silanes suffers analogous oxidation to silanols upon reaction with DDO. This reaction takes place with retention of configuration and is, as expected, more facile than C-H oxidations.[25]

Oxidation of Nitrogen Functional Groups.

Selective oxidations of nitrogen compounds are often difficult to achieve, but DDO methodology has been shown to be very useful in a number of instances. For example, one of the first applications of this reagent was in the conversion of primary amines to the corresponding nitro compounds (eq 18).[26] This process probably proceeds by successive oxidation steps via hydroxylamine and nitroso intermediates. Complications arise with unhindered primary aliphatic amines, owing to dimerization of the intermediate nitrosoalkanes and their tautomerization to oximes.[27] In oxidations of amino sugar and amino acid derivatives, it is possible to isolate the initially formed hydroxylamines (eq 19).[28]

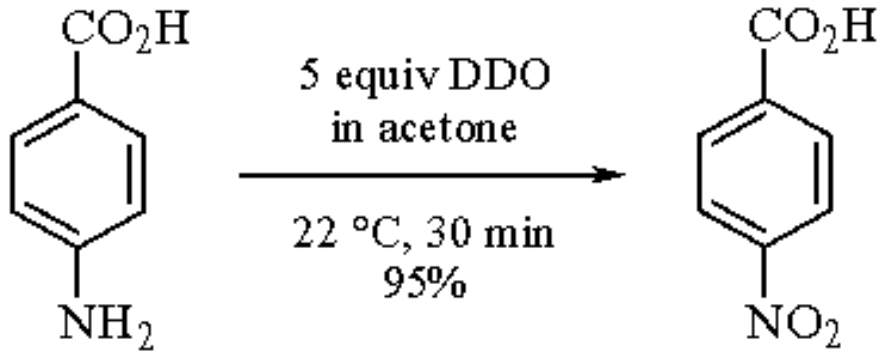

(18)

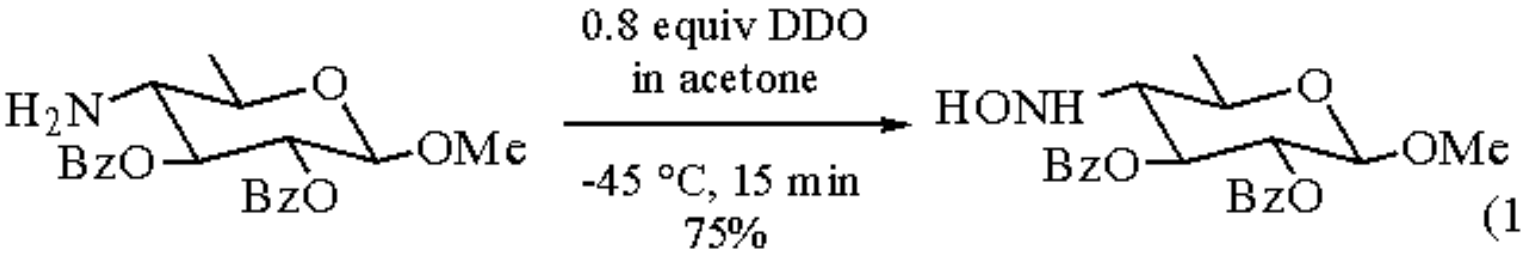

(19)

The oxidation of secondary amines to hydroxylamines is readily achieved with 1 equiv of DDO (eq 20).[29] The use of 2 equiv of DDO results in further oxidation, the nature of which depends on the structure of the amine. Thus cyclic secondary amines which do not possess α-hydrogens are converted to nitroxides,[30] as illustrated in eq 21. Secondary benzylamines give nitrones (eq 22).[31]

$$(PhCH_2)_2NH \xrightarrow[\text{0 °C, 15 min, 98\%}]{\text{1 equiv DDO in acetone}} (PhCH_2)_2NOH \qquad (20)$$

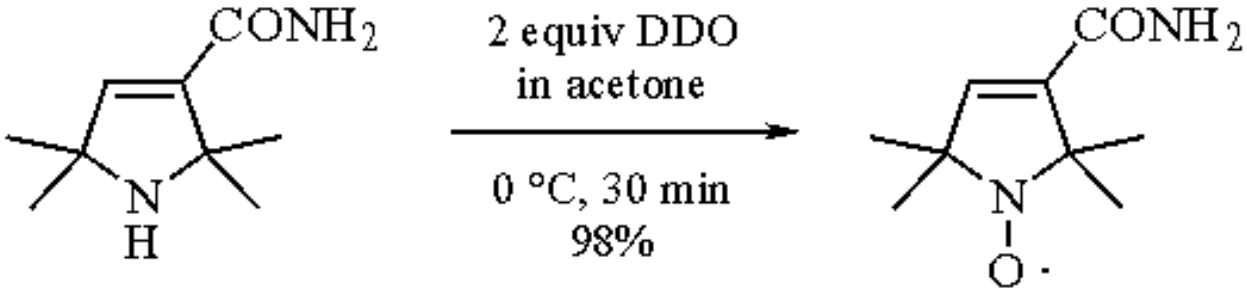

(21)

$$PhCH_2NH\text{-}t\text{-}Bu \xrightarrow[\text{0 °C, 10 min, 96\%}]{\text{2 equiv DDO in acetone}} PhCH{=}N(O)\text{-}t\text{-}Bu \qquad (22)$$

A related transformation is the oxidation of imines to nitrones by DDO (eq 23).[32] It is interesting that the isomeric oxaziridines are not produced here, given that peracids favor these heterocycles.

$$C_6Me_5CH{=}NMe \xrightarrow[\text{CH}_2\text{Cl}_2\text{, 0 °C, 2 h, 71\%}]{\text{1.1 equiv DDO in acetone}} C_6Me_5CH{=}N(O)Me \qquad (23)$$

Reaction of α-diazo ketones with DDO leads to α-keto aldehyde hydrates (eq 24).[33] Oximes are converted to the free ketones by DDO.[34]

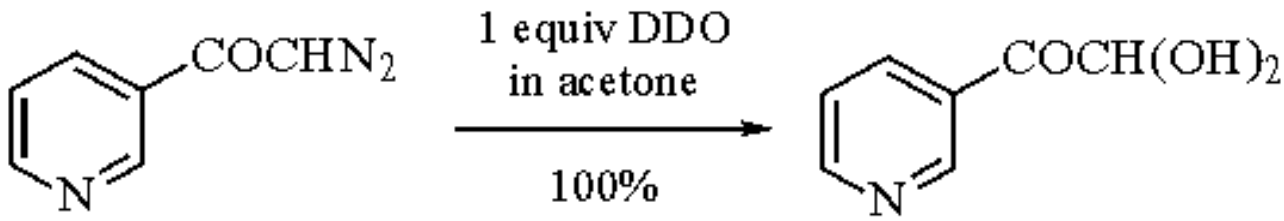

(24)

Oxidation of Sulfur Functional Groups.

Dimethyldioxirane rapidly oxidizes sulfides to sulfoxides and converts sulfoxides to sulfones (eq 25).[4,35] The partial oxidation of sulfides to sulfoxides can be controlled by limiting the quantity of DDO. Since Oxone is one of the many reagents that can perform these reactions, the extra effort involved in preparing DDO solutions is often not warranted. An exception involves the transformation of thiophenes to the corresponding sulfones (eq 26).[36] A similar procedure gives α-oxo sulfones by DDO oxidation of thiol esters (eq 27).[37]

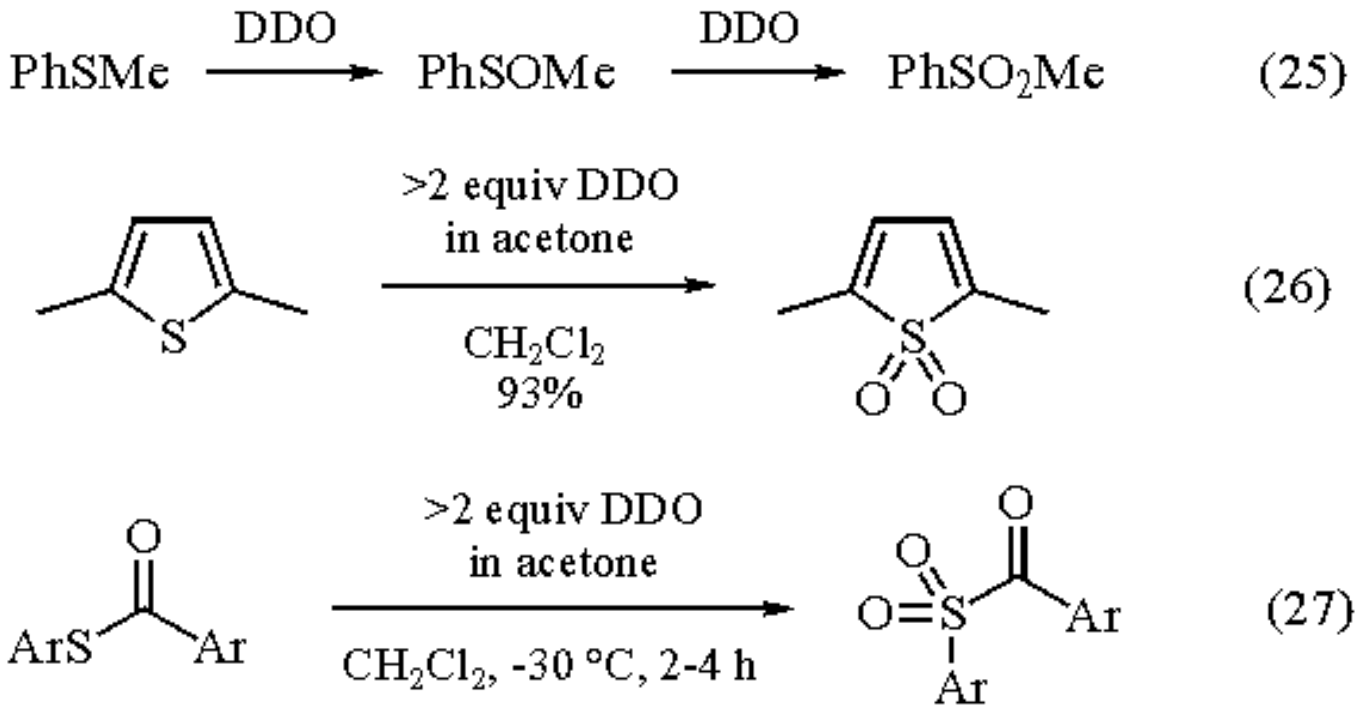

Alkanethiols are selectively oxidized to alkanesulfinic acids by DDO (eq 28).[38] Air oxidation of an intermediate species appears to be important in this transformation.

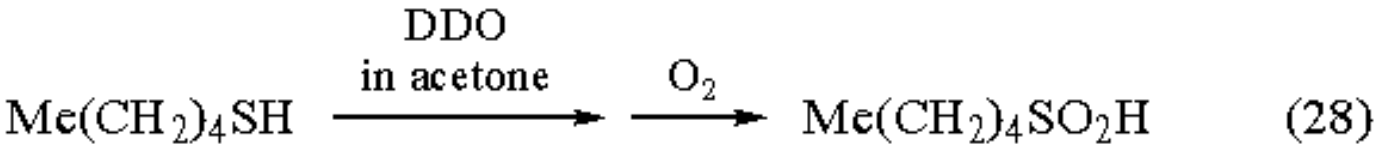

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N,N-Dimethyl-*O*-(diphenylphosphinyl)hydroxylamine[1]

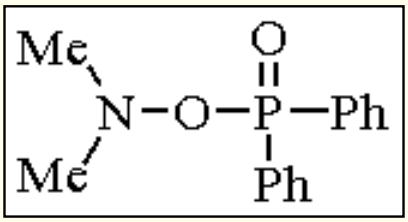

[83575-89-7] · $C_{14}H_{16}NO_2P$ · *N,N*-Dimethyl-*O*-(diphenylphosphinyl)hydroxylamine · (MW 261.28)

(electrophilic aminations)

Physical Data: mp 129-131 °C.[2]

Solubility: slightly sol THF, diethyl ether; sol $CHCl_3$, CH_2Cl_2.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$, ppm): 2.78 (s, 6 H, Me_2N), 7.36-8.18 (m, 10 H, phenyl).

Preparative Methods: (1) to 9.67 g (100 mmol) *N,N*-dimethylhydroxylamine suspended in 80 mL CH_2Cl_2 are added dropwise at -20 °C under stirring 20.3 g (200 mmol) triethylamine. Then 23.7 g (100 mmol) diphenylphosphinyl chloride dissolved in 80 mL CH_2Cl_2 are added within 1 h. After extraction of the salts with ice water (2-3 times) the solution is dried ($MgSO_4$), and the solvent removed. Recrystallization from diethyl ether affords 17.7 g (68%) colorless crystals of *N,N*-dimethyl-*O*-(diphenylphosphinyl)hydroxylamine (**1**).[2,3]

(2) To a solution of 2.00 g (4.60 mmol) bis(diphenylphosphinyl) peroxide in 50 mL CH_2Cl_2, cooled to -60 °C, is added under stirring within 1 h 10.8 mL of a 0.86 M solution of dimethylamine in CH_2Cl_2 (9.20 mmol dimethylamine). The reaction is continued overnight under warming to 0 °C. Then the organic layer is washed 4 times with cold water, dried, and the solvent removed. After crystallization from diethyl ether, 1.18 g (98%) (**1**) are isolated. This is a general procedure which allows the preparation of other *N,N*-di- as well as *N*-alkyl-*O*-(phosphinyl)hydroxylamines.[4]

Handling, Storage, and Precautions: stable for more than a year if stored at -30 °C.

Electrophilic Aminations.

N,N-Dimethylaminocyclopentadiene and *N,N*-Dimethylaminocyclopentadienyllithium.

Reaction of cyclopentadienyllithium (**2**) with (**1**) leads to an equilibrium dominated by *N,N*-dimethylaminocyclopentadiene (**3b**) (eq 1).[3] Aminocyclopentadienes are not easily accessible by methodologies other than electrophilic amination. For this amination reaction, ***N,N-Dimethyl-O-(methylsulfonyl)hydroxylamine***[3] and *N,N*-dimethyl-*O*-(diphenoxyphosphoryl)hydroxylamine[3] can also be used.

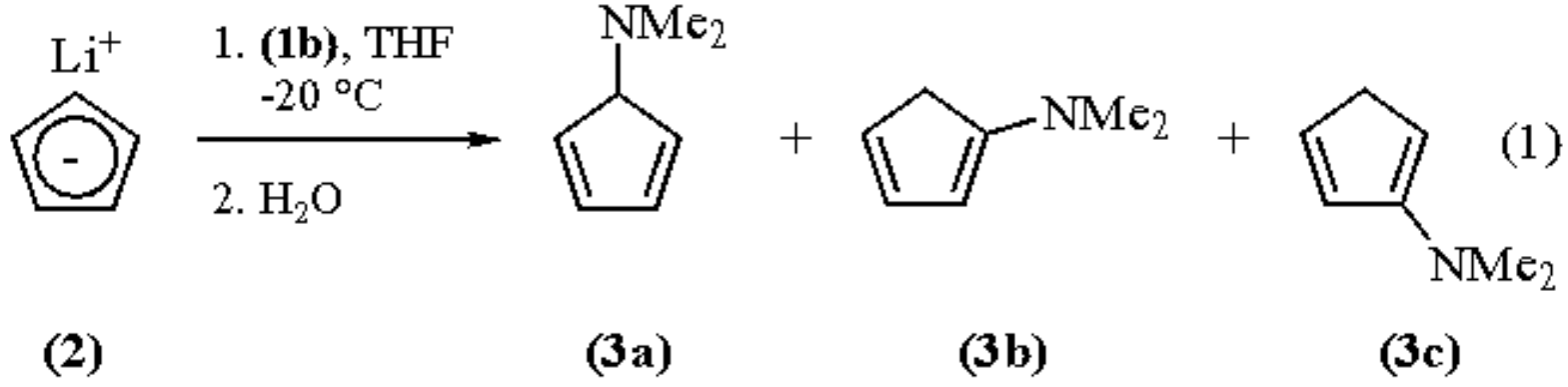

Reaction of (**3**) with ***n-Butyllithium*** affords *N,N*-dimethylaminocyclopentadienyllithium (**4**), which is a precursor for the preparation of the corresponding metallocenes, e.g. (**5**) (eq 2),[3] and others.[5]

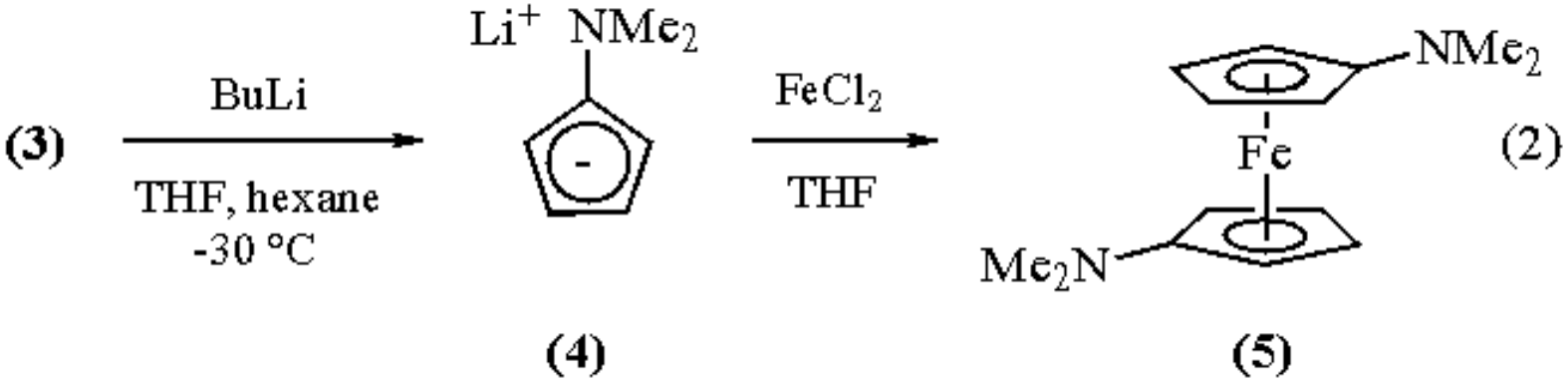

Amination of Lithiated Trimethylsilyl Cyanides: A Mild Oxidation of Aromatic Aldehydes to Amides.

(**1**) aminates lithiated *O*-(trimethylsilyl) aldehyde cyanohydrins (**8**) (eq 4), derived from aromatic aldehydes (**6**) and ***Cyanotrimethylsilane*** via the corresponding cyanohydrins (**7**) (eq 3).[6]

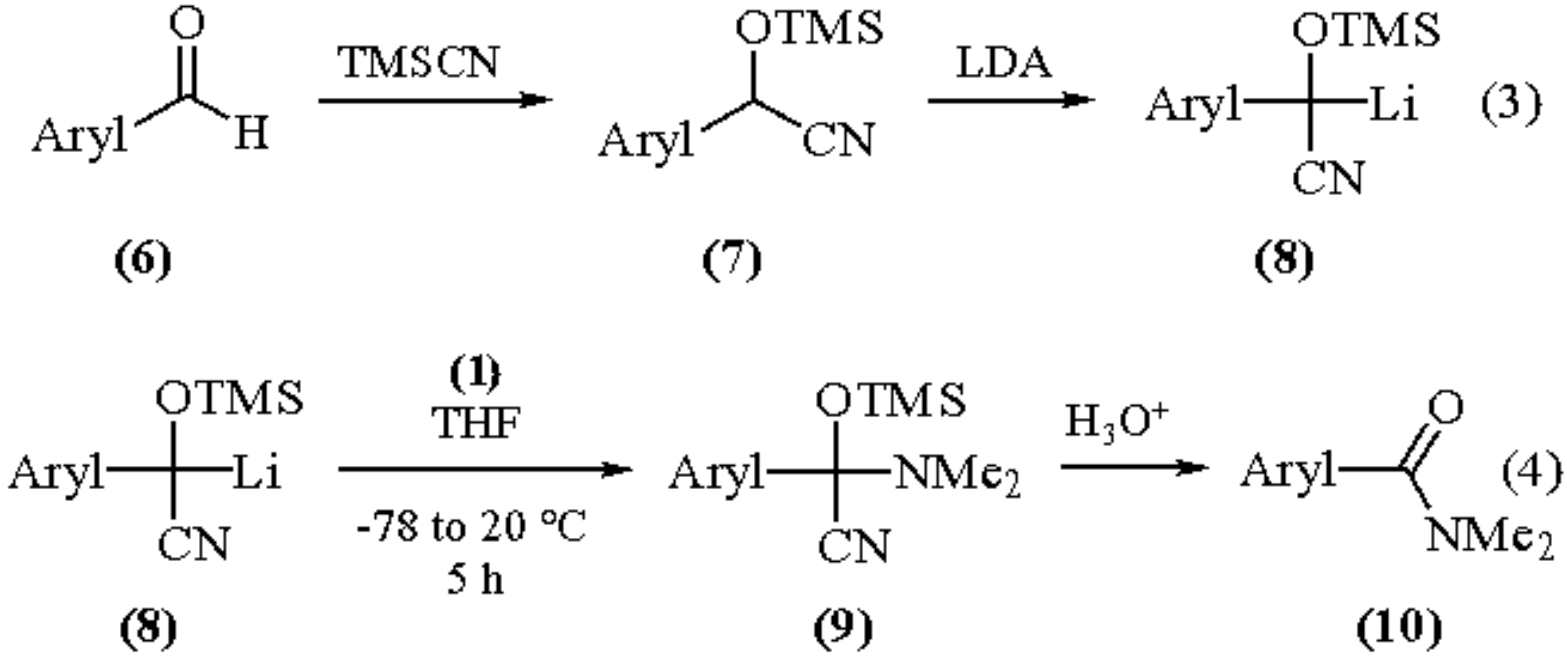

Since (**9**) (which is not isolated) is easily hydrolyzed (2 N HCl) to the amides (**10**), the reaction sequence (**6**) -> (**10**) amounts to a mild and selective oxidation of an aromatic aldehyde to an amide.

Alkynylcuprates to Ynamines.

(**1**) (or its amination equivalent *N*,*N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine) reacts with metallated alkynes.[7] Although the reactions with RC&tbond;CLi and RC&tbond;CMgX do not lead to ynamines, the cuprates (**11**), prepared by one of three methods (eqs 5-7), do give ynamines.

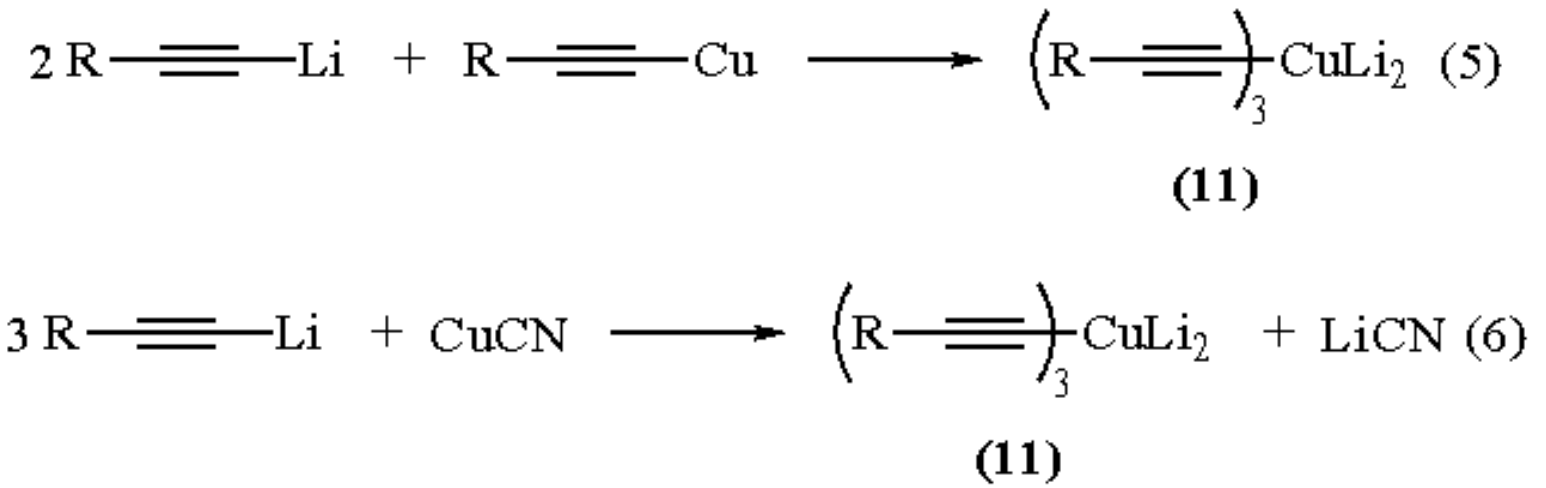

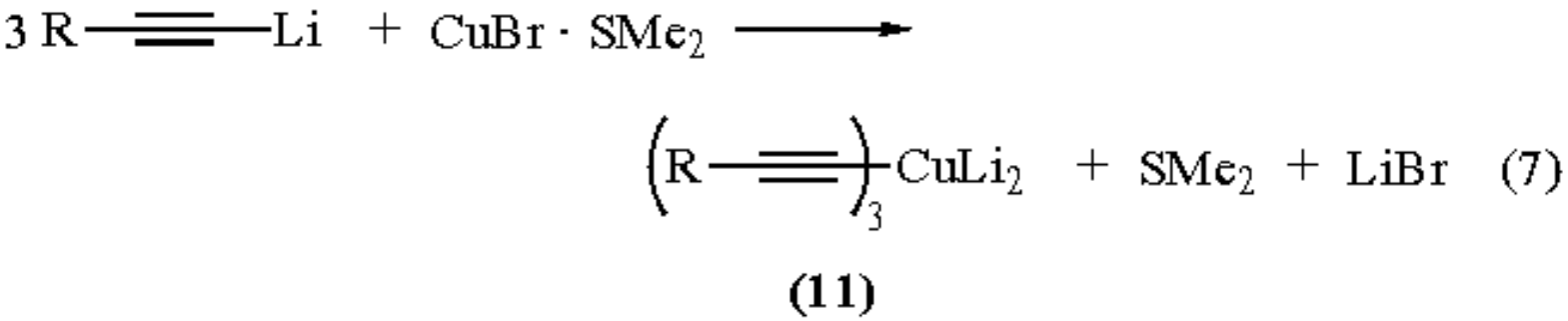

(**11**) transfers only two R groups onto (**1**) (eq 8). The R groups can be Ph, *n*-Pr, *n*-Bu, *n*-C_6H_{13}, Cy, *t*-Bu, Me_3Si, or PhS, for example. The yields of the ynamines are usually in the range of 60-70%.

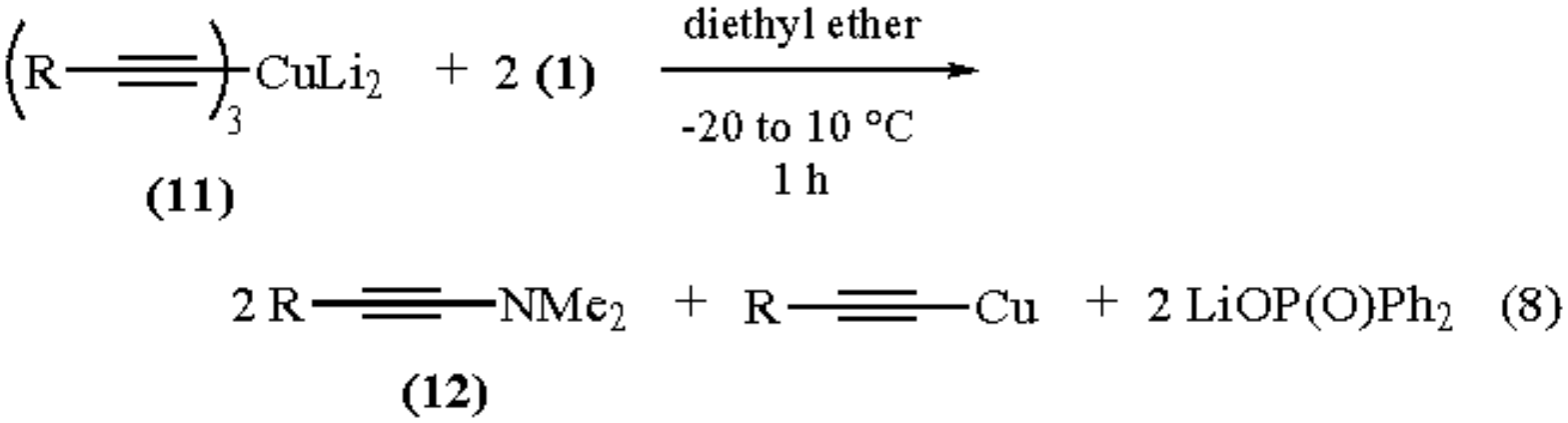

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Dimethyl Disulfide

MeSSMe

[624-92-0] · $C_2H_6S_2$ · Dimethyl Disulfide · (MW 94.22)

(electrophilic trap for carbanions to prepare methyl sulfides; undergoes homolytic substitution at sulfur with radicals)

Physical Data: mp -85 °C; bp 110 °C; *d* 1.063 g cm^{-3}.

Solubility: insol H_2O; sol alcohol and ether.

Form Supplied in: liquid, widely available.

Purification: passage through neutral alumina.

Handling, Storage, and Precautions: use in a fume hood.

Electrophilic Carbanion Trap.

Dimethyl disulfide undergoes electrophilic attack by carbanions, with cleavage of the weak S-S bond to yield methyl sulfides. Aryllithiums have been most widely used; generation by *ortho*-lithiation (eq 1),[1] metal-halogen exchange (eq 2),[2] and intramolecular benzyne trapping (eq 3)[3] has been demonstrated. Aryl Grignard reagents[4] can also be used. Vinyllithiums effectively trap dimethyl disulfide, providing vinyl sulfides,[5] which can be converted into the corresponding ketones. This procedure can be used to effect a 1,2 keto transposition (eq 4).[6] Vinyl sulfides have also been prepared via lithiated diphenylphosphine oxide trapping of dimethyl disulfide followed by alkenation with aldehydes or ketones (eq 5).[7]

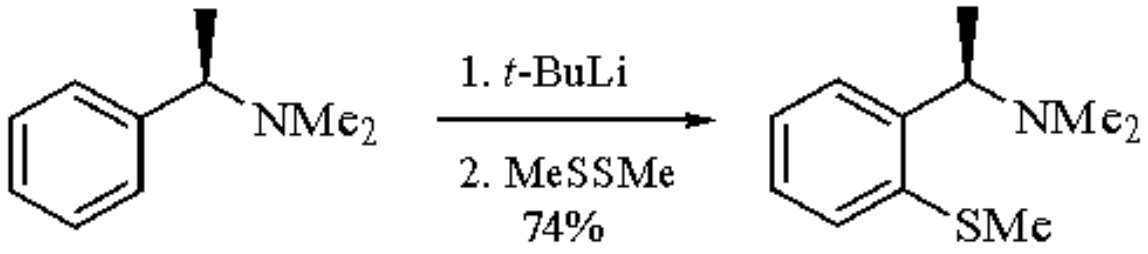

(1)

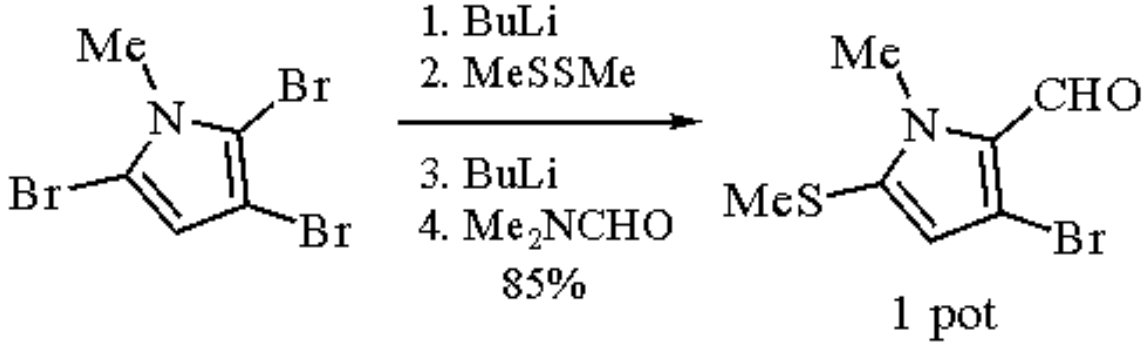
Me
N
Br
Br
Br
1. BuLi
2. MeSSMe
3. BuLi
4. Me2NCHO
85%
Me
N
CHO
MeS
Br
1 pot

(2)

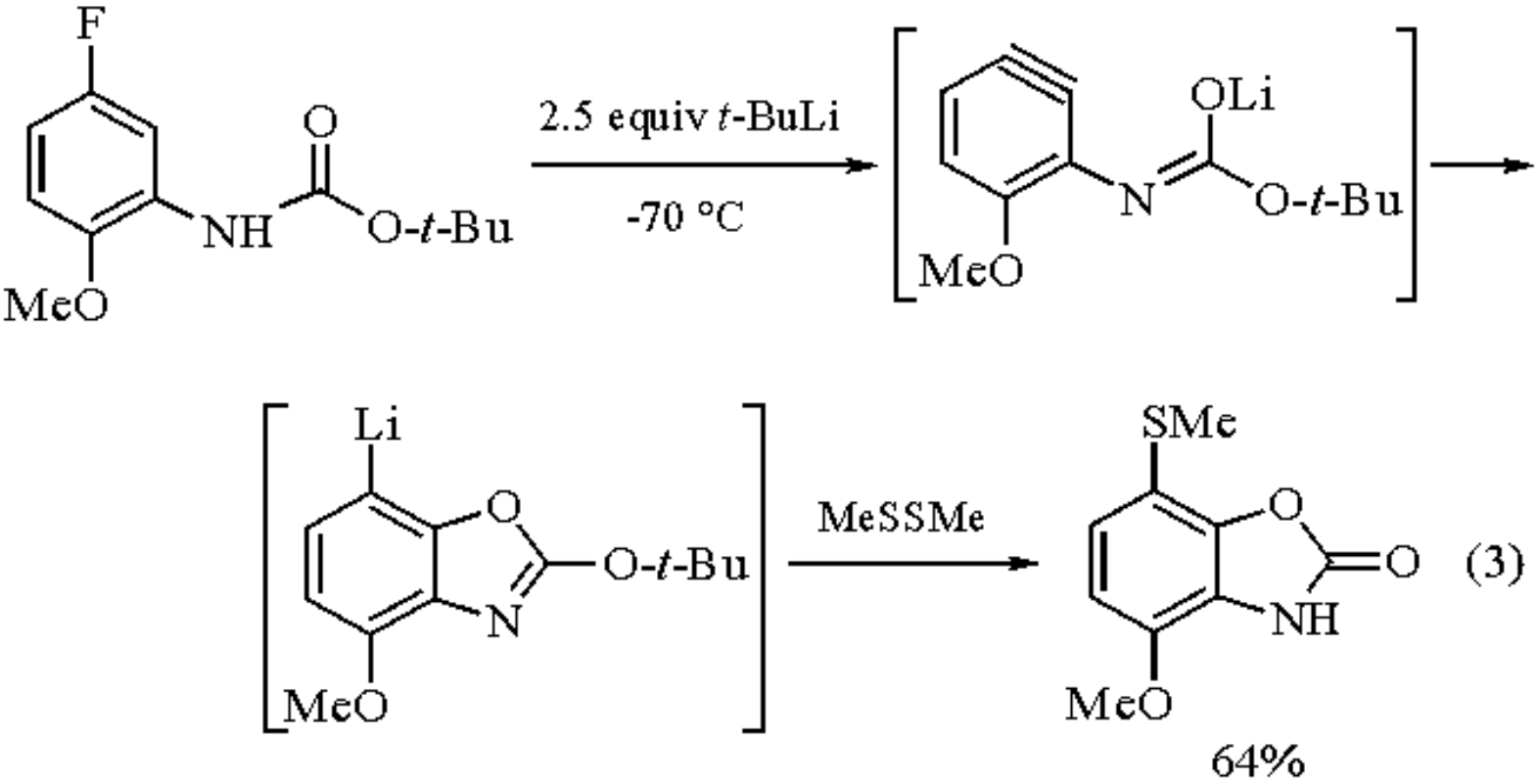
F
O
NH
O-t-Bu
MeO
2.5 equiv t-BuLi
-70 °C
OLi
N
O-t-Bu
MeO
Li
O
O-t-Bu
N
MeO
MeSSMe
SMe
O
O
NH
MeO
64%

(3)

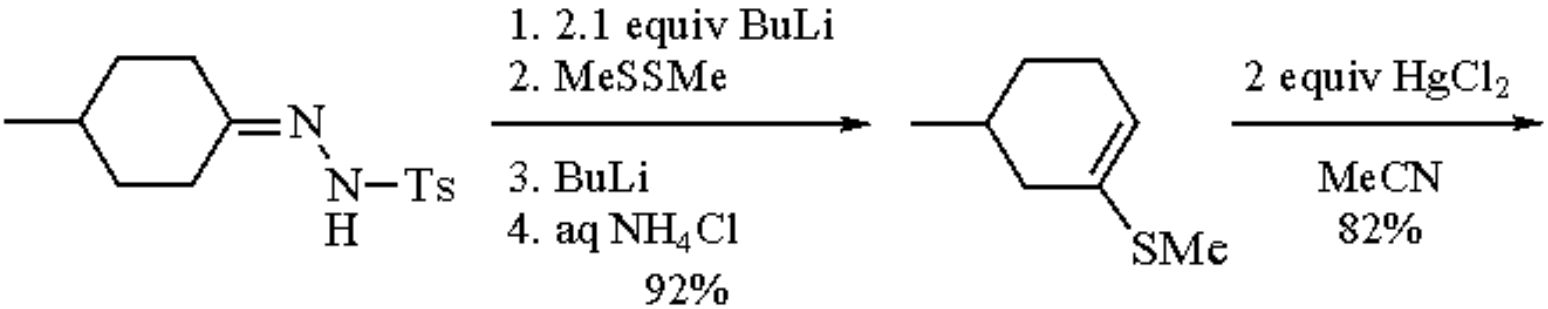
N
N—Ts
H
1. 2.1 equiv BuLi
2. MeSSMe
3. BuLi
4. aq NH4Cl
92%
SMe
2 equiv HgCl2
MeCN
82%

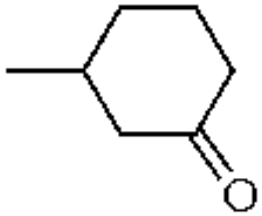
O

(4)

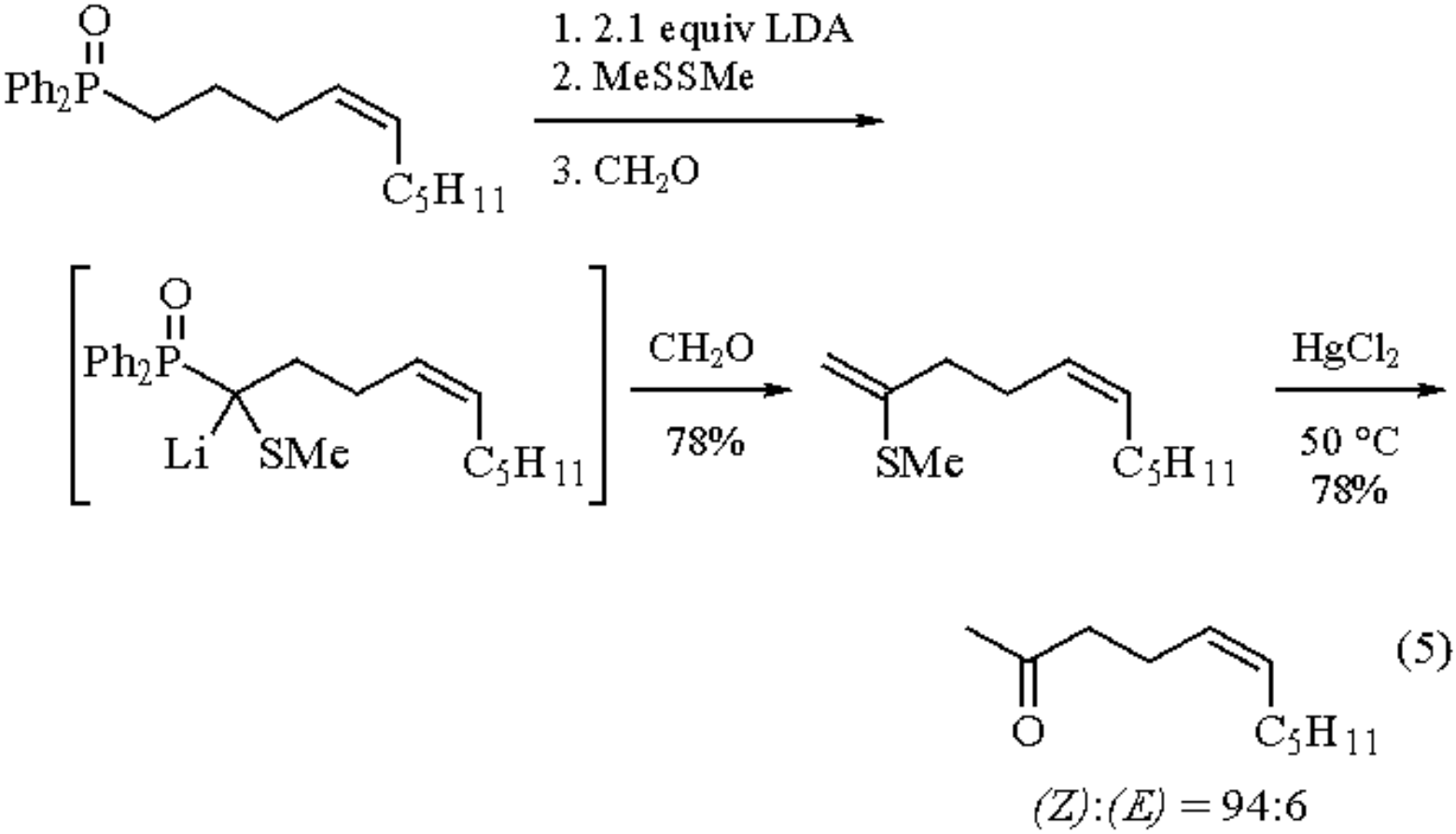

(5)

Dithioketene acetals can be prepared by metalation of geminal vinyl diiodides (eq 6);[8] allenyl enol ethers can also be sulfenated (eq 7).[9] Alkyllithiums are effectively sulfenylated (eq 8).[10] Less reactive carbanions are also easily trapped by dimethyl disulfide; allyllithiums react to give allylmethyl sulfides (eq 9),[11] and benzyllithiums provide benzyl sulfides.[12]

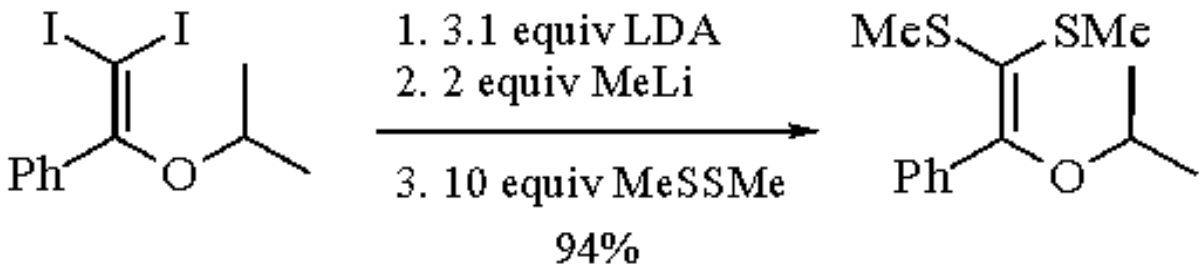

(6)

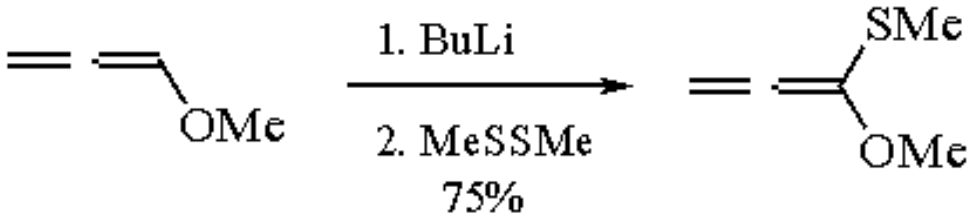

(7)

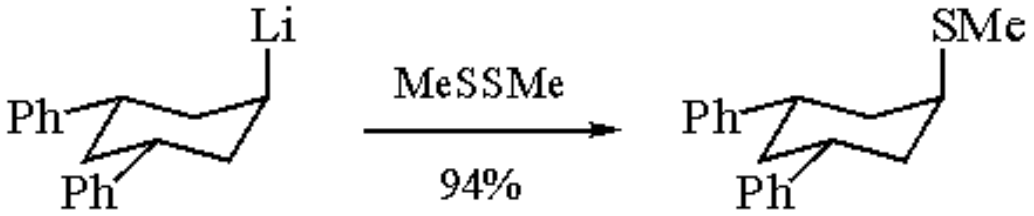

(8)

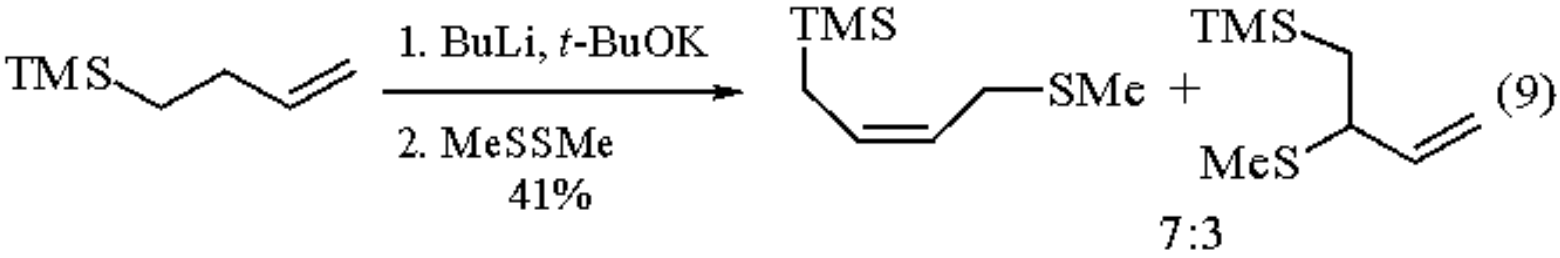

(9)

Sulfenylation α to carbonyl groups is accomplished via the respective enolates.[13] Oxidation and subsequent thermally induced elimination provides a route to α,β-unsaturated carbonyls;[14] however, this method has been largely supplanted by the corresponding selenenylation sequence[15] in which the selenoxide elimination occurs at or below ambient temperature. The advantages of the sulfur variant are the lower cost and lower toxicity of the reagent. Sulfenylation α to carboxylic acids followed by oxidation by ***N-Chlorosuccinimide*** or ***Sodium Periodate*** effects oxidative decarboxylation[16] via a putative Pummerer-like intermediate (eq 10). Introduction of a methyl sulfide group α to benzylic nitriles is best accomplished with the coaddition of ***Iodomethane*** (eq 11).[17] Lithiated 1,3-dithianes (see ***2-Lithio-1,3-dithiane***) react readily to provide orthothioformates.[18] Addition of an excess of ***Silver(I) Trifluoromethanesulfonate*** results in the um polung formation of dithiin carbocations (eq 12),[19] whereas ***Mercury(II) Chloride*** alcoholysis provides a route to esters.[20]

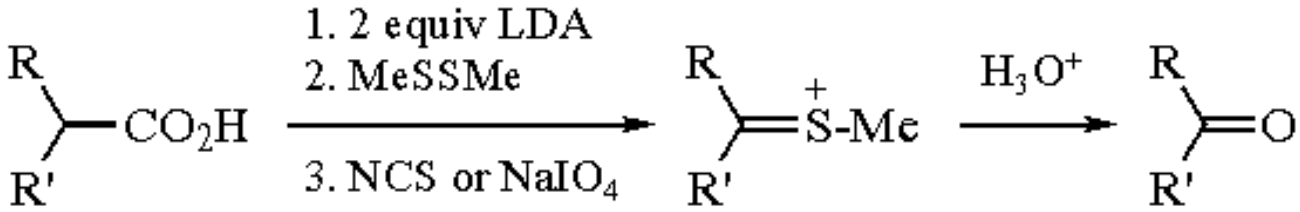

(10)

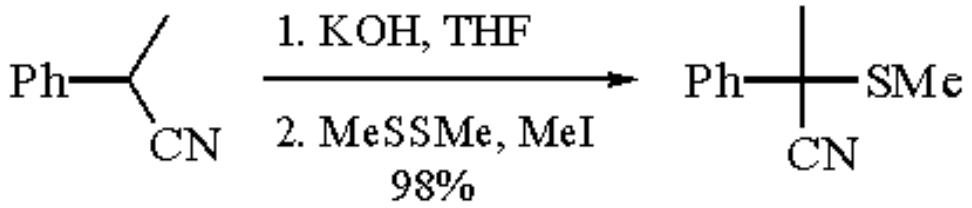

(11)

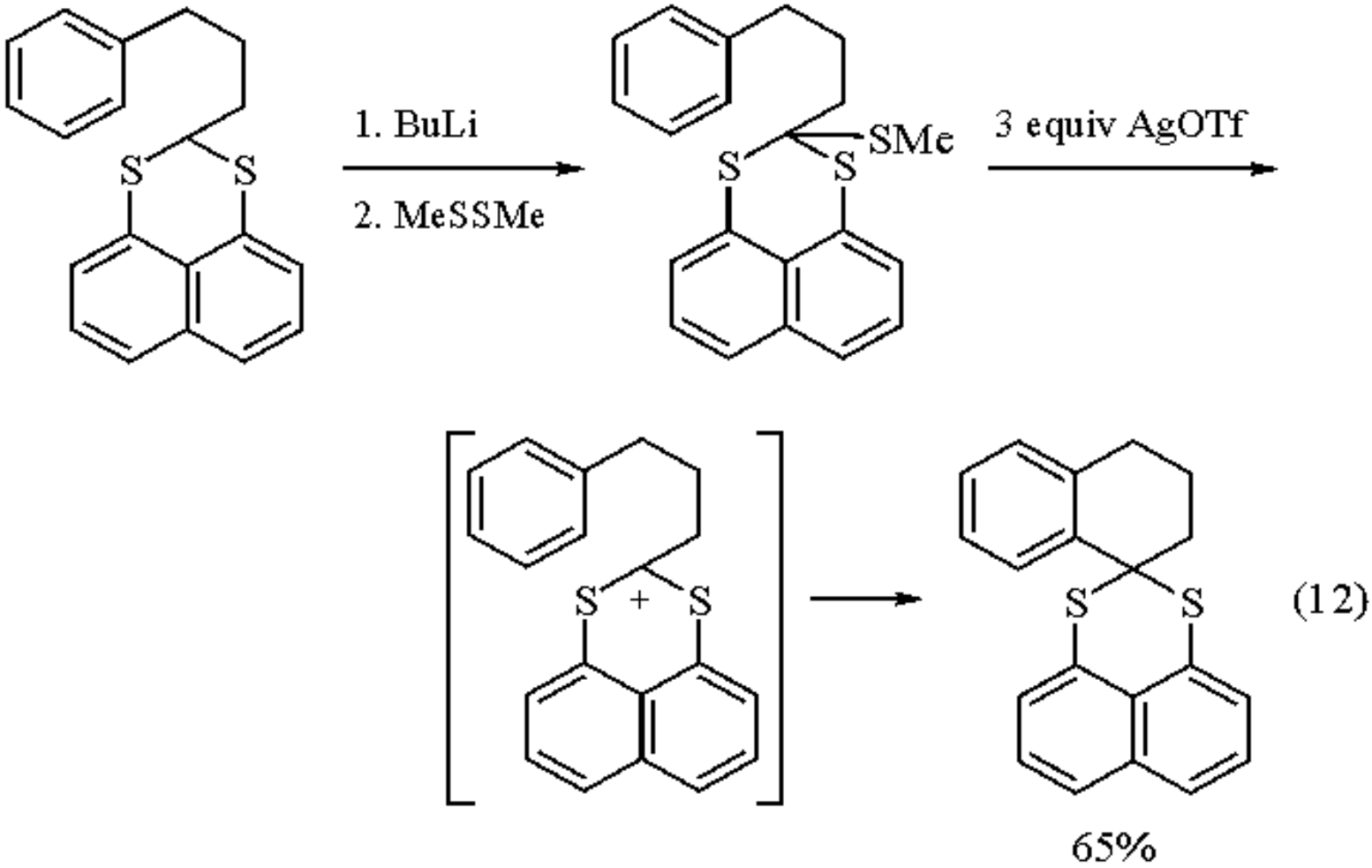

(12)

Activated Electrophilic Forms of Dimethyl Disulfide.

Electrophilic attack on dimethyl disulfide by non-anionic carbon nucleophiles is best accomplished by the addition of a Lewis acid or a methylating agent to enhance the electrophilicity of the sulfur trap. Electron-rich aromatics and indoles[21] are sulfenylated with dimethyl disulfide in the presence of Lewis acids. A combination of dimethyl disulfide and ***Sulfuryl Chloride*** can also be used, probably forming sulfenyl chloride in situ as the actual trapping agent (eq 13).[22]

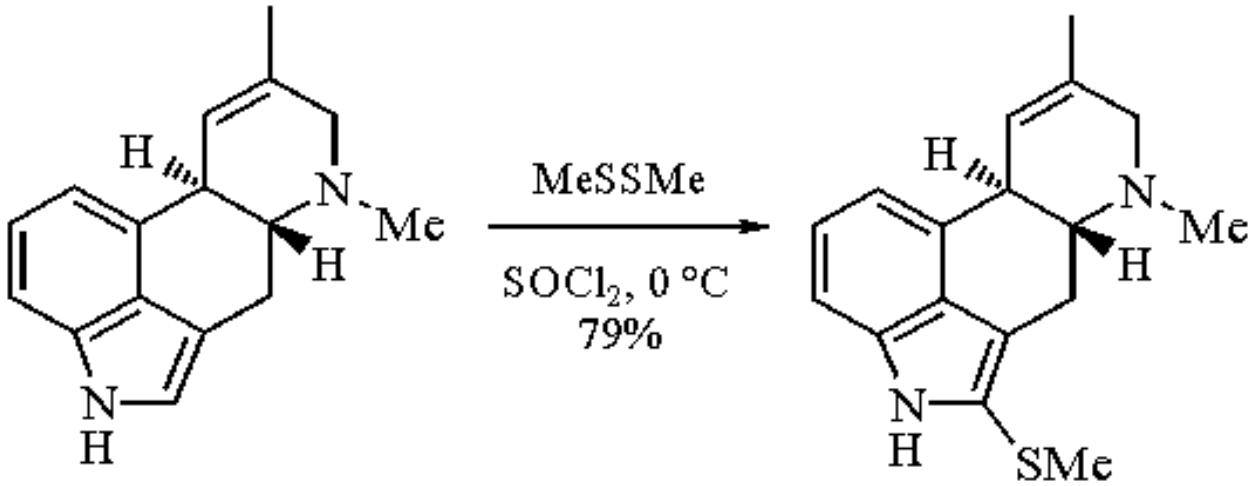

(13)

A number of preformed electrophilic salt derivatives have been developed; the most popular is

Dimethyl(methylthio)sulfonium Tetrafluoroborate (DMTSF),[23] although sulfonate counterions[24] are sometimes used. These reagents react with alkenes to give intermediate episulfonium ions which can be intercepted by nucleophiles such as azide,[25] amines,[26] acetate, carboxylate, DMSO, cyano,[27] ***Triphenylphosphine***,[28] and alkynylaluminates (eq 14).[29]

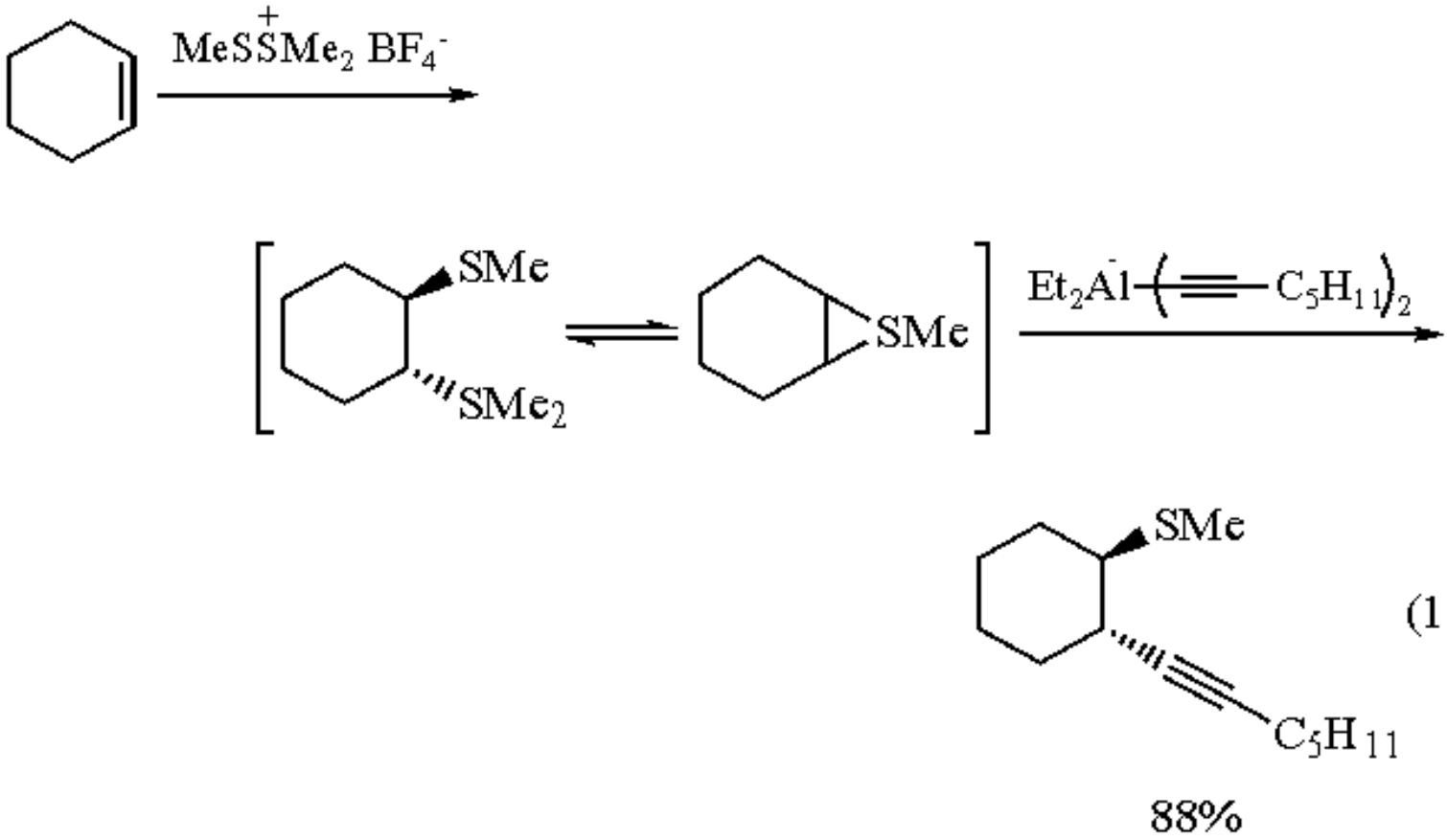

(14)

Disulfenylation of alkenes using a premixed combination of ***Trifluoromethanesulfonic Acid*** and ***Iodosylbenzene*** with dimethyl disulfide is also effective.[30] Reaction of dithioacetals with DMTSF results in thionium ions which can be trapped with allylstannanes (eq 15),[31] vinylsilanes, and silyl enol ethers.[32] Orthothioesters can be similarly ionized upon treatment with DMTSF.[33]

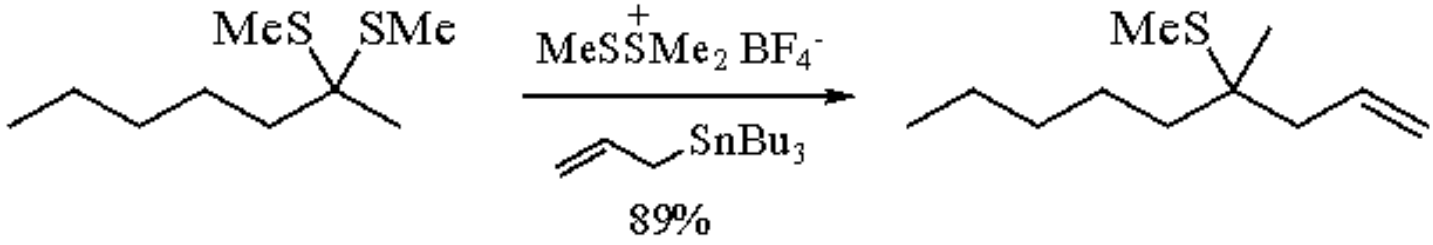

(15)

Higher order sulfenating reagents (see ***Methylbis(methylthio)sulfonium Hexachloroantimonate***)[34] have been developed to generate episulfonium intermediates from alkenes. In these cases, the byproduct dimethyl disulfide is less nucleophilic than the dimethyl sulfide present with DMTSF reactions (eq 16).

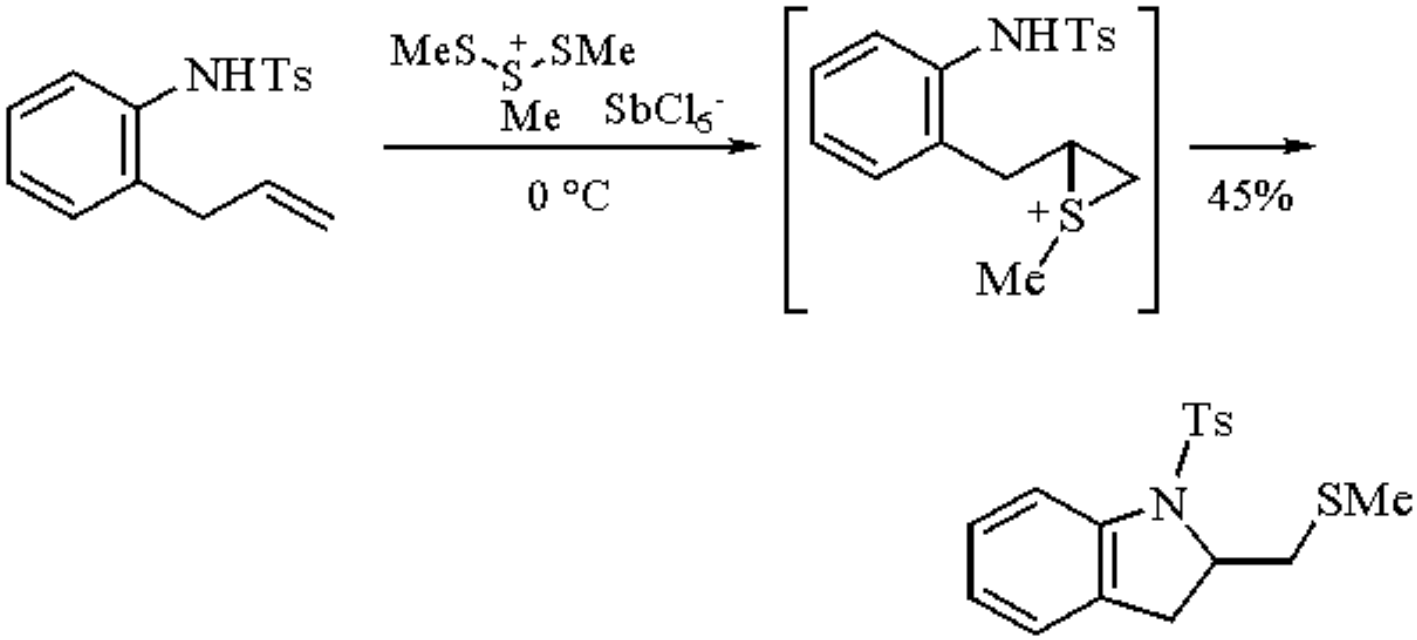

(16)

Preparation of Isolable Sulfenylation or Sulfoxylation Reagents.

Dimethyl disulfide is used in the preparation of ***Methanesulfenyl Chloride***,[35] methanesulfinyl chloride,[36] and methyl methanesulfinate.[37]

Thiol Radical Source and Radical Trap Undergoing S_H2 Reaction.

Photolysis of dimethyl disulfide and other disulfides causes homolytic cleavage of the disulfide bond, resulting in formation of thiol radicals, which can be observed by ESR via nitroxyl spin traps.[38] Aryl,[39] alkyl,[40] and perfluoro[41] radicals react with dimethyl disulfide in an S_H2 displacement to yield the corresponding sulfides (eq 17). Distonic radical cations behave similarly, whereas conventional radical cations do not abstract the methyl sulfide group.[42] Dialkyl and diaryl disulfides add to terminal alkenes by a radical mechanism (eq 18).[43] The addition of dimethyl disulfide across the cyclopropyl bond of a [3.1.1]propellane is believed to occur by thiol radical attack followed by methyl sulfide abstraction (eq 19).[44]

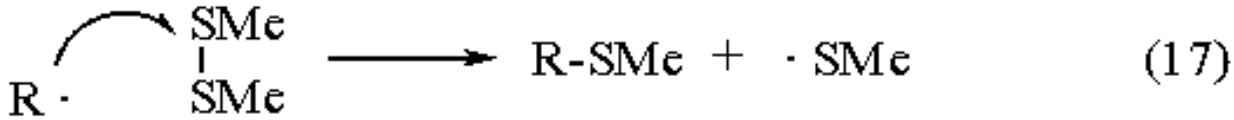

(17)

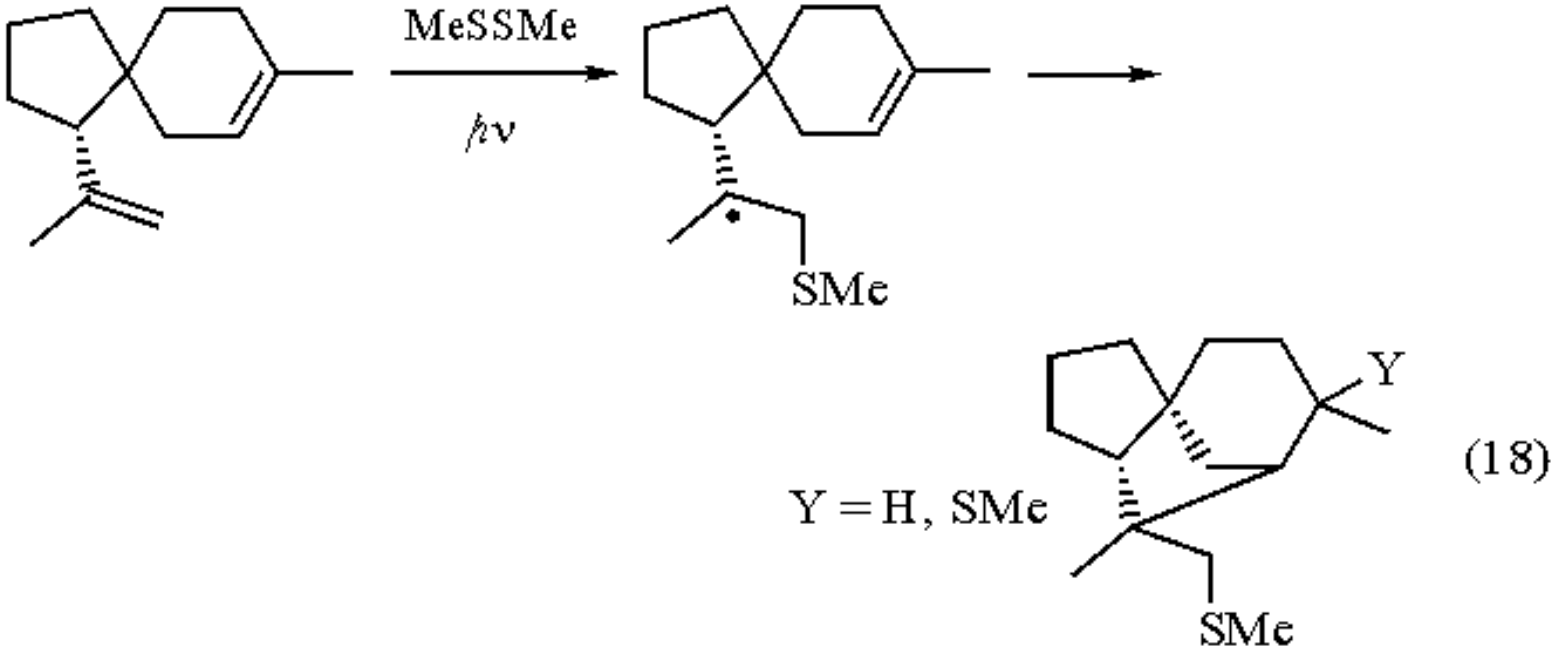

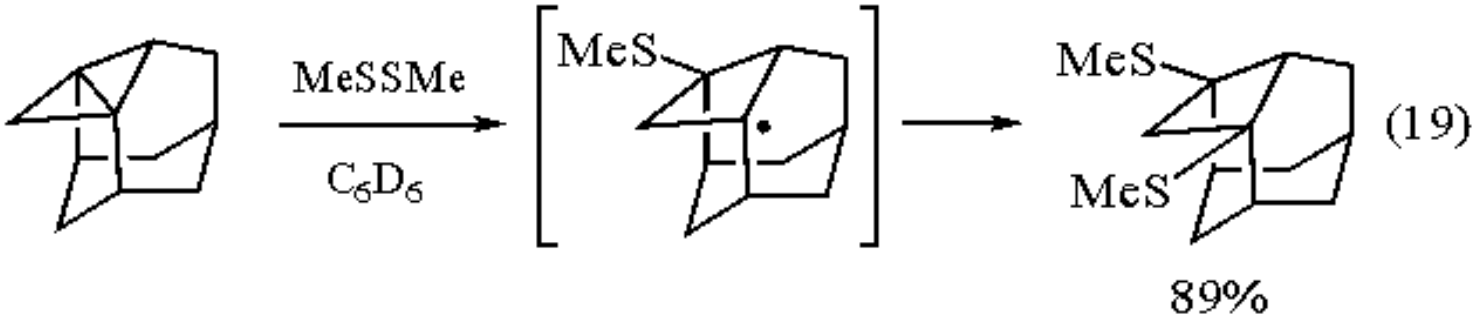

Related Reagents.

Diphenyl Disulfide; ***2,2´-Dipyridyl Disulfide***.

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Dimethyl Dithiobis(thioformate)[1]

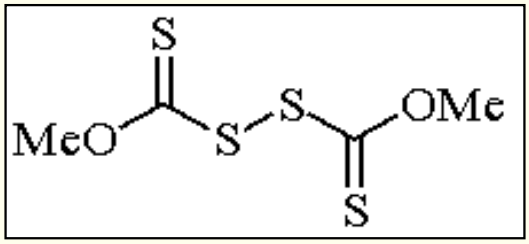

[1468-37-7] · $C_4H_6O_2S_4$ · Dimethyl Dithiobis(thioformate) · (MW 214.38)

(oxidizing reagent for conversion of thiols to disulfides;[2] electrophilic sulfurization reagent[3])

Physical Data: mp 23-23.5 °C; bp 90-94 °C/0.1 mmHg.

Solubility: readily sol common organic solvents.

Form Supplied in: colorless crystals or yellow oil.

Analysis of Reagent Purity: ^{1}H NMR: δ 4.30 (6H, s, OCH_3); TLC, R_f 0.3 (silica gel, hexane).

Preparative Method: [1,2] oxidation of potassium *O*-methyl dithiocarbonate (prepared from potassium methoxide and carbon disulfide) with ***Nitric Acid*** or ***Chloramine-T***.

Purification: recrystallization from ethanol.

Handling, Storage, and Precautions: decomposes at temperatures over 140 °C to yield *O,S*-dimethyl dithiocarbonate;[1] stable for several months storage at rt. Handle in a fume hood.

Oxidation of Thiols to Disulfides.[2]

Most thiols are readily oxidized with this reagent in the presence of ***Pyridine*** as a catalyst to give the corresponding disulfides in excellent yields (eqs 1 and 2) (Table 1). In particular, this reagent is a clean and highly chemoselective oxidant for the conversion of thiols to disulfides without overoxidation to thiosulfinates, sulfinic acids, etc. The reactions are complete in a few minutes at rt. After evaporation of methanol and carbon disulfide (byproducts, eq 3) and pyridine (catalyst), most disulfides can readily be purified by recrystallization from the reaction mixture without chromatography.

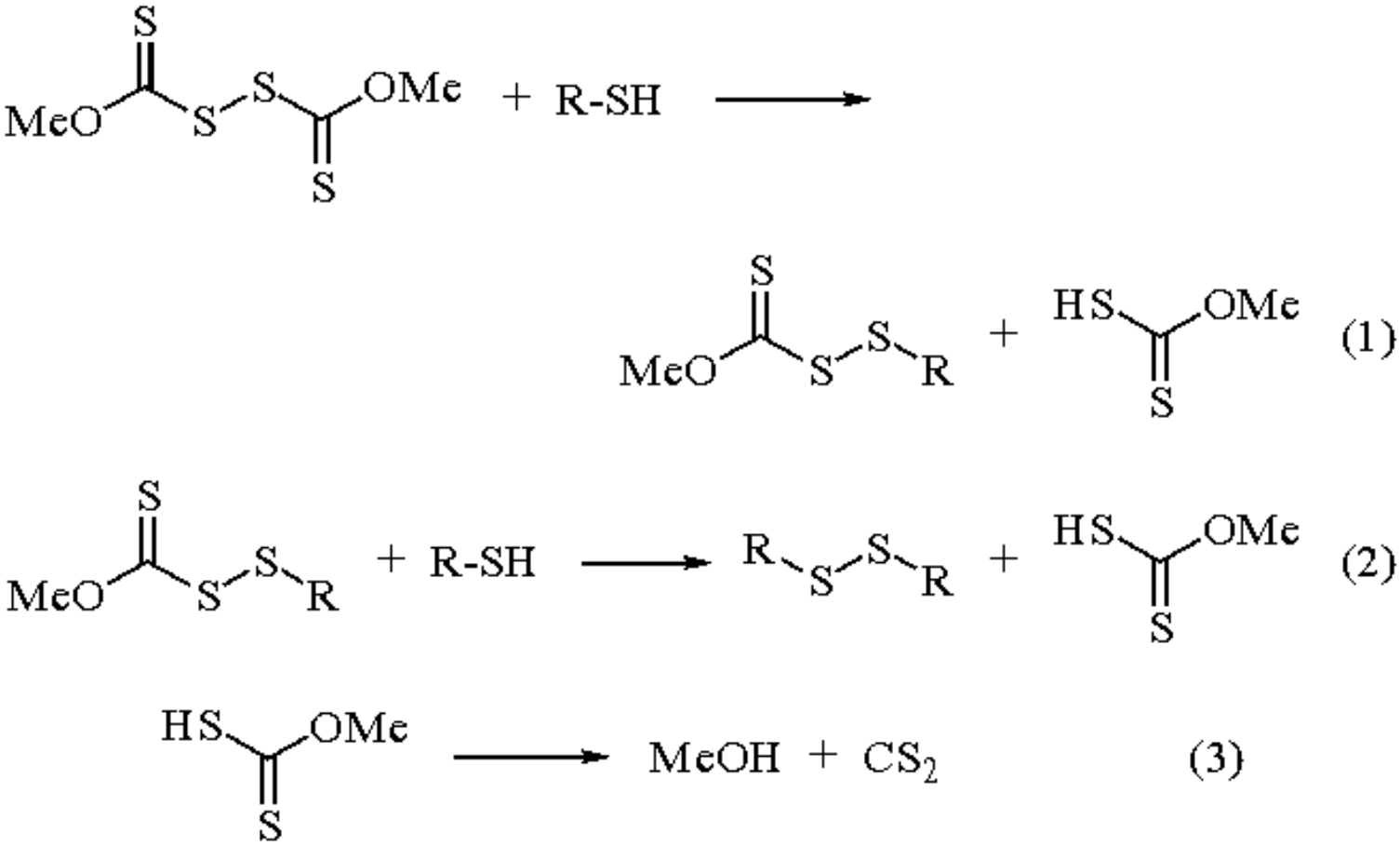

Table 1 Preparation of Disulfides from Thiols

Thiol	Yield of disulfide (%)
PhSH	100
p-ClC_6H_4SH	100
$HSCH_2CH(NH_2)CO_2H$	89
$HSCH_2CH_2SH$	71[a]
p-HOC_6H_4SH	92
$HSCH_2CH_2CO_2H$	100

[a] Product is poly(ethylene disulfide).

Stereoselective α-Alkylidenation of γ-Butyrolactone.[3]

In the presence of 2 equiv of ***Lithium Diisopropylamide***, treatment of γ-***Butyrolactone*** with this reagent and aldehydes in

THF at -78 °C produces α-alkylidene-γ-butyrolactones (eq 4) (Table 2), the (*E*)-isomer being produced with high stereoselectivity. As shown in eq 5, the reaction proceeds via sulfurization of the lactone enolate, aldol condensation with the aldehyde, and final desulfurization of a thiirane.[4,5] When a metal halide such as ***Zinc Chloride*** or ***Copper(I) Iodide*** is added to the reaction mixture, the (*Z*)-isomer becomes the predominant product. The excellent stereoselectivity observed in this reaction has been attributed to repulsion between the β-methylene of the lactone and the aldehyde substitutent in the transition state for aldol addition, the transition state being different in the presence or absence of an added metal halide (eqs 6-9). This procedure has advantages for the stereoselective preparation of either the (*E*)- or (*Z*)-isomer of 2-alkylidene carbonyl compounds.

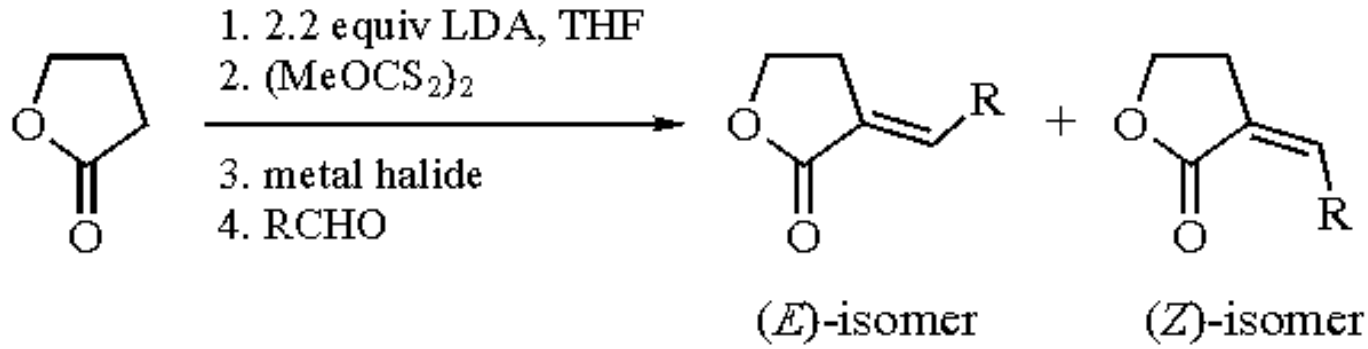

(4)

Table 2 Stereoselective Synthesis of a-Alkylidene-g-butyrolactone

Aldehyde	Metal halide (1.5 equiv)	Product	Yield (%)	(*E*):(*Z*) ratio
n-PrCHO		R = *n*-Pr	57	96:4
n-PrCHO	$ZnCl_2$	R = *n*-Pr	58	9:91
n-PrCHO	CuI	R = *n*-Pr	56	7:93
$Me(CH_2)_5CHO$		R = $Me(CH_2)_5$	54	88:12
$Me(CH_2)_5CHO$	$ZnCl_2$	R = $Me(CH_2)_5$	63	16:84
$Me(CH_2)_5CHO$	CuI	R = $Me(CH_2)_5$	69	15:85
i-PrCHO		R = *i*-Pr	49	97:3
i-PrCHO	$ZnCl_2$	R = *i*-Pr	49	4:96
PhCHO		R = Ph	52	100:0
PhCHO	CuI	R = Ph	51	4:96

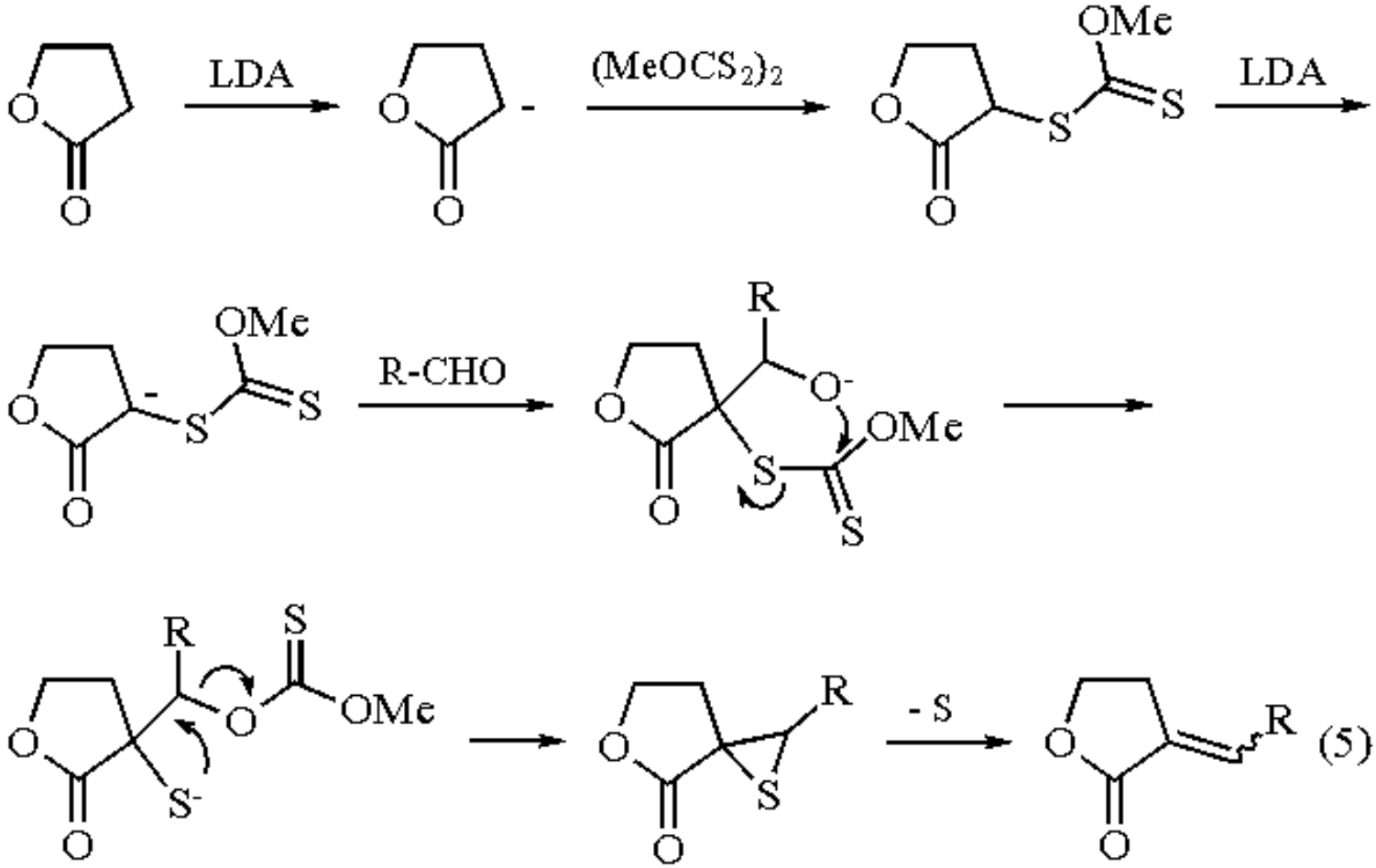

(5)

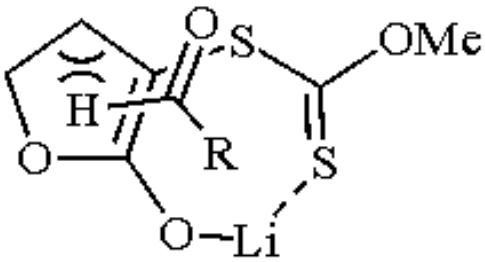

(*E*)-isomer (6)

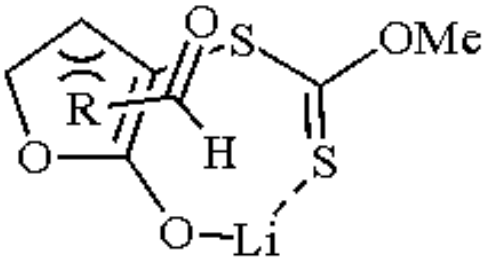

(*Z*)-isomer (7)

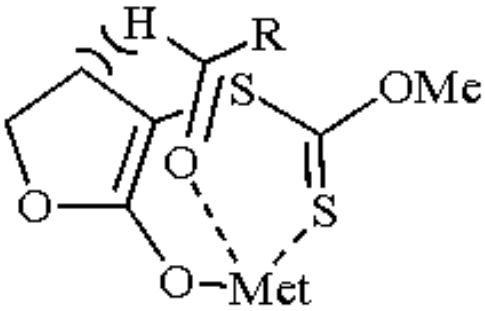

(*Z*)-isomer (8)

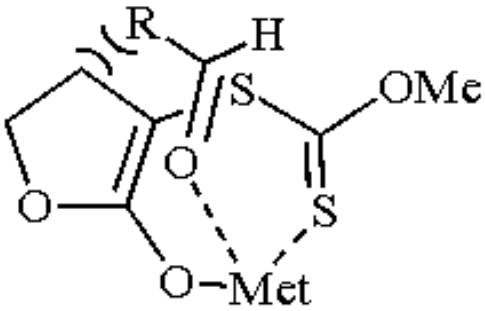

(*E*)-isomer (9)

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N,N-Dimethyldithiocarbamoylacetonitrile[1]

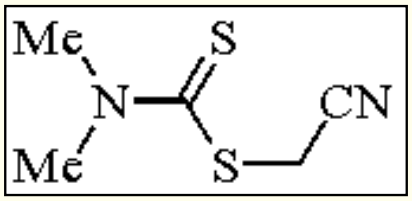

[61540-35-0] · $C_5H_8N_2S_2$ · *N,N*-Dimethyldithiocarbamoylacetonitrile · (MW 160.29)

(alkylation;[2] arylation;[3] transformation to other functional groups;[2,4] reductive desulfurization[3,5])

Physical Data: mp 73-74 °C.

Solubility: insol H_2O; sol THF, dichloromethane, DMF; slightly sol alcohol.

Form Supplied in: white crystalline solid.

Preparative Method: quantitatively prepared from ***Chloroacetonitrile*** and sodium *N,N*-dimethyldithiocarbamate at rt in methanol.

Purification: recrystallized from ethanol.

Handling, Storage, and Precautions: can be used and be stored at rt under air. Use in a fume hood.

Nucleophilic Substitutions.

N,N-Dimethyldithiocarbamoylacetonitrile (**1**) serves as an active methylene compound, because its carbanion is stabilized by sulfur and cyano groups. It can be alkylated stepwise in aqueous sodium hydroxide under phase transfer catalysis (eq 1).[2] The anion undergoes nucleophilic aromatic substitution to give nitroarenes, with elimination of the dithiocarbamate group (eq 2).[3] Nucleophilic addition of (**1**) to phenyl isothiocyanate also occurs readily.[6]

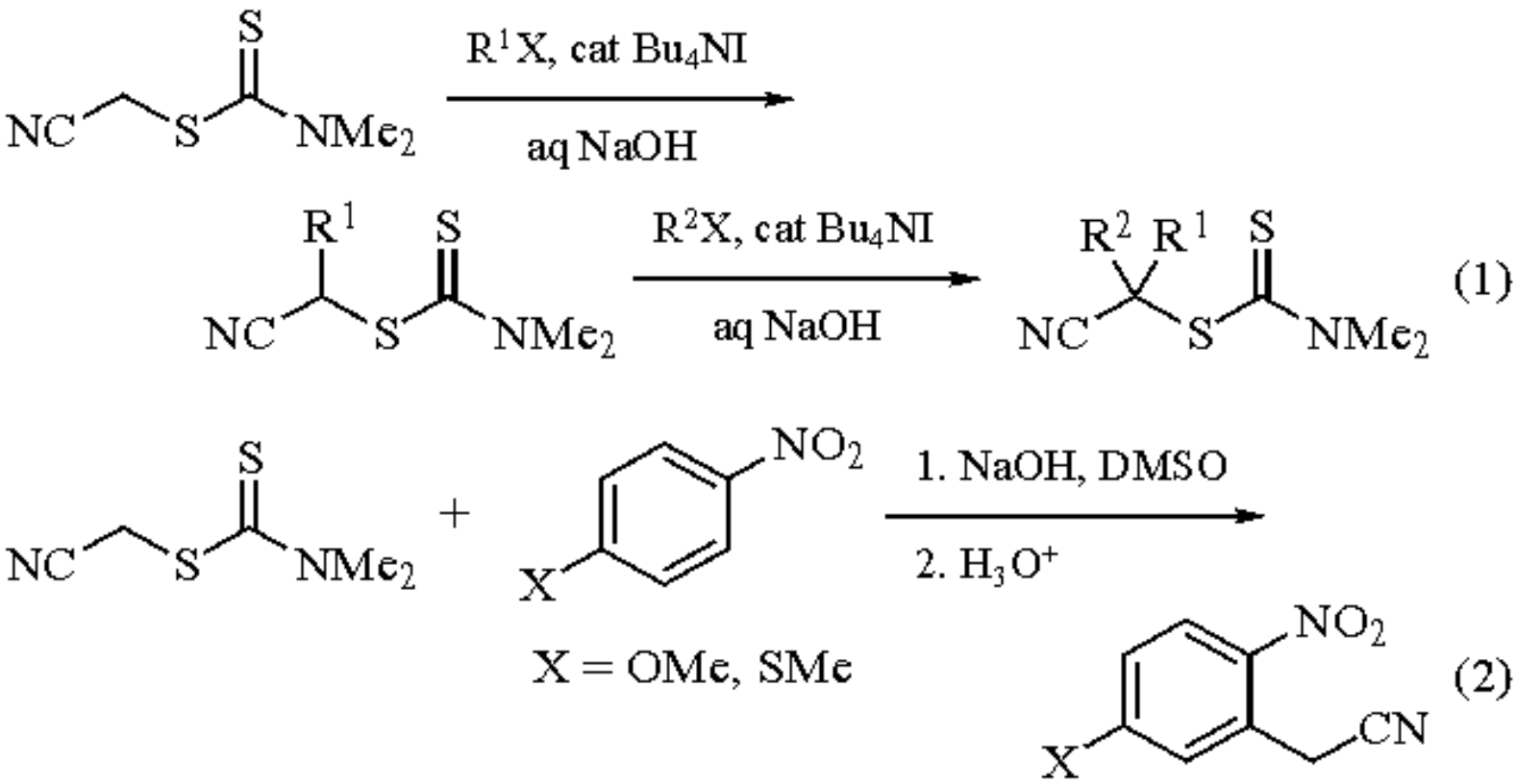

Transformations.

Dialkylated *N,N*-dimethyldithiocarbamoylacetonitriles are transformed into ketones by ***N-Bromosuccinimide*** bromination or by basic hydrolysis (eq 3),[2] and they are hydrolyzed in acidic ethanol to produce α-mercapto carboxylates.[4] Bromination of (**1**) in methanol leads to the formation of 1,3-dithietan-2-ylium ion.[7] Alkylated *N,N*-dimethyldithiocarbamoylacetonitriles are reductively desulfurized to α-branched nitriles with ***Tri-n-butylstannane*** in the presence of a catalytic amount of ***Azobisisobutyronitrile*** (eq 4).[5]

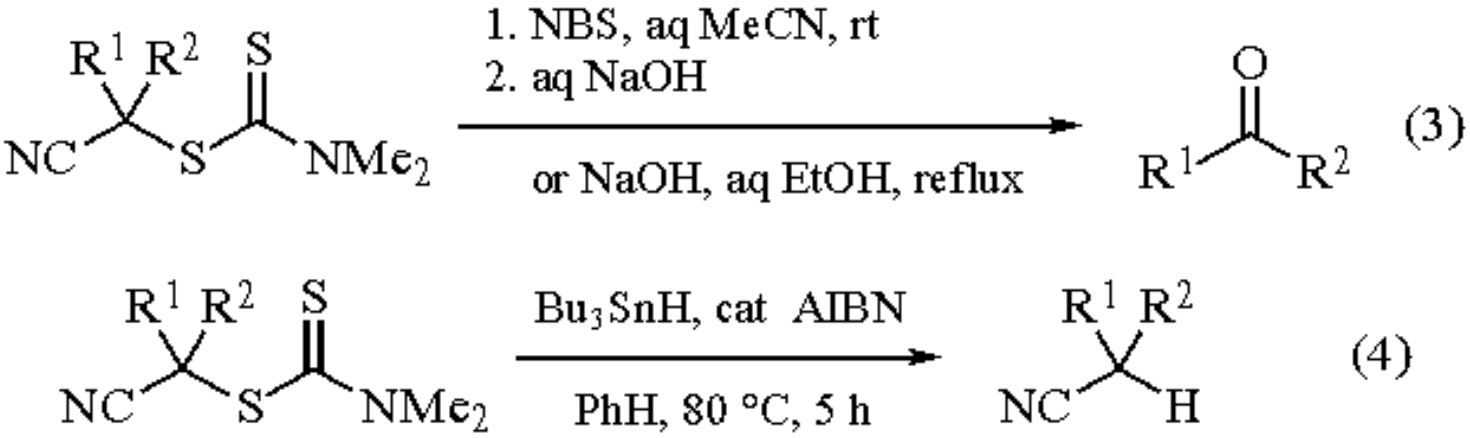

Related Reagents.

N,N-Diethylaminoacetonitrile; ***2-(2,6-Dimethylpiperidino)acetonitrile***; ***Lithioacetonitrile***; ***Methoxyacetonitrile***.

1. (a) Jensen, K. A. *JPR* **1941**, *159*, 189 (b) Nachmias, G. *AC(R)* **1952**, *7*, 584 (*CA* **1954**, *48*, 597).
2. Masuyama, Y.; Ueno, Y.; Okawara, M. *TL* **1976**, 2967.
3. Makosza, M.; Winiarski, J. *JOC* **1984**, *49*, 1494.
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N,N-Dimethylformamide[1]

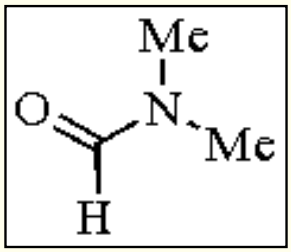

[68-12-2] · C_3H_7NO · *N,N*-Dimethylformamide · (MW 73.11)

(formylating agent for certain organometallics[2-5]; used in combination with $POCl_3$ or acid halides to form the reactive Vilsmeier reagent[8,9])

Alternate Name: DMF.

Physical Data: mp -61 °C; bp 153 °C; *d* 0.944 g cm^{-3}; fp 57 °C.

Solubility: miscible with water and most organic solvents.

Form Supplied in: clear liquid; both d_7 and ^{13}C forms are available commercially; widely available.

Purification: decomposes slightly at its normal boiling point to give small quantities of of dimethylamine and carbon monoxide. The decomposition is catalyzed by acidic or basic materials so that even at rt DMF is appreciably decomposed if allowed to stand for several hours with solid KOH, NaOH, or CaH_2. Drying agents suitable for DMF are $CaSO_4$, $MgSO_4$, silica gel, and 4Å molecular sieves. After drying, distillation under reduced pressure will give reasonably dry DMF adequate for most laboratory purposes. Anhydrous DMF can be prepared by using certain desiccants.[1b]

Handling, Storage, and Precautions: anhydrous DMF should be stored under a nitrogen atmosphere in sure seal bottles or metallic cylinders; vapors are harmful, irritating to skin, eyes, and mucous membranes; it is suspected to be a carcinogen; use in a fume hood.

Reaction with Organometallics.

DMF is a good formylating agent for certain organometallic compounds. Even though formylation of some alkyllithium or Grignard reagents with DMF does not always give good yields of products due to side reactions,[1] sonication of a mixture of alkyl or aryl halide, lithium, and DMF substantially increases the rate of organometallic formation and yield of the formylated product.[2] Allenyl and vinyl organolithiums undergo formylation with DMF to

produce good yields of unsaturated aldehydes.[3] DMF can be added to the dianion of cyclohexanone oxime to give an isoxazole in good yield (eq 1).[4] Many organometallic compounds have been formylated on reaction with DMF.[5]

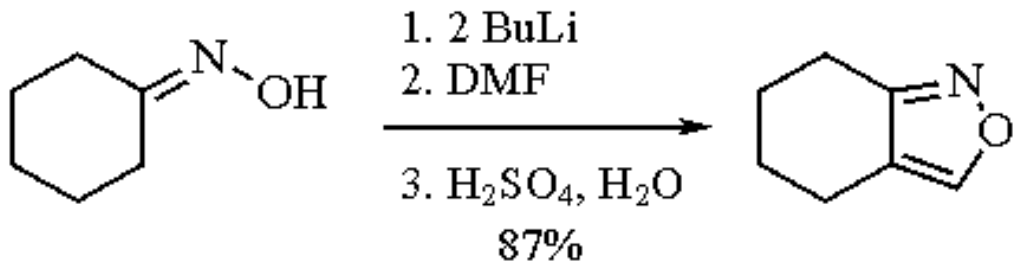

(1)

Alkali metal reduction of arylalkenes in the presence of DMF results in α-hydroxy amides in high yield (eq 2).[6] Through a novel three-component alkene formation involving DMF, an organolithium reagent, and a Wittig reagent, alkenes can be synthesized in high yield (eq 3).[7]

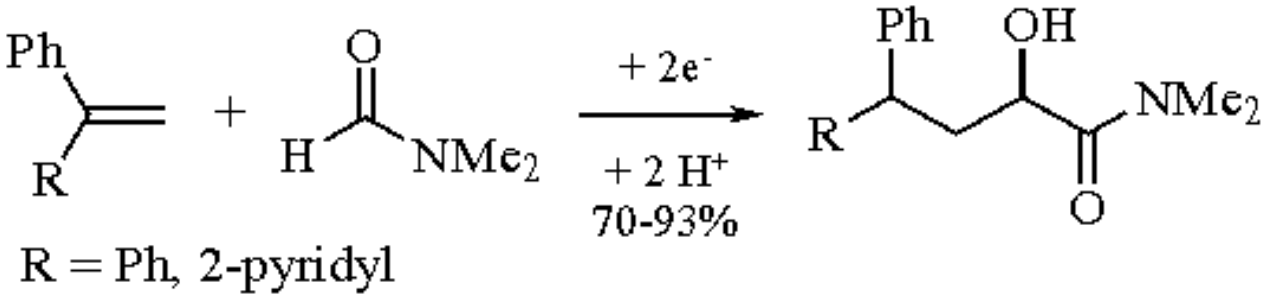

(2)

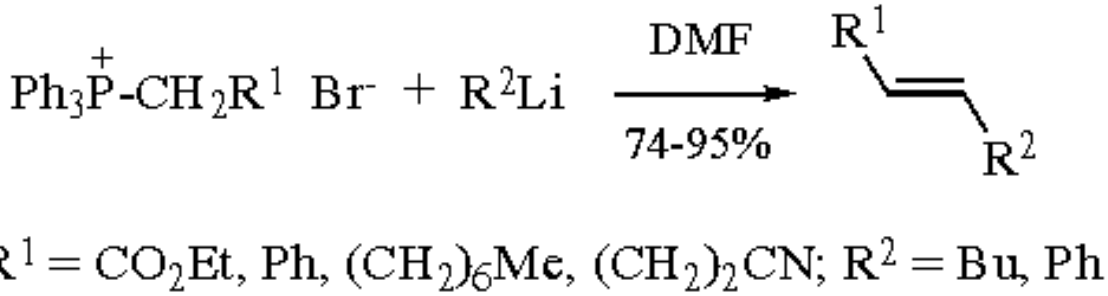

(3)

Vilsmeier Reaction.

A Vilsmeier reagent is generated when DMF is treated with ***Phosphorus Oxychloride*** or other acid chlorides; this reagent has found extensive use as a formylating, halogenating, and dehydroxylating agent (see also ***Dimethylchloromethyleneammonium Chloride***).[8]

Formylation.

Formylation can be achieved using the Vilsmeier reagent generated by treating DMF with an acid chloride. Indoles substituted at C-3 react with DMF-$POCl_3$ at 100 °C to give 2-formylindoles (eq 4).[9a] Similarly, 1,2-dihydropyridines[9b-d] and 1,4-dihydropyridines[9d] have been regioselectively formylated using DMF-$POCl_3$.

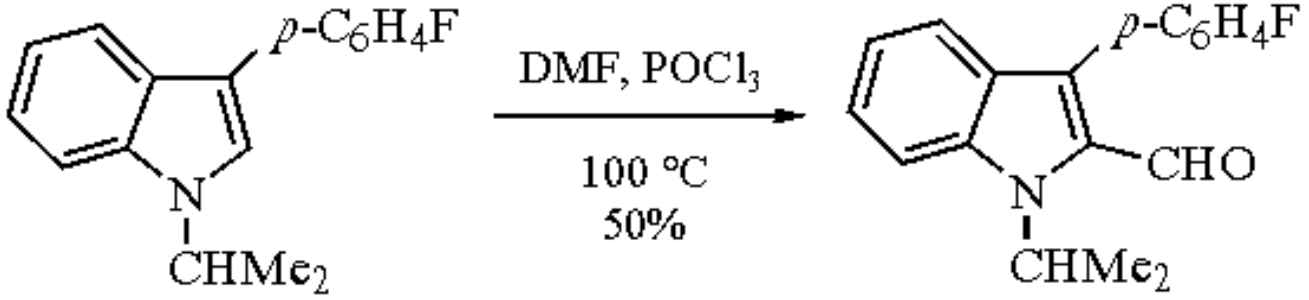

(4)

Alcohols undergo *O*-formylation when treated with DMF and benzoyl chloride, providing good yields of formates (eq 5).[10]

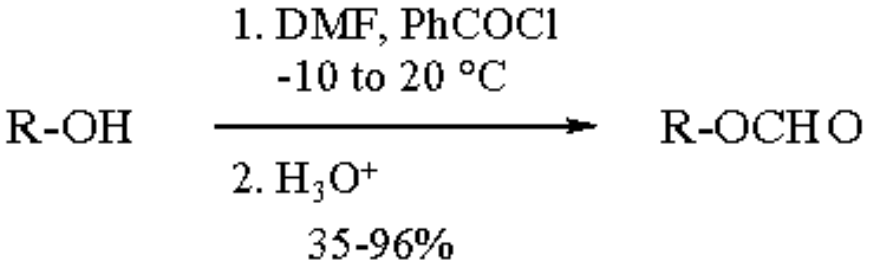

(5)

A similar transformation can be achieved by treating an amine with ***Chlorotrimethylsilane*** and ***Imidazole*** in DMF.[11] In contrast, primary amines form the formamidine on treatment with DMF-$POCl_3$ (eq 6).[12] Phthalimides undergo a one-pot deprotection and *N*-formylation on reaction with DMF and hydrazine.[13]

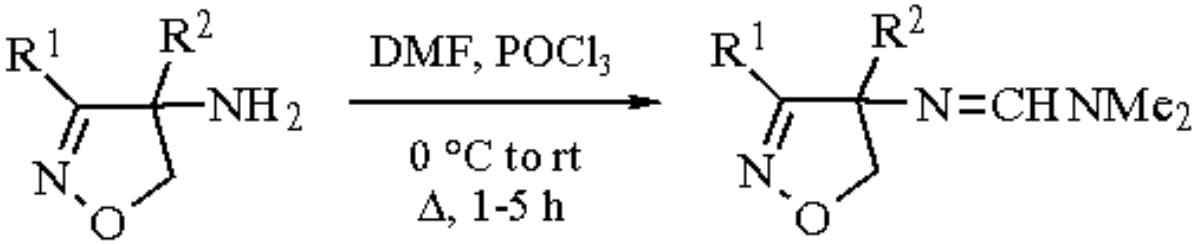

(6)

Reaction with Alcohols.

Alkyl halides can be easily synthesized on reaction of an alcohol with DMF and ***Phosgene***.[14] In an analogous manner, 1-triptycyl carbinols undergo a deoxygenative rearrangement and halogenation on treatment with ***Thionyl Chloride***-DMF.[15]

Reaction with Enolizable Ketones.

Both acyclic and cyclic enolizable ketones react with DMF-$POCl_3$ to form the β-chloro-α,β-unsaturated aldehydes. The regioselectivity of this reaction in substituted cyclohexanones is dependent on steric effects (eq 7).[16]

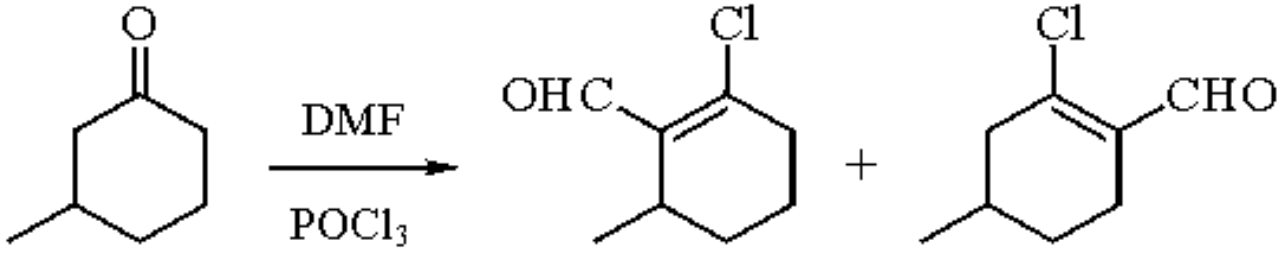

(7)

10:90

Several unsaturated alkenones have been converted to chlorobenzene mono-, di-, and tricarbaldehydes.[8] An illustrative example is the conversion of 2-hexen-4-one to 5-methyl-4-chloro-1,3-benzenedicarbaldehyde using DMF-$POCl_3$ (eq 8).[17]

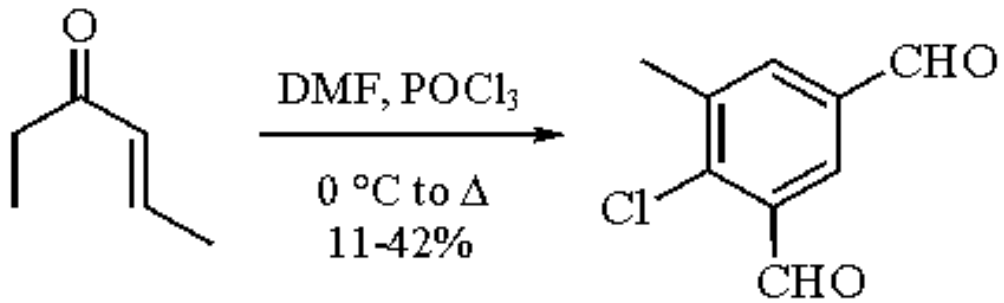

(8)

Benzofurans result on reaction of α-phenoxyacetophenones with DMF-$POCl_3$ (eq 9).[18]

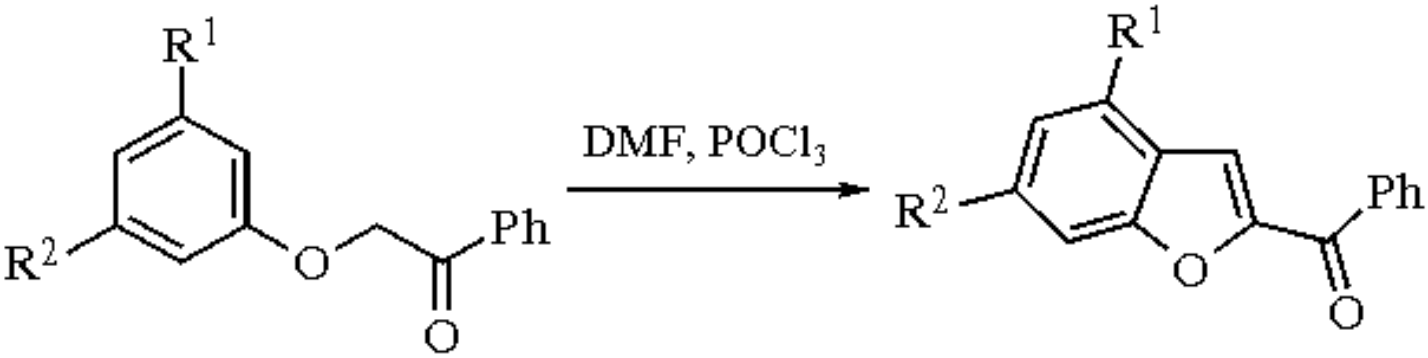

(9)

$R^1 = R^2 = OMe$

$R^1 = H,\ R^2 = OMe,\ OEt,\ NEt_2$

Tetrahydro-4*H*-thiopyran-1-one and tetrahydro-4*H*-pyran-4-one are converted to the respective chlorovinyl aldehydes on treatment with DMF-$POCl_3$ at ambient temperature.[19] Thiachroman-4-one affords the β-chlorovinyl aldehyde on treatment with DMF-$POCl_3$ below 50 °C, but at 100 °C 3-formylthiachromone is formed in modest yield (eq 10).[19]

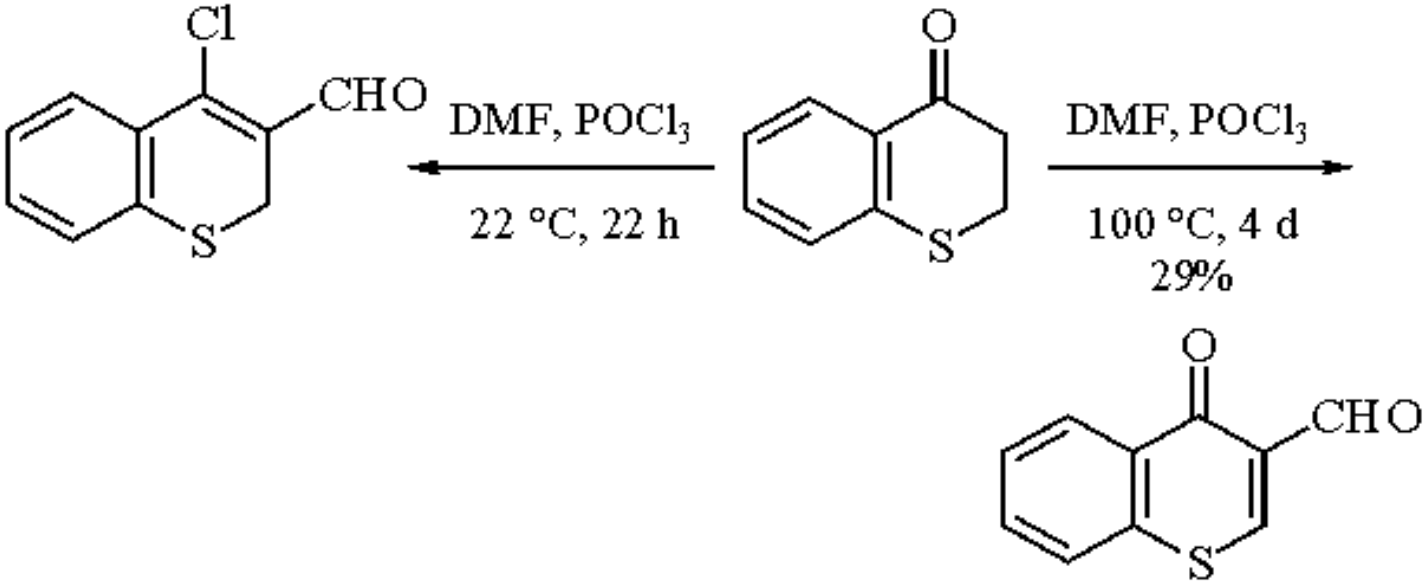

(10)

Certain ketones can be converted to chloroalkenes on reaction with the Vilsmeier reagent. 3-Halo-2-cyclopenten-1-one has been prepared in excellent yield by reaction of cyclopentene-1,3-dione with DMF and ***Oxalyl Chloride*** or ***Oxalyl Bromide***.[20] In contrast, cyclohexane-1,3-diones afford cross-conjugated dialdehydes on treatment with DMF-$POCl_3$ (eq 11).[21]

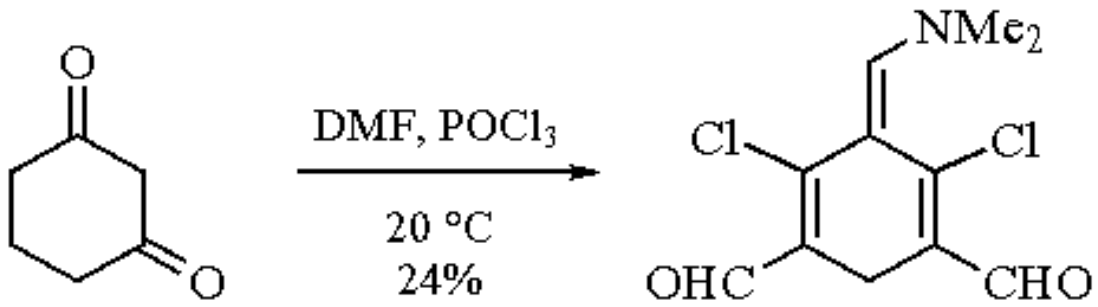

(11)

In a similar manner, 2,3-dihydro-4-pyridones have been converted to 4-chloro-1,2-dihydropyridines on treatment with DMF-$POCl_3$ (eq 12).[22]

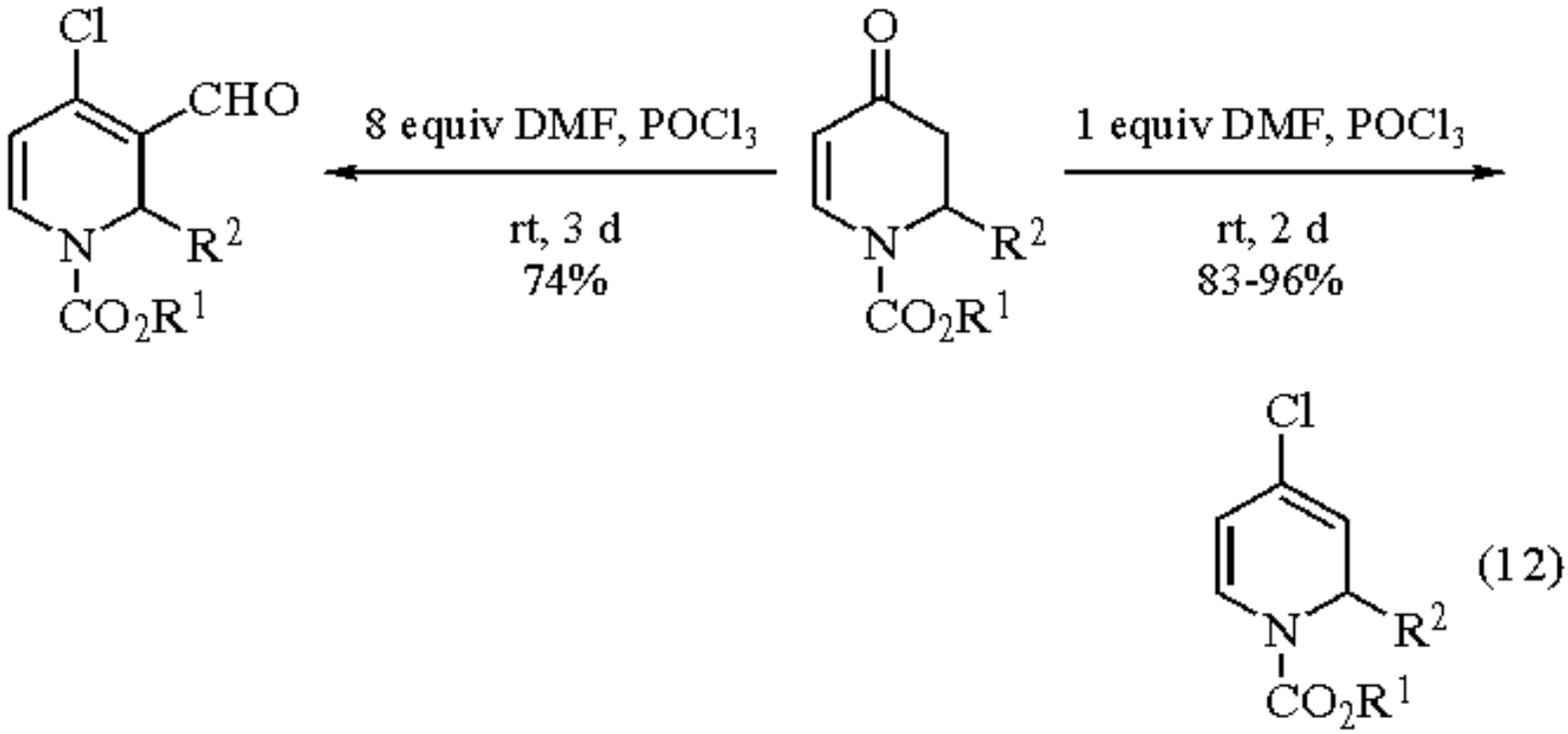

Reaction with Amides.

Quinoline-3-carbaldehydes can be prepared by reaction of acylanilides with DMF-$POCl_3$ (eq 13).[23]

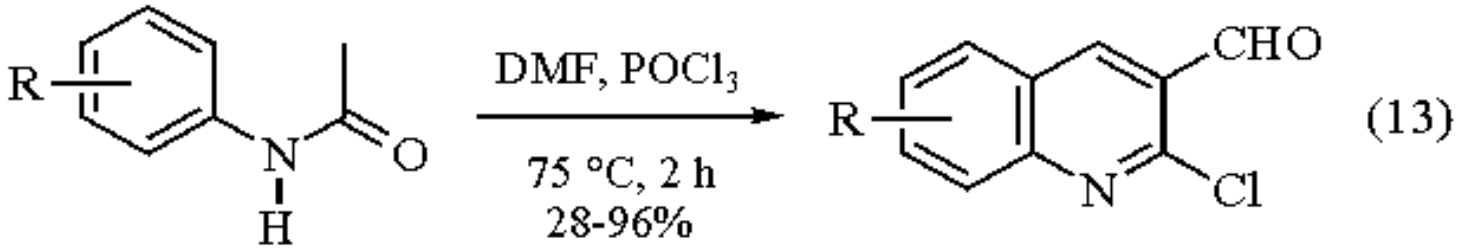

In an analogous manner, dihydroisoquinolin-3-ones can be treated with DMF-$POCl_3$ followed by oxidation to give 3-chloro-4-formylisoquinolines.[24] Pyridines and related systems can be prepared using the reaction of the DMF-acid chloride adduct with carboxamides.[8]

Reaction with Acids.

The adduct generated from DMF and oxalyl chloride easily converts a carboxylic acid to its acid chloride.[25] The same adduct in combination with a hydride reagent can be used to reduce acids to aldehydes.[26] DMF and $SOCl_2$ convert a carboxylic acid to an acyl azide in the presence of ***Sodium Azide***, pyridine, and tetrabutylammonium chloride as a catalyst.[27] Using the dehydrating ability of the DMF-$SOCl_2$ adduct, β-lactams can be synthesized from an imine and a carboxylic acid in the presence of ***Triethylamine*** (eq 14).[27] Generally a mixture of *cis*- and *trans*-azetidinones is formed.

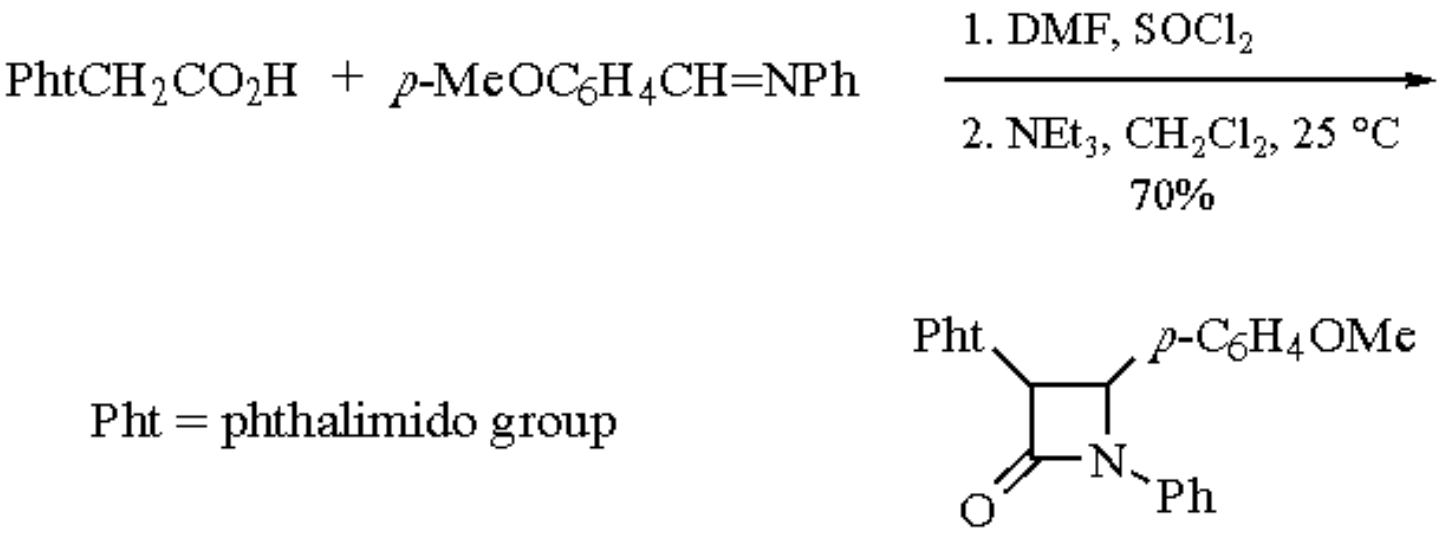

(14)

1,4-Dihydrobenzoic acids react with DMF-$POCl_3$ to give benzene mono-, di-, and tricarbaldehydes. This procedure also affords naphthalenedicarbaldehyde (eq 15).[28]

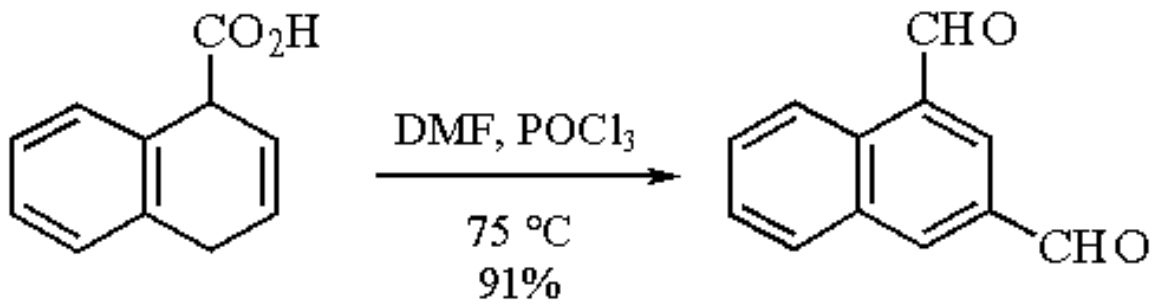

(15)

Reaction with Esters and Lactonic Carbonyl Groups.

Esters are normally inert to DMF-$POCl_3$ in the presence of other reactive groups.[29] The reaction of coumarone and DMF-$POCl_3$ gives a mixture of products.[30] 1,3-Oxazin-6-ones can be obtained by reaction of isoxazolin-5-ones with DMF-$POCl_3$ (eq 16).[31]

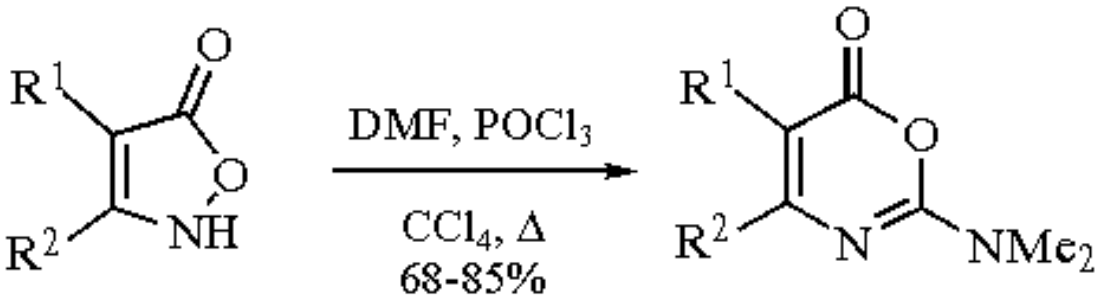

(16)

In contrast, 3-phenyl-5-isoxazolinone reacts with DMF-$POCl_3$ to give different products depending on conditions (eq 17).[32]

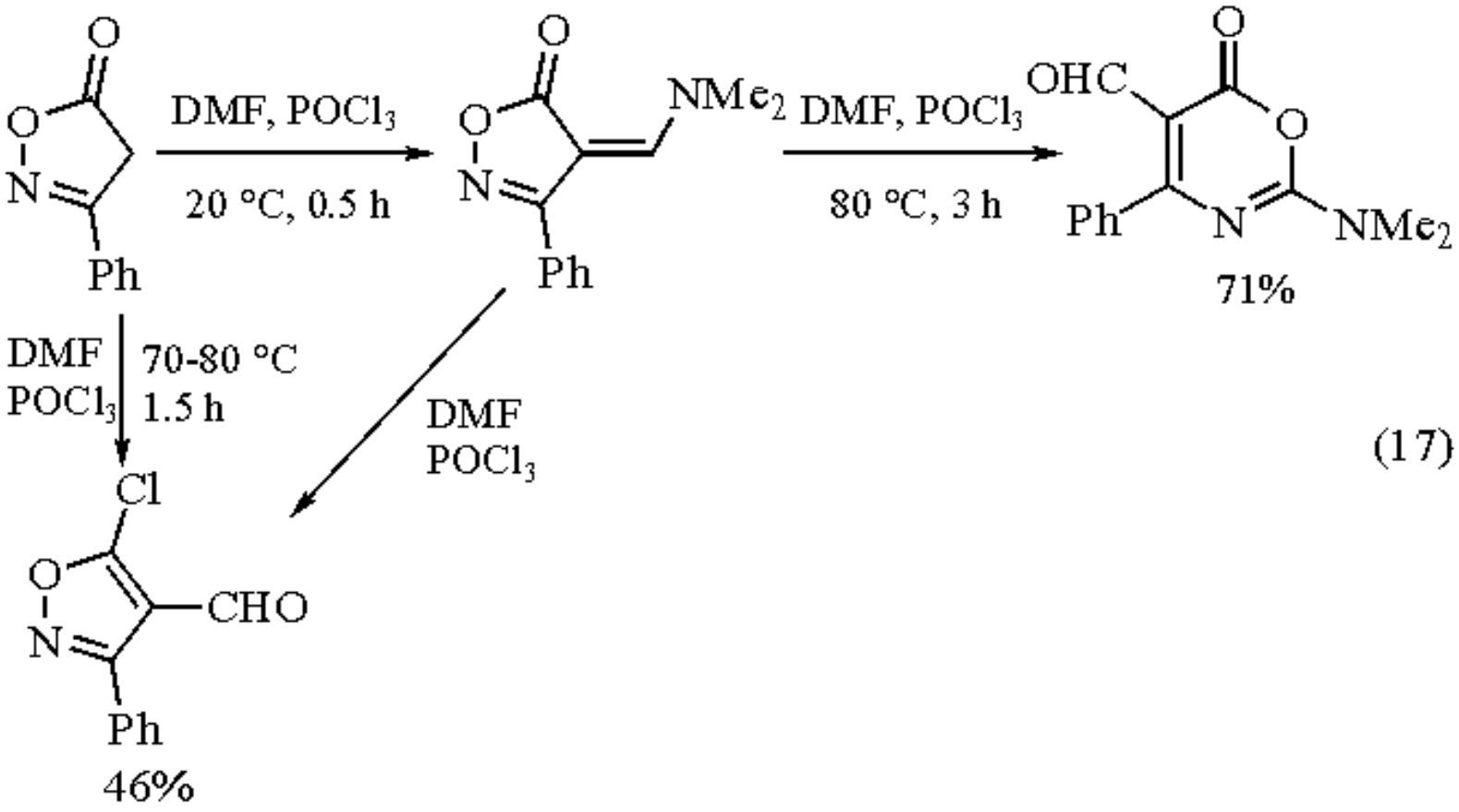

(17)

Miscellaneous Reactions.

DMF reacts with α-bromopropionamides in presence of ***Sodium Hydride*** or ***Silver(I) Oxide*** to form oxazolidinones, where the carbonyl group of DMF becomes incorporated (eq 18).[33]

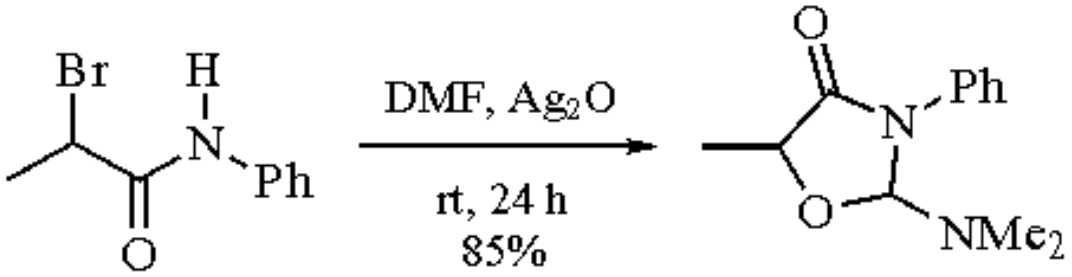

(18)

Formylation of secondary amines can be achieved on reaction with DMF and 2,3-dihydro-1,4-phthalazinedione.[34] The combination of DMF and $SOCl_2$ can dehydrate oximes to nitriles.[27] Trifluoromethylsulfonylalkynes react with DMF to form enamides.[35] *N,N*-Bis(trimethylsilyl)enamines give azabutadienes on reaction with ***Sodium Methoxide*** in DMF.[36] α,α-Dichlorination of ketones can be achieved with ***Chlorine*** using DMF as solvent or as catalyst at 80-100 °C.[37] Reaction of an α-bromo ketone with ***Lithium Bromide*** and ***Lithium Carbonate*** in DMF at 140 °C results in a cyclic ether (eq 19).[38]

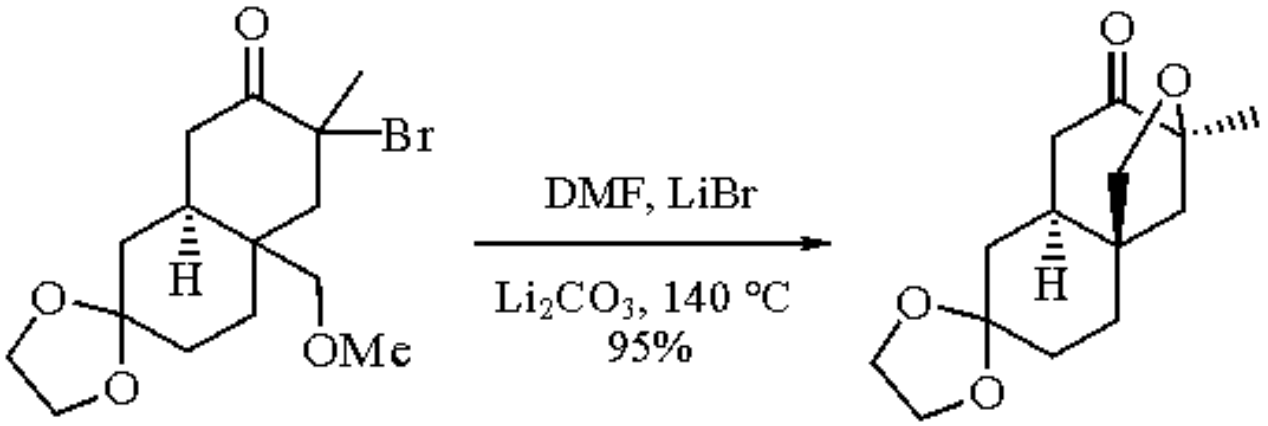

(19)

Related Reagents.

Acetic Formic Anhydride; ***Dimethylbromomethyleneammonium Bromide***; ***Dimethylchloromethyleneammonium Chloride***; ***Formyl Chloride***; ***N-Formylpiperidine***; ***N-Methylformanilide***; ***Methyl Formate***; ***N-Methyl-N-phenyl(chloromethylene)ammonium Phosphorochloridate***; ***N-Methyl-N-(2-pyridyl)formamide***.

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N,N-Dimethylformamide Diethyl Acetal

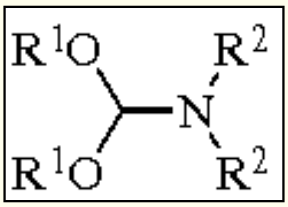

(**1**; R^1 = Et, R^2 = Me)

[1188-33-6] · $C_7H_{17}NO_2$ · *N,N*-Dimethylformamide Diethyl Acetal · (MW 147.25) (**2**; R^1 = Me, R^2 = Me)

[4637-24-5] · $C_5H_{13}NO_2$ · *N,N*-Dimethylformamide Dimethyl Acetal · (MW 119.19) (**3**; R^1 = $PhCH_2$, R^2 = Me)

[2016-04-8] · $C_{17}H_{21}NO_2$ · *N,N*-Dimethylformamide Dibenzyl Acetal · (MW 271.39) (**4**; R^1 = Et, R^2 = Et)

[22630-13-3] · $C_9H_{21}NO_2$ · *N,N*-Diethylformamide Diethyl Acetal · (MW 175.31)

(mild and selective reagents for alkylation, formylation, and aminomethylenation[1])

Alternate Name: DMF diethyl acetal.

Physical Data: (**1**) bp 134-136 °C/760 mmHg; pK_b 6.2.[5] (**2**) bp 102-104 °C/720 mmHg; pK_b 6.25.[5] (**3**) bp 138-140 °C/0.5 mmHg; pK_b 6.2.[5] (**4**) bp 57-58 °C/20 mmHg; pK_b 6.4.[5]

Solubility: sol a variety of inert solvents.

Form Supplied in: pure liquid.

Preparative Methods: (1) a solution of sodium alkoxide (1 mol) and the secondary amine (1.1 mol) in 200-300 mL of the respective alcohol is refluxed as chloroform (39.5 g, 0.33 mol) is added. The mixture is refluxed for 2 h and the filtrate obtained is distilled in vacuo. For example, *N,N*-diethylformamide diethyl acetal is obtained in 32% yield.[7] (2) A solution of *N,N*-dialkyl(chloromethylene)ammonium chloride (Vilsmeier reagent, 1 mol) in 640-500 mL of chloroform is stirred while sodium alkoxide (2.1 mol) in 1 L of the respective alcohol is added. After 1 h at 20 °C the sodium chloride is separated and the mixture is distilled in vacuo. For example, the yield of DMF dimethyl acetal is 55%.[2]

Handling, Storage, and Precautions: most of the known orthoamide derivatives are colorless, distillable liquids with an amine-like smell. If moisture and presence of acids and high temperature are avoided, most of the reagents can be stored almost indefinitely. No significant toxicity has been reported.

Reactions and Synthetic Applications: General.

The formamide acetals enter into two main categories of reactions, namely alkylation and formylation, mostly via generation of aza-oxo-stabilized carbenium ions (eq 1).[1-7] As alkylation reagents they have been used in the synthesis of esters from acids, in the synthesis of ethers and thioethers from phenols and aromatic and heterocyclic thiols, and in the alkylation of CH-active methines. As formylating agents, formamide acetals are useful in the synthesis of enamines from active methylene compounds and amidines from amines and amides, as well as in the formation and modification of many types of heterocyclic compounds. They can be used for the dehydrative decarboxylation of β-hydroxy carboxylic acids to alkenes, and for the cyclization of *trans* vicinal diols to epoxides.[1] From the numerous literature reports on applications of these reagents,[1-7] some representative reactions are discussed in the following sections.

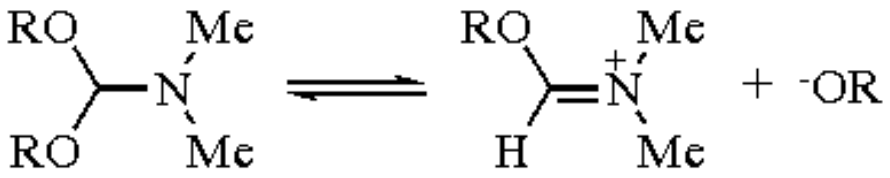

(1)

Alkylation Reactions.

DMF dialkyl acetals undergo a variety of reactions with 1,2-diols.[1] For example, the reaction of *trans*-cyclohexane-1,2-diol with DMF dimethyl acetal leads to the formation of cyclohexane epoxide (eq 2)[8] with inversion of configuration. Similarly, *meso*-1,2-diphenyl-1,2-ethanediol gives *trans*-stilbene epoxide stereospecifically (eq 3).[8,9a] This method has also been applied in the synthesis of cholestane epoxide from vicinal diols.[8] If the intermediate 2-dimethylamino-1,3-dioxolane is treated with ***Acetic Anhydride***, reductive elimination to the alkene occurs with retention of stereochemistry (eq 4).[9b]

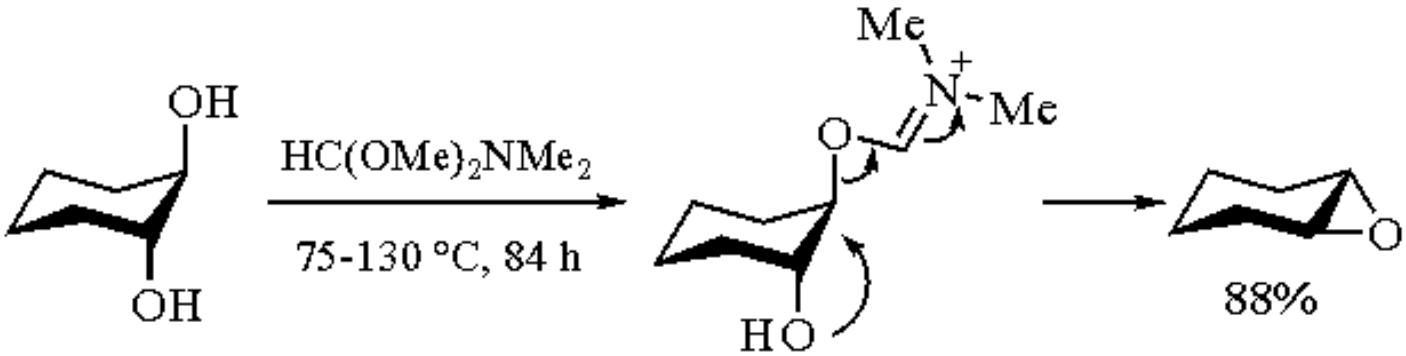

(2)

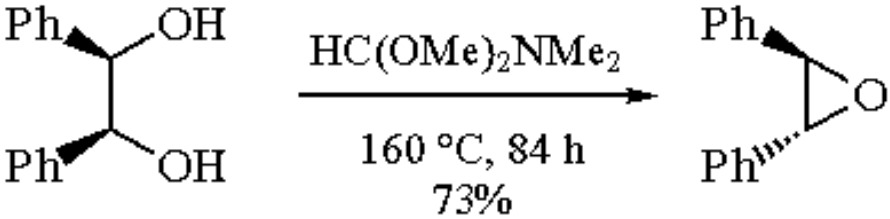

(3)

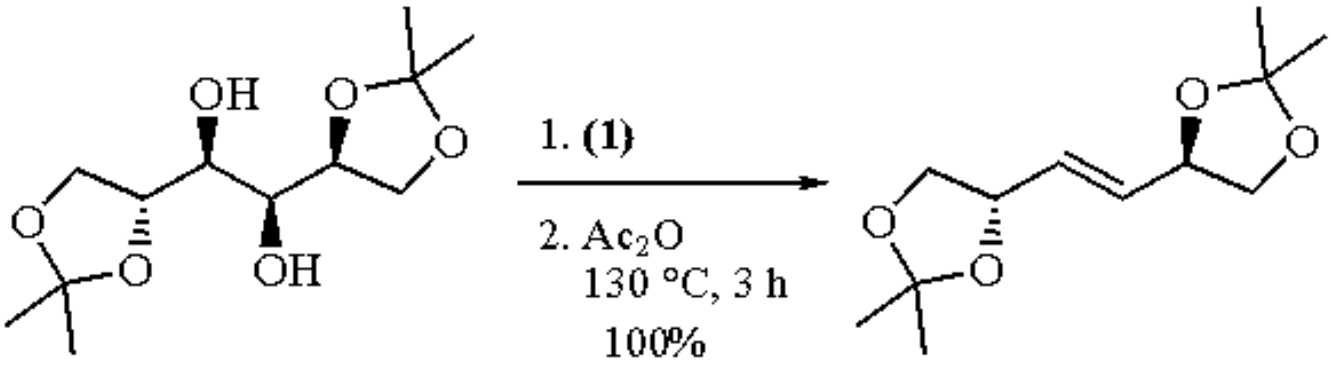

(4)

DMF dimethyl acetal is an effective methylating reagent. For example, heterocyclic thiols are transformed to *S*-methyl heterocycles in high yields (76-86%).[10] DMF dibenzyl acetal is an interesting reagent for selective protection of nucleosides. For example, uridine and guanosine are selectively blocked at the -CONH function (eq 5).[11]

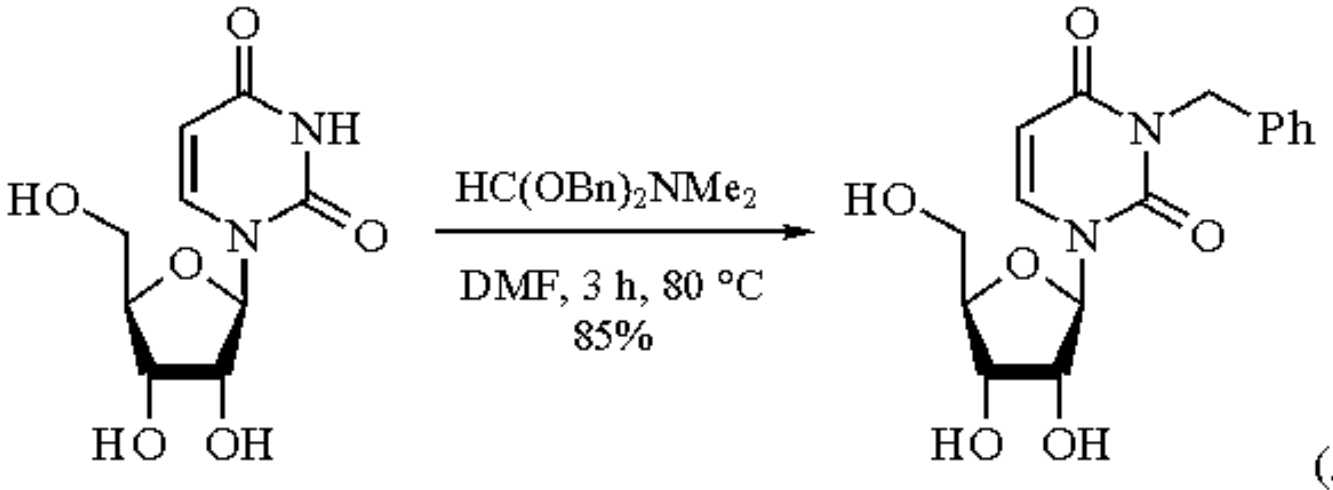

(5)

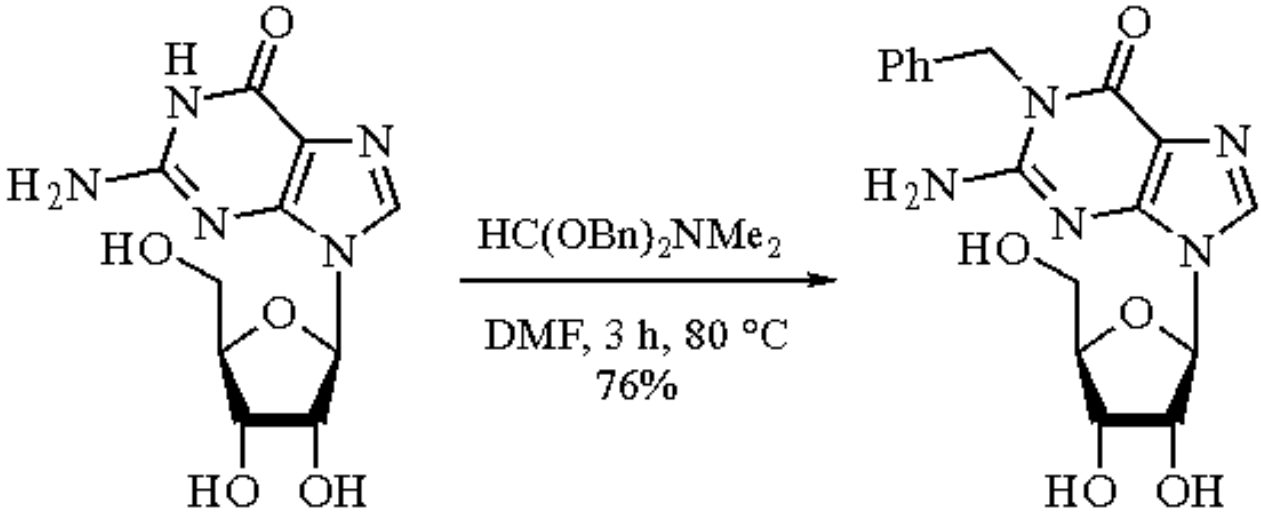

In a very simple procedure, carboxylic acids can be esterified under mild conditions with DMF dialkyl acetals. Some interesting uses are the conversion of carboxylic acids to ethyl and benzyl esters with DMF diethyl and dibenzyl acetals (yield 64-75%).[12] The dibenzyl acetal has been widely used as protecting group reagent for the carboxyl end group in peptides.[13] In several cases, DMF bis(4-dodecylbenzyl) acetal has also been used.[13,14] Some examples are given in Table 1.

Table 1 Esterification of Amino Acid and Peptide Derivatives with DMF Dibenzyl Acetal (**3**) and DMF Bis(4-dodecylbenzyl) Acetal (**5**)

RCO_2H[a]	Acetal	Reaction conditions	Yield (%)
N-DOBC-L-Val	(**3**)	C_6H_6, 80 °C, 1.5 h	97[13,14]
N-DOBC-L-Phe	(**3**)	C_6H_6, 80 °C, 48 h	90[14]
N-DOBC-L-Try	(**3**)	C_6H_6, 80 °C, 2 h	78[13,14]
N-DOBC-Gly-L-Leu	(**3**)	C_6H_6, 80 °C, 1 h	73[13,14]
N-DOBC-Gly-L-Tyr	(**3**)	CH_2Cl_2, 25 °C, 48 h	80[14]
N-Boc-Gly-L-Phe	(**3**)	CH_2Cl_2, 25 °C, 90 h	80[14]
N-DOBC-L-Phe	(**5**)	CH_2Cl_2, 20 °C, 18 h	84[13]
N-DOBC-L-Try	(**5**)	CH_2Cl_2, 20 °C, 50 h	68[13]
N-DOBC-L-Phe-L-Ala	(**5**)	CH_2Cl_2, 20 °C, 120 h	75[13]

[a] DOBC = 4-decyloxybenzyloxycarbonyl; Boc = *t*-butoxycarbonyl.

DMF dineopentyl acetal has been used as a reagent for dehydrative decarboxylation in order to avoid the possibility of competing *O*-alkylation of the carboxyl group.[15] This conversion of β-hydroxy carboxylic acids to alkenes by reaction with a DMF acetal involves an *anti* elimination, and it is thus complementary to the *syn* elimination of these hydroxy acids via the β-lactone. These reactions have been used to obtain both (*E*)- and (*Z*)-1-alkoxy-1,3-butadienes (eq 6).[15] For additional examples of alkenes obtained from β-hydroxy acids with DMF acetals, see Scheeren et al.[7]

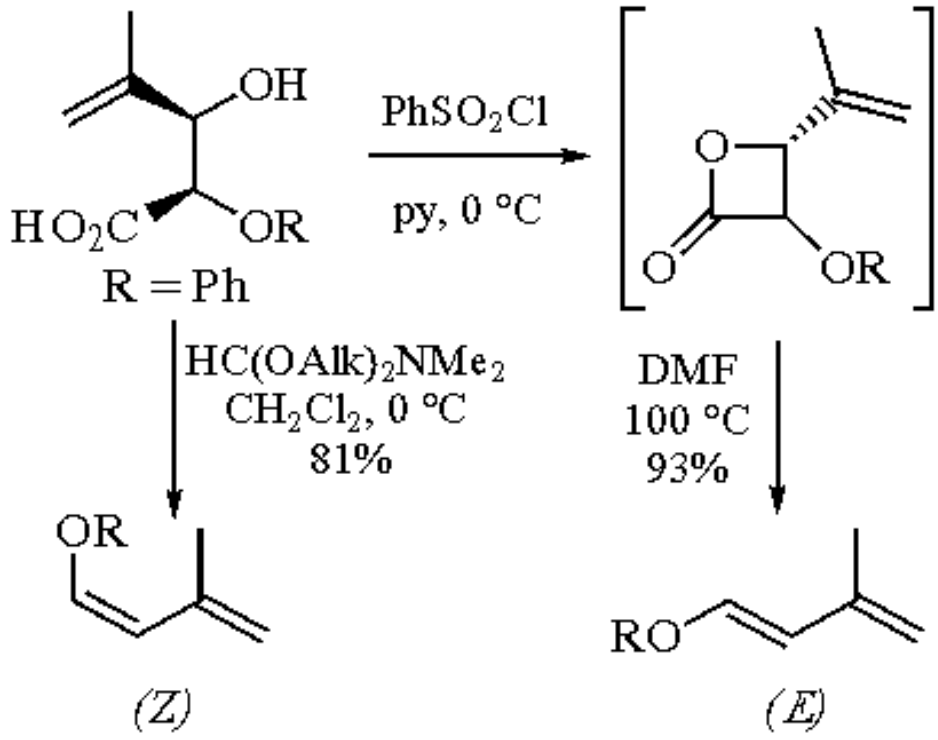

(6)

Formylation Reactions.

DMF dialkyl acetals exhibit reactivity as a formyl cation synthon by introducing a C_1 unit at many nucleophilic centers (e.g. at N, S, O, or CH). For example, DMF dimethyl acetal can be used instead of formic acid for conversion of *o*-disubstituted aromatic systems into annulated heterocycles (eq 7).[16]

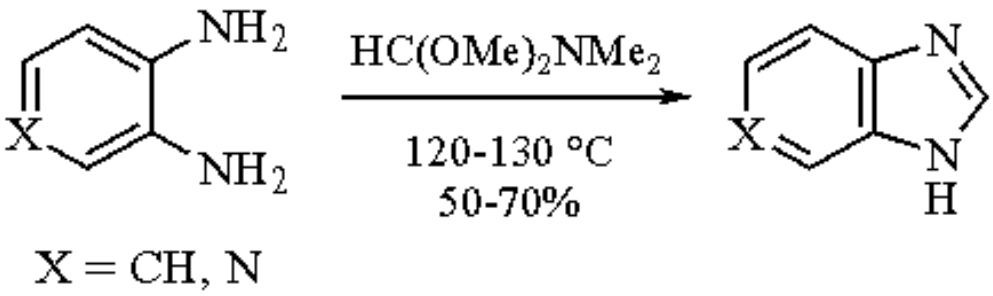

(7)

A nonacidic and regioselective route to Mannich bases from ketones and esters involves reaction with DMF acetals at a high temperature to form enamino ketones which are readily reduced by ***Lithium Aluminum Hydride*** to the Mannich bases (eq 8).[17]

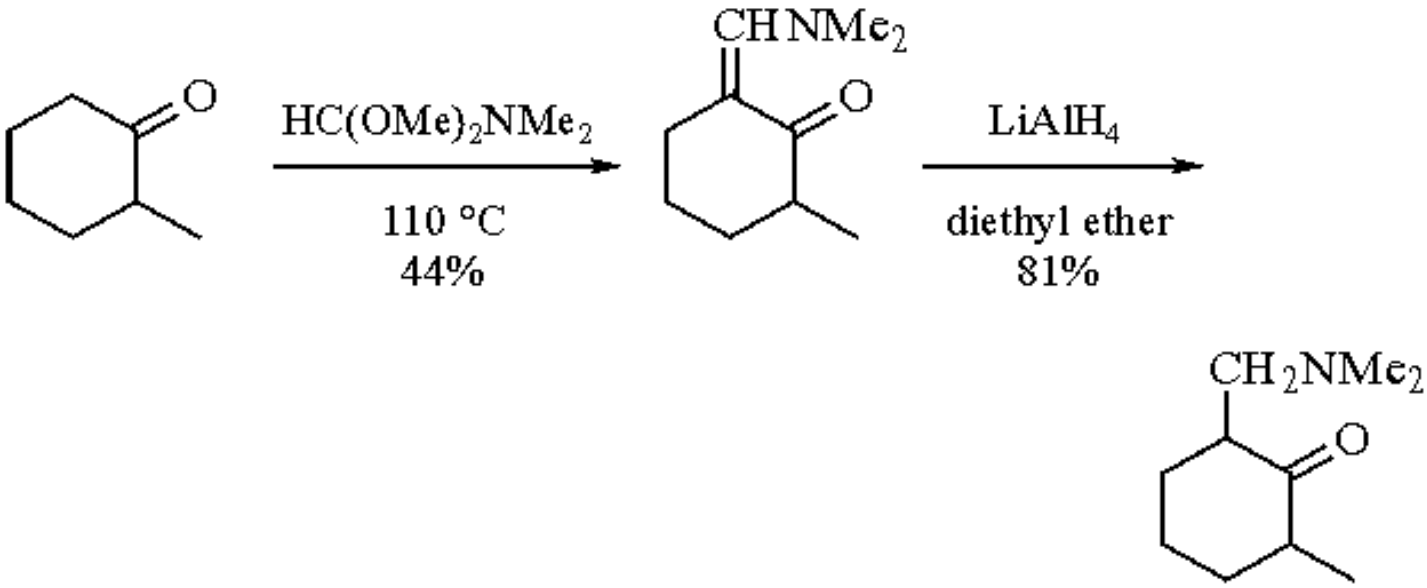

(8)

CH-acidic groups (including methyl) react with DMF acetals via carbon-carbon bond formation and subsequent elimination of the respective alkanols to form enamines (aminomethylenation). Thus 2,4,7-trimethyl-1,3-dithia-5,6-diazepine reacts with DMF dialkyl acetals to give mono- or bis-aminomethylenated products depending on the amount of reagent and the reaction conditions (eq 9).[18a] The same reagents convert the more nucleophilic 2,5-dimethyl-1,3,4-thiadiazolium salts to the monoenamines (eq 10).[18a] Similarly, 1,2-dimethyl-3-cyano-5-nitroindole condenses with DMF diethyl acetal to give the (*E*)-indol-2-yl enamine (eq 11).[18b]

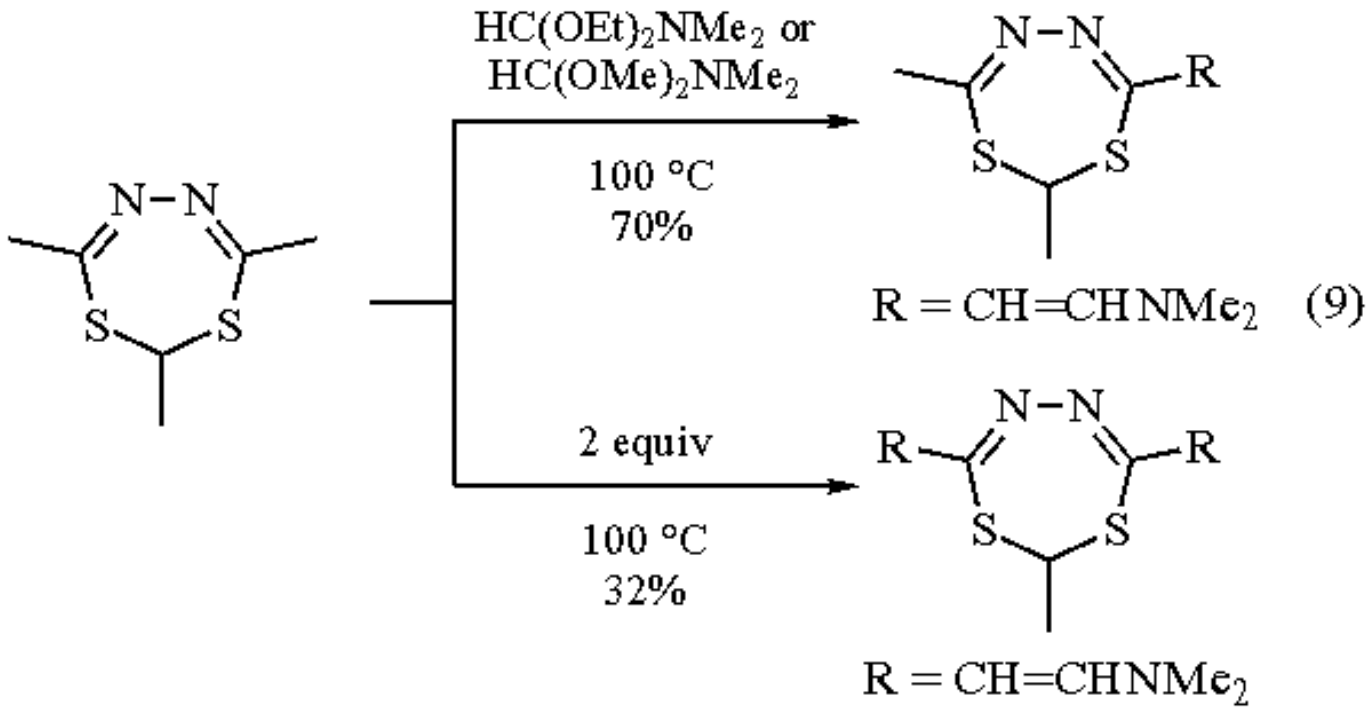

(9)

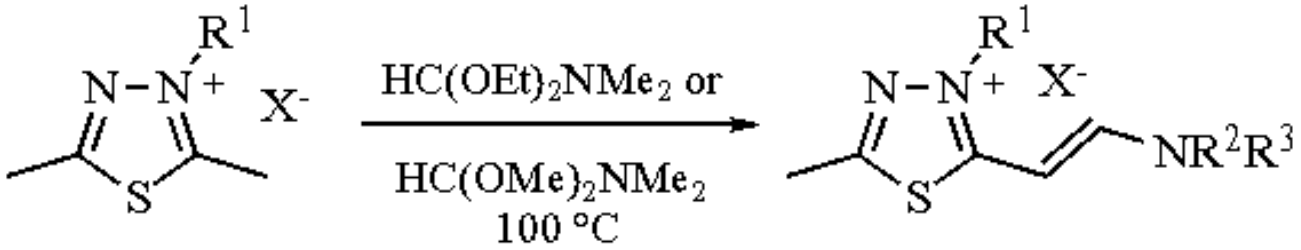

(10)

R^1	R^2	R^3	X	Yield (%)
Me	Me	Me	$MeSO_4$	93
Bz	Me	Me	Br	85
C_8H_{17}	Me	Me	I	85

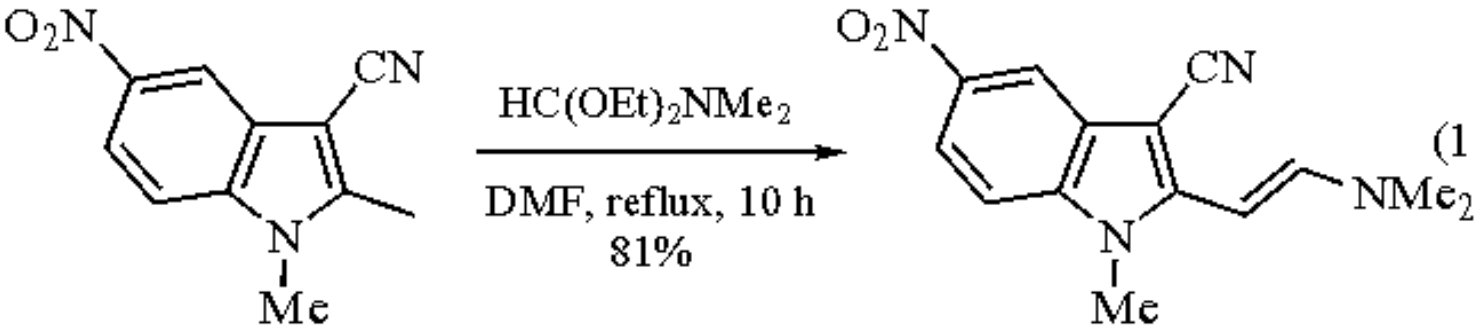

(11)

A general indole synthesis involves reaction of an *o*-nitrotoluene derivative with DMF dimethyl acetal in refluxing DMF (eq 12).[19,20] The initially formed *o*-nitroaryl-substituted (*E*)-*N*,*N*-dimethylenamine is submitted to catalytic hydrogenation to give the indole by spontaneous cyclization. According to a variation of this methodology,[20] 2-arylindoles are readily available by reaction of *o*-nitrotoluene with DMF diethyl acetal and *o*-halobenzoyl chloride. This reaction proceeds via benzoylation of the respective enamine.

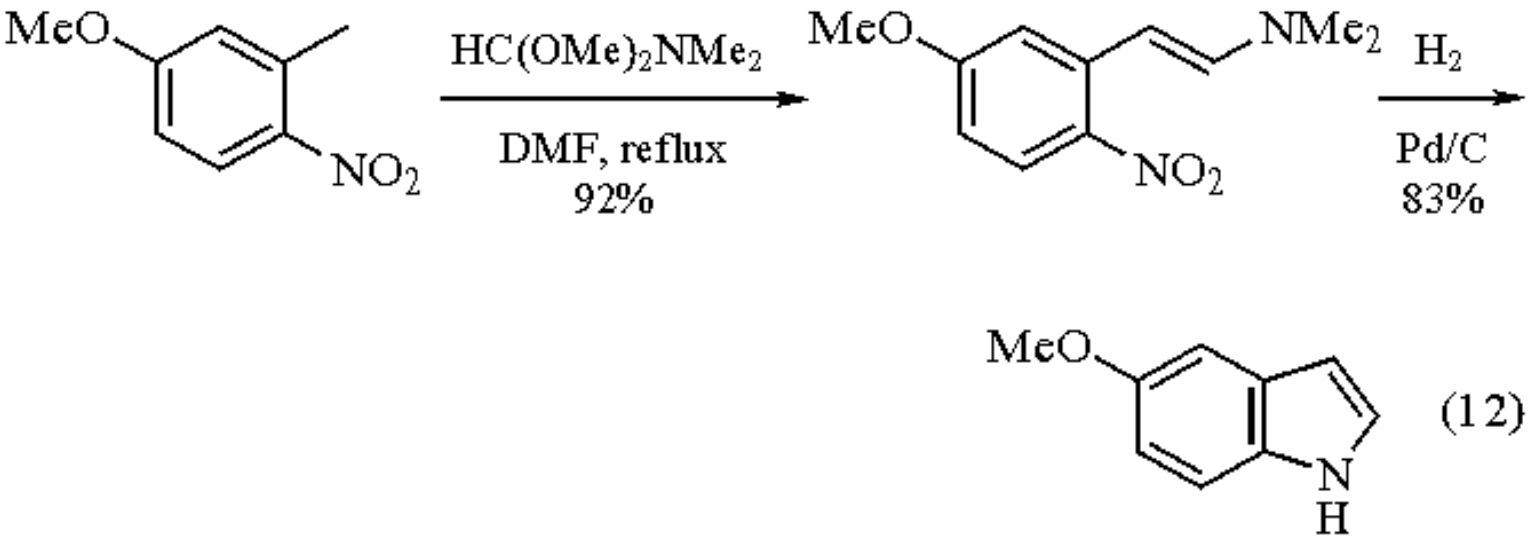

(12)

4-Dimethylamino-2-azabutadienes are readily accessible by the reaction of azomethines (imines) with DMF diethyl acetal (eq 13).[21] 1-Dimethylamino-1,3-butadienes can be synthesized in the same manner.[21] Reactions of 2-azavinamidinium

salts with DMF diethyl acetal give rise to 2-aza- and 2,4-diazapentamethinium salts (eq 14).[22]

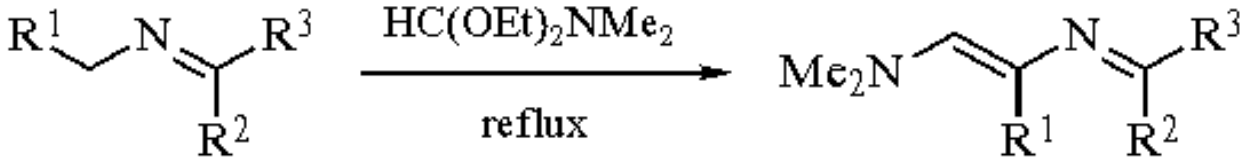

(13)

R^1	R^2	R^3	Yield (%)
CO_2Me	H	Ph	83
CO_2Me	H	*p*-ClC_6H_4	70
CO_2Me	H	*p*-Tol	82

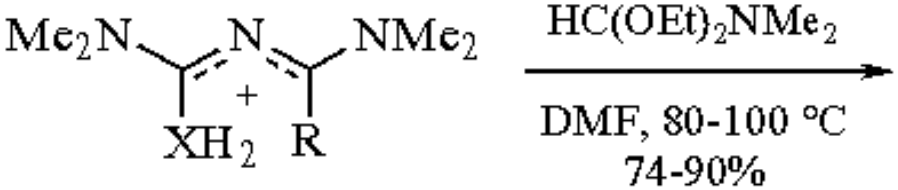

X = CH, N

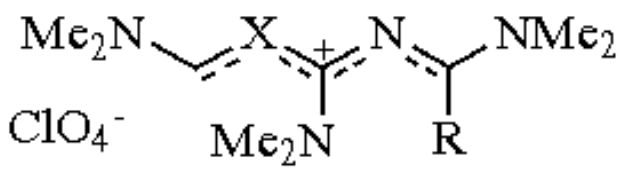

(14)

Miscellaneous Reactions.

DMF acetals catalyze rearrangement reactions of allylic alcohols to β,γ-unsaturated amides.[23] This reaction, which involves a [2,3]-sigmatropic rearrangement, occurs with complete transfer of chirality. Thus the reaction of the (*R*,*Z*)-allylic alcohol (eq 15) with DMF dimethyl acetal gives the enantiomerically pure (*R*,*E*)-β,γ-unsaturated amide as the only product. The (*S*,*E*)-isomer also rearranges mainly to the (*R*,*E*)-amide, with only a trace of the (*S*,*Z*)-isomer. It has been suggested that both rearrangements proceed via a five-membered cyclic transition state with a carbene-like function.[23]

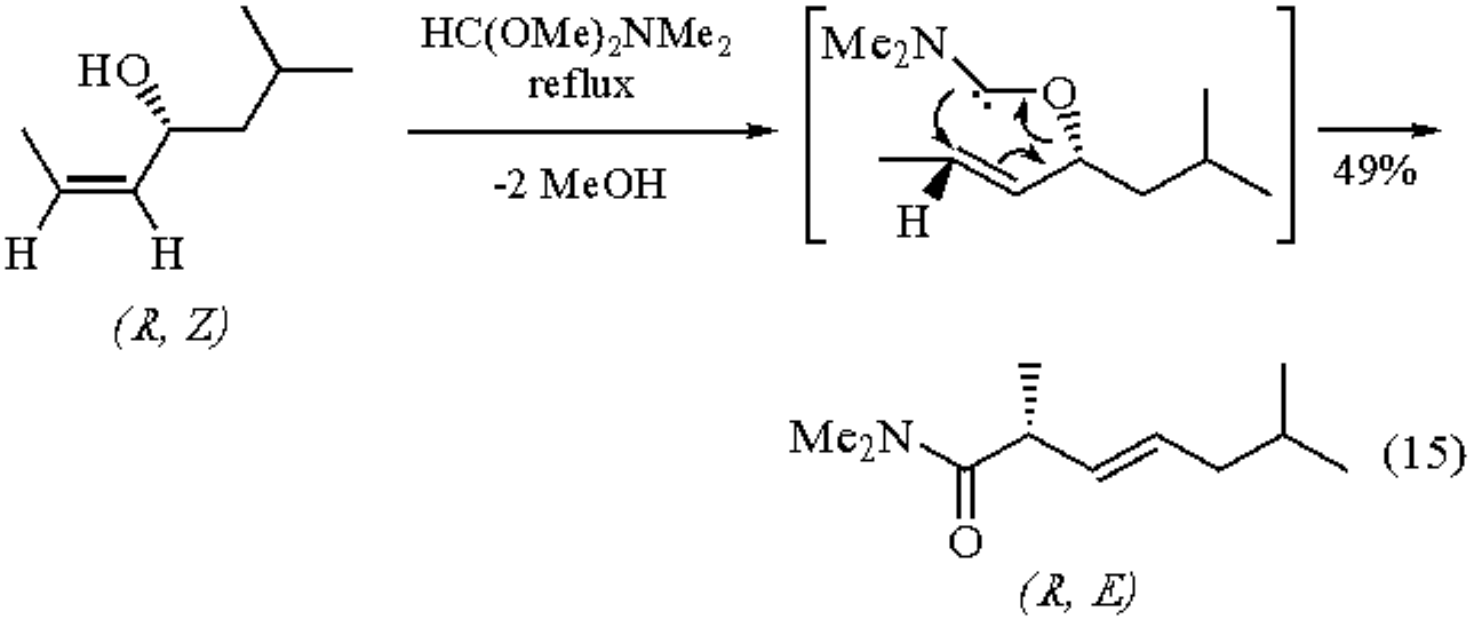

Enol acetates of oxo nucleosides are readily accessible by reaction of the nucleoside with DMF acetal and then with acetic anhydride (eq 16).[24] However, this method is limited to compounds with an oxo group in the 4´-position and with a free CO-NH group in the pyrimidine ring. This reaction is the first synthesis of oxo nucleoside enol acetates by direct enolization. Previous methods of enol formation fail with oxo nucleosides because of their instability in alkaline media.

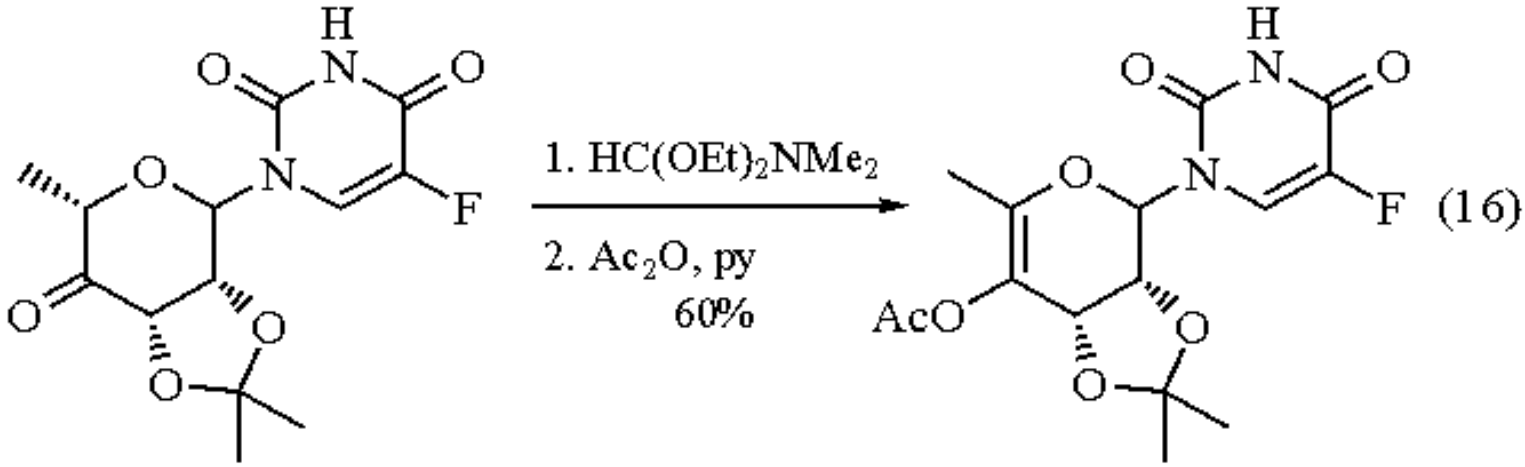

Related Reagents.

t-Butoxybis(dimethylamino)methane; ***N,N-Dimethylacetamide Dimethyl Acetal***; ***Dimethylchloromethyleneammonium Chloride***; ***N,N-Dimethylpropionamide Dimethyl Acetal***; ***Triethyl Orthoformate***; ***Tris(dimethylamino)methane***; ***Tris(formylamino)methane***.

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6,6-Dimethylfulvene[1]

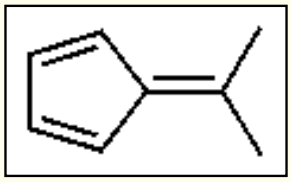

[2175-91-9] · C_8H_{10} · 6,6-Dimethylfulvene · (MW 106.18)

(hydroazulene synthesis;[2] alkene protection[3])

Physical Data: bp 40-43 °C/8 mmHg.[4]

Form Supplied in: liquid; commercially available.

Preparative Method: by reaction of cyclopentadiene with acetone under basic conditions.[4-7] The condensation has also been accomplished using pyrrolidine.[8]

Purification: distillation; chromatography on silica gel.

Handling, Storage, and Precautions: reported to undergo autoxidation to form an insoluble peroxide ($C_8H_{10}O_4$) which explodes upon heating to 130 °C. Mixing the peroxide with ether in a mortar has resulted in ignition.[9] Addition of hydroquinone is reported to suppress formation of this peroxide.[10] Sensitized photooxygenation of 6,6-dimethylfulvene at -70 °C yields a crystalline endoperoxide which explodes at -10 °C upon attempted isolation.[11]

Hydroazulene Synthesis.

Fulvenes can react as a 2π-, 4π-, or 6π-electron system in cycloaddition reactions.[1] 6,6-Dimethylfulvene serves as a 6π-addend in a cycloaddition route to hydroazulene derivatives. Treatment of 1-diethylaminobutadiene (**1**) with 3 equiv of 6,6-dimethylfulvene at rt for 2 days yields a hydroazulene product (**2**) in 65% yield (eq 1). The isolated material is the product of a [6 + 4] cycloaddition followed by elimination of diethylamine.[2,12]

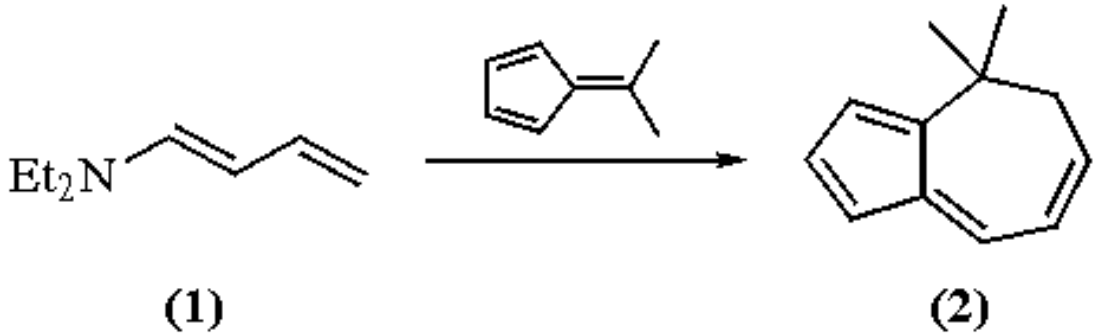

(1)

Alkene Protection.

The reaction of 2-hydroxymethyl-1,4-benzoquinone (**3**) with 6,6-dimethylfulvene results in the formation of a 1:1 Diels-Alder adduct. The [4 + 2] cycloaddition product (**4**) is isolated after subsequent alkene epoxidation. Following ketone reduction and hydroxy protection, a retro-Diels-Alder reaction is accomplished by heating in diglyme (eq 2). The conditions for this retro-cycloaddition are milder than those required for cyclopentadiene Diels-Alder adducts. Analogous reactions have been used in syntheses of DL-senepoxide and DL-crotepoxide.[3,13,14]

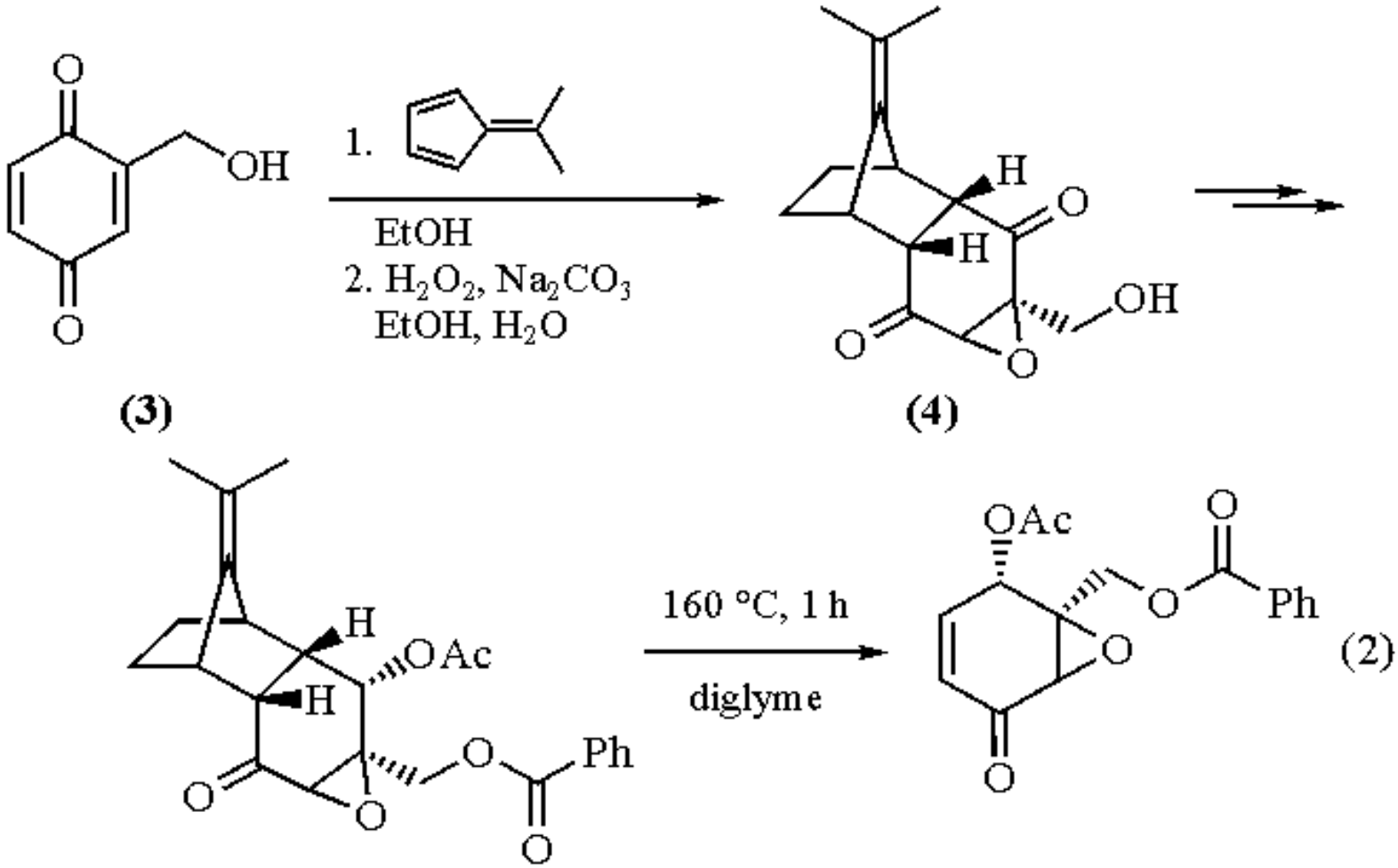

(2)

Substituted Fulvenes.

Reaction of the lithium anion of 6,6-dimethylfulvene with aldehydes at low temperature results in functionalization at

the 7-position (eq 3).[15] Regioselective allylation at the 7-position may be accomplished in the presence of a palladium(0) catalyst (eq 4).[16]

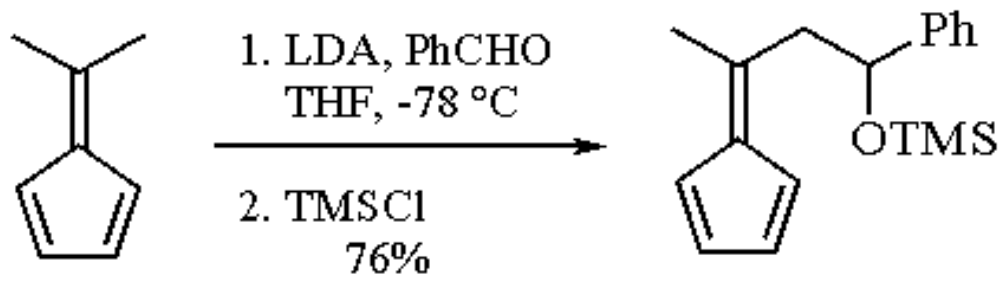

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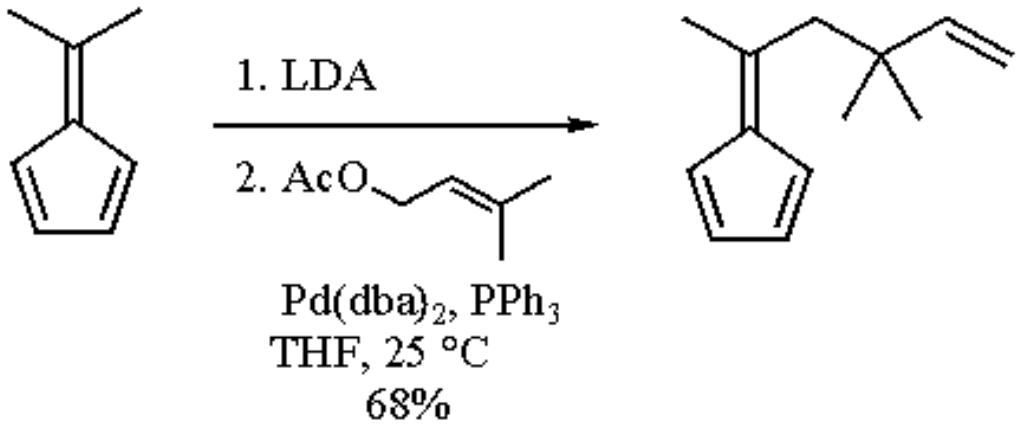

(4)

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Dimethyl Fumarate

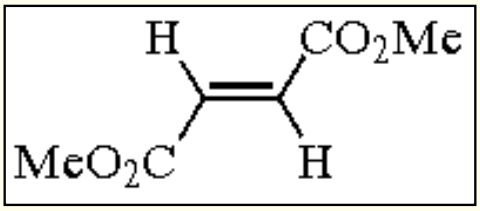

[624-49-7] · $C_6H_8O_4$ · Dimethyl Fumarate · (MW 144.14)

(reactive dienophile; dipolarophile; radical acceptor)

Physical Data: mp 103-104 °C; bp 192-193 °C; *d* 1.37 g cm^{-3}.

Solubility: sol acetone, chloroform, methanol.

Form Supplied in: white solid.

Purification: recrystallized from benzene.

Handling, Storage, and Precautions: mutagen.

Cycloadditions.

Dimethyl fumarate has frequently been employed as a dienophile in Diels-Alder reactions. Dialkyl fumarates undergo Diels-Alder cycloadditions with aromatic dienes such as anthracene and dihydroquinone (eq 1).[1] Dienophiles which are more reactive than dialkyl fumarates include ***Tetracyanoethylene***, *N*-methylmaleimide, fumaronitrile, and maleonitrile. The [4 + 2] cycloaddition reaction of dimethyl fumarate with a diene is a stereospecific reaction and has been used to determine the geometry and stereoselectivity of Diels-Alder reactions of substituted *o*-quinodimethanes (eqs 2 and 3).[2] High diastereoselectivity has been observed in the organoaluminum catalyzed Diels-Alder reaction of (-)-dimenthyl fumarate with a variety of dienes (eq 4).[3] A diastereoselective Diels-Alder addition of the bis-lacate fumarate to an α-hydroxyorthoquinodimethane has also been reported.[4]

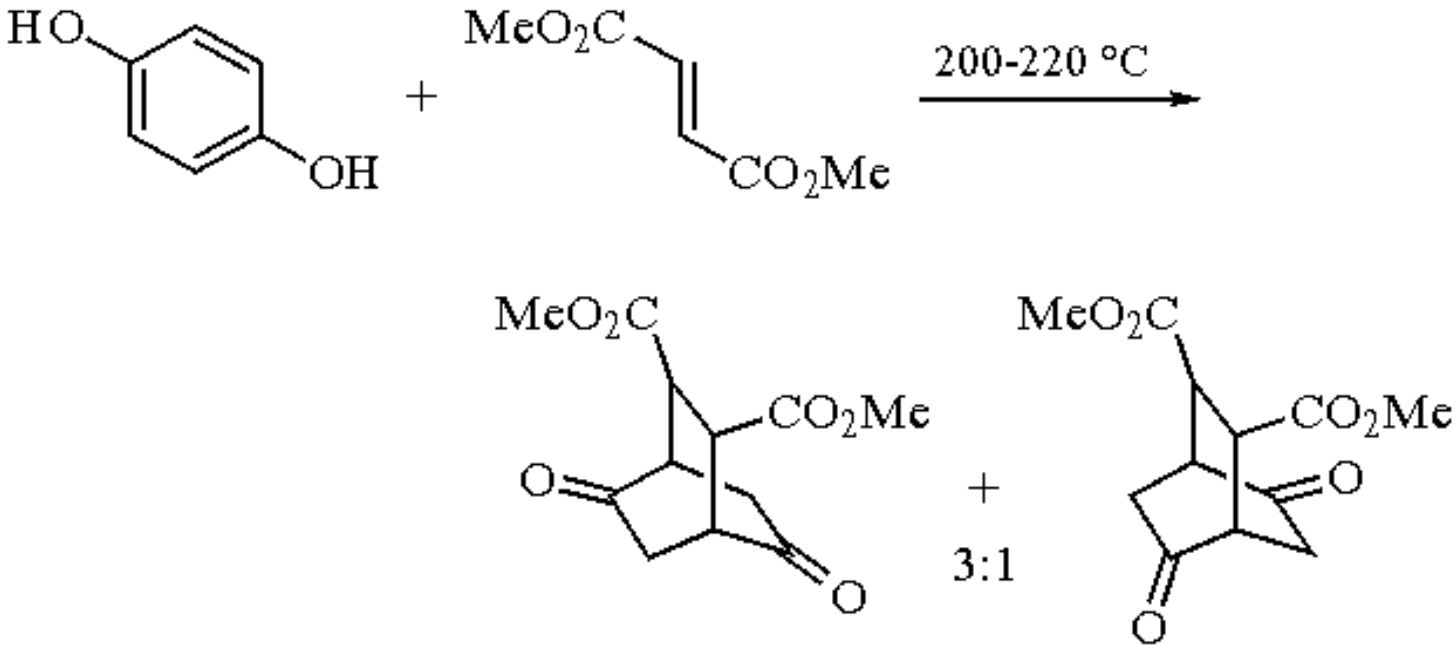
HO
OH
MeO2C
CO2Me
200-220 °C
MeO2C
CO2Me
O
O
3:1
MeO2C
CO2Me
O
O

(1)

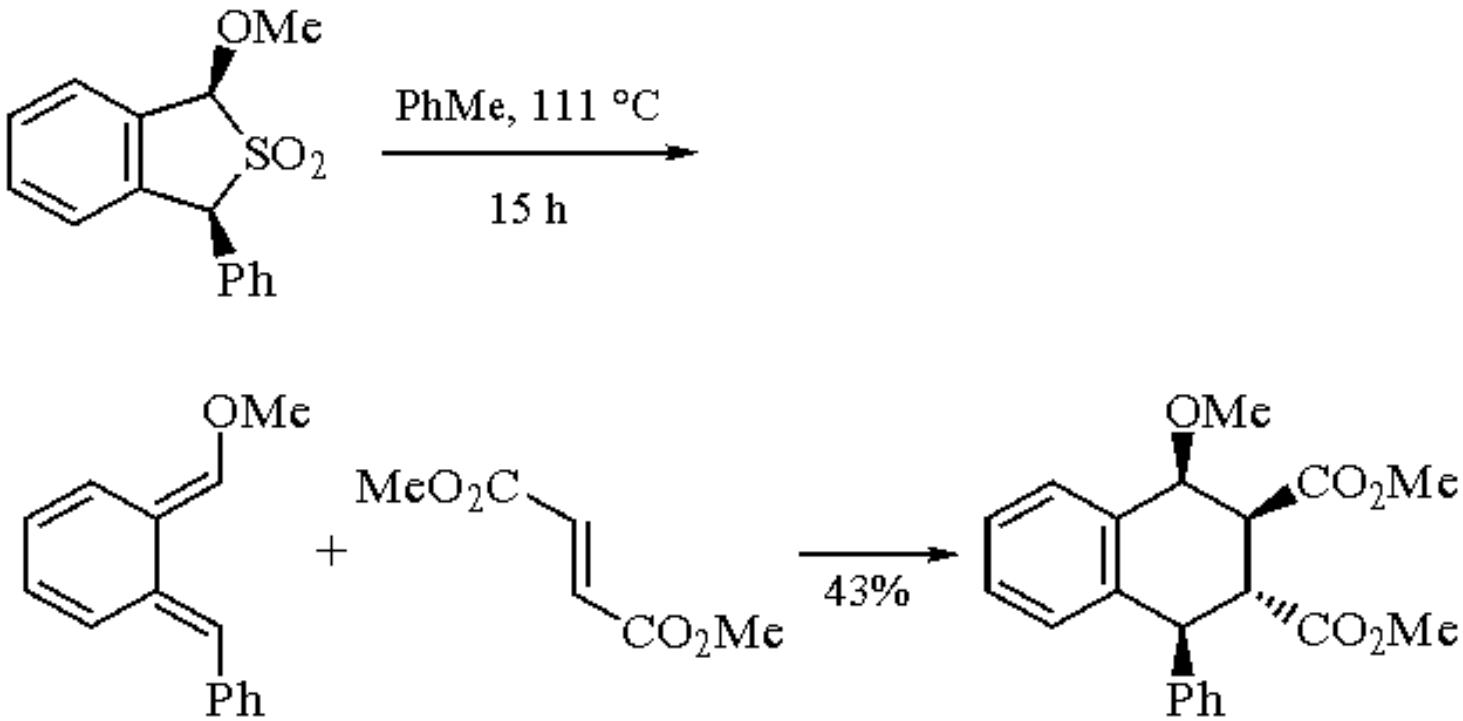
OMe
SO2
Ph
PhMe, 111 °C
15 h
OMe
Ph
MeO2C
CO2Me
43%
OMe
CO2Me
CO2Me
Ph

(2)

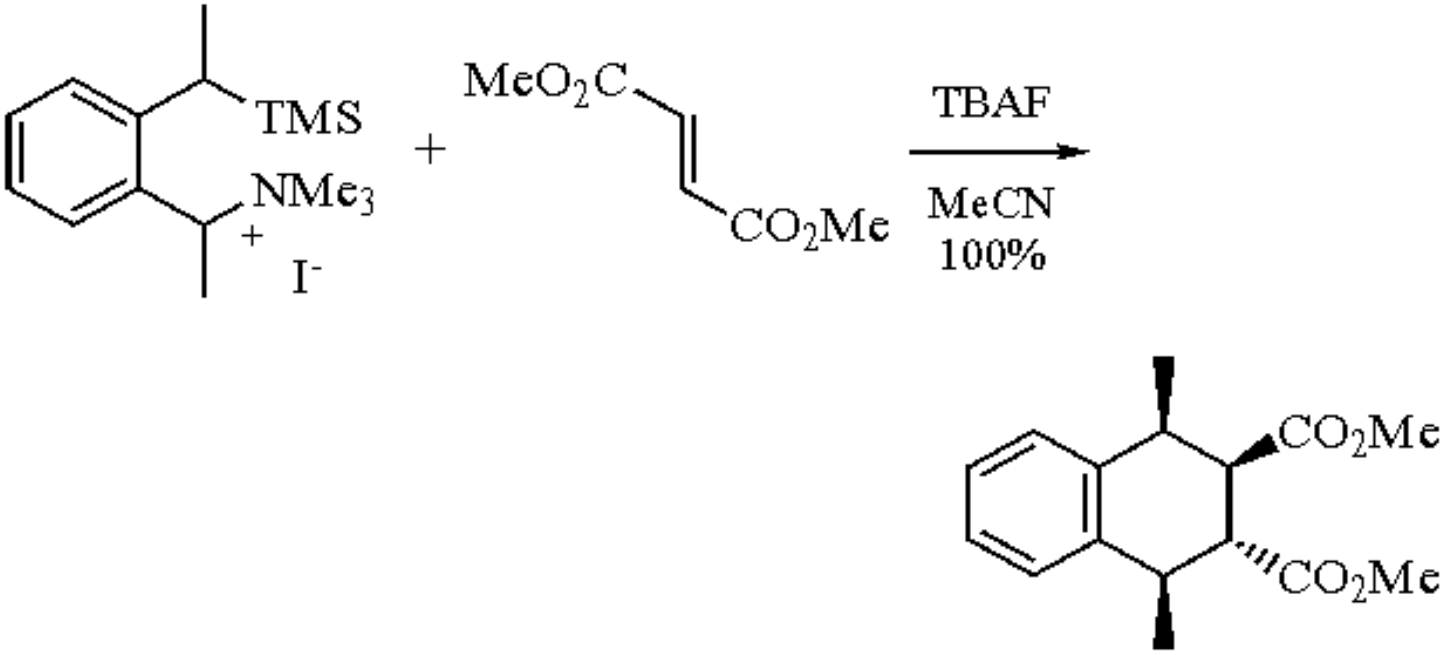

(3)

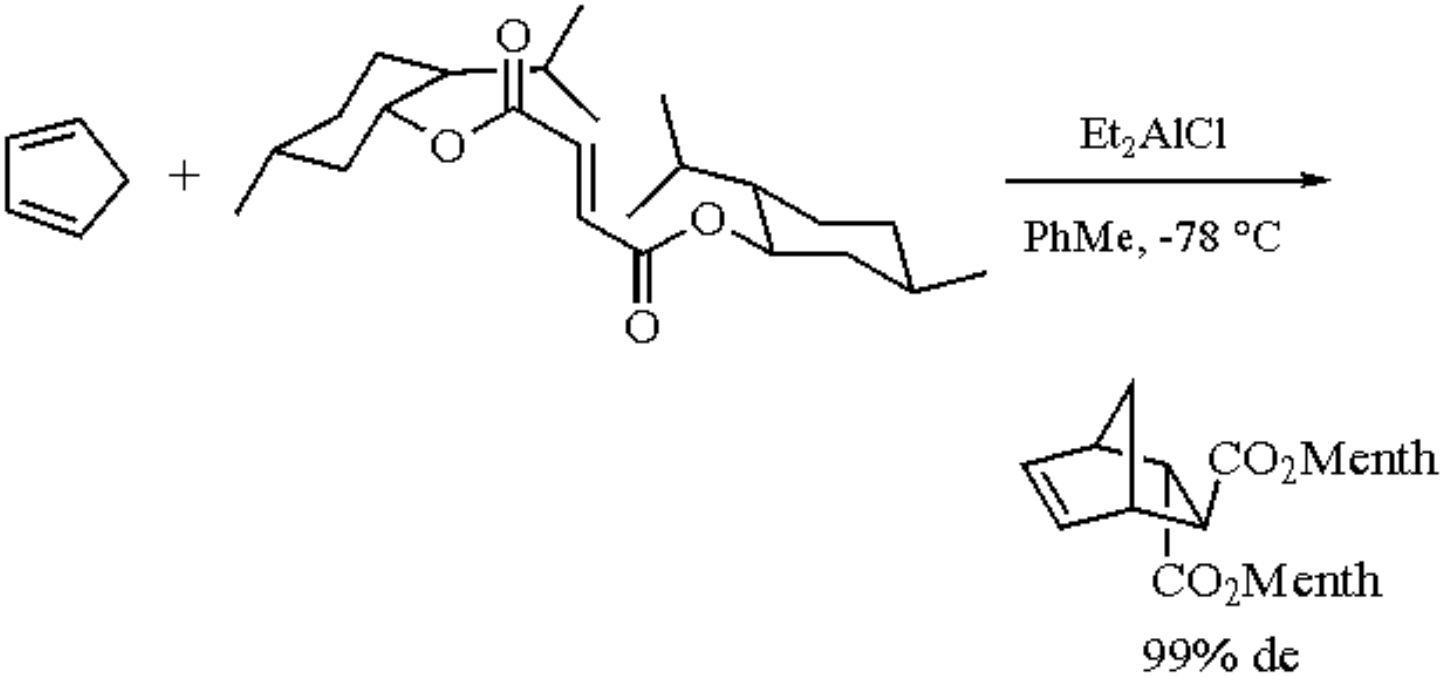

(4)

A range of 1,3-dipoles have been trapped by dimethyl and related dialkyl fumarates. Dimethyl fumarate and maleate have been used in experiments which examine the concertedness of cycloadditions through examination of the stereoselectivity of the cycloaddition process. Dipoles which have been trapped with dimethyl fumarate include nitrile (eq 5), azomethine,[5] carbonyl, and thiocarbonyl ylides.[6,7] Also nitrile oxides, nitrones,[8] and nitronates have been trapped by dimethyl fumarate.

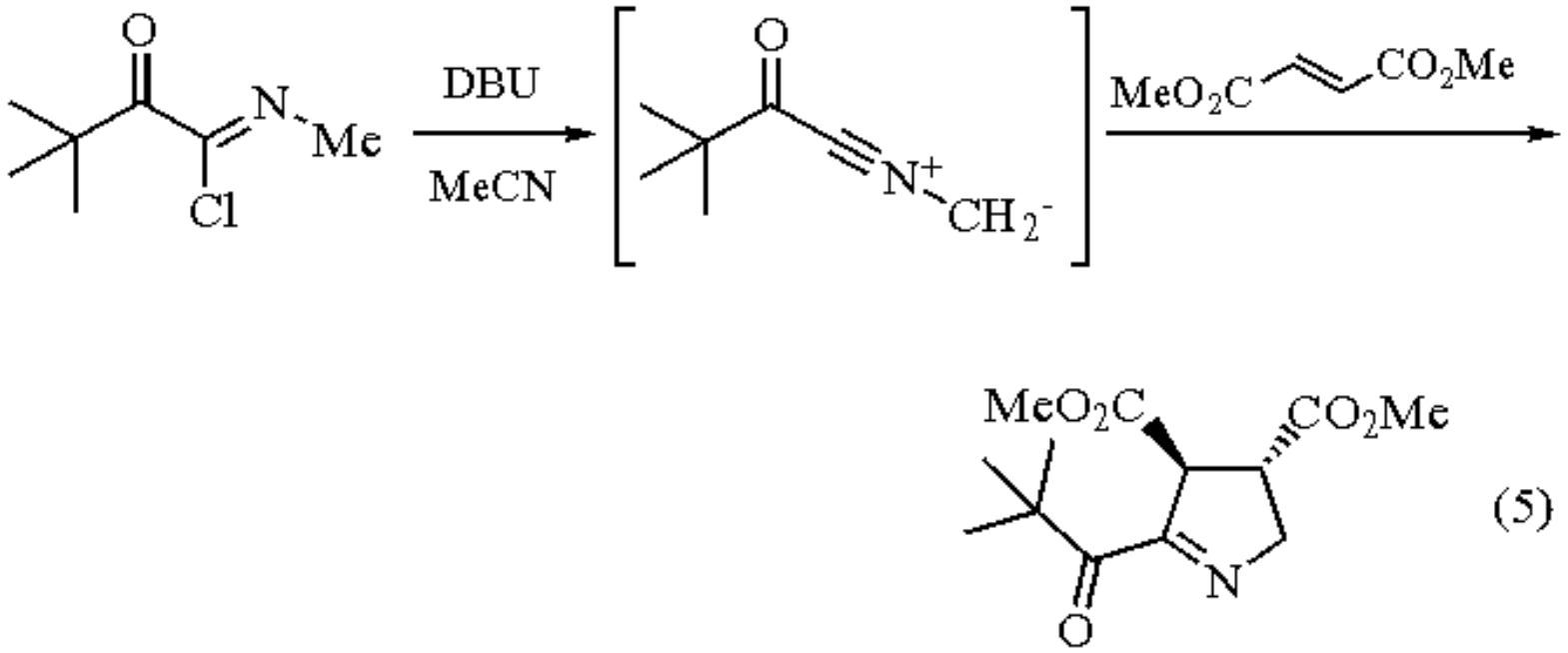

Electron rich alkenes such as ketene dithioacetals and enamines react thermally with dimethyl fumarate to yield substituted cyclobutanes.[9] Asymmetric [2 + 2] cycloadditions have been developed which employ oxazolidone derivatives in combination with chiral titanium catalyst generated in situ from dichlorodiisopropoxytitanium and a tartrate-derived chiral diol (eq 6).[10] Dimethyl fumarate traps carbenoids generated photochemically and thermally (eq 7).[11,12]

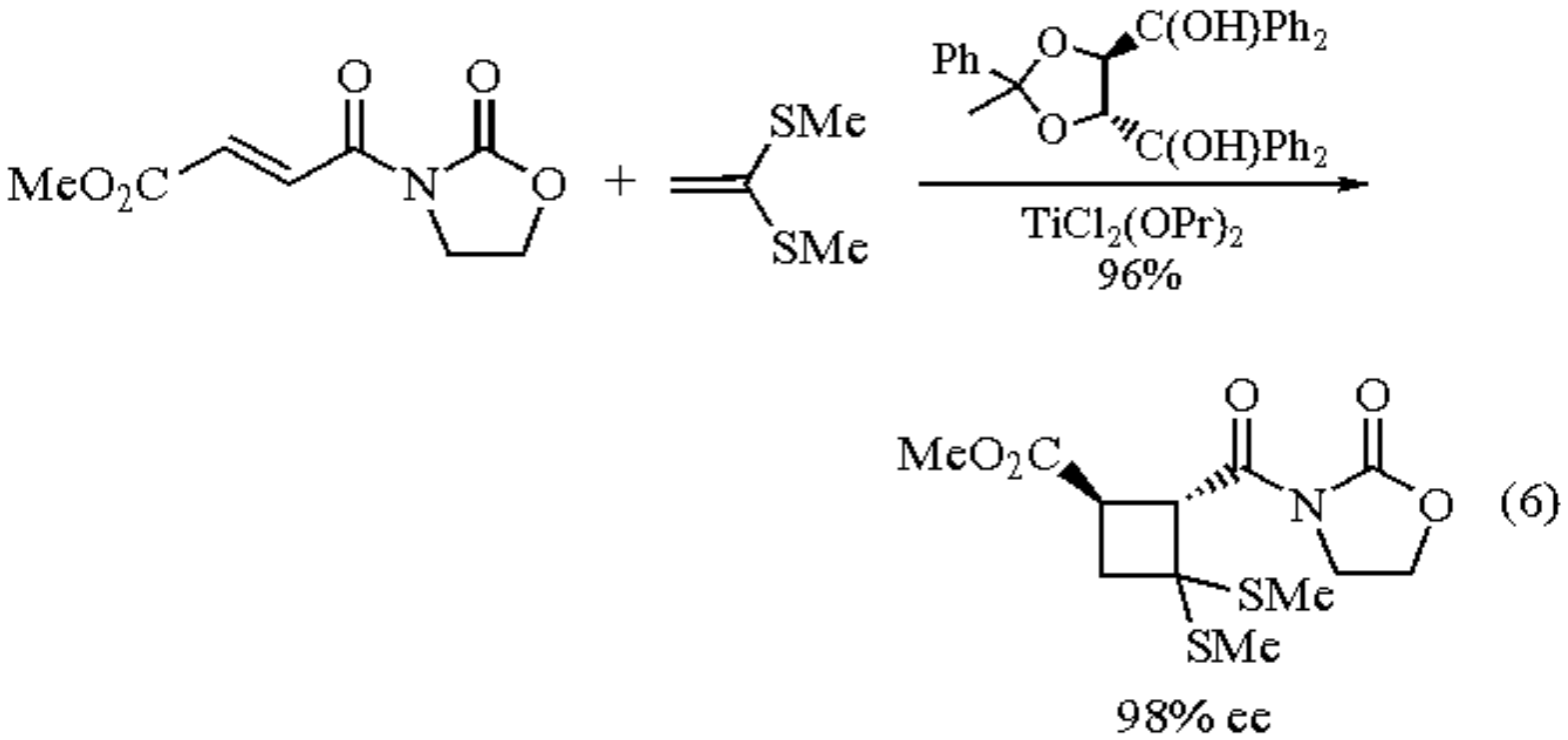

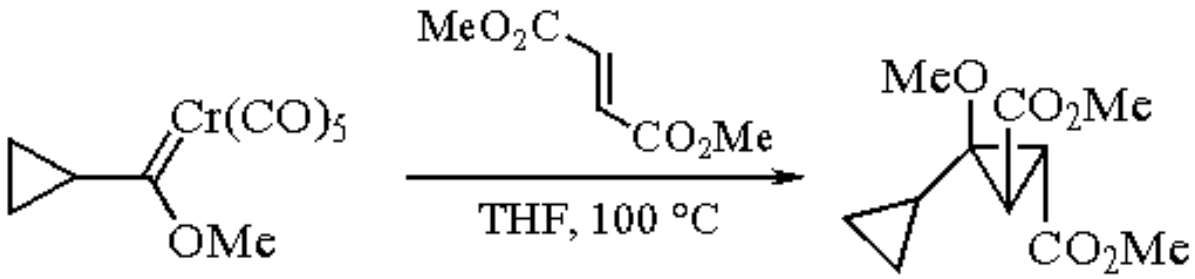

(7)

Miscellaneous.

Dimethyl fumarate serves as an excellent radical trap (eq 8).[13] Asymmetric dihydroxylation of dimethyl fumarate provides dimethyl tartrate of good optical purity.[14]

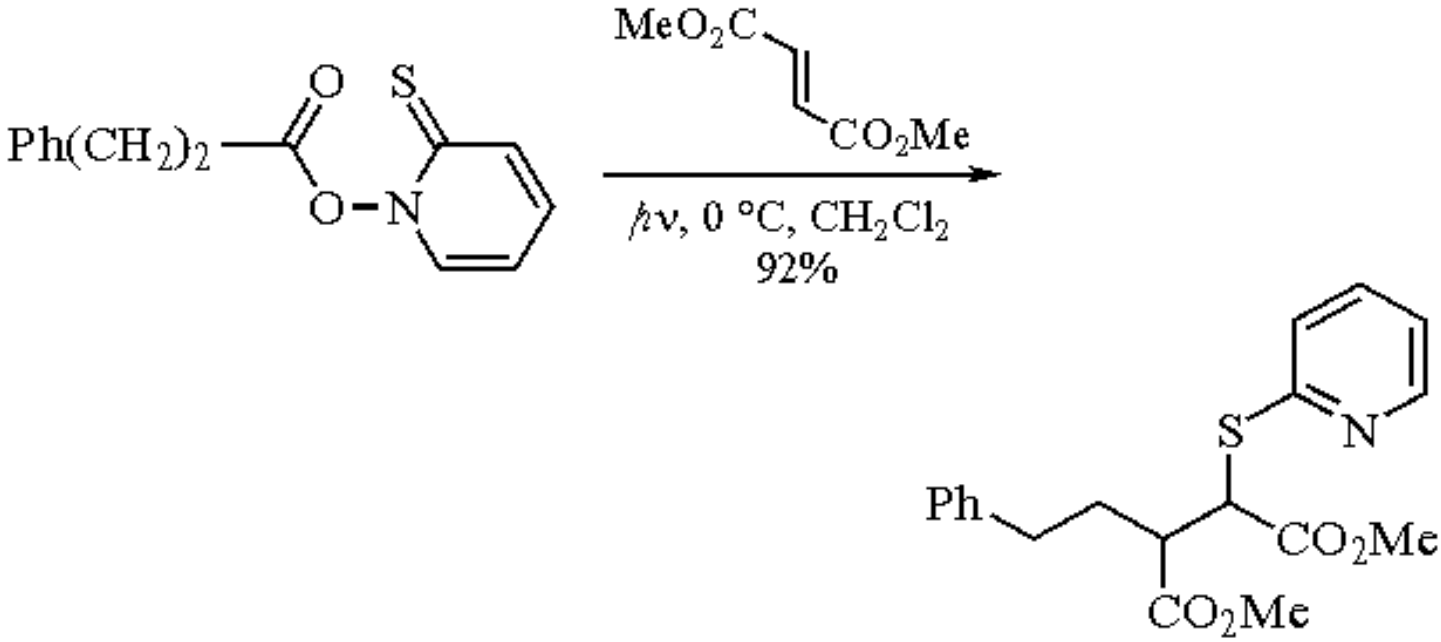

(8)

Related Reagents.

Dimethyl Maleate; ***Maleic Anhydride***; ***N-Phenylmaleimide***; ***Tetracyanoethylene***.

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Dimethyliodonium Hexafluoroantimonate

$Me_2X^+ Y^-$

($Me_2I^+ SbF_6^-$)

[24400-13-3] · $C_2H_6F_6ISb$ · Dimethyliodonium Hexafluoroantimonate · (MW 392.73) ($Me_2Br^+ Sb_2F_{11}^-$)

[24400-14-4] · $C_2H_6BrF_{11}Sb_2$ · Dimethylbromonium Undecafluorodiantimonate · (MW 562.48) ($Me_2Cl^+ Sb_2F_{11}^-$)

[24400-15-5] · $C_2H_6ClF_{11}Sb_2$ · Dimethylchloronium Undecafluorodiantimonate · (MW 518.03) ($MeF.SbF_5$)

[24400-12-2; 35873-33-7] · CH_3F_6Sb · Fluoromethane-Antimony Pentafluoride · (MW 250.79) (Me_2F^+)

[64710-12-9] · C_2H_6F · Dimethyliodonium Hexafluoroantimonate · (MW 49.08) ($MeOSO^+$)

[59970-36-4] · CH_3O_2S · Dimethyliodonium Hexafluoroantimonate · (MW 79.11) ($MeOSO^+ SbF_6^-$)

[85611-60-5] · $CH_3F_6O_2SSb$ · Methoxysulfoxonium Hexafluoroantimonate · (MW 314.86)

(powerful methylating agents[1])

Physical Data: $Me_2I^+ SbF_6^-$ dec. 153-157 °C. $Me_2Br^+ Sb_2F_{11}^-$ dec. 74-79 °C. $Me_2Cl^+ Sb_2F_{11}^-$ mp 108-113 °C, dec. 116 °C.[2] IR and Raman spectra indicate that R_2X^+ have C_{2v} geometry and are sp^3 hybridized.[1] Most reactions of these species have been monitored by NMR.[1] In ^1H and ^{13}C NMR spectra, the shielding order is as expected, F < Cl < Br < I. δ_H: d, 5.68 ($MeF.SbF_5/SO_2F_2$); s, 5.63 ($MeOSOClF^+/SO_2ClF$); s, 5.50 ($MeOSO^+/SO_2$); s, 4.20

(Me_2Cl^+/SO_2); s, 4.13 (Me_2Br^+/SO_2); s, 3.60 (Me_2I^+/SO_2). δ_C: 96.8 ($MeF.SbF_5/SO_2F_2$); 81.9 ($MeOSOClF^+/SO_2ClF$); 74.9 ($MeOSO^+/SO_2$); 48.9 (Me_2Cl^+/SO_2); 37.6 (Me_2Br^+/SO_2); 9.5 (Me_2I^+/SO_2).

Solubility: sol SO_2, SO_2ClF, etc. React with protic and heteroorganic solvents.

Preparative Methods: $MeF.SbF_5$ and related reagents: the Me_2F^+ ion does not exist in solution, and the $MeF.SbF_5$ complex is only obtained in SO_2F_2 and CH_2F_2 solution.[3] When MeF and SbF_5 are mixed in other solvents, solvent-derived species are obtained. For example, addition of MeF in SO_2 to SbF_5 in SO_2 at -78 °C gives the $MeOSO^+$ ion.[3] The reaction of MeOSOCl with $SOCl_2.SbCl_5$ at -78 °C also generates the $MeOSO^+$ ion and has the advantage of using the cheaper and safer $SbCl_5$ and MeOSOCl (conveniently prepared from $MeOH/SOCl_2$).[4] Solutions of $MeF.SbF_5$, etc. are not stable: on warming to 0 °C $MeOSO^+$ SbF_6^- ($MeF.SbF_5/SO_2$) forms $FS(OMe)_2^+$ slowly,[3] whereas $MeOSO^+$ $SbCl_6^-$ decomposes to MeCl and SO_2.[4]

Me_2X^+ salts (X = Cl, Br, I): there are a large number of methods of preparing the Me_2X^+ ions, usually as perfluoro- or halofluoroantimonate salts. The four principal methods involve the addition of the appropriate MeX to an SO_2 solution of (i) SbF_5, (ii) $HSbF_6$, (iii) $AgSbF_6$, or (iv) $MeF.SbF_5$ at -78 to -68 °C.[1] Method (i) is generally preferred, since this leads to fewer impurities and side products. New methods to generate Me_2X^+ have been reported recently.[5,6]

Handling, Storage, and Precautions: these reagents should all be regarded as extremely hazardous, but no data on toxicity have been reported. Me_2X^+ (X = Cl, Br, I) can be isolated as crystalline, highly deliquescent salts,[1,2] and are stable at rt under dry N_2. The $MeF.SbF_5$ complex can only be obtained in SO_2F_2 and CH_2F_2 solution,[3] but $MeOSO^+$ salts can be isolated by evaporation of SO_2 solutions.[3] Use in a fume hood.

Reactivity.

The general reactivity order is $MeF.SbF_5$ >> Me_2Cl^+ > Me_2Br^+ > Me_2I^+; $MeF.SbF_5$ is the strongest methylating agent known. The ability of $MeF.SbF_5$ solutions to *O*-methylate the solvent (SO_2, SO_2F_2, SO_2ClF) has already been mentioned. At the other extreme, Me_2I^+ will not effect the same methylations as the other halonium ions below 0 °C, and often reacts less quickly than ***Methyl Trifluoromethanesulfonate*** (MeOTf) towards n-donors (heteroatoms).

σ-Donors (i.e. *C*-alkylation).

Neat $MeF.SbF_5$ rapidly self-condenses at rt to *t*-Bu^+ with concomitant formation of HF.[7] $MeF.SbF_5.SO_2ClF$ reacts with alkanes slowly at -78 °C.[8] The major product is always CH_4 via hydrogen transfer. Propane and higher straight-chained hydrocarbons also form straight and branched higher homologs. The reactions are thought to proceed via 2-electron-3-center bound carbenium ions and hydrogen abstraction.

π-Donors (i.e. *C*-alkylation): Arenes.[9]

Friedel-Crafts-type methylation of benzene and toluene has been studied in SO_2ClF at low temperatures. $MeF.SbF_5$ reacts at -78 °C in <1 min, forming benzenium ions.[10] Me_2X^+ (X = Cl, Br) reacts quickly at -50 °C, whereas Me_2I^+ requires temperatures above 0 °C.[2] Quenching yields the methylation product. The *o*:*m*:*p* ratios for methylation of toluene with all the ions are similar to those obtained from $MeOSO_2F/SbF_5$ or conventional Friedel-Crafts reagents at higher temperatures.[2]

π-Donors: Alkenes.

Methylation of alkenes in SO_2 with any of these reagents leads initially to carbenium ion formation. The reaction of $MeF.SbF_5.SO_2$ with highly substituted alkenes gives stable carbenium ions, whereas mono- or 1,2-dialkyl-substituted alkenes react further, resulting in polymerization and fluorination.[10] In contrast, Me_2X^+ ions (e.g. Me_2Br^+)[2,11] cause rapid polymerization under the reaction conditions studied.

n-Donors.

Reaction of Me_2X^+ (X = Cl, Br)[2,12] and $MeF.SbF_5$[10] with a range of heteroorganic compounds in SO_2 or SO_2ClF at -78 °C is rapid and quantitative. Methylation with Me_2I^+ usually requires temperatures >0 °C. In addition to methylations effected by MeOTf (often at higher temperatures), Me_2X^+ species also methylate RNO_2, R_2SO_2, RCO_2H, $R^1CO_2R^2$, and enolizable aldehydes and ketones. The greater reactivity of $MeF.SbF_5$ is exemplified by the formation of $MeOSO_2F$ from $MeF.SbF_5$ and SO_3.[10] $MeF.SbF_5$ has also been reported to effect *Cl*-, *Br*-, *I*-, *N*-, *O*-, *P*-, and *S*-methylations with a large variety of heteroorganic and inorganic substrates.[10,13]

Other Uses.

Dimethylhalonium ions (X = Br, I) have been used as lactone polymerization catalysts.[14] 1-Alkyl-2-methyleneaziridines have been successfully *N*-methylated with Me_2Cl^+ at -78 °C, whereas reaction with $MeOSO_2F$ in $CHCl_3$ (-60 °C) results in polymerization.[15] $MeF.SbF_5/SO_2$ (i.e. $MeOSO^+$) has been reported to undergo the ene reaction with vinyl halides at -65 °C to yield β,γ-unsaturated methyl sulfinates after the addition of MeOH (70-80%).[16] The reaction is reversed by the addition of base.

Related Reagents.

Dimethoxycarbenium Tetrafluoroborate; ***O-Methyldibenzofuranium Tetrafluoroborate***; ***Methyl Trifluoromethanesulfonate***; ***Triethyloxonium Tetrafluoroborate***.

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N,N-Dimethylhydrazine

H_2NNMe_2

[57-14-7] · $C_2H_8N_2$ · *N,N*-Dimethylhydrazine · (MW 60.1)

(useful reagent for the preparation of *N,N*-dimethylhydrazones;[1-8] metalated derivatives are useful for stereoselective alkylations;[9-11] useful nucleophile for electrophiles other than aldehydes and ketones;[13-15] useful reagent for the formation of functionalized Wittig reagents[16])

Physical Data: bp 63 °C; *d* 0.786 g cm^{-3}.

Solubility: sol polar aprotic and nonpolar solvents.

Form Supplied in: colorless liquid, widely available.

Handling, Storage, and Precautions: highly toxic and is a cancer suspect agent. A well-ventilated fume hood should be used when handling this compound. Adequate skin and eye protection should also be worn.

Formation and Reactions of *N,N*-Dimethylhydrazones.

Hydrazones are easily prepared from carbonyl compounds and are susceptible to nucleophilic attack at the hydrazone carbon. Several recent examples are illustrative of this approach. For instance, treatment of hydrocinnamaldehyde with *N,N*-dimethylhydrazine afforded (*E*)-3-phenylpropanal *N,N*-dimethylhydrazone in 95% yield as a single isomer (eq 1).[1] Subsequent addition of a variety of alkylcerium, alkyllithium, and Grignard reagents afforded the nucleophilic addition products. Treatment of (α*R*,2*S*,3*S*,5*S*)-1-(1-oxopropyl)-*N*-methoxy-*N*,3,5-trimethyl-α-ethyltetrahydro-2-furanacetamide with *N,N*-dimethylhydrazine afforded the hydrazone (α*R*,2*S*,3*S*,5*S*)-5-[1-(*N,N*-dimethylhydrazono)propyl]-*N*-methoxy-*N*,3,5-trimethyl-α-ethyltetrahydro-2-furanacetamide in 92% yield (eq 2), which was then used in the construction of the C(10)-C(23) synthon for the natural product ferensimycin B.[2] Finally, reaction of ***Glyoxal*** with *N,N*-dimethylhydrazine afforded the monohydrazone, which was then treated with chiral 1,2-diamines to afford the chiral aminals (eq 3).[3] Addition of organolithium reagents to these aminals afforded the nucleophilic addition products with high diastereomeric purity.

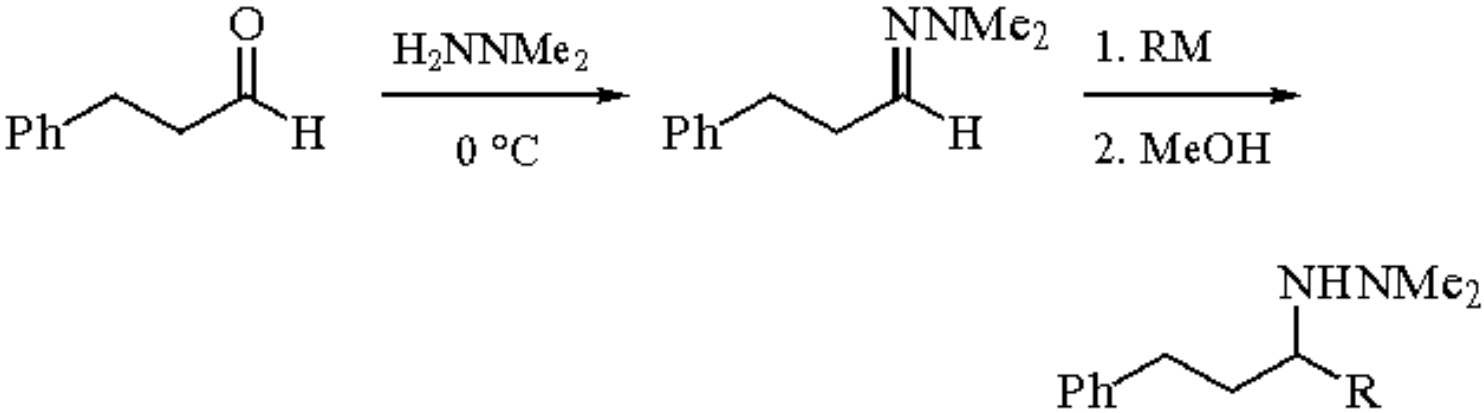

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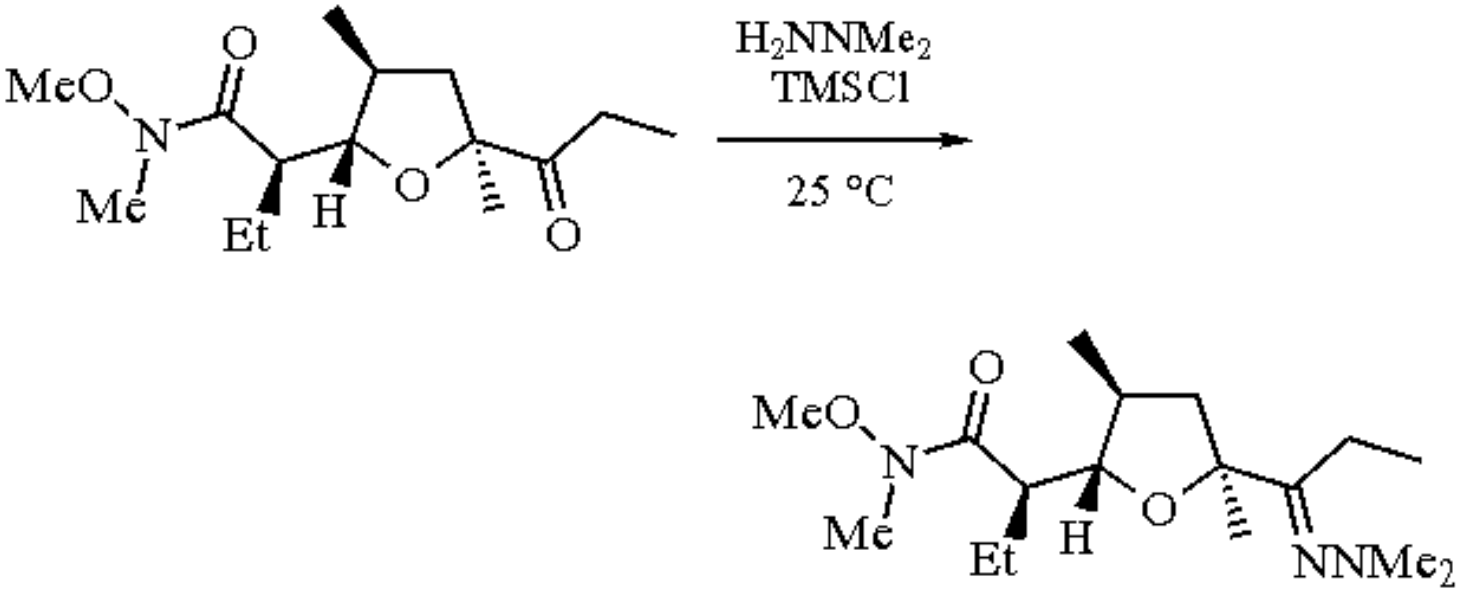

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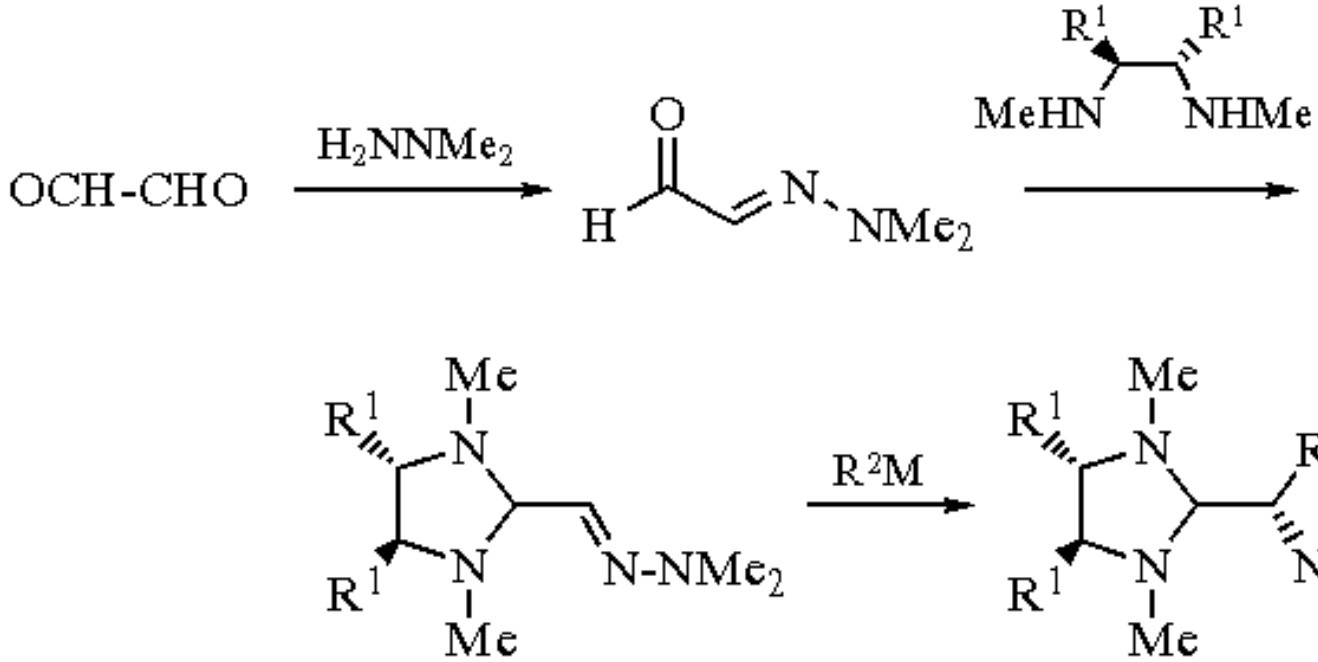

(3)

N,*N*-Dimethylhydrazones participate in a variety of cyclization reactions. For example, dimethylhydrazones derived from aldehydes and ketones undergo an efficient thermal [2 + 2] cyclization with phenoxyketene to afford β-lactams in

good yields (eq 4).[4] 3,4-Dihydro-6-methoxy-2-(2-methyl-1-oxocyclopent-2-enyl)naphthalene-1-carbaldehyde *N*,*N*-dimethylhydrazone undergoes cycloaddition in refluxing bromobenzene to form 10,11-dihydro-2-methoxy-7-methyl-7*H*-benzo[*h*]cyclopent[*c*]isoquinolin-7-ol in 38% yield (eq 5).[5] An efficient synthesis of piperidines was achieved through treatment of *N*,*N*-dimethylhydrazine with ***Glutaraldehyde*** and 2 equiv of benzotriazole (eq 6).[6] The intermediate 2,6-bis(benzotriazolyl)piperidine was converted to dimethylaminopiperidine upon treatment with ***Sodium Borohydride*** in THF. Finally, the trifluoromethylated dimethylhydrazones derived from aryl aldehydes and *N*,*N*-dimethylhydrazine undergo cyclization to 4-trifluoroimidazoles upon refluxing in toluene (eq 7).[7] Several other cyclization reactions involving *N*,*N*-dimethylhydrazones have been reported.[8]

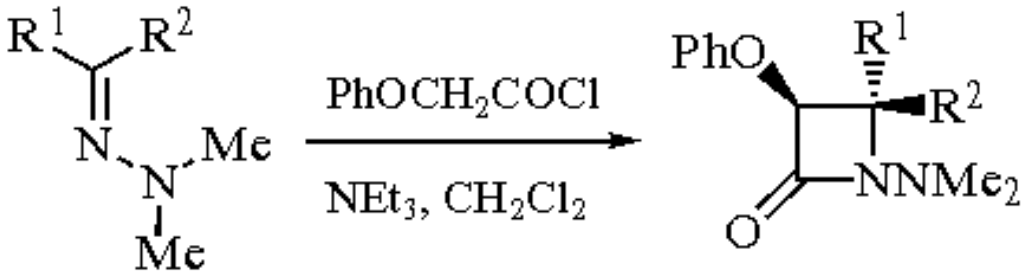

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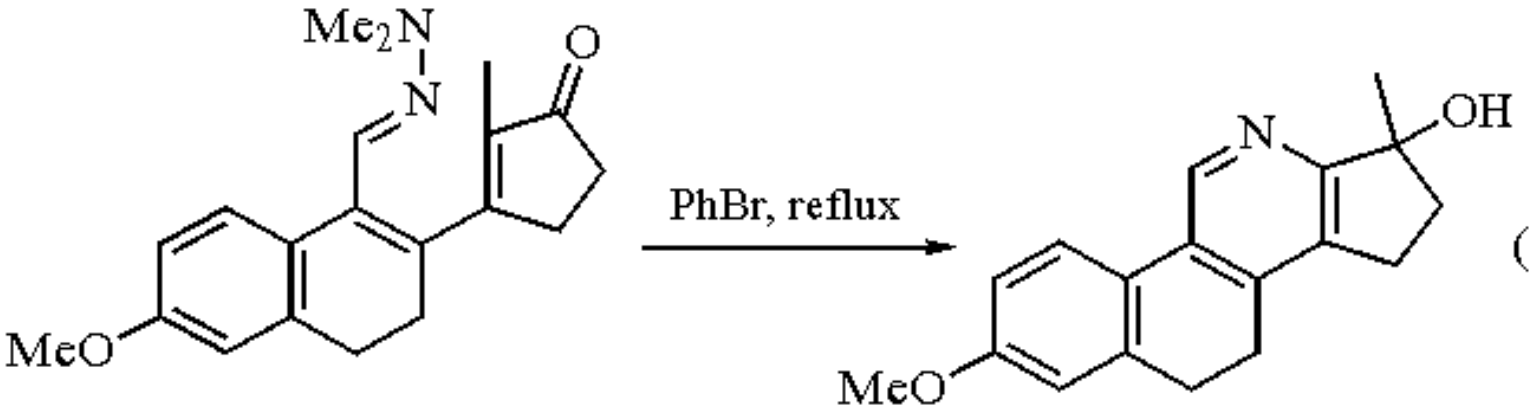

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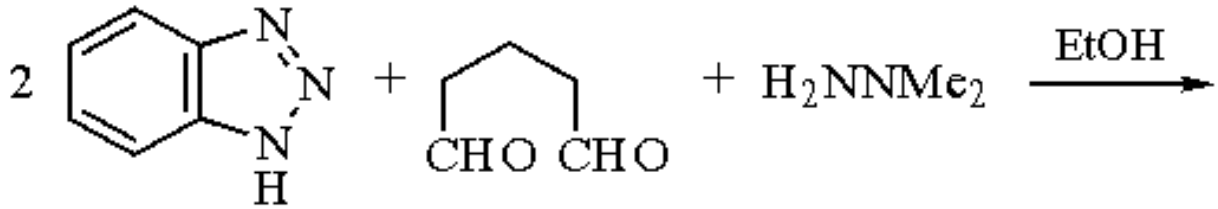

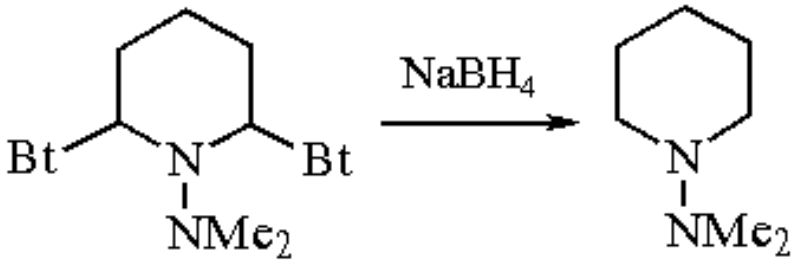

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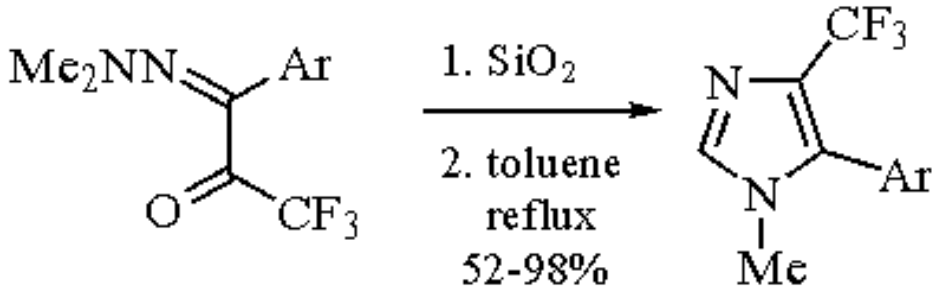

(7)

Metaloenamines derived from dimethylhydrazones can be alkylated with alkyl halides. For example, treatment of acetone dimethylhydrazone with ***n-Butyllithium***, followed by addition of 1,10-dibromodecane (0.5 equiv), afforded 2,15-hexadecanedione in 66% yield, after hydrolysis of the dihydrazone (eq 8).[9] The dimethylhydrazone of 3-methylcyclohexanone was alkylated with 2-(2-bromoethyl)-1,3-dioxolane (BED) to afford two monoalkylated regioisomers (eq 9).[10] Subsequent cyclization afforded two isomeric tetrahydroquinolines in an 8:92 ratio and 48% overall yield from 3-methylcyclohexanone. It is noteworthy that metalated Schiff base derivatives of conformationally locked cyclohexanones often display axial alkylation preferences exceeding 98%.[11]

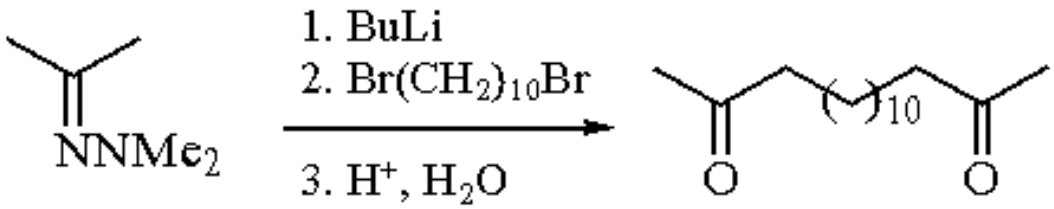

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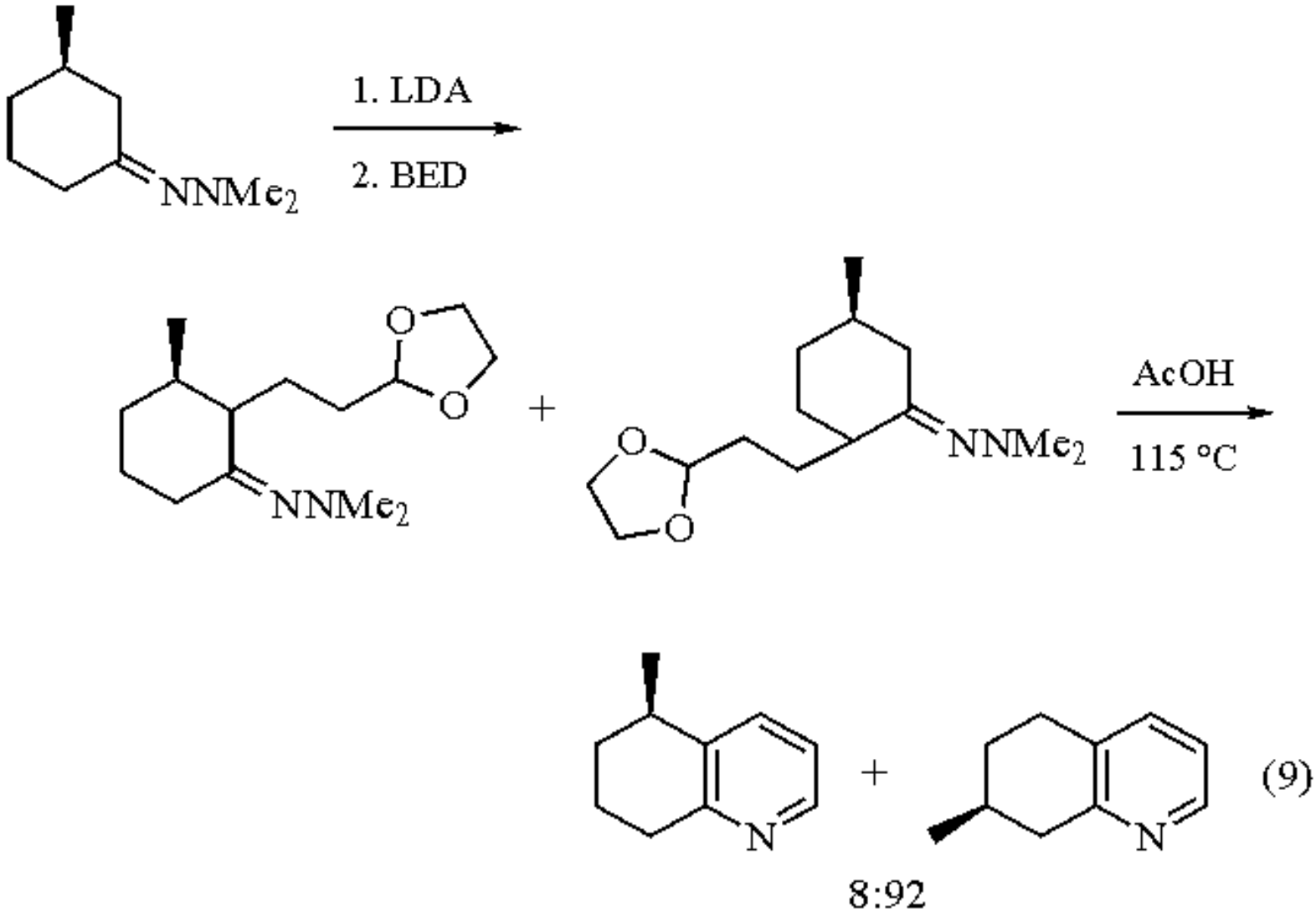

Aldehydes can be converted to the corresponding nitriles by oxidation of the aldehyde dimethylhydrazones. For example, treatment of 2-naphthaldehyde *N*,*N*-dimethylhydrazone with aqueous ***Hydrogen Peroxide*** and a catalytic amount of ***Selenium(IV) Oxide*** afforded 2-cyanonaphthalene in 95% yield (eq 10).[12] ***m-Chloroperbenzoic Acid*** could also be used to transform the dimethylhydrazone to the nitrile.

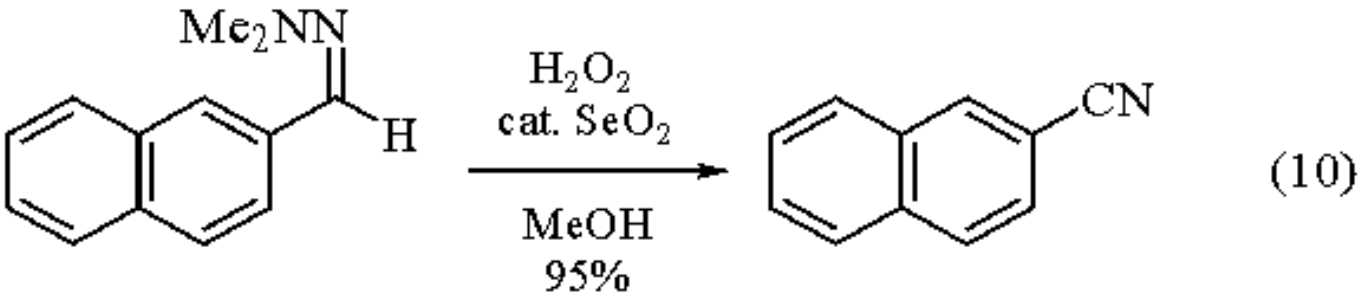

Nucleophilic Attack by *N,N*-Dimethylhydrazine.

N,*N*-Dimethylhydrazine is a useful nucleophile for electrophiles other than aldehydes and ketones. 1,4,2-Dithiazolium salts react with *N*,*N*-dimethylhydrazine to form two products (eq 11).[13] The major 5-imino-1,4,2-dithiazole is formed by nucleophilic displacement of the dimethylamino group by the *N*,*N*-dimethylhydrazine. The minor thiourea

derivative is formed by spontaneous fragmentation of the dithiazole ring; benzonitrile and sulfur are also produced. Treatment of 2-chloro-9-(4-hydroxy-3-hydroxymethylbutyl)hypoxanthine with *N*,*N*-dimethylhydrazine affords a mixture of 2-*N*-amino-9-(4-hydroxy-3-hydroxymethylbutyl)-2-*N*-methylguanine (12%) and 9-(4-hydroxy-3-hydroxymethylbutyl)-2-*N*-dimethylguanine (11% yield; eq 12.[14] Treatment of 4,4-disubstituted thiazolidine-2,5-dithiones with *N*,*N*-dimethylhydrazine in ethanol affords the 5,5-disubstituted 3-dialkylaminoimidazolidine-2,4-dithiones in 67-98% yields (eq 13).[15] Finally, *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine undergoes a nucleophilic aromatic N-N exchange reaction with *N*,*N*-dimethylhydrazine to afford *N*,*N*-dimethyl-*N*´-[2,4-bis(trifluoroacetyl)-1-naphthyl]hydrazine in quantitative yield (eq 14).[16] This product underwent an acid-promoted cyclization to afford the 2*H*-benz[*g*]indazole derivative upon refluxing in xylenes.

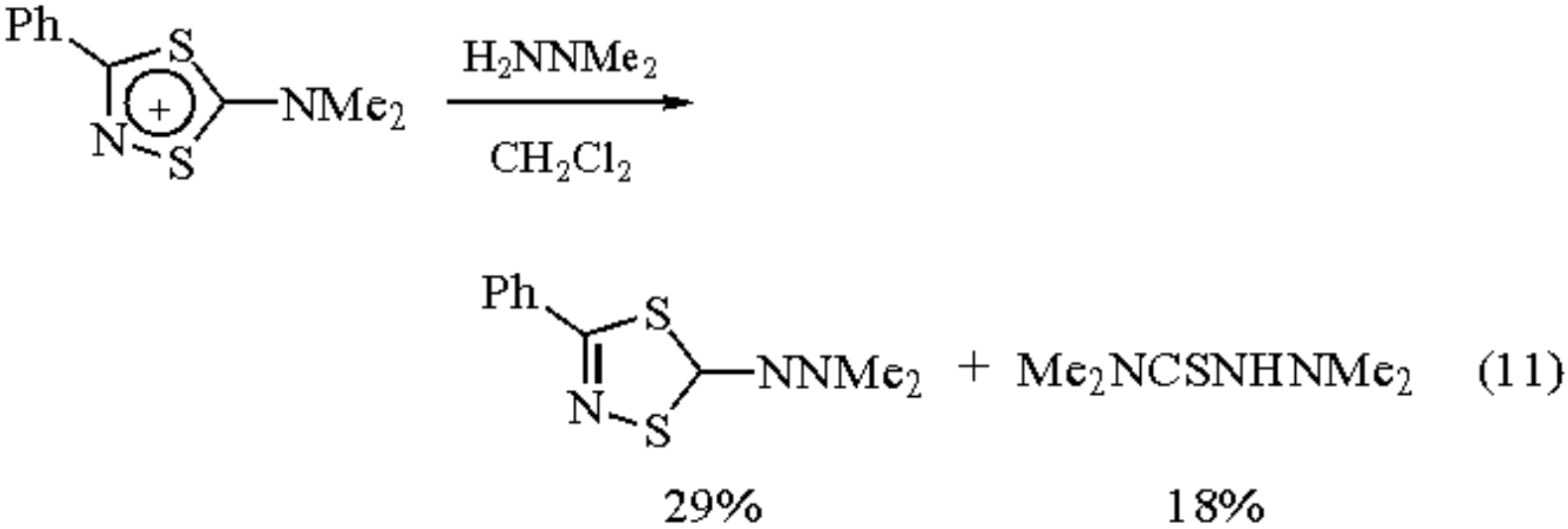

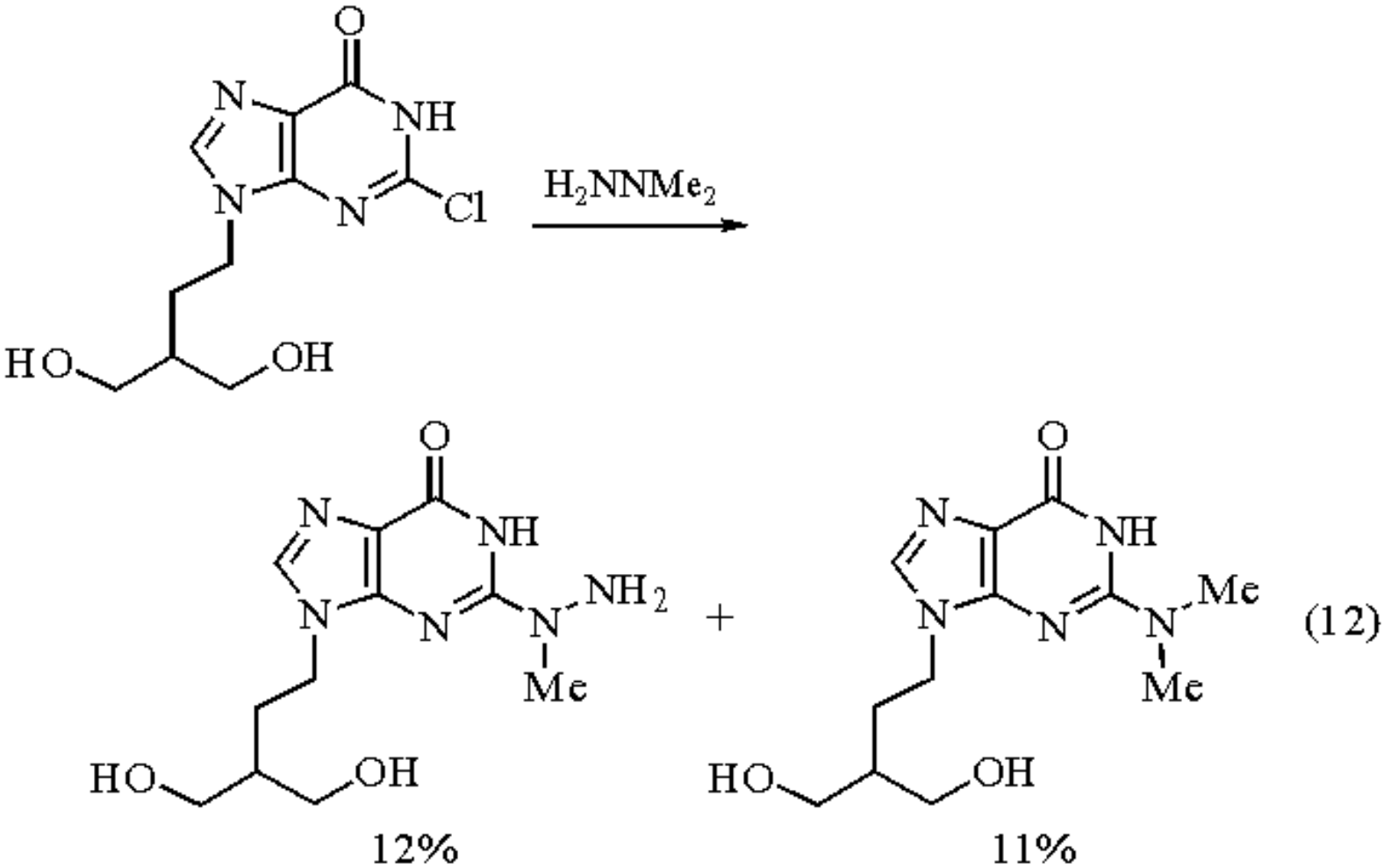

(12)

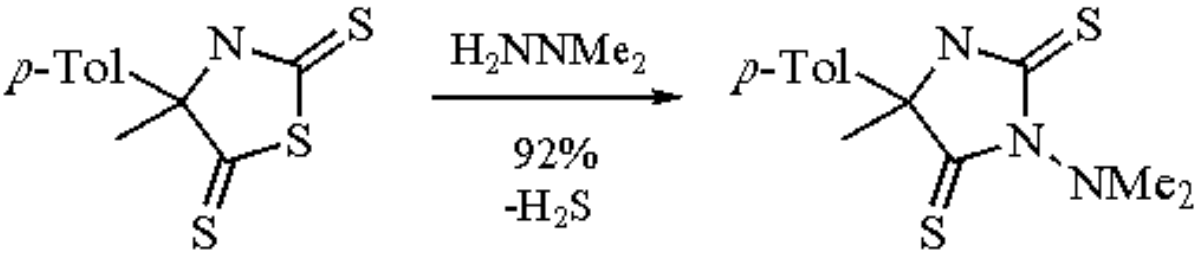

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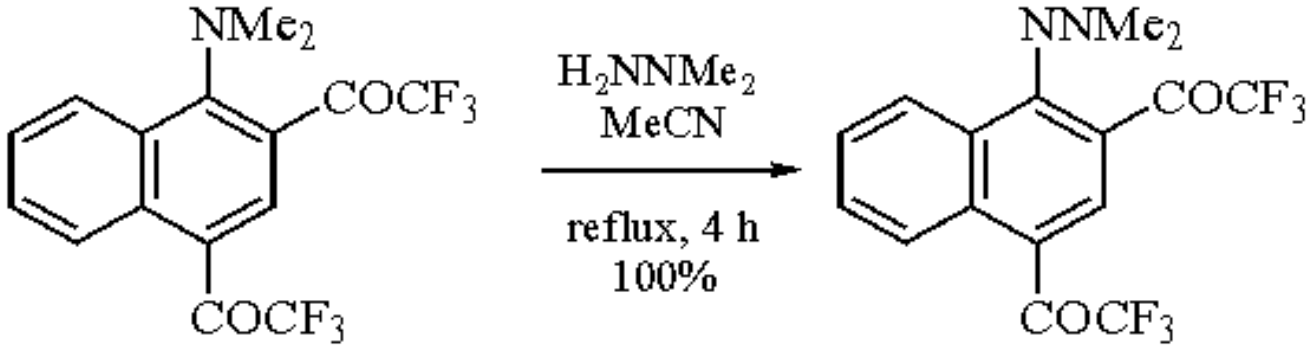

(14)

Formation of Functionalized Wittig Reagents.

Treatment of 1,2-vinylenebis(triphenylphosphonium) bromide with *N*,*N*-dimethylhydrazine afforded the functionalized

phosphonium salt, along with triphenylphosphine (eq 15).[17] The Wittig derivative was obtained by treatment with ***Potassium t-Butoxide***, and addition of a variety of aldehydes and ketones afforded the α,β-unsaturated hydrazones in 8-82% yields.

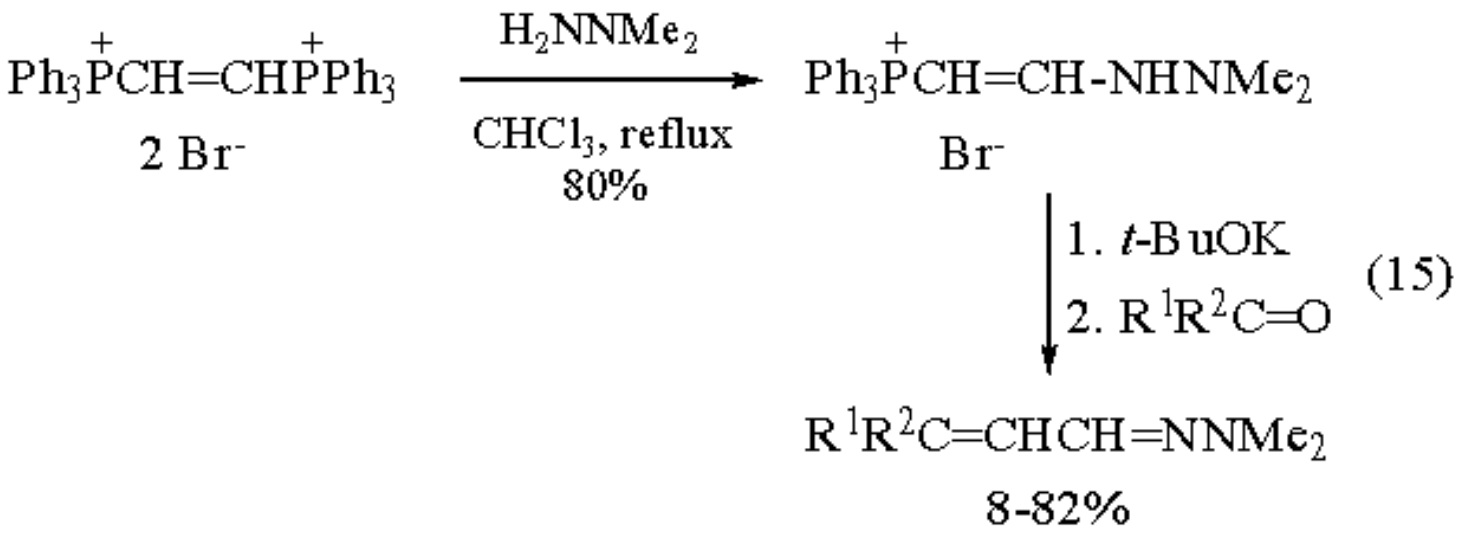

(15)

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N,O-Dimethylhydroxylamine[1]

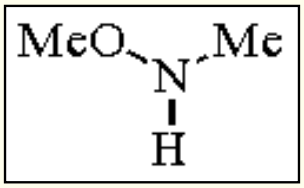

[1117-97-1] · C_2H_7NO · *N,O*-Dimethylhydroxylamine · (MW 61.10) (.HCl)

[6638-79-5] · C_2H_8ClNO · *N,O*-Dimethylhydroxylamine Hydrochloride · (MW 97.56)

(used extensively in the formation of *N*-methoxy-*N*-methylamides[2] and ureas,[3] which are valuable acylating agents)

Physical Data: mp -97 °C; bp 43.2 °C. .HCl salt, mp 115-116 °C.

Form Supplied in: commercially available as the HCl salt.

Handling, Storage, and Precautions: the free amine decomposes readily. However, the HCl salt is stable indefinitely.

Formation.

N,O-Dimethylhydroxylamine hydrochloride, although commercially available, can be generated from ***Ethyl Chloroformate*** and ***Hydroxylamine*** in excellent yield (eq 1).[4] The hydrochloride salt can be converted to the distillable free amine by reaction with strong base (eq 2),[5] but is generally formed in situ for most reactions.

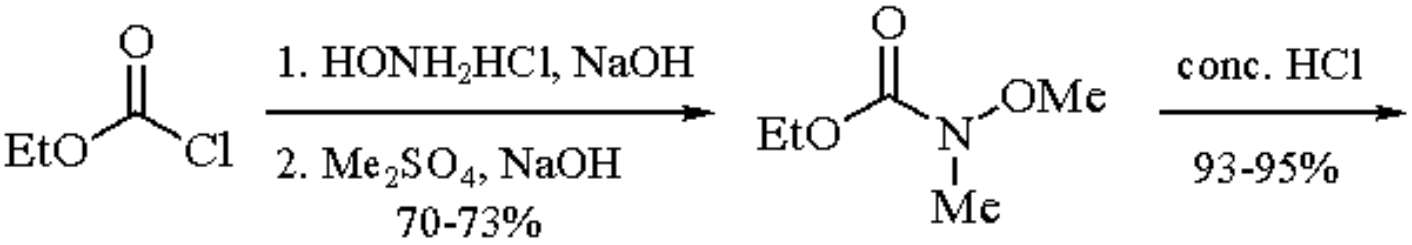

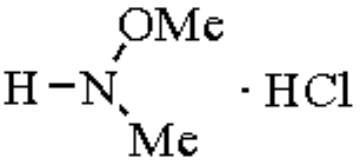

(1)

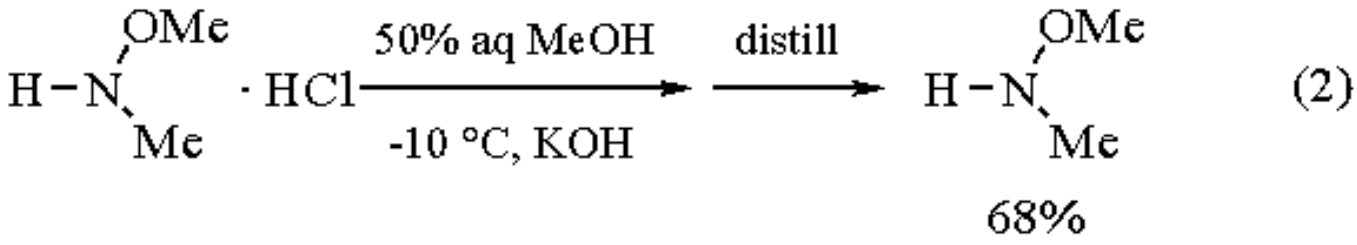

Preparation of *N*-Methoxy-*N*-methylamides.

The widest use of the title compound is in the synthesis of *N*-methoxy-*N*-methylamides, which can be prepared from acid chlorides in good to excellent yield (eq 3).[6] The amides can also be prepared from carboxylic acids via anhydrides (eq 4)[7,8] or by using peptide coupling reagents such as ***1,3-Dicyclohexylcarbodiimide*** (eq 5)[9] and others.[10] A mild method for the generation of *N*-methoxy-*N*-methylamides from carboxylic acids using ***Carbon Tetrabromide*** and ***Triphenylphosphine*** has been published (eq 6).[11] *N,O*-Dimethylhydroxylamine reacts with cyclic anhydrides to produce amide acids (eq 7).[12] Esters can also be converted to their corresponding amides via dialkylaluminum amides, formed by the reaction of *N,O*-dimethylhydroxylamine or the hydrochloride with trialkylaluminum reagents (eq 8)[13] (see also ***Dimethylaluminum Amide***).

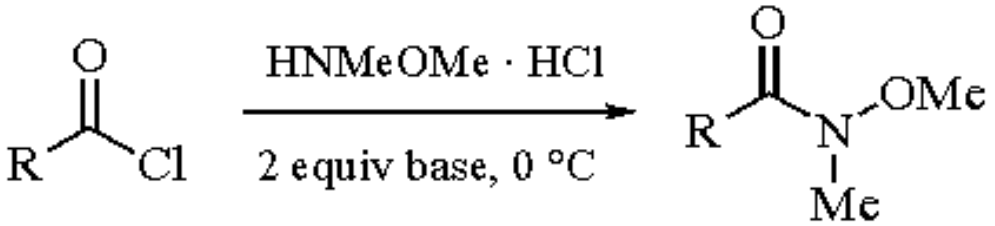

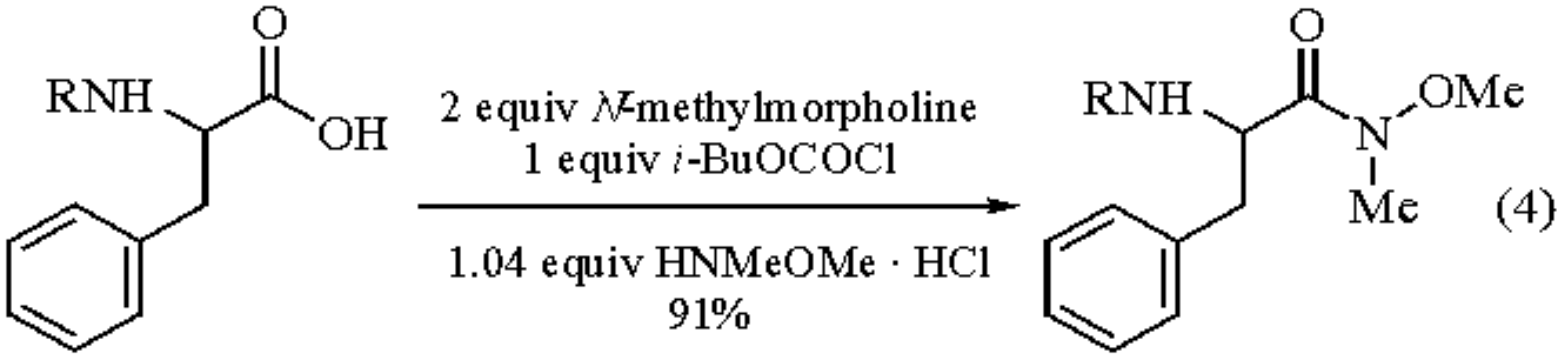

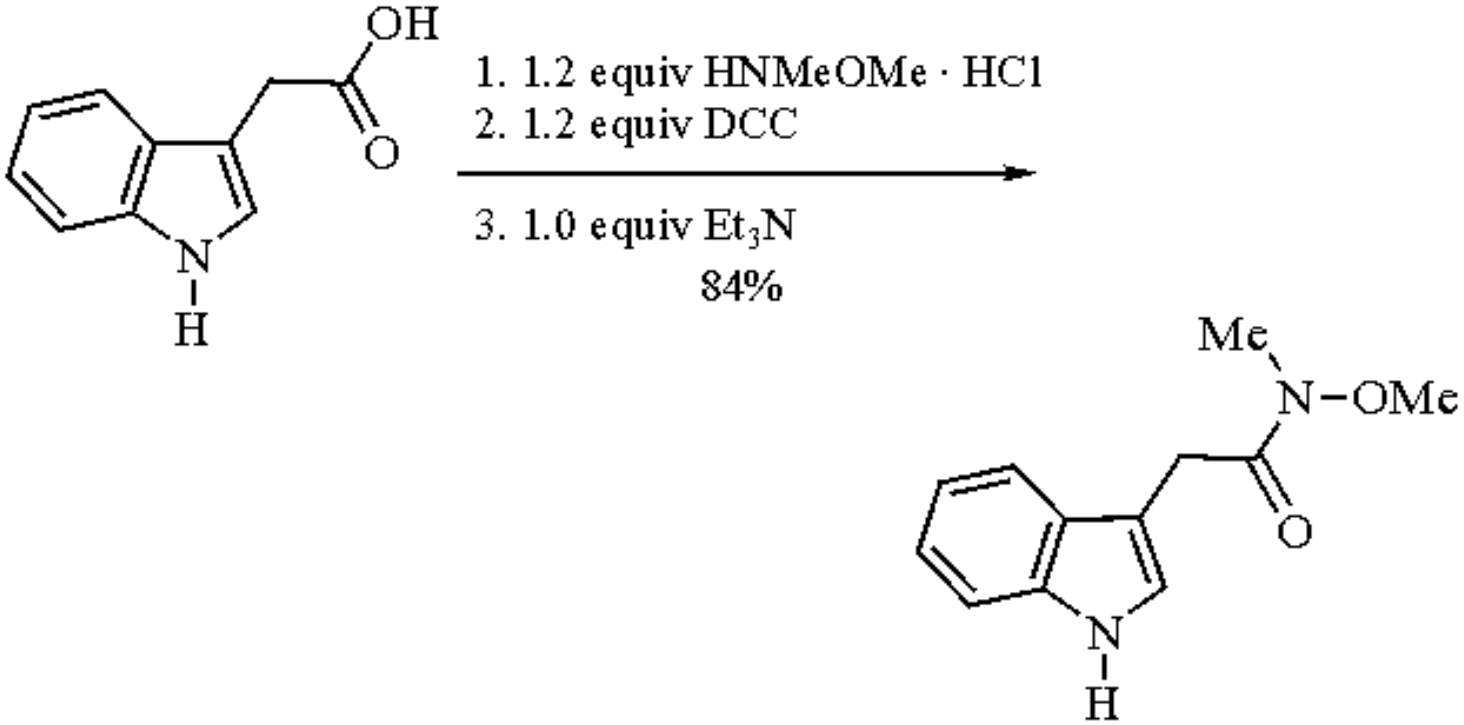

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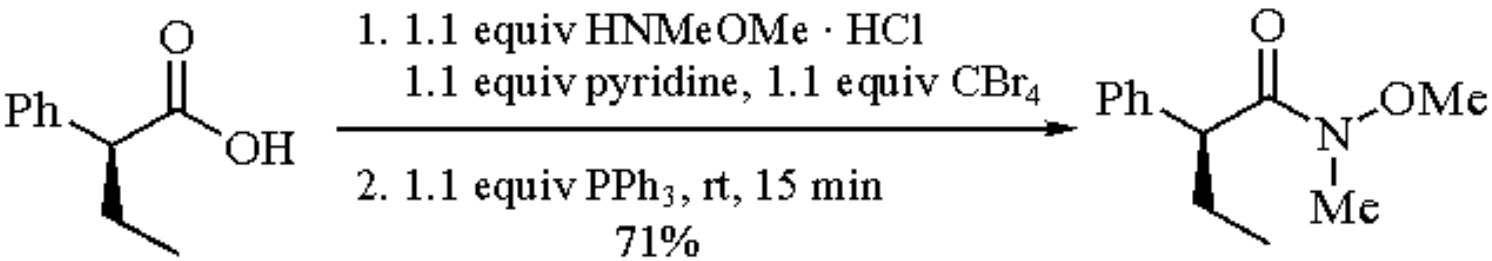

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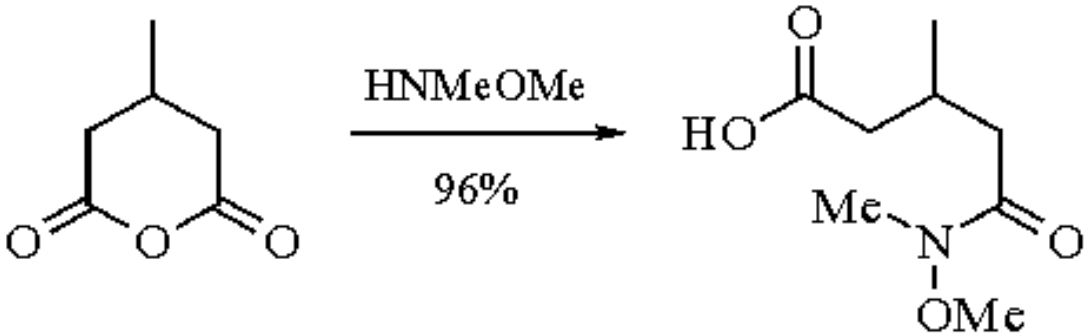

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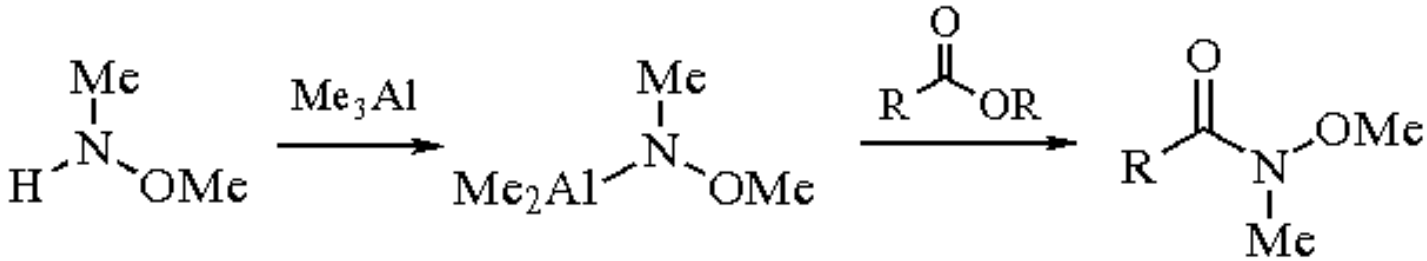

(8)

R = H, alkyl, aryl

Alkylation of *N*-Methoxy-*N*-methylamides.

N-Methoxy-*N*-methylamides have advantages over *N*,*N*-dialkylamides in that they give fewer side products in nucleophilic addition reactions, with little or no overaddition. Addition of a nucleophile to an *N*-methoxy-*N*-methylamide results in the formation of a stable chelated tetrahedral intermediate that is not susceptible to additional nucleophilic attack. Thus even in the presence of a large excess of a nucleophile, only monoalkylation occurs. The general reaction works well with alkyllithiums and Grignard reagents at low temperatures (eq 9).[2] Many nucleophiles have been used with these amides to produce symmetrical and unsymmetrical ketones,[2,14] α-amino ketones,[15] β-dicarbonyl compounds (eq 10),[16] and 1,4- and 1,5-dicarbonyl compounds (eq 11).[17,18] It has also been shown that *N*,*N*´-dimethoxy-*N*,*N*´-dimethylethanediamides, formed from ***Oxalyl Chloride***, undergo monoalkylation with alkyllithium or Grignard reagents to form α-keto amides (eq 12), which can subsequently be converted to 1,2-diketones.[19]

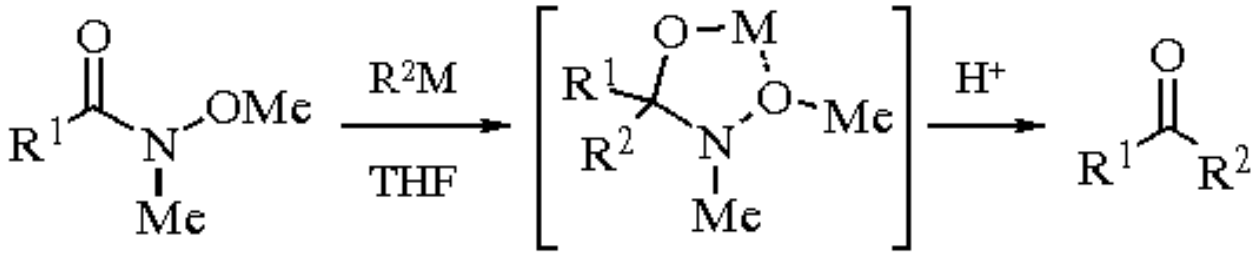

(9)

R^1	R^2M (equiv)	Isolatable yields (%)
Ph	MeMgBr (1.1)	93
Ph	PhC≡CLi (1.1)	90
$C_{17}H_{35}$	MeMgBr (2.0)	94
$MeCO_2(CH_2)_3$-	PhMgBr (6.0)	98

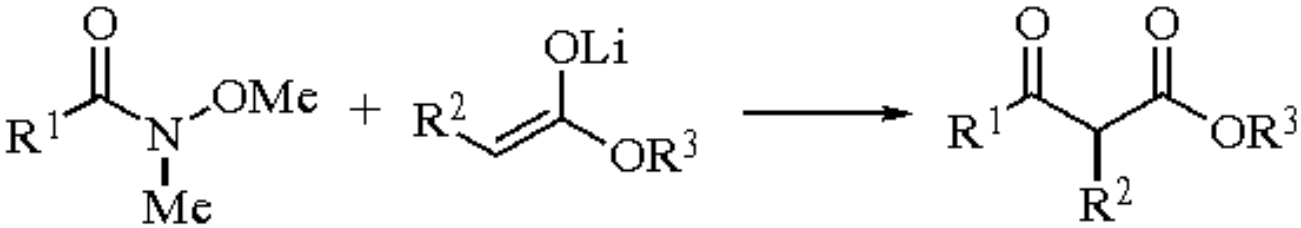

(10)

R^1	R^2	R^3	Yield (%)
C_5H_{11}	H	Et	82
Ph	Me	Et	84
4-MeC_6H_4	H	*t*-Bu	73

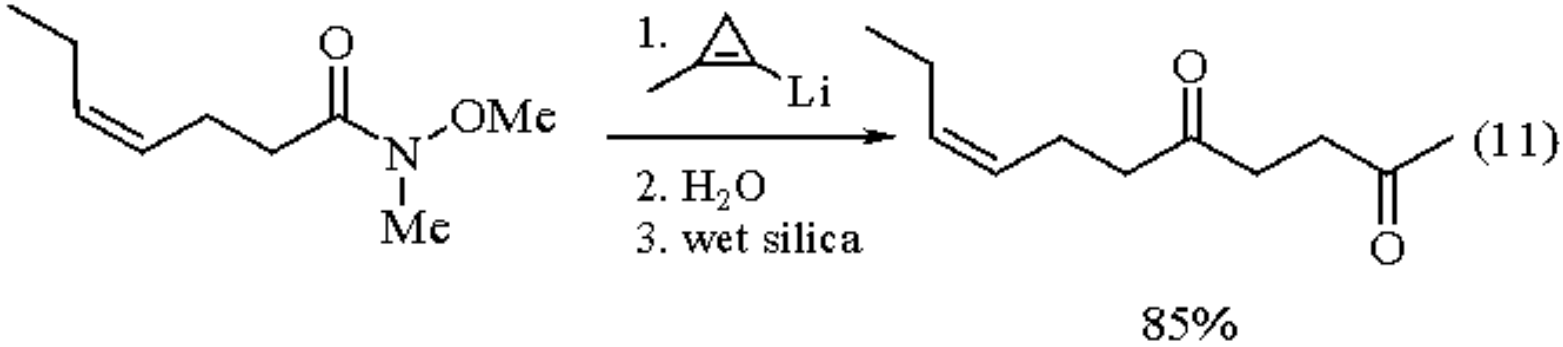

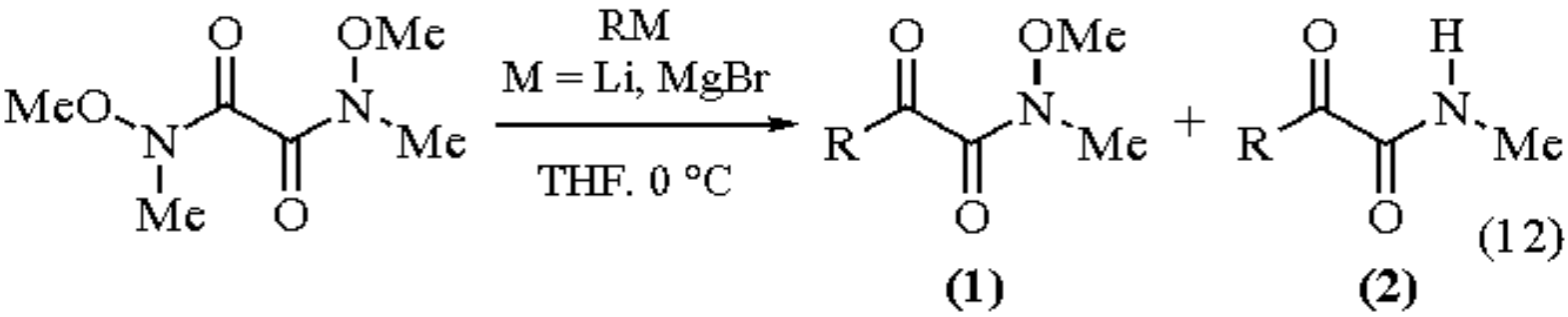

RM (equiv)	Yield (%) (1)	(2)
4-ClC_6H_4Li (1.5)	90	-
4-ClC_6H_4Li (4.0)	66	9

Acylation of the enolates of di-, tri-, and tetraketones with *N*-methoxy-*N*-methylamides results in high yield of the desired product (eq 13),[20] in contrast to acylations using esters which give lower yields and are generally problematic.

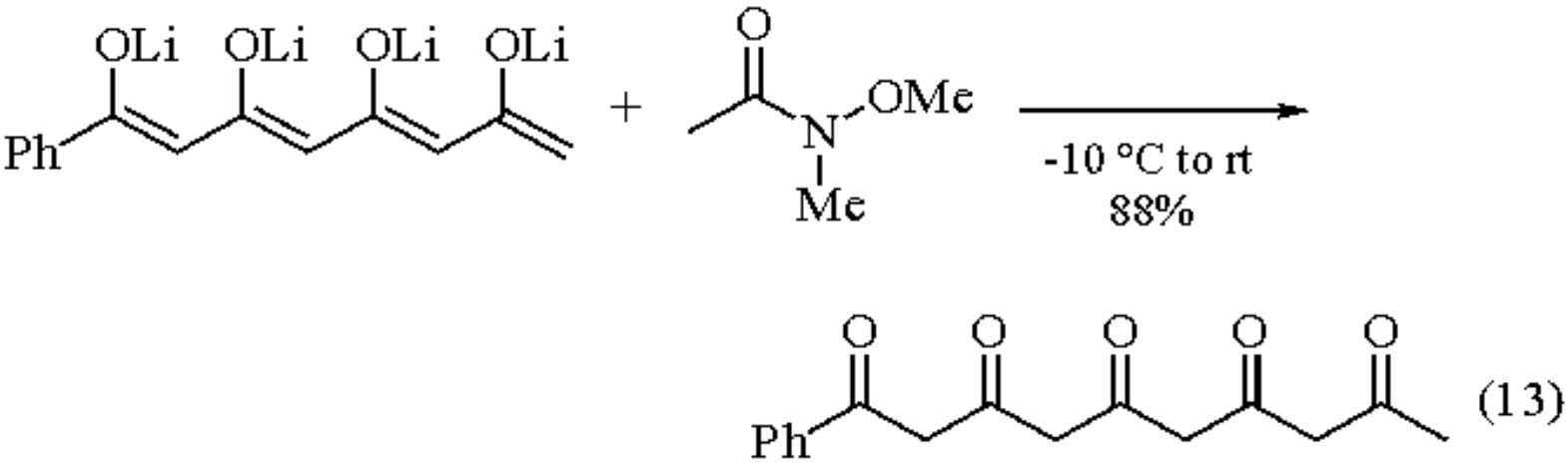

The dianions of β-keto esters react with α,β-unsaturated *N*-methoxy-*N*-methylamides to give the β,δ-diketo ester in moderate yields, with no trace of conjugate addition (eq 14).[21]

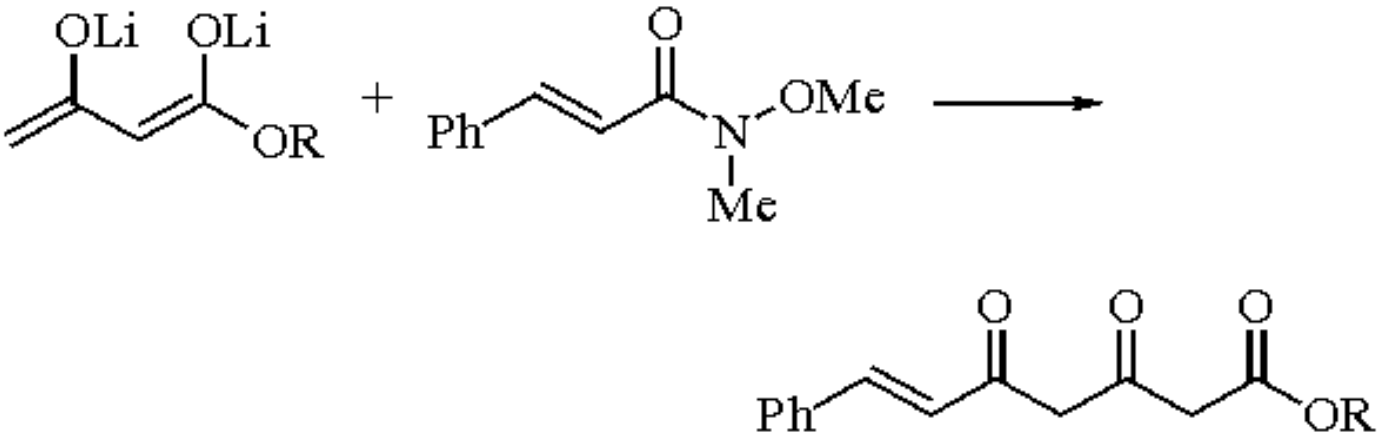

(14)

R = *t*-Bu, 49%; Et, 49%; Me, 57%

N-Methoxy-*N*-methylamides have recently been used to prepare regiocontrolled cross-aldol products, by using ***Zinc*** powder and ***Chlorotrimethylsilane*** to generate the intermediate β-siloxyamides, followed by reaction with a Grignard reagent. This reaction works with both enolizable and nonenolizable carbonyl compounds (eq 15).[22]

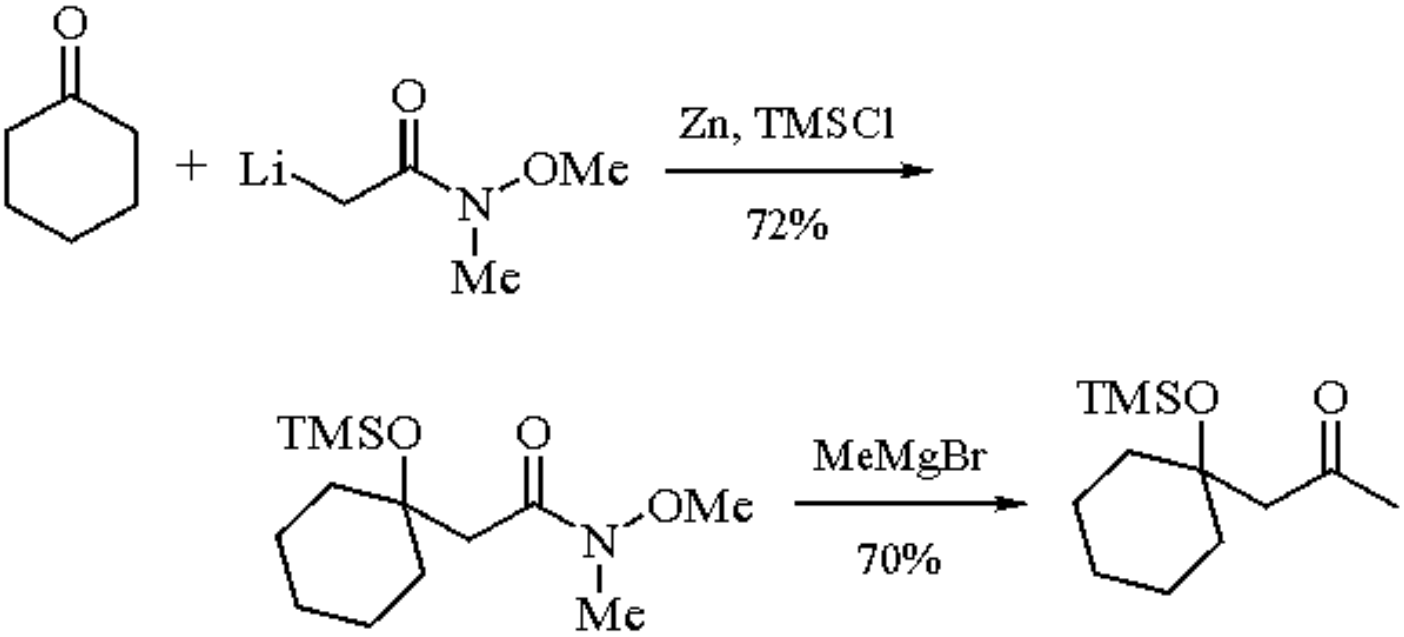

(15)

Reductions of *N*-Methoxy-*N*-methylamides.

Reduction of *N*-methoxy-*N*-methylamides occurs under mild conditions to give high yields of aldehydes, in contrast to *N*,*N*-dialkylamides which tend to give considerable quantities of amine and alcohol side products (eqs 16 and 17).[2] One area of recent interest involves the formation of *N*-protected α-amino aldehydes from the corresponding *N*-methoxy-*N*-methylamides in high yields without racemization (eq 18).[23]

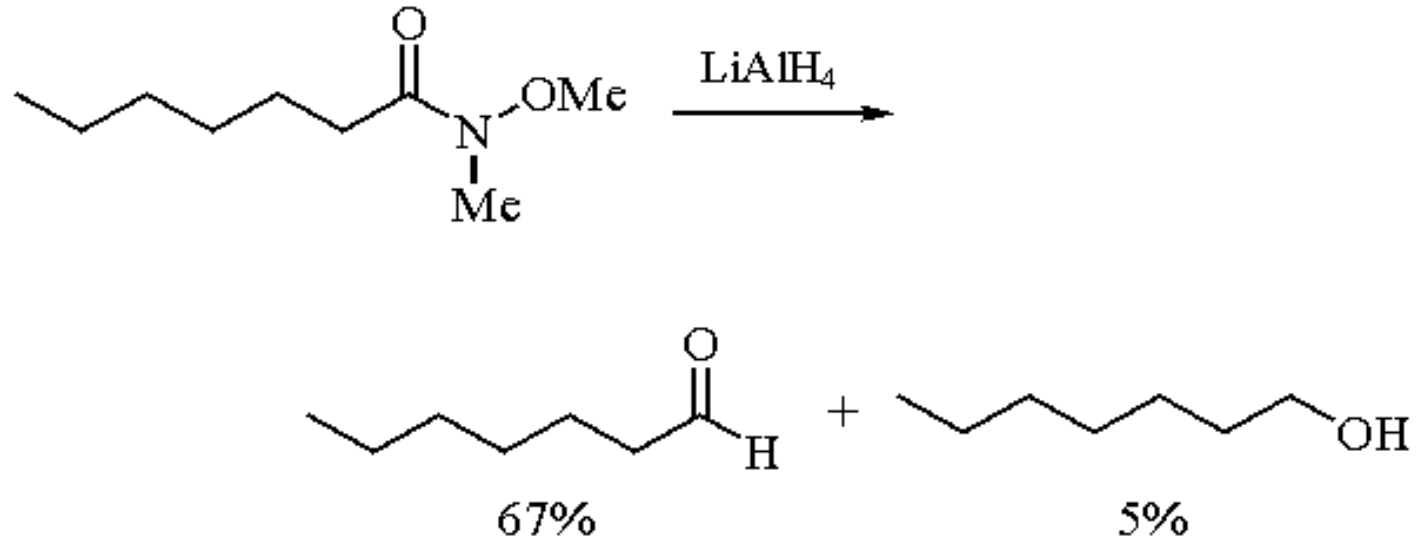

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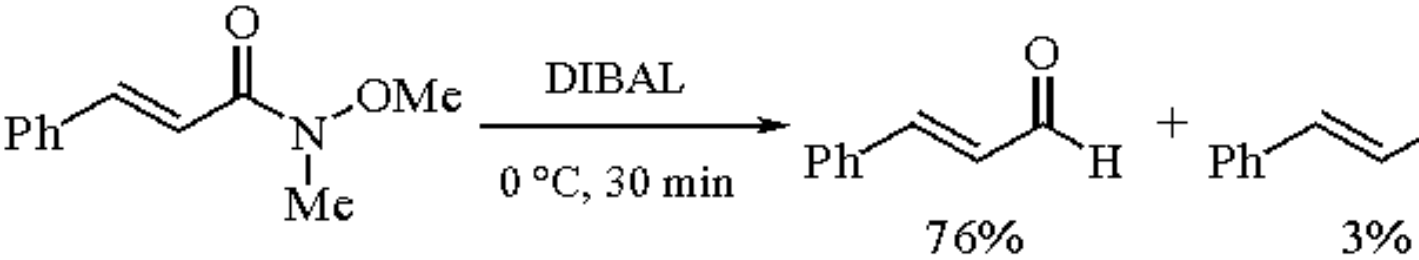

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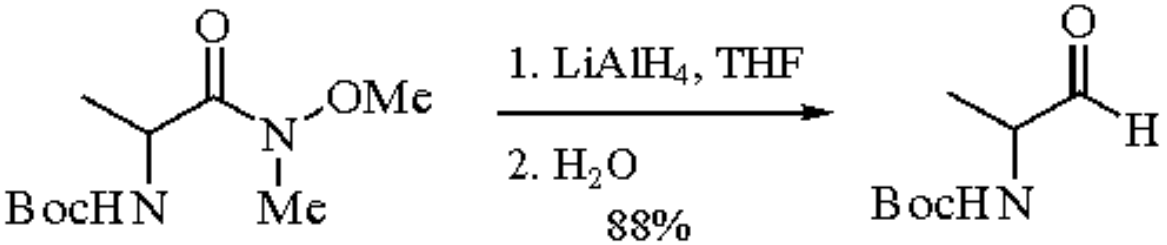

(18)

Preparation and Uses of *N*-Methoxy-*N*-methylureas.

N,*O*-Dimethylhydroxylamine has also been used in the preparation of ureas by reaction with the appropriate carbonyl compound (eqs 19 and 20).[3]

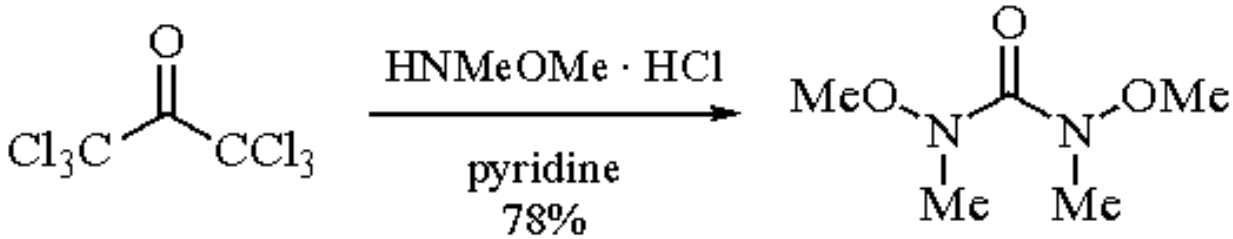

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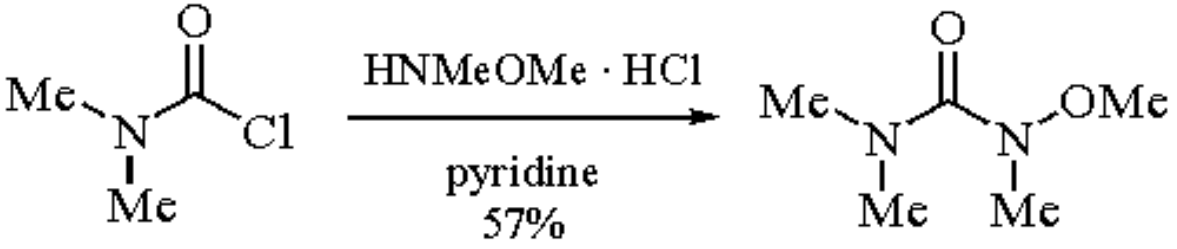

(20)

The resultant ureas have been used as carbon dioxide equivalents in the formation of a variety of symmetrical and unsymmetrical ketones (eqs 21-23).[3]

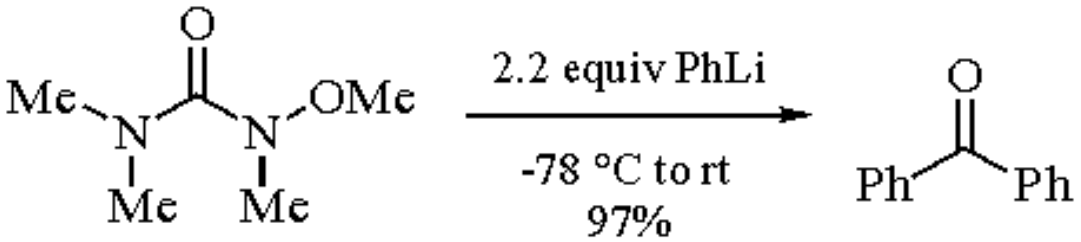

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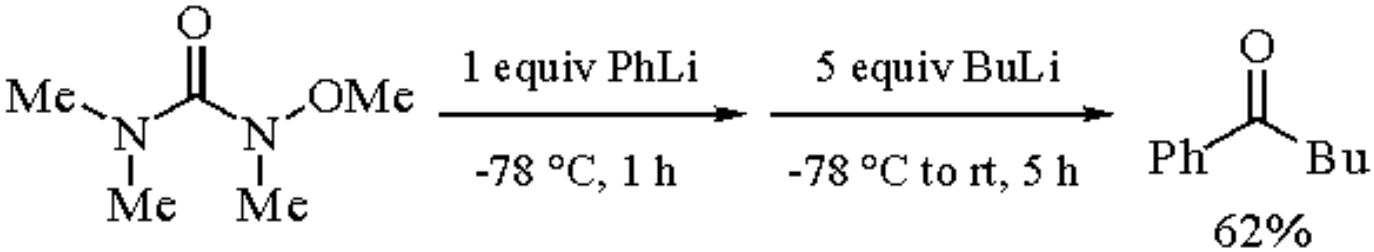

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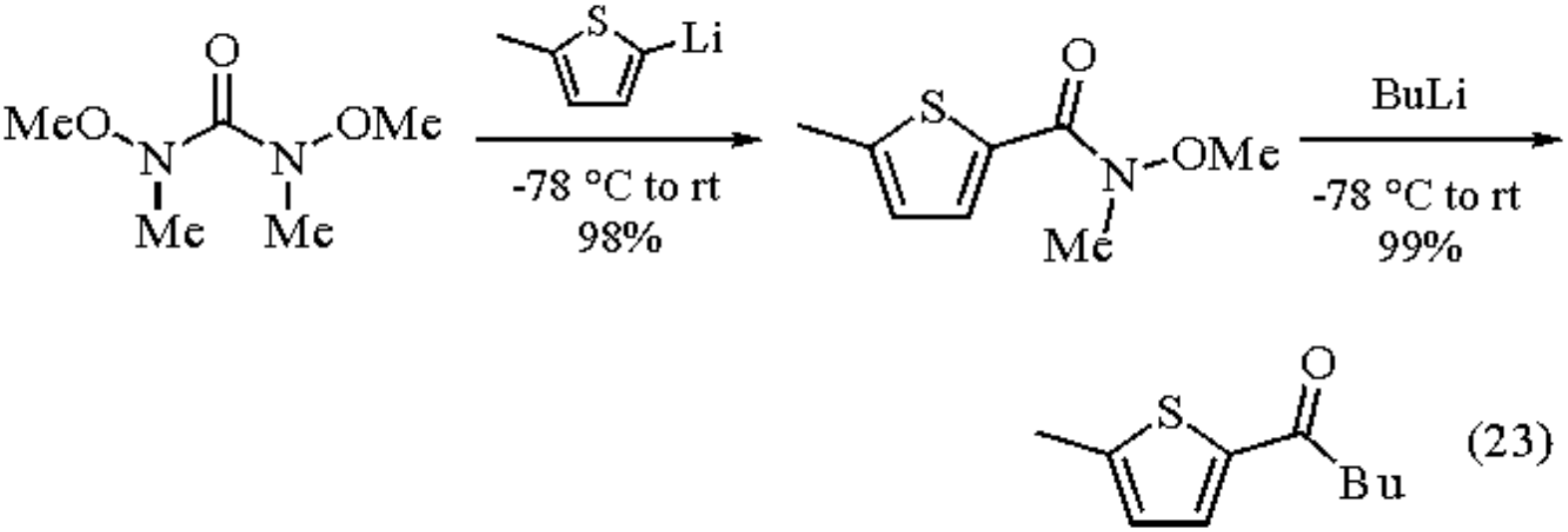

(23)

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1,3-Dimethyl-2-imidazolidinone

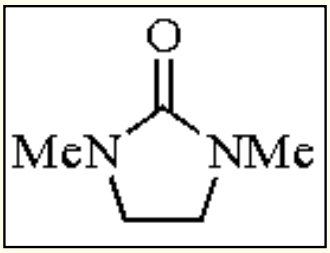

[80-73-9] · $C_5H_{10}N_2O$ · 1,3-Dimethyl-2-imidazolidinone · (MW 114.17)

(dipolar aprotic solvent[1] with characteristics between THF and HMPA; solvent of choice for many types of organic reactions, especially organometallic reactions[2])

Alternate Name: DMI.

Physical Data: bp 221-223 °C; *d* 1.044 g cm^{-3}.

Solubility: sol water, DMF, and THF.

Form Supplied in: clear, colorless liquid; commercially available.

Analysis of Reagent Purity: bp, NMR.

Purification: distillation over calcium hydride under reduced pressure.

Handling, Storage, and Precautions: for best results, this solvent should be stored under an inert atmosphere over 4Å molecular sieves. Handle in a fume hood.

Synthesis of Homoallylic Alcohols.

DMI is the solvent of choice for palladium-catalyzed carbonyl allylation of allylic alcohols (eq 1).[3] Allylation of ketones requires higher temperatures (eq 2). Preferential reaction of an aldehyde in the presence of a ketone can be achieved (eq 3). Allylic iodides can also be reacted with aldehydes and ketones in the presence of ***Tin(II) Fluoride***[4] to form homoallylic alcohols in good yield without the use of Lewis acids as additives (eq 4).

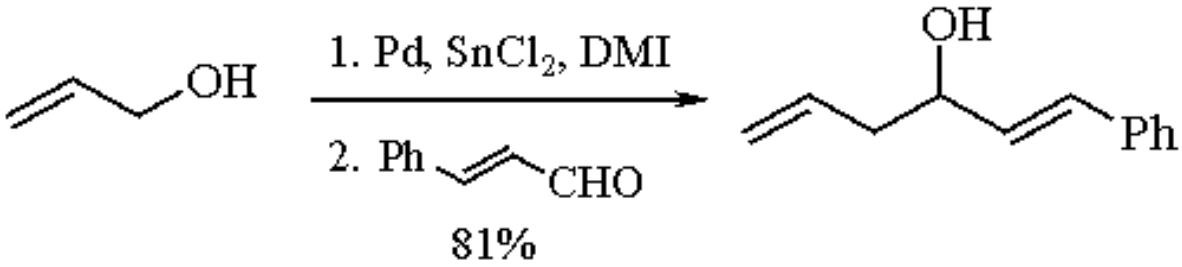

(1)

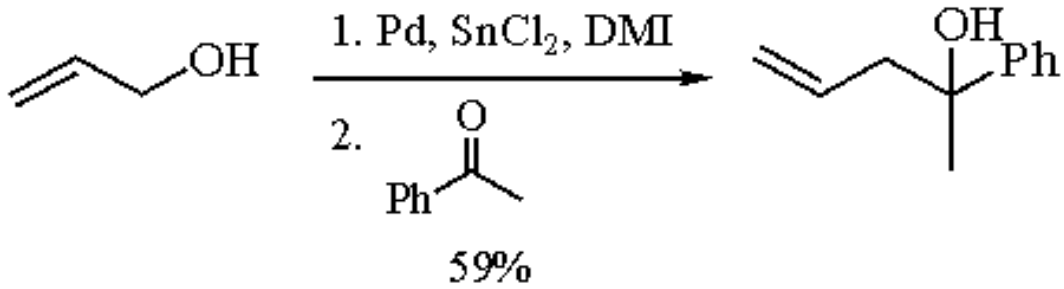

(2)

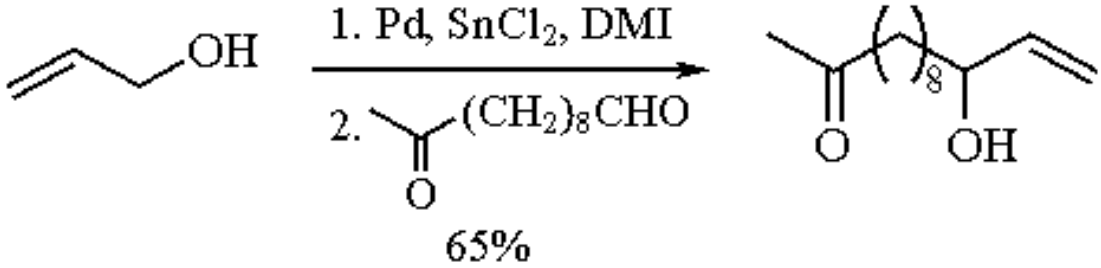

(3)

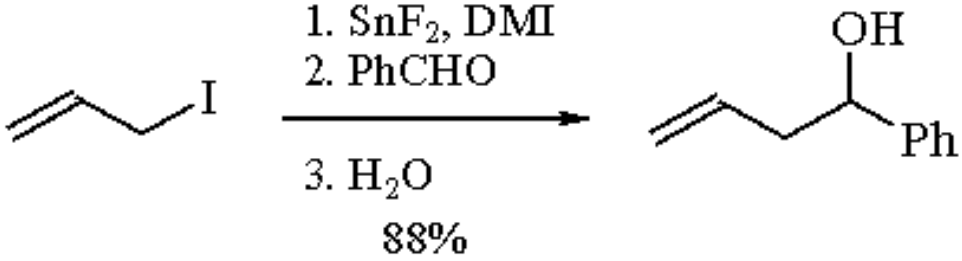

(4)

Synthesis of α-Methylene-γ-butyrolactones.

Palladium-catalyzed allylation of aldehydes and ketones with ethyl α-(hydroxymethyl)acrylate in the presence of ***Tin(II) Chloride*** in DMI/water provides α-methylene-γ-butyrolactones (eq 5).[5] *Syn* selectivity has been achieved when the reactions are run using a substituted hydroxymethylacrylate.

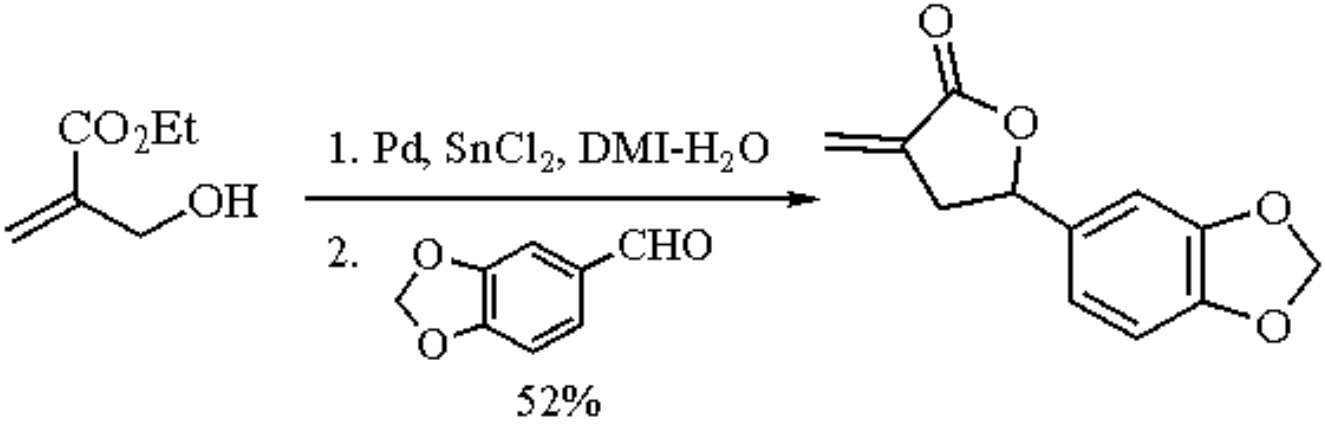

Preparation of Trimethylsilylsodium, Trimethylsilylpotassium, and Trimethylsilyllithium.

DMI is the solvent of choice for the preparation of TMSNa, ***Trimethylsilylpotassium***, and ***Trimethylsilyllithium*** (eq 6).[6] Other polar aprotic solvents such as DMF, DMSO, and tetramethylurea (TMU) are not suitable due to their reactivity toward strong base and alkali metals. Reactions of these species are also run in DMI (eqs 7 and 8).[2]

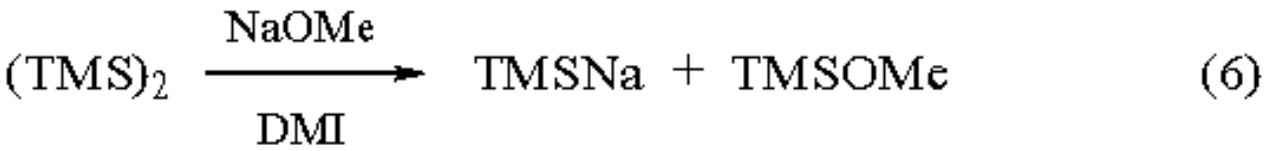

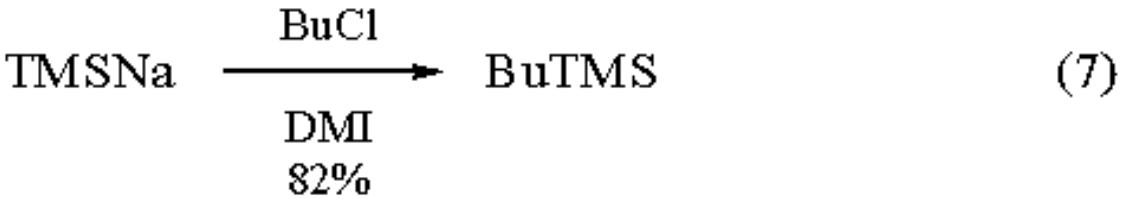

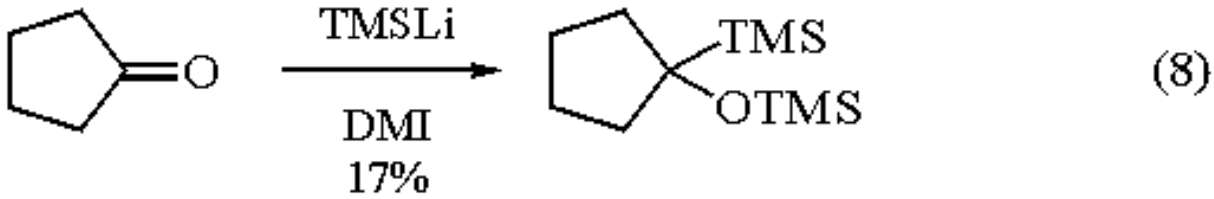

Dehydrations and Dehydrohalogenation Reactions.

DMI can be used as an alternative for HMPA[7] in dehydration and dehydrohalogenation reactions using ***Methyltriphenoxyphosphonium Iodide*** (MTPI) (eq 9).

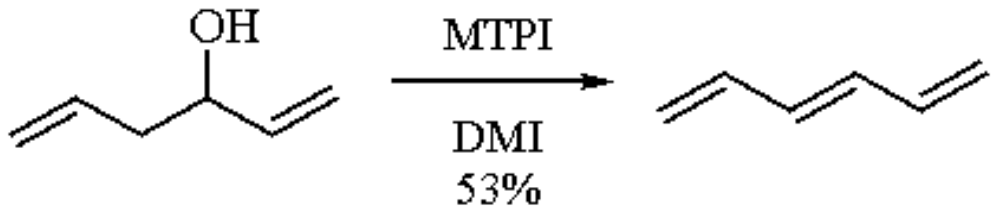

(9)

Ullmann Ether Synthesis.

Preparation of *m*-phenoxybenzyl alcohol by condensation of *m*-hydroxybenzyl alcohol with chlorobenzene works best in DMI (eq 10).[8] Lower yields result when the reaction is run using DMSO or DMF.

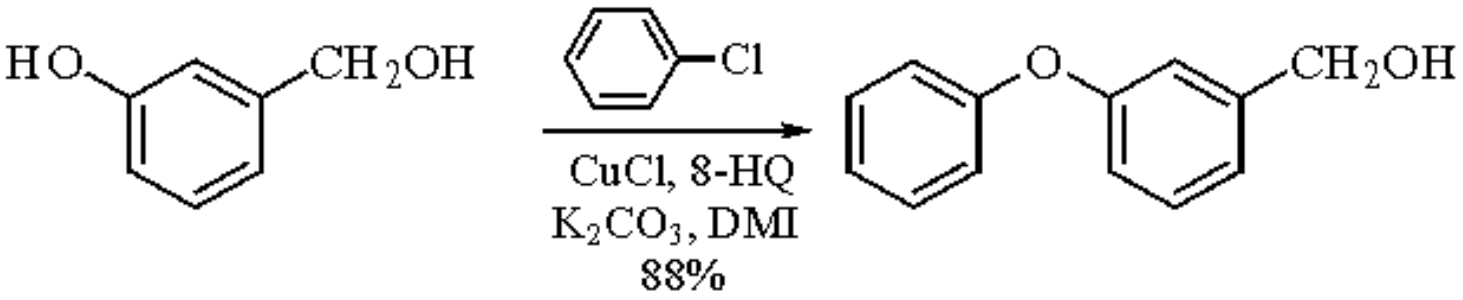

(10)

Synthesis of α-Hydroxyallenes.

Reactions of propargyl iodides with aldehydes in the presence of $SnCl_2$ in DMI/DMF yield a mixture of α-hydroxylallenes and β-hydroxyalkynes[9] (eq 11).

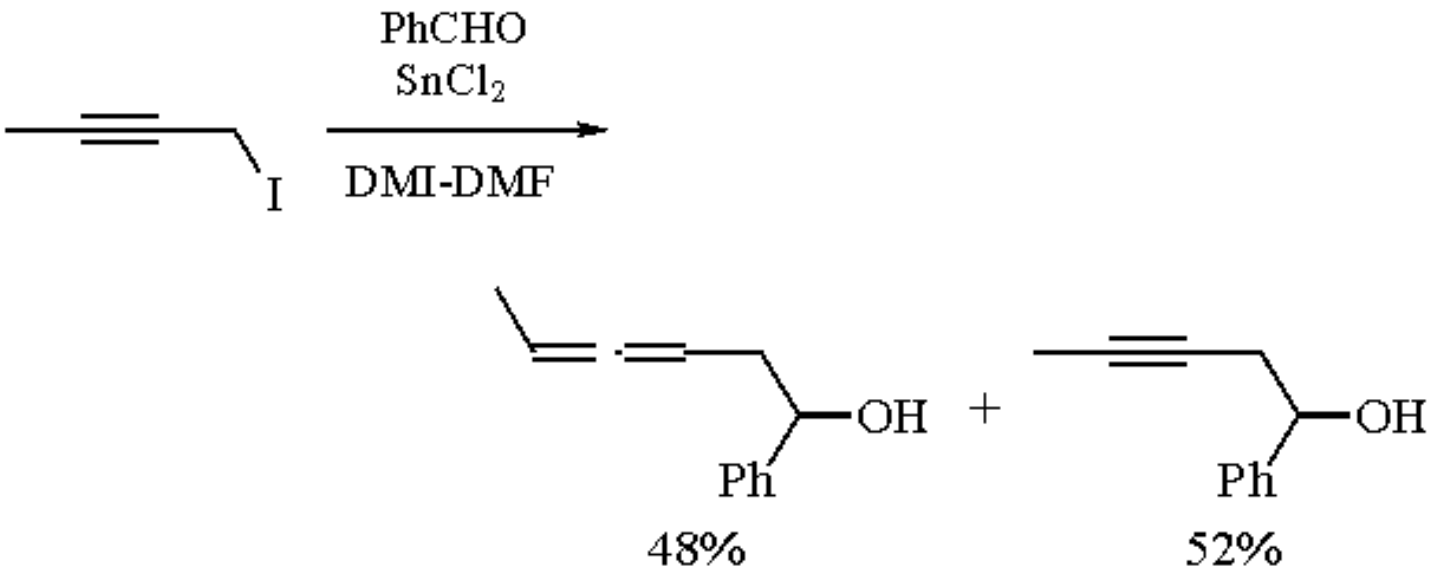

(11)

Wittig-Horner Reactions.

High *syn* selectivity is achieved in Wittig-Horner reactions between aldehydes and diphenylphosphonates when run in THF/DMI at low temperature.[10] Subsequent stereospecific elimination yields *cis*-alkenes (eq 12).

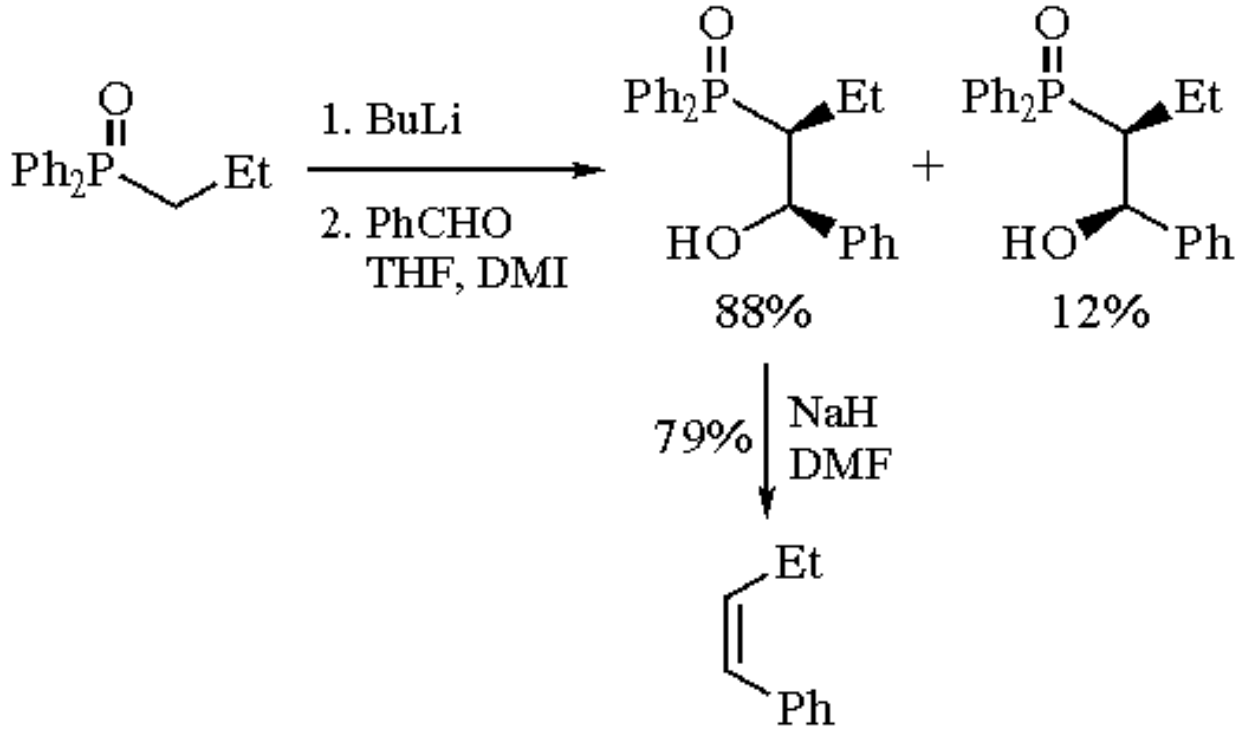

(12)

1. Barker, B. J.; Rosenfarb, J.; Caruso, J. A. *AG(E)* **1979**, *18*, 503.
2. Sakurai, H.; Kondo, F. *JOM* **1976**, *117*, 149.
3. Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *JACS* **1988**, *110*, 4473.
4. Mukaiyama, T.; Harada, T.; Shoda, S. *CL* **1980**, 1507.
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6. Sakurai, H.; Kondo, F. *JOM* **1975**, *92*, C46.
7. Spangler, C. W.; Kjell, D. P.; Wellander, L. L.; Kinsella, M. A. *JCS(P1)* **1981**, 2287.
8. Oi, R.; Shimakawa, C.; Takenaka, S. *CL* **1988**, 899.
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10. Buss, A. D.; Warren, J. *TL* **1983**, *24*, 3931.

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Dimethyl Maleate

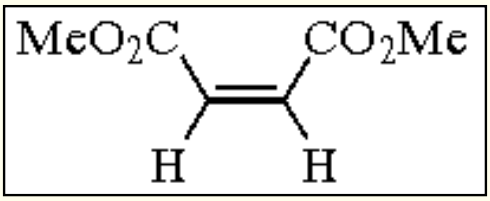

[624-48-6] · $C_6H_8O_4$ · Dimethyl Maleate · (MW 144.14)

(useful as a dienophile; dipolarophile; Michael acceptor; radical acceptor)

Physical Data: bp 204-205 °C; *d* 1.152 g cm^{-3}.

Solubility: sol most ethers and methanol.

Form Supplied in: colorless liquid; <=4% impurity of dimethyl fumarate.

Purification: distilled under reduced pressure.

Handling, Storage, and Precautions: toxic, irritant. Store in a brown bottle; avoid exposure to light.

Cycloadditions.

Dimethyl maleate is a doubly activated dienophile which reacts stereospecifically with a variety of dienes (see also ***Dimethyl Fumarate***). Dimethyl maleate has been utilized in examining the stereoselectivity in the Diels-Alder reaction of substituted *o*-quinodimethanes (eq 1).[1] The [4 + 2] cycloaddition between dimethyl maleate and a 1-amino-2-azadiene produces a dihydropyridine (eq 2).[2] Dimethyl maleate is an excellent dipolarophile which may be used to probe the concertedness of a cycloaddition process. However, caution needs to be exercised in drawing conclusions regarding the concertedness of a reaction based upon the stereoselectivity since maleate has been observed to isomerize quantitatively to fumarate by basic catalysis prior to cycloaddition.[3] The [3 + 2] cycloaddition of a variety of dipoles including trimethylenemethane (eq 3),[4] azomethine ylide (eq 4),[5] and nitrone (eq 5)[6] proceed *endo* stereoselectively with retention of alkene geometry.

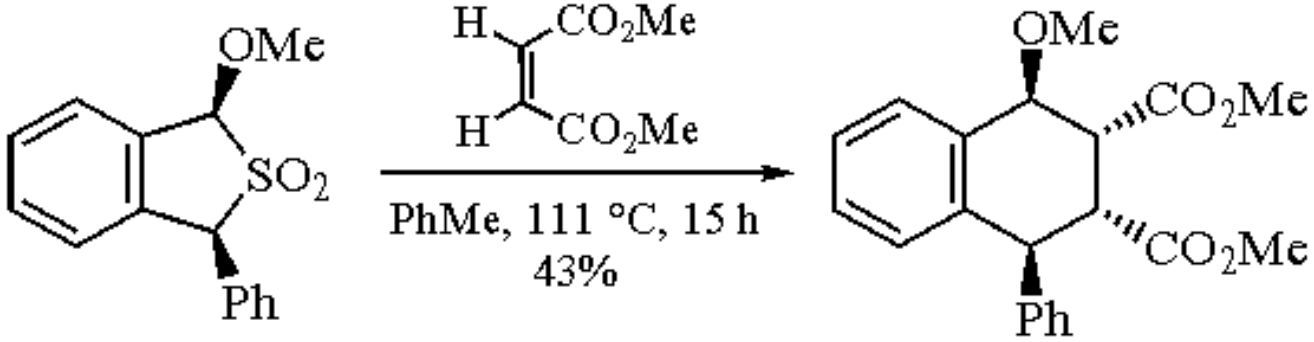
OMe
SO2
Ph
H
CO2Me
H
CO2Me
PhMe, 111 °C, 15 h
43%
OMe
CO2Me
CO2Me
Ph

(1)

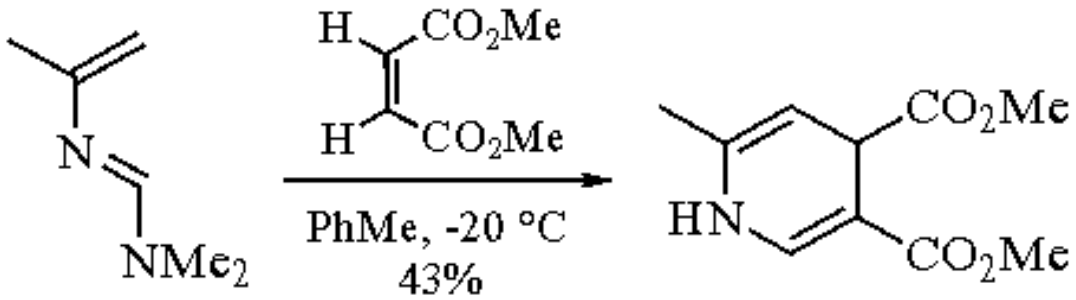
N
NMe2
H
CO2Me
H
CO2Me
PhMe, -20 °C
43%
CO2Me
HN
CO2Me

(2)

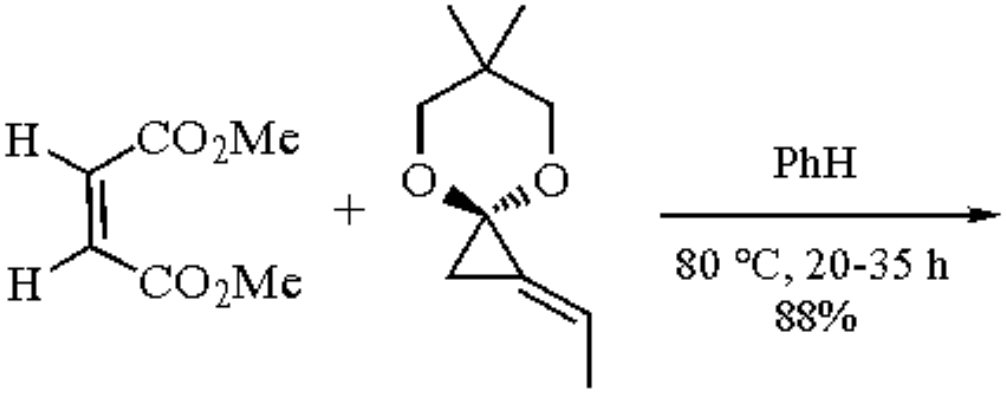
H
CO2Me
H
CO2Me
+
O
O
PhH
80 °C, 20-35 h
88%

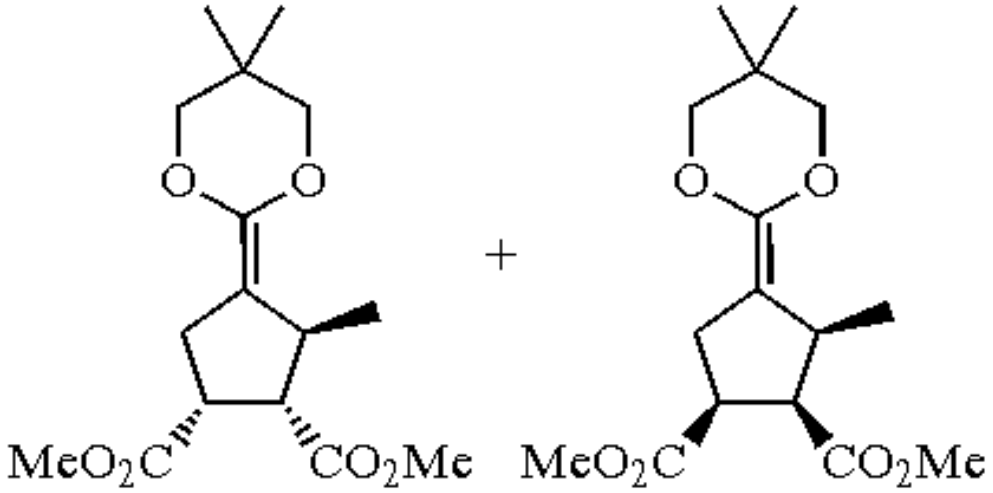
O
O
MeO2C
CO2Me
+
O
O
MeO2C
CO2Me

95:5

(3)

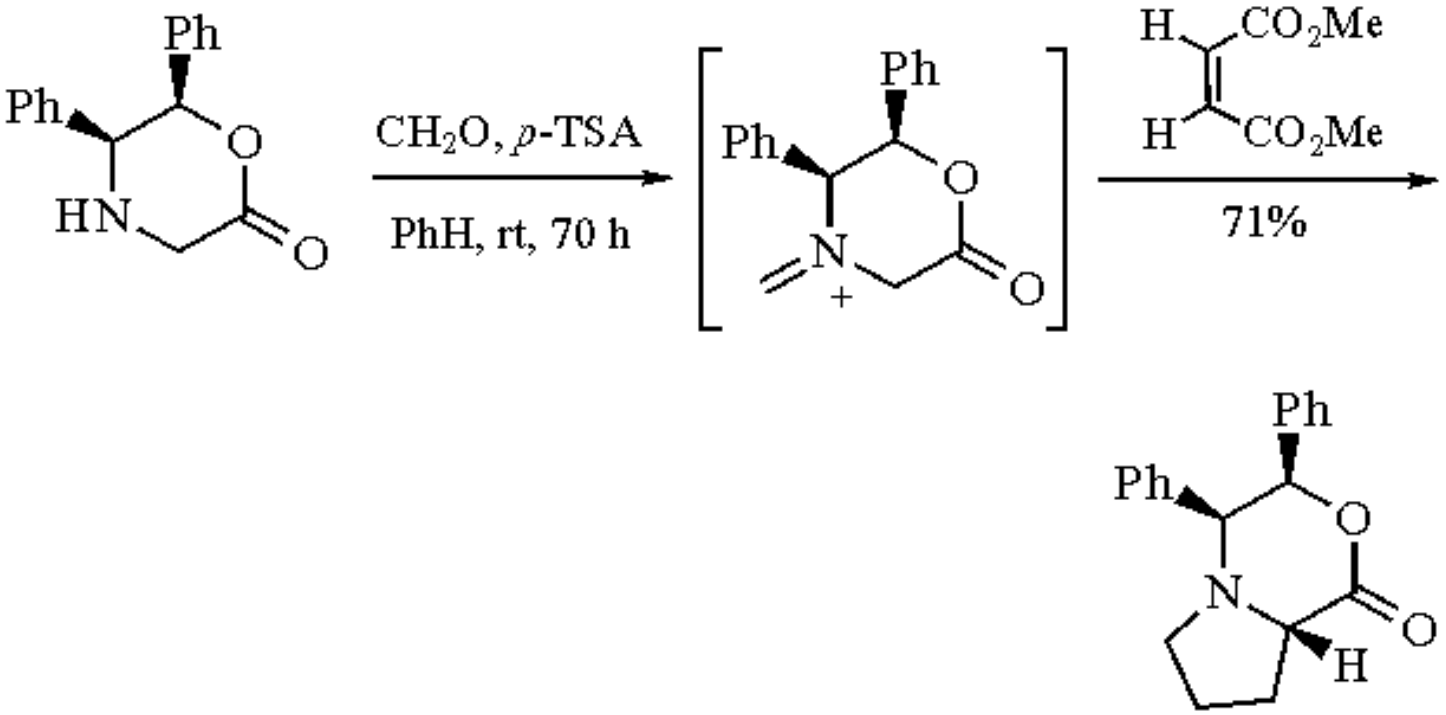

(4)

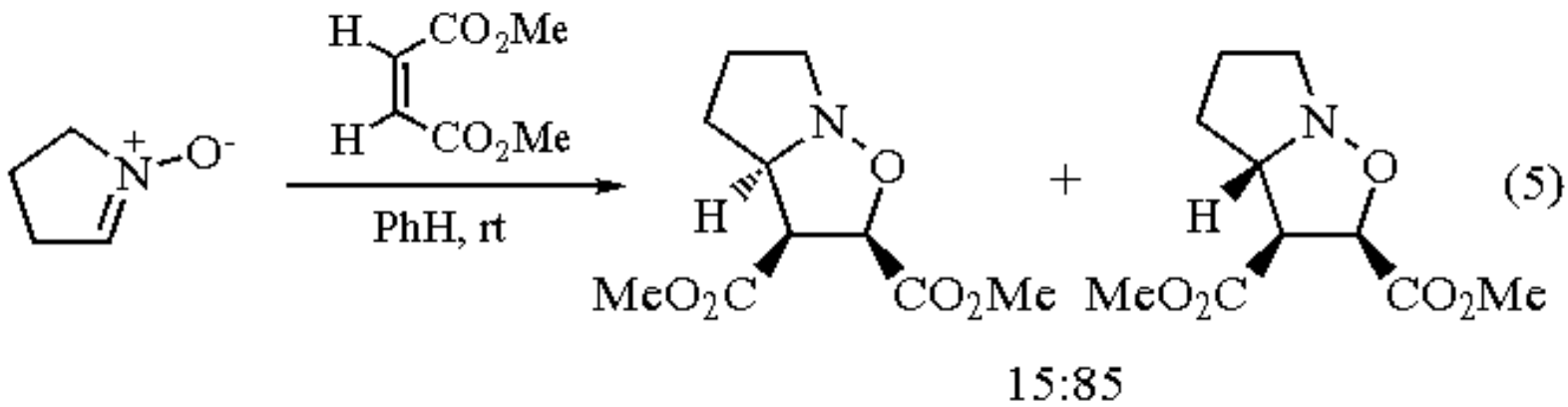

(5)

The photochemical[7] and thermal[8] cycloadditions of dimethyl maleate to alkenes have been examined. Thermal reactions require the use of electron-rich alkenes such as ketene dithioacetals or enamines (eq 6). As expected, the alkene geometry is not retained in either thermal or photochemical [2 + 2] cycloadditions of dimethyl maleate. The photochemical addition of dimethyl maleate proceeds in low chemical yield with poor stereoselectivity.

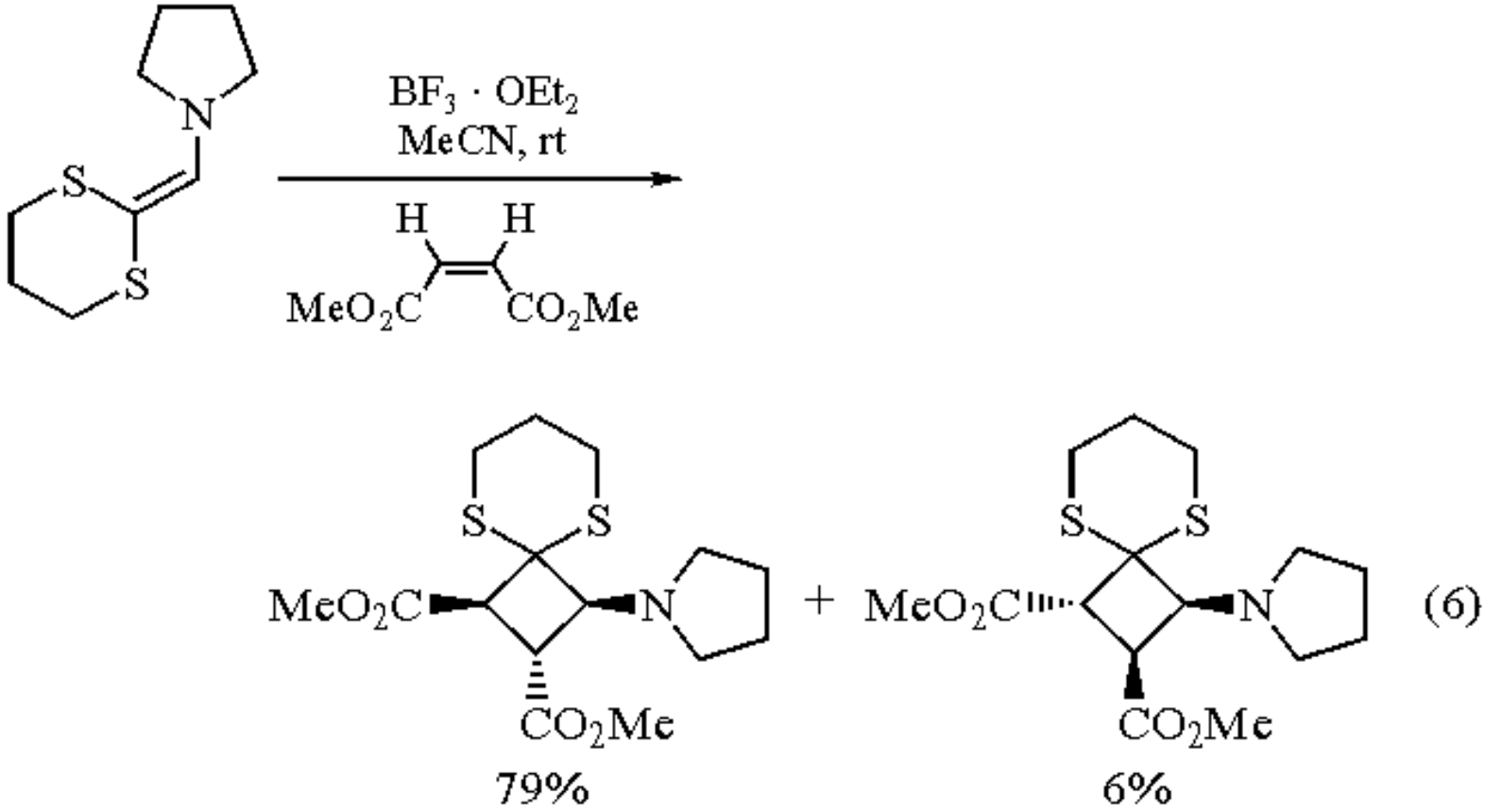

Miscellaneous.

Higher homologs of carbohydrates have been prepared through ***Tri-n-butylstannane-Azobisisobutyronitrile*** induced radical addition to dimethyl maleate (eq 7) (see also ***N-Phenylmaleimide*** and ***Dimethyl Fumarate***).[9] Other electron-deficient alkenes which have been utilized as radical acceptors include ***Acrylonitrile***, ***Methyl Acrylate***, ***Methyl Vinyl Ketone***, and *N*-ethylmaleimide.

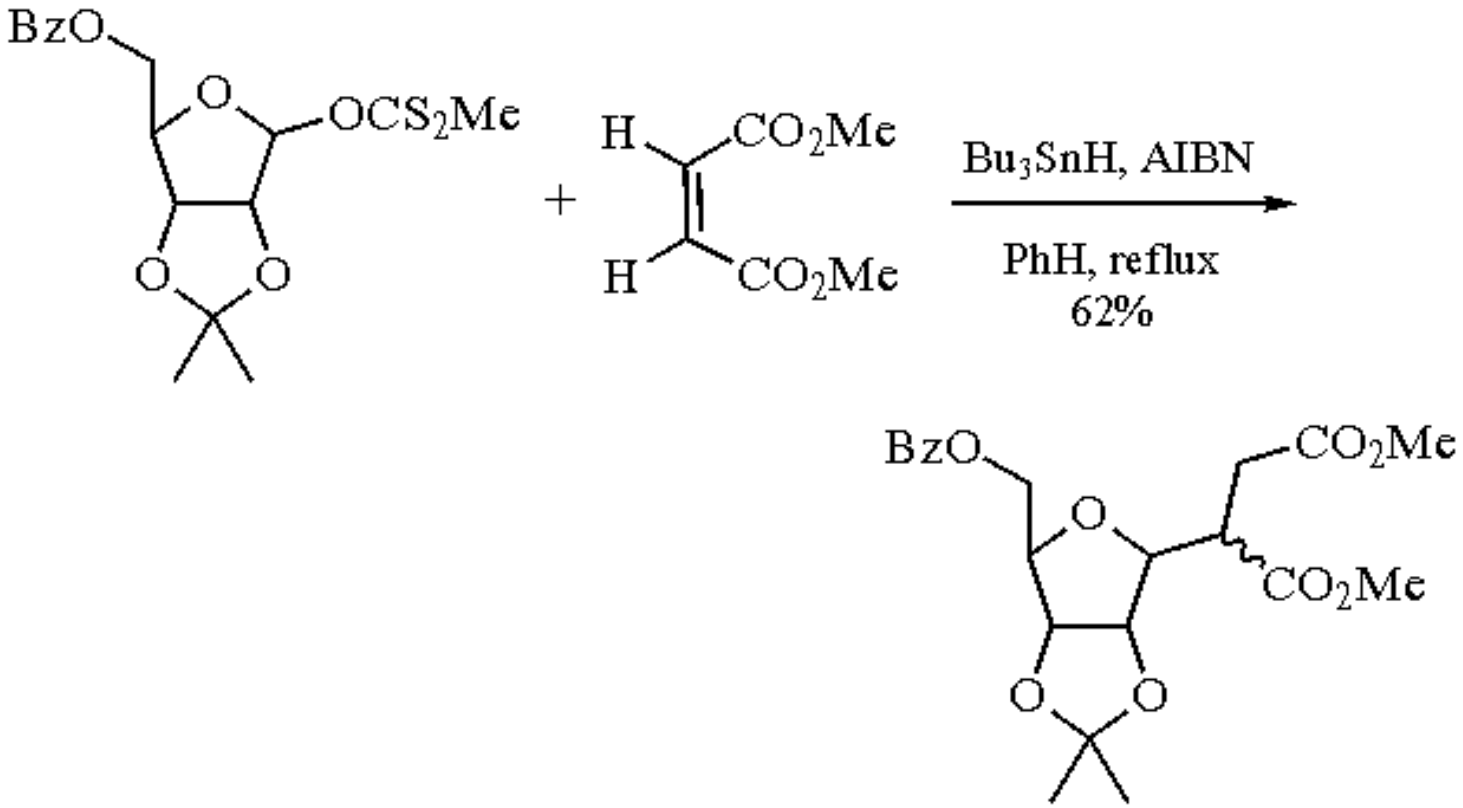

(7)

A useful phosphonate for the preparation of a variety of alkylidenesuccinates by an Emmons-Wadsworth-Horner reaction is prepared by refluxing a mixture of ***Trimethyl Phosphite*** and dimethyl maleate in phenol (eq 8).[10]

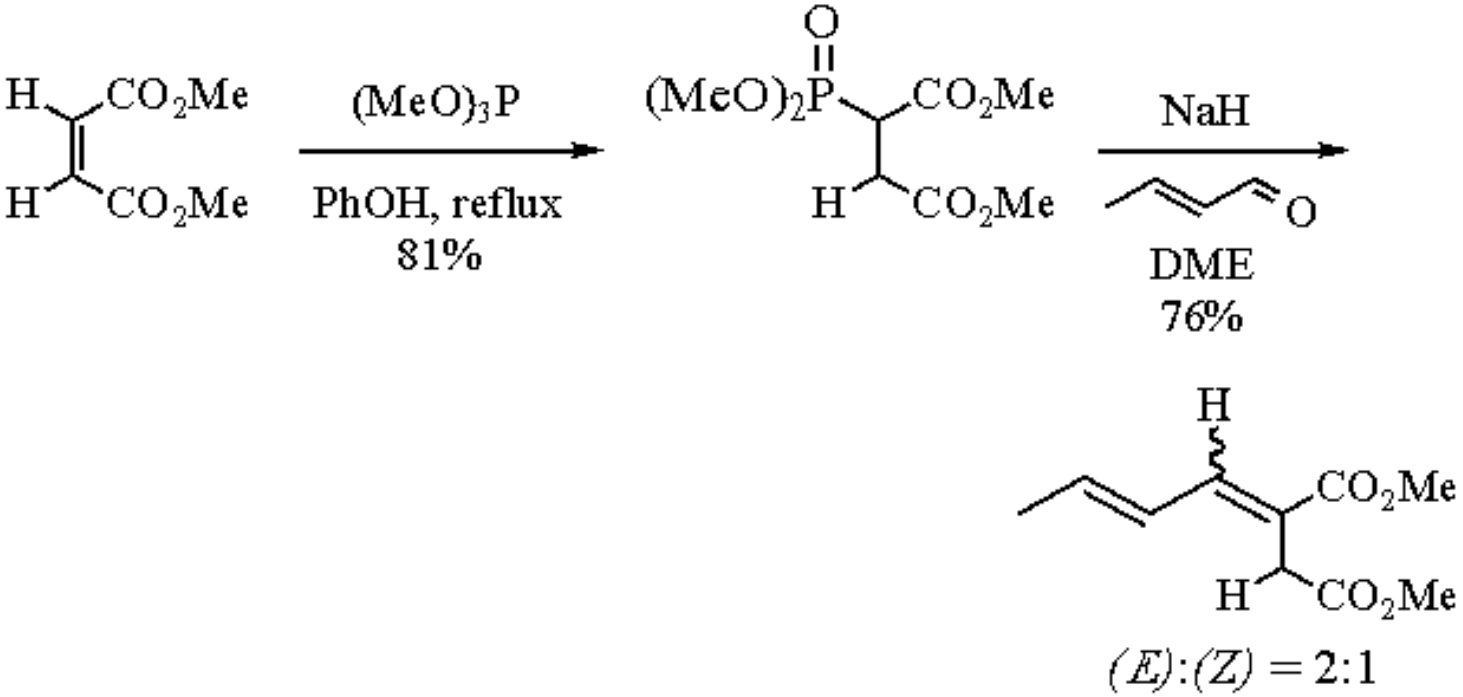

(8)

Related Reagents.

Dimethyl Fumarate.

1. Durst, T.; Kozma, E. C.; Charlton, J. L. *JOC* **1985**, *50*, 4829. (b) Charlton, J. L.; Alauddin, M. M.; Penner, G. H. *CJC* **1986**, *64*, 793. (c) Ito, Y.; Nakatsuka, M.; Saegusa, T. *JACS* **1982**, *104*, 7609.
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7. Goe, G. L. *JOC* **1973**, *38*, 4285.
8. Johnson, C. R.; De Jon, R. *JOC* **1992**, *57*, 594.
9. (a) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *TL* **1988**, *29*, 351. (b) Araki, Y.; Endo, T.; Tanji, M.; Arai, Y.; Ishido, Y. *TL* **1988**, *29*, 2335. (c) Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *TL* **1988**, *29*, 5297. (d) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J. *TL* **1987**, *28*, 5853.
10. (a) Harvey, R. G. *T* **1966**, *22*, 2561. (b) Trost, B. M.; Melvin, L. S. *JACS* **1976**, *98*, 1204.

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Dimethyl(methylene)ammonium Iodide[1]

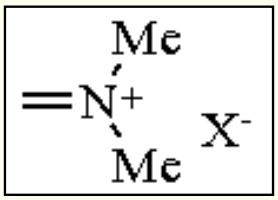

(**1**; X = I^-)

[36627-00-6] · C_3H_8IN · Dimethyl(methylene)ammonium Iodide · (MW 185.02) (**2**; X = Cl^-)

[30438-74-5] · C_3H_8ClN · Dimethyl(methylene)ammonium Chloride · (MW 93.57) (**3**; X = $CF_3CO_2^-$)

[85413-84-9] · $C_5H_8F_3NO_2$ · Dimethyl(methylene)ammonium Trifluoroacetate · (MW 171.14)

(electrophilic aminomethylation (Mannich reaction) agent which condenses with active methylene compounds,[1] organometallic reagents,[2] and electron-rich aromatics and heteroaromatics[3] to produce tertiary amines; useful for the synthesis of α,β-unsaturated carbonyl compounds by elimination of the dimethylamino group[1])

Alternate Names: (**1**) Eschenmoser's salt; (**2**) Böhme's salt.

Physical Data: (**1**) mp 219 °C (dec). (**2**) mp 116 °C. (**3**) bp 100 °C/14 mmHg.

Solubility: sol DMF; partially sol[4] MeCN, CH_2Cl_2, THF (reactions in these solvents occur even though the reagent is not completely soluble).

Form Supplied in: salts (**1**) and (**2**) are widely available as solids.

Preparative Methods: salt (**1**) is prepared by thermolysis of (iodomethyl)trimethylammonium iodide[5] or cleavage of *N,N,N´,N´*-tetramethylmethanediamine by TMSI.[6] It is purified by recrystallization from tetrahydrothiophene dioxide or by sublimation at 120 °C/0.05 mmHg.[5] Salt (**2**) is prepared by cleavage of *N,N,N´,N´*-tetramethylmethanediamine by AcCl[7] or cleavage of methyl dimethylaminomethyl ether by TMSCl.[8] Salt (**3**), a liquid, is prepared by Polonovksi reaction of trimethylamine oxide with TFAA or cleavage of *N,N,N´,N´*-tetramethylmethanediamine with TFA. It is purified by distillation.[9]

Handling, Storage, and Precautions: salts (**1**)-(**3**) are very hygroscopic and must be used under anhydrous conditions to preserve their reactivity.

Dimethyl(methylene)ammonium Salts.

These reagents comprise a special family of preformed iminium salts which have been widely utilized in condensation reactions with active methylene compounds and arenes in a variant of the Mannich reaction. They have their origins in the work of Böhme,[10] who prepared the first dimethyl(methylene)ammonium salt (**2**).[11] Higher concentrations of iminium salts are achieved using salts such as (**1**)-(**3**) than under the conditions of the classical Mannich reaction in which the iminium salt is generated reversibly; hence reactions are faster, proceed under milder conditions, and are more compatible with sensitive functionality. Preformed iminium salts are sufficiently soluble in many aprotic solvents, enabling the use of highly reactive nucleophiles which would ordinarily decompose under the protic conditions of the classical Mannich reaction. Moreover, salts (**1**)-(**3**) have special applications as one-carbon synthons for an *exo* methylene group, owing to the leaving group ability of the dimethylamino group on subsequent quaternization. In addition to the iodide salt (**1**), the chloride (**2**) and trifluoroacetate (**3**) have been increasingly utilized in recent years and are essentially equivalent Mannich reagents. In choosing a particular counterion form, factors such as solubility, ease of preparation and purification, and moisture sensitivity should be considered. A comparison study of the three reagents[12a] favors the trifluoroacetate (**3**) because it is the most soluble and can be transferred by syringe, although it is more tedious to prepare. Several other counterion forms have been prepared by anion exchange of the chloride but have had minimal synthetic applications.[10,13]

Reactions with Active Methylene Compounds and their Derivatives.

Active methylene compounds with acidity comparable to or greater than that of a simple ketone or aldehyde condense directly and without prior activation with salts (**1**)-(**3**) in aprotic solvents to produce Mannich bases. Reaction conditions vary depending on the acidity of the substrate and may employ elevated temperatures and base additives to promote enolization. A comparison study finds that ketone Mannich bases are obtained in generally higher yields using salt (**2**) than under the conditions of the classical Mannich reaction, especially in the case of sterically crowded and α,β-unsaturated ketones.[7] For example, α-methylpropiophenone reacts with (**2**) to produce the corresponding Mannich base in 53% yield (eq 1), whereas under the classical conditions the yield is only 6%. Other ketone substrates reported to react with salts (**1**)-(**3**) in a superior manner to the classical Mannich reaction include chromanones,[14] thiochromanones,[14] and 1*H*-pyrido[3,2,1-*k*]phenothiazin-3(2*H*)-ones.[15] The regiochemistry of the reactions of unsymmetrical methyl ketones with salt (**3**) in TFA has been studied.[16] Under kinetic control, attack at the more substituted enol predominates in parallel to the classical Mannich reaction[17] to give the more substituted Mannich base, while under thermodynamic control reversibility favors the less substituted Mannich base (eq 2).[18] In addition to simple ketones and aldehydes, other classes of active methylene compounds known to react in this variant of the Mannich reaction include 2*H*-benzo[*b*]furan-3-ones,[19] 2*H*-benzo[*b*]thiophen-3-ones,[19] 1,3-dithian-5-ones,[20] α-methylene-β-diketones,[21] β-diketones,[22] malonates,[6,23-25] α-diazo ketones,[26] and *N*,*N*-diphenylglycinate esters.[27] These reactions have been used in the modification of natural products such as steroids,[9] hydrocodone,[28] oxycodone,[28] and spectinomycin.[26]

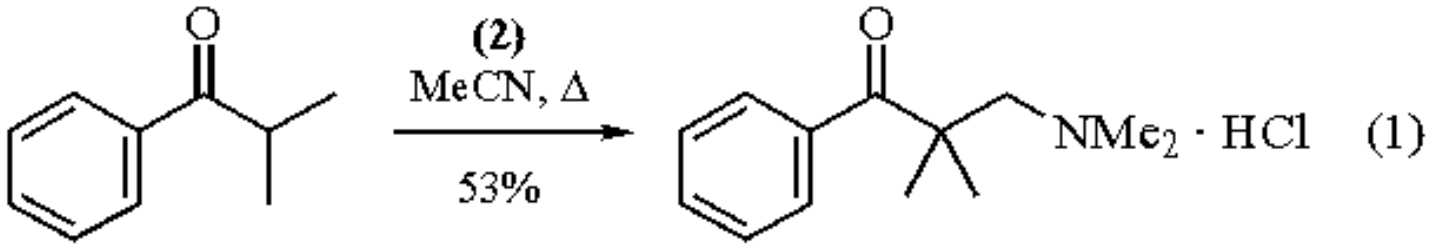

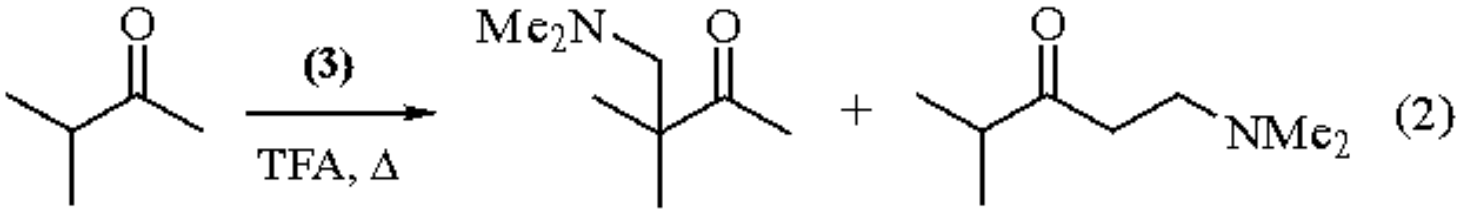

Temp		
72 °C	77%	16%
145 °C	-	55%

Preformed kinetic enolates undergo alkylation with salts (**1**)-(**3**), extending the scope of the Mannich reaction to weakly acidic active methylene components such as esters (eq 3),[12b,29,30] lactones,[12b,29,31-34] unsaturated lactones,[35] carboxylic acids,[12b] and nitriles.[36] Because of their enhanced nucleophilicity, enolates are able to add under extremely mild conditions (-78 °C to rt). Moreover, in the case of unsymmetrical ketones, predictable regiocontrol can be achieved if the enolate is prepared regiospecifically. Enolates used in these reactions have generally been prepared by deprotonation with strong bases such as ***Lithium Diisopropylamide***[29-35] or ***Potassium Hydride***,[12,29] cleavage of silyl enol ethers[12b] or enol carbonates[37] with ***Methyllithium***, or by decomposition of α-diazo ketones in the presence of trialkylboranes to generate the corresponding boron enolate.[38] The latter method, which reliably generates ketone enolates regiospecifically, is excellent for the regiospecific synthesis of Mannich bases derived from simple unsymmetrical ketones (eq 4). Also, ester enolates generated by cleavage of cyclopropyl esters in the presence of ***Trimethylsilyl Trifluoromethanesulfonate*** add to salt (**2**).[39]

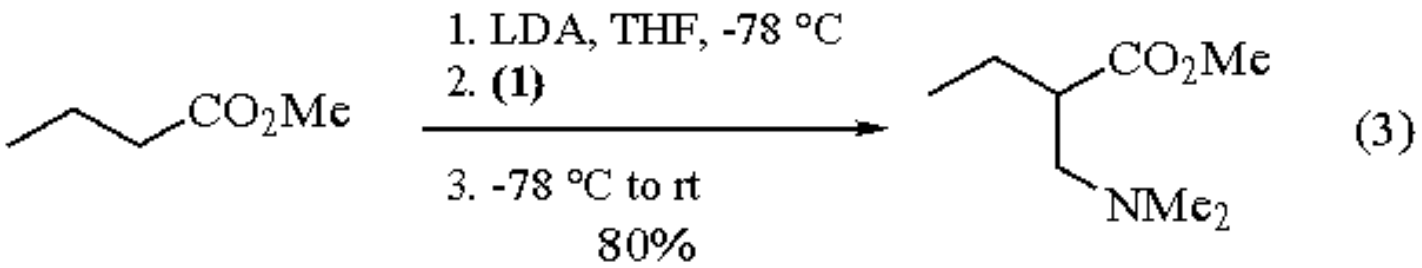

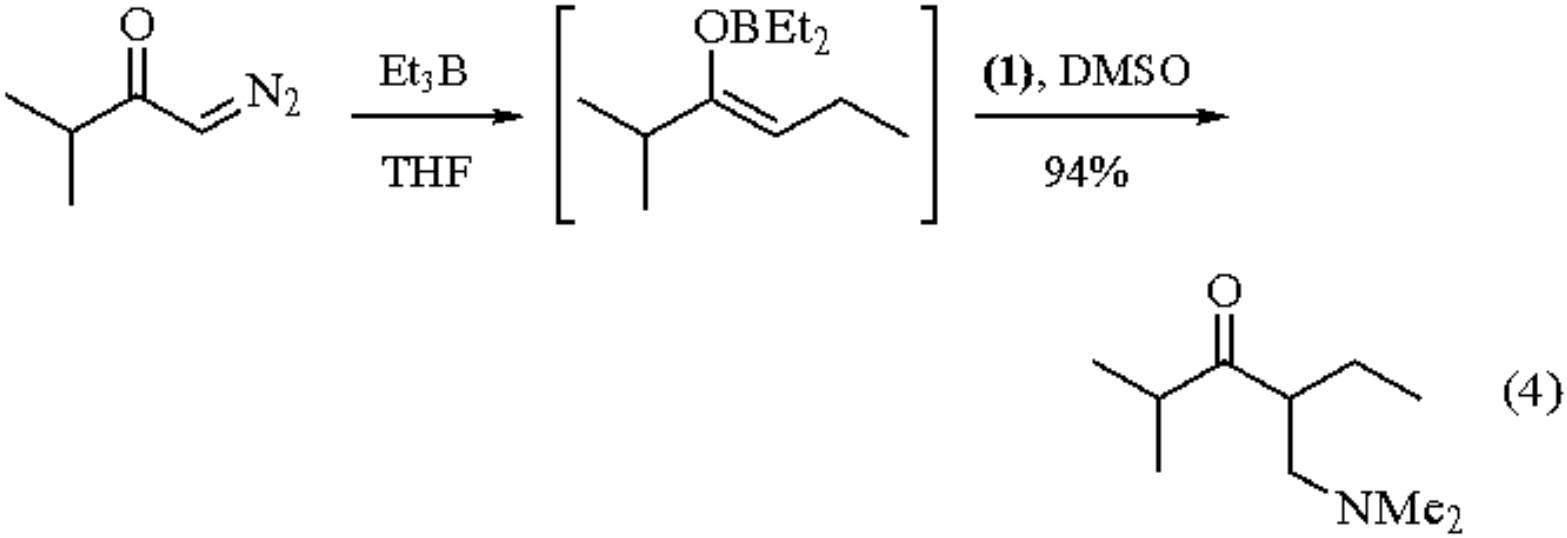

Trimethylsilyl enol ethers derived from ketones and aldehydes add to salts (**1**)-(**3**) in a complementary fashion to enolates.[12a,32] The reaction proceeds via a silyloxonium ion which hydrolyzes on aqueous workup (eq 5). This method has been used for the synthesis of the two regioisomeric Mannich bases of 2-methylcyclohexanone starting from the individual silyl enol ethers[40] and for the synthesis of the *exo* Mannich base of (+)-camphor,[41] which does not undergo aminomethylation under the conditions of the classical Mannich reaction. Chromanone[42] and enone[40,43] trimethylsilyl enol ethers also react. In situ methods for the generation of salt (**1**), involving cleavage of *N*,*N*,*N*´,*N*´-tetramethylmethanediamine by ***Chloroiodomethane***[44] or cleavage of *n*-butyldimethylaminomethyl ether[45] by ***Iodotrimethylsilane***, are also compatible with these reactions and avoid handling the moisture-sensitive reagent (eq 6). In a minor variant of this reaction employing more stable *t*-butyldimethyl silyl enol ethers, the product retains the silyl enol ether following workup with retention or migration of the original position of the enol ether double bond, depending on the substrate (eq 7).[46]

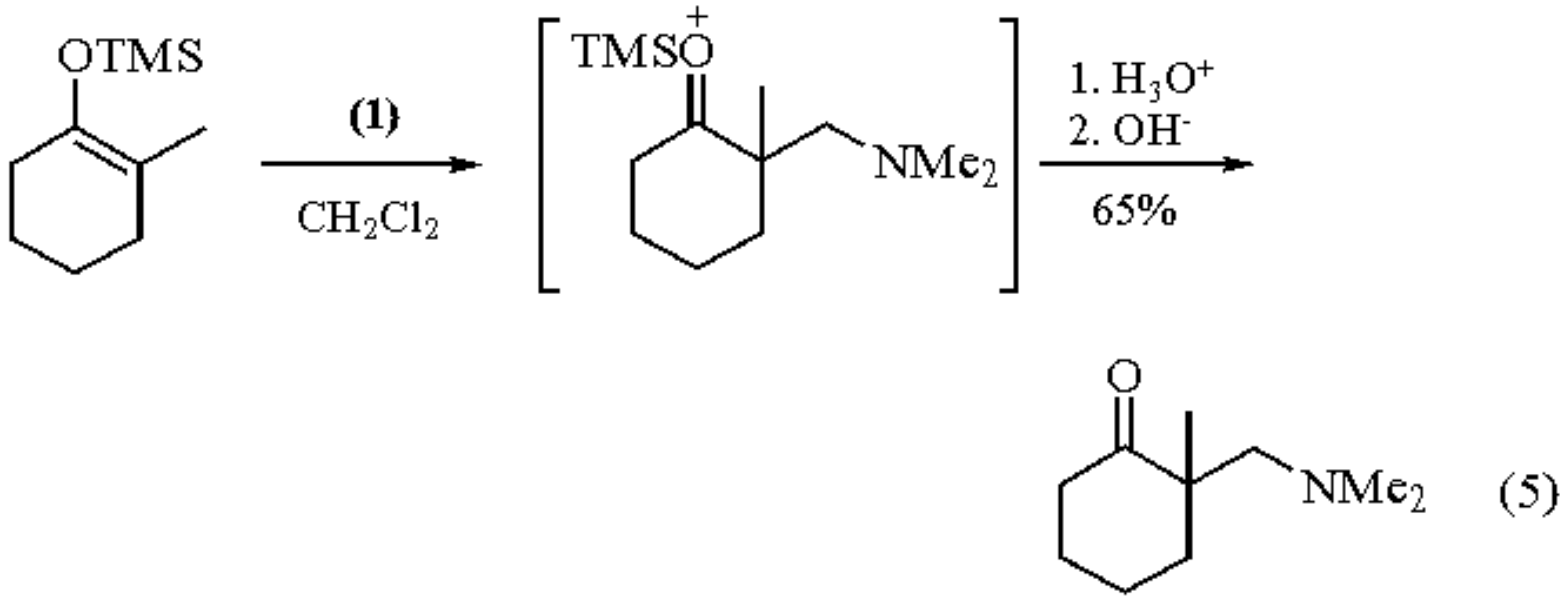

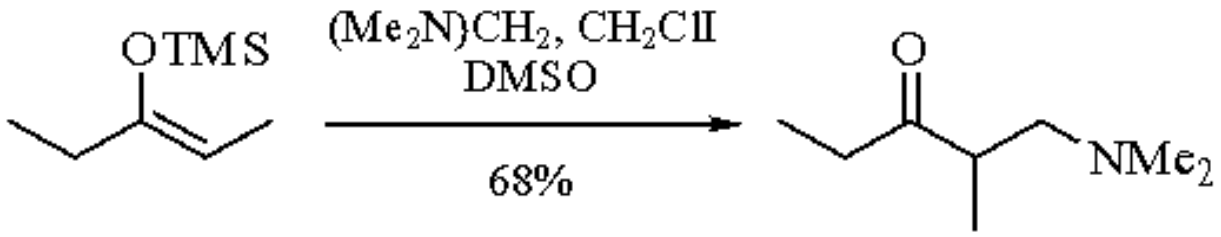

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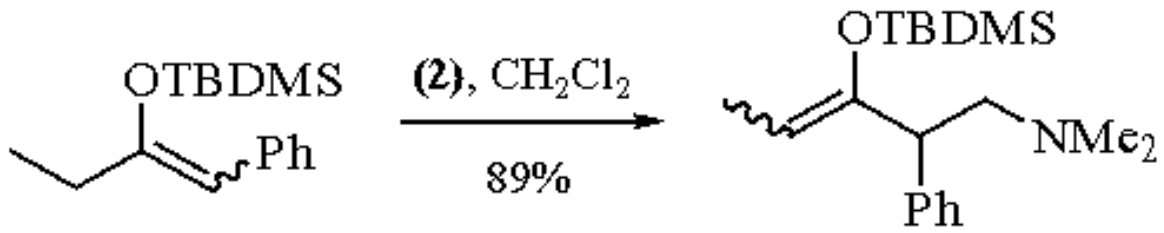

(7)

Reactions with Organometallic Reagents.

In analogy to enolate anion additions, organometallic reagents such as alkyl bromomagnesium and lithium reagents,[2] vinyl and aromatic bromomagnesium reagents,[6] vinylcuprates,[47] and cyclopropyllithiums[48] add to salt (**1**) to produce *N*,*N*-dimethylamines (eq 8). Salt (**1**) is also capable of condensing directly with less nucleophilic organometallic reagents such as 1,4-bis(trimethylstannyl)-2-butyne to afford 2,3-bis(dimethylamino)methyl-1,3-butadiene.[49]

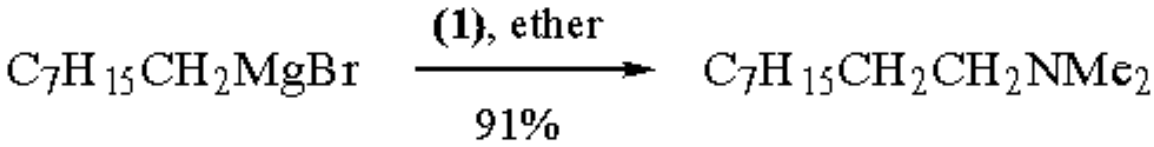

(8)

Synthesis of α,β-Unsaturated Carbonyl Compounds and Terminal Alkenes.

Salts (**1**)-(**3**) serve as excellent one-carbon units for an α-methylene group, since the dimethylamino group of the derived Mannich base can be easily eliminated by quaternization with ***Iodomethane*** followed by treatment with base (eq 9). Active methylene compounds that have been converted to their α-methylene derivatives by this method include esters,[27,29,30,39] lactones,[29,32-34,50] and ketones.[37,51] Similarly, γ-methylene enones,[40] and γ-methylene butenolides[35] have been prepared from their respective Mannich bases. Quaternary ammonium salts from Mannich bases of α-alkoxymalonates[23,52] and α-alkoxy-α-methoxycarbonyl lactones[24] undergo base or thermal fragmentation to provide enolpyruvates for the synthesis of chorismic acid and related natural products (eq 10). Mannich base hydrochlorides derived from β-diketones and salt (**2**) undergo spontaneous elimination by addition of water to give enediones.[22] Tertiary amines derived from the addition of organometallic reagents to salts (**1**)-(**3**) can also be converted to terminal alkenes by thermolysis of the corresponding *N*-oxides.[2]

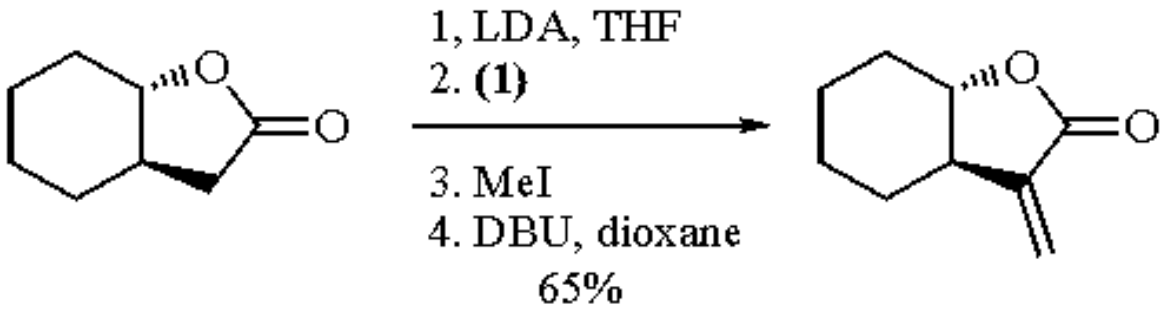

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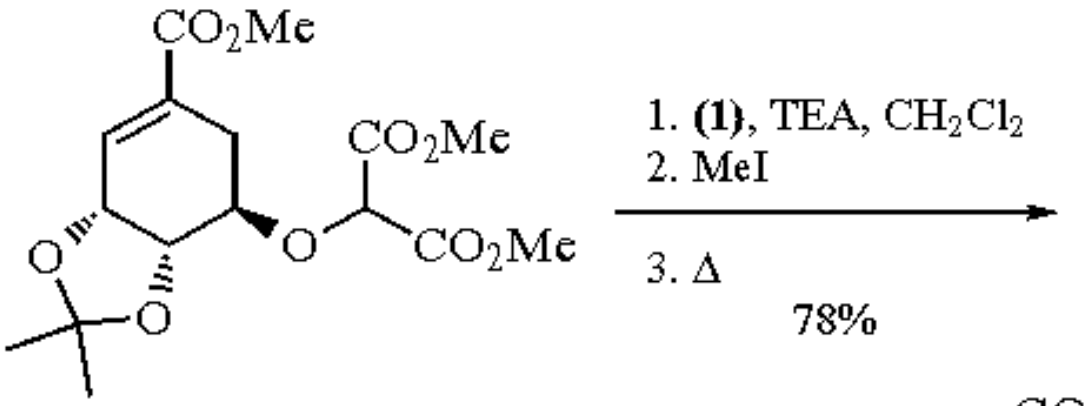

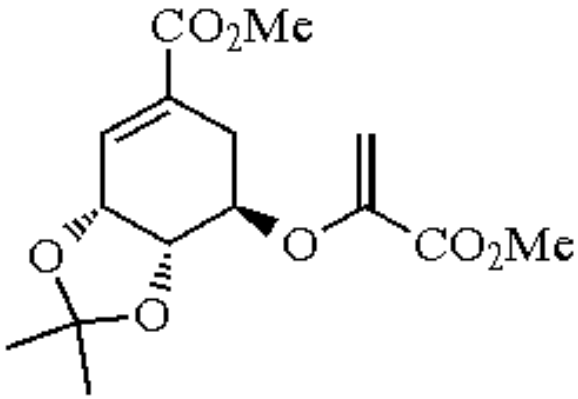

(10)

Reactions with Aromatic Compounds.

Several electron-rich aromatic and heteroaromatic systems have been shown to undergo condensation reactions with salts (**1**)-(**3**) with improved yields and regiocontrol over the conventional method. Monosubstituted phenols, which typically give mixtures of *ortho*, *para*, and diaminomethylated products under conventional conditions, react with salt (**1**) or (**2**) in the presence of ***Potassium Carbonate*** to afford the corresponding *ortho*-substituted Mannich base in high yield (eq 11).[53] An ion pair interaction between the phenoxide anion and the iminium salt is believed to be responsible for the directing effect. This reaction is also successful with deactivating groups in the *para* position. 2,3-Dimethylphenol,[54] 1-naphthol,[55] and 2-methyl-1-naphthol[56] also react in a superior manner with respect to yield and regiospecificity by simple treatment with salts (**1**) or (**2**) in aprotic solvents. In the case of 1-naphthol derivatives, 4-substituted Mannich bases mainly result. The reaction has been exploited for the preparation of aminomethylated derivatives of papulacandin A, a resorcinol-containing antibiotic,[57] and 4,4´- and 3,3´-dihydroxy-α,β-diethylstilbenes.[58] Among heterocyclic systems, salt (**2**) has been used to effect aminomethylation at the 2-position of furan[59] and thiophene,[60] the 3-position of 4-substituted indoles,[61-63] the 8-position of a 2,3-dihydro-5(1*H*)-indolizinone derivative,[64] and the 5-position of a 1,4-dihydropyridine derivative.[65] The cases of furan and thiophene are noteworthy, since they fail or condense poorly in the classical Mannich reaction. In situ methods for the generation of dimethyl(methylene)ammonium species involving cleavage of *N*,*N*,*N´*,*N´*-tetramethylmethanediamine by ***Sulfur***

Dioxide[66] and by chlorosilanes[67] has been investigated in the Mannich reactions of *N*-methylpyrrole, indole, and *N*-methylindole (eq 12). Evidence suggests, however, that free iminium species are not involved in these reactions. An unusual out-of-ring aminomethylation reaction catalyzed by ***Acetyl Chloride*** occurs at the 1-methyl of a 1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine derivative using salt (**2**), generated in situ by cleavage of *N*,*N*,*N*´,*N*´-tetramethylmethanediamine with excess AcCl.[68] In an interesting variant of the Mannich reaction, aryl- and heteroarylstannanes react with salt (**2**) to produce Mannich bases obtained by *ipso*-substitution of the stannyl group.[69] The directing effect of tin allows for the preparation of Mannich bases with substitution patterns not ordinarily obtained in the Mannich reaction, as in the case of 3-(*N*,*N*-dimethylaminomethyl)thiophene (eq 13).

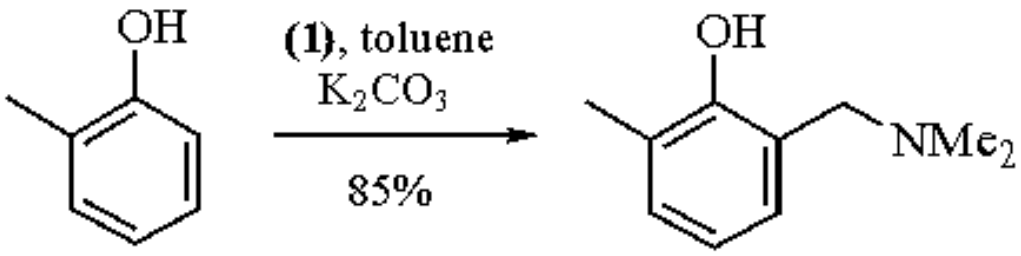

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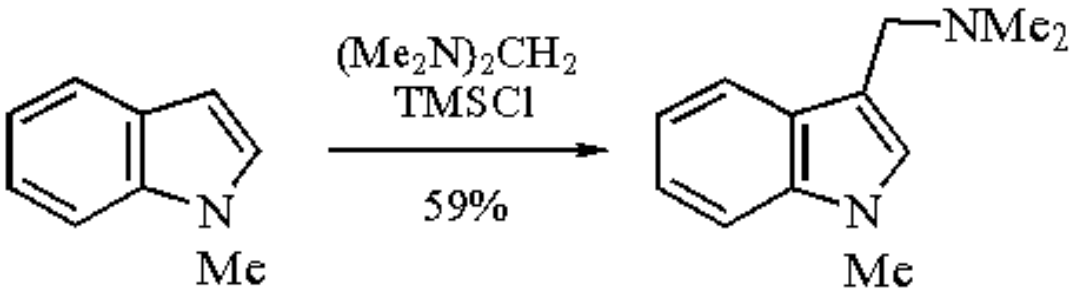

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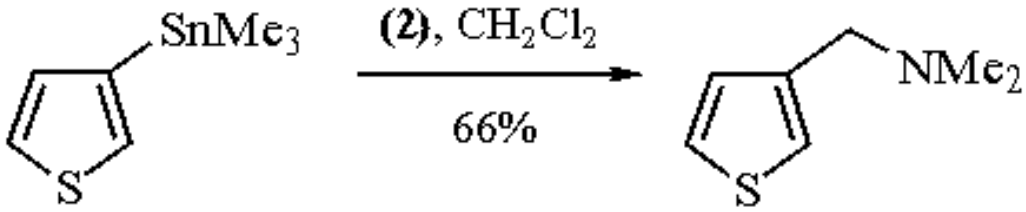

(13)

Heteroatom Addition.

Salt (**2**) undergoes heteroatom addition to amides,[70] phosphoramides,[71] hydrazines,[72] oximes,[73] and secondary phosphines and arsines.[4]

Related Reagents.

(Methylene)ammonium salts containing different *N*-alkyl substitution have been synthesized and undergo similar reactions to those of dimethyl(methylene)ammonium salts.[1,3,10]

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(*S,S*)-2,2´-(Dimethylmethylene)bis(4-*t*-butyl-2-oxazoline)[1]

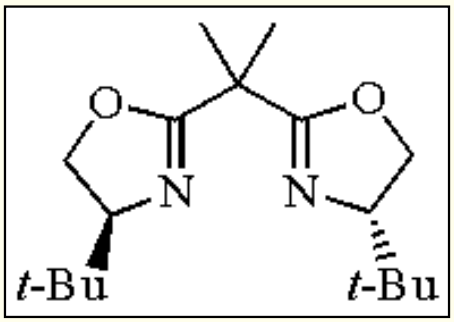

[131833-93-7] · $C_{17}H_{30}N_2O_2$ · (*S,S*)-2,2´-(Dimethylmethylene)bis(4-*t*-butyl-2-oxazoline) · (MW 294.49)

(versatile chiral ligands for enantiocontrol of metal-catalyzed reactions such as copper-catalyzed cyclopropanation[2-5] and aziridination of alkenes,[6] addition of cyanotrimethylsilane to aldehydes,[7] or Lewis acid-catalyzed Diels-Alder reactions[8,9])

Physical Data: mp 88-89 °C; $[\alpha]_D$ -108°; $[\alpha]_{365}$ -394° (*c* 0.97, CH_2Cl_2).

Solubility: insol H_2O; sol all common organic solvents.

Preparative Methods: ligand (**1**) and related C_2-symmetric bisoxazolines are readily prepared from chiral β-amino alcohols using standard methods for the synthesis of 2-oxazolines.[1] This is exemplified by the simple three-step procedure shown in eq 1, involving amide formation, conversion of the resulting bis(2-hydroxyalkyl)amide to the corresponding bis(2-chloroalkyl)amide, and subsequent base-induced cyclization.[3a,4,8a,10,11]

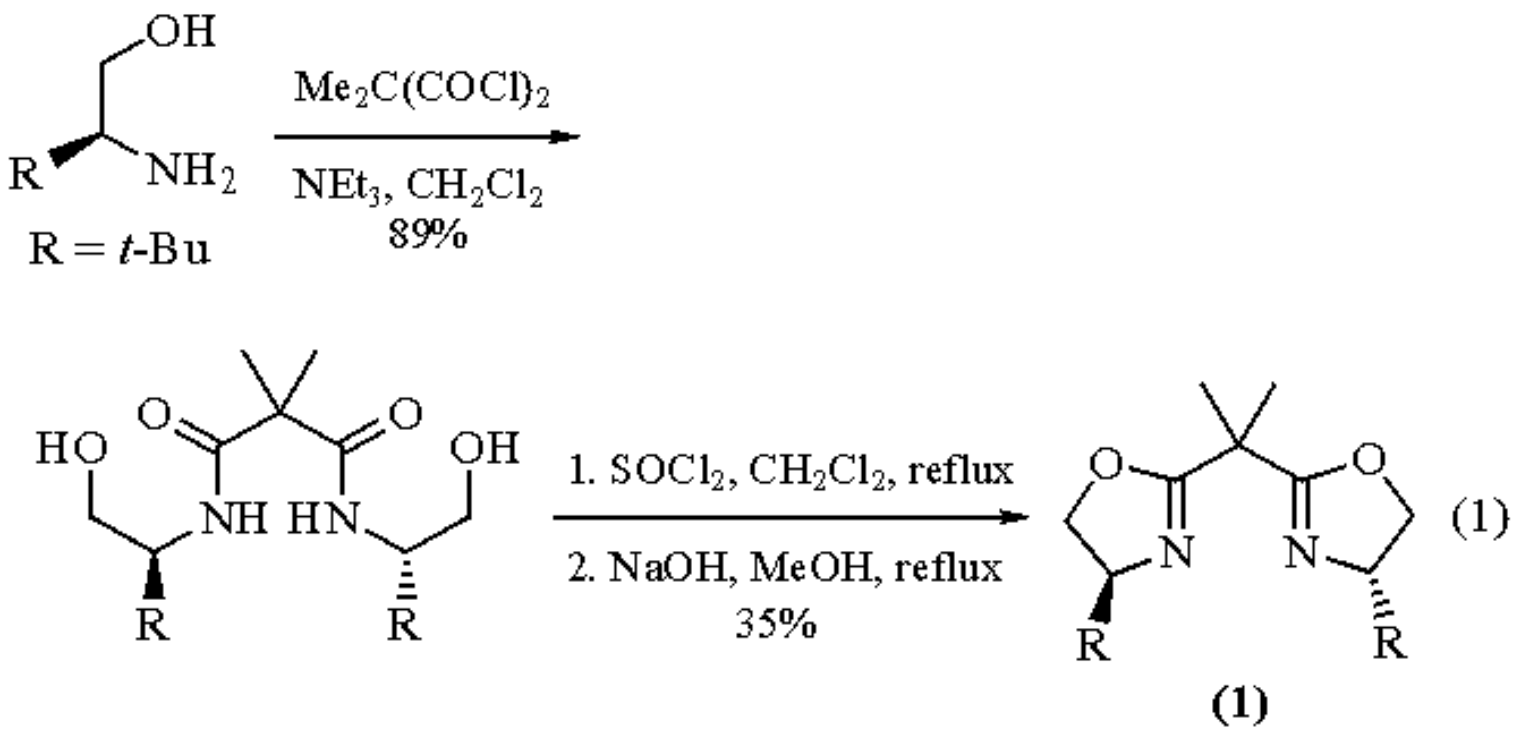

There are several other convenient one- and two-step syntheses leading to enantiomerically pure bisoxazolines, e.g. condensation of amino alcohols with dicarboxylic acids,[2,7] dinitriles,[10a,12] or diimino esters[4,10,13] (cf. eq 2),[4,10a] or acid-catalyzed cyclization of (2-hydroxyalkyl)amides.[8b] By these methods, various types of differently substituted bisoxazoline ligands are readily available in both enantiomeric forms, often in high overall yield.

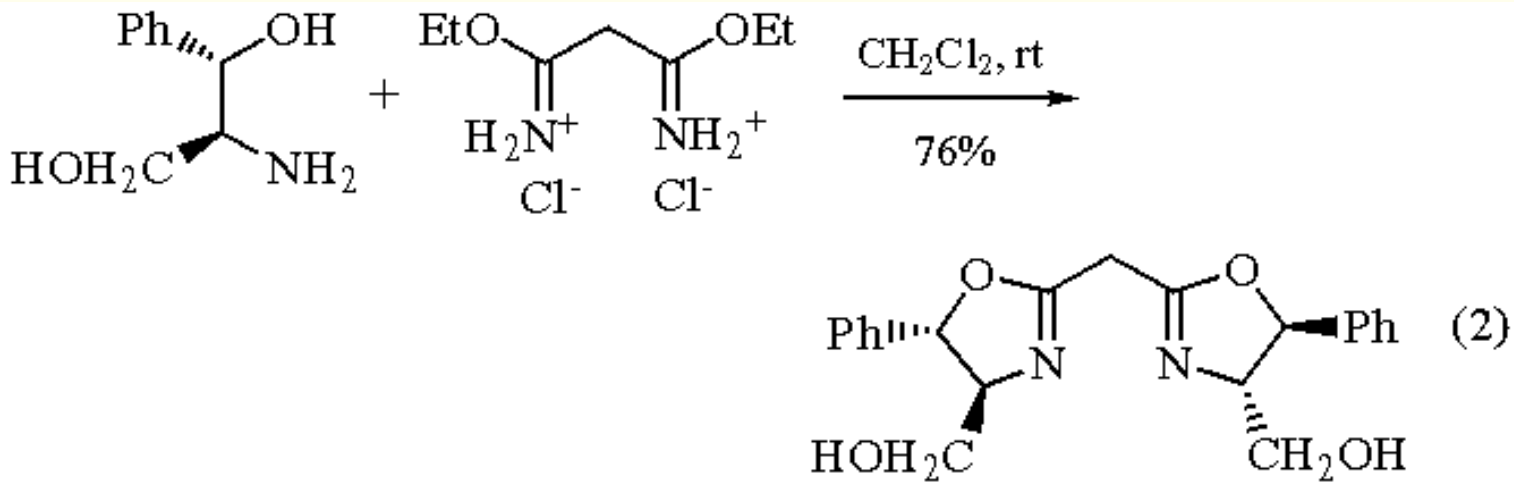

Purification: (**1**) can be purified by column chromatography (silica gel, hexane/EtOAc 7:3) and by recrystallization from pentane.

Handling, Storage, and Precautions: as a crystalline solid, (**1**) is stable at ambient temperature; for longer periods, storage at -20 °C is recommended.

C_2-Symmetric Bisoxazolines as Ligands in Asymmetric Catalysis.

Methylenebis(oxazolines) such as (**1**), (**3**), and (**5**) are patterned after the semicorrins,[1] which have been successfully employed as ligands in enantioselective Cu-catalyzed cyclopropanations and other reactions (see ***(1S,9S)-1,9-Bis{[(t-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin***). The potential of bisoxazoline ligands of this type, which has been recognized independently by a number of research groups,[1-11,13-15] is demonstrated by a remarkable variety of different applications in asymmetric catalysis.

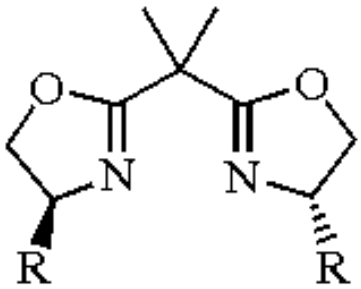

(1) R = *t*-Bu
(2) R = Ph

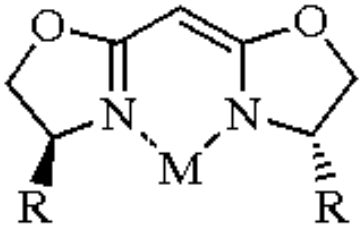

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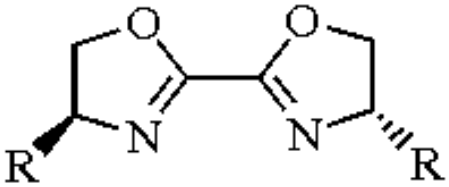

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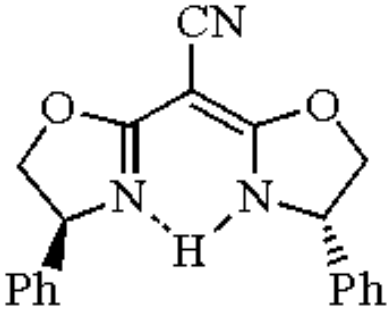

(5)

The short and simple syntheses of these compounds and the ease of modifying their structures make them ideal ligands for the stereocontrol of metal-catalyzed reactions. Using different amino alcohols and dicarboxylic acid derivatives as precursors, the steric and electronic properties, as well as the coordination geometry, can be adjusted to the specific requirements of a particular application. The neutral methylenebis(oxazoline) ligands (**1**) and (**2**), which form six-membered chelate rings, the bioxazolines (**4**), a class of neutral ligands with π-acceptor properties forming five-membered chelate rings, and the anionic methylenebis(oxazolines) of type (**3**) and (**5**) are representative examples.

Enantioselective Cyclopropanation of Alkenes.

Cationic Cu^{I} complexes of methylenebis(oxazolines) such as (**1**), which have been developed by Evans and co-workers,[3] are remarkably efficient catalysts for the cyclopropanation of terminal alkenes with diazoacetates. The reaction of styrene with ethyl diazoacetate in the presence of 1 mol % of catalyst, generated in situ from ***Copper(I) Trifluoromethanesulfonate*** and ligand (**1**), affords the *trans*-2-phenylcyclopropanecarboxylate in good yield and with 99% ee (eq 3). As with other catalysts, only moderate *trans*/*cis* selectivity is observed. Higher *trans*/*cis* selectivities can be obtained with more bulky esters such as 2,6-di-*t*-butyl-4-methylphenyl[3] or dicyclohexylmethyl diazoacetate[5] (94:6 and 95:5, respectively). The efficiency of this catalyst system is illustrated by the cyclopropanation of isobutene, which has been carried out on a 0.3 molar scale using 0.1 mol % of catalyst derived from the (*R*,*R*)-enantiomer of ligand (**1**) (eq 4).[3] The remarkable selectivity of >99% ee exceeds that of Aratani's catalyst[16] which is used in this reaction on an industrial scale.

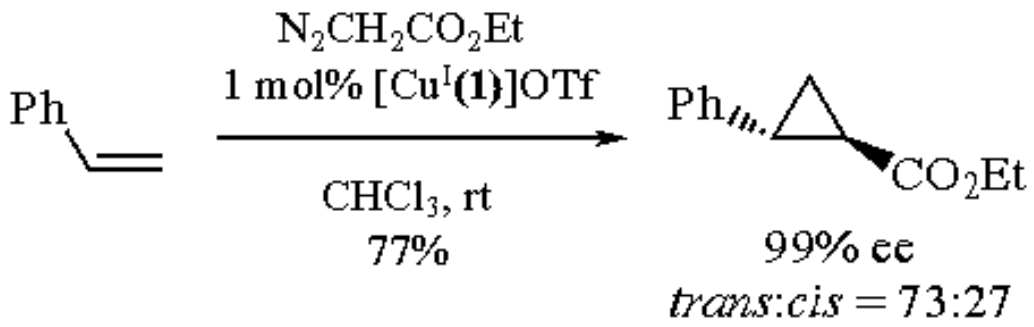

(3)

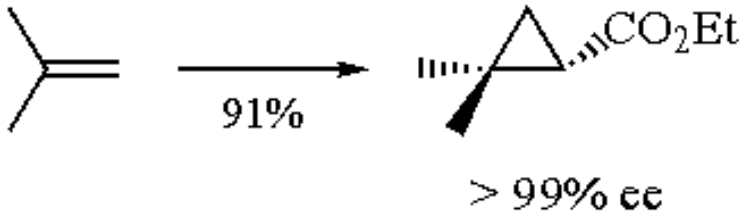

(4)

For the cyclopropanation of terminal mono- and disubstituted alkenes, the cationic Cu^I complex derived from ligand (**1**) is clearly the most efficient catalyst available today, giving consistently higher enantiomeric excesses than related neutral semicorrin[1,17] or bisoxazoline Cu^I complexes of type (**3**),[1,2,4] which can induce enantiomeric excesses of up to 92% ee in the cyclopropanation of styrene with ethyl diazoacetate. High enantioselectivities, ranging between the selectivities of the Evans catalyst (eq 3) and complex (**3**) (M = Cu^I, R = *t*-Bu), have also been observed with cationic Cu^I complexes of azasemicorrins.[1,10a,18]

For analogous cyclopropanation reactions of trisubstituted and 1,2-disubstituted (*Z*)-alkenes, ligand (**1**) is less well suited. In these cases, better results have been obtained with the bisoxazoline ligand (**6**).[5] This is illustrated by the enantioselective cyclopropanation of 1,5-dimethyl-2,4-hexadiene, leading to chrysanthemates (eq 5).[5] The enantioselectivity in this reaction is comparable to the best results reported for Aratani's catalyst.[16] Ligand (**6**) has also been reported to induce high enantiomeric excesses in the cyclopropanation of (*Z*)-4,4-dimethyl-2-pentene, (*Z*)-1-phenylpropene, and 1,1-dichloro-4-methyl-1,3-pentadiene with (-)-menthyl diazoacetate (92-95% ee).[5] A mechanistic model rationalizing the stereoselectivity of Cu catalysts of this type has been published;[17] a comparison of different cyclopropanation catalysts is also available.[19]

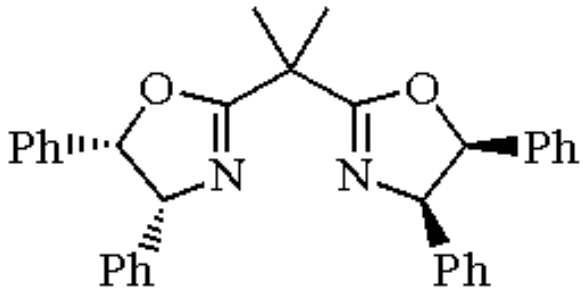

(6)

(S,S)-2,2´-(Dimethylmethylene)bis(4-t-butyl-2-oxazoline)

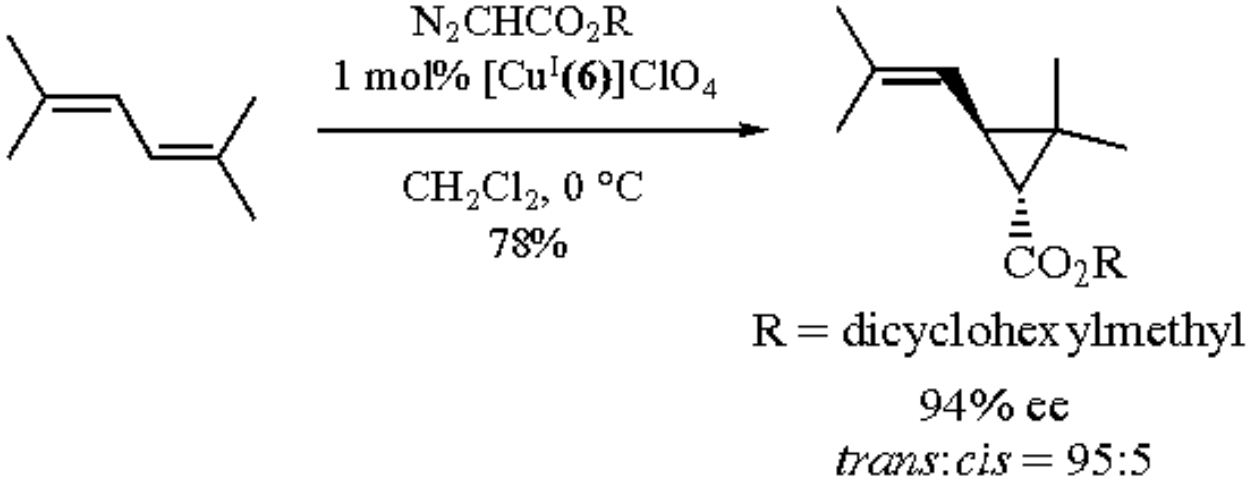

(5)

Enantioselective Aziridination of Alkenes.

Copper complexes with neutral methylenebis(oxazoline) ligands (**1**) and (**2**) have also been employed as enantioselective catalysts for the reaction of alkenes with (*N*-tosylimino)phenyliodinane, leading to *N*-tosylaziridines.[6] The best results have been reported for cinnamate esters as substrates, using 5 mol % of catalyst prepared from CuOTf and the phenyl-substituted ligand (**2**) (eq 6). The highest enantiomeric excesses are obtained in benzene, whereas in more polar and Lewis basic solvents, such as acetonitrile, the selectivities are markedly lower. The chemical yield can be substantially improved by addition of 4Å molecular sieves. Both Cu^{I}- and Cu^{II}-bisoxazoline complexes, prepared from Cu^{I} or Cu^{II} triflate, respectively, are active catalysts, giving similar results. In contrast to the Cu-catalyzed cyclopropanation reactions discussed above, in which only Cu^{I} complexes are catalytically active, here Cu^{II} complexes are postulated as the actual catalysts.[6]

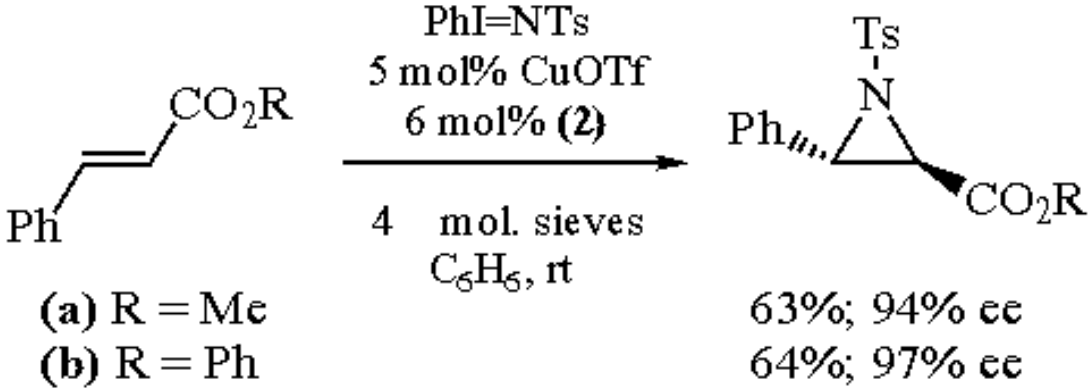

(6)

Analogous naphthylacrylates also react with excellent enantioselectivity under these conditions. Styrene and (*E*)-β-methylstyrene afford the corresponding *N*-tosylaziridines with 63 and 70% ee, respectively. For these two substrates, the *t*-butyl-substituted bisoxazoline (**1**) rather than (**2**) proved to be the most effective ligand.

Similarly high enantioselectivities in aziridination reactions of this type have been reported for Cu catalysts with C_2-symmetric diimine ligands, derived from 1,2-diaminocyclohexane and aromatic aldehydes.[20] The best results in this case have been obtained with 7-cyano-2,2-dimethylchromene as substrate (>98% ee). At present, it is difficult to compare the diimine-based with the bisoxazoline-based catalysts because different substrates were examined in these studies, with the exception of styrene which gave very similar results with the two catalysts (66 and 63% ee, respectively).[20,6] Thus further work will be necessary to establish the full scope of these promising catalyst systems.

Enantioselective Diels-Alder Reactions.

Methylenebis(oxazoline) complexes of Fe^{III}, Mg^{II}, and more recently also Cu^{II}, have been successfully employed as enantioselective Lewis acid catalysts in Diels-Alder reactions.[8,9] The most promising results have been obtained with Cu^{II} catalysts prepared from ligand (**1**) and ***Copper(II) Trifluoromethanesulfonate*** (eq 7).[9] In the presence of 10 mol % of catalyst in CH_2Cl_2 at -78 °C, acrylimide (**7a**) smoothly reacts with cyclopentadiene to afford the Diels-Alder product (**8a**) in 86% yield with excellent enantio and *endo*/*exo* selectivity. The crotonate derivative (**7b**) is less reactive, but at higher temperature also undergoes highly selective cycloaddition with cyclopentadiene. The fumarate (**7c**) gives similar results. In terms of selectivity and efficiency, this catalyst system can compete against the most effective chiral Lewis acid catalysts developed so far.[21]

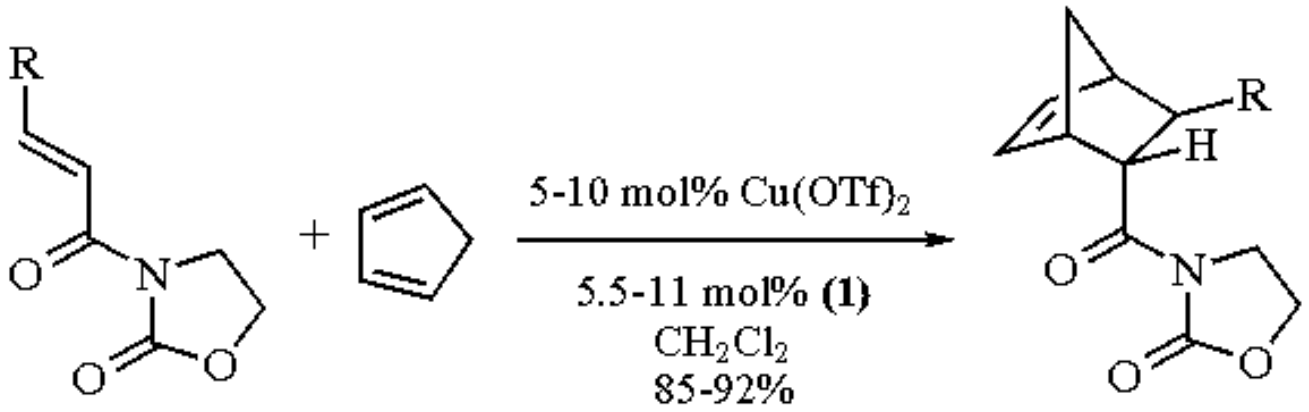

(7) (8)

(a) R = H	-78 °C	>98% ee	*endo*:*exo* = 98:2
(b) R = Me	-15 °C	97% ee	*endo*:*exo* = 96:4
(c) R = CO_2Et	-55 °C	95% ee	*endo*:*exo* = 94:6

The thiazolidine-2-thione analogs of (**7b**) and (**7c**) are more reactive dienophiles and, therefore, the cycloaddition can be carried out at lower temperature. However, the selectivities and yields are similar as with (**7b**) and (**7c**).[9] The corresponding cinnamate derivative (**7**) (R = Ph), on the other hand, reacts with substantially lower enantioselectivity than the corresponding thiazolidine-2-thione analog (90% vs. 97% ee).

The stereochemical course of these reactions has been rationalized assuming a chelate complex between the (bisoxazoline)Cu catalyst and the dienophile as the reactive intermediate, with square planar coordination geometry of the Cu^{II} ion.[9]

Enantioselective Cyanohydrin Formation.

Magnesium complexes formed with the anionic semicorrin-type ligand (**5**) catalyze the addition of ***Cyanotrimethylsilane*** to aldehydes, leading to optically active trimethylsilyl-protected cyanohydrins.[7] In the presence of 20 mol % of the chloromagnesium complex (**9**), prepared from equimolar amounts of (**5**) and BuMgCl, cyclohexanecarbaldehyde is smoothly converted to the corresponding cyanohydrin derivative with 65% ee. Addition of 12 mol % of the bisoxazoline (**10**) results in a dramatic increase of enantioselectivity to 94% ee (eq 8). Replacement of (**10**) by its enantiomer reduces the selectivity to 38% ee. This remarkable effect has been proposed to arise from hydrogen-bond formation between the bisoxazoline (**10**) and HCN, which is generated in small amounts by hydrolysis of Me_3SiCN due to traces of water present

(S,S)-2,2´-(Dimethylmethylene)bis(4-t-butyl-2-oxazoline)

in the reaction mixture. The chiral [(**10**)&dotbond;HCN] aggregate is postulated as the reactive species undergoing nucleophilic addition to the aldehyde which, at the same time, is activated by coordination with the chiral magnesium complex (**9**).

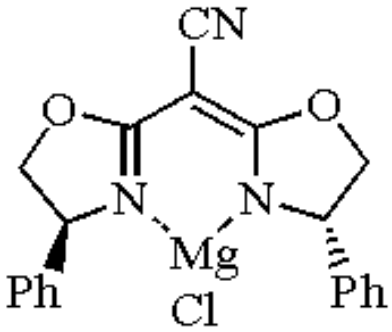

(9)

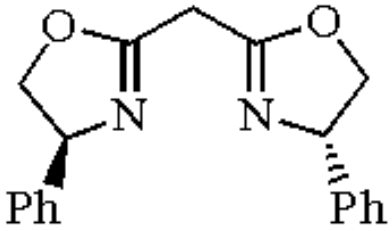

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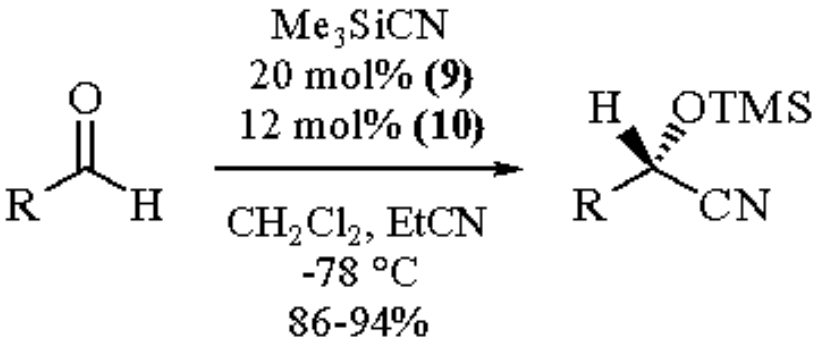

(8)

(a) R = C_6H_{13} 95% ee
(b) R = Et_2CH 91% ee
(c) R = Cy 94% ee

Heptanal, 2-ethylbutanal, and pivalaldehyde react with similarly high enantioselectivities, whereas benzaldehyde (52% ee) and certain α,β-unsaturated aldehydes such as geranial (63% ee) afford considerably lower enantiomeric excesses. Most other catalysts used for the addition of HCN or Me_3SiCN to aldehydes usually exhibit higher enantioselectivities with aromatic or α,β-unsaturated aldehydes than with alkyl carbaldehydes.[22]

Enantioselective Allylic Alkylation.

Most ligands that have been employed in enantioselective Pd-catalyzed allylic substitutions are chiral diphosphines.[23] Recently, it has been found that chiral nitrogen ligands can also induce high enantioselectivities in such reactions.[1,18,24] The best results have been obtained with neutral azasemicorrin and methylenebis(oxazoline) ligands. In the presence of 1-2 mol % of catalyst, generated in situ from ***Bis(allyl)di-μ-chlorodipalladium*** and ligand (**11**), and a mixture of ***N,O-Bis(trimethylsilyl)acetamide*** (BSA) and catalytic amounts of KOAc in an apolar solvent like CH_2Cl_2 or toluene, racemic 1,3-diphenyl-2-propenyl acetate smoothly reacts with dimethyl malonate to afford the corresponding substitution product in high yield and with excellent enantioselectivity (eq 9).

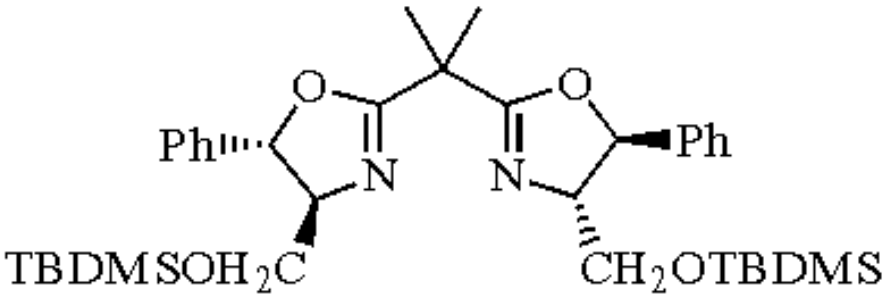

(11)

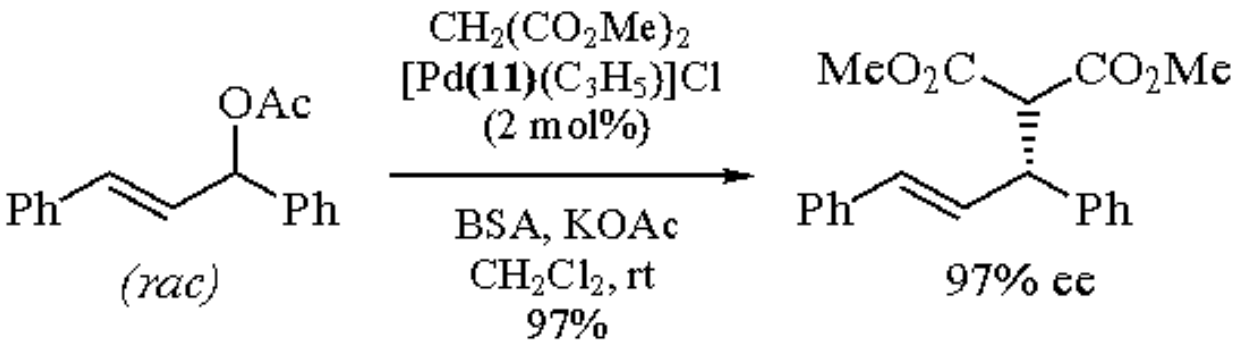

(9)

More recently, even higher selectivities of up to 99% ee have been achieved in this reaction with chiral phosphinooxazolines (see ***(S)-2-[2-(Diphenylphosphino)phenyl]-4-phenyloxazoline***).[24-26] The application range of (bisoxazoline)Pd catalysts is limited to relatively reactive substrates such as aryl-substituted allylic acetates.[24] Analogous reactions of 1,3-dialkyl-2-propenyl acetates, for example, are impracticably slow and unselective. In this case, phosphinooxazolines have proved to be the ligands of choice.[24,25]

The crystal structures of some (allyl)Pd^{II}-bisoxazoline complexes have been determined by X-ray analysis.[1] The structural data of these complexes provide some clues about how the chiral ligand controls the stereochemical course of eq 9.

Other Applications.

In the reactions discussed so far, methylenebis(oxazolines) were found to be superior to bioxazolines of type (**4**). However, there are some enantioselective metal-catalyzed processes for which the bioxazolines (**4**) are better suited than neutral or anionic methylenebis(oxazolines). Two examples, the Ir-catalyzed transfer hydrogenation of aryl alkyl ketones[4] and the Rh-catalyzed hydrosilylation of acetophenone,[11] are given in eqs 10 and 11.

(S,S)-2,2´-(Dimethylmethylene)bis(4-t-butyl-2-oxazoline)

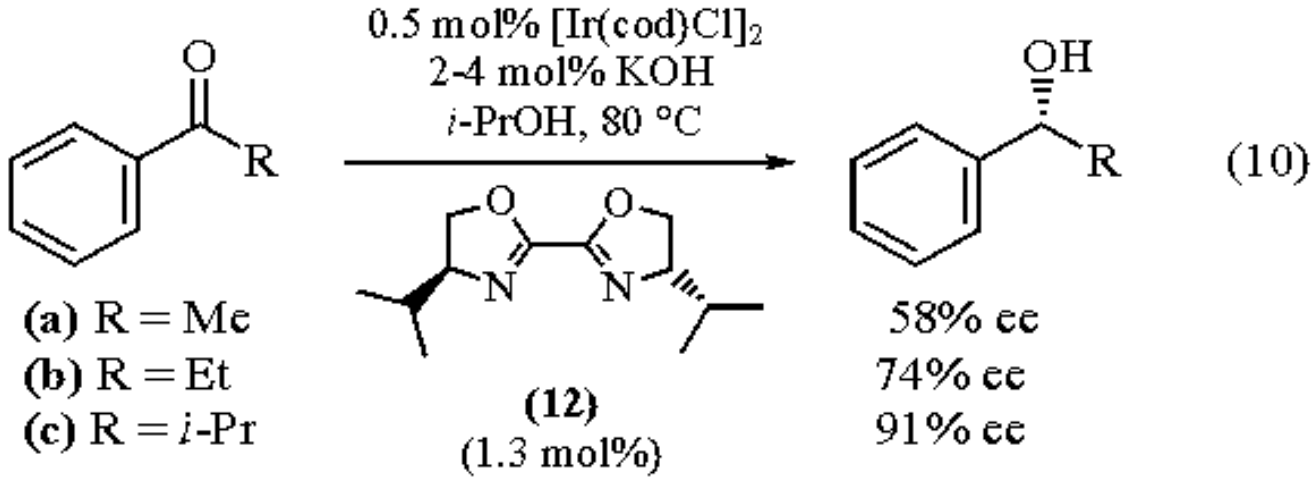

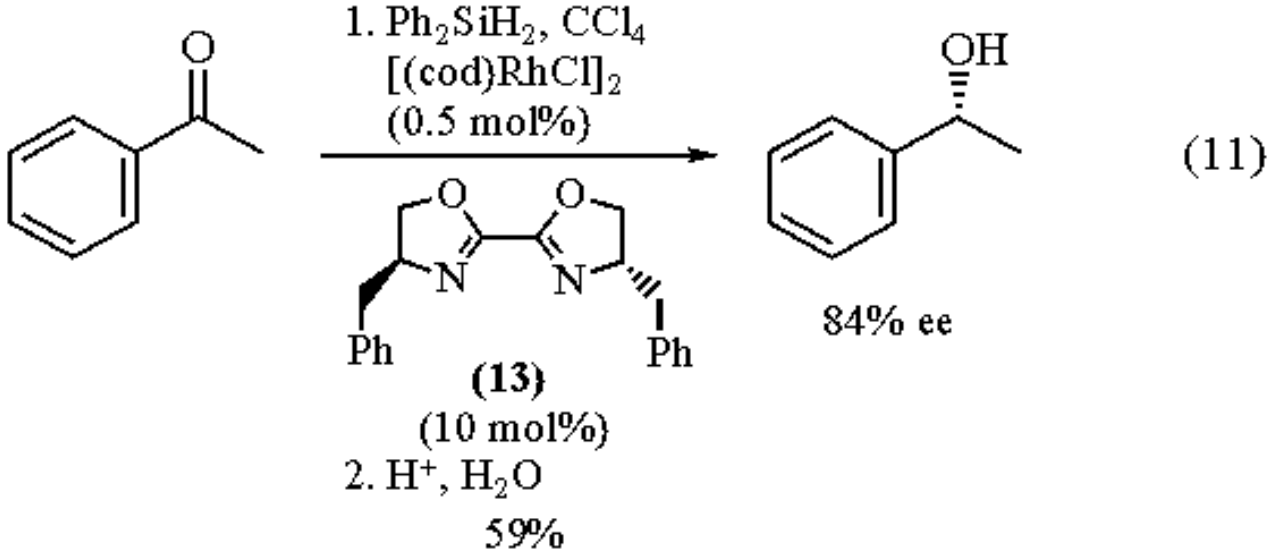

Using 1 mol % of catalyst generated in situ from ***Di-μ-chlorobis(1,5-cyclooctadiene)diiridium(I)*** and the bioxazoline (**12**) in refluxing isopropanol, various aryl alkyl ketones have been reduced in good yield with enantioselectivities ranging between 50-90% ee (eq 10).[10b] Dialkyl ketones are unreactive under these conditions. The highest enantiomeric excesses are obtained with phenyl isopropyl ketone (91% ee at 70% conversion, 88% ee at 93% conversion). Although these results compare favorably with the enantioselectivities reported for other Ir catalysts,[27] at present, (bioxazoline)Ir complexes cannot compete with the most efficient catalysts available for the enantioselective reduction of ketones[28] (see ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***). Recently, high enantioselectivities in the transfer hydrogenation of certain aryl alkyl ketones have been achieved with chiral samarium catalysts.[29]

The dibenzylbioxazoline derivative (**13**) has been found to induce up to 84% ee in the Rh-catalyzed hydrosilylation of acetophenone with diphenylsilane (eq 11).[11] A large excess of ligand relative to [Rh] is necessary for optimal selectivity. Analogous bithiazoline derivatives were also investigated, but gave lower selectivities. In this case too, there are more selective catalysts available which afford high enantiomeric excesses in the hydrolsilylation of a wide range of ketones.[30]

Bioxazolines have also been employed in the enantioselective dihydroxylation of alkenes with ***Osmium Tetroxide***.[15] The best results have been obtained in the dihydroxylation of 1-phenylcyclohexene with a complex, formed between OsO_4 and the diisobutylbioxazoline (**4**) (R = CH_2CHMe_2), as a stoichiometric reagent (70% ee). Styrene and *trans*-stilbene afford enantioselectivities below 20% ee under these conditions (for highly enantioselective dihydroxylation catalysts,[31] see ***Dihydroquinine Acetate*** and ***Osmium Tetroxide***).

Related Reagents.

(R)-1,1´-Bi-2,2´-naphthotitanium Dichloride; ***(R)-1,1´-Bi-2,2´-naphthotitanium Diisopropoxide***; ***Dihydroquinine Acetate***; ***(1S,9S)-1,9-Bis{[(t-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin***; ***2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide***.

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Dimethyl Methylphosphonate[1]

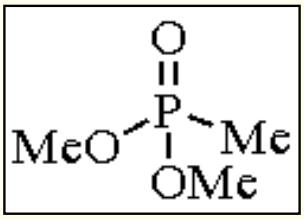

[756-79-6] · $C_3H_9O_3P$ · Dimethyl Methylphosphonate · (MW 124.09)

(treatment with BuLi gives a carbanion that reacts with aldehydes,[1] ketones,[1,2] esters,[1,3] acid chlorides,[4] enol lactones[5] and other electrophiles[6-11])

Alternate Names: dimethyl methylphosphate; dimethyl methanephosphate.

Physical Data: bp 180-181 °C; *d* 1.145 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: flammable; irritant; stench. Store under N_2.

Reactions with Aldehydes and Ketones.

$(MeO)_2P(O)Me$ in THF (or less commonly Et_2O, DME, DMF, or MeCN) is deprotonated by ***n-Butyllithium***[1] or ***Lithium Diisopropylamide***,[2,11] at -78 °C, to give $(MeO)_2P(O)CH_2Li$. Unlike the carbanions of phosphonate esters which possess a charge-stabilizing electron withdrawing group (see discussion on ***Triethyl Phosphonoacetate*** and ***Trimethyl Phosphonoacetate***), $(MeO)_2P(O)CH_2Li$ does not react directly with aldehydes or ketones to give an alkene.[1] Rather, the reaction gives a β-hydroxyalkylphosphonate which has a low efficiency of cycloelimination (eq 1).[1a,12,13] Cycloelimination, and hence alkene formation, is induced by treating the β-hydroxyalkylphosphonate with ***Cesium Fluoride*** in DMF (eq 1).[12] Thioalkylated acetophenones react directly with $(MeO)_2P(O)CH_2Li$ to give 2-aryl-1-thioalkyl-2-propenes (eq 2).[14] α-Lithio derivatives of alkylphosphonothioates [$(MeO)_2P(S)Me$] react directly with aldehydes and ketones to give 1,1-disubstituted, trisubstituted, and tetrasubstituted alkenes.[1a,15] Ligand exchanged derivatives of $(MeO)_2P(O)Me$ such as alkylphosphonic diamides, alkylphosphonothioates, alkyldiphenylphosphine oxides, and alkyldiphenylphosphinothioic amides also form alkenes directly.[12]

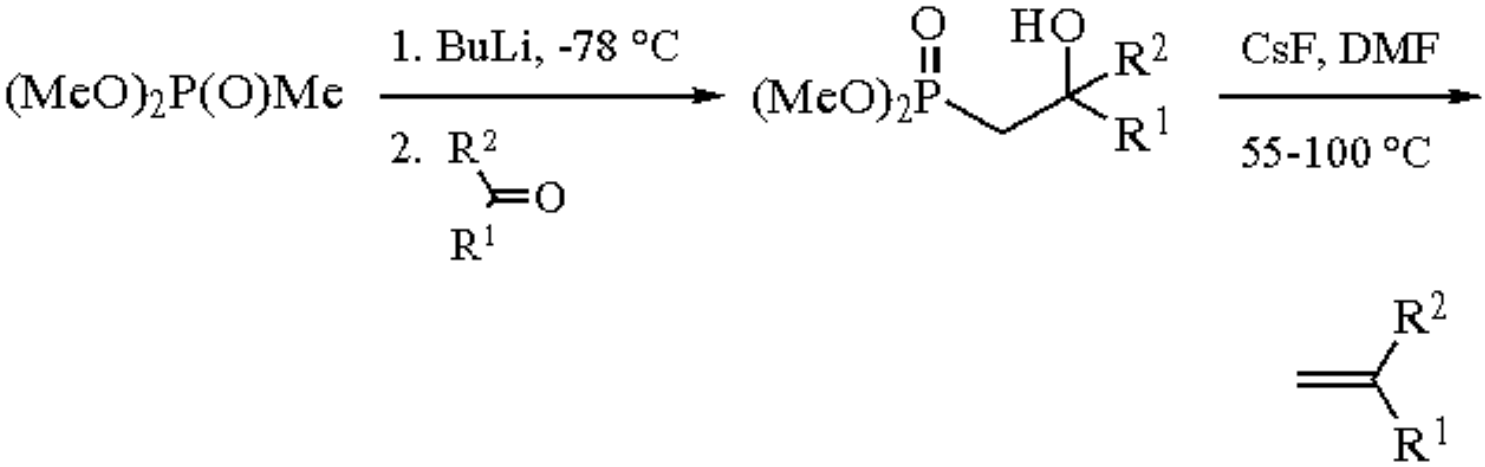

(1)

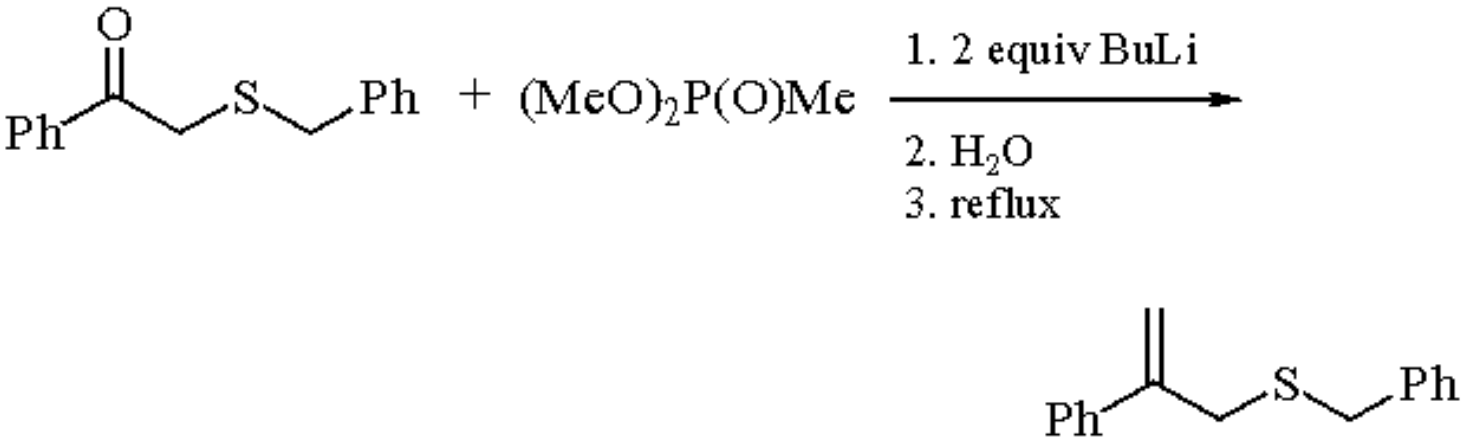

(2)

β-Hydroxyalkylphosphonates are precursors to copper β-metalated alkylphosphonates (eq 3).[16] These versatile d^2 reagents react in excellent yields in with a range of electrophiles such as acyl chlorides, aldehydes, enones, alkynic esters, allylic and alkynyl halides, trialkyltin halides and nitroalkenes (eq 3).[16]

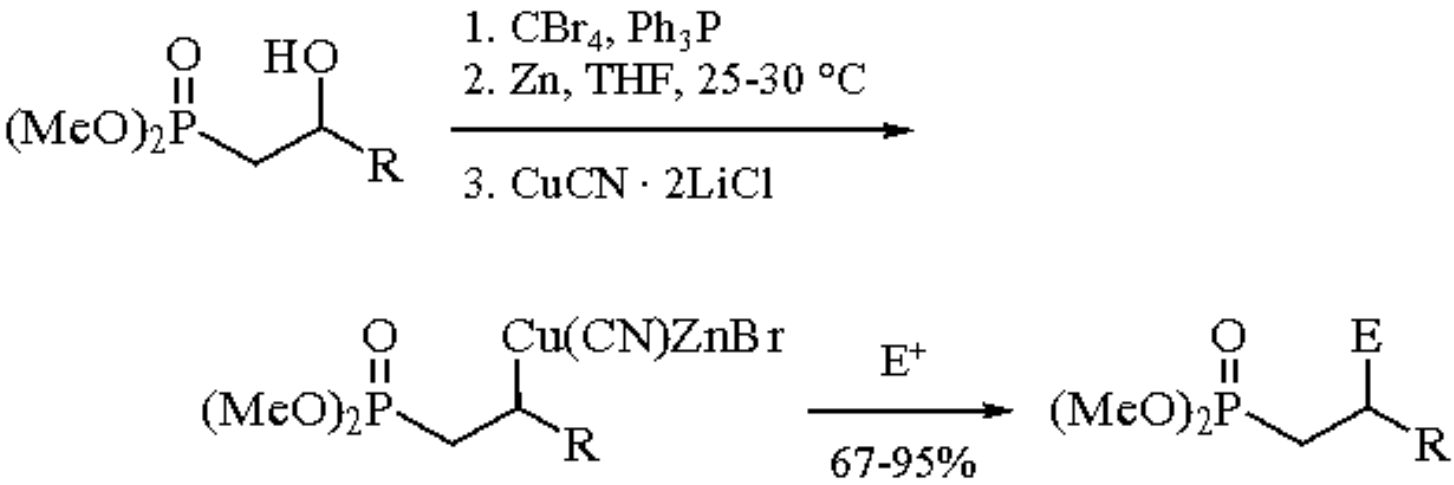

(3)

Reactions with Esters.

The reaction of $(MeO)_2P(O)CH_2Li$ with an ester[3a,b] (eq 4)[3b] or a lactone[3c] gives a β-ketophosphonate. The condensation has been carried out in the presence of a number of functional groups.[3a] For example, $(MeO)_2P(O)CH_2Li$

reacts preferentially with a methyl ester in the presence of a phenylethyl ester (eq 5, entry 1)[17a] and a Weinreb amide in the presence of a methyl ester (eq 5, entry 2).[17b] Some problems were encountered with β-elimination and retro-aldol reactions.[3a,17] The condensation of an ester or equivalent with $(MeO)_2P(O)CH_2Li$ has also been carried out in the presence of an acid[3a,b,18] (eq 5, entry 3[18] and 4[3a]), ketone (eq 6),[19] and an acetal.[3c,20] An acid chloride reacts with $(MeO)_2P(O)CH_2Li$ to give a β-ketophosphonate.[4] Anhydrous ***Magnesium Bromide*** promotes the preferential reaction of $(MeO)_2P(O)CH_2Li$ with an acid chloride in the presence of an ester (eq 7).[4] β-Ketophosphonates have also been prepared by oxidation of a β-hydroxyphosphonate obtained from the reaction of $(MeO)_2P(O)CH_2Li$ with an aldehyde.[13]

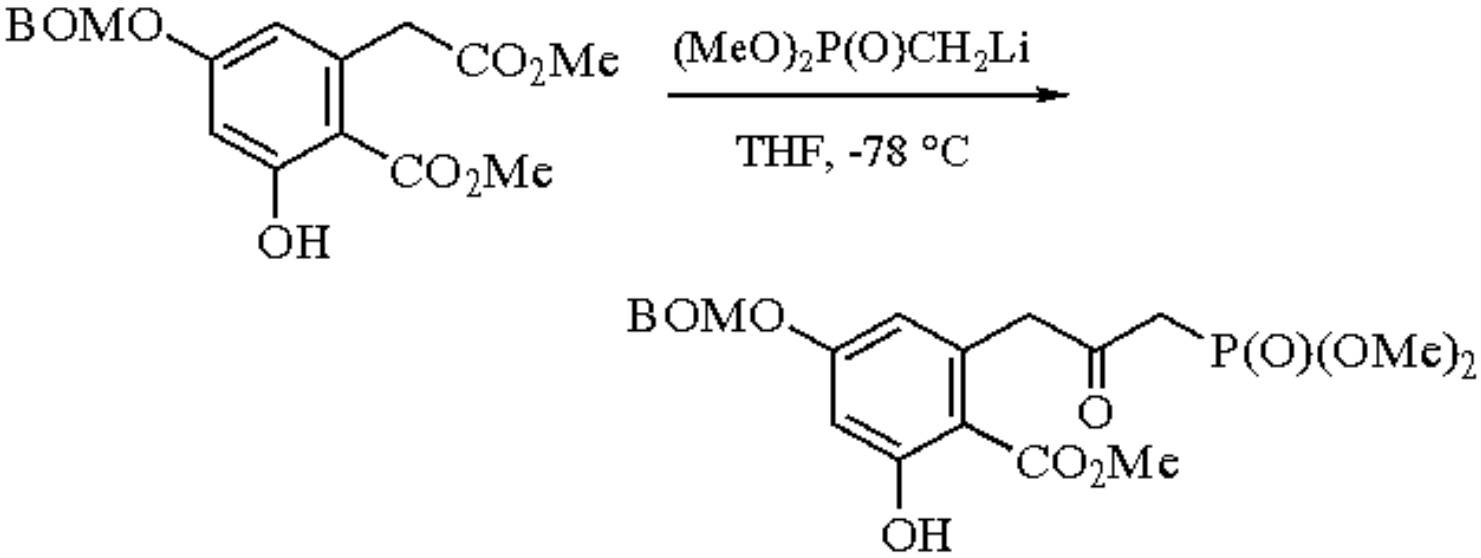

(4)

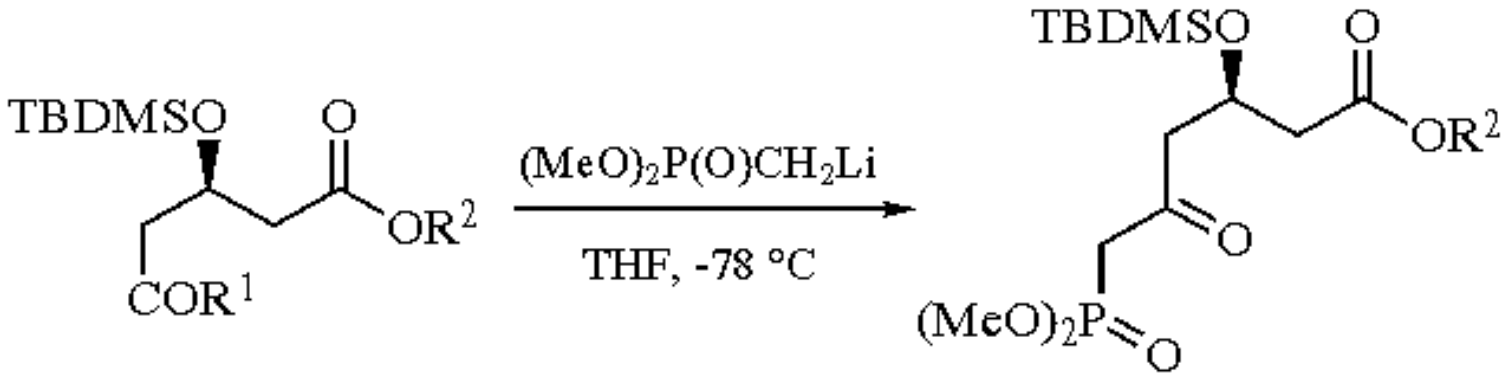

(5)

$R^1 = OMe$, $R^2 = CHMePh$	34%
$R^1 = N(OMe)Me$, $R^2 = Me$	82%
$R^1 = N(OMe)Me$, $R^2 = H$	>77%
$R^1 = OMe$, $R^2 = 1\text{-}AdNH_2$ salt	>78%

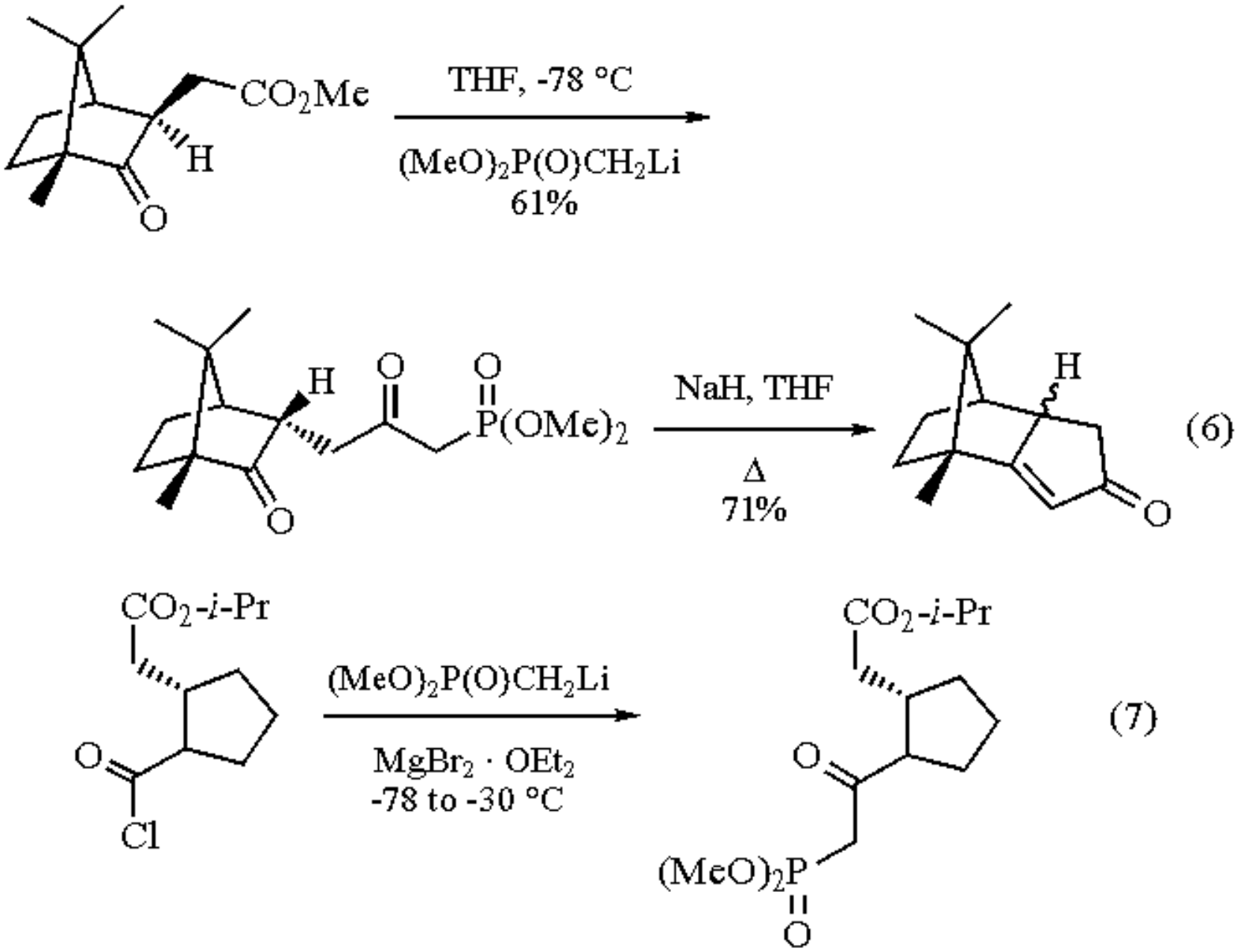

The β-ketophosphonates are versatile synthetic intermediates and react with aldehydes to give α,β-unsaturated esters under Roush-Masamune[18,21] and other basic conditions[13,18,22] (also see discussion on Horner-Emmons reactions of ***Triethyl Phosphonoacetate*** and ***Trimethyl Phosphonoacetate***). β-Ketophosphonates also react intramolecularly with ketones to give cyclohexenones and cyclopentenones[19,20,23] (eq 6[19]). In some cases the ketone is protected as an acetal prior to the preparation of the β-ketophosphonate.[20,23] Higher esters of phosphonic acids are prepared by α-alkylation of the ***Sodium Hydride***-generated carbanion of β-ketophosphonates.[20a,24] The corresponding dianion, generated by the sequential addition of NaH and BuLi to a β-ketophosphonate, undergoes γ-alkylation.[20a,25]

Reactions with Enol Lactones.

An enol lactone reacts with $(MeO)_2P(O)CH_2Li$, at low temperatures, to give an α,β-unsaturated ketone[5,10] (eq 8[5c]). The reaction does not proceed with α-unsubstituted five-membered endocyclic enol lactones.[20a] Perhydroazulenones have also been prepared from a lactam and $(MeO)_2P(O)CH_2Li$ in a related reaction (eq 9).[26] The analogous Wittig reaction of enol lactones proceeds with nonstabilized ylides[5a,27] but not readily with stabilized ylides.[27,28]

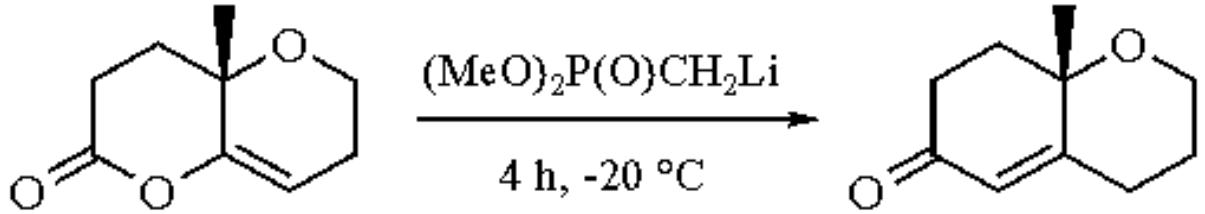

(8)

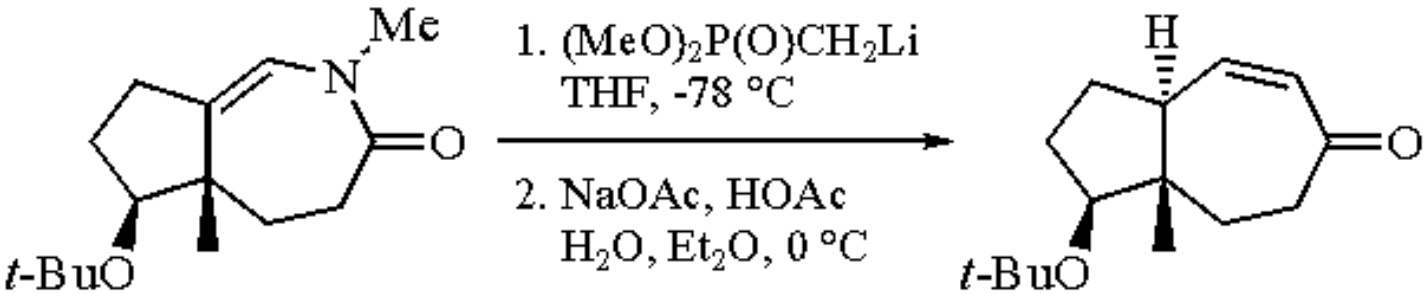

(9)

Reactions with 1,3-Diketones.

The reaction of 2,2-disubstituted 1,3-cyclohexanediones with $(MeO)_2P(O)CH_2Li$ in the presence of ***Chlorotrimethylsilane*** gives 3-substituted 2-cyclohexanones in good yields (22-93%) (eq 10).[2] The reaction proceeds by a retro-aldol cleavage followed by a Horner-Emmons reaction.[2] The use of BuLi rather than LDA to generate $(MeO)_2P(O)CH_2Li$ results in reduced yields.[2]

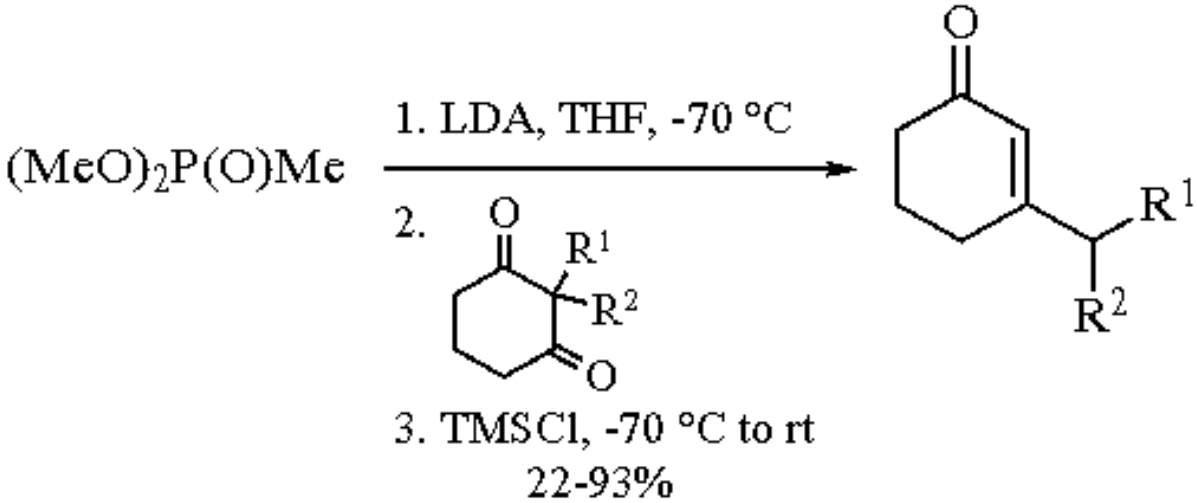

(10)

Other Reactions.

Dimethyl (alkylthio)methylphosphonates, $(MeO)_2P(O)CH_2SR$, are prepared by sulfenylation of $(MeO)_2P(O)CH_2Li$ with alkyl and aryl benzenethiosulfonates.[6] Treatment of $(MeO)_2P(O)CH_2Li$ with ***Copper(I) Iodide*** gives the corresponding 1-copper derivative, $(MeO)_2P(O)CH_2Cu$. Dimethyl 1-(trimethylsilyl)- and 1-(trimethylstannyl) methanephosphonates are prepared by subsequent reaction of $(MeO)_2P(O)CH_2Cu$ with Me_3SiCl (eq 11, entry 1)[7a,c] and ***Chlorotrimethylstannane*** (eq 11, entry 2),[7a] respectively. The reaction of $(MeO)_2P(O)CH_2Cu$ with *O*-alkyl carbonochloridothioates gives a phosphorylthiocarbonyl compound (eq 11, entry 3), a precursor to α-unsubstituted

thiono esters.[7b,d,e]

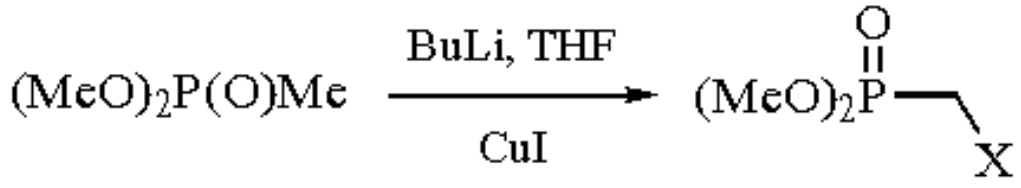

(11)

	X	
TMSCl, -30 to 22 °C	TMS	70%
Me_3SnCl, -30 to 22 °C	Me_3Sn	68%
ROC(S)Cl, -70 °C to rt	ROC=S	54-59%

Treatment of $(MeO)_2P(O)Me$ with ***Triphenylphosphine Dichloride*** gives a single ester linkage replacement by a chloride (eq 12, entry 1).[8a] An analogous reaction with ***Phosphorus(V) Chloride*** gives the dichloride (eq 12, entry 2).[8b] $(MeO)_2P(O)CH_2Li$ *N*-methylates purines,[9] is alkylated by an alkyl iodide,[10] and also undergoes a Michael addition with 4-chloro-β-nitrostyrenes.[11]

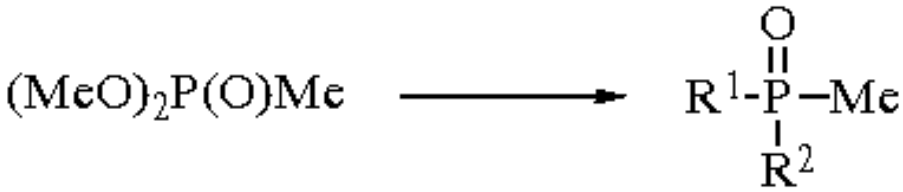

(12)

	R^1	R^2	
Ph_3PCl_2, $CHCl_3$, 22 °C	OMe	Cl	90%
PCl_5, reflux	Cl	Cl	73%

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N,N-Dimethyl-*O*-(methylsulfonyl)hydroxylamine[1]

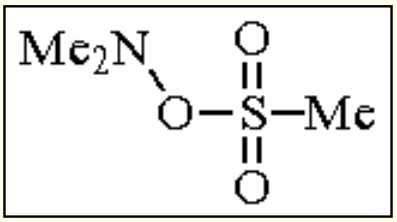

[75812-61-2] · $C_3H_9NO_3S$ · *N,N*-Dimethyl-*O*-(methylsulfonyl)hydroxylamine · (MW 139.20)

(reagent for electrophilic aminations, Me_2N transfers to nucleophiles)

Physical Data: mp 33-35 °C.[2]

Solubility: sol THF, diethyl ether; very sol $CHCl_3$, CH_2Cl_2.[2]

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) (ppm) 2.90 (s, 6 H, Me_2N), 3.08 (s, 3 H, $MeSO_2$).[2]

Preparative Methods: to a solution of 29.3 g (300 mmol) *N,N*-dimethylhydroxylamine hydrochloride and 35.6 g (300 mmol) ***Methanesulfonyl Chloride*** in 360 mL CH_2Cl_2 is added dropwise under stirring at -20 °C a solution of 60.7 g (600 mmol) ***Triethylamine*** in 240 mL CH_2Cl_2. After stirring for 30 min at 0 °C the reaction mixture is poured into ice water, the organic phase is extracted another two times with ice water and then dried over $MgSO_4$ at 0 °C. After removal of the solvent at 0 °C the noncrystalline residue is dissolved in 60 mL diethyl ether. On standing at -30 °C, *N,N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine (**1**) crystallizes in colorless needles which are separated in a cooled frit. After one (or two) recrystallization(s) from diethyl ether between 21.9 and 26.4 g (53-63%) (**1**) are isolated.[3,4] In a similar fashion the following compounds have been prepared and used in electrophilic amination reactions: *N,N*-dimethyl-*O*-(phenylsulfonyl)hydroxylamine, mp 18-19 °C;[2b,3] *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine, mp 103-104 °C;[2b,3] *N,N*-diethyl-*O*-(phenylsulfonyl)hydroxylamine, mp 46-47 °C;[2b] *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine, mp 68-69 °C;[2b,3] *N*-(*O*-phenylsulfonyl)hydroxypiperidine, mp 57-58 °C;[2b] *N*-(*O*-mesitylsulfonyl)hydroxypiperidine, mp 50-51 °C;[2b] *N*-(*O*-mesitylsulfonyl)hydroxypyrrolidine, mp 23-24 °C.[2b]

Handling, Storage, and Precautions: reagents for electrophilic aminations with *N,N*-dimethyl(dialkyl) functionality like (**1**) are much more stable than their NH_2 analogs. Thus the pure compound (**1**) can be stored at -30 °C for at least 1 year.[2,3] Impure (**1**) (and related compounds), however, may decompose at rt,[2,3] as also reported for *N,N*-diethyl-*O*-(mesitylsulfonyl)hydroxylamine.[5]

Electrophilic Aminations.

N,*N*-Dimethyl-*O*-(methylsulfonyl)hydroxylamine (**1**) reacts with organometallic compounds RM to give *N*,*N*-dimethylamines (**2**) (eq 1). *N*,*N*-Dimethylamines prepared via eq 1 from RM and (**1**) together with a specification of RM are shown in (**3**)-(**19**).

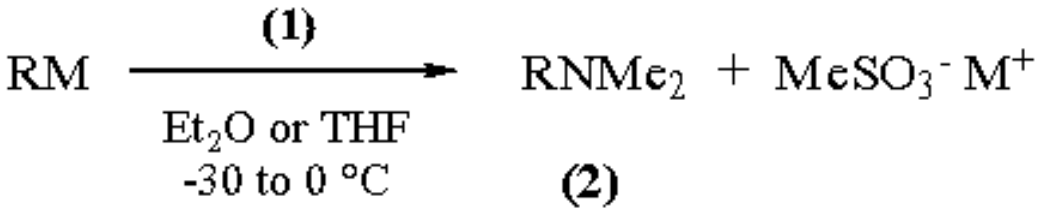

(1)

(3) 70% (RMgBr)

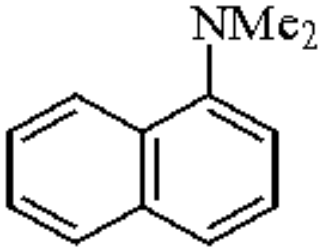

(4) 50% (RMgBr)

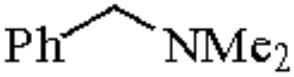

(5) 43% (RMgCl)

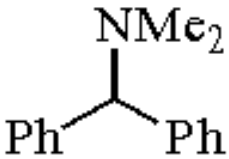

(6) 84% (RLi)

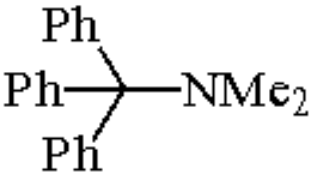

(7) 60% (RLi)

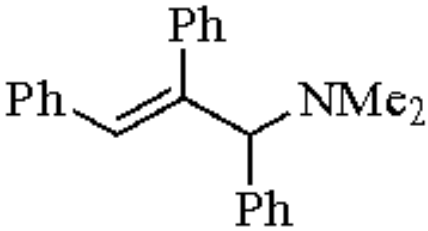

(8) 31% (RLi)

(9) 61% (RLi)

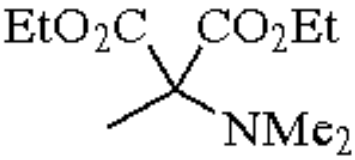

(10) 50% (RNa)
50% (RLi)

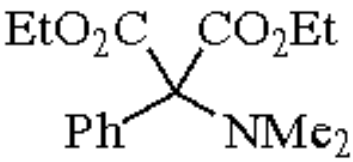

(11) 52% (RLi)
39% (RNa)

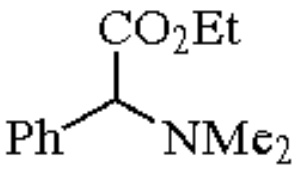

(12) 48% (RLi)

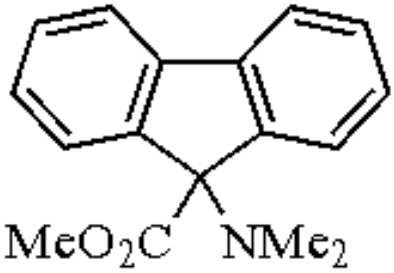

(13) 54% (RNa)

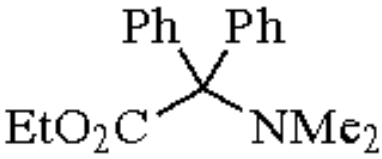

(14) 34% (RLi)

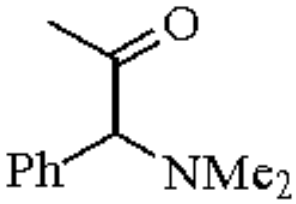

(15) 52% (RLi)

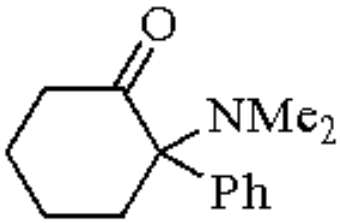

(16) 50% (RLi)

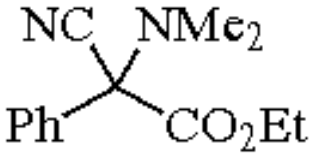

(17) 95% (RLi)

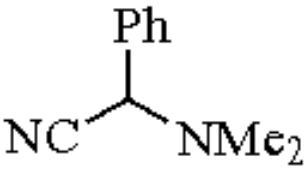

(18) 69% (RLi)

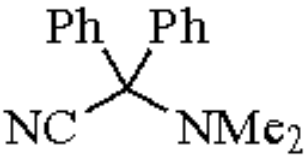

(19) 67% (RLi)

As can be seen from the structures shown, *N*,*N*-dimethyl-*O*-(methylsulfonyl)hydroxylamine (**1**) aminates alkyl Grignard compounds (to give **3**) and aryl Grignard compounds (to give **4**) with moderate yields. The same is true for benzylic anion type carbon atoms (**5**-**9**). Compounds (**10**) and (**11**) are formed from the corresponding malonates, while (**12**)-(**16**) are derived from (ester)enolates, although with aryl-stabilized anionic carbon atoms. Metalated cyanides lead to (**17**)-(**19**).

Related amination reactions of organometallic compounds RM have been performed with *N*,*N*-dimethyl-*O*-(mesitylsulfonyl)hydroxylamine (**20**),[3] *N*,*N*-dimethyl-*O*-(phenylsulfonyl)hydroxylamine (**21**),[3] and *N*,*N*-dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine (**22**).[4a] Structures (**23**)-(**26**) provide examples of *N*,*N*-dimethylamines formed by reactions of RM with the mesitylsulfonyl species (**20**).[3,6]

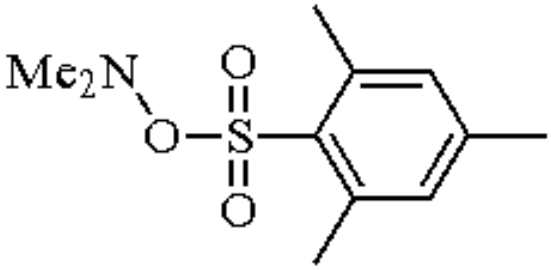

(20)

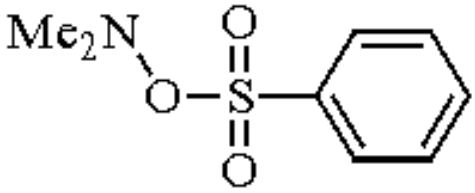

(21)

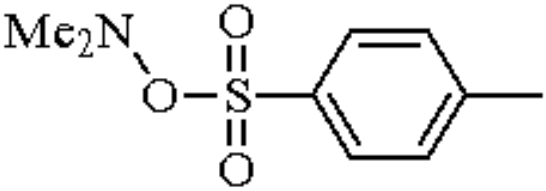

(22)

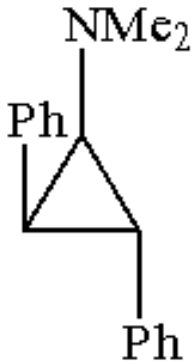

(23) 47% (RMgBr)

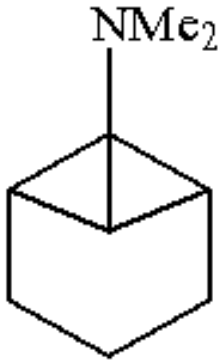

(24) 54% (RLi)

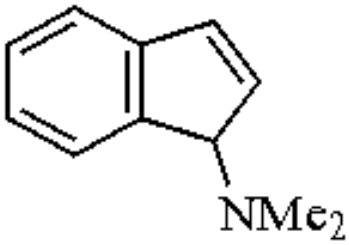

(25) 57% (RLi)

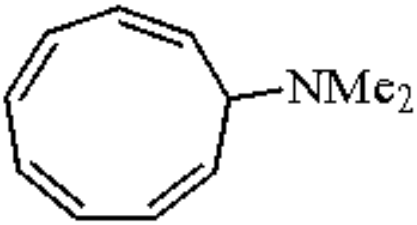

(26) 69% (RLi)

N,*N*-Dimethylamines of strained hydrocarbons like (**23**) and especially (**24**) are otherwise not easily accessible. The same is true for the cyclononatetraenylamine (**26**).[6] *N*,*N*-Dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine (**22**) is reported to react with ***Phenylmagnesium Bromide*** and cyclohexylmagnesium bromide to give the corresponding *N*,*N*-dimethylamines in 54% and 14% yield, respectively.[4a] For further and comparable electrophilic amination reactions with transfer of a Me_2N group to give, for example, (**27**)-(**29**), see ***N,N-Dimethyl-O-(diphenylphosphinyl)hydroxylamine***.

(27)

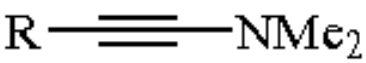

(28)

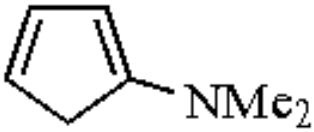

(29)

Disadvantages.

Normal enolates are not aminated by (**1**), (**20**), (**21**), or (**22**), probably because of a β-elimination of $MeSO_3H$ initiated by deprotonation at one of the *N*-methyl groups.[4a] α-Lithiated sulfones like (**30**) are aminated to give (**31**) (eq 2); however, the reaction does not stop there. Rather, the α-aminosulfone (**31**) leads with unreacted (**30**) to the β-aminosulfone (**32**) (eq 3). Without the phenyl substituent at the anionic carbon atom, only the cuprate (**33**) gives (**34**) (eq 4).[2b]

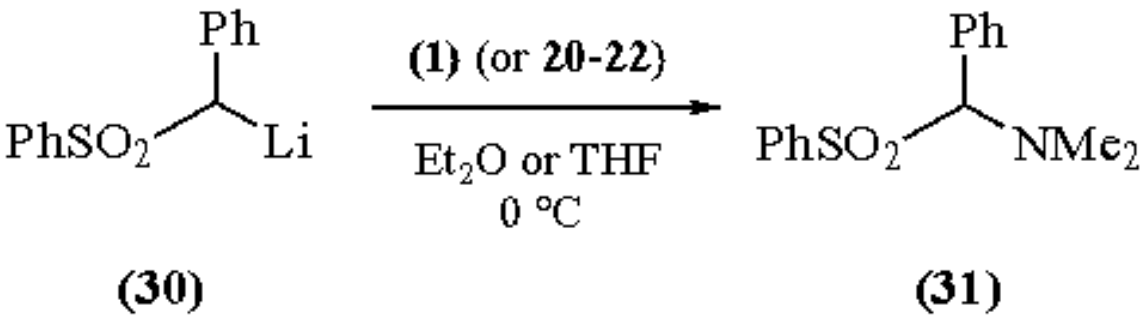

(2)

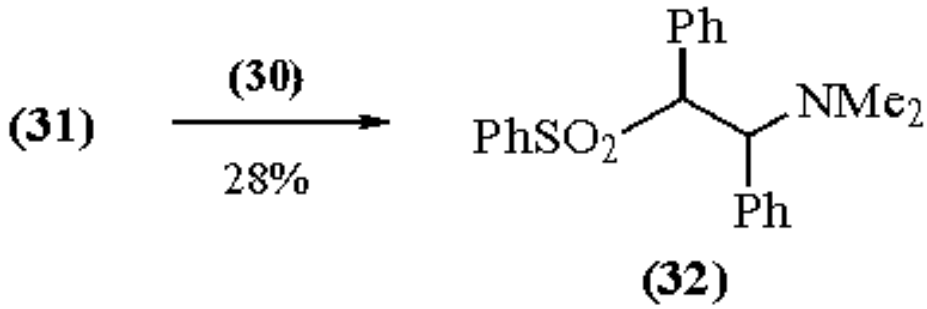

(3)

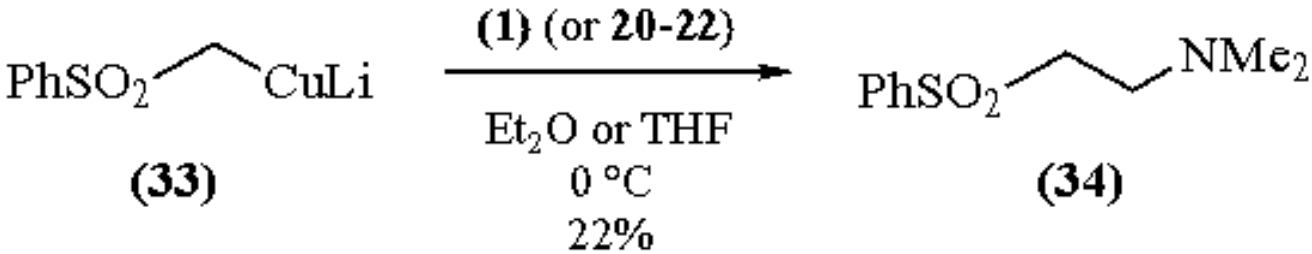

(4)

The corresponding Li compound deprotonates (**1**) (or **20-22**). With the dibenzylamine reagent (**35**), amination of RLi is not observed because of the comparatively fast β-elimination to give (**36**) due to the rather acidic benzylic hydrogen atoms (eq 5).[4b]

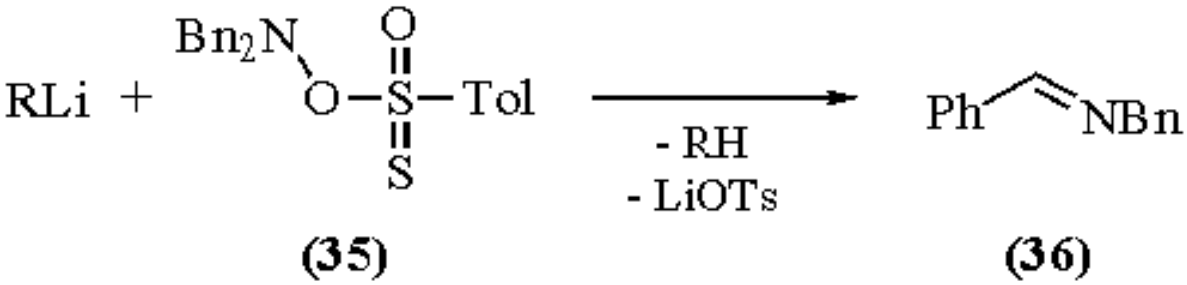

(5)

Reactions with organometallic compounds in which iodide I^- is present (e.g. in Grignard reagents of the type RMgI) should be avoided because I^- reduces (**1**); a similar reaction is not observed with Cl^- and Br^- containing organometallic compounds.

---

1. Erdik, E.; Ay, M. *CRV* **1989**, *89*, 1947.
2. (a) Nieβner, M., Diploma Thesis, Universität Marburg, 1980. (b) Bernheim, M. Ph.D. Thesis, Universität München, 1981.
3. Boche, G.; Mayer, N.; Bernheim, M.; Wagner, K. *AG(E)* **1978**, *17*, 687.
4. Other syntheses of *O*-sulfonylhydroxylamines. (a) *N*,*N*-Dimethyl-*O*-(*p*-tolylsulfonyl)hydroxylamine: Barton, D. H. R.; Bould, L.; Clive, D. L. J.; Magnus, P. D.; Hase, T. *JCS(C)* **1971**, 2204. (b) *N*,*N*-Dibenzyl-*O*-(*p*-tolylsulfonyl)hydroxylamine: Sheradsky, T.; Itzhak, N. *JCS(P1)* **1986**, 13. See also: (c) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *JOC* **1973**, *38*, 1239. (d) Carpino, L. A. *JACS* **1960**, *82*, 3133. (e) Carpino, L. A. *JOC* **1964**, *29*, 2820.
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6. Boche, G.; Bernheim, M.; Lawaldt, D.; Ruisinger, B. *TL* **1979**, 4285.

Gernot Boche

Philipps-Universität Marburg, Germany

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Dimethyl(methylthio)sulfonium Tetrafluoroborate[1]

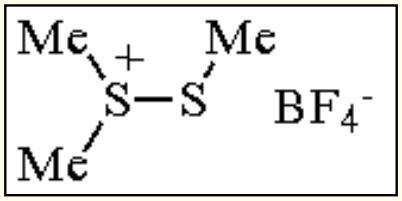

[5799-67-7] · $C_3H_9BF_4S_2$ · Dimethyl(methylthio)sulfonium Tetrafluoroborate · (MW 196.07)

(electrophilic sulfenylation reagent capable of reacting with nucleophilic atoms;[2] reacts with electron-rich alkenes to promote addition reactions,[3] cyclizations;[4] activates dithioacetals,[5] trithioorthoesters,[6] and thioglycosides[7] for carbon-carbon or carbon-heteroatom bond forming reactions)

Alternate Name: DMTSF.

Physical Data: mp 89-92 °C.

Solubility: sol MeCN, $MeNO_2$; insol in ether, pet ether; reacts with H_2O and other protic solvents.

Form Supplied in: cream-colored to white solid; available from various suppliers.

Preparative Method: DMTSF can be conveniently prepared from ***Dimethyl Disulfide*** and ***Trimethyloxonium Tetrafluoroborate*** (Me_3O^+ BF_4^-) in MeCN.[8] Precipitation of the product results after addition of ether and isolation requires filtration under anhydrous conditions.

Handling, Storage, and Precautions: DMTSF must be stored under anhydrous conditions, preferably in a well sealed bottle under nitrogen. Exposure to moisture results in a stench and the reagent is corrosive. Use in a fume hood.

Methylsulfenylation of Nucleophilic Atoms.

DMTSF reacts with ***Potassium Cyanide*** to yield MeSCN and with ***Phenylmagnesium Bromide*** to yield thioanisole.[8] Extensive investigations addressed the reactivity of DMTSF with nucleophilic agents.[9] DMTSF does not react with phenol at rt, but reacts slowly at 60 °C to yield the methylthiophenols (*ortho*/*para* = 0.22). The reaction with anisole also requires a temperature of 60 °C and results in *p*-methylthioanisole and *p*-methylthiophenol, a consequence of ether cleavage under the reaction conditions. Unlike phenol, dimethylaniline reacts rapidly with DMTSF at rt, yielding *p*-methylthio-*N*,*N*-dimethylaniline in 60% yield (eq 1). Despite the presence of an electron-withdrawing group, *p*-nitro-

N,*N*-dimethylaniline also reacts rapidly with DMTSF to yield *p*-nitro-*N*,*N*-dimethyl-*N*-methylthioanilinium tetrafluoroborate.

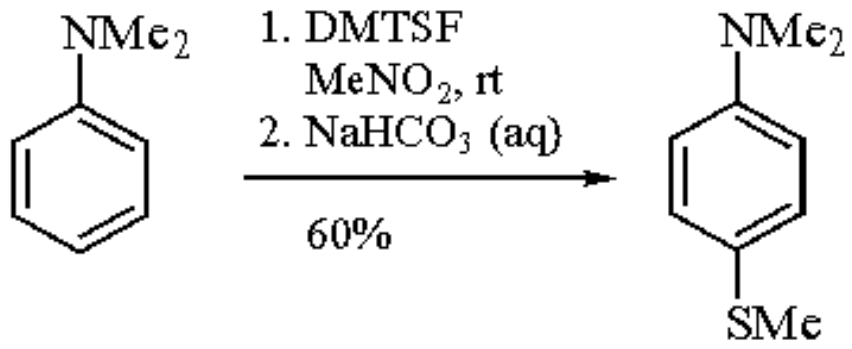

(1)

DMTSF reacts rapidly at rt with pyridine to yield the hydrolytically unstable methylthiopyridinium ion, which failed to methylate the MeSMe byproduct. When 4-cyanopyridine was used, an equilibrium mixture was detected by NMR.

Triphenyl Phosphite reacts rapidly with DMTSF at rt to yield the methylthiophosphonium salt which, unlike the pyridinium analog, methylates the MeSMe byproduct to yield $Me_3S^+ BF_4^-$. This salt is removed by precipitation with ether and chromatography provides triphenyl thionophosphate in an 86% yield (eq 2). This technique complements other methods of thionophosphate synthesis from phosphites.[10]

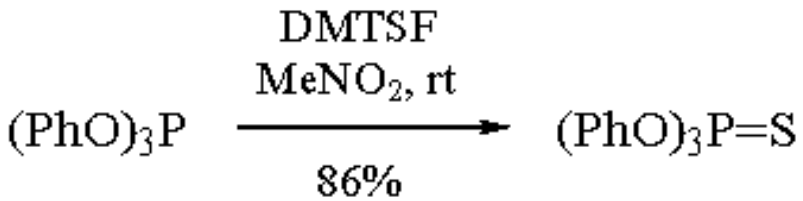

(2)

Synthesis of mixed disulfides involving a methylthio unit may utilize DMTSF. Thiols and thiolates react rapidly with the reagent to yield mixed disulfides. Unfortunately, disproportionation occurs, resulting in a mixture of products.[9] Subsequent investigations suggest that the addition of a sterically hindered base (eq 3),[11] or the use of a 2-(trimethylsilyl)ethanethiol derived component (eq 4),[12] permit high yields of unsymmetrical disulfides.

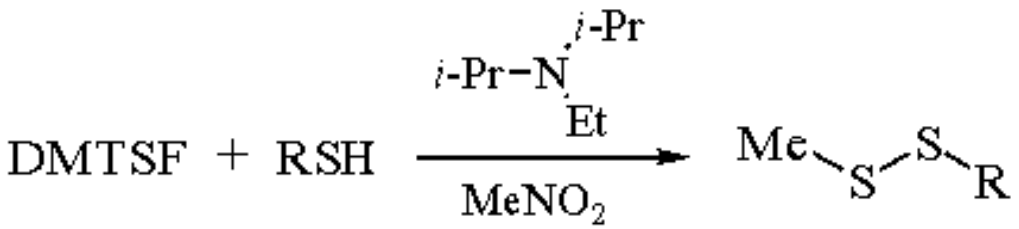

(3)

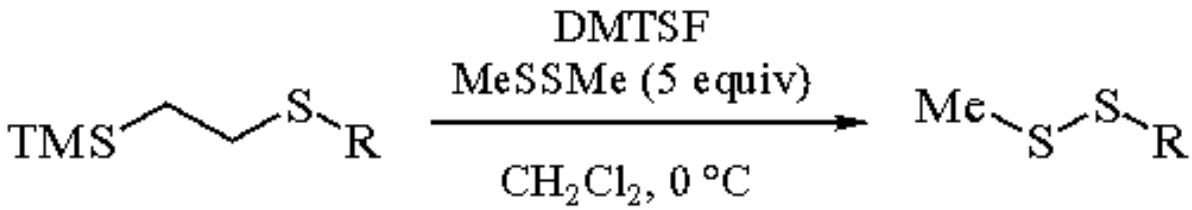

(4)

In systems having a tertiary amine and a sulfide unit, DMTSF demonstrates a chemoselectivity for sulfur (eq 5).[13]

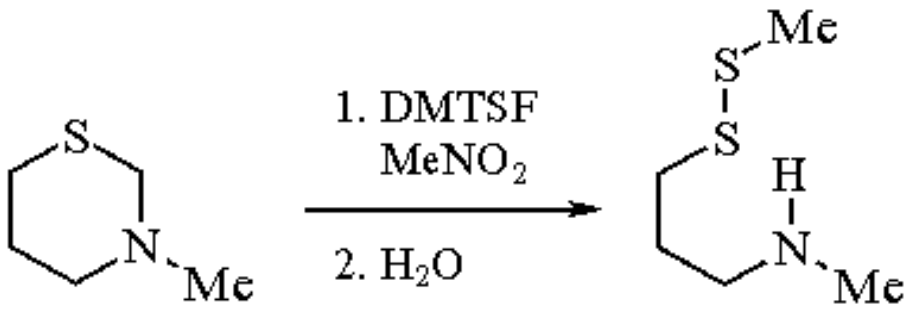

(5)

Allylic sulfides react with DMTSF chemoselectively at the sulfur atom, generating thiosulfonium ions. This ion formation is reversible and the allylic thiosulfonium ion is capable of a [2,3]-sigmatropic rearrangement before subsequent electrophilic addition to the alkene.[14]

Methylsulfenylation of Alkenes.

A key application of DMTSF in organic synthesis involves electrophilic addition to alkenes and subsequent addition of a nucleophile to the bridged sulfonium ion. Support for this mechanism is provided by the *anti* addition products observed.[15]

Carbon Nucleophiles.

Most nucleophilic carbon sources are too basic for application to these reaction conditions. Alkynylalane ate complexes demonstrate an exception (eq 6).[16]

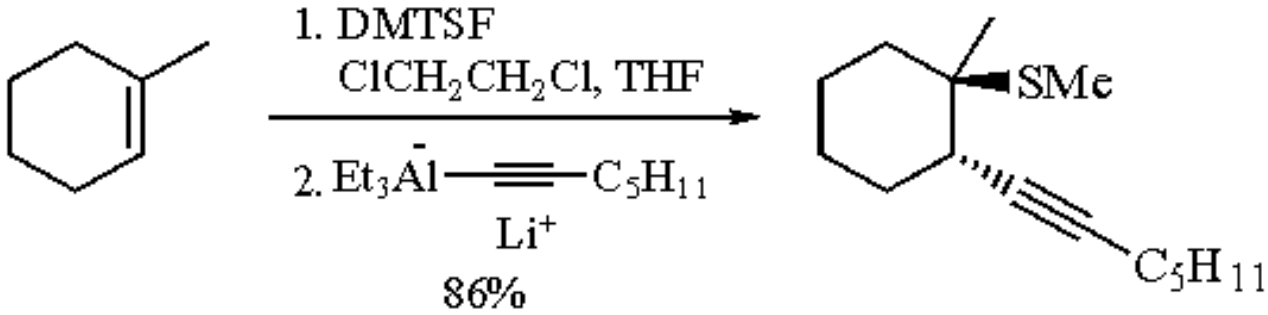

(6)

Nitrogen Nucleophiles.

Nitrogen nucleophiles, specifically NH_3, amines, azide, and nitrite, resulted in high yields of alkene addition products (eq 7).[15a] In the absence of additional nucleophiles, the resulting sulfonium salt reacted with a tertiary amine to yield the demethylated product or the ammonium salt with a retention of configuration (eq 8).[15b]

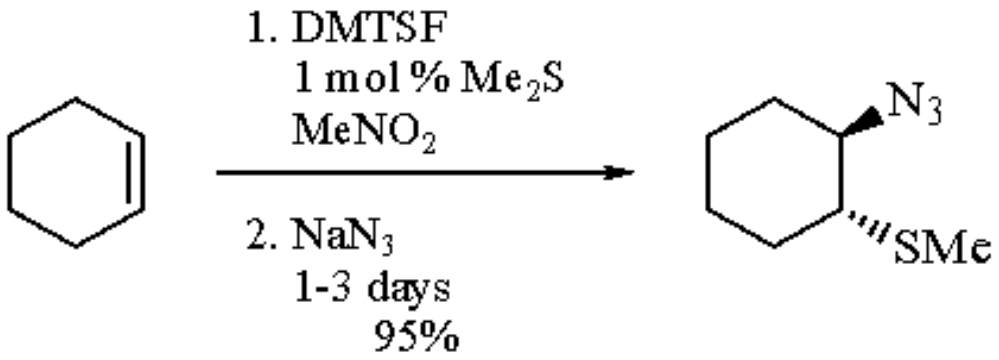

(7)

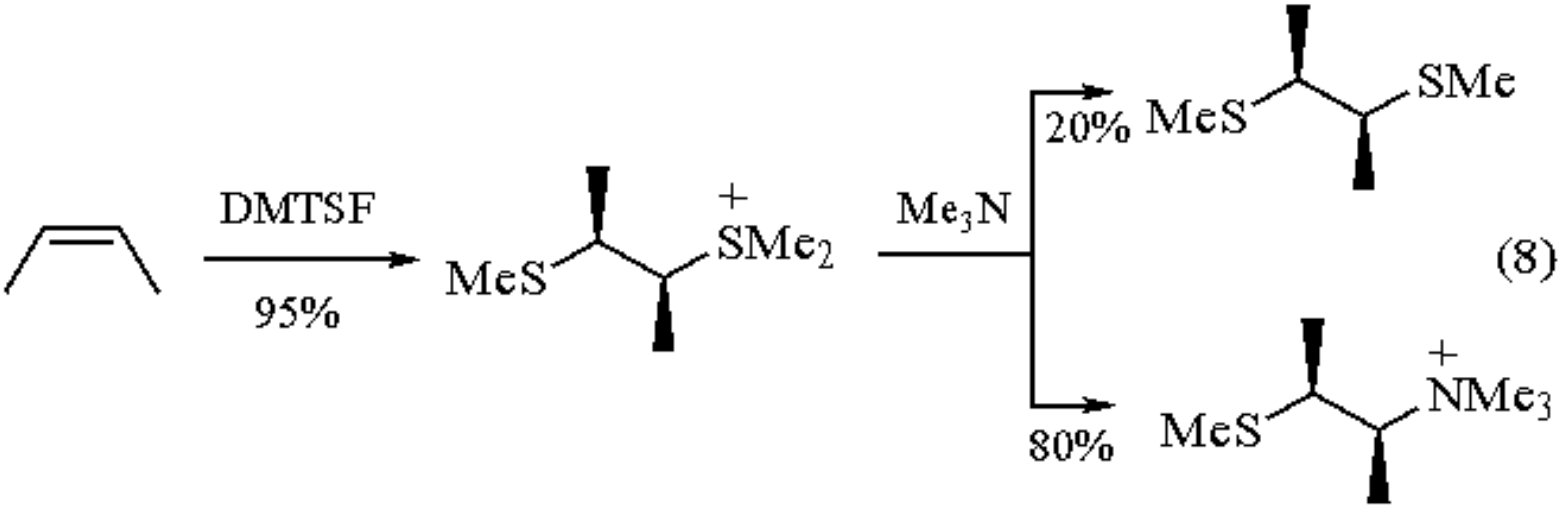

(8)

Oxygen Nucleophiles.

Successful application of oxygen nucleophiles includes anhydrous KOAc (anti-Markovnikov product), $H_2O/CaCO_3$ (Markovnikov product), and DMSO which, upon treatment with ***Diisopropylethylamine***, yields α-methyl thioketones (eq 9).[17]

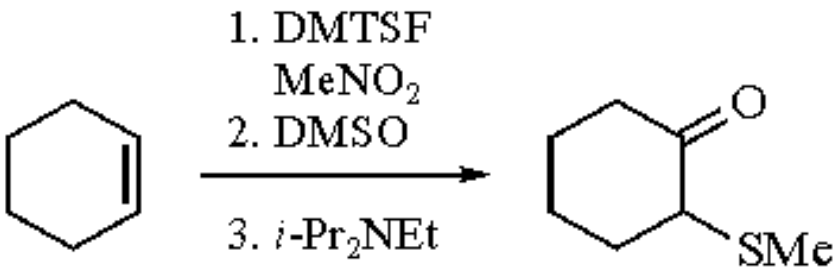

(9)

Electrophilic ring closure demonstrates another utility of DMTSF. Examples of sulfenyl etherification and sulfenyl lactonization have been reported (eq 10).[18]

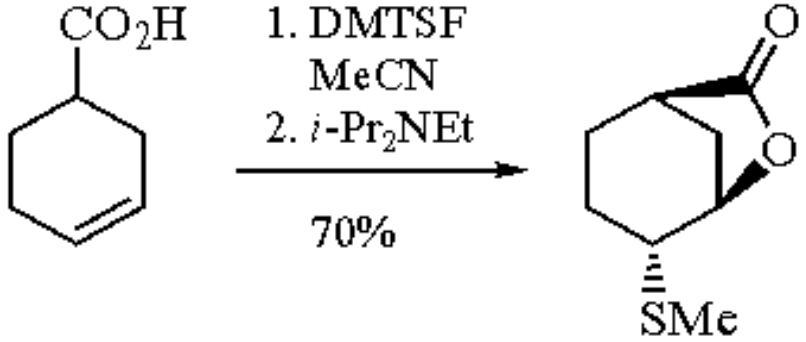

(10)

Phosphorus Nucleophiles.

Triphenylphosphine is an effective nucleophile for reacting with the bridged sulfonium ion in high yield. The phosphonium salts generated eliminate MeSH upon reaction with base, such as ***1,8-Diazabicyclo[5.4.0]undec-7-ene***, resulting in a synthesis of vinylphosphonium salts. If NaOH is used, a vinylphosphine oxide is generated.[19]

Other Nucleophiles.

DMTSF and $Et_3N.3HF$ react with alkenes to yield products formally of a MeSF addition. Yields are in excess of 80% and the reaction proceeds rapidly.[20] Homoallylic sulfides cyclized in the presence of DMTSF. The resulting sulfonium salt was successfully demethylated with Me_3N to yield 3-methylthiotetrahydrothiophenes.[21]

Dithioacetal, Trithioorthoester, and Thioglycoside Activation.

DMTSF provides a chemoselective reagent for dithioacetal activation in the presence of electron-rich alkenes.[22] This bond-forming procedure complements the $TiCl_4$ mediated reaction between acetals and silyl enol ethers demonstrated by Mukaiyama (see also ***Titanium(IV) Chloride*** and ***Trimethylsilyl Trifluoromethanesulfonate***). The generation of ketone precursors through dithioacetal carbanion (acyl anion equivalents) chemistry further amplifies the significance of DMTSF activation.

Dithioacetal Activation.

DMTSF chemoselectively reacts with dithioacetals in the presence of a vinylsilane[22] and in the presence of a silyl enol ether (eq 11), resulting in cyclization.[23]

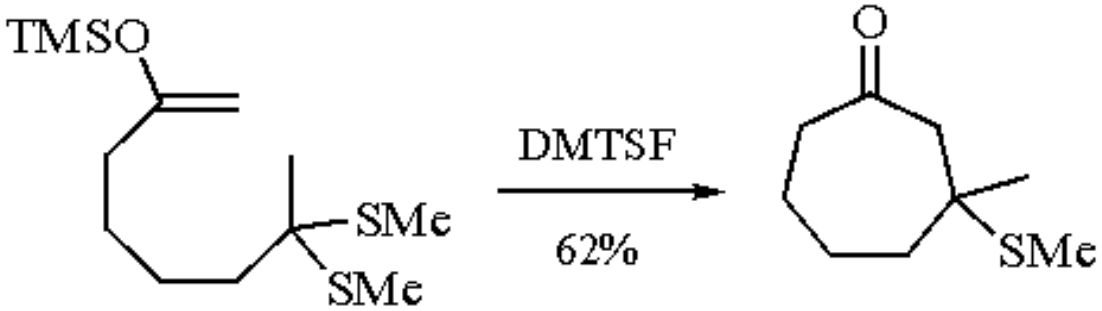

(11)

Many carbon nucleophiles tend to be too basic for successful addition to the carbocationic center provided by DMTSF activation of dithioacetals and usually result in vinyl sulfide formation. In addition, the Me_2S generated competes for the electrophilic center. Allylstannanes overcome these constraints and successfully generate new carbon-carbon bonds (eq 12).[24] DMTSF activation of a thioacetal resulted in an electrophilic cyclization at the 3-position of a 3-substituted indole.[25]

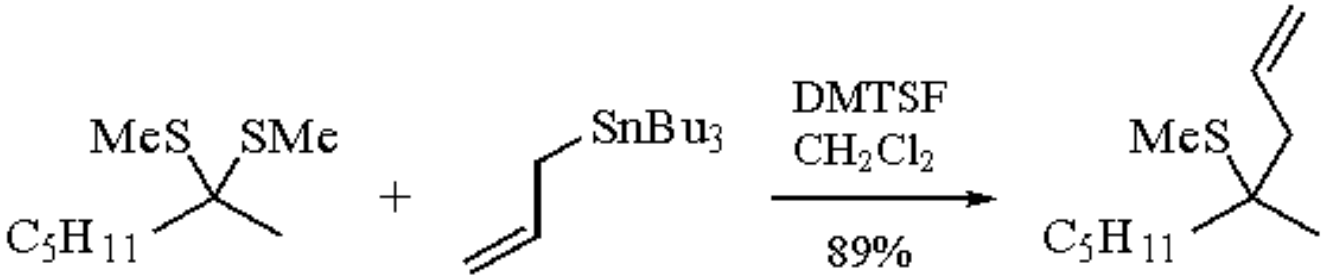

(12)

Trithioorthoester Activation.

Electron-rich aromatic rings undergo electrophilic aromatic substitution with ***Tris(phenylthio)methane*** in the presence of DMTSF. Subsequent hydrolysis results in an aldehyde and a net electrophilic formylation.[6] Intramolecular reaction between a tris(phenylthio)methane unit and an alcohol represents an approach to lactone formation which utilizes the chemoselectivity of DMTSF.[26]

Thioglycoside Activation.

A thioglycoside was successfully converted into a glycosyl fluoride with DMTSF.[7]

---

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Dimethyl (*E*)-4-Oxo-2-pentenedioate

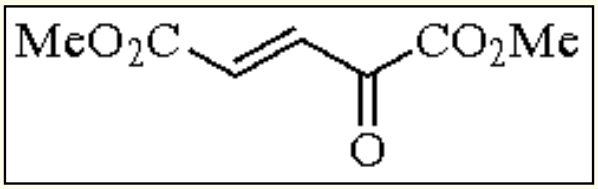

[78939-37-4] · $C_7H_8O_5$ · Dimethyl (*E*)-4-Oxo-2-pentenedioate · (MW 172.15)

(useful reagent for Doebner-von Miller-type annulations, quinoline synthesis; a potential dienophile)

Alternate Name: dimethyl 2-oxoglutaconate.

Physical Data: mp 61-62 °C.

Preparative Methods: dimethyl 2-oxoglutaconate (**1**) has been known since 1946, when it was prepared in low yield by the oxidation of dimethyl glutaconate.[1] Although the preparation by this route was recently improved,[2] the following procedure, as previously described, has been shown to be a more efficient synthesis.[3] A solution of bromine in dry methylene chloride (1.01 equiv) is added dropwise to a solution of dimethyl 2-oxoglutarate in the same solvent at reflux, followed by removal of solvent (and HBr) in vacuo. The resulting α-bromo ketone is treated with ***Triethylamine*** (TEA, 1 equiv) in ether at 25 °C for 20 min followed by filtration, passing the filtrate through a pad of silica gel, and concentration in vacuo to provide (**1**).

Handling, Storage, and Precautions: the enone functional group is remarkably reactive with amines at rt. Care should be exercised to avoid addition of excess TEA in its preparation. Handle in a fume hood.

Annulation Reactions.

The applications of (**1**) have been primarily as a synthon in the Doebner-von Miller-type synthesis of elaborated quinolines. Aryl amines with a free *ortho* position are excellent candidates for annulations with (**1**). In its original application, the reaction of (**1**) with aminoindole (**2**) provided in a one-pot preparation an advanced intermediate in the synthesis of the oxidative enzyme cofactor PQQ.[3] The first step in such annulations involves the conjugate addition of the amino group, followed by cyclization to a tetrahydroquinolinol intermediate. Addition of an acid catalyst (HCl, TsOH, or $BF_3.Et_2O$) promotes dehydration and aromatization to give, in the example cited, the pyrroloquinoline (**3**) (eq 1).

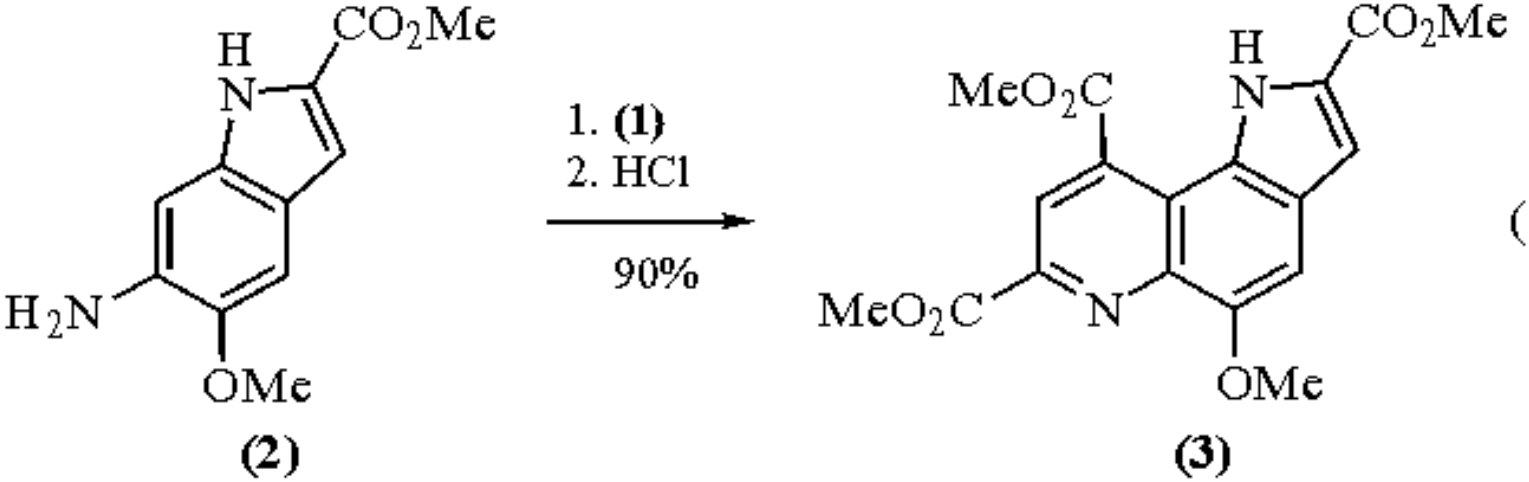

(1)

Cyclization with substituted anilines can occur with high regioselectivity. For example, there are two available sites *ortho* to the amine of (**4**); however, no product of the cyclization to the 5-position was observed.[4] The exclusive formation of (**5**) as a result of cyclization at the 7-position was anticipated due to the bond fixation of indoles (eq 2).

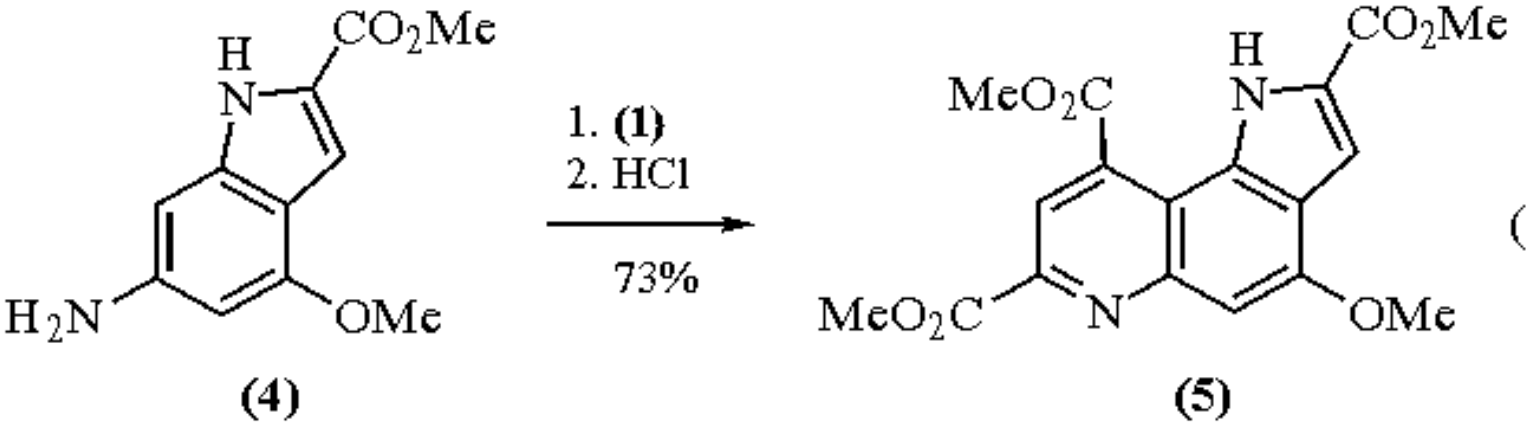

(2)

As a consequence of the facile one-step annulations with a variety of aniline derivatives, the reagent has been invaluable in the preparation of several biologically significant quinolines,[5,6] benzoquinolines,[7] and pyrroloquinolines.[8,9] In this capacity the reagent affords easy access to the quinoline dicarboxylates. Other alkyl esters can be obtained by starting with the corresponding alkyl 2-oxoglutaconate as evidenced in an example utilizing a didecyl ester derivative.[10]

The potential utility of reagent (**1**) as a dienophile in Diels-Alder cycloadditions has been recognized in one report.[2]

Related Reagents.

Dimethyl 2,3-Pentadienedioate; ***Methyl 5-Methoxy-3-oxopentanoate***; ***Methyl 3-Oxo-4-pentenoate***.

---

1. Cornforth, J. W.; Cornforth, R. H. *JCS* **1946**, 755.
2. Ananda, G. D. S.; Cremins, P. J.; Stoodley, R. J. *CC* **1987**, 882.
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7. Itoh, S.; Fukui, Y.; Haranou, S.; Ogino, M.; Komatsu, M.; Ohshiro, Y. *JOC* **1992**, *57*, 452.
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9. Jongejan, J. A.; Bezemer, R. P.; Duine, J. A. *TL* **1988**, *29*, 3709.
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Dimethyl 2,3-Pentadienedioate

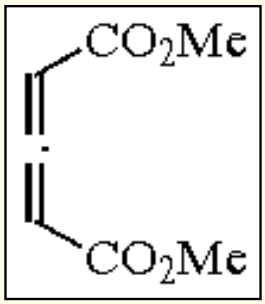

[1712-36-3] · $C_7H_8O_4$ · Dimethyl 2,3-Pentadienedioate · (MW 156.15)

(reactive in Diels-Alder cycloadditions that yield homophthalate diesters[1] and six-membered heterocycles,[2] in dipolar cycloadditions that yield five-membered heterocycles,[3] and in tandem conjugate addition-cyclization reactions to yield various heterocyclic systems[4])

Alternate Name: 1,3-dimethoxycarbonylallene.

Physical Data: bp 58 °C/0.02 mmHg.

Solubility: sol THF, benzene, acetonitrile, DME, MeOH.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H), 6.10 (s, 2H). IR (film) cm^{-1} 1970, 1720, 1440.

Preparative Methods: although not commercially available, dimethyl 2,3-pentadienedioate can be prepared by the route outlined in eq 1[5] to give approximately 13 g of the reagent per run.

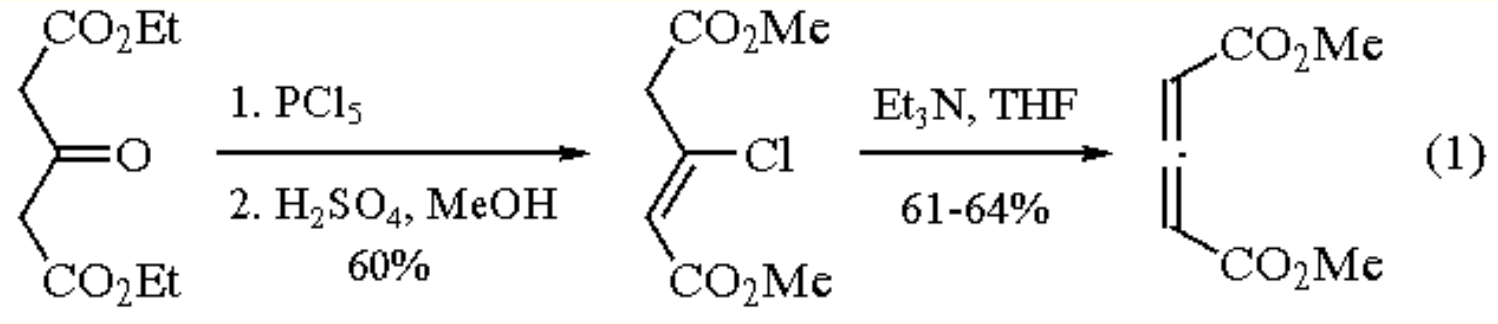

Purification: vacuum distillation.

Handling, Storage, and Precautions: dimethyl 2,3-pentadienedioate (**1**) polymerizes during distillation, necessitating that purification by this method be carried out in small batches. Upon standing, even overnight at refrigerator temperature, (**1**) becomes yellow and then orange and viscous. Preparation of amounts of (**1**) that will be immediately consumed, or storage of the vinyl chloride precursor and conversion to (**1**) as

needed, appear to be warranted. This reagent should be handled in a fume hood.

Homophthalate Diester Synthesis through Diels-Alder Cycloadditions.

By reaction with suitable dienes, especially reactive oxygenated examples, and subsequent aromatization, (**1**) serves as a building block for the synthesis of substituted homophthalate esters. In the example shown (eq 2),[1a] aromatization occurs by loss of methanol from the primary cycloadduct.

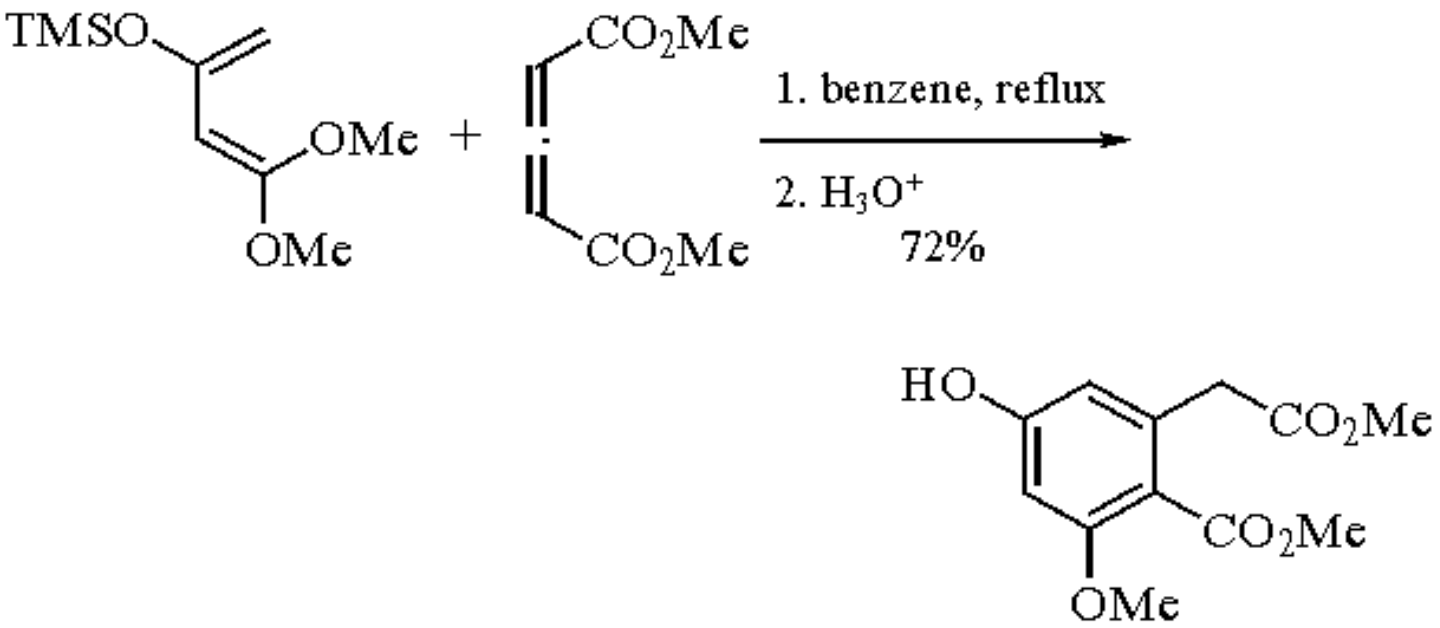

(2)

Alternatively, loss of carbon dioxide (eq 3)[6] or ethylene[7] from appropriate primary cycloadducts give homophthalate esters.

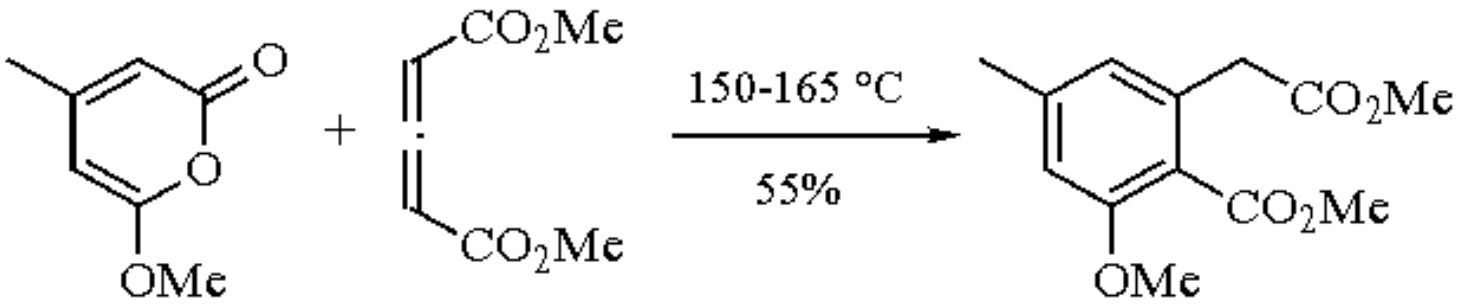

(3)

Six-Membered Heterocycle Synthesis through Hetero-Diels-Alder Cycloadditions.

Reagent (**1**) has been shown to engage certain heterodienes[2,8] in [4 + 2] cycloadditions to yield six-membered heterocyclic systems (eq 4).

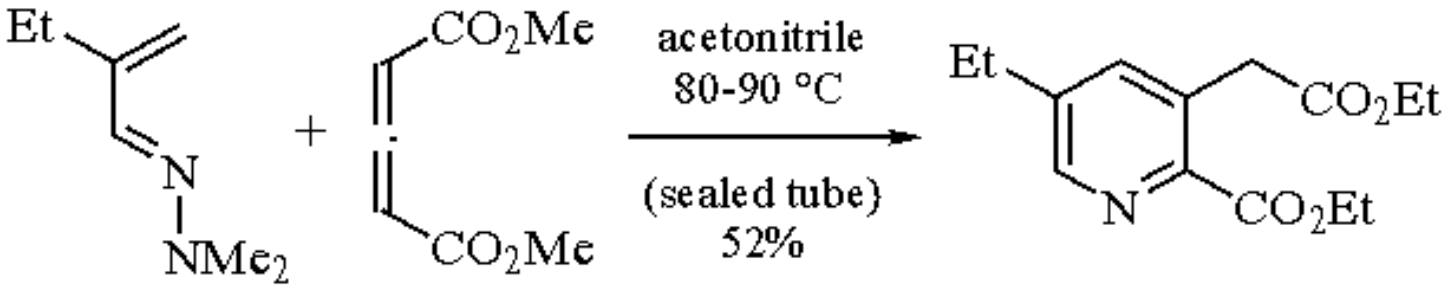

(4)

Five-Membered Heterocycle Synthesis through Dipolar Cycloadditions.

Reagent (**1**) also enters into dipolar cycloadditions, examples involving nitrones (eq 5)[3a] and azides[3b] being well documented.

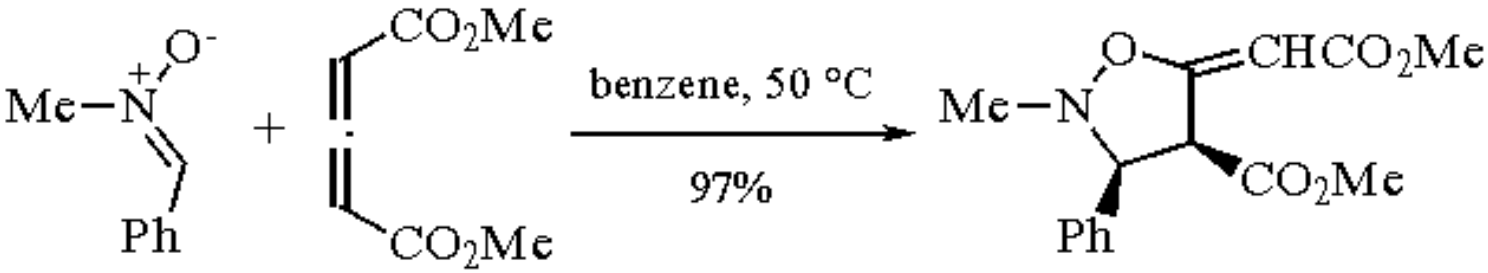

(5)

Heterocycle Synthesis through Tandem Conjugate Addition-Cyclization Reactions.

A number of applications of this reagent in transformations that are best characterized as tandem conjugate addition-cyclization reactions have been reported. These processes may combine conjugate addition of a carbon nucleophile with acylation of a heteroatom, as in eq 6,[4a] or conjugate addition of a heteroatom and acylation at carbon, as in eq 7.[4b] However, most often, heteroatoms play both nucleophilic roles (eqs 8 and 9).[4c-e]

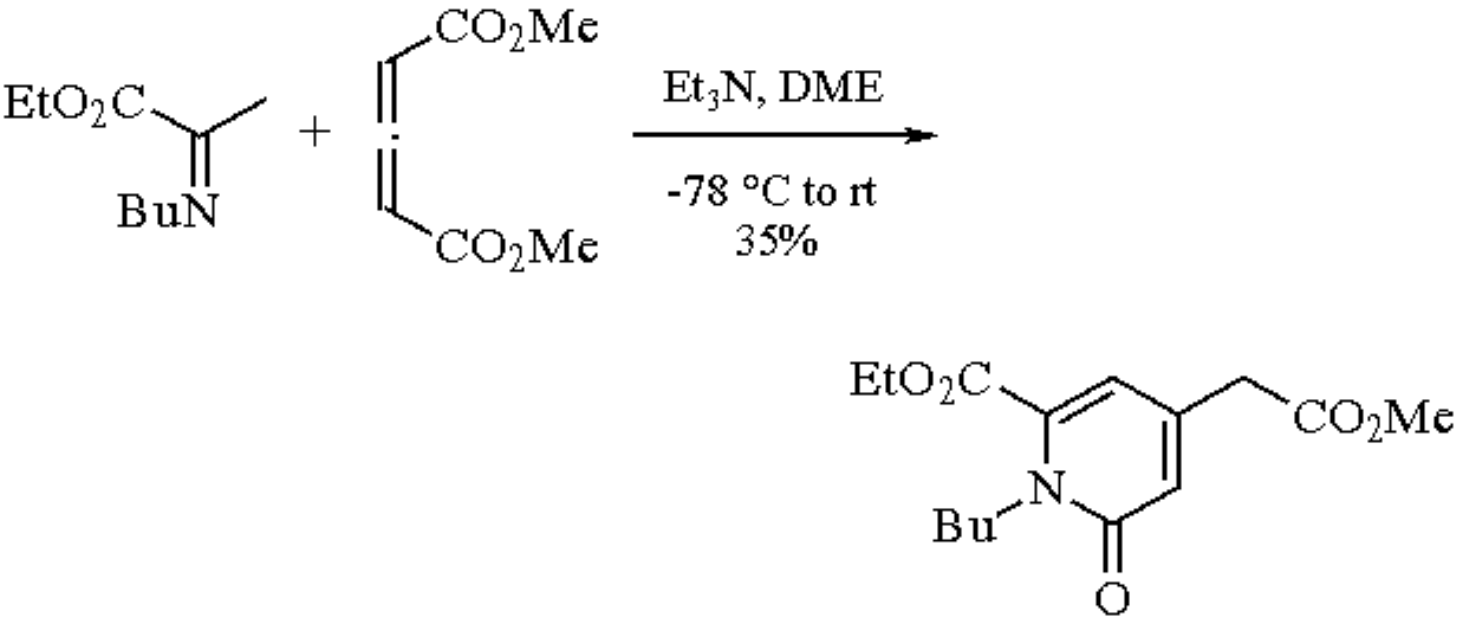
EtO2C
BuN
CO2Me
CO2Me
Et3N, DME
-78 °C to rt
35%
EtO2C
CO2Me
N
Bu
O

(6)

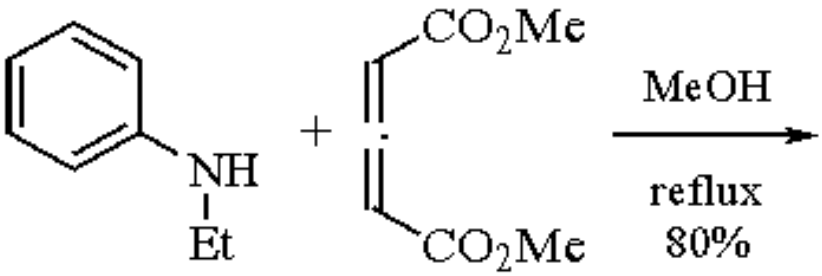
NH
Et
CO2Me
CO2Me
MeOH
reflux
80%

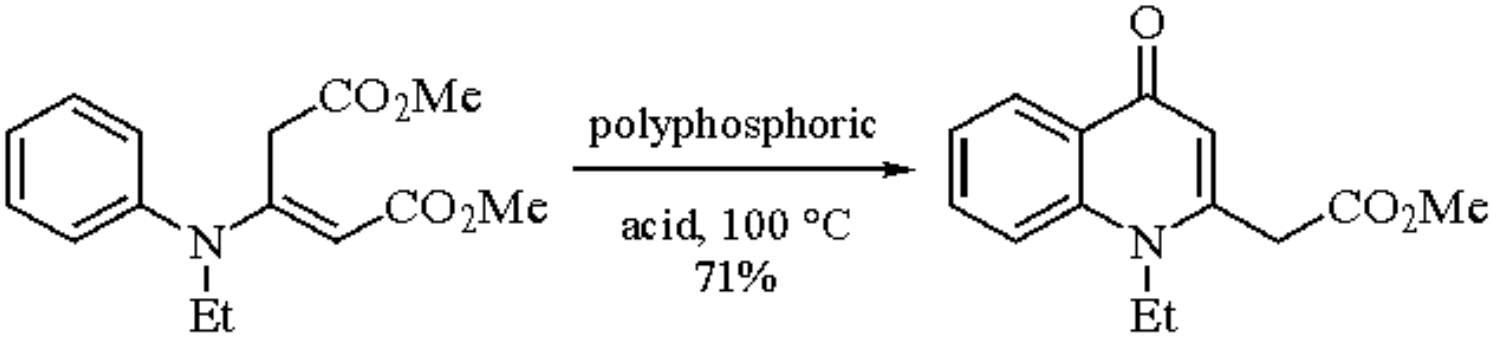
CO2Me
CO2Me
N
Et
polyphosphoric
acid, 100 °C
71%
O
CO2Me
N
Et

(7)

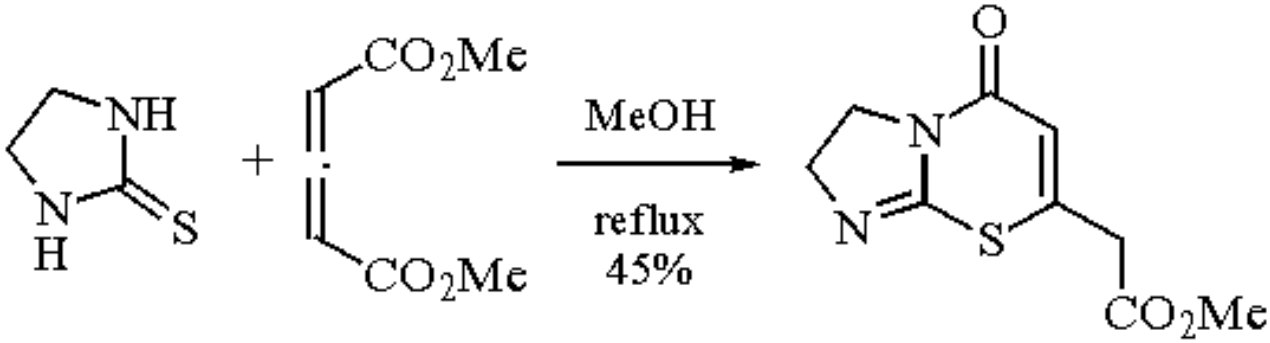
NH
N
H
S
CO2Me
CO2Me
MeOH
reflux
45%
O
N
N
S
CO2Me

(8)

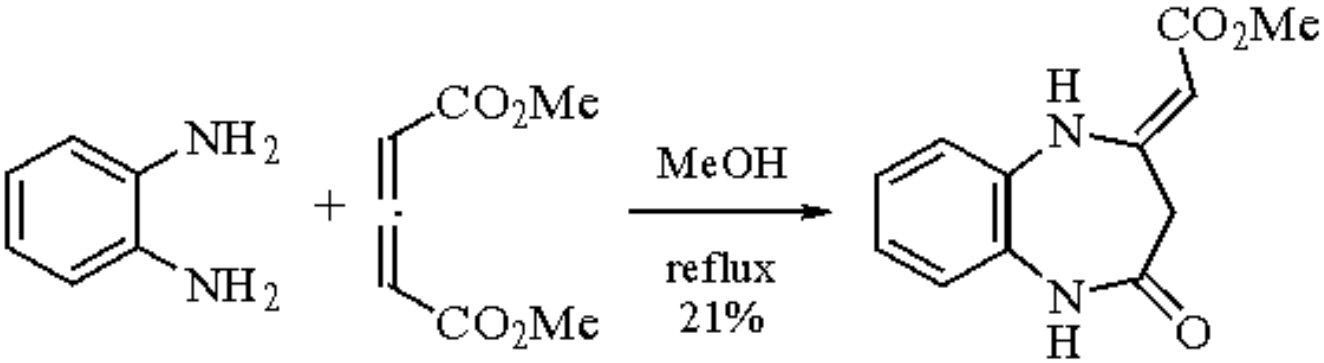

(9)

Alternatively, heteroatom conjugate additions in tandem with aldol (eq 10)[8] and Dieckmann (eq 11)[4c] condensations allow (**1**) to give rise to heterocyclic structures in which both reagent-derived carboxyl groups appear as substituents.

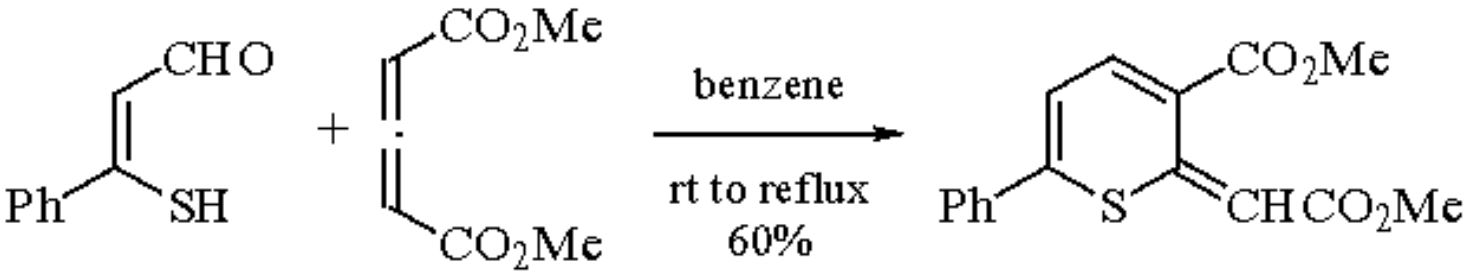

(10)

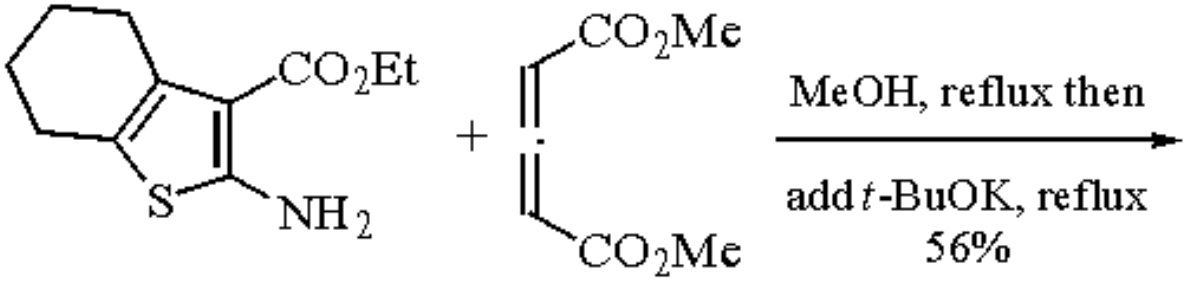

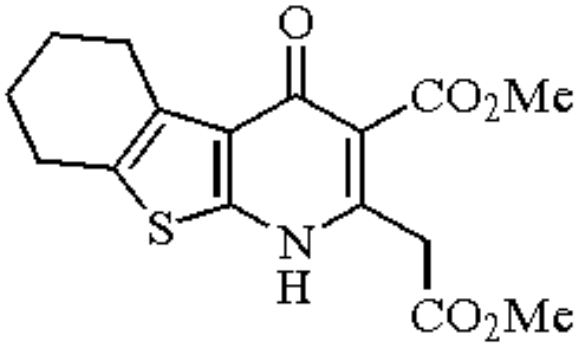

(11)

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1. (a) Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, Jr., P. M.; Fritsch, N.; Clardy, J. *JACS* **1979**, *101*, 7001. (b) Roush, W. R.; Murphy, M. *JOC* **1992**, *57*, 6622. For other Diels-Alder reactions of this reagent, see, for example: (c) Kozikowski, A. P.; Nieduzak, T. R.; Springer, J. P. *TL* **1986**, *27*, 819. (d) Dell, C. P.; Smith, E. H.; Warburton, D. *JCS(P1)* **1985**, 747.
2. Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. *S* **1984**, 930.

3. (a) Padwa, A.; Kline, D. N.; Koehler, K. F.; Matzinger, M.; Venkatramanan, M. K. *JOC* **1987**, *52*, 3909. (b) Barraclough, D.; Moorhouse, N. P.; Onwuyali, E. I.; Scheinmann, F.; Hursthouse, M. B.; Galas, A. M. R. *JCR(S)* **1984**, 102. *JCR(M)* **1984**, 1101.
4. (a) Quick, J. *TL* **1977**, 327. (b) Nixon, N. S.; Scheinman, F.; Suschitzky, J. L. *JCR(S)* **1984**, 380. *JCR(M)* **1984**, 3401. (c) Doad, G. J. S.; Okor, D. I.; Scheinmann, F.; Bates, P. A.; Hursthouse, M. B. *JCS(P1)* **1988**, 2993. (d) Acheson, R. M.; Wallis, J. D. *JCS(P1)* **1982**, 1905. (e) Ackroyd, J.; Scheinmann, F. *JCR(S)* **1982**, 89; *JCR(M)* **1982**, 1012.
5. Bryson, T. A.; Dolak, T. M. *OS* **1977**, *57*, 62; *OSC* **1988**, *6*, 505.
6. Mehta, G.; Venkateswarlu, Y. *JCS(C)* **1988**, 1200.
7. Arai, Y.; Kamikawa, T.; Kubota, T. *TL* **1972**, 1615.
8. Pulst, M.; Greif, D.; Weissenfels, M.; Doad, G. J. S.; Scheinmann, F. *JCR(S)* **1989**, 300; *JCR(M)* **1989**, 2301.

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cis-3-[*N*-(3,5-Dimethylphenyl)benzenesulfonamido]borneol[1]

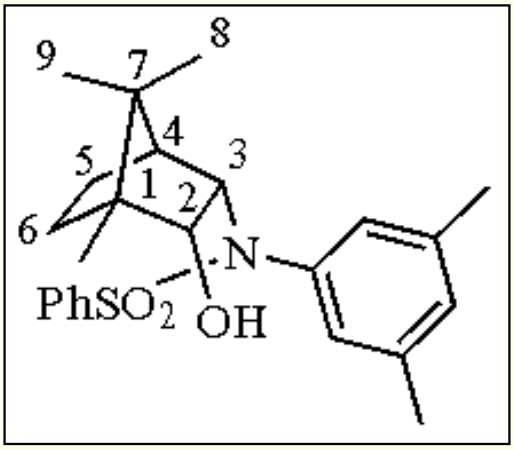

(1*R*) (*endo,endo*)

[87360-02-9] · $C_{24}H_{31}NO_3S$ · *cis*-3-[*N*-(3,5-Dimethylphenyl)benzenesulfonamido]borneol · (MW 413.63)

(chiral auxiliary; ester enolate derivatives undergo stereoselective alkylations[2] and enantioselective *anti*-aldol reactions;[3] enoate derivatives undergo stereoselective 1,4-conjugate additions of organocopper reagents[4])

Alternate Name: *N*-(3,5-dimethylphenyl)-*N*-(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl)benzenesulfonamide.

Physical Data: (1*R*) (*endo,endo*): mp 147-150 °C; [α]20D -26.0° (*c* = 4.0, $CHCl_3$).

Handling, Storage, and Precautions: the auxiliary is stable indefinitely at ambient temperatures in a sealed container.

Introduction.

One of several auxiliaries that exploit the asymmetry of naturally occurring (+)-camphor, the 3-(*N*-(3,5-dimethylphenyl)benzenesulfonamido)borneol auxiliary has proven significant utility in the π-facial differentiation of ester enolates and enoate derivatives. The *endo* orientation of the C(2) and C(3) substituents places the reactive functionality within the concave pocket created by the bornane skeleton as well as the shielding ability of the *N*-arylbenzenesulfonamide.

Preparation of the Auxiliary.

A synthesis of the (1*R*) auxiliary has been reported starting from (+)-camphor (eq 1). ***Zinc*** reduction of the intermediate

imine (**2**) followed by sulfonylation and ketone reduction with $Ca(BH_4)_2$ afforded the *cis,endo* product in 70-75% overall yield from camphorquinone (**1**).

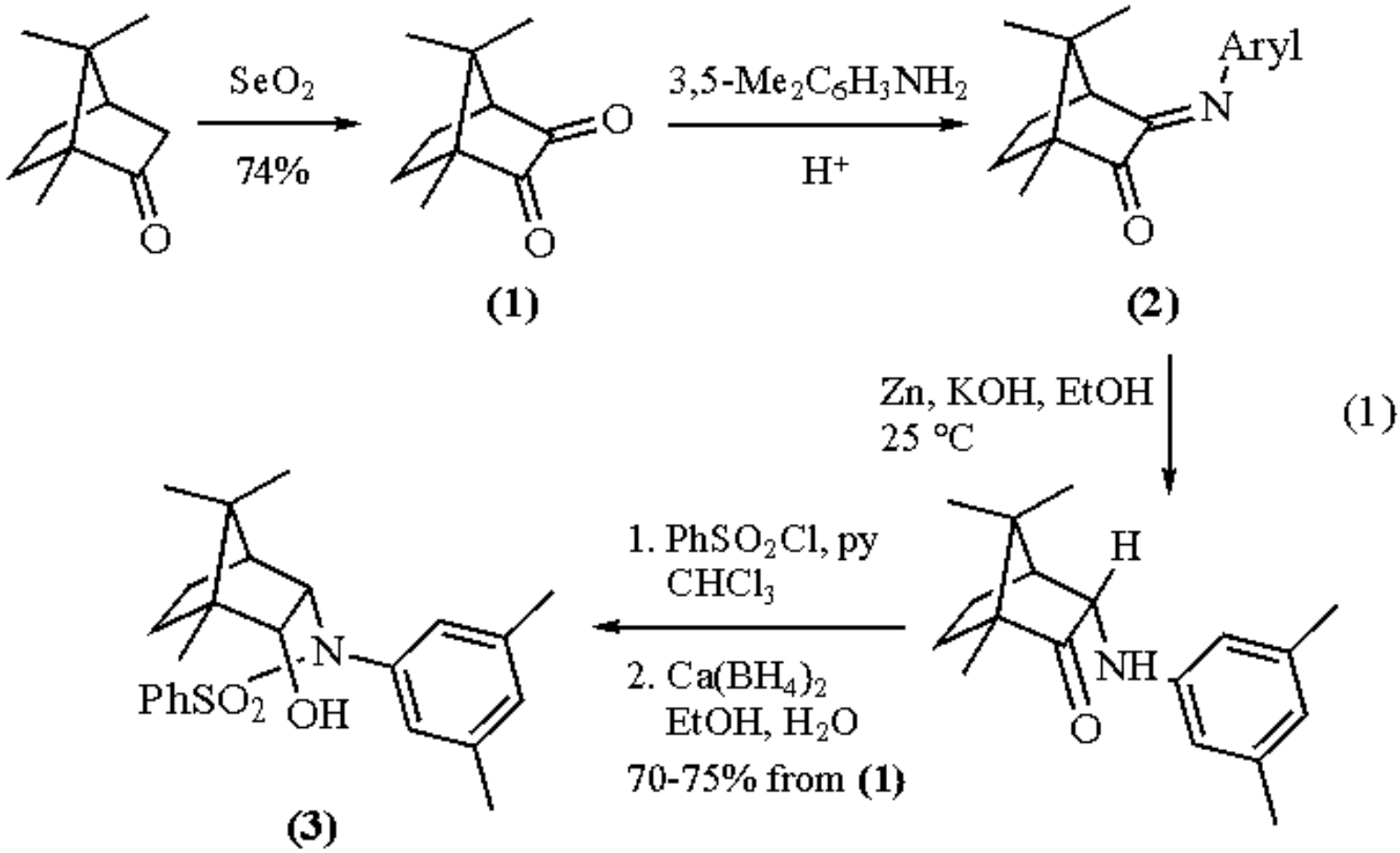

Preparation of Derivatives.

Enoate derivatives were prepared by Horner-Wittig reactions between aldehydes and the ethyl phosphonate derived from the chloroacetyl ester of (**3**) in high (*E*) selectivity (97:3).[4b] Ester derivatives were obtained by treating alcohol (**3**) with the corresponding carboxylic acid chloride.[5]

α-Alkylation of Ester Derivatives.[2]

Alkylation of ester enolate derivatives, prepared by metalation with lithium cyclohexylisopropylamide (LICA), proceeds with high stereoselectivity. The configuration of the product is dependent on the solvent employed (eqs 2 and 3). When performed in THF with the addition of HMPA the product with the (*S*) configuration was formed preferentially; however, without HMPA the (*R*) configuration predominated. Silyl chloride trapping studies suggest that in the presence of HMPA the (*E*)-ester enolate is stereoselectively formed, as opposed to the (*Z*)-ester enolate in THF alone.[2b] The stereochemical outcome has been explained by alkylation of the corresponding enolate π-face opposite to the shielding 3,5-dimethylphenyl moiety. *O*-Benzylglycolates have also been employed in stereoselective alkylations, affording diastereomeric excesses of 88-95%.[2c] In this case the solvent-dependent stereochemical reversal does not occur and the (*E*)-ester enolate is stereoselectively formed in both cases.

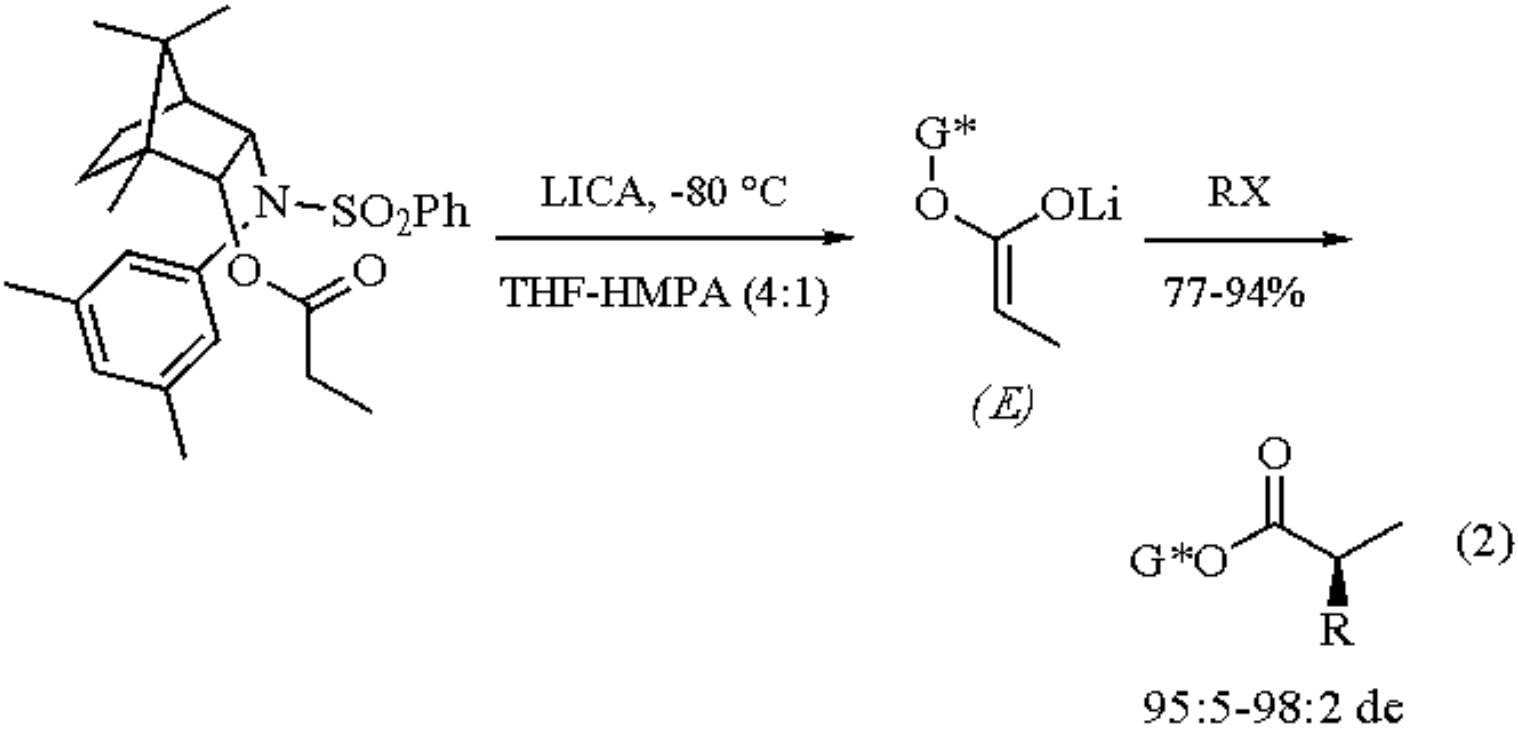

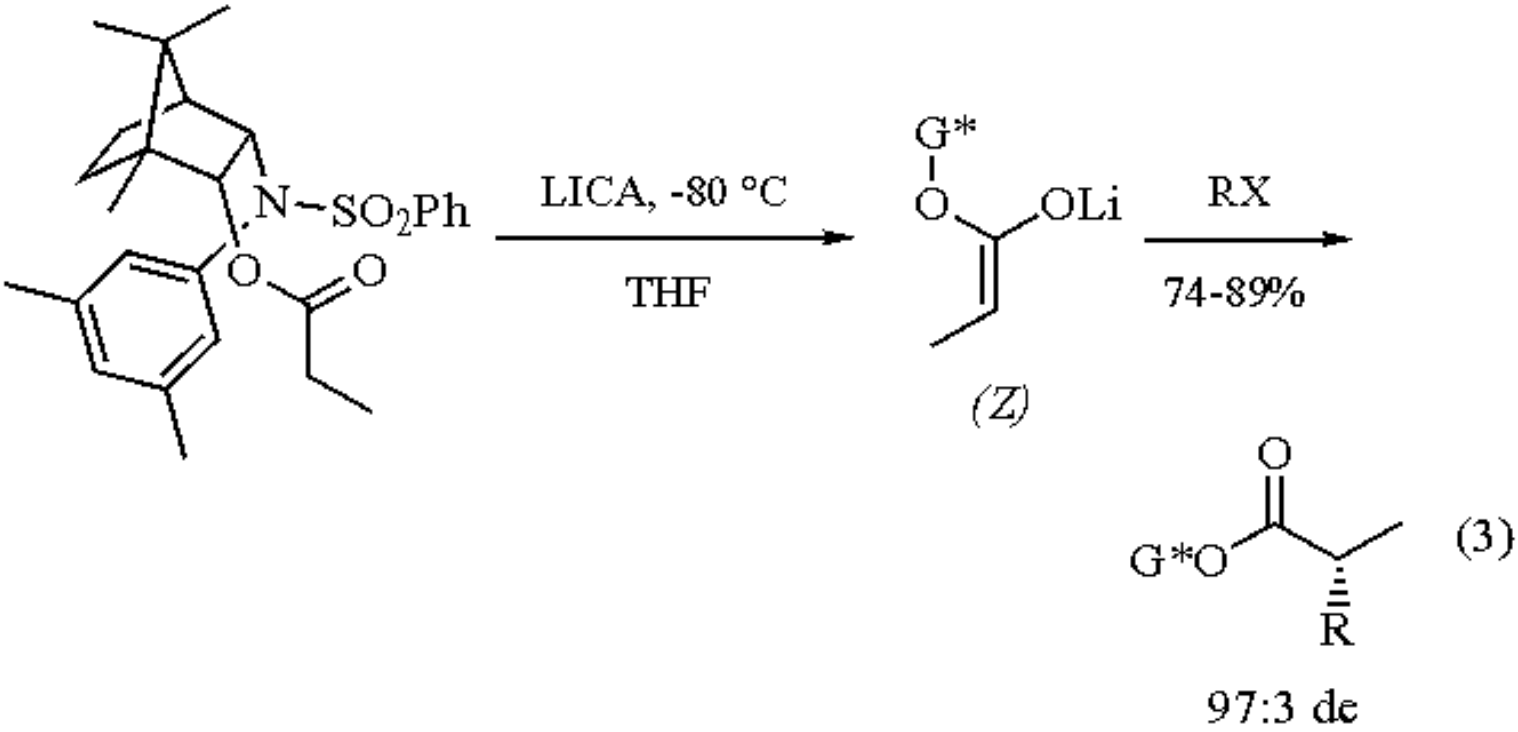

Aldol Reactions of Ester Derivatives.[3]

The ***Titanium(IV) Chloride***-catalyzed addition of aldehydes to *O*-silyl ketene acetals derived from acetate and propionate esters proceeds with high stereoselectivity. Formation of the silyl ketene acetal was found to be essential for high diastereoselectivity. Treatment of the silyl ketene acetal, derived from deprotonation of the acetate ester with LICA in THF and silyl trapping, with a corresponding aldehyde in the presence of $TiCl_4$ (1.1 equiv) afforded the addition products in 93:7 diastereoselectivity and moderate yield (51-67%). Similarly, the propionate ester provides the *anti*-aldol product in high *anti*/*syn* selectivity (14:1) and facial selectivity (eq 4).

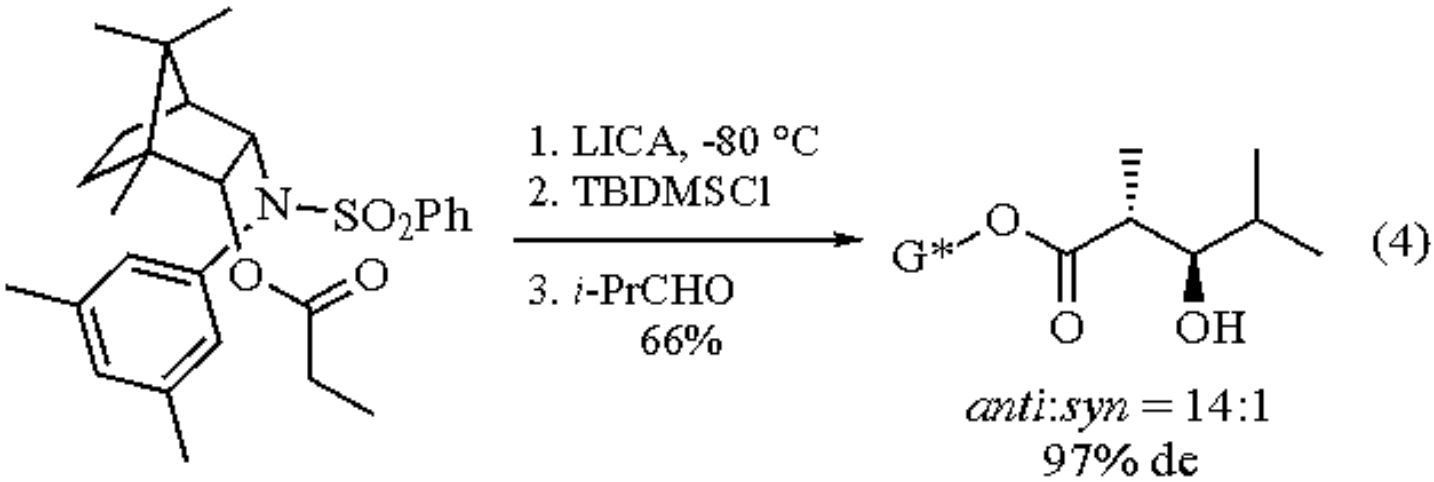

1,4-Conjugate Additions to Enoate Derivatives.[4]

High diastereoselectivity has been observed for ***Boron Trifluoride***-promoted addition of alkyl and aryl organocopper reagents to enoate derivatives (eq 5).[4b] When the organocopper reagent was prepared from alkyl- or aryllithiums, diethyl ether was found to be the solvent of choice; however, with Grignard reagents, THF was superior. The addition of boron trifluoride exhibited little influence on reactivity of the copper reagent but did enhance the stereoselectivity of the addition. It is believed that the enoate adopts an *s-trans* conformation and the observed stereochemical preference results from approach of the organocopper reagent to the less sterically hindered face opposite the aryl moiety.

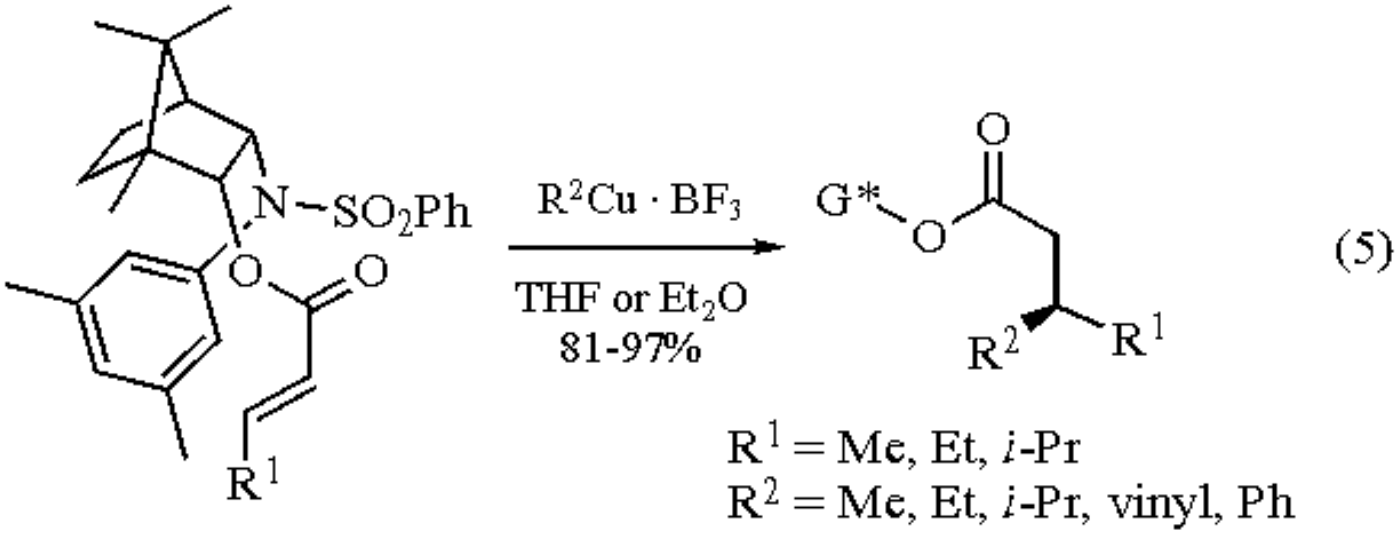

Nondestructive Removal of the Auxiliary.

Primary alcohols are obtained by ***Lithium Aluminum Hydride*** reduction of the corresponding chiral esters. Also, hydrolysis of the auxiliary under basic conditions, 2N KOH in methanol,[4b] provides the carboxylic acid and recovered alcohol (**3**).

Related Reagents.

3-Hydroxyisoborneol; ***(1R,2S)-N-Methylephedrine***.

---

1. Oppolzer, W. *T* **1987**, *43*, 1969.
2. (a) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *AG(E)* **1981**, *20*, 207. (b) Helmchen, G.; Selim, A.; Dorsch, D.; Taufer, I. *TL* **1983**, *24*, 3213. (c) Helmchen, G.; Wierzchowski, R. *AG(E)* **1984**, *23*, 60.
3. Helmchen, G.; Leifauf, U.; Taufer-Knöpfel, I. *AG(E)* **1985**, *24*, 874.
4. (a) Rossiter, B.; Swingle, N. M. *CRV* **1992**, *92*, 771. (b) Helmchen, G.; Wegner, G. *TL* **1985**, *26*, 6051.
5. Dorsch, D.; Kunz, E.; Helmchen, G. *TL* **1985**, *26*, 3319.

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1,3-Dimethyl-2-phenylbenzimidazoline

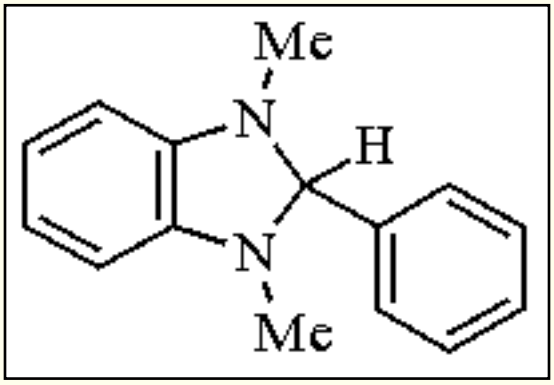

[3652-92-4] · $C_{15}H_{16}N_2$ · 1,3-Dimethyl-2-phenylbenzimidazoline · (MW 224.33)

(heterocycle capable of reducing α-halo ketones, α,β-unsaturated carbonyl compounds, and α-nitro sulfones)

Alternate Name: DMBI.

Physical Data: mp 94 °C.

Preparative Method: N^1,N^2-dimethyl-*o*-phenylenediamine is condensed with benzaldehyde in methanol-acetic acid. The product is purified by recrystallization from petroleum ether.[1] The spent reagent may be recovered and reactivated by ***Sodium Borohydride*** in methanol.[5]

DMBI has been found to dehalogenate α-halo ketones and halogenated benzophenones without affecting the carbonyl group (eq 1) (see also ***Tri-n-butylstannane***). The mechanism was identified as a radical chain process containing a SET-hydrogen atom abstraction/propagation sequence.[2] The reaction typically requires initiation, e.g. by ***Azobisisobutyronitrile*** (AIBN) or ***Di-t-butyl Peroxyoxalate*** (DBPO). Thiophenol may be used to catalyze the transformation, for sluggish tertiary halo ketones, by facilitating the hydrogen atom transfer step.[3]

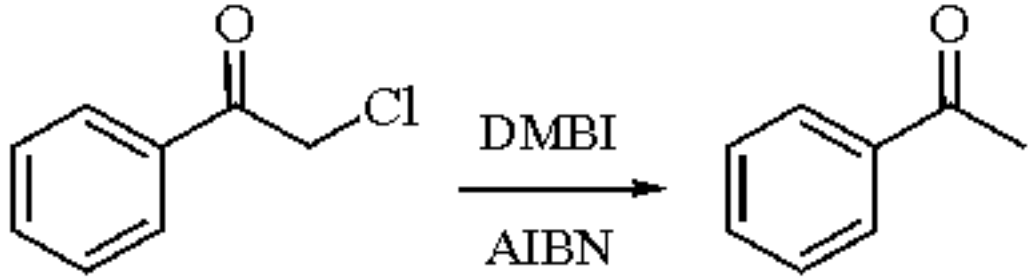

(1)

DMBI was reported to reduce α,β-unsaturated ketones to the corresponding saturated ketones in the presence of a Lewis acid (eq 2). ***Aluminum Chloride*** was found to be the acid of choice, with stoichiometric quantities being required.[4] The reaction failed for α,β-unsaturated aldehydes and in the absence of a Lewis acid.

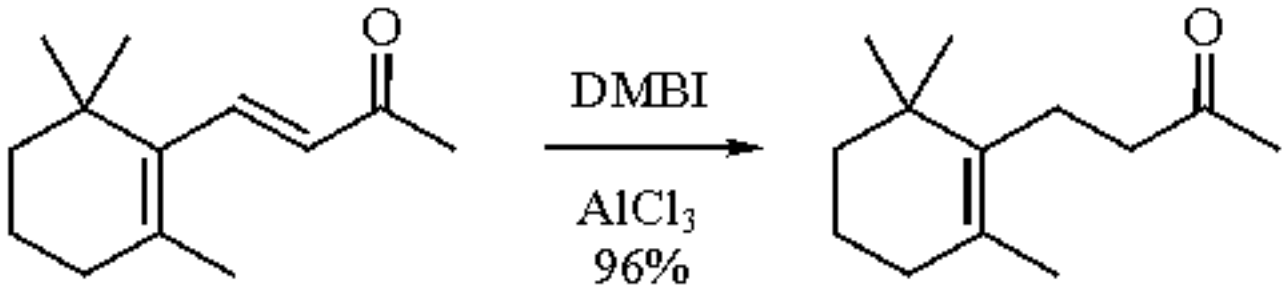

(2)

α-Nitro sulfones were desulfurized when exposed to DMBI (eq 3).[5] The mechanism was found to be a radical chain process which typically requires initiation. More well-known desulfurization reagents, such as ***Raney Nickel*** or catalytic hydrogenation, would not be expected to leave the nitro group intact. DMBI was also superior to *N*-benzyl-1,4-dihydronicotinamide for this transformation.

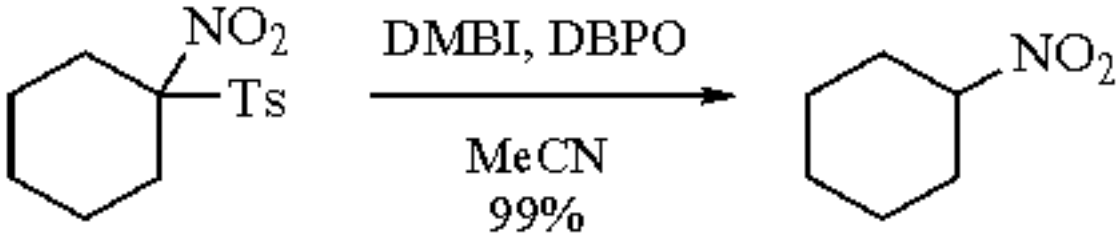

(3)

DMBI is conveniently prepared from available starting materials. The reagent may be recovered and recycled. The reagent is most often used in mechanistic studies. No preparative (i.e. 0.1 mol) uses are available in the current literature.

---

1. Reddy, P. R.; Veeranagaiah, V.; Ratnam, C. V. *IJC(B)* **1985**, *24*, 367.
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3. Tanner, D. D.; Chen, J. J. *JOC* **1992**, *57*, 662.

4. Chikashita, H.; Itoh, K. *BCJ* **1986**, *59*, 1747.
5. Tanner, D. D.; Chen, J. *JOC* **1988**, *53*, 3897.

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2,6-Dimethylphenyl Propionate[1]

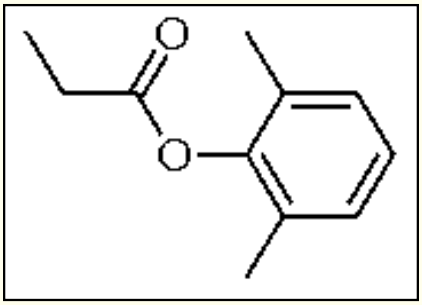

[51233-80-8] · $C_{11}H_{14}O_2$ · 2,6-Dimethylphenyl Propionate · (MW 178.25)

(lithium, titanium, and zirconium enolates used in the stereoselective synthesis of *anti*[2] or *syn*[4] β-hydroxy acid derivatives)

Physical Data: bp 60-65 °C/0.05 mmHg.

Preparative Methods: the reagent is prepared in excellent yield by the reaction of the sodium or lithium salt of 2,6-dimethylphenol with propionyl chloride.[2a,2b]

Stereoselection in Reactions of Lithium Enolates.

The (*E*)-lithium enolate (**2**) obtained from reaction of 2,6-dimethylphenyl propionate (**1**) with ***Lithium Diisopropylamide*** reacts with aldehydes to afford the *anti*-β-hydroxy ester (**3**) in a highly selective or specific manner (eq 1).[2-4] Table 1 illustrates the level of diastereoselection possible with a variety of structurally simple aldehydes. In general, reaction with aromatic and straight-chain aliphatic aldehydes results in lower degrees of diastereoselection than reaction with aldehydes containing branching at the α-carbon. The β-hydroxy esters are hydrolyzed to the corresponding *anti*-β-hydroxy acid under mild reaction conditions.

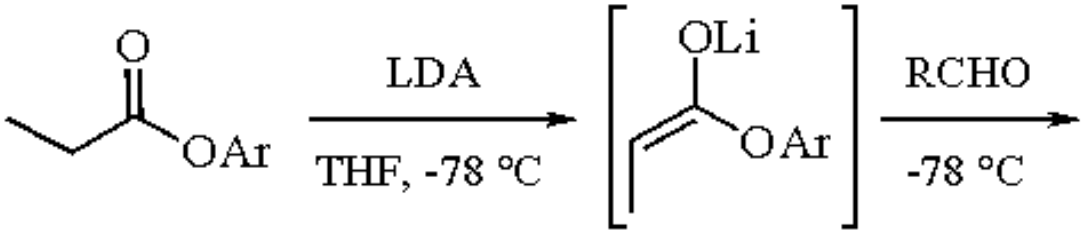

Ar = 2,6-dimethylphenyl (*E*)-(**2**)

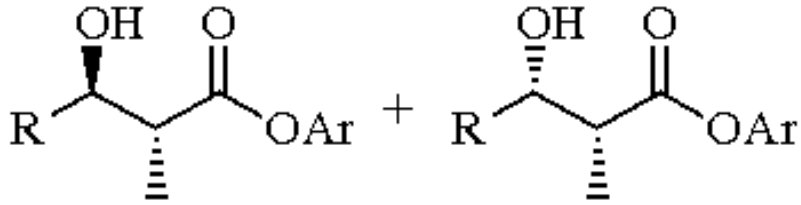

(1)

(**3**) *anti* (**4**) *syn*

Table 1 Ratios of Diastereomeric b-Hydroxy Esters (**3**):(**4**) from the Reaction of the (*E*)-Lithium Enolate of (**1**) with Various Aldehydes (RCHO)

R	(**3**):(**4**)
n-Pr	>32:1[4]
n-C_5H_{11}	6:1[2]
n-C_6H_{13}	7:1[3]
CH_2=CH	4:1[4]
Ph	7:1[2 4]
i-Pr	>49:1[a 2]
t-Bu	>49:1[b 2]
CH_2=C(Me)	24:1[4]

[a] A lower ratio of (**3**):(**4**) (13:1) was reported by another author.[4]
[b] A lower ratio of (**3**):(**4**) (8:1) was reported by another author.[4]

Condensations of the enolate (**2**) with more complex aldehydes (i.e. **5**-**20**) containing additional functional groups and stereocenters have been reported.[2b,5-12] Excellent levels of diastereocontrol are observed in formation of the 2,3-*anti*-β-hydroxy esters in all instances except the reaction with the α-alkoxy aldehydes.[6] With aldehydes that contain resident

stereocenters, the facial selectivity in the attack of enolate (**2**) on the aldehyde varies widely. Aldehydes (**5**)-(**7**) react with modest degrees of stereoselection (2-4:1) in favor of formation of the product predicted by Cram's rule (i.e. *syn* relationship between C-3 and C-4 in the β-hydroxy ester).[2,11] The aldehydes possessing a phenylthio group at the α-position (**8-13**) yield β-hydroxy esters in which the hydroxy groups and phenylthio groups are *anti* with a high degree of selectivity.[7] Aldehydes (**14**)-(**19**) appear to follow Cram's rule exclusively or highly selectively.[8,9] Facial selectivity in reaction of lithium enolate (**2**) with aldehyde (**20**) is modest (approximately 2:1).[12]

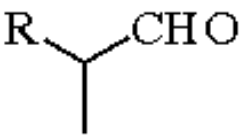

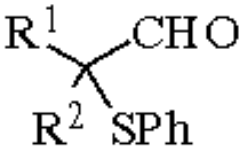

(5) R = Ph
(6) R = $(CH_2)_2CO_2Me$
(7) R = $(CH_2)_2CH{=}CH_2$

(8) R^1 = Et, R^2 = H
(9) R^1 = Et, R^2 = Me
(10) $R^1 = CH_2CH_2CHMe_2$, R^2 = Me
(11) $R^1 = (CH_2)_2$(3,4-methylenedioxyphenyl) R^2 = Me
(12) $R^1 = (CH_2)_3OTBDPS$, R^2 = Me

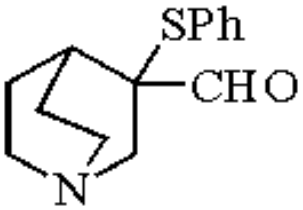

(13)

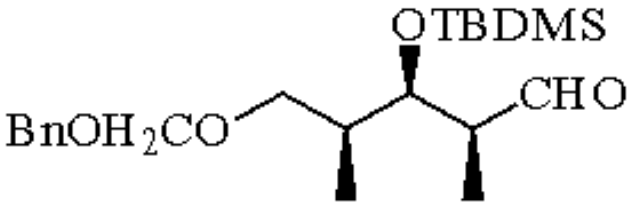

(14)

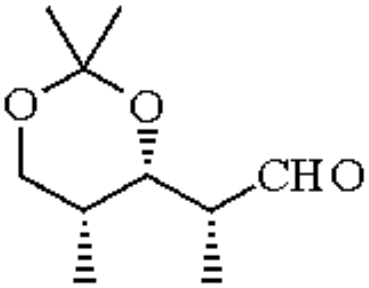

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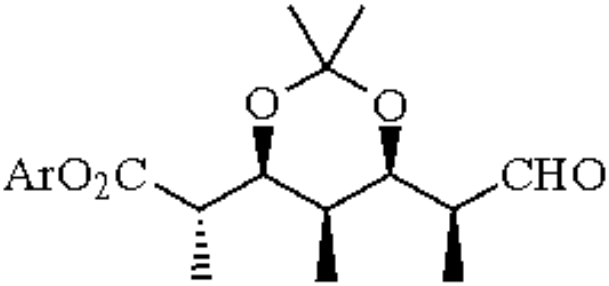

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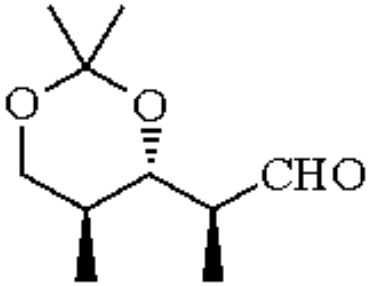

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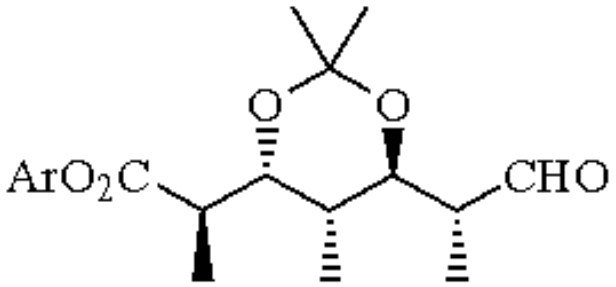

(18)

Ar = 2,6-dimethylphenyl

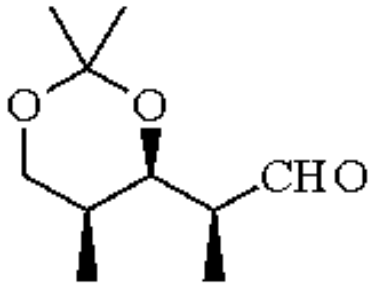

(19)

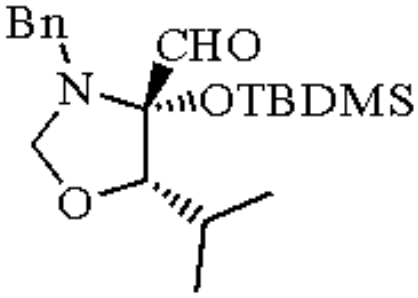

(20)

Lithium enolates derived from propionate esters of other highly hindered phenols (e.g. 2,6-di-*t*-butyl-4-methylphenol (BHT) and 2,6-di-*t*-butyl-4-hydroxyanisole (DBHA)) are known to be more selective than (**2**) in condensation reactions with aldehydes to yield *anti*-β-hydroxy esters.[2] However, these esters cannot be removed by simple hydrolytic procedures without complications from retro-aldol reactions. Removal of the BHT or DBHA group in these *anti*-β-hydroxy esters requires reduction to the corresponding 1,3-diol with ***Lithium Aluminum Hydride*** or conversion to the corresponding *anti*-β-hydroxy acids under oxidative conditions (e.g. ***Cerium(IV) Ammonium Nitrate***).[2b,c] Yields in the latter process are highly variable.[2a] The oxidations are often performed on the acetate esters of the *anti*-β-hydroxy esters in an attempt to produce reliable yields.[2b] Lithium enolates derived from other esters of 2,6-dimethylphenol are reported to be highly *anti* selective in condensations with aldehydes.[2]

Reactions of Titanium Enolates.

In contrast to reactions of (*E*)-lithium enolate (**2**), (*E*)-titanium enolates (**21**) are reported to afford the *syn*-β-hydroxy ester predominantly (eq 2).[4] The (*E*)-titanium enolates (**21**) are prepared by transmetalation of the corresponding (*E*)-lithium enolate. Achiral (*E*)-enolates (**21a**) yield predominantly *syn*-β-hydroxy esters in reactions with aldehydes (Table 2). The yield and degree of stereoselection are excellent in all cases except in reaction with pivaldehyde. With (*E*)-titanium enolates bearing chiral ligands (i.e. (**21b**) R = diacetoneglucose (DAG)), the *syn*-β-hydroxy ester of (*R*) configuration at C(2) is formed with high optical purity.

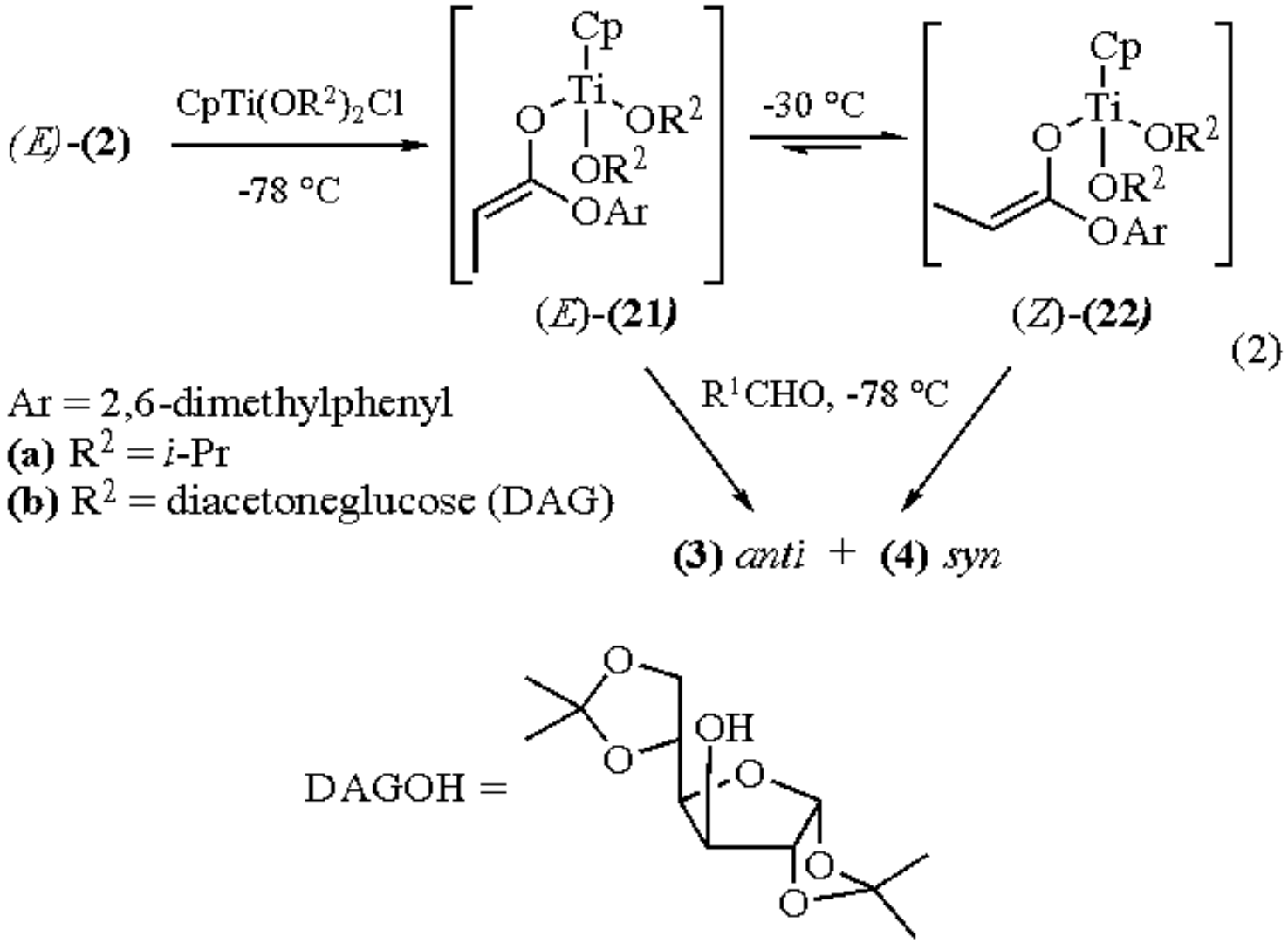
(E)-(2)
CpTi(OR2)2Cl
-78 °C
Cp
Ti
O
OR2
OR2
OAr
-30 °C
(E)-(21)
(Z)-(22)
(2)
R1CHO, -78 °C
Ar = 2,6-dimethylphenyl
(a) R2 = i-Pr
(b) R2 = diacetoneglucose (DAG)
(3) anti + (4) syn
DAGOH =
OH

Table 2 Ratios of Isomeric b-Hydroxy Esters (**4**):(**3**) from the Reaction of (*E*)-Titanium Enolate (**21**) with Aldehydes (eq 2)

R^1	R^2	(**4**):(**3**)	Optical purity of (**4**) ee (%)	Yield (%)
n-Pr	*i*-Pr	19:1	NA	62
i-Pr	*i*-Pr	13:1	NA	59
t-Bu	*i*-Pr	4:1	NA	53
CH_2=CH	*i*-Pr	49:1	NA	65
CH_2=C(Me)	*i*-Pr	49:1	NA	63
Ph	*i*-Pr	55:1	NA	68
n-Pr	DAG[a]	12:1	95	87
i-Pr	DAG	17:1	97	76
t-Bu	DAG	8:1	91	71
CH_2=CH	DAG	32:1	96	79
CH_2=C(Me)	DAG	25:1	93	61
Ph	DAG	26:1	94	82

[a] DAG = diacetoneglucose.

The (*E*)-titanium enolates (**21**) can be equilibrated to a mixture of (*E*)- and (*Z*)-enolates in which the (*Z*)-enolate (**22**) predominates by standing at -30 °C for several hours.[4] The degree of diastereoselection in reaction of the equilibrated enolate mixture with aldehydes is not as consistently high as it is in the case of the reaction with the (*E*)-enolate (Table 3); however, the *anti*-β-hydroxy ester is usually the major product. The optical purity of the *anti*-isomer is very high in all cases.

Table 3 Reaction of an Equilibrated Mixture of Chiral Titanium Enolates (**21**) and (**22**) with Aldehydes (eq 2)

R^1	R^2	(**3**):(**4**)	Optical purity of (**3**) ee (%)	Yield (%)
n-Pr	DAG[a]	8:1	95	74
i-Pr	DAG	9:1	96	76
t-Bu	DAG	5:1	98	59
CH_2=CH	DAG	4:1	98	61
CH_2=C(Me)	DAG	1:1	94	50
Ph	DAG	1:3	94	70

[a] DAG = diacetoneglucose.

Reactions of Zirconium Enolates.

Reaction of the zirconium enolate of (**1**) with isobutyraldehyde gave a 6:1 mixture of *syn*- and *anti*-β-hydroxy esters (**4** and **3**).[4]

Related Reagents.

(R)-(+)-t-Butyl 2-(p-Tolylsulfinyl)propionate; ***Ethyl Lithioacetate***; ***Ethyl Bromozincacetate***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***2-Methyl-2-(trimethylsilyloxy)-3-pentanone***; ***(S)-4-Benzyl-2-oxazolidinone***; ***3-Propionylthiazolidine-2-thione***; ***(R)-(+)-3-(p-Tolylsulfinyl)propionic Acid***; ***1,1,2-Triphenyl-1,2-ethanediol***.

---

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H.; Villa, M.-J.; Warren, S. *TL* **1988**, *29*, 4885. (e) Aggarwal, V. K.; Warren, S. *TL* **1987**, *28*, 1925.
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Dimethyl(phenyl)silane

$PhMe_2SiH$

[766-77-8] · $C_8H_{12}Si$ · Dimethyl(phenyl)silane · (MW 136.29)

(hydrosilylating reagent; reductant in combination with acid or F^-)

Physical Data: bp 157 °C/744 mmHg; *d* 0.889 g cm^{-3}.

Solubility: sol common organic solvent such as chloroform, 1,2-dichloroethane, benzene, ether, acetone, dioxane, THF; insol H_2O.

Form Supplied in: oil, commercially available.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$-Me_4Si) δ 7.6-7.4 (m, 2 H), 7.4-7.2 (m, 3 H), 4.42 (septet, *J* = 3.6 Hz, 1 H), 0.34 (d, *J* = 3.6 Hz, 6 H). ^{13}C and ^{29}Si NMR have also been reported.[2]

Preparative Method: see Benkeser and Foster.[1]

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; evolves H_2 when added to wet piperidine.

Diastereoselective Reduction of Carbonyl Compounds.[3]

Dimethyl(phenyl)silane reduces aldehyde and ketone carbonyls with the aid of fluoride ion or acid. α-Acylpropionamides, 1-aminoethyl ketones, and 1-alkoxyethyl ketones are readily converted into the corresponding β-hydroxy amides, α-amino alcohols, and α-alkoxy alcohols, respectively. The stereoselectivity is complementary and generally high: *erythro* (or *syn*) isomers are obtained with ***Trifluoroacetic Acid*** (TFA), whereas *threo* (or *anti*) isomers are obtained with fluoride ion activator (eq 1). The *erythro* selectivity in the acid-promoted carbonyl reduction is ascribed to a proton-bridged Cram's cyclic transition state. On the other hand, the *threo* selectivity in the fluoride-mediated reduction is explained in terms of the Felkin-Anh type model, wherein a penta- or hexacoordinated fluorosilicate is involved. No epimerization at the chiral center is observed during the reaction.

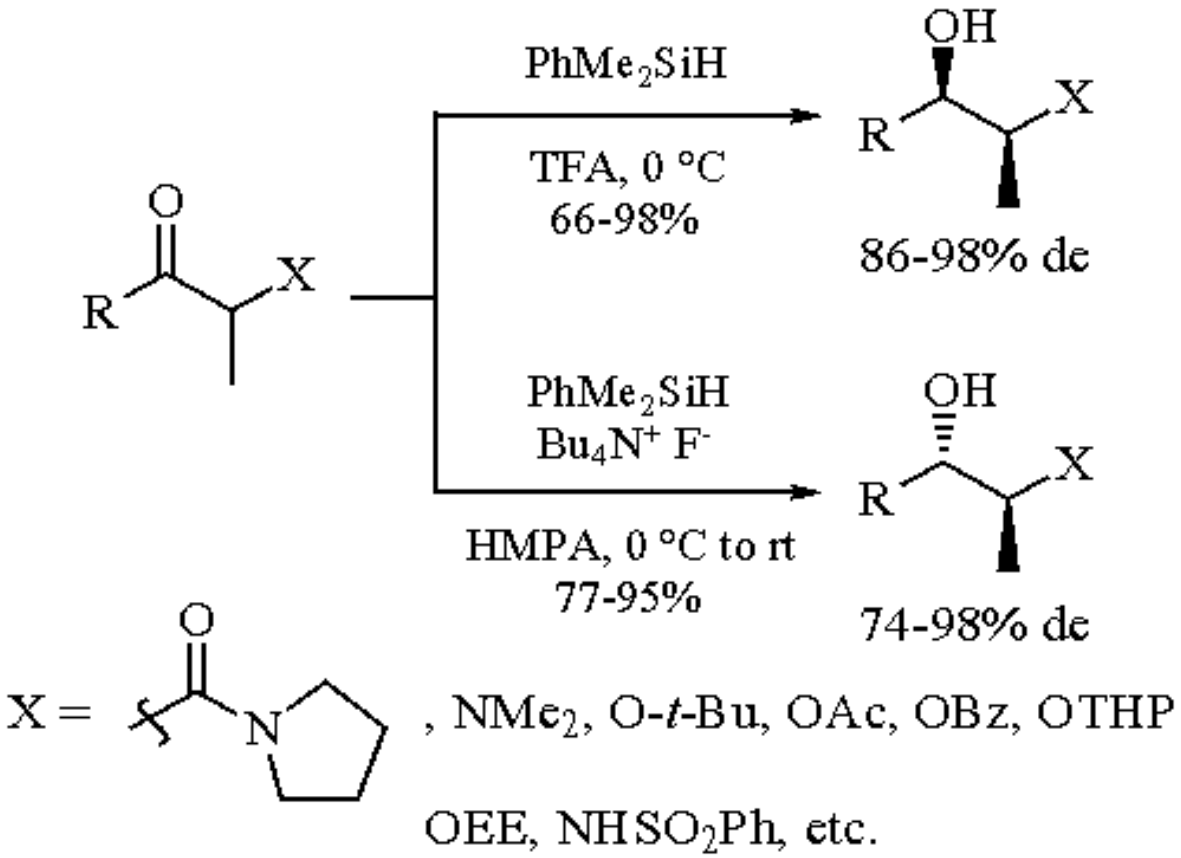

(1)

Hydrosilylation.[4]

With a transition metal catalyst, the hydrosilane adds to carbon-carbon double or triple bonds to give alkylsilanes or alkenylsilanes. Hydrosilylation of deoxydiisopropylidene-*arabino*-hexenopyranose (**1**) catalyzed by $[Rh(norbornadiene)Cl]_2$ (***Bis(bicyclo[2.2.1]hepta-2,5-diene)dichlorodirhodium***) gives 6-deoxy-6-phenyldimethylsilyldiisopropylidenealtrose (**2**), which is desilylated by ***Tetra-n-butylammonium Fluoride*** to yield 6-deoxydiisopropylidenealtrose (**3**) (eq 2).[5]

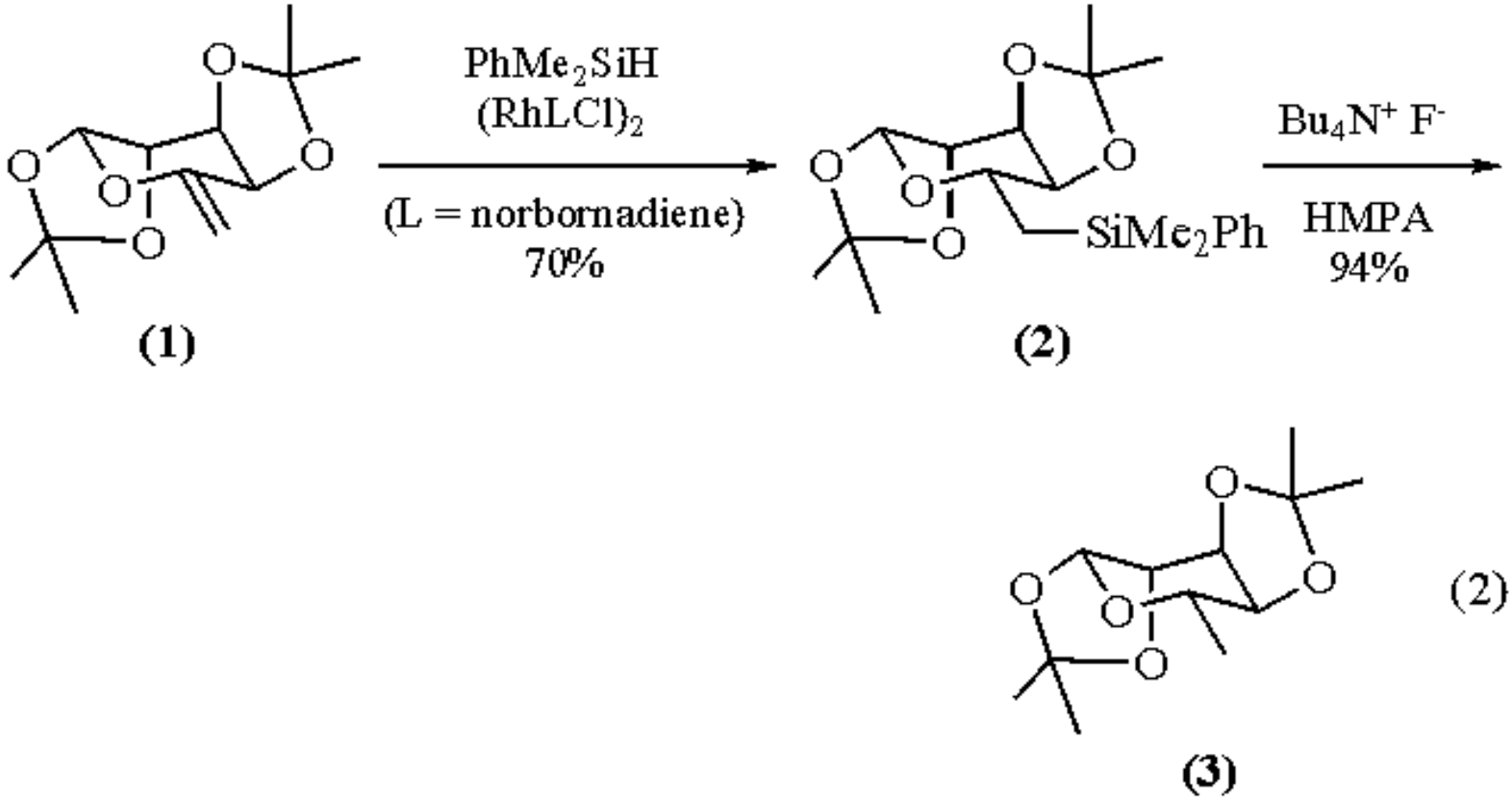

In the presence of a Pt complex like bis(η-divinyltetramethyldisiloxane)tri-*t*-butylphosphineplatinum(0) (**4**), phenyldimethylsilane reacts with 1-butyn-3-ol to give an 8:1 mixture of alkenylsilanes (**5** and **6**) (eq 3). The major product 1-dimethylphenylsilyl-1-buten-3-ol (**5**) is separated and resolved by lipase-catalyzed esterification.[6]

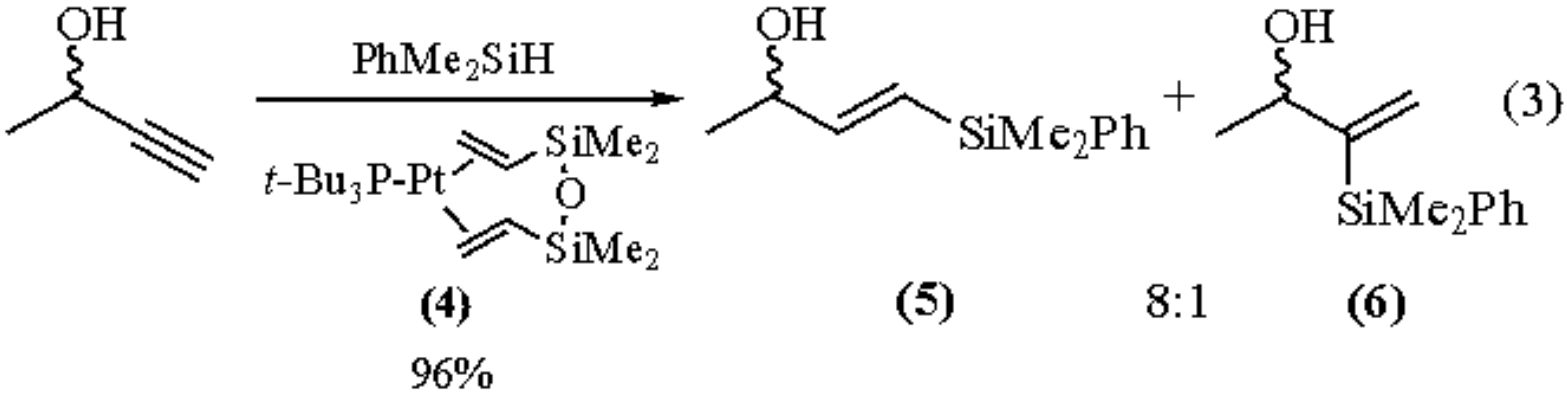

Hydrosilylation of 1,4-bis(trimethylsilyl)-1,3-butadiyne (**7**) gives 1,4-bis(trimethylsilyl)-1,3-bis(dimethylphenylsilyl)-1,2-butadiene (**8**) (***Chlorotris(triphenylphosphine)rhodium(I)***, 100 °C) or 1,4-bis(trimethylsilyl)-2-(dimethylphenylsilyl)-1-buten-3-yne (**9**) ($Pt(PPh_3)_4$, 100 °C) (eq 4) depending on the catalyst.[7] The enyne (**9**) is considered to be a precursor of the allene (**8**).

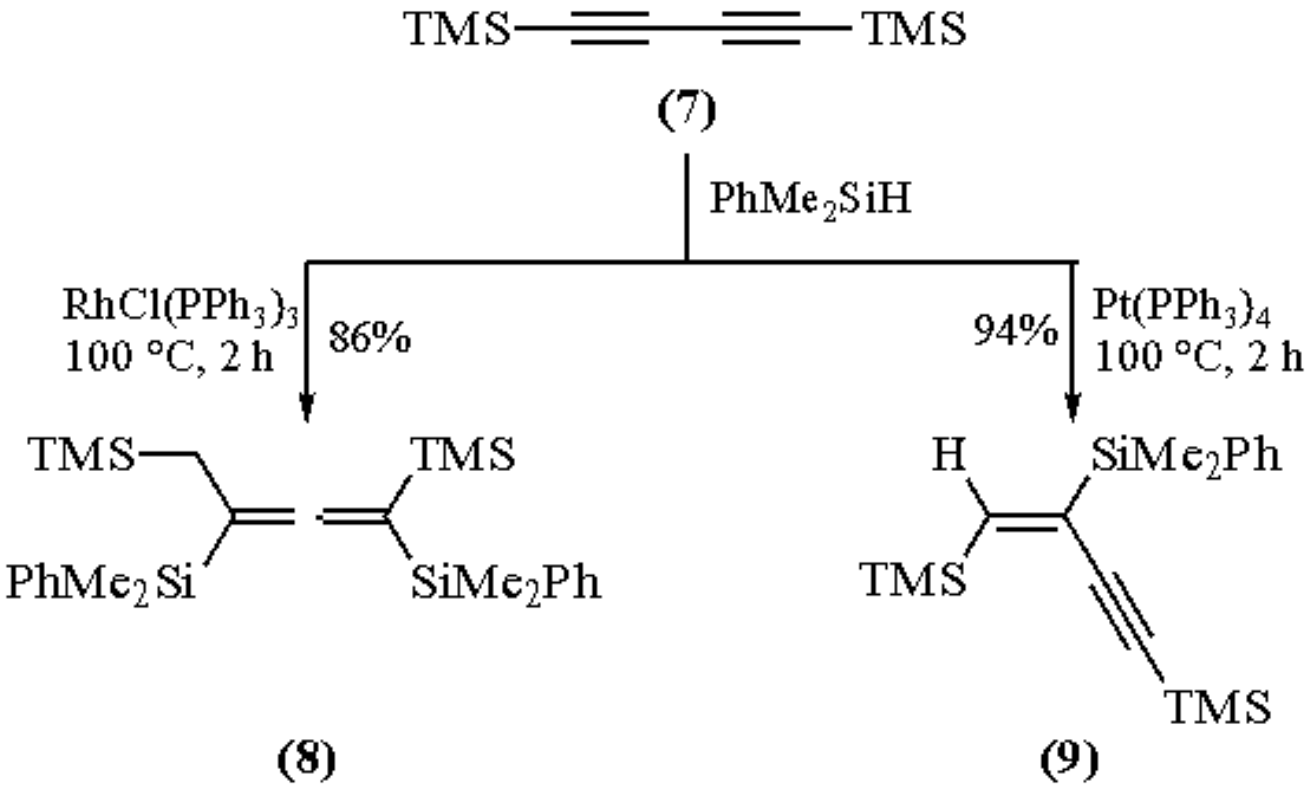

(4)

Transition metal-catalyzed hydrosilylation of α,β-unsaturated ketones and aldehydes with $PhMe_2SiH$ proceeds in a 1,4-fashion to give silyl vinyl ethers, which are hydrolyzed to give ketones and aldehydes. Asymmetric 1,4-reduction has been studied using a chiral transition metal catalyst, but with little success (eq 5).[8]

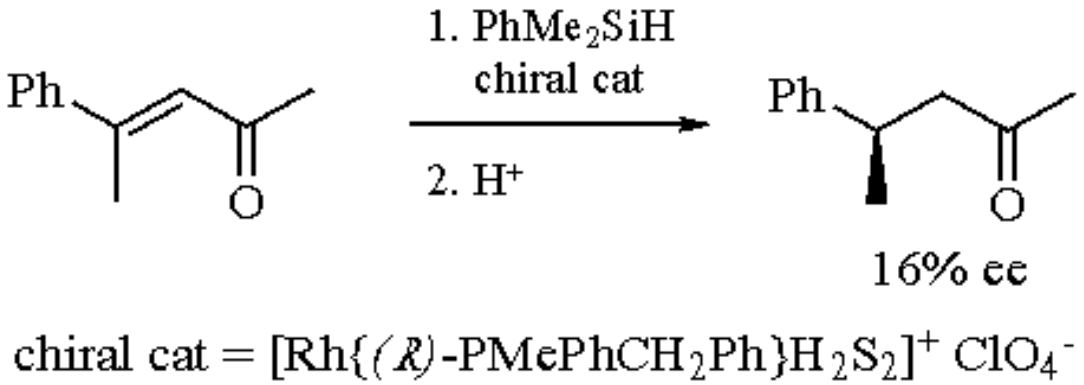

(5)

chiral cat = $[Rh\{(R)\text{-}PMePhCH_2Ph\}H_2S_2]^+ ClO_4^-$

Dimethyl (*Z*,*Z*)-2,4-hexadienedioate is hydrosilylated with $PhMe_2SiH/RhCl(PPh_3)_3$ to give the 1,6-hydrosilylation product, methyl (3*E*)-6-methoxy-6-(phenyldimethylsilyloxy)-3,5-hexadienoate (eq 6).[9]

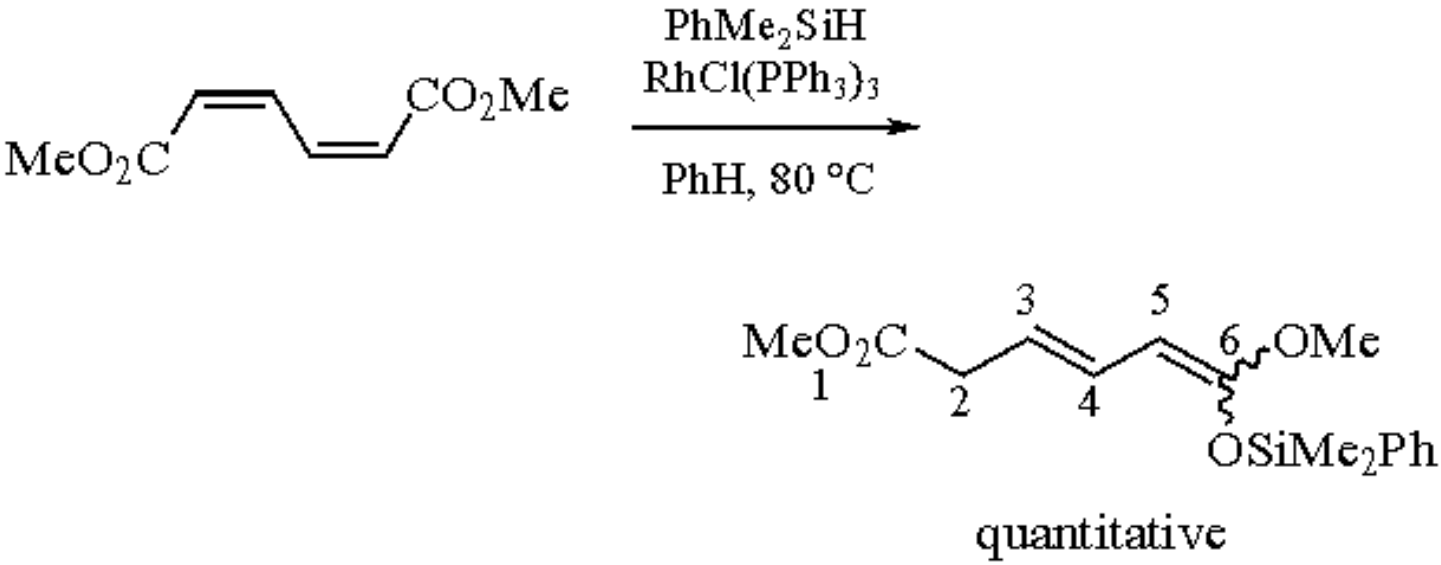

(6)

Formylsilylation.

Under a ***Carbon Monoxide*** atmosphere (1-4 MPa), silylformylation of alkynes occurs in the reaction of alkynes and $PhMe_2SiH$ to give β-silyl enals in the presence of a rhodium catalyst (eq 7).[10] Terminal alkynes exclusively give products having the $SiMe_2Ph$ group at the terminal carbon. Depending on the structure of the alkyne, the isomer ratio (*E*/*Z*) varies from 0:100 to 100:0. Hydroxyl groups survive these conditions; however, in the presence of a tertiary amine, alkynols are converted into α-(dimethylphenylsilylmethylene) β-lactones (eq 8).[11]

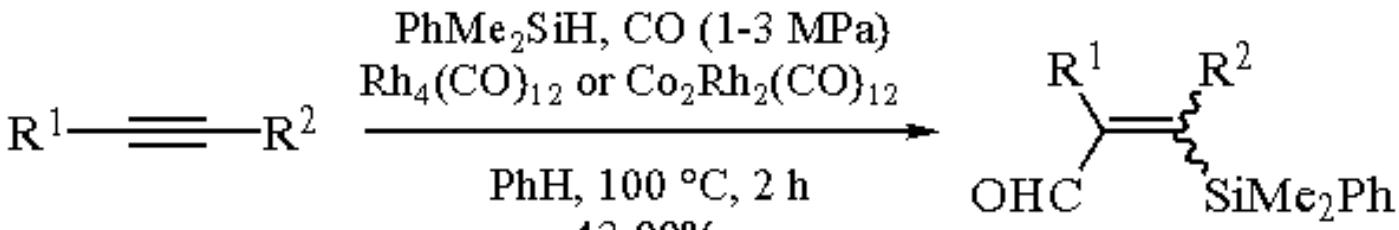

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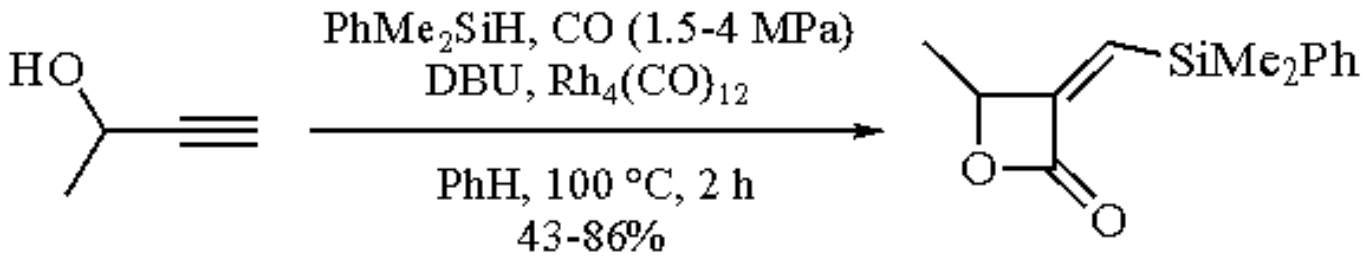

(8)

Silylformylation of *N*-propargyl tosylamides gives normal β-silyl enal products, whereas the same reaction in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** or ***Triethylamine*** affords α-(dimethylphenylsilyl)methylene β-lactams (eq 9).[12] Propargylamines are transformed to 2-(dimethylphenylsilyl)methyl-2-propenals (eq 10).[13]

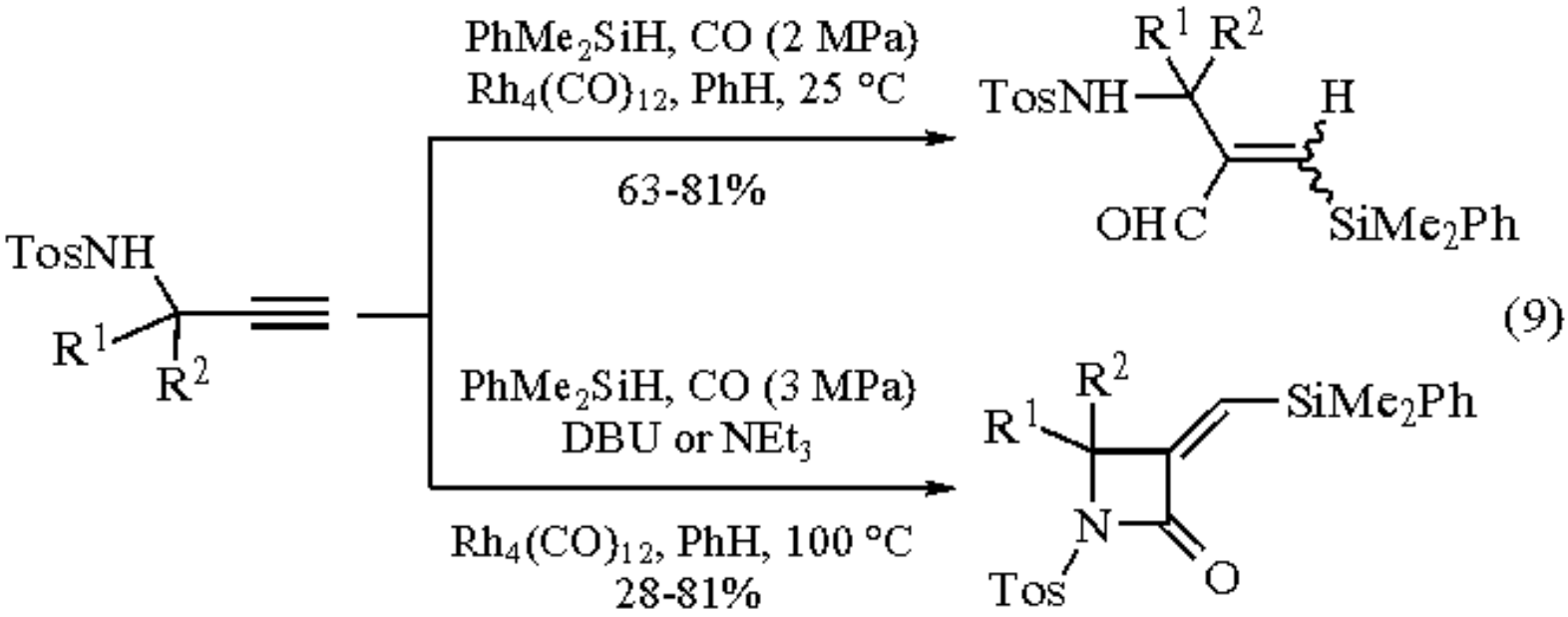

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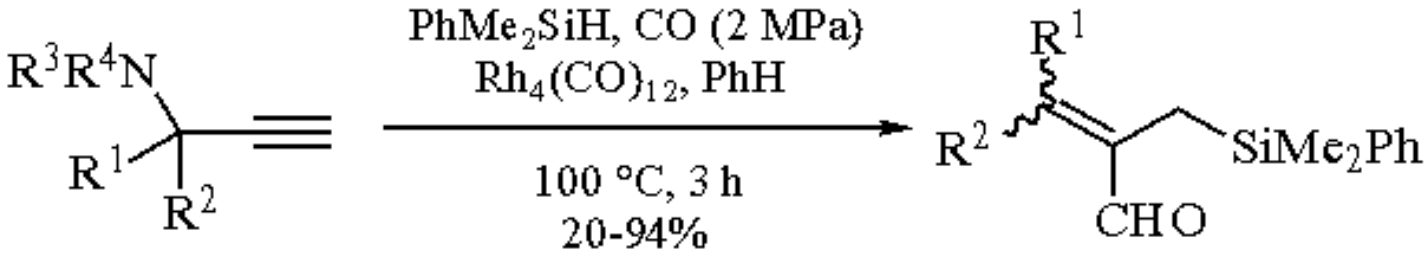

(10)

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Dimethylphenylsilyllithium[1]

$PhMe_2SiLi$

[3839-31-4] · $C_8H_{11}LiSi$ · Dimethylphenylsilyllithium · (MW 142.22)

(reagent for addition to carbonyl compounds;[2] deoxygenation reactions;[3,4] in presence of copper(I) salts, an effective reagent for conjugate addition to α,β-unsaturated compounds,[5] conjugate displacement of tertiary allylic acetates,[6,7] and silylcupration of alkynes[8] and allenes[9])

Physical Data: NMR studies have shown the reagent is monomeric in ether.[10c]

Solubility: sol THF, Et_2O.

Preparative Methods: readily prepared from the reaction of $PhMe_2SiCl$ with 2 equiv of Li metal in THF or from the reaction of $PhMe_2SiSiMe_2Ph$ with Li metal in THF.[10a,b] Typical reaction procedure involves stirring ***Chlorodimethylphenylsilane*** with ***Lithium*** in THF at -8 °C under N_2 for 36 h.[8a] The supernatant reagent solution is calibrated using standard methods and used without further purification for reactions.[8a] It is advantageous to activate the Li metal prior to use by ultrasound irradiation of a hexane suspension,[11a] and to use argon as the inert gas to prevent formation of lithium nitrides.[11b]

Handling, Storage, and Precautions: the reagent solution in THF can be stored under argon or nitrogen at -20 °C for several weeks without significant degradation.[8a] Lithium is a highly flammable solid and must be handled and stored in an inert atmosphere (preferably argon).

Addition to Carbonyl Compounds.

$PhMe_2SiLi$ in THF undergoes addition to aldehydes and ketones under mild conditions to afford α-silyl alcohols upon aqueous workup. The α-silyl alcohols are versatile synthetic intermediates which can be readily manipulated into a variety of products. Consequently, these reactions have been widely utilized in organic syntheses,[12-15] for example in the synthesis of cytochalasin D cycloundecanone ring system (eq 1),[12] and in the synthesis of (±)-pregn-4-en-20-one.[13] Enones react with $PhMe_2SiLi$ predominantly via 1,2-addition to afford α-silyl alcohols which can be converted to silyl enol ethers via Brook rearrangement (eq 2).[15]

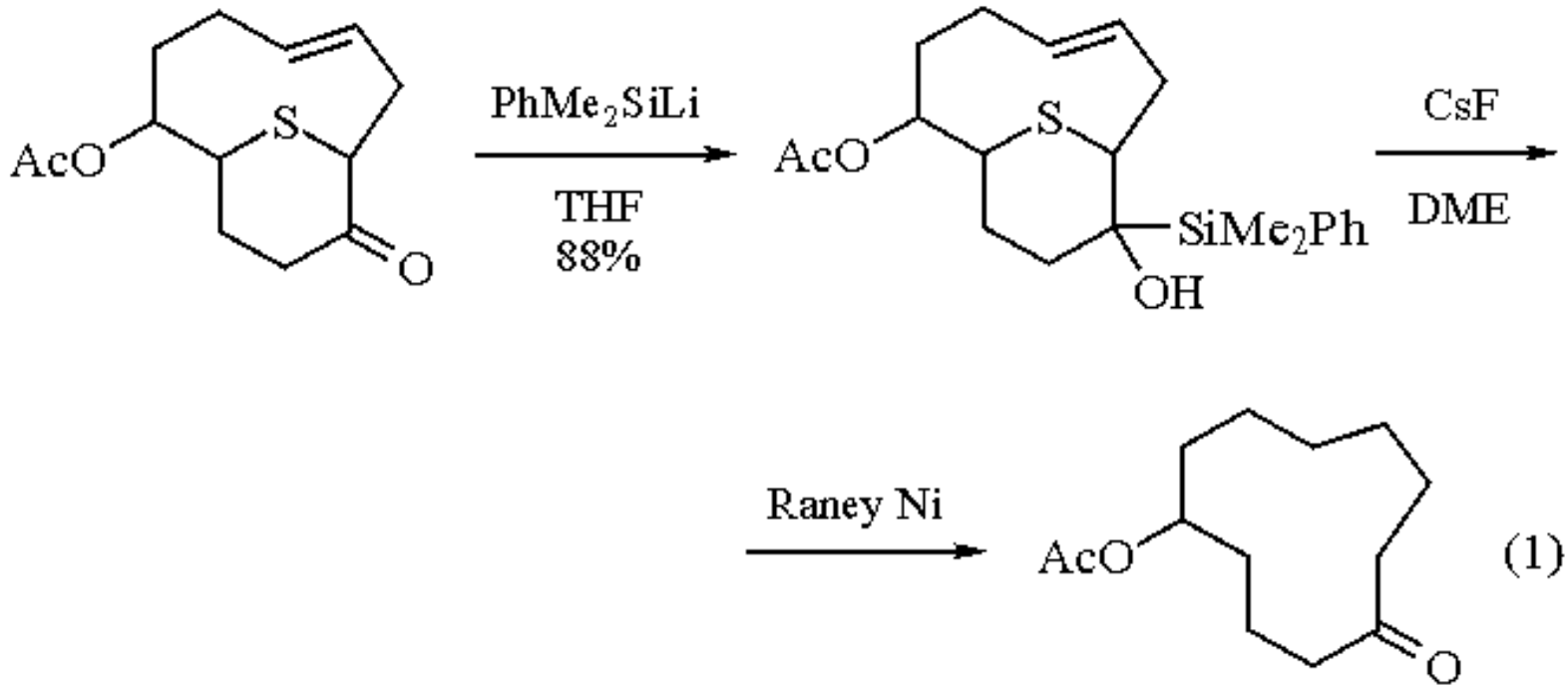

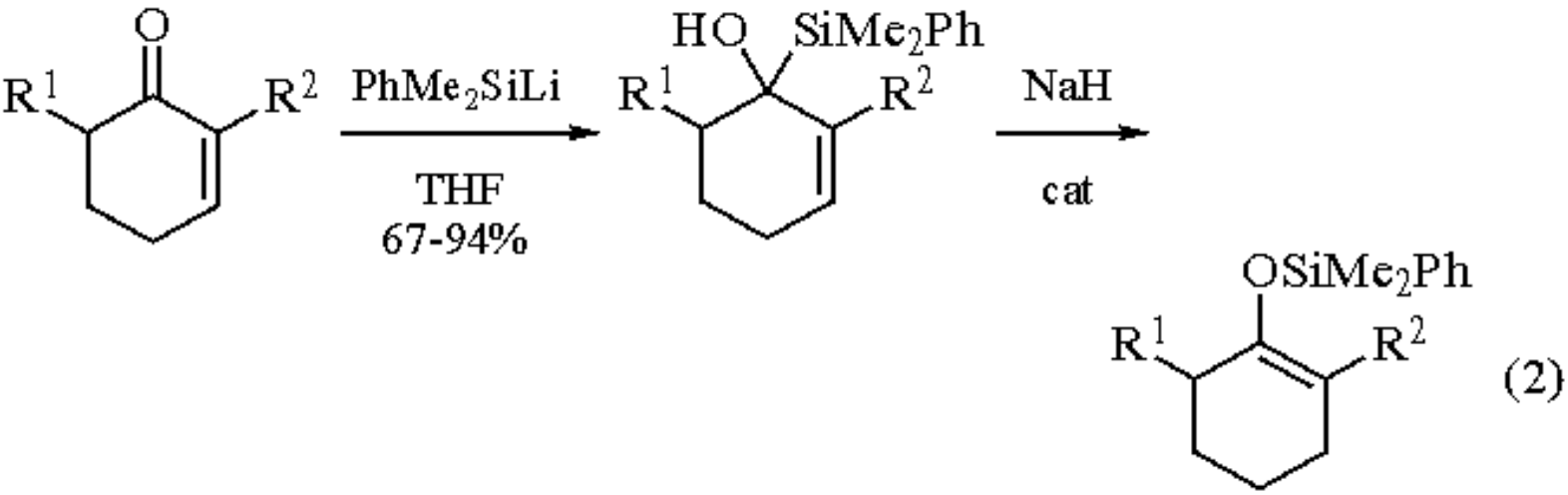

Addition of $PhMe_2SiLi$ to α-phenylthio ketones directly affords silyl enol ethers with very high (*Z*)-stereoselectivity (eq 3).[16]

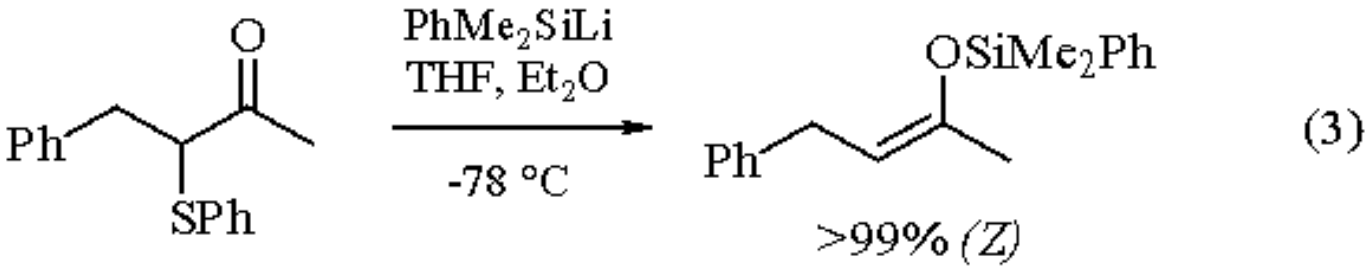

Addition of $PhMe_2SiLi$ to aldehydes and subsequent *O*-sulfonylation of the generated alkoxides with ***p-Toluenesulfonyl Chloride*** affords α-silyl tosylates in good yields.[2] Conversion of these intermediates into α-silyl selenocyanates followed by fluoride-induced cyanide elimination reaction permitted the synthesis and study of reactivity of previously unknown selenoaldehydes (eq 4).[2]

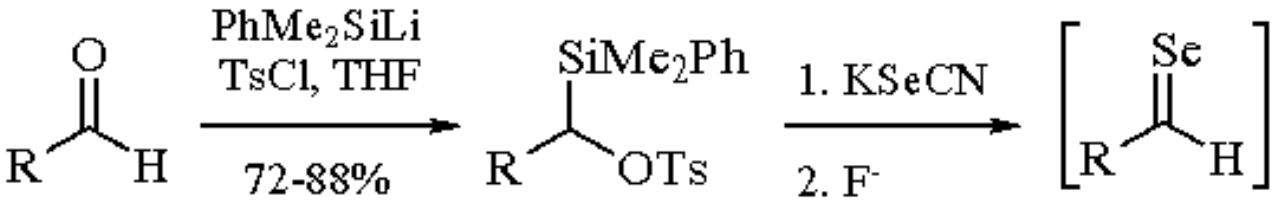

(4)

Deoxygenation Reactions.

$PhMe_2SiLi$ reacts with oxabicyclo[2.2.1]heptenes in Et_2O at 0 °C to afford 1,3-cyclohexadienes (eq 5).[3] 6-8 equiv of $PhMe_2SiLi$ are required for complete consumption of the starting bicyclic compound. The excess stoichiometry sometimes leads to further reaction of the 1,3-cyclohexadiene product with the unreacted reagent. Use of the silylcuprate reagent $PhMe_2SiCu.LiCN$ in THF at 0 °C alleviates this problem.[3]

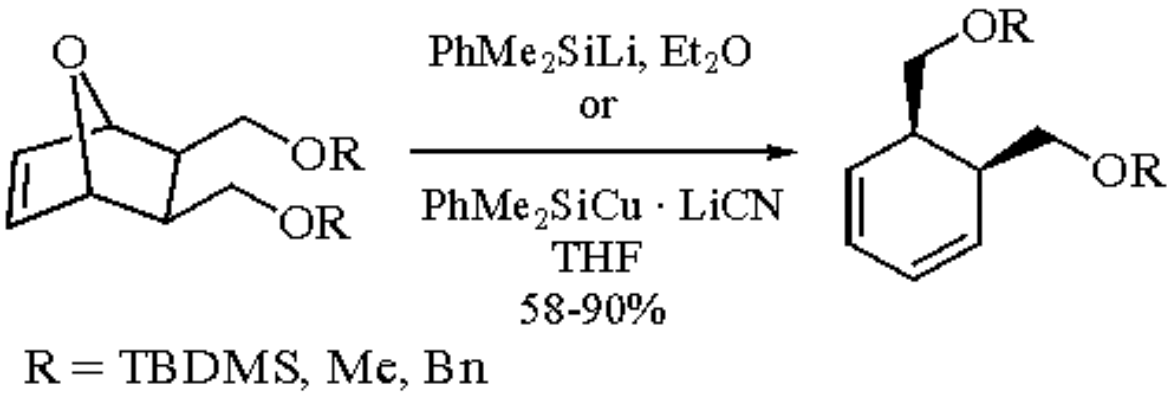

(5)

Epoxides are stereospecifically deoxygenated to alkenes with inversion of stereochemistry upon treatment with $PhMe_2SiLi$ in THF.[4] *trans*-Stilbene is obtained in 83% yield and >99% stereoselectivity from the reaction of oxide of *cis*-stilbene with $PhMe_2SiLi$. Similarly, *trans*-stilbene oxide is converted to *cis*-stilbene.

Reactions via Cuprates.

Dimethylphenylsilylcuprates [$(PhMe_2Si)_2CuLi.LiX$] (X = CN or halide), generated in situ from the reaction of 2 equiv of $PhMe_2SiLi$ with copper(I) salts (***Copper(I) Cyanide***, ***Copper(I) Iodide***), are popular reagents for the incorporation of $PhMe_2Si$ unit into organic molecules.[5-9,17] In general, these reagents react with substrates under milder conditions and tolerate polar functional groups better than $PhMe_2SiLi$. However, these reagents suffer from one major drawback in that not all the Si anions bound to copper are transferred to the substrate. Consequently, reaction workup affords nonvolatile byproducts which complicate product isolation.[5-9] This problem can be avoided by using the mixed cuprate $(PhMe_2Si)MeCuLi$, prepared from the reaction of 1 equiv of $PhMe_2SiLi$ and 1 equiv of MeLi with CuCN.[18] The mixed cuprate specifically transfers the silyl group (not the methyl group) to the substrate and exhibits reactivity comparable to that of ***Lithium Bis[dimethyl(phenyl)silyl]cuprate***. Synthetically useful reactions of dimethylphenylsilylcuprates include addition to saturated aldehydes, 1,4-addition to α,β-unsaturated enones, conjugate displacement of tertiary allylic acetates, and silylcupration of alkynes and allenes.

The addition of $(PhMe_2Si)_2CuLi$ to aldehydes has been utilized in the elegant synthesis of isocarbacyclin (eq 6).[19]

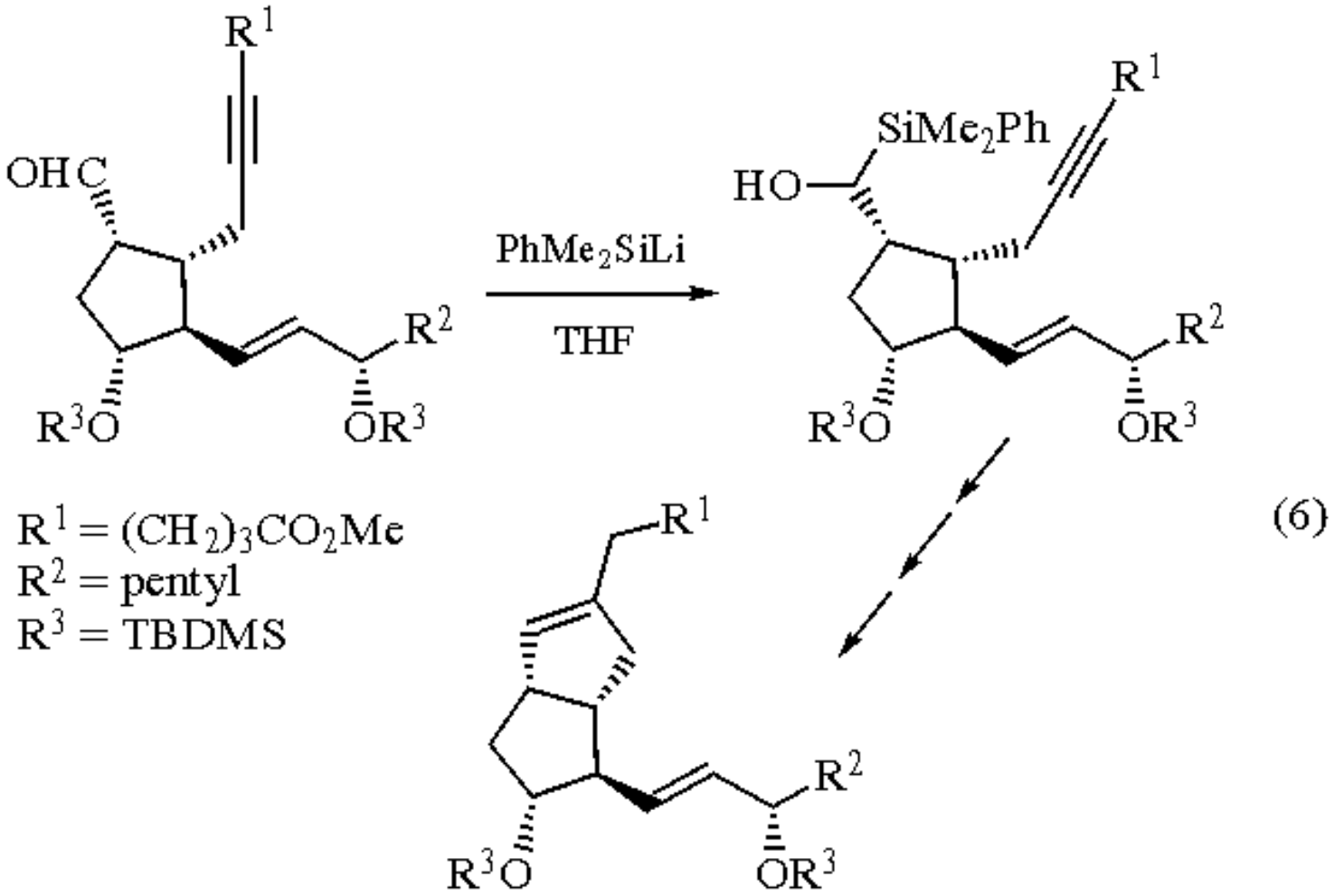

$(PhMe_2Si)_2CuLi$ undergoes 1,4- (conjugate) addition to a variety of cyclic and acyclic α,β-unsaturated enones to afford saturated β-silyl carbonyl compounds (eq 7).[5,20-22] In acyclic systems, enones can be regenerated from the β-silyl carbonyl compounds by bromination (***Bromine***-CCl_4) followed by desilylbromination (***Sodium Fluoride***-EtOH).[22] In cyclic systems, treatment of the β-silyl carbonyl compounds with ***Copper(II) Bromide*** affords the enones directly (eq 7).[20] This overall silylation-desilylation protocol not only represents a method for the protection of α,β-unsaturation but can also be used advantageously by alkylating the intermediate enolate of conjugate silyl addition prior to desilylation (eq 7). This methodology has been successfully applied in the synthesis of carvone and dihydrojasmone.[5a] The alkylation of intermediate enolates is highly diastereoselective, favoring the isomer in which the silyl group and the alkyl group are in *anti* orientation (eq 8). The silyl functionality of the β-silyl carbonyl compounds also can be converted into a hydroxy group with retention of configuration (eq 8).[5b]

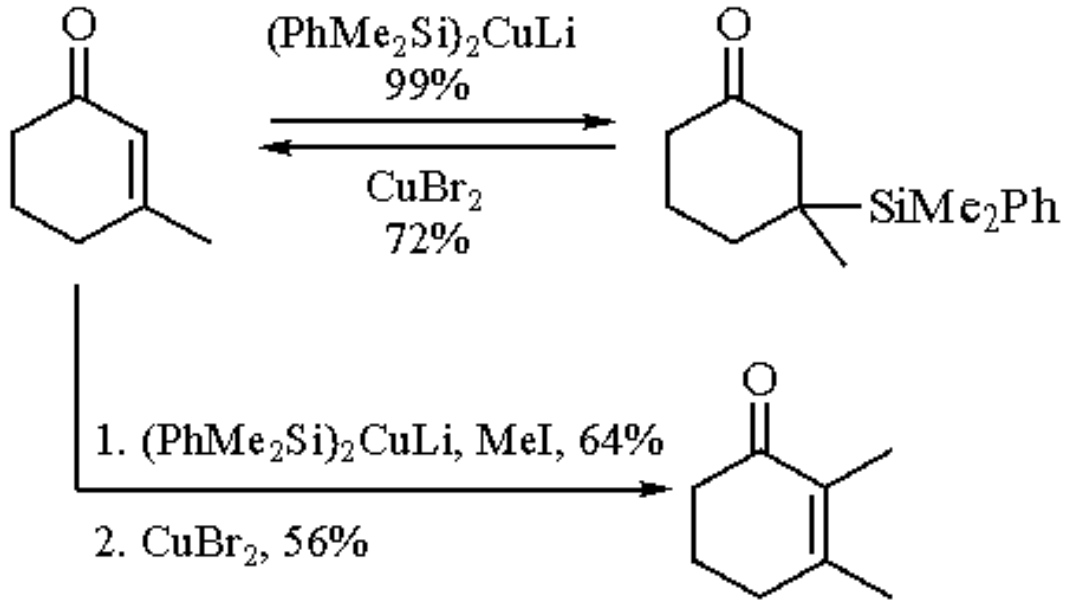

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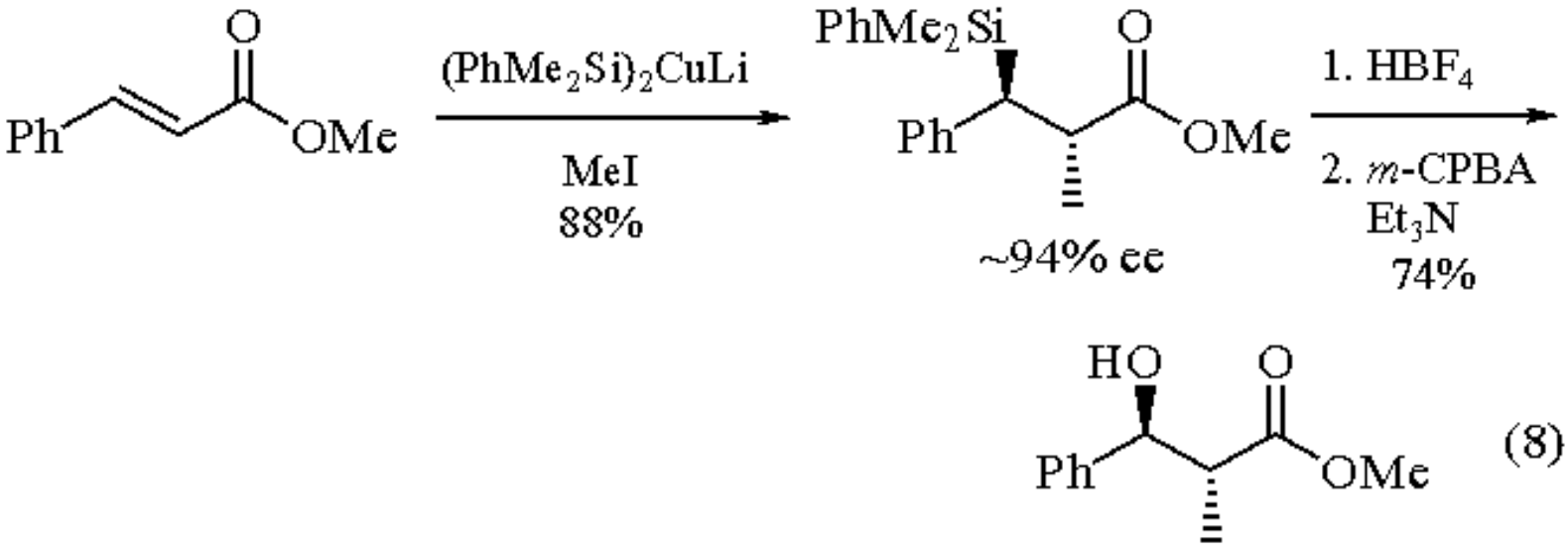

(8)

$(PhMe_2Si)_2CuLi$ reacts with allylic acetates via stereospecific (*anti*) conjugate displacement of the acetate group to afford allylsilanes in excellent yields.[7,23] Similar stereospecificity is observed in reactions with propargyl acetates.[7a]

$(PhMe_2Si)_2CuLi$ reacts with alkynes via *syn* addition of the silyl group and copper to the carbon-carbon triple bond.[8] In reactions with terminal alkynes, the silyl group becomes attached predominantly to the terminal carbon. The acidic hydrogen of terminal alkynes does not get abstracted under the reaction conditions. The vinylcuprate intermediates react with electrophiles including alkyl/acyl halides, iodine, epoxides, and enones to regio/stereoselectively afford a variety of vinylsilanes.[8]

Silylcupration of allene with $(PhMe_2Si)_2CuLi$ followed by treatment of the intermediate cuprate with H^+, carbon electrophiles, and Cl_2 affords the corresponding vinylsilanes (eq 9).[9] However, reaction of the intermediate cuprate with I_2 affords an allylsilane, from which other more highly substituted allylsilanes are readily obtainable (eq 9). In reaction with substituted allenes, the product ratio (vinylsilane vs. allylsilane) is dependent upon the degree of substitution.[9]

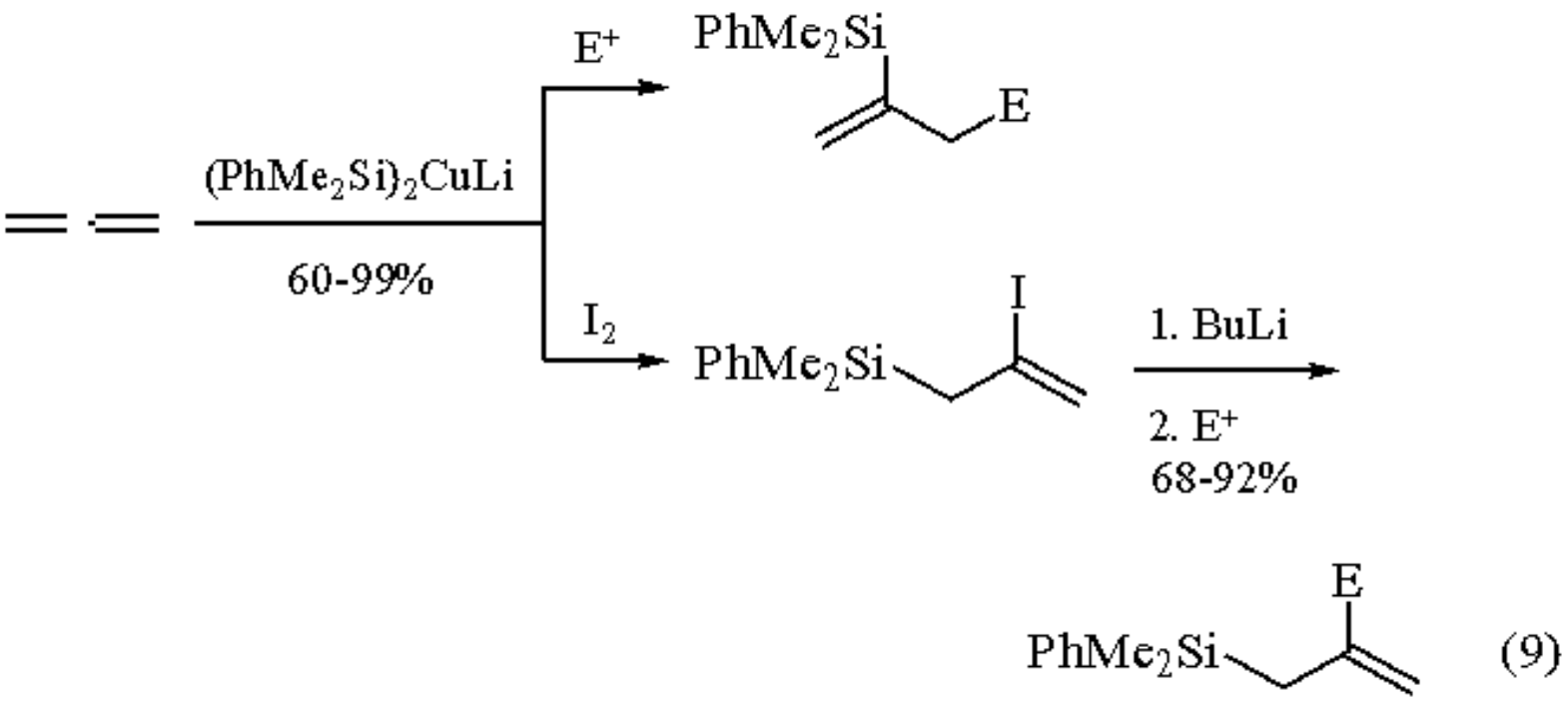

Related Reactions.

In contrast to $PhMe_2SiLi$, related R_3SiLi reagents either are appreciably less stable, may require generation in toxic solvents (***Hexamethylphosphoric Triamide***), and can be less nucleophilic, favoring deprotonation or electron transfer reactions. Nevertheless, complementary synthetic organic transformations have been described for these reagents,[24] for example the 1,4-addition of ***Trimethylsilyllithium*** to enones[25] and the reduction of isocyanates to isocyanides with *t*-$BuPh_2SiLi$.[26] The wide synthetic utility of $PhMe_2SiLi$ and $(PhMe_2Si)_2CuLi$ in organic synthesis has also encouraged the development and use of related $PhMe_2Si^-$ derivatives of Al,[27] Mg,[28] Mn,[28] and Zn.[27a,29]

Related Reagents.

Dimethylphenylsilyl(methyl)magnesium; ***Lithium Bis[dimethyl(phenyl)silyl]cuprate***; ***Trimethylsilylcopper***; ***Trimethylsilyllithium***.

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Dimethylphenylsilyl(methyl)magnesium

$PhMe_2SiMgMe$

[87436-97-3] · $C_9H_{14}MgSi$ · Dimethylphenylsilyl(methyl)magnesium · (MW 174.63)

(silyl magnesiation of alkynes; synthesis of vinylsilanes; disilylation of alkynes)

Solubility: sol ethereal solvents (ether, THF, DME, etc.).

Form Supplied in: not commercially available. The reagent is best prepared and used immediately.

Analysis of Reagent Purity: a suitable analytical method is not available. The reagent must be prepared immediately after titration of dimethylphenylsilyllithium and methylmagnesium iodide.

Preparative Method: an ethereal solution of methylmagnesium iodide (1.0 equiv) is added to a THF solution of ***Dimethylphenylsilyllithium***[1] (1.0 equiv) at 0 °C under an argon atmosphere. The mixture is stirred for 15 min and the resulting dimethylphenylsilyl(methyl)magnesium is used directly for further reactions.

Handling, Storage, and Precautions: the reagent is sensitive to moisture and should be handled under a dry, inert atmosphere. The reagent must be used immediately after preparation.

Silylmagnesiation of Alkynic Compounds.

Platinum- or copper-catalyzed silylmagnesiation[2,3] of 1-dodecyne followed by aqueous workup provides (*E*)-1-dimethylphenylsilyl-1-dodecene (eq 1), which has also been produced by stoichiometric silylcupration[4] or silyltitanation.[5] Electrophiles such as iodine, methyl iodide, and valeraldehyde react with the intermediate derived from $PtCl_2(P\text{-}n\text{-}Bu_3)_2$-catalyzed silylmagnesiation of 1-dodecyne to give the corresponding functionalized alkenylsilanes (eq 2).

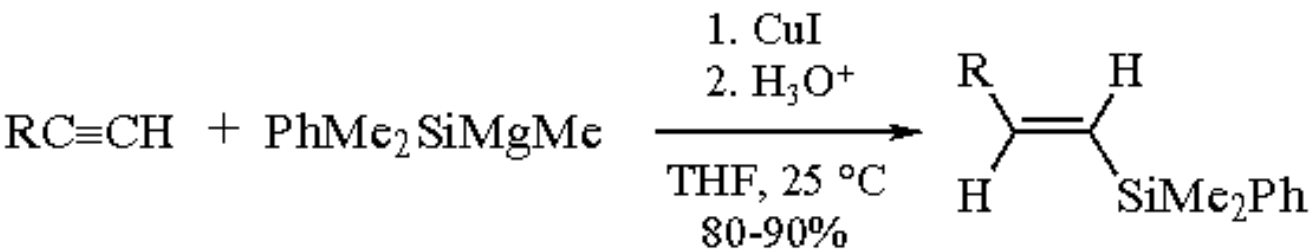

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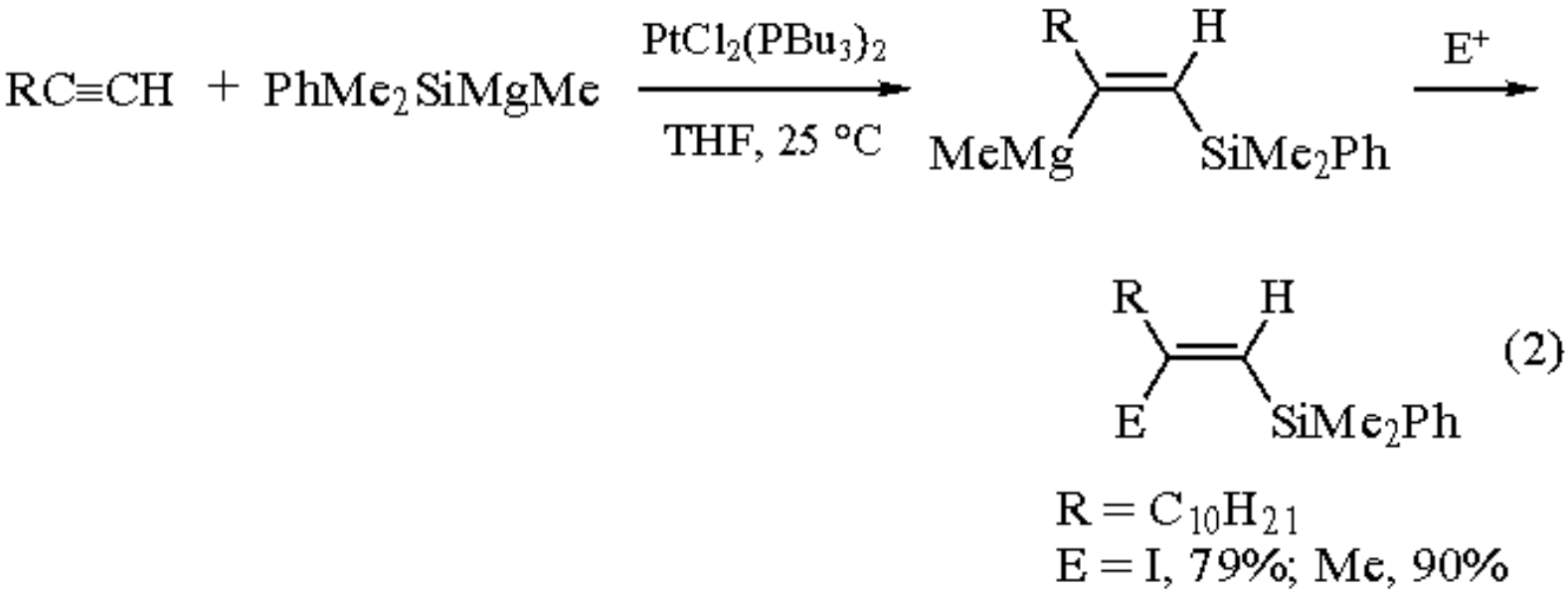

Silylmagnesiation of 1,2-alkadienes in the presence of a ***Copper(I) Iodide*** catalyst, followed by aqueous workup, produces exclusively 1-(dimethylphenylsilyl)-1-cycloalkenes in which a $PhMe_2Si$ group is attached to the central carbon of the allene (eq 3).[6] The initial adducts can undergo an intramolecular cyclization when the R group is substituted at the terminal position by a leaving group, to provide cycloalkanes with a dimethylphenylsilylmethylene substituent (eqs 4 and 5).[7]

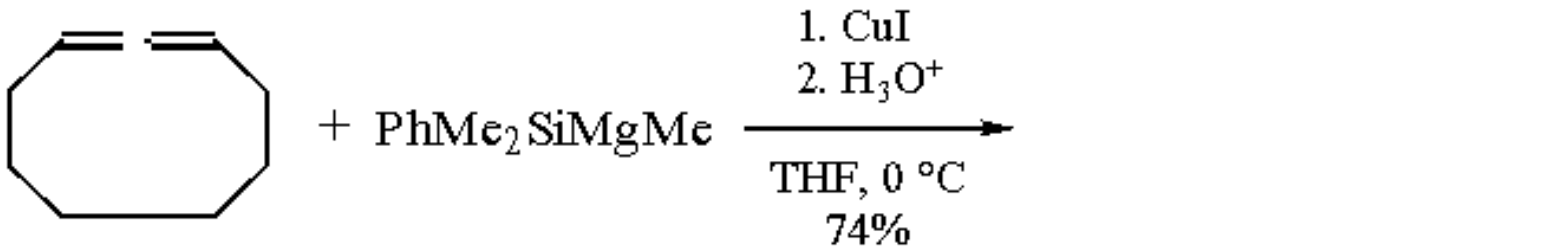

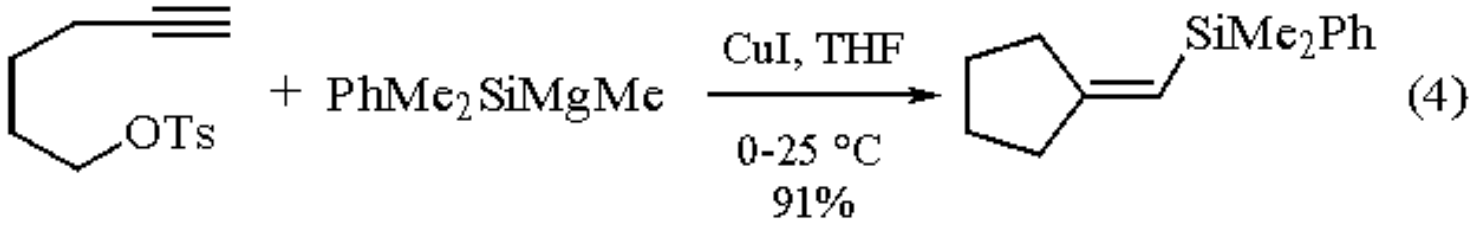

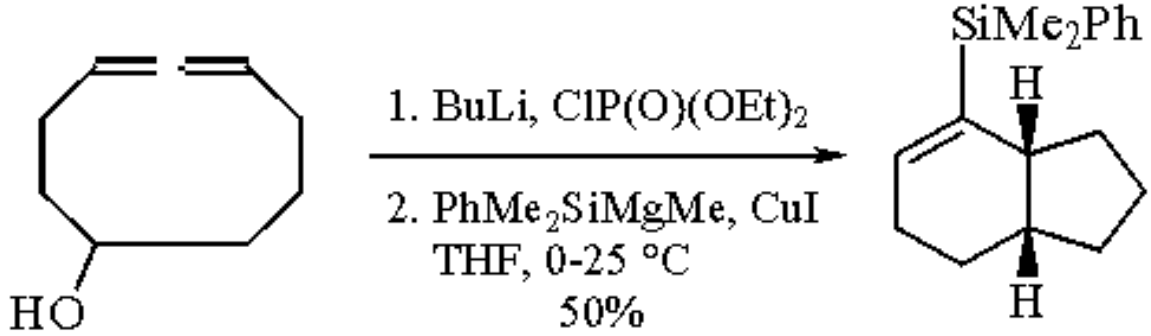

(5)

Synthesis of Vinylsilanes.

In the presence of a Pd catalyst, $PhMe_2SiMgMe$ converts enol phosphates into vinylsilanes (eq 6).[8] The reagent, which is believed to be $(PhMe_2Si)_3MnMgMe$ (prepared in situ from 3 equiv of $PhMe_2SiMgMe$ and ***Manganese(II) Chloride***), also transforms alkenyl halides, alkenyl sulfides, or enol phosphates into vinylsilanes (eq 7).[9]

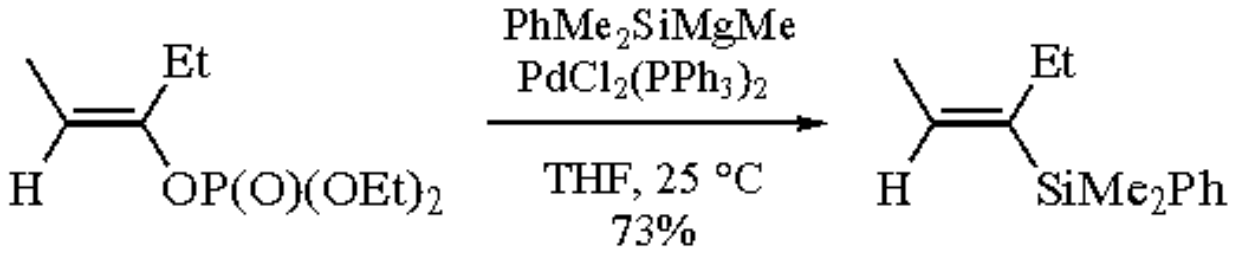

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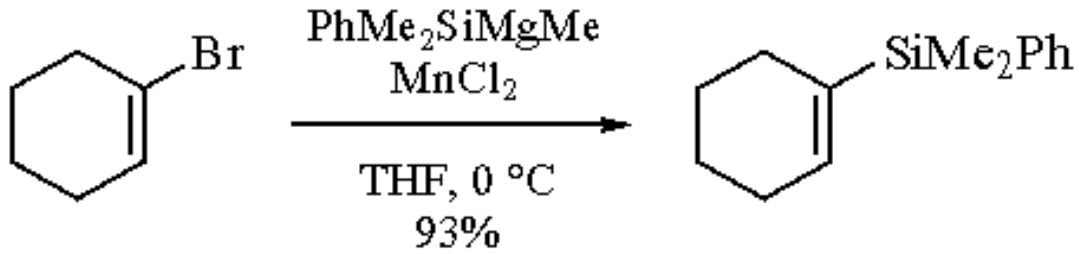

(7)

Disilylation of Alkynes.

Addition of 1-alkynes to the reagent $(PhMe_2Si)_3MnMgMe$ affords (*E*,*Z*) mixtures of 1,2-bis(dimethylphenylsilyl)-1-alkenes (eq 8).[10] Trimethylsilyl(methyl)magnesium in place of $PhMe_2SiMgMe$ gives the corresponding disilylation product. The reaction can be successfully applied to the synthesis of highly strained tetrakis(trimethylsilyl)ethylene (eq 9).

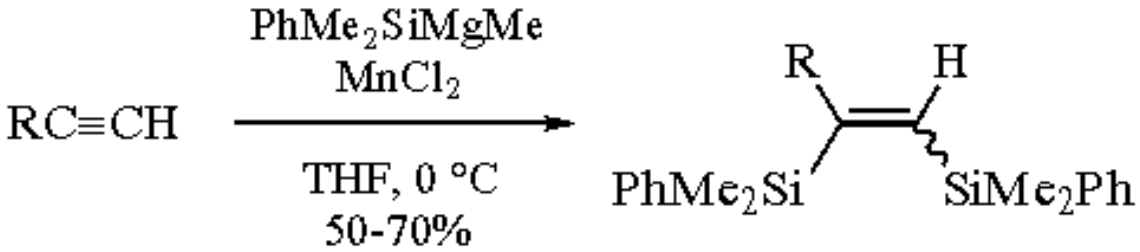

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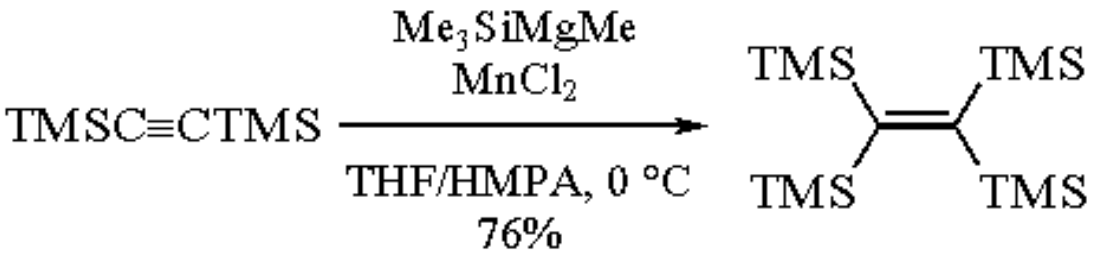

(9)

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N,S-Dimethyl-*S*-phenylsulfoximine[1]

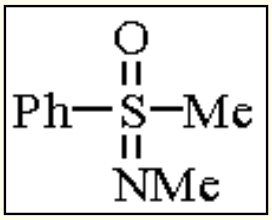

(±)

[30004-67-2] · $C_8H_{11}NOS$ · *N,S*-Dimethyl-*S*-phenylsulfoximine · (MW 169.27) (*R*)-(-)

[80482-67-3] (*S*)-(+)

[33993-53-2]

(chiral sulfone analog useful in methylenation of carbonyl compounds[1,2] and resolution of ketones[1,3])

Physical Data: oil; $[\alpha]_D$ 184° (*c* 3, acetone); pK_a (DMSO) ~32.[1]

Solubility: sparingly sol water; sol dil acid, aq Cu^{II}; highly sol THF, alcohols, etc.

Preparative Methods: methyl phenyl sulfoxide is treated with ***Hydrazoic Acid*** (generated by addition of sulfuric acid to a slurry of sodium azide) in chloroform maintained at 45 °C to produce *S*-methyl-*S*-phenylsulfoximine.[4,5] The latter can be readily resolved using ***10-Camphorsulfonic Acid***; from the (+)-acid the salt of (+)-(*S*)-*S*-methyl-*S*-phenylsulfoximine is obtained pure by recrystallization.[6,7] The Clarke-Eschweiler procedure using ***Formaldehyde*** and ***Formic Acid*** provides an effective method for conversion of the N-H sulfoximine to the title compound.[7]

Handling, Storage, and Precautions: due care should be taken in the synthetic step using hydrazoic acid. *N,S*-Dimethyl-*S*-phenylsulfoximine is apparently of low toxicity. The compound, which is stable to acids and bases, as well as to most oxidizing and reducing conditions, maintains chemical and enantiopurity on long term storage.

N,S-Dimethyl-*S*-phenylsulfoximine is rapidly deprotonated with ***n-Butyllithium*** in THF at 0 °C; the deprotonation can be conveniently monitored by use of a trace of Ph_3CH as an indicator. The lithio reagent is an excellent nucleophile, particularly with respect to addition to carbonyl compounds (eq 1). Addition occurs in high yields with a wide range of carbonyl compounds in the temperature range of -78 to 25 °C. The reaction is often reversible in the cases of hindered carbonyl compounds. The major side reaction is enolization. Both the enolization and reversibility problems can be circumvented by conducting the addition and subsequent quenching at low temperatures; in this manner, β-

hydroxysulfoximines are obtained in high yield.[3] β-Hydroxysulfoximines are thermally unstable and revert to starting carbonyl compounds and sulfoximine in the temperature range 80-120 °C; the reversion is the basis for a ketone resolution method. The addition of optically pure sulfoximine (as its lithio derivative) to (±)-ketones which exhibit very high or complete diastereofacial selectivity results in the formation of two diastereomers which are generally responsive to separation by silica gel chromatography. Thermolysis of the separated diastereomers results in resolution of the ketone (eq 2).[3] Treatment of the separated diastereomers with ***Raney Nickel*** results in optically pure methyl carbinols (at the expense of destruction of the chiral *S* center).[8] The ketone resolution technique has reciprocity and a number of optically pure ketones, particularly (-)-menthone, have been found useful to resolve *N,S*-dimethyl-*S*-phenylsulfoximine.[3]

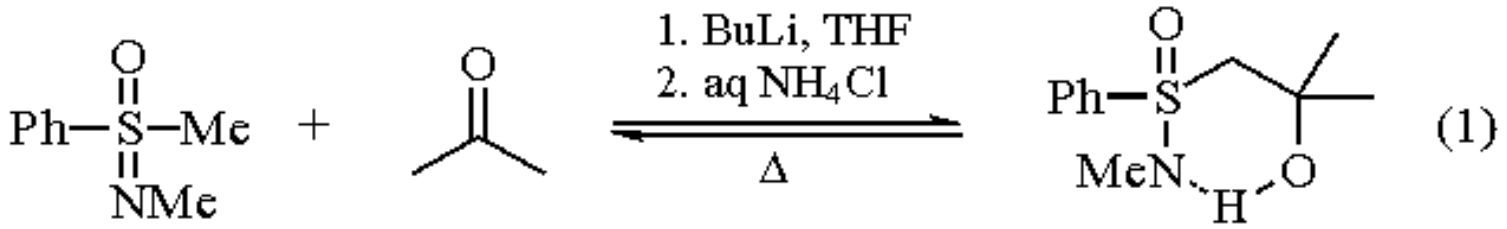

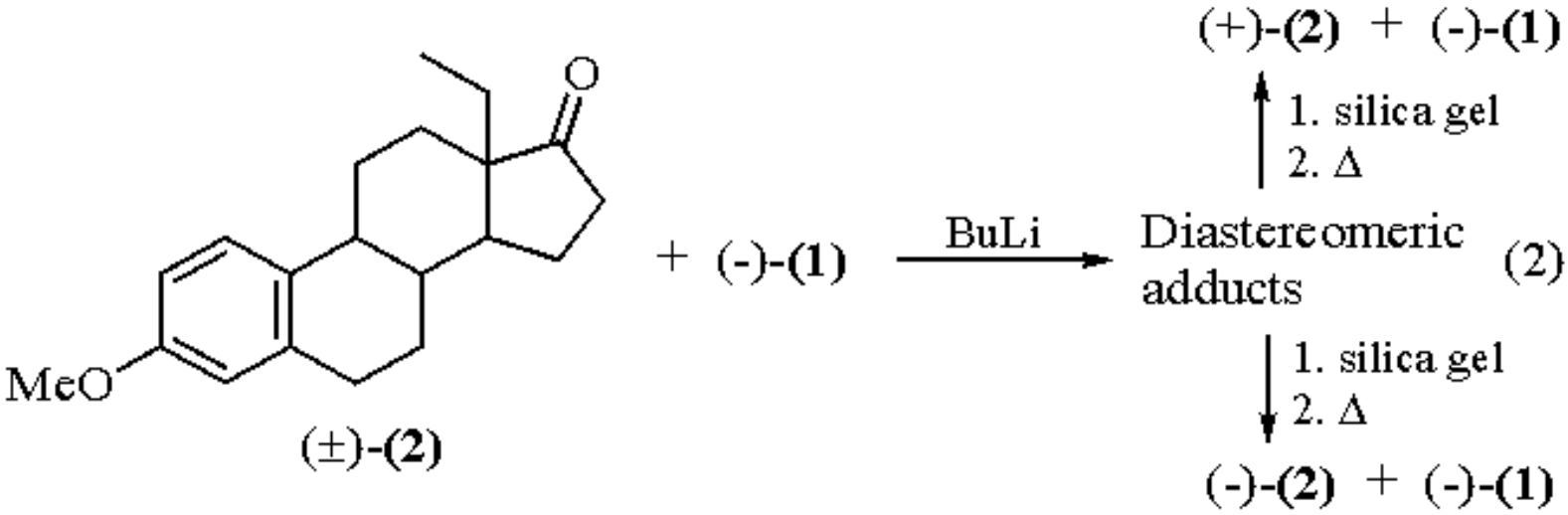

β-Hydroxysulfoximines undergo reductive elimination to yield alkenes upon treatment with ***Aluminum Amalgam*** in a mixture of THF, water, and acetic acid. In the case of conjugated enones and dienones the addition of the lithiosulfoximine occurs at the carbonyl; when the resulting adducts are reduced, dienes and trienes, respectively, are produced (eq 3).[9] The sulfoximine method often works where methylenation with triphenylphosphonium methylide fails[10] (eq 4).[11]

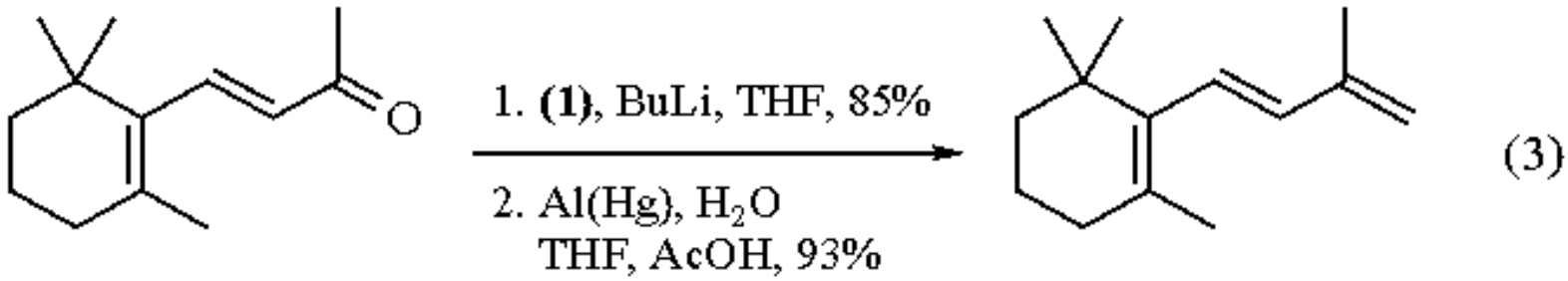

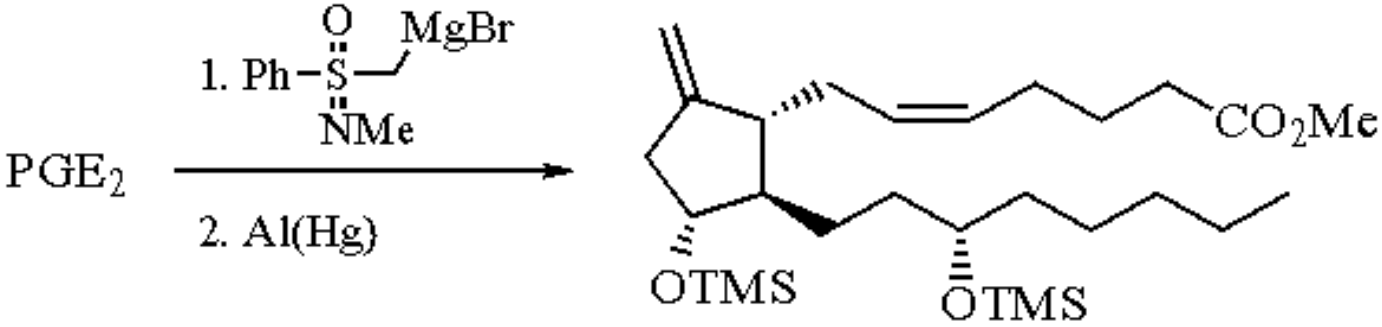

(4)

The combination of the chromatographic separation of enantiopure β-hydroxysulfoximine diastereomers and reductive elimination results in a method of ketone methylenation with optical resolution. The technique is illustrated in the synthesis of the ginseng sesquiterpene (-)-β-panasinsene and its enantiomer (eq 5).[12] The addition of the enantiopure lithiosulfoximine to prochiral enones or the diastereoface selective addition to racemic enones results in the formation of two diastereomeric adducts. The hydroxy group in these adducts can be used to direct the Simmons-Smith cyclopropanation (eqs 6 and 7).[13] Catalytic osmylation of such adducts is directed by the *anti* effect of the hydroxy augmented by chelation by the methylimino group (eq 7).[14]

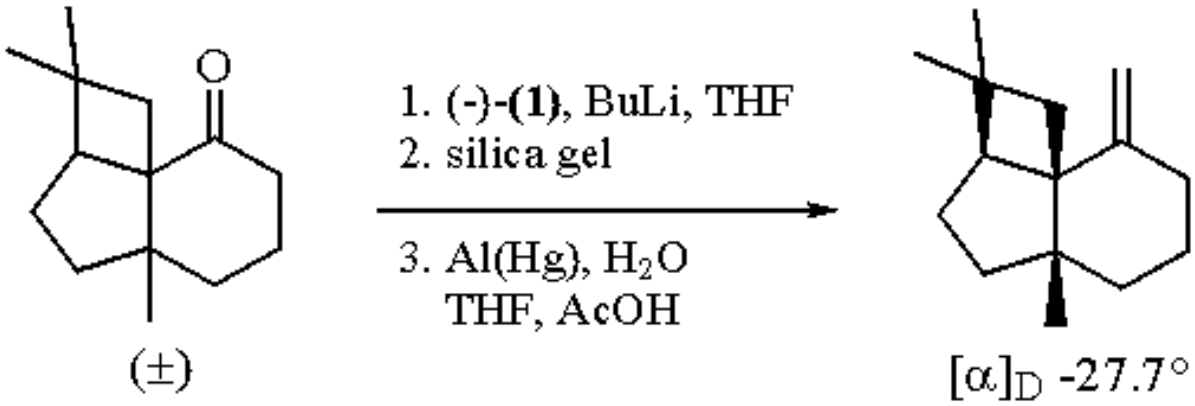

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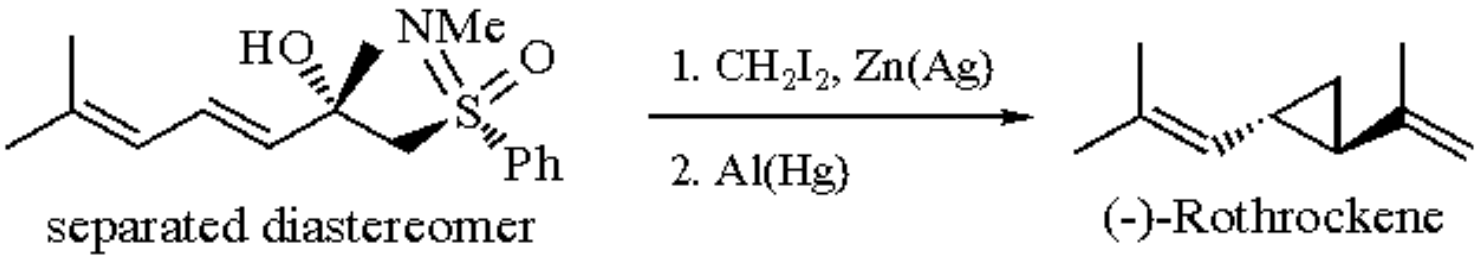

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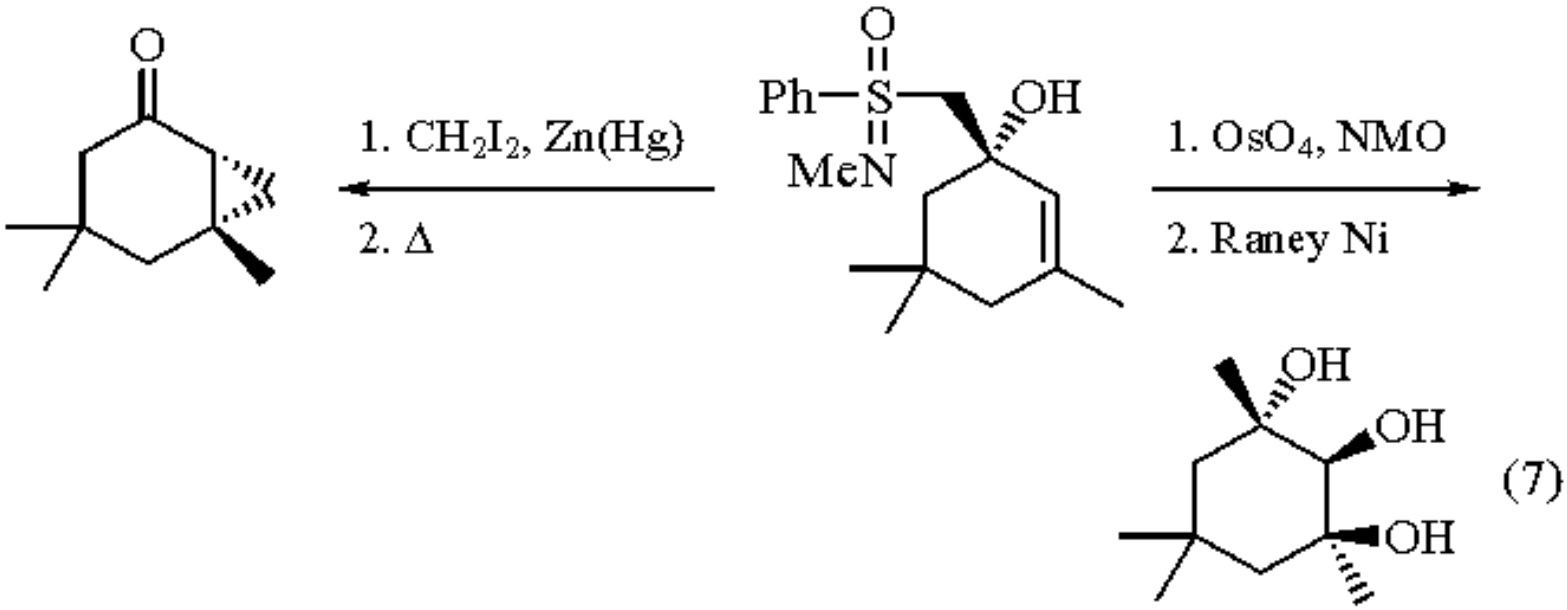

Ylides derived from the salts obtained by *N,N*-dialkylation of sulfoximines and anions derived from *N*-tosylsulfoximines are useful reagents for the synthesis of epoxides or cyclopropanes from aldehydes and ketones or enones.[1]

Related Reagents.

Dibromomethane-Zinc-Titanium(IV) Chloride; ***Methylenetriphenylphosphorane***.

---

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Dimethyl(phenylthiomethyl)amine

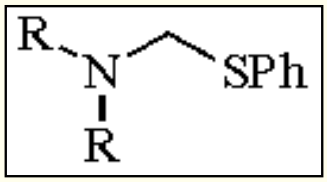

(**1**; R = Me)

[43180-39-8] · $C_9H_{13}NS$ · Dimethyl(phenylthiomethyl)amine · (MW 167.30) (**2**; R = Et)

[13865-52-6] · $C_{11}H_{17}NS$ · Diethyl(phenylthiomethyl)amine · (MW 195.36)

(sources of the $R_2NCH_2^+$ synthon for reactions with many organometallics;[6] phenylthiomethylation reagents for enamines;[12] a modified Sommelet-Hauser rearrangement route[15] from benzyl bromides to *o*-tolualdehydes)

Physical Data: (**1**) bp 112-116 °C/9-11 mmHg. (**2**) bp 110-112 °C/5-6 mmHg; *d* 0.9878 g cm^{-3}; *n*25D 1.5500.

Preparative Methods: PhSH + R_2NH + CH_2O (71%);[1] PhSH + CH_2=+NMe_2 I^- (80%).[2]

Dialkylaminomethylation of Nucleophiles.

The dialkyl(phenylthiomethyl)amines are good sources of the $R_2NCH_2^+$ synthon for reactions with alkyl,[3] allyl (eq 1),[4] and aryl[5] Grignards, and alkenyl[6] copper reagents (eq 2); these C-C couplings give alkyl,[3] homoallylic,[4] benzylic,[5] and allylic[6] tertiary amines, respectively. Silyl-[7] and germyllithiums[8] give the corresponding dialkylaminomethylsilanes and -germanes. An alternative route to Me_2NCH_2-R (or -Ar) type tertiary amines from Grignards and other organometallics involves the use of methylene immonium salts[9] (Eschenmoser salt, CH_2=+NMe_2 Cl^-, is a commercial reagent; see ***Dimethyl(methylene)ammonium Iodide***), and benzotriazole-derived aminals[10] or amine *N*-oxides[11] can be used as sources of the $R_2NCH_2^+$ synthon in general. The above procedures are particularly valuable for the synthesis of tertiary benzylic amines where the usual Mannich conditions do not work owing to insufficient nucleophilicity of the starting aromatic reactant.

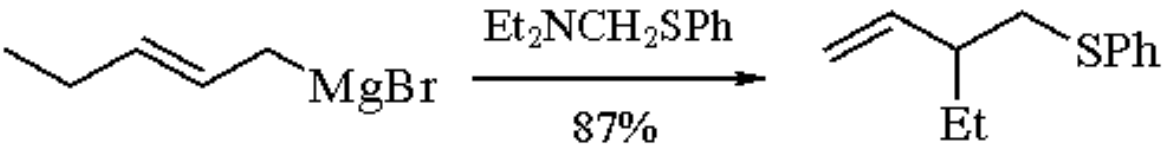

(1)

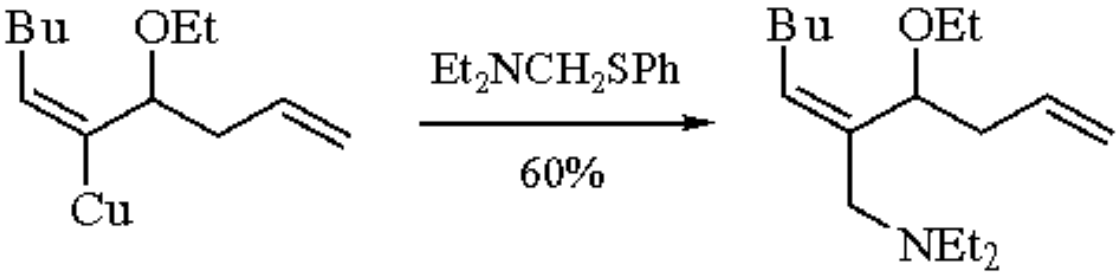

(2)

Phenylthiomethylation of Nucleophiles.

Under acidic conditions, the dialkylamino moiety becomes the leaving group and $PhSCH_2^+$ is thus delivered to a nucleophile. β-Phenylthio ketones are obtained from enamines (eq 3)[12] in a procedure that avoids the use of the obnoxious alternative ***Chloromethyl Phenyl Sulfide***.[13] However, good yields are only reported with enamines derived from MeCOR (or MeCOAr), and those derived from α-branched carbonyl compounds do not react at all (the chloromethyl sulfide alternative[12] is more versatile). Highly reactive aromatics[14] (indole, 2-naphthol; eq 4) are phenylthiomethylated in good yield, in contrast to simple phenols and aryl amines, halides, and ethers.

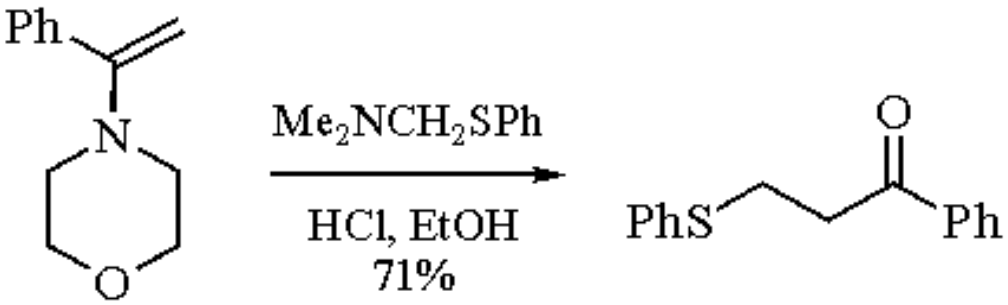

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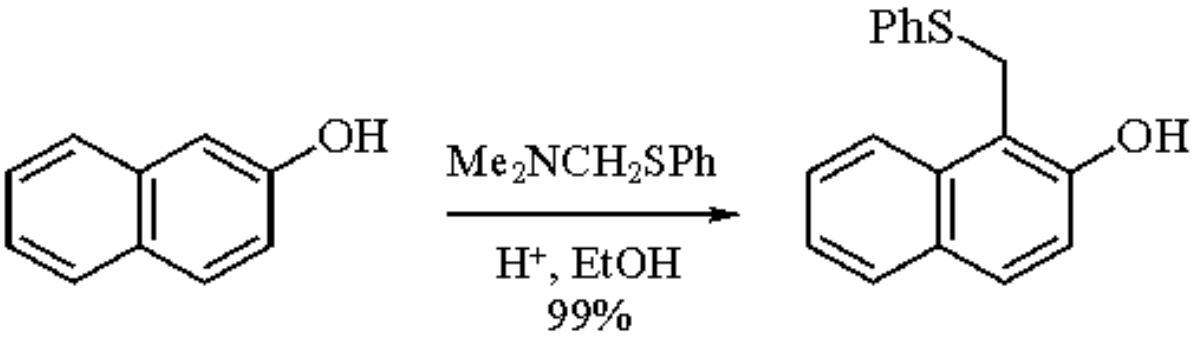

(4)

Modified Sommelet-Hauser Rearrangement.

The quaternary ammonium salts from dimethyl(phenylthiomethyl)amine and benzyl bromides give *o*-tolualdehydes in good yield.[15] This reaction was used in two different syntheses,[16,17] of juncusol (eq 5; R = H, 87%; R = CO_2Me, 54%).[16] The product from benzyl bromide and pyrrolidinoacetonitrile[18] undergoes an analogous reaction to give *o*-tolualdehyde in 85% yield. The classical alternatives, such as a reduction of the bromide or its precursor aldehyde to methyl, followed by formylation, cannot compete with these highly expedient synthetic routes.

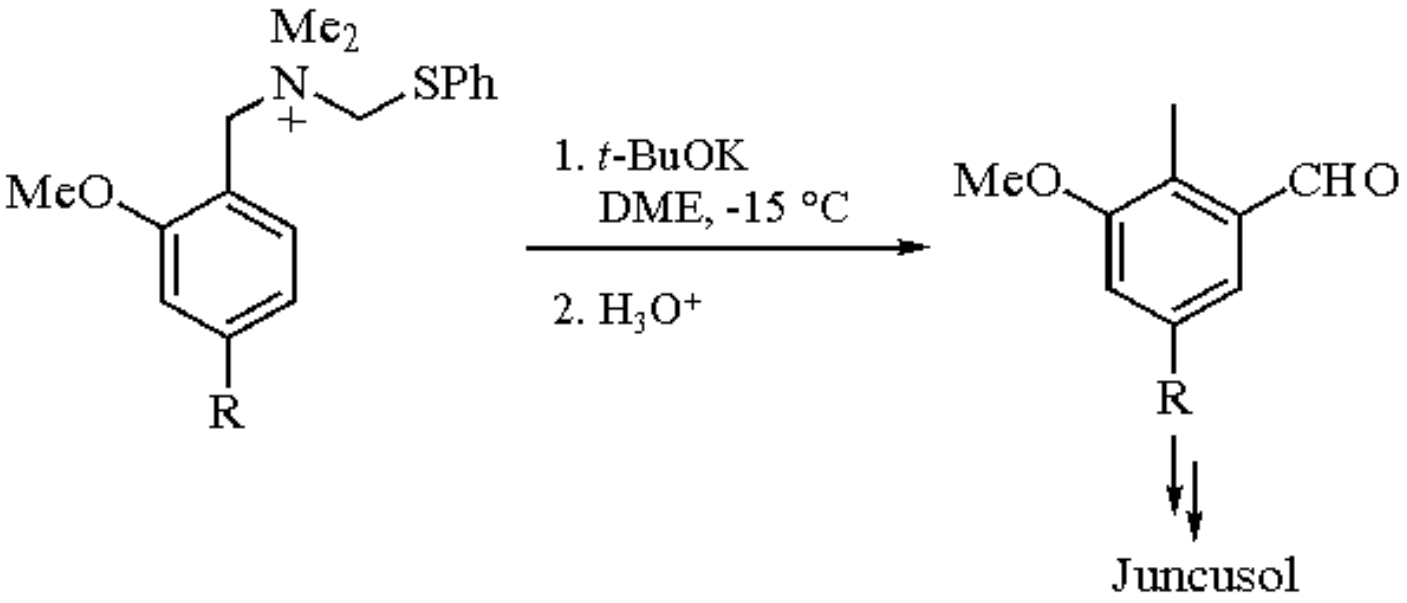

(5)

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Dimethylphosphinothioyl Chloride

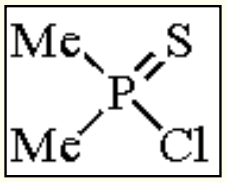

[993-12-4] · C_2H_6ClPS · Dimethylphosphinothioyl Chloride · (MW 128.57)

(reagent for protection in peptide[1,2] and carbohydrate[3,4] synthesis)

Alternate Name: Mpt-Cl.

Physical Data: mp 24-25 °C; bp 107-107.5 °C/16 mmHg; bp 69-70 °C/11 mmHg;[5] n_D^{20} 1.546.

Form Supplied in: liquid; commercially available.

Preparative Method: chlorination of tetramethyldiphosphine disulfide[7] with ***Sulfuryl Chloride***.[1,6]

Handling, Storage, and Precautions: stable for several months in a refrigerator.[1] Should be handled in the fume hood.

Peptide Synthesis.

The dimethylphosphinothioyl (Mpt) group has been used to protect *N*-amino acids. It is more readily removed than *t*-butoxycarbonyl group, making it a convenient reagent for solid phase synthesis (eq 1).[1]

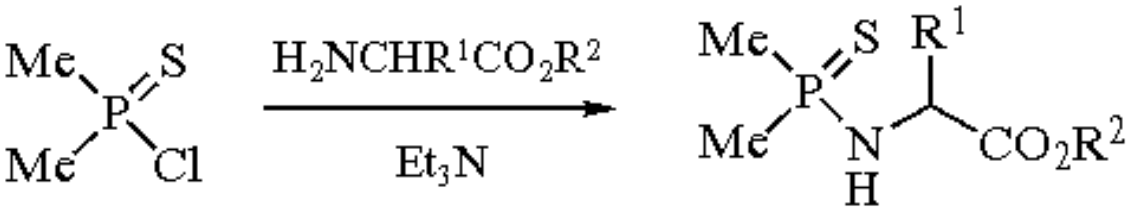

(1)

This method has been effectively demonstrated in the synthesis of the opioid agonist L-Leu-enkaphalin (L-Tyr-Gly-Gly-L-Phe-L-Leu).

Mpt-Cl also reacts rapidly with *N*-protected amino acids in the presence of ***Triethylamine*** to afford Mpt mixed anhydrides (Mpt-MA). These mixed anhydrides can be isolated by silica-gel column chromatography and stored without decomposition in a freezer. Cbz-Ser-Mpt-MA has been isolated in 17% yield, without protection of the side-

chain hydroxy group (eq 2).[8,9] As a consequence, these active Mpt-MAs have been used for peptide synthesis in methanol or ethanol rather than the usual dipolar aprotic solvents (HMPA, DMF, or DMSO). Synthesis of a heptapeptide (**1**) has been completed by this method.[2]

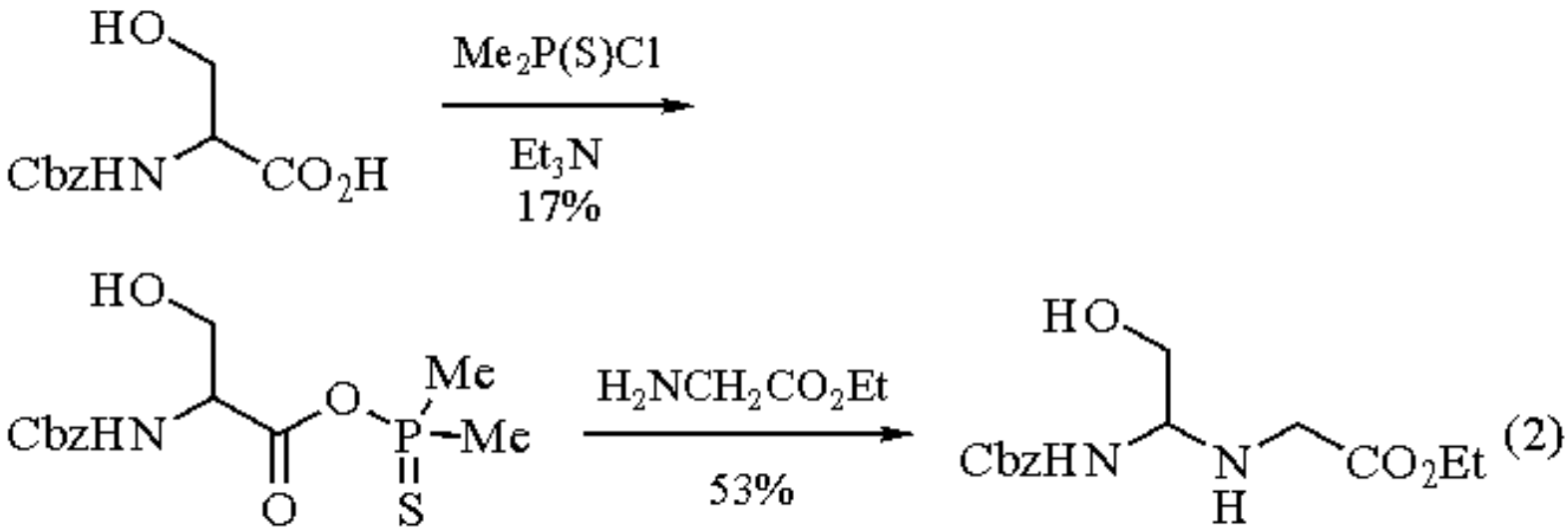

Cbz-Tyr-Leu-Asn-Ser-Ile-Asn-NH_2

(1)

Carbohydrate Protection/Synthesis.

Hydroxy groups of carbohydrates can be protected using Mpt-Cl in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** and catalytic amounts of ***4-Dimethylaminopyridine***. The Mpt group is stable to acidic hydrolysis conditions that cleave trityl and isopropylidene (acetonide) groups, DBU/MeOH, Bu_4NF, Bu_3SnH, Grignard reagents, and cat. NaOMe/MeOH. The Mpt group does not migrate as do acyl groups (carboxylate esters) under acidic and basic conditions.[4]

Mpt-Cl has been used in the stereoselective synthesis of B-glucopyranomides.[3]

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Harjinder S. Bansal

2-(2,6-Dimethylpiperidino)acetonitrile

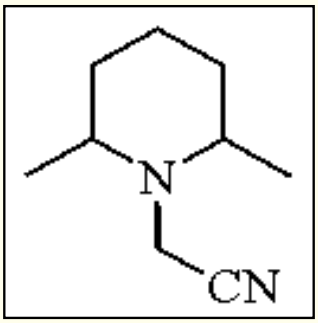

[825-28-5] · $C_9H_{16}N_2$ · 2-(2,6-Dimethylpiperidino)acetonitrile · (MW 152.27)

(α-lithiation affords a formyl anion equivalent)

Physical Data: bp 99-102 °C/15 mmHg.[1]

Preparative Method: by the condensation of 2,6-dimethylpiperidine and ***Chloroacetonitrile***.[1]

One-Carbon Homologation of Alkyl Halides to Aldehydes.

Following deprotonation, this latent formyl anion equivalent -CHO can be alkylated with alkyl halides and then hydrolyzed to the homologous aldehyde or ethanolyzed to the acetal (eq 1).[2]

2-(2,6-Dimethylpiperidino)acetonitrile

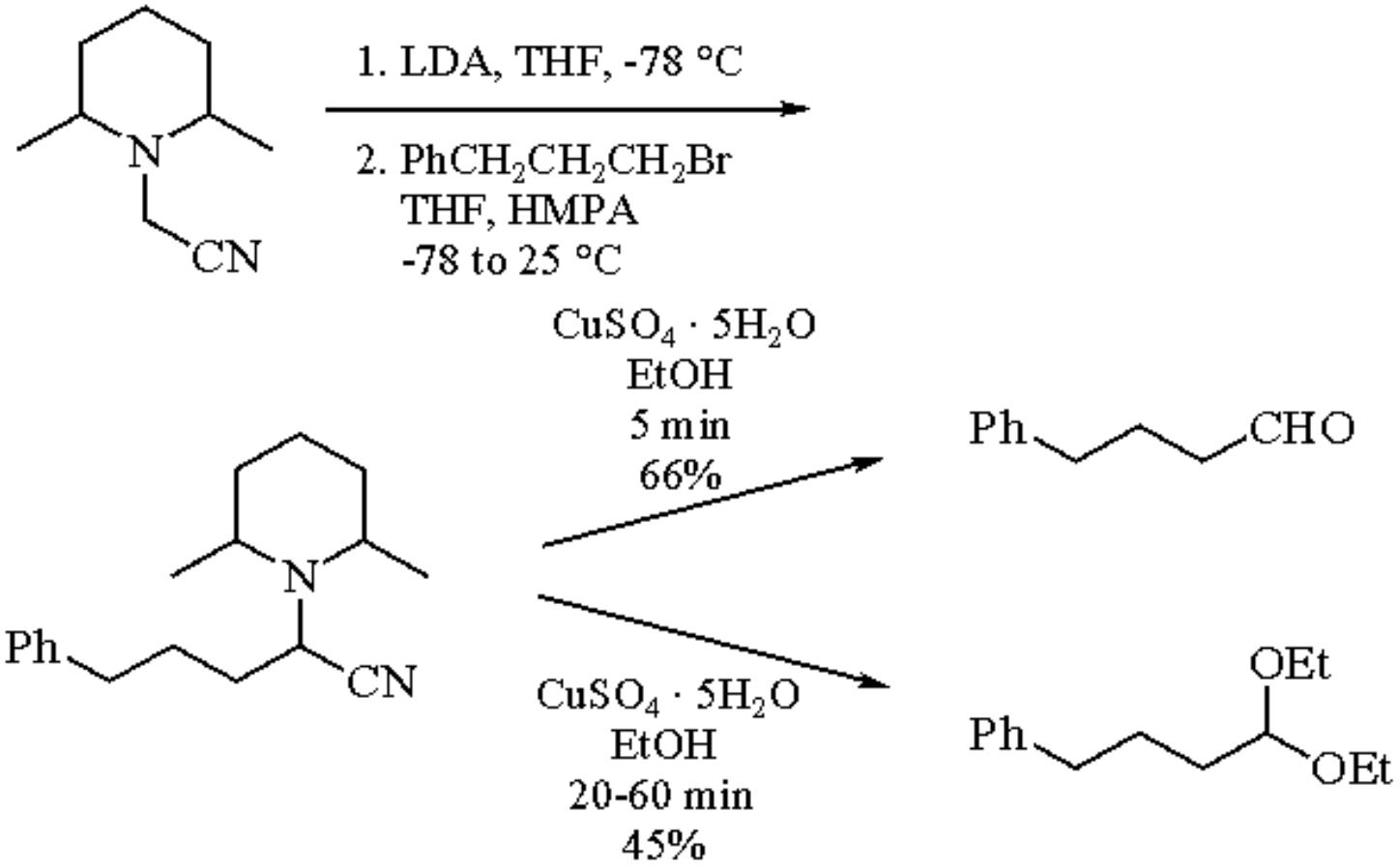

Synthesis of Aromatic Compounds.

Alkyl halides containing an electron-rich aromatic ring undergo subsequent cyclization via an iminium intermediate (eq 2).[2]

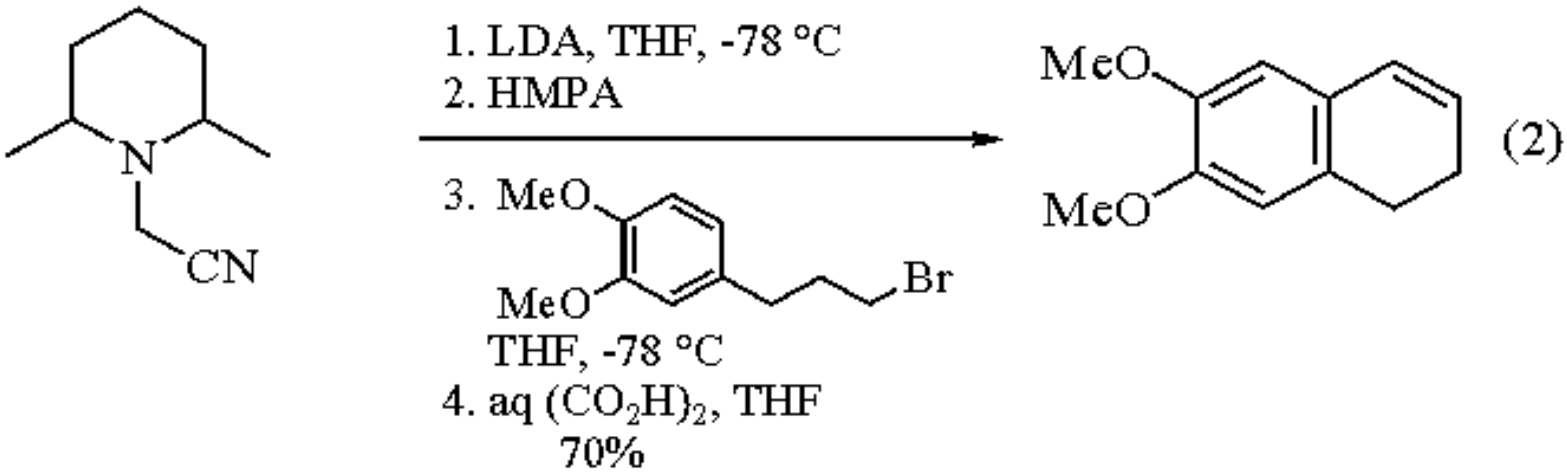

Formylation of α,β-Unsaturated Ketones.

Michael addition to 2-cyclohexen-1-one followed by reduction and methanolysis yields a hydroxy acetal derivative (eq 3).[3]

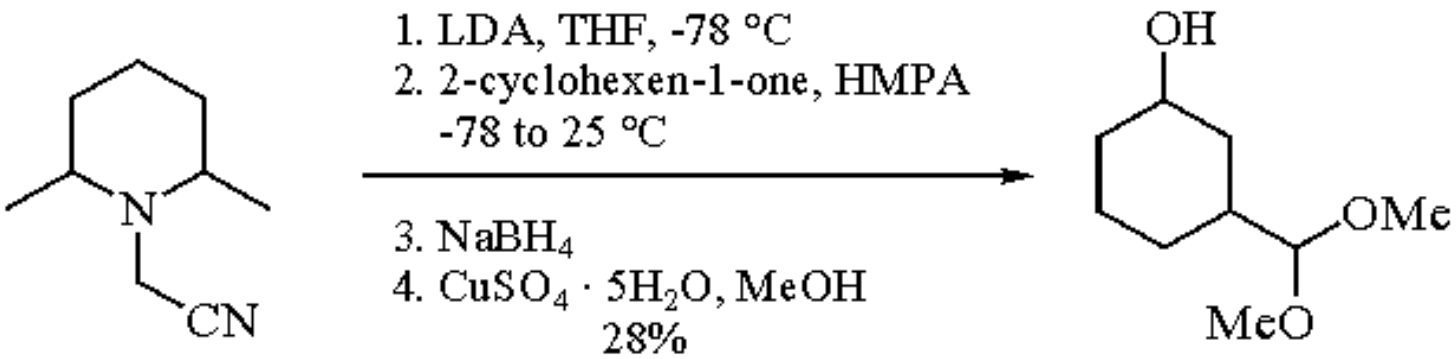

(3)

Related Reagents.

N,N-Diethylaminoacetonitrile; ***N,N-Dimethyldithiocarbamoylacetonitrile***; ***(4aR)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin***; ***2-Lithio-1,3-dithiane***; ***Methoxyacetonitrile***; ***Nitromethane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***; ***2-(Trimethylsilyl)thiazole***.

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2,2-Dimethyl-1,3-propanediol

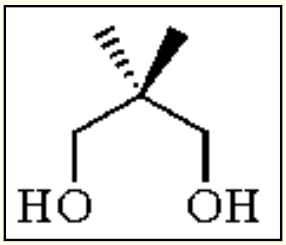

[126-30-7] · $C_5H_{12}O_2$ · 2,2-Dimethyl-1,3-propanediol · (MW 104.17)

(protecting group for aldehydes and ketones;[9] a ligand used in boron chemistry[12])

Physical Data: mp 123-127 °C.[1]

Solubility: sol H_2O, chloroform, benzene; very sol ethyl alcohol, diethyl ether.[2]

Form Supplied in: white crystals.

Handling, Storage, and Precautions: skin irritant; hygroscopic; store in cool dry place.[1]

Cyclic Acetals.

2,2-Dimethyl-1,3-propanediol (**1**) has been used effectively as a protecting group for ketones and aldehydes. The formation of the cyclic acetal can be accomplished in many ways. The most common is to reflux the ketone and diol (**1**) with a catalytic amount of acid and force the reaction to completion by removing H_2O, usually with a Dean-Stark trap (eq 1).[3] Other methods involve treating the ketone-diol mixture with ***Chlorotrimethylsilane*** (eq 2)[4] or ***Boron Trifluoride Etherate*** (eq 3).[5]

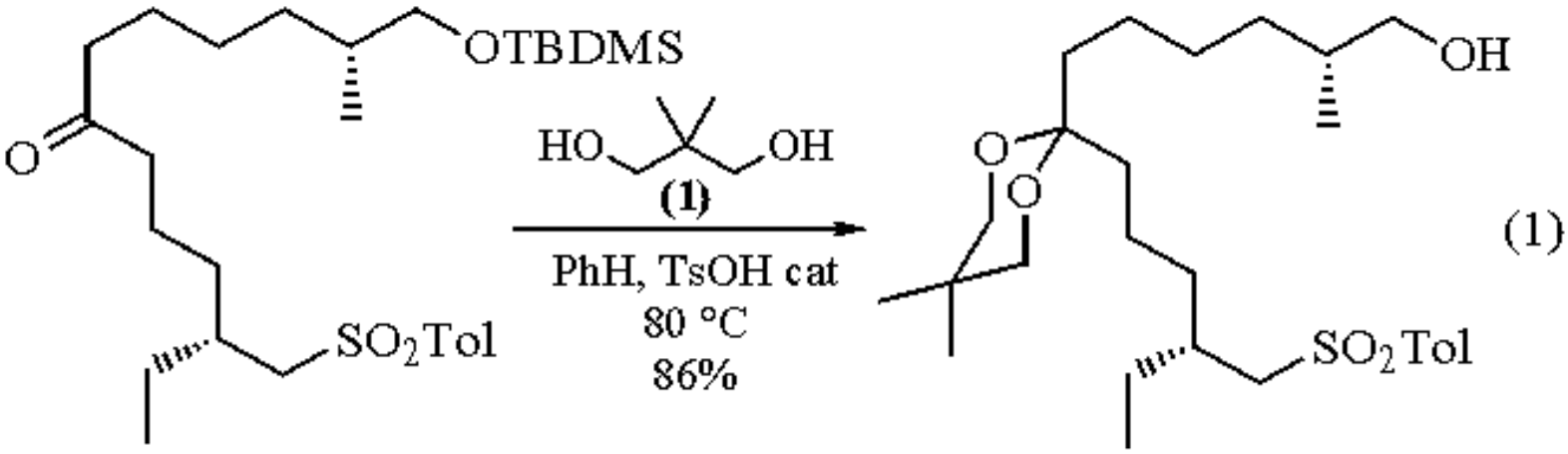

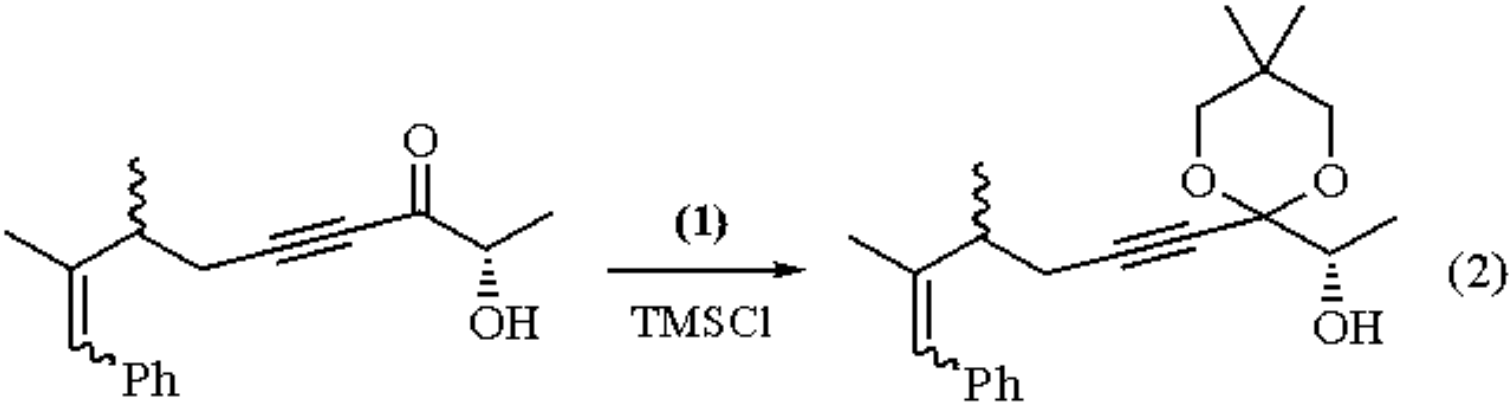

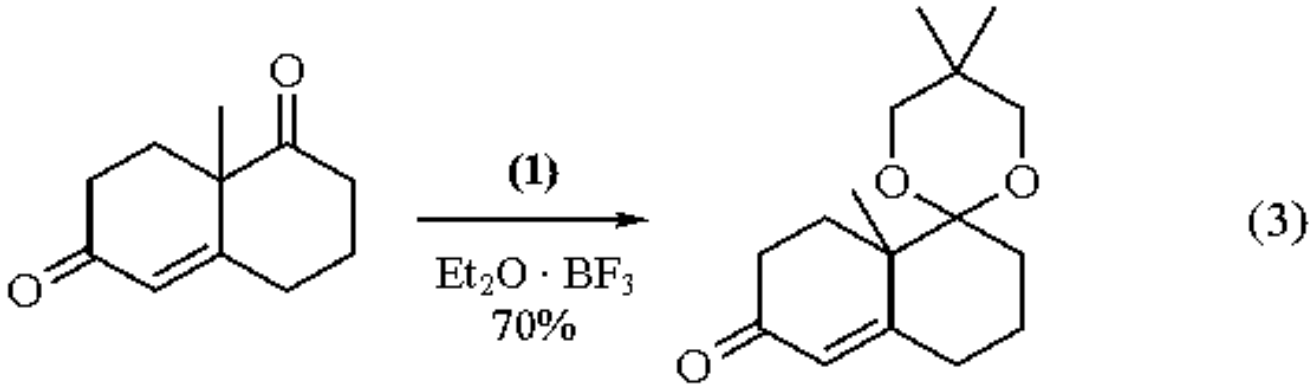

The advantages of diol (**1**) compared to other diols depend on the compound being protected. In the formation of β-halo acetals, for example, reagent (**1**) was found to be more effective than ***Ethylene Glycol*** because of easier separation and a longer shelf life of the product.[6] Diol (**1**) was also considered to be superior to ethylene glycol when Grignard reagents were prepared from β-halo acetals (eq 4).[7]

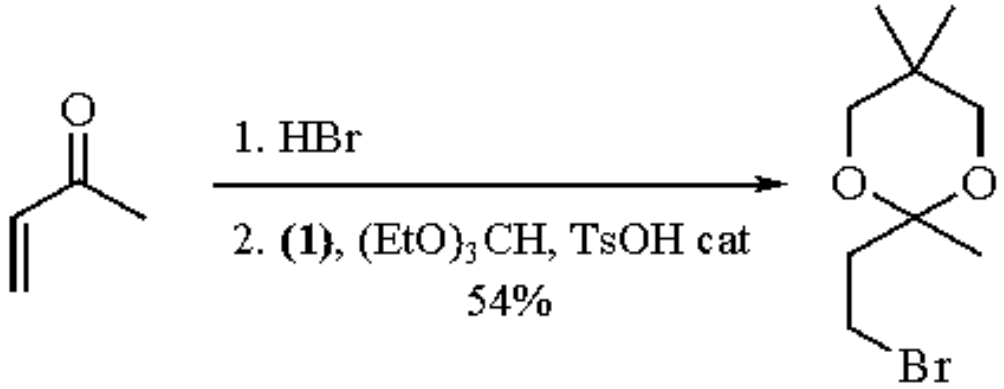

(4)

In comparing rates of acid hydrolysis of different cyclic acetals formed from a variety of diols, the following order was discovered; 1,3-propanediol >> (**1**) > ethylene glycol > 2,2-diethyl-1,3-propanediol > 2,2-diisopropyl-1,3-propanediol.[8] This has been attributed to the *gem*-dialkyl effect which serves to stabilize the cyclic acetal. Cleavage of the protecting group formed from diol (**1**) is easily accomplished via acidic hydrolysis using acids such as H_2SO_4, HCl, or TsOH.

Reagent (**1**) has been used in a variety of syntheses where its merits have not been elucidated. The following reactions show some of these transformations (eqs 5-7).[9-11]

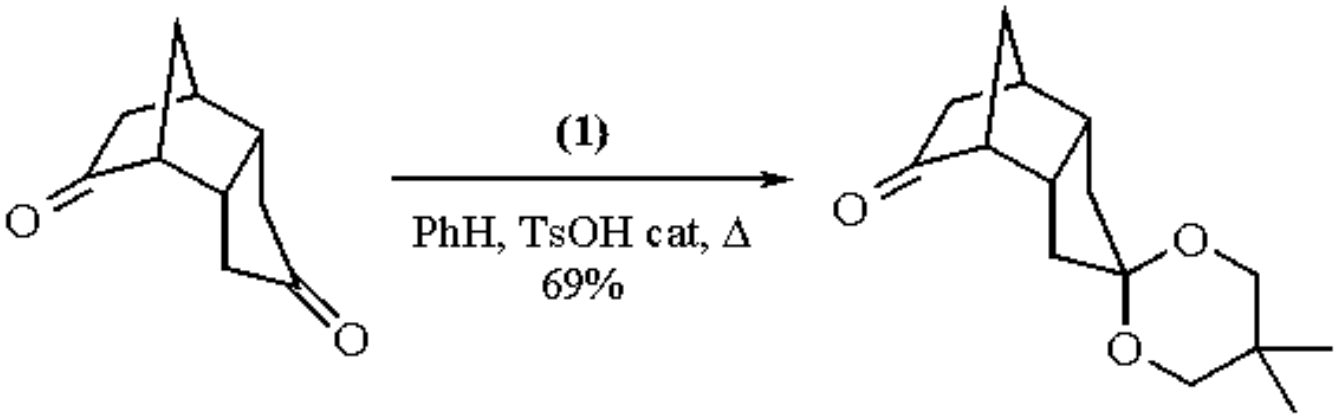

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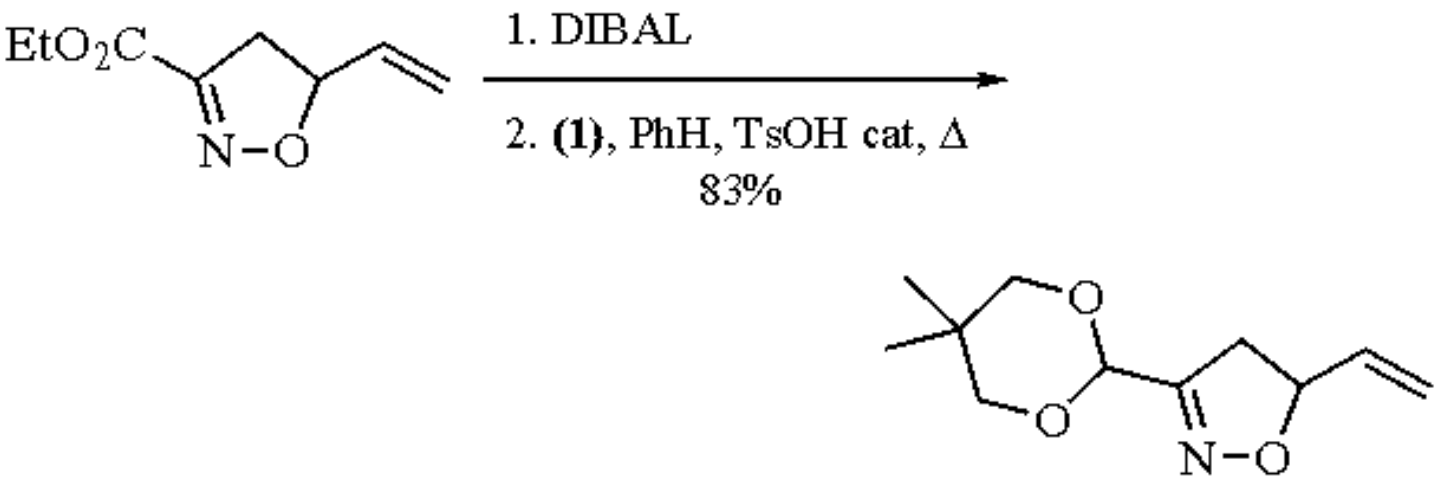

(6)

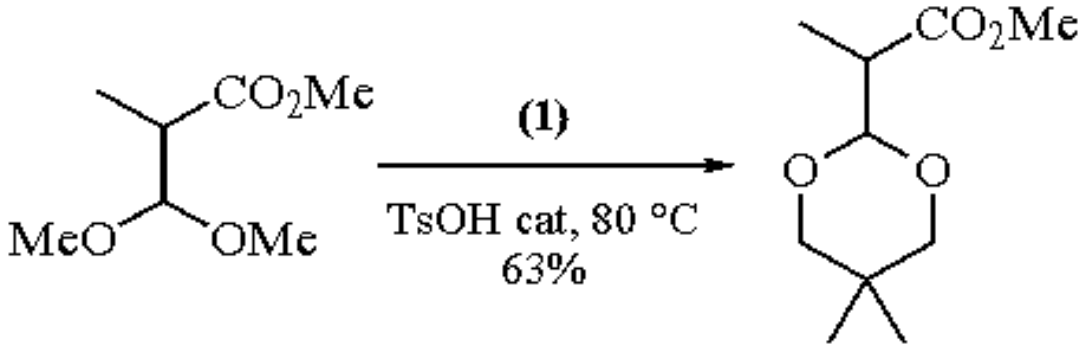

(7)

Use as a Boron Ligand.

This diol has been used to complex boron.[12] For example, diol (**1**) was employed to remove the phenylboronic acid template from a Diels-Alder adduct under neutral conditions (eq 8).[13]

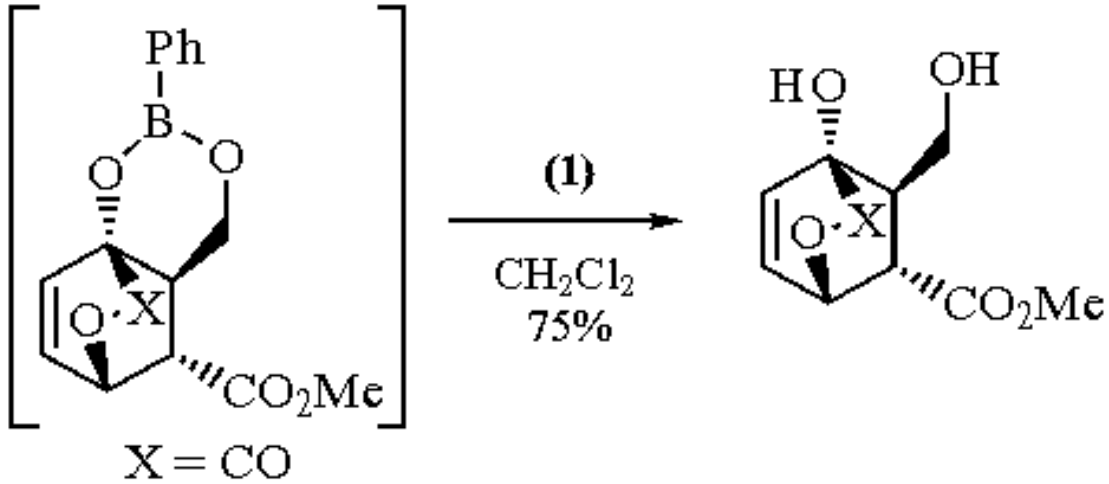

(8)

Related Reagents.

3-Bromo-1,2-propanediol; ***2,3-Butanediol***; ***Ethylene Glycol***; ***(2R,4R)-2,4-Pentanediol***; ***1,3-Propanediol***.

---

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N,N-Dimethylpropionamide Dimethyl Acetal[1]

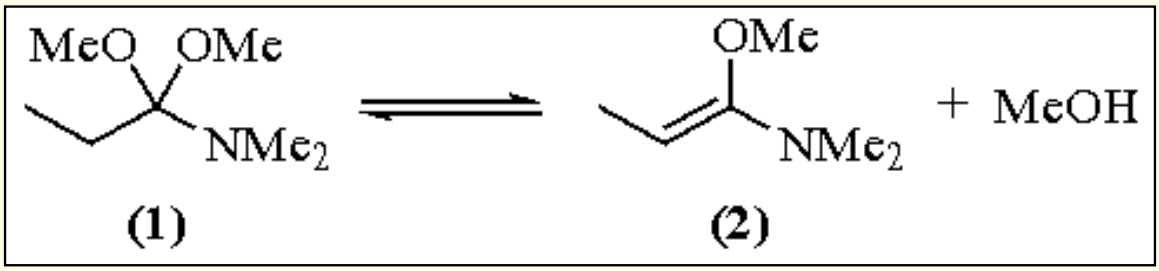

(**1**)

[19429-86-8] · $C_7H_{17}NO_2$ · *N,N*-Dimethylpropionamide Dimethyl Acetal · (MW 147.25) (**2**)

[816-05-7] · $C_6H_{13}NO$ · *N,N*-Dimethylpropionamide Dimethyl Acetal · (MW 115.20)

(reagents for stereoselective Eschenmoser-Claisen rearrangements[2] to give γ,δ-unsaturated amides, or, via subsequent protodesilation, to give β,γ-unsaturated amides)

Physical Data: (**1**) and (**2**) mixture: bp 117-120 °C. (**2**): bp 117-118 °C.

Solubility: sol benzene and xylene.

Preparative Methods: a mixture of (**1**) and (**2**) is prepared by *O*-methylation of *N,N*-dimethylpropionamide with ***Dimethyl Sulfate***, followed by reaction with ***Sodium Methoxide*** in methanol.[3] Fractional distillation affords a mixture of (**1**) and (**2**). Treatment with calcium metal and distillation gives the *N,O*-ketene acetal (**2**) (57%). Either a mixture of (**1**) and (**2**) or pure (**2**) may be used in sigmatropic rearrangements.

Handling, Storage, and Precautions: the reagents are potentially toxic and flammable. They should be handled in a fume hood.

Eschenmoser-Claisen Rearrangement.

Reagents (**1** + **2**) or (**2**) condense with allyl alcohols to produce *N,O*-ketene acetal intermediates that undergo [3,3]-sigmatropic rearrangements to afford γ,δ-unsaturated amides. Studies performed by Sucrow and Richter show that the overall transformation of the allylic alcohol is highly stereoselective, with the *trans* allylic alcohol affording the *erythro* product and the *cis* allylic alcohol affording the *threo* product (eq 1).[4]

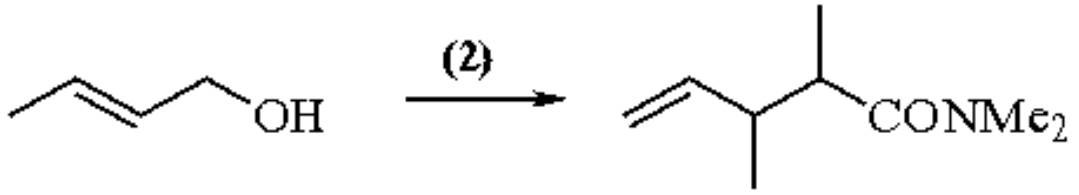

(1)

trans — *erythro*:*threo* = 95:5
cis — *threo*:*erythro* = 97:3

This result has been rationalized in terms of a chair-like transition state in which the methyl group from the acetal occupies the axial position *anti* to the bulky dialkyl amino group (eq 2).

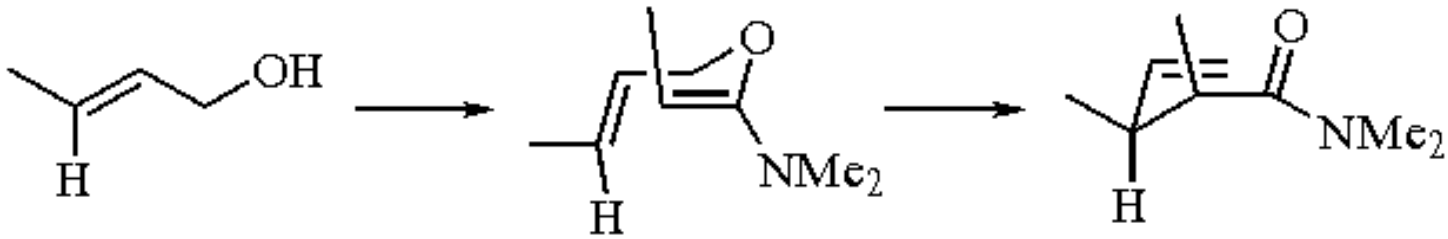

(2)

An X-ray structure of a cyclic *N*,*O*-ketene acetal derived from reagent (**1**) showed that the methyl substituent occupied the position *trans* to the nitrogen (eq 3).[5]

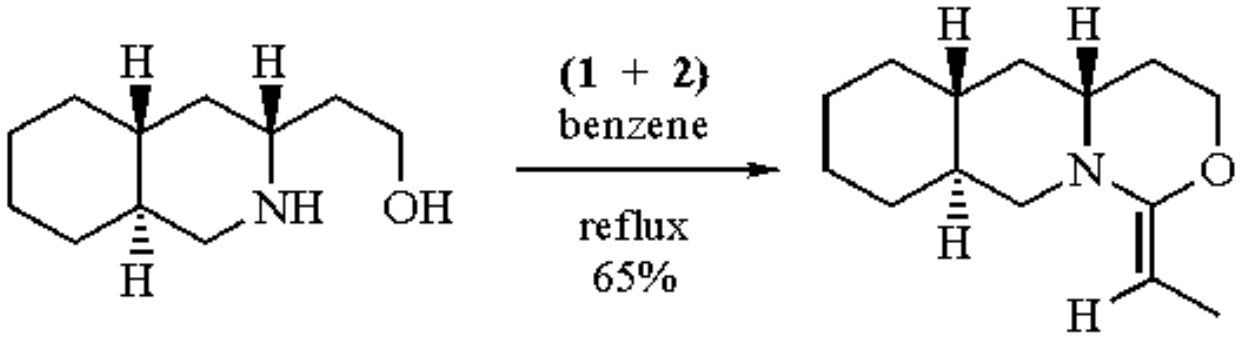

(3)

trans β,γ-Unsaturated carboxylic acid derivatives were prepared by amide acetal rearrangement of 3-(trimethylsilyl)allyl alcohols and subsequent desilylation with allylic rearrangement (eq 4).[6]

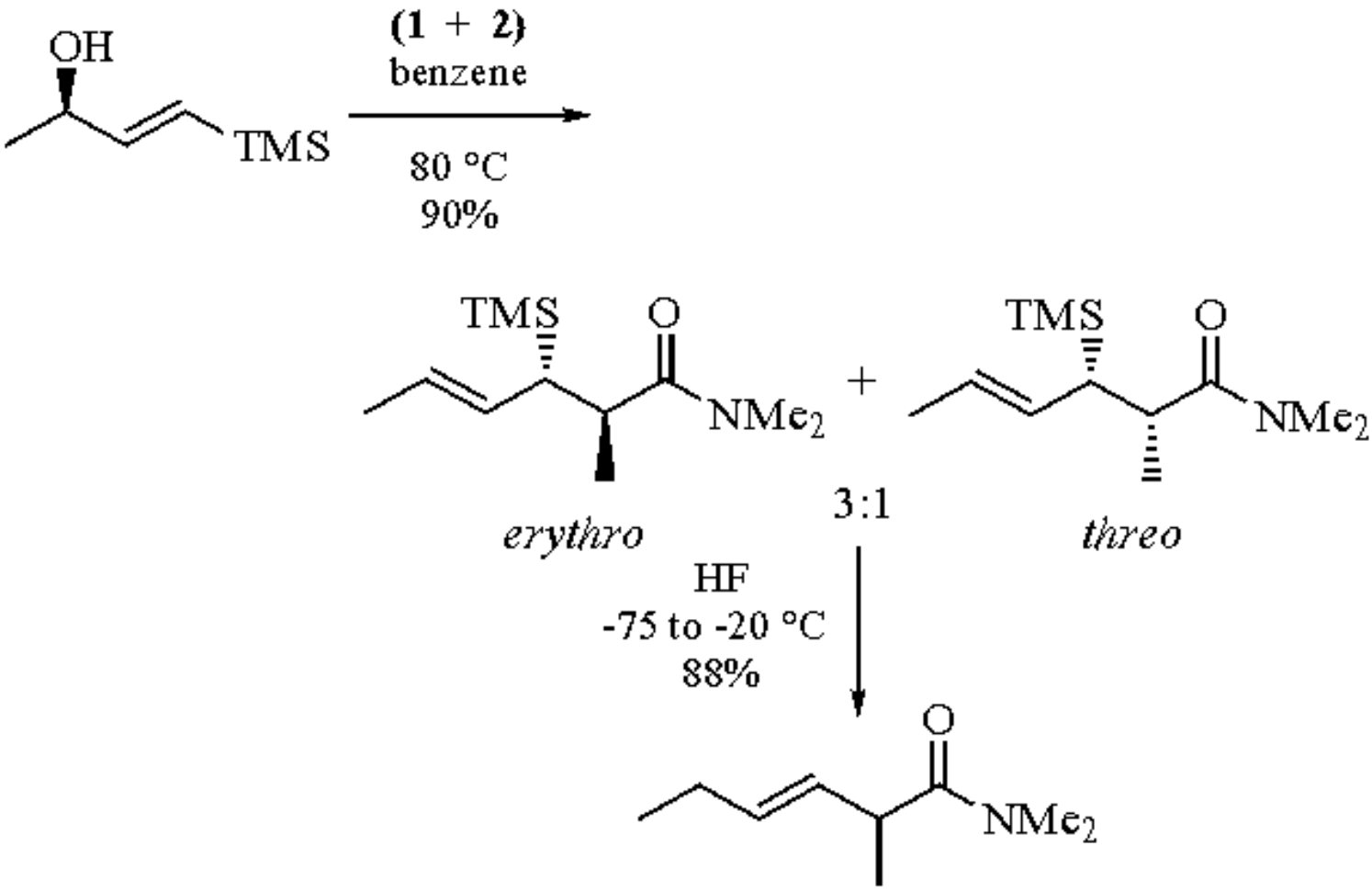

(4)

The propionamide acetal rearrangement was used to establish the *threo* stereochemistry in intermediates for prostaglandin H analog synthesis (eq 5).[7]

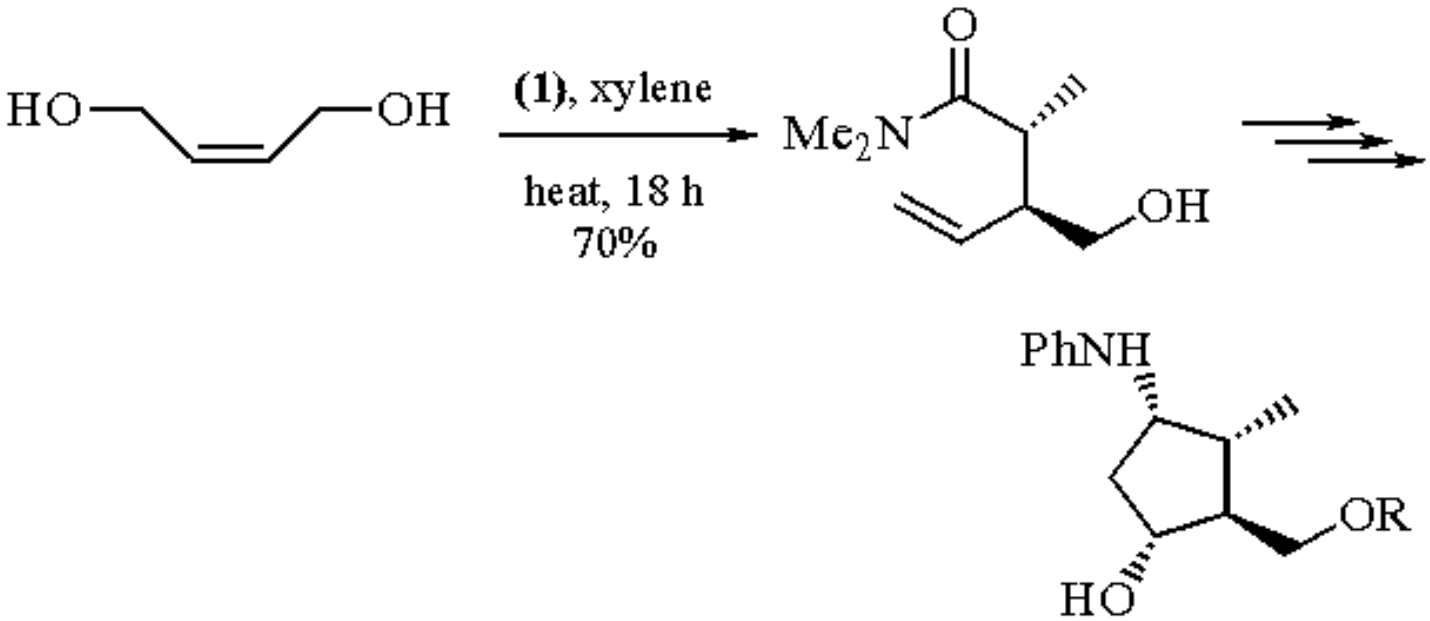

(5)

Other Applications.

The reaction of the reagent with an amide oxime gives 5-ethyl-1,2,4-oxadiazoles (eq 6).[8]

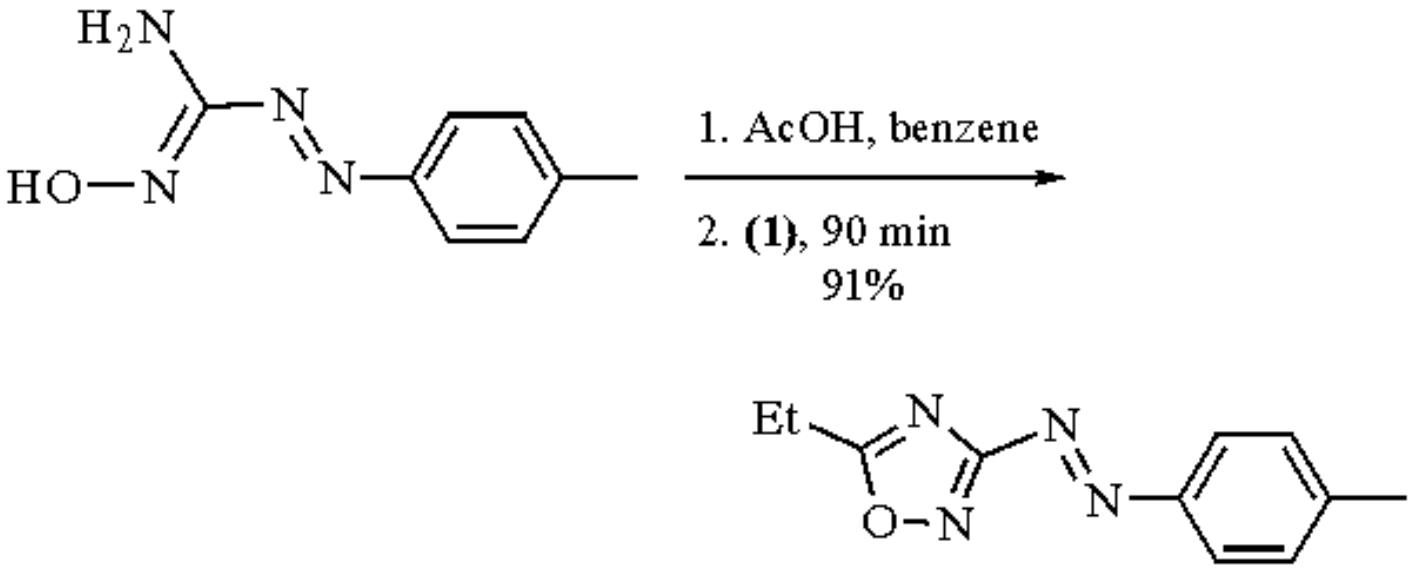

(6)

Related Reagents.

1,1-Dimethoxypropene, ***N,N-Dimethylacetamide Dimethyl Acetal***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Dimethyl Sulfate***; ***Methylketene Dimethyl Acetal***; ***Triethyl Orthoacetate***.

---

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N,N´-Dimethylpropyleneurea[1,2]

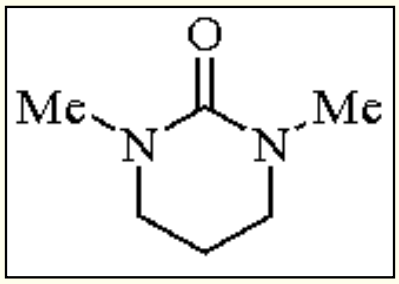

[7226-23-5] · $C_6H_{12}N_2O$ · *N,N´*-Dimethylpropyleneurea · (MW 128.18)

(dipolar aprotic solvent and cosolvent with properties very similar to those of HMPA; usually a somewhat larger amount is required in order to observe the same cosolvent effect as with HMPA; unlike HMPA, it was found to be nonmutagenic in a comparative investigation[1])

Alternate Names: DMPU; 1,3-dimethyltetrahydro-2(1*H*)-pyrimidone.

Physical Data: bp 110 °C/10 mmHg; mp ca. -20 °C; *d* 1.064 g cm^{-3}; ε$_r$ = 36.

Solubility: miscible with most organic solvents, and with water; a ca. 25% solution in THF can be cooled to dry-ice temperature without crystallization or phase separation.[3]

Form Supplied in: colorless, hygroscopic liquid; commercially available.

Purification: predry over KOH (only necessary with rather wet material), and distill from CaH_2 in vacuo.

Handling, Storage, and Precautions: store at rt in a bottle with a three-way stop cock and a serum cap, over freshly activated molecular sieve (4 Å) and under an inert atmosphere; if stored as indicated, DMPU is stable and ready for use for many months; samples should be withdrawn by syringe technique.

Like HMPA,[4] the cyclic urea DMPU is the prototype of a dipolar aprotic solvent (cf. DMSO, DMF, NMP). As a solvent and cosolvent, DMPU causes increased basicity and nucleophilicity of reagents. It was found to be especially useful for reactions of polyanionic species. Surprisingly, it may have a stabilizing effect on anionic systems that have a tendency to undergo fragmentation. A crystal structure of a Li enolate solvated by DMPU has been described.[5] The lower homolog ***1,3-Dimethyl-2-imidazolidinone*** (DMI) has also been recommended, but it is less useful for low-temperature work due to its greater tendency to crystallize.[6] Although DMPU is a carbonyl compound, it may be used as a cosolvent under the most vigorous metallating conditions (BuLi), at least at low temperatures. The similarity of effects observed with DMPU and the mutagenic HMPA is striking in many cases. (The effects of HMPA on the structure of Li compounds and Li enolates have been thoroughly investigated.[7]) For a detailed discussion of the many uses of HMPA in organic synthesis see ***Hexamethylphosphoric Triamide***. For safety reasons it is recommended that

DMPU is tested as a substitute for HMPA in each case, even in research laboratories; large-scale industrial applications of HMPA have been banned.

The reactions discussed in the following paragraphs are taken from work in which HMPA and DMPU have been compared. In an increasing number of publications on DMPU applications, no comparison is mentioned; some of these are included in the list of references.

Chiral DMPU derivatives have been synthesized; the best induction with one of them gave an aldol of 15% ee.[8]

Generation and Stereoselective Reactions of Lithium Enolates.

Bulky Li amide bases deprotonate ketones and esters to *trans* Li enolates (the trivial *cis*/*trans* nomenclature is used in order to avoid unnecessarily cumbersome language). This has been proved by the X-ray crystal structure analysis of several ester Li enolate derivatives[9] and by numerous NMR investigations of the silyl enol ethers, the trapping products of Li enolates with chlorosilanes. In connection with studies on the Ireland-Claisen rearrangement it was discovered[10] that the *cis* Li enolates are formed when the reaction is carried out in the presence of HMPA, under otherwise identical conditions. As can be seen from eq 1[3] and eq 2,[11] this cosolvent effect can be fully reproduced with DMPU; a review about the careful optimization of this enolate formation includes all details.[11] The diastereoselectivity of most enolate reactions is determined by the geometry of the enolate double bond, and therefore the DMPU effect outlined in eqs 1 and 2 is most important in organic synthesis.[12]

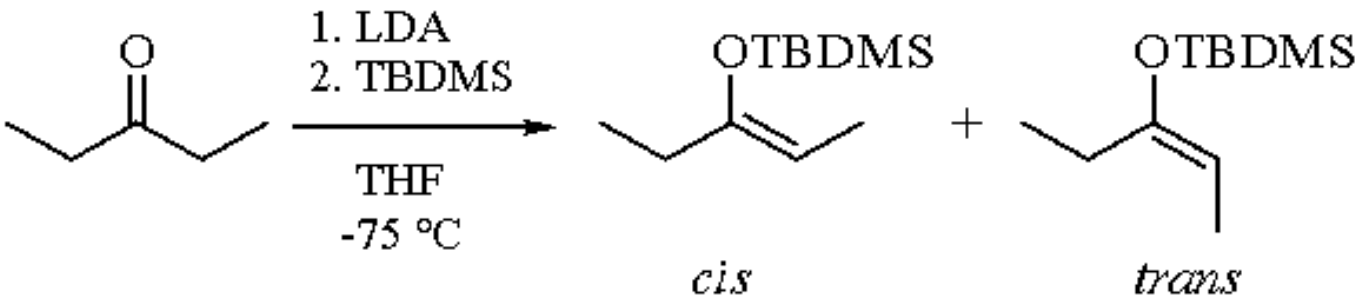

(1)

Cosolvent	
-	30:70
HMPA	95: 5
DMPU	94: 6

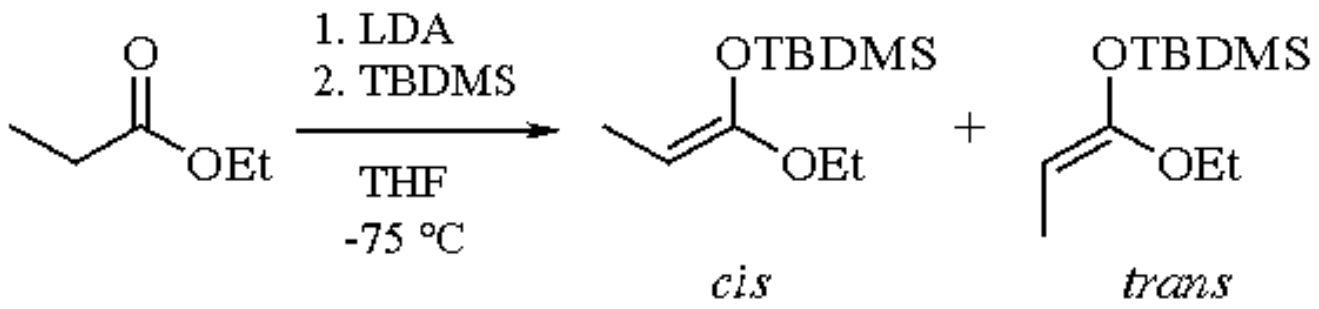

(2)

Cosolvent	
-	6:94
HMPA (23%)	85:15
DMPU (30%)	98: 2

Another useful application of the dipolar cosolvent is shown in eq 3[3] and eq 4.[13] The Li enolates from dimethyl tartrate acetonide (**1**) and from the threonine-derived oxazoline (**2**) have a tendency to undergo destructive β-elimination which can be suppressed to some extent by the presence of DMPU, allowing these enolates to be alkylated in reasonable to excellent yields. It is remarkable that a cosolvent which most chemists would expect to remove cations from their counterions (i.e. to generate naked anions) stabilizes species in which a migration of negative charge (i.e. elimination/fragmentation) leads to decomposition (cf. the use of the novel phosphazene bases (see ***Phosphazene Base P_4-t-Bu***)[14,15] for the same purpose[14a]); notice that the alkylation of the tartrate derivative (**1**) occurs from the face *cis* to the CO_2Me group.[13]

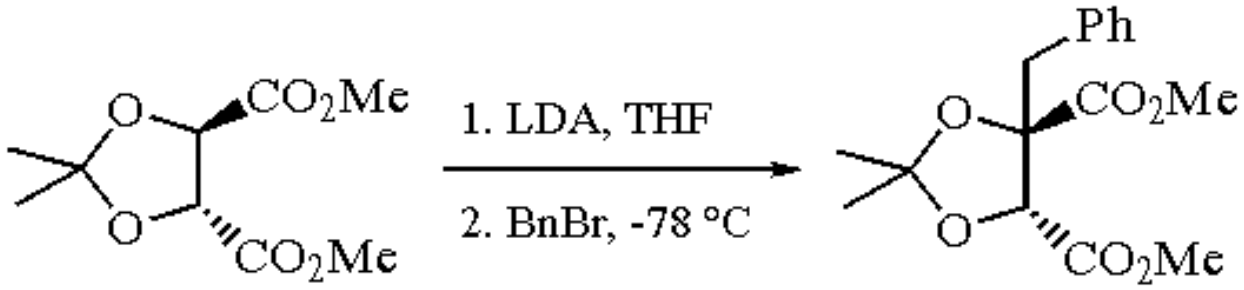

(3)

(1)

Cosolvent	Yield (%)
-	<5
HMPA (17%)	54
DMPU (33%)	52

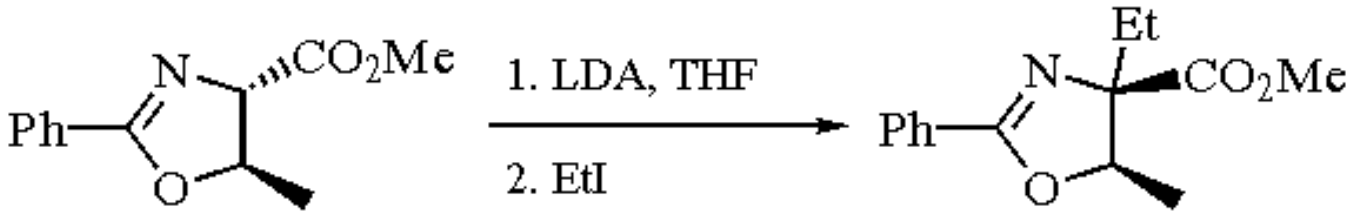

(4)

(2)

Cosolvent	Yield (%)
-	66
HMPA (17%)	94
DMPU (25%)	91

Generation and Reactions of Polylithiated Derivatives.

The reactivity of strong bases as necessary for double and polylithiations is often enhanced in the presence of DMPU, and at the same time the resulting species become more reactive. Some examples of such species are the peptide Li_3 enolate (**3**),[16] ***Methyl Dilithioacetoacetate*** (**4**),[17] the Li_2 nitronate-enolate (**5**)[3] (see ***Methyl 3-Nitropropanoate***), the lithio lithium nitronate (**6**)[3,18] (see ***O,O-Dilithio-1-nitropropene***), and the doubly lithiated iminonitrocyclohexane (**7**)[19] and ergolinylurea (**8**).[20] (We are aware of only one case in which HMPA could not be replaced at all by DMPU: the double lithiation of 1,1,1-trifluoro-2-nitropropane.[18])

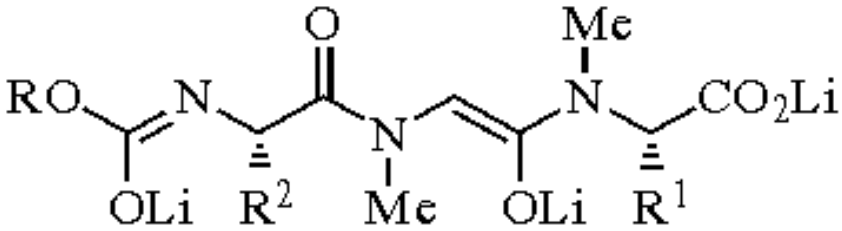

(3)

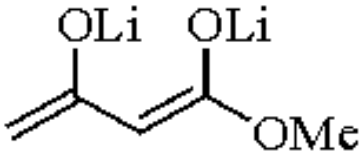

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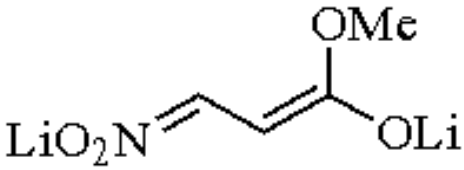

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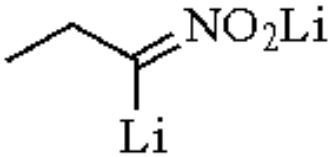

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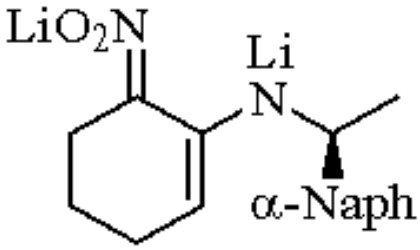

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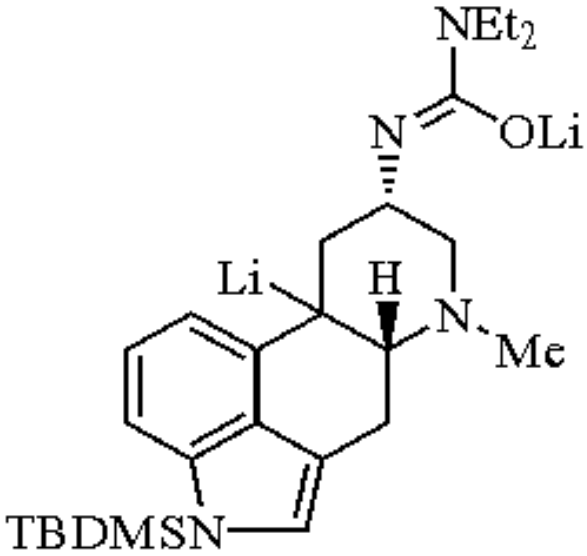

(8)

For four of these intermediates the corresponding DMPU effects are specified in eqs 5-8. Thus the nitropropionate is not doubly lithiated at all in the absence of cosolvent, and HMPA and DMPU have the same effect on the yields of products (**9**) formed with various electrophiles (eq 5).[3] The addition of doubly lithiated nitropropane to benzaldehyde is not diastereoselective in THF alone, and gives the nitroaldol of (*l*) configuration preferentially in the presence of DMPU (eq 6);[3] this means that the intermediate nitronate-alkoxide is protonated diastereoselectively upon quenching the reaction mixture in the presence of cosolvent.[21] (see ***Trimethylsilyl Methanenitronate***). The chiral imine of 2-nitrocyclohexanone shown in eq 7 is doubly lithiated to a solution containing (**7**) and ***Lithium Diisopropylamide*** (since ***Diisopropylamine*** forms complexes with lithiated species, which are responsible for poor yields, the amine is converted to LDA for better results),[22] and allylation gives best yields of product (**10**) and highest diastereoselectivity in the presence of DMPU.[19] Finally, the conversion delineated in eq 8 shows a reversal of the stereochemical course of a benzylic lithiation/methylation in THF as compared to THF/DMPU (see epimers (**11a**) and (**11b**) in eq 8).[20] This case also exemplifies the compatibility of DMPU with a large excess of ***t-Butyllithium*** at -75 °C.

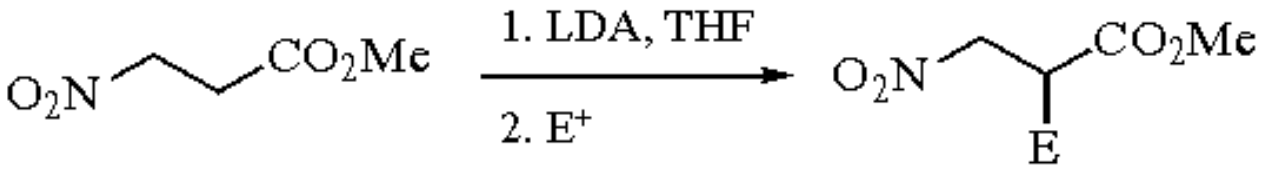

(5)

(9)

Cosolvent	Yield (%)
-	<5
HMPA	50-85
DMPU	50-85

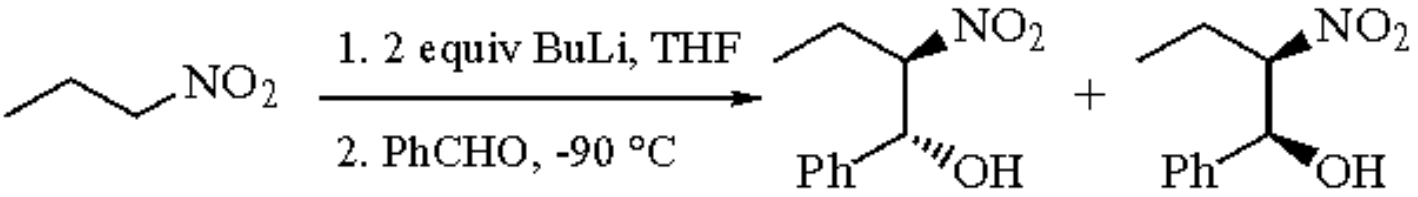

(6)

Cosolvent	*(l)*:*(u)*
-	1:1
HMPA (20%)	9:1
DMPU (25%)	9:1

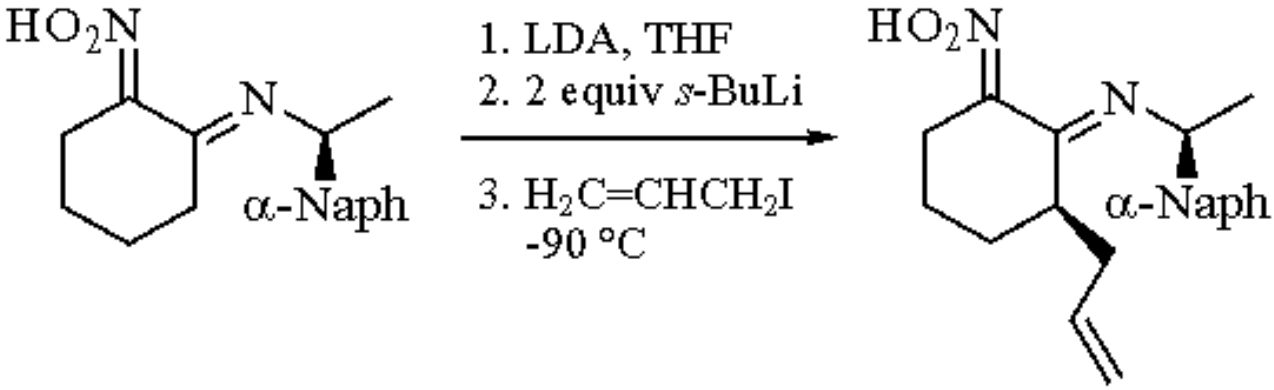

(7)

(10)

Cosolvent	dr	Yield (%)
-	4:1	34
HMPA	6.5:1	73
DMPU	9:1	74

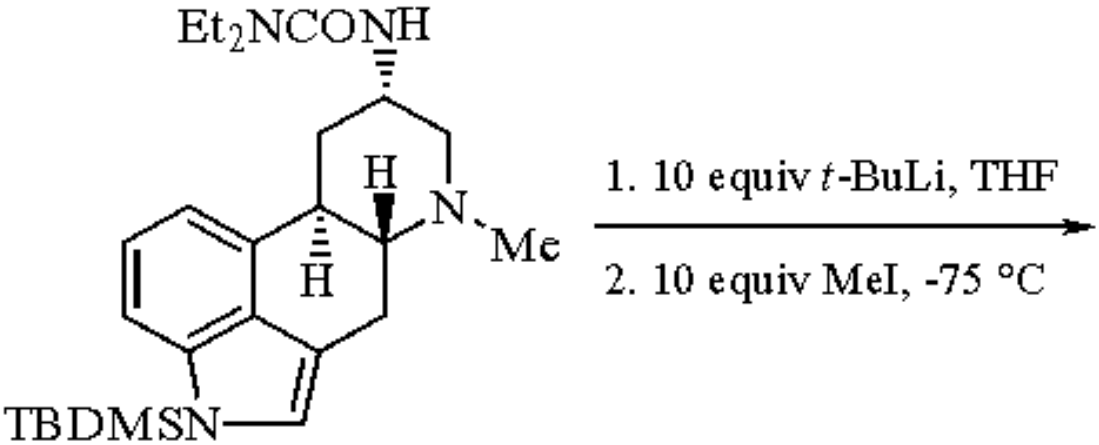

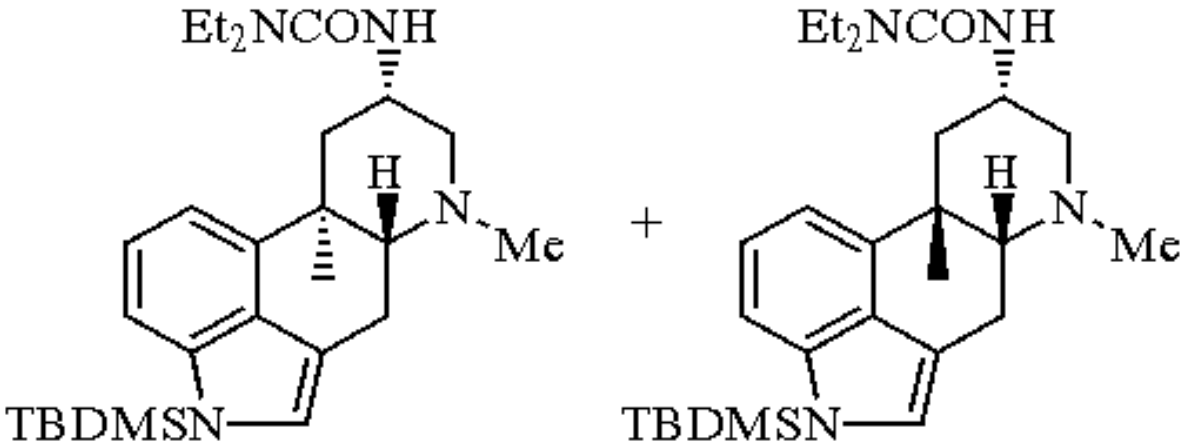

(8)

(11a) **(11b)**

Cosolvent	Yield (%)	
	(11a)	**(11b)**
-	6	73
DMPU	82	10

Nucleophilicity Enhancement in the Presence of DMPU.

Very often, nucleophilic substitutions of the S_N2 type are greatly accelerated by HMPA.[4] Again this effect is fully reproduced by DMPU. Thus sluggish alkylations of Li dithianes can be accelerated as shown in eq 9 for a reaction which is part of a ca. 50-step total syntheses[23] of myxovirescine A_1 and M_2.[24] Epoxide ring opening by acetylides is a classical case of a reaction which requires a boost, and this may be supplied by DMPU, being not quite as effective as HMPA (eq 10);[3] alkylations of acetylides by alkyl bromides and iodides have also been shown to give better yields in the presence of DMPU.[25,26] An interesting solvent effect is shown in eq 11: the ***Tetra-n-butylammonium Fluoride***-mediated addition of a silane to an aldehyde at room temperature occurs only at a reasonable rate in a dipolar aprotic solvent, and HMPA or DMPU win![27]

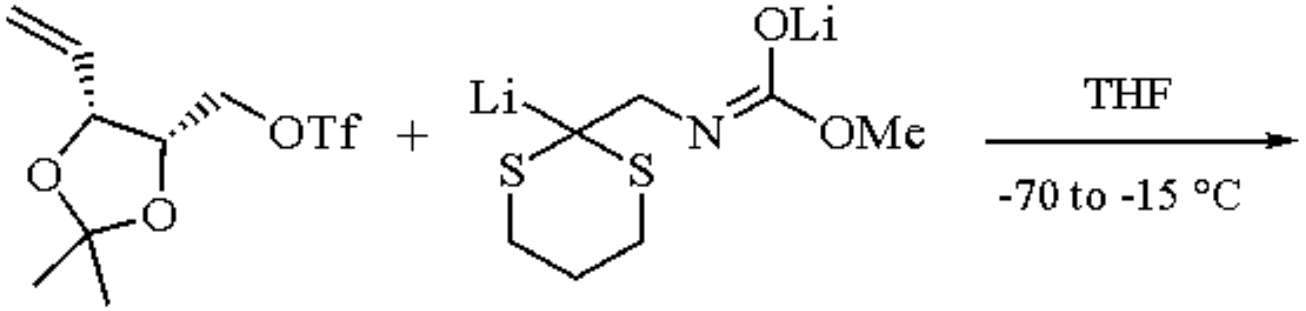

Cosolvent	Yield (%)
-	25
HMPA (1 equiv)	55
DMPU (2 equiv)	73

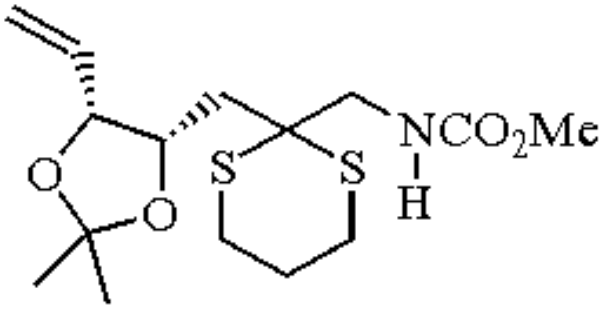

(9)

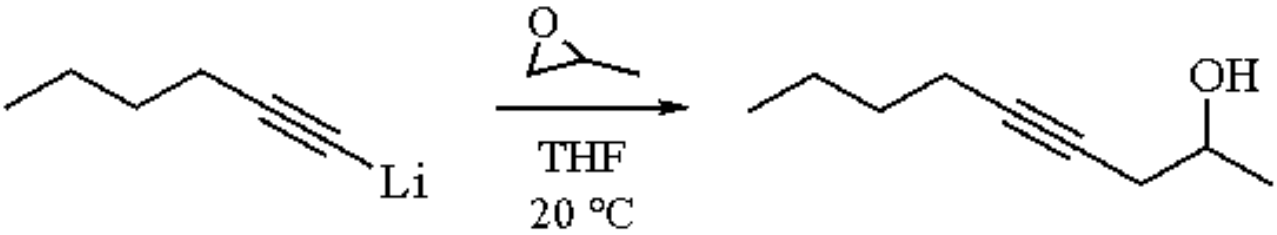

(10)

Cosolvent	Yield (%)
-	<5
HMPA (17%)	70
DMPU (50%)	59

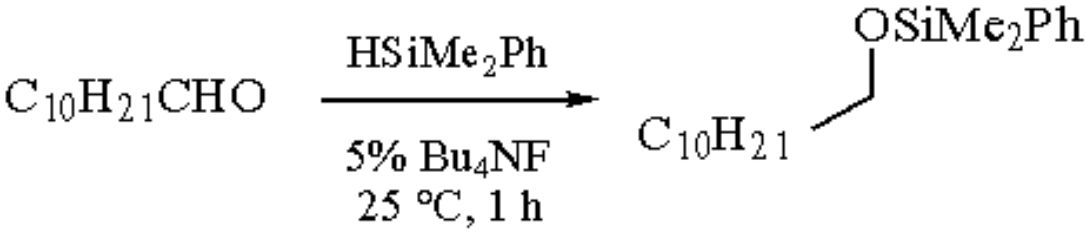

(11)

Solvent	CH_2Cl_2	THF	DMF	HMPA	DMPU
Yield (%)	1	9	56	91	89

A different type of effect on the nucleophilicity of a reagent is exhibited in the addition of ***2-Lithio-1,3-dithiane*** to cyclohexenone. Under standard conditions (THF, dry-ice temperature), 1,2-addition occurs almost exclusively;[28] in the presence of HMPA[29] or DMPU,[3] 1,4-addition takes place (eq 12). Again, this is a remarkable effect, because hard nucleophilic centers should prefer attack at the harder center of the enone, which is the carbonyl carbon (charge control), and soft centers should combine with the softer β-carbon (in fact, lithiated thioacetals bearing Si or Sn on the

carbanionoid center add to enones in a 1,4-fashion[30]); thus the polar cosolvent renders the lithio dithiane C(2) carbon softer! (It was shown that the Li alkoxide of (**12**) does not rearrange to the Li enolate of (**13**) even after 24 h at rt[29]).

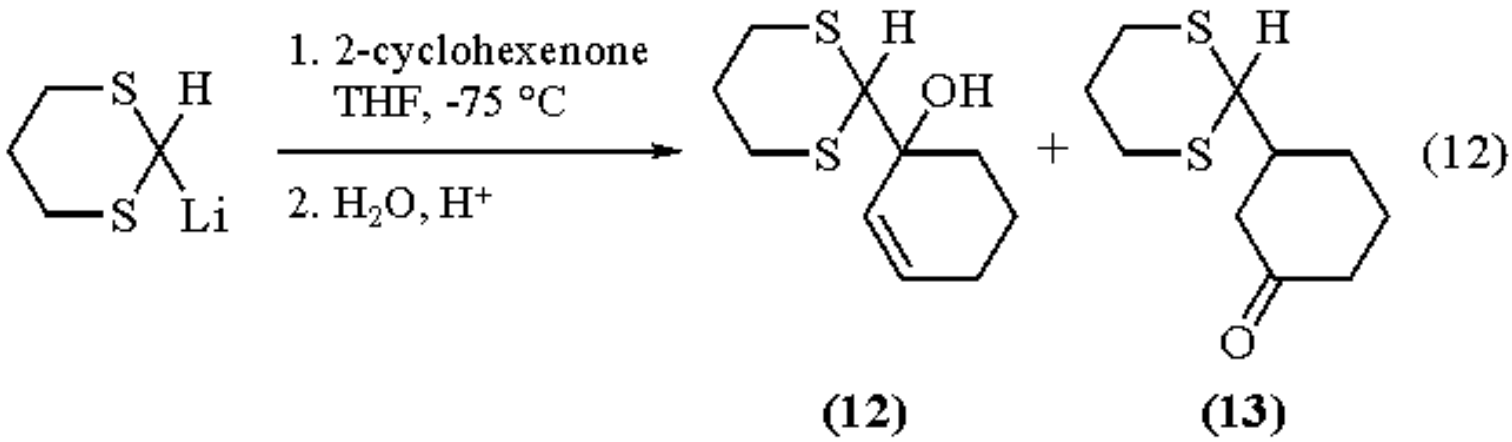

Cosolvent	
-	98: 2
HMPA (2 equiv)	5:95
DMPU (4 equiv)	8:92

Transition Metal and Lanthanide Chemistry.

In an increasing number of publications, DMPU is described as a solvent or cosolvent in redox and radical reactions. Two examples are presented here. The spectacular, highly diastereoselective radical cyclization of the cyclopentene (**14**) to the tricyclic compound (**15**) in eq 13 is very slow in THF even at reflux temperature, while the addition of a tiny amount of DMPU accelerates it to such an extent that a respectable yield of 60% of the desired product is obtained at 0 °C (the authors call it a titration).[31] Other ***Samarium(II) Iodide*** reductive coupling reactions (for instance, of α,β-unsaturated esters to 3,4-disubstituted adipic esters)[32] and reductions (of ketones to alcohols and of enones to ketones)[33] are also improved in the presence of DMPU cosolvent.

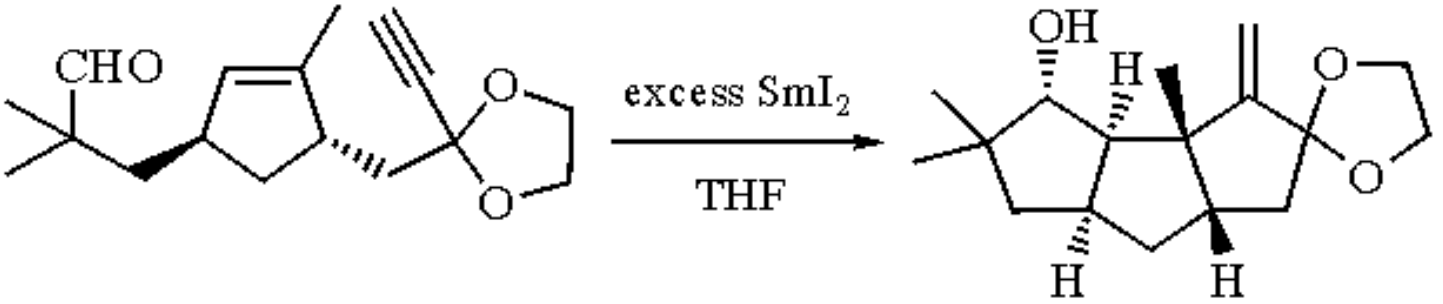

(13)

(14) **(15)**

Cosolvent	°C	Yield (%)
-	64	<11
HMPA (5%)	0	67 (as free ketone)
DMPU (5%)	0	69 (as free ketone)

Finally, a complex of MoO_5 with pyridine and DMPU can be used instead of the corresponding HMPA complex ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** for hydroxylations of Li enolates (eq 14).[34] Even the crystal structures of the two complexes are similar.[35] In this case, switching from HMPA to DMPU does not remove all hazards: MoO_5.py.DMPU has been reported to be explosive, so must be handled behind appropriate safety equipment.[36]

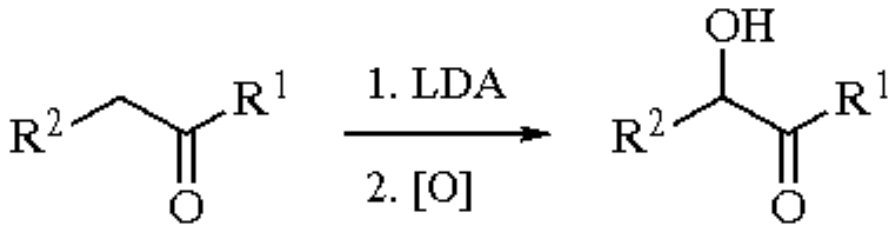

(14)

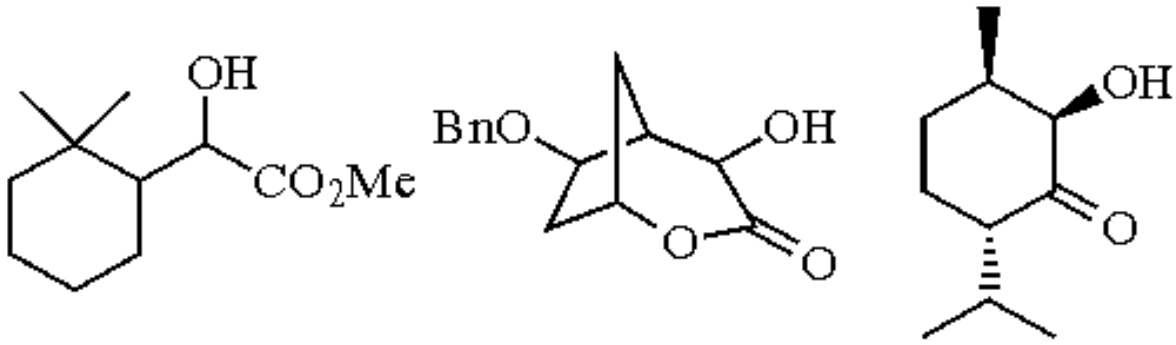

$MoO_5 \cdot py \cdot HMPA$	63%	72%	74%
$MoO_5 \cdot py \cdot DMPU$	72%	72%	43%

Related Reagents.

Dimethyl Sulfoxide; ***Hexamethylphosphoric Triamide***; ***1-Methyl-2-pyrrolidinone***; ***N,N,N´,N´´,N´´-***

Pentamethyldiethylenetriamine; ***N,N,N´,N´-Tetramethylethylenediamine***.

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trans-2,5-Dimethylpyrrolidine

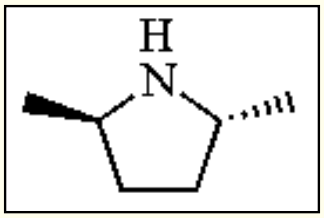

(racemate)

[62617-69-0; 39713-72-9] · $C_6H_{13}N$ · *trans*-2,5-Dimethylpyrrolidine · (MW 99.18) (2*S*,5*S*)

[117968-50-0] (2*R*,5*R*)

[62617-70-3] (.HCl, racemate) · $C_6H_{14}ClN$ · *trans*-2,5-Dimethylpyrrolidine Hydrochloride · (MW 135.64)

[114143-75-8; 4832-49-9] (.HCl, 2*S*,5*S*)

[138133-34-3] (.HCl, 2*R*,5*R*)

[70144-18-2]

(C_2 symmetric chiral pyrrolidine,[1] useful in optically active form as a chiral auxiliary in a variety of asymmetric reactions)

Physical Data: free amine: bp 102-103 °C; (2*S*,5*S*) [α]25D +10.6° (*c* 1.0, EtOH);[2] (2*R*,5*R*) [α]25D -11.5° (*c* 1.0, EtOH).[2] Hydrochloride: racemate mp 187-189 °C;[3] (2*S*,5*S*) mp 200-201 °C,[4] [α]25D -5.63° (*c* 0.67, CH_2Cl_2);[4] (2*R*,5*R*) mp 200-203 °C,[5] [α]25D +5.57° (*c* 1.18, CH_2Cl_2).[5]

Form Supplied in: colorless oil; commercially available as a mixture of (±)-*trans* and *cis* isomers (the mixture is not easily separated).[6]

Purification: the free amine can be purified by fractional distillation; the hydrochloride salt can be recrystallized from absolute ethanol and diethyl ether.

Handling, Storage, and Precautions: irritant; flammable. Use in a fume hood.

Synthesis.

Several routes are available for the synthesis of *trans*-2,5-dimethylpyrrolidine.[2-9,22] Discussed below are preparative

scale procedures for the synthesis of the pure *trans* compound in racemic and enantiomerically pure form.

The racemic hydrochloride salt can be prepared in four steps and 70% overall yield (eq 1).[3] The synthesis is carried out on 2 mmol scale and starts with commercially available 5-hexen-2-one. The key step involves a mercury-catalyzed intramolecular amidomercuration to form the pyrrolidine ring. If desired, the racemate can be resolved via the salts of ***Mandelic Acid***.[2]

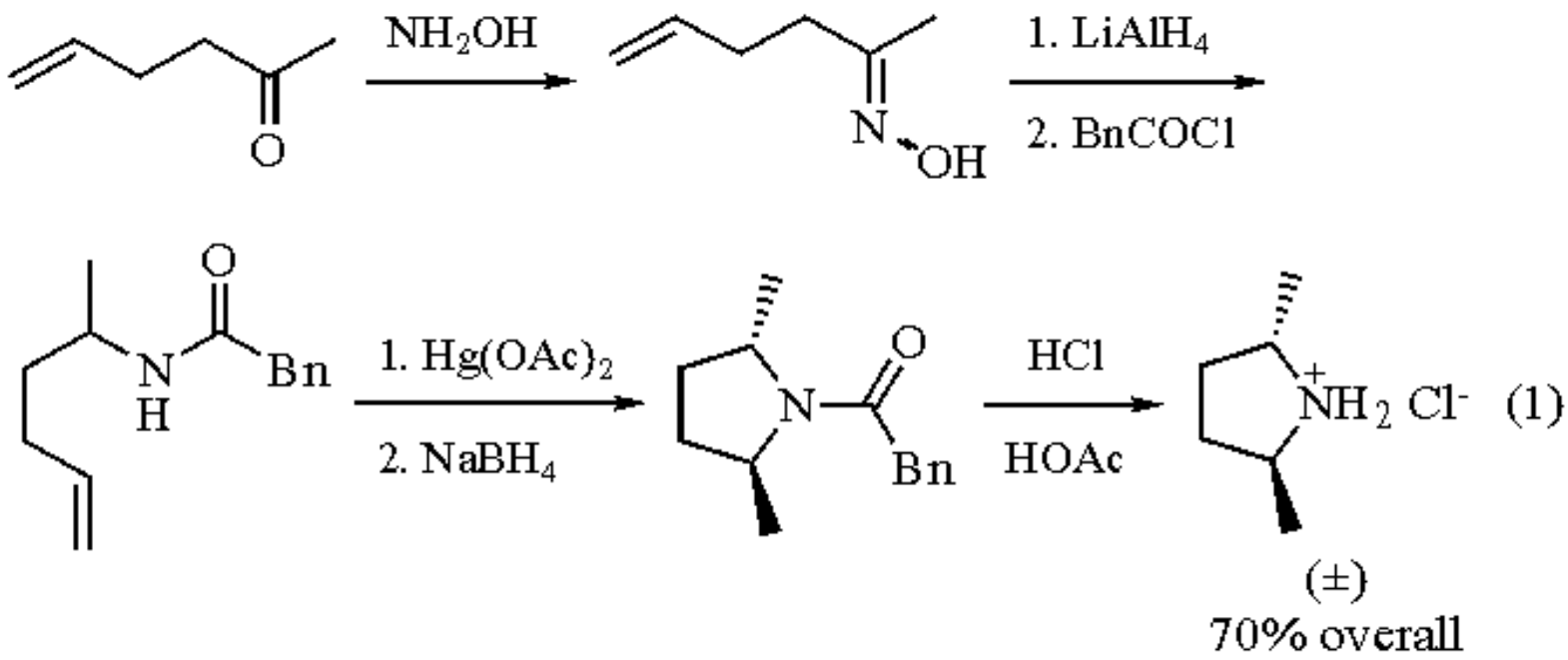

Alternatively, an efficient synthesis of either antipode starting from D- or L-alanine has been reported (eq 2).[9] The asymmetric synthesis conducted on 10 mmol scale involves a six-step sequence which incorporates the amidomercuration method.[3] The enantiomerically pure product is isolated as its hydrochloride salt in 44% overall yield. Furthermore, an optimization of the capricious cuprate reaction which improves both the yield and reproducibility has been described.[4]

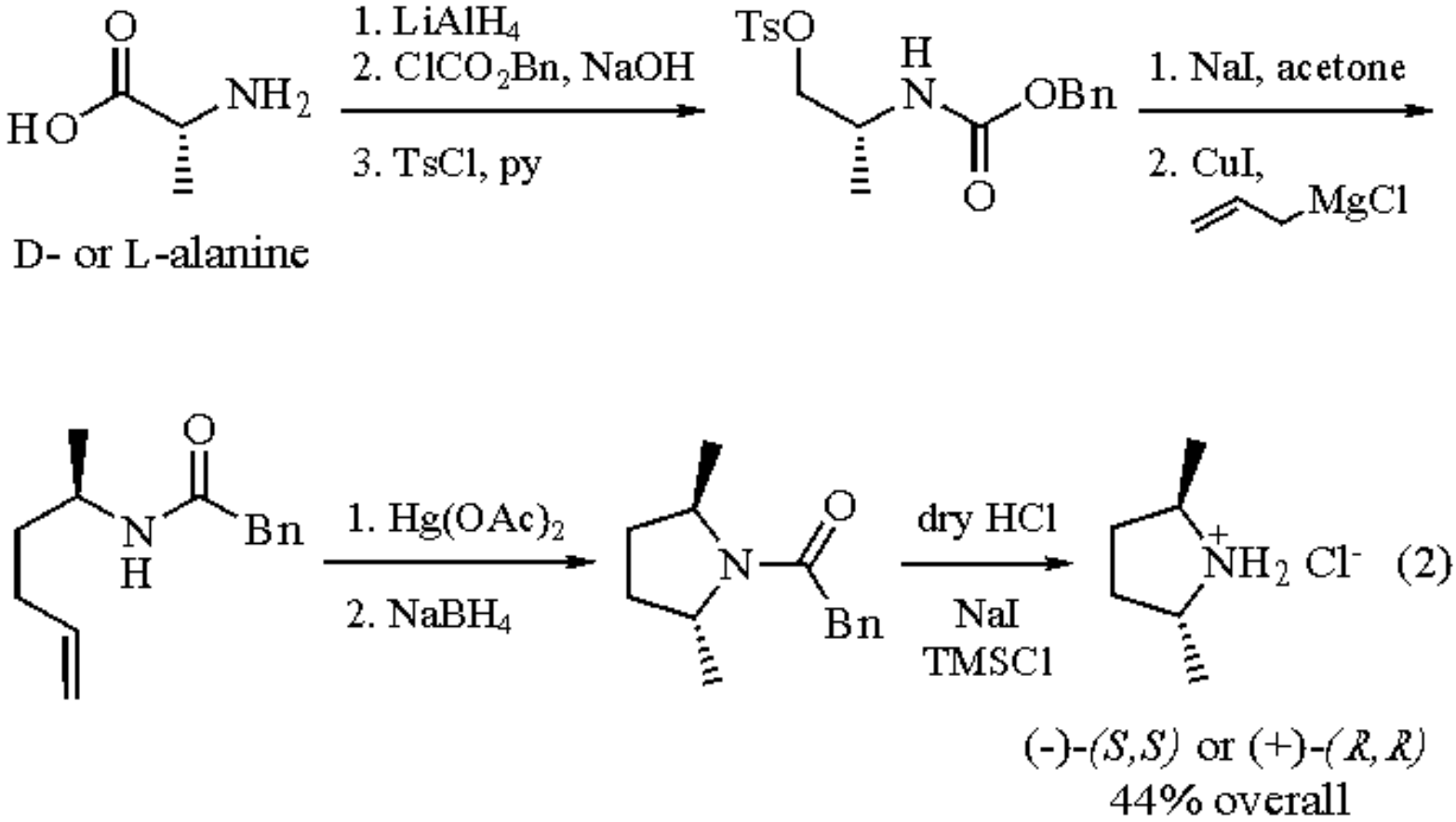

More recently, a four-step synthetic sequence which provides expedient access to the (-)-(*R*,*R*)-enantiomer in 42% overall yield has been reported.[5] This route is convenient for large-scale preparation (0.2 mol scale), and is highlighted by an asymmetric ***Baker's Yeast*** reduction of 2,5-hexanedione. Subsequent mesylation, *N*,*N*-dialkylation, and deprotection provides the enantiomerically pure free pyrrolidine (eq 3). Alternatively, either enantiomer of the chiral pyrrolidine can be obtained in 15% overall yield from an isomeric mixture of 2,5-hexanediol, via a similar sequence in which (***S***)-α-methylbenzylamine is used as a chiral auxiliary.[22] Also, an enantioselective route to either (2*S*,5*S*)- or (2*R*,5*R*)-hexanediol has been reported.[23]

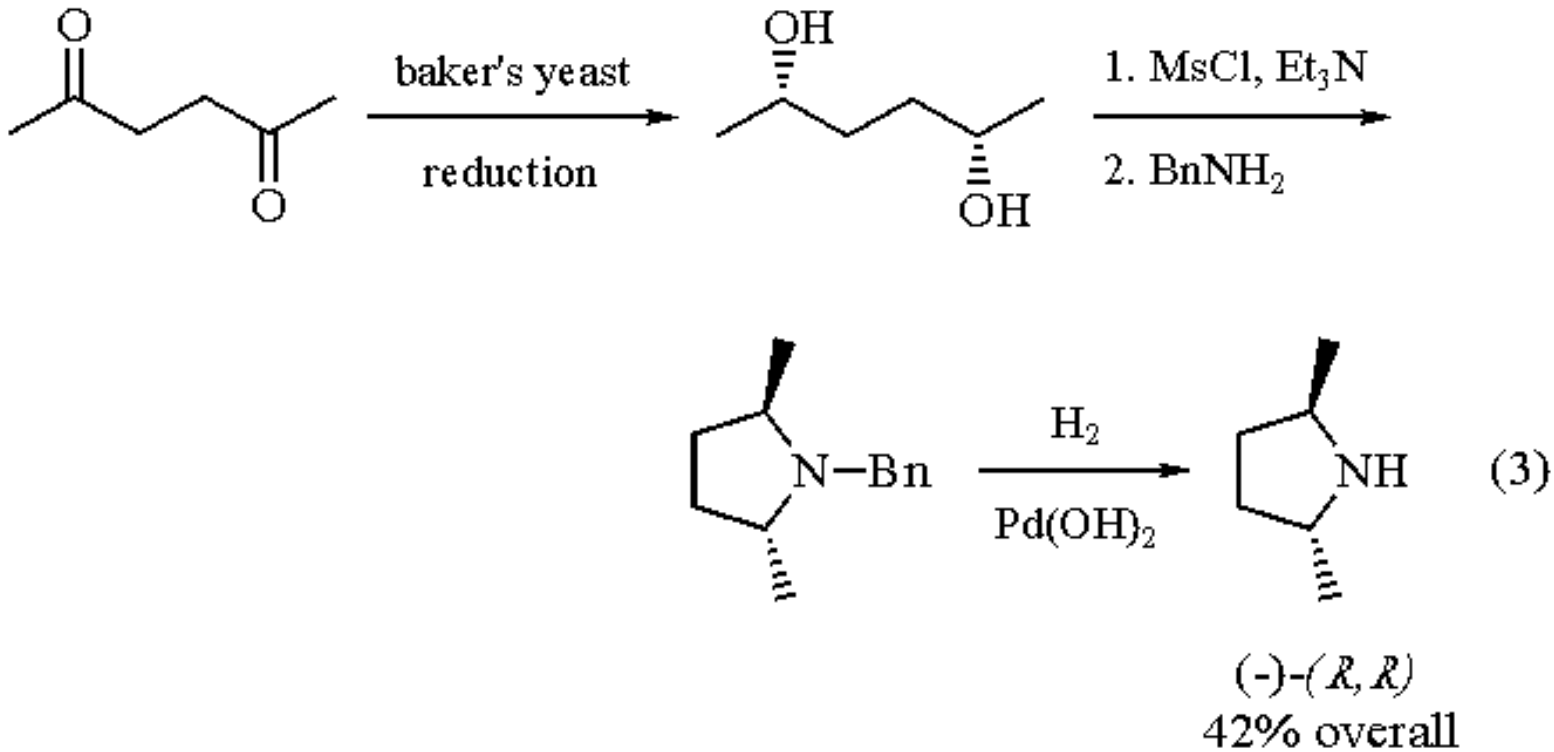

Asymmetric Alkylations and Michael Additions.

Asymmetric alkylation of the cyclohexanone enamine derived from (+)-*trans*-2,5-dimethylpyrrolidine has been studied (eq 4).[2] Alkylation with ***Iodomethane***, *n*-propyl bromide, and ***Allyl Bromide*** afforded the corresponding 2-*n*-alkylcyclohexanones in yields of 50-80% and with enantiomeric purities of 66, 86, and 64%, respectively.

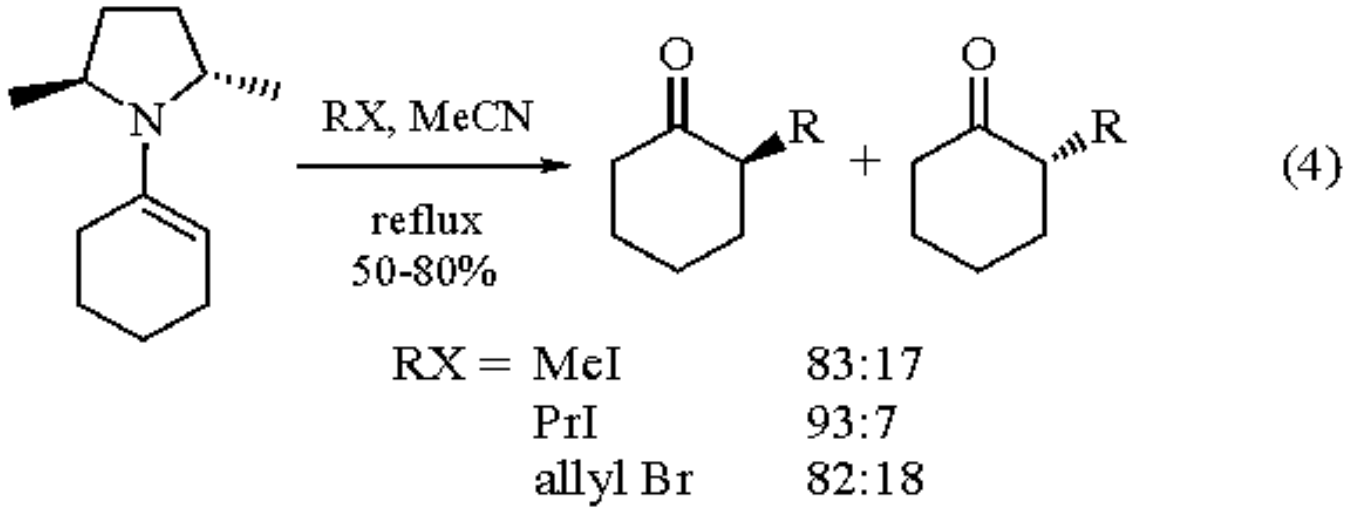

The lithium enolates from tetronic acid-derived vinylogous urethanes have been generated and their reactivity investigated with a variety of electrophiles (eq 5).[10,11] The reactions proceed with excellent regio- and diastereoselectivity and a variety of alkylating agents can be utilized.

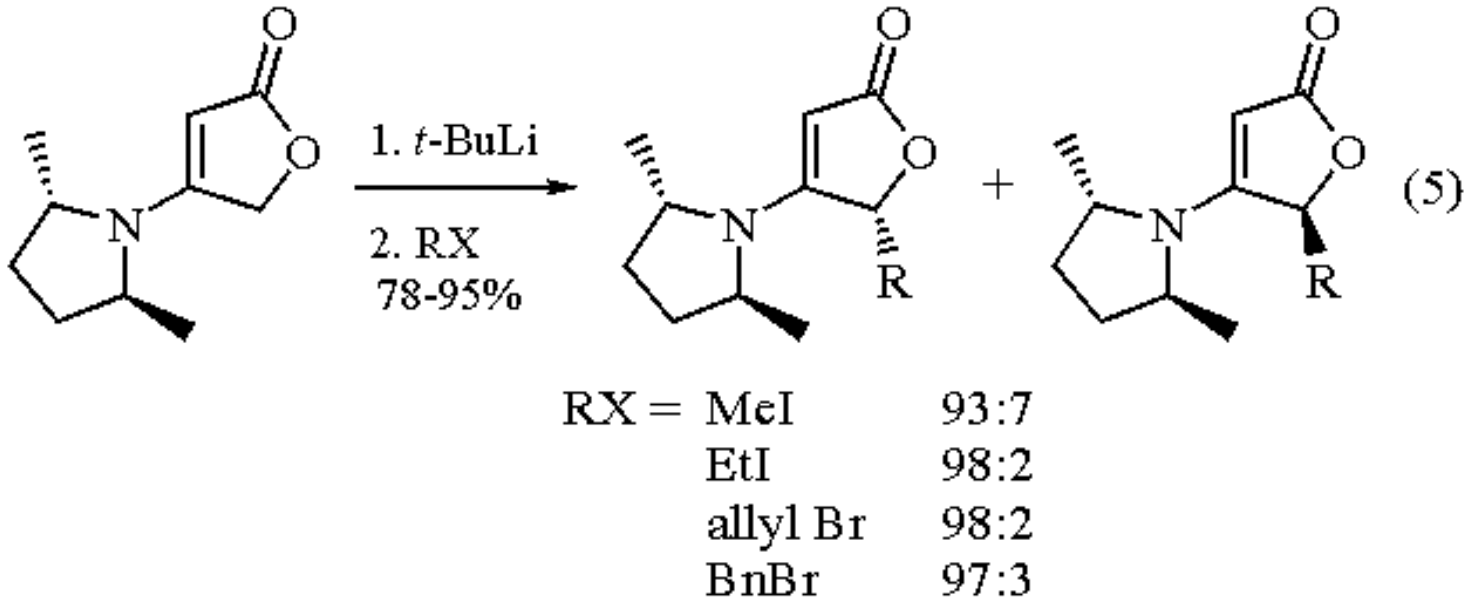

In the total synthesis of (-)-secodaphniphylline an asymmetric [1,4]-conjugate addition was used to establish relative and absolute stereocontrol.[12] The lithium enolate of a *trans*-2,5-dimethylpyrrolidine-derived amide adds in a Michael fashion to a cyclic α,β-unsaturated ester, with subsequent enolate trapping, to afford the desired product in 64% yield and 92:8 diastereoselection (eq 6).

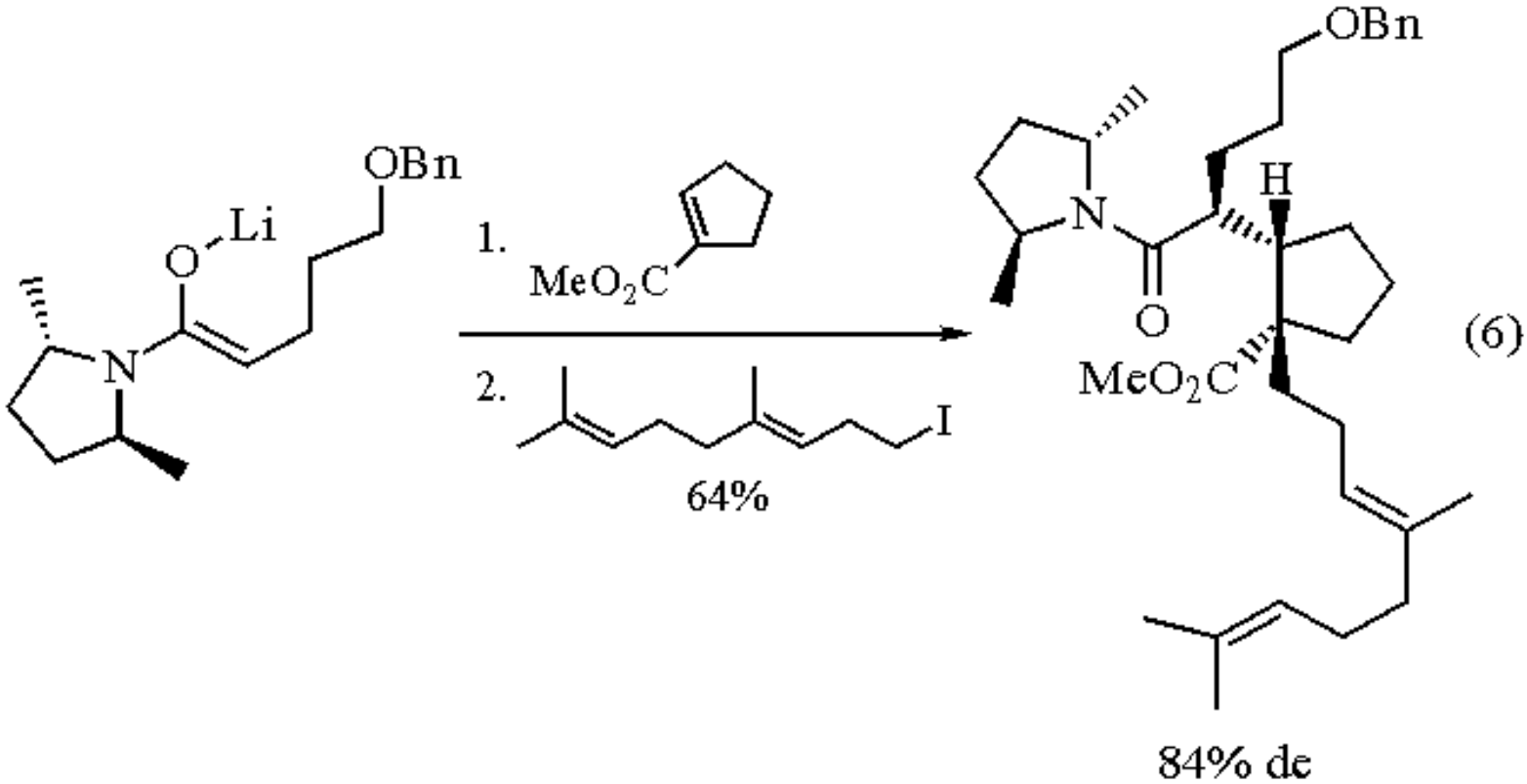

Asymmetric Radical Reactions.

Several reports have documented the utility of nonracemic *trans*-2,5-dimethylpyrrolidine as a chiral auxiliary in asymmetric radical reactions.[13] For example, the addition of *n*-hexyl, cyclohexyl, and *t*-butyl radicals to the chiral

acrylamide of 4-oxopentenoic acid provided four diastereomeric products resulting from α- and β-addition (eq 7).[14] The isomers resulting from β-addition were formed with no diastereoselectivity; however, the isomers resulting from α-addition were formed in ratios of 16:1, 24:1, and 49:1. Unfortunately, the application of this chemistry is limited due to the poor regioselectivity in the addition and difficulty in removal of the chiral auxiliary.

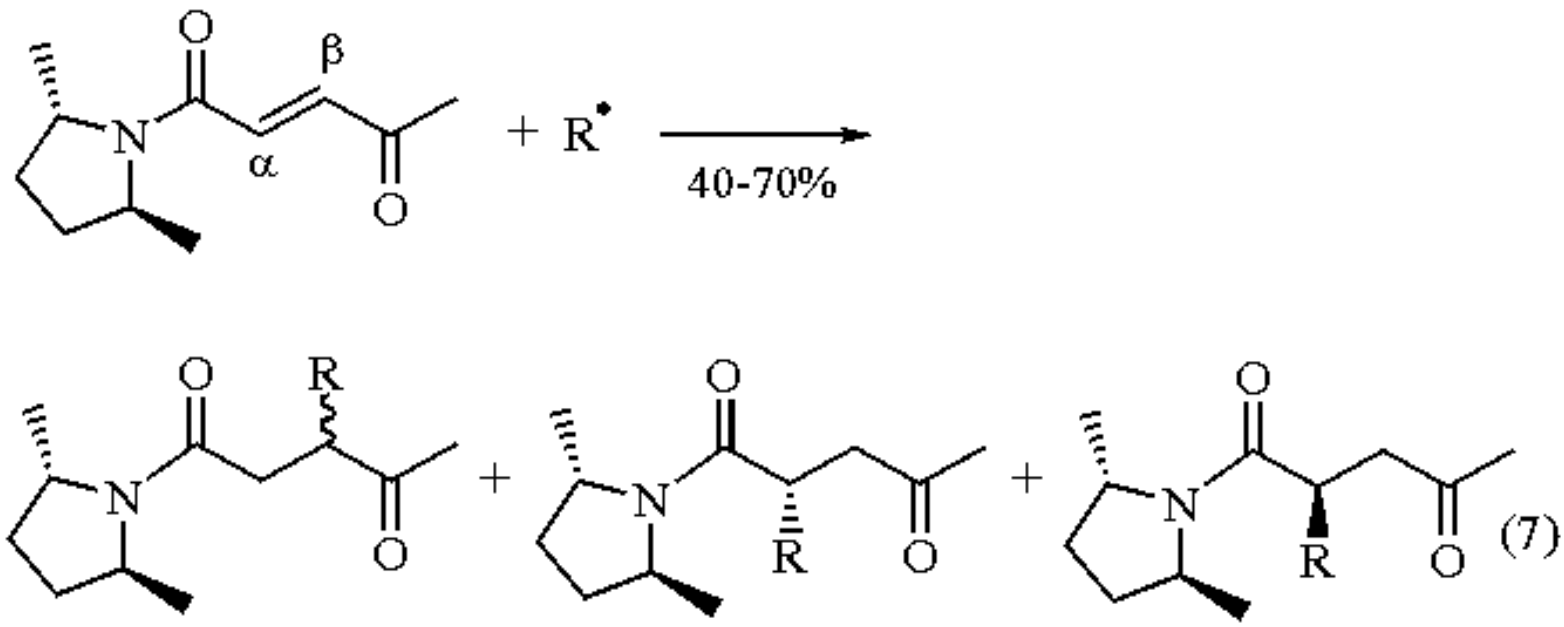

R =	C_6H_{13}	16:16:1
	Cy	25:24:1
	t-Bu	50:49:1

Similar results have been achieved in the addition of chiral amide radicals to activated alkenes.[13] For instance, a chiral amide radical, derived from (-)-*trans*-2,5-dimethylpyrrolidine, adds in a 1,4-fashion to ethyl acrylate in 35% yield and with 12:1 diastereoselectivity (eq 8).[15] Unfortunately, substantial amounts of higher oligomers are also formed. The radical telomerization of chiral acrylamides to afford nonracemic lower-order telomers (n = 1-5) has also been described.[16]

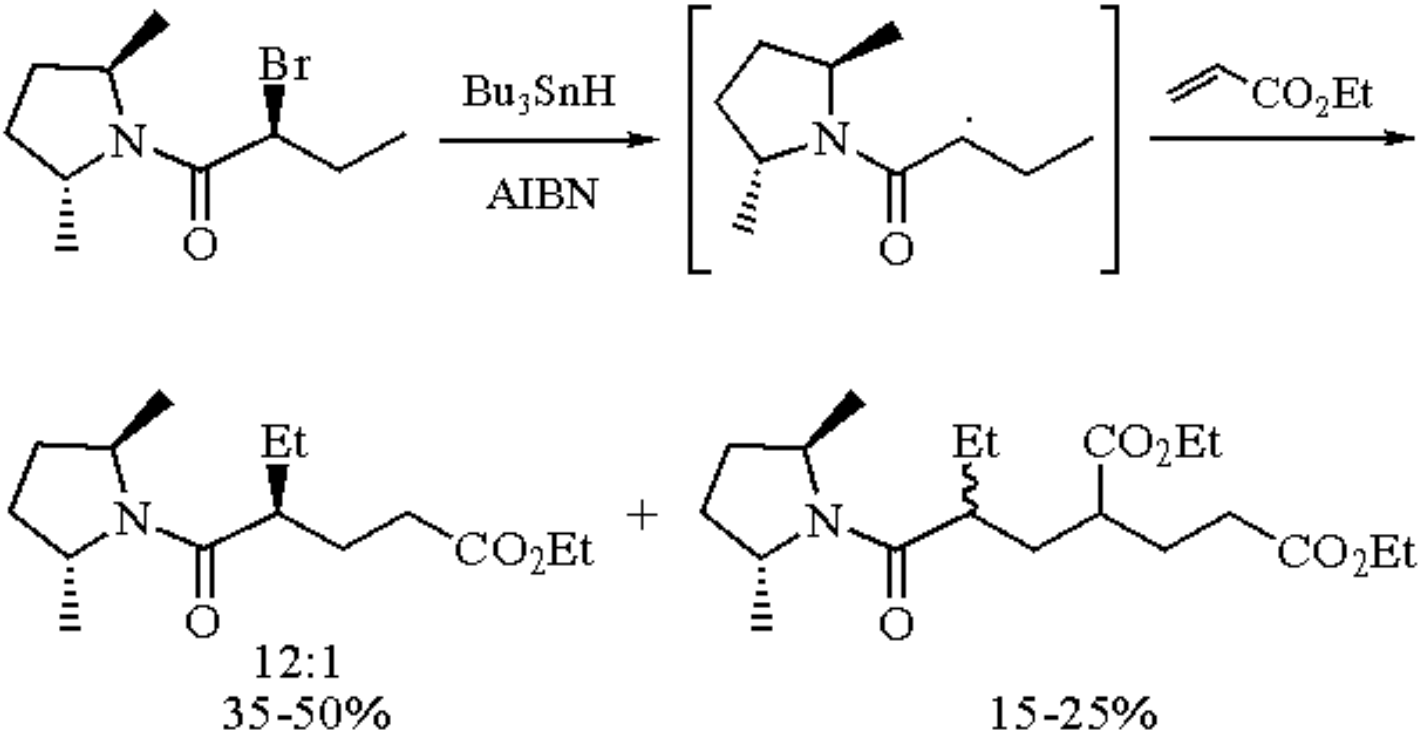

(8)

Asymmetric Pericyclic Reactions.

Several reports illustrate the utility of *trans*-2,5-dimethylpyrrolidine as a chiral auxiliary in asymmetric Claisen-type rearrangements,[17] [4 + 2],[18,19] and [2 + 2] cycloaddition reactions.[20] The enantioselective Claisen-type rearrangement of *N*,*O*-ketene acetals derived from *trans*-2,5-dimethylpyrrolidine has been studied.[17] For example, the rearrangement of the *N*,*O*-ketene acetal, formed in situ by the reaction of *N*-propionyl-*trans*-(2*S*,5*S*)-dimethylpyrrolidine with (*E*)-crotyl alcohol, affords the [3,3]-rearrangement product in 50% yield and 10:1 diastereoselectivity (eq 9).

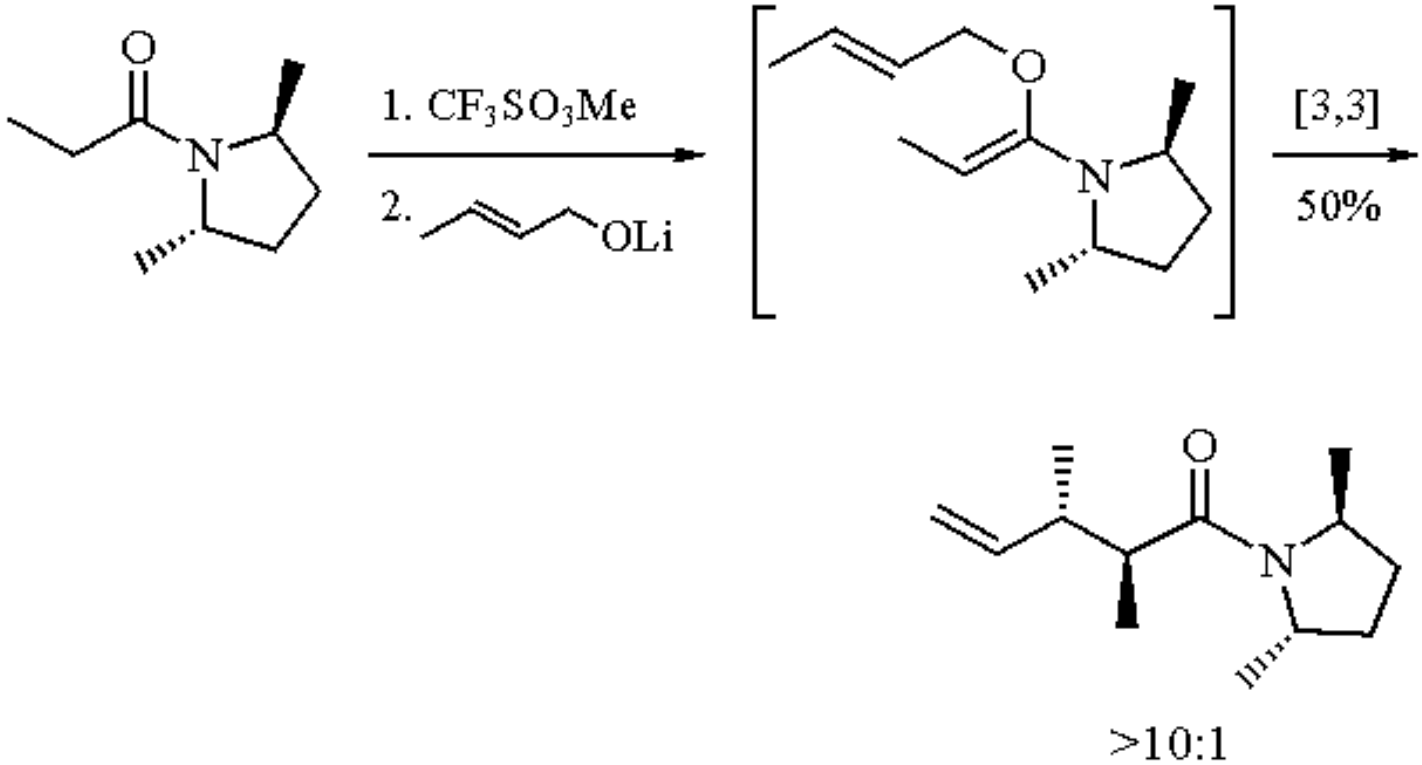

(9)

Carbamoyl nitroso dienophiles, derived from chiral pyrrolidines, have been generated and their reactivity with cyclohexadiene investigated.[18] Using (-)-*trans*-2,5-dimethylpyrrolidine as the auxiliary, the [4 + 2] cycloadduct is isolated in 82% yield and with 98% diastereomeric excess (eq 10). Similarly, chiral ynamine dienophiles have been utilized in asymmetric [4 + 2] cycloadditions with α,β-unsaturated nitroalkenes to afford cyclic nitronic esters.[19] The resulting esters subsequently undergo a rapid [1,3]-rearrangement to afford chiral cyclic nitrones in moderate yield and high diastereoselectivity (eq 11).

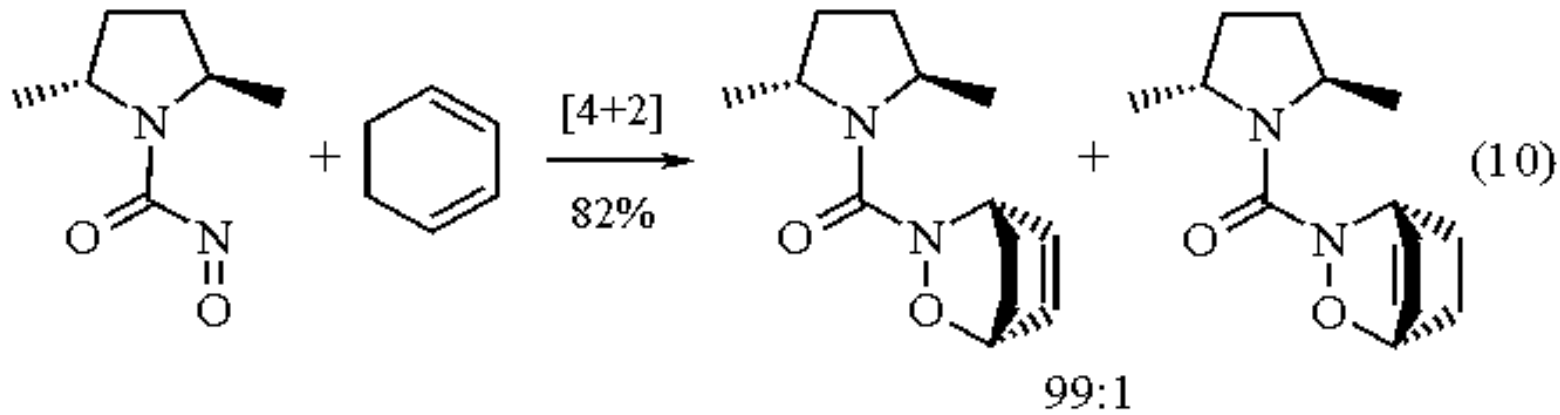

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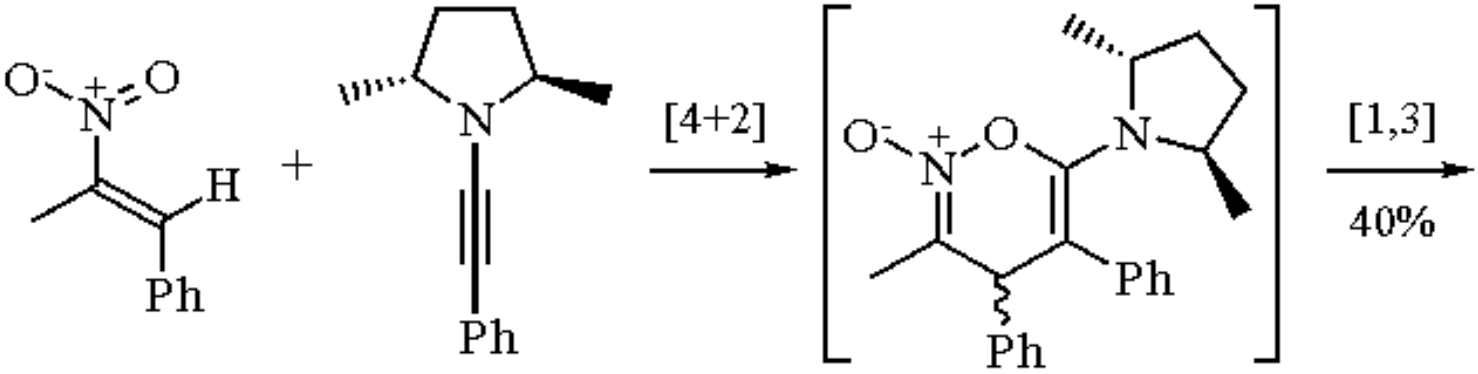

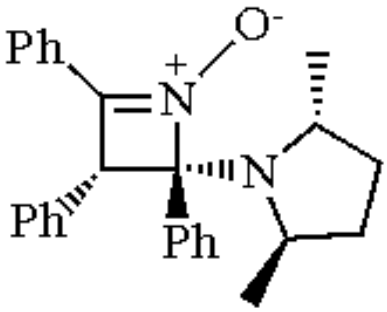

(11)

> 95% de

An asymmetric, thermal [2 + 2] cycloaddition of keteniminium salts derived from *trans*-2,5-dimethylpyrrolidine has been employed in the synthesis of prostaglandins.[20] An intramolecular [2 + 2] cycloaddition affords a *cis*-fused bicyclic system which is then further transformed into a common prostaglandin intermediate (eq 12).

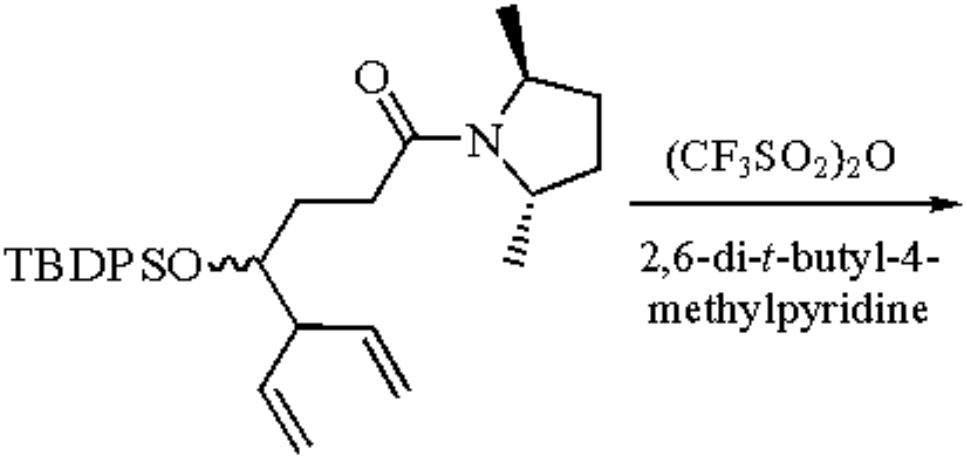

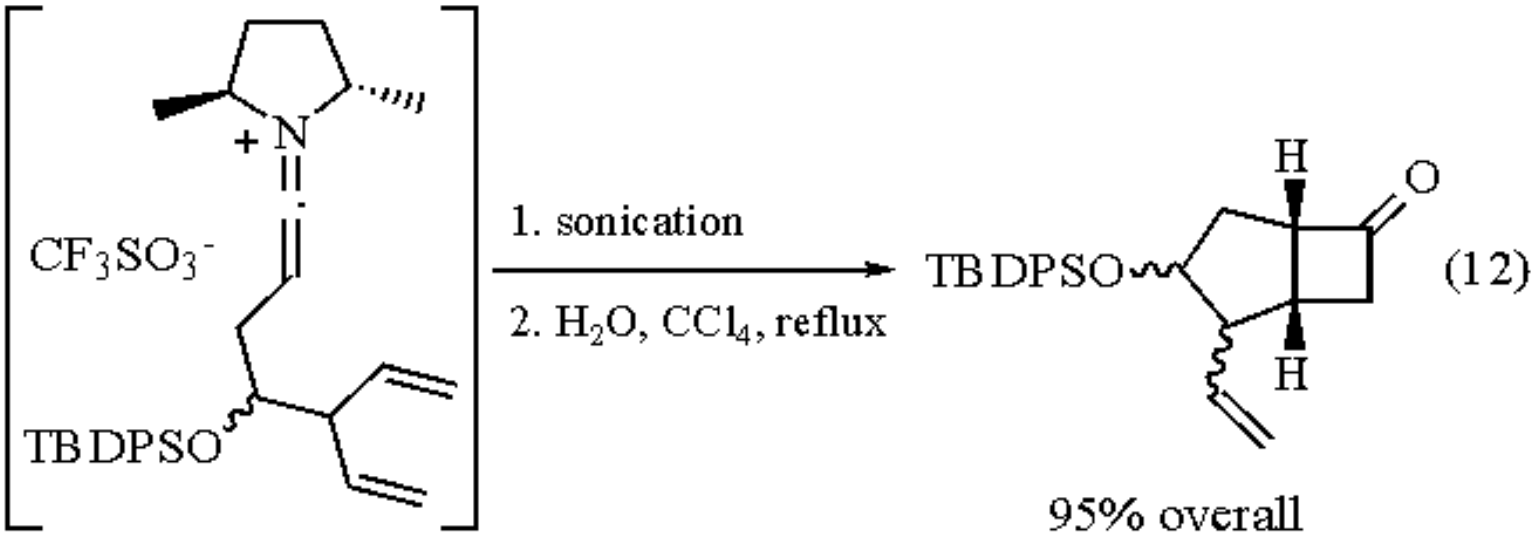

Miscellaneous.

trans-2,5-Dimethylpyrrolidine has been utilized as a chiral auxiliary for an asymmetric iodolactonization in the total synthesis of (±)-pleurotin and (±)-dihydropleurotin.[21] The reaction affords the desired lactone in 47% yield and only 30% enantiomeric excess.

Related Reagents.

trans-2,5-Bis(methoxymethyl)pyrrolidine.

---

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Dimethyl Selenoxide

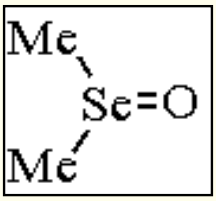

[4371-90-8] · C_2H_6OSe · Dimethyl Selenoxide · (MW 125.03)

(mild oxidizing agent;[1,2] electrophilic reagent for oxyselenation of alkenes;[3] electrophile for aromatic substitutions[4,5])

Physical Data: mp 94 °C.

Solubility: sol water, ethanol, acetone, chloroform.

Preparative Methods: readily obtained by oxidation of dimethyl selenide with 30% aqueous ***Hydrogen Peroxide*** at -10 °C, or with ***Ozone*** in chloroform at -50 °C; also prepared by treating dimethylselenium dibromide with ***Silver(II) Oxide*** in methanol.

Purification: recrystallization from benzene gives the pure material as colorless needles.

Handling, Storage, and Precautions: hygroscopic; decomposes in ether, acetonitrile, THF, and CS_2; since the reactions of dimethyl selenoxide often produce volatile organoselenium derivatives having a highly unpleasant odor, use in a well-ventilated fume hood.

Oxidation.

Several selenoxides, such as dimethyl selenoxide,[1,2] dibenzyl selenoxide,[6] diphenyl selenoxide,[7] and bis(*p*-methoxyphenyl) selenoxide,[8] are mild and selective agents for the oxidation of various functional groups. Dimethyl selenoxide oxidizes trivalent phosphorus compounds and thio- and selenophosphonyl compounds to their oxygenated analogs more effectively than ***Dimethyl Sulfoxide***.[1] The reactions for the acyclic derivatives occur with nearly complete inversion of configuration (eq 1) and for cyclic derivatives with almost full retention (eq 2). The reagent also oxidizes thioureas and thiouracils to the corresponding carbonyl compounds in high yields. This reaction is useful for selective modifications of the 4-thiouracil group in transfer ribonucleic acids (eq 3).

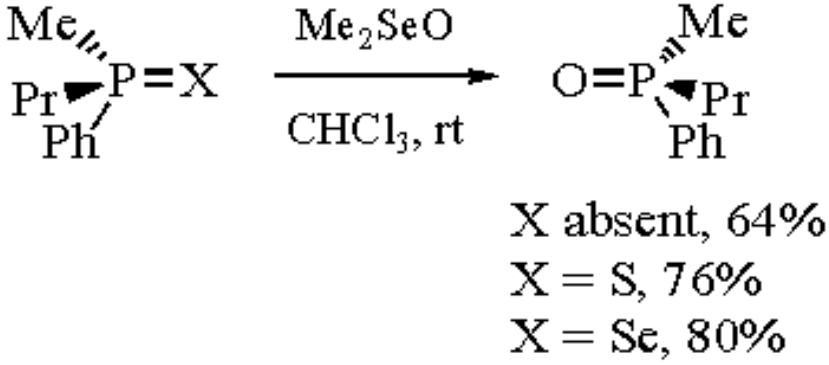

(1)

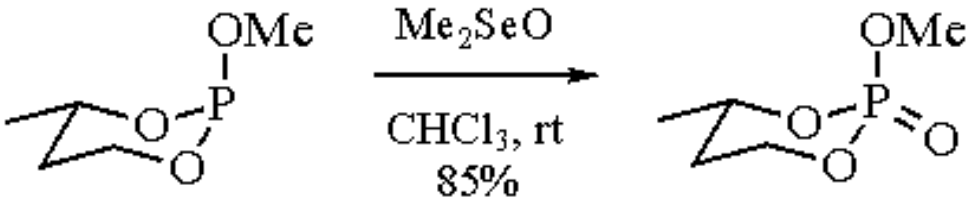

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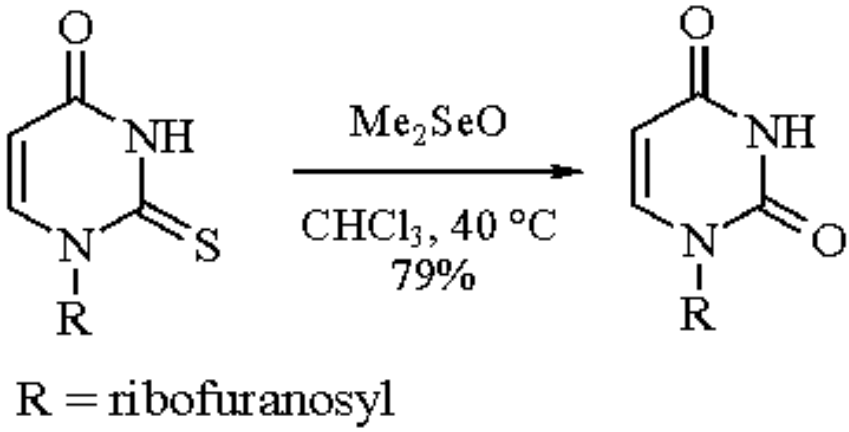

(3)

The oxidation of halomethylarenes with dimethyl selenoxide in refluxing 1,2-dichloroethane gives polysubstituted aromatic aldehydes bearing substituents reactive toward acids, bases, or water (eq 4).[2]

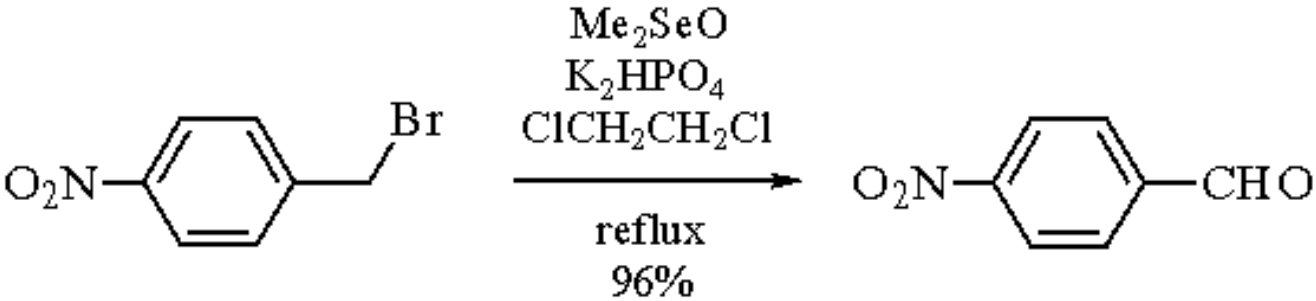

(4)

Oxyselenation of Alkenes.

The reagent reacts with alkenes in AcOH-$CHCl_3$ at 60 °C to give 2-acetoxyalkyl methyl selenides (eqs 5 and 6).[3] This addition reaction is regioselective and *trans* stereospecific. Presumably MeSeOAc is the reactive species.

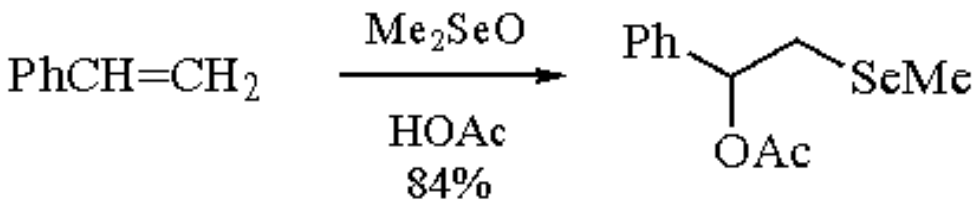

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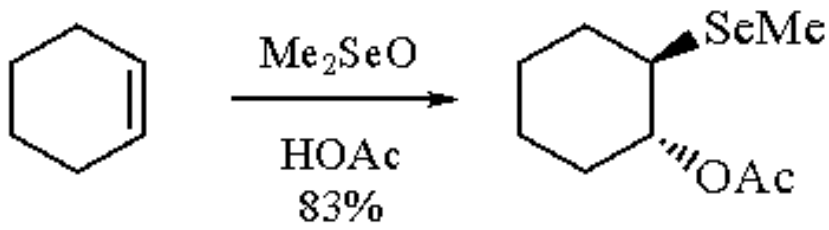

(6)

Electrophilic Aromatic Substitution Reactions.

Dimethyl selenoxide effects electrophilic substitution of phenols in the presence of hydrogen chloride at 0-20 °C to give dimethyl(hydroxyphenyl)selenonium chlorides, whose pyrolyses in refluxing toluene afford methyl hydroxyphenyl selenides in high yields (eq 7).[4]

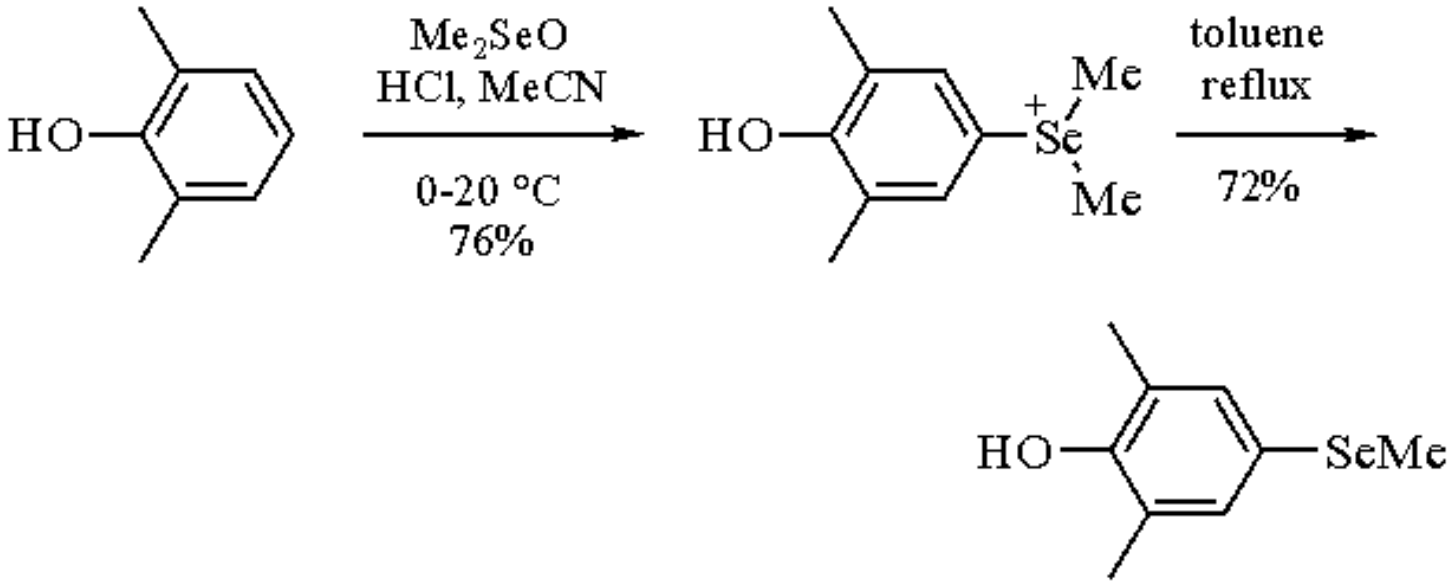

(7)

The substitution reaction of 5-(trimethylsilyl)cyclopentadiene with dimethyl selenoxide forms the selenoniocyclopentadienide in an excellent yield (eq 8).[5] Similar reactions of pentafulvene, indole, and pyrrole give the corresponding selenonium salts.

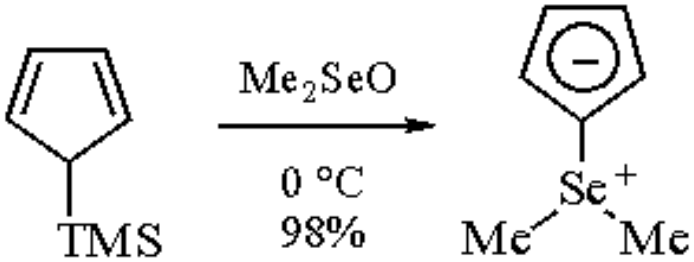

(8)

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Fumio Ogura & Tetsuo Otsubo

Hiroshima University, Japan

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Dimethylsuccinimidosulfonium Tetrafluoroborate

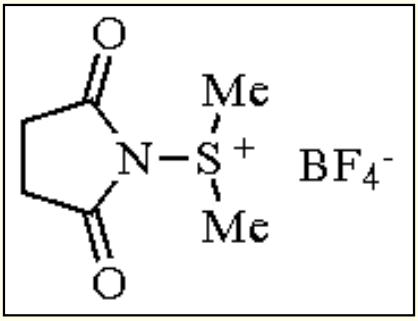

[54884-50-3] · $C_6H_{10}BF_4NO_2S$ · Dimethylsuccinimidosulfonium Tetrafluoroborate · (MW 247.02)

(stable sulfonium salt for the mild oxidation of alcohols and catechols in the presence of a tertiary amine; also used for the introduction of a methylthiomethylene substituent in the *ortho* position of simple phenols, or the transfer of a dimethylsulfonium group to nucleophiles)

Alternate Name: succinimidodimethylsulfonium tetrafluoroborate.

Physical Data: mp 169-171 °C

Solubility: very sol methylene chloride, acetonitrile; insol ether.

Form Supplied in: colorless solid; not commercially available.

Analysis of Reagent Purity: mp, ^{1}H NMR, or elemental analysis.

Preparative Method: an acetonitrile solution of ***N-Chlorosuccinimide*** and ***Dimethyl Sulfide*** produces the unstable dimethylsuccinimidosulfonium chloride at -25 °C, which is then treated with ***Triethyloxonium Tetrafluoroborate*** (eq 1).

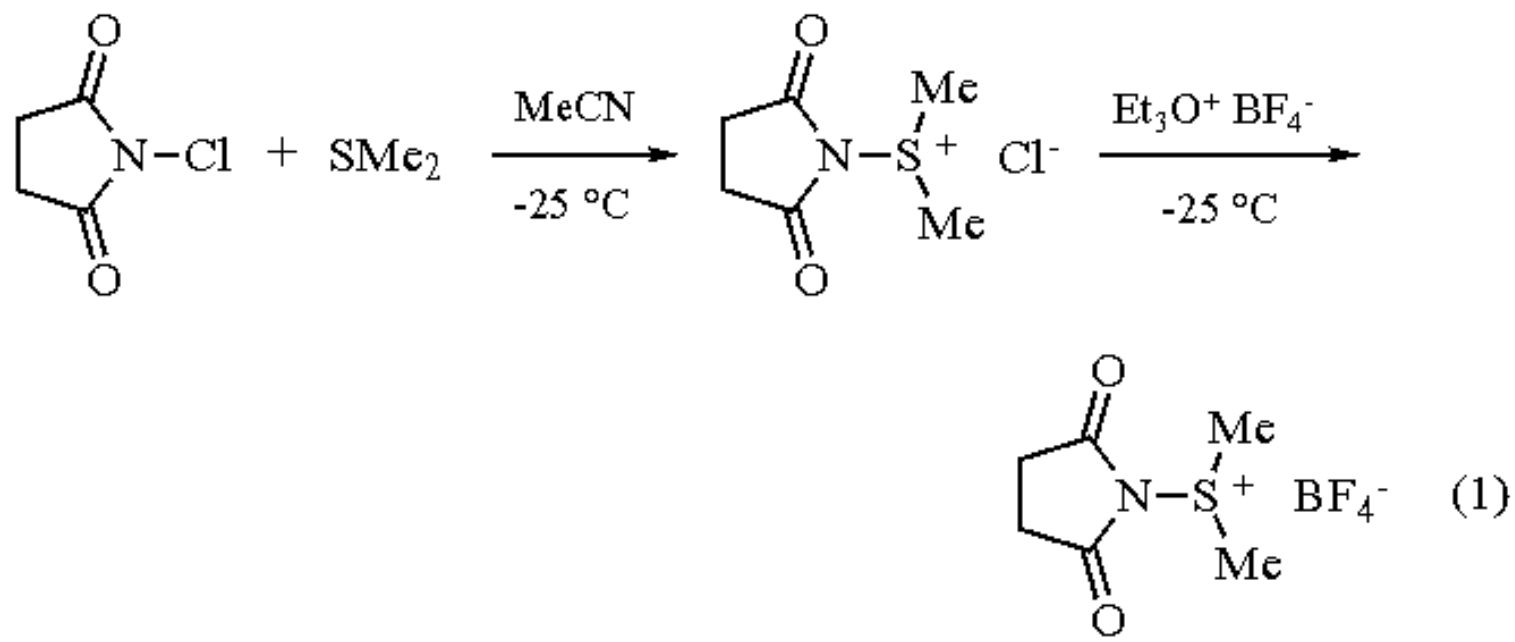

Handling, Storage, and Precautions: hygroscopic, but thermally and air stable; can be stored indefinitely under N_2 in sealed flasks in the absence of moisture.

Introduction.

The general class of dimethylsuccinimidosulfonium salts are reagents useful for the transfer of the dimethylsulfonium moiety to nucleophilic species.[1] The main variation in this group of reagents is the nature of the counteranion (Cl, Br, BF_4). The title reagent incorporating the tetrafluoroborate anion is a thermally stable and isolable salt of this series. Both the chloride and bromide are generally generated in situ for the purpose of oxidations of alcohols[2] or the sulfonium aminations of anilines.[3]

Experimental Procedure.

NCS (22.7 g, 0.17 mol) was dissolved in freshly distilled acetonitrile under a nitrogen atmosphere. The solution was cooled to -25 °C with stirring while 10 mL (0.2 mol) of DMS was added dropwise. After stirring for 15 min, the reaction mixture was cooled to -50 °C until crystals formed. A solution of 25 g (0.17 mol) of triethyloxonium tetrafluoroborate in 100 mL of acetonitrile was added dropwise to the reaction mixture. After addition was complete (about 1 h), the flask was cooled to -78 °C until the solution solidified. The solid mass was slowly brought to rt over a period of 4 h; then 500 mL of anhyd ether was added slowly to precipitate the dimethylsuccinimidosulfonium tetrafluoroborate as a white solid. Recrystallization from acetonitrile/ether gave 33.6 g (80%) of the product as white needles (mp 169-171 °C).

Oxidation Reactions.

The advantage of the stable tetrafluoroborate reagent lies in its stoichiometric use in a variety of solvents under controlled reaction conditions in the absence of a nucleophilic anion. A particularly mild and selective oxidation of catechols to *o*-quinones can be effected with the title reagent and 1 equiv of ***Triethylamine*** in acetonitrile below 0 °C (eq 2).

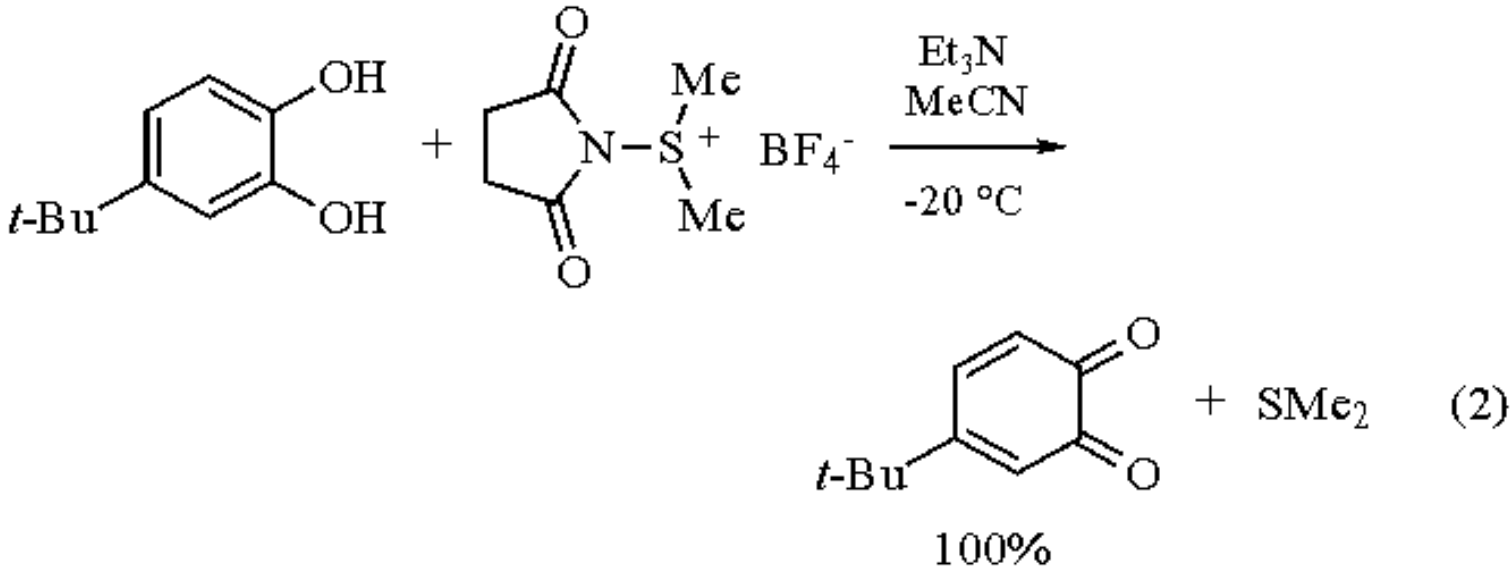

These oxidations can be carried out between -20 and -50 °C in order to extend the lifetime of the sensitive and very reactive *o*-quinones.[4] The mechanism of this oxidation process involves the intermediacy of an aryloxysulfonium cation which undergoes base-promoted elimination of dimethyl sulfide (eq 3). The merits of this procedure include the absence of deleterious byproducts which could react with the quinone product and the lack of opportunity for overoxidation.

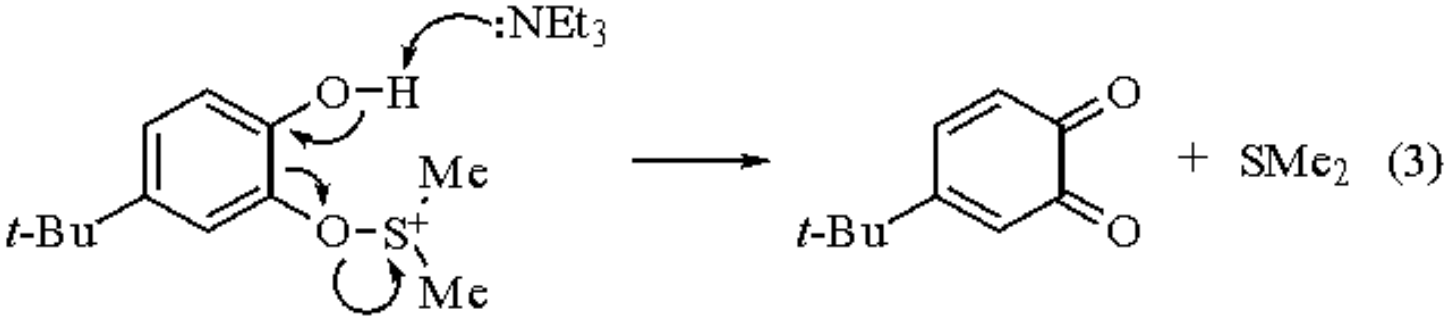

The title reagent is also effective for the oxidation of *p*-hydroquinones to *p*-quinones in quantitative yields (eq 4). The employment of an amine base is essential for this oxidation process.

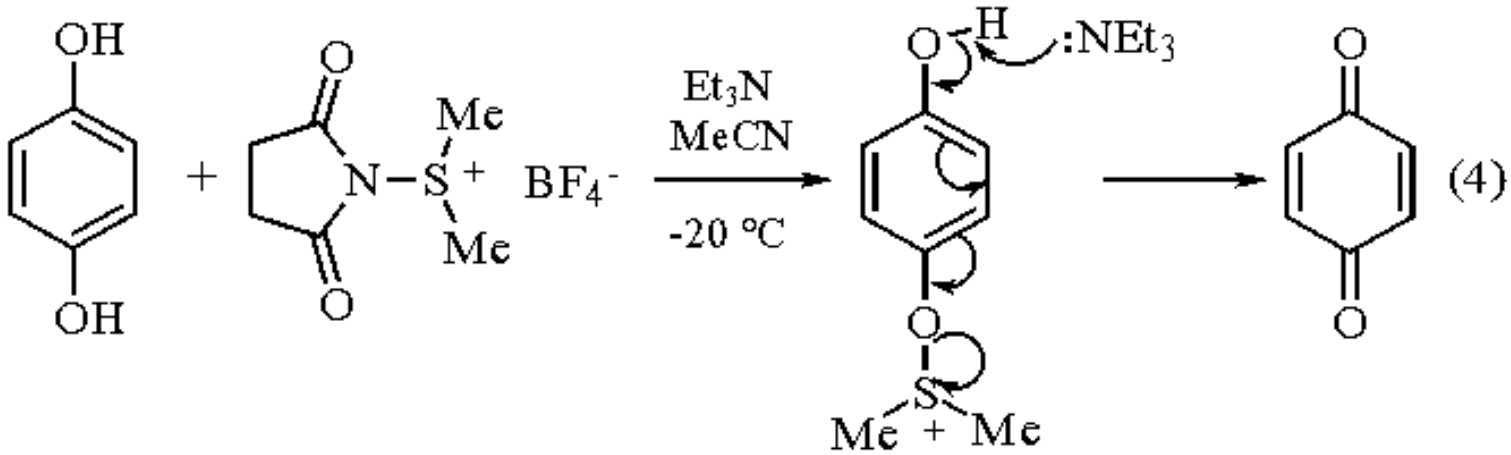

Nucleophilic Additions to Succinimidosulfonium Cations.

The title reagent can also be considered as a source of the dimethylsulfonium cation through reaction with nucleophiles. Thus the nucleophilic addition of a phenolic oxygen atom to the reagent leads to an intermediate aryloxysulfonium species, which rapidly gives up a proton to generate a sulfonium ylide.[5] This latter intermediate undergoes a facile [2,3]-sigmatropic rearrangement to produce cyclohexadienones with 2,6-disubstituted phenols (eq 5).[6] In the case of unsubstituted phenols, the sigmatropic rearrangement takes place and the dienone rearomatizes to give the *ortho*-methylthiomethylene phenol.[7]

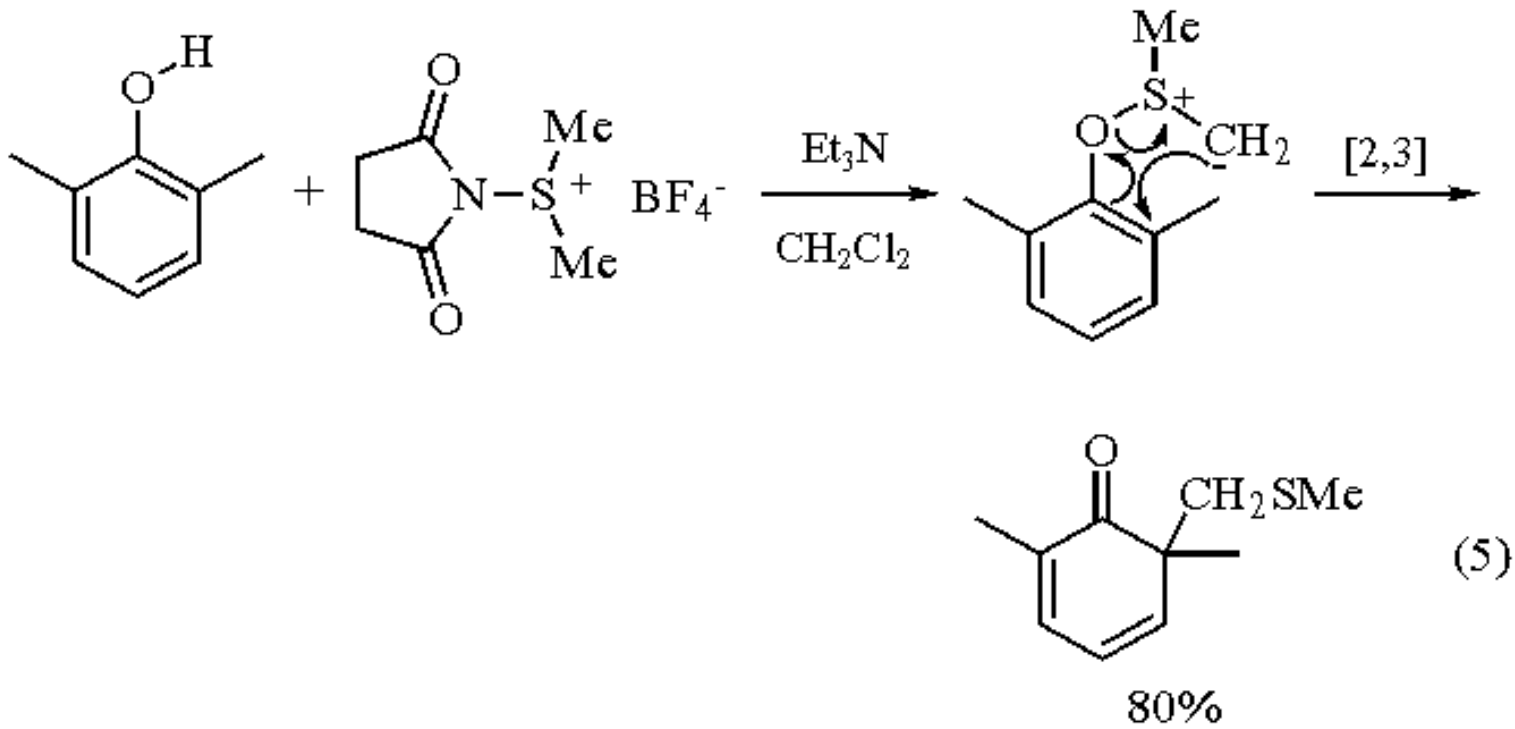

(5)

Other heteroatoms such as nitrogen and sulfur behave as good nucleophiles in reactions with the title reagent and related salts.[8] Stabilized carbanions such as substituted α-cyanoacetates react readily with the succinimidosulfonium reagent to give several rearangement products.[8] The initial combination of the reagent with the cyanoacetate anion is thought to generate a σ-sulfurane intermediate which could ionize to form the succinimido anion and a sulfonium cation (eq 6). In the presence of a weak base, the sulfonium cation is deprotonated to an ylide which can undergo a [1,2]-rearrangement to a methylthiomethylene derivative of the starting carbanion or, alternatively, the ylide may undergo a [2,3]-sigmatropic rearrangement to yield a substituted ketenimine (eq 7). In most cases, the ketenimine is the major product.

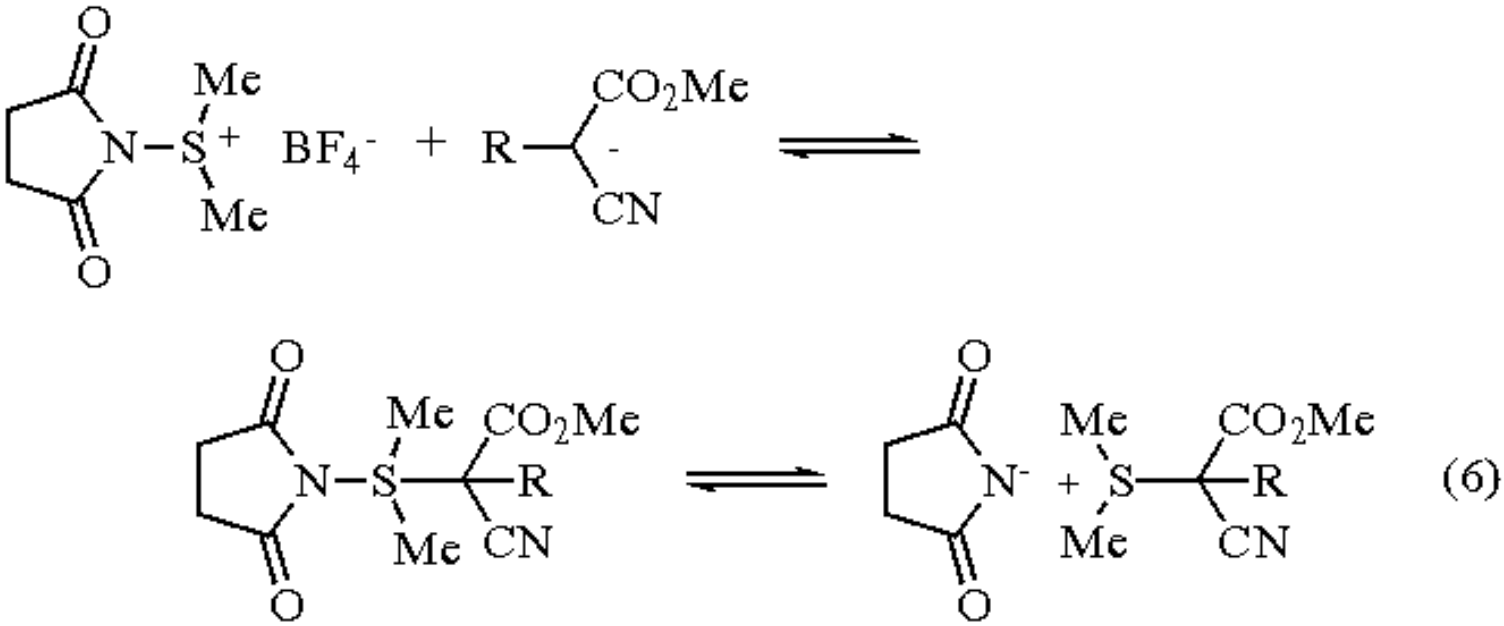

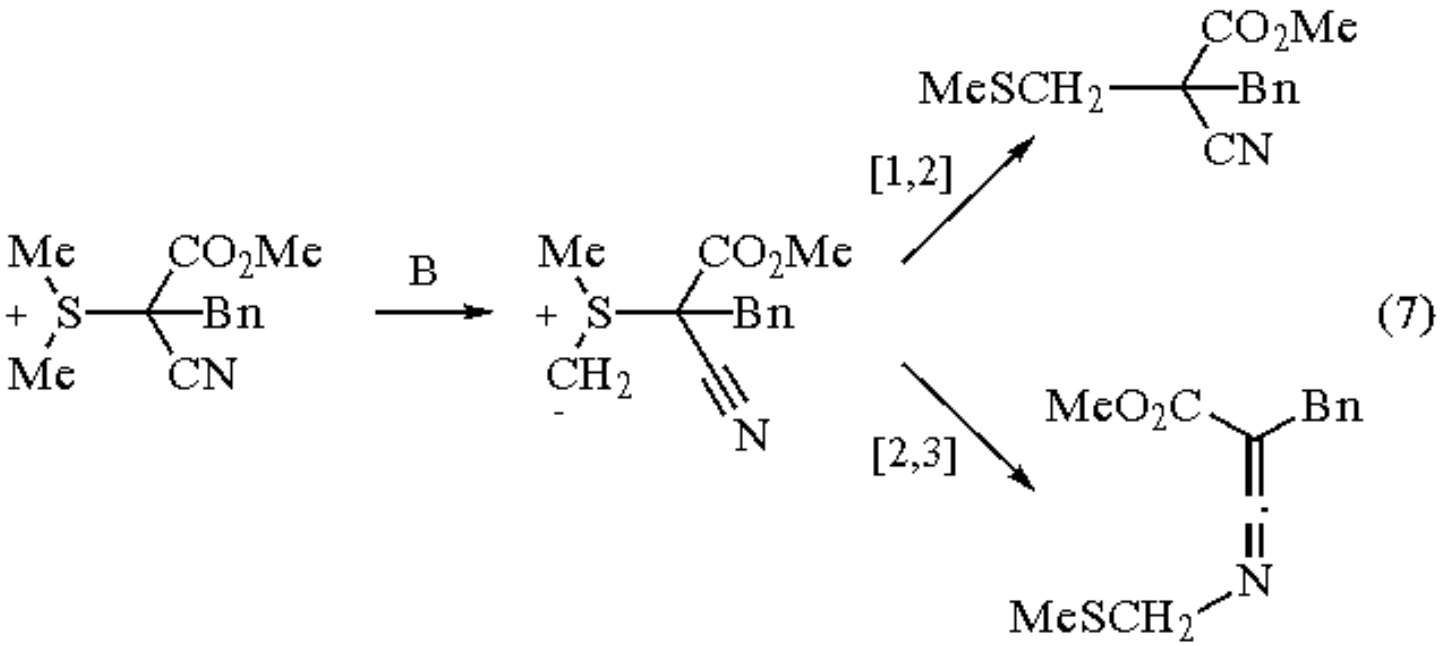

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Joseph P. Marino & David P. Holub

Dimethyl Sulfate[1]

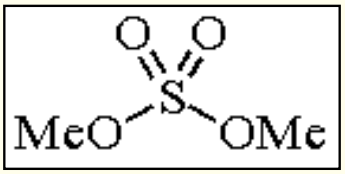

[77-78-1] · $C_2H_6O_4S$ · Dimethyl Sulfate · (MW 126.13)

(effective methylating reagent[1])

Physical Data: bp 188 °C; mp -32 °C; *d* 1.333 g cm^{-3}; fp 83 °C.

Form Supplied in: water-white liquid; widely available.

Handling, Storage, and Precautions: extremely toxic and carcinogenic; use in a fume hood with adequate protection.[2]

O-Alkylation.

Dimethyl sulfate is a powerful alkylating agent and has been used for the methylation of almost every imaginable nucleophile over the years.[1] The variety of oxygen nucleophiles include carboxylic acids,[3] alcohols,[4] phenols,[5] lactams,[6] oximes,[7] pyridine *N*-oxides,[8] hydroxylamines,[9] hydroxamic acids,[10] and hydroperoxides.[11]

Carboxylic acids react with dimethyl sulfate in the presence of ***Dicyclohexyl(ethyl)amine*** (DICE) to afford methyl esters in high yield.[3] The method is reported to be facile and particularly useful when ester formation using ***Diazomethane*** or strongly acidic conditions is not possible. For example, β-9,10,12-trihydroxyoctadecanoic acid is readily converted to its methyl ester in 97% yield using this procedure (eq 1). Another example of this type of esterification was demonstrated with the preparation of bile acid methyl esters (eq 2).[12] These steroidal carboxylic acids were methylated using ***Potassium Carbonate*** as a base in refluxing acetone. Both of the aforementioned procedures avoid significant side reactions such as dehydration or ether formation resulting from competing alkylation of free hydroxy groups.

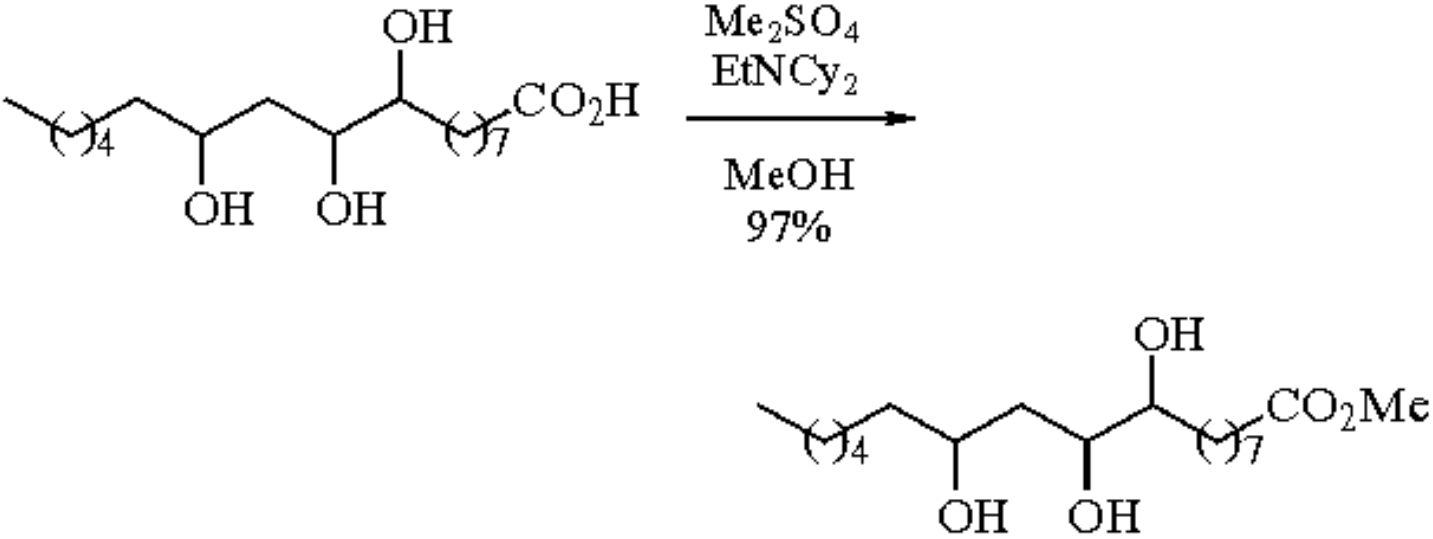

(1)

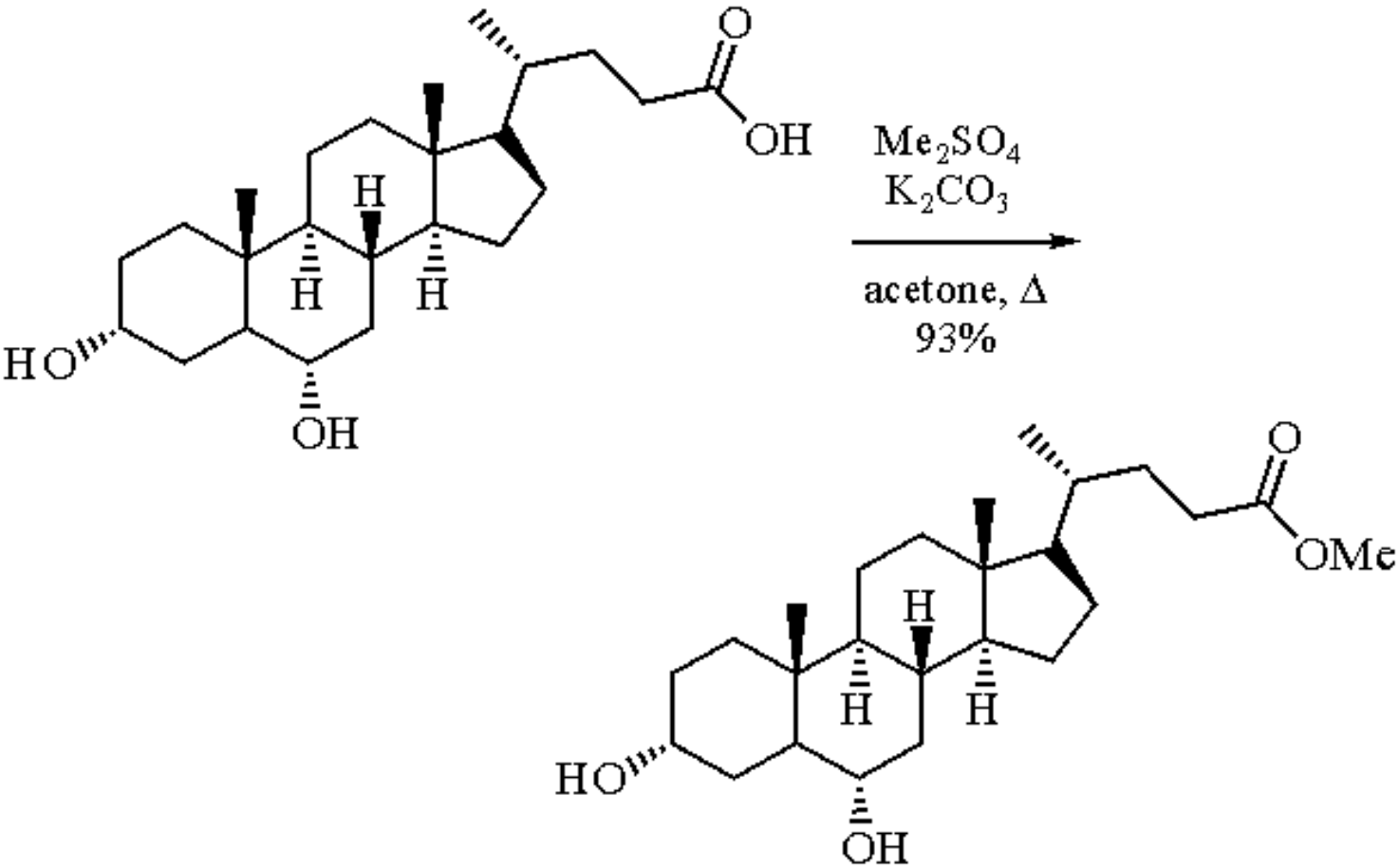

(2)

Syntheses of aryl and alkyl methyl ethers using dimethyl sulfate have also been reported. Simple alcohols and phenols may be alkylated using dimethyl sulfate in slightly hydrated solid/liquid heterogeneous media with 1,4-dioxane or triglyme/potassium hydroxide and small amounts of water to give the corresponding methyl ethers in excellent yield.[4] For example, *t*-butyl alcohol is converted to *t*-butyl methyl ether in nearly quantitative yield (eq 3). The procedure calls for the use of only a stoichiometric amount of dimethyl sulfate, which reduces problems associated in the workup and the potential toxicity of remaining dimethyl sulfate. In addition, methylation of alcohols using dimethyl sulfate and ***Alumina*** as a solid adsorbent reaction medium affords excellent yields of the corresponding alkyl alcohols.[13] Phenols and carboxylic acids, however, gave lower yields of methylated product using this procedure. A second example involves the stereospecific formation of highly substituted tetrahydrofurans. Treatment of a 2,5-dihydroxy-4-phenyl

sulfide with dimethyl sulfate in dichloromethane at 0 °C cleanly afforded the substituted tetrahydrofuran in excellent yield (eq 4).[14] It has been suggested that the reaction proceeds via methylation of a free hydroxy group followed by solvolysis of methanol assisted by the neighboring thiophenyl group. Subsequent cyclization gave the tetrahydrofuran as a single stereoisomer.

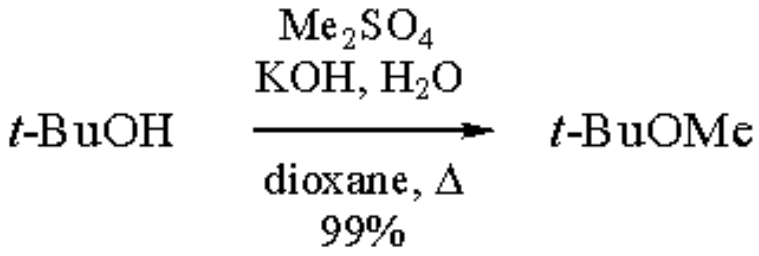

(3)

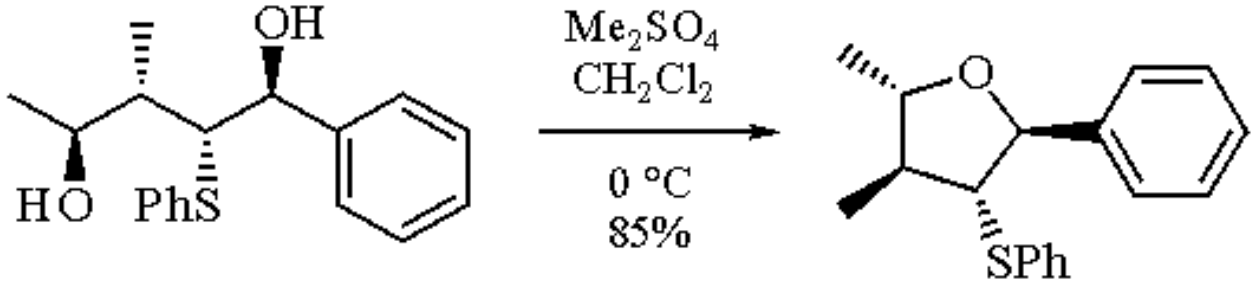

(4)

Several methods have been described for preparing aryl methyl ethers from phenols using dimethyl sulfate. For example, defucogilvocarcin M was completed by methylating a sterically hindered C-12 hydroxyl group using dimethyl sulfate and potassium carbonate (eq 5).[5] In addition, the synthesis of a carbazole alkaloid was completed via the selective alkylation of a 5-indolyl alcohol using dimethyl sulfate and ***Sodium Hydride*** to give 4-deoxycarbazomycin B in 96% yield (eq 6).[15]

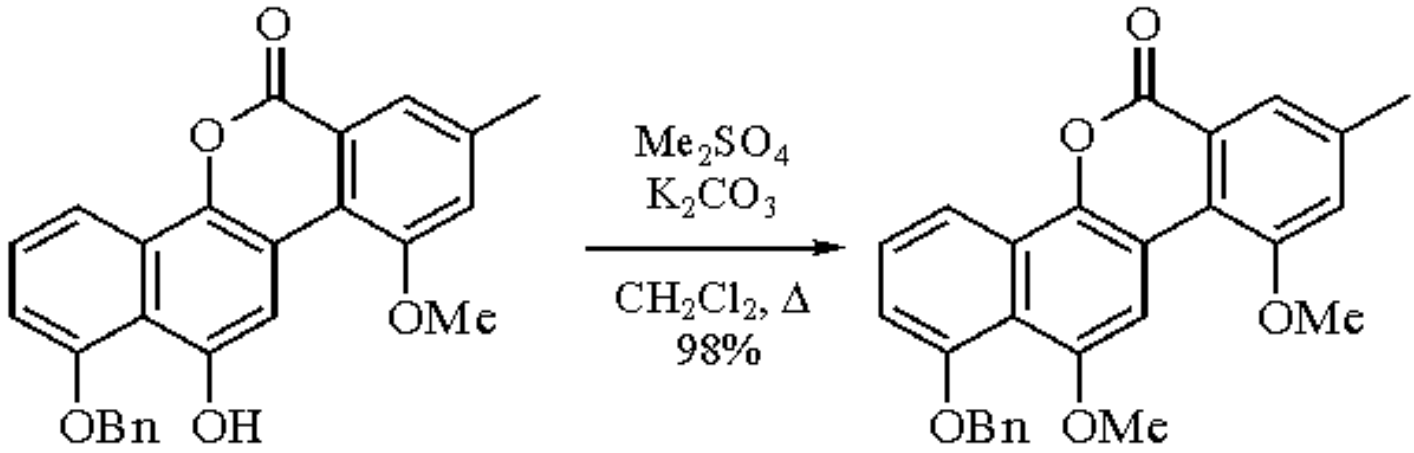

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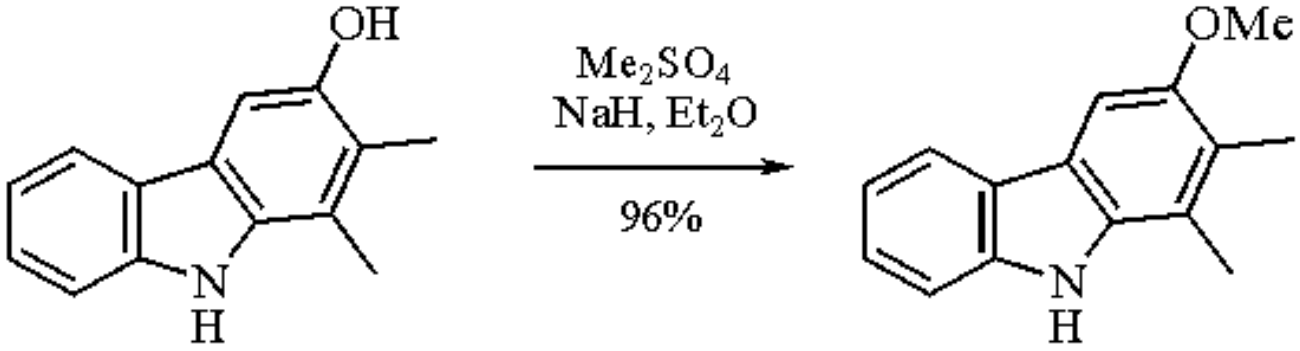

(6)

The *O*-methylation of lactams to afford *O*-alkylimino ethers has also been reported. For example, the large-scale preparation of *O*-methylcaprolactim proceeds in good yield using caprolactam and 1 equiv of dimethyl sulfate in benzene (eq 7).[6] The treatment of caprolactam with excess dimethyl sulfate gives *N*-methyllactam as the major product.

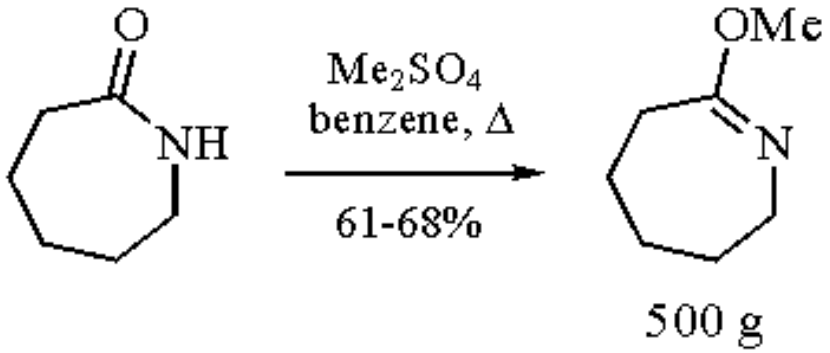

(7)

Other alkylation processes include the *O*-methylation of oximes, *N*-oxides, hydroxylamines, and hydroxamic acids. The preparation of oxime ethers using dimethyl sulfate has proven an effective methodology for the construction of sidechains designed for new cephalosporin antibiotics. Treatment of α-oxime esters with dimethyl sulfate afforded the α-methoximino esters, which were subsequently hydrolyzed to the acid and used as sidechains via acylation chemistry (eq 8).[7]

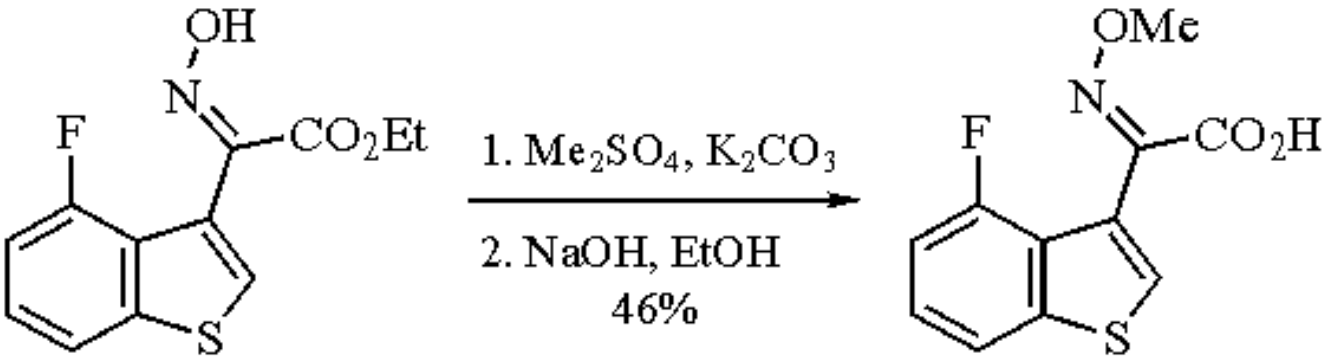

(8)

The methylation of pyridine, quinoline, and isoquinoline *N*-oxides to afford *N*-methoxy salts has also been investigated. For example, treatment of quinoline *N*-oxide with dimethyl sulfate provides the *N*-methoxy methylsulfate salt in excellent yield (eq 9).[8] The resulting salts were subsequently treated with cyanide ion to afford cyanopyridines in a mild overall process.

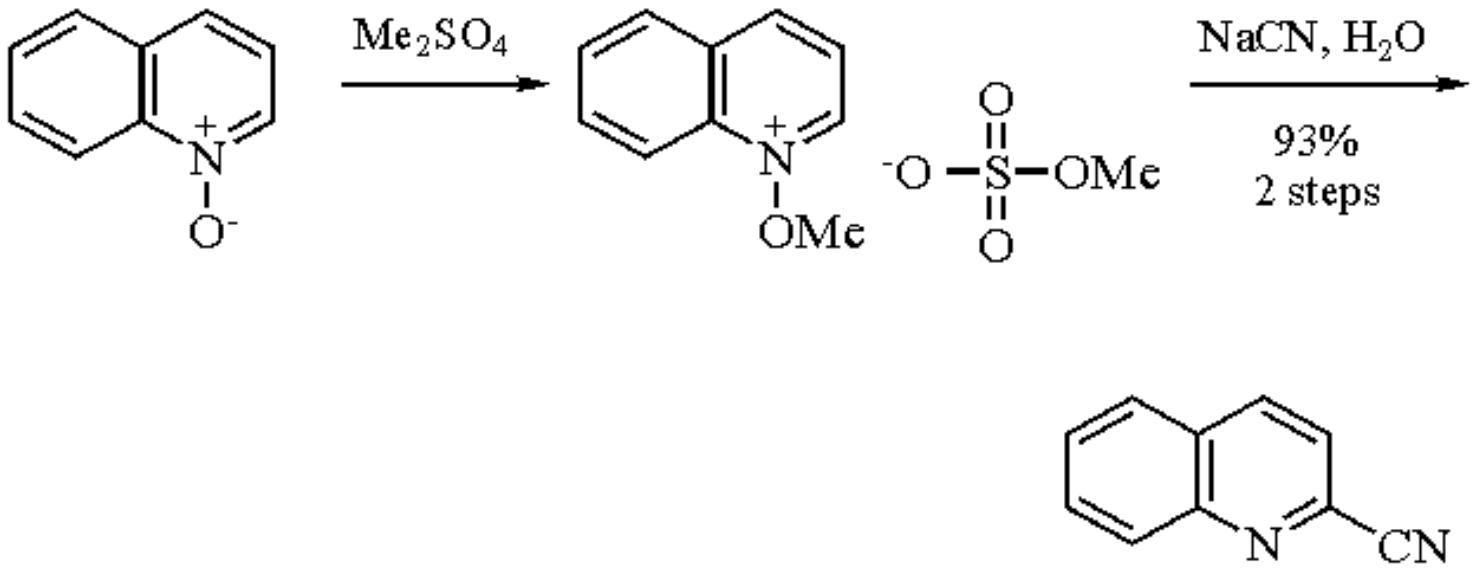

(9)

A new route to 2-substituted indoles derived from 1-methoxyindole was recently described. Dimethyl sulfate proved to be the reagent of choice for the methylation of the unstable 1-hydroxyindole to give 1-methoxyindole in 51% yield (eq 10).[9] The resulting methoxyindole undergoes *O*-lithiation at the 2-position using ***n-Butyllithium***, and can be trapped with appropriate electrophiles. It should be noted that methylation of 1-hydroxyindole using ***Iodomethane*** afforded only very low yields of the desired methoxyindole.

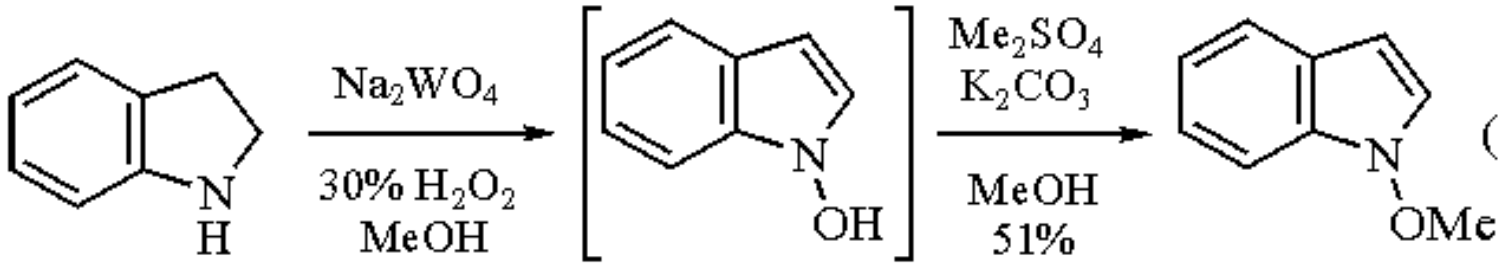

(10)

Finally, a convenient synthesis of ***N,O-Dimethylhydroxylamine***, a reagent used to prepare aldehydes from *N*-methoxy-*N*-methylamides, has been reported. It includes a key dimethylation of an intermediate ethyl hydroxycarbamate using dimethyl sulfate and sodium hydroxide (eq 11).[10]

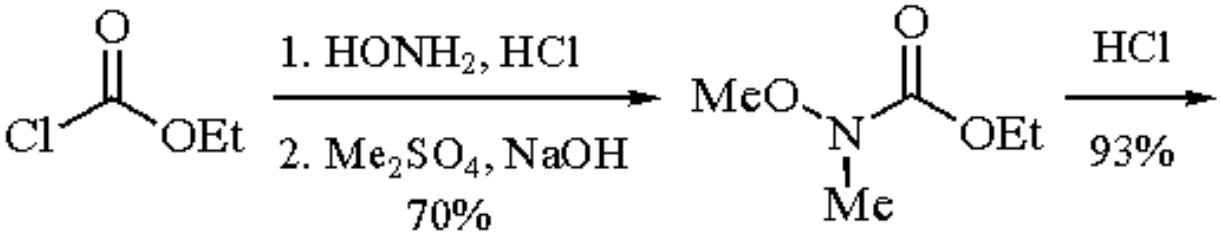

MeNHOMe · HCl (11)
200 g

N-Alkylation.

Dimethyl sulfate has also been a useful reagent for the preparation of *N*-methyl alkyl- and aryl-substituted amines, amides, and quaternary ammonium salts. Simple primary amines can be selectively methylated to afford secondary amines by first protecting the amine as a Schiff base or amidine ester,[16] amide,[17] or carbamate,[18] followed by alkylation using dimethyl sulfate and hydrolysis of the resulting amide or iminium ion. For example, the methylation of amidines has been employed in a route to *N*-alkyl amino acids. The amidine of phenylalanine methyl ester was prepared from the amino ester using dimethylformamide dimethyl acetal (see ***N,N-Dimethylformamide Diethyl Acetal***), followed by methylation and hydrolysis to afford the corresponding *N*-methylphenylalanine in good yield without racemization (eq 12).[16] Certain substrates such as phenylglycine methyl ester required the use of ***Methyl Trifluoromethanesulfonate*** as the alkylating agent and lower reaction temperatures to retain optical purity throughout the process. The selective synthesis of substituted *N*-monoalkylaromatic amines has also been reported. For example, 2-nitroacetanilide is cleanly converted to 2-nitro-*N*-methylaniline in one pot using phase-transfer conditions (eq 13).[17]

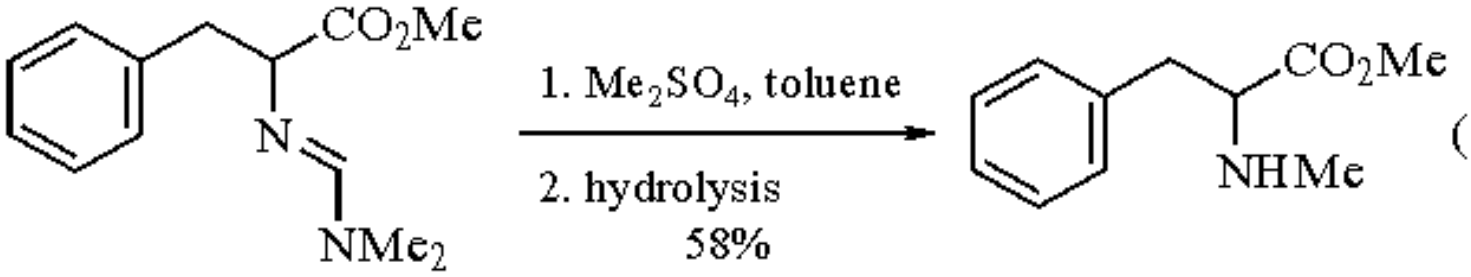

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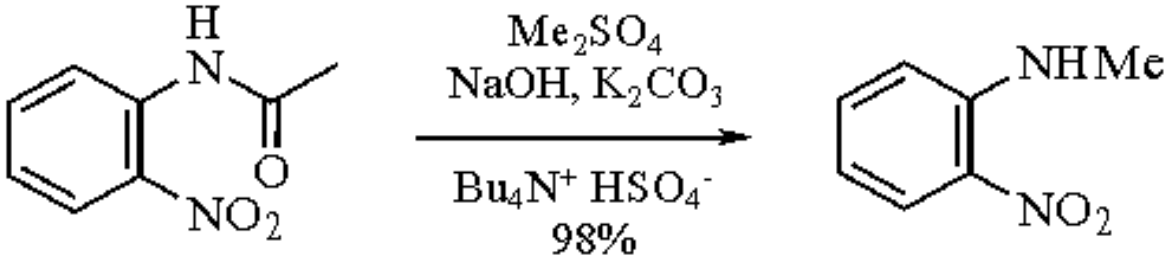

(13)

Tertiary alkyl and aromatic amines are also conveniently quaternized using dimethyl sulfate. For example, a series of thioquinanthrenediinium salts for use as potential antibiotics were prepared via methylation of their quinoline precursors using dimethyl sulfate (eq 14).[19]

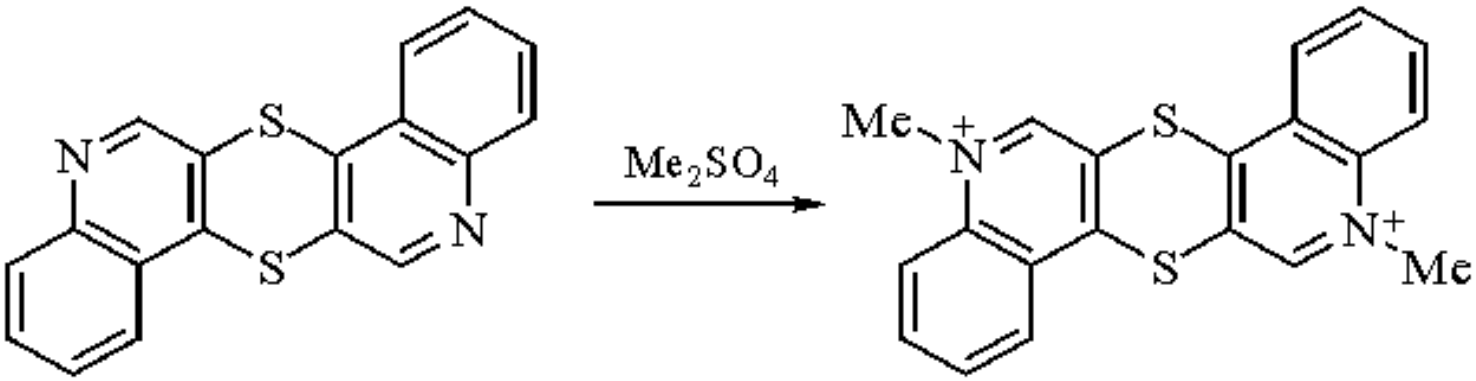

(14)

S-Alkylation.

The methylation of sulfur-containing compounds using dimethyl sulfate to afford sulfides and sulfonium ions has also been explored. For example, trimethylsulfonium methyl sulfate has been prepared on a large scale via methylation of

dimethyl sulfide.[20] This salt has been subsequently used as a precursor of ***Dimethylsulfonium Methylide***, a popular reagent for the preparation of epoxides from ketones (eq 15). *O*-Alkyl *S*-methyl dithiocarbamates have also been prepared via condensation of an alkoxide with ***Carbon Disulfide***, followed by methylation using dimethyl sulfate (eq 16).[21] The resulting dithiocarbamates can then be reduced via radical chemistry to afford the alkane.

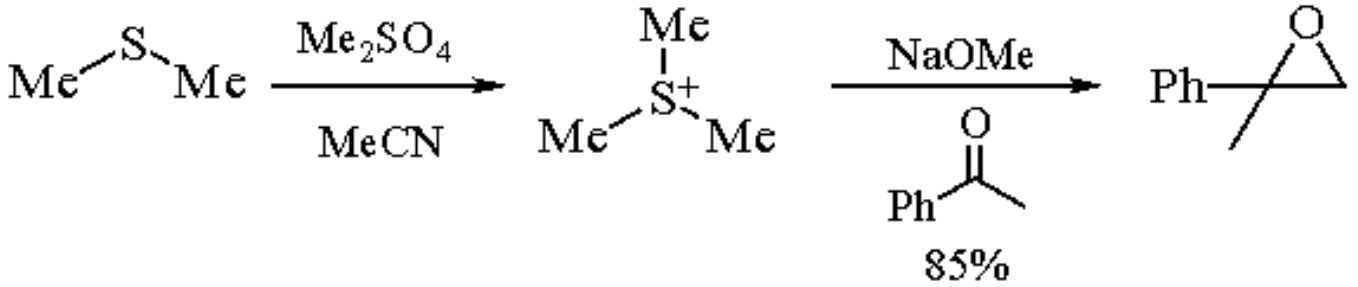

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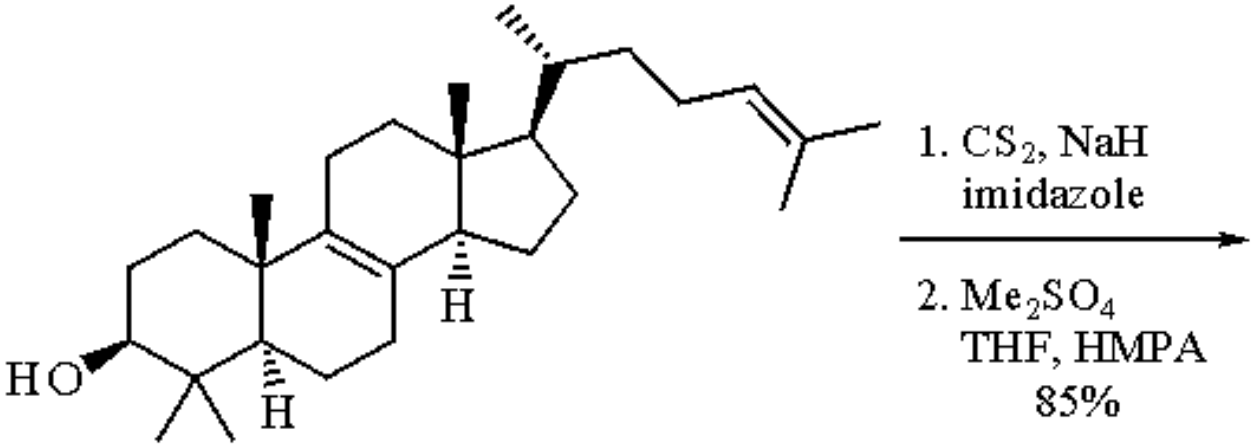

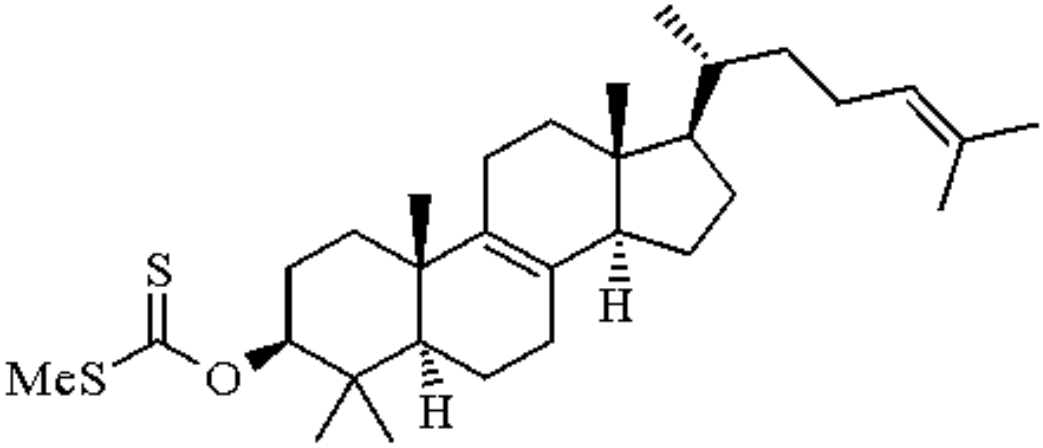

(16)

C-Alkylation.

Several processes involving the formation of C-C bonds via methylation of organometallics using dimethyl sulfate have been reported. For example, a series of 2-methylbutyrolactones and -valerolactones were prepared via asymmetric alkylation using chiral oxazolines and ***Lithium Diisopropylamide*** followed by treatment with dimethyl sulfate (eq 17).[22] The resulting oxazoline was then hydrolyzed to afford the optically active lactone. Aryllithium species also undergo rapid alkylation using dimethyl sulfate as the electrophile. For example, 3,4-bis(tributylstannyl)furan undergoes a single tin-lithium exchange and upon treatment with dimethyl sulfate and ***N,N´-Dimethylpropyleneurea***

(DMPU) affords the monomethylated product (eq 18).[23] The resulting compounds were then subjected to various palladium-mediated cross-coupling reactions to give 3,4-disubstituted unsymmetrical furans. Dimethyl sulfate was found to be superior to methyl iodide for this particular application.

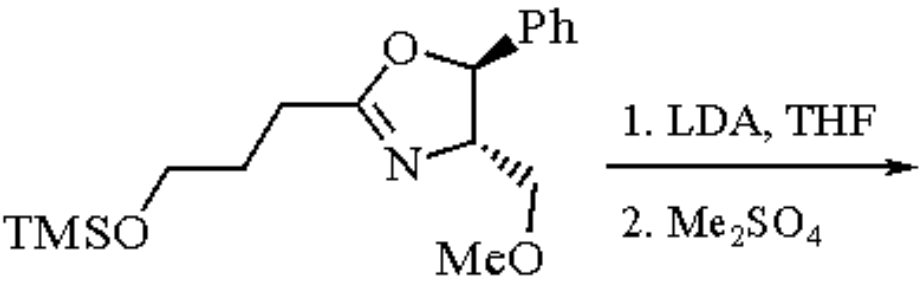

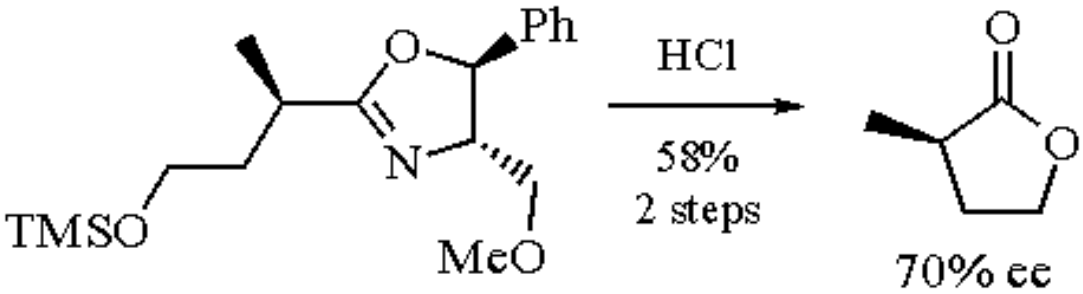

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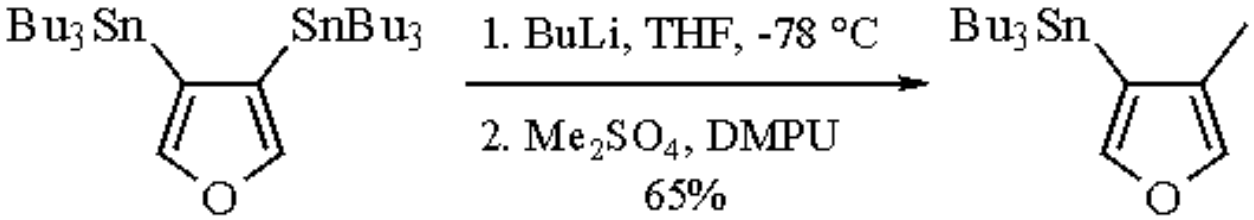

(18)

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Dimethyl Sulfide

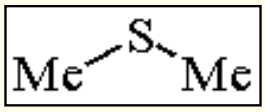

[75-18-3] · C_2H_6S · Dimethyl Sulfide · (MW 62.13)

(reducing reagent; methylation; sulfide complex; ylide formation)

Alternate Names: DMS; methyl sulfide.

Physical Data: mp -98 °C; bp 38 °C; *d* 0.85 g cm^{-3}.

Solubility: insol water; sol ethanol, diethyl ether.

Handling, Storage, and Precautions: disagreeable odor; use in a fume hood.

Reduction of Ozonides and Sulfoxides.

Diacetals are obtained in high yields when the ozonolysis products of alkenes are treated with dimethyl sulfide and trimethyl orthoformate (see ***Triethyl Orthoformate***) (eq 1).[1] Hydrolysis to the diacetals is performed by heating in water containing tartaric acid. Ozonolysis (see ***Ozone***) of maleic acid followed by reduction with dimethyl sulfide gives ***Glyoxylic Acid*** (eq 2).[2]

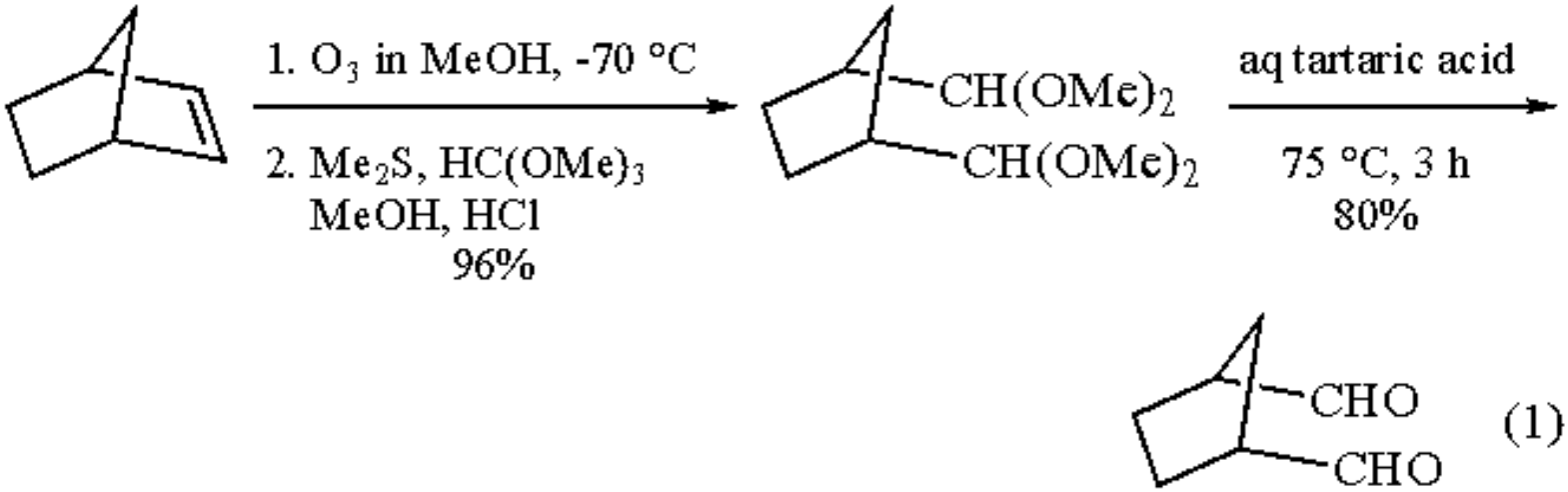

(1)

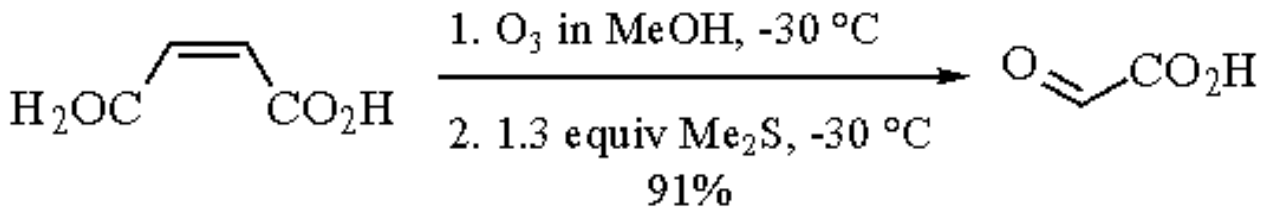

(2)

Methyl phenyl sulfoxide is quantitatively reduced to the corresponding sulfide by treatment with dimethyl sulfide (2 equiv) and ***Trifluoroacetic Anhydride*** at 0 °C in CH_2Cl_2 (eq 3).[3] Trifluoroacetic anhydride can be replaced by acetyl trifluoroacetate or ***Thionyl Chloride***.

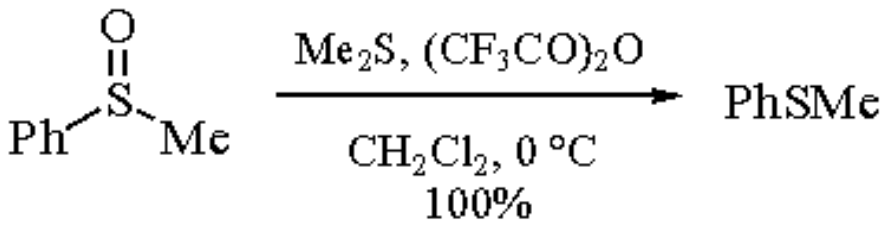

(3)

ortho-Alkylation.

Aromatic and heteroaromatic amines are methylated at the *o*-position via *N*-chloro derivatives. Aniline is treated with ***t-Butyl Hypochlorite*** or ***N-Chlorosuccinimide*** (1 equiv) in CH_2Cl_2 at -65 °C, and dimethyl sulfide (3 equiv) is added, followed by sodium methoxide (1.2 equiv) in methanol. 2-(Methylthiomethyl)aniline is obtained in 90% yield; its desulfurization by ***Raney Nickel*** gives *o*-toluidine (eq 4).[4] 2-Amino-3-methylpyridine is obtained in 50% overall yield by a similar sequence of reactions starting from 2-aminopyridine (eq 5).[5]

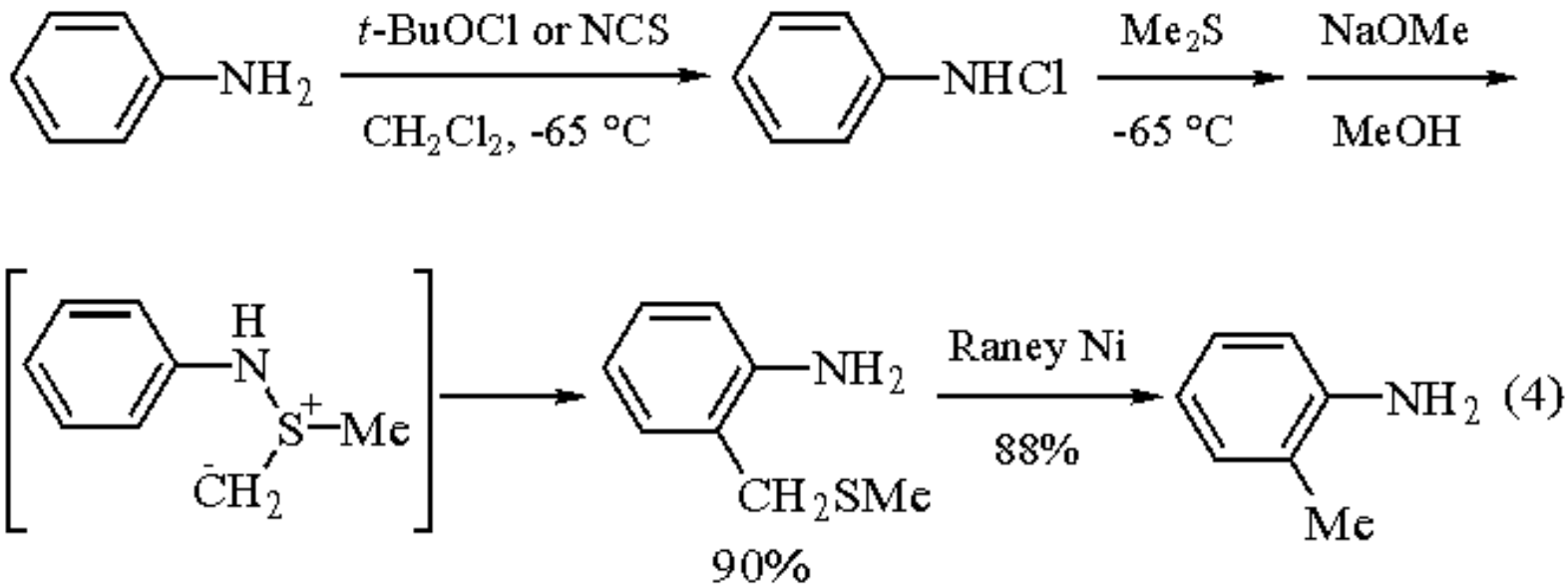

(4)

(5)

The above *o*-methylation can be successfully extended to *o*-alkylation[4] and also to the synthesis of indoles and hetero analogs. Use of methylthio-2-propanone (**1**), methylthioethanal (**2**), or methylthioethanal dimethyl acetal (**3**) instead of dimethyl sulfide, in similar processes using aniline and 2-aminopyridine, provides an elegant entry to indoles and hetero analogs (**4**)-(**7**).[6]

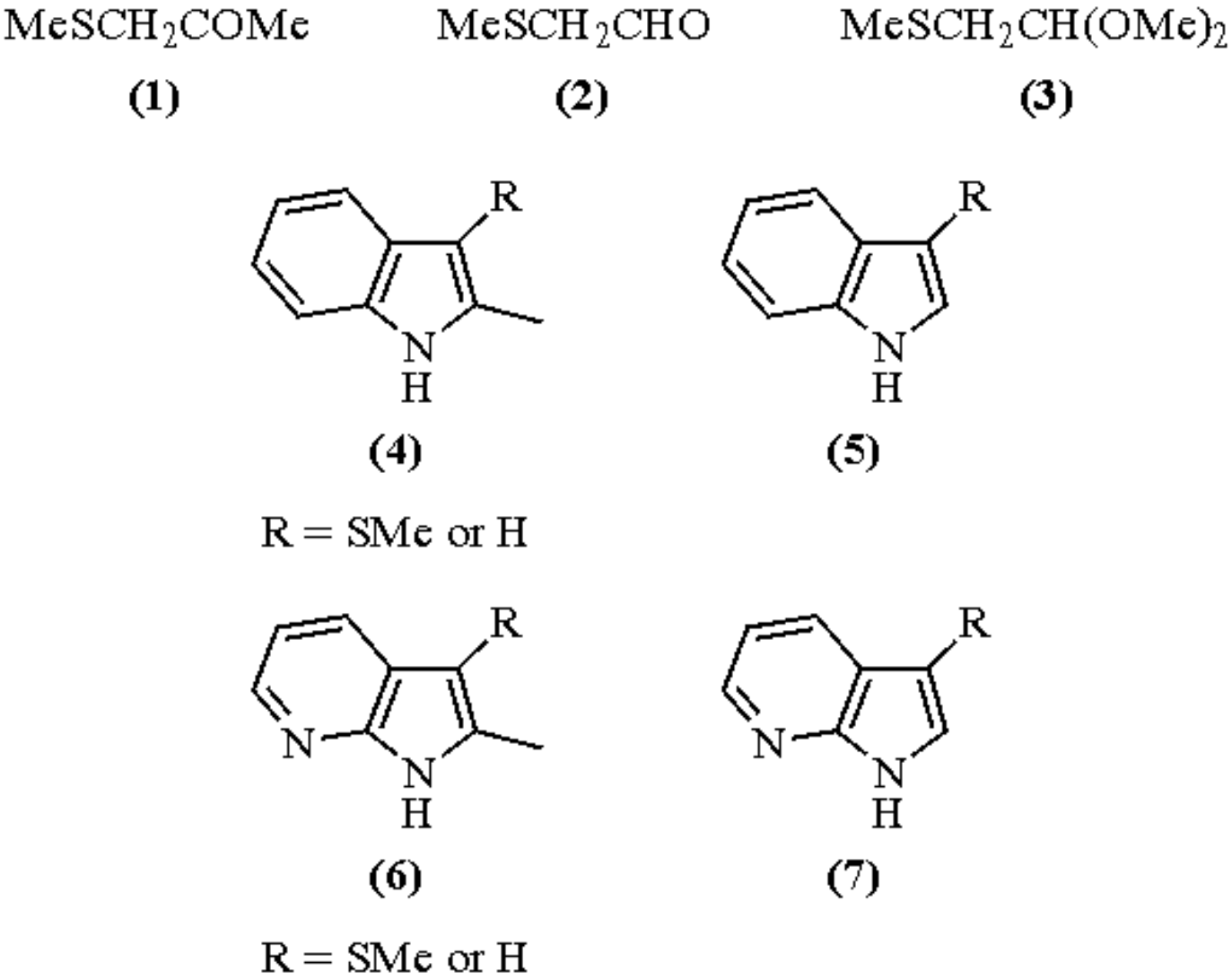

Dimethyl Sulfide Complexes.

Dimethyl sulfide rapidly reacts with ***Chlorine*** (1 equiv) in carbon tetrachloride at 0 °C to give the complex (**8**) as an insoluble solid. This complex (***Dimethyl Sulfide-Chlorine***; Corey-Kim reagent) is useful for oxidation of primary and secondary alcohols. Treatment of 4-*t*-butylcyclohexanol with (**8**) at -25 °C and then with ***Triethylamine*** gives 4-*t*-butylcyclohexanone (eq 6).[7] For the oxidation of primary alcohols, e.g. cyclohexanemethanol, ***N-Chlorosuccinimide-Dimethyl Sulfide*** (**9**)[8] is superior.

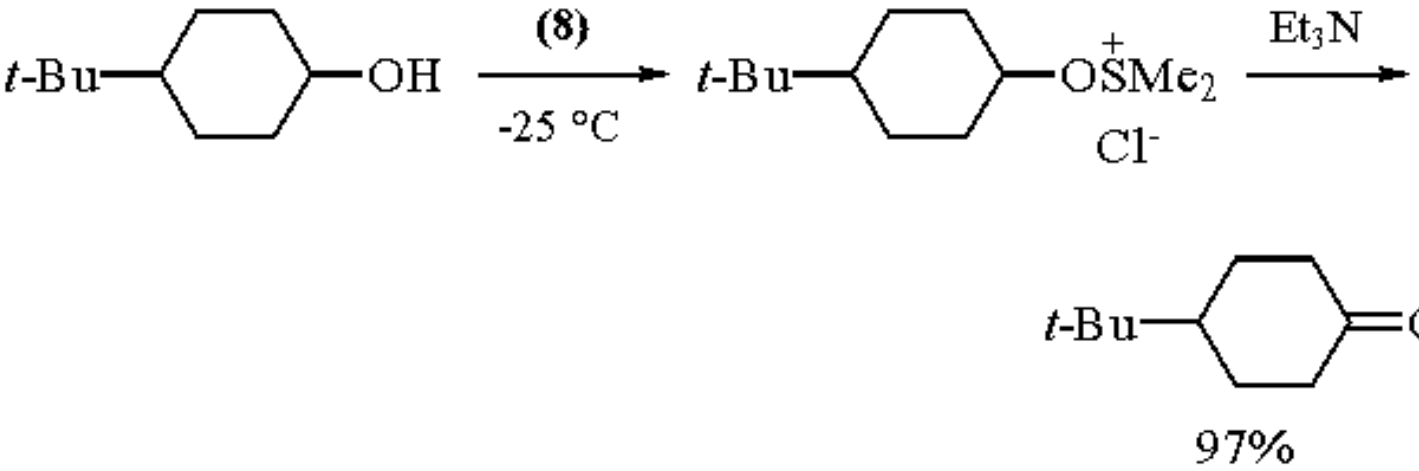

(6)

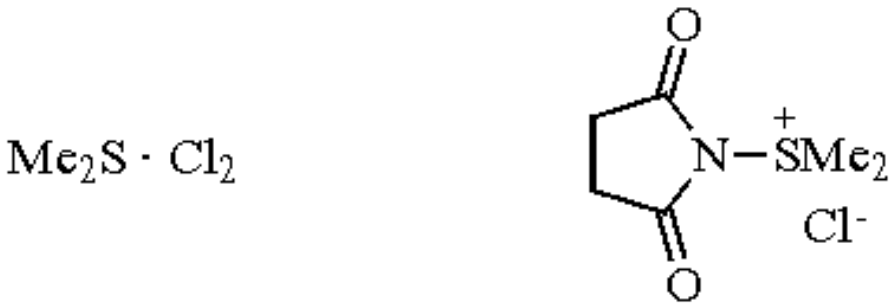

(8) **(9)**

Allylic and benzylic alcohols are not oxidized with the complex (**8**), but instead are converted into the corresponding chlorides. Of particular interest is the chemoselective chlorination of (*Z*)-3-methyl-2-pentene-1,5-diol, which bears allylic and homoallylic alcohol moieties in the same molecule (eq 7).[9] The allylic chloride is the only product obtained.

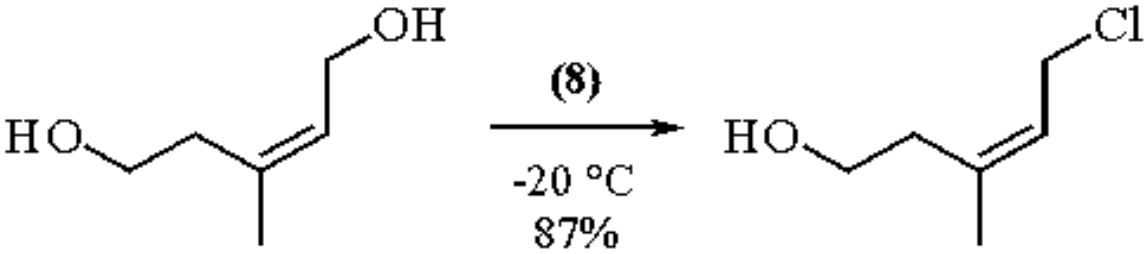

(7)

The ***Borane-Dimethyl Sulfide*** complex is a useful substitute for diborane and has been widely used for hydroborations and reductions, although it is a little less reactive than diborane itself.[10]

Sulphonium Ylides.

Heating of α-bromo esters with dimethyl sulfide leads to methyl sulfides. Subsequent *S*-methylation with ***Trimethyloxonium Tetrafluoroborate*** followed by α-deprotonation provides dimethylsulfonium ylides (eq 8).[11] These ylides undergo smooth reactions with electron-deficient alkenes, producing cyclopropanes. In the case shown in eq 8, a better yield (90%) of cyclopropane formation results when the ylide is generated in situ by treatment with ***Sodium Hydride*** rather than when the isolated ylide is used.

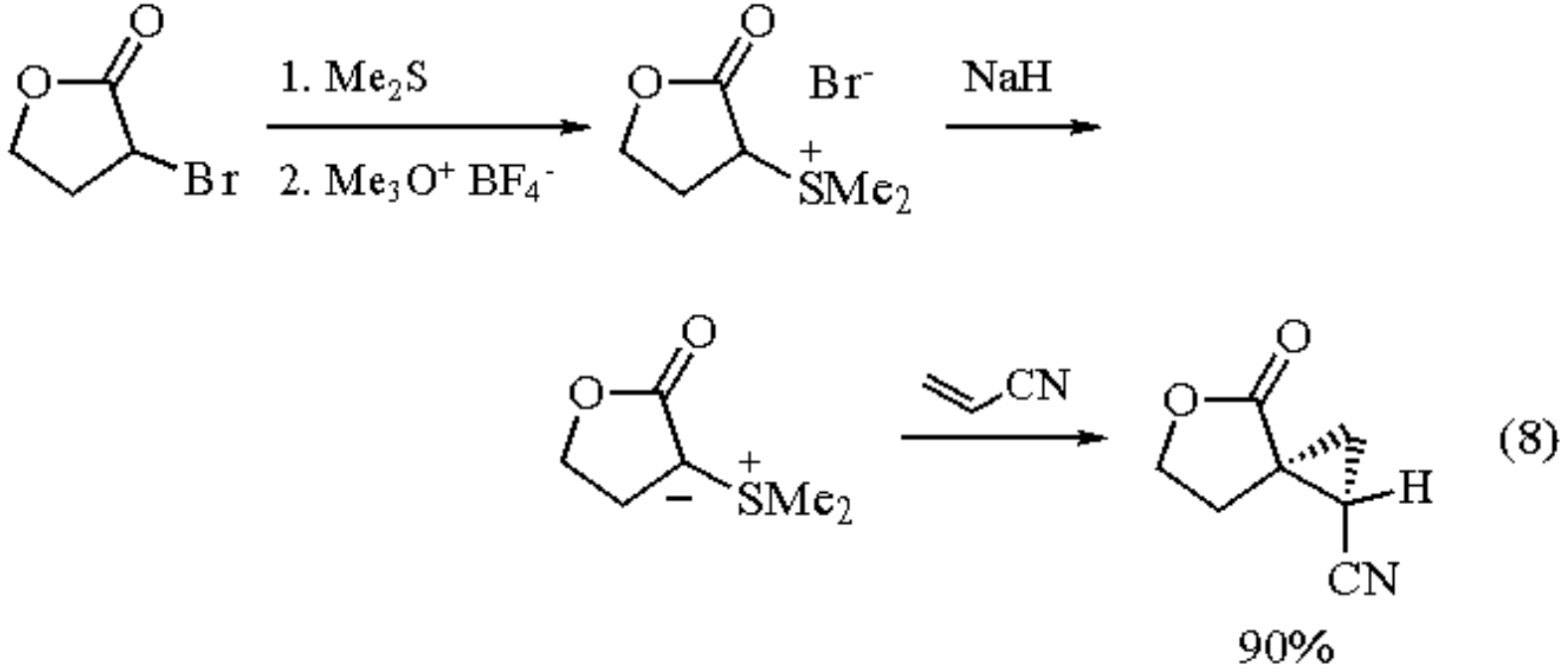

Related Reagents.

Boron Trifluoride-Dimethyl Sulfide; ***N-Bromosuccinimide-Dimethyl Sulfide***; ***Chloro(thexyl)borane-Dimethyl Sulfide***; ***Dibromoborane-Dimethyl Sulfide***; ***Dichloroborane-Dimethyl Sulfide***; ***Monochloroborane-Dimethyl Sulfide***; ***Trimethylstannylcopper-Dimethyl Sulfide***.

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Dimethyl Sulfide-Chlorine[1]

Me_2S-Cl_2

(DMS)

[75-18-3] · C_2H_6S · Dimethyl Sulfide-Chlorine · (MW 62.15) (Cl_2)

[7782-50-5] · Cl_2 · Dimethyl Sulfide-Chlorine · (MW 70.90)

(mild oxidizing agent for primary and secondary alcohols[2] and vicinal diols;[3] chlorinating agent for phenols, phenol ethers, and anilines;[4] reagent for synthesis of methylthiomethyl esters,[5] for dehydration of aldoximes to nitriles,[6] and for synthesis of α-chloro ketones[7])

Alternate Name: chlorodimethylsulfonium chloride

Solubility: sol CH_2Cl_2, CCl_4, toluene, acetonitrile.

Preparative Method: prepared in situ by slow addition of a solution of ***Dimethyl Sulfide*** (1.25 equiv) in CH_2Cl_2 to a solution of ***Chlorine*** (1 equiv) in CH_2Cl_2 at -25 °C under an inert atmosphere;[4] typical scale is 3 mmol in 10 mL CH_2Cl_2.

Handling, Storage, and Precautions: chlorine gas is toxic and corrosive; when introducing the gas to CH_2Cl_2, ensure that the apparatus is properly trapped and vented in a fume hood to avoid escape of chlorine and overpressurization of the reaction vessel.

Oxidation of Alcohols to Aldehydes or Ketones.

Dimethyl sulfide-chlorine (DMS-Cl_2) and its derivatives (e.g. chlorine-methyl phenyl sulfide) have shown excellent utility as oxidizing agents for primary and secondary alcohols.[2] This reagent system is part of a family of halosulfonium salt reagents (see ***Dimethyl Sulfoxide-Oxalyl Chloride***, ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***, ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***, ***Dimethyl Sulfoxide-Phosphorus Pentoxide***)[1b] and is closely related in its oxidizing properties to ***N-Chlorosuccinimide-Dimethyl Sulfide*** (DMS-NCS). The oxidation proceeds through a sulfoxonium ion complex (**2**), which is converted to the carbonyl by addition of ***Triethylamine*** (eq 1).[2]

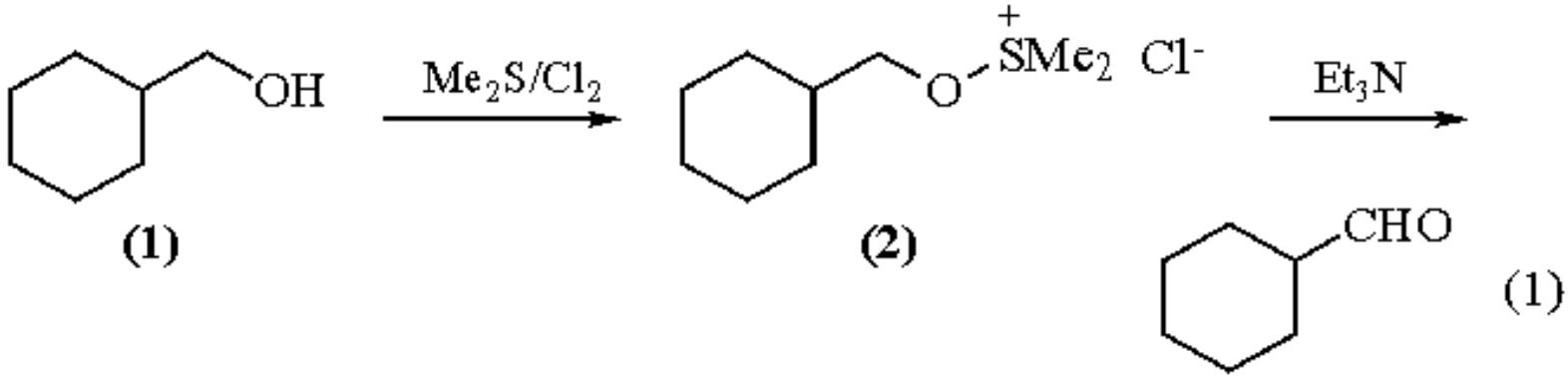

The oxidation of vicinal diols has been problematic with some oxidizing agents.[3] Carbon-carbon bond cleavage occurs with certain of these reagents (***Chromic Acid***, ***Pyridinium Chlorochromate***, ***Pyridinium Dichromate***, ***Silver(I) Carbonate***). DMS-Cl_2 oxidizes *s*,*t*-1,2-diols to α-hydroxy ketones as illustrated in eq 2[3] and eq 3.[6] The yields are moderate; in eq 2 they can be improved to 85% by substituting methyl phenyl sulfide for dimethyl sulfide. In some instances methyl phenyl sulfide has been found to be superior to dimethyl sulfide.[3,9,10] Two good alternative reagents to DMS-Cl_2 are ***Dimethyl Sulfoxide-Chlorine***[3] and DMS-NCS, which also give good to excellent yields of keto alcohols without C-C cleavage. The oxidation shown in eq 3 was attempted with silver carbonate but gave only a 12% yield of hydroxy ketone.[8]

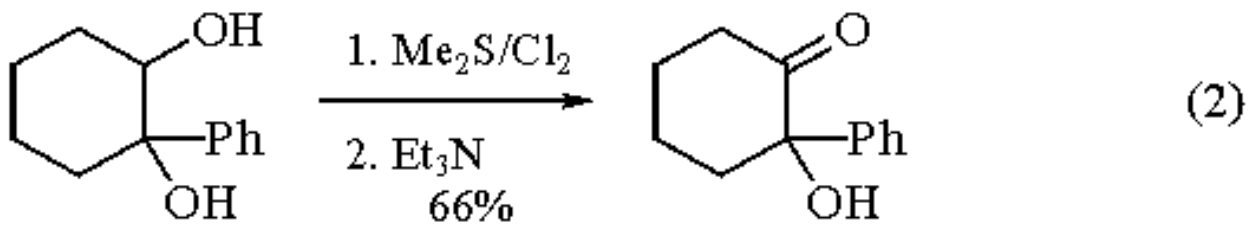

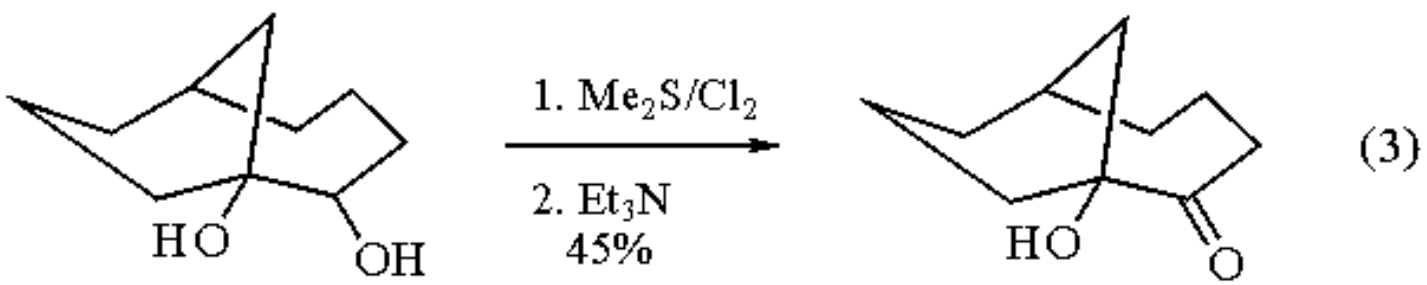

Another advantage of DMS-Cl_2 is its potential use in large-scale processes. The reagent is very inexpensive and the reaction byproducts are dimethyl sulfide (which can be recycled) and HCl.

Chlorination of Activated Aromatic Compounds.

DMS-Cl_2 regioselectively *p*-chlorinates activated aromatic compounds such as phenol, anisole, and *N*,*N*-dimethylaniline in good to excellent yields.[4] Eq 4 shows three general examples of this reaction. The reaction is complete in 5 min at -25 °C.

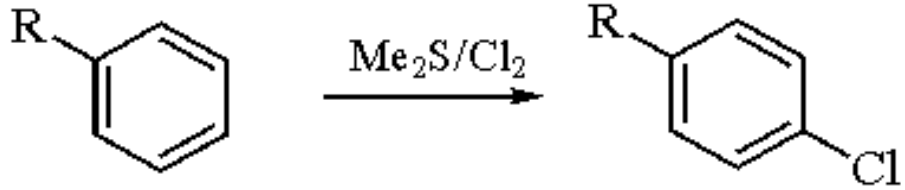

(4)

R = OH, 84%; OMe, 80%; NMe_2, 75%

Synthesis of Methylthiomethyl Esters.

Methythiomethyl esters can be synthesized by reaction of the triethylamine salt of a carboxylic acid with freshly prepared DMS-Cl_2 at -70 °C to rt (e.g. eq 5).[5] Yields for simple alkyl and aryl carboxylates range from 80 to 85%.

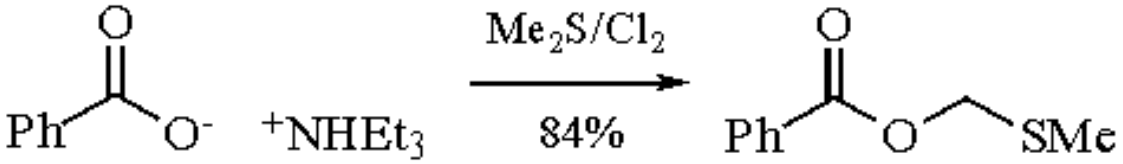

(5)

Dehydration of Aldoximes to Nitriles.

DMS-Cl_2 rapidly dehydrates aldoximes at low temperature.[6] Excess DMS-Cl_2 is formed at -78 °C in acetonitrile and treated with an aldoxime. Warming to -25 °C and addition of triethylamine affords the nitrile in excellent yield (eq 6).

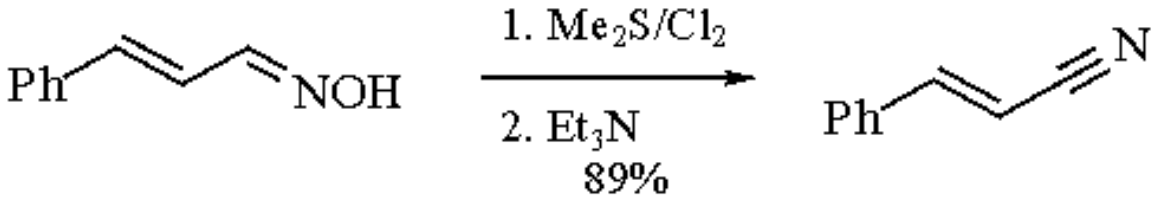

(6)

Synthesis of α-Chloro Ketones.

α-Chloro ketones can be synthesized by treatment of an epoxide with DMS-Cl_2 in CH_2Cl_2 at low temperature.[7] Triethylamine is required to decompose the intermediate sulfonium salt to the α-chloro ketone (eq 7). Yields are greater than 80% but in some cases there is no control of regiochemistry.

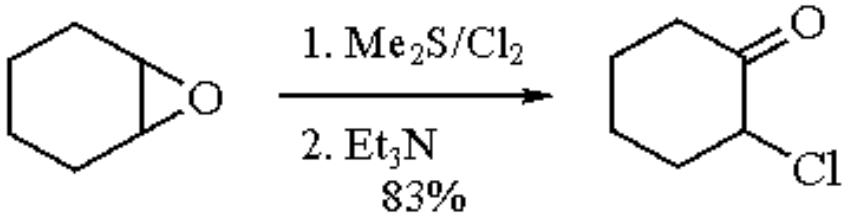

(7)

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Dimethyl Sulfone

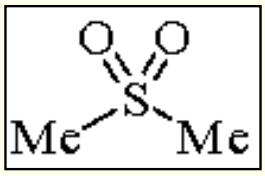

[67-71-0] · $C_2H_6O_2S$ · Dimethyl Sulfone · (MW 94.15)

((methanesulfonyl)methylation agent; may be used as a dipolar aprotic solvent)

Physical Data: mp 108-110 °C; bp 238 °C; *d* 1.1707 g cm^{-3} (110 °C); pK_a 31.1 (DMSO) and 23 (water).

Solubility: sol in hot H_2O, EtOH, benzene.

Form Supplied in: white solid; commercially available.

Purification: recrystallized from $CHCl_3$ or H_2O and then dried over P_2O_5.

Handling, Storage, and Precautions: stable indefinitely at rt.

As a Solvent.

Because of its high boiling point, dimethyl sulfone is a convenient solvent for high-temperature reactions, e.g. treatment of 2-chloropyridine with ***Potassium Fluoride*** in dimethyl sulfone at 110 °C for 21 days results in the displacement of the chlorine by fluorine.[1]

Reactivity and Applications.

Dimethyl sulfone can be deprotonated by organolithium compounds, Grignard reagents, or alkali metal alkoxides,[2] amides,[3,4] or hydrides[5] to give (methanesulfonyl)methyllithium or (methanesulfonyl)methyldilithium, depending upon the amount of base added.[3] The choice of the solvent (THF, DMSO, or liquid ammonia) is dictated by the nature of the base. The resultant carbanions react with halides, aldehydes,[4] ketones, esters, nitriles,[3] or amides. Under phase transfer catalysis, condensation of dimethyl sulfone with aldehydes occurs without dehydration to give the corresponding β-hydroxysulfones.[6] The acidity of dimethyl sulfone (pK_a = 31) is greatly enhanced by forming ***Trifluoromethanesulfonylmethyl Methyl Sulfone*** (pK_a = 4) via reaction of (methanesulfonyl)methylmagnesium bromide with trifluoromethanesulfonyl fluoride or ***Trifluoromethanesulfonic Anhydride***. The trifluoromethanesulfonyl group serves the dual role of acidity enhancer and leaving group in a Ramberg-Bäcklund reaction, leading to a synthesis of alkenes.[7] The principles are illustrated in a synthesis of the cyclopentenone ring of

dihydrojasmone (eq 1).[8]

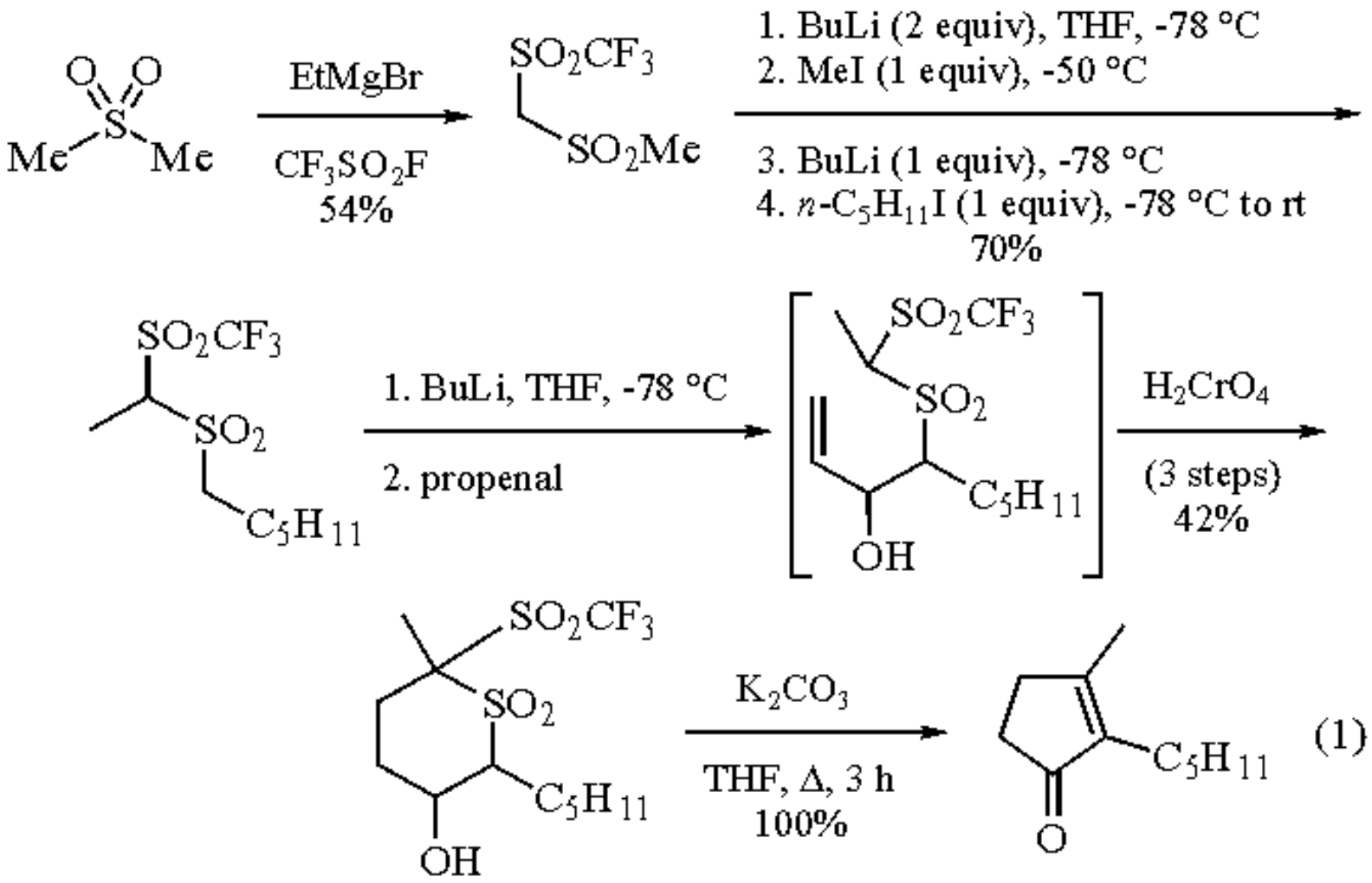

Related Reagents.

Methyl Phenyl Sulfone; ***Trifluoromethanesulfonylmethyl Methyl Sulfone***.

---

1. Finger, G. C.; Starr, L. D.; Dickerson, D. R.; Gutowsky, H. S.; Hamer, J. *JOC* **1963**, *28*, 1666.
2. Becker, H.-D.; Russell, G. A. *JOC* **1963**, *28*, 1896.
3. Kaiser, E. M.; Beard, R. D.; Hauser, C. R. *JOM* **1973**, *59*, 53.
4. Gokel, G. W.; Gerdes, H. M.; Rebert, N. W. *TL* **1976**, 653.
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6. Villemin, D.; Richard, M. *TL* **1984**, *25*, 1059.
7. Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S. *TL* **1984**, *25*, 4617.
8. Hendrickson, J. B.; Palumbo, P. S. *JOC* **1985**, *50*, 2110.

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Dimethylsulfonium Methylide

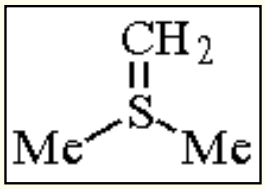

[6814-64-8] · C_3H_8S · Dimethylsulfonium Methylide · (MW 76.18)

(exceedingly selective methylene transfer reagent capable of converting carbonyl compounds into oxiranes,[1] and imines into aziridines[2])

Form Supplied in: reactive intermediate generated in situ.

Preparative Methods: Method A.[1a,b] A solution of dimethylsulfonium methylide is readily prepared by addition of a solution of ***Trimethylsulfonium Iodide*** in ***Dimethyl Sulfoxide*** (800 mL per mol of sulfonium salt) with stirring (below 5 °C, because of the marked thermal instability of the methylide) to an equivalent molar amount of a 1.5-2 M solution of methylsulfinyl carbanion,[3] which is prepared by treatment of dry DMSO with ***Sodium Hydride*** under nitrogen followed by dilution with an equal amount of dry THF (to prevent solidification).

Method B.[1b] Alternatively, a solution of ***n-Butyllithium*** (11 mmol) in 8 mL of pentane may be added dropwise to a stirred suspension of 2.45 g (12 mmol) of powdered trimethylsulfonium iodide in 30 mL of dry THF under nitrogen at 0 °C.

Method C.[4] To a solution of ***Dimethyl Sulfate*** (189.2 g, 1.50 mol) in acetonitrile (700 mL) is added a solution of ***Dimethyl Sulfide*** (102.5 g, 1.65 mol) in acetonitrile (300 mL) with stirring at rt. After standing overnight, ***Sodium Methoxide*** (89.1 g, 1.65 mol) is added to the mixture at rt to give a solution of dimethylsulfonium methylide, which is successfully applied to the preparation of oxiranes from various kinds of carbonyl compound. In comparison with the former methods, this process is more favorable for preparing oxiranes on a large scale under mild conditions without using expensive alkylating agents and intractable solvents.

Method D.[1d] To a mixture of 0.1 mol of aldehyde (or ketone) and 22 g (0.14 mol) of trimethylsulfonium bromide dissolved in 60 mL of DMSO is added a solution of 14 g of ***Potassium t-Butoxide*** in 60 mL of DMSO with stirring and cooling under nitrogen over 30-45 min. After workup, the expected oxiranes can be separated and purified by distillation or recrystallization. In this method, ***Sodium Amide*** or sodium hydride can be used as a base instead of potassium *t*-butoxide, and DMF may be used as solvent. Benzalaniline may be converted by this method into the corresponding aziridine.

Method E.[5] Dimethylsulfonium methylide can also be obtained by phase-transfer catalysis. Thus trimethylsulfonium iodide does not react with benzaldehyde in the system CH_2Cl_2-NaOH, but on addition of

1-5 mol % of ***Tetra-n-butylammonium Iodide***, 2-phenyloxirane is obtained in >90% yield via the intermediate sulfonium methylide. Yields of oxiranes are rather low (20-35%) when ketones are used in this procedure.

Formation of Oxiranes.

Dimethylsulfonium methylide reacts with a variety of aldehydes and ketones by net methylene transfer to form oxiranes. Thus several compounds, including benzophenone, benzaldehyde, and cycloheptanone were converted into the corresponding oxiranes by selective addition of methylene to the carbonyl group (eqs 1-3).[1b]

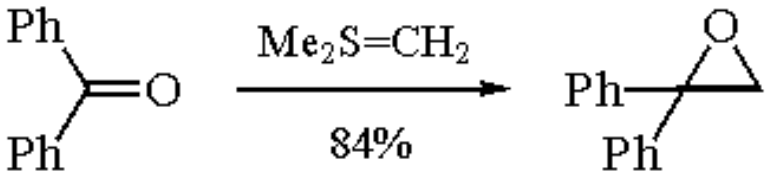

(1)

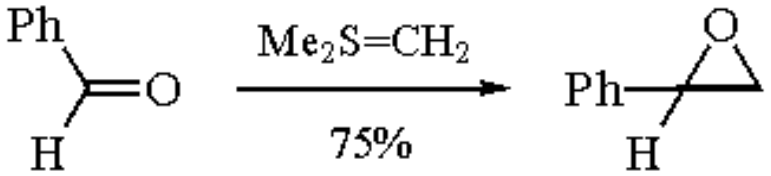

(2)

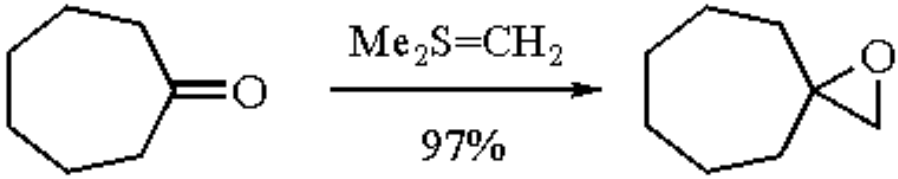

(3)

It should be noted that dimethylsulfonium methylide prefers addition to the carbonyl group of α,β-unsaturated carbonyl compounds while ***Dimethylsulfoxonium Methylide***, which is a closely related reagent for methylene transfer to unsaturated compounds, tends to attack the α,β-double bond. For example, carvone was converted to the corresponding oxirane by treatment with the sulfonium ylide, whereas the sulfoxonium ylide reacts with carvone to give the cyclopropyl ketone (eq 4).[1b]

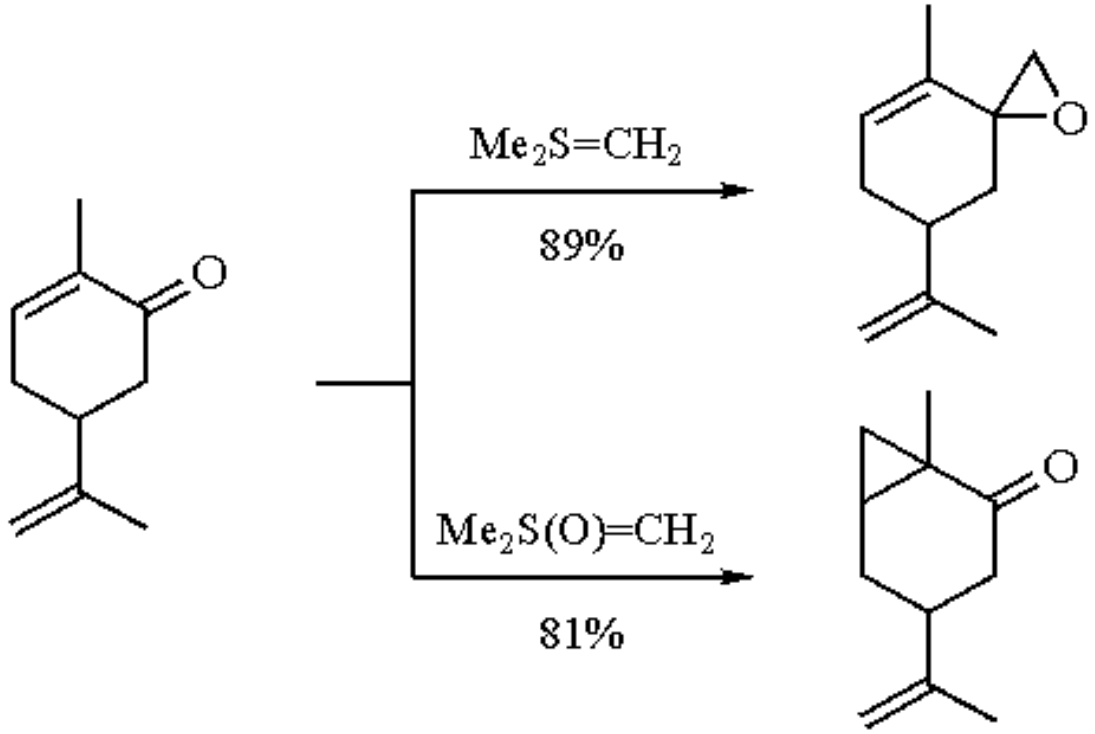

(4)

Similarly, selective oxirane formation was achieved in the cases of other α,β-unsaturated ketones such as eucarvone (93%), benzalacetone (87%), and pulegone (90%).[1b]

Epoxidation of β-ionone can also be achieved by the treatment of a mixture of trimethylsulfonium chloride (24 g), β-ionone (38.4 g), CH_2Cl_2 (100 mL), and ***Benzyltriethylammonium Chloride*** (1 g) with aqueous NaOH (18 M, 125 mL) at rt (eq 5).[6]

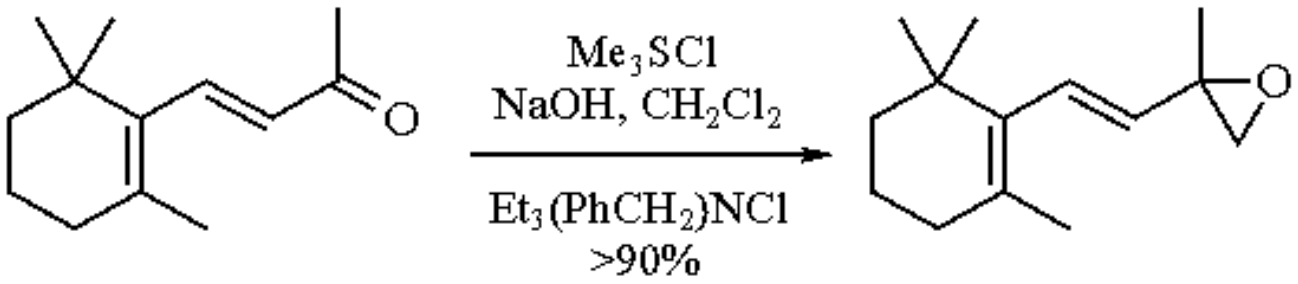

(5)

No epoxide is obtained, however, by reaction of β-ionone with dimethylsulfonium methylide generated by the conventional methods using other trimethylsulfonium halides[5,7] or trimethylsulfonium methylsulfate[4] as a precursor.

Dimethylsulfonium methylide undergoes stereoselective addition of two methylene units to 9,10-anthraquinone to afford the corresponding *trans*-bisepoxide (eq 6).[8]

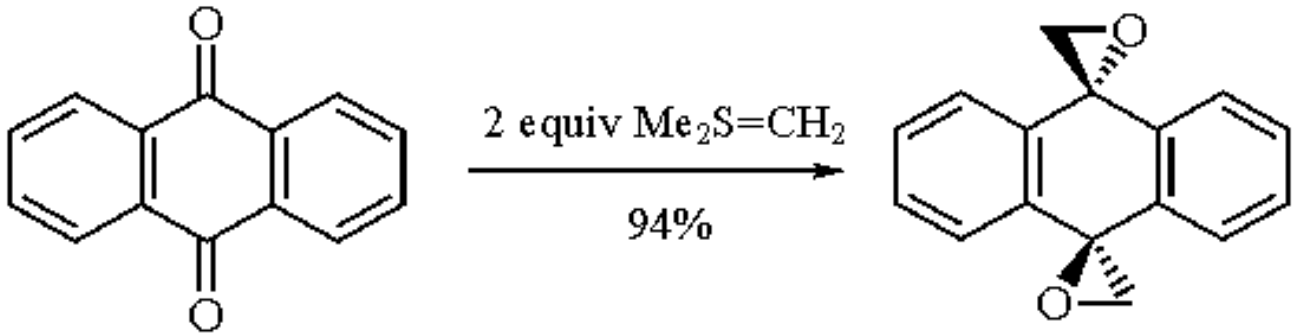

(6)

Asymmetric Oxirane Synthesis.

A striking asymmetric synthesis of 2-phenyloxirane can be achieved by the reaction of benzaldehyde and dimethylsulfonium methylide generated from trimethylsulfonium iodide in 50% NaOH with the chiral phase-transfer catalyst (-)-*N*,*N*-dimethylephedrinium bromide (0.2 equiv) (eq 7).[9]

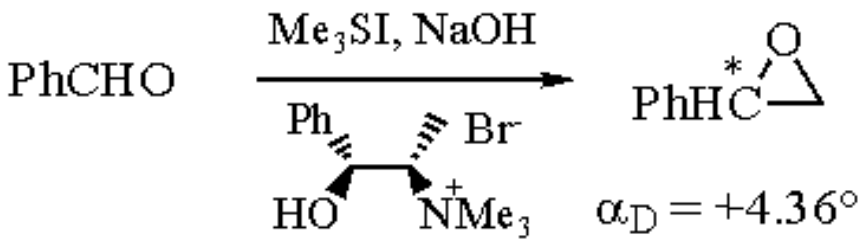

(7)

The optical yield of oxirane in eq 7 is 67%. If the asymmetric salt derived from ψ-ephedrine is used, the enantiomeric oxirane is formed preferentially. In this system the choice of the solvent is important. Little asymmetric induction is observed with THF or acetonitrile as solvent, while the use of benzene results in a high degree of induction.

Synthesis of Butenolides.

The reaction of a cyclic α-keto ketene dithioacetal with dimethylsulfonium methylide followed by acid hydrolysis produced the corresponding butenolide in high yield (eq 8).[10]

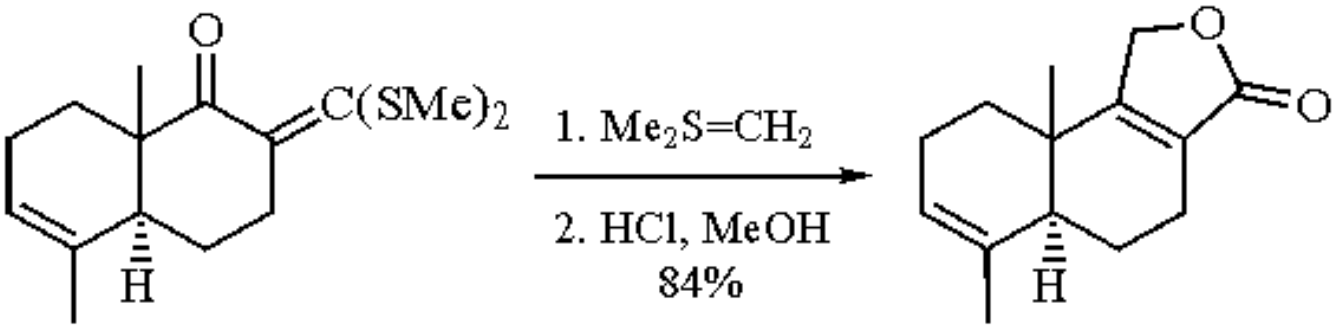

(8)

The reaction of dimethylsulfonium methylide with acyclic α-keto ketene dithioacetals also provides a simple synthesis of dihydrofurans, which can be converted into various furans and butenolides (eqs 9 and 10).[11]

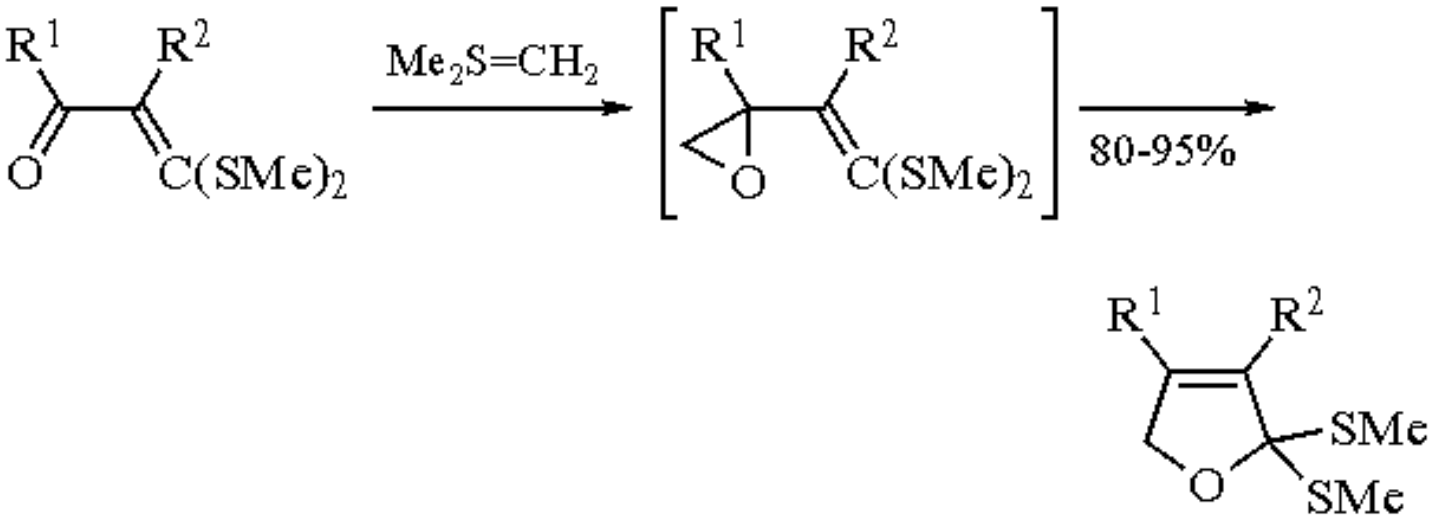

(9)

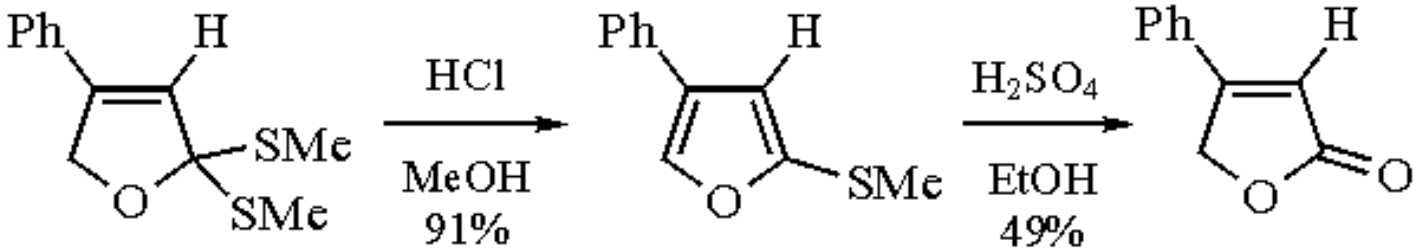

(10)

Cyclopropanation via Methylene Transfer to Carbon-Carbon Double Bonds.

In contrast to α,β-unsaturated ketones, ethyl cinnamate, an α,β-unsaturated carboxylic acid ester, was transformed into 2-phenyl-1-cyclopropane carboxylate (eq 11).[1d]

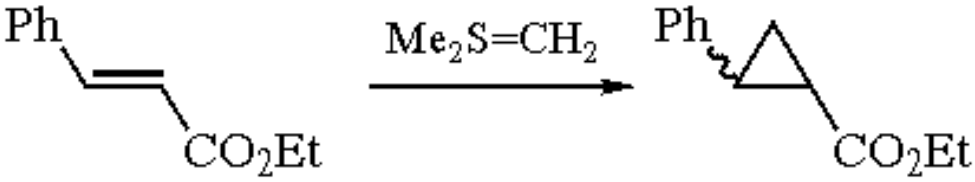

(11)

Since dimethylsulfonium methylide is a far more powerful methylene transfer reagent than dimethylsulfoxonium methylide, it can convert 1,1-diphenylethylene into 1,1-diphenylcyclopropane in 60% yield though it is necessary to use an excess amount of methylide (5 equiv) (eq 12).[1b] However, dimethylsulfonium methylide is inactive toward tolan or *trans*-stilbene, and unreactive toward nonconjugated carbon-carbon double bond compounds.

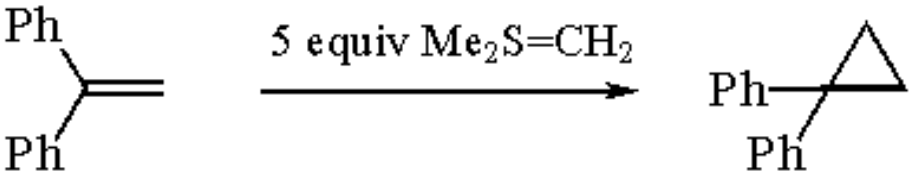

(12)

Methylation of Aromatic Rings.

Dimethylsulfonium methylide reacts with acenaphthylene in DMSO-THF to give 3-methylacenaphthylene together with some 5-methylacenaphthylene (eq 13).[12] Similarly, fluoranthrene gives a mixture of 1- and 3-methylfluoranthrenes upon treatment with dimethylsulfonium methylide (eq 14).[12]

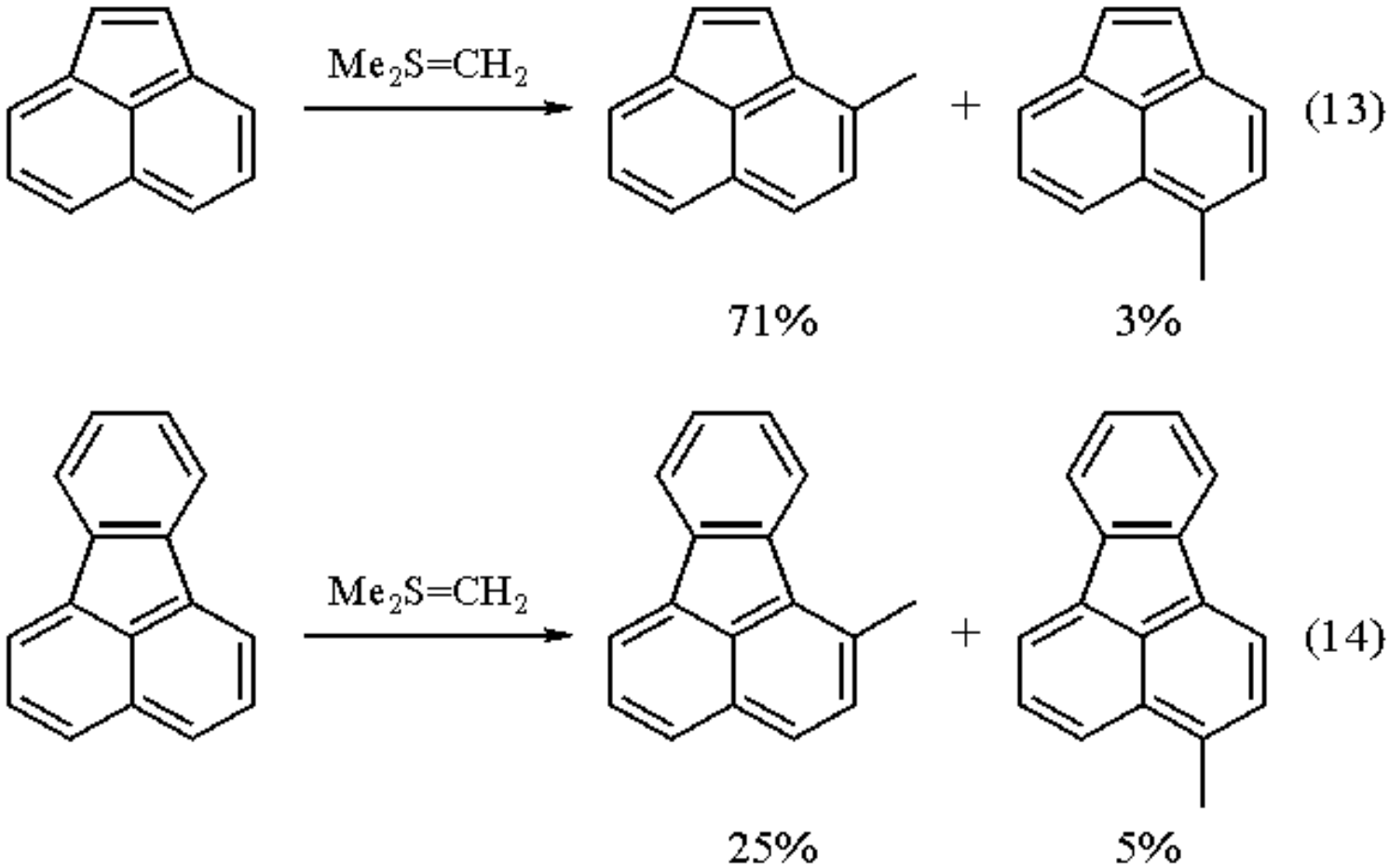

N-Methylation of Indoles.

Indoles can be selectively *N*-methylated by dimethylsulfonium methylide in THF at rt (eq 15).[13]

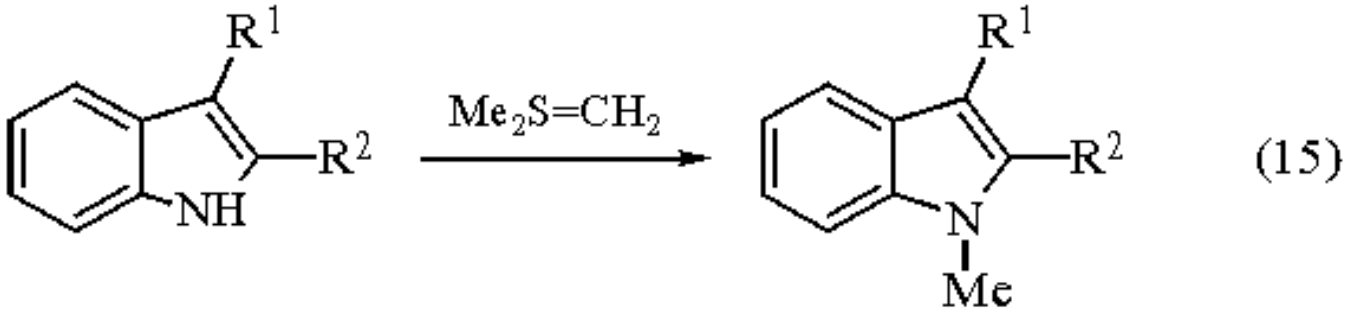

Aziridine Formation.

Dimethylsulfonium methylide reacts smoothly with imines. For example, benzalaniline can be converted to the

corresponding aziridine in 91% yield (eq 16).[1b,d]

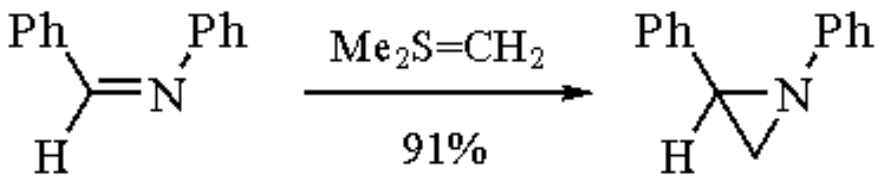

(16)

Using this methodology, the first known heterocyclic analog of bicyclobutane, 3-phenyl-1-azabicyclo[1.1.0]butane, has been obtained by the reaction of 3-phenyl-2*H*-azirine with dimethylsulfonium methylide in dry THF at -10 °C (eq 17).[2]

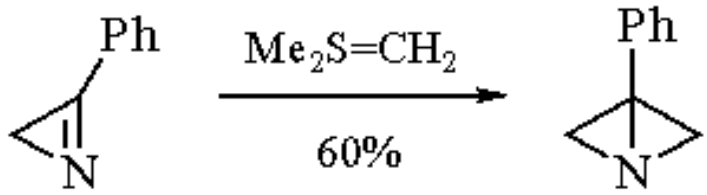

(17)

Alkene Formation.

Dimethylsulfonium methylide reacts with benzyl chloride in the presence of excess amount of base to give styrene (eq 18).[1d]

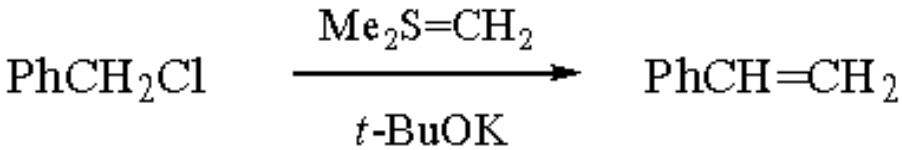

(18)

Related Reagents.

Dimethylsulfoxonium Methylide.

---

1. (a) Corey, E. J.; Chaykovsky, M. *JACS* **1962**, *84*, 3782. (b) Corey, E. J.; Chaykovsky, M. *JACS* **1965**, *87*, 1353. (c) Franzen, V.; Driesen, H. E. *TL* **1962**, 661. (d) Franzen, V.; Driesen, H. E. *CB* **1963**, *96*, 1881.
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3. Corey, E. J.; Chaykovsky, M. *JACS* **1962**, *84*, 866.
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5. Merz, A.; Märkl, G. *AG(E)* **1973**, *12*, 845.
6. Rosenberger, M.; Jackson, W.; Saucy, G. *HCA* **1980**, *63*, 1665.
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11. (a) Okazaki, R.; Negishi, Y.; Inamoto, N. *CC* **1982**, 1055. (b) Okazaki, R.; Negishi, Y.; Inamoto, N. *JOC* **1984**, *49*, 3819.

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13. Bravo, P.; Gaudiano, G.; Umani-Ronchi, A. *G* **1970**, *100*, 652.

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Dimethyl Sulfoxide[1]

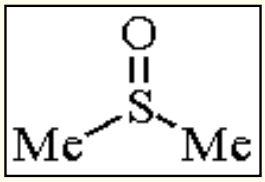

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide · (MW 78.13)

(polar aprotic solvent: acidity scale;[2] displacement reactions;[3-11] dealkoxycarbonylations;[12-21] oxidations[22-31])

Alternate Name: DMSO.

Physical Data: mp 18.4 °C; bp 189 °C; *d* 0.917 g cm^{-3}.

Solubility: miscible with water and numerous organic solvents in all proportions.

Form Supplied in: colorless, odorless liquid; widely available. *Drying:* anhyd material available by vacuum distillation from calcium hydride.

Handling, Storage, and Precautions: is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with ***Potassium Permanganate*** solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C.

Solvent.

Acidity Scale.

Equilibrium acidities for numerous compounds in DMSO (pK_a = 35.1) as the solvent have been determined. These acidities provide fundamental data for the evaluation of electronic and steric effects which occur on structural modification in organic molecules. The comparison of structural effects of acidities in DMSO with those found in the gas-phase are important in understanding solvation effects.[2]

Displacement Reactions.

Regiospecific displacement reactions are fundamental synthetic procedures for functional group interconversions. Although the rates of nucleophilic displacement reactions are dependent on solvent, substrate structure, nucleofuge, and nucleophile, the particular property of DMSO (and other polar aprotic solvents) is partially based on its ability to solvate cationic species. In effect, this leads to a less solvent-encumbered and more nucleophilic anion than in protic media.[3] The order of anion nucleophilicity can be reversed in the change from a protic solvent ($I^- > F^-$) to DMSO ($F^- > I^-$). Numerous nucleophiles such as acetylides, azide, cyanide, halides, carboxylates, hydroxide, and alkoxides have been used in DMSO for displacement reactions. Hydroxide and alkoxide anions exhibit a dramatic enhancement in basicity in DMSO relative to protic media.

Representative displacements (S_N2) are the conversion of the ditosylate to the dichloride (eq 1)[4] and the formation of large-ring macrocycles by intramolecular cyclizations of o-bromocarboxylic acids (eq 2).[5]

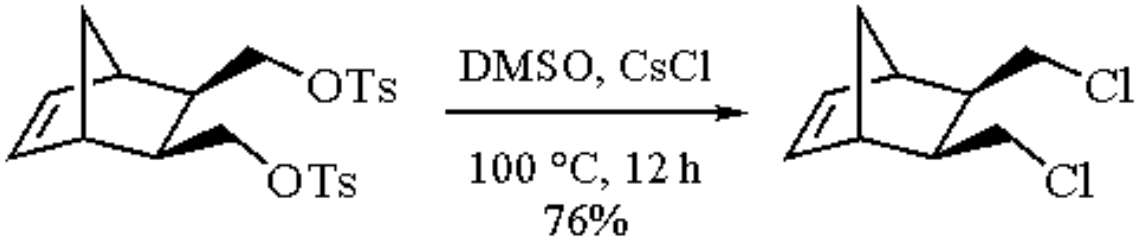

(1)

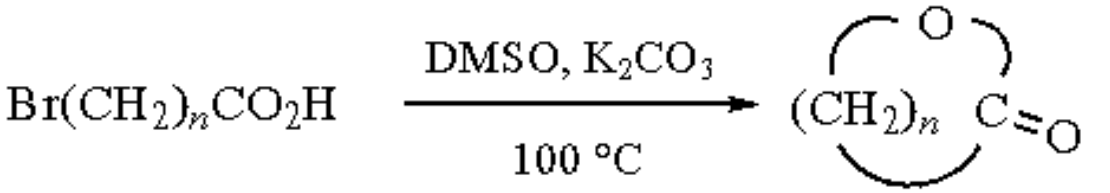

(2)

$n = 10$, 79-83%
$n = 14$, 95%
$n = 16$, 95%

Monosubstituted aryl fluorides can be prepared via S_NAr displacements of chloride from activated aryl chlorides (eq 3).[6]

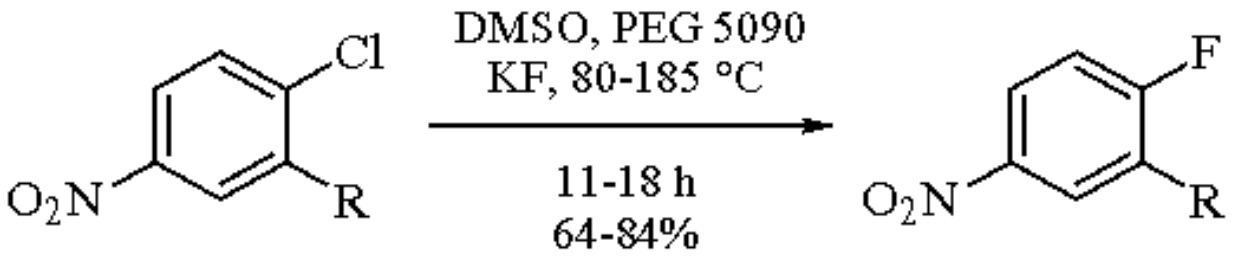

(3)

R = H, Cl, CO_2Me, COPh, CN

The N-benzylation of indole was readily accomplished by treatment with ***Benzyl Bromide*** in the presence of ***Potassium Hydroxide*** in DMSO at rt.[7]

Since the cyanide group is a synthon for a carboxyl group and related derivatives, cyanations in DMSO are valuable synthetic transformations for the conversions of appropriate alkyl halides or tosylates to nitriles.[8] The conversion of a chiral propyl tosylate to a chiral nitrile has been reported (eq 4).[9]

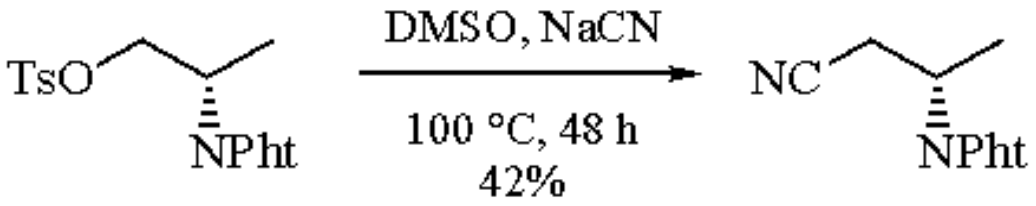

(4)

Neutral nucleophiles such as amines in DMSO effect faster displacements than in comparable reactions performed in protic media.[10] Treatment of an α-bromo ester with ***Ammonia*** in DMSO at rt yielded the α-amino ester (eq 5).

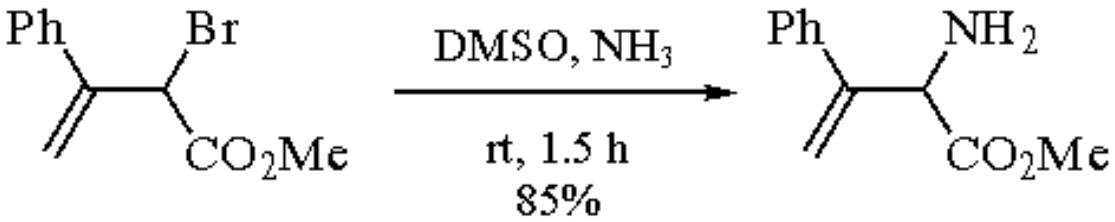

(5)

Sodium Borohydride in DMSO is an effective source of hydride anion for reductive displacements of halide or sulfonate groups.[11] The selective removal of halide in the presence of an ester functionality was shown in the reduction of ethyl 2-bromohexanoate to ethyl hexanoate (86% yield, $NaBH_4$, DMSO, 15 °C, 0.75 h).

Dealkoxycarbonylations.

Activated substrates such as malonate esters (see ***Ethyl Malonate***), β-keto esters (see ***Ethyl Acetoacetate***), and α-cyano esters (see ***Ethyl Cyanoacetate***) find extensive utility in synthesis. The presence of these types of functionality lowers the pK_a of the adjacent C-H bond, and deprotonation can be effected by relatively weak and inexpensive bases. The regioselective C-alkylation (or treatment with other electrophilic agents) of these enolates leads to the incorporation of a new C-C bond. The regiospecific substitution of the alkoxycarbonyl group by hydrogen (or other groups such as alkyl) is then desirable. Traditionally, this transformation has been performed via a basic or acidic hydrolysis of the substrate followed by thermolysis of the resultant diacid or acid. In commencing from malonate esters, a reesterification is then necessary to obtain the monoester. Substrates which bear other acidic or base-sensitive groups cannot be utilized in the hydrol ysis-decarboxylation procedure.

A useful methodology for the dealkoxycarbonylations of malonate esters, β-keto esters, α-cyano esters and α-alkyl- or arylsulfonyl esters to prepare esters, ketones, nitrile, and sulfonyl analogs, respectively, has recently been developed.[12] This preparative procedure simply involves heating the substrate with water, or with water with added salts in a polar aprotic solvent such as DMSO (other aprotic solvents such as ***N,N-Dimethylformamide*** or ***Hexamethylphosphoric Triamide*** have found some use). Many salts have been utilized including sodium chloride, ***Lithium Chloride***, ***Sodium Cyanide***, and magnesium chloride.[12] The mechanistic pathways for the dealkoxycarbonations are highly dependent on substrate structure.

Some monosubstituted malonate esters and β-keto esters undergo dealkoxycarbonylation in water-DMSO (eq 6). Selective dealkoxycarbonylations have been found for mixed malonate esters.[12b]

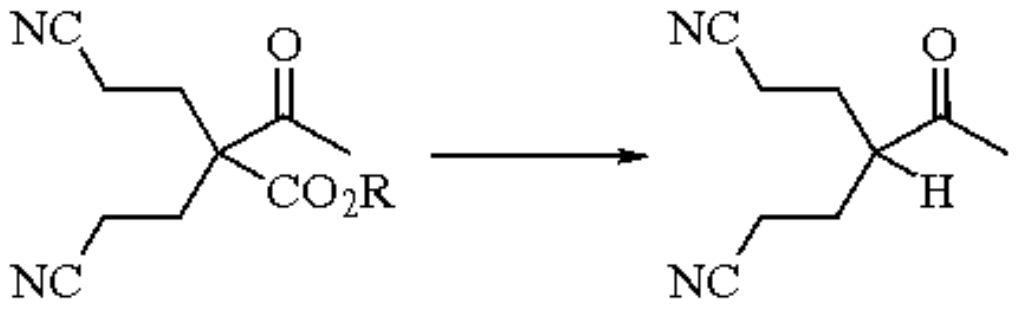

(6)

(a) R = Et
(b) R = *t*-Bu

(a) DMSO, H_2O, LiCl; 60%
no LiCl; 10%
(b) R = DMSO, H_2O, 60%

The synthetic utility of the DMSO/salt/water dealkoxycarbonylations can be illustrated by some recent applications. In a total synthesis of racemic β-vetivone, the chemoselective demethoxycarbonylation of a β-keto ester in the presence of another ester functionality was readily accomplished (eq 7).[13] The silyl protective group was stable to the reaction conditions.

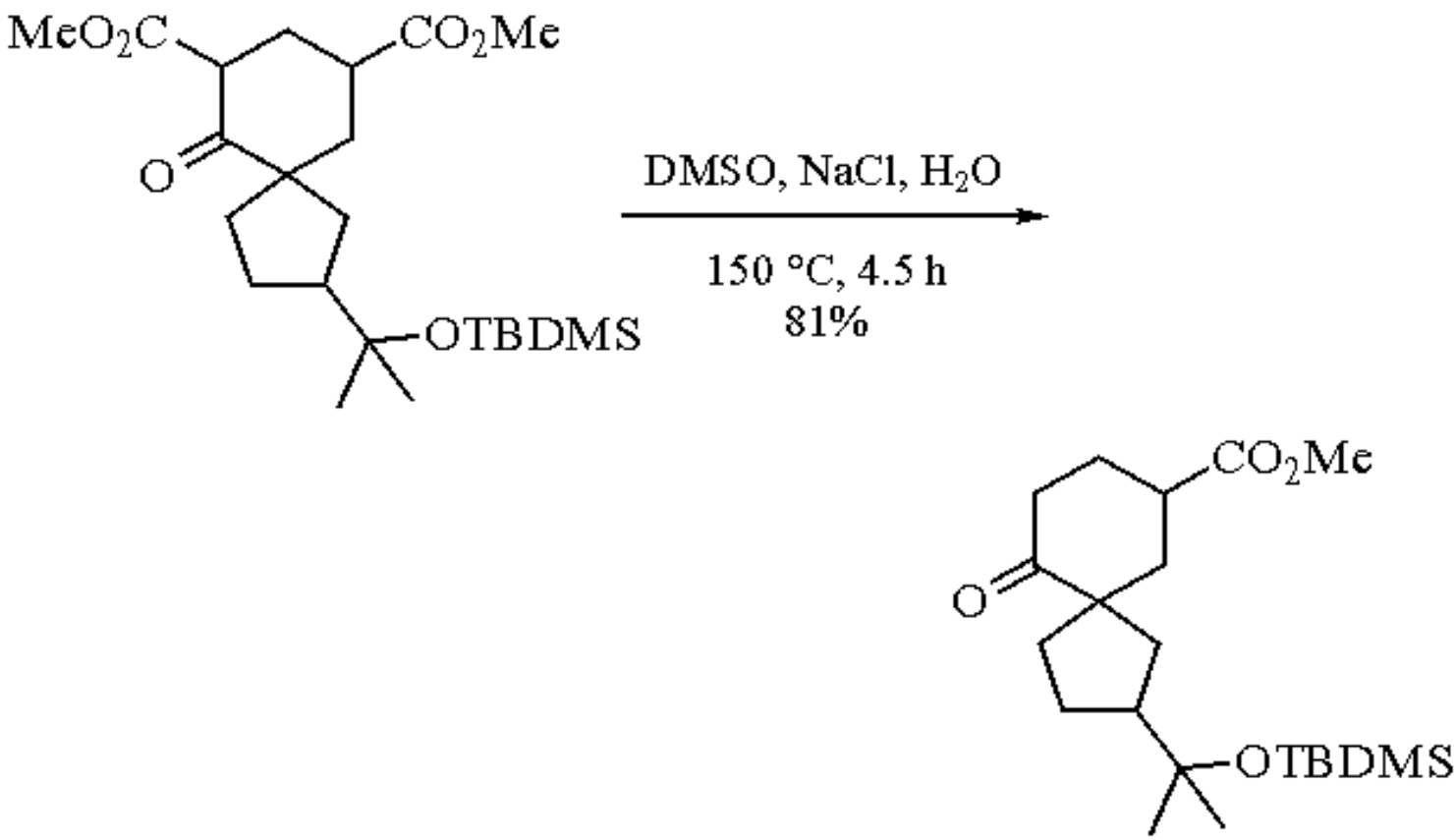

(7)

The demethoxycarbonylation of a β-keto ester led to racemic β-vetivone and epi-β-vetivone, from which pure racemic β-vetivone could be obtained by chromatography (eq 8).

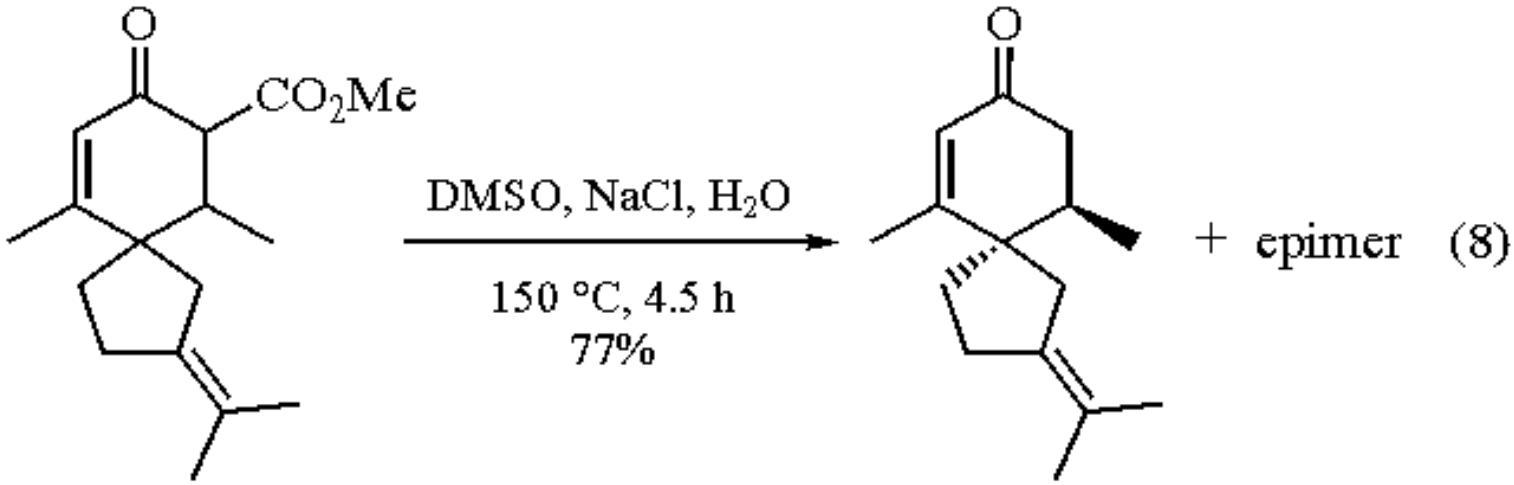

In synthetic pathways to chiral α- and β-cuparenones, the demethoxycarbonylation of a β-keto ester in the presence of a benzyl ester was performed using ***Sodium Iodide*** in DMSO (eq 9).[14]

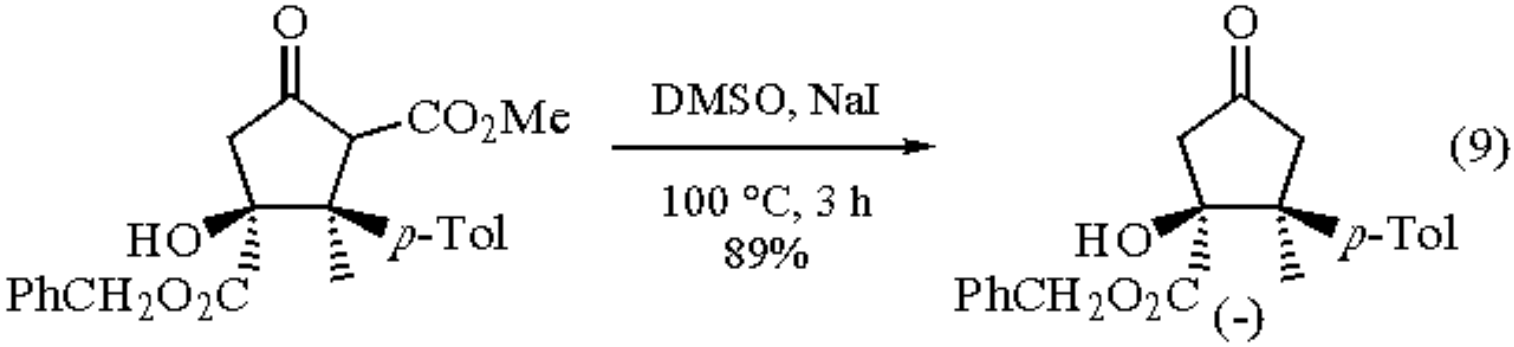

In a synthetic route leading to carbovir, the deethoxycarbonylation of a substituted α-nitro acetate analog was successful (eq 10).[15]

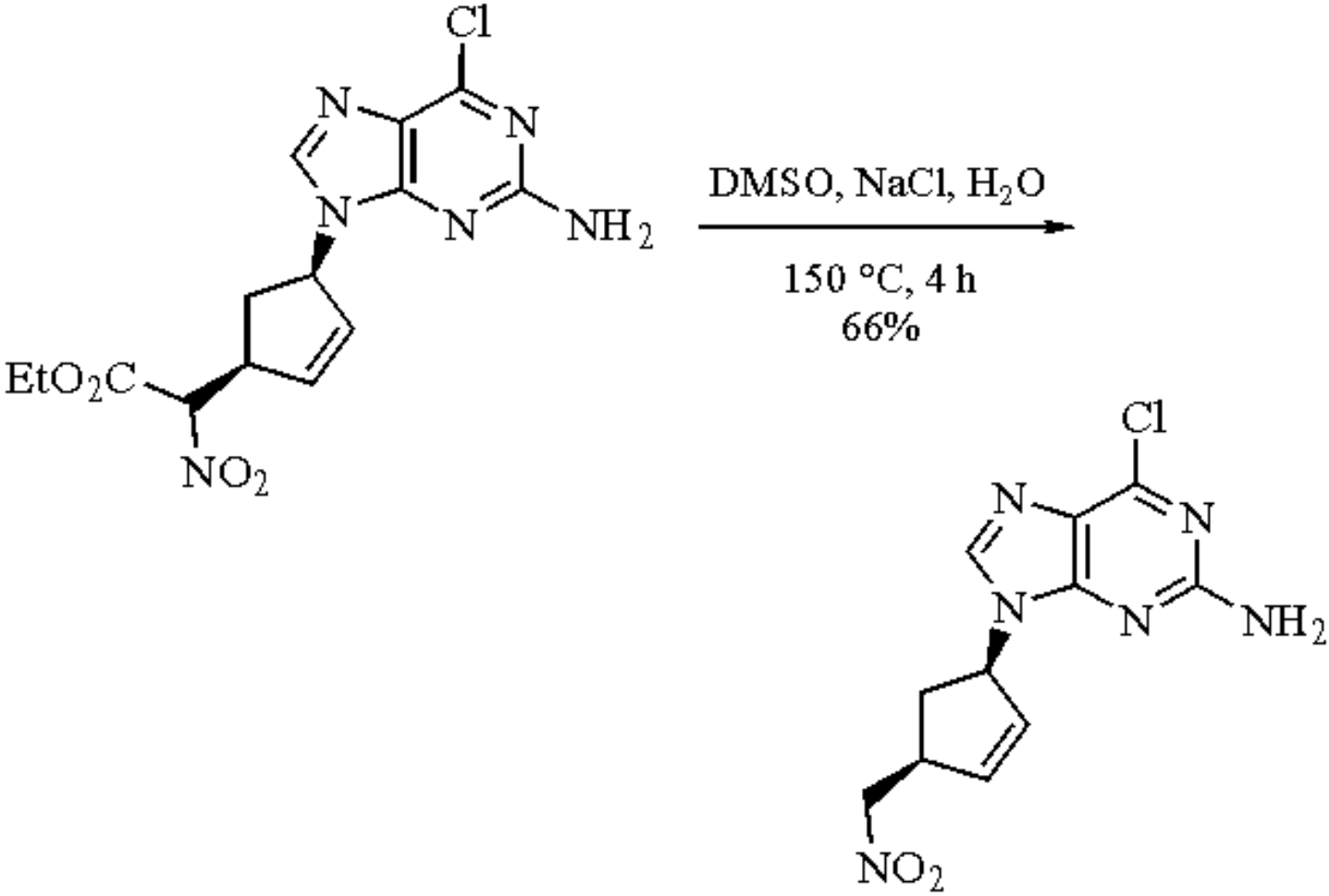

(10)

In a route to furanoid terpenes (eq 11)[16] and in a synthetic step leading to the pheromone of the monarch butterfly (eq 12)[17], substituted malonate esters have been readily demethoxycarbonylated.

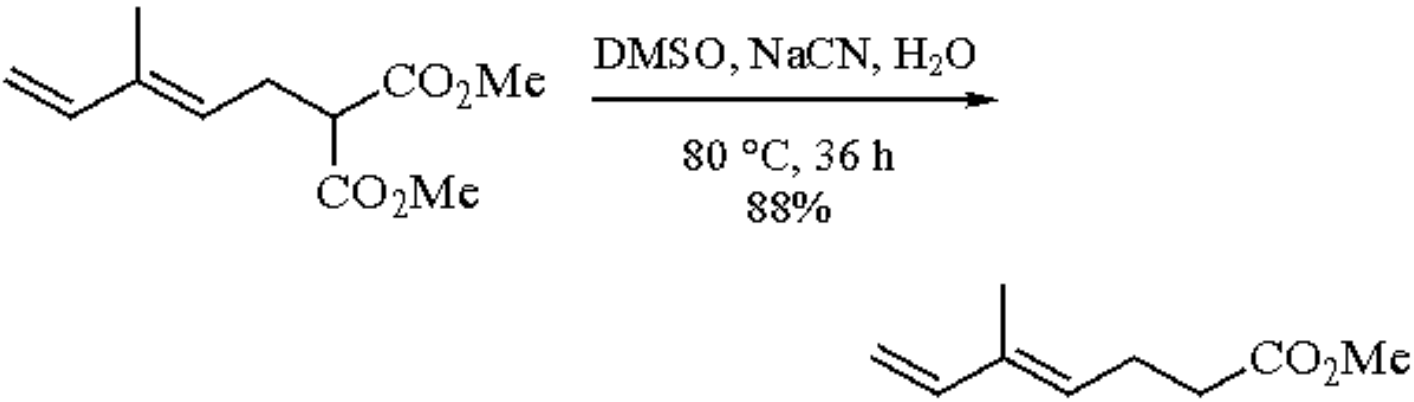

(11)

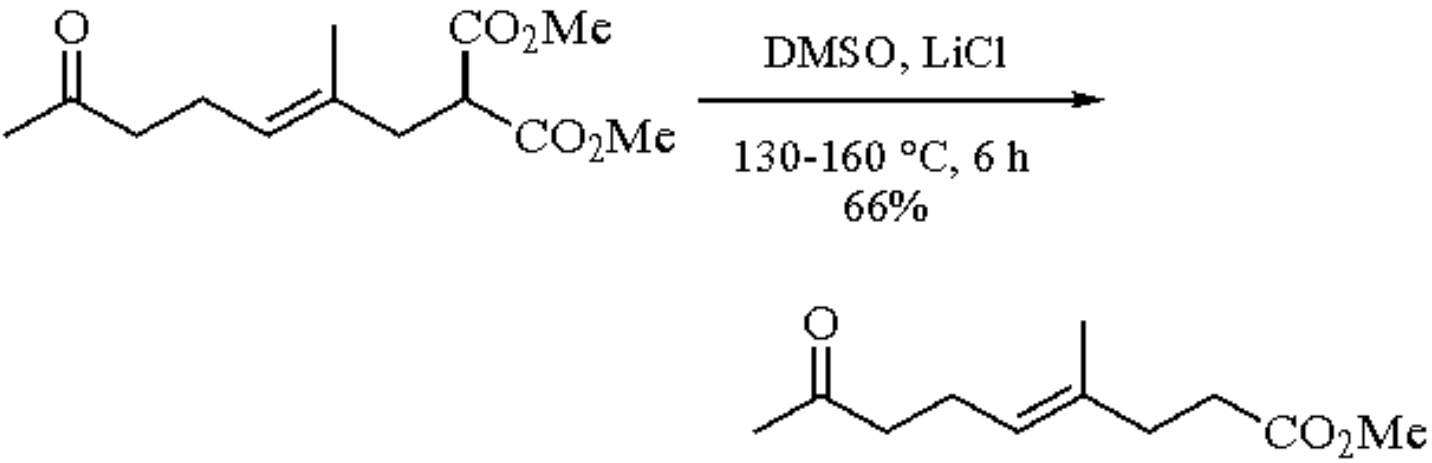

(12)

The chemoselective removal of the malonate ester from a triester has been reported (eq 13).[18]

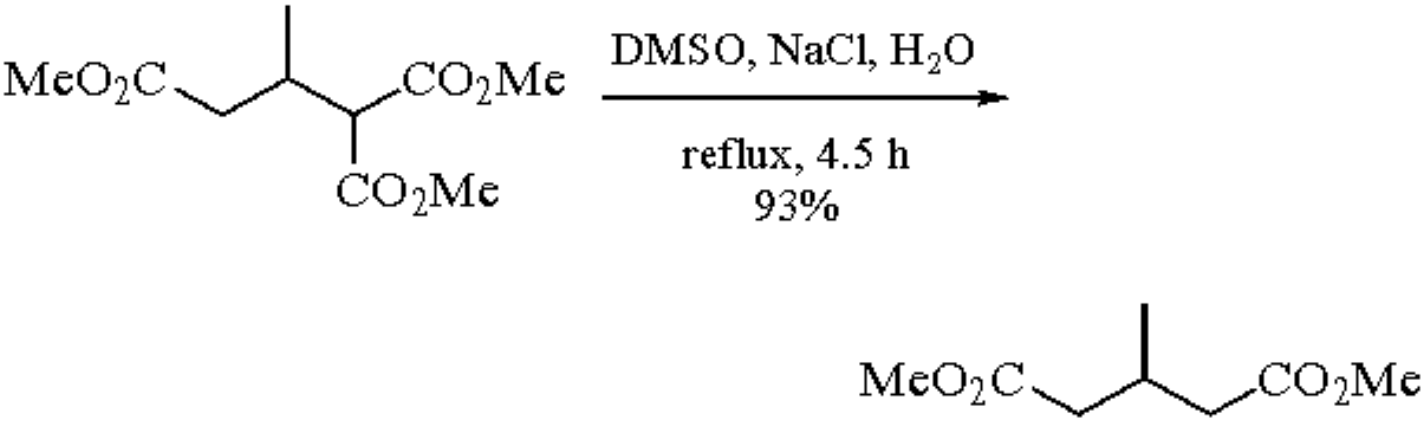

(13)

The demethoxycarbonylation of a phenyl sulfoxide substituted cyclopropyl malonate ester was reported to occur with 100% (*E*) diastereoselectivity (eq 14).[19]

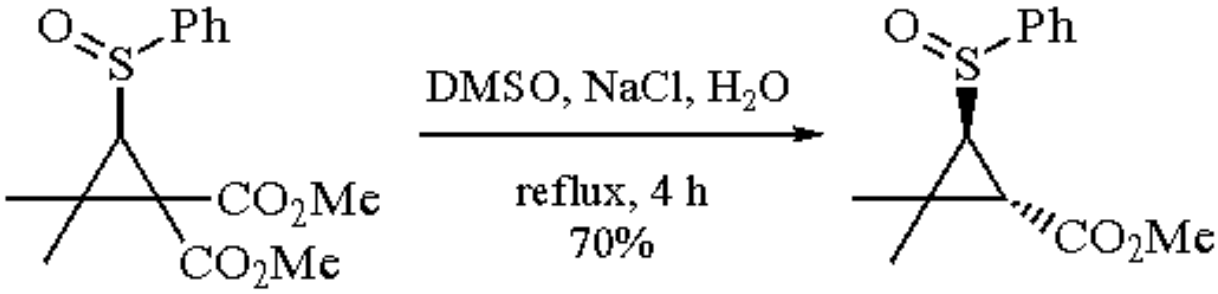

(14)

In a pathway to erythrina alkaloids, a β-keto ester was deethoxycarbonylated with magnesium chloride in DMSO (eq 15).[20]

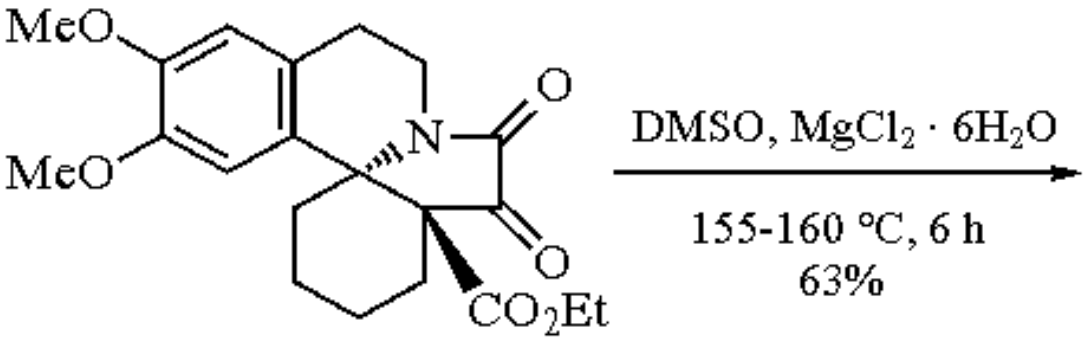

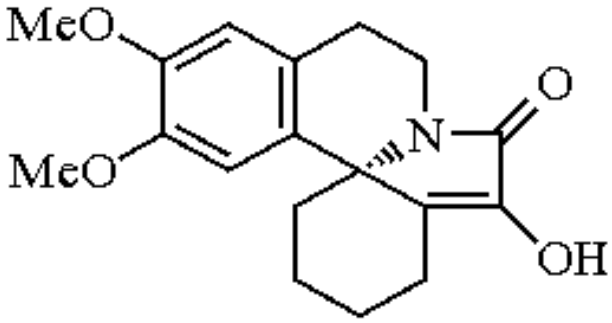

(15)

The deethoxycarbonylation of an α-cyano ester was also readily accomplished (eq 16).[21]

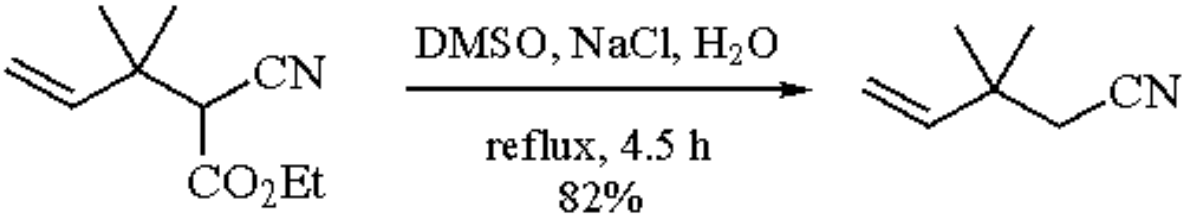

(16)

Oxidations.

The conversions of alkyl halides or tosylates to the corresponding aldehydes or ketones using DMSO as the oxidizing agent has found some synthetic application.[22] Reactive halides or tosylates react with DMSO, initially forming the *O*-alkyl analogs which generally rearrange to the more stable oxosulfonium salts. If the *O*-alkyl intermediates undergo a facile elimination of dimethyl sulfide, carbonyl compounds are formed. This methodology was discovered by Kornblum and co-workers, who reported that α-bromo ketones were transformed into α-keto aldehydes by treatment with DMSO at rt.[23] Other investigators reported similar transformations.[24]

Benzyl halides are readily converted on heating in DMSO into the corresponding aldehydes (eq 17).[25]

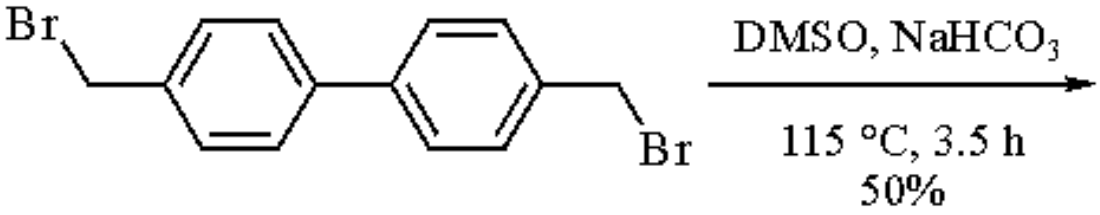

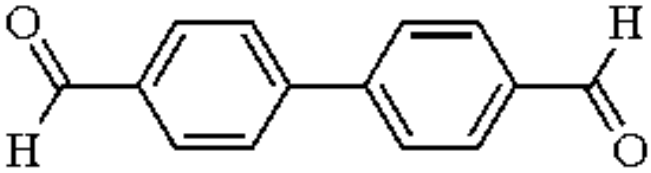

(17)

Benzylic tosylates can be converted to the corresponding aldehydes by treatment with DMSO in the presence of sodium bicarbonate at 100 °C for 5 min. Saturated primary halides can be converted to the tosylates and then oxidized by treatment with DMSO at 150 °C for a short period.[23b]

Although simple alkyl chlorides or bromides are inert to DMSO even at high temperatures, the conversion of 3-bromonortricyclene to nortricyclanone (69%) was accomplished by treatment with ***Silver(I) Tetrafluoroborate*** in DMSO for 1 h at rt followed by addition of ***Triethylamine***.[26] This silver-assisted DMSO oxidation procedure was studied more extensively and is a useful procedure for the synthesis of aldehydes and some ketones.[27] The conversion of 1-bromobutane to butanal (83%) can be effected by a solution of $AgBF_4$ in DMSO at room temperature.

Since the direct oxidation of aliphatic iodides can be accomplished using DMSO and sodium bicarbonate at 150 °C,[28] the oxidation of alkyl chlorides or bromides with DMSO has been performed in the presence of ***Sodium Iodide***.[29] For example, treatment of 1-chloro- or 1-bromooctane with DMSO in the presence of sodium bicarbonate and NaI and heating the mixture at 105-115 °C for 1-2 h leads to octanal (73 and 60%, respectively).

Benzylamine hydrobromides and benzyl trialkyl quaternary salts can be oxidized to the corresponding aldehydes by DMSO.[30] The oxidation of benzylamine hydrobromide with DMSO at 100-160 °C yielded benzaldehyde (95%).

The oxidation of aryl- or alkyl-substituted oxiranes by DMSO in the presence of molecular sieves and a catalytic amount of ***Trifluoroacetic Acid*** leads to α-hydroxy ketones (eq 18).[31]

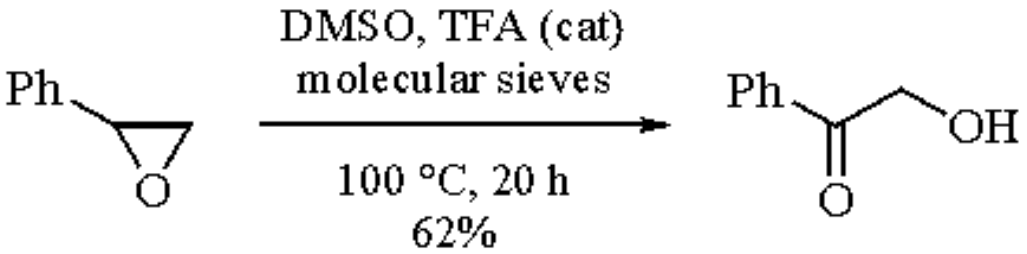

(18)

Related Reagents.

See the articles immediately following and ***N,N´-Dimethylpropyleneurea***; ***Hexamethylphosphoric Triamide***; ***1-Methyl-2-pyrrolidinone***; ***Potassium t-Butoxide-Dimethyl Sulfoxide***; ***Potassium Hydroxide-Dimethyl Sulfoxide***; ***Potassium***

Methoxide-Dimethyl Sulfoxide; ***RS029-***.

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A. Paul Krapcho

Dimethyl Sulfoxide-Acetic Anhydride[1]

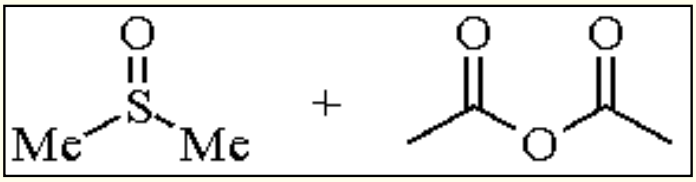

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Acetic Anhydride · (MW 78.13) (Ac_2O)

[108-24-7] · $C_4H_6O_3$ · Dimethyl Sulfoxide-Acetic Anhydride · (MW 102.09)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with variable amounts of byproduct methylthiomethyl ethers)

Alternate Name: Albright-Goldman reagent.

Physical Data: DMSO mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. Ac_2O: mp -78 °C; bp 138-140 °C; *d* 1.082 g cm^{-3}.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. Ac_2O: sol ether, acetone, CH_2Cl_2.

Form Supplied in: colorless liquids; widely available, including anhydrous grades of DMSO packed under N_2.

Preparative Method: the active reagent, presumably Me_2+SOAc, forms slowly from a mixture of the coreactants over a period of hours at rt and reacts with the alcohol in situ.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. Ac_2O: distillation from aluminum chloride or calcium carbide.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] ***Acetic Anhydride*** is a corrosive lachrymator.

The title reagent is useful for the oxidation of primary or secondary alcohols to aldehydes and ketones, respectively, at rt without added base. The reagents are inexpensive and the procedure is adaptable to large-scale reactions, such as the oxidation of yohimbine on a 2.5 mol scale.[3] The mechanism of this reaction appears to involve formation of activated DMSO by the rather slow reaction of DMSO with Ac_2O at rt to form the acyloxysulfonium ion (**1**); this then reacts with the alcohol to give the alkoxysulfonium ion (**2**) (eq 1). By analogy to other DMSO-based oxidations, (**2**) undergoes deprotonation to (**3**), which forms the oxidation product intramolecularly (eq 2).[1a,b] A common side reaction of alcohols ROH with activated DMSO is formation of methylthiomethyl ethers $ROCH_2SMe$ (**4**), which probably arise from dissociation of (**3**) or some other activated form of DMSO to form (**5**) due to the operational temperature of 25 °C and the long reaction times (12-24 h) (eq 3). Alternatively, (**5**) could be formed by an intramolecular proton abstraction in (**1**) via a six-membered transition state. The effect of pressure on the reaction has been examined, and the large negative entropy of activation is consistent with an associative mechanism.[4] The reaction is also greatly accelerated by pressure when carried out on a preparative scale.[4] Some examples of the procedure are shown in eqs 4-6.[5a,b,c]

$$Me_2SO + Ac_2O \longrightarrow \underset{(1)}{Me_2\overset{+}{S}O_2CMe} \xrightarrow{R^1R^2CHOH} \underset{(2)}{R^1R^2CHO\overset{+}{S}Me_2} \qquad (1)$$

$$(2) \xrightarrow{base} \underset{(3)}{R^1R^2CHO\overset{+}{S}MeCH_2^-} \longrightarrow R^1R^2CO + Me_2S \qquad (2)$$

$$(3) \longrightarrow \underset{(5)}{MeSCH_2^+} \xrightarrow{ROH} \underset{(4)}{ROCH_2SMe} \qquad (3)$$

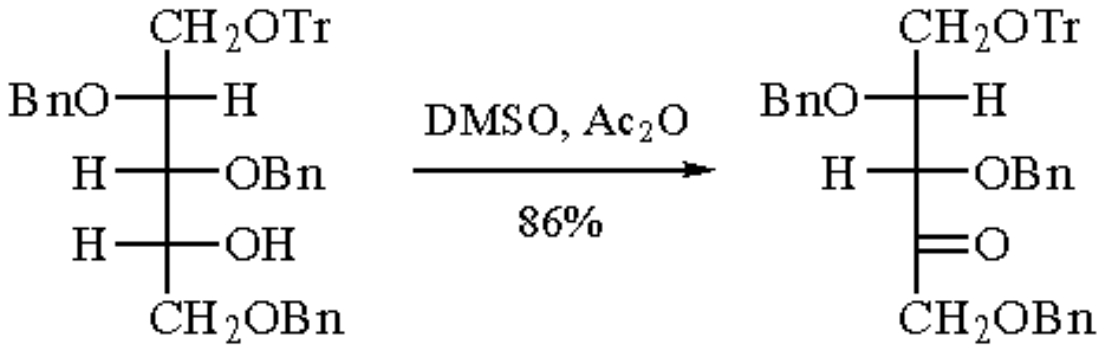

(4)

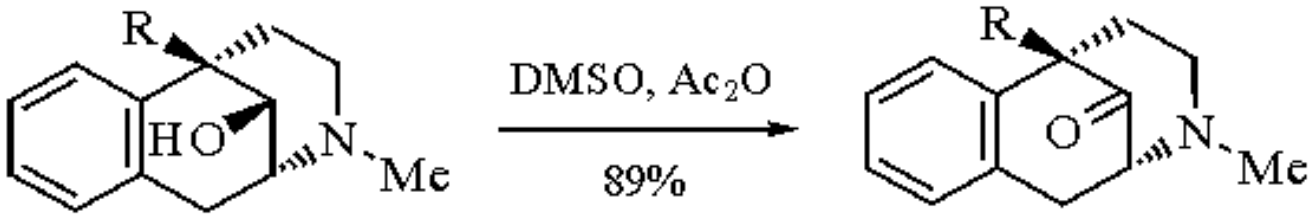

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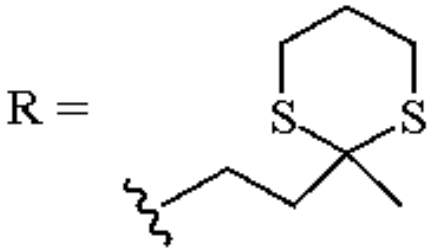

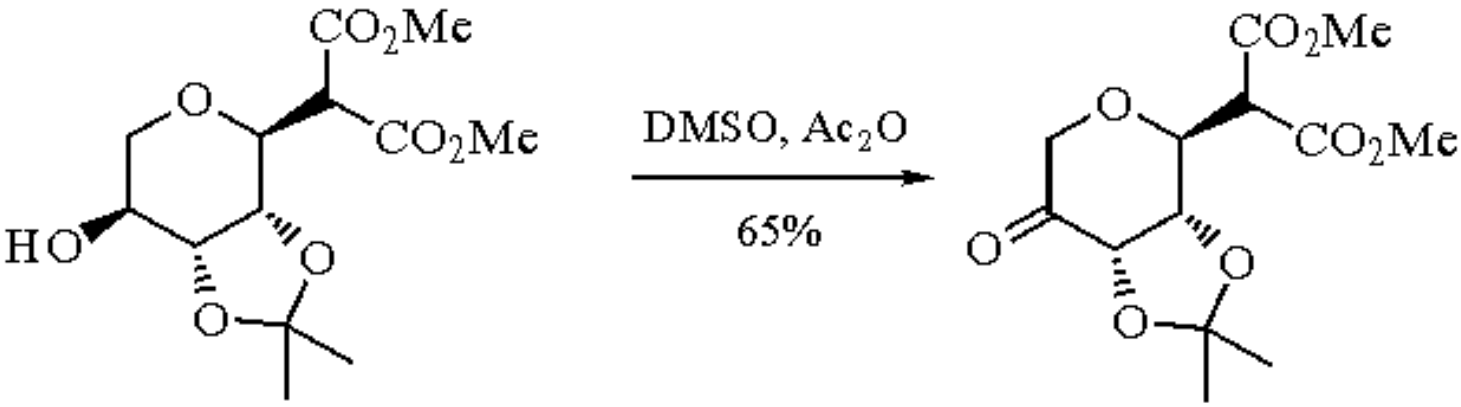

(6)

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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Dimethyl Sulfoxide-Dicyclohexylcarbodiimide[1]

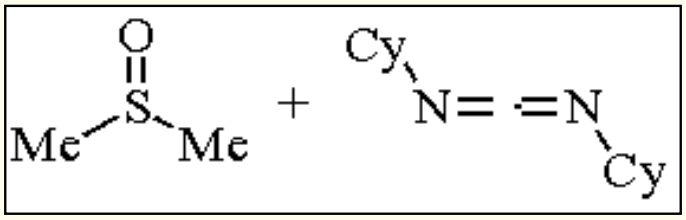

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Dicyclohexylcarbodiimide · (MW 78.13) (DCC)

[538-75-0] · $C_{13}H_{22}N_2$ · Dimethyl Sulfoxide-Dicyclohexylcarbodiimide · (MW 206.33)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with variable amounts of byproduct methylthiomethyl ethers)

Alternate Name: DMSO-DCC; Pfitzner-Moffatt reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. DCC: mp 34-35 °C; bp 122-124 °C/6 mmHg.

Solubility: DMSO: sol H_2O, alcohol, acetone, CH_2Cl_2, THF.

Form Supplied in: DMSO is a colorless liquid that is widely available, including anhydrous grades of 99%+ purity and <0.005% H_2O under N_2; DCC is a low-melting but crystalline solid that is widely available.

Preparative Method: the active oxidant, $CyNHC(O{+}SMe_2)NCy$, is generated in the presence of the alcohol substrate by the reaction of DCC, an acid, and pyridine, and reacts with the alcohol in situ.

Purification: DMSO: distillation from CaH_2 at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3&AAring; molecular sieves. DCC: distillation at reduced pressure.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] ***1,3-Dicyclohexylcarbodiimide*** is moisture sensitive and should be dry, crystalline material, otherwise it can be

distilled at 140 °C/5 mmHg;[4a] it is toxic and corrosive and should be handled with gloves in a fume hood.

The title reagent was the first of the activated DMSO reagents to be developed,[3] and offers the advantage not shared by many oxidizing methods of giving rapid oxidation at rt, without problems of overoxidation to give carboxylic acids. The disadvantages of the reagent are that the yields, though good, are not excellent, methylthiomethyl ethers occur as byproducts, and removal of the byproduct dicyclohexylurea can be a problem. The reaction mechanism has subtle differences from those of other DMSO-based oxidations and has been thoroughly documented by isotopic studies.[1a,g] The first step involves catalysis by acids such as ***Phosphoric Acid*** or ***Trifluoroacetic Acid*** in the presence of ***Pyridine*** (eq 1). Intramolecular proton abstraction via (**2**) is unique to this process, providing the ylide (**3**) (eq 2) common to all DMSO-based alcohol oxidations, which gives the carbonyl product by an intramolecular process (eq 3). In addition to previously summarized mechanistic studies, the effect of pressure on this reaction has also been examined, and the negative activation volume is consistent with an associative process.[2d]

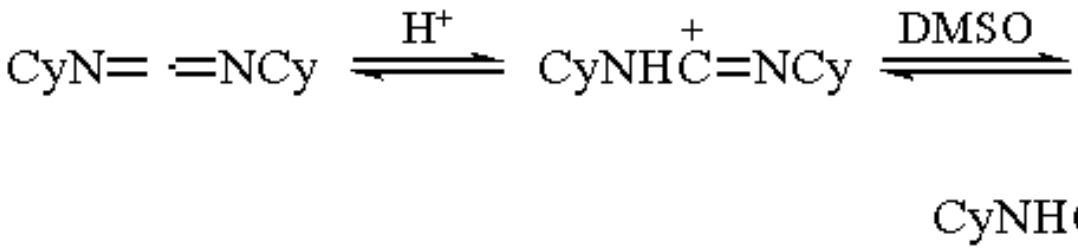

$$CyNHC(O\overset{+}{S}Me_2)=NCy \quad (1)$$

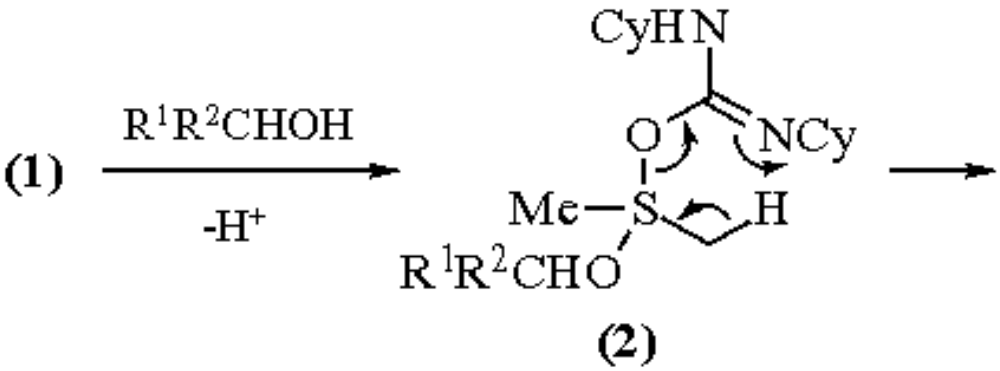

$$CyNHCONHCy + Me\overset{+}{S}(OCHR^1R^2)CH_2^- \quad (2)$$

(3)

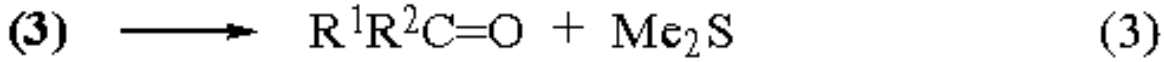

(3)

Some typical examples of this process are shown in eqs 4 and 5.[4] Water-soluble[4c] and polymeric[4d] carbodiimides have also been utilized to assist in the separation of the product from the product urea. Other recent examples shown include oxidation of a nucleoside (eq 6),[4e] formation of an α-hydroxy ketone (eq 7),[4f] and formation of a diketone (eq 8).[4g] Elimination occurs in substrates sensitive to the acidic conditions (eq 9).[4h]

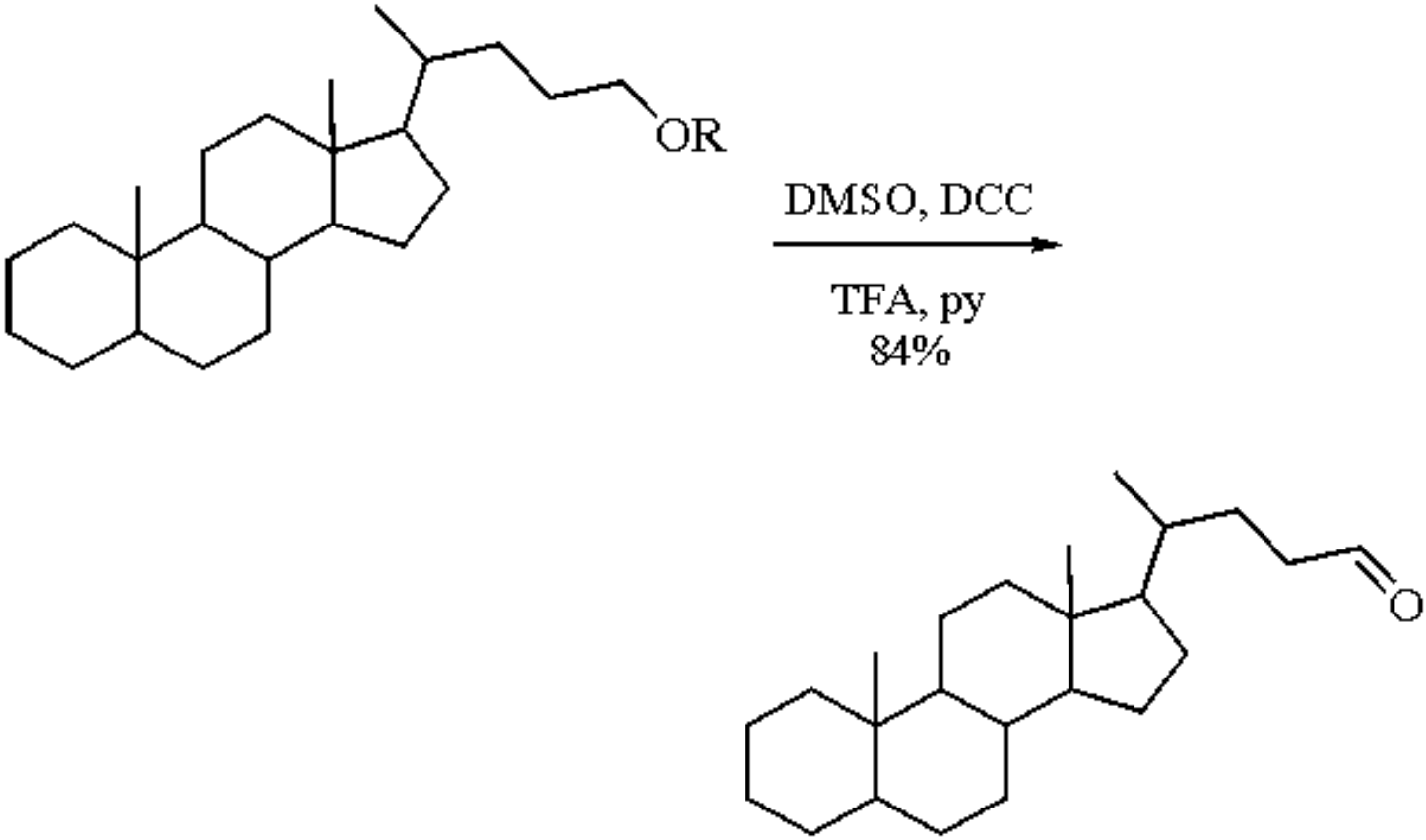
OR
DMSO, DCC
TFA, py
84%
O

(4)

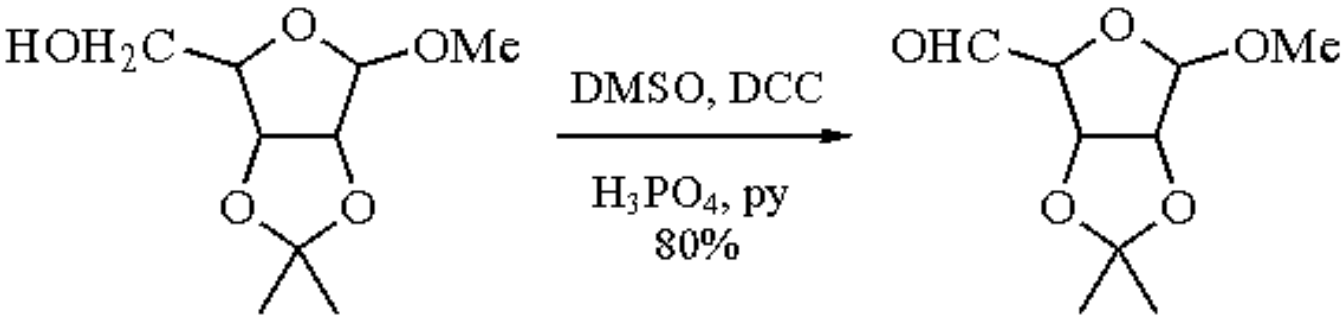
HOH2C
O
OMe
O
O
DMSO, DCC
H3PO4, py
80%
OHC
O
OMe
O
O

(5)

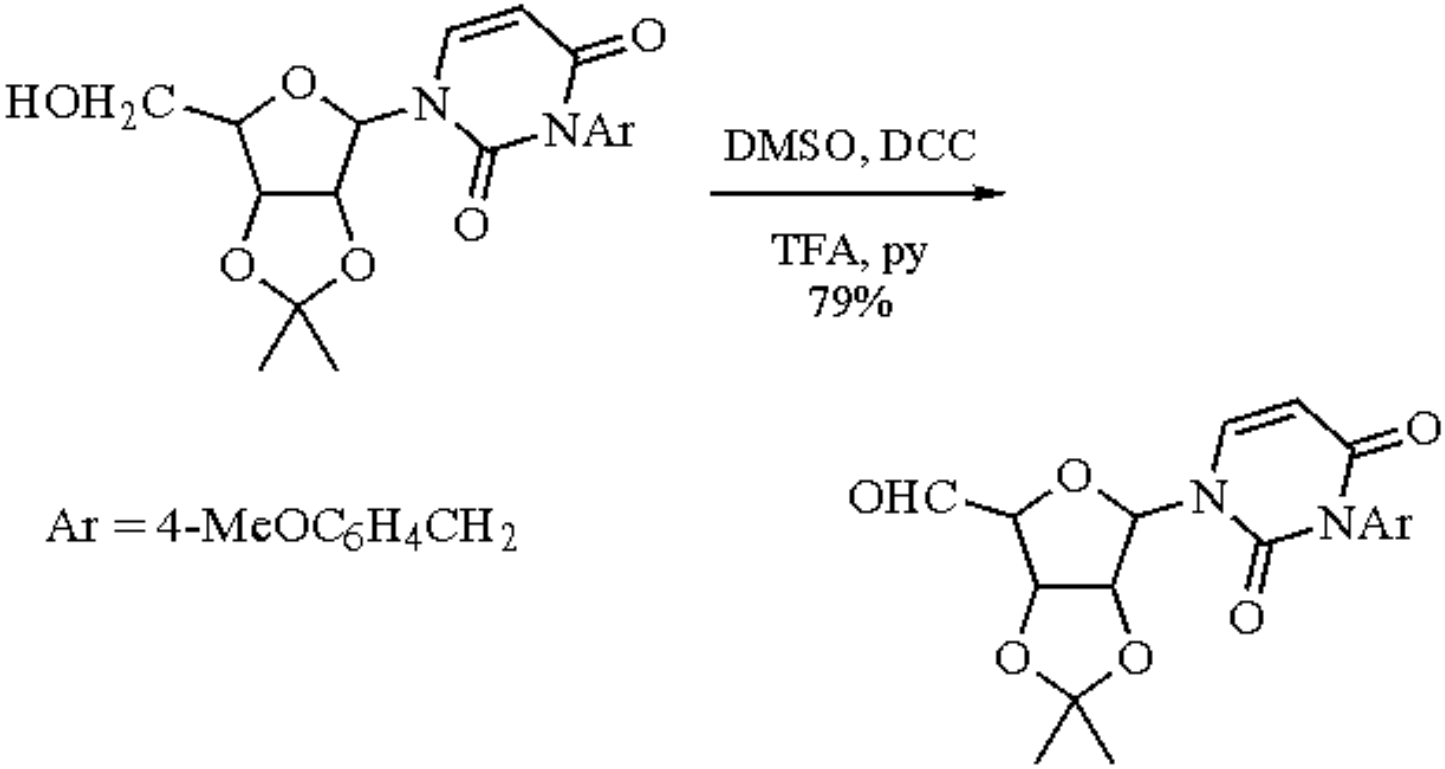

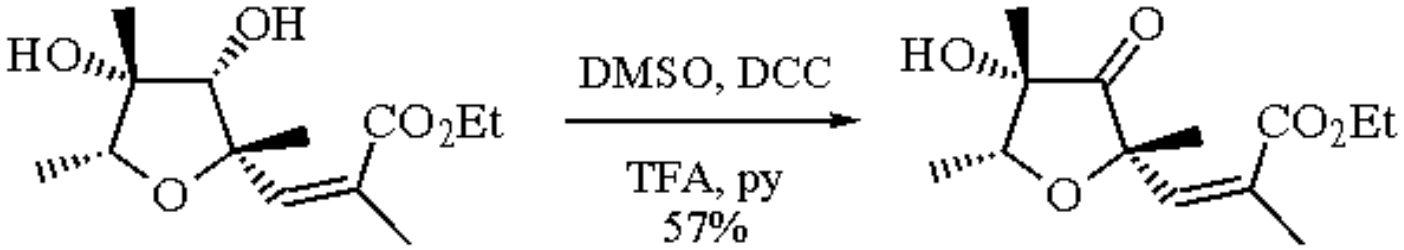

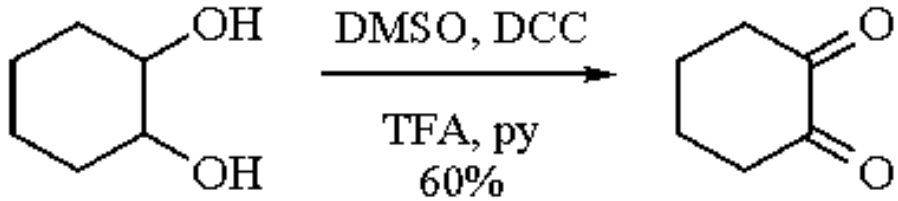

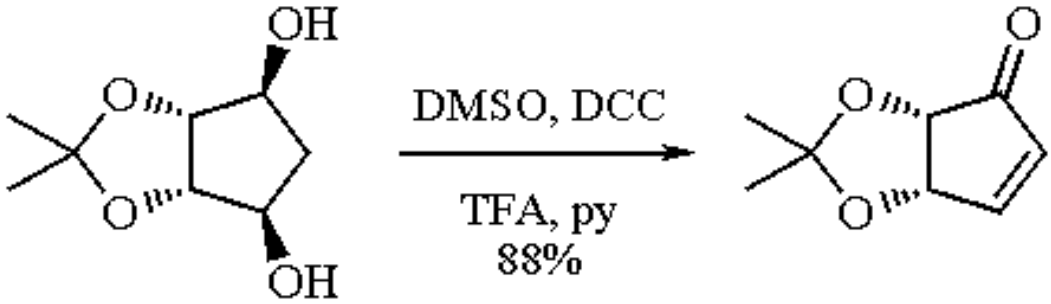

In the procedure of eq 10 the crude aldehyde from the first step was subjected directly to allylboration with (*E*)-crotyldiisopinocampheylborane (see ***B-Crotyldiisopinocampheylborane***) to give the product in 70% yield for the two steps.[5a] The product aldehydes have also been used in Wittig homologations; prior isolation of the aldehydes is required.[5b,c]

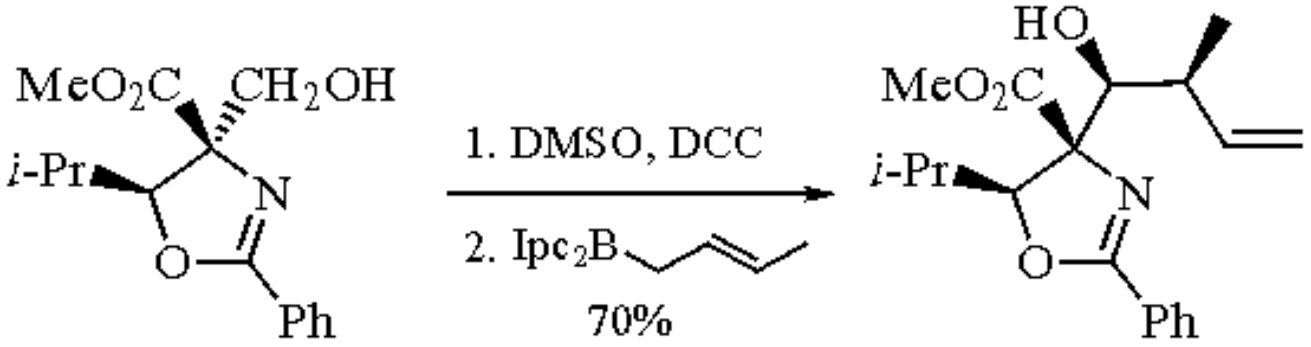

(10)

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D. *S* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.
2. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755. (d) Isaacs, N. S.; Laila, A. H. *JPOC* **1991**, *4*, 639.
3. (a) Pfitzner, K. E.; Moffatt, J. G. *JACS* **1963**, *85*, 3027. (b) Pfitzner, K. E.; Moffatt, J. G. *JACS* **1965**, *87*, 5661.
4. (a) Moffatt, J. G. *OSC* **1973**, *5*, 242. (b) Jones, G. H.; Moffatt, J. G. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; BeMiller, J. N., Eds; Academic: New York, 1972; Vol. 6, p 315. (c) Hanessian, S.; Lavallee, P. *CJC* **1981**, *59*, 870. (d) Weinshenker, N. M.; Shen, C. M.; Wong, J.-Y. *OSC* **1988**, *6*, 218. (e) Danishefsky, S. J.; DeNinno, S. L.; Chen, S.; Boisvert, L.; Barbachyn, M. *JACS* **1989**, *111*, 5810. (f) Bowden, M. C.; Pattenden, G. *TL* **1988**, *29*, 711. (g) Schobert, R. *S* **1987**, 741. (h) Johnson, C. R.; Penning, T. D. *JACS* **1988**, *110*, 4726.
5. (a) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; &OOmacr;mura, S.; Smith, A. B., III. *JACS* **1993**, *115*, 5302. (b) Jones, R. J.; Swaminathan, S.; Milligan, J. F.; Wadwani, S.; Froehler, B. C.; Matteucci, M. D. *JACS* **1993**, *115*, 9816. (c) Montgomery, J. A.; Thomas, H. J. *JOC* **1981**, *46*, 594.

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Dimethyl Sulfoxide-Iodine

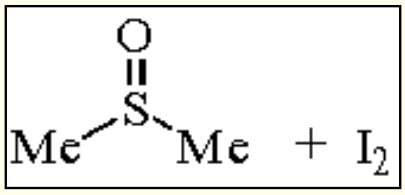

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Iodine · (MW 78.13) (I_2)

[7553-56-2] · I_2 · Dimethyl Sulfoxide-Iodine · (MW 253.81)

(oxidant with diverse applicability, including the conversion of benzoyl methylene groups to di- and triketones, thioacetals to carbonyl compounds, and ketones to α,β-unsaturated ketones)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. I_2: mp 113 °C; bp 184 °C; *d* 4.930 g cm^{-3}.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. I_2: sol ether, $CHCl_3$, CS_2, aq soln HI.

Form Supplied in: DMSO is a colorless liquid; widely available, including anhydrous grades of 99%+ DMSO packed under N_2. I_2 is a widely available crystalline solid.

Preparative Methods: the actual reagent may differ from one reaction to another, and the specific procedures also differ.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg[1a] or 83-85 °C/17 mmHg;[1b] storage over 3Å molecular sieves. I_2: sublimation.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[1c] ***Iodine*** is corrosive and toxic.

The formation of dicarbonyl compounds by this reagent is a variation of the Kornblum oxidation[2] and presumably involves acid-catalyzed iodination of the carbonyl compound (**1**) to give an α-iodo ketone (**2**) which undergoes displacement by DMSO to give an alkoxysulfonium ion (**3**); this gives a dicarbonyl compound (**4**) in a 1,2-elimination with assistance by base (eq 1).[3a]

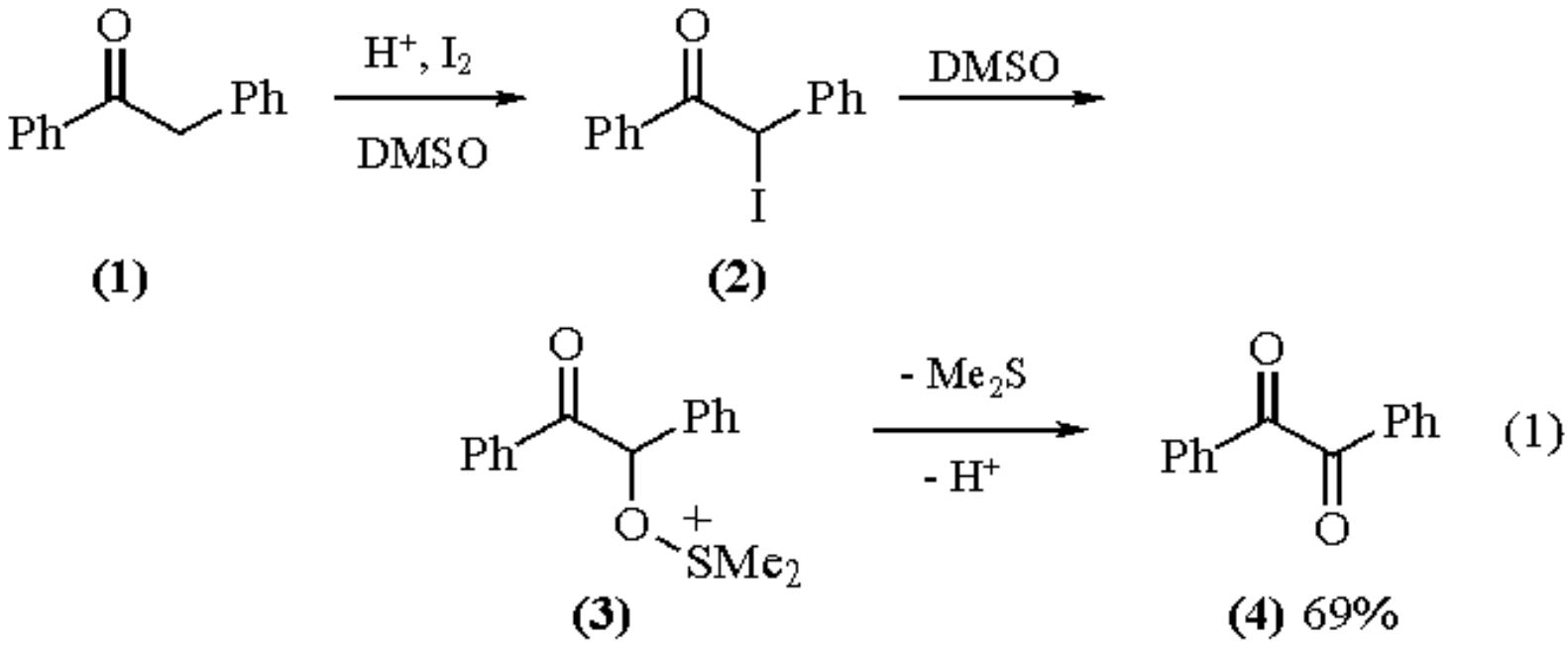

Reaction of the flavanone (**5**) to give (**6**) presumably involves an α-iodo ketone which undergoes elimination (eq 2).[3b] The ethylene thioacetal of cyclohexanone gives cyclohexanone (eq 3),[3c] and phosphine sulfides and selenides give the oxo analogs (eq 4).[3d]

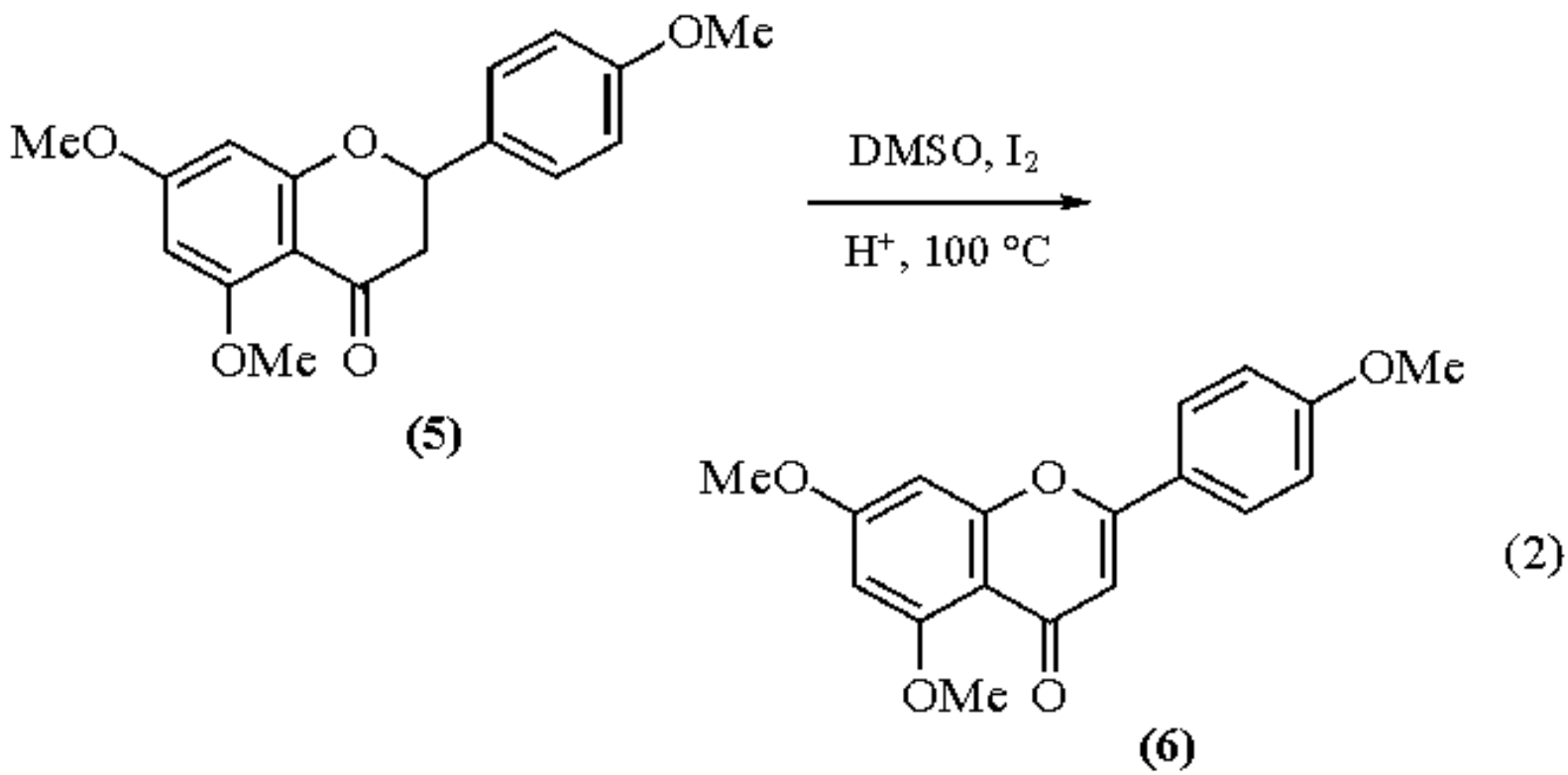

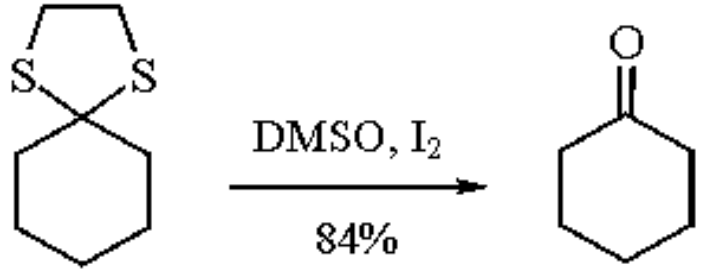

(3)

$$Bu_3P{=}S \xrightarrow[89\%]{DMSO,\ I_2} Bu_3P{=}O \qquad (4)$$

Related Reagents.

Dimethyl Sulfoxide-Acetic Anhydride; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosgene***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***.

---

1. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755.
2. (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *JACS* **1957**, *79*, 6562. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. *JACS* **1959**, *81*, 4113. (c) Kilenyi, S. N. *COS* **1991**, *7*, 653.
3. (a) Furukawa, N.; Akasaka, T.; Aida, T.; Oae, S. *JCS(P1)* **1977**, 372. (b) Fatma, W.; Iqbal, J.; Ismail, H.; Ishratullah, K.; Shaida, W. A.; Rahman, W. *CI(L)* **1979**, 315. (c) Chattopadhyaya, J. B.; Rao, A. V. R. *TL* **1973**, 3735. (d) Mikolajczyk, M.; Luczak, J. *S* **1975**, 114.

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Dimethyl Sulfoxide-Methanesulfonic Anhydride[1]

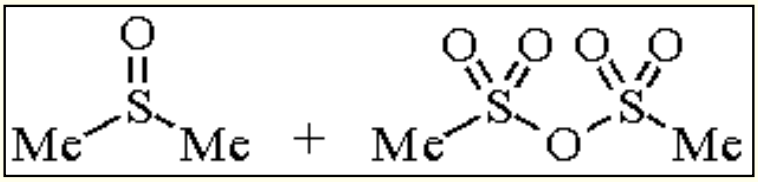

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Methanesulfonic Anhydride · (MW 78.13) (Ms_2O)

[7143-01-3] · $C_2H_6O_5S_2$ · Dimethyl Sulfoxide-Methanesulfonic Anhydride · (MW 174.20)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with minimal amounts of byproduct methylthiomethyl ethers)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. Ms_2O: mp 69-70 °C; bp 125 °C/4 mmHg.

Solubility: DMSO: sol H_2O, alcohol, acetone, CH_2Cl_2, THF. Ms_2O: reacts H_2O; sol CH_2CH_2, THF.

Form Supplied in: DMSO is a colorless liquid that is widely available, including anhydrous grades of 99+% purity packed under N_2; Ms_2O is a crystalline solid that is widely available.

Preparative Method: the active oxidant is presumably Me_2+SOMs, and is generated in situ by adding Ms_2O to the alcohol in DMSO-HMPA.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg,[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] ***Methanesulfonic Anhydride*** is corrosive and moisture-sensitive.

DMSO-Ms_2O is occasionally used for the oxidation of primary and secondary alcohols to aldehydes and ketones,

respectively, and gives good yields of products with minimal formation of byproducts (eq 1).[3a,b] The use of the toxic ***Hexamethylphosphoric Triamide*** in some procedures is a disadvantage.[3a,b]

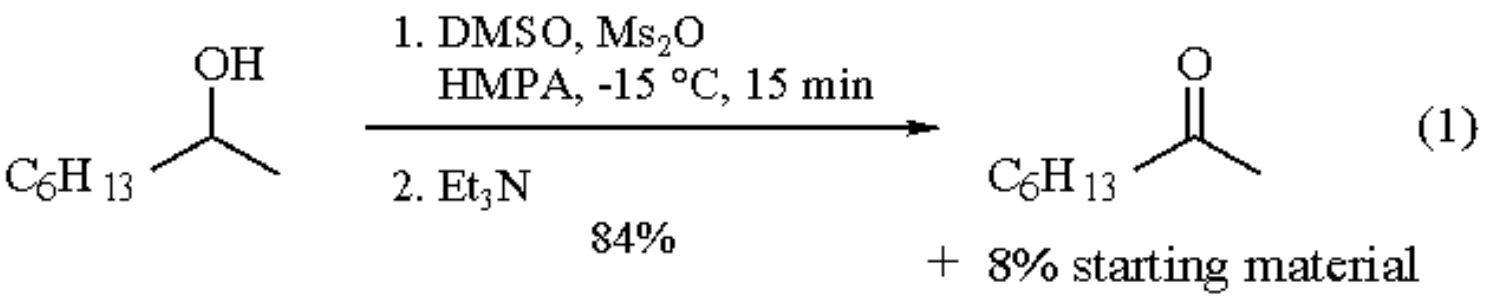

Reaction of the L-tryptophan derivative (**1**) with DMSO-Ms_2O gave (**2**) (eq 2).[3c]

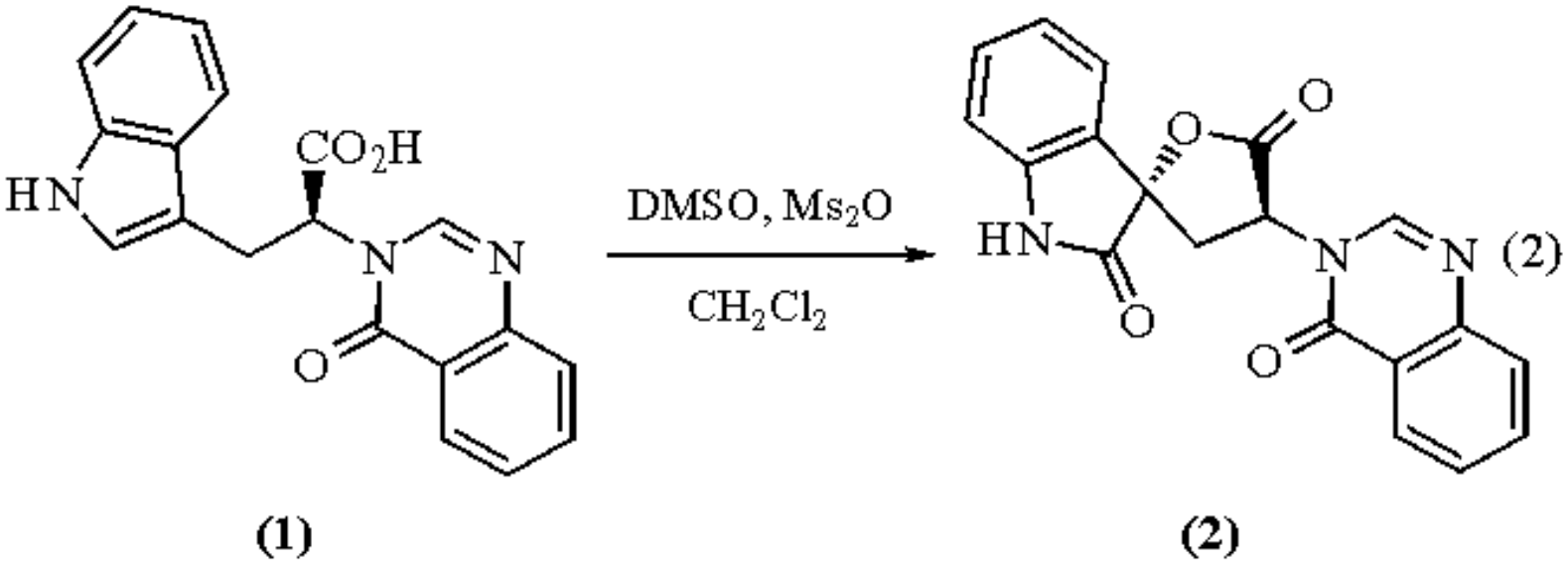

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: New York, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (e) Mancuso, A. J.; Swern, D. *S* **1981**, 165.
2. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755.
3. (a) Omura, K.; Swern, D. *T* **1978**, *34*, 1651. (b) Albright, J. D. *JOC* **1974**, *39*, 1977. (c) Büchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *JACS* **1979**, *101*, 5084.

Dimethyl Sulfoxide-Oxalyl Chloride[1]

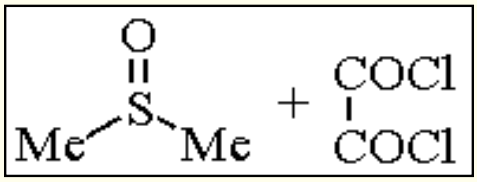

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Oxalyl Chloride · (MW 78.13) ($(COCl)_2$)

[79-37-8] · $C_2Cl_2O_2$ · Dimethyl Sulfoxide-Oxalyl Chloride · (MW 126.93)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with minimal amounts of byproduct methylthiomethyl ethers)

Alternate Name: Swern reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. $(COCl)_2$: bp 63-64 °C/763 mmHg; *d* 1.455 g cm^{-3}.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. $(COCl)_2$: reacts H_2O; sol CH_2Cl_2, THF.

Form Supplied in: colorless liquids; widely available, including anhydrous grades of 99%+ DMSO packed under N_2, and 2M $(COCl)_2$ in CH_2Cl_2 under N_2.

Preparative Method: the active reagent, Me_2+SCl, is formed rapidly from DMSO-$(COCl)_2$ at -78 °C in CH_2Cl_2.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. $(COCl)_2$: distillation under N_2.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] ***Oxalyl Chloride*** is corrosive and moisture-sensitive, and is said to react explosively with DMSO at rt.

DMSO-oxalyl chloride is the most widely used of the DMSO-based reagents for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, and usually gives excellent yields with short reaction times and minimal formation of byproducts.[3] The active reagent (**1**) is generated in situ at low temperature by the addition of DMSO to $(COCl)_2$ in a solvent such as CH_2Cl_2, ether, or THF (eq 1). Addition of the alcohol to (**1**) gives the alkoxysulfonium ion (**2**) (eq 2), which on addition of an amine base is deprotonated to (**3**); the latter forms the carbonyl product (**4**) by intramolecular proton abstraction (eq 3).

$$Me_2S{=}O + (COCl)_2 \longrightarrow \underset{\textbf{(1)}}{Me_2\overset{+}{S}Cl\ Cl^-} + CO + CO_2 \qquad (1)$$

$$\textbf{(1)} + RR^1CHOH \longrightarrow \underset{\textbf{(2)}}{RR^1CHO\overset{+}{S}Me_2} \qquad (2)$$

$$\textbf{(2)} + \text{base} \longrightarrow \underset{\textbf{(3)}}{RR^1CHO\overset{+}{S}(Me)CH_2^-} \longrightarrow \underset{\textbf{(4)}}{RR^1C{=}O} + Me_2S \qquad (3)$$

In a typical procedure using ***Triethylamine*** as base, DMSO (2.4 equiv) is added to $(COCl)_2$ (1.2 equiv) in CH_2Cl_2 cooled to -50 to -60 °C, and then geraniol (**5**) (1.0 equiv) is added, followed by Et_3N (5 equiv). Washing and distillation give geranial (**6**) in 94% yield (eq 4).[4a] The sensitive alcohol (**7**) is oxidized to the aldehyde (**8**) in 83% yield, with less than 8% racemization (eq 5).[4b] The use of ***Diisopropylethylamine*** (DIPEA) as the base helps prevent epimerization (eq 6).[4c] This procedure has been applied on a 1 mol scale in a conversion that gave only a 40% yield with ***Chromium(VI) Oxide*** and H_2SO_4 (eq 7).[4d]

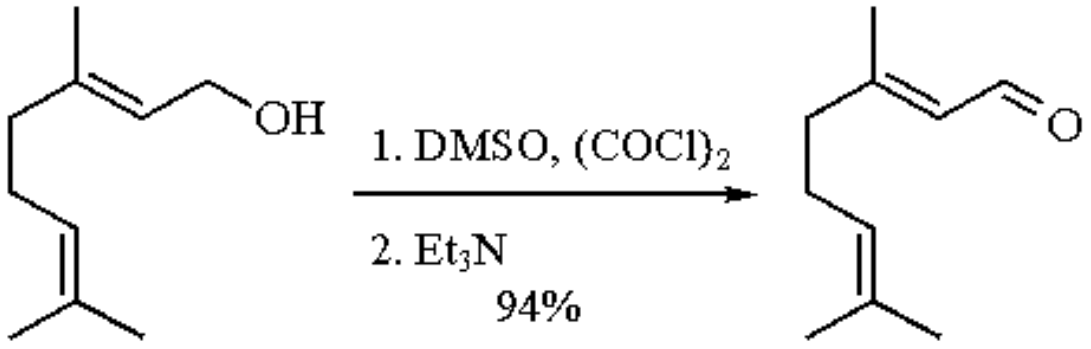

(5) (6) (4)

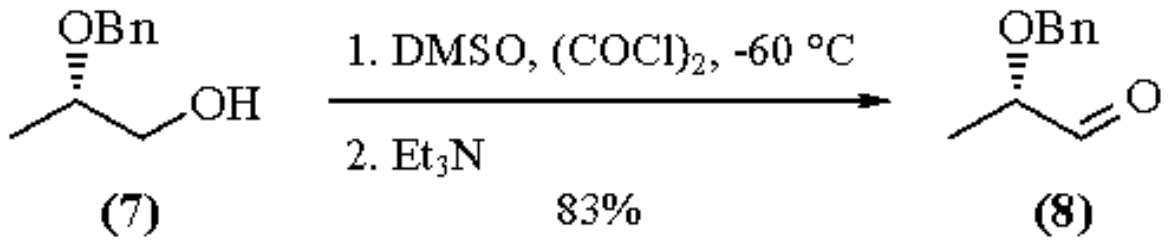

(5)

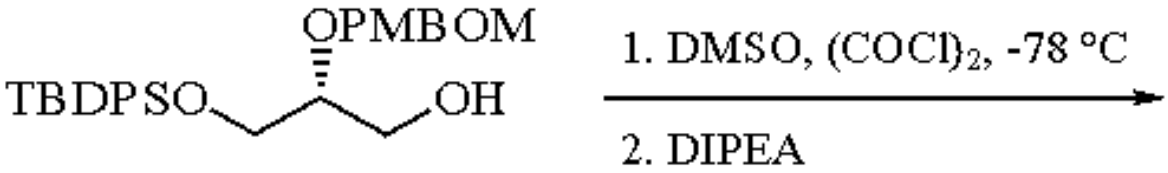

PMBOM = 4-MeOC$_6$H$_4$CH$_2$OCH$_2$

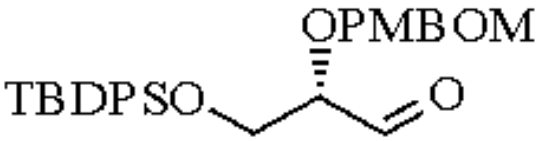

(6)

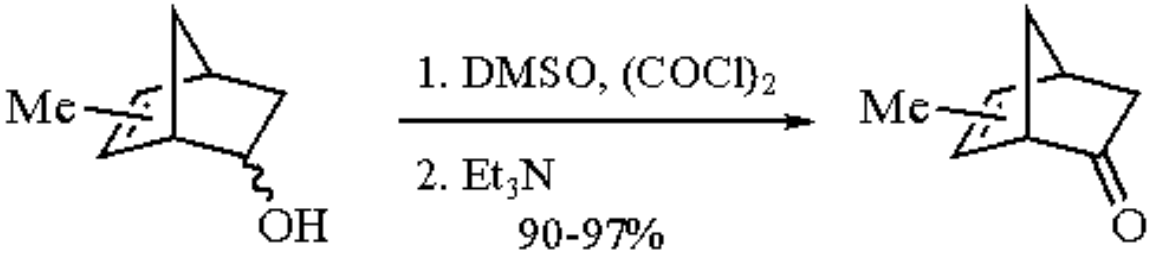

(7)

Diols are efficiently oxidized by this procedure (eqs 8 and 9),[4e,f] and selectivity for oxidation of less crowded hydroxy groups can be achieved (eq 10).[4g,h] Isolation of the ketoaldehyde (**10**) from oxidation of (**9**) proved difficult, so oxidation using the stronger base ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** was employed to give (**11**) directly from (**9**) (eq 11).[4i] Aryl dimethanols are oxidized to *ortho*-phthalaldehydes.[4j]

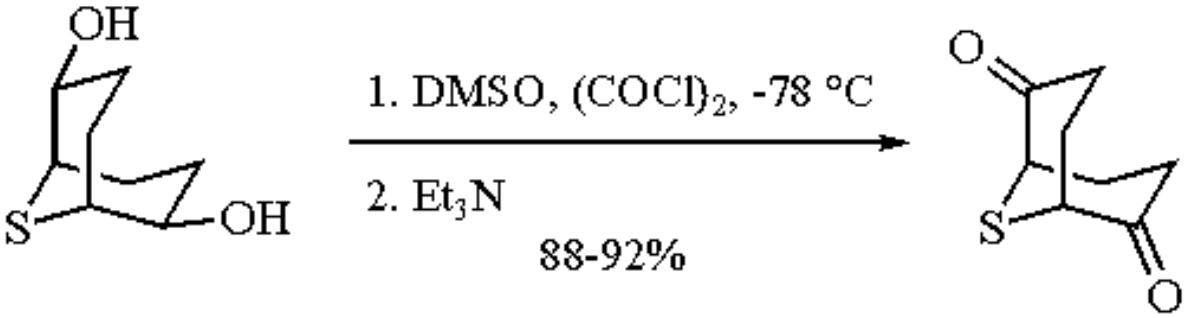

(8)

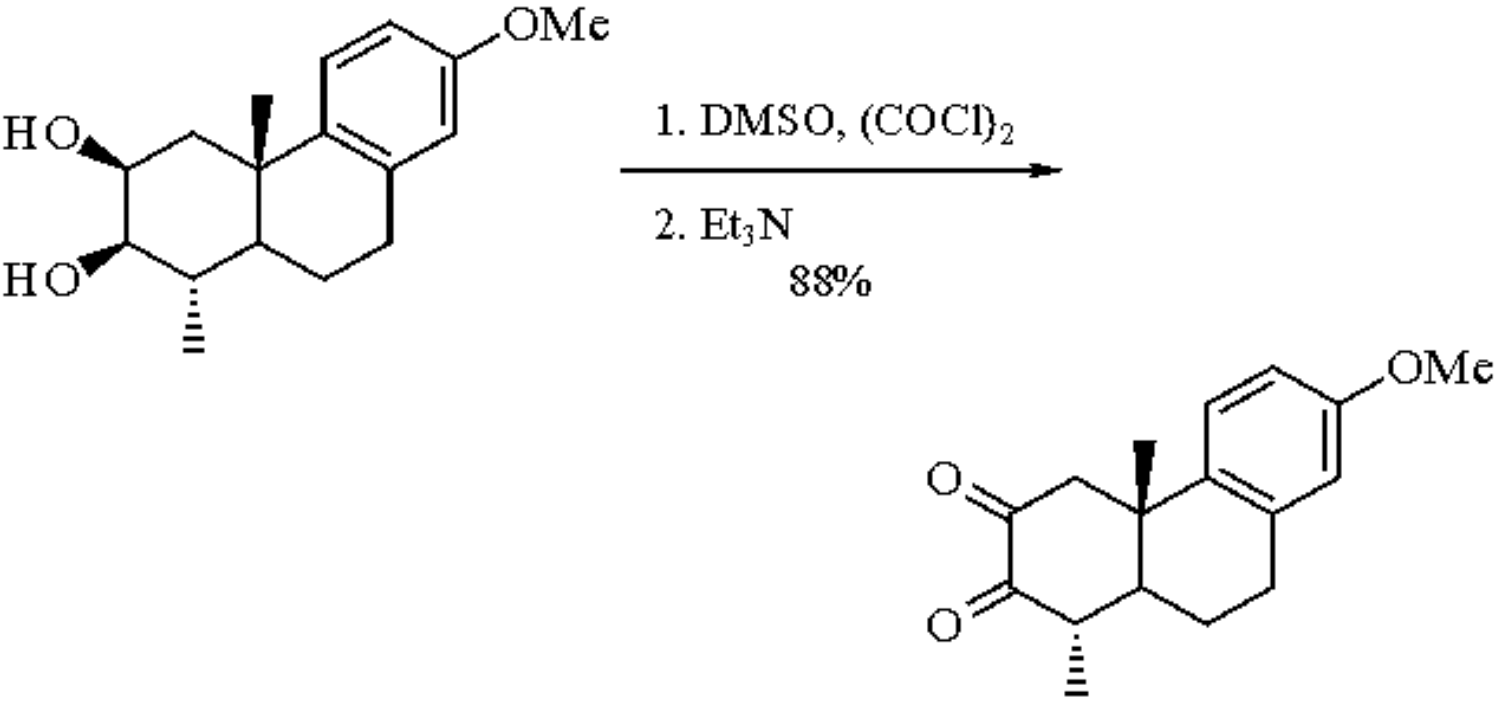
OMe
HO
HO
1. DMSO, (COCl)2
2. Et3N
88%
OMe
O
O

(9)

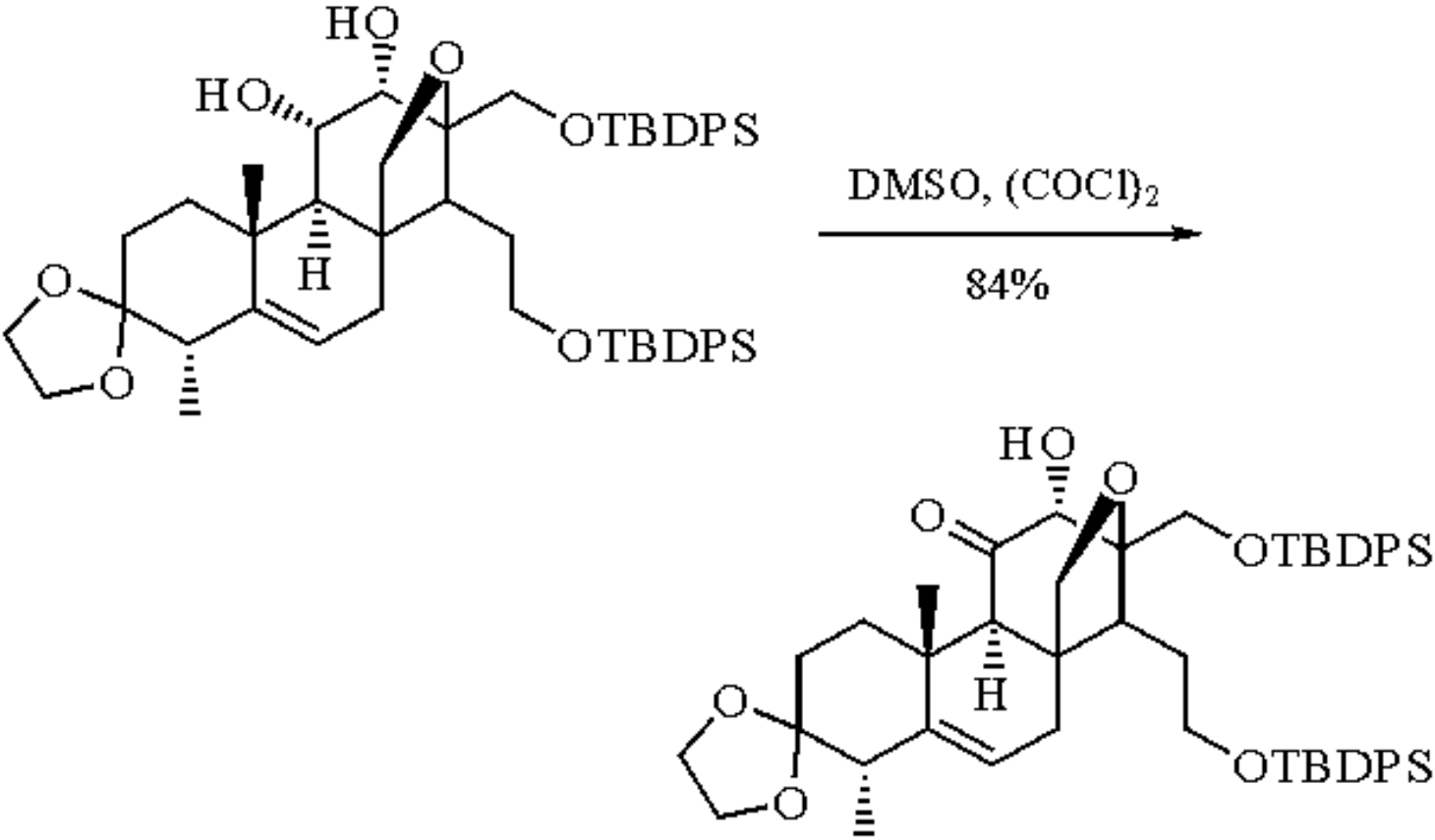
HO
HO
O
OTBDPS
H
O
O
OTBDPS
DMSO, (COCl)2
84%
HO
O
O
OTBDPS
H
O
O
OTBDPS

(10)

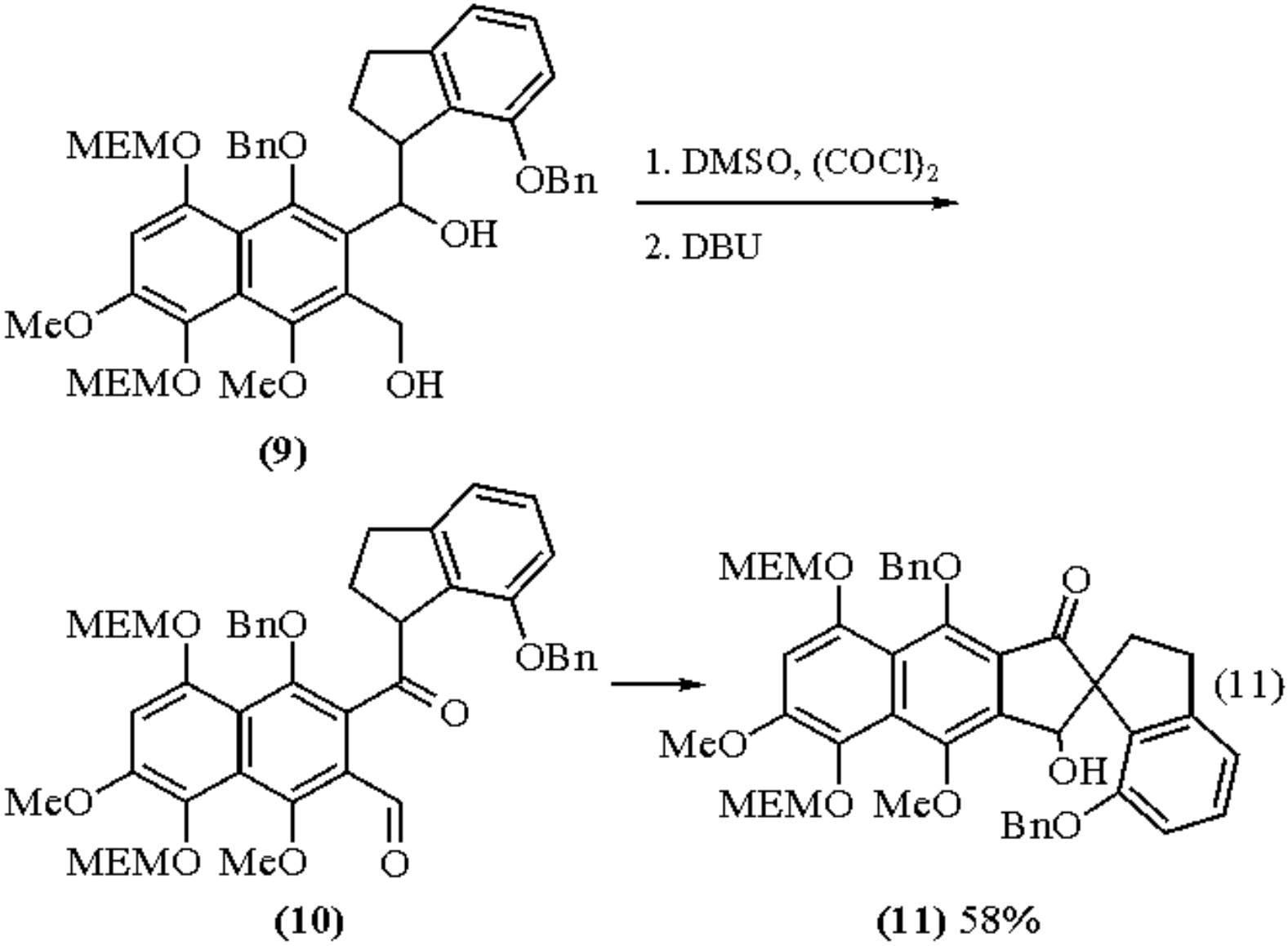

DMSO activated by $(COCl)_2$ without the addition of base has also been used for the conversion of β-triketides such as (**12**) to γ-pyrones (**13**) (eq 12).[5] A mechanism was proposed in which DMSO was regenerated (eq 13). In the presence of Et_3N the formation of (**14**) (30%) along with (**13**) (33%) was attributed to the intermediate (**15**) (eq 14).[5]

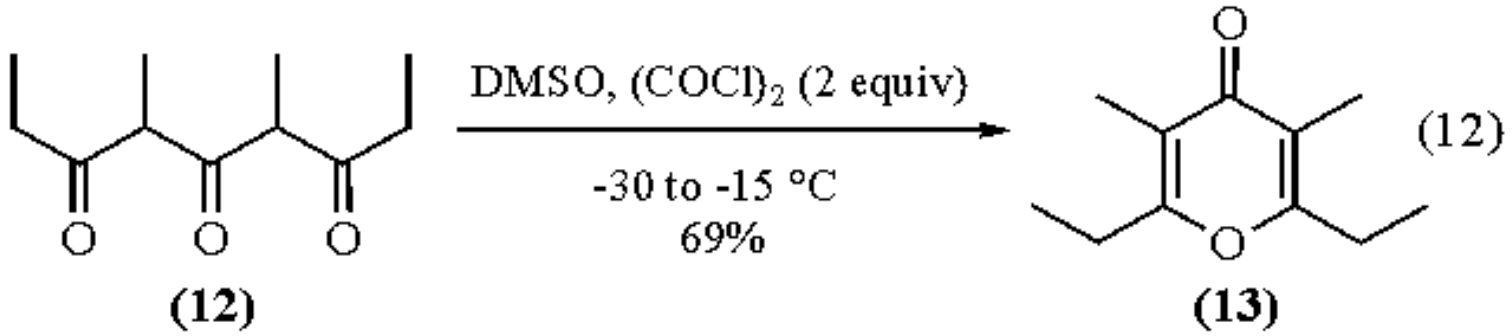

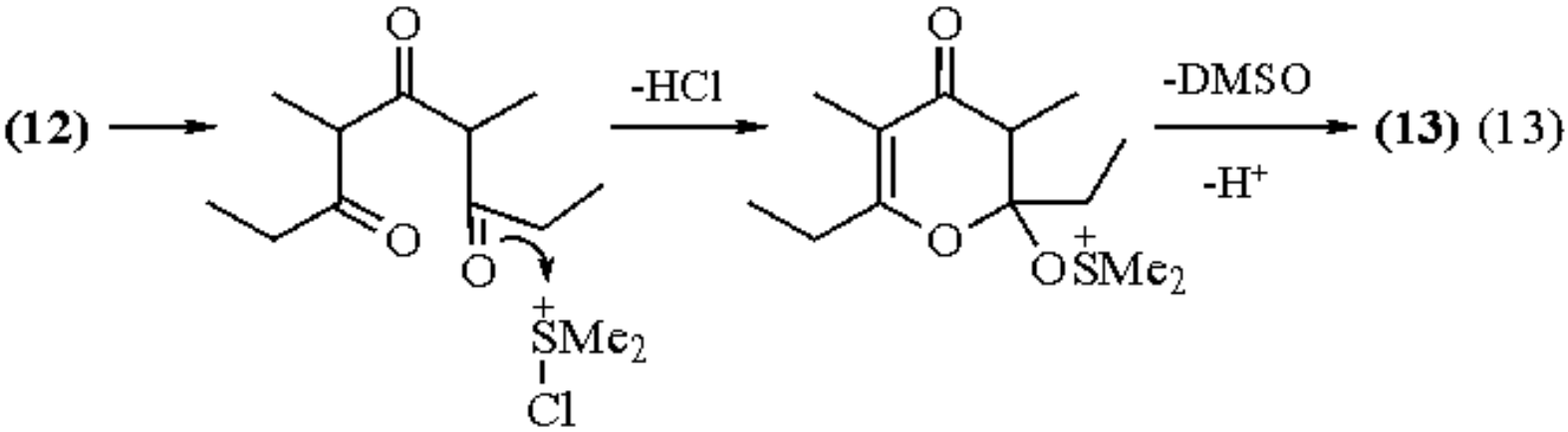

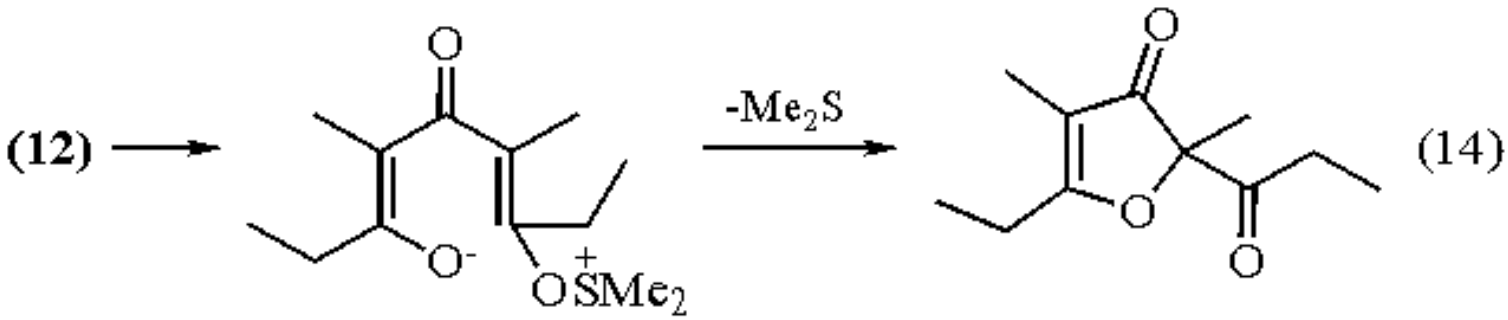

(15) **(14)** 30%

Examples of oxidation of alcohols to carbonyl compounds by DMSO-$(COCl)_2$ followed by in situ reaction of the product with another reagent include the use of alkynyllithiums (eq 15),[6a] Wittig reagents (eq 16),[6b] and Mannich reagents (eq 17).[6c] Extraction of the crude product followed by reaction with ***Hydroxylamine*** gives oximes (eq 18),[6d] and oxidation in the presence of MeOH gave an ester (eq 19).[6e]

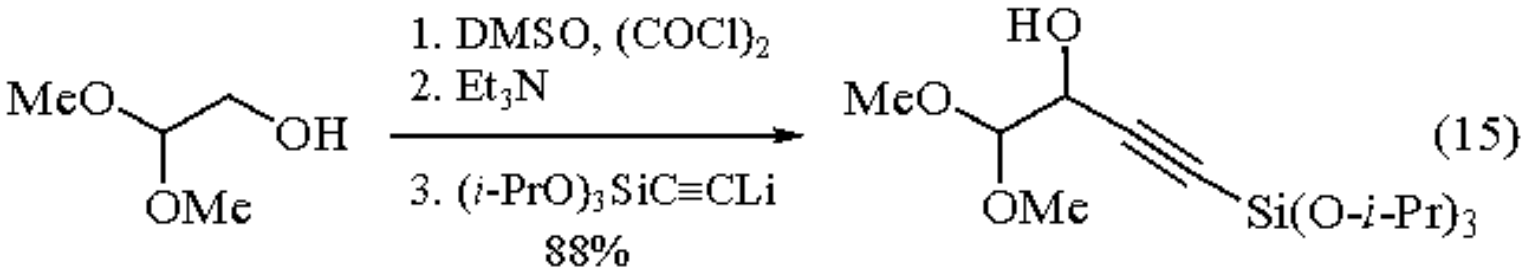

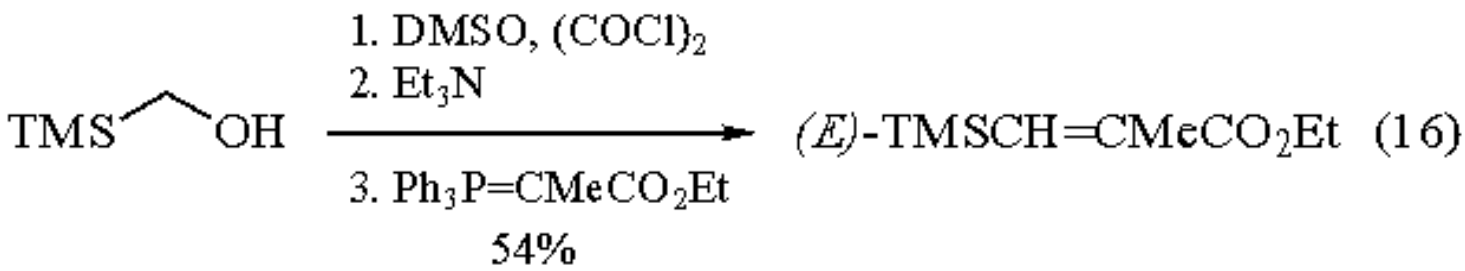

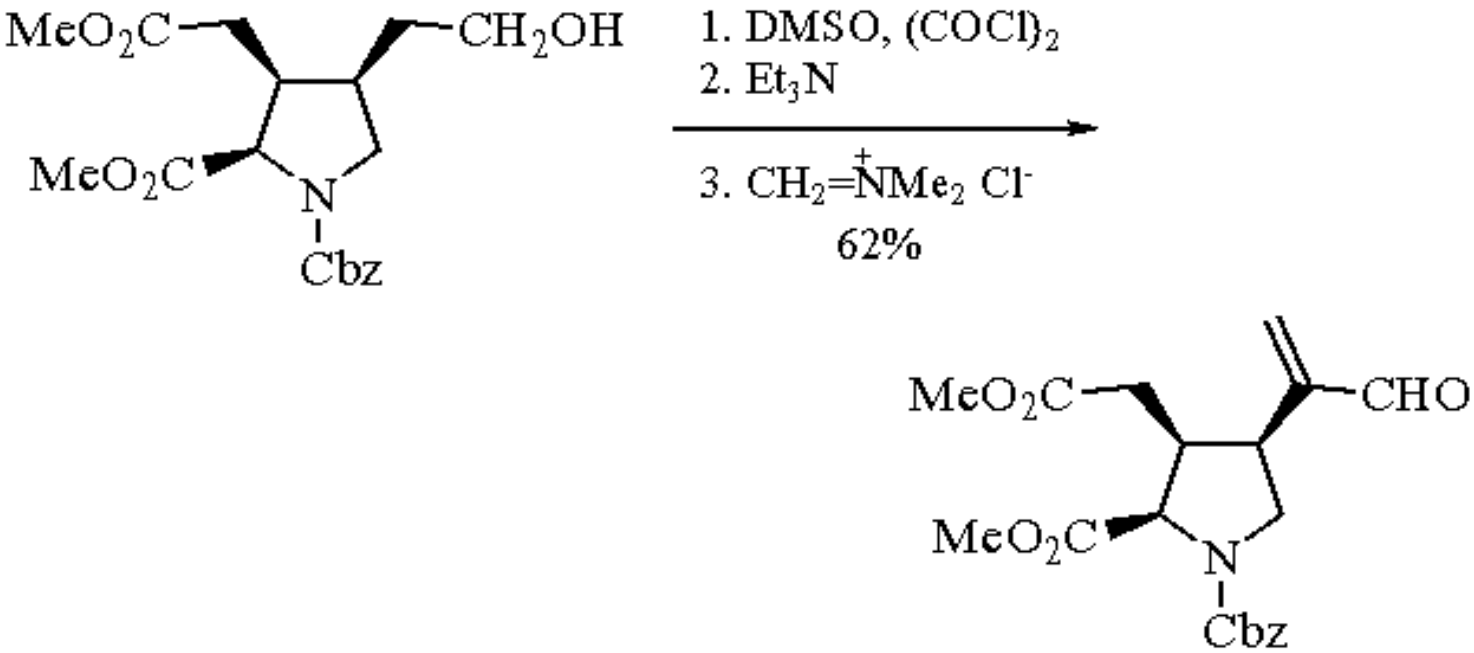

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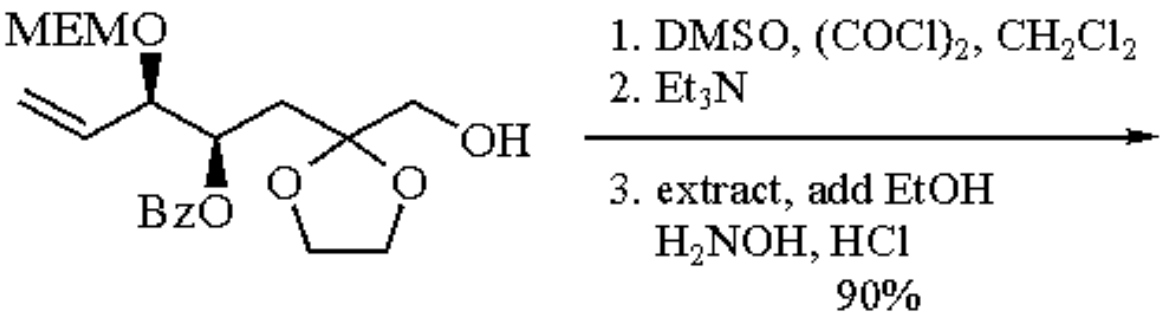

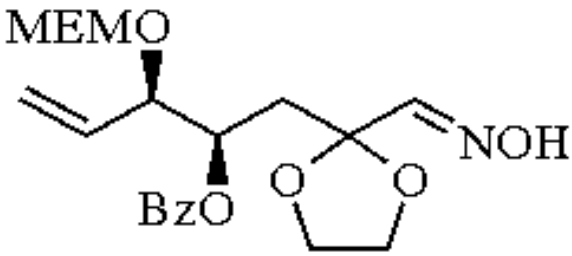

(18)

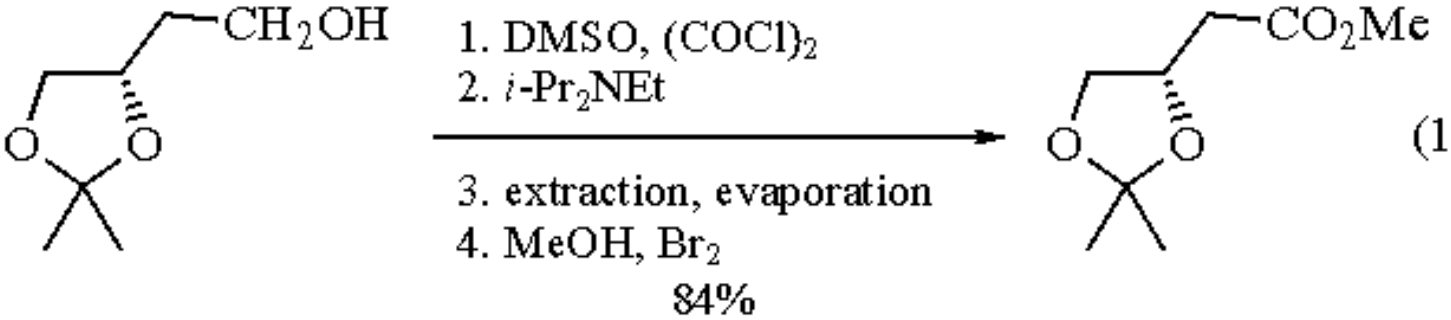

(19)

The sequence of eqs 20 and 21 illustrates the use of consecutive Swern oxidations and further conversions.[6f] Reaction of trimethylsilylallyl alcohol on a 0.3 mol scale gave the ketone in 78% yield (eq 22).[6g]

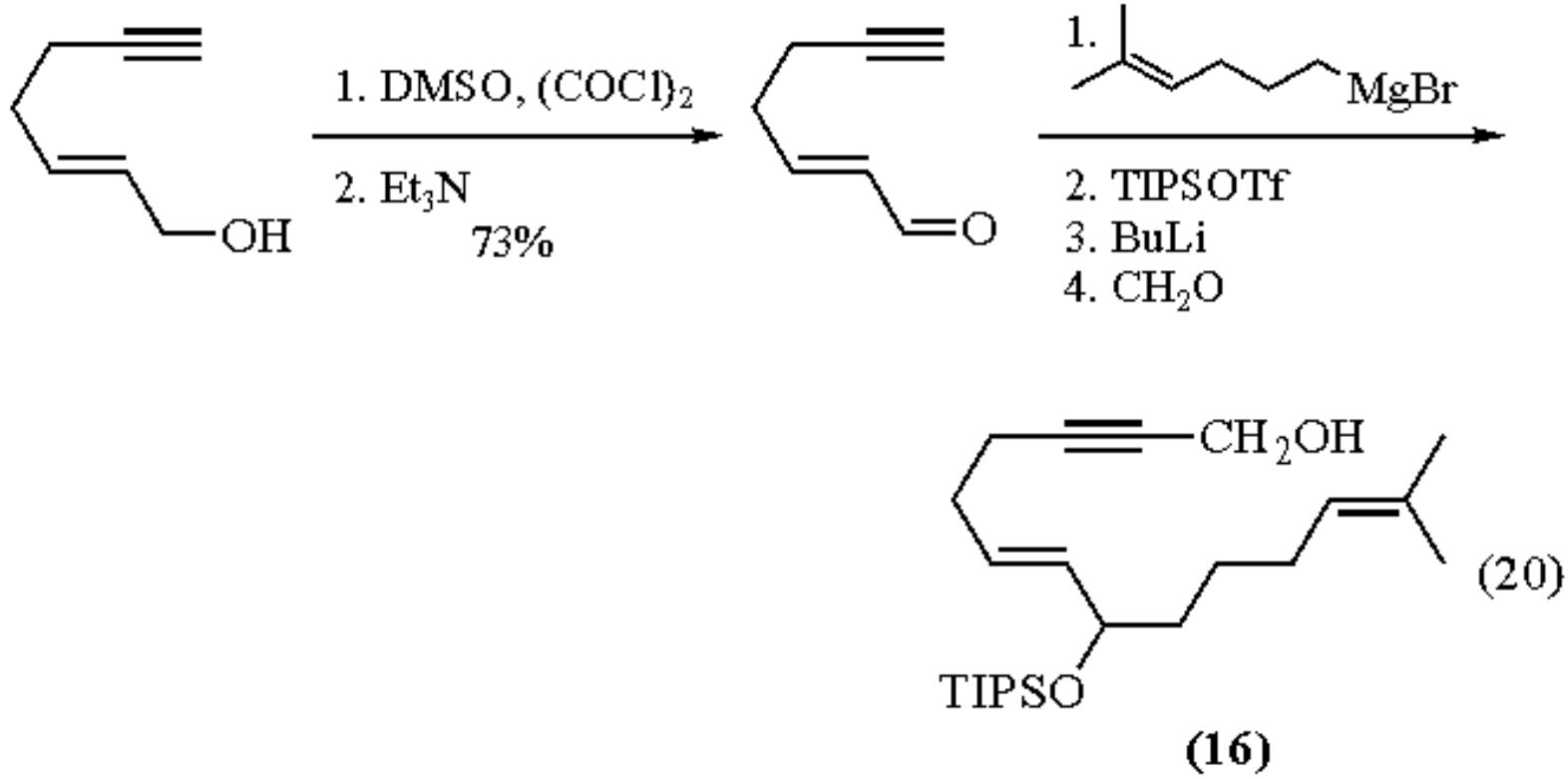

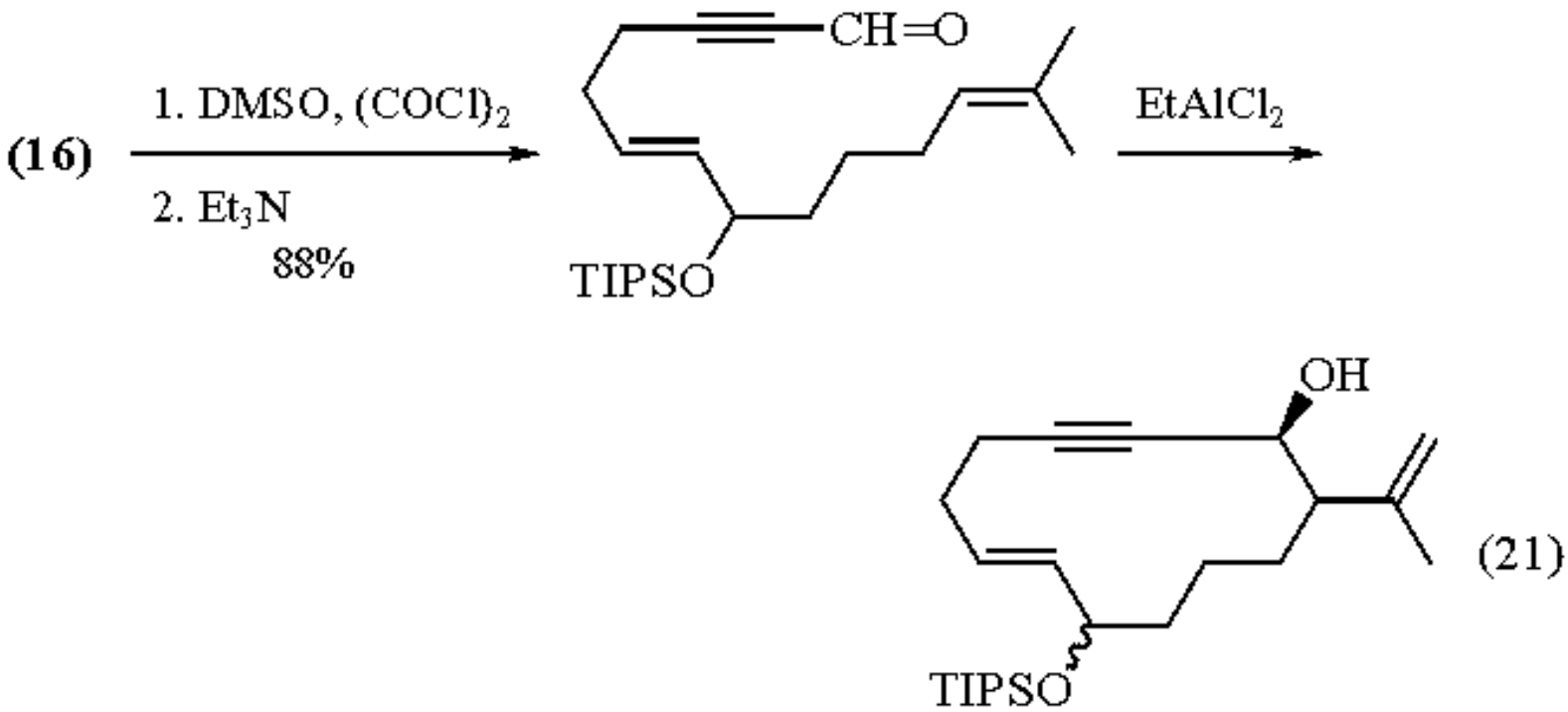

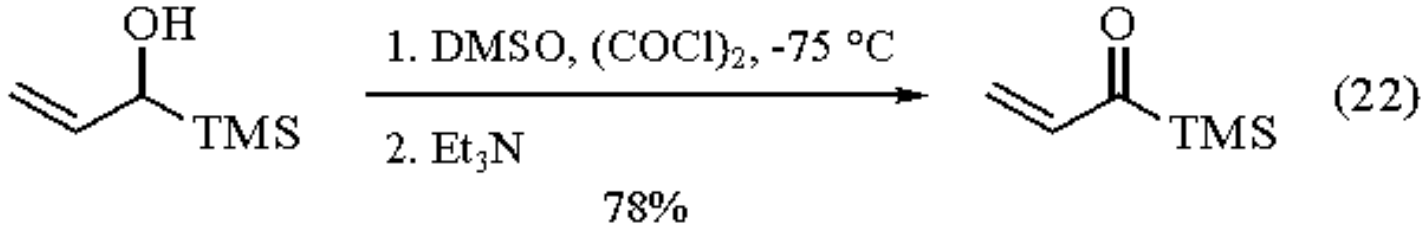

Trimethylsilyl and triethylsilyl ethers are oxidized to carbonyl products by DMSO-$(COCl)_2$, but *t*-butyldimethylsilyl, *t*-

butyldiphenylsilyl, and *t*-butoxydiphenylsilyl ethers are not (eq 23).[7a-d] Chloride attack on silicon is thought to assist the reaction.[7b] Primary triethylsilyl ethers are selectively oxidized by DMSO-$(COCl)_2$ in the presence of tertiary triethylsilyl ethers (eq 24).[7e] This subject has been reviewed.[7f]

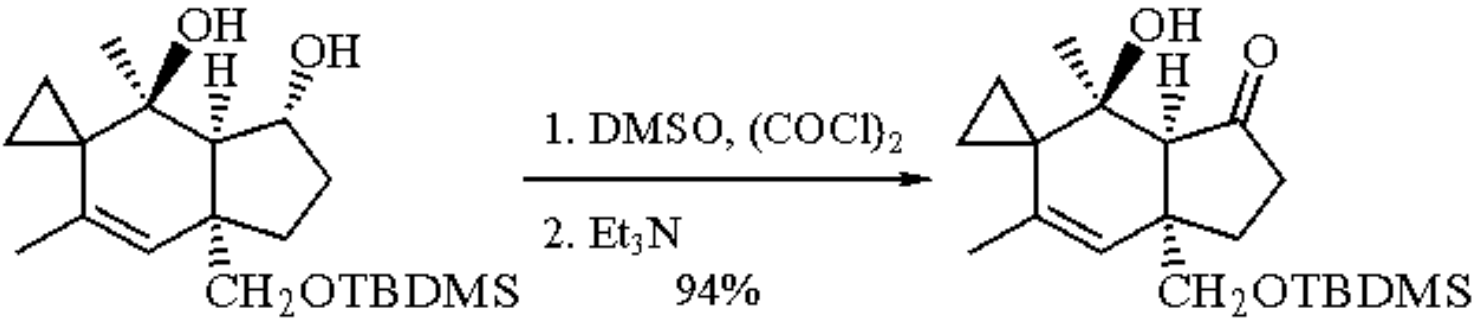

(23)

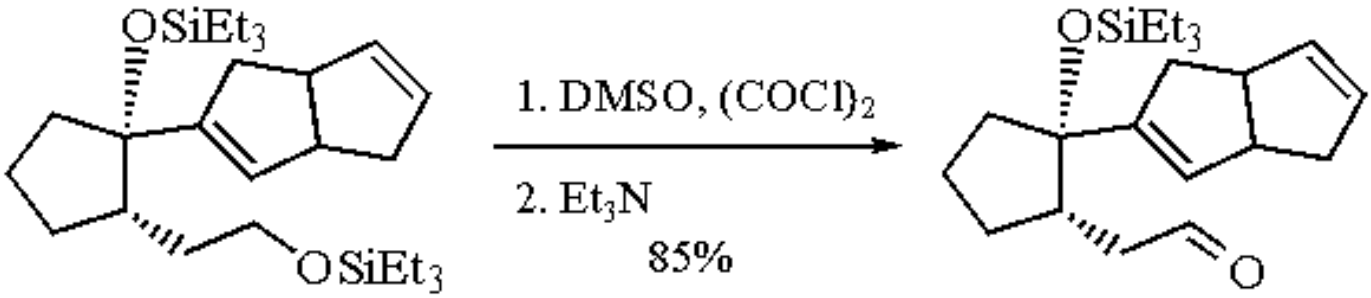

(24)

Elimination can occur from the carbonyl products resulting from oxidation of sensitive substrates (eq 25).[8]

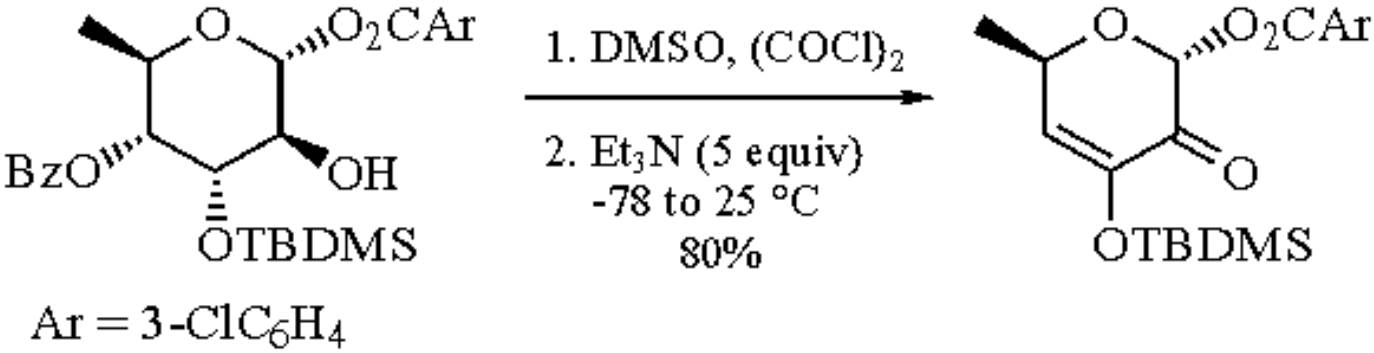

(25)

Allylic alcohols can be converted to chlorides by treatment with DMSO-$(COCl)_2$ without the use of added base, presumably by chloride displacement of DMSO from the alkoxysulfonium ion (eq 26).[9a,b] DMSO-$(COCl)_2$ also acts as an electrophilic chlorinating reagent toward ketones (eq 27).[9c] Oxidation to the nonchlorinated ketone was achieved with ***Dimethyl Sulfoxide-Acetic Anhydride***.[9c]

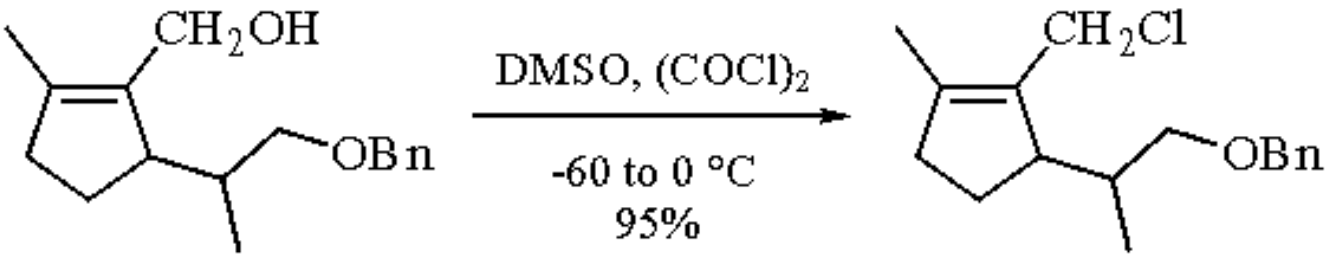

(26)

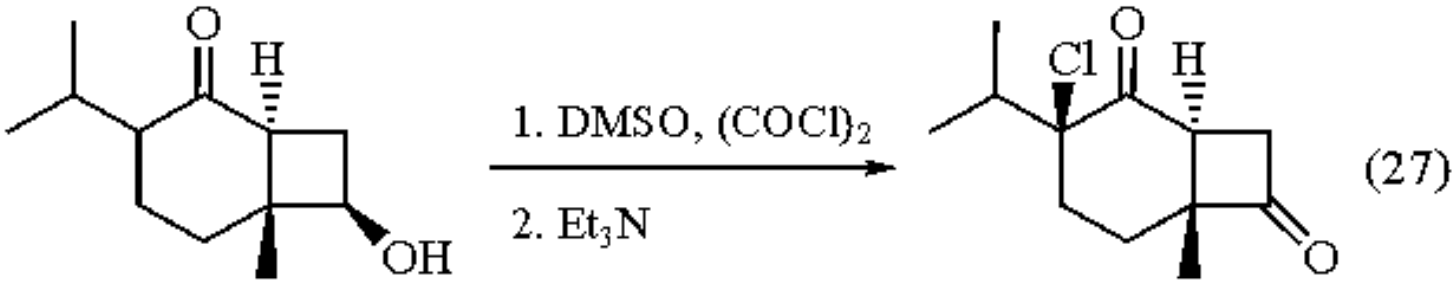

Oxidation of diaziridines with DMSO-$(COCl)_2$ gives diazirines (eq 28),[10a] and dibenzylamine gives partial conversion to an imine (eq 29).[10b]

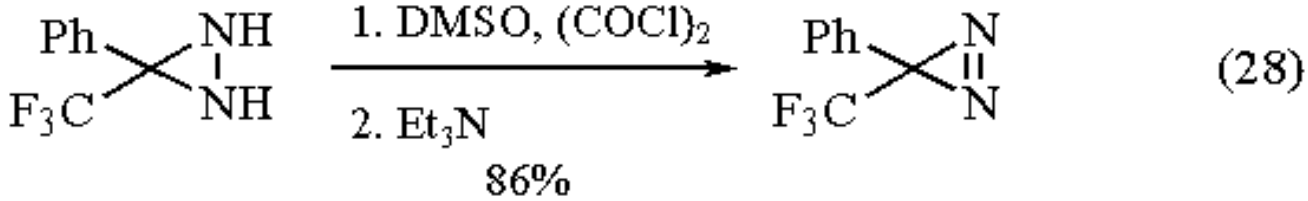

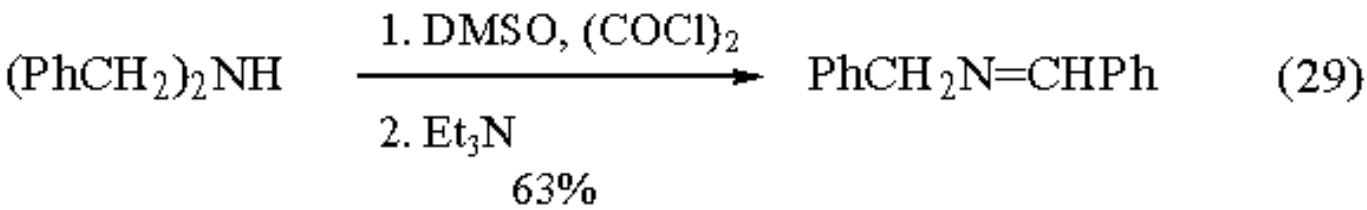

A related reagent for the activation of DMSO for oxidation of alcohols is ***Phenyl Dichlorophosphate*** ($PhOP(O)Cl_2$),[11a-c] which is more effective than DMSO-$(COCl)_2$ in the oxidation of benzyl alcohol (eq 30).[11a] Cyanuric chloride also activates DMSO for oxidation of alcohols.[11d]

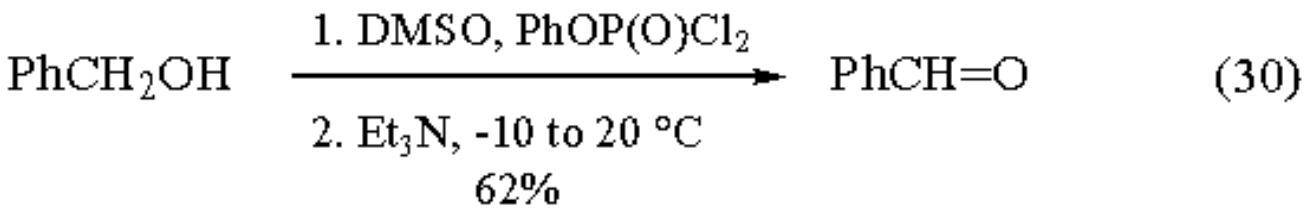

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Iodine***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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10. (a) Richardson, S. K.; Ife, R. J. *JCS(P1)* **1989**, 1172. (b) Keirs, D.; Overton, K. *CC* **1987**, 1660.
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Dimethyl Sulfoxide-Phosgene[1]

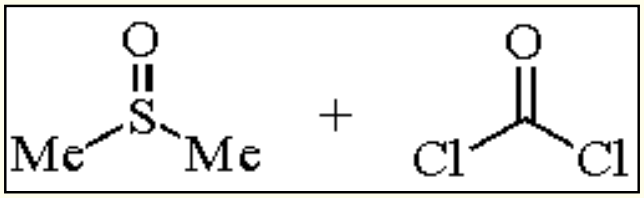

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Phosgene · (MW 78.13) ($COCl_2$)

[75-44-5] · CCl_2O · Dimethyl Sulfoxide-Phosgene · (MW 98.92)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; because of the high toxicity of phosgene and the absence of any clear advantages, the use of this procedure is not recommended)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. $COCl_2$: bp 8.2 °C/760 mmHg; *d* 1.432 g cm^{-3} (4 °C).

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. $COCl_2$: reacts slowly H_2O; sol CH_2Cl_2, THF, benzene.

Form Supplied in: DMSO is a colorless liquid; widely available, including anhydrous grades of DMSO packed under N_2; $COCl_2$ is a gas available in cylinders.

Preparative Method: the active reagent is proposed[2] to be $(CH_3)_2{+}SOCO_2CHRR^1$, formed from the reaction with DMSO of the chloroformate RR^1CHO_2CCl separately generated from phosgene and the alcohol.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg,[3a] or 83-85 °C/17 mmHg;[3b] storage over 3Å molecular sieves. $COCl_2$: distillation.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[3c] ***Phosgene***, also known as carbonic dichloride, is corrosive, moisture sensitive, and highly toxic, and

should only be used with extreme caution.

In this procedure, chloroformates are generated from $COCl_2$ and the alcohols are proposed to react with DMSO to form dimethylsulfonium salts (**2**) via decarboxylation of the intermediates (**1**) (eqs 1 and 2). This procedure has been used in the oxidation of various alcohols, including steroids, in 20-80% yields.[2] The use of 1,2-epoxypropane as an acid scavenger in the process has been suggested.[2b] This procedure is inconvenient and dangerous, and offers no apparent advantages.

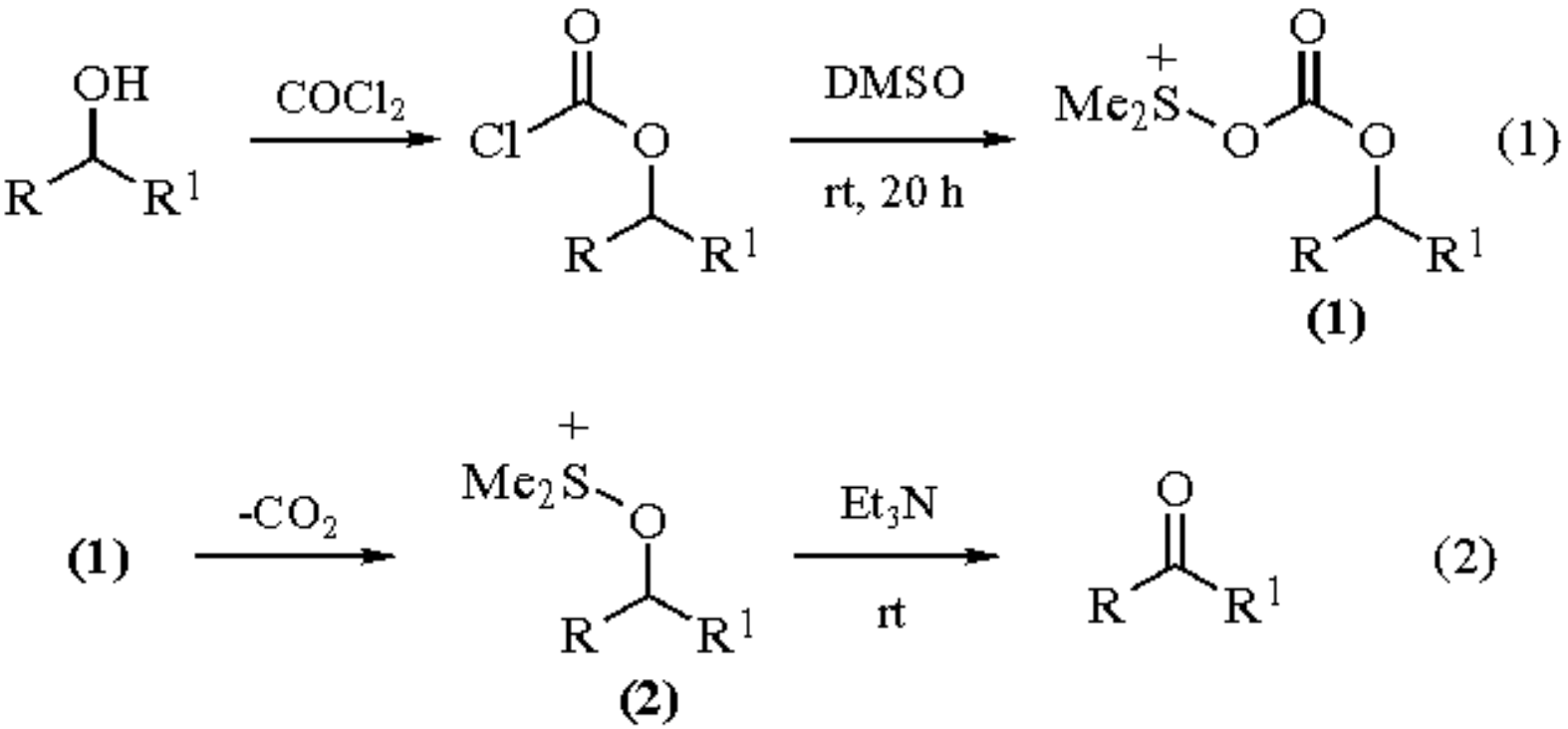

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic Press: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, DC, 1990. (f) Mancuso, A. J.; Swern, D. *S* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*, Augustine, R. L.; Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.

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3. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755.

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Dimethyl Sulfoxide-Phosphorus Pentoxide[1]

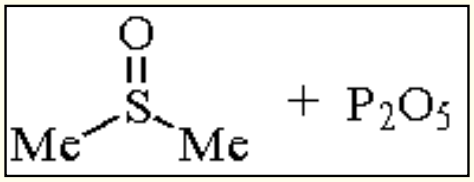

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Phosphorus Pentoxide · (MW 78.13) (P_2O_5)

[1314-56-3] · O_5P_2 · Dimethyl Sulfoxide-Phosphorus Pentoxide · (MW 141.95)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; modified procedure gives very good yields with short reaction times at 0 °C with minimal formation of byproducts; inexpensive).

Alternate Name: Onodera reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. P_2O_5: sublimes 360 °C/760 mmHg.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. P_2O_5: sol H_2O.

Form Supplied in: DMSO is a colorless liquid; widely available, including anhydrous grades of DMSO packed under N_2; P_2O_5 (more accurately P_4O_{10}) is a white crystalline solid; widely available.

Preparative Method: the active oxidant, formulated as $Me_2{+}SO(P_2O_5)^-$, is generated in situ from the reaction of DMSO and P_2O_5 in the presence of the alcohol.

Purification: DMSO: distillation from CaH_2 at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. P_2O_5: sublimation.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] ***Phosphorus(V) Oxide*** is corrosive and a strong desiccant.

DMSO-P_2O_5 has long been used,[3a] but the early procedures involved elevated temperatures with no added base, and required long reaction times, as in the example of eq 1.[3b] This procedure has been used in conjunction with a reduction step for the inversion of hydroxy group configuration (eq 2).[3c] More recently the addition of ***Triethylamine*** base permits shorter reaction times and lower temperatures, but dry ice temperatures are not required, and this can be an advantage relative to the use of ***Dimethyl Sulfoxide-Oxalyl Chloride*** (eq 3).[4] The DMSO and P_2O_5 react to form $Me_2{+}SO(P_2O_5)^-$, which reacts in situ with the alcohol ROH to give the alkoxysulfonium ion $Me_2{+}SOR$ common to most oxidations by activated DMSO.

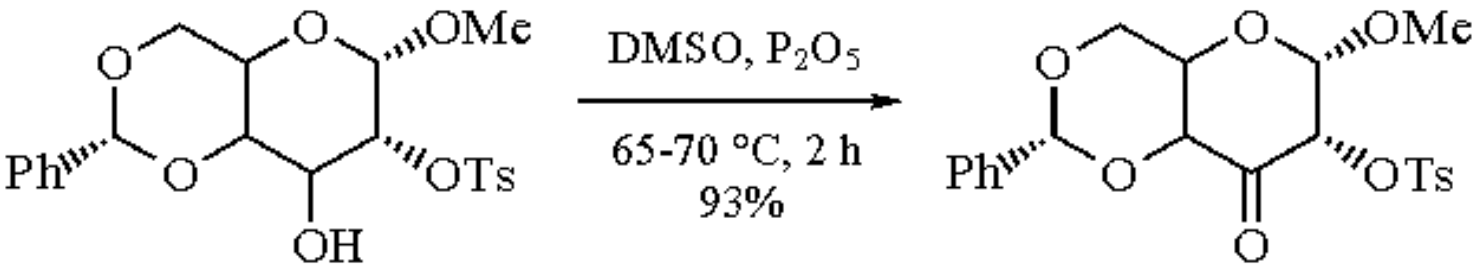

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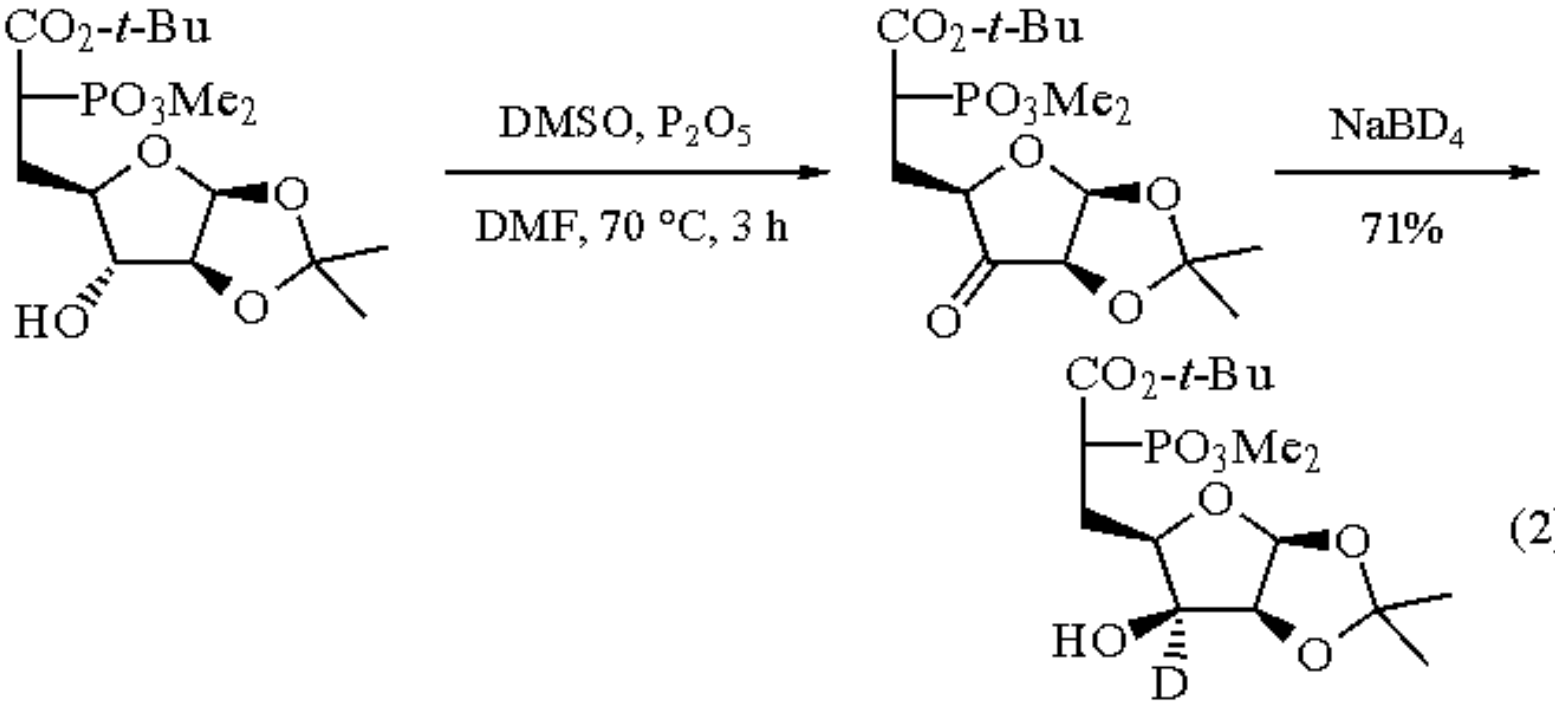

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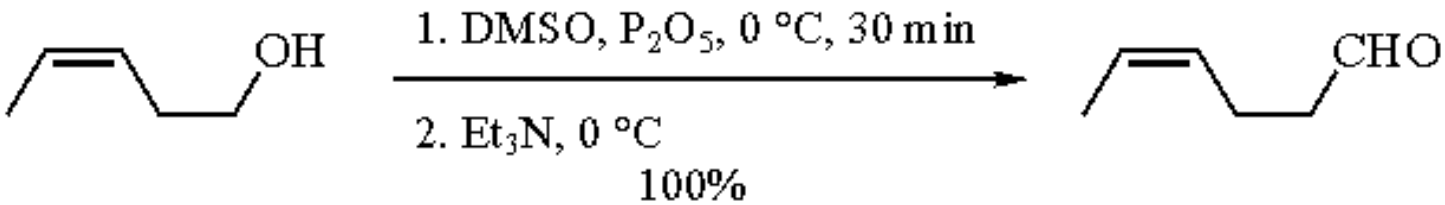

(3)

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***;

Dimethyl Sulfoxide-Oxalyl Chloride; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D. *S* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J.; Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.
2. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755.
3. (a) Onodera, K.; Hirano, S.; Kashimura, N. *JACS* **1965**, *87*, 4651. (b) Jones, G. H.; Moffatt, J. G. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; BeMiller, J. N., Eds; Academic: New York, 1972; Vol. 6, p 315. (c) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K. A.; Mocek, U.; Beale, J. M.; Floss, H. G. *JACS* **1993**, *115*, 5254.
4. (a) Taber, D. F.; Amedio, J. C., Jr.; Jung, K.-Y. *JOC* **1987**, *52*, 5621. (b) Taber, D. F.; Amedio, J. C., Jr.; Raman, K. *JOC* **1988**, *53*, 2984.

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Dimethyl Sulfoxide-Silver Tetrafluoroborate

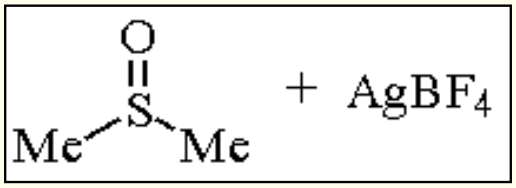

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Silver Tetrafluoroborate · (MW 78.13) ($AgBF_4$)

[14104-20-2] · $AgBF_4$ · Dimethyl Sulfoxide-Silver Tetrafluoroborate · (MW 194.68)

(reagent for conversion of alkyl halides to aldehydes and ketones)

Physical Data: DMSO: mp 18.55 °C; bp 189 °C/760 mmHg; 76 °C/16 mmHg; *d* (25 °C) 1.0958 g cm^{-3}; dielectric constant (25 °C) 46.7. $AgBF_4$: mp 200 °C.

Solubility: DMSO: miscible with water and most organic solvents. $AgBF_4$: sol water, ether, toluene, nitromethane, DMSO; moderately sol benzene and cyclohexane.

Form Supplied in: DMSO: clear anhyd liquid, widely available. $AgBF_4$: crystalline white solid, widely available. *Drying:* DMSO: generally quite dry when freshly opened, but very hygroscopic; distill from CaH_2 under reduced pressure. $AgBF_4$: very hygroscopic; dry in vacuo at 80 °C.

Handling, Storage, and Precautions: see ***Dimethyl Sulfoxide*** and ***Silver(I) Tetrafluoroborate***.

Silver-assisted nucleophilic displacement of halide to form an alkoxysulfonium ion, followed by deprotonation, most commonly by ***Triethylamine***,[1] effectively converts benzylic and allylic halides and some primary[1b] and secondary alkyl halides[1a,b,f,5] to the corresponding aldehydes or ketones at room temperature (eq 1,[1d] eq 2,[1e] eq 3,[1f] and eq 4[1j]). While avoiding the higher temperatures generally required by the Kornblum method[2] ($NaHCO_3$ (+NaI[3]), DMSO, 100-150 °C), the silver-assisted reaction has the disadvantage of higher cost. Most oxidations have been accomplished with silver tetrafluoroborate; however, there are successful examples which used ***Silver(I) Nitrate***[4] or hexafluorophosphate.[5] The same type of conversion has been accomplished with trialkylamine oxides,[6] ion-exchange polymer-bound chromate ion,[7] the classical Sommelet reaction,[8] and other methods.[9] Oxidation of the corresponding alcohols is the obvious alternative.[1e,k] On the other hand, bromination of an allylic or benzylic methyl group with ***N-Bromosuccinimide*** followed by DMSO-$AgBF_4$ oxidation[1h,i,j] is a useful substitute for direct oxidation of the

hydrocarbon.[10]

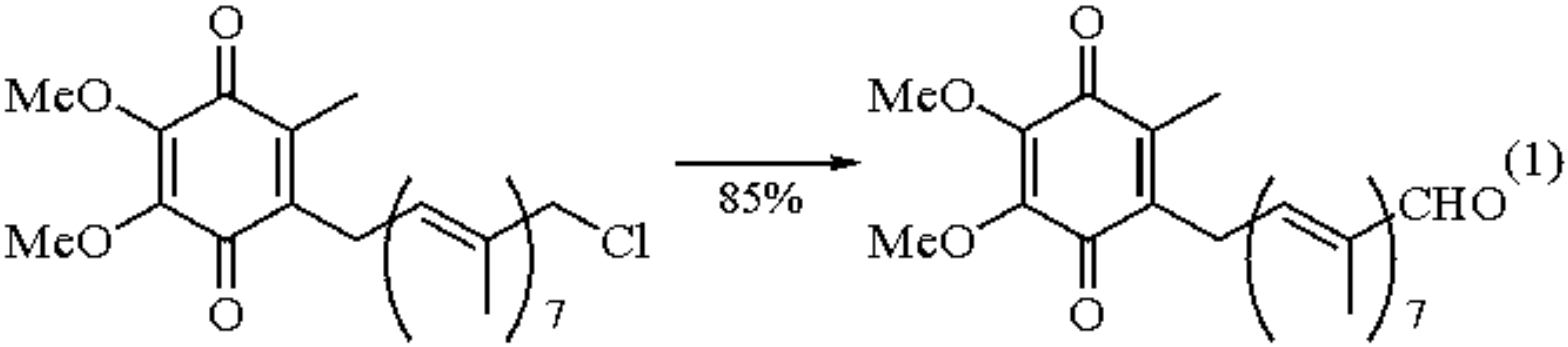

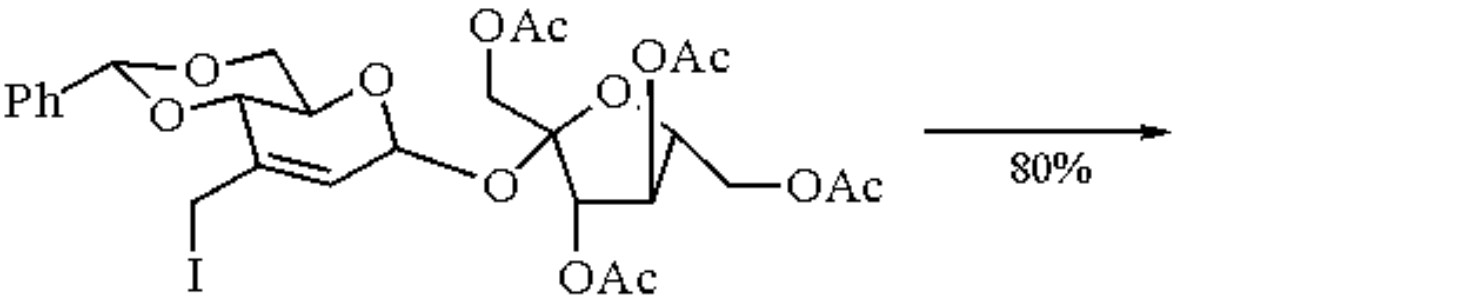

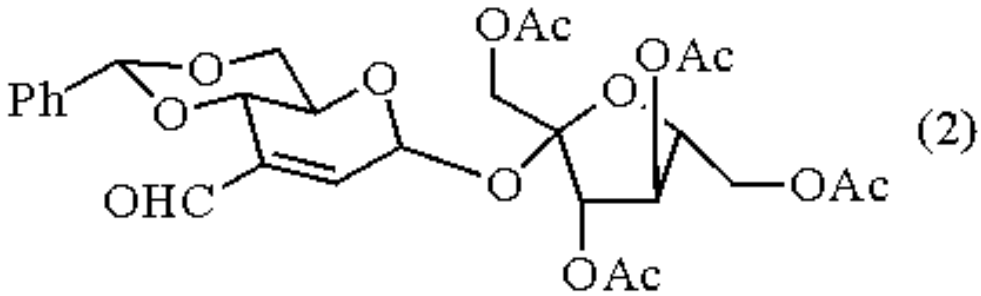

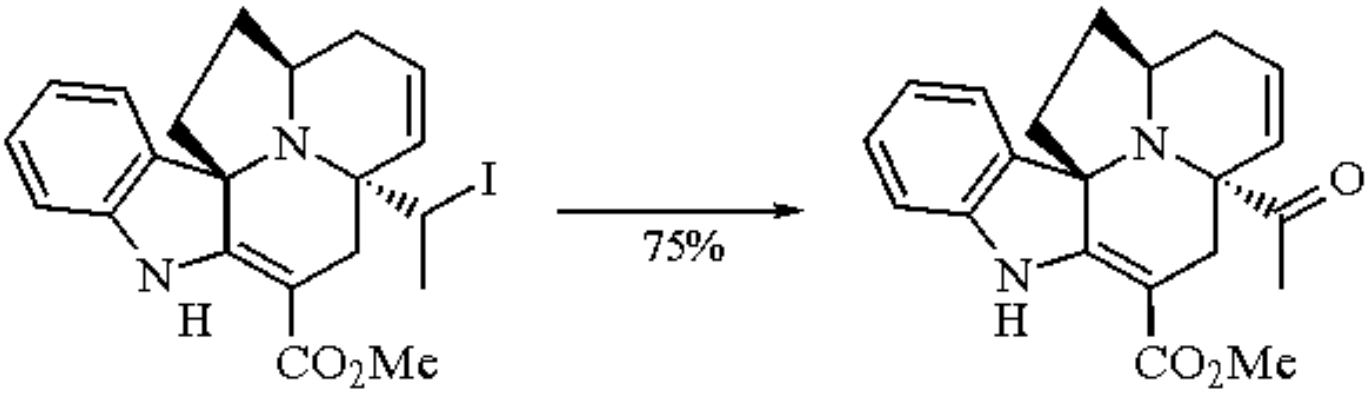

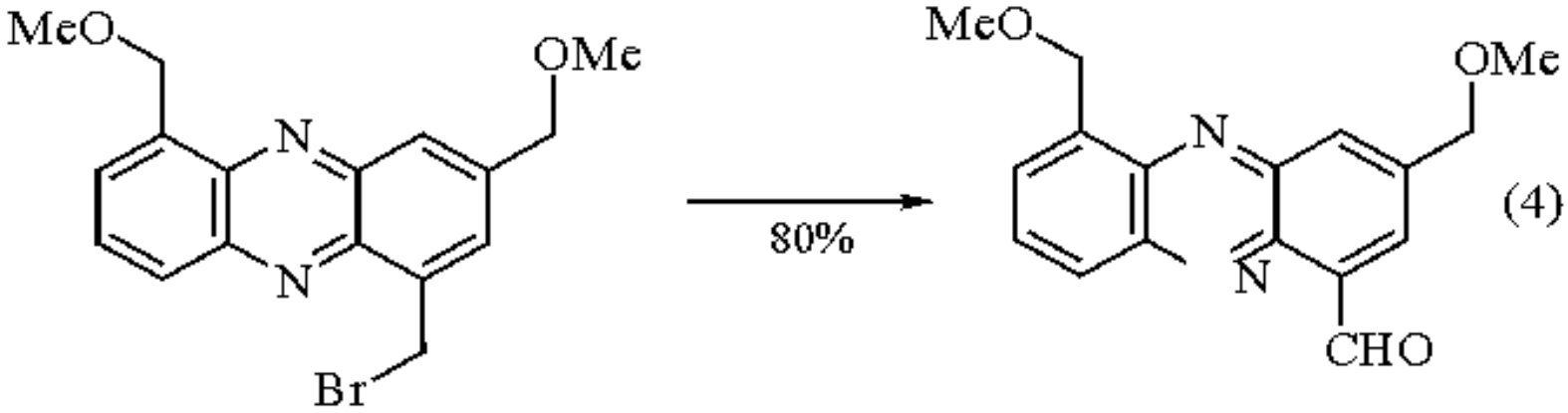

Typically, a solution of 1 mmol of halide (usually bromide or iodide) and 1.1-2.0 mmol of silver salt in 1-5 mL of DMSO is stirred at rt for 10 min to 24 h. Excess triethylamine is then added, the mixture is stirred for an additional 15 min and diluted with water. The product is isolated in the usual fashion. Several examples are given in Table 1.[1a,1b]

Table 1 Syntheses Employing DMSO-$AgBF_4$

Halide	Product	Yield (%)
		83 (0) [1b]
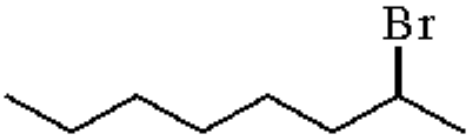	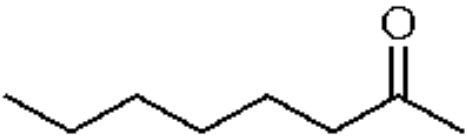	80 [1b]
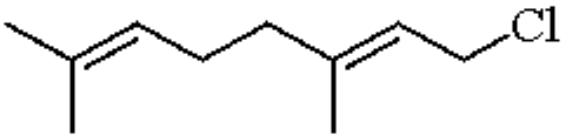	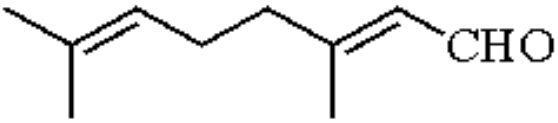	90 [1b]
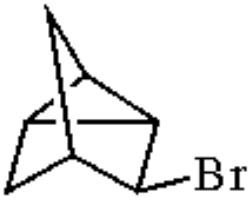	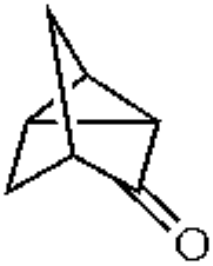	69 [1a]

1. (a) Lemal, D. M.; Fry, A. J. *JOC* **1964**, *29*, 1673. (b) Ganem, B.; Boeckman, R. K., Jr. *TL* **1974**, 917. (c) Roedig, A.; Fouré, M.; Försch, M. *CB* **1977**, *110*, 322. (d) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *JCS(P1)* **1978**, 1101. (e) Fraser-Reid, B.; Iley, D. E. *CJC* **1979**, *57*, 645. (f) Langlois, N.; Andriamialisoa, R. Z. *JOC* **1979**, *44*, 2468. (g) Tyrell, J. A., III; McEwen, W. E. *JOC* **1981**, *46*, 2476. (h) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *JOC* **1981**, *46*, 4825. (i) Nagao, Y.; Yamada, S.; Fujita, E. *TL* **1983**, *24*, 2291. (j) Liu, W.-C.; Parker, W. L.; Brandt, S. S.; Atwal, K. S.; Ruby, E. P. *J. Antibiot.* **1984**, *37*, 1313. (k) Frei, B.; Huxley, P.; Maienfisch, P.; Mereyala, H. B.; Rist,

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4. Ghera, E.; Plemenitas, A.; Ben-David, Y. *S* **1984**, 504.
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7. Cardillo, G.; Orena, M.; Sandri, S. *TL* **1976**, *44*, 3985.
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9. (a) Koyama, Y.; Huang, S-P.; Ikeda, D.; Kondo, S. *Synlett* **1990**, 389. (b) Tanaka, H.; Taniguchi, M.; Kameyama, Y.; Yamaguchi, T.; Sasaoka, M.; Shiroi, T.; Torii, S. *Synlett* **1990**, 660. (c) Kilenyi, S. N. *COS*, **1991**, *7*, 653. (d) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 599-600.
10. Ref. 9d, pp 591-593.

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Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine[1]

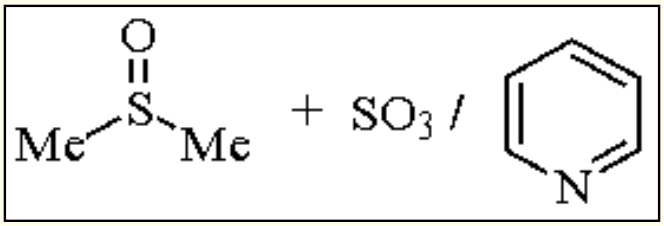

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine · (MW 78.13) (SO_3)

[7446-11-9] · O_3S · Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine · (MW 80.06) (SO_3/pyridine)

[26412-87-3] · $C_5H_5NO_3S$ · Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine · (MW 159.16)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; gives very good yields with short reaction times near rt with minimal formation of byproducts)

Alternate Name: Parikh-Doering reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. SO_3: mp 16.8 °C; bp 44.7 °C; *d* 1.970 g cm^{-3}. SO_3/pyridine: mp 175 °C.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. SO_3: reacts with H_2O. SO_3/pyridine: sol DMSO; reacts with H_2O.

Form Supplied in: DMSO is a colorless liquid; SO_3 is a low-boiling liquid, and the SO_3/pyridine complex is a crystalline solid; widely available, including SO_3/pyridine complex and anhydrous grades of DMSO packed under N_2. For the preparation of SO_3/pyridine complex see ***Sulfur Trioxide-Pyridine***.

Preparative Method: the active oxidant, formulated as $Me_2{+}SOSO_3^-$,[2d] is generated in situ by mixing DMSO and the SO_3/pyridine complex.

Purification: DMSO: distillation from CaH_2 at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; ***Sulfur Trioxide*** and SO_3/pyridine are toxic and corrosive, and react strongly with H_2O; reactions with DMSO form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide and dimethyl sulfone above 90 °C.[2c]

DMSO-SO_3/pyridine[3a] is a convenient oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively. The complex $Me_2{+}SOSO_3^-$ evidently forms on mixing DMSO and SO_3/pyridine, and upon addition of the alcohol and ***Triethylamine*** this forms the $RO{+}SMe_2$ species common to most DMSO oxidations; this alkoxysulfonium ion then reacts with added Et_3N, leading to the carbonyl product. This procedure involves operation near rt, which can be an advantage relative to the use of ***Dimethyl Sulfoxide-Oxalyl Chloride*** and usually gives fast reactions and good yields with minimal formation of byproducts. Some examples are shown in eqs 1 and 2.[3b,c] Oxidation with DMSO-SO_3/pyridine avoids the side reaction of chlorination of a pyrrole nucleus encountered with DMSO/$(COCl)_2$, but it was found necessary to add the SO_3/pyridine complex as a solid and not as a DMSO solution to the alcohol in DMSO-Et_3N-THF for oxidation to occur.[3d]

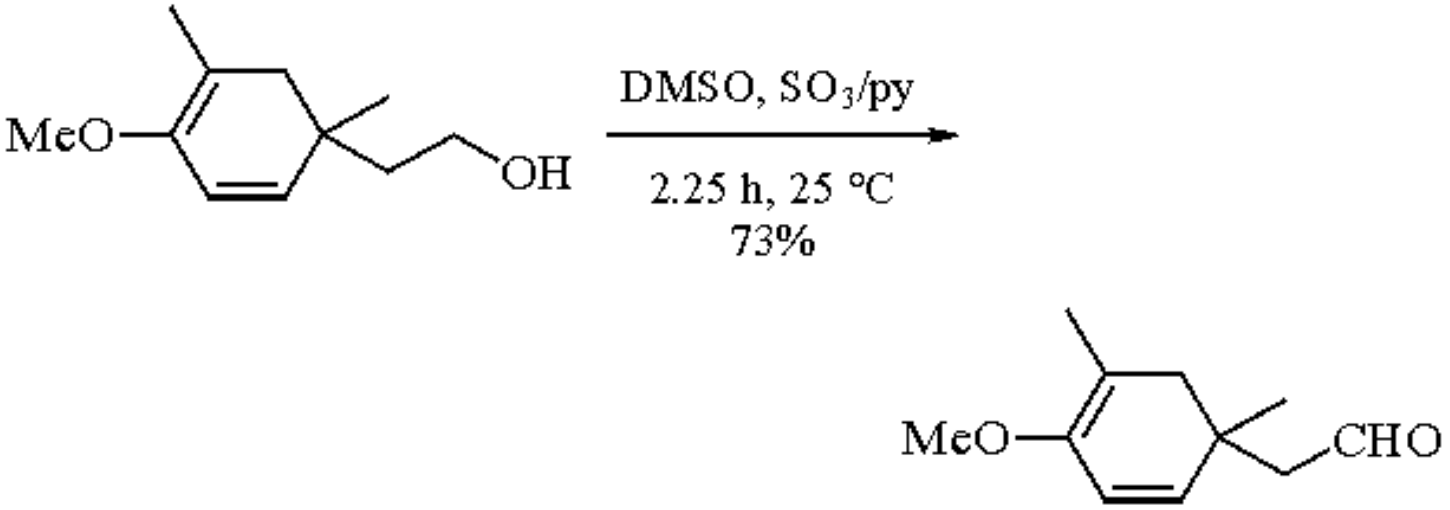

(1)

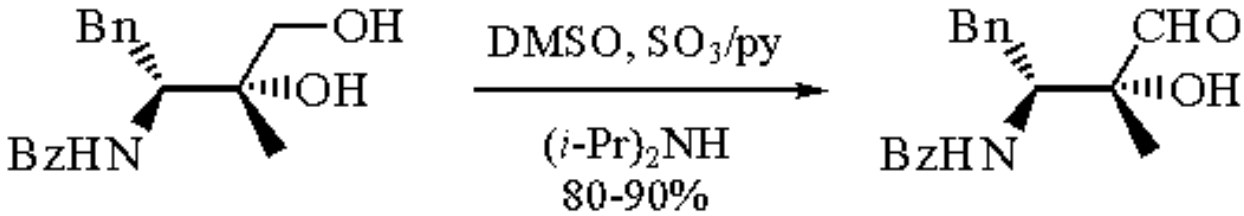

(2)

In the procedure of eq 3, Et_3N and SO_3/py were added to 0.1 mol of (**1**) at 0 °C, and after stirring the solution was diluted with EtOAc, extracted, and evaporated, and the crude product was dissolved in THF and added to Wittig reagent to give (**2**).[4]

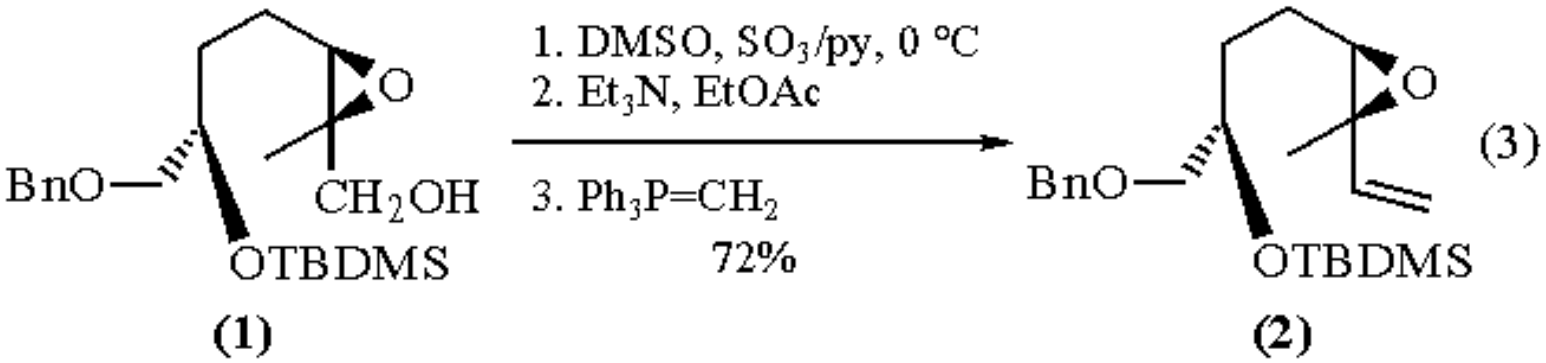

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

---

1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D. *S* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.
2. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755. (d) Varkey, T. E.; Whitfield, G. F.; Swern, D. *JOC* **1974**, *39*, 3365.
3. (a) Parikh, J. R.; Doering, W. v. E. *JACS* **1967**, *89*, 5505. (b) Schiehser, G. A.; White, J. D. *JOC* **1980**, *45*, 1864. (c) Godfrey, J. D., Jr.; Gordon, E. M.; Von Langen, D. J. *TL* **1987**, *28*, 1603. (d) Baker, R.; Castro, J. L. *JCS(P1)* **1990**, 47.
4. Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *JACS* **1993**, *115*, 3558.

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Dimethyl Sulfoxide-Trifluoroacetic Anhydride[1]

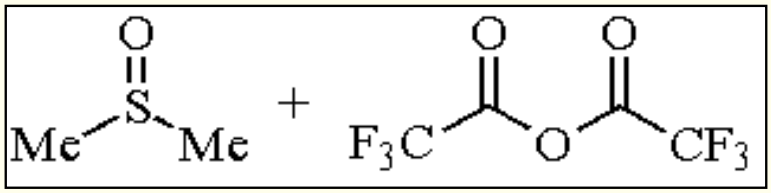

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Trifluoroacetic Anhydride · (MW 78.13) (TFAA)

[407-25-0] · $C_4F_6O_3$ · Dimethyl Sulfoxide-Trifluoroacetic Anhydride · (MW 210.03)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields with only small amounts of byproduct methylthiomethyl ethers but alcohols can be converted to trifluoroacetate esters, particularly at higher temperatures; also used for the conversion of primary amines to sulfilimines)

Alternate Name: Swern reagent.

Physical Data: DMSO: mp 18.4 °C; bp 189 °C *d* 1.101 g cm^{-3}. TFAA: mp -65 °C; bp 39.5-40 °C; *d* 1.487 g cm^{-3}.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. TFAA: sol CH_2Cl_2, ether, THF.
Drying: DMSO: distillation from CaH_2 at 56-57 °C/5 mmHg[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. TFAA: distillation.

Form Supplied in: colorless liquids; widely available, including anhydrous grades of DMSO packed under N_2, and 99%+ TFAA.

Preparative Method: The active reagent $Me_2{+}SO_2CCF_3$ is formed rapidly on the addition of TFAA to DMSO in CH_2Cl_2 at -78 °C, and is used in situ.

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; reactions with DMSO form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C on distillation at atmospheric pressure;[2c] ***Trifluoroacetic Anhydride*** is toxic, corrosive, and water-sensitive, and reacts

violently with DMSO at rt.

DMSO-TFAA is commonly used for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, and usually gives excellent yields with short reaction times and minimal formation of byproducts. The active reagent (**1**) is generated in situ at low temperature by the addition of TFAA to DMSO in a solvent such as CH_2Cl_2 (eq 1).[3a-c] Addition of the alcohol to (**1**) gives the alkoxysulfonium ion (**2**) (eq 2), which on addition of an amine base is deprotonated to (**3**); the latter forms the carbonyl product (**4**) by intramolecular proton abstraction (eq 3). Trifluoroacetates are sometimes byproducts in these reactions, but the use of ***Trichloroacetic Anhydride*** instead of TFAA prevents this problem.[3d]

$$Me_2S{=}O + (CF_3CO)_2O \longrightarrow \underset{\textbf{(1)}}{Me_2\overset{+}{S}O_2CCF_3\ CF_3CO_2^-} \qquad (1)$$

$$\textbf{(1)} + RR^1CHOH \longrightarrow \underset{\textbf{(2)}}{RR^1CHO\overset{+}{S}Me_2} \qquad (2)$$

$$\textbf{(2)} \xrightarrow{\text{base}} \underset{\textbf{(3)}}{RR^1CHO\overset{+}{S}MeCH_2^-} \longrightarrow \underset{\textbf{(4)}}{RR^1C{=}O} + Me_2S \qquad (3)$$

The examples shown in eq 4[4a] and eq 5[4b] illustrate the preparation of ketones in good yield with this reagent, while eq 6,[4c] eq 7,[4d] and eq 8[4e] show the oxidation of diols. The example of eq 6 gave only a 25% yield with ***Oxalyl Chloride*** activation.[4c] In the reaction of eq 8, ring opening and elimination of HBr also occurs.[4e] The addition of 2-propanol has been used to quench excess oxidant in this procedure.[4f]

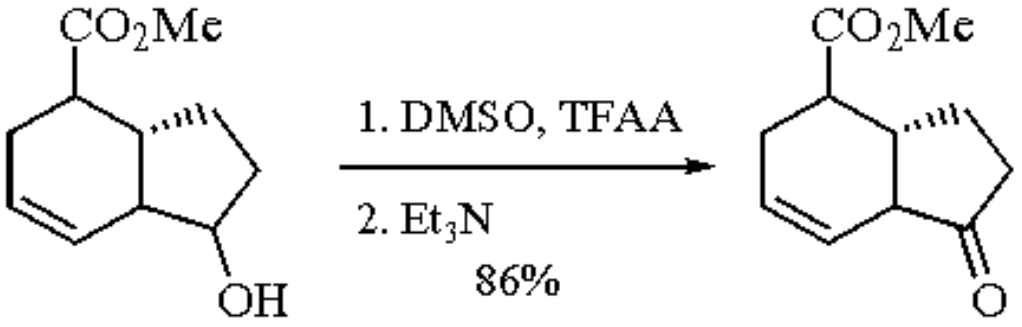

(4)

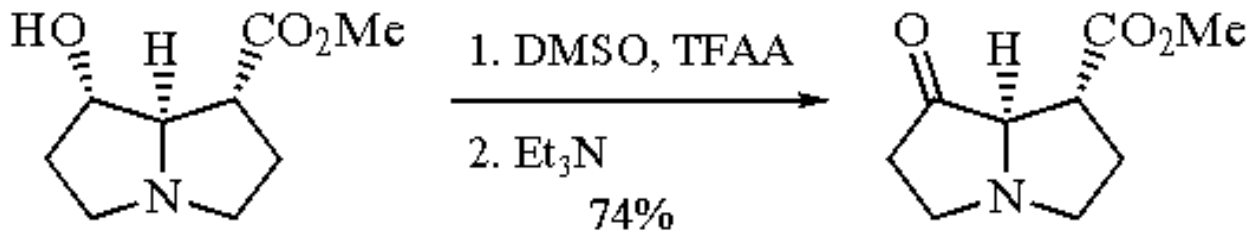

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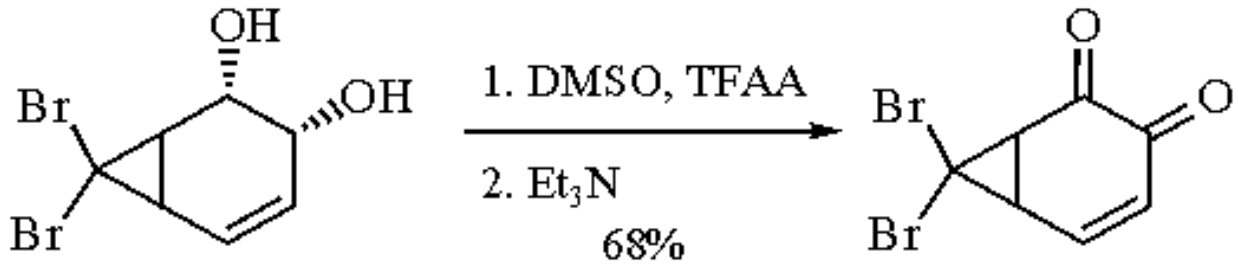

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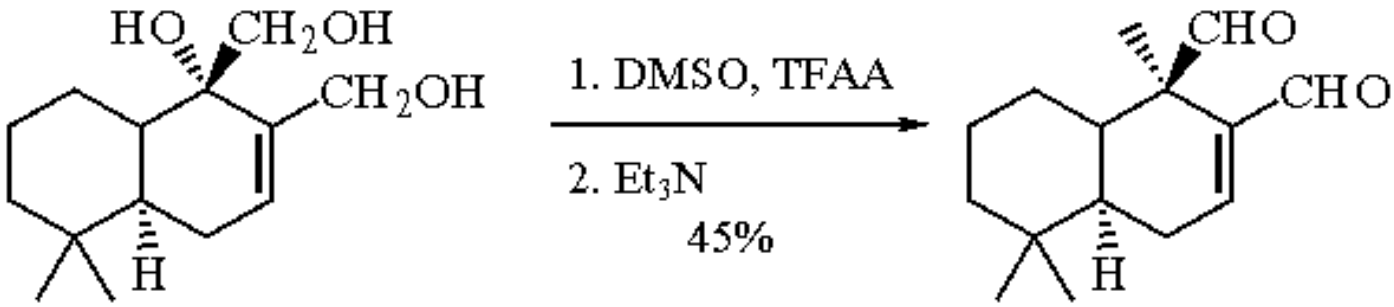

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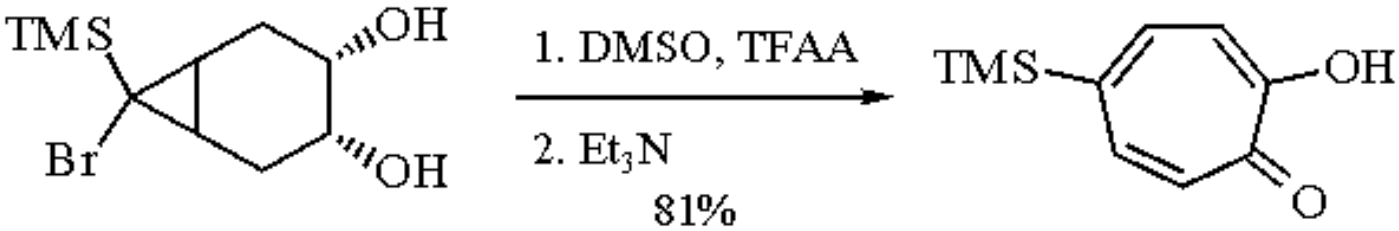

(8)

The title reagent can react with electron-rich aromatic compounds to give aryldimethylsulfonium salts (eq 9).[5a] DMSO and ***Trifluoroacetic Acid*** (TFA) oxidize sulfides to disulfides, and the activation of the DMSO in this case was proposed to occur by protonation of the DMSO (eq 10).[5b] Oxidations with DMSO-TFAA followed by ***Triethylamine*** can result in formation of the byproduct (**5**), which is suggested to arise by a single electron transfer process (eq 11).[4c] Activation of DMSO by TFAA for oxidation of a dithiane avoids the problem of dithiane monosulfoxide formation encountered with $(COCl)_2$ activation.[5c] Sulfilimines are formed by reaction of DMSO-TFAA with primary amines (eq 12).[1e,5d]

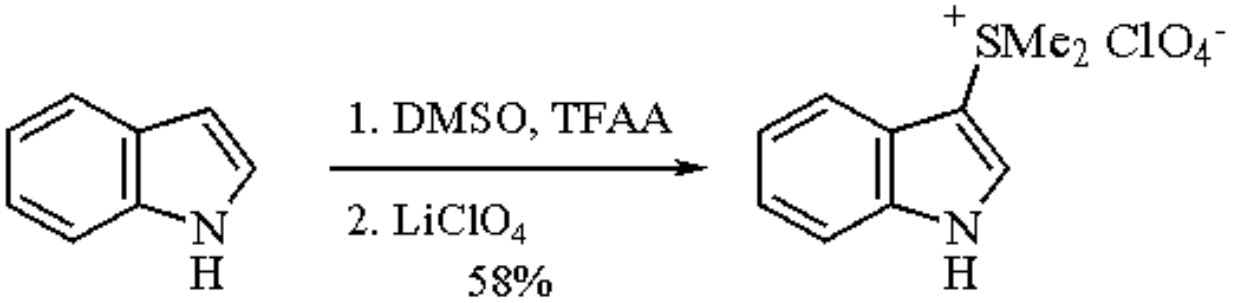

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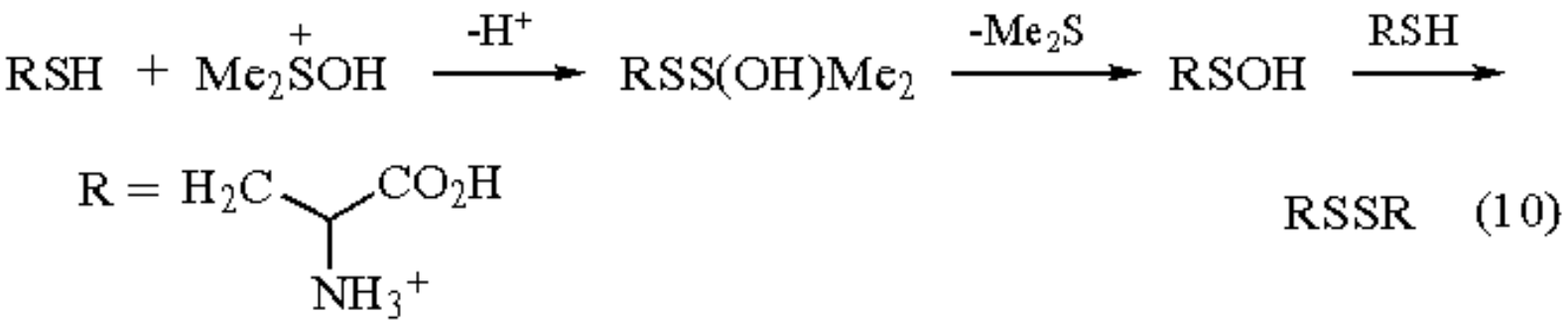

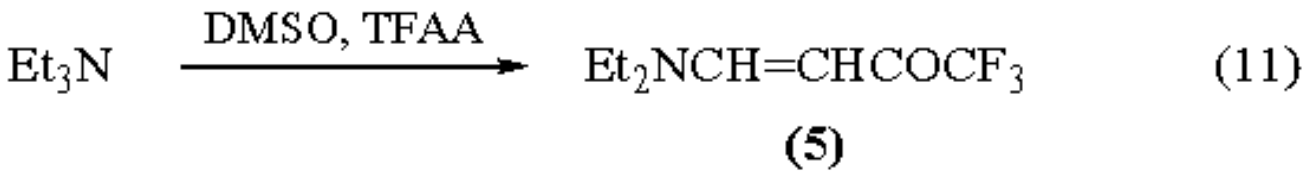

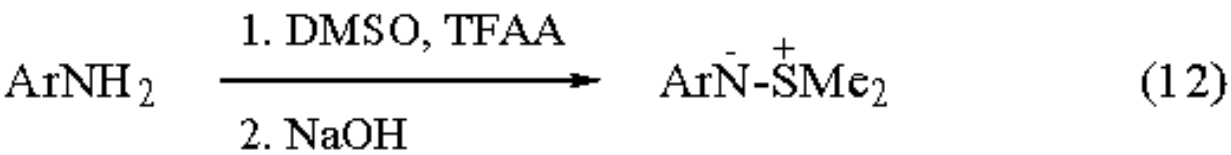

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Triphosgene***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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2. (a) Iwai, I.; Ide, J. *OSC* **1988**, *6*, 531. (b) Insalaco, M. A.; Tarbell, D. S. *OSC* **1988**, *6*, 207. (c) Corey, E. J.; Chaykovsky, M. *OSC* **1973**, *5*, 755.
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4. (a) Roush, W. R.; Gillis, H. R.; Ko, A. I. *JACS* **1982**, *104*, 2269. (b) Chamberlin, A. R.; Chung, J. Y. L. *JOC* **1985**, *50*, 4425. (c) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *JOC* **1987**, *52*, 4851. (d) Ley, S. V.; Mahon, M. *TL* **1981**, *22*, 3909. (e) Banwell, M. G.; Onrust, R. *TL* **1985**, *26*, 4543. (f) Barrett, A. G. M.; Barta, T. E.; Flygare, J. A.; Sabat, M.; Spilling, C. D. *JOC* **1990**, *55*, 2409.
5. (a) Hartke, K.; Teuber, D.; Gerber, H.-D. *T* **1988**, *44*, 3261. (b) Otaka, A.; Koide, T.; Shide, A.; Fujii, N. *TL* **1991**, *32*, 1223. (c) Braish, T. F.; Saddler, J. C.; Fuchs, P. L. *JOC* **1988**, *53*, 3647. (d) Hyde, C. B.; Welham, K. J.; Mascagni, P. *JCS(P2)* **1989**, 2011.

Dimethyl Sulfoxide-Triphosgene[1]

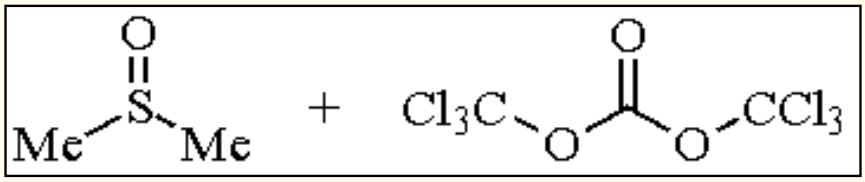

(DMSO)

[67-68-5] · C_2H_6OS · Dimethyl Sulfoxide-Triphosgene · (MW 78.13) ($(CCl_3O)_2CO$)

[32315-10-9] · $C_3Cl_6O_3$ · Dimethyl Sulfoxide-Triphosgene · (MW 296.75)

(oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones, respectively; avoids overoxidation to carboxylic acids; suitable for large-scale oxidation; gives good yields of high-purity products; more convenient than the use of phosgene)

Physical Data: DMSO: mp 18.4 °C; bp 189 °C; *d* 1.101 g cm^{-3}. $(CCl_3O)_2CO$: bp 203-206 °C; mp 79-83 °C.

Solubility: DMSO: sol H_2O, alcohol, acetone, THF, CH_2Cl_2. $(CCl_3O)_2CO$: reacts H_2O; sol CH_2Cl_2, THF, *o*-dichlorobenzene.

Form Supplied in: DMSO: colorless liquid; widely available, including anhydrous grades of DMSO packed under N_2. $(CCl_3O)_2CO$: crystalline solid, widely available.

Preparative Method: the active reagent is not known, but may be $Me_2{+}SCl$, formed from DMSO and triphosgene at -78 °C in CH_2Cl_2, or may be $Me_2{+}SOCO_2CHRR^1$, generated after addition of the alcohol, as in the case of phosgene.

Purification: DMSO: distillation from calcium hydride at 56-57 °C/5 mmHg,[2a] or 83-85 °C/17 mmHg;[2b] storage over 3Å molecular sieves. $(CCl_3O)_2CO$: drying at 0.1 mmHg.[3a]

Handling, Storage, and Precautions: ***Dimethyl Sulfoxide*** is readily absorbed through the skin and should always be handled with gloves in a fume hood; its reactions form foul-smelling byproducts and should be carried out with good ventilation, and the waste byproducts and liquids used for washing should be treated with $KMnO_4$ solution to oxidize volatile sulfur compounds; DMSO undergoes appreciable disproportionation to dimethyl sulfide (stench!) and dimethyl sulfone above 90 °C;[2c] $(CCl_3O)_2CO$ is a lachrymator, is moisture sensitive, and decomposes to ***Phosgene***; it therefore should be used with the same precautions as used for phosgene, which is highly toxic;[3b] use in a fume hood.

Triphosgene, or ***Bis(trichloromethyl) Carbonate***, is a solid reagent that is easier to handle than phosgene,[3c] and that can be used as a phosgene substitute in many applications.[3] However, triphosgene forms highly toxic phosgene on heating and should be used with due precautions.[3b] DMSO-triphosgene has been used in the oxidation of alcohols on a 0.1 M scale (eqs 1, 2).[4] The reactions are carried out by adding DMSO to triphosgene in CH_2Cl_2 at -78 °C, followed by addition of the alcohol and then ***Triethylamine***. Presumably the alkoxysulfonium ion Me_2+SOR common to most DMSO base oxidations is formed, but the mechanism has not been studied.

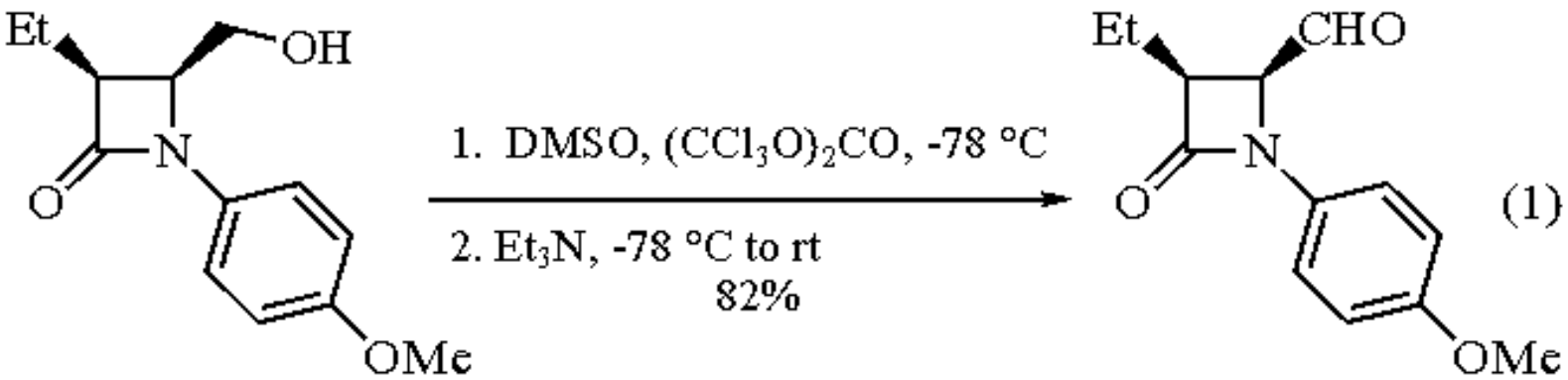

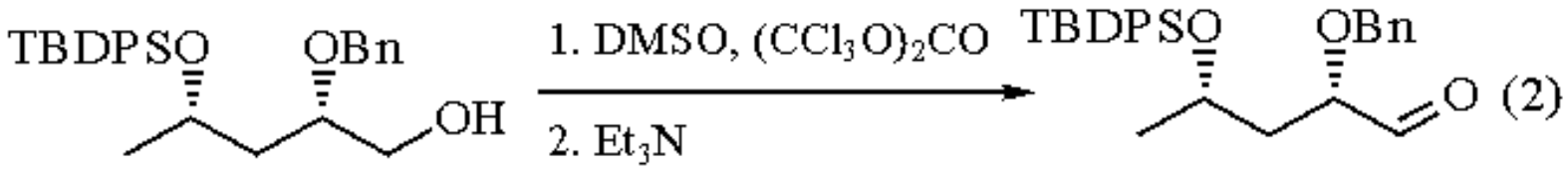

Related Reagents.

N-Chlorosuccinimide-Dimethyl Sulfide; ***Chromic Acid***; ***Dimethyl Sulfide-Chlorine***; ***Dimethyl Sulfoxide-Acetic Anhydride***; ***Dimethyl Sulfoxide-Dicyclohexylcarbodiimide***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Dimethyl Sulfoxide-Oxalyl Chloride***; ***Dimethyl Sulfoxide-Phosgene***; ***Dimethyl Sulfoxide-Phosphorus Pentoxide***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***; ***Manganese Dioxide***; ***Pyridinium Chlorochromate***; ***Pyridinium Dichromate***; ***Ruthenium(VIII) Oxide***; ***Silver(I) Carbonate***; ***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***.

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1. (a) Tidwell, T. T. *OR* **1990**, *39*, 297. (b) Tidwell, T. T. *S* **1990**, 857. (c) Lee, T. V. *COS* **1991**, *7*, 291. (d) Haines, A. H. *Methods for the Oxidation of Organic Compounds*; Academic: London, 1988. (e) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS: Washington, 1990. (f) Mancuso, A. J.; Swern, D. *S* **1981**, 165. (g) Moffatt, J. G. In *Oxidation*; Augustine, R. L.; Trecker, D. J., Eds.; Dekker: New York, 1971; Vol. 2, Chapter 1.
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3. (a) Eckert, H.; Forster, B. *AG(E)* **1987**, *26*, 894. (b) Damle, S. B. *Chem. Eng. News* **1993**, *71* (6), 4. (c) Barton, D. H. R.; Garner, B. J.; Wightman, R. H. *JCS* **1964**, 1855.
4. (a) Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *JOC* **1991**, *56*, 5948. (b) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Garcia, J. M. *JOC* **1993**, *58*, 1646.

Thomas T. Tidwell

Dimethylsulfoxonium Methylide[1]

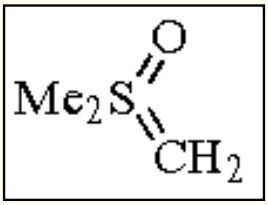

[6814-64-8] · C_3H_8OS · Dimethylsulfoxonium Methylide · (MW 92.16)

(widely used methylene transfer reagent; used for the epoxidation of ketones and aldehydes,[1] cyclopropanation of α,β-unsaturated carbonyl compounds[1] and also as a methylation reagent[2])

Physical Data: pK_a of sulfoxonium ion (Me_3+S(O)) at 25 °C in DMSO is 18.2;[3] mp 9-10 °C, bp 41-43 °C/0.1 mmHg.[4]

Solubility: sol THF, DMSO, 1,4-dioxane, DMF.

Preparative Method: usually generated in situ by the reaction of trimethylsulfoxonium iodide or chloride with strong base in a appropriate solvent without drying or further purification; not commercially available.

Analysis of Reagent Purity: determined by adding a small quantity of the reagent to water and titrating with standard acid using phenolphthalein as indicator.[5]

Handling, Storage, and Precautions: reactions using this nucleophilic reagent should be carried out under an inert atmosphere; it is more stable than ***Dimethylsulfonium Methylide*** and can be stored in solution under N_2 at 0 °C for months without appreciable decomposition.

Preparation.

Dimethylsulfoxonium methylide is a stabilized ylide which is generally prepared and used at rt.[1,6,7] Typically, the reagent is obtained by the reaction of finely powdered ***Trimethylsulfoxonium Iodide*** (or trimethylsulfoxonium chloride) with a strong base such as ***Sodium Hydride*** or ***n-Butyllithium*** under nitrogen in a suitable solvent. A variety of anhydrous solvents such as DMSO, THF, DMF, and 1,4-dioxane are reported to work well for this reaction. When NaH is used as the base, after hydrogen evolution has completed, the resulting ylide is ready for further reaction.[8]

Recently, a less hazardous modification for large-scale production has been reported. This method involves the reaction of ***Potassium t-Butoxide*** with trimethylsulfoxonium iodide in DMSO. Use of potassium *t*-butoxide eliminates the hazards of handling sodium hydride on a large scale, and also eliminates problems with the isolation of products which may be contaminated with the mineral oil from sodium hydride dispersions.[9] Preparation of dimethylsulfoxonium

methylide can also be achieved by using *t*-BuOK in *t*-butanol.[10] Alternatively, dimethylsulfoxonium methylide is accessible via a desilylation process.[11]

Preparations of sulfur ylides under phase-transfer catalyzed conditions have also been reported. One such system involved the use of CH_2Cl_2, ***Tetra-n-butylammonium Iodide*** (TBAI), NaOH, and trimethylsulfoxonium iodide.[12] *N*-Benzyl-*N*,*N*,*N*-trimethylammonium chloride has also been reported as an efficient catalyst for this reaction.[13] An alternative system using trimethylsulfoxonium iodide, cetrimide (cetyltrimethylammonium bromide), aqueous NaOH, and 1,1,1-trichloroethane has also been reported.[14] Usually, the phase-transfer catalyzed reactions are performed at elevated temperatures from 50 to 75 °C.

Epoxidation.

Dimethylsulfoxonium methylide is commonly used for epoxide preparation by reaction with a variety of compounds which contain an aldehyde or a ketone group (eqs 1-5).[1,3,7,8,15-19] Normally very high yields and purities of the desired epoxides are obtained. Use of trimethylsulfoxonium iodide instead of trimethylsulfonium iodide eliminates the need for removal of the noxious byproduct Me_2S. The byproduct DMSO generated from dimethylsulfoxonium methylide preparation can be readily removed by using standard organic/aqueous extractions. The reaction involves initial nucleophilic addition (dimethylsulfoxonium methylide) to the carbonyl group and subsequent elimination of DMSO and epoxide formation. Enolization usually does not compete with nucleophilic addition to the carbonyl group.[3]

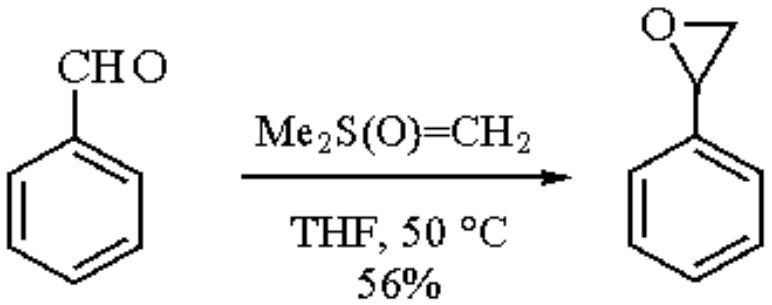

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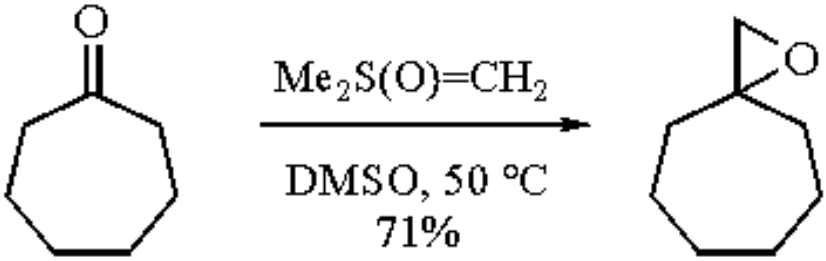

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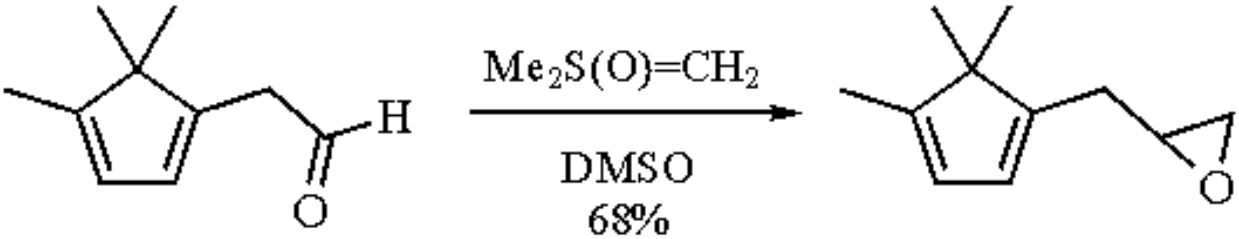

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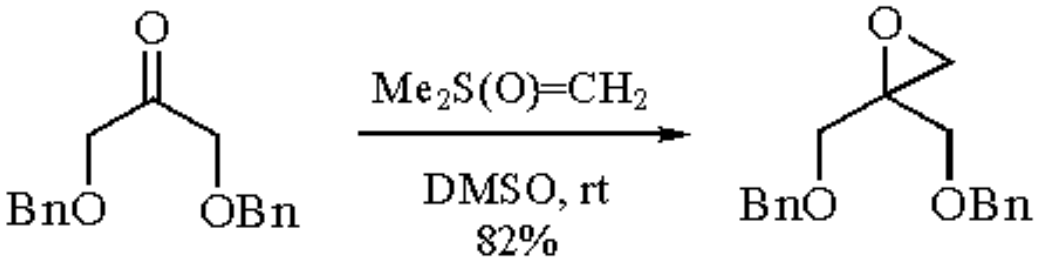

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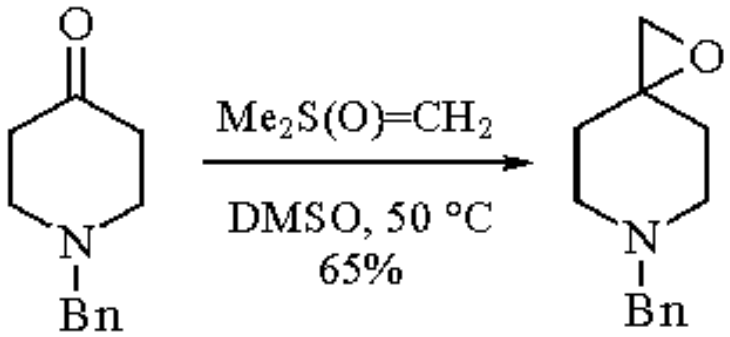

(5)

Instead of using strong base in an anhydrous media, epoxides have also been prepared under phase-transfer catalysis conditions with a sulfur ylide.[12-14,20,21] Activated ***Barium Hydroxide*** was reported to catalyze the oxirane formation in interfacial solid-liquid conditions.[22,23] These reactions were performed in MeCN in the presence of $Ba(OH)_2$ with a small amount of H_2O.

The condensation of 1-tetralone with dimethylsulfoxonium methylide affords the corresponding oxirane in 75% yield.[24,25] However, if this parent ketone possesses an aromatic electron-releasing substituent such as a methoxy group, the resulting spiro-oxirane may not be stable and may readily rearrange to give ring-opened compounds.

Dimethylsulfoxonium methylide has also been employed in nucleoside preparations.[26] The reagent has been used to introduce the spiro epoxy group at the C-2´ position of 2´-keto-β-L-nucleosides. In this case, better yields of oxiranes are obtained with the use of trimethylsulfoxonium chloride instead of trimethylsulfoxonium iodide. Variation of the base used has a major effect on the course of the reaction. Only 2-L-galacto-spiro-epoxynucleoside is obtained if the dimethylsulfoxonium methylide is prepared from BuLi (eq 6).[27]

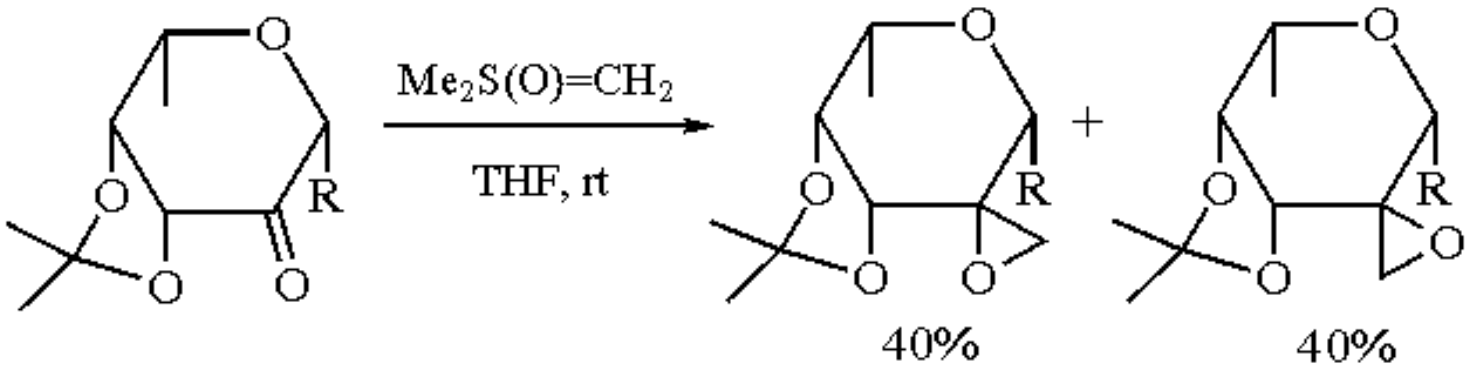

(6)

R = thyminyl, theophyllinyl

In some examples, selective epoxidations were observed in the reaction of dimethylsulfoxonium methylide with dicarbonyl compounds. Selective condensation (83% yield) of dimethylsulfoxonium methylide with the six-membered-

ring carbonyl group of *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione was observed, while the cyclopentanone remained unreacted (eq 7).[28]

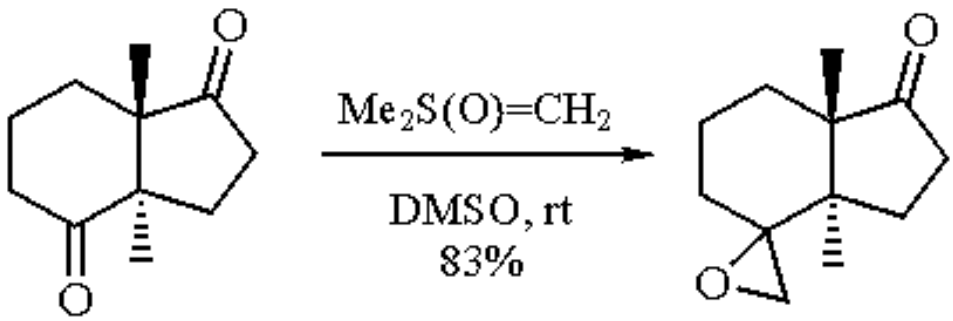

(7)

The further transformation of the product epoxides to other functionalities by treatment with nucleophiles or Lewis acids has been widely reported. Epoxidation of quadricyclanone and adamantanone with dimethylsulfoxonium methylide provided spiro-oxirane products in good yields.[29,30] In the case of adamantanone, the product oxirane was further converted to the rearranged acid by reaction with ***Boron Trifluoride Etherate*** followed by oxidation with Jones' reagent (eq 8). Similarly, reaction of dimethylsulfoxonium methylide with methylheptenone followed by treatment of $BF_3.OEt_2$ provided the rearranged 2-isopropyl-5-methylcyclopentanone (eq 9).[17]

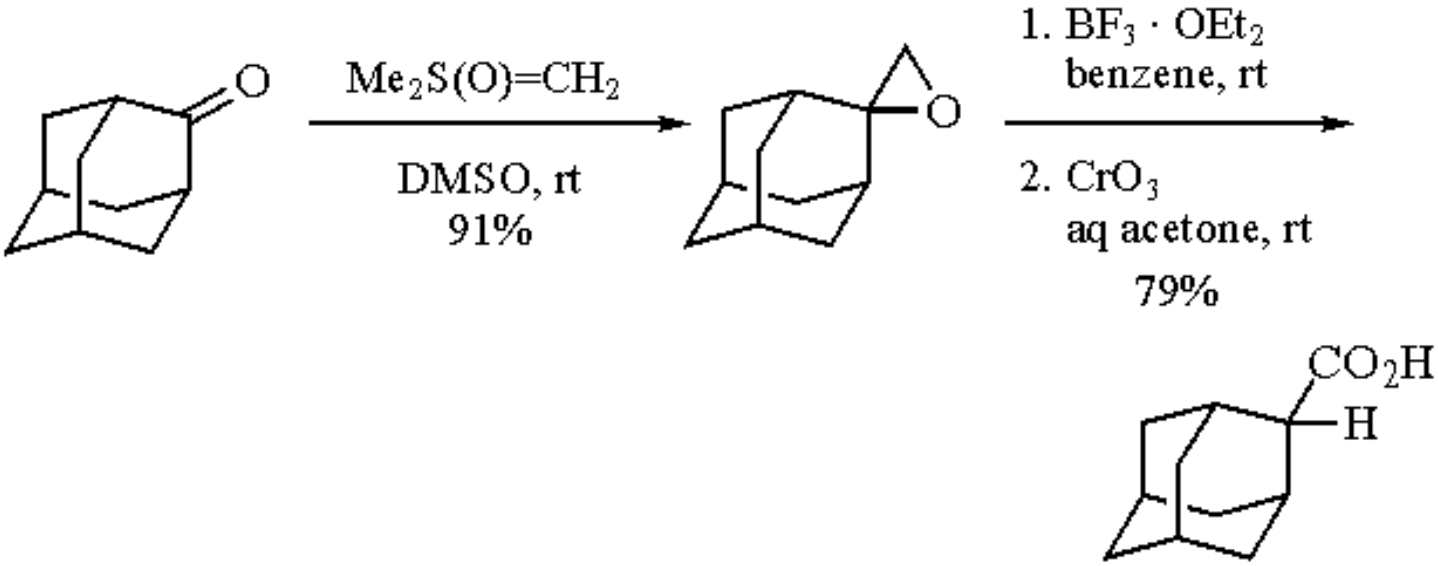

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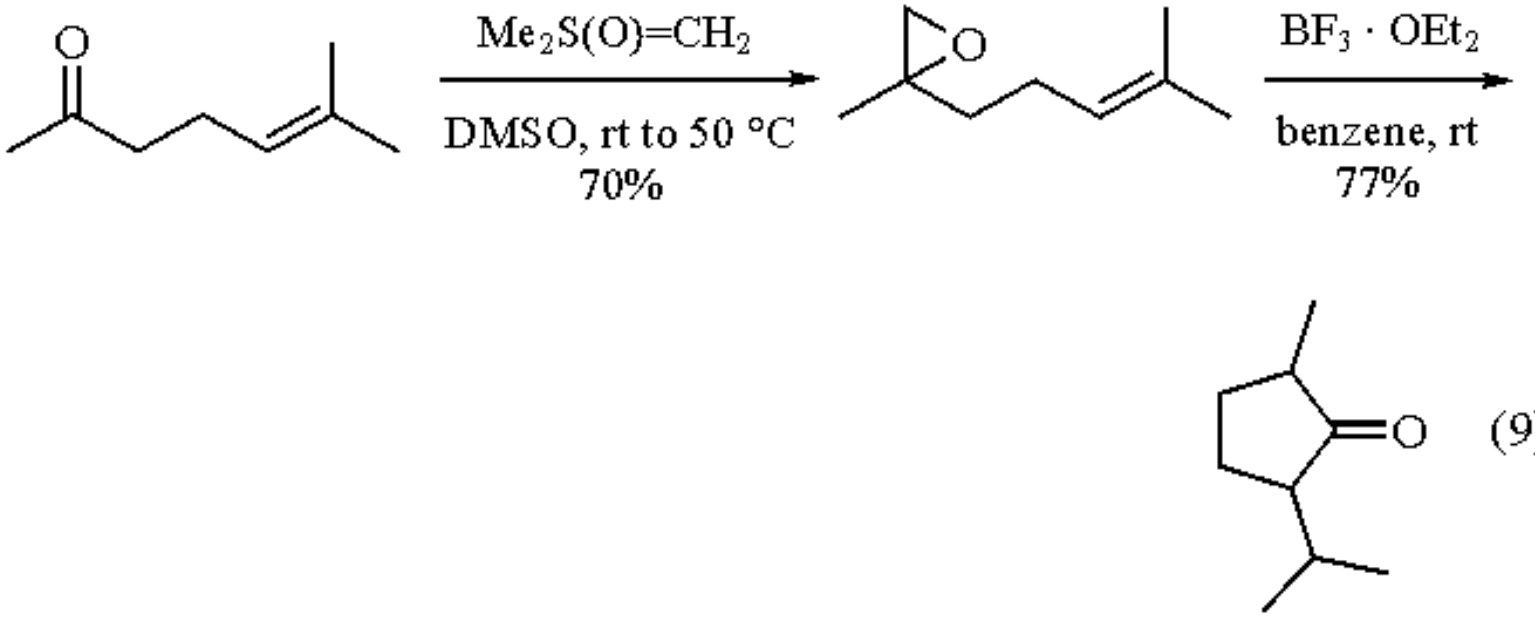

Reactions of hydroxybenzopyranones, hydroxyphenylalkanones, and 2-(*o*-hydroxyphenyl)alkyl ketones with dimethylsulfoxonium methylide provide an efficient route to oxygen heterocycles (eq 10).[31-33] The mechanism involves an intramolecular ring opening of the oxirane intermediate.

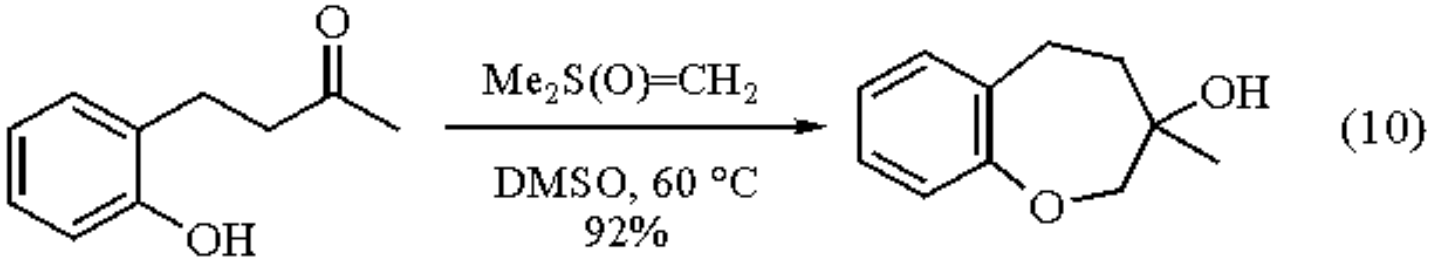

Stereoselective Epoxide Synthesis.

Dimethylsulfoxonium methylide has been reported to show higher stereoselectivity in reactions with aldehydes and ketones than its sulfonium analog. Reaction of 4-*t*-butylcyclohexanone with dimethylsulfoxonium methylide gave exclusively the *cis*-oxirane, while reaction with ***Dimethylsulfonium Methylide*** gave products with a ratio of 17:83 of the *trans* and *cis* isomers (eq 11).[1,34] Presumably the sulfoxonium ylide provided the kinetically controlled product, while the smaller sulfonium ylide gave a mixture of the kinetically and thermodynamically favored products. Similarly, epoxidation of 4-protoadamantanone with dimethylsulfoxonium methylide gave almost exclusively the *exo* isomer (*exo*:*endo* = 15:1), while the dimethylsulfonium methylide provided a mixture of the *exo* and *endo* isomers in a 3:2 ratio (eq 12).[35]

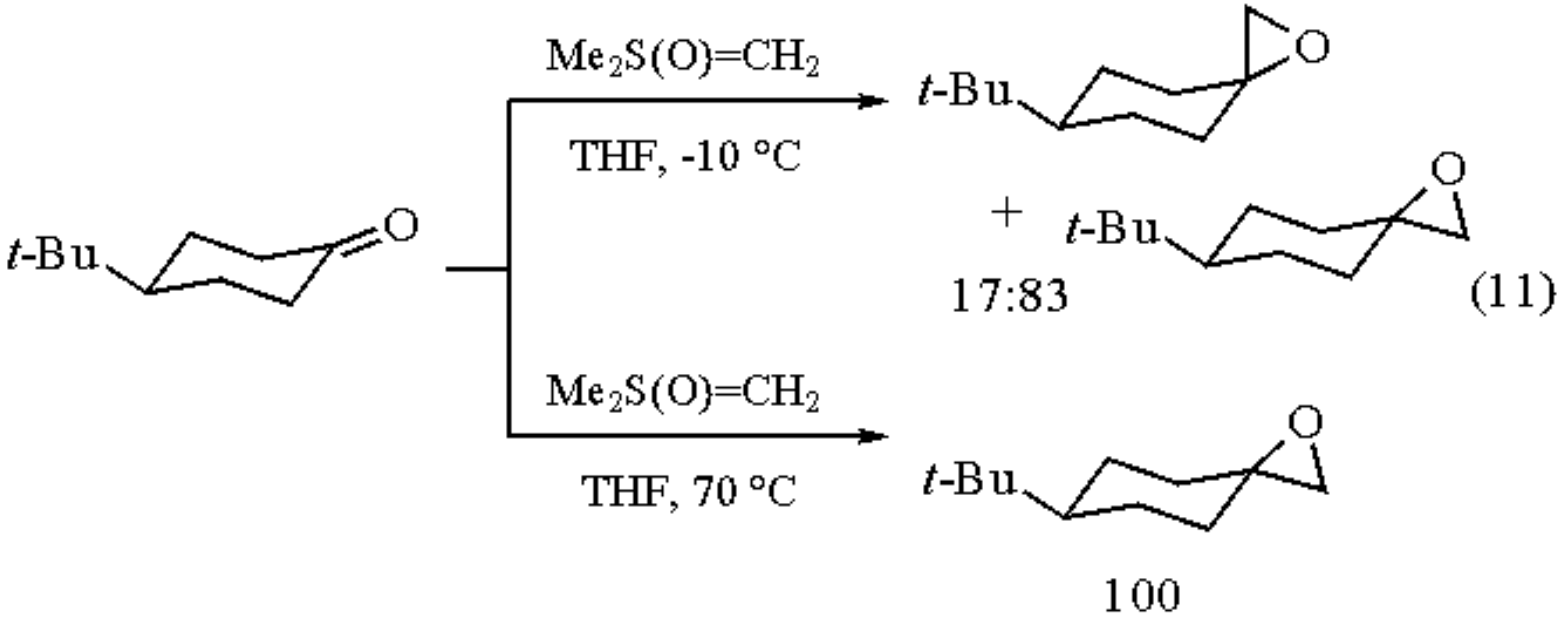

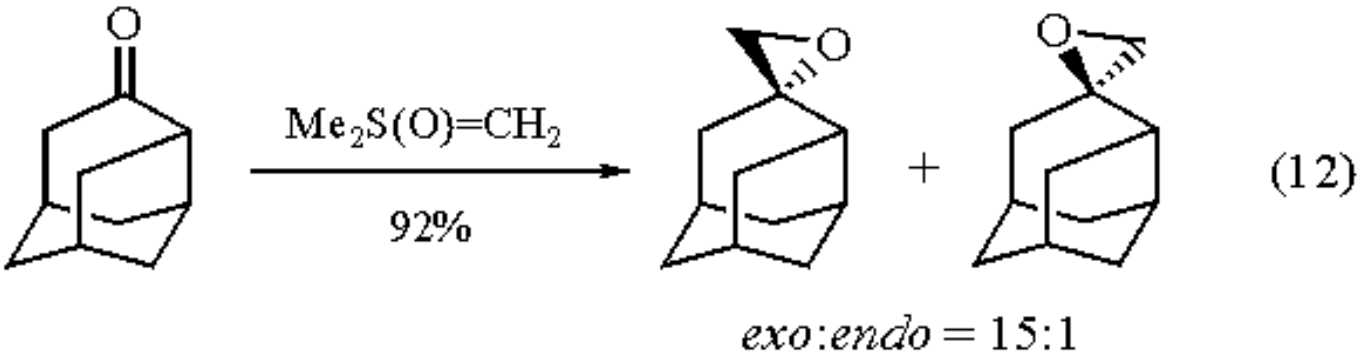

Several examples of conversion of chiral ketones and aldehydes to epoxides with high diastereomeric purity have been reported.[36-38] Stereoselective reaction of the nucleoside 2´-keto-3´,5´-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine with dimethylsulfoxonium methylide at 0 °C afforded only one isomer of the product epoxide in 63% yield.[39] Reaction of the heterocyclic carbonyl compounds with dimethylsulfoxonium methylide also provided the corresponding oxiranes, such as 1-oxa-6-heterospiro[2,5]octanes, in good yields and isomeric purities.[40,41] One example showed that dimethylsulfoxonium methylide reacted chemoselectively with the five-membered ketone ring in the presence of the six-membered carbonyl function to give the monoepoxide in good yield (eq 13).

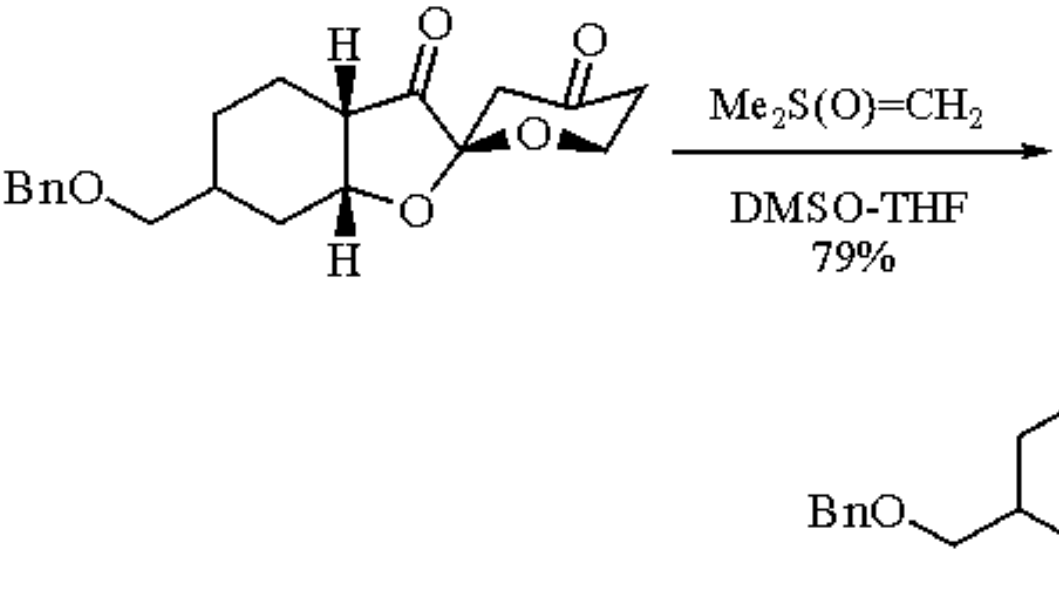

(13)

In some cases, solvent appears to affect the stereoselectivity of the oxirane formation. Reaction of 3α,18-dihydroxy-17-noraphidicolan-16-one with dimethylsulfoxonium methylide in THF gives a 1:1 mixture of epoxides. When THF is replaced by DMSO as the solvent, the isomeric ratio is improved to 1:3. In the mixed solvent DMSO/DMI system, the ratio is further improved to 1:4.[42]

Generation of New Sulfur Ylides.

Treatment of cyclic β-chloro-substituted enones and chloropyrimidines with dimethylsulfoxonium methylide results in the formation of new sulfoxonium ylides.[43-47] Dimethylsulfoxonium methylide also reacts with acid anhydride,[48] acid chloride,[49] isocyanate,[50] and other activated carbonyl groups[51,52] to generate new sulfur ylides for further reactions. This method has been used to prepare acylated stable ylides[53] which can be converted to other products or further reacted with a second mole of the α,β-unsaturated carbonyl compounds (eqs 14-16).

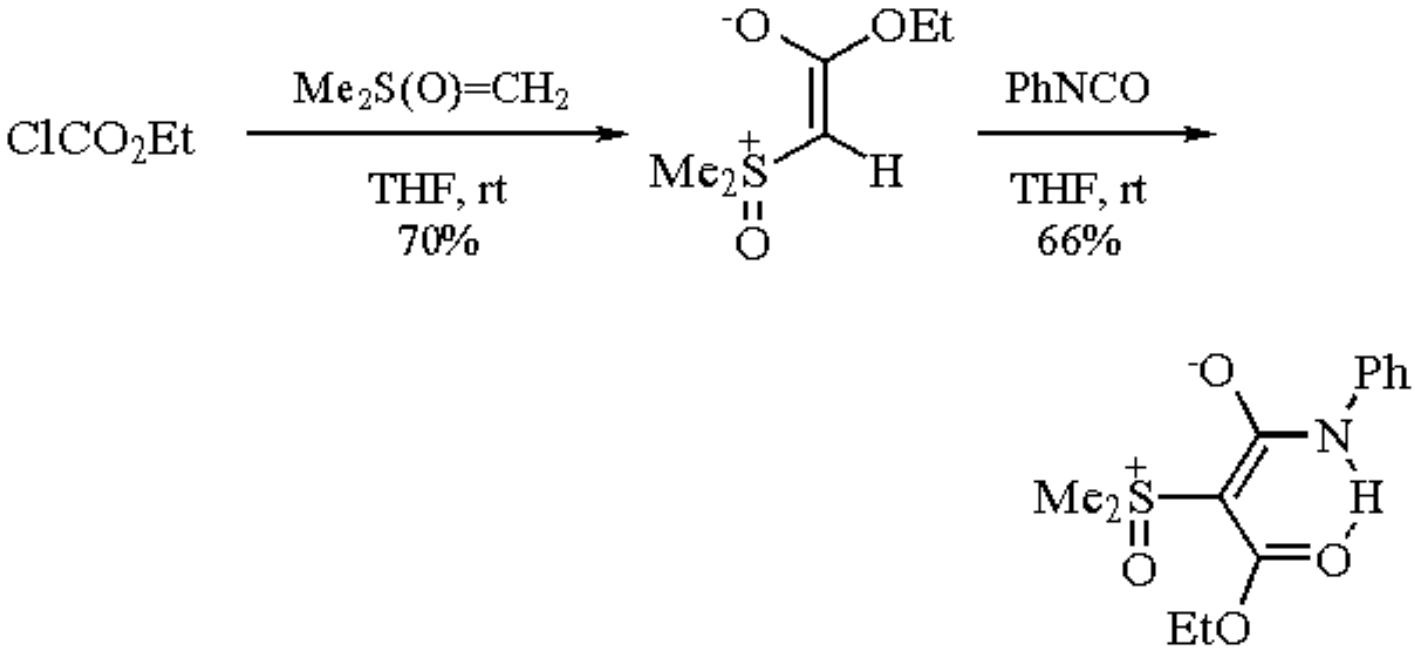

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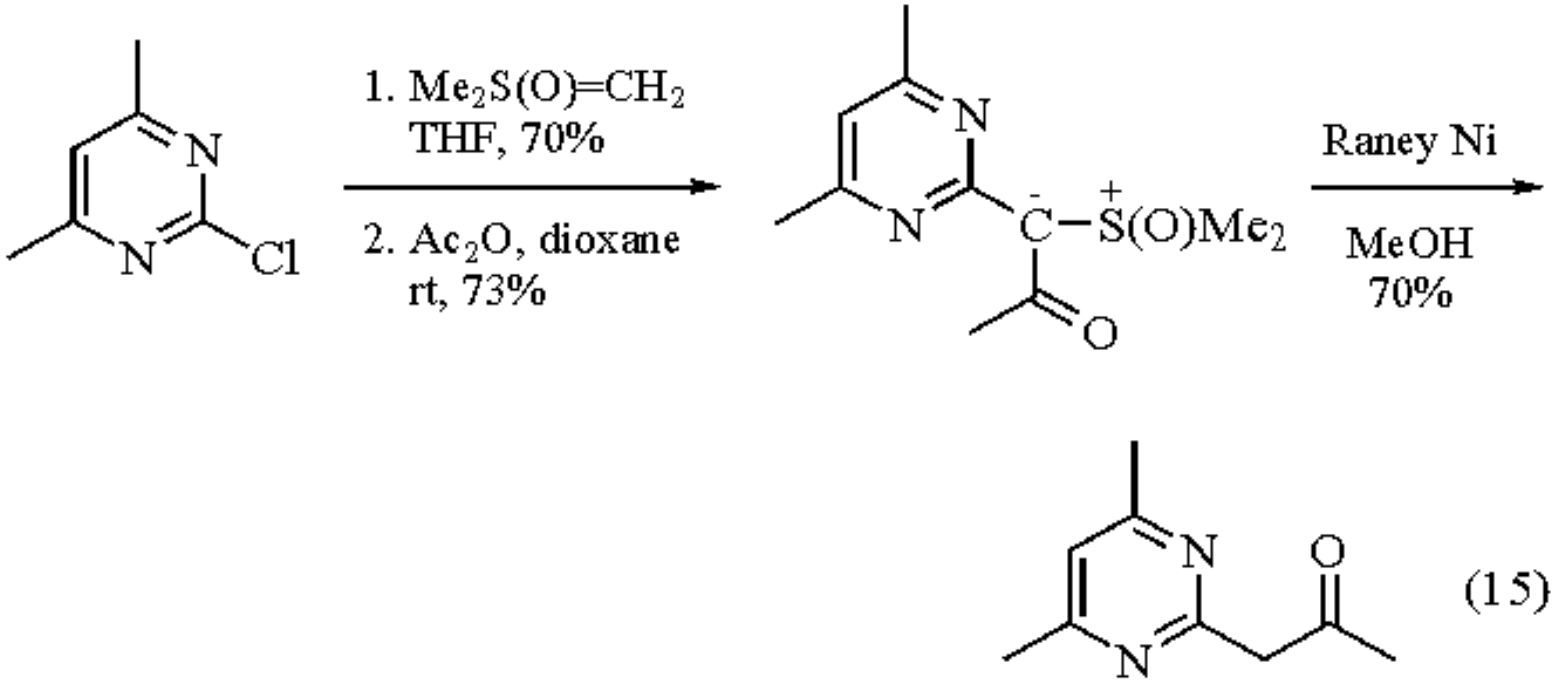

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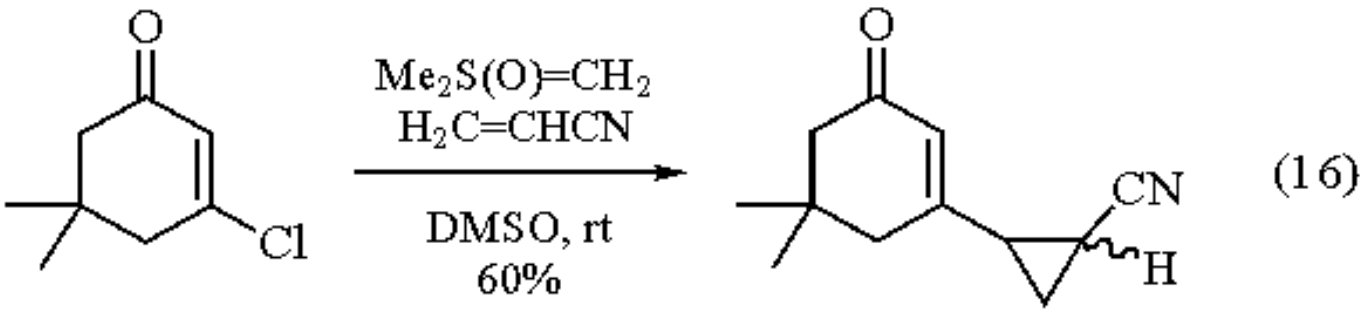

(16)

Methylation.

Dimethylsulfoxonium methylide is a useful methylation reagent for the conversion of acids,[54] oximes,[55] N-heterocycles,[56] and aromatic hydrocarbons[57] to the corresponding methylated products. For example, nitrobenzene and 6-benzyladenine were methylated with dimethylsulfoxonium methylide in 67% and 63% yields (eqs 17 and 18).[2]

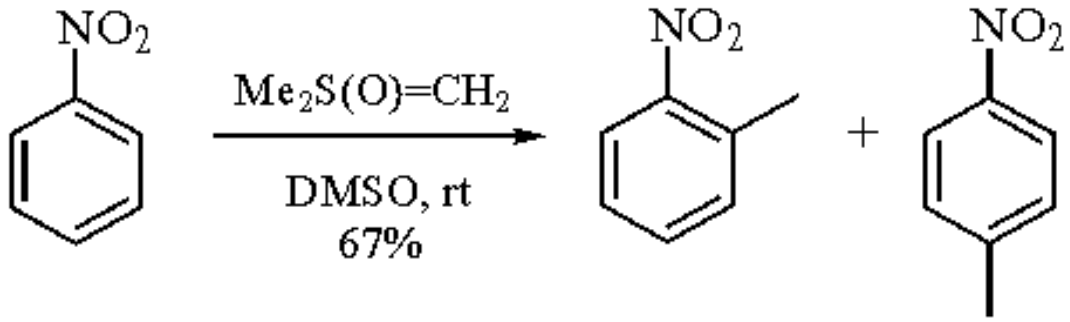

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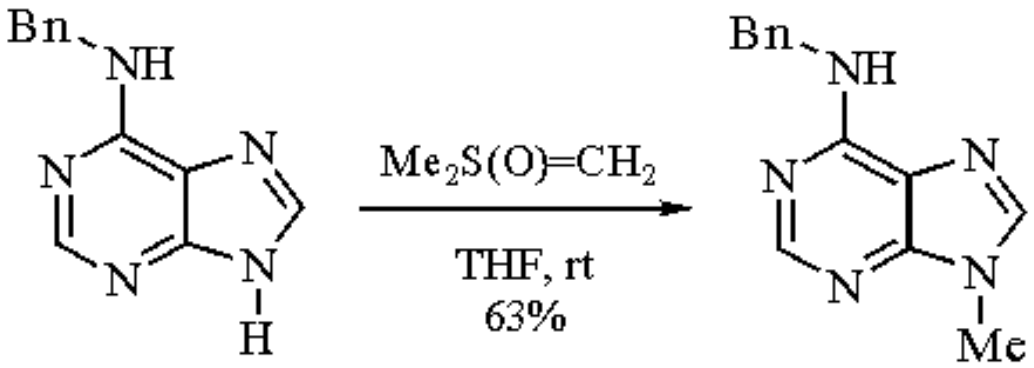

(18)

Preparation of Azetidine Derivatives.

N-Arylsulfonyl-2-phenylazetidines can be prepared by reaction of dimethylsulfoxonium methylide with *N*-arylsulfonyl-2-phenylaziridines in 51-72% yield.[58] Stereospecific conversion of *N*-arylsulfonylaziridines to *N*-arylsulfonylazetidines has also been reported. Reactions with *cis*-aziridines give *trans*-azetidines, and reactions with *trans*-aziridines produce the *cis*-azetidines. Presumably an S_N2 1,4-elimination mechanism is involved (eq 19).[59] Although several 2- and 2,3-substituted *N*-arylsulfonylazetidines have also been synthesized in good yields from reactions with dimethylsulfoxonium methylide, the fused azetidines could not be prepared by this procedure.[60] Dimethylsulfoxonium methylide also converts *N*-arylsulfonyloxaziridines to azetidines via a methylene transfer reaction. Similar reactions with *N*-alkyloxaziridines give only the deoxygenated product.[61]

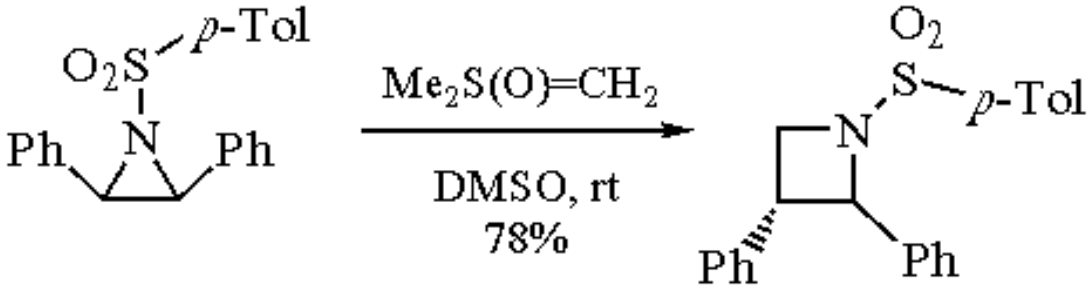

(19)

Preparation of Oxetanes.

Dimethylsulfoxonium methylide is an efficient methylene transfer reagent in reactions with terminal epoxides to provide the corresponding oxetanes (eq 20).[10,62,63] The oxetanes can also be prepared from ketones or aldehydes with dimethylsulfoxonium methylide via double methylene transfer reactions.

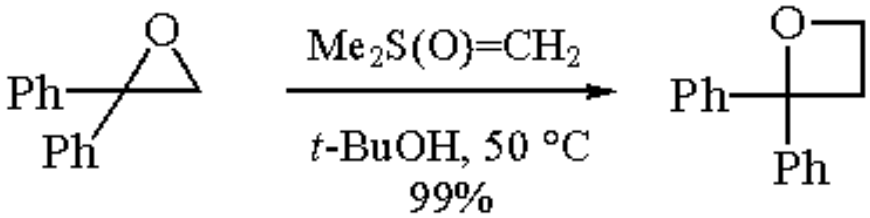

(20)

Cyclopropanation.

Cyclopropanation using the Simmons-Smith conditions (see ***Iodomethylzinc Iodide***) does not work well for α,β-unsaturated carbonyl compounds. This difficulty has been overcome by the use of dimethylsulfoxonium methylide as the methylene transfer reagent. This method has been successfully applied to unsaturated ketones,[64-66] esters,[67-70] lactones,[71] amides,[72] nitriles,[73] and nitro compounds.[74,75] Dimethylsulfoxonium methylide appears to work better than the corresponding sulfonium analog in these reactions. Reaction of the sulfonium methylide with α,β-unsaturated carbonyl compounds gives the kinetically controlled 1,2-addition oxirane product,[1,66] while reaction with dimethylsulfoxonium methylide gives the 1,4-addition cyclopropane derivatives in synthetically useful yields (eqs 21-23).[64,70]

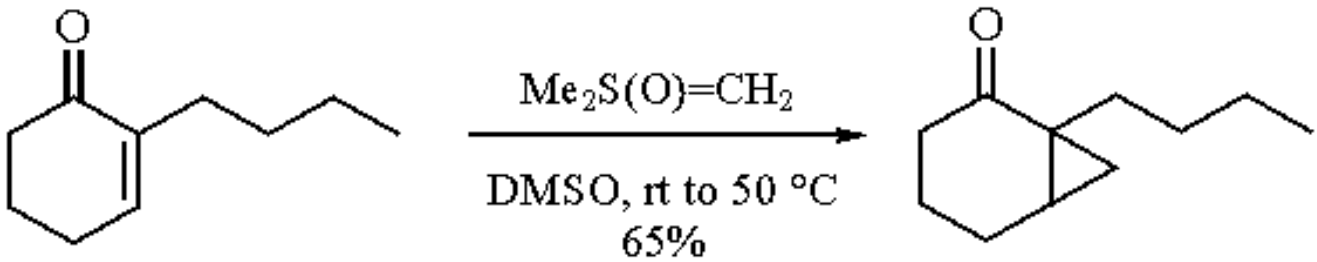

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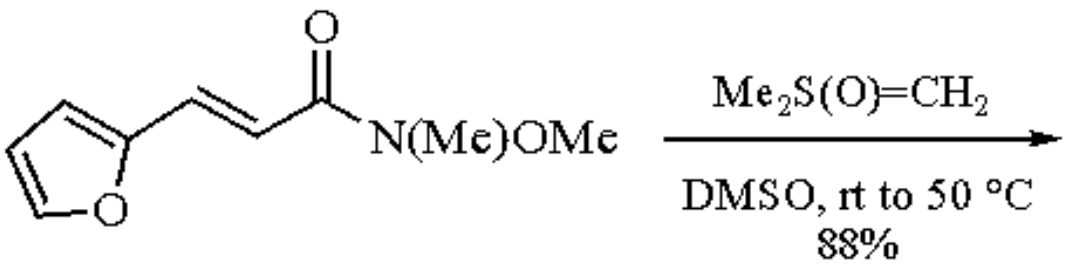

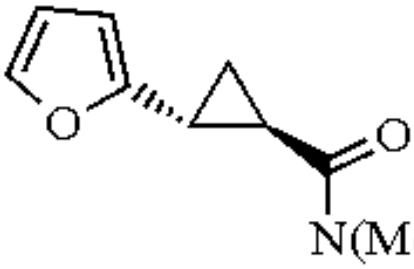

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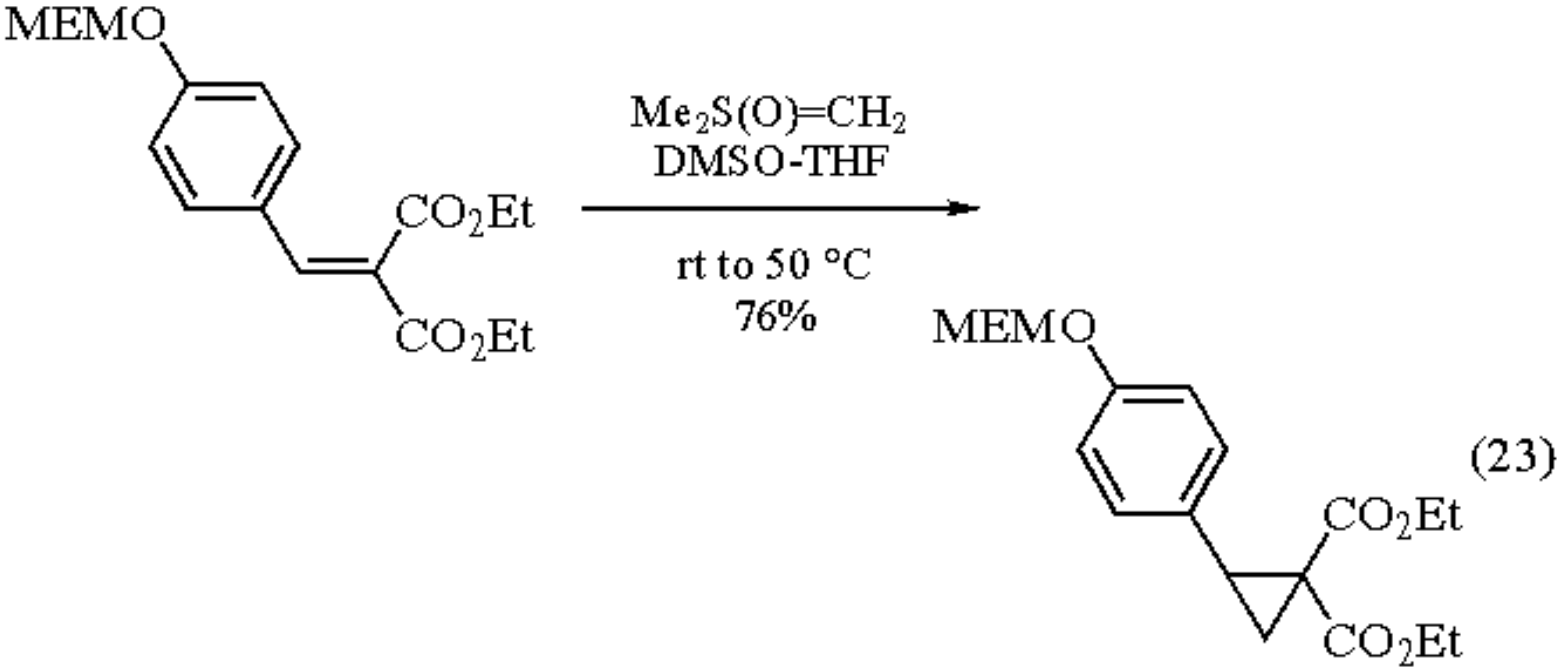

The mechanism of cyclopropanation involves an initial reversible conjugate addition of dimethylsulfoxonium methylide to the α,β-unsaturated carbonyl compound, followed by an irreversible ring closure; if excess dimethylsulfoxonium methylide is used in the reaction, epoxidation of carbonyl group may follow the cyclopropanation (eq 24).[76] Usually, the reaction is carried out in DMSO over a wide range of temperatures under an inert atmosphere. Cyclopropanation using TBAI as phase-transfer catalyst in an aqueous system was also reported.[12] Reaction of dimethylsulfoxonium methylide with fluorine-containing α,β-unsaturated ketones can result in products from different reaction pathways.[38,77,78] Reaction of dimethylsulfoxonium methylide with α-fluoro-substituted enones gives the corresponding fluoro-epoxides only.[79]

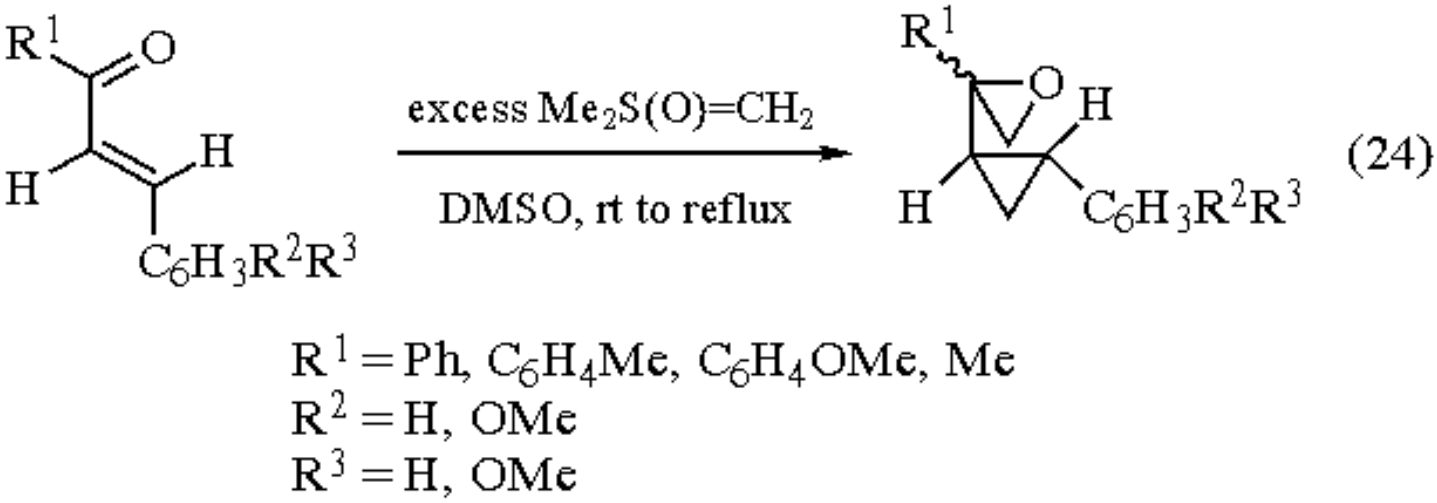

The cyclopropanated carbonyl compounds can readily be further transformed to other functionalities.[72,80,81] For example, a substituted vinyl phenyl ketone was converted to the cyclopropane intermediate with dimethylsulfoxonium methylide and the product was further transformed to a 1-tetralone derivative by acid-catalyzed cyclization.[80] The cyclopropyl amide which is derived from reaction of an α,β-unsaturated amide with dimethylsulfoxonium methylide can be further converted to a ketone or an acid derivative by reaction with an organometallic nucleophile or an anhydrous base.[72]

Cyclopropanation with dimethylsulfoxonium methylide in multifunctional compounds can be chemoselective.[66,82,83] Dimethylsulfoxonium methylide reacts preferentially with the less sterically hindered α,β-unsaturated carbonyl function to give the corresponding cyclopropane (eq 25).[65,84,85] On the other hand, reaction of dimethylsulfoxonium methylide with bifunctional cyclic enediones affords the oxirane product instead of generating the cyclopropyl derivative (eq 26).[85]

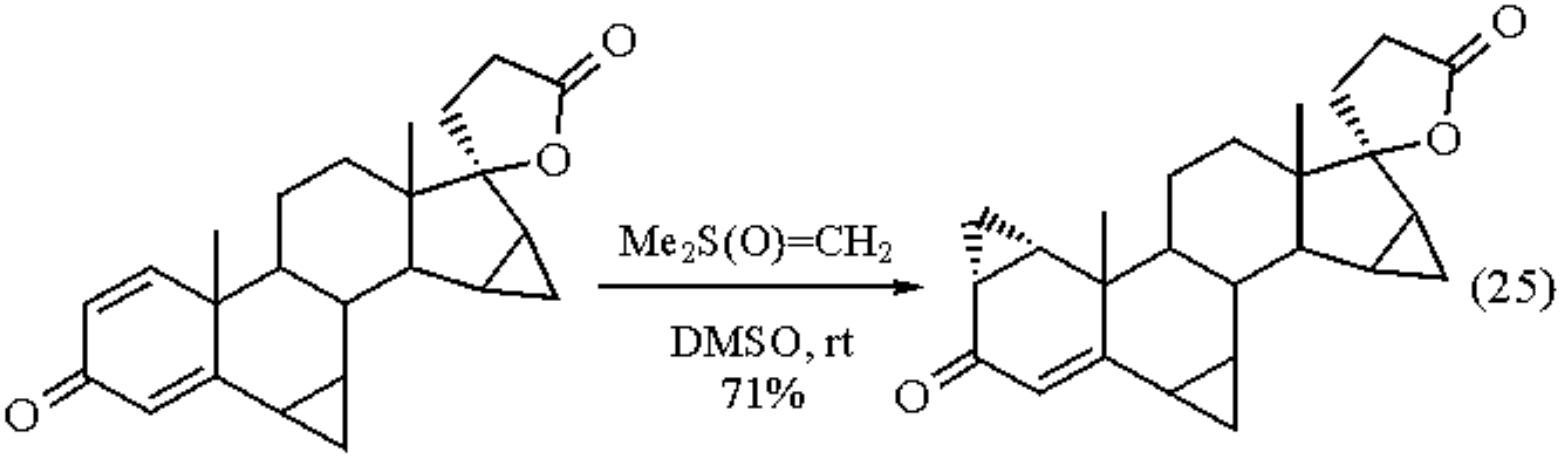

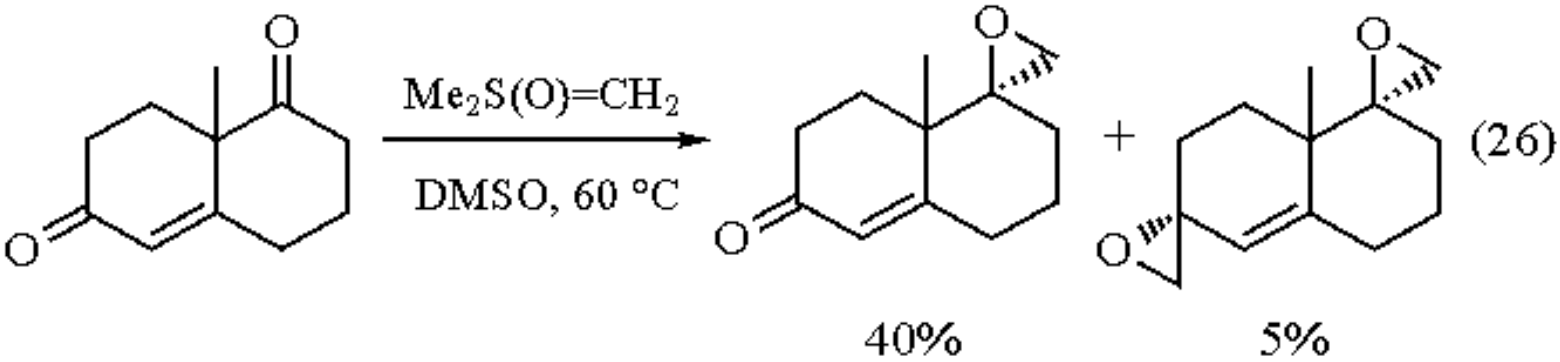

Chemoselective reaction of a methoxy-substituted dienone with dimethylsulfoxonium methylide results in cyclopropanation of the unsubstituted double bond.[83] Reaction of dimethylsulfoxonium methylide with the conjugated dienone 2,3-benzotropone gives a 1.1:1 mixture of the mono- and dicyclopropanated products.[86] One conjugated dienone, however, gave only the 1,6-addition product (eq 27).[82]

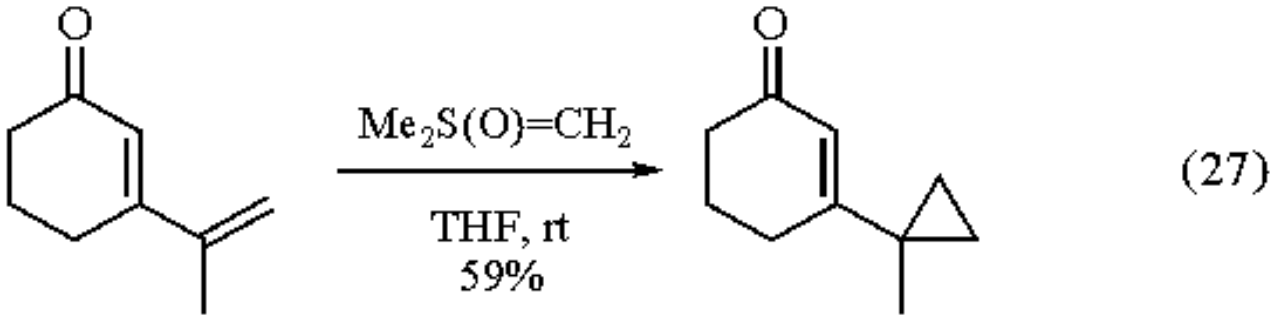

Stereoselectivity of Cyclopropanation.

Cyclopropanation of α,β-unsaturated carbonyl compounds with dimethylsulfoxonium methylide can be highly

stereoselective. Reaction of methyl 2-(4-oxo-2-cyclohexenyl)acetate with dimethylsulfoxonium methylide gave the corresponding *anti*- and *syn*-cyclopropane derivatives in a 85:15 ratio; the favored *anti* isomer results from the nucleophilic addition of the dimethylsulfoxonium methylide to the less hindered side of the α,β-unsaturated ketone (eq 28).[87] This steric effect was also observed in the cyclopropanation of 3β-acetoxy-16α,17α-methylene-5-pregnen-20-one.[88] Stereoselective cyclopropanation of a ten-membered enone with dimethylsulfoxonium methylide gives the bicyclohumulenone in 90% yield, with none of the *cis* isomer observed. Peripheral addition of oxysulfurane proceeds through the lower-energy conformation which leads to the most likely enolate intermediate. Subsequent ring closure gives the *trans* cyclopropane.[89] A recently reported asymmetric cyclopropanation of a chiral vinyl sulfoxide with dimethylsulfoxonium methylide gave high yield and stereoselectivity ((*R*,*S*):(*S*,*S*) = 5.9:1) (eq 29).[90]

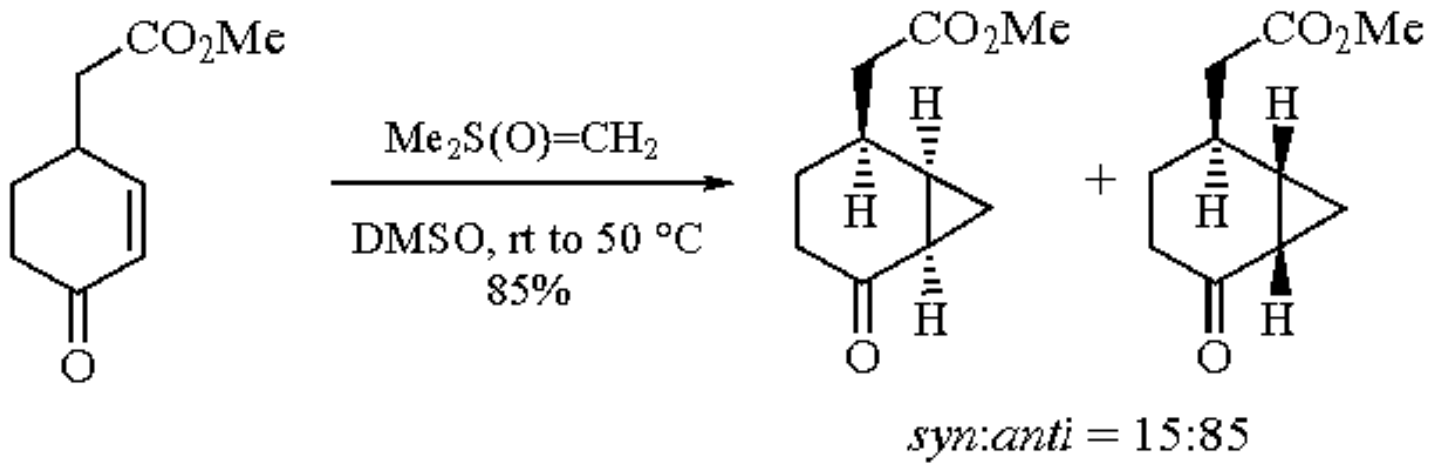

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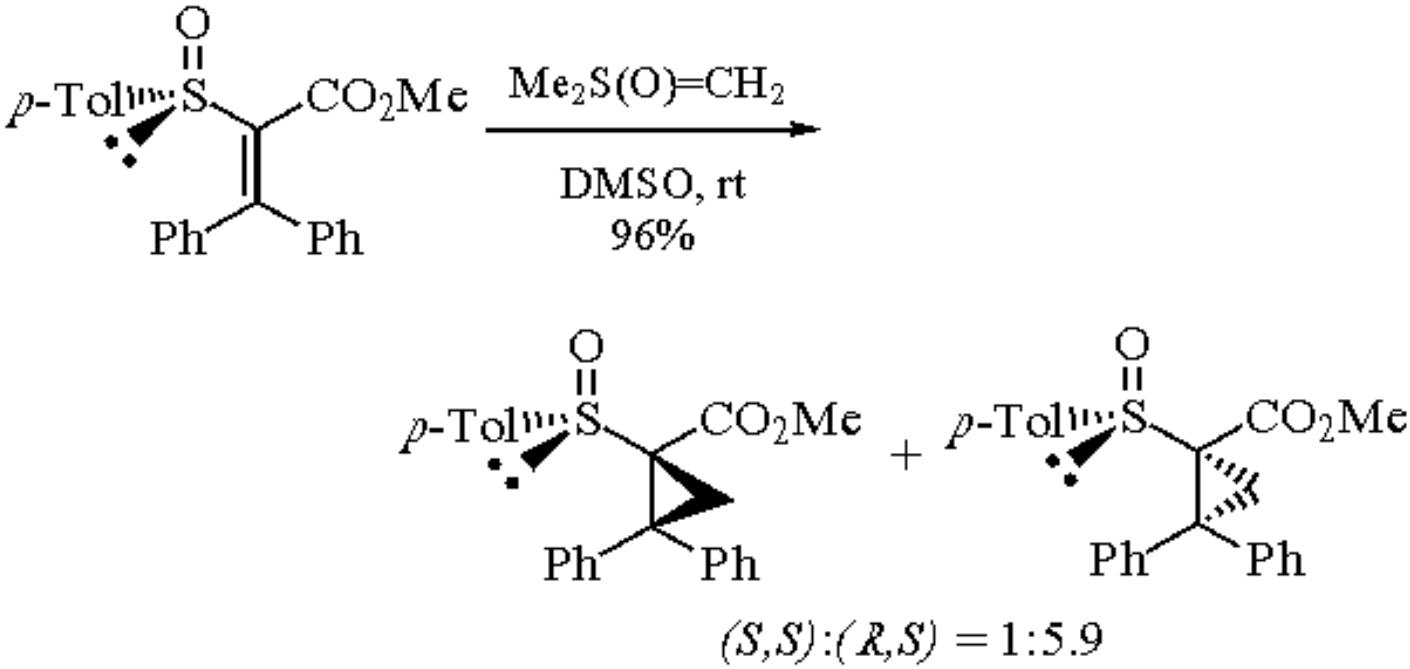

(29)

Cyclopropanation of α,β-unsaturated bicyclic lactams with dimethylsulfoxonium methylide also proceeds with high diastereoselectivity. In these cases, a change of the angular substituent in the bicyclic lactam leads to a complete reversal in *endo-exo* selectivity (eq 30).[91]

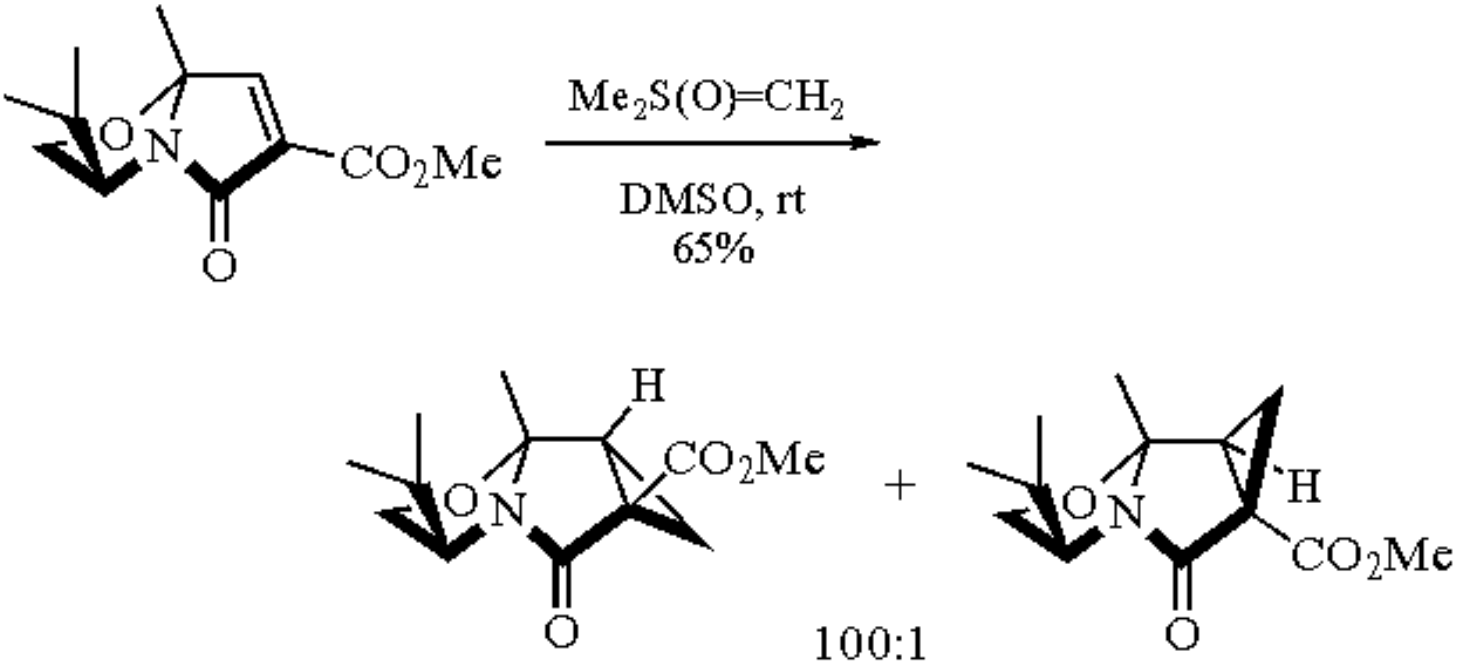

Reaction with Other Functional Groups.

Reaction of α-halo carbonyl compounds with dimethylsulfoxonium methylide provides the α-cyclopropyl carbonyl derivatives rather than the oxirane.[92] Presumably the mechanism involves a double methylene transfer with the dimethylsulfoxonium methylide. Dimethylsulfoxonium methylide has also been reported to react with 1,3-dipolar compounds for the preparation of heterocyclic products (eq 31).[93]

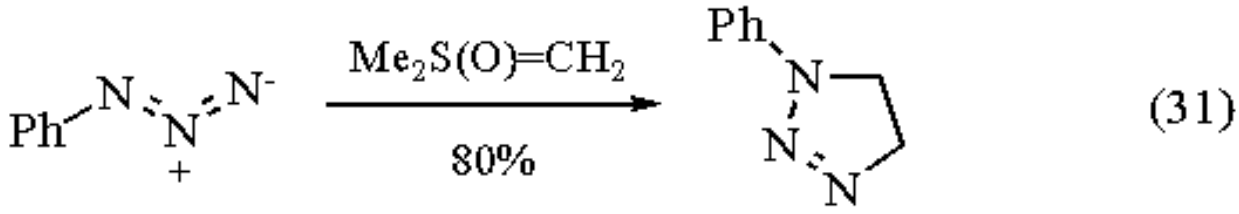

Methylene transfer onto the triple bond of α,β-alkynyl ketones by reaction with dimethylsulfoxonium methylide has not been observed. Reaction of 1,3-diphenyl-2-propyn-1-one with dimethylsulfoxonium methylide gives only the Michael addition complex 1-methyl-3,5-diphenylthiabenzene 1-oxide.[94,95] Reaction of dimethylsulfoxonium methylide with thiobenzophenone gives 1,1-diphenylethylene sulfide in 71% yield.[96] Treatment of 4-dimethylamino-1-thia-3-azabutadienes with dimethylsulfoxonium methylide provided thiazol-2-ine derivatives. The mechanism involves regioselective ylide addition to the amidine group, followed by cyclization with elimination of DMSO (eq 32).[97]

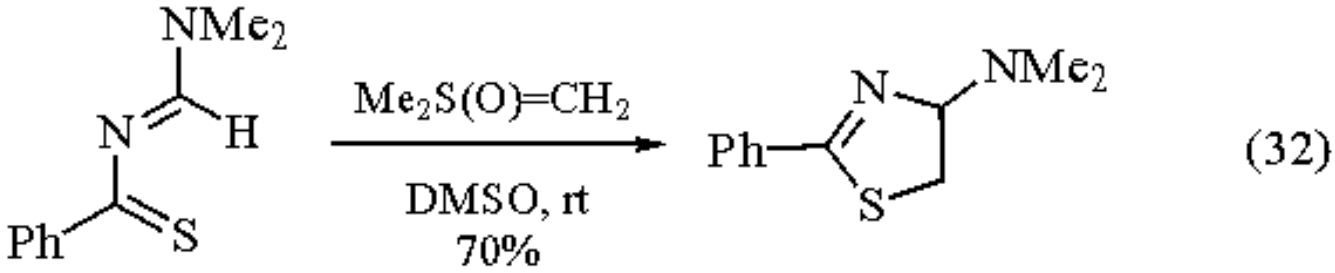

Methylene transfer of dimethylsulfoxonium methylide to imines results in aziridine derivatives.[98] A facile procedure for the preparation of 3-amino-2,3-dihydrobenzofuran from dimethylsulfoxonium methylide and *o*-hydroxybenzylideneaniline has been reported. The mechanism involves a ring opening of the initial aziridine intermediate (eq 33).[99,100]

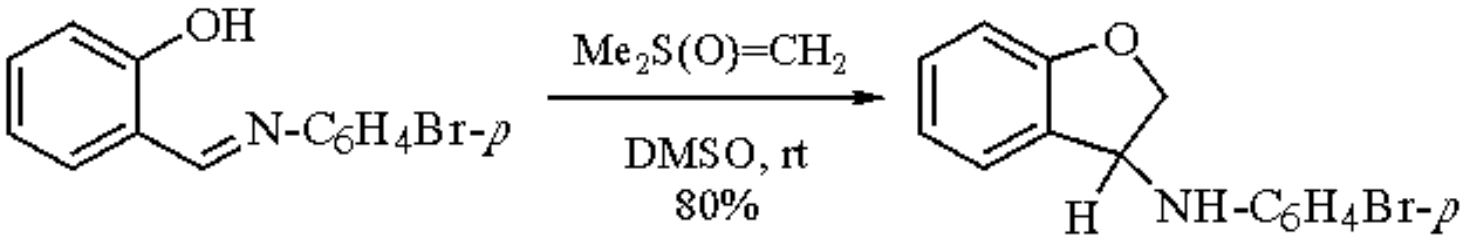

(33)

Reaction with Organometallics.

Dimethylsulfoxonium methylide has been reported to react with transition metal organometallic compounds as simple terminal ligands, bridging groups, or chelating moieties.[101-106] For example, the reaction of two equivalents of dimethylsulfoxonium methylide with the metal-functionalized 1,3-diphospha-2-propanone $Fe_2(CO)_6[(i\text{-Pr})_2N\text{-}PC(O)P\text{-}N(i\text{-Pr})_2]$ affords the 1,5-diphospha-3-pentanone derivative, a product resulting from the insertion of a CH_2 group into the P-(CO) bond.[107]

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Dimethyl L-Tartrate[1]

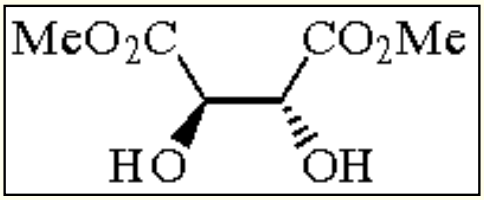

[608-68-4] · $C_6H_{10}O_6$ · Dimethyl L-Tartrate · (MW 178.14)

(synthon for chiral auxiliary/ligand preparation; chiral ligand for asymmetric catalysis)

Physical Data: mp 57-60 °C (dec); bp 163 °C/23 mmHg; *d* 1.238 g cm^{-3}; $[\alpha]^{23}$ +21° (*c* = 2.5, H_2O).

Solubility: sol most organic solvents, water.

Form Supplied in: moist white crystals.

Handling, Storage, and Precautions: may cause irritation; store in a cool, dry place.

Synthon for Chiral Auxiliary/Ligand Preparation.

(*R,R*)-Dimethyl L-tartrate, a derivative of natural L-tartaric acid, is readily transformed into useful chiral auxiliaries and ligands for asymmetric synthesis.[1] Many of these transformations involve initial acetalization of the 2,3-vicinal hydroxy groups.[2-6] Thus α,α,α´,α´-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) are prepared from the corresponding acetals of dimethyl L-tartrate (eq 1) and, as the Ti^{IV} complexes (see ***2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide***), are useful catalysts for enantioselective additions of dialkylzinc reagents to aldehydes,[5] Diels-Alder reactions,[6,7] asymmetric hydrocyanations of aldehydes,[8] and others.[9] The enolate of the acetonide of dimethyl L-tartrate alkylates with good selectivity to give, after acetonide hydrolysis, allyl- or benzylated derivatives (eq 2).[10] Orthoesters are also prepared from dimethyl tartrate, and acylate silyl enol ethers in good yield and selectivity to give monoprotected 1,3-diketones (eq 3).[11]

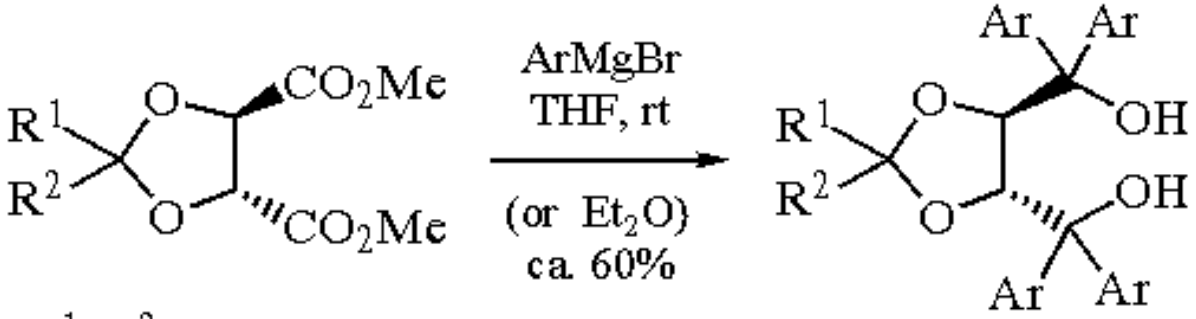

(1)

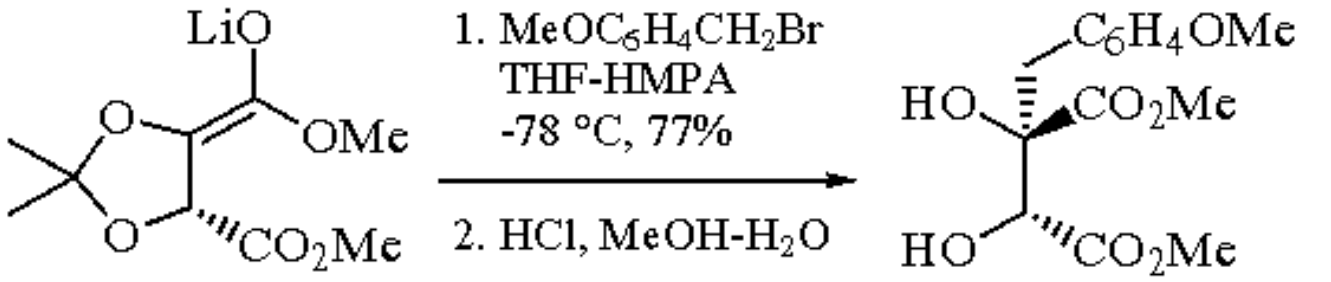

94% ee (82:18, *threo*)

(2)

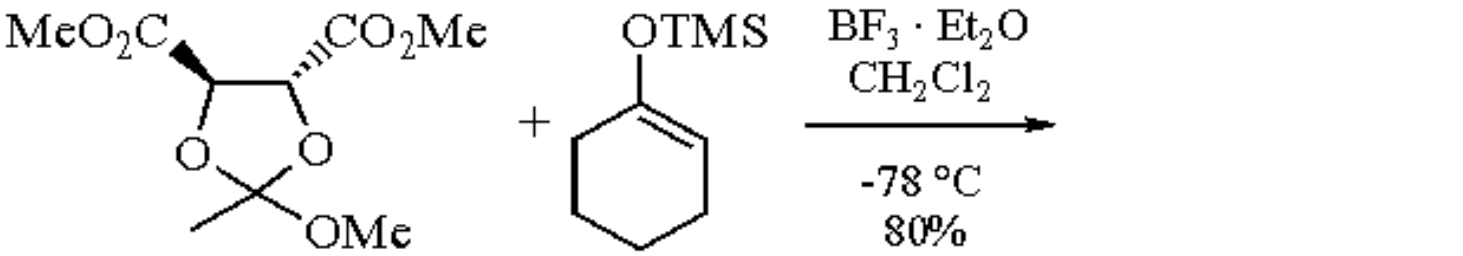

(3)

78% de

In an industrial asymmetric synthesis en route to the antiinflammatory agent naproxen, the dimethyl L-tartrate acetals of ethyl aryl ketones are brominated in high yield and selectivity to give the corresponding α-bromo derivatives.[12,13] Subsequent stereospecific Ag^{I}-promoted 1,2-aryl migration provides the 2-alkyl-2-arylacetic acid after hydrolysis of the tartrate auxiliary, which is recovered (e.g. eq 4).

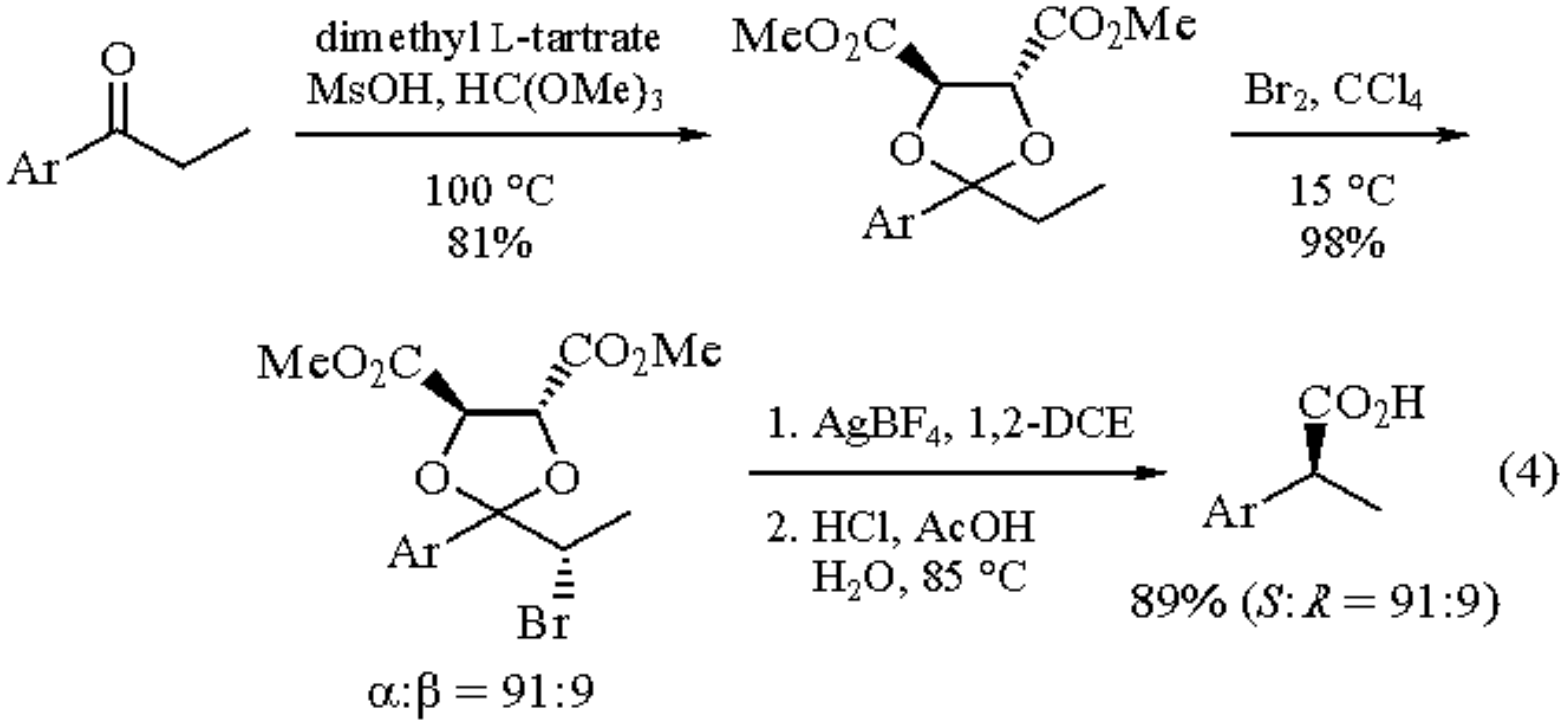

The vicinal diol cyclic sulfate from dimethyl tartrate undergoes nucleophilic opening to give substituted malate esters.[14,15] However, for this application diethyl and diisopropyl L-tartrates give superior yields and selectivities. The asymmetric cyclopropanation of the 1-alkenylboronic ester derived from dimethyl L-tartrate (eq 5) is another example where other tartaric acid derivatives surpass the performance of dimethyl tartrate.[16]

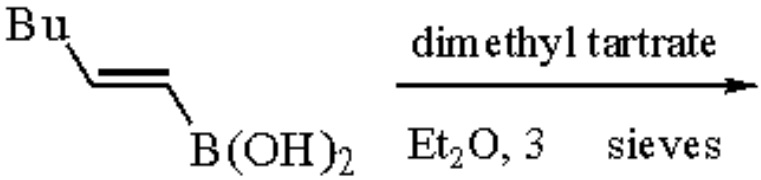

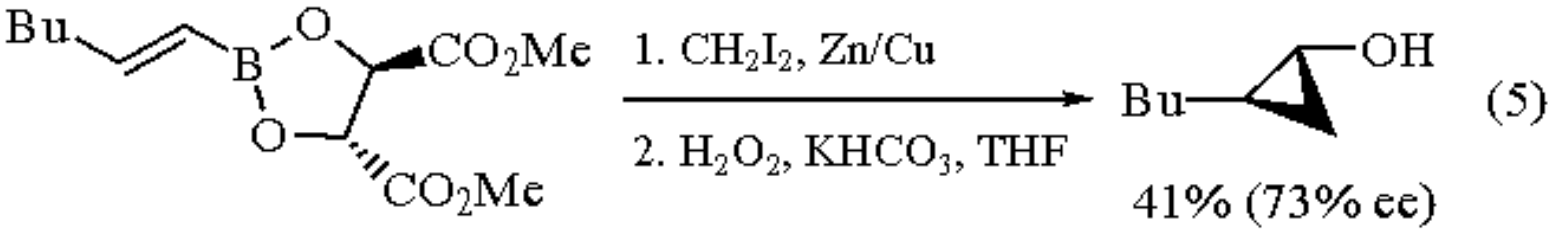

Chiral Ligand for Asymmetric Catalysis.

Dimethyl L-tartrate is a demonstrated chiral ligand for the Ti^{IV}-catalyzed asymmetric epoxidation of allylic alcohols (Sharpless epoxidation),[17] and the Zn^{II}-mediated asymmetric cyclopropanation of allylic alcohols (Simmons-Smith reaction), see ***Iodomethylzinc Iodide***.[18] Enantioselectivities in these reactions are, however, better with the use of diethyl L-tartrate as the chiral modifier.

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2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide[1]

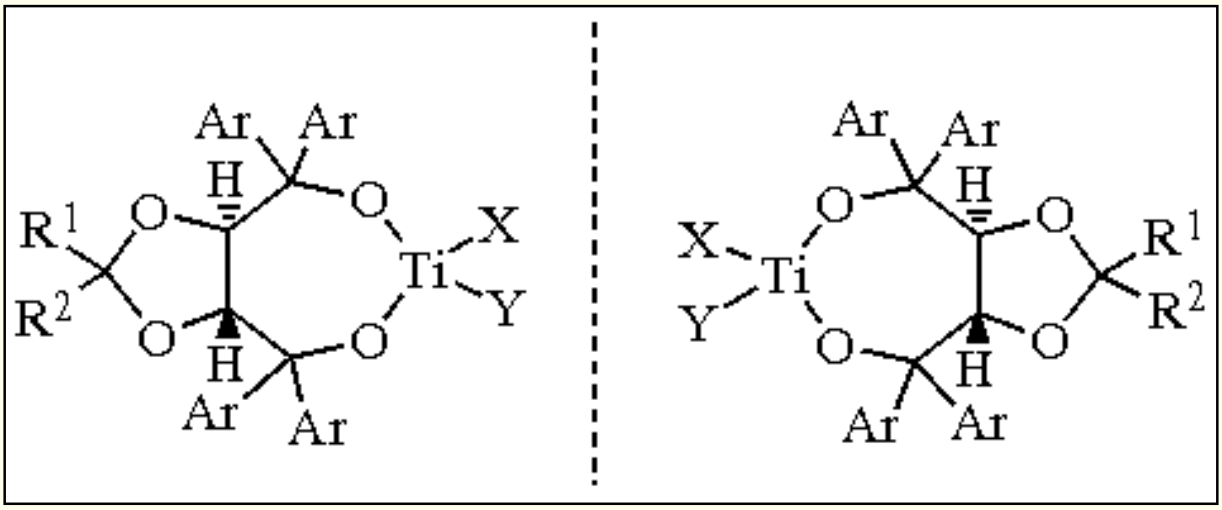

(**1a**; $R^1 = R^2$ = Me; Ar = Ph; X = Y = *i*-PrO)

[144121-63-1] · $C_{37}H_{42}O_6Ti$ · 2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide · (MW 630.66) (**1b**; $R^1 = R^2$ = Me; Ar = Ph; X = Y = Cl)

[109457-91-2] · $C_{31}H_{28}Cl_2O_4Ti$ · 2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Dichloride · (MW 583.37) (***ent*-1b**; $R^1 = R^2$ = Me; Ar = Ph; X = Y = Cl)

[139341-84-7] · $C_{31}H_{28}Cl_2O_4Ti$ · 2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide · (MW 583.37) (**1c**; $R^1 = R^2$ = Me; Ar = Ph; X = *i*-PrO; Y = Cl)

[114031-33-3] · $C_{34}H_{35}ClO_5Ti$ · 2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Chloride Isopropoxide · (MW 607.02) (**1d**; $R^1 = R^2$ = Me; Ar = 2-naphthyl; X = Y = *i*-PrO)

[144121-64-2] · $C_{53}H_{50}O_6Ti$ · 2,2-Dimethyl-α,α,α´,α´-tetrakis(2-naphthyl)-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide · (MW 830.90) (**1e**; R^1 = Me; R^2 = Ar = Ph; X = Y = Cl)

[109414-72-4] · $C_{36}H_{30}Cl_2O_4Ti$ · 2-Methyl-2,α,α,α´,α´-pentaphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Dichloride · (MW 645.44) (**1f**; R^1 = R^2 = Me; Ar = Ph; X = Cp; Y = Cl)

[132068-98-5] · $C_{36}H_{33}ClO_4Ti$ · Chloro(η^5-cyclopentadienyl)[(4*R*,*trans*)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O^{α},$O^{\alpha'}$]titanium · (MW 613.02)

(chiral auxiliaries and Lewis acids for stoichiometric and catalytic enantioselective transformations)

Alternate Name: Ti-TADDOLates.

Introduction.

Ti-TADDOLates are α,α,α´,α´-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanolatotitanium derivatives. The most common substituents are R^1, R^2 = Me/Me and Ph/Me, Ar = Ph and 2-naphthyl, X, Y = Cl/Cl, *i*-PrO/Cl, Cp/Cl, and *i*-PrO/*i*-PrO. The corresponding TADDOLs (**2**) are available in both enantiomeric forms from tartrate esters which are acetalized (R^1R^2CO) and allowed to react with aryl Grignard reagents.[1a,g,2] The reactions performed in the presence of Ti-TADDOLates or with Ti-TADDOLate derivatives include: nucleophilic additions to aldehydes[1a,b,f,g,j,2a,3-5] and nitroalkenes[6] of alkyl,[1a,b,g,2a,3-5] aryl,[5] and allylic[1d,f] groups; aldol additions;[1d,f] hydrophosphonylations[7] and cyanohydrin reactions[1j] of aldehydes; inter- and intramolecular Diels-Alder additions;[1e,h,i,2a,8,9] [2 + 2] cycloadditions;[1e,h,i,10] intra-[1e,h,i] and intermolecular[11] ene reactions; iodolactonizations;[12] and transesterifications.[1h,i] Analogous compounds of other metals, and TADDOL derivatives containing one or two amino,[13] phosphinic, phosphonic, and/or phosphite groups,[13,14] have also been made and used for various reactions such as: $LiAlH_4$ reductions;[15] Grignard additions to ketones;[16] Li enolate additions to nitroalkenes;[17] hydrosilylations of ketones;[14a] Pd-catalyzed allylations;[14b] and metathesis reactions.[18] Finally, the TADDOLs themselves have been proved to be useful as NMR shift reagents;[2c,19] as components for enantioselective formation of host-guest complexes;[20,21] and for enantioselective solid-state reactions.[22] (*R*,*R*)-Ti-TADDOLates and (*P*)-Ti-BINOLates often give the same products in enantioselective reactions.[9]

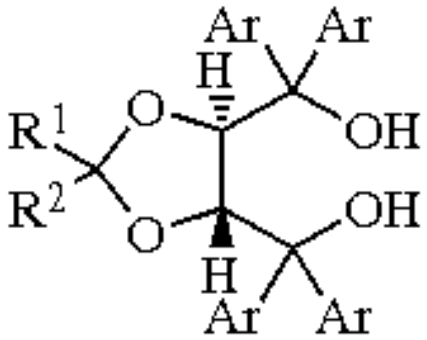

(2)

Preparation of Ti-TADDOLate Solutions.

Five different procedures have been mostly used for the preparation of TADDOLates (**1**).

- 1)TADDOLate (**1f**) can be obtained from ***Trichloro(cyclopentadienyl)titanium*** and TADDOL (**2**), with removal of HCl (eq 1).[1d,f]
- 2)TADDOLates (**1b**) and (**1e**) are prepared from (**2**) and ***Dichlorotitanium Diisopropoxide***, without removal of the *i*-PrOH formed (eq 2). They are typically used in the presence of 4 Å molecular sieves.[1e,h,i,8b,c,9,10]
- 3)Diisopropoxy Ti-TADDOLates (**1a**) and (**1d**) are conveniently made from (**2**) and ***Titanium Tetraisopropoxide*** with removal of *i*-PrOH by evaporation under reduced pressure or by azeotropic distillation (eq 3).[1a,b,g,2a,3e]
- 4)TADDOLate (**1a**) can be synthesized alcohol-free from spirotitanate (**3**) and $(i\text{-PrO})_4$Ti (eq 4).
- 5)Likewise, TADDOLate (**1b**) can be prepared from (**3**) and ***Titanium(IV) Chloride*** (eq 5).

An additional procedure leading from a titanate (**1**) (X = Y = *i*-PrO) to the corresponding dichloride (X = Y = Cl) is to treat the former with ***Tetrachlorosilane*** and pump off $(i\text{-PrO})_2SiCl_2$.[8a] A method in which the Ti-TADDOLate is present together with another Lewis acid (***Lithium Chloride***) is to treat a TADDOL (**2**) with 2 equiv ***n-Butyllithium***, followed by $TiCl_4$.[9]

Spirotitanate (**3**) was obtained by reacting TADDOL and 0.5 equiv $(EtO)_4$Ti or $(i\text{-PrO})_4$Ti, with azeotropic removal of the alcohol in refluxing toluene (eq 6). In the solid state it is rather stable to air (storage form);[3a,d,e] its crystal structure has been determined.[1g] Numerous TADDOLates of type (**1**) have been prepared and identified by NMR spectroscopy.[1g,3e,8a,23] Normally, they are used in situ in solvents such as toluene, petroleum ethers, CH_2Cl_2, Et_2O, or THF between -75 and +20 °C.

$$\text{CpTiCl}_3 + \mathbf{(2)} \xrightarrow{\text{-HCl}} \mathbf{(1f)} \qquad (1)$$

$$\mathbf{(2)} + (i\text{-PrO})_2\text{TiCl}_2 \longrightarrow \mathbf{(1b)}\ \text{or}\ \mathbf{(1e)} + 2\ i\text{-PrOH} \qquad (2)$$

$$\mathbf{(2)} + (i\text{-PrO})_4\text{Ti} \xrightarrow{\text{-}i\text{-PrOH}} \mathbf{(1a)}\ \text{or}\ \mathbf{(1d)} \qquad (3)$$

$$\mathbf{(3)} + (i\text{-PrO})_4\text{Ti} \longrightarrow \mathbf{(1a)} \qquad (4)$$

$$\mathbf{(3)} + \text{TiCl}_4 \longrightarrow \mathbf{(1b)} \qquad (5)$$

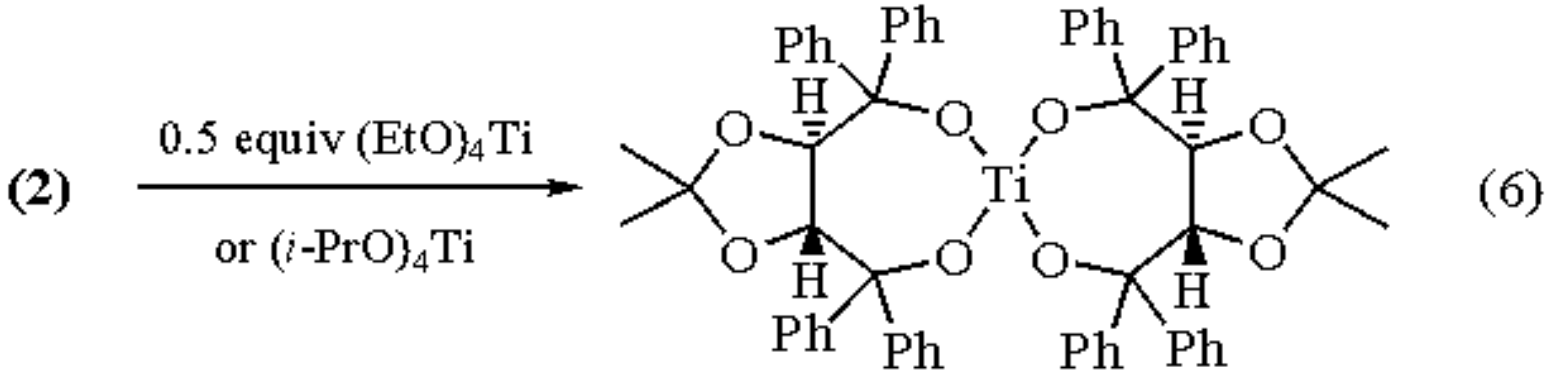

(3)

Nucleophilic Additions of Polar Organometallic Compounds to Aldehydes.

Ti-TADDOLates (**1**) have been used for both stoichiometric and catalytic nucleophilic additions to aldehydes. Thus the alcohols (**4**), (**9**), and (**10**) (eq 7) were obtained with the corresponding R_2Zn reagents[3d] in the presence of 0.2 equiv of (**1d**)[3c,e] or *ent*-(**1d**) and 1.2 equiv $(i\text{-PrO})_4Ti$. Alcohol (**5**) results from acetaldehyde and $(i\text{-PrO})_3TiPh$ mediated by 0.2 equiv of (**1a**).[5] (*R*)-Cyanohydrins such as (**6**) are formed from equimolar amounts of aldehydes, ***Cyanotrimethylsilane***, and (**1e**).[1e,h-j,24] Alcohol (**7**) and threonine derivative (**8**) are the result of additions to aldehydes of the CpTi-TADDOLates prepared in situ from (**1f**) and crotyl Grignard reagent[1f,25] or a glycine Li enolate derivative.[1f] As can be seen, highly diastereoselective (dr = diastereomer ratio) and enantioselective (er = enantiomer ratio) conversions can be achieved. A number of examples have been reported in the literature.[1-7] (*R*,*R*)-TADDOL derivatives (**1**) always give rise to *Si* addition (rel. topicity *unlike*);[26] the mechanism of these reactions has been discussed.[1g,9]

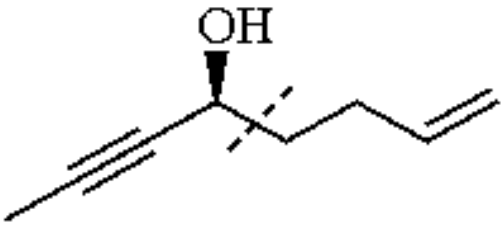

(4) er >98:2

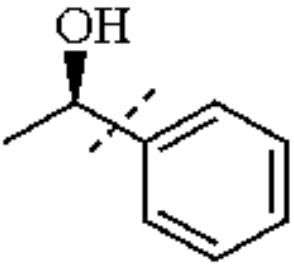

(5) er 98.5:1.5

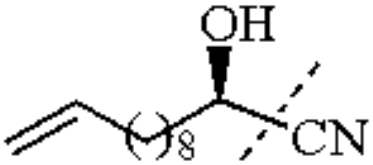

(6) er 97:3

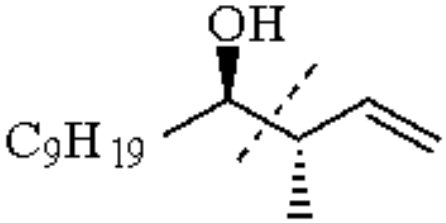

(7) dr >99:1; er >99:1

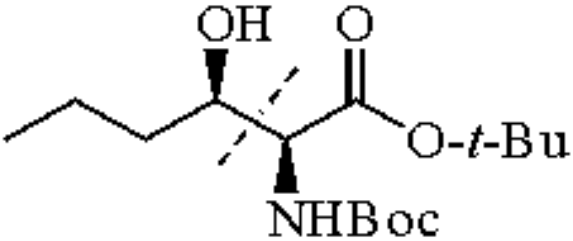

(8) dr 98:2; er 97:3

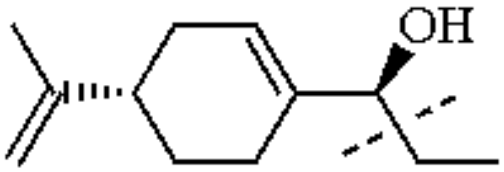

(9) dr 97:3

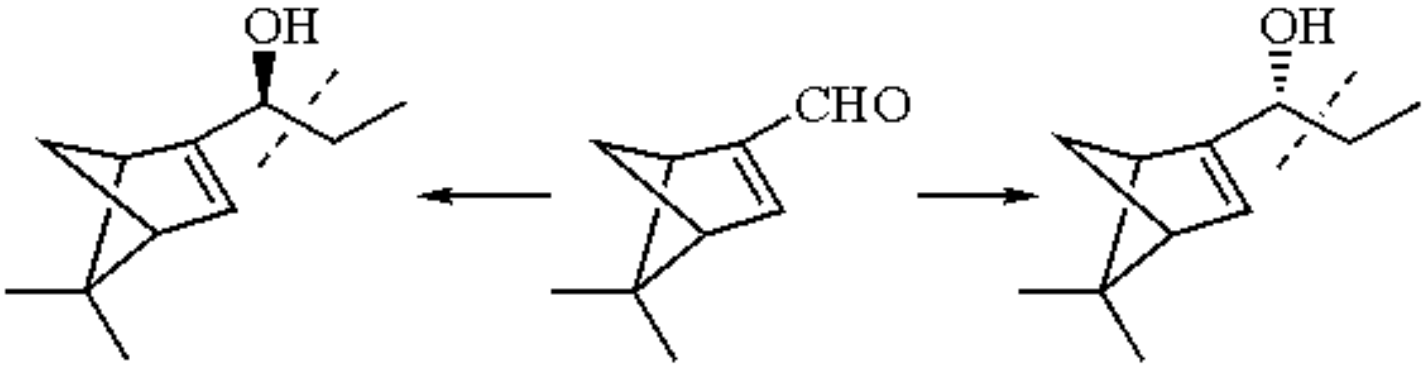

(7)

(10a) dr 95:5 **(10b)** dr 96:4

Cycloadditions and Ene Reactions.

These reactions were mostly studied with the Cl_2Ti-TADDOLate (**1e**) as prepared by the procedure shown in eq 2. In all cases, conditions are critical. There are numerous examples in the literature,[1c,e,h,i] including the Diels-Alder addition of 3-crotonyl-1,2-oxazolidin-2-one to cyclopentadiene[8a,27] (leading to (**11**) (X = 1,3-oxazolidin-2-on-3-yl) in (**11**), (**12**), (**14**), and (**16**)) and to open-chain dienes,[27] as well as the intramolecular version of this reaction (see, for instance, (**12**)[1i]). It was shown that the Diels-Alder reaction leading to (**11**) can be done with (**1**), (Ar = 2-naphthyl, $R^1 = R^2$ = Me, X = Y = Cl) with almost the same results as with (**1e**); with the analogous 1-naphthyl derivative the stereochemical course of the reaction reverses.[9] All these reactions are highly enantioselective and require ca. 10 mol % of the chiral catalyst. Some of these reactions have been carried out on a 45 mmolar scale.[9b,27] Other dienophiles such as methoxyquinones can also be employed. For the reactions leading to (**13**) and (**15**), somewhat different procedures were used.[8b,10b] Thus (**13**) was obtained

with excellent enantioselectivity using stoichiometric amounts of a Ti-TADDOLate (**1e**).[8b] Likewise, [2 + 2] cycloadditions, again with the acyloxazolidinone (see the cyclobutene **14**)[10a] or with methoxyquinone (see **15**, a precursor to benzodihydrofurans),[10b] have been studied and occur with high regio-, diastereo-, and enantioselectivities; the nucleophilic components of these cycloadditions are electron-rich alkenes, allenes, or alkynes (cation-stabilizing substituents on the double or triple bond) such as o-methylstyrenes,[10b] thioenol ethers,[1i] allenyl thioethers,[28] ketene dithioacetals,[28] or sulfenylated alkynes.[10a,28] The acyloxazolidinones derived from α,β-unsaturated carboxylic acids also lend themselves for intramolecular ene reactions. For instance, cyclopentane derivative (**16**) was formed from the corresponding open-chain 2,7-nonadienoic acid derivative.[29]

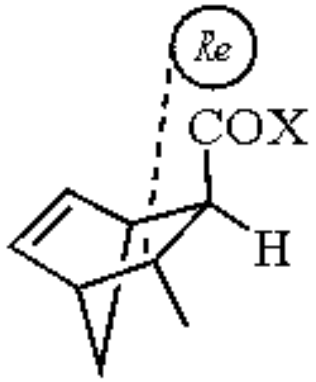

(11) dr 87:13; er 97:3

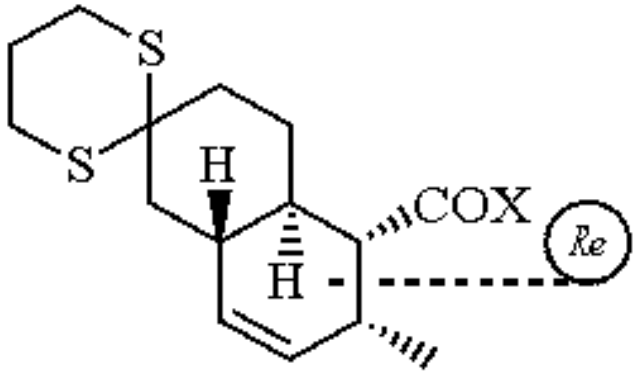

(12) er 99:1

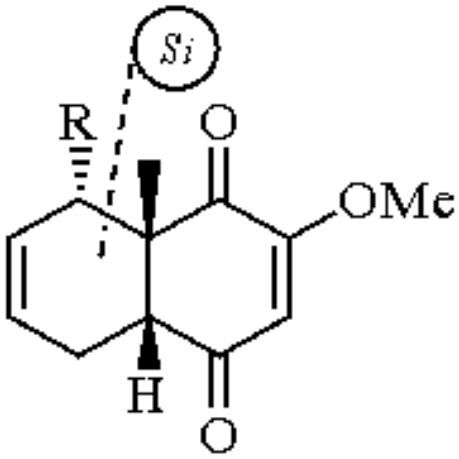

(13) R = *i*-Pr
dr >20:1; er 96:4

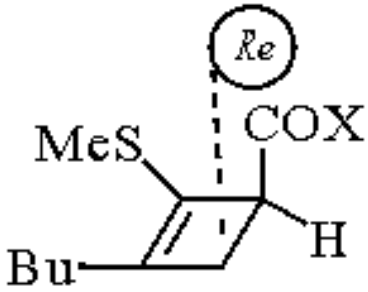

(14) er 99:1

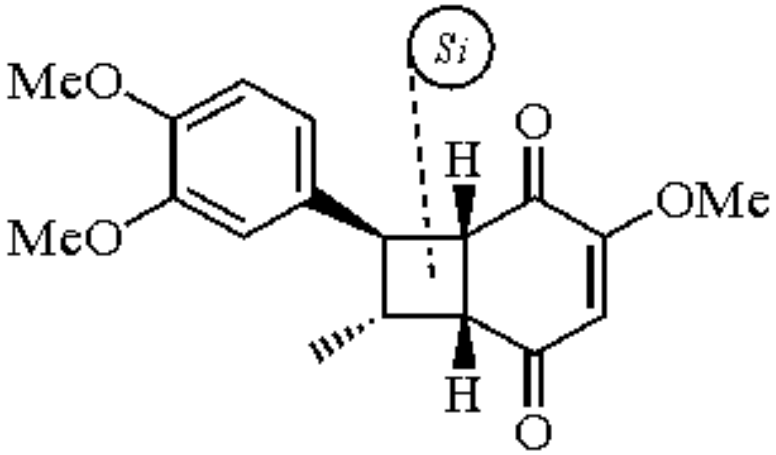

(15) er 96:4

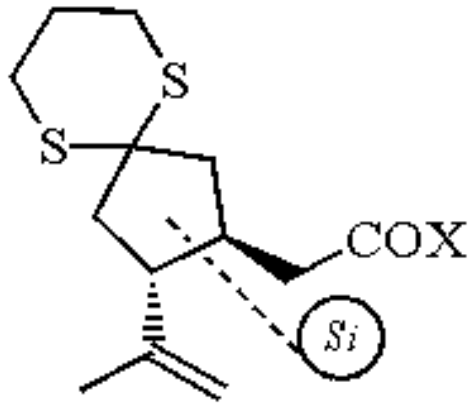

(16) er 98:2

As in other applications of *N*-acyl-1,3-oxazolidin-2-ones,[30] -2-thiones, and -thiazolidine-2-thiones,[31] chelation of the Lewis acid center for restricted rotation is considered decisive for the reactions occurring under the influence of the Ti-TADDOLates. Generally, the attack of the nucleophilic component (diene or ene) on the chelated electrophile occurs from the bottom face if the chelate ring is drawn as shown in structures (**17**) and (**18**),[8a,9,27] (**19**),[8b,f] and (**20**).[8d,e] For the oxazolidinones, this means that the trigonal α-carbonyl center is approached from the (*Re*)-face when an (*R,R*)-Ti-TADDOLate is used (rel. topicity *like*);[26] the mechanism of this reaction has been discussed.[1g,9]

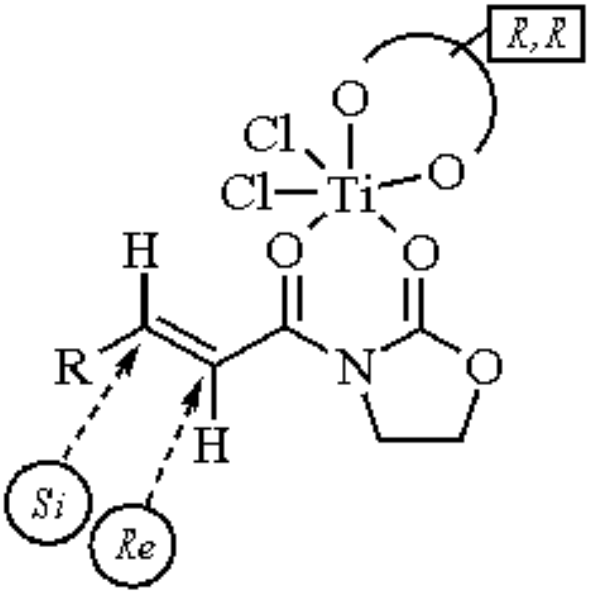

(17)

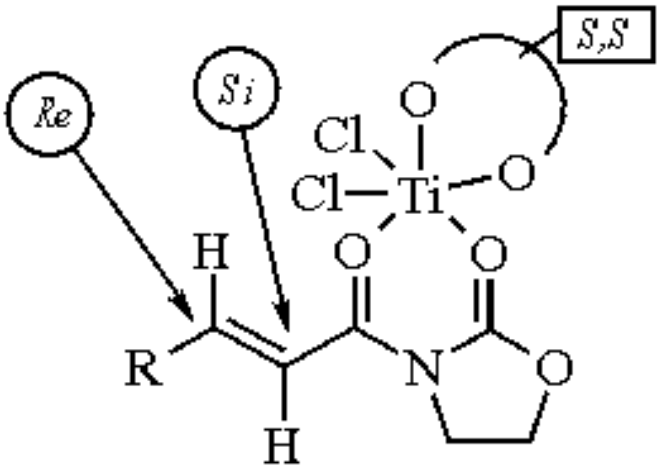

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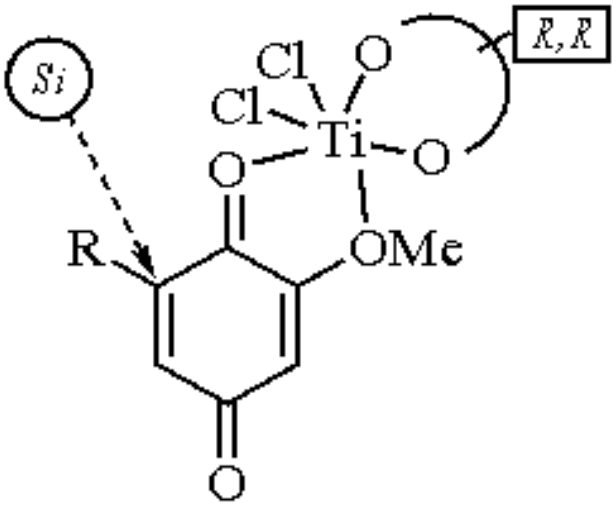

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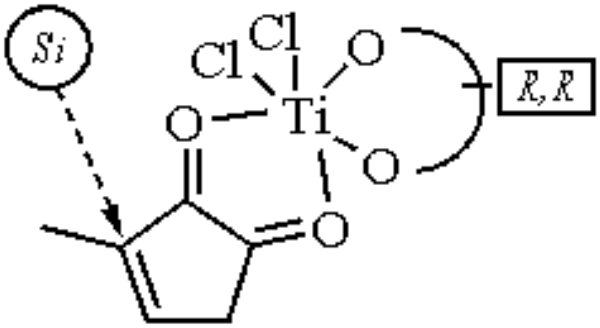

(20)

Other Enantioselective Transformations Mediated by Ti-TADDOLates.

The iodolactonization of 2-allyl-2-hydroxy-4-pentenoic acid shown in eq 8 gives (**21**) in a 67% yield (after cyclization of some iodo isopropyl ester formed as a side product),[12] the iodolactone is a single (-)-diastereoisomer with a 5:1 (*S*,*S*)/(*R*,*R*) ratio. The TADDOLate generated in situ was employed in stoichiometric amount. The two enantiomers of 2-pyridyl 2-phenylthiobutyrate react with a rate difference of 39:1 with excess isopropanol in the presence of 0.1 equiv of a Ti-TADDOLate under the conditions specified in eq 9. This leads to the isopropyl ester (**22**) containing 96% of the (*R*)-enantiomer in a 69% yield.[32] Thus the complex (**23**) reacts much faster than the (*R*,*R*)/(*S*) isomer in the S/O transesterification.

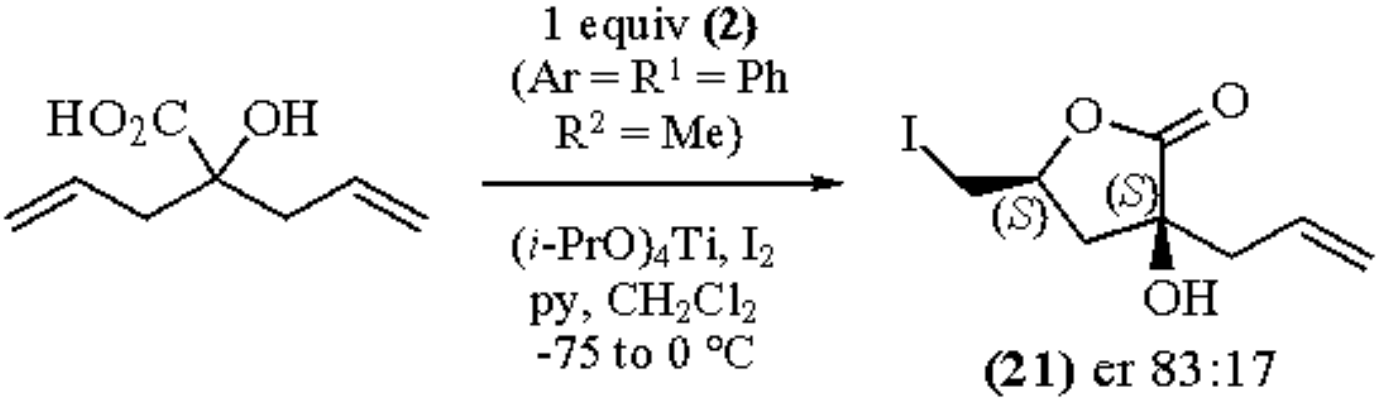

(8)

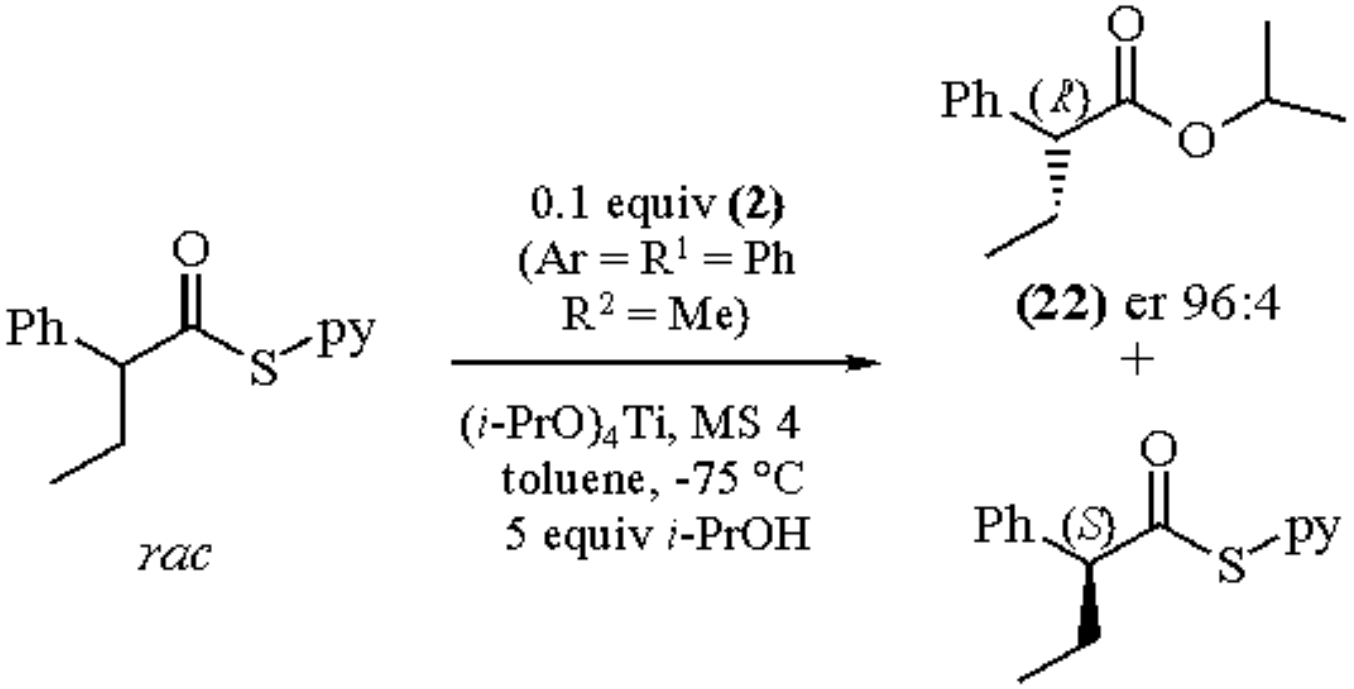

(9)

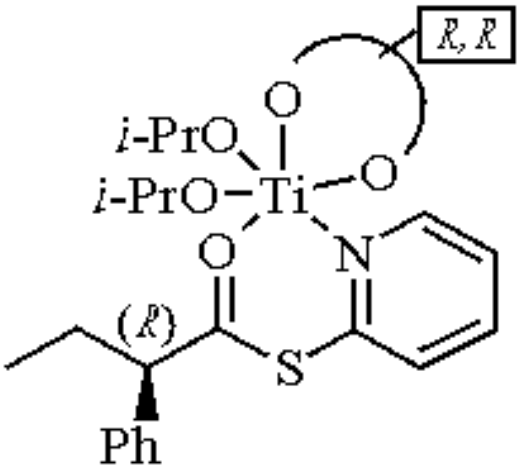

(23)

Use of TADDOLate Ligands on Other Metal Centers.

Of the many possible and actually studied applications of the readily available TADDOLs, only two may be mentioned here: enantioselective reduction and Grignard addition to aryl ketones. A chiral ***Lithium Aluminum Hydride*** derivative prepared from (**2**) reduces aryl ketones in THF to the corresponding alcohols of (*S*)-configuration with an enantioselectivity of ca. 20:1 (eq 10).[15]

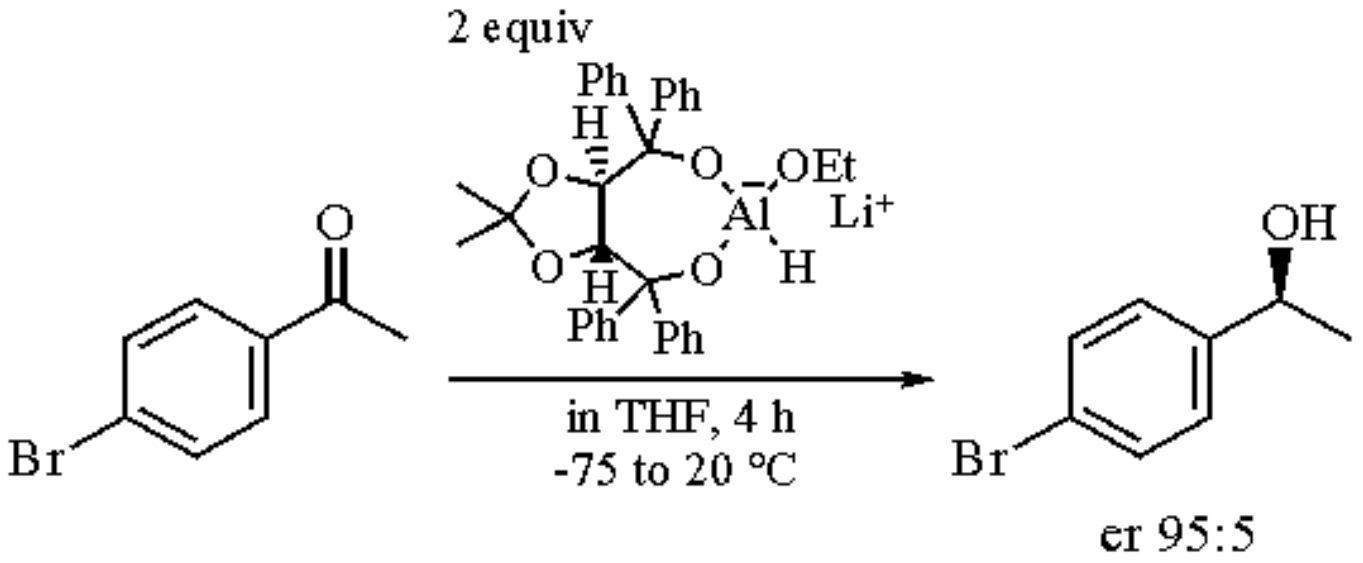

(10)

This procedure works with a smaller reagent excess and at higher temperatures than the analogous procedure using ***(R)-1,1´-Bi-2,2´-naphthol*** for similar results.[33] There is an added benefit in that the enantiomer excess of the alcohols formed in the reduction may sometimes be increased by a clathrating effect during the workup and isolation step (cf. the reviews).[20] Another useful application of the TADDOL (**2**) (Ar = Ph, $R^1 = R^2$ = Me) is the highly enantioselective Grignard addition to aryl ketones. The procedure involves in situ reaction of 3 equiv RMgX with the TADDOL, followed by addition of the ketone at -100 °C in THF (eq 11).[16]

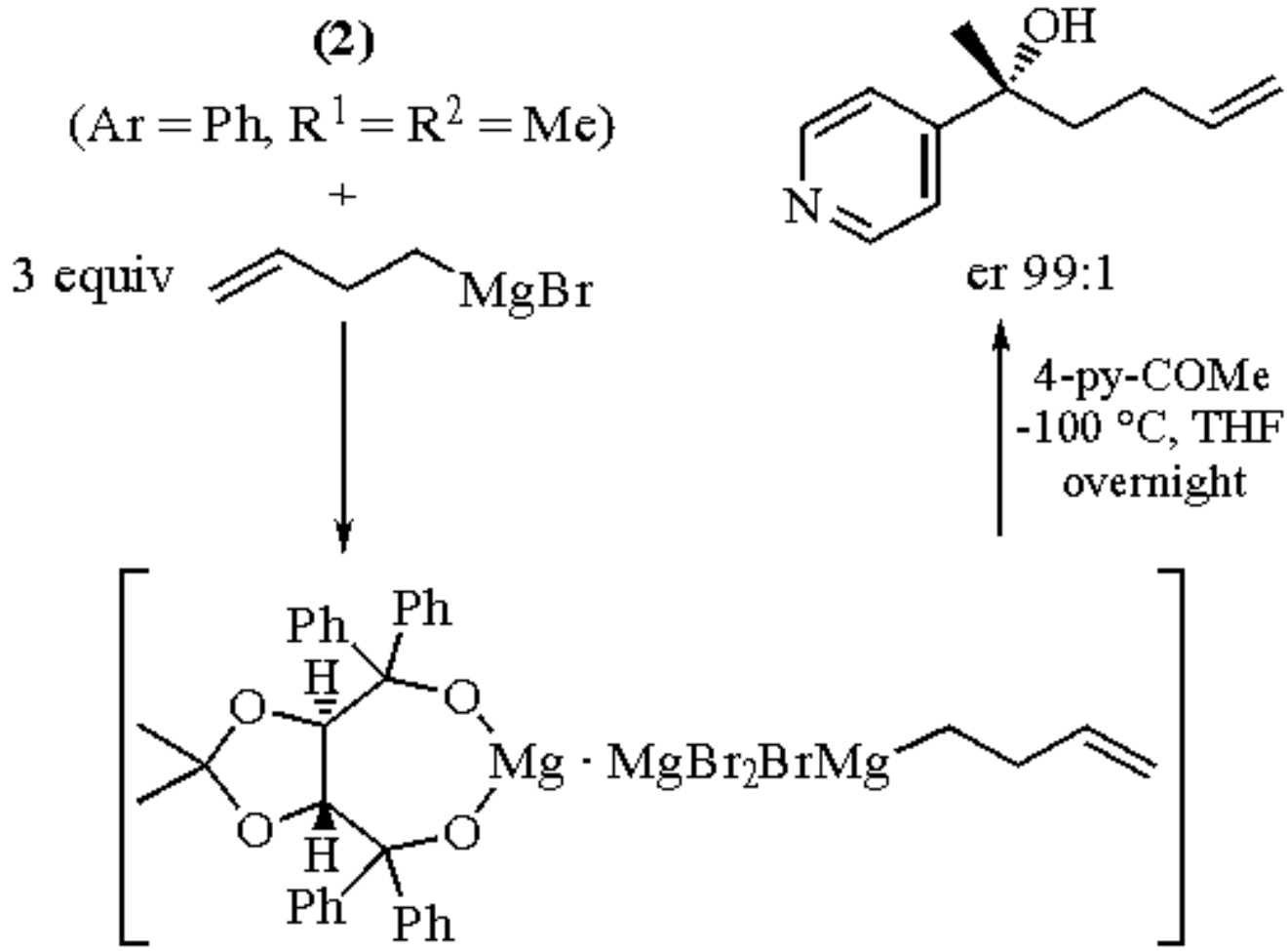

(11)

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Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate[1]

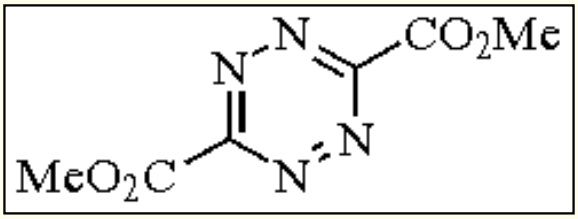

[2166-14-5] · $C_6H_6N_4O_4$ · Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate · (MW 198.138)

(reactive heteroaromatic azadiene for inverse electron demand Diels-Alder reactions with a wide range of dienophiles and heterodienophiles; used to prepare substituted 1,2-diazines, 1,2,4-triazines, pyrroles, pyridines, indolines, and related condensed heterocycles)

Alternate Name: bis(methoxycarbonyl)-*s*-tetrazine.

Physical Data: mp 175-177 °C.

Solubility: sol dioxane, CH_2Cl_2, THF, C_6H_6; insol H_2O.

Form Supplied in: bright red crystalline solid.

Preparative Method: ***Ethyl Diazoacetate*** (0.90 mol) is added dropwise to a stirred solution of NaOH (4.0 mol) in 250 mL of H_2O at such a rate so as to maintain the temperature of the reaction between 60 and 80 °C. After cooling to 25 °C, the reaction slurry is poured onto 1 L of 95% EtOH, mixed well, and the liquid decanted. This washing procedure is repeated 5 times before the precipitate is collected by filtration, washed with absolute EtOH (0.5 L) and Et_2O (0.5 L) sequentially, and air-dried to afford disodium dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (**2**) (85-97%).

A stirred slurry of (**2**) (0.39 mol) in 200 mL of ice-water at 0 °C is treated dropwise with 1.95 equiv of concentrated HCl. The yellow solid formed is immediately collected by suction filtration, washed with cold H_2O (50 mL) and Et_2O (50 mL) sequentially, and dried at 60 °C overnight to afford dihydro-1,2,4,5-tetrazine-3,6-dicarboxylic acid (**3**) (72-74%).

The solid (**3**) (0.16 mol) is added in small portions over 20 min to a stirred solution of $SOCl_2$ (27.5 mL) in dry MeOH (375 mL) at -30 °C. After completion of the addition, the reaction mixture is allowed to warm to 25 °C over 2 h, and then concentrated under reduced pressure. Extraction of the residue with CH_2Cl_2 (400 mL × 5) from H_2O (400 mL) followed by removal of the solvent from the organic phase in vacuo affords dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (**4**) (44-51%).

Nitrous gases generated by dropwise addition of a 6 N $NaNO_2$ solution (200 mL) to 125 mL of concentrated HCl

are bubbled into a stirred slurry of (**4**) (0.1 mol) in CH_2Cl_2 (800 mL) at 0 °C using a N_2 stream until the addition of $NaNO_2$ solution is complete. The solvent and excess nitrous gases are removed in vacuo to afford dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) (99%).[2]

Handling, Storage, and Precautions: dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate is a very reactive diene which is unstable to acid, base, H_2O, or protic solvents and should be stored moisture-free and refrigerated.

Cycloaddition Reactions.

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) is one of the most reactive heteroaromatic azadienes examined to date and it reacts with a wide range of dienophiles and heterodienophiles including electron-rich, neutral, strained, or electron-deficient alkenes, alkynes, dienes, enol ethers and acetates, enamines, ynamines, ketene acetals, enolates, benzynes, selected aromatics and heteroaromatics, imidates, thioimidates, aldehyde *N*,*N*-dimethylhydrazones, imines, azirines, and cyanamides. Extensive reviews have summarized[1] and compiled[1a] the results of such studies. Cycloaddition reactions occur exclusively across C-3/C-6 of the 1,2,4,5-tetrazine nucleus and is accompanied by a retro Diels-Alder reaction with extrusion of N_2 to afford substituted dihydro-1,2-diazines (dihydropyridazines) (eq 1),[3] or substituted 1,2-diazines (pyridazines) when the dienophiles are alkynes (eq 2),[4] or contain leaving groups capable of elimination with aromatization (eqs 3, 4 and 8).[3,5] Imines, imidates, and thioimidates prefer to react through their more reactive tautomeric enamine and ketene acetal forms, respectively (eq 5),[6] although cycloaddition of the C=N double bond may take place when such tautomerization is blocked (eq 6).[7] In selected instances, a preference for C&tbond;N triple bond addition over C=N double bond has been observed (eq 7).[8] Recent studies have illustrated the use of selenophene, oxazole, *N*-methylpyrazole,[9] 2-vinylindoles,[10] and naphthalenes[11] as dienophiles and an extensive and complete compilation of relative dienophile reactivities toward dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (Table 1)[12] has been described.

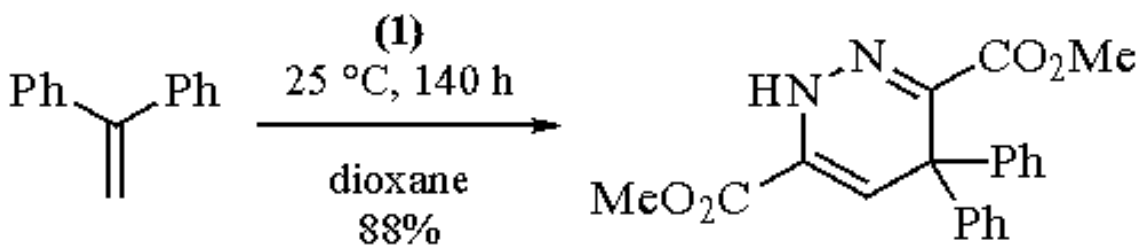

(1)

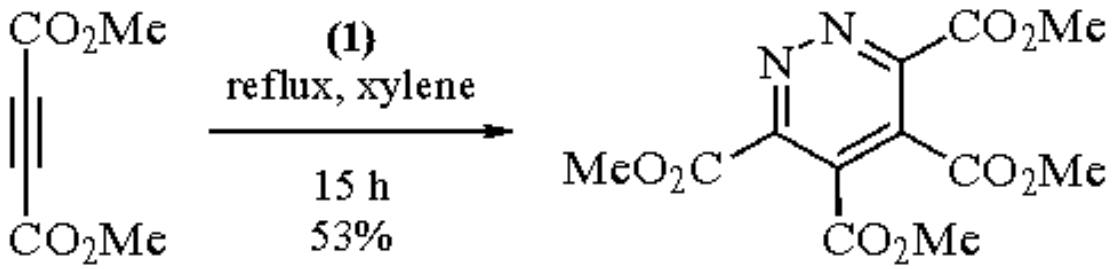

(2)

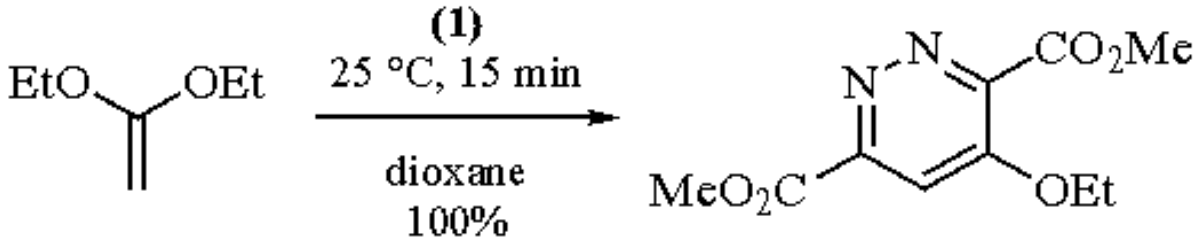
EtO
OEt
(1)
25 °C, 15 min
dioxane
100%
N
N
CO2Me
MeO2C
OEt

(3)

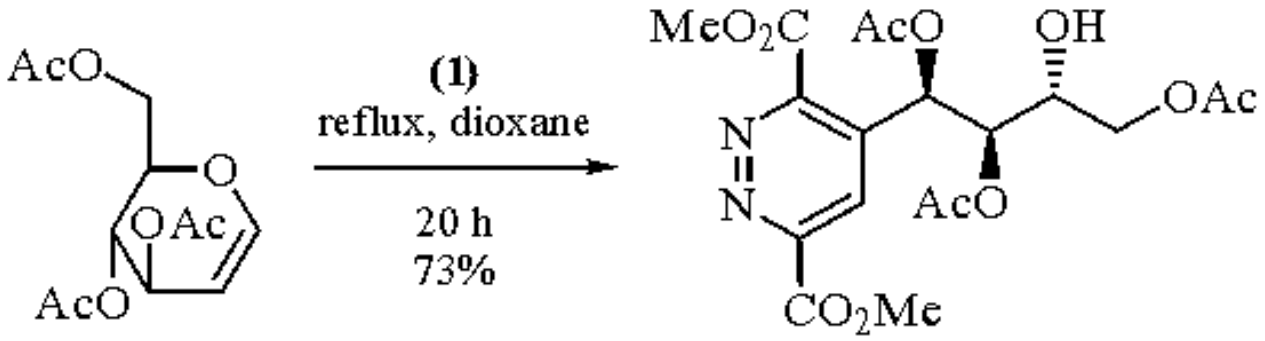
AcO
O
OAc
AcO
(1)
reflux, dioxane
20 h
73%
MeO2C
AcO
OH
OAc
N
N
AcO
CO2Me

(4)

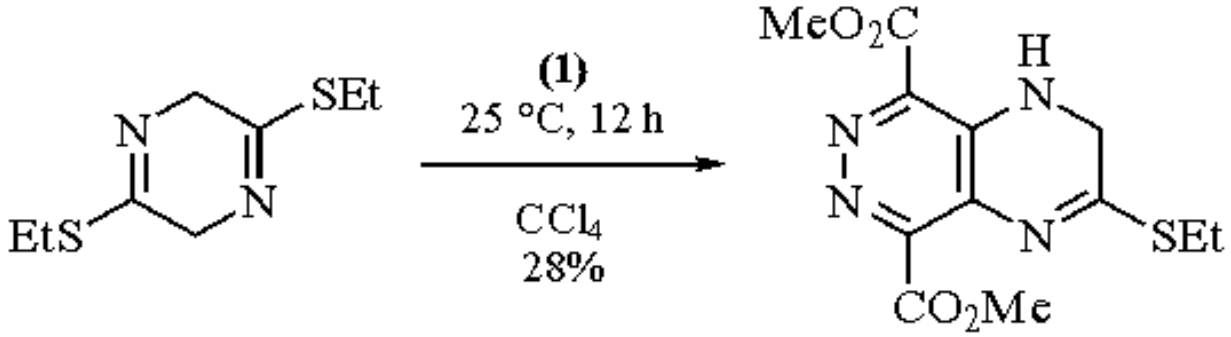
SEt
N
N
EtS
(1)
25 °C, 12 h
CCl4
28%
MeO2C
H
N
N
N
N
SEt
CO2Me

(5)

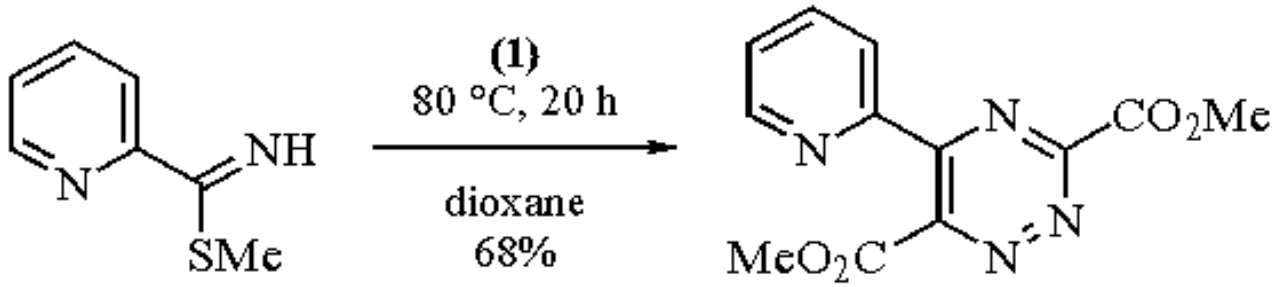
NH
N
SMe
(1)
80 °C, 20 h
dioxane
68%
N
N
CO2Me
N
MeO2C
N

(6)

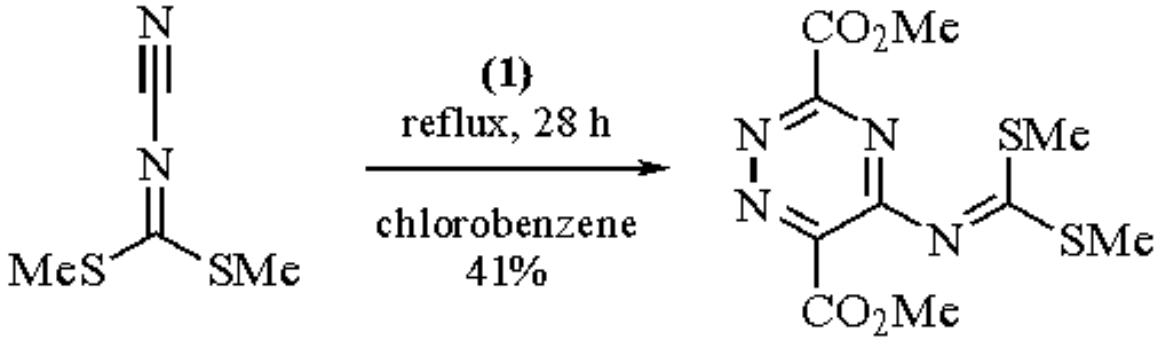
N
N
MeS
SMe
(1)
reflux, 28 h
chlorobenzene
41%
CO2Me
N
N
SMe
N
N
SMe
CO2Me

(7)

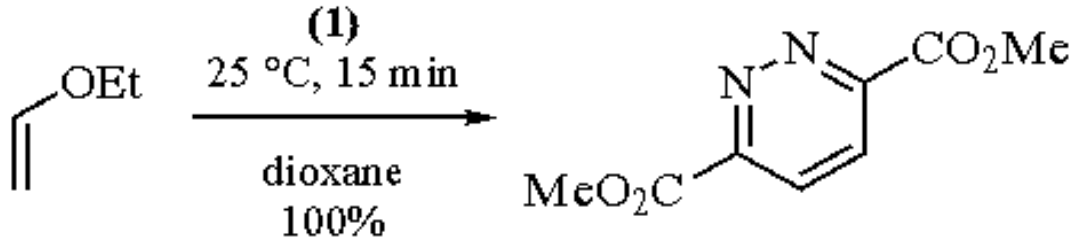

(8)

Table 1 Relative Dienophile Reactivity Toward Tetrazine **(1)**

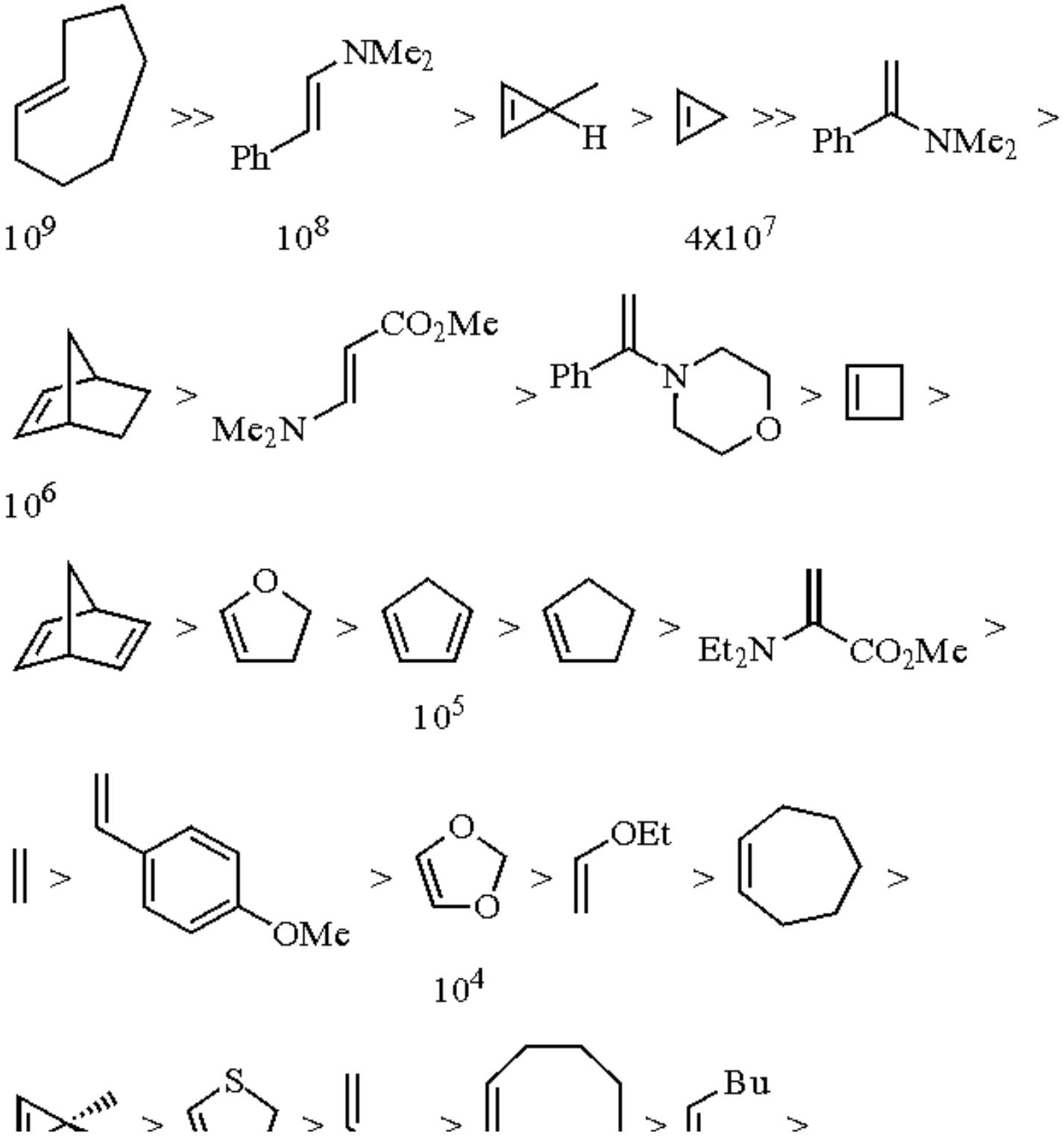

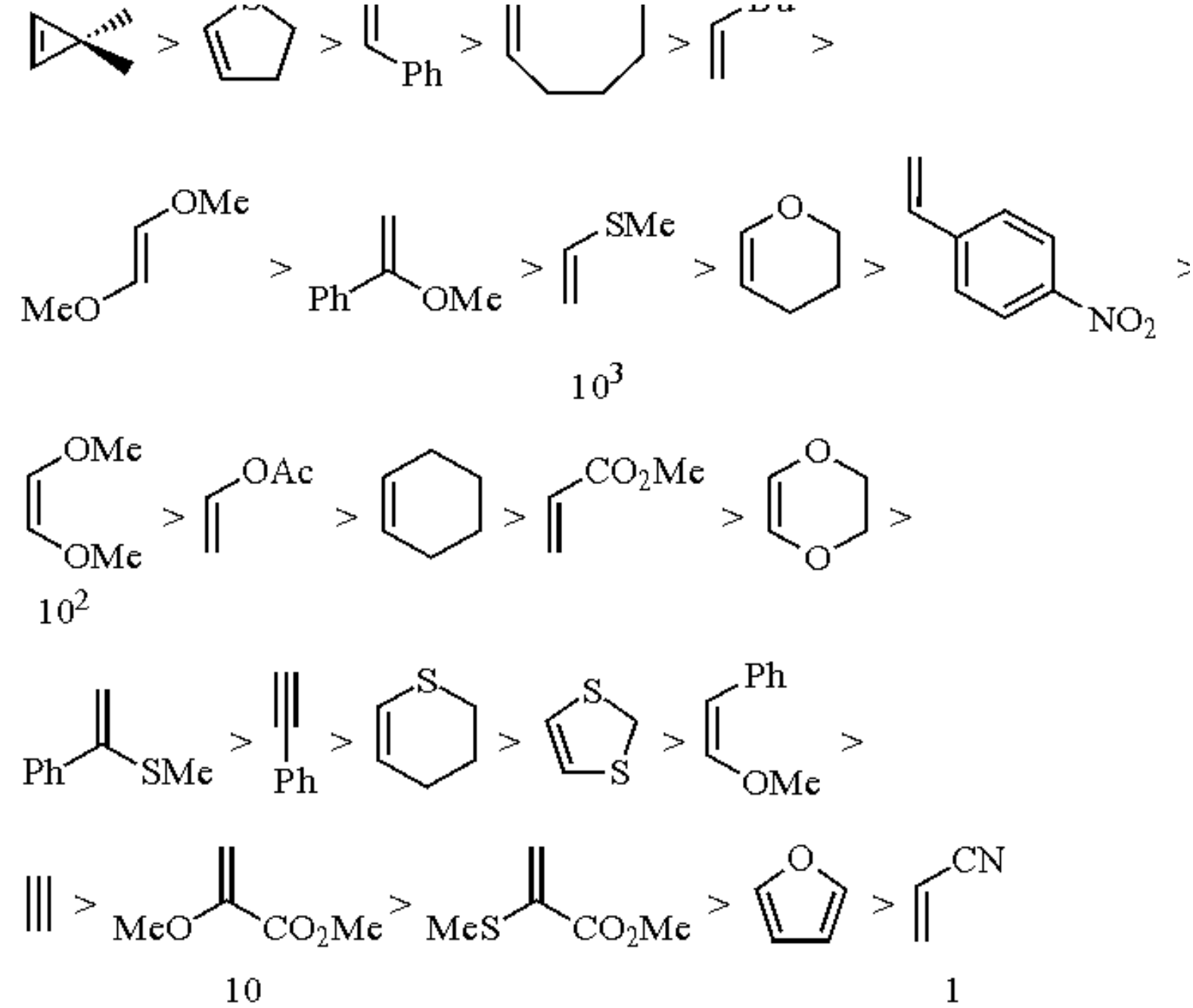

Indoline Synthesis.

The 1,2-diazine (pyridazine) products obtained from the Diels-Alder reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**1**) are poor dienes for further Diels-Alder reactions.[13] However, the entropic assistance provided in intramolecular reactions has been utilized to promote their participation in Diels-Alder reactions with unactivated alkynes.[14] Thus a general 1,2,4,5-tetrazine -> 1,2-diazine -> indoline strategy based on sequential inverse electron demand Diels-Alder reactions of (**1**) has been developed and applied to the total synthesis of PDE-I and PDE-II (eq 9),[15,16] (+)-CC-1065 (**5**),[17] and related agents.[18]

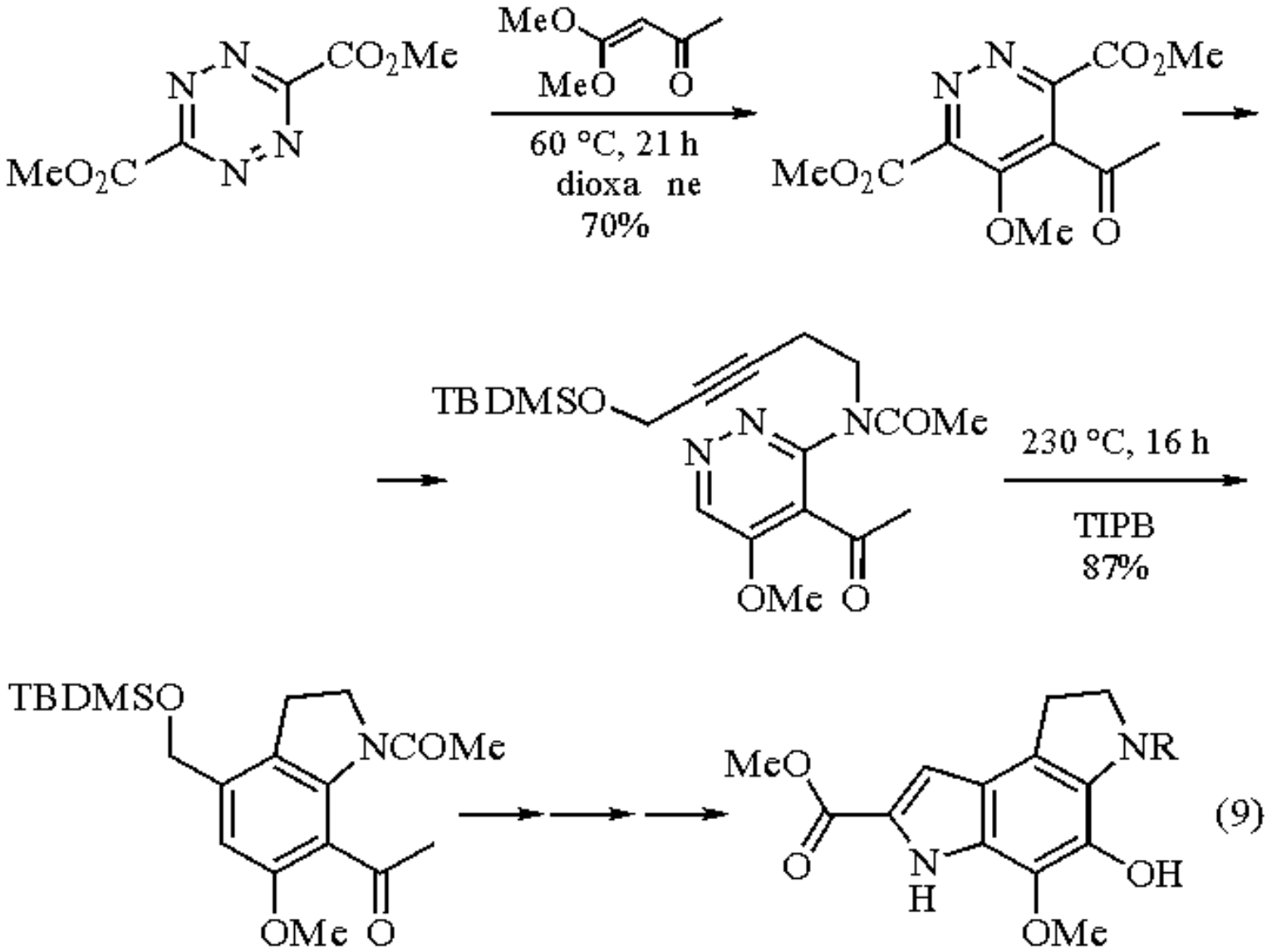

(9)

R = $CONH_2$, PDE-I methyl ester
R = COMe, PDE-II methyl ester

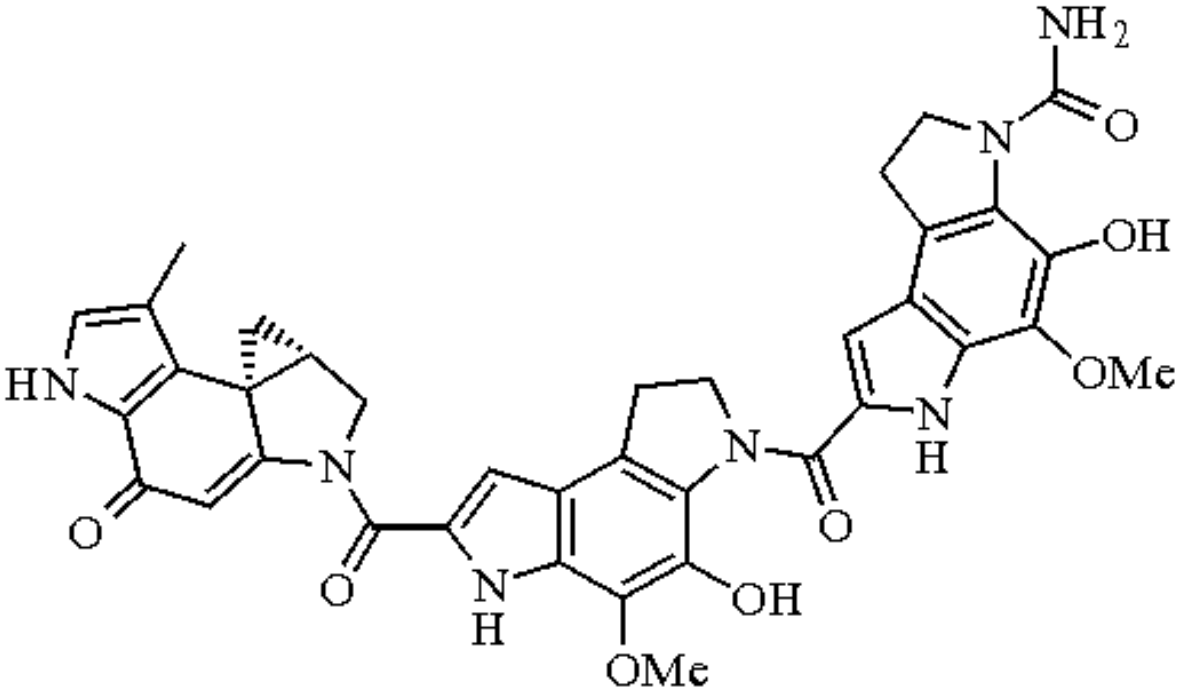

(5) (+)-CC-1065

Pyrrole Synthesis.

A novel reductive ring contraction reaction of dimethyl 1,2-diazine-3,6-dicarboxylates to provide dimethyl pyrrole-2,5-dicarboxylates[19] has been developed and provides an attractive 1,2,4,5-tetrazine -> 1,2-diazine -> pyrrole synthetic strategy (eq 10).[20] Successful applications of this strategy in the total syntheses of octamethylporphyrin (**6**),[20] prodigiosin (**7**) (eq 11),[21] and isochrysohermidin (**8**) (eq 12)[22] have been reported.

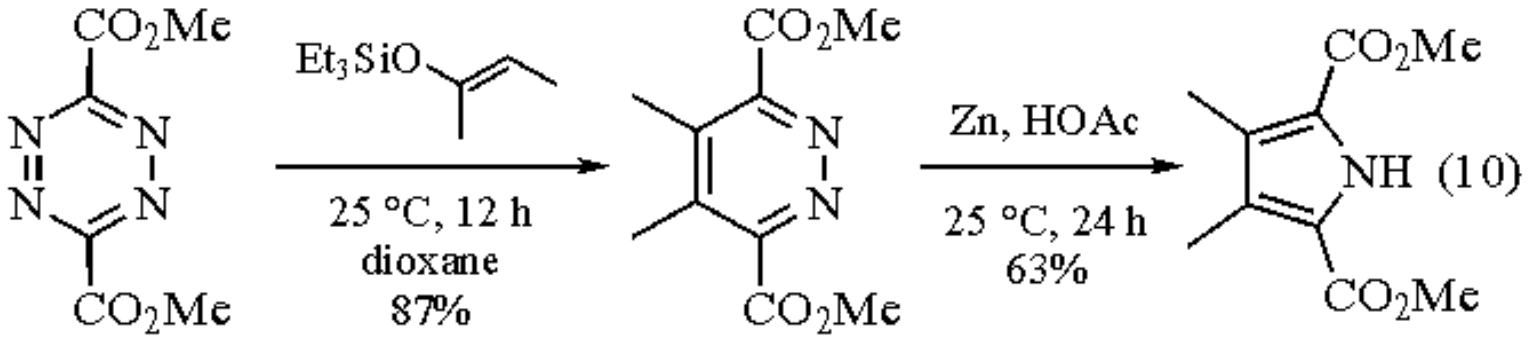

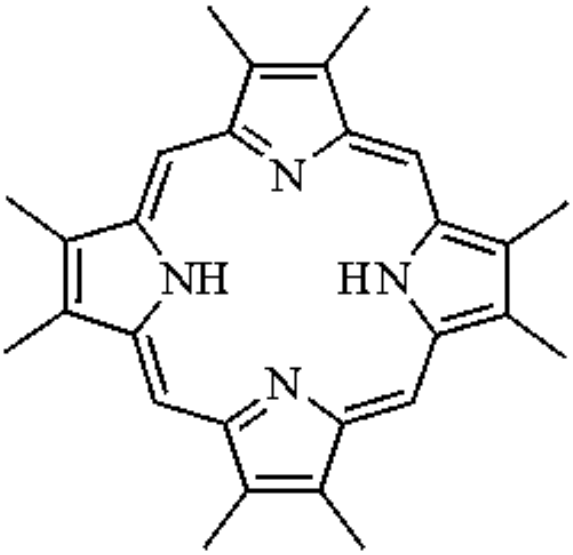

(6) Octamethylporphyrin (OMP)

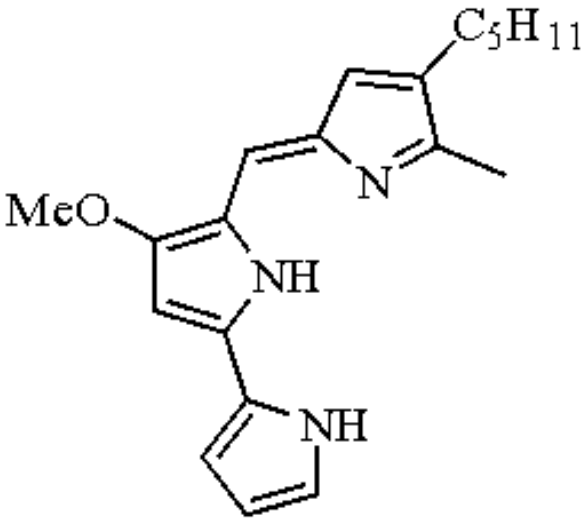

(7) Prodigiosin

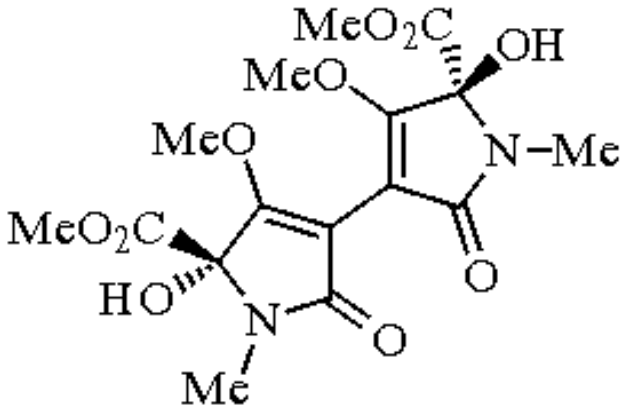

(8) Isochrysohermidin

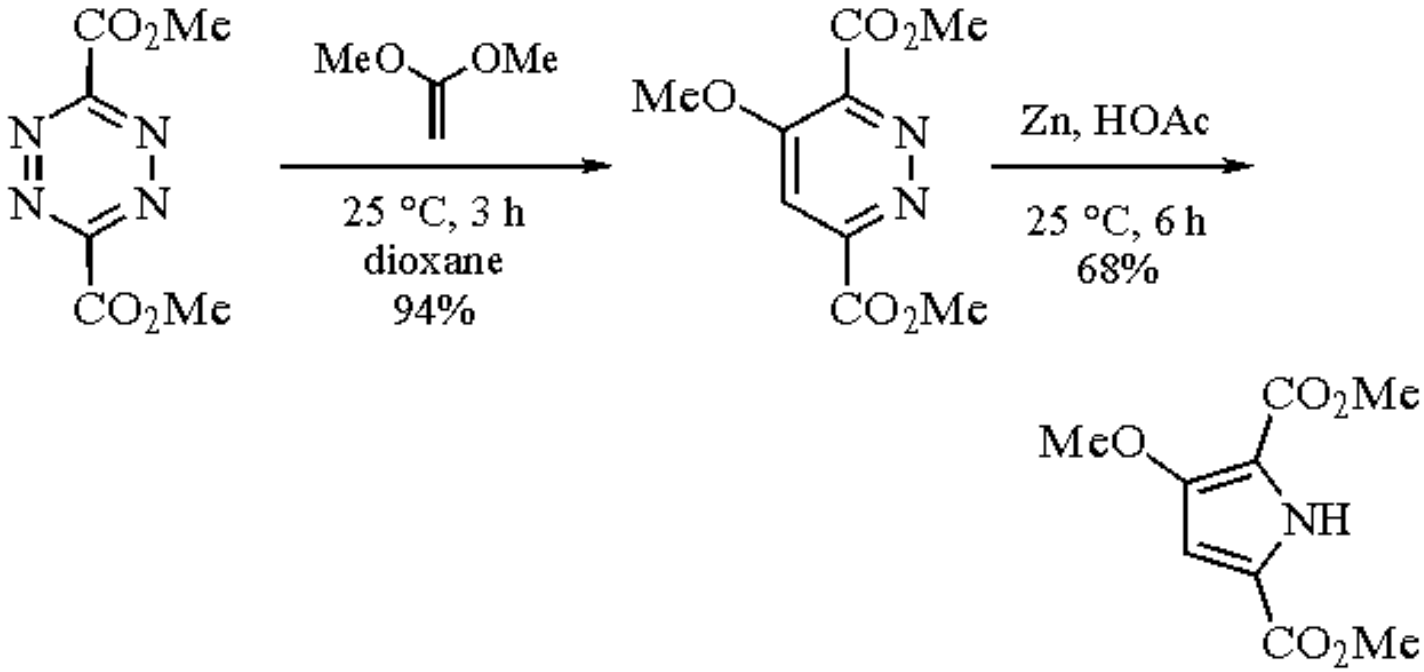

(11)

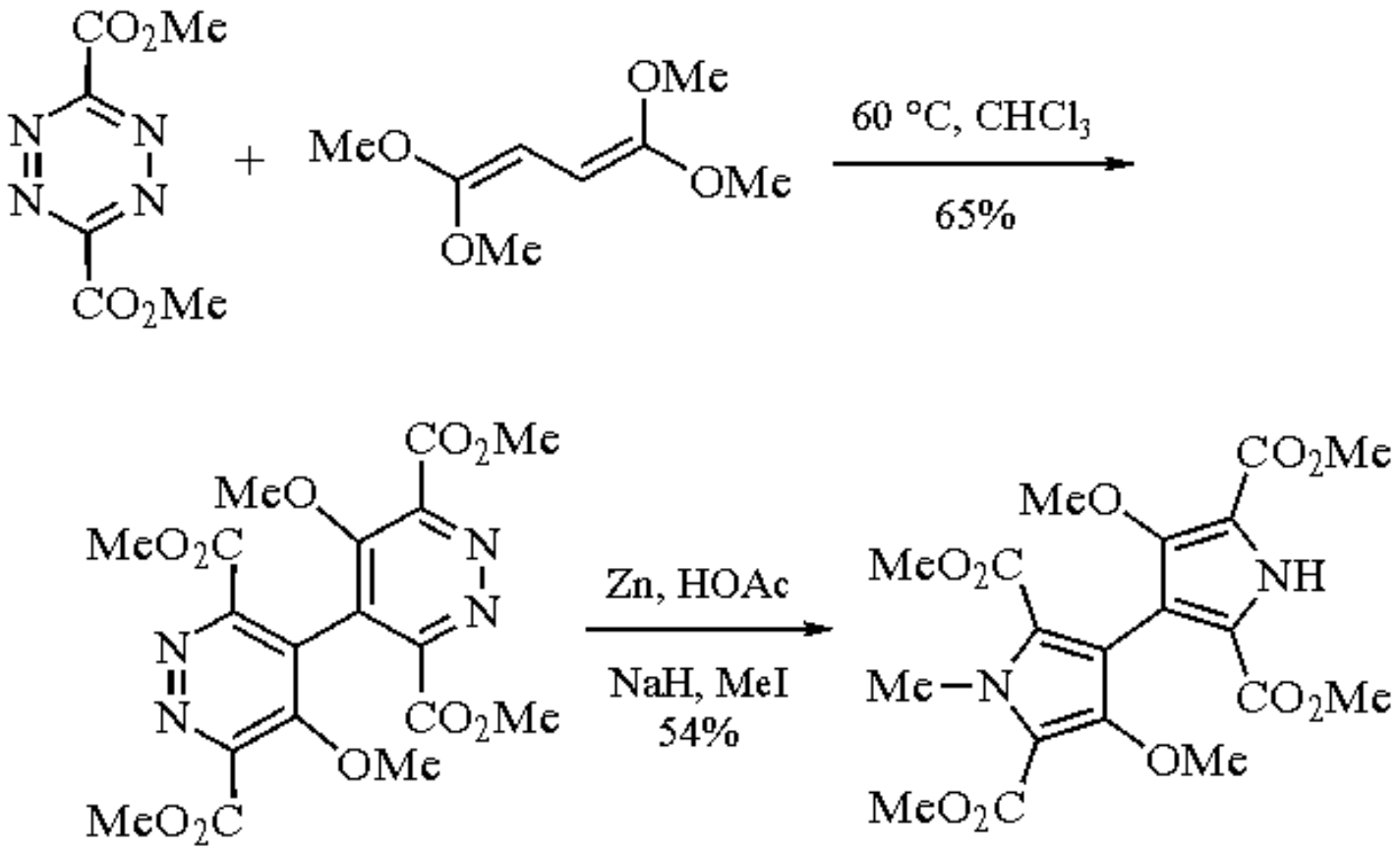

(12)

Pyridine Synthesis.

The triazine products derived from the [4 + 2] cycloaddition reactions of (**1**) with aryl imidates or aryl thioimidates are themselves electron-deficient heteroaromatic azadienes capable of participation in further regioselective inverse electron demand Diels-Alder reactions. Such triazines have proven useful in the preparation of substituted pyridines (see also ***Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate*** and ***1,2,4-Triazine***). Consequently, a 1,2,4,5-tetrazine -> 1,2,4-triazine -> pyridine synthetic strategy has been developed based on two consecutive [4 + 2] cycloaddition reactions and successfully

applied in the total synthesis of streptonigrin (**9**) (eq 13).[23]

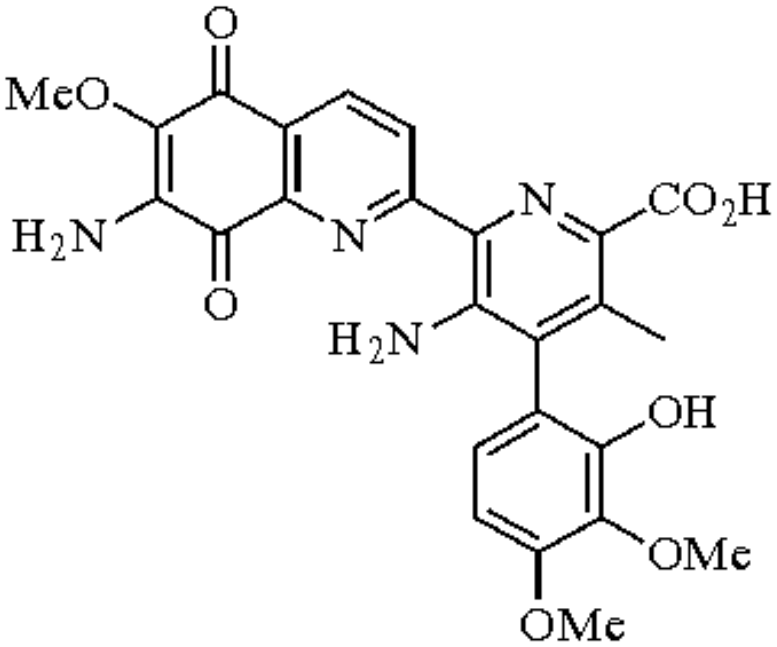

(9) Streptonigrin

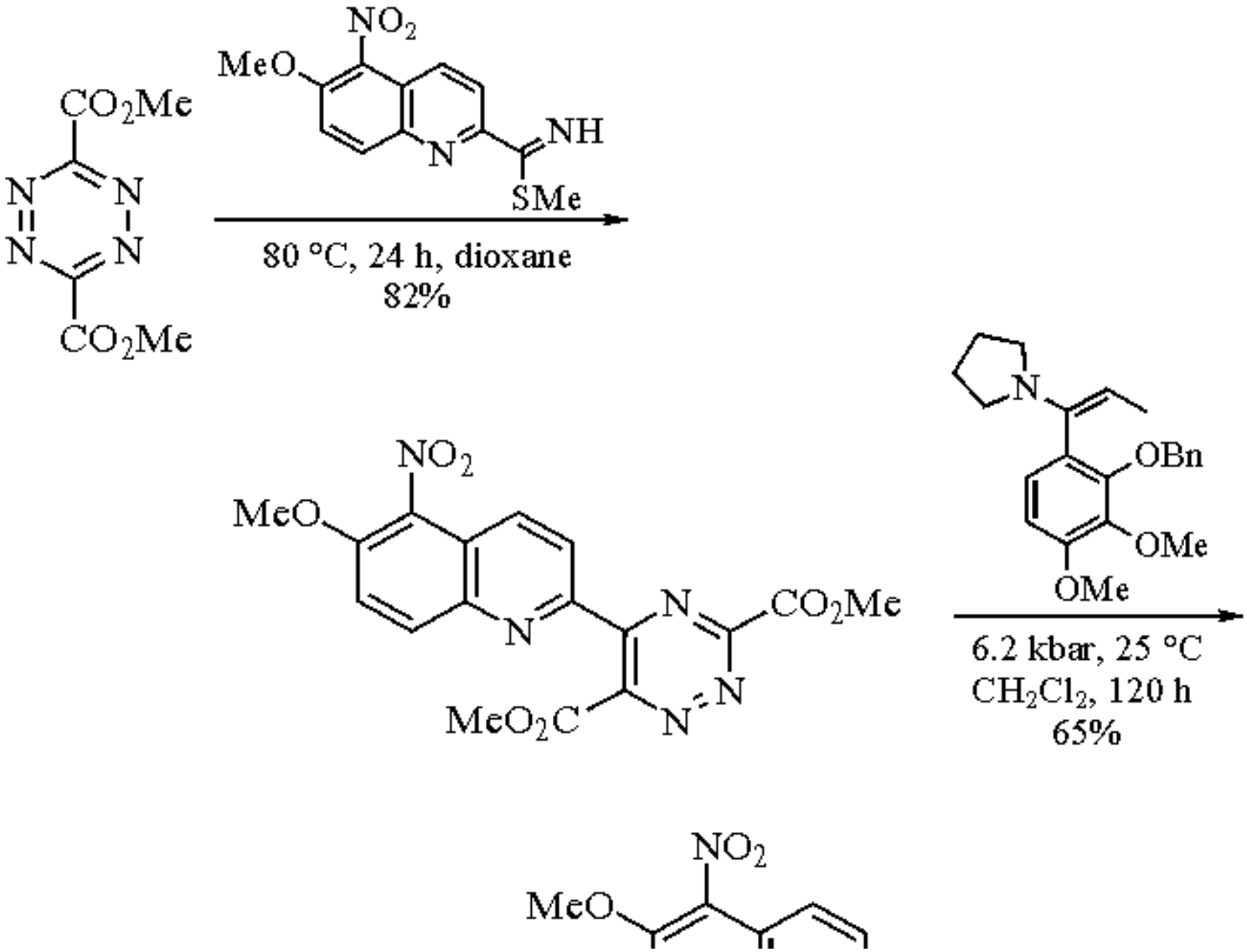

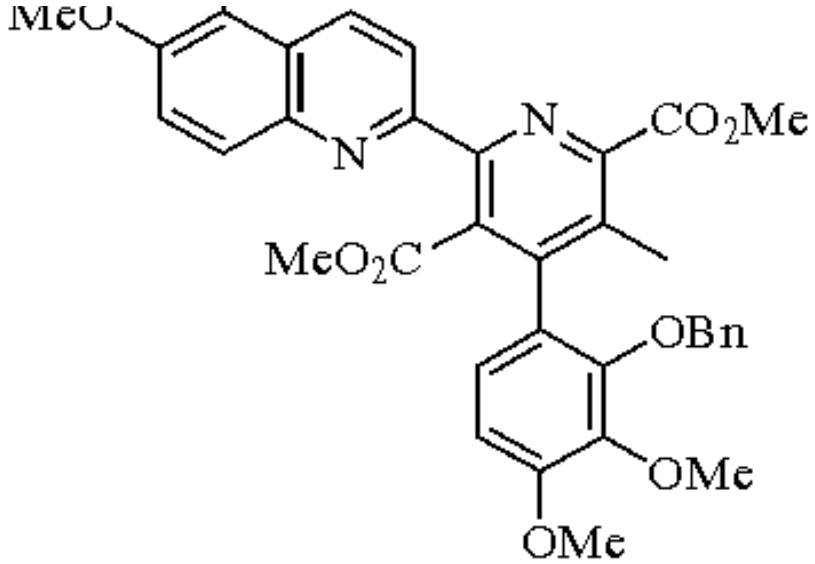

(13)

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Dimethylthiocarbamoyl Chloride[1]

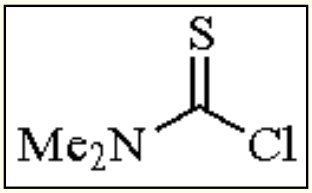

[16420-13-6] · C_3H_6ClNS · Dimethylthiocarbamoyl Chloride · (MW 123.62)

(conversion of phenols to thiophenols;[2] and, through subsequent desulfurization, for deoxygenation of phenols;[2] conversion of allylic alcohols to 1,3-rearranged *S*-allyl dimethylthiocarbamates[3] which can be hydrolyzed to the thiols or further oxidized to α,β-unsaturated carbonyl compounds;[4] conversion of α-hydroxy-α,β-unsaturated ketones (diosphenols) to α-chloro- and α-bromo-α,β-unsaturated ketones;[5a,b] deoxygenation of diosphenols to α,β-unsaturated ketones;[5c] deoxygenation of pyridine *N*-oxides;[6] dehydration of primary and secondary alcohols[7])

Physical Data: mp 42-44 °C; bp 90-95 °C/0.5 mmHg; 62-65 °C/0.2 mmHg.

Solubility: very sol chloroform, THF; reacts (slowly) with protic solvents.

Form Supplied in: large lumps; commercially available.

Preparative Methods: treatment of tetramethylthiuram disulfide with ***Chlorine***[7] or ***Sulfuryl Chloride***.[8]

Purification: vacuum distillation.

Handling, Storage, and Precautions: stable for years at 0 °C.

Conversion of Phenols to Thiophenols.

O-Aryl dimethylthiocarbamates (**1**), prepared by sequential treatment of phenols with base (usually ***Sodium Hydride*** in DMF) and dimethylthiocarbamoyl chloride, rearrange to *S*-aryl dimethylthiocarbamates (**2**) when heated at typically 200-300 °C (the Newman-Kwart rearrangement) (eq 1).[2] For the purpose of preparing aryl-sulfur compounds, this process is a significant improvement over the pyrolysis of di-*O*-aryl thiocarbonates (the Schönberg rearrangement),[9] where only one of the two aryl groups becomes connected to sulfur.

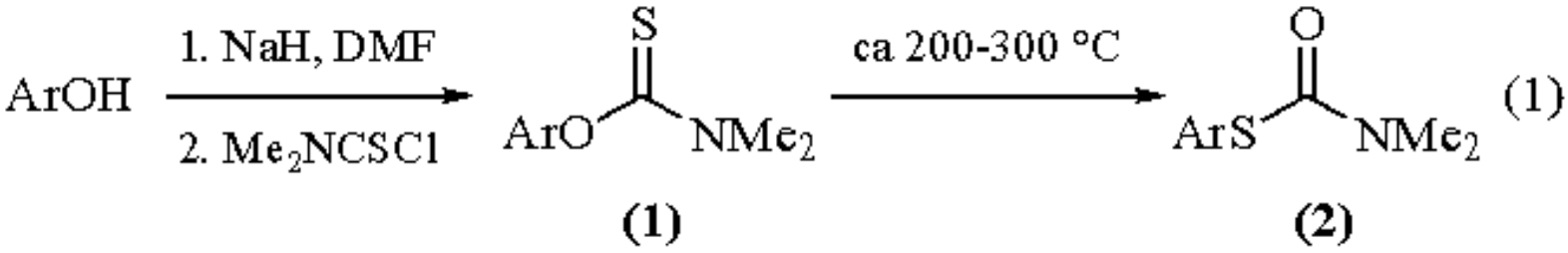

The product (**2**) may be transformed to the corresponding thiophenol by hydrolysis, or by reduction with ***Lithium Aluminum Hydride***[10a] or ***Sodium-Ammonia***.[10b] Alternatively, (**2**) may be oxidized with ***Hydrogen Peroxide***/***Formic Acid*** to the arenesulfonic acid,[11a] oxidized with ***Chlorine***/***Acetic Acid*** to the arenesulfonyl chloride,[11b,c] or desulfurized with ***Raney Nickel***.[12] Derivatization of phenols with the analog diethylthiocarbamoyl chloride sets the stage for *ortho*-deprotonation and alkylation with various electrophiles prior to effecting *O*-aryl -> *S*-aryl rearrangement.[13] A wide variety of phenols has been successfully utilized in these processes; consequently the Newman-Kwart reaction is one of the most important methods for preparing aryl-sulfur compounds. Applications of the rearrangement can be found in medicinal chemistry,[14] molecular recognition and supramolecular chemistry,[15] and inorganic chemistry.[16]

Phenols bearing an electron-withdrawing group at the *ortho* or *para* position rearrange most readily (2-nitrophenol requires 20 min at 170 °C), consistent with the intermediacy of (**4**) (eq 2);[2,9b] this mechanism is supported by the correlation of rearrangement rates with σ-values.[17]

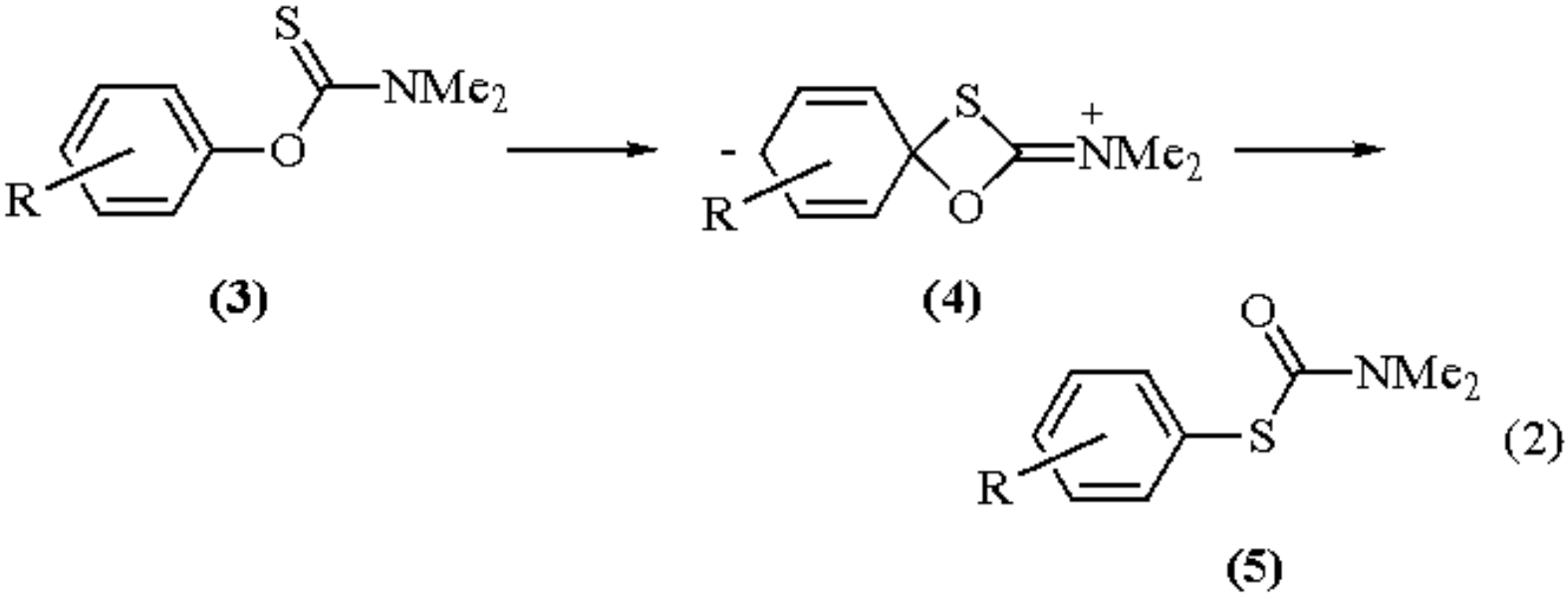

If two *o*,*p*-electron-withdrawing groups are present, as in (**6**) (eq 3),[18] or if an aza-aromatic system can be activated through protonation, as in (**8**) (eq 4),[2a] rearrangements occur much more readily. Conversely, electron-donating groups retard the reaction (e.g. 4-dimethylaminophenol requires 20 min at 295 °C).

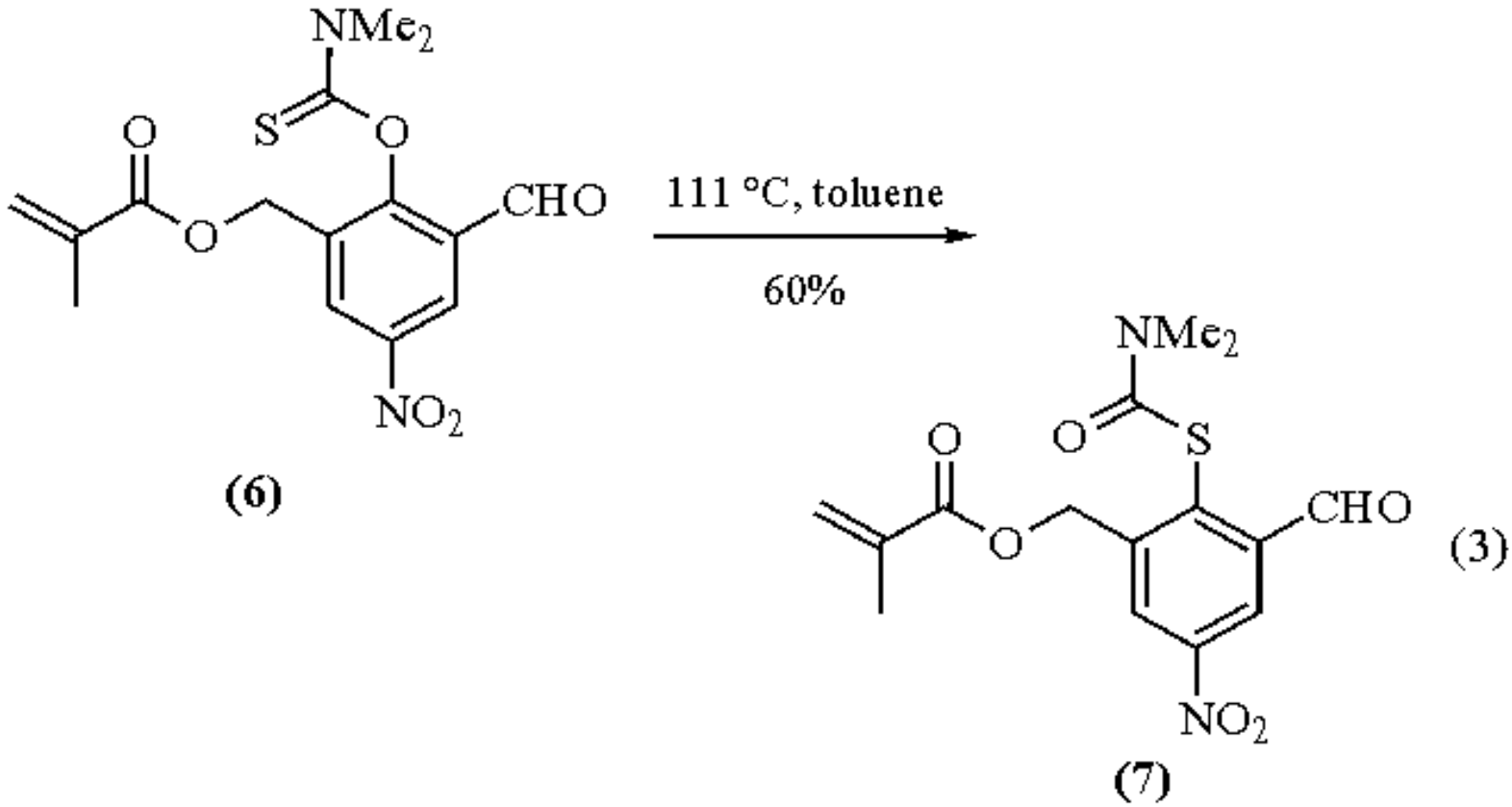

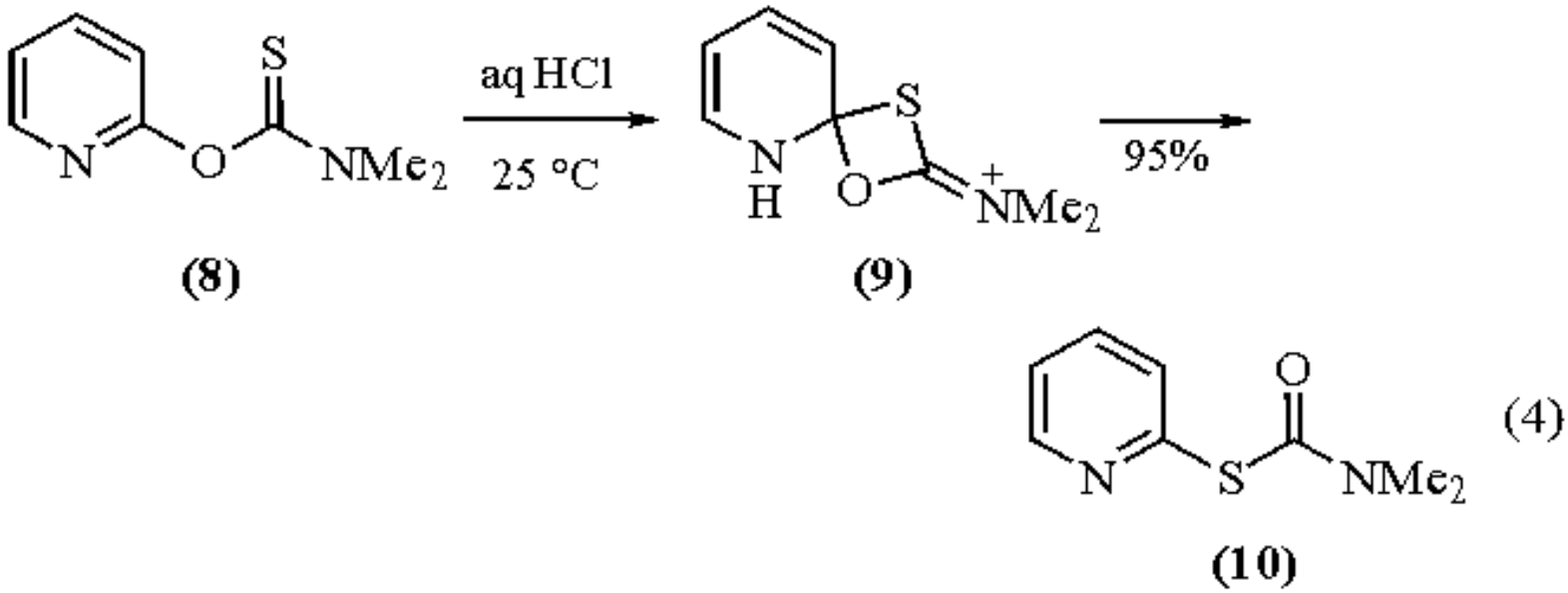

Large alkyl or aryl groups at *ortho* positions slow the reaction[2a,19a] and, in general, cause lower yields.[2a,14a,16b,c] In some cases the preparation of dimethylthiocarbamates from hindered phenols is attended by thioacylation of the aromatic ring.[19b] Reactive functional groups at *ortho* positions can divert the course of the reaction (e.g. eq 5);[19c] in some cases these difficulties can be minimized by careful selection of reaction conditions.[20]

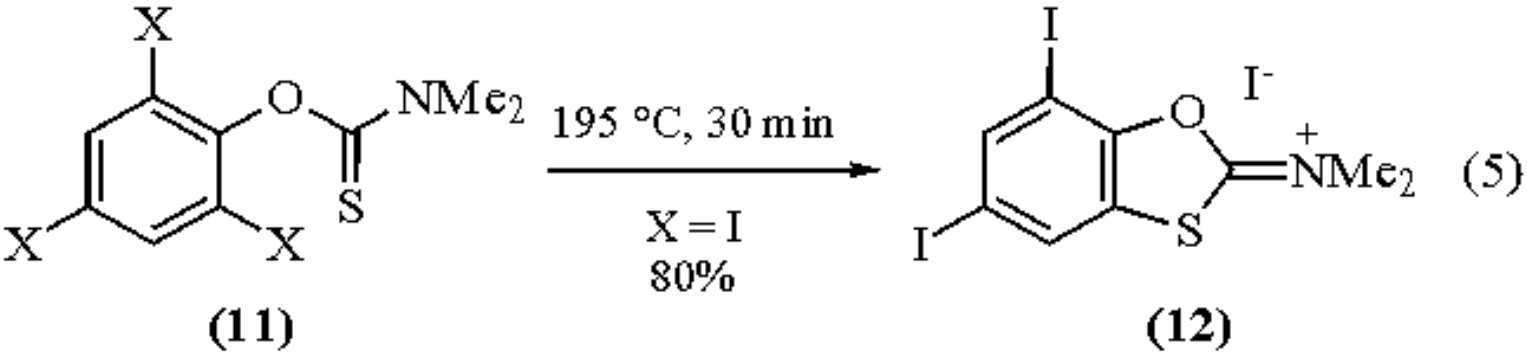

X = Cl gives normal Newman-Kwart rearrangement

Whereas rearrangement fails in the case of 1-naphthol,[21a] exemplary results are obtained with 2-naphthol,[2a,21b] 6-nitro-2-naphthol,[21c] and 3-phenanthrol.[2a] The enantiomerically pure bis(dimethylthiocarbamate) (**13**) undergoes rearrangement without racemization (eq 6).[15e] *O*-Thioacylation of 2-azulenol and 6-azulenol is complicated by concurrent *C*-thioacylation; use of the 1,3-bis(methoxycarbonyl) analogs, followed by hydrolysis/decarboxylation, circumvents this problem.[22a] There is only one hydroxythiophene example in the literature,[22b] and no examples involving hydroxyfurans or hydroxypyrroles.

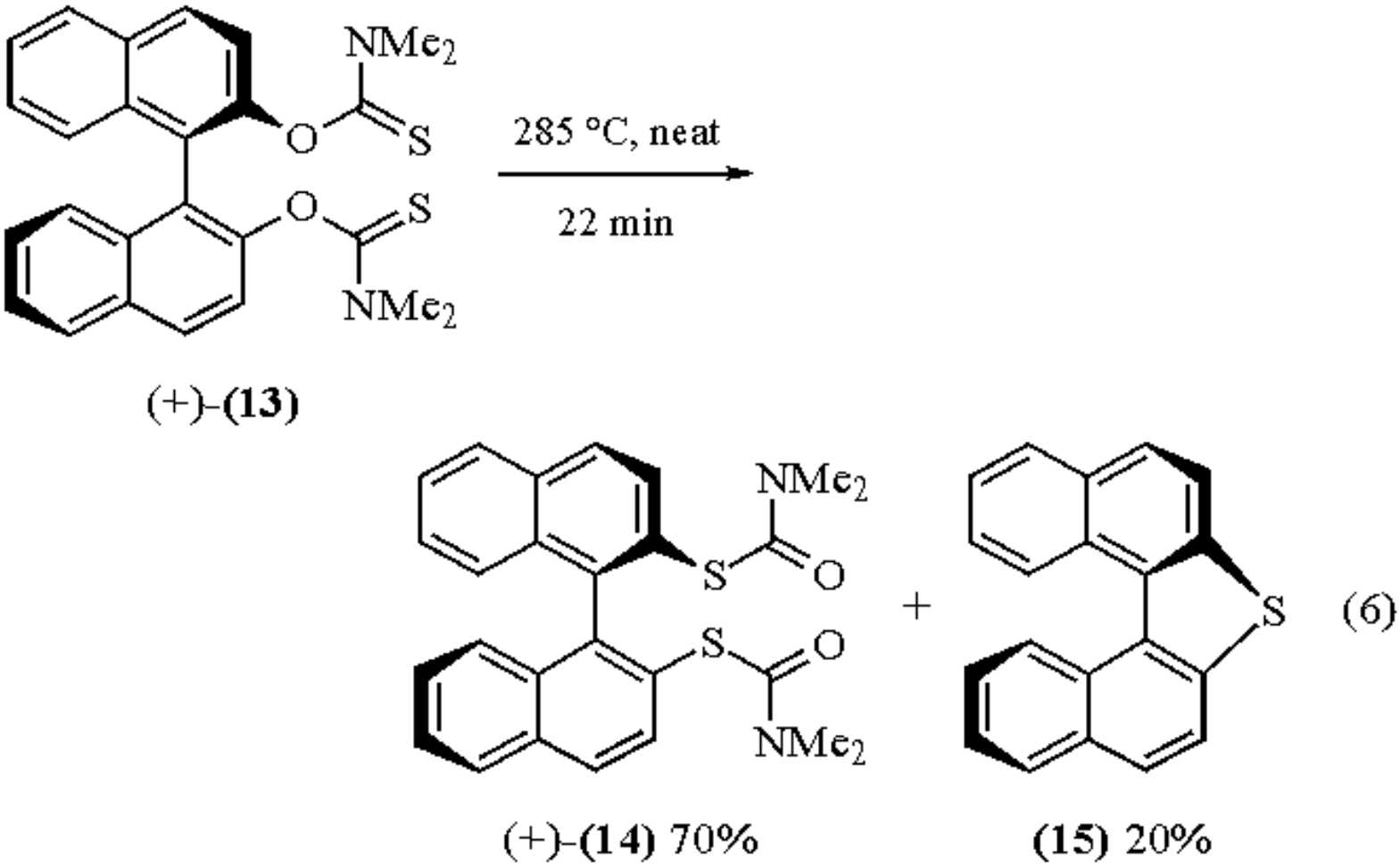

A nice application of the Newman-Kwart rearrangement is seen in the preparation of the otherwise difficult to access 5-hydroxyisoflavone (**19**) from the easily accessible 5,7-dihydroxyisoflavone (**16**) (eq 7).[12]

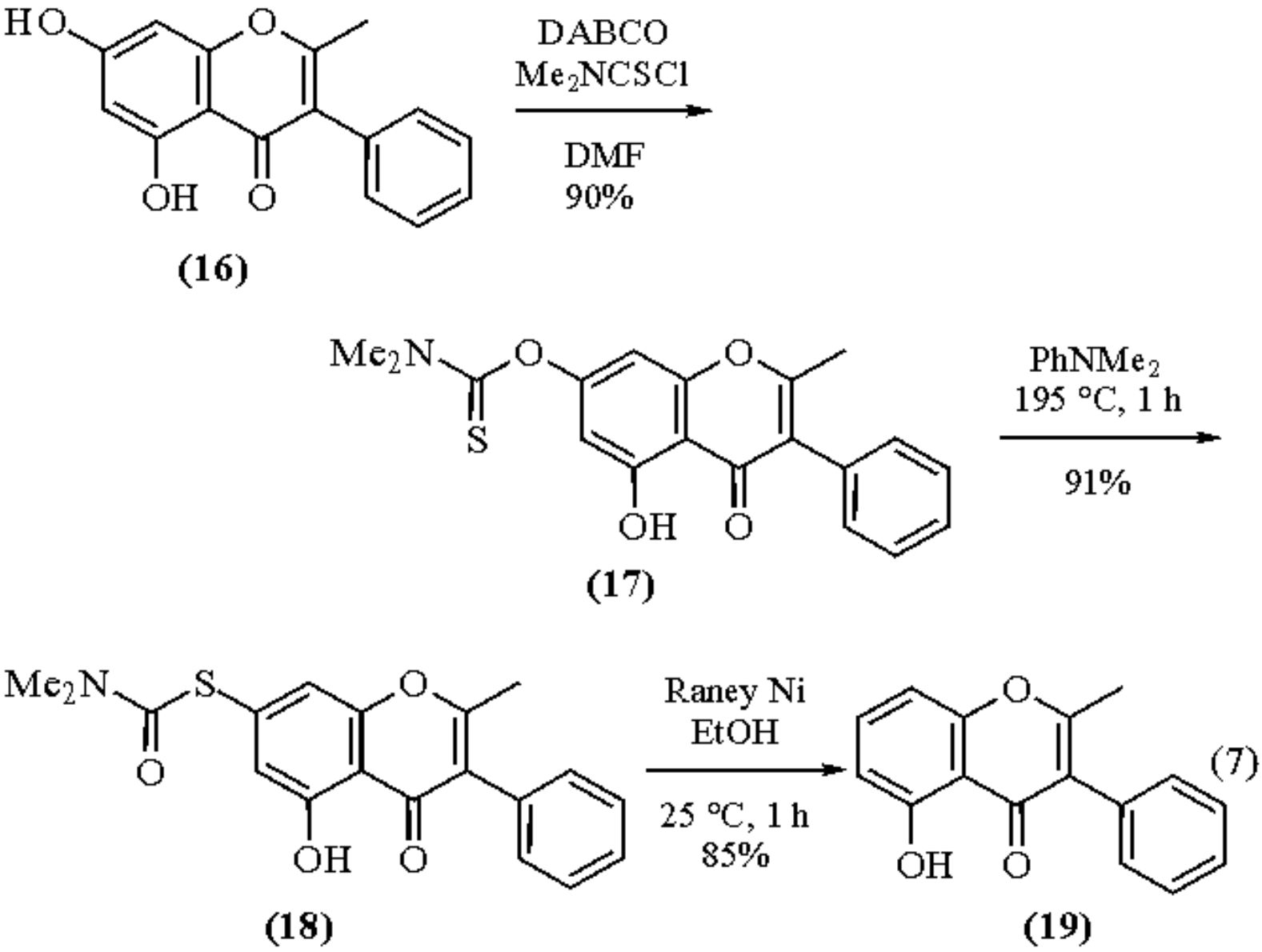

Conversion of Allylic Alcohols to 1,3-Rearranged *S*-Allyl Dimethylthiocarbamates.

Allylic dimethylthiocarbamates (from reaction of allylic alcoholates with dimethylthiocarbamoyl chloride) undergo [3,3]-sigmatropic rearrangement when heated at 100-130 °C.[3] The products may be hydrolyzed with base or (better) reduced with lithium aluminum hydride to the allylic thiols (note: tertiary allylic thiols undergo allylic equilibration during aqueous hydrolysis). Although the rearrangement is somewhat slower[3b] than the more familiar rearrangement of allylic xanthates,[23] the products lend themselves to deprotonation and alkylation with electrophiles. This sequence has been used by Nakai, et al. for the synthesis of several acyclic terpenes such as the ant pheromone manicone (**24**) (eq 8).[4]

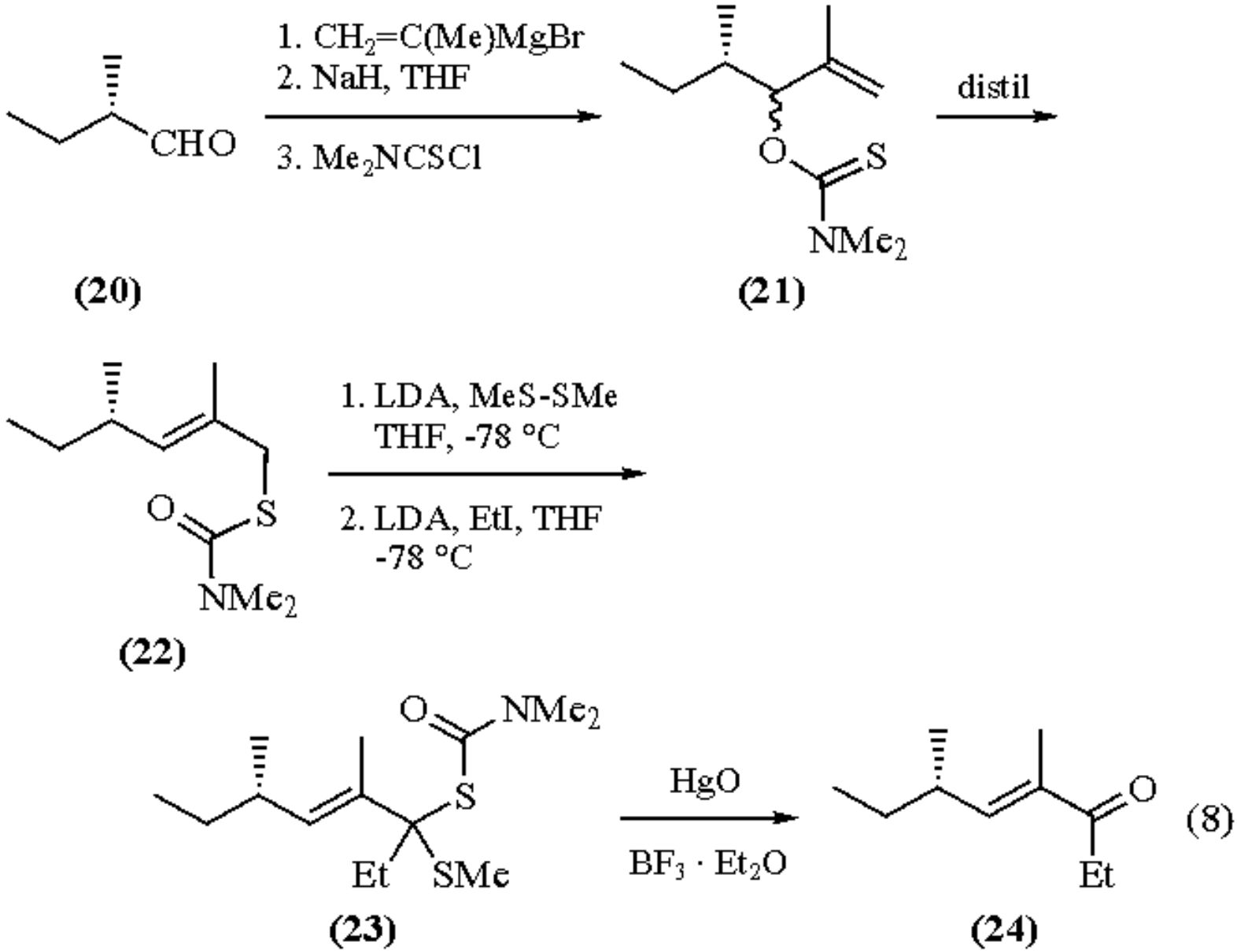

Conversion of α-Hydroxy-α,β-Unsaturated Ketones (Diosphenols) to α-X-α,β-Unsaturated Ketones (X = H, Cl or Br).

The hydroxy group of diosphenols may be activated towards substitution by conversion to the dimethylthiocarbamate. These derivatives, irrespective of substitution pattern in the diosphenol, are deoxygenated in near-quantitative yield to α,β-unsaturated ketones by ***Lithium Iodide*** in hot acetic acid.[5c] Dimethylthiocarbamates of diosphenols whose β-carbon atom is unhindered react with ***Lithium Chloride*** or ***Lithium Bromide*** in acetic acid to furnish the corresponding halo compounds;[5a] if the β-carbon atom is substituted, a variety of products is obtained.[5b] Evidence is provided for the intermediacy of cyclized compounds like (**27**) in these reactions (eq 9).[5]

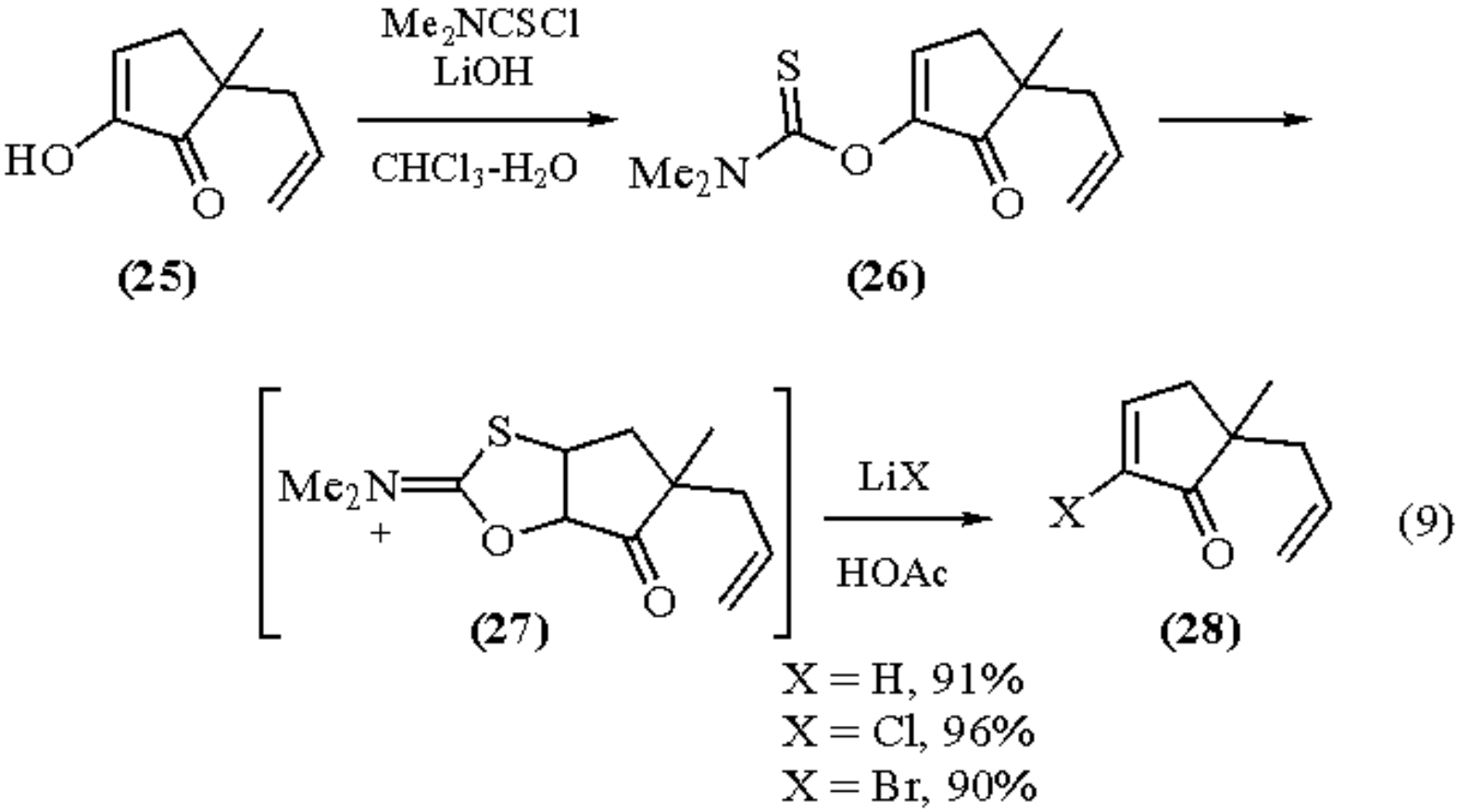

(9)

Deoxygenation of Pyridine *N*-Oxides and Related Compounds.

Treatment of pyridine *N*-oxides with dimethylthiocarbamoyl chloride and lithium iodide in acetonitrile at rt or below gives chemoselective deoxygenation (eq 10).[6] Neither oxalyl chloride nor tosyl chloride can be used as activating agents, and it is speculated that the reaction proceeds through an intermediate like (**30**), analogous to (**27**).

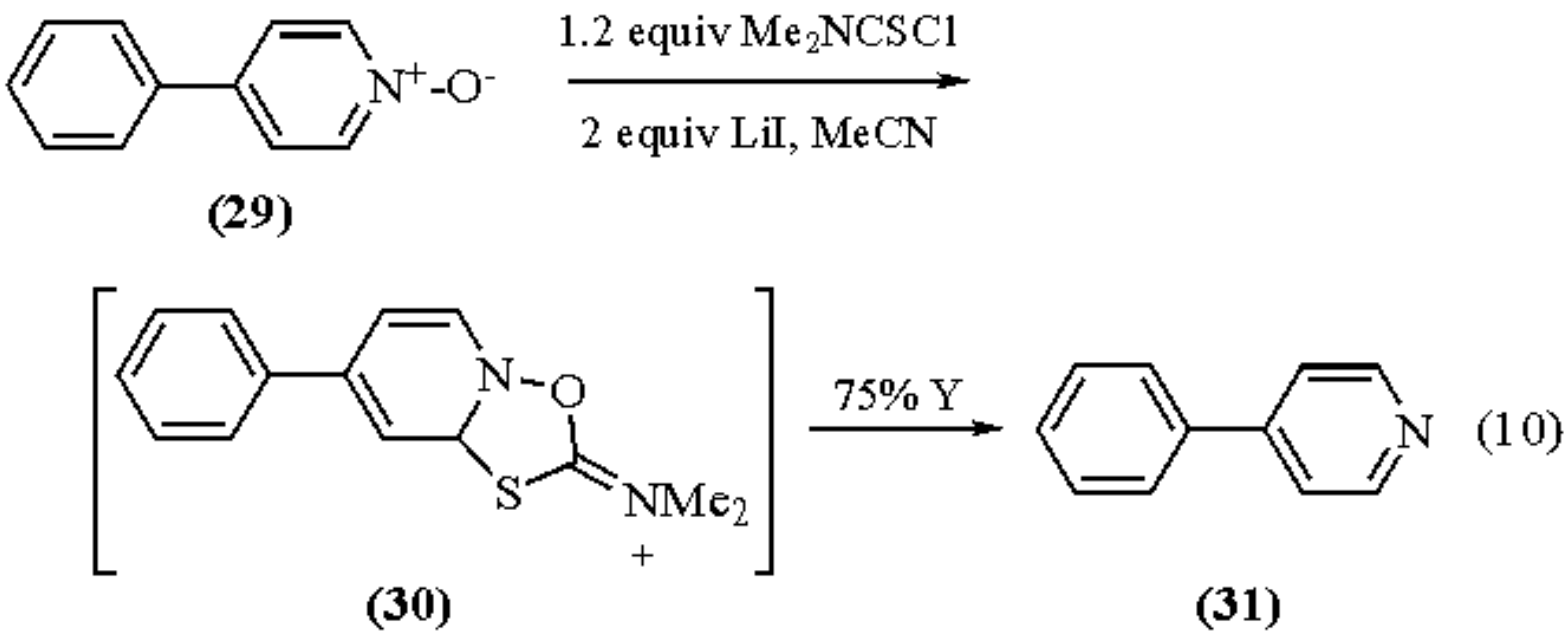

(10)

Dehydration of Primary and Secondary Alcohols.

Dimethylthiocarbamates of primary and secondary alcohols bearing a β-hydrogen give alkenes when heated at 180-200 °C.[7] This procedure has some advantages over xanthate pyrolysis:[24] (a) one-step preparation of derivatives; (b) yields of elimination products are often better; and (c) no thiol is produced upon pyrolysis. This latter consideration is important in the dehydration-aromatization of (**33**) (eq 11).[25]

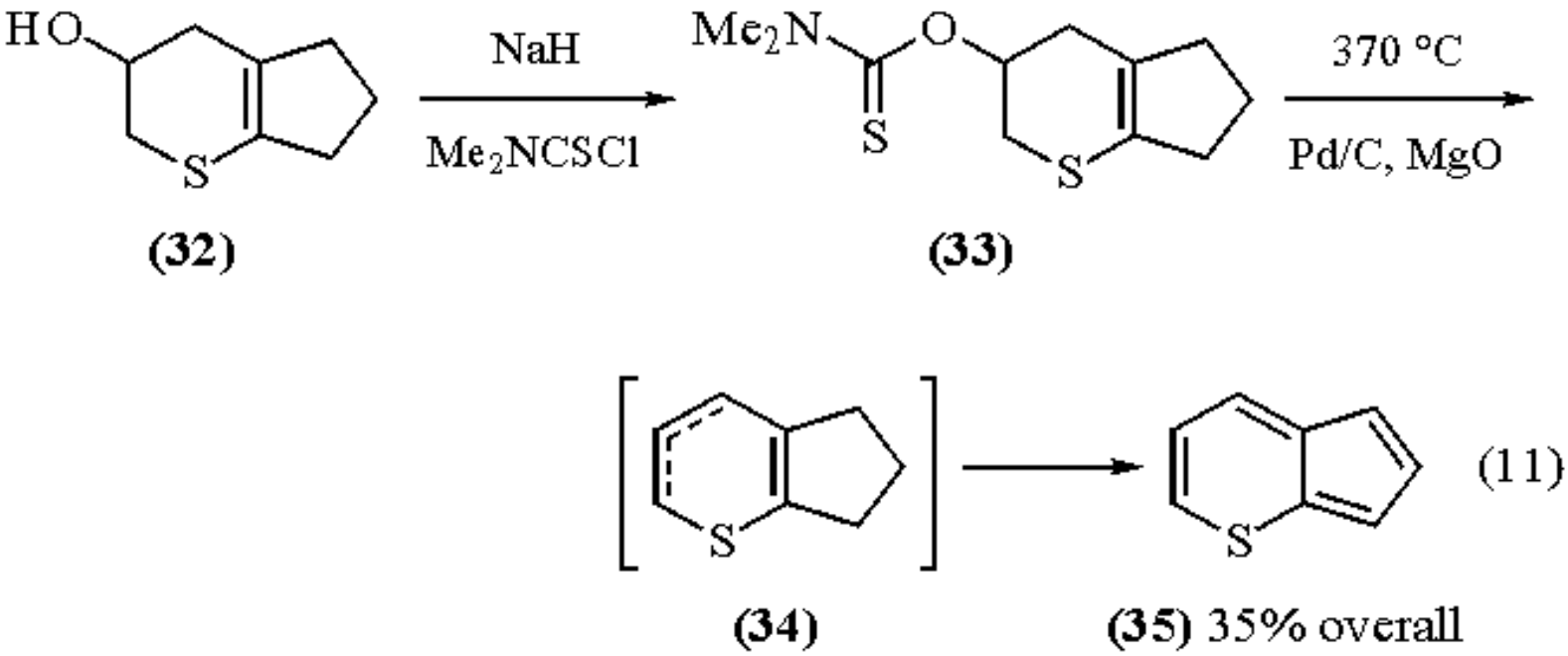

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N,N-Dimethylthioformamide[1]

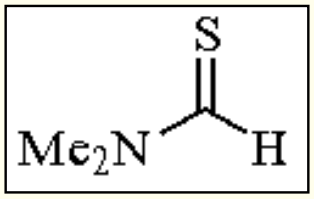

[758-16-7] · C_3H_7NS · *N,N*-Dimethylthioformamide · (MW 89.18)

(Vilsmeier reagent for formylation of aliphatic, aromatic, and heteroaromatic systems; acyl anion equivalent; thiolysis of alkyl, aryl, and acyl halides; conversion of oximes into nitriles; reduction of sulfoxides; formation of some sulfur heterocycles and formamidines)

Alternate Name: TDMF.

Physical Data: bp 58-60 °C/1 mmHg; *d* 1.047 g cm^{-3}; n_D^{20} 1.5760; fp 99 °C.

Solubility: sol THF, ethyl acetate, toluene, DMF; may react with some halogenated solvents.

Form Supplied in: yellow to colorless liquid.

Analysis of Reagent Purity: characterized by ^1H and ^{13}C NMR spectroscopy.[2]

Preparative Methods: various methods have been reported[3] for the preparation of TDMF. As with other thioamides, it is best obtained by treatment of the parent amide with a suitable thionating reagent (see also ***2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide***) (eq 1).[3d] More recently, efficient conversion has been effected using ***Phosphorus(V) Sulfide*** that has been activated using solid ***Sodium Carbonate*** (eq 2).[3a]

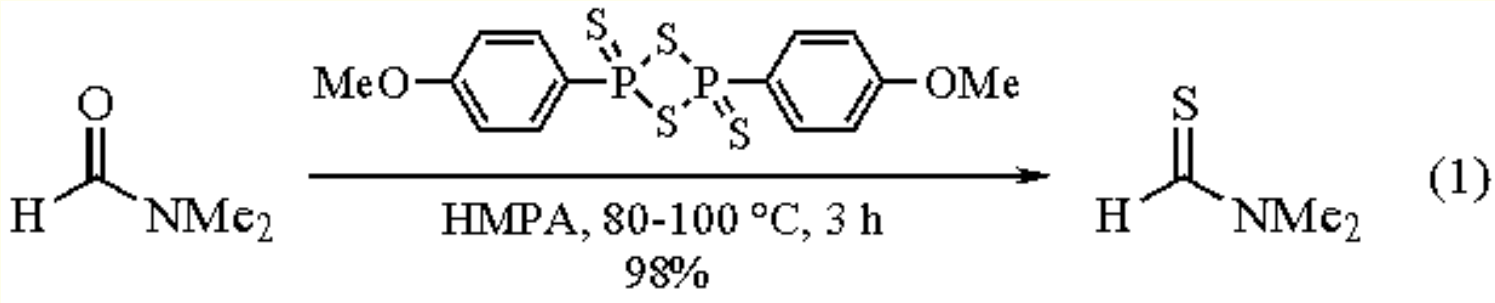

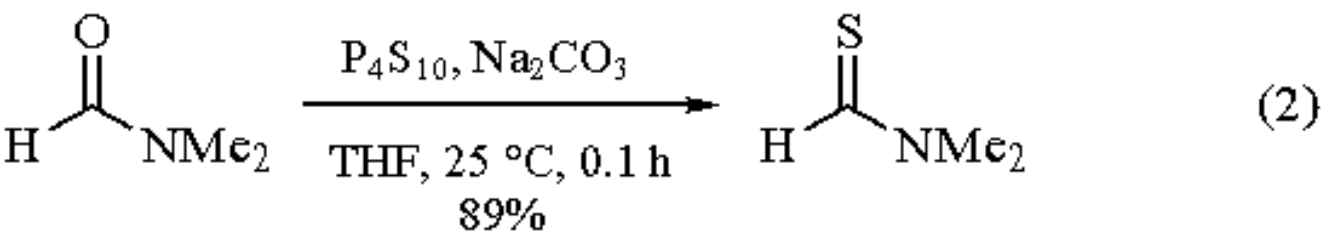

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: can be stored for long periods of time at rt if kept sealed under inert atmosphere and out of direct contact with light; use in a fume hood.

Acyl Anion Equivalent.[1c-e]

TDMF can be readily deprotonated at low temperature to give a nucleophilic acylating reagent directly, and thus it serves as an acyl anion equivalent.[4] However, due to the thermal instability of the anion, very low temperatures and rapid trapping of the incipient anion are required. Moderate to good yields have been obtained in this manner in reactions where ketones or aldehydes serve as electrophiles (eq 3).[4e] Recent protocols alleviate the need for precise low temperature control and provide for comparable yields by requiring admixing of the TDMF and electrophile followed by slow addition of the mixture to a chilled solution of ***Lithium Diisopropylamide*** (-78 °C).[4a,b]

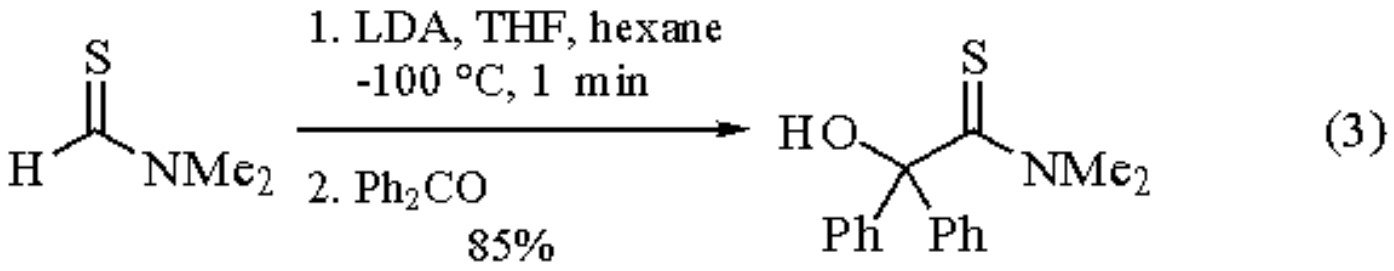

Formylation.

TDMF is a very effective formylating reagent[5] (see also ***Dimethylchloromethyleneammonium Chloride***), providing intermediate enamines in good yields in situations where other more traditional reagent combinations, such as DMF/acetic anhydride, fail (eq 4).[5c]

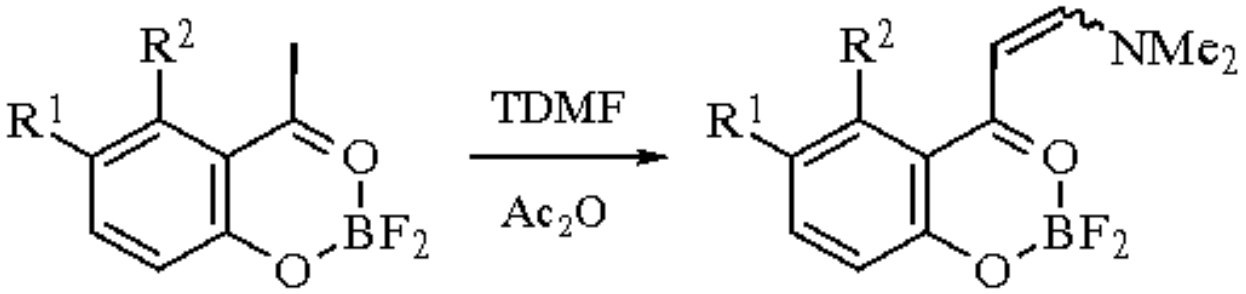

(4)

R^1R^2 = Benzo 93%
$R^1 = R^2 = H$ 85%

Recently, TDMF has shown potential as a formylating reagent, yielding enaminones using a modified protocol of the Eschenmoser coupling of thioamides (eq 5).[5a,1b]

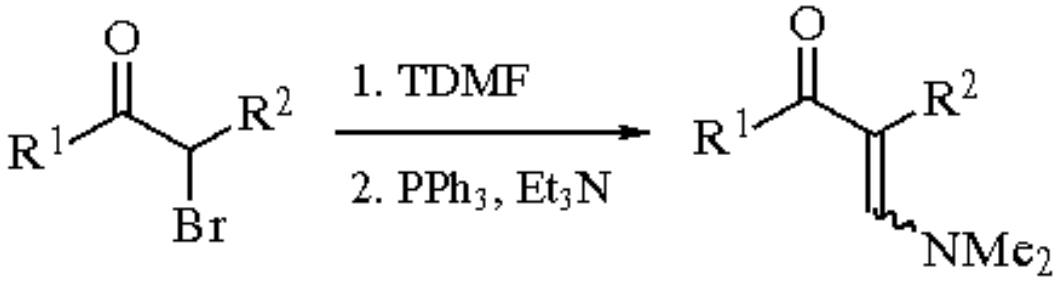

(5)

Preparation of Thiols.

Thiols can be obtained in excellent yield from the methanolysis of the adduct formed between an organic halide and TDMF (eq 6).[6]

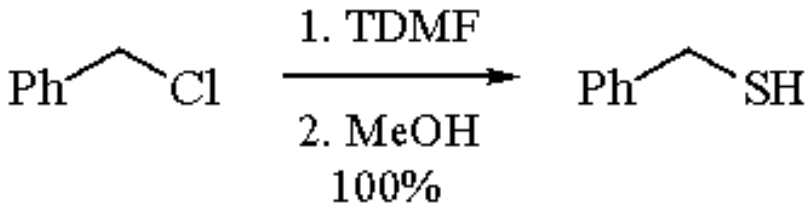

(6)

Thiopyran Generation.

TDMF undergoes a Diels-Alder reaction with an electron-deficient diene with concomitant loss of the dimethylamino group to yield a 2*H*-thiopyran (eq 7).[7]

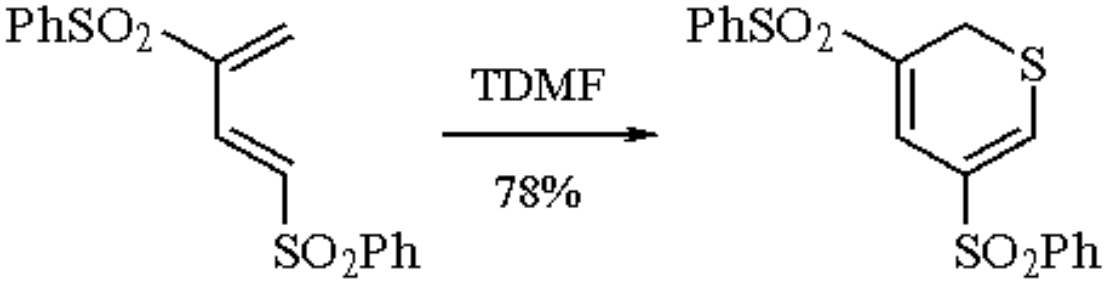

(7)

Thiirane Generation.

Thiiranes can be obtained in good to excellent yields from treatment of the corresponding epoxides with TDMF in the presence of a strong acid (eq 8).[8]

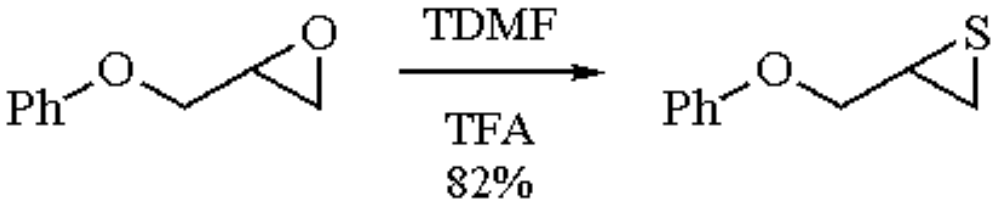

(8)

Reduction of Sulfoxides.

Thioformamidium ions, formed from the combination of TDMF and an alkyl halide, serve as excellent reagents for the reduction of sulfoxides (eq 9).[9]

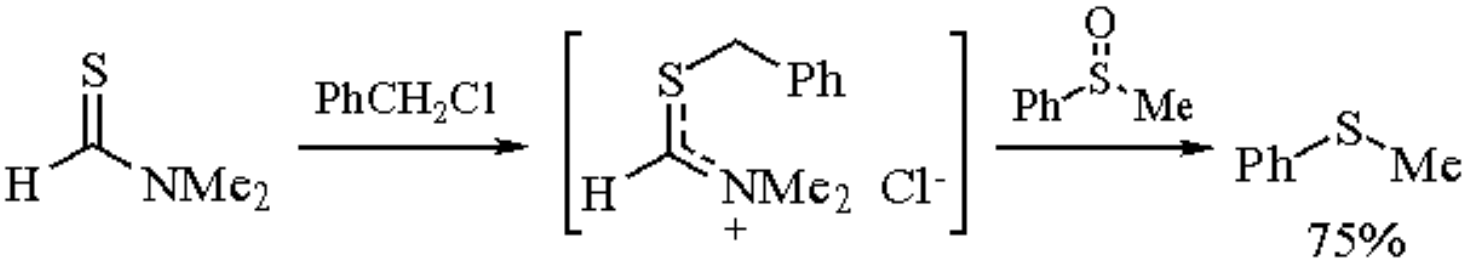

(9)

Preparation of Nitriles.

Thioformamidium ions have also been used to convert oximes to nitriles (eq 10).[10]

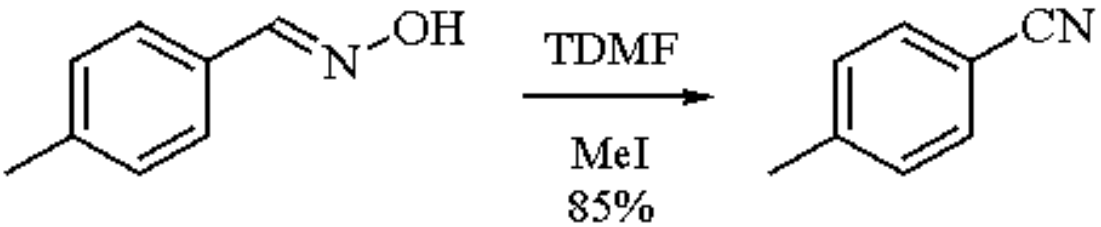

(10)

Reaction with Amines.

TDMF reacts with primary amines (aryl and alkyl) to yield formamidines (eq 11),[11] whereas upon heating TDMF in the presence of a secondary amine, the dimethylamino group is readily displaced by an amines of higher molecular weight, thereby leading to alternative thioformamide derivatives.[4c,12]

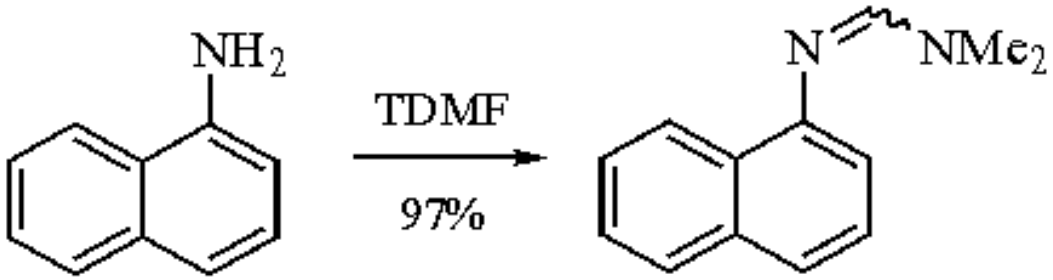

(11)

Related Reagents.

Acetic Anhydride; ***N,N-Dimethylformamide***; ***Potassium Thiocyanate***; ***Thiourea***; ***Tris(methylthio)methane***.

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Dichlorodimethyltitanium[1]

Me_2TiCl_2

[35739-70-9] · $C_2H_6Cl_2Ti$ · Dichlorodimethyltitanium · (MW 148.86)

(Lewis acidic reagent[2] capable of geminal dimethylation of ketones[3] and aromatic aldehydes,[4] substitution reactions of tertiary alkyl halides and alcohols,[5] and stereoselective Grignard-type additions to aldehydes and ketones[6-9])

Physical Data: reliable data not available; dark violet in crystalline form (dec. at -10 °C); yellow in hydrocarbon solvents; violet in diethyl ether.

Preparative Methods: several methylmetal reagents such as ***Methyllithium***, ***Methylmagnesium Bromide***, Me_2Zn, and ***Trimethylaluminum*** react stoichiometrically with ***Titanium(IV) Chloride*** to form Me_2TiCl_2.[1-3] In the presence of ether, the Lewis acidic compound forms etherates. For a number of synthetic organic applications, ether-free solutions of Me_2TiCl_2 are required.[1,3,5] In these cases, the preparation of choice is the reaction of Me_2Zn with $TiCl_4$ in dry CH_2Cl_2 (eq 1).[3,5] *Caution*: Although Me_2Zn is highly pyrophoric, CH_2Cl_2 solutions are less so and are easy to handle.[3]

$$Me_2Zn + TiCl_4 \longrightarrow Me_2TiCl_2 \qquad (1)$$

Handling, Storage, and Precautions: although Me_2TiCl_2 can be crystallized, it is best not to isolate the compound (due to its thermal lability and light sensitivity). In situ reaction modes under an inert gas atmosphere (e.g. argon) in the absence of direct sunlight are recommended.

Methylation of Carbonyl Groups.

The most important synthetic applications of Me_2TiCl_2 pertain to carbonyl addition and S_N1 substitution reactions, sometimes in a one-pot tandem process, as in the geminal dimethylation of ketones (eq 2).[3] A two-fold excess of reagent is required which ensures Grignard-type reaction to a tertiary titanium alcoholate which then interacts with more Me_2TiCl_2 to form the final product via tertiary carbocations. The reactions need to be performed in nonethereal solvents such as CH_2Cl_2 at -30 to 0 °C (1-4 h).[3] $Me_3Al/TiCl_4$ can also be employed.[3] These reactions are milder and much more efficient than the previously reported reactions of ketones with an excess of Me_3Al at 120-180 °C.[10]

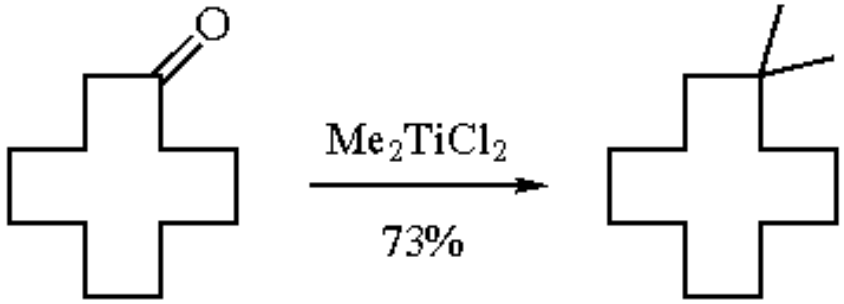

(2)

A fairly wide range of ketones is amenable to such geminal dimethylation, but the yields are drastically lowered when sterically hindered ketones are used.[3] The intermediacy of tertiary carbocations means that in relevant cases rearrangements may occur,[3] as in the case of (+)-cuparenone which affords racemic (±)-cuparene.[11]

Another restriction concerns the use of highly functionalized substrates which bind the reagent and do not undergo geminal dimethylation. However, for simple systems, Me_2TiCl_2 is ideally suited[3,5,12] and is to be preferred over multistep procedures such as Wittig alkenation of the ketone followed by Simmons-Smith cyclopropanation and ring-opening hydrogenation.[13] Furthermore, aromatic (but not aliphatic) aldehydes are also geminal dimethylated.[4]

Ketones can be reacted with ether-free alkyllithium reagents in pentane or hexane, and the resulting insoluble tertiary lithium alcoholates treated with Me_2TiCl_2 to form the mixed geminal dialkylated products.[14] This protocol allows for a simple access to synthetic tetrahydrocannabinoids (eq 3).[14]

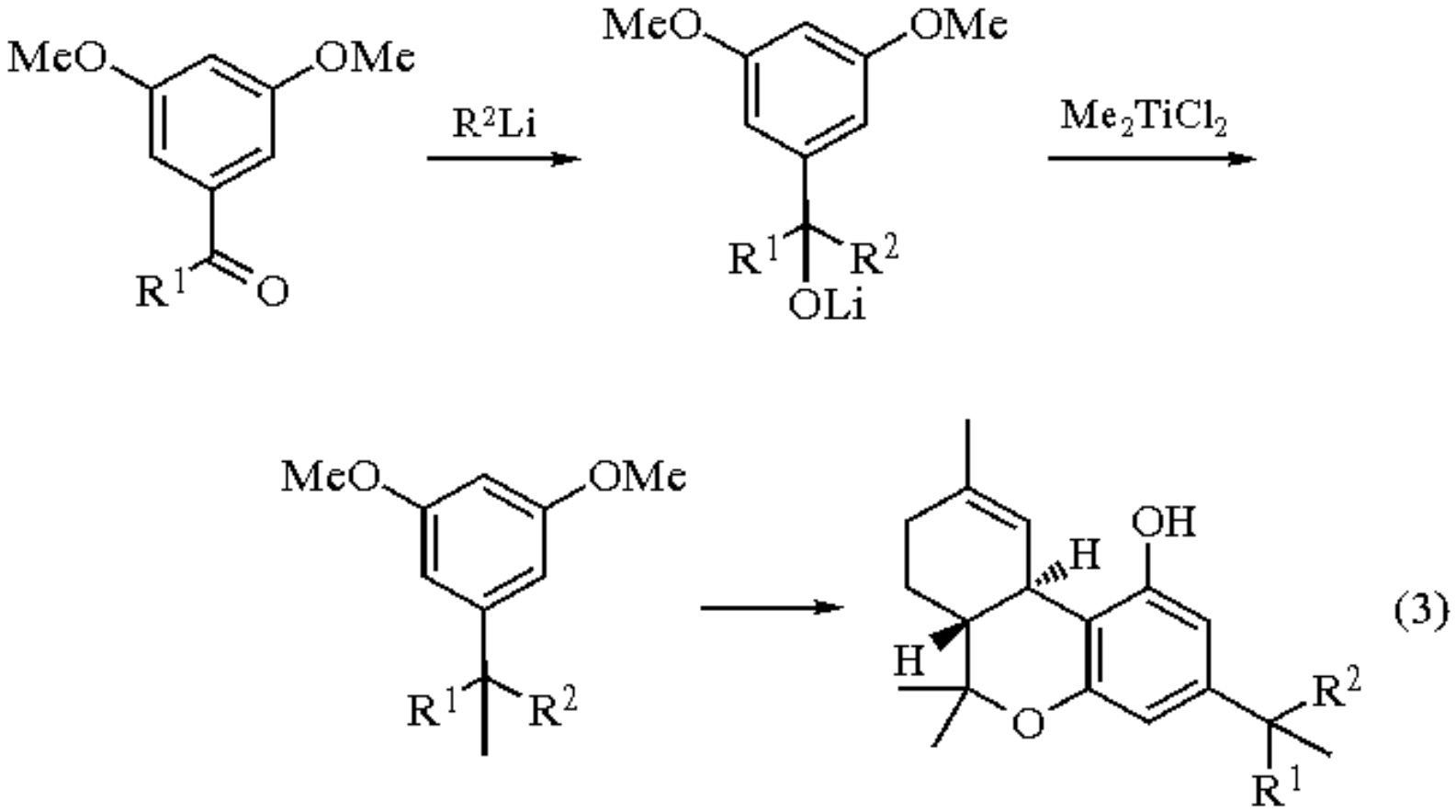

R^1	R^2	Yield
Me	Et	77%
Me	Bu	80%
Bu	Bu	68%

Methylation of Tertiary Halides and Alcohols.

Me_2TiCl_2 prepared from $Me_2Zn/TiCl_4$ has also been used to methylate tertiary alkyl halides and tertiary alcohols.[5] In the former case, Me_2Zn and catalytic amounts of $TiCl_4$ can also be employed.[15] This method is also applicable to substitution reactions of chiral β-chloro sulfides which react with intermediate Me_2TiCl_2 stereospecifically with retention of configuration due to neighboring group participation.[15c]

Grignard-Type Additions to Carbonyl Compounds.

The above reactions all involve S_N1 ionization, which means that a Lewis acidic medium is required, including nonethereal solvents. This precludes the use of MeLi or MeMgX because these reagents always contain ether. In the case of Grignard-type carbonyl addition reactions of Me_2TiCl_2, ether can usually be tolerated. This means that MeLi or MeMgX can be transmetalated with $TiCl_4$ and the intermediate Me_2TiCl_2/etherate reacted with aldehydes or ketones. Interesting degrees of diastereoselectivities have been observed,[1,7] as in the stereocontrolled reactions of chiral α-keto

amides (eq 4).[8] Nevertheless, Me_2TiCl_2/etherate has not been used often in the general area of stereoselective carbonyl addition reactions. Usually 1 equiv of MeLi or MeMgX per one part of $TiCl_4$ has been employed, generating $MeTiCl_3$/etherate which is a nonbasic, chemo- and stereoselective Grignard analog.[16] Like MeLi/$CeCl_3$, it is useful in addition reactions of enolizable ketones.[17] Since carbonyl reactivity increases in the series $MeTiCl_3 < Me_2TiCl_2 < Me_4Ti$, the combination 2 MeLi/$TiCl_4$ in ether is a viable alternative.[1]

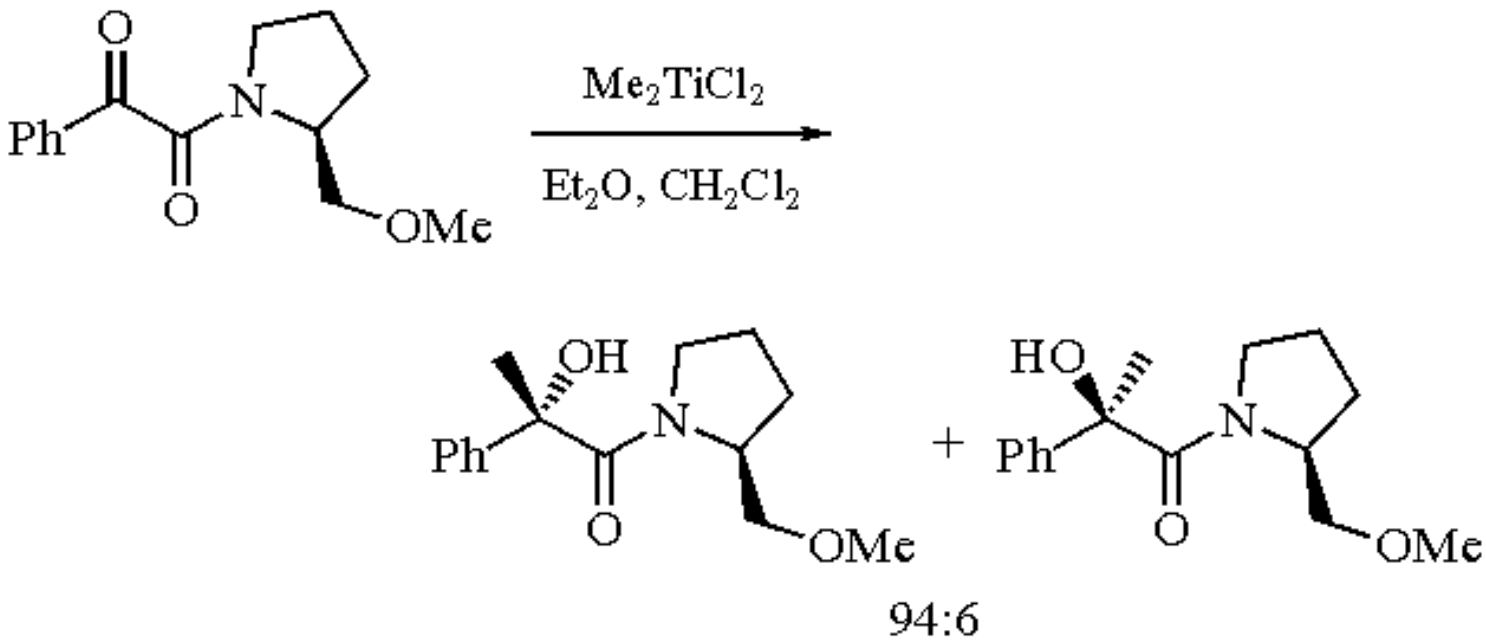

(4)

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S,S-Dimethyl-*N*-(*p*-toluenesulfonyl)sulfilimine[1,2]

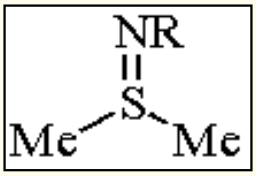

(**1**; R = *p*-$MeC_6H_4SO_2$)

[13150-75-9] · $C_9H_{13}NO_2S_2$ · *S,S*-Dimethyl-*N*-(*p*-toluenesulfonyl)sulfilimine · (MW 231.37) (**2**; R = 2,4-$(NO_2)_2C_6H_3$)

[37873-98-6] · $C_8H_9N_3O_4S$ · *S,S*-Dimethyl-*N*-(2,4-dinitrophenyl)sulfilimine · (MW 243.27)

(reagents for α-*S,S*-dimethylsulfuranylation of active methylene compounds,[2] and *ortho*-methylation of phenols;[3,4] (**1**) is a methylene transfer agent which converts carbonyl compounds into epoxides[5])

Alternate Names: (**1**) DMTS; (**2**) DMDNS.

Physical Data: (**1**) mp 154-155 °C; (**2**) mp 175-176 °C (dec).

Solubility: insol H_2O; sol ethyl and methyl alcohols, acetone, chloroform, and other common polar organic solvents.

Form Supplied in: (**1**) white solid; (**2**) orange solid.

Preparative Methods: (**1**) is conveniently prepared by adding a slight excess of ***Dimethyl Sulfide*** to an aqueous solution of ***Chloramine-T***, and collecting the deposited crystals by filtration and recrystallization from ethanol.[1] The yield of white crystalline solid is >95% based on chloramine T.

For preparation of (**2**), ***Phosphorus(V) Oxide*** (60 mmol) is added with stirring to 25 mL of DMF at 0 °C. After 30 min, ***Dimethyl Sulfoxide*** (60 mmol) is added. After stirring for 1 h, 20 mmol of 2,4-dinitroaniline in 25 mL of DMF is added dropwise at 0 °C with continued stirring. After 3 h, 180 mmol of ***Triethylamine*** is added at 0-5 °C, and stirring is continued for 3 h. The deposited crystals are collected by filtration and recrystallized from THF. The yield of orange crystalline material is 96% based on 2,4-dinitroaniline.[2,3]

Handling, Storage, and Precautions: stable at rt in a sealed bottle, but storage at lower temperature is recommended for (**2**). Use in a fume hood.

Reagent (**2**) reacts with *p*-toluenesulfonamide (at 90 °C for 7 h in DMF) to give (**1**) (58%), in an ylide exchange reaction.

Reactions of (**1**) and (**2**) with active methylene compounds in DMF give the corresponding sulfuranes (eq 1). Reagent (**2**), which is more basic than (**1**), gives higher yields of sulfuranes. Furthermore, the yields of the ylide exchange reactions depend on the pK_a value of the active methylene compounds, as shown in Table 1. The lower the pK_a value, the higher the yield of sulfurane.[2,3]

$$Me_2S{=}NR + CH_2R^1R^2 \xrightarrow[90\ °C,\ 7\ h]{DMF} Me_2S{=}CR^1R^2 + H_2NR \quad (1)$$

$$R = Tos,\ 2,4\text{-}(NO_2)_2C_6H_3$$

Table 1 Results of the Reactions of Sulfilimines (**1**) and (**2**) with Active Methylene Compounds in DMF at 90 °C for 9 h

Sulfilimine	Active methylene compound R^1	Active methylene compound R^2	pK_a	Sulfurane yield (%)
(**2**)	COMe	COMe	8.94	94
(**2**)	COMe	CO_2Et	10.7	80
(**2**)	CN	CN	11.2	98
(**1**)	CN	CN	11.2	12.5
(**2**)	CO_2Me	CO_2Me		58
(**2**)	CO_2Et	CO_2Et	13.3	48
(**2**)	Ph	Ph	34.1	0

Reactions of (**1**) and (**2**) with phenols give *o*-methylthiomethylated phenols (eq 2).[3,4] Mixtures of the phenols and 0.5 equiv of (**1**) or (**2**) are heated without solvent at 120-130 °C for 3-7 h. 2-Methylthiomethylphenols are obtained from 2- and 4-methyl, 2,5- and 3,5-dimethyl-, 2,3,5-trimethyl-, and 2-methoxyphenols in 55-95% yield (Table 2). In some case, significant amounts of bis(methylthiomethyl) products are also formed. The yields using (**2**) are higher than those using (**1**).

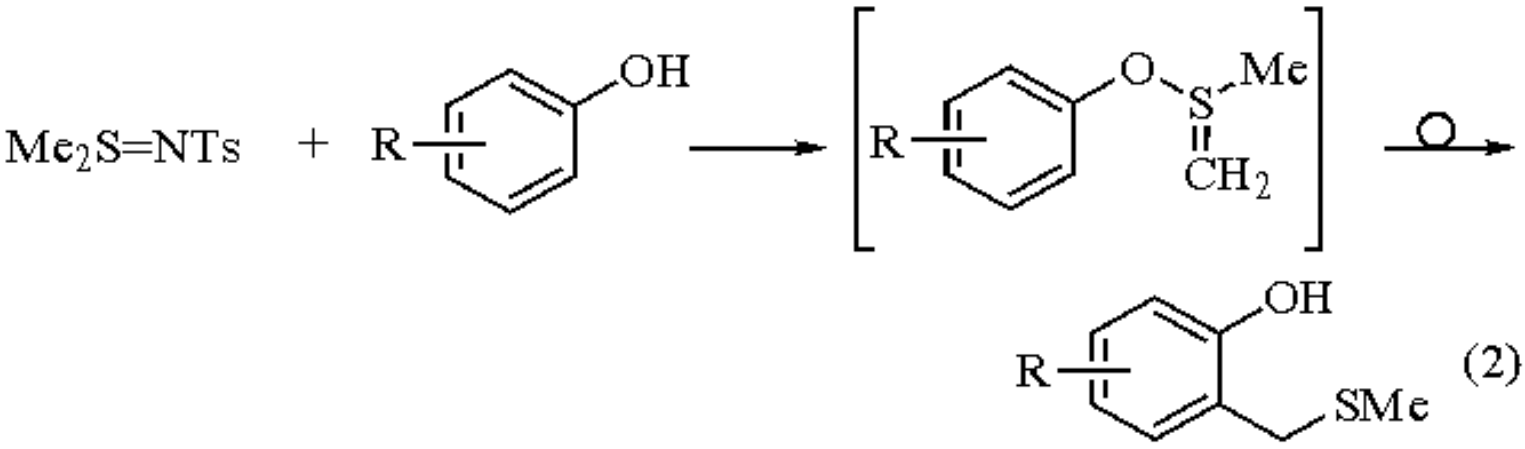

R = Tos, 2,4-$(NO_2)_2C_6H_3$

Table 2 Methylthiomethylation of Phenols with the Sulfilimines (**1**) and (**2**) at 120 130 °C for 3 7 h

Sulfilimine	Phenol	Yield (%)[a]	Sulfilimine	Phenol	Yield (%)[a]
(**2**)	2-MeO	82	(**1**)	2-MeO	78
(**2**)	2-Me	95	(**1**)	2-Me	73
(**2**)	4-Me	55 (24)[b]	(**1**)	2,5-Me_2	96
(**2**)	H	41	(**1**)	3,5-Me_2	58 (35)[b]
(**2**)	4-NO_2	0	(**1**)	2,3,5-Me_3	64

[a] Yields based on reacted sulfilimine. [b] Data in parentheses show the yields of bis(methylthiomethyl)phenols.

Like ***S,S-Dimethyl-N-(p-toluenesulfonyl)sulfoximine***[6] and (dimethylamino)dimethyloxosulfonium tetrafluoroborate,[7] the *N*-tosylsulfilimine (**1**) reacts as a methylene transfer reagent, converting aldehydes and ketones to epoxides (eq 3). Thus (**1**) is heated at 80-90 °C for 0.5 h in DMSO in the presence of ***Sodium Hydride***, and the resulting anion is allowed to react with carbonyl compounds to give 1-mono- and 1,1-disubstituted oxiranes in 46-56% yields.[5]

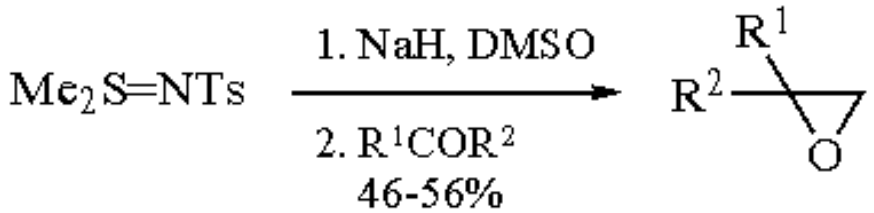

(3)

$R^1 = Ph$, $R^2 = H$, Me; $R^1R^2 = (CH_2)_6$

Related Reagents.

N,S-Dimethyl-S-phenylsulfoximine; ***Dimethylsulfonium Methylide***; ***Dimethylsulfoxonium Methylide***; ***S,S-Dimethyl-N-(p-toluenesulfonyl)sulfoximine***; ***S,S-Diphenylsulfilimine***.

---

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S,S-Dimethyl-*N*-(*p*-toluenesulfonyl)sulfoximine[1]

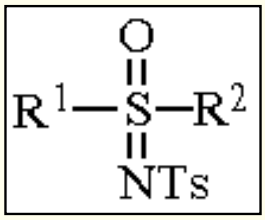

(**1**; R^1 = Me, R^2 = Me)

[22236-45-9] · $C_9H_{13}NO_3S_2$ · *S,S*-Dimethyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 247.37) (**2**; R^1 = Et, R^2 = Et)

[42153-72-0] · $C_{11}H_{17}NO_3S_2$ · *S,S*-Diethyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 275.43) (**3**; R^1 = *i*-Pr, R^2 = *i*-Pr)

[42153-73-1] · $C_{13}H_{21}NO_3S_2$ · *S,S*-Diisopropyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 303.49) (**4**; R^1 = Ph, R^2 = Me)

[42153-74-2] · $C_{14}H_{15}NO_3S_2$ · *S*-Methyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 309.44) (**5**; R^1 = Ph, R^2 = *c*-C_5H_9)

[33332-99-9] · $C_{18}H_{21}NO_3S_2$ · *S*-Cyclopentyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 363.54) (**6**; R^1 = Ph, R^2 = Cy)

[33367-88-3] · $C_{19}H_{23}NO_3S_2$ · *S*-Cyclohexyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 377.57) (**7**; R^1 = Ph, R^2 = Bn)

[38764-59-9] · $C_{20}H_{19}NO_3S_2$ · *S*-Benzyl-*S*-phenyl-*N*-(*p*-toluenesulfonyl)sulfoximine · (MW 385.54)

(conversion of aldehydes and ketones to oxiranes,[1,2] ketones or oxiranes to oxetanes,[3] imines to aziridines,[1,2] and electrophilic alkenes to cyclopropanes[1,2])

Alternate Name: S,S-dimethyl-*N*-tosylsulfoximine.

Physical Data: (**1**) mp 167-169 °C, 170 °C (from ethanol);[2,4] (**2**) mp 89-91 °C; (**3**) mp 75-77 °C; (**4**) mp 107-109 °C; (**5**) mp 143-144 °C; (**6**) mp 145-146 °C; (**7**) mp 148-149 °C.

Solubility: moderately sol EtOH, THF, DMSO.

Form Supplied in: (**1**) white solid; commercially available.

Preparative Methods: excess DMSO containing ***Copper(II) Chloride*** (or another copper catalyst)[2,4] is treated with ***Chloramine-T*** trihydrate. (**1**) is obtained in 90% yield after aqueous EDTA workup and recrystallization from ethanol.

The other *N*-tosylsulfoximines can be prepared by the tosylation of N-H sulfoximines with ***p-Toluenesulfonyl Chloride*** in the presence of base,[2] but the two most useful and general methods are the oxidation of *N*-tosylsulfilimines with basic ***Hydrogen Peroxide***,[5] ***m-Chloroperbenzoic Acid*** anion,[6] ***Sodium Hypochlorite***,[8] or ***Ruthenium(VIII) Oxide***/sodium metaperiodate[7] and the copper powder-promoted reaction of sulfoxides with ***p-Toluenesulfonyl Azide***.[2,9]

Handling, Storage, and Precautions: (**1**) is a highly crystalline compound with no known toxicity and unlimited shelf life.

The generation of *N*-*p*-toluenesulfonyl-sulfonimidoyl-stabilized carbanions is best accomplished by stirring a slurry of *N*-tosylsulfoximine, e.g. (**1**), and ***Sodium Hydride*** in DMSO at rt until hydrogen evolution ceases (2-4 h). THF solutions of the lithium salts of *N*-tosylsulfoximines can be prepared by deprotonation with ***n-Butyllithium***. These anions, which are quite stable at room or slightly elevated temperatures, form a class of nucleophilic alkylidene transfer reagents. The mechanism of these transfer reactions is similar to that of sulfonium ylide reactions but the leaving groups are water-soluble anions rather than neutral molecules (eq 1). The nucleophilic transfer chemistry of sodium *N*-tosylmethanesulfonimidoylmethide (**8**) is similar to that of dimethylsulfoxonium methylide[10] in regard to regio- and stereochemical selectivity in that the products reflect thermodynamic control.[11] Anion (**8**) has been reported to be superior to dimethylsulfonium and dimethylsulfoxonium methylides for reactions in which enolate formation is a serious problem.[12]

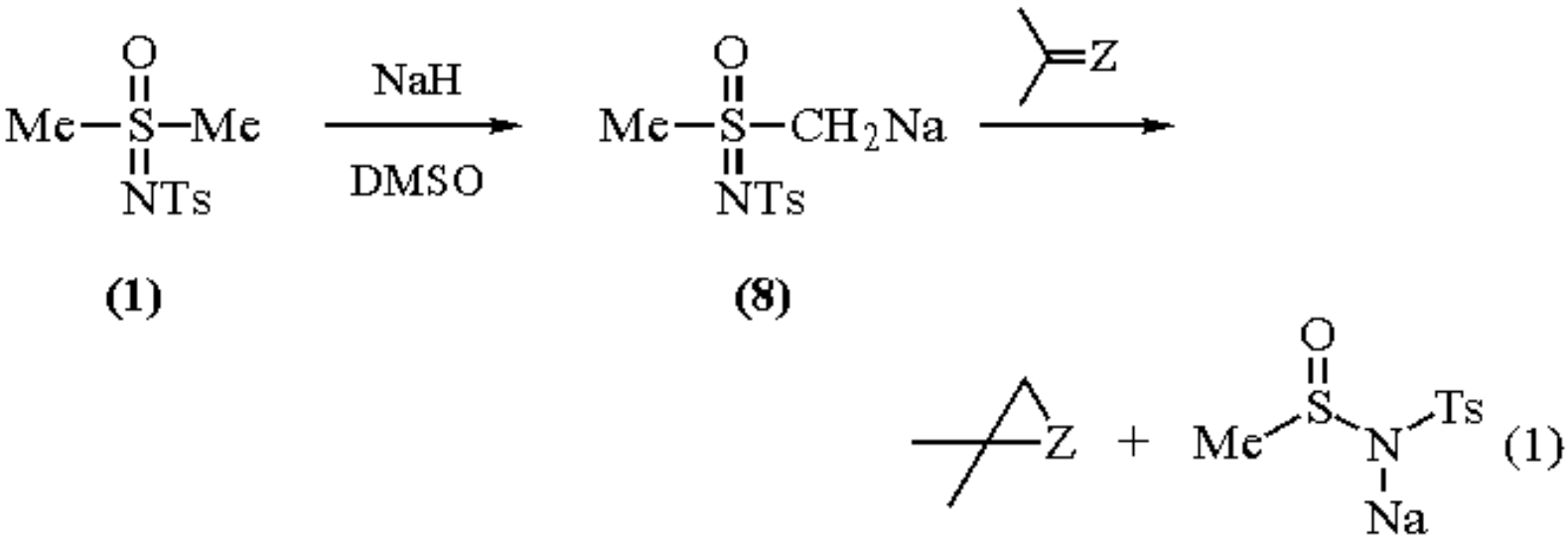

These salts have been used to prepare oxiranes from aldehydes and ketones (eqs 2 and 3),[2] cyclopropanes from enones (eq 4),[2] and aziridines from imines (eq 5).[2] Alkylidene groups which have been transferred using reagents in this series include methylene, ethylidene, isopropylidene, benzylidene, cyclopentylidene, and cyclohexylidene. Optically active

versions of these reagents have been studied, but enantiomeric excesses of the resulting alkylidene transfer products have only been modest.[2] The reaction of carbanion (**8**) with epoxides results in the expansion of the ring by one carbon (eq 2). This unique oxetane synthesis, which can be carried out in one step by simply treating the ketone with 3 equiv of (**8**), is quite general and illustrates the use of (**1**) as a [$^{-}CH_2CH_2^{+}$] synthon.[3]

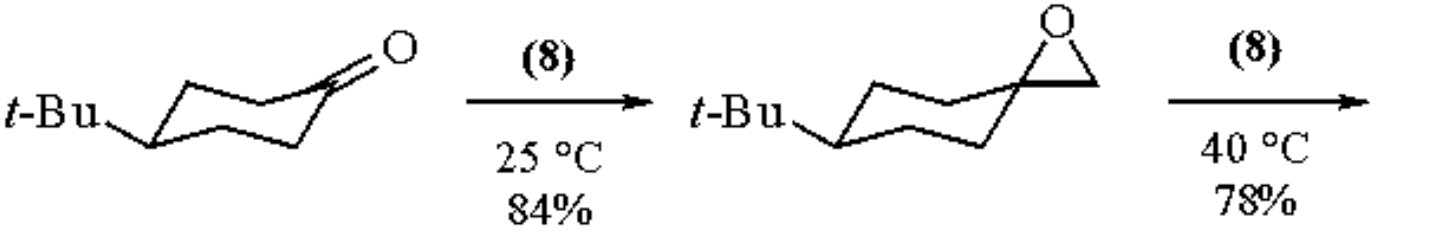

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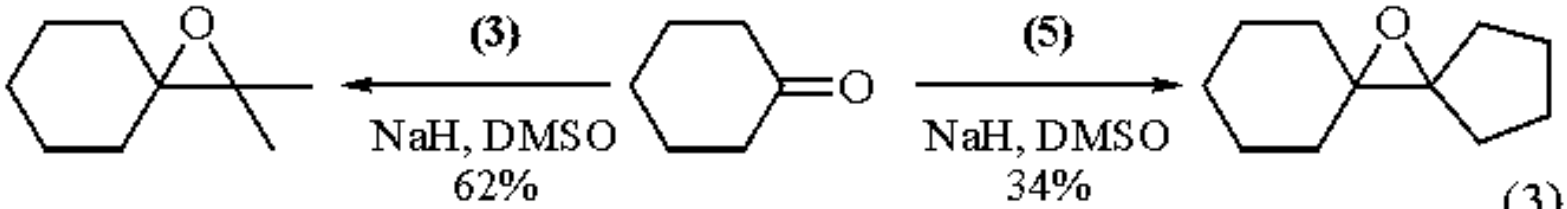

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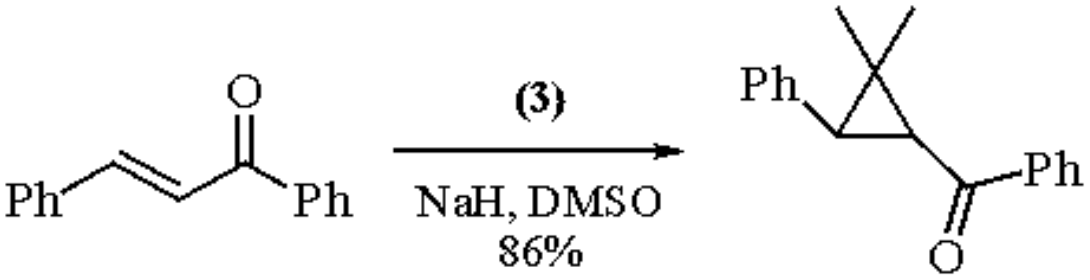

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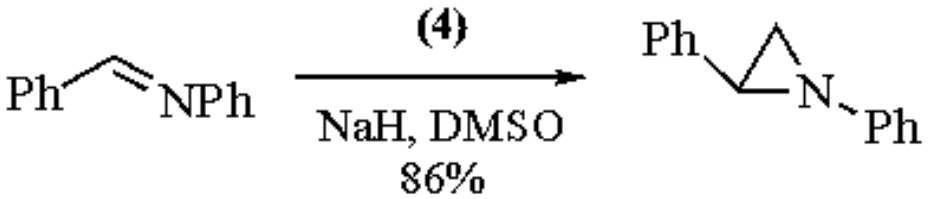

(5)

Reagent (**1**) can also be converted to an ethylene transfer reagent by condensation with benzonitrile, followed by reduction of the ketosulfoximine and dehydration (eq 6). The resulting *S*-vinyl-*N*-tosylsulfoximine reacts with stabilized anions to give cyclopropanes.[13] The *N*-tosyl group in *N*-tosylsulfoximines can be cleaved reductively using ***Sodium Anthracenide***.[14]

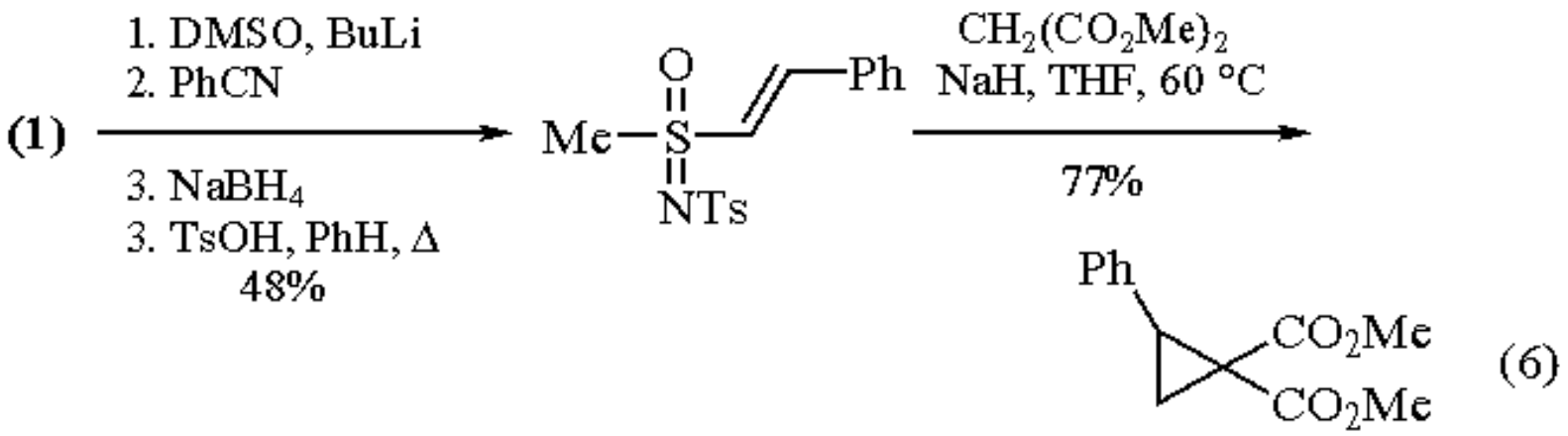

Related Reagents.

N,S-Dimethyl-S-phenylsulfoximine; ***Dimethylsulfonium Methylide***; ***Dimethylsulfoxonium Methylide***; ***Diphenylsulfonium Methylide***; ***Isopropyldiphenylsulfonium Tetrafluoroborate***.

---

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N,N-Dimethyl-2-(trimethylsilyl)acetamide

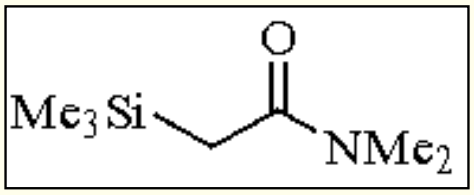

[23184-28-3] · $C_7H_{17}NOSi$ · *N,N*-Dimethyl-2-(trimethylsilyl)acetamide · (MW 159.34)

(preparation of α,β-unsaturated amides,[1] β-enamino amides,[2] and γ-trimethylsiloxy amides[3])

Physical Data: bp 67-69 °C/4 mmHg; 47-49 °C/0.2 mmHg.

Preparative Methods: although the direct trimethylsilylation of the lithium enolate of *N,N*-dimethylacetamide[3a] is the most straightforward approach to the title reagent, other α-silyl amides have been prepared by amidation of the corresponding esters.[4] The reaction of aminosilanes with ketene gives the *O*-trimethylsilylated isomer, which thermally rearranges to the α-trimethylsilylamide.[5] In reactions of chlorosilanes with the lithium enolates of amides, larger silyl groups such as the *t*-butyldimethylsilyl group tend towards *O*-silylation, and smaller groups on nitrogen lead to *C*-silylation.[3a] Thermal isomerization leads to the *C*-silylated tautomer as the major product (eq 1). The direct *C*-dimethylphenylsilylation of the lithium enolate of *N*-methyl-δ-valerolactam has been reported (eq 2).[6]

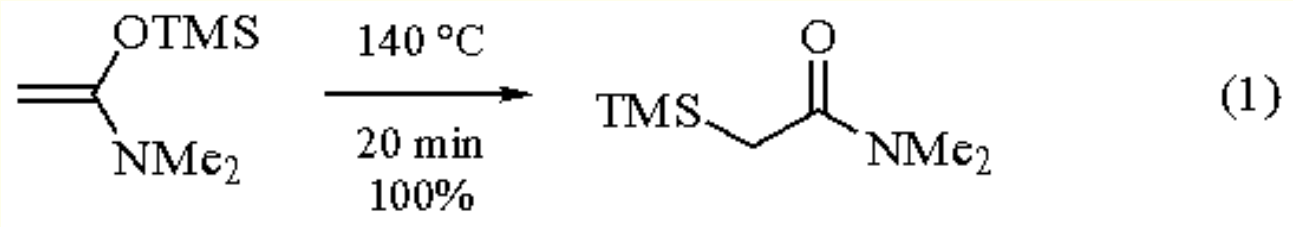

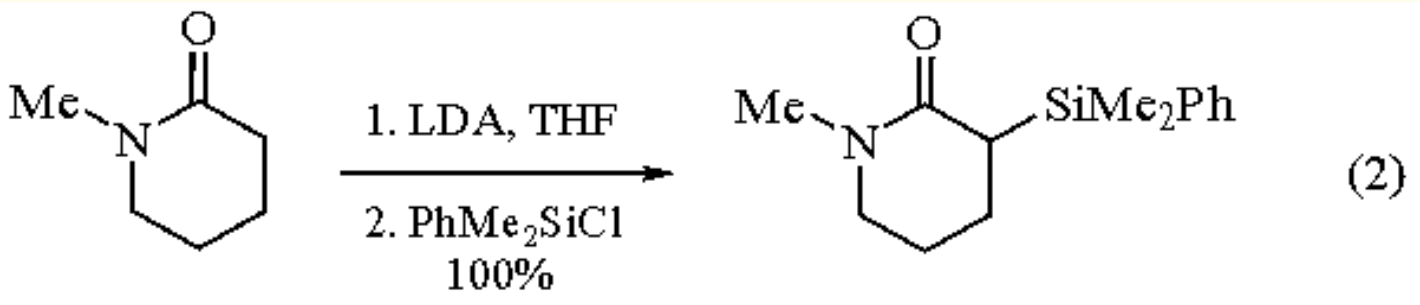

Preparation of α,β-Unsaturated Amides.

Reaction of *N,N*-dimethyl-2-(trimethylsilyl)acetamide with either ***Lithium Diisopropylamide*** or ***n-Butyllithium*** in THF

at 0 °C provides the lithium enolate, which is stable at rt for several days. This enolate reacts with aldehydes and ketones to produce α,β-unsaturated amides via the condensation-Peterson elimination sequence (eq 3). This reaction was employed in an approach to (±) cherylline (eq 4).[7]

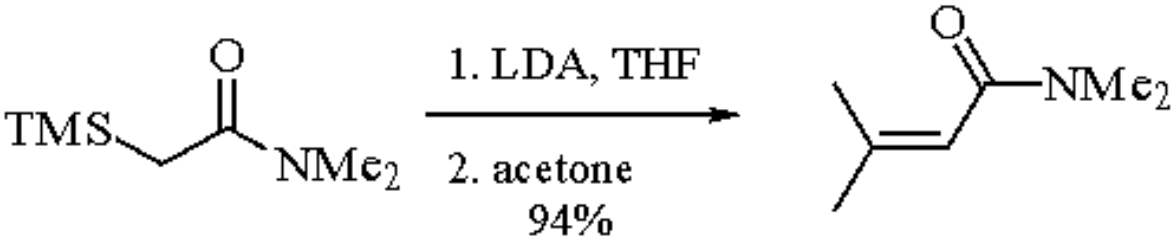

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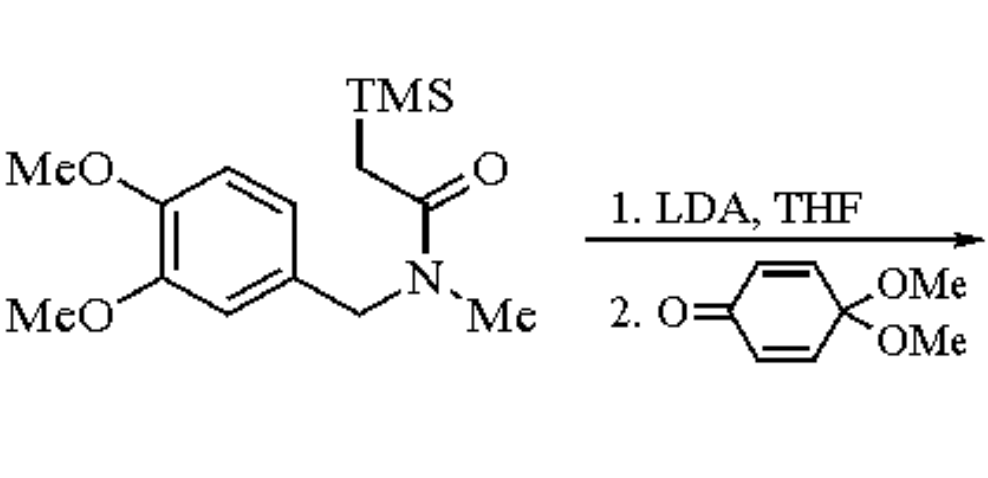

(4)

The reaction of the lithium enolate of *N*,*N*-dimethyl-2-(trimethylsilyl)acetamide with aromatic nitrones gives α-aryl-α,β-unsaturated amides in modest yields (eq 5).[8] The reaction of the lithium enolate with amides yields β-amino-α,β-unsaturated amides (eq 6),[2] and the reaction with propene oxide leads to *N*,*N*-dimethyl-4-(trimethylsiloxy)pentanamide (eq 7).[1]

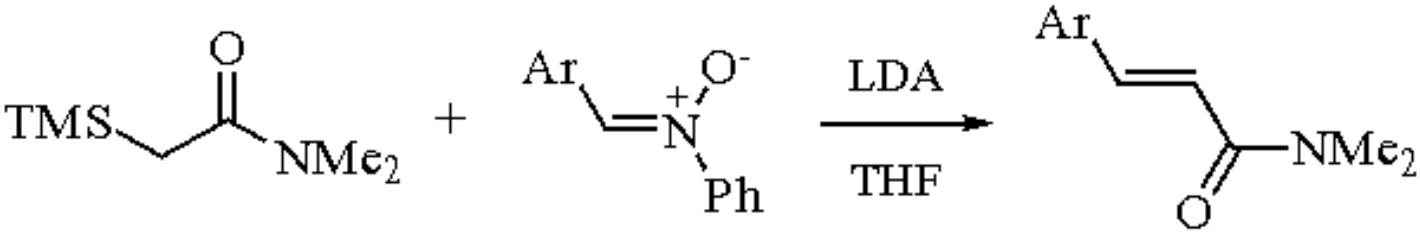

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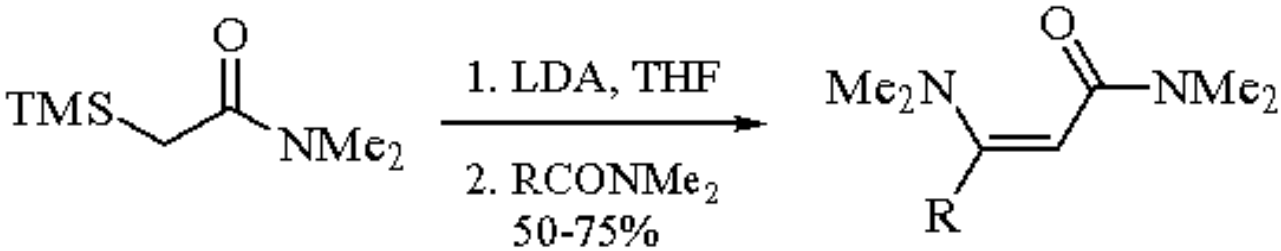

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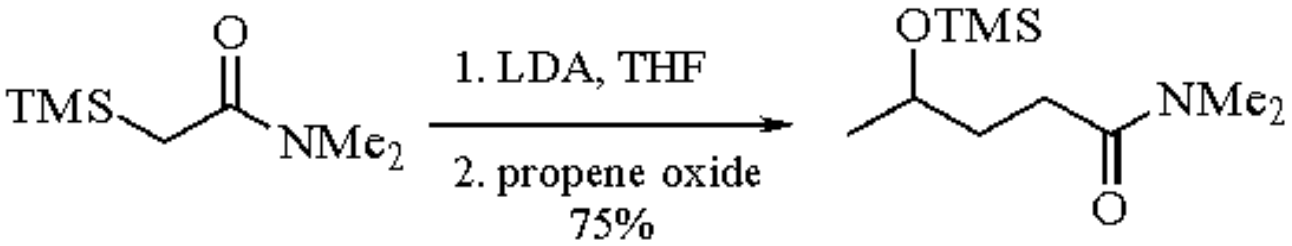

(7)

Other Applications.

The direct α-trimethylsilylation of β-lactams and the intermediates used in the synthesis of this important class of compounds have been reported.[9]

Related Reagents.

t-Butyl Trimethylsilylacetate; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***Ethyl Trimethylsilylacetate***; ***Trimethylsilylacetic Acid***; ***Trimethylsilylacetone***.

---

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Dinitratocerium(IV) Chromate Dihydrate[1]

$[Ce(NO_3)_2]CrO_4.2H_2O$

[92989-80-5] · $CeCrH_4N_2O_{12}$ · Dinitratocerium(IV) Chromate Dihydrate · (MW 416.18)

(mild oxidizing reagent for the transformation of several functional groups in dry benzene[2])

Alternate Name: DCCD.

Solubility: sol DMF, DMSO; moderately sol H_2O; insol MeCN, EtOH, PhH.

Form Supplied in: orange-red solid; readily available.

Preparative Method: to a hot solution of ***Potassium Dichromate*** (0.1 mol) a solution of ***Cerium(IV) Ammonium Nitrate*** (0.1 mol) is added. After cooling, the precipitate is washed with H_2O and acetone and dried in the air (79%).[2]

Handling, Storage, and Precautions: stable >220 °C, and at rt for months. Chromium is a cancer suspect agent and inhalation of this reagent should be avoided.

Oxidations.

Oxidations with this reagent proceed heterogeneously in dry benzene at reflux. Evaporation of the solvent followed by chromatography gives pure product(s). Drawbacks encountered with Ce^{IV} oxidations[1,3] are not observed when using DCCD.[2]

The reagent effects the oxidation of benzylic alcohols to the corresponding aldehydes in high yield (eq 1).[2] Deactivated benzyl and allylic alcohols are not easily oxidized. Oxidation of arylethylene glycols is accompanied by carbon-carbon bond cleavage and produces the degraded aldehydes in high yields (eq 2).[2] α-Hydroxy carboxylic acids are similarly converted to aldehydes efficiently (eq 3).[2]

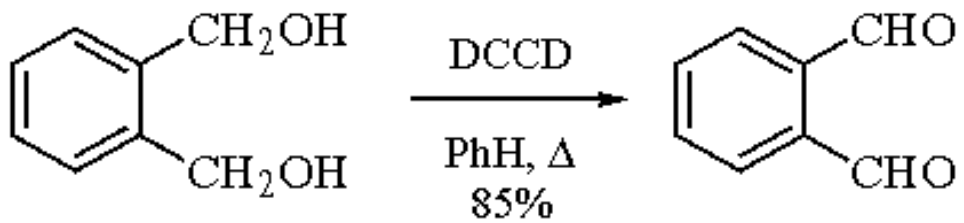

(1)

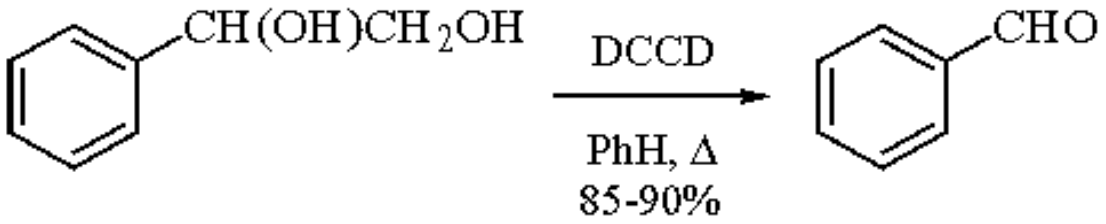

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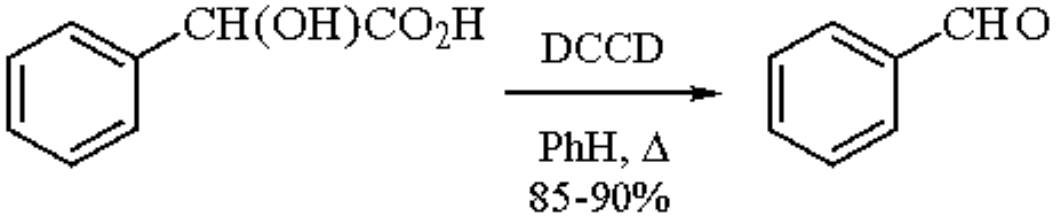

(3)

Primary benzylamines are easily transformed to the corresponding aldehydes in quantitative yields (eq 4).[2] Disulfides are produced in good yields by the oxidation of thiols (eq 5).[2] The reagent oxidizes hydroquinones to quinones in high yields (eq 6).[2] Benzoins are not oxidized efficiently.

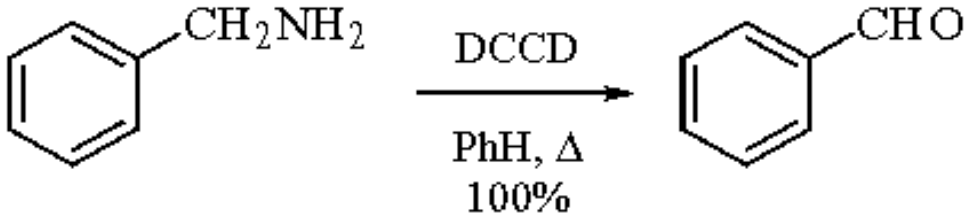

(4)

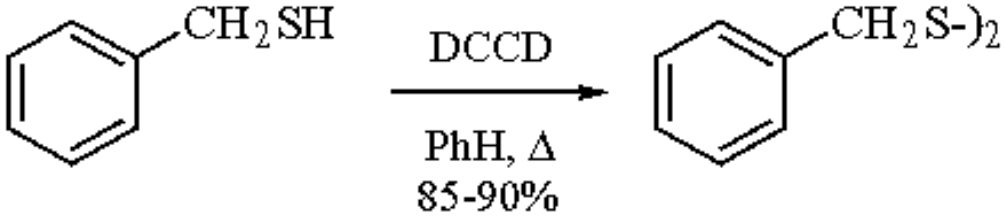

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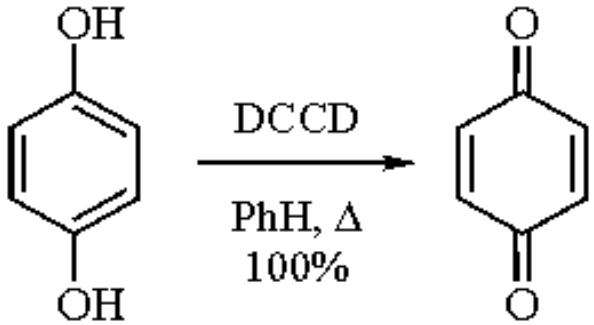

(6)

A brief comparison between DCCD, ***Cerium(IV) Ammonium Nitrate*** (CAN),[1a,3,4] ***Barium Manganate*** (BM),[5] and ***Bis(pyridine)silver(I) Permanganate*** (BPSP)[6] is given in Table 1.

Table 1 Comparison of Yields Achieved by Various Oxidizing Agents

Substrate	Product	DCCD	CAN	BM	BPSP
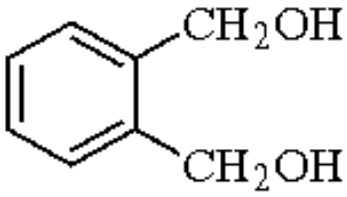	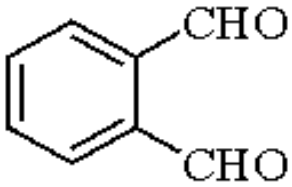	85	-	80	95
Hydroquinone	p-Benzoquinone	100	83	75	90
Benzylamine	Benzaldehyde	100	-	95	95
Cinnamyl alcohol	Cinnamaldehyde	20	-	100	-
Furoin	Furil	30	5	-	-
Benzyl alcohol	Benzaldehyde	100	94	90	100

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2,4-Dinitrobenzeneseleninic Acid

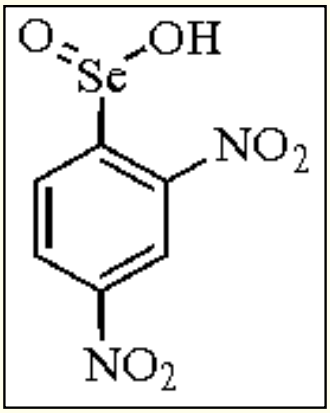

[65252-77-9] · $C_6H_4N_2O_6Se$ · 2,4-Dinitrobenzeneseleninic Acid · (MW 279.07)

(catalyst with hydrogen peroxide for the epoxidation of alkenes[1,2] and the Baeyer-Villiger oxidation of aromatic aldehydes and ketones[3])

Physical Data: mp 140-143 °C (dec).

Solubility: slightly sol water; sol dioxane, ethyl acetate.

Preparative Methods: obtained from the oxidation of bis(2,4-dinitrophenyl) diselenide with 85% ***Hydrogen Peroxide***[4] or fuming ***Nitric Acid***.[5] Bis(2,4-dinitrophenyl) diselenide is prepared from the reaction of ***Lithium Diselenide*** with 2,4-dinitrochlorobenzene[6] or from the base hydrolysis of 2,4-dinitrophenyl selenocyanate.[5]

Handling, Storage, and Precautions: both 2,4-dinitrobenzeneseleninic acid and bis(2,4-dinitrophenyl) diselenide are stable indefinitely at rt. Selenium compounds are potentially toxic and should be handled in a fume hood.

2,4-Dinitrobenzeneseleninic acid, conveniently generated in situ from bis(2,4-dinitrophenyl) diselenide (**1**), catalyzes the epoxidation of alkenes in CH_2Cl_2 under two-phase reaction conditions with 30% H_2O_2 (eq 1).[1,2] The addition of anhydrous $MgSO_4$ removes excess water, enhancing the reaction rate[1] and inhibiting diol formation.[7] Catalyst levels of 0.5-5% are effective for epoxidizing di-, tri-, and tetrasubstituted alkenes in high yields. With less reactive terminal alkenes, such as styrene, the addition of 30% H_2O_2 in portions over 14 h and the presence of radical inhibitor are needed to achieve good yields of epoxide.[8] Allylic alcohols exhibit little, if any, stereoselectivity (eq 2) or regioselectivity (eq 3), in contrast to epoxidations with peroxycarboxylic acids or with alkyl hydroperoxides in the presence of vanadium and molybdenum catalysts.[1]

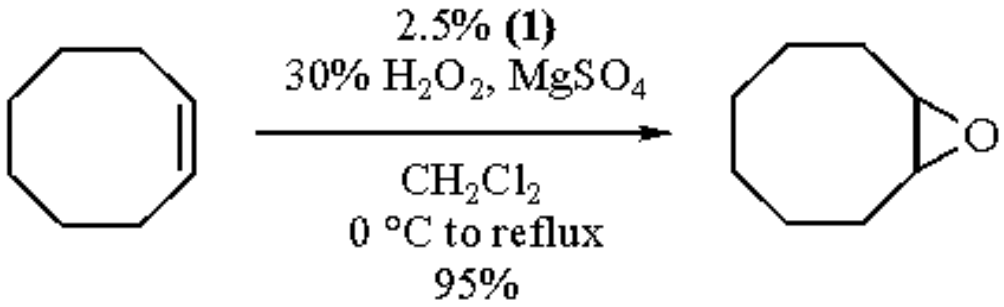

(1)

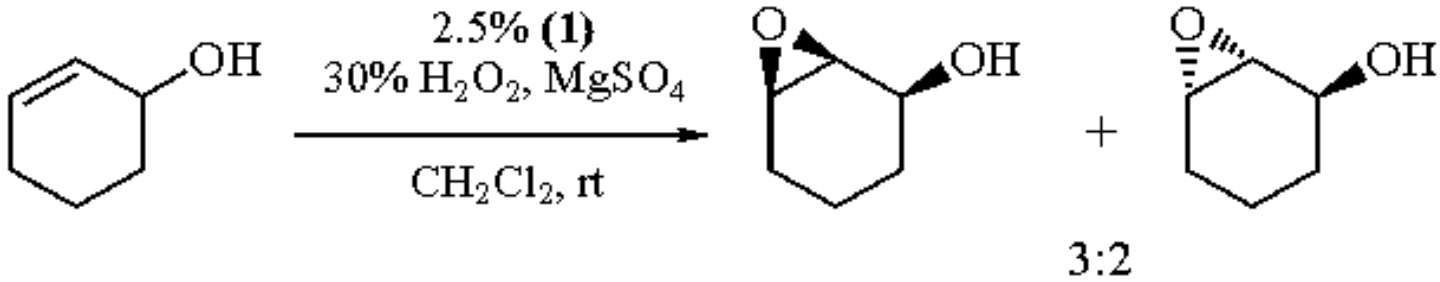

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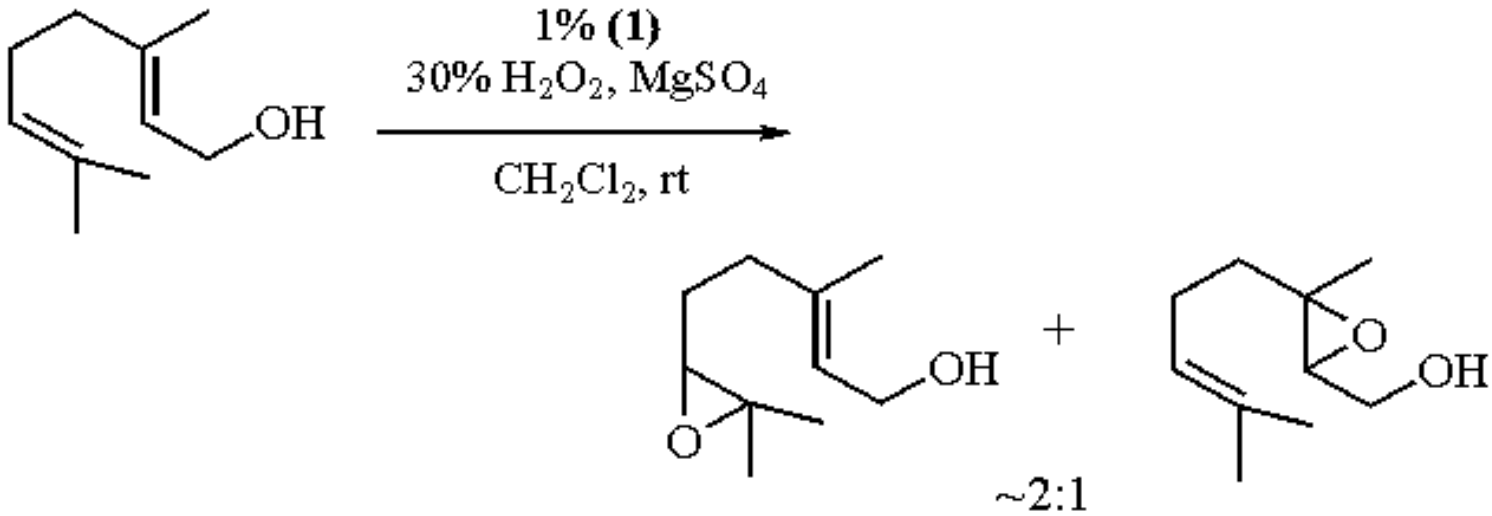

(3)

The use of safe and inexpensive 30% H_2O_2, the ease of product isolation (mild base extraction removes the traces of catalyst from the CH_2Cl_2 layer), and the potential for catalyst recycle[3] make the in situ generation of 2,4-dinitroperoxybenzeneseleninic acid (eq 4)[9] an attractive alternative to the stoichiometric use of peroxycarboxylic acids for Baeyer-Villiger oxidations.

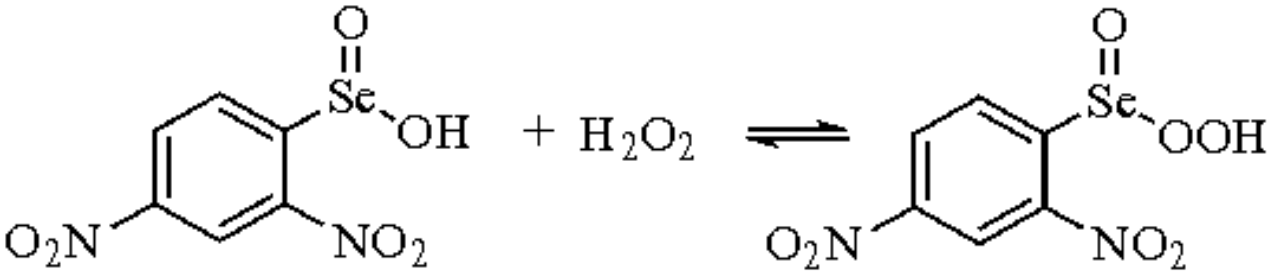

(4)

Phenols are obtained from aromatic aldehydes via their corresponding aryl formates in high yield with 30% H_2O_2 (eq 5), while 90% H_2O_2 is needed to convert polymethoxyacetophenones to phenols in moderate yields. α,β-Unsaturated aldehydes react similarly to aromatic aldehydes to give vinyl formates (see also ***o-Nitrobenzeneseleninic Acid***).[10]

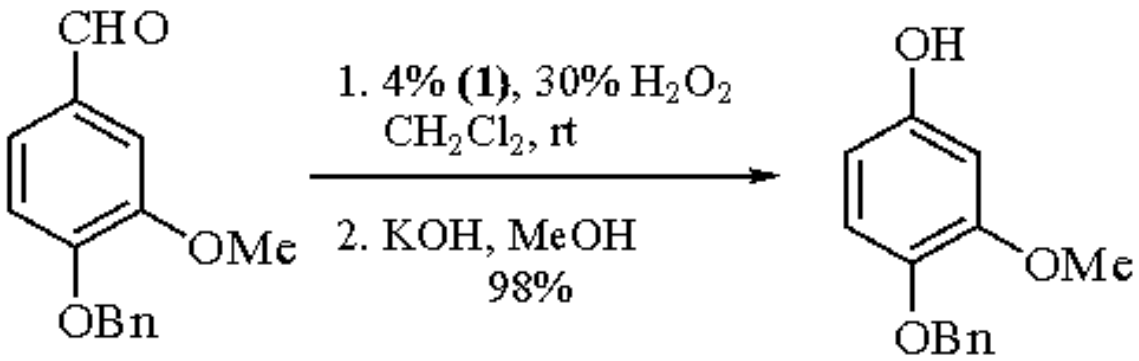

(5)

A variety of other seleninic acids (see also ***Benzeneseleninic Acid*** and ***o-Nitrobenzeneseleninic Acid***) and diselenides have been studied using the two-phase oxidation conditions. However, from an activity standpoint, 2,4-dinitrobenzeneseleninic acid is the catalyst of choice for large scale syntheses, particularly epoxidations.[1,8]

---

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2,4-Dinitrobenzenesulfenyl Chloride

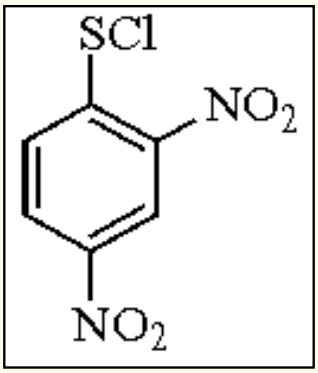

[528-76-7] · $C_6H_3ClN_2O_4S$ · 2,4-Dinitrobenzenesulfenyl Chloride · (MW 234.63)

(sulfenylation agent used in electrophilic additions,[1,2] diene synthesis,[12] protection of nucleosides,[13] and preparation of propargyl alcohol synthons for use in cycloaddition chemistry[15])

Alternate Name: 2,4-dinitrophenylsulfenyl chloride.

Physical Data: mp 94-97 °C.

Solubility: sol most common organic solvents.

Form Supplied in: commercially available as a solid (96% pure).

Handling, Storage, and Precautions: corrosive; lachrymator. This reagent should be handled in a fume hood.

Electrophilic Additions.

The most common use of 2,4-dinitrobenzenesulfenyl chloride is in electrophilic additions. The reagent reacts with a variety of nucleophiles by displacement of the chlorine atom (eq 1).[1] The electrophilic addition of this reagent to alkenes (eq 2),[2] alkynes,[3] and allenes[4] has been extensively studied. The addition occurs in a *trans* stereospecific fashion. Additives to the reaction, such as ***Lithium Perchlorate*** and ***Formic Acid***, reportedly increase the electrophilicity of the reagent.[5,6] Mechanistic aspects, along with stereo- and regioselectivity, have been reported.[2b,7-11]

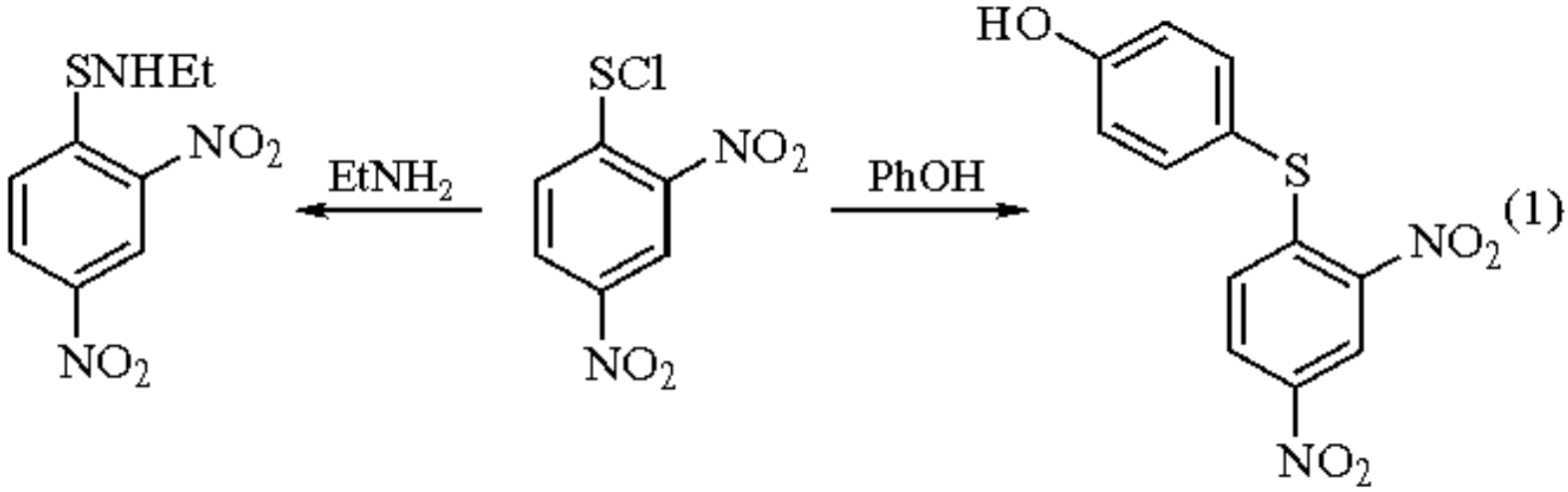

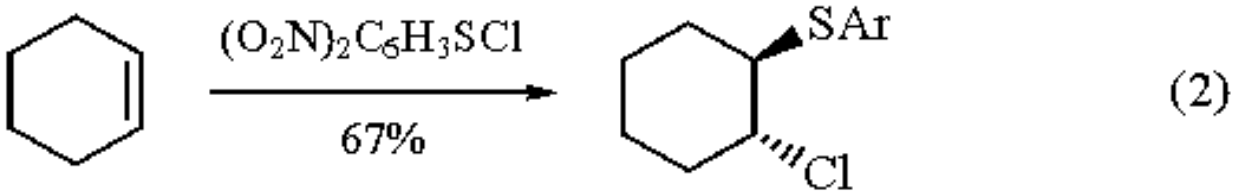

Diene Synthesis.

The 1,4-dehydration of allylic alcohols using 2,4-dinitrobenzenesulfenyl chloride and ***Triethylamine*** provides 1,3-dienes in good yields (eq 3).[12] The reaction involves a 2,3-sigmatropic rearrangement of the sulfenate ester, followed by a thermal *syn* elimination. Selenenate esters can also be converted to the 1,3-dienes, but the conditions are more severe and the reaction is less general than with this reagent.

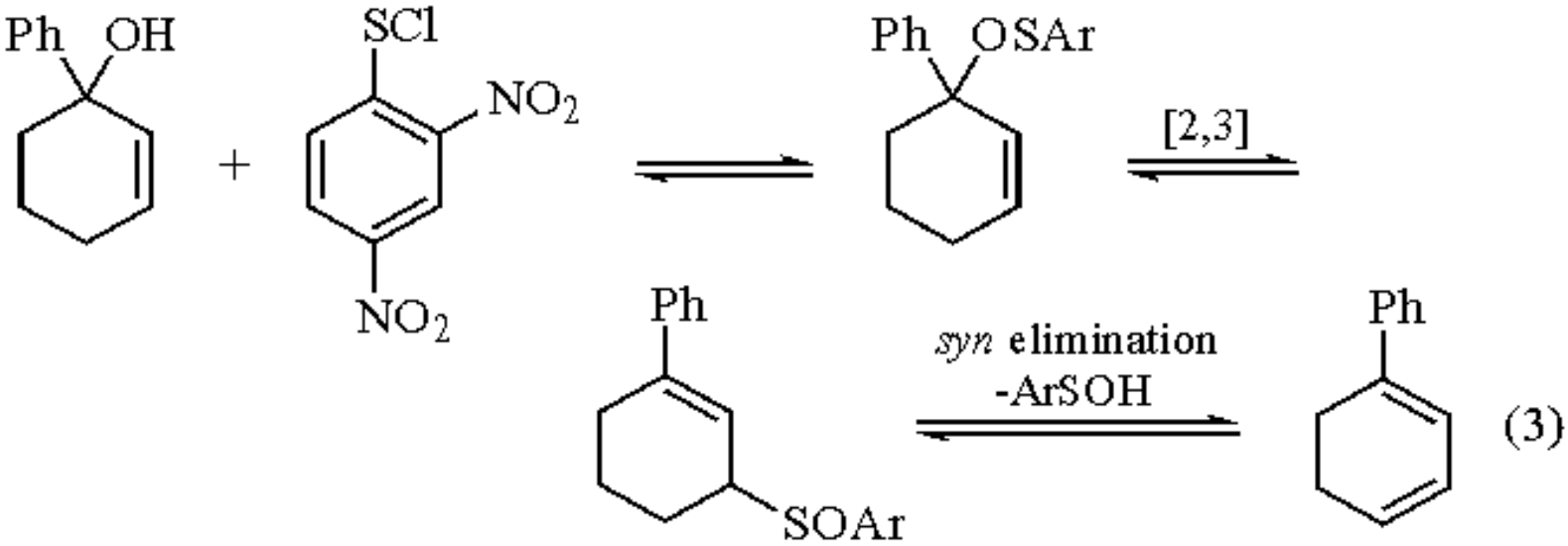

Protection of Nucleosides.

The 2,4-dinitrobenzenesulfenyl group serves as a protecting group for both the hydroxy functionalities and the base in nucleosides (eq 4).[13,14] Dinitrobenzenesulfenic esters are stable to pyridine solutions of ***Acetic Anhydride*** or ***p-***

Toluenesulfonyl Chloride. ***1,3-Dicyclohexylcarbodiimide*** conditions for forming oligonucleosides also do not affect this protecting group. Deprotection is readily accomplished with nucleophilic reagents such as ***Sodium Thiosulfate***, ***Thiophenol***, or ***Potassium Cyanide***.

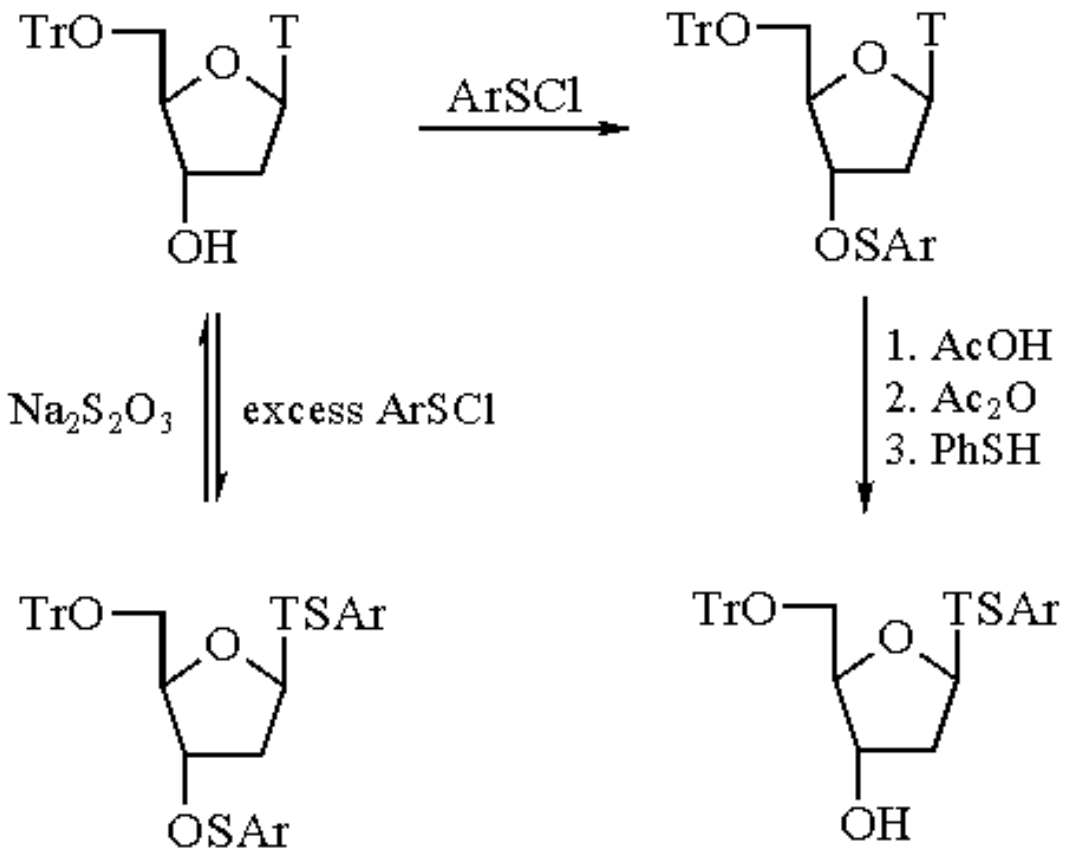

(4)

Propargyl Alcohol Synthons in Cycloadditions.

Allenic sulfoxides can serve as propargyl alcohol equivalents in 1,3-dipolar cycloaddition reactions.[15] Treatment of propargyl alcohol with 2,4-dinitrobenzenesulfenyl chloride and triethylamine gives the transient sulfenate ester that spontaneously rearranges to the allenic sulfoxide. The (2,4-dinitrophenyl)sulfinyl-substituted allene reacts smoothly with a variety of nitrones. The initially formed cycloadduct undergoes a 2,3-sigmatropic rearrangement to produce sulfenate esters of isoxazolidines (eq 5).

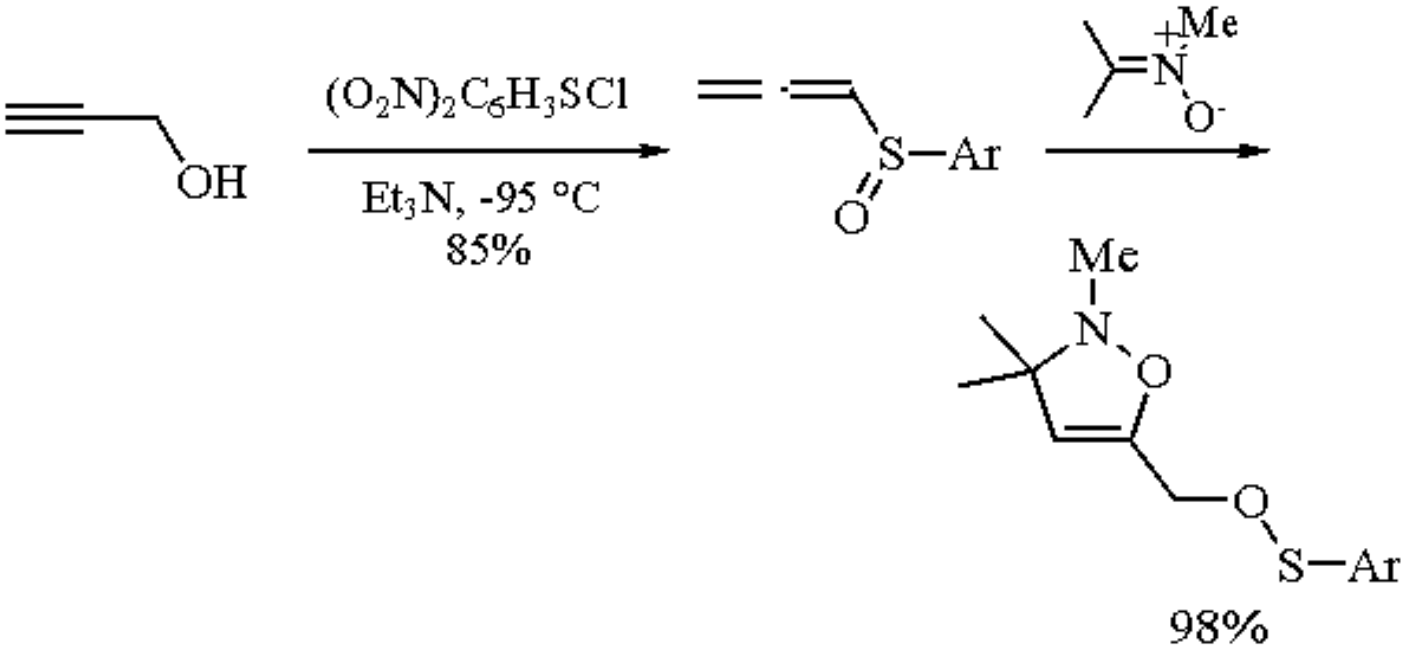

(5)

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3,5-Dinitrobenzenesulfonyl Chloride

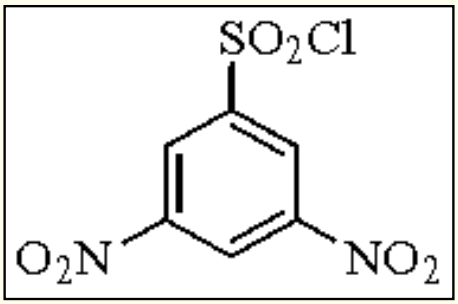

[31206-25-4] · $C_6H_3ClN_2O_6S$ · 3,5-Dinitrobenzenesulfonyl Chloride · (MW 266.63)

(sulfonylating agent for the preparation of crystalline sulfonamides and sulfonate esters; 3,5-dinitrobenzenesulfonate esters exhibit high reactivity in solvolysis reactions[1,2])

Physical Data: mp 98.5 °C.

Solubility: sol AcOH, pyridine; insol diethyl ether.

Form Supplied in: not commercially available; easily prepared.

Preparative Method: by a modified Sandmeyer reaction.[3,4] Diazotization of 3,5-dinitroaniline (0.25 mol) at -15 °C in aqueous acetic acid/conc HCl followed by addition to a saturated solution of SO_2 in acetic acid gives the product, which is precipitated by the addition of water, washed with water then diethyl ether, and dried under vacuum (81% yield).

Handling, Storage, and Precautions: reactive sulfonylating agent: avoid contact with skin and mucous membranes. Can be stored at rt for prolonged periods when dried and kept free of moisture.

General Reactions.

Arenesulfonyl chlorides are vital precursors for the preparation of a wide variety of functional groups including sulfonate esters, sulfonamides, and sulfones. A variety of substituted arenesulfonyl chlorides can be used to derivatize alcohols and primary and secondary amines forming sulfonate esters and sulfonamides, respectively. Substituted arenesulfonate esters exhibit varying rates of S_N1 and S_N2 reactions which are dependent on the aryl substituents.[2]

Solvolysis of 3,5-Dinitrobenzenesulfonates.

Solvolysis of the crystalline 3,5-dinitrobenzenesulfonate of 3-pentyn-1-ol in CF_3CO_2H-CF_3CO_2Na gives 2-

methylcyclobutanone[1] in 73% yield (eq 1). The yield of 2-methylcyclobutanone was reduced when the *p*-toluene- and *m*-nitrobenzenesulfonates were used. Cyclobutanone[5] and other alkyl-substituted cyclobutanones[6] have also been prepared via this participation of an alkynic bond during solvolysis of homopropargylic sulfonate esters, but the former requires the use of the more reactive trifluoromethanesulfonate.

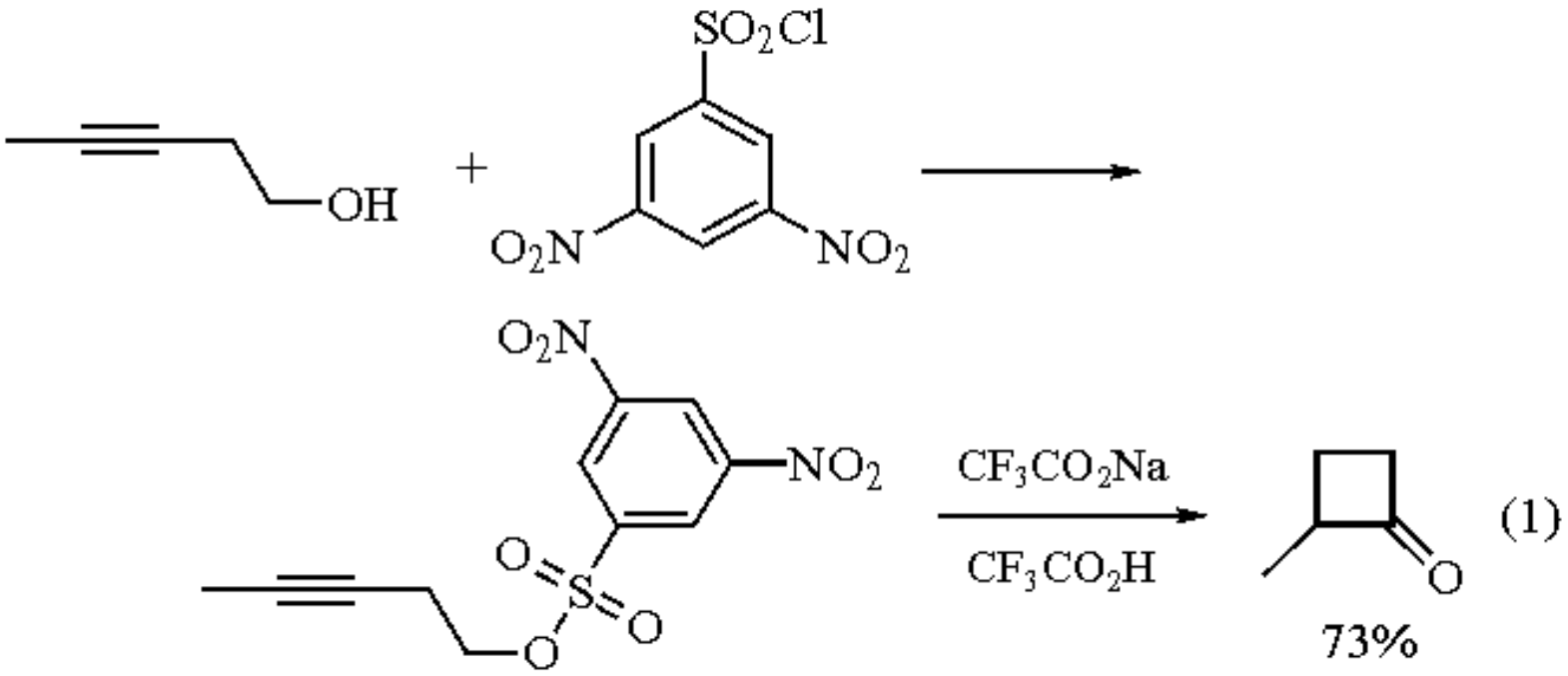

Related Reagents.

p-Anisolesulfonyl Chloride; ***Benzenesulfonyl Chloride***; ***4-Bromobenzenesulfonyl Chloride***; ***Methanesulfonyl Chloride***; ***p-Toluenesulfonyl Chloride***; ***Trifluoromethanesulfonyl Chloride***.

---

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2,4-Dinitrobenzenesulfonylhydrazide

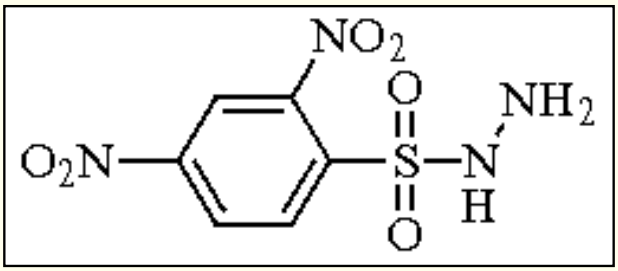

[53777-75-6] · $C_6H_6N_4O_6S$ · 2,4-Dinitrobenzenesulfonylhydrazide · (MW 262.23)

(an effective reagent for preparing propargyl ketones and aldehydes via the Eschenmoser fragmentation[2])

Alternate Name: DNSH.

Physical Data: mp 120 °C.

Solubility: sol most organic solvents.

Analysis of Reagent Purity: IR, NMR.

Preparative Method: by treatment of 2,4-dinitrobenzenesulfonyl chloride with 95% hydrazine in THF and crystallized from EtOH/THF.[1]

Handling, Storage, and Precautions: thermally labile; should be stored in a freezer. It is a toxic and potentially flammable solid that should be handled with gloves under inert atmosphere and freshly prepared as needed.

Eschenmoser Fragmentation.

Despite reports of the superiority of 2,4-dinitrobenzenesulfonyl hydrazide (DNSH) in the Eschenmoser fragmentation, this reagent has received very little attention as a mild alternative to ***p-Toluenesulfonylhydrazide*** and *N*-aminoaziridines.[2,3] Condensation of DNSH with α,β-epoxy ketones in THF or dichloromethane gives smooth cleavage to alkynones and alkynals between 0 °C and rt (eqs 1-3) when treated with catalytic amounts of base (pyridine, sodium bicarbonate, or sodium carbonate). Yields are good to excellent. The fragmentation shown in eq 2 cannot be effected with ***p-Toluenesulfonylhydrazide***, and *N*-aminoaziridines give low, irreproducible yields.[1]

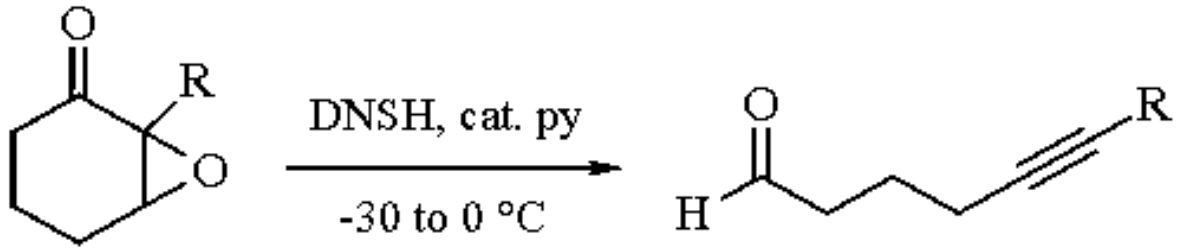

R = H, 62%; Me, 62%

(1)

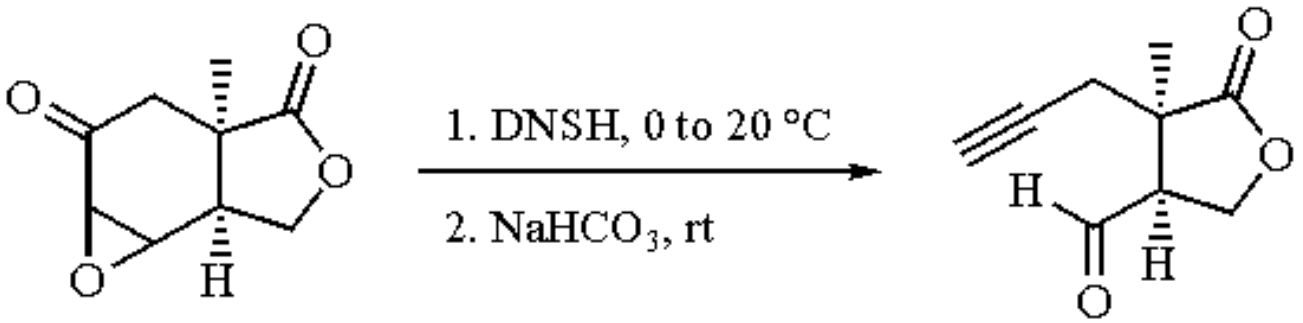

(2)

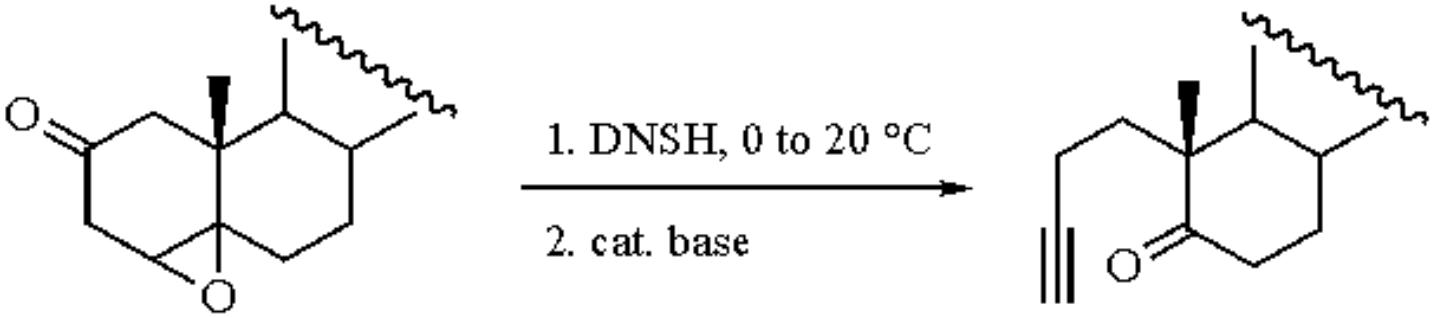

(3)

Use of this reagent for synthesis of selenosulfonates has also been briefly examined, but ***Mesitylenesulfonylhydrazide*** is more efficient.[4,5]

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3,5-Dinitrobenzoyl Chloride

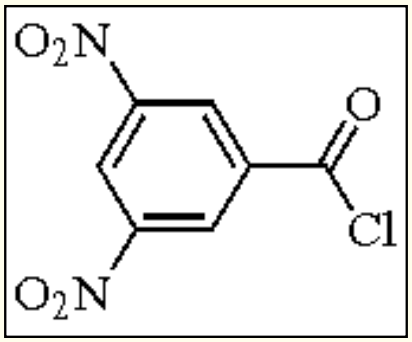

[99-33-2] · $C_7H_3ClN_2O_5$ · 3,5-Dinitrobenzoyl Chloride · (MW 230.57)

(activation of hydroxy groups by conversion to the corresponding ester;[1] preparation of 3,5-dinitrobenzoates and 3,5-dinitrobenzamides for characterization purposes[3])

Physical Data: mp 69-71 °C; bp 196 °C/11 mmHg.

Solubility: sol ether; reacts with water and protic solvents.

Form Supplied in: 98% pure form as yellow solid (2% impurity as carboxylate); widely available.

Purification: recrystallization from carbon tetrachloride/petroleum ether (40-60 °C) or from benzene.

Handling, Storage, and Precautions: lachrymator; corrosive and moisture sensitive. Avoid inhalation. Store in sealed tube or under petroleum ether.

Preparation of 3,5-Dinitrobenzoates.

3,5-Dinitrobenzoates, prepared by the acylation of a hydroxy group with 3,5-dinitrobenzoyl chloride, have been utilized in solvolysis studies,[1] S_N2' displacement of propargylic alcohols,[2] and derivatization of alcohols for characterization purposes.[3,4] A variety of functional groups are stable under the benzoylation conditions (eqs 1 and 2). An alternative preparation of 3,5-dinitrobenzoates entails the direct coupling of 3,5-dinitrobenzoic acid and an alcohol using an activating reagent such as ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride*** (eq 3).[2b]

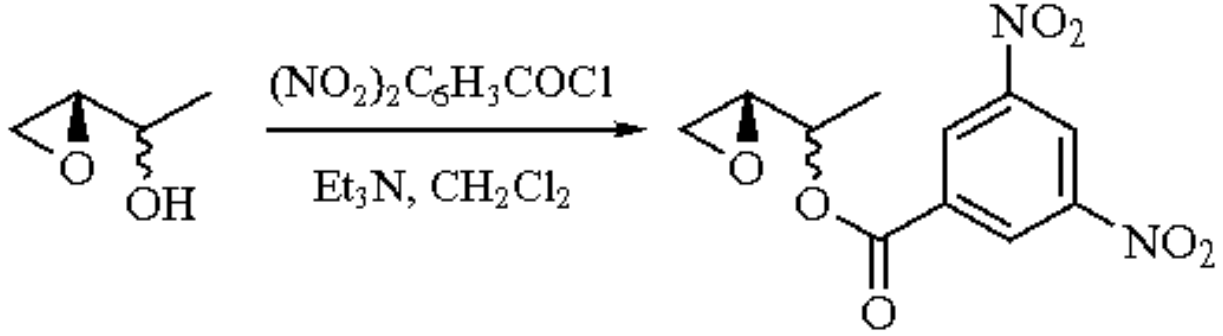
(NO2)2C6H3COCl
Et3N, CH2Cl2
O
OH
NO2
NO2
O
O
O

(1)

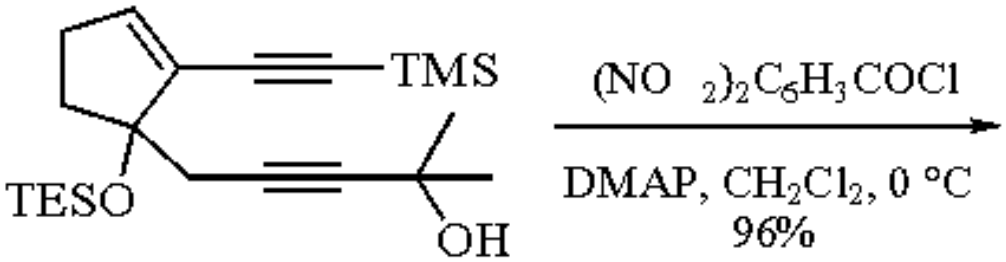
TMS
TESO
OH
(NO 2)2C6H3COCl
DMAP, CH2Cl2, 0 °C
96%

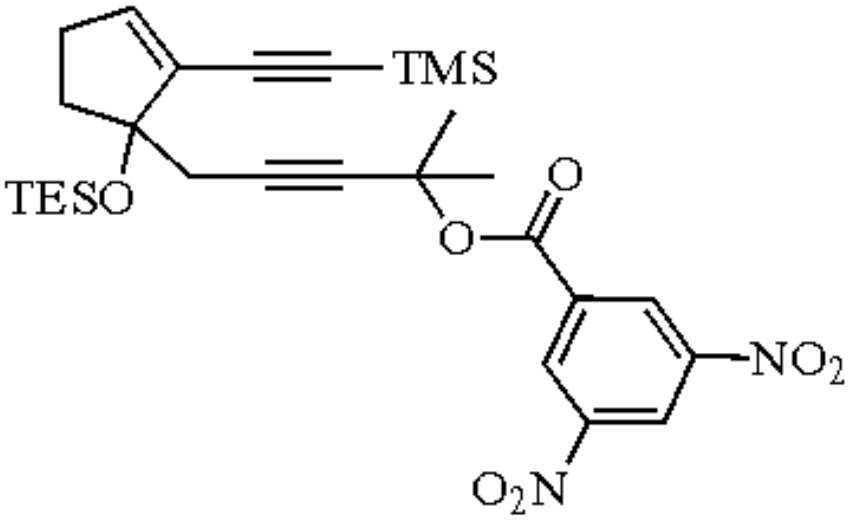
TMS
TESO
O
O
NO2
O2N

(2)

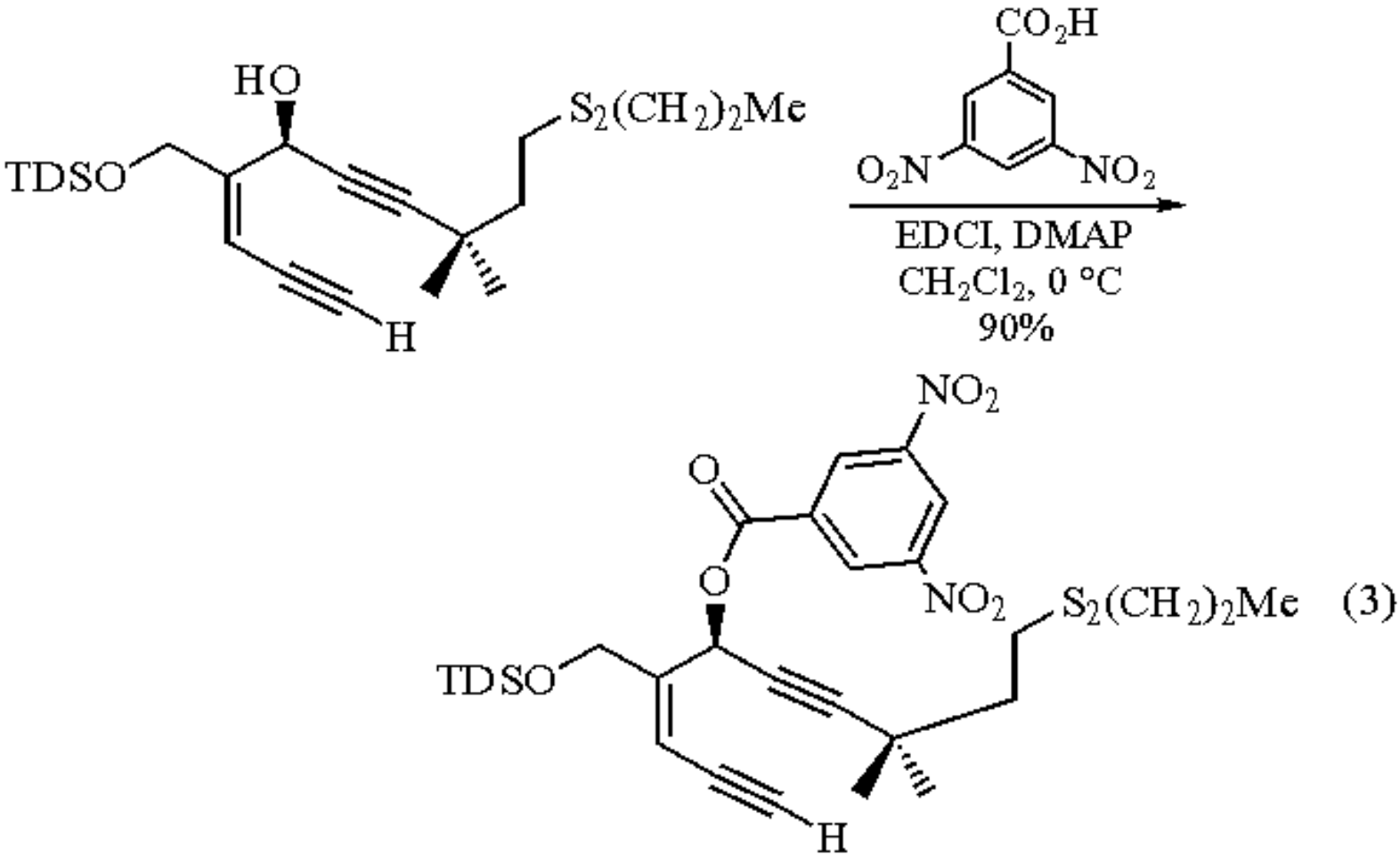

The 3,5-dinitrobenzoate esters of alcohols are often crystalline derivatives and have been used for characterization purposes.[3] For example, selective benzoylation of the secondary hydroxy group of an isomer of 25-hydroxyvitamin D_3 affords the corresponding crystalline 3,5-dinitrobenzoate derivative (eq 4).[3b]

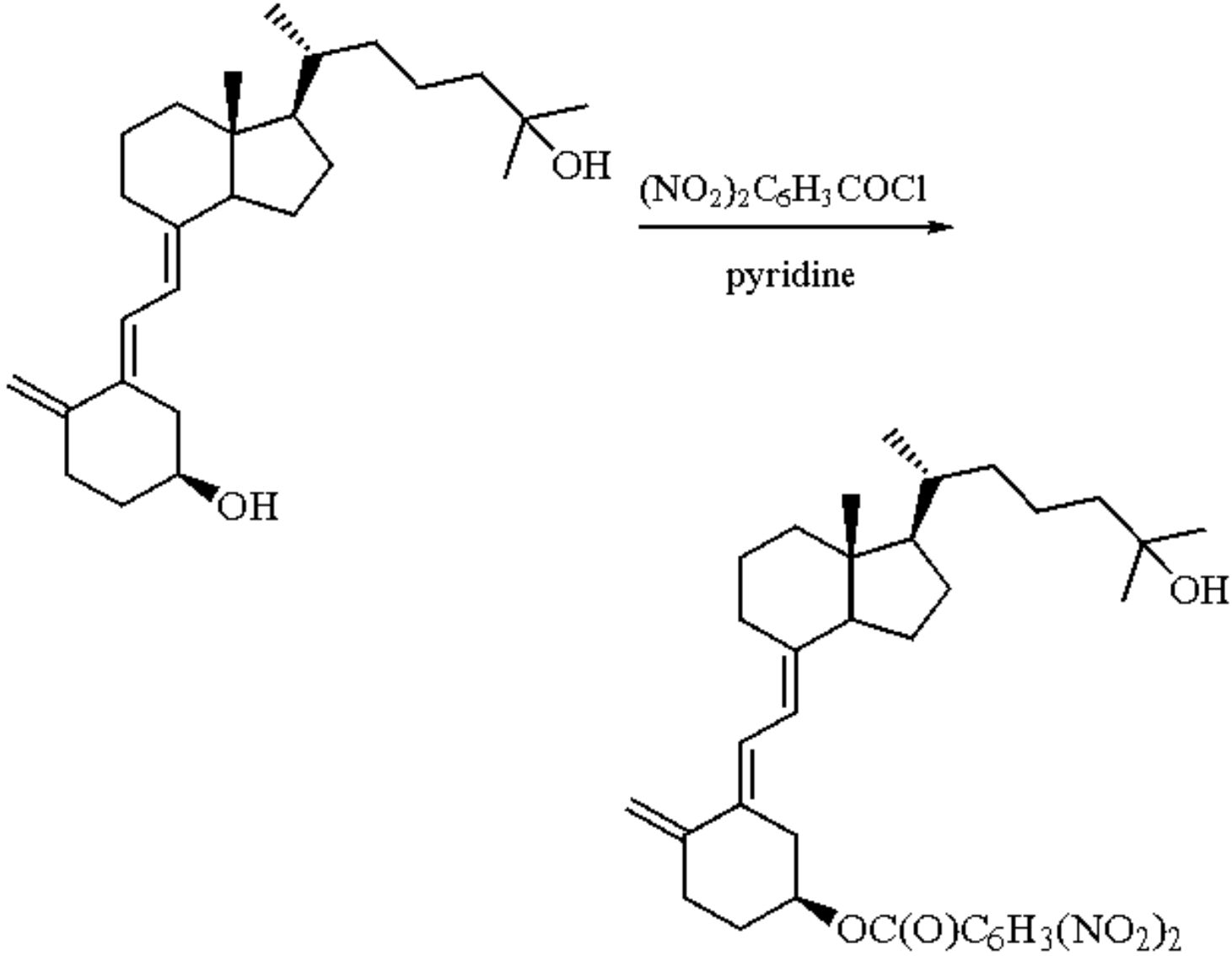

(4)

The chromatographic separation of the enantiomers of alcohols, using a chiral stationary phase, is enhanced by the preparation of the corresponding 3,5-dinitrobenzoate derivatives.[4]

Benzoylation of Amino Groups.

3,5-Dinitrobenzamides are useful derivatives of amines for characterization purposes (eqs 5 and 6). The 3,5-dinitrobenzamides of amines have been particularly useful for the chromatographic separation of amines, amino acids, and amino alcohols using chiral stationary phases.[4,5]

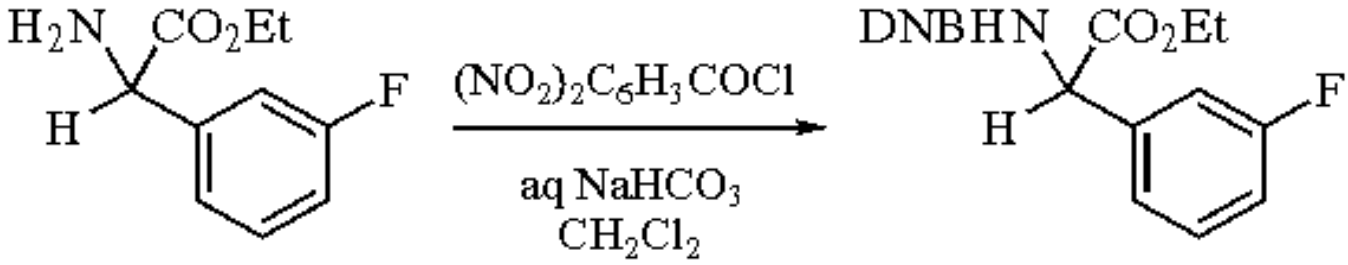

(5)

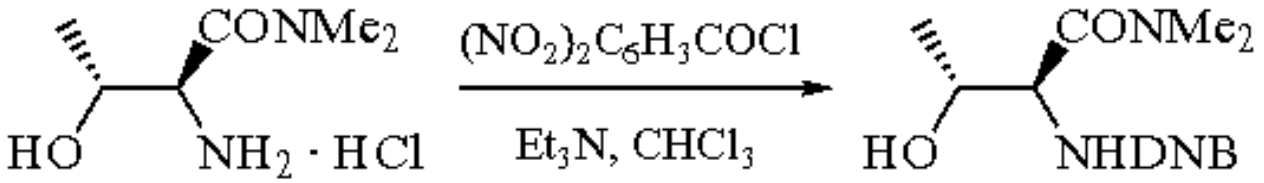

(6)

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2,4-Dinitrophenylhydrazine

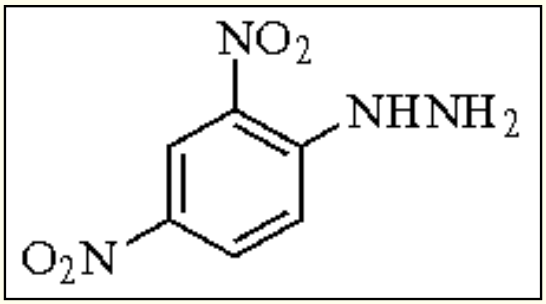

[119-26-6] · $C_6H_6N_4O_4$ · 2,4-Dinitrophenylhydrazine · (MW 198.16)

(readily forms derivatives with aldehydes and ketones;[1,2] synthesis of heterocycles;[3-5] reduction of carbonyls[6])

Alternate Name: $DNPH_2$.

Physical Data: mp 194 °C (198 °C dec).

Solubility: sol DMF, DMSO, aniline, hot EtOAc; mod sol hot EtOH; slightly sol Et_2O, $CHCl_3$, benzene, CS_2.

Form Supplied in: moist, orange-red solid (contains 20-35% H_2O).

Preparative Method: from 2,4-dinitrochlorobenzene and hydrazine in 81-85% yield.[7]

Handling, Storage, and Precautions: toxic; irritant; flammable solid.

Derivatives of Aldehydes and Ketones.

The reaction of 2,4-dinitrophenylhydrazine with aldehydes and ketones represents an extensively studied qualitative test and usually leads to the formation of yellow to orange crystals of the corresponding 2,4-dinitrophenylhydrazone (DNP) derivatives (eq 1).[1] Some long-chain aliphatic ketones (e.g. 2-decanone and 6-undecanone) fail to provide solid DNP derivatives.[2] Further caution needs to be exercised in interpreting the results since primary and secondary alcohols containing two or more vinyl or aromatic substituents can be oxidized to the carbonyls which then form the corresponding hydrazones in low yields.[8] Tertiary alcohols tend to undergo condensation reactions with $DNPH_2$ (eq 2).[9]

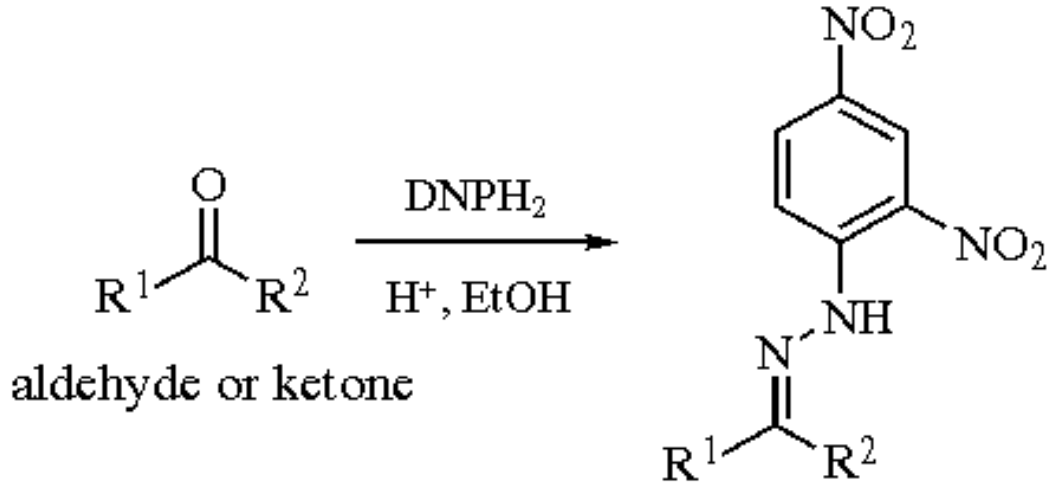

(1)

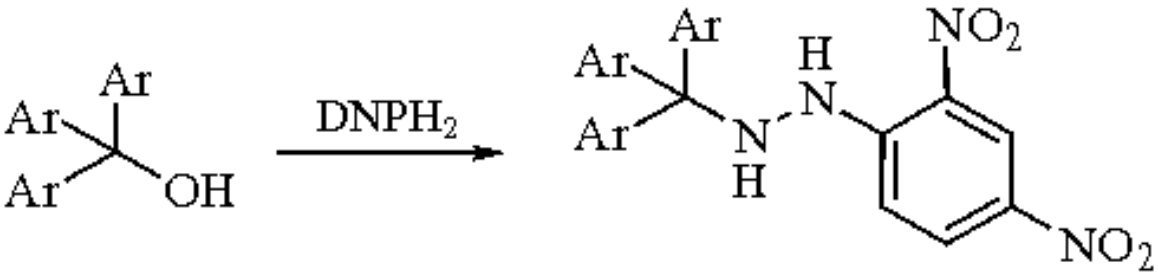

+ H_2O (2)

Formation of Heterocycles.

The reactivity of $DNPH_2$ has also been utilized in the syntheses of nitrogen-containing heterocycles.[3] Imino ester hydrochlorides, generated from nitriles, react with $DNPH_2$ to provide amidazones, which are converted in situ to 1,3,5-substituted triazoles by reaction with acid chlorides (eq 3).[4] Treatment of acyldimedone derivatives with $DNPH_2$ provides indole derivatives (eq 4).[5]

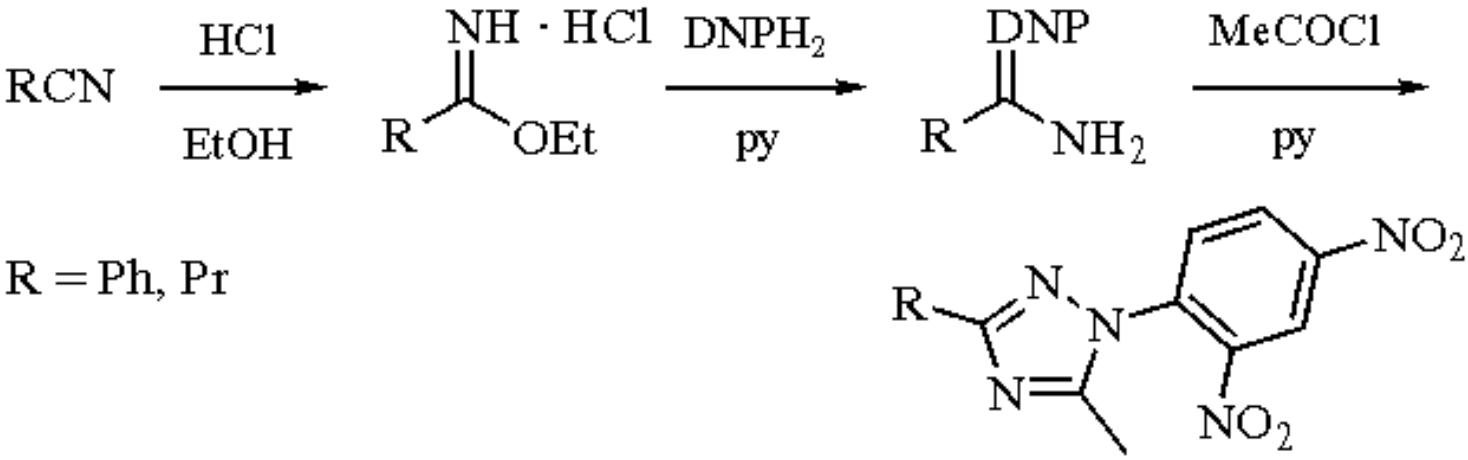

(3)

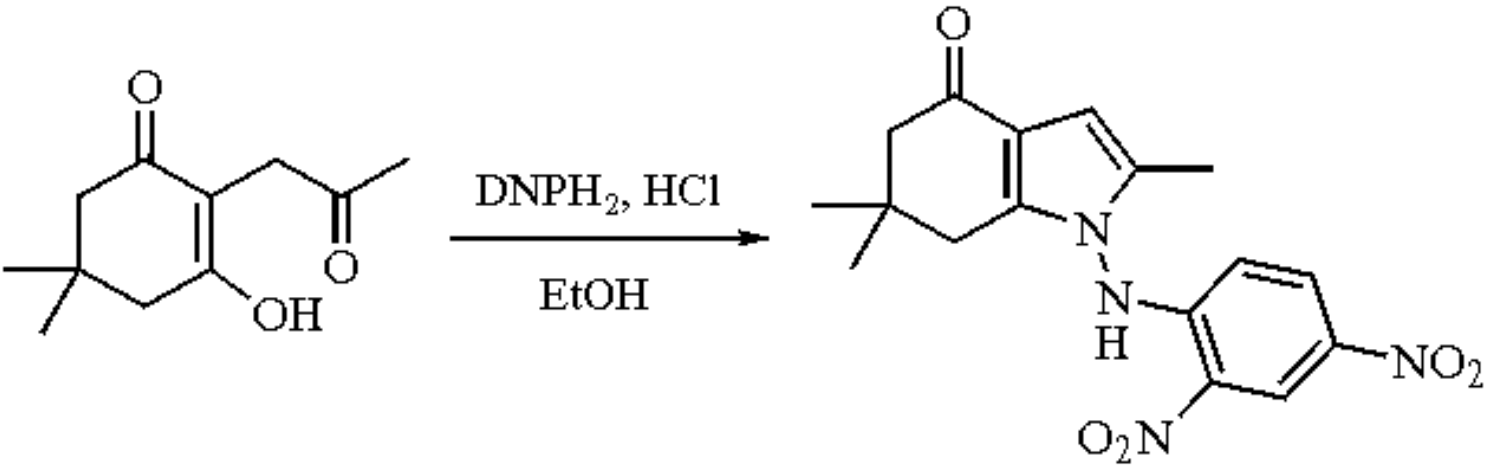

(4)

Reduction.

Catalytic hydrogenolysis of DNP derivatives of alkyl aryl or diaryl ketones leads to the formation of corresponding methylene derivatives and represents a useful alternative to Wolff-Kishner and Clemmenson reductions (eq 5).[6] In the steroid series, where ordinary methods fail to induce unsaturation in α-bromo ketones, $DNPH_2$ has been used to effect dehydrohalogenation.[10]

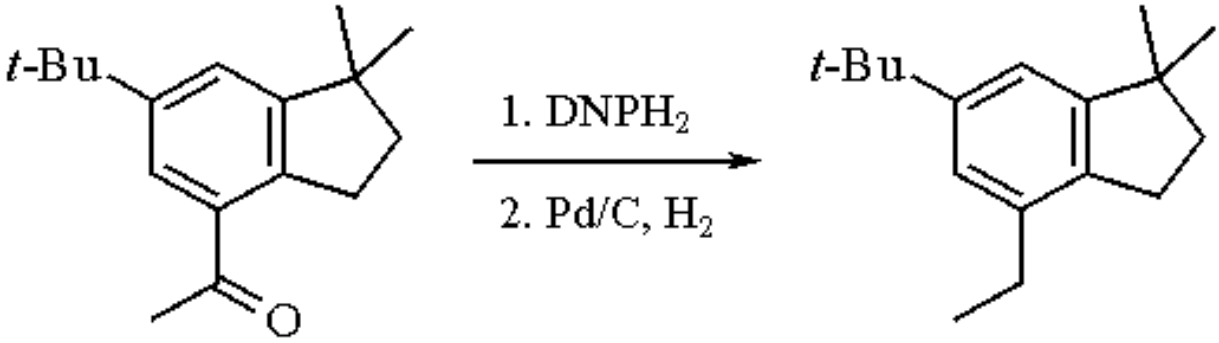

(5)

Carbonyl Regeneration.

DNP derivatives can be cleaved to regenerate the carbonyl functionality. Efficient techniques for affecting this transformation include DNP exchange with pyruvate,[10a] Amberlyst 15 catalyst,[11] clay-supported iron(III) nitrate,[12] and aqueous titanium(III) ion.[13]

Related Reagents.

N,N-Dimethylhydrazine; ***O-2,4-Dinitrophenylhydroxylamine***; ***Phenylhydrazine***.

---

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O-2,4-Dinitrophenylhydroxylamine

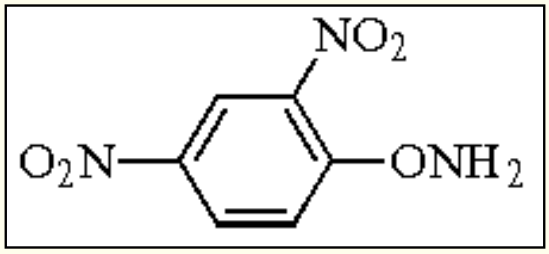

[17508-17-7] · $C_6H_5N_3O_5$ · *O*-2,4-Dinitrophenylhydroxylamine · (MW 199.14)

(widely applicable electrophilic amination reagent; converts aldoximes to cyanides and benzofurans)

Alternate Names: DNPHA; NH_2ODNP.

Physical Data: pale yellow needles, mp 112-113 °C. A rapid active-site-directed inhibitor of D-amino acid oxidase.[1]

Preparative Methods: can be generated economically from the reaction of 2,4-dinitrochlorobenzene and ethyl *N*-hydroxyacetimidate with subsequent hydrolysis.[2] *t*-Butyl *N*-hydroxycarbamate[3] and *N*-hydroxy-5-norbornene-2,3-dicarboximide[4] can be used in place of ethyl *N*-hydroxyacetimidate.

Handling, Storage, and Precautions: an otherwise stable, crystalline solid, DNPHA has been known to detonate when combined with ***Potassium Hydride*** and therefore direct combination of these two reagents should be avoided.[5] 2,4-Dinitrophenol, a byproduct of amination reactions involving DNPHA, is a highly toxic, flammable solid. Use in a fume hood.

Conversion of Aldoximes to Cyanides and Benzofurans.

The title compound has been used in a convenient, high-yield conversion of aldehydes to nitriles via oximes.[6] Oximes derived from a variety of aldehydes and ketones have also been used in the formation of 5,7-dinitrobenzofurans via the Fischer reaction (eq 1).[7]

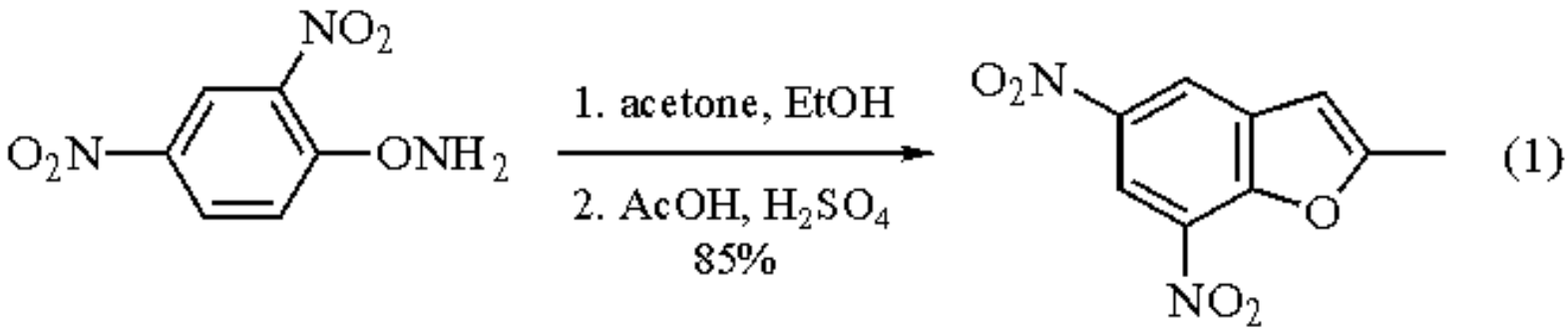

Preparation of Dialkylamines.

A number of reagents exist for the preparation of primary,[8] secondary,[9] and tertiary amines[10] from organoboranes; a common feature of all these reagents is the lone leaving group on nitrogen. Consequently, these reagents are suitable for transferring only one alkyl group from the organoborane; transfer of two alkyl groups from the organoborane to the same nitrogen requires two leaving groups on the nitrogen. This dual transfer can be achieved with the use of *N*-chloro-*O*-(2,4-dinitrophenyl)hydroxylamine generated in situ from DNPHA. In the following example, reaction of DNPHA with ***t-Butyl Hypochlorite*** followed by addition of perhydroboraphenalene and subsequent peroxide oxidation gives the amino alcohol (eq 2).[11]

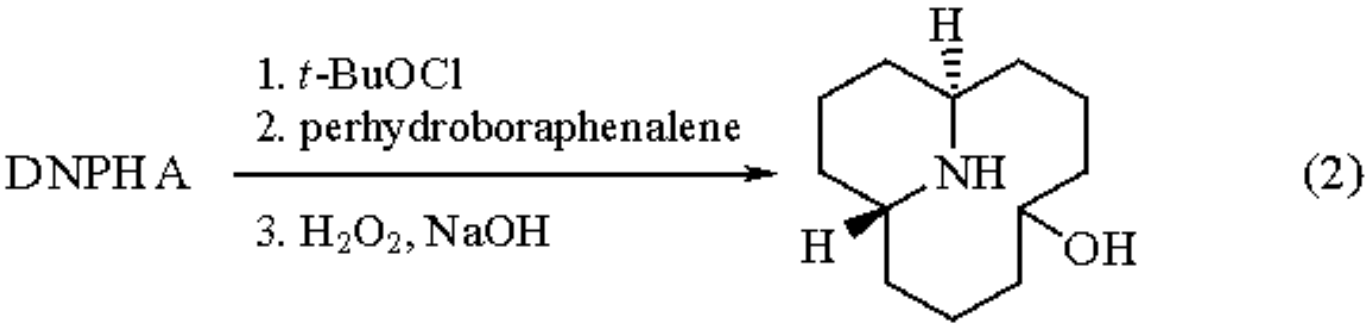

Amination Reactions.

Electrophilic amination constitutes the major use of DNPHA in synthesis; attack on the amine nitrogen of DNPHA readily occurs in an S_N2 fashion. The stability of DNPHA relative to the corresponding *O*-arylsulfonylhydroxylamines,[7c] which also have been used for these transformations, and the good leaving-group ability of the 2,4-dinitrophenolate anion both enhance its usefulness. The primary substrates for amination by DNPHA are nitrogen-containing compounds in the form of heterocycles or disubstituted amino derivatives. Many species have been *N*-aminated, including pyrroles,[3] pyridines,[12] nucleosides,[13-16] carbamates,[17-19] amides,[18] phthalimides,[3,20] sulfonamides,[3] thiazolidines,[21] and triazin-5(2*H*)-ones;[22-24] an example of a sulfonamide is given in eq 3.[3] In the case of guanine[14] and 2-amido- and 2-carbamoylthiophenes,[18] however, other amination reagents have proven more efficacious; furthermore, nucleosides are aminated at the most basic *endo* nitrogen position.[13] Primary[25] and tertiary[26] amines have also been *N*-aminated by this method.

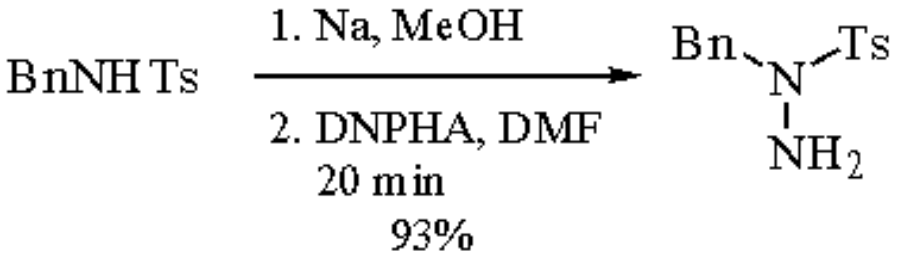

(3)

DNPHA has been used to aminate other heteroatoms as well. Phenol derivatives[27] (including hydroxycoumarins),[28] thiophenol derivatives,[11] and phosphines[11] have all been successfully converted to their *O*- *S*-, and *P*-amino derivatives by this reagent. In addition, aliphatic compounds such as malonates[5] and aromatic compounds such as fluorene derivatives[3] have been aminated at the active carbon center. An interesting reaction involving a boraalkane has also been reported.[29]

The kinetics of DNPHA addition are first-order with respect to both substrate and nucleophile and are second-order overall.[11]

---

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29. Mikhailov, B. M.; Shagova, E. A.; Etinger, M. Yu. *JOM* **1981**, *220*, 1.

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1,3,2-Dioxathiolane 2,2-Dioxide[1]

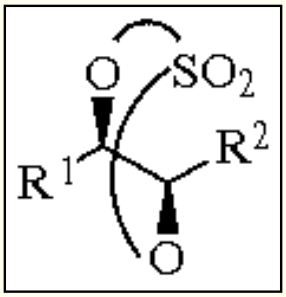

($R^1 = R^2 = H$)

[1072-53-3] · $C_2H_4O_4S$ · 1,3,2-Dioxathiolane 2,2-Dioxide · (MW 124.13) ($R^1 = R^2 =$ *n*-Bu)

[127901-92-3] · $C_{10}H_{20}O_4S$ · 4,5-Dibutyl-1,3,2-Dioxathiolane 2,2-Dioxide · (MW 236.37)

(display epoxide-like reactivity;[2,3] nucleophilic displacement of both oxygen functions is feasible[4-6])

Alternate Names: ethylene sulfate; cyclic sulfates.

Preparative Methods: cyclic sulfates of 1,2-diols (1,3,2-dioxathiolane 2,2-dioxides) are most easily prepared in a two-step procedure (eq 1).[2] Reaction of a 1,2-diol with ***Thionyl Chloride*** leads to a cyclic sulfite which is then oxidized to the corresponding cyclic sulfate (**1**). Direct conversion of a 1,2-diol to a cyclic sulfate using ***Sulfuryl Chloride*** is generally less efficient.[2,3]

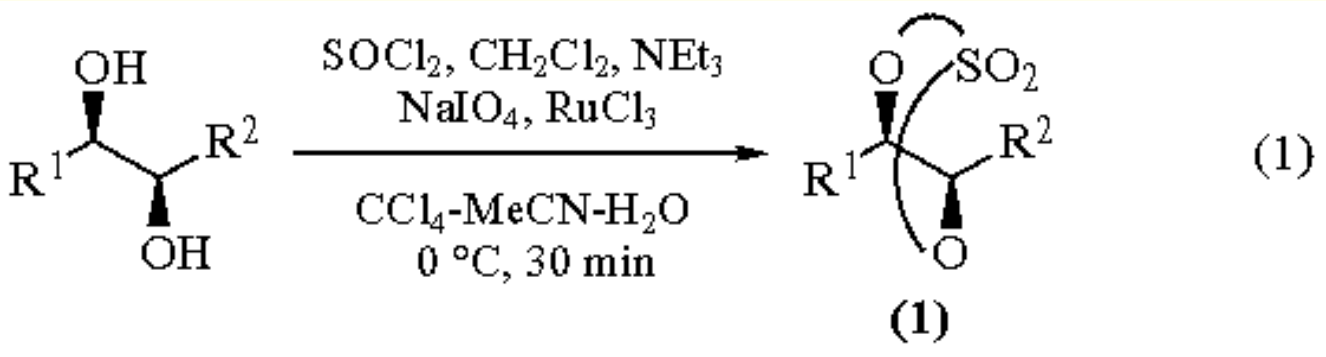

(1)

Handling, Storage, and Precautions: the structural similarity between cyclic sulfates and ***Dimethyl Sulfate*** must be recognized. Dimethyl sulfate, and to a lesser extent ethylene sulfate, are carcinogenic and potent alkylating agents that are toxic by inhalation and ingestion.[1] **Cyclic sulfates must, as a result, be treated with extreme care**.

Cyclic sulfates of 1,2-diols are an important group of reagents and recent advances in the asymmetric dihydroxylation

of alkenes (see ***Osmium Tetroxide***) will serve to increase further their synthetic potential.[7] Cyclic sulfates display reactivity towards nucleophiles that is closely related to that of epoxides and react in a regioselective fashion with hydride (eq 2)[2] and a wide range of heteroatoms (eqs 3-5)[2,3,8,9] and carbon-based nucleophiles (eq 6).[2,5,6]

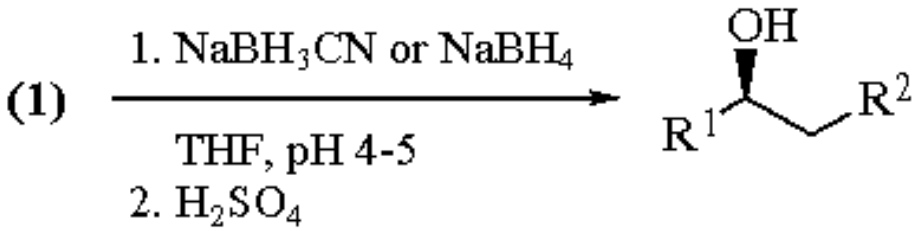

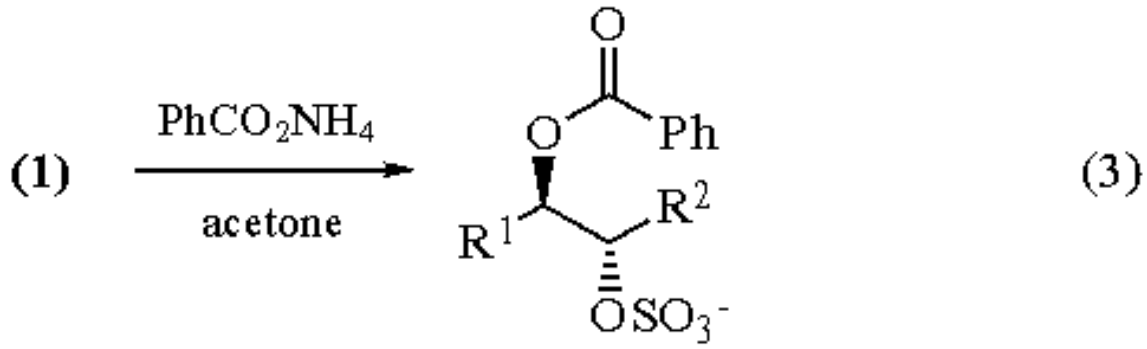

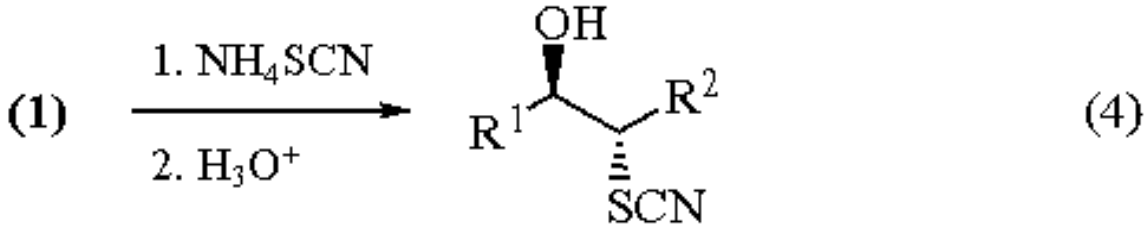

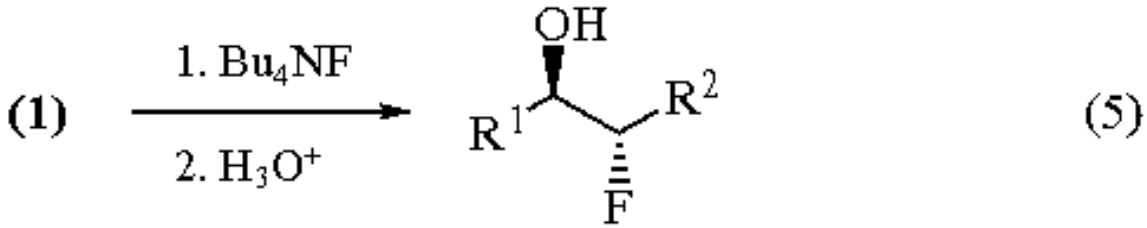

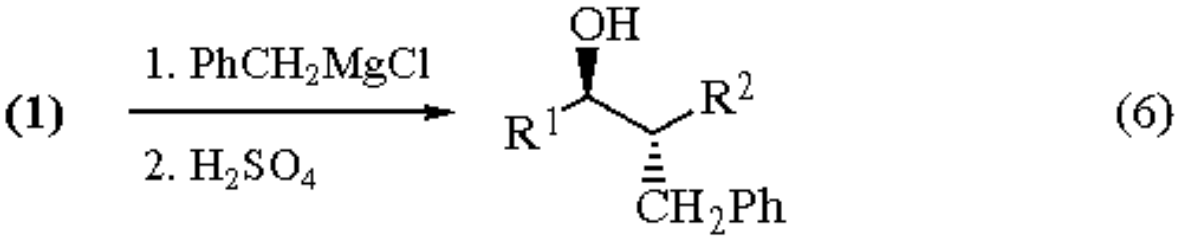

The reactivity of nitrogen nucleophiles towards cyclic sulfates has attracted considerable interest and provides an efficient entry into 1,2-amino alcohols (eq 7).[4,10]

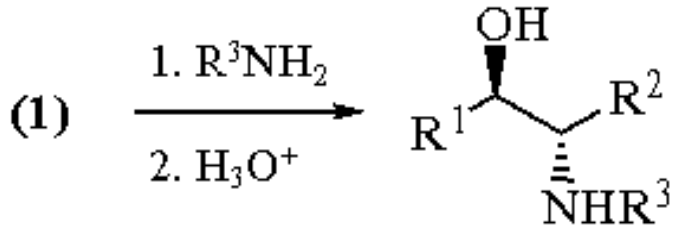

(7)

It is, however, important to appreciate the additional scope offered by cyclic sulfates over epoxides as electrophilic components in displacement processes. Following nucleophilic ring-opening, the intermediate β-sulfate, e.g. (**2**), functions as a leaving group and can undergo a second displacement.[2] This provides a direct access to aziridines (including *N*-unsubstituted variants) (eq 8),[4,10] to 1,2-diamines (eq 9),[11] and, with activated carbon nucleophiles, to cyclopropanes (eq 10).[5,6]

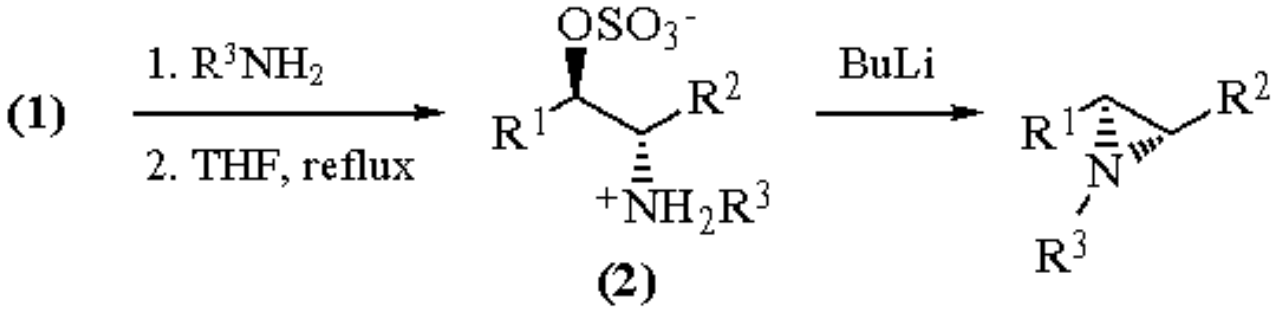

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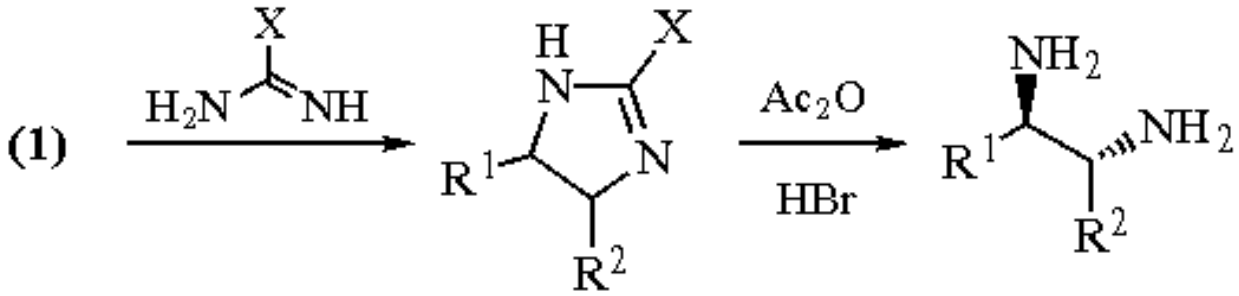

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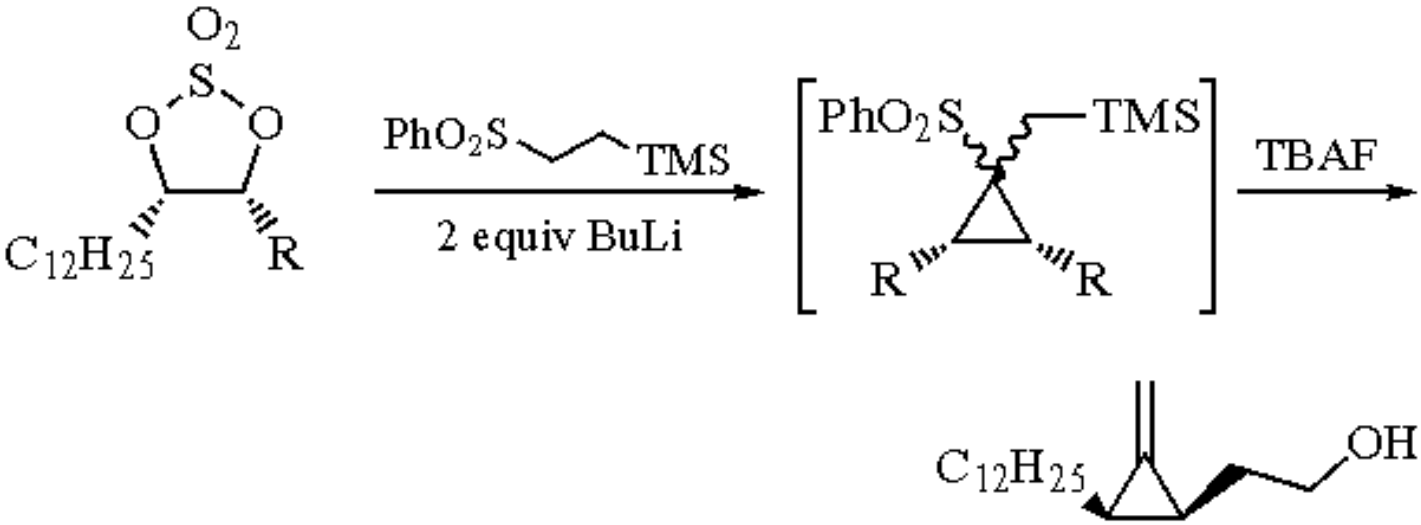

(10)

In cyclic sulfates derived from α,β-unsaturated esters, regioselective nucleophilic attack has been observed (eq 11);[2] the corresponding epoxide undergoes ring opening with a lower level of regioselectivity.

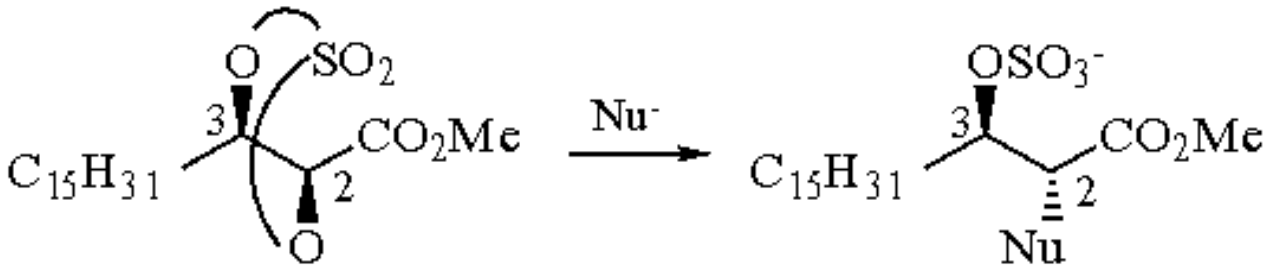

(11)

Cyclic sulfates are stable towards L-selectride (***Lithium Tri-s-butylborohydride***)[12] and are also compatible with acid (and the sulfate cleaved in the presence of acid-labile protecting groups, e.g. OTBDMS, acetonide).[13]

1.Lohray, B. B. *S* **1992**, 1035.
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3. Berridge, M. S.; Franceschini, M. P.; Rosenfeld, E.; Tewson, T. J. *JOC* **1990**, *55*, 1211.
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10. Lohray, B. B.; Gao, Y.; Sharpless, K. B. *TL* **1989**, *30*, 2623.
11. Oi, R.; Sharpless, K. B. *TL* **1991**, *32*, 999.
12. Wang, W.-B.; Roskamp, E. J. *TL* **1992**, *33*, 7631.
13. Kim, B. M.; Sharpless, K. B. *TL* **1989**, *30*, 655.

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4*H*-1,3-Dioxin

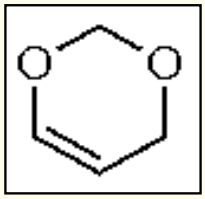

[290-13-1] · $C_4H_6O_2$ · 4*H*-1,3-Dioxin · (MW 86.10)

(precursor to a β-formylvinyl anion equivalent;[1] useful for the preparation of β-substituted acroleins,[1-3] *syn*-1,3-diols,[4] and *anti,anti*-1,2,3-triols[4])

Physical Data: bp 97-99 °C.

Solubility: sol THF, ether, hexanes.

Preparative Methods: by elimination of 5-tosyloxy-1,3-dioxane in DMSO using ***Potassium t-Butoxide***[5] or $KOCMe_2C_6H_{13}$[6] as the base. A more convenient procedure employs triethylene glycol as the solvent and ***Potassium Hydroxide*** as the base.[2]

Handling, Storage, and Precautions: thermally labile. A rapid distillation is required in order to prevent decomposition via retrocycloaddition to acrolein and formaldehyde.

β-Formylvinyl Anion Equivalent.

4*H*-1,3-Dioxin undergoes rapid metalation upon treatment with ***s-Butyllithium*** or ***t-Butyllithium*** to provide the allylic anion (**1**).[1] A variety of electrophiles such as alkyl halides, epoxides, aldehydes, and ketones can be employed in subsequent alkylation reactions to afford 4-substituted dioxins which smoothly undergo bis-hetero retrocycloaddition reactions upon refluxing in toluene (4-12 h) to provide (*E*)-α,β-unsaturated aldehydes, presumably through a boat-like transition state with the alkyl substituent in a pseudoequatorial position (eq 1).[1] Moreover, the thermal generation of β-substituted acroleins has been exploited in a one-pot retrocycloaddition-cycloaddition sequence (eq 2).[1]

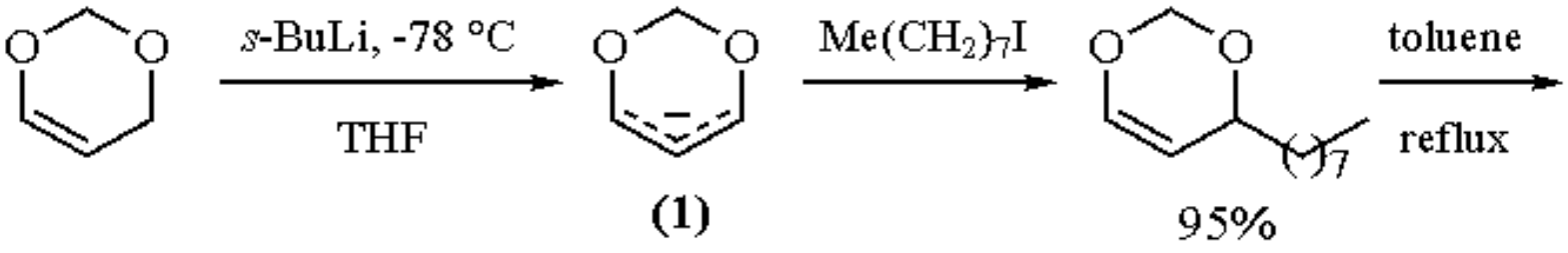

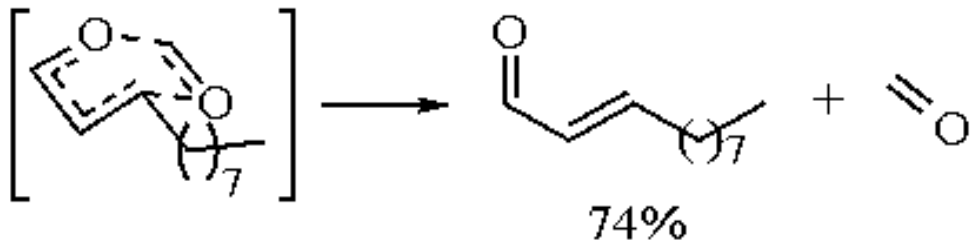

(1)

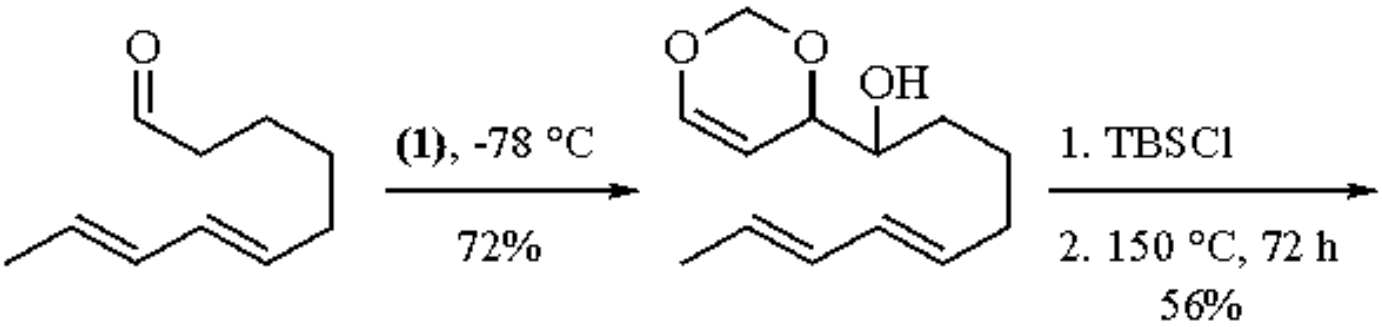

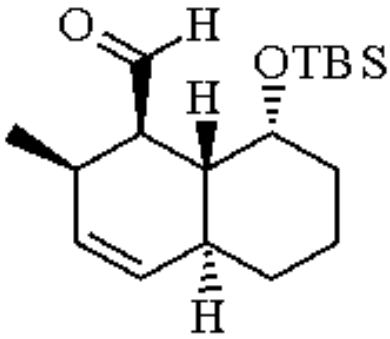

(2)

Numerous β-formylvinyl anion equivalents have been previously reported. However, the use of all of these equivalents requires at least one reagent-mediated step to unravel the α,β-unsaturated aldehyde after the alkylation step, e.g.: (**2**) $HgCl_2$, MeCN, H_2O, 50 °C;[7] (**3**) H_2O_2;[8] (**4**) H_3O^+;[9] (**5**) H_3O^+;[10] (**6**) 1 H_3O^+, 2 NEt_3;[11] and (**7**) 1 Pt, e^-, 2 NEt_3.[12]

(2)

(3)

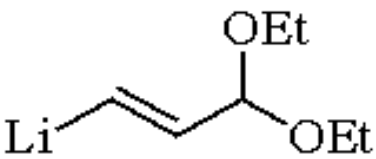

(4)

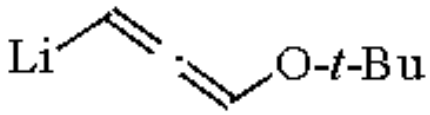

(5)

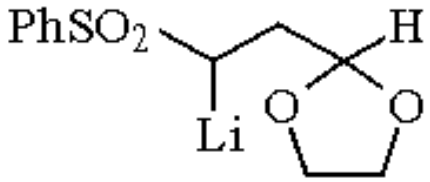

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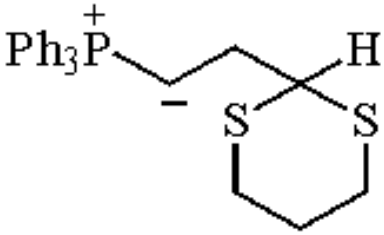

(7)

syn-1,3-Dihydroxy- and *anti,anti*-1,2,3-Trihydroxypropanediyl 1,3-Dianion Equivalents.

4-Alkyl-1,3-dioxins, such as the one shown in eq 1, can be further metalated and alkylated with excellent regioselectivity to provide 4,6-dialkyl-1,3-dioxins (eq 3). Hydroboration reactions of 4,6-dialkyl-1,3-dioxins proceed with complete stereoselectivity from the face opposite the 6-alkyl substituent to provide, after oxidative workup, a single 5-hydroxy-substituted dioxin which can be hydrolyzed to an *anti,anti*-1,2,3-triol (eq 4). Excellent diastereofacial discrimination is similarly observed in the hydrogenation reactions of 4,6-dialkyl-1,3-dioxins to provide only a *syn*-1,3-diol after hydrolysis (eq 5).

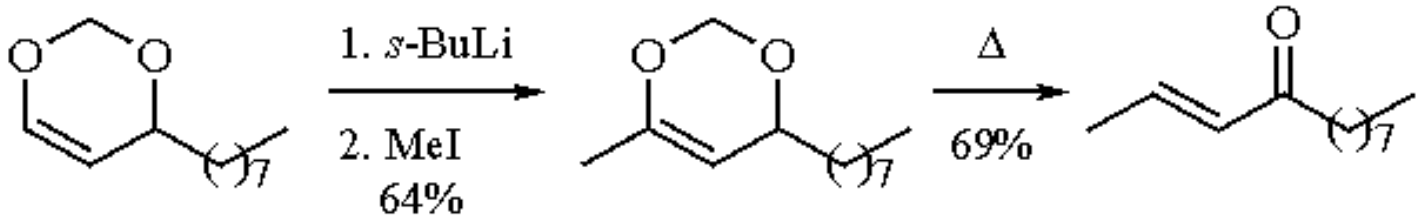

(3)

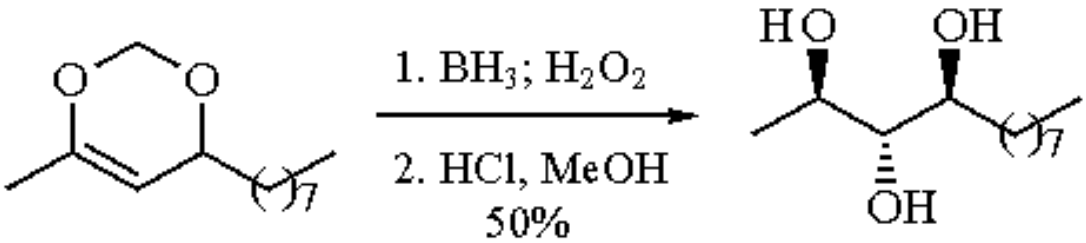

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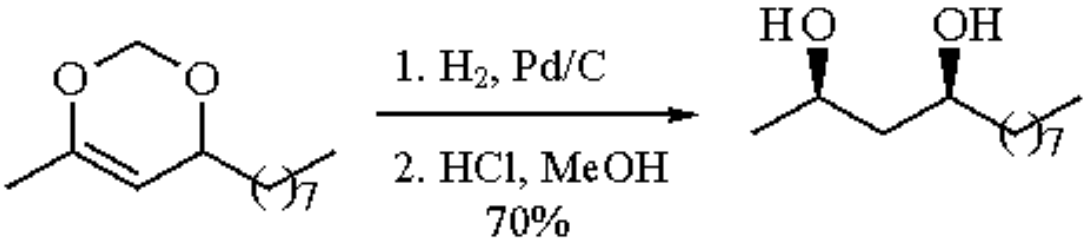

(5)

β-Formylvinyl Cation Equivalent.

4*H*-1,3-Dioxin participates in Heck reactions with a variety of aryl halides and aryl triflates to afford 4-aryl-substituted dioxins which, upon thermolysis in refluxing toluene, are transformed to 3-arylacroleins (eq 6).[3]

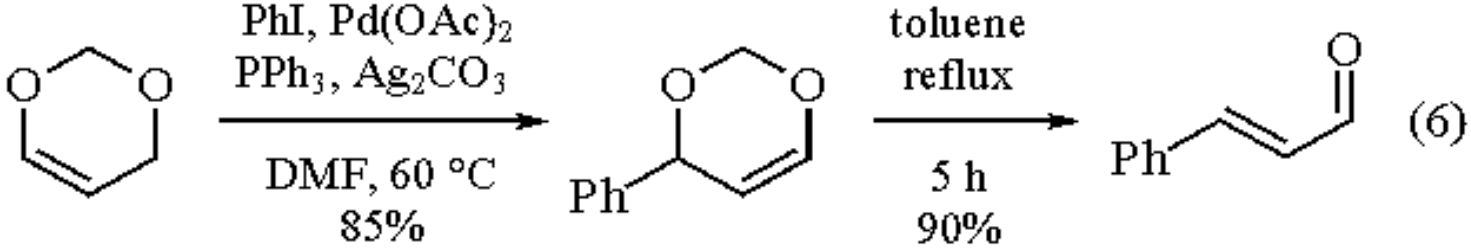

Related Reagents.

1,3-Dibutoxy-1-lithio-1-propene.

---

1. Funk, R. L.; Bolton, G. L. *JACS* **1988**, *110*, 1290.
2. Grothe, U.; Schöllkopf, U.; Tiller, T. *T* **1991**, *47*, 2835.
3. Sakamoto, T.; Kondo, Y.; Yamanaka, H. *TL* **1992**, *33*, 6845.
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8. (a) Reich, H. J.; Clark, M. C.; Willis, W. W., Jr. *JOC* **1982**, *47*, 1618. (b) For the related 1,3-dilithio-2-propynyl phenyl selenide, see: Reich, H. J.; Shah, S. K.; Gold, P. M.; Olson, R. E. *JACS* **1981**, *103*, 3112.
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10. (a) Clinet, J.-C.; Linstrumelle, G. *TL* **1978**, 1137. (b) For the related 3-lithio-1-methoxy-1,2-propadienyltrimethylsilane, see: Clinet, J.-C.; Linstrumelle, G. *TL* **1980**, *21*, 3987.
11. (a) Kondo, K.; Tunemoto, D. *TL* **1975**, 1007. (b) Julia, M.; Badet, B. *BSF(2)* **1975**, 1363.
12. (a) Cristau, H. J.; Chabaud, B.; Niangoran, C. *JOC* **1983**, *48*, 1527. (b) For the related (3,3-diisopropoxypropyl)triphenylarsonium ylide, see: Chabert, P.; Ousset, J. B.; Mioskowski, C. *TL* **1989**, *30*, 179.

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(1,3-Dioxolan-2-ylmethyl)triphenylphosphonium Bromide

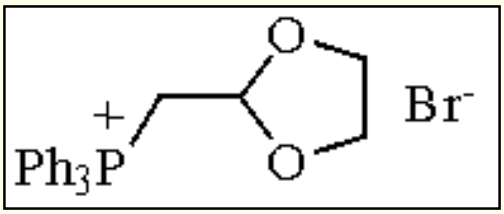

[52509-14-5] · $C_{22}H_{22}BrO_2P$ · (1,3-Dioxolan-2-ylmethyl)triphenylphosphonium Bromide · (MW 429.31)

(generation of the nonstabilized ylide (1,3-dioxolan-2-ylmethylene)triphenylphosphorane for Wittig alkenation; synthesis of masked α,β-unsaturated aldehydes from aldehydes; reagent for two-carbon chain homologation[1])

Physical Data: mp 193-195 °C.

Form Supplied in: white solid, 98%.

Preparative Method: from 2-bromomethyl-1,3-dioxolane and triphenylphosphine at 100 °C (36 h).[2]

Purification: recrystallized from methylene chloride/ether.[2]

α,β-Unsaturated Aldehydes.

This phosphonium salt reacts with base to give (1,3-dioxolan-2-ylmethylene)triphenylphosphorane, which is used in situ. Wittig reaction of this nonstabilized phosphorus ylide with aldehydes affords α,β-unsaturated acetals; acidic hydrolysis then provides the corresponding aldehydes. The alkene stereochemistry obtained is highly dependent on the base or solvent used. (*E*)-Alkenes are predominant with lithium methoxide or potassium carbonate in DMF (e.g. eq 1).[2-6] Reactions of the ylide with ketones are generally poor.

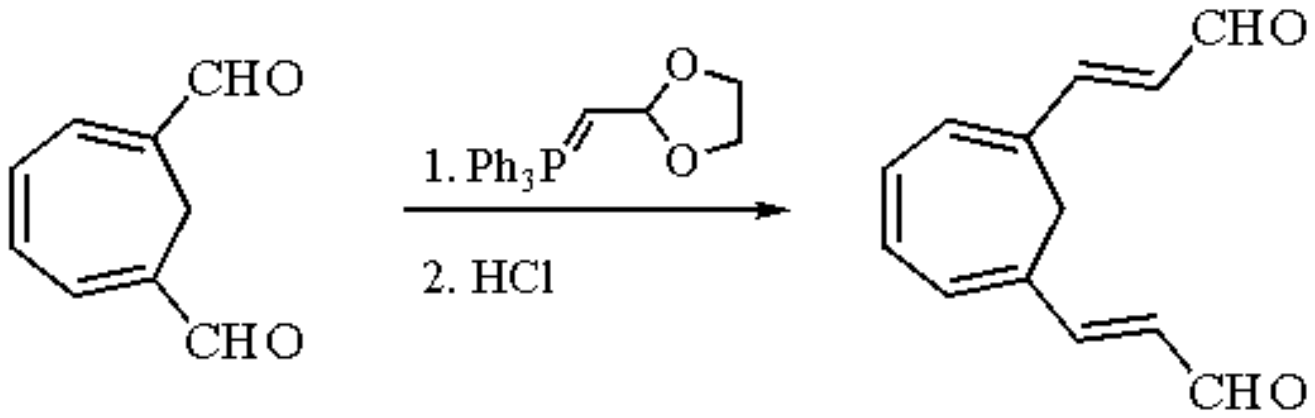

(1)

Fraser-Reid and co-workers studied the stereoselectivity of this reagent in reactions with benzaldehyde involving different bases. When the phosphorane was prepared in THF with ***n-Butyllithium***, only the (*E*)-alkene is formed. With dimsylsodium (***Sodium Methylsulfinylmethylide***) in DMSO a 3:1 ratio of (*Z*)- to (*E*)-isomers is obtained, while addition of THF to the DMSO reaction results in a 8:1 preference for the (*Z*)-isomer.[7] These reaction conditions have been applied to ansamycin precursors (eq 2).[7-9]

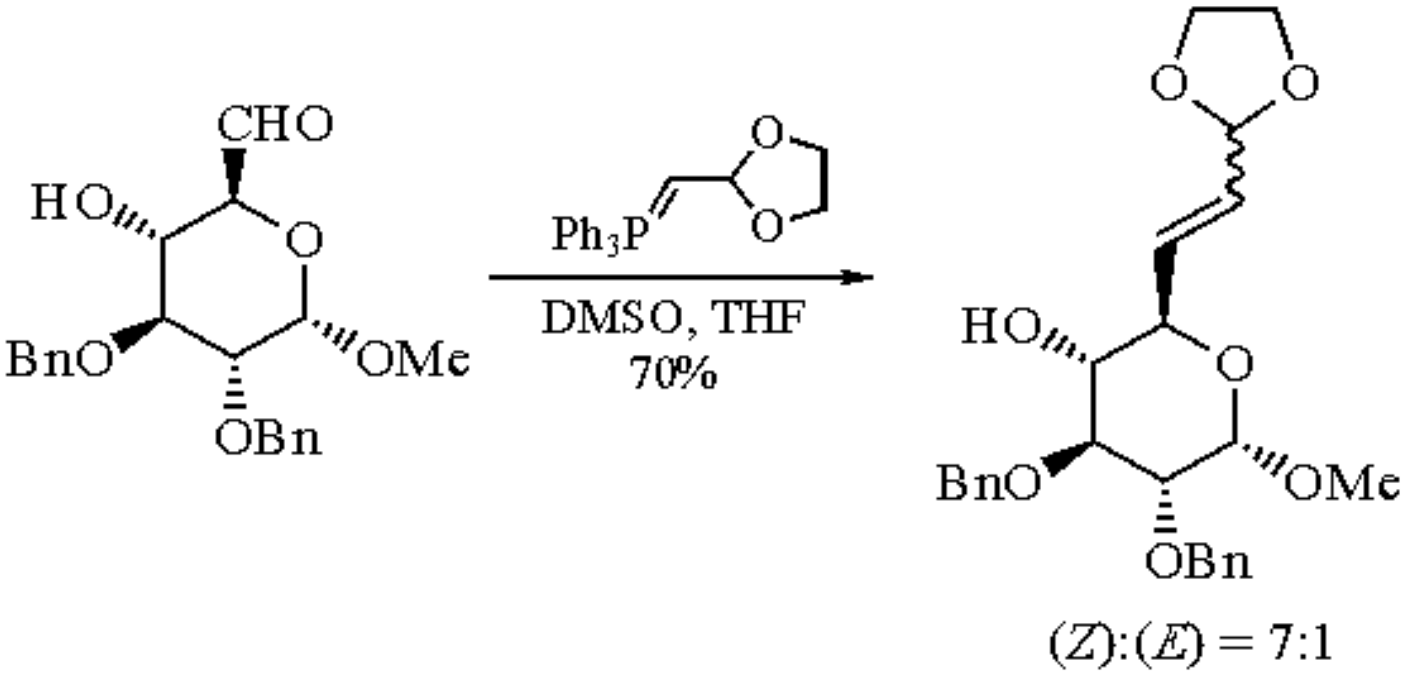

(2)

Also, whereas α-alkoxy aldehydes usually furnish (*E*)-alkenes almost exclusively with ***Formylmethylenetriphenylphosphorane***, Sakai et al. found that (1,3-dioxolan-2-ylmethylene)triphenylphosphorane, generated from the phosphonium reagent by using ***Sodium Hydride*** in THF-HMPA, gives mainly (*Z*)-alkenes (eq 3).[10] Replacing the THF with DMF reduces this preference to ca. 75:25.

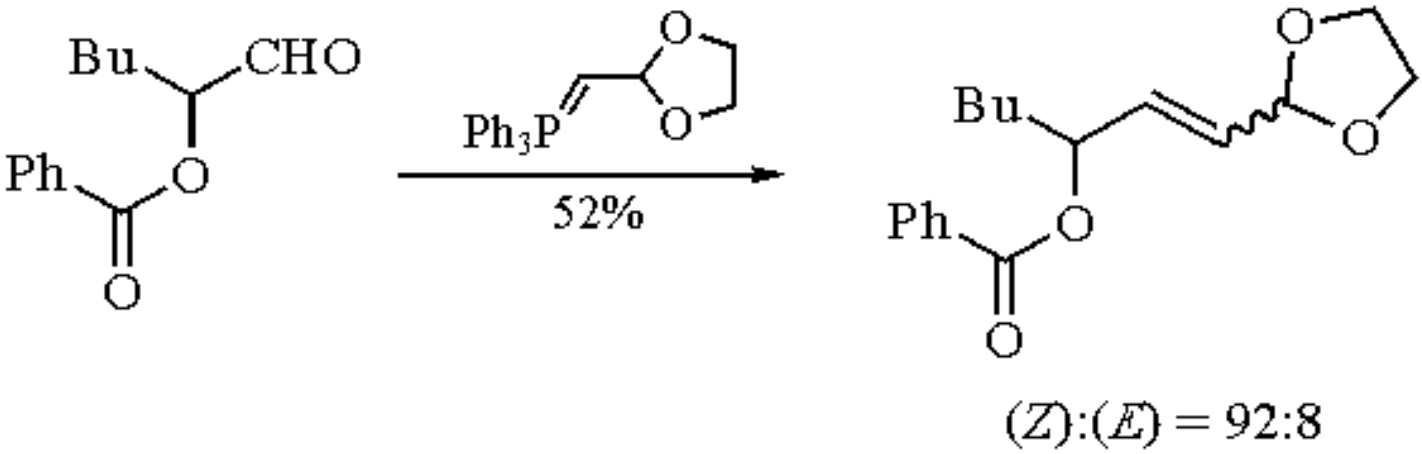

(3)

The Bestmann protocol with formylmethylenetriphenylphosphorane, which involves treatment with EtBr and NaOEt to form a diethyl acetal intermediate, offers a similar means for elaboration of aldehydes into α,β-unsaturated aldehydes chain-extended by two carbons, with high (*Z*) stereoselectivity.[11,12] Related ylide reagents have also been used for such two-carbon homologations.[13]

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Diphenylacetylene

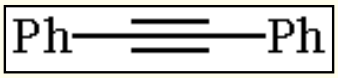

[501-65-5] · $C_{14}H_{10}$ · Diphenylacetylene · (MW 178.24)

(precursor to substituted stilbenes[1,2] and benzil;[3] participant in cycloaddition chemistry;[4] symmetrical π-acidic ligand used widely in organometallic chemistry[5])

Physical Data: mp 62.5 °C; bp 90-97 °C/0.3 mmHg; *d* 0.990 g cm^{-3}.

Solubility: sol ether, hot alcohol.

Form Supplied in: colorless solid; widely available.

Handling, Storage, and Precautions: low oral toxicity; possible danger from absorption through skin.

Introduction.

Due to the symmetry and high degree of planarity of diphenylacetylene, it has enjoyed enormous success as a highly Lewis acidic and sterically accessible alkyne for use in various areas of organic chemistry, as well as in organometallic chemistry where it serves as an excellent ligand of varying hapticity.

Oxidation and Reduction.

The oxidation of diphenylacetylene is reported to proceed under a variety of conditions. Its cleavage to benzoic acid has been accomplished by molybdenum(VI) and tungsten(VI) polyoxometalates,[6] as well as by [bis(trifluoroacetoxy)iodo]pentafluorobenzene.[7] Chromium-based complexes,[3] zinc/chromium,[8] electrooxidation,[9] and ***Barium Manganate***,[10] among others,[11] have been successfully utilized in the oxidation of diphenylacetylene to benzil. However, methods for its oxidation to the monoketone are scarce.[12]

The reduced states of diphenylacetylene are attainable via several efficient methods. (*E*)-Stilbene is produced in 80% yield with the aid of $NiCl_2.4PPh_3$.[1] Hydrogenation over a ruthenium catalyst[2] provides (*Z*)-stilbene, as does the use of $CoCl_2.4PPh_3/SmI_2/AcOH$[13] or zinc in combination with Pd/C.[14] Reduction of the alkyne bond to the alkane level is achieved with the use of hydrogen and a montmorillonite-(diphenylphosphine)palladium(II) complex,[15] or zinc in combination with Pd/C.[14]

Addition of X-Y Across the Alkyne π-Bond.

Addition across the alkynic bond occurs with a number of reagents. Formal addition of RS-Cl (eq 1),[16] PhSe-F,[17] Me_3Sn-PPh_2, PhS-F, PhS-SPh,[18] and ClHg-OAc[19] proceeds in *trans* fashion in each instance. However, similar addition of Bu_3Sn-H (eq 2),[20] RNH-H,[21] and HO_2C-H[22] leads to the formation of *cis*-stilbene derivatives. H-CN,[23] TMS-CN,[24] X_2 (X = halogen),[25] Et-$AlEt_2$,[26] and Al-H[27] additions to diphenylacetylene have also been reported.

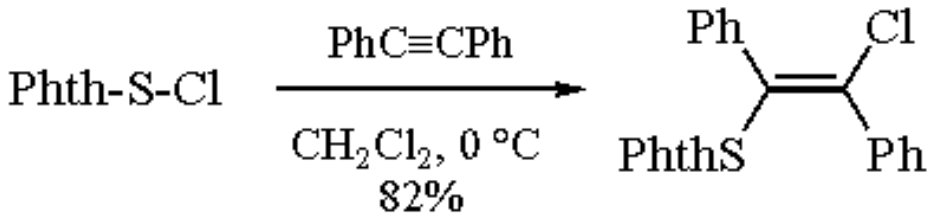

(1)

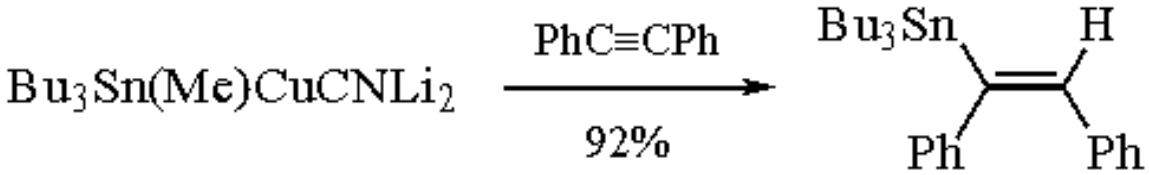

(2)

Susceptibility to Carbene Addition.

Diphenylacetylene undergoes addition with chromium, tungsten, and cobalt[28] carbenes. Chromium Fischer-type carbenes react with diphenylacetylene to form cyclopentenones (eq 3).[29] Pyrrolinones are accessed when nitrogen is present in the chromium carbene reagent (eqs 4 and 5).[30] Tungsten carbenes of the Fischer class respond differently in that they form seven-membered rings (eq 6).[31] Diphenylacetylene has also demonstrated an ability to undergo facile cycloaddition with *ortho*-manganated aryl ketones to afford inden-1-ols (eq 7).[32]

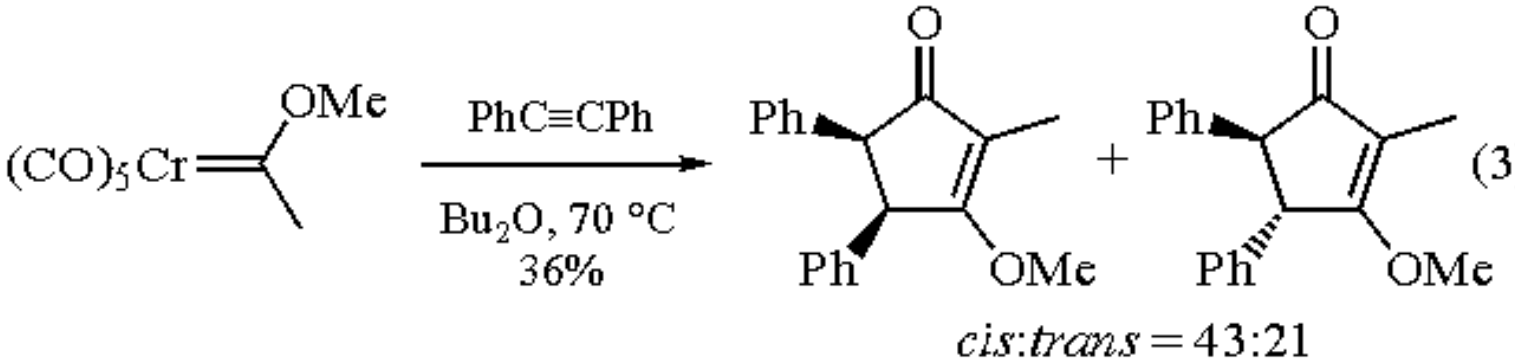

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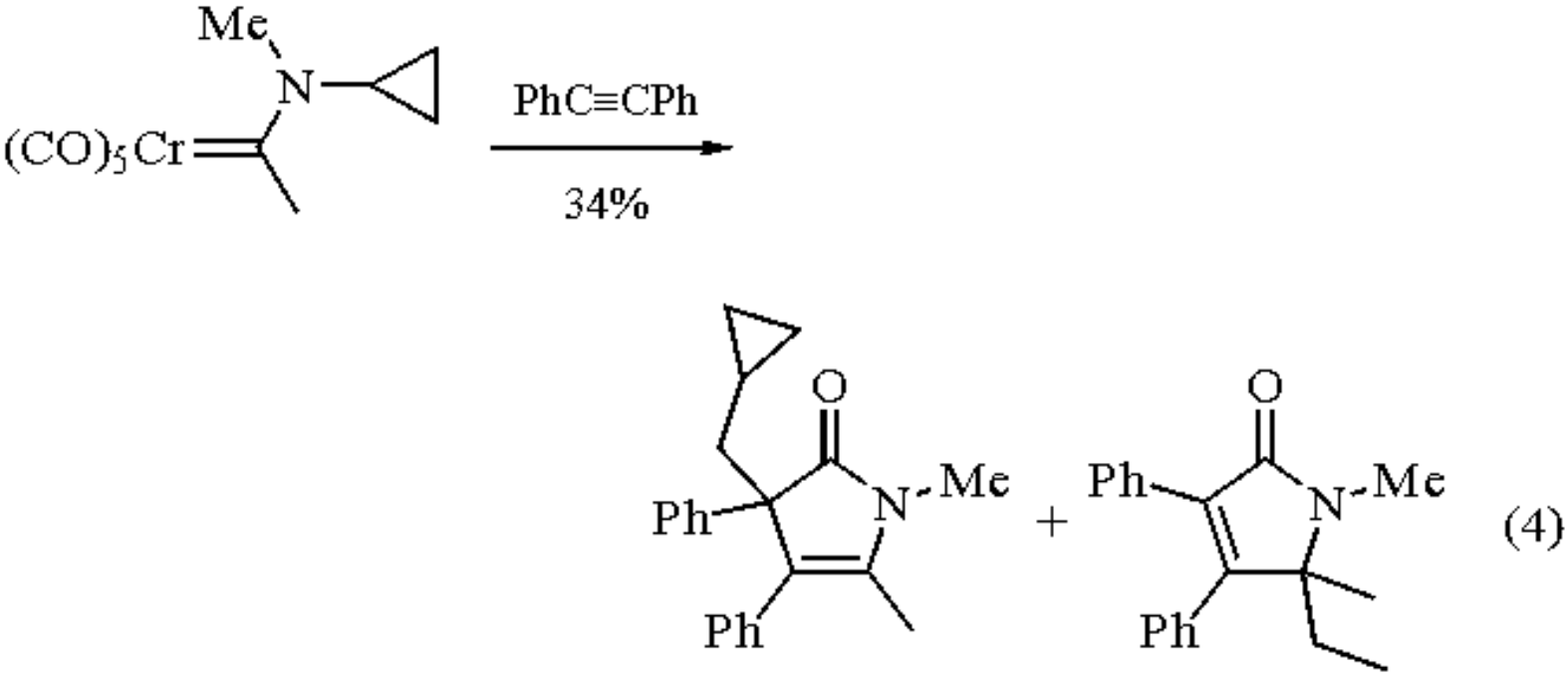

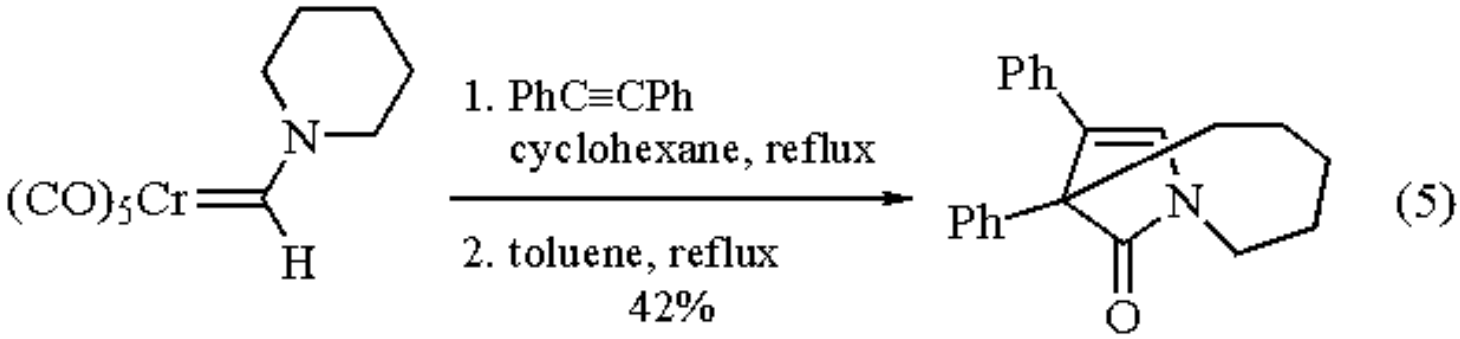

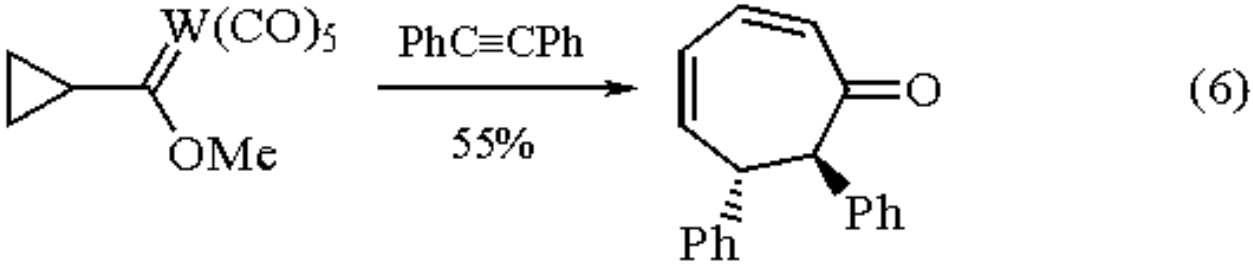

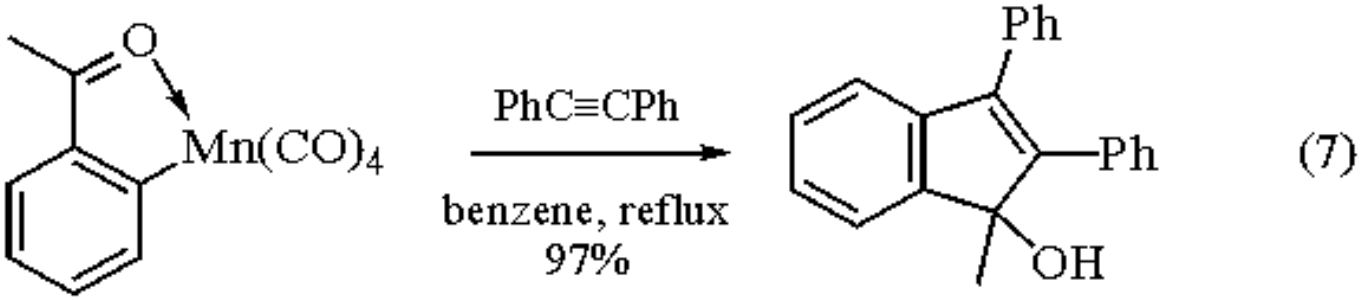

Interaction with Various Metals.

The response of diphenylacetylene to palladium in coupling[33] and annulation (eq 8)[34] transformations is well documented. Spiroannulation has been effected with the aid of nickel (eq 9),[35] and insertion into zirconium complexes has been shown to provide a variety of unsaturated molecules.[36] Finally, diphenylacetylene has exhibited a general propensity for ligating to organometallic complexes[37] and clusters,[38] and to be capable of engaging in metathesis reactions.[39]

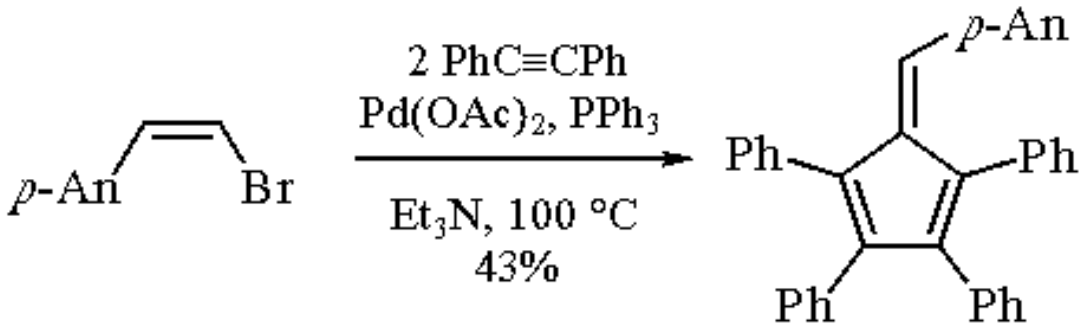

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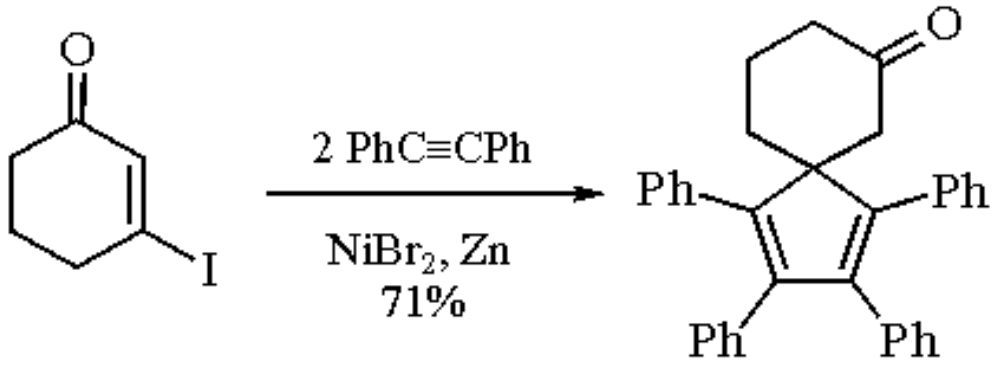

(9)

Ring Formation and Cycloaddition.

Incorporation of a vicinal diphenyl group into rings of various types has been demonstrated repeatedly. Oxazoles,[40] benzothiophenes,[41] indoles,[42] pyrroles,[43] and furan-2(5*H*)-ones[44] among others[45] containing this arrangement have been reported. Ring construction that involves the diphenylacetylene moiety has been accomplished in various ways. Diphenylacetylene undergoes cycloaddition to ketenes of several types, with subsequent fragmentation and rearrangement (eqs 10 and 11).[46]

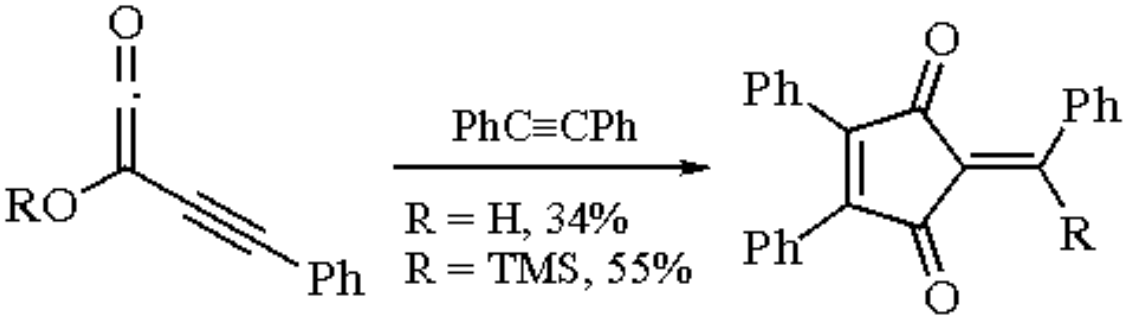

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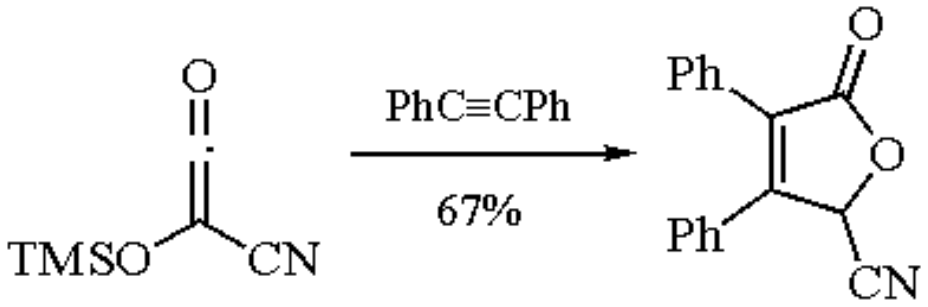

(11)

Diphenylacetylene participates satisfactorily in Pauson-Khand reactions.[47] Furthermore, [3 + 3] cycloaddition with azomethine ylides provides the respective pyrrole in good yield (eq 12).[48] Examples of [4 + 2],[49] [2 + 2],[50] 1,3-dipolar,[51] and other cycloadditions[52] have been widely reported.

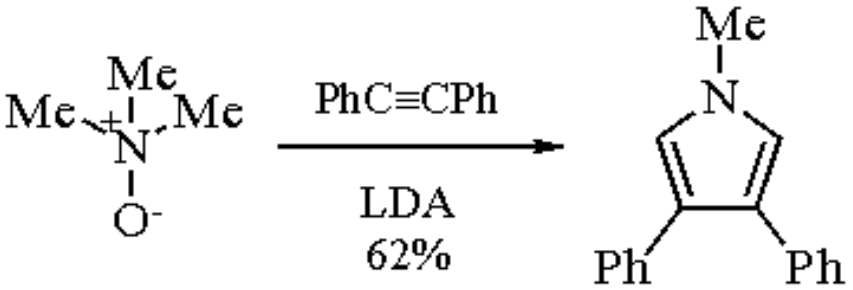

(12)

Related Reagents.

Dimethyl Acetylenedicarboxylate.

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Jeffrey N. Johnston

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Diphenylacetyl Chloride

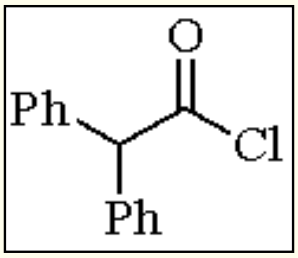

[1871-76-7] · $C_{14}H_{11}ClO$ · Diphenylacetyl Chloride · (MW 230.70)

(preparation of diphenylketene[1])

Physical Data: mp 49-53 °C; bp 175-176 °C/17 mmHg.

Form Supplied in: 90% technical grade.

Preparative Method: by the action of ***Thionyl Chloride*** on diphenylacetic acid.[2]

Handling, Storage, and Precautions: corrosive; a lachrymator. Use in a fume hood.

Diphenylacetyl chloride is used as the principal reagent in the preparation of diphenylketene.[1] Diphenylacetyl chloride reacts with ***Triethylamine*** in an inert solvent such as ether or benzene, at rt, to give 53-57% yield of diphenylketene (eq 1). The ketene may be isolated for subsequent use (eq 2).[2] More frequently, diphenylketene is generated in situ (eq 3).[3]

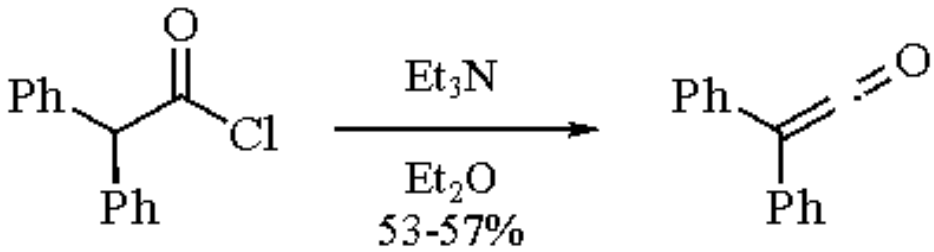

(1)

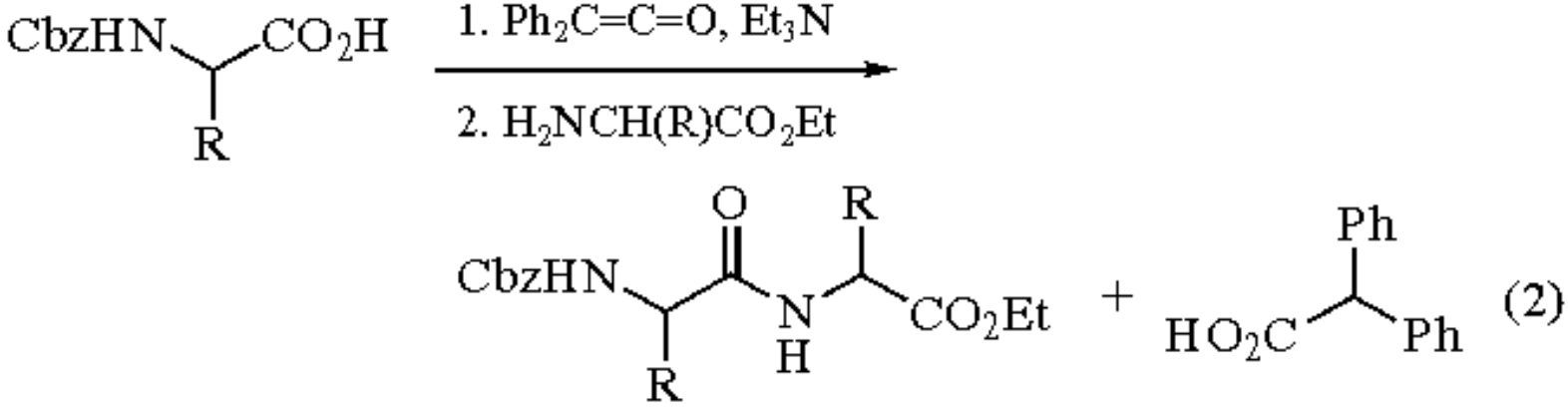

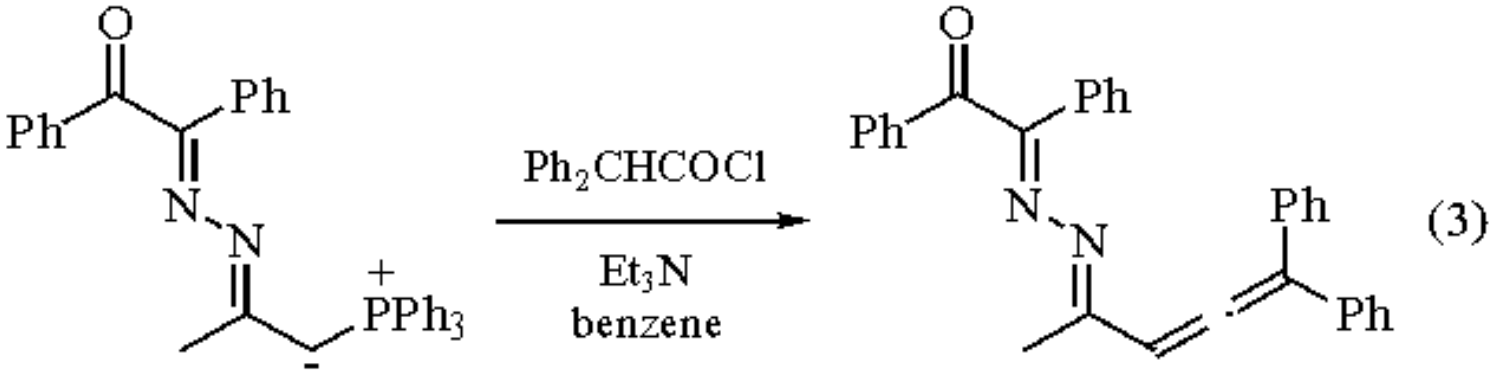

Diphenylacetyl chloride has been used in the synthesis of thiol esters via thiolate ions supported on the anion exchanger Amberlyst A-26. Many acid chlorides have been reacted in this manner (eq 4).[4]

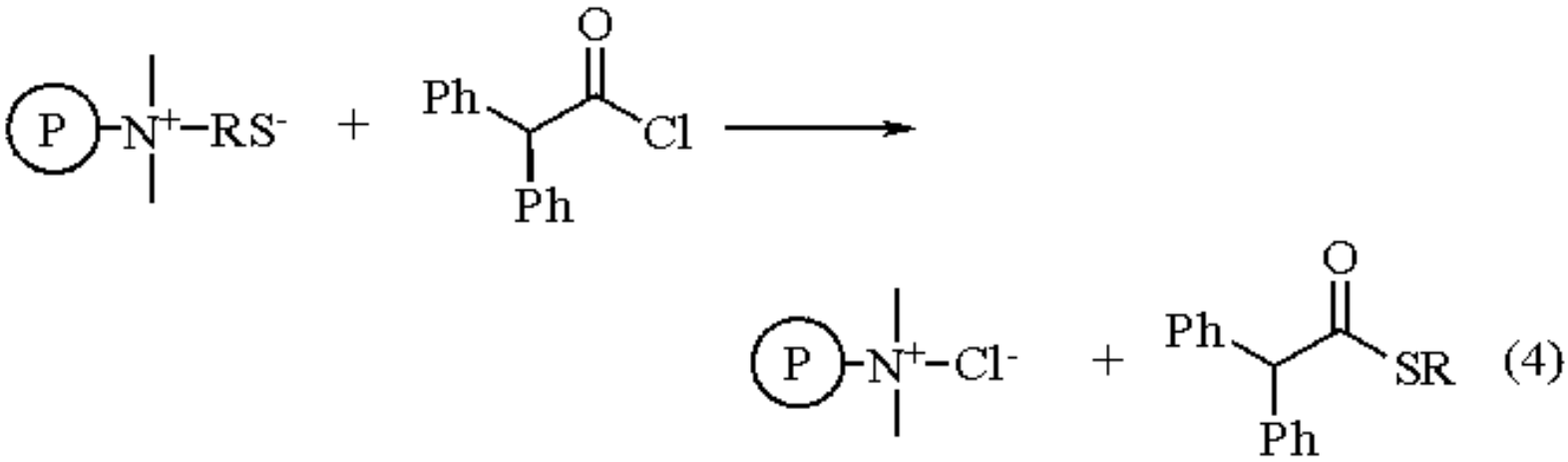

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Regina Zibuck

(Diphenylarsinyl)methyllithium[1]

$Ph_2As(O)CH_2Li$

[61024-99-5] · $C_{13}H_{12}AsLiO$ · (Diphenylarsinyl)methyllithium · (MW 266.11)

(indirect nucleophilic halomethylation[2] and haloalkylation[3] of aldehydes, ketones, alkyl halides, and epoxides; synthesis of 2-hydroxy-1,2λ^5-oxarsolanes,[1,4] 1,2-bis(diphenylarsinyl)ethane, 1,2-bis(diphenylarsino)ethane (diars), and 1-diphenylarsino-2-(diphenylarsinyl)ethane[5])

Solubility: sol THF.

Preparative Method: quantitatively formed as a yellow solution in THF by treating the easily accessible (diphenylarsinyl)methane[6] with LDA at -40 °C (eq 1).

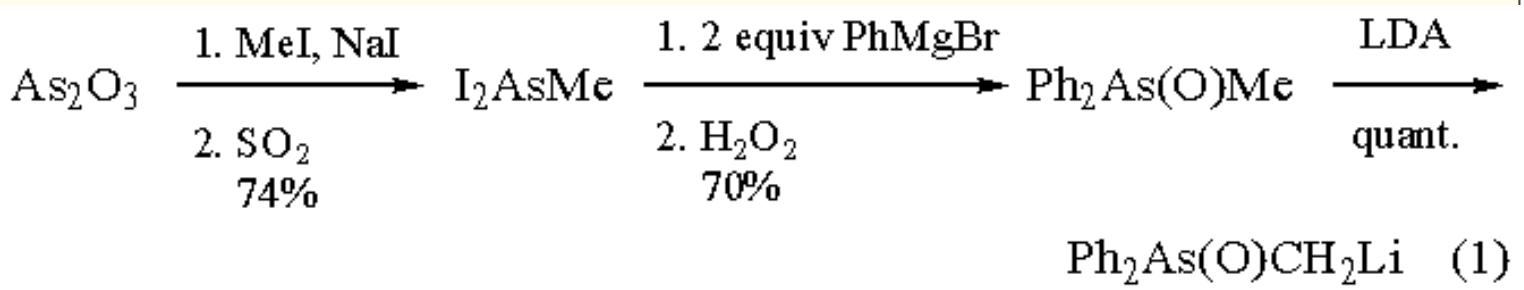

Handling, Storage, and Precautions: handle and store the THF solution of $Ph_2As(O)CH_2Li$ under N_2 or Ar; $Ph_2As(O)Me$ (mp 153-154 °C) is stable in air but toxic. Use in a fume hood.

Indirect Nucleophilic Halomethylation and α-Haloalkylation.

$HalCH_2Li$ and HalCH(Alk)Li would be interesting reagents for nucleophilic halomethylation and α-haloalkylation, but they are quite unstable due to carbene formation. Ph_2AsCH_2Li[7] is an attractive synthetic equivalent for $HalCH_2Li$, but $Ph_2As(O)CH_2Li$ is more accessible and more reactive. Treatment of this reagent with electrophiles (aldehydes, ketones, alkyl halides) followed by ***Lithium Aluminum Hydride*** and then with halogen (Br_2, I_2) or ***Thionyl Chloride*** affords halogen compounds (e.g. β-hydroxy alkyl halides) in preparatively useful yields (eq 2; R = H).[2] The yield determining step is the reaction with the electrophile, according to eqs 3 and 4.

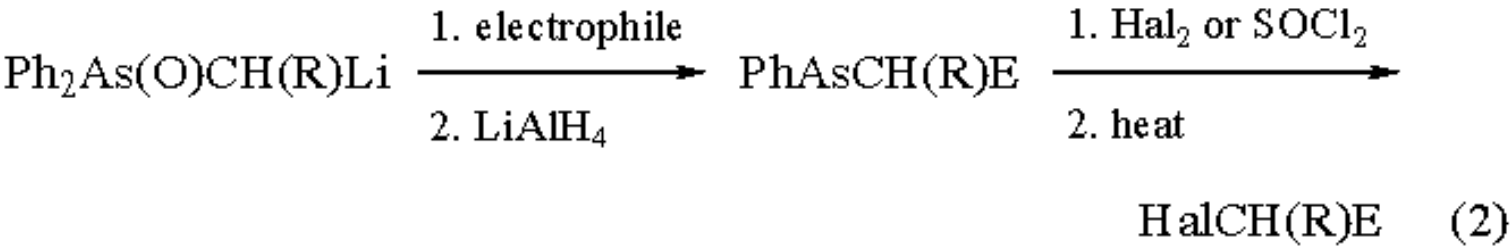

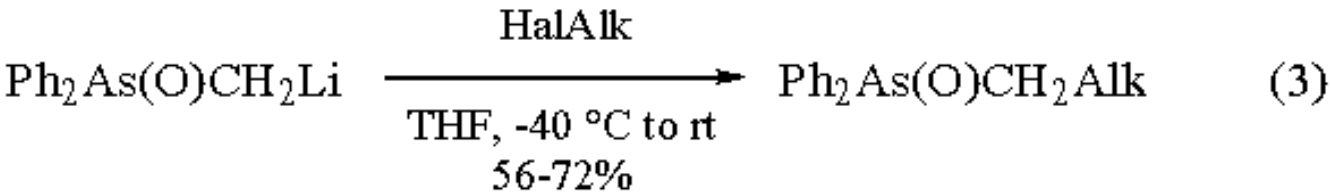

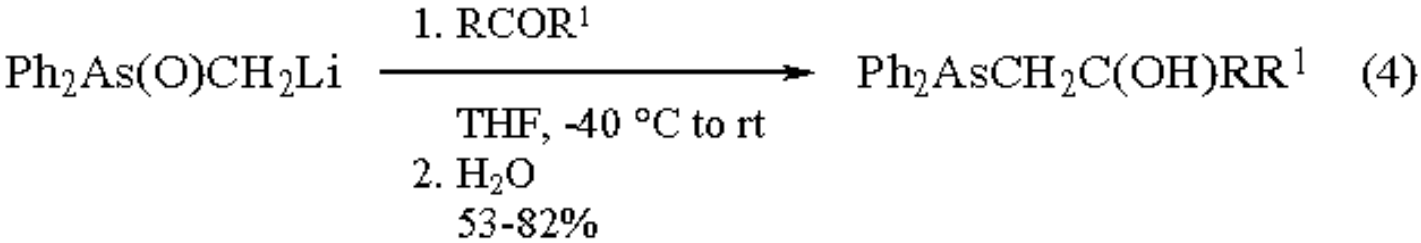

Like $Ph_2As(O)Me$, the higher homologs (prepared as in eq 3) can be lithiated at the methylene group α to the As atom by ***Lithium Diisopropylamide***. The resulting compounds provide entry to functionalized hydrocarbons according to eq 2 (R = Alkyl).[3] ***Sulfuryl Chloride*** is particularly useful as a reagent for replacing the diphenylarsino group by chlorine. Also the methine group of *s*-butyldiphenylarsine oxide is lithiated by LDA (80%). α-Lithiated alkyldiphenylarsine oxides react extremely diastereoselectively with benzaldehyde or acetophenone.[3b]

Synthesis of 2,2-Diphenyl-2-hydroxy-1,2λ^5-oxarsolanes.

The treatment of terminal epoxides with $Ph_2As(O)CH_2Li$ and subsequently with H_2O leads to 2,2-diphenyl-2-hydroxy-1,2λ^5-oxarsolanes (eq 5), which are smoothly reduced by $LiAlH_4$ to γ-hydroxy alkyl arsines. These undergo halogenolysis to give γ-hydroxy alkyl halides.[1,4]

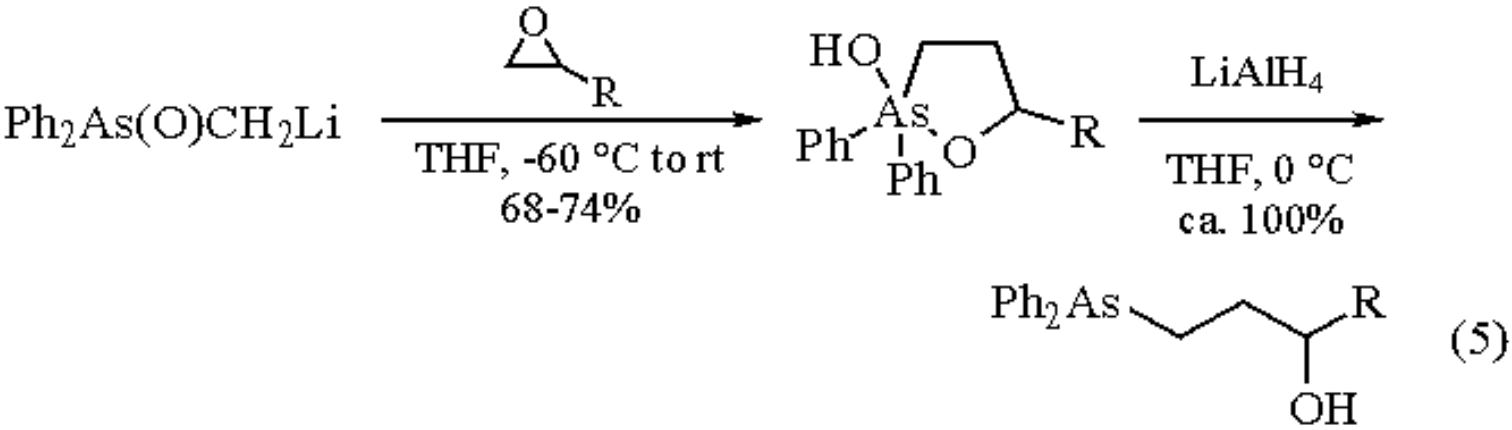

Coupling.

$Ph_2As(O)CH_2Li$ reacts with ***Copper(II) Chloride*** to give 1,2-bis(diphenylarsinyl)ethane (64%), which is quantitatively reduced by $LiAlH_4$ to 1,2-bis(diphenylarsino)ethane, the important ligand diars for transition metals (eq 6). ***Sodium Borohydride*** can be used to obtain the corresponding monooxide (88%).[5]

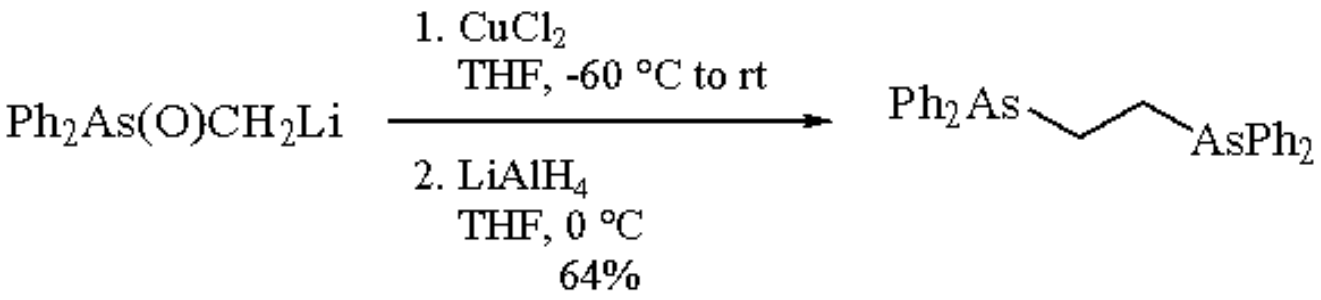

(6)

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1,1-Diphenyl-2-azaallyllithium[1]

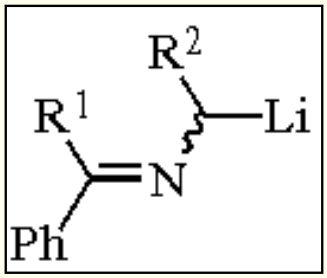

(**1**; R^1 = Ph, R^2 = H)

[64042-43-9] · $C_{14}H_{12}LiN$ · 1,1-Diphenyl-2-azaallyllithium · (MW 201.21) (**2**; R^1 = H, R^2 = Ph)

[37019-83-3]

(agents for the nucleophilic aminomethylation of ketones and alkyl halides;[2] react with C=C, C=N, C=S, and N=N double bonds as well as with C&tbond;C and C&tbond;N triple bonds by [3 + 2] cycloaddition with high regioselectivity and stereospecificity;[3] corresponding cycloadditions with *N*-benzylidenebenzylamine[1])

Solubility: sol THF; slightly sol Et_2O.

Preparative Methods: 1,1-diphenyl- (**1**) and 1,3-diphenyl-2-azaallyllithium (**2**)[4] are prepared by deprotonation of *N*-(diphenylmethylene)methylamine or *N*-benzylidenebenzylamine, respectively, with ***Lithium Diisopropylamide*** in THF or Et_2O/THF at ca. -60 °C. Solutions thus prepared contain diisopropylamine. Amine-free solutions of *cis,trans*-(**2**) are obtained by thermal conrotatory ring opening of *N*-lithio-*cis*-2,3-diphenylaziridine in THF.[4] *cis,trans*-(**2**) is labile[4] and isomerizes readily at 20 °C[1] to give *trans,trans*-(**2**); 1-phenyl-2-azaallyllithium is prepared similarly.[1] Aliphatic substituted 2-azaallyllithium reagents are prepared by stannyl-lithium exchange.[5]

Handling, Storage, and Precautions: solutions of (**1**) and *trans,trans*-(**2**) in THF are stable at -30 °C under N_2 or Ar for days. No special precautions are necessary.

Indirect Nucleophilic Aminomethylation and Synthesis of 2-Azabutadienes.

Reaction of (**1**) with ketones yields hydroxy azomethines which are of preparative interest since they provide β-amino alcohols on hydrolytic cleavage with acids (eq 1).[2] Dehydration of the hydroxy azomethines with ***Thionyl Chloride***/***Pyridine*** provides an entry to 2-azabutadienes.[2c] Nucleophilic aminomethylation of alkyl bromides is also

possible (eq 2).[2a,c] With a chiral, optically active derivative of (**2**), a highly enantioselective amine synthesis has been developed (eq 3).[6] In addition, from the 3-cyano analog a synthesis of α-amino acids (eq 4) has been developed,[7] and the 3-vinyl analog is known.[8]

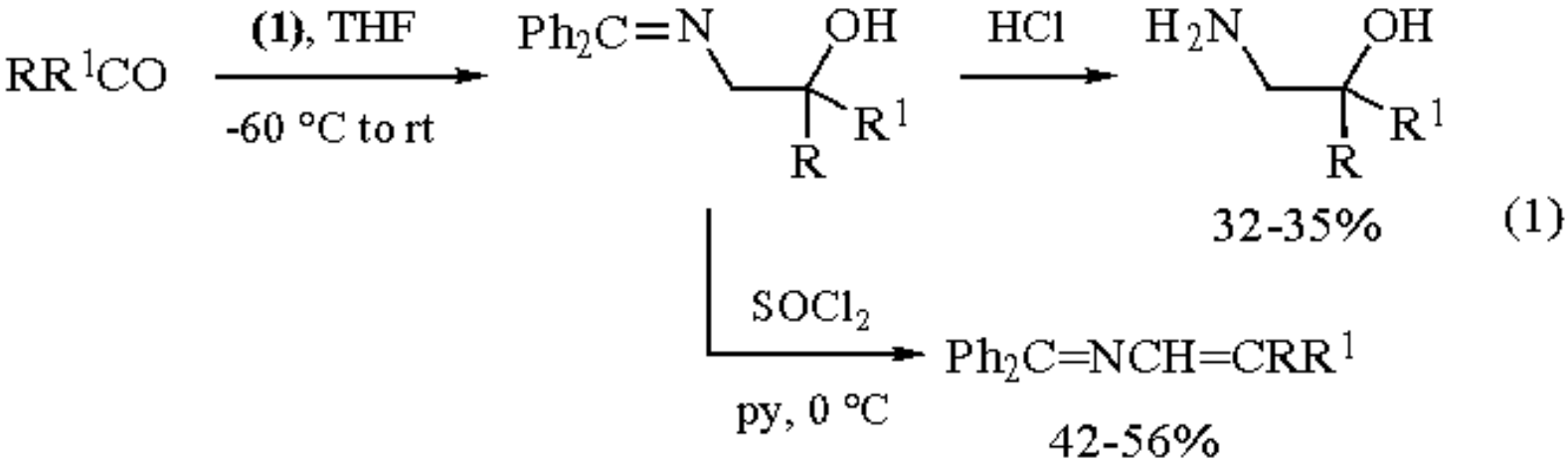

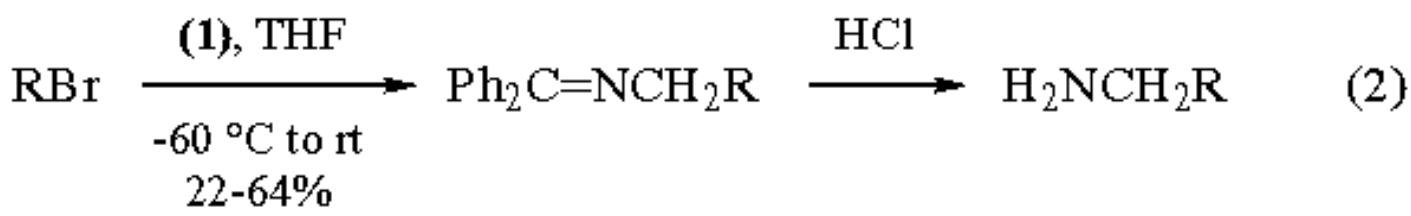

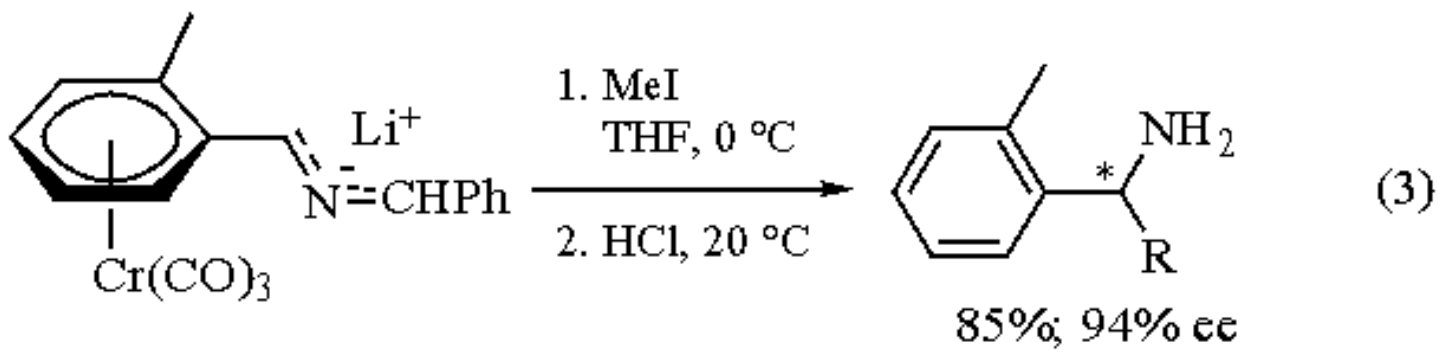

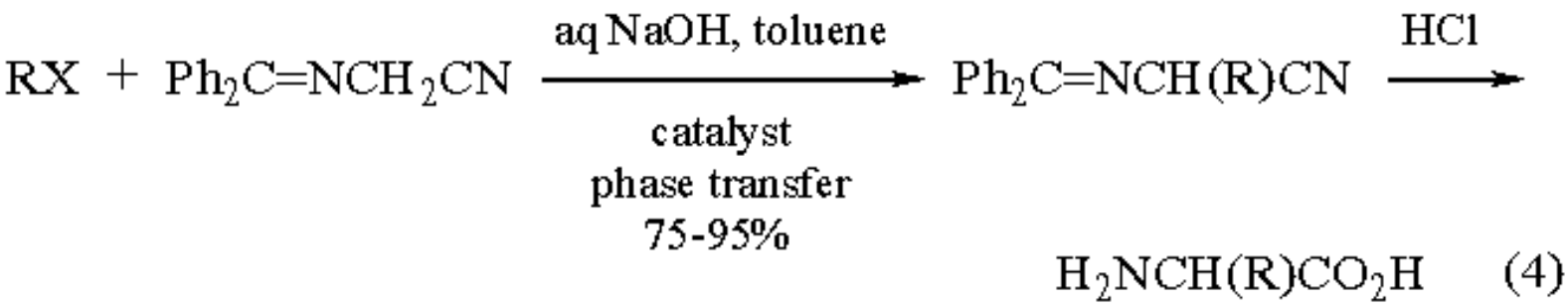

Stoichiometric 1,3-Anionic Cycloaddition.

(**1**) and (**2**) react with C=C, C=N, N=N, and C=S double bonds as well as with C&tbond;C and C&tbond;N triple bonds by [3 + 2] cycloadditions. In contrast to unstrained isolated C=C double bonds, one of the strained isolated C=C double bonds of norbornadiene undergoes 1,3-anionic cycloaddition with (**1**) or (**2**) to give pyrrolidines.[1] Compounds

with an alkenic double bond conjugated with an aromatic system[3,9] or an organoelement group[10] (PhS-, PhSe-, Ph_2P-, Ph_2As-, Ph_3Ge-, $Ph_2(O)P$-, $Ph_2(O)As$-; not PhTe-, Ph_2Sb-, Ph_3Sn-, Ph_3Pb-) are better 1,3-anionophiles. The cycloadditions with (**1**) can occur with high regioselectivity (e.g. eq 5) with aryl alkenes.[4] In addition, the cycloaddition of *cis,trans*-(**2**) with *trans*-stilbene (eq 6) or of *trans,trans*-(**2**) with *trans*-stilbene (eq 7) or with *cis*-stilbene occurs stereospecifically with respect to the alkene and the 2-azaallyl component (*cis* addition in each case).[4,11]

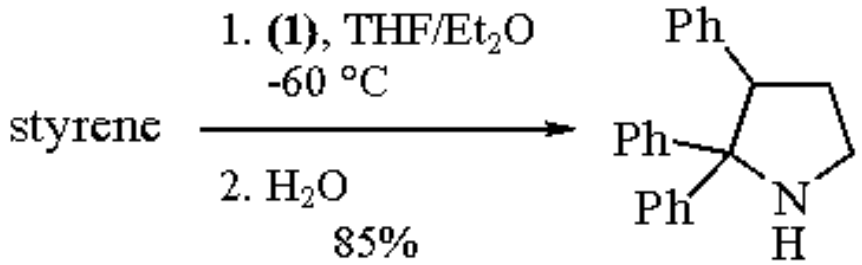

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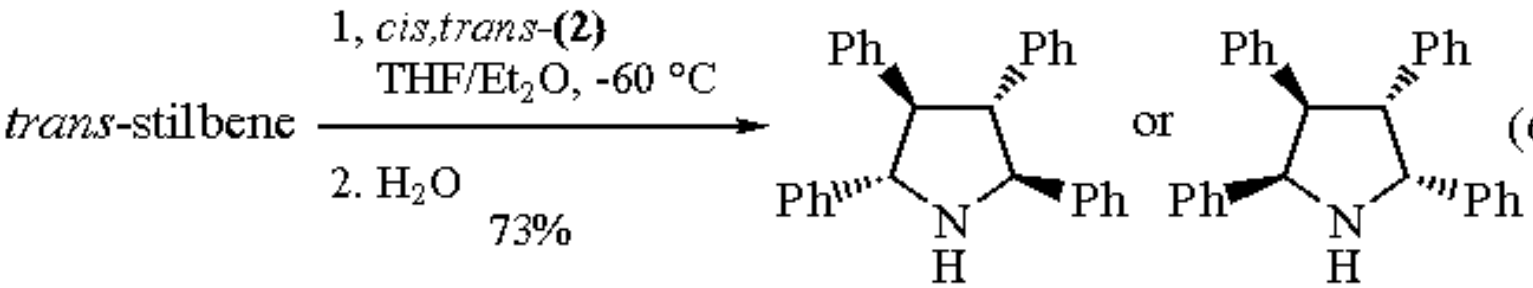

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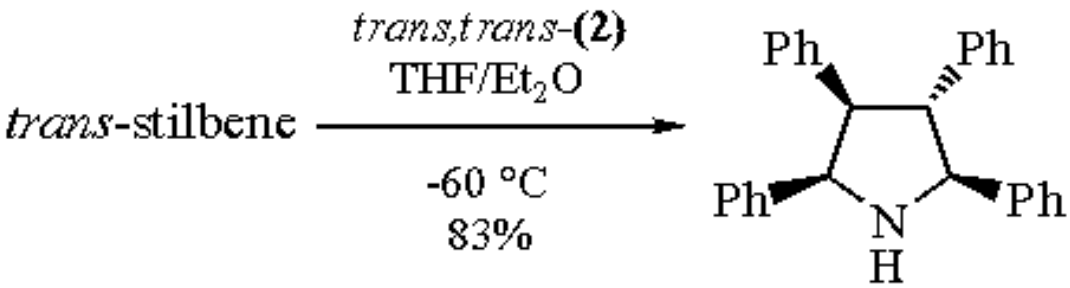

(7)

Cycloaddition of the 1,3-diphenyl-2-azaallyl anion (generated by a phase transfer technique) to cyclohex-2-enone derivatives yields bicyclic pyrrolidine derivatives (eq 8).[12] An intramolecular 2-azaallyl anion [3 + 2] cycloaddition has also been reported (eq 9).[5]

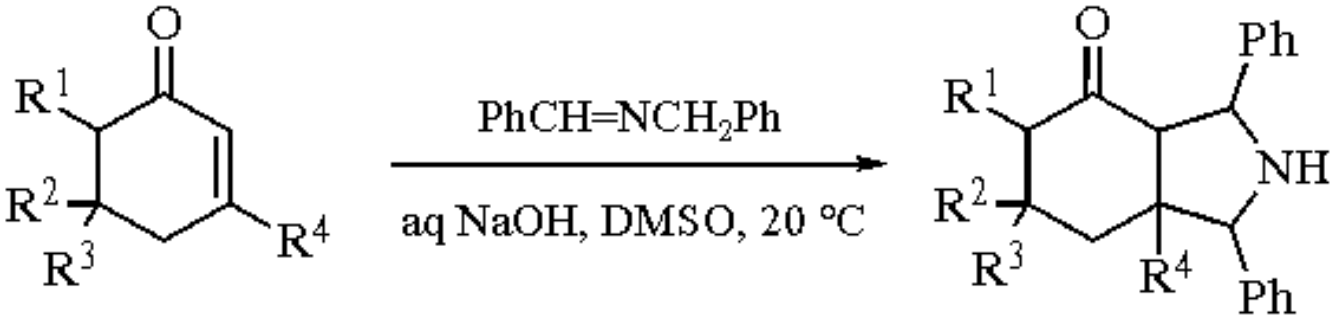

(8)

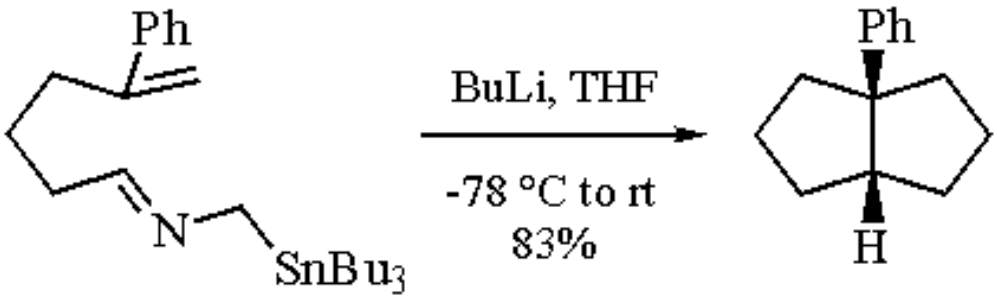

(9)

(**1**) and (**2**) react with 1,3-dienes[13] to afford pyrrolidines (e.g. eq 10); seven-membered cycloadducts cannot be detected.

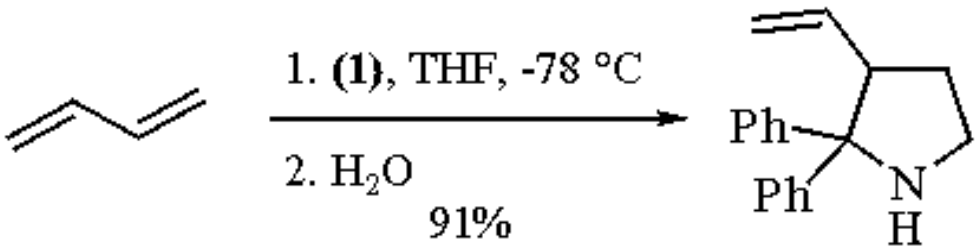

(10)

(**2**) undergoes cycloaddition to aromatic azomethines and azo compounds (e.g. eq 11).[14] In contrast, (**1**) (which is generally more prone to form open-chain adducts than **2**) gives the expected cycloadduct only with *p,p´*-azotoluene, but with azobenzene and azomethines open-chain adducts are formed.[1]

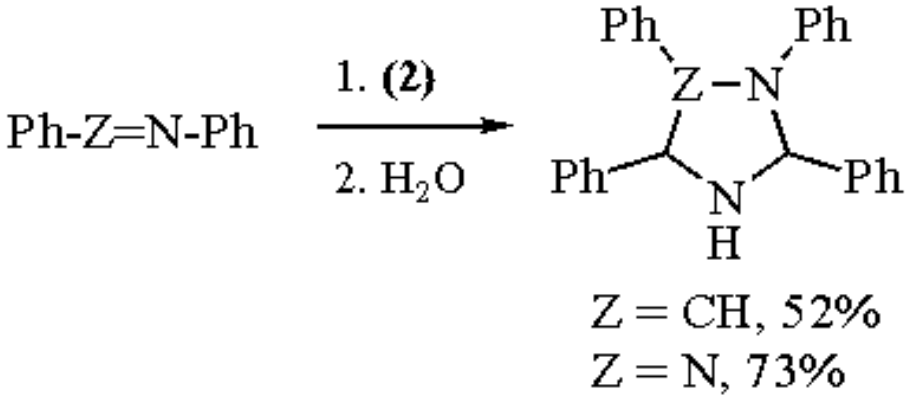

(11)

(**2**) reacts with ***Phenyl Isocyanate*** and ***Phenyl Isothiocyanate*** according to eq 12.[15] (**2**) also reacts with phenylallenes[16] to produce methylenepyrrolidines. The use of diphenylcarbodiimide and CS_2 as substrates generates cycloadducts to which a secondary reaction occurs (e.g. eq 13), whereas CO_2 gives an open-chain product.

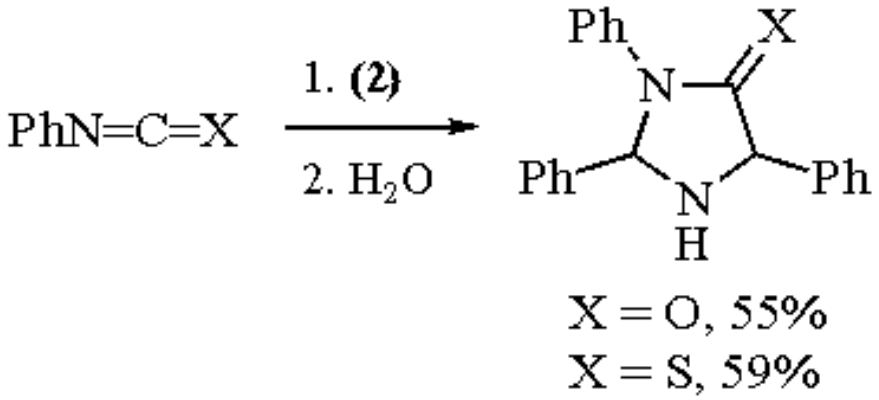

(12)

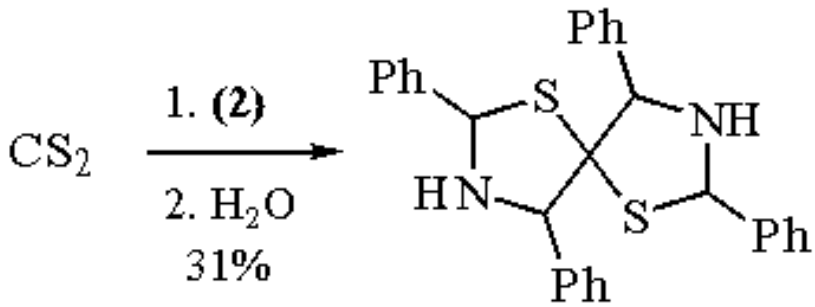

(13)

It has proved impossible to effect cycloaddition of (**1**) and (**2**) with terminal alkynes or with aliphatic nitriles having a hydrogen in the α-position to the cyano group. Internal alkynes and nitriles[1,17] normally react with (**1**) to give a cycloaddition product (e.g. eq 14). However, with (**2**), the corresponding aromatic ring system is generated instead of the cycloadduct (e.g. eq 15).

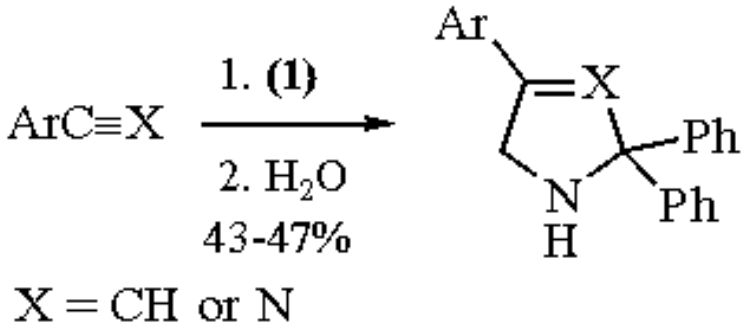

(14)

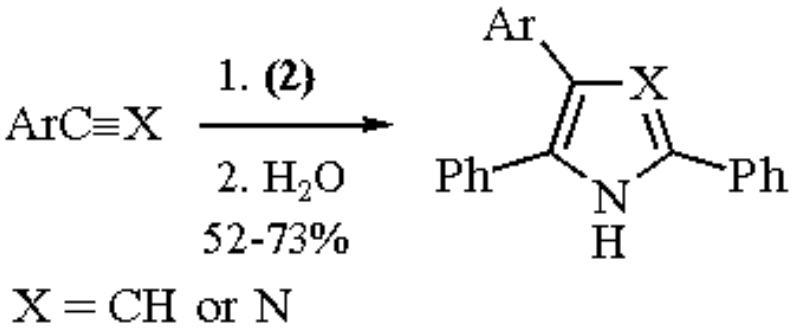

(15)

Catalytic 1,3-Anionic Cycloaddition with LDA as Catalyst.

Whereas, for unknown reasons, the use of *N*-(diphenylmethylene)methylamine (educt of **1**) in such reactions has

produced satisfactory results only in two cases, the yields of the cycloadducts obtained with benzylidenebenzylamine (educt of **2**) are generally good, and both *trans,trans*-(**2**) and *cis,trans*-(**2**) participate in cycloaddition.[1] Eq 16 shows the LDA-catalyzed polymerization of a vinyl derivative of *N*-benzylidenebenzylamine.[1]

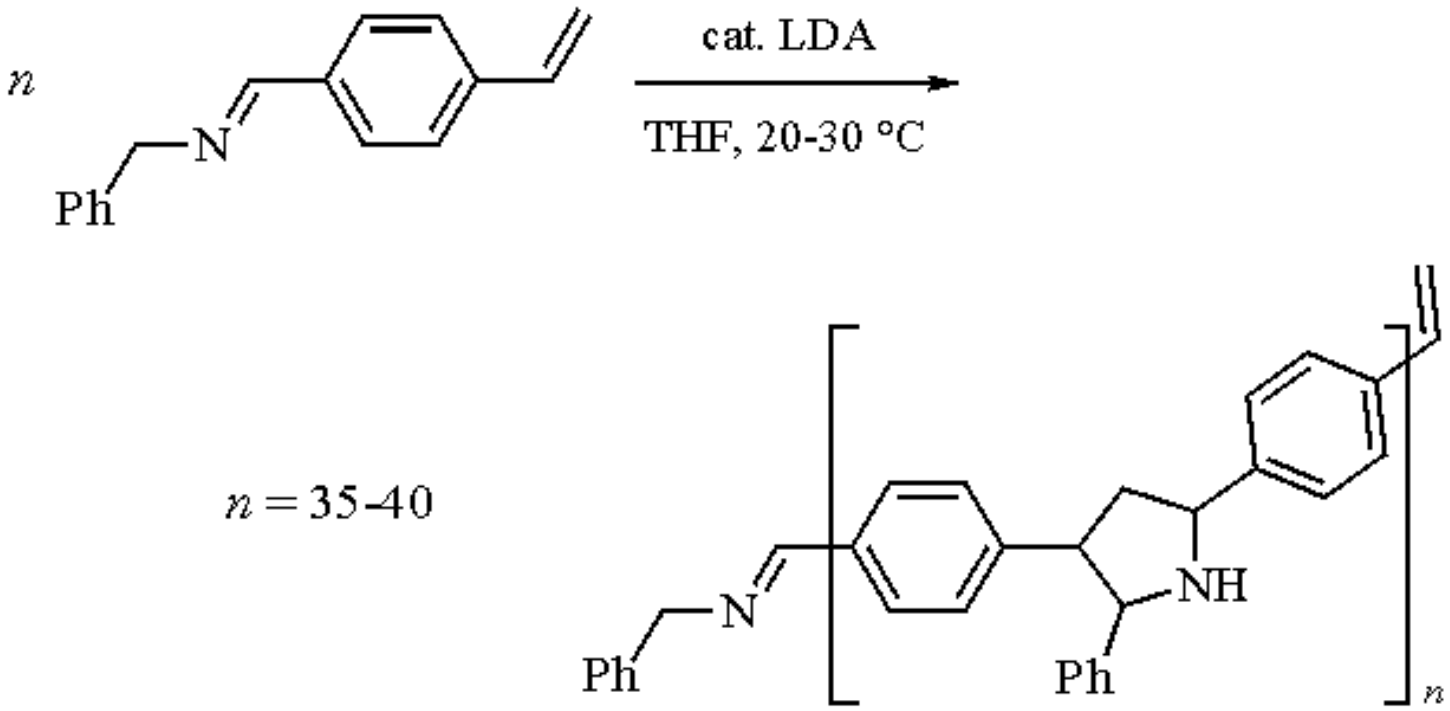

(16)

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Thomas Kauffmann

Diphenylbis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)sulfurane[1]

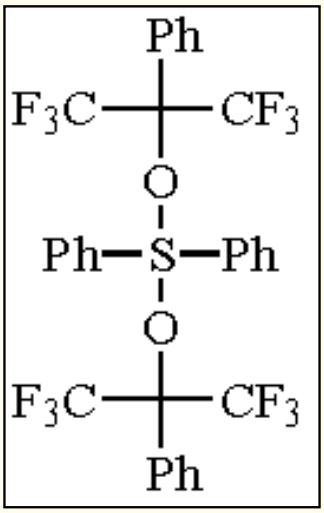

[32133-82-7] · $C_{30}H_{20}F_{12}O_2S$ · Diphenylbis(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxy)sulfurane · (MW 672.57)

(dehydration of alcohols;[2] synthesis of epoxides and cyclic ethers;[3] cleavage of amides;[5] oxidation of amines[6])

Physical Data: mp 107-109 °C.

Solubility: sol ether, benzene, acetone, alcohols.

Form Supplied in: white crystals.

Analysis of Reagent Purity: NMR, IR.

Preparative Method: by the reaction of the potassium salt of 1,1,1,3,3,3-hexafluoro-2-phenylisopropanol with diphenyl sulfide in the presence of chlorine in ether at -78 °C.[1a]

Handling, Storage, and Precautions: avoid moisture; readily hydrolyzed; stable at rt; decomposes slowly at rt in solution.

Dehydration of Alcohols.

The title reagent (**1**) is useful for the dehydration of alcohols. In general, tertiary alcohols are dehydrated

instantaneously at rt. Some secondary alcohols are dehydrated. In cyclohexane rings, a *trans*-diaxial orientation of the leaving groups significantly increases the rate of elimination (eq 1). Primary alcohols do not yield products of dehydration unless the β-proton is sufficiently acidic. In most cases, the ether [$(CF_3)_2PhCOR$] is obtained.[2]

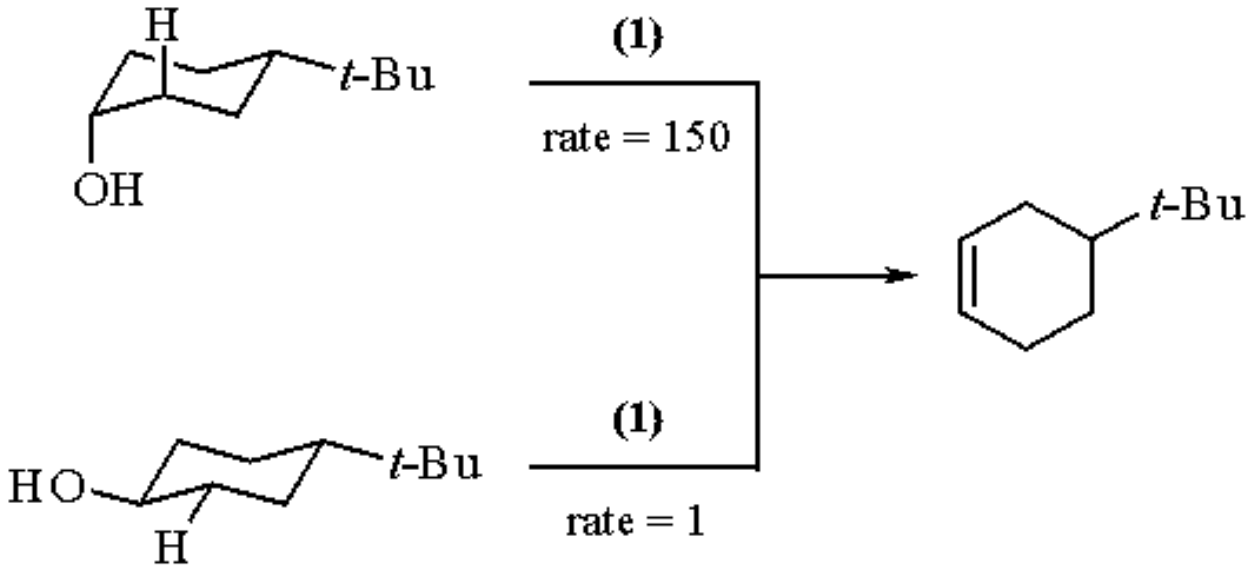

(1)

Epoxides.

Vicinal diols, capable of attaining an antiperiplanar relationship, can be converted to epoxides (eq 2). The reaction requires 1-2 equiv of (**1**) in chloroform, ether, or carbon tetrachloride and takes place at rt. The reaction is postulated to take place via ligand exchange with the sulfone followed by decomposition to the epoxide, diphenyl sulfoxide, and 1,1,1,3,3,3-hexafluoro-2-phenylisopropanol.

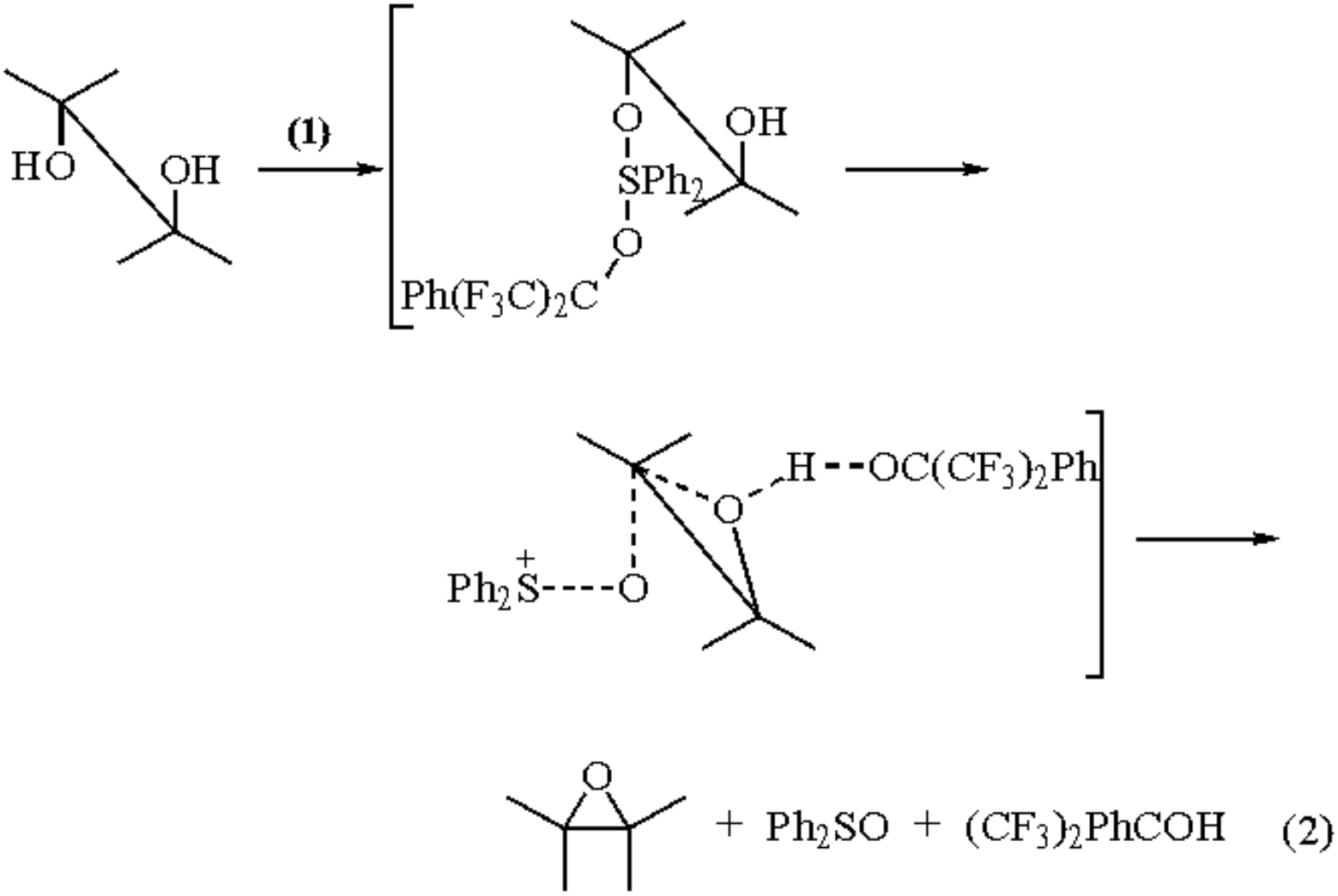

Other cyclic ethers have been prepared, but yields are highly dependent on product ring size. The following transformations are representative: 2,2-dimethyl-1,3-propanediol to 3,3-dimethyloxetane (86%), 1,4-butanediol to tetrahydrofuran (72%), 1,5-pentanediol to tetrahydropyran (39%), and diethylene glycol to dioxane (40%). Longer chain diols yield ethers [$(CF_3)_2PhCO(CH_2)_nOCPh(CF_3)_2$].[3]

Eschenmoser used this method to convert (5*R*,6*R*)-5,6-dihydro-β,β-carotene-5,6-diol to its epoxide (eq 3). This reagent is more effective than other reagents due to the unique solubility profile of the dihydrocarotenediol.[4]

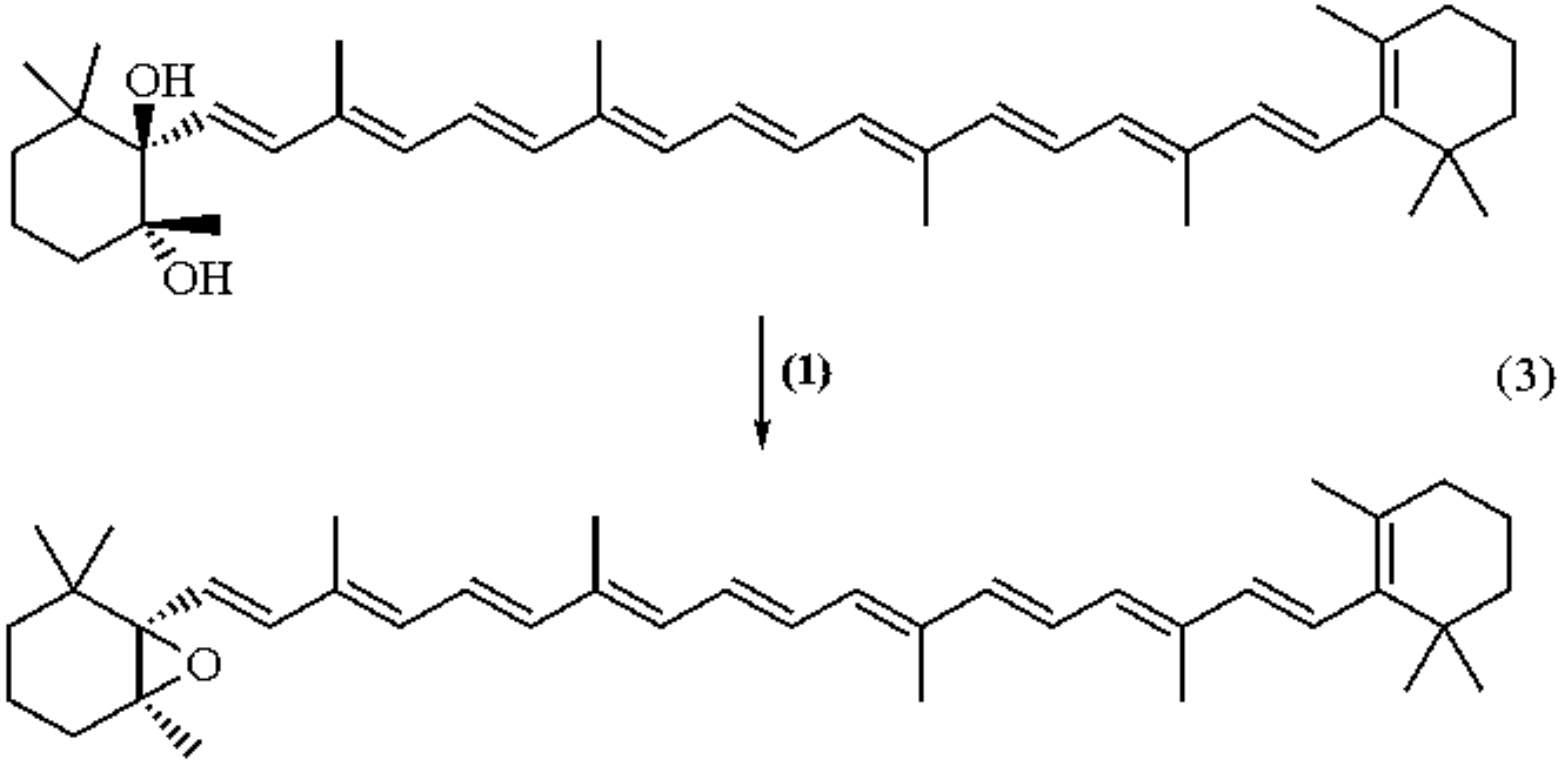

Cleavage of Amides.

Secondary amides can be converted to esters with (**1**). The rate is sensitive to steric constraints at the nitrogen and the acyl carbon. In most cases the amine portion is trapped as the sulfilimine and/or the imidate, which are easily converted back to the amine (eq 4). The dual nature of this reaction affords a mild conversion of amides to esters as well as a simple method for deprotection of *N*-acylated amines.[5]

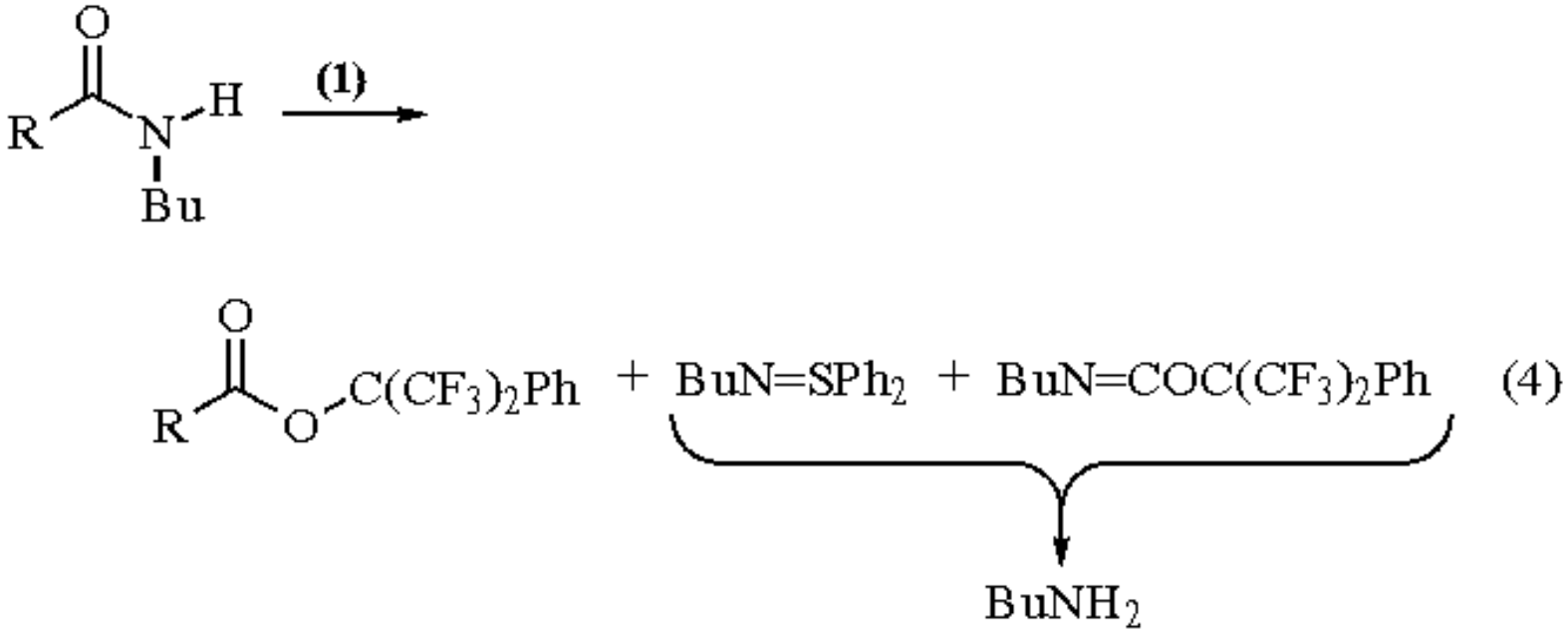

Oxidation of Amines.

In a related reaction, (**1**) reacts with primary amines (as well as amides and sulfonamides) to give sulfilimines (eq 5). Secondary amines are converted to imines on reaction with (**1**) whereas benzylamine is converted to benzonitrile (89%) with 2 equiv of (**1**).[6]

$$H_2N\text{-}R \xrightarrow{(1)} Ph_2S{=}N\text{-}R + 2\,(CF_3)_2PhC\text{-}OH \qquad (5)$$

---

1. (a) *FF* **1974**, *4*, 205. (b) *FF* **1975**, *5*, 270. (c) *FF* **1977**, *6*, 239. (d) *FF* **1980**, *8*, 208.
2. Martin, J. C.; Arhart, R. J. *JACS* **1971**, *93*, 4327.
3. Martin, J. C.; Franz, J. A.; Arhart, R. J. *JACS* **1974**, *96*, 4604.
4. Eschenmoser, W.; Engster, C. H. *HCA* **1978**, *61*, 822.
5. (a) Franz, J. A.; Martin, J. C. *JACS* **1973**, *95*, 2017. (b) Franz, J. A.; Martin, J. C. *JACS* **1975**, *97*, 6137.
6. Franz, J. A.; Martin, J. C. *JACS* **1975**, *97*, 583.

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Diphenylboryl Trifluoromethanesulfonate

$Ph_2B\text{-}OSO_2CF_3$

[100696-94-4] · $C_{13}H_{10}BF_3O_3S$ · Diphenylboryl Trifluoromethanesulfonate · (MW 314.11)

(Lewis acid utilized for the preparation of homoallyl alcohols and ethers;[1,2] catalyst for asymmetric esterification of cyclic *meso*[3] and racemic dicarboxylic acid anhydrides;[4] catalyst for Friedel-Crafts acylation of acid anhydrides and acid chlorides[5])

Alternate Name: diphenylboryl triflate.

Solubility: sol common inert organic solvents such as CH_2Cl_2 and toluene.

Preparative Method: generated in situ from equimolar amounts of ***Silver(I) Trifluoromethanesulfonate*** and diphenylchloroborane. The reactants are mixed in toluene at 0 °C and stirred for 1 h. The reagent is then used immediately.

Handling, Storage, and Precautions: solutions are moisture and air sensitive and therefore they should be used under a dry inert atmosphere.

Allylation.

Ph_2BOTf is a mild and effective catalyst for the addition of allylsilanes to acetals to afford the corresponding homoallyl ethers. These reactions proceed at -78 °C in good yield, and with modest diastereoselectivity when a substituted allylsilane is utilized (eq 1). The allylation reaction of acetals is not catalyzed by either Ph_2BCl or AgOTf, nor is it catalyzed by Bu_2BOTf. Thus it has been postulated that stabilization of the boryl triflate by the two phenyl groups yields a boron atom with significant cationic character and it is this property that allows Ph_2BOTf to serve as the activator of the reaction.[1]

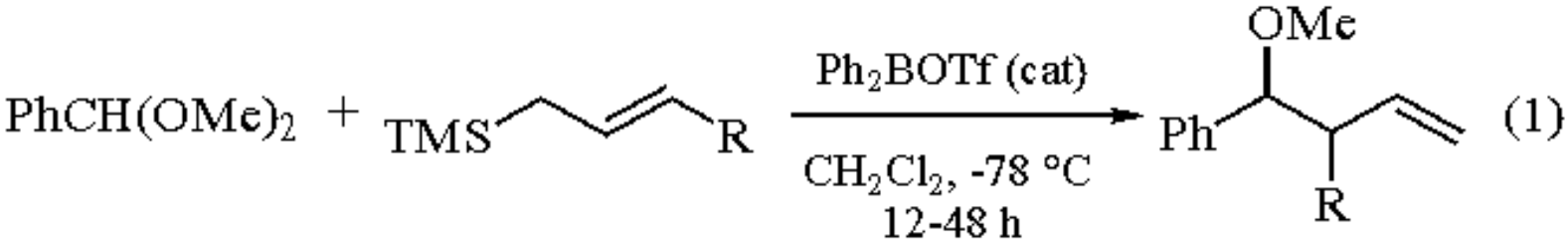

R	Diastereomer ratio	Yield
H	-	71%
Me	76:24	69%
Ph	82:18	73%

Ph_2BOTf has been utilized for the one-pot asymmetric allylation of aldehydes utilizing enantiomerically pure 1-phenylethyl trimethylsilyl ether as a coreactant and source of asymmetric induction (eq 2). The highest diastereomeric product ratios are typically observed with reactions run at -78 °C in toluene. The protecting group on the resulting homoallylic ethers can be easily removed via catalytic hydrogenation or by treatment with ***Iodotrimethylsilane***.[2]

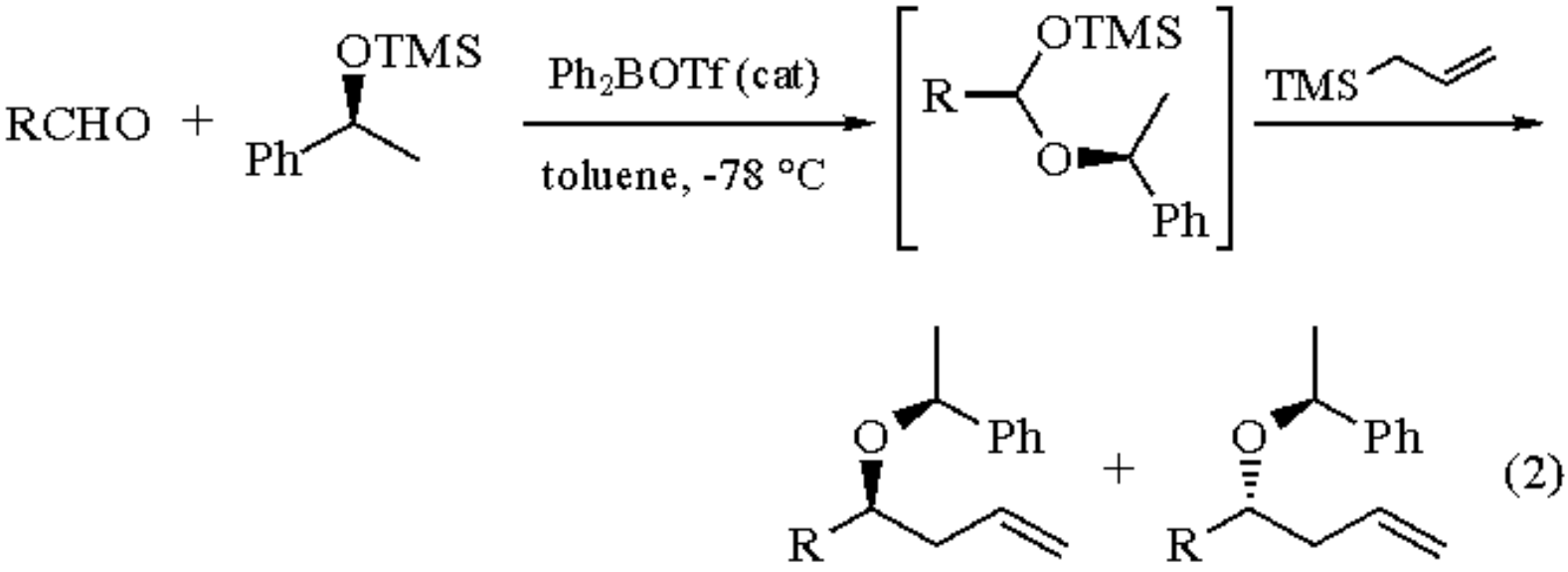

R		
$Ph(CH_2)_2$	96:4	71%
Cy	93:7	74%
Ph	74:26	77%

Asymmetric Esterification.

Ph_2BOTf is a very efficient catalyst for the asymmetric esterification of cyclic *meso* and racemic dicarboxylic anhydrides. Various enantiomerically pure derivatives of mandelic acid have been utilized in reactions with anhydrides

of cyclic *meso*-dicarboxylic acids with good to excellent degrees of asymmetric induction. The best results are achieved when the reaction is run with 2 equiv of the diphenylborate of a single enantiomer of 2-methoxy-1-phenylethanol as the nucleophilic species. When (*R*)-2-methoxy-1-phenylethanol is used, the (1*S*, 2*R*) diastereomer predominates, as shown for *meso*-1,2-cyclohexanedicarboxylic anhydride in eq 3.[3] This method has been extended to the ring opening of racemic cyclic dicarboxylic anhydrides as well. In these cases the best results are achieved when >2 equiv of the anhydride per equivalent of nucleophile are used. Yields for the reported examples average approximately 75%, a typical example being shown in eq 4.[4]

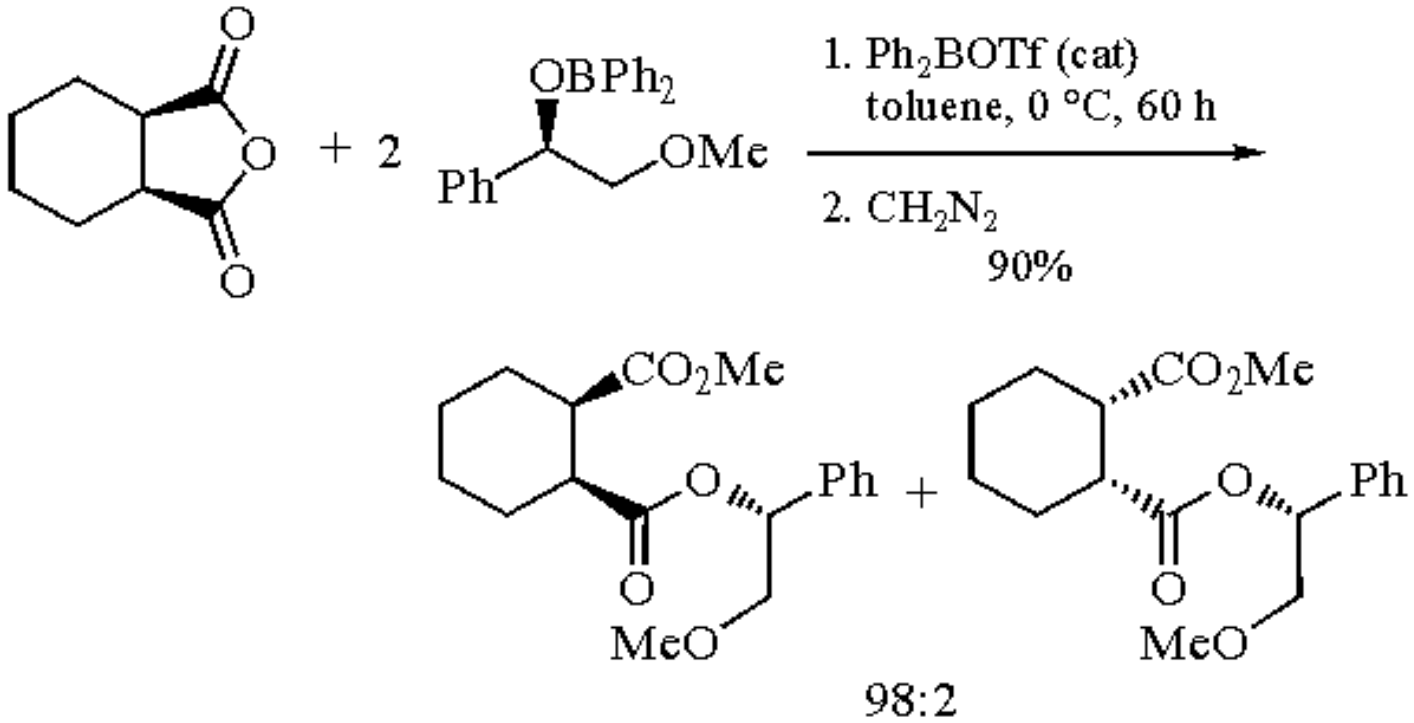

(3)

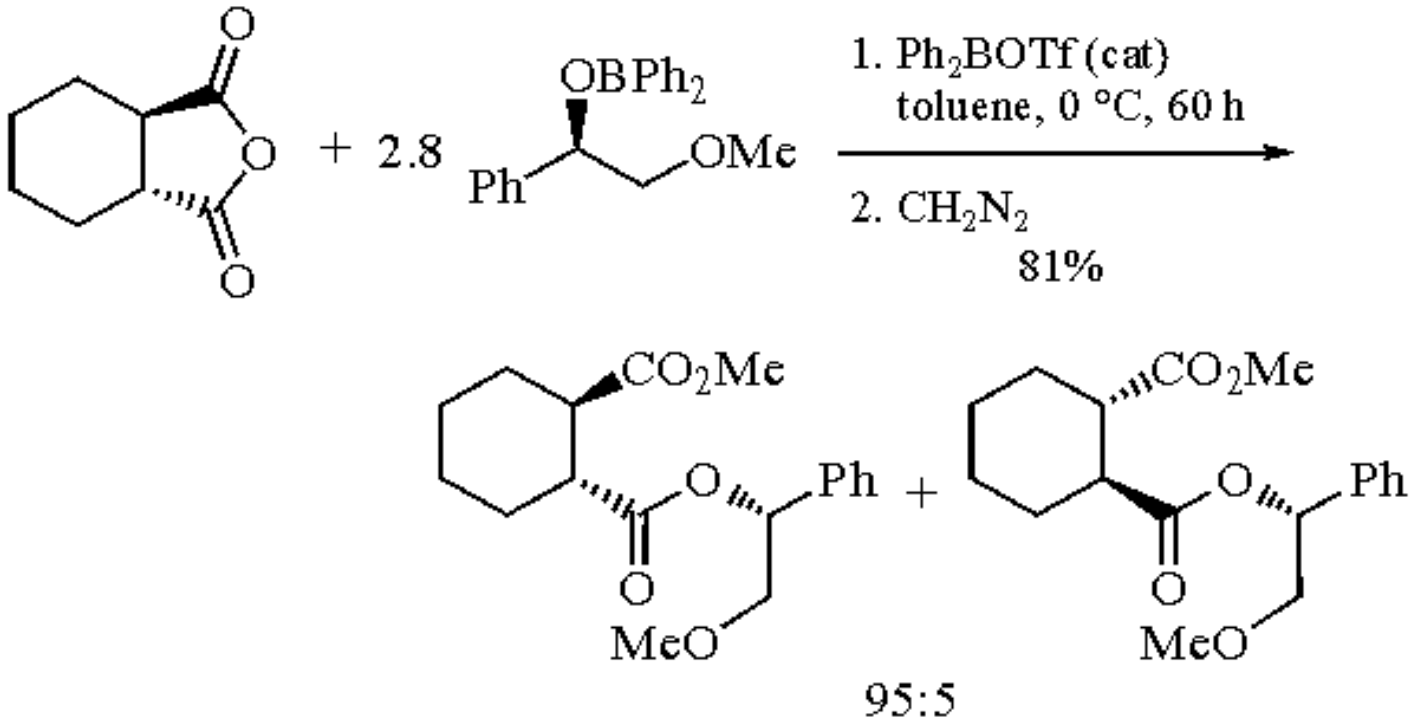

(4)

Friedel-Crafts Acylation.

Ph_2BOTf has been reported to be an effective catalyst for the acylation of aromatic compounds with acid chlorides or acid anhydrides under mild conditions (eq 5).[5]

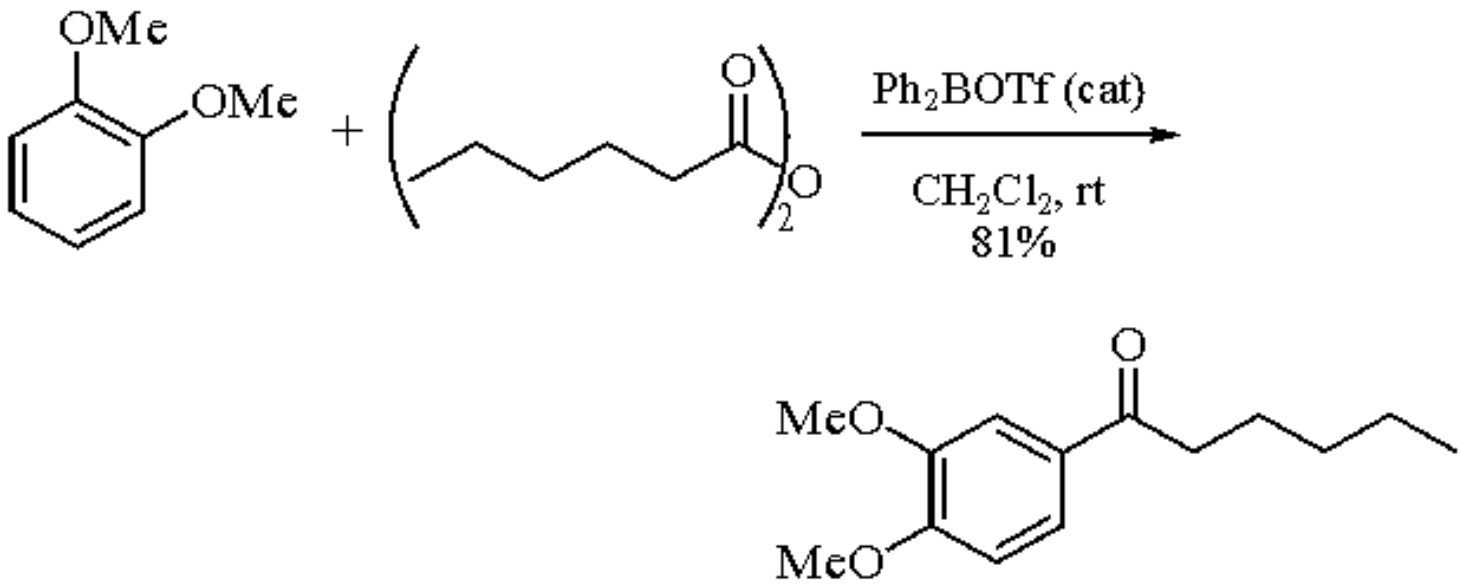

(5)

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1. Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Ohshima, M. *CL* **1985**, 977.
2. Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *CL* **1987**, 1121.
3. Ohshima, M.; Mukaiyama, T. *CL* **1987**, 377.
4. Ohshima, M.; Miyoshi, N.; Mukaiyama, T. *CL* **1987**, 1233.
5. Mukaiyama, T.; Nagaoka, H.; Ohshima, M.; Murakami, M. *CL* **1986**, 165.

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Diphenylcarbamoyl Chloride

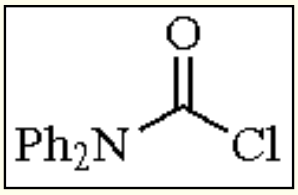

[83-01-2] · $C_{13}H_{10}ClNO$ · Diphenylcarbamoyl Chloride · (MW 231.69)

(acylating agent in Friedel-Crafts reactions;[1] acylating agent for amines,[2] amino acids,[3] thiols,[2] phenols,[4] and carboxylic acid salts;[5] protecting group in oligonucleotide synthesis[6])

Alternate Name: DPC-Cl.

Physical Data: mp 85 °C.

Solubility: sol most common solvents.

Form Supplied in: white to off-white powder; widely available.

Handling, Storage, and Precautions: incompatible with strong oxidizing agents and strong bases; corrosive; moisture sensitive. Unlike dimethyl-, diethyl-, and methylphenylcarbamoyl chloride, it is not carcinogenic.

Acylating Agent in Friedel-Crafts Reactions.[1]

Diphenylcarbamoyl chloride can be used to introduce a carboxylic group into an aromatic compound. Friedel-Crafts acylation in ethylene chloride in the presence of ***Aluminum Chloride*** as catalyst gives a diphenylamide. Alkyl- or alkoxy-substituted benzenes are readily acylated, whereas fluoro or chloro derivatives are unreactive. With the exception of the sterically hindered amides obtained from mesitylene, durene, and pentamethylbenzene, the resultant diphenylamides are readily hydrolyzed by alkali (NaOH in 85% aq. EtOH or DMSO) to the parent carboxylic acids (eq 1).[7]

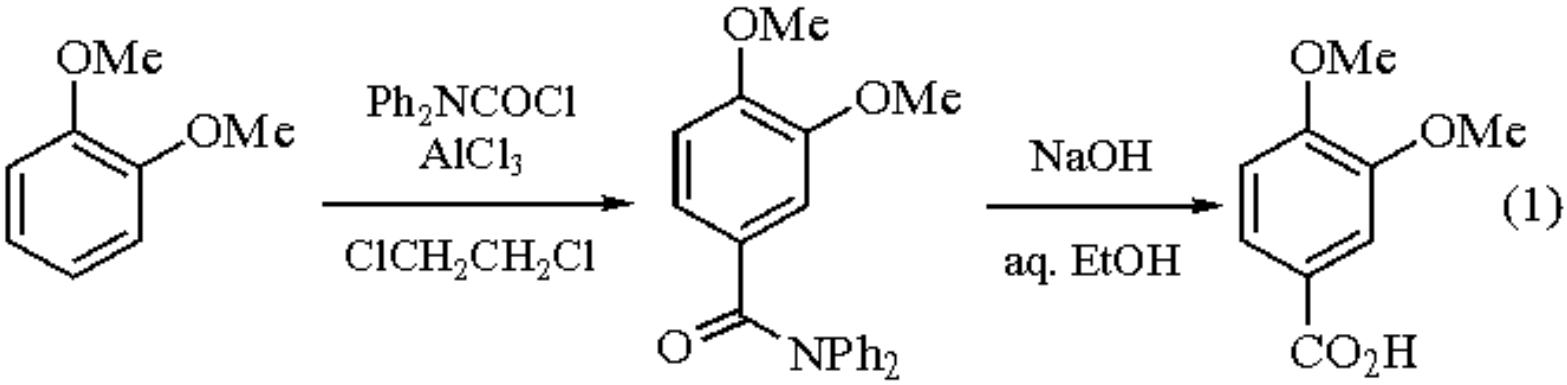

Acylating Agent for Amines, Amino Acids, Thiols, Phenols, and Carboxylic Acid Salts.

DPC-Cl reacts readily with primary and secondary aliphatic or cyclic amines,[2] and with the α-amino group of a wide variety of amino acids,[3] to give tri- or tetrasubstituted ureas (eq 2). In the case of amino acids, some racemization takes place on longer exposure to the basic conditions.[3]

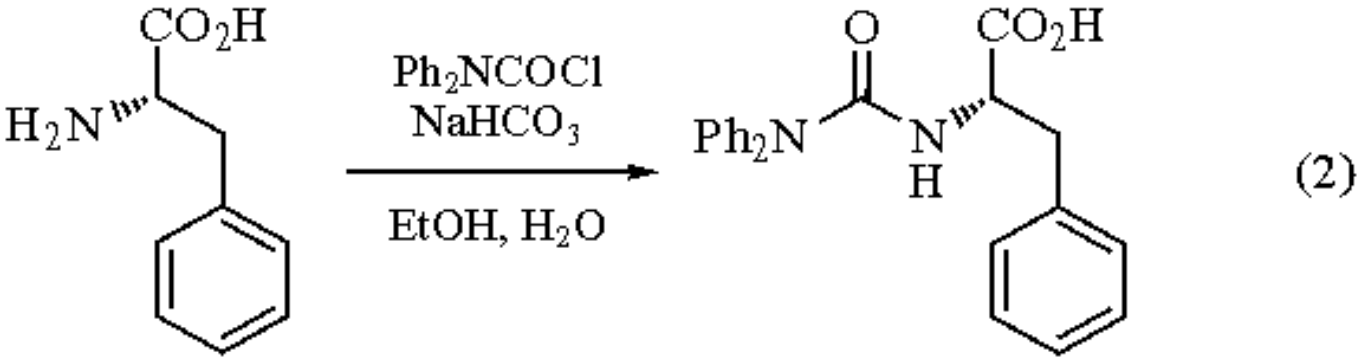

Reactions with thiols[2] can be carried out in aq. EtOH under basic conditions ($NaHCO_3$), to give good yields of *N*,*N*-diphenylthiocarbamates. Other carbamoyl derivatives such as dimethyl- and dibutylcarbamoyl chloride are not as useful because they are too unstable to basic conditions in water.[2] Imidazole in acetone or EtOH can be converted into its DPC derivative using an excess of imidazole as the base.[2] O-Methylhydroxylamine reacts readily with DPC-Cl in THF to give *N*´-methoxy-*N*,*N*-diphenylurea in 62% yield.[8] The reaction of 5-methylene-1,3-thiazolidine-2-thione with DPC-Cl traps only the aromatic thiazole tautomer, giving the *S*-substitution product (eq 3).[9]

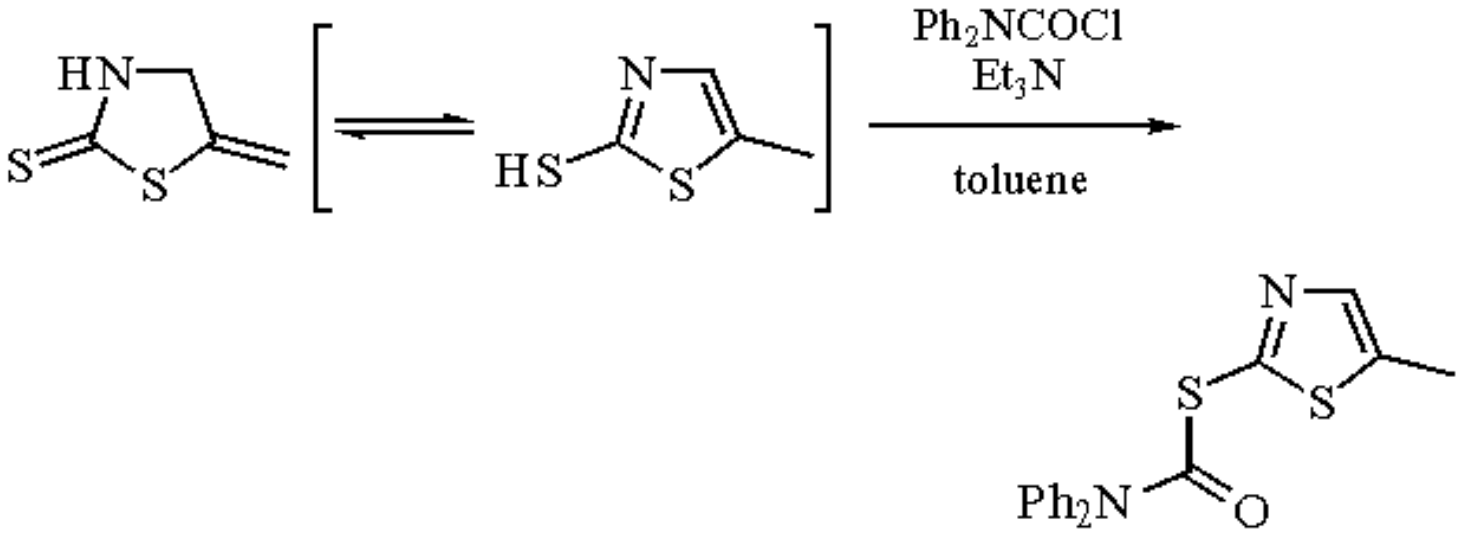

(3)

Phenols can be acylated by DPC-Cl in acetone[4] in the presence of ***Potassium Carbonate*** or in pyridine to give *N*,*N*-diphenylcarbamates.[10] Carboxylic *N*,*N*-diphenylcarbamic anhydrides have been isolated from the reaction of carboxylate salts with 1-(*N*,*N*-diphenylcarbamoyl)pyridinium chloride, prepared from DPC-Cl and pyridine, in aqueous or ethanolic solutions. In the presence of amino groups the reaction under these conditions is chemoselective and no carbamate is formed. These mixed anhydrides are stable, crystalline derivatives and are very reactive in acylation reactions (eq 4).[5]

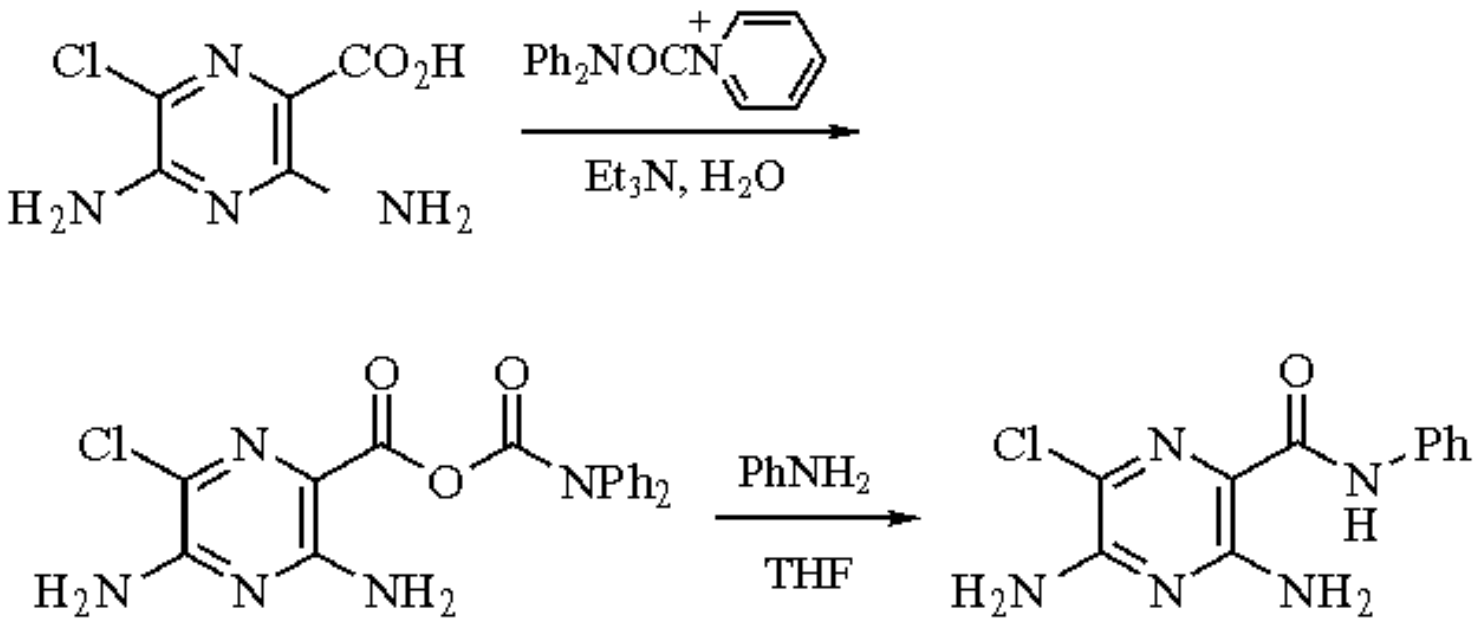

(4)

The DPC group has been introduced in many pharmaceutical products. Hence the toxicity and tumor affinity of 5-fluorouracil have been modified by reacting it with DPC-Cl in DMA in the presence of ***Sodium Hydride*** to give the 1-DPC derivative (eq 5).[11] When excess DPC-Cl is employed in the presence of K_2CO_3, the 1,3-disubstituted derivative is also produced. Treatment of an 85/15 *endo*/*exo* mixture of bicyclo[2.2.1]hept-5-en-2-ylmethylamine obtained by Diels-Alder reaction with DPC-Cl, followed by crystallization, gives a 74% yield of pure *endo* product. This product can then be condensed with a sulfonamide to give a sulfamylurea, which is a highly potent hypoglycemic agent (eq 6).[12]

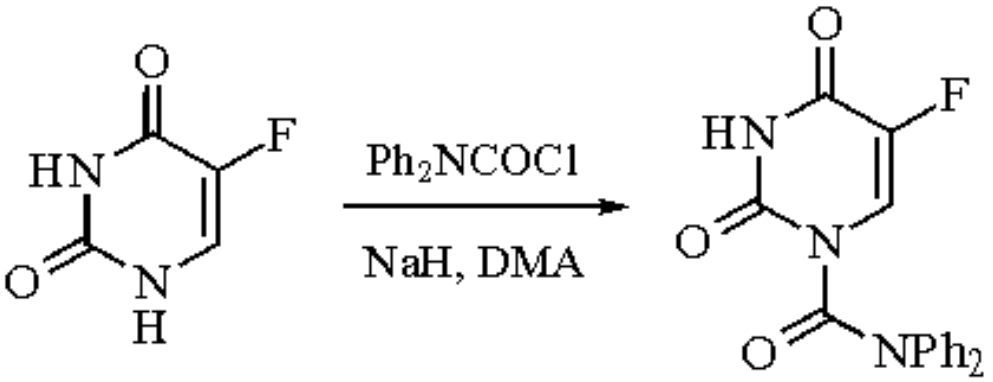

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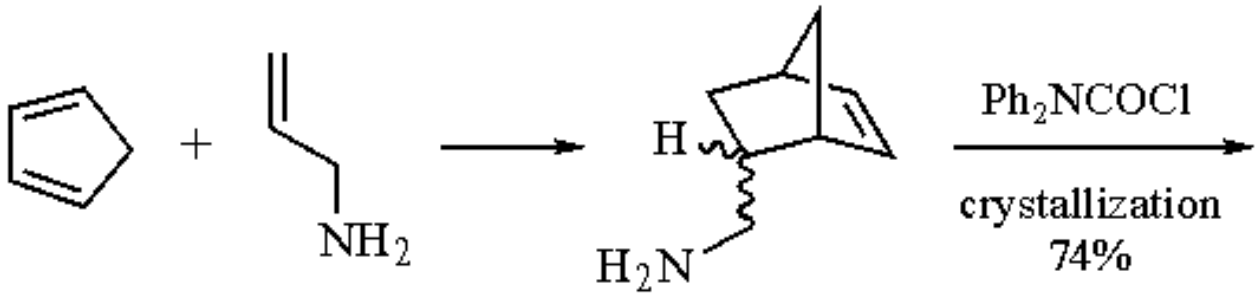

endo:*exo* = 85:15

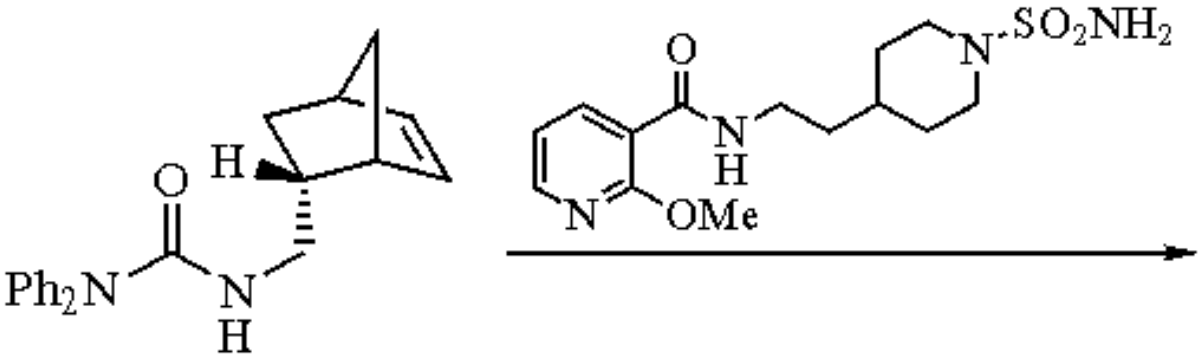

endo 100%

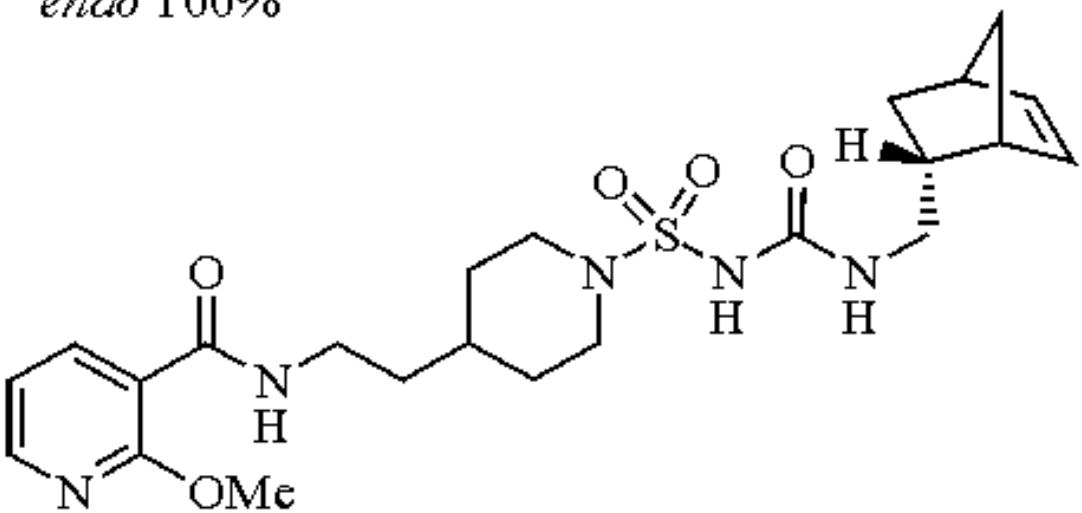

(6)

Protecting Group in Oligonucleotide Synthesis.

The lactam function of the guanine residue is subject to side-reaction during oligonucleotide synthesis. It can be protected according to a widely used procedure originally devised by Kamimura et al.[5,13] Treatment of the amino-protected oligonucleotide with DPC-Cl in dry pyridine containing ***Triethylamine*** or ***Diisopropylethylamine*** gives, after silica gel chromatography, the corresponding O^6-(diphenylcarbamoyl)guanosine in excellent yield (eq 7).[5] DPC-Cl is superior to dimethyl- and dimethylthiocarbamoyl chloride for this purpose. In addition to the successful protection of the guanine residue, introduction of DPC improves the solubility and chromatographic properties of the resultant derivatives. Deprotection occurs in conc. ammonia-MeOH (9:1, v/v) over 3 h at 60 °C, which are the conventional conditions for deprotection of the *exo*-amino acyl groups of other nucleoside bases.[5] Modified deoxyguanosines[14] are protected in the same way. Stannylation of the guanosine followed by electrophilic attack of the DPC-Cl at the stannyl intermediate has been reported.[15] In the case of 2-aza-2´-inosine, N^1-acylation instead of O^6-acylation occurs.[16]

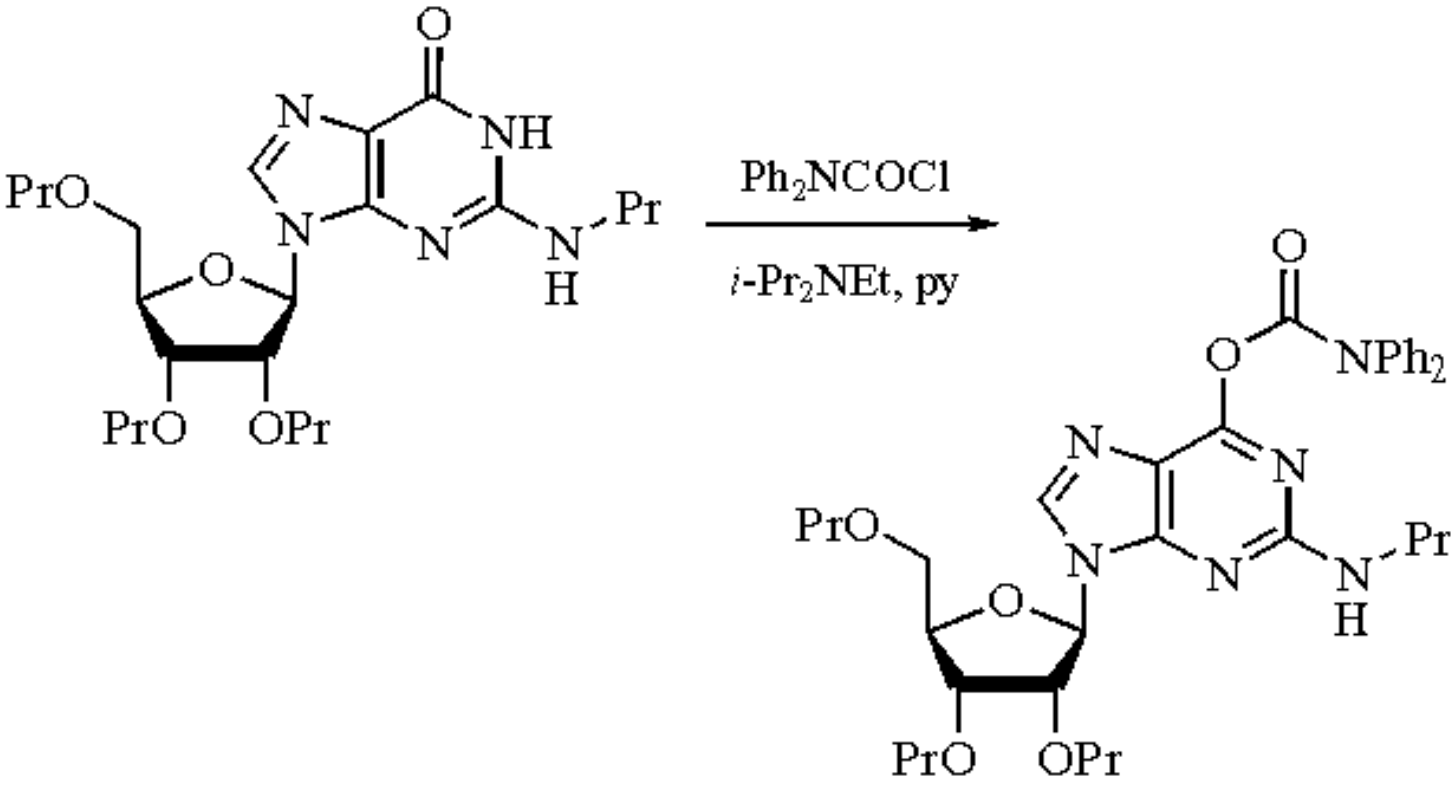

1. (a) *FF* **1967**, *1*, 337. (b) *FF* **1969**, *2*, 177.
2. Rivett, D. E.; Wilshire, J. F. *AJC* **1966**, *19*, 165.
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4. Schmidt, B.; Hoffmann, H. M. R. *CB* **1992**, *125*, 1501.
5. Shepard, K. L.; Halczenko, W. *JHC* **1979**, *16*, 321.
6. (a) Kamimura, T.; Tsuchiya, M.; Koura, K.; Sekine, M.; Hata, T. *TL* **1983**, *24*, 2775. (b) Kamimura, T.; Tsuchiya, M.; Urakami, K.; Koura, K.; Sekine, M.; Shinozaki, K.; Miura, K.; Hata, T. *JACS* **1984**, *106*, 4552.
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Diphenyl Cyanocarbonimidate

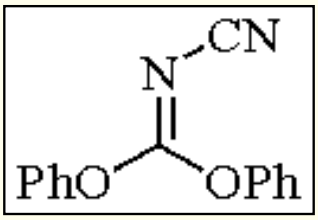

[79463-77-7] · $C_{14}H_{10}N_2O_2$ · Diphenyl Cyanocarbonimidate · (MW 238.26)

(preparation of heterocycles,[1,2] 1,2,4-triazoles,[1] 4-oxa-1,3-diazoles,[2] benzimidazoles,[1] hexahydropyrimidines,[3] and hydroquinazolines;[3] synthesis of *O*-phenylisoureas,[1] *N*-cyanoguanidines,[2] and guanidines;[4] modification of peptides;[5] reverse electron demand Diels-Alder heterodieneophile[6])

Alternate Names: DPCC; diphenoxymethylenecyanamide; diphenyl *N*-cyanoimidocarbonate.

Physical Data: mp 156-158 °C,[1] 161-163 °C (Aldrich).

Solubility: sol THF, propan-2-ol.

Form Supplied in: commercially available in ca. 97% purity.

Preparative Method: from diphenyl carbonate by treatment with PCl_5 followed by cyanamide.[1]

Handling, Storage, and Precautions: harmful if swallowed and irritating to the eyes and respiratory system. Care should be taken not to inhale the powder nor to allow it to come in contact with the skin. It is sensitive to moisture. It should be disposed of by dissolving in a solvent and burning the solution in an approved incinerator. Use in a fume hood.

Synthesis of Heterocycles.

Diphenyl cyanocarbonimidate was originally described as a synthon for heterocyclic synthesis by Webb and Labaw.[1] With *o*-phenylenediamine in boiling propan-2-ol, 2-cyanoaminobenzimidazole is formed. At rt the *O*-phenylisourea, the product of a single displacement, can be isolated and converted to the benzimidazole on warming (eq 1). The sequential displacement of the two phenoxide ions illustrates a major advantage of DPCC as a reagent. Sequential reaction of aniline followed by ***Hydrazine*** gives 5-phenylamino-3-amino-1,2,4-triazole (eq 1). A variety of 1,2,4-triazoles have been prepared by this method.[7]

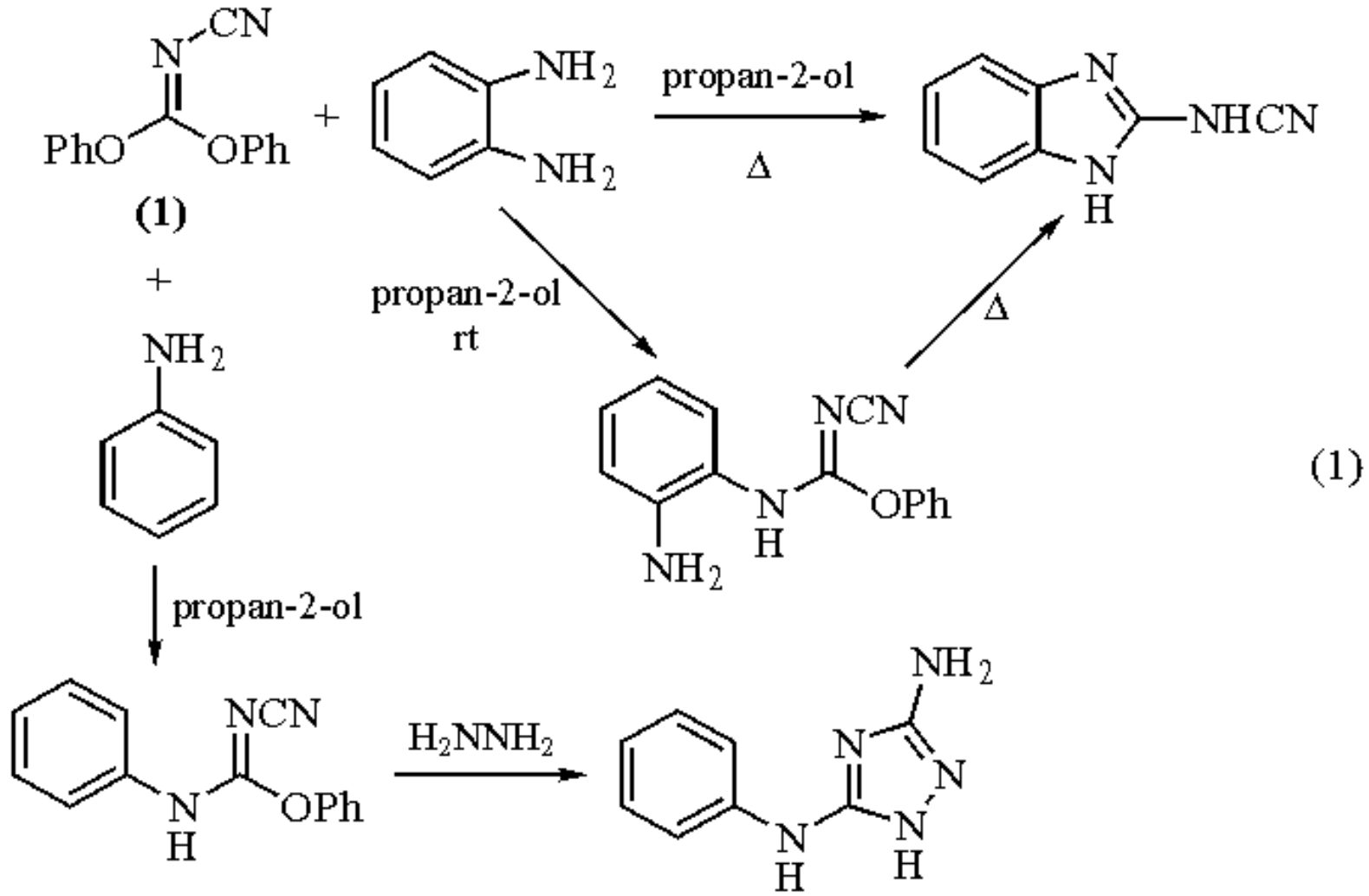

(1)

Treatment of the *O*-phenylisourea with ***Hydroxylamine*** gives two isomeric oxadiazoles, the predominant isomer arising from initial nucleophilic attack by the hydroxylamine nitrogen (eq 2).[2] Cyclization to give six-membered rings also occurs, forming substituted hydropyrimidines (eq 3).[8] Imidazole ring formation to give a tricyclic structure has been accomplished by reaction of DPCC with a diamine (eq 4).[9]

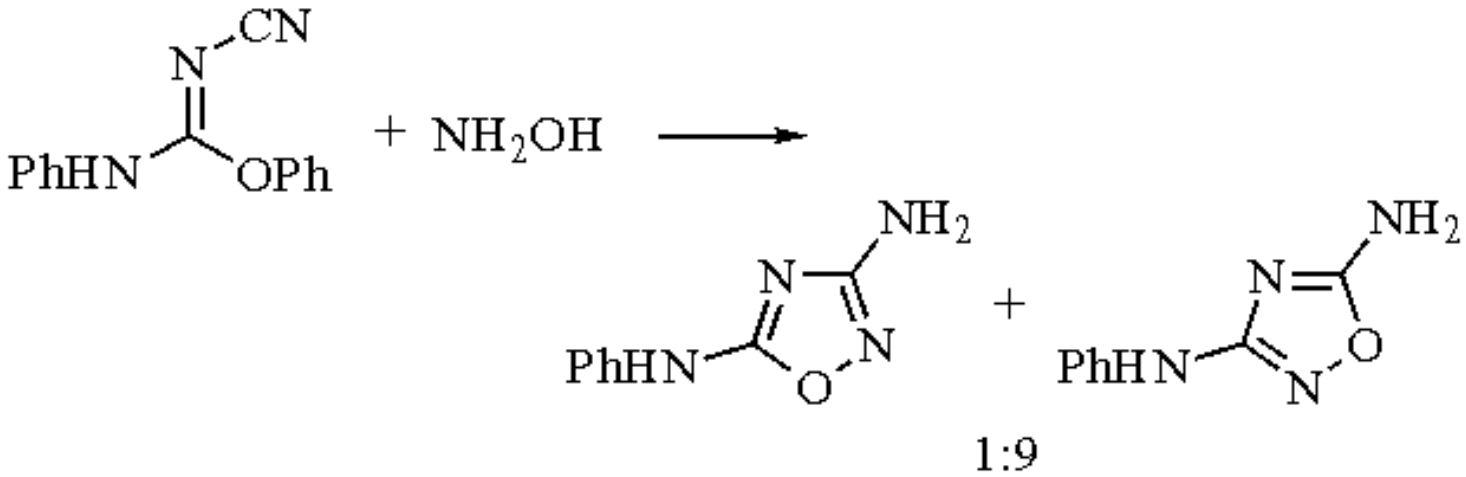

(2)

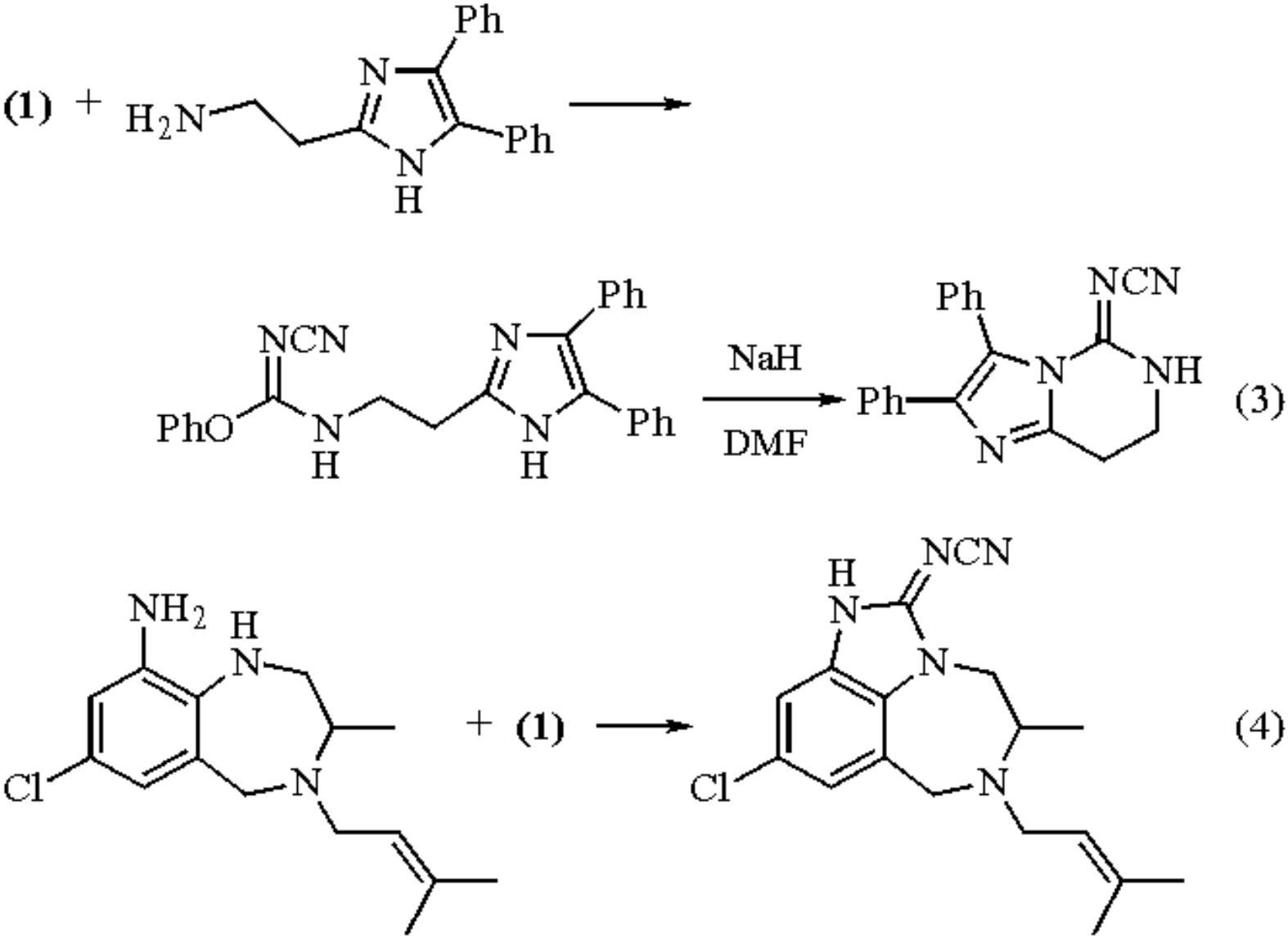

Oxadiazole ring formation occurs with a hydrazide in the presence of ***Triethylamine***, presumably involving the enol in the second nucleophilic displacement (eq 5).[10] Reaction of DPCC with 2-aminobenzyl alcohol gives a six-membered benzoazine.[11]

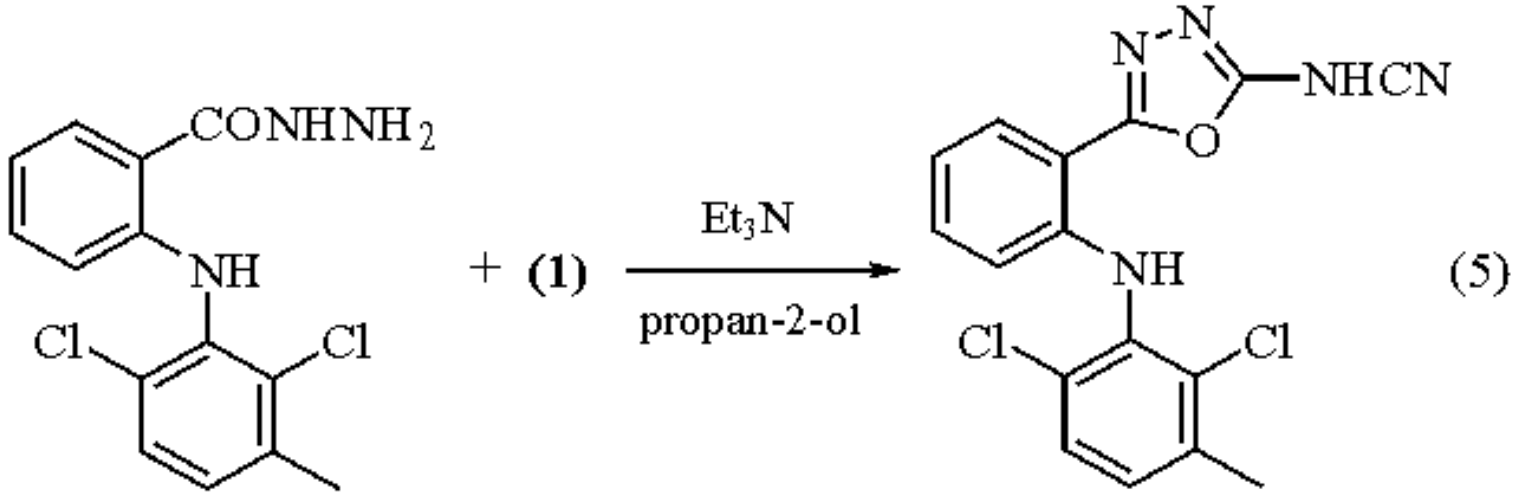

An alternative mode of ring formation involves sequential substitution with two different nitrogen nucleophiles, followed by ring closure between one nitrogen and a reactive center on the other nucleophile. Thus β-alanine methyl ester gives an *O*-phenylisourea, which on treatment with benzylamine gives a hexahydropyrimidine (eq 6).[3]

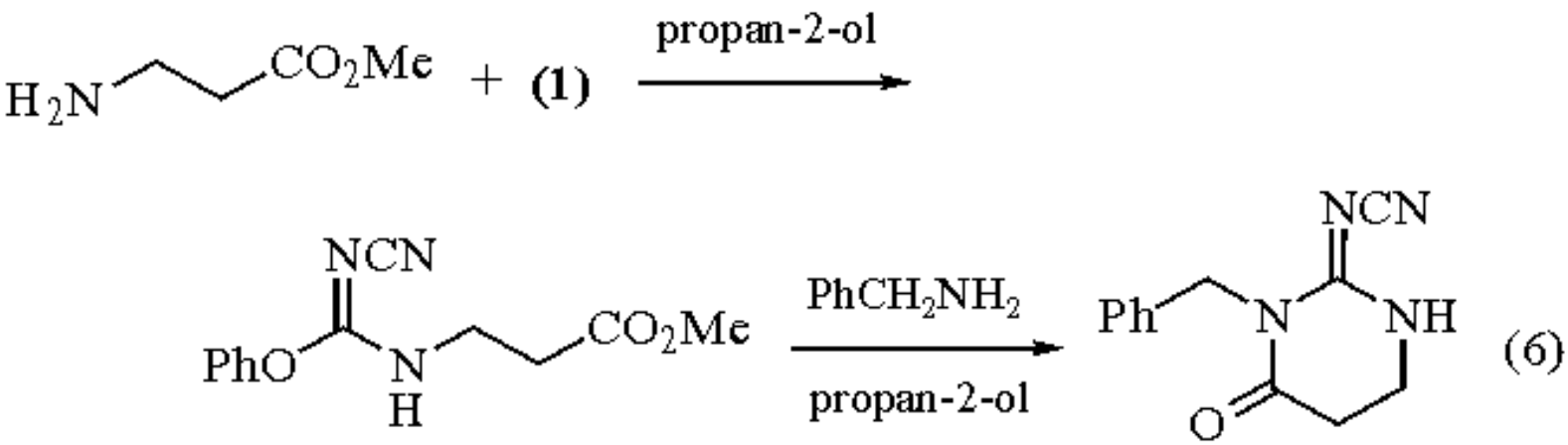

If two modes of ring closure are possible then the five-membered ring is favored,[12] and this can only partially be reversed by discriminating between the ester functions (eq 7).[13] Rearrangement of the five-membered imidazolone to the corresponding acid of the hexahydropyrimidine takes place under mild base treatment, but racemization occurs.[14]

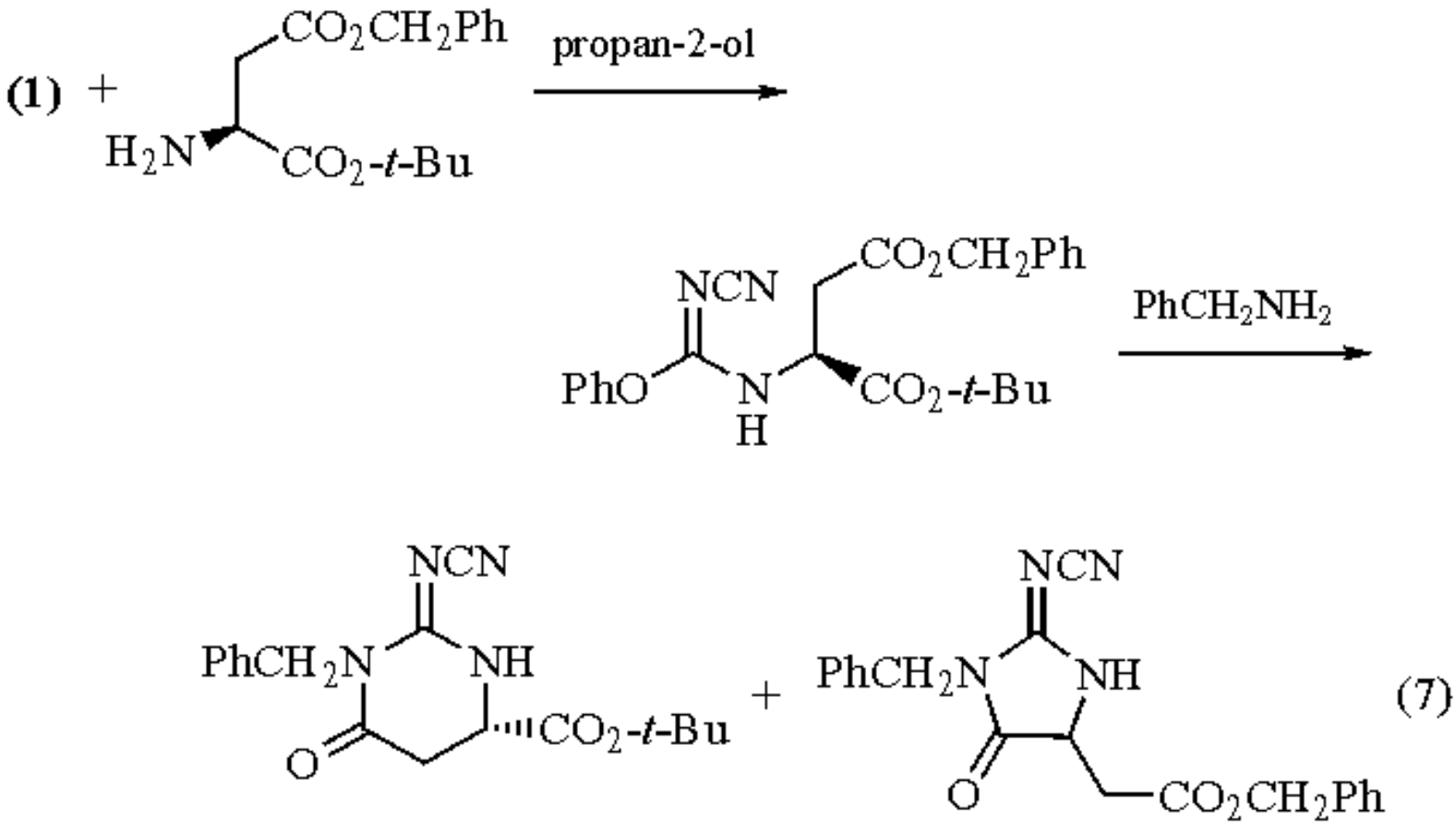

A combination of these two modes of cyclization occurs in the reaction of hydrazine with certain *O*-phenylisoureas to give 1,2,4,6-tetraazabicyclo[3.3.0]octanes (eq 8).[15]

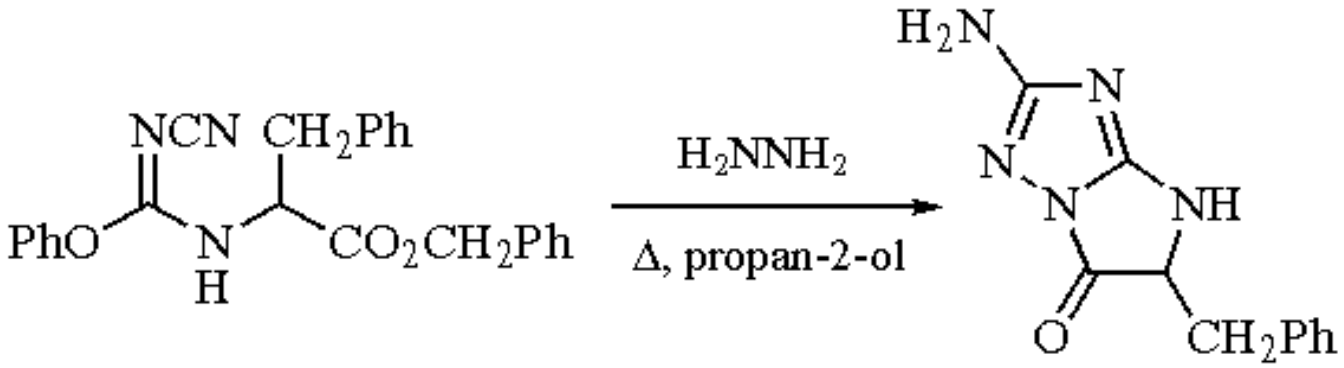

(8)

Synthesis of *N*-Cyanoguanidines and Guanidines.

The *N*-cyanoguanidine drug cimetidine was prepared by Webb and Labaw from the sequential reaction of two different amines, and was their original reason for preparing DPCC (eq 9).[2] Guanidines can be prepared from the *N*-cyanoguanidines by acid hydrolysis.[16] Treatment of the *N*-cyanoguanidines with ***Trifluoroacetic Acid*** gives *N*-trifluoroacetates or, in the presence of water, the corresponding ureas.[5,11,17]

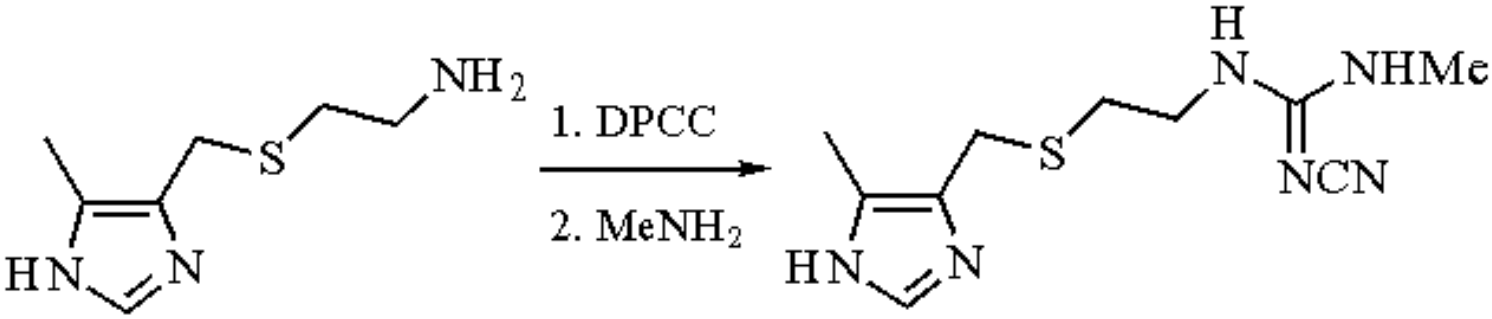

(9)

Modification of Peptides.

The o-amino function of lysine in peptides has been modified by treatment with DPCC to give the isourea, followed by an amine to give the *N*-cyanoguanidine (eq 10).[5] Capsaicin analogs containing *N*-cyanoguanidine groups have been prepared,[18] and methods have been described to prepare various *N*-guanidino-modified arginines.[19]

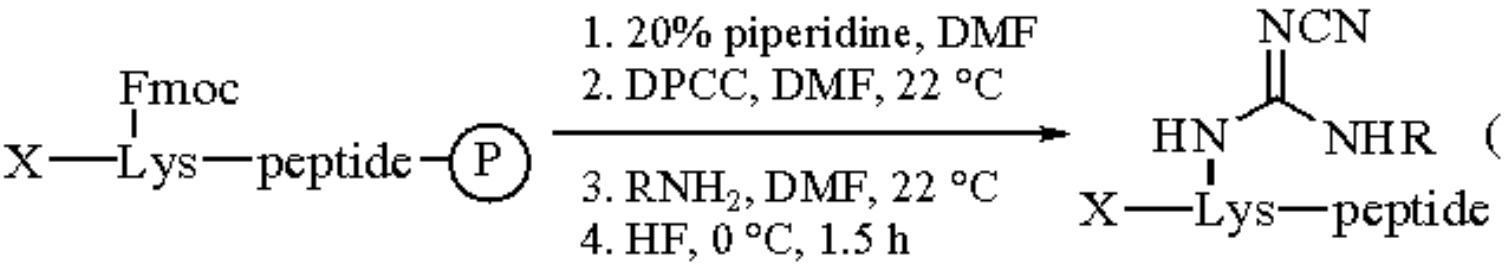

(10)

Diels-Alder Reaction.

The cyano group of DPCC acts as a heterodienophile in a reverse electron-demand Diels-Alder reaction with 3,6-bis(methoxycarbonyl)-1,2,4,5-tetraazabenzene to give a 1,2,4-triazabenzene derivative (eq 11).[6]

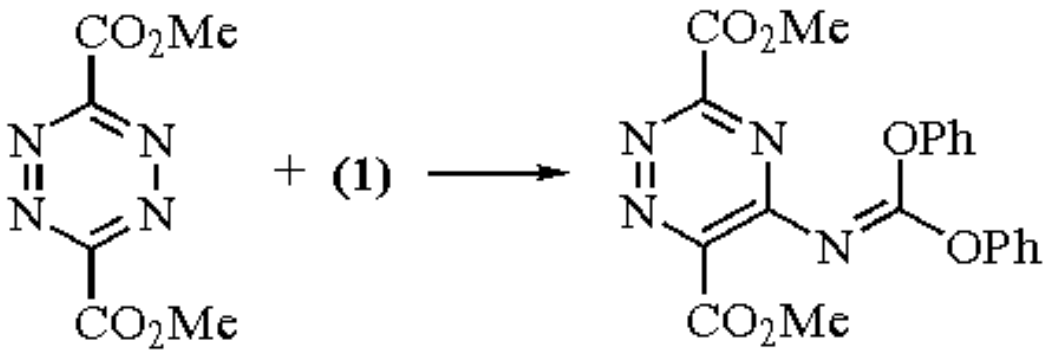

(11)

Related Reagents.

Aminoiminomethanesulfonic Acid; ***Cyanamide***; ***N-Dichloromethylene-N,N-dimethyliminium Chloride***; ***Guanidine***; ***S-Methylisothiosemicarbazide***; ***S-Methylisothiourea***; ***O-Methylisourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

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(*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N´*-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]

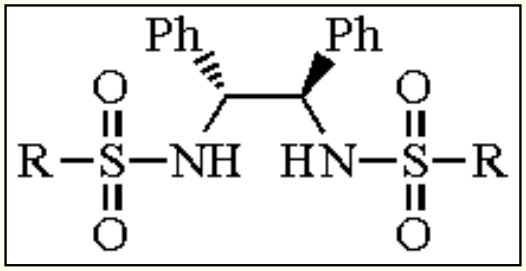

(**1**; R = 3,5-$(CF_3)_2C_6H_3$)

[127445-51-6] · $C_{30}H_{20}F_{12}N_2O_4S_2$ · (*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N´*-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide] · (MW 764.66) (**2**; R = CF_3)

[121788-73-6] · $C_{16}H_{14}F_6N_2O_4S_2$ · (*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N´*-Bis(trifluoromethanesulfonamide) · (MW 476.46) (**3**; R = 4-MeC_6H_4)

[121758-19-8] · $C_{28}H_{28}N_2O_4S_2$ · (*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N´*-Bis(*p*-toluenesulfonamide) · (MW 520.72) (**4**; R = 4-$NO_2C_6H_4$)

[121809-00-5] · $C_{26}H_{22}N_4O_8S_2$ · (*R,R*)-1,2-Diphenyl-1,2-diaminoethane *N,N´*-Bis(4-nitrobenzenesulfonamide) · (MW 582.66)

(chiral controller group for enantioselective Diels-Alder reactions,[1] aldol additions,[2] Ireland-Claisen rearrangements,[3] ester-Mannich additions,[4] and carbonyl allylation[5] and propargylation[6])

Alternate Name: (*R,R*)-stilbenediamine *N,N´*-bis-3,5-bis(trifluoromethyl)benzenesulfonamide.

Physical Data: (**1**) mp 155-156 °C; α_D +83.7° (*c* = 1, $CHCl_3$). (**2**) mp 213-214 °C; α_D +6.6° (*c* = 1.4, $CHCl_3$). (**3**) mp 213-214 °C; α_D +43.9° (*c* = 1.74, $CHCl_3$). (**4**) mp 243 °C (dec); α_D 122° (*c* = 0.107, acetone).

Solubility: except for the nitro derivative, the sulfonamides are sol CH_2Cl_2.

Preparative Methods: the most convenient preparation of (*R,R*)-stilbenediamine is described in *Organic Syntheses*.[7] Condensation of benzil and cyclohexanone in the presence of ammonium acetate and acetic acid (eq 1) produces a spirocyclic 2*H*-imidazole (mp 105-106 °C). Reduction with ***Lithium*** in THF/NH_3 followed

by an ethanol quench and hydrolysis with aqueous HCl (eq 2) affords the racemic diamine as a pale yellow solid (mp 81-82 °C). Resolution is achieved by multiple recrystallizations of the tartaric acid salts from water/ethanol. The sulfonamides are prepared by reaction of the enantiomerically pure diamine with the appropriate anhydride[1b] or sulfonyl chloride[2a] in CH_2Cl_2 in the presence of ***Triethylamine*** and a catalytic amount of ***4-Dimethylaminopyridine*** (eq 3).

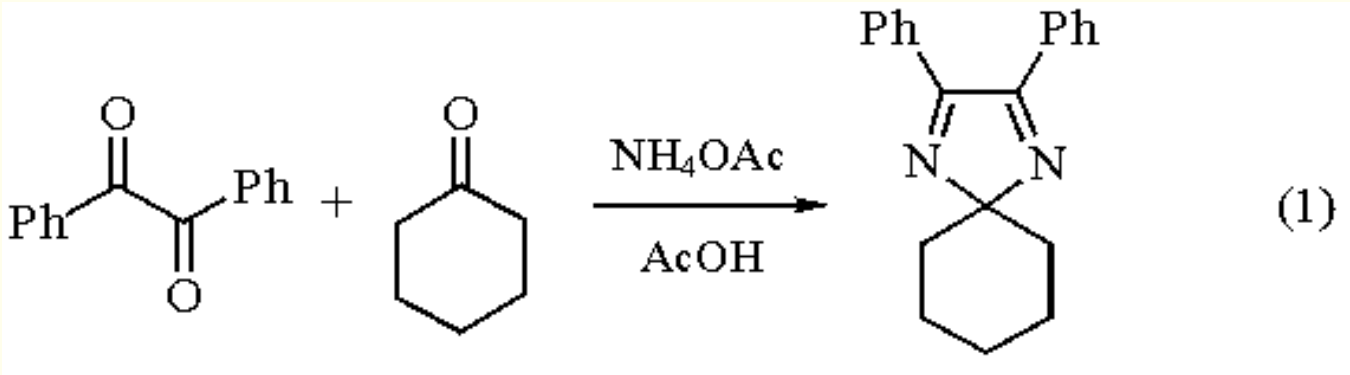

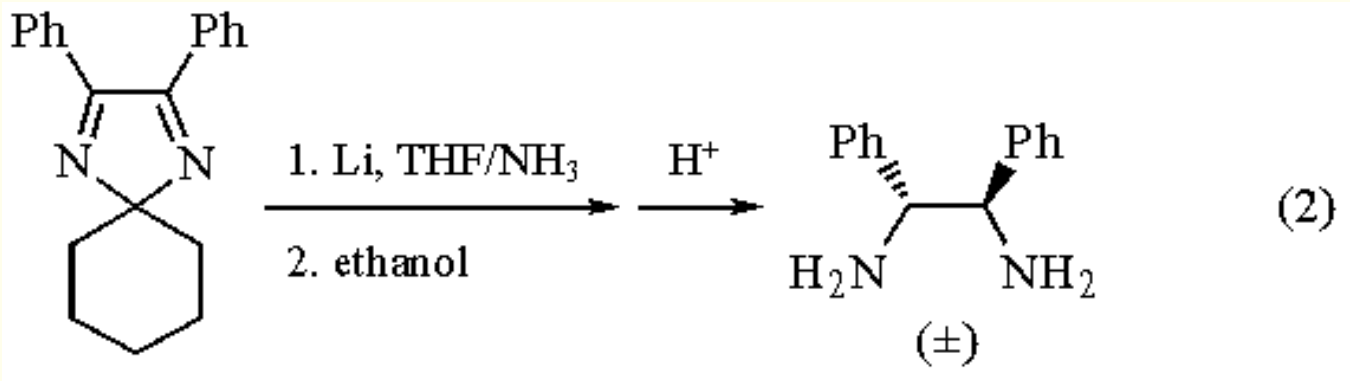

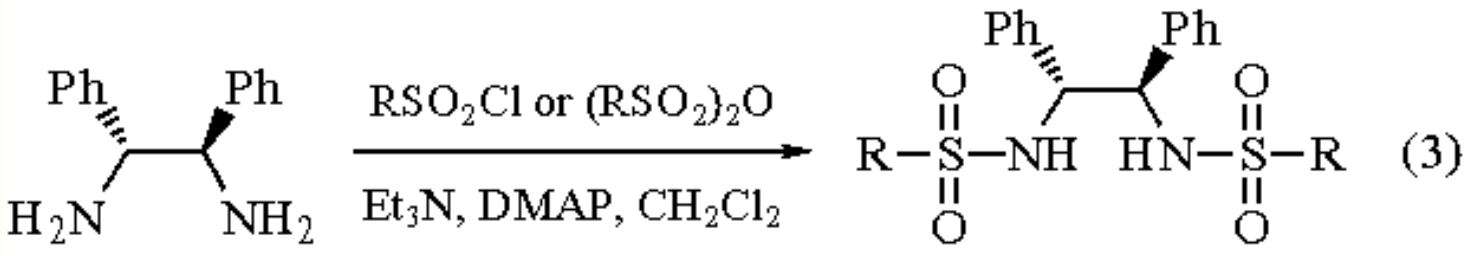

Handling, Storage, and Precautions: the sulfonamides are all stable, crystalline compounds that do not require any special precautions for storage or handling.

Diels-Alder Reactions.

Reaction of the bis(triflamide) (**2**) with ***Diisobutylaluminum Hydride*** or ***Trimethylaluminum*** affords chiral Lewis acids that catalyze Diels-Alder reactions of acryloyl or crotonoyl derivatives with cyclopentadienes (eq 4).[1] The aluminum complex must be crystallized before use to remove traces of trimethylaluminum. High diastereo- and enantioselectivities are achieved with as little as 0.1 equiv of the Lewis acid, and the chiral sulfonamide is recoverable.

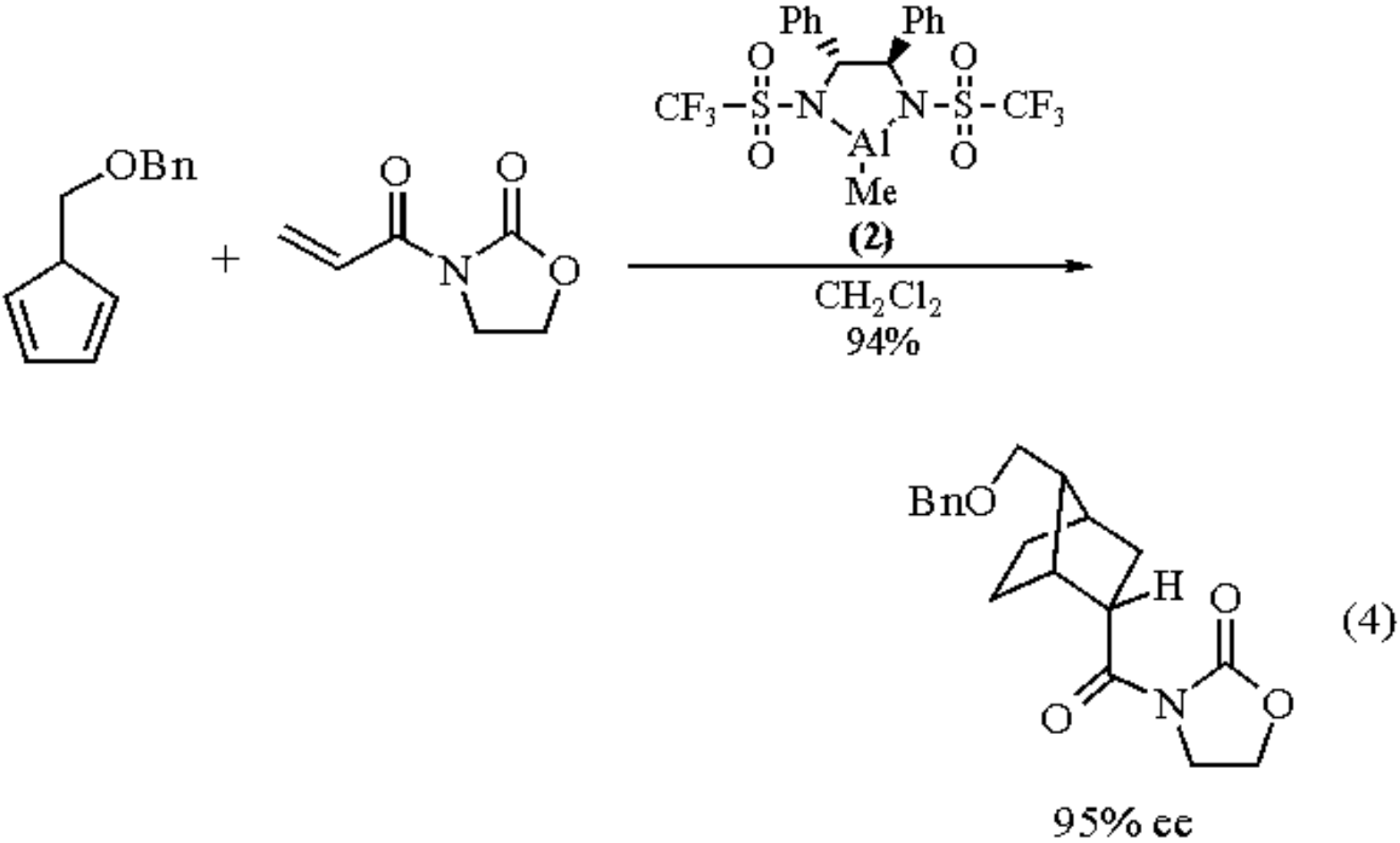

Asymmetric Aldol Reactions.

Reaction of (**1**) with ***Boron Tribromide*** in CH_2Cl_2 affords, after removal of solvent and HBr, a complex (**5**) useful for the preparation of chiral enolates (eq 5).[1a] Complex (**5**) is moisture sensitive and is generally prepared immediately before use. For propionate derivatives, either *syn* or, less selectively, *anti* aldol adducts may be obtained by selection of the appropriate ester derivative and conditions.[2a] Thus reaction of *t*-butyl propionate with (**5**) and triethylamine produces the corresponding *E*(O) enolate, leading to formation of *anti* aldol adducts upon addition to an aldehyde (eq 6). Selectivities may be enhanced by substitution of the *t*-butyl ester with the (+)-menthyl ester. Conversely, reaction of *S*-phenyl thiopropionate with (**5**) and ***Diisopropylethylamine*** affords the corresponding *Z*(O) enolates and *syn* aldol products (eq 7).[2a,c]

(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]

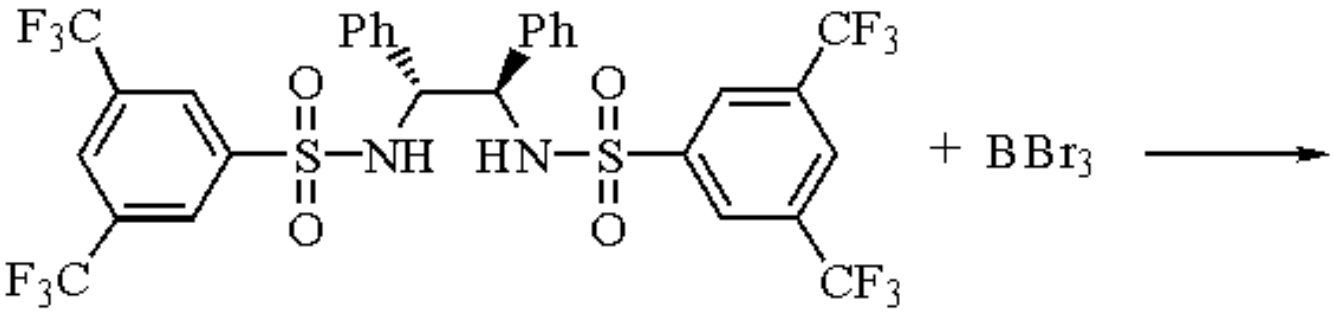

(1)

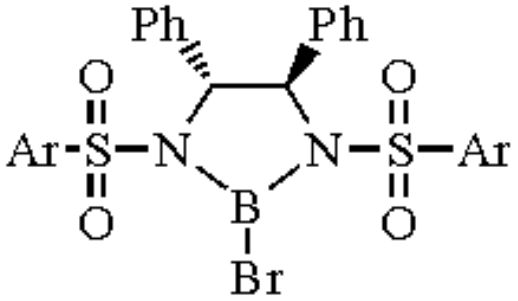

(5)

(5)

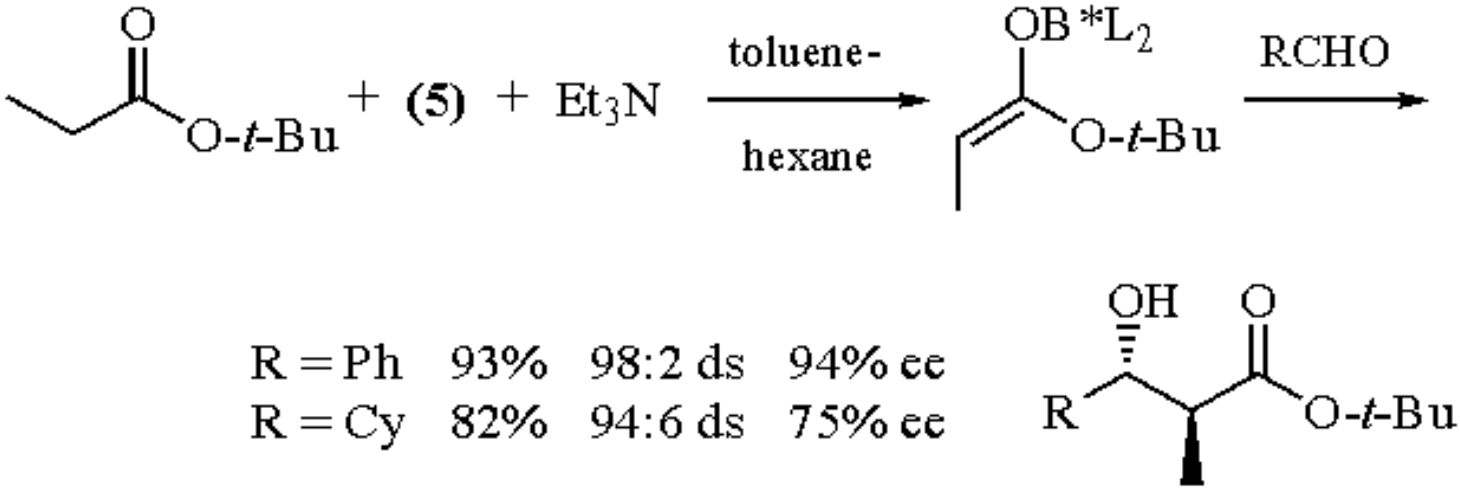

R = Ph 93% 98:2 ds 94% ee
R = Cy 82% 94:6 ds 75% ee

(6)

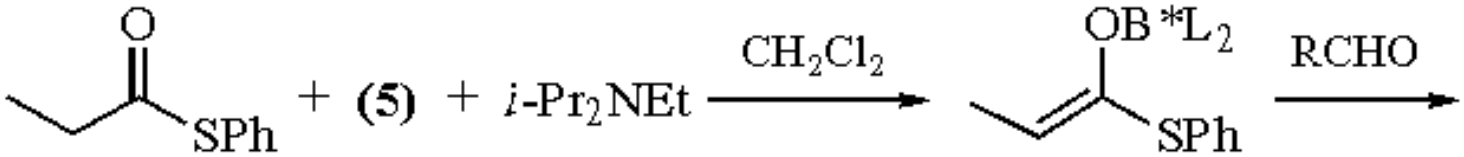

R = Ph 93% 99:1 ds 97% ee
R = Cy 86% 98:2 ds 91% ee

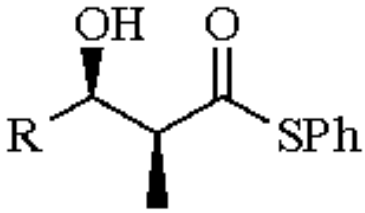

(7)

Products with low enantiomeric purity are obtained by direct application of this chemistry to unsubstituted acetate

esters. However, aldol reactions of *t*-butyl bromoacetate mediated by (**5**) afford synthetically useful bromohydrins (**6**) with high selectivities (eq 8).[2b] These may be reductively dehalogenated or converted to a variety of compounds by way of the derived epoxides.

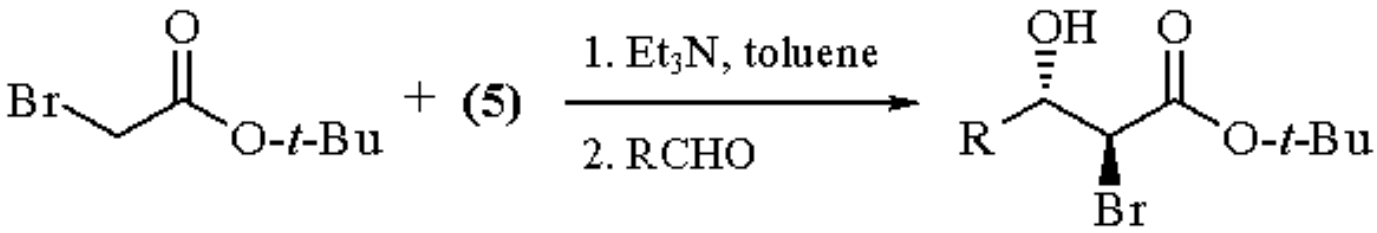

(8)

R = Ph	94%	99:1 ds	98% ee
R = Cy	65%	98:2 ds	91% ee

Asymmetric Ireland-Claisen Rearrangements.

Chiral enolates derived from the boron complex (**5**) and allyl esters rearrange with excellent selectivity upon warming to -20 °C for a period of 1-2 weeks (eqs 9 and 10).[3] As discussed above, the geometry of the intermediate enolate can be controlled by appropriate choice of base and solvent, thus allowing access to either *syn* or *anti* configuration in the product. The reaction can be completed in 2-4 days with little erosion in selectivity when run at 4 °C.

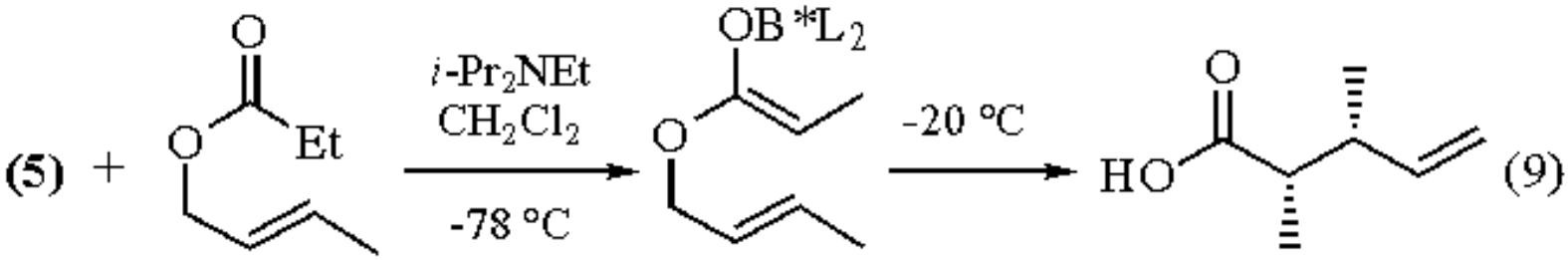

(9)

75%, 99:1 ds, >97% ee

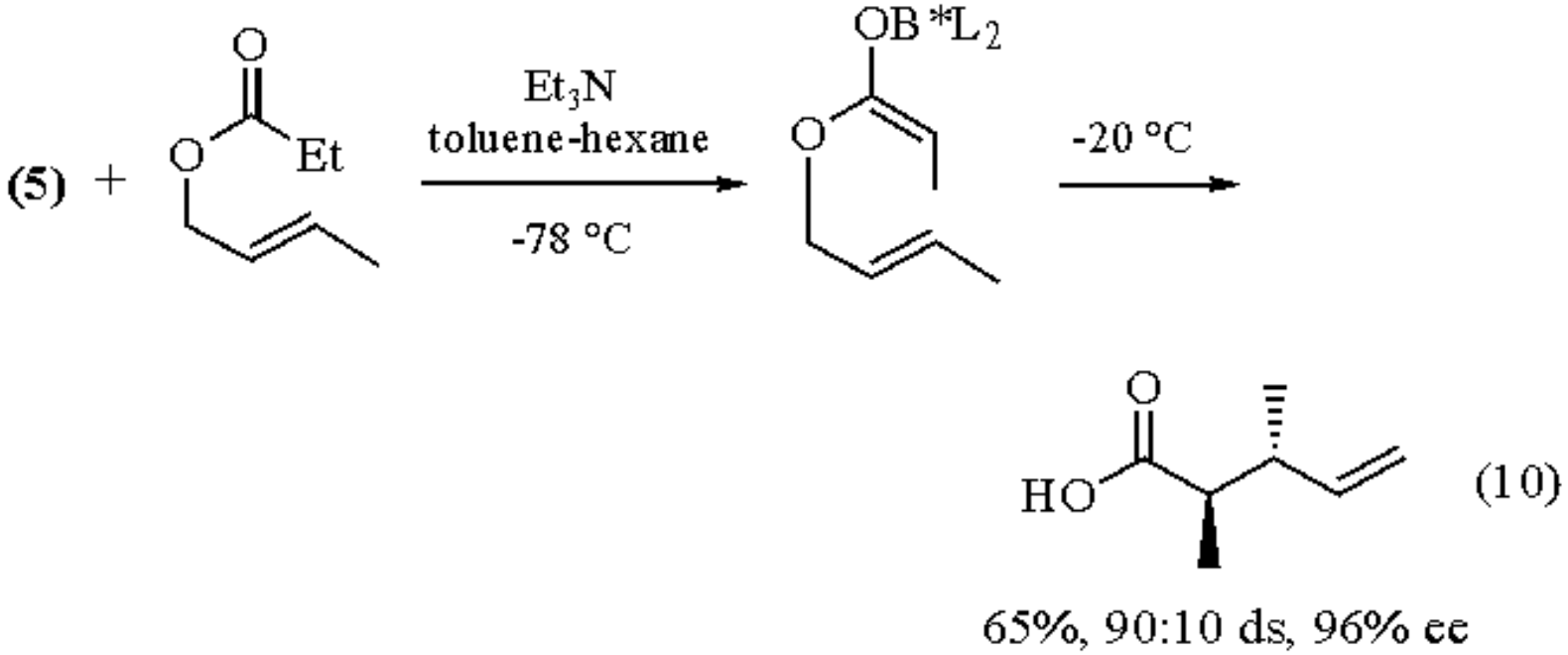

Ester-Mannich Additions.

The *E*(O) enolate (**7**) reacts with *N*-allyl or *N*-benzyl aldimines to afford chiral β-amino esters (eq 11).[4] As with the aldol reactions, best selectivities are achieved with imines derived from aromatic or unsaturated aldehydes. The method appears to have good potential for the synthesis of useful β-lactams if extended to other enolates.

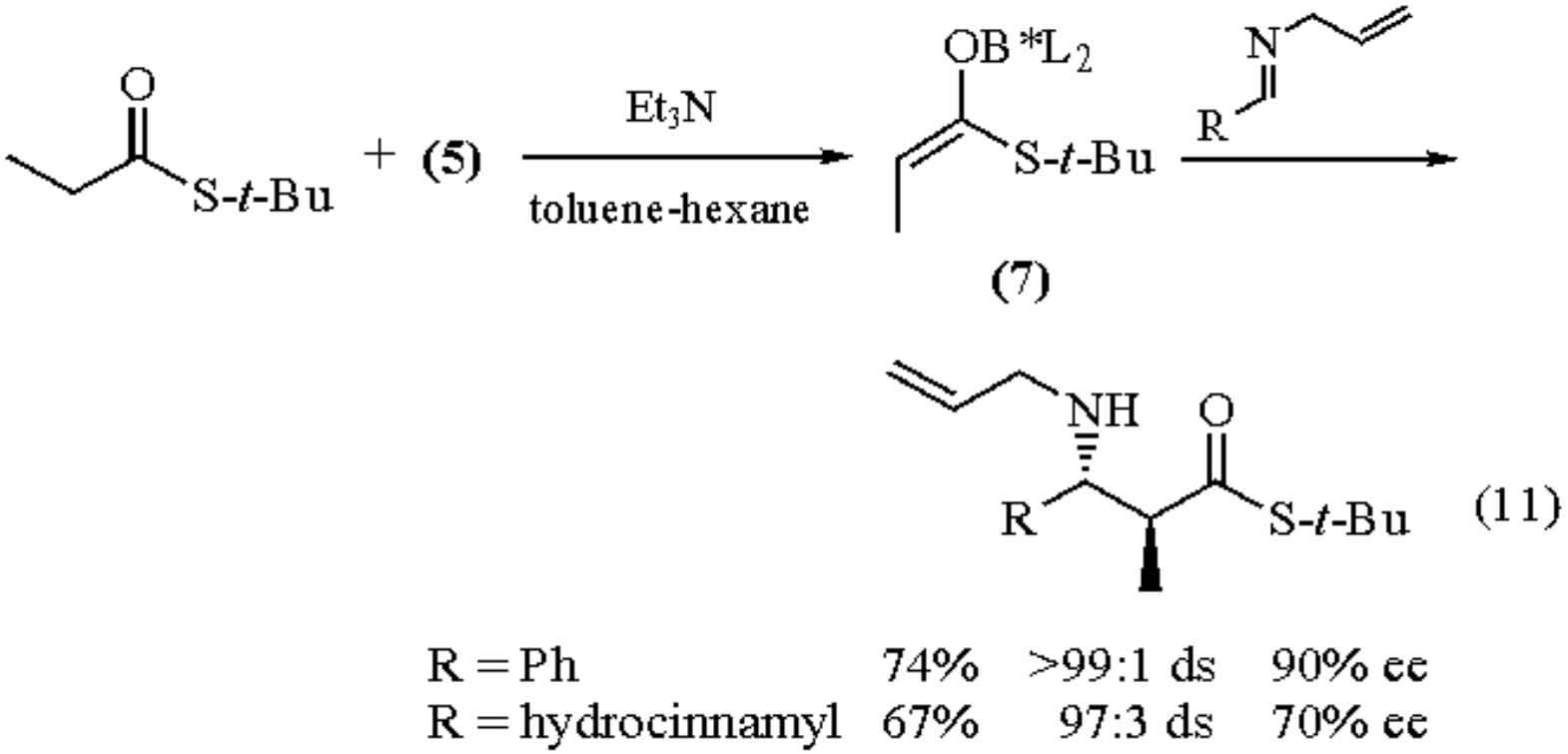

Carbonyl Allylation and Propargylation.

(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]

Boron complex (**8**), derived from the bis(tosylamide) compound (**3**), transmetalates allylstannanes to form allylboranes (eq 12). The allylboranes can be combined without isolation with aldehydes at -78 °C to afford homoallylic alcohols with high enantioselectivity (eq 13).[5] On the basis of a single reported example, reagent control might be expected to overcome substrate control in additions to aldehydes containing an adjacent asymmetric center. The sulfonamide can be recovered by precipitation with diethyl ether during aqueous workup. Ease of preparation and recovery of the chiral controller makes this method one of the more useful available for allylation reactions.

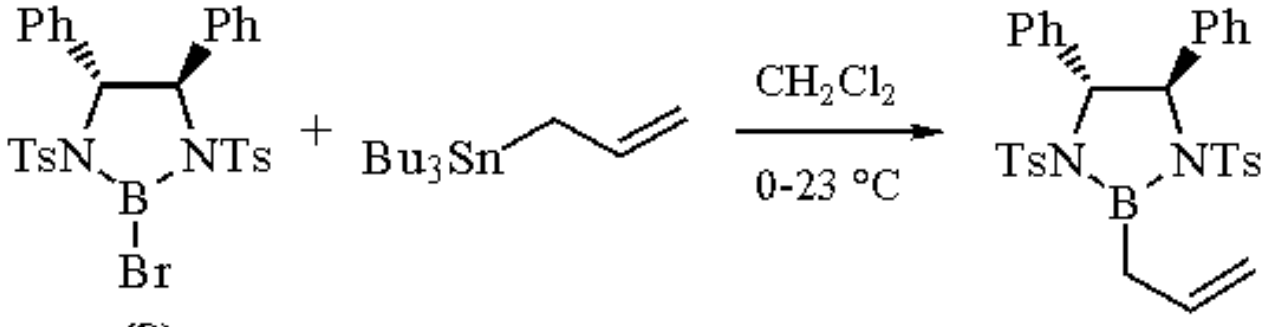

(12)

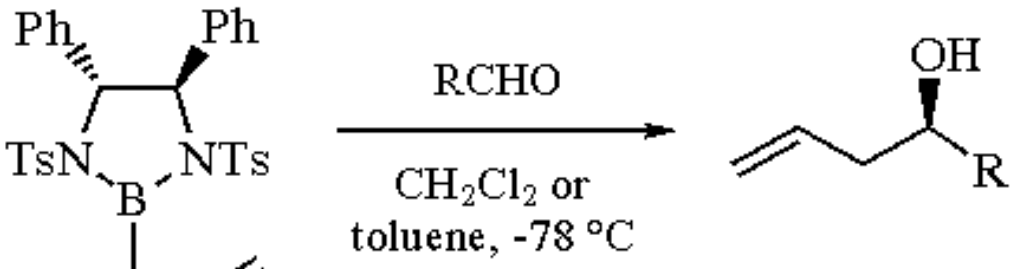

(13)

R = Ph	94% ee
R = cinnamyl	98% ee
R = cyclohexyl	93% ee
R = hexyl	90% ee

In the same way, reaction of (**8**) with allenyl- or propargylstannanes affords intermediate borane derivatives which, upon reaction with aldehydes, produce the expected adducts with high selectivities (eqs 14 and 15).[6]

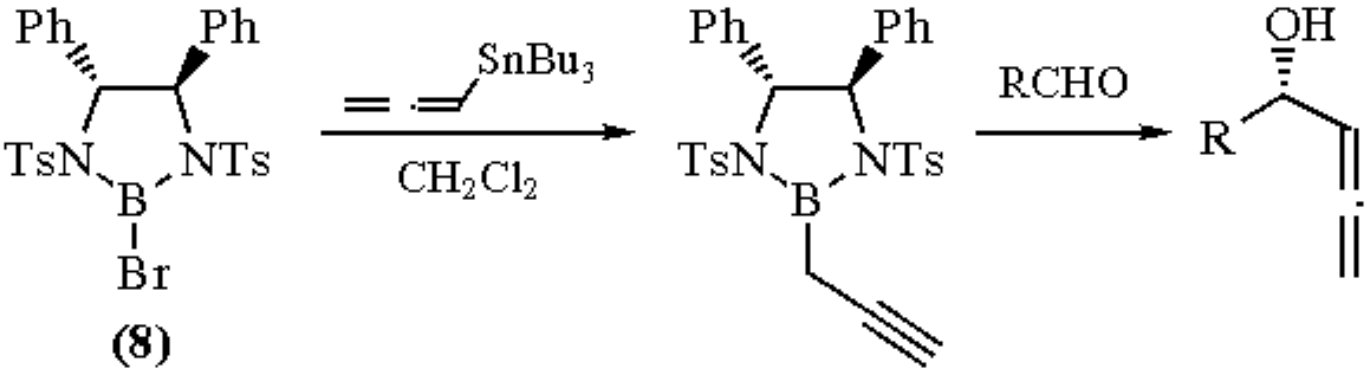

(14)

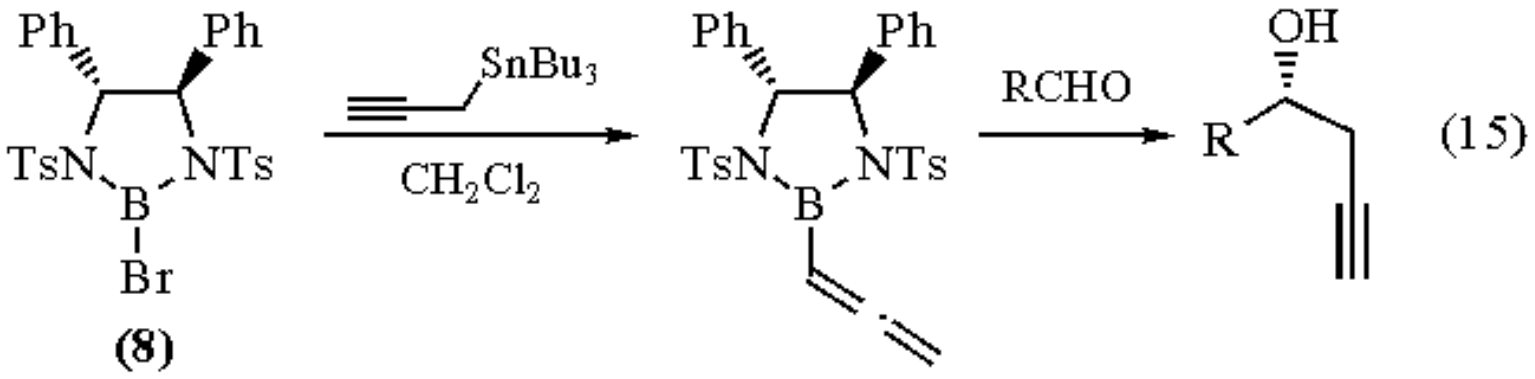

Other Applications.

Other (*R,R*)-stilbenediamine derivatives have been used to direct the stereochemical course of alkene dihydroxylation[8] (with stoichiometric quantities of ***Osmium Tetroxide*** and epoxidation of simple alkenes with ***Sodium Hypochlorite*** and manganese(III) complexes.[9]

Related Reagents.

B-Allyldiisopinocampheylborane; ***Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O$^{\alpha}$,O$^{\alpha'}$]titanium***; ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium***; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***Diisopropyl 2-Allyl-1,3,2-dioxaborolane-4,5-dicarboxylate***; ***(4R,5R)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane-Titanium(IV) Chloride***; ***2,2-Dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide***.

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1. (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *JACS* **1989**, *111*, 5493. (b) Pikul, S.; Corey, E. J. *OS* **1992**, *71*, 30.
2. (a) Corey, E. J.; Kim, S. S. *JACS* **1990**, *112*, 4976. (b) Corey, E. J.; Choi, S. *TL* **1991**, *32*, 2857. (c) Corey, E. J.; Lee, D.-H. *TL* **1993**, *34*, 1737.
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Diphenyldiazomethane[1]

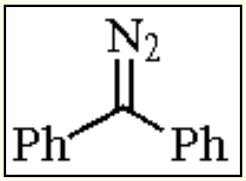

[883-40-9] · $C_{13}H_{10}N_2$ · Diphenyldiazomethane · (MW 194.25)

(alkylating agent for carboxylic acids; reagent for the synthesis of diphenylcyclopropanes from alkenes[1])

Physical Data: red solid, mp 29-32 °C.

Solubility: sol most organic solvents including ether, dichloromethane, petroleum ether, ethanol.

Preparative Methods: most commonly prepared by the oxidation of benzophenone hydrazone. The oxidants that are most frequently used are ***Mercury(II) Oxide***[2] and ***Nickel(II) Peroxide***,[3] though the use of ***Manganese Dioxide***,[4] ***Silver(II) Oxide***,[5] and ***Peracetic Acid***[6] have been reported. Typical reaction conditions involve addition of the oxidant to a solution of the hydrazone in a suitable solvent at rt. The oxidation requires 1-6 h to complete, depending on the conditions employed. Solvents that have been used are petroleum ether, diethyl ether and other ethereal solvents, and dichloromethane. When mercury(II) oxide is used, the addition of a basic ethanol solution speeds up the reaction and allows the oxidation to occur at a lower temperature. The reagent is typically not stored and is synthesized immediately prior to use. If the reagent is to be used for the esterification of a carboxylic acid, then an in situ oxidation can be employed using phenyliodine(III) diacetate (***(Diacetoxyiodo)benzene***)[7] or peracetic acid with a trace of iodine.[8] Interestingly, phenyliodine(III) diacetate provides a low yield of diphenyldiazomethane when used in the absence of a carboxylic acid, this has led the authors to suggest that the active alkylating agent is a species other than diphenyldiazomethane.

Handling, Storage, and Precautions: diphenyldiazomethane is potentially explosive. For this reason, extreme care must be observed in the synthesis and use of this compound with all operations being conducted behind a blast shield in a fume hood. There are also health related hazards that must be considered. Diazo compounds, as a class, are toxic and irritating and can be sensitizers. For a description of the hazards associated with this class of compounds, see the handling and storage precautions listed for ***Diazomethane***.

Alkylation of Carboxylic Acids.

Diphenyldiazomethane is an effective reagent for the alkylation of carboxylic acids. As with other diazoalkanes, the reaction occurs upon addition to a carboxylic acid. The only byproduct is N_2, thus reducing the workup to simple

removal of the solvent. The reaction requires the protonation of the diazoalkane on carbon by the carboxylic acid to give the corresponding diphenylmethyl diazonium salt. This then undergoes nucleophilic attack by the carboxylate to give the diphenylmethyl ester and N_2. This method has been used to protect carboxylic acids as their diphenylmethyl esters. Liberation of the acid can be accomplished by acid-catalyzed hydrolysis, or hydrogenolysis, making this a useful method for the protection of carboxylic acids which are base sensitive and cannot tolerate saponification. This reagent has been used for the esterification of free amino acids. Treatment of amino acids with diphenyldiazomethane does not lead to a reaction, due to the low acidity of the zwitterionic amino acid. However, the addition of a strong acid protonates the amino acid and thereby provides a reagent which will undergo alkylation with diphenyldiazomethane (eq 1).[9] Both serine and cysteine provide high yields of the desired ester in this reaction, indicating that hydroxyl and thiol groups do not interfere with this reagent. If the free amino group is converted to an amide or a urethane, then the reaction will proceed without the addition of an equivalent of acid. Thus *N*-protected amino acids have been esterified by the in situ conversion of benzophenone hydrazone to diphenyldiazomethane using phenyliodine(III) diacetate.[7] Common nitrogen protecting groups such as Boc, Cbz, Fmoc, and Troc are all effective in this reaction (eq 2). A wide range of substrates have been esterified with diphenyldiazomethane, including carbohydrates (eq 3)[10] and β-lactam derivatives (eq 4).[8] In the case of the β-lactam esterification, the diphenyldiazomethane was produced in situ by oxidation with peracetic acid. Interestingly, the acetic acid that is present as a contaminant in peracetic acid does not compete effectively for the diazo compound and a near stoichiometric amount of oxidant can be employed.

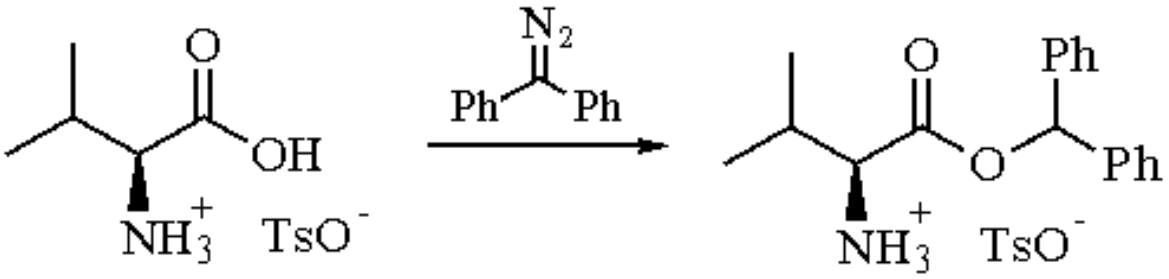

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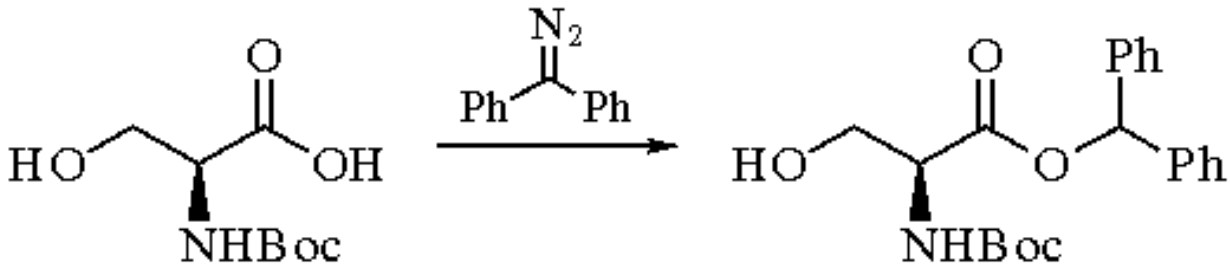

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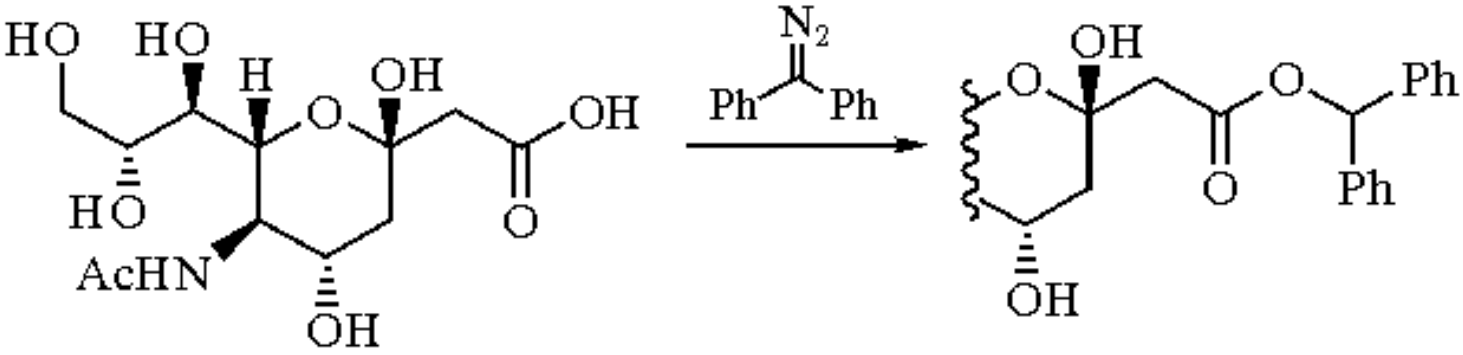

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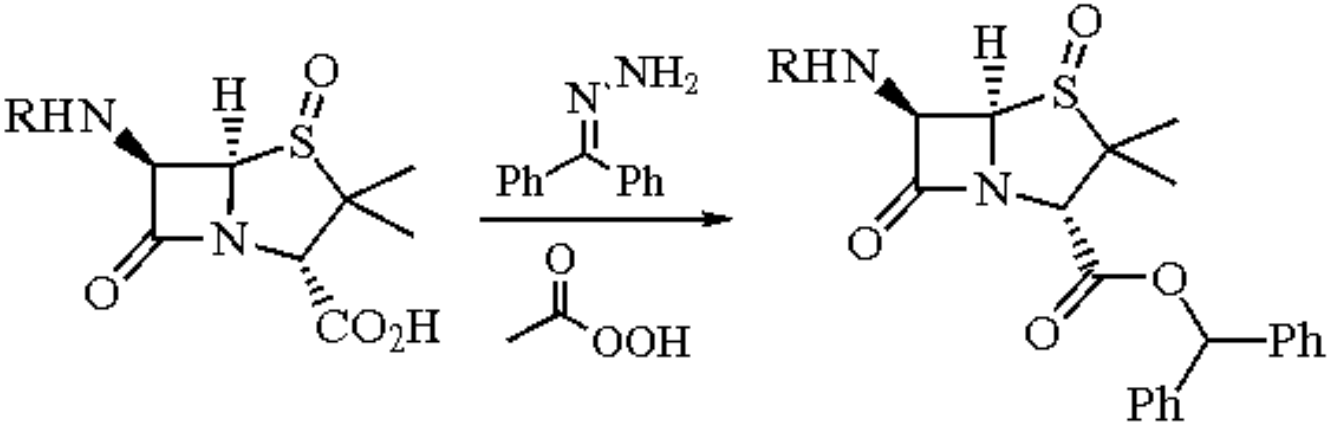

(4)

Cycloadditions.[11]

Diphenyldiazomethane undergoes cycloadditions with electron deficient alkenes to provide the corresponding diphenylpyrazolines. In the presence of a trace of acid the pyrazolines so obtained spontaneously undergo loss of N_2 to provide the corresponding cyclopropane.[12] This reaction is so sensitive to acid that base-washed glassware must be used in order to isolate the pyrazoline with certain substrates such as methyl acrylate (eq 5). If no acid is present, or if a mild base such as ***Triethylamine*** is added, then the pyrazolines must be heated in order to extrude N_2. Thus treatment of the azlactone derivative shown in eq 6 with diphenyldiazomethane and triethylamine at 80 °C provides the diphenylcyclopropane derivative in good yield. Interestingly, in this case, reaction in the absence of base provides none of the cycloadduct. The reaction can also be promoted by photolysis (eq 7).[13] The evidence suggests that this reaction proceeds by the extrusion of N_2 to provide diphenylcarbene, which then undergoes addition to the alkene.

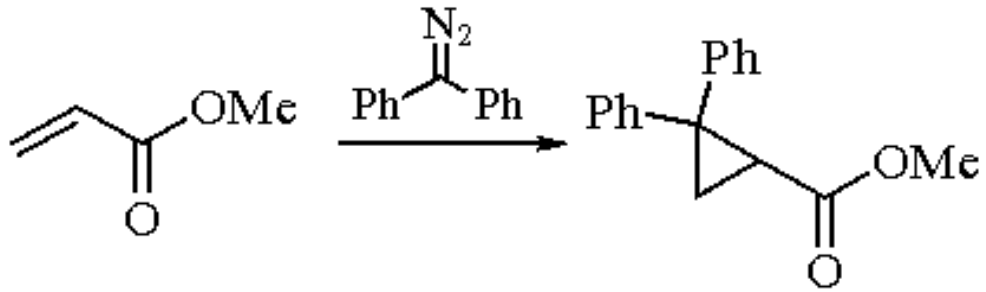

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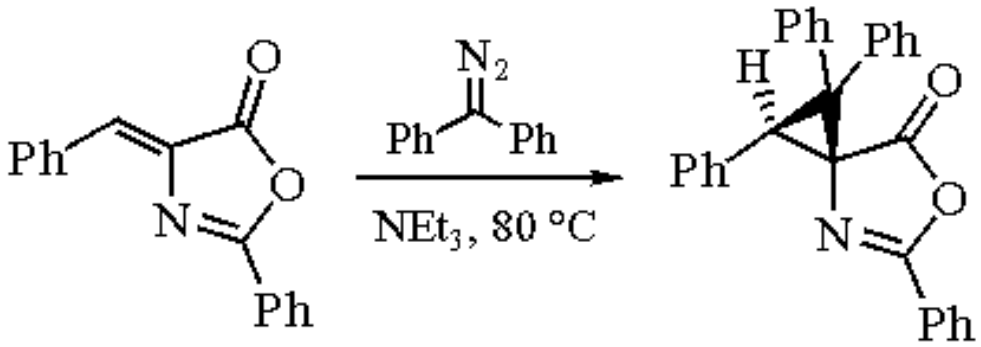

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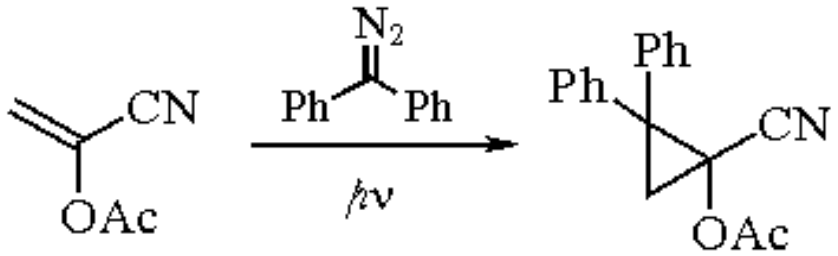

(7)

Formation of cyclopropanes with diphenyldiazomethane and transition metal catalysts has also been studied. Various transition metals can be used, including Cu, Pd, and Rh. The chemoselectivity of the reaction depends on the metal complex used. Thus cyclopropanation of the norbornene derivative shown in eq 8 with diphenyldiazomethane under ***Palladium(II) Chloride*** catalysis provides the cyclopropane derived from the internal alkene, whereas the same reaction with $Rh_2(OAc)_2$ provides the cyclopropane derived from the exocyclic alkene.[14] Cyclopropanation of enamines with ***Copper(II) Acetylacetonate*** has also been reported (eq 9).[15] This catalyst is less active and will not cyclopropanate ethyl vinyl ether or cyclohexene.

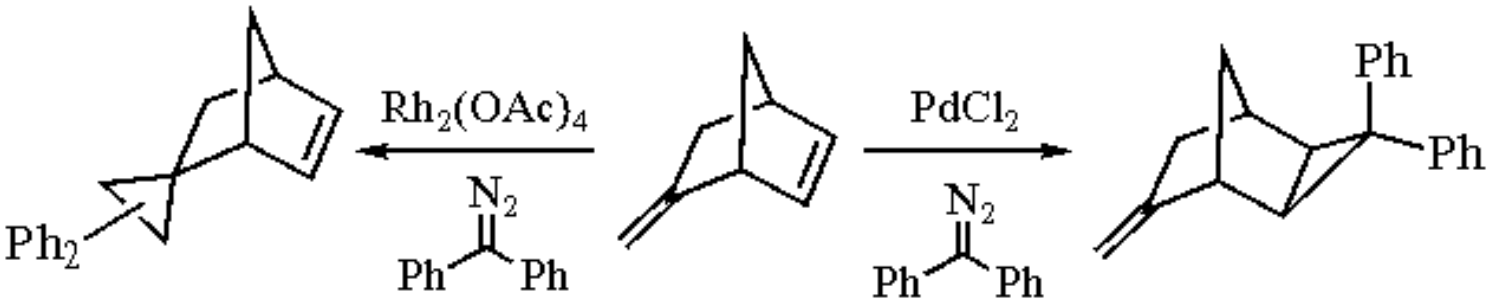

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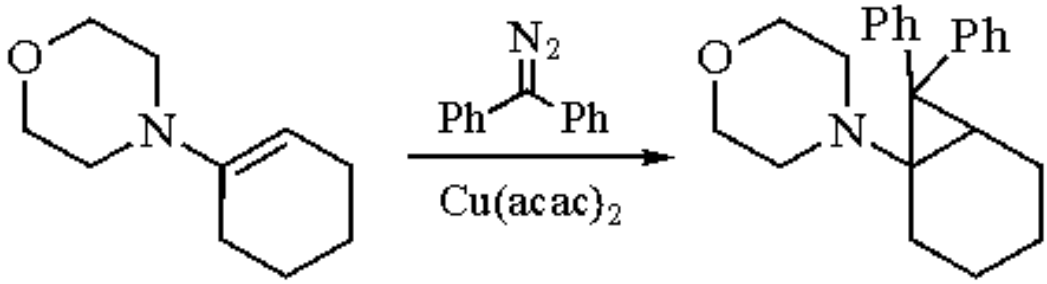

(9)

Acetal Formation.

Treatment of diphenyldiazomethane with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** and an alcohol (or thiol) produces the corresponding benzophenone acetal (or thioacetal) (eq 10).[16] If the starting alcohol component is a diol, the reaction produces a cyclic acetal. Macrocyclic crown ether acetals have been synthesized by this method in moderate to high yields (eq 11).[17]

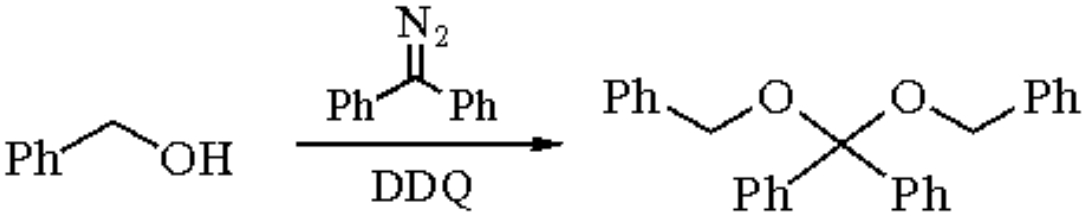

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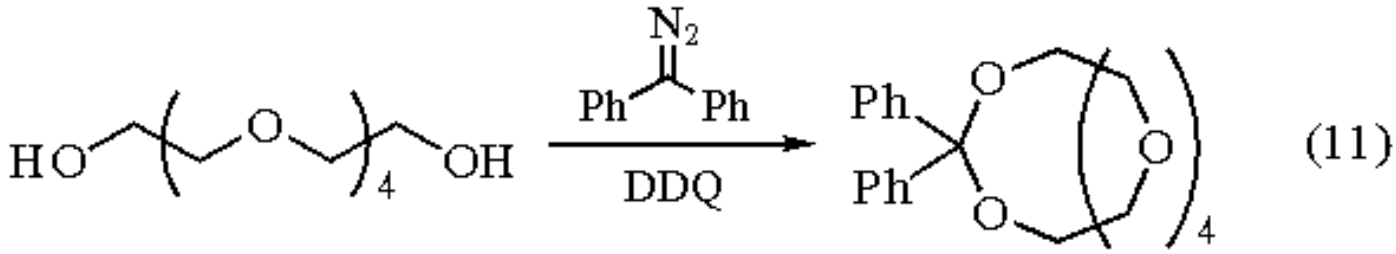

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Diphenyl Diselenide[1]

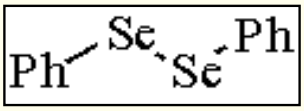

[1666-13-3] · $C_{12}H_{10}Se_2$ · Diphenyl Diselenide · (MW 312.14)

(source of phenylseleno functionality, reactive with wide variety of organic nucleophiles,[2-13] electrophiles,[14-24] and radicals;[25-27] source of phenylseleno radicals[28-31])

Physical Data: mp 63-64 °C.

Solubility: sol MeOH, EtOH, ether, THF, toluene, and most common organic solvents; insol water.

Form Supplied in: yellow powder; widely available.

Preparative Methods: synthesized by reaction of ***Phenylmagnesium Bromide*** with ***Selenium***, followed by treatment with ***Bromine***.[32] This method is superior to older methods[33] in that it does not generate the toxic byproducts H_2Se and PhSeH.

Handling, Storage, and Precautions: is air stable, has a faint odor, and is not appreciably hygroscopic. Organoselenides are reputed to be highly toxic, although not as toxic as inorganic selenium compounds such as H_2Se or SeO_2.[1b] Use in a fume hood.

Introduction.

Diphenyl diselenide is most frequently used as a reagent for incorporation of the phenylseleno functionality into molecules. The phenylseleno group provides useful functionality arising from the variety of reactions in which it can be subsequently involved. The most noted reaction of organoselenides is their oxidative elimination, which generates alkenes from phenyl selenides under mild, neutral conditions.[34] Phenyl selenides can also undergo radical reduction[35] and certain radical alkylation reactions.[36] Other potentially valuable synthetic uses of phenyl selenides include reductive lithiation[37] and α-deprotonation.[38]

Incorporation of Nucleophilic Phenylseleno Reagents.

Diphenyl diselenide and ***Benzeneselenol*** are the most popular reagents for the generation of nucleophilic phenyl selenide. Diphenyl diselenide is usually the preferred precursor due to its greater ease in handling. Selenolate anions are potent, soft nucleophiles.[2]

There are many popular and generally applicable procedures for the generation of benzeneselenolate anions from PhSeSePh. Treatment of PhSeSePh with ***Sodium Borohydride*** provides a very convenient method for the generation of the benzeneselenolate anion.[3] The nucleophilicity of the anion thus formed is apparently decreased due to complexation with borane.[4] Uncomplexed sodium benzeneselenolate can be generated upon reduction of PhSeSePh with ***Sodium Hydride***[5] or ***Sodium*** metal.[4] Generation of sodium benzeneselenolate upon treatment of PhSeSePh with Rongalite (***Sodium Hydroxymethanesulfinate***) has been mentioned as being particularly amenable to large scale preparations, due to the absence of H_2 evolution.[6]

The benzeneselenolate anion is reactive with a variety of carbon electrophiles. It is reactive with benzyl (eq 1) and alkyl halides,[8] leading to the formation of simple alkyl phenyl selenides. The benzeneselenolate anion is also useful in the nucleophilic ring opening of oxiranes (eq 2).[3] This method can be of limited value with unsymmetrical oxiranes, as regioselectivity is often poor. While the borane-complexed benzeneselenolate anion generated from treatment of PhSeSePh with $NaBH_4$ is not a reactive enough nucleophile to cleave esters,[4,9] a variety of more reactive benzeneselenolate anions are quite effective in this regard (eq 3).[4,9,10] A particularly reactive form can be formed by reaction of PhSeSePh with ***Lithium Aluminum Hydride***. This species is capable of reaction with oxetanes and oxolanes, cleaving the ethereal carbon-oxygen bond (eq 4).[11]

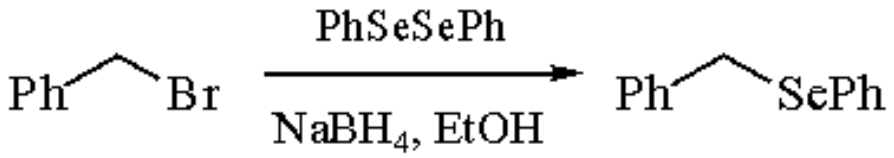

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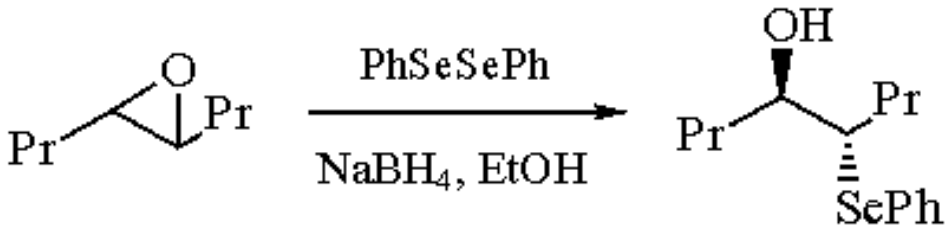

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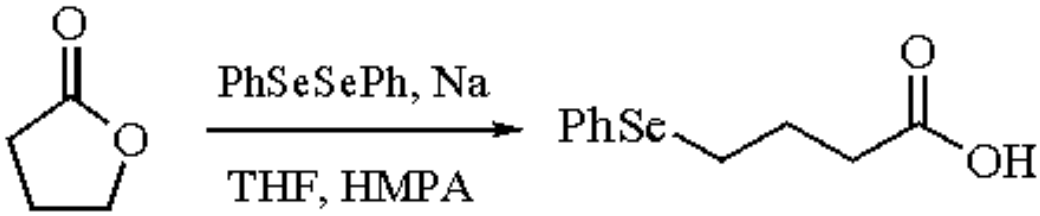

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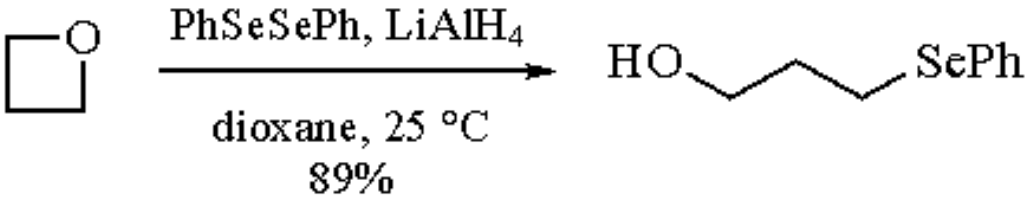

(4)

The benzeneselenolate anion also adds in a conjugate fashion to unsaturated carbonyl compounds. Addition to α-methylene lactones proceeds quite readily (eq 5). Given the facility with which subsequent oxidative elimination of the phenylseleno group can be carried out, thus regenerating unsaturation, an effective means of protecting a labile α-methylene lactone is available.[12] The benzeneselenolate anion can also be generated electrochemically and added to

unsaturated ketones and esters in a conjugate fashion (eq 6).[13]

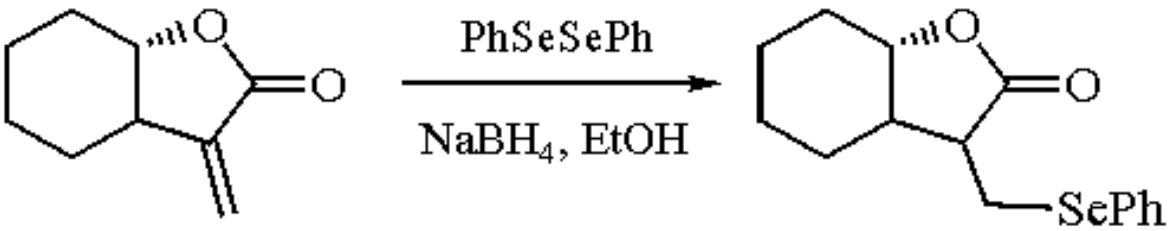

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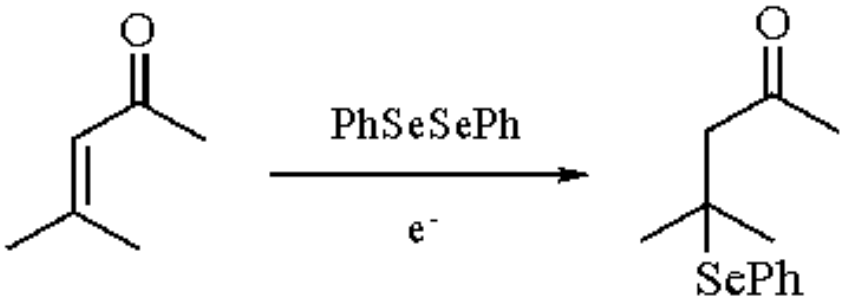

(6)

Incorporation of Electrophilic Phenylseleno Reagents.

A variety of carbanion nucleophiles react with PhSeSePh to generate the corresponding phenylseleno-substituted product. While PhSeSePh is not as electrophilic as other organoselenium reagents, such as ***Benzeneselenenyl Chloride***, ***Benzeneselenenyl Bromide***, or ***N-Phenylselenophthalimide***, there are numerous situations where it can be used to supply electrophilic phenyl selenide.

Diphenyl diselenide reacts readily with many organometallic species (eq 7).[14] Similar reactivity has also been observed with ester and lactone enolates (eq 8)[15] and nitrile-stabilized carbanions.[16] The reaction of ketone enolates with PhSeSePh usually fails due to an unfavorable equilibrium constant (eq 9).[17] However, this unfavorable equilibrium can be driven to completion upon addition of O_2,[18] which converts the $PhSe^-$ formed in the reaction to PhSeSePh.

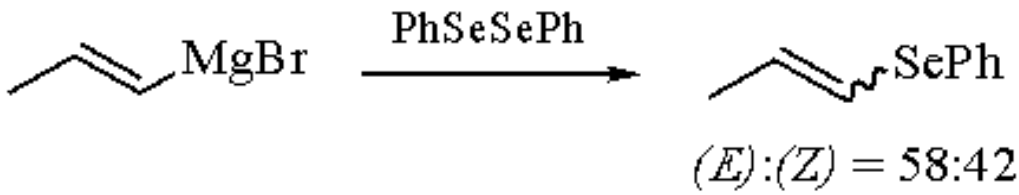

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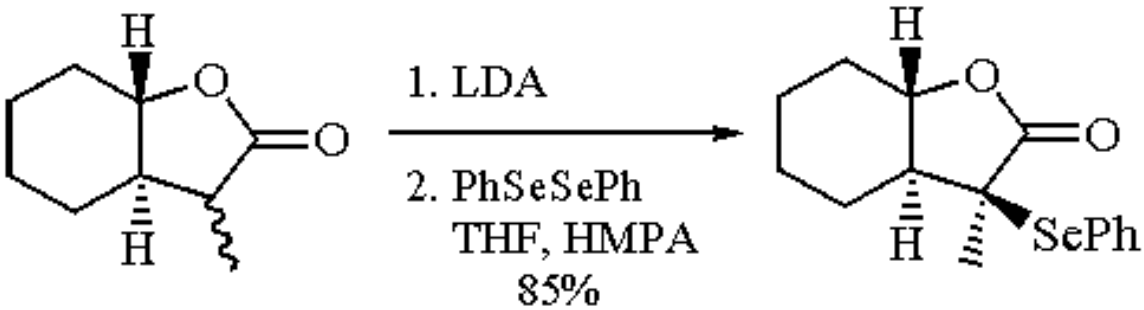

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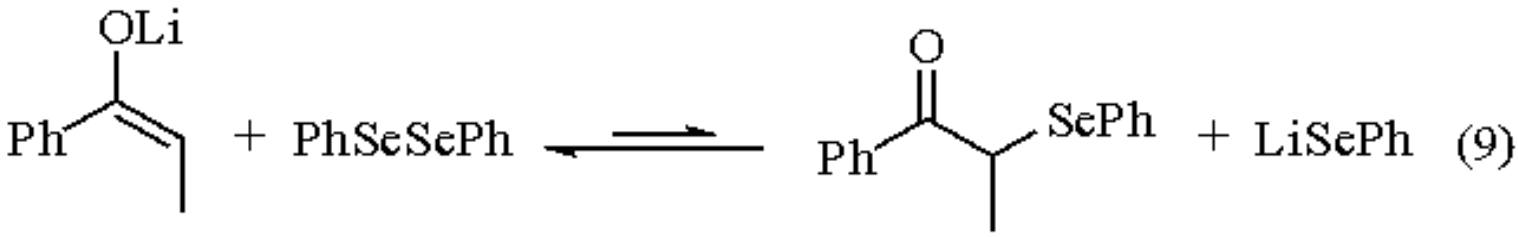

Methods involving the reaction of less reactive nucleophiles with PhSeSePh usually involve in situ generation of the phenylselenium cation, or some other highly reactive phenyl selenide species. A variety of dialkyl ketones, aliphatic aldehydes, and even β-keto esters or β-diketones react with PhSeSePh in the presence of ***Selenium(IV) Oxide*** and a trace of H_2SO_4 (eq 10).[19] Enol acetates react with PhSeSePh upon electrochemical anodic oxidation in the presence of $Et_4N^+Br^-$ (eq 11).[20] It has been proposed that this method involves the in situ generation of PhSeBr. Phenyl selenoacetate is probably generated in situ upon reaction of PhSeSePh with ***Copper(II) Acetate*** or ***Lead(IV) Acetate***.[21] This reagent effects the *trans*-acetoxyselenation of alkenes. The phenylselenium cation has been generated from PhSeSePh upon photolysis in the presence of DCN, proceeding through a mechanism involving photoinduced electron transfer (eq 12),[22] or upon treatment of PhSeSePh with $(NH_4)_2S_2O_8$.[23] The phenylselenium cation thus generated induces selenolactonization and selenoetherification. Stereospecific selenoamination, proceeding through the possible intermediacy of a selenonium ion, has been reported upon reaction of cyclohexene with PhSeSePh in the presence of ***Chloramine-T*** (eq 13).[24]

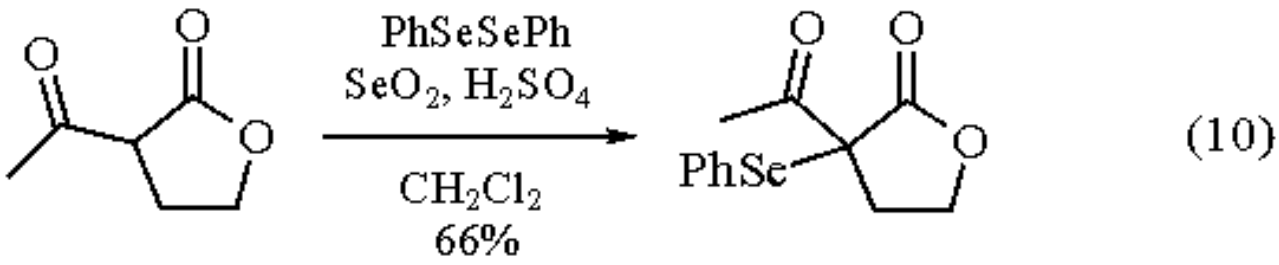

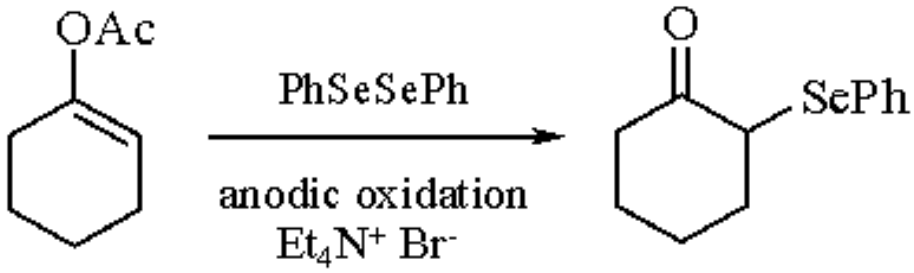

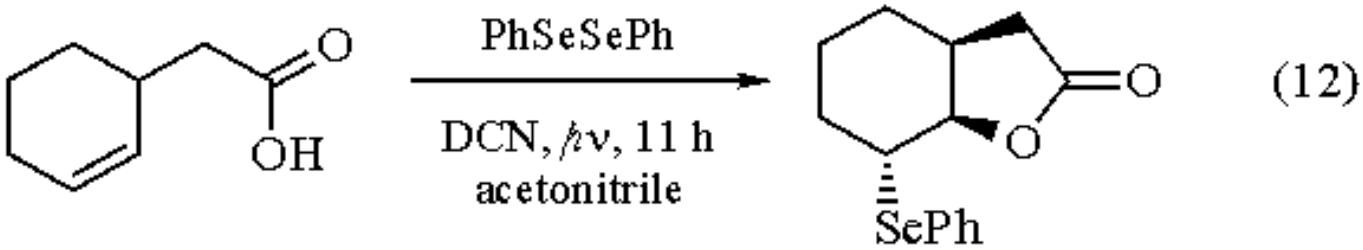

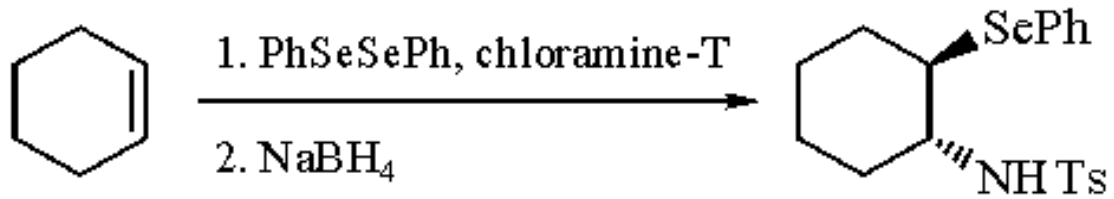

(13)

Uses in Radical Reactions.

Diphenyl diselenide has been used as a source of phenylseleno radicals and as a radical trap, allowing for the introduction of phenylseleno functionality via radical reactions. Whereas photolysis of PhSeSePh has been shown to generate phenylseleno radicals reversibly, products arising from addition to simple alkenes have not been observed due to the reversible nature of this addition.[28] This reversible addition has, however, been used to isomerize alkenes, as exemplified in the photochemical isomerization of vitamin D_2 to 5,6-*trans*-vitamin D_2 in the presence of PhSeSePh, which proceeds in 57% yield (eq 14).[29] This isomerization only proceeds in 20-40% yield in the presence of ***Iodine***.[39]

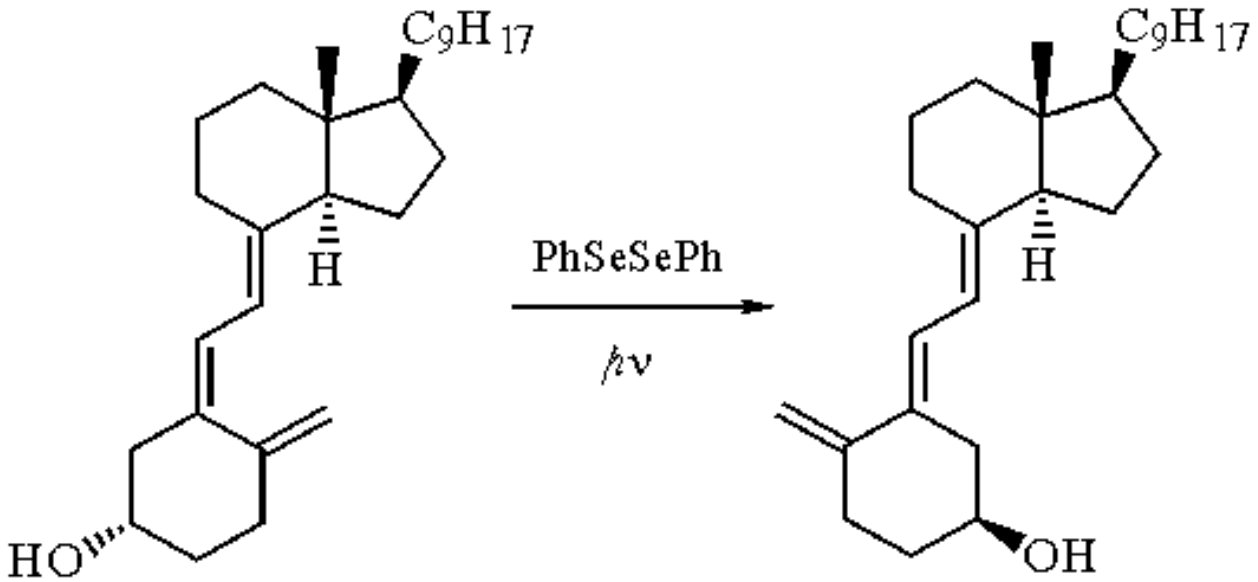

(14)

The addition of PhSeSePh to alkynes, however, has been observed under thermal (eq 15)[30] or photochemical[31] conditions, leading to predominantly (*E*) products.

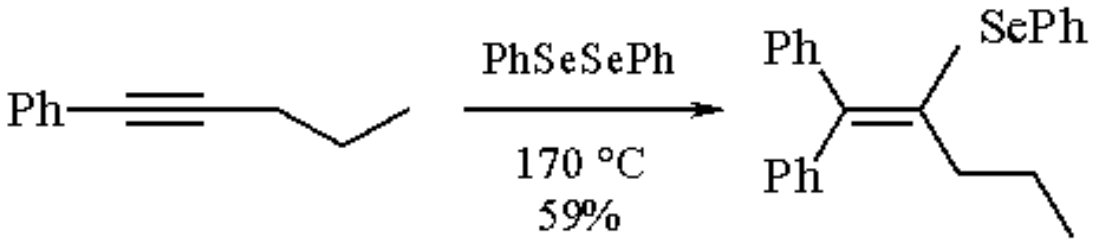

(15)

Diphenyl diselenide can also be used as an effective radical trap. Generation of the 5-hexenyl radical from a suitable alkylmercury(II) chloride in the presence of PhSeSePh generates both a cyclized and uncyclized alkyl phenyl selenide (eq 16). By analysis of the product ratios under various reaction conditions, and the known rate of the hexenyl radical cyclization, a rate constant of 2.6×10^7 L mol^{-1} s^{-1} at 45 °C was obtained for the S_H2 reaction of a primary alkyl radical with PhSeSePh.[25] Diphenyl diselenide has also been used to trap radicals generated from a variety of other

sources,[26] including those generated photochemically from thiohydroxamate esters (eq 17).[27]

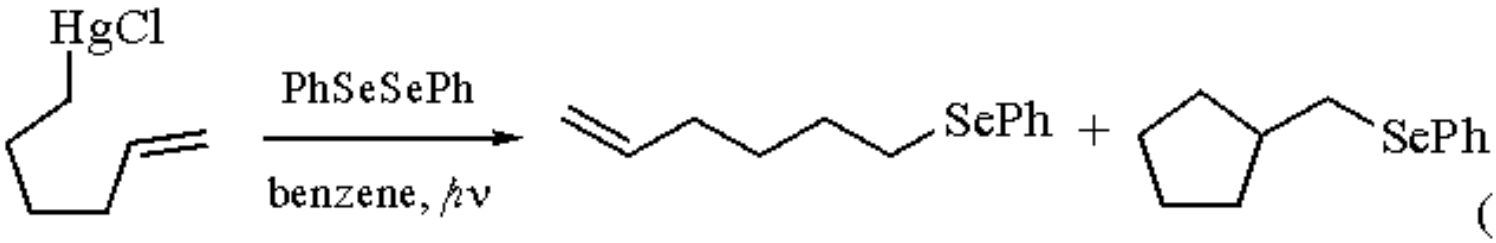

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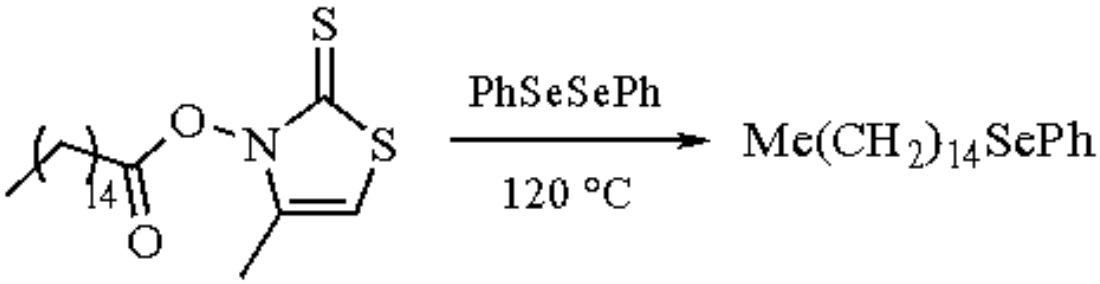

(17)

Other Uses.

Diphenyl diselenide can catalyze the allylic chlorination of alkenes with ***N-Chlorosuccinimide***. The major product is usually a rearranged allylic chloride. This reaction is not believed to proceed through a radical mechanism, in contrast with most procedures for allylic chlorination (eq 18).[40] Phenylselenoalkynes are formed in good yield upon reaction of terminal alkynes with ***(Diacetoxyiodo)benzene*** and PhSeSePh (eq 19).[41]

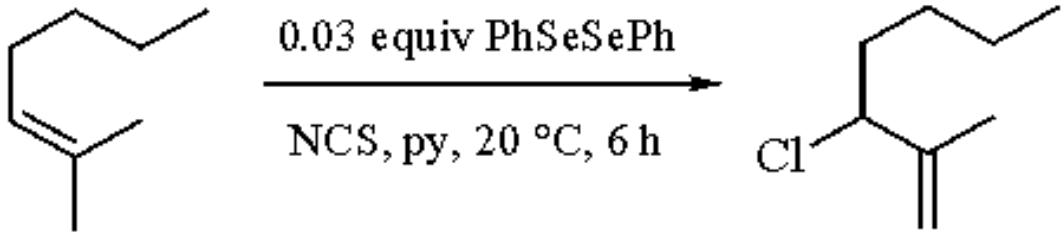

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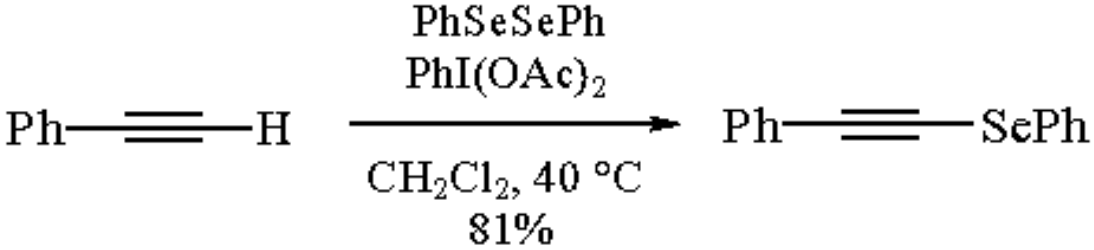

(19)

The carbene or carbenoid species generated from ***Diazomethane***,[42] α-diazo esters,[43] or 6-diazopenicillinates[44] will insert in the Se-Se bond of PhSeSePh to generate bis(phenylseleno) acetals (eq 20).

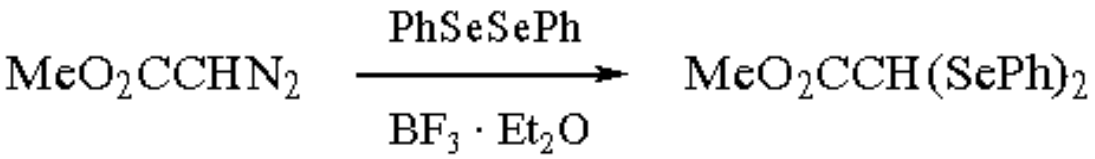

(20)

Terminal alkenes can be converted to α-phenylseleno ketones upon reaction with PhSeSePh, ***Bis(tri-n-butyltin) Oxide***, and Br_2 (eq 21).[45] The initially formed reagent in this procedure is thought to be $PhSeOSnBu_3$.

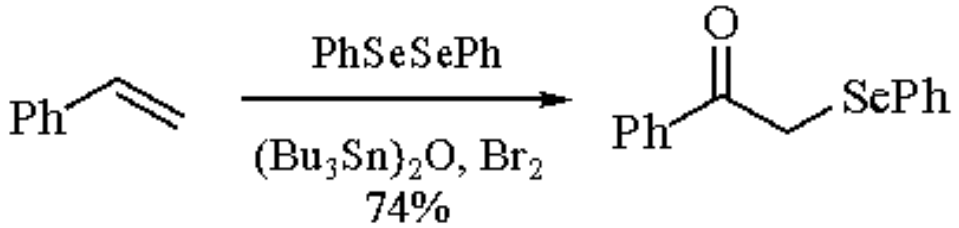

(21)

Related Reagents.

Diphenyl Disulfide; ***Diphenyl Ditelluride***; ***2,2´-Dipyridyl Diselenide***.

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Diphenyl Disulfide[1]

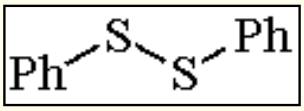

[882-33-7] · $C_{12}H_{10}S_2$ · Diphenyl Disulfide · (MW 218.36)

(source of phenylthio functionality, reactive with wide variety of organic nucleophiles,[2-12] radicals;[13-18] source of phenylthio radicals;[19-27] incorporates phenylthio functionality with deoxygenation when used in conjunction with Bu_3P[28-30])

Alternate Name: phenyl disulfide.

Physical Data: mp 61-62 °C.

Solubility: sol EtOH, ether, THF, benzene, CS_2; insol water.

Form Supplied in: white crystals; widely available in high purity.

Handling, Storage, and Precautions: air-stable; usually used as supplied. The odor of PhSSPh, while disagreeable, is not nearly as objectionable as that of the corresponding SH compound, thiophenol. Use in a fume hood. It has been reported that repeated skin contact with disulfides may cause irritation.[31]

Introduction.

Diphenyl disulfide is most frequently used as a reagent for incorporation of a phenylthio functionality into molecules. The phenylthio group is a useful functionality because of the variety of reactions in which it can be subsequently used. For example, phenyl sulfides undergo oxidative elimination, generating alkenes under relatively mild, neutral conditions.[2,32] Certain allylic phenyl sulfides undergo [2,3]-sigmatropic shifts upon oxidation to sulfoxides, leading to allylic alcohols.[33] Phenyl sulfides can also serve as a source of carbon-centered radicals in radical reactions, although they are usually not as reactive as alkyl halides and organoselenides in this regard.[34] Other valuable synthetic uses of phenyl sulfides include reductive lithiation[35] and α-deprotonation.[36]

Reactions of Diphenyl Disulfide with Carbon Nucleophiles.

The most common use of PhSSPh in organic synthesis is as an electrophilic source of the phenylthio functionality. Other related, and somewhat more reactive sulfenylating agents derived from PhSSPh include ***Benzenesulfenyl Chloride*** (PhSCl) and ***Phenyl Benzenethiosulfonate*** ($PhSO_2SPh$).[37] Phenyl benzenethiosulfonate is prepared from

PhSSPh by a wide variety of oxidizing agents.[38] While PhSCl is much more electrophilic than PhSSPh, it must be generated in situ from PhSSPh, and is therefore less convenient.

Ketone[2,3] (eq 1) and ester[2] (eq 2) enolates react readily with PhSSPh to generate the corresponding α-phenylthio carbonyl compound. Lactone[4] enolates also react with PhSSPh, leading to synthetic intermediates which have been carried on to form α-methylene lactones (eq 3). Ketoester dianions have been successfully sulfenylated to generate α-phenylthio ketones (eq 4).[5]

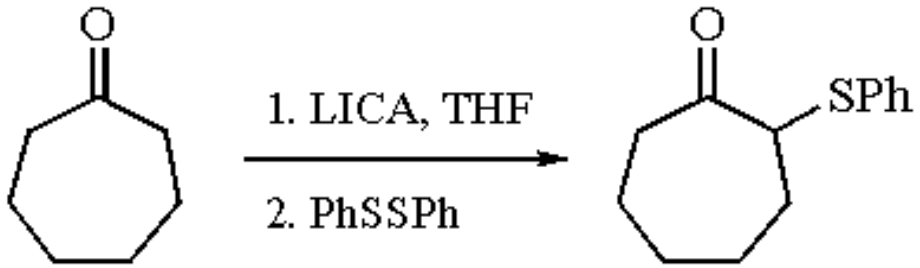

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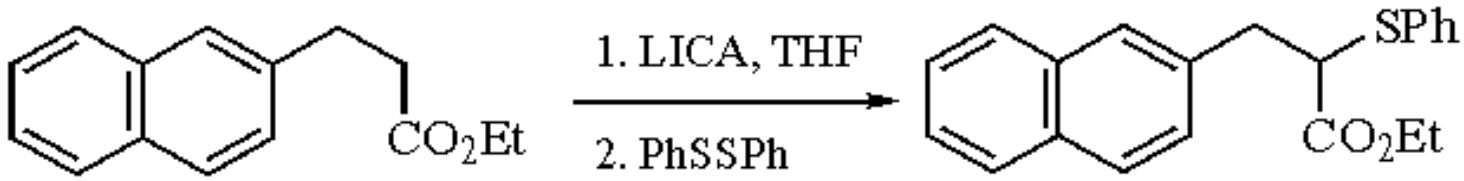

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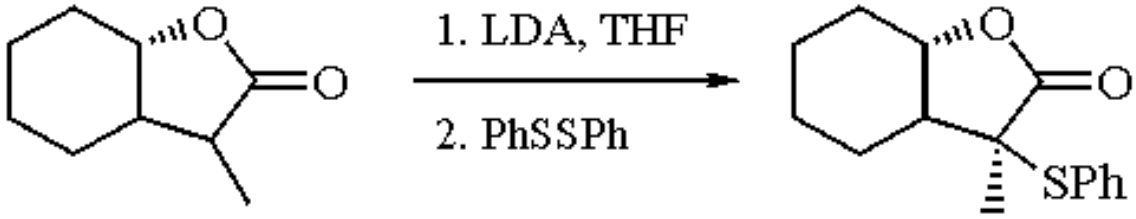

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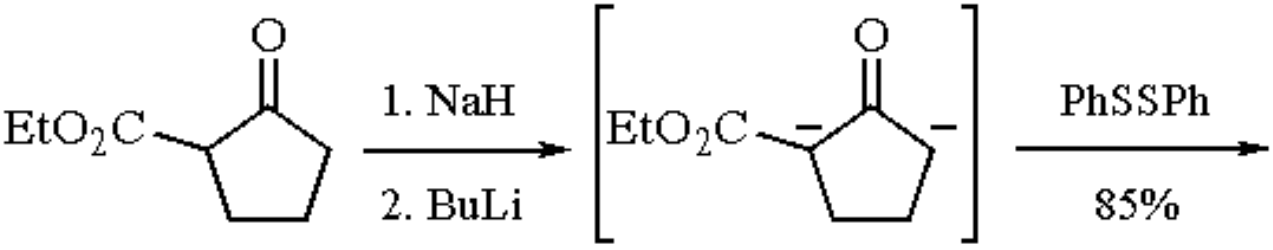

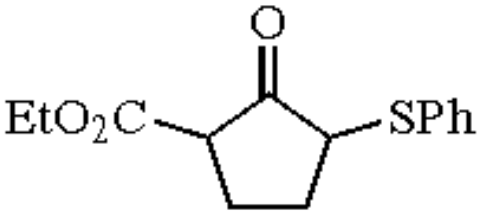

(4)

Aldehydes have been converted to α-phenylthio aldehydes by sulfenylation of an *N*-cyclohexyl imine (eq 5).[6] Modest enantiomeric excesses have been obtained when the imine generated from *R*-(+)-α-phenylethylamine is employed.[7]

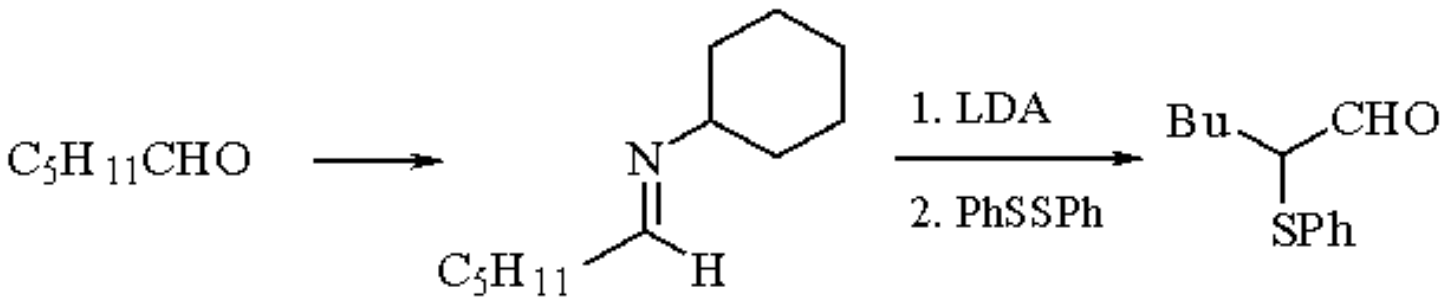

(5)

Reaction of spirocyclobutanones with an excess of PhSSPh in the presence of ***Sodium Methoxide*** leads initially to α-bis(phenylthio) ketones, which can undergo in situ ring opening arising from nucleophilic attack of methoxide at the cyclobutanone carbonyl, to form γ-bis(phenylthio) esters (eq 6).[8]

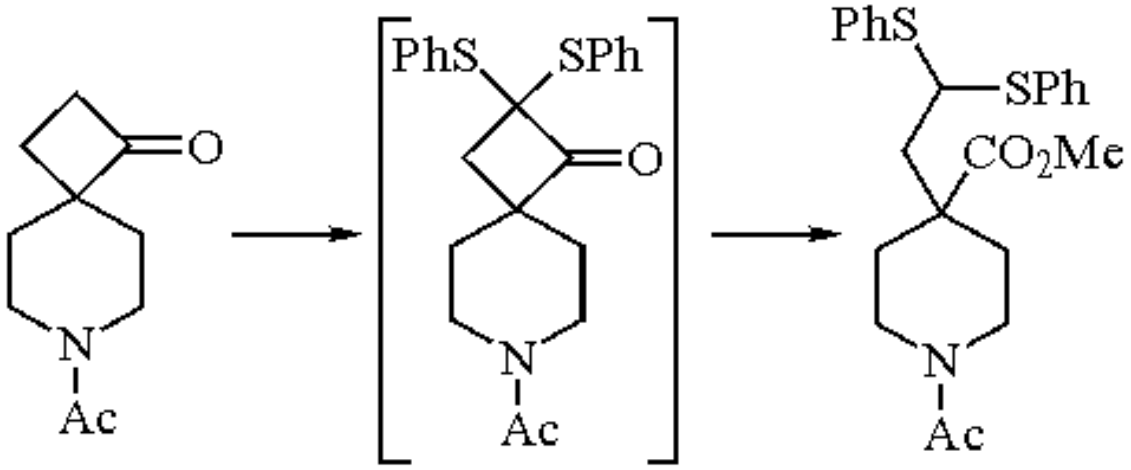

(6)

Cyclohexanones undergo dehydrogenative sulfenylation upon reaction with PhSSPh in methanolic NaOMe to give *o*-phenylthio phenols (eq 7).[9] This reaction is interesting, in that the PhSSPh appears to behave both as a source of electrophilic phenylthio functionality and as an oxidizing agent in the course of the transformation.

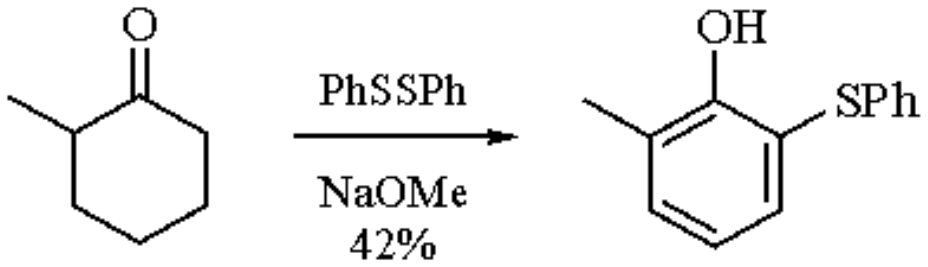

(7)

The reaction of strongly nucleophilic organometallic reagents such as Grignard and organolithium species with PhSSPh, leading to the corresponding phenyl sulfide, is quite general. This type of reaction has seen extensive use in the chemistry of heterocycles as a method for incorporating the phenylthio functionality. Several illustrations of this mode of reaction are shown here.

A phenylthio group can be introduced at the 5-position of 2-alkylfurans (eq 8).[10] This serves to block subsequent additions at C-5 and activate C-4 towards electrophilic attack. 3-Phenylthioindoles have been synthesized by metalation of indoles, with subsequent anion quenching by PhSSPh (eq 9).[11] Lithiation of pyridyl phenyl sulfoxides with ***Lithium Diisopropylamide***, followed by quenching with PhSSPh yields the corresponding phenylthio derivatives

(eq 10).[12]

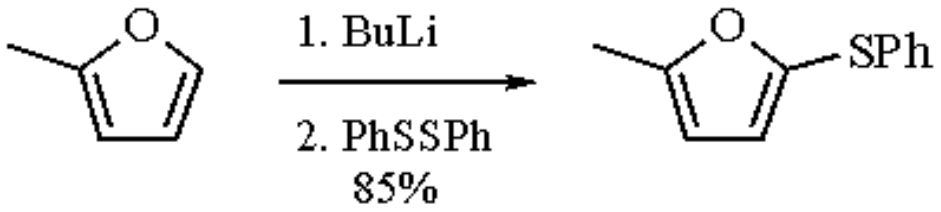

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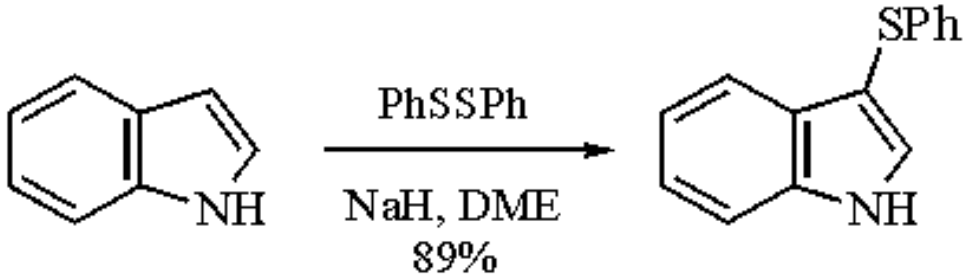

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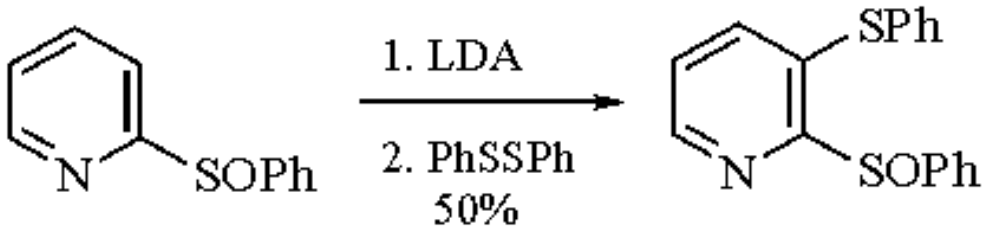

(10)

Reactions of Diphenyl Disulfide with Alkenes.

Diphenyl disulfide adds cleanly to many alkenes and dienes upon catalysis by $BF_3.OMe_2$.[39] The trifluoroacetoxysulfenylation of unsaturated esters, carboxylic acids, nitriles, and amides has recently been described (eq 11).[40] In this versatile addition reaction, the PhSSPh is oxidized to the phenylthio cation by ***Manganese(III) Acetate***. The electrophilic sulfur species is believed to add to the alkene, activating it towards nucleophilic attack by ***Trifluoroacetic Acid***. Mild aqueous hydrolysis leads to β-hydroxyalkyl phenyl sulfides in good yield and high regioselectivity.

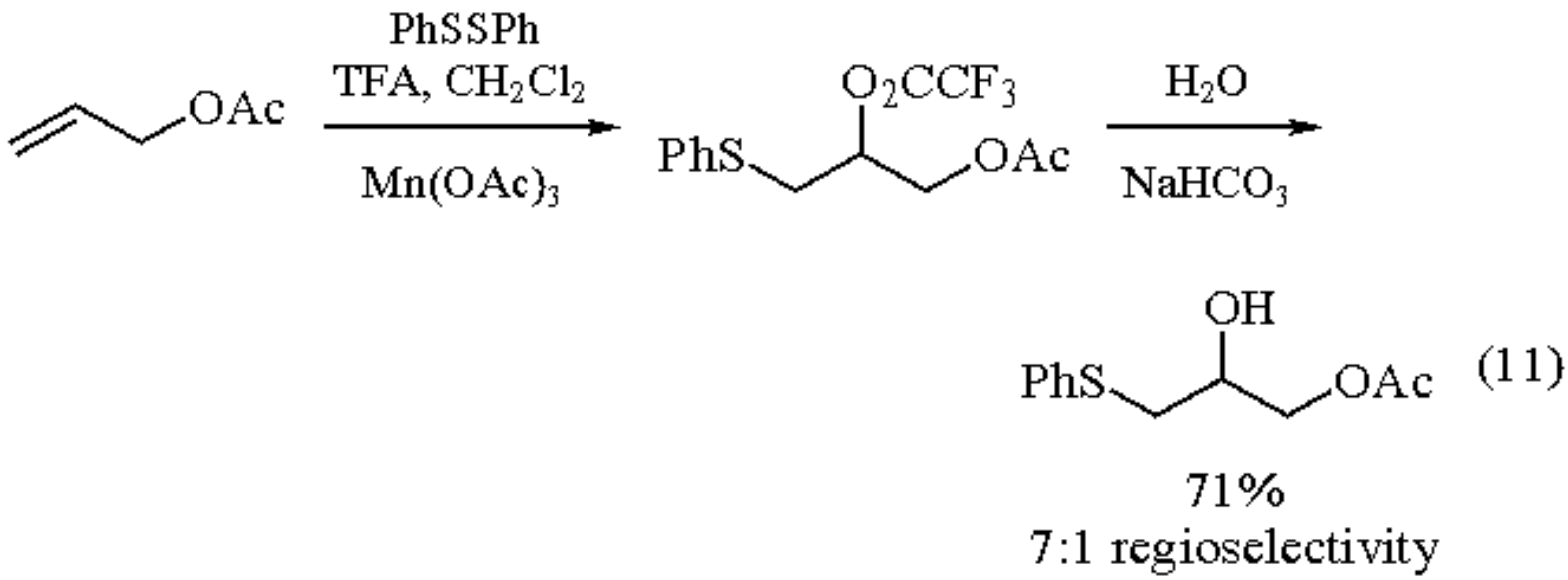

Other Reactions of (Formally) Electrophilic Diphenyl Disulfide.

While PhSSPh is not electrophilic enough to react with alkynyltrimethylsilanes, a more reactive phenylthio electrophile is generated upon addition of ***Copper(I) Trifluoromethanesulfonate*** and ***Calcium Carbonate*** to the mixture. This reagent combination effects the conversion of alkynyltrimethylsilanes to alkynyl phenyl sulfides (eq 12).[41]

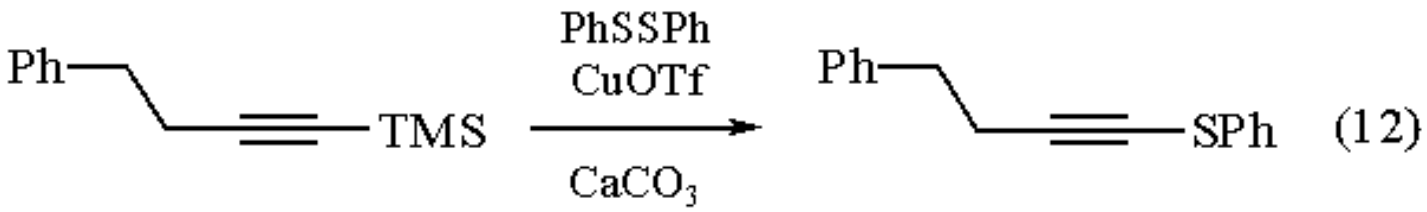

The coupling of 5-(chloromercurio)-2-deoxyuridine with PhSSPh, as well as with other diaryl and dialkyl disulfides, has been observed, leading to the corresponding phenylthio derivative (eq 13).[42]

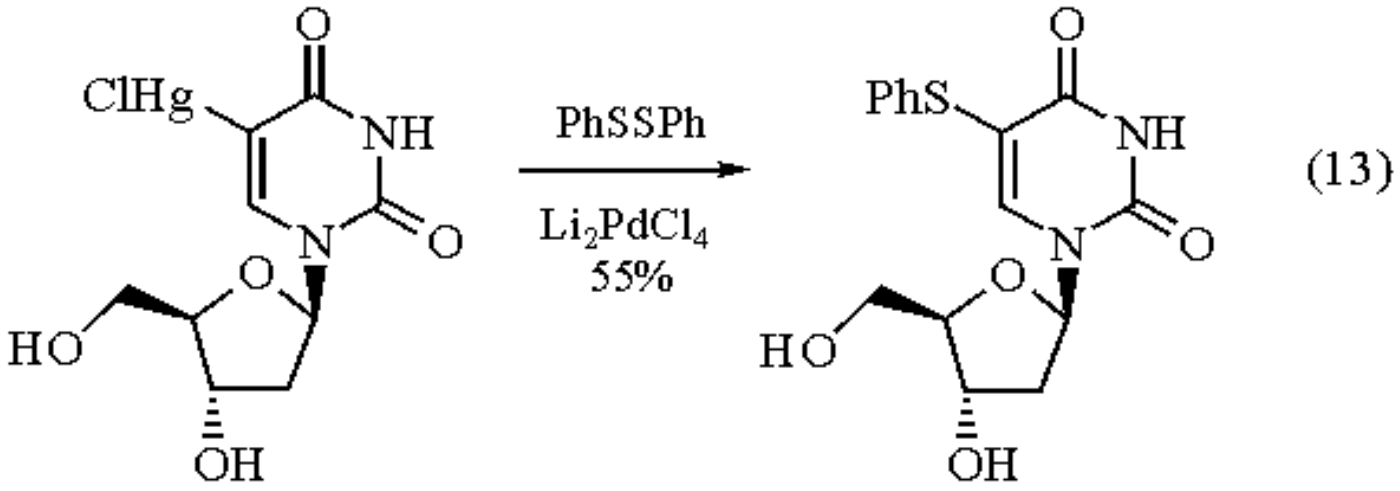

Diphenyl Disulfide as a Source of Thiiyl Radicals.

Thiiyl radicals can be generated from PhSSPh upon photolysis, or thermolysis, or in the presence of radical initiators. The radicals thus generated add reversibly to alkenes[19] and alkynes,[20] generating β-phenylthio alkyl and vinyl radicals, respectively. Diphenyl disulfide adds to alkynes irreversibly to generate bis(phenylthio)alkenes only under forcing conditions (eq 14).[21] The aniline and *n*-pentyl nitrite used in this example serve to generate phenyl radicals which initiate the radical chain process. The major product obtained is a substituted benzothiophene upon reaction with phenyl and *t*-butyl alkynes.[21,22]

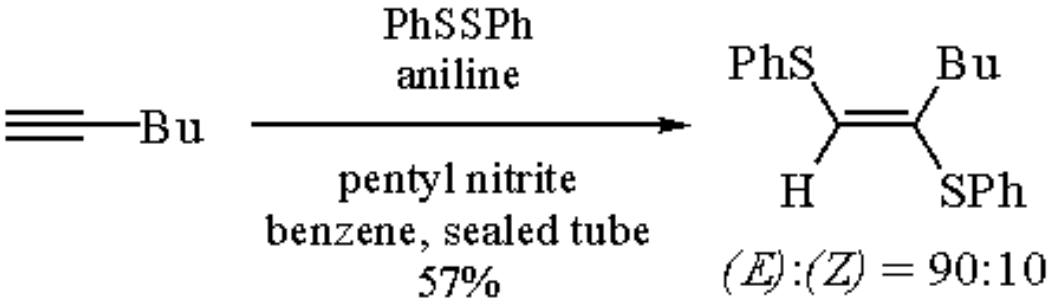

(14)

The reversible addition of PhSSPh to alkenes under photolytic conditions has been used extensively for the isomerization of alkenes[23] as illustrated in the synthesis of humulene (eq 15).[23b]

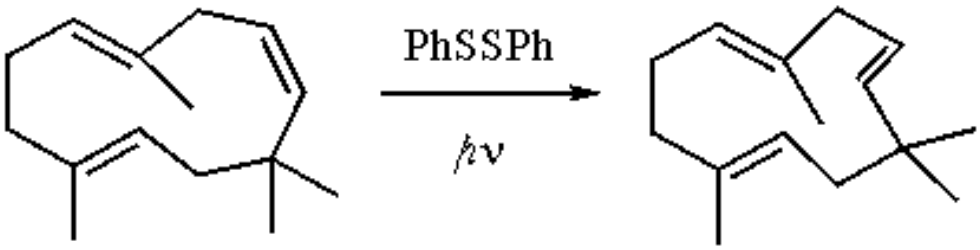

(15)

The reversible addition of a thiiyl radical arising from catalytic PhSSPh has been recently used in more complex radical processes. In eq 16,[24] the addition of a thiiyl radical initiates a cascade of radical processes leading to carbocyclization via an epoxide fragmentation, which terminates with expulsion of the initially added radical. Thiiyl radical-induced ring opening of a vinylcyclopropane, followed by intermolecular addition to an acrylate ester and subsequent cyclopentane formation, is illustrated in eq 17.[25] This transformation can also be accomplished upon addition of ***Trimethylaluminum***. A mechanistically analogous process involving addition of O_2 to vinylcyclopropanes, leading to formation of five-membered endoperoxides, has also been described.[26]

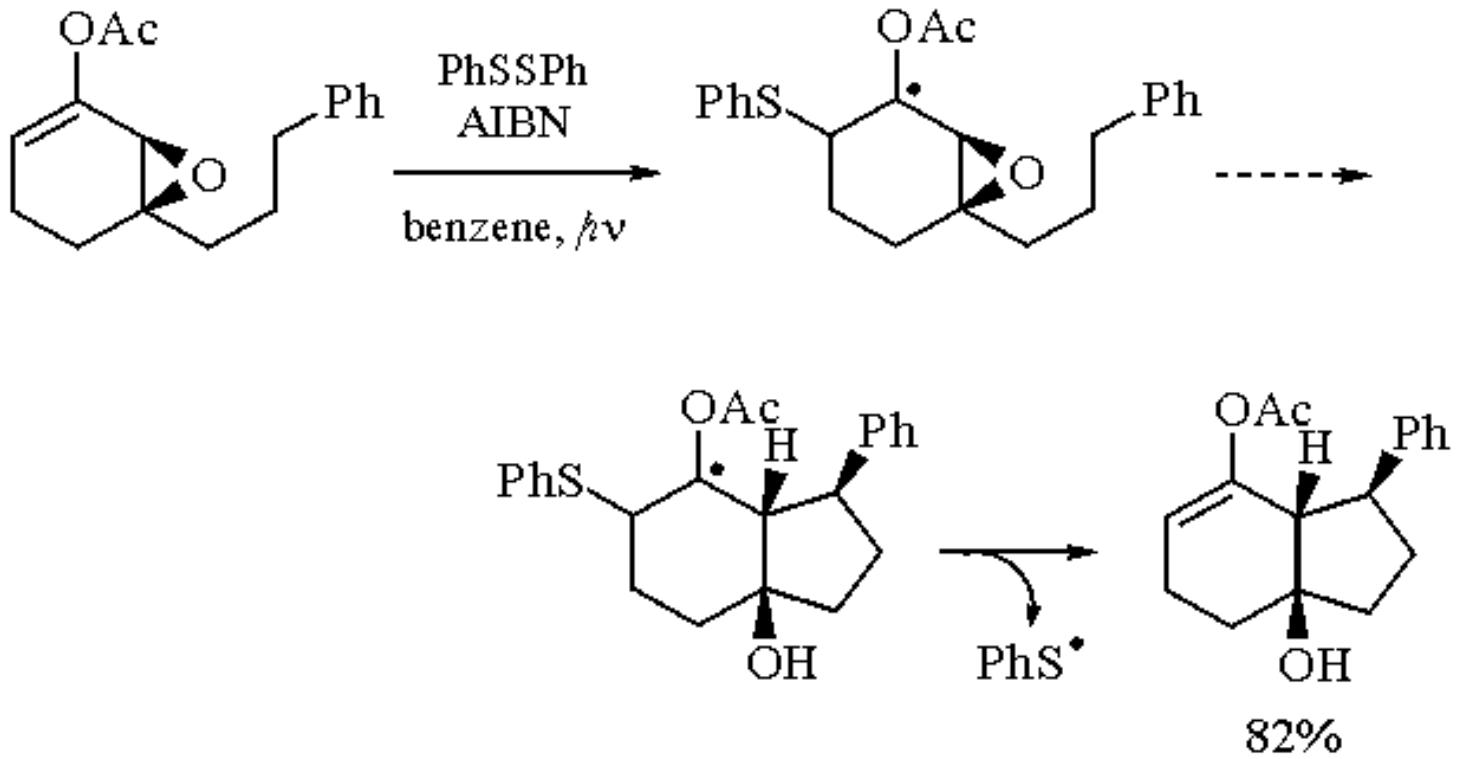

(16)

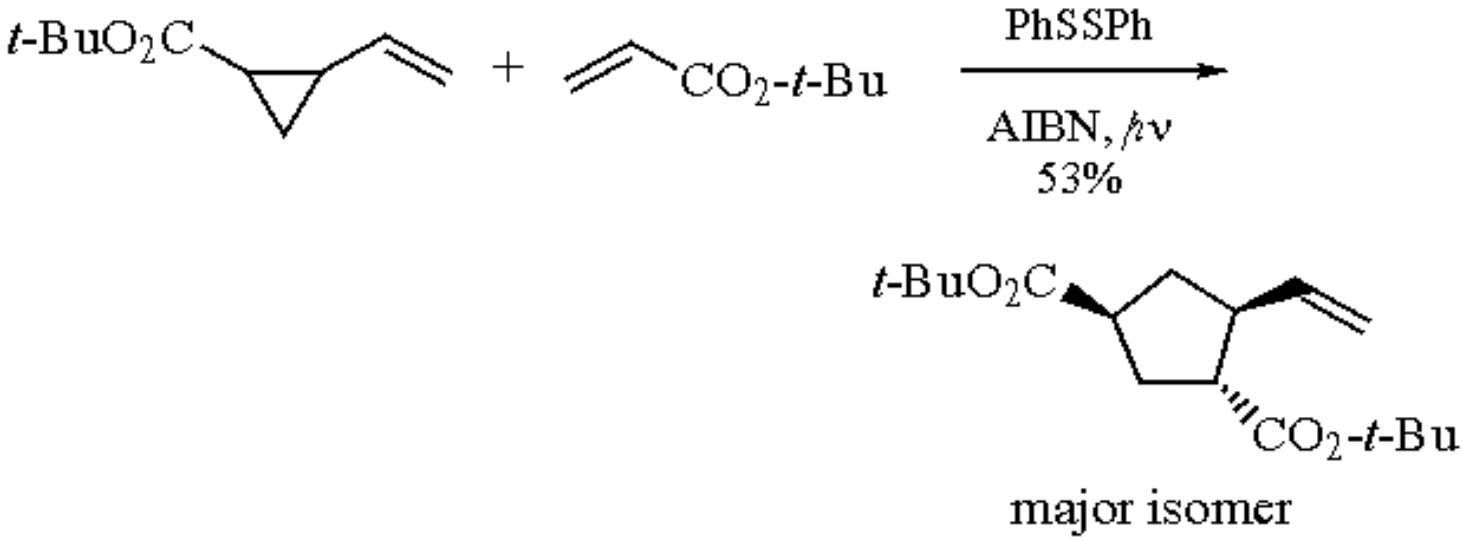

(17)

Thiiyl radicals have been incorporated into molecules via radical addition-elimination processes. Diphenyl disulfide reacts with β-tributylstannylacrylates upon photolysis to generate the corresponding β-phenylthioacrylate (eq 18).[27]

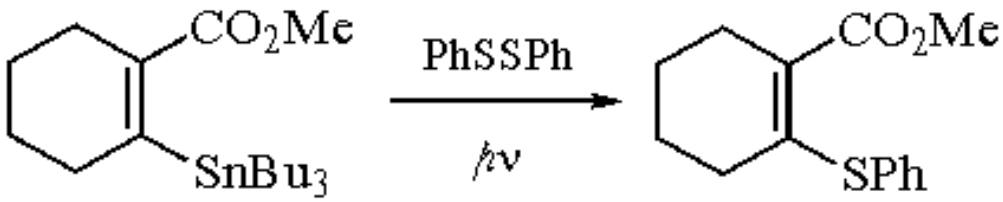

(18)

Diphenyl Disulfide as a Radical Trapping Agent.

Diphenyl disulfide is an effective radical trapping reagent, leading to formation of phenyl sulfides. Reactions of this

type may proceed through an S_H2 mechanism, or possibly through the intermediacy of a trivalent sulfuranyl radical species.[13] Photolysis of 5-hexenylmercury(II) chloride in the presence of varying concentrations of PhSSPh leads to mixtures of uncyclized 5-hexenyl phenyl sulfide and cyclized product (eq 19). Upon analysis of these product ratios, a rate constant of 7.6×10^4 sec^{-1} was obtained for the reaction of the hexenyl radical with PhSSPh.[14] Radicals generated from benzoylmethylmercury(II) chlorides add to alkenes prior to termination by attack at PhSSPh, leading to more synthetically interesting products (eq 20).[15]

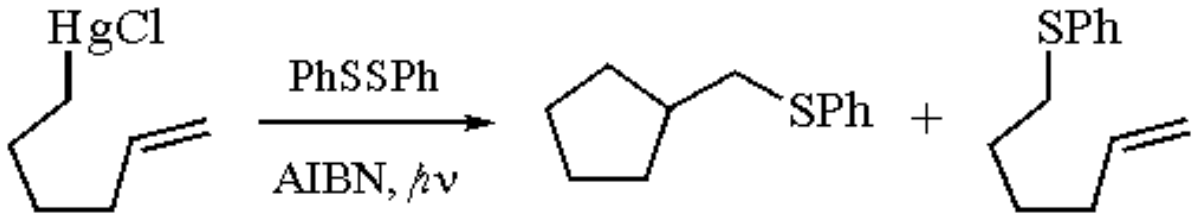

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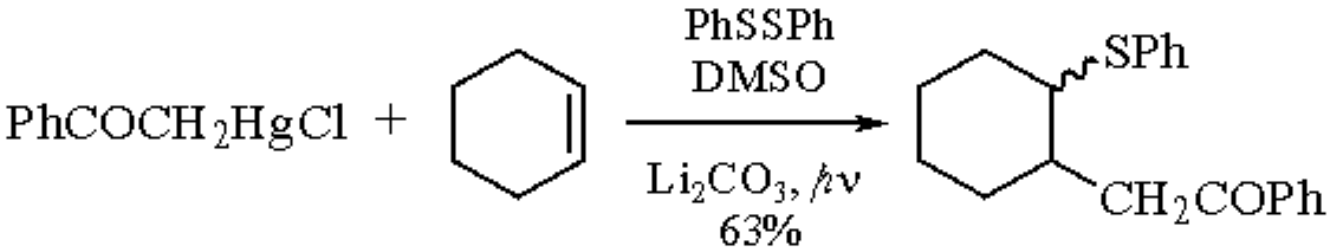

(20)

The carbon-centered radicals generated upon heating thiohydroxamate esters can react with PhSSPh to generate the corresponding phenyl sulfide (eq 21).[16] Diphenyl disulfide has also been used to trap radicals generated upon homolyses of organocobalt species.[17] The alkyl radicals generated from trialkylboranes upon photolysis or exposure to O_2 have also been trapped by PhSSPh in synthetically useful yields.[18]

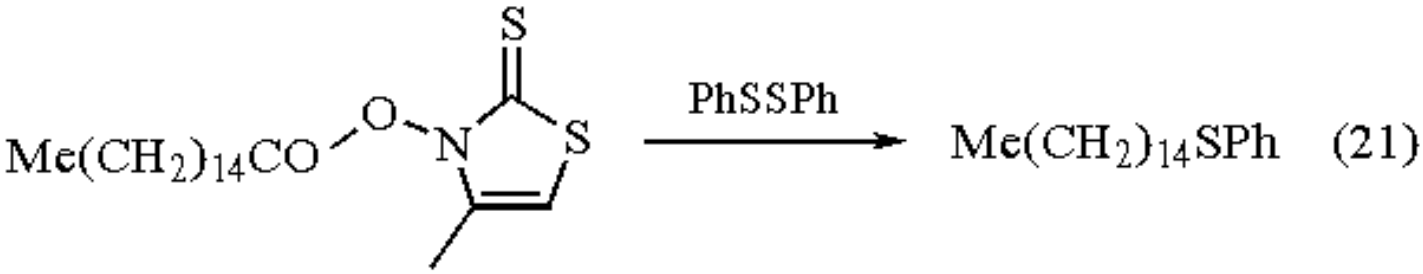

(21)

Diphenyl Disulfide/Tributylphosphine.

The mixture of PhSSPh and ***Tri-n-butylphosphine*** has proven to be of use for a variety of transformations. Aldehydes can be readily converted to diphenyl thioacetals upon treatment with these reagents (eq 22), while ketones are converted to diphenyl thioacetals only in poor yield.[28] The thioacetals thus formed are of synthetic interest due to their potential use as acyl anion synthons. Similar conditions convert oxiranes to vicinal diphenyl thioethers (eq 23).[28] The PhSSPh/Bu_3P reagent is also useful for the conversion of carboxylic acids to phenyl thioesters[29] and the related conversion of alcohols to phenyl thioethers (eq 24).[30]

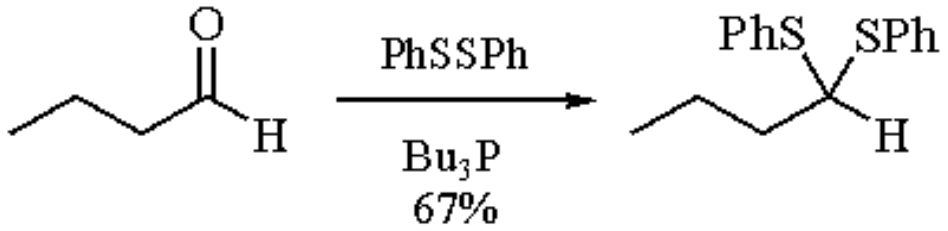

(22)

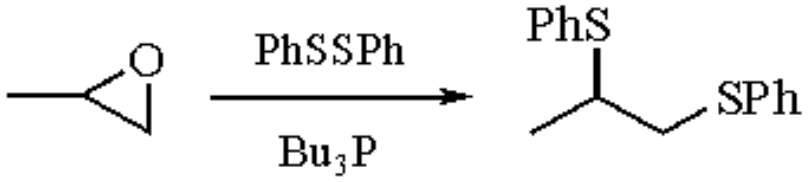

(23)

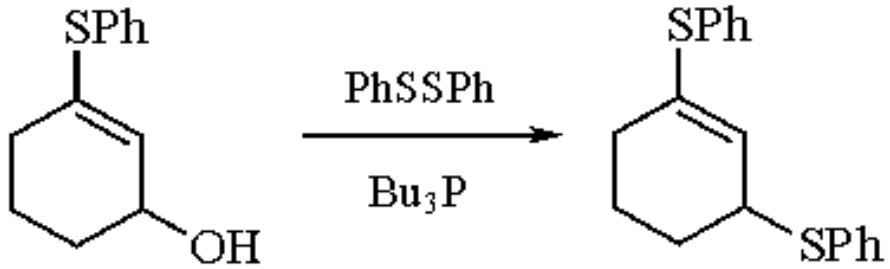

(24)

The reduction of nitro[43] and oxime[44] functionality to imines has been accomplished by this reagent system. The PhSSPh used in this reaction is also reduced to thiophenol. In several examples, the imine thus formed has been trapped intramolecularly to generate a pyrrole (eq 25). In each of these examples the phosphine serves as a deoxygenating agent through its conversion to Bu_3PO.

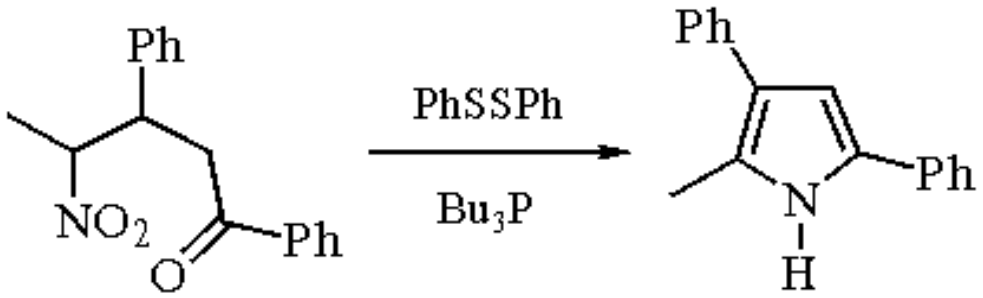

(25)

Related Reagents.

Dimethyl Disulfide; ***Diphenyl Disulfide***; ***2,2´-Dipyridyl Disulfide***.

---

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Diphenyl Ditelluride[1]

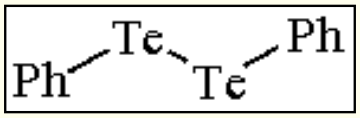

[32294-60-3] · $C_{12}H_{10}Te_2$ · Diphenyl Ditelluride · (MW 409.42)

(parent member of the diaryl ditellurides, useful reagents for the formation of alkyl, aryl, and vinyl tellurides by either nucleophilic, electrophilic, or radical pathways; alkyl and vinyl tellurides and especially alkyl 2-thienyl tellurides undergo very clean transmetalation reactions, providing alkyl and vinyl metal reagents;[1] alkyl aryl tellurides give alkyl radicals with tributyltin hydride[1])

Physical Data: mp 66-67 °C; *d* 2.23 g cm^{-3}.

Solubility: sol acetone, chloroform, tetrachloromethane; moderately sol ether; slightly sol ethanol.

Form Supplied in: nonvolatile, orange crystals.

Preparative Methods: diaryl ditellurides are prepared by the action of aryllithium or arylmagnesium halides on tellurium powder followed by oxidation with air or with aqueous potassium ferricyanide.[2] Electron-rich diaryl ditellurides (e.g. bis(2,4-dimethoxyphenyl) ditelluride[3]) are prepared by reaction of the arene with tellurium tetrachloride to give the aryltellurium trichloride followed by reduction with $Na_2S_2O_5$.

Purification: crystallization from ethanol.

Handling, Storage, and Precautions: air stable; unknown toxicity. Use in a fume hood.

Arenetellurolates.

Diaryl ditellurides are reduced with ***Sodium*** wire in THF/DMF, ***Samarium(II) Iodide*** in THF/HMPA, or ***Sodium Borohydride*** in ethanol to give the powerfully nucleophilic arenetellurolates which take part in substitution reactions with alkyl, aryl, and benzyl halides (eq 1).[4] PhTeTePh may also be reduced electrochemically or with sodium in liquid ammonia and the resulting PhTeNa used as an effective nucleophile in the $S_{RN}1$ substitution of haloarenes.[5] Substitution of iodoarenes to give mixed diaryl tellurides also takes place, with catalysis by ***Copper(I) Iodide***, with benzenetellurolate formed from PhTeTePh and $NaBH_4$ in HMPA.[6] Acyl chlorides react with benzenetellurolate derived from $NaBH_4$ and PhTeTePh in THF/EtOH to give acyl aryl tellurides, which are effective precursors of acyl radicals[7] and acyl lithiums.[8] Trapping with ***Chlorotrimethylsilane*** gives $PhTeSiMe_3$ which, in the presence of ***Zinc Iodide***, reacts with lactones to give Me_3Si esters of o-phenyltelluro acids and with cyclic ethers to give o-phenyltelluro

alcohols as their Me_3Si ethers.[9]

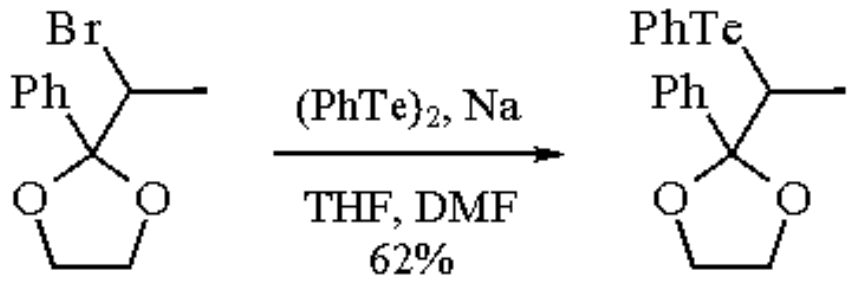

(1)

Reduction with ***Diisobutylaluminum Hydride*** gives PhTeAl(i-Bu)$_2$ (see also ***Diisobutylaluminum Phenyl Selenide***), which undergoes conjugate addition to α,β-unsaturated carbonyl compounds. The intermediate aluminum enolates react with aldehydes to give aldols. Subsequent treatment with ***m-Chloroperbenzoic Acid*** gives α-alkylidene aldols (eq 2).[10] PhTeAl(i-Bu)$_2$ is also an excellent nucleophile toward acetals, alkyl sulfonates, and oxiranes.[11]

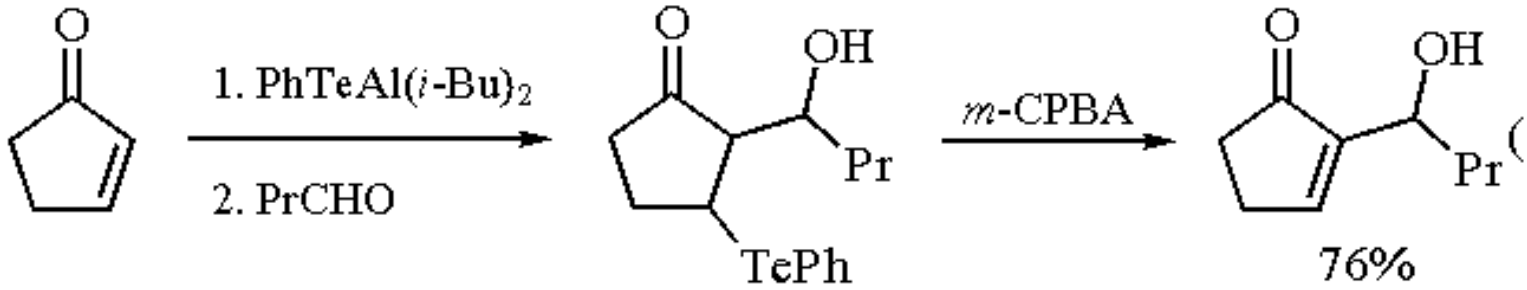

(2)

Electrophilic Species.

Diaryl ditellurides react with Grignard and organolithium reagents to give alkyl aryl tellurides. The reaction has been used to titrate these organometallics.[12] Activation of PhTeTePh with ***Bromine*** and ***t-Butyl Hydroperoxide*** (TBHP) in alcohols provides electrophilic reagents for alkoxytelluration of alkenes.[13] PhTeTePh readily takes part in telluro-cycloetherifications and lactonizations of hydroxy and carboxy alkenes on activation with ***p-Nitrobenzenesulfonyl Peroxide*** (NBSP) (eq 3).[14]

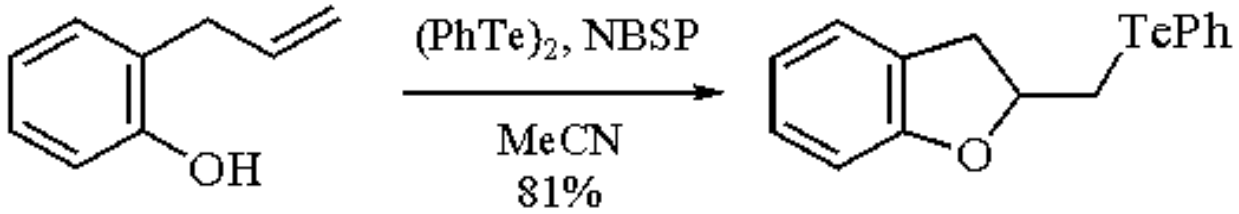

(3)

Radical Reactions.

Diaryl ditellurides are very efficient traps for alkyl radicals generated by a variety of means, as in eq 4.[15] PhTeTePh adds across alkynes on initiation with ***Azobisisobutyronitrile*** (AIBN) to give 1,2-bis(phenyltelluro)-alkenes.[16] Vinyl-, allyl- and alkylmercurials undergo photostimulated radical substitution with PhTeTePh to give the corresponding phenyl tellurides.[17]

$$Ph_2B(CH_2)_{15}Me \xrightarrow[O_2,\ THF]{(PhTe)_2} \underset{64\%}{PhTe(CH_2)_{15}Me} + \underset{33\%}{TePh_2} \qquad (4)$$

Reductions.[1]

1,2-Dibromides are converted to alkenes with a catalytic amount of ditelluride and $NaBH_4$.[18] A variation is the generation of *o*-quinodimethane from α,α´-dibromo-*o*-xylene with PhTeNa.[19] $NaBH_4$ reduces nitrobenzene to azoxybenzene in aqueous methanolic NaOH at rt with a catalytic amount of PhTeTePh. At reflux the product is azobenzene.[20]

Related Reagents.

Diphenyl Diselenide; ***Diphenyl Disulfide***.

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Diphenyliodonium Carboxylate

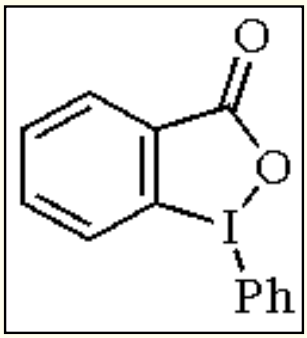

[1488-42-2] · $C_{13}H_9IO_2$ · Diphenyliodonium Carboxylate · (MW 324.12)

(starting point for the synthesis of *N*-substituted anthranilic acids;[4] useful benzyne precursor[7])

Alternate Name: (carboxyphenyl)phenyliodonium hydroxide inner salt.

Physical Data: $C_{13}H_9IO_2.H_2O$: mp 220-222 °C (dec). $C_{13}H_9IO_2$: mp 215-216 °C (dec).

Solubility: sol dichloromethane, hot water.

Preparative Method: by oxidation of 2-iodobenzoic acid with potassium persulfate in H_2SO_4, followed by addition of benzene. It is isolated as colorless prisms of the monohydrate. Anhydrous material can be obtained in quantitative yield by extraction of the monohydrate with dichloromethane and evaporation of the solvent.[1]

Handling, Storage, and Precautions: described as a stable, easy to handle, safe, crystalline compound.[1]

Structure.

Although diphenyliodonium carboxylate is usually represented as an acyclic iodonium salt (**1**), NMR[2] and X-ray diffraction[3] studies indicate a cyclic structure (**2**).

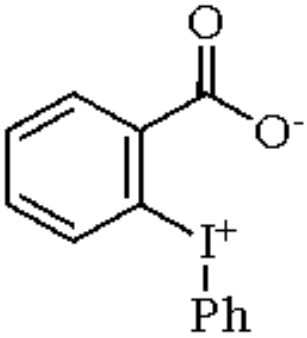

(1)

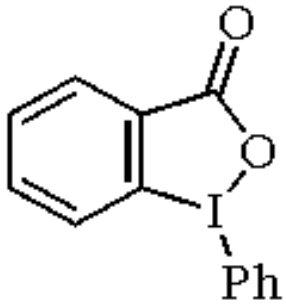

(2)

Synthesis of Anthranilic Acid Derivatives.

Ullmann-type reaction of diphenyliodonium carboxylate with amines yields anthranilic acid derivatives. Diphenyliodonium carboxylate reacts with anilines in the presence of ***Copper(II) Acetate*** to afford the corresponding anthranilic acids (eq 1).[4]

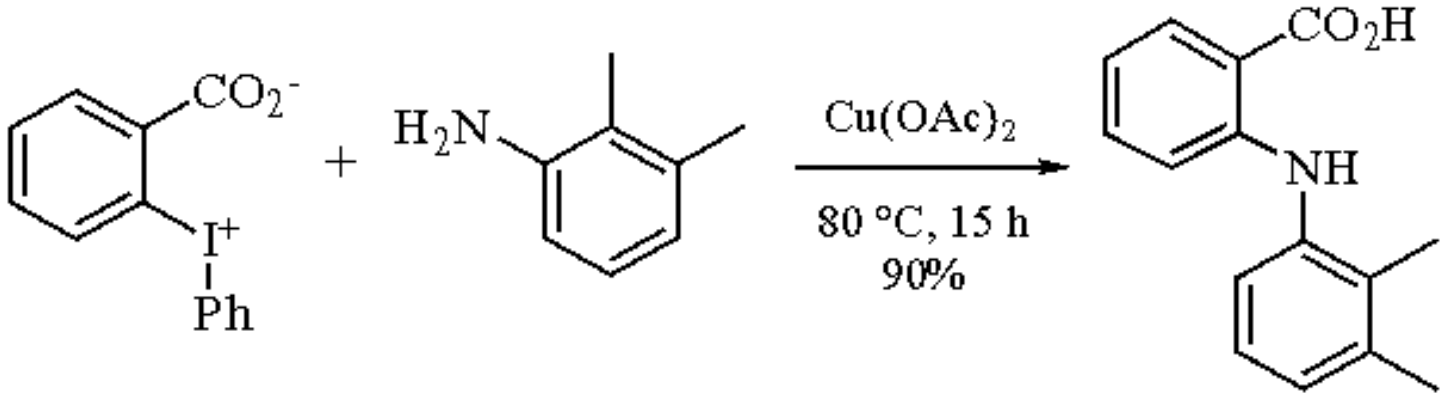

(1)

A protocol for the synthesis of 9-oxoacridan-4-carboxylic acids has also been developed (eq 2).[5] This Ullmann-type coupling has been applied to the synthesis of several products of pharmacological interest.[6]

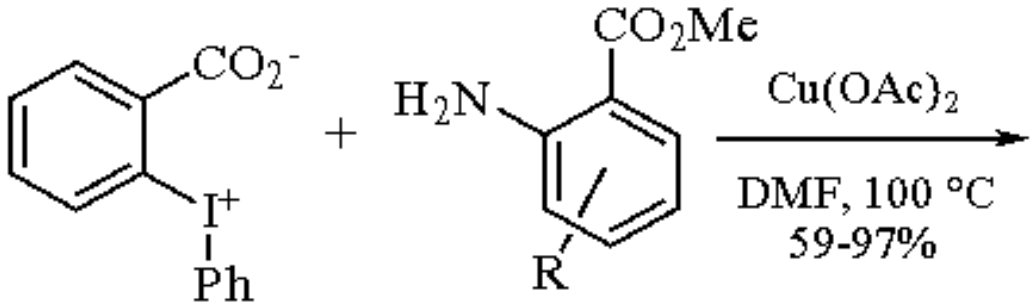

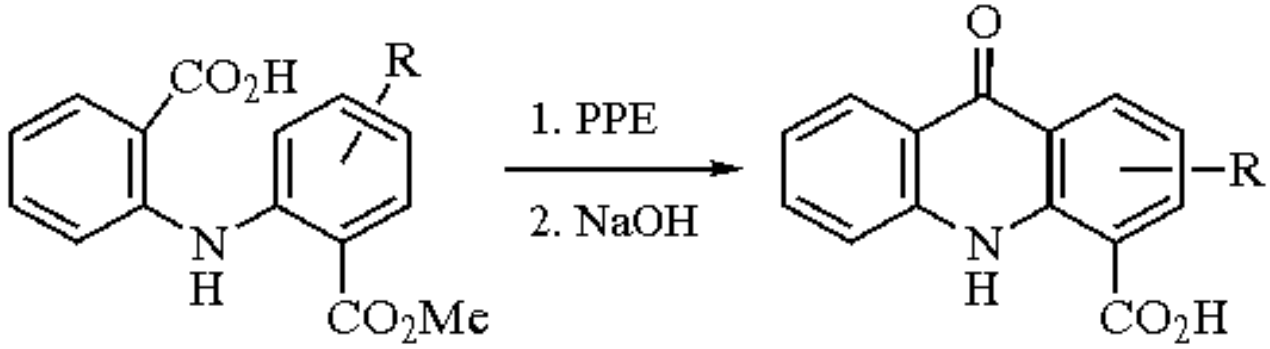

(2)

Generation of Benzyne.[7]

When a solution of diphenyliodonium carboxylate is heated to 160 °C, decomposition to benzyne, CO_2, and iodobenzene takes place (eq 3). This reaction is usually carried out in diglyme (160 °C), although butyrolactone (205 °C) and triglyme (220 °C) have been used in some cases.[8]

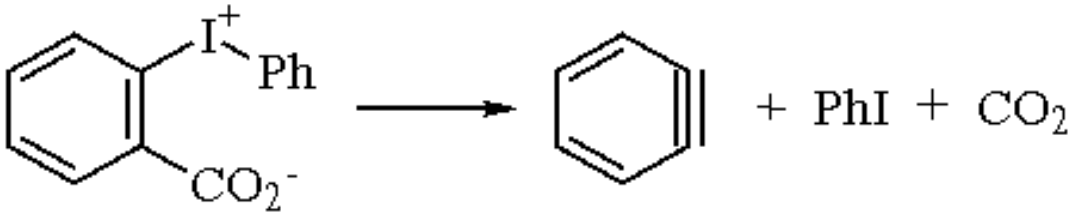

(3)

This procedure uses neither basic nor oxidative reagents. The high temperature that is required for decomposition of diphenyliodonium carboxylate leads in some cases to lower yields than alternative procedures, particularly if a thermally unstable reaction partner is used. However, diphenyliodonium carboxylate might be a convenient benzyne precursor for use with substrates of low reactivity; a comparative study of the reactivity of benzyne generated from several precursors (and therefore under a variety of conditions) with the weakly reactive diene thiophene showed that best yields of cycloadduct were obtained using high temperature generation from diphenyliodonium carboxylate.[9]

Benzyne generated from this precursor has been trapped as a Diels-Alder adduct by several dienes. Trapping efficiency increases in the order anthracene < 1,3-diphenylisobenzofuran < 2,3,4,5-tetraphenylcyclopentadienone (tetracyclone) < 2,5-bis(*p*-dimethylaminophenyl)-3,4-diphenylcyclopentadienone < 2,5-di-*p*-anisyl-3,4-diphenylcyclopentadienone.[8] When the last of these dienes is used, the adduct is isolated in 79% yield (eq 4).

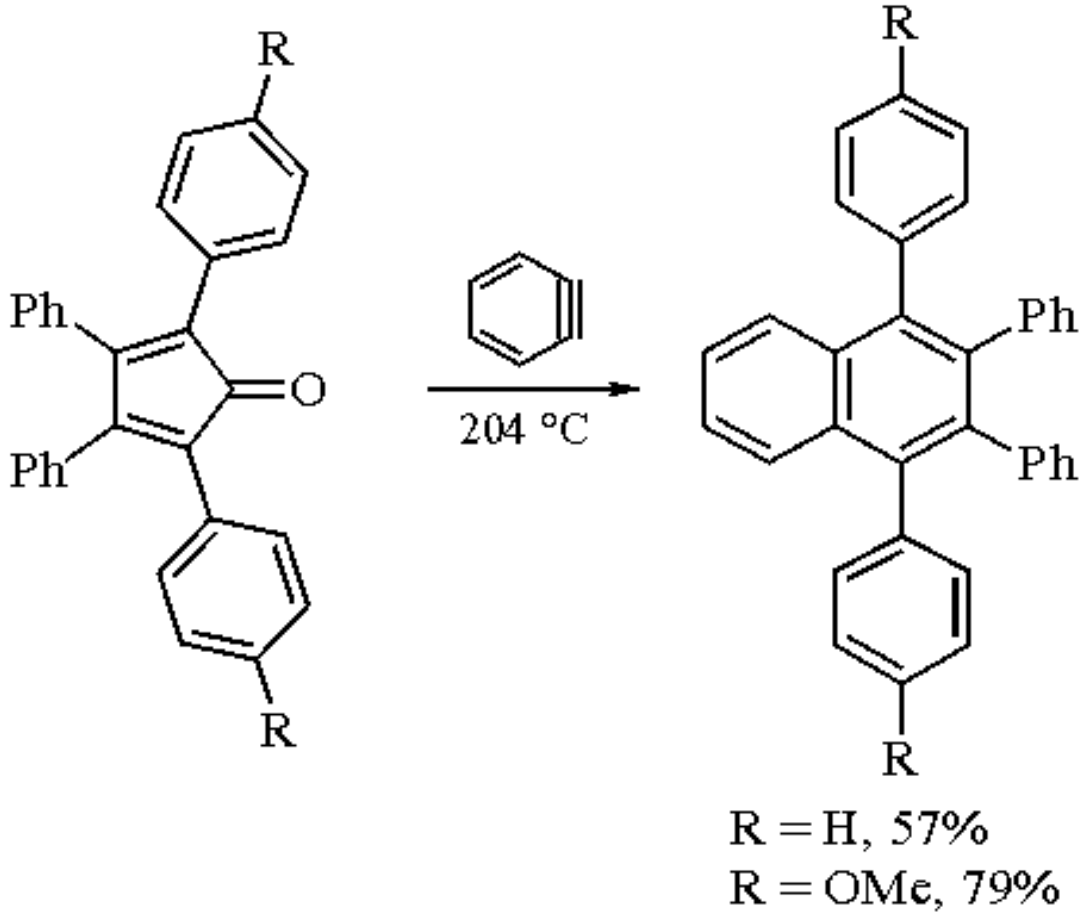

(4)

Benzyne generated by decomposition of diphenyliodonium carboxylate undergoes 1,3-dipolar cycloaddition with pyridinium dicyanomethylide to afford 6-cyanobenz[*a*]indolizine (eq 5).[10]

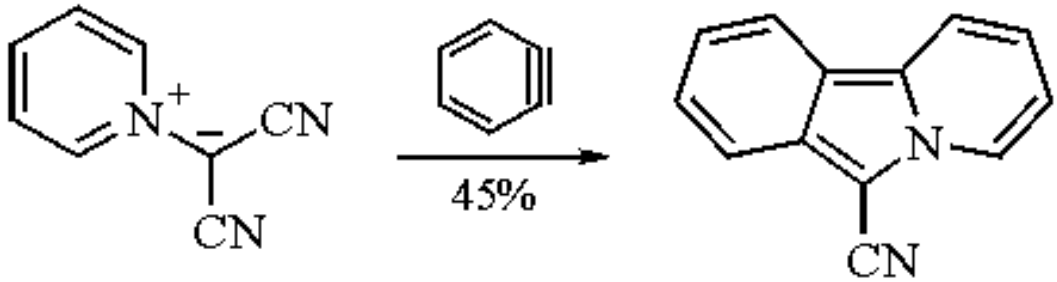

(5)

1,4-Diphenyl-1,2,4-triazolium-3-olate does not react with benzyne generated by oxidation of 1-aminobenzotriazole, but if diphenyliodonium carboxylate is used as the benzyne precursor, 2-phenylindazole is obtained by cycloaddition-extrusion reactions (eq 6).[11]

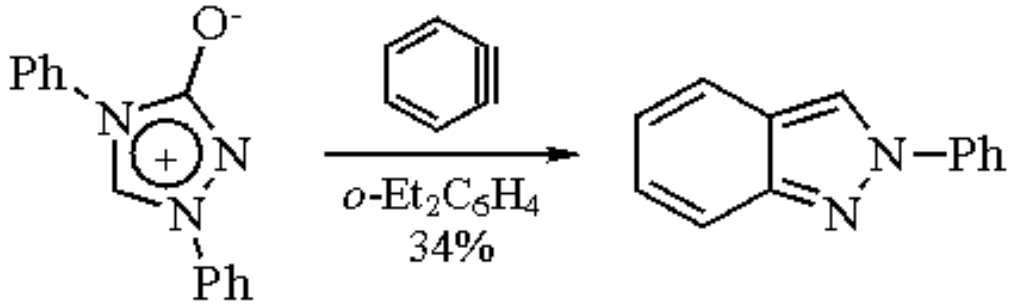

(6)

Disulfides, ditellurides, diselenides, and related compounds undergo insertion of benzyne (eq 7).[12,13]

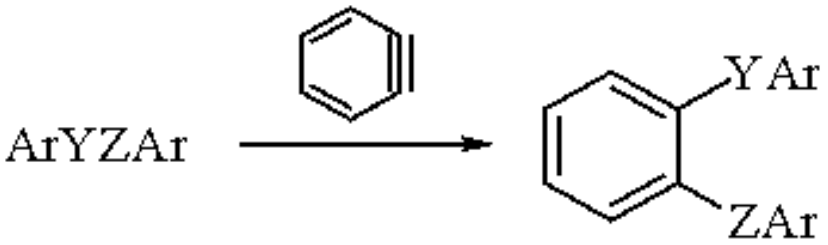

(7)

YZ = SS, SeSe, TeTe, SeTe

Related Reagents.

Benzenediazonium-2-carboxylate; ***1,2,3-Benzothiadiazole 1,1-Dioxide***.

---

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Diphenyliodonium Chloride[1]

$Ph_2I^+ Cl^-$

[1483-72-3] · $C_{12}H_{10}ClI$ · Diphenyliodonium Chloride · (MW 316.57)

(phenylation of carbanions,[2-8] oxygen anions,[9-16] nitrogen[17-22] and sulfur groups,[23-29] inorganic anions[30-32])

Physical Data: mp 233-235 °C (subl).

Solubility: sol H_2O, MeOH, *t*-BuOH, DMF/EtOH.

Form Supplied in: white solid; commercially available.

Handling, Storage, and Precautions: stable; can be stored at rt without decomposition.

Introduction.

A general observation concerning diphenyliodonium chloride is that other salts can be formed by anion metathesis in H_2O, 90% HCO_2H, or MeOH (eq 1). In most synthetic applications, Ph_2ICl is equivalent to Ph_2IBr.

$$Ph_2I^+ \ Cl^- \xrightarrow{M^+ \ X^-} Ph_2I^+ \ X^- \qquad (1)$$

$$X^- = F^-, Br^-, HSO_4^-, SO_4^{2-}, RCO_2^-, CF_3CO_2^-, IO_3^-, ClO_4^-, BF_4^-$$
$$Ph_4B^-, ArSO_3^-, PF_6^-, AsF_6^-, OH^-, HgCl_3^-, NO_3^-$$

Nucleophilic Displacement Resulting in Phenylation.

A major reaction of Ph_2ICl is nucleophilic displacement according to the overall reaction in eq 2. The nucleophile may be carbon, oxygen, nitrogen, or sulfur based systems, as well as phosphorus, selenium, and tellurium.

$$Ph_2I^+ \ Cl^- + Z^- \longrightarrow Ph\text{-}Z + PhI + Cl^- \qquad (2)$$

Phenylation of Carbanions.

The following reactions of carbanions using *t*-butyl alcohol as solvent are representative (eqs 3-12). Among the better substrates are 1,3-dicarbonyl compounds (eqs 3, 4, 8, and 9),[2,3,5] α-cyano ketones (eq 6),[4] aromatic ketones (eqs 5 and 7),[4] acetone enolates (eq 10),[6] and nitronate ions (eqs 11 and 12).[7,8]

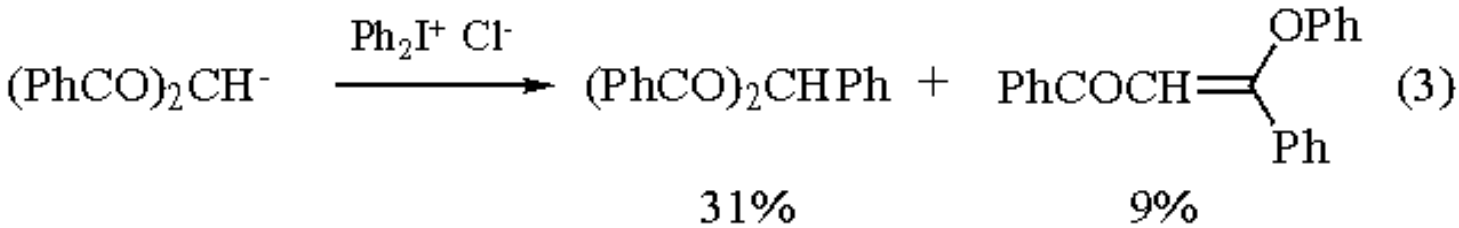

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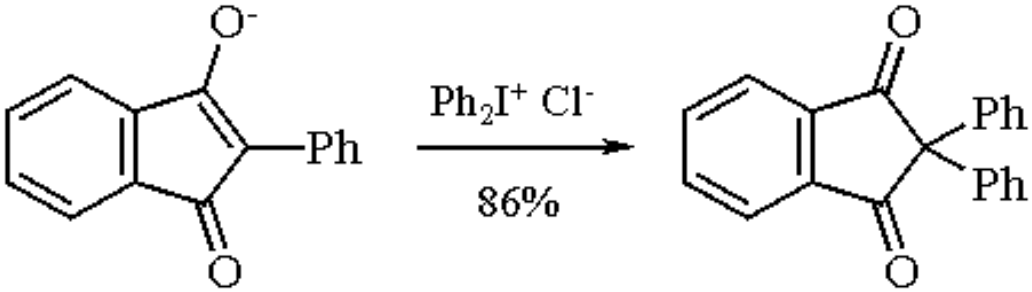

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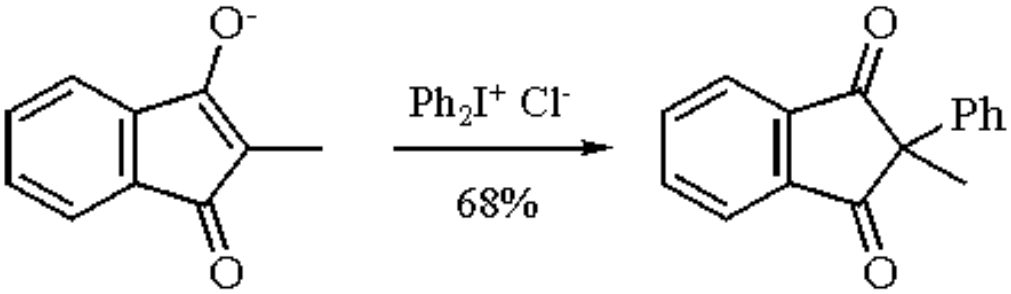

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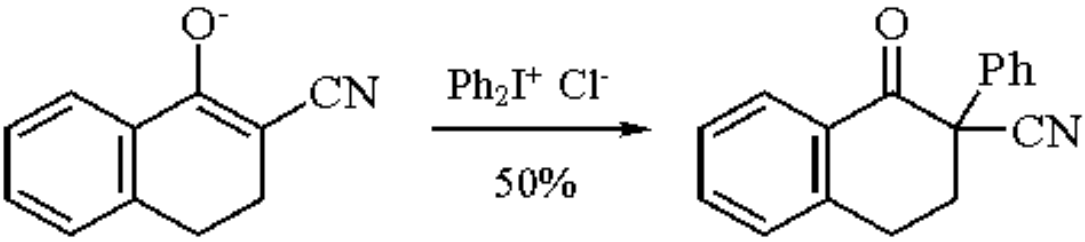

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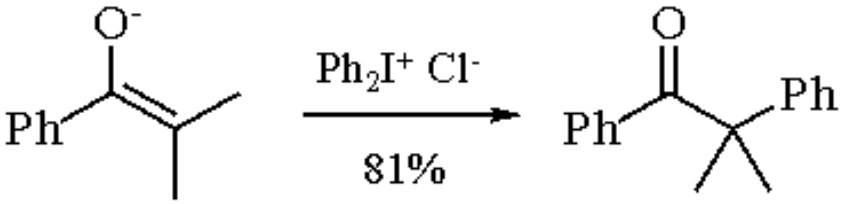

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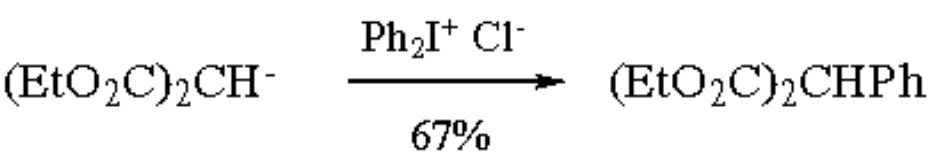

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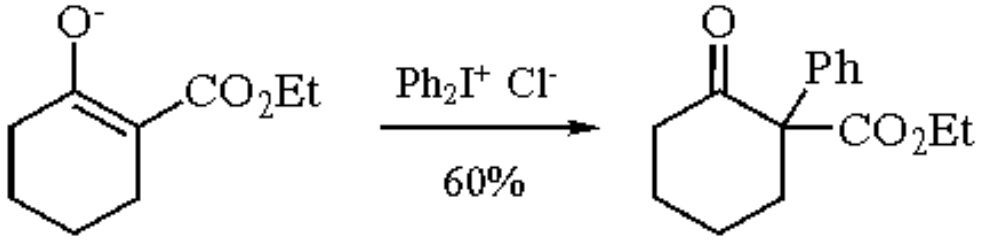

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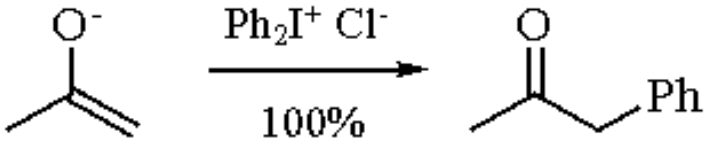

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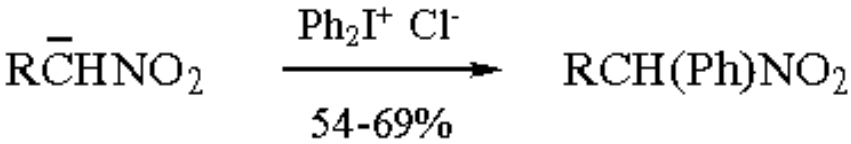

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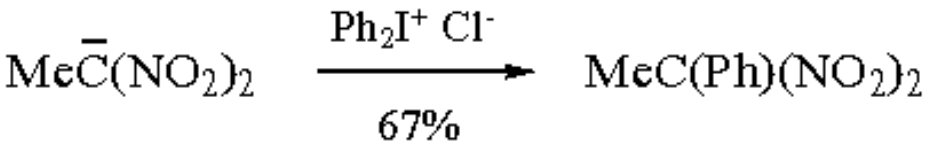

(12)

Phenylation of Oxygen Anions and Oxygen Nucleophiles.

Ph_2ICl is valuable as a phenylating reagent at oxygen (Table 1).[9-16] Representative examples include alkoxides,[9] phenoxides,[10] carboxylates,[9] sulfonates,[9] *N*-oxides,[11] oximes,[12,16] hydroxylamines,[14,15] and nitroso compounds.[13]

Table 1 Phenylation of Oxygen Anions with Diphenyliodonium Salts

Substrate	Product	Yield (%)
RONa	ROPh	67-80 [9]
Ar'ONa	Ar'OPh	26-96 [10]
$PhCO_2Na$	$PhCO_2Ph$	40 [9]
p-TsONa	*p*-TsOPh	56 [9]
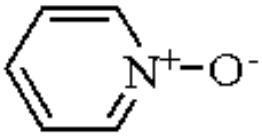	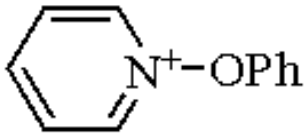	90-99 [11]
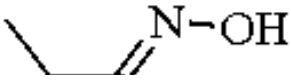	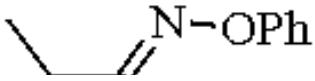	

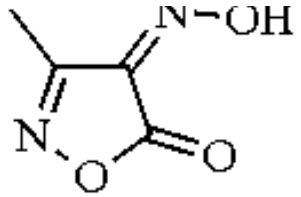	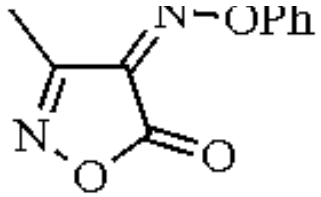	-[12]
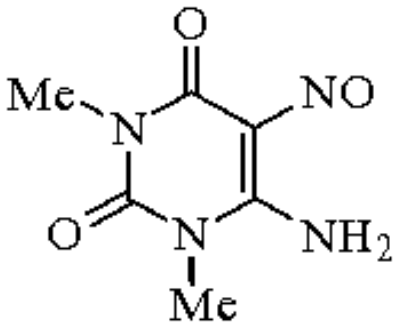	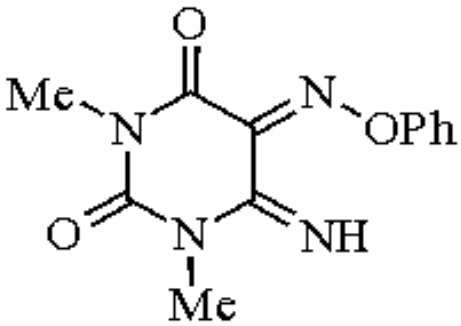	96[13]
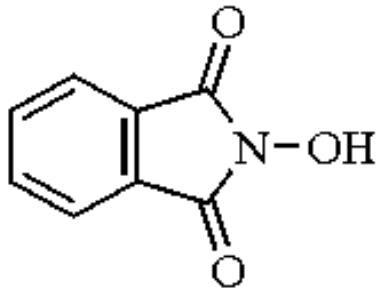	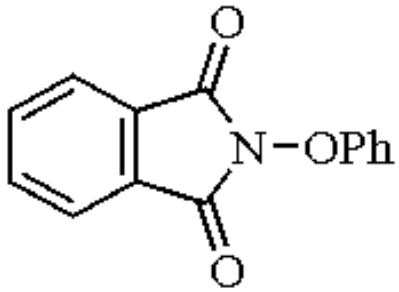	90[14]
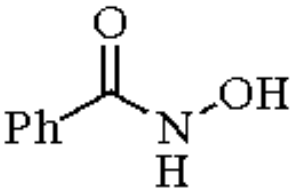	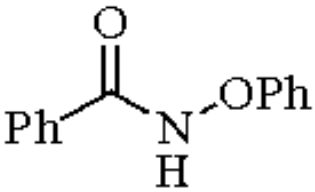	66[15]
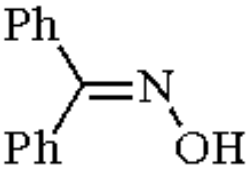	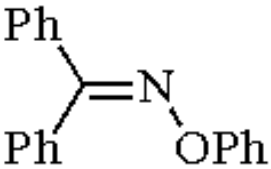	70[16]

Phenylation at Nitrogen.

Phenylation at nitrogen is not generally useful for aliphatic and aromatic amines. However, the reaction is valuable for hydroxamic acid derivatives, imides, sulfonamides, and certain other nitrogen heterocycles, as shown in Table 2.[17-22]

Table 2 Phenylation of Nitrogen with Diphenyliodonium Salts

Substrate	Product	Yield (%)

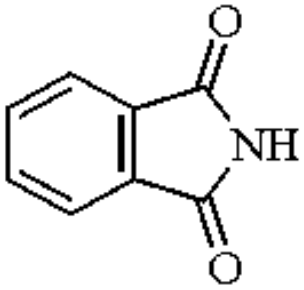

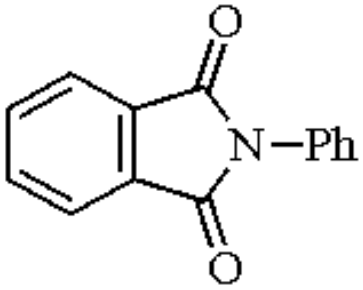

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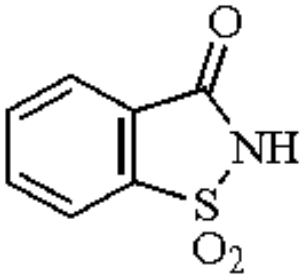

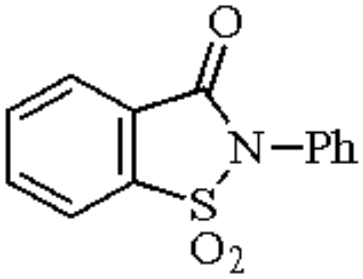

75[18]

p-TsONH$_2$ *p*-TsONHPh 45[18]

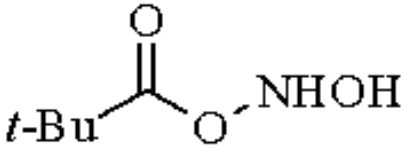

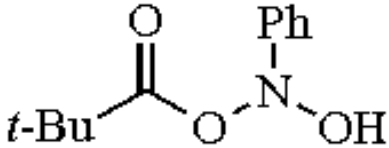

-[19]

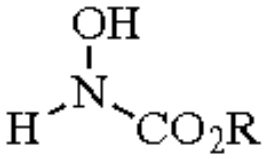

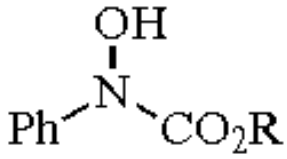

39-45[20]

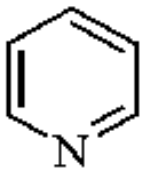

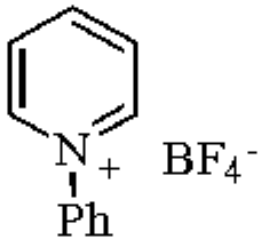

88[17]

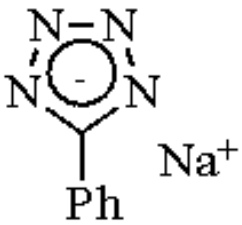

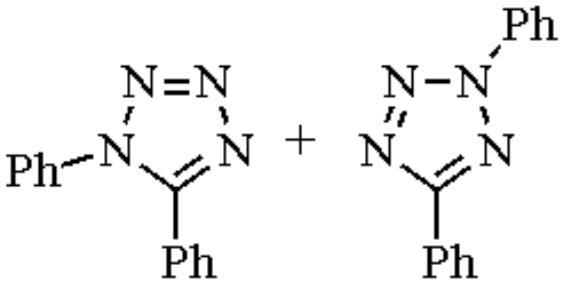

-[21]

61[22]

Phenylation at Sulfur.

Phenylation at sulfur is most effective for the formation of various sulfonium salts from diaryl or dialkyl sulfides (eqs 13-15).[23-25]

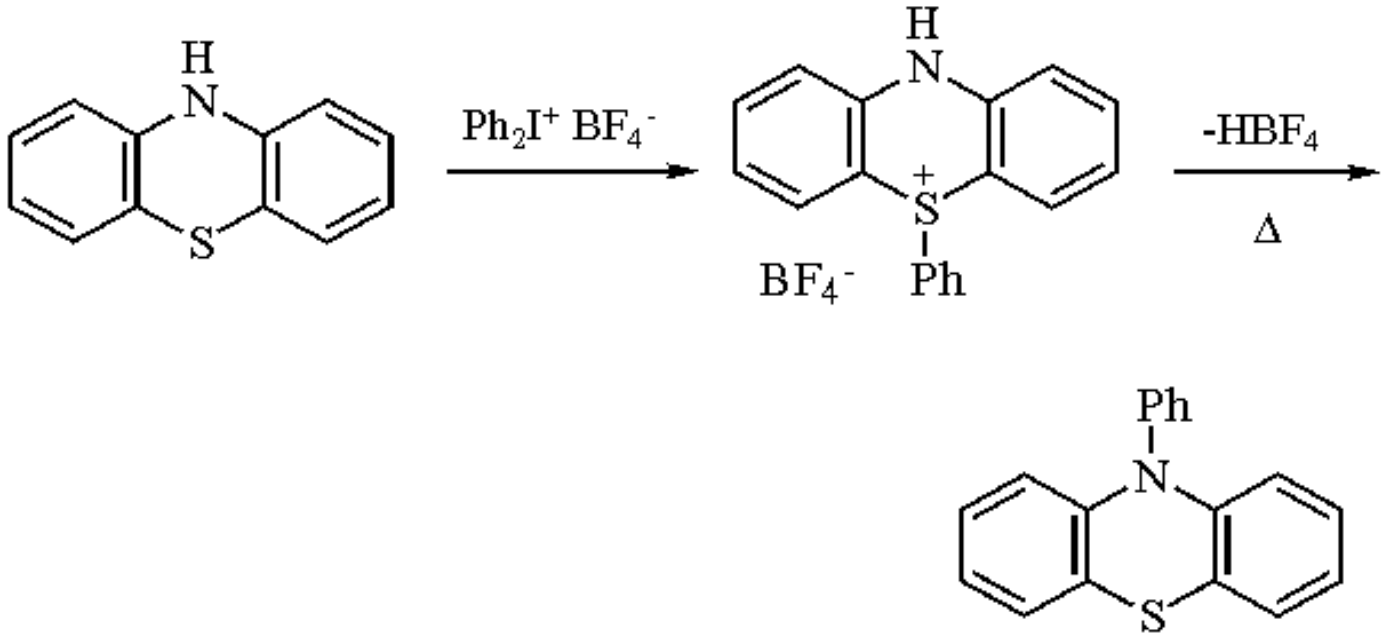

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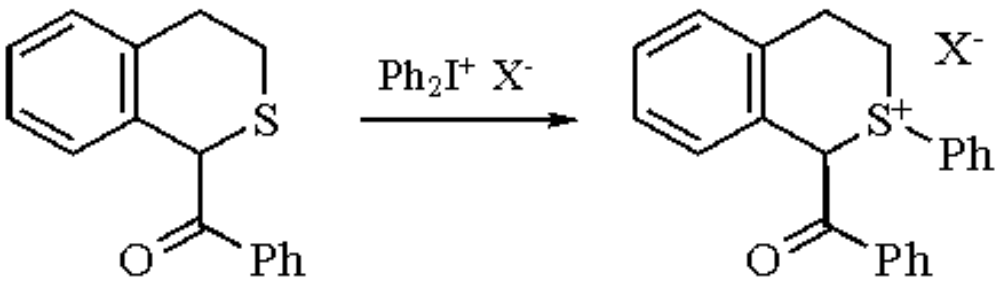

(14)

$$Ph_2S \xrightarrow{Ph_2I^+ Cl^-} Ph_3S^+ Cl^- \qquad (15)$$

S-Phenylation of bis(4-methoxyphenyl)-2-arylthiopyrimidines has been used in the syntheses of nonsteroidal anti-inflammatory drugs (eq 16).[26]

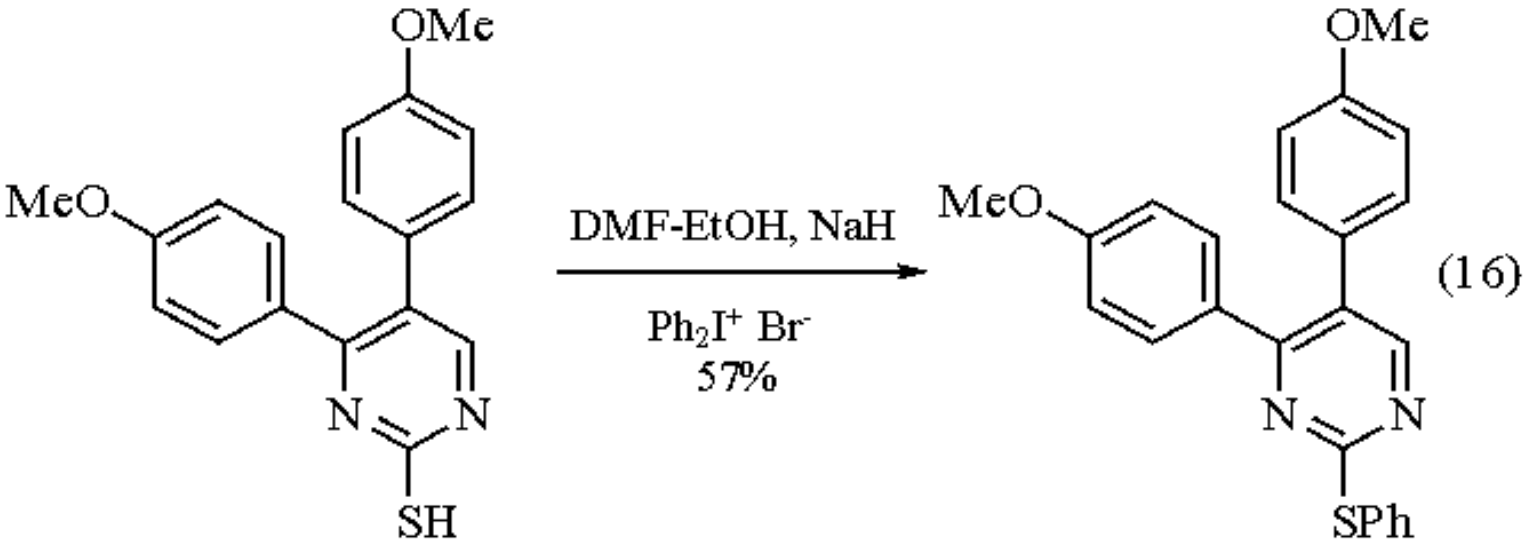

Other substrates which undergo *S*-phenylation are *p*-$TolSO_2^-Na^+$,[18] $EtOCSS^-Na^+$,[27] $ArCSS^-Na^+$,[28] and $R_2NCSS^-Na^+$.[23] Elemental tellurium can be phenylated with Ph_2IBr to yield Ph_2Te,[33] while Ph_2Se yields $Ph_3Se^+Br^-$ and Ph_3P yields $Ph_4P^+Br^-$.[34]

Phenylation of Inorganic Anions.

The phenylation of inorganic anions is a useful synthetic method. The examples collected in Table 3 include nitrite,[30] azide,[9] cyanide,[18] thiocyanate,[18] fluoride,[31] and sulfite.[32]

Table 3 Phenylation of Inorganic Anions

Substrate	Product	Yield (%)
$NaNO_2$[30]	$PhNO_2$	37 88
NaN_3[9]	PhN_3	95 98
NaCN[18]	PhCN	23 58
NaSCN[18]	PhSCN	17 98
NaF[31]	PhF	38 96
Na_2SO_3[32]	$PhSO_3H$	Up to 95

Related Reagents.

Triphenylbismuth Carbonate; ***Triphenylbismuth Dichloride***.

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University of Illinois at Chicago, IL, USA

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1,3-Diphenylisobenzofuran[1]

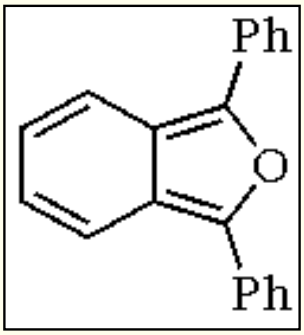

[5471-63-6] · $C_{20}H_{14}O$ · 1,3-Diphenylisobenzofuran · (MW 270.34)

(highly reactive diene,[1] suitable for the trapping of unstable or transient dienophiles as their Diels-Alder adducts; standard reagent for the determination of singlet oxygen; useful reagent in the synthesis of polyaromatic species)

Physical Data: yellow crystalline needles, mp 128-130 °C.

Solubility: sol acetonitrile, benzene, chloroform, dichloromethane, DMSO, THF, toluene.

Handling, Storage, and Precautions: air sensitive; light sensitive.

Properties.

The majority of isobenzofurans should only be viewed as reactive intermediates. 1,3-Diphenylisobenzofuran (**1**) is a moderately stable compound and is commercially available. On the other hand, isobenzofuran (**2**) has only been isolated at low temperatures.[2] The reactivity of these species is confined to the furanoid ring. Isobenzofurans have been described as the most reactive Diels-Alder dienes known.[3] The reactivity is attributable to the extra resonance energy gained by formation of an aromatic ring during the cycloaddition.

Synthesis.

Owing to the extensive interest in isobenzofurans in recent years, numerous technologies for their preparation have been forwarded, and these have been amply reviewed.[4] Synthesis from phthalan precursors is most popular and useful (eq 1).[5]

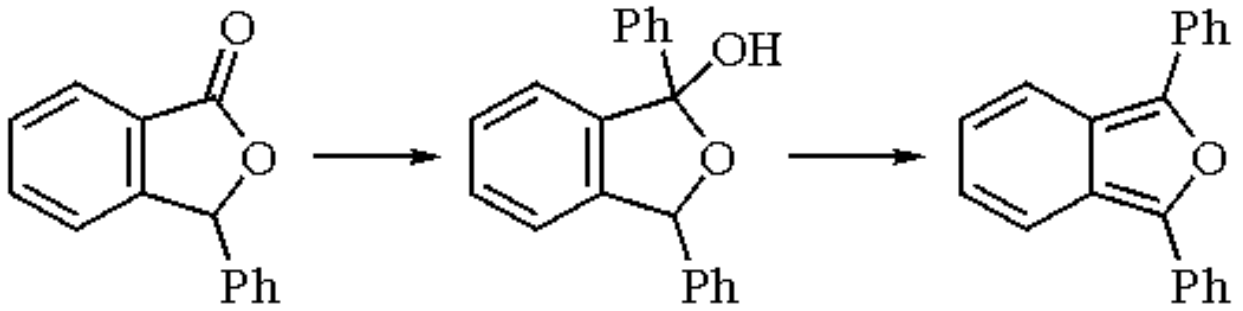

(1)

(1)

In a convenient protocol, 3,6-di-2´-pyridyl-*s*-tetrazine and 1,4-dihydro-1,4-endoxynaphthalene react in two steps to yield isobenzofuran, which can subsequently react with the dienophile of interest (eq 2).[6]

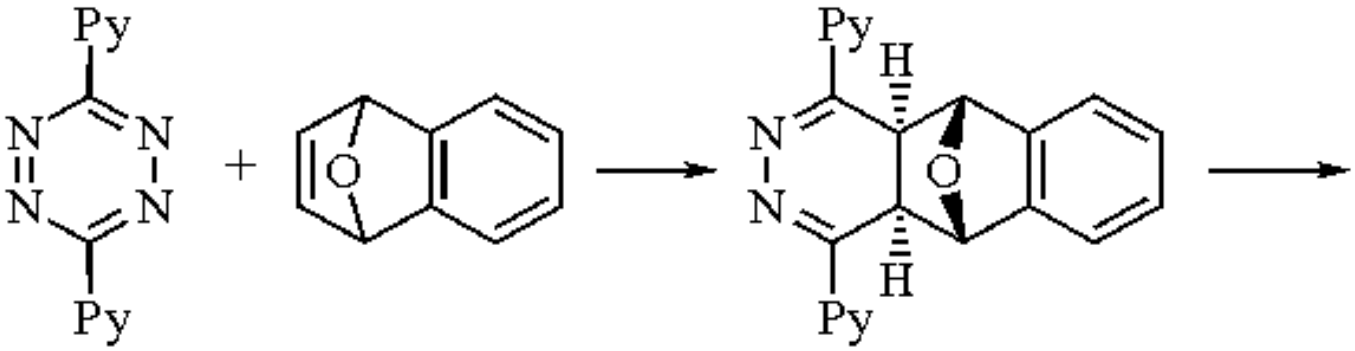

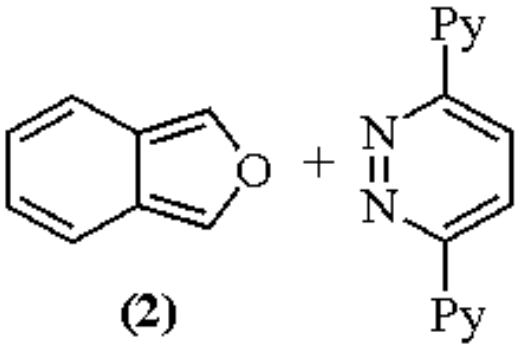

(2)

(2)

Trapping of Unstable Dienophiles as Diels-Alder Adducts.

Cycloaddition reactions of 1,3-diphenylisobenzofuran have been extensively exploited for trapping unstable dienophiles. The Diels-Alder cycloaddition of the parent isobenzofuran is some 11 times faster than of the 1,3-diphenyl analog,[7] and hence this species is often used in instances where the highest level of reactivity is required. Exceedingly unstable species, such as Dewar furan, can be generated and trapped in this manner (eq 3).[8]

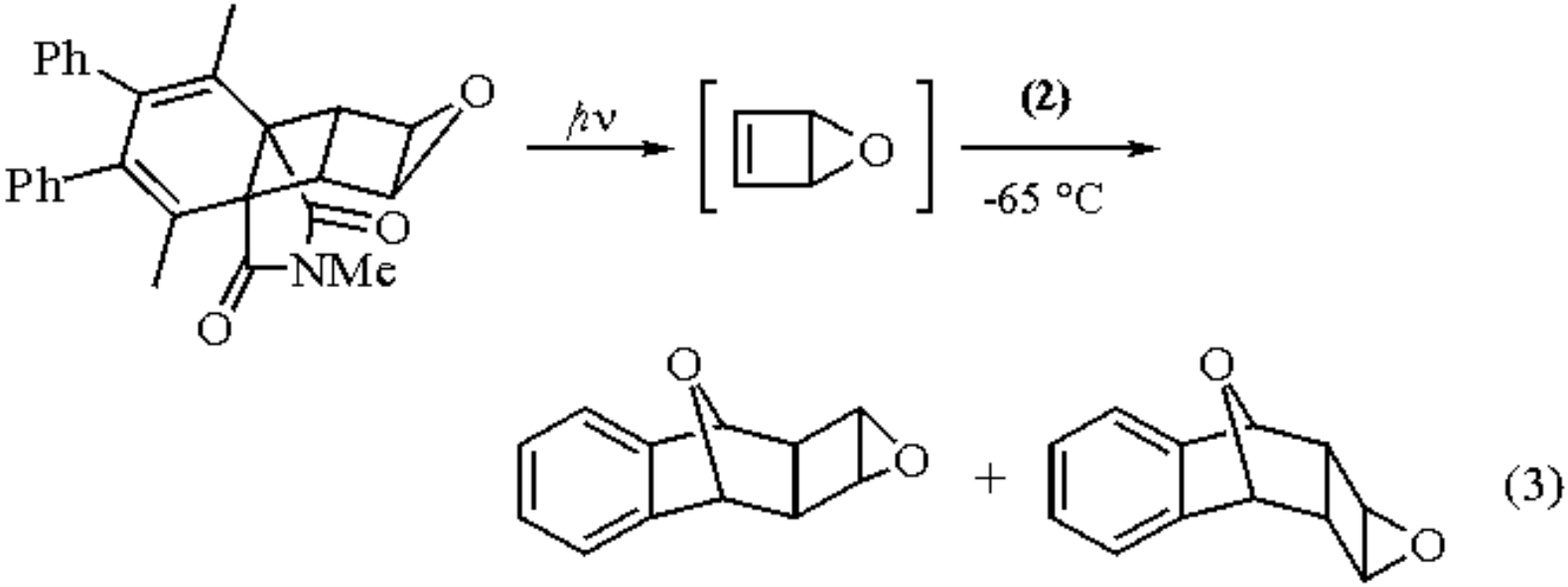

The isobenzofuran must, however, itself be generated immediately prior to carrying out the reaction.[9] The more stable 1,3-diphenylisobenzofuran is an excellent trapping agent for reactive or unstable alkenes and alkynes and has extensively been exploited in this application. Adducts with species such as arynes, cycloalkenes, and cycloalkynes are commonly prepared. For example, 3,4-pyridynes readily form cycloadducts with 1,3-diphenylisobenzofuran (eq 4).[10]

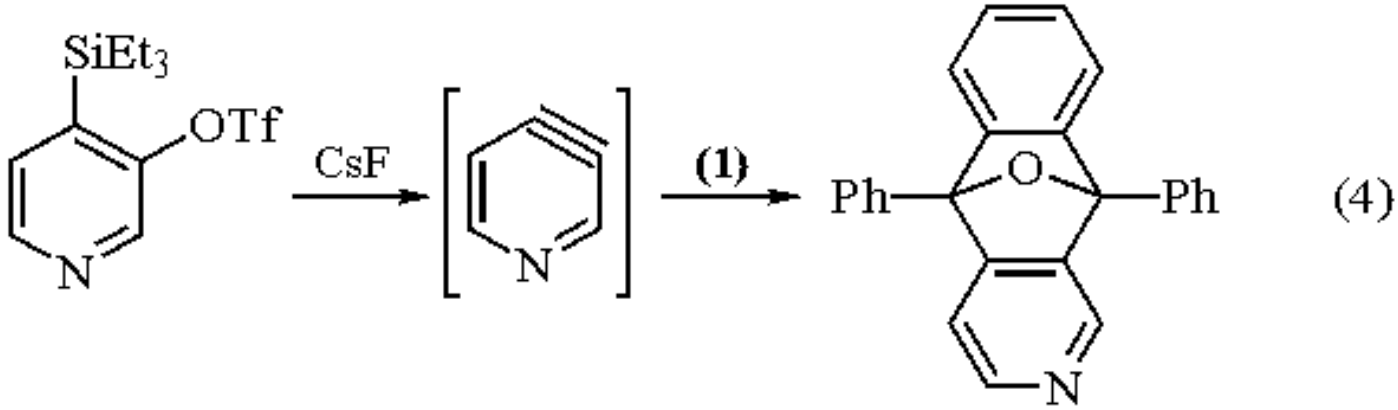

A highly strained polycyclic alkyne, 4-homoadamantyne, has been generated and trapped as a cycloadduct with 1,3-diphenylisobenzofuran (eq 5).[11] Similarly, a highly strained cyclopropene, tricyclo[3.2.1.0^{2,4}]oct-2(4)-ene, has been synthesized and trapped in this manner (eq 6).[12] The related species 5,6-dimethyl-1,3-diphenylisobenzofuran is purported to be more stable and yield more easily characterized adducts.[13]

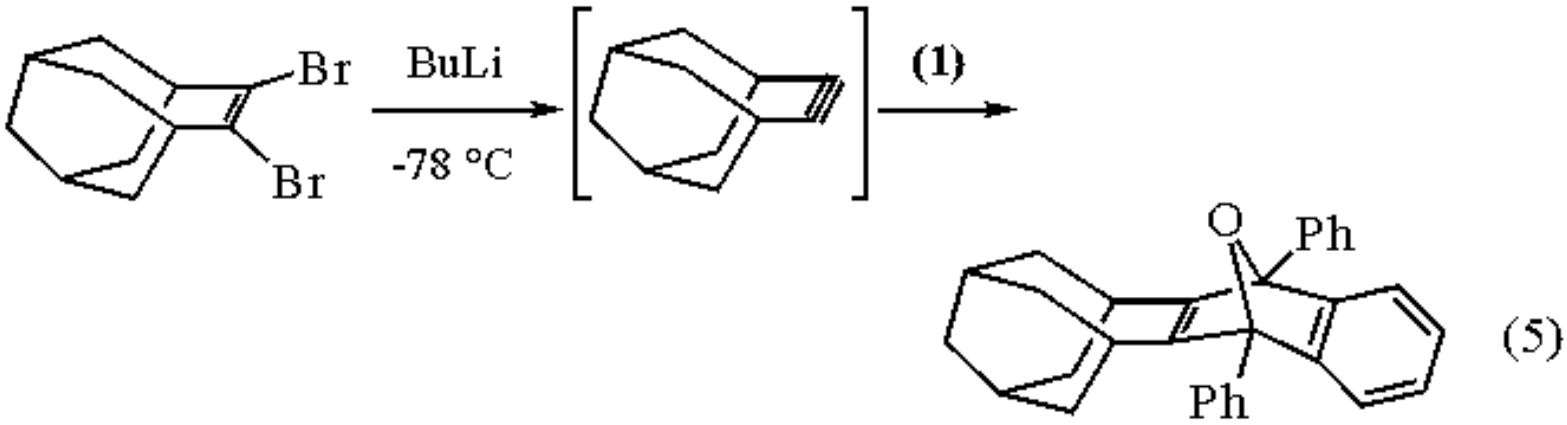

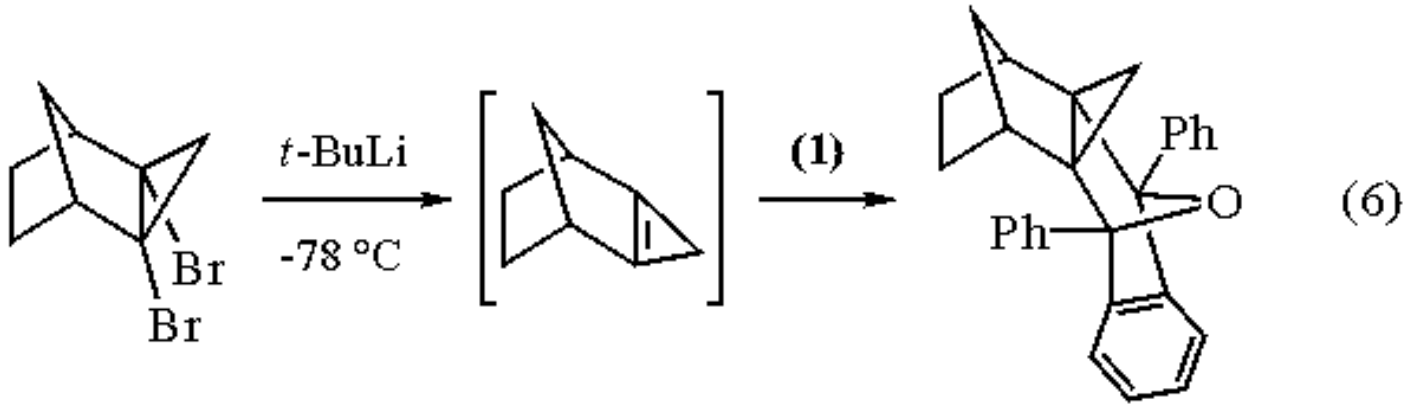

The Diels-Alder reaction of 1,3-diphenylisobenzofuran can be accelerated by catalysis with Lewis acids, such as ***Boron Trifluoride Etherate***. Cycloaddition with diethyl vinylphosphonate yields a mixture of two isomers in high yields (75%) (eq 7).[14]

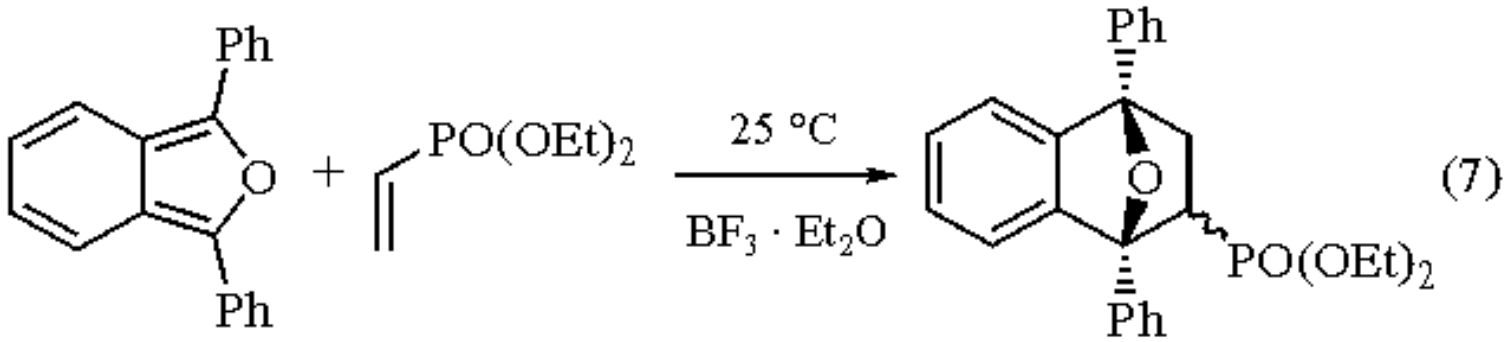

Diels-Alder additions of isobenzofurans with alkenic dienophiles normally yield mixtures of *exo* and *endo* adducts. Reversible cycloadditions tend to favour *exo* isomers, presumably on thermodynamic grounds.

Higher Order Cycloadditions.

Isobenzofurans are frequently utilized as 4π components in cycloaddition reactions. These can be Diels-Alder $[4_\pi + 2_\pi]$ or higher order $[4_\pi + 4_\pi]$ and $[4_\pi + 6_\pi]$ cycloadditions. Tropone yields the $[\pi_4 + \pi_6]$ thermal cycloadduct (eq 8).[15]

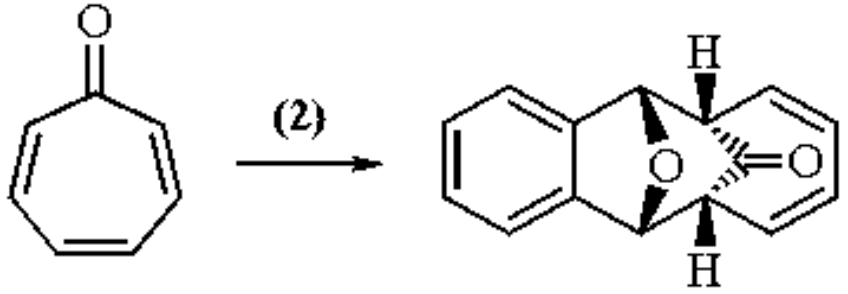

(8)

Synthesis of Polyaryl Systems.

Cycloaddition of isobenzofurans followed by deoxygenation of the cycloadducts constitutes a powerful methodology for the synthesis of polyaromatic species (eq 9).[16]

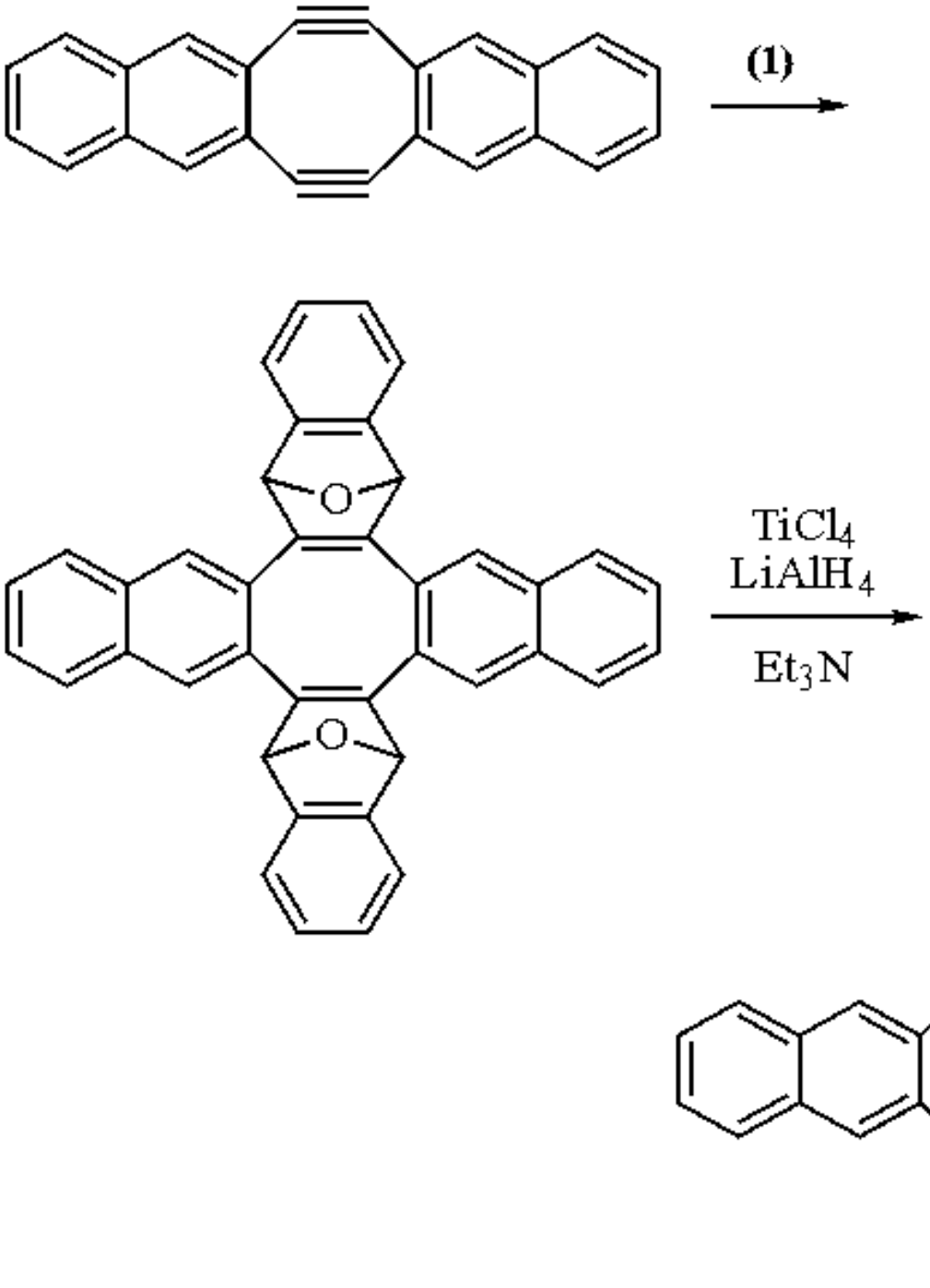

(9)

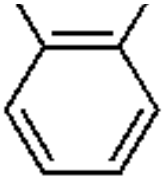

Reaction with Singlet Oxygen.

1,3-Diphenylisobenzofuran reacts rapidly with singlet oxygen to yield an unstable endoperoxide[17] which subsequently decomposes to *o*-dibenzoylbenzene (eq 10), although the details of this reaction are controversial.[18] The quenching reaction has become a standard in the field of singlet oxygen chemistry.[19] Disappearance of 1,3-diphenylisobenzofuran can be monitored by measurement of absorbance at 415 nm or by loss of fluorescence emission at 458 nm.[20]

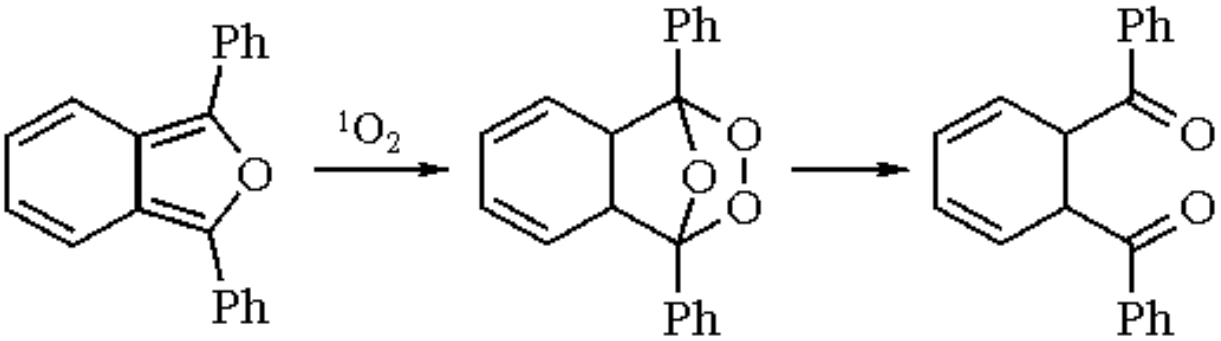

(10)

Lithiation of Isobenzofuran.

Deprotonation of isobenzofuran occurs readily to yield the 1-lithio species. In practice, the phthalan precursor is lithiated (0.05 equiv diisopropylamine/2.1 equiv MeLi/0 °C), yielding 1-lithioisobenzofuran, which reacts smoothly with electrophiles (eq 11).[21]

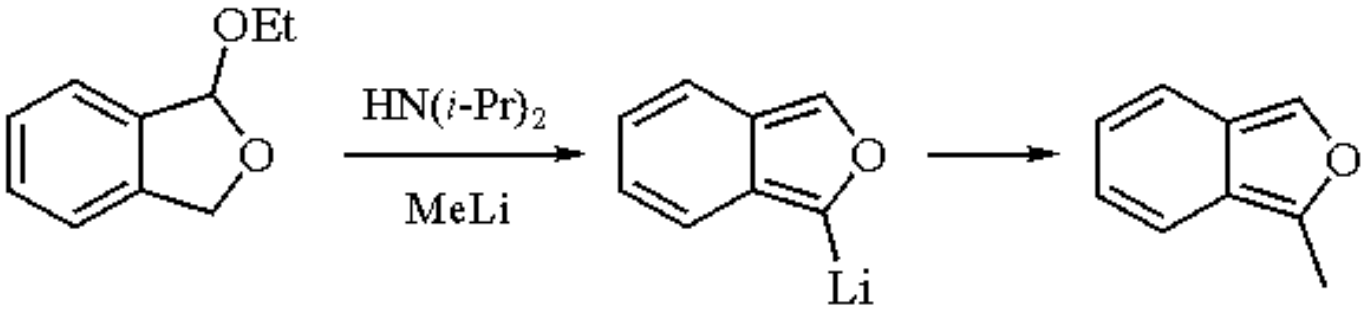

(11)

Photochemistry.

1,3-Diphenylisobenzofuran[22] and isobenzofuran[23] photodimerize to form head-to-head [$8_\pi + 8_\pi$] adducts (eq 12). The latter adduct has been determined to have *anti* stereochemistry. The reaction is reversible for the 1,3-diphenylisobenzofuran adduct. Thermolysis returns the starting material.[24] This head-to-head dimer can also be generated thermally[25] and is encountered in the product mixture of cycloaddition reactions.[26]

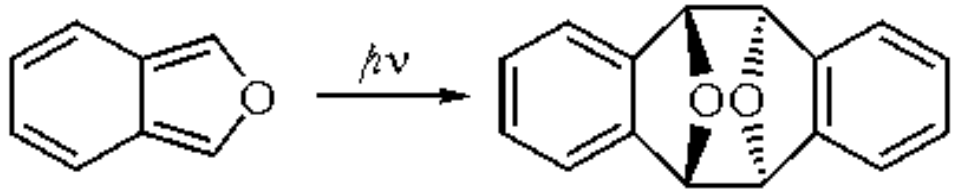

(12)

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Paul Ch. Kierkus

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Diphenylketene[1]

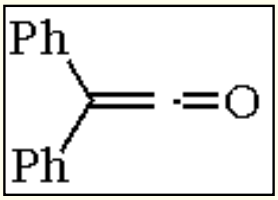

[525-06-4] · $C_{14}H_{10}O$ · Diphenylketene · (MW 194.24)

(acylation of carboxylic acids to give mixed anhydrides;[2] cycloaddition with a variety of unsaturated compounds;[3] synthetic source of diphenylallenes[4])

Physical Data: bp 118-120 °C/1 mmHg.

Solubility: sol benzene, THF.

Form Supplied in: not commercially available.

Preparative Methods: originally prepared by zinc reduction of α-chlorodiphenylacetyl chloride;[5] oxidation of benzil monohydrazone with yellow ***Mercury(II) Oxide*** followed by thermal rearrangement of the α-diazo ketone;[6] dehydrohalogenation of diphenylacetyl chloride with ***Triethylamine***;[7] debromination of α-bromodiphenylacetyl bromide by the action of ***Triphenylphosphine***.[8]

Purification: vacuum distillation at 118-120 °C/1 mmHg.

Handling, Storage, and Precautions: material stored in a tightly stoppered bottle at 0 °C is stable for several weeks. Trace amounts of hydroquinone and storage under nitrogen inhibit polymerization and lead to increased stability. Given the reactivity of diphenylketene with amino acids, care should be taken to avoid skin contact.

Acylation of Carboxylic Acids.

Diphenylketene provides a neutral method for the conversion of carboxylic acids into mixed anhydrides.[2] Amino acids can be transformed into activated esters through the intermediacy of these mixed anhydrides without racemization (eq 1).[9]

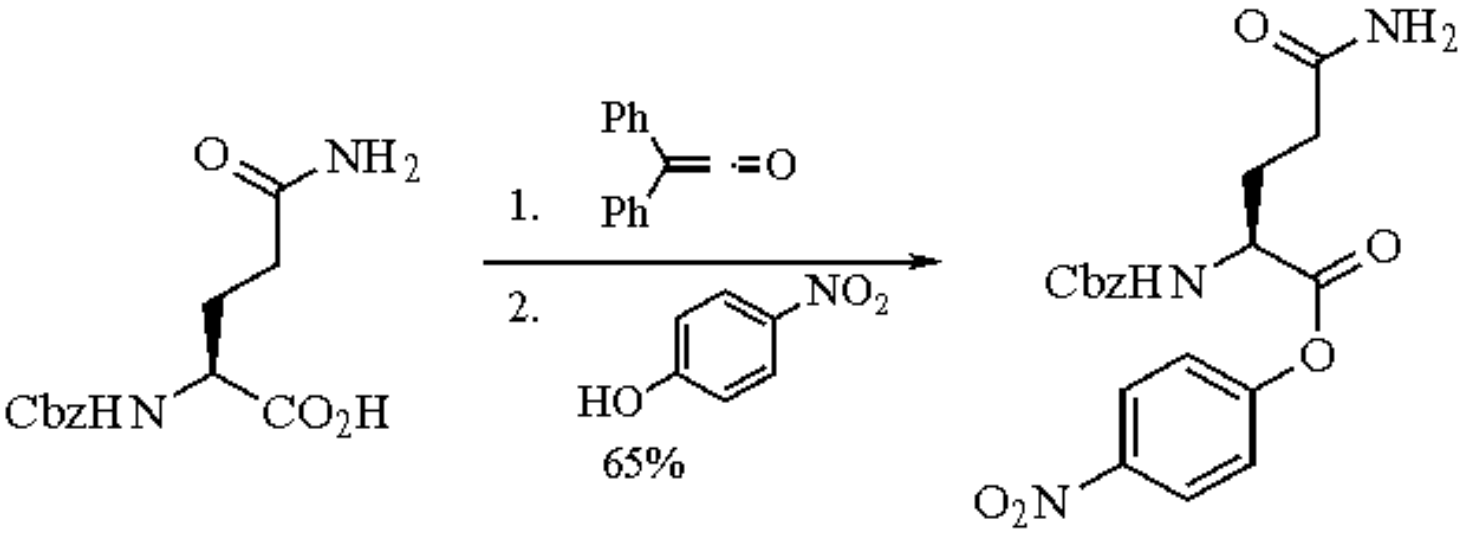

(1)

Cyclization Reactions.

Diphenylketene undergoes most of the cyclization reactions that are characteristic of ketenes.[1] For example, cyclization with hexafluoroacetone leads to a β-lactone (eq 2).[10] Reaction with simple alkenes leads to cyclobutanones (eq 3),[11] although many of these reactions are prohibitively slow.[12] Cyclizations have also been observed with numerous other functionalities, including allenes,[13] alkynes,[14] azides,[15] diimides,[16] imines,[17] phosphinimides,[18] phosphaalkynes,[19] and 1,3-dipoles.[20]

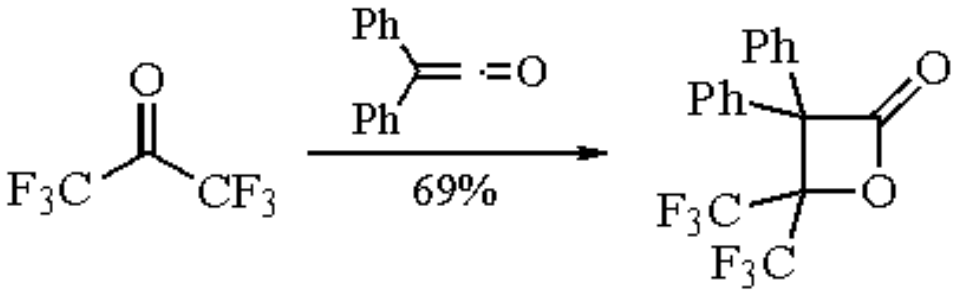

(2)

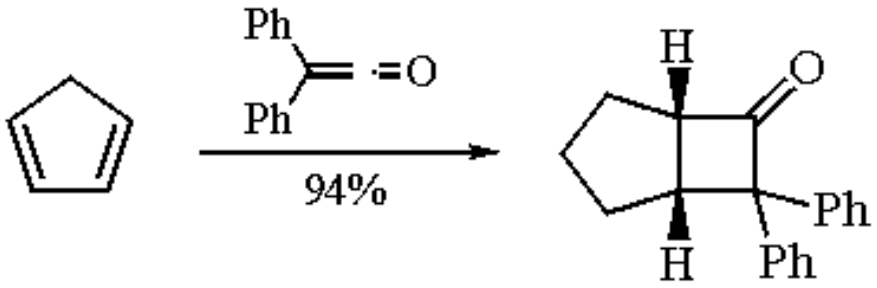

(3)

Miscellaneous Reactions.

Wittig reaction of diphenylketene leads to the synthesis of allenes (eq 4).[4] In fact, tetraphenylallene can be made upon heating diphenylketene in the presence of HMPA.[21] Amines also react with diphenylketene; for example, reaction of 2-azabicyclo[2.2.1]hept-5-enes leads to the formation of 2-piperidinones (eq 5).[22] Epoxides and oxetanes can be opened with diphenylketene and tetraphenylantimony iodide to generate γ- and δ-lactones in good yield (eq 6).[23]

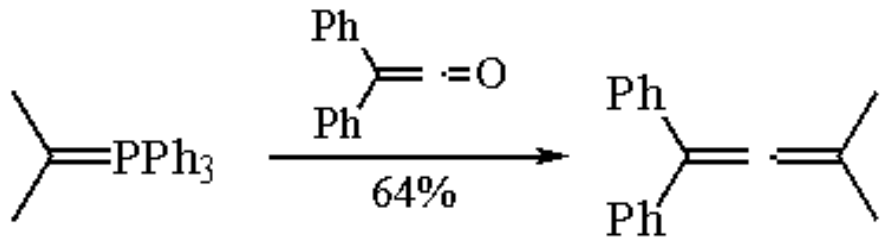

(4)

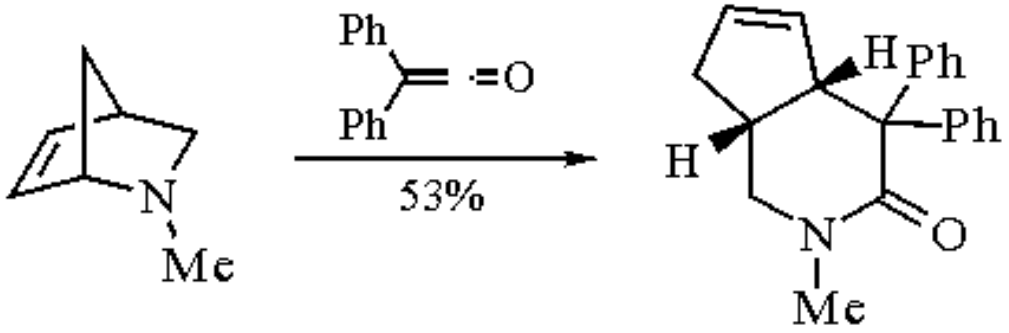

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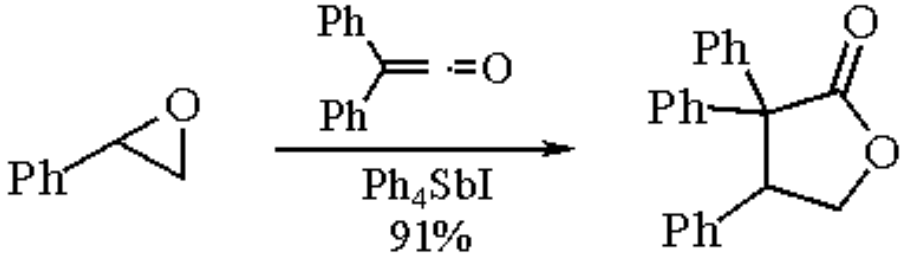

(6)

Related Reagents.

Dichloroketene.

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Diphenylmercury

Ph_2Hg

[587-85-9] · $C_{12}H_{10}Hg$ · Diphenylmercury · (MW 354.81)

(mild reagent for the incorporation of the phenyl group into organic substrates;[1] transmetalation processes[2])

Physical Data: mp 128-129 °C; d_4^{20} 2.30 g cm^{-3}.

Solubility: sol diethyl ether, dichloromethane.

Form Supplied in: commercially available as a white solid; widely available.

Handling, Storage, and Precautions: harmful if swallowed, inhaled, or absorbed through the skin. Inhalation may be fatal as a result of spasm, inflammation and edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema. Use in a fume hood.

Phenylation of Organic Substrates.

In general, the reaction of diphenylmercury with haloalkanes is unsuccessful. However, it has been reported that diphenylbromomethane reacts with diphenylmercury to afford triphenylmethane (eq 1).[3]

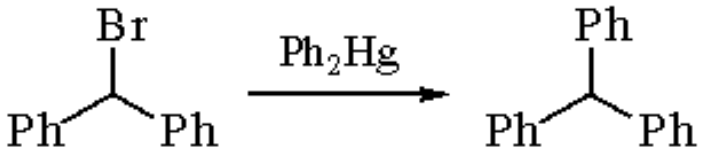

(1)

Heck has demonstrated the use of diphenylmercury as a coupling partner in palladium-promoted and -catalyzed phenylation of alkenes.[1] Thus treatment of an alkene with diphenylmercury in the presence of a stoichiometric amount of a palladium salt affords the phenyl-substituted alkene (eq 2). The results of this reaction are summarized in Table 1.[1]

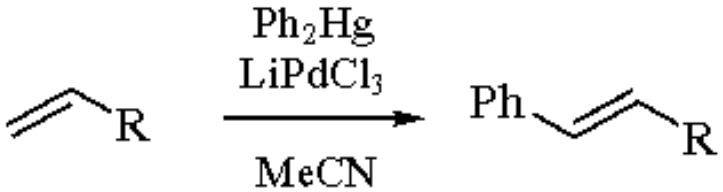

(2)

Table 1 Phenylation of Alkenes with Ph_2Hg

Starting alkene	Product	Yield (%)
		63[1a]
		49 (*E*), 10 (*Z*)[1a]
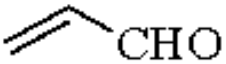	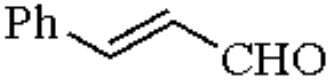	60[1a]
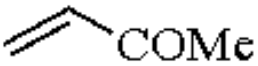	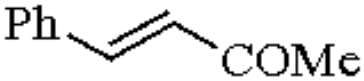	64[1a]
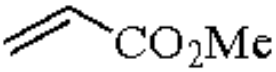	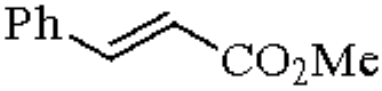	88[1a]
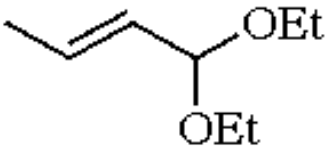	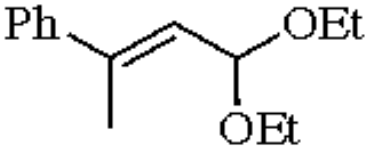	52[1b]

To some extent, this reaction has been superseded by the more conventional Heck reaction using aryl iodides as the coupling partner.[4] However, a palladium-catalyzed procedure has also been reported, where a reoxidant is added to regenerate the palladium catalyst.[1] Diphenylmercury reacts with acid chlorides in the presence of sodium iodide and a palladium catalyst. For example, under these conditions, cinnamoyl chloride can be converted into chalcone (eq 3).[5]

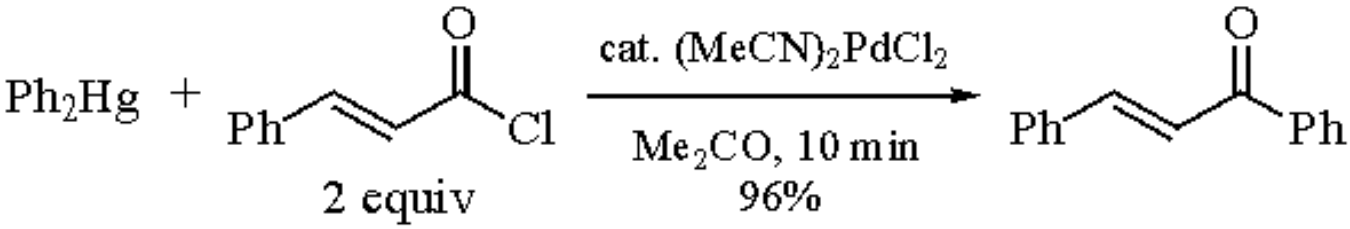

(3)

The palladium- and rhodium-catalyzed carbonylation of diphenylmercury is also possible. The reaction of diphenylmercury with ***Carbon Monoxide*** in the presence of a rhodium catalyst affords benzophenone (eq 4).[6] The carbonylation of diphenylmercury and related compounds by ***Octacarbonyldicobalt*** has also been reported.[7]

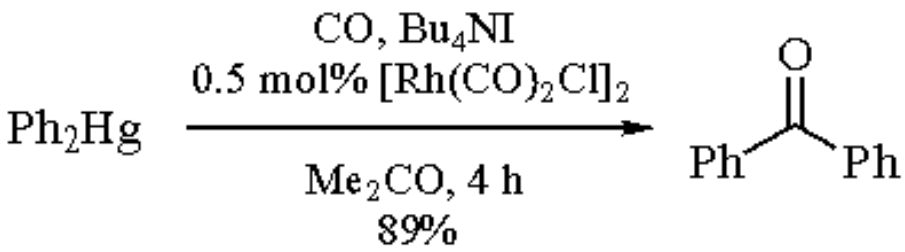

(4)

Radical Reactions.

Diphenylmercury undergoes radical reactions. Treatment of a tetrachloromethane solution of diphenylmercury in the presence of ***Dibenzoyl Peroxide*** catalyst affords the products of radical reaction (eq 5).[8] The reaction of diphenylmercury with a fluoroxy compound affords the product of electrophilic fluorination, fluorobenzene (eq 6).[9] Treatment of diphenylmercury with ***Thiocyanogen*** affords phenyl thiocyanate and phenylmercury thiocyanate (eq 7).[10]

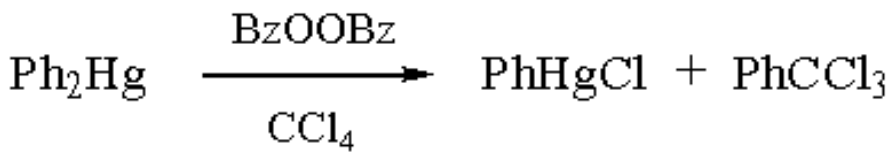

(5)

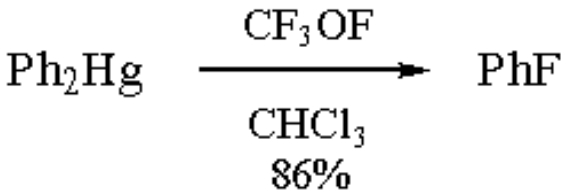

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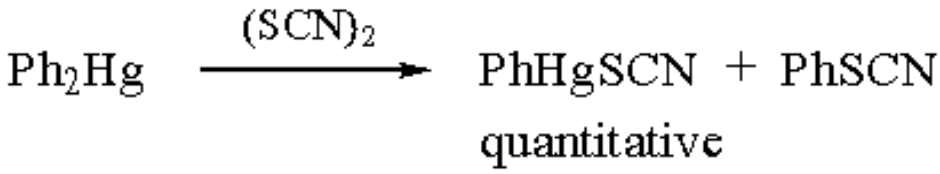

(7)

Transmetalation Reactions.

Diphenylmercury has been widely exploited for the preparation of other organometallic reagents by transmetalation processes.[2] While a simple method for the preparation of diphenylmercury is from the Grignard reagent phenylmagnesium bromide,[11] there has nevertheless been an interest in the preparation of diphenylmagnesium from diphenylmercury. Thus treatment of diphenylmercury in THF with ***Magnesium*** metal affords a solution of diphenylmagnesium (eq 8).[12]

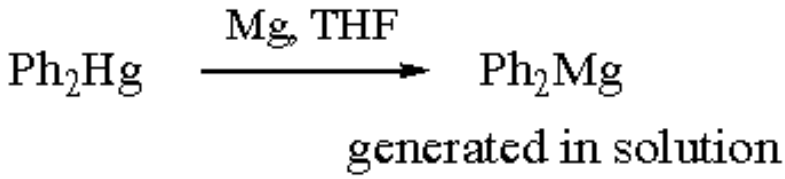

(8)

Diphenylzinc has been prepared by treatment of diphenylmercury with ***Zinc*** metal (eq 9) which afforded the product with sufficient quality that, after crystallization, an X-ray crystal structure determination could be carried out. The fact that the diphenylzinc can be obtained under salt-free conditions is useful.[13]

$$Ph_2Hg \xrightarrow{Zn,\ Et_2O} Ph_2Zn \qquad (9)$$

The reaction between a trichlorotin complex and diphenylmercury results in ligand exchange of one of the chlorides for a phenyl group (eq 10).[14] Reaction of an osmium hydrido complex with diphenylmercury results in the formation of a coordinatively unsaturated σ-aryl osmium complex (eq 11).[15] Similar reactions have also been reported for ruthenium complexes and, independently, rhodium complexes.[16]

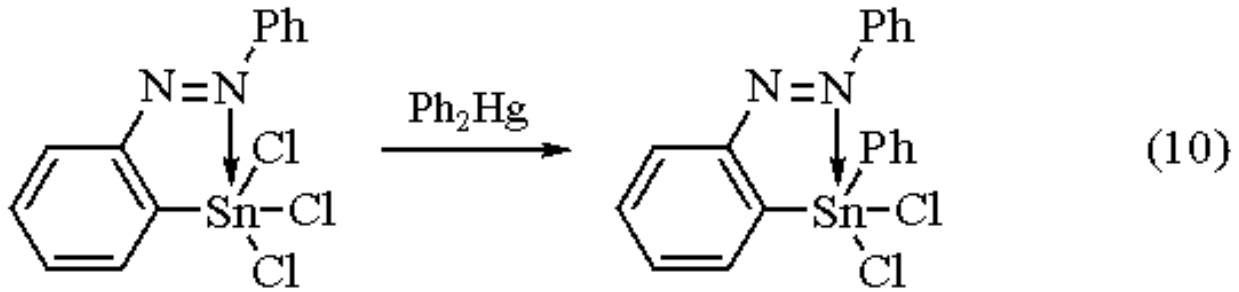

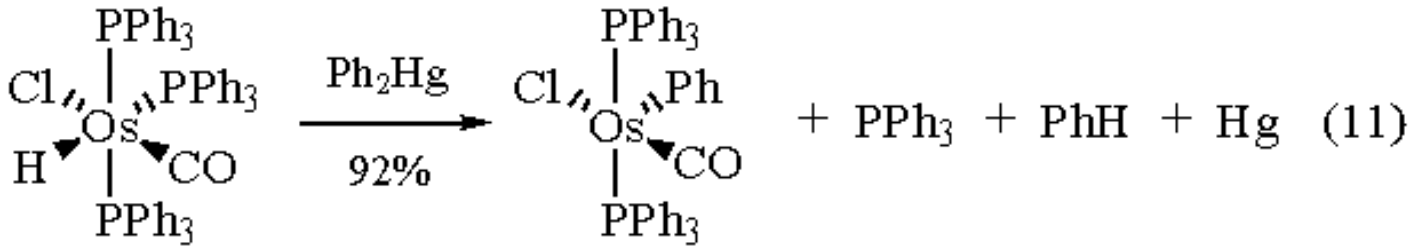

The transmetalation of diphenylmercury can lead to other phenylmetal species which can be used synthetically in situ. For example, the reaction between diphenylmercury and ***Lead(IV) Acetate*** affords phenyllead triacetate,[17] which reacts with nucleophiles. In the presence of ***2-Nitropropane***, 2-phenyl-2-nitropropane is produced in 63% yield (eq 12).[18]

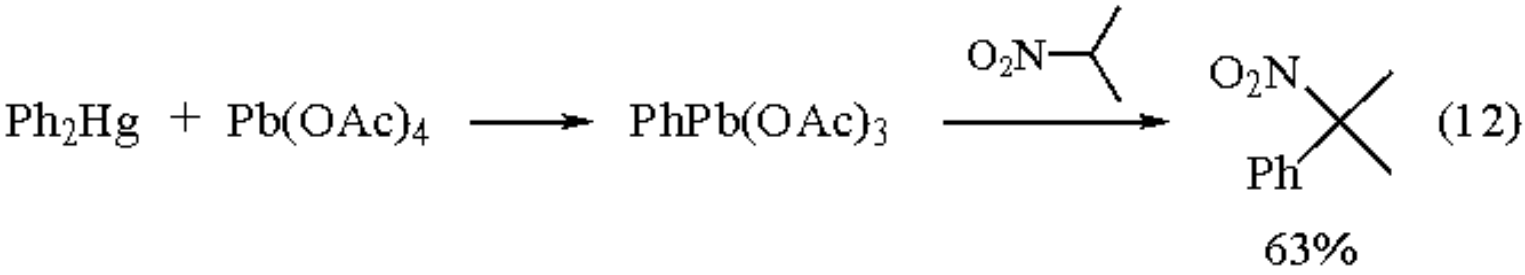

Diphenylmercury has been converted into the corresponding bis(chromium tricarbonyl) adduct. The reaction with 2 equiv of ***n-Butyllithium*** affords the aryllithium, which can be trapped with a variety of electrophiles including ***Carbon Dioxide*** (eq 13).[19]

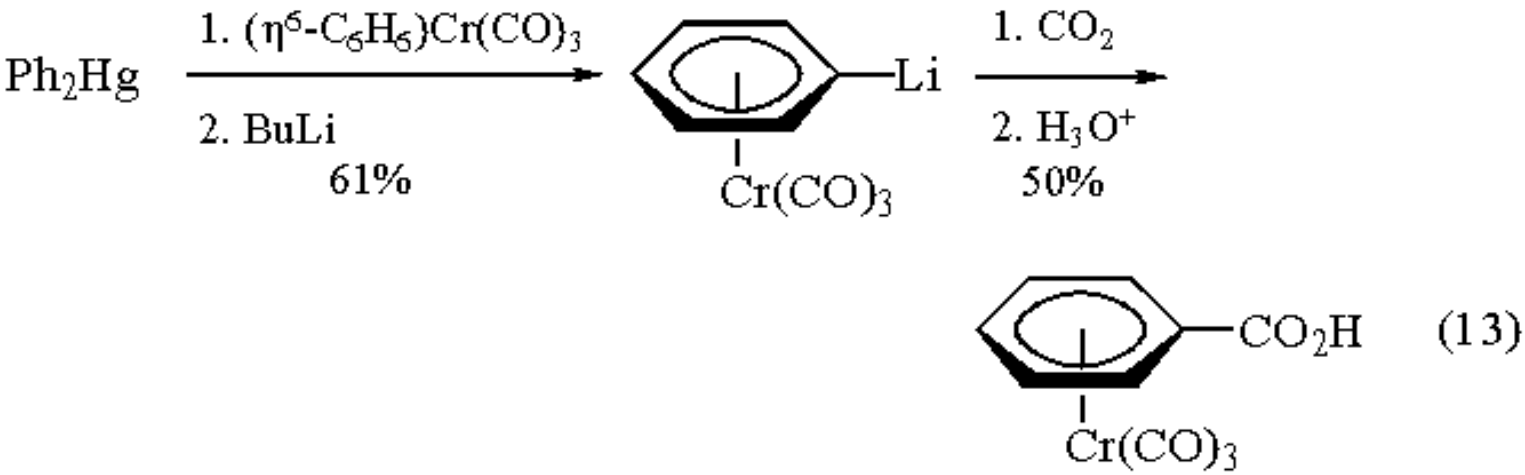

The reaction of diphenylmercury with excess ***Borane-Tetrahydrofuran*** affords an intermediate arylboron species, which upon oxidative workup affords a good yield of phenol (eq 14).[20]

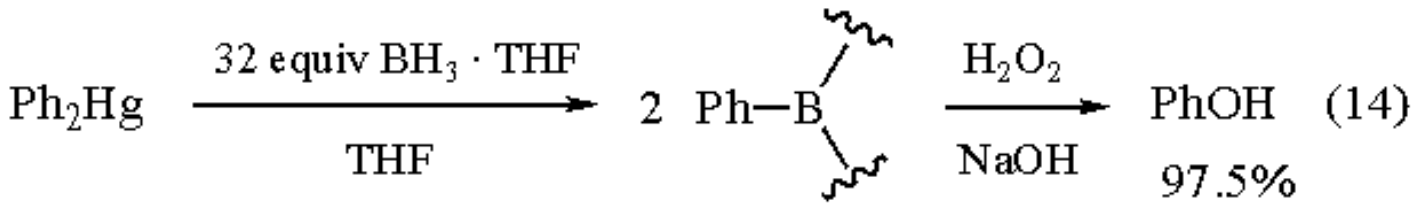

Other metals (or their complexes) which have been phenylated by diphenylmercury include cadmium,[2] antimony,[2] silicon,[2] arsenic,[2] ytterbium,[21] palladium,[22] and tellurium.[23]

---

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Diphenyl(methoxymethyl)phosphine

Ph_2PCH_2OMe

[43139-94-2] · $C_{14}H_{15}OP$ · Diphenyl(methoxymethyl)phosphine · (MW 230.26)

(one-carbon homologation of hindered ketones to the corresponding aldehydes via the methyl enol ethers[1])

Physical Data: bp 134-135 °C/0.25 mmHg);[2] *n*20D 1.6085;[3] ^{1}H NMR ($CDCl_3$) δ 7.70-7.20 (m), 4.14 (d, *J* = 8 Hz), 3.38 (s).[2]

Solubility: sol THF, ether.

Preparative Methods: from the reduction of diphenyl(methoxymethyl)phosphine oxide with ***Hexachlorodisilane*** (50% yield)[2] or ***Lithium Aluminum Hydride*** (ca. 50% yield).[7] Nucleophilic addition of methoxymethylmagnesium chloride to diphenylchlorophosphine[3] furnishes the reagent (**1**) in 80% yield. An alternative synthesis (eq 1), which is suitable for large scale preparation, involves reductive lithiation of diphenylchlorophosphine with 2.2 equiv of ***Lithium*** in liquid ammonia, followed by trapping of the phosphide anion at low temperature with ***Chloromethyl Methyl Ether*** (**caution: carcinogen**).[1] Workup of the reaction is performed under argon.

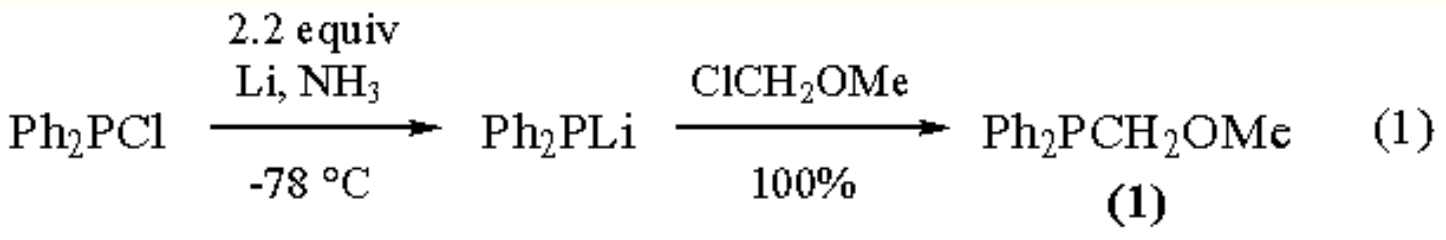

Handling, Storage, and Precautions: stench. Undergoes oxidation to the phosphine oxide on standing in air.

Ketone Homologation.

The conversion of hindered or enolizable ketones to the corresponding one-carbon homologous aldehydes is often an inefficient process because of competing enolization. The common Wittig reagent for carrying out this reaction, ***Methoxymethylenetriphenylphosphorane*** (**2**),[4] often fails to provide acceptable yields of the intermediate enol ethers.[5] The lithio anion (**3**) of diphenylmethoxymethylphosphine oxide is more effective;[6] however, it is not satisfactory for all applications. For example (eq 2), spiroketone (**4**) affords approximately equal amounts of enol ether (**5**) and starting ketone from the reaction with (**3**).[1] The design of diphenyl(methoxymethyl)phosphine (**1**) as an improved reagent was predicated on the assumption that it would have both a smaller steric requirement than (**2**) or (**3**), and that for electronic

reasons it would be a more aggressive nucleophile.

(2) **(3)**

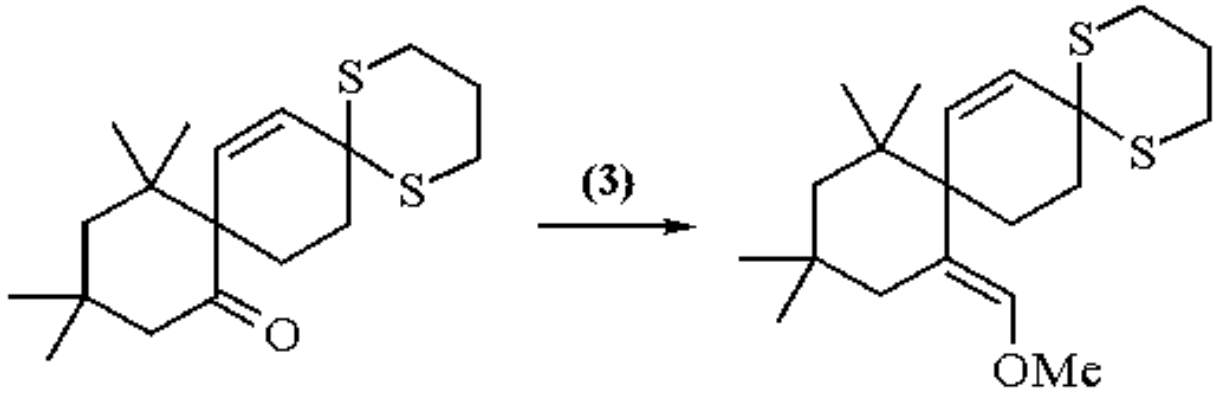

(2)

(4) **(5)**

The anion of (**1**) is prepared by deprotonation at -95 °C in THF with ***s-Butyllithium***. Addition of a THF solution of the ketone to the lithio anion of (**1**) followed by warming to 25 °C affords a β-hydroxy phosphine. Subsequent addition of methanol and excess ***Iodomethane*** leads to the methyl enol ether which undergoes hydrolysis to the aldehyde in the presence of ***Trichloroacetic Acid*** in dichloromethane. The reaction sequence has been applied successfully to the total synthesis of warburganal (eq 3),[8] and in somewhat lower yield to phyllanthocin (eq 4).[9] Spiroketone (**4**) is converted completely to the methyl enol ether.[1] Fenchone, an extraordinarily hindered ketone, undergoes homologation to the aldehyde in 79% yield.[1]

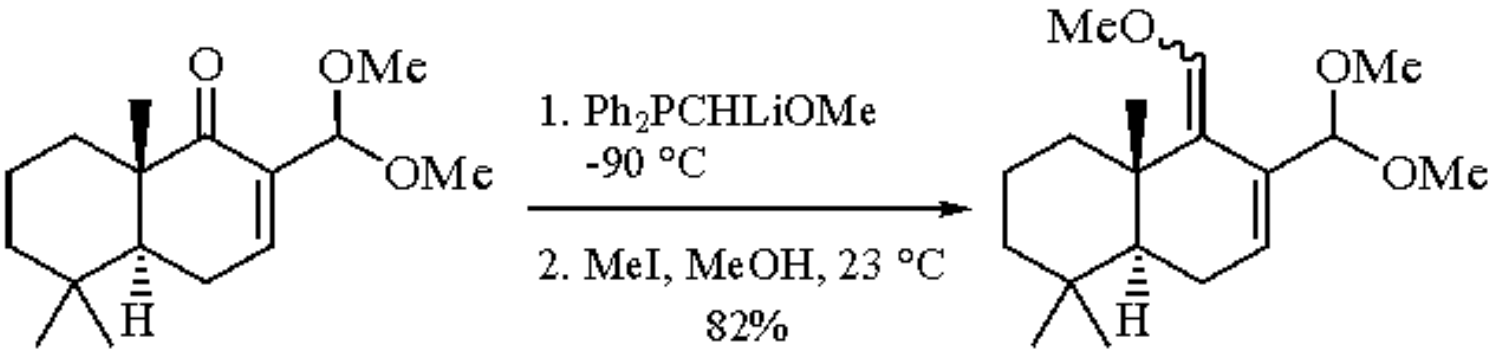

(3)

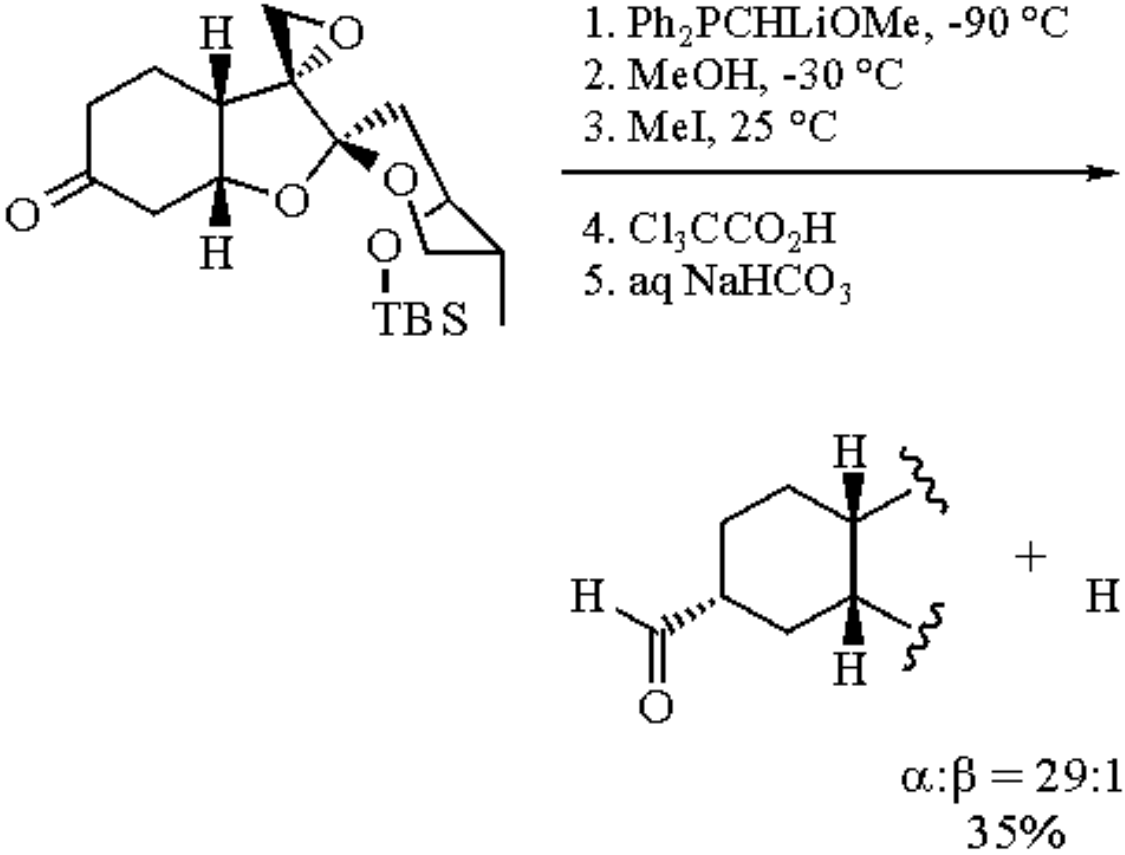

(4)

A limitation of the reagent is seen in its failure to add to propellane (**6**).[10] The reaction of lithio-(**1**) with camphor proceeds only to the extent of 10%.[1] Contrast this with the behavior of diethyl (α-lithioisocyanomethyl)phosphonate,[11] which reacts with camphor to produce the homologous aldehyde in 97% yield, thus suggesting the superiority of the phosphonate for some applications.

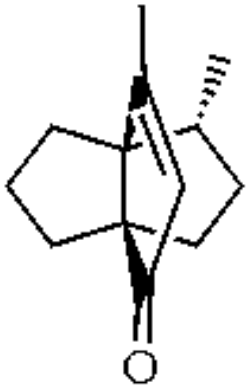

(6)

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N-(Diphenylmethylene)aminoacetonitrile

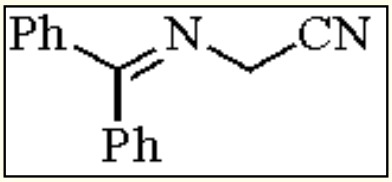

[70591-20-7] · $C_{15}H_{12}N_2$ · *N*-(Diphenylmethylene)aminoacetonitrile · (MW 220.29)

(glycine anion equivalent for amino acid synthesis by phase transfer catalysis)

Alternate Names: aminoacetonitrile benzophenone imine; O'Donnell's Schiff base.

Physical Data: mp 81-82 °C; pK_a (DMSO) = 17.8.[1]

Form Supplied in: commercially available.

Preparative Method: by transimination of benzophenone imine with aminoacetonitrile hydrochloride.[2,3] The crude product can often be used as it is or it can be recrystallized (Et_2O/hexane or CCl_4).

Handling, Storage, and Precautions: stable to flash chromatography and stable at rt. It is best stored under argon to avoid contact with moisture. The hydrolysis product, benzophenone, can be detected either by TLC (EtOAc/hexane) or by NMR.

Amino Acid Synthesis by Alkylation using Phase Transfer Catalysis.

The benzophenone imine of aminoacetonitrile is a versatile glycine anion equivalent[4] for the synthesis of higher amino acid derivatives by alkylation of a variety of alkyl halides (methyl, benzylic, allylic, primary, secondary) under phase transfer catalysis (PTC) conditions.[5] The PTC method involves a simple reaction procedure, mild conditions, inexpensive and safe reagents and solvents, and the ability to easily scale-up the reaction. Typically the substrate is stirred at rt in a two-phase system (liquid-liquid (with aqueous base)[5] or solid-liquid (with solid base)[6] PTC) in the presence of the alkyl halide and the phase transfer catalyst, a tetraalkylammonium salt. The monoalkylated product is readily hydrolyzed to the racemic higher amino acid (eq 1).[7,8] Combination with enzymatic resolution provides optically active amino acids.[9] Labeled amino acids for various biochemical studies are prepared from deuterio-substituted alkyl halides[10-12] or by α-deuteration with 50% aq. NaOD.[13] Boronation of the propargylated derivative and hydrolysis leads to *o*-carboranylalanine (eq 2), a boron-containing amino acid of use in the treatment of melanoma by boron neutron capture therapy (BNCT).[14] Palladium-catalyzed allylation leads to γ,δ-unsaturated amino acids.[15]

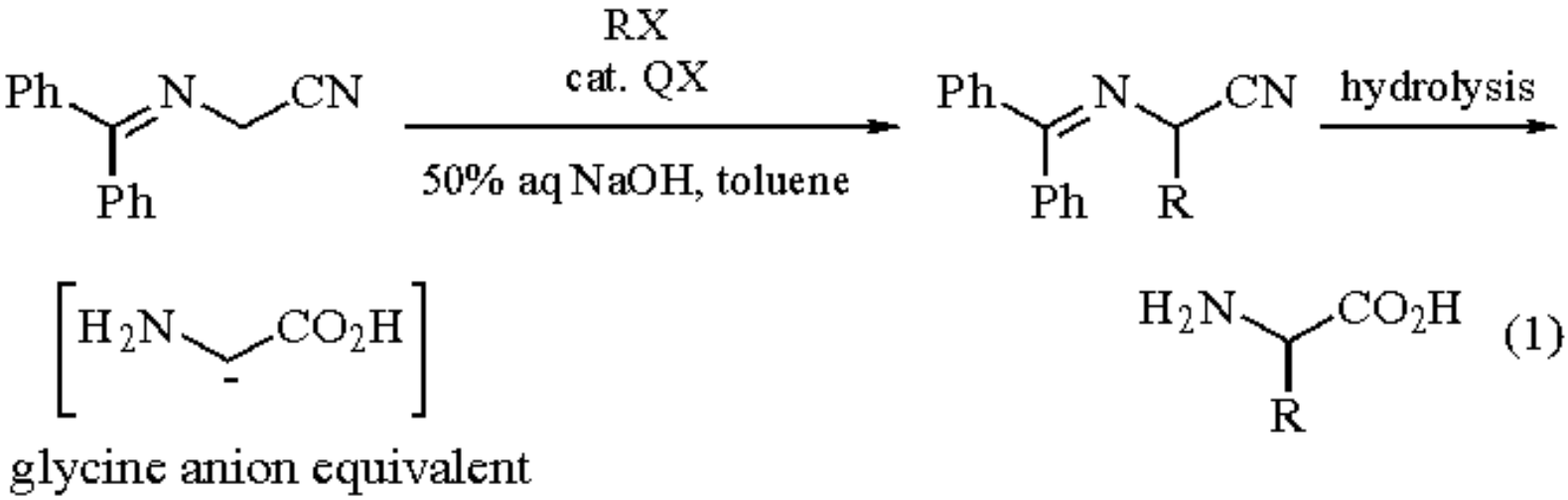

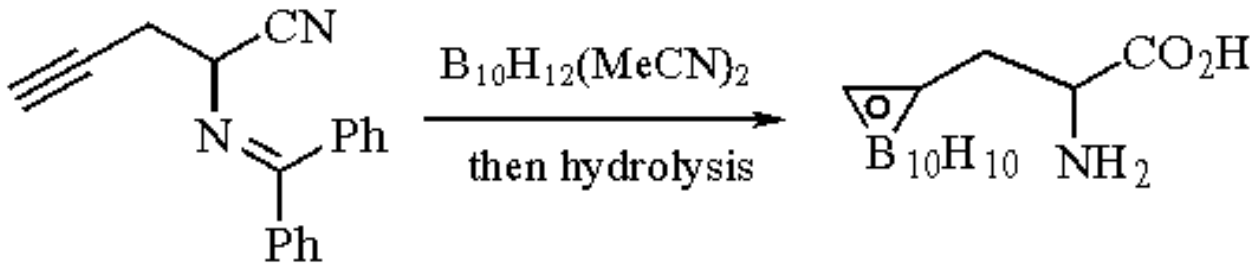

1-Aminocyclopropane-1-carboxylic acid (ACC), the biosynthetic precursor of ethylene in plants, can be prepared by PTC alkylation with ***1,2-Dibromoethane*** followed by hydrolysis (eq 3).[16] Reduction of the initial alkylation product gives 1-amino-1-(aminomethyl)cyclopropane, which can be differentially protected.[17] Alkylation with 1,3-dibromopropane and modified stoichiometry yields 2,6-diaminopimelic acid (DAP), a key structural component of bacterial cell walls.[16]

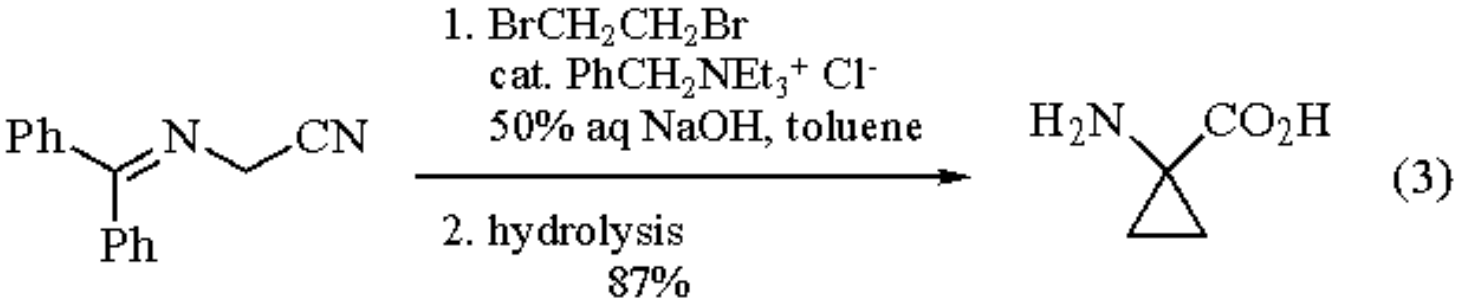

Other Reactions.

Michael addition to phenyl vinyl sulfoxide under solid-liquid PTC conditions in the absence of solvent followed by thermolysis gives the α,β-dehydroamino acid derivative by double bond migration.[18] Reaction with aromatic aldehydes results in 1,2-carbonyl addition followed by elimination of water,[19] while reaction with imines gives the 1,2-adduct.[20] Arylation by nucleophilic aromatic substitution occurs with either (halobenzene)tricarbonylchromium complexes[21] or cationic arenetricarbonylmanganese complexes.[22]

Related Reagents.

Benzophenone Imine; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***N,N-Diethylaminoacetonitrile***; ***2-(2,6-Dimethylpiperidino)acetonitrile***; ***N-(Diphenylmethylene)methanamine***; ***Ethyl N-(Diphenylmethylene)-2-acetoxyglycinate***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Methyl N-Benzylidenealaninate***.

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N-(Diphenylmethylene)methanamine

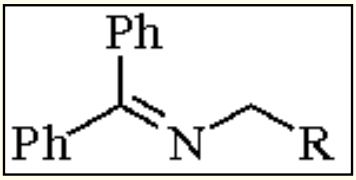

(R = H)

[13280-16-5] · $C_{14}H_{13}N$ · *N*-(Diphenylmethylene)methanamine · (MW 195.28) (R = Li)

[64042-43-9] · $C_{14}H_{12}LiN$ · 1,1-Diphenyl-2-azaallyllithium · (MW 201.21)

(lithiation produces an α-amino carbanion equivalent)

Alternate Names: benzophenone *N*-methylimine; *N*-(diphenylmethylene)methylamine.

Preparative Methods: prepared by condensation of benzophenone with methylamine in the presence of $TiCl_4$[1] or by various other methods.[2,3]

Amine Synthesis by Reaction of 2-Azaallyl Anions with Electrophiles.[4,5]

The benzophenone imine of methylamine is deprotonated to a 2-azaallyl anion which reacts with electrophiles (alkyl halides, epoxides, aldehydes, and ketones)[6-9] at the methylene terminus. Hydrolysis yields nucleophilic aminomethylation products derived from a synthetic equivalent of the α-carbanion of a primary amine (eq 1).

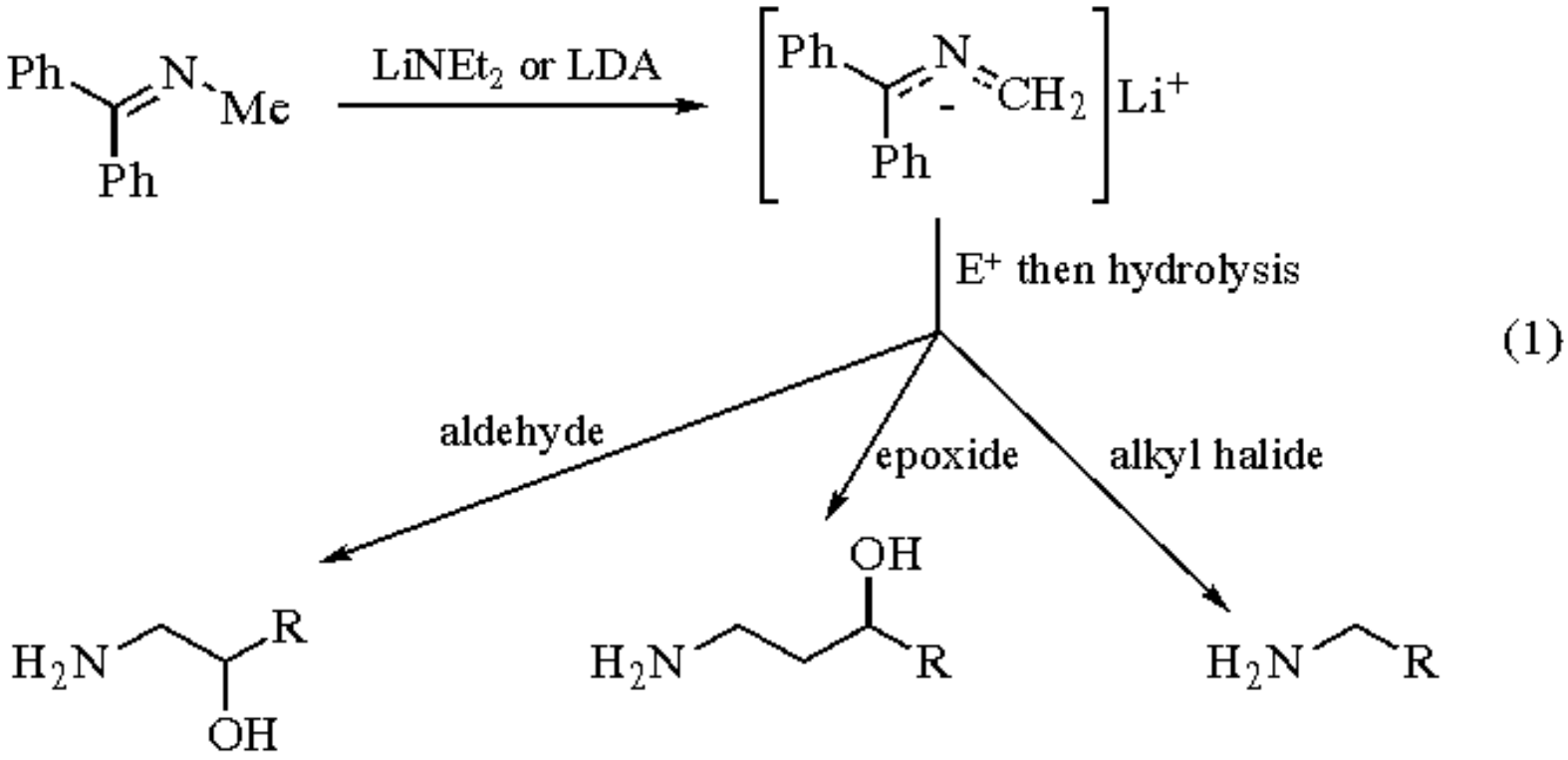

Interesting derivatives of silicon, germanium, and tin ($Ph_2C{=}N\text{-}CH_2SiR_3$, $Ph_2C{=}N\text{-}CH_2GeR_3$, and $Ph_2C{=}N\text{-}CH_2SnR_3$) have been prepared by lithium-metal exchange.[10] Reaction with cyclic carbamates followed by hydrolysis has been reported (eq 2).[11,12]

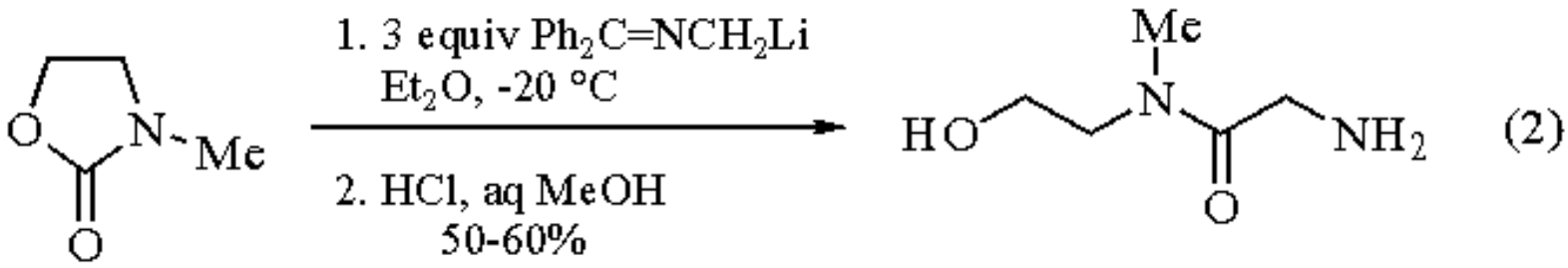

Other Reactions.

Various cycloaddition reactions ([2 + 2];[13-16] [2 + 2 + 2];[13-15] [3 + 2];[17,18] [4 + 2];[19] [6 + 3$^-$][20]) of either the neutral parent or anionic derivative have been reported. Reaction with the chromium carbene complex [$(CO)_5Cr{=}C(OMe)Me$] under photochemical conditions gives a β-lactam by a formal [2 + 2] cycloaddition.[21]

The parent Schiff base has also served as the electrophile for reaction with ***n-Butyllithium***[22] or an active methylene compound.[23] Orthometalation by reaction with ***Tin(IV) Chloride***,[24] as well as oxidation to either oxaziridine or nitrone,[25-27] has been reported.

Related Reagents.

Benzophenone Imine; ***N-t-Butoxycarbonyl-N-methylaminomethyllithium***; ***Dimethylaminomethyllithium***; ***N-***

(Diphenylmethylene)aminoacetonitrile; ***Ethyl N-(Diphenylmethylene)glycinate***; ***N´-t-Butyl-N-methyl-N-trimethylsilylmethylformamidine***; ***Nitromethane***; ***N-Nitrosodimethylamine***.

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(*S*)-Diphenyl(1-methylpyrrolidin-2-yl)methanol[1]

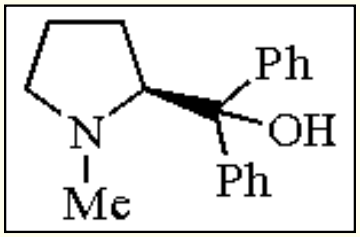

[110529-22-1] · $C_{18}H_{21}NO$ · (*S*)-Diphenyl(1-methylpyrrolidin-2-yl)methanol · (MW 267.40)

(chiral ligand for the enantioselective addition of dialkylzincs,[2] alkynylzinc,[3b] and cyanomethylzinc bromide[4] to aldehydes; chiral ligand for the enantioselective Reformatsky reaction;[5] chiral ligand for the enantioselective Diels-Alder reaction;[6] chiral auxiliary for asymmetric polymerization[7])

Alternate Name: DPMPM.

Physical Data: mp 68.5-68.9 °C; [α]23D + 57.0° (*c* 1.0, $CHCl_3$).

Solubility: sol hexane, benzene, toluene, Et_2O, cyclohexane, dichloromethane.

Form Supplied in: colorless crystals; available in either enantiomeric form.

Preparative Method: reaction of ***Phenylmagnesium Bromide*** with (*S*)-*N*-[(benzyloxy)carbonyl]proline methyl ester and subsequent reduction with ***Lithium Aluminum Hydride*** affords the title compound in 83% overall yield.[2b]

Catalytic Enantioselective Addition of Dialkylzincs to Aldehydes.

DPMPM (**1**) is a chiral amino alcohol which is a precursor to a chiral catalyst for the enantioselective addition of dialkylzincs to aldehydes.[2] In the presence of 2 mol % of (*S*)-(**1**), optically active alcohols of up to 100% ee are obtained from the enantioselective addition of dialkylzincs to aldehydes (eq 1, Table 1). When benzaldehyde is allowed to react with ***Diethylzinc*** using (*S*)-(**1**) (2 mol %), (*S*)-1-phenylpropan-1-ol with 97% ee is obtained in quantitative yield (entry 1). When the lithium alkoxide of (*S*)-(**1**) (5 mol %) is employed as a chiral ligand in the addition to aromatic aldehydes, ee's of the alcohols obtained increase to 99.5-100% ee (entries 4 and 5). Amino alcohol (**1**) is also effective in the enantioselective addition of Et_2Zn to the aliphatic aldehyde heptanal, and (*S*)-nonan-3-ol with 91% ee is obtained (entry 2). In the addition to aromatic aldehydes, enantioselectivities using DPMPM are comparable with those obtained with 3-*exo*-(dimethylamino)isoborneol (DAIB).[8] In the addition to heptanal, DPMPM (**1**) is more enantioselective than DAIB (61%

ee). However, in the addition to aliphatic aldehydes of wider range, *N*,*N*-dibutylnorephedrine[9] is more enantioselective than (**1**).

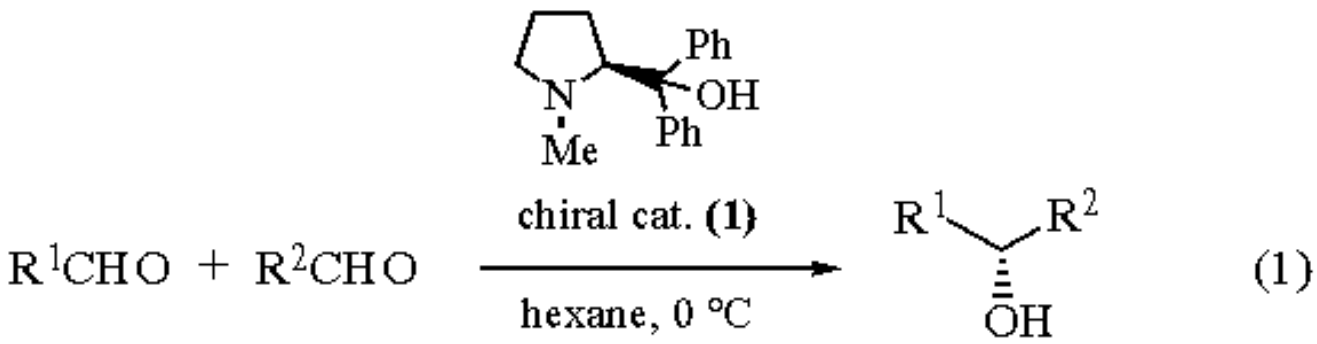

Table 1 Enantioselective Addition of Dialkylzincs to Aldehydes Using (**1**) or (**2**) as Chiral Catalysts

Entry	R^1	R^2	Catalyst	Yield (%)	ee (%)	Config.
1.[2b]	Ph	Et	(*S*)-(**1**)	100	97	(*S*)
2.[2b]	*n*-Hexyl	Et	(*S*)-(**1**)	96	91	(*S*)
3.[2b]	Ph	Et	(*S*)-(**2**)	100	100	(*R*)
4.[2b]	Ph	Et	Li-(*S*)-(**1**)	100	99.5	(*S*)
5.[2b]	4-$MeOC_6H_4$	Et	Li-(*S*)-(**1**)	96	100	(*S*)
6.[10]	4-$CF_3C_6H_4$	Et	(Li-*S*)-(**1**)	80	91	(*S*)
7.[11]	PhCDO	Et	(*S*)-(**1**)	86	91	(*S*)
8.[2a]	PhCH=CH	Et	(*S*)-(**1**)	91	97	(*S*)
9.[2b]	PhCH=CH	Me	(Li-*S*)-(**1**)	47	89	(*S*)
10.[3]	$Me_3SiC^{o}C$	Et	(*S*)-(**1**)	67	78	

The sense of the asymmetric induction is dependent on the structure of the catalyst. (1*R*,2´*S*)-Phenyl(1-neopentylpyrrolidin-2-yl)methanol (**2**) mediates the addition of Et_2Zn to aldehydes to afford (*R*)-alcohols in up to 100% ee (entry 3).[2b] By using (**1**) as a chiral ligand, optically active fluorine-containing alcohols[10] and deuterio alcohols[11] of high optical purities have been synthesized (entries 6 and 7). The enantioselective addition to α,β-unsaturated aldehydes (e.g. cinnamaldehyde) using (**1**) affords optically active allylic alcohols with 89-97% ee (entries 8 and 9).[2] Enantioselective addition of dialkylzincs to alkynyl aldehydes and furyl aldehydes using (**1**) as a chiral catalyst affords optically active alkynyl alcohols (78% ee, entry

10)[3] and furyl alcohols (88-94% ee).[12] When terephthalaldehyde is allowed to react with Et_2Zn using (**1**) as a chiral ligand, the corresponding optically pure diol is obtained.[13]

Unlike alkyllithium and Grignard reagents, dialkylzinc does not add to ketones even in the presence of (**1**). Thus the chemo- and enantioselective alkylation of a keto aldehyde (4-benzoylbenzaldehyde) with Et_2Zn using (*S*)-(**1**) affords the corresponding optically active hydroxy ketone with 93% ee in 99% yield.[14]

Enantioselective Addition of Cyanomethylzinc Bromide, Reformatsky Reagent, and Alkynylzinc Reagents to Aldehydes.

The enantioselective additions of cyanomethylzinc bromide,[4] Reformatsky reagent (see ***Ethyl Bromozincacetate***),[5] and alkynylzinc[3b] reagent to aldehydes using (**1**) as chiral catalyst or ligand afford optically active β-hydroxy nitrile (93% ee),[4] β-hydroxy ester (78% ee) (eq 2),[5] and alkynyl alcohol (43% ee).[3b]

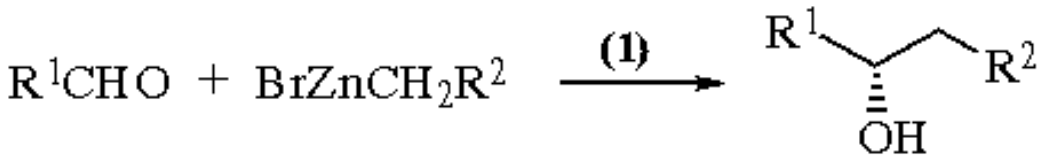

(2)

$R^1 = Ph$, $R^2 = CN$, 76%, 93% ee; $R^1 = 2$-naphthyl, $R^2 = CO_2$-*t*-Bu, 82%, 78% ee

Catalytic Asymmetric Diels-Alder Reaction.

Amino alcohol (**1**) combined with ***Boron Tribromide*** generates a chiral catalyst for the asymmetric Diels-Alder reaction (97% ee) of unsaturated aldehydes and dienes.[6]

Asymmetric Polymerization.

Polymerization of methacrylate derived from (**1**) affords optically active polymer of helical conformation of single screw sense.[7]

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Diphenyl 2-Oxo-3-oxazolinylphosphonate

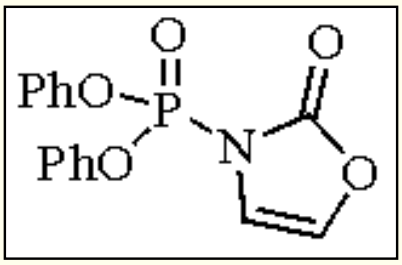

[78605-38-6] · $C_{15}H_{12}NO_5P$ · Diphenyl 2-Oxo-3-oxazolinylphosphonate · (MW 317.25)

(activation of carboxylic acids; formation of amides, β-lactams, and thiol esters; phosphorylation of alcohols)

Alternate Name: DPPOx.

Physical Data: colorless solid, mp 51 °C (*n*-hexane); bp 150-160 °C/0.03 mmHg.

Solubility: sol acetonitrile, THF, DMF, CH_2Cl_2.

Preparative Method: by reacting equimolar quantities of ***Diphenyl Phosphorochloridate*** and 2-oxazolone together with ***Triethylamine*** in CH_2Cl_2 at rt.[1,2] The product is isolated in 96% yield by filtration of the triethylamine hydrochloride salts, concentration in vacuo below 30 °C, and chromatography of the residue on silica gel.

Analysis of Reagent Purity: ^{1}H NMR: 6.74 (dd, *J* = 2.4 and 2.5 Hz, 1H), 6.81 (dd, *J* = 1.7 and 2.4 Hz, 1H), 7.32 (bs, 10H).

Handling, Storage, and Precautions: stable at rt, protected from moisture (over anhydrous silica gel), for several years. Complete hydrolysis occurs within 24 h in 50% aqueous THF at rt.

Activation of Carboxylic Acids.[1,2]

Reaction of diphenyl 2-oxo-3-oxazolinylphosphonate with alkyl, aryl, and unsaturated carboxylic acids yields the corresponding 3-acyl oxazolides under mild neutral conditions (eq 1). Alkoxycarbonyl-protected amino acids are amenable to the reaction conditions, except in cases where elimination is competitive, e.g. *N*-Cbz-serine. Sterically hindered 2,4,6-trimethylbenzoic acid failed to form the oxazolide, but instead gave the acid anhydride. 3-Acyl oxazolides of chiral acids, formed in this way, have been used in the synthesis of chiral amino alcohols,[3] amino sugars,[4] and hydroxy amino acids.[5] The carboxyl group of the 3-acyl oxazolides is activated toward nucleophilic

attack.

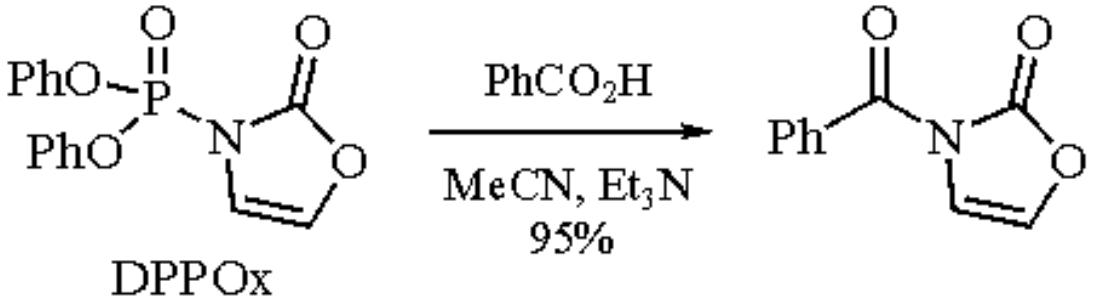

(1)

Amide Formation.[1,2]

Acyl oxazolides undergo facile aminolysis, leading to amides. Diphenyl 2-oxo-3-oxazolinylphosphonate reacts very slowly with amines. Thus the coupling can be achieved in one step by mixing an amine and a carboxylic acid in acetonitrile at rt with 1.2 equiv of DPPOx. This reaction has been successfully applied to peptide formation using Cbz and *t*-Boc protected amino acids and amino acid ethyl esters (eq 2) without racemization.

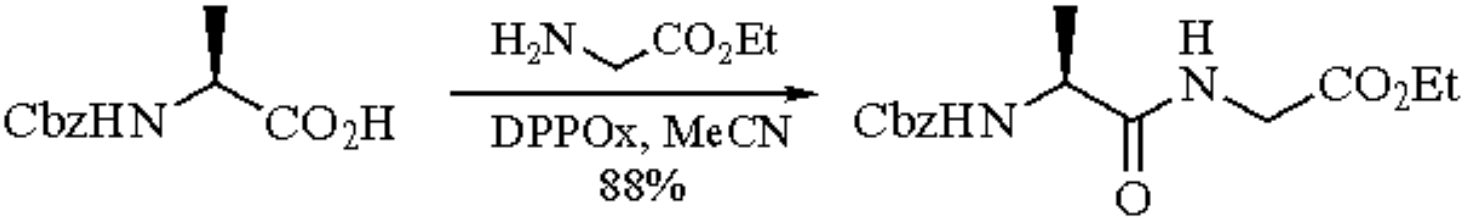

(2)

β-Lactam Formation.[6]

Treatment of β-amino carboxylic acids with diphenyl 2-oxo-3-oxazolinylphosphonate and triethylamine in refluxing acetonitrile (eq 3) gives good yields of monocyclic β-lactams (50-89%).

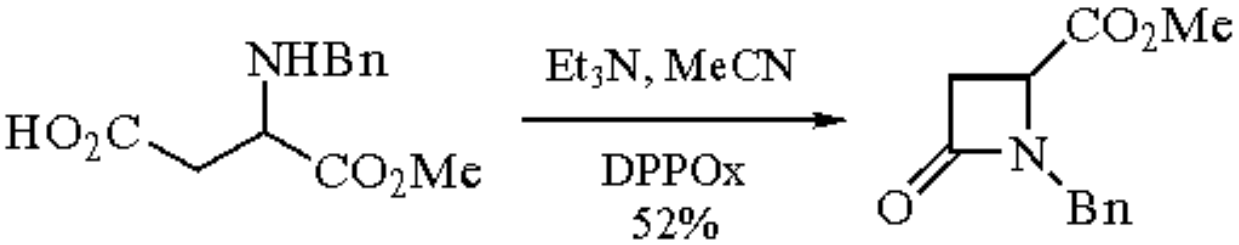

(3)

DPPOx was unsuccessful in cyclizing 2-thiazolidineacetic acid; however, the related tris(2-oxo-3-oxazolinyl)phosphine oxide (eq 4) gives the bicyclic β-lactam in 57% yield.

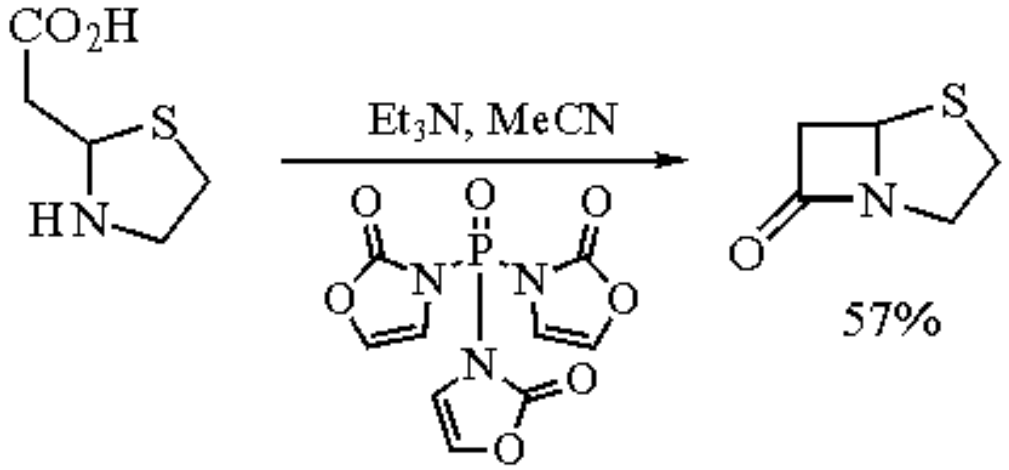

(4)

Thiol Ester Formation.[7]

Thiol esters are formed in 68-96% yield by reaction of thiols with carboxylic acids, DPPOx, and triethylamine in acetonitrile at rt (eq 5). Sterically hindered thiols require longer reaction times for comparable yields.

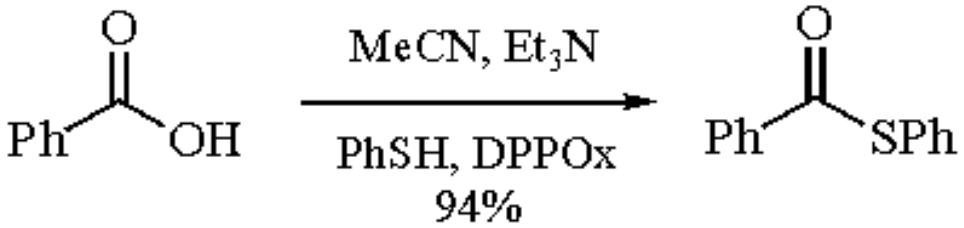

(5)

Phosphorylation of Alcohols.[8]

DPPOx reacts very sluggishly with alcohols at rt. However, the reaction is greatly accelerated by ***Cesium Fluoride*** and transition metal acetylacetone complexes to give mixed phosphates in good yields (eq 6). The catalytic ability of the complexes is in the activity order $Zr^{IV} > Ce^{III} > Zn^{II} > Mn^{III} > Mn^{II}$.

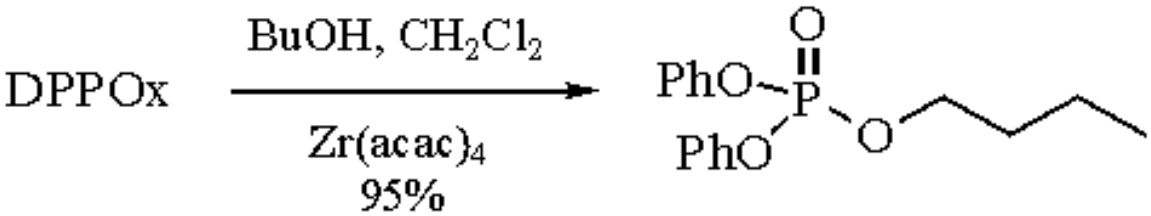

(6)

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Diphenylphosphine

Ph_2PH

[829-85-6] · $C_{12}H_{11}P$ · Diphenylphosphine · (MW 186.20)

(readily deprotonated to give diphenylphosphide;[1a] useful for the synthesis of phosphorus-based alkenation reagents;[2] source of phosphorus-centered radical[3])

Physical Data: bp 280 °C; *d* 1.070 g cm^{-3}.

Solubility: sol ethanol, ether, benzene, concd HCl; insol H_2O.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: ^1H NMR (P-H) δ 5.14; ^{31}P NMR (P-H, 85% H_3PO_4) δ +40.7.[4]

Preparative Methods: from Ph_3P,[1b] Ph_2PCl_3,[5] or Ph_2POCl.[5]

Purification: distillation.[1b]

Handling, Storage, and Precautions: foul-smelling liquid. Very easily oxidized in air; pyrophoric; light-sensitive.

Alkylation.

The alkylation of diphenylphosphine has been used extensively for the preparation of novel phosphine ligands, Wittig-Horner reagents, and phosphonium salts. Deprotonation of diphenylphosphine with ***n-Butyllithium*** gives the characteristically orange solution of lithium diphenylphosphide,[1] providing access to the desired tertiary phosphines via an S_N2 or S_N2' displacement.[2] Phosphonium salts are also readily available by direct reaction of an appropriate alkylating agent and diphenylphosphine.[6] Optically active bis(diphenylphosphino) ligands can be prepared through tosylate displacement/epoxide ring opening. In some cases, complete regio- and stereoselectivity can be achieved (eq 1).[7] Elaborate diphenylphosphine oxide-based alkenation reagents can be synthesized by alkylation, followed by direct oxidation to provide advanced precursors of complex natural products (eq 2).[2]

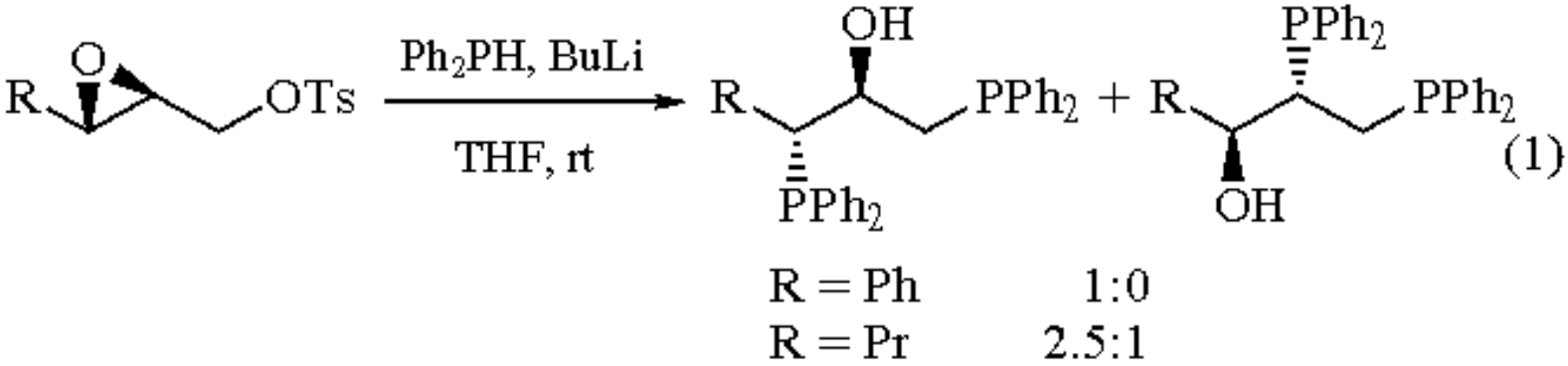

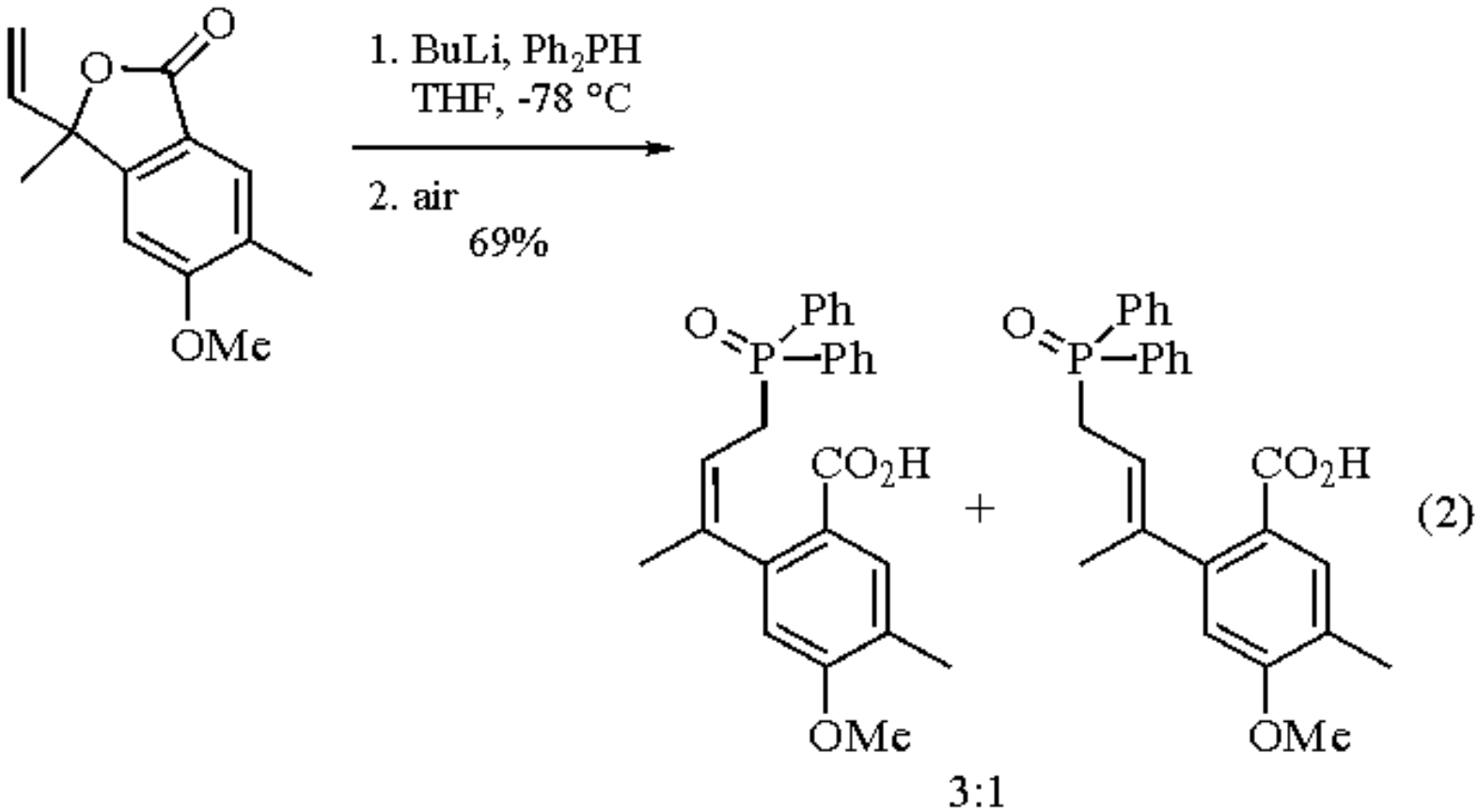

During the preparation of many phosphines, due care must be taken to avoid phosphorus oxidation. The use of the diphenylphosphine-borane complex circumvents the problem of phosphine oxidation. The diphenylphosphine-borane complex is not only protected from oxidation, but is also activated so that it can be reacted under mild conditions (methanolic KOH, 0 °C) with a variety of electrophiles (eq 3). The desired tertiary phosphine can be obtained by decomplexation with a large excess of a secondary amine.[8]

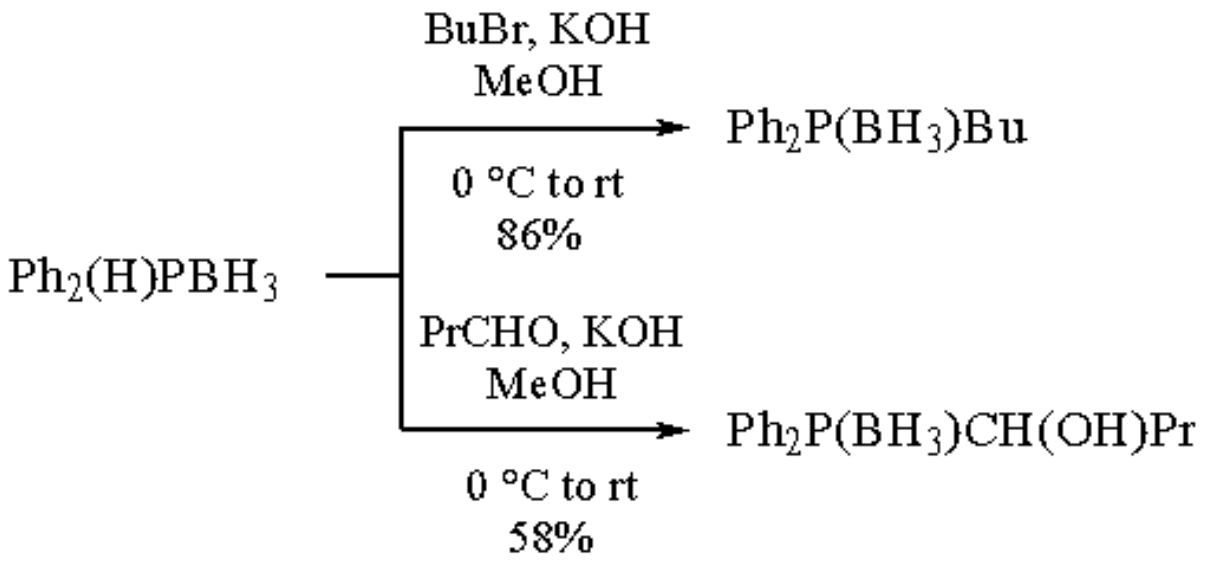

(3)

Addition to Alkenes and Alkynes.

The addition of diphenylphosphine to unsaturated systems under radical conditions provides access to a variety of functionalized phosphines.[9] Phosphorus-centered radicals can be formed under standard (***Azobisisobutyronitrile***, refluxing benzene) or photochemical conditions in a manner similar to silicon-, tin-, and selenium-based radicals. Highly functionalized phosphines are obtained upon radical cyclization of dienes or enynes (eq 4).[3] Tin- and silicon-substituted phosphines are available from the corresponding vinylstannane[10] or -silane.[11] Phosphine radical addition to diketene provides access to phosphine-substituted lactones.[12]

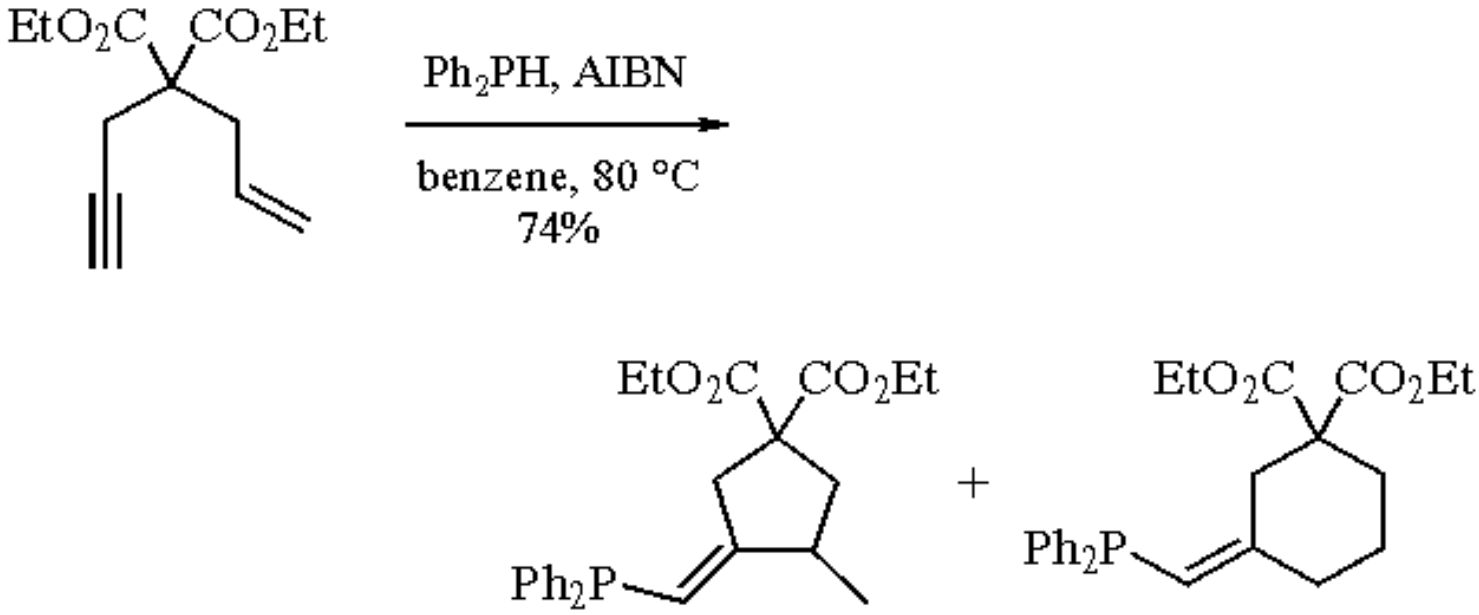

(4)

Michael addition of diphenylphosphine to activated alkenes provides products useful for the construction of phosphine ligands. These reactions can be carried out under neutral,[13] acidic,[14] or basic conditions,[15] or via the preformed diphenylphosphide.[16] Diastereoselective addition of lithium diphenylphosphide to lactone (**1**) provides a good yield of the *trans* adduct (eq 5).[16] Double addition to bromomaleic anhydride provides useful yields of the bis(diphenylphosphino) adduct as the *trans* isomer (eq 6).[14]

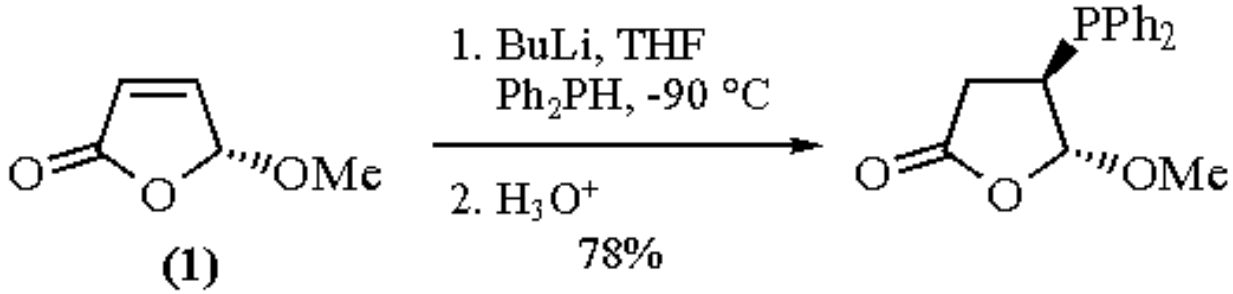

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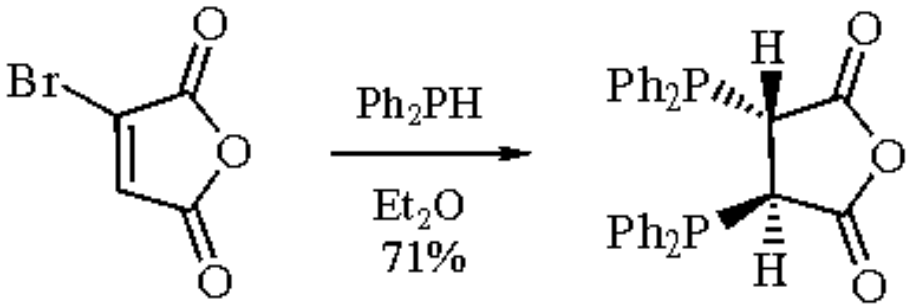

(6)

Addition to C=X Bonds.

The nucleophilic nature of diphenylphosphine (and diphenylphosphide) can be utilized in the addition to carbon-heteroatom double bonds. The 1,2-addition to aldehydes,[17] ketones,[18] imines,[19] isocyanates, isothiocyanates, carbodiimides,[20] cyclic carbonates,[21] and 2-halo heterocycles[22] provide a host of interesting phosphines. Addition of diphenylphosphine to aromatic aldehydes in alcoholic media or dilute acid gives α-alkoxy[17] or α-hydroxy[18a] benzylphosphines, respectively. Alternatively, employment of a typical Lewis acid in aprotic media also leads to α-hydroxy phosphines, which air oxidize to the α-hydroxy phosphine oxides. However, addition to aldehydes in the presence of a Lewis acid and a catalytic amount of niobium(V) chloride provides phosphine oxides (eq 7).[18b,c] The use of concentrated protic acid media also provides a simple, high-yielding synthesis of unsymmetrical phosphine oxides (eq 8).[18a]

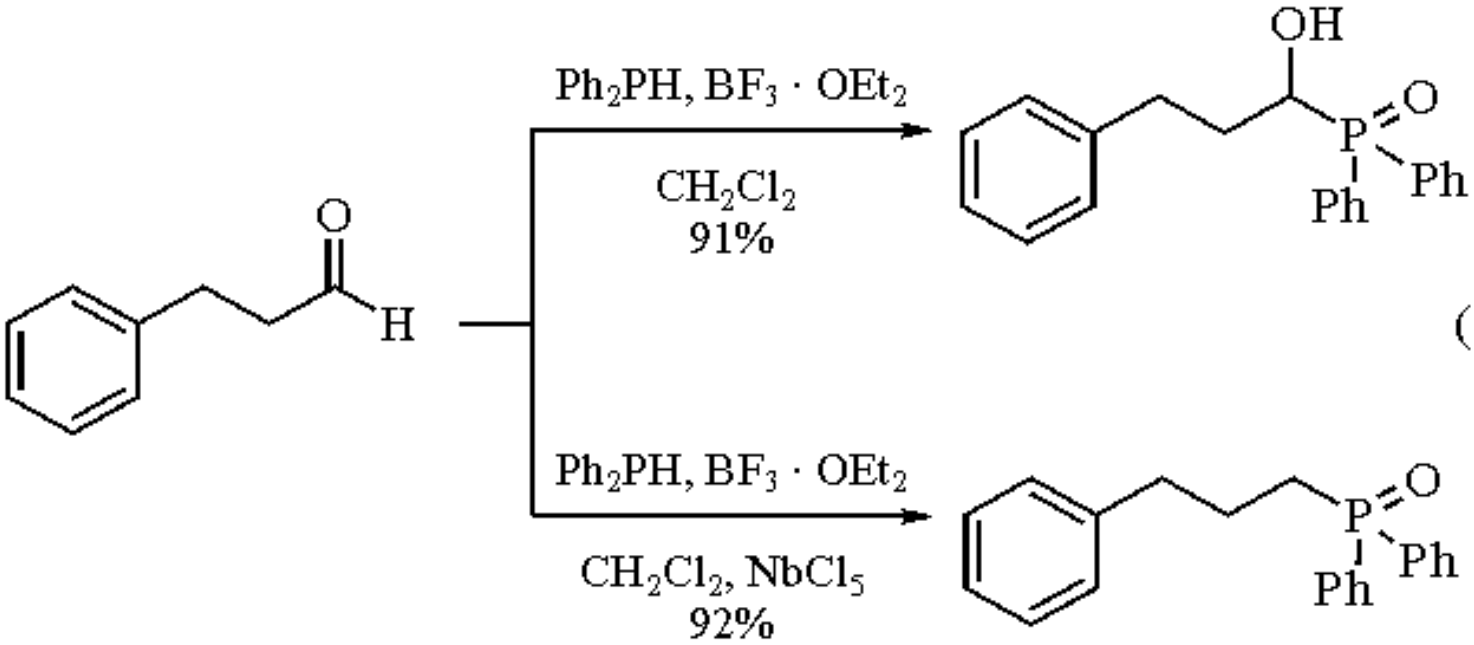

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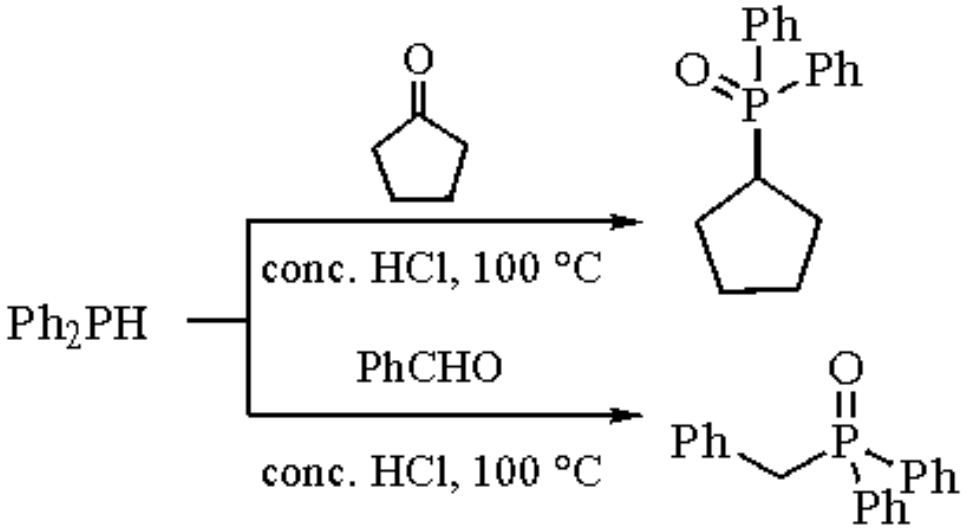

(8)

Other Applications.

Lithium diphenylphosphide can be used to effect a number of functional group interconversions, such as the dealkylation of alkyl aryl ethers,[23,1b] or the dehydroxylation of α-hydroxy ketones.[24] In some cases, 1,2-dibromoalkenes can be converted into alkynes by treatment with lithium diphenylphosphide in refluxing THF.[25] Treatment of epoxides with lithium diphenylphosphide followed by phosphine oxidation,[26] or conversion into the phosphonium salt[27] ultimately provides a method for alkene inversion (eq 9).

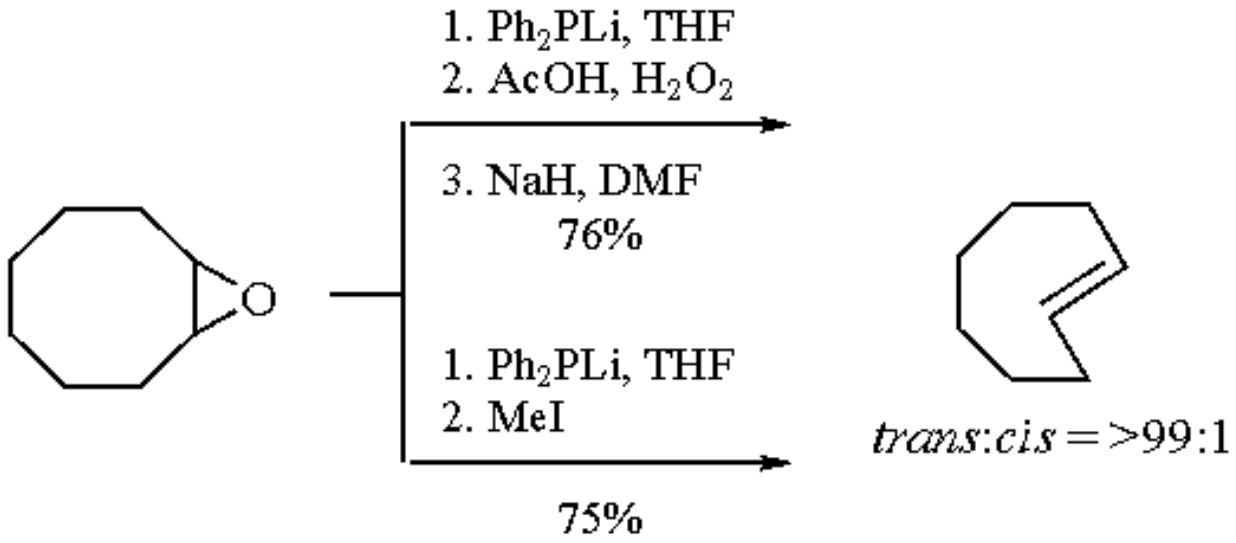

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Diphenylphosphine Oxide

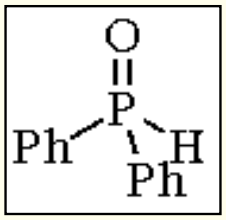

[4559-70-0] · $C_{12}H_{11}OP$ · Diphenylphosphine Oxide · (MW 202.20)

(preparation of triarylphosphine oxides,[1] important as asymmetric catalysts; preparation of alkenyldiphenylphosphine oxides[3,4] and Horner-Wittig reagents[5])

Physical Data: mp 56-57 °C.

Form Supplied in: white solid; widely commercially available.

Handling, Storage, and Precautions: moisture sensitive; irritant.

Palladium-Catalyzed Coupling with Aryl Triflates.

In the synthesis of P-N chelating ligands for asymmetric catalysis,[1] aryl triflates are coupled with $Ph_2P(O)H$ under Pd catalysis, with subsequent reduction of the resulting phosphine oxides to the aryldiphenylphosphines (eq 1). (*R*)-(-)-1,1´-Binaphthol triflate provides the monophosphorylation product[2] in good yield with maintainance of enantiomeric purity (eq 2).

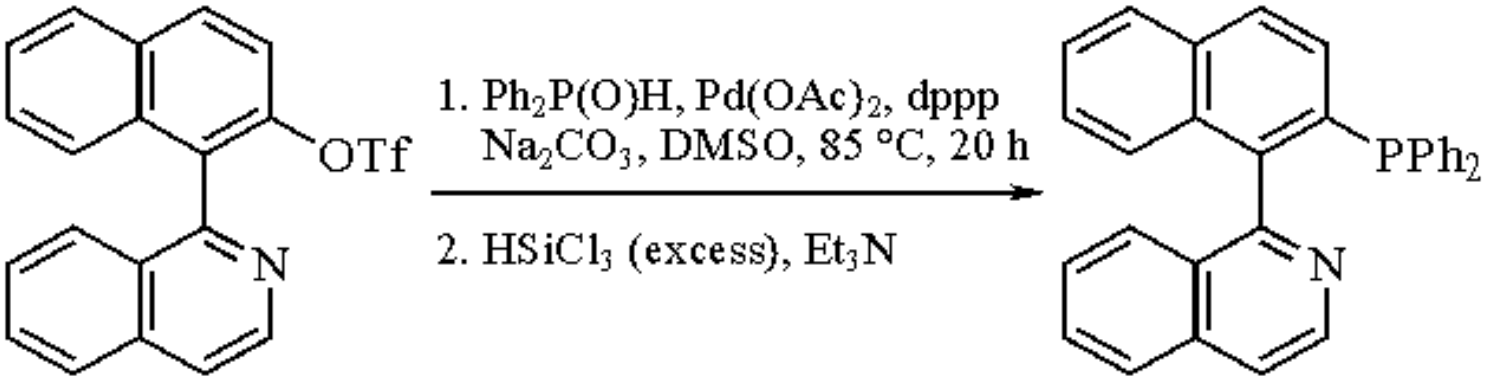

(1)

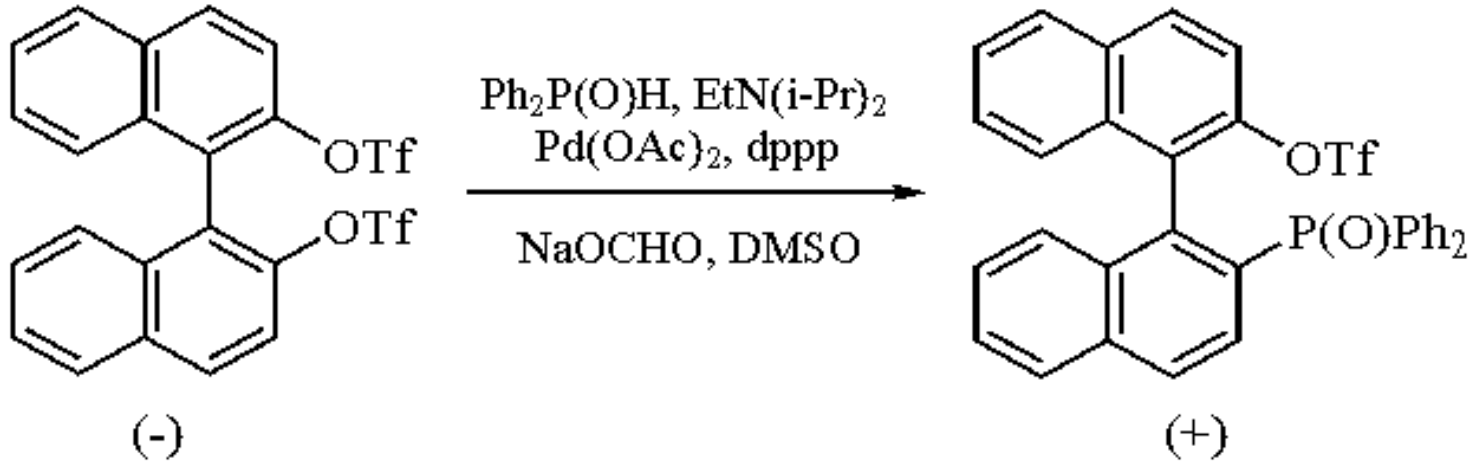

Preparation of Diphenylvinylphosphine Oxides.

Treatment of α-keto tosylates with diphenylphosphine oxide gives epoxyphosphine oxides, which provide vinylphosphine oxides via deoxygenation with ***Diphosphorus Tetraiodide*** (eq 3).[3] Alternatively, alkenyl bromides react with diphenylphosphine oxide under palladium catalysis to yield vinylphosphine oxides (eq 4).[4]

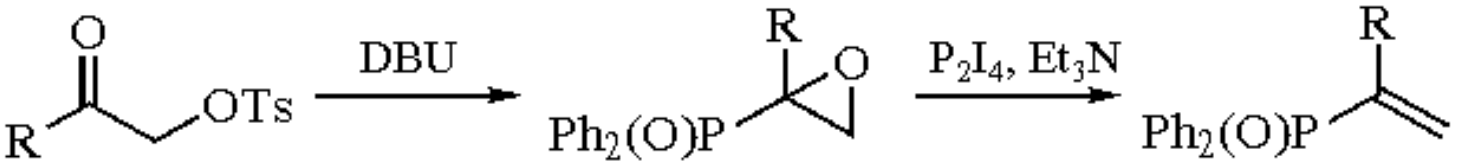

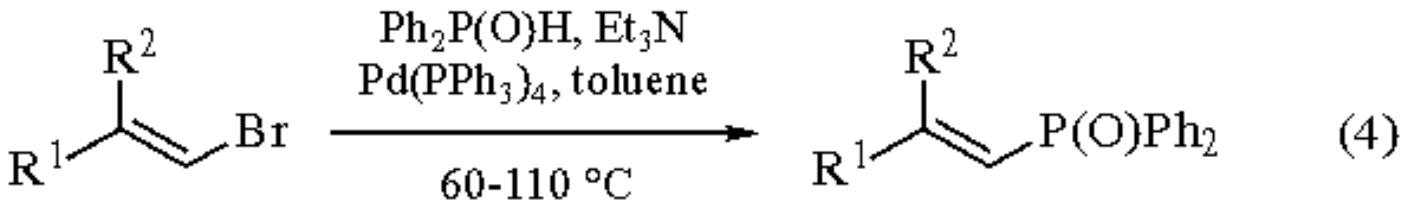

Reaction with Chlorodifluoromethane.

Difluoromethyldiphenylphosphine oxide, synthesized from diphenylphosphine oxide and chlorodifluoromethane, reacts with aldehydes and ketones to yield 1,1-difluoroalkenes (eq 5).[5] Alkenation proceeds in increasing (12-81%) yields over a range of more to less electron-deficient carbonyl compounds.

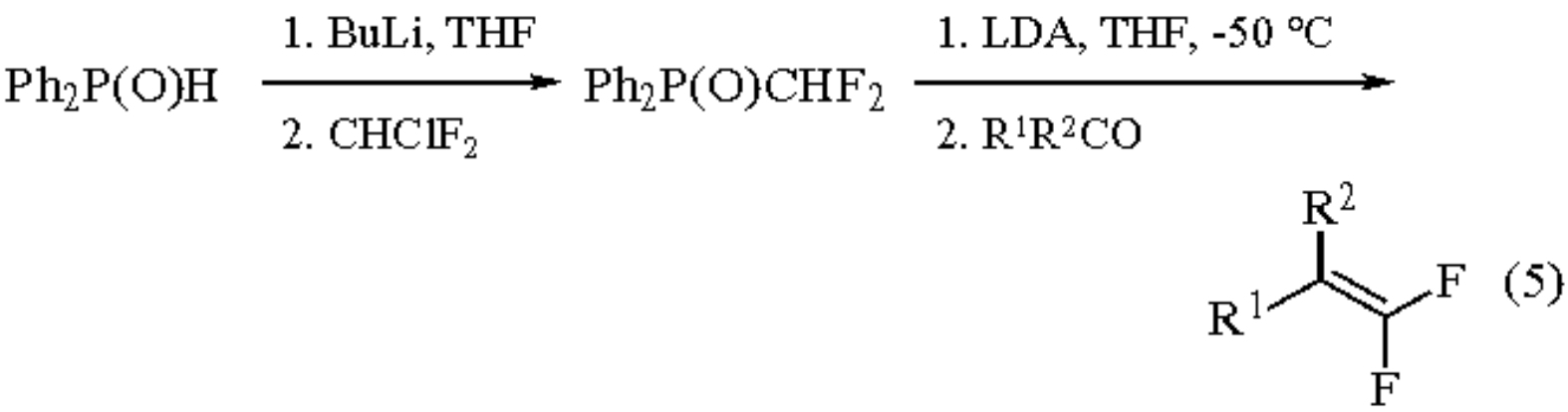

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Jeffrey O. Saunders

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Diphenylphosphinic Chloride

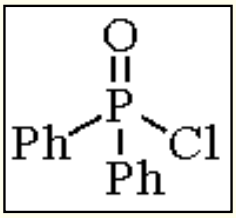

[1499-21-4] · $C_{12}H_{10}ClOP$ · Diphenylphosphinic Chloride · (MW 236.64)

(agent for acid activation,[1] alkylphosphine oxide formation,[2] and amine protection[3])

Alternate Name: chlorodiphenylphosphine oxide.

Physical Data: bp 222 °C/16 mmHg; *d* 1.240 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: handle only in a chemical fume hood, wear chemical-resistant gloves and safety goggles, do not breathe vapor, and avoid contact with eyes or skin. Store in a flammable storage cabinet under nitrogen. Contact with water generates hydrogen chloride gas.

Acid Activation.

Chlorodiphenylphosphine oxide has been utilized for the activation of acids via in situ formation of the diphenylphosphinic (DPP) mixed anhydrides. These anhydrides are superior to carbon-based mixed anhydrides because they do not suffer from disproportionation to symmetrical anhydrides.[1] Also, nucleophiles prefer to attack at carbon rather than phosphorus, solving the regioselectivity problem associated with carbon-based mixed anhydrides.[4] Additionally, diphenylphosphinic mixed anhydrides are more electrophilic. Finally, diphenylphosphinic mixed anhydrides form rapidly allowing shorter activation times.

Diphenylphosphinic mixed anhydrides have been utilized to form peptide bonds.[5] Peptides are easier to isolate by this method than by employing ***1,3-Dicyclohexylcarbodiimide***. These anhydrides are the method of choice for the formation of amides of 2-alkenoic acids (eq 1).[6] Carbodiimide and acyl carbonate methods proved to be inferior. Primary amines result in better yields than secondary amines. This activation protocol can be employed to form thiol esters.[7] β-Amino acids are readily converted to β-lactams with chlorodiphenylphosphine oxide (eq 2).[8] Secondary amines work best. This activation protocol has been utilized to convert acids to amines via a Curtius rearrangement (eq 3).[9] Phenols have been generated from diene acids, presumably via base-induced elimination of diphenylphosphinic acid from the mixed anhydrides to form ketenes which spontaneously cyclize (eq 4).[10] Acids have been converted to ketones via activation followed by reaction with organometallic reagents (eq 5).[11]

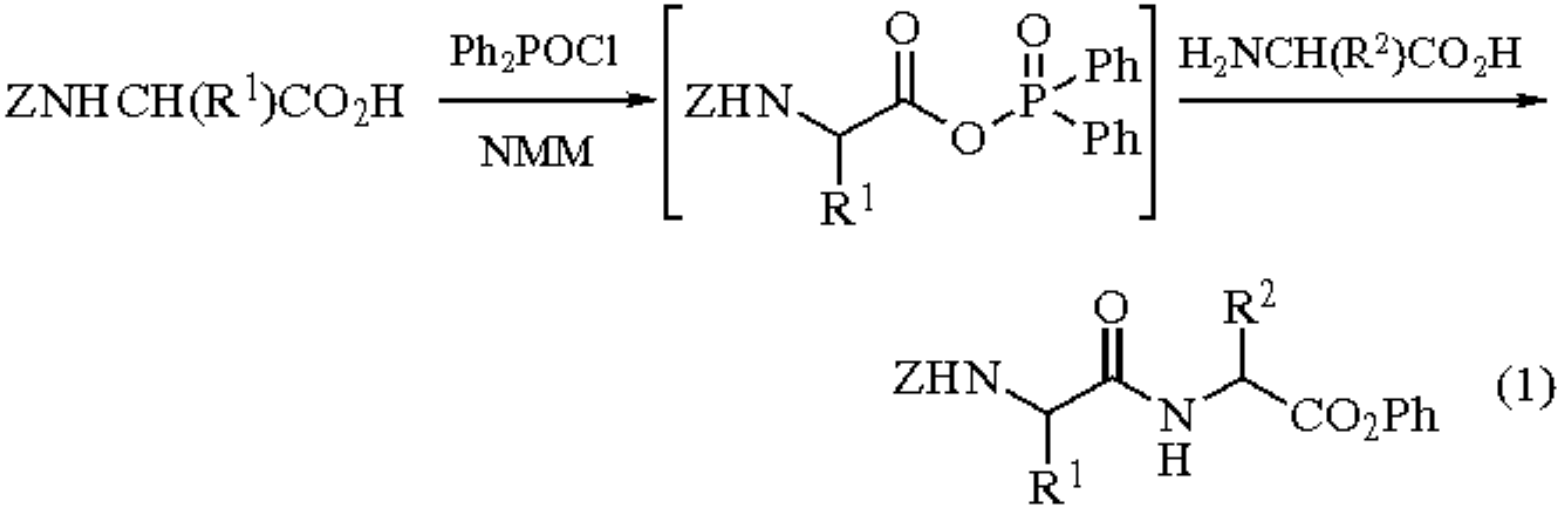
ZNHCH(R1)CO2H
Ph2POCl
NMM
ZHN
O
O
Ph
P
Ph
O
R1
H2NCH(R2)CO2H
ZHN
O
R2
N
H
CO2Ph
R1

(1)

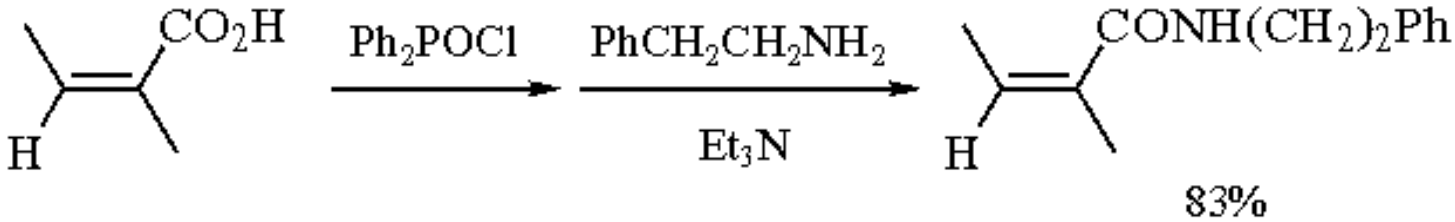
CO2H
H
Ph2POCl
PhCH2CH2NH2
Et3N
CONH(CH2)2Ph
H
83%

(2)

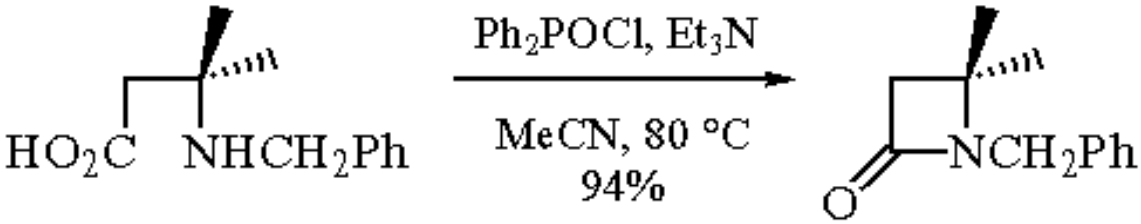
HO2C
NHCH2Ph
Ph2POCl, Et3N
MeCN, 80 °C
94%
NCH2Ph
O

(3)

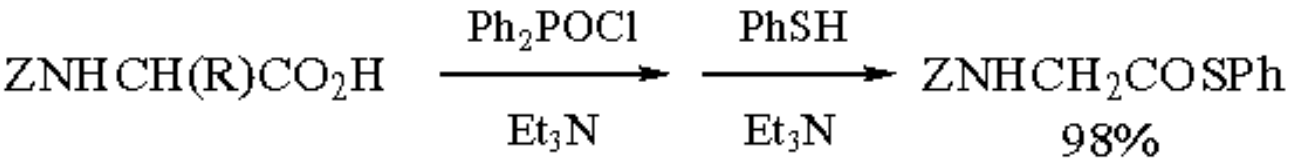
ZNHCH(R)CO2H
Ph2POCl
Et3N
PhSH
Et3N
ZNHCH2COSPh
98%

(4)

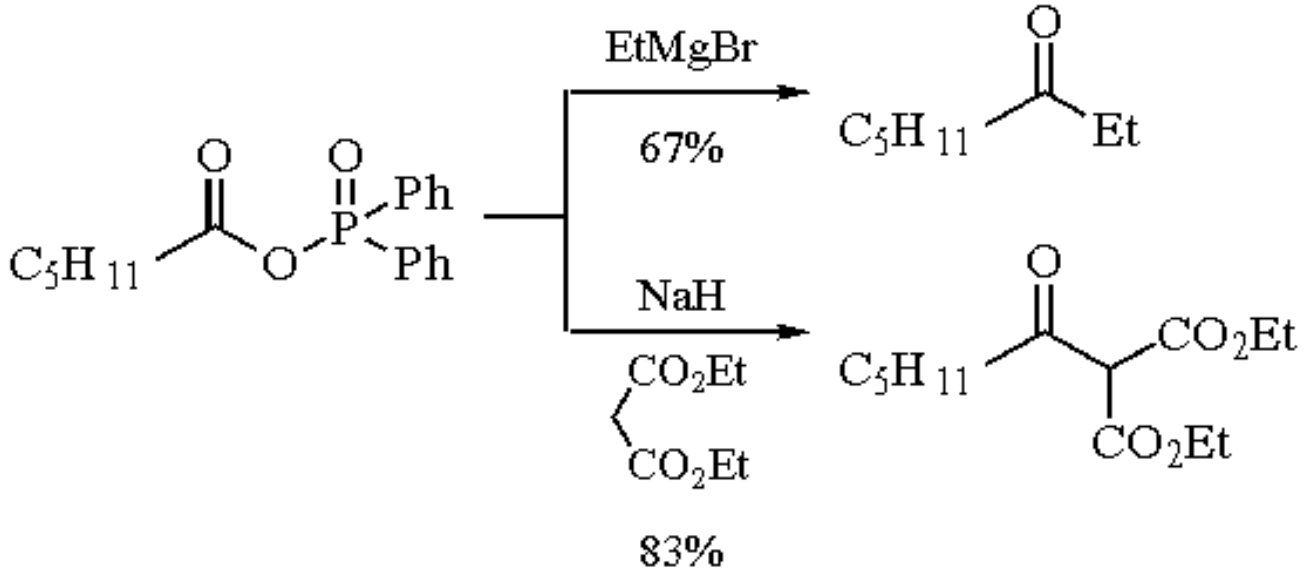

Phosphine Oxides.

This reagent reacts with organometallic reagents to form phosphine oxides.[2] Alkyl phosphonates have been converted to diphenylvinylphosphine oxides via trapping of the α-lithioalkylphosphonate with diphenylchlorophosphine oxide, deprotonation, and reaction with aldehydes (eq 6).[12] Organometallic reagents have been converted to 1,3-dienes utilizing $Ph_2P(O)Cl$ and carbonyl compounds (eq 7).[13]

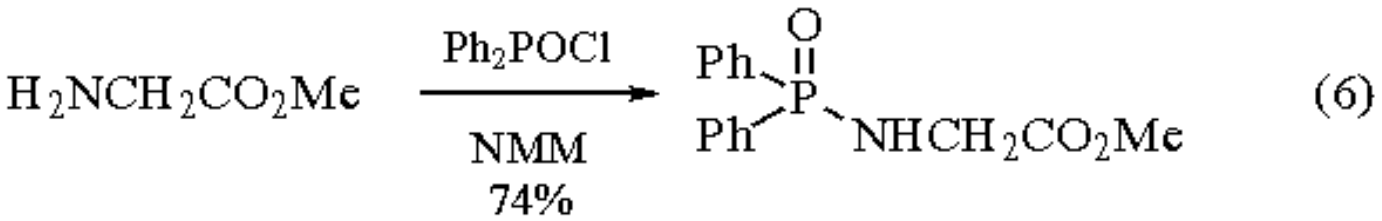

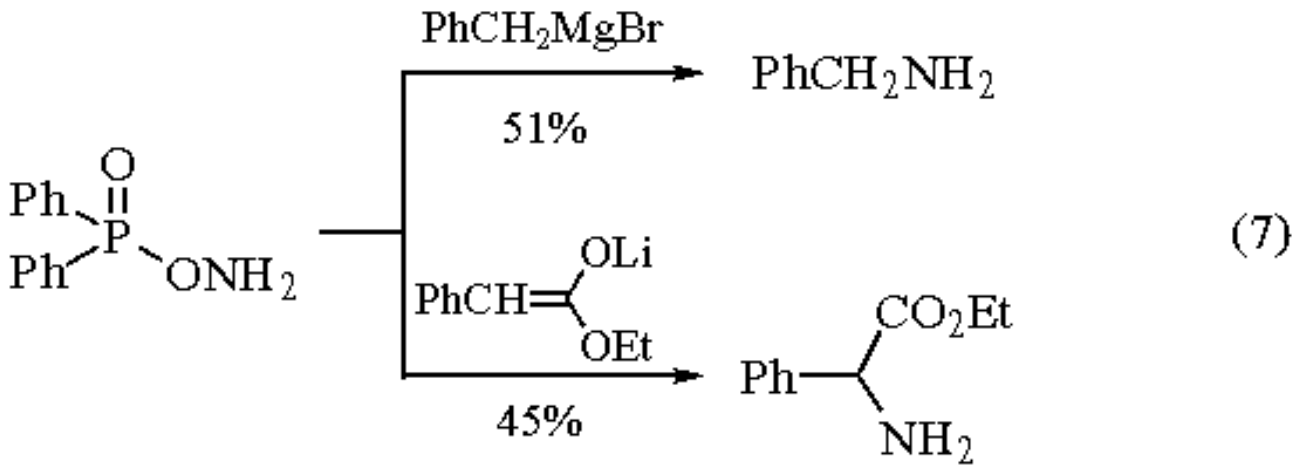

Thiol Esters and Ketones.

The Dpp mixed anhydrides react with thiols to yield thiol esters (eq 8)[7] and undergo carbon-acylation reactions with

both Grignard reagents and diethyl sodiomalonate in good yields (eq 9).[14]

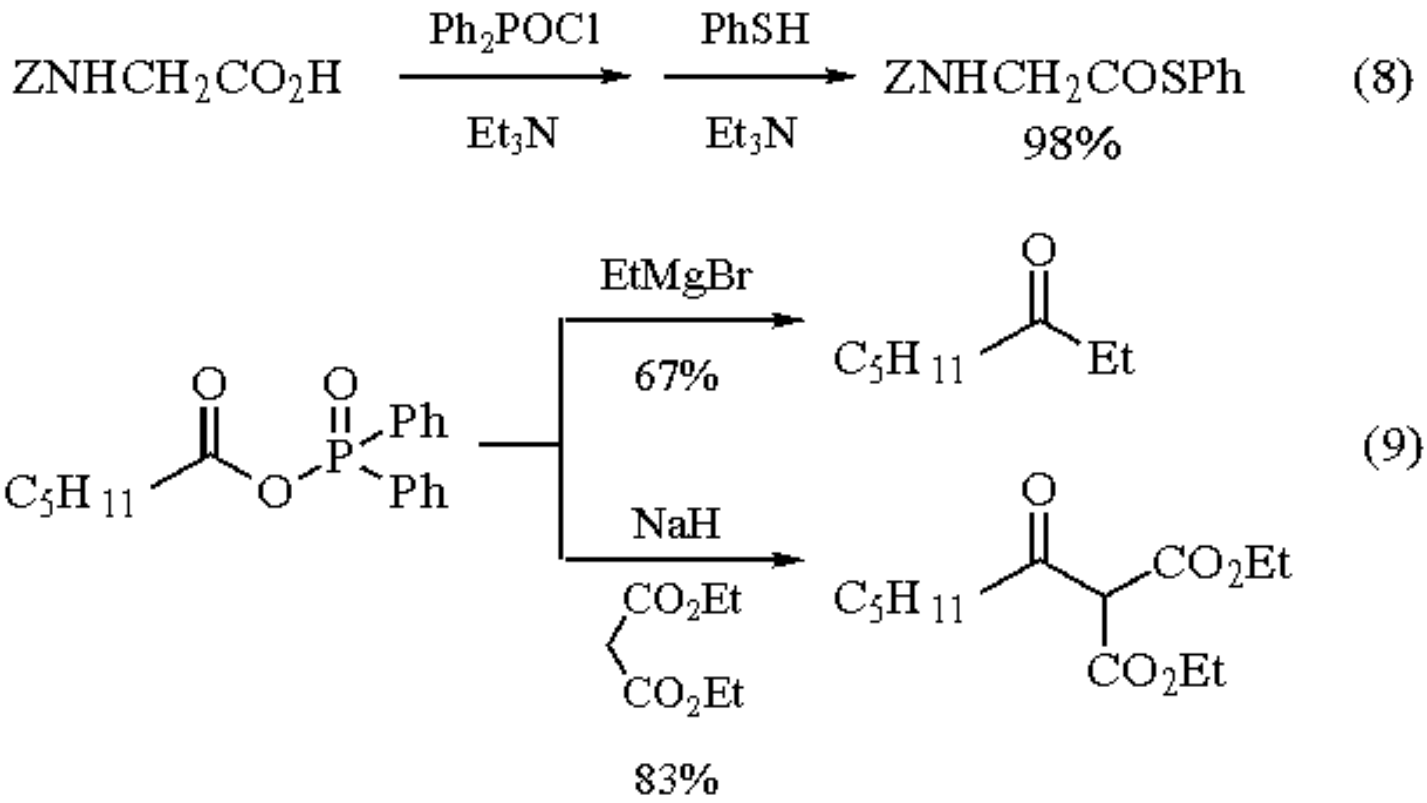

Protection of Amino Groups.

In the presence of *N*-methylmorpholine, Ph_2POCl reacts with amino acid esters in CH_2Cl_2 at 0 °C in 1.5-2 h to give *N*-diphenylphosphinyl (Dpp) amino acid esters (65-80%), which are then hydrolyzed under mild alkaline conditions to give *N*-Dpp amino acids (eq 10).[3,4] Since Ph_2POCl hydrolyzes extremely quickly under aqueous conditions, it is not possible to prepare *N*-Dpp amino acids directly.

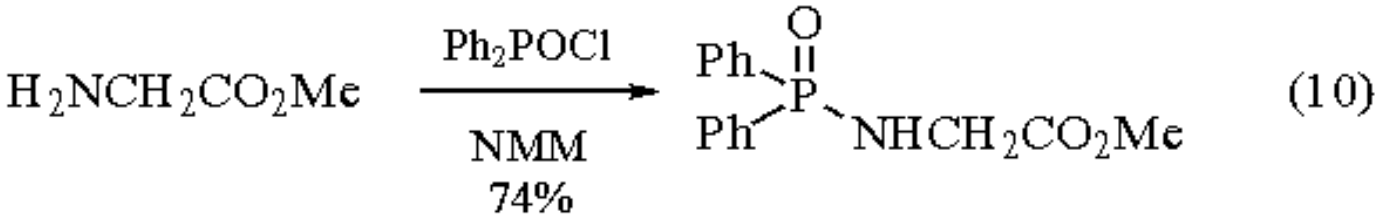

The Dpp derivatives are slightly more acid-labile than the Boc derivatives and are cleaved by HOAc-HCOOH-H_2O (7:1:2) (24 h), 1 M HCl in H_2O-dioxane (2:1) (3 h), TFA-CH_2Cl_2 (1:1) (40 min), and 95% TFA (10 min). Selective cleavage of the Dpp group in the presence of a *t*-butyl ester and a phenyl ester is possible.

Amination.

Ph_2POCl reacts with ***Hydroxylamine*** to yield *O*-(diphenylphosphinyl)hydroxylamine.[15] This reagent aminates stabilized carbanions and Grignard reagents in moderate yields (eq 11).[16] Electrophilic *N*-amination of imide sodium salts is also possible using this reagent (eq 12).[17]

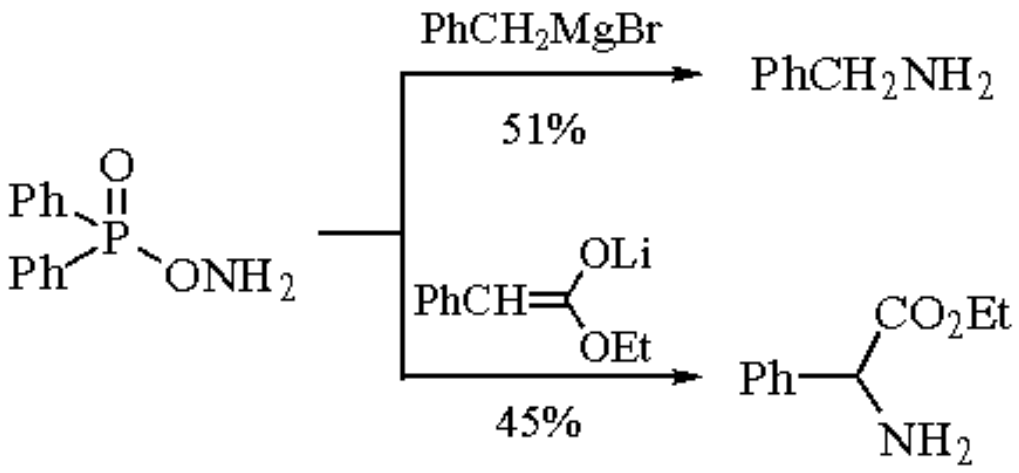

(11)

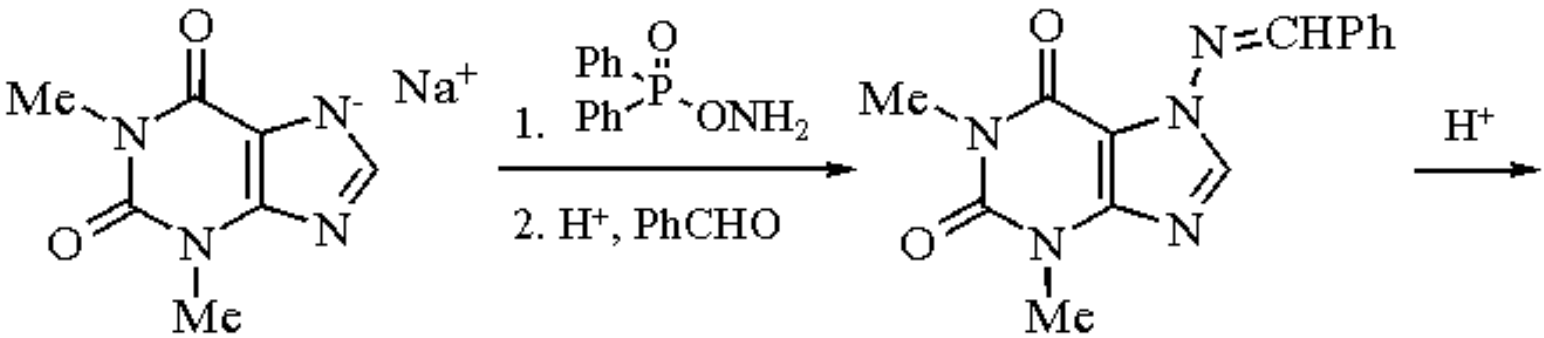

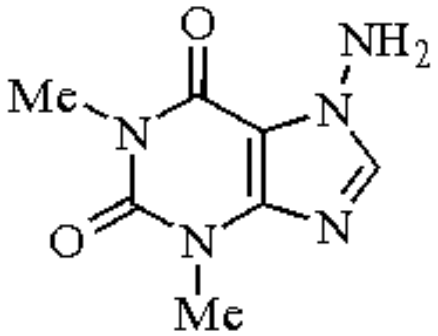

(12)

60%

Diphenylphosphinamide[18] and 1-diphenylphosphinyl-2,2-dimethylaziridine,[19] which are derived from Ph_2POCl, react with Grignard reagents to give high yields of primary amines and moderate yields of α,α-dimethylarylalkylamines, respectively.

---

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3. (a) Kenner, G. W.; Moore, G. A.; Ramage, R. *TL* **1976**, 3623. (b) Ramage, R.; Atrash, B.; Hopton, D.; Parrott, M. J. *JCS(P1)* **1985**, 1217.
4. Ramage, R.; Atrash, B.; Hopton, D.; Parrott, M. J. *JCS(P1)* **1985**, 1617.
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7. Horiki, K. *SC* **1977**, *7*, 251.
8. Kim, S.; Lee, P. H.; Lee, T. A. *CC* **1988**, 1242.
9. (a) Armstrong, V. W.; Coulton, S.; Ramage, R. *TL* **1976**, 4311. (b) Ramage, R.; Armstrong, V. W.; Coulton, S. *T* **1981**, *37*, Supplement No. 1, 157.
10. Clinch, K.; Marquez, C. J.; Parrott, M. J.; Ramage, R. *T* **1989**, *45*, 239.
11. Soai, K.; Ookawa, A. *CC* **1986**, 412.
12. (a) Savignac, P.; Teulade, M.-P.; Aboujaoude, E. E.; Collignon, N. *SC* **1987**, *17*, 1559. (b) Aboujaoude, E. E.; Lietje, S.; Collignon, N. *TL* **1985**, *26*, 4435.
13. Davidson, A. H.; Warren, S. *CC* **1975**, 148.
14. Kende, A. S.; Scholz, D.; Schneider, J. *SC* **1978**, 59.
15. (a) Harger, M. J. P. *CC* **1979**, 768. (b) Harger, M. J. P. *JCS(P1)* **1981**, 3284.
16. (a) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *TL* **1982**, *23*, 3835. (b) Boche, G.; Bernheim, M.; Schrott, W. *TL* **1982**, *23*, 5399.
17. Klotzer, W.; Stadlwieser, J.; Raneburger, J. *OS* **1985**, *64*, 96.
18. Zwierzak, A.; Slusarska, E. *S* **1979**, 691.
19. Buchowiecki, W.; Grosman-Zjawiona, Z.; Zjawiony, J. *TL* **1985**, *26*, 1245.

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Sunggak Kim

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(*R*)-*N*,*N*-Dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine

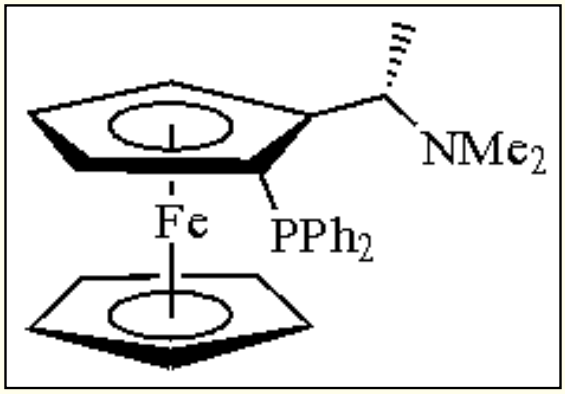

(*R*)-(*S*)-PPFA

[55700-44-2] · $C_{26}H_{28}FeNP$ · (*R*)-*N*,*N*-Dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine · (MW 441.37) (*S*)-(*R*)-PPFA

[55650-58-3]

(effective chiral phosphine ligand[1] for nickel- or palladium-catalyzed asymmetric cross coupling of organomagnesium or -zinc reagents with alkenyl bromides,[2-4] and for palladium-catalyzed asymmetric hydrosilylation of 1,3-dienes[5])

Alternate Name: (*R*)-(*S*)-PPFA.

Physical Data: mp 139 °C; [α]25D -361° (*c* 0.6, ethanol).[1a]

Purification: recrystallization from ethanol.[1a]

Handling, Storage, and Precautions: stable in air for years, but best kept sealed in a refrigerator.

Asymmetric Cross Coupling.

In the presence of a nickel catalyst, generated in situ from ***Nickel(II) Chloride*** and (*R*)-(*S*)-PPFA, secondary alkyl Grignard reagents, represented by 1-phenylethylmagnesium chloride, react with alkenyl halides to give optically active alkenes of up to 68% ee (eq 1). The isolated palladium complex, $PdCl_2$[(*R*)-(*S*)-PPFA], can be also used for the cross coupling.[2] Use of a zinc reagent in place of the Grignard reagent increases the enantioselectivity to 86% ee.[3]

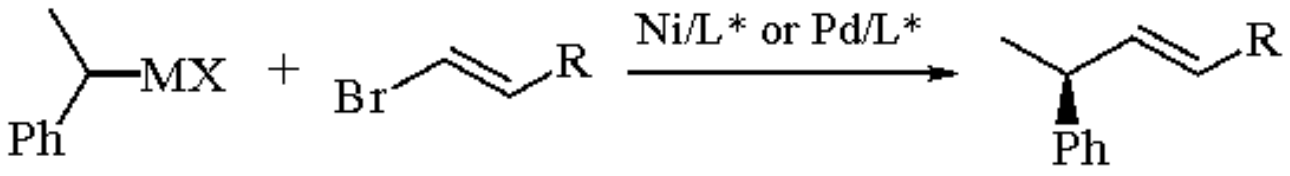

(1)

M = Mg, Zn

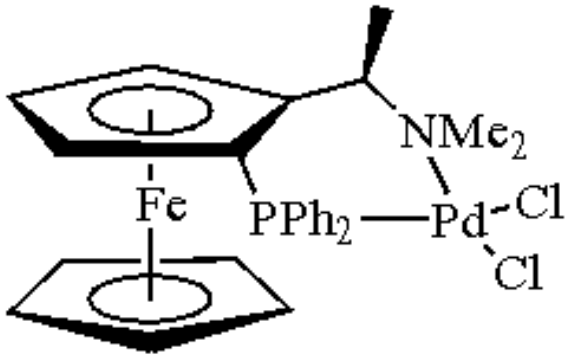

$PdCl_2$[(*R*)-(*S*)-PPFA]

The stereoselectivity obtained with the PPFA ligand is generally higher than that obtained with ***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane*** (DIOP) (7-16% ee), 1,2-bis(diphenylphosphino)propane (prophos) (0% ee), and 2,2´-bis(diphenylphosphinomethyl)-1,1´-binaphthyl (NAPHOS) (11% ee).

The asymmetric cross coupling with the chiral ferrocenylphosphine-palladium catalyst has been successfully applied to the synthesis of optically active allylsilanes (eq 2).[4] The reaction of α-(trimethylsilyl)benzylmagnesium bromide with vinyl bromide and (*E*)-β-bromostyrene catalyzed by 0.5 mol % of $PdCl_2$[(*R*)-(*S*)-PPFA] gives a quantitative yield of the corresponding allylsilanes of 95% ee. High enantioselectivity is also observed in the cross coupling of 1-(triethylsilyl)ethylmagnesium chloride with (*E*)-β-bromostyrene.

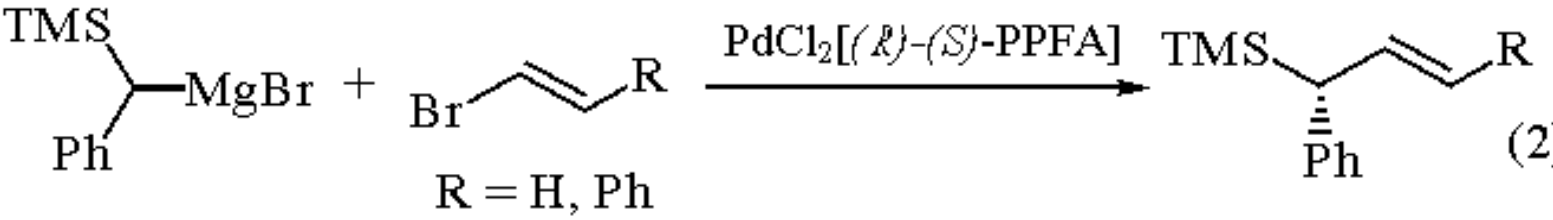

(2)

Asymmetric Hydrosilylation of Alkenes.

The palladium complex $PdCl_2$[(*R*)-(*S*)-PPFA] catalyzes the asymmetric hydrosilylation of norbornene, styrene, and 1,3-dienes (eq 3).[5] The hydrosilylation of 1-phenyl-1,3-butadiene with ***Trichlorosilane*** proceeds regioselectively in a 1,4-fashion to give (*Z*)-1-phenyl-1-silyl-2-butene of 64% ee.

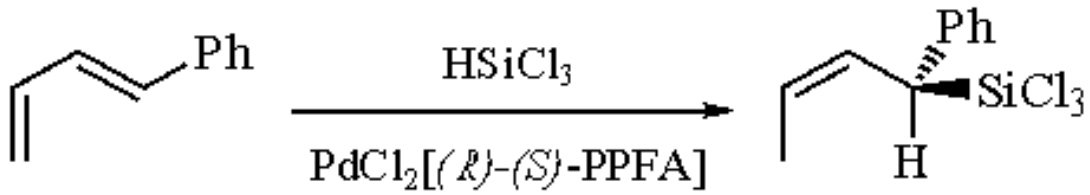

(3)

Optically active ferrocenylbisphosphines, (*R*)-*N*,*N*-dimethyl-1-[(*S*)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-BPPFA] and its derivatives, are efficient chiral bisphosphine ligands for rhodium-catalyzed asymmetric hydrogenation, palladium-catalyzed asymmetric allylic substitution reactions, and gold-catalyzed asymmetric aldol-type reactions of α-isocyano carboxylates.[1,6]

Synthesis of Chiral Phosphorane.

(*S*)-(*R*)-PPFA has been converted to an enantiomerically pure ferrocenylphosphonium salt (**1**) in two steps in 54% yield (eq 4). The chiral phosphorane (**2**), generated in situ from (**1**) by ***n-Butyllithium*** in THF, reacts with aldehydes in the presence of a Lewis acid, ***Diethylaluminum Ethoxide*** to give vinylation products (**3**) (eq 5) with variable enantiomeric excess (up to 70%).[7]

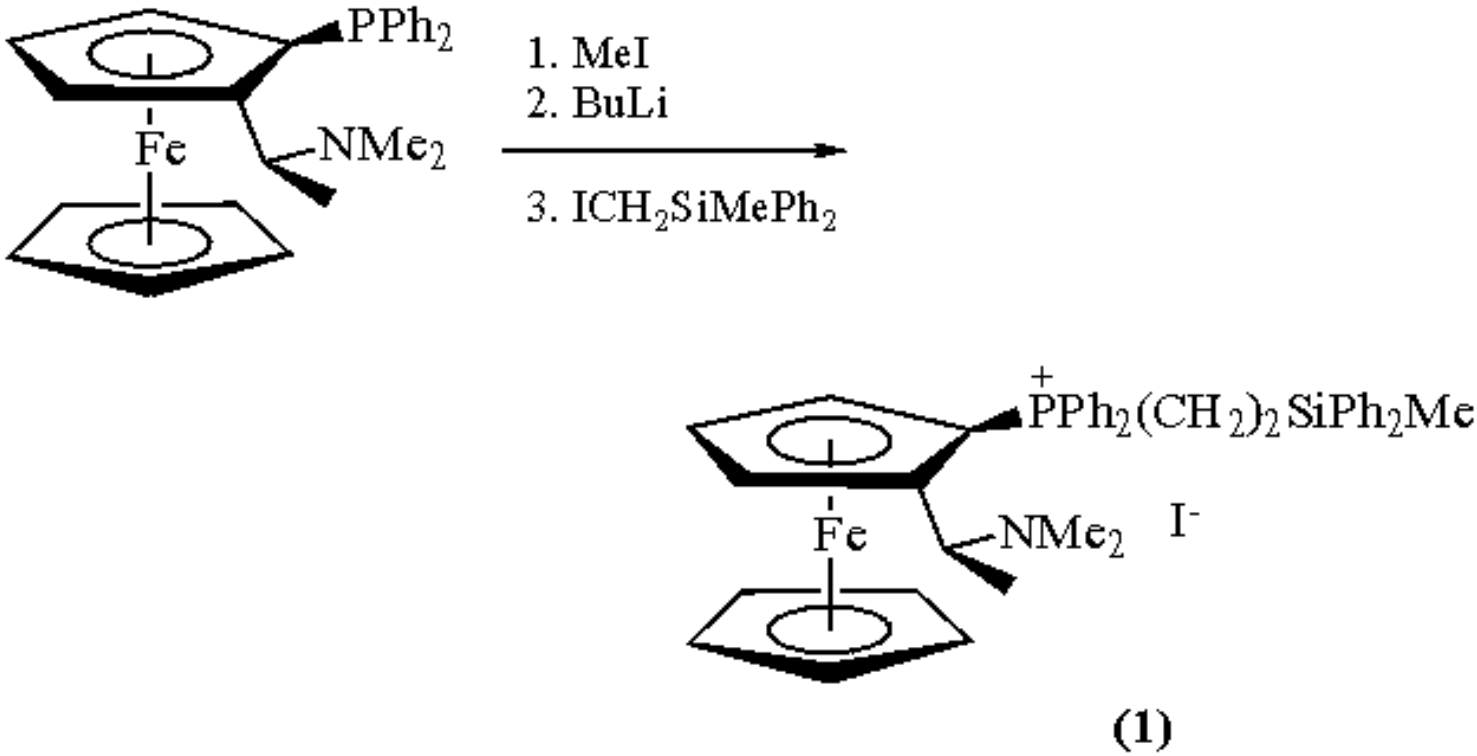

(4)

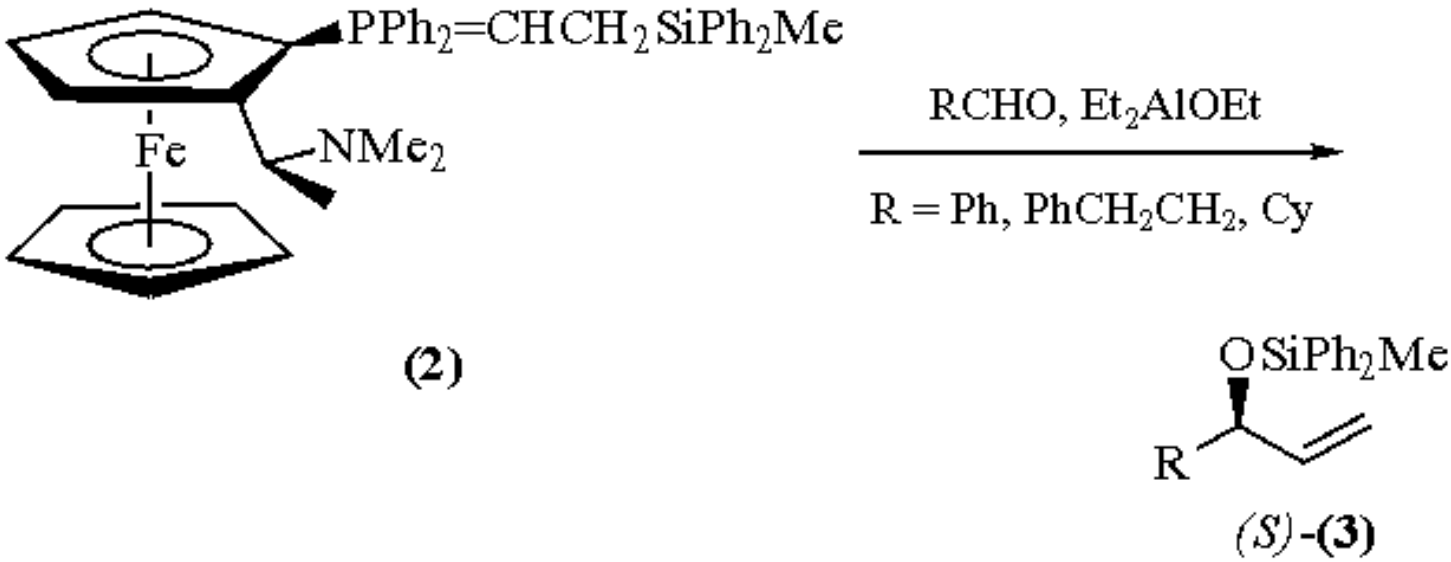

(5)

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(*S*)-2-[2-(Diphenylphosphino)phenyl]-4-phenyloxazoline

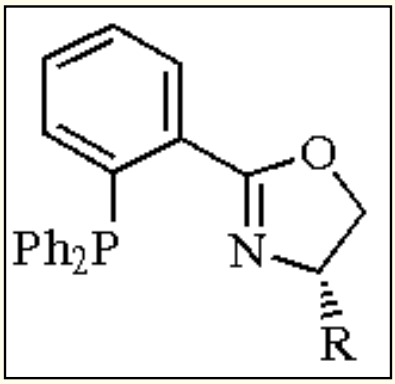

(**1**; R = Ph)

[148461-15-8] · $C_{27}H_{22}NOP$ · (*S*)-2-[2-(Diphenylphosphino)phenyl]-4-phenyloxazoline · (MW 407.47)
(**2**; R = *i*-Pr)

[148461-14-7] · $C_{24}H_{24}NOP$ · (*S*)-2-[2-(Diphenylphosphino)phenyl]-4-isopropyloxazoline · (MW 373.46)
(**3**; R = *t*-Bu)

[148461-16-9] · $C_{25}H_{26}NOP$ · (*S*)-2-[2-(Diphenylphosphino)phenyl]-4-*t*-butyloxazoline · (MW 387.49)

(readily available chiral ligands for enantiocontrol of palladium-catalyzed allylic substitution reactions[1,2])

Physical Data: (**1**) amorphous solid; $[\alpha]_D$ +30.8° (*c* = 1.0, $CHCl_3$). (**2**) amorphous solid; $[\alpha]_D$ -44.9° (*c* = 1.4, $CHCl_3$). (**3**) mp 105 °C; $[\alpha]_D$ 58.2° (*c* = 1.2, $CHCl_3$).

Solubility: insol H_2O; sol most organic solvents.

Preparative Methods: chiral phosphinoaryloxazolines, a class of ligands developed independently in three different laboratories,[1,3,4] are readily prepared in enantiomerically pure form starting from chiral amino alcohols and aromatic carboxylic acids or nitriles. Several short, convenient syntheses from 2-bromobenzonitrile (eq 1),[1,5] 2-bromobenzoic acid (eq 2),[3] or 2-fluorobenzonitrile (eq 3)[4] have been described. Alternatively, derivatives such as (**2**), which do not contain any reactive groups in the oxazoline ring that are attacked by BuLi, can be prepared from aryloxazolines by orthometalation and subsequent reaction with Ph_2PCl (eq 4).[1] Phosphino-oxazolines with an additional stereogenic center at the phosphorus atom, such as (**4**), and phosphinomethyl oxazolines of type (**5**) have also been reported.[3] The different synthetic routes allow for a wide range of structural modifications at the oxazoline ring, the phosphine group, and the ligand backbone.

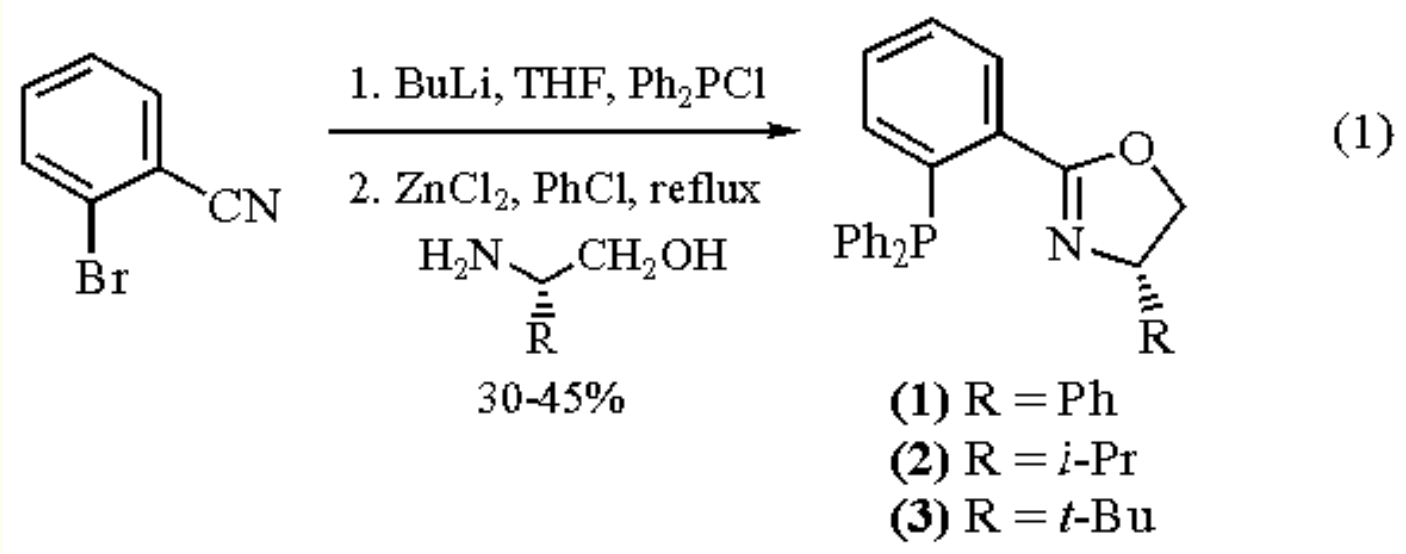
1. BuLi, THF, Ph2PCl
2. ZnCl2, PhCl, reflux
H2N CH2OH
R
30-45%
CN
Br
Ph2P
O
N
R
(1) R = Ph
(2) R = i-Pr
(3) R = t-Bu

(1)

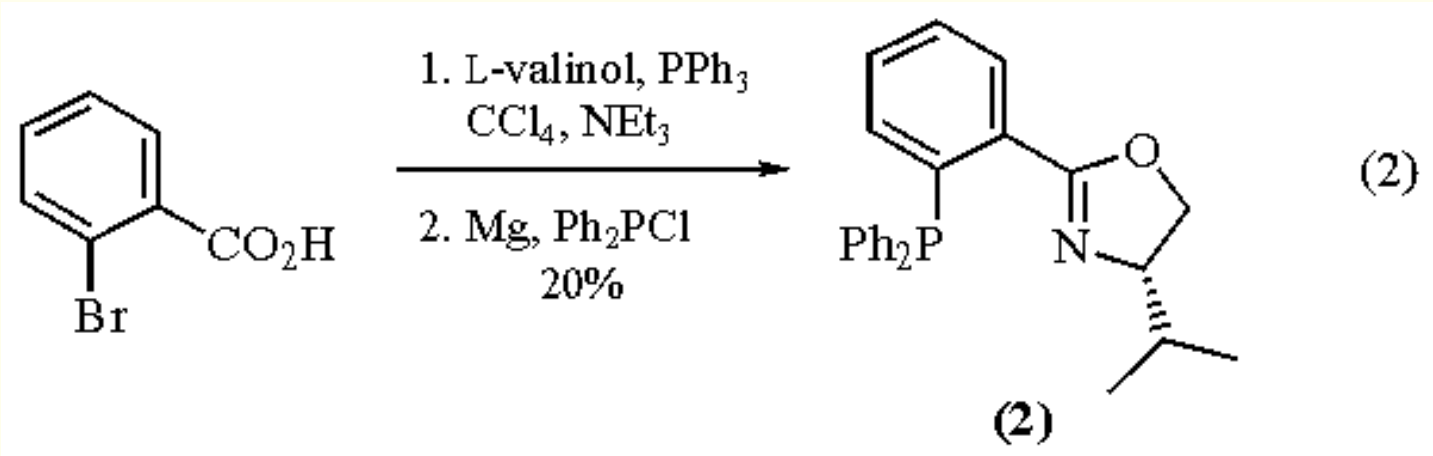
1. L-valinol, PPh3
CCl4, NEt3
2. Mg, Ph2PCl
20%
CO2H
Br
Ph2P
O
N
(2)

(2)

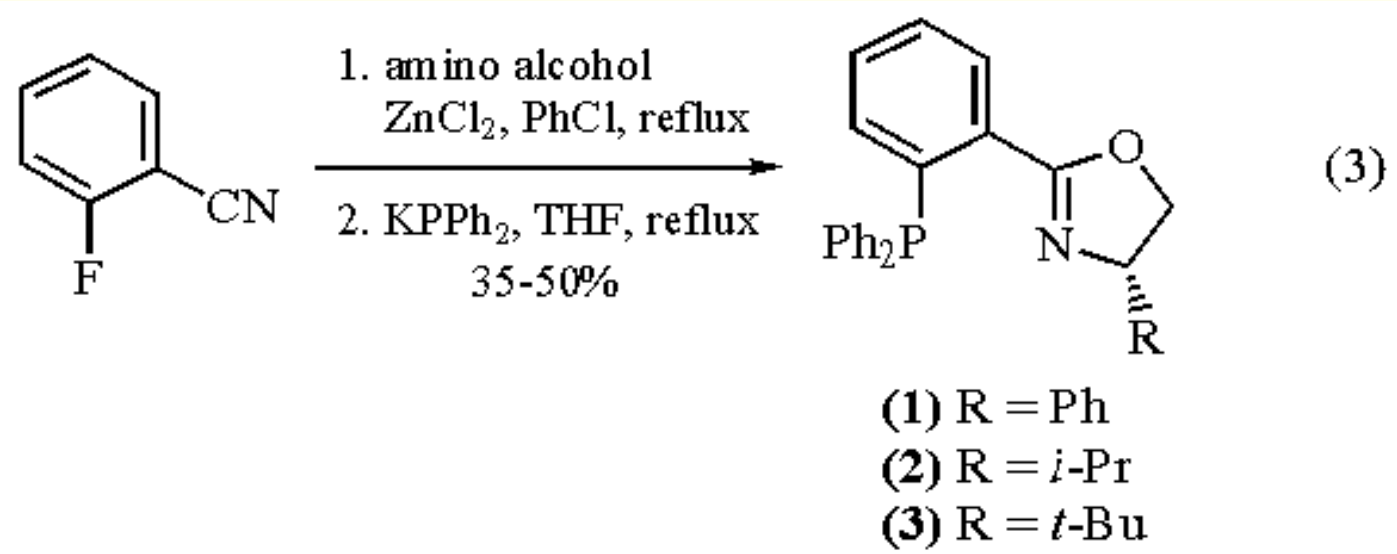
1. amino alcohol
ZnCl2, PhCl, reflux
2. KPPh2, THF, reflux
35-50%
CN
F
Ph2P
O
N
R
(1) R = Ph
(2) R = i-Pr
(3) R = t-Bu

(3)

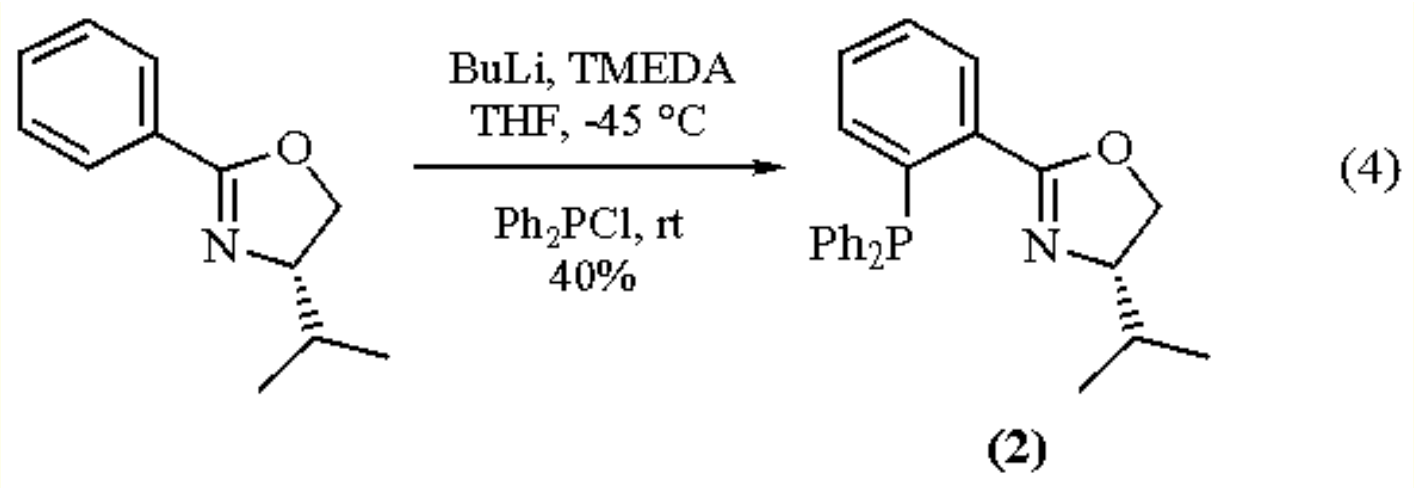

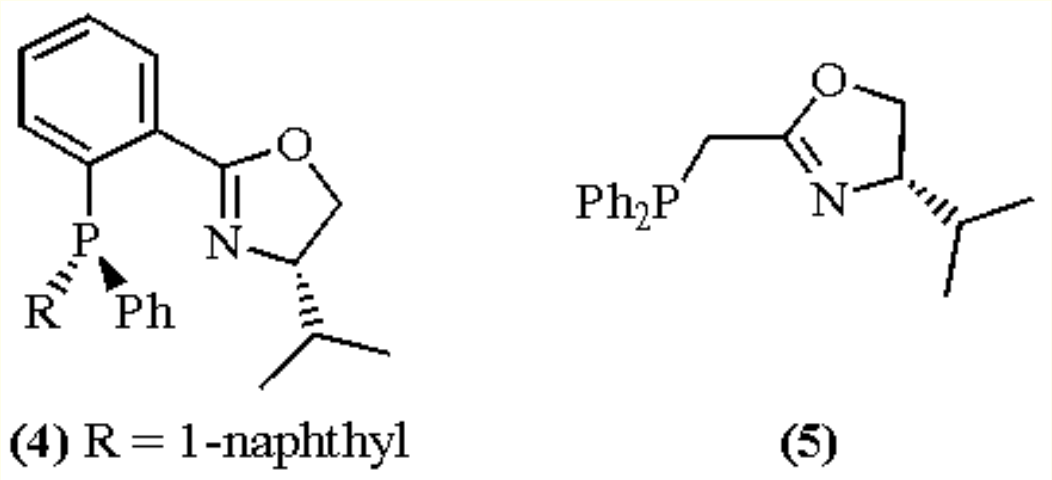

Purification: impurities such as phosphine oxides, formed by air oxidation, can be removed by column chromatography on silica gel or, for crystalline derivatives, by recrystallization.

Handling, Storage, and Precautions: Phosphino oxazolines of this type are sufficiently stable to be handled in air. For longer periods of time, they should be stored at -20 °C under argon.

Palladium-Catalyzed Allylic Substitution.

Palladium complexes of chiral phosphino oxazolines are highly effective catalysts for enantioselective allylic substitution reactions.[1-4] The catalysts are usually prepared in situ from ***Bis(allyl)di-μ-chlorodipalladium*** and the corresponding ligands. In the presence of 1-2 mol % of catalyst and a mixture of ***N,O-Bis(trimethylsilyl)acetamide*** (BSA) and catalytic amounts of KOAc as a base, racemic 1,3-diphenyl-2-propenyl acetate reacts smoothly at rt with dimethyl malonate to afford the substitution product in essentially quantitative yield and with excellent enantioselectivity (eq 5). For this substrate, the phenyloxazoline (**1**) is the optimal ligand.[1] The observed ee of 99% exceeds the selectivities previously obtained with other ligands such as ferrocenyl phosphines,[6] chiraphos,[7] BINAP,[7] 5-azasemicorrins,[8] or bis(oxazolines).[8,9] The corresponding isopropyl- and *t*-butyl-oxazolines (**2**) and (**3**) afford slightly lower en antiomeric excesses (98 and 95% ee, respectively).[1,3] Acetylacetonate[1] and diethyl acetaminomalonate,[1] as well as *N*-nucleophiles such as benzylamine, *p*-toluenesulfonamide, benzoylhydrazine, and $(Boc)_2NNa$,[10] also react with excellent enantioselectivity (eq 6).

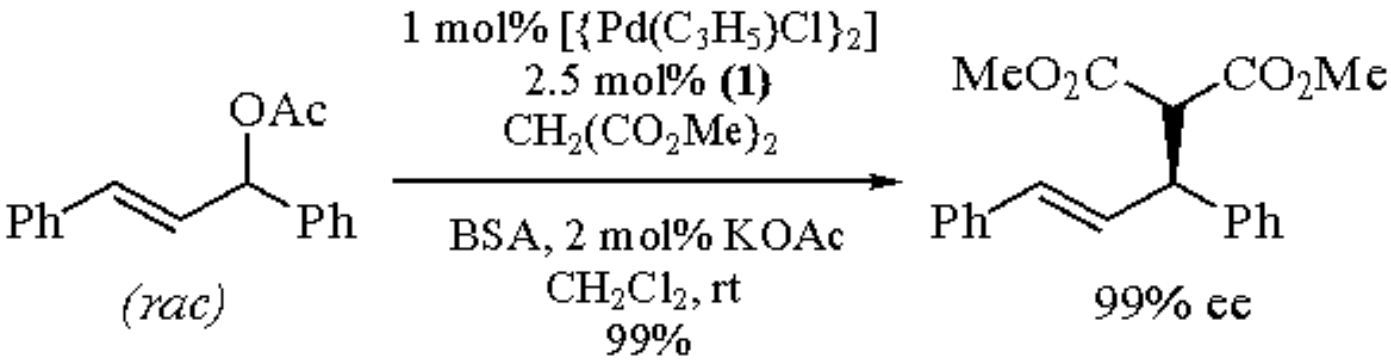

(5)

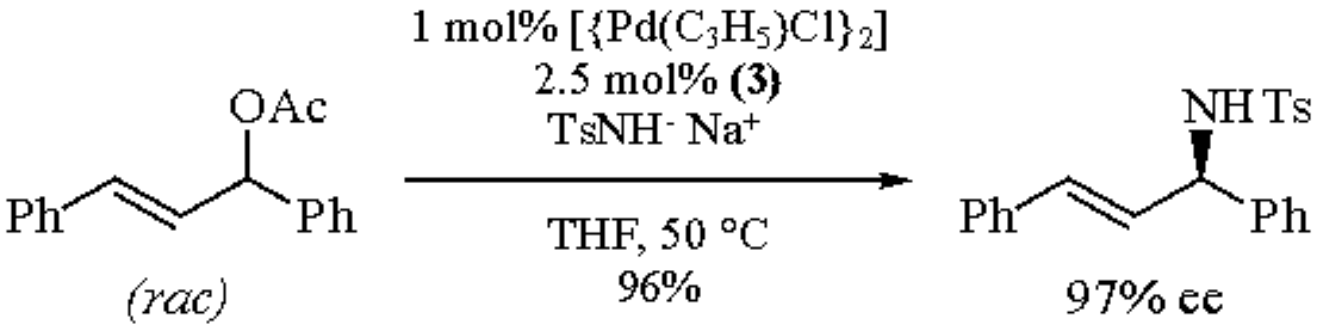

(6)

Moderate to high selectivities have been observed in allylic alkylations of 1,3-dialkyl-2-propenyl acetates.[1] Here, the *t*-butyloxazoline derivative (**3**) is the ligand of choice. Under standard conditions, *n*-alkyl-substituted allylic acetates smoothly react at rt with selectivities of 70-80% ee (eq 7). Similar results have been obtained with various *N*-nucleophiles.[10] The corresponding diisopropylallyl acetate is much less reactive, but under more vigorous conditions with $NaCH(CO_2Me)_2$ in DMF at 65 °C the reaction proceeds in good yield with high enantioselectivity (eq 8).[1] Analogous reactions of this substrate with *N*-nucleophiles are impracticably slow. In this case, the corresponding diethyl phosphate gives much better results (eq 9).[10]

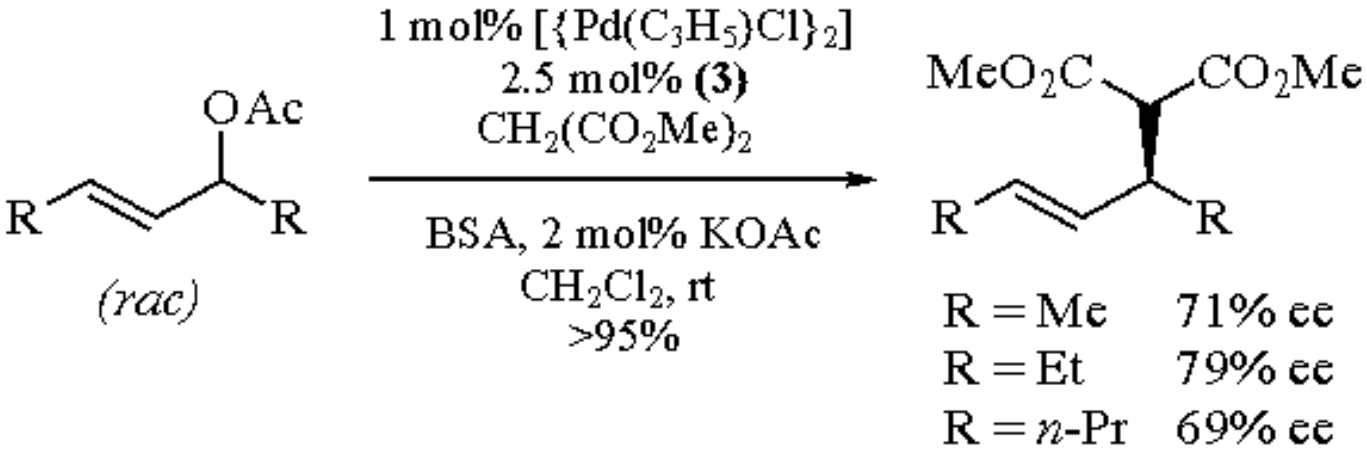

(7)

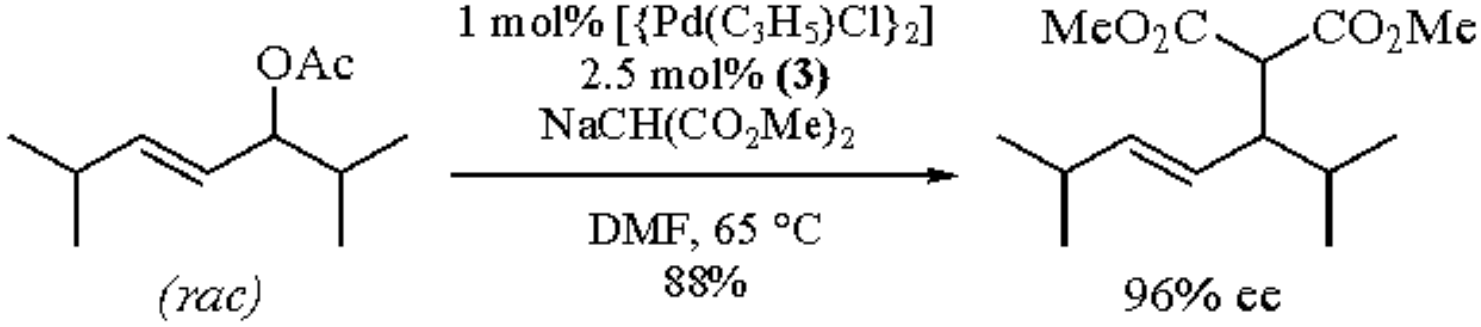

(8)

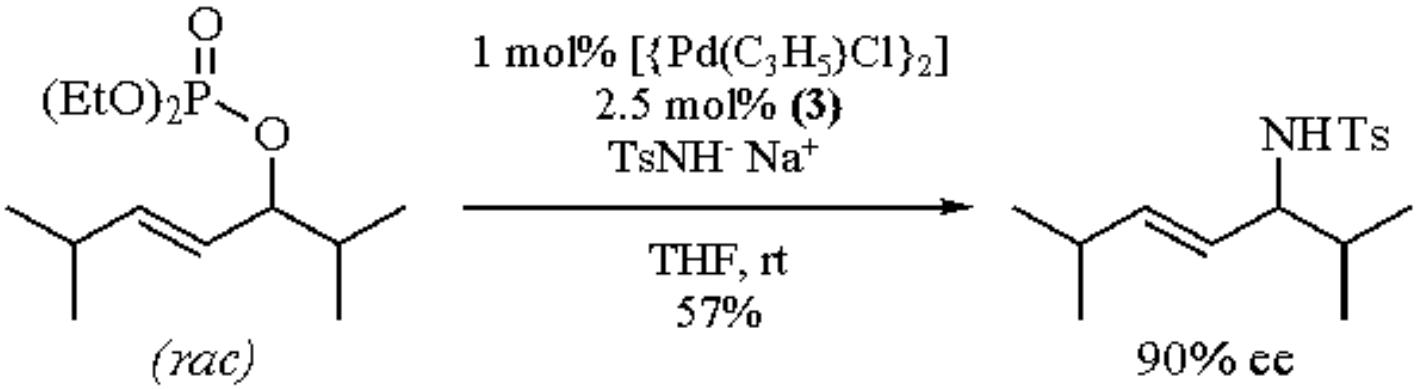

(9)

Related Reagents.

2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl; ***2,3-Bis(diphenylphosphino)butane***; ***(R)-N-[2-(N,N-Dimethylamino)ethyl]-N-methyl-1-[(S)-1´,2-bis(diphenylphosphino)ferrocenyl]ethylamine***; ***(1S,9S)-1,9-Bis{[(t-butyl)dimethylsilyloxy]methyl}-5-cyanosemicorrin***; ***(R)-N,N-Dimethyl-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethylamine***.

---

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O-(Diphenylphosphinyl)hydroxylamine[1,2]

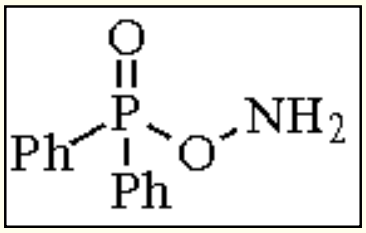

[72804-96-7] · $C_{12}H_{12}NO_2P$ · *O*-(Diphenylphosphinyl)hydroxylamine · (MW 233.22)

(reagent for electrophilic aminations; H_2N transfers to nucleophiles)

Physical Data: mp 133-134 °C.[1]

Solubility: very low in aprotic organic solvents.

Analysis of Reagent Purity: IR (cm^{-1}): 3270, 3170, 1210.[3]

Preparative Methods: [1-7] ***Triethylamine*** (12.4 g, 120 mmol) in methylene chloride (20 mL) is added with stirring to a mixture of ***Hydroxylamine*** hydrochloride (3.82 g, 55.0 mmol) in methylene chloride (100 mL) at -20 °C. After stirring at -20 °C for 1.5 h, ***Diphenylphosphinic Chloride*** (11.6 g, 49.0 mmol) in methylene chloride (20 mL) is added with stirring and cooling to maintain the temperature at -20 °C. The solution is stirred for another 1.5 h. During this time the reaction mixture attains 25 °C and a precipitate is formed, composed of triethylamine hydrochloride and *O*-(diphenylphosphinyl)hydroxylamine (**1**). To this mixture, water (100 mL) is added to dissolve the triethylamine hydrochloride salts, and the remaining (**1**) is filtered. This product is washed with anhydrous ether, and dried over phosphorus pentoxide at 25 °C/10 mmHg overnight to yield 6.81 g (60%) (**1**).

Handling, Storage, and Precautions: in contrast to *O*-(mesitylsulfonyl)hydroxylamine, an explosion with (**1**) has never been observed. (**1**) decomposes if heated above the melting point (~140 °C). It is stable for a year if stored below 0 °C.[3]

Reactions with the NH group of Imidazoles and Xanthines.

The *N*-amination of the imidazole and xanthine NH groups in (**2**) and isolation of the products (**3**) is achieved via deprotonation, amination, and imine crystallization (eqs 1-3). The amination occurs at the N-1(7) (R^3) position of the imidazole ring if this position is unsubstituted (examples **a-d**), and at the N-1 position of the pyrimidine ring in xanthines if the N-7 position is substituted (example **e**).

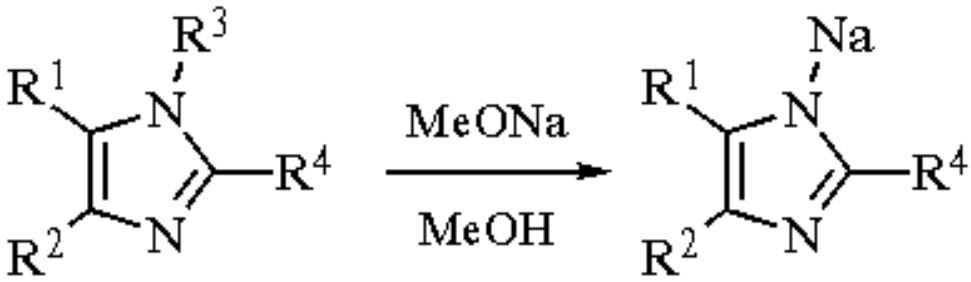

(1)

(2)

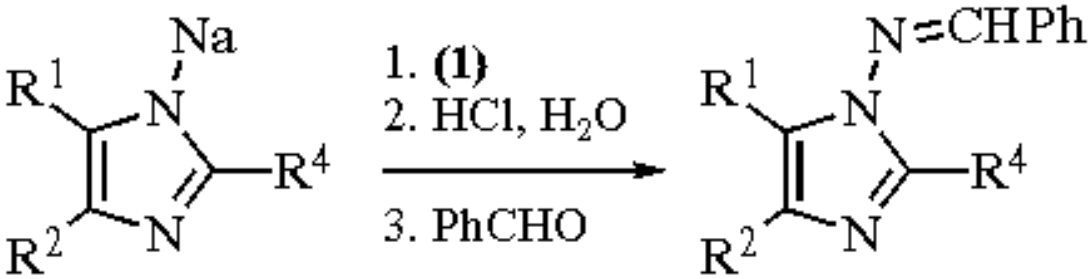

(2)

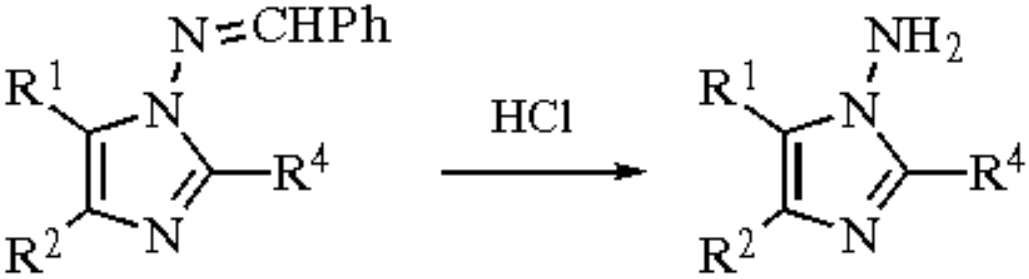

(3)

(3)

(a) $R^1 = R^2 = R^3 = R^4 = H$

(b) $R^1 = R^2 = R^3 = H;\ R^4 = NO_2$

(c) $R^1 = R^3 = H;\ R^2 = NO_2;\ R^4 = Me$

(d) 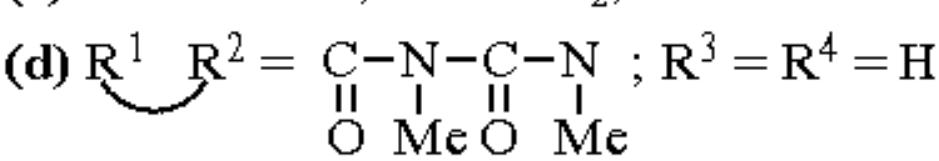

(e) 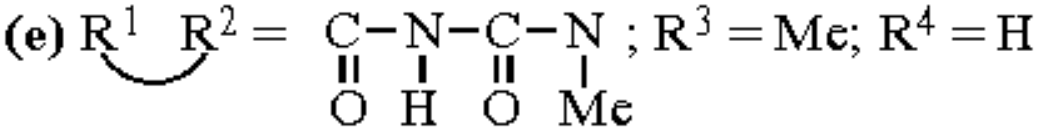

The yields of (**3**) are usually better than 70%.[2,7] In a similar fashion, indole and carbazole have been *N*-aminated to give (**4**) and (**5**) in 52-62% yields.[2,7]

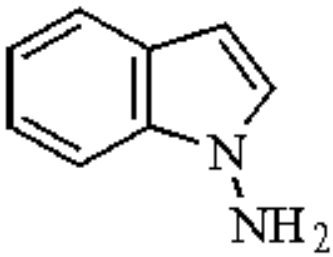

(4)

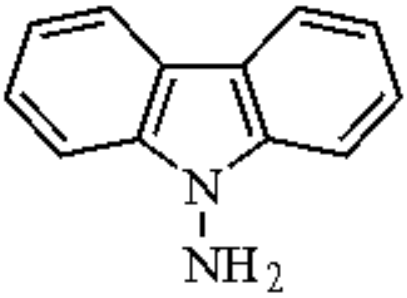

(5)

The *N*-amination of pyridine (and related compounds), although possible,[2,7] is more successful with ***O-(Mesitylsulfonyl)hydroxylamine***. Amination of a tertiary amine has been also reported.[8] Aminations at phosphorus and sulfur have been observed, (one example in each case);[4] again, *O*-(mesitylsulfonyl)hydroxylamine is the reagent of choice.

Reactions with Carbanions.

(**1**) aminates many types of carbanions RM to give primary amines, although the yields are low to moderate.[1,5,6,9,10] With *O*-(mesitylsulfonyl)hydroxylamine, only more stabilized carbanions are aminated; in this case, deprotonation of the aminating reagent is more likely to occur. The amines (**6**)-(**9**) are some examples of primary amines prepared using (**1**).[6]

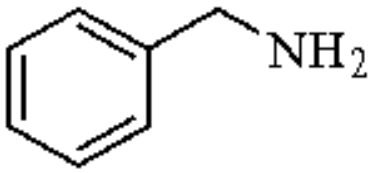

(6) 30% (RLi)
51% (RMgBr)
70% (RMgCl)

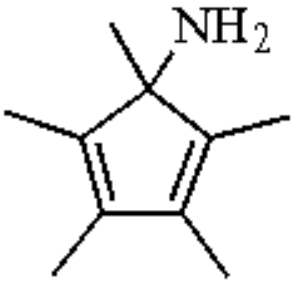

(7) 37% (RLi)

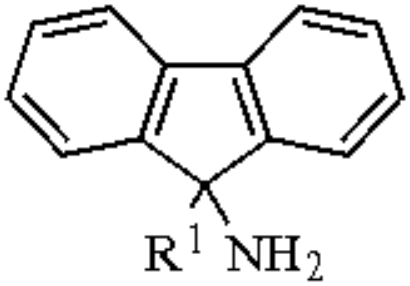

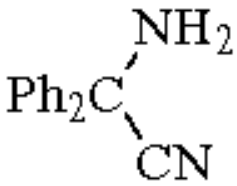

(8) $R^1 = H$, 30% (RLi)
$R^1 = CO_2Me$, 47% (RLi)
$R^1 = CO_2$-*t*-Bu, 78% (RLi)

(9) 67% (RLi)

If the alkynylcuprate (**10**) is aminated with (**1**), the nitrile (**12**) is formed via the unstable primary ynamine (**11**) (eq 4).[6]

$$\underset{\textbf{(10)}}{(Ph\text{-}C{\equiv}C)_2CuLi} \xrightarrow{\textbf{(1)}} \underset{\textbf{(11)}}{[Ph\text{-}C{\equiv}C\text{-}NH_2]} \xrightarrow{-O} \underset{\textbf{(12)}}{PhCH_2\text{-}C{\equiv}N} \qquad (4)$$

Carbanions RM can also be aminated with (**13**)[10,11] and (**14**),[12] which receive their high electrophilicity only after lithiation. (**13**) and, especially, (**14**) are less prone to deprotonation by RM than are (**1**) and, especially, *O*-(mesitylsulfonyl)hydroxylamine. There is an excellent review on the amination of carbanions.[10]

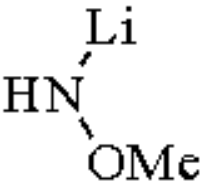

(13)

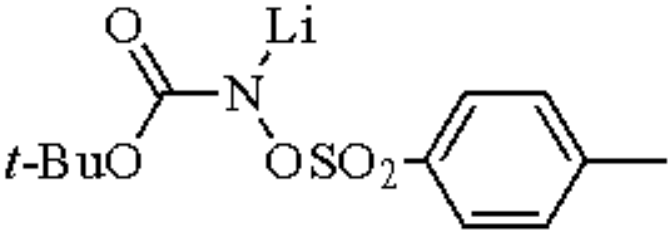

(14)

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Diphenyl Phosphonate[1]

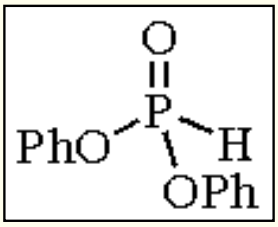

[4712-55-4] · $C_{12}H_{11}O_3P$ · Diphenyl Phosphonate · (MW 234.20)

(mild coupling agent for synthesis of esters and amides)

Alternate Name: diphenyl phosphite.

Physical Data: mp 12 °C (25 °C);[1a] bp 100 °C/0.008 mmHg, 218-219 °C/26 mmHg; *n*25D 1.5564-1.5570; δ ^{31}P 1.9 ($^1J_{PH}$ 756 Hz).

Solubility: misc most organic solvents; hydrolyzes readily to the monoester, δ ^{31}P 4.0 ($^1J_{PH}$ 719).

Form Supplied in: colorless liquid, widely available, containing up to 15% of phenol.

Purification: distillation.[2] Best done in small batches since decomposition frequently occurs. Phenol can be substantially removed by heating at 150 °C at water pump vacuum.

Handling, Storage, and Precautions: no toxicity data have been reported but the invariable presence of phenol and its ready hydrolysis by atmospheric moisture makes the commerical material corrosive.

In the presence of tertiary amines, preferably ***Pyridine*** or ***Imidazole***, the ester acts as an efficient coupling agent in the formation of peptides (eq 1).[1,3] Ureas and thioureas may be similarly prepared from ***Carbon Dioxide*** or ***Carbon Disulfide*** (eq 2).[4]

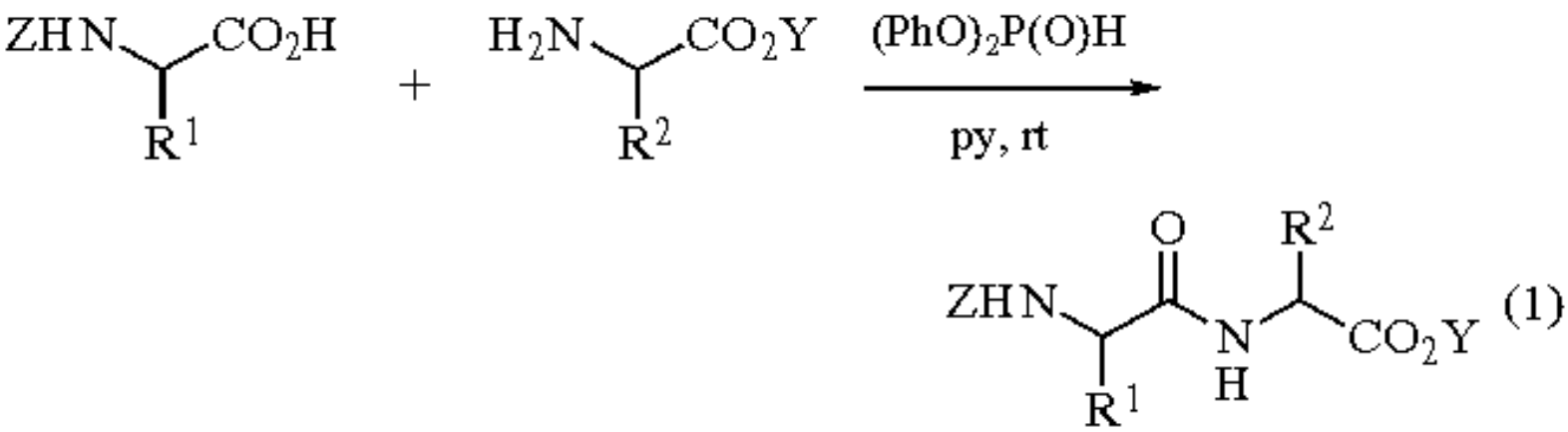

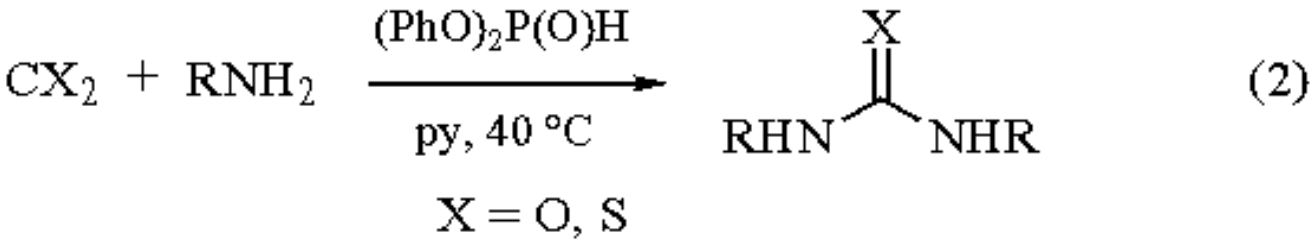

The diester undergoes easy transesterification in two distinct stages, allowing the preparation of unsymmetrical diesters (eq 3).[5]

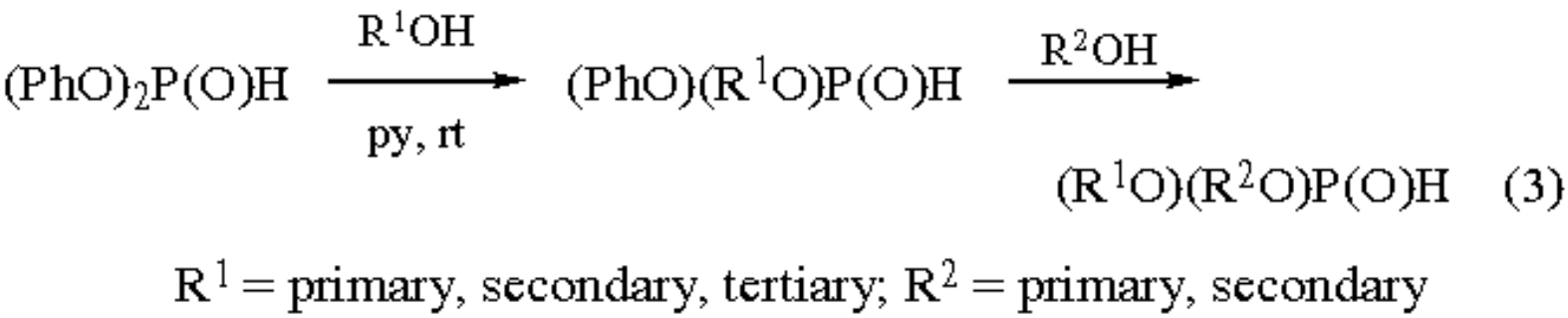

The use of stronger bases than pyridine, e.g. ***Triethylamine***, causes rapid disproportionation to $(PhO)_3P$ and $PhOPHO_2^-$.[2c,5]

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Diphenyl Phosphorazidate

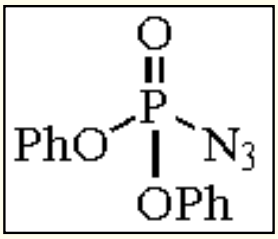

[26386-88-9] · $C_{12}H_{10}N_3O_3P$ · Diphenyl Phosphorazidate · (MW 275.22)

(peptide synthesis;[1] synthesis of α-aryl carboxylic acids;[4] synthesis of thiol esters;[7,8] stereospecific conversion of alcohols to azides;[9] ring contraction of cycloalkanones;[13] decarbonylation of aldehydes[26])

Alternate Names: DPPA; *O,O*-diphenylphosphoryl azide.

Physical Data: bp 157 °C/0.17 mmHg; *d* 1.277 g cm^{-3}; fp >110 °C.

Solubility: sol toluene, THF, DMF, *t*-butyl alcohol.

Form Supplied in: colorless liquid; commercially available in kilogram quantities.

Preparative Method: by the reaction of ***Diphenyl Phosphorochloridate*** with a slight excess of ***Sodium Azide*** in acetone at rt (85-90% yield).[1]

Purification: vacuum distillation (bath temp <200 °C, dec >200 °C)

Handling, Storage, and Precautions: handle and store under nitrogen. Refrigerate. Decomposes at >200 °C and may produce toxic fumes of phosphorus oxides and/or phosphine. Toxic, irritant. Harmful if swallowed, inhaled, or absorbed through the skin. Use in fume hood. Incompatible with oxidizing agents and acids. Hazardous combustion or decomposition products include carbon monoxide, carbon dioxide, and nitrogen oxides. Prolonged contact with moisture may produce explosive hydrogen azide (HN_3).

General.

Diphenyl phosphorazidate is a readily available, nonexplosive, and relatively stable azide widely used as a reagent in peptide synthesis,[1-3] and as a versatile reagent in a wide array of organic transformations. DPPA has been successfully utilized in the synthesis of α-amino acids[4] and α-aryl carboxylic acids;[5,6] direct preparation of thiol esters from carboxylic acids and thiols;[7,8] the stereospecific preparation of alkyl azides;[9] and the phosphorylation of alcohols and amines.[10] The application of DPPA in a modified Curtius[11] reaction permits a simple one-step conversion of

carboxylic acids to urethanes under mild reaction conditions. DPPA acts as a nitrene source,[12] and can undergo 1,3-dipolar cycloaddition reactions.[5,13] The Curtius degradation[14] of carboxylic acids in the presence of *t*-butanol gives the Boc-protected amine directly (eq 1).

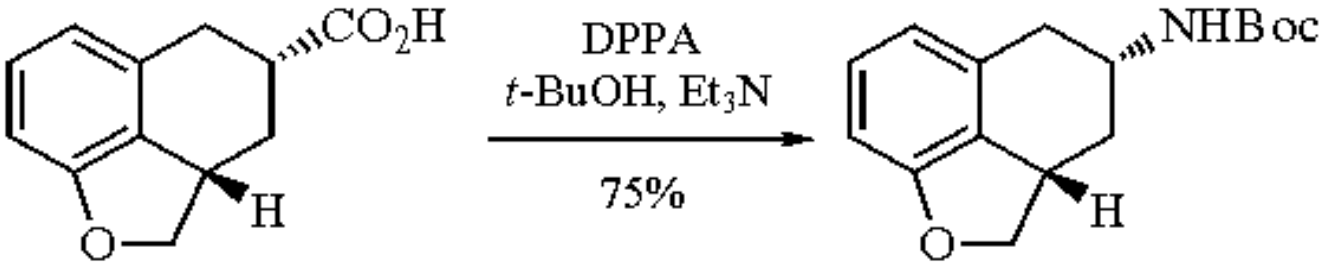

(1)

DPPA has been utilized in the synthesis of 1,4-dinitrocubane by Eaton and co-workers.[15] Refluxing cubane-1,4-dicarboxylic acid with DPPA and ***Triethylamine*** in *t*-butanol forms the intermediate *t*-butyl carbamate in nearly quantitative yield. This method avoids the formation of the explosive diacyl azide.

Peptide Synthesis.

Urethanes are readily prepared by refluxing equimolar mixtures of DPPA, a carboxylic acid, an alcohol, and triethylamine. The reaction involves transfer of the azide group from DPPA to the carboxylic acid. The resulting acyl azide subsequently undergoes a Curtius rearrangement. This reaction has been successfully applied in the area of peptide synthesis.[1] The coupling of acylamino acids or peptides with amino acid esters or peptide esters in the presence of base proceeds in high yields without racemization, and is compatible with a variety of functional groups. The reaction of malonic acid half-esters results in the corresponding α-amino acid derivatives[4] (eq 2). It should be noted that addition of the alcohol at the beginning of the reaction results in esterification.

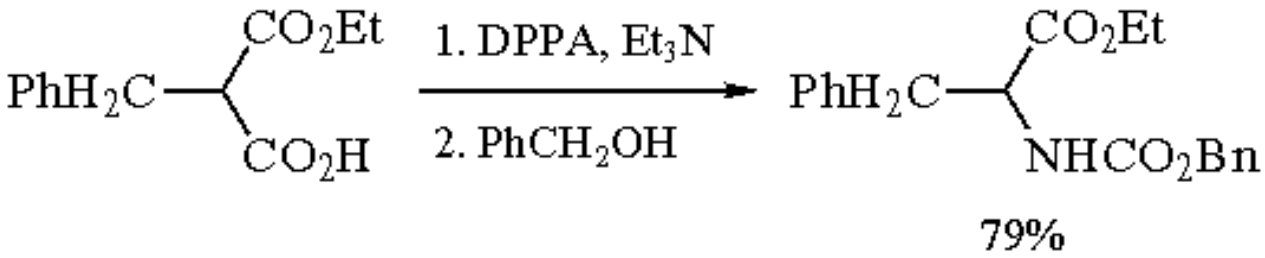

(2)

α-Aryl Carboxylic Acids.

Alkyl aryl ketones are converted into the corresponding α-aryl alkanoic acids[4] via a three-step sequence. Yields of >90% are possible if the synthesis is carried out in a one-flask procedure. The sequence includes a 1,3-dipolar cycloaddition of DPPA to the corresponding enamines (eq 3). Although ***Thallium(III) Nitrate*** has also been used in similar oxidative rearrangements,[16] the DPPA method exhibits higher functional specificity, uses less toxic reagents, and gives preparatively useful yields. Naproxen, a nonsterodial anti-inflammatory therapeutic, has been prepared by this route.[6]

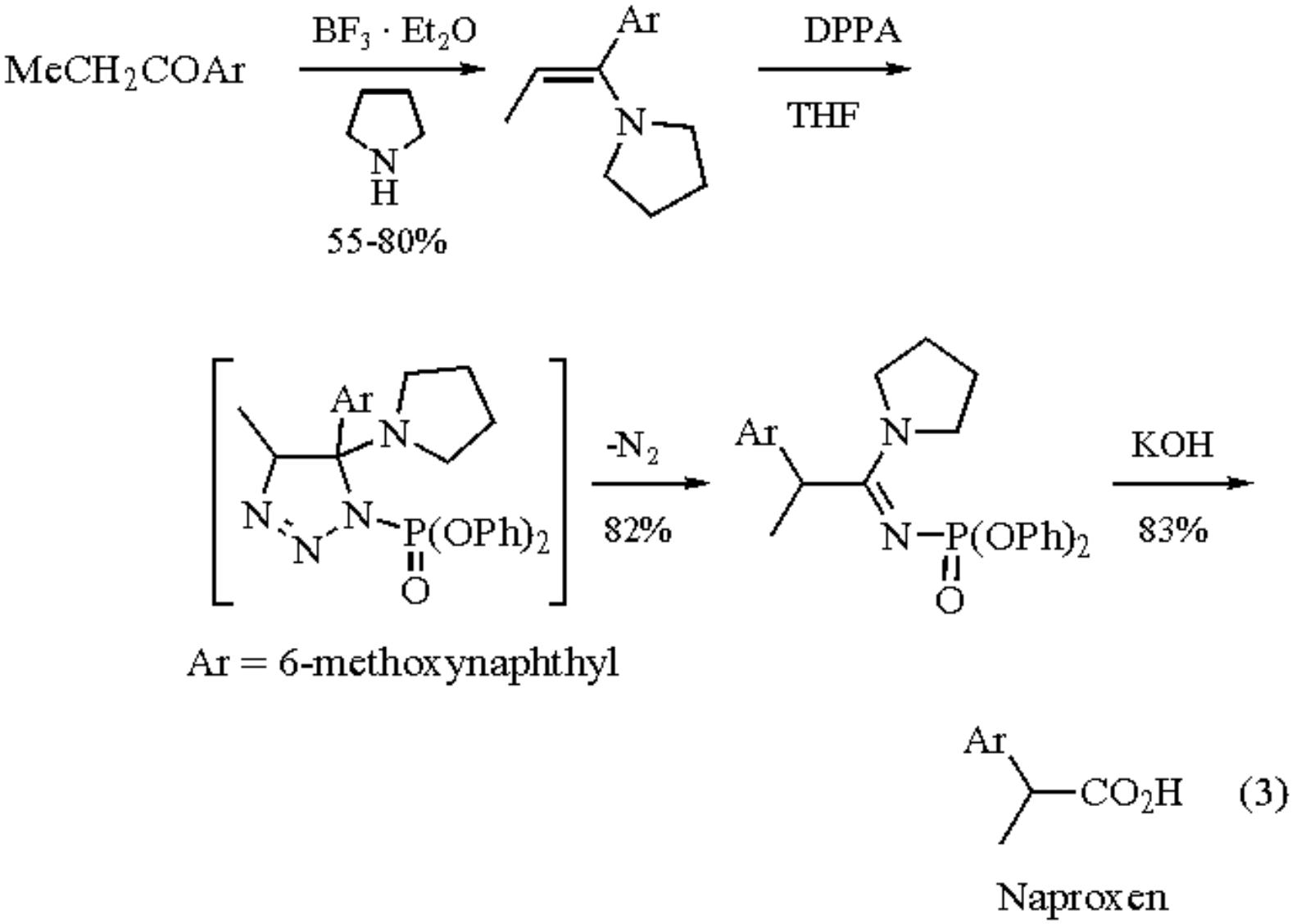

Stereospecific Conversion of Alcohols to Azides.

Reaction of an alcohol with DPPA, ***Triphenylphosphine***, and ***Diethyl Azodicarboxylate*** forms the corresponding azides in 60-90% yields.[9] The stereospecific nature of this reaction permits the conversion of Δ^5-sterols such as 3β-cholestanol exclusively to the 3α-cholestanyl azide in 75% yield. This synthesis is clearly superior to the alcohol -> tosylate -> azide route which is longer and also prone to competing elimination reactions.

Ring Contraction Reactions.

DPPA undergoes 1,3-dipolar cycloadditions to the enamines of cyclic ketones.[13] The resulting Δ^2-triazolines, which are not isolated, undergo loss of nitrogen to form ring-contracted products, which, on hydrolysis, yield cycloalkanoic acids. In the case of six- to eight-membered cycloalkanones, overall yields as high as 75% have been reported (eq 4).

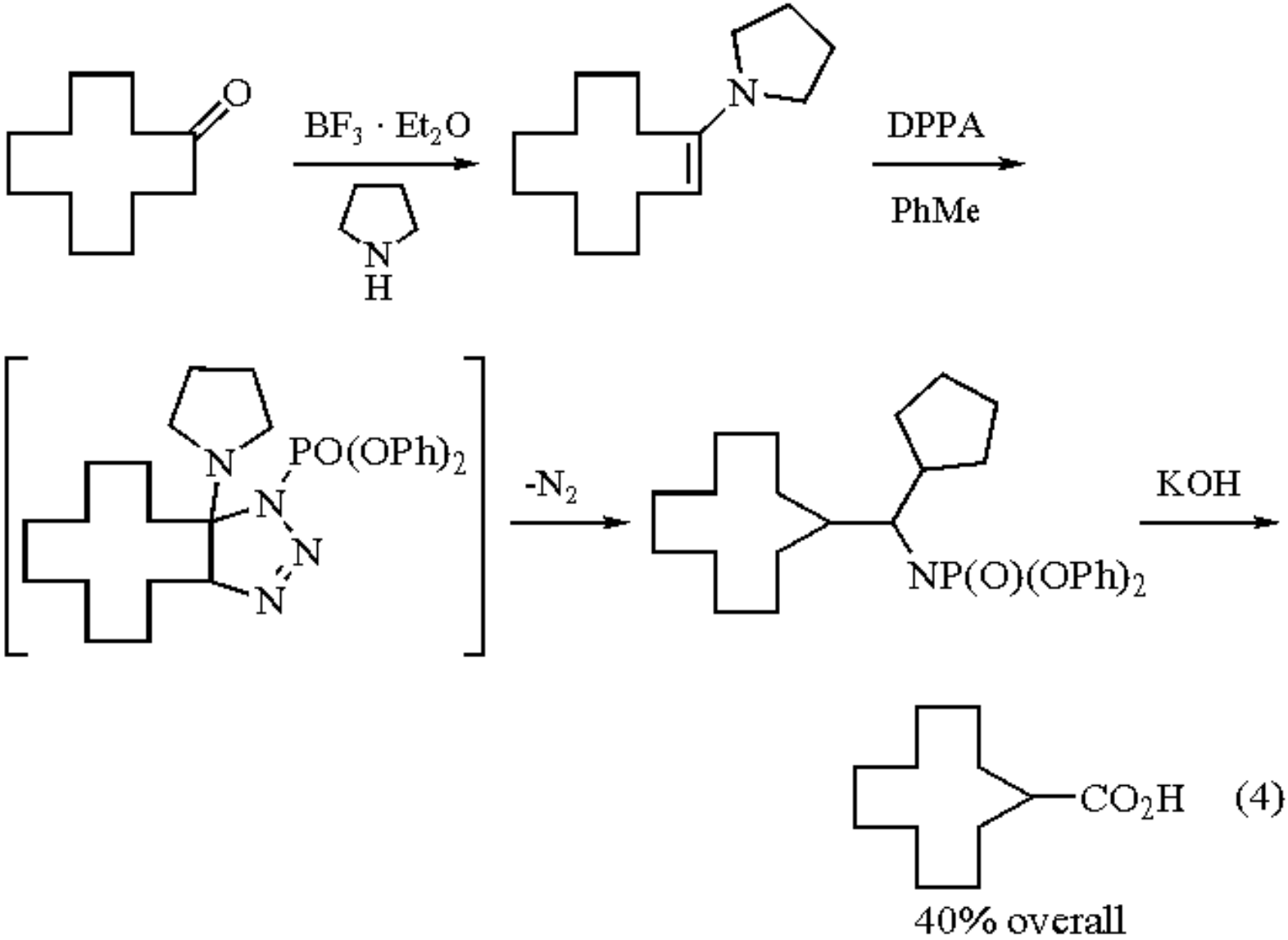

Amination of Aromatic and Heteroaromatic Organometallics.

Reaction of organic azides with Grignard and lithium compounds gives 1,3-disubstituted triazenes,[17] which are readily converted to amines by reductive[18,19] or hydrolytic[20,21] workup. These methods are limited to either the aromatic Grignard[18,20] or lithium[21] compounds, and have not been very successful with heteroaromatic organometallics. Aromatic and heteroaromatic organometallics (Grignard and lithium compounds) are aminated in good yields in a one-pot process by treatment with DPPA and reduction of the resulting phosphoryltriazenes with ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (eq 5).[22]

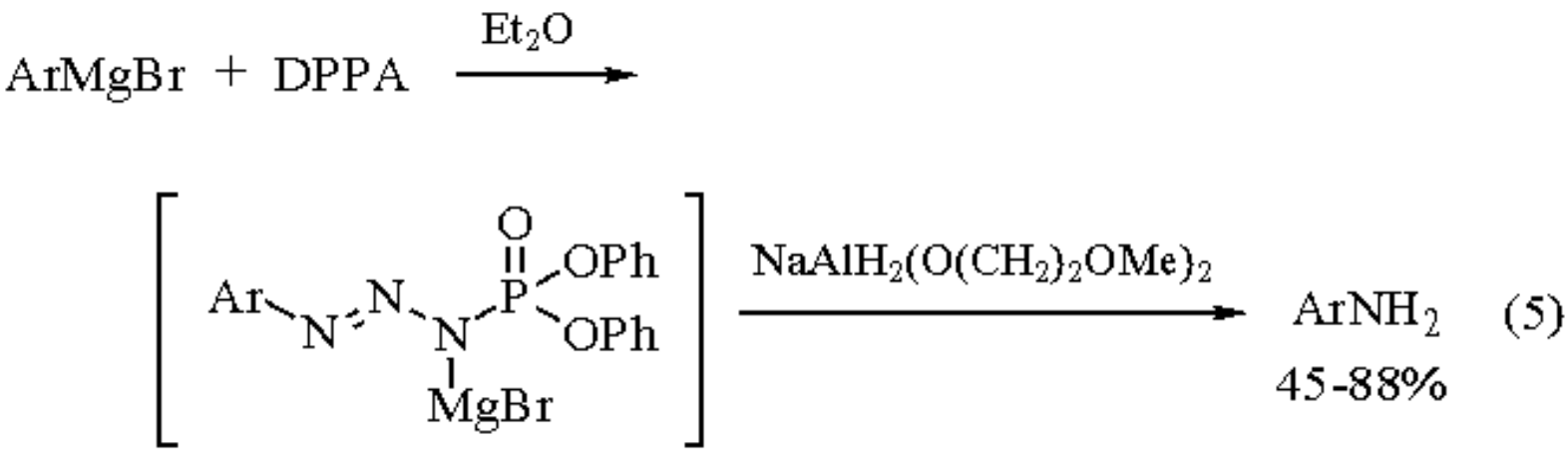

Metal-Catalyzed Decarbonylation of Primary Aldehydes.

The decarbonylation of primary aldehydes under catalytic conditions is difficult, requiring high temperatures or involving radical mechanisms;[23] the rt decarbonylations[24,25] using stoichiometric ***Chlorotris(triphenylphosphine)rhodium(I)*** have had limited practicality due to the high cost of the reagent. Recently, a high-yielding, rt decarbonylation of primary aldehydes using catalytic amounts (5 mol %) of $Rh(PPh_3)_3Cl$ and stoichiometric amounts of DPPA, with minimal formation of alkene byproducts, has been developed[26] (eq 6).

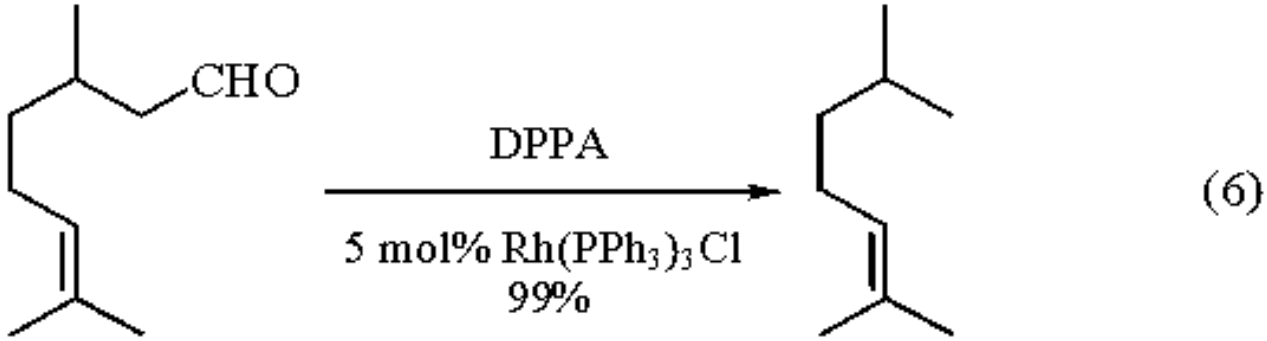

Synthesis of Macrocyclic Lactams.

Macrocyclic lactams are conventionally prepared by the reaction of dicarboxylic acid chlorides with diamines, a method which is effective with simple acyl chlorides. Activation of the carboxylic groups in order to overcome the drawbacks of high dilution and the low yields and purity encountered with larger acyl chlorides has seen only limited success.[27] The superior activating ability of DPPA has recently been demonstrated.[28] The reactions of dicarboxylic acids and diamines in the presence of DPPA form macrobicyclic lactams in yields as high as 82%. By comparison, in a control experiment using conventional high-dilution techniques, the corresponding acyl chlorides cyclized with the diamine to form the lactam in only 24% yield.

DPPA has been used for the direct *C*-acylation of methyl isocyanoacetate with carboxylic acids to give 4-methoxycarbonyloxazoles.[29] L-Daunosamine, the glycone component of anticancer anthracycline antibiotics, has been synthesized from L-lactic acid in 9 steps with a 24% overall yield,[30] where a key step in the sequence is the direct *C*-acylation of methyl isocyanoacetate with the lithium salt of the lactate ester using diphenyl phosphorazidate (eq 7).

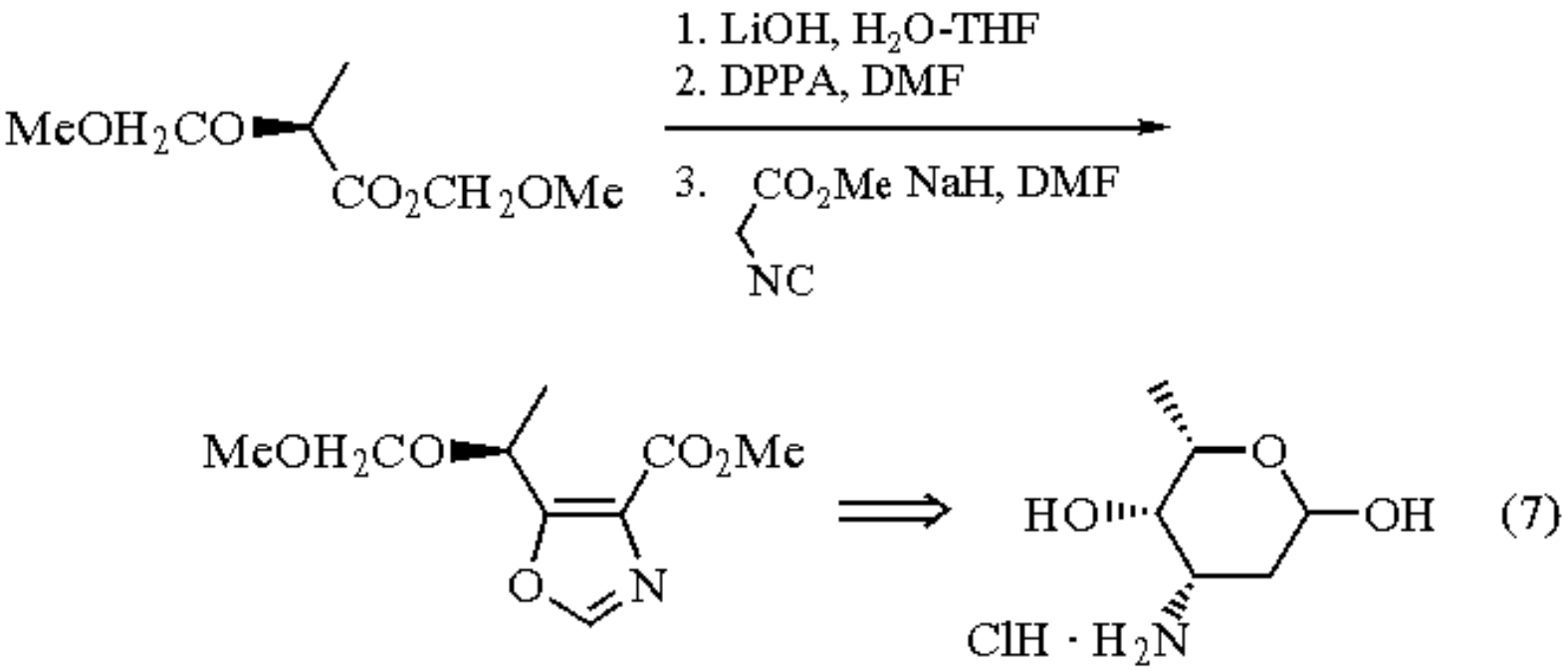

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Diphenyl Phosphorochloridate

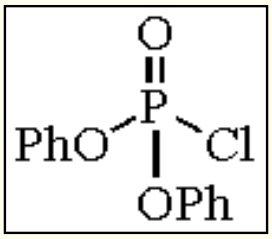

[2524-64-3] · $C_{12}H_{10}ClO_3P$ · Diphenyl Phosphorochloridate · (MW 268.64)

(phosphorylation;[1] synthesis of α-substituted β-lactams;[14] synthesis of anhydrides, esters, and thioesters;[18] conversion of aldoximes to nitriles;[22] preparation and reaction of enol phosphates[25,26,29])

Alternate Names: diphenyl chlorophosphate; diphenylphosphoryl chloride.

Physical Data: bp 314-316 °C/272 mmHg; *d* 1.296 g cm^{-3}; fp >110 °C.

Solubility: sol dichloromethane, THF.

Form Supplied in: viscous colorless liquid; commercially available.

Preparative Methods: by heating a mixture of 1.1 equiv phosphoryl chloride and 2 equiv of phenol to 180 °C, and distilling the product.[1] Prepared in situ by the reaction of diphenyl hydrogen phosphonate and carbon tetrachloride.

Purification: vacuum distillation.

Handling, Storage, and Precautions: moisture sensitive; handle and store under nitrogen. Store in a cool place. Harmful liquid and fumes; inhalation may be fatal. Use in a fume hood. Extremely corrosive; causes burns. Incompatible with strong bases and oxidizing agents. Combustion or decomposition products include carbon monoxide, hydrogen chloride gas, phosphorus oxides, and/or phosphine.

General.

As first demonstrated by Brigl and Müller[1] in the synthesis of glucose and fructose phosphates, diphenyl phosphorochloridate is an excellent reagent for the synthesis of monoalkyl phosphates. The reagent has been used to block the amino group in amino sugar and nucleoside synthesis,[2] and in the synthesis of glycosyl phosphates,[3] key intermediates in the synthesis of nucleotide sugars. The reagent has been used in peptide synthesis,[4] one-pot syntheses of sulfinates, sulfinamides, and thiosulfinates,[5] and as an intermediate in the synthesis of ***Diphenyl Phosphorazidate***[6,7]

and diphenyl phosphoroisothiocyanatidate.[8] The reagent has been utilized in the study of the β-(phosphonooxy)alkyl radical rearrangements,[9] involving the 1,2-migration of phosphate esters.

α-Substituted β-Lactams.

Azidoacetyl Chloride, a valuable reagent for β-lactam synthesis[10-12] by Sheehan's acid chloride-imine method,[13] tends to decompose explosively unless rigorous precautions are observed. The application of phosphorylating reagents provides a safe and viable alternative to this reaction. The reaction of a Schiff base and carboxylic acid in the presence of diphenyl phosphorochloridate and ***Triethylamine*** (eq 1) results in substituted β-lactams in 50-70% yield.[14]

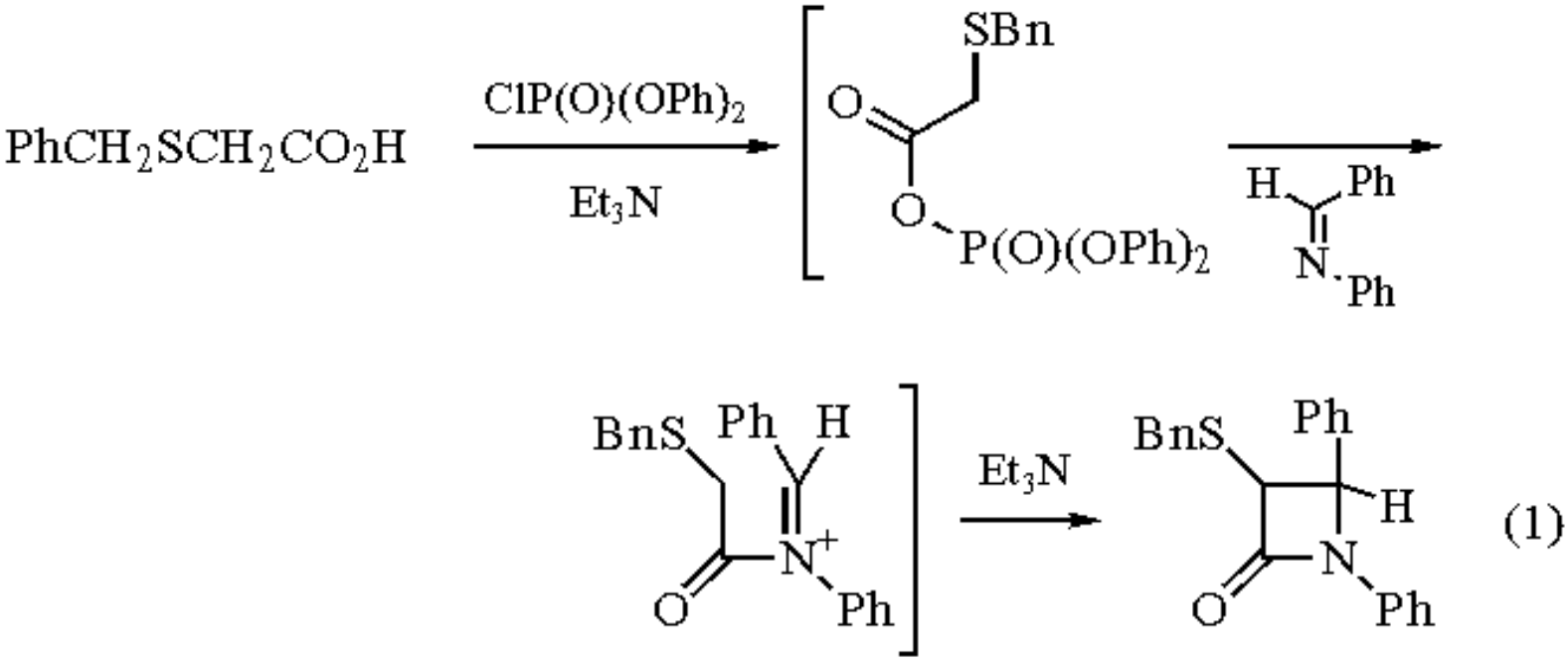

Synthesis of Anhydrides, Esters, and Thioesters.

Phosphorus reagents such as diphenyl phosphorazidate[15] and diphenyl phosphorochloridate[16] have been used for carboxy group activation through the respective mixed phosphoric acid anhydrides. These have been found suitable for the one-pot preparation of carboxylic acid anhydrides, esters, and thioesters.[17] The hydroxy acid (eq 2) does not undergo lactonization under conventional conditions. Activation with diphenyl phosphorochloridate, however, and treatment with ***4-Dimethylaminopyridine***, results in cyclization to the lactone and a dimer in 32% yield and 25% yield, respectively.[18] The diol is generated in quantitative yield with ***Trifluoroacetic Acid*** in aqueous acetonitrile.

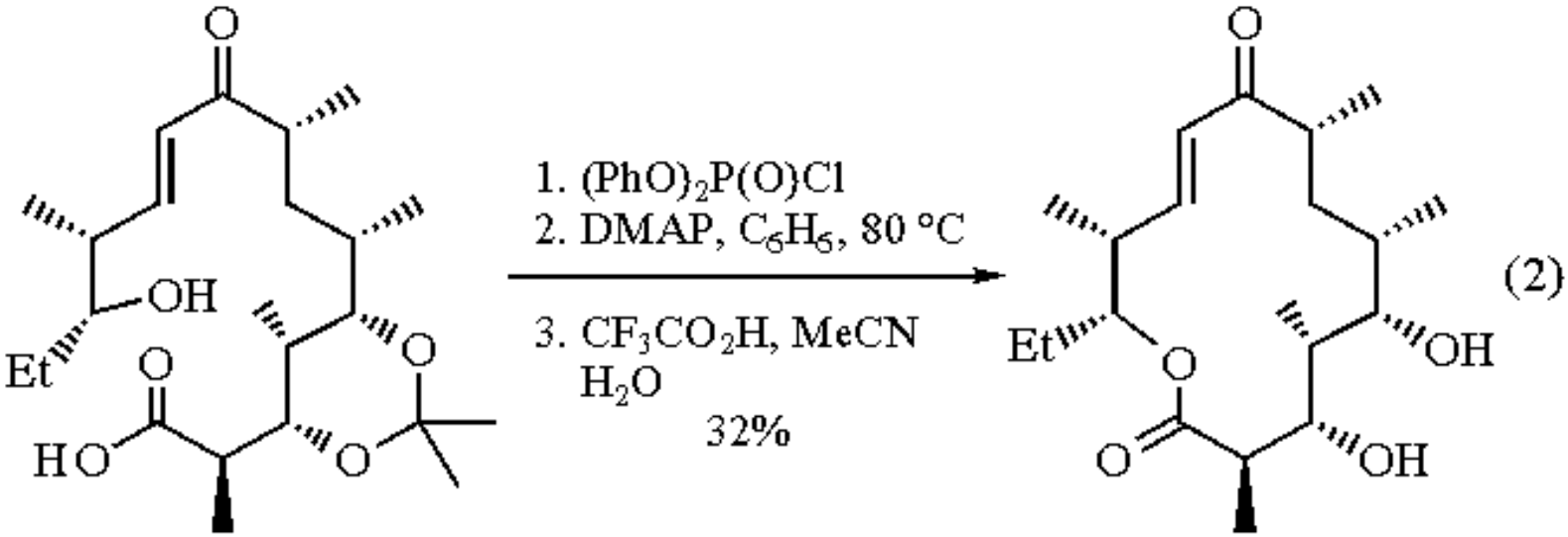

Reaction with Amide Enolates.

The synthesis of 3-amino-2*H*-azirines is generally accomplished by the reaction of α-chloro enamines with sodium azide.[19] The less stable 2-monosubstituted 3-amino-2*H*-azirines require a modified synthesis and difficult experimental conditions.[20] A new and simpler route to these compounds involves the reaction of diphenyl phosphorochloridate with amide enolates,[21] followed by reaction with ***Sodium Azide*** to give moderate yields of 2-monosubstituted 3-amino-2*H*-azirines (eq 3).

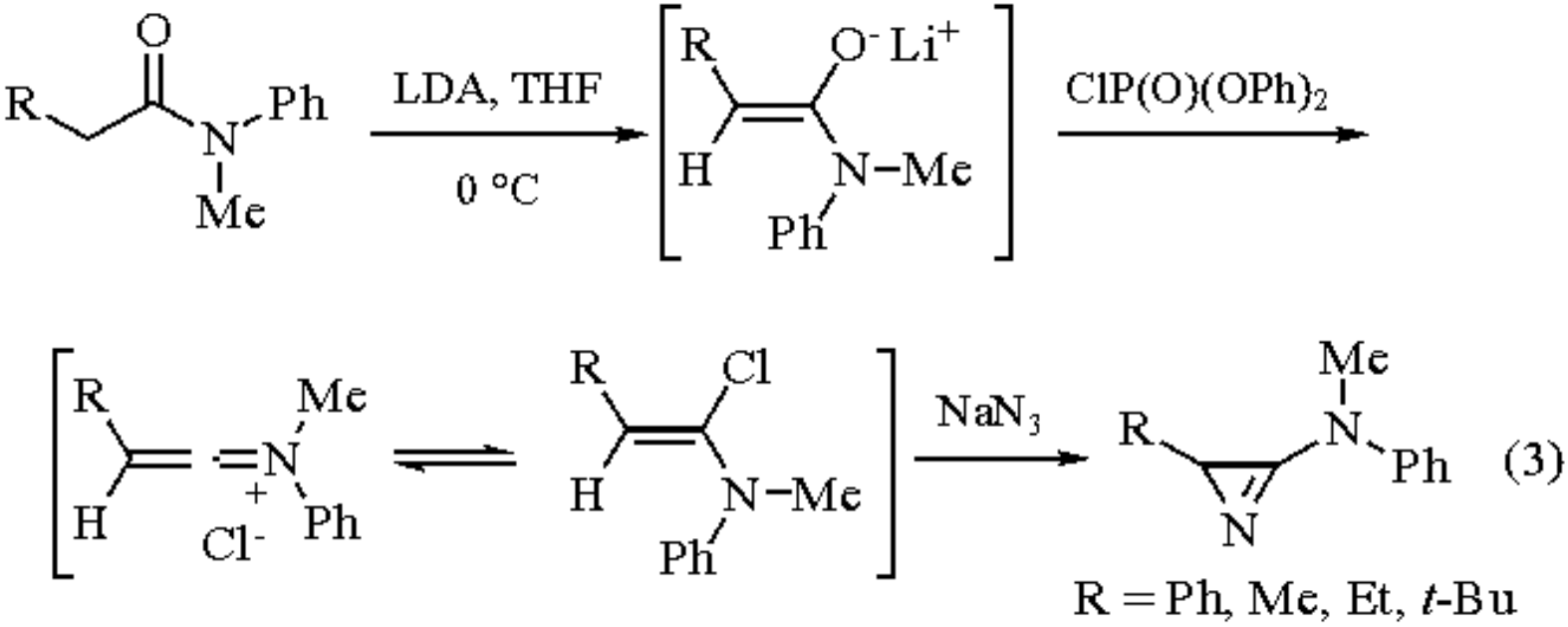

These 2-substituted aminoazirines react with carboxylic and thiocarboxylic acids to form the respective amides and thioamides (eq 4).

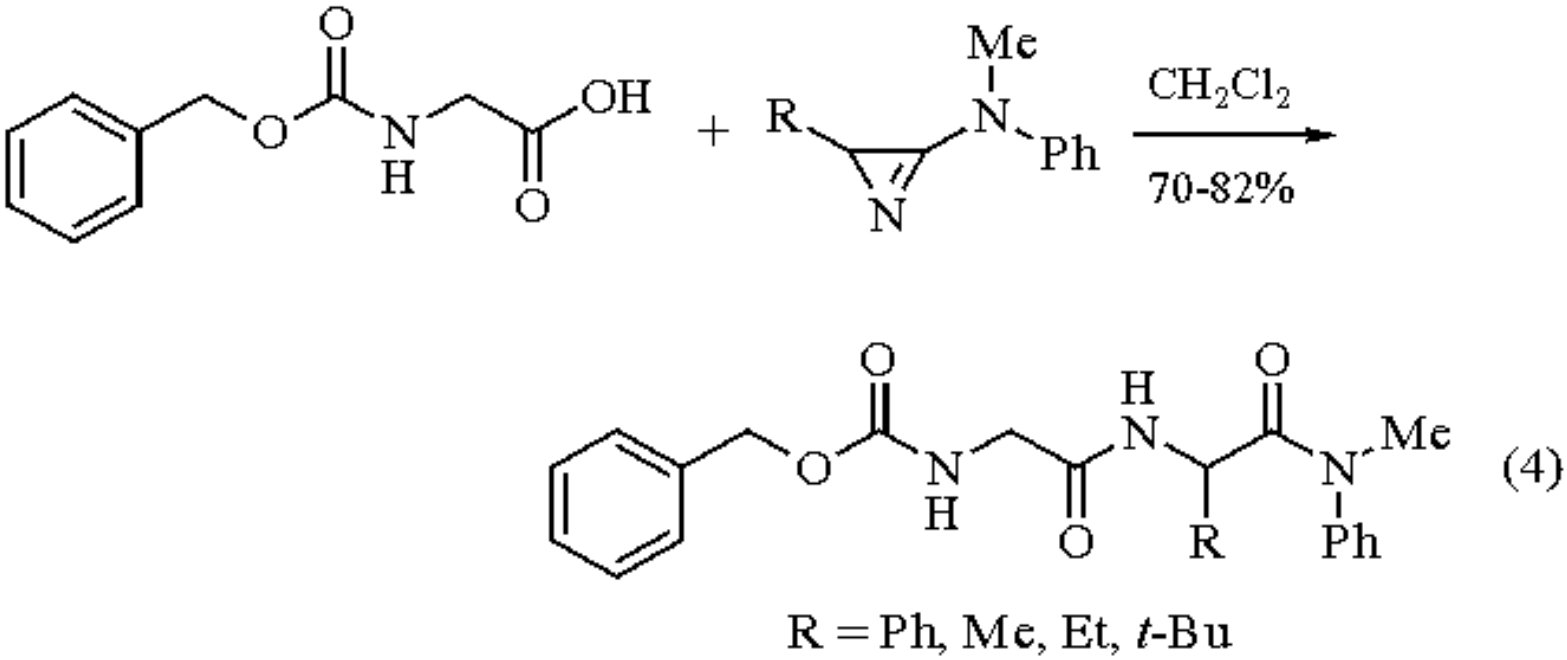

Conversion of Aldoximes to Nitriles.

The reaction of aldoximes with dialkyl hydrogen phosphonates (R = Ph, Me, *n*-Bu), carbon tetrachloride, and triethylamine at ambient temperatures results in the formation of nitriles in high yields.[22] Diphenyl hydrogen phosphonate gives the best yields (85-95%). The reaction proceeds via the in situ generation of diphenyl phosphorochloridate (eq 5),[23] followed by the esterification of the aldoxime, and subsequent Beckmann fragmentation (eq 6).

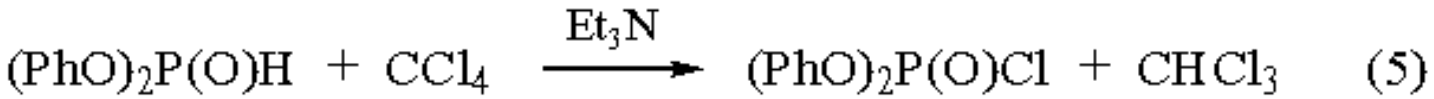

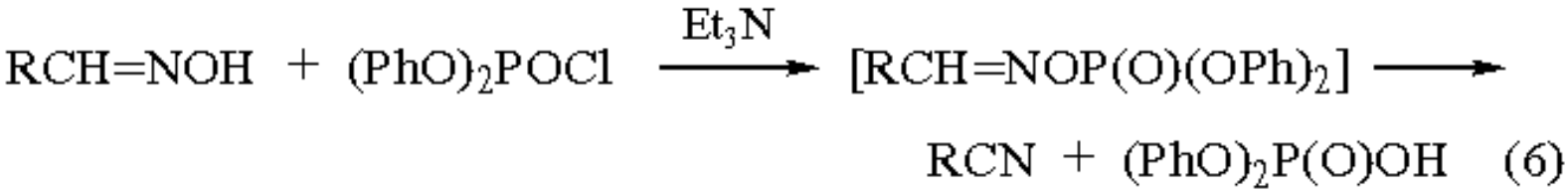

Synthesis and Reactions of Enol (Vinyl) Phosphates.

A general method for the preparation of enol phosphates involves the reaction of lithium enolates with dialkyl phosphorochloridates.[24] Enol phosphates have been prepared by a novel cycloaddition reaction. Reaction of the enolate of methyl vinyl ketone with diphenyl phosphorochloridate yields the phosphate diene, which then undergoes [4 + 2] cycloaddition (eq 7) to form the Diels-Alder adduct in 90% yield.[25] With relatively poor dienophiles like cyclohexenone, Lewis acid catalysts such as ***Aluminum Chloride*** may be required.

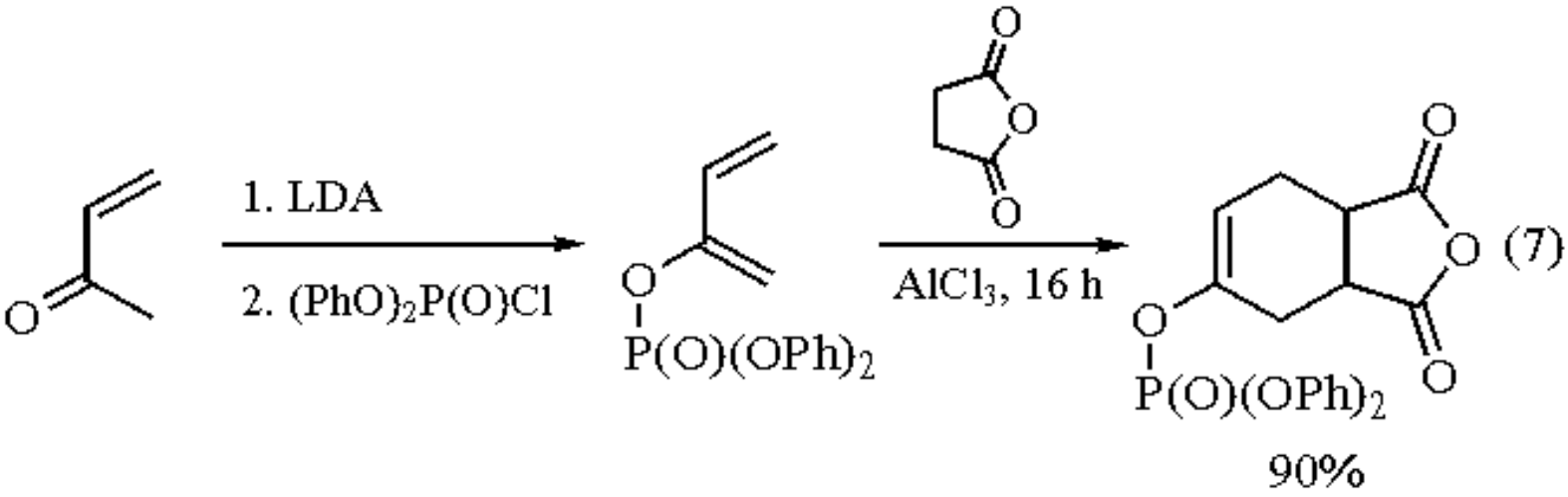

Enol phosphates are versatile intermediates which undergo many synthetically useful transformations. The coupling of enol phosphates with lithium dialkylcuprates provides alkyl-substituted alkenes in good yields (eq 8).[26]

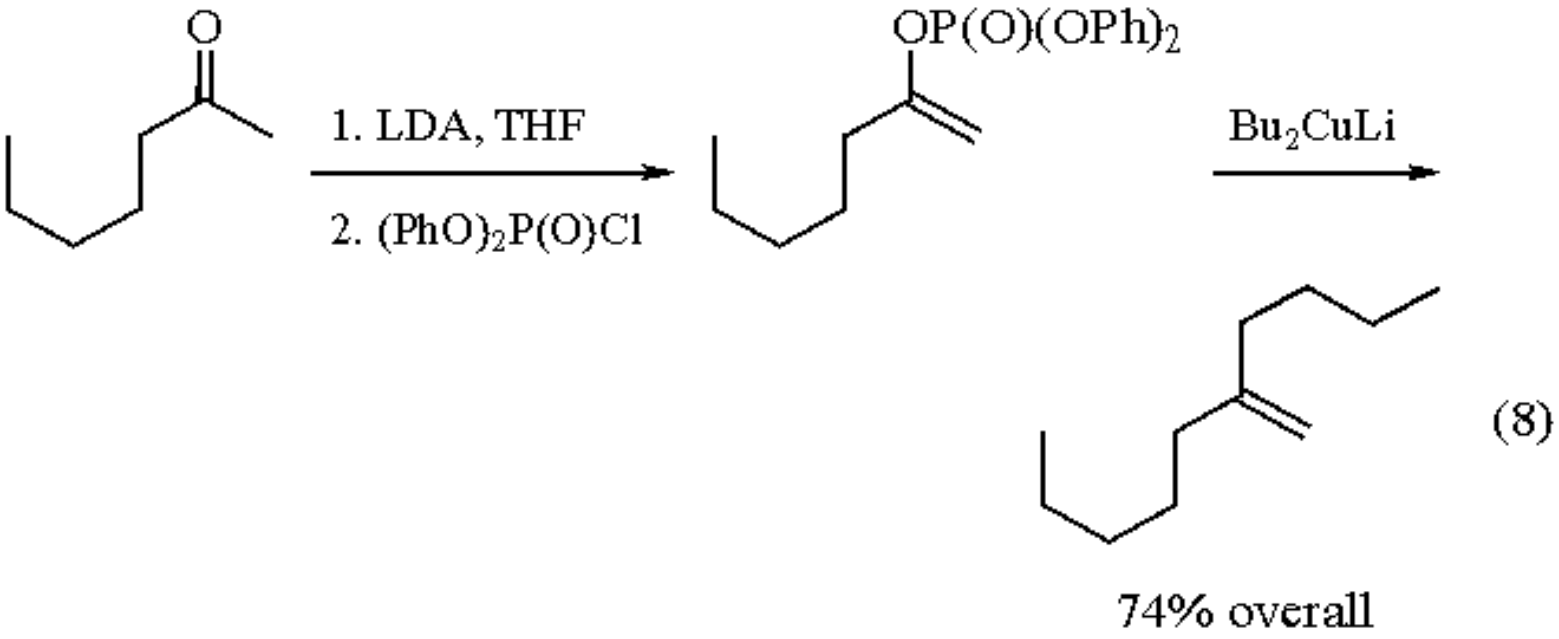

The Pd^0-catalyzed cross coupling of organometallics and organic halides has generally been limited to aryl and alkenyl halides.[27,28] Thus the palladium-catalyzed cross coupling of vinyl phosphates and organoaluminum compounds, reported by Oshima and co-workers,[29] provides an effective tool for the transformation of enolizable ketones into alkyl-, alkenyl-, and alkynyl-substituted alkenes (eq 9).

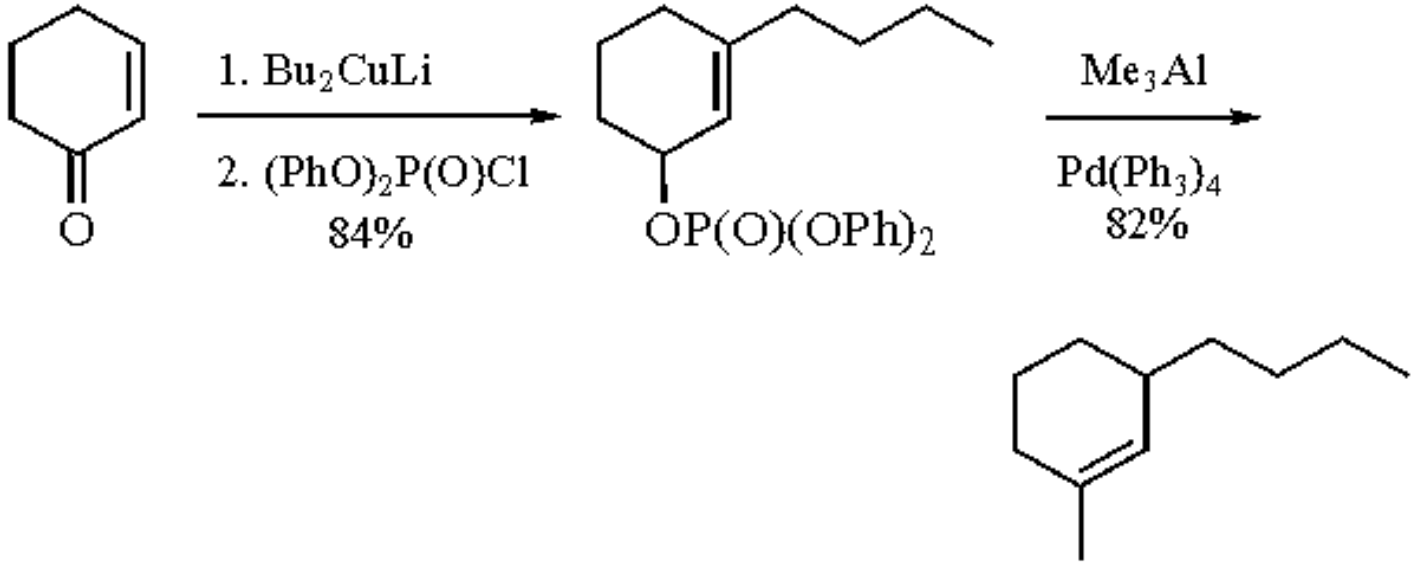

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α,α-Diphenyl-2-pyrrolidinemethanol[1]

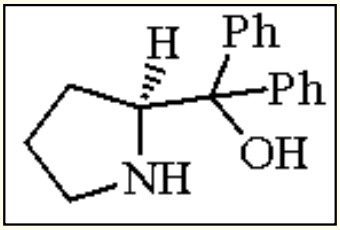

(*S*)

[112068-01-6] · $C_{17}H_{19}NO$ · α,α-Diphenyl-2-pyrrolidinemethanol · (MW 253.37) (*R*)

[22348-32-9] ((*S*) .HCl)

[16226-54-3] · $C_{17}H_{20}ClNO$ · α,α-Diphenyl-2-pyrrolidinemethanol Hydrochloride · (MW 289.83)

(precursor to several chiral oxazaborolidine catalysts[1] used for the enantioselective reduction of prochiral ketones[2,3])

Alternate Name: diphenylprolinol.

Physical Data: mp 79-79.5 °C (hexane); 80-82 °C (EtOH). $[\alpha]_{589}$ -54.3° (*c* 0.261, MeOH); -68.1° (*c* 3.17, $CHCl_3$) for the (*S*)-enantiomer.

Solubility: very sol THF, CH_2Cl_2, MeOH, toluene.

Preparative Methods: addition of ***Phenylmagnesium Bromide*** to (*S*)-proline-*N*-carboxyanhydride (73% overall from proline).[4] Addition of *N*-benzyl-(*S*)-proline ethyl ester to phenylmagnesium chloride followed by catalytic hydrogenolysis (49% overall from proline).[5] Addition of *N*-(benzyloxycarbonyl)-(*S*)-proline methyl ester to phenylmagnesium chloride (50% overall yield from proline).[3a,c] Addition of phenylmagnesium bromide to *N*-(ethyloxycarbonyl)-(*S*)-proline methyl ester followed by alkaline hydrolysis (65% overall yield from proline).[6] Addition of (*S*)-proline ethyl ester hydrochloride to phenylmagnesium chloride (20-26% overall yield from proline, ca. 80% ee).[7] Enantioselective deprotonation of *N*-Boc-pyrrolidine with ***s-Butyllithium/(-)-Sparteine*** followed by reaction with benzophenone to give (*R*)-diphenylprolinol (63% yield from pyrrolidine).[8] Add ition of phenylmagnesium chloride to methyl pyroglutamate followed by reduction with borane to give racemic diphenylprolinol (51% yield) which can be resolved as its *O*-acetylmandelate salt to give the (*R*)- and (*S*)-enantiomers (30% yield from the racemate).[3b] Addition of lithiated *N*-nitrosopyrrolidine to benzophenone to give racemic diphenylprolinol (58-60% yield based on benzophenone).[9]

Purification: recrystallization from hexane, ethanol, or methanol/water.

Handling, Storage, and Precautions: no special information available. In general, however, it is advisable that

all reactions with this reagent be conducted in a well ventilated fume hood. Care should be exercised to avoid contact of this reagent and the derived oxazaborolidine catalyst with the eyes and skin.

Enantioselective Ketone Reduction.

Following Itsuno's lead for enantioselective reductions using diphenylvalinol,[10] Kraatz was the first to describe the use of a 1:2 mixture of (*S*)-diphenylprolinol (**1**) and ***Borane-Tetrahydrofuran*** for the stoichiometric enantioselective reduction of ketone (**2**) to obtain the plant growth regulator triapenthenol (**3**) (eq 1).[2] Although not characterized at the time, the species responsible for the enantioselectivity observed was presumed to be an oxazaborolidine-borane complex.[10b]

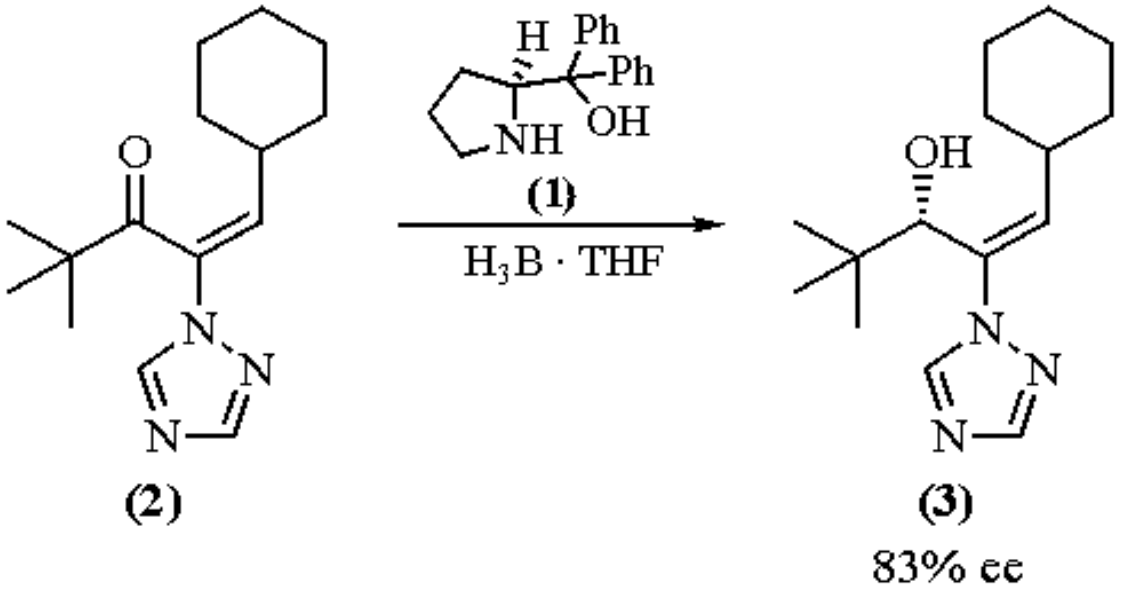

(1)

Diphenylprolinol (**1**) and borane-THF react in a multistep process to give the unsubstituted oxazaborolidine-borane complex (**7**) (eq 2). Formation of amine-borane complex (**4**) is exothermic, and this intermediate can be isolated as a stable crystalline solid.[4b] Subsequent conversion to oxazaborolidine (**6**) requires heating the THF solution under pressure (1.7 bar) at 70-75 °C for 48-72 h. Corey isolated and characterized free oxazaborolidine (**6**) as a solid (mp 107-124 °C), which was reported to be a mixture of monomer and dimer (NMR).[3a] Finally, addition of borane-THF to a solution of oxazaborolidine (**6**) affords oxazaborolidine-borane complex (**7**) which was not isolated and was identified based on ^{11}B NMR evidence.

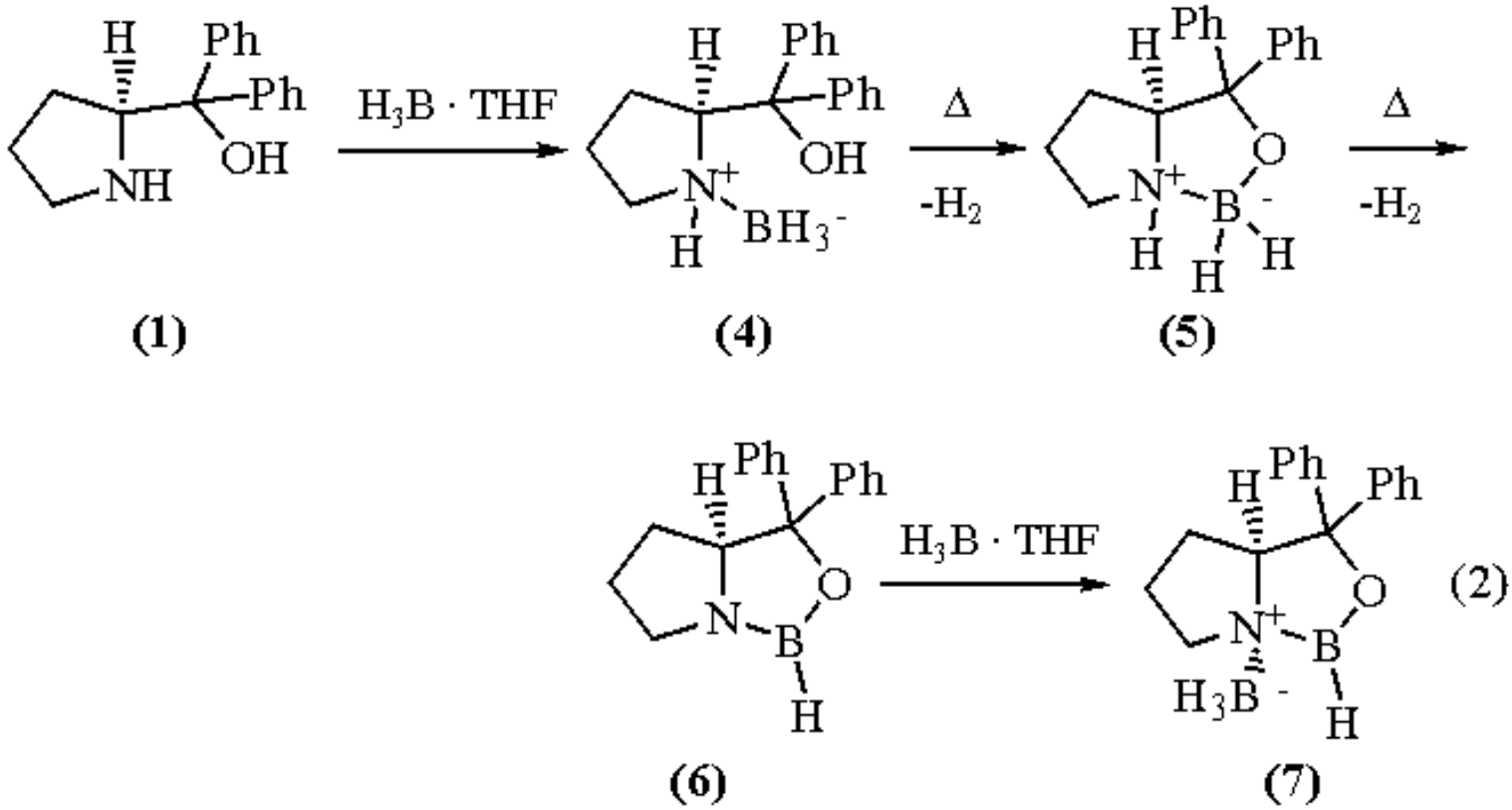

Corey demonstrated that oxazaborolidine (**6**) can be used catalytically (2.5-100 mol %) with excess borane (60-200 mol %) for the enantioselective reduction of prochiral ketones (eq 3 Table 1).[3a,c]

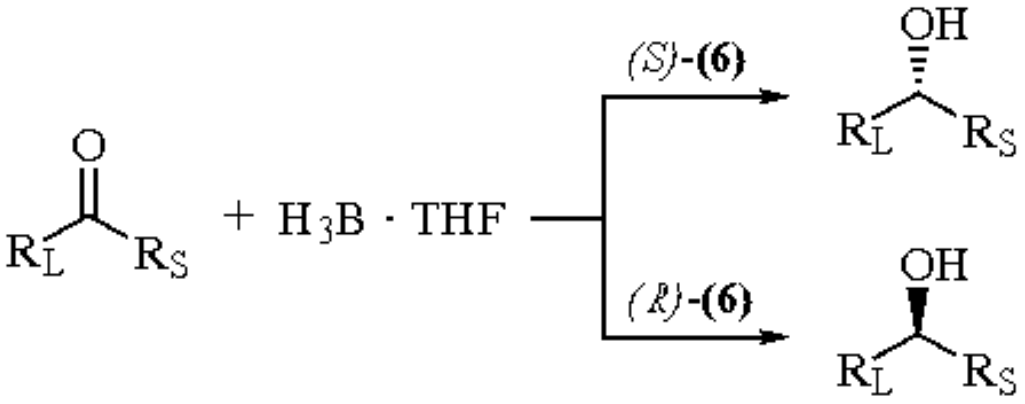

(3)

Table 1 Catalytic Enantioselective Reduction of Ketones using Oxazaborolidine (*S*)-(**6**)

Ketone	$H_3B{\cdot}THF$ (mol %)	Catalyst (*S*)-(**6**) (mol %)	Enantio-meric purity[a]	Absolute configuration
PhCOMe	100	10	97%	(*R*)
PhCOEt	60	5	90%	(*R*)
t-BuCOMe	60	10	92%	(*R*)
1-Tetralone	60	5	89%	(*R*)
$PhCOCH_2Cl$	60	5	97%	(*S*)

[a] Enantiomeric purities determined by capillary GC analysis of the (-)-menthyloxycarbonyl derivative, and have been corrected by adding 1% to the experimentally observed values to correspond to values for optically pure catalyst.[3a]

The following catalytic cycle was proposed to explain the behavior of the oxazaborolidine catalyst (eq 4).[3a,11] Oxazaborolidine (**6**) reacts with borane to give oxazaborolidine-borane complex (**7**). Coordination between the Lewis acidic ring boron and the carbonyl oxygen activates the ketone toward reduction. Intramolecular hydride transfer from the BH_3 coordinated to the ring nitrogen then occurs via a six-membered ring chair transition state.[12] Following hydride transfer, the alkoxy-BH_2 dissociates, and oxazaborolidine (**6**) is free to begin the cycle again. For a more detailed discussion, see the entry for ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***.

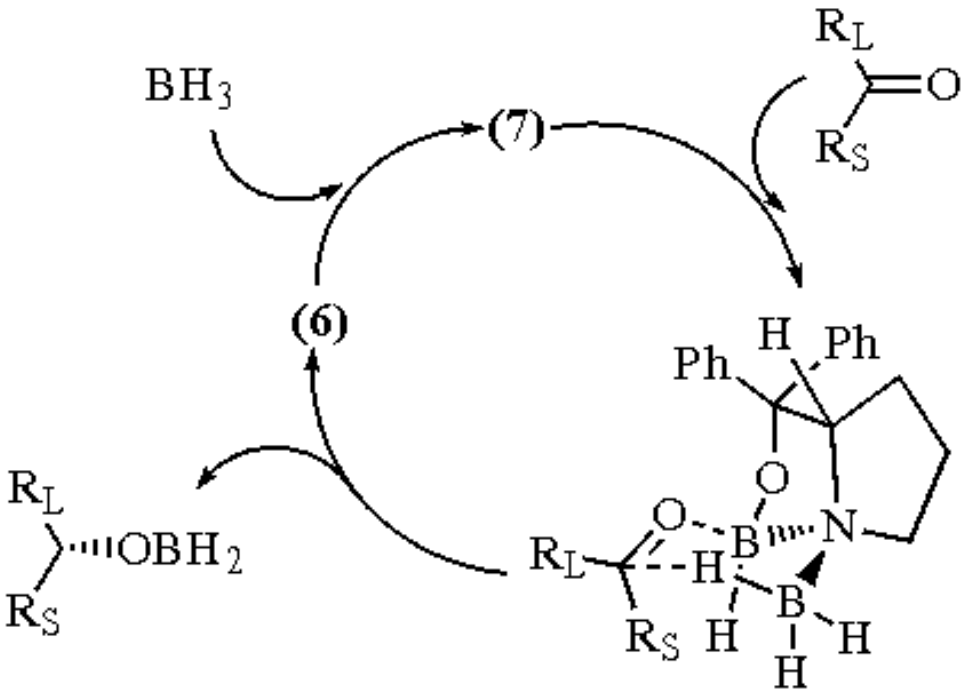

(4)

Problems with the preparation and stability of oxazaborolidine (**6**) led to the development of a series of *B*-substituted oxazaborolidines derived from diphenylprolinol. The *B*-methyl substituted oxazaborolidine (**9a**) was first prepared (eq 5) by reaction of diphenylprolinol (**1**) with methylboronic acid under dehydrating conditions (toluene at 23 °C in the presence of 4 Å molecular sieves or toluene at reflux using a Dean-Stark trap) followed by vacuum distillation (0.1 mmHg, 170 °C)[3a,c] Based on NMR evidence, the product (mp 74-87 °C) was reported to be a mixture of monomer and dimer.[3a] The corresponding *B*-butyloxazaborolidine (**9c**), prepared in a similar manner from *n*-butylboronic acid, was also reported to be a mixture of monomer and dimer.[13] Subsequent investigations demonstrated that the reported dimers were in fact the intermediate (**8**) and the more stable disproportionation product (**10**) (eq 6).[4] Furthermore, the presence of (**8**) or (**10**) was demonstrated to be deleterious to the enantioselectivity of the catalyst.[14]

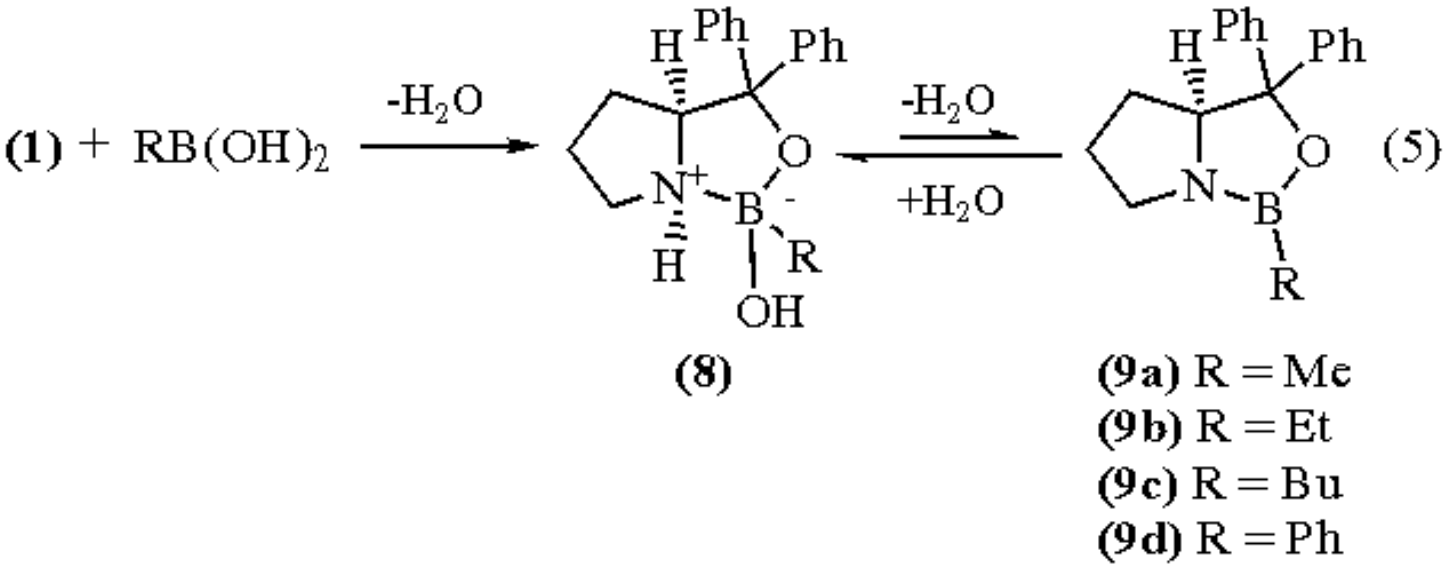

(5)

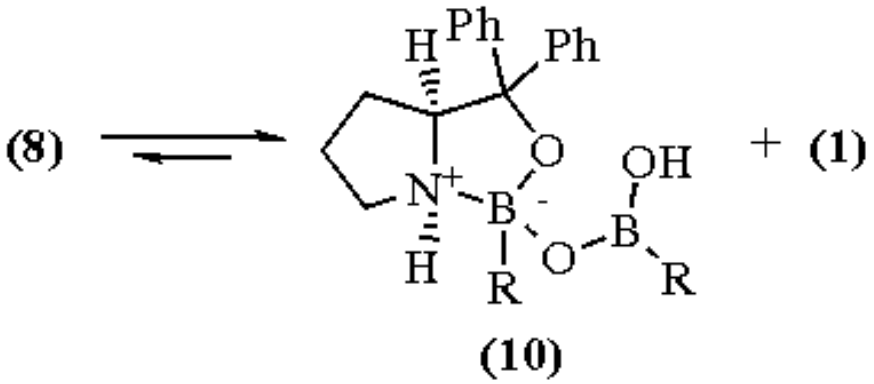

(6)

A small-scale procedure, based on the reaction of bis(trifluoroethyl) alkylboronates with diphenylprolinol (eq 7) was reported for the preparation of the *B*-ethyl- (**9b**) and *B*-butyl- (**9c**) oxazaborolidines.[15] The bis(trifluoroethyl) alkylboronates were prepared from the disproportionation of tris(trifluoroethyl) borate and the corresponding trialkylborane. Since trimethylborane is not commercially available, this procedure is not applicable for the preparation of *B*-methyloxazaborolidine (**9a**).

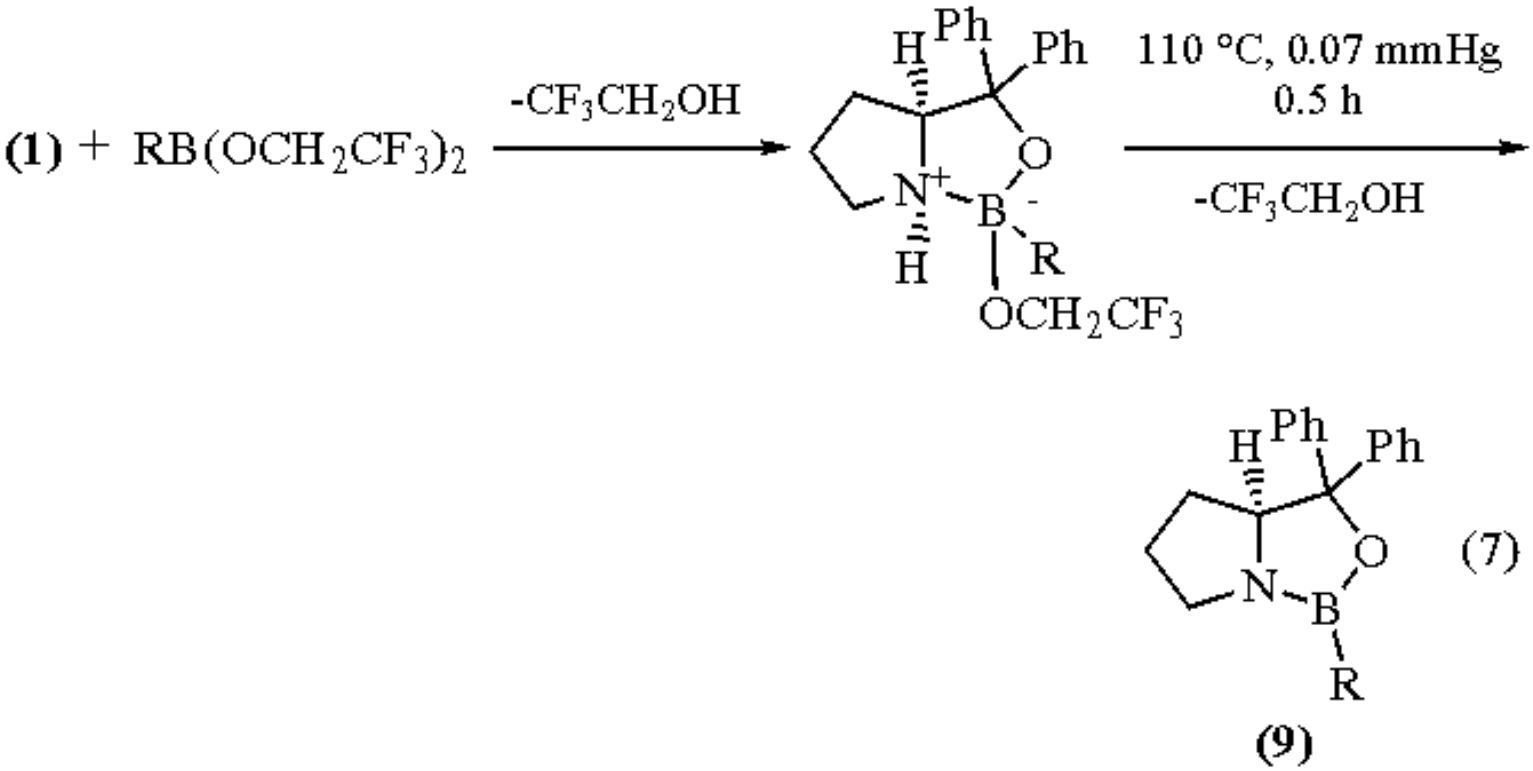

(7)

A practical large-scale process for the synthesis of *B*-methyloxazaborolidine (**9a**) was developed using commercially available trimethylboroxine (eq 8), which affords the product as an analytically pure, colorless crystalline solid (mp 79-81 °C).[4,16] The *B*-ethyl- (**9b**), *B*-butyl- (**9c**), and *B*-phenyloxazaborolidines (**9d**) were also prepared from the corresponding triethyl-, tributyl-, or triphenylboroxine. The free oxazaborolidines, thus prepared, are stable if rigorously protected from moisture.

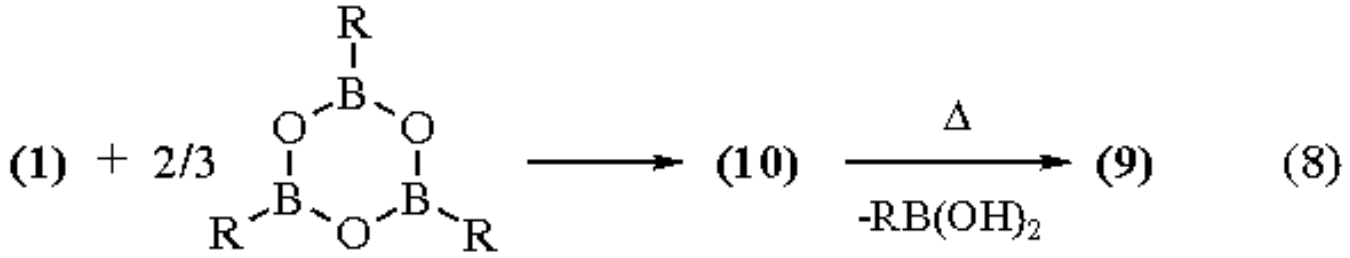

A significantly more stable form of the catalyst is the crystalline oxazaborolidine-borane complex (**11**).[4b,16,17] This borane complex is readily prepared from oxazaborolidine (**9a**) and ***Borane-Dimethyl Sulfide*** complex (BMS) (eq 9).

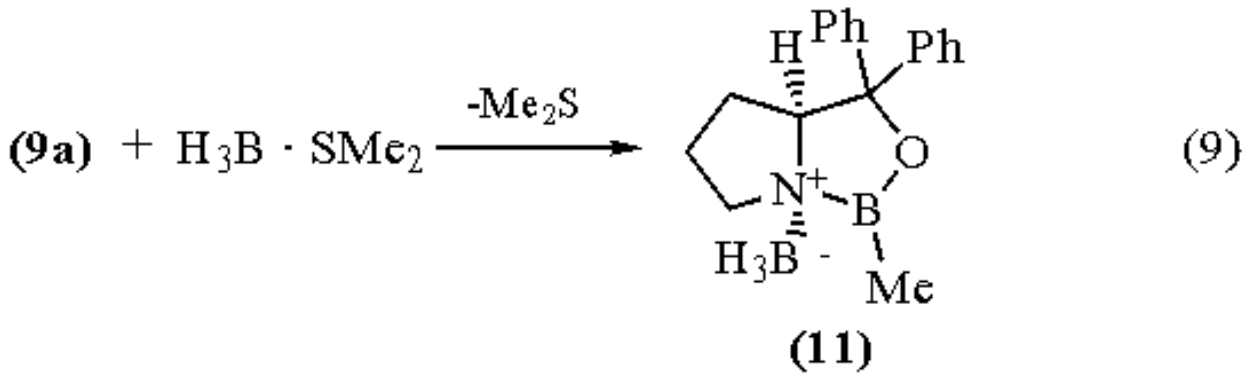

The enantioselectivities reported for the reduction of acetophenone and α-tetralone using the different catalysts (5-10 mol %) and borane-THF or BMS are summarized in Table 2. The best results are obtained by slowly adding the substrate (neat or as a solution in dichloromethane) to a solution of borane complex (**11**) (5 mol %) and BMS (0.6-1.0 mol equiv) in dichloromethane at -20 °C.[16]

Table 2 Enantioselective Reduction of Acetophenone and a-Tetralone

Catalyst	Prep.	mol %	Aceto-phenone	a-Tetralone
(**9a**) (R = Me)	eq 5	10	96.5% ee	83.3% ee
(**9a**) (R = Me)	eq 8	10	98% ee	94% ee
(**9b**) (R = Et)	eq 7	10	96% ee	
(**9c**) (R = Bu)	eq 7	10	96% ee	
(**9d**) (R = Ph)	eq 8	10	72% ee	94% ee
(**11**)	eqs 8 and 9	5	97.6% ee	99.2% ee
(**11**)	eqs 8 and 9	100	>99.8% ee	99.2% ee

In addition to these simple examples, oxazaborolidines derived from diphenylprolinol have been used as enantioselective catalysts for the preparation of prostaglandins,[3a] PAF antagonists,[3a] a key intermediate of ginkgolide B,[18] a key intermediate of forskolin,[19] (*R*)- and (*S*)-fluoxetine,[20] (*R*)- and (*S*)-isopreterenol,[21] vitamin D analogs,[22] the carbonic anhydrase inhibitor MK-0417,[14] the dopamine D1 agonist A-77636,[23] taxol,[24] the LTD_4 antagonists L-695,499 and L-699,392,[25] the β-adenergic agonist CL 316,243,[26] and MK-0499.[27] Recently, Bringmann employed oxazaborolidines (**9a**) and (**9c**) to catalyze the atropo-enantioselective ring opening of achiral biaryl lactones (eq 10).[28]

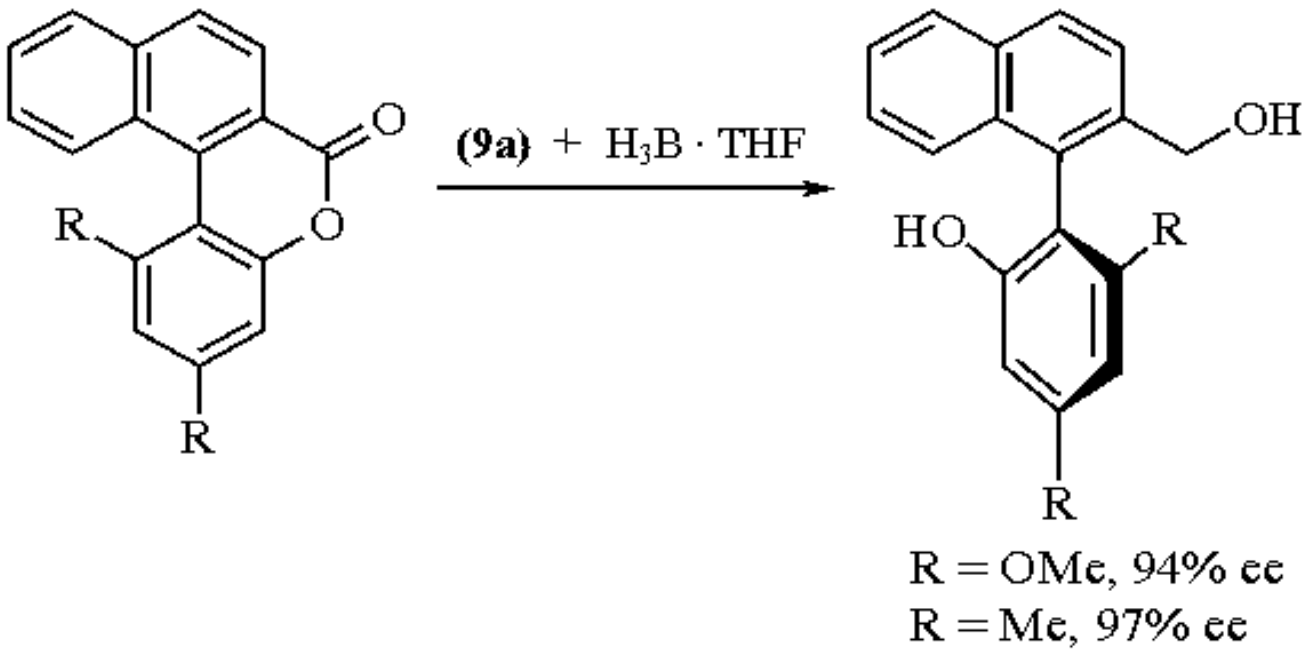

(10)

Related Reagents.

2-Amino-3-methyl-1,1-diphenyl-1-butanol; ***Ephedrine-borane***; ***Norephedrine-Borane***; ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***.

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Diphenylselenium Bis(trifluoroacetate)

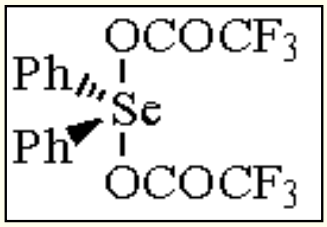

[42572-21-4] · $C_{16}H_{10}F_6O_4Se$ · Diphenylselenium Bis(trifluoroacetate) · (MW 459.22)

(two-electron oxidant for phenolic compounds and amines under nonaqueous conditions; source of diphenylselenonium cations in reactions with certain phenols)

Physical Data: mp 175-176 °C.

Solubility: very sol dimethoxyethane, methylene chloride; reacts with protic or nucleophilic solvents.

Form Supplied in: colorless solid; not commercially available.

Analysis of Reagent Purity: mp, IR, and elemental analysis.

Preparative Method: predried diphenyl selenoxide (0.001 mol) is dissolved in 10 mL of dry dimethoxyethane and 0.15 mL (0.001 mol) of freshly distilled ***Trifluoroacetic Anhydride*** is added by syringe. After the reaction mixture has been stirred for 15 min at 0 °C, the solvent is removed in vacuo to give a white solid (eq 1).[1]

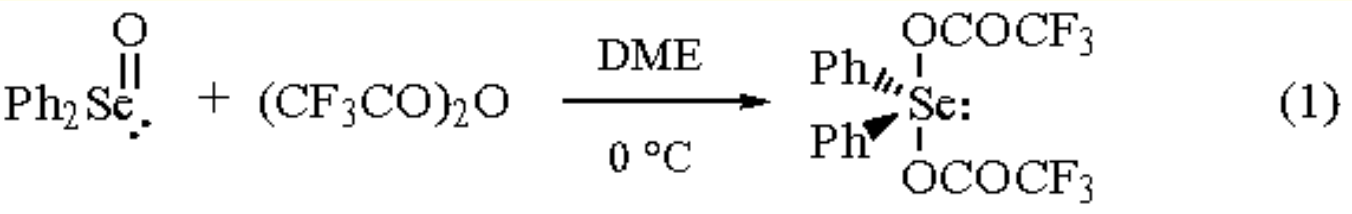

Handling, Storage, and Precautions: thermally stable, but very hygroscopic. While the reagent may be isolated in an inert atmosphere, it is most conveniently used by generating it in situ. This reagent should be handled in a fume hood.

Structure and Properties of the Reagent.

By analogy to other tetrasubstituted sulfuranes and selenuranes,[2] the diphenylselenium bis(trifluoroacetate) reagent is believed to exist in a trigonal bipyramidal geometry in which the trifluoroacetoxy groups assume the apical positions.[3]

The covalent and symmetrical selenurane structure is confirmed by the normal IR absorption for the acyl groups (1738, 1718 cm^{-1}) and the singlet ^{19}F NMR absorption at 2.0 ppm downfield from an external trifluoroacetic acid standard. While the reagent is highly hygroscopic, it can easily be handled to obtain an elemental analysis.

Oxidations of Phenolic Compounds.

The title reagent serves as a mild two-electron oxidant for phenols and catechols. The presence of the two trifluoroacetates as leaving groups in the reagent provide a facile exchange mechanism for the incorporation of nucleophiles. There are three modes of oxidation observed for phenols with this reagent: phenolic coupling, benzylic oxidation, and hydroxylation. Some of the prime advantages of this reagent over the more traditional metal oxidants for oxidations of phenols include the homogeneous nature of the reagent in organic solvents, the stoichiometric control of oxidation, and the selectivity found for the oxidation sites. As a typical oxidation process for phenols, 2,6-dimethylphenol undergoes a clean *para-para* oxidative coupling with subsequent oxidation of the hydroquinone with 2 equiv of the reagent at rt (eq 2).[1]

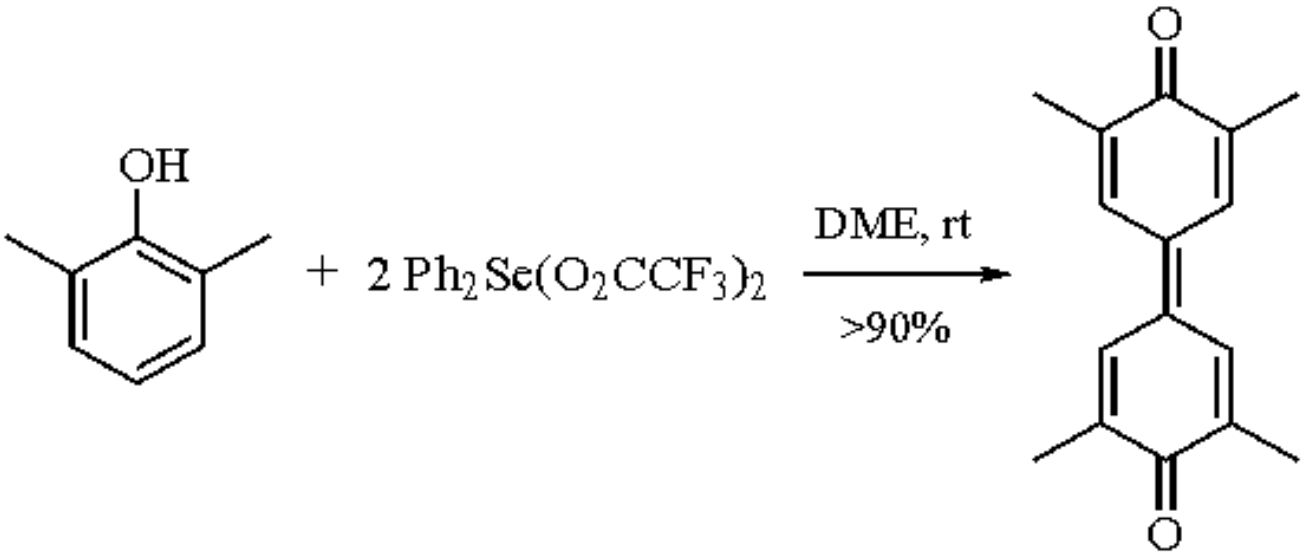

(2)

The coupling reaction (eq 2) occurs exclusively when the oxidizing reagent is added to the phenol. In contrast, when the phenol is added to a solution of the oxidant at rt, the major oxidation pathway involves *para*-hydroxylation and subsequent oxidation to yield 2,6-dimethylbenzoquinone (eq 3). This process involves a unique nucleophilic addition of trifluoroacetate to an aromatic ring.

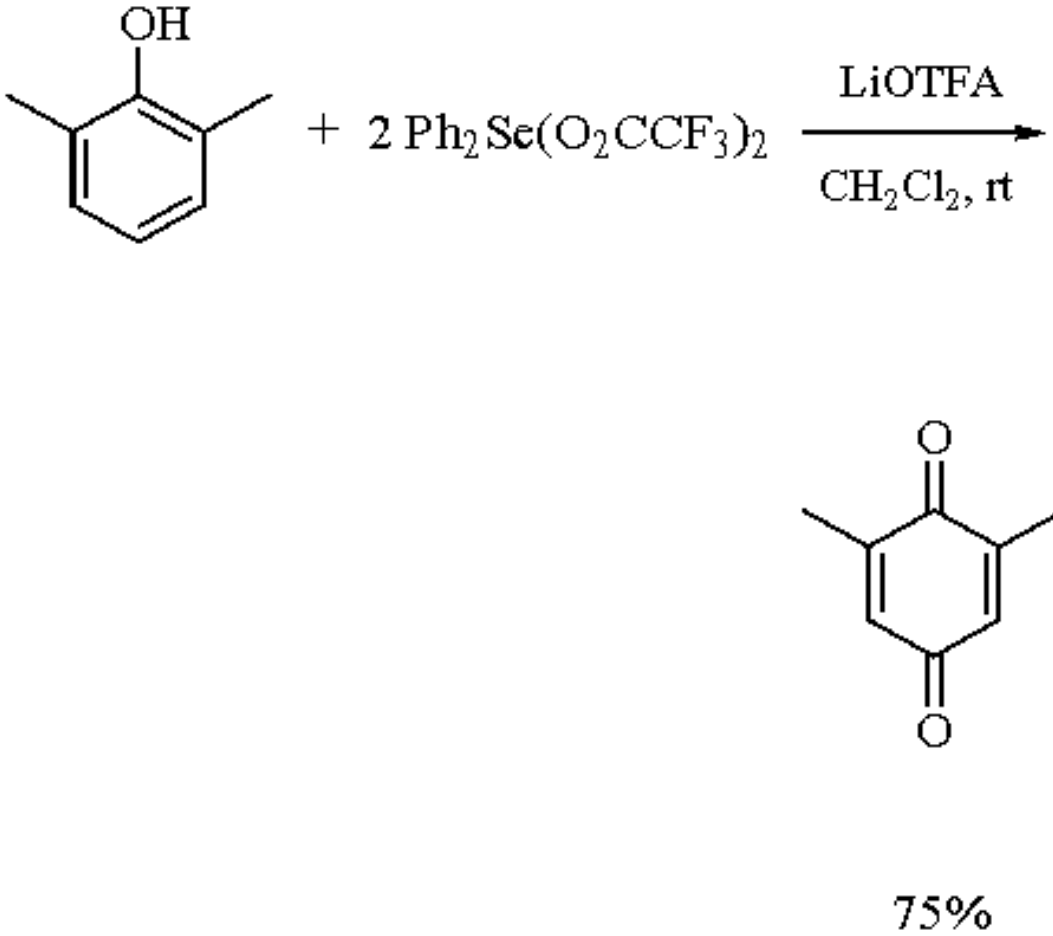

(3)

The mechanistic interpretation of these reactions involves the initial ligand exchange of a trifluoroacetate for the phenol. The newly formed aryloxyselenurane is an activated aromatic ring susceptible to nucleophilic attack either by another phenol (eq 2) or the trifluoroacetate anion (eq 3). The latter process is accentuated by an increase of the *p*-benzoquinone product when additional lithium trifluoroacetate is added to the reaction solution (eq 4).[1]

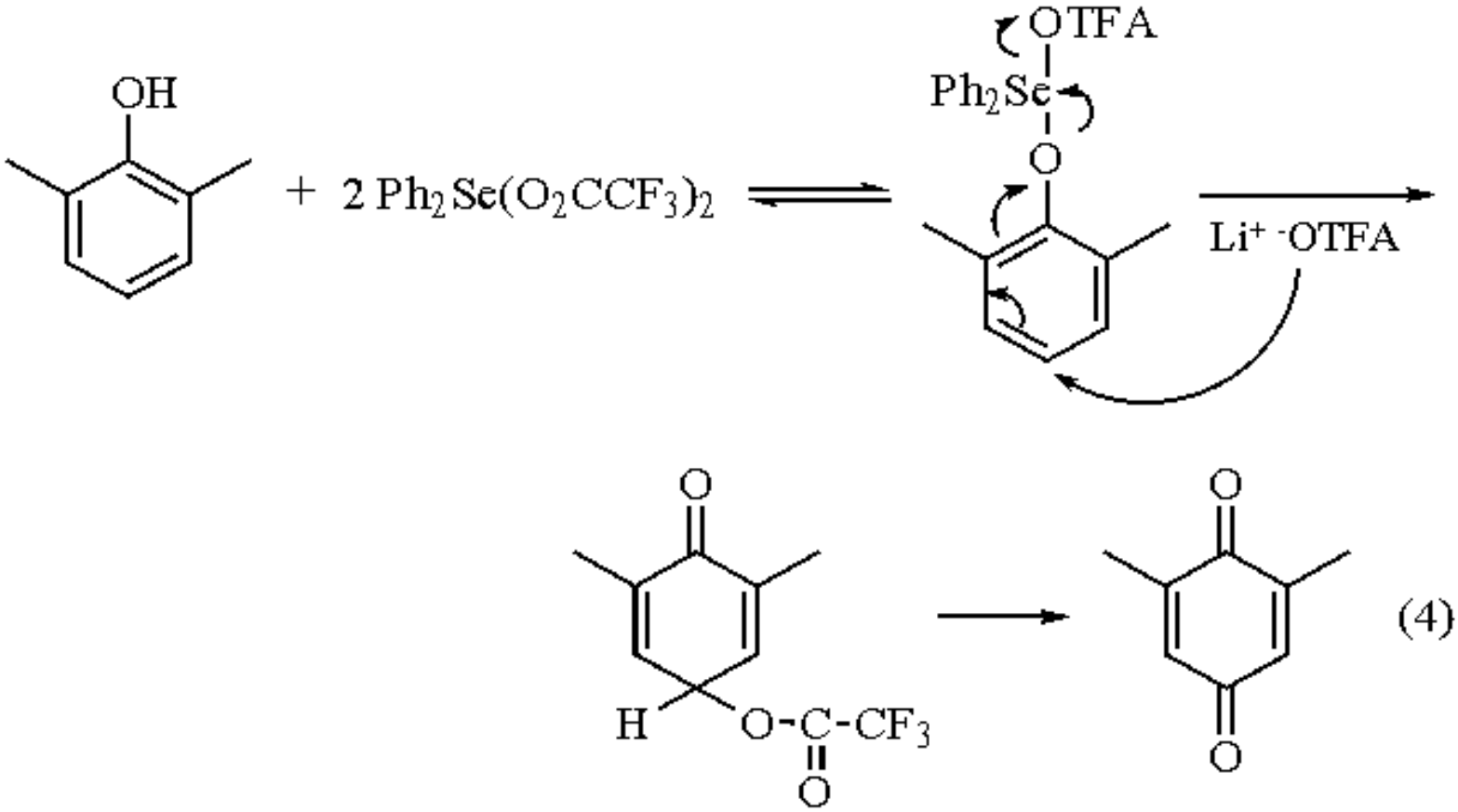

Other phenols that undergo the *para*-oxidation to form benzoquinones include thymol (eq 5) and 3,5-dimethylphenol (eq 6).

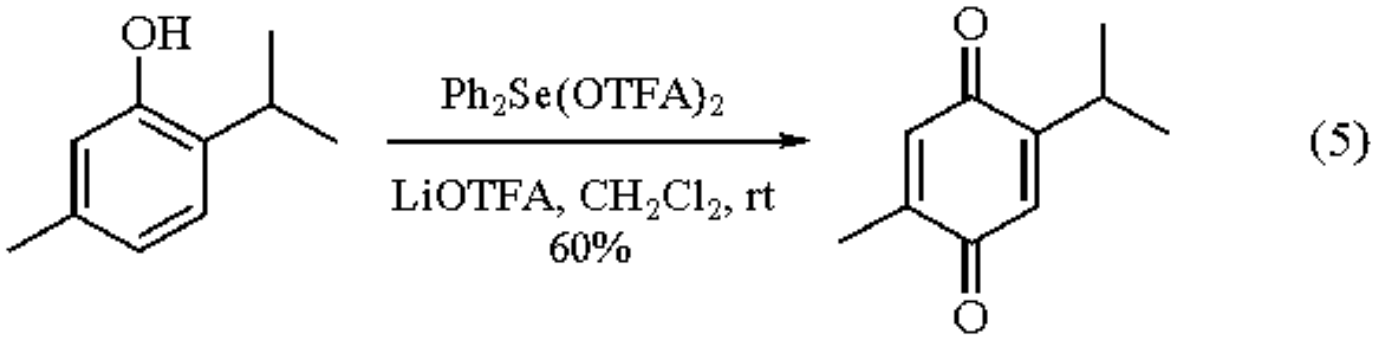

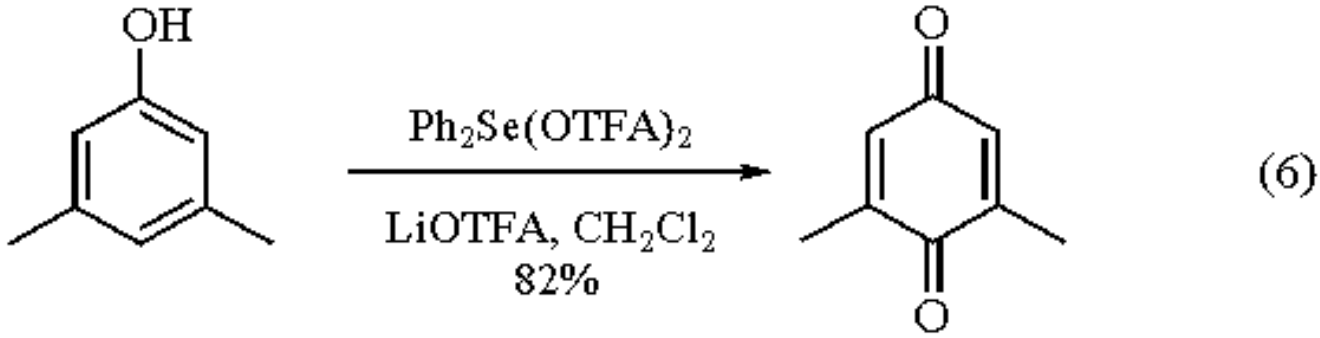

Intramolecular phenolic coupling reactions are also possible with the title reagent. At low temperatures the diphenolic compound in eq 7 undergoes oxidative coupling to produce the spirodienone product.

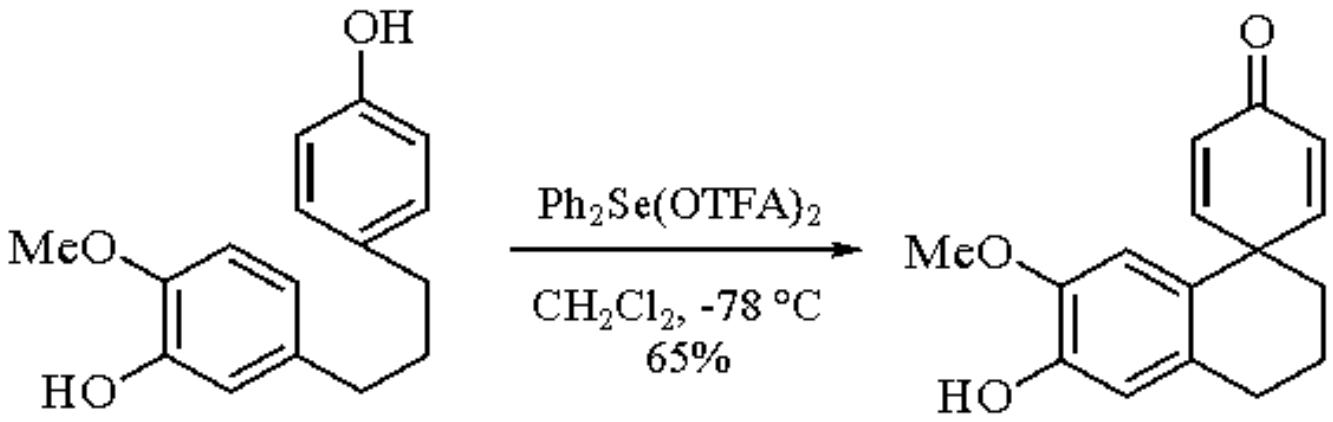

(7)

Applications of the diphenylselenium bis(trifluoroacetate) reagent to the synthesis of tetrahydrobenzylisoquinoline alkaloids have revealed some very selective and clean benzylic oxidative processes. In the tetrahydroisoquinoline system of eq 8, the benzylic carbon *para* to the free phenol is initially oxidized to the *para*-quinone methide which rapidly isomerizes to the dihydroisoquinoline system.[1]

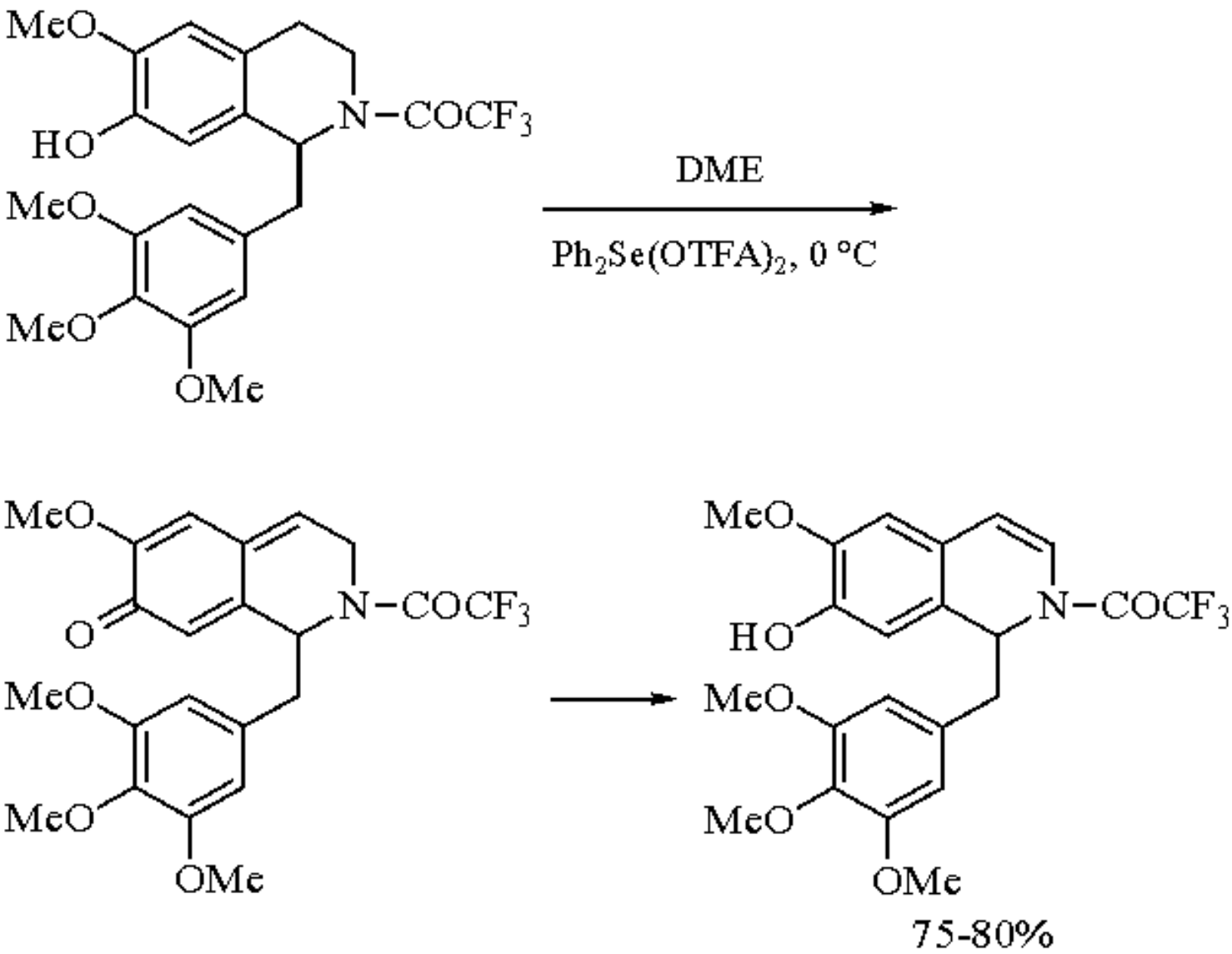

(8)

Oxidations of Heterocyclic Amines.

The diphenylselenium bis(trifluoroacetate) reagent is a powerful two-electron oxidant for primary, secondary, and tertiary amines. In the tetrahydroisoquinoline system, the major oxidation products are the imines (eq 9).[4] In some cases (R = Me), a minor reaction product is the fully oxidized quinoline (10%). Thus the controlled oxidation of a secondary amine to an imine can be effected under very mild conditions.[5] When tertiary amines are oxidized with the reagent, regiospecific iminium ions are formed under nonaqueous conditions. Workup of this reaction with cyanide salts gives rise to the well-known Reissert compounds (eq 10).[4]

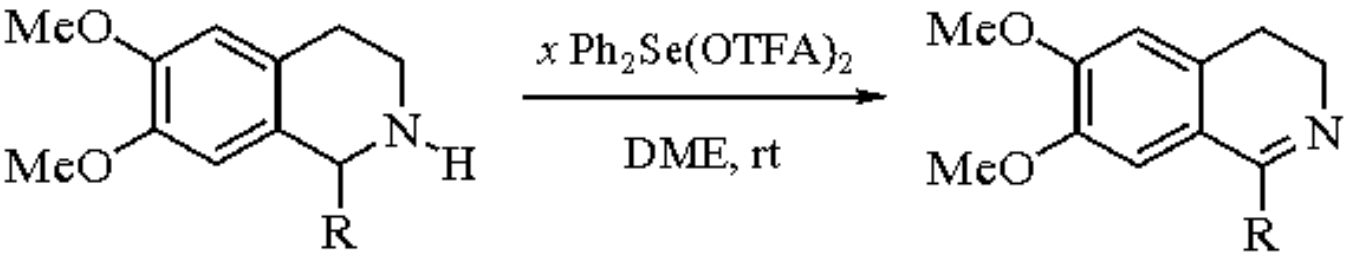

(9)

R = H	x = 2 equiv	80%
R = Me	x = 3 equiv	81%
R = CO_2H	x = 2 equiv	100%

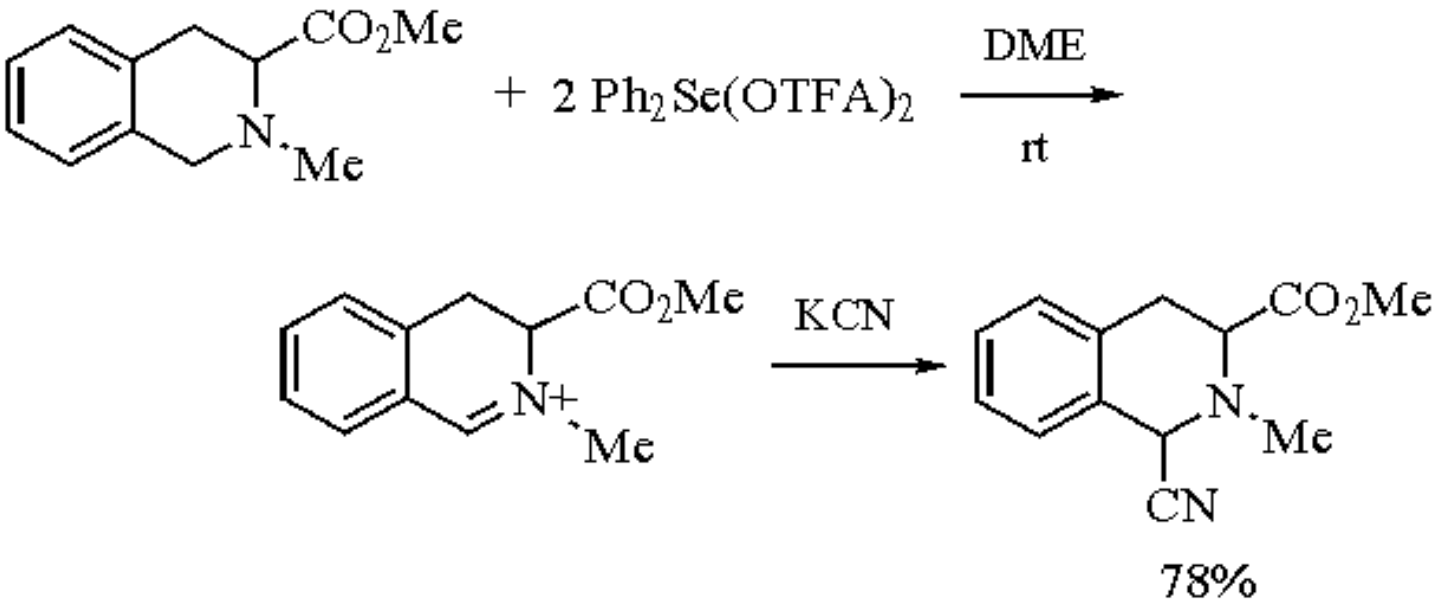

(10)

Transfer of Diphenylselenonium Cations.

In systems where phenolic coupling, benzylic oxidation, or hydroxylation processes are restricted, reactions of the reagent with certain phenols yield selenonium phenoxides or rearrangement products. For example, estrone is converted to its *ortho*-diphenylselenonium zwitterion with 1 equiv of the reagent (eq 11).[1]

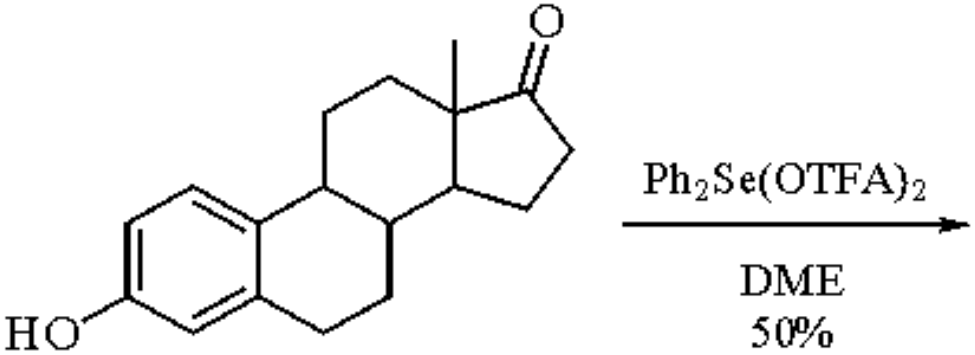

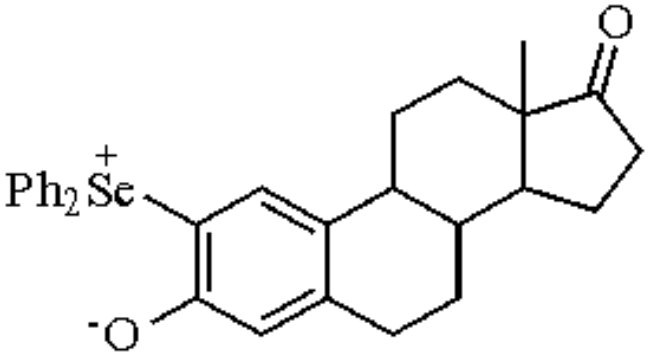

(11)

A similar *ortho*-selenonium phenoxide was observed in the reaction of the trisubstituted phenol shown in eq 12, accompanied by an unusual rearrangement product of the zwitterion.[6] The phenoxide zwitterion is a precursor to the diaryl ether.

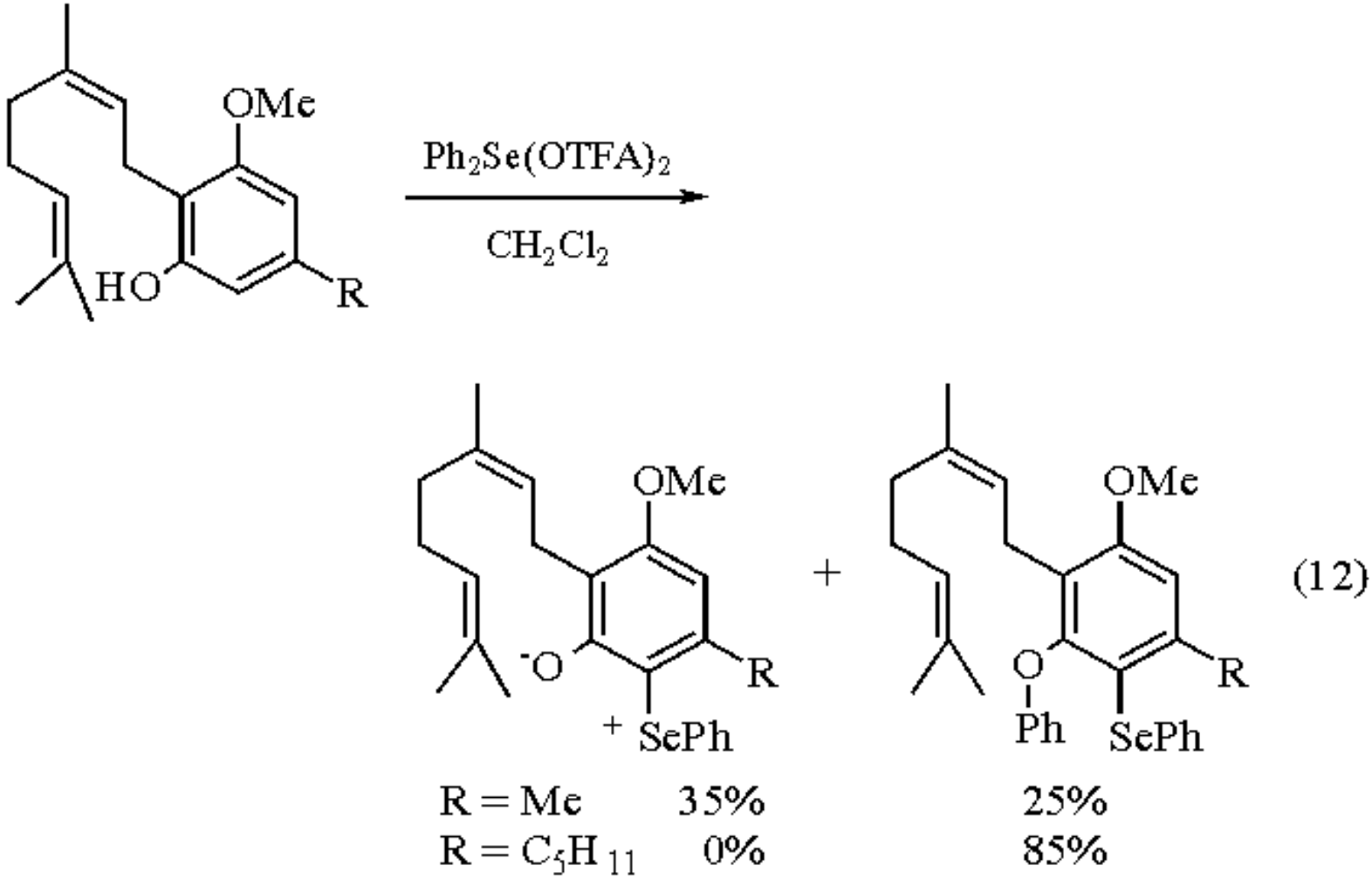

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1. Schwartz, A. Ph.D. Thesis, University of Michigan, 1978.
2. The title reagent was first reported by Paetzold, but there was no characterization of the compound: Horn, V.; Paetzold, R. *Z. Anorg. Allg. Chem.* **1973**, *398*, 186.
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4. Marino, J. P.; Larsen, R. D., Jr. *JACS* **1981**, *103*, 4642.
5. Larsen, R. D., Jr. Ph.D. Thesis, University of Michigan, 1982.
6. Marino, J. P.; Dax, S. *TL* **1987**, *28*, 4007.

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Diphenylsilane-Cesium Fluoride

Ph_2SiH_2-CsF

Ph_2SiH_2

[775-12-2] · $C_{12}H_{12}Si$ · Diphenylsilane-Cesium Fluoride · (MW 184.33) CsF

[13400-13-0] · CsF · Diphenylsilane-Cesium Fluoride · (MW 151.91)

(reagent for the reduction of aldehydes,[1,2] ketones,[1,2] and esters;[3] selective 1,2-reduction of enones[2,4] and enals[2,4])

Physical Data: Ph_2SiH_2: bp 95-97 °C; *d* 0.993 g cm^{-3}. CsF: mp 683 °C.

Solubility: Ph_2SiH_2: sol THF. CsF: sol H_2O; slightly sol THF, MeCN.

Form Supplied in: Ph_2SiH_2: clear liquid; widely available. CsF: white solid; widely available.
Drying: anhydrous CsF is prepared by flame drying under vacuum, taking care not to fuse the salt.

Handling, Storage, and Precautions: Ph_2SiH_2 should be used in a fume hood.

Carbonyl Reduction.

The Ph_2SiH_2-CsF reagent can reduce neat aldehydes and ketones to alcohols at 25 °C in <30 min[1,2] (eq 1), though ***Triethoxysilane*** activated with either ***Cesium Fluoride*** or ***Potassium Fluoride*** is generally a better reagent for these solvent-free reductions.[4]

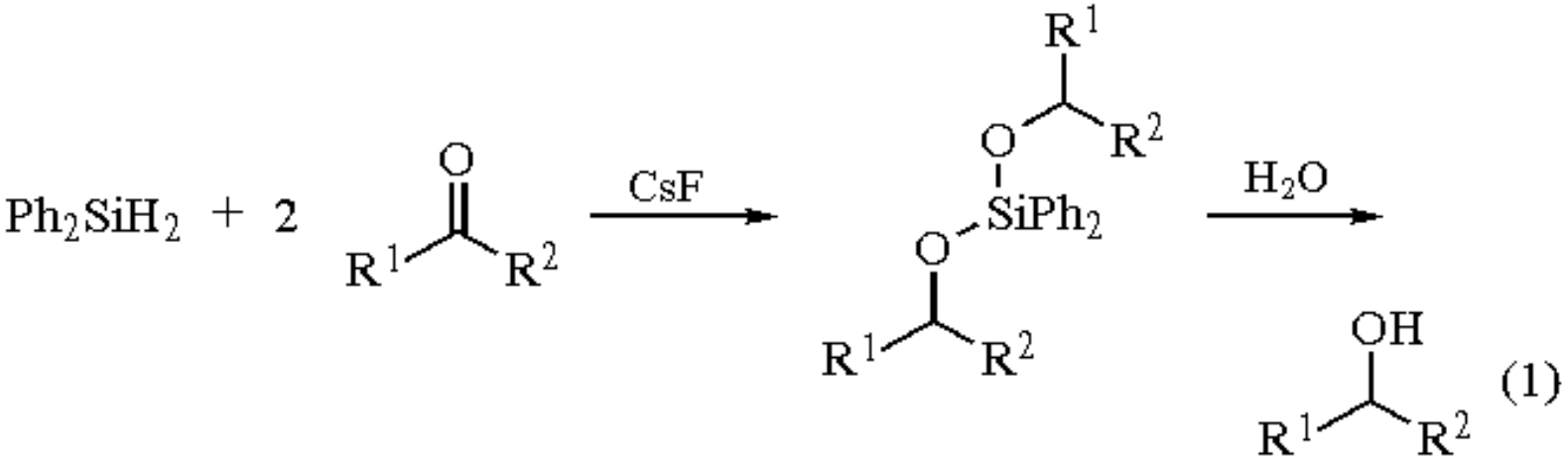

Esters can be reduced to alcohols with Ph_2SiH_2-CsF at elevated temperatures in 65-90% yield; however, the more reactive silane $(EtO)_3SiH$ with CsF activation will do the reduction at 25 °C.[3] Several enones and enals undergo selective 1,2-reduction with Ph_2SiH_2-CsF[2,4] (eq 2), although cyclohexenone reduction is not as selective and there is a tendency for overreduction to cyclohexanol to occur.[2]

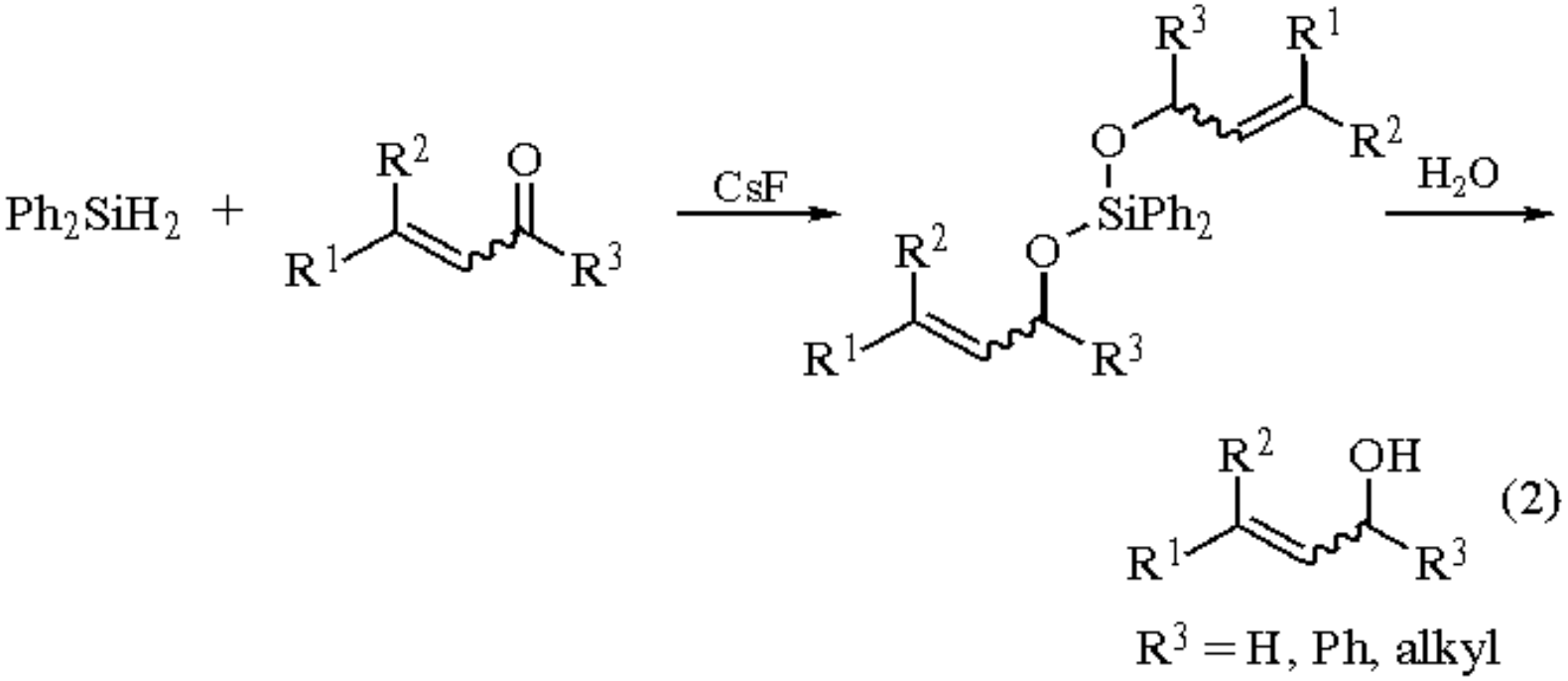

Related Reagents.

Phenylsilane-Cesium Fluoride; ***Triethoxysilane***; ***Triethylsilane***.

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1. Boyer, J.; Corriu, R. J. P; Perz, R.; Reye, C. *JOM* **1978**, *148*, C1. (*CA* **1978**, *89*, 23 216b).
2. Boyer, J.; Corriu, R. J. P; Perz, R.; Reye, C. *JOM* **1979**, *172*, 143. (*CA* **1979**, *91*, 108 039n).
3. Boyer, J.; Corriu, R. J. P.; Perz, R.; Poirier, M.; Reye, C. *S* **1981**, 558.
4. Corriu, R. J. P.; Perz, R.; Reye, C. *T* **1983**, *39*, 999.

Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride[1]

Ph_2SiH_2-$(Ph_3P)_4Pd$-$ZnCl_2$

(Ph_2SiH_2)

[775-12-2] · $C_{12}H_{12}Si$ · Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride · (MW 184.33) ($(Ph_3P)_4Pd$)

[14221-01-3] · $C_{72}H_{60}P_4Pd$ · Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride · (MW 1155.62) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride · (MW 136.29)

(mild reducing agent for the reduction of α,β-unsaturated systems[2] and allylic hetero substituents[7])

Physical Data: Ph_2SiH_2: bp 95-97 °C/13 mmHg; *d* 0.993 g cm^{-3}.

Solubility: Ph_2SiH_2: sol usual organic solvents; insol H_2O.

Form Supplied in: Ph_2SiH_2: liquid; widely available.

Handling, Storage, and Precautions: Ph_2SiH_2: irritant; avoid inhalation, ingestion, or skin contact. Use in a fume hood.

1,4-Reduction of α,β-Unsaturated Aldehydes and Ketones.[2]

α,β-Unsaturated aldehydes and ketones are readily reduced using a combination of diphenylsilane, ***Tetrakis(triphenylphosphine)palladium(0)***, and ***Zinc Chloride*** in chloroform at ambient temperature.[3] The reduction is highly chemoselective, occurring in a 1,4-fashion (eqs 1 and 2).[4] Although α,β-unsaturated esters, amides, and nitriles are reduced under these conditions, the reaction is much slower, allowing the possibility of selective reduction

of unsaturated aldehydes or ketones (eq 3).

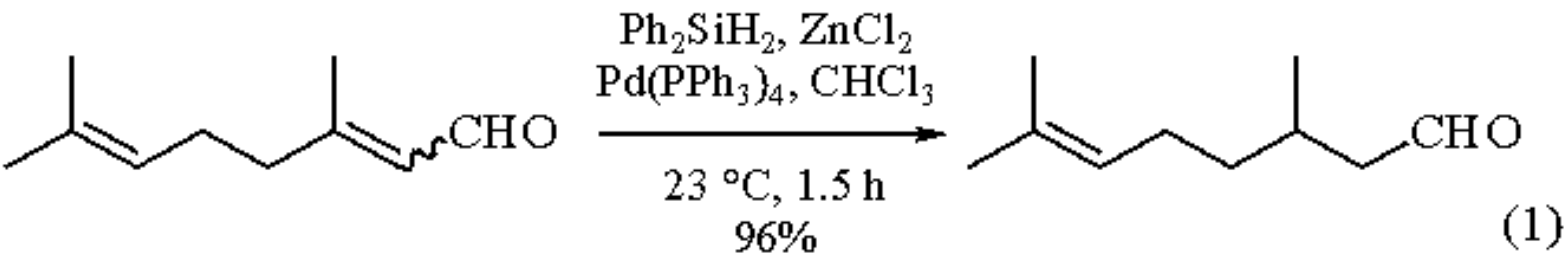

(1)

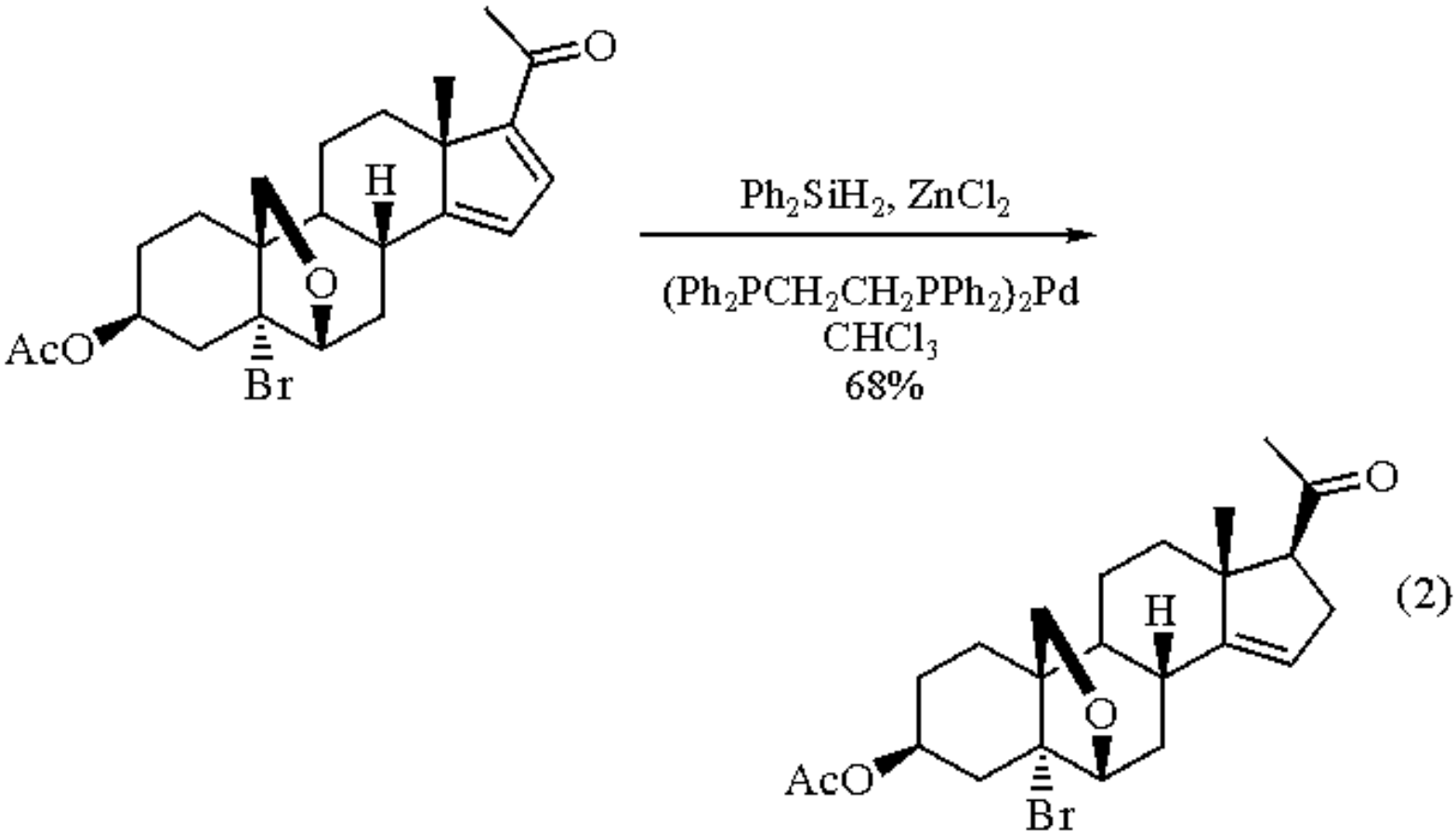

(2)

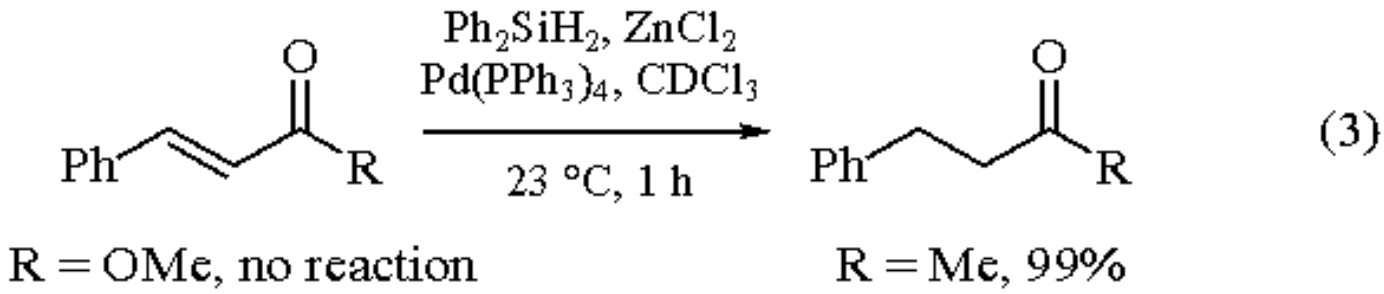

(3)

Typical reaction conditions employ a slight excess of diphenylsilane, 1-2% of the palladium catalyst, and 10-50% of zinc chloride. No special precautions such as dry or oxygen free conditions are required; this allows commercial solvents and wet zinc chloride to be used as supplied without purification. Anhydrous conditions have in fact been found to result in slower reaction rates.

The stereoselectivity of the reduction has been examined by the use of diphenyldideuteriosilane, which has shown that

deuterium is introduced from the least hindered face of the enone (eq 4).[2,5]

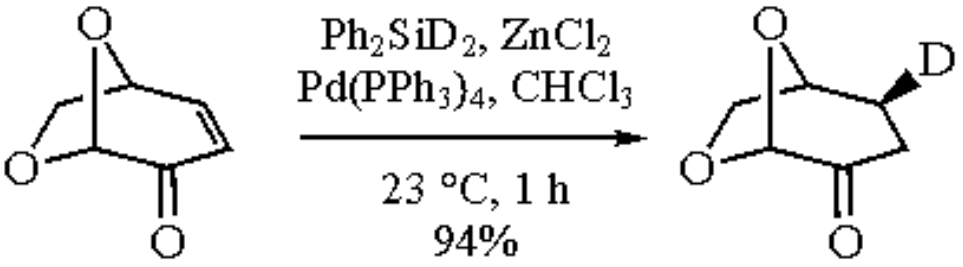

(4)

A variation on the above conditions involving the inclusion of a catalytic quantity of ***Copper(II) Chloride*** has been used by an Australian group to selectively reduce an α,β-unsaturated ketone in the presence of a vinylic phosphine oxide (eq 5).[6]

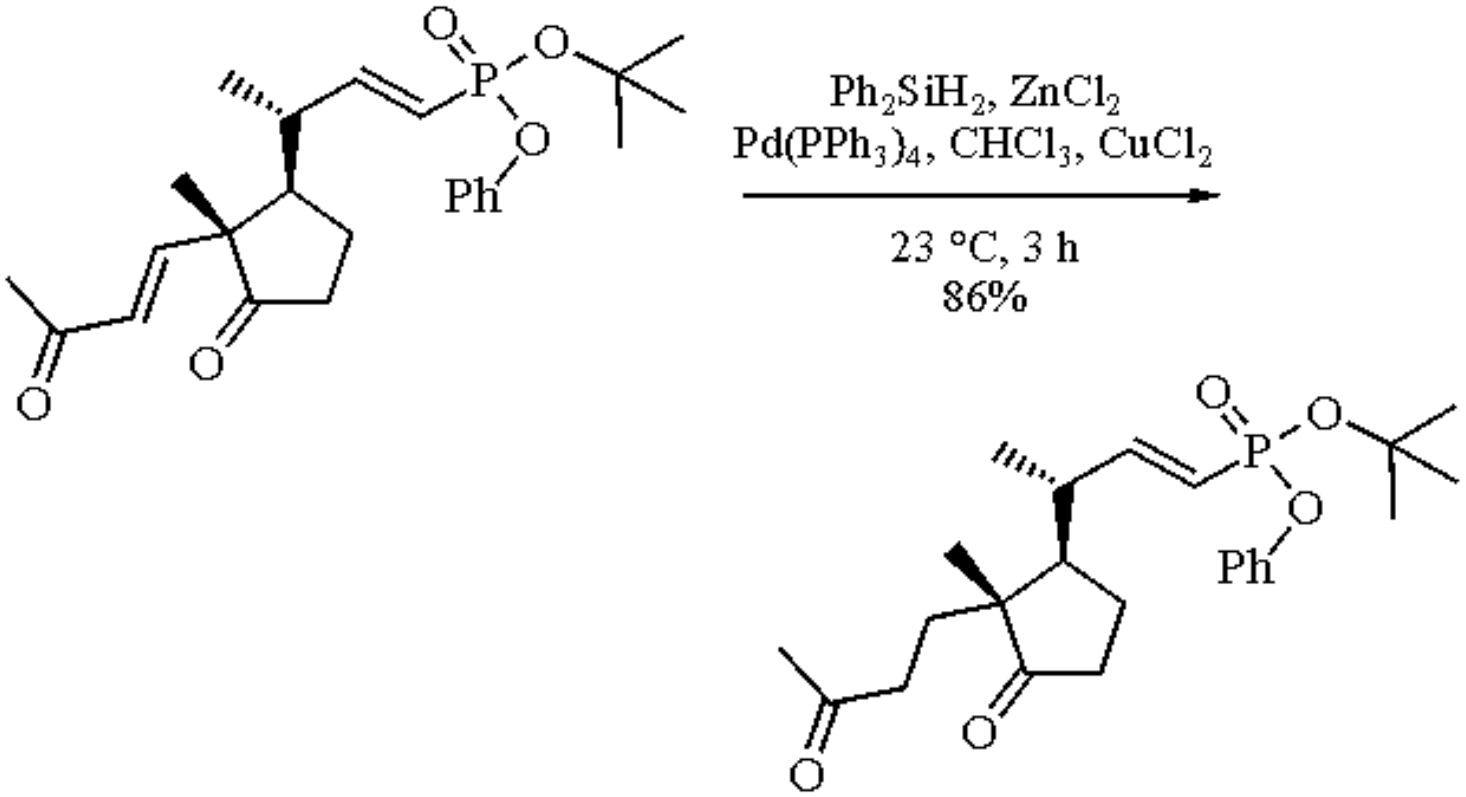

(5)

Allylic Reductions.

The reduction of allylic heterosubstituents can readily be achieved using the diphenylsilane-tetrakis(triphenylphosphine)palladium-zinc chloride system in THF (eq 6).[7] Reduction also occurs with diphenylsilane and tetrakis(triphenylphosphine)palladium alone, conditions that will not reduce α,β-unsaturated ketones. This provides a complementary chemoselectivity to that of the corresponding ***Tri-n-butylstannane*** system which favors reduction of the enone (eq 7).[8] The allylic displacement occurs with absolute inversion of configuration, consistent with a mechanism of palladium complexation from the opposite side to the leaving group followed by transfer of hydride to the ligand from palladium. An apparent exception to this was found when tri-*O*-acetylglucal was reduced under these conditions with retention of configuration. This has been explained by a neighboring group participation by the 4-acetoxy substituent.[9]

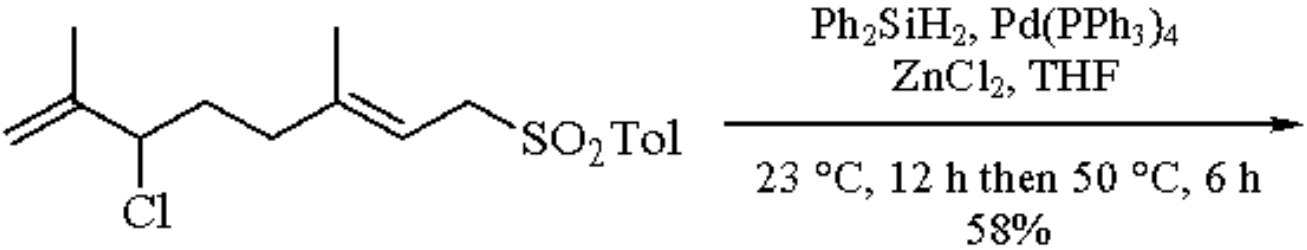

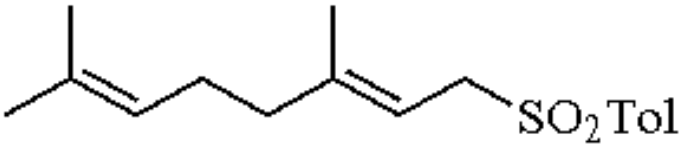

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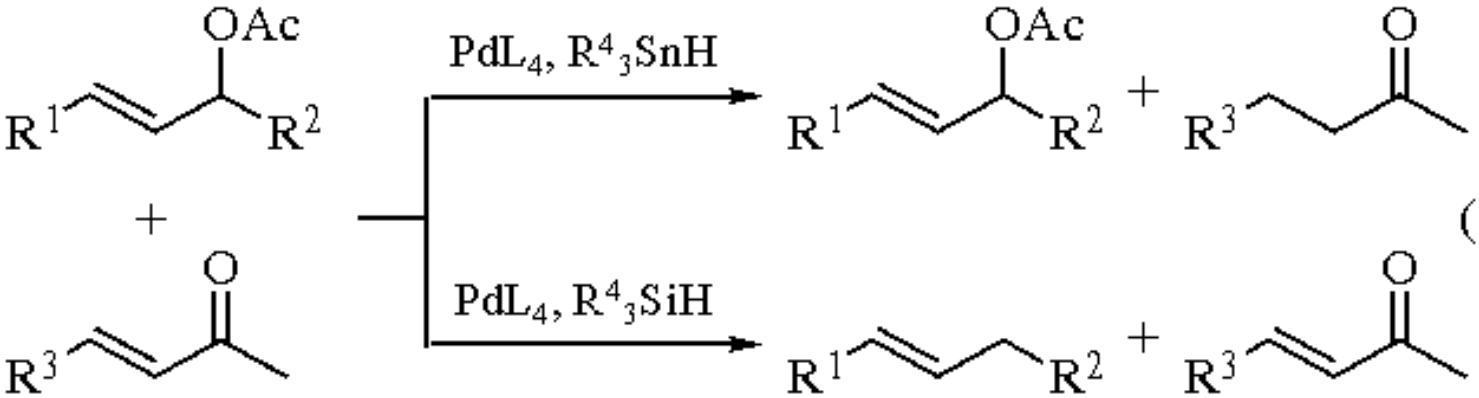

(7)

Related Reagents.

Palladium(II) Hydroxide; ***Tri-n-butylstannane***.

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1. Keinan, E.; Greenspoon, N. *COS* **1991**, *8*, 546.
2. Keinan, E.; Greenspoon, N. *JACS* **1986**, *108*, 7314.
3. (a) Archer, D. A.; Bromidge, S. M.; Sammes, P. G. *JCS(P1)* **1988**, 3223. (b) Pietrusiewicz, K. M.; Salamonczyk, I. *JOC* **1988**, *53*, 2837. (c) Asaoka, M.; Sonoda, S.; Takei, H. *CL* **1989**, 1847.
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8. Keinan, E. *PAC* **1989**, *61*, 1737.
9. Keinan, E.; Greenspoon, N. *JOC* **1988**, *53*, 3723.

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S,S-Diphenylsulfilimine[1]

$Ph_2S{=}NH.H_2O$

(monohydrate)

[68837-61-6] · $C_{12}H_{13}NOS$ · *S,S*-Diphenylsulfilimine · (MW 219.33) (anhydrous)

[36744-90-8] · $C_{12}H_{11}NS$ · *S,S*-Diphenylsulfilimine · (MW 201.31)

(nucleophilic imino transfer reagent;[2-5] one-step conversion of aldehydes to nitriles;[6,7] synthesis of nitrogen compounds from *N*-substituted diphenylsulfilimines;[8-11] synthetic intermediate for organic sulfur compounds[12-17])

Physical Data: mp 70-71 °C; pK_a 8.56.[2]

Solubility: slightly sol H_2O, hexane; sol alcohol, benzene, THF, chloroform, acetone.

Form Supplied in: white needles; commercially available.

Analysis of Reagent Purity: IR: S=N 940 cm^{-1} (monohydrate), 910 cm^{-1} (anhydrous); titration.

Purification: the sulfilimine is dissolved in 3% aqueous sulfuric acid. The aq solution is treated with charcoal and then made alkaline under ice-cooling to precipitate the sulfilimine, which is recrystallized from benzene or benzene-hexane.

Handling, Storage, and Precautions: for most purposes the monohydrate is utilized without dehydration; store in the dark; storage at rt for several months causes a smell of diphenyl sulfide; decomposes at 100 °C without solvent; anhydrous sulfilimine is hygroscopic; use in a fume hood.

Nucleophilic Imino Transfer Reagent.

Conjugate addition of Ph_2SNH to β-substituted α,β-unsaturated ketones gives the imino transfer products, *N*-unsubstituted 2-acylaziridines or 2-acyl-1-aminoethylenes (enamines) or both compounds (eqs 1-3).[2-5] Optically active 2-acylaziridines can be synthesized using optically active *S*-(*o*-methoxyphenyl)-*S*-phenylsulfilimine by asymmetric induction.[2]

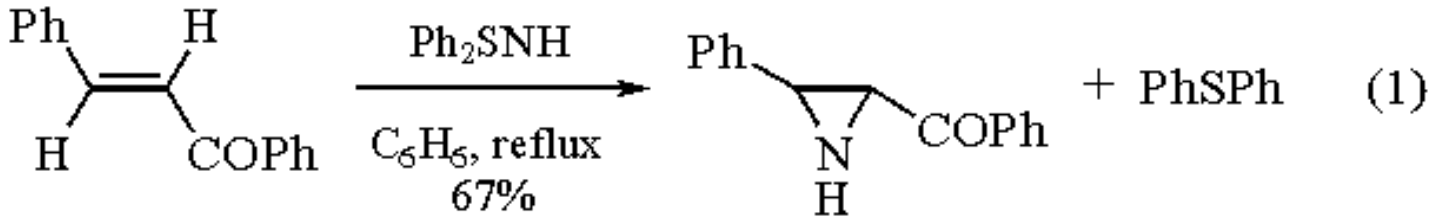

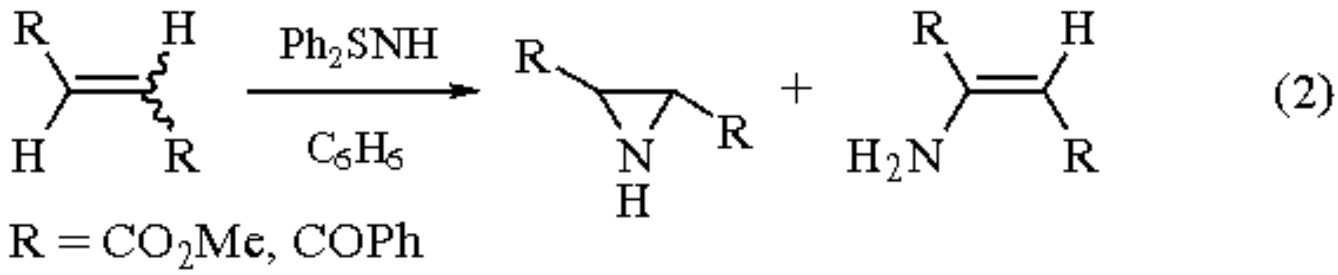

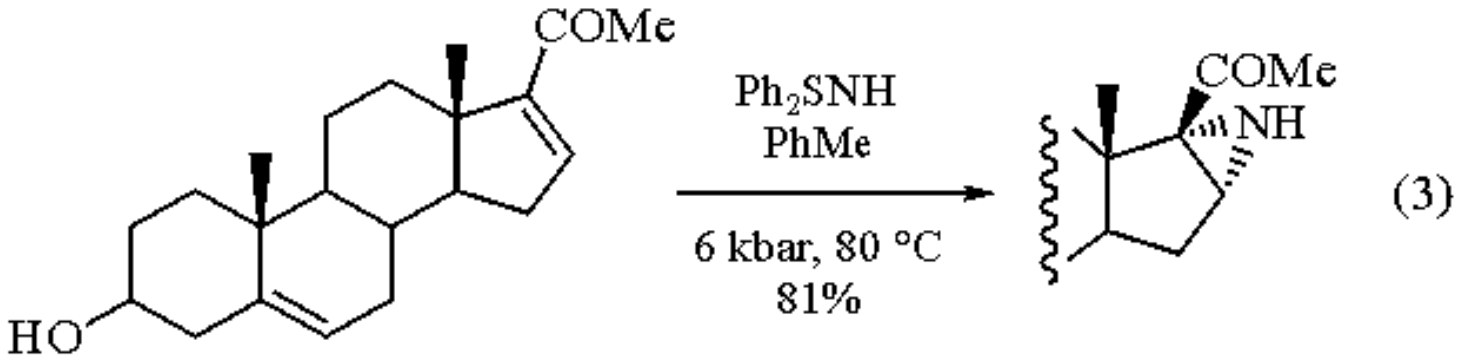

S,*S*-Diphenyl-*N*-(2-benzoylethenyl)sulfilimines, obtained from addition with benzoylalkynes, undergo pyrolysis to afford 3-substituted 5-phenylisoxazoles in good yields (eq 4).[3]

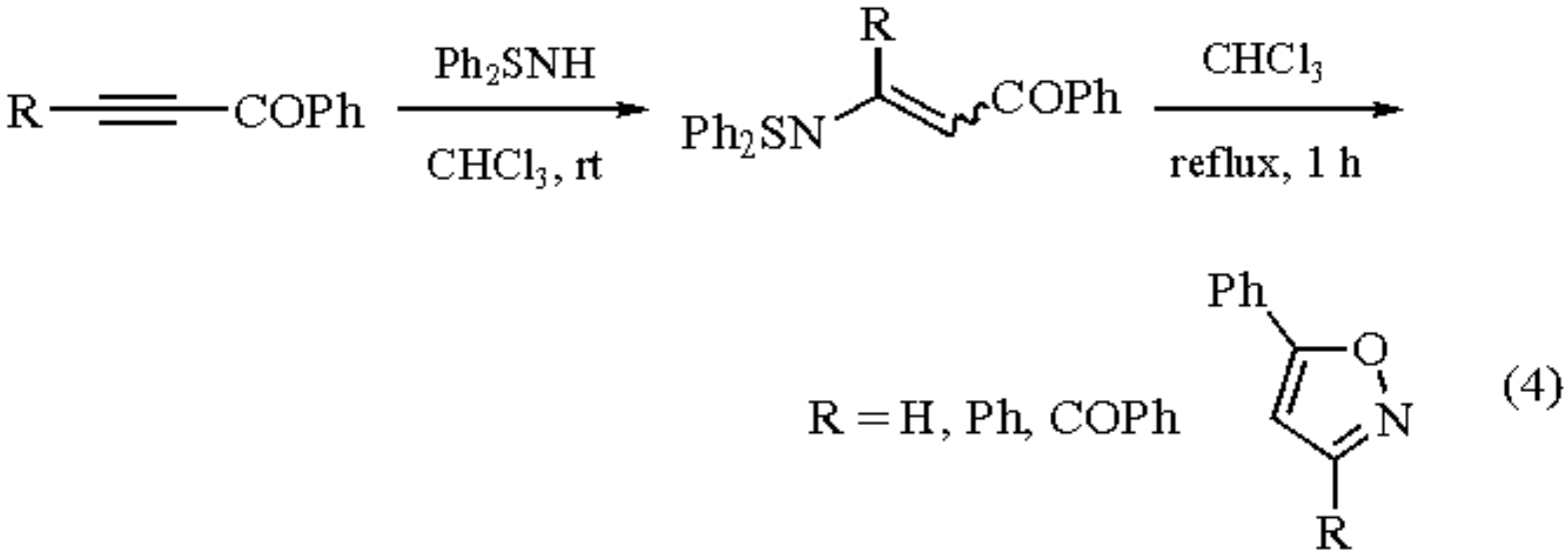

One-Step Synthesis of Nitriles.

Treatment of Ph_2SNH with aliphatic and aromatic mono- and dialdehydes affords the corresponding nitriles in high yields (eq 5).[6,7]

$$RCHO + Ph_2SNH \xrightarrow[80\ ^\circ C]{C_6H_6} RCN + H_2O + PhSPh \qquad (5)$$

R = Ph, *p*-Tol, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-HOC_6H_4, 3-py, *t*-Bu, C_7H_{15}, C_8H_{17}, $PhCH{=}CH_2$

N-Substituted Diphenylsulfilimines.

By alkylation[8] and acylation,[1,3] Ph_2SNH can readily be converted to the corresponding *N*-substituted sulfilimines, which have been further utilized for synthesis of various nitrogen-containing compounds[3] by pyrolysis and reactions with other electrophilic reagents (eqs 6-9).[8-11]

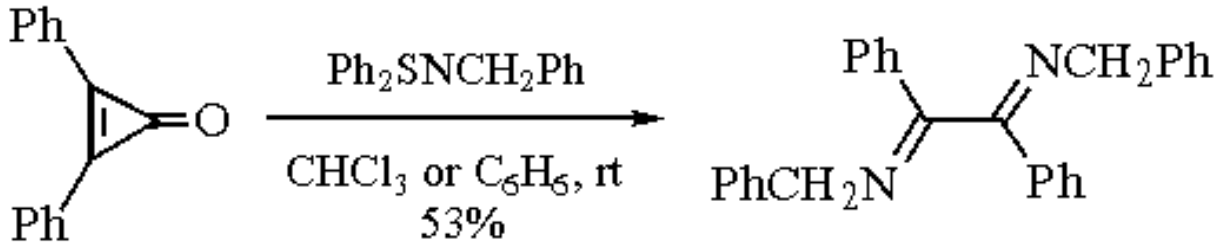

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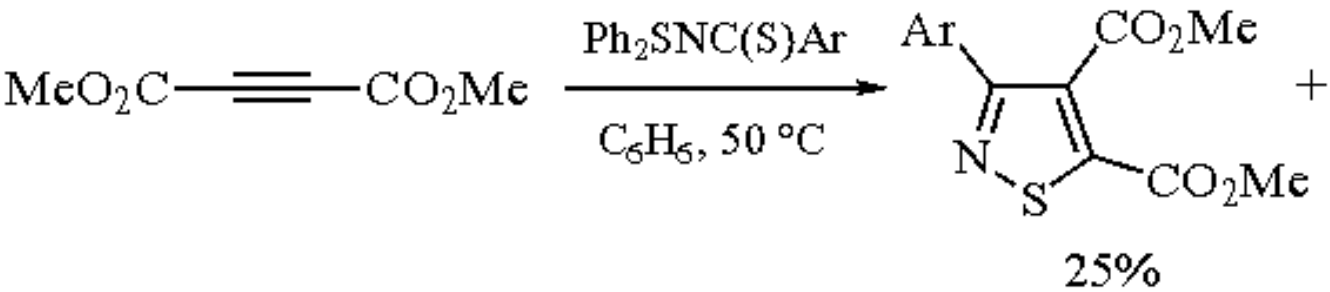

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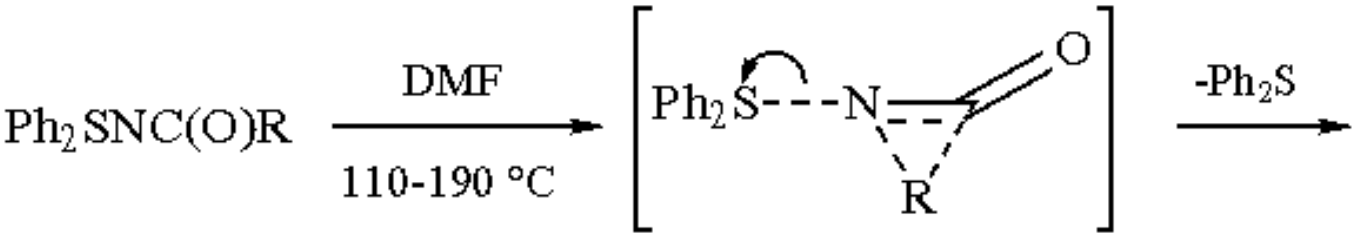

$RN{=}{\cdot}{=}O$ (8)

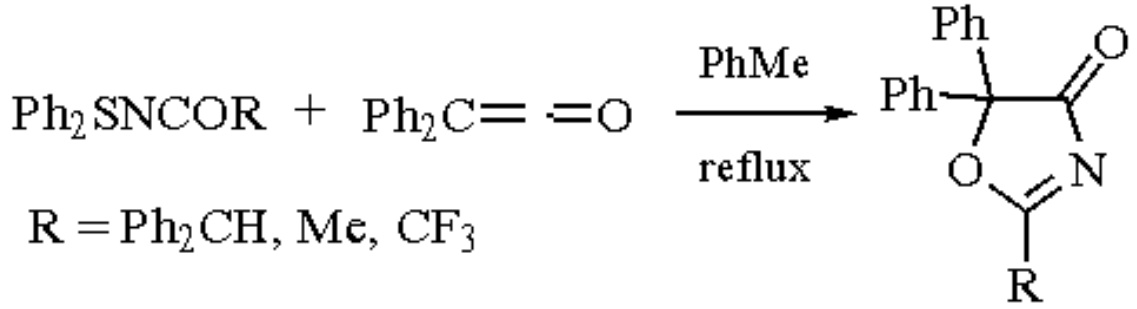

(9)

Synthetic Intermediate for Organic Sulfur Compounds.

N-Unsubstituted diarylsulfilimines are the most convenient reagents for the synthesis of diarylsulfoximines and sulfonediimines, which are aza analogs of sulfones and have interesting pharmacological properties. Treatment of the sulfilimines with ***Sodium Hypochlorite*** in aqueous methanol and then with aqueous ***Sodium Hydroxide*** results in the formation of the corresponding sulfoximines in high yields (eq 10).[12] Synthesis of *N*-tosylsulfonediimines can only be performed by the reaction of the sulfilimine with dry ***Chloramine-T*** and the dry sodium salt of tosylamide in dry MeCN (eq 11).[12,13] *N*-Unsubstituted sulfonediimines are prepared directly from the sulfilimines with ***t-Butyl Hypochlorite*** and liquid NH_3 via *N*-halosulfilimines[15] (eq 12).[14]

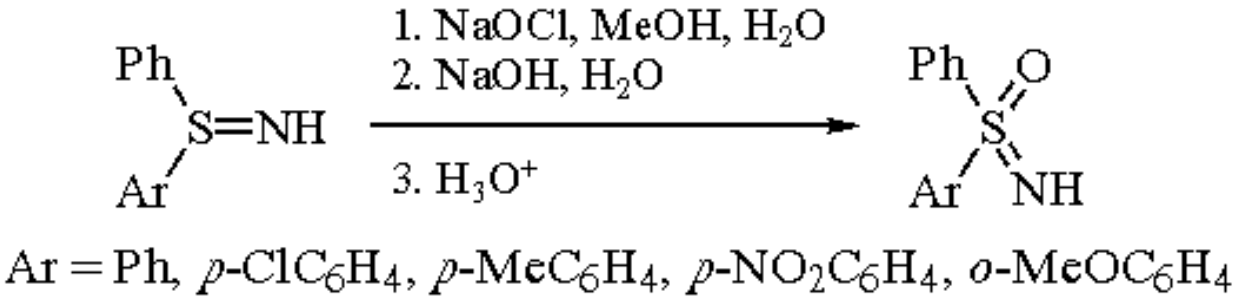

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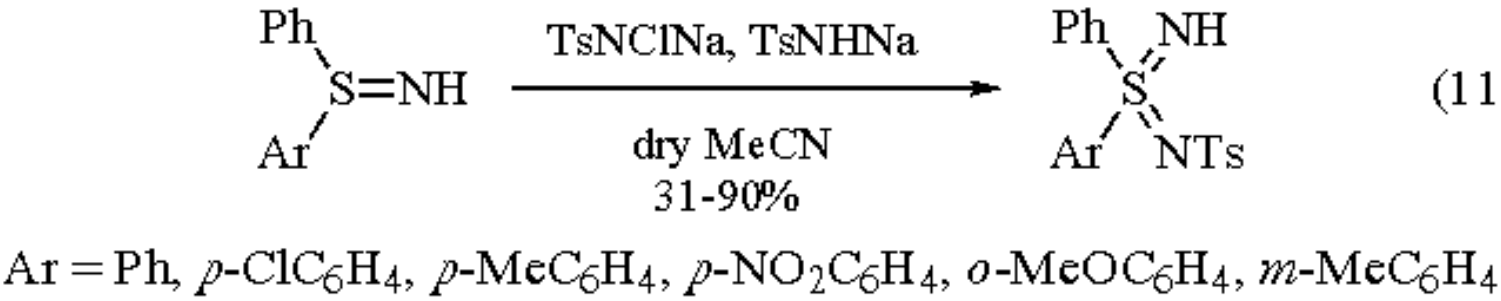

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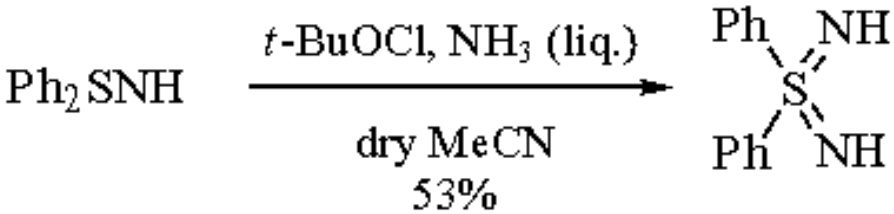

(12)

The alkaline hydrolysis of *N*-halosulfilimines[15] in aqueous MeOH forms an unusual type of organic sulfur compound, *S*,*S*-diphenyl-*S*-methoxythiazyne, which is readily converted to the sulfoximine upon treatment with aqueous acid (eq 13).[16] With ***Tetra-n-butylammonium Fluoride*** the *N*-bromosulfilimine is also converted to *S*,*S*-diphenyl-*S*-

fluorothiazyne, which is further converted to the corresponding *S*-alkoxythiazynes by sodium alkoxides and to *S*-aminothiazynes by cyclic secondary amines.[17]

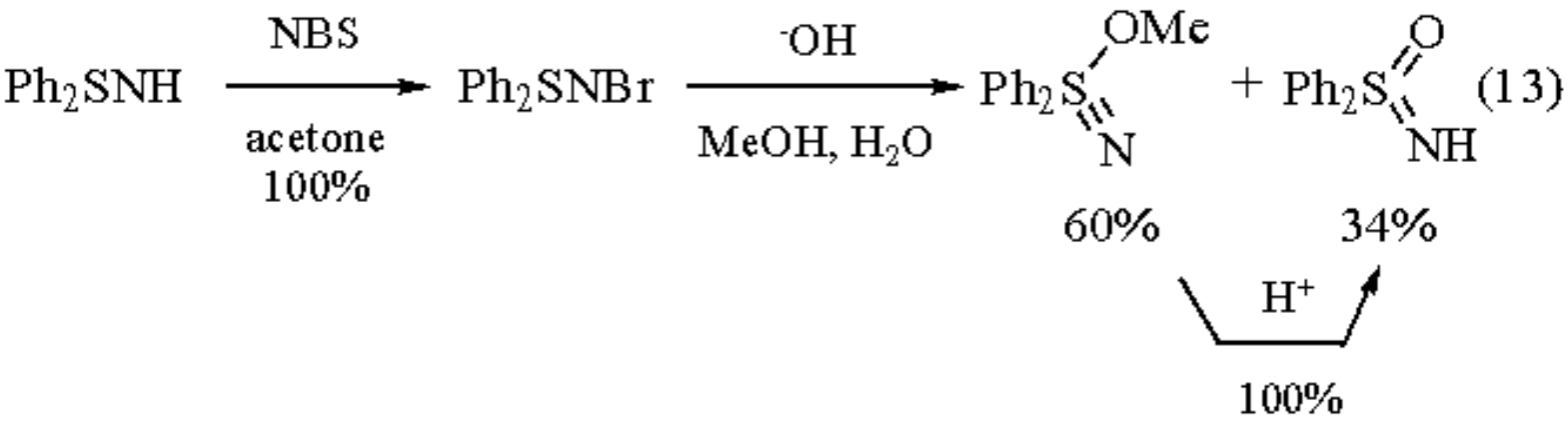

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Diphenylsulfonium Methylide[1]

Ph_2SR

(R = $=CH_2$)

[40411-90-3] · $C_{13}H_{12}S$ · Diphenylsulfonium Methylide · (MW 200.32) (R = $-Me^+BF_4^-$)

[10504-60-6] · $C_{13}H_{13}BF_4S$ · Methyldiphenylsulfonium Tetrafluoroborate · (MW 288.14)

(methylene transfer reagent[1,3])

Physical Data: $Ph_2SMe^+BF_4^-$: white powder, mp 63-66 °C; positive SIMS (secondary ion mass spectra) in glycerol have been reported.[4]

Solubility: $Ph_2SMe^+BF_4^-$: sol CH_2Cl_2, THF, DMF, DMSO, alcohols, H_2O.

Form Supplied in: $Ph_2SMe^+BF_4^-$: white powder; commercially available.

Analysis of Reagent Purity: the purity of $Ph_2SMe^+BF_4^-$ can be determined by HPLC analysis using a Hypersil 5 SAS column with 80/20 acetonitrile/low UV PIC B8 + 0.1% triethylamine as a mobile phase (document of analysis provided by Lancaster).

Preparative Methods: $Ph_2SMe^+BF_4^-$ is usually prepared by direct methylation of diphenyl sulfide.[2] Concentrated H_2SO_4 is added slowly to a mixture of MeOH (which serves as solvent as well as reactant) and Ph_2S. After 18 h at 80 °C, the solution is cooled to 0 °C and washed with Et_2O. After phase separation, tetrafluoroboric acid is then introduced to the reaction mixture at rt followed by addition of H_2O. The reaction mixture is extracted with CH_2Cl_2. The combined organic layer is then washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to give the crude product which is purified by recrystallization from MeOH/Et_2O in 65% yield.[2] $Ph_2SMe^+BF_4^-$ can also be prepared by the reaction of diphenyl sulfide with excess methyl iodide in nitromethane at rt in the absence of light. Silver tetrafluoroborate is then added to precipitate the iodide ion. After the reaction is complete, the silver iodide salt is removed by filtration.[5-9] The filtrate is then condensed to give the crude product as a pale yellow oil. Stirring of the oily residue in Et_2O overnight provides a white powder. After filtration and drying under vacuum, diphenylmethylsulfonium tetrafluoroborate is isolated in 71% yield. Diphenylsulfonium methylide is generated by treatment of $Ph_2SMe^+BF_4^-$ with a strong base such as NaH, LDA, *n*-BuLi, or *t*-BuLi[1,10] under an inert atmosphere. Solvents such as DME and THF are generally used in the reaction to generate the ylide. Alternatively, $Ph_2S{=}CH_2$ can be prepared in situ by the reaction of benzyne with PhSMe.[11] $Ph_2S{=}CH_2$ is usually prepared and used immediately without purification.

Handling, Storage, and Precautions: $Ph_2SMe^+BF_4^-$ can be stored in a desiccator at rt for months or stored in closed vessels in a dry place away from sources of heat. It is incompatible with strong oxidizing agents.

Introduction.

Like ***Dimethylsulfonium Methylide*** and ***Dimethylsulfoxonium Methylide***, diphenylsulfonium methylide is a methylene transfer reagent. Although it has not been as commonly used as dimethylsulfonium and dimethylsulfoxonium methylide in the preparation of epoxides and cyclopropanes, it has been reported to offer the advantage of avoiding sulfur-containing byproducts resulting from the Sommelet rearrangement.[12]

Epoxidation.

Treatment of 2 equiv of diphenylsulfonium methylide with a heterocycle possessing a leaving group produces a new sulfonium ylide which can be subsequently reacted with a ketone or aldehyde to generate an epoxide. The resultant epoxide can be converted to an acyl derivative by reacting with ***Lithium Diethylamide*** (eq 1).[3]

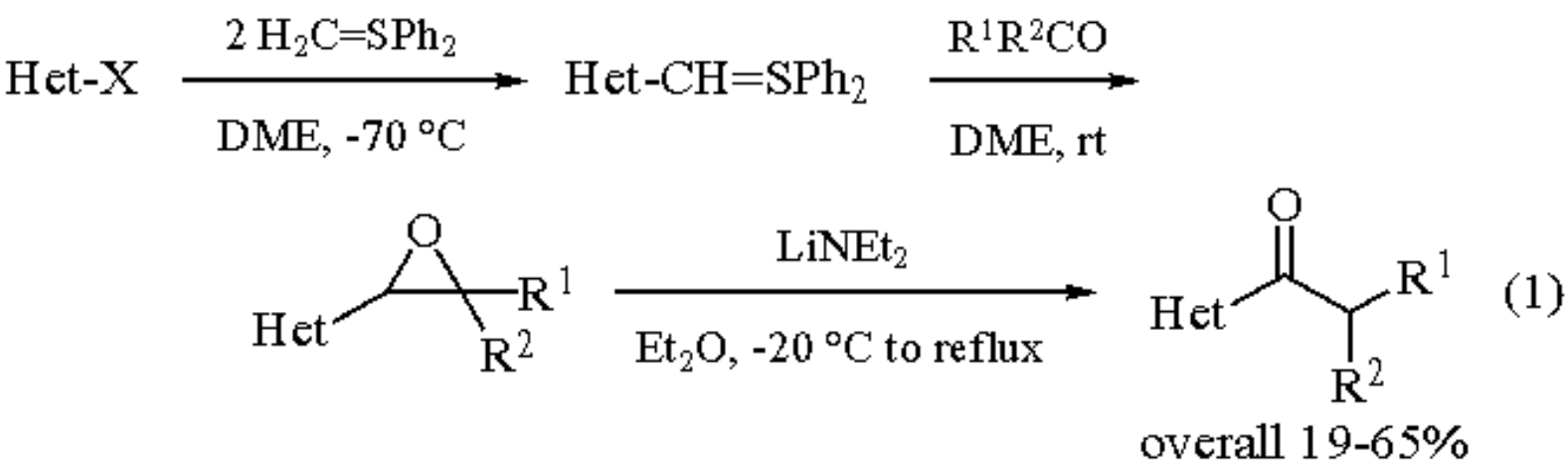

Het = quinoline, quinazoline, quinoxaline, benzoxazole; X = Cl, methylsulfonyl; R^1R^2CO = acetaldehyde, acetone, benzaldehyde, cyclohexanone, propionaldehyde

Cyclopropanation of Double Bonds.

Unlike many other sulfur ylides, diphenylsulfonium methylide can react directly with unactivated alkenes to produce cyclopropane derivatives. ***Copper(II) Acetylacetonate*** catalyzed cyclopropanation of alkenes with diphenylsulfonium methylide was reported in 1974. This transition metal induced methylene transfer might involve an intermediate metal-carbene complex.[1] Better yields of cyclopropanes are achieved when copper bis(η-3-pentylacetylacetonate) is used instead of $Cu(acac)_2$ in the methylenation of alkenes (eq 2).[13]

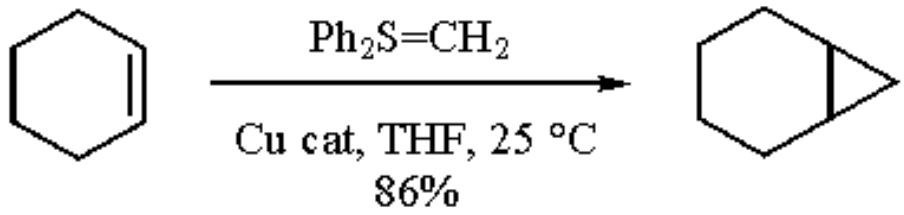

(2)

Cyclopropanation of Enones.

Diphenylsulfonium methylide is not commonly used in the cyclopropanation of enones. Reaction of diphenylsulfonium methylide with the enedione resulting from benzoquinone-cyclopentadiene Diels-Alder addition gives the corresponding cyclopropane derivative in only 9% yield.[14]

Methylation.

Diphenylmethylsulfonium tetrafluoroborate is a powerful alkylation reagent. Alkylation of $PhCO_2K$ with diphenylmethylsulfonium tetrafluoroborate in acetonitrile at 20 °C for 7 h provides the corresponding methyl ester in 66% yield.[15] Methyl transfer to pyridine-d_5 by diphenylmethylsulfonium tetrafluoroborate is reported to be 1300 times faster than that using σ-ammoniomethylsulfurane.[16] Diphenylmethylsulfonium tetrafluoroborate has also been used in the methylation of nitrogen heterocyclic compounds such as indole, benzimidazole, thymine, and uracil. These reactions are carried out in CH_2Cl_2 or DMF with bases such as aqueous NaOH, aqueous KOH, or powdered KOH (eq 3).[2]

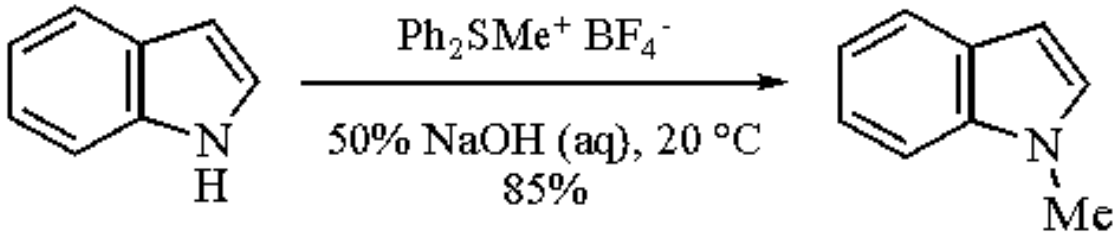

(3)

O-Methylation of amides such as DMF, DMA, and caprolactam can readily be accomplished with diphenylmethylsulfonium tetrafluoroborate in excellent yields.[17] Alkylation of β-keto esters with diphenylmethylsulfonium tetrafluoroborate is also reported to provide the *C*-alkylated products in excellent yields under aprotic conditions.[18]

Other Applications.

Diphenylmethylsulfonium tetrafluoroborate has been utilized in the presence of ***Aluminum Chloride*** to prepare a low temperature molten salt electrolyte.[19,20] It has also been used as a cationic photoinitiator in polymer chemistry.[21]

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3,6-Diphenyl-1,2,4,5-tetrazine[1]

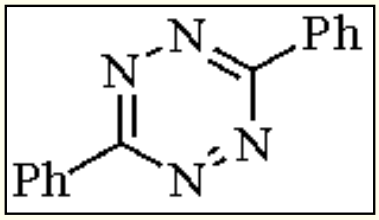

[6830-78-0] · $C_{14}H_{10}N_4$ · 3,6-Diphenyl-1,2,4,5-tetrazine · (MW 234.28)

(an electron-deficient heteroaromatic azadiene capable of participation in inverse electron demand cycloaddition reactions with a wide range of dienophiles[1])

Alternate Name: diphenyl-*s*-tetrazine.

Physical Data: mp 195 °C.

Solubility: sol toluene, CH_2Cl_2, MeOH; insol H_2O.

Form Supplied in: carmine-red needles.

Preparative Method: [2] a mixture of benzonitrile (84 mmol) and 95% hydrazine (100 mL) is heated at 100 °C for 72 h. The resulting orange-yellow solid is broken up, washed with H_2O, air dried, ground to a fine powder, and added to 100 mL of 10% acetic acid. Small portions of sodium nitrite are added to this solution while warming at 100 °C for 1 h. The red solid thus produced is collected, washed with H_2O, and recrystallized from EtOH.

Handling, Storage, and Precautions: stable at rt.

Cycloaddition Reactions.

3,6-Diphenyl-1,2,4,5-tetrazine (**1**) is one of the oldest and most extensively studied electron-deficient heteroaromatic azadienes capable of participation in inverse electron demand Diels-Alder reactions with a wide range of dienophiles and heterodienophiles including electron-rich, neutral, strained, and electron-deficient alkenes, alkynes, dienes, enol ethers, enamines, ynamines, ketene acetals, enolates, benzynes, amidines, imines, and azirines.[1] These cycloaddition reactions occur exclusively across C-3/C-6 of the 1,2,4,5-tetrazine nucleus and are accompanied by a retro Diels-Alder reaction with extrusion of N_2 to afford substituted 4,5-dihydro-1,2-diazines (eq 1),[3] their 1,4-dihydro tautomers (when possible) (eq 2),[4] or substituted 1,2-diazines (pyridazines) when the dienophiles are alkynes (eq 3)[4] or contain leaving groups capable of elimination with aromatization (eqs 4 and 5).[5,6] Aromatization of the dihydro-1,2-diazines may also

be effected by subsequent oxidation of the alkene [4 + 2] cycloadducts for dienophiles which lack a built-in leaving group (eq 6).[7]

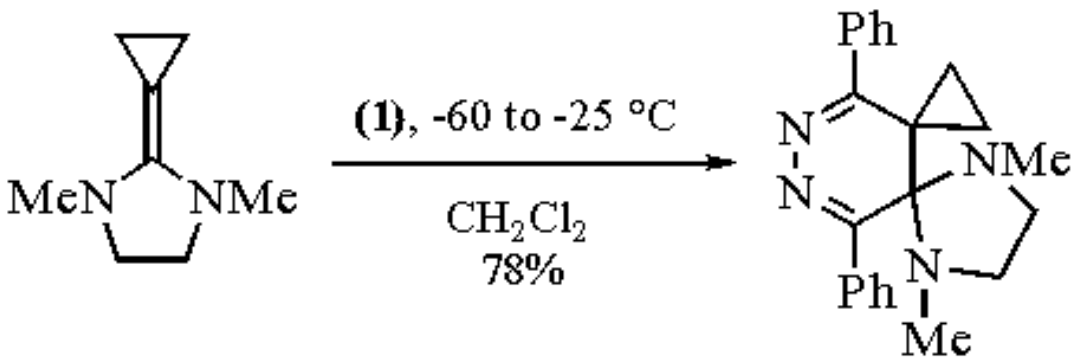

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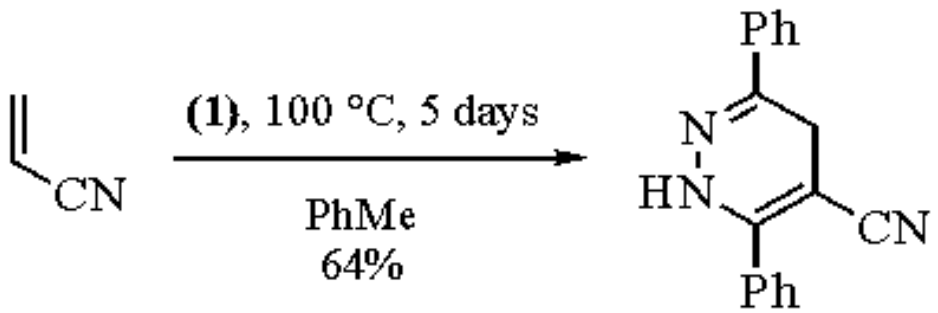

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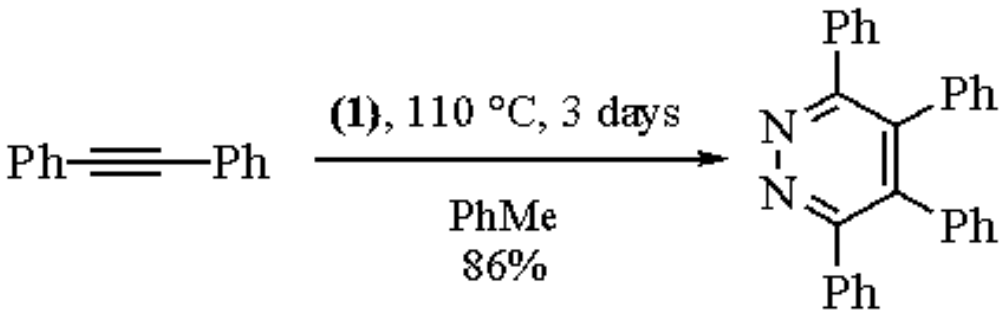

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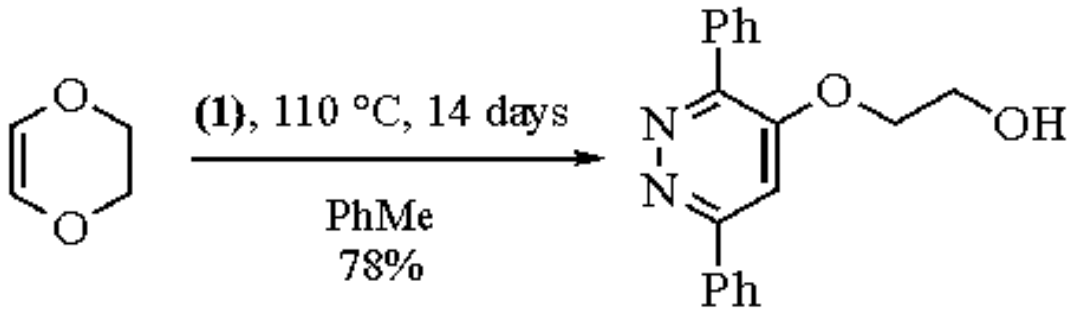

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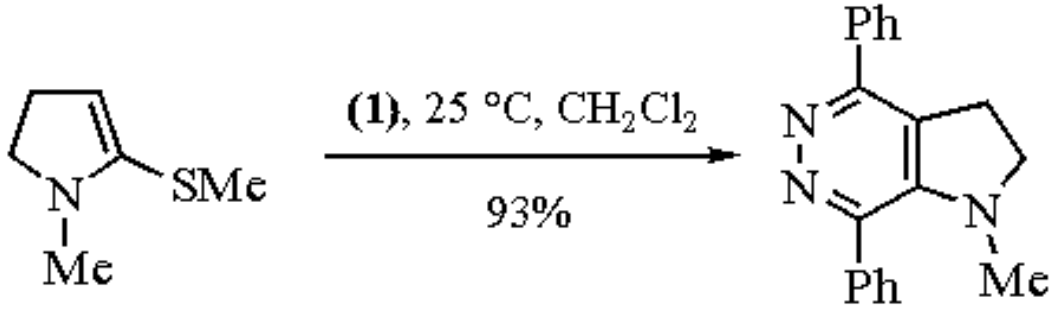

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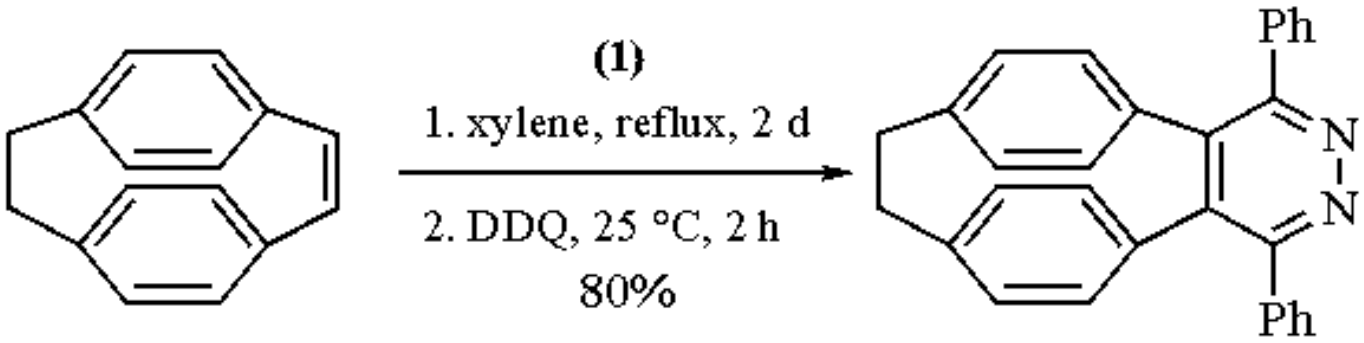

(6)

Imines and amidines often cycloadd to 3,6-diphenyl-1,2,4,5-tetrazine through their more reactive tautomeric enamine and *N*,*N*-ketene aminal forms, respectively (eqs 7 and 9).[8,9] Cycloaddition of imines and amidines with (**1**) with reaction of the C=N double bond takes place when such tautomerization is not accessible (eqs 8 and 10).[8,10] Cycloadditions with azirines result in ring-expanded products derived from [3,3]-sigmatropic rearrangement of a dihydro-1,2-diazine intermediate followed by [1,5]-hydrogen shift (eq 11).[11] Ring expansion has also been observed with other strained dienophiles (eqs 12 and 13).[12] In addition, the 4π participation of 3,6-diphenyl-1,2,4,5-tetrazine in [4 + 1] and [6 + 4] cycloaddition reactions has also been described.[13]

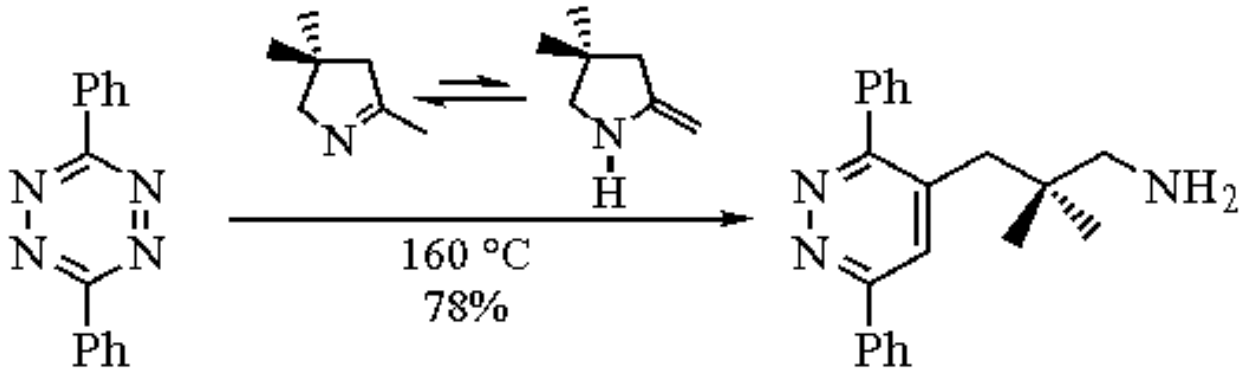

(7)

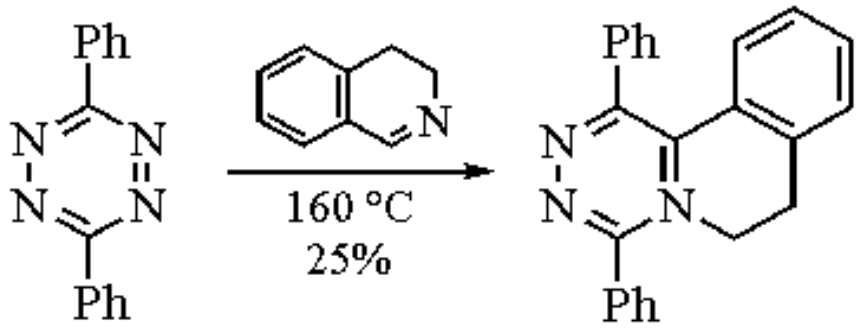

(8)

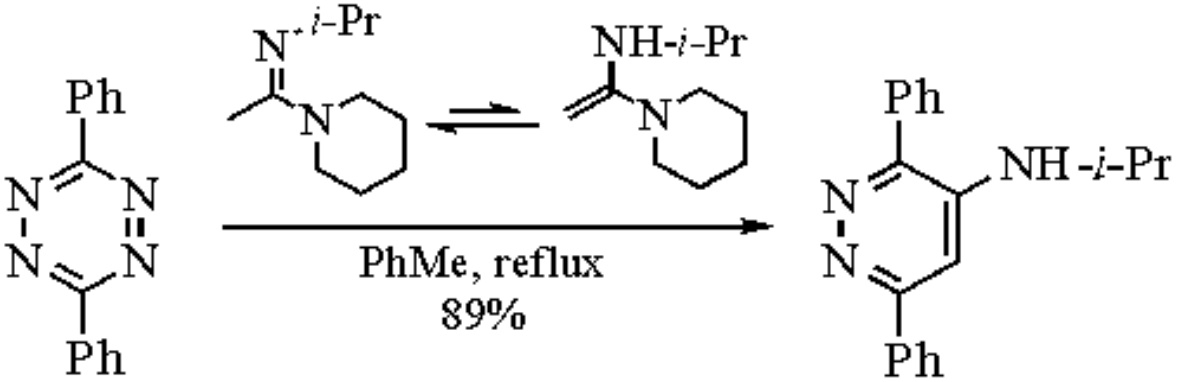
Ph
N
N
N
N
Ph
N
i-Pr
N
NH-i-Pr
N
PhMe, reflux
89%
Ph
NH-i-Pr
N
N
Ph

(9)

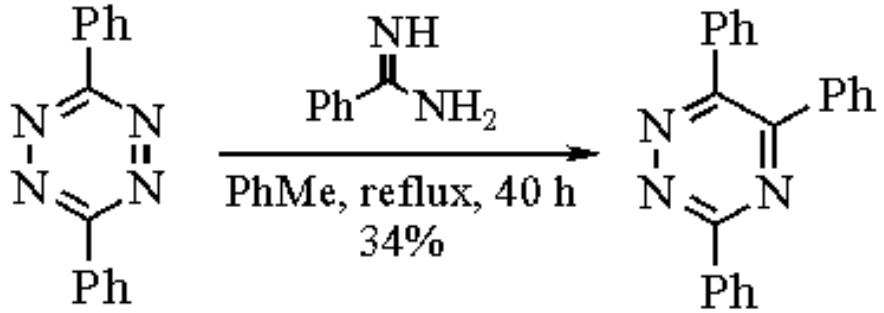
Ph
N
N
N
N
Ph
NH
Ph
NH2
PhMe, reflux, 40 h
34%
Ph
Ph
N
N
N
N
Ph

(10)

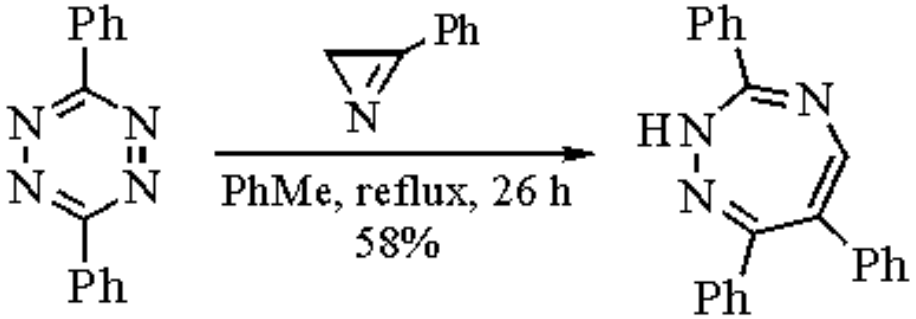
Ph
N
N
N
N
Ph
Ph
N
PhMe, reflux, 26 h
58%
Ph
N
HN
N
Ph
Ph

(11)

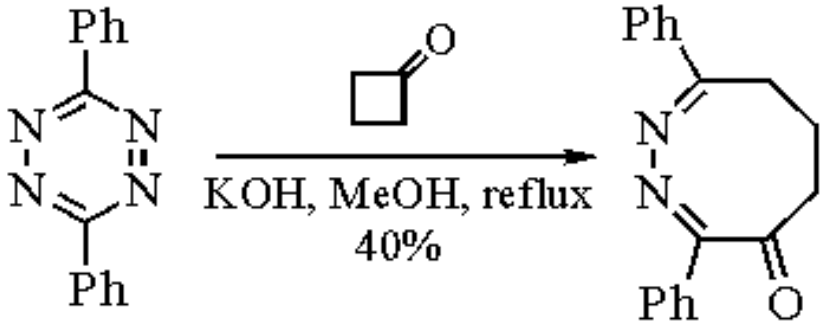
Ph
N
N
N
N
Ph
O
KOH, MeOH, reflux
40%
Ph
N
N
Ph
O

(12)

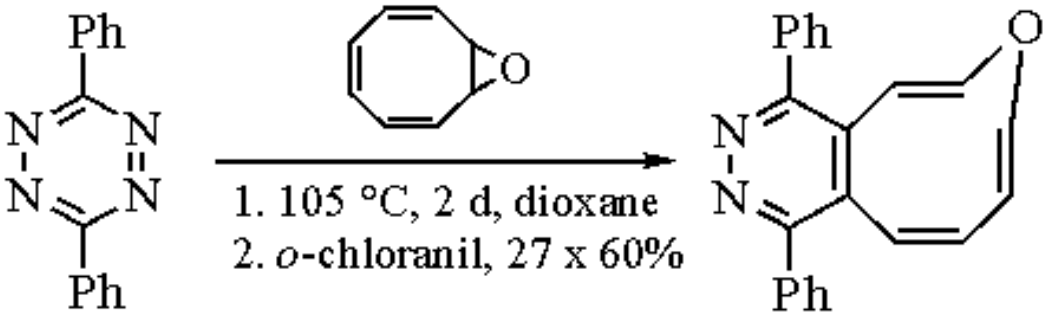
Ph
N
N
N
N
Ph
O
1. 105 °C, 2 d, dioxane
2. o-chloranil, 27 x 60%
Ph
O
N
N
Ph

(13)

Despite the extensive studies with 3,6-diphenyl-1,2,4,5-tetrazine and its broad range of reactivity toward a wide spectrum of dienophiles, synthetic applications of this reagent are limited due to the presence of the phenyl substituents which are incompatible with many synthetic targets. However, a large number of 1,2,4,5-tetrazines with a range of substituents are available[1b,14] and many are amenable to further synthetic manipulations for specific applications. One notable example is the development of a general approach to the preparation of substituted indoles and indolines through use of the sequential [4 + 2] cycloaddition reactions of 3,6-bis(methylthio)-1,2,4,5-tetrazine.[15] The application of a 1,2,4,5-tetrazine -> 1,2-diazine -> indole synthetic strategy based on the use of 3,6-bis(methylthio)-1,2,4,5-tetrazine in the total synthesis of *cis*- and *trans*-trikentrin A (**2**) and (**3**) has been detailed (eq 14).[16]

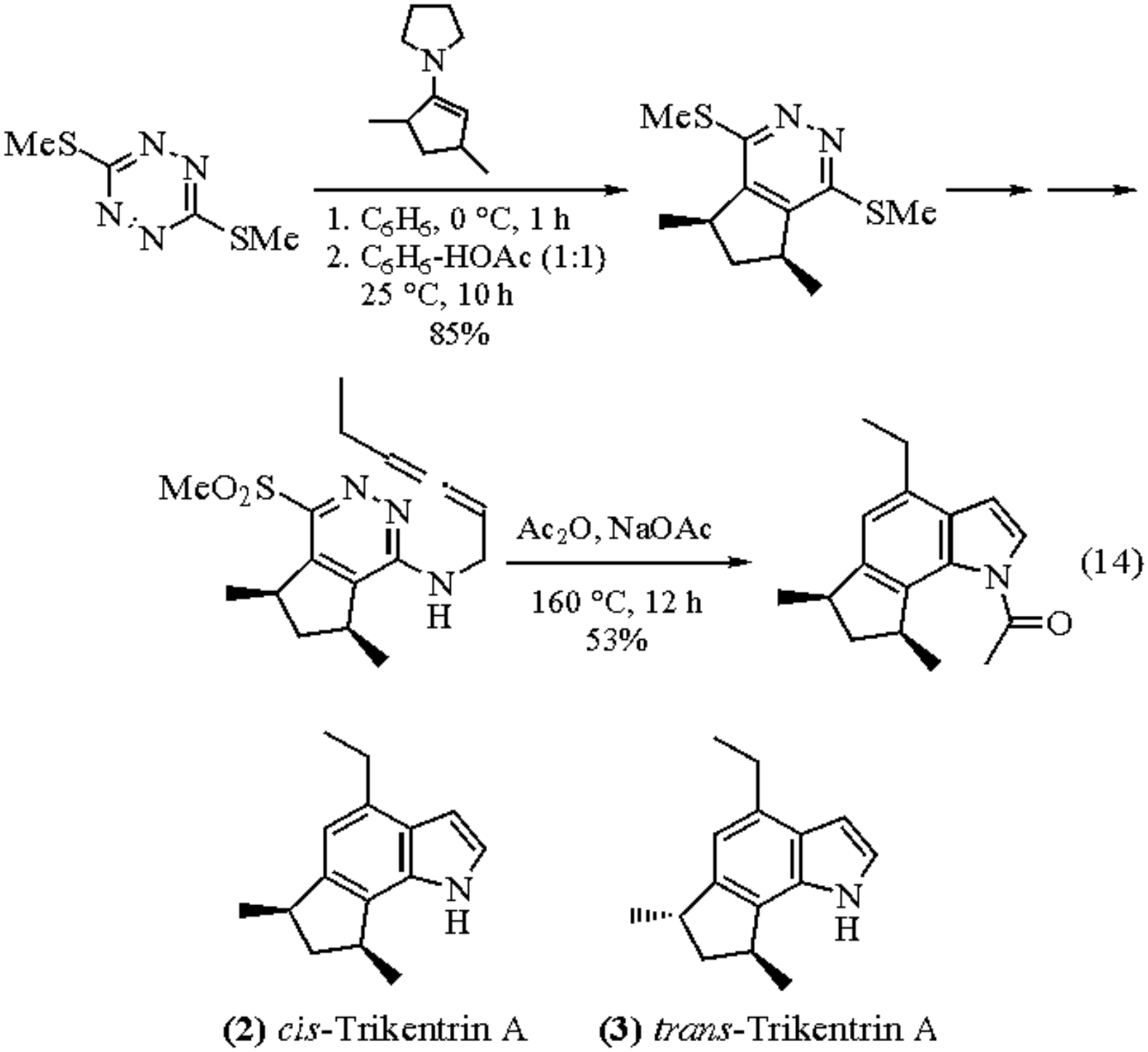

Related Reagents.

Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate; ***4-Methyl-1,2,3-triazine***; ***1,2,4-Triazine***; ***1,3,5-Triazine***; ***Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate***.

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5. (a) Roffey, P.; Verge, J. P. *JHC* **1969**, *6*, 497. (b) Sauer, J.; Mielert, A.; Lang, D.; Peter, D. *CB* **1965**, *98*, 1435.
6. (a) Marcelis, A. T. M.; Van der Plas, H. C. *JHC* **1987**, *24*, 545. (b) Möhrle, H.; Dwuletzki, H. *CB* **1986**, *119*, 3600.
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10. (a) Figeys, H. P.; Mathy, A. *TL* **1981**, *22*, 1393. (b) Takahashi, M.; Hikita, Y.; Fukui, M. *H* **1989**, *29*, 1379.
11. (a) Anderson, D. J.; Hassner, A. *CC* **1974**, 45. (b) Takahashi, M.; Suzuki, N.; Igari, Y. *BCJ* **1975**, *48*, 2605.
12. (a) Haddadin, M. J.; Agha, B. J.; Salka, M. S. *TL* **1984**, *25*, 2577. (b) Anastassiou, A. G.; Girgenti, S. J. *AG* **1975**, *87*, 842. (c) Anastassiou, A. G.; Reichmanis, E. *CC* **1976**, 313. (d) Battiste, M. A.; Barton, T. J. *TL* **1967**, 1227.
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14. Neunhoeffer, H.; Wiley, P. F. *Chemistry of Heterocyclic Compounds*; Wiley: New York, 1978; Vol. 33, pp 1075-1109.
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16. Boger, D. L.; Zhang, M. *JACS* **1991**, *113*, 4230.

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The Scripps Research Institute, La Jolla, CA, USA

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4,6-Diphenylthieno[3,4-*d*]dioxol-2-one 5,5-Dioxide[1]

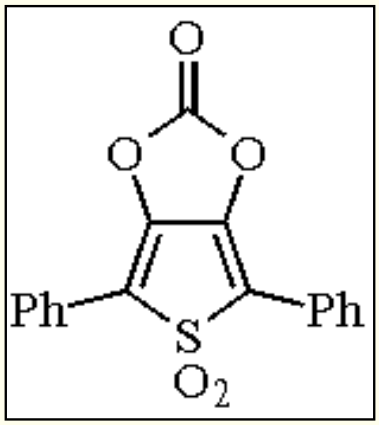

[54714-11-3] · $C_{17}H_{10}O_5S$ · 4,6-Diphenylthieno[3,4-*d*]dioxol-2-one 5,5-Dioxide · (MW 326.34)

(acylating agent in peptide synthesis;[1] synthesis of substituted ureas and isocyanates;[6] acylating agent in Friedel-Crafts reaction)

Physical Data: mp 230-290 °C.

Solubility: sol THF, CH_2Cl_2, dioxane.

Form Supplied in: yellow powder, 95%.

Preparative Method: by reaction of 4-hydroxy-3-oxo-2,5-diphenyl-2,3-dihydrothiophene 1,1-dioxide[2] with ***Phosgene*** (eq 1).[1]

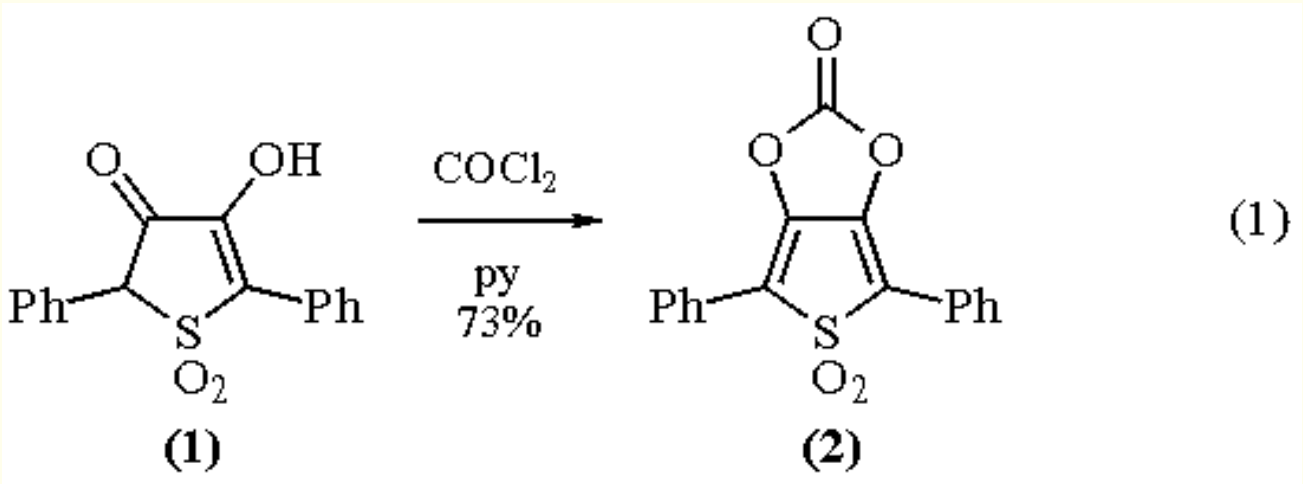

Handling, Storage, and Precautions: irritant; chemical, physical, and toxicological properties have not been thoroughly investigated.

Acylating Agent in Peptide Synthesis.

The reagent (**2**) reacts smoothly with carboxylic acids and pyridine in anhydrous aprotic solvents to give active esters (**3**) (eq 2), which are easily crystallizable, stable compounds. Compound (**3**) is an excellent acyl transfer agent. Reaction of (**3**) with amines readily affords amides (eq 2)[1] under mild conditions in high yield. In several experiments it has been demonstrated that these esters are more effective acyl transferring agents than the *p*- and *o*-nitrophenyl esters commonly employed in peptide synthesis.

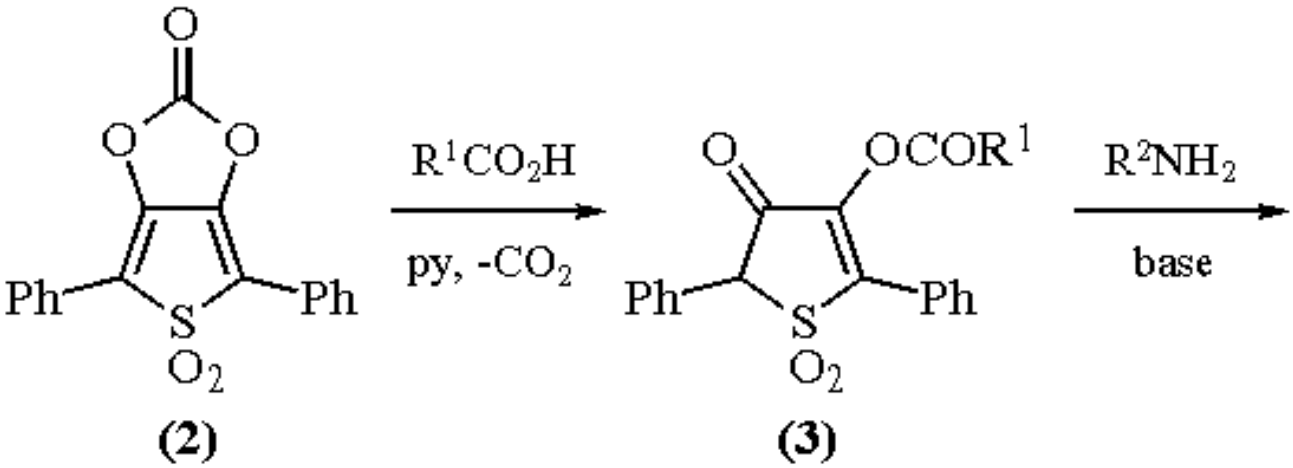

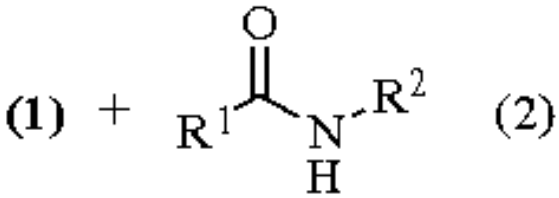

Synthesis of Boc-Amino Acid Esters.

The reagent (**2**) can be employed in a one-pot preparation of activated Boc-amino acid esters when used for both activation of the Boc-amino acid and for introduction of the Boc group (eq 3).[3] The reagent (**2**) has been successfully utilized in peptide synthesis[4] and in the formation of activated matrices for HPLC that require formation of an amide bond.[5]

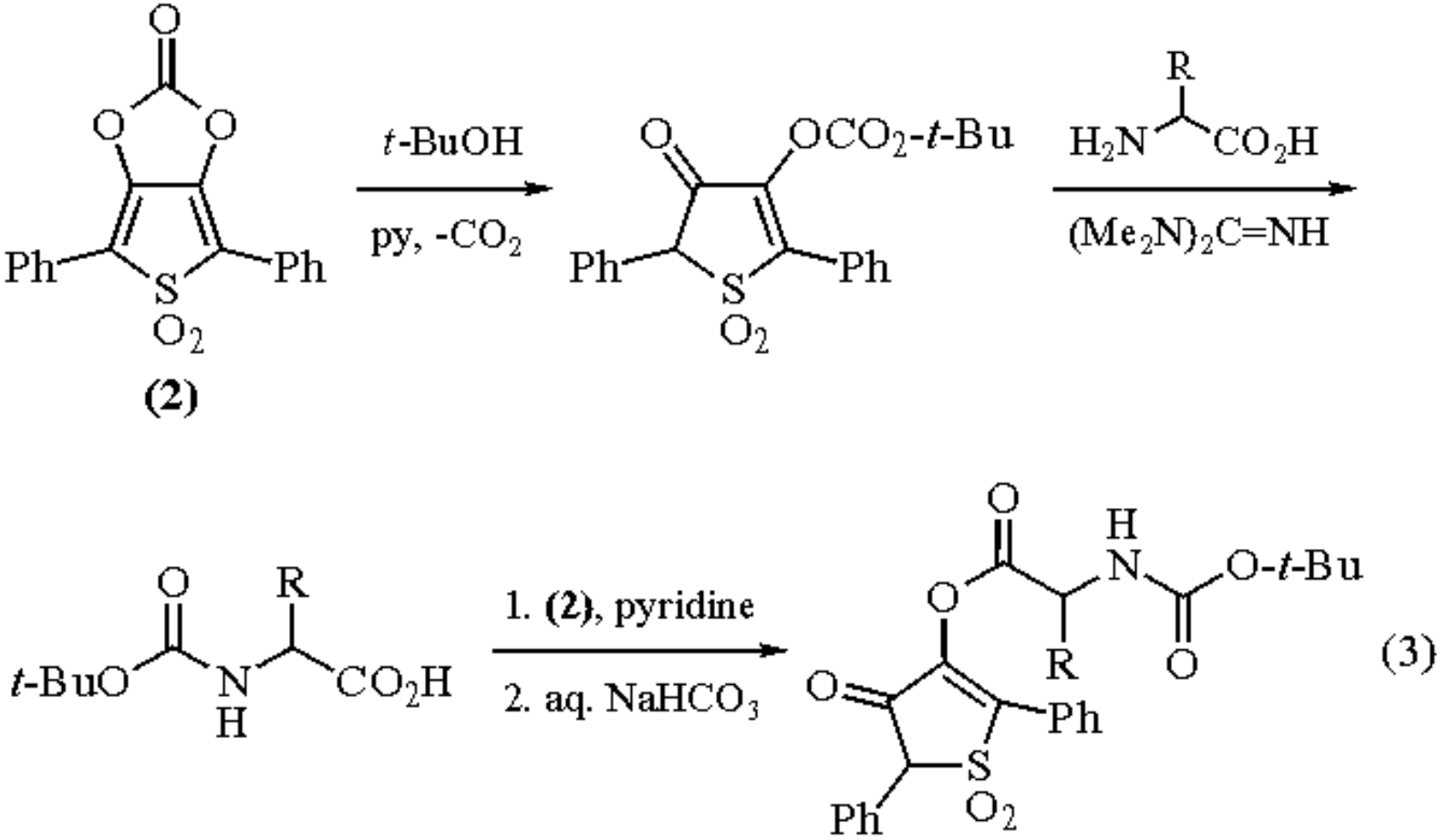

Di- and Trisubstituted Ureas and Urethanes.

Similar to Boc activation, reaction of (**2**) with amines forms an intermediate carbamate (eq 4), which upon heating in dichlorobenzene gives the corresponding isocyanate or upon treatment with another molecule of amine gives the corresponding urea derivative.[6] The products are obtained in 78-92% yield.

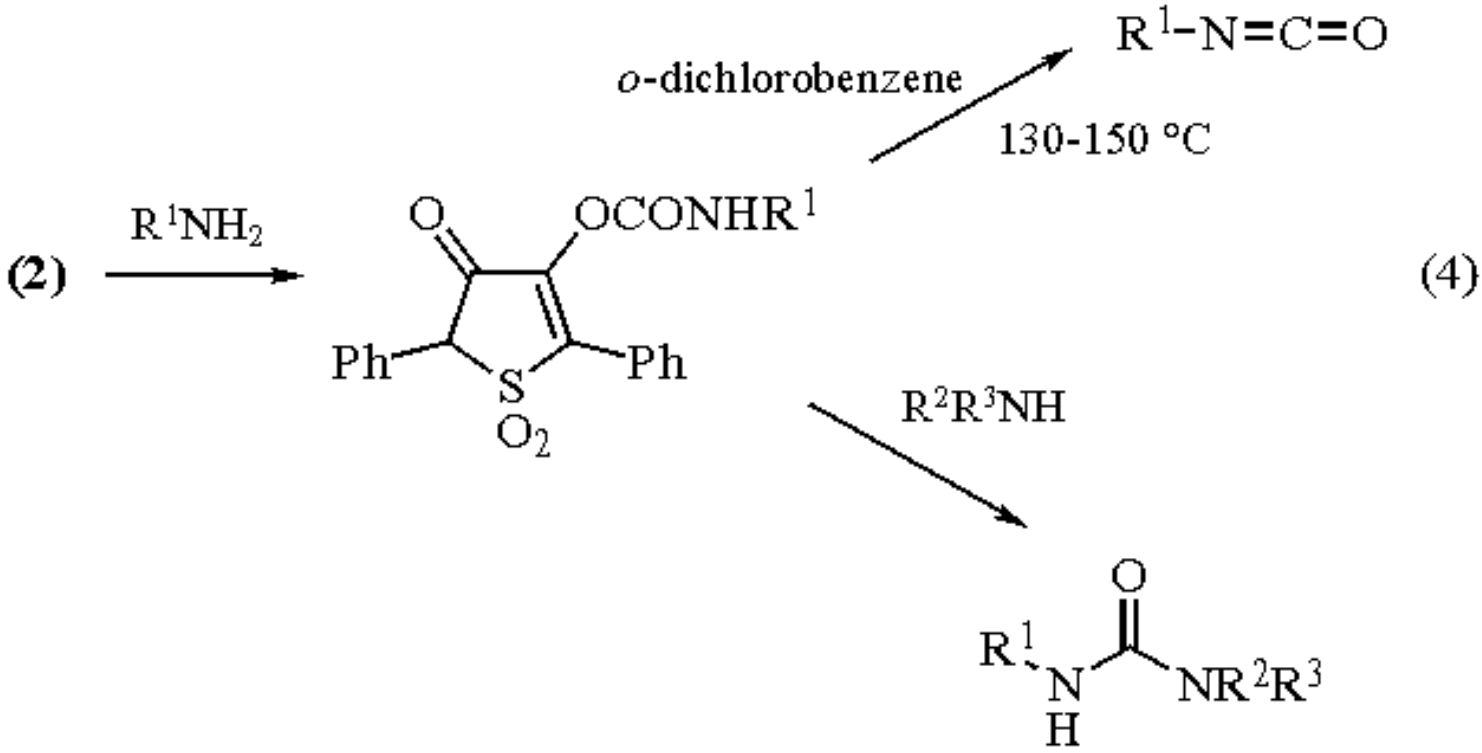

Active Ester in Friedel-Crafts Acylation Reactions.

A variety of active esters have been prepared from the reaction of (**2**) and carboxylic acids (eq 5). This product is an active agent in Friedel-Crafts acylation of aromatic substrates.[7] The method can be applied under milder conditions than the methods that use corresponding acid anhydrides or acyl chlorides, and fewer byproducts are formed.

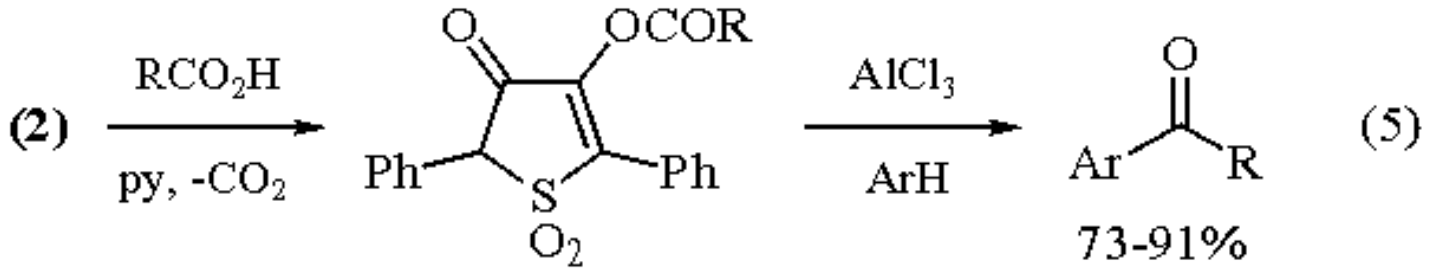

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7. Ree, T. V. *S. Afr. J. Chem.* **1989**, *42*, 139.

Hemantkumar H. Patel

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Diphenylstannane[1]

Ph_2SnH_2

[1011-95-6] · $C_{12}H_{12}Sn$ · Diphenylstannane · (MW 274.95)

(hydrostannylation of alkenes and alkynes; reduction of aldehydes and ketones; hydride transfer reactions with other organometallic reagents)

Alternate Name: diphenyltin dihydride.

Physical Data: colorless oil; bp 89-93 °C/0.3 mmHg, 74 °C/0.001 mmHg; mp -17 °C; *d* 1.39 g cm^{-3}; *n*20D 1.5951.

Solubility: sol most organic solvents. Many polar aprotic solvents catalyze the decomposition to diphenyltin oligomer and hydrogen (e.g. MeOH, Et_2NH, pyridine, morpholine, DMF, DMSO). Diphenylstannane reacts (exothermically) with all protic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: ^{119}Sn NMR recommended (δ -234 ppm, $^1J(^{119}Sn\text{-}^1H)$ 1928 Hz).[4]

Preparative Methods: from Ph_2SnCl_2 and $LiAlH_4$[2] or Et_2AlH[3] in diethyl ether; yield 70-89%. The ***Lithium Aluminum Hydride*** method is recommended.

Handling, Storage, and Precautions: must be stored in the absence of oxygen, moisture, and light (preferably under argon). Use in a fume hood.

Introduction.

All aspects of the preparation, spectroscopic properties, and chemical reactions of diphenylstannane are discussed in the Gmelin Handbuch volume dealing with organotin hydrides (literature covered up to the end of 1974),[1a] while more general aspects of the preparation and chemistry of organotin hydrides (and deuterides) are reviewed in the Houben-Weyl volume on organotin compounds (literature coverage up to 1977).[1b]

Hydrostannylation.

The hydrostannylation of monoalkenes (e.g. acrylonitrile, methyl acrylate, methyl methacrylate) or monoalkynes affords monomeric products (eq 1).[5] Dialkenes (e.g. 1,4-divinylbenzene) or dialkynes (e.g. 1,4-diethynylbenzene), in contrast, yield polymeric materials.[6] In some cases (e.g. 1,2-divinylbenzene, 1,2-diethynylbenzene) a mixture of polymeric and monomeric products is formed (eq 2).[7]

$$Ph_2SnH_2 + 2\,H_2C{=}CHCN \xrightarrow{70\ ^\circ C} Ph_2Sn(CH_2CH_2CN)_2 \quad (1)$$

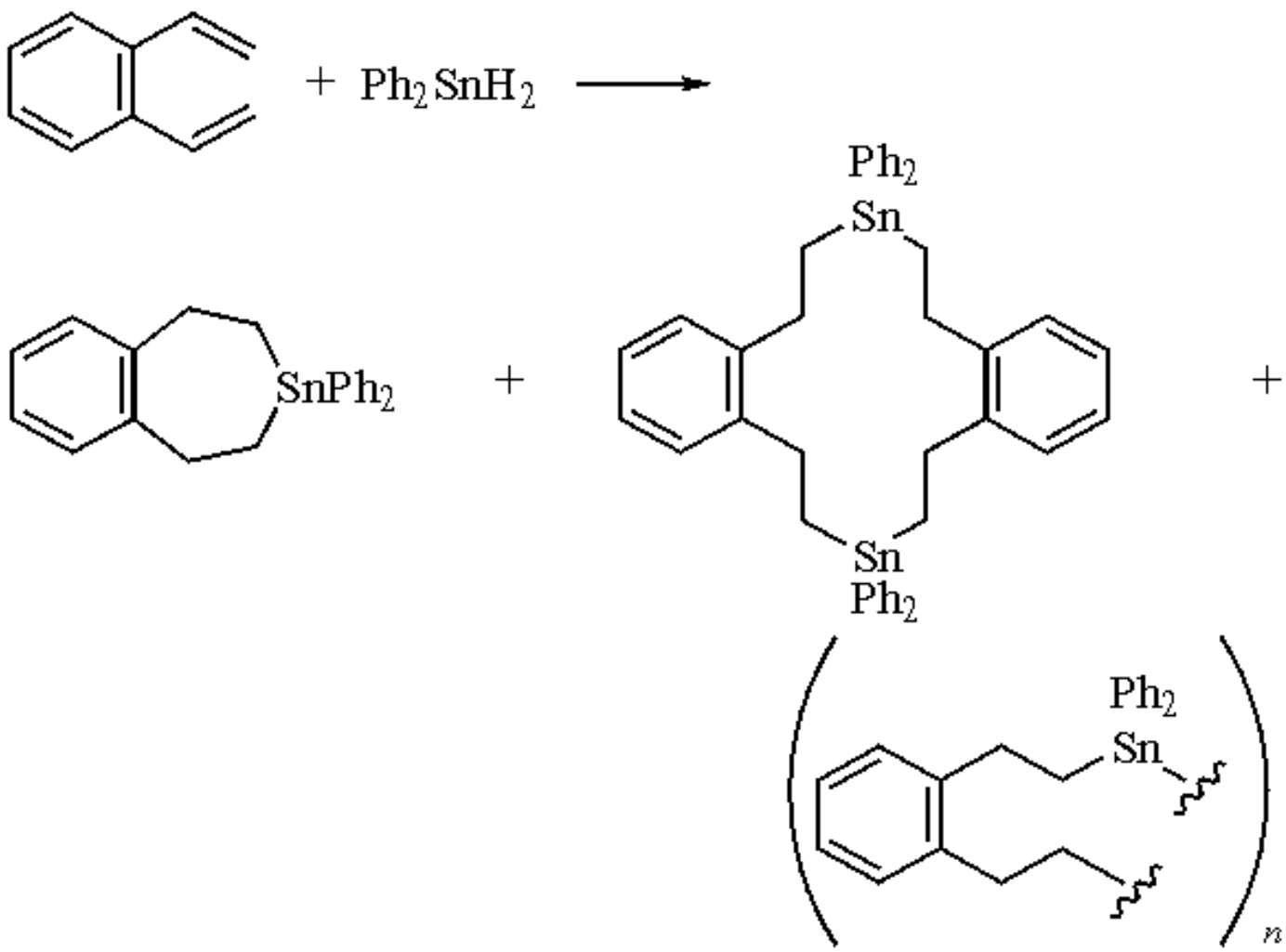

(2)

Reduction of Aldehydes and Ketones.

Aldehydes and ketones are reduced by diphenylstannane to primary and secondary alcohols, respectively. This reaction is of preparative interest in the case of α,β-unsaturated ketones, since here only the carbonyl group is normally reduced, the alkenic double bond remaining unaffected (eq 3).[8] Some cases are known, however, in which the double bond is reduced while the carbonyl group remains intact.[9]

$$Ph_2SnH_2 + H_2C{=}CHCOMe \longrightarrow 1/n\,(Ph_2Sn)_n + H_2C{=}CHCH(OH)Me \quad (3)$$

Hydride Transfer Reactions.

Diphenylstannane undergoes reversible exchange reactions with diphenyltin dihalides to afford halodiphenylstannanes,[10] which in turn can be used as reducing agents. Many other ligand exchange reactions are known, but these have not so far been shown to be of interest for synthetic organic chemistry.

Virtually no synthetic work has been published since 1974. The reason for this is likely to be the fact that, in general, diphenylstannane has no notable advantage over the dimethyltin or dibutyltin analogs. Its disadvantage lies in the high boiling points of diphenyltin compounds, which make it difficult to remove tin-containing residues completely from reaction products. Its one potential advantage lies in the fact that such compounds are in some cases solids at rt. However, even these generally have a residual solubility in organic compounds. It will indeed not generally be necessary to resort to the use of tin dihydrides in order to carry out chemistry of the nature described above, except when polymeric or cyclic organotin products are required. The monohydrides are chemically very versatile and in addition much more stable (see in particular ***Trimethylstannane*** and ***Tri-n-butylstannane***). The problem of the toxicity of organotin compounds and their interaction with the environment or their effect on animals has been dealt with in some detail in the literature; relevant work on triphenyltin compounds has resulted in the detection of diphenyltin species, as reported in several publications.[11]

Related Reagents.

Tri-n-butylstannane; ***Triphenylstannane***.

---

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Diphenyl(vinyl)phosphine Oxide[1]

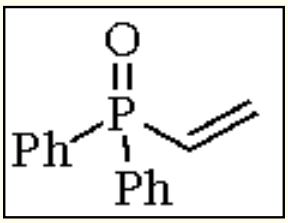

[2096-78-8] · $C_{14}H_{13}OP$ · Diphenyl(vinyl)phosphine Oxide · (MW 228.24)

(Horner-Wittig[2] reagent for the preparation of allylic amines; undergoes a variety of cycloaddition[3] and conjugate addition reactions[4])

Physical Data: mp 115-117 °C; bp 180-210 °C/1 mmHg.

Solubility: sol THF, CH_2Cl_2, toluene; insol H_2O.

Preparative Methods: can be prepared (eq 1) by four methods: (a) dehydrohalogenation of a haloethyldiphenylphosphine oxide,[5,6] (b) reaction of diphenylphosphinic chloride and vinylmagnesium bromide,[7] (c) palladium-catalyzed coupling of vinyl bromide and diphenylphosphine oxide,[8] (d) oxidation of commercially available diphenyl(vinyl)phosphine.[9]

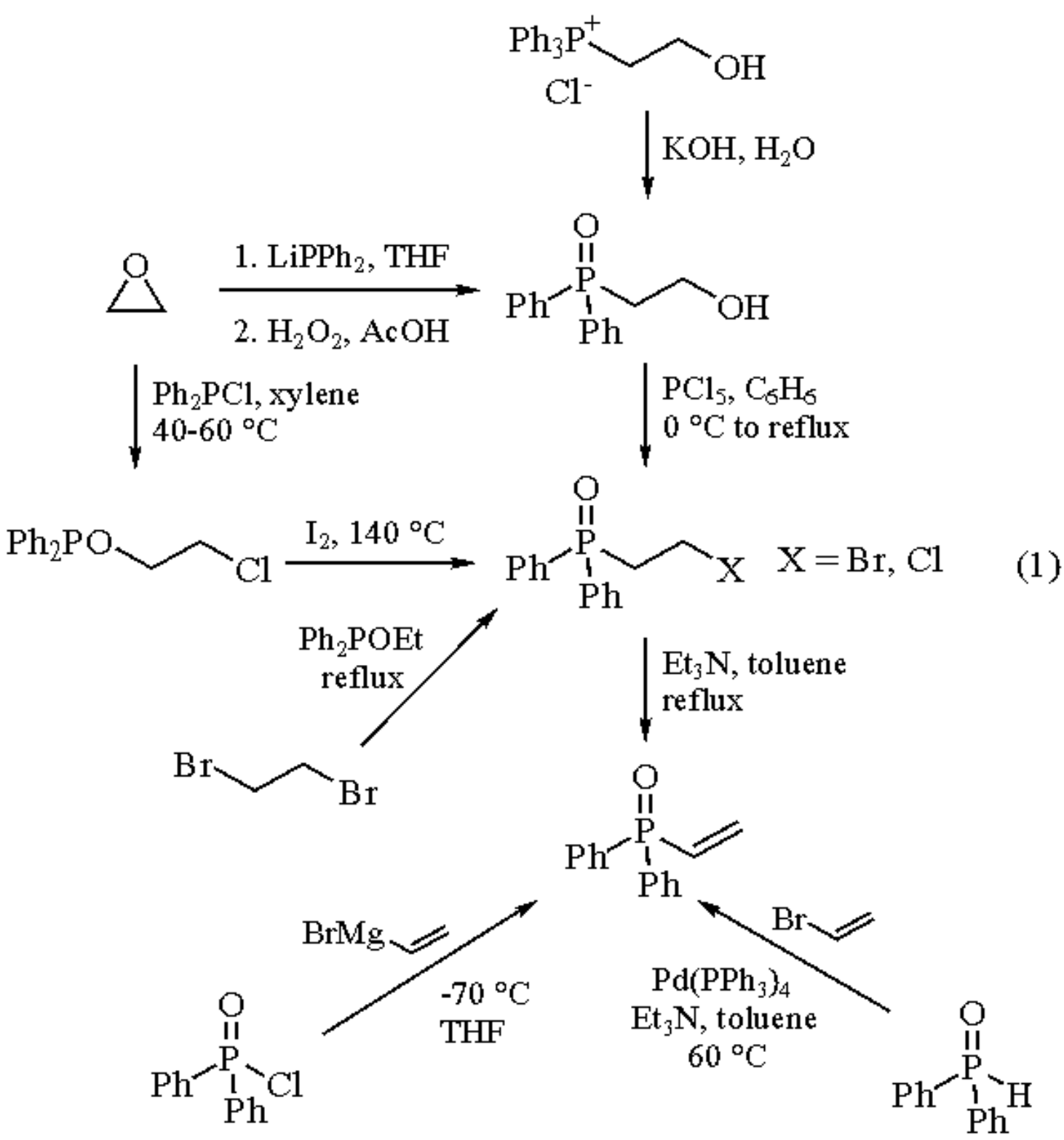

Handling, Storage, and Precautions: the toxicological properties of the reagent are unknown; however, by analogy with other Michael acceptors it should be assumed to be toxic. While radical polymerization is sluggish, diphenyl(vinyl)phosphine oxide readily undergoes anionic polymerization in the presence of Grignard reagents.[5]

Conjugate Additions.

Diphenyl(vinyl)phosphine oxide readily undergoes conjugate addition with carbon,[4] nitrogen,[4,10,11] oxygen,[4,12] and sulfur[4,13] nucleophiles. Of particular interest is the addition of chiral amines (eq 2)[11] and alcohols (eq 3),[12] which provide precursors of chiral phosphines, potentially useful ligands for various transition metal catalyzed processes.

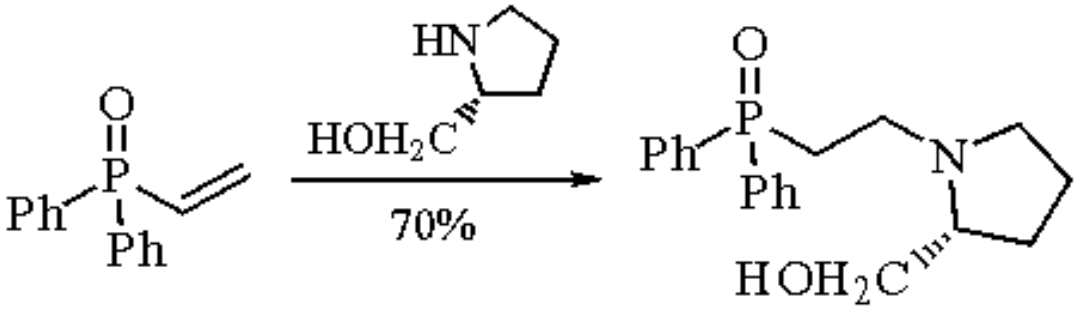

(2)

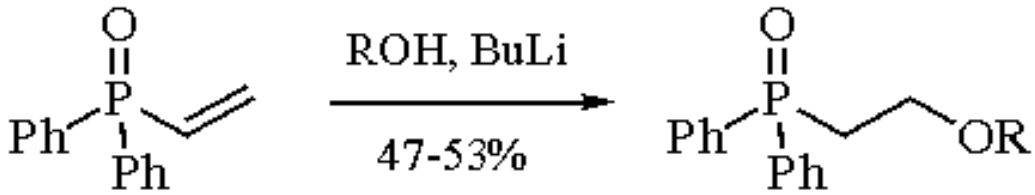

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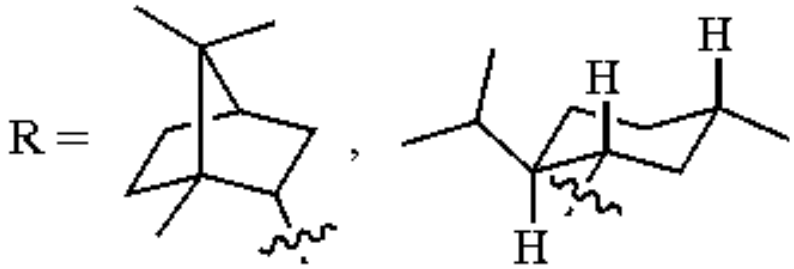

Alkylation of the pyrrolidine enamine of cyclohexanone, followed by a Baeyer-Villiger oxidation and acyl transfer, leads to a two-carbon ring expansion (eq 4).[14]

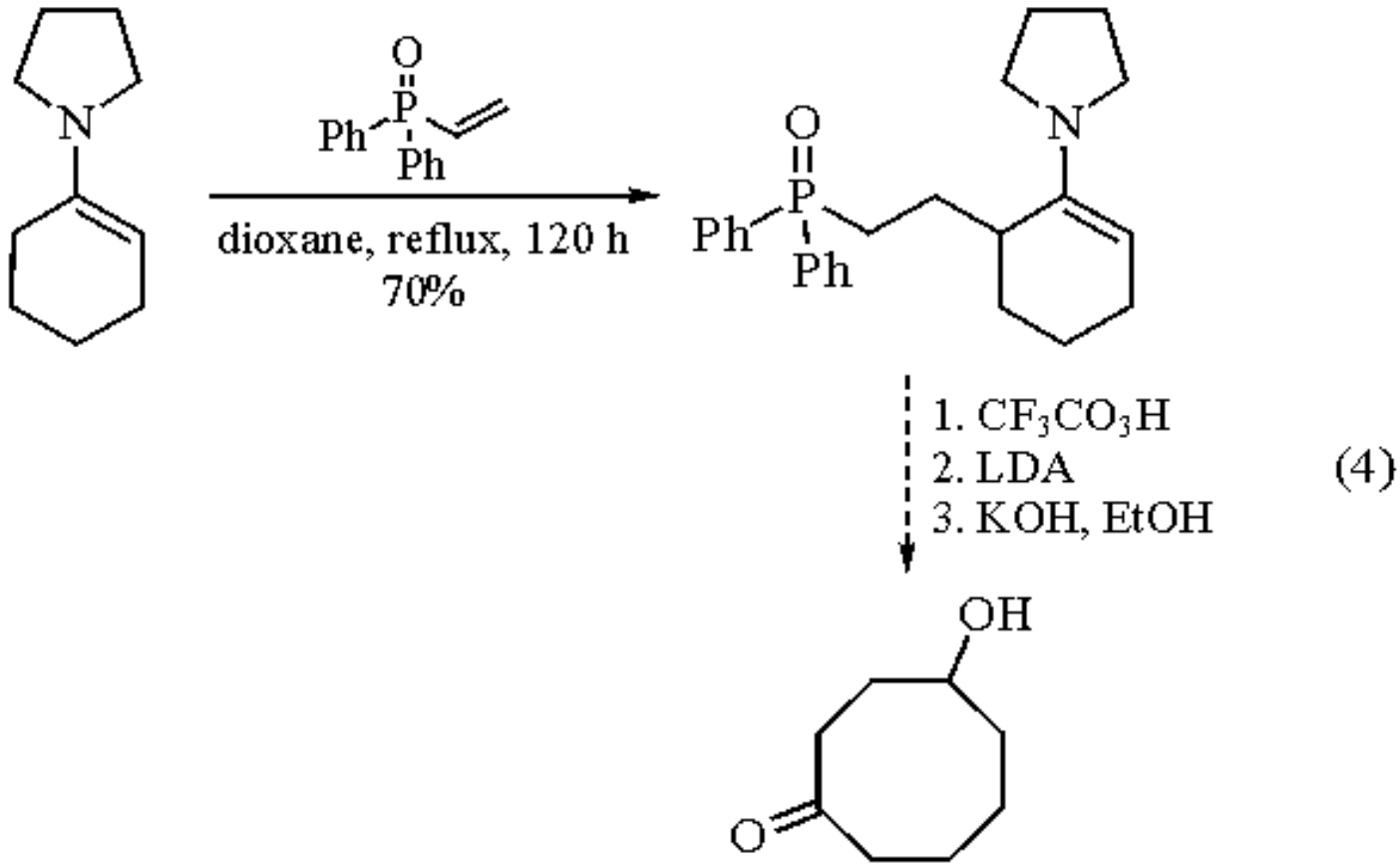

(4)

Horner-Wittig Reactions.

Simple amines such as ***Morpholine***, ***Piperidine***, and ***Pyrrolidine*** add to the vinylphosphine oxide to furnish adducts[11] which can be used in the regio and stereospecific Horner-Wittig synthesis of allylic tertiary amines (eq 5).[2] The anions, generated with ***n-Butyllithium*** in THF at 0 °C, react with aldehydes and ketones (including enolizable ones) at -78 °C to give isolable β-hydroxyphosphine oxides. Completion of the Horner-Wittig reaction (***Sodium Hydride***, DMF, 30 °C) gives allylamines in high yield. In the cases where R^1 &neq; R^2 the diastereoisomeric β-hydroxyphosphine oxides can be separated by chromatography or fractional crystallization. Stereospecific *syn* elimination of $Ph_2PO_2^-$ then enables isolation of both the (*Z*)- and (*E*)-alkenes. In contrast, the conventional Wittig reaction often gives inseparable mixtures of geometric isomers.

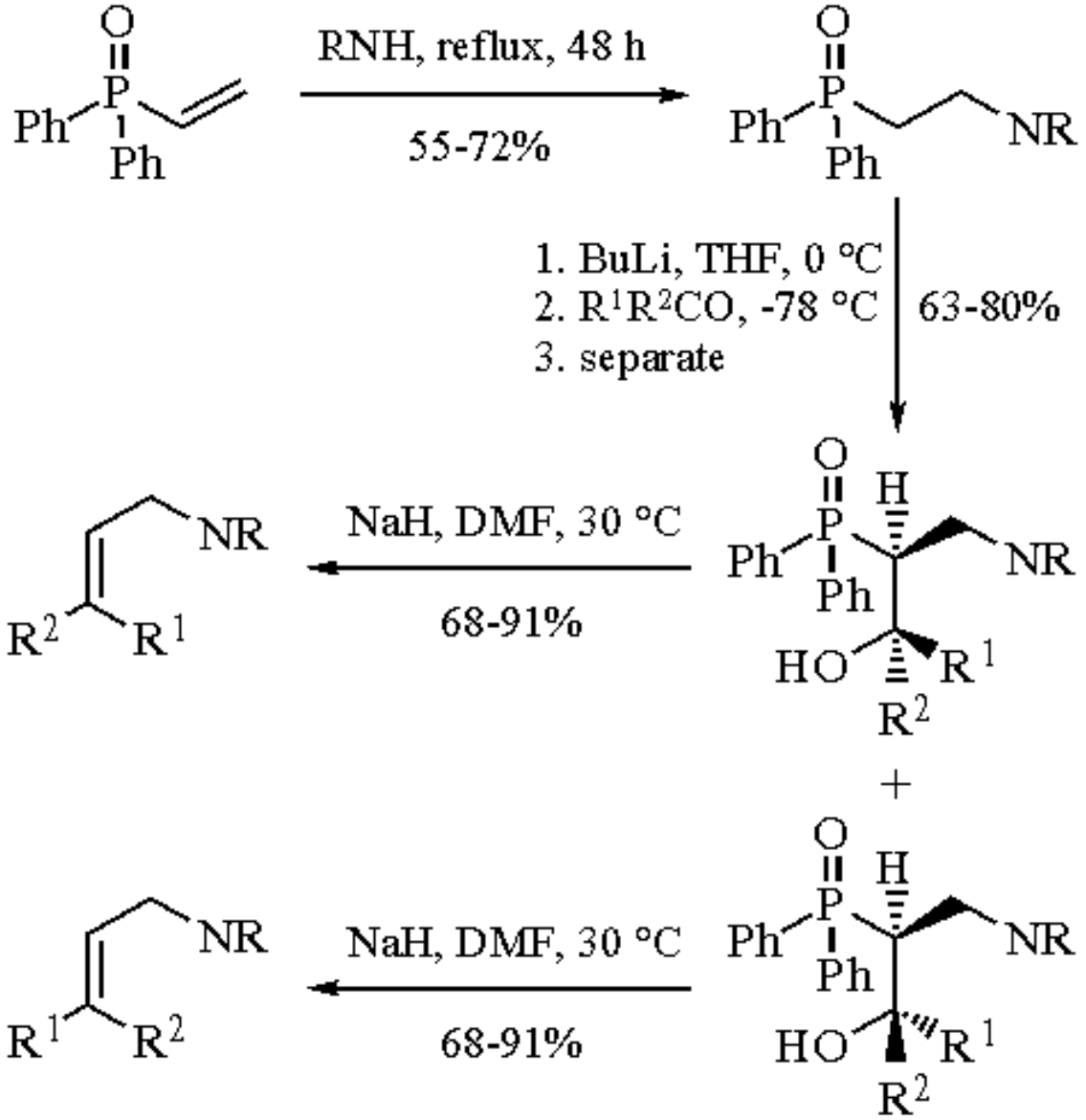

(5)

NR = morpholine, piperidine, pyrrolidine

Cycloaddition Reactions.

Diphenyl(vinyl)phosphine oxide undergoes 1,3-dipolar cycloaddition reactions with a variety of nitrones, giving mixtures of regioisomeric isoxazolidines.[3] The regiochemistry of the cycloaddition is very sensitive to minor structural changes in the nitrone (eqs 6-8). The chemistry has been extended to chiral nitrones.[15]

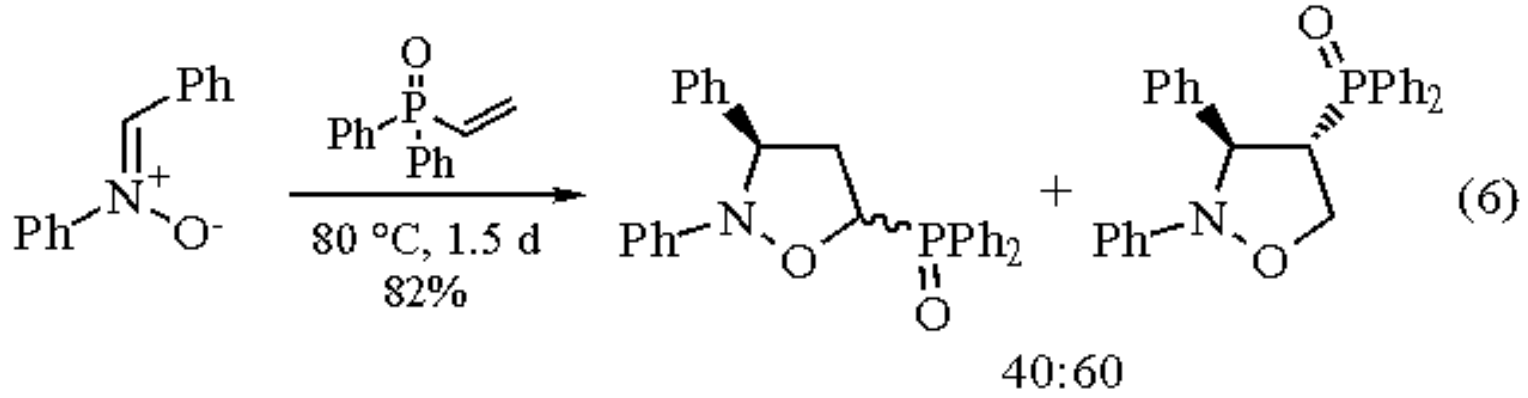

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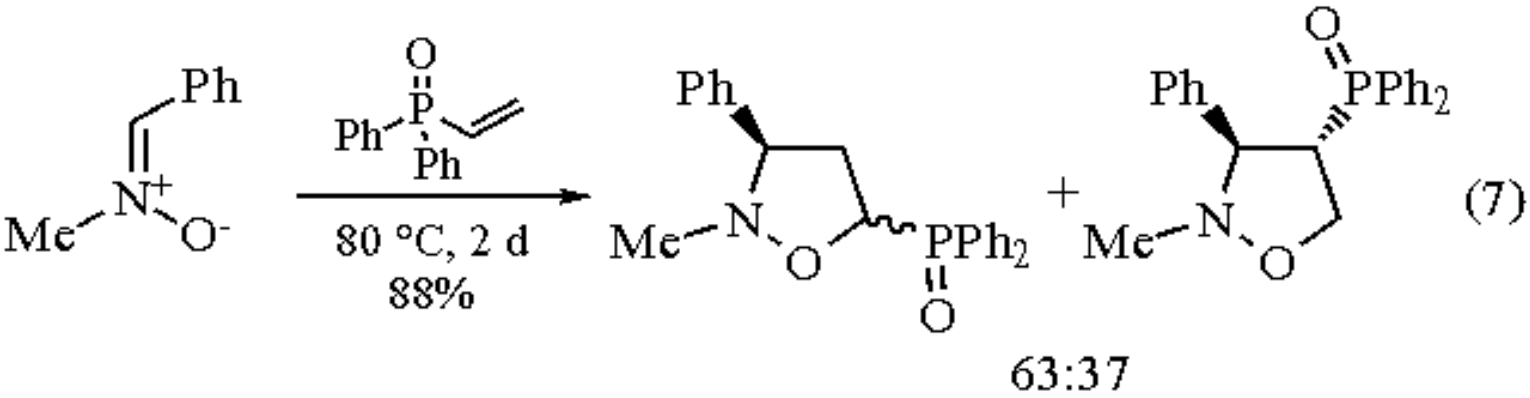

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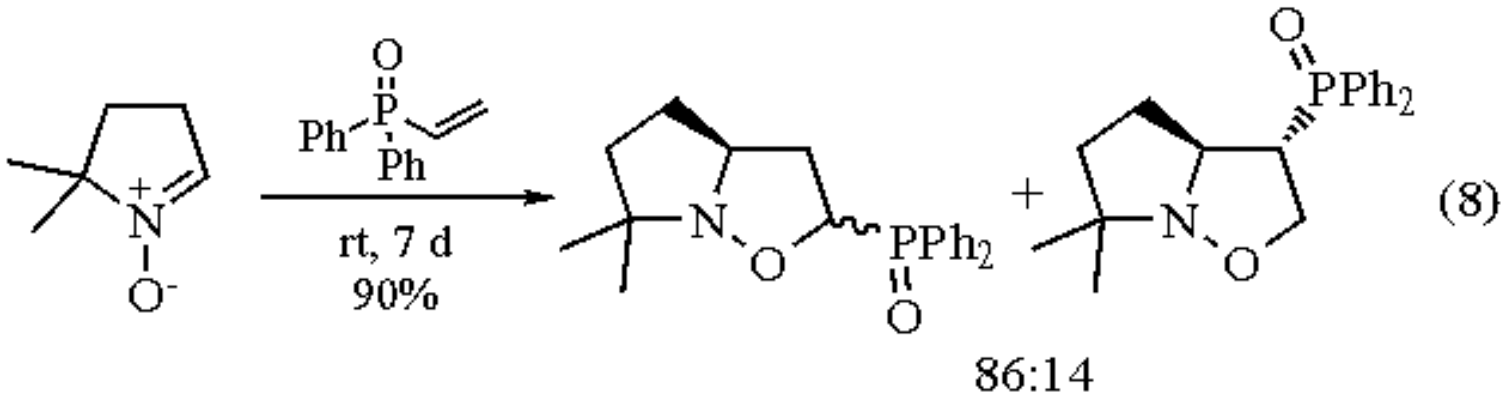

(8)

Lewis acid catalyzed Diels-Alder reactions with ***Cyclopentadiene*** giving predominantly *endo* selectivity have been described (eq 9).[16]

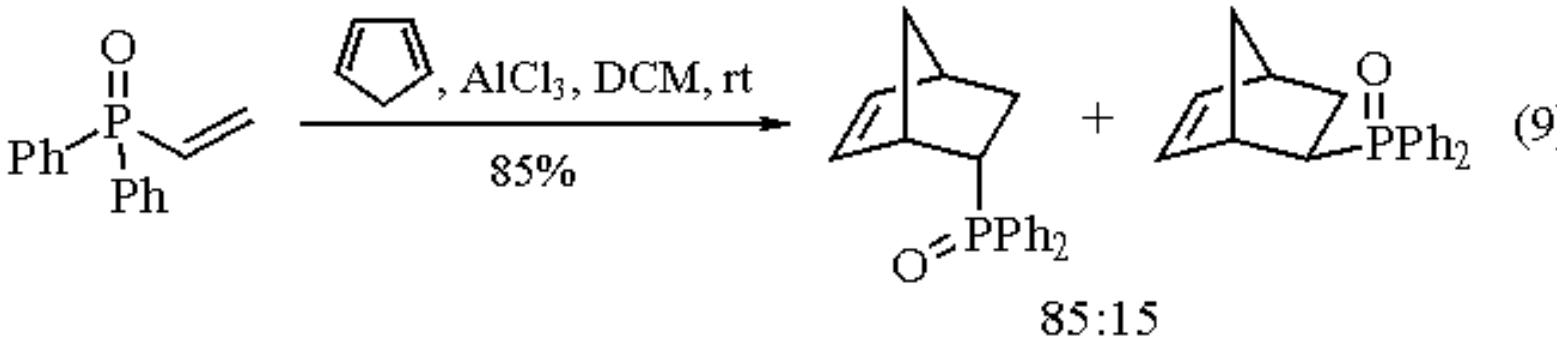

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Diphosphorus Tetraiodide[1,2]

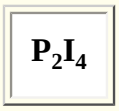

[13455-00-0] · I_4P_2 · Diphosphorus Tetraiodide · (MW 569.54)

(exhibits a high affinity for oxygen and acts as a unique reagent able to promote substitution, dehydration, and reduction reactions)

Physical Data: mp 124 °C (from CS_2);[3] X-ray;[4] ^{31}P NMR.[5]

Solubility: sol CS_2; partly sol CH_2Cl_2.

Form Supplied in: bright orange solid; commercially available.

Handling, Storage, and Precautions: can be weighed out rapidly in air into vials flushed with nitrogen. Store under nitrogen in the absence of moisture. This reagent should be handled in a fume hood.

Introduction.

Diphosphorus tetraiodide is a bright orange solid which fumes in air, probably due to the presence of trace amounts of white phosphorus. It is most conveniently prepared by mixing, at rt, stoichiometric amounts of white phosphorus and iodine in CS_2,[3] or by reaction of phosphorus trichloride with potassium iodide in ether (3 equiv KI, reflux, 12 h, 75%).[6] Diphosphorus tetraiodide often exhibits similar reactivity to ***Phosphorus(III) Iodide***. P_2I_4 exhibits a high affinity for oxygen and acts as a unique reagent able to promote substitution and dehydration, as well as reduction, reactions. In the last case, a mixture of phosphorus acids (including hypophosphorous acid) and iodine is formed. The characteristic reactivity of P_2I_4 was disclosed very early by Berthelot in 1855, when he described the synthesis of allyl iodide from glycerol and P_2I_4.[7] In this transformation, H_2O_2 is formally removed and one hydroxy group is substituted by an iodide ion.

P_2I_4 was first used in the early 1920s by Kuhn[8,9] and later by Inhoffen[10] for the reduction of unsaturated diols to *trans*-polyenes or enepolyynes (eq 1).

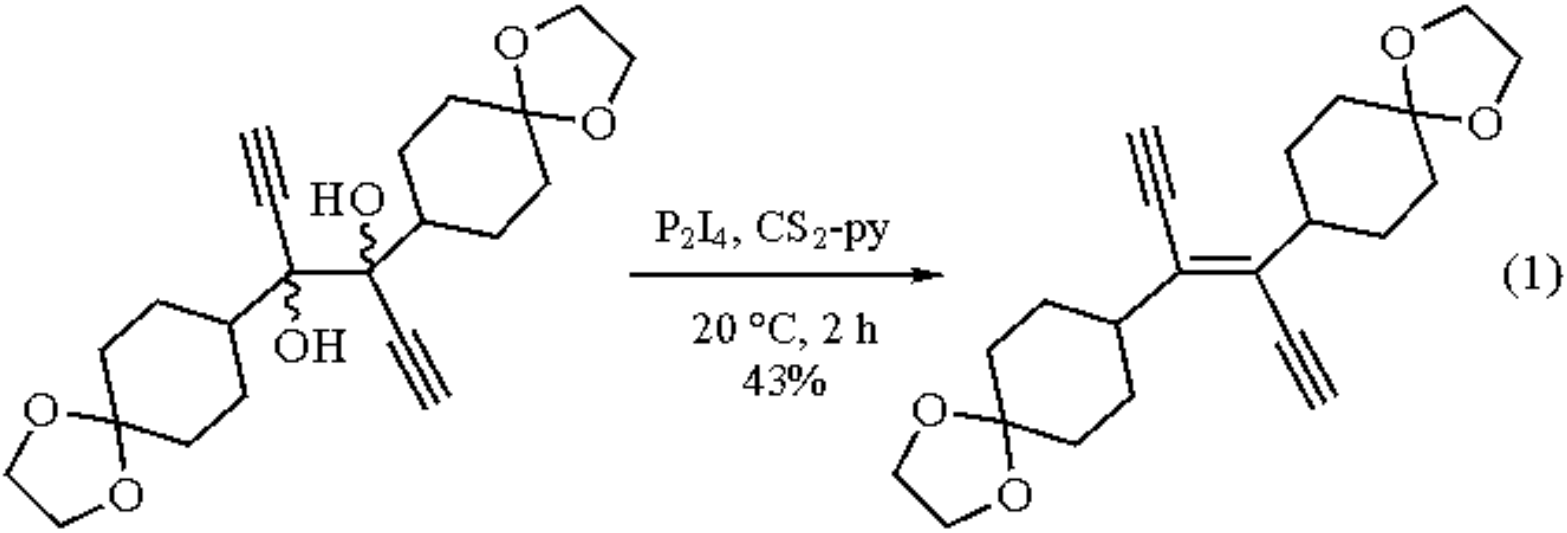

Reactions of P_2I_4 Involving Substitutions with Iodide Ion.

P_2I_4 reacts with alcohols (CS_2, 20 °C, 0.5-24 h) to form alkyl iodides in good to very good yields (eq 2).[3] The reaction is quite general and occurs with primary, secondary, and tertiary alcohols,[3,11] as well as with benzyl[3] and allyl alcohols.[12] The reaction is very fast (<0.5 h) with *t*-alkyl, benzyl, and allyl alcohols, but quite slow (24 h for completion) with primary and secondary alcohols, especially with neopentyl derivatives (144 h). It has also been successfully carried out in special cases (i.e. for the preparation of [^{11}C]methyl iodide (99.5% purity, 3.4 Ci μmol^{-1})[13] and [^{11}C]allyl iodide[3]), under vacuum (10^{-2} mmHg), in the gas phase, and on solid supports (VGSR).

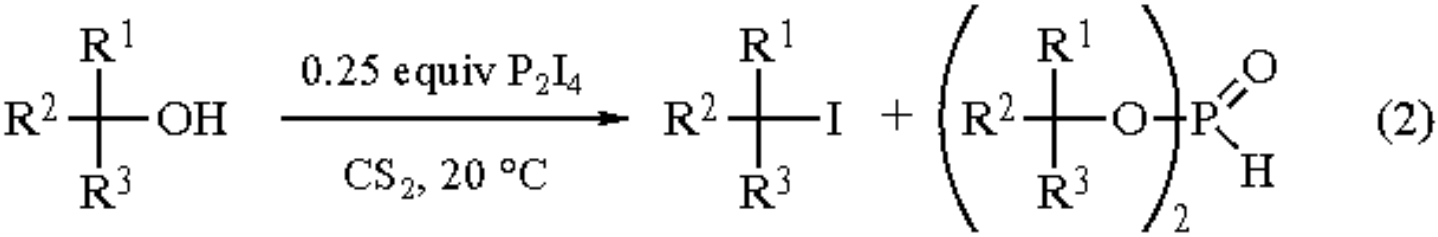

R^1, R^2, R^3 = H, Me, Hex	24 h	70%	0%
R^1, R^2, R^3 = H, H, Pr	0.1 h	33%	55%
R^1, R^2, R^3 = Me, Me, Bu	0.5 h	82%	0%
R^1, R^2, R^3 = Me, Me, Ph	0.5 h	90%	0%

Rearrangement does not usually occur[3] except with allyl alcohols[12] and only in rare cases are elimination reactions observed (for example from *cis*-4-*t*-butyl-1-cyclohexanol and a little from its *trans* stereoisomer).[3] The reaction is stereoselective with secondary alkyl halides and occurs by net inversion of configuration.[3] The reaction takes another course (i) when carried out on primary and secondary alcohols if it is rapidly quenched by water (after 0.1 h instead of 24 h), where it mainly produces dialkyl phosphites (eq 2),[3] and (ii) when carried out on benzyl alcohols bearing electron-withdrawing groups (or whose benzylic carbon is quite hindered by a *t*-butyl group or by two methyl groups in 2,6-positions on the aromatic ring), which undergo reduction in refluxing benzene to form the parent hydrocarbons in good to moderate yields.[14] Under the same conditions, but in the presence of disulfides, benzyl alcohols afford the corresponding benzyl sulfides (0.5 equiv P_2I_4, benzene, reflux 4-10 h, 6-90% yield).[15]

α,o-Diols, with the exception of 1,2-glycols (see below), produce the corresponding diiodides on reaction with 0.5 equiv of P_2I_4[3] and form monoiodides if half the amount of P_2I_4 is used instead.[16] Selective transformation of primary over secondary carbinols has been achieved. Cyclopropyl carbinols which do not bear a fully alkyl substituted carbinol carbon produce the corresponding iodides in good yield (70%), in addition to trace amounts of 3-alkenyl iodides resulting from cyclopropane ring opening (eq 3).[17] However, these cleavage products are formed as predominant products[17] (i) from alcohols where the carbinol carbon is fully alkyl substituted, (ii) from cyclopropyl carbinols bearing a silyl substituent on the cyclopropane ring (eq 3), and (iii) from seleno analogs which possess hydroxy groups at an allylic position.[17]

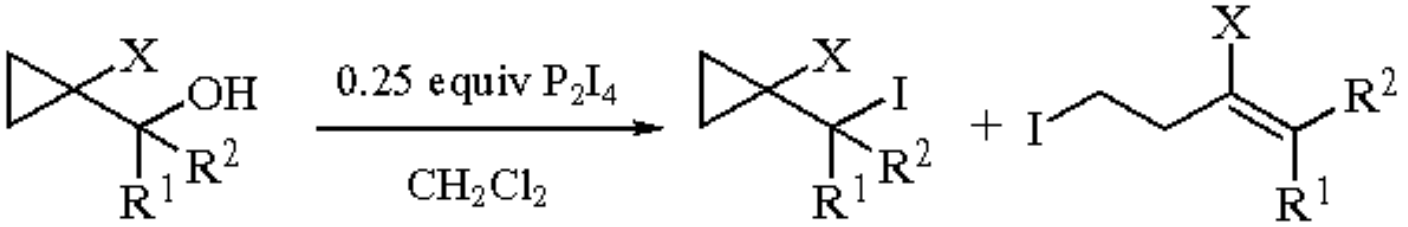

(3)

X = H	R^1 = H	R^2 = H	20 °C, 20 h	69%	2%
X = SPh	R^1 = H	R^2 = H	55 °C, 24 h	62%	0%
X = H	R^1 = H	R^2 = Me	-10 °C, 1.5 h	69%	9%
X = H	R^1 = Me	R^2 = Me	-20 °C, 1.5 h	0%	72%
X = TMS	R^1 = H	R^2 = Dec	0 °C, 1 h	0%	73%

β-Aminoalkyl carbinols are cyclized to aziridines (P_2I_4, benzene, 20 °C, 24 h, 45-75% yield).[18]

The high oxygenophilicity of the phosphorus atom of P_2I_4 coupled with the high nucleophilicity of iodide ion allows the ring opening of cyclopropyl ketones to γ-iodo ketones,[17] oxetanes,[19] tetrahydrofurans,[19] and tetrahydropyrans[19] to the corresponding o-diiodides (60, 50, and 15% yield, respectively, reaction carried out at 20 °C) and of γ-butyrolactone (90 °C, 24 h) to 4-iodobutyric acid or to methyl butyrate, depending upon the reagent (H_2O or methanol) used to quench the reaction.[1])

P_2I_4 can be employed for the deprotection of α,α-bis(methoxy)- and α,α-bis(ethoxy)alkanes, leading to the corresponding aldehydes or ketones together with methyl or ethyl iodide. The reaction is particularly easy with α,α-bis(methoxy)alkanes (20 °C, 0.2 h), but does not occur with dioxolanes even under drastic conditions.[20] This reaction has been successfully used[21] for the cleavage of alkoxymethyl aryl ethers to give hydroxyarenes and has been applied to the synthesis of the antibiotic ascofuranone.[21]

P_2I_4 also reacts with thioacetals, orthothioesters, and their seleno analogs to produce vinyl sulfides, ketene thioacetals, vinyl selenides, and ketene selenoacetals, respectively.[22]

Reactions of P_2I_4 Involving Reduction.

P_2I_4 reacts differently with glycols (eq 1) or related α,δ-diols whose β,γ-carbons are both sp^2, sp, or part of a cyclopropane ring. These substrates lose two hydroxy groups and are converted to alkenes,[8-10] 1,3-dienes,[10] 1,2,3-trienes,[6] or 1,4-dienes,[23] respectively. β-Thioalkyl carbinols[24] and β-selenoalkyl carbinols[1,17] also behave differently from β-aminoalkyl carbinols (see above) and afford alkenes. The reaction is best achieved in the presence of ***Triethylamine***, occurs in a few hours at rt, is more efficient with methylseleno than with methylthio, phenylseleno, or phenylthio derivatives (which are the least reactive), and allows the regioselective synthesis of terminal, di-, tri-, and tetrasubstituted alkenes. The synthesis of alkylidenecyclopropanes[17] and allenes[25] via this approach can only be achieved from β-hydroxyalkyl methyl selenides. The elimination is in general antistereospecific,[1,17] except with β-hydroxyalkyl phenyl sulfides[24] which are the least reactive compounds and probably react via the intermediate formation of a thiiranium or a seleniranium ion (eq 4). Since β-hydroxyalkyl selenides can be synthesized from α-selenoalkyllithiums and carbonyl compounds, even hindered and/or enolizable ones such as 2,2,6-trimethylcyclohexanone or deoxybenzoin,[26] this set of reactions allows the synthesis of the corresponding alkenes which are not available via the Wittig reaction (eq 5).[27-29]

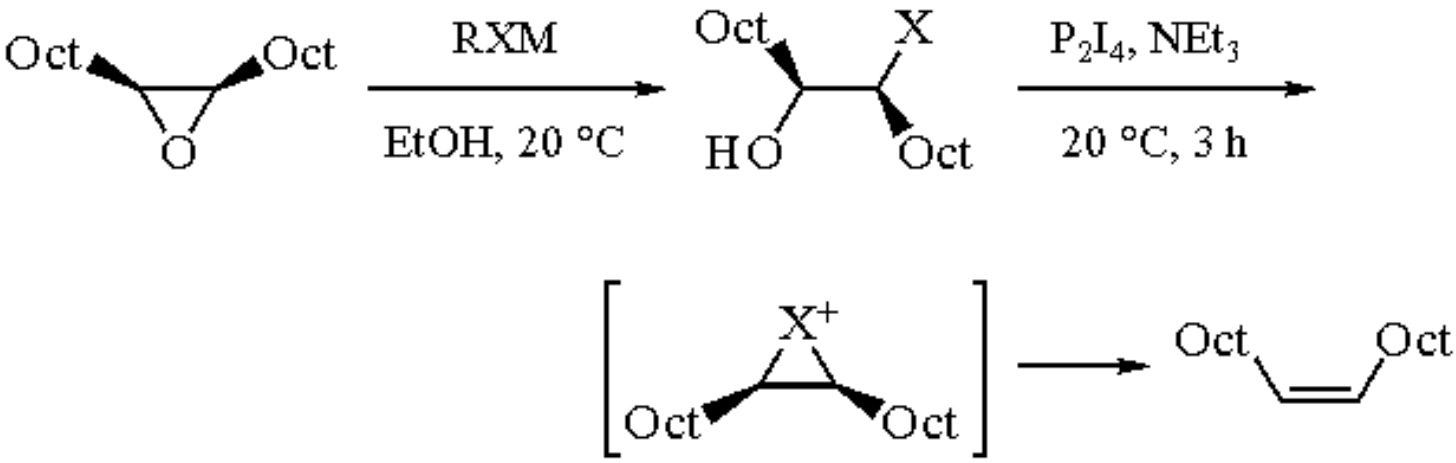

(4)

X = SeMe, SePh, SMe de > 94%
X = SPh de = 50%

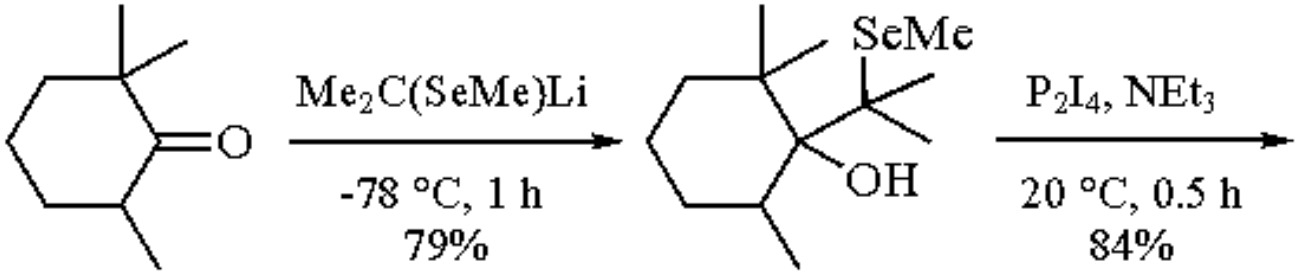

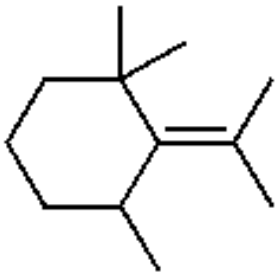

(5)

P_2I_4 also reduces epoxides (eq 6)[1,19,30] and thiiranes[31] to alkenes. The reduction of epoxides takes place at rt in methylene chloride in the presence of a base such as triethylamine or pyridine.[19] The reduction of thiiranes requires more drastic conditions (DMF, 80 °C).[31] Both reactions are regioselective and highly stereoselective, allowing the synthesis of a variety of alkenes (terminal, di-, tri-, and tetrasubstituted)[19,30,31] whose stereochemistry is derived from that of the starting epoxides or thiiranes (eq 6).[19,30,31]

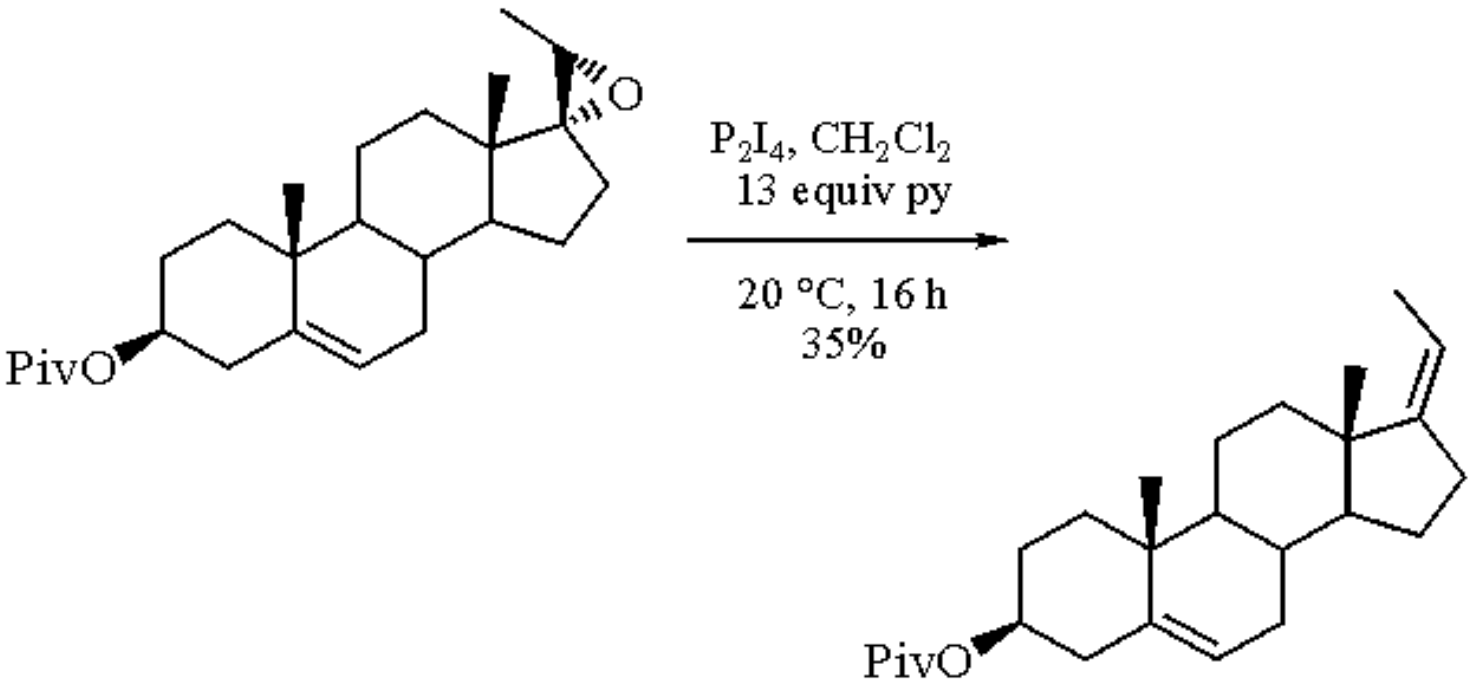

(6)

This reaction allows the synthesis of polyfunctionalized alkenes such as enones,[19,30] diphenylvinylphosphine oxides,[32] vinylcyclopropanes,[30] and 1,3-dienes[19,30] from the corresponding epoxides. The ethylidene derivative shown in eq 6 is produced in modest yield as the pure (*E*) stereoisomer.[33] Other reagents able to deoxygenate epoxides, such as ***Tungsten(VI) Chloride-n-Butyllithium*** and [*n*-Bu_3SnAlMe]Li, result in considerable scrambling of alkene stereochemistry.[33]

P_2I_4 is a valuable reducing agent, able to reduce under mild conditions iodo,[34] bromo,[34] and seleno ketones,[17] including cyclic ones (0.5 equiv, 25 °C, 1-7 h, 54-97% yield; eq 7). Sequential reaction of terminal epoxides with ***Iodotrimethylsilane***, Jones reagent, and P_2I_4 allows the one-pot chemoselective synthesis of the corresponding methyl ketone resulting from the reduction of the iodomethyl ketone intermediate (eq 7).[34]

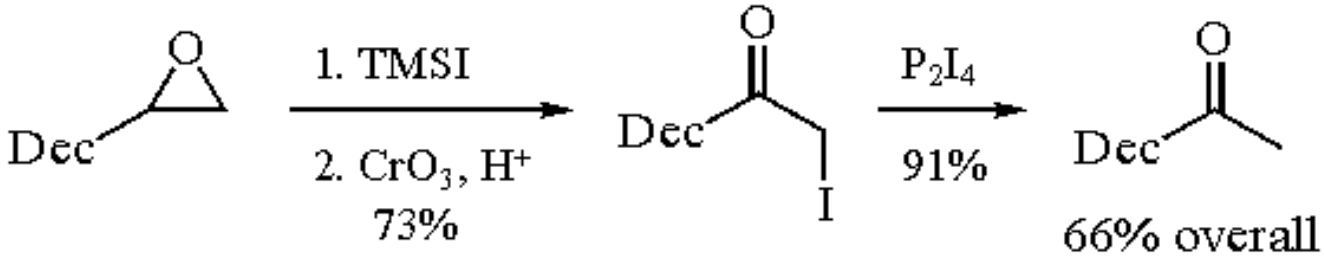

(7)

P_2I_4 also reduces, under mild conditions, aminoxides,[35] sulfoxides,[36,37] and selenoxides[36] to amines, sulfides, and selenides, respectively (eq 8). These conditions are sufficiently mild so that the very easy selenoxide elimination leading to alkenes does not compete.

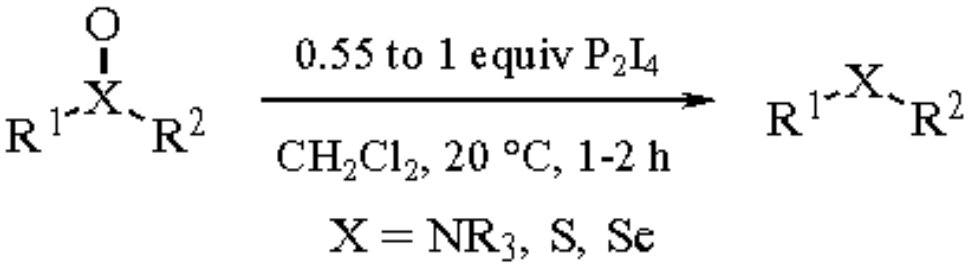

(8)

P_2I_4 reduces ozonides very rapidly at -78 °C;[17] promotes, under unusually mild conditions, the reduction of nitroalkanes to nitriles (eq 9);[36] and transforms, in boiling acetonitrile, arenesulfonic acids, their salts, their chlorides, and their esters to diaryl disulfides.[38] Arenesulfonamides are stable towards P_2I_4 in boiling acetonitrile, but are successfully reduced at much higher temperature and under neat conditions to give diaryl disulfides as the sole products.[38]

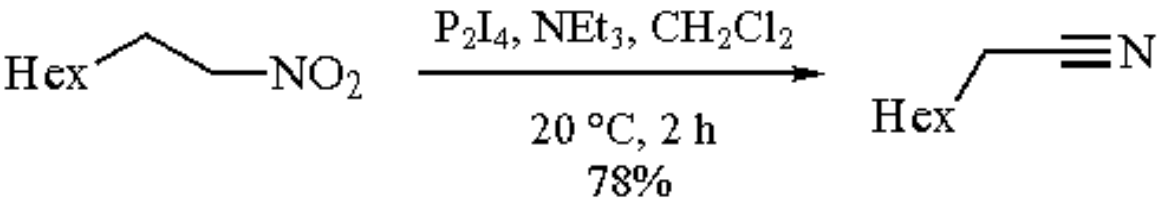

(9)

Reactions of P_2I_4 Involving Dehydration or Related Reactions.

P_2I_4 has proved to be a valuable dehydrating agent. Thus 2-amino alcohols are transformed to aziridines (see above);[18] aldoximes[30,39] and amides[40] are smoothly transformed to nitriles, and thioamides behave similarly.[41] P_2I_4 also allows the dehydrative condensation of carboxylic acids with amines.[42] The latter reaction seems to be attractive for converting weak or hindered amines into amides and has been used for the synthesis of a few peptides.[42]

Related Reagents.

Lithium Aluminum Hydride-Diphosphorus Tetraiodide.

---

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(2*R*,3*R*)-Dipivaloyltartaric Acid

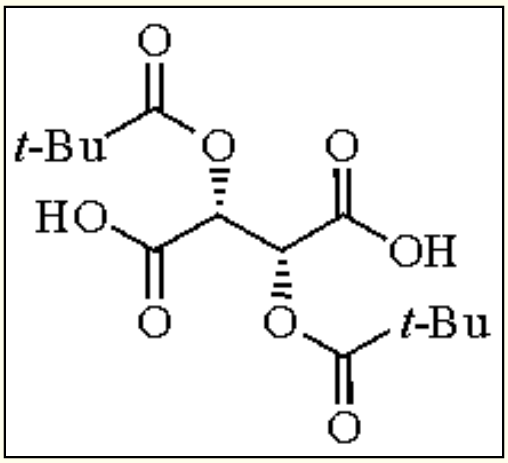

[65259-81-6] · $C_{14}H_{22}O_8$ · (2*R*,3*R*)-Dipivaloyltartaric Acid · (MW 318.36)

(chiral auxiliary for enantioselective protonation (deracemization) and asymmetric transformation; starting material for synthesis of chiral succinimides and polyhydroxy compounds)

Alternate Name: (2*R*,3*R*)-DPTA.

Physical Data: mp 135 °C; [α]25D -24.2° (1.7, dioxane).[1]

Solubility: sol Et_2O, THF, aq $NaHCO_3$ solution; insol cold H_2O.

Preparative Method: hydrolysis of the corresponding anhydride obtained by heating (2*R*,3*R*)-tartaric acid and pivaloyl chloride at 120-140 °C for 4 h.[1] *Drying:* over P_2O_5 in vacuo, controlled by ^1H NMR and optical rotations.

Handling, Storage, and Precautions: the anhydrous solid can be stored at rt in the absence of moisture. It is retrievable from its basic solution (10 % aq $NaHCO_3$), after acidification (HCl), with a quantitative yield.[2] On heating it transforms into an anhydride with elimination of one molecule of water.

Chiral Auxiliary Used for Enantioselective Protonation (Kinetic Control).

(2*R*,3*R*)-Dipivaloyltartaric acid has been essentially used for enantioselective protonations.[3] Surprisingly, for the creation of the chirality during the formation of the C-H linkage, this type of reaction has received attention only recently, unlike enantioselective hydrogenations or enantioselective reductions with hydride anion, widely used in asymmetric syntheses. (2*R*,3*R*)-DPTA was the first protonating reagent leading to appreciable enantioselections (up to 80 %) when applied to

different classes of substrates such as enamines,[4] enolates of functionalized esters,[5] and carbonyl compounds.[4] At the present time, high enantioselectivities have also been reached with other protonating agents,[6] but often limited to one target molecule.

The first reported experiments concerned the protonation of enamines with (2*R*,3*R*)-DPTA leading, after hydrolysis of the iminium salts formed in situ, to optically active carbonyl compounds.[7] Starting from the (*Z*)- and (*E*)-morpholino enamines of 2-phenylpropanal, it was possible to establish, in spite of modest results (ee 13-18%), that the protonation step was kinetically controlled: the (*Z*)- and (*E*)-isomers led to 2-phenylpropanal with a reverse configuration, excluding an equilibrium of the intermediate diastereoisomeric salts (eq 1).[7]

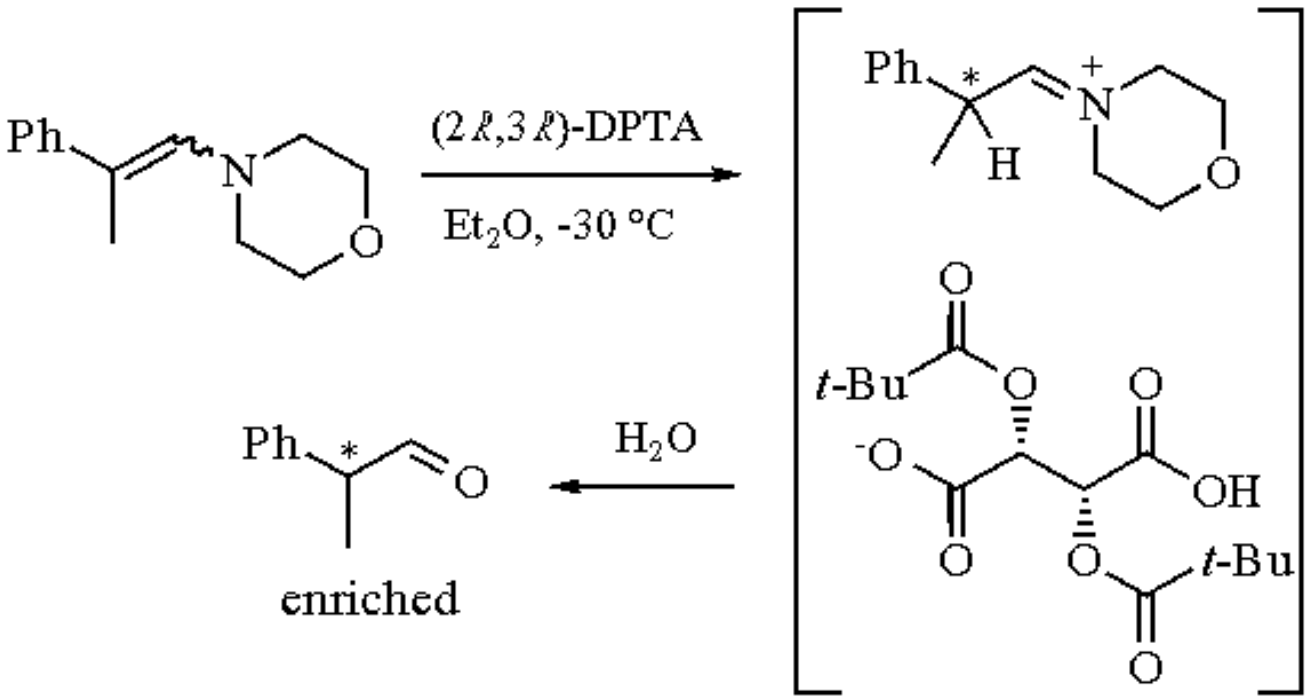

(1)

The protonation of lithium enolates of Schiff bases of racemic α-amino esters leads, after the workup, to α-amino acids of (*S*) configuration with ee as high as 70% (eq 2).[2,5,8,9]

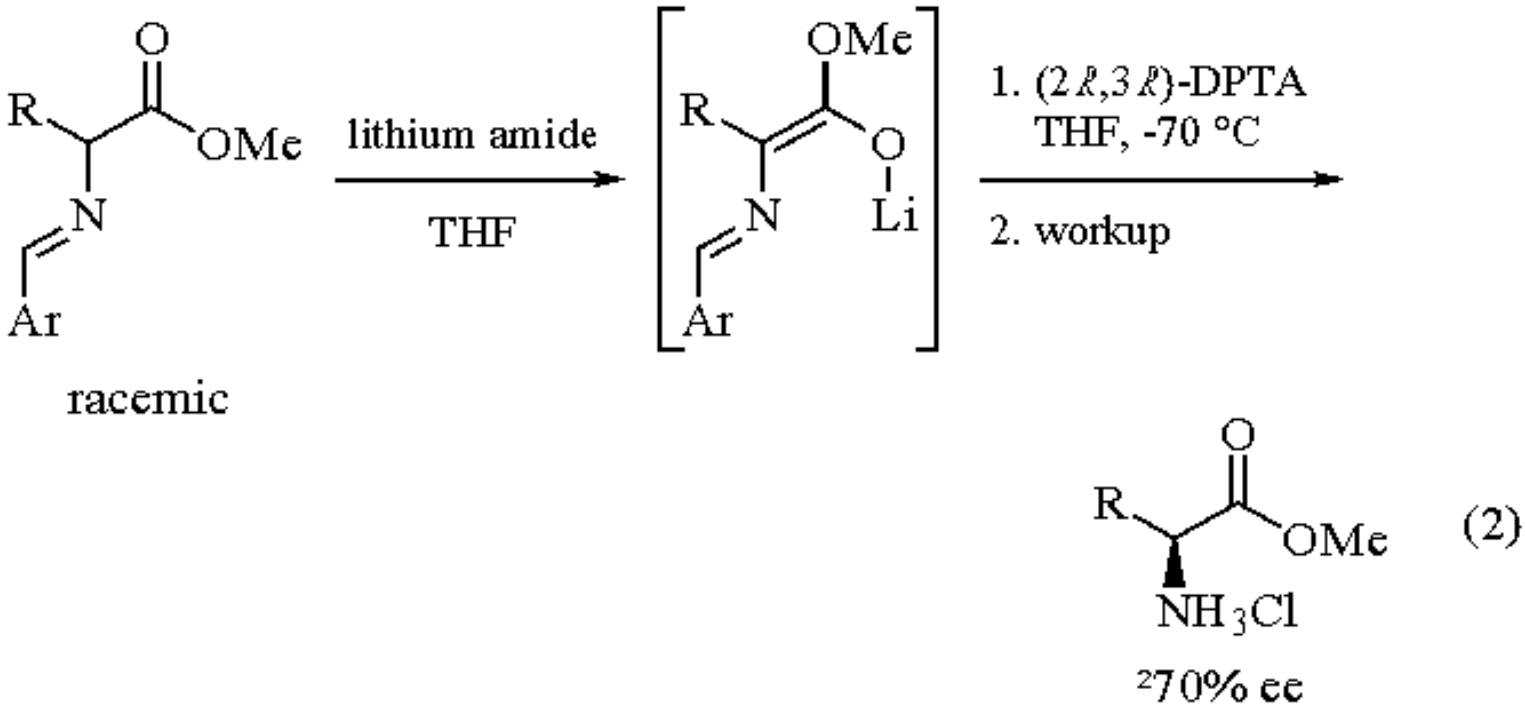

A first set of experiments, the study of the protonation of enolates obtained from benzaldehyde Schiff bases and ***Lithium Diisopropylamide***, showed that the asymmetric induction was not significantly affected by the size of the R moiety of the amino acid (R = Me, Et, *i*-Pr, *n*-Bu, *t*-Bu, Ph; ee = 44-56%).[2,9] The two main factors improving the enantioselection were the Ar substituent of the Schiff base and the lithium amide used for the deprotonation.[5,8,10] The following results (Table 1) indicate clearly that the enantioselectivity increases with the electron-donating power of substituents *para* to the Schiff base (eq 3),[5] leading to 70% ee with the Schiff base of *p*-methoxybenzaldehyde derived from phenylglycine.[9]

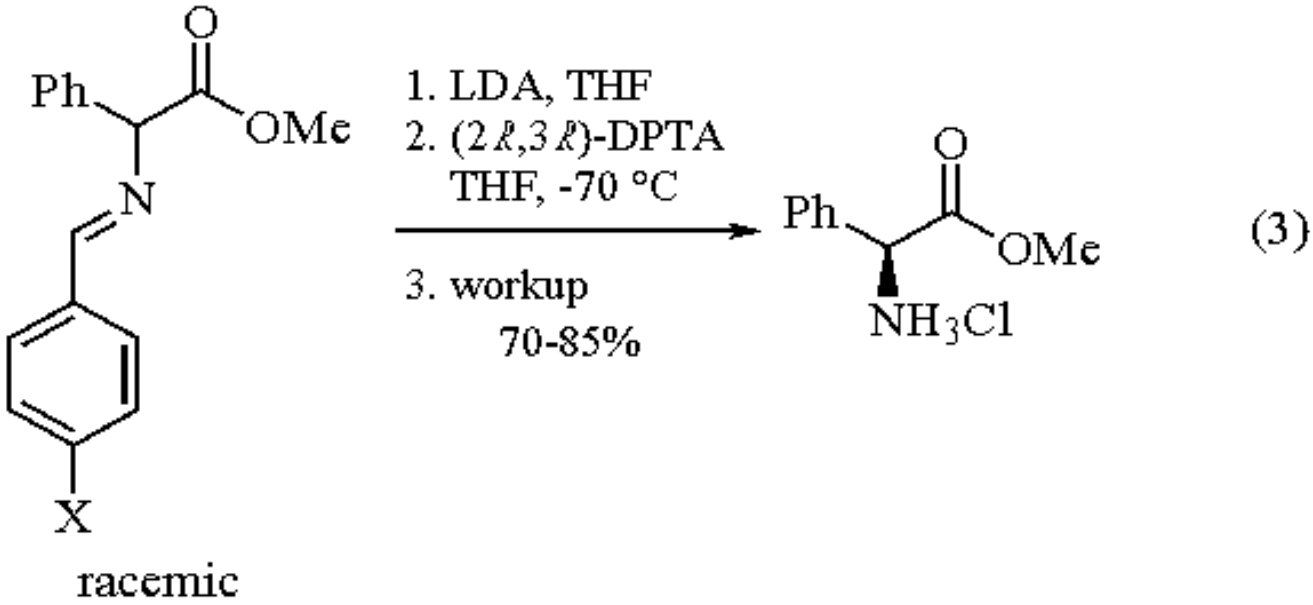

Table 1 Influence of the *para*-Substituent

X	ee (%)	X	ee (%)
NC	12	Me	53
Cl	31	MeO	57 (70)[a]
H	50	Me_2N	61

[a] Protonation carried out at - 105 °C.

The favorable effect of electron-donating substituents X, interpreted as the structure of the enolate becomes more rigid due to the increase of the coordination between the lithium and the nitrogen atoms, was confirmed on a series of α-amino acids.[9]

The enantioselectivity was dramatically affected by the structure of the lithium amide used for the deprotonation, indicating that the secondary amine liberated during the metalation step participates in the protonation step.[3,8,10] The utilization of chiral lithium amides allowed higher enantioselections than with classical LDA (eq 4) (Table 2).[8,10]

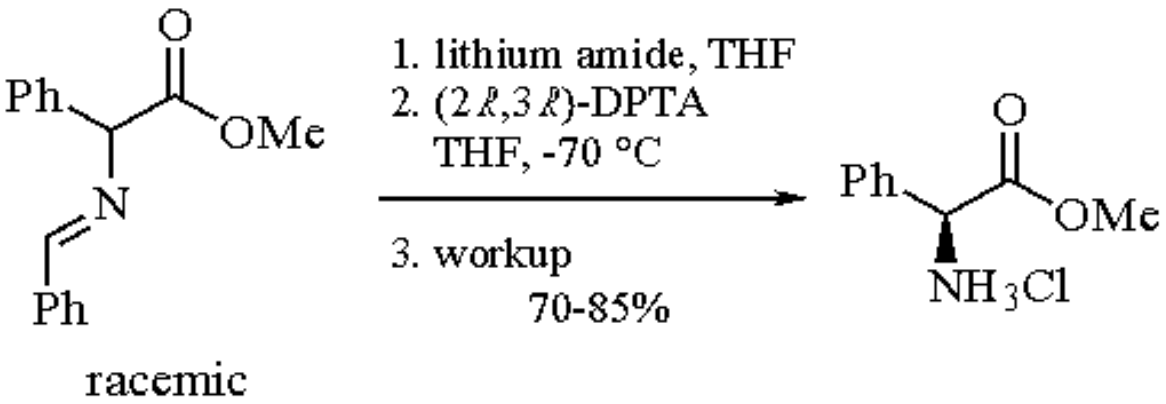

(4)

Table 2 Influence of the Lithium Amide used for Deprotonation

Lithium amide	ee (%)	Lithium amide	ee (%)
$LiN(i\text{-}Pr)_2$	50	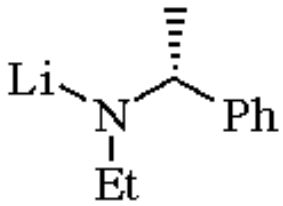	70
$LiNEt_2$	28	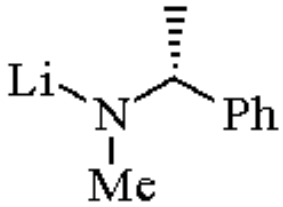	60
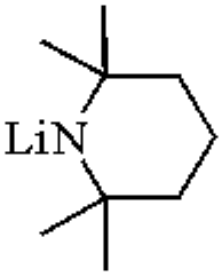	22		

The crucial role of the secondary liberated amine was also reported in experiments involving deprotonation with lithium (*R*)-*N*-ethyl(1-phenylethyl)amide and reprotonation at -70 °C with 2*R*,3*R*, racemic, and *meso*-DPTA, yielding, respectively, 70, 39, and 24% ee of the (*S*)-enantiomer. In the two last cases, significant inductions were obtained with the sole secondary chiral amine as chiral inductor in the medium.[8] Since these first results, chiral lithium amides have been widely used for asymmetric synthesis.

Owing to the importance of the amine, probably acting as a ligand of lithium or a proton carrier [ammonium salt of (2*R*,3*R*)-DPTA],[3,10] a process was proposed allowing the introduction of different amines and consequently a modification of the selectivity of the protonation: after deprotonation of a Schiff base of methyl valinate with ***Lithium Hexamethyldisilazide*** (LHMDS), the liberated HMDS was replaced by a more basic primary, secondary, or tertiary amine prior to the addition of (2*R*,3*R*)-DPTA (eq 5) (Table 3). In some cases, higher ee were observed compared to the classical procedure with LHMDS (34% ee) or LDA (47% ee).[10]

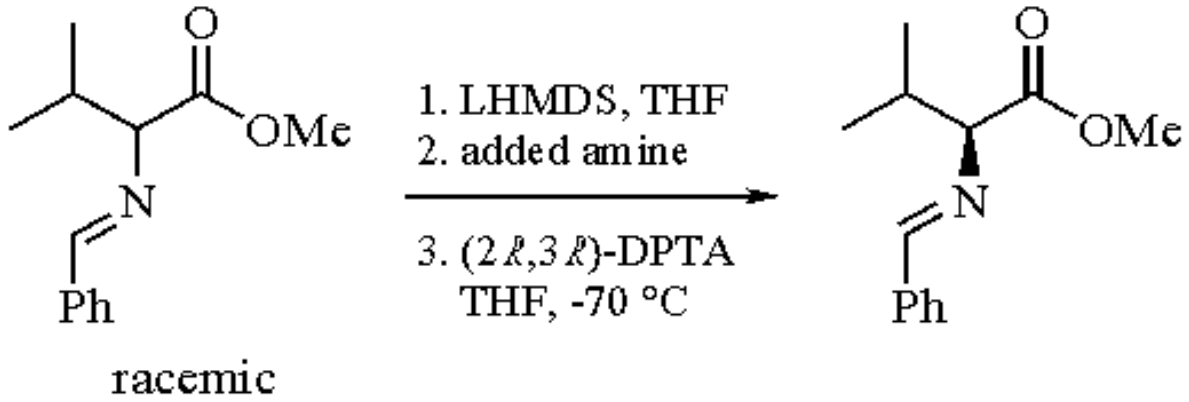

(5)

Table 3 Influence of the Added Amine

Added amine	ee (%)	Added amine	ee (%)
-	34	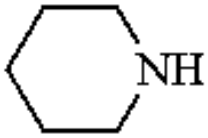	50
Et_2NH	44	$EtNH_2$	55
i-Pr_2NH	47	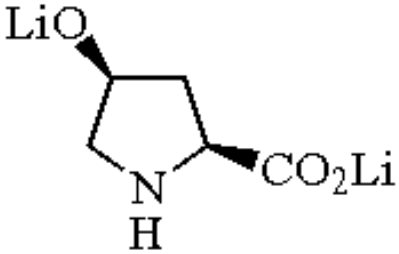	64

Enantioselective protonation of lithium dienolates obtained from Schiff bases of methyl α-aminobutenoates was carried out using (2*R*,3*R*)-DPTA, in order to synthesize vinylglycine by deconjugation (ee 36%).[9] Protonation of a cyclic lithium enolate derived from mandelic acid with (2*R*,3*R*)-DPTA was reported to occur with a low ee.[6b]

The potassium (*Z*)-enediolate obtained from racemic benzoin and ***Potassium Hydride*** when treated with (2*R*,3*R*)-DPTA affords (*S*)-benzoin with 80% ee (optically pure after one recrystallization in methanol).[11] In the reaction conditions, the enediolate is first *O*-protonated, then the resulting enediol slowly tautomerizes at low temperature into optically active benzoin with a high enantioselectivity. In the cases of incomplete tautomerization the residual enediol was immediately oxidized to benzil by the oxygen of the air during the workup. It was shown that the tautomerization of the enediol was hindered by the presence of an excess of (2*R*,3*R*)-DPTA (eq 6).[11]

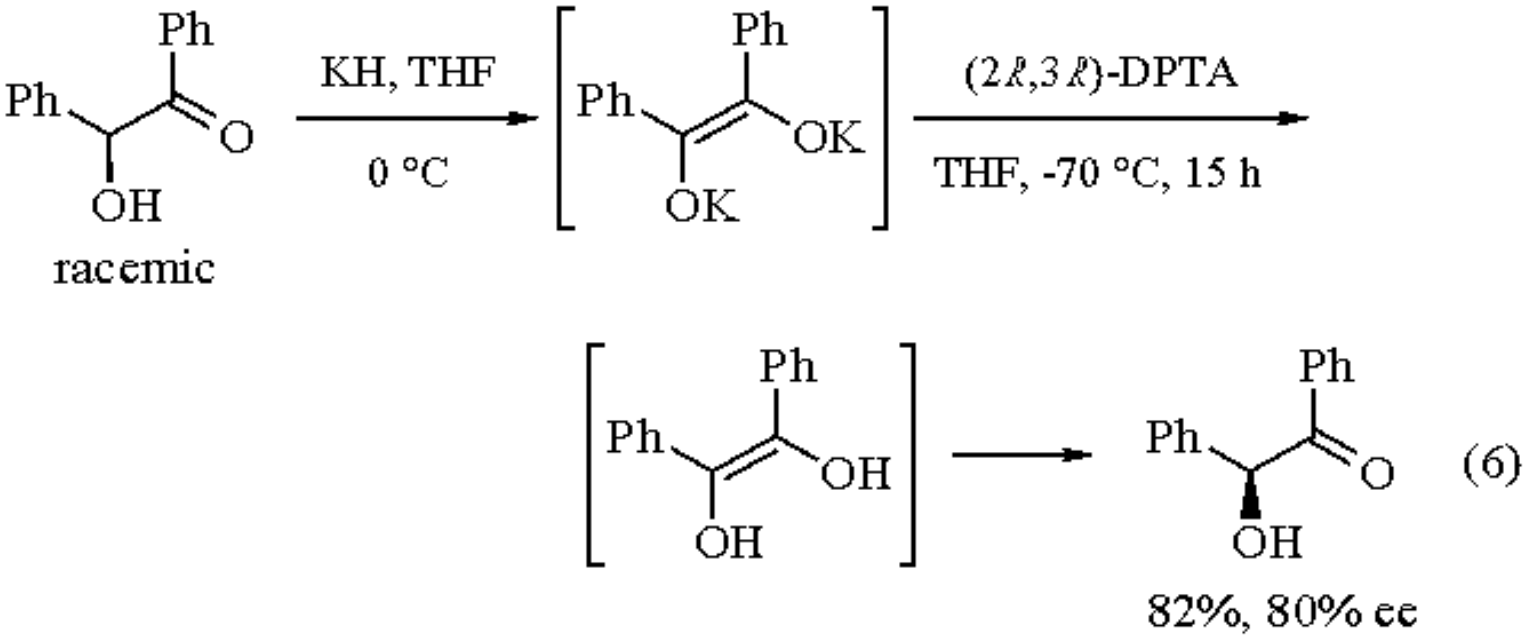

Finally, the configuration of the protonation product is predictable using the L Rule. The prochiral substrate is represented according to the letter L, where the vertical line represents the C=C bond and the horizontal line the C-X bond (X = nucleophilic atom). In such a case, protonation with (2*R*,3*R*)-DPTA is favored on the L-face, i.e. on the side of the reader. As an example, the protonation of a lithium enolate of a Schiff base of an α-amino ester, leading to the (*S*)-enantiomer, is given in eq 7.[3]

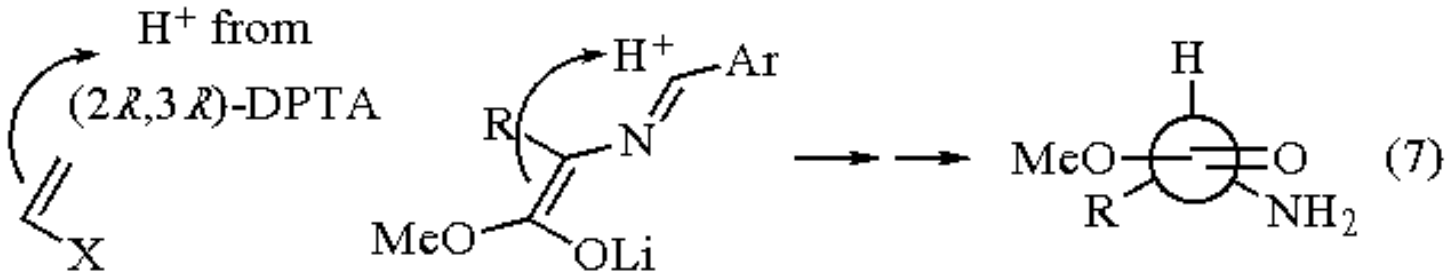

In enantioselective protonations, the final optically active product is generally chemically identical to the starting racemic material, precursor of the prochiral substrate on which the protonation is carried out. That is why the term deracemization was proposed for this type of process.[3,4,12] In a deracemization, the protonation step is kinetically controlled. Therefore a deracemization differs from an asymmetric transformation in which the reactions are thermodynamically controlled.[3,4]

Chiral Auxiliary Used for Asymmetric Transformations (Thermodynamic Control).

Racemic *N*-benzyl-*N*-methyl-α-amino propiophenone mixed with (2*R*,3*R*)-DPTA in acetone or dichloromethane leads with 90% yield to the corresponding salt of the (*S*)-amino ketone, which was reduced over ***Palladium on Carbon*** to a mixture of ephedrine (80%) and pseudo-ephedrine (20%) (eq 8).[13]

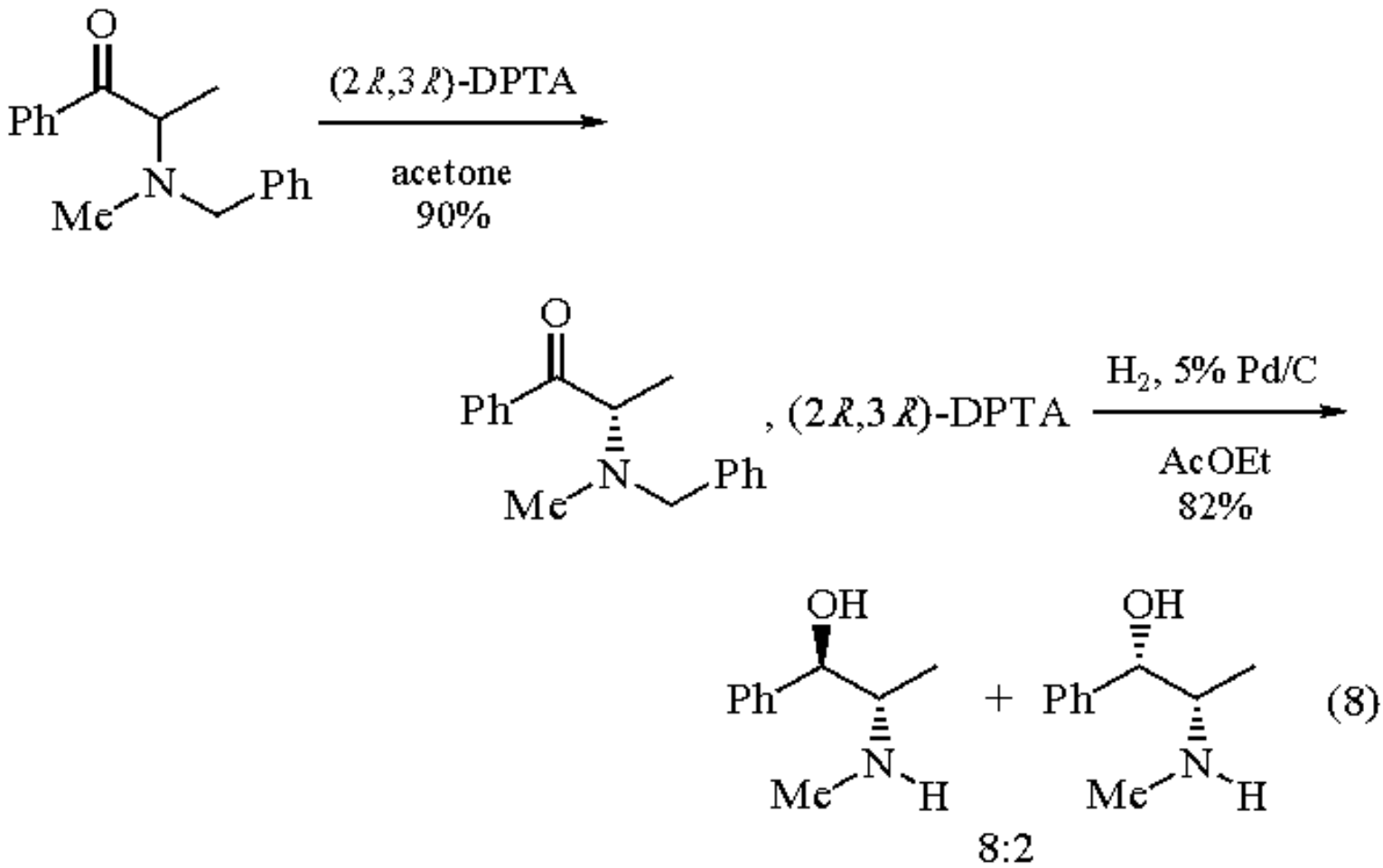

Starting Material for Asymmetric Syntheses.

(3*R*,4*R*)-Dipivaloyltartaric anhydride, the direct precursor of (2*R*,3*R*)-DPTA, has been used as starting material for the synthesis of (3*R*,4*R*)-dipivaloyltartrimide,[14] its *N*-chloro and *N*-bromo derivatives (eq 9)[15], and epimeric (3*R*,4*R*)-dipivaloyl-5-alkyl lactones (eq 10), which are valuable intermediates for access to optically active polyhydroxy compounds.[16]

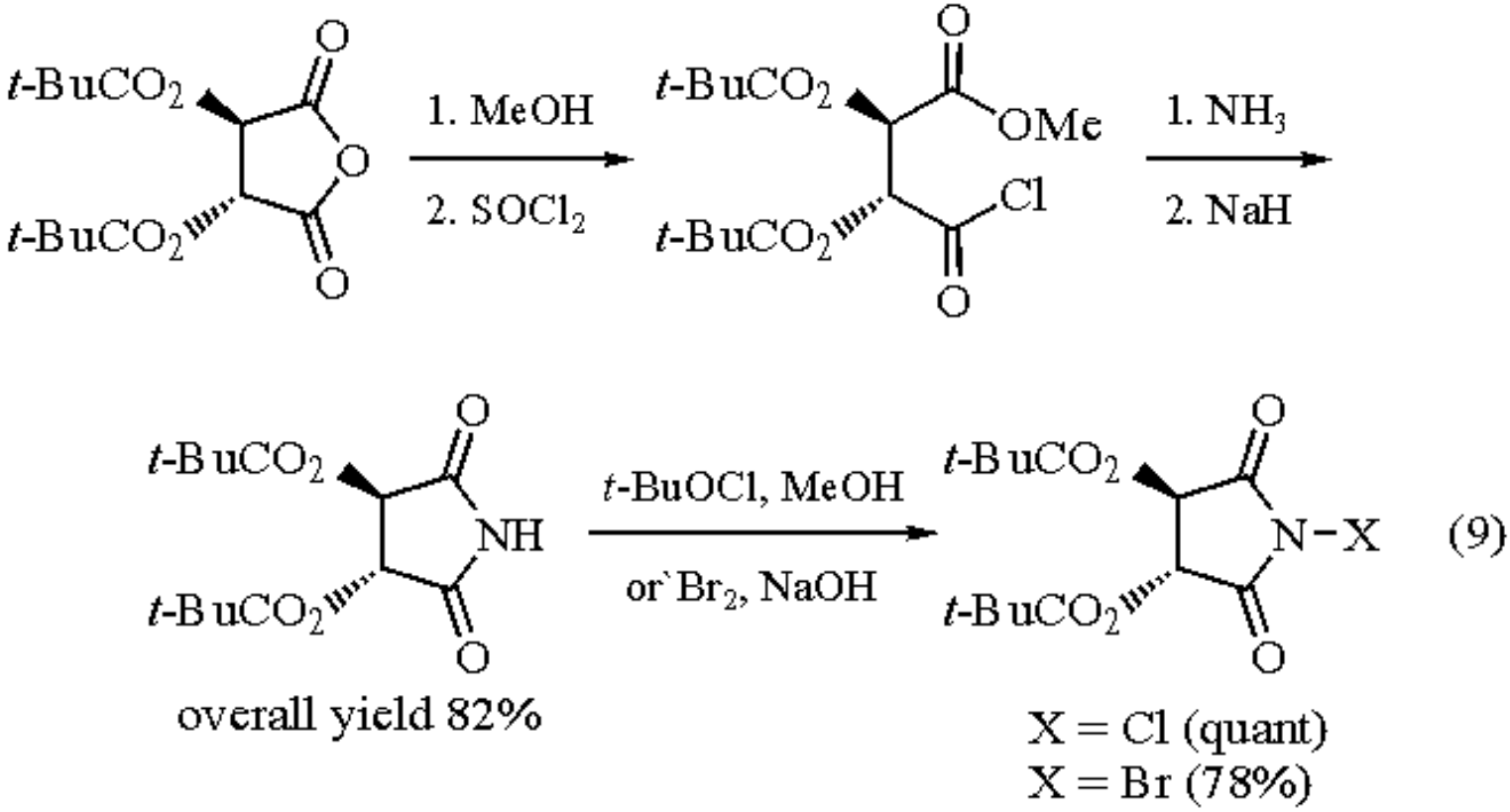
t-BuCO2
t-BuCO2
1. MeOH
2. SOCl2
OMe
Cl
1. NH3
2. NaH
NH
overall yield 82%
t-BuOCl, MeOH
or Br2, NaOH
N−X
X = Cl (quant)
X = Br (78%)

(9)

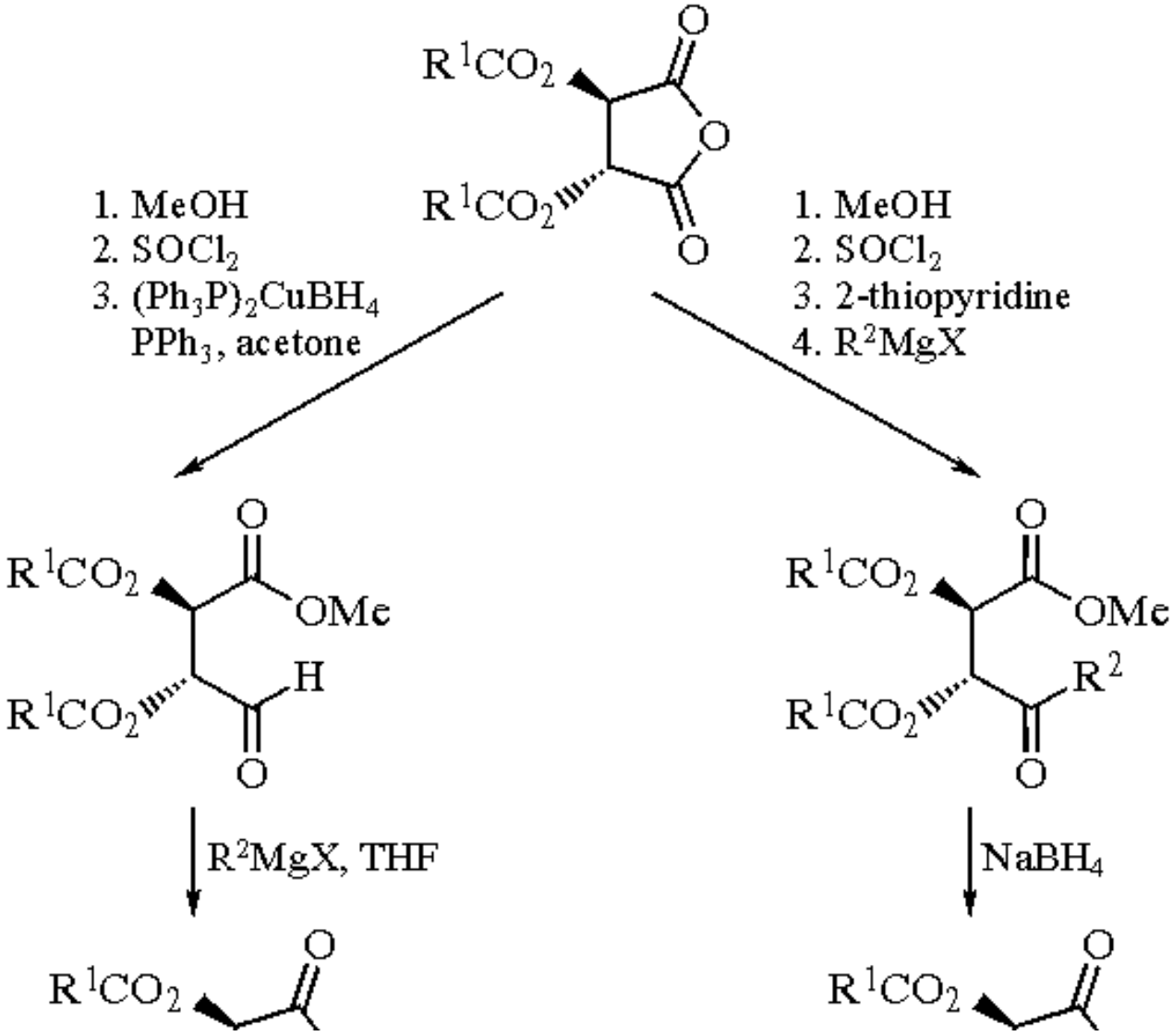
R1CO2
R1CO2
1. MeOH
2. SOCl2
3. (Ph3P)2CuBH4
PPh3, acetone
1. MeOH
2. SOCl2
3. 2-thiopyridine
4. R2MgX
OMe
H
R2
R2MgX, THF
NaBH4

(10)

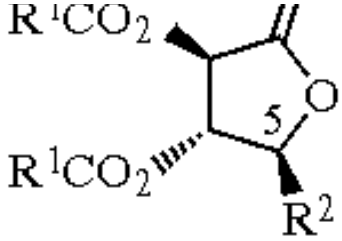

(5S):(5R) = >95:5

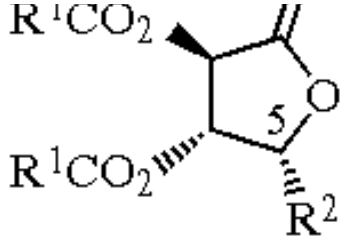

(5R):(5S) = >95:5

$R^1 = t\text{-Bu}$; $R^2 = \text{Me, Et, Bu, } C_8H_{17}$

---

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Dipotassium Acetylide[1]

KC&tbond;CK

[22754-96-7] · C_2K_2 · Dipotassium Acetylide · (MW 102.22)

(useful C_2 nucleophile for preparation of ethynyl steroids[2-5] and 1,4-dicarbonyl compounds[6])

Alternate Names: 1,2-ethynediyldipotassium; potassium acetylide; potassium carbide.

Solubility: low sol THF at 25 °C.[3]

Preparative Methods: dipotassium acetylide is prepared in situ and has not been isolated. Preparative routes include treatment of acetylene with potassium hydroxide in 1,2-dimethoxyethane or acetal solvents at temperatures between -10 °C and 20 °C,[1] addition of acetylene to a solution of potassium *t*-pentoxide,[2] and addition of 1 equiv of acetylene to 2 equiv of potassium *t*-butoxide in THF at 25 °C.[3] Solutions produced by the above methods are then used immediately. The reaction of dipotassium acetylide with ***N,O-Bis(trimethylsilyl)acetamide*** affords bis(trimethylsilyl)acetylene (eq 1), which confirms the nature of the reactive species. Because dipotassium acetylide has not been isolated, there is little physical data that is available for it.

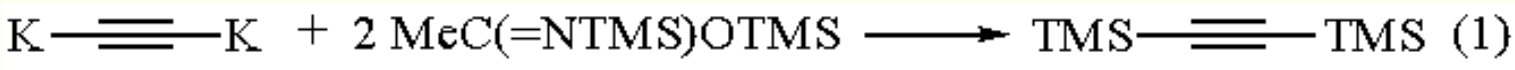

Preparation of Ethynyl Steroids.

Treatment of androsta-4,9(11)-diene-3,17-dione with dipotassium acetylide (prepared from ***Acetylene*** (1 equiv) and ***Potassium t-Butoxide*** (2 equiv) in THF) afforded the propargyl alcohol derived from exclusive attack at C-17 (eq 2).[3] Trapping experiments using ***Chlorotrimethylsilane*** revealed that the C-3 ketone was completely enolized, whereas the C-17 was only partially ionized. Apparently, the C-17 ketone was sufficiently ketonic at equilibrium to allow acetylide addition to proceed to completion.

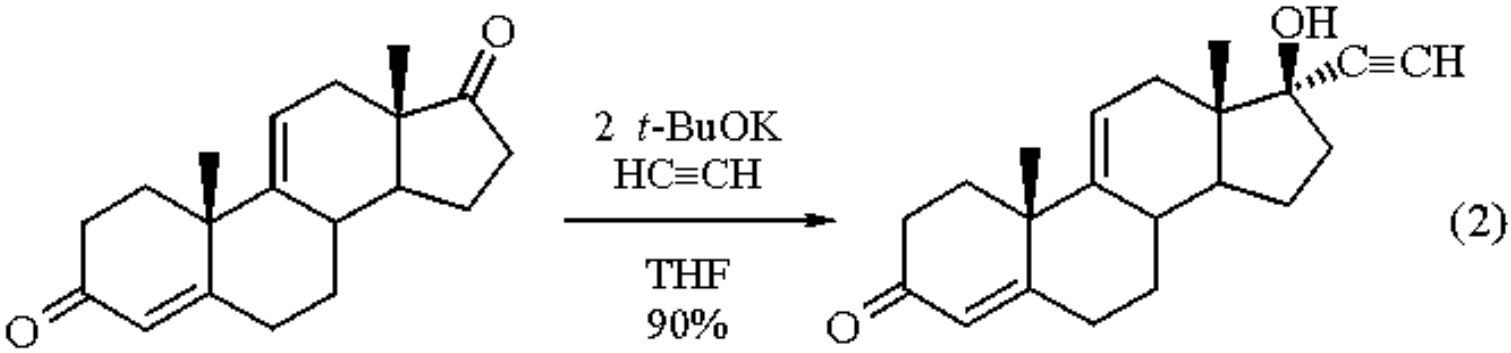

In a related study, treatment of androsta-1,4-diene-3,17-dione with dipotassium acetylide afforded 17α-ethynyl-17β-hydroxyandrosta-1,4-dien-3-one (97%; eq 3). Again, the C-3 ketone was not alkylated.

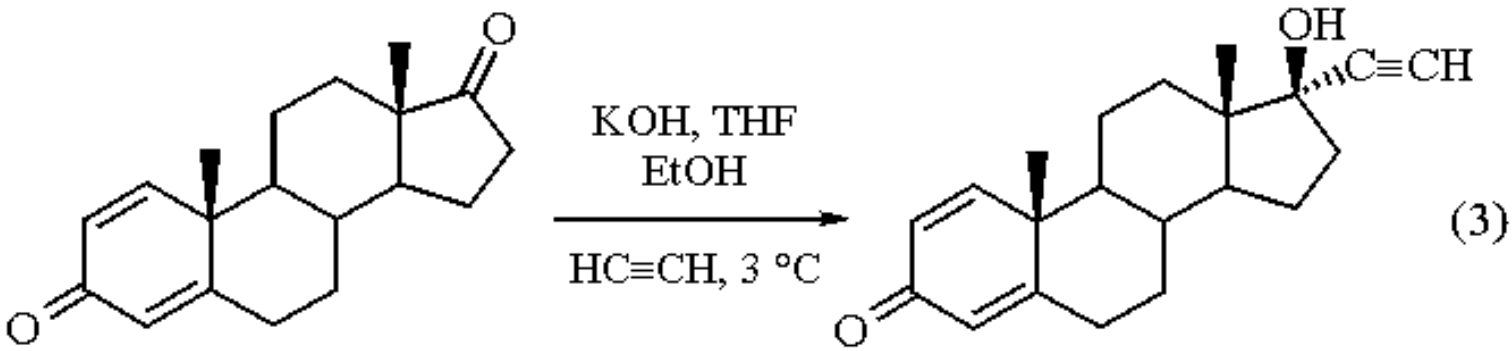

Treatment of 9α-hydroxyandrost-4-ene-3,17-dione with dipotassium acetylide did not afford the desired 9α,17β-dihydroxy-17α-ethynylandrost-4-en-3-one, but rather gave a mixture of the rearranged steroids 4-methyl-19-norandrosta-4,9-diene-1,17-dione, 4ε-methyl-19-norandrosta-5(10),9(11)-diene-1,17-dione, the two corresponding C-17 hydroxyethynylated products, and the two C-10 diastereomers of 17α-ethynyl-17β-hydroxy-9,10-secoandrost-4-ene-3,9-dione (eq 4). Yields were not reported. The desired 9α,17β-dihydroxy-17α-ethynylandrost-4-en-3-one was prepared by treatment of 9α-hydroxy-3-methoxyandrosta-3,5-dien-17-one with ***Lithium Acetylide-1,2-Diaminoethane*** in dry THF, followed by acidic workup (eq 5).

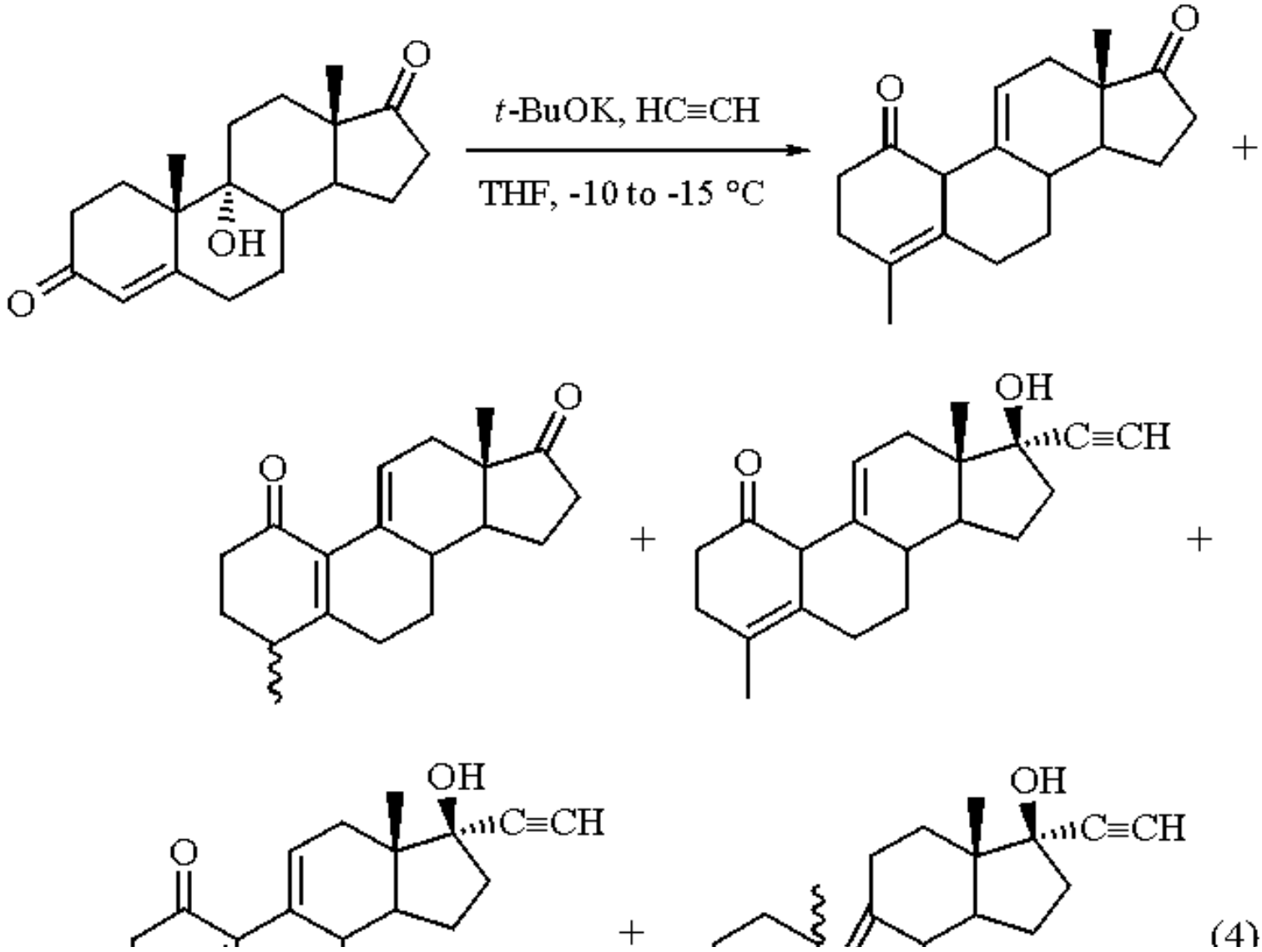

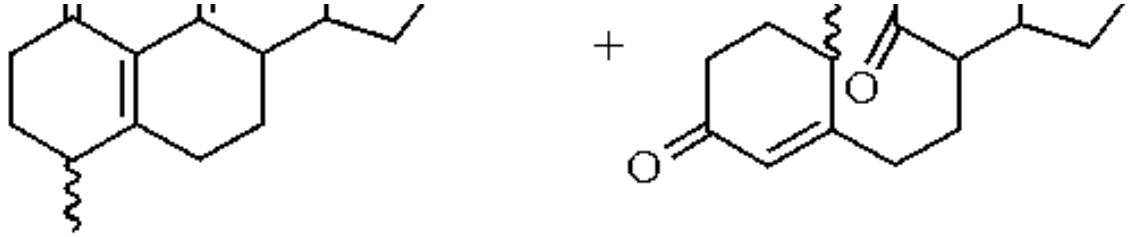

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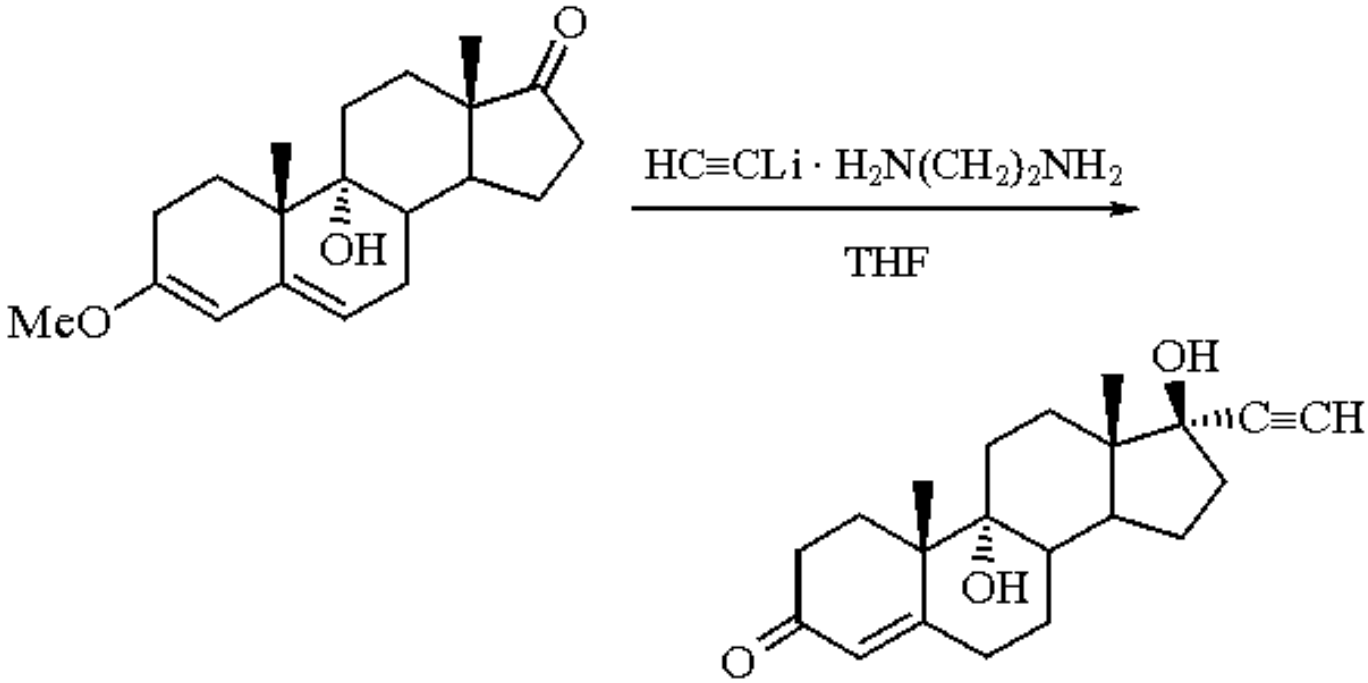

(5)

Preparation of 1,4-Dicarbonyl Compounds.

Treatment of pivalaldehyde with dipotassium acetylide in *p*-dioxane/diethyl ether afforded the corresponding alkynic glycol after acidic workup (22%; eq 6). Hydrogenation of the alkynic glycol, followed by oxidation of the alcohols, afforded 2,2,7,7-tetramethyloctane-3,6-dione in 82% yield. In the same study, comparison was made with the dimetalloacetylides acetylenebismagnesium bromide and dilithium acetylide. Both of these acetylides afforded moderate yields of alkynic glycols upon condensation with aliphatic and aromatic aldehydes. In a direct comparison, treatment of acetylenebismagnesium bromide with pivalaldehyde afforded 2,2,7,7-tetramethyloctane-3,6-diol in 36% yield, while reaction of dipotassium acetylide with pivalaldehyde afforded the same diol in 22% yield.

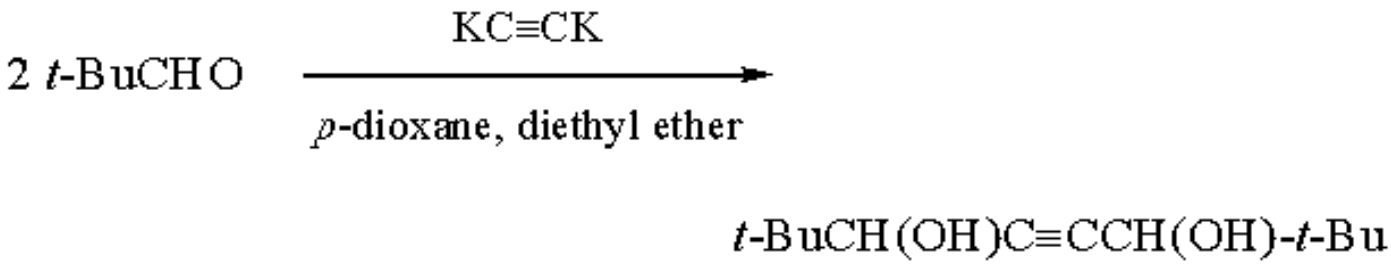

(6)

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Dipotassium Tetrachloroplatinate(II)[1]

K_2PtCl_4

[10025-99-7] · Cl_4K_2Pt · Dipotassium Tetrachloroplatinate(II) · (MW 415.08)

(homogeneous hydrogen isotope exchange catalyst;[2] selective oxidative functionalization of alkane C-H bonds;[3] used for the synthesis of various platinum complexes)

Physical Data: dark red crystals; *d* 3.38 g cm^{-3}.

Solubility: sol H_2O (0.93 g/100 mL at 15 °C, 5.3 g/100 mL at 100 °C); insol ethanol, acetone.

Form Supplied in: solid; widely available. *Drying:* at 120 °C/0.1 mmHg for 24 h.

Handling, Storage, and Precautions: should be stored in the absence of moisture; irritating to skin, eyes, and respiratory organs; corrosive.

Hydrogen Isotope Exchange Catalyst.

Aromatic and aliphatic compounds undergo exchange of isotopic hydrogen with a catalytic amount of this reagent. This system is valuable for labeling compounds with deuterium and/or tritium in one step and constitutes the homogeneous equivalent of the well-known heterogeneous platinum technique. A wide range of compounds, including alkanes,[4] cycloalkanes,[5] saturated carboxylic acids,[6] benzoic acid,[7] benzyl alcohol,[8] β-phenylpropionic acid,[9] phenylalanine, phenylglycine,[10] and tyrosine[11] have been D and/or T labeled using this technique (see also ***Disodium Tetrachloroplatinate(II)***).

Functionalization of Saturated Hydrocarbons.

K_2PtCl_4 or the combination K_2PtCl_4/K_2PtCl_6 in aqueous medium is often used for the selective oxidation of isolated C-H bonds of saturated hydrocarbons (see also ***Disodium Tetrachloroplatinate(II)***). Ethane can be selectively oxidized to acetic or glycolic acid.[12] Tetrahydrofuran is oxidized to γ-butyrolactone (eq 1),[13] and isovaleric acid to γ-valerolactone (eq 2).[14]

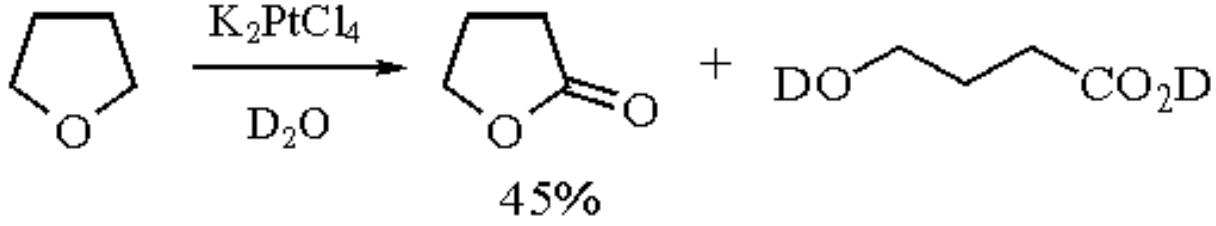

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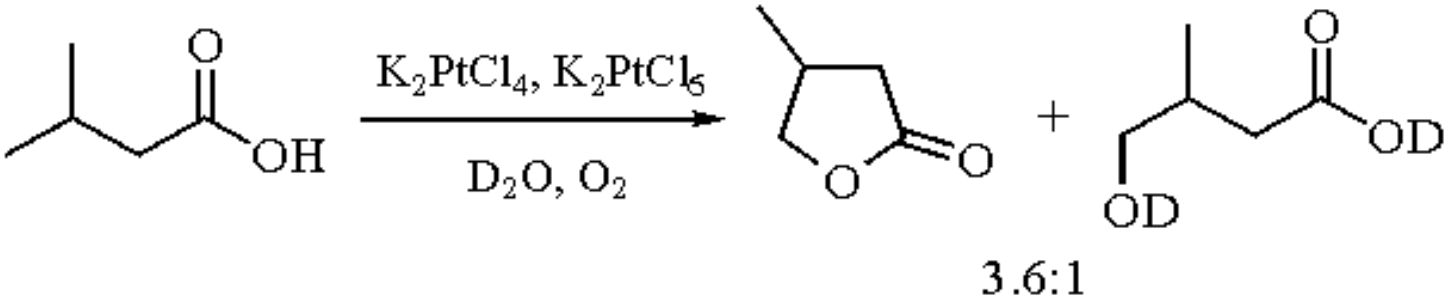

(2)

Complexes.

The reaction of 1,2-diamines and similar ligands with K_2PtCl_4 is widely used for the synthesis of cisplatin analogs, powerful antitumor agents (eq 3).[15]

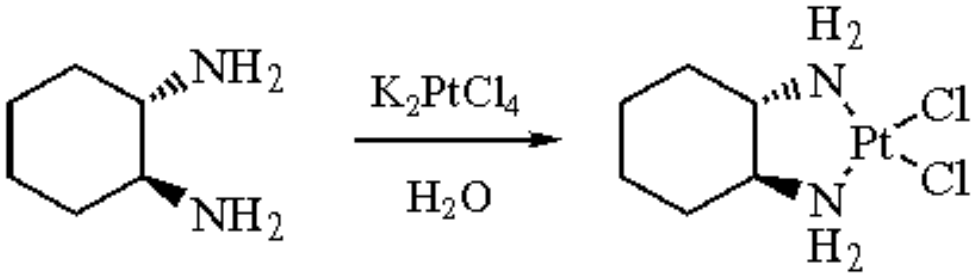

(3)

Alkenes,[16] including ethylene,[17] and dienes,[18] readily coordinate with K_2PtCl_4, forming complexes (eq 4). These complexes readily undergo displacement reactions with free alkene in the solution.[19]

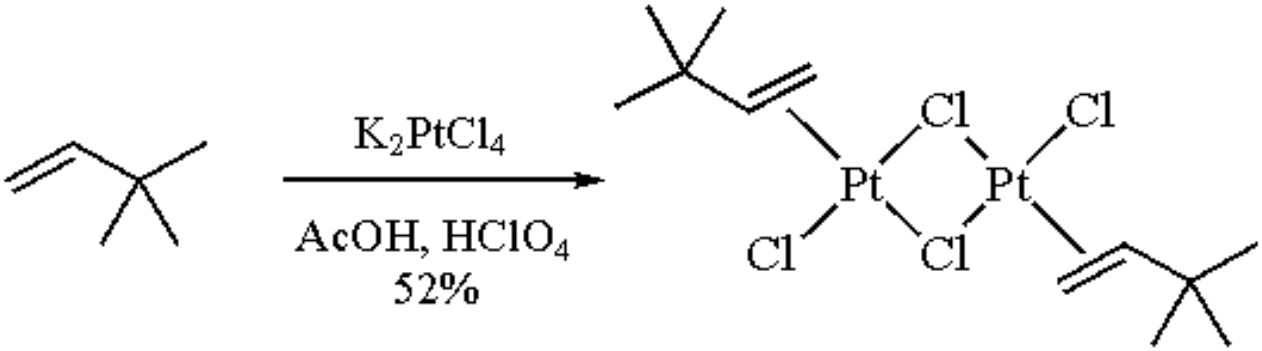

(4)

A number of aromatic and heteroaromatic compounds, substituted with suitable donor ligands, undergo cycloplatination reactions when treated with K_2PtCl_4 (eq 5).[20]

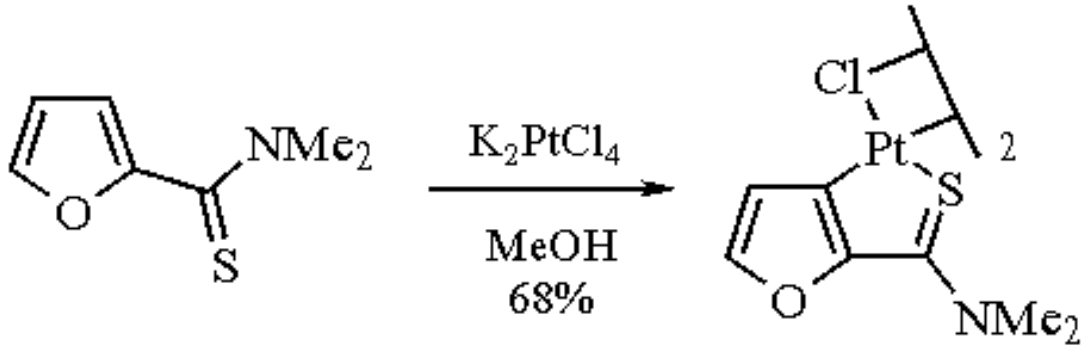

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Dipropenylmercury

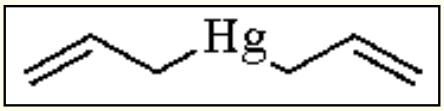

[2097-71-4] · $C_6H_{10}Hg$ · Dipropenylmercury · (MW 282.75)

(transmetalation reactions by tin[2] and lithium;[3] metallo-ene reactions;[4] interaction with sulfur-containing compounds[5,6])

Physical Data: liquid; bp 90-92 °C/6.5 mmHg, 58-58.5 °C/1.5 mmHg; *n*20D 1.6309, *d*204 2.3180 g cm^{-3}.

Solubility: sol diethyl ether.

Preparative Methods: there have been several reports of the synthesis of dipropenylmercury.[7] The most straightforward synthesis is probably that reported by Borisov and co-workers.[1] ***Allylmagnesium Bromide***, prepared in ether, is reacted with mercury(II) bromide in THF at 5 °C. After 1 h, the reaction is quenched with saturated ammonium chloride. Evaporation and then distillation affords dipropenylmercury.

Handling, Storage, and Precautions: reported to be an unstable material, and is best used immediately after preparation. Despite the lack of specific toxicity data, it is reasonable to assume that as with all mercury compounds, care should be taken in handling these toxic reagents. Use in a fume hood.

The use of dipropenylmercury as a reagent in organic synthesis is not extensive, although this compound has been studied by IR[8] and NMR spectroscopy[9] and polarography[10] in some depth.

The use of dipropenylmercury, as well as other mercury-containing reagents, has been explored in the reaction with ***Trimethylstannane***.[2] Trimethylpropenylstannane is formed as the product (eq 1).

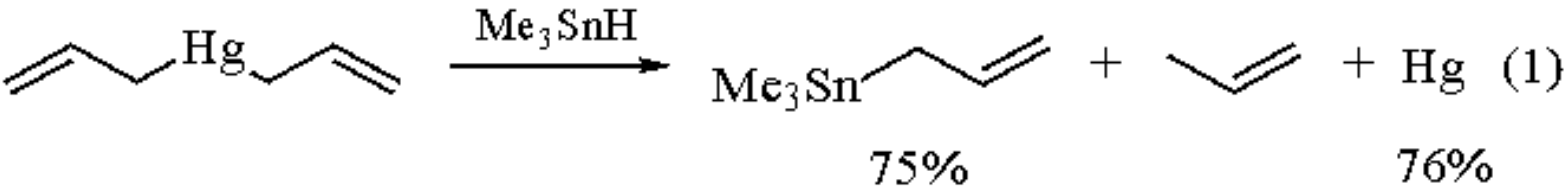

The use of dipropenylmercury as a precursor to a trianion has been described.[3] Thus treatment of dipropenylmercury with aniline and ***Mercury(II) Acetate***, followed by acetate/bromide exchange with potassium bromide, affords an aminomercurial. Treatment of this aminomercurial with ***Phenyllithium*** and then ***Lithium*** powder affords the trianion derivative, which was characterized by quenching with D_2O and then aqueous hydrochloric acid to afford the corresponding dideuterio compound (eq 2). A variety of other electrophiles were also employed.

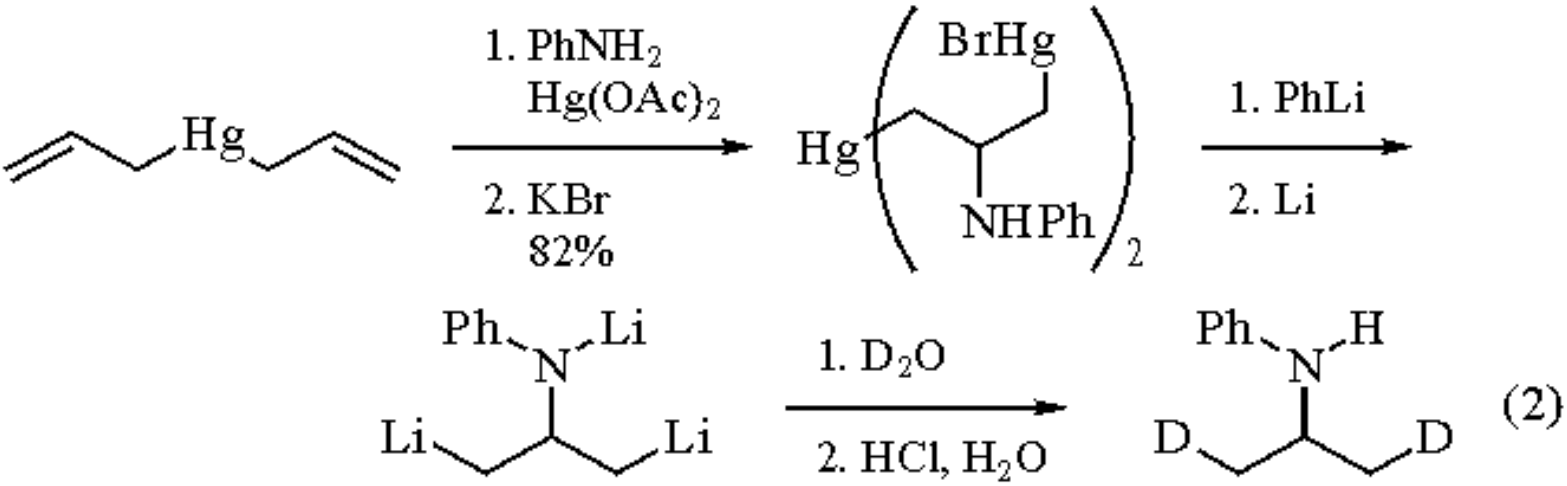

The Hg-C bonds in dipropenylmercury are sensitive to homolysis.[10] Thus in the reaction between dipropenylmercury and oxygen in the presence of tetraphenylporphyrin (TPP), the expected ene product is observed as a minor product, whereas acrolein is formed as the major product (eq 3), which, it was suggested, arises from oxidation of the propenyl radical formed upon homolysis of the Hg-C bond. However, other allylmercury reagents successfully undergo ene reactions with alternative ene coupling partners (which do not require photosensitization), and so there appears to be further scope for metallo-ene reactions of allylmercury reagents.

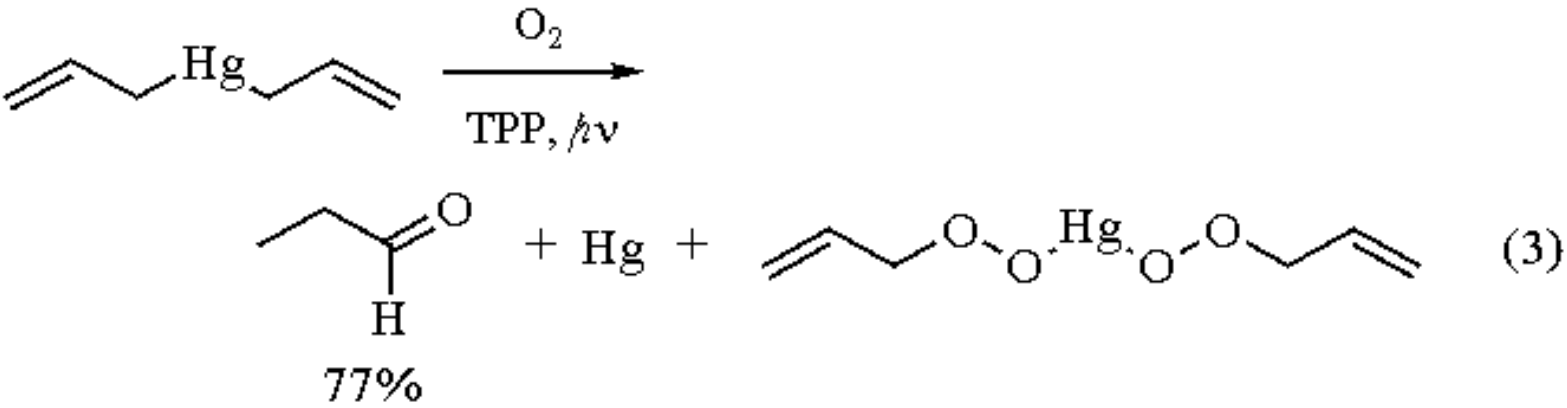

Treatment of dipropenylmercury with ***Thiophenol*** gives an exothermic reaction which results in the formation of mercury bis(thiophenolate), phenyl(propenyl)sulfide, and mercury metal.[5] The reaction of dipropenylmercury with the sulfur-containing thianthrene cation radical has also been reported.[6]

---

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Dipyridine Chromium(VI) Oxide[1]

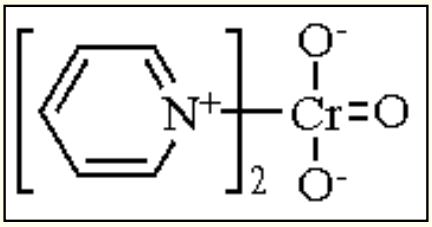

[26412-88-4] · $C_{10}H_{10}CrN_2O_3$ · Dipyridine Chromium(VI) Oxide · (MW 258.22)

(reagent for oxidizing alcohols to carbonyl compounds)

Alternate Names: Collins reagent; chromium(VI) oxide-pyridine.

Solubility: sol CH_2Cl_2; (*Z*)-1,2-dichloroethylene; pyridine; $CHCl_3$.

Form Supplied in: red crystals; not commercially available.

Preparative Methods: prepared in 85-91% yield from ***Chromium(VI) Oxide*** and ***Pyridine***.[2,3] Caution: the reaction is extremely exothermic. The chromium(VI) oxide should be added to dry pyridine at such a rate that the temperature does not exceed 20 °C and in such a way that the oxide mixes rapidly with pyridine. Other chromium(VI) oxide-pyridine complexes are known. These include the Ratcliffe reagent (dipyridine chromium(VI) oxide prepared in situ in CH_2Cl_2),[4,5] and the Sarett reagent ($CrO_3.(C_5H_5N)_2$ in pyridine).[6] The preparation and workup of the Sarett reagent is sometimes tedious. The hygroscopic nature of the Collins reagent and its propensity to inflame may be avoided by the in situ preparation of the complex according to the Ratcliffe procedure.

Handling, Storage, and Precautions: Caution: the Collins reagent is extremely hygroscopic; exposure to moisture rapidly converts it to the yellow dipyridinium dichromate. The reagent should be stored at 0 °C under nitrogen or argon in a sealed container, protected from light. All chromium(VI) reagents must be handled with care; their mutagenicity is well documented.[7] This reagent should be prepared and handled in a fume hood.

Allylic Oxidation to Form α,β-Unsaturated Ketones.

Although a solution of chromium(VI) oxide in pyridine is not very useful for allylic oxidation, the isolated dry chromium(VI) oxide-dipyridine complex in dichloromethane oxidizes allylic methylene groups to enones at rt in good to excellent yields. Δ^5-Androsten-7-one-3β,17β-diol diacetate is thus obtained (82%) from the oxidation of Δ^5-androstene-3β,17β-diacetate.[8] Attack at an allylic methine position yields the isomeric enone when possible; for

example, 3-(4-fluorophenyl)cyclohexenol is oxidized to the isomeric enone (eq 1).[8] Similar rearrangements occur in methylene systems with steric hindrance.[8] If more than one allylic methylene group is present in a conformationally flexible molecule, isomeric enones resulting from attack at both positions are formed (eq 2).[8] Selectivity is observed in conformationally rigid molecules.[8] Methyl groups are not easily oxidized. In general, the Collins reagent gives higher yields and less overoxidation than ***Di-t-butyl Chromate*** or ***Chromium(VI) Oxide*** in acetic acid.

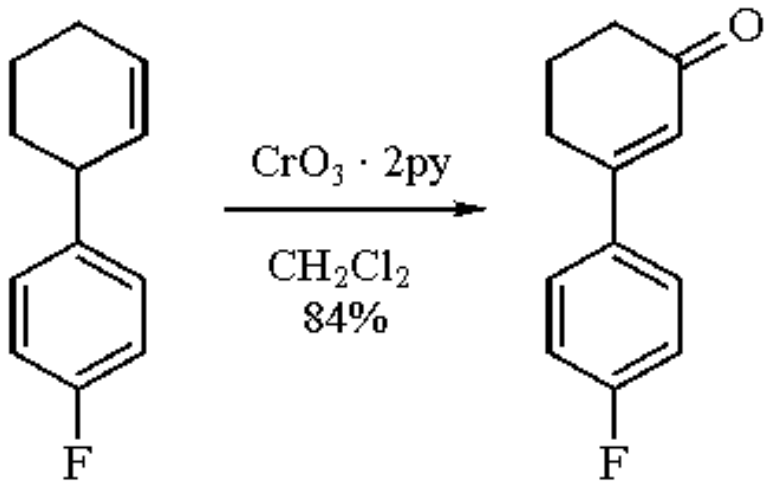

(1)

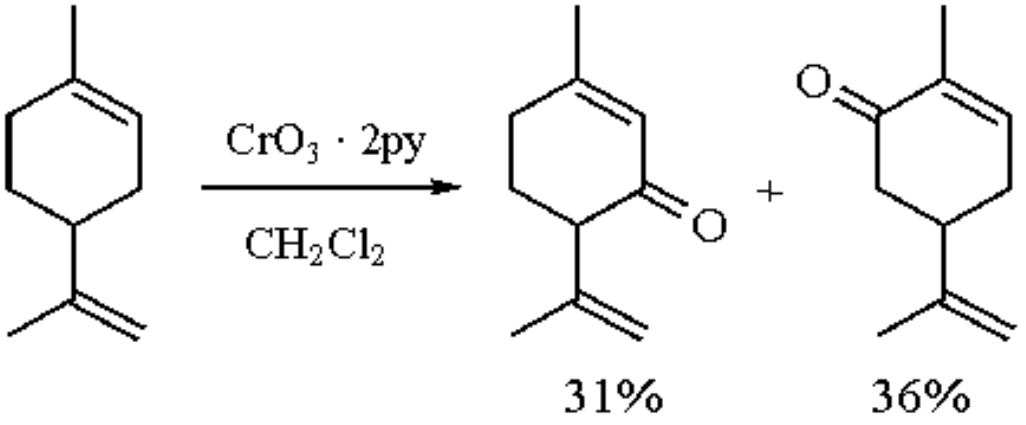

(2)

Alkynes are oxidized to conjugated alkynic ketones (ynones) by the Collins reagent.[9] The Collins reagent oxidizes 4-octyne to 4-octyn-3-one (eq 3). Oxidation of alkynes by ***t-Butyl Hydroperoxide*** and catalytic amounts of ***Selenium(IV) Oxide***[10] effects oxidation at both centers adjacent to a triple bond. A catalytic amount of chromium(VI) oxide in benzene and *t*-butyl hydroperoxide selectively oxidizes alkynes to ynones in about 50% yield.[11]

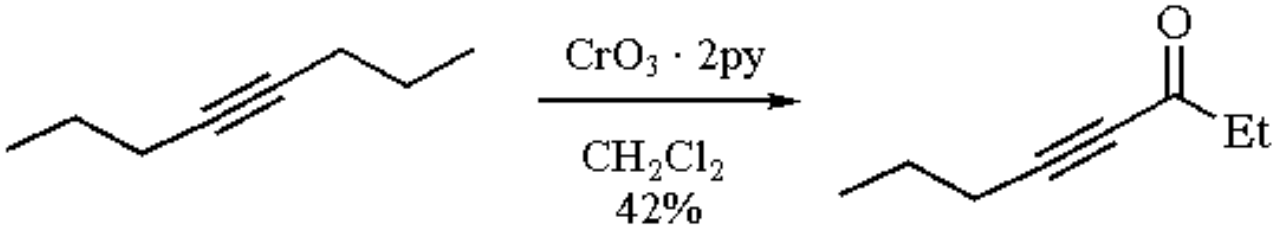

(3)

Oxidation of Primary Alcohols to Aldehydes.

The oxidation of alcohols is generally performed in dichloromethane with a sixfold excess of the Collins reagent. The

Collins reagent[3] gives higher yields than the Sarett reagent[6] and comparable yields to the Ratcliffe reagent.[5] The Collins reagent oxidizes 1-heptanol to 1-heptanal in 70-84% yield[3] and the Ratcliffe reagent oxidizes 1-decanol to 1-decanal in 83% yield.[4,5] The Collins reagent oxidizes the primary allylic alcohols geraniol (eq 4) and nerol (eq 5) to geranial and neral, respectively, without isomerization.[12] The Ratcliffe reagent oxidizes cinnamyl alcohol to cinnamaldehyde in 96% yield.[5] The Collins reagent has been used to oxidize primary hydroxy groups of sugars to aldehydes in 50-75% yield.[13] Although the Sarett reagent is useful for the conversion of primary allylic and benzylic alcohols to their corresponding aldehydes, its use for primary saturated alcohols (with the exception of some steroidal ones) is less effective than the Collins or Ratcliffe reagent.

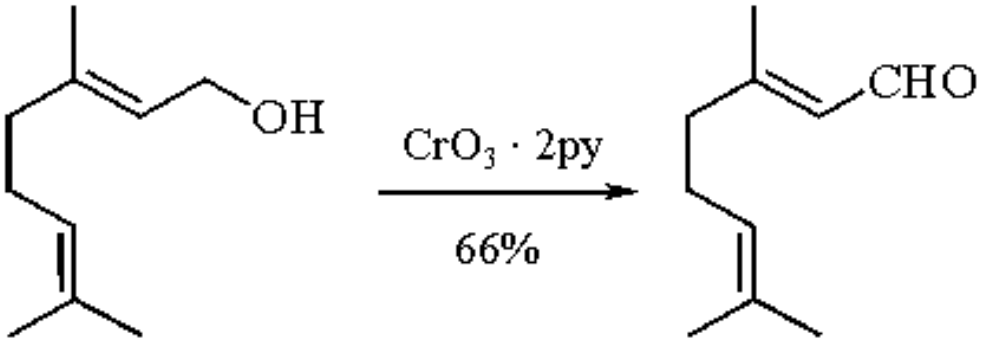

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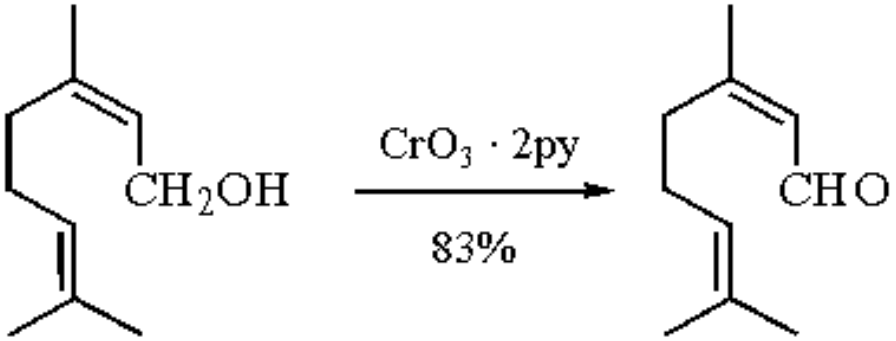

(5)

The oxidation of allylic alcohols to aldehydes is facilitated by use of Celite-supported Collins reagent (eq 6).[14,15] This method has been used to prepare intermediates in the synthesis of bulnesol[14] and guaiol.[15] A modified Ratcliffe reagent, CrO_3.2py in acetonitrile on Celite, was used to oxidize primary alcohols to aldehydes.[16]

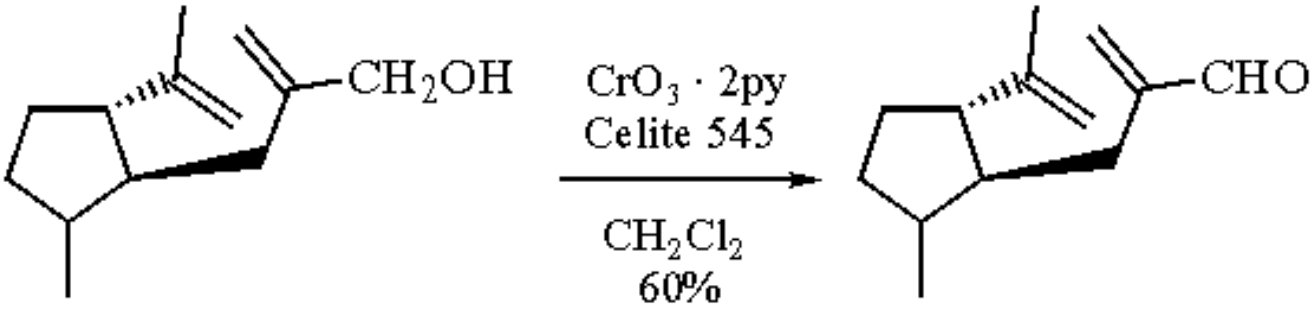

(6)

The (*S*)-alcohol (**1**) is oxidized by the Collins reagent to the aldehyde (**2**) with no more than 5% racemization (eq 7).[17]

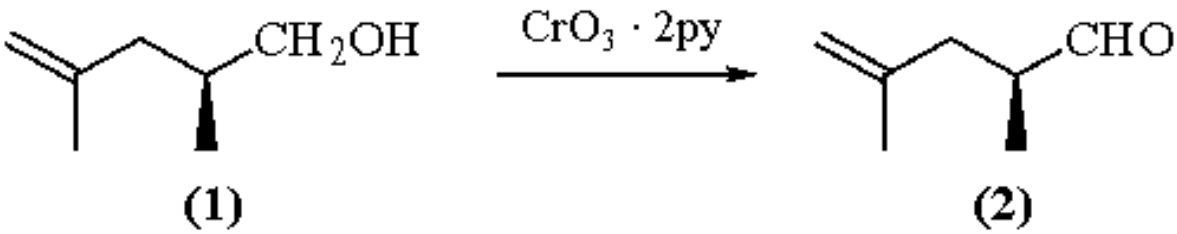

(7)

Primary alcohols are converted to the corresponding *t*-butyl esters by Collins reagent in CH_2Cl_2/DMF/Ac_2O and a large excess of *t*-butyl alcohol (eq 8).[18] This conversion is probably general except for aromatic aldehydes.

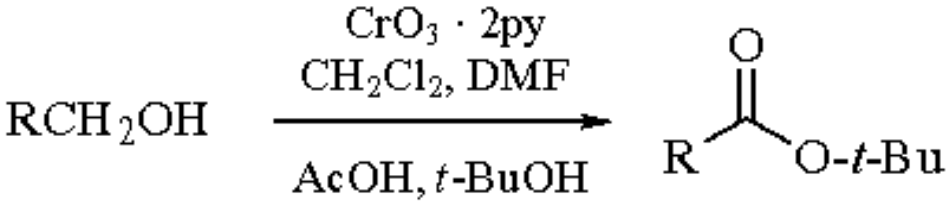

(8)

Oxidation of Secondary Alcohols to Ketones.

The Collins reagent (eq 9),[19] the Ratcliffe reagent,[5] and the Sarett reagent[20,21] are effective in oxidizing secondary alcohols to ketones. Generally, acid sensitive functional groups such as acetals, double bonds, oxiranes, and thioethers are not affected, although there are exceptions. The Collins reagent oxidizes *exo*-7-hydroxybicyclo[4.3.1]deca-2,4,8-triene to bicyclo[4.4.1]deca-2,4,8-triene-7-one (64%).[22] Collins reagent oxidizes the secondary alcohol functional groups in β-hydroxy-(*Z*)-*O*-alkyloximes to the corresponding β-keto-*O*-alkyloximes.[23]

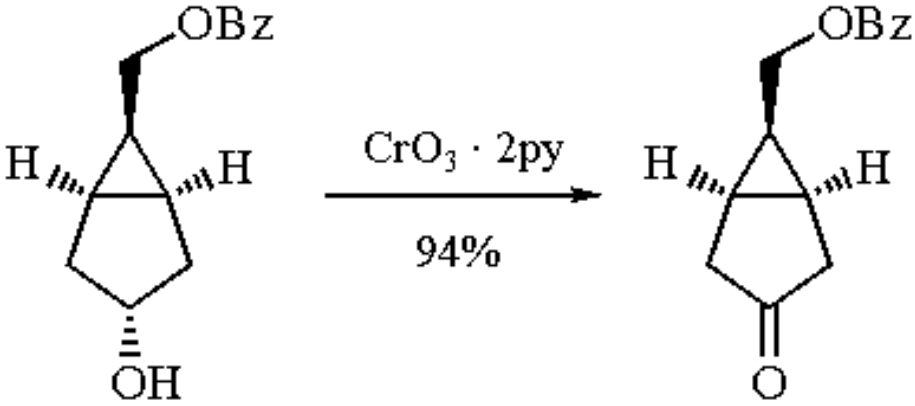

(9)

A number of alternative reagents are available for the oxidation of primary and secondary alcohols to aldehydes and ketones. Related chromium-based reagents include ***Chromium(VI) Oxide-3,5-Dimethylpyrazole***, ***Chromium(VI) Oxide-Quinoline***, ***Pyridinium Chlorochromate***, and ***Pyridinium Dichromate***.

Oxidation of Tertiary Allylic Alcohols to Epoxy Aldehydes.

The Collins reagent oxidizes tertiary allylic alcohols to epoxy aldehydes (eq 10).[24]

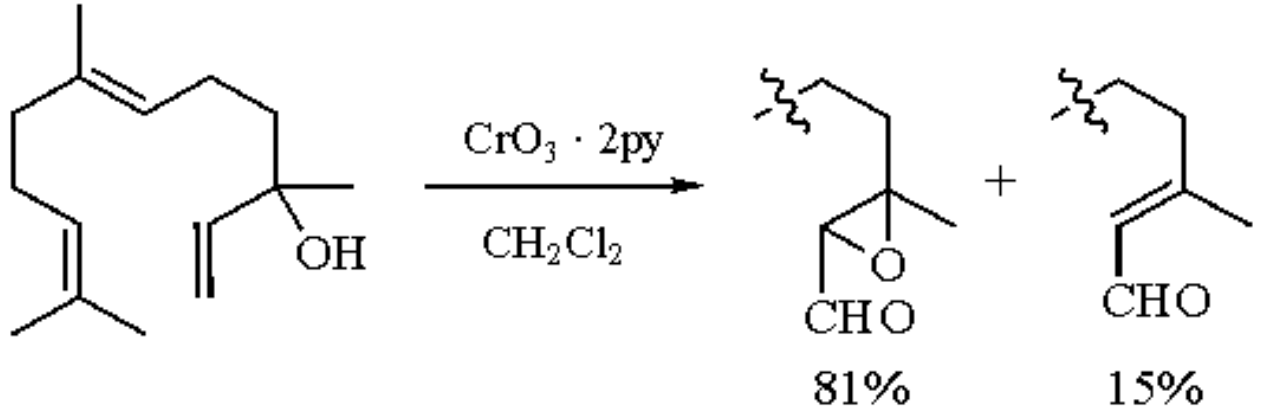

Oxidation of Carbohydrates.

Addition of acetic anhydride to the Collins reagent increases the yields (>90%) for the oxidation of secondary hydroxy groups to carbonyl groups in carbohydrates.[13,25,26]

Oxidation of β-Hydroxy Ketones to 1,3-Diketones.

Collins reagent oxidizes β-hydroxy ketones to 1,3-diketones (eq 11).[26,27] Higher yields are generally obtained with ***Dimethyl Sulfoxide-Oxalyl Chloride*** (Swern reagent).

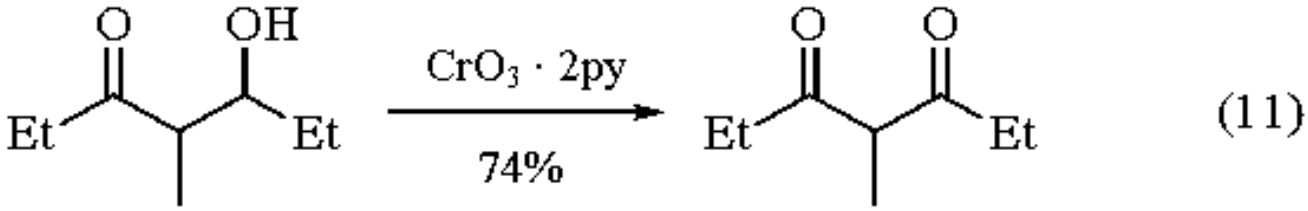

Oxidation of β-Hydroxy Esters to β-Keto Esters.

Collins reagent oxidizes β-hydroxy esters to β-keto esters (eq 12).[27]

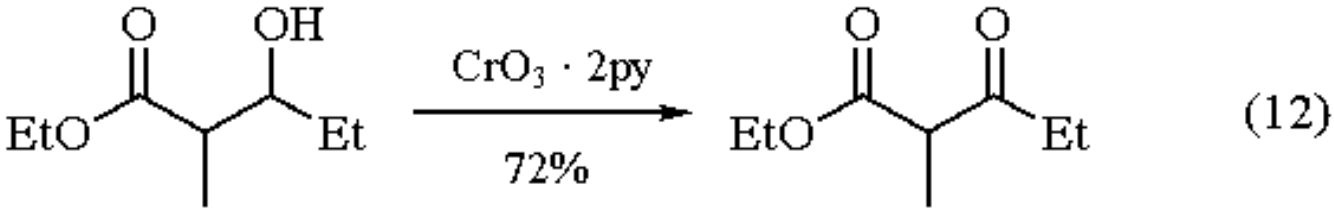

Oxidative Cyclization of 5,6-Dihydroxyalkenes.

Collins reagent oxidizes the unsaturated diols (**3**) to the corresponding *cis*-tetrahydrofurandiols (**4**) (eq 13).[28]

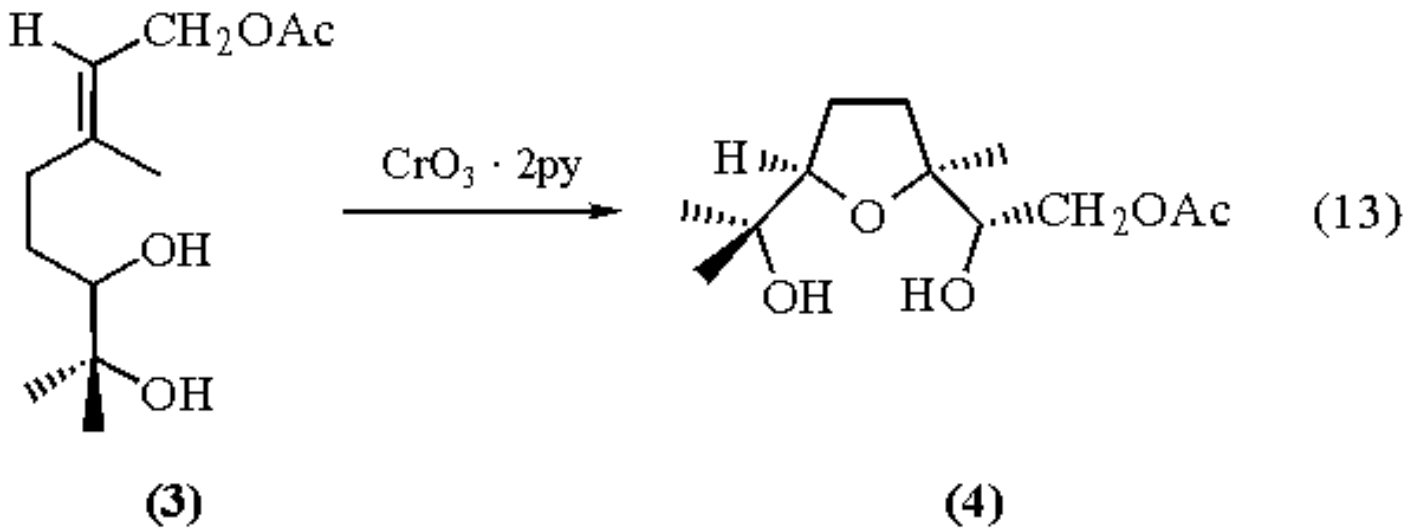

Oxidation of 1,4-Dienes.

Oxidation of the 1,4-diene (**5**) with Collins reagent or ***Di-t-butyl Chromate*** yields dienones (**6**) and (**7**) in the ratio of 1:3 (~65% total yield) (eq 14).[29] Complementary regioselectivity (**6**)/(**7**) = 9:1 (~70% total yield) is obtained with ***Pyridinium Chlorochromate*** (PCC).

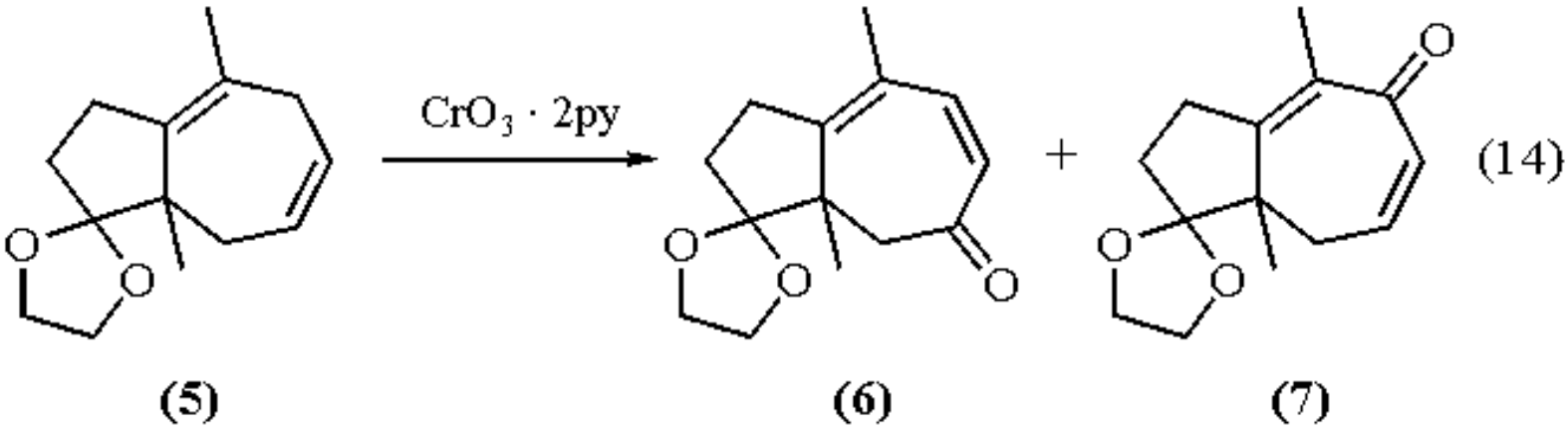

Other Applications.

Collins reagent, Jones' reagent, and chromic acid in 50% acetic acid oxidatively deoximate ketoximes to the corresponding carbonyl compounds.[30]

Secondary alkylstannanes are converted into the corresponding carbonyl compounds by oxidation with Collins reagent (eq 15).[31,32] Mixtures of alcohols and dehydration products are obtained from tertiary alkylstannanes.

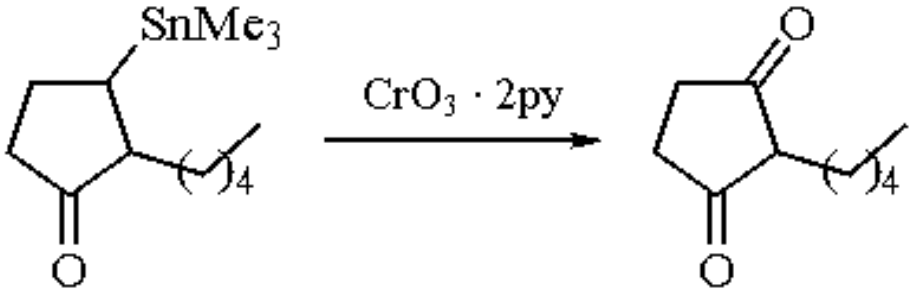

(15)

Collins reagent oxidizes trimethylsiloxy-substituted 1,4-cyclohexadienes to phenols (eq 16).[32]

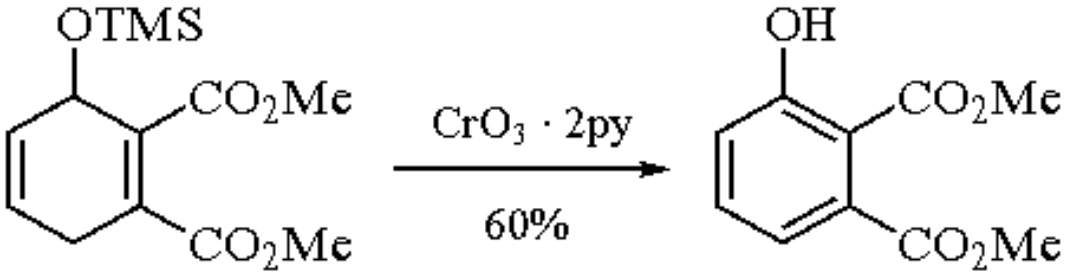

(16)

Collins reagent oxidizes steroidal tertiary amines to *N*-formyl derivatives (eq 17).[3]

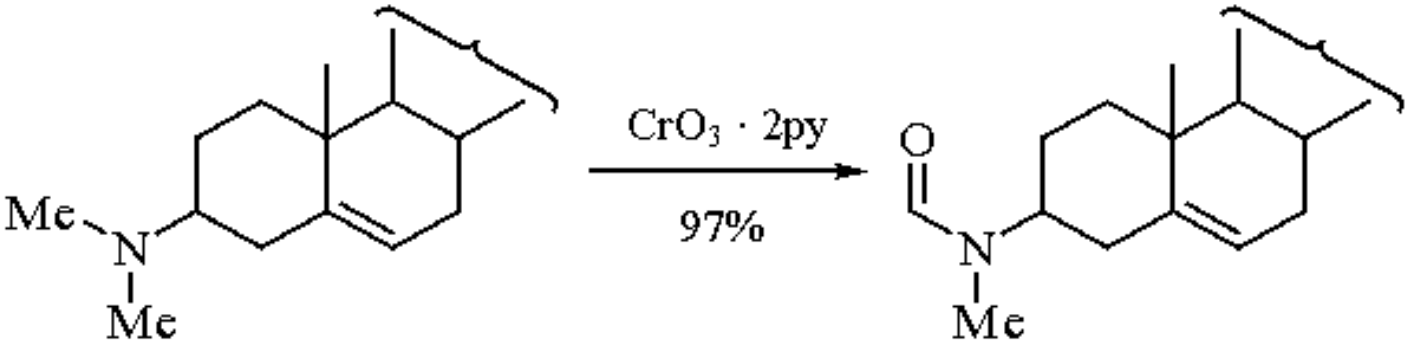

(17)

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Di-2-pyridyl Carbonate[1]

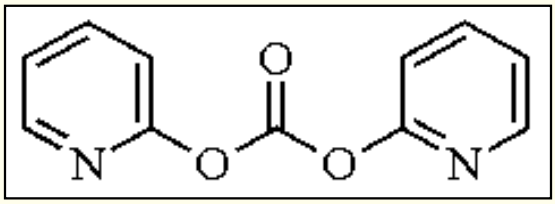

[1659-31-0] · $C_{11}H_8N_2O_3$ · Di-2-pyridyl Carbonate · (MW 216.21)

(dehydration agent; preparation of esters,[3] amides,[4] nitriles;[5] alkoxycarbonylation[6] or protection[7] of amines; carbonyl transfer[8])

Alternate Name: 2-DPC.

Physical Data: mp 76-78 °C.

Solubility: sol CH_2Cl_2.

Form Supplied in: white solid.

Preparative Methods: from ***Phosgene*** and ***2-Hydroxypyridine*** in the presence of ***Pyridine*** in THF[9] or ***Triethylamine*** in CH_2Cl_2 (eq 1).[3,7] Phosgene can also be replaced with triphosgene (***Bis(trichloromethyl) Carbonate***).[2] The usual yield is about 80%.

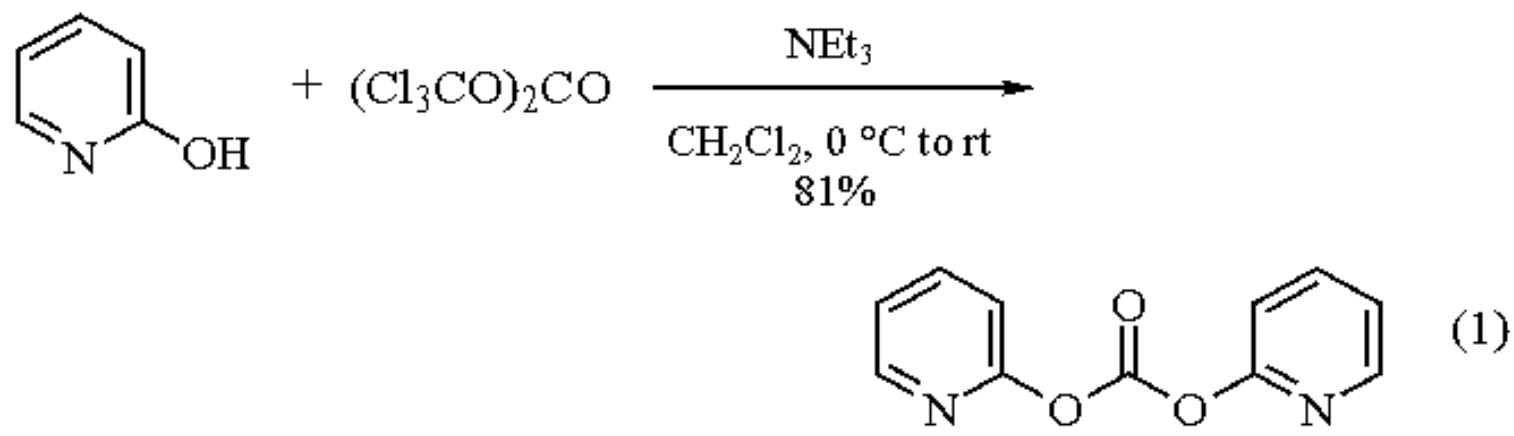

Handling, Storage, and Precautions: quite stable and can be stored under nitrogen at rt for several months without any noticeable decomposition.

Introduction.

The advantages of using 2-DPC are the following: 2-hydroxypyridine is a neutral compound and can be removed completely from the reaction mixture by the usual aqueous workup. The 2-pyridyl esters are also highly reactive.[10]

As a Dehydrating Agent.

2-DPC can be used for the direct esterification of carboxylic acids in good yield and under mild conditions.[1,3] The reaction can be carried out with equimolar amounts of acids, alcohols, and 2-DPC in the presence of 0.1 equiv ***4-Dimethylaminopyridine*** (DMAP) in CH_2Cl_2 at rt. The reaction of diphenylacetic acid and benzyl alcohol gave the corresponding ester in 90% yield (eq 2).

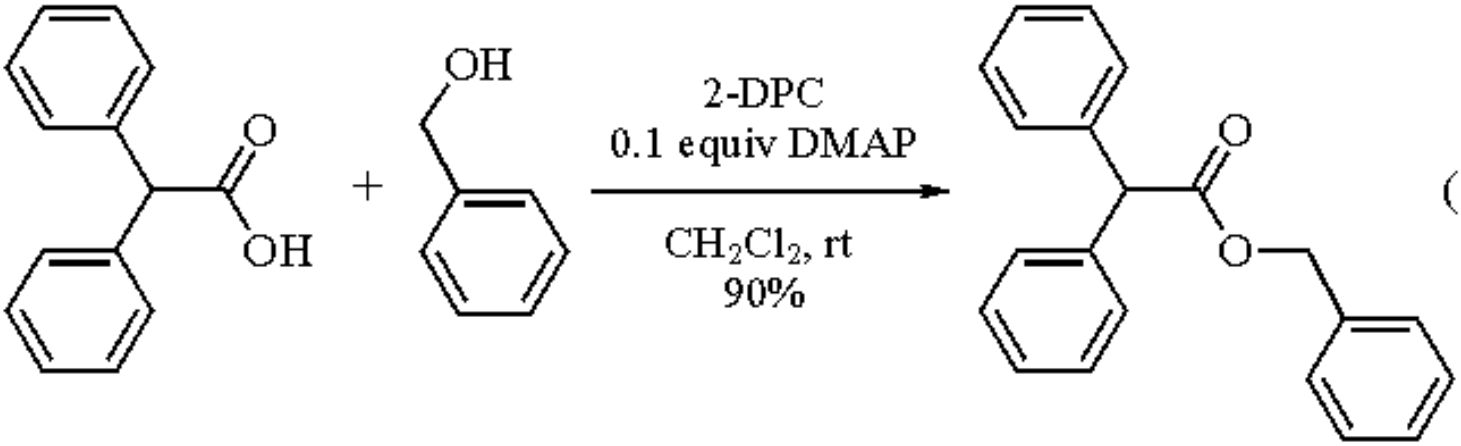

(2)

Typical yields are as follows: methyl diphenylacetate, 95%; benzyl octanoate, 94%; isopropyl phenylacetate, 90%. With aromatic acids and hindered carboxylic acids the esterification is not very satisfactory. The yields drop to 68% for ethyl benzoate or 42% for benzyl pivalate. In these cases the corresponding 2-pyridyl benzoate and pivalate are isolated.

For the preparation of amides a stepwise procedure must be used.[4,11] Formation of activated pyridyl esters and subsequent treatment with amines provide the carboxylic amides. This reaction gave benzyloctanamide in 80% and cyclohexylbenzamide in 85% yield.[1]

2-DPC can also be used to form nitriles via dehydration of the corresponding aldoximes. The reaction was carried out in refluxing toluene or in presence of 0.1 equiv of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** in CH_2Cl_2 at rt.[5] The last procedure gave benzonitrile in 83% yield.

Alkoxycarbonylation of Amines.

2-DPC is useful for the *N*-protection of amino acids via an activated carbonate.[7] The mixed carbonate is obtained by the reaction of 2-DPC with an equimolar amount of *t*-butyl alcohol in the presence of 0.1 equiv DMAP in CH_2Cl_2. The isolated carbonate obtained in 80% yield was added to a solution of L-proline and ***Triethylamine*** in DMF-water (eq 3). After crystallization the yield of *N*-Boc-proline was 98%. Some other typical yields were as follows: *N*-Boc-Ala, 84%; *N*-Boc-Leu, 95%.

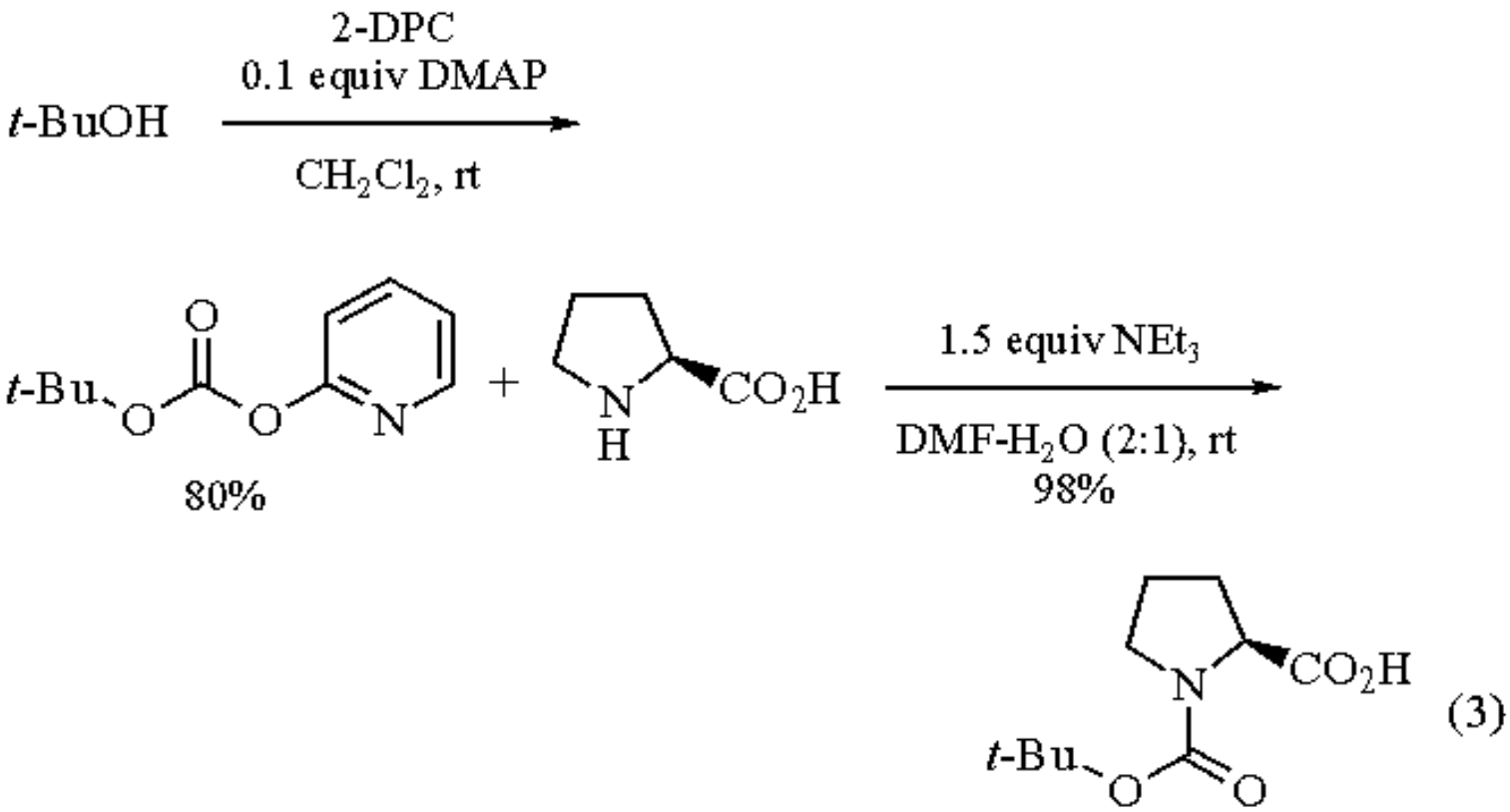

The same strategy was used to synthesize functionalized carbamates.[2] The reaction between (+)-menthol and 2-DPC in the presence of triethylamine (CH_2Cl_2) gave the mixed carbonate which was used directly, after classical workup. The reaction of this carbonate and the amine gave the carbamate in 81% yield (eq 4). Amines produced in situ by reduction of the azide can also be transformed into the corresponding carbamate.[6]

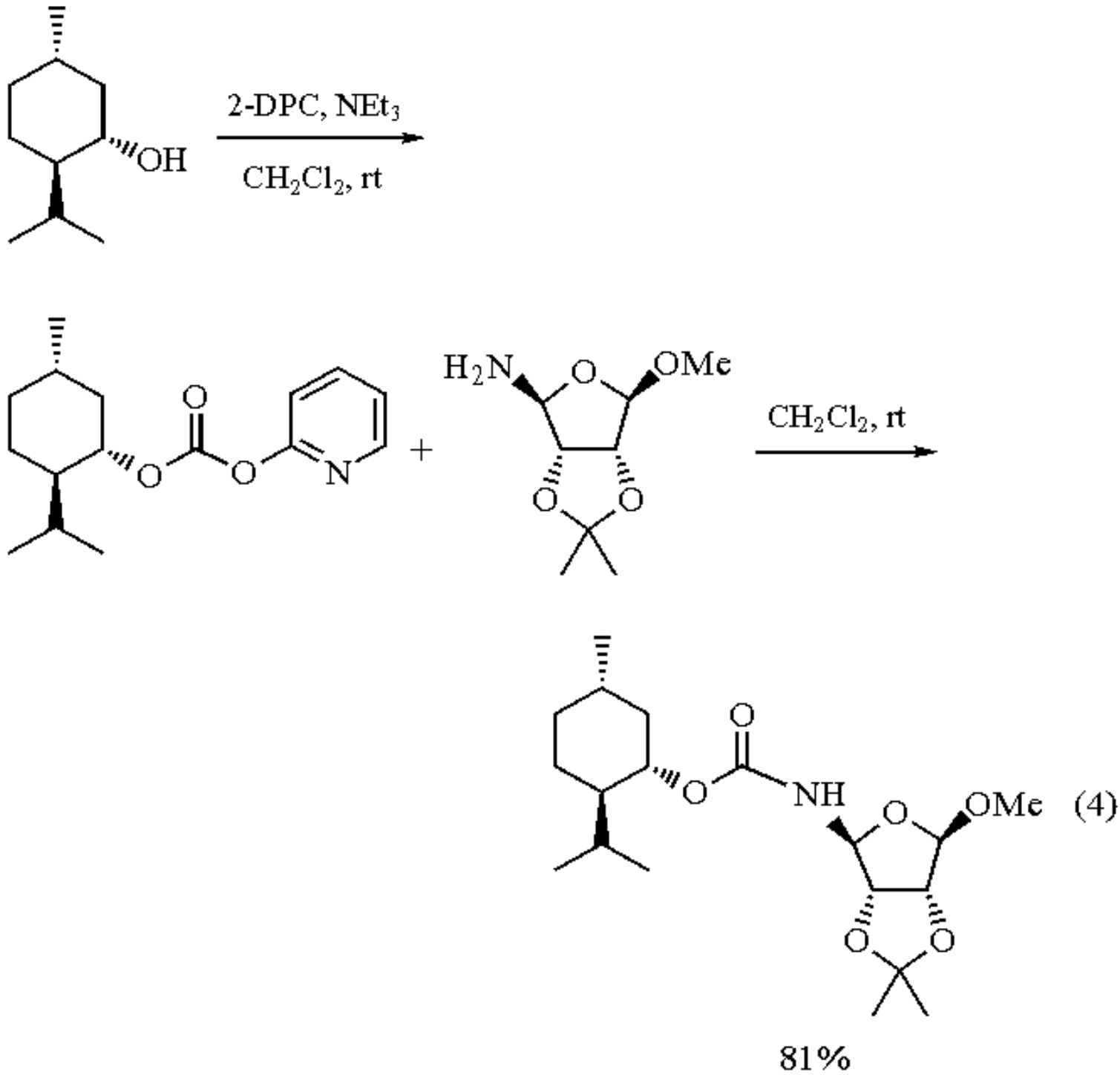

Carbonyl Transfer Reaction.

2-DPC is useful for the preparation of cyclic carbonates or 2-oxazolidones.[1,8] The reaction with diols is carried out in refluxing toluene. The reaction of ethylene glycol gave an 85% yield of the corresponding carbonate. In the presence of DMAP in CH_2Cl_2 at rt, 1,3-butanediol gave the cyclic carbonate in 85% yield. The reaction of 2-DPC with β-amino alcohols in CH_2Cl_2 at rt gave good yields of the corresponding 2-oxazolidone: 1-aminopropan-2-ol, 87%; 1-phenyl-2-aminoethanol, 93%; 2-amino-4-nitrophenol, 96% (eq 5).

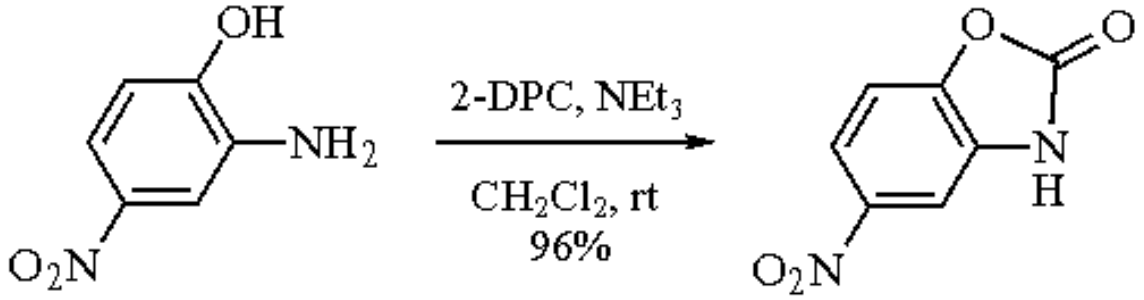

(5)

Related Reagents.

1-(t-Butoxycarbonyl)imidazole; ***1-N-(t-Butoxycarbonyl)-1H-benzotriazole 3-N-Oxide***; ***2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile***; ***t-Butyl Chloroformate***; ***Di-t-butyl Dicarbonate***.

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2,2´-Dipyridyl Diselenide

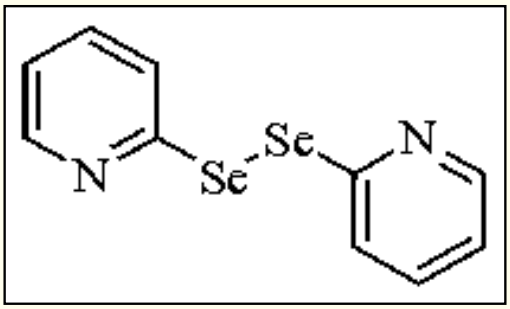

[59957-75-4] · $C_{10}H_8N_2Se_2$ · 2,2´-Dipyridyl Diselenide · (MW 314.12)

(selenoxide elimination to afford alkenes;[1] can mediate the formation of chiral oxazolines;[2,3] a coupling reagent of nucleosides;[4] can catalyze allylic oxidation[5])

Physical Data: mp 50 °C.

Solubility: sol THF, acetonitrile, dichloromethane, methanol.

Preparative Methods: by reaction of 2-bromopyridine with ***Sodium Hydrogen Selenide*** (prepared from ***Selenium*** and ***Sodium Borohydride***) in ethanol followed by oxidation[1,4] or with ***Lithium Diselenide*** (prepared from selenium and ***Lithium*** in the presence of ***Diphenylacetylene*** as catalyst) in THF-HMPA.[6]

Purification: column chromatography on silica gel using hexane-ethyl acetate (2:1) or light petroleum ether-ethyl ether (1:1) as eluent. Recrystallization from petroleum ether (30-70 °C) or diisopropyl ether-ethyl acetate.

Handling, Storage, and Precautions: the reaction of sodium hydrogen selenide should be carried out in a well-ventilated hood (H_2, containing H_2Se, is produced). Selenium is reputed to be toxic. 2,2´-Dipyridyl diselenide should be stored in the dark.

Selenoxide Elimination.

In the selenoxide elimination reactions to afford alkenes, the 2-pyridineseleninyl group has been reported to be a better leaving group than the benzeneseleninyl group. Typical examples are the formation of cyclooctenone[1] and monosubstituted terminal alkenes.[7] 2,2´-Dipyridyl diselenide was used in the preparation of starting selenides, for example 2-(2-pyridylseleno)cyclooctanone, by reaction with the lithium enolate of cyclooctanone (eq 1). In another method, 2,2´-dipyridyl diselenide was treated with sodium borohydride to afford sodium 2-pyridineselenolate, which was used in the subsequent nucleophilic substitution reactions (eq 2).

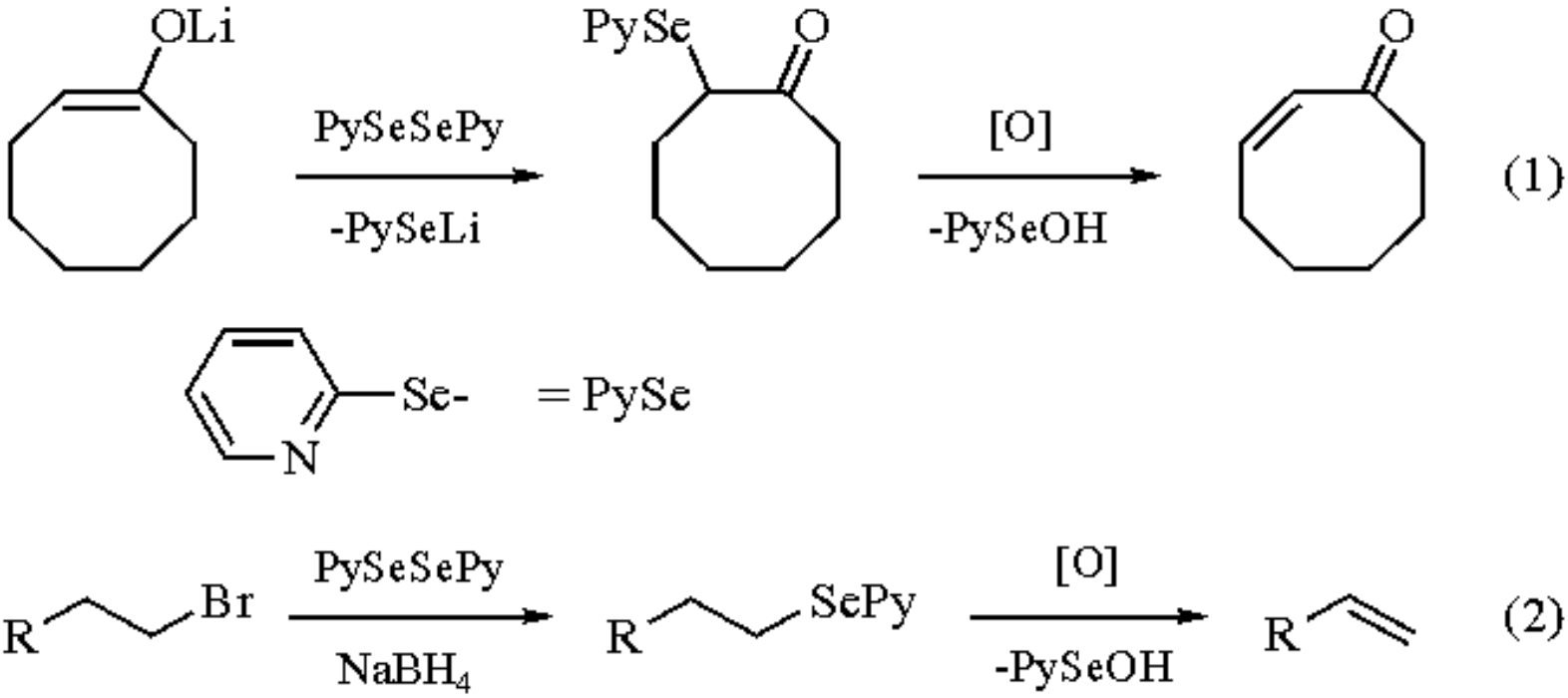

Neighboring Group Participation.

In the Ritter-type substitution of a hydroxy group by nitriles through the anchimeric assistance of the areneselenenyl group onto the chiral carbon, chiral amides were obtained without loss of optical purity by the use of the 2-pyridineselenenyl group (eq 3), whereas racemic amides were obtained by the use of the benzeneselenenyl group. Subsequent oxidation of the selenides to selenones and treatment with base induces the intramolecular substitution of the 2-pyridineselenonyl group by the oxygen atom of the amide to afford chiral oxazolines (eq 4).[3]

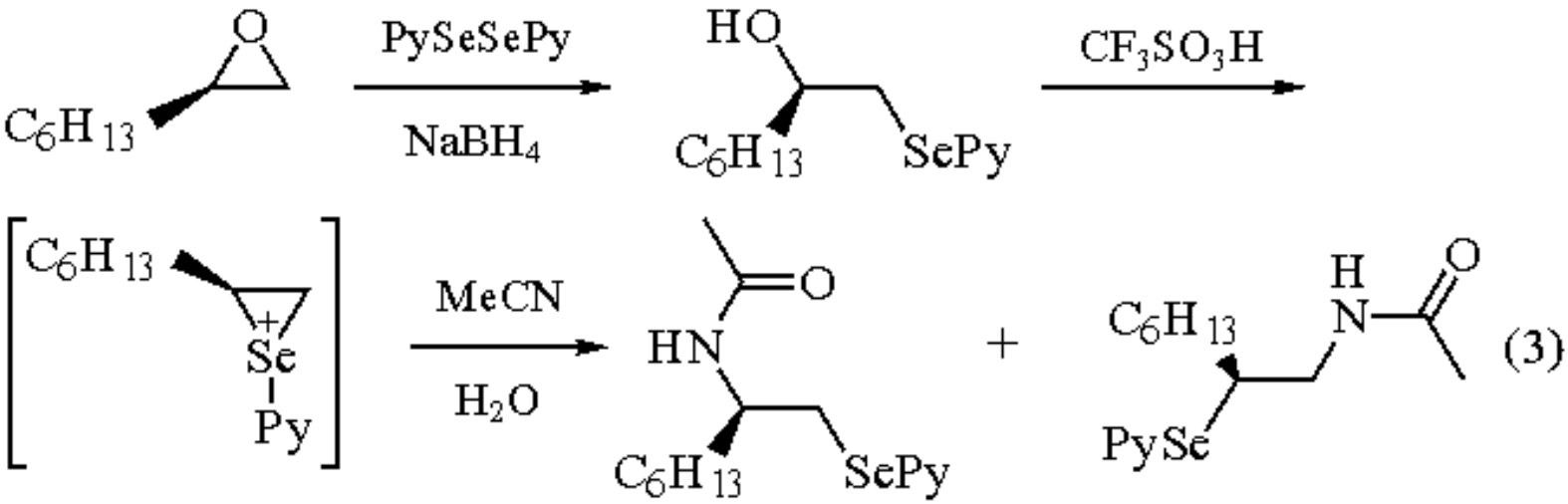

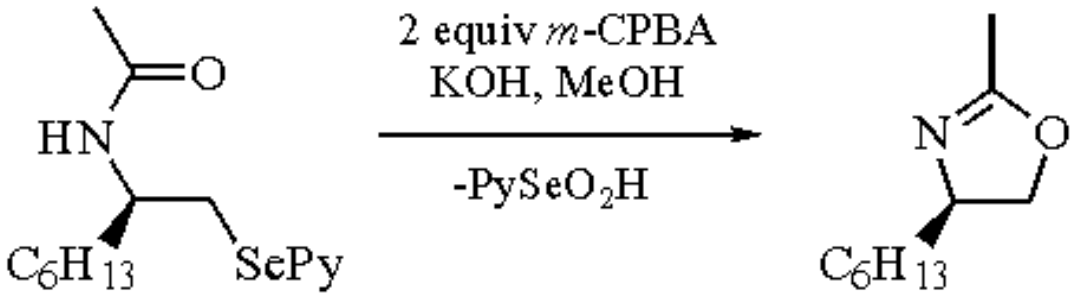

(4)

Coupling Reagent of Nucleosides.

A combination of 2,2´-dipyridyl diselenide and ***Triphenyl Phosphite*** has been utilized in the synthesis of oligonucleotides (eq 5).[4] This reagent has been reported to be superior to sulfur analogs such as ***2,2´-Dipyridyl Disulfide*** and ***Triphenylphosphine***[8] in that the reaction using this combination is free from undesirable byproducts. A combination of 2,2´-dipyridyl diselenide and triphenylphosphine has also been used in the selective phosphorylation of 5´-hydroxy group of oligoribonucleotides.[9]

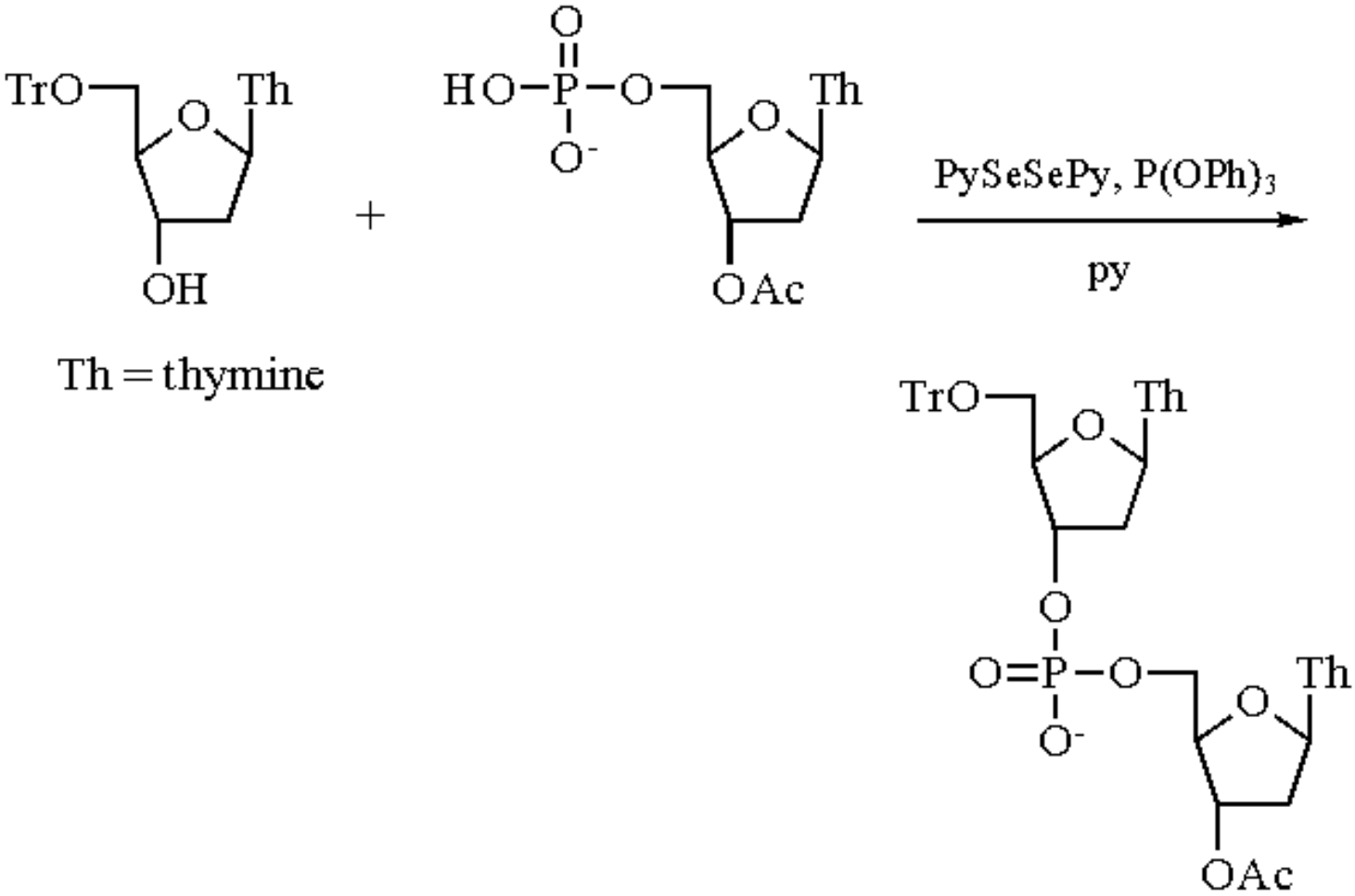

(5)

Allylic Oxidation.

2,2´-Dipyridyl diselenide catalyzes the oxidation of alkenes to unsaturated ketones by ***Iodylbenzene*** (eq 6).[5] The reactive species is considered to be 2-pyridineseleninic anhydride, which is much more reactive to alkenes than

benzeneseleninic anhydride.

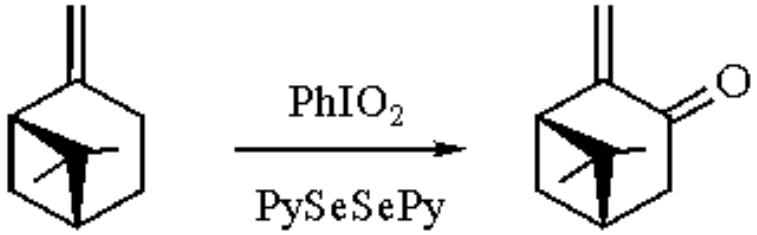

(6)

Related Reagents.

Diphenyl Diselenide; ***Diphenyl Disulfide***; ***2-Pyridineselenenyl Bromide***.

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2,2´-Dipyridyl Disulfide[1]

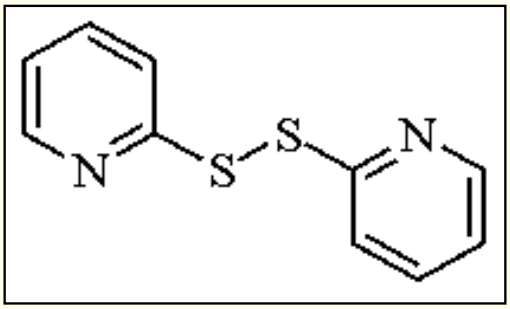

[2127-03-9] · $C_{10}H_8N_2S_2$ · 2,2´-Dipyridyl Disulfide · (MW 220.34)

(macrolactonization of o-hydroxy acids,[6] acylation of pyrroles,[22] couplings at anomeric centers[27])

Alternate Names: 2,2´-dithiopyridine.

Physical Data: mp 57-58 °C.

Solubility: benzene, THF, CH_2Cl_2, MeCN, DMF.

Form Supplied in: white (colorless) crystalline solid.

Preparative Methods: although 2,2´-dipyridyl disulfide is commercially available, it can be readily prepared from 2-pyridinethione by oxidation with a number of reagents.[2]

Purification: recrystallization from hexane at 30 mL g^{-1} concentration.[3]

Handling, Storage, and Precautions: the solid is irritating to eyes, mucus membranes, and respiratory tract, and physical contact should be avoided. Combustion produces toxic byproducts including nitrogen oxides. Cold storage in air-tight containers is recommended. Use in a fume hood.

Macrolactonization.[4]

When a carboxylic acid is treated with 2,2´-dipyridyl disulfide in the presence of ***Triphenylphosphine***, the corresponding 2-pyridinethiol ester is formed.[5] Corey and Nicolaou have developed an efficient method for the synthesis of macrocyclic lactones based on these 2-pyridinethiol esters.[6] When an o-hydroxy thiolester is heated in refluxing xylene under high dilution conditions (10^{-5} M, typically accomplished with syringe pump techniques), macrolactonization occurs, liberating triphenylphosphine oxide and pyridinethione. The reaction is quite general and is believed to proceed by a double activation mechanism in which the basic 2-pyridinethiol ester simultaneously activates

both the hydroxy and the carboxylic acid moieties with a single proton transfer. It has been shown that the cyclization rate is not affected by the presence of acids, bases, or any of the possible reaction contaminants.[7]

This method is mild, highly efficient for the preparation of medium to large rings (7-16,[6] 12-21[7]), and has been applied to the synthesis of a number of important macrocyclic targets including monensin,[8] brefeldin A (eq 1) and erythronolide B,[9] (±)-11-hydroxy-*trans*-8-dodecenoic acid lactone,[10] (±)-vermiculine,[11] enterobactin,[12] and prostaglandins.[8,13]

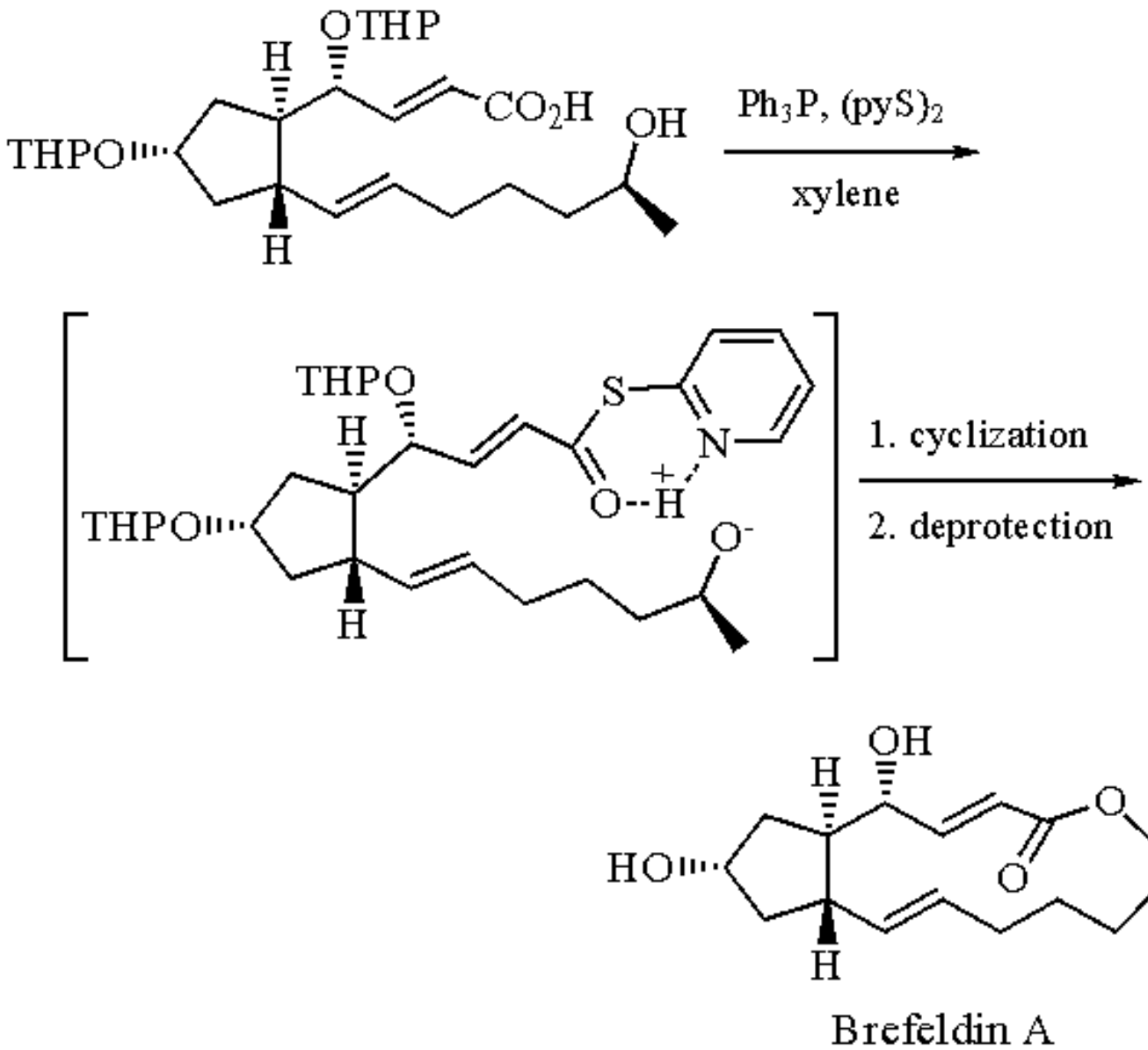

(1)

In an effort to develop an even milder lactonization protocol, other diaryl disulfides were explored, the most promising being imidazole derivatives (**1**) and (**2**).[14] The formation of dilides (dimers of macrocyclic lactones) is occasionally a problem, necessitating the use of other cyclization methods.[4,15] A variation of Corey's method using silver salts has been developed.[3,16]

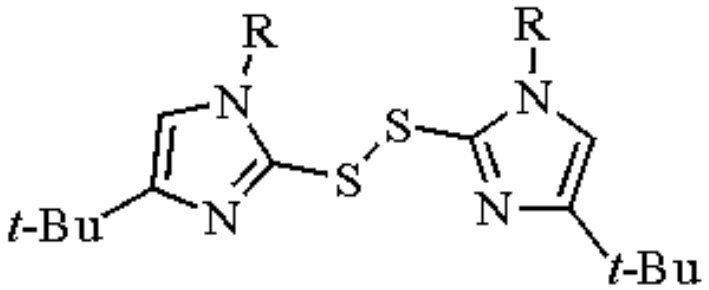

(1) R = Me
(2) R = *i*-Pr

If an o-aminopyridinethiol ester is used, macrolactamization occurs.[17] A method for the synthesis of β-lactams from β-amino acids has also been developed where the use of MeCN has been found to be critical (eq 2).[18] The intermolecular version of this reaction is a powerful peptide coupling method.[19,20]

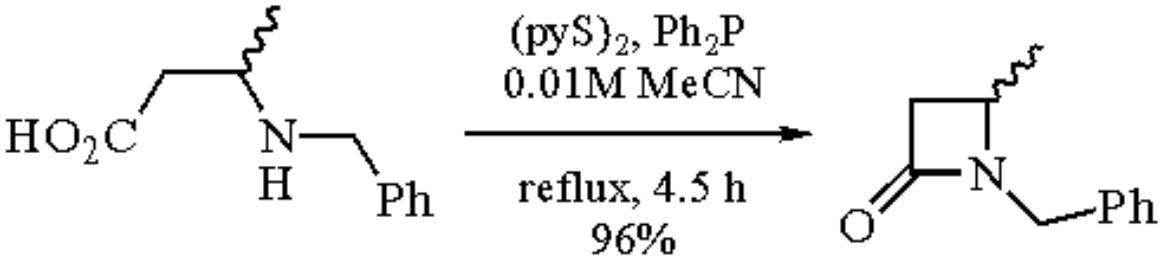

(2)

Related Reactions of 2-Pyridinethiol Esters.

In the absence of an internal nucleophile, the thiopyridyl esters generated by the reaction of carboxylic acids with 2,2´-dipyridyl disulfide and triphenylphosphine exhibit other reactivities. Thiolesters are potent acylating agents, reacting with Grignard reagents to yield ketones instead of tertiary alcohols.[21,22] This activity has been exploited for the synthesis of 2-acylpyrroles using pyrrylmagnesium salts as the nucleophilic species. Nicolaou and co-workers have exploited 2-pyridinethiol esters in the synthesis of a number of complex 2-acylpyrroles (eq 3).[23] In certain troublesome cases, the use of stoichiometric ***Copper(I) Iodide*** has been found to significantly improve yields.[24]

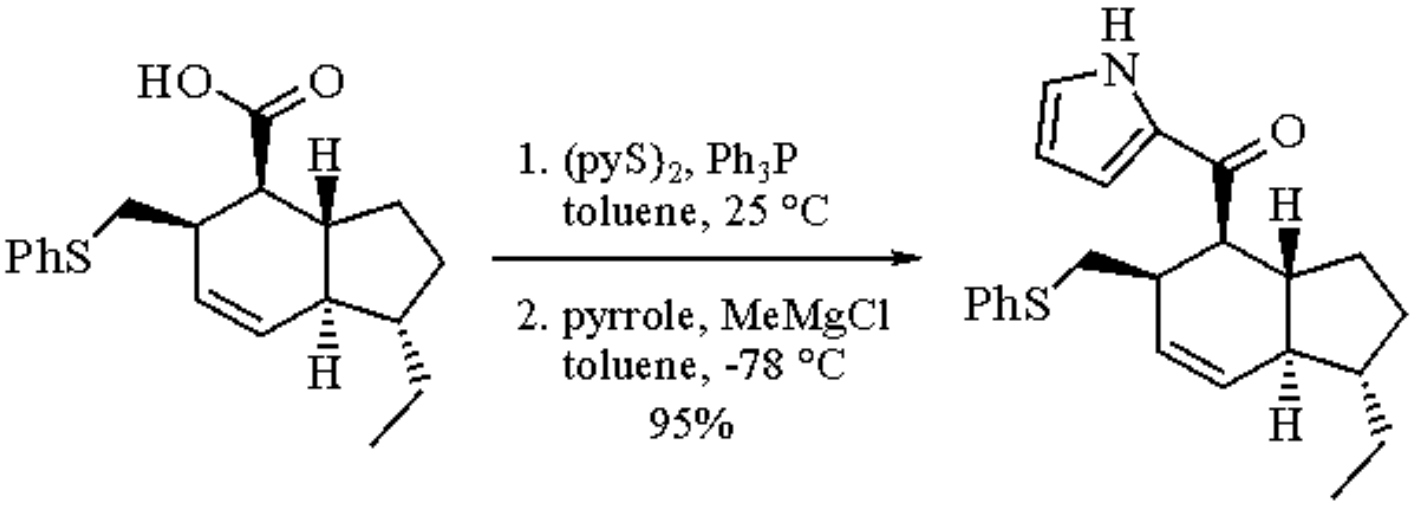

(3)

2-Pyridinethiol esters are readily reduced with ***Sodium Borohydride*** in the presence of isopropanol.[25] Activation of 2-pyridinethiol esters with ***Iodomethane*** allows for mild trapping with alcohols or benzenethiol, yielding esters or thiolesters.[26] In these cases the use of iodomethane avoids the need for thiophilic silver or mercury salts and allows for transthiolesterification.

Disaccharide Formation.

Treatment of glycoside (**3**) with 2,2´-dipyridyl disulfide and ***Tri-n-butylphosphine*** in CH_2Cl_2 rapidly yields thiopyridyl derivative (**4**) as a mixture of anomers. Activation of (**4**) with iodomethane, followed by treatment with glycoside acceptor (**5**), affords the disaccharide fragment of avermectin (**6**),[27] exclusively α-linked in 78% yield (eq 4).[28] Although other methods are available, this protocol offers advantages in practicality and stereoselectivity.

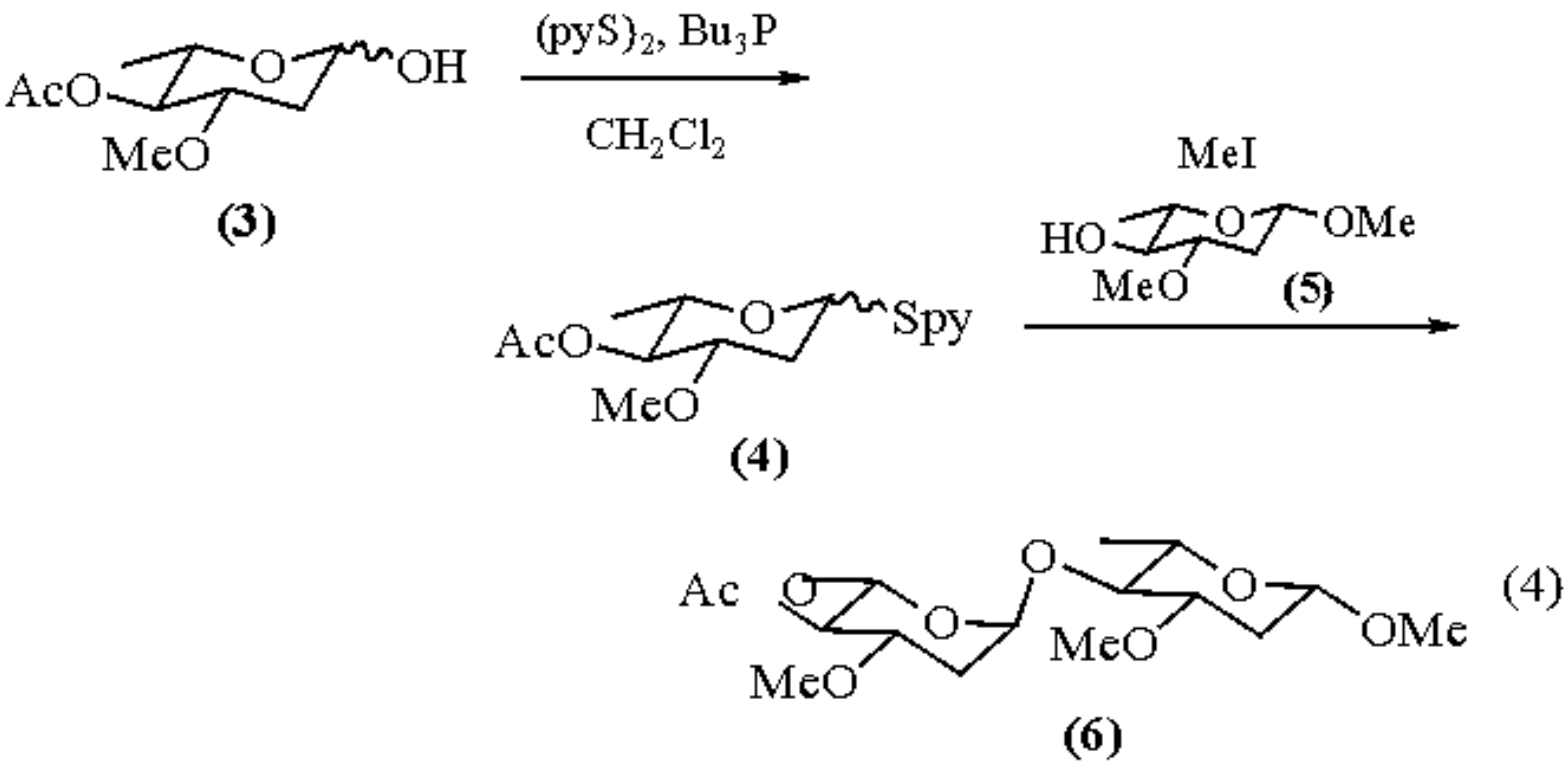

Carbon-carbon bonds can be similarly formed at the anomeric center of carbohydrates. Oxonium ions, formed by the treatment of 1-(2´-thiopyridyl)glycosides with ***Silver(I) Trifluoromethanesulfonate***, can be trapped with silyl enol ethers, silyl ketene acetals, and reactive aromatic compounds, where the stereoselectivity of the addition is determined by solvent and nucleophile choice.[29] The intramolecular version of this process has also been examined (eq 5).[30] Similarly, bicyclic piperazinediones are available by the intramolecular trapping of iminium ions, generated from the appropriate thiopyridyl derivatives with $PhHgClO_4$ (eq 6).[31]

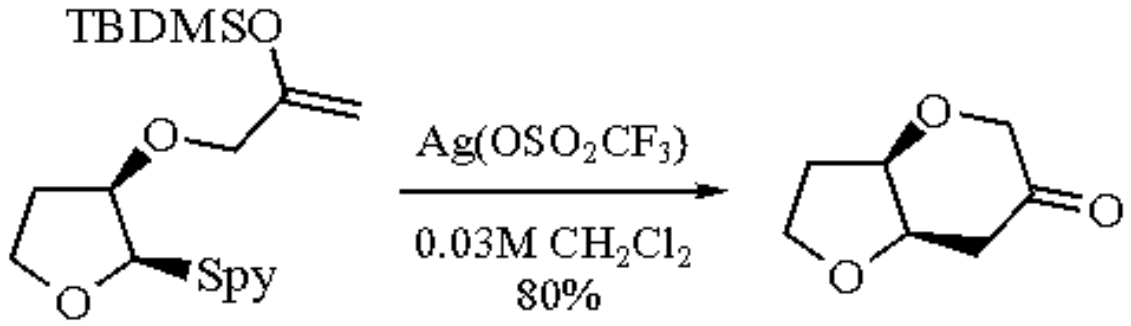

(5)

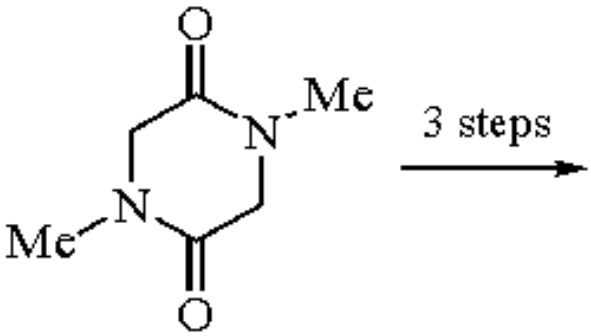

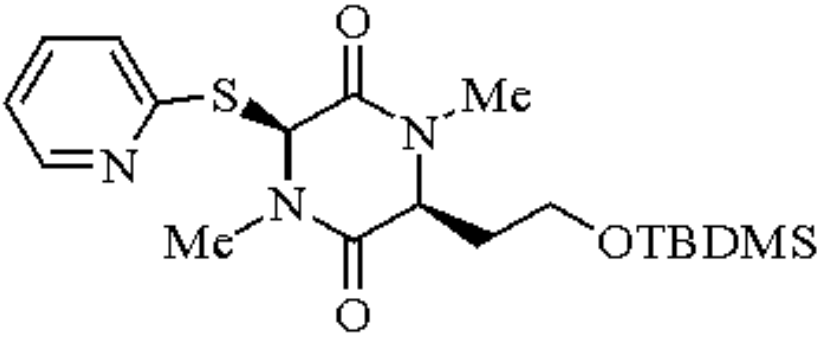

(6)

Alkene Formation.

The elimination of pyridinethione or 2-pyridylsulfenic acid forms the basis of a number of alkene syntheses. For example, treatment of dithioacetal anions with 2,2´-dipyridyl disulfide affords the α-thiopyridyl derivative, which undergoes elimination at below room temperature to give ketene dithioacetals.[32] Ester enolates have been similarly treated, although ***m-Chloroperbenzoic Acid*** is first used to generate the sulfoxide which reacts further to yield an α,β-unsaturated ester.[33] This methodology has been applied to the synthesis of methyl dehydrojasmonate (**7**) (eq 7).[34]

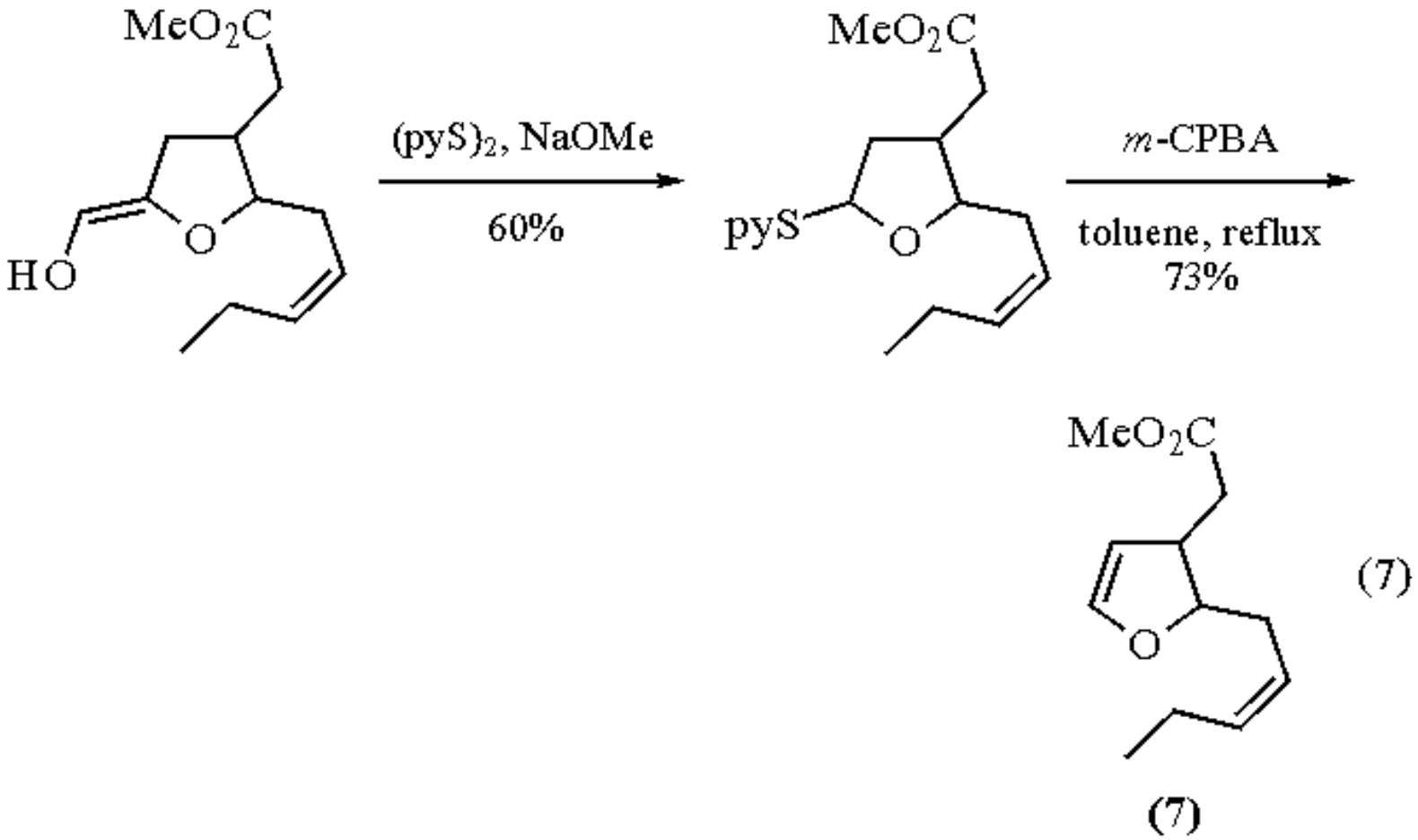

Other Reactions.

Treatment of an active hydroxy compound with 2,2´-dipyridyl disulfide and *n*-Bu_3P yields the corresponding thiopyridyl derivative. This methodology has been applied to the preparation of 5-arylthio-5´-deoxyribonucleosides (eq 8).[35] Monophosphate esters [$ROP(O)(OH)_2$] will react similarly to form the activated triphenylphosphonium adduct, which, in the absence of an added external nucleophile, dimerizes yielding a pyrophosphate.[36] *N*-Methylimidazole has been found to catalyze this transformation. The addition of alcohols or amines, however, traps the phosphoryloxyphosphonium salt as the mixed diphosphate ester or mixed ester/amide, respectively (eq 9).[37] ***Chlorotrimethylsilane*** and $(pyS)_2$ have also been reported to facilitate the oxidation of phosphites to phosphates.[38]

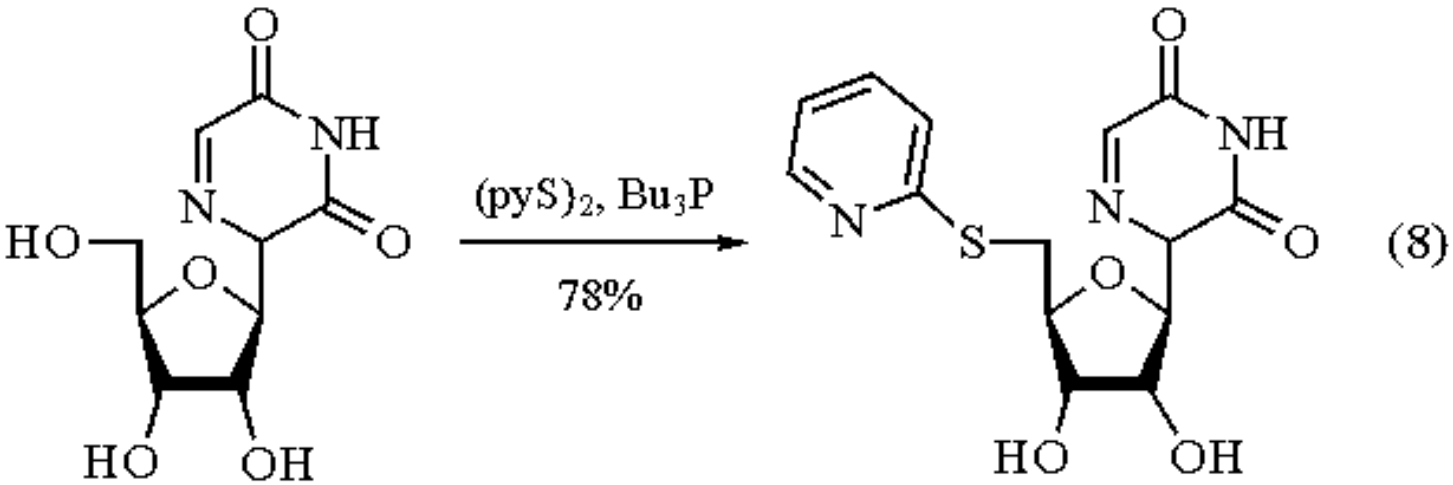

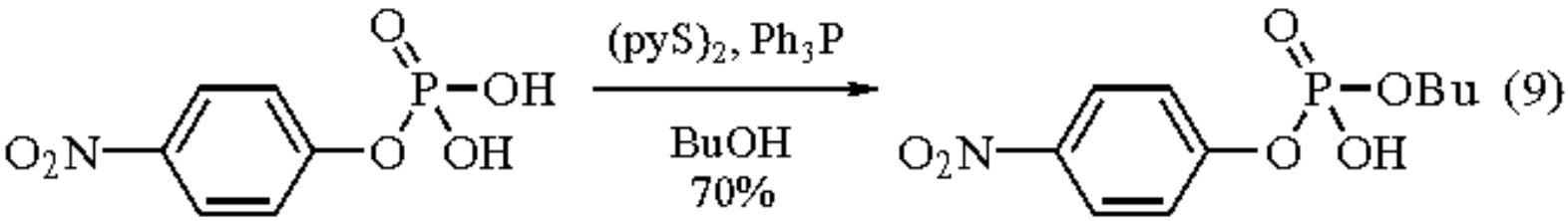

General Reactions of Diaryl Disulfides.[1]

2,2´-Dipyridyl disulfide reacts with a variety of carbon nucleophiles, yielding the corresponding thiopyridyl derivatives. These include phosphonate stabilized anions,[39] bromouridine derivatives,[40] indole anions,[41] and heterocyclic stabilized anions.[42]

---

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Dirhodium(II) Tetraacetamide

$Rh_2(NHCOMe)_4$

[87985-40-8] · $C_8H_{16}N_4O_4Rh_2$ · Dirhodium(II) Tetraacetamide · (MW 438.10)

(catalyst for selective carbenoid reactions of diazo compounds[1])

Physical Data: UV/vis (MeCN) 500 (2.2), 345 (shoulder) nm.[2] NMR (CD_3CN): δ 2.20 (s).[3]

Solubility: sol MeOH, MeCN, pyridine, DMSO; insol CH_2Cl_2, toluene.

Form Supplied in: blue solid for anhydrous form; purple solid as hydrate.

Preparative Method: by ligand substitution from $Rh_2(OAc)_4$.[3]

Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Introduction.

Dirhodium(II) tetraacetamide, $Rh_2(acam)_4$, was first prepared from ***Dirhodium(II) Tetraacetate*** in a melt of acetamide.[4] However, this method gave a mixture of $Rh_2(OAc)_{4-n}(acam)_n$, of which $Rh_2(acam)_4$ was the dominant product but could not be conveniently separated. The preferred procedure is to treat $Rh_2(OAc)_4$ with acetamide in refluxing chlorobenzene under conditions where acetic acid is trapped by sodium carbonate in a Soxhlet extraction apparatus (eq 1).[3] Four acetamidates are ligated to one dirhodium(II) nucleus, and each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* geometry.[5] Incomplete substitution, when only three acetamides have replaced acetate, yielding $Rh_2(acam)_3(OAc)$, produced a catalyst whose selectivity is not optimum.

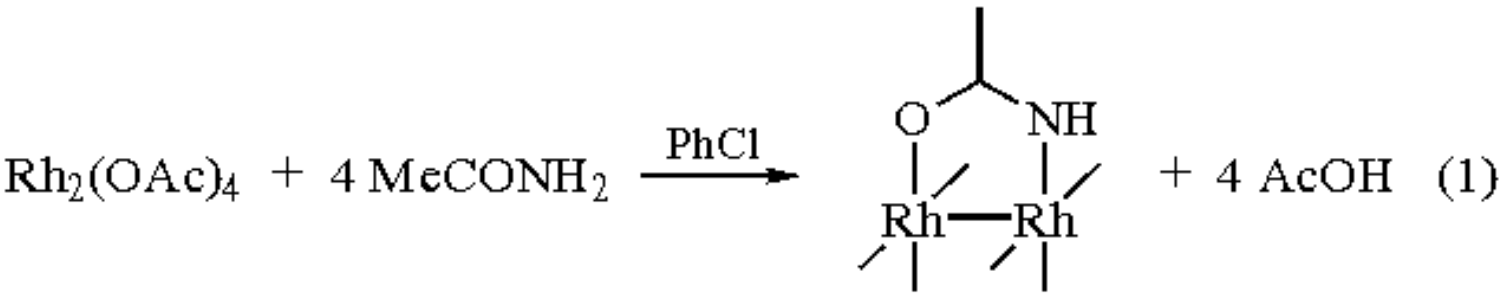

Metal Carbene Transformations.

Although insoluble in the solvents in which catalytic metal carbene transformations are performed, $Rh_2(acam)_4$ enters solution after addition of the diazo compound. The principal advantage of this catalyst is its selectivity for product formation from reactions with diazocarbonyl compounds, but its reactivity towards dinitrogen extrusion is less than that of dirhodium(II) tetra(carboxylates).

Stereoselectivity in Cyclopropanation Reactions.

Use of $Rh_2(acam)_4$ for intermolecular cyclopropanation of alkenes results in higher *trans* (*anti*) selectivity which, when the diazo compound is 2,6-di-*t*-butyl-4-methylphenyl diazoacetate (BDA), is exceptional (e.g. eq 2: 98% *trans*).[3] Product yields are high (75-96%), and byproducts are often minimal. Relative reactivities are also enhanced by $Rh_2(acam)_4$, which has made possible highly regioselective cyclopropanation of selected dienes (e.g. eq 3).[3] However, $Rh_2(acam)_4$ is unsuitable, relative to ***Dirhodium(II) Tetraacetate***, for intermolecular cyclopropanation of styrene by the pantolactone ester of *trans*-2-diazo-4-phenyl-3-butenoate.[6] Substitution of $Rh_2(acam)_4$ by the more soluble ***Dirhodium(II) Tetra(caprolactam)***, $RH_2(cap)_4$, does not provide any obvious advantage in reactivity or selectivity for cyclopropanation.

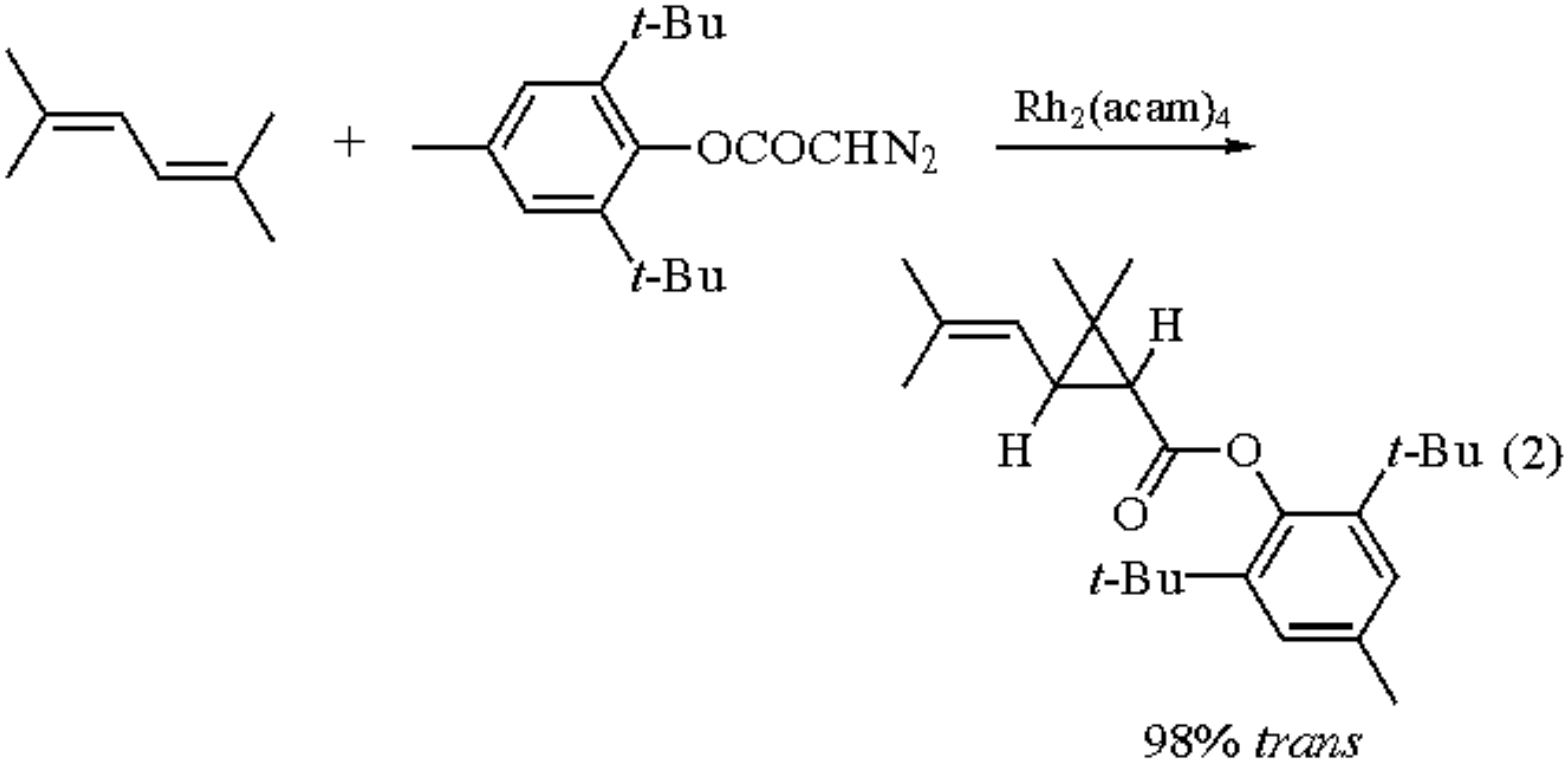

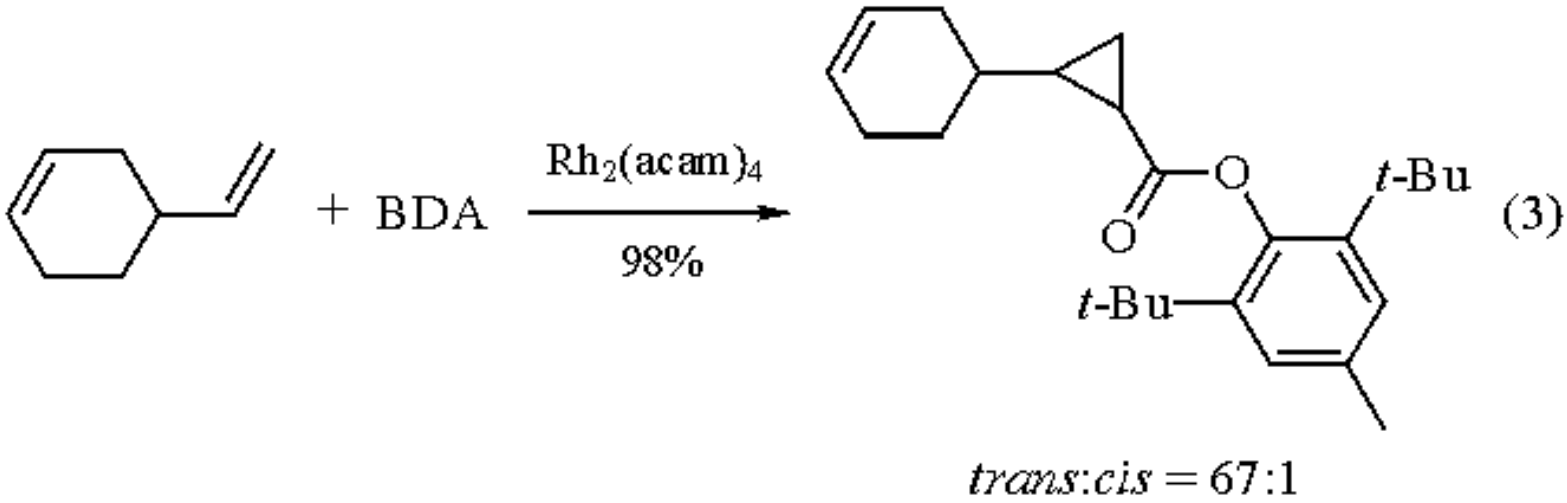

Carbon-Hydrogen Insertion Reactions.

Use of $Rh_2(acam)_4$ provides an increase in regioselectivity for competitive insertion into carbon-hydrogen bonds (tertiary > secondary > primary) that result in the formation of five-membered ring carbonyl compounds (e.g. eq 4; pfb = perfluorobutyrate).[7,8]

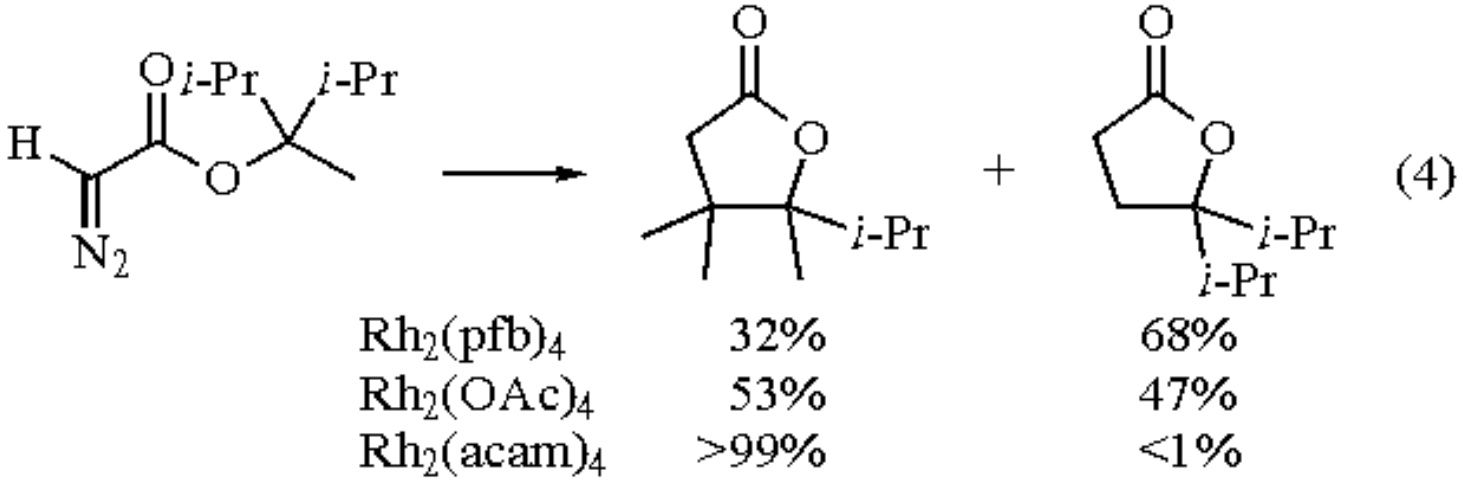

Both diazoacetoacetates and diazoacetates show exceptional selectivity enhancement with $Rh_2(acam)_4$. However, the same degree of control is not evident in the competition from diazoacetoacetamides for β-lactam versus γ-lactam formation.[9-11] The use of $Rh_2(cap)_4$ in place of $Rh_2(acam)_4$ does not provide any obvious advantage in regioselectivity for carbon-hydrogen insertion.

Chemoselectivity.

Few comparisons have been made with $Rh_2(acam)_4$ and $Rh_2(cap)_4$, but those that have suggest that $Rh_2(cap)_4$ holds an advantage.[11] *N*-(2-Arylethyl)-*N*-*t*-butyldiazoacetamides, for example, exhibit competition between aromatic cycloaddition and carbon-hydrogen insertion (e.g. eq 5), and chemoselectivity for C-H insertion with $Rh_2(cap)_4$ is greater than with $Rh_2(acam)_4$, but both are more selective than is $Rh_2(OAc)_4$.

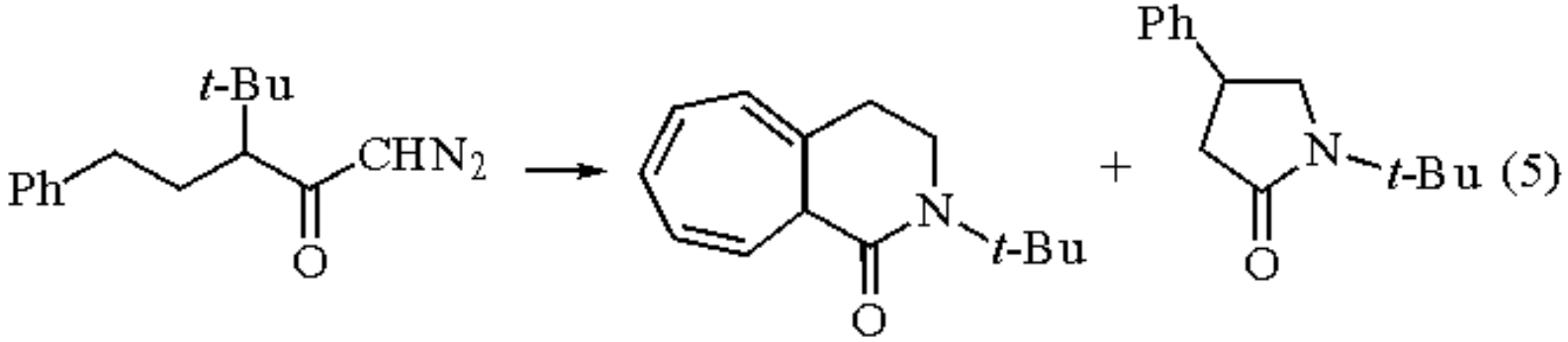

$Rh_2(acam)_4$	23%	77%
$Rh_2(cap)_4$	3%	97%

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Dirhodium(II) Tetraacetate

$Rh_2(O_2CMe)_4$

[15956-28-2] · $C_8H_{12}O_8Rh_2$ · Dirhodium(II) Tetraacetate · (MW 442.02)

(catalyst for carbenoid reactions of diazo compounds,[1] hydroboration of alkenes and alkynes,[2] hydrocarbon oxidation[3])

Physical Data: λ 590 nm, ε 210 (EtOH); λ 552 nm, ε 235 (MeCN).[4] IR -ν (CO_2) 1585 cm^{-1}.[5]

Solubility: sol MeOH, acetic acid, MeCN, acetone; slightly sol toluene; insol Et_2O, 1,2-dichloroethane, CH_2Cl_2.

Form Supplied in: emerald-green solid for anhydrous form.

Preparative Method: prepared from $RhCl_3.xH_2O$.[6]

Handling, Storage, and Precautions: air stable, moderately hygroscopic; stored in desiccator. Removal of axially coordinated solvent can be achieved in vacuum oven at 60-80 °C.

Metal Carbene Transformations.

When used in amounts as low as 0.05 mol %,[7] $Rh_2(OAc)_4$ serves as a highly effective and efficient catalyst for dinitrogen extrusion from diazo carbonyl compounds and subsequent metal carbene directed alkene[1,8] and alkyne[9] addition reactions, σ-bond insertion reactions,[1,10] ylide generation,[1,11] and carbene coupling processes,[12] among others. With diazoacetates and diazo ketones, catalytic reactions are generally performed in dichloromethane at rt. The diazo compound is added at such a rate so as to minimize its concentration in the reaction solution.[6] The less reactive α-diazo-β-carbonyl alkanoates, including diazomalonates and diazoacetoacetates, and related diazo dicarbonyl compounds require refluxing 1,2-dichloroethane or refluxing benzene for efficient catalyst turnovers. In laboratory scale reactions, $Rh_2(OAc)_4$ is removed from the reaction solution by filtering through a short column of silica or alumina, or the product(s) are distilled directly from the catalyst-containing mixture. (Rhodium acetate undergoes thermal decomposition at temperatures near 250 °C.)

Cyclopropanation/Cyclopropenation.

Its catalytic uses for intermolecular cyclopropanation and cyclopropenation reactions, discovered only recently by

Teyssié and co-workers,[9,13] have been the standard through which mechanistic[14] and synthetic (selectivity)[8,15] understanding of metal carbene addition reactions have been derived.[1] Intermolecular addition reactions of diazoacetates with alkenes occur at 25 °C in high yield. Their stereoselectivities and regioselectivities[16] are lower than those achieved with the use of ***Dirhodium(II) Tetraacetamide***,[8] but high selectivities are observed with vinylcarbenoid addition (eq 1)[17] and nitrocarbenoid addition[18] to alkenes. Cyclopropene formation occurs with a broad selection of alkynes (eq 2),[19a] but not phenylacetylene.[9,19] Neither cyclopropanation nor cyclopropenation occurs readily with α,β-unsaturated carbonyl compounds or nitriles.[20]

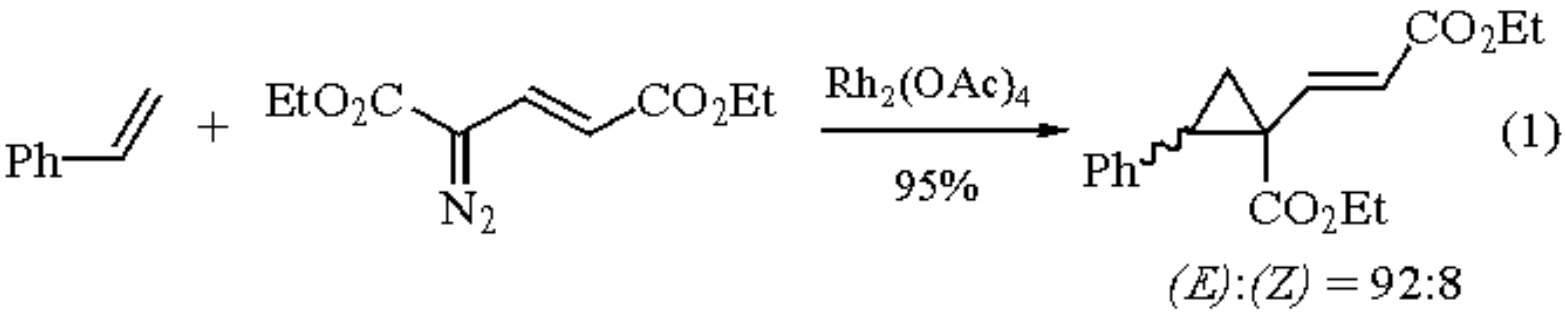

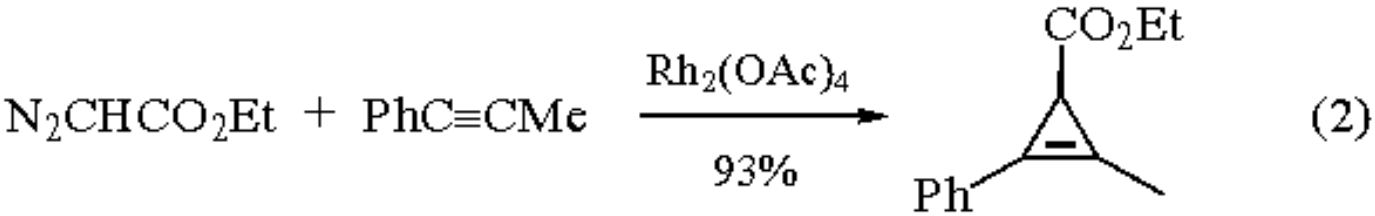

Intramolecular analogs of these reactions suggest the overall viability of $Rh_2(OAc)_4$ catalysis (eqs 3 and 4),[21-23] although for alkyne addition the presumed cyclopropene intermediate is unstable and undergoes reactions characteristic of vinylcarbenoid species,[22,23] of which the most frequently encountered involve rearrangement to furans. The intramolecular Büchner reaction of aryl diazoketones (eq 5)[24] is, formally, cyclopropanation of an aromatic ring, for which $Rh_2(OAc)_4$ is especially suitable;[24] the diazoamide analog of this transformation is particularly facile.[25]

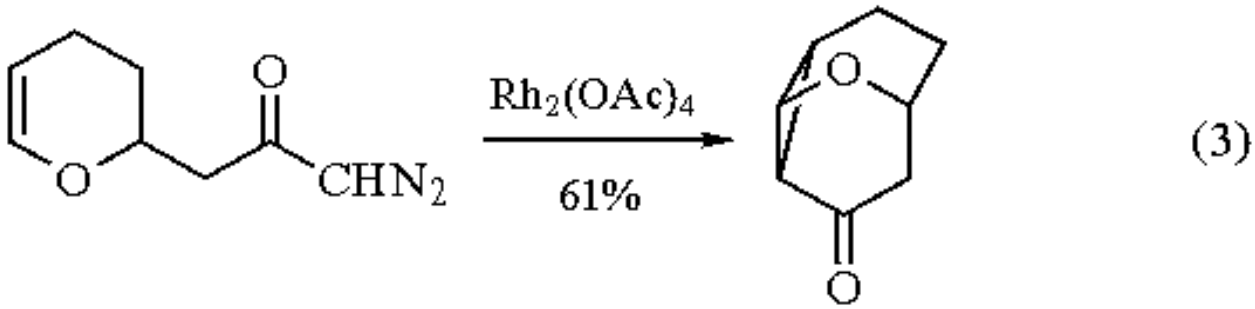

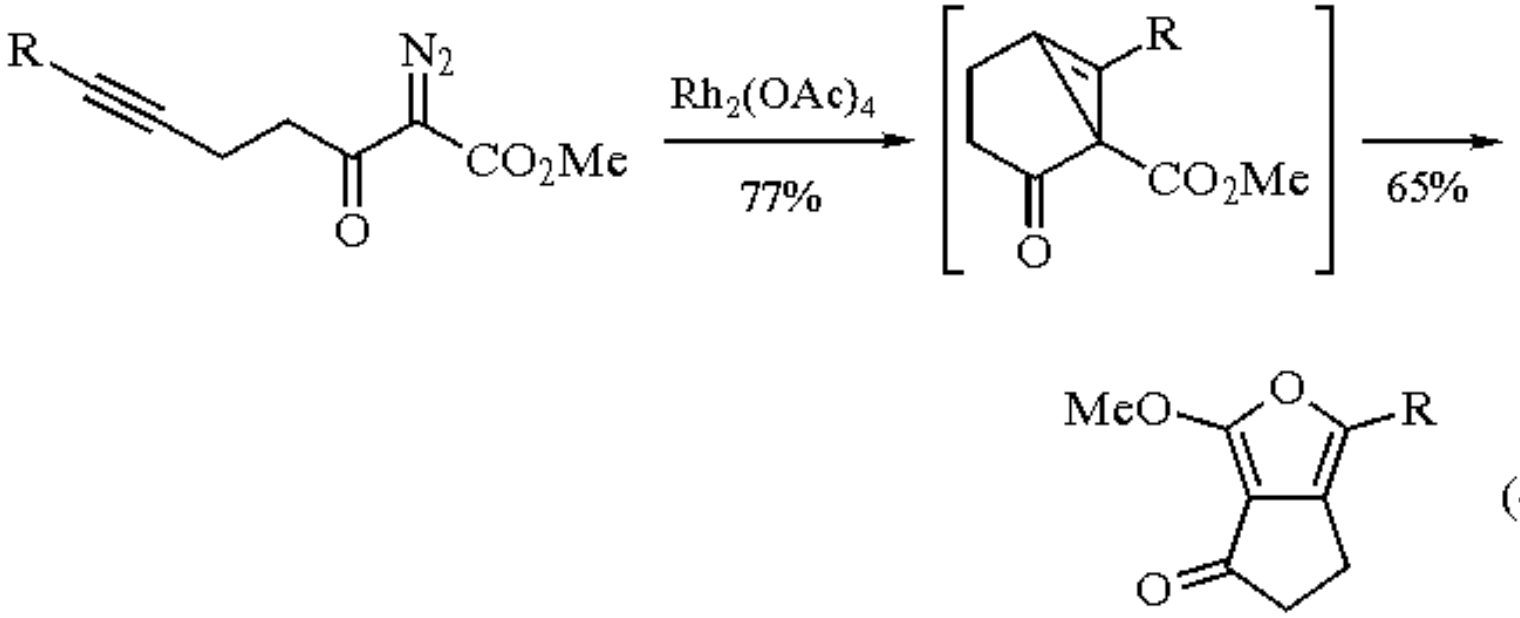

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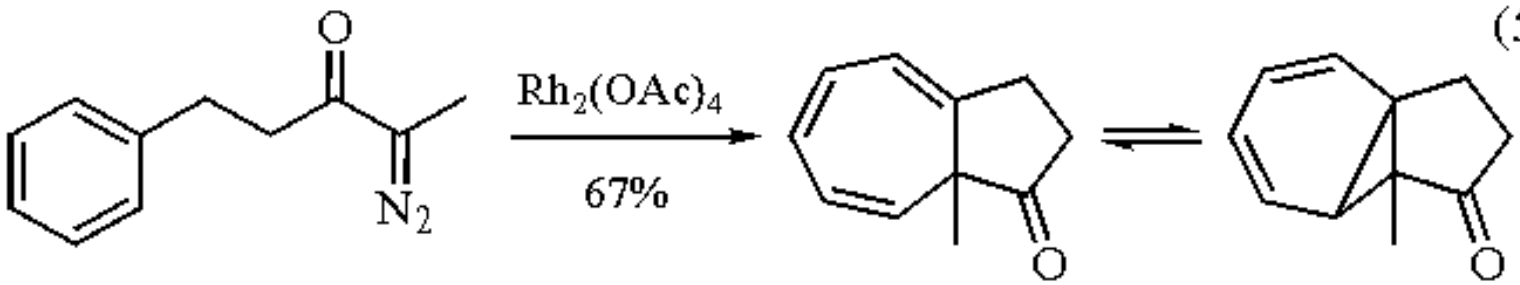

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Carbon-Hydrogen Insertion.

The utility of $Rh_2(OAc)_4$ as a catalyst for metal carbene transformations is most evident in its ability to effect insertion into unactivated carbon-hydrogen bonds.[1,10] Preference for the formation of five-membered rings is pronounced (eq 6),[26] and selectivity for insertion into tertiary C-H bonds is usually greater than for insertion into secondary C-H bonds, and primary C-H bonds are the least reactive.[27] Although these controlling influences are pervasive, an increasing number of examples suggest that the factors which control regioselectivity in these reactions are complex (e.g. eq 7).[28]

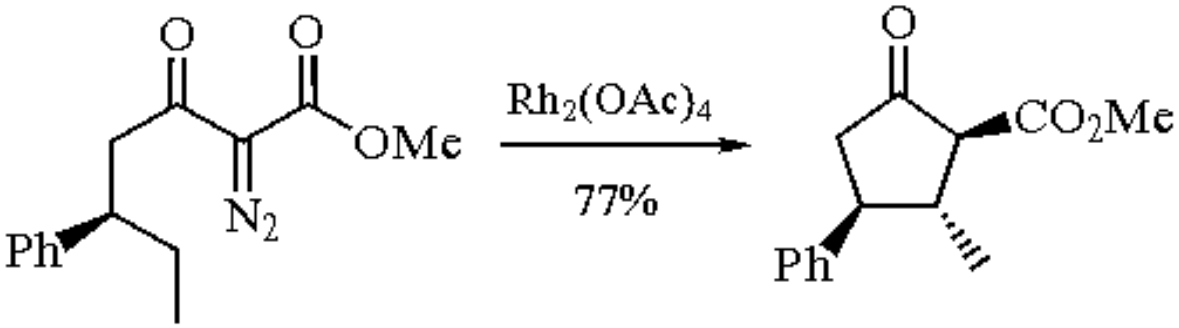

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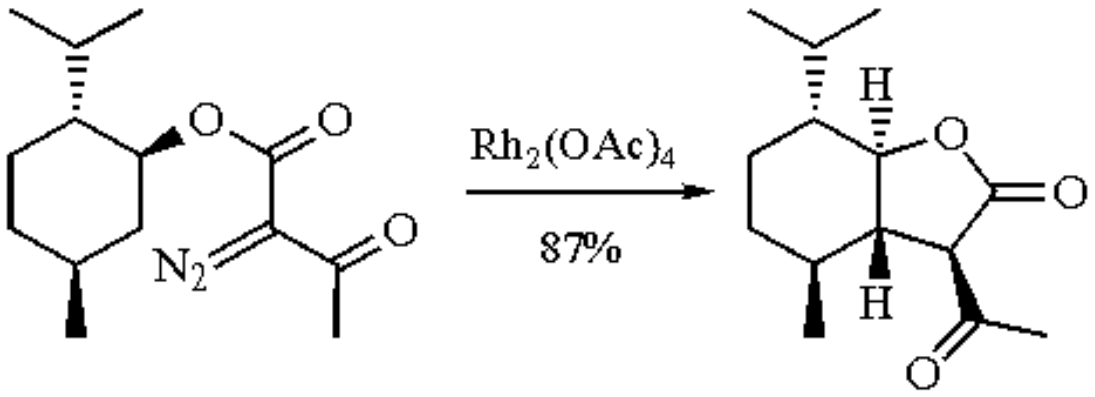

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Heteroatom activation of adjacent C-H bonds[29] has made possible the construction of β-lactam derivatives from diazoacetoacetamides (eq 8)[30] and of β-lactones from selected diazomalonates.[31] With *N*-benzyl derivatives, the presence or absence of an acyl group uniquely defines the course of the catalytic reaction (eq 9; R = *t*-Bu; S = H, Me, OMe, Br).[32] Both electronic and conformational (steric) effects are responsible for the selectivity in these reactions.

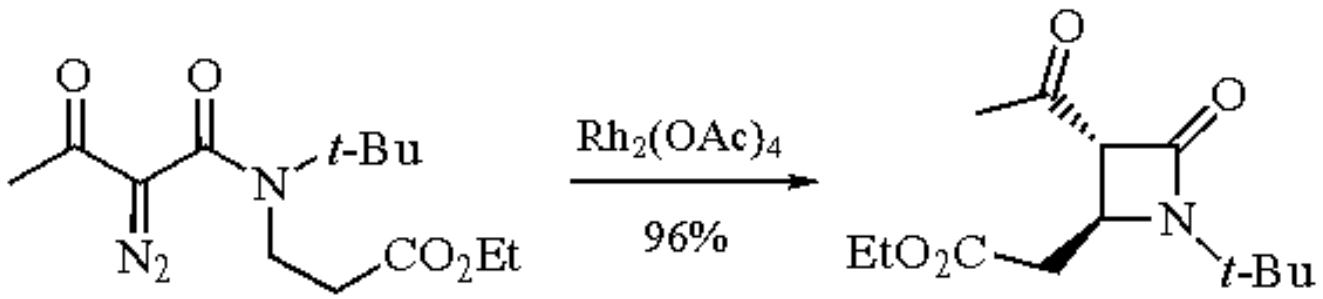

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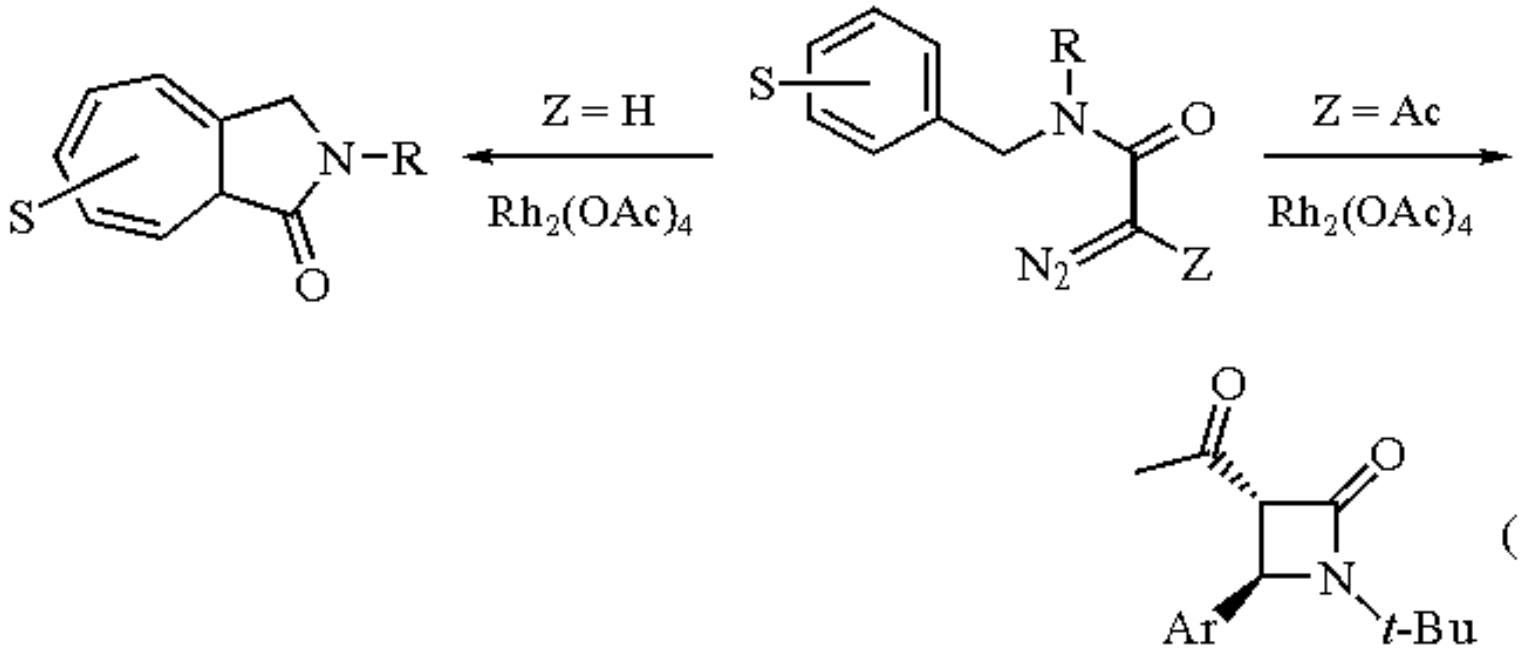

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Intermolecular variants of carbon-hydrogen insertion reactions are generally of limited value because of lower reactivity and selectivity.[1] Insertion into vinylic or alkynic C-H bonds is not competitive with cyclopropanation or cyclopropenation under ordinary circumstances. The so-called allylic C-H insertion reaction, commonly observed in copper-catalyzed reactions of diazomalonates or β-diazo-α-keto esters,[33] is not common with $Rh_2(OAc)_4$ catalysis.[14b]

In contrast to the paucity of examples for C-H insertion into vinylic or alkynic C-H bonds, intramolecular insertion into aromatic C-H bonds is well documented.[1] These reactions are most pronounced when the aromatic ring is activated for substitution by oxygen[34] or nitrogen[35] (e.g. eqs 10 and 11),[34,35a] and they are more suitably described as aromatic substitution reactions than as C-H insertion reactions. Aryl-substituted diazo ketones,[36] diazoacetates,[34] diazoacetoacetates,[34] and their corresponding amide derivatives[35] are all effective. The formation of a five-membered ring is preferred, but, with suitable structural demands in the diazo carbonyl reactant, six-membered ring formation occurs.[37]

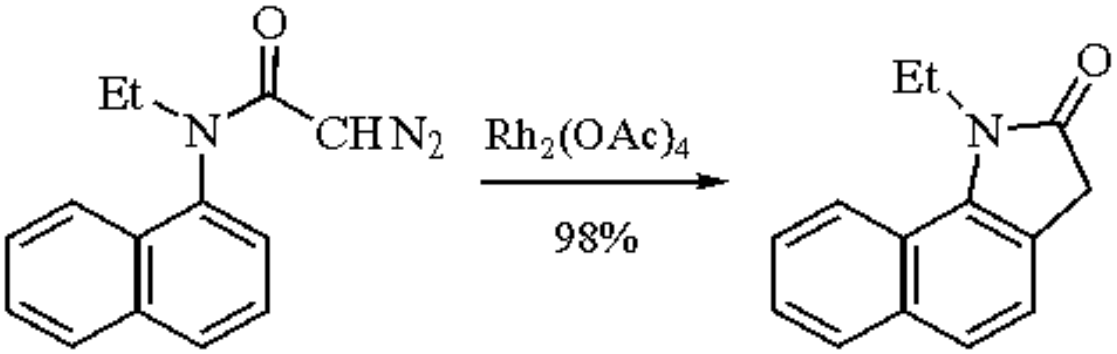

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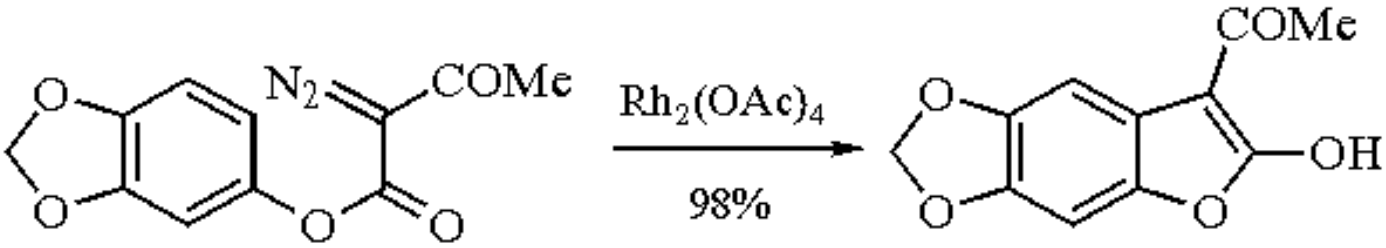

(11)

Heteroatom-Hydrogen Insertion.

One of the most important applications of metal carbene chemistry has been in the syntheses of penems, exemplified in eq 12, which is key step in the total synthesis of the carbapenem thienamycin.[38] This reaction has become the method of choice for the synthesis of bicyclic β-lactams from 2-azetidinones substituted through the 4-position to a diazocarbonyl group.[39]

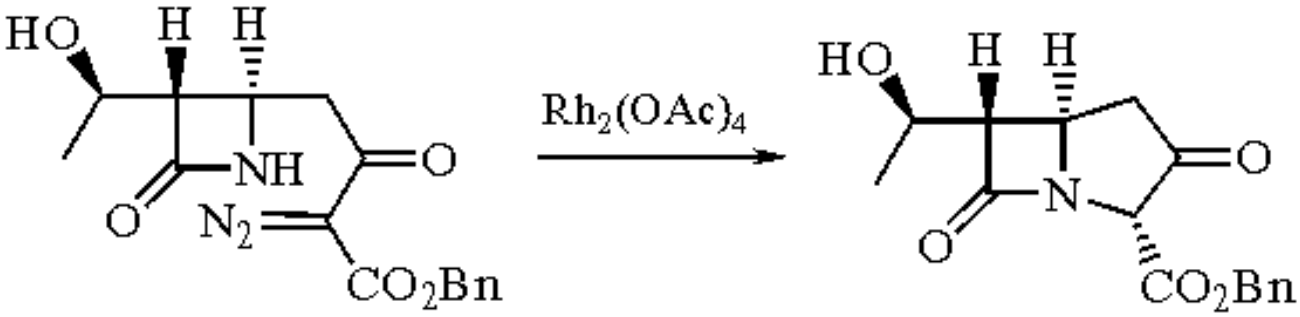

(12)

Oxygen-hydrogen insertion (with water) is a common undesirable side reaction in $Rh_2(OAc)_4$ catalyzed transformations, but its synthetic importance is evident in intramolecular processes. Cyclization via O-H insertion occurs readily and in high yield for five-, six-, and seven-membered ring formation (eq 13),[40] but C-H insertion becomes competitive in attempts to effect eight-membered ring formation. Intermolecular processes have also been examined,[41] but they have

more limited usefulness.

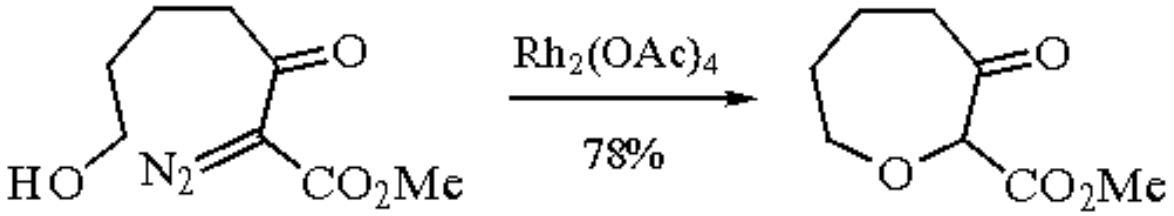

(13)

Thiol insertion also occurs in both intermolecular and intramolecular transformations,[42,43] but these reactions are more difficult to perform because of the facile coordination of thiols and sulfides with $Rh_2(OAc)_4$. Intermolecular silicon-hydrogen insertion provides a convenient methodology for the synthesis of α-silyl esters and ketones (eq 14).[44] Overall, $Rh_2(OAc)_4$ is generally suitable, and often the catalyst of choice, for heteroatom-hydrogen insertion reactions of diazo esters and ketones.[43]

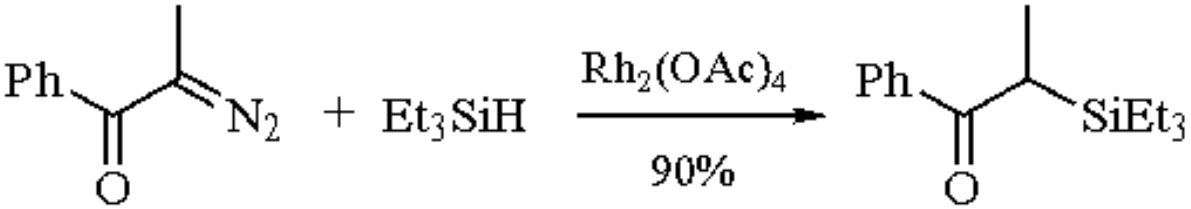

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Ylide Generation.

Metal carbenes produced by $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion from diazo compounds are electrophilic.[1] Reactions of these reactive intermediates, which resemble metal-stabilized carbocations, with Lewis bases constitute a generally effective methodology for ylide generation (eq 15).[11] The relative reactivity of Lewis bases towards ylide generation follows the expected order of basicity for carbon-heteroatom compounds. Ylide products are further transformed by insertion, sigmatropic rearrangement, or dipolar addition reactions, dependent on the design of the ylide. Heteroatom-hydrogen insertion is reasonably regarded as an ylide transformation.

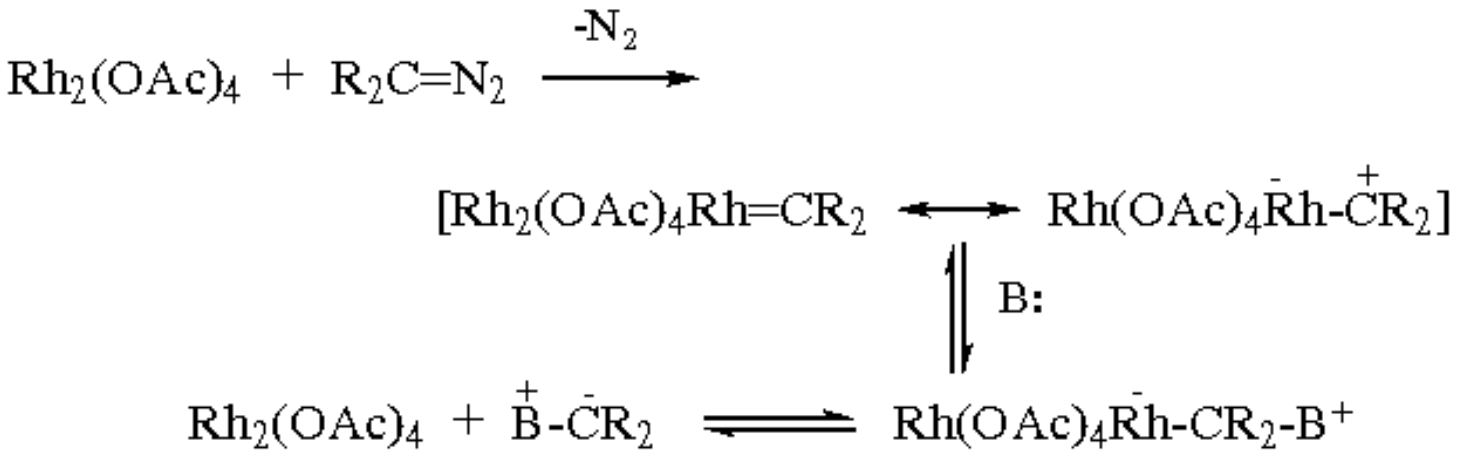

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The relative reactivity for ylide generation, determined from subsequent [2,3]-sigmatropic rearrangement of the initially formed ylide in competition with cyclopropanation (eq 16),[45,46] shows that ylide formation increases in the order RI > RBr > RCl, R_3N > R_2O, and R_2S > R_2O. Allyl substituents facilitate ylide generation (eq 17),[46,47] and their

influences on relative reactivities suggest that the formation of the metal-stabilized ylide and metal dissociation (eq 15) are equilibrium processes.

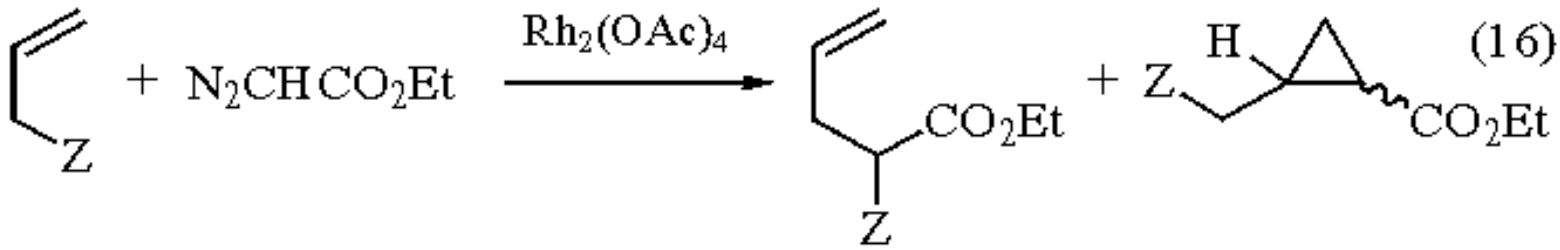

(16)

Z	Yield (%)	
NMe_2	95	100:0
SMe	96	100:0
I	98	100:0
Br	76	28:72
Cl	95	5:95
OEt	88	10:90

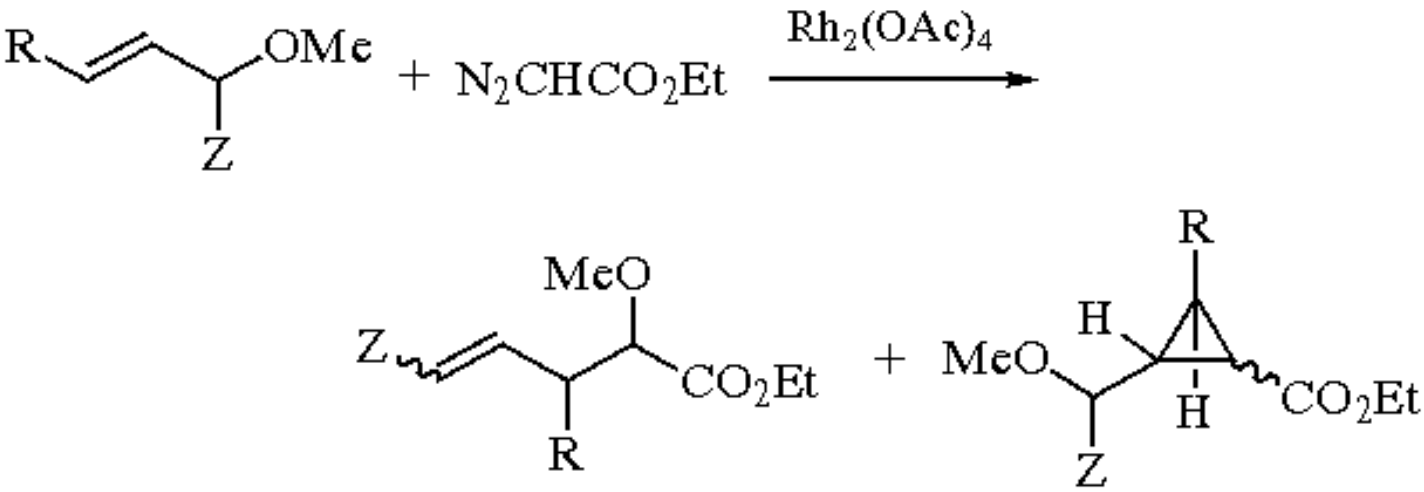

(17)

R	Z		Yield (%)
H	H	10:90	88
Me	H	92:8	86
Ph	H	73:27	95
TMS	H	94:6	68
H	OMe	77:23	75

Rhodium(II) acetate has two axial coordination sites at which reactions with diazo compounds occur. Strongly coordinating compounds, either reactants or solvents, occupy these sites and inhibit electrophilic addition to diazo

compounds. Consequently, whereas reactions with diazo compounds that possess chloride, bromide, iodide, or ether functional groups take place at rt, those with sulfide or amine functional groups require higher temperatures for dinitrogen extrusion.

Stable sulfonium ylides have been produced by intermolecular reactions of thiophenes with dimethyl diazomalonate, catalyzed by $Rh_2(OAc)_4$ (eq 18),[48] as well as by intramolecular reactions (eq 19).[49] The formation of four- to seven-membered rings has been possible,[49,50] but C-H insertion is competitive with seven-membered ring ylide generation. The stability of the ylide is dependent on the sulfur substituent (Ph > $PhCH_2$ > allyl) as well as on ring size. Stable sulfoxonium ylides have also been formed in $Rh_2(OAc)_4$-catalyzed reactions.[51]

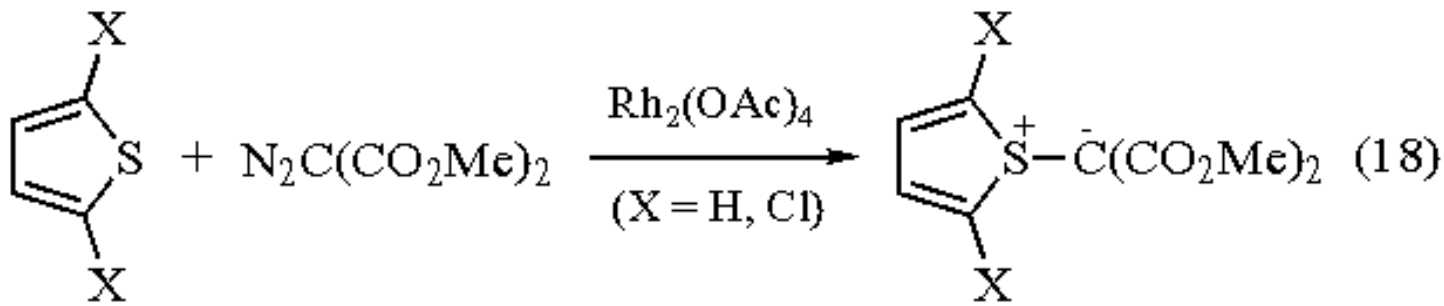

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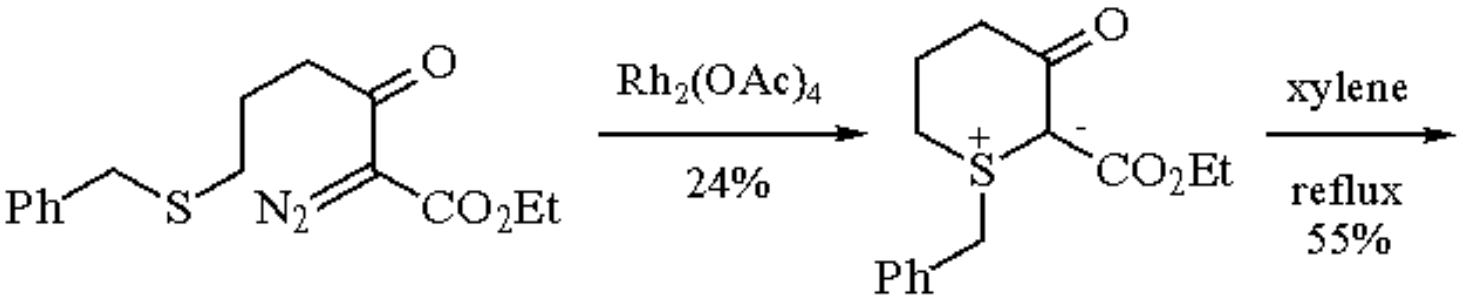

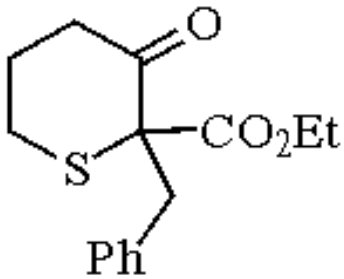

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Use of the [2,3]-sigmatropic rearrangement of sulfonium ylides for ring enlargement has made possible the construction of medium ring compounds (eq 20).[47] β-Elimination is a competing process and becomes the favored transformation with the proper stereoelectronic arrangement in the reactant ylide (e.g. eq 21).[52] An intramolecular ring contraction methodology is also effectively promoted through sulfonium ylide generation with $Rh_2(OAc)_4$ catalysis (e.g. eq 22).[53] Sulfur ylides derived from $Rh_2(OAc)_4$-catalyzed reactions of diazo compounds have played important roles in β-lactam antibiotic syntheses.[54-56]

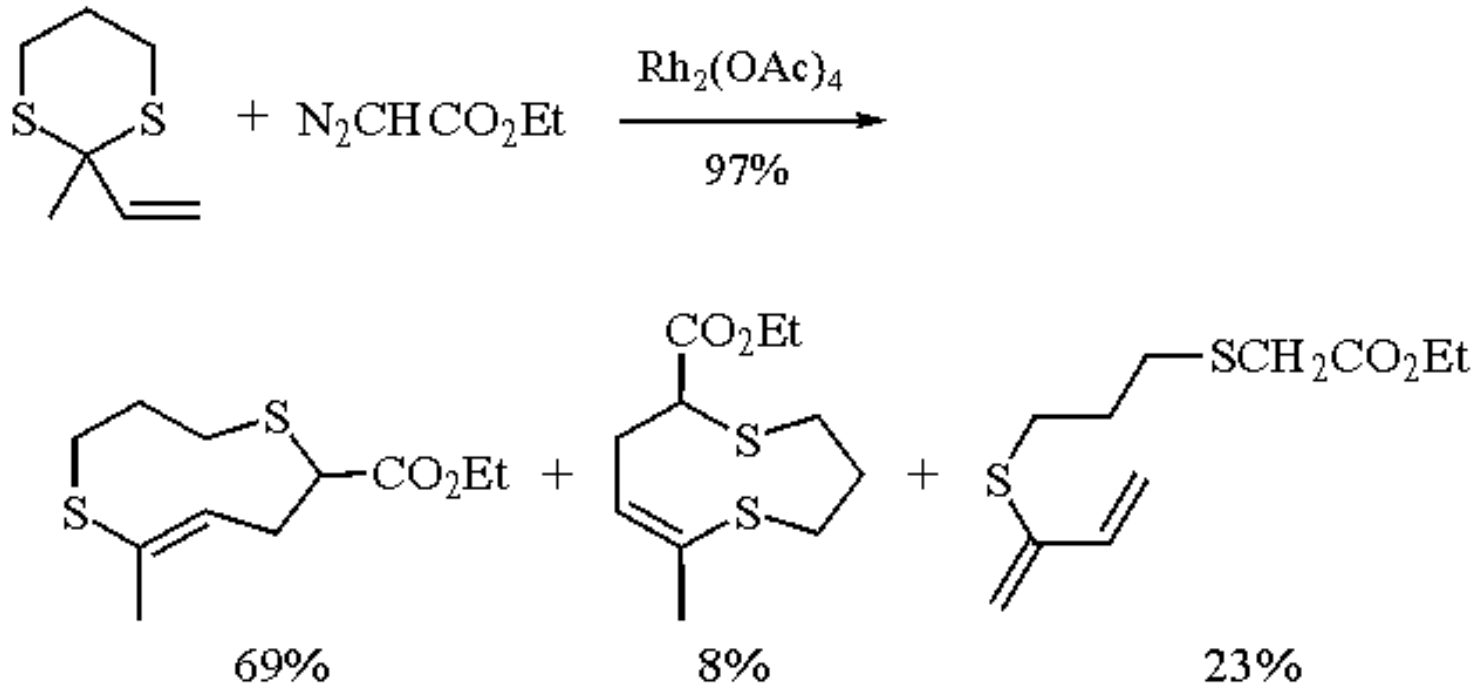

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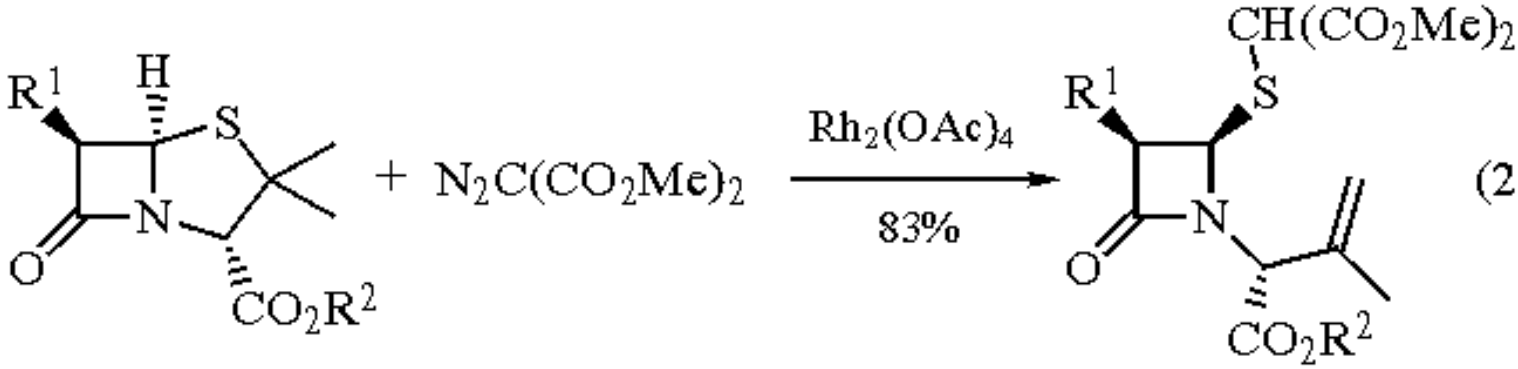

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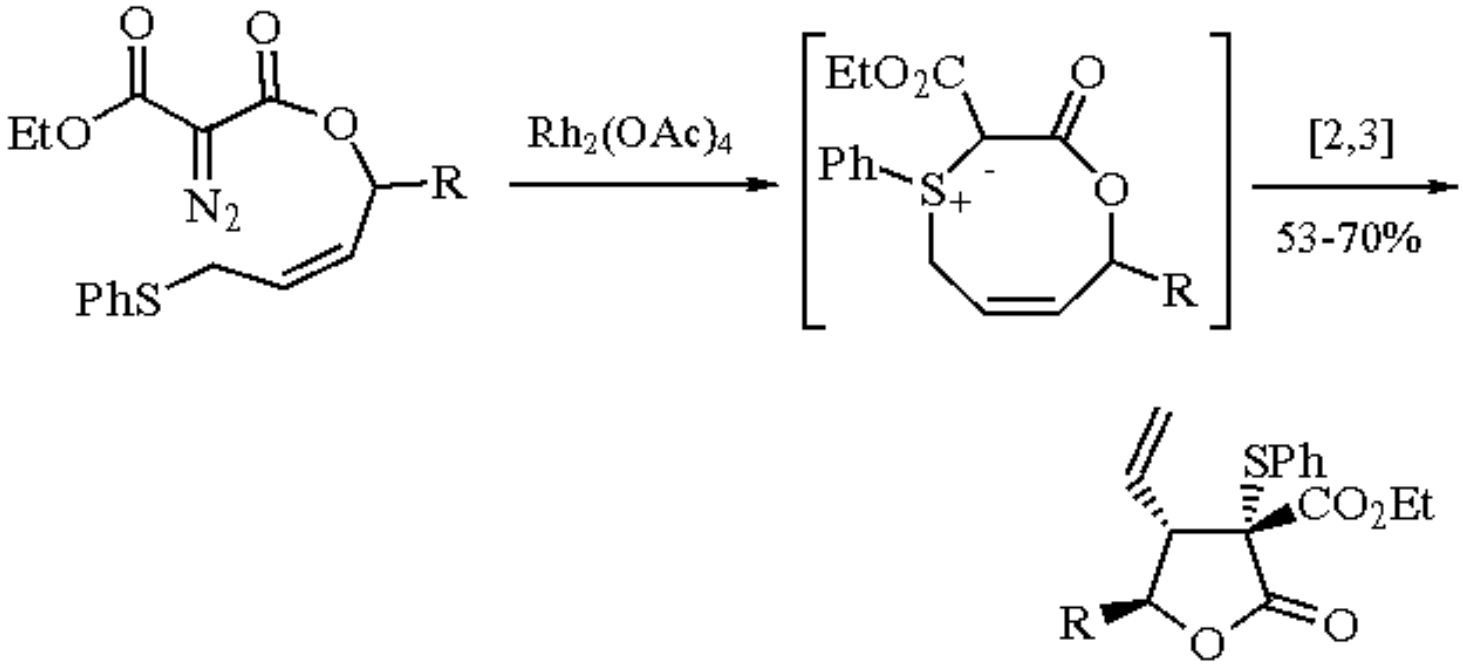

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Nitrogen ylide formation is not reported as extensively as is sulfur ylide generation, but sufficient examples exist to

suggest its versatility. The synthesis of allenes by [2,3]-sigmatropic rearrangement (eq 23)[57] of prop-2-yn-1-yl-dimethylammonium ylides exemplifies the potential diversity of its applications. A general methodology for oxazole synthesis has been developed through the use of nitrile ylides (eq 24).[58] Additional examples that suggest the advantages of the catalytic route to ylide generation are reported elsewhere.[11]

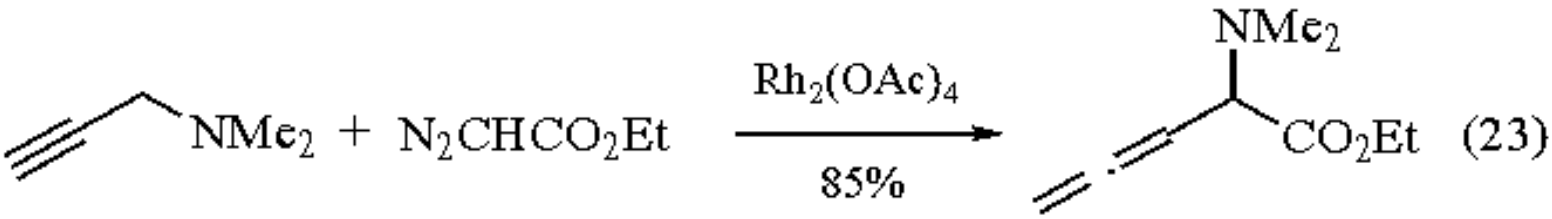

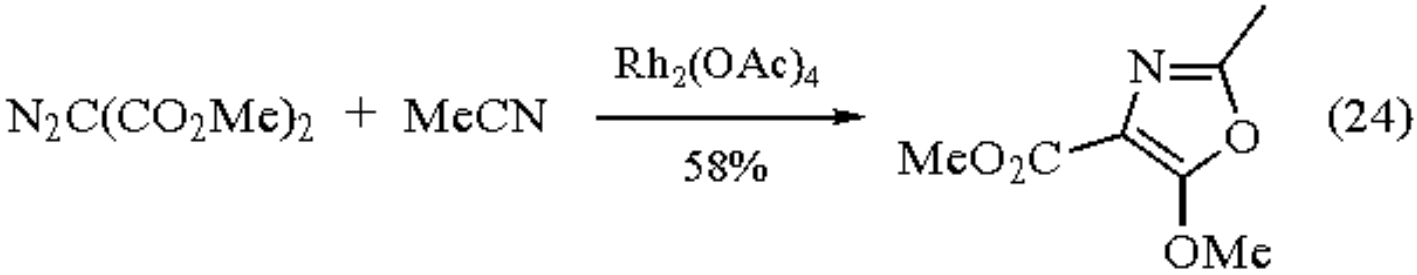

Relative to cyclopropanation (of alkenes) or cyclopropenation (of alkynes), oxonium ylide formation is generally disfavored in $Rh_2(OAc)_4$-catalyzed reactions of diazo compounds. Notable exceptions include those described in eq 17 and in intramolecular transformations. Cyclobutanone formation is the outcome of $Rh_2(OAc)_4$-catalyzed dinitrogen extrusion from 4-alkoxydiazo ketones (eq 25).[59] Allyl ethers offer a pathway to [2,3]-sigmatropic rearrangement products, including those leading to medium ring ethers (eq 26),[60,61] and tetrahydrofuran-3-ones have been prepared by a carbon-oxygen insertion methodology involving ylide intermediates,[62] but few other successful demonstrations of oxonium ylide generation have been reported.

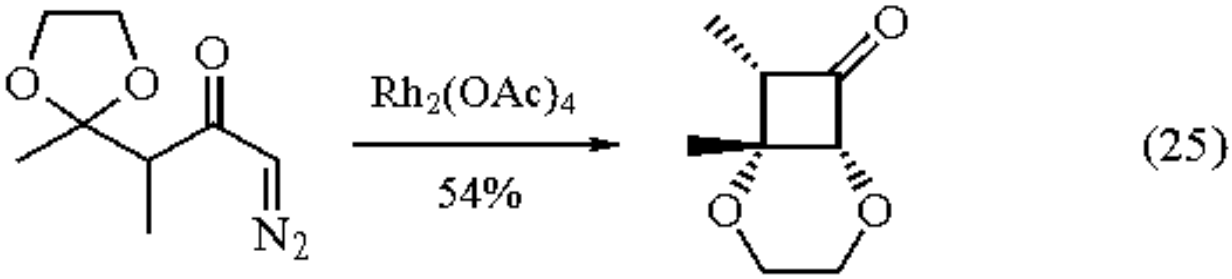

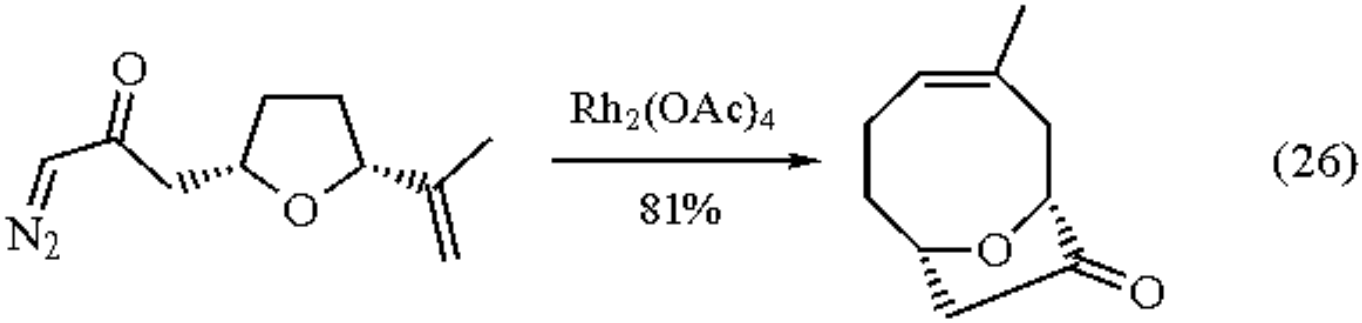

Dirhodium(II) tetraacetate has been shown to have superior capabilities for carbonyl ylide generation with diazo

ketones,[11] especially in intramolecular reactions. The carbonyl ylide, when generated in the presence of selected dipolarophiles, readily undergoes 1,3-dipolar addition (e.g. eqs 27 and 28)[63,64] either intermolecularly (***Dimethyl Acetylenedicarboxylate***, ***N-Phenylmaleimide***, diethyl fumarate, aldehydes) or intramolecularly. Regioselectivity is predictable by frontier molecular orbital interactions.[64b] Carbonyl ylide generation with carboxylate esters is rare,[30b] but with amides, carbamates, and imides, carbonyl ylide formation is well documented (e.g. eq 29).[11,65]

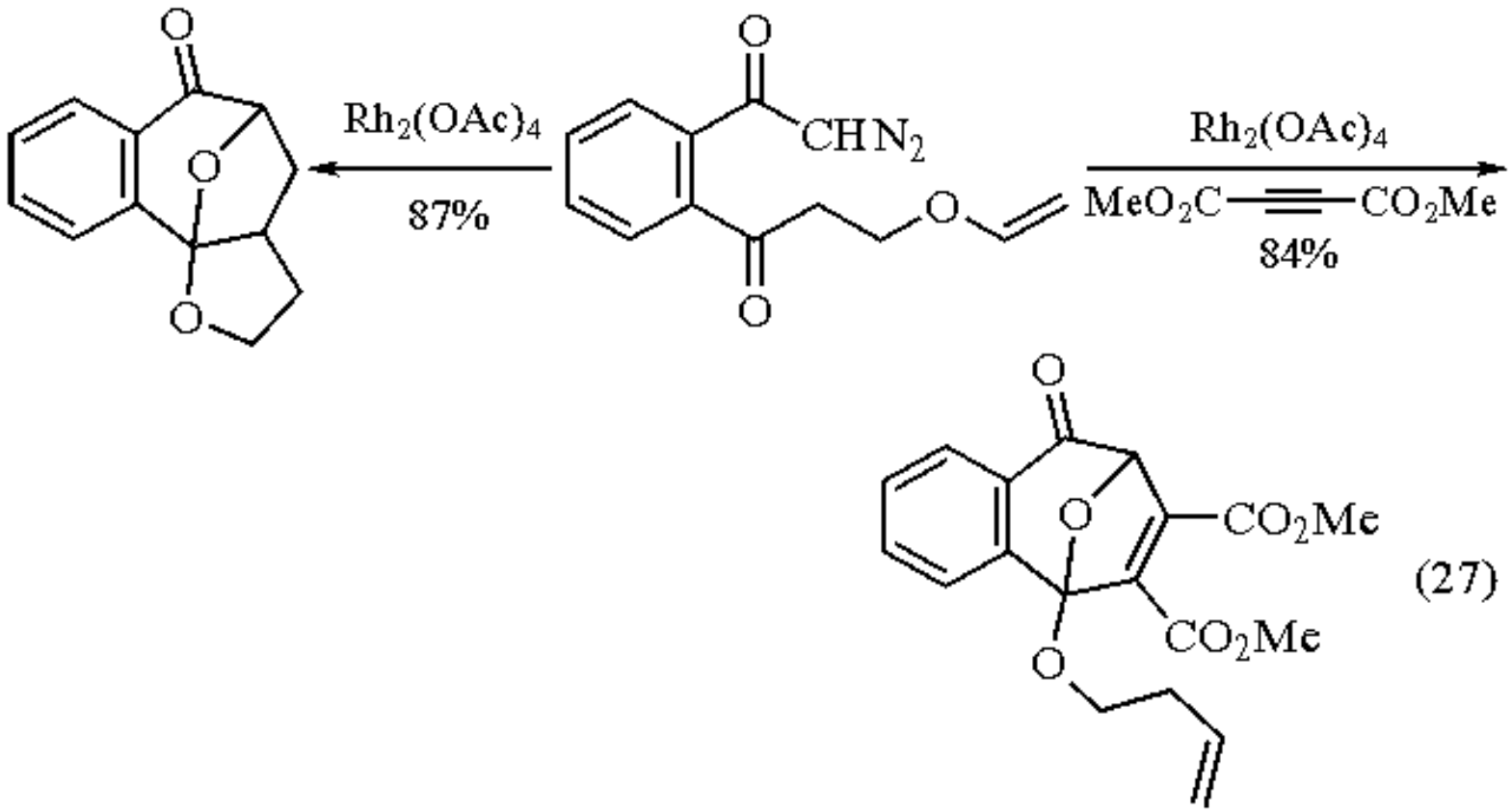

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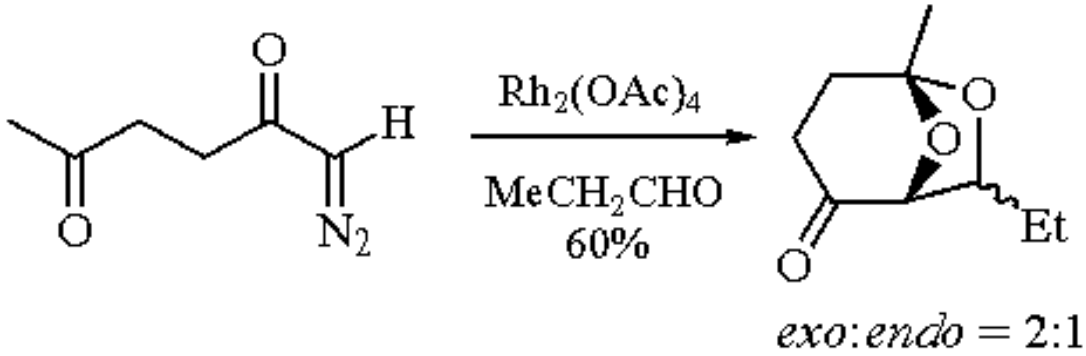

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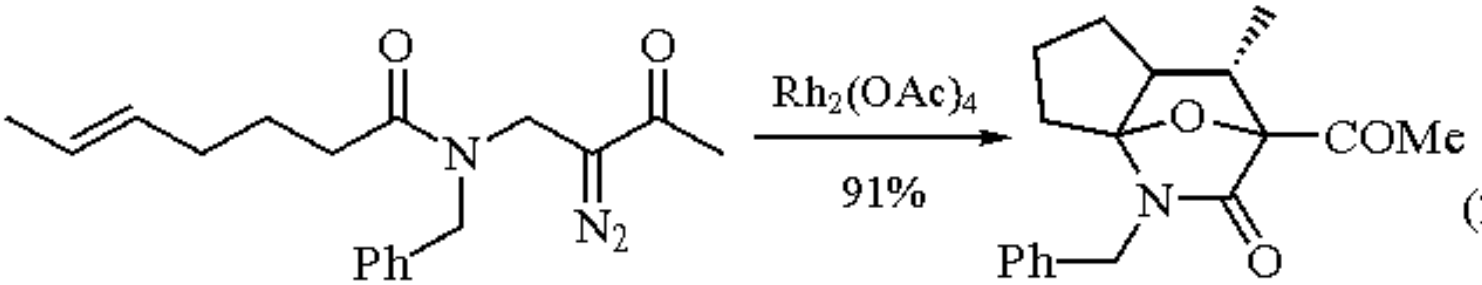

(29)

Selectivity in Metal Carbene Transformations.

The high reactivity of catalytically generated metal carbenes often limits their selectivity when more than one site for addition and/or insertion exists in a molecule. In this regard, $Rh_2(OAc)_4$ is often less selective for metal carbene transformations than is either ***Dirhodium(II) Tetrakis(perfluorobutyrate)*** or rhodium(II) carboxamides (either ***Dirhodium(II) Tetraacetamide*** or ***Dirhodium(II) Tetra(caprolactam)***).[8,28,66] In addition, use of $Rh_2(OAc)_4$ can lead to lower product yields than does use of alternative dirhodium(II) catalysts. Nevertheless, for most transformations where there is one preferred site for metal carbene reaction, $Rh_2(OAc)_4$ remains the catalyst of choice.

High diastereocontrol complements exceptional stereocontrol for geometrical isomer formation in the cyclopropanation of styrene with vinyldiazocarboxylates that possess the pantolactone chiral auxiliary (eq 30).[67] However, with pantolactone diazoacetate in the cyclopropanation of styrene, a 76:24 *trans*:*cis* product mixture forms in only 72% yield and 28-30% diastereomeric excess (de).[68] Similarly, in competitive reactions between cyclopropanation and C-H insertion, use of $Rh_2(OAc)_4$ provides very little selectivity (eq 31),[66] but dirhodium(II) tetrakis(perfluorobutyrate) promotes exclusive C-H insertion and use of dirhodium tetra(caprolactam) leads to exclusive cyclopropanation. A variety of examples of high and low selectivities has been reported for $Rh_2(OAc)_4$-catalyzed reactions,[1] and no simple explanation has emerged that will account for all of the results. Predictions are often empirical, but changing the ligands of the catalyst often provides a dirhodium(II) compound with the desired selectivity enhancement.

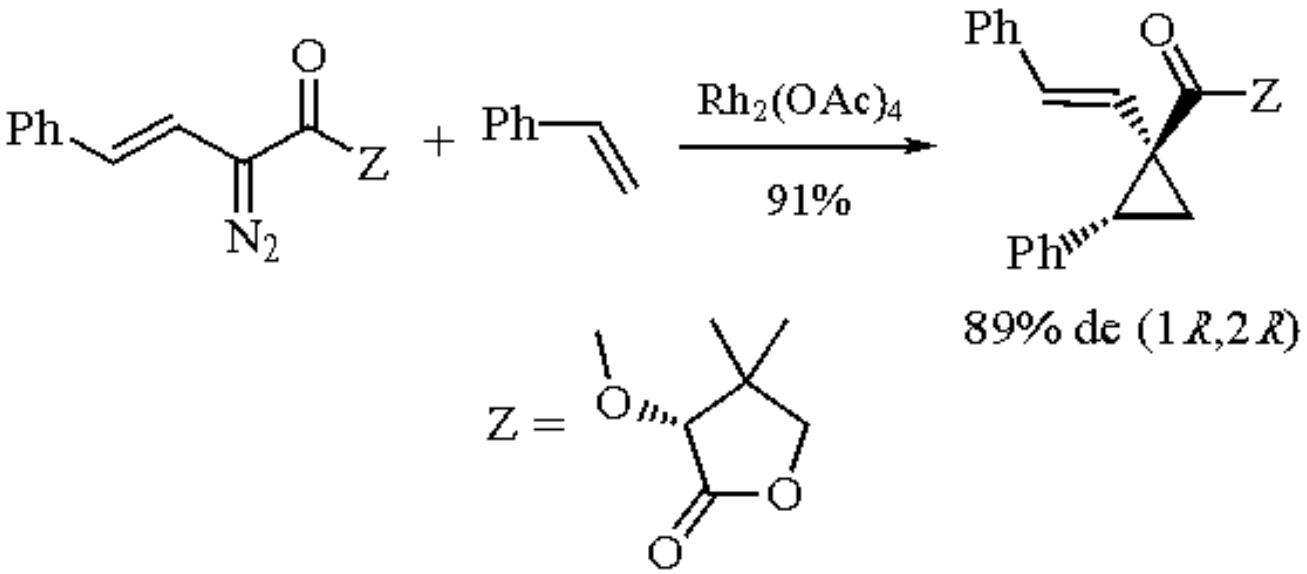

(30)

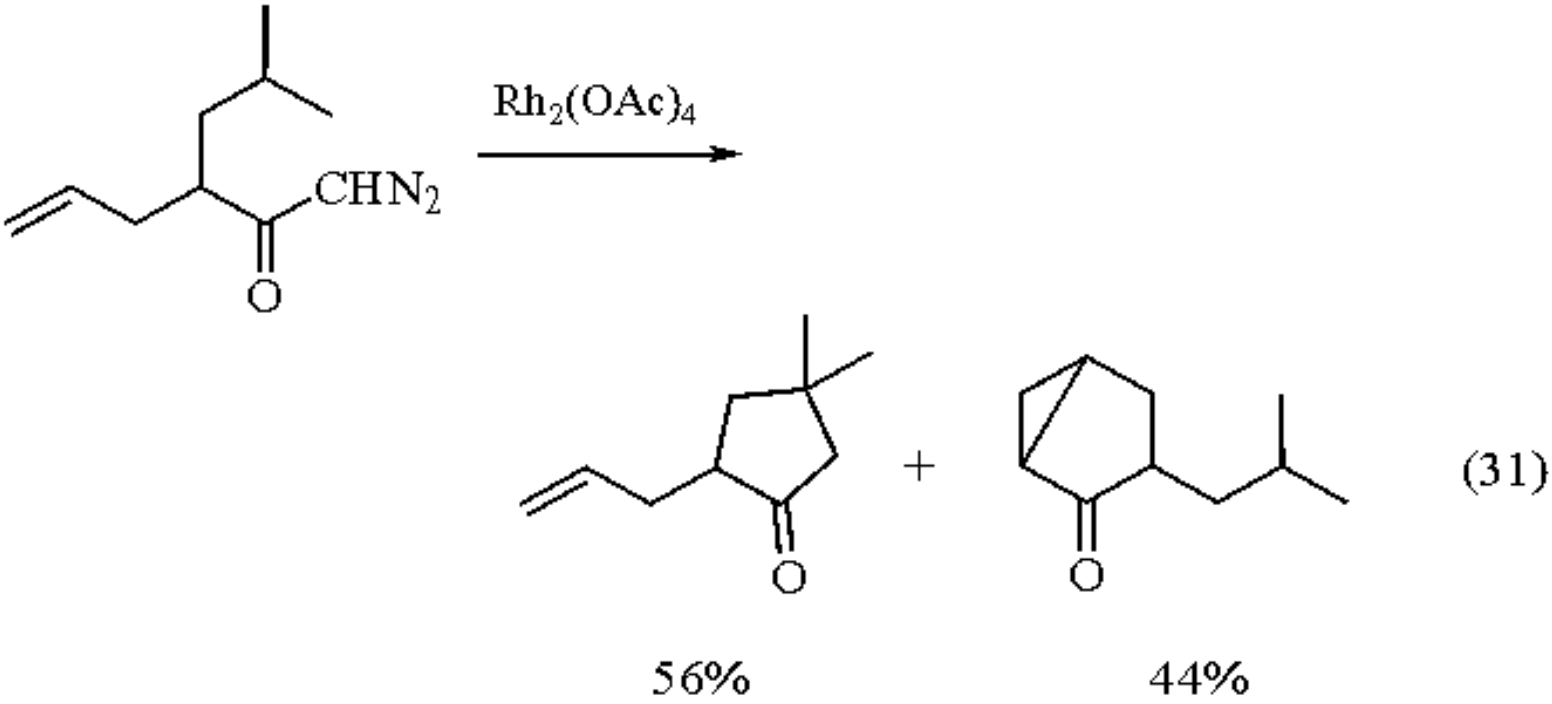

Catalytic Hydroboration of Alkenes and Alkynes.

The use of $Rh_2(OAc)_4$ to catalyze the hydroboration of alkenes and alkynes with ***Catecholborane*** represents a novel application of this transition metal compound.[2] In laboratory scale reactions, 0.5 mol % $Rh_2(OAc)_4$ is effective. Selectivity is dependent on the alkene (eq 32) and often differs from that found with ***Chlorotris(triphenylphosphine)rhodium(I)*** (Wilkinson's catalyst).[69]

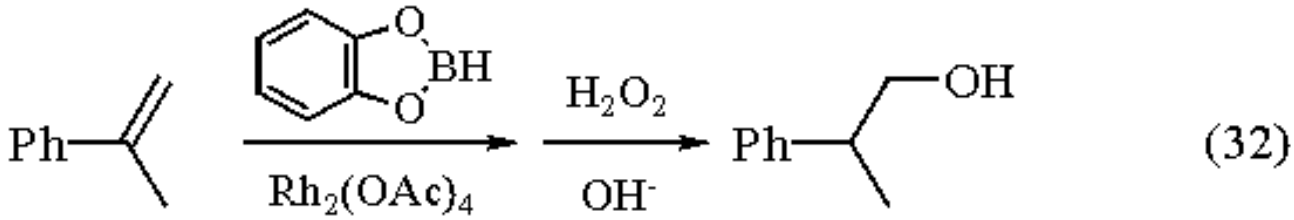

The hydroboration of alkynes is also promoted by rhodium acetate. However, since $Rh_2(OAc)_4$ is transformed during hydroboration, the nature of the active catalyst is at present unknown. The combination of catecholborane and $Rh_2(OAc)_4$, both in catalytic amounts, catalyzes isomerization of terminal alkenes.[2]

Autooxidation of Alkenes.

In the presence of catalytic amounts of $Rh_2(OAc)_4$, cyclohexadienes undergo aromatization (eq 33), and dienes undergo oxidative cleavage (eq 34),[3a] at atmospheric pressure. *p*-Cymene is also reported to be oxidized to the tertiary alcohol. Hydroperoxide decomposition to alcohol and dioxygen, catalyzed by $Rh_2(OAc)_4$, has been demonstrated.

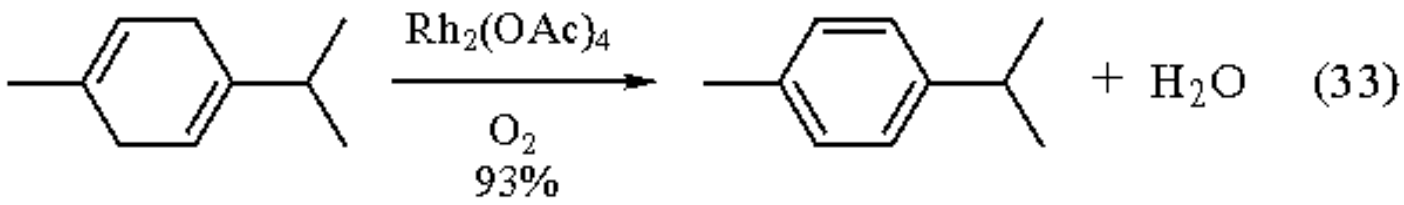

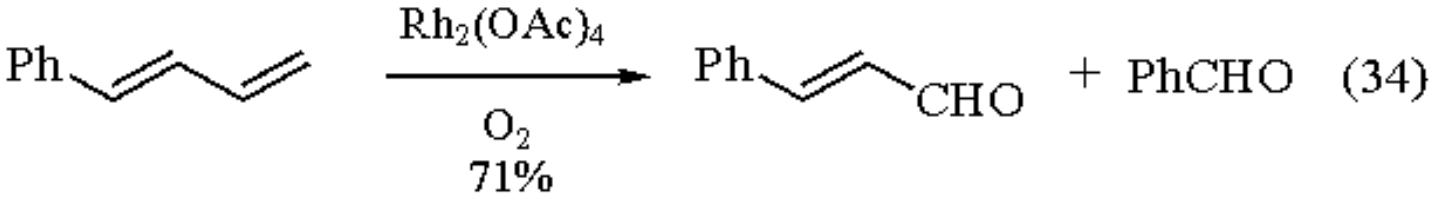

Other Catalytic Reactions.

Hydrogenation activity for $Rh_2(OAc)_4$ has been reported,[70] but these results could not be repeated.[71] Hydrosilylation of alkenes is catalyzed by $Rh_2(OAc)_4$, but reactions are much less efficient than those catalyzed by dirhodium(II) tetrakis(perfluorobutyrate).[71] The same is true of silylcarbonylation reactions with alkynes,[72] and $Rh_2(OAc)_4$ is not a hydroformylation catalyst.

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Dirhodium(II) Tetra(caprolactam)

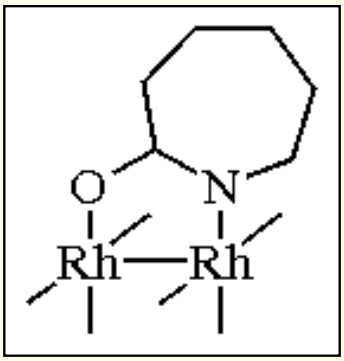

[138984-26-1] · $C_{24}H_{44}N_4O_4Rh_2$ · Dirhodium(II) Tetra(caprolactam) · (MW 658.54)

(catalyst for selective carbenoid reactions of diazo compounds[1])

Solubility: sol MeOH, MeCN; slightly sol toluene, 1,2-dichloroethane, CH_2Cl_2.

Form Supplied in: blue solid for anhydrous form; purple solid as hydrate.

Preparative Method: prepared by ligand substitution from $Rh_2(OAc)_4$.[2]

Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Introduction.

Dirhodium(II) tetra(caprolactam), $Rh_2(cap)_4$, which is much more soluble in organic solvents than is the corresponding acetamide,[3] is prepared by ligand substitution of acetate by caprolactam on ***Dirhodium(II) Tetraacetate*** (eq 1) in refluxing chlorobenzene. When performed in a Soxhlet extraction apparatus where the extractor thimble contains sodium carbonate, acetic acid is trapped and ligand substitution is forced to completion. Four caprolactam molecules ligate one dirhodium(II) nucleus, and each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* configuration.[4]

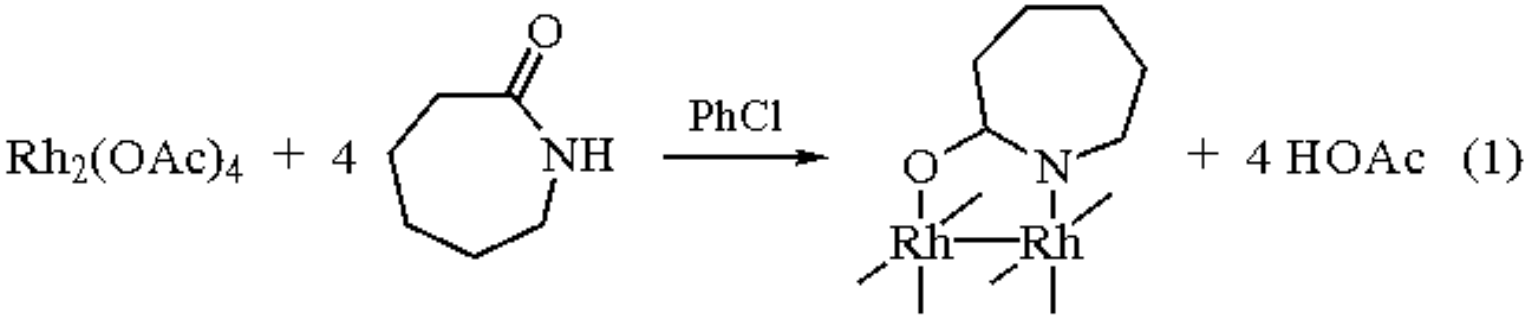

Metal Carbene Transformations.

The principal advantages of $Rh_2(cap)_4$ are its solubility and its selectivity for product formation in reactions with diazocarbonyl compounds, relative to dirhodium(II) tetra(carboxylates). Having lower Lewis acidity than dirhodium(II) tetra(carboxylates), $Rh_2(cap)_4$ is less reactive towards diazo compounds; reactions with diazoacetates, diazoacetamides, and diazo ketones usually occur in refluxing dichloromethane, and reactions with diazoacetoacetates and diazoacetoacetamides ordinarily occur at temperatures above 80 °C.

Regioselectivity in Carbon-Hydrogen Insertion Reactions.

The use of $Rh_2(cap)_4$ provides high levels of regiocontrol in carbon-hydrogen insertion reactions of diazoacetate and diazoacetoacetate esters.[2] Whereas 2,3,4-trimethyl-3-pentyl diazoacetate forms γ-lactone products from insertion into primary and tertiary C-H bonds in a statistical distribution with ***Dirhodium(II) Tetrakis(perfluorobutyrate)*** ($Rh_2(pfb)_4$), only tertiary C-H insertion is observed with $Rh_2(cap)_4$ (eq 2). Similarly, when competition for C-H insertion is between primary and secondary C-H bonds, $Rh_2(cap)_4$ directs insertion to the secondary C-H bond with high selectivity (eq 3). Nearly identical selectivities are observed with ***Dirhodium(II) Tetraacetamide*** so, by extrapolation, $Rh_2(cap)_4$ will also be the catalyst of choice for regioselective cyclopropanation reactions with dienes.[3]

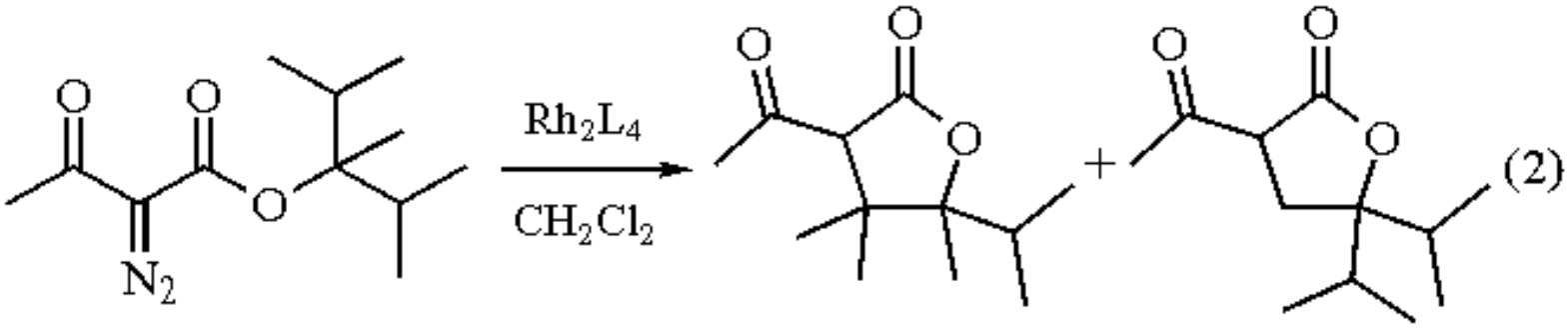

$Rh_2(pfb)_4$	39%	61%
$Rh_2(OAc)_4$	90%	10%
$Rh_2(cap)_4$	>99%	<1%

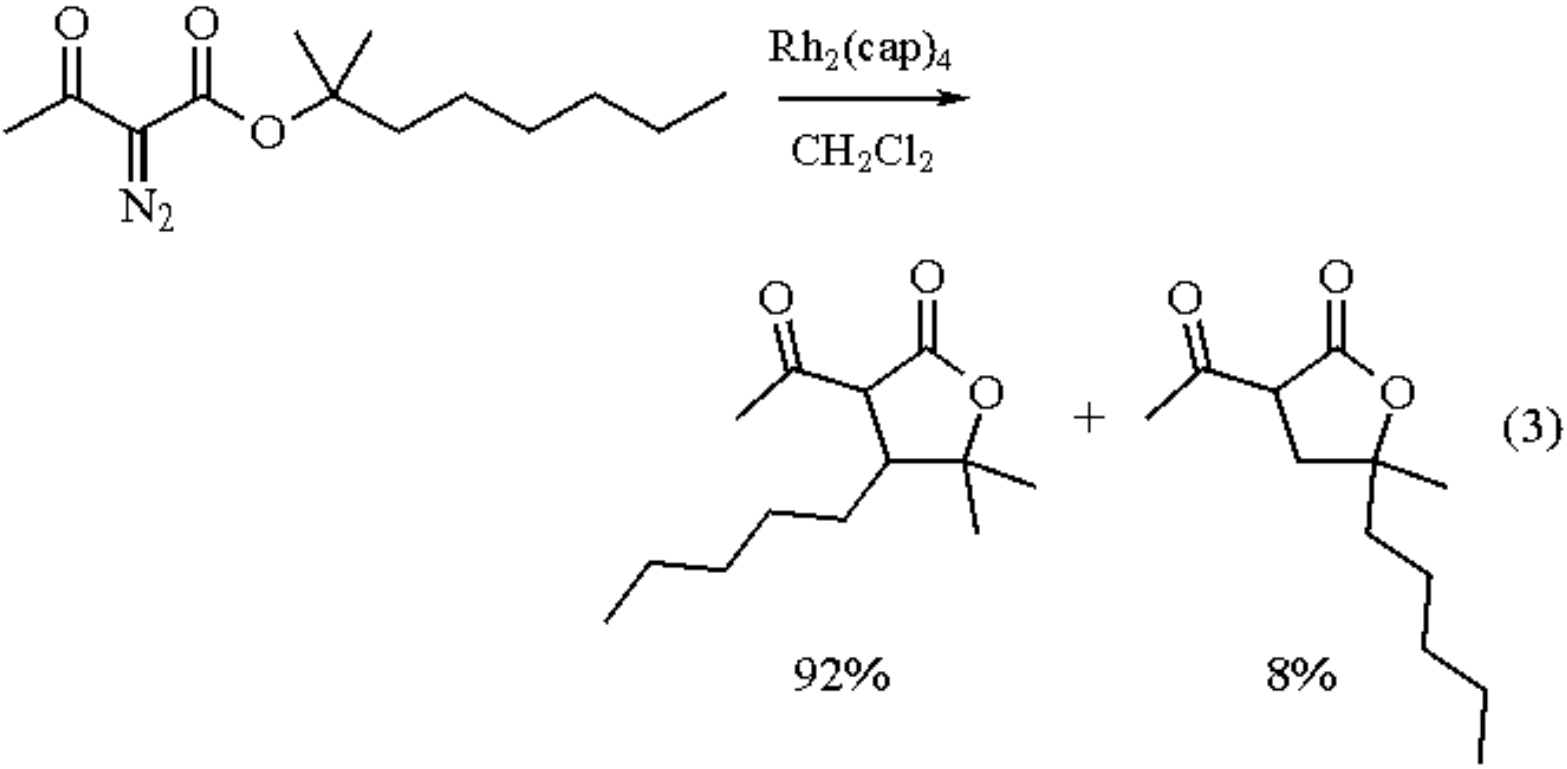

Chemoselectivity in Metal Carbene Transformations.

When there are two reaction centers for intramolecular carbenoid reactions, the use of $Rh_2(cap)_4$ often leads to the production of only one product.[5,6] Cyclopropanation is favored over aromatic substitution (eq 4), over tertiary carbon-hydrogen insertion (eq 5), and over aromatic cycloaddition (eq 6). Product yields are high in each case. The order of reactivity for metal carbenes generated from $Rh_2(cap)_4$ is cyclopropanation > tertiary C-H insertion > secondary C-H insertion > aromatic cycloaddition,[6] and the rate differences between them are as much as 100-fold.

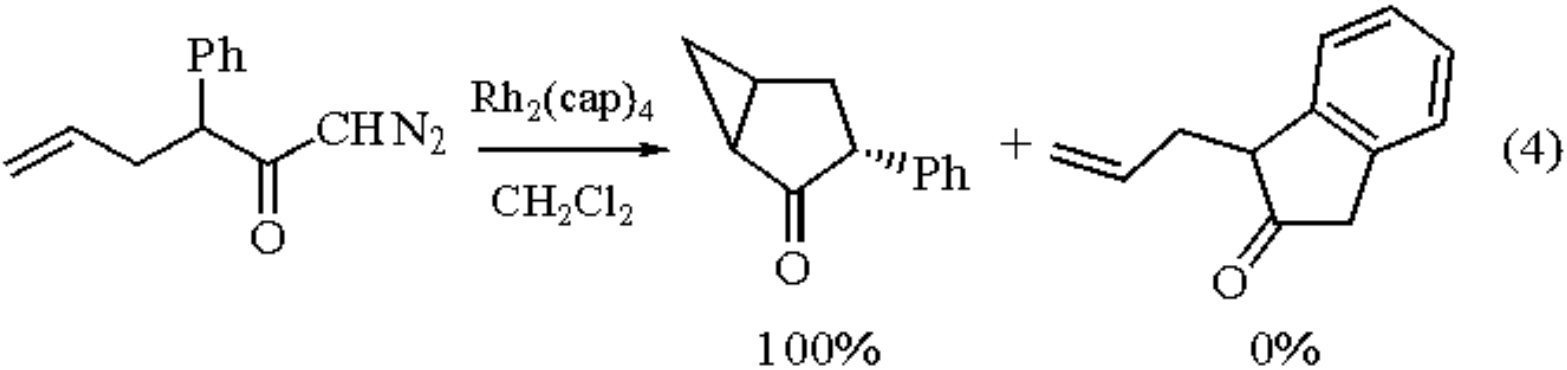

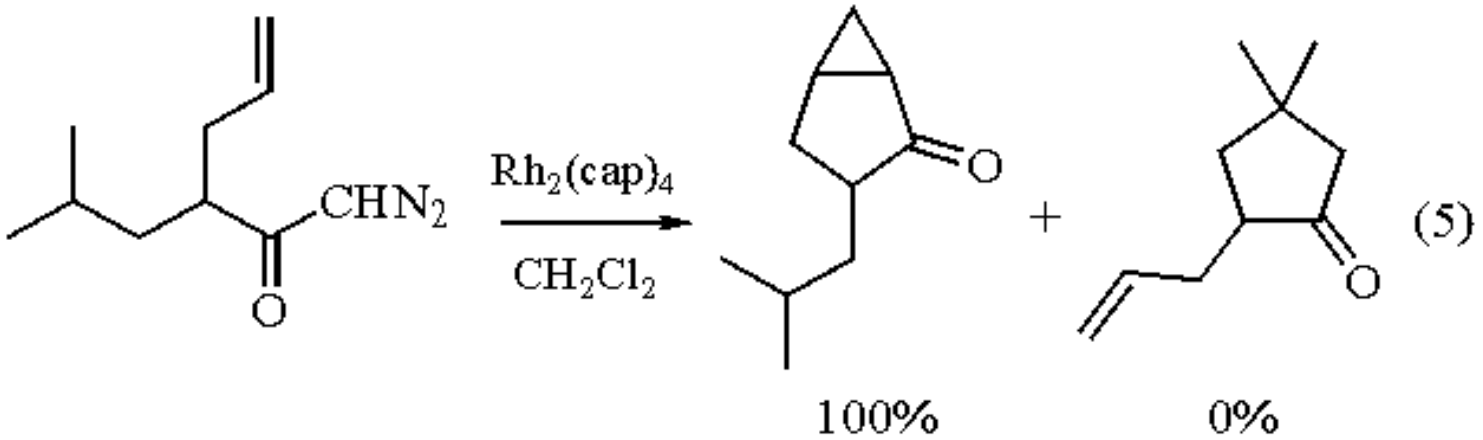

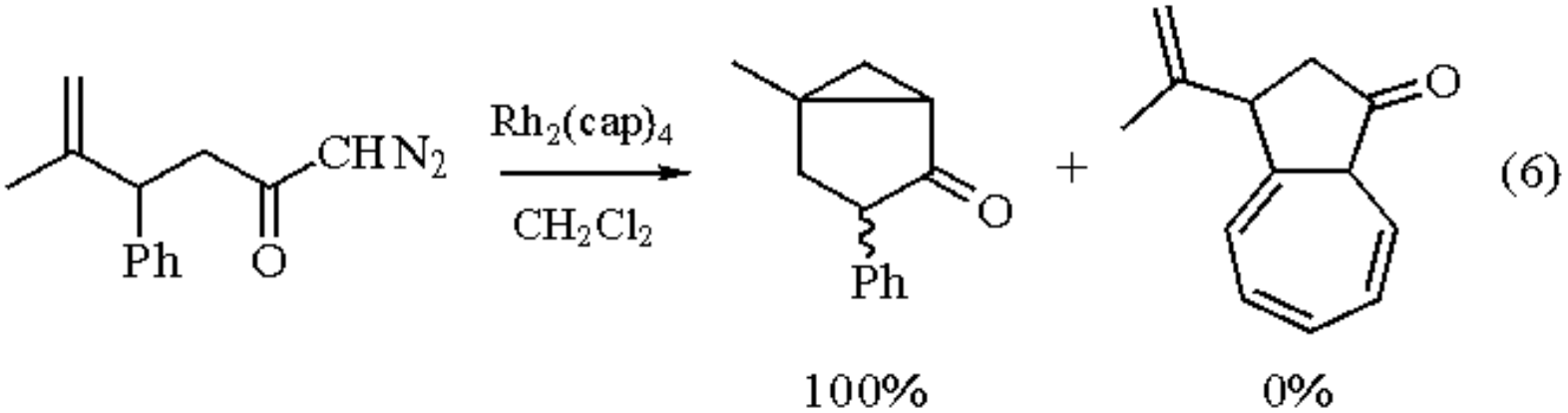

Carbonyl ylide generation is favored over aromatic cycloaddition with $Rh_2(cap)_4$ (eq 7),[7] but in competition with cyclopropanation both ylide generation and alkene cycloaddition occur with equivalent facility.[5,8] Except for ylide generation, these catalytic metal carbene transformations exhibit an overwhelming preference for five-membered ring formation,[9] but within this controlling limitation, both chemoselectivity and regioselectivity are greatly influenced by the ligand of dirhodium(II).

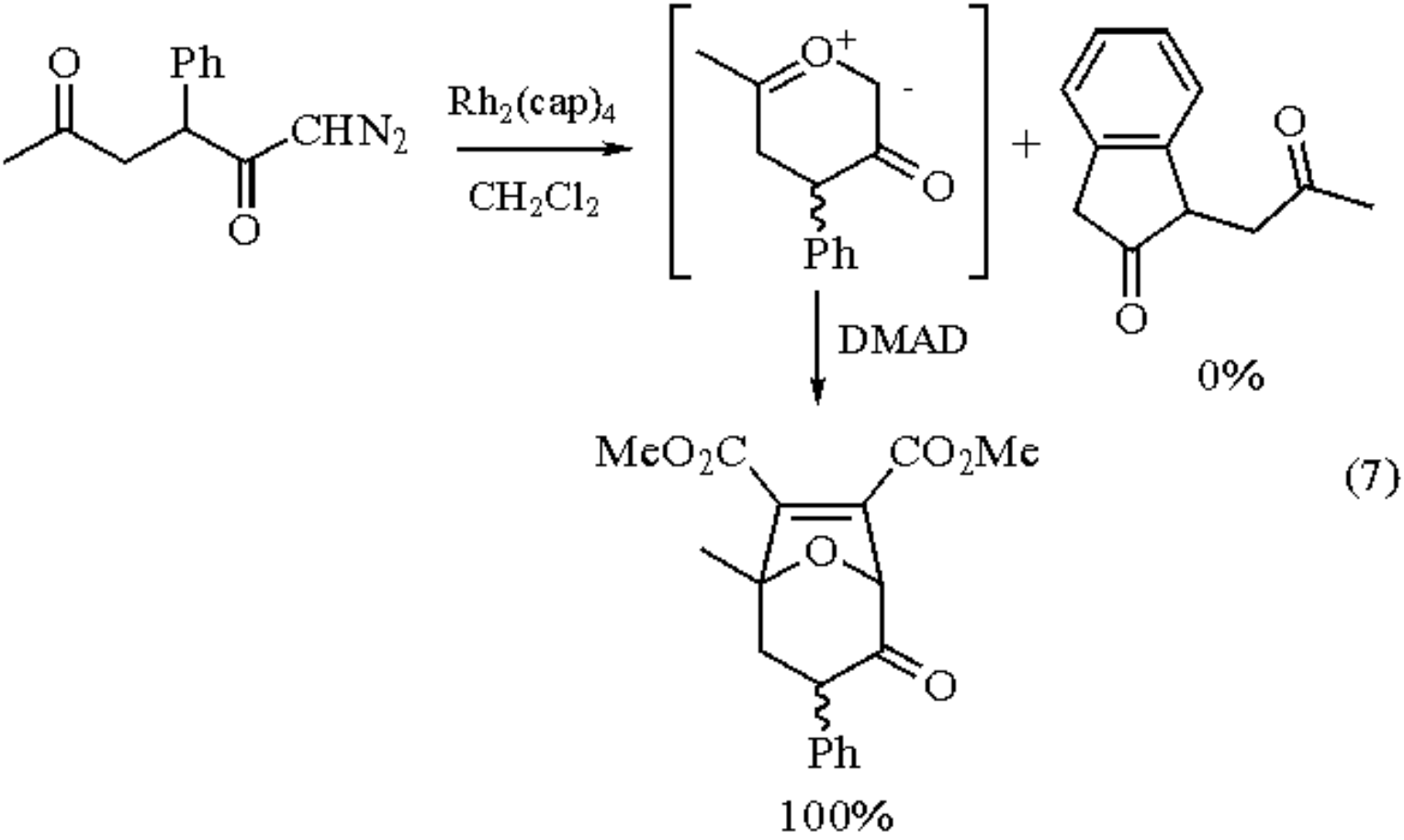

(7)

The selectivities achieved with changes in dirhodium(II) ligands are due, in part, to the degree of charge localization on the carbene carbon.[6] However, conformational restrictions from the carbene system that is bound to dirhodium(II) can also influence selectivity,[2] so broad generalizations regarding selectivity with $Rh_2(cap)_4$ are inappropriate.

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Michael P. Doyle

Dirhodium(II) Tetrakis(methyl 2-pyrrolidone-5(*S*)-carboxylate)

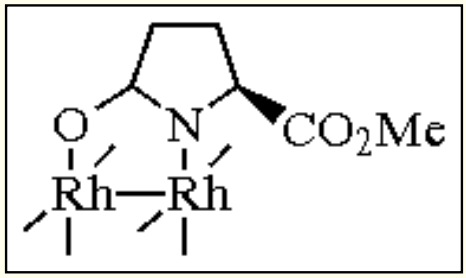

[131766-06-8] · $C_{24}H_{36}N_4O_{12}Rh_2$ · Dirhodium(II) Tetrakis(methyl 2-pyrrolidone-5(*S*)-carboxylate) · (MW 778.46)

(highly enantioselective catalyst for carbenoid reactions of diazo compounds)[1-3]

Physical Data: λ 615 nm, ε 211 ($ClCH_2CH_2Cl$). ^1H NMR ($CDCl_3$) of Rh_2(5*S*-MEPY)$_4$(MeCN)$_2$: δ 4.32 (dd, *J* = 8.8, 3.0 Hz, 2H), 3.95 (dd, *J* = 8.6, 2.1 Hz, 2H), 3.70 (s, 6H), 3.68 (s, 6H), 2.70-2.55 (m, 4H), 2.26 (s, 6H), 1.8-2.4 (m, 12H). $[\alpha]_D^{23}$ = -259.5° (MeCN, *c* = 0.098).

Solubility: sol MeOH, MeCN, acetone; slightly sol CH_2Cl_2, $ClCH_2CH_2Cl$, toluene.

Form Supplied in: red crystals as the bis-acetonitrile complex; blue solid after removal of the axial nitrile ligands.

Preparative Method: from ***Dirhodium(II) Tetraacetate*** by ligand substitution with methyl 2-pyrrolidone-5(*S*)-carboxylate.[4,5]

Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Introduction.

The preparation of the title reagent, Rh_2(5*S*-MEPY)$_4$, is the same as that used for ***Dirhodium(II) Tetraacetamide***[6] or ***Dirhodium(II) Tetra(caprolactam)***.[7] Ligand exchange occurs in refluxing chlorobenzene, and the acetic acid that is liberated is trapped in a Soxhlet extraction apparatus by sodium carbonate. Purification occurs by chromatography on a CN-capped silica column; recrystallization from acetonitrile-2-propanol (1:1) provides Rh_2(5*S*-MEPY)$_4$(MeCN)$_2$(*i*-PrOH). Four 2-pyrrolidone-5(*S*)-carboxylate molecules ligate one dirhodium(II) nucleus; each rhodium is bound to two nitrogen and two oxygen donor atoms arranged in a *cis* configuration.[4] The methyl carboxylate substituents are positioned with a counterclockwise orientation on each rhodium face.

Metal Carbene Transformations.

The effectiveness of $Rh_2(5S\text{-MEPY})_4$ and its 5*R*-form, $Rh_2(5R\text{-MEPY})_4$, is exceptional for highly enantioselective intramolecular cyclopropanation[8] and carbon-hydrogen insertion[9] reactions. Intermolecular cyclopropanation occurs with lower enantiomeric excesses[10] than with alternative chiral copper salicylaldimine[11] or C_2-symmetric semicorrin[12] or bis-oxazoline[13] copper catalysts, but intermolecular cyclopropenation exhibits higher enantiocontrol with $Rh_2(MEPY)_4$ catalysts.[14] The methyl carboxylate attachment of $Rh_2(5S\text{-MEPY})_4$ is far more effective than sterically similar benzyl or isopropyl attachments for enantioselective metal carbene transformations.[4] The significant enhancement in enantiocontrol is believed to be due to carboxylate carbonyl stabilization of the intermediate metal carbene and/or to dipolar influences on substrate approach to the carbene center.

Enantioselective Intramolecular Cyclopropanation Reactions.

The exceptional capabilities of the $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ catalysts for enantiocontrol are evident in results obtained with a series of allyl diazoacetates (eq 1).[5,8] Both high product yields and enantiomeric excess (ee's) are characteristic. Intramolecular cyclopropanation of (*Z*)-alkenes proceeds with a higher level of enantiocontrol than does intramolecular cyclopropanation of (*E*)-alkenes. In preparative scale reactions, less than 0.25 mol% of catalyst can be employed to achieve high yields of pure product.[5]

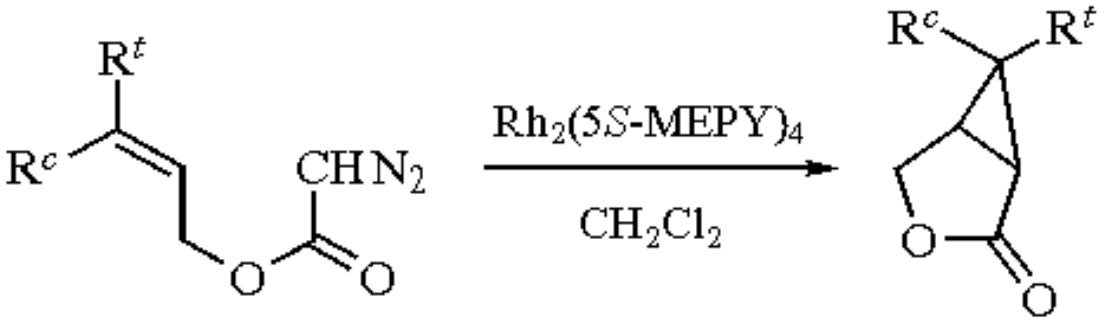

(1)

R^t	R^c	% ee
H	H	95
Me	Me	98
H	Ph, Et, Bn, Bu_3Sn	≥94
Pr	H	83
Ph	H	65

Similar success in enantiocontrol has been achieved for intramolecular cyclopropanation of homoallyl diazoacetates (eq 2).[15] With these substrates the enantiomeric excesses do not extend beyond 90%, but they are virtually independent of double bond substituents.

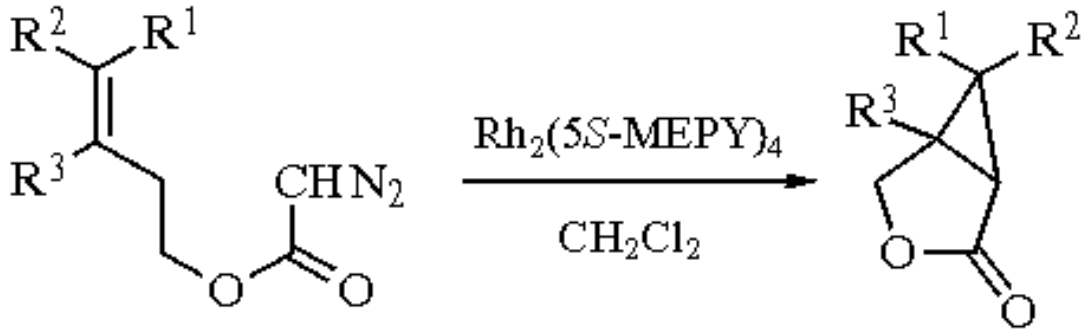

(2)

R^1	R^2	R^3	% ee
Me	Me	H	77
Et, Ph, Bn, TMS	H	H	80-90
H	Et, Ph	H	73-82
H	H	Me	79

Enantioselective Intermolecular Cyclopropenation Reactions.

The use of $Rh_2(MEPY)_4$ catalysts for intermolecular cyclopropenation of 1-alkynes results in moderate to high selectivity. With propargyl methyl ether (or acetate), for example, reactions with (-)-menthyl [(+)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-1-cyclohexyl] diazoacetate catalyzed by $Rh_2(5S\text{-MEPY})_4$ produces the corresponding cyclopropene product (eq 3) with 98% diastereomeric excess (de).[14,16]

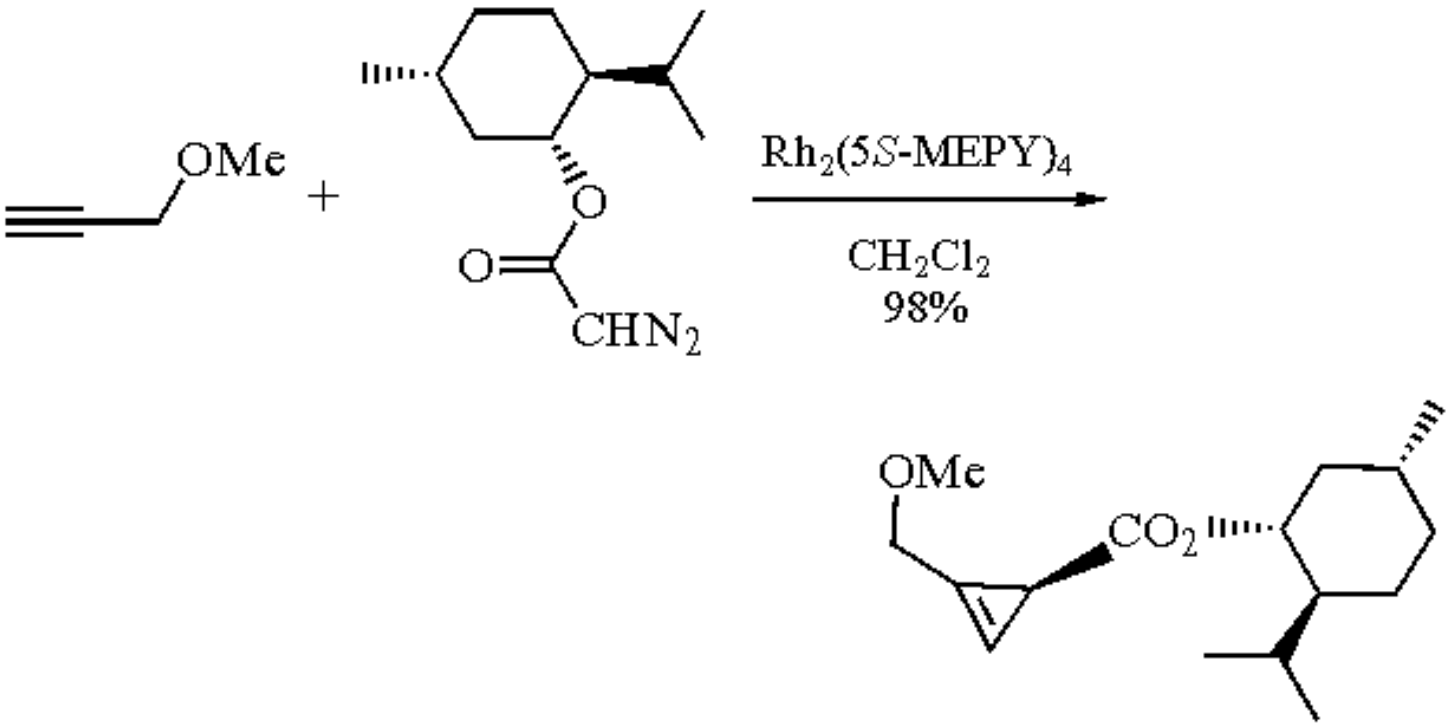

(3)

These reactions are subject to significant double diastereoselection with (+)- and (-)-menthyl diazoacetates. With ethyl diazoacetate, enantiomeric excesses are moderate (54-69% ee), but they increase up to 78% ee with *t*-butyl diazoacetate.[14] These are the first examples of enantioselective catalytic cyclopropenation reactions.

Enantioselective Intramolecular Carbon-Hydrogen Insertion Reactions.

The suitability of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ for enantioselective intramolecular C-H insertion reactions is evident in results with 2-alkoxyethyl diazoacetates (eq 4).[9] Both lactone enantiomers are available from a single diazo ester. Other examples have also been reported, especially those with highly branched diazo substrate structures.[9]

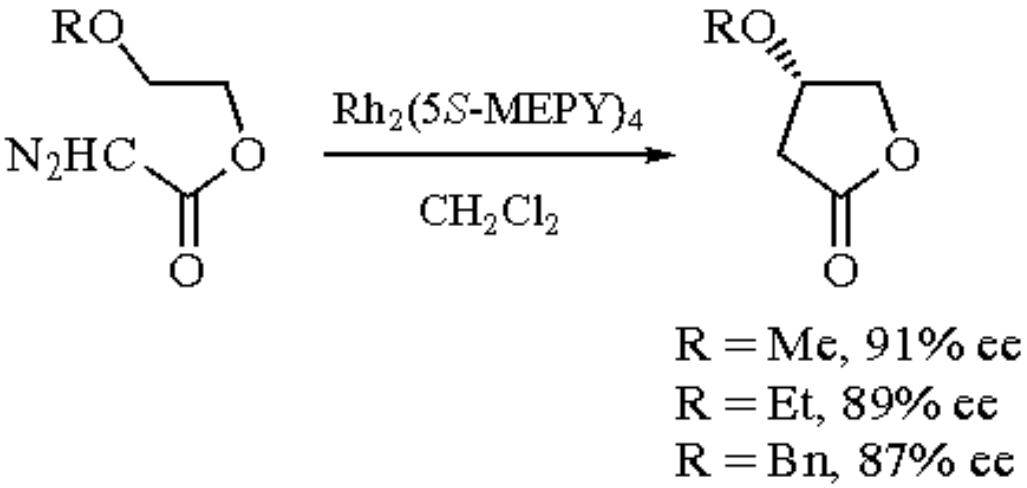

(4)

Diazoacetamides are robust diazo substrates, but they generally give lower enantioselection, and regioselectivity for γ-lactam formation is dependent on the substituents on carbon at which insertion occurs (e.g. eq 5).[17] With *N*-(*n*-butyl)-*N*-(*t*-butyl)diazoacetamide the ratio of γ:β-lactam is 88:12. A significant improvement in enantioselection (up to 78% ee) occurs with the use of the oxazolidinone analog of $Rh_2(5S\text{-MEPY})_4$.[17]

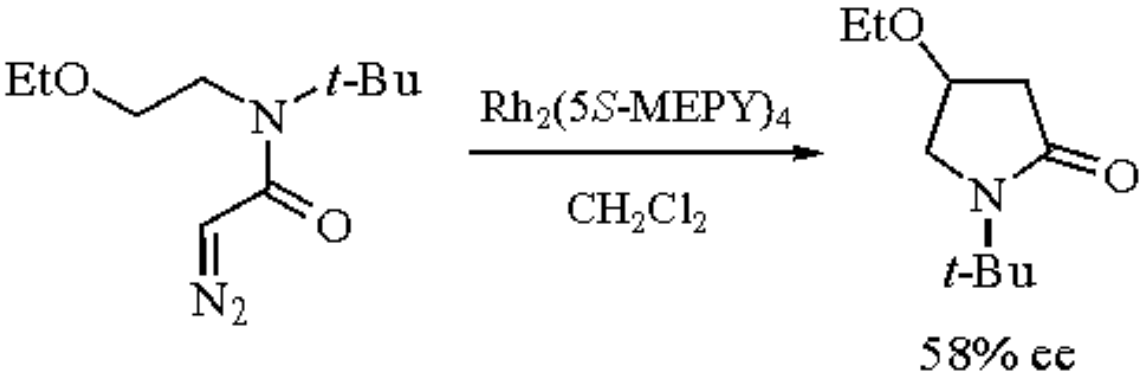

(5)

Polyethylene-Bound, Soluble, Recoverable Dirhodium(II) 2-Pyrrolidone-5(*S*)-carboxylate.

The homogeneous Rh_2(5*S*-MEPY)$_4$ catalyst has been attached to a polyethylene chain that is soluble in organic solvents at about 70 °C.[18] Ligand displacement of 2-pyrrolidone-5(*S*)-carboxylate from Rh_2(5*S*-MEPY)$_4$ by a soluble polyethylene-bound 2-pyrrolidone-5(*S*)-carboxylate produces a recoverable dirhodium(II) catalyst, PE-Rh_2(5*S*-PYCA)$_4$, in high yield. The effectiveness of this catalyst has been demonstrated by high enantioselection for intramolecular cyclopropanation of 3-methyl-2-buten-1-yl diazoacetate (see eq 1) in refluxing benzene solution (98% ee) and for intramolecular C-H insertion of 2-methoxyethyl diazoacetate (see eq 4) under the same conditions (72% ee). For both transformations, reactions catalyzed by Rh_2(5*S*-MEPY)$_4$ that occur at the same temperature give lower % ee values. Although diminished selectivity can occur with catalyst recovery and reuse under standard conditions, retention of catalyst effectiveness is achieved by using 2-3 mol % of the pyrrolidone ligand in up to seven subsequent runs with recovered, reused PE-Rh_2(5*S*-PYCA)$_4$.

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Dirhodium(II) Tetrakis(perfluorobutyrate)

$Rh_2(O_2CC_3F_7)_4$

[73755-28-9] · $C_{16}F_{28}O_8Rh_2$ · Dirhodium(II) Tetrakis(perfluorobutyrate) · (MW 1057.98)

(catalyst for carbenoid reactions of diazo compounds,[1] hydrosilylation of alkenes and alkynes,[2] and silylcarbonylation of alkynes[3])

Physical Data: λ 626 nm, ε 248 (CH_2Cl_2).[4]

Solubility: sol MeCN, DMSO, pyridine, benzene, CH_2Cl_2, alkenes.

Form Supplied in: anhydrous form is green; hydrate is blue.

Preparative Methods: from ***Dirhodium(II) Tetraacetate*** by ligand displacement in refluxing perfluorobutyric acid containing perfluorobutyric anhydride.[5]

Handling, Storage, and Precautions: air stable, very hygroscopic; stored in desiccator.

Metal Carbene Transformations.

Alkene Coordination.

Dirhodium(II) tetrakis(perfluorobutyrate), $Rh_2(pfb)_4$, and ***Dirhodium(II) Tetrakis(trifluoroacetate)***, $Rh_2(tfa)_4$, are unique among dirhodium(II) carboxylates and carboxamides in their ability to form association complexes with alkenes and alkynes in solution.[2,4] Equilibrium constants range from 70 M^{-1} (styrene) to 932 M^{-1} (2-methoxypropene). However, alkene coordination with $Rh_2(pfb)_4$ has no effect on relative reactivity or selectivity in cyclopropanation reactions with ethyl diazoacetate. Being more soluble in weakly polar solvents than is $Rh_2(tfa)_4$, removal of $Rh_2(pfb)_4$ from reaction solutions by simple chromatography on silica is more difficult.

Stereoselectivity and Regioselectivity.

The strongly electron-withdrawing perfluorobutyrate ligands render $Rh_2(pfb)_4$ significantly more electrophilic than ***Dirhodium(II) Tetraacetate*** or ***Dirhodium(II) Tetraacetamide***. As a result, reactivity towards diazo compounds is substantially increased, relative to $Rh_2(OAc)_4$, and stereoselectivity and regioselectivity in cyclopropanation and

carbon-hydrogen insertion reactions are greatly diminished (e.g. eqs 1-3).[6] Regioselectivity for C-H insertion into primary and secondary carbon-hydrogen bonds (eq 3) is nearly statistical, demonstrating that relative reactivities for insertion are essentially equal.[7-11]

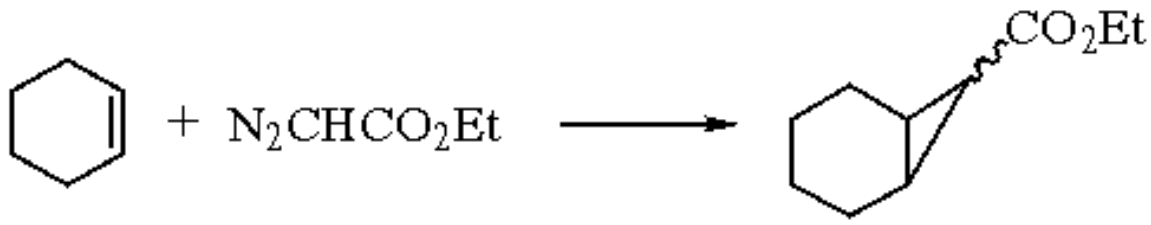

(1)

	anti:*syn*
$Rh_2(pfb)_4$	1.9:1
$Rh_2(OAc)_4$	3.8:1
$Rh_2(acam)_4$	10:1

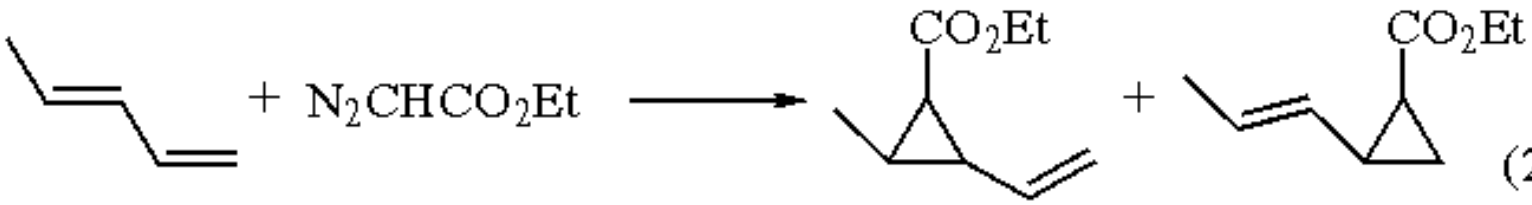

(2)

	%	%
$Rh_2(pfb)_4$	21	79
$Rh_2(OAc)_4$	12	88
$Rh_2(acam)_4$	7	93

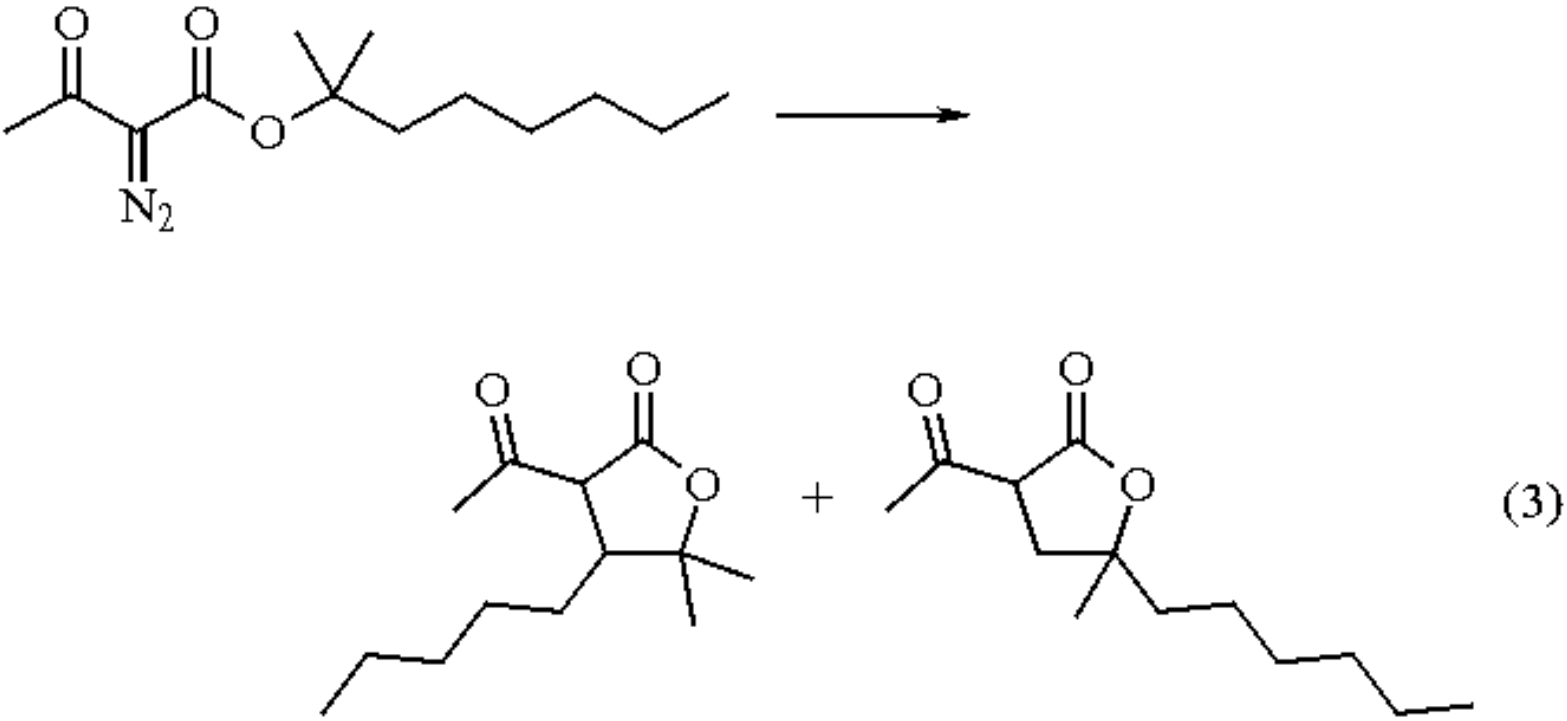

	%	%
$Rh_2(pfb)_4$	34	66
$Rh_2(OAc)_4$	75	25
$Rh_2(acam)_4$	92	8

(3)

Chemoselectivity.

Dirhodium(II) perfluorobutyrate has proven to be highly selective in competitive intramolecular metal carbene transformations.[12] In contrast to results with ***Dirhodium(II) Tetra(caprolactam)***, the use of $Rh_2(pfb)_4$ favors aromatic substitution over cyclopropanation (eq 4),[13] insertion over cyclopropanation (eq 5),[13] and aromatic substitution over carbonyl ylide generation (eq 6).[14] Product yields are high in each case. The order of reactivity for metal carbenes generated from $Rh_2(pfb)_4$ is aromatic substitution > tertiary C-H insertion > cyclopropanation &AApprox; aromatic cycloaddition > secondary C-H insertion, and the rate differences between them are as much as 100-fold.[13]

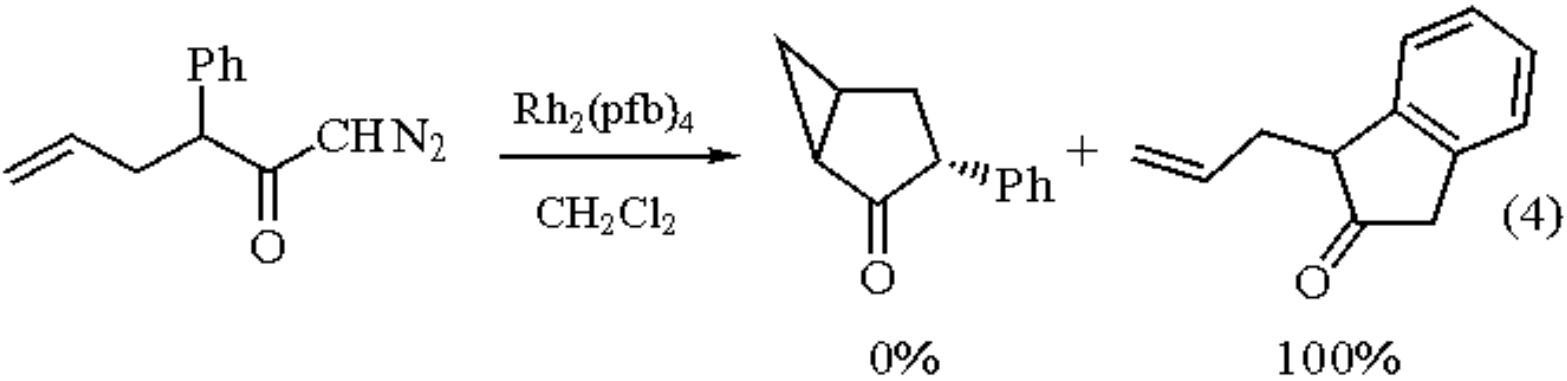

(4)

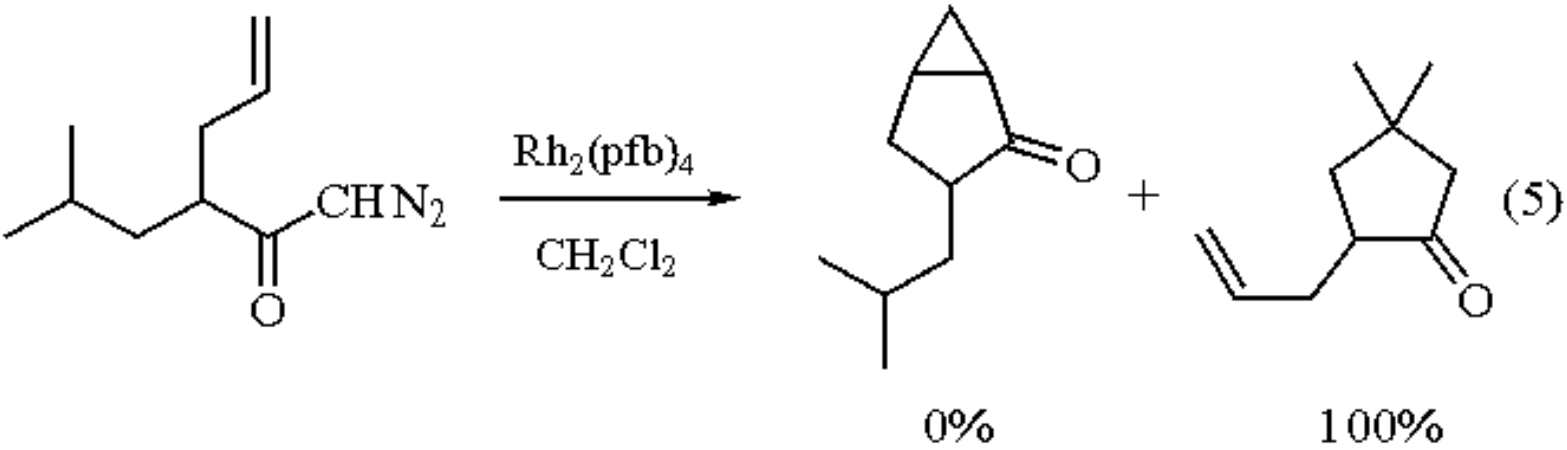

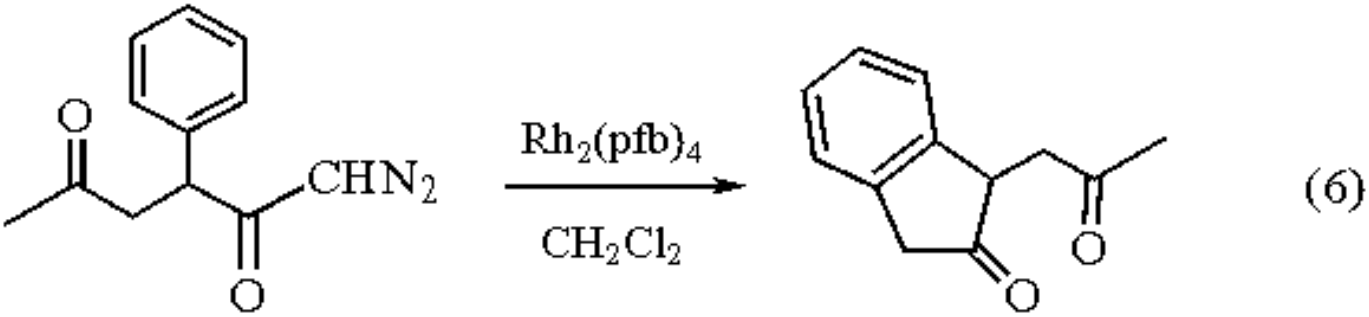

Additional applications of $Rh_2(pfb)_4$ to metal carbene transformations include intramolecular O-H insertion (eq 7),[14] where intramolecular cyclopropanation would also be a viable pathway. For intramolecular cyclopropenation reactions of diazo ketones which undergo subsequent vinylcarbene formation, use of $Rh_2(pfb)_4$ leads to different products than those from dirhodium(II) octanoate.[15] In contrast to the use of rhodium(II) octanoate in pentane which effects exclusive cyclopropanation, $Rh_2(pfb)_4$ in CH_2Cl_2 promotes [3 + 2] annulation in reactions of a vinyldiazomethane with vinyl ethers (eq 8),[16] and this result further exemplifies the influence of the highly electrophilic $Rh_2(pfb)_4$ on selectivity.

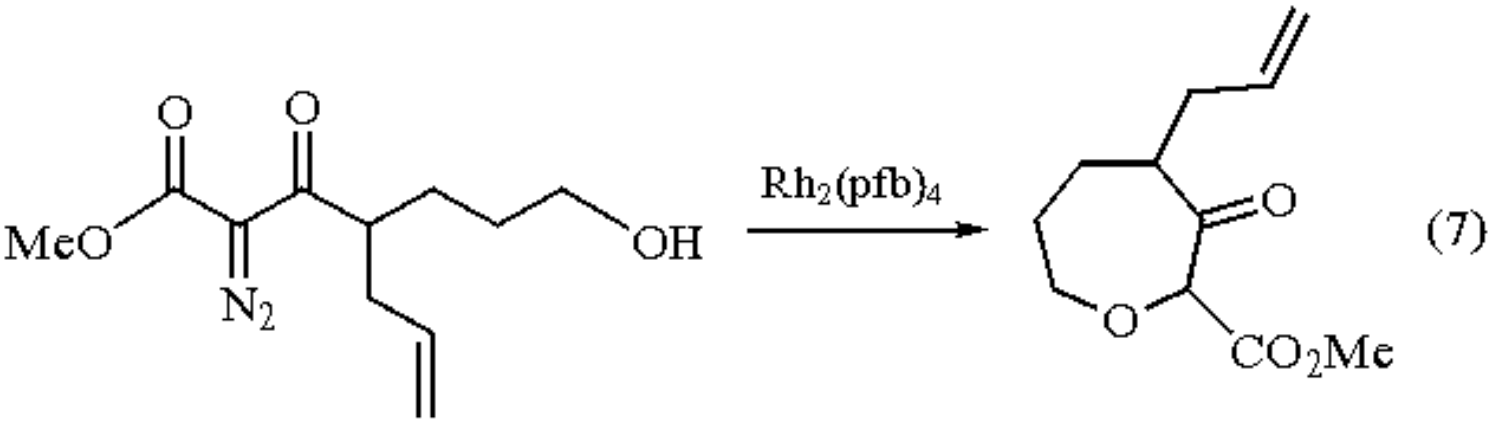

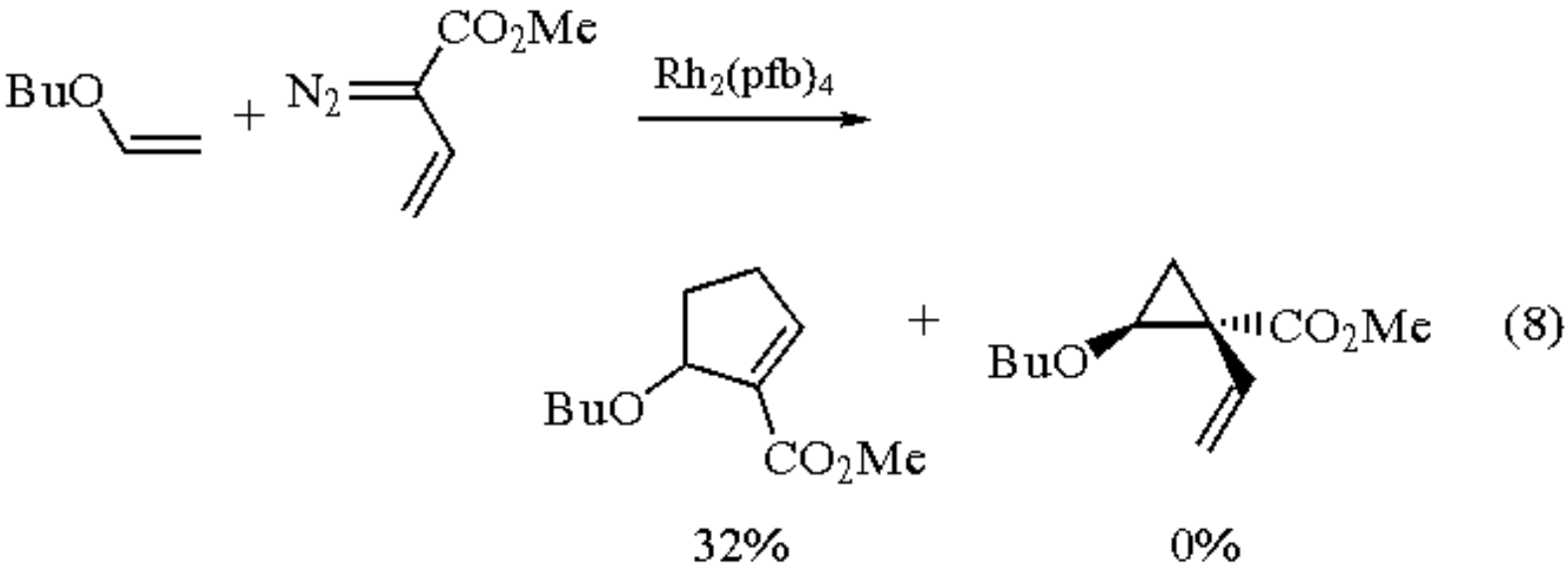

Isomerizations of Cyclopropenes.

Cyclopropenes undergo facile rearrangements catalyzed by $Rh_2(pfb)_4$ to yield products that are structurally different from those obtained with the use of copper, platinum, or silver catalysts.[17] The selectivity achieved with $Rh_2(pfb)_4$ is remarkable (Scheme 1), and, as suggested by eq 9, the involvement of $Rh_2(pfb)_4$ is consistent with the generation of a vinylcarbene intermediate.

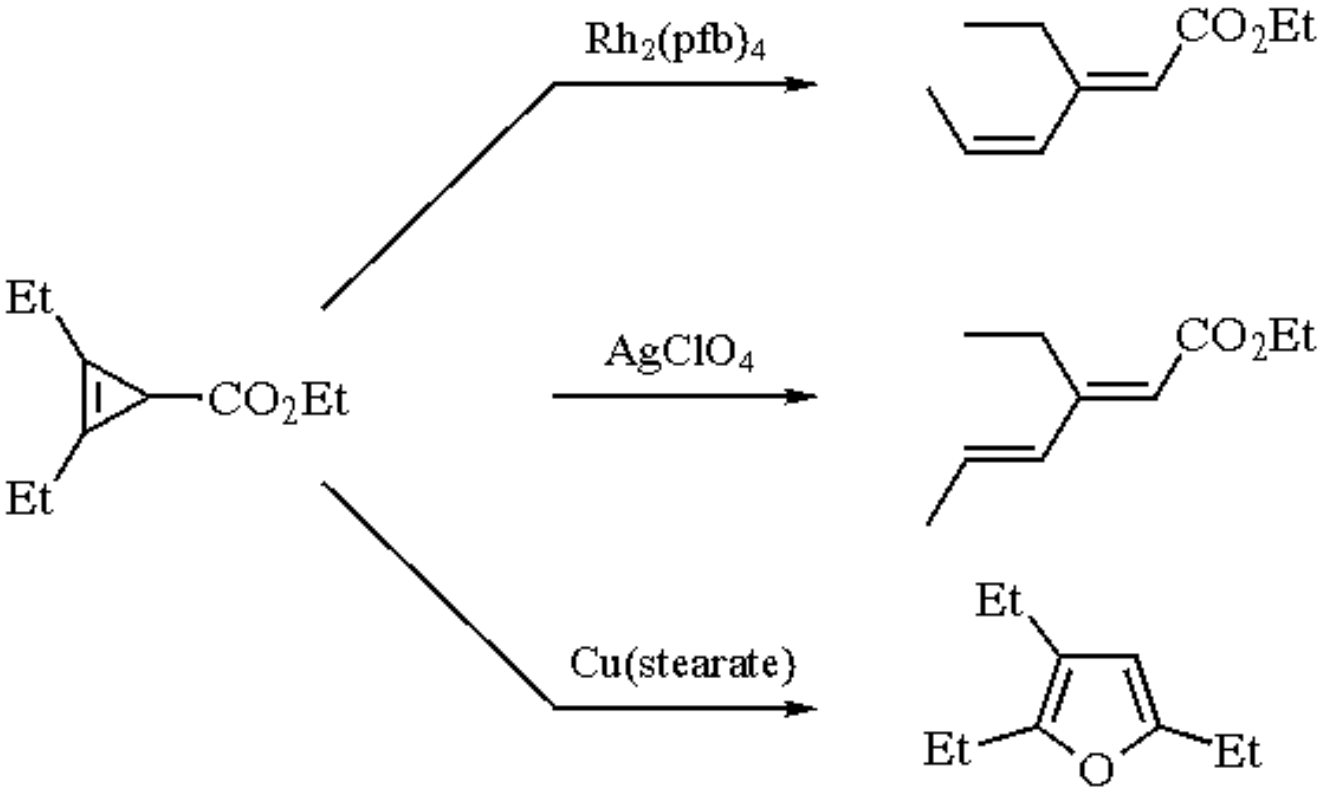

Scheme 1

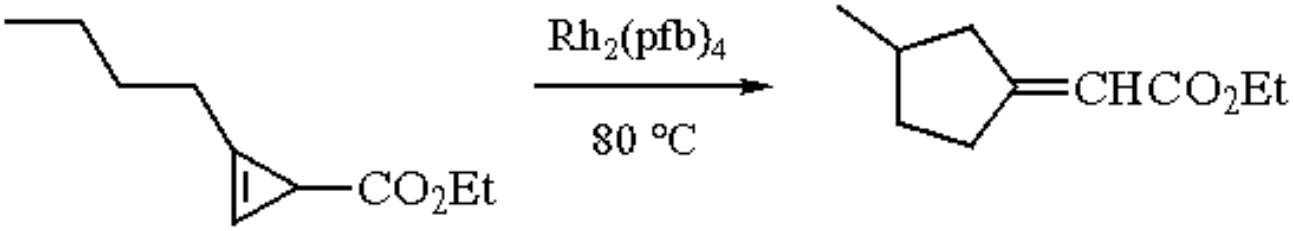

(9)

Hydrosilylation of Alkenes and Alkynes.

Hydrosilylation of 1-alkenes is catalyzed by $Rh_2(pfb)_4$ under mild conditions.[18] The mode of addition determines the products that are formed. When the alkene is added to triethylsilane in the presence of $Rh_2(pfb)_4$, normal hydrosilylation (eq 10) occurs; reversed addition causes the formation of vinyl- or allylsilanes (eq 11). Alkene isomerization catalyzed by the combination of $Rh_2(pfb)_4$ with triethylsilanes has also been reported.[18]

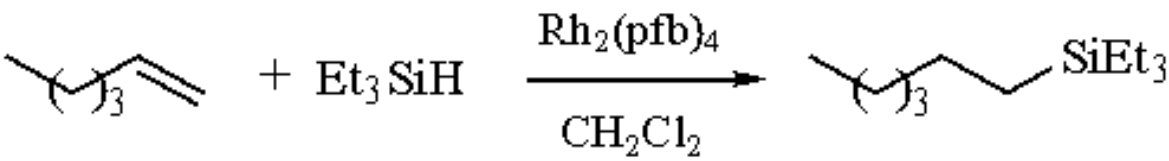

(10)

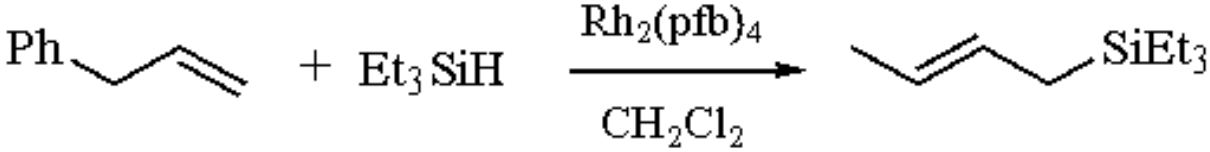

(11)

Hydrosilylation of 1-alkynes catalyzed by $Rh_2(pfb)_4$ forms either vinylsilanes (*trans* addition) or allylsilanes in moderate to high isolated yields, dependent on the mode of addition.[19] Addition of triethylsilane to 1-alkynes in dichloromethane containing $Rh_2(pfb)_4$ results in the formation of vinylsilanes, whereas addition of the alkynes to triethylsilane produces allylsilanes (eq 12) in high yield. Product dependence on the mode of addition is associated with organosilane coordination with $Rh_2(pfb)_4$. Organosilane alcoholysis is also catalyzed by $Rh_2(pfb)_4$ (eq 13);[20] primary alcohols react with triethylsilane approximately five times faster than do secondary alcohols.

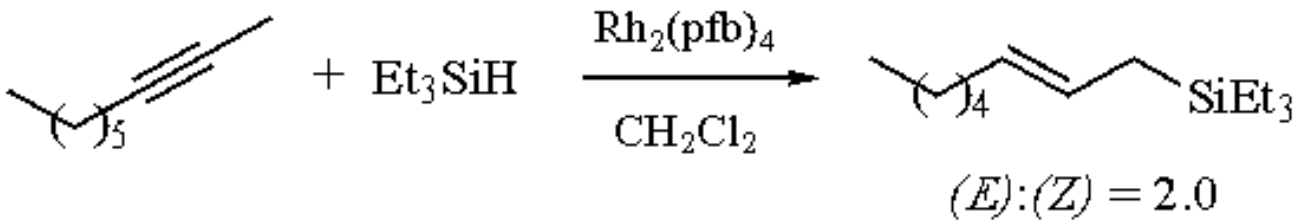

(12)

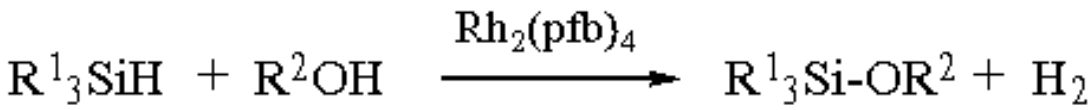

(13)

Silylcarbonylation of Alkynes.

$Rh_2(pfb)_4$ is a highly effective catalyst for silylation of terminal alkynes in reactions performed at atmospheric pressure or at 10 atm CO pressure and at or below rt.[3] At atmospheric CO pressure, addition of the alkyne to the organosilane is critical to the success of this transformation (eq 14), which is characterized by virtually complete regioselectivity and (*Z*/*E*) selectivity that is greater than 10:1, often reaching >30:1. ***Dirhodium(II) Tetraacetate*** is relatively ineffective as a catalyst for silylcarbonylation. The advantages of $Rh_2(pfb)_4$ as a catalyst for silylcarbonylation of alkynes lie in the mild conditions employed, high catalysts turnovers, and exceptional (*E*/*Z*) ratios.

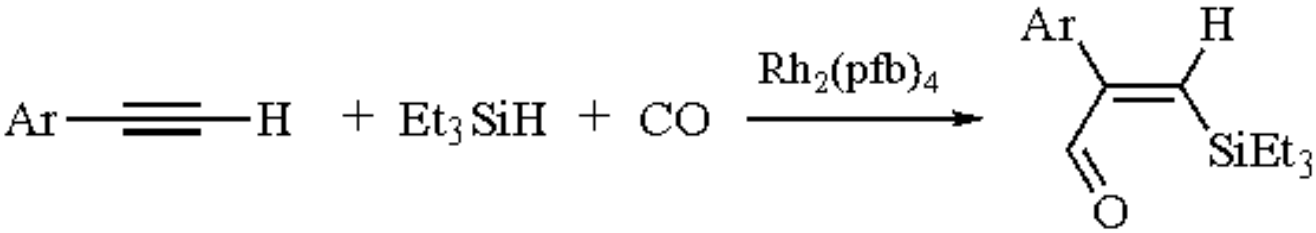

(14)

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Dirhodium(II) Tetrakis(trifluoroacetate)

$Rh_2(O_2CCF_3)_4$

[31126-95-1] · $C_8F_{12}O_8Rh_2$ · Dirhodium(II) Tetrakis(trifluoroacetate) · (MW 657.90)

(catalyst for carbenoid reactions of diazo compounds[1])

Physical Data: λ 610 nm, ε 210 (CH_2Cl_2).[2]

Solubility: sol MeCN, DMSO, pyridine; slightly sol dichloromethane, benzene.

Form Supplied in: anhydrous form is green; hydrate is blue.

Preparative Method: from ***Dirhodium(II) Tetraacetate*** by ligand displacement in refluxing trifluoroacetic acid containing trifluoroacetic anhydride.[3]

Handling, Storage, and Precautions: air stable, very hygroscopic; stored in desiccator.

Alkene Coordination.

Dirhodium(II) tetrakis(trifluoroacetate), $Rh_2(tfa)_4$, like the corresponding ***Dirhodium(II) Tetrakis(perfluorobutyrate)***, $Rh_2(pfb)_4$, forms π-complexes with alkenes.[2,4] Equilibrium constants for alkene coordination are 2-3 times less than those for $Rh_2(pfb)_4$, and they are relatively insensitive to steric influences. Coordination causes substantial changes in chemical shifts for vinyl protons.[4] A determination of chirality has been made through an axial bis-alkene complex of $Rh_2(tfa)_4$.[5] Nitroxide and phosphine complexes have also been characterized.[6,7]

Metal Carbene Transformations.

Fluoroalkanoate complexes of dirhodium(II) were first employed to effect intermolecular carbon-hydrogen insertion reactions (eq 1).[8,9] Although insertion product yields are relatively high, selectivity is low. A similar low level of selectivity occurs in intermolecular cyclopropanation of alkenes[10,11] and dienes.[12] However, relative to $Rh_2(tfa)_4$, $Rh_2(pfb)_4$ exhibits even lower levels of stereocontrol and regiocontrol in cyclopropanation reactions.

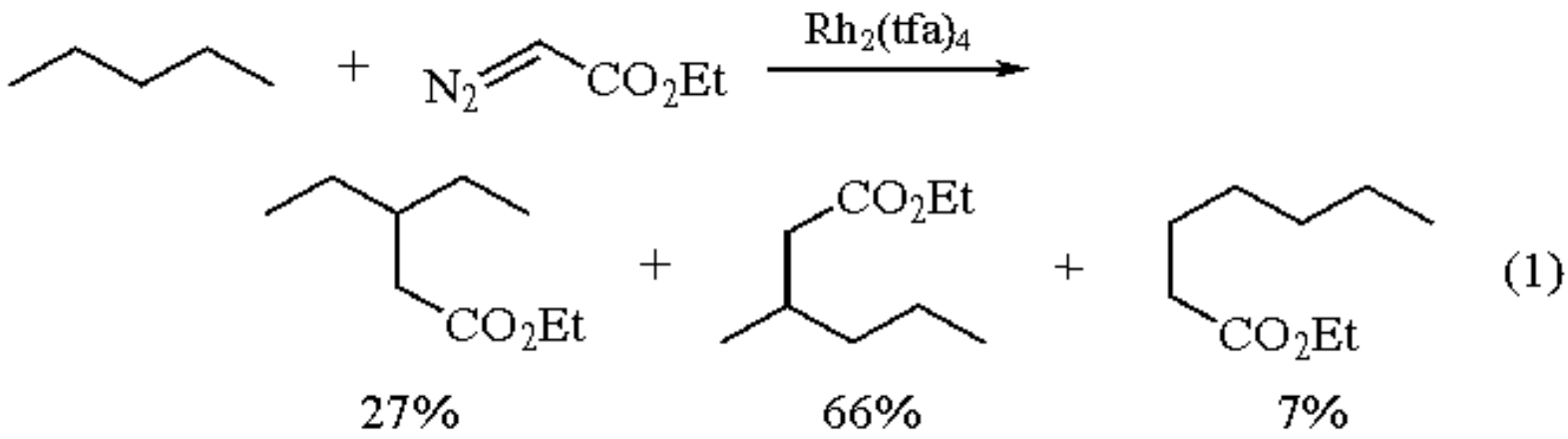

Both reactivity and solubility in weakly polar solvents render $Rh_2(pfb)_4$ superior to $Rh_2(tfa)_4$ for metal carbene transformations.

The cationic character of the intermediate metal carbene formed from a vinyldiazo compound is evident in the formation of the bicyclo[2.2.1]heptene system in eq 2.[13] Here, use of $Rh_2(tfa)_4$ favors this carbocation addition product even in pentane, whereas use of ***Dirhodium(II) Tetraacetate*** in pentane reduces the yield of this product to only 5%. Electrophilic substitution products have also been reported from $Rh_2(tfa)_4$-catalyzed reactions of vinyldiazomethane derivatives with *N*-(methoxycarbonyl)pyrrole.[14] Overall $Rh_2(tfa)_4$ is not as effective as $Rh_2(pfb)_4$, nor is its selectivity in reactions of metal carbenes significantly different.

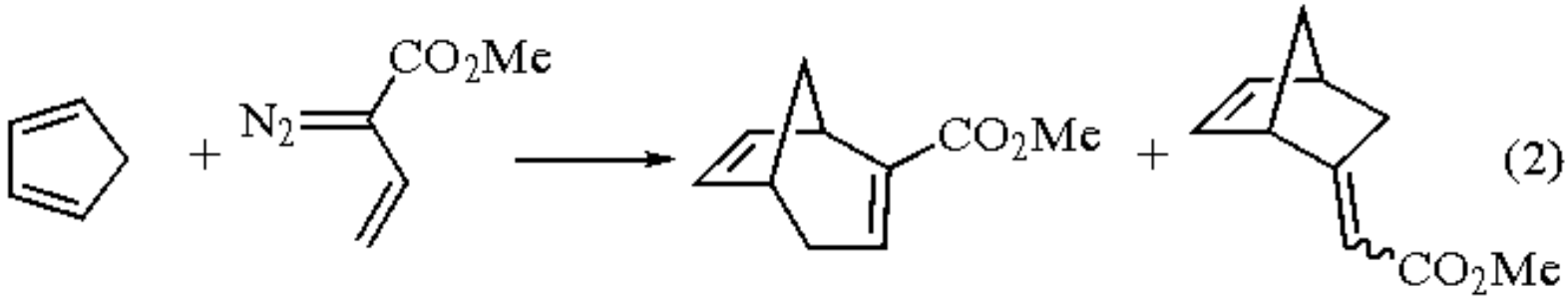

$Rh_2(tfa)_4$, CH_2Cl_2	32%	68%
$Rh_2(tfa)_4$, pentane	46%	54%
$Rh_2(OAc)_4$, CH_2Cl_2	67%	33%
$Rh_2(OAc)_4$, pentane	95%	5%

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Dirhodium(II) Tetraoctanoate

$Rh_2(O_2CC_7H_{15})_4$

[73482-96-9] · $C_{32}H_{60}O_8Rh_2$ · Dirhodium(II) Tetraoctanoate · (MW 778.74)

(nonpolar solvent-soluble catalyst for carbenoid reactions of diazo compounds)

Solubility: sol MeOH, MeCN, Et_2O, CH_2Cl_2, toluene, hexane, pentane.

Form Supplied in: green solid; commercially available.

Preparative Method: prepared by ligand substitution from $Rh_2(OAc)_4$.[1]

Handling, Storage, and Precautions: air stable, weakly hygroscopic; stored in desiccator.

Metal Carbene Transformations.

Because of its solubility in organic solvents, dirhodium(II) tetraoctanoate, $Rh_2(oct)_4$, has seen wide use as an alternative for ***Dirhodium(II) Tetraacetate*** as a catalyst for reactions of diazo compounds. However, although $Rh_2(oct)_4$ is initially soluble in relatively nonpolar organic solvents, whereas $Rh_2(OAc)_4$ is not, there are few other advantages to its use as a laboratory scale catalyst. Thus $Rh_2(OAc)_4$ can be chromatographically separated on silica or alumina from reaction products, but $Rh_2(oct)_4$ is often resistant to chromatographic separation.

Temperature Effects.

Uses of $Rh_2(oct)_4$ for catalytic reactions with diazo compounds parallel those of $Rh_2(OAc)_4$.[2,3] Although product yields are higher with $Rh_2(OAc)_4$, use of $Rh_2(oct)_4$ at 0 °C in dichloromethane causes exceptionally high diastereocontrol (97% de) for the intermolecular cyclopropanation of styrene by the (*R*)-(-)-pantolactone ester of *trans*-2-diazo-4-phenyl-3-butenoate (eq 1).[4] Here temperature seems to be important since in refluxing dichloromethane both $Rh_2(OAc)_4$ and $Rh_2(oct)_4$ gave this cyclopropane product with a diastereomeric excess of 88 ± 1%.

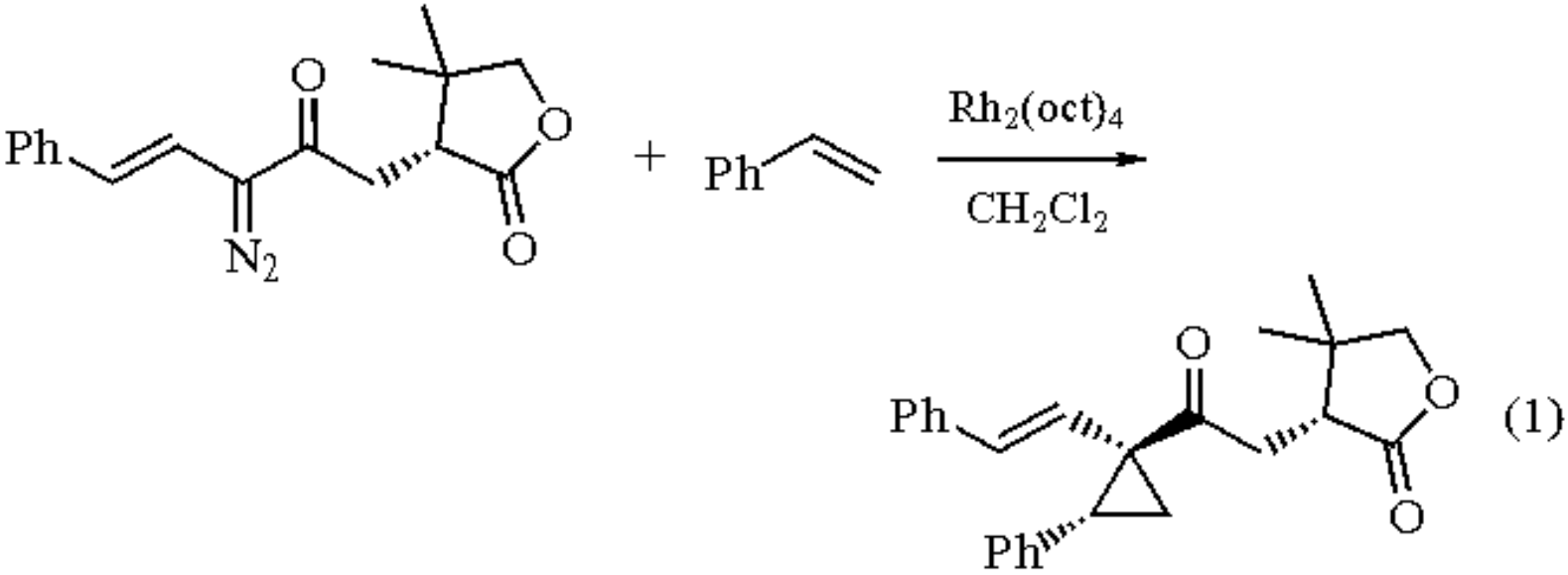

Temperature control in $Rh_2(oct)_4$-catalyzed reactions of a vinyldiazomethane (Scheme 1) in CH_2Cl_2 (0 and 40 °C) or benzene (80 °C) affords selective entry to intramolecular aromatic cycloaddition (0 °C), [3 + 4] annulation (40 °C), and [3 + 2] annulation (80 °C).[5]

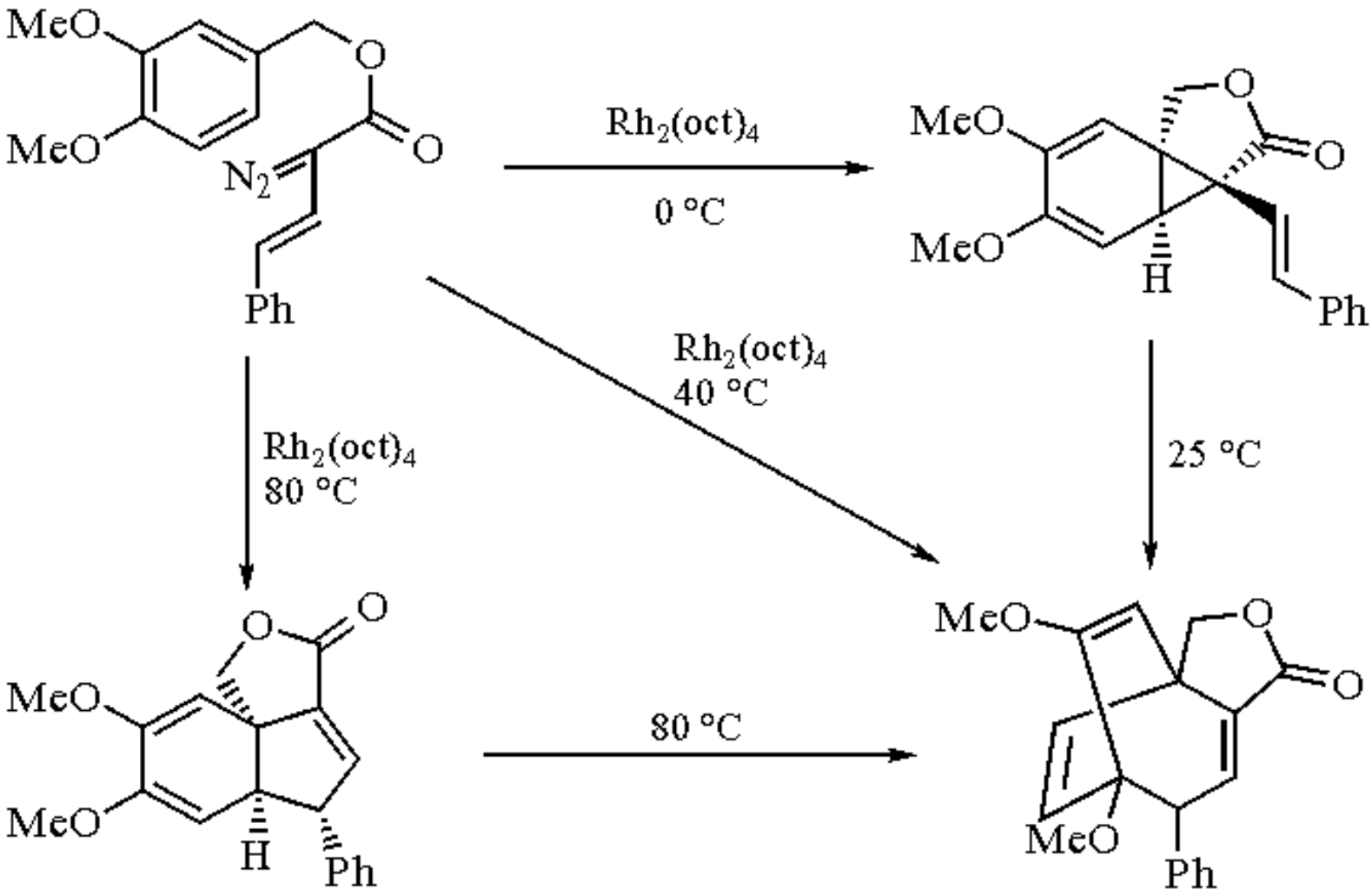

Scheme 1

Solvent Effects.

Use of $Rh_2(oct)_4$ in pentane significantly influences product control in catalytic carbenoid reactions. Cyclopropanation occurs to the exclusion of [3 + 2] annulation in reactions of vinyldiazomethanes with vinyl ethers (eq 2); with $Rh_2(OAc)_4$ in dichloromethane, both products are formed.[6] Intramolecular reactions of diazo ketones show a similar solvent dependence with systems designed for tandem cyclopropenation/vinylcarbene formation/cyclopropenation versus hydrogen migration (eq 3).[7] In other cases the influence of solvent on selectivity is not as great,[8,9] but for the synthesis of tropanes the use of $Rh_2(oct)_4$ in pentane has advantages not demonstrated by $Rh_2(OAc)_4$ in dichloromethane (eq 4).[10] Solvent control of the reaction pathway is associated with the degree of charge development in the transition state for the carbenoid reaction.

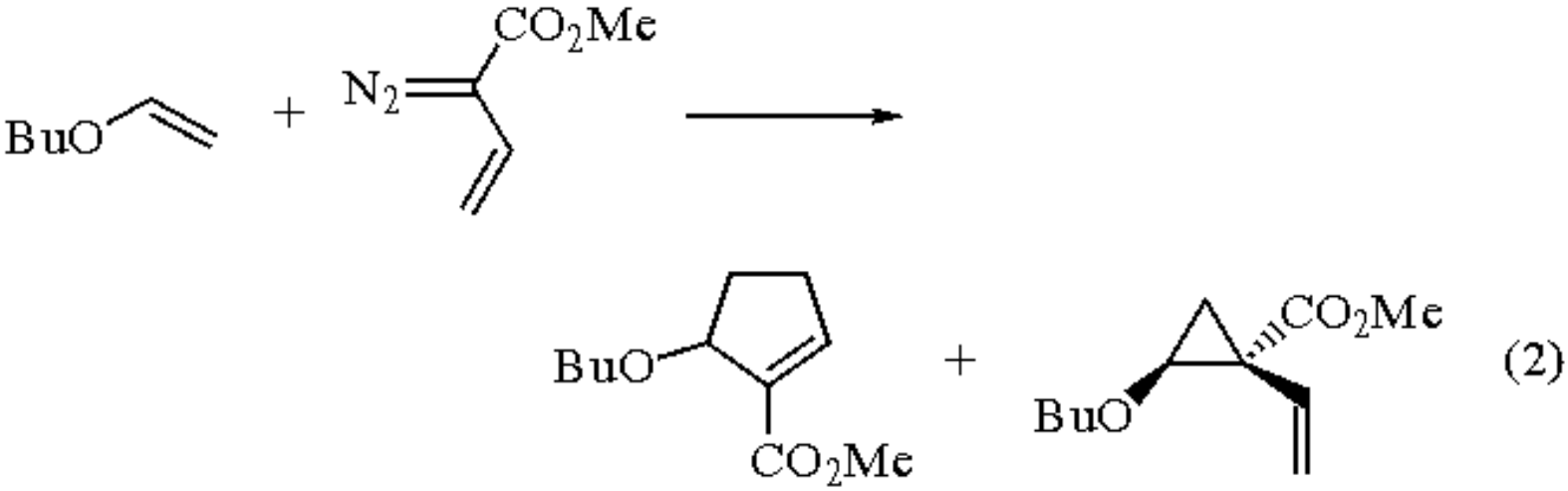

$Rh_2(oct)_4$, pentane	0%	91%
$Rh_2(OAc)_4$, CH_2Cl_2	24%	37%

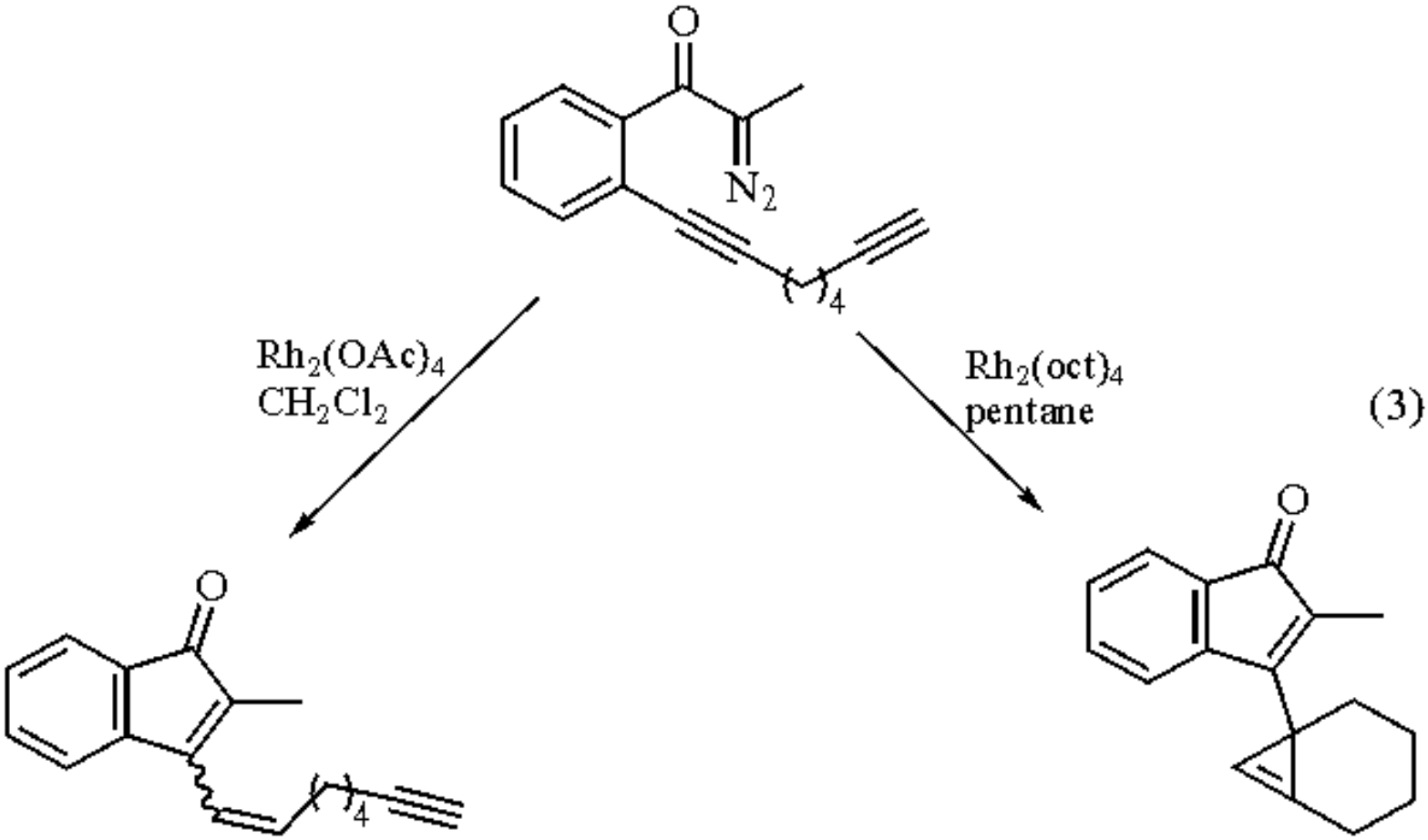

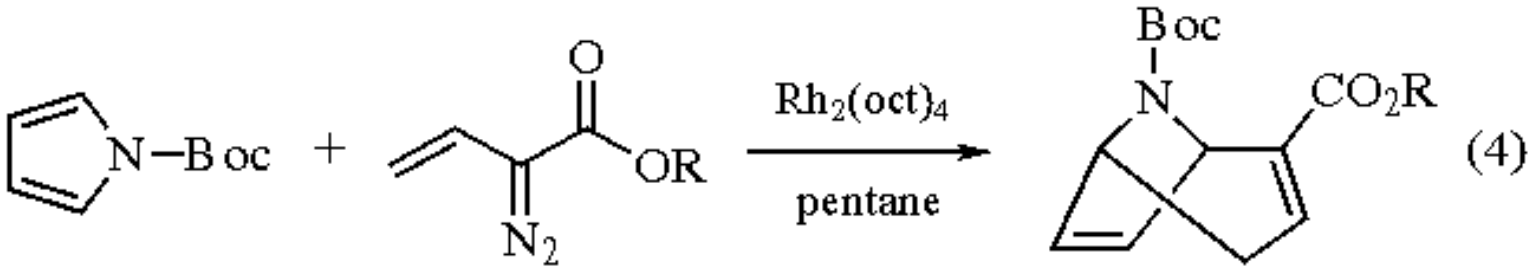

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Disiamylborane[1]

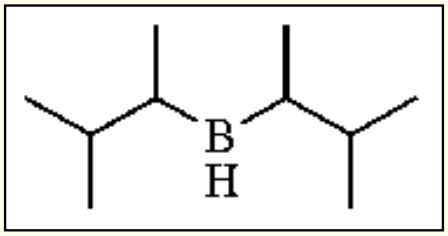

[1069-54-1] · $C_{10}H_{23}B$ · Disiamylborane · (MW 154.14)

(hindered organoborane for chemo-[2] and regioselective[3] hydroboration and chemo-[4] and stereoselective[5] reduction; can be used to mediate couplings of alkenes[6] and alkynes[7])

Alternate Name: bis(1,2-dimethylpropyl)borane.

Physical Data: mp 35-40 °C; fp -17 °C.

Solubility: sol THF, ether, diglyme.

Form Supplied in: prepared in situ; kits are available.

Preparative Methods: generally prepared by reaction of ***Diborane*** with 2-methyl-2-butene in ethereal solvents at 0 °C;[8] alternatively by substituting borane-1,4-thioxane.[9]

Handling, Storage, and Precautions: flammable; very air- and moisture-sensitive. Generally prepared immediately prior to use. Handle in a fume hood.

Hydroboration of Alkenes.

Compounds containing double bonds react with disiamylborane (Sia_2BH) to give tertiary boranes of the form Sia_2BR (eq 1). These trialkylboranes are generally not isolated, but are submitted to further reactions to provide a variety of products. The reactions of disiamylborane adducts are typical of organoboranes. If the intermediate is quenched with acid, the borane is replaced with a proton (eq 2); the net result is a *syn* hydrogenation.[10]

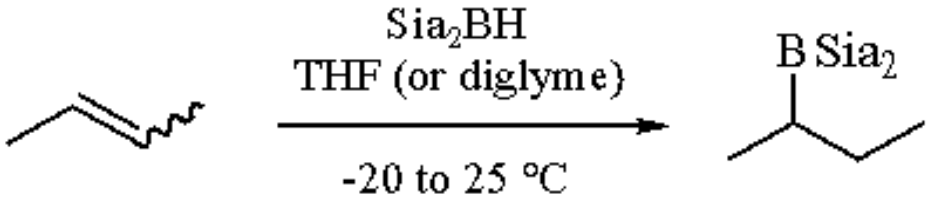

(1)

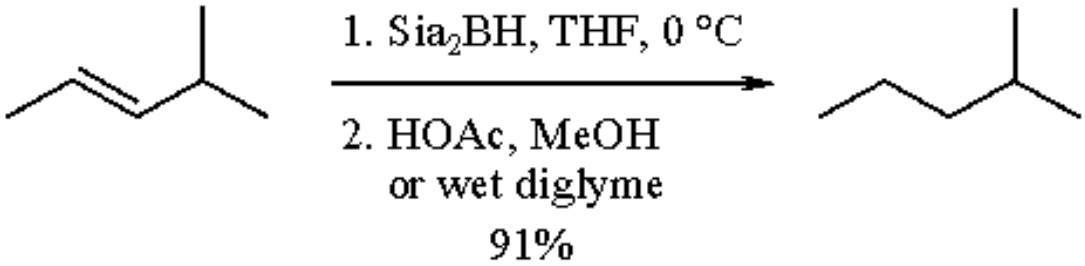

(2)

The organoborane may also be oxidized with alkaline peroxide to give an alcohol which retains the position and configuration of the borane adduct. Thus, for example, Sia_2BH is the reagent of choice for anti-Markovnikov hydration of o-unsaturated esters due to its high selectivity for terminal hydroboration (eq 3).[11] Alternatively, direct oxidation of the intermediate resulting from hydroboration of a terminal alkene with ***Pyridinium Chlorochromate*** provides the aldehyde (eq 4).[12] Once again, Sia_2BH is the reagent of choice for this reaction because of its high selectivity for the alkenic terminus. Reaction of Sia_2BR with ***Iodine*** under basic conditions provides the corresponding iodide.[13] When R is primary, the formation of RI proceeds in high yield, because transfer of the siamyl groups occurs only slowly (eqs 5 and 6). A similar transformation may be accomplished using borane, but yields are generally lower because R_3B gives only partial conversion to RI.[14] This Sia_2BH-based approach was found to be clearly superior to a hydrozirconation route for the iodination of the (η^6-hexabutenylbenzene)(η^5-cyclopentadienyl)iron cationic complex illustrated in eq 7.[15]

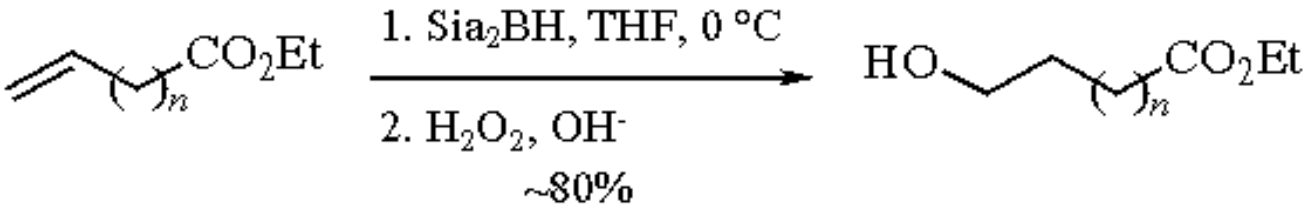

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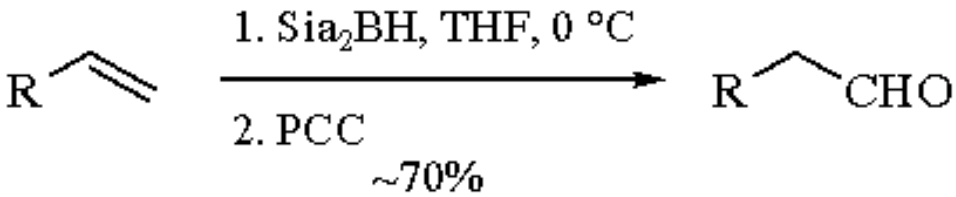

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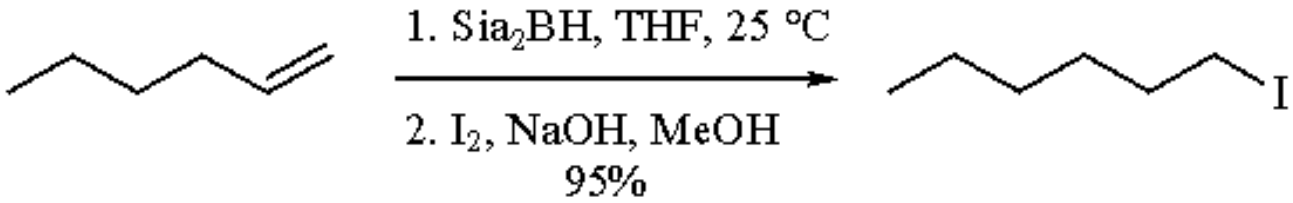

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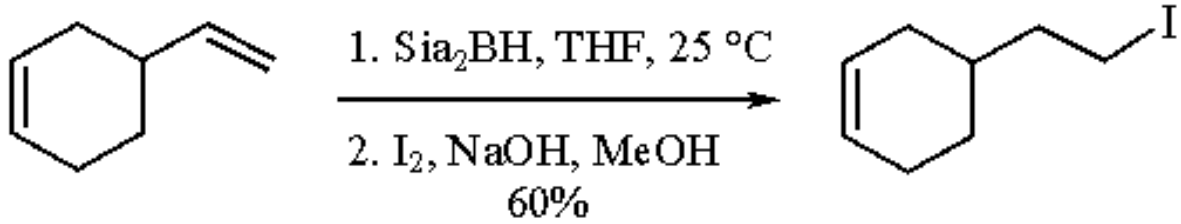

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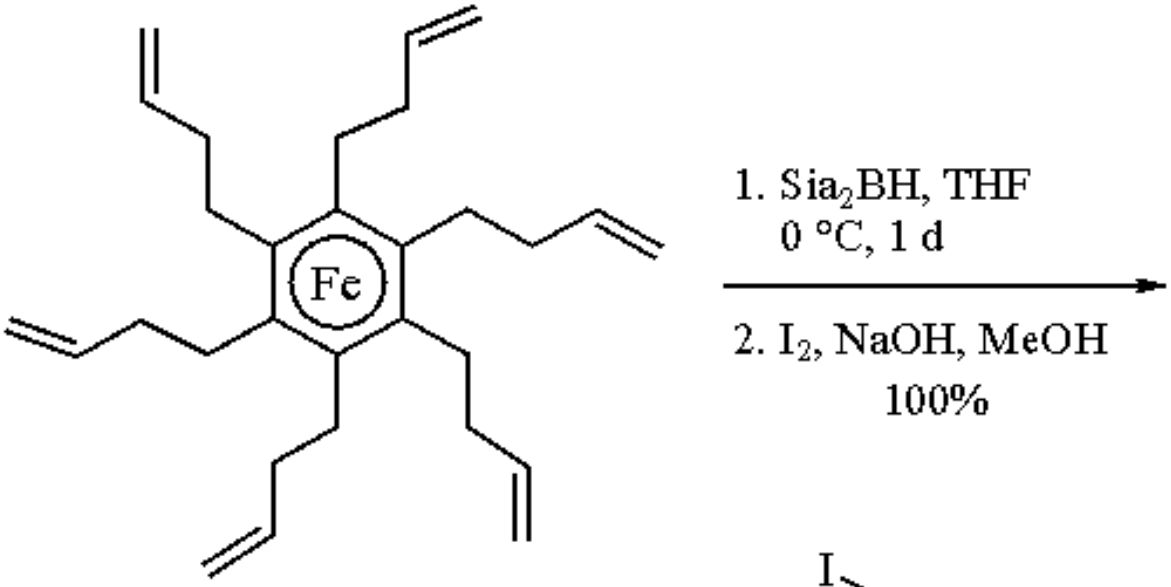

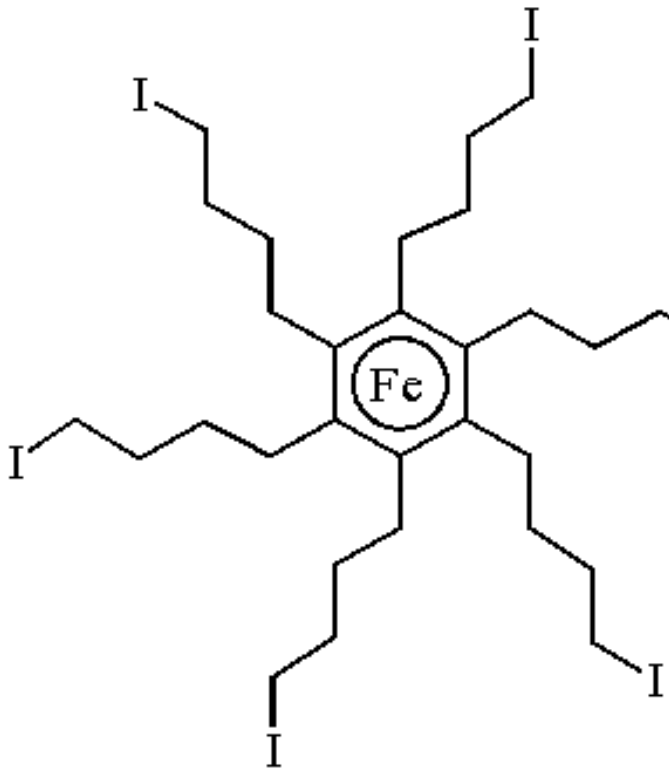

(7)

Unlike diborane, disiamylborane exists as a dimer even in solution in THF.[16] This failure to dissociate in a coordinating solvent, presumably due to the steric bulk of the siamyl groups which disfavor the borane/ether complex, causes Sia_2BH to act as a highly hindered hydroborating agent. As a general rule, Sia_2BH reacts preferentially with less sterically hindered alkenes. An extensive comparative study has determined the relative rates of reaction of double bonds with a variety of substitution patterns.[17]

Reaction occurs to place the borane at the least encumbered position. These differences in reaction rate are often large enough to be synthetically useful; thus 1-hexene reacts at the terminal position with >99:1 selectivity (with diborane the selectivity for the 1-position is ~15:1).[18] Sia_2BH even responds to the bulk of the substituents on the double bond; 4-methyl-*trans*-2-pentene reacts slowly with the reagent (12 h at 0 °C) to give mainly the 2-alcohol (Scheme 1).[18]

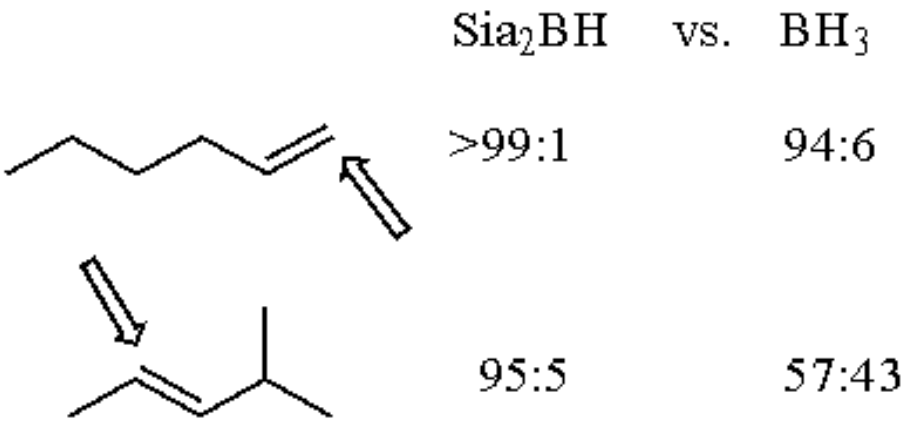

Scheme 1

This high level of steric discrimination makes Sia_2BH a useful reagent for selective reaction with one double bond of a polyunsaturated compound; for example, hydroboration of limonene (eq 8) gives (after oxidative workup) a good yield of α-terpineol,[19] while the diene of eq 9 reacts selectively at one of the four possible alkenic positions.[20]

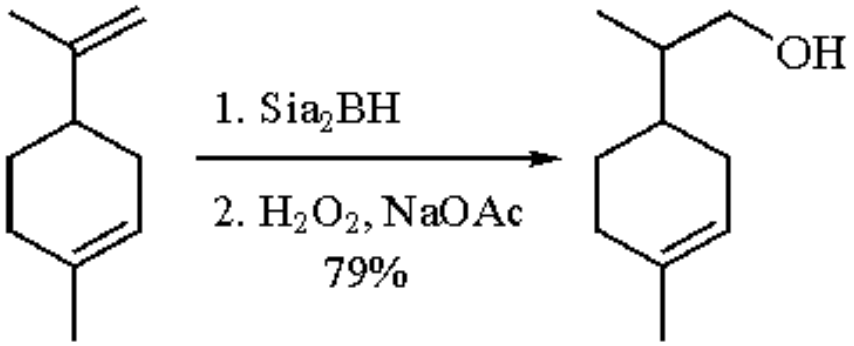

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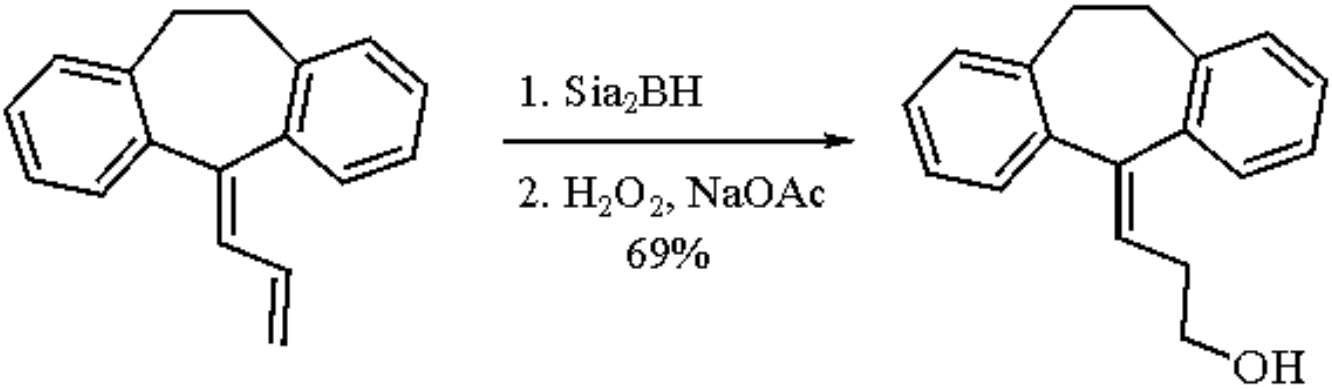

(9)

Sia_2BH-mediated hydroboration is a key step in a unique carbocyclization reaction (eq 10).[6] Thus dienyl iodide is selectively hydroborated at the less-substituted alkene; oxidative cyclization of this intermediate provides a cycloalkene. The borane route provides a useful alternative to methods involving palladium catalysis.

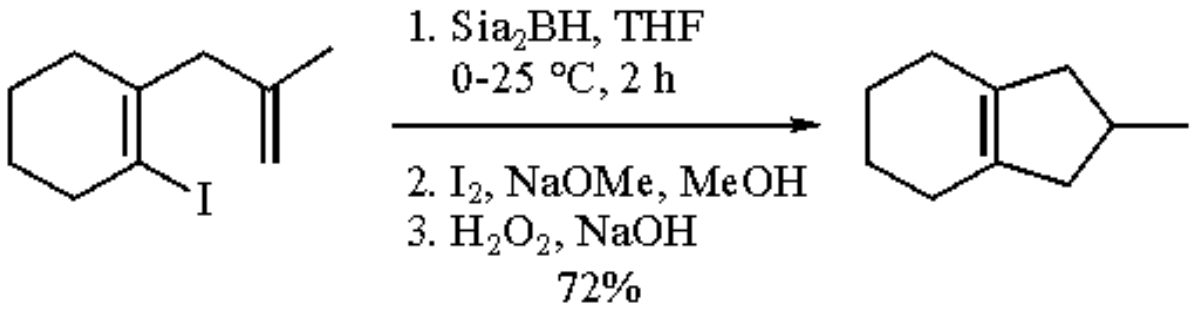

(10)

Hydroboration of Alkynes.

Sia_2BH is a valuable reagent for the chemo- and regioselective hydroboration of alkynes. The reagent is more selective for terminal hydroboration than diborane; it is also more selective for monoaddition.[8] Reaction of 1-hexyne with Sia_2BH gives a vinylborane as an intermediate. Hydrolysis gives 1-hexene as the product (eq 11). In the case of internal alkynes, this process results in a net *syn* hydrogenation to give a (*Z*)-alkene (eq 14).[21] Oxidative workup of the vinylborane provides an aldehyde (eq 12).[8] The intermediate can also be oxidized with copper salts in the presence of cyanide ion to give an α,β-unsaturated nitrile (eq 13).[22] Sia_2BH is superior to ***Dicyclohexylborane*** for this transformation, which provides an alternative to the hydroalumination/cyanogen sequence.[23]

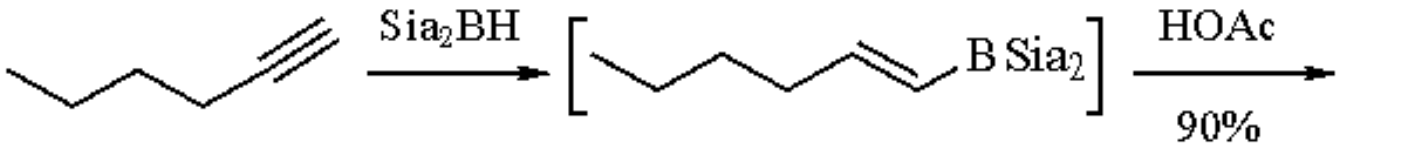

(11)

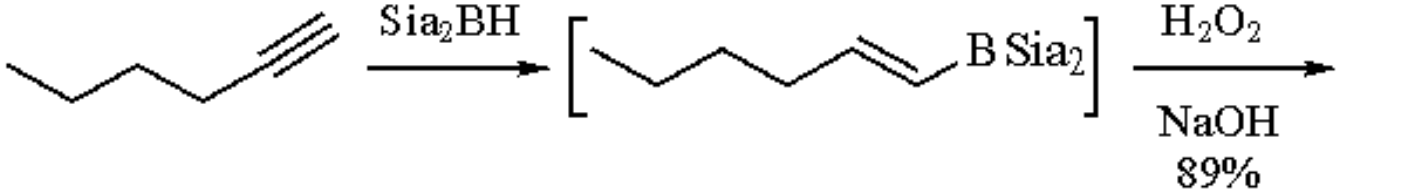

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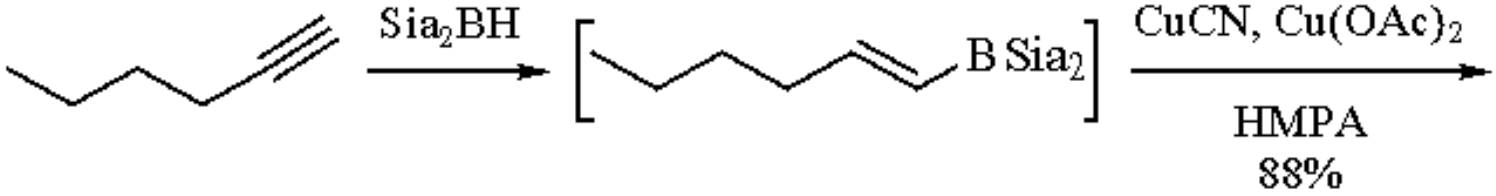

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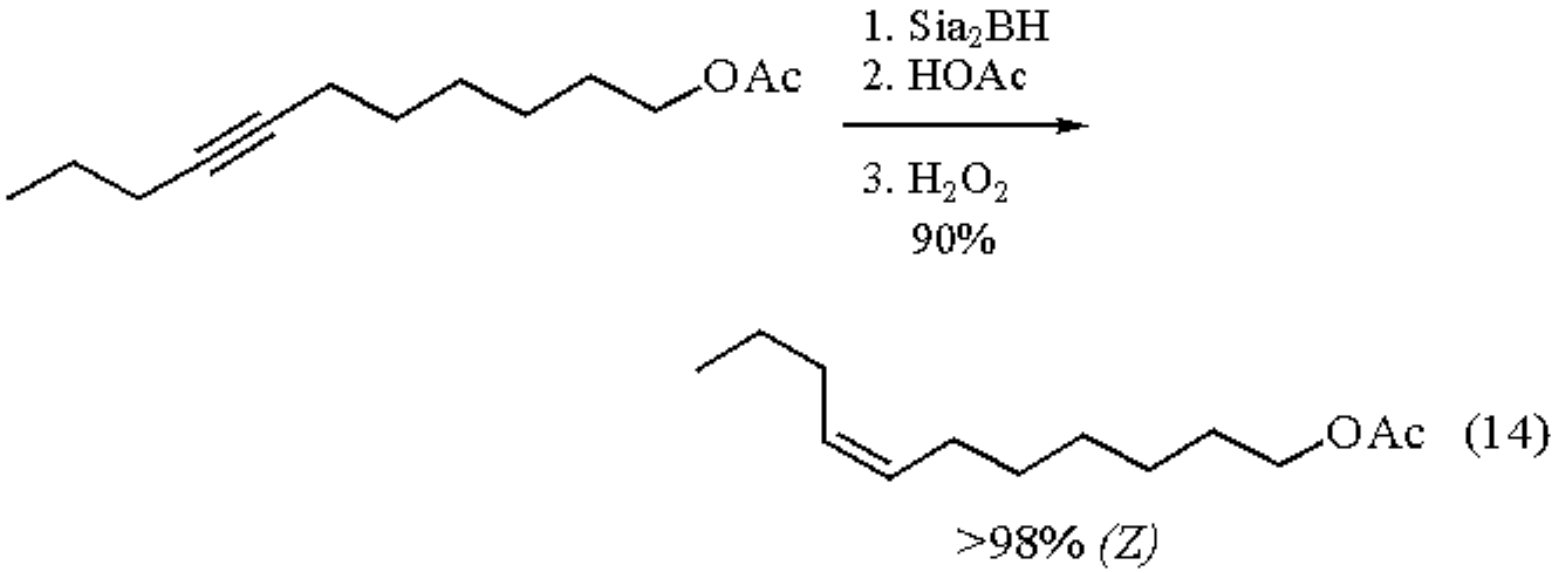

The reaction of Sia_2BH with 1,4-dichloro-2-butyne, followed by treatment of the intermediate with a thiolate anion, provides a one-pot synthesis of 2-thioalkylbutadienes (eq 15).[24] A similar strategy, replacing the thiolate with an organolithium reagent, is unsuccessful for the synthesis of 2-alkylbutadienes, as the siamyl group migrates preferentially to primary alkyl.[25]

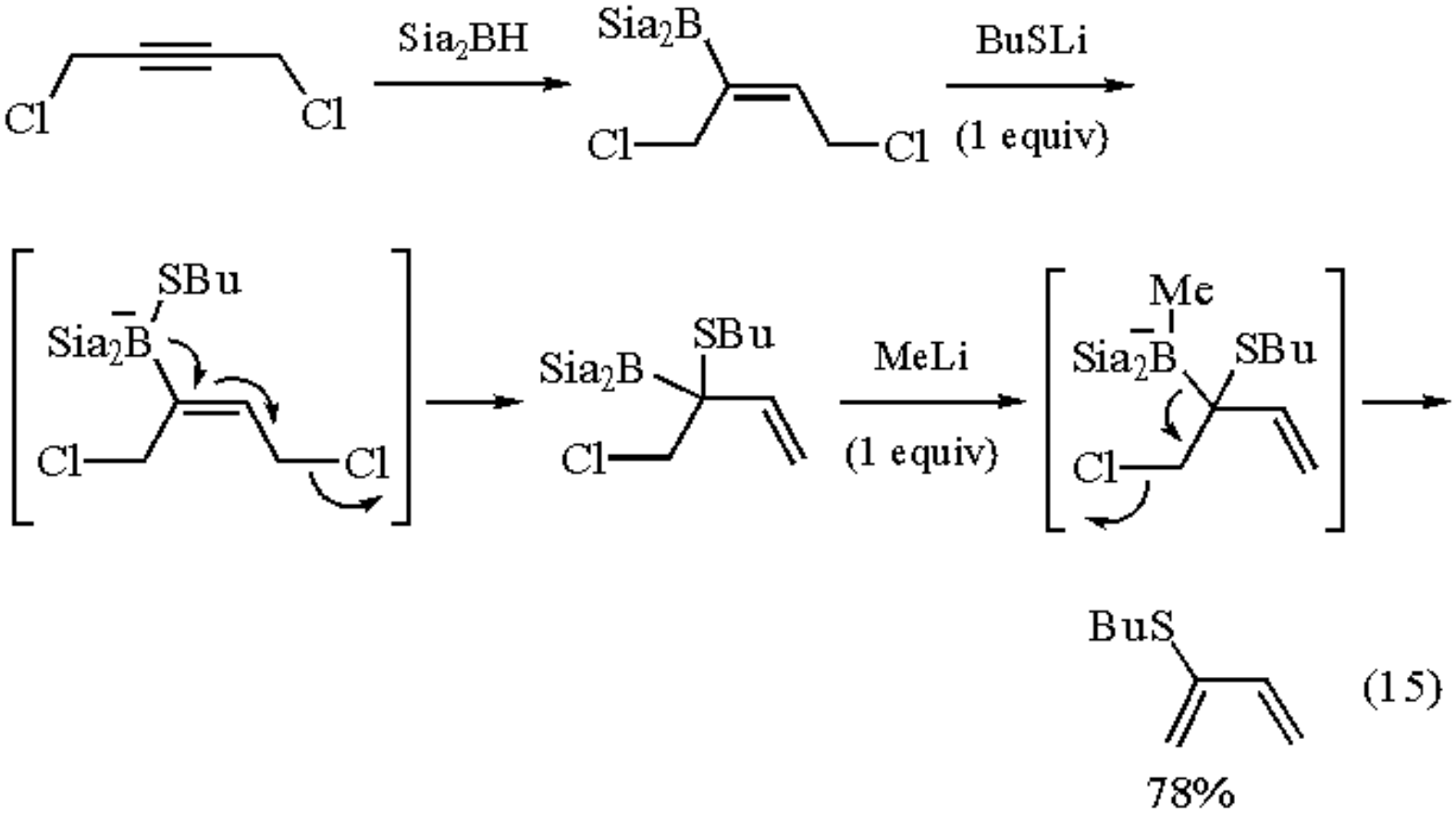

Sia_2BH adds regioselectively to a variety of asymmetrically substituted alkynes. Reaction with alkynyl sulfides occurs primarily α to sulfur; processing of the vinylborane intermediate by hydrolysis (of the corresponding ate complex) or oxidation leads to a vinyl sulfide (eq 17) or thiolester (eq 16), respectively.[26] Cyclohexylborane is more selective

(83:17) for α-boration than Sia_2BH (72:28) in this reaction. The reagent also reacts selectively at the 2-position of 1-chloro-2-heptyne; acid hydrolysis leads to a (*Z*)-allyl chloride (eq 18), while base treatment gives the terminal allene (eq 19).[27] Similarly, alkynyl acetals react with Sia_2BH to place the borane proximal to the heteroatom.[28]

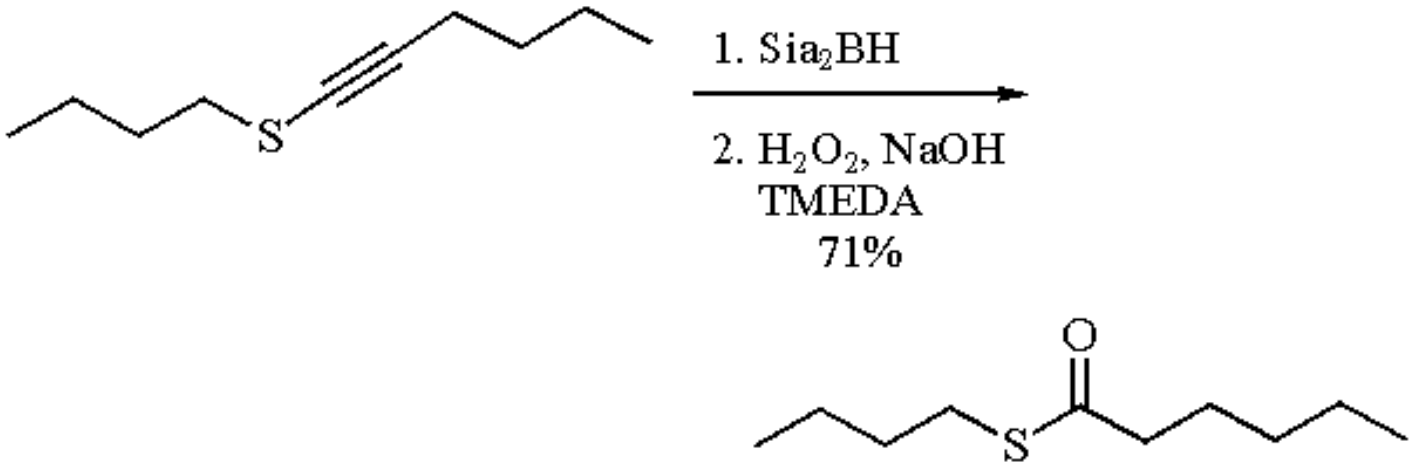

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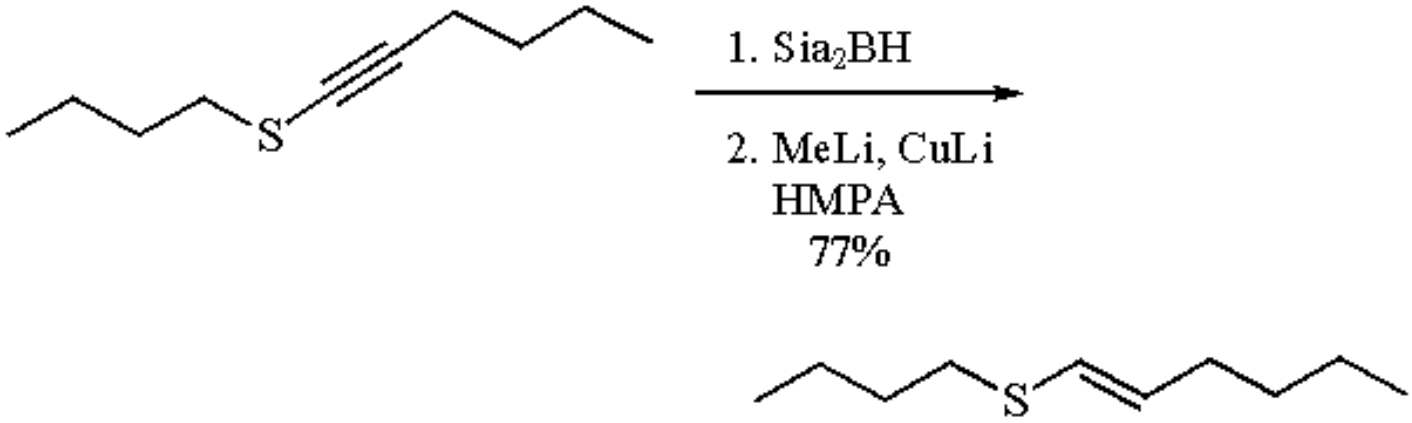

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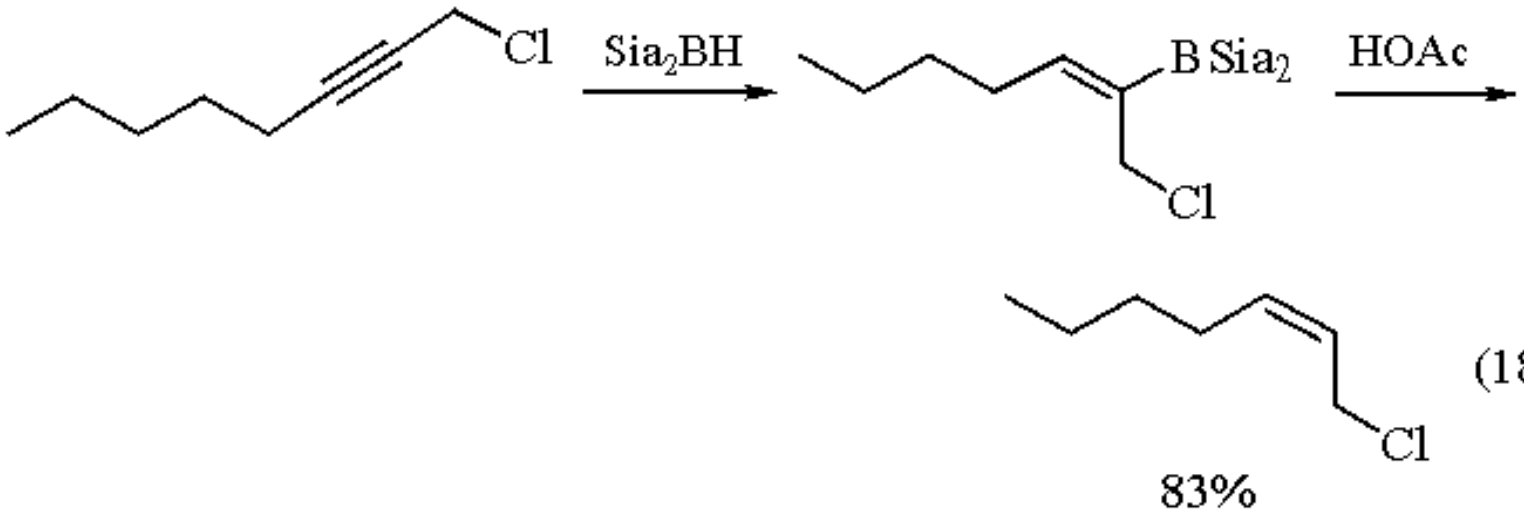

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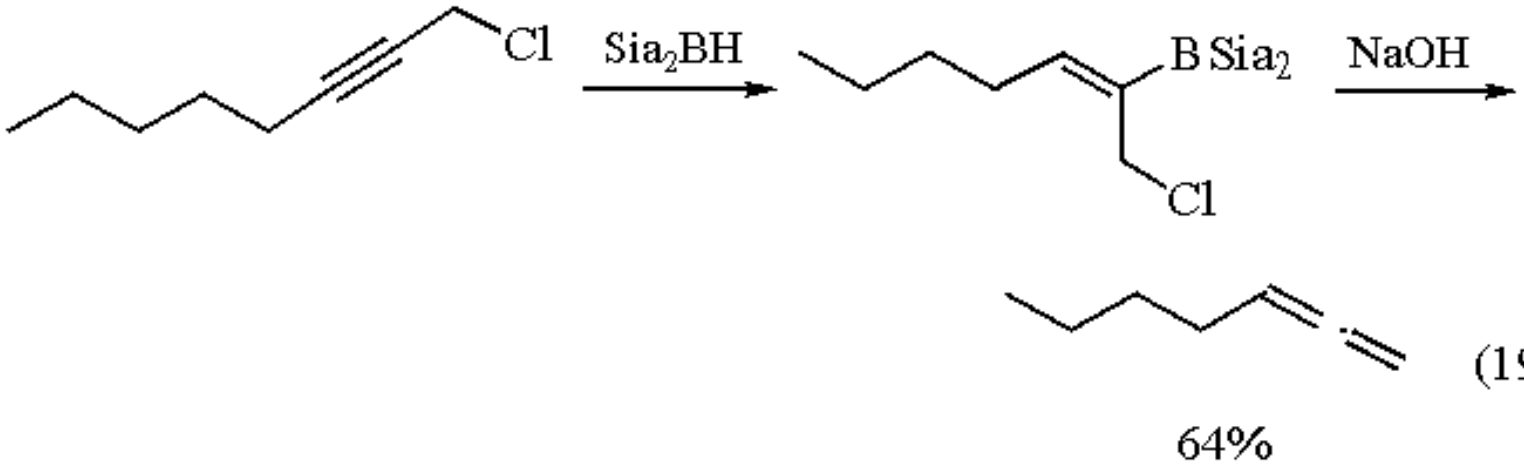

(19)

Hydroboration of alkynes with Sia_2BH is more rapid than the corresponding reaction of alkenes, allowing for the selective conversion of enynes into dienes (eq 21)[2] or enones (eq 20).[29]

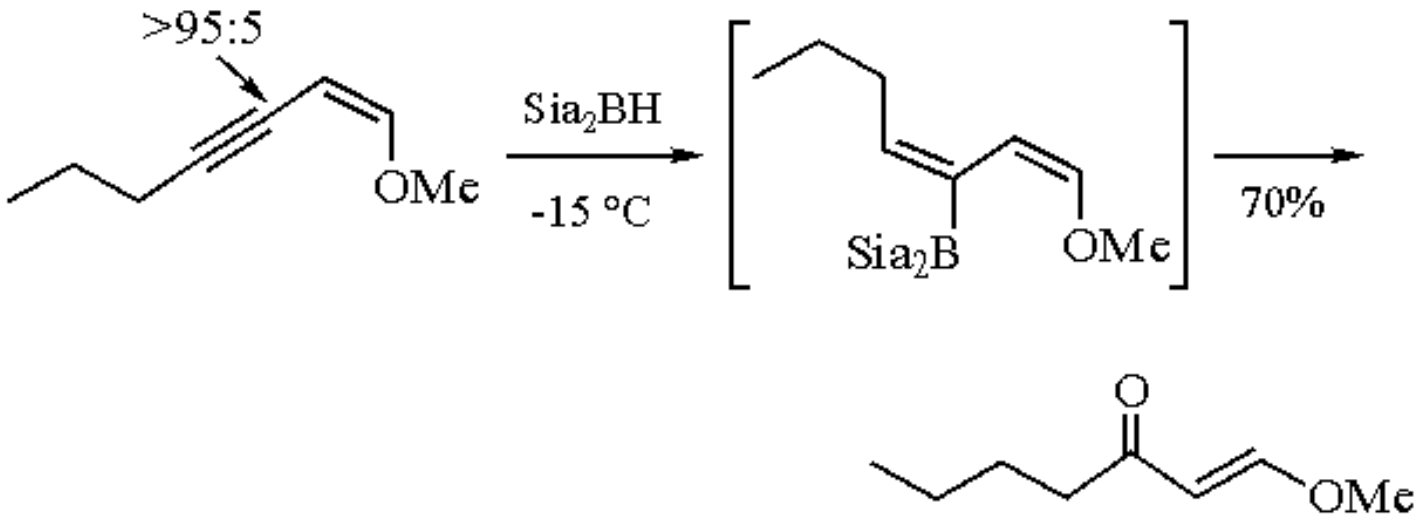

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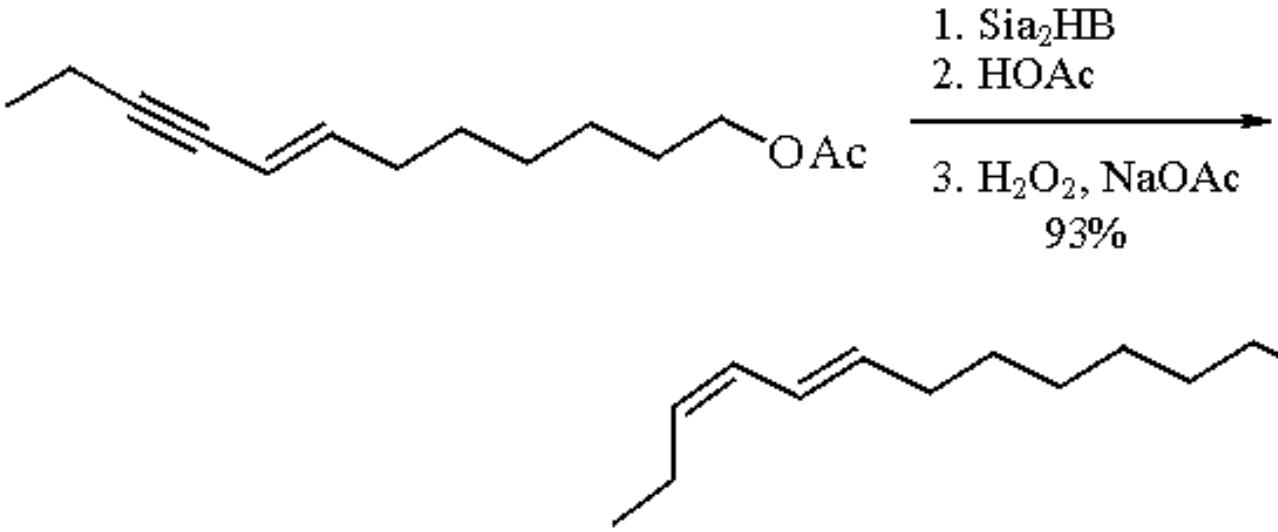

(21)

The enynes themselves can be prepared in Sia_2BH-mediated reactions. Hydroboration of diynes protected by bulky silyl groups occurs in a highly regioselective fashion; hydrolysis of the resultant organoboranes gives silylated enynes (eq 22).[30] Alternatively the vinylborane resulting from reaction of a terminal alkyne with Sia_2BH undergoes further reaction

with an alkynyllithium to give an ate complex, oxidation of which with iodine leads to carbon-carbon bond formation (eq 23).[7]

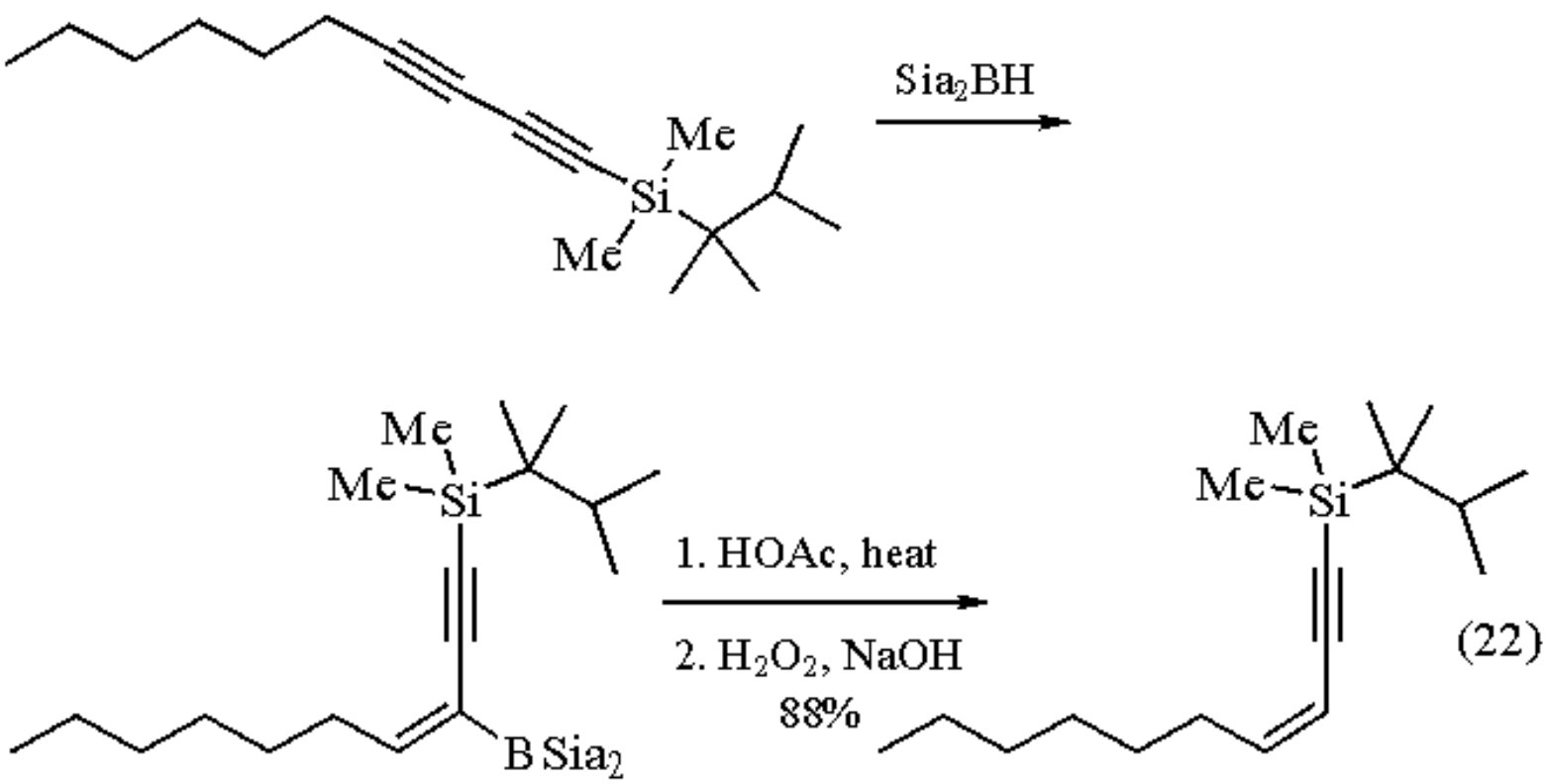

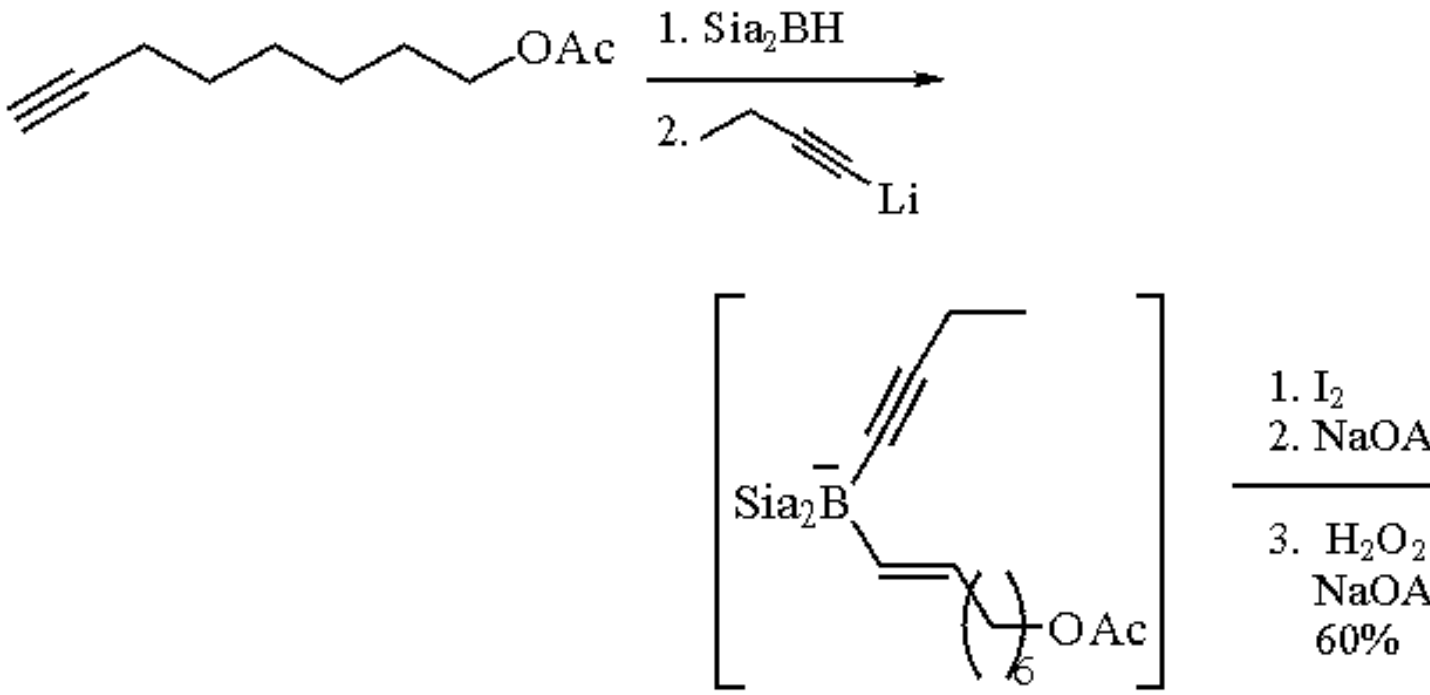

(23)

Functional Group Reductions.

An unusual mix of chemo- and stereoselectivity makes Sia_2BH a useful reducing agent for carbonyl compounds. While aldehydes and ketones are reduced rapidly, a variety of other functionalities including carboxylic and sulfonic acids, acid chlorides, and sulfones are inert.[4] Ketone reduction is often highly stereoselective, with the bulky reducing reagent delivering hydride from the less hindered face of the carbonyl (eqs 24 and 25).[5]

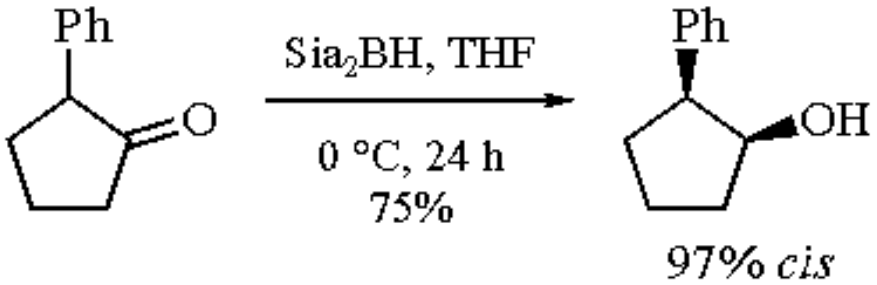

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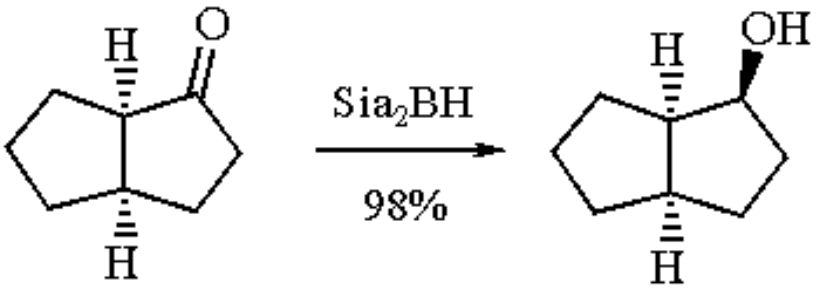

(25)

Sia_2BH is superior to ***Lithium Aluminum Hydride*** or borane for this transformation, but is generally less stereoselective than ***Diisopinocampheylborane***. While esters are unreactive, γ-lactones may be reduced to the corresponding lactols, a selectivity which has been used to advantage in carbohydrate synthesis (eq 26).[31] Amides also show a unique pattern of reactivity; while Sia_2BH fails to reduce primary amides, tertiary amides are converted to the corresponding aldehydes (eq 27).[31]

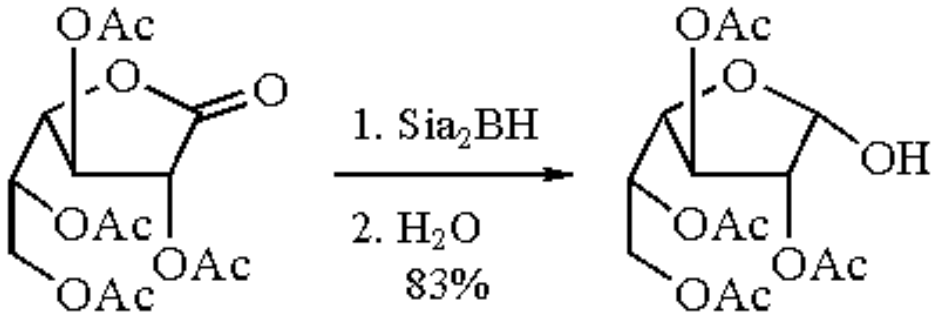

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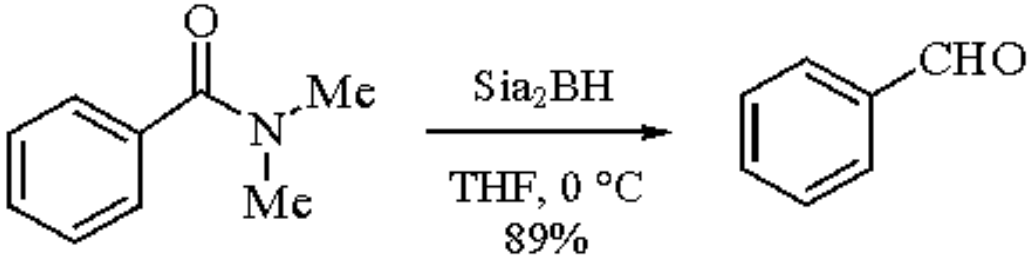

(27)

Sia_2BH also reacts with α,β-unsaturated ketones, with reduction occurring in a 1,4-sense.[32] The resultant boron enolate may be hydrolyzed to provide the saturated ketone (eq 28), or alternatively may be treated with an aldehyde to give *syn*-aldol products (eq 29).

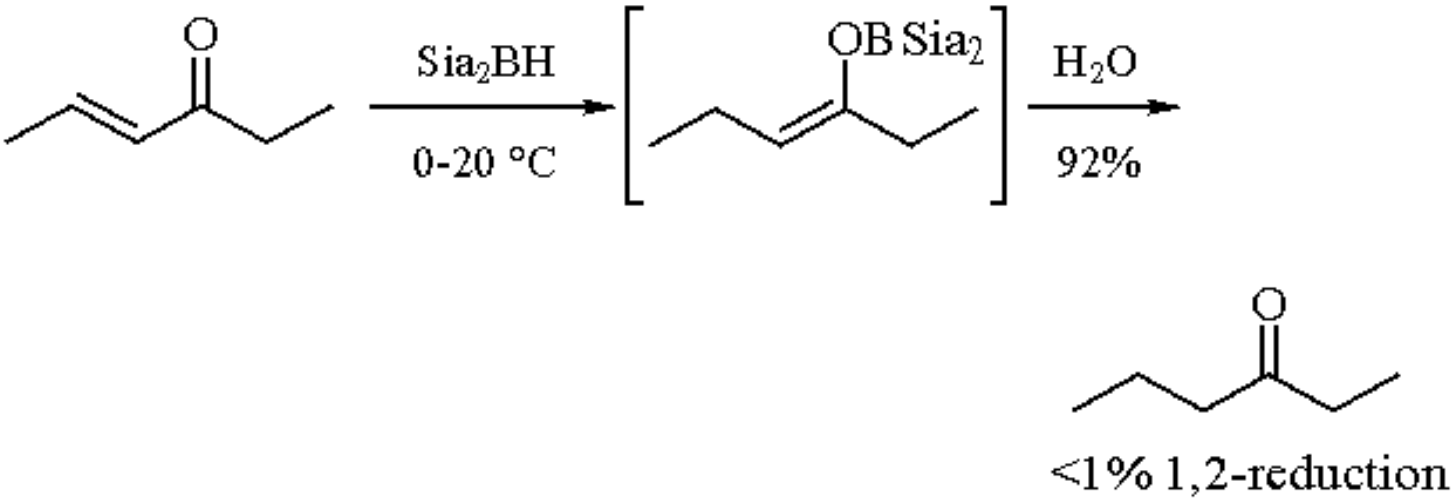

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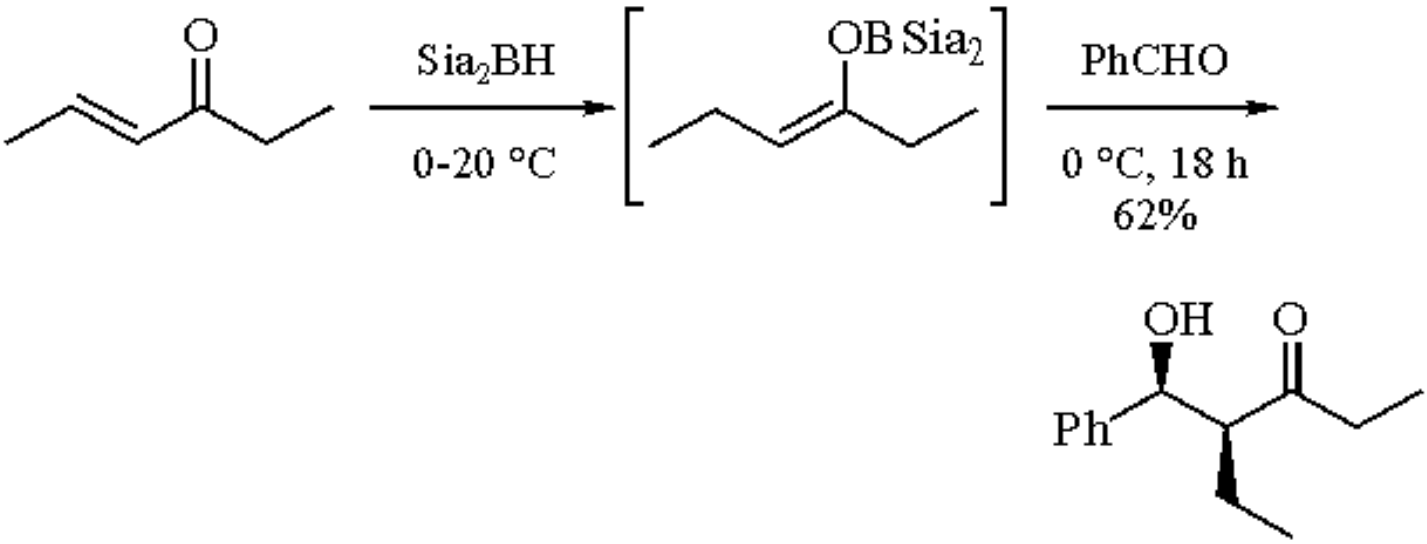

(29)

Dicyclohexylborane, diisopinocampheylborane, and diisocaranylborane all accomplish a similar transformation; 9-BBN is inferior because it leads to significantly more 1,2-reduction.

Related Reagents.

Borane-Tetrahydrofuran; ***Diborane***; ***Dicyclohexylborane***.

---

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Disodium Phenanthrenide

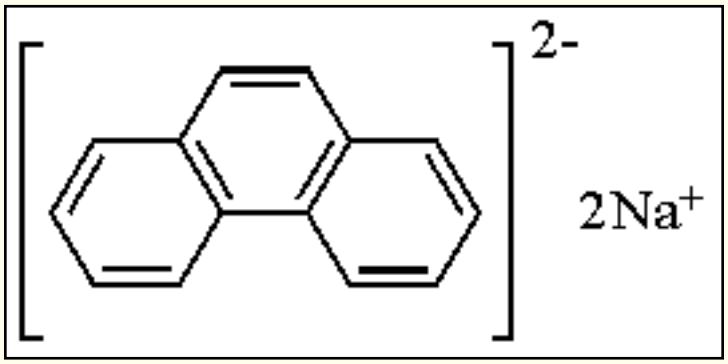

[84810-06-0] · $C_{14}H_{10}Na_2$ · Disodium Phenanthrenide · (MW 224.22)

(organohalide reducing agent)

Preparative Method: prepared in situ by reaction of parent hydrocarbon with ***Sodium*** in dimethyl ether.[1]

The first reference to the use of the disodio derivative of phenanthrene is a fleeting comment on the similarity of the parent hydrocarbon to naphthalene in the presence of sodium metal in dimethyl ether.[1] This tantalizing reference was exploited by Vogel et al. in the first efficient synthesis of bicyclo[4.2.0]octa-2,4,7-triene (**1**) (eq 1).[2] Disodium phenanthrenide was found to be superior to the previously examined methods for preparation of this elusive cyclooctatetraene tautomer.[3]

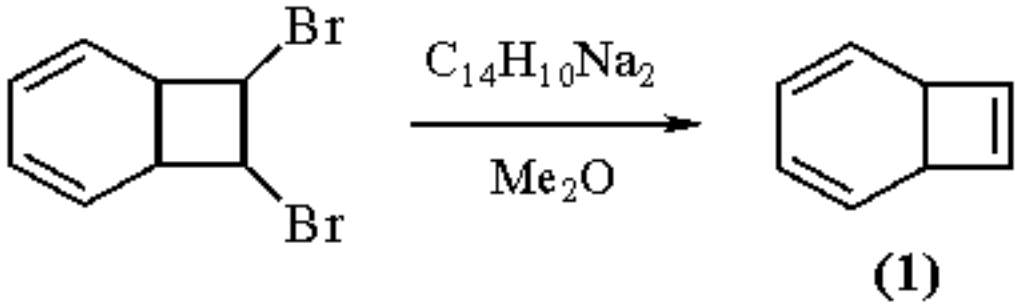

(1)

The main employment of sodium phenanthrenide has been in the preparation of exotic hydrocarbons such as that shown above. For instance, this reductive dehalogenating reagent was used in preparation of hemi-Dewar naphthalene, benzobicyclo[2.2.0]hexa-2,5-diene (**2**) (eq 2). Sodium phenanthrenide was the only reagent able to carry out the reduction used to prepare this sensitive substrate.[3,4]

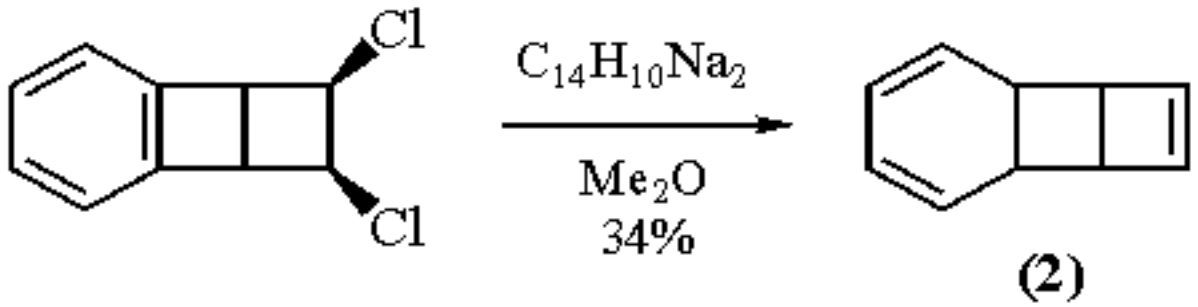

(2)

Finally, 5 mol equiv of disodium phenanthrenide reductively dechlorinates tetrachloride (**3**) to give functionalized Dewar benzene (**4**) (eq 3).[5]

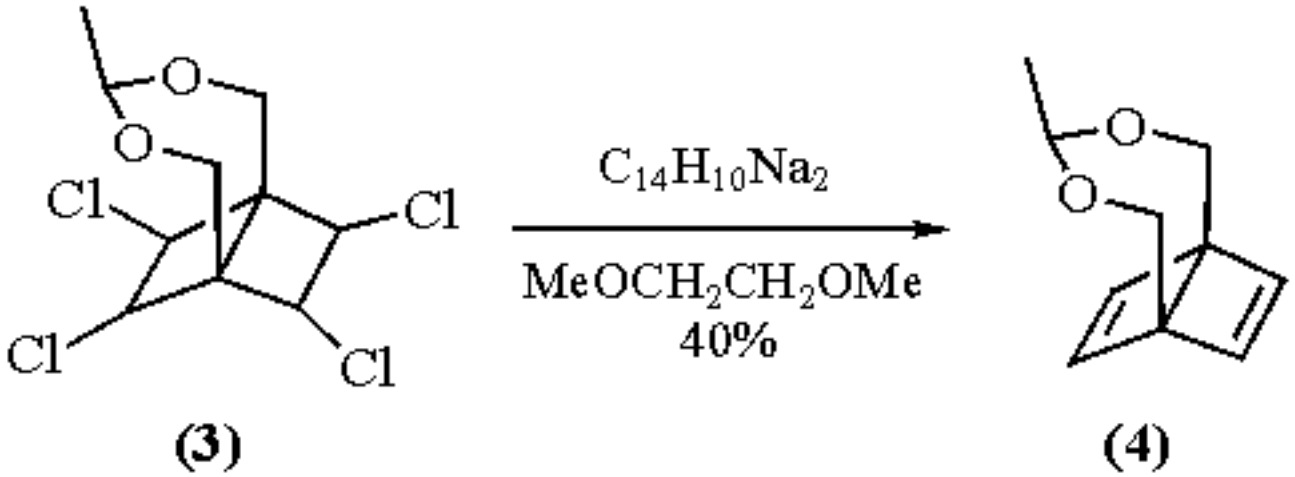

(3)

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Disodium Tetracarbonylferrate(-II)[1]

$Na_2Fe(CO)_4$

($Na_2Fe(CO)_4$)

[14878-31-0] · $C_4FeNa_2O_4$ · Disodium Tetracarbonylferrate(-II) · (MW 213.87) ($Na_2Fe(CO)_4$.1.5(1,4-dioxane))

[59733-73-2] ($K_2Fe(CO)_4$)

[16182-63-1] · $C_4FeK_2O_4$ · Dipotassium Tetracarbonylferrate(-II) · (MW 246.09) ($[Fe(CO)_4]^{2-}$)

[22321-35-3] · C_4FeO_4 · Disodium Tetracarbonylferrate(-II) · (MW 167.89)

(carbonylating agent for halides, producing aldehydes and ketones;[1] hydroacylates Michael acceptors;[2] forms cyclic ketones from β- and γ-haloalkenes;[3] selectively reduces unsaturations α to a carbonyl;[4] catalyst for dismutation of aromatic aldehydes to esters;[5] produces [(η^4-diene)$Fe(CO)_3$] complexes via nucleophilic displacement[6])

Physical Data: mp (K^+_2 salt) 270-273 °C (dec).

Solubility: sol THF, DMF, *N*-methylpyrrolidone (NMP), EtOH.

Form Supplied in: colorless to red solid; commercially available as 1:1.5 complex with 1,4-dioxane.

Preparative Methods: preparations of the sodium salt-dioxane complex[7] and of the free sodium[8] and potassium[9] salts of tetracarbonylferrate have been published.

Handling, Storage, and Precautions: $Na_2Fe(CO)_4$ is very air sensitive and is pyrophoric. The solid is stable over moderately long periods of time under inert atmosphere at rt, if kept in the dark. The potassium salt is also air sensitive but is not pyrophoric. These materials are best stored and handled in a nitrogen or argon filled dry box. Tetracarbonylferrate is considered to be a neural, renal, and hepatic toxin and is a cancer suspect agent.

Carbonylation Reactions.

The tetracarbonylferrate dianion is a potent nucleophile. Its principal use is in the functionalization of halide compounds. Although $Na_2Fe(CO)_4$ does not enjoy the widespread popularity of its main group rival, the Grignard reagent, it does

have the advantage of usually adding a carbonyl group to the substrate. Tetracarbonylferrate typically reacts readily with alkyl halides or tosylates (RX) at rt to generate $RFe(CO)_4^-$, a useful synthetic intermediate. The reaction proceeds with stereochemical inversion and is typically carried out in THF. However, more polar solvents, such as NMP, DMF, or *N*,*N*-dimethylacetamide (DMA) are often used to help decrease $Na_2Fe(CO)_4$ ion-pairing and hence accelerate the rate of reaction with less reactive substrates, such as alkyl chlorides. The formation of the alkyltetracarbonylferrate has been shown to fail on occasion, however. For example, when a β-lactam functionality is present, reductive ring opening occurs.[10] Acylferrates, $RCOFe(CO)_3L^-$ (L = CO, PPh_3), may be prepared either by reaction of $Fe(CO)_4^{2-}$ with an acid halide or, more commonly, by migratory insertion through reaction of $Fe(CO)_4^{2-}$ with RX in the presence of CO or PPh_3. The chemistry of $RCOFe(CO)_3L^-$ in many cases is similar to that of $RFe(CO)_4^-$ (eq 1), since the latter is subject to carbonyl insertion. Both produce unsymmetrical ketones upon addition of a second alkyl halide reagent.[11-13]

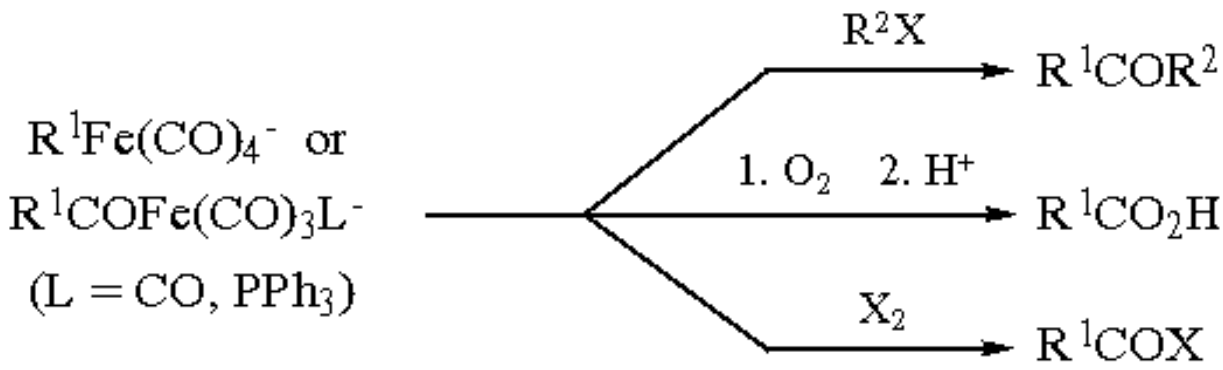

(1)

The utility of this chemistry has been enhanced (eq 2) through the use of catalytic Pd^0. Aryl iodides oxidatively add to palladium and transmetalation occurs, opening a single-step route to aryl ketones.[14] Alkyl- or acylferrates, when treated with oxygen (eq 1) followed by acidic workup, are converted to acids, allowing the overall transformation of RX to RCO_2H.[15]

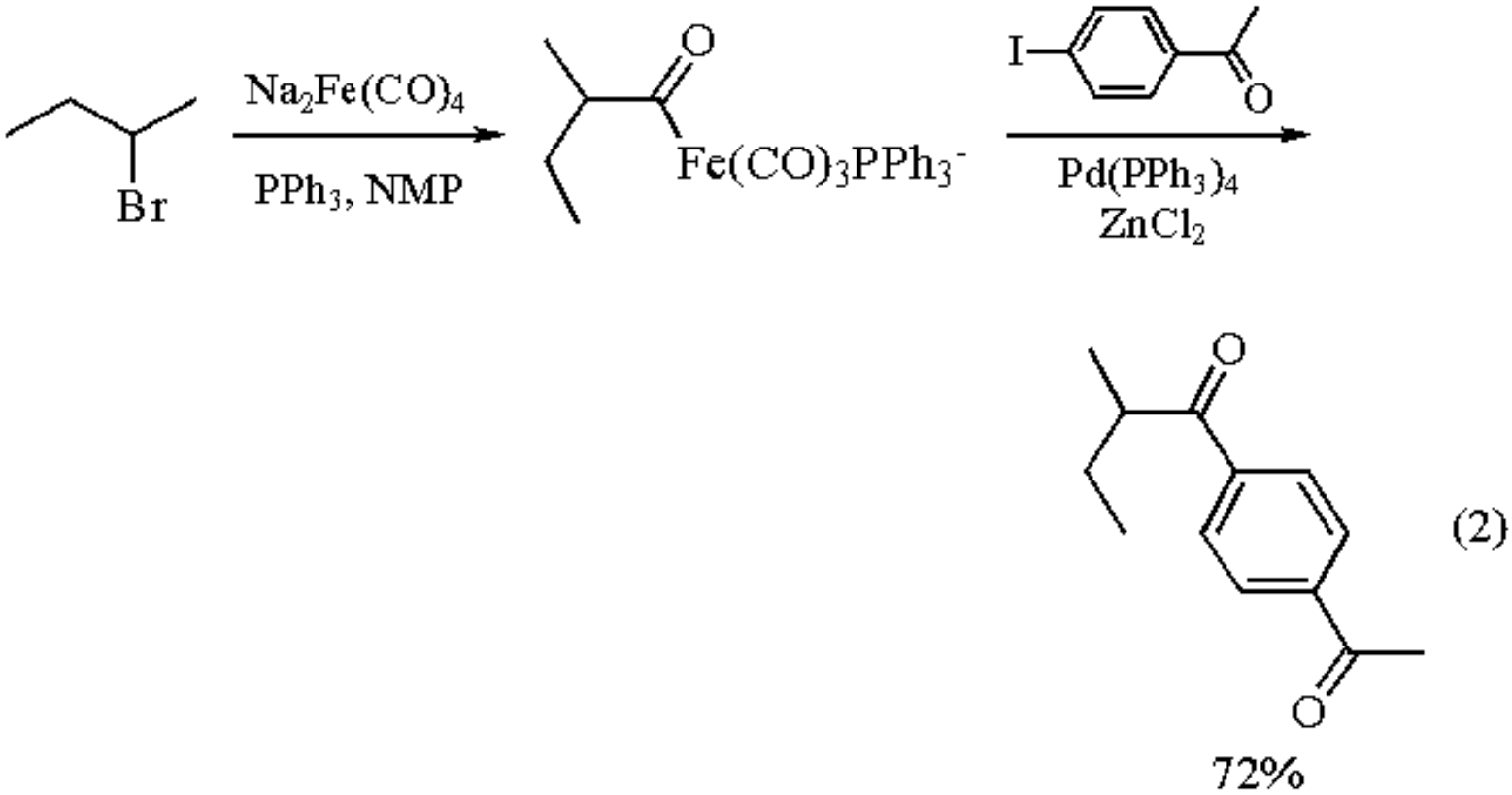

Similarly, the use of halogen gives acid halides, which are converted in situ to amides, esters, or acids. The acylferrates will react in situ with acid to produce aldehydes[12] and are subject to Cu^{I} coupling, giving symmetrical α-diketones, RCOCOR.[16] Tetracarbonylferrate may be used to produce cyclopentanones from δ-dibromides (eq 3).[17] However the formation of six- and seven-membered rings suffers from low yields.

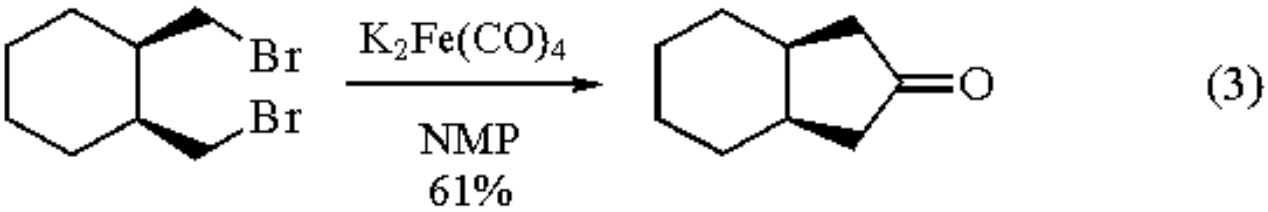

Alkyl- and acyltetracarbonylferrates are susceptible to alkene insertion reactions. This phenomenon was initially recognized through the single-step preparation of alkyl ethyl ketones from RX, ethylene, and $Fe(CO)_4^{2-}$.[18] Later, reactions between these ferrates and various Michael acceptor alkenes were uncovered.[2] Precursors to jasmone and γ-jasmolactone have been produced (eq 4). Allenes insert into $RFe(CO)_4^-$ to give [(η^4-hydroxytrimethylenemethane)$Fe(CO)_3$] complexes, which thermally rearrange to [(η^4-enone)$Fe(CO)_3$] complexes.[19] ***Ethylene Oxide*** also inserts into the iron-acyl bond in $RCOFe(CO)_4^-$, giving an unisolated β-hydroxy ketone, which dehydrates to an α,β-unsaturated ketone.[20] Yields of 60-80% are found. Cyclizations may be accomplished via alkene insertion. Cyclopentanones and cyclohexanones are produced by the tetracarbonylferrate treatment of monosubstituted alkenes bearing a β- or γ-halide.[1,3,21,22] The less hindered product prevails. 5-Bromo-1,2-pentadiene cyclizes to 2-methylcyclopenten-3-one. These cyclization reactions, which are carried out in THF with an acid workup, generally give moderate yields (30-75%); nevertheless some of the higher yields are found for the synthesis of the spirocyclic ketones which are otherwise accessible only with difficulty.

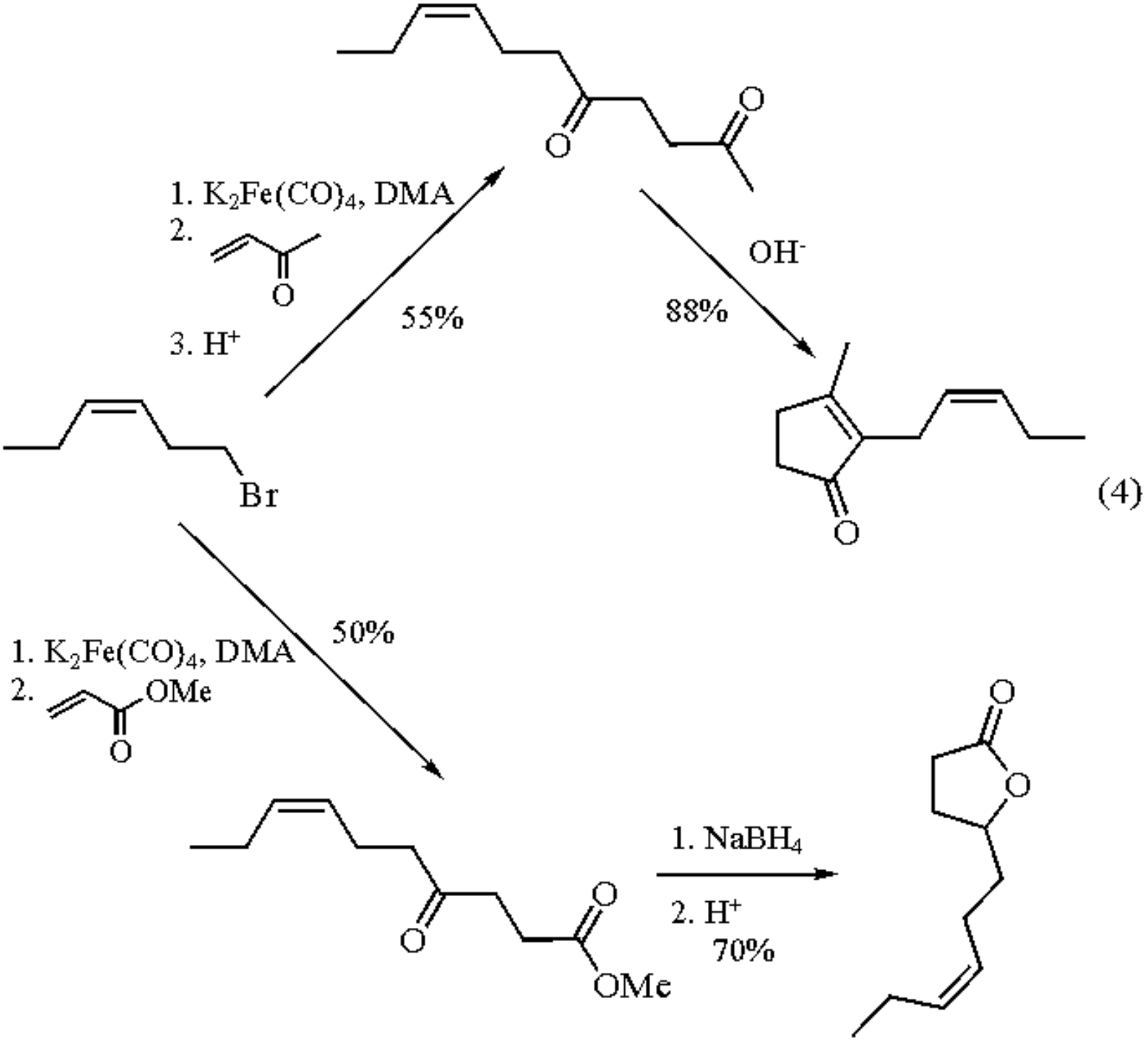

Reduction Reactions.

Tetracarbonylferrate more commonly functions as a nucleophile than as a reducing agent. Nevertheless, several valuable transformations involving selective reduction have been demonstrated. The most desirable of these allows reduction of an unsaturated group α to a carbonyl. The key step in the synthesis of 9,10-dihydroretinal (the reduction of the conjugated 9,10-alkene) was accomplished (eq 5) with the use of $Fe(CO)_4^{2-}$.[4] However, as illustrated, there is some tendency toward simultaneous reduction of the carbonyl group. The ability to reduce carbonyls mildly is exploited in the synthesis of *cis*-caronaldehyde (eq 6).[23]

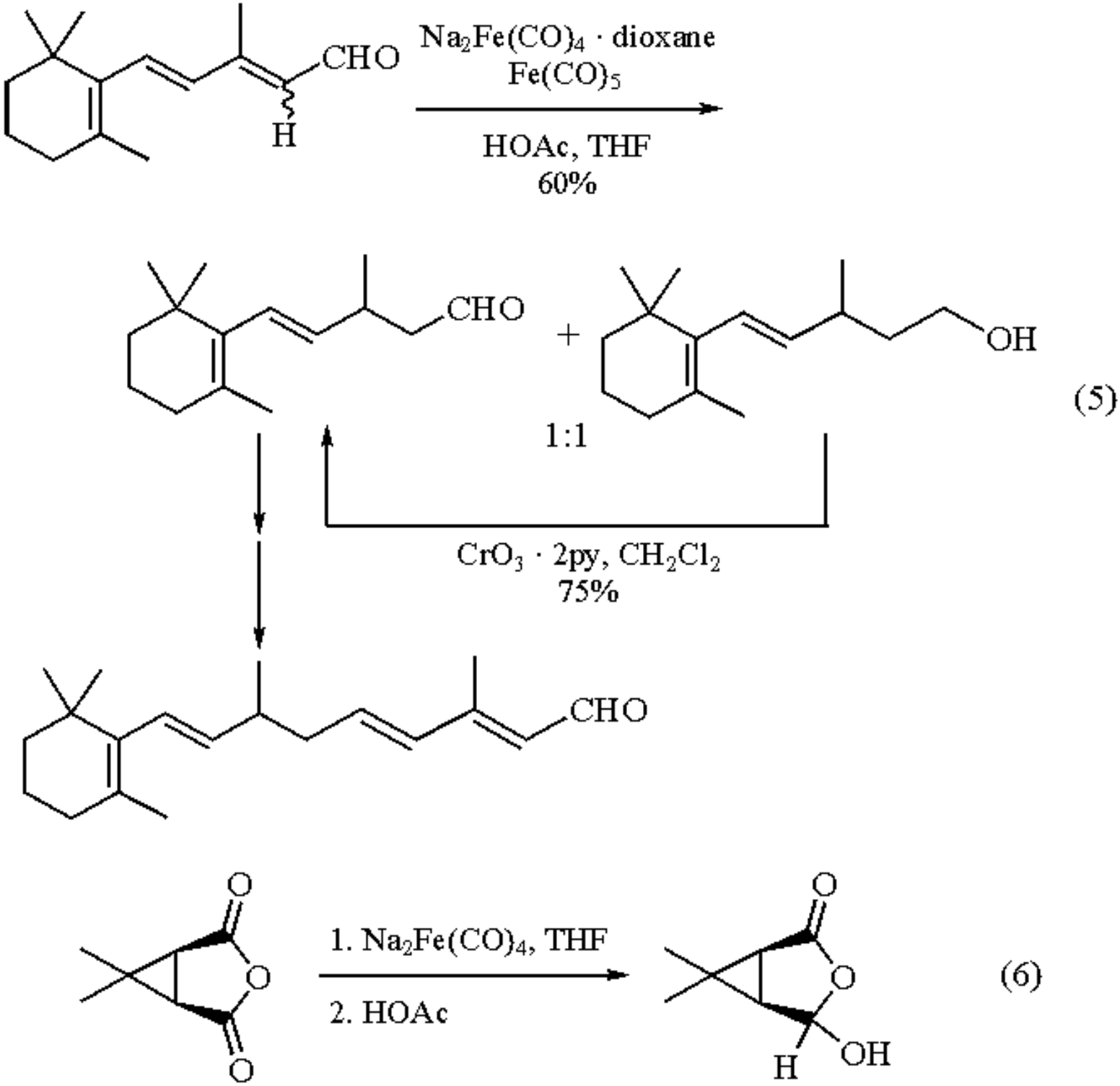

More typically acid anhydrides are reduced to aldehydes (or occasionally to acids) by $Na_2Fe(CO)_4$ in THF.[24] Intramolecular anhydrides produce aldehydic acids. Tetracarbonylferrate functions as a catalyst in the high yield dismutation of aromatic aldehydes.[5] A plausible mechanism is presented (eq 7). The complex resulting from nucleophilic attack of $Fe(CO)_4^{2-}$ on RCHO is apparently sufficiently nucleophilic itself to attack another molecule of aldehyde. The aldehyde complex can also be partially alkylated in a competitive stoichiometric process. However, this reaction does not appear to be efficient enough to be of synthetic value. Alkyl- or acyltetracarbonylferrates give reductive coupling products with nitroaromatics.[25] Upon reaction with nitrobenzene, they produce *N*-phenylamides.

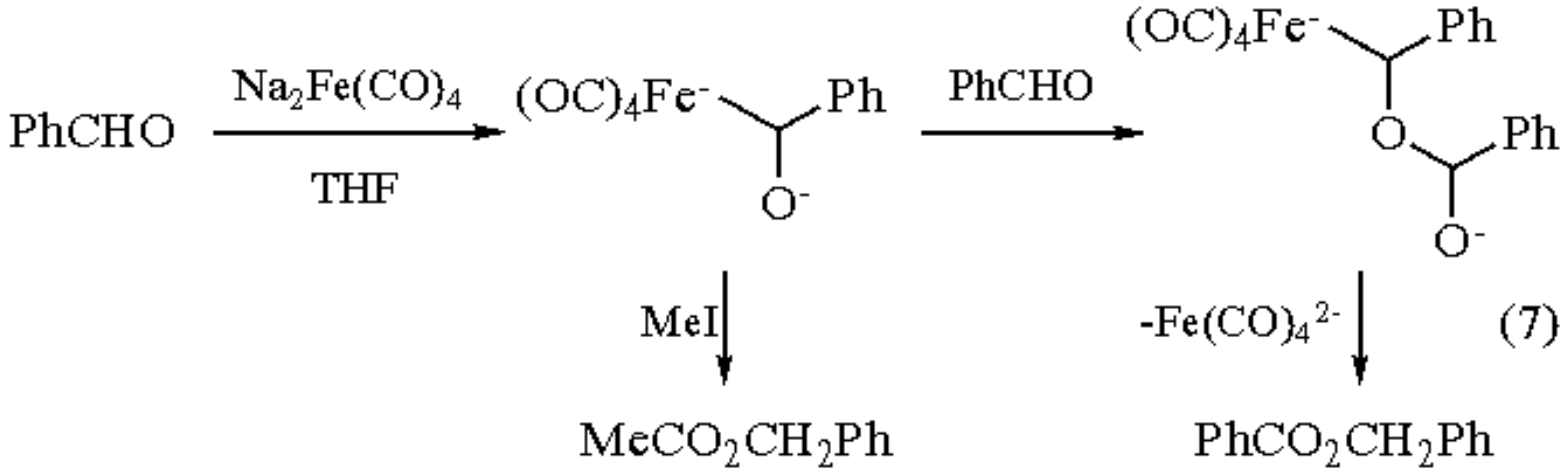

Other Nucleophilic Substitutions.

The $Fe(CO)_4^{2-}$ anion forms *S*-bound complexes with nonenolizable thioketones.[26] These can be acylated at the sulfur to produce thioesters. However, thioketones bearing enolizable protons are deprotonated by $Fe(CO)_4^{2-}$. 1,1-Cyclopropanedicarboxylates are ring opened by tetracarbonylferrate to produce stabilized carbanions (eq 8).[27] Alkylation may then be carried out at both ends of the dianion. Tetracarbonylferrate will also displace chloride from $[(\eta^6\text{-}C_6H_5Cl)Cr(CO)_3]$.[28] A variety of $[(\eta^4\text{-1,3-diene})Fe(CO)_3]$ complexes are accessible through the reaction of 1-methylallylic halides or phosphates with $K_2Fe(CO)_4$.[6] Nevertheless, the direct synthesis of these complexes from the diene and ***Pentacarbonyliron*** or ***Nonacarbonyldiiron*** remains the preferred route.

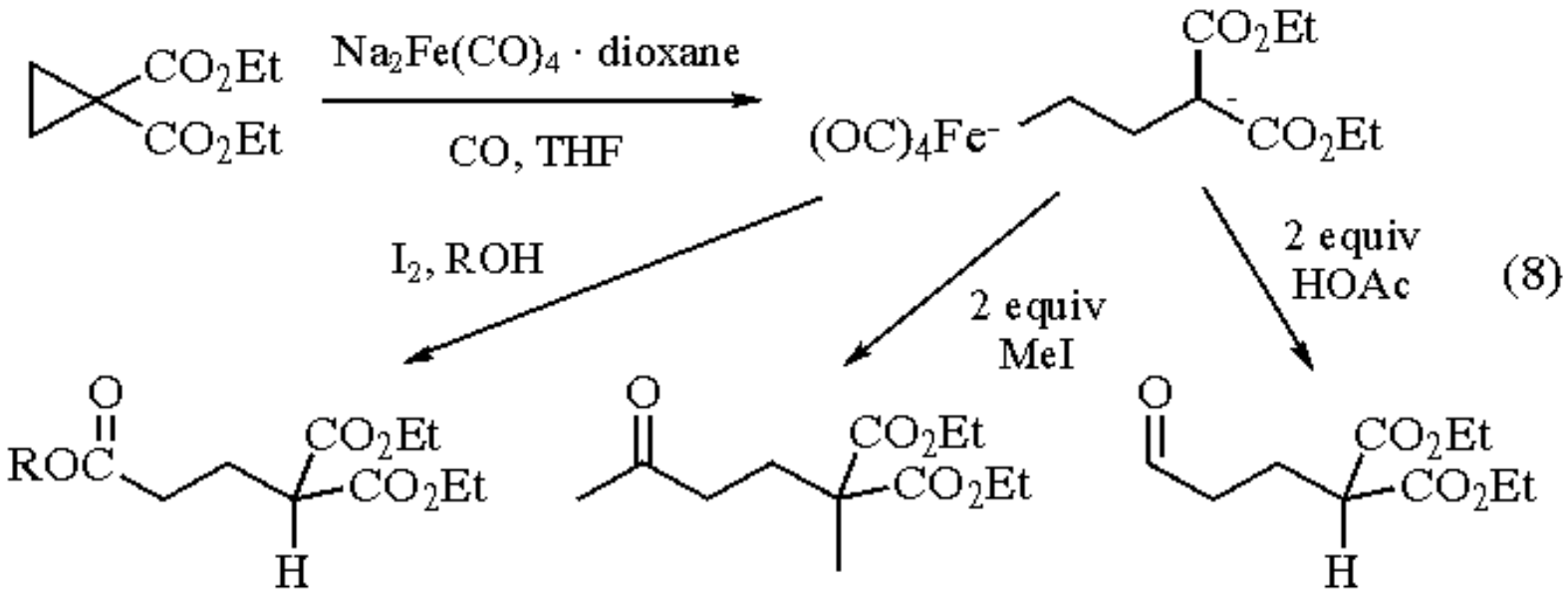

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Disodium Tetrachloropalladate(II)[1]

Na_2PdCl_4

[13820-53-6] · Cl_4Na_2Pd · Disodium Tetrachloropalladate(II) · (MW 294.20)

(can cyclopalladate aromatic and heteroaromatic compounds;[2] homogeneous catalyst for vinylation of imides and lactams;[3] homogeneous catalyst for carbonylation of allyl chlorides;[4] catalyst for oxidation of alkenes to ketones[5])

Solubility: very sol H_2O; slightly sol ethanol, acetone, acetic acid.

Form Supplied in: brown-red solid. *Drying:* at 100 °C/0.1 mmHg for 24 h.

Preparative Method: very often prepared in situ from 1 equiv of ***Palladium(II) Chloride*** and 2 equiv of ***Lithium Chloride*** in the appropriate solvent (MeOH, EtOH, $MeCO_2H$).

Handling, Storage, and Precautions: is hygroscopic and should be stored in the absence of moisture. The trihydrate is formed in aqueous solution. Toxicity data are not available.

Organopalladium Reagents.

Various aromatic and heteroaromatic compounds containing nitrogen and sulfur atoms undergo cyclopalladation upon treatment with Na_2PdCl_4 to form dimeric complexes (eq 1).[6] Similarly, oximes of α,α´-dialkyl ketones react with Na_2PdCl_4 to give five-membered ring palladacycles.[7] These complexes are readily oxidized to the β-acetoxy oximes (eq 2). Functionalized hexopyranosides can be prepared using this reaction.[8]

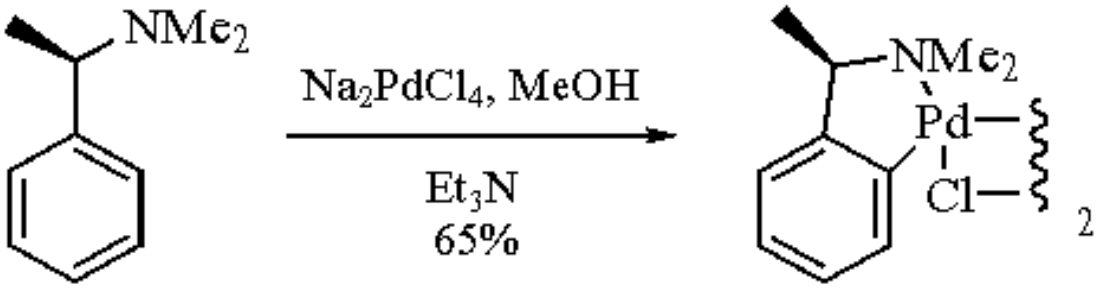

(1)

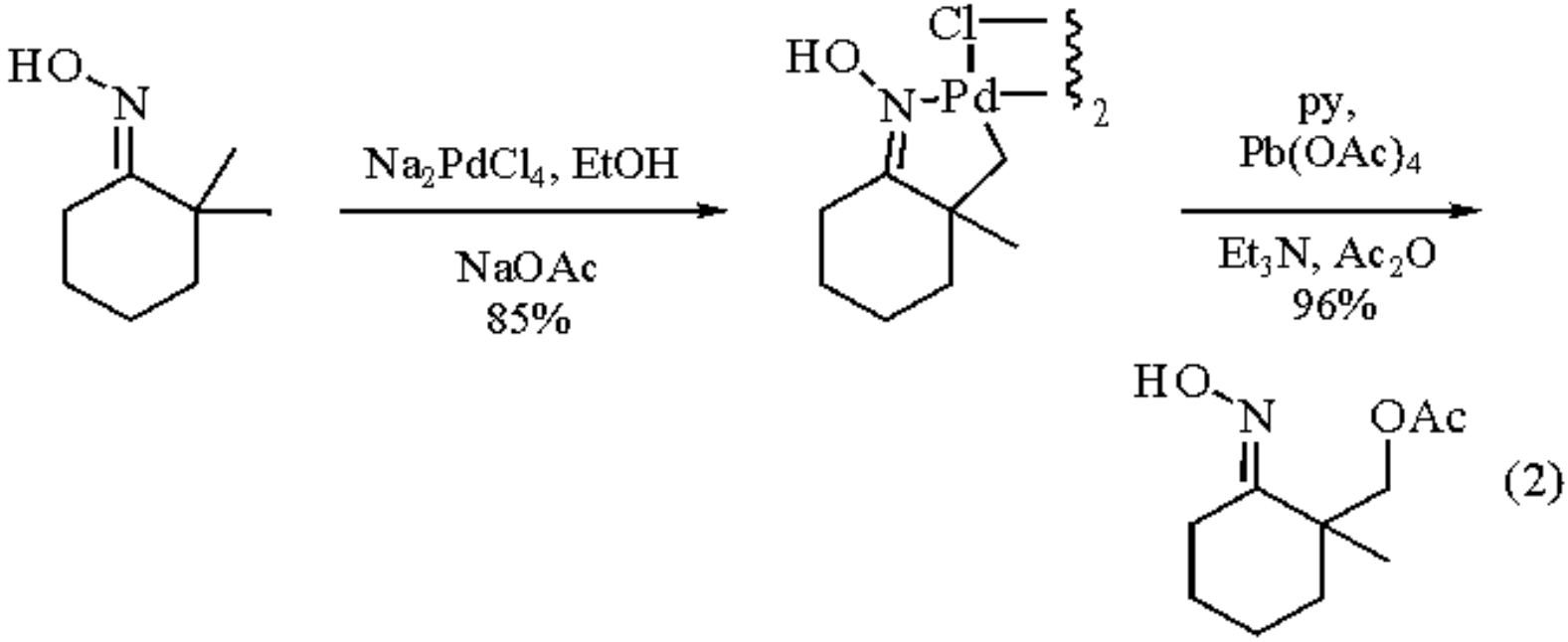

Alkenes react with Na_2PdCl_4 to give π-complexes,[9] π-allyl complexes,[10] or π-benzyl complexes,[11] depending on nature of the compound. π-Allyl complexes are readily available by coupling of arylmercurials with alkenes.[12] These complexes are electrophilic in character and react with a variety of nucleophiles.[13]

Vinylation and Carbonylation.

Imides and lactams are converted to *N*-vinyl derivatives when heated with ***Vinyl Acetate*** in the presence of Na_2PdCl_4 (eq 3).[3] Allylic halides can be carbonylated at atmospheric pressure in the presence of Na_2PdCl_4 to form either β,γ-unsaturated acids or esters (eq 4).[4] Aromatic aldehydes can be carbonylated in the presence of amines to afford α-keto amides.[14]

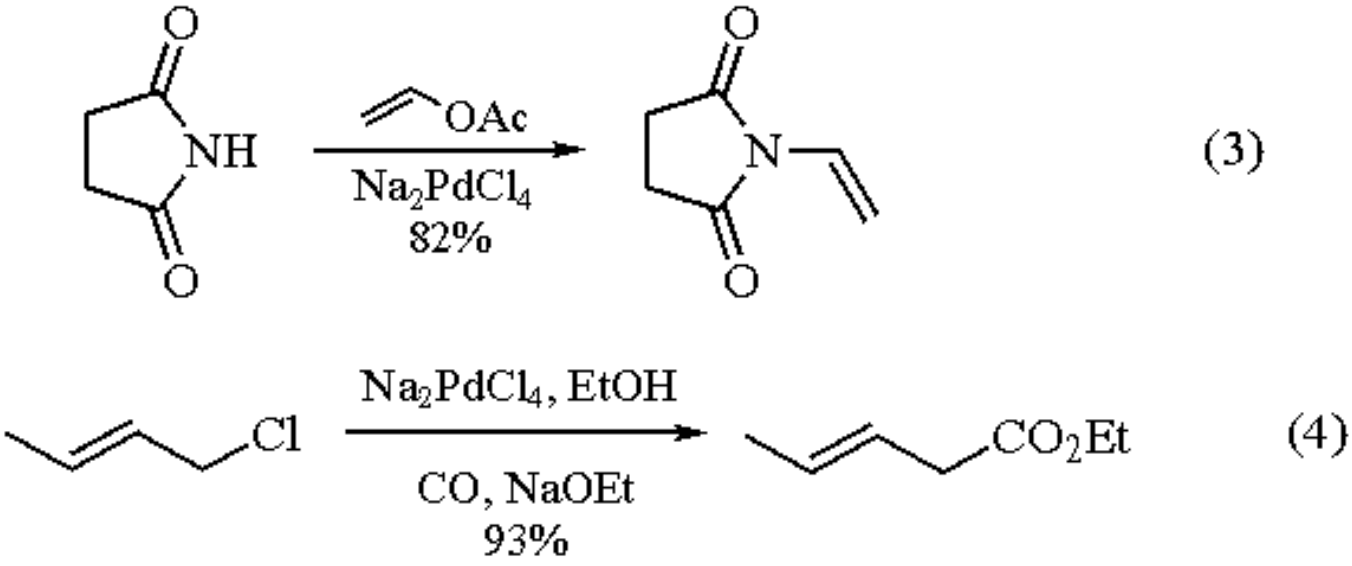

Oxidations.

Oxidations are usually with either ***t-Butyl Hydroperoxide*** or ***Hydrogen Peroxide*** in conjunction with Na_2PdCl_4 as a catalyst. Simple alkenes give mixtures of products by this method.[15] α,β-Unsaturated esters and ketones are oxidized to β-keto esters and β-diketones, respectively.[5] α,β-Unsaturated phosphonates give β-ketophosphonates (eq 5).[16]

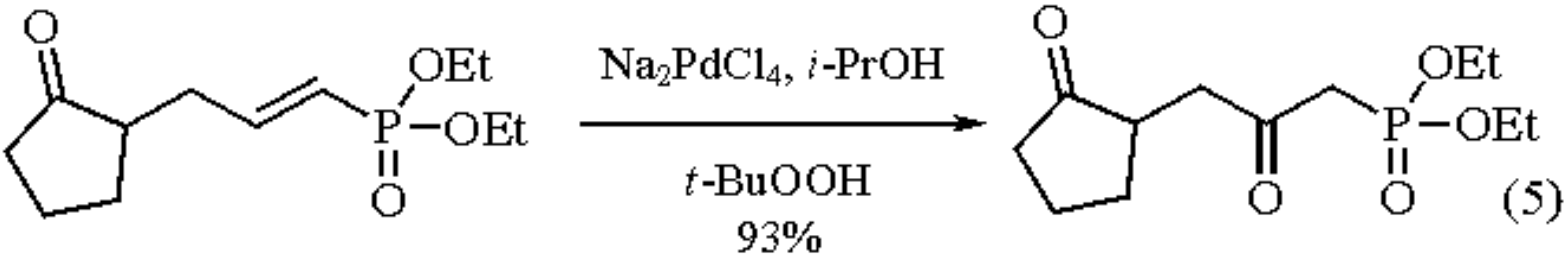

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Disodium Tetrachloroplatinate(II)[1]

Na_2PtCl_4

[10026-00-3] · Cl_4Na_2Pt · Disodium Tetrachloroplatinate(II) · (MW 382.86)

(homogeneous hydrogen isotope exchange catalyst;[2] selective oxidative functionalization of alkane C-H bonds;[3] isomerization of alkenes[4])

Solubility: sol H_2O (8 g/100 mL); slightly sol alcohol, acetone, acetic acid.

Form Supplied in: red-brown solid; available as a tetrahydrate $Na_2PtCl_4.4H_2O$. *Drying:* at 120 °C/0.1 mmHg for 24 h.

Handling, Storage, and Precautions: should be stored in the absence of moisture; irritating to skin, eyes, and respiratory organs; corrosive.

Hydrogen Isotope Exchange Catalyst.

Aromatic and aliphatic compounds undergo exchange of isotopic hydrogen with a catalytic amount of this reagent (see also ***Dipotassium Tetrachloroplatinate(II)***). This system is valuable for labeling compounds with deuterium and/or tritium in one step and constitutes the homogeneous equivalent of the well-known heterogeneous platinum technique. A wide range of compounds, including benzene and substituted benzenes,[5] polyphenyls,[6] polycyclic hydrocarbons,[7] and some steroids[8] undergo D and/or T exchange. Deuteration in the side chain of long-chain alkylbenzenes occurs predominately at the benzylic and the terminal carbons.[9] Aromatics are generally quite reactive, whereas aliphatics such as cyclohexane exchange very slowly.[10] Nitrobenzene has similar reactivity to toluene[11] and bromobenzene.[12] Exchange usually occurs only in the sterically unhindered *meta* and *para* positions (eq 1).[11] Aromatic α-hydroxy acids undergo oxidative decarboxylation during the Na_2PtCl_4-catalyzed homogeneous deuteration (eq 2).[13]

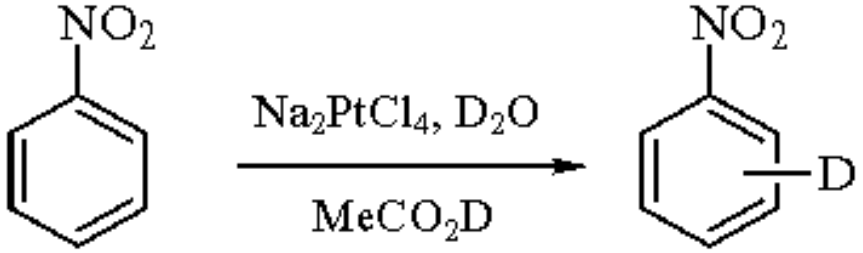

(1)

deuterium distribution (% per H) *ortho*, 12.5; *meta*, *para*, 82.7

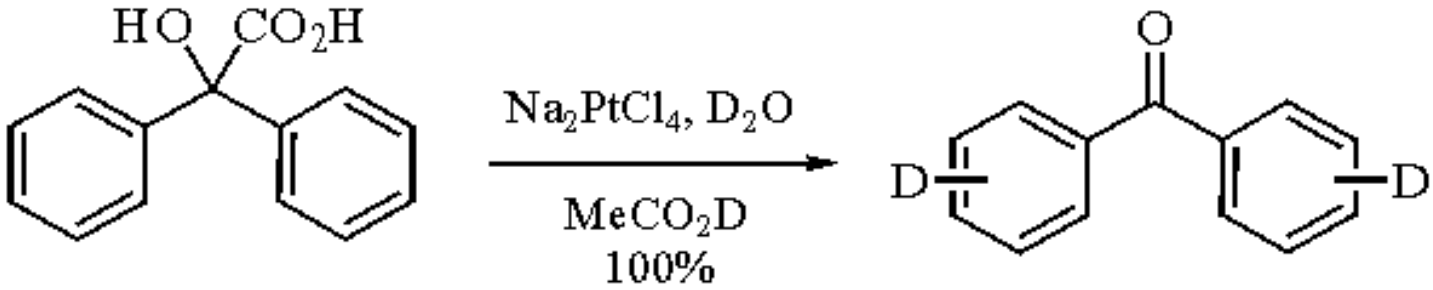

(2)

23.1% D incorporation

Functionalization of Saturated Hydrocarbons.

Na_2PtCl_4 or the combination Na_2PtCl_4/Na_2PtCl_6 in aqueous solution can be used to functionalize saturated hydrocarbons (see also ***Dipotassium Tetrachloroplatinate(II)***). Unusual and often very high selectivity is observed for oxidation at what are more commonly the least reactive positions. The products from oxidation of alkanes are mainly alcohols together with chloroalkanes, ethers, and acids. Ethanol can be selectively converted to ethylene glycol.[14] The methyl group of *p*-toluenesulfonic acid is selectively oxidized to the corresponding alcohol and aldehyde.[15] In spite of the simplicity of these systems, there is little recent work on them that shows promise for the development of preparative-scale processes.

Alkene Isomerization.

α,β-Unsaturated ketones can be isomerized to β,γ-unsaturated ketones through the formation of a π-complex with Na_2PtCl_4 (eq 3).[4] Analogous reaction with Na_2PdCl_4 gives a stable π-allyl complex (eq 4) (see ***Disodium Tetrachloropalladate(II)***).[16]

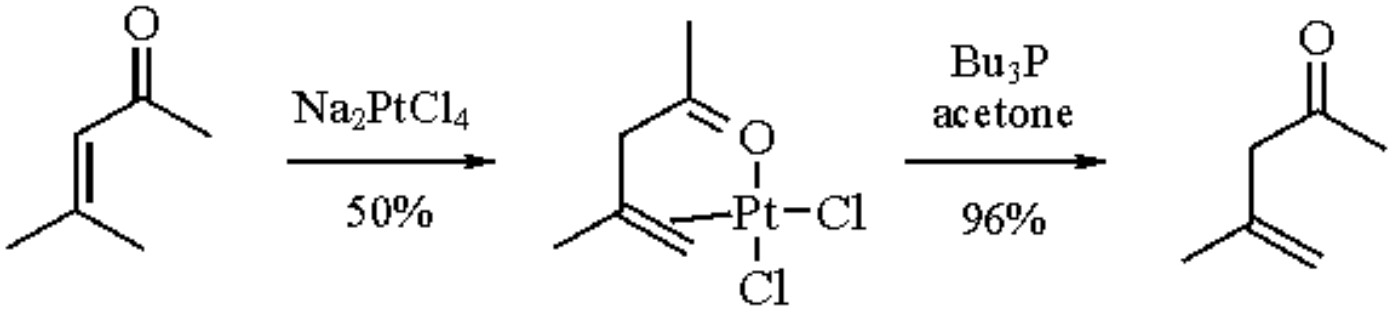

(3)

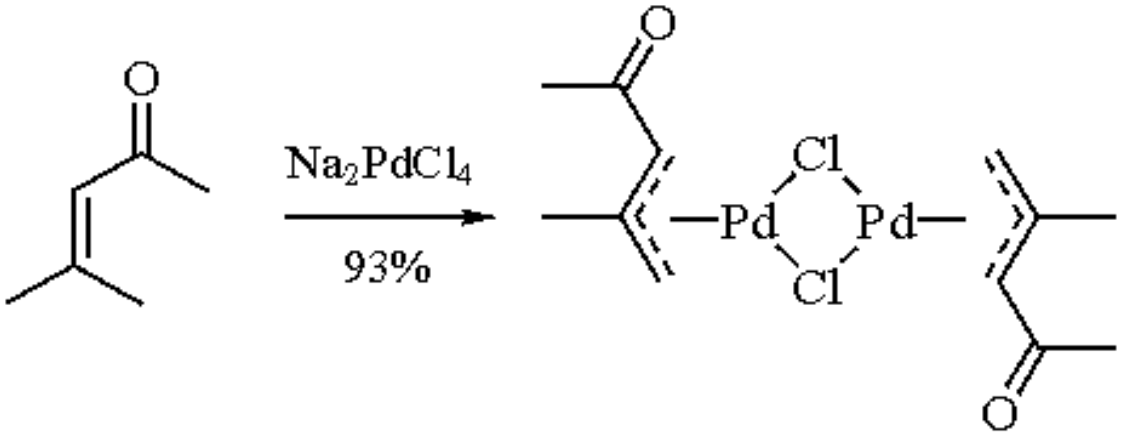

(4)

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Disodium Tetracyanonickelate(II)

$Na_2Ni(CN)_4$

[14038-85-8] · $C_4N_4Na_2Ni$ · Disodium Tetracyanonickelate(II) · (MW 208.75)

(catalyst for hydrocyanation of alkynes[1])

Physical Data: yellow solid.

Solubility: sol water, ethylene glycol.

Preparative Method: prepared by first precipitating and isolating nickel dicyanide from an aqueous nickel nitrate solution,[2] followed by dissolution with a stoichiometric quantity of aqueous sodium cyanide.[3] Yellow needle-like crystals of disodium tetracyanonickelate crystallize from water with three molecules of water of recrystallization. Anhydrous material can be prepared by drying at 100 °C.

Handling, Storage, and Precautions: cyanides are highly toxic and appropriate precautions should be taken.

Catalytic Hydrocyanation of Alkynes.

Treatment of alkynes with catalytic amounts of $Na_2Ni(CN)_4$ along with excess cyanide ion (in the form of ***Potassium Cyanide***) and either ***Sodium Borohydride*** (in ethylene glycol) or ***Zinc*** (in water) as the reducing agent leads to saturated secondary nitriles. The advantages of using this reagent is that it avoids the use of toxic HCN and can be performed under mild conditions (45 °C). Terminal alkynes give exclusively secondary nitriles in good yields (eq 1), while internal alkynes lead to mixtures of products (eq 2).[1]

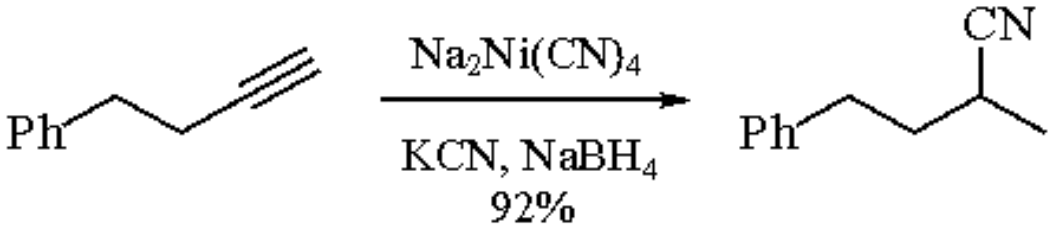

(1)

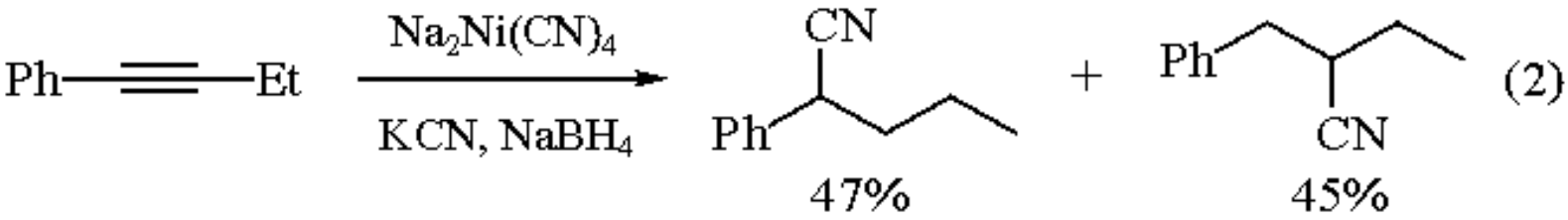

Aromatic nitriles can also be prepared from aromatic amines by initial conversion to the corresponding diazonium tetrafluoroborates, followed by treatment with $Na_2Ni(CN)_4$ in the presence of ***Sodium Carbonate*** or sodium phosphate at a pH of around 10 (eq 3).[4]

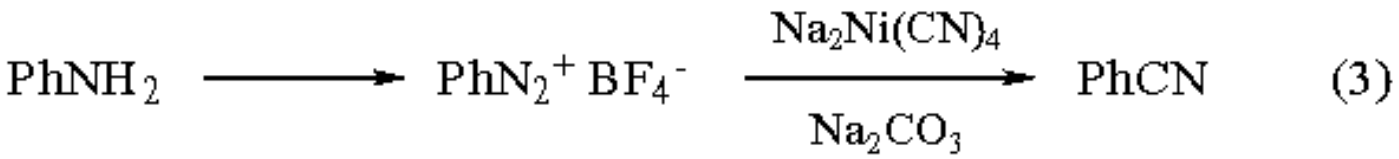

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N,N´-Disuccinimidyl Carbonate

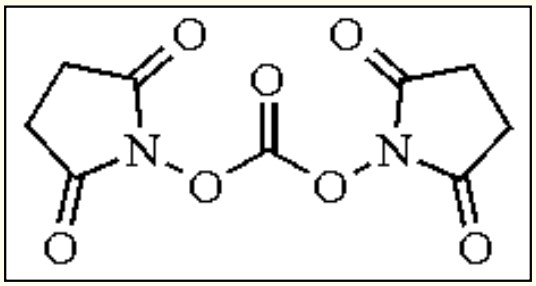

[74124-79-1] · $C_9H_8N_2O_7$ · *N,N´*-Disuccinimidyl Carbonate · (MW 256.19)

(reagent for the preparation of (active) esters in peptide chemistry;[1] β-eliminations[2] and carbonyl insertions in heterocyclic and especially peptide chemistry;[3] useful in preparation of some carbamates, ureas, and nitrosoureas[4])

Alternate Name: DSC.

Physical Data: mp 211-215 °C (dec); prisms.[5]

Form Supplied in: white to off-white powder.

Preparative Methods: by treatment of ***N-Hydroxysuccinimide*** (HOSu) with ***Trichloromethyl Chloroformate*** (TCF, $Cl_3COCOCl$) or using trimethylsilylated *N*-hydroxysuccinimide and phosgene, both giving DSC in good yield (eq 1).[1]

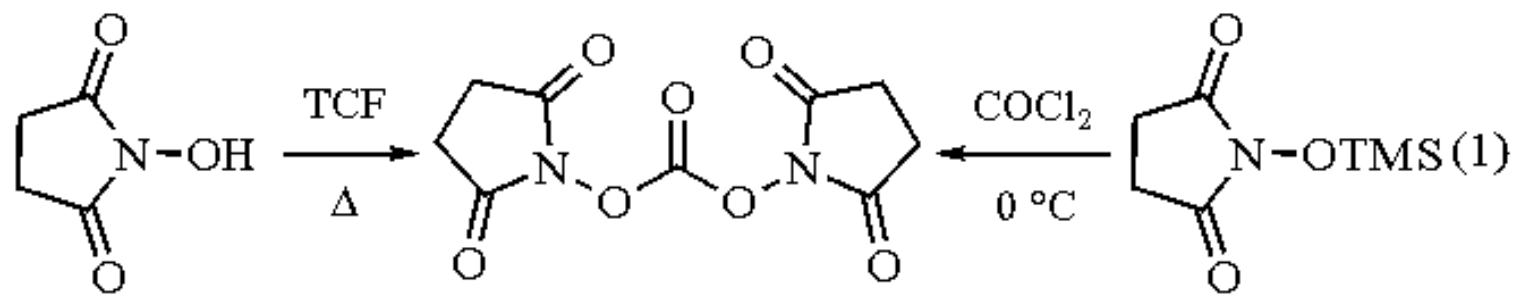

Handling, Storage, and Precautions: moisture sensitive; stable under refrigeration; irritant.

Active Ester Preparation in Peptide Chemistry.

Eq 2 shows the method for activating acids for subsequent reaction with amines, to give peptide bonds.[1]

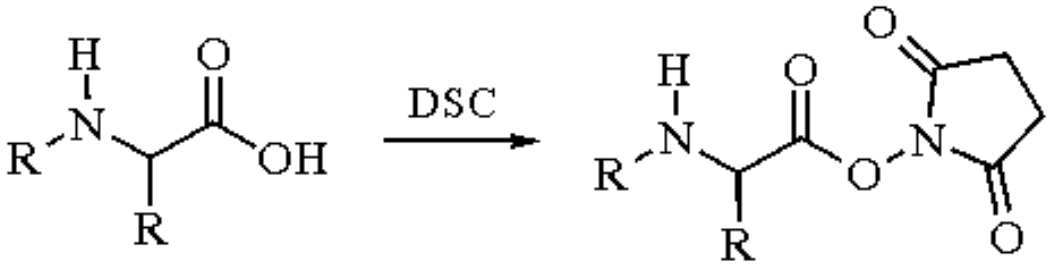

(2)

Di(N-succinimidyl) Oxalate (DSO) has also been used as an alternative to DSC in the preparation of esters.[8]

Carbamate Preparation.

DSC reacts with primary and secondary amines to give carbamates (eq 3),[4] in which the carbonyl group is activated by the electron withdrawal of the succinimidyl group. Further attack by the amino groups on the carbonyl of such active carbamates gives ureas. Such carbamates produced by DSC have been used in the preparation of chiral derivatizing agents for amino compounds[6] and in the preparation of nucleoside analogs.[7]

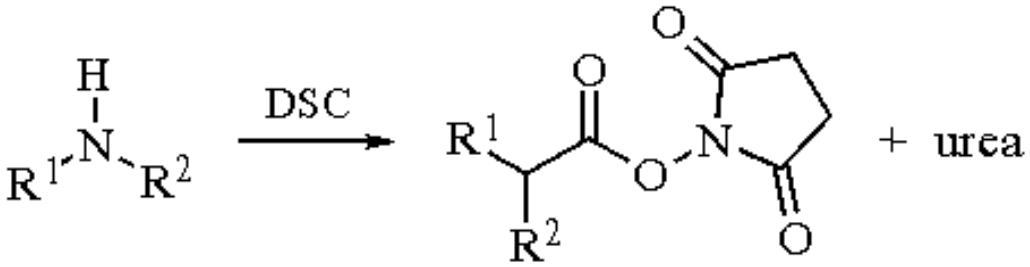

(3)

β-Eliminations.

β-Elimination of the hydroxy group of *N*-protected β-hydroxy-α-amino acids has been effected using DSC and ***Triethylamine***.[2] Reaction of Z-threonine with equimolar DSC/Et_3N in acetonitrile gave exclusively the (*Z*)-isomer of Z-DBut-OMe (eq 4). Similarly, use of a 1:2 molar ratio of DSC gave the (*Z*)-isomer of Boc-DBut-OSuc, which on treatment with the methyl ester of alanine gave Z-DBut-Ala-OMe (eq 5).

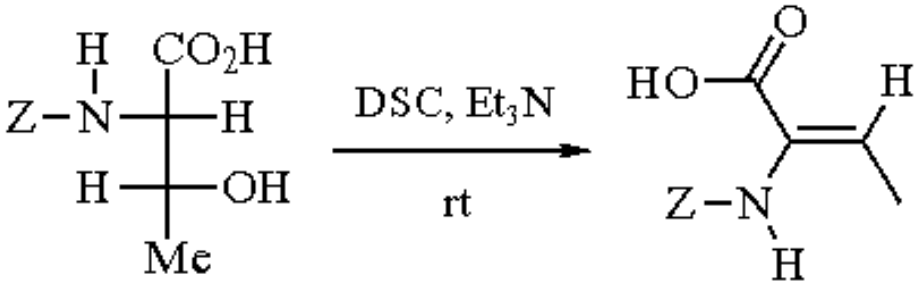

(4)

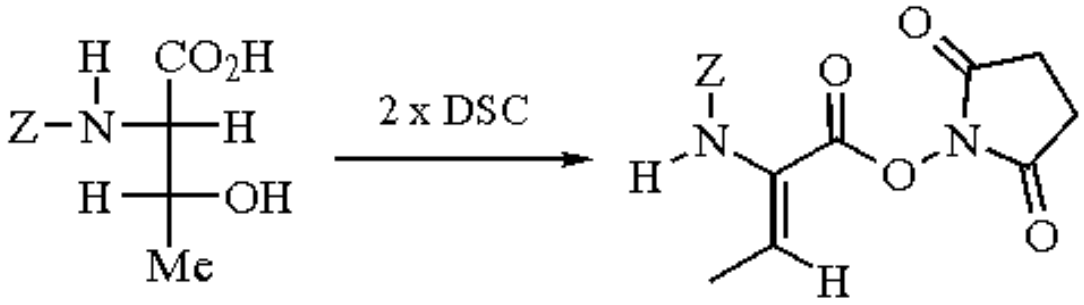

(5)

Carbonyl Insertions.

DSC has been used as a replacement for ***Phosgene*** in the cyclization of *N*-aralkyl α-amino acids to *N*-carboxyanhydrides (eq 6).[9] This method releases *N*-hydroxysuccinimide as a byproduct, which is only weakly acidic and so does not affect any acid sensitive groups, whereas phosgene releases 2 equiv of hydrogen chloride. Unlike in ester formation using carboxylates, where the central carbonyl group of DSC is released as CO_2, with better nucleophiles, such as secondary α-amino functions, incorporation of the carbonyl group occurs. This is assumed to be by *N*-substitution by R-CO-, followed by intramolecular anhydride formation by tertiary amine. Similar carbonyl insertions by ***N,N´-Carbonyldiimidazole*** (CDI) to give heterocycles[10,11] leads to racemization. Use of DSC as a carbonyl insertion reagent has led to its use in the preparation of ureas and various heterocycles.[3] Reaction with amines (to give ureas), 1,2-diamines (to give cyclic ureas), 1,2-aminothiols (to give cyclic thiocarbamates), and 1,2-hydroxyamines have all been observed. One simple example is the action of DSC on cyclohexylamine to give dicyclohexylurea. A series of (thio)carbamates used as muscle relaxants have also been prepared, e.g. chloroxazone (5-chloro-2-hydroxybenzoxazole) (eq 7). 3-(Benzoxazolyl, benzimidazolyl)pyrazole derivatives have also been made using DSC in MeCN.

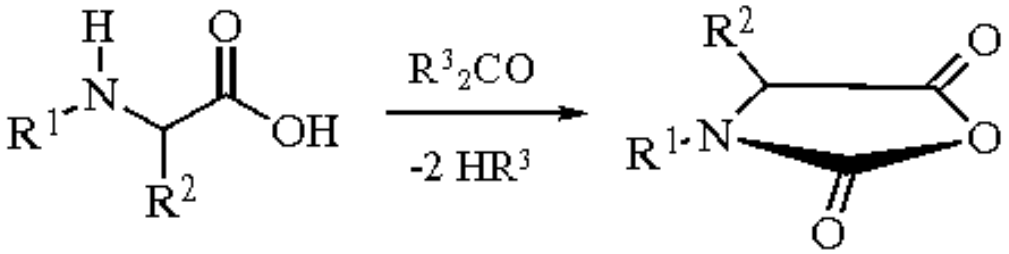

(6)

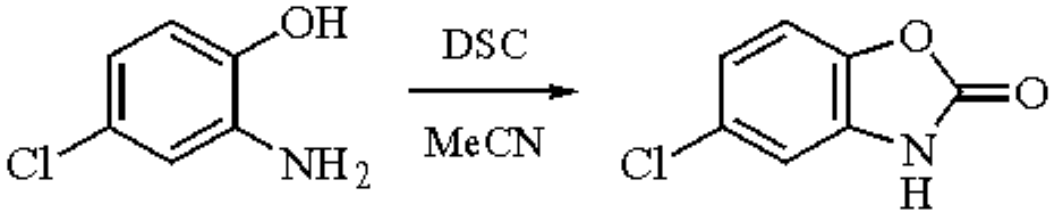

(7)

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Di(*N*-succinimidyl) Oxalate

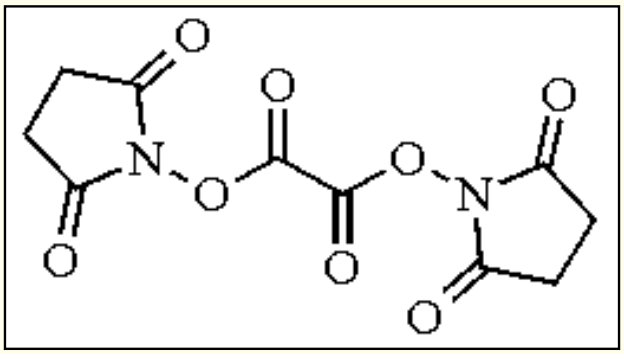

[57296-03-4] · $C_{10}H_8N_2O_8$ · Di(*N*-succinimidyl) Oxalate · (MW 284.20)

(forms active ester with *N*-protected amino acids for peptide synthesis,[1] succinimide/glutarimide synthesis,[7] as activated carriers for analysis, enzyme immobilization, and chromatographic chiral stationary phases preparation;[8] curing agent in photographic sensitive materials[9])

Alternate Name: DSO.

Physical Data: mp 245-247 °C (dec).

Solubility: acetonitrile (5 g/100 mL suspension).

Form Supplied in: solid; 85-98%+, dependent on supplier.

Handling, Storage, and Precautions: moisture sensitive; irritating to eyes, respiratory system, and skin; harmful by inhalation, in contact with skin, and if swallowed.

Peptide Synthesis.[1]

Unlike ***N-Hydroxysuccinimide***, *N*-protected amino acids can be reacted directly with DSO to produce an ester and either gaseous or water-soluble byproducts. The ester can then be used to form peptides (Scheme 1).

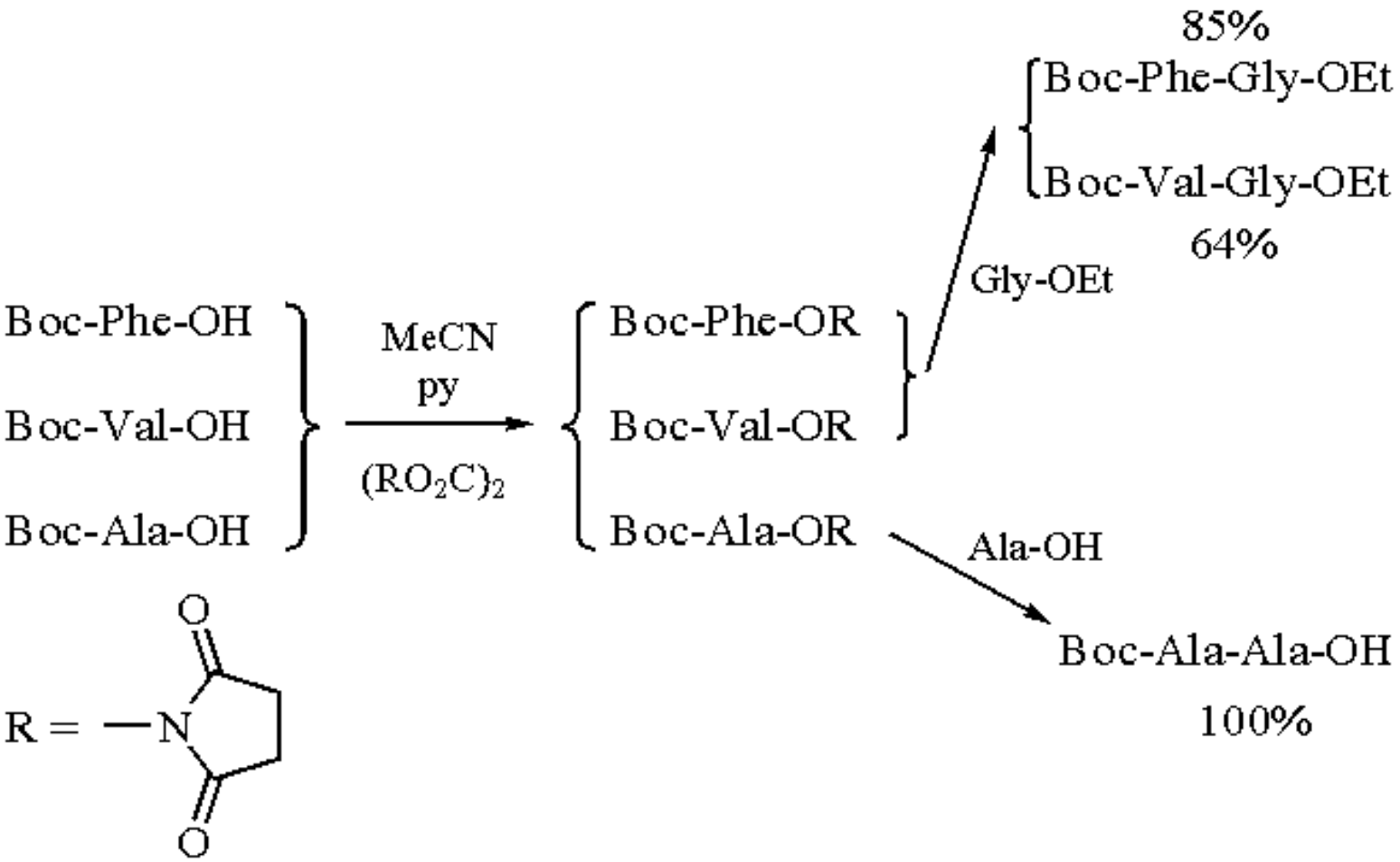

Scheme 1

This reagent is part of a family of oxalates, all of which give similarly high yields.[1] They are more convenient than the standard ***1,3-Dicyclohexylcarbodiimide*** coupling method for active ester and peptide syntheses. They are also more economical than the related compounds ***N,N´-Disuccinimidyl Carbonate***[2] and *N*-succinimidyl diphenyl phosphate,[3] which have been used previously as active ester and peptide synthesis reagents.

Succinimide and Glutarimide Synthesis.

Conventional glutarimide syntheses proceed via the dehydration of either glutaric acids[4] or ammonium glutarates,[5] or by the pyrolysis of bisglutarimides.[6] All these methods give poor yields (10-40%), although corresponding succinimide syntheses do work better.[7] The use of DSO, however, provides a more general route to these and other cyclic systems and the yields are typically around 80% (eq 1).[7]

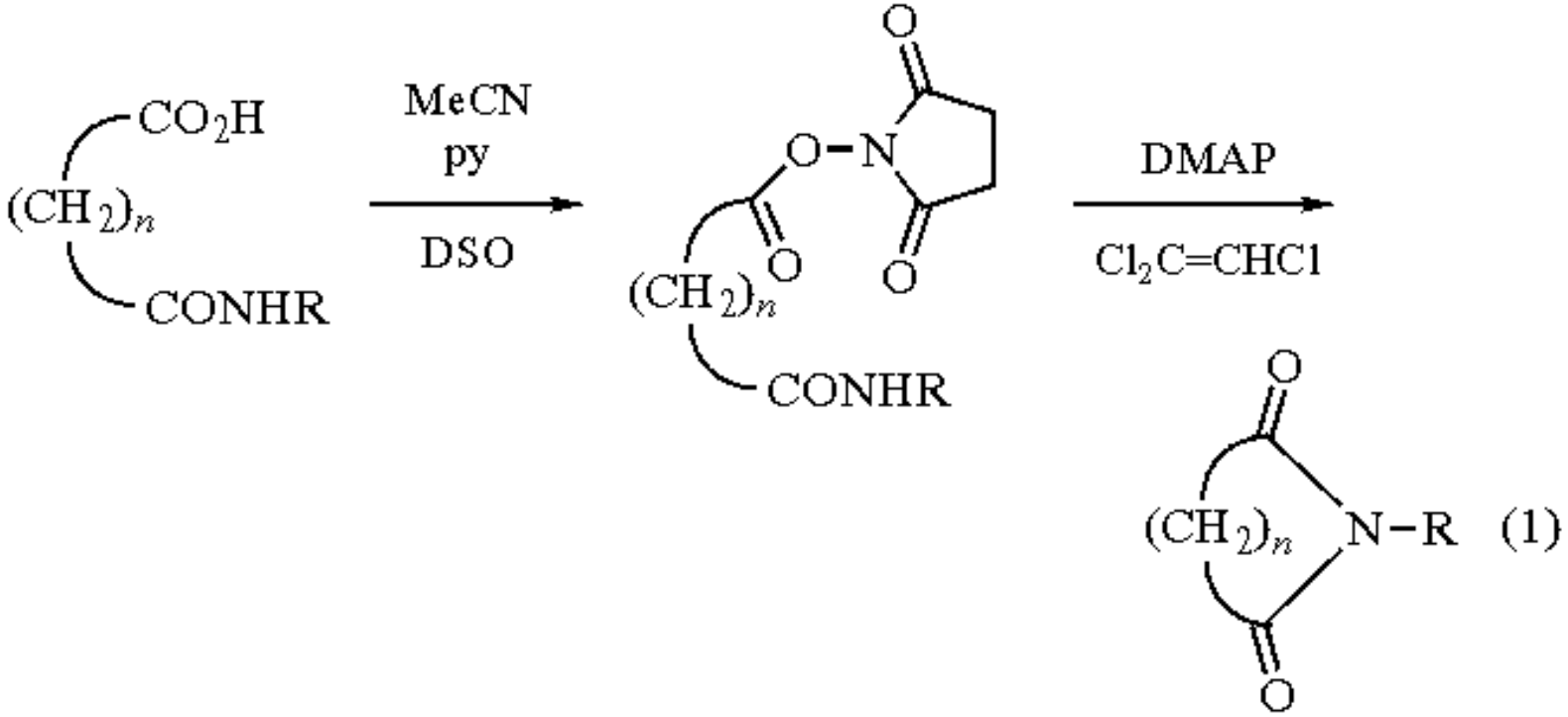

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Disulfur Dichloride

ClS-SCl

[10025-67-9] · Cl_2S_2 · Disulfur Dichloride · (MW 135.04)

(synthesis of thioketones and thioaldehydes from hydrazones;[1] synthesis of dithiazoles[2] and episulfides[3])

Alternate Name: sulfur monochloride.

Physical Data: mp -77 °C; bp 138 °C; *d* 1.688 g cm^{-3}; n_D^{20} 1.6700.

Solubility: sol benzene, ether; readily sol CS_2.

Form Supplied in: golden yellow, oily liquid; pungent odor; fumes in moist air; impure sample can be reddish orange due to SCl_2; commercially available.

Purification: distillation of 500 g from 20 g of sulfur and 5 g of charcoal; fraction from 135 to 137 °C is collected.

Handling, Storage, and Precautions: refrigerate in dark bottle; air and moisture sensitive; incompatible with acids, bases, alcohols, and amines. Avoid contact with metals; harmful if swallowed; inhalation may be fatal. Use in a fume hood.

Synthesis of Thioketones and Thioaldehydes.

Based on the resulting tautomers from a synthesis of hindered *N*-thiosulfinylanilines (Ar-N=S=S) from anilines (eq 1),[4] a synthesis for thioketones and thioaldehydes has been worked out from hydrazone derivatives and S_2Cl_2.[5]

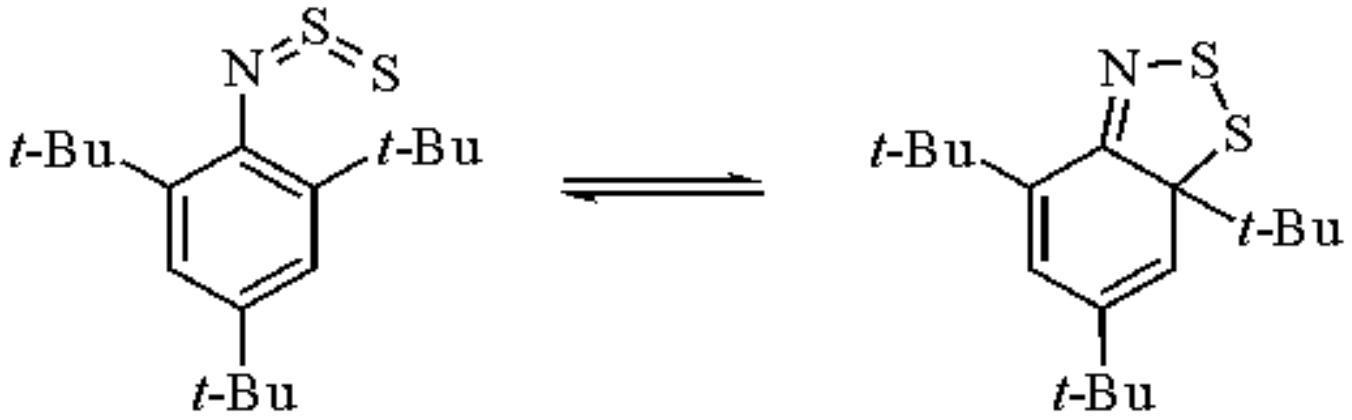

(1)

Hydrazone derivatives are treated with S_2Cl_2 to produce an *N*-thiosulfinylamine which undergoes cyclization, followed by molecular extrusion of N_2 (g) to give an *S*-thioxothioketone. The *S*-thioxothioketones ($R_2C{=}S{=}S$) are not isolable, as they decompose to the thioketones and sulfur (eq 2).[2,6] The yield of 2,2,4,4-tetramethylthiopentanone is the isolated yield; spectra showed near quantitative conversion.

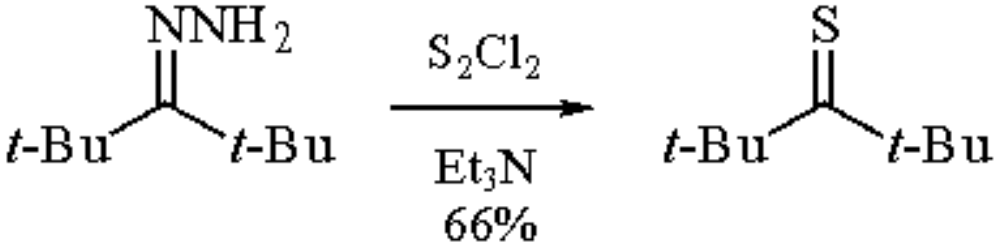

(2)

2,4,6-Tri-*t*-butylthiobenzaldehyde was the first stable thiobenzaldehyde synthesized. It was prepared from the corresponding hydrazone in 40% yield using S_2Cl_2 in the presence of ***Triethylamine*** (eq 3). In the absence of oxygen, no decomposition was observed after 1 year at rt in the solid phase. In the presence of air, it is quantitatively converted to 2,4,6-tri-*t*-butylbenzaldehyde.[7]

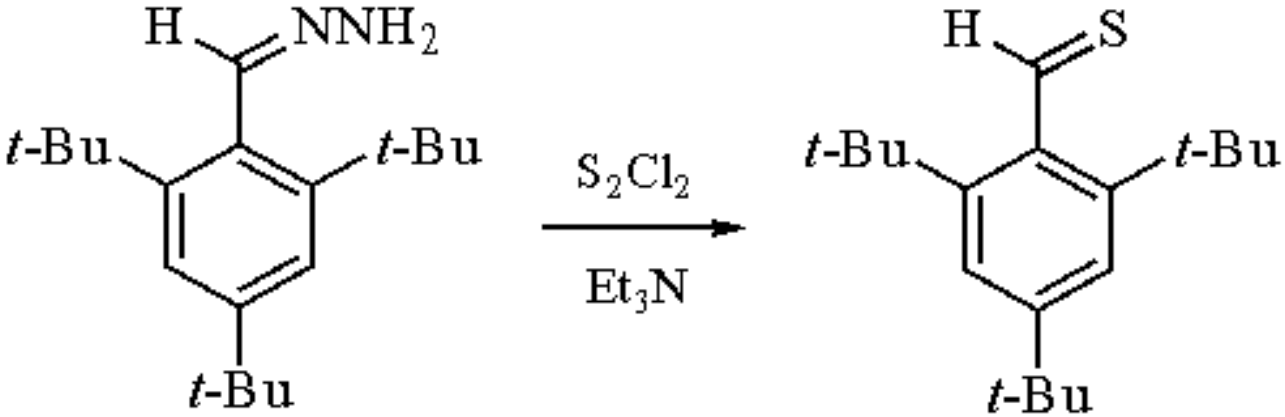

(3)

Synthesis of Dithiazoles.

Treatment of unsaturated oxime derivatives with disulfur dichloride in the presence of Hünig's base gives high yields of cyclopenta-1,2,3-dithiazoles (eq 4).[3] Treatment of saturated oximes such as cyclopentanone oxime gives unsaturated, perchlorinated dithiazoles (eq 5) in significantly reduced yield.

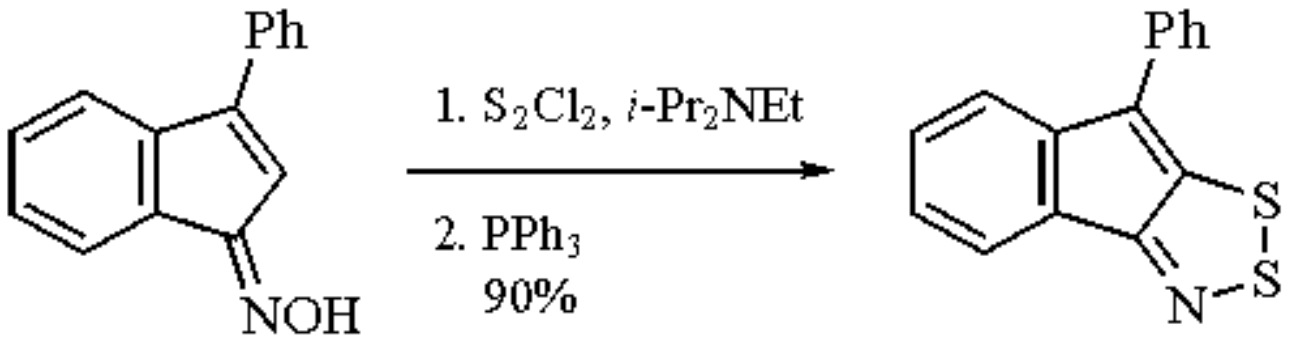

(4)

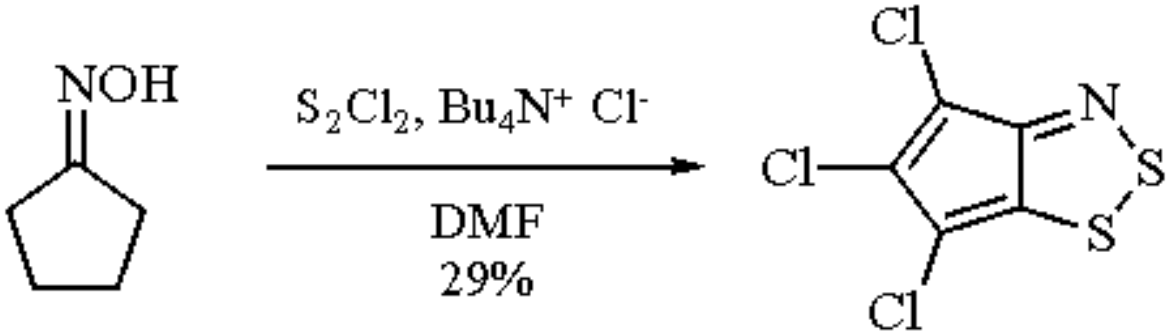

(5)

Episulfides from Alkenes.

Disulfur dichloride adds to alkenes to form β-chloroalkyl mono-, di-, and trisulfides. The monosulfides, however, cannot be converted into episulfides. Their production is minimized by the addition of dichloropolysulfanes, S_xCl_2. The β-chloroalkyl sulfides are then reduced with ***Aluminum Amalgam*** or ***Sodium Sulfide*** to the episulfide (eq 6).[3b]

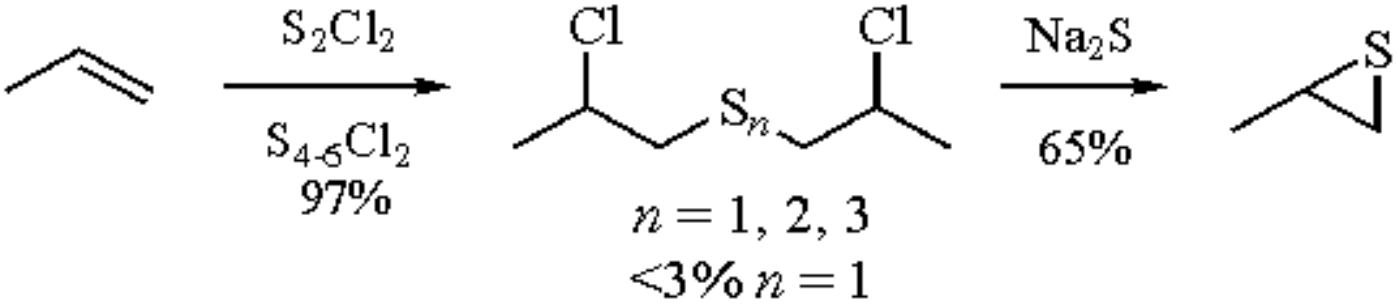

(6)

Miscellaneous.

Disulfur dichloride can also be used to synthesize *N*,*N*-dithiobissulfoximines,[7] to synthesize macrocyclic, polysulfur compounds,[8] and is part of an extremely powerful chlorinating agent for perchlorination of

aromatic systems (see also ***Aluminum Chloride*** and ***Sulfuryl Chloride***).[9] It is also a reagent for the synthesis of aranotins, a small group of sulfur-bridged diketopiperazines,[10] and it was tried in conjunction with sulfur dichloride for one-step episulfide synthesis.[11]

---

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1,3-Dithiane[1]

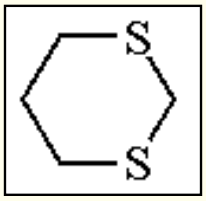

[505-23-7] · $C_4H_8S_2$ · 1,3-Dithiane · (MW 120.26)

(functional group equivalent; umpolung; C-C bond formation)

Physical Data: mp 53-54 °C; fp 90 °C; bp 207-208 °C/760 mmHg, 60-62 °C/12 mmHg.

Solubility: very sol C_6H_6, ether, $CHCl_3$, THF; slightly sol H_2O.

Form Supplied in: slightly yellow needles; hygroscopic.

Analysis of Reagent Purity: mp, as well as by visual inspection; freshly sublimed reagent is snow white.

Purification: sublimes 45-48 °C (bath temp)/0.1-0.5 mmHg; recryst MeOH (0.5 g mL^{-1}).

Handling, Storage, and Precautions: IPR-MUS LD_{50}: 1500 mg/kg; RTECS No. J05070000. May be harmful by inhalation, ingestion, or skin absorption; may cause irritation; exposure can cause nausea, headache, and vomiting; toxicological properties have not been thoroughly investigated. Stench! Use in a well ventilated fume hood.

Synthesis of 1,3-Dithianes.

The standard procedure to prepare 1,3-dithianes involves the Lewis-acid catalyzed derivatization of aldehydes or acetals with ***1,3-Propanedithiol***[1c,2-4] or with a derivative of the dithiol with an oxophile.[5,6] The use of ketones,[3] acids,[7] or methyl ethers[8] as starting material has been reported. As an alternative, the thioacetal formation can be initiated by a Brønsted acid, e.g. the clay montmorillonite KSF.[9] Also, the reaction of 1,3-propanedithiol with *gem*-diiodoalkanes catalyzed by $Ph_2PCH_2PPh_2/Pt^{2+}$ gives access to 1,3-dithianes,[10] as does a double Michael addition reaction sequence on 2-ynone derivatives.[11]

1,3-Dithianes as Functional Group Equivalents.

R_2CO.

The use of the 1,3-dithiane functionality as a protecting group for a ketone or aldehyde (**1**) has been recognized for some time (Scheme 1).[3,4] The good stability of this dithioacetal and its compatibility with a wide variety of reagents are an advantage in this respect. There is a plethora of conditions reported in the literature for unmasking the carbonyl function,[1,4,12-14] spanning from oxidative,[15] alkylative,[16] and photochemical[17] to metal-catalyzed procedures.[18]

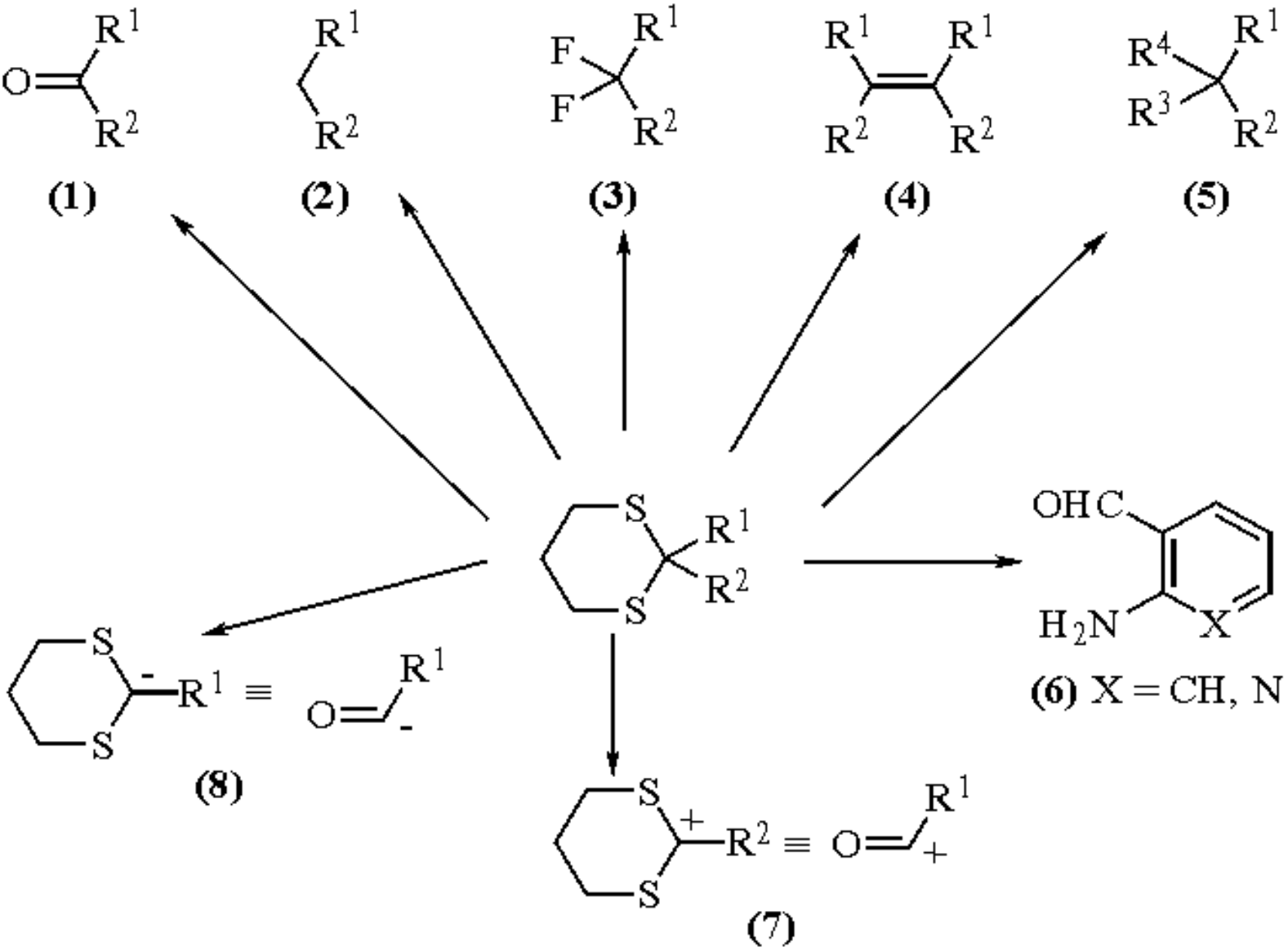

Scheme 1

R_2CH_2.

Reduction of 1,3-dithianes to the corresponding alkane (**2**) is a well-established transformation.[14b]

R_2CF_2.

gem-Difluoro compounds (**3**) can be prepared from ketones and aldehydes via the corresponding 1,3-dithiane in good yield.[19] In combination with the potential of 1,3-dithianes for reactivity umpolung, this sequence represents an interesting access to the CF_2^{2-} synthon.

1,3-Dithianes in Carbon-Carbon Bond Formation.

In addition to the exploitation of its metallated derivative as a versatile reagent for C-C bond formation (see ***2-Lithio-1,3-dithiane***), 1,3-dithianes have been used in transition metal-catalyzed alkenations to give (**4**) and *gem*-dialkylations to yield (**5**).[20] Amino pyridines and anilines can be *ortho*-formylated on treatment with 1,3-dithiane in the presence of pivaloyl chloride (***Trimethylacetyl Chloride***) and then base to give (**6**).[21,22] Another option in this category is to use the reagent's cationic counterpart (**7**), which reacts with enol ethers to give 1,3- or 1,5-dicarbonyl arrangements (see ***2-Chloro-1,3-dithiane***).[23]

1,3-Dithianes in Reactivity Umpolung.

The singular most important aspect in 1,3-dithiane chemistry is its use as a carbonyl equivalent which provides umpolung of the normal pattern of reactivity, e.g. acyl anion (**8**) chemistry.[1,24] A comprehensive view of this facet of the 1,3-dithiane reagent is covered under ***2-Lithio-1,3-dithiane***.

Related Reagents.

Bis(phenylthio)methane; ***Methoxy(phenylthio)methane***.

---

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1,4-Dithiothreitol[1]

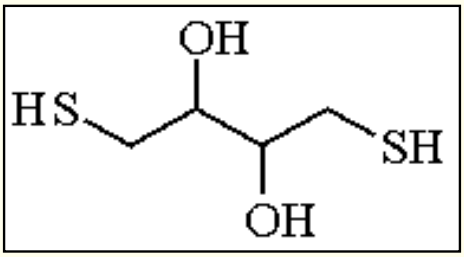

[27565-41-9] · $C_4H_{10}O_2S_2$ · 1,4-Dithiothreitol · (MW 154.28)

(reducing agent for disulfides;[1,2] protection of thiols and proteins containing free SH groups from air oxidation[3])

Alternate Names: DTT; *threo*-2,3-dihydroxybutane-1,4-dithiol.

Physical Data: mp 42-44 °C (racemate); redox potential -0.33 V, pH 7, varying -0.06 V per pH unit; p*K* 9.2 and 10.1.

Solubility: very sol water, alcohols.

Form Supplied in: white solid; widely available; normally supplied as the racemate, but chiral 1,4-dithio-L-threitol [*16096-97-2*],[4] mp 49-51 °C, is also available. The *erythro* isomer (1,4-dithioerythritol, DTE, [*6892-68-8*], mp 82-84 °C)[1] has redox properties similar to the *threo* isomer (*E*°´ is more positive by 0.004 V)[5] and is also available. The oxidized cyclic form (*trans*-1,2-dithiane-4,5-diol [*14193-38-5*], mp 130-132 °C)[1] is available; it has a UV spectrum (λ_{max} 283 nm; ε = 273). DTT and DTE are colorless above 260 nm, but both reduced and oxidized forms absorb below 240 nm.

Analysis of Reagent Purity: the presence of monothiols can be detected by addition of arsenite (which forms a tight tridentate complex with DTT),[6] followed by addition of 5,5´-dithiobis(2-nitrobenzoate).[7] Total thiol content is determined by omitting arsenite.

Handling, Storage, and Precautions: solid material should be stored under refrigeration in a closed bottle. Solutions will slowly oxidize in the presence of air to the cyclic disulfide, which is inert. The concentration of reduced material can be determined by assay with 5,5´-dithiobis(2-nitrobenzoate).[8]

Reduction of Disulfides.

DTT and DTE are the reagents of choice for reducing disulfide bonds, and protecting thiols and the thiol groups on proteins from air oxidation to disulfides.[1-3] DTT also reduces diselenides.[9] The equilibrium constant for reduction of

the disulfide of glutathione by DTT is 210 M.[10] DTT undergoes disulfide interchange to liberate the thiol with the lowest pK (eq 1). The mixed disulfide then cyclizes rapidly, releasing the other monothiol (eq 2).

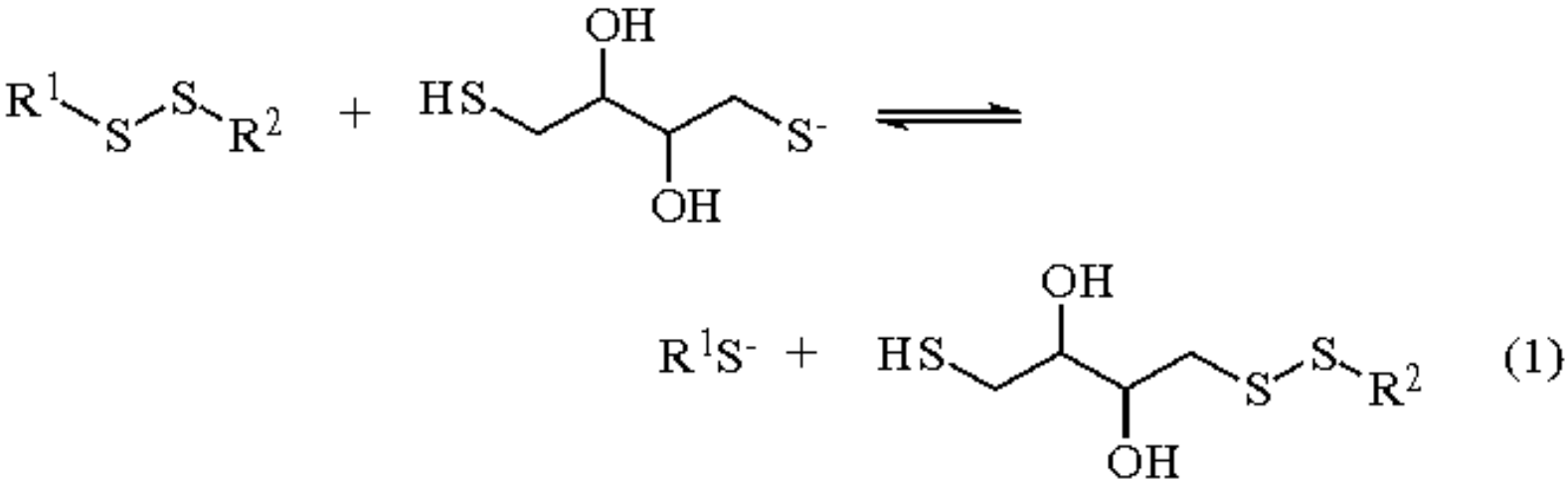

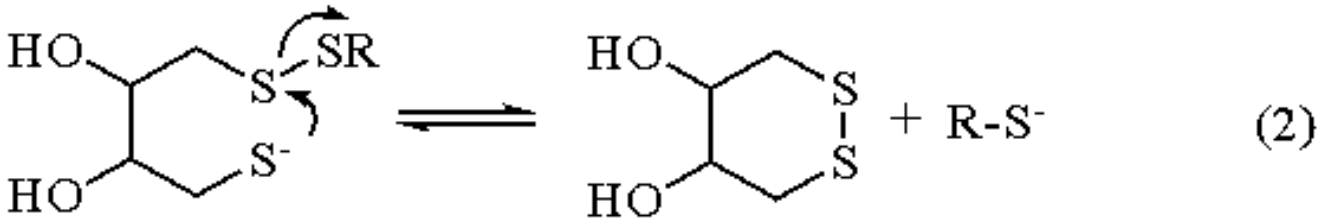

The high equilibrium constant for this cyclization reaction produces the low redox potential for DTT. The hydroxy groups at C-2 and C-3 convey water solubility and reduce the stench (the solid has an odor, but only at very close range). Since the active form for disulfide interchange is the thiolate anion, these reactions go faster at higher pH. With the first p*K* at 9.2, however, there is sufficient thiolate even at pH 7 to give a reasonable rate.

The rates of reduction of disulfides by DTT show a normal dependence on the p*K* of the thiol being liberated,[11] and this fact has been used to determine the p*K*'s of SH groups on proteins. For example, the p*K* of the active site cysteine in papain was 4.1 at pH 6 and 8.4 at pH 9, with the change resulting from a group titrating with a p*K* of 7.5.[11b] The equation used in this work was: $\log k = 7.03 + 0.5\ pK_{nuc} - 0.27\ pK_c - 0.73\ pK_{1g}$, where k is the rate constant in $M^{-1}\ min^{-1}$ for reaction of the monoanion of DTT with the disulfide, and the subscripts nuc, c, and 1g refer to DTT, the center sulfur in the transition state, and the leaving thiol on the protein.

A series of other dithiols have been prepared as potential reducing agents, but none of them that are water soluble have lower redox potentials than DTT.[10,12] Two that have lower p*K*'s (7.6-7.8) and thus react faster at neutral pH have higher redox potentials of -0.27 V at pH 7 and are less effective reducing agents than DTT.[13] So far, none of these is commercially available.

Reagent for Studies of Protein Folding.

DTT and its oxidized form have found use in studying disulfide interchange reactions during protein folding and unfolding.[14] Mixtures of these provide a redox buffer that can be adjusted to match the redox potential of individual disulfide bonds.

Other Properties and Problems.

The low redox potential of dithiothreitol interferes with its use in the presence of certain reagents. While it gives full color yield in reactions with aromatic disulfides such as 5,5´-dithiobis(2-nitrobenzoate)[8] or 2,2´- or 4,4´-dipyridyl disulfide,[15] it gives only 4% the expected color in the nitroprusside assay for thiols,[1,16] presumably because it reduces the iron. It reduces Cr^{III} or Co^{III}, so inert complexes of nucleotides with these metal ions cannot be used in its presence. Dithiothreitol also undergoes transesterification with thioesters of coenzyme A.[17]

DTT and DTE chelate heavy metal ions tightly, which can be helpful at times, but deleterious with autooxidizable ions such as Fe^{II}. While they oxidize only slowly in air in the absence of heavy metal ions, DTT and DTE are readily oxidized in air in the presence of Fe^{II}, so solutions containing Fe^{II} and DTT must be kept anaerobic.[18]

---

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Di-*p*-tolylcarbodiimide

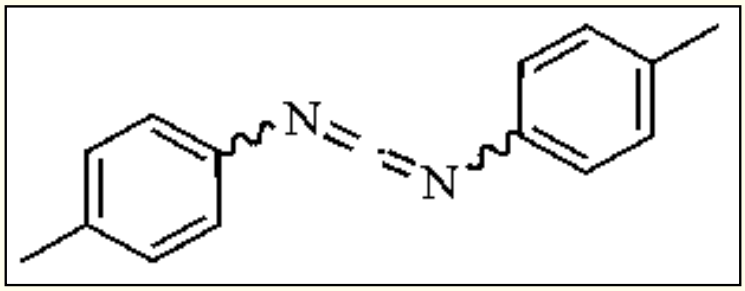

[726-42-1] · $C_{15}H_{14}N_2$ · Di-*p*-tolylcarbodiimide · (MW 222.31)

(synthesis of nitrogen heterocycles)

Physical Data: bp 221-223 °C/20 mmHg, 114 °C/0.02 mmHg; mp 56-58 °C.

Solubility: sol diethyl ether, benzene, pyridine, *t*-butanol.

Form Supplied in: off-white crystalline solid.

Preparative Methods: although di-*p*-tolylcarbodiimide is commercially available, it is quite expensive. It can be conveniently prepared from di-*p*-tolylthiourea by oxidation with ***Mercury(II) Oxide***,[1] ***Triphenylphosphine*** in the presence of ***Diethyl Azodicarboxylate***,[2] or with mercury(II) benzamide.[3] A synthetic method dimerizing *p*-tolyl isocyanate has been reported.[4]

Purification: recrystallizations from diethyl ether and other solvents have been reported.[1]

Handling, Storage, and Precautions: harmful by inhalation, ingestion, or skin absorption and exposure causes strong eye and lung irritation. The solid is light- and moisture-sensitive and should be stored refrigerated in dark, well-sealed containers under an inert atmosphere. It should be used in a fume hood.

Heterocycle Synthesis.

Di-*p*-tolylcarbodiimide is a potent electrophile which reacts with a wide variety of nucleophiles to yield formamidine derivatives substituted at the central carbon. This reactivity has been exploited to prepare a large number of nitrogen heterocycles. Treatment of di-*p*-tolylcarbodiimide (**1**) with ethyl allophanate, for example, results in the formation of 2-substituted quinazolin-4(3*H*)-ones (eq 1).[5] β-Lactams can also be prepared by the reaction of carbodiimides with α-halo esters in a Reformatsky-type reaction (eq 2).[6]

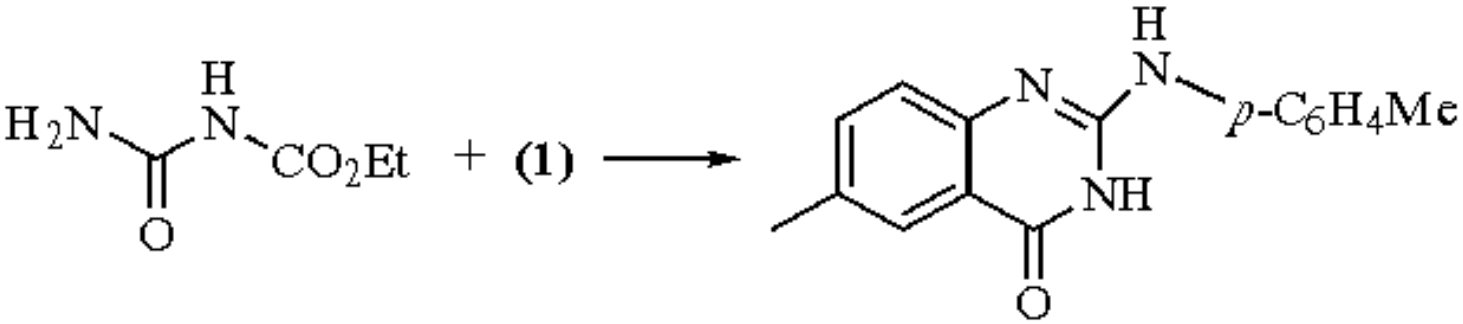

(1)

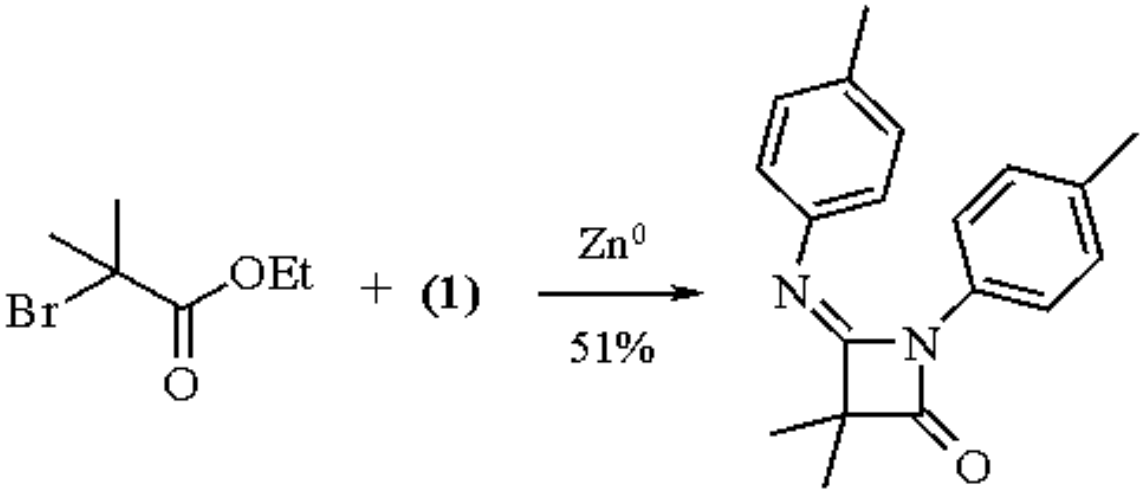

(2)

The reaction of (**1**) with thiazolium ylides related to thiamine has been extensively studied by Takimazawa and co-workers. They have found that, depending upon reaction conditions and the substrate used, a wide variety of thiamine-annulated heterocycles can be prepared (eq 3).[7]

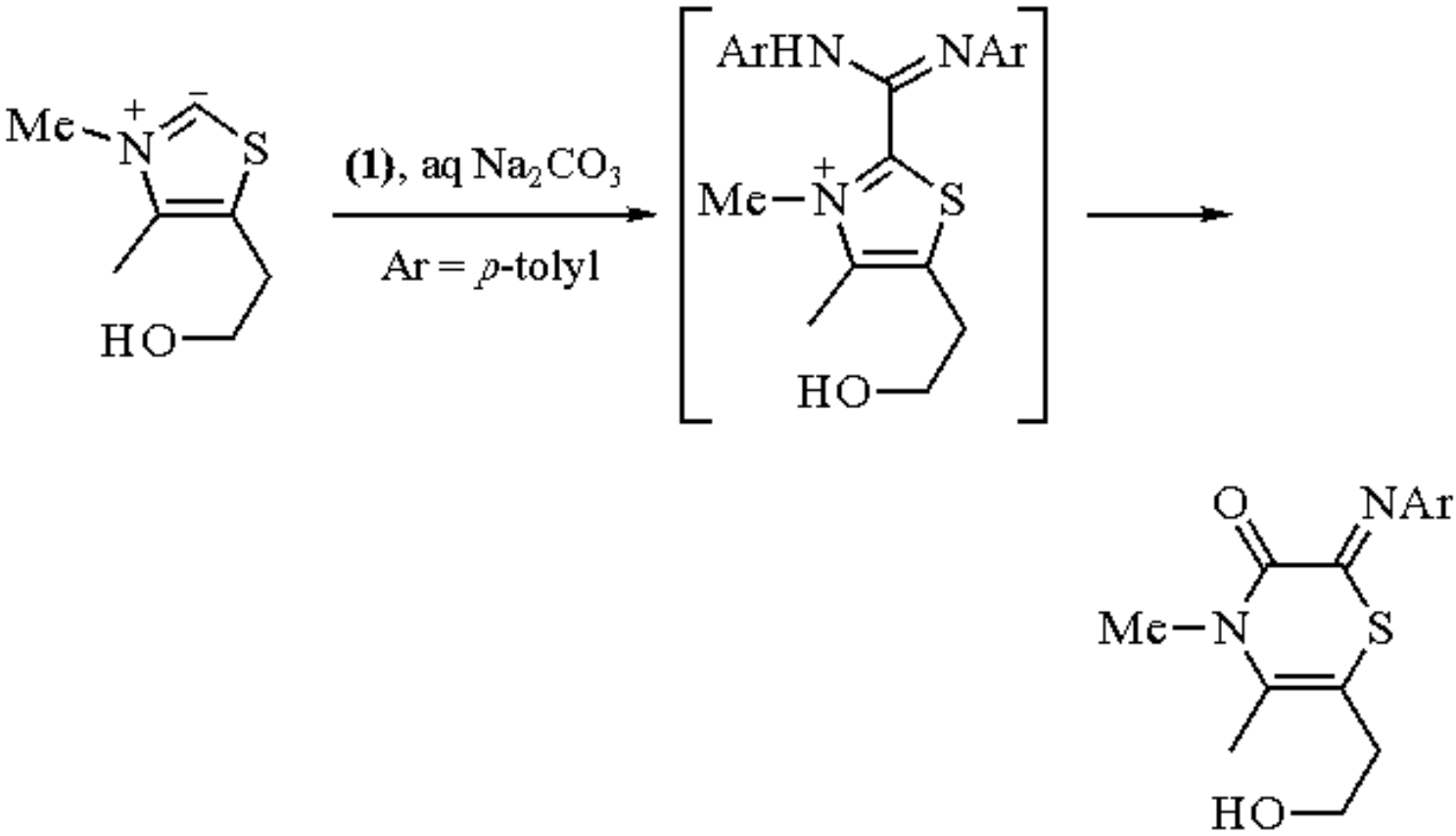

(3)

Treatment of (**1**) with amidrazones in MeCN at 80-90 °C yields 5-tolylamino-1,2,4-triazoles in good yields.[8] Similarly, Molina and co-workers have found that (**1**) reacts with a variety of *N*-amino heterocycles to yield triazoles from *N*-amino-2-thioxo-4-imidazolidinones (eq 4),[9] ring annulated [1,2,4]triazolo[4,3-*b*]triazoles from [1,2,4]triazoles,[10] and [1,2,4] triazolo[5,1-*c*][1,2,4]triazines from 3,4-diamino[1,2,4]triazine.[11] Related additions have also been reported for thiadiazolines.[12]

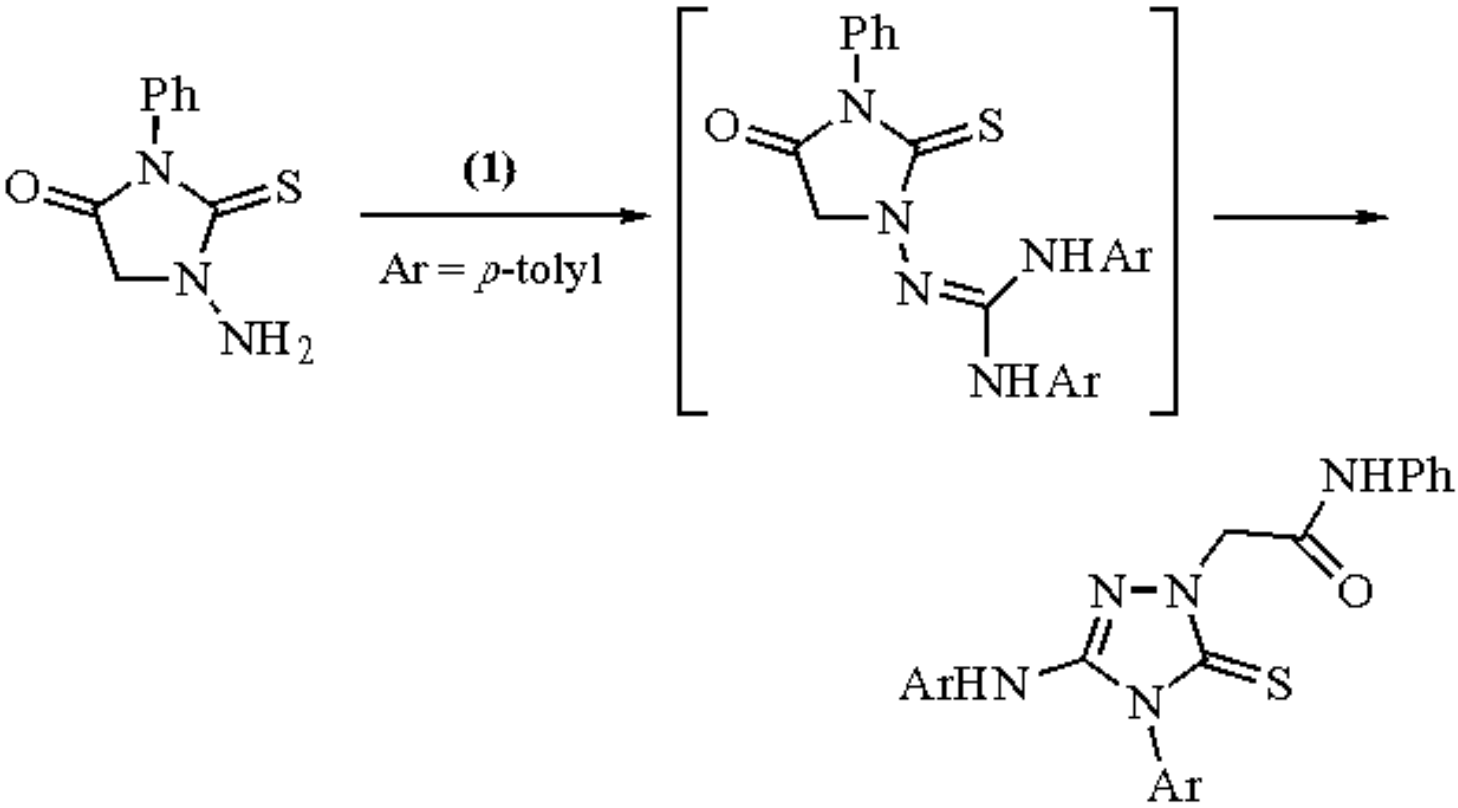

(4)

Other Reactions with Nucleophiles.

Di-*p*-tolylcarbodiimide reacts with sulfonic acids to afford the corresponding sulfonic anhydride (and di-*p*-tolylurea).[13] Treatment of (**1**) with an alcohol in the presence of base yields the corresponding *N,N´*-di-*p*-tolyl-*O*-alkyl pseudourea ethers. These ethers decompose in the presence of mono- and disubstituted hydrogen phosphates to afford tertiary phosphates in high yields (eq 5).[14] A variation of this methodology has been widely applied for the preparation of nucleoside phosphites.[15]

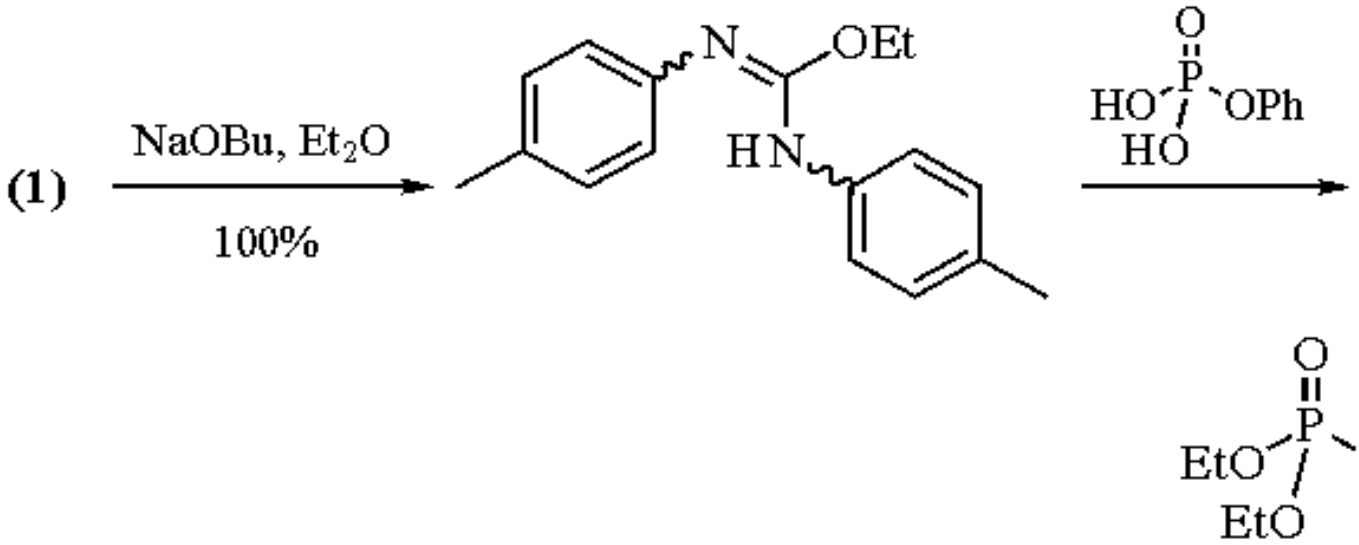

(5)

Other Reactions.

Di-*p*-tolylcarbodiimide is reduced with ***Sodium Borohydride*** in isopropanol to afford formamidines in good yields.[16] Diarylcarbodiimides have been found to help carboxylate active methylene compounds such as fluorene, where the diimide acts as model for biotin.[17]

---

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Divinyl Ketone

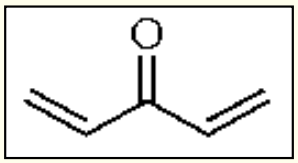

[1890-28-4] · C_5H_6O · Divinyl Ketone · (MW 82.11)

(highly reactive, easily polymerized, polyfunctional annulation reagent; generally reacts by adding nucleophiles, dienes or radicals)

Alternate Name: 1,4-pentadien-3-one.

Physical Data: bp 38-40 °C/65 mmHg, 30 °C/16 mmHg.

Solubility: sol most common solvents.

Form Supplied in: unstable; prepare immediately before use as described below.

Preparative Methods: the title reagent has been prepared from the precursors listed in Table 1. For example, dehydrohalogenation of 1,5-dihalo-3-pentanones may be effected by distillation from anhydrous ***Sodium Carbonate*** (35-80%)[1] or from ***Quinoline*** (95%).[2] Under milder conditions (1.1 equiv Na_2CO_3 and lower temperature) the dichloro ketone gave 5-chloro-1-penten-3-one (37-80%).[1c,3] The dihalo ketone precursors are usually prepared by Friedel-Crafts acylation of ***Ethylene***,[1c,4] or from the methyl β-halopropionate via a novel titanium-catalyzed ethyl Grignard addition, followed by ***N-Bromosuccinimide*** oxidation of the resulting cyclopropanol.[1b] The Mannich base precursors in Table 1 have been prepared from 1-methyl-4-piperidone (**1**) by conversion to its *N*-methyl iodide salt,[5] by reaction of this salt with dimethylamine,[6] or by reaction of (**1**) with ***p-Toluenesulfonyl Chloride*** and amines.[7] These reagents are normally used for in situ generation of divinyl ketone.

Table 1 Divinyl Ketone Precursors

Compound	CAS No.	MW	Bp (°C)/mmHg
$(ClCH_2CH_2)_2CO$	[*3592-25-4*]	155.02	65 70/0.2; 78/0.8
$ClCH_2CH_2$-$COCH{=}CH_2$	[*20757-87-3*]	118.56	25/0.08
$(BrCH_2CH_2)_2CO$	[*140200-76-6*]	243.93	104 106/2.5
$(Me_2NCH_2CH_2)_2$-CO	[*21061-85-8*]	172.27	47/0.15[a]
$[TsN(Me)CH_2CH_2]_2$-CO	[*119352-89-5*]	452.58	mp 73 74 °C
$TsN(Me)CH_2CH_2$-$COCH{=}CH_2$	[*119352-88-4*]	267.34	mp 39 °C
$MeN(CH_2CH_2)_2$-CO (**1**)	[*1445-73-4*]	113.16	49 51/0.5; 68 71/17[b]
$[Me_2N(CH_2CH_2)_2$-$CO]^+I^-$	[*26822-37-7*]	255.10	mp 186 188 °C (dec)

[a] Dihydrochloride salt, mp 191 192 °C. [b] Hydrochloride salt, mp 164 167 °C.

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: brief storage in solution (ether or hydrocarbon) at low temperature due to ease of polymerization. A toxic, flammable, lachrymatory liquid which must be used with care. As a dialkylating agent, it may be mutagenic. Wastes may be disposed of by treatment with ammonium hydroxide. Use in a fume hood.

Substituted Divinyl Ketones.

Since the late 1970s, a large number of substituted divinyl ketones (**2**) have been prepared, many as substrates for the Nazarov reaction.[8] Tables 2 and 3 list a few simple methyl-, phenyl-, silyl-, and halogen-substituted examples. Other examples have been cataloged.[9-20]

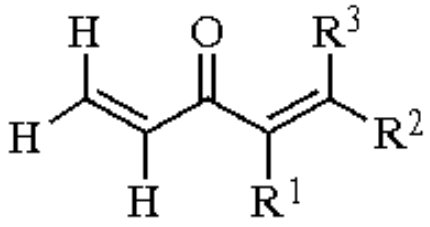

(2)

Table 2 Simple Derivatives of Divinyl Ketone (**2**).

R^1	R^2	R^3	CAS No.	MW	Bp (°C)/mmHg
Me	H	H	[*25461-87-4*]	96.13	61 63/95
H	Me	H	[*10575-36-7*]	96.13	39 41/12; 30 31/7.5
Me	Me	H	[*69084-15-7*]	110.16	62 64/21
H	Me	Me	[*13058-38-3*]	110.16	30/0.8; 57/20
H	Ph	H	[*73291-51-7*]	158.20	100 101/1.0
H	$SiMe_3$	H	[*82201-88-5*]	154.28	[a]
H	Cl	H	[*117921-40-1*]	116.55	48 49.5/14
H	Br	H	[*103067-89-6*]	161.00	44 46/4.0

[a] Characterized by IR, ^{1}H NMR, MS.[20b]

Table 3 Some Polysubstituted Divinyl Ketones

Compound	CAS No.	MW	Bp (°C)/mmHg
(*E, E*)-$(MeCH{=}CH)_2$-CO	[*7778-46-2*]	110.16	67 70/20
$[CH_2{=}C(Me)]_2CO$	[*27132-81-6*]	110.16	73 74/110
(*E*)-MeCH=CHCO-C(Me)=CH_2	[*105645-99-6*]	110.16	55/16
(*E, E*)-MeCH=CHCO-C(Me)=CHMe	[*36685-36-6*]	124.18	90 91/22
(*E*)-MeCH=CHCO-CH=CMe_2	[*38011-55-1*]	124.18	72/16; 84/20
$(Me_2C{=}CH)_2CO$	[*504-20-1*]	138.21	198 199; mp 27 °C
(*E, E*)-MeCH=CHCO-CH=CHPh	[*91897-73-3*]	172.23	98/0.5
(*E, E*)-$(PhCH{=}CH)_2$-CO	[*35225-79-7*]	234.30	mp 110 111 °C
(*E, E*)-MeCH=CHCO-CH=$CHSiMe_3$	[*59376-60-2*]	168.31	125/18
(*E*)-CH_2=C(Me)CO-CH=$CHSiMe_3$	[*81255-89-2*]	168.31	100/12
(*E, E*)-PhCH=CHCO-CH=$CHSiMe_3$	[*59376-62-4*]	230.38	135/0.07
(*E, E*)-$(ClCH{=}CH)_2$-CO	[*73838-83-2*]	150.99	125 130/10; mp 80 °C
(*E, E*)-ClCH=CHCO-CH=CHMe	[*21179-83-9*]	130.57	70 72/10; mp 38 °C
(*E*)-ClCH=CHCO-CH=CMe_2	[*110456-84-3*]	144.60	71 73/10
$(Cl_2C{=}CCl)_2CO$	[*13340-09-5*]	288.77	94 95/0.6

General Synthetic Methods.

A variety of synthetic methods have been applied to the preparation of substituted divinyl ketones. Among the most general and effective of these are: (a) acylation of alkenyl silanes,[9] stannanes,[10] and cuprates[11] with α,β-unsaturated acyl chlorides; (b) transition metal-catalyzed carbonylation of alkenyl stannanes[12] and mercurials;[13] (c) formation of dialkenyl secondary carbinols by organometallic addition to aldehydes, followed by oxidation with ***Chromic Acid***,[14] ***Dimethyl Sulfoxide***,[15] ***Manganese Dioxide***,[16] ***Nickel(II) Peroxide***,[17] or ***Barium Manganate***;[17b,18] (d) palladium-catalyzed coupling of metallated methoxyallenes with alkenyl halides (eq 1);[19] and (e) orthoester alkylation of trimethylsilyloxydienes,[20a] followed by β-elimination.

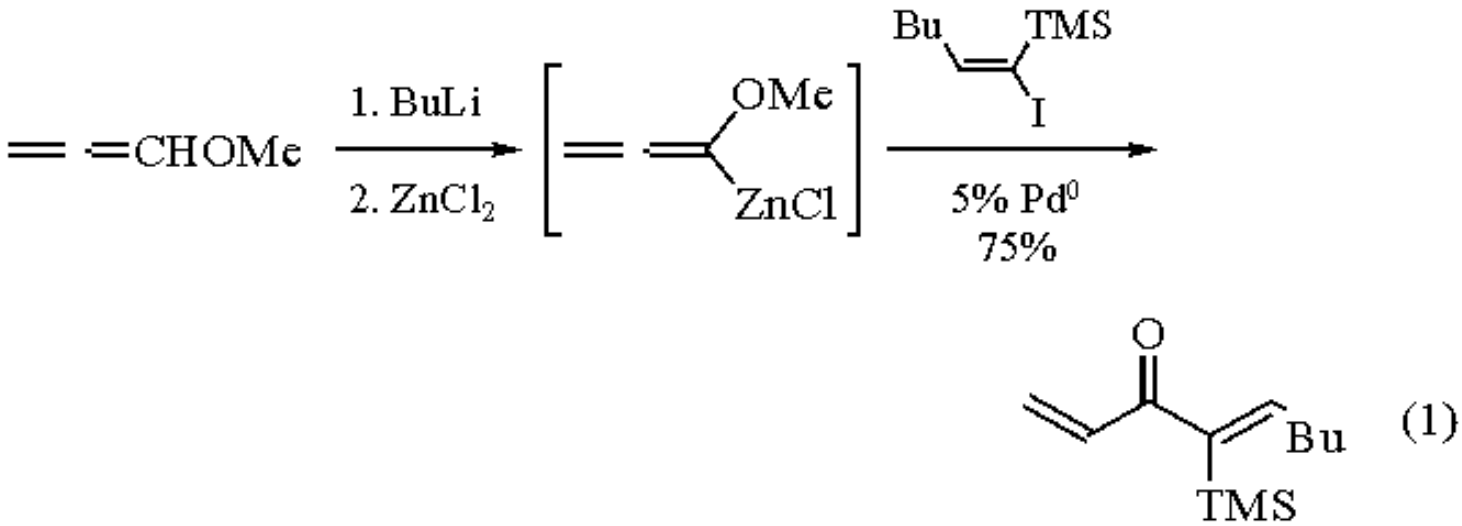

(1)

Many less general, but potentially useful, procedures have been reported. These include: (f) α,α´-dibromination of ketone acetals, followed by dehydrohalogenation and acetal hydrolysis;[21] (g) retro-ene reaction of substituted vinylcyclopropane derivatives (eq 2);[22] (h) pyrolysis of norbornenyl precursors;[23] and (i) isomerization of alkynones to dienones.[24]

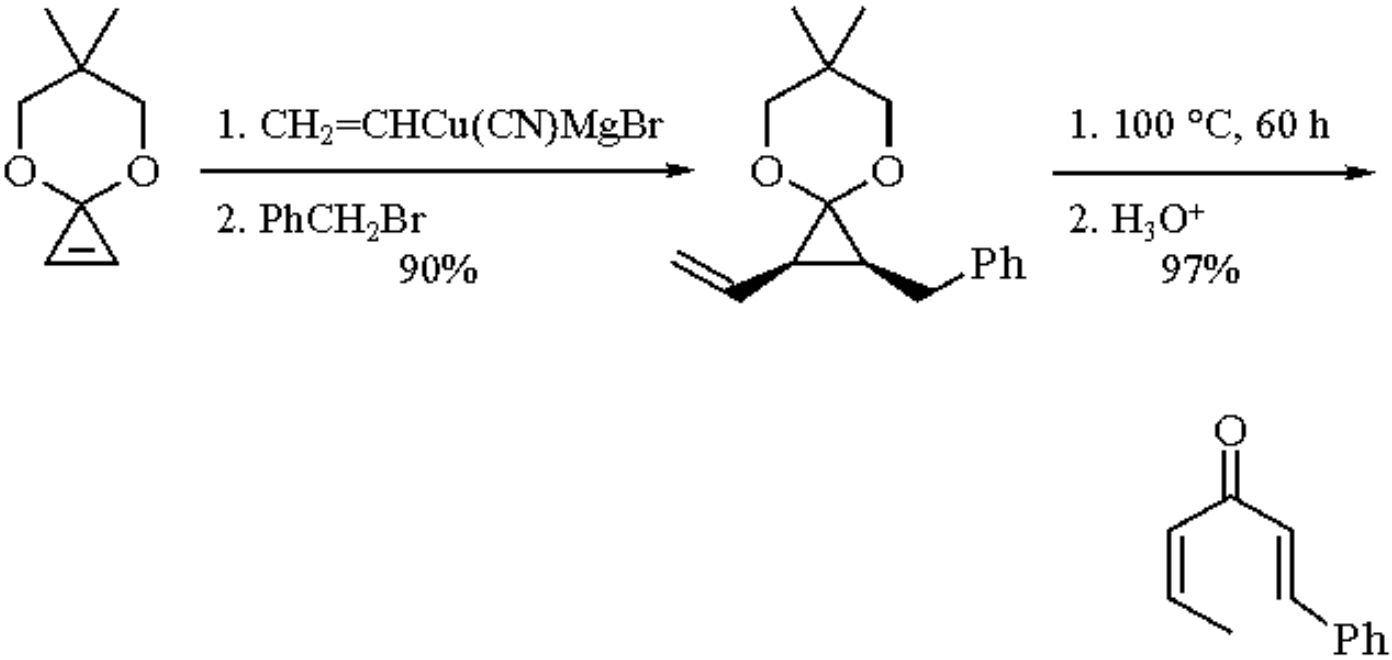

(2)

Reactions of Divinyl Ketones.

As noted above, many divinyl ketones have been used as substrates for the Nazarov cyclization.[8] In addition, the polyfunctional nature of these compounds makes them versatile participants in a variety of other reactions.

Conjugate Addition of Heteronucleophiles.

Tetrahydro-4*H*-pyran-4-one,[4b,25] and its sulfur and selenium analogs,[1b,5,26] may be prepared by nucleophilic addition (or substitution) to divinyl ketone (or 1,5-dichloro-3-pentanone). Similar reactions have been used in synthetic approaches to alkaloids related to catharanthine[15b] and emetine[6b] (eq 3). In the latter example, subsequent Mannich alkylations culminate in bonding to four of the five carbon atoms in divinyl ketone.

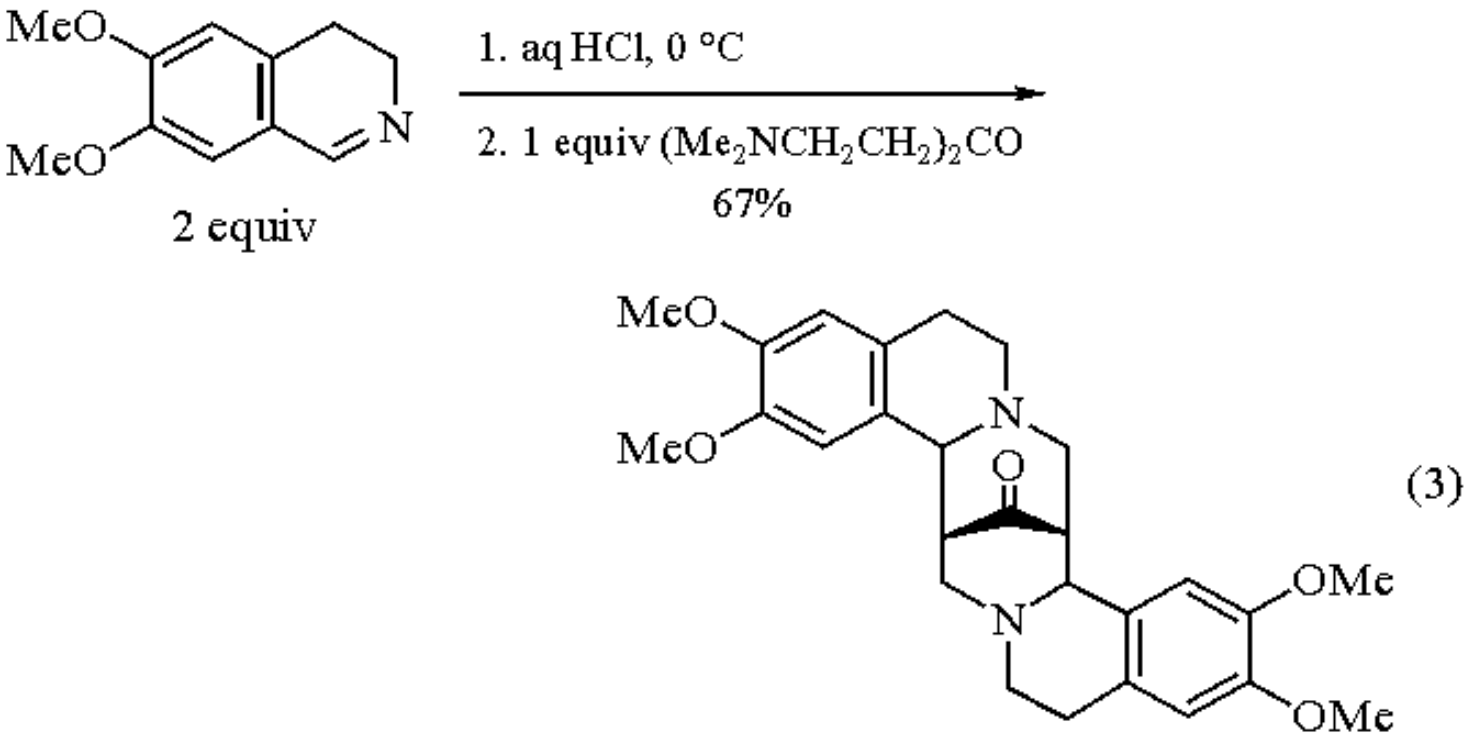

Michael Addition of Carbon Nucleophiles.

The umpolung aldehyde intermediates generated by thiazolium salt catalysis have been used by Stetter et al. to prepare polyketones (eq 4).[1c,27] Carboannulations may be effected by sequential Michael reactions[28] or a combination of Michael and aldol reactions.[3] However, attempts to generate the tricyclo[5.3.1.0^{3,8}]undecane ring system by three sequential Michael reactions between divinyl ketone and cyclohexenone enolate failed.[29] The desired assembly was eventually achieved by an initial Diels-Alder cycloaddition, followed by a Michael reaction (eq 5),[2] and provided the foundation of a synthesis of seychellene.[2] A similar case, employing acid catalysis in the cycloaddition step, was interpreted as a threefold sequence of Michael reactions.[30]

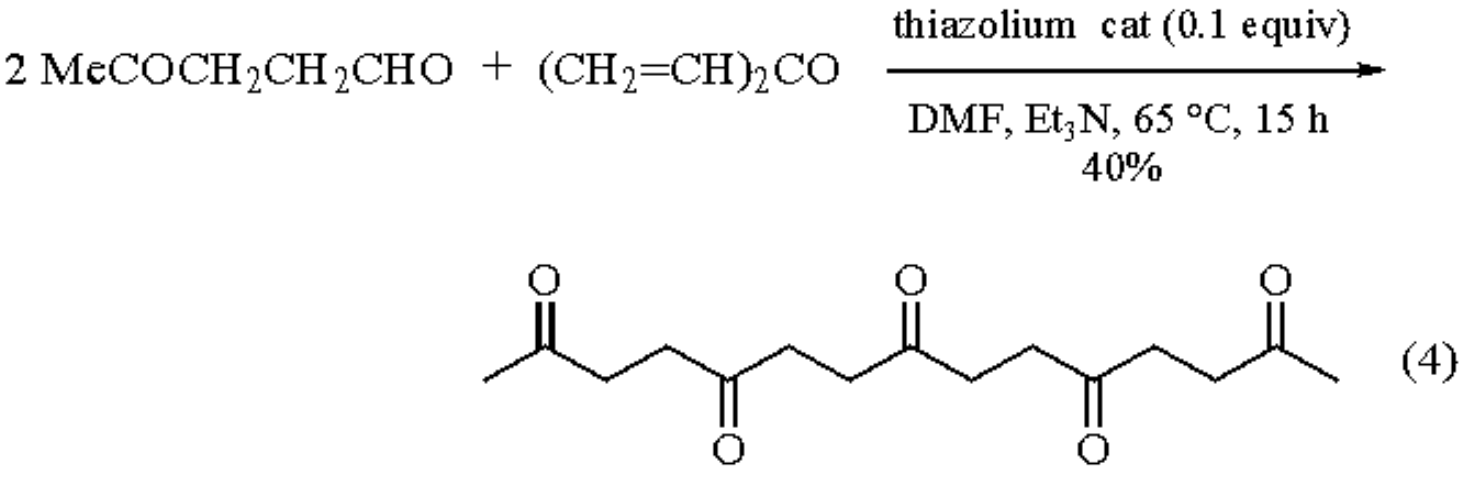

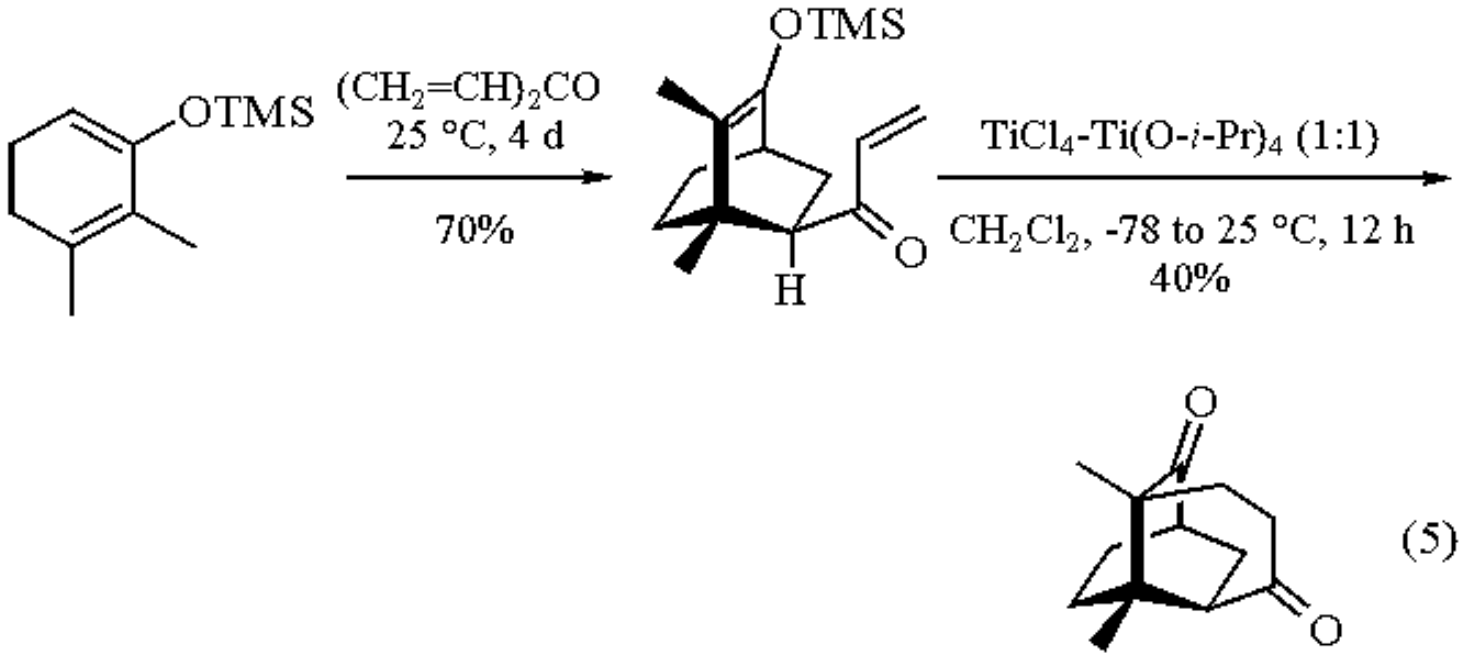

Cycloadditions.

Unsaturated ketones are excellent dienophiles. An interesting study of sequential Diels-Alder reactions of conjugated tetraenes with dialkenyl ketones to give tricyclic products has been reported.[23a] Dimethylhydrazone derivatives of divinyl ketone react with strong dienophiles to give heterocyclic products.[31]

Other Reactions.

Addition of carbon radicals to divinyl ketone may yield useful polyfunctional products (eq 6).[32] 1,2-Carbonyl addition reactions are best accomplished with precursors (Table 1). In this manner, cross-conjugated allenes were prepared by ***Lithium Acetylide*** addition to 1,5-dichloro-3-pentanone, followed by organocuprate substitution.[33]

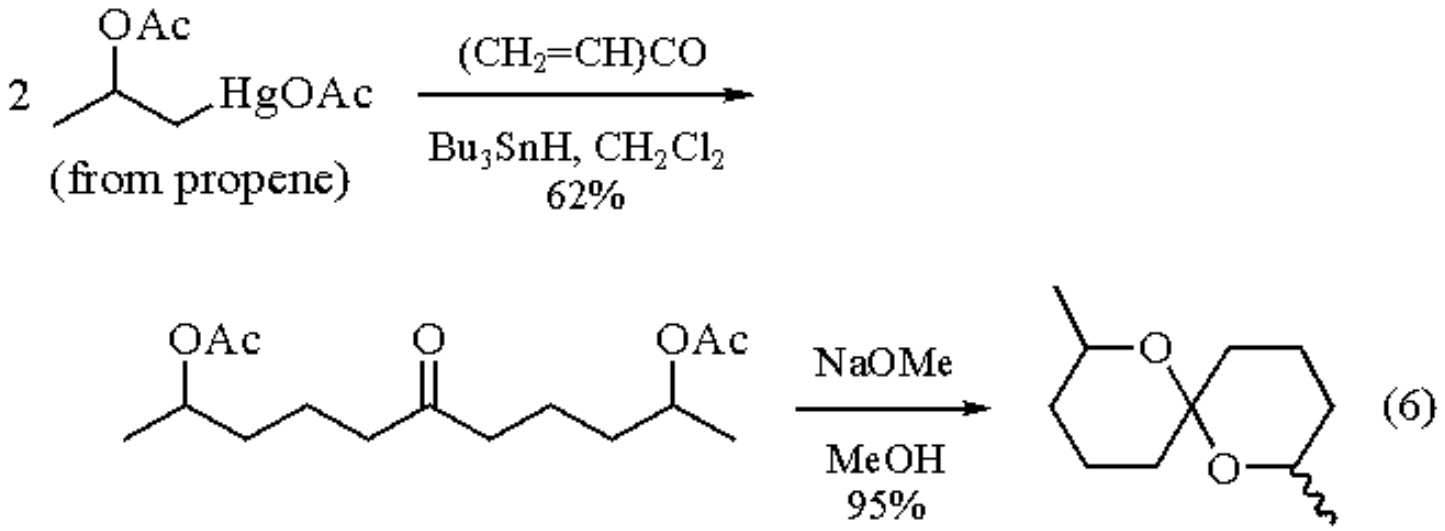

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Divinyl Sulfone

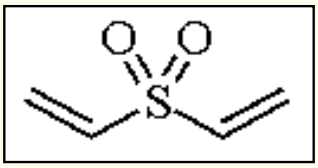

[77-77-0] · $C_4H_6O_2S$ · Divinyl Sulfone · (MW 118.17)

(bifunctional Michael acceptor that gives six-membered ring heterocycles with primary amines[1] or analogous reagents;[2] furnishes γ-diketones in the reaction with aldehydes and a thiazolium salt (Stetter reaction);[3] reasonably powerful dienophile[4])

Physical Data: bp 233-234 °C; bp 90-92 °C/8mmHg; mp ca. -26 °C; *d* 1.177 g cm^{-3}.

Form Supplied in: colorless liquid; commonly stabilized with hydroquinone; widely available.

Preparative Methods: by dehydration of bis-β-hydroxyethyl sulfone with phosphoric acid at 280 °C or by pyrolysis of bis-β-acetoxyethyl sulfone at 500 °C.[5]

Handling, Storage, and Precautions: toxic, corrosive liquid; vesicant and mild lachrymator; to be handled with care; use in a fume hood.

Addition Reactions.

The two vinyl groups of the title reagent are activated towards nucleophilic additions, but they react also with electrophiles and radicals. Among the electrophilic additions is the reaction with aromatic diazonium salts (eq 1),[6] while for supposed radical additions, the reaction of ketene alkyl trimethylsilyl acetals promoted by ***Titanium(IV) Chloride*** is representative (eq 2).[7] The product of the latter reaction depends upon the substitution pattern at the α-carbon.

$$p\text{-}ClC_6H_4N_2 + (CH_2{=}CH)_2SO_2 \xrightarrow[\substack{CuCl_2,\ rt \\ 23\%}]{Me_2CO} (p\text{-}ClC_6H_4CH_2CHCl)_2SO_2 \quad (1)$$

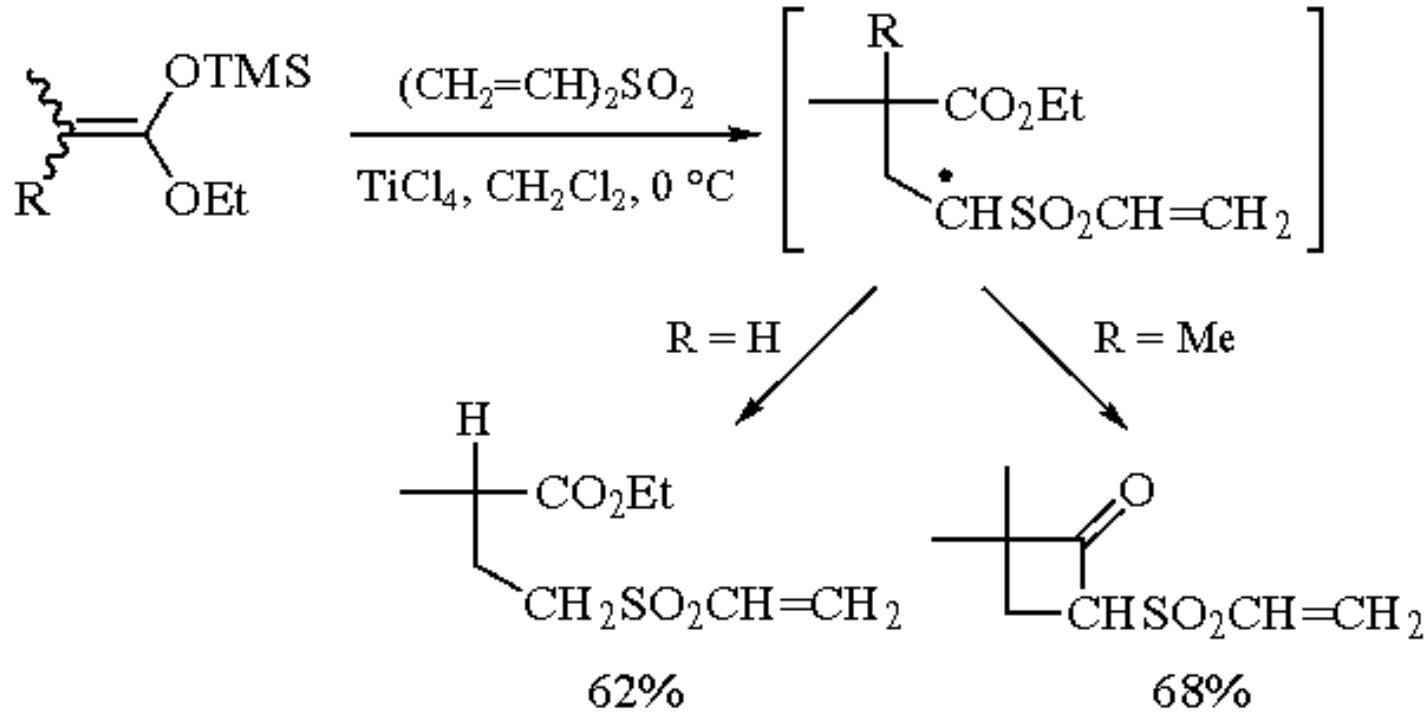

(2)

Other nucleophilic additions include reactions with primary amines (eq 3),[1] phosphines (eq 4),[2] and sodium peroxide (eq 5).[8]

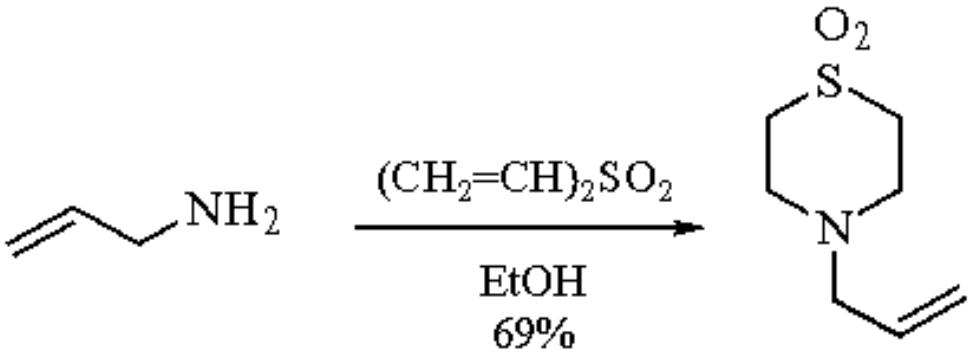

(3)

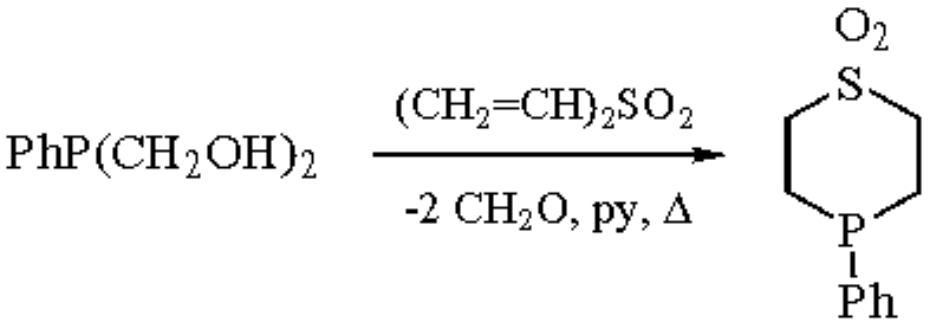

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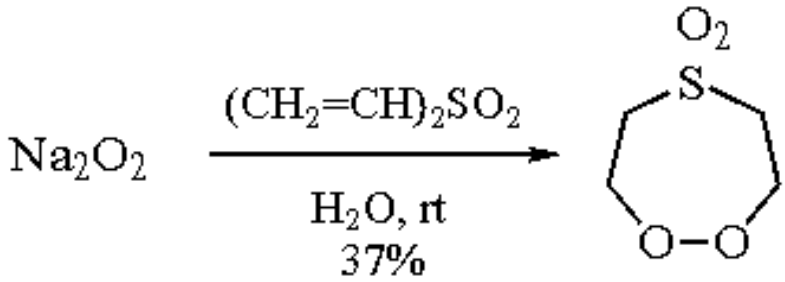

(5)

Of synthetic relevance is the Stetter reaction,[3] which provides a general route to polyfurans, polypyrroles, and polythiophenes,[9] as represented in eq 6 for a terpyrrole.[9b]

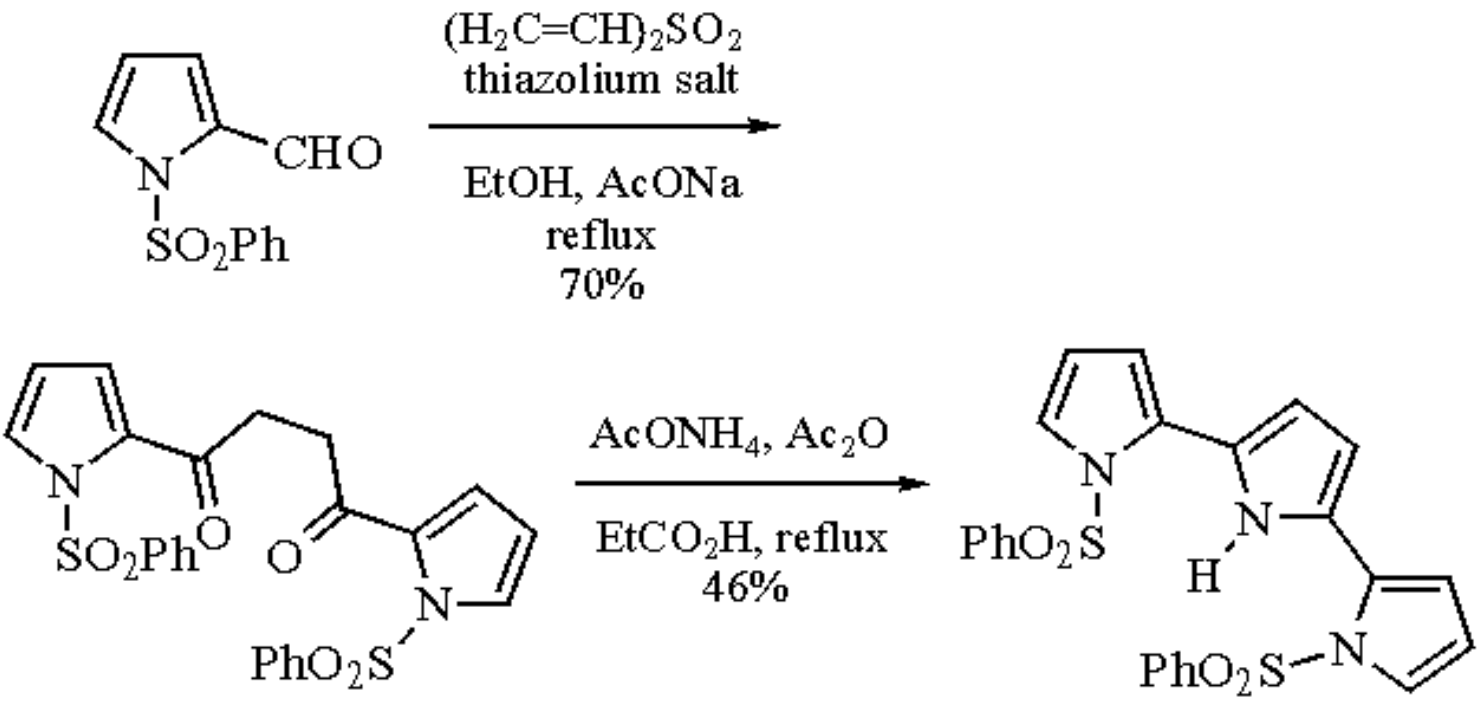

(6)

Cycloadditions.

Divinyl sulfone has been shown to react as both a dienophile and a dipolarophile. Examples of [4 + 2] cycloaddition[10] include the reaction with cyclopentadiene (eq 7)[4] and indole-2,3-quinodimethane (eq 8).[10a] In the former reaction the monoadduct can be isolated and reacted with another diene, while in the latter the first addition is followed by elimination of CO_2 and $CH_2{=}CHSO_2H$, with direct formation of the aromatic carbazole. Dipolar cycloadditions are represented in eqs 9 and 10.[11] In the latter example the 1,3-dipolar cycloaddition is preceded by a Michael addition.

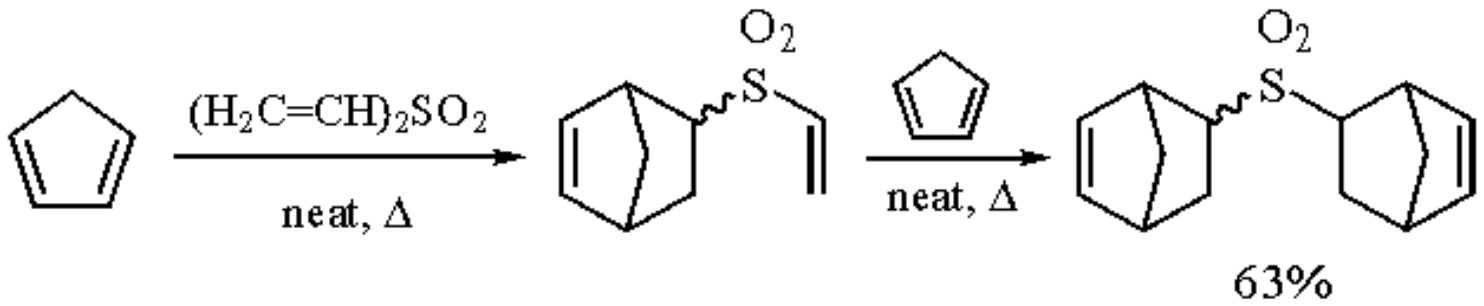

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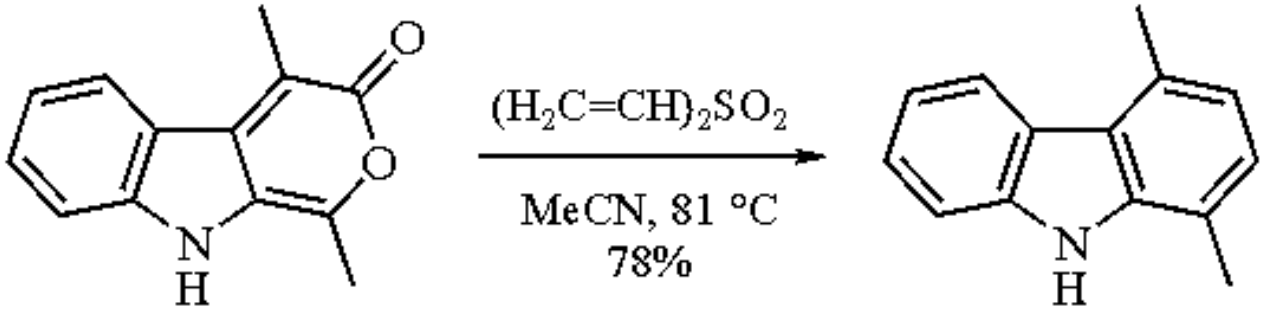

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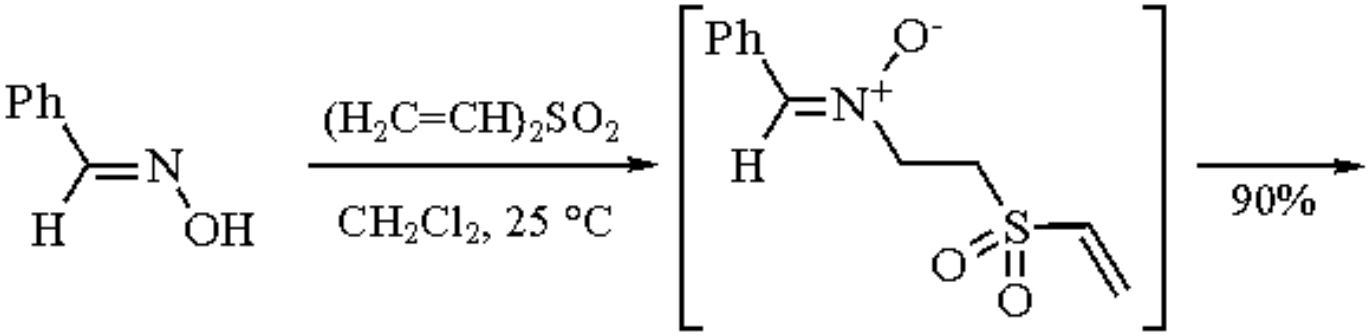

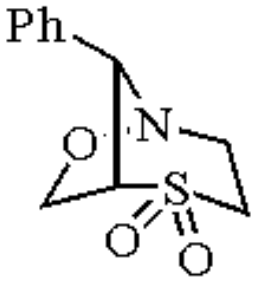

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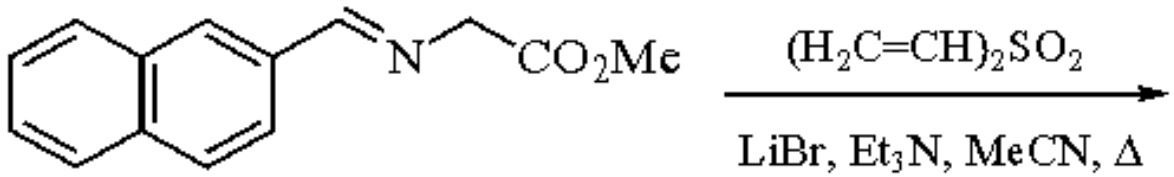

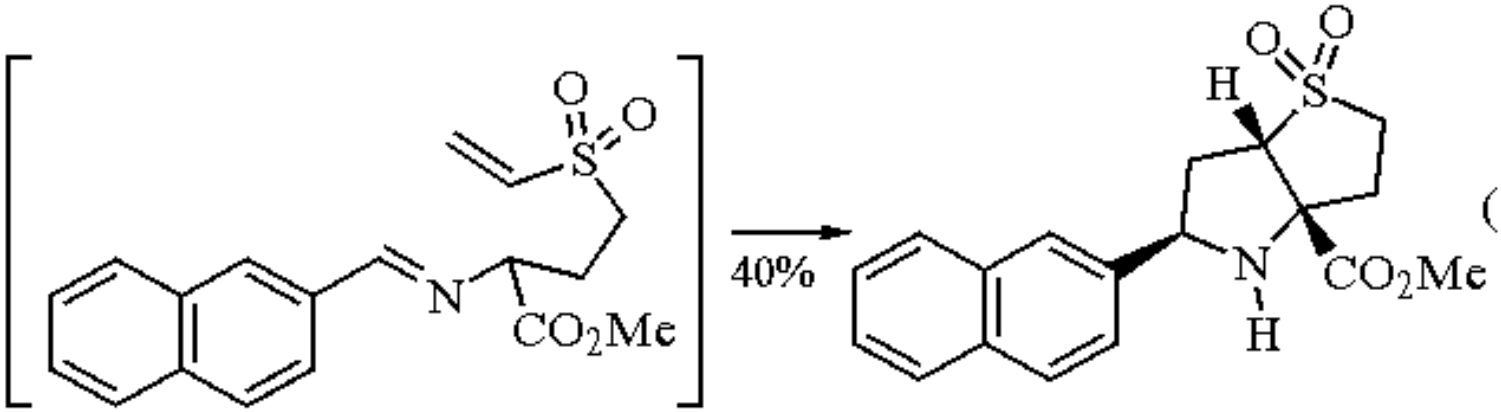

(10)

Cycloaddition reactions of divinyl sulfone with benzyne (eq 11)[12a] and cobalt complexes of alkynes (eq 12)[12b] are also known.

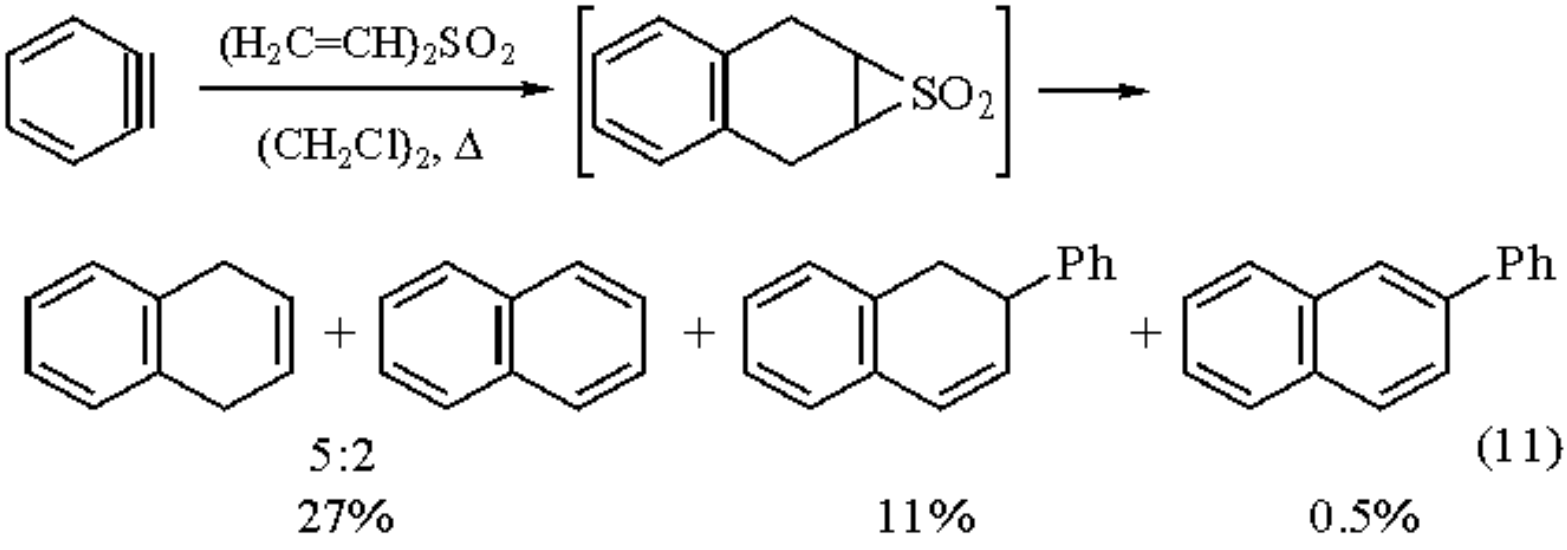

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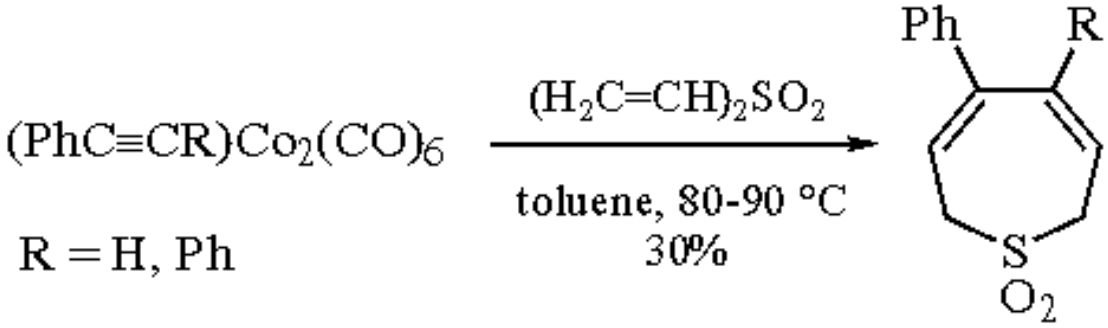

(12)

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Dodecacarbonyltetrarhodium[1]

$Rh_4(CO)_{12}$

[19584-30-6] · $C_{12}O_{12}Rh_4$ · Dodecacarbonyltetrarhodium · (MW 747.76)

(catalyst for hydrogenation, hydroformylation, silylformylation, hydroboration, aldol reactions)

Physical Data: mp 150 °C (dec);[2] IR (nujol) 2089, 2079, 2056, 2043, 2035, 1875 cm^{-1}.[3]

Solubility: sol hexane, benzene, toluene, acetone, dichloromethane.

Form Supplied in: dark red crystalline solid; commercially available.

Preparative Method: prepared from ***Tetracarbonyl(di-μ-chloro)dirhodium***[4]

Handling, Storage, and Precautions: air sensitive; should be handled under nitrogen or argon; water sensitive (decomposes to $Rh_6(CO)_{16}$ in the presence of water); heat sensitive; store in refrigerator under carbon monoxide. Use in a fume hood.

Catalytic Hydrogenation.

$Rh_4(CO)_{12}$, either in solution or bound to alumina, is an effective catalyst for the hydrogenation of alkenes to alkanes[5] in good yield. Asymmetric hydrogenations with enantioselectivities up to 70% have also been achieved by using $Rh_4(CO)_{12}$ in combination with chiral phosphines such as (**1**) and (**2**).[6]

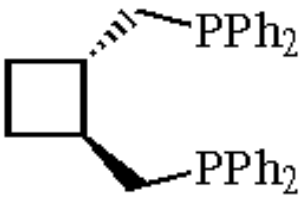

(1)

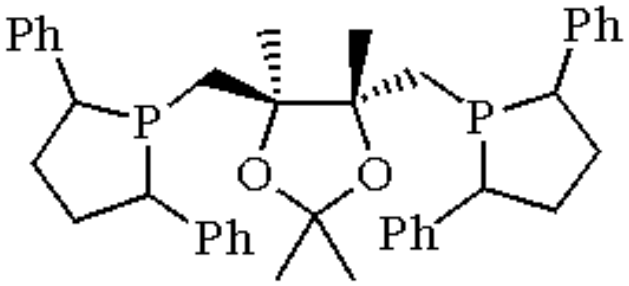

(2)

Hydroformylation.

Alkenes are hydroformylated to aldehydes under mild conditions using $Rh_4(CO)_{12}$ as the catalyst,[7] while alkynes react under water-gas shift conditions to give furan-2(5*H*)-ones (eq 1) as a mixture of isomers when unsymmetrical alkynes are used.[8] Both mono- and disubstituted alkynes have also been found to undergo cross-hydroformylation with ethylene to give exclusively *trans*-α,β-unsaturated ketones in good yield.[9]

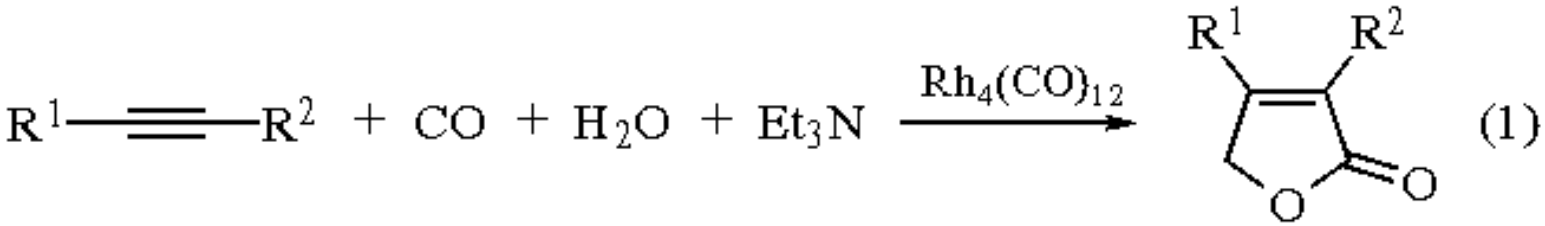

Silylformylation and Hydrosilylation.

The addition of trialkylsilanes and carbon monoxide across the carbon-carbon triple bond of alkynes (silylformylation) is catalyzed by $Rh_4(CO)_{12}$. β-Silylacrylaldehydes are formed in good yield with a high degree of stereocontrol for the (*Z*) isomer (eq 2) (see also ***Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide***).[10] In the presence of a base such as ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) and the highly hindered silane *t*-butyldimethylsilane, propargyl alcohols[11] and propargyl amines[12] can be cyclized to α-silylmethylene-β-lactones and lactams (eq 3; Z = O, NR^3) in good yield. The addition of hydrosilanes across the double bond of alkenes is also catalyzed by $Rh_4(CO)_{12}$.[13]

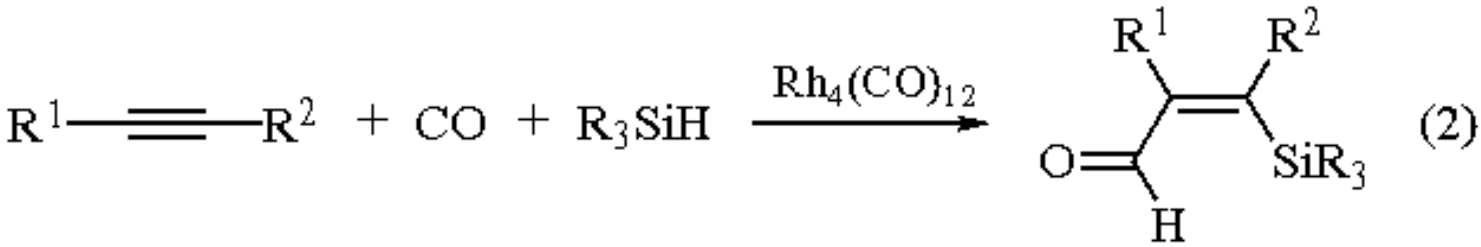

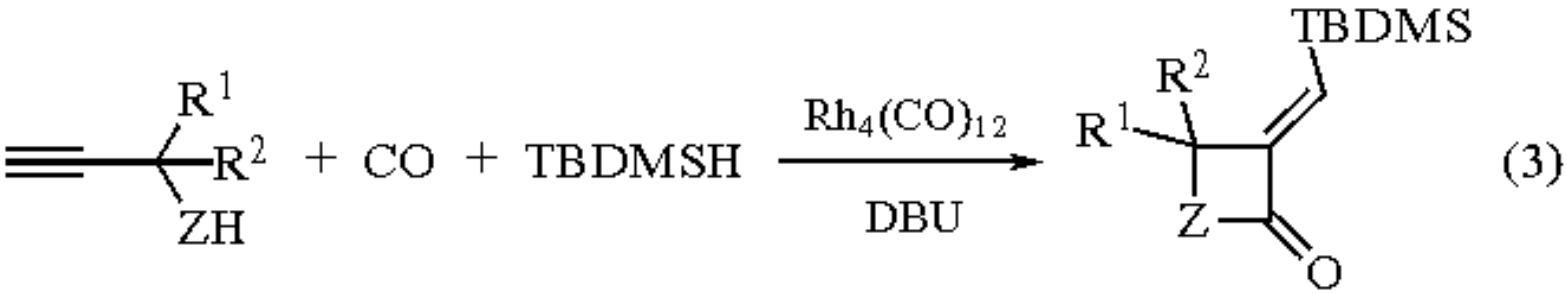

Preparation of (*Z*)-Allylic Boronates.

1,3-Dienes undergo hydroboration with ***Catecholborane*** in the presence of $Rh_4(CO)_{12}$ to give, exclusively, (*Z*)-allylic boronates in good yield.[14] These compounds react with aldehydes to give *erythro*-alcohols (eq 4).

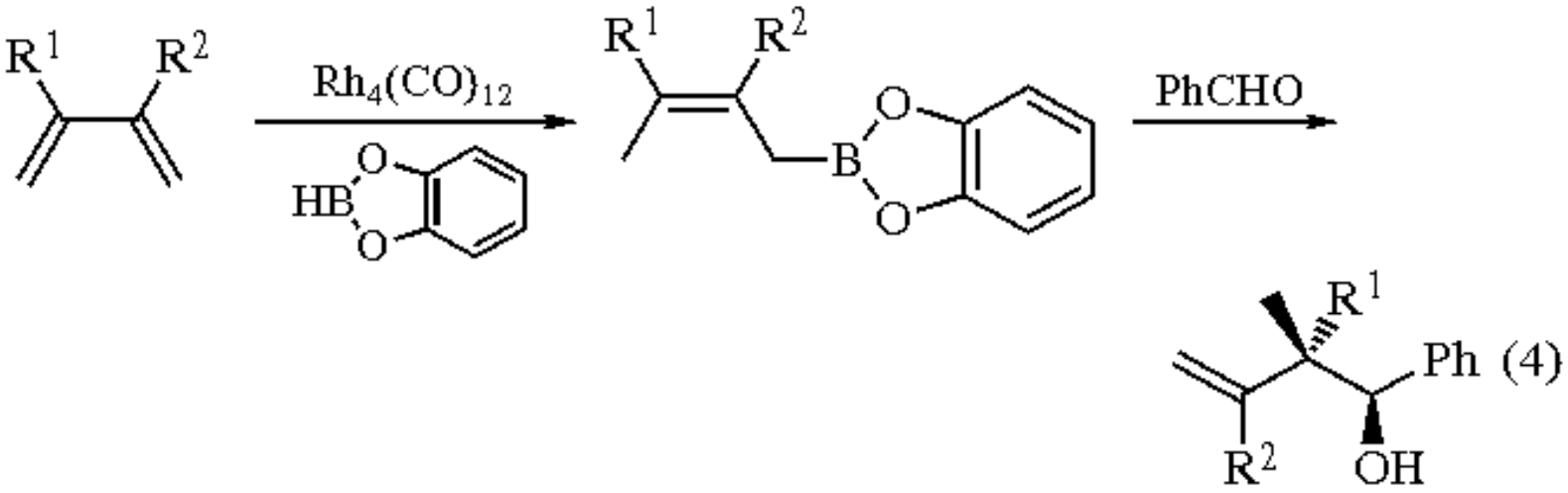

Crossed Aldol Reactions with Enol Trimethylsilyl Ethers.

Crossed aldol reactions of enol trimethylsilyl ethers and aldehydes and ketones occur rapidly in the presence of a catalytic amount of $Rh_4(CO)_{12}$ to give β-trimethylsiloxyalkanones (eq 5), while the reaction of enol trimethylsilyl ethers with acetals yields β-methoxy ketones.[15]

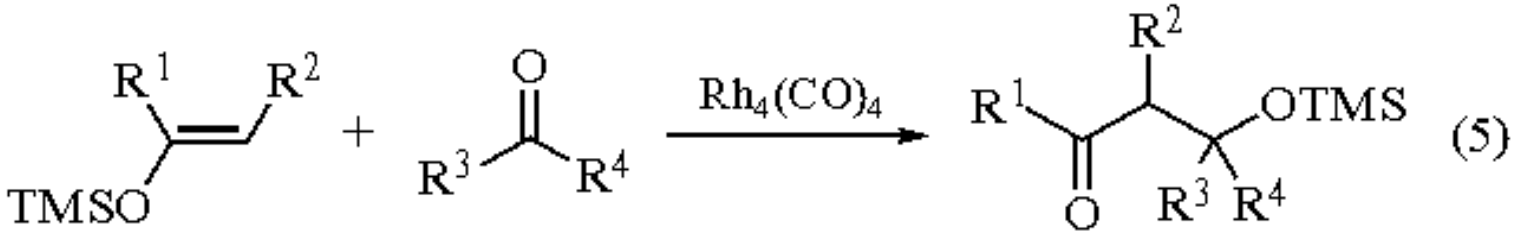

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Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide

$Rh_4(CO)_{12}$-$HSiMe_2Ph$-CO

($Rh_4(CO)_{12}$)

[19584-30-6] · $C_{12}O_{12}Rh_4$ · Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide · (MW 747.76) ($HSiMe_2Ph$)

[766-77-8] · $C_8H_{12}Si$ · Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide · (MW 136.29) (CO)

[630-08-0] · CO · Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide · (MW 28.01)

(silylformylation of alkynes,[1] aldehydes,[8] and oxiranes;[11] siloxymethylenation of enamines[10])

Physical Data: $Rh_4(CO)_{12}$: decomposes to $Rh_6(CO)_{16}$ at 130-140 °C under N_2. $HSiMe_2Ph$: bp 157 °C/744 mmHg; n_D^{20} 1.4995; d_4^{20} 0.889 g cm^{-3}.

Solubility: $Rh_4(CO)_{12}$: readily sol CH_2Cl_2, $CHCl_3$; sol THF, acetone, toluene, pentane; less sol MeOH, cyclohexane.

Form Supplied in: $Rh_4(CO)_{12}$: dark red when crystalline; orange when powdered. $HSiMe_2Ph$: colorless oil.

Purification: $Rh_4(CO)_{12}$: a typical impurity is a trace amount of $Rh_6(CO)_{16}$. A $Rh_6(CO)_{16}$-free product can be obtained by extraction, under CO with pentane, followed by crystallization at -70 °C, filtration at this temperature, and drying in a stream of CO.

Handling, Storage, and Precautions: $Rh_4(CO)_{12}$: stable in air, although on prolonged standing decomposition occurs; best stored under a CO atmosphere.

Silylformylation.

Silylformylation of alkynes with ***Dimethyl(phenyl)silane*** and ***Carbon Monoxide*** leading to β-silylacrylaldehydes is catalyzed by ***Dodecacarbonyltetrarhodium/Triethylamine*** (eq 1).[1] $Co_2Rh_2(CO)_{12}$[2] and ***Dirhodium(II) Tetrakis(perfluorobutyrate)***[3] are also effective for the silylformylation of alkynes. The reaction has been applied to the

formation of β-lactones from propargyl alcohols (eq 2).[4] The products in the reaction of propargyl amines depend on the nature of substituents on nitrogen (eqs 3 and 4).[5] The $Rh_4(CO)_{12}$/$HSiMe_2Ph$/CO combination acts on a diyne to afford a bicyclic ketone (eq 5).[6] Rh-catalyzed silylformylation of alkynes has also been applied to the synthesis of pyrrolizidine alkaloids.[7]

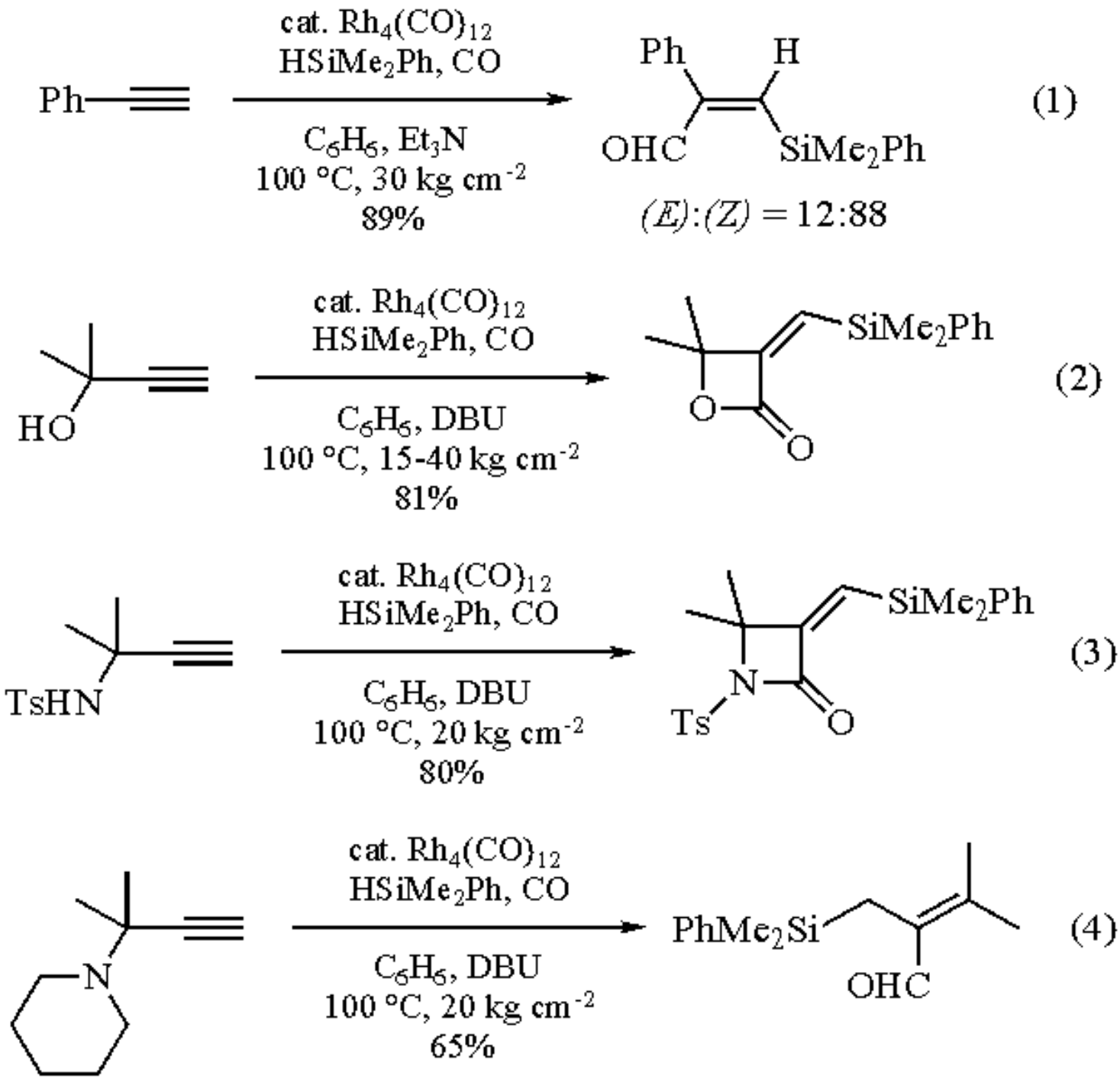

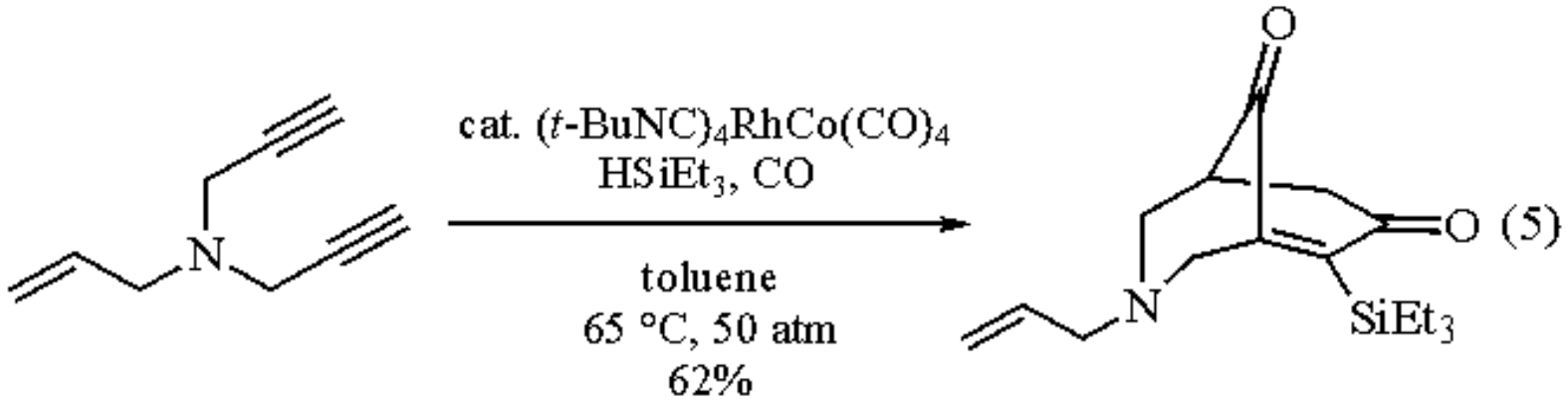

Di-μ-chlorobis(1,5-cyclooctadiene)dirhodium(I) is also an active catalyst for silylformylation of aldehydes, leading to α-siloxy aldehydes under mild reaction conditions (eq 6).[8] Hydrosilanes such as $HSiEt_3$ and $HSiPh_3$ are not effective reagents for Rh-catalyzed silylformylation of aldehydes and $HSiEt_3$ was recovered intact.

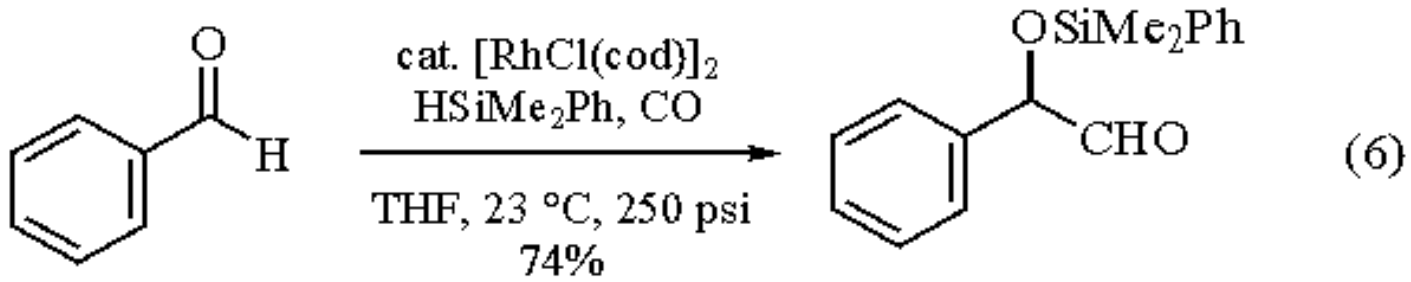

$[RhCl(CO)_2]_2$/$HSiEt_2Me$/CO.

This similar reaction system has been found to be effective for the incorporation of CO into the α-carbon atom of enamines to give α-(siloxymethylene)amines, which can be easily converted into α-siloxy ketones by hydrolysis (eq 7).[9] The system has also been utilized for the incorporation of CO into *N*,*N*-acetals (eq 8).[10] Ring-opening silylformylation of oxiranes is also catalyzed by ***Tetracarbonyl(di-μ-chloro)dirhodium*** (eq 9).[11] The use of $HSiMe_2Ph$ as the hydrosilane gives a higher product yield than with $HSiEt_2Me$.

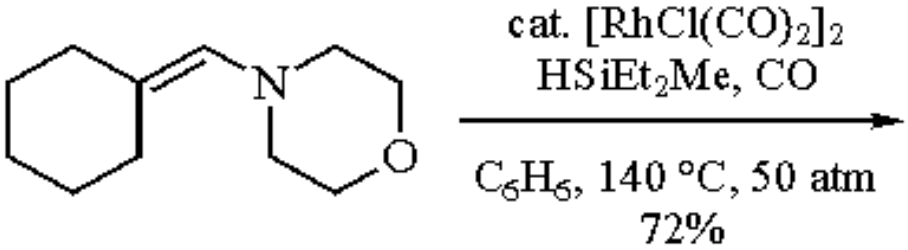

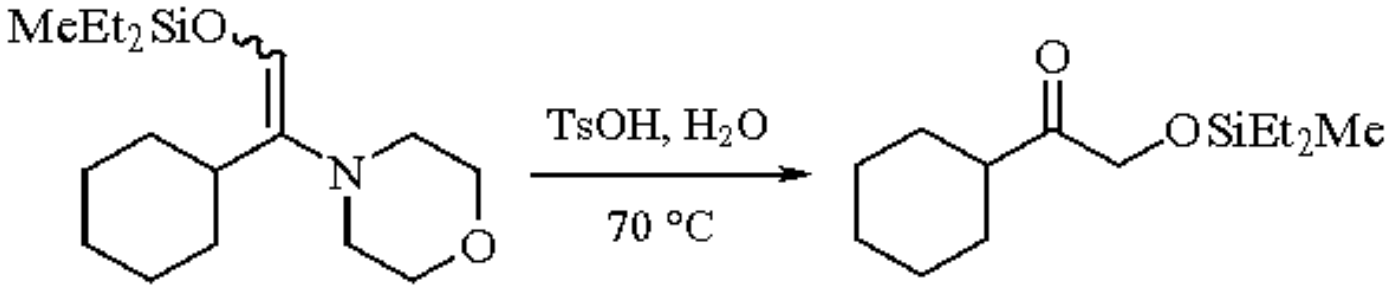

(*E*):(*Z*) = 52:48

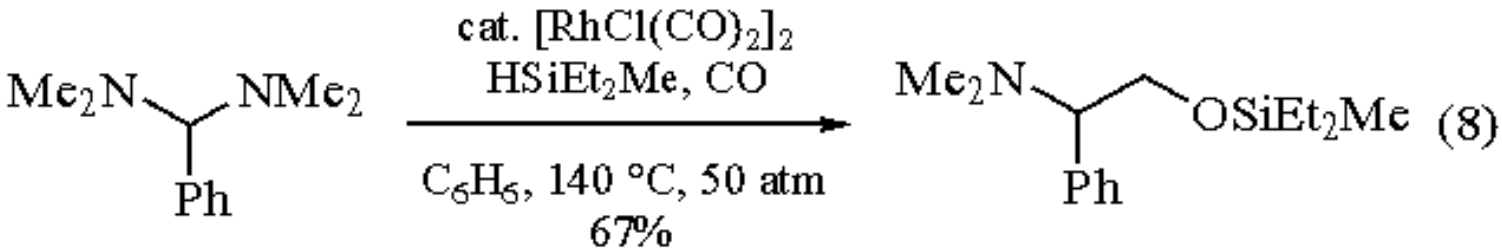

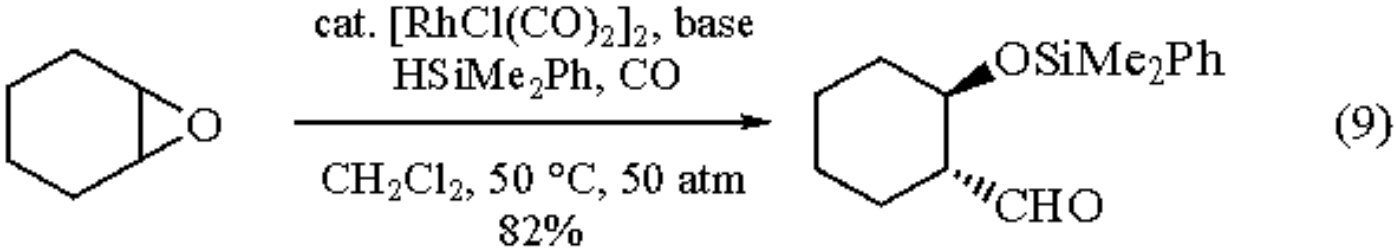

base = 1-methylpyrazole

Related Reagents.

Carbon Monoxide; ***Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide***; ***Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide***.

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Dodecacarbonyltriiron[1]

$Fe_3(CO)_{12}$

[17658-52-8] · $C_{12}Fe_3O_{12}$ · Dodecacarbonyltriiron · (MW 503.67)

(reduces $ArNO_2$ to $ArNH_2$;[1c,5,6] alkyne cyclotrimerization catalyst;[1d,1e,7] isomerizes alkenes;[1f,8] desulfurizes episulfides[1c,9])

Physical Data: mp 140 °C dec.[1]

Solubility: partially sol organic solvents.

Form Supplied in: black air-sensitive solid, stabilized with ~10% methanol which can be removed by leaving on a vacuum pump at 25 °C for at least 5 h.[2]

Analysis of Reagent Purity: IR, ^{13}C NMR.[3]

Purification: sublimation at 70 °C/0.1 mmHg.[1b]

Handling, Storage, and Precautions: store under an inert atmosphere in a freezer; old samples may ignite spontaneously upon exposure to air; emits acrid smoke and fumes when heated to decomposition.[1b,4] Use in a fume hood.

Reduction of Aromatic Nitro Groups to Amines.[1c]

Methanolic solutions of dodecacarbonyltriiron reduce aromatic nitro groups to primary aromatic amines while leaving a variety of functional groups unaffected (Table 1).[5a] Dienes are not reduced by this reagent, but do form a complex with an iron tricarbonyl fragment. These reactions occur under conditions which produce the hydridodecacarbonyltriferrate anion [$HFe_3(CO)_{11}^-$], which is probably the active reducing agent.

Table 1 Reduction of Aromatic Nitro Groups with Methanolic Dodecacarbonyltriion

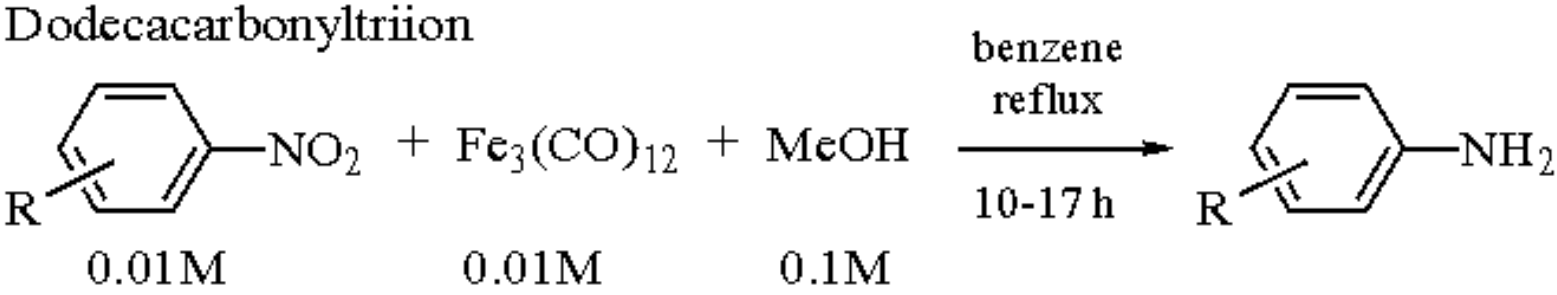

R	Yield $ArNH_2$ (%)
H	77
p-Cl	86
o-Cl	83
m-NH_2	95
p-NH_2	63
p-OMe	84
p-OH	38
m-OH	66
p-NHCOMe	77

Imines are also reduced in reasonable to good yields under the same conditions. Interestingly, the reagent will reduce phthalazine selectively to 1,2-dihydrophthalazine, constituting one of a few methods to accomplish this selective transformation (eq 1).[5b]

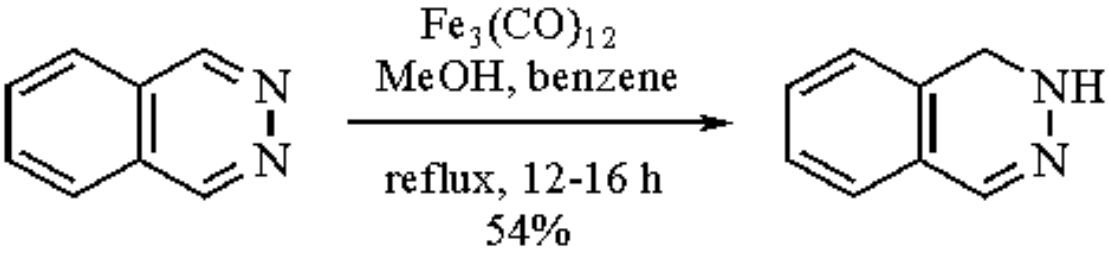

(1)

A number of improvements have been made to the original dodecacarbonyltriiron reduction. A significant rate acceleration was accomplished under phase-transfer conditions in which hydroxide rather than methanol is responsible for the formation of hydridodecacarbonyltriferrate anion (Table 2).[6a] In a similar manner, use of ***18-Crown-6*** in conjunction with 1 N ***Potassium Hydroxide*** in a two-phase reaction medium also leads to short reaction times and good yields of aromatic amines.[6b] A very convenient method for performing these reductions involves stirring the aromatic substrate in hexane solution overnight with dodecacarbonyltriiron adsorbed on basic alumina. Yields obtained from this procedure are good, conditions are significantly milder than the homogeneous reaction, and the workup is quite simple.[6c]

Table 2 Reduction of Aromatic Nitro Groups with Dodecacarbonyltriiron under Phase Transfer Conditions

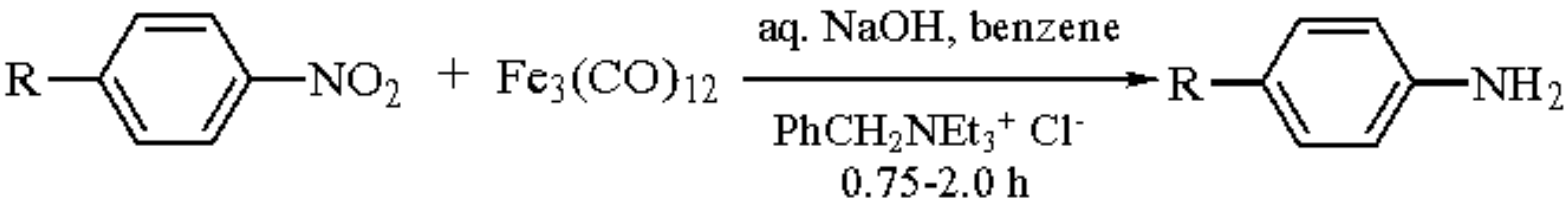

R	Time (h)	Yield $ArNH_2$ (%)
Me	2.0	85
OMe	2.0	92
Cl	0.75	88
COMe	2.0	60

Alkyne Cyclotrimerization.[1d,1e]

Dodecacarbonyltriiron has been reported to catalyze the cyclotrimerization of alkynes, forming substituted benzenes. For example, ***Diphenylacetylene*** forms hexaphenylbenzene upon heating with dodecacarbonyltriiron in a sealed tube (eq 2).[7a,7b] Hexacyclopropylbenzene has also been prepared in this manner from dicyclopropylacetylene in 20% yield with 2,3,4,5-tetracyclopropylcyclopentadienone being formed in ~30% yield as the major byproduct (eq 2).[7c] In fact, cyclopentadienones can be obtained using this reagent and they may be used as precursors to substituted benzenes (eq 3).[7b,7c]

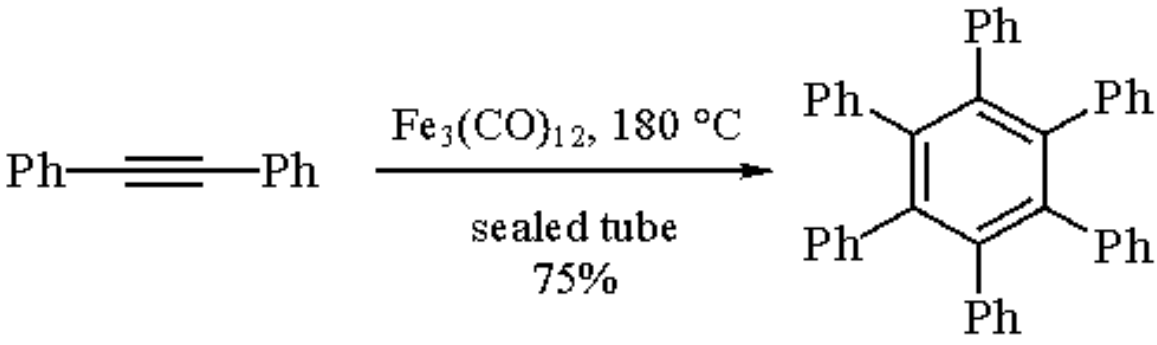

(2)

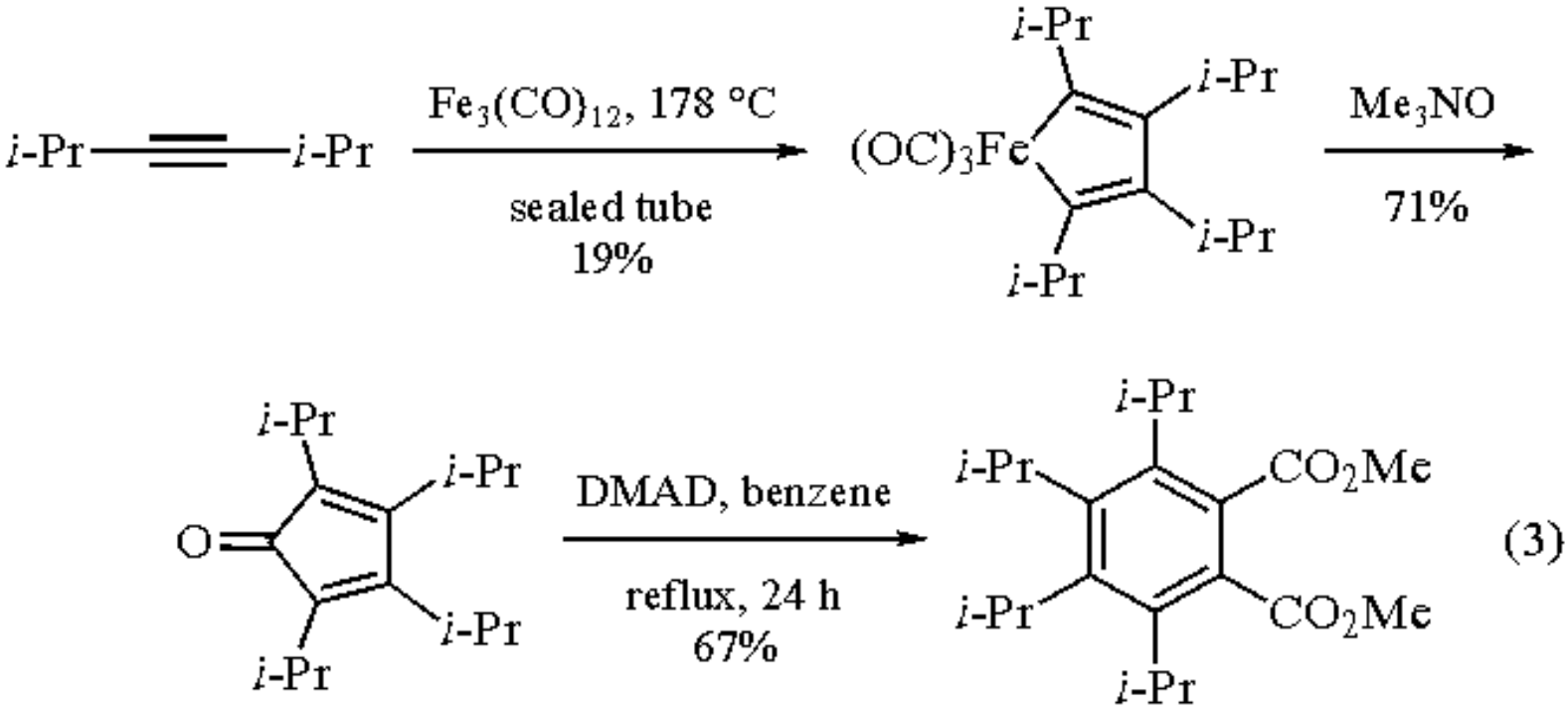

Alkene Isomerization.[1f]

Many metal carbonyl complexes are known to isomerize alkenes, often giving thermodynamic mixtures of alkene isomers. Usually unconjugated dienes are brought into conjugation.[1f] This latter property has been exploited in the isomerization of the cyclopentene double bond of prostaglandin precursors. The free diene is obtained upon oxidation with excess Collins reagent (***Dipyridine Chromium(VI) Oxide***) (eq 4).[8a]

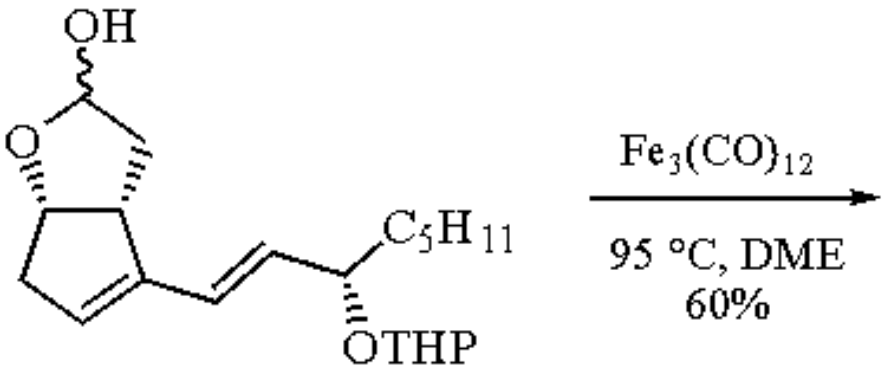

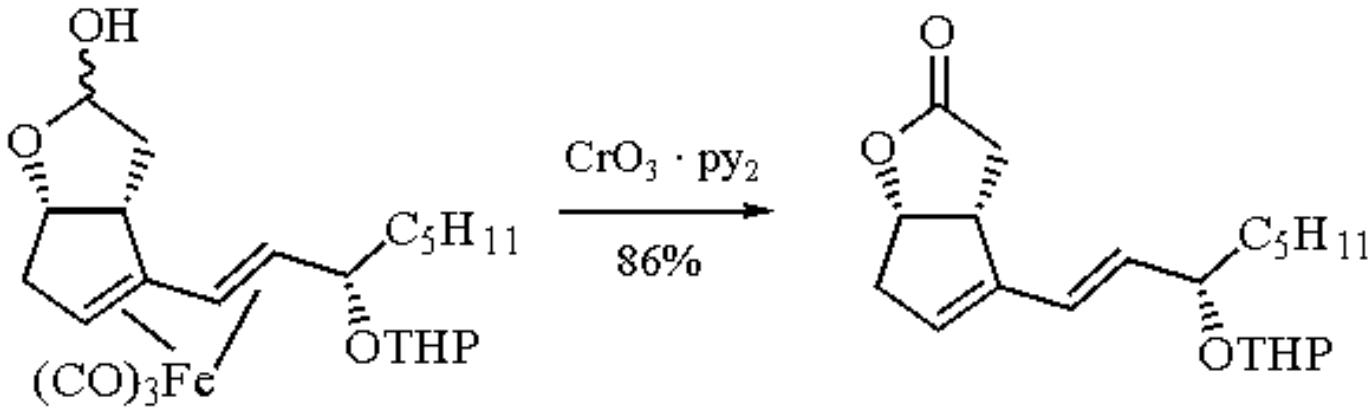

(4)

More recently, it has been shown that dodecacarbonyltriiron will photochemically catalyze the isomerization of allyl alcohols to ketones or aldehydes and allyl ethers and acetates to the corresponding enol ethers and acetates (eqs 5-8).[8b] These isomerization reactions apparently involve a π-allyl-iron hydride intermediate.[8c] The inaccessibility of the allylic hydrogen may account for the *exo*-alcohol's relative inertness to the reagent (eq 8).[8b]

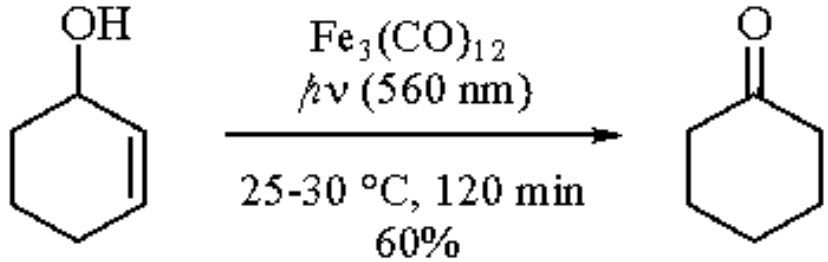

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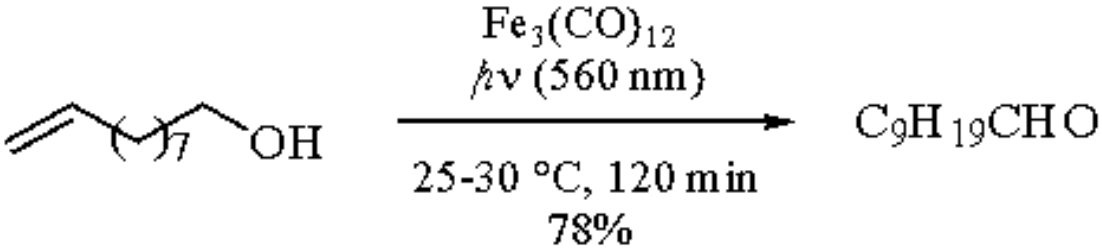

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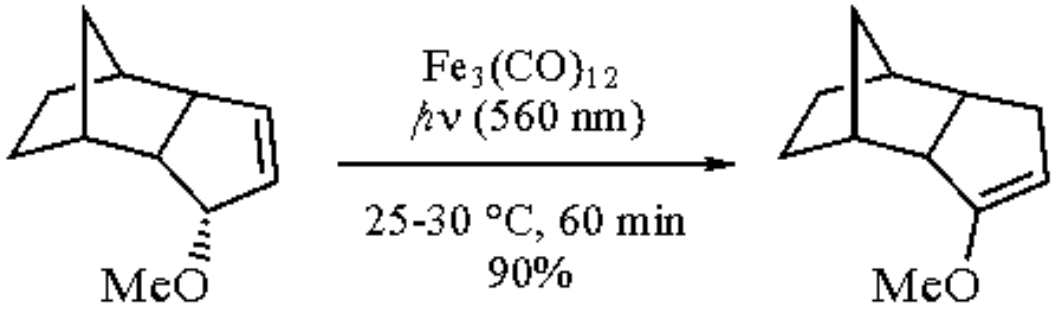

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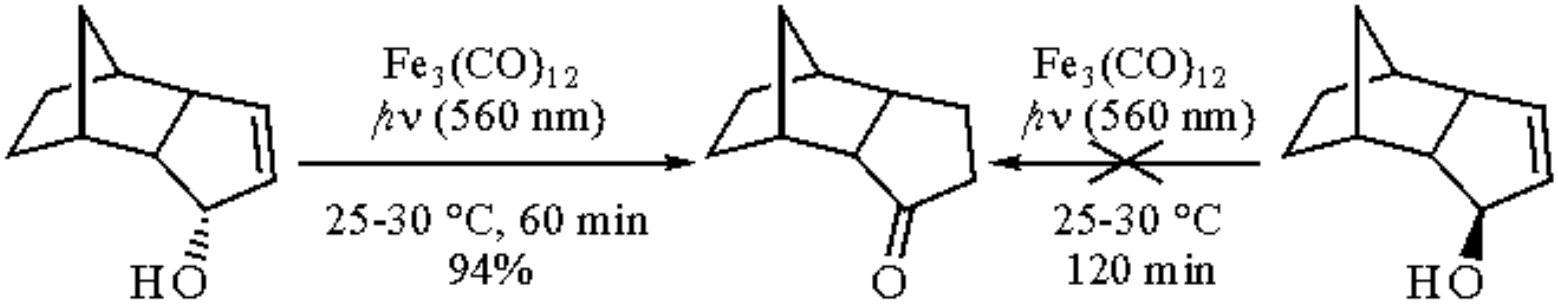

(8)

Episulfide Desulfurization.[1c]

Episulfides are stereospecifically desulfurized by dodecacarbonyltriiron. Thus when heated at reflux in benzene with dodecacarbonyltriiron, *cis*- and *trans*-2-butene episulfide form *cis*- and *trans*-2-butene in 95:5 and 3:97 ratios, respectively.[9]

Related Reagents.

Octacarbonyldicobalt; ***Pentacarbonyliron***.

---

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p-Dodecylbenzenesulfonyl Azide

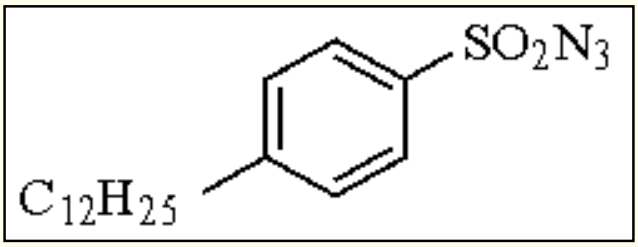

[79791-38-1; 119652-78-7] · $C_{18}H_{29}N_3O_2S$ · *p*-Dodecylbenzenesulfonyl Azide · (MW 351.57)

(diazo-transfer reagent for activated methylene groups[1])

Alternate Name: *p*-DBSA.

Physical Data: liquid mixture of isomers without precise mp or bp.

Solubility: sol pentane, acetone, and most organic solvents.

Form Supplied in: viscous liquid.

Analysis of Reagent Purity: elemental analysis (C, H, N, S) and HPLC.

Preparative Method: prepared by addition of granular ***Sodium Azide*** (1.3 equiv) to a mixture of isomeric sulfonyl chlorides (from a commercial mixture of isomers of *p*-dodecylbenzenesulfonic acid) in acetone solution.[1]

Purification: elution through short column containing silica gel G with methylene chloride-hexane (1:4) as eluant.[1]

Handling, Storage, and Precautions: is the safest of the usual arenesulfonyl azides (tosyl azide, etc.) employed in diazo-transfer processes;[1] appropriate care should be taken, as with all azides. Use in a fume hood.

Reagent for Diazo-Function Transfer.

The title reagent has been called a safer diazo-transfer reagent, and is a mixture of 12 or more isomeric *p*-dodecylbenzenesulfonyl azides, ranging by HPLC from 24% to 1% in area and giving essentially a single spot

by TLC.[1]

The title reagent has been shown to be very useful for the synthesis of various crystalline diazocarbonyl compounds such as diazobarbituric and diazoisopropylidenemalonic acids,[1] derivatives and homologs of diazoacetoacetic acid,[1,2] and 9-diazoanthrone (eq 1).[1]

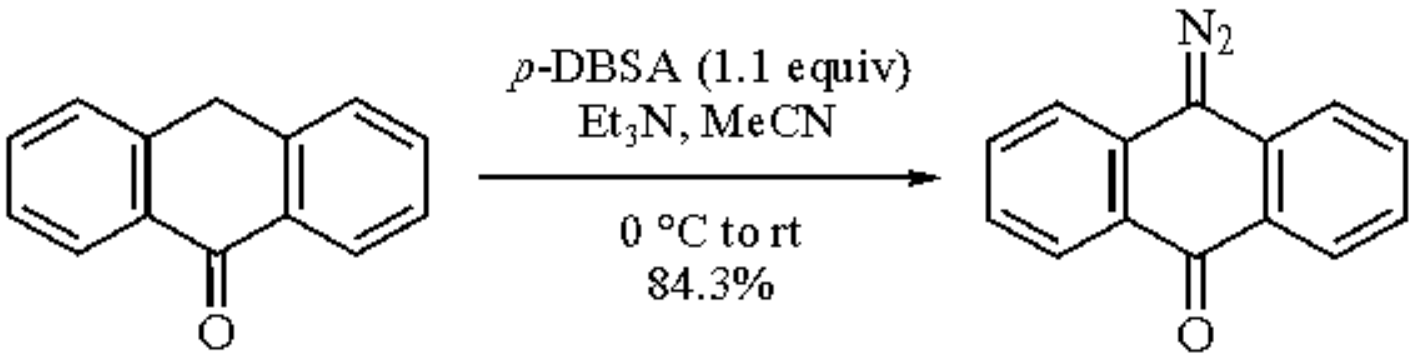

(1)

Formation of noncrystalline byproduct dodecylsulfonamides facilitates the workup procedure and isolation of the target crystalline diazo compounds from the reaction mixture.[1]

Vinyldiazomethanes containing two electron-withdrawing groups are readily available using *p*-DBSA in the presence of ***Triethylamine*** (eq 2).[3]

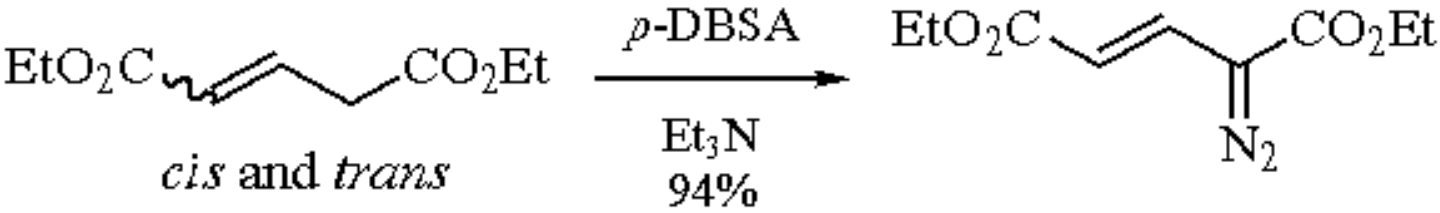

(2)

The process seems to be nonstereospecific. From a mixture of diethyl *cis*- and *trans*-glutaconates, exclusively the *trans*-diazo compound was isolated in high yield, indicating that equilibration occurs under the reaction conditions.[3]

The reagent is also effective in the case of allyl methyl ketone, which has a less acidic methylene group than the previous substrate (eq 3).[4]

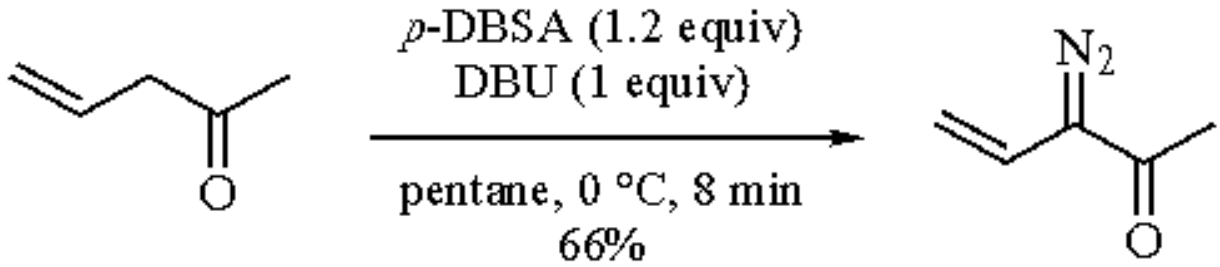

(3)

The reaction is complete in a few minutes but a stronger base, ***1,8-Diazabicyclo[5.4.0]undec-7-ene***, is required

for initial anion formation.

---

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Electrochemical Methods

Electrochemical methods have a long history in organic chemistry dating back (1849!) to the original Kolbe electrolytic dimerization of carboxylic acids. Unfortunately, most organic chemists have considered this an esoteric area as far as synthetic applications are concerned, even though useful selectivity principles have been delineated in considerable detail, and a large number of synthetic applications have been published. Economic advantages of electrochemical methods, in spite of the commercialization of the Monsanto process for the hydrodimerization of acrylonitrile, have not been fully appreciated. Publication of several highly readable books and articles that deal with experimental procedures and listing of equipment suppliers should prompt organic chemists to consider electrochemical methods in synthesis. A list of such references that deal with the practical aspects of electrochemical synthetic methods is given below.[1-9]

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(1*R*,2*S*)-Ephedrine

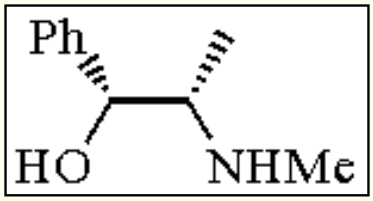

[299-42-3] · $C_{10}H_{15}NO$ · (1*R*,2*S*)-Ephedrine · (MW 165.23)

(chiral auxiliary for the following: diastereoselective alkylation and reduction of chiral hydrazones; diastereoselective alkylation of chiral amides; diastereoselective conjugate addition of organometallic reagents to unsaturated amides and imidazolidinones; diastereoselective alkylation and cyclopropanation of oxazepinediones and oxazolidines; diastereoselective homoaldol addition of *N*-allylimidazolidinone, and asymmetric coupling reaction of Grignard reagents; chiral ligand for enantioselective conjugate addition of organometallic reagents to enones; chiral ligand for enantioselective addition of dialkylzincs to aldehydes)

Alternate Name: [*R*-(*R**,*S**)]-α-[1-(Methylamino)ethyl]benzenemethanol

Physical Data: mp 37-39 °C; bp 255 °C; [α]21D -41° (*c* 5, 1M HCl). Hydrochloride, mp 216-220 °C; [α]20D -34° (*c* 4, H_2O).

Solubility: sol alcohol, chloroform, ether, water.

Form Supplied in: waxy solid or crystals; also available as hydrochloride in either enantiomeric form.

General Features of Ephedrine.

Ephedrine is a chiral β-amino alcohol which is available in either enantiomeric form. It is often utilized as a chiral auxiliary in asymmetric synthesis. Via bond formation with the amino group of ephedrine, ephedrine can be derived into chiral hydrazones[2,3] and amides.[5,6] Highly diastereoselective asymmetric reactions are known using these chiral compounds. In reactions using organometallic reagents, the hydroxy groups of hydrazones and amides become metal alkoxides. Metal atoms of the alkoxide may chelate with nitrogen or oxygen atoms of chiral hydrazones and amides. This chelation may reduce the number of possible conformations of reactive species, and this may increase the diastereoselectivities.

On the other hand, by bond formation with amino and hydroxy groups of ephedrine, ephedrine can be converted into chiral ring systems such as imidazolidinones,[12,13] oxazepinediones,[14-18] and oxazolidines.[20,21] Diastereoselective reactions of derivatives of these chiral ring systems afford compounds with high de. The relatively rigid conformation of these ring systems is one of the reasons for high diastereoselectivities.

(1R,2S)-Ephedrine

Ephedrine becomes a chiral ligand of metal atoms by the deprotonation of the hydroxy group and by the presence of the nitrogen atom.[22-26] Highly enantioselective asymmetric reactions are known using chiral ephedrine-type ligands.

In addition, ephedrine is a chiral base catalyst because of the presence of the amine group.[29-32] A highly enantioselective base-catalyzed reaction is known.

Diastereoselective Alkylation and Reduction of Chiral Hydrazones Derived from Ephedrine.[2]

Methylmagnesium Bromide adds to the chiral hydrazone derived from *N*-aminoephedrine and benzaldehyde to afford the optically active chiral hydrazine in almost 100% de. Hydrogenolysis of the chiral hydrazine gives (*R*)-α-phenylethylamine with more than 97% ee (eq 1). Ephedrine is recovered in good yield and without any loss of optical purity.

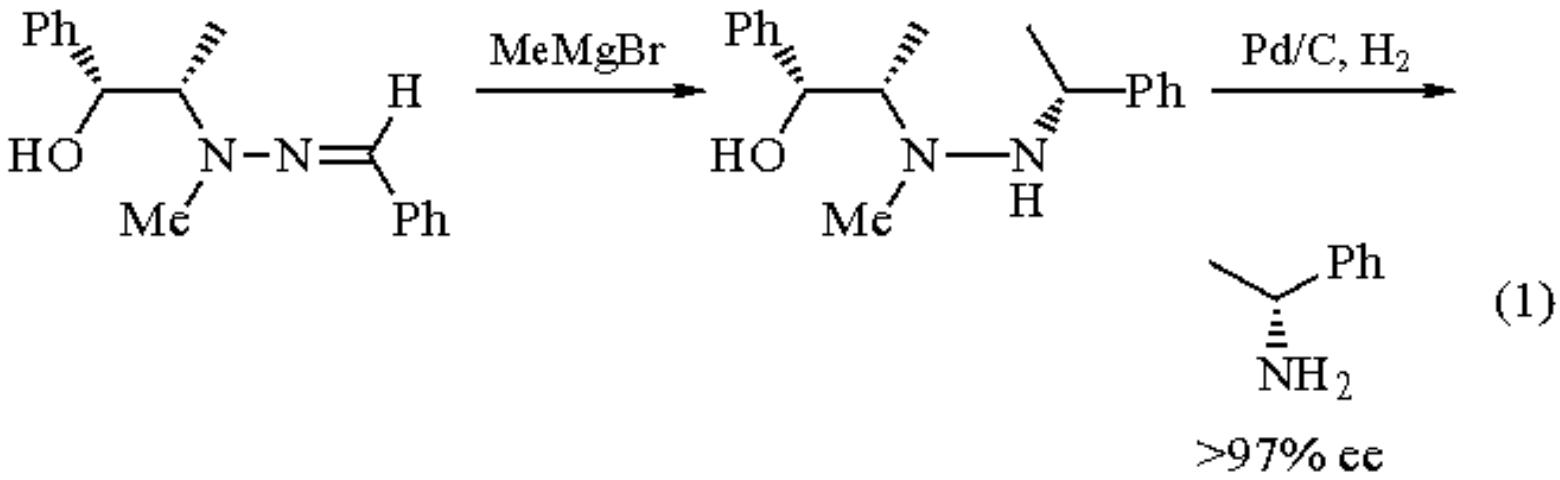

On the other hand, the diastereoselective reduction of the chiral hydrazone derived from *N*-aminoephedrine and acetophenone and subsequent hydrogenolysis affords (*S*)-α-phenylethylamine with 30% ee.[3] Optically active α-phenylethylamine with high ee is obtained from the diastereoselective alkylation of chiral hydrazones derived from (*R*)- or (*S*)-1-amino-2-(methoxymethyl)pyrrolidine.[4a]

Diastereoselective Alkylation of Chiral Amides Derived from Ephedrine.

Chiral amides derived from ephedrine are converted to the corresponding dianion. The subsequent diastereoselective alkylation with alkyl iodides affords chiral α-substituted amides with >90% de.[5] Acid hydrolysis affords optically active α-substituted acids with 78% ee as a result of racemization in the cleavage step (eq 2).

(1R,2S)-Ephedrine

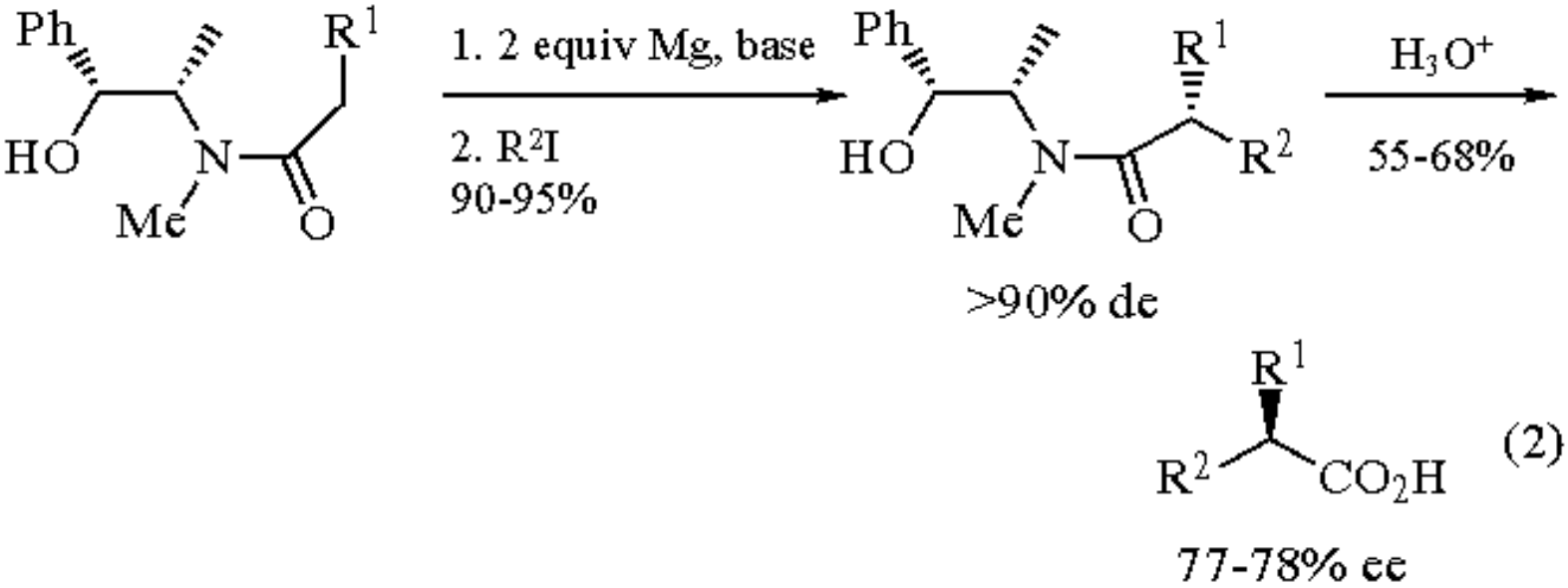

On the other hand, treatment with ***Methyllithium*** affords optically active methyl ketone in 44-74% ee, also as a result of racemization. α-Chiral ketones with higher ee (99% ee) are obtained from the diastereoselective alkylation of chiral hydrazones derived from (*R*)- or (*S*)-1-amino-2-methoxymethylproline.[4b]

Diastereoselective Conjugate Addition of Organometallic Reagents to Chiral α,β-Unsaturated Amides and Imidazolidinones Derived from Ephedrine.

Grignard reagents (2 equiv) add to chiral α,β-unsaturated amides derived from ephedrine in a 1,4-addition manner with high diastereoselectivities. Subsequent acidic hydrolysis affords optically active β-substituted carboxylic acids with 85-99% ee (eq 3).[6]

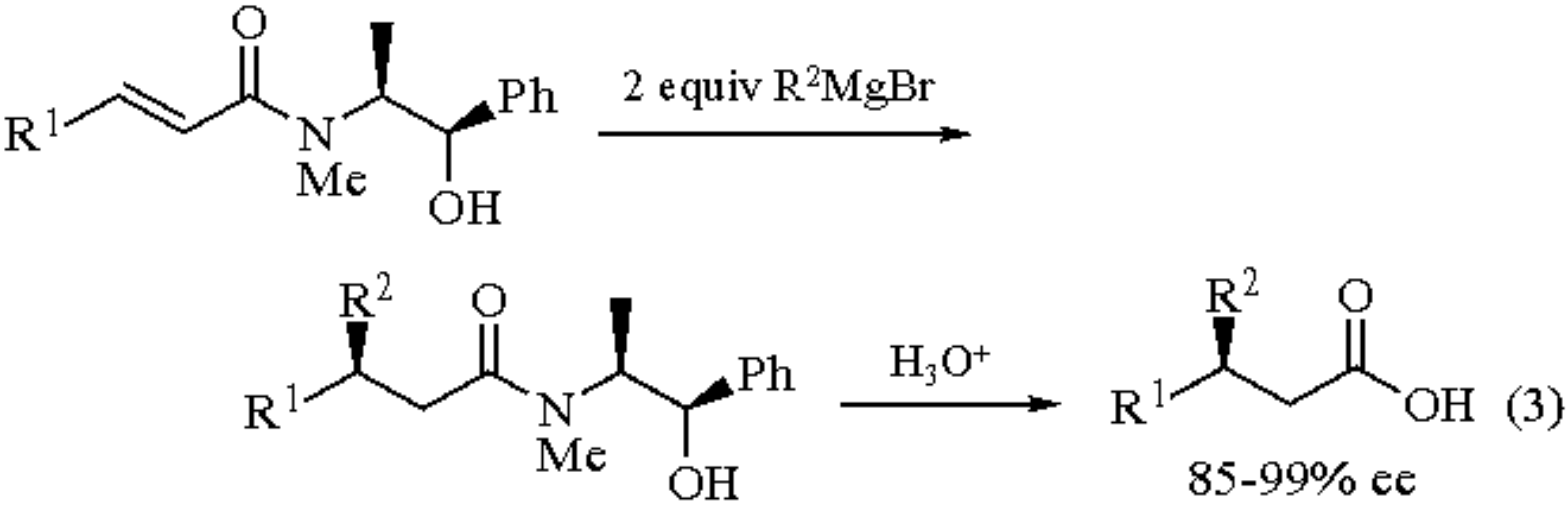

A seven-membered chelate intermediate is one of the reasons for the very high diastereoselectivities. The method is successfully applied to the asymmetric synthesis of malingolide.[7] Similar results are obtained in diastereoselective conjugate addition of Grignard reagents to unsaturated amides derived from (*S*)-2-(1-hydroxy-1-

methylethyl)pyrrolidine. The presence of a tertiary amine (e.g. ***1,8-Diazabicyclo[5.4.0]undec-7-ene***) increases the diastereoselectivity, and subsequent hydrolysis affords β-substituted carboxylic acids with up to 100% ee.[8] Conjugate additions of alkyllithium or Grignard reagents to chiral *N*-crotonoylproline,[9] imides,[10] and *N*-enoyl sultams[11] also afford β-substituted carboxylic acids with 60% ee, 96% ee, and 96% ee, respectively.

The chiral imidazolidinone[12] derived from urea and ephedrine hydrochloride is utilized in a diastereoselective conjugate methylation.[13] Subsequent hydrolysis affords optically pure (-)-citronellic acid (eq 4).

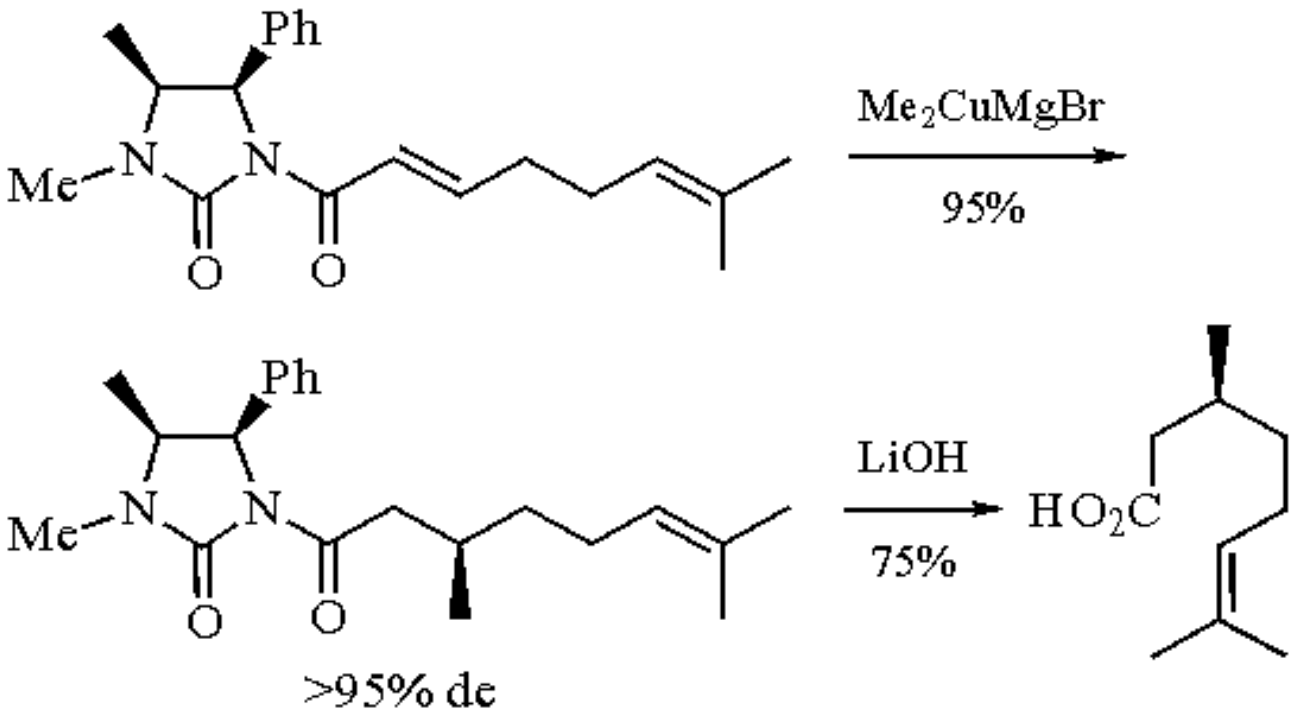

(4)

Diastereoselective Conjugate Additions to Chiral Oxazepinediones Derived from Ephedrine.

Ephedrine can form a chiral seven-membered relatively rigid oxazepinedione ring by condensation with malonic acid monoester. Alkylidene derivatives of chiral oxazepinediones undergo highly diastereoselective additions with nucleophilic reagents. Grignard reagents in the presence of a catalytic amount of ***Nickel(II) Chloride*** add to chiral alkylideneoxazepinediones. Acid hydrolysis affords optically active β-substituted acids with up to >99% ee (eq 5).[14] The method is applied to the diastereoselective synthesis of (-)-indolmycin with 93% ee.[15]

(1R,2S)-Ephedrine

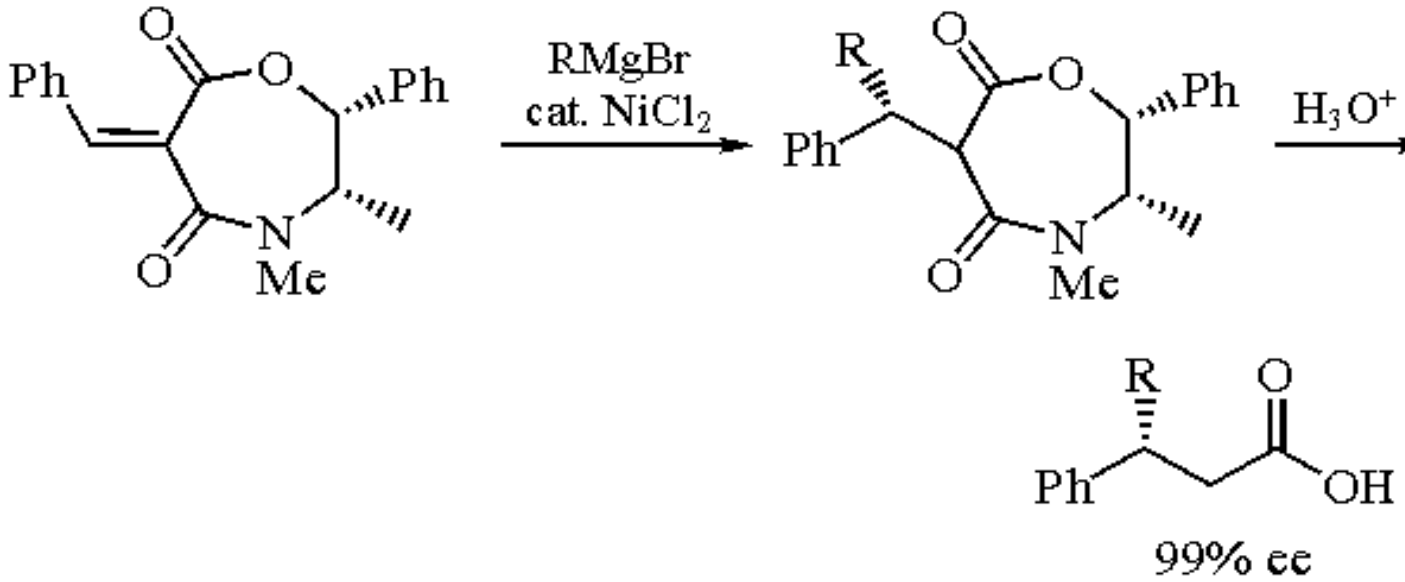

(5)

Diastereoselective addition of sulfonium ylides affords enantiomerically pure cyclopropanedicarboxylic acid diesters after removal of the chiral auxiliary (eq 6).[16]

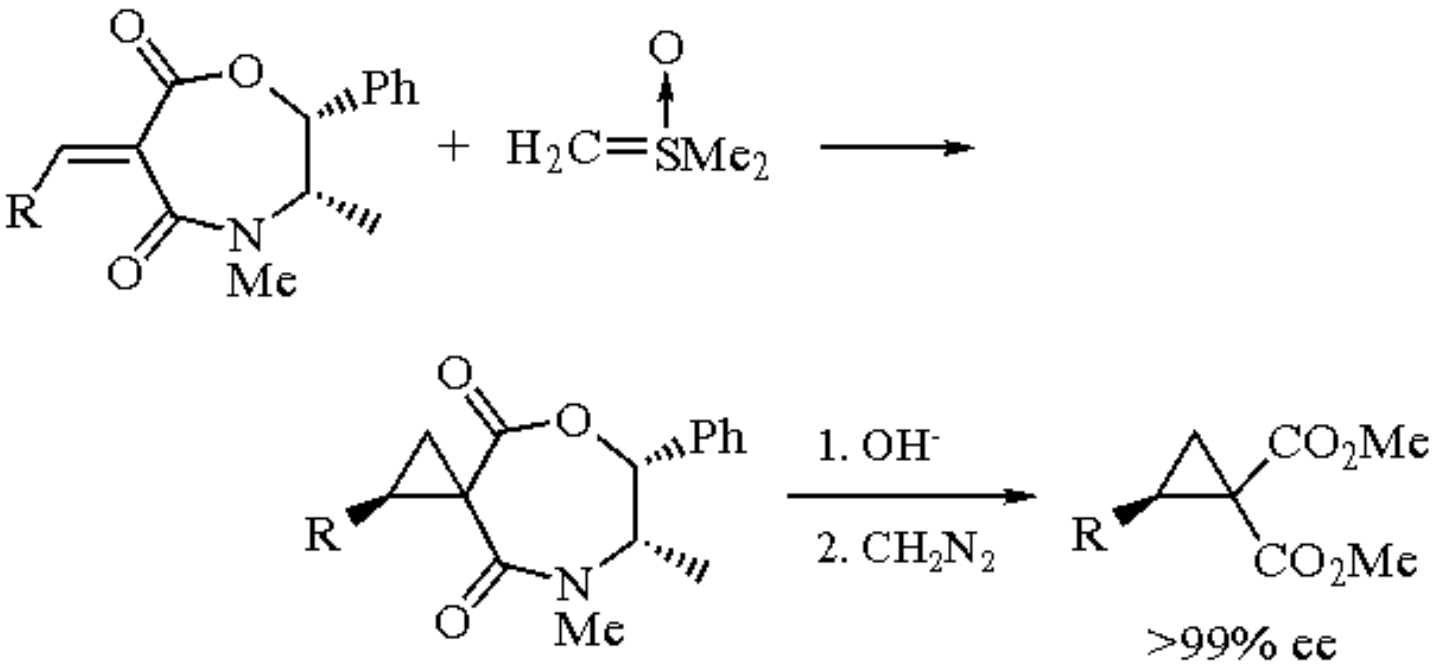

(6)

Diastereoselective addition of ***Phenylthiomethyllithium*** and subsequent treatment affords optically active lactones with >90% ee (eq 7).[17]

(1R,2S)-Ephedrine

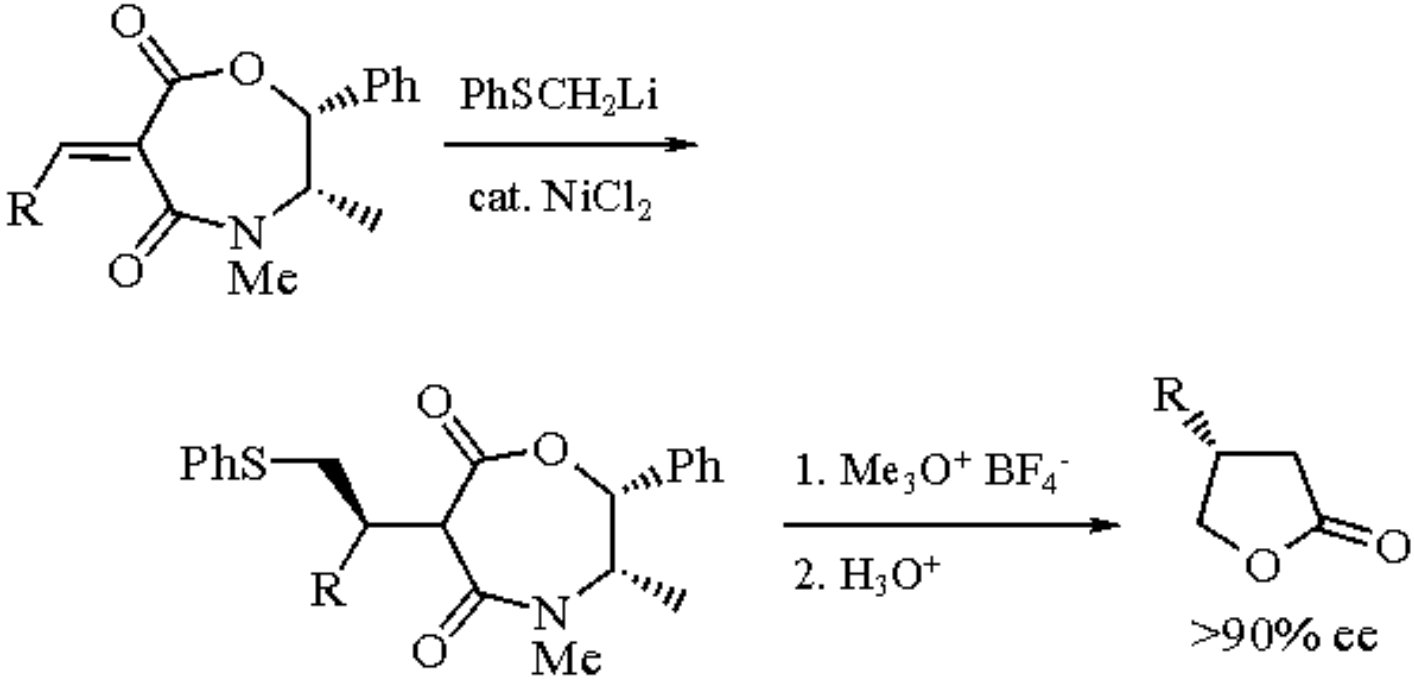

(7)

In addition, a chiral oxazepinedione plays the role of a nucleophile in the reaction with nitroalkenes in the presence of ***Potassium t-Butoxide*** and crown ether (eq 8).[18]

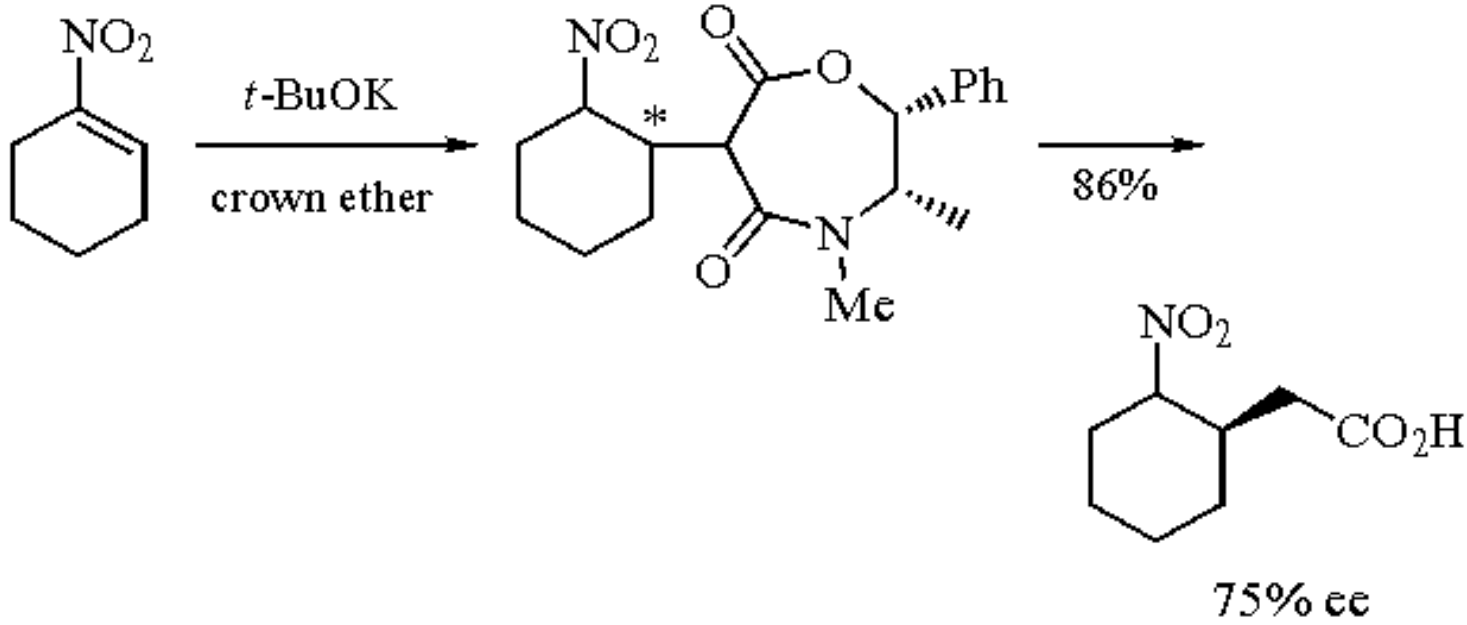

(8)

Homoaldol Addition with Chiral *N*-Allylimidazolidinone Derived from Ephedrine.

The chiral allyltitanium compound derived from ephedrine reacts with carbonyl compounds with very high (>200:1) de. Subsequent hydrolysis and oxidation affords optically pure 4-substituted γ-lactones (eq 9).[12] 4-Substituted γ-lactones with 92% ee can also be synthesized by catalytic enantioselective alkylation of 3-formyl esters.[19]

(1R,2S)-Ephedrine

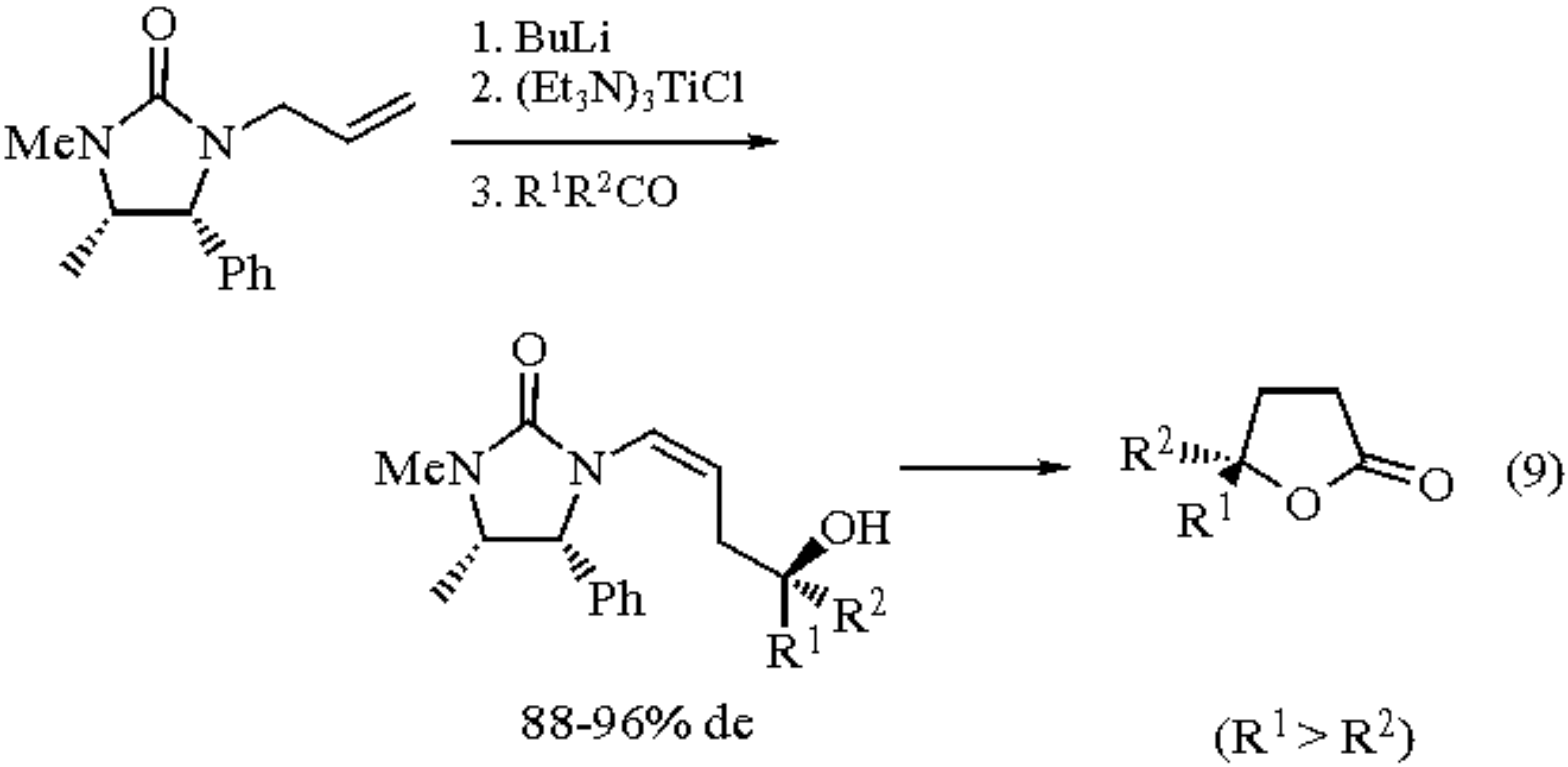

Diastereoselective Cyclopropanation and Alkylation of Chiral Oxazolidines Derived from Ephedrine.

Ephedrine forms oxazolidines upon reaction with aldehydes. Chiral unsaturated oxazolidines derived from ephedrine and unsaturated aldehydes are treated with diazomethane in the presence of ***Palladium(II) Acetate***. Hydrolysis of the oxazolidine ring affords optically active formylcyclopropanes with >90% ee (eq 10).[20]

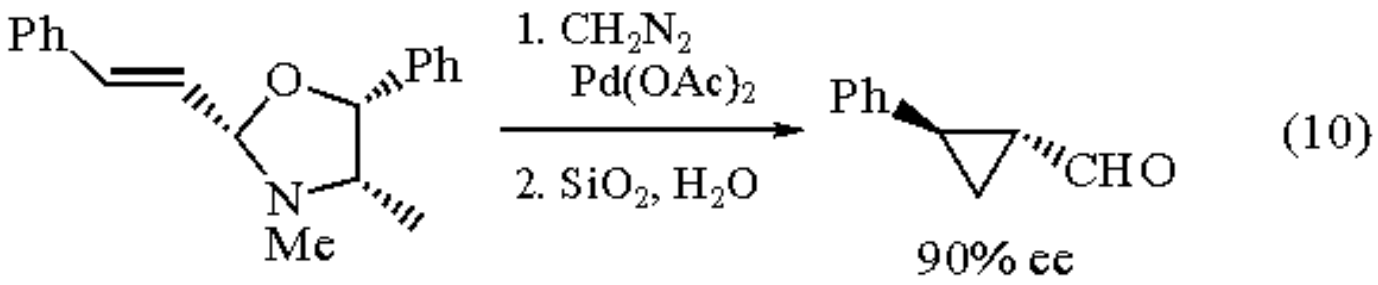

Diastereoselective addition of cuprate reagents to unsaturated oxazolidines and subsequent hydrolysis affords 3-substituted aldehydes with up to 81% ee (eq 11).[21]

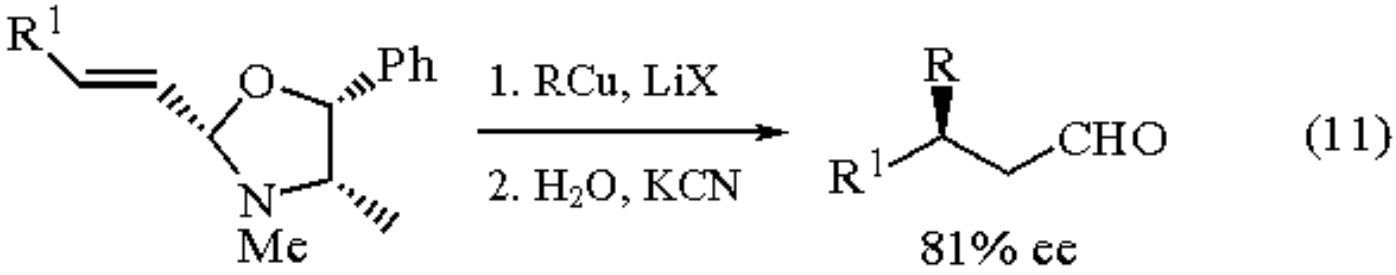

Asymmetric Coupling Reactions of Chiral Grignard Reagents Derived from Ephedrine Derivatives.

Asymmetric coupling reactions of ***Allyl Bromide*** and chiral Grignard reagents derived from ephedrine methyl ether in the presence of ***Copper(I) Iodide*** (10 mol %) followed by oxidation affords optically active homoallyl alcohols with 60% ee (eq 12).[22]

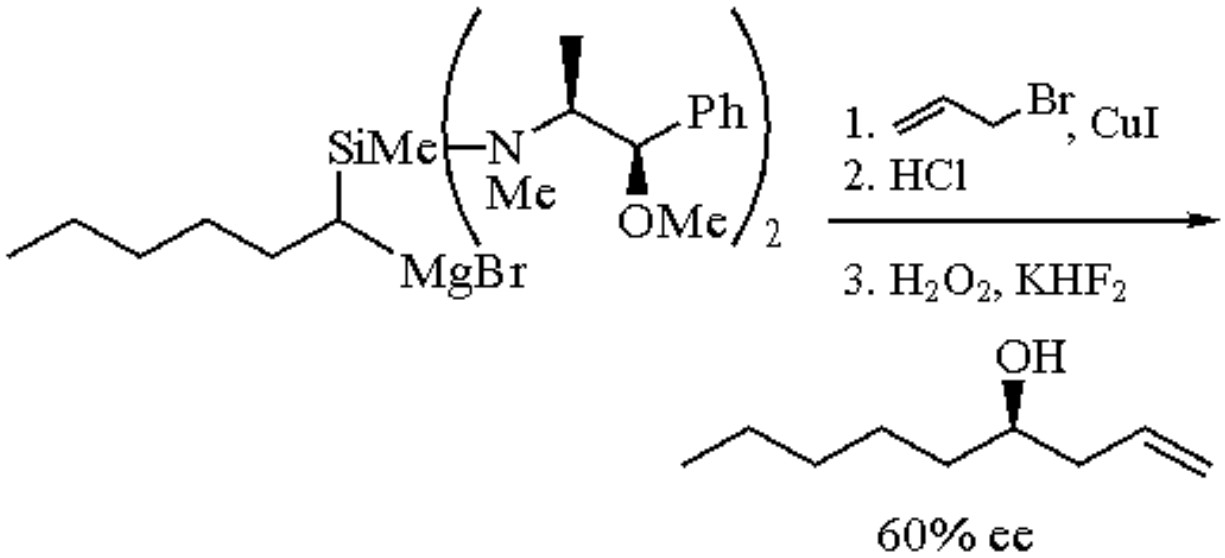

(12)

Enantioselective Conjugate Addition to Prochiral Enones of Organometallic Reagents Modified with Ephedrine.

Enantioselective conjugate addition to 2-cyclohexenone with chiral organo(alkoxo)cuprates [MCu(OR*)R] has been studied.[1a] When the cuprate is prepared from the lithium alkoxide of ephedrine, ***Phenyllithium***, and CuI, 3-phenylcyclohexanone with 50% ee is obtained.[23] The enantioselectivity reaches 92% ee in enantioselective ethylation when a chiral diamino alcohol derived from ephedrine is employed (eq 13).[24]

(1R,2S)-Ephedrine

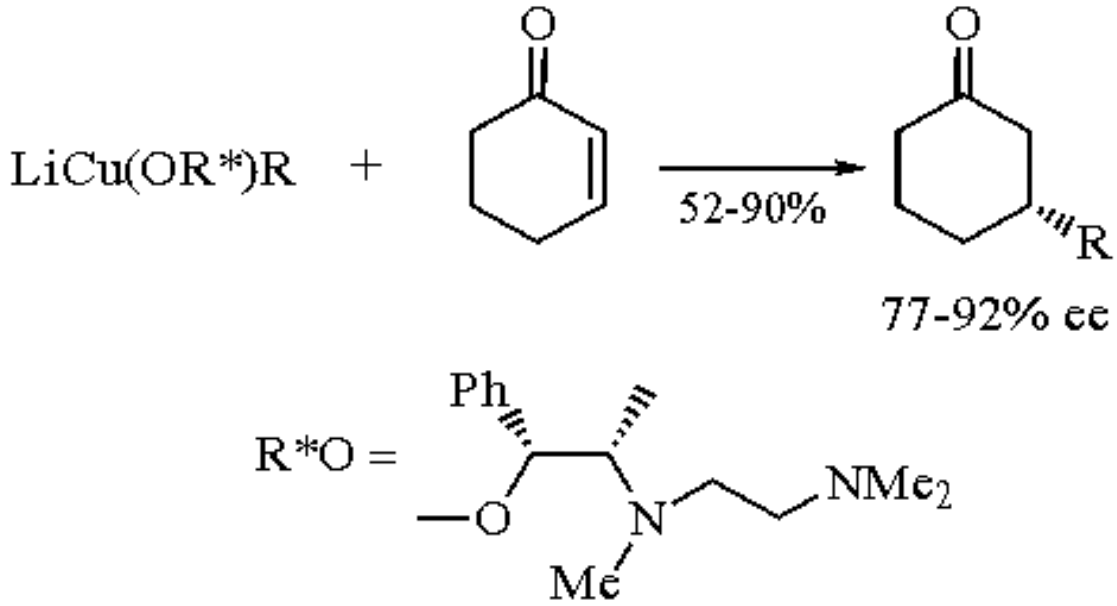

(13)

On the other hand, enantioselective conjugate addition to 2-cyclohexenone with lithium dibutylcuprates (having a noncovalently bound chiral phosphorus ligand derived from ephedrine) affords 3-butylcyclohexanone with up to 76% ee (eq 14).[25]

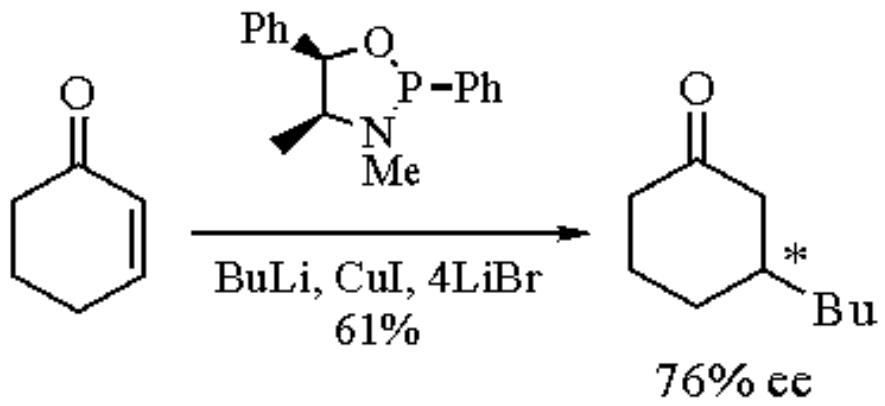

(14)

Isopropylmagnesium chloride adds to 2-cyclohexenone in 17% ee in the presence of a catalytic amount of chiral alkoxyzinc chloride derived from ephedrine and ***Zinc Chloride*** (eq 15).[26]

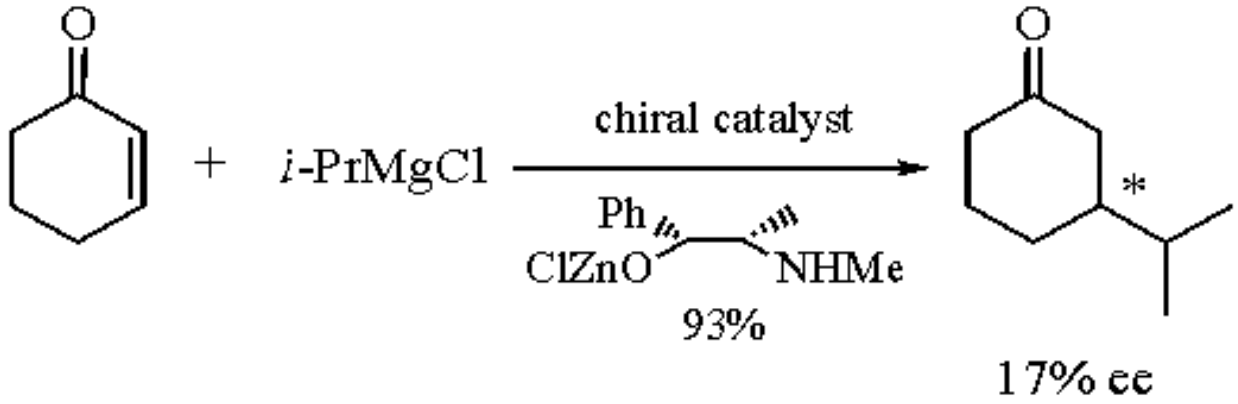

(15)

Concerning the catalytic enantioselective conjugate addition reaction, conjugate addition of dialkylzinc to chalcone in

the presence of a catalytic amount of the chiral nickel complex derived from norephedrine affords β-substituted ketones with up to 90% ee (eq 16).[27]

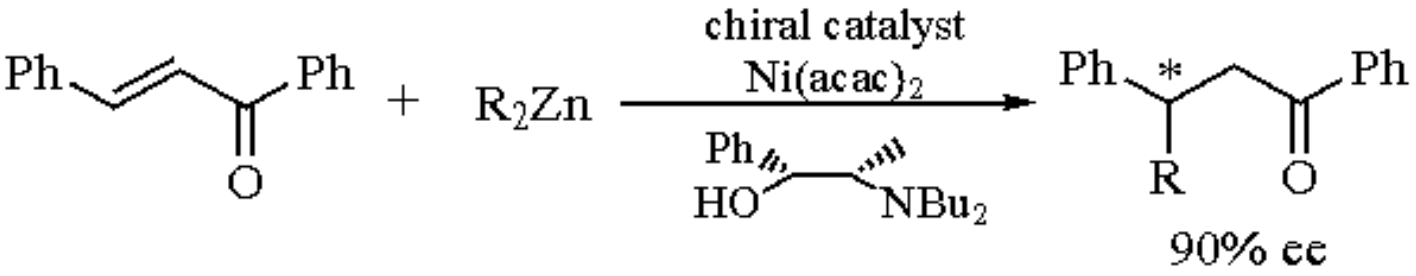

(16)

Enantioselective Addition of Dialkylzincs to Aldehydes Using Chiral Amino Alcohols Derived from Ephedrine.

Nucleophilic addition of dialkylzinc to aldehydes is usually very slow. Amino alcohols facilitate the addition of ***Diethylzinc*** to benzaldehyde to afford 1-phenylpropanol.[1b,28] When chiral amino alcohols possessing the appropriate structure are used as a precatalyst, optically active secondary alcohols are obtained.[1b] Highly enantioselective chiral catalysts derived from ephedrine are known. (1*R*,2*S*)-*N*-Isopropylephedrine functions as a precatalyst for the enantioselective addition of diethylzinc to benzaldehyde to afford (*R*)-1-phenylpropanol with 80% ee in 72% yield.[29] The use of an excess amount of diethylzinc increases the enantioselectivity up to 97% ee (eq 17).[30]

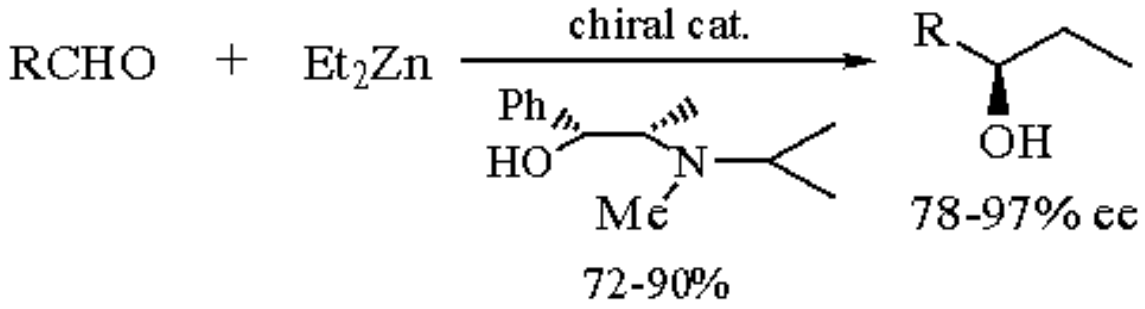

(17)

The lithium salt of (1*R*,2*S*)-*N*-[2-(dimethylamino)ethyl]ephedrine acts as a precatalyst for the addition of diethylzinc to afford the alcohol with 90% ee (eq 18).[31]

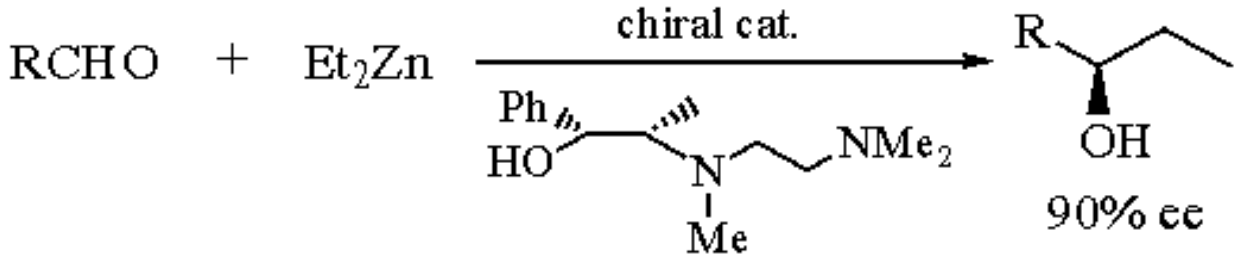

(18)

The dilithium salt of a chiral diaminodiol derived from ephedrine mediates the enantioselective addition of dialkylzinc to aldehydes to afford (*R*)-1-phenylethanol with 85% ee (eq 19).[32]

(1R,2S)-Ephedrine

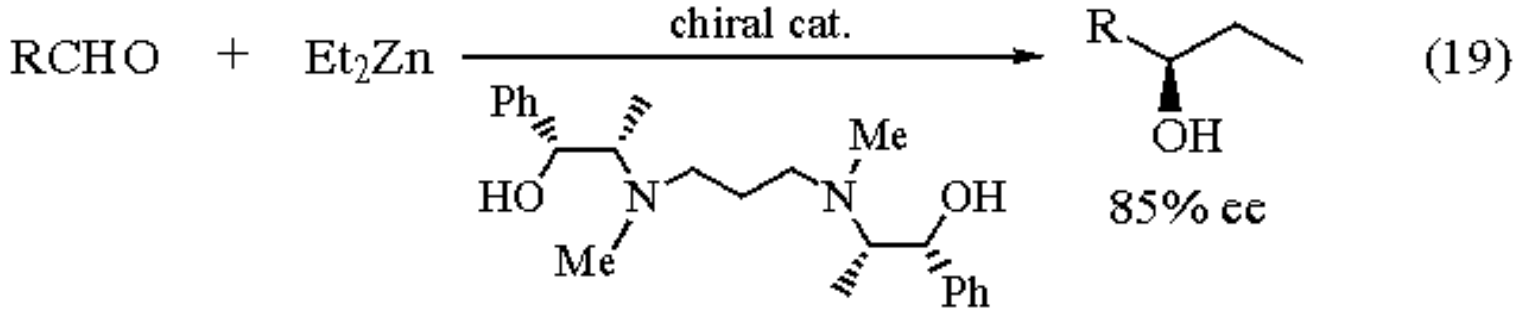

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Ephedrine-borane[1]

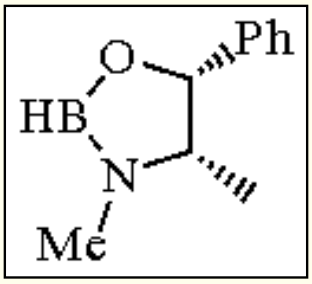

[126874-38-2] · $C_{10}H_{14}BNO$ · Ephedrine-borane · (MW 175.04)

(chiral Lewis acid catalyst for carbonyl additions, reductions, and hydroborations[1])

Alternate Name: (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine.

Physical Data: [2,4] colorless liquid, bp 110-112 °C/20 mmHg, 45 °C (bath)/0.1 mmHg; [α]20D = -108° (*c* 1.0 $CHCl_3$). For the corresponding reagent prepared from pseudoephedrine (1*S*,2*S*), [α]20D = +59° (*c* 1.0 $CHCl_3$). Spectral data:[2a,3,4] ^{1}H NMR selected data δ ($CDCl_3$) 3.68 (m), 5.58 (d, *J* = 8.5 Hz); ^{1}H NMR δ (C_6D_6) 0.43 (d, *J* = 6.6 Hz), 2.50 (s), 3.28 (m), 5.41 (d, *J* = 8.6 Hz); ^{11}B NMR δ +29 ppm (d, *J* = 147 Hz); ^{13}C NMR δ (C_6D_6) 15.42, 30.25, 59.62, 83.58, 126.59, 127.32, 128.13, 140.02; IR_{B-H} 2562 cm^{-1}. For the corresponding reagent from pseudoephedrine (1*S*,2*S*): ^{1}H NMR selected data δ ($CDCl_3$) 3.30 (m), 4.90 (d, *J* = 7.0 Hz).

Solubility: sol THF.

Form Supplied in: not commercially available.

Preparative Methods: [2] a solution of (1*R*,2*S*)-(-)-ephedrine (8.25 g, 50 mmol) in anhydrous THF (50 ml) was treated with ***Borane-Dimethyl Sulfide*** complex (50 mmol, 5 mL of 10 M solution). The reaction mixture was stirred at 25 °C for 1 h, at which time one equivalent of hydrogen had evolved. The volatiles were removed in vacuo to furnish a white solid, ^{11}B NMR (δ ~8 ppm). The solid was gradually heated to 100 °C and maintained at that temperature until the second equivalent of hydrogen had evolved. The product was distilled under reduced pressure to provide the pure oxazaborolidine (86%). An alternative procedure is available.[3]

Handling, Storage, and Precautions: the reagent is sensitive to moisture and should be handled under a dry, inert atmosphere.

Enantioselective Addition of Diethylzinc to Aldehydes.

The reagent catalyzes the enantioselective addition of ***Diethylzinc*** to aldehydes (eq 1).[2]

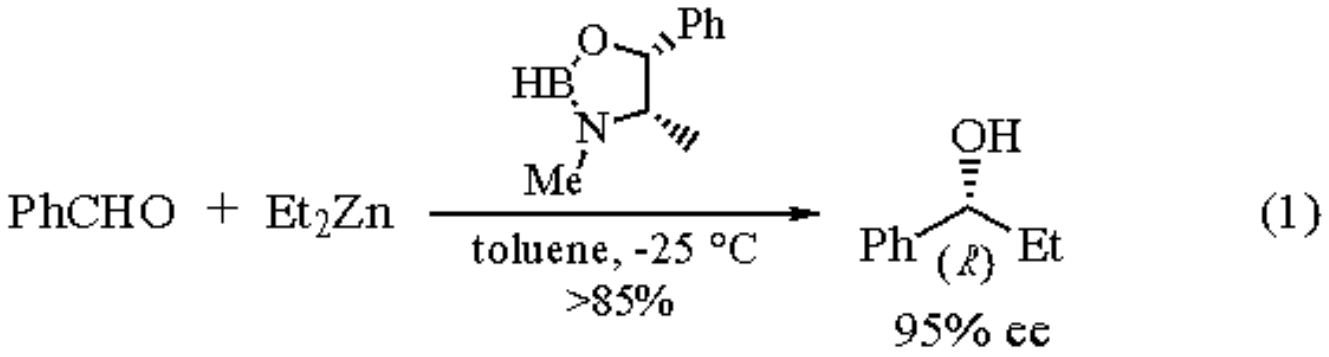

Enantioselective Alkene Hydroboration.

Substituted styrene derivatives undergo rhodium-catalyzed hydroboration in the presence of a catalytic amount of the title reagent. However, optimal regio- as well as enantioselection is attained by using the corresponding reagent derived from pseudoephedrine (eq 2).[4]

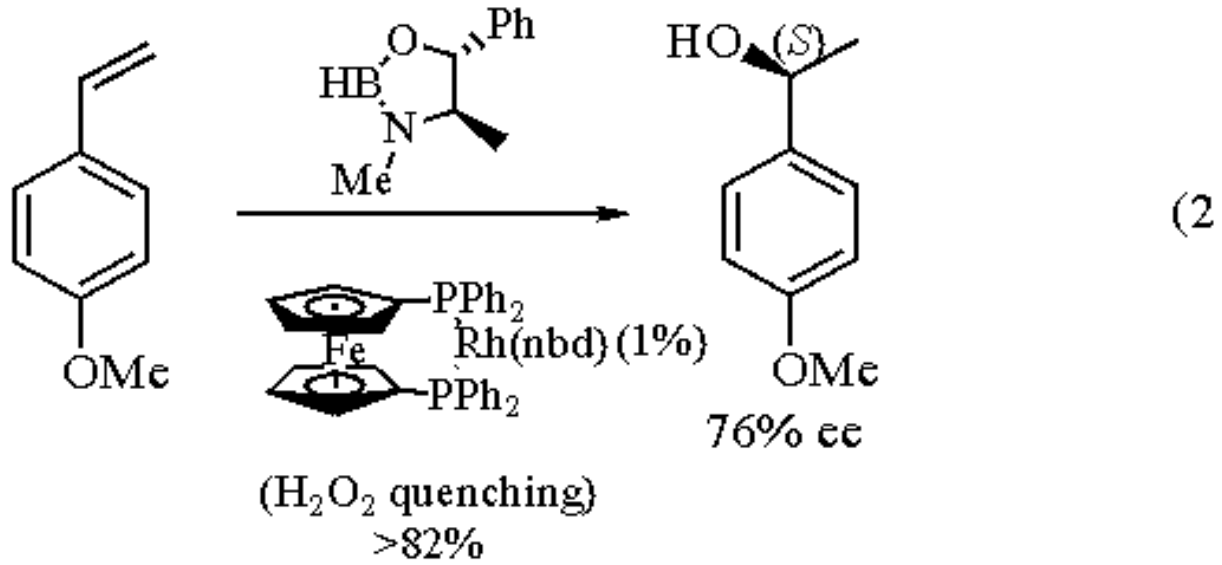

If the *N*-isopropyl analog of the borane reagent is used in conjunction with bis(4-methoxystyrene)rhodium chloride dimer as catalyst, the corresponding (*E*)-vinylborane and 4-methoxyethylbenzene are obtained in equal proportions (eq 3).[5]

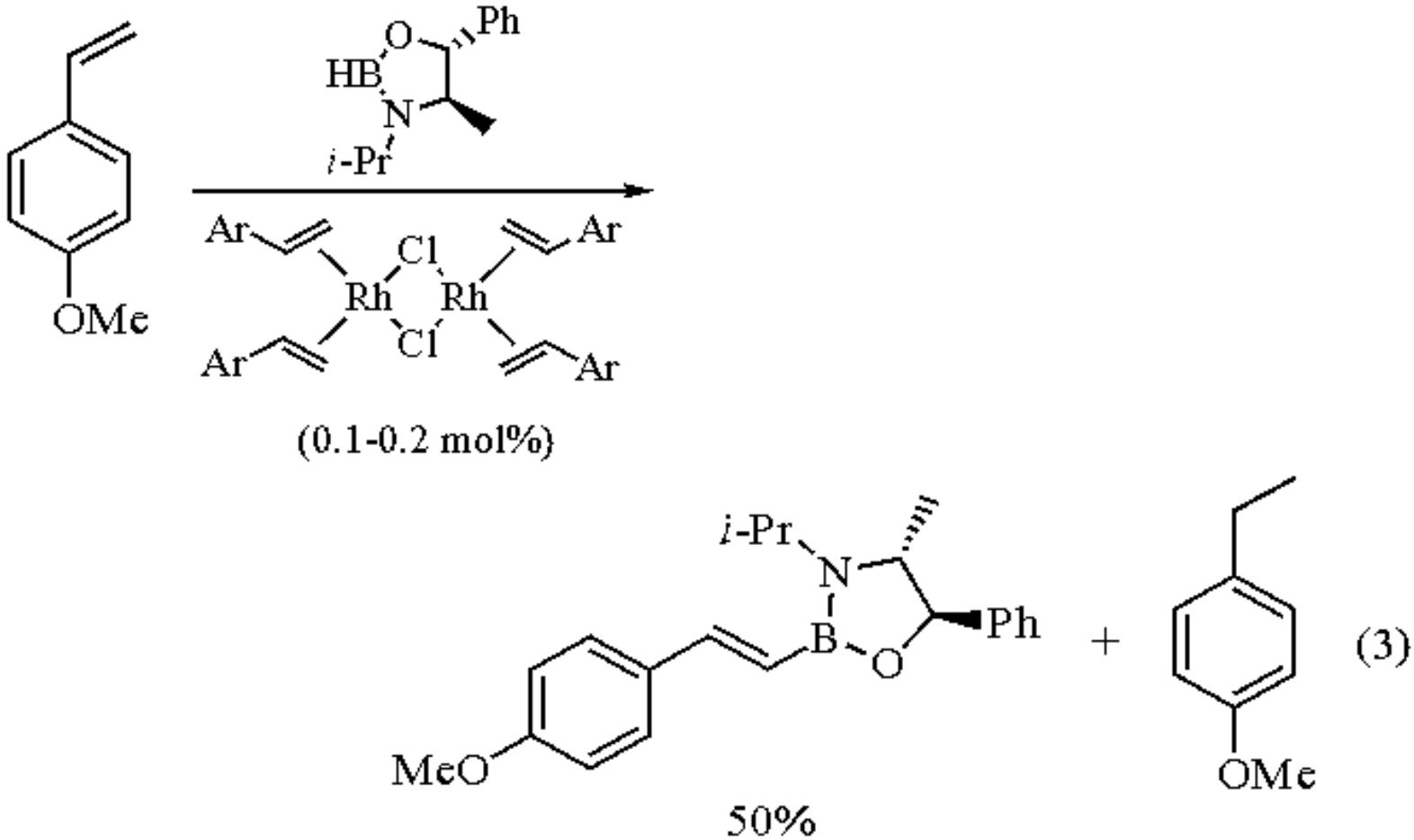

Enantioselective Carbonyl Reduction.

The title reagent reacts with borane through N->B coordination. This complexation enhances the Lewis acidity at the ring boron atom, thereby triggering dimerization of the adduct via hydride bridging.[6] This complex is capable of reducing acetophenone with good enantioselectivity (eq 4). The proposed reactive complex features *anti* coordination of acetophenone to the ring boron atom and *syn* to the coordinated BH_3.[7]

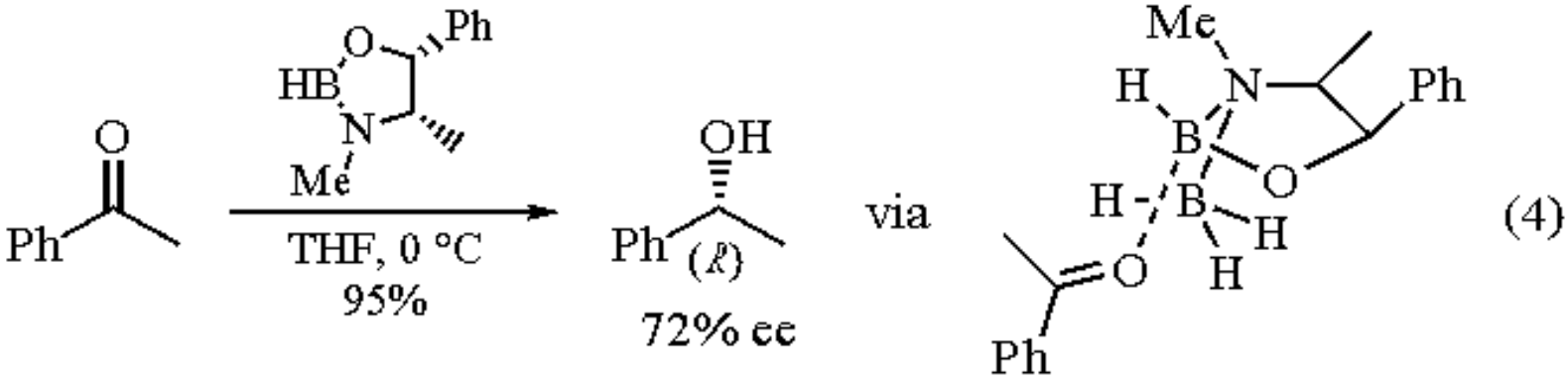

Several other 1,3,2-oxazaborolidines have been successfully used as chiral catalysts or reagents in borane-promoted reduction of ketones,[8] imines and oxime ethers,[9] and lactones[10] as well as in aldol condensations,[11] Diels-Alder cycloadditions,[12] and allylmetal additions to aldehydes.[13]

Related Reagents.

α,α-Diphenyl-2-pyrrolidinemethanol; ***Norephedrine-Borane***; ***Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole***.

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Epichlorohydrin[1]

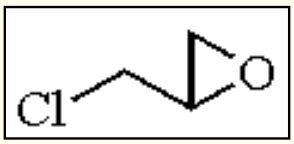

[106-89-8] · C_3H_5ClO · Epichlorohydrin · (MW 92.53) (*R*)

[51594-55-9] (*S*)

[67843-74-7]

(readily available three-carbon unit functionalized on every carbon; convenient HCl or HBr trap; linker for various polymers)

Alternate Name: chloromethyloxirane.

Physical Data: mp -57 °C; bp 115-117 °C; *d* 1.183 g cm^{-3}.

Solubility: 6.6 wt% in water; sol alcohol, acetone, THF, toluene, *n*-heptane.

Form Supplied in: neat liquid; both enantiomers available.

Handling, Storage, and Precautions: should only be handled in a well ventilated fume hood because of its low permissible exposure limit of 2 ppm and reports of allergic skin reactions and lung, liver, and kidney damage. MSDSs are available from the two principal manufacturers (Dow and Shell). The material is not moisture or air sensitive.

Introduction.

Epichlorohydrin (**1**) is most widely used in polymer synthesis.[2] Other common uses include an in situ trapping agent for HCl, HBr,[3] or the alcohol generated during formation of Meerwein's reagent (eq 1).[4]

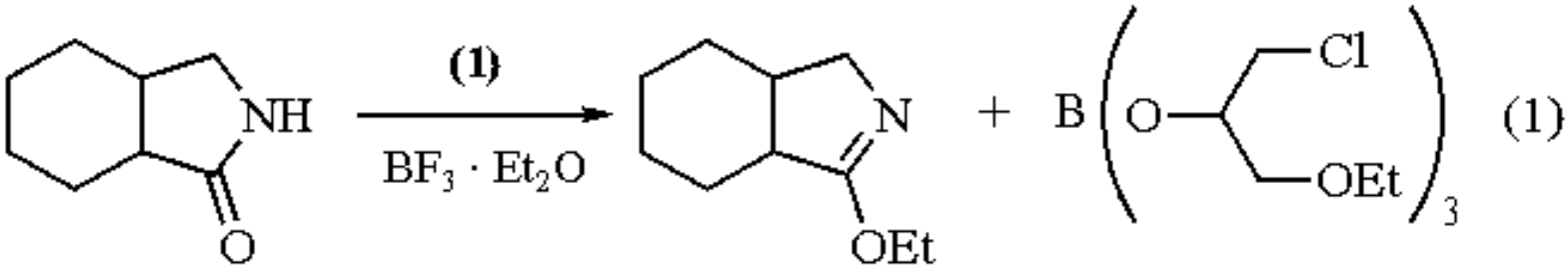

Reactions with Nucleophiles.

The epoxide is, by far, the more reactive site and a wide variety of nucleophiles have been used (eq 2) to open the ring at C-3 such as HCl (96%),[5] HOAc (>50%),[6] H_2S (65% as cyclized product 3-thietanol),[7] HCN (66%),[8] ethanol (90%),[9] *t*-butanol (86%),[10] phenyl or benzyl thiol (99% or 93%, respectively),[11] and phenyl selenide (generated in situ from the diselenide and sodium hydroxymethyl sulfite) (>55%).[12] If desired, the epoxide is easily formed from the chlorohydrin by treatment with excess KOH or Et_3N.

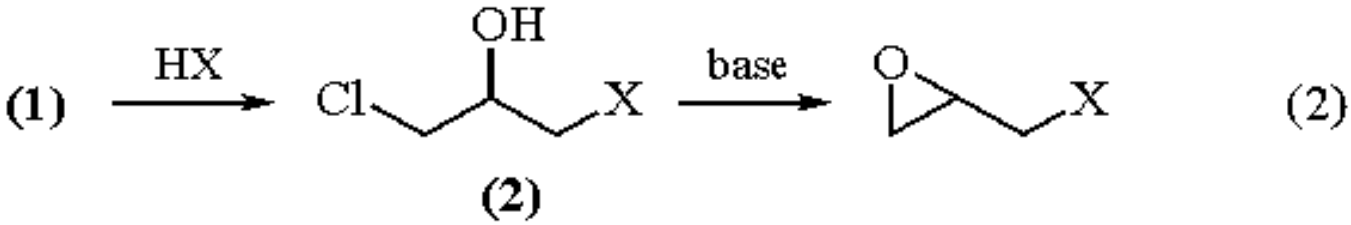

The epoxide is also opened at C-3 by various electrophilic reagents that fit into the generalized scheme in eq 3. Examples include ***Chlorotrimethylsilane*** (TMSCl) (85%),[13] TMSCl/NaBr (X = Br) (85%),[14] ***Cyanotrimethylsilane*** (91%),[15] ***Azidotrimethylsilane*** (83%),[16] ***Thionyl Chloride*** (70%),[17] H_2NCOCl (96%),[18] and MeCH=CHCOCl (80%).[19] The only report of unusual selectivity for opening the epoxide at C-2 was for ***Sulfuryl Chloride*** (eq 4).[20]

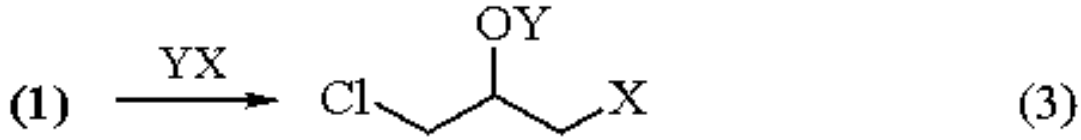

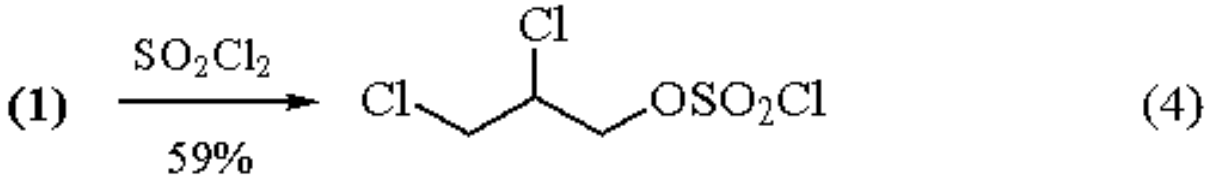

A number of special catalysts have been developed to facilitate ring opening and improve the regioselectivity for reaction at C-3. For example, Sn^{II} halides are useful in preparations of (**2**) (X = Cl, 70%; X = Br, 63%; X = I, 90%).[21] An equimolar mixture of ***Lithium Bromide*** and ***Copper(II) Bromide*** gave (**2**) (X = Br, 93%).[22] The ring can be opened selectively by anilines in the presence of other amines when ***Cobalt(II) Chloride*** is the catalyst.[23] $MgSO_4$ was found to catalyze the addition of 2 mol of CN^- to (**1**) to afford 3-hydroxyglutaronitrile.[24] CaF_2 supported on KF was used in the conversion of (**1**) to epifluorohydrin.[25] A catalyst composed of a 1:2 mole ratio of ***Di-n-butyltin Oxide***

and tributyl phosphate was developed for ring opening by alcohols.[26] Other catalysts shown to be of value for the examples given above include $FeCl_3$,[6] $LiClO_4$,[11] Et_3N,[11] CAN,[9] DDQ,[10] Ti(O-*i*-Pr)$_4$,[15b] $CoCl_2$,[13,19] $YbCl_3$,[15a] and Al(O-*i*-Pr)$_3$.[16]

A variety of carbon nucleophiles react at C-3 with high regioselectivity. Examples include Grignard reagents,[27] aryllithium,[28] alkynyllithium,[29] and others (eqs 5-8).[30-33]

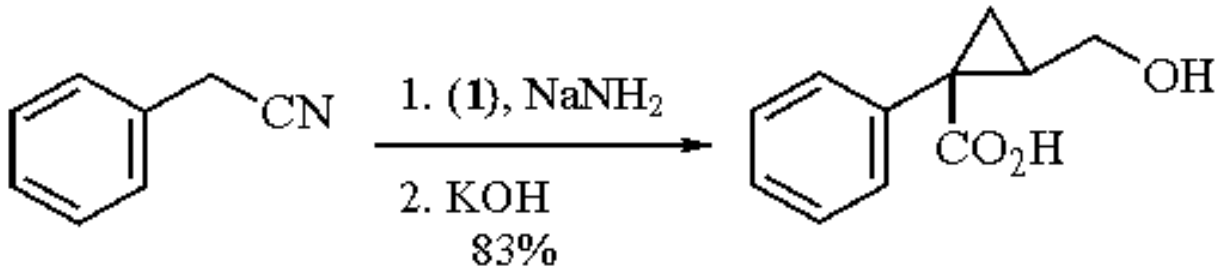

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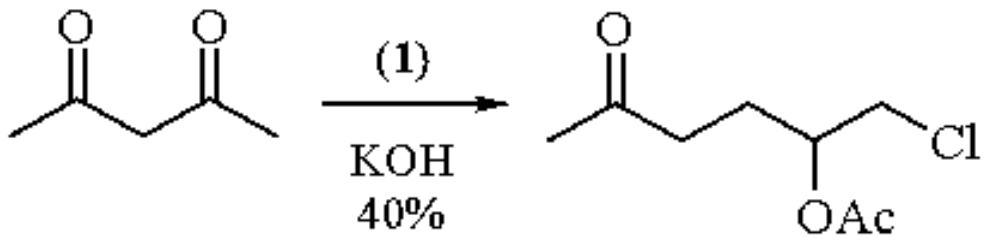

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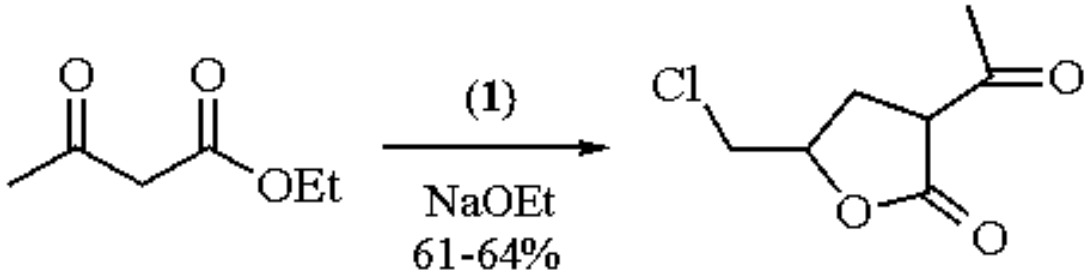

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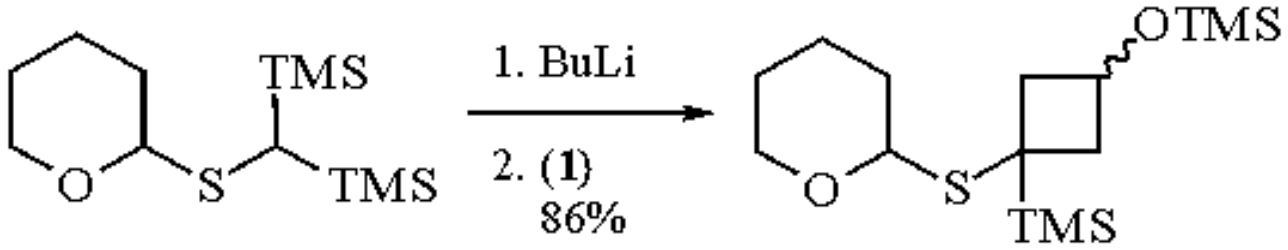

(8)

Compound (**1**) can be chain extended by one carbon by a Co-catalyzed CO insertion followed by reduction (eq 9).[34] A whole class of medicinally important compounds called β-blockers are prepared from (**1**) as illustrated in eq 10 for the synthesis of a propranolol analog.[35]

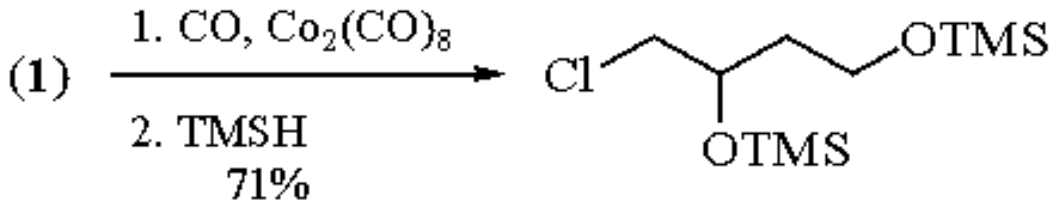

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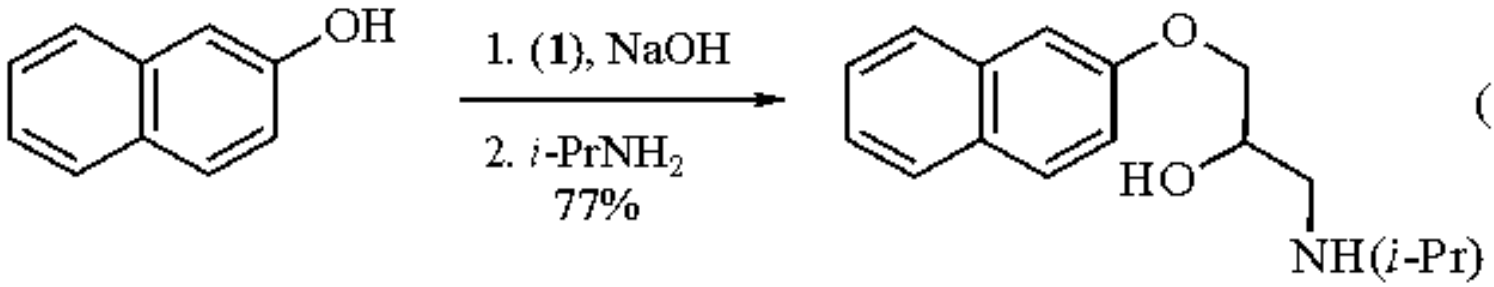

(10)

Preparation of Heterocycles.

A wide array of heterocycles are available from (**1**). A few examples are shown in eqs 11-16).[36-41]

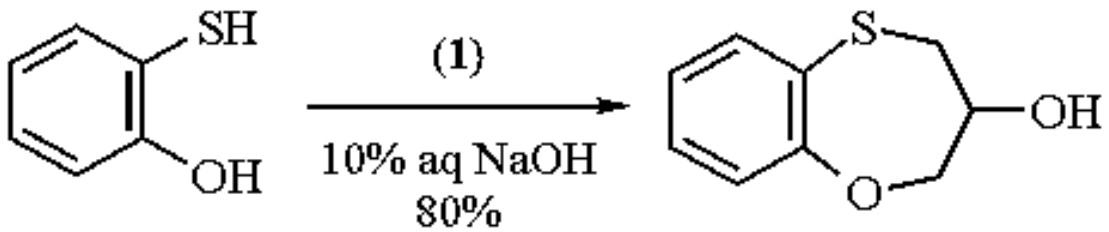

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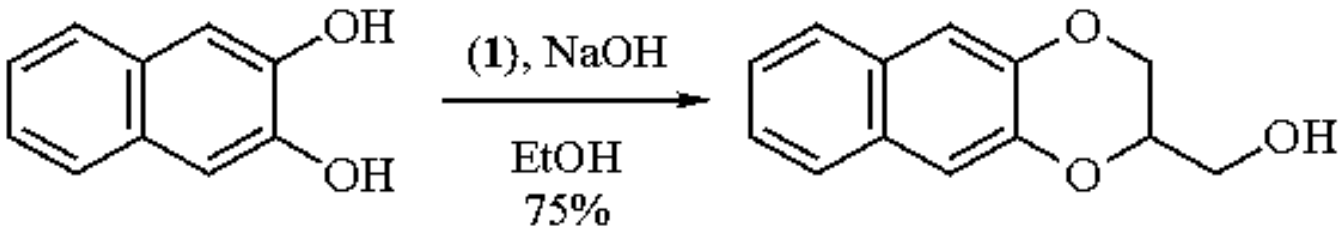

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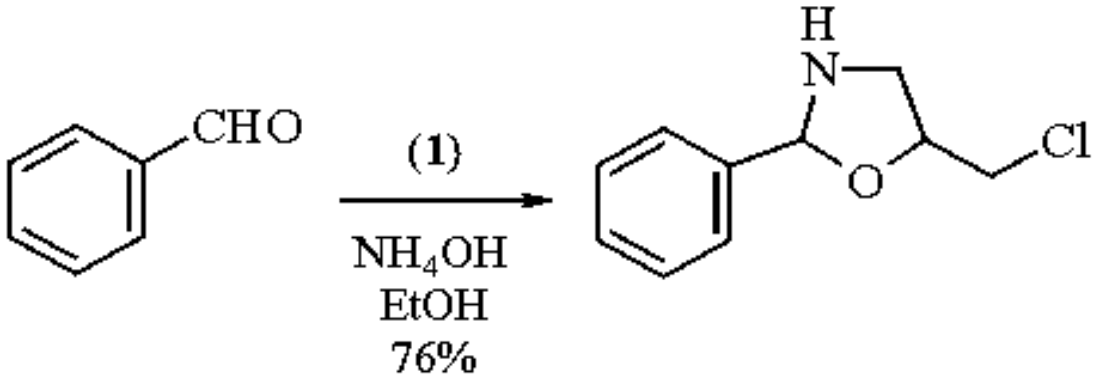

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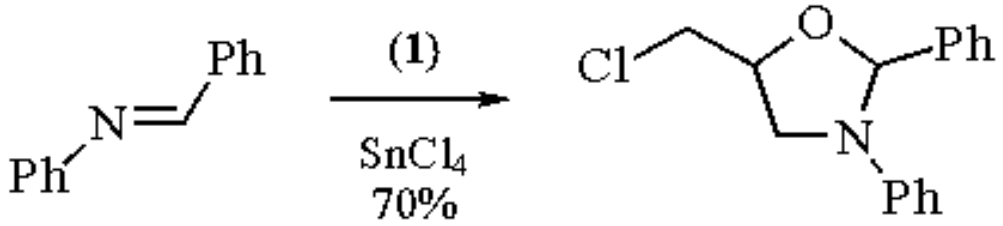

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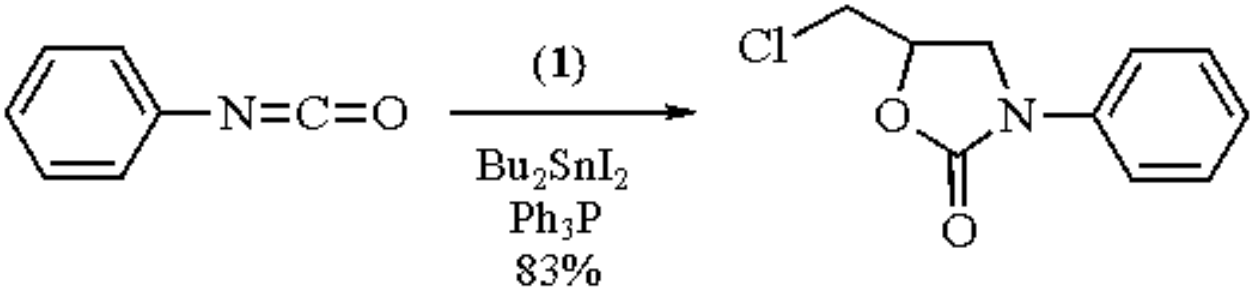

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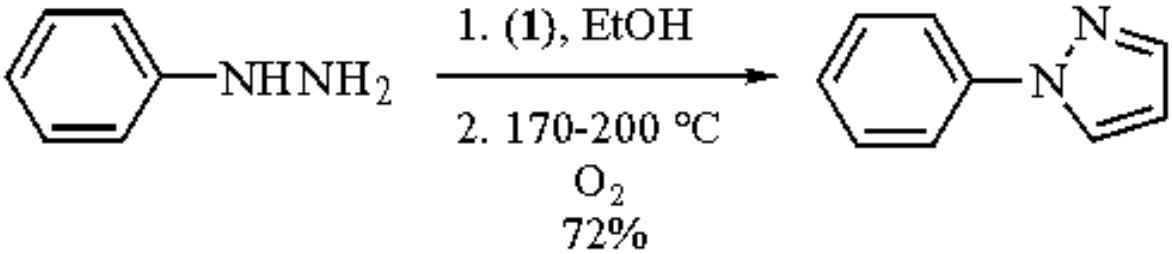

(16)

In some cases the reaction rate and yield are dramatically improved if the product can be trapped as the TMS ether (eq 17).[42] Also, (**1**) lends itself well to nucleophilic opening under phase transfer conditions (eq 18).[43]

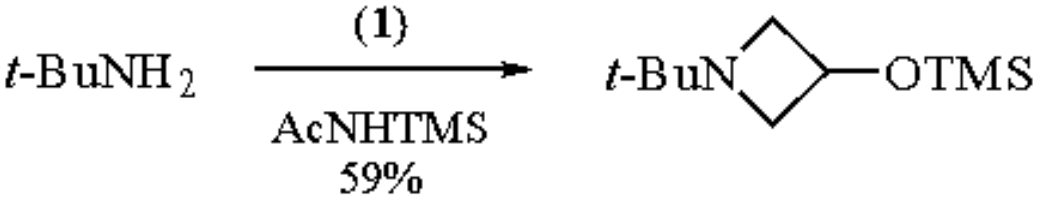

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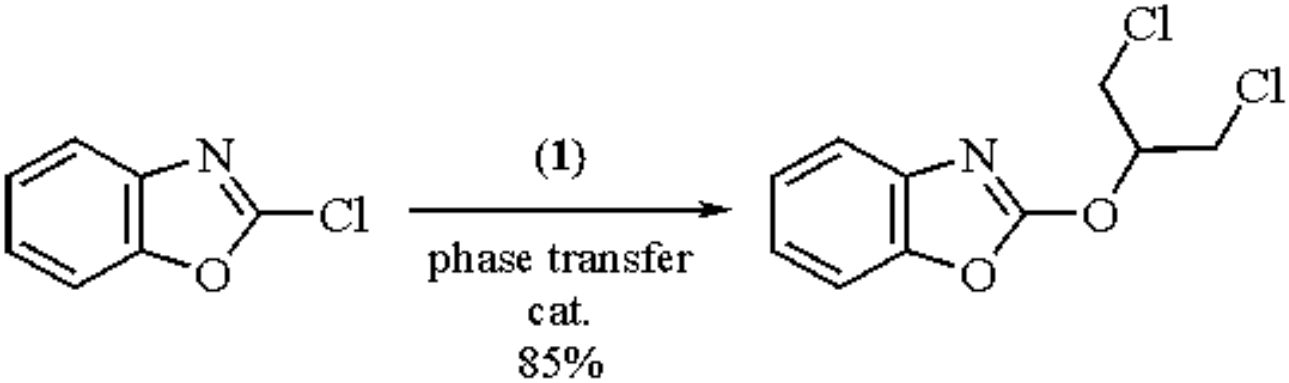

(18)

The ready availability[44] of both enantiomers of (**1**) has greatly enhanced its value as a synthetic intermediate. The pheromone (*S*)-(-)-ipsenol (**2**), prepared[45] in 16% overall yield in four steps from (*R*)-(**1**), is just one of many examples of this utility. In practice, either isomer can sometimes be used by adjusting the order of addition of the groups at C-1 and C-3. The synthesis of (-)-anisomycin (**3**) illustrates this point.[46]

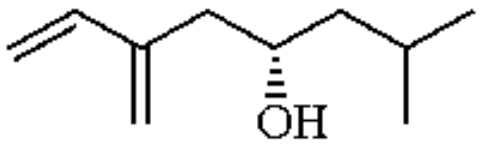

(2) (*S*)-(-)-Ipsenol

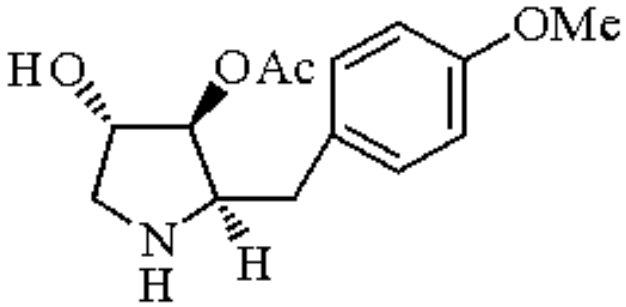

(3) (-)-Anisomycin

Related Reagents.

Glycidol.

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Erbium(III) Chloride[1]

$ErCl_3.6H_2O$

[10138-41-7] · Cl_3Er · Erbium(III) Chloride · (MW 381.73) (.$6H_2O$)

[10025-75-9]

(mild Lewis acid for selective acetalization;[2] used with $NaBH_4$ as a selective reducing agent;[3] catalyst for Friedel-Crafts-type reactions;[4] forms enolates from α-bromo ketones[5] and oxyallyl cations[6] from α,α´-dibromo ketones)

Physical Data: mp 774 °C; bp 1500 °C; *d* 4.1 g cm^{-3}.

Solubility: sol H_2O, methanol, ethanol; slightly sol 2-propanol, THF.

Form Supplied in: pink crystals, deliquescent. *Drying:* anhydrous erbium chloride is prepared from the hydrate by reflux in ***Thionyl Chloride***, or heating to 400 °C in the presence of a two-fold excess of ammonium chloride in a vacuum with intense mixing.

Handling, Storage, and Precautions: anhydrous $ErCl_3$ should be used after drying without delay. Erbium exhibits an oral toxicity of LD_{50} in rats 6.7 g kg^{-1}.

Selective Acetalization.

Erbium trichloride is an efficient catalyst for acetalization.[2] In methanol solution, $ErCl_3$ rapidly promotes an equilibrium between aldehydes and their acetals which is shifted to completion by the addition of trimethyl orthoformate as a water scavenger. High yields are obtained after short reaction times at room temperature with most substrates (eqs 1-3).

$$C_7H_{15}CHO \xrightarrow[\text{MeOH, rt}]{\substack{ErCl_3 \cdot 6H_2O \\ HC(OMe)_3}} C_7H_{15}CH(OMe)_2 \qquad (1)$$

10 min
100%

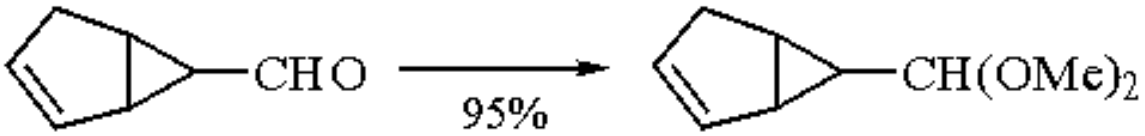

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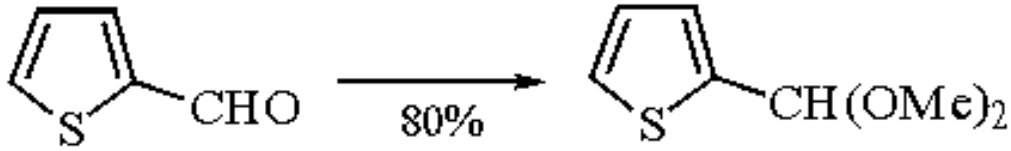

(3)

Acetalization of ketones is more difficult.[3] As a rule, conjugated ketones (i.e. aromatic and α,β-unsaturated) do not react (eq 4), but cycloalkanones give excellent yields (eq 5). The reaction is sensitive to steric hindrance, permitting selective reactions with dicarbonyl substrates (eq 6).

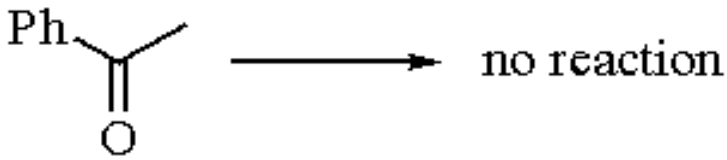

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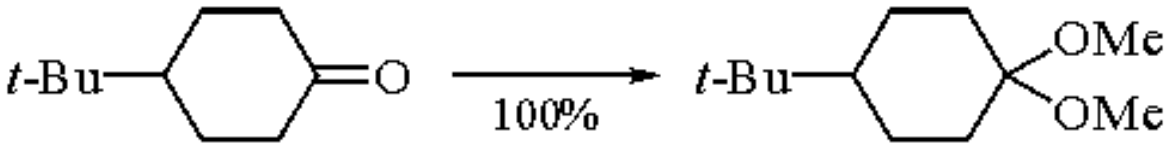

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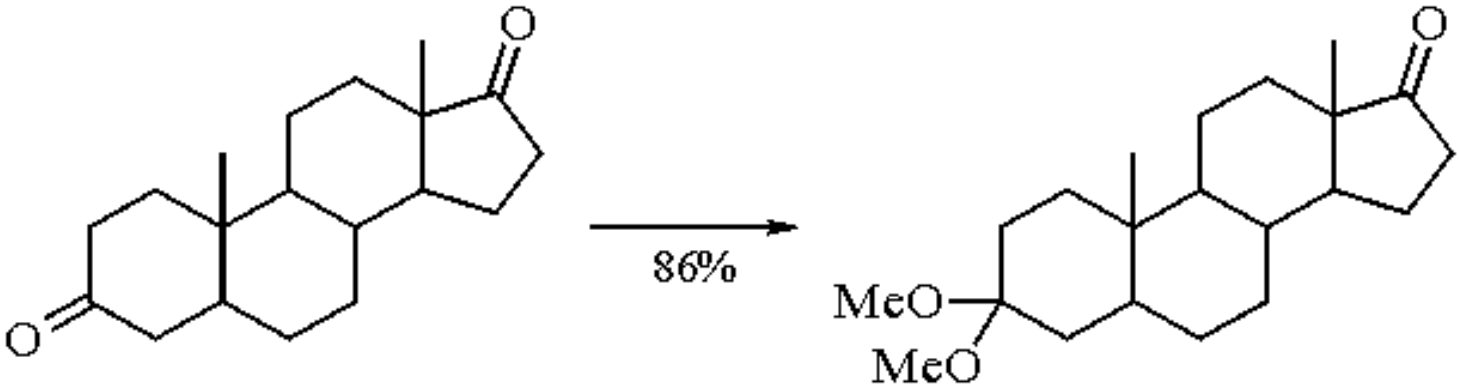

(6)

Selective Reductions of Carbonyl Compounds.

$ErCl_3$ induces regiospecific reduction of α,β-unsaturated ketones to allylic alcohols in the presence of ***Sodium Borohydride*** in a fashion similar to ***Cerium(III) Chloride***. The major use of $ErCl_3$ involves the selective reduction of dicarbonyl compounds which is based on the in situ acetalization of the more reactive carbonyl group by methanol.[3,7] The unprotected, less reactive group is thus reduced. The acetal need not necessarily be isolated, and the overall process can thus be run in one pot (eqs 7 and 8).

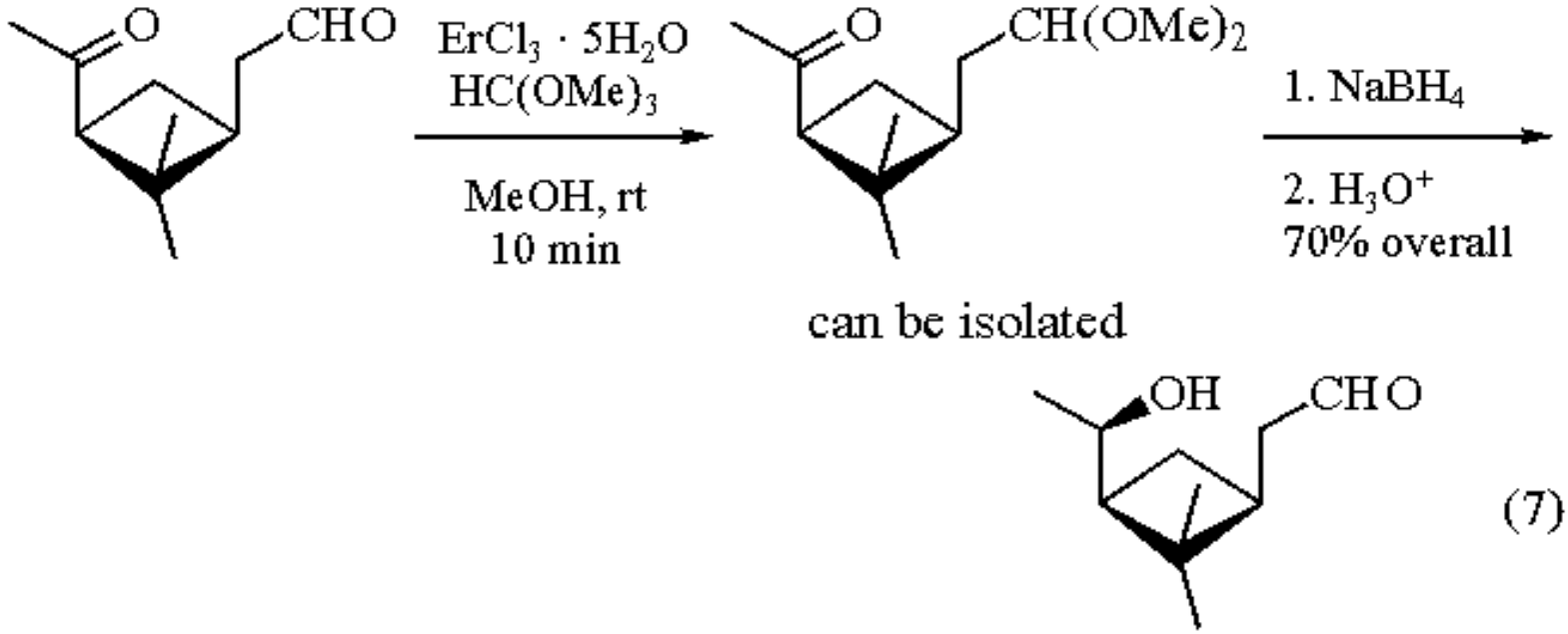

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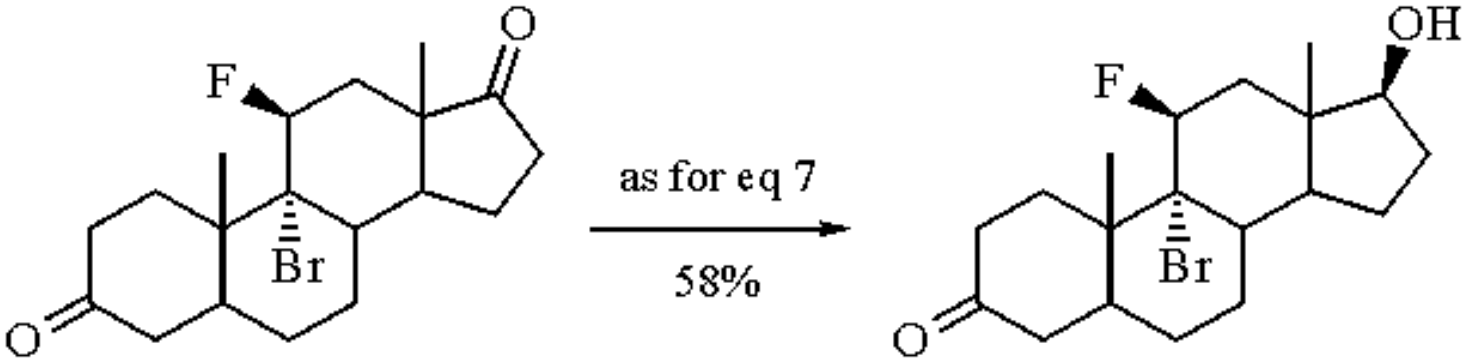

(8)

In aqueous ethanol the hydrate or hemiacetal rather than the acetal is formed, and these derivatives function as transient protecting groups. The deprotection step can thus be avoided, making the overall process shorter.[8,9]

Friedel-Crafts Alkylation Catalyst.

Benzyl halides react with benzene in the presence of catalytic amounts (0.3 equiv) of a series of lanthanide (including erbium) chlorides.[4] Yields of ~60% are obtained after 18 h at 75 °C. In this procedure the catalyst is easily recovered and reused (eq 9). Double alkylation is observed in the reaction of acetyl chloride and benzaldehyde in benzene or toluene (eq 10).[10] Chloromethylation has been reported using chloromethyl methyl ether.[10]

$$PhCH_2Cl + PhH \xrightarrow[\text{75 °C, 18 h; 63\%}]{ErCl_3} PhCH_2Ph \qquad (9)$$

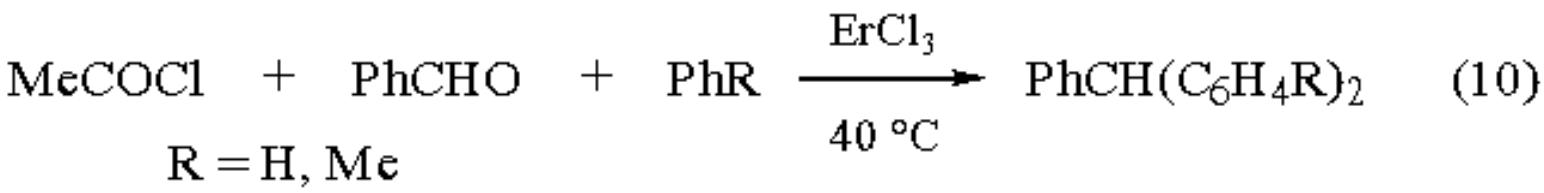

Erbium Enolates from α-Bromo ketones.

α-Bromo ketones, treated with lanthanide chlorides and ***Sodium Iodide*** or ***Tin(II) Chloride***, yield the corresponding enolates which undergo cross-aldol reaction upon addition of a carbonyl compound.[5] $ErCl_3$-$SnCl_2$ gives a 76% yield of the aldol product (eq 11), lower than that obtained with La or Ce, but the stereoselectivity is higher.

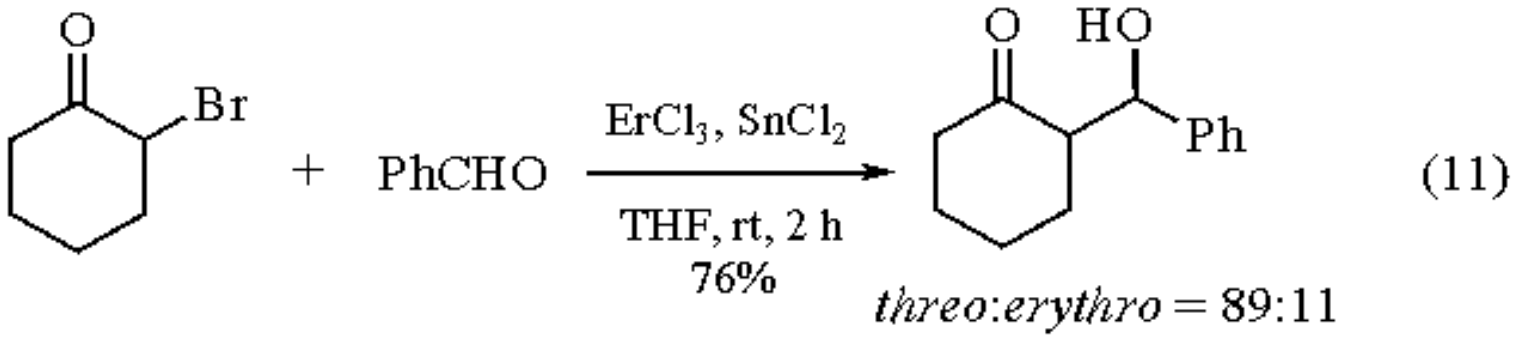

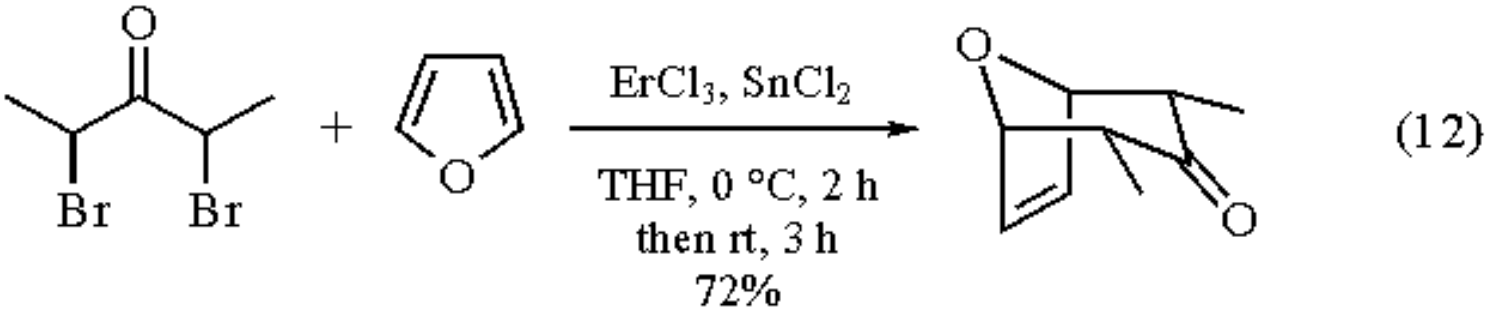

Oxyallyl Cations from α,α´-Dibromo Ketones.

With lanthanide chlorides, including erbium, and $SnCl_2$, α,α´-dibromo ketones furnish oxyallyl cations, which can be trapped with various dienes.[6] The corresponding [3 + 2] cycloadducts are isolated in good yield (eq 12) although comparable or better yields are obtained with the corresponding cerium salt.

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Esterases

(enzymes of the class of hydrolases, which catalyze the hydrolysis of carboxylic acid esters[1])

Solubility: insol cold and warm H_2O.

Form Supplied in: available from various sources (microorganisms and mammalian) as powders or water suspensions.

Handling, Storage, and Precautions: stable at a pH range 6-10; can be stored at 0-4 °C for months.

Esterase-Catalyzed Hydrolysis.

Hydrolytic enzymes have been accepted in organic synthesis as valuable biocatalysts, since they are commercially available at relatively low price and possess a broad substrate specificity, without necessitating use of expensive cofactors.[2] Esterases are such useful enzymes and have been widely used for the preparation of enantiomerically pure chiral compounds, by hydrolytic resolution of racemic esters or asymmetrization of prochiral substrates.[3] Well defined experimental procedures for a pig liver esterase-catalyzed saponification have been documented.[4] Generally, the enzymatic hydrolysis is carried out in an aqueous buffer, sometimes containing cosolvents,[5] at pH 7-9 and keeping the temperature at 20-25 °C. Generally, the molar equivalent NaOH for the hydrolysis is added maintaining the pH constant with an automatic titrator and, after acidification, the product is extracted with organic solvents. Esterases are commercially available from various sources, either microbial or mammalian, and in some instances also crude acetone powders can be used for the same purpose.

Pig Liver Esterase (PLE).

This is the more used carboxylesterase (carboxylic-ester hydrolase, EC 3.1.1.1, *CAS 9016-18-6*) which physiologically catalyzes the hydrolysis of carboxylic acid esters to the free acid anion and alcohol.[1] PLE is a serine hydrolase which has been widely used for the preparation of chiral synthons and these applications have been fully reviewed.[6] An active-site model for interpreting and predicting the specificity of the enzyme has been published.[7] In the pioneering studies of the enzyme applications field, PLE was used for the chiral synthesis of mevalonolactone.[8] Prochiral 3-substituted glutaric acid diesters are well suited for a PLE-catalyzed asymmetrization, which leads to optically active monoesters (eq 1).[9]

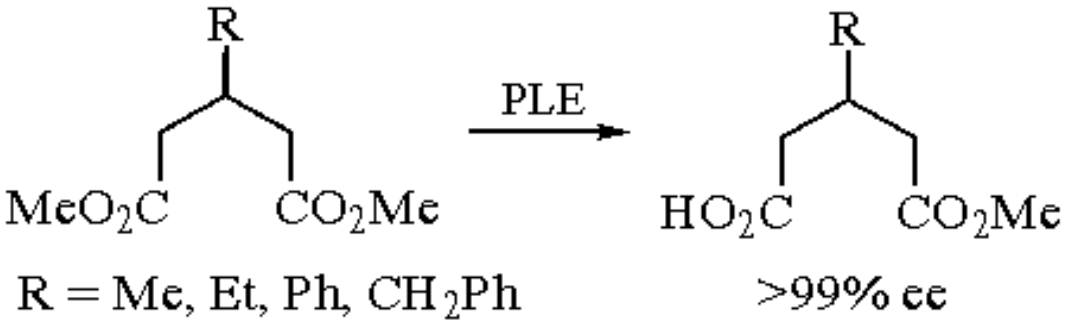

(1)

The asymmetrization of prochiral disubstituted malonates has been enantioselectively realized in the presence of PLE (eq 2).[10]

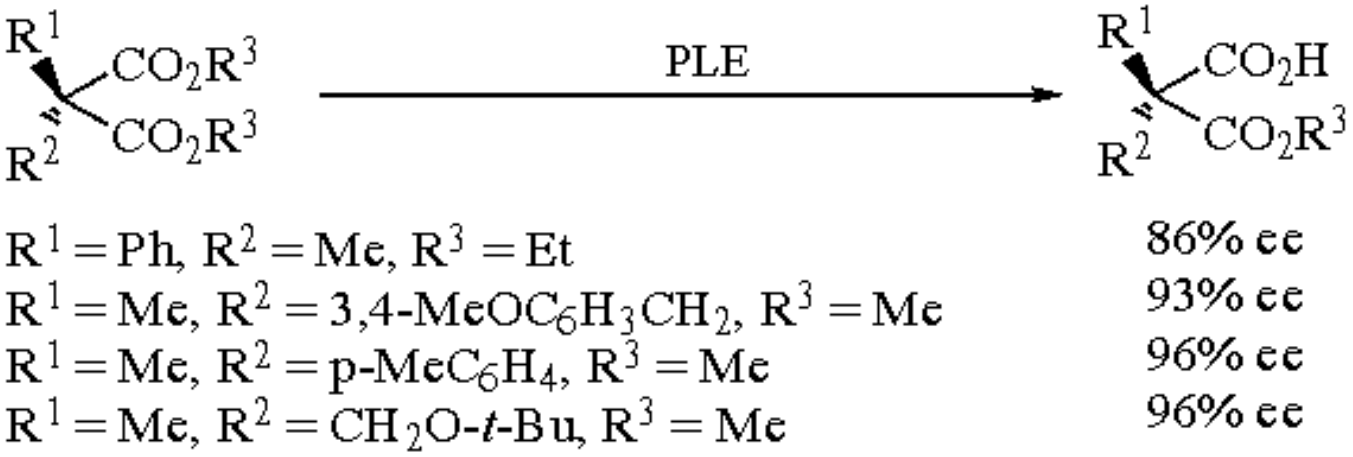

(2)

The asymmetric hydrolysis of several cyclic *meso*-diesters has been accomplished and optically pure monoesters have been obtained.[11] A classical example is the hydrolysis of dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate, which affords the corresponding nearly optically pure half ester, a versatile synthon for various chiral cyclohexane derivatives (eq 3).[12]

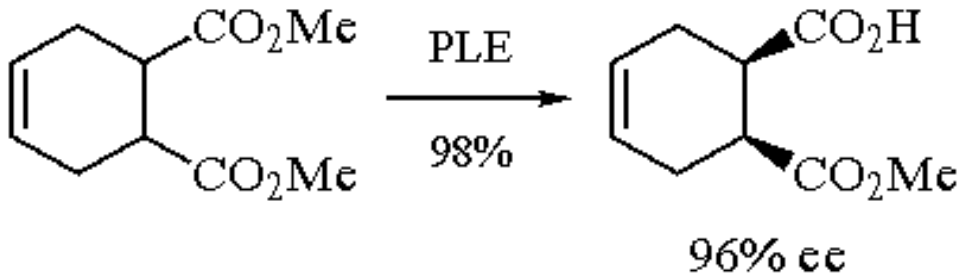

(3)

The PLE-catalyzed asymmetric hydrolysis of *meso*-1,3-*cis*-3,5-*cis*-1,3-diacetoxy-5-benzyloxycyclohexane afforded (1*S*,3*S*,5*R*)-1-acetoxy-5-benzyloxycyclohexan-3-ol, which could be used as chiral building block for the synthesis of the compactin lactone moiety and quinic acid (eq 4).[13]

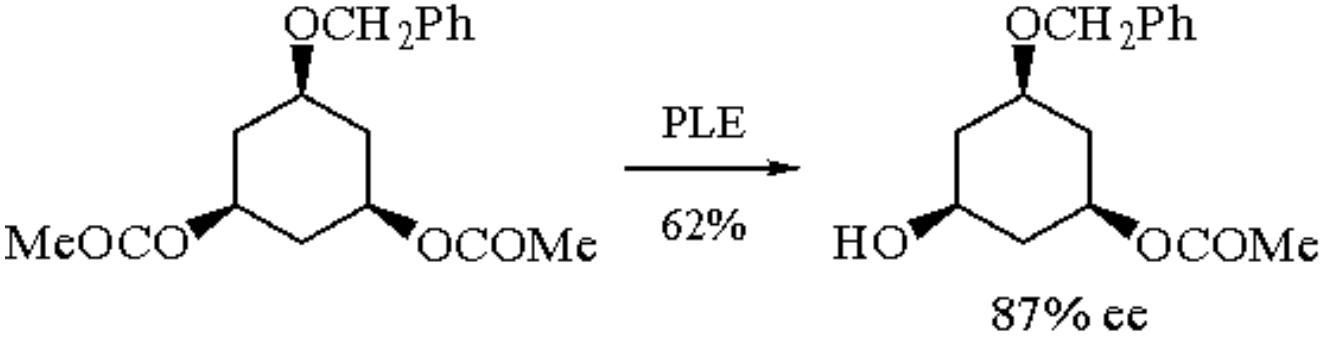

(4)

Organometallic *meso*-diesters can be asymmetrized as well to the corresponding half ester, as shown for an (arene)tricarbonylchromium diester (eq 5).[14]

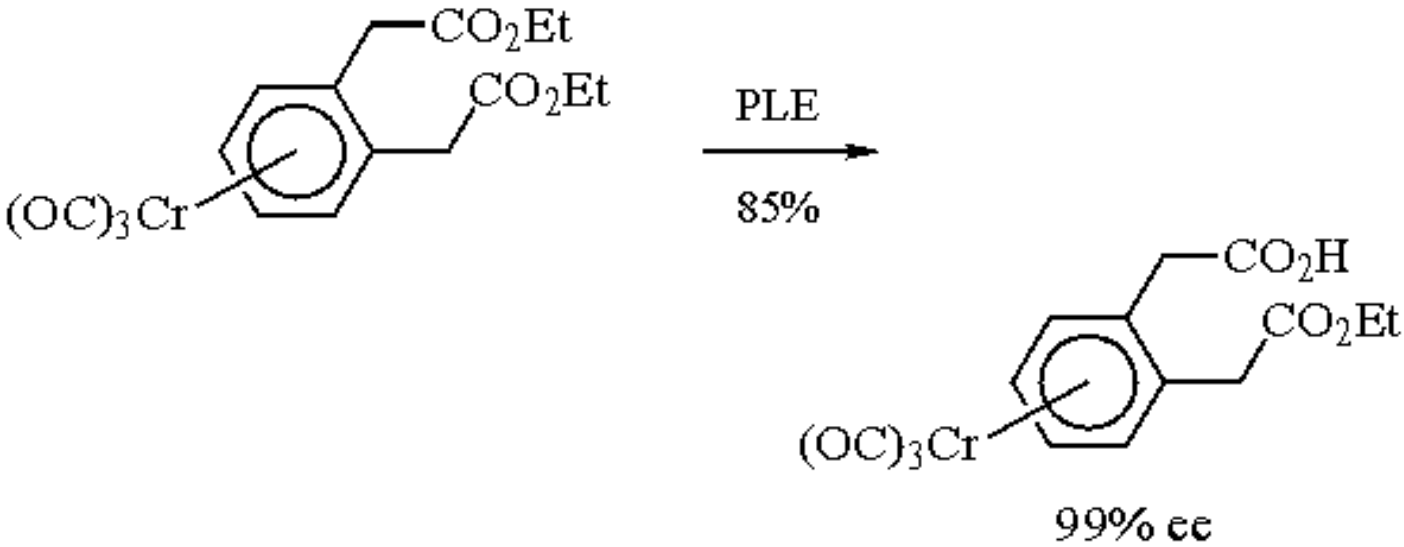

(5)

The resolution of racemic esters is catalyzed by PLE in a highly enantioselective fashion.[3,6] Several interesting applications of this method are available. The hydrolysis of *trans*-bicyclo[2.2.1]heptane diesters has been studied to ascertain the structural requirements for the PLE hydrolysis.[15] A bulky tricyclodecadienone ester can be resolved by an highly enantioselective reaction (eq 6).[16]

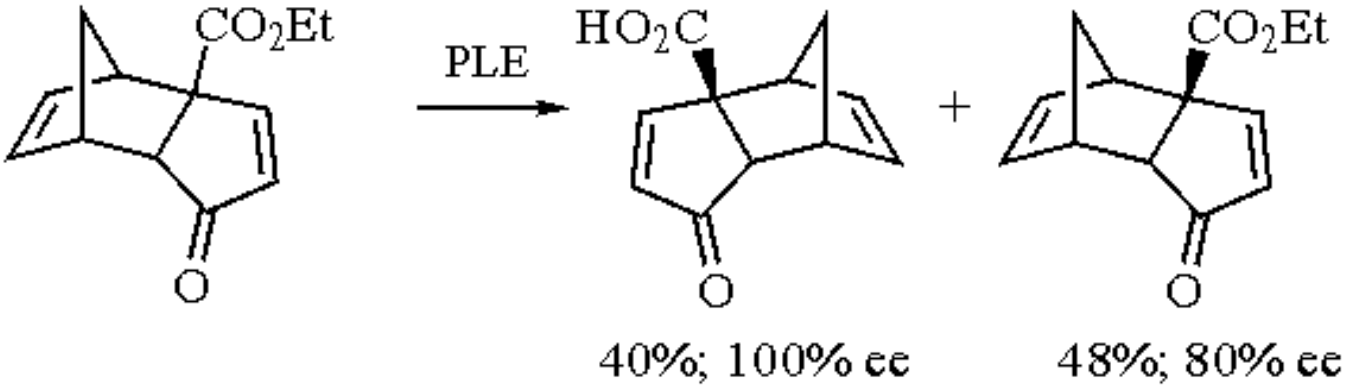

(6)

The resolution procedure applies to racemic organometallic esters[17] and to the esters of a thianucleoside, for the preparation of pure enantiomers of an antiviral agent (2´,3´-dideoxy-5-fluoro-3´-thiacytidine) (eq 7).[18]

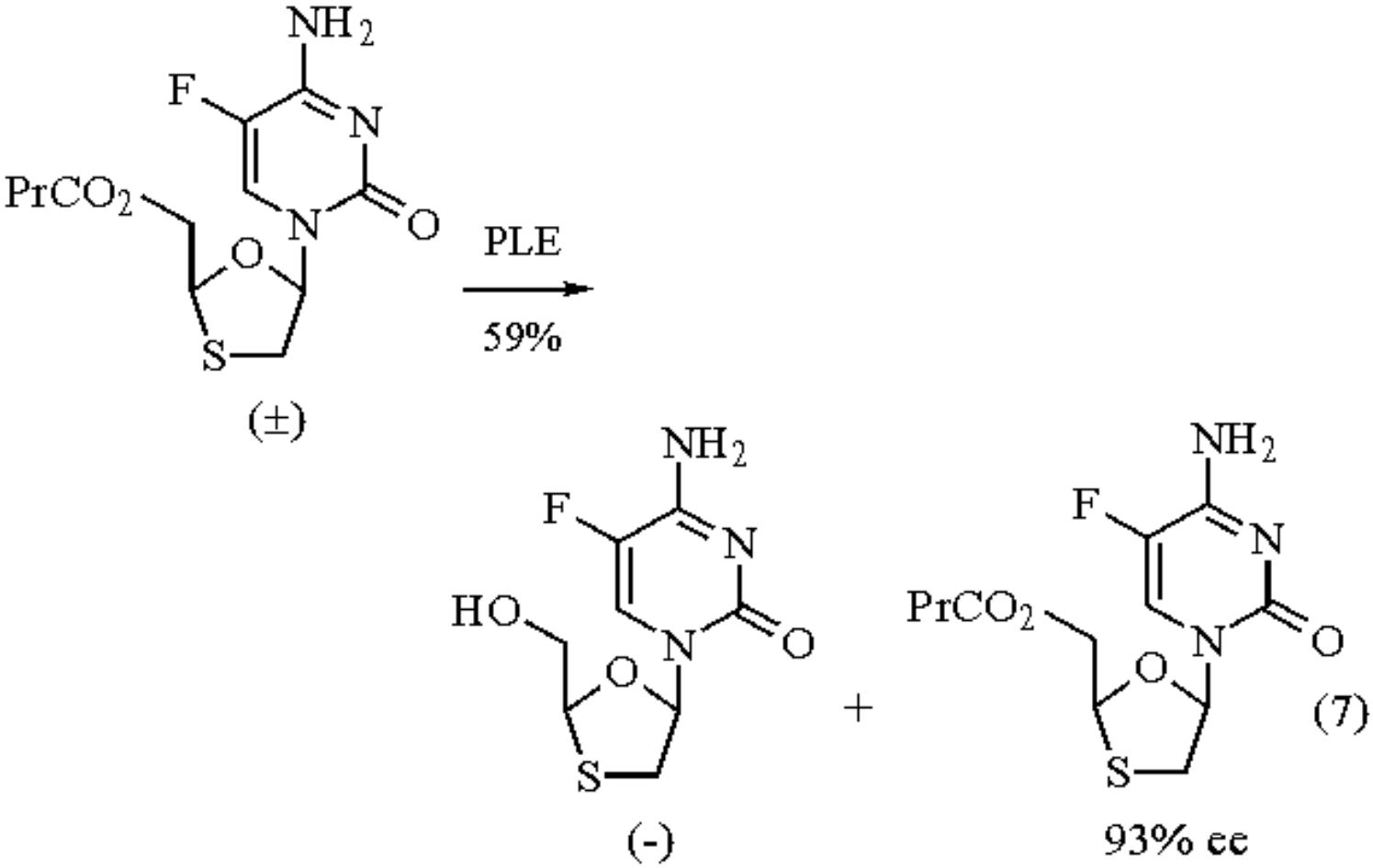

PLE has usually been applied to the enantioselective preparation of optically active compounds, but its use can be extended to chemo- or regioselective hydrolyses. A continuous process for the separation of a *cis*/*trans* unsaturated ester was realized using immobilized PLE (eq 8).[19]

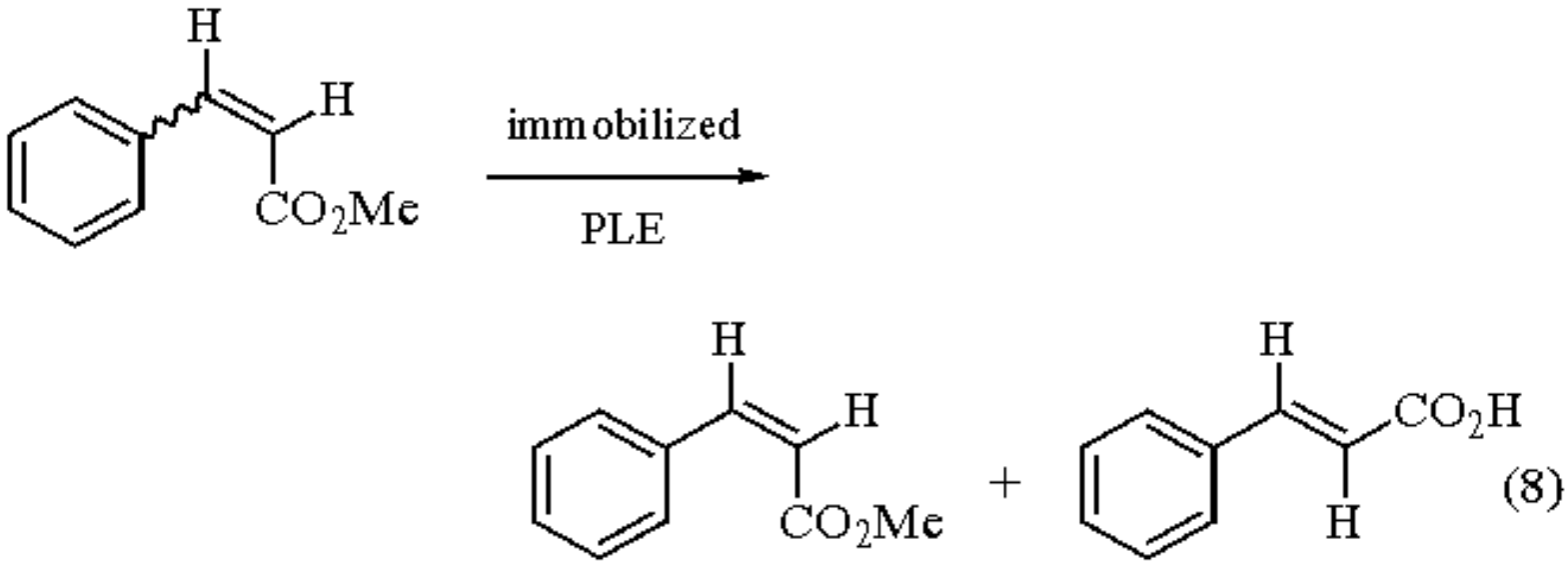

The chemoselective hydrolysis of an acetoxy group in the presence of a γ-lactone ring has been reported in the presence of PLE (eq 9).[20] In a benzylpenicillin, PLE catalyzes the chemoselective hydrolytic opening of the β-lactam ring, the methoxycarbonyl moiety remaining uneffected (eq 10).[21]

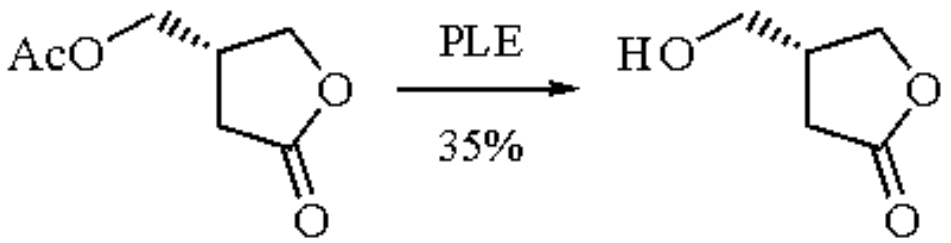

(9)

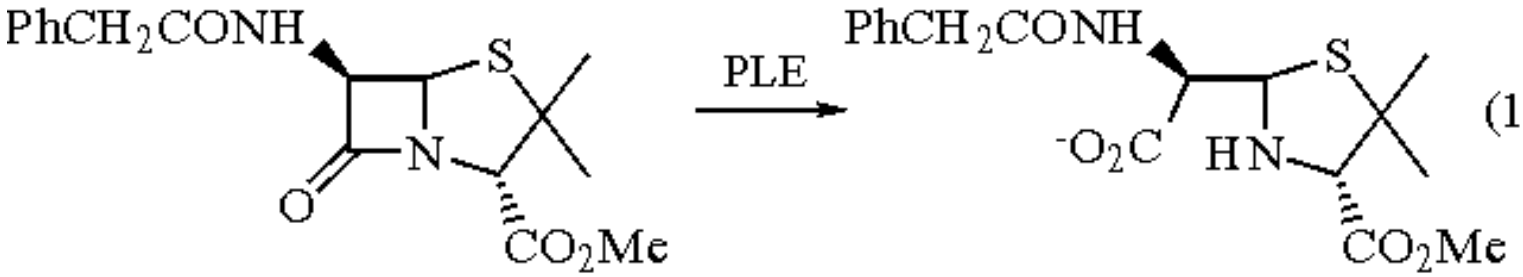

(10)

Dimethyl malate presents two ester functions α and β with respect to a hydroxy group, and PLE is able to regioselectively discriminate between these two moieties.[22]

Acetone Powder Containing Esterase Activity.

The main advantage in using crude homogenates or acetone powders of organs such as liver is to have a cheap source of different enzymes. If one of these is desired for a specific substrate, the crude enzymatic mixture can be used with some advantage, compared to the purified enzymes. Pig liver acetone powder (PLAP), together with other extracts, is commercially available or can be prepared from fresh pig liver.[23] PLAP has been used for the enantioselective hydrolysis of the racemic acetate of *trans*-2-phenylcyclohexanol (eq 11).[24]

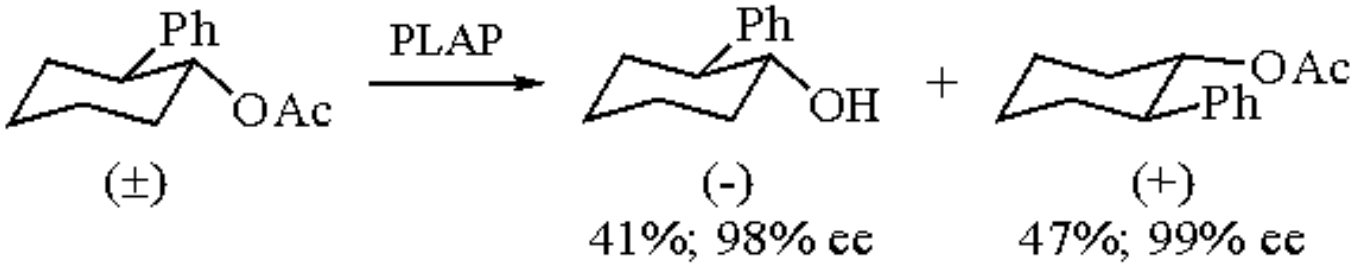

(11)

The acetates of 1-arylalkan-1-ols were successfully resolved by acetone powders (PLAP and goat liver acetone powder, GLAP) containing esterase activity (eq 12).[25]

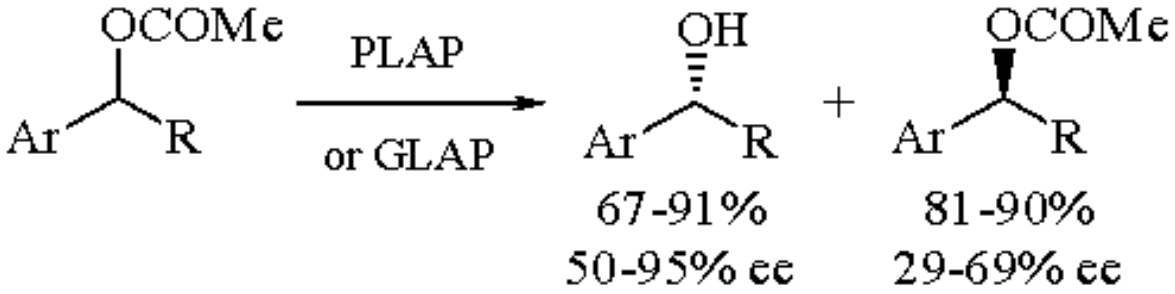

(12)

An interesting application of the esterase activity of horse liver acetone powder (HLE) has been the enantioselective hydrolysis of racemic lactones. The powder proved to be more effective than PLE in this hydrolysis, from which the unreacted lactone was recovered with high enantiomeric excess. The process seems more effective for δ and medium size lactones (eq 13).[26]

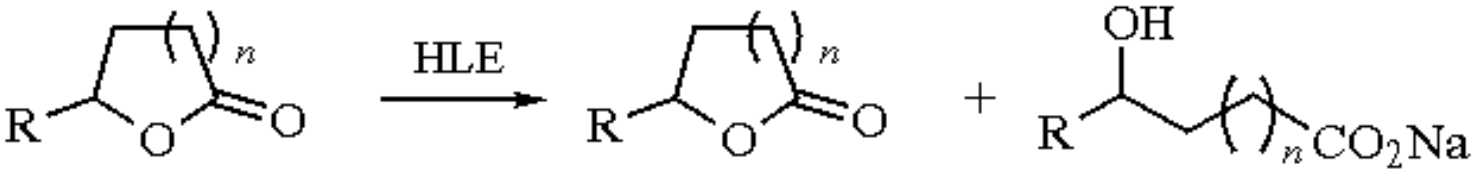

(13)

R = Pr; $n = 1$	72% ee
R = C_5H_{11}; $n = 2$	78% ee
R = C_7H_{15}; $n = 2$	92% ee
R = Me; $n = 6$	>95% ee

Cholesterol Esterase.

This enzyme (EC 3.1.1.13; *CAS 9026-00-0*) physiologically catalyzes the hydrolysis of cholesterol esters, monoacylglycerols, and vitamin esters.[27] It has also been used for several cyclic and noncyclic substrates with variable enantioselectivity.[28] The resolution of racemic esters has been reported[29] and an interesting example is the application to the racemic acetate of an hemiacetal (eq 14).[30]

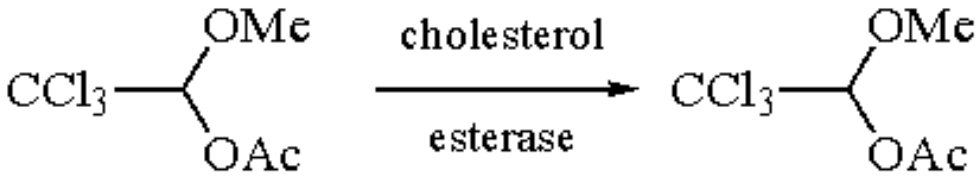

(14)

(±) (-) >97% ee

Acyl Cholinesterases.

Acetylcholinesterase (AChE; EC 3.1.1.7; *CAS 9000-81-1*) is the serine esterase which catalyzes the hydrolysis of acetylcholine and possesses an esteratic site,[31] and which is responsible for unspecific hydrolyses of several substrates. Also, butyrylcholinesterase (EC 3.1.1.8; *CAS 9001-08-5*) has been sometimes used for asymmetric hydrolysis of esters.[32] Acetylcholinesterase has been used for the hydrolysis of noncyclic substrates and the results have shown satisfactory enantioselectivity.[32a,33] The enzyme from electric eel seems especially well suited to the hydrolysis of cyclic diols.[34] The asymmetrization of *cis*-3,5-diacetoxycyclopent-1-ene to (3*R*)-acetoxy-(5*S*)-hydroxycyclopent-1-ene (eq 15)[35] and the preparation of an optically active triol monoacetate starting from the triacetate of 1,3,6-trihydroxycyclohept-4-ene (eq 16)[36] are good examples of successful reactions catalyzed by acetylcholinesterase.

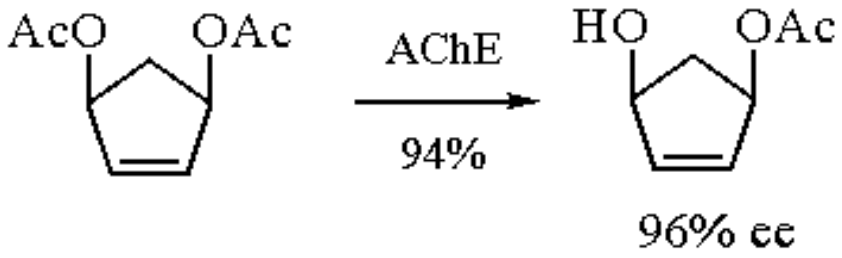

(15)

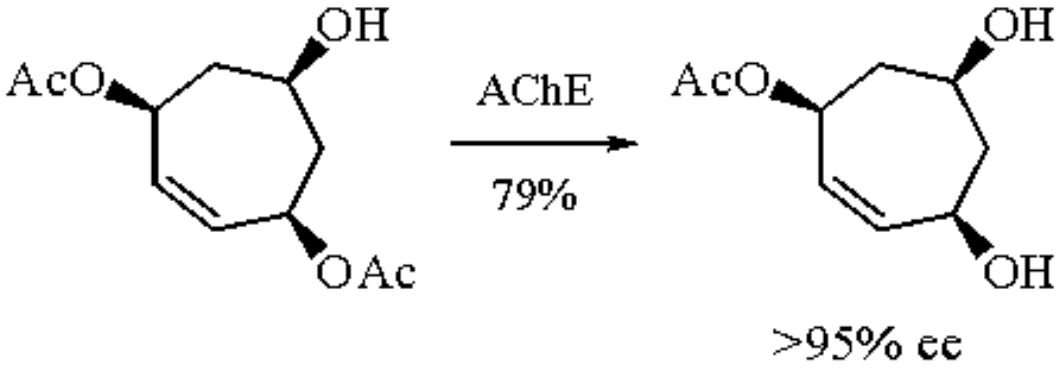

(16)

Other Esterases.

Other less common esterases have been sometimes used for biocatalytic applications in organic synthesis.[37] The enzymatic approach can be the method of choice for the preparation of optically pure drugs, although sometimes special enzymes have to be prepared for this aim. By cloning a carboxylesterase into a microorganism, high level production of the esterase is made possible for the production of 2-(aryloxy)propionates and (*S*)-naproxen.[38] The esterase activity of rabbit plasma has been used for a chemoselective hydrolysis of a methylthiomethyl ester.[39] An esterase from *Candida lypolitica* has been used for the resolution of a tertiary α-substituted carboxylic acid ester.[40] Recently, a carboxyl esterase of molecular weight 30 000 (Esterase 30 000) has been introduced for the asymmetric hydrolysis of diesters. A cyclopropyl malonate has been hydrolyzed by the esterase and the unreacted diester was recovered nearly optically pure (eq 17).[41] Diethyl 3-hydroxyglutarate, a substrate which is asymmetrized with modest enantioselectivity with PLE or other enzymes,[9e,f] has been enantioselectively hydrolyzed in the presence of Esterase 30 000 (eq 18).[42]

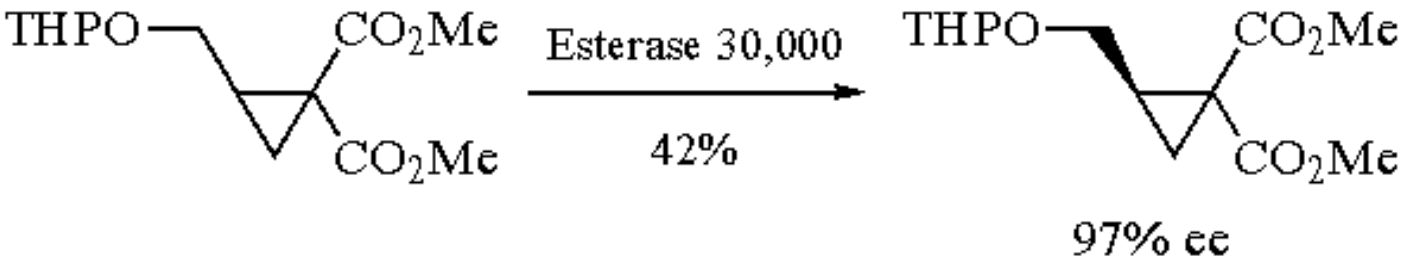

(17)

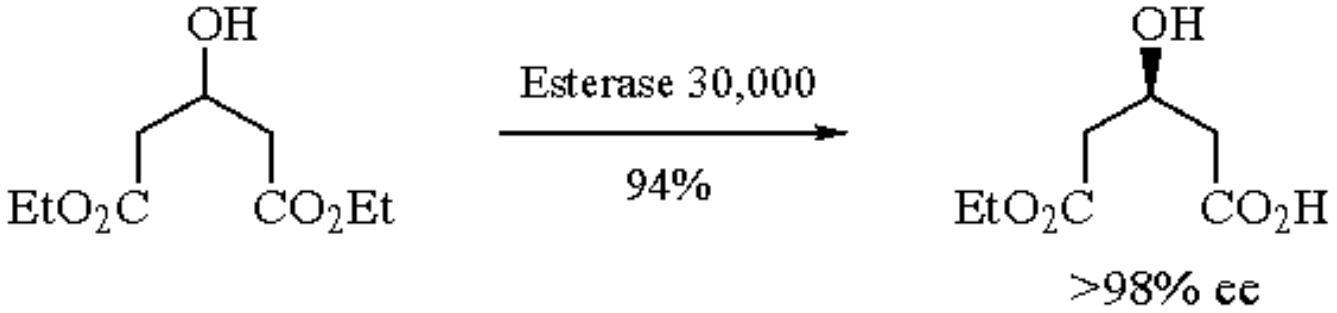

(18)

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1,2-Ethanedithiol[1]

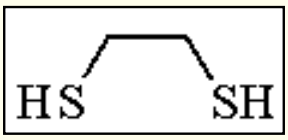

[540-63-6] · $C_2H_6S_2$ · 1,2-Ethanedithiol · (MW 94.20)

(1,3-dithiolane formation; ether cleavage; reduction (carbonyl to methylene; sulfoxide to thioether); *gem*-difluoride formation; dithiolenium ion formation)

Physical Data: d 1.123 g cm^{-3} (23.5 °C); bp 146 °C/760 mmHg; 63 °C/46 mmHg.

Solubility: slightly sol water; miscible with many organic solvents.

Form Supplied in: widely available.

Handling, Storage, and Precautions: stench! Inhalation can cause chest pain, headache, nausea, pulmonary edema; LD_{50} (oral, mouse) 342 mg kg^{-1}; see ***1,3-Propanedithiol***. Use in a fume hood.

1,3-Dithiolane Formation.

1,2-Ethanedithiol (**1**) condenses with aldehydes, ketones, and acetals to afford 1,3-dithiolanes,[1,2] useful for carbonyl protection (eqs 1 and 2).[3a,b] Stability, condensation selectivity, and conditions for carbonyl regeneration parallel those discussed for ***1,3-Propanedithiol***.[4] Esters and lactones can be protected as ketene dithioacetals and/or dithioortholactones, resistant to nucleophilic attack, using the bis(dimethylalanyl) derivative of (**1**).[5]

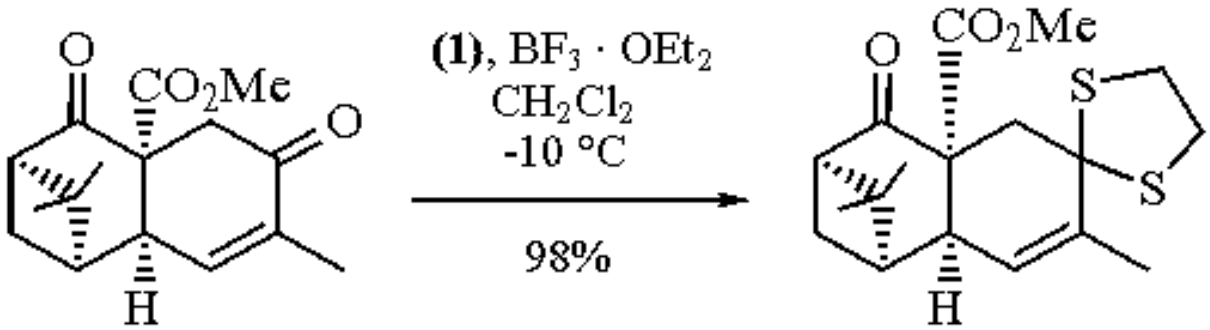

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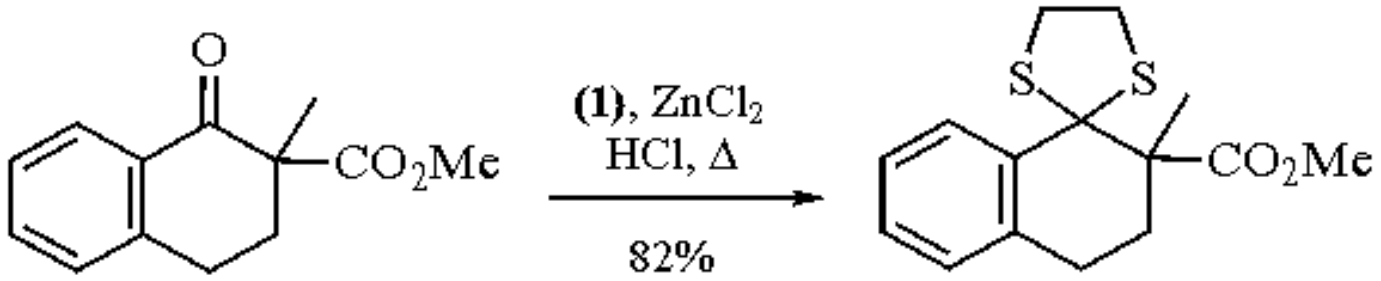

(2)

Ether Cleavage.

An acetonide can be cleaved in the presence of a nearby *t*-butyldiphenylsilyl ether with (**1**).[6a] Under more vigorous conditions, aliphatic methyl ethers are cleaved (eq 3).[6b]

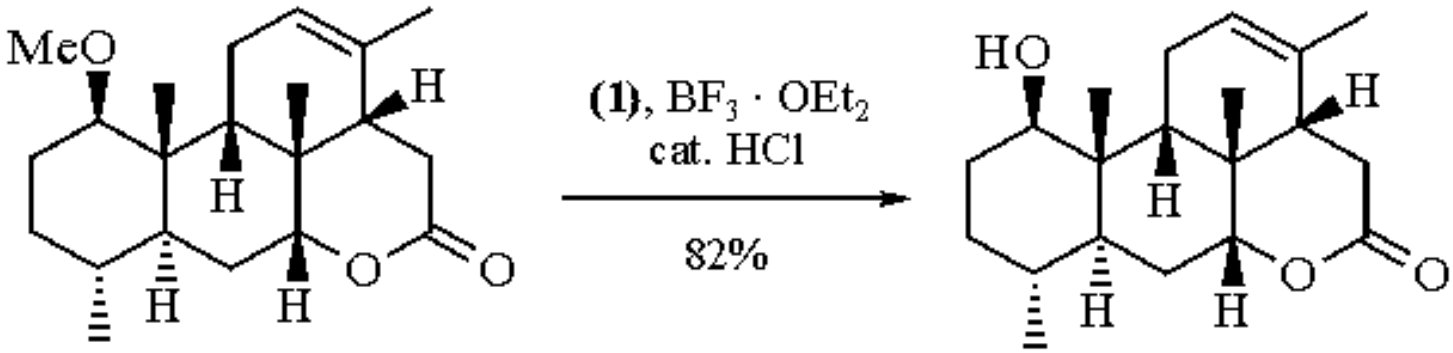

(3)

Reduction.

Raney Nickel desulfurization of 1,3-dithiolanes effects overall reduction of C=O to CH_2, as does ***Sodium-Ammonia*** in THF (eqs 4 and 5).[7a,b] Na/hydrazine is an alternative reagent (eq 6).[10a] Peptidic sulfoxides are reduced to thioethers with (**1**) and an electrophilic catalyst.[11a]

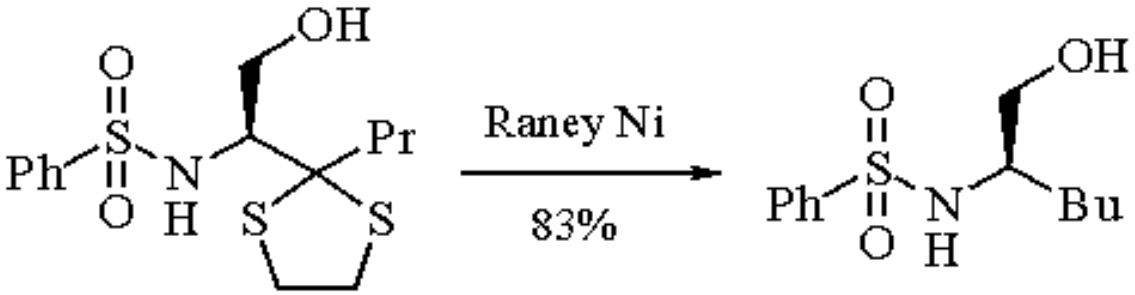

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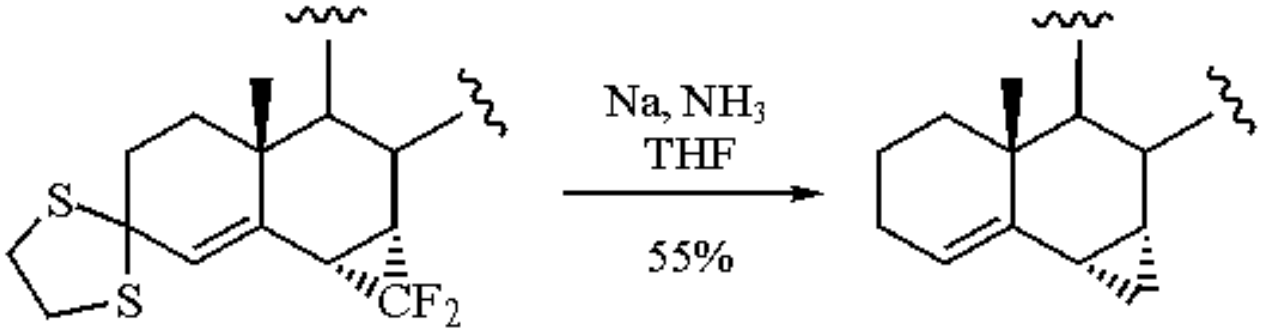

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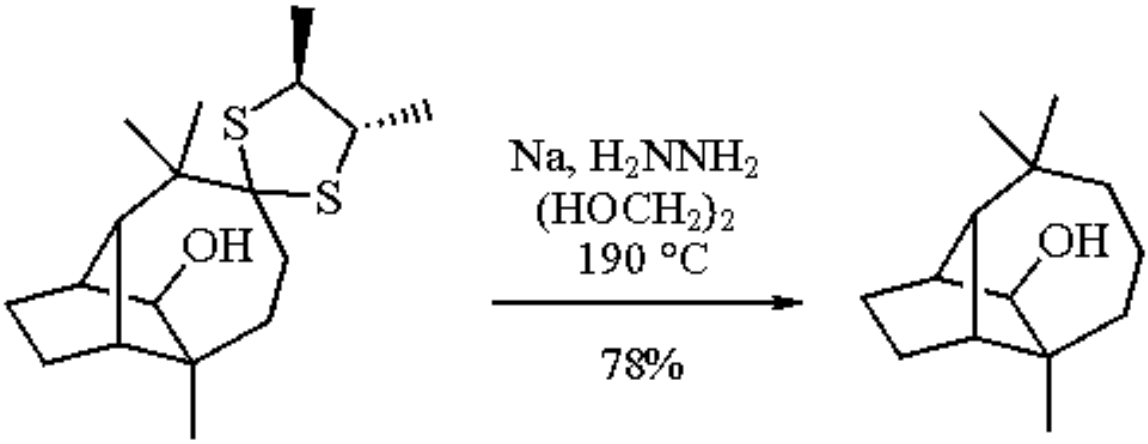

(6)

(resolved)

gem-Difluoride Formation.

1,3-Dithiolanes yield geminal difluorides on treatment with ***Pyridinium Poly(hydrogen fluoride)*** and a mild oxidant (eq 7).[8a,b] 1,3-Dithianes react more slowly and give lower yields.[8a]

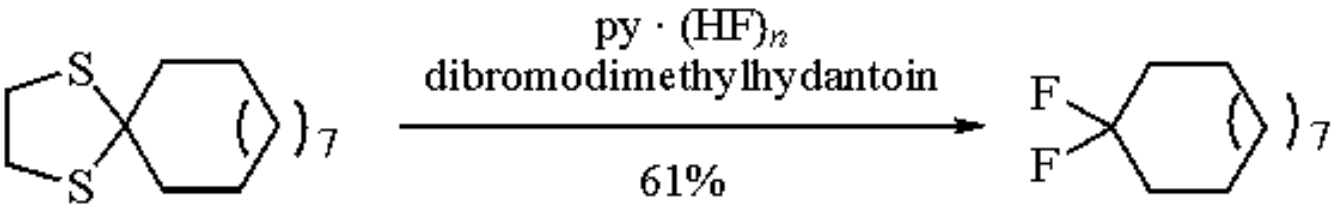

(7)

Dithiolenium Ion Formation.

Acid chlorides, anhydrides, esters, and orthoesters, upon treatment with (**1**) and a Lewis acid, can produce electrophilic 1,3-dithiolenium cations which react with a variety of carbon nucleophiles.[9] Selective indole formylation in the presence of a primary carboxamide could thus be achieved (eq 8).[9a]

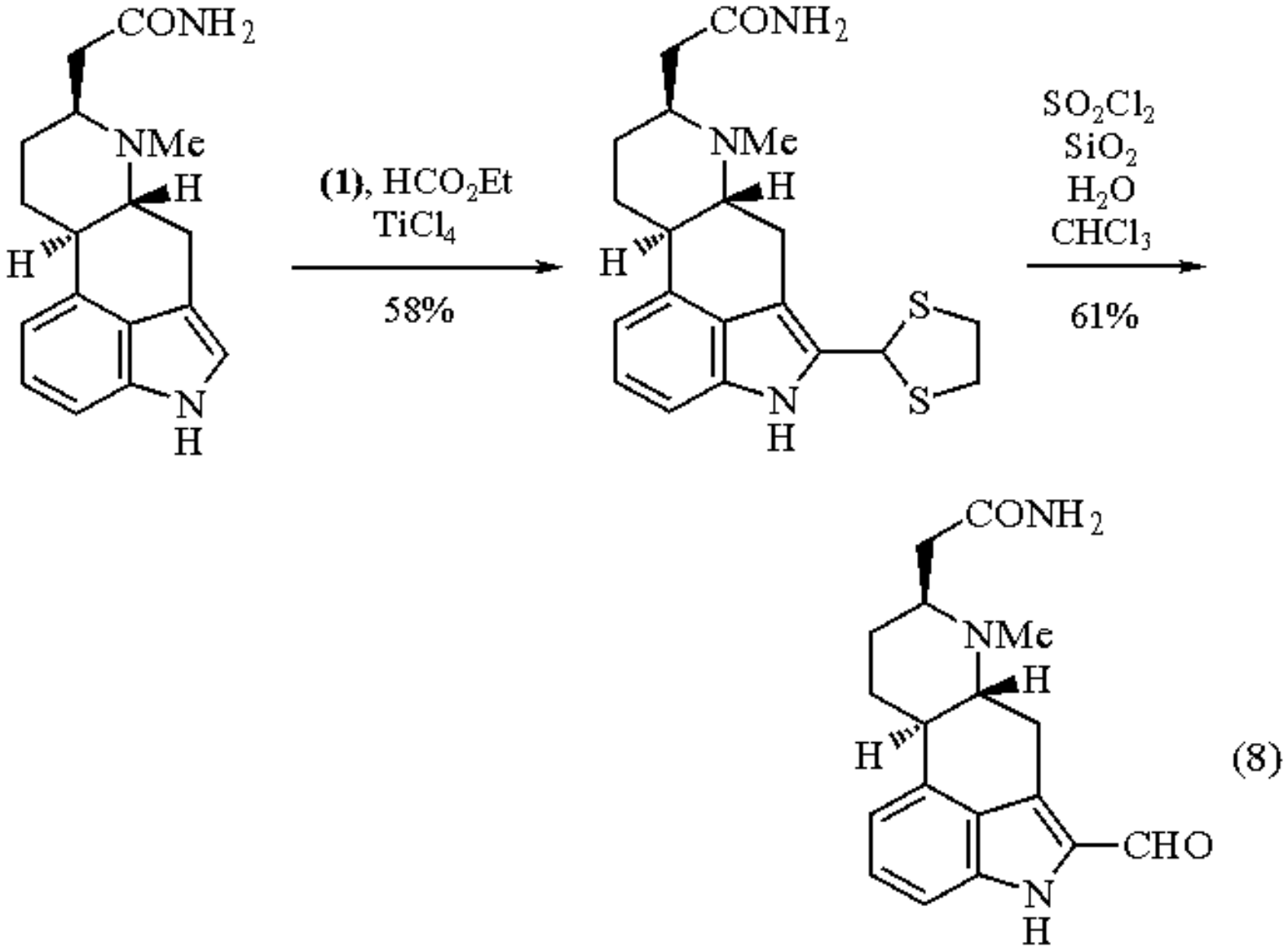

(8)

Miscellaneous.

Racemic ketones have been resolved by condensation with (*R*,*R*)- or (*S*,*S*)-2,3-butanedithiol, then reduced as above to give resolved deoxy compounds (eq 6).[10a,b] Oxidation of prochiral 1,3-dithiolanes under modified Katsuki-Sharpless conditions yields monosulfoxides of high ee.[10c] In peptide synthesis, (**1**) is frequently used as a cation scavenger during deprotection.[11a,b] Transition metal cations are strongly chelated by (**1**), as exemplified by demetalation of Cu^{II} and Ni^{II} metalloporphyrins.[11c]

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Ethanethiol

EtSH

[75-08-1] · C_2H_6S · Ethanethiol · (MW 62.13)

(thioacetal formation; nucleophilic reagent;[1-4] cation scavenger and hydrogen donor)

Physical Data: bp 35 °C; *d* 0.839 g cm^{-3}.

Solubility: sol alcohols, ether, acetone.

Form Supplied in: colorless liquid; widely available.

Purification: dissolve in aqueous 20% NaOH, extract with benzene, steam distill until clear. Cool, acidify with 15% H_2SO_4, distill ethanethiol. Dry with $CaSO_4$, $CaCl_2$, or 4Å sieves followed by fractional distillation under nitrogen.

Handling, Storage, and Precautions: stench; irritant and flammable liquid. Keep in cool place in a tightly sealed bottle. Refrigerate before opening due to possible pressure build-up. Use only in a well-ventilated fume hood.

Nucleophilic Reagent.

Ethanethiol undergoes reactions typical of a nucleophilic species, including displacement at saturated carbon, addition to electron-deficient alkenes and alkynes, epoxides, and acylations (eqs 1-3).[1-4]

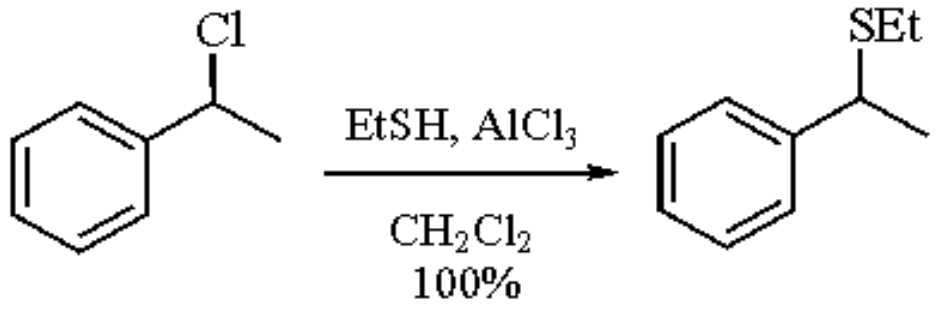

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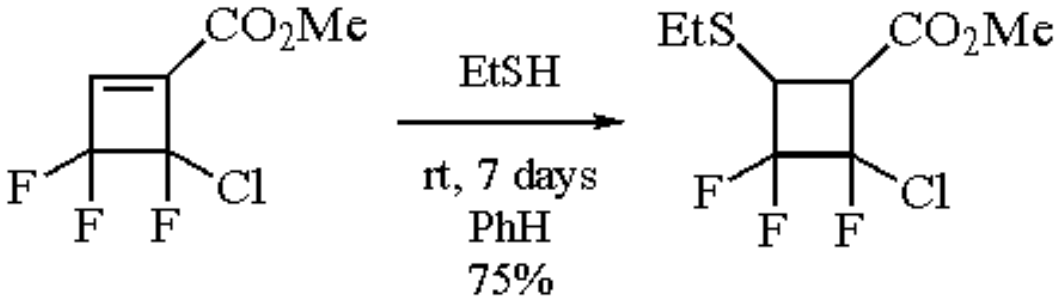

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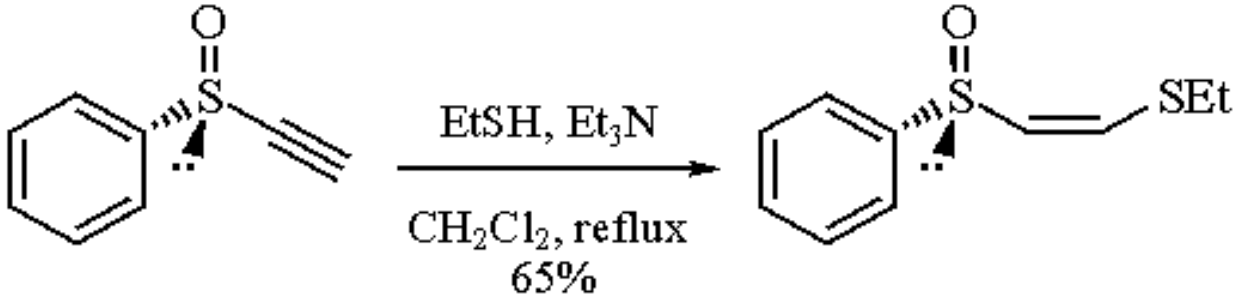

(3)

A useful reaction is the formation of dithioacetals by the acid-catalyzed condensation of carbonyl compounds and ethanethiol (see also ***1,2-Ethanedithiol*** and ***1,3-Propanedithiol***).[5,6] Acid catalysts used include ***Boron Trifluoride***, ***Zinc Chloride***, ***Lanthanum(III) Chloride***, ***Tetrachlorosilane***, ***Chlorotrimethylsilane***, and ***Tellurium(IV) Chloride*** (eq 4).[7] Acid-catalyzed thioacetalization of lactols produces the corresponding acyclic thioacetal (eq 5).[8]

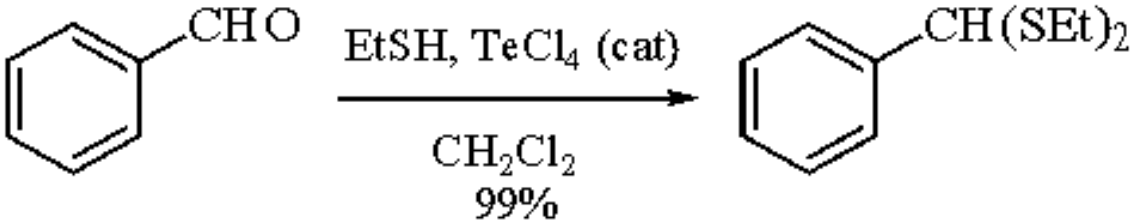

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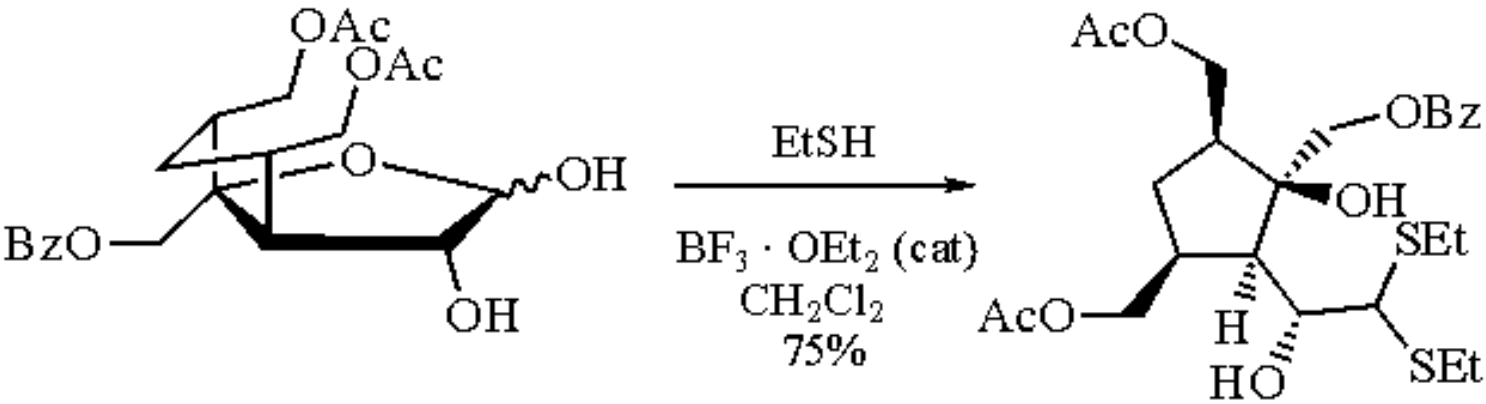

(5)

Ethylthiosilane is a useful reagent for effecting nucleophilic additions to carbonyl compounds.[9] Ethylthiosilane is most readily prepared by heating a mixture of ethanethiol, ***Hexamethyldisilazane***, and a trace of chlorotrimethylsilane.[9a] Both the thermal and catalyzed carbonyl addition reactions of ethylthiosilane have been investigated.[10,11] The combination of alkylthiosilanes and Lewis acids have proven useful in the preparation of thioacetals and hemithioacetals under buffered conditions (eq 6). Small amounts of tetrabutylammonium cyanide, ***Tetra-n-butylammonium Fluoride***, or ***Potassium Cyanide-18-Crown-6*** complex effect anionic-initiated addition of ethylthiosilane to carbonyl compounds. Under these reaction conditions, saturated aldehydes produce hemithioacetals,

the product of 1,2-addition (eq 7). Unsaturated ketones and aldehydes yields exclusively silyl enol ethers via the 1,4-addition reaction pathway (eq 8). The 1,4-addition pathway has been used advantageously to generate enol ethers which then undergo stereoselective aldol reaction (eq 9).[12]

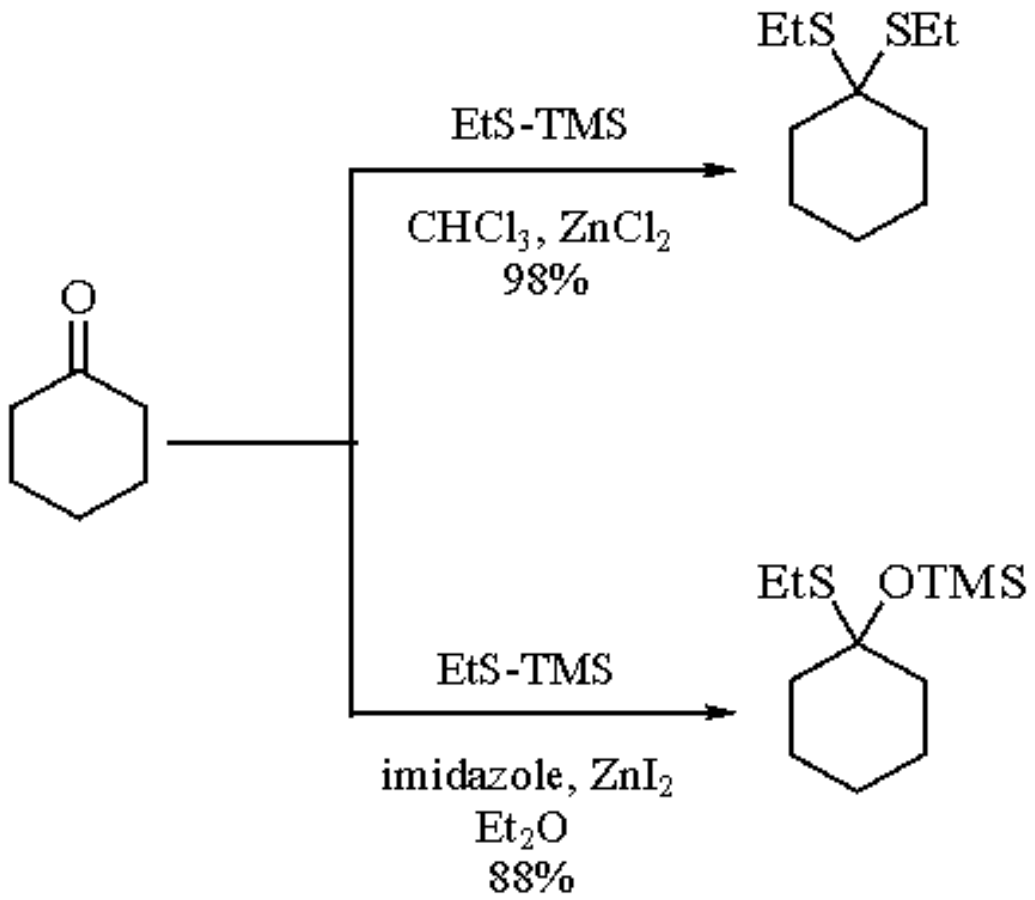

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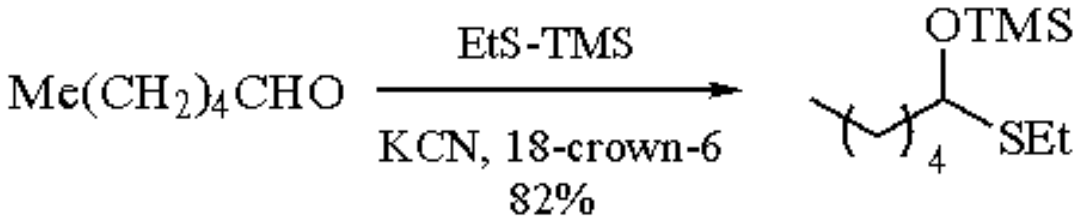

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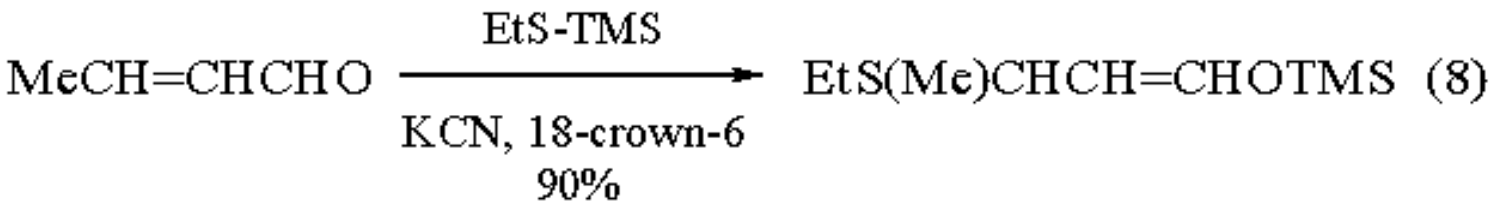

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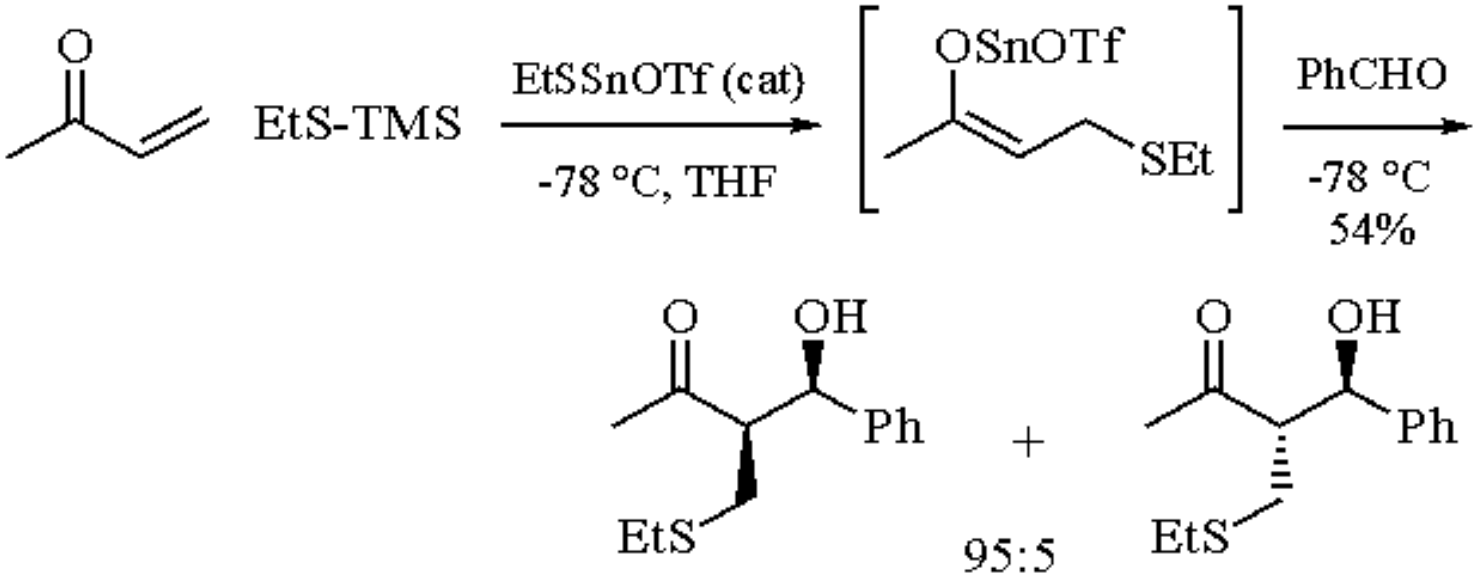

Ethanethiol is weakly acidic (pK_a ~10-11) and upon deprotonation generates ethanethiolate.[1a,13] The metal salts of ethanethiolate are highly nucleophilic and relatively nonbasic. The combination of these two properties has led to the development of sodium thiolate, and other metal salts of alkanethiolates, as useful reagents in organic synthesis. For example, the cleavage of methyl aryl ethers is accomplished using sodium ethanethiolate in refluxing DMF (eqs 10 and 11).[14-16] Sodium ethanethiolate is generated in situ by the deprotonation of ethanethiol with sodium hydroxide under an inert atmosphere.

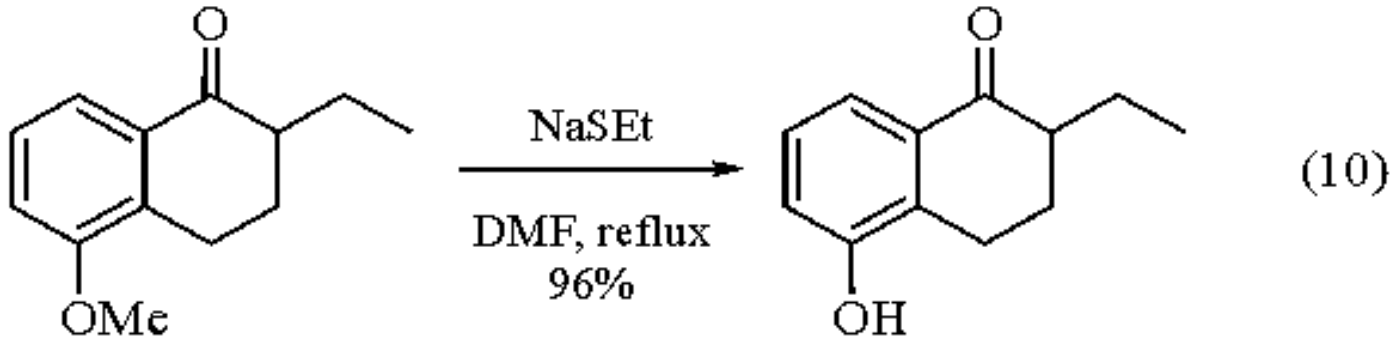

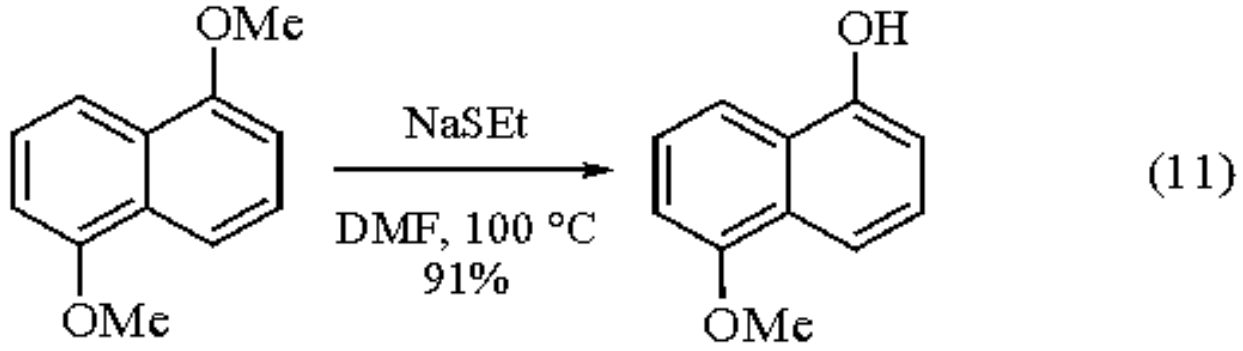

Alternative nucleophiles for inducing cleavage of aryl methyl ethers include sodium thiophenoxide, sodium benzylselenide, sodium thiocresolate, ***Sodium Cyanide***, ***Lithium Iodide***, and ***Iodotrimethylsilane***. Metal thiolates, such as sodium ethanethiolate, in dipolar aprotic medium have also been used to cleave alkyl esters.[17-20] The use of metal thiolates in HMPA is one of the mildest methods devised for effecting cleavage of alkyl esters through an S_N2

mechanism (eq 12).[19,20] The dealkylation of methyl esters via metal thiolates is particularly useful in cases of hindered ester groups. Ethanethiol also reportedly cleaves aryl methyl ethers and alkyl esters in combination with Lewis acids (eqs 13 and 14).[21,22]

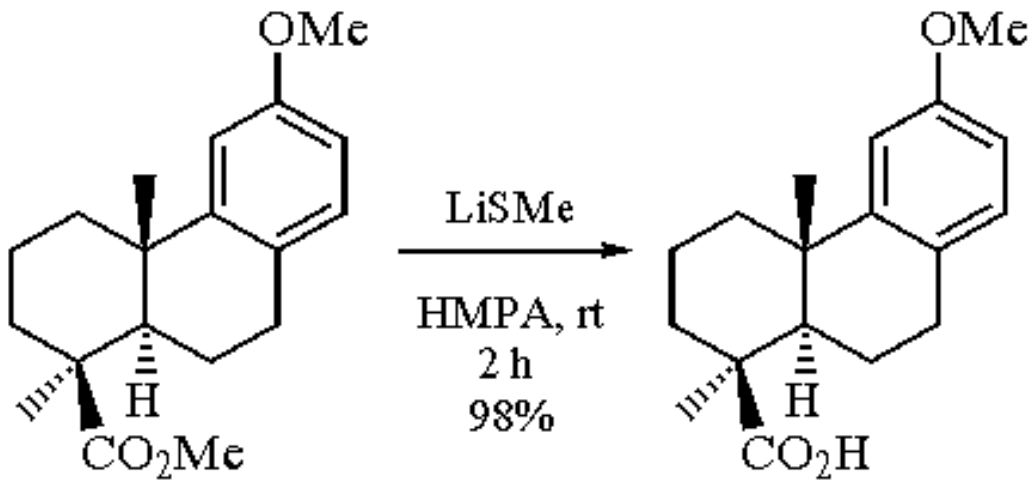

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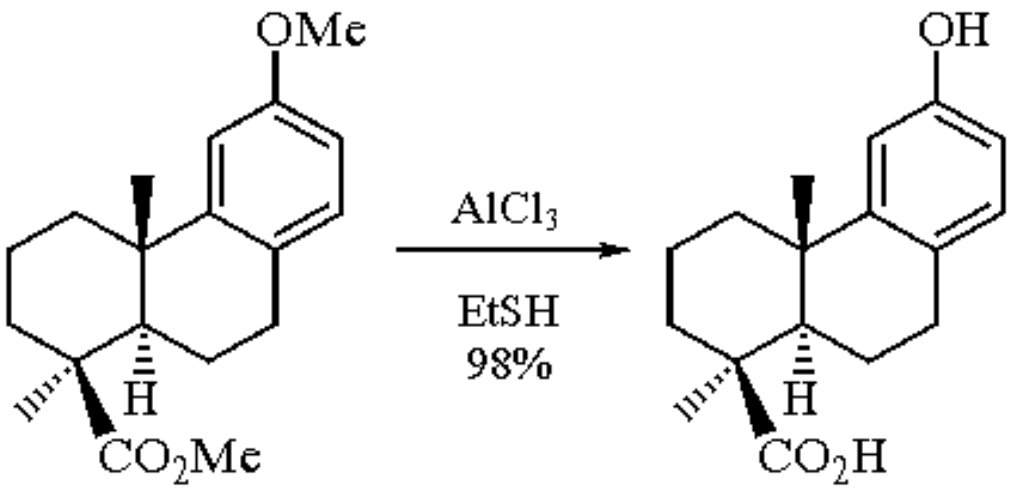

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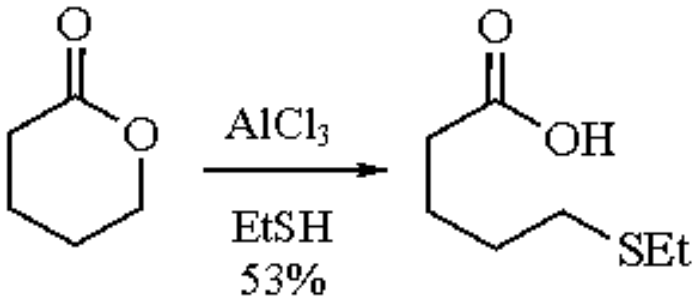

(14)

Cation Scavenger.

Thiols, such as ethanethiol, have been used to scavenge liberated cations in organic reactions. For example, protic cleavage of the *t*-butyl carbamate protecting group used in peptide synthesis liberates *t*-butyl cations and may alkylate methionine or tryptophan.[23,24] ***Thiophenol*** is most commonly used to scavenge cations. In a similar fashion, protodesilylation utilizes ethanethiol to scavenge the silyl cation (eq 15).[25]

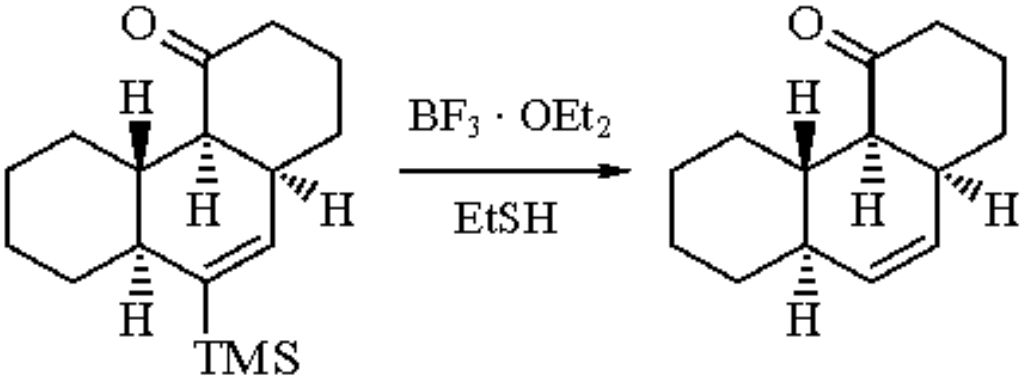

(15)

Hydrogen Atom Donor.

The sulfur-hydrogen bond of ethanethiol is prone to homolytic cleavage by either the intervention of a radical or photolytic cleavage. Ethanethiol has been utilized as a hydrogen atom donor in radical reactions (eq 16).[26] The photoaddition of thiols to a carbon-carbon double bond has also been examined (eq 17).[1b]

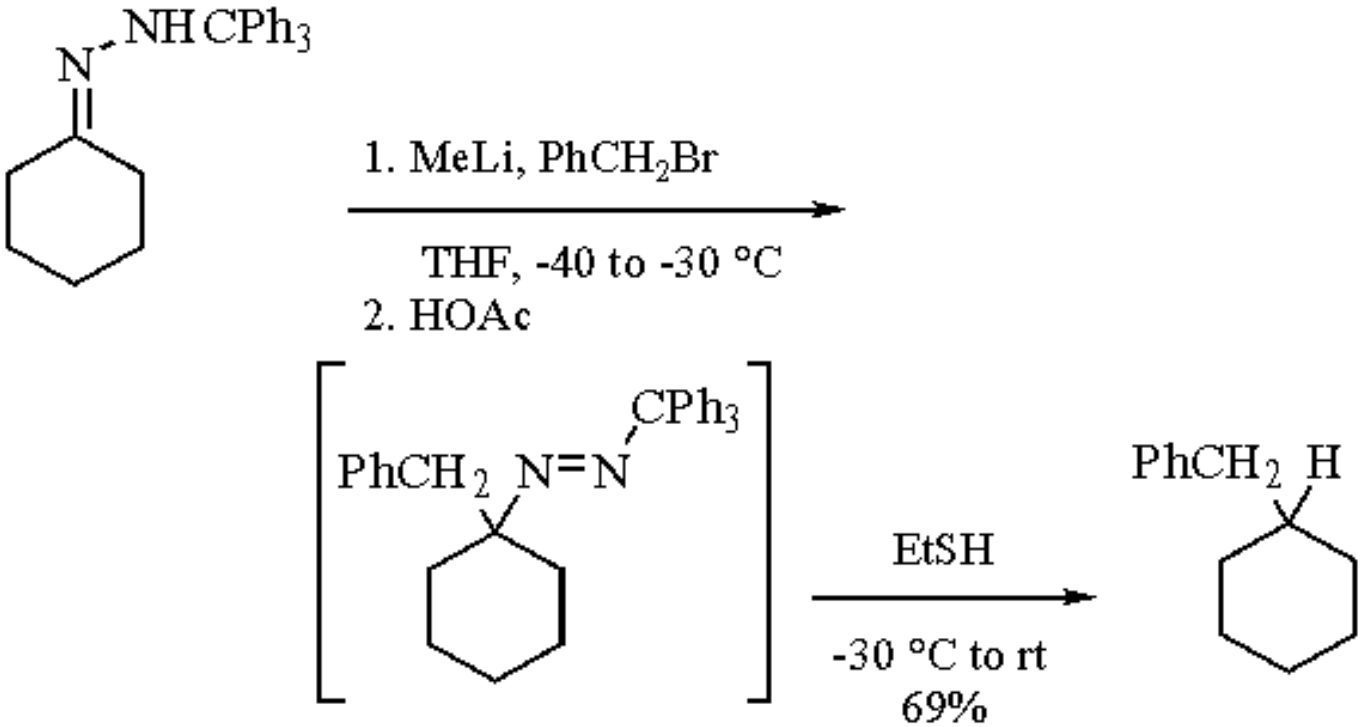

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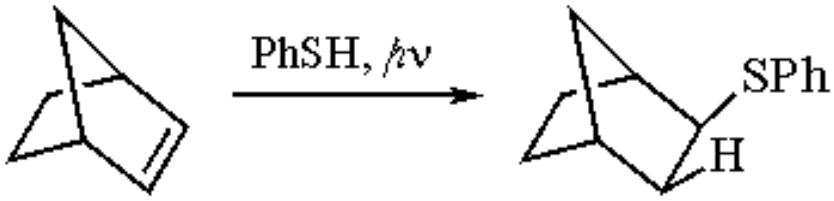

(17)

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Ethanolamine

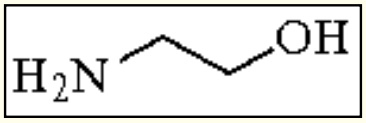

[141-43-5] · C_2H_7NO · Ethanolamine · (MW 61.08)

(synthesis of oxazolidines,[1] oxazolidinones,[2] 2-oxazolines;[3] hydroboration workup[4])

Alternate Names: 2-aminoethanol; monoethanolamine; MEA.

Physical Data: viscous liquid; bp 170 °C; 58 °C/5 mmHg; mp 10.3 °C; *d* 1.018 g cm^{-3}; pH = 12.1 (25 w/w % aqueous solution); pK_a = 9.4 (25 °C).

Solubility: sol H_2O, alcohol, $CHCl_3$; slightly sol ether, benzene; insol hydrocarbons.

Preparative Methods: large-scale preparation by ammonolysis of ***Ethylene Oxide***.[5]

Purification: azeotrope with benzene followed by fractional distillation under reduced pressure.

Handling, Storage, and Precautions: hygroscopic; absorbs CO_2 from atmosphere; corrosive.

N-Arylation and Alkylation.

MEA can be used to introduce β-hydroxyethylamino functionality onto aromatics containing electron-withdrawing groups (eq 1)[6] or heterocycles (eq 2)[7] by nucleophilic substitution. *N*-Alkyl or *N*,*N*-dialkylated derivatives of MEA can be obtained in good yields under mild conditions by alkylation (e.g. ***Benzyl Chloride***, ***Sodium Hydroxide***; mono, 68%; di, 72%)[8] or reductive amination (e.g. ***Acetone***, ***Platinum(IV) Oxide***, 95%;[9] ***Acetaldehyde***, ***Sodium Borohydride***, 76%[1c]). MEA derives its versatility by conversion to derivatives that serve in other transformations. Substituted ethanolamines are used in many asymmetric reactions.

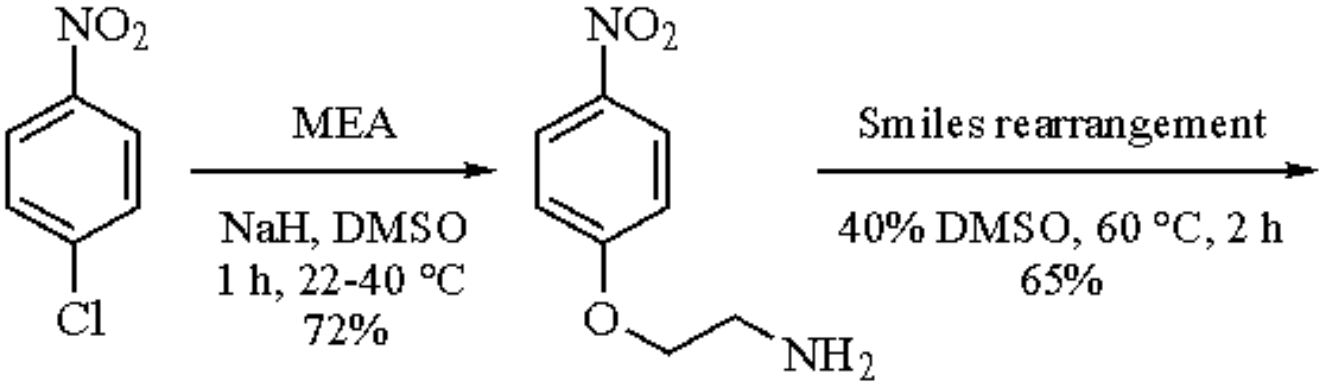

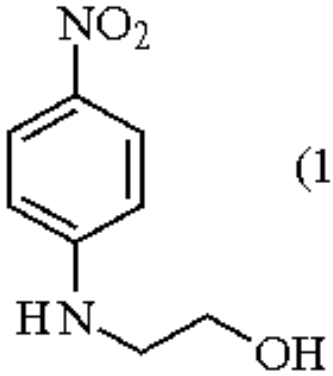

(1)

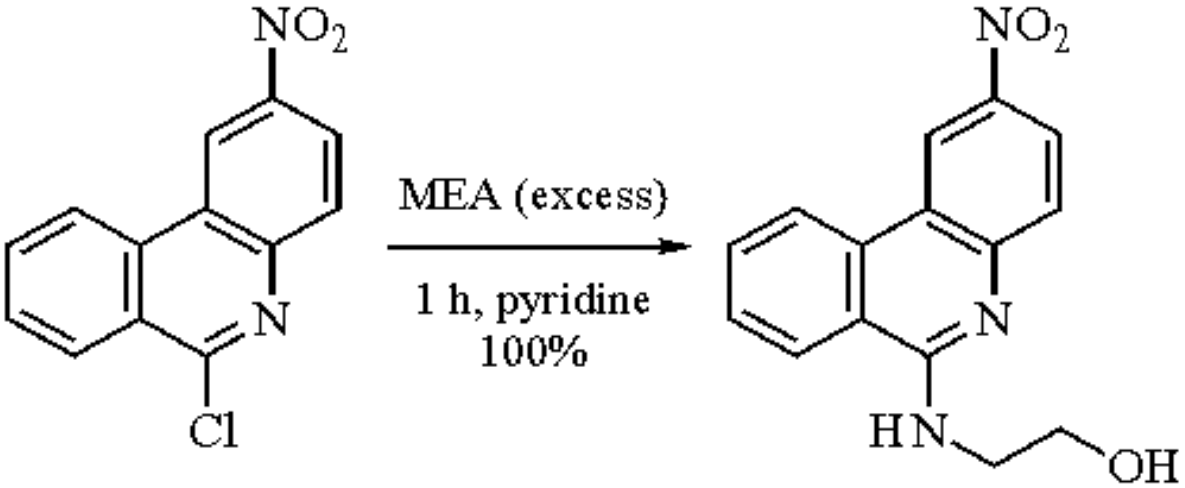

(2)

Reactions with Carbonyls.

MEA condenses with aldehydes and ketones to give oxazolidines (**1**),[1] carbonates to give oxazolidinones (**2**),[2] acids to give oxazolines (**3**),[3] and standard acylating agents (eq 3). These heterocycles are used as intermediates in natural product and polymer synthesis. It selectively deacylates acyl glycosides[10] and replaces hydrazine for cleavage of Gabriel synthesis intermediates.[11]

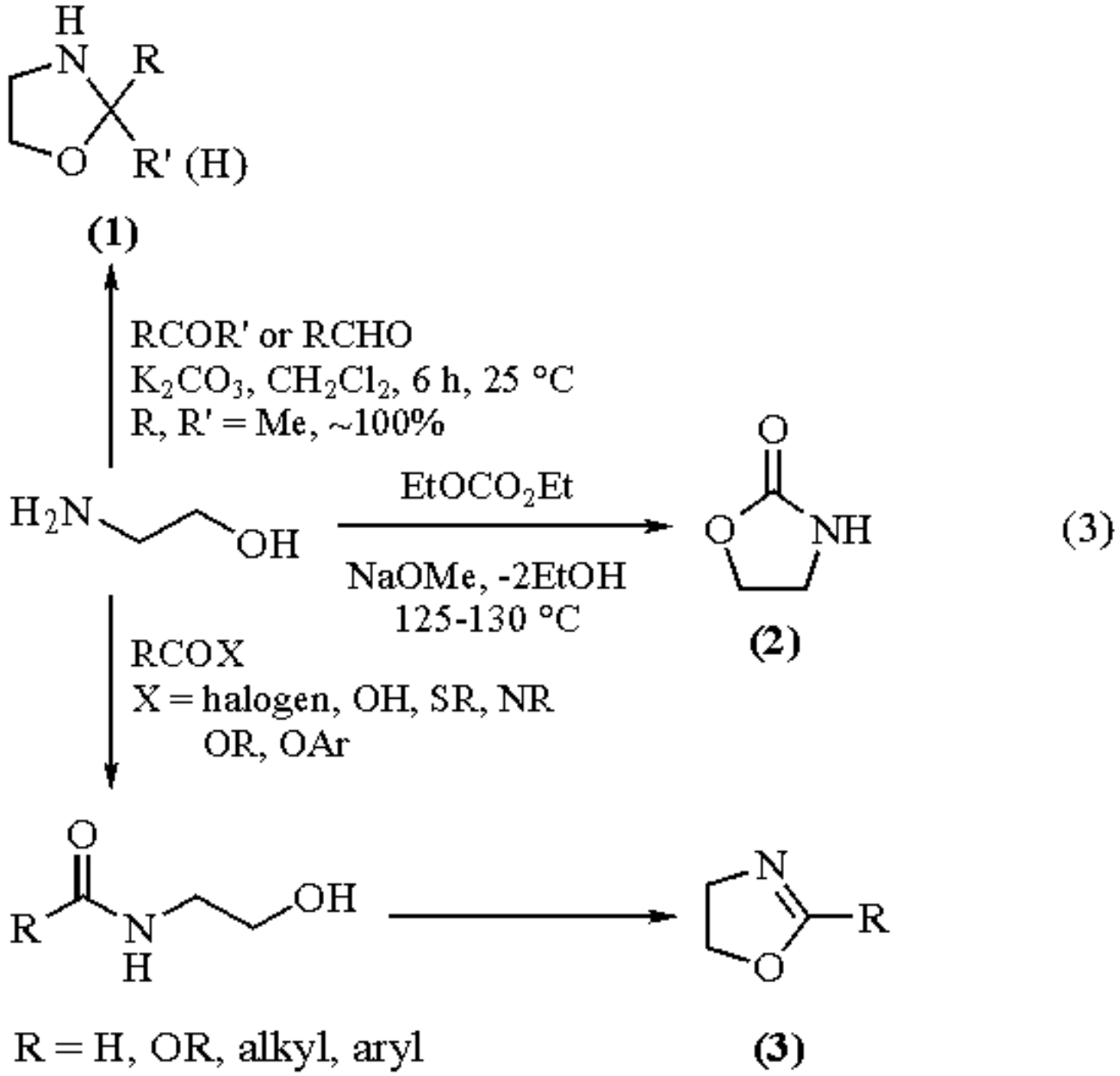

Hydroborations.

MEA aids hydroboration reaction workup by transesterifying the borate ester to give the product alcohol and a borinate precipitate (eq 4).[4] MEA has also been used to increase optical purities by crystallization of the resulting MEA esters.[12]

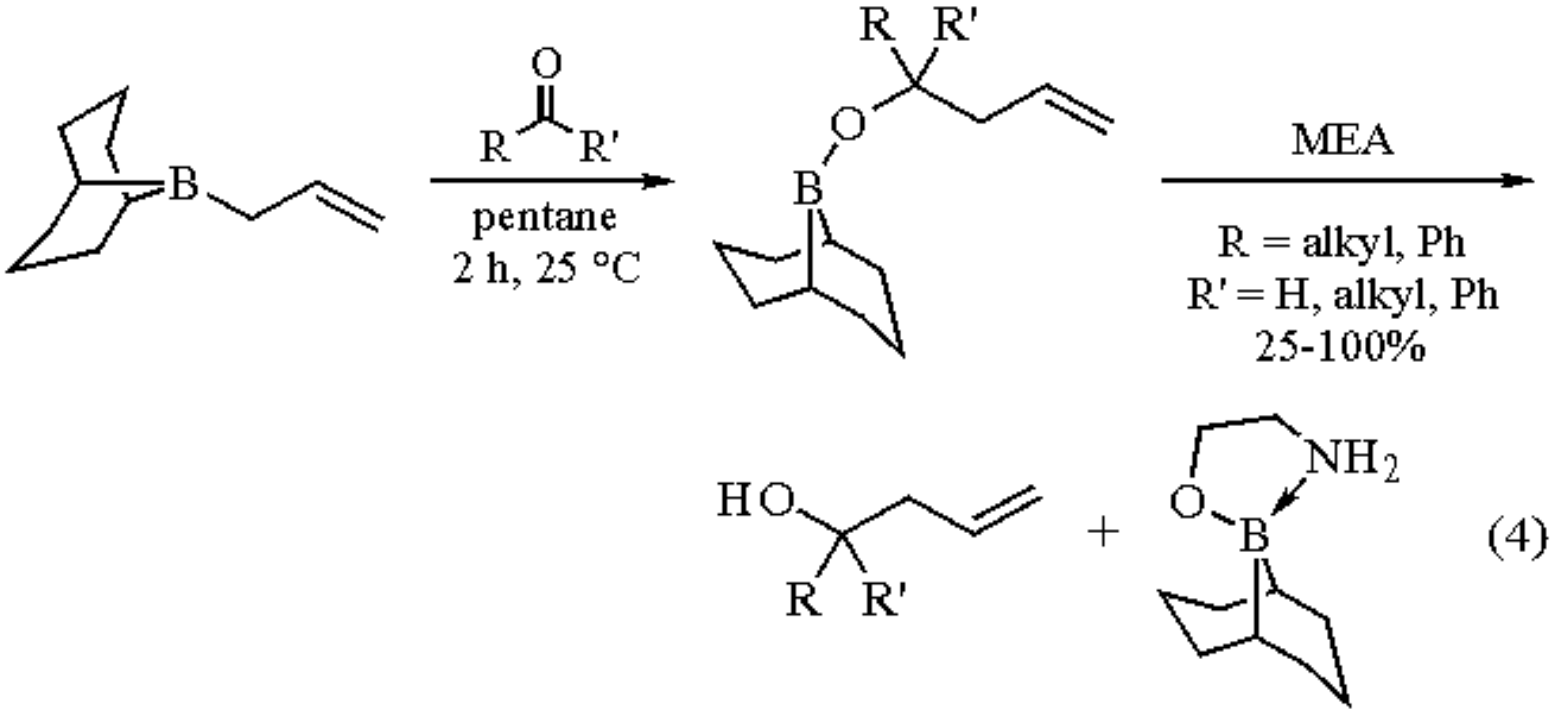

Heterocycle Synthesis.

Besides the heterocyclic systems shown in eq 3, different ring systems are obtained on reaction of MEA with CO_2, CS_2, isocyanates, nitriles, α-diketones [(**4**) and (**5**) depending on the reaction conditions],[13] and with 1,4-butenediol to give (**6**).[14]

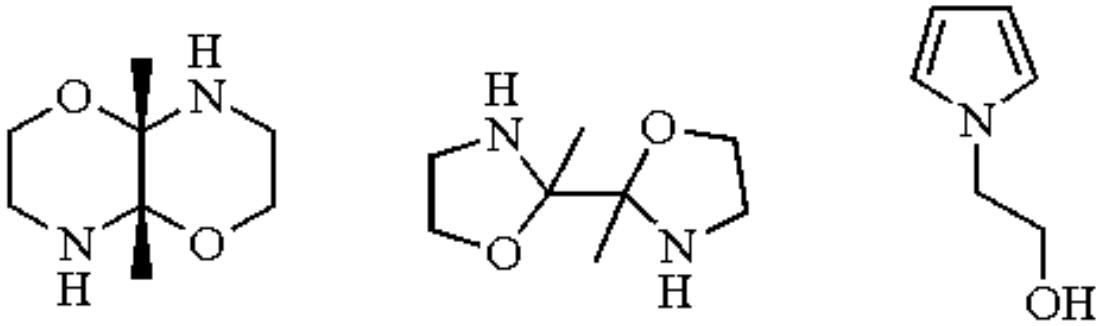

(4) **(5)** **(6)**

MEA is converted into a dienophile that has been used to prepare vicinal *cis*-amino alcohols (eq 5).[15]

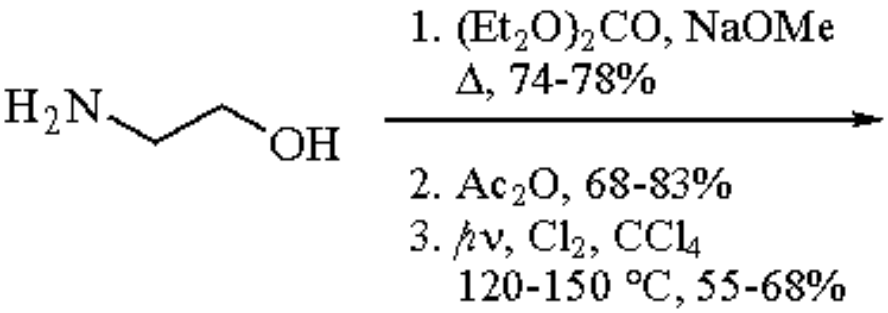

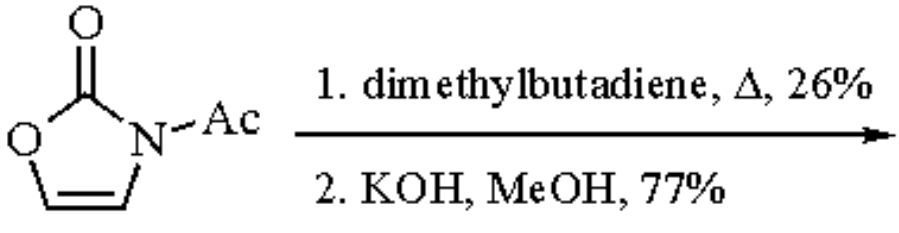

(5)

Quaternary Amine Dealkylation.

MEA dealkylates quaternary ammonium salts (methyl groups) prepared during exhaustive methylation of amines (eq 6).[15]

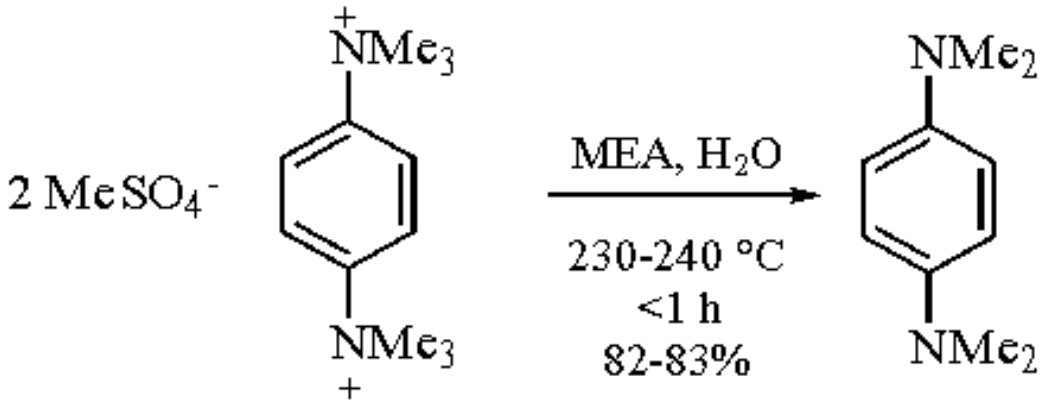

(6)

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Ethoxyacetylene[1]

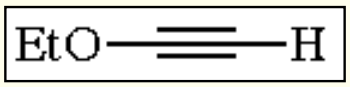

[927-80-0] · C_4H_6O · Ethoxyacetylene · (MW 79.09)

(preparation of alkenylcuprates,[2] anhydrides,[3] ketenes,[4,5] lactones;[6] reacts with allylboranes[7])

Alternate Name: ethyl ethynyl ether.

Physical Data: bp 48-50 °C; *d* 0.800 g cm^{-3} (0.745 g cm^{-3} in hexane).

Solubility: sol alcohol, ether, benzene, hexane.

Preparative Methods: from chloroacetaldehyde diethyl acetal (70%).[8,9]

Form Supplied in: 50 w/w % solution in hexane(s).

Handling, Storage, and Precautions: moisture sensitive; potential fire hazard with certain metal salts.[8] Use in a fume hood.

Cycloaddition Reactions.

Ethoxyacetylene (**1**) participates in [2 + 2], [4 + 2], and 1,3-dipolar cycloaddition reactions. Diels-Alder reactions with oxazinones give substituted 3,5-disubstituted 2,6-dichloropyrimidines (eq 1).[10] 1,3-Dipolar cycloaddition reactions with aldoximes (eq 2)[11] and with nitrile oxides[12] give isoxazoles.

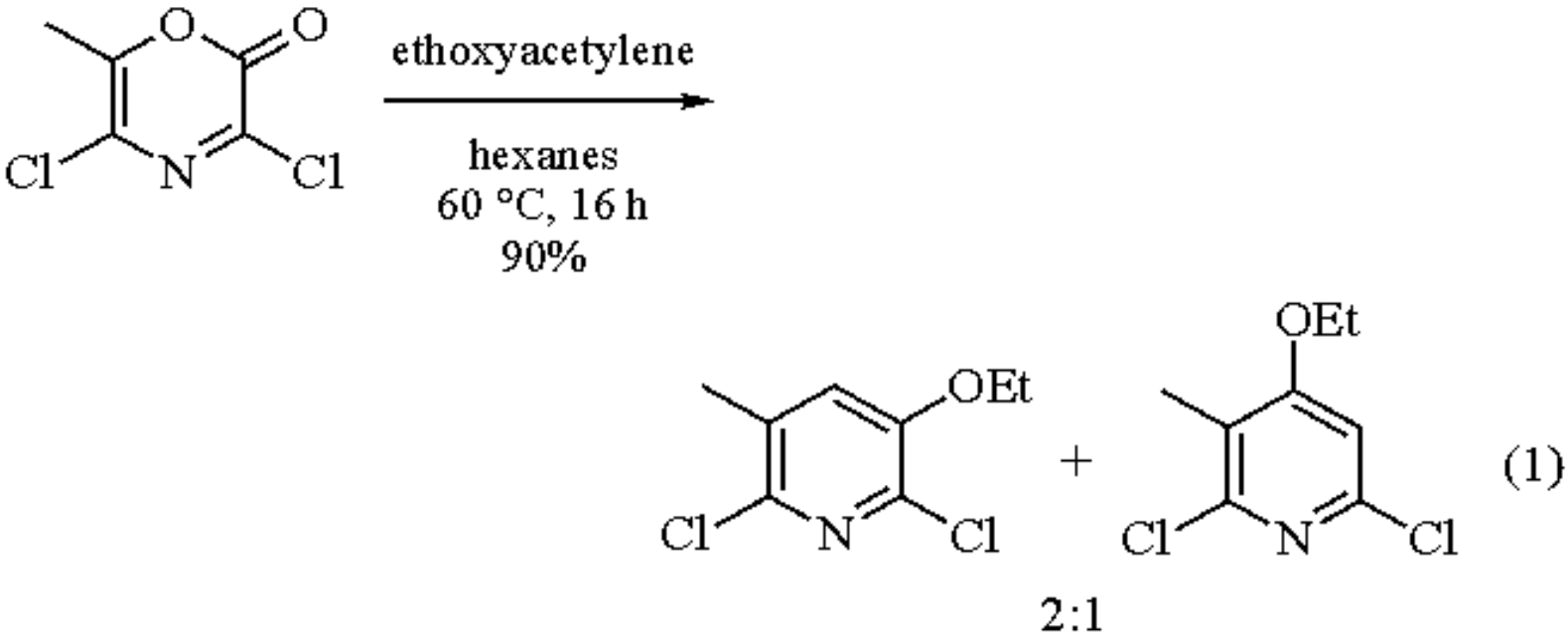

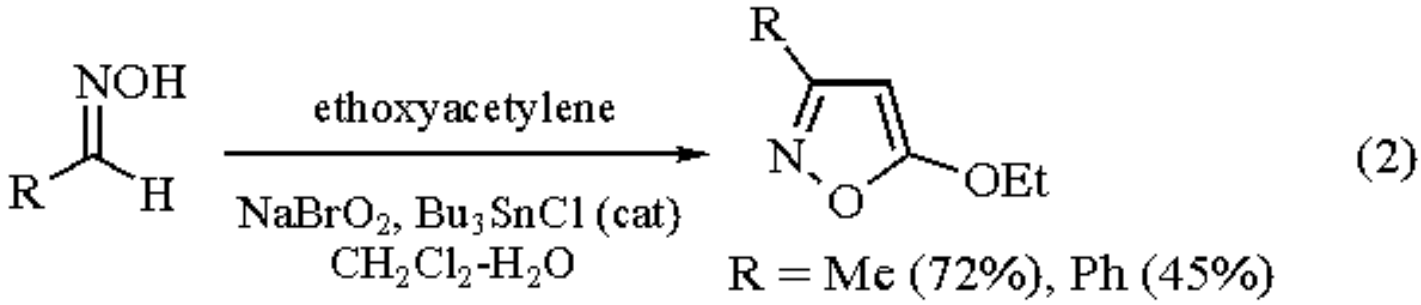

Ethoxyacetylene and its derivatives thermally decompose to generate ketenes[4,5,13] which either add to themselves or undergo further cycloaddition reactions. In addition, other ketenes, such as dimethylketene, add to (**1**) to give cyclobutanone derivatives (eq 3).[14]

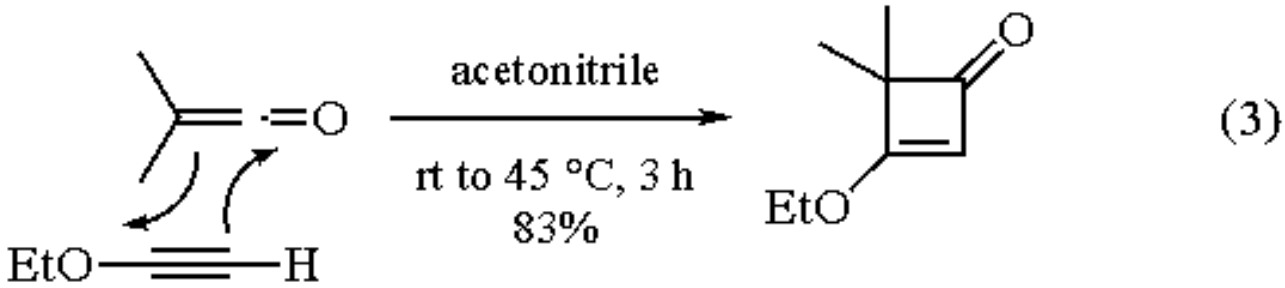

Ethoxyacetylene gives pyrazoles with ***Diazomethane***, triazoles with aryl and substituted alkyl azides, 2-quinolines with aryl isocyanates, and *o*-ethoxyphenylacetylene with benzyne.[1] Phospholes may be prepared in a [2 + 2 + 1] cycloaddition of a terminal phosphinidene complex with (**1**).[15] Organometallic reagents add to ethoxyacetylene to give 1,4-naphthoquinone-cobalt[16] and 2*H*-pyrrole-tungsten complexes,[17] and phenols.[18]

Nucleophilic Additions to Ethoxyacetylene.

Vinyl anions can be generated by nucleophilic addition to ethoxyacetylene. Alkyl cuprates tend to transfer only one group while (*Z*)-alkenyl cuprates transfer both groups to give (*E*)-α,β-unsaturated ketones after hydrolysis of the initial enol ethers (eq 4).[19] These vinylcopper reagents have been coupled, condensed with alkyl and vinyl iodides, acid chlorides, vinylogous acid chlorides, and iodine to give a variety of derivatives.[2]

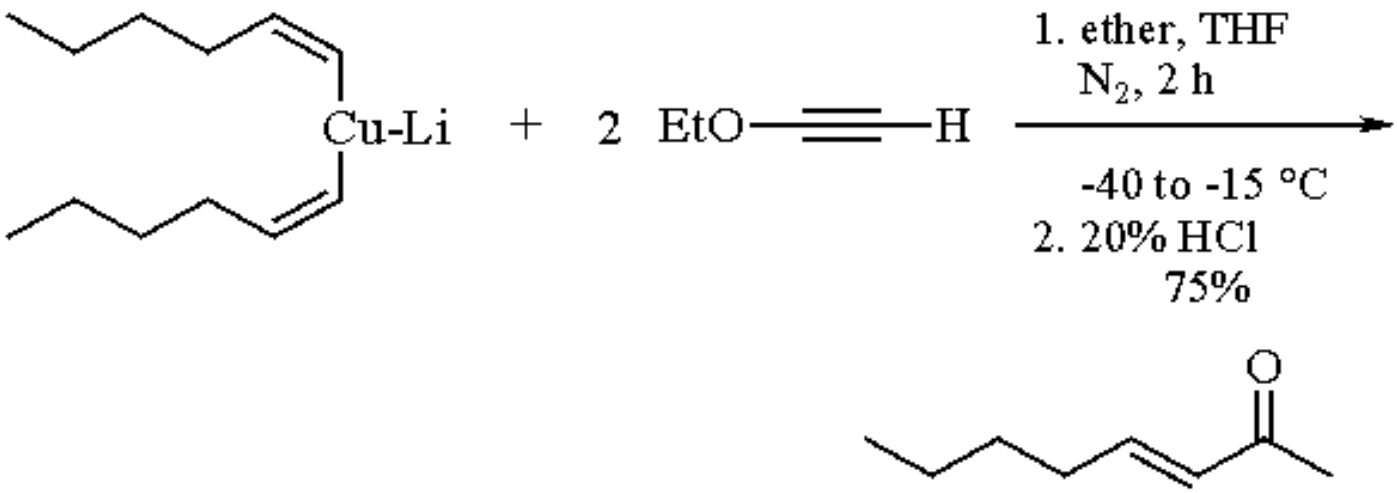

(4)

Trimethylsilylmethylcopper adds to ethoxyacetylene with *cis* addition to give allylic silane (**2**) that, when quenched with electrophiles, gives (*E*)-3-substituted 2-alkoxy-2-alkenylsilanes (eq 5).[20]

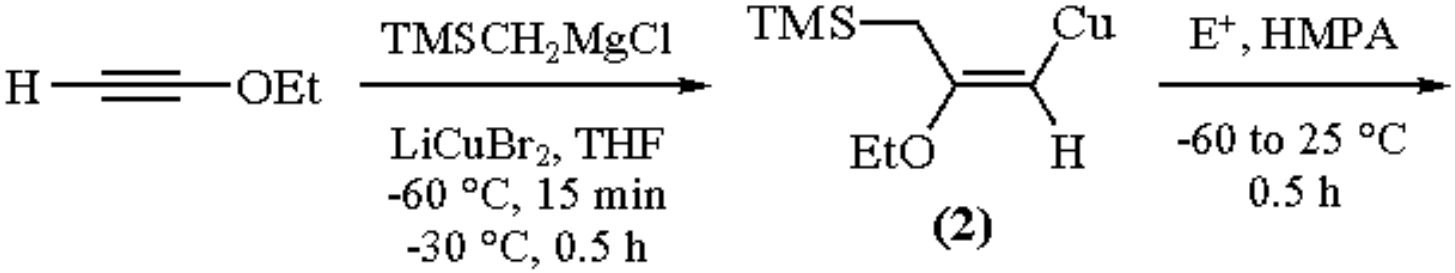

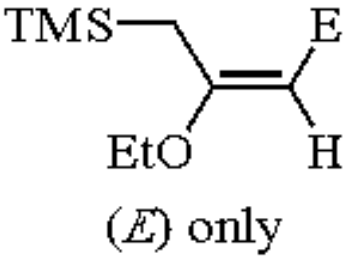

E	yield (%)
H	95
Cl	90
I	95
$CH_2{=}CHCH_2$	98
CO_2Me	70

(5)

Arylcopper reagents extend this chemistry. Thus, by coupling a Grignard reaction with a Wacker oxidation, 1,4-diketones can be prepared (eq 6).[21]

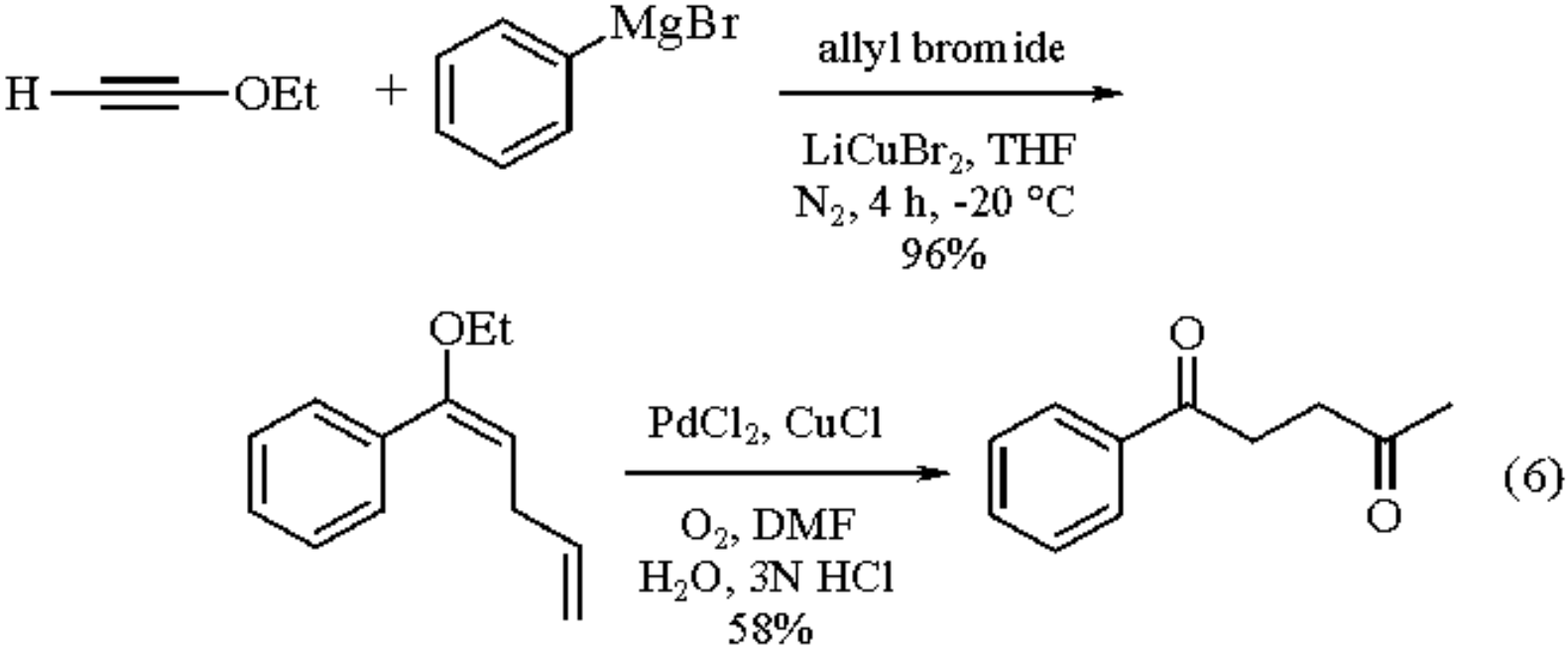

Nucleophilic Reactions of Ethoxyacetylene.

Anions derived from ethoxyacetylene, generated as the Grignard reagent,[22] or lithium[8,23] or aluminum[24] salts, add to alkyl halides,[25] aldehydes, ketones, and epoxides[22] to give precursors of α-hydroxy ketones,[26] aldehydes, acids, or α,β-unsaturated esters. Cyclohexene epoxide and ethoxyacetylene give a lactone upon treatment of the intermediate alcohol with acid. Conversion to the alane is necessary as no ring opening occurs with lithium ethoxyacetylide (eq 7). This methodology is superior to that which uses lithium *t*-butylacetate (Rathke's salt), which fails to react with hindered epoxides.[24]

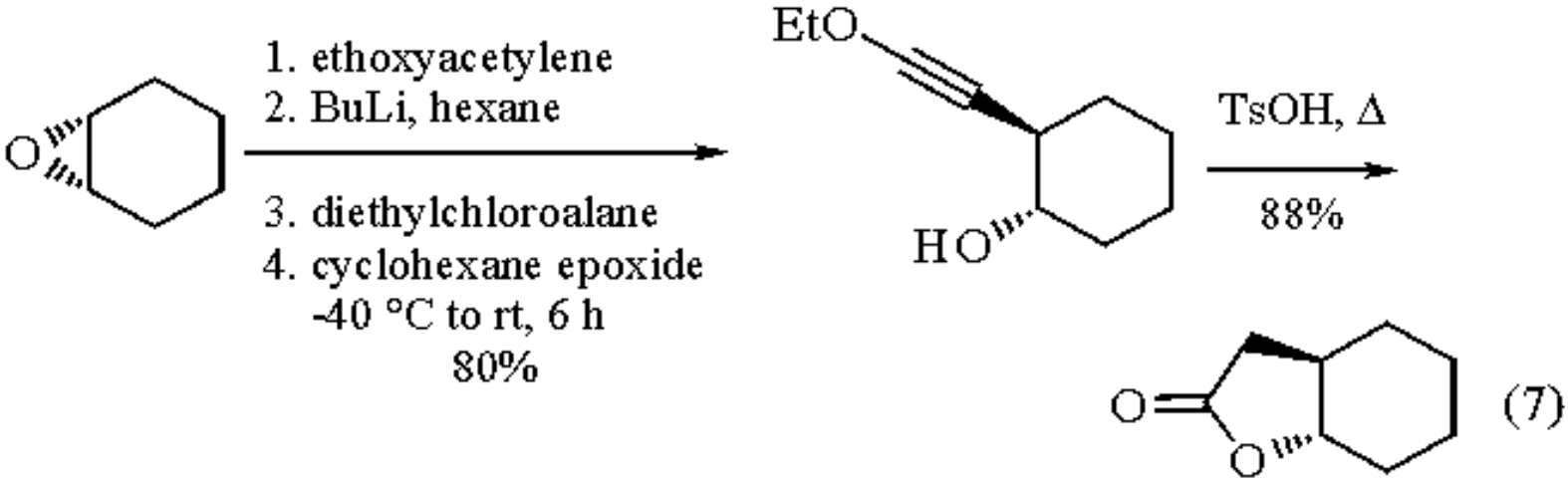

Ethoxyacetylene reacts with aldehydes and ketones in the presence of ***Boron Trifluoride*** to give α,β-unsaturated esters.[27]

Acylation Reactions.

Amines can be acylated by ethoxyacetylene to give carboxylic acid derivatives in good yields.[13] 1-Ethoxyvinyl esters, which are useful as acylating agents, have been prepared from carboxylic acids and ethoxyacetylene in a Ru^{II}-catalyzed reaction.[28] Cyclic anhydrides have been formed by dehydrating diacids with (**1**) (eqs 8 and 9).[3,29] Weakly nucleophilic 2-fluoro-2,2-dinitroethanol yields bis(2-fluoro-2,2-dinitroethyl)ethoxy ethyl orthoester in a 95% yield in a Hg^{II}-catalyzed reaction with ethoxyacetylene.[30]

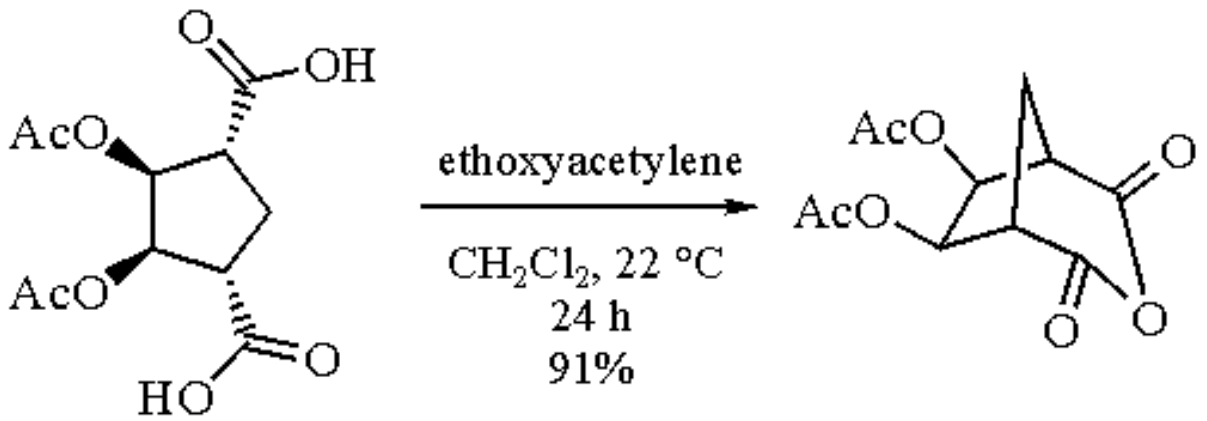

(8)

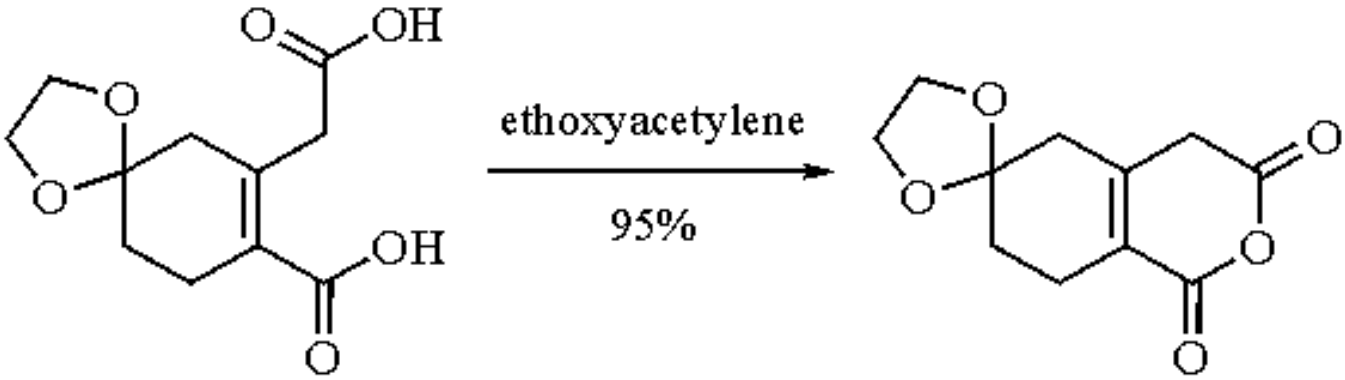

(9)

Lactones have been prepared by thermolysis of adducts formed from lithium ethoxyacetylide and hydroxy ketones (eq 10). Higher reaction temperatures increase conversion and lower reaction times. Good yields are reported for five-, six-, and seven-membered rings. Larger macrocycles (9-, 10-, 15-membered) require Bu_3N as a catalyst to get respectable yields and to minimize oligomeric products (see also ***2-Chloro-1-methylpyridinium Iodide***).[6]

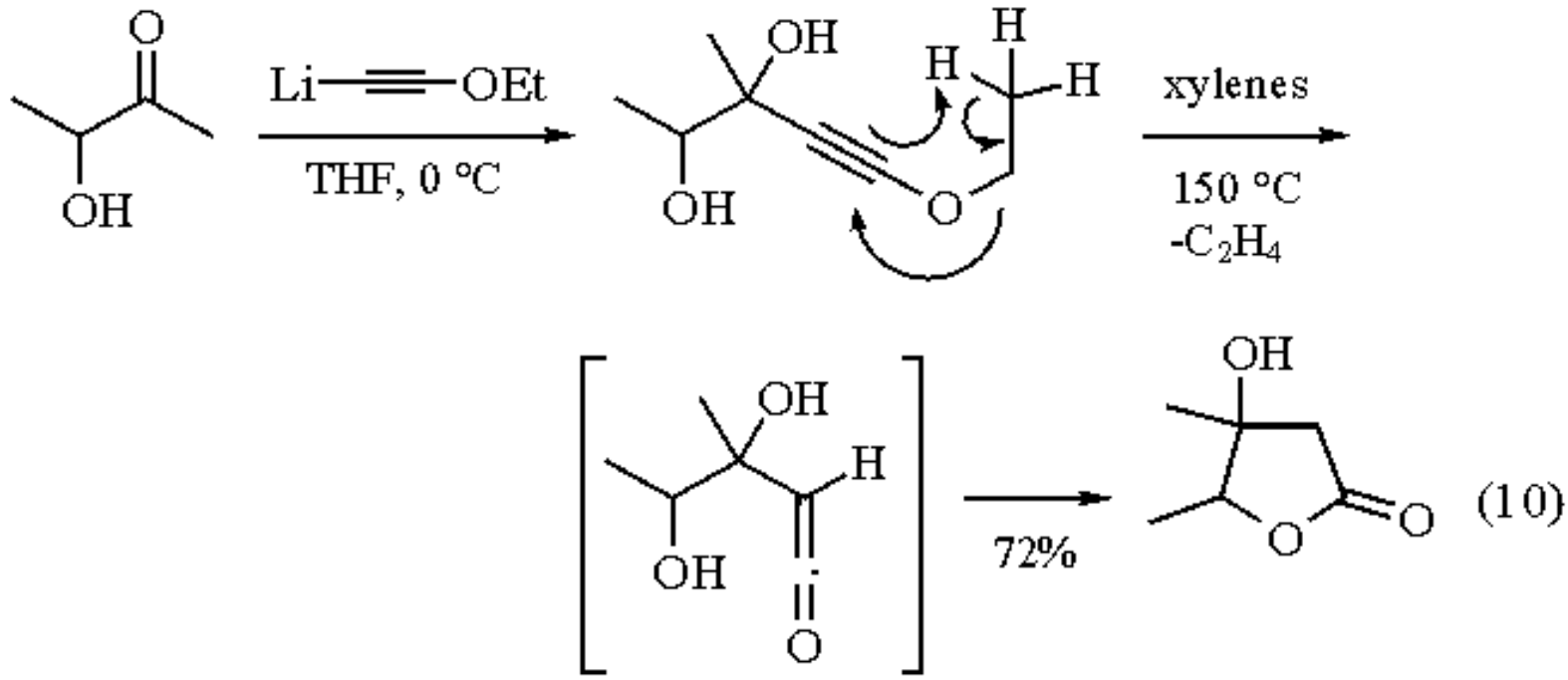

Insertion Reactions.

Allyl(dialkyl)boranes react with ethoxyacetylene to give dialkyl(alkoxypentadienyl)boranes which may be converted to 2-alkoxy-1,4-pentadienes[7] or methyl allyl ketone[31] on protonolysis. In a one-pot reaction, triallylboranes and ethoxyacetylene give 1,4-pentenynes as shown in eq 11.[7] Similar chemistry is observed with tribenzylboranes.[31] The ethoxyacetylene/(iodo-9-BBN) adduct reacts with acyclic α,β-unsaturated ketones to give δ-keto esters (74-95%)[32] and with aryl aldehydes to give cinnamic esters (89% yield, 99% (*E*)).[33] Unlike Wittig chemistry, this methodology tolerates base-sensitive functional groups. In a ***Mercury(II) Acetate*** catalyzed reaction, ethoxyacetylene, diphenylboronic acid, and alkyl or aryl aldehydes give β-hydroxy and β-acetoxy esters.[34]

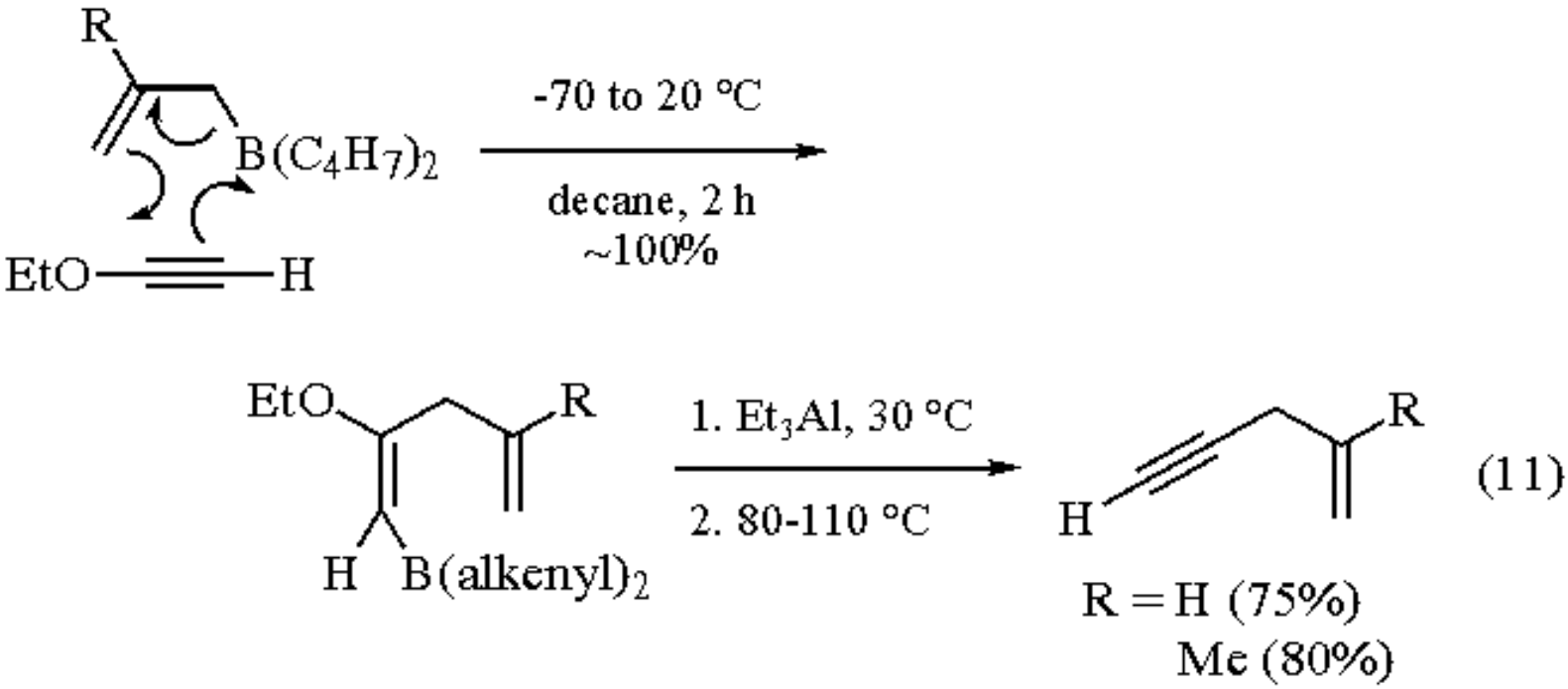

Transition Metal Catalyzed Reactions.

Zirconium reagents catalyze a one-pot addition of ethoxyacetylene to aryl iodides or bromides to give (*E*)-β-ethoxyalkene derivatives (eq 12). A variety of functional groups are tolerated on the aryl halide (Cl, OMe, CN, CO_2Me).[35] This chemistry has been extended to indoles.[36] Ethoxyacetylene gives pyrones with CO_2 and ***Bis(1,5-cyclooctadiene)nickel(0)***,[37] and indenols with acetophenone and $PhCH_2Mn(CO)_5$.[38]

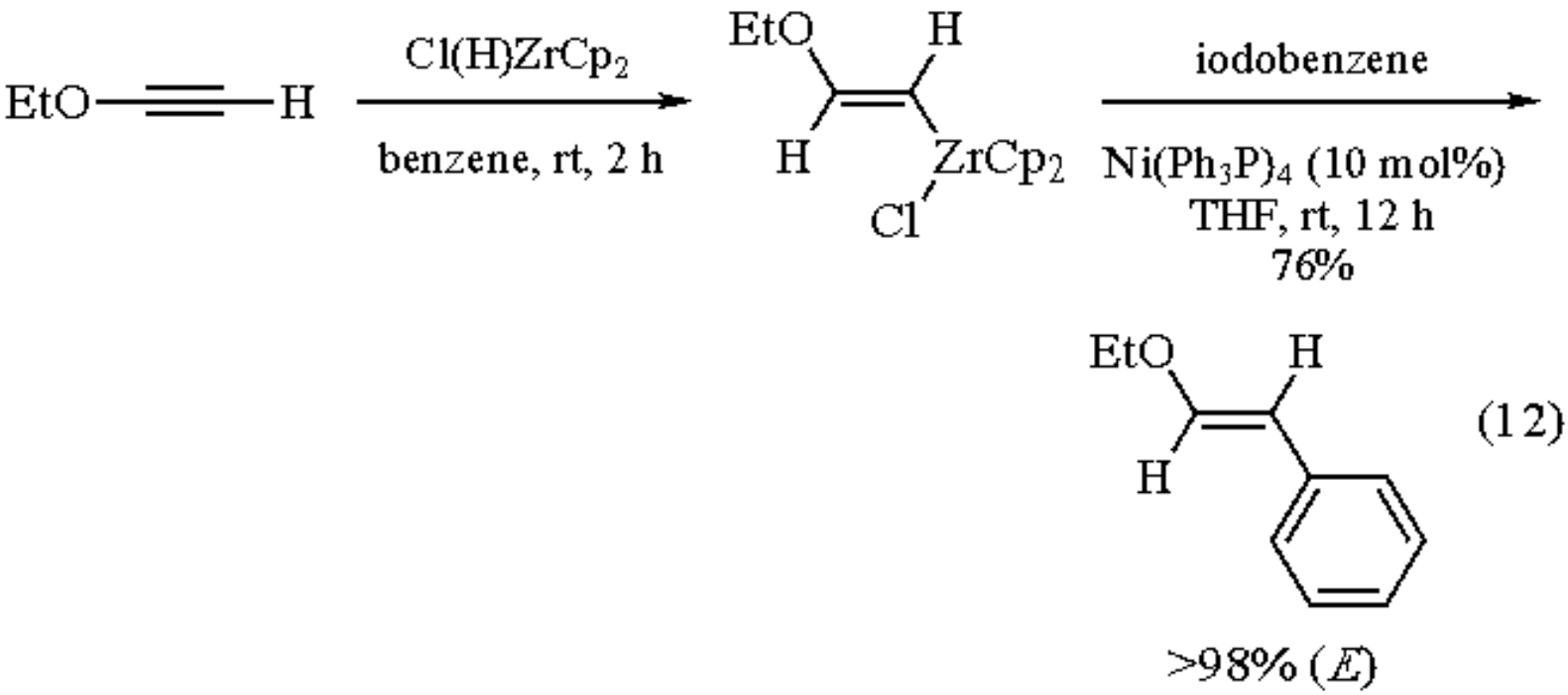

(12)

Miscellaneous Synthetic Transformations.

Ethoxyacetylene has been used to prepare substituted acylketenes,[39] (alkoxyethynyl)phosphonites,[40] and alkoxy metal carbenes.[41]

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3-Ethoxyacrolein[1]

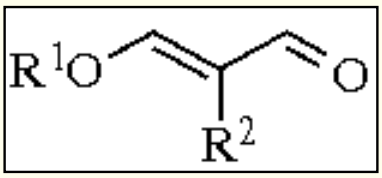

(**1**; R^1 = Et, R^2 = H)

[19060-08-3] · $C_5H_8O_2$ · 3-Ethoxyacrolein · (MW 100.12) (*E*)-(**1**)

[764-63-6] (*Z*)-(**1**)

[57155-16-5] (**2**; R^1 = Et, R^2 = Me)

[42588-57-8] · $C_6H_{10}O_2$ · 3-Ethoxy-2-methylacrolein · (MW 114.15) (*E*)-(**2**)

[62055-46-3] (**3**; R^1 = Me, R^2 = H)

[4652-35-1] · $C_4H_6O_2$ · 3-Methoxyacrolein · (MW 86.09) (*E*)-(**3**)

[78923-06-5] (*Z*)-(**3**)

[78906-20-4]

(mono- and bifunctional three-carbon electrophile in carbonyl reactions, vinylogous acylations[2] and various cyclocondensation reactions[1,3])

Alternate Name: 3-ethoxy-2-propenal.

Physical Data: (**1**) bp 68-72 °C/11 mmHg; *d* 0.9835 g cm^{-3}; *n*20D 1.473-1.474. (**2**) bp 78-81 °C/14 mmHg; *d* 0.957-0.960 g cm^{-3}; *n*20D 1.474-1.479. (**3**) mp 25 °C; bp 36-37 °C/1.5 mmHg; *d* 1.0306 g cm^{-3}; *n*20D 1.481-1.482.

Form Supplied in: colorless liquid(s); 3-ethoxy-2-methylacrolein (**2**) is commercially available.

Preparative Methods: 3-ethoxyacrolein (**1**) and its 2-alkyl analogs (**4**) are obtained by mild hydrolysis of malonic dialdehyde bisacetals,[4a,b] and the former also by decarboxylation of β-acroleinyl carbonate.[4c] 3-Methoxyacrolein (**3**) is prepared via the carbonate[5a,b] or by methylation of malonic dialdehyde sodium salt.[5c]

Handling, Storage, and Precautions: to avoid polymerization the ethoxyacroleins should be stored in a refrigerator, and the 2-unsubstituted compound kept in a freezer. They are slight lachrymators. Use in a fume hood.

Cyclization with Amino Compounds.

3-Alkoxyacroleins are vinylogous formates. As bifunctional electrophiles they cyclize with amino compounds to give a variety of nitrogen heterocycles. They can replace unstable malonic dialdehydes and the less reactive tetraacetals. Related are 3-aminoacroleins, which can be used for the synthesis of pyridines.[6] Amidines cyclocondense with 2-alkyl-3-ethoxyacroleins (**2**) and (**4**) to give 2,5-dialkylpyrimidines in better yield than with malonic dialdehyde tetraacetals (eq 1).[3] Reaction with ***Urea***, ***Thiourea***, or ***Guanidine*** affords 2-hydroxypyrimidines, 2-pyrimidinethiones, or 2-aminopyrimidines, respectively.[3]

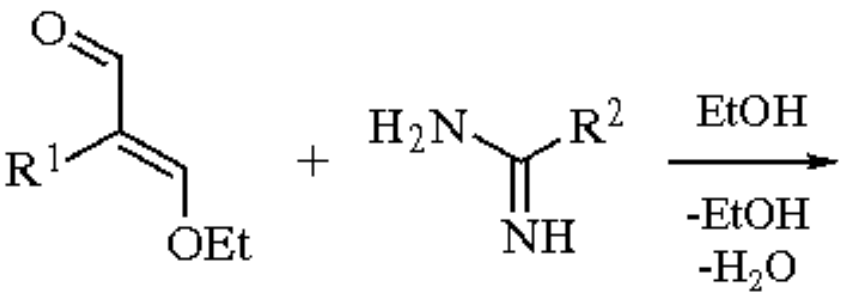

$R^1 = C_1\text{-}C_5$ alkyl

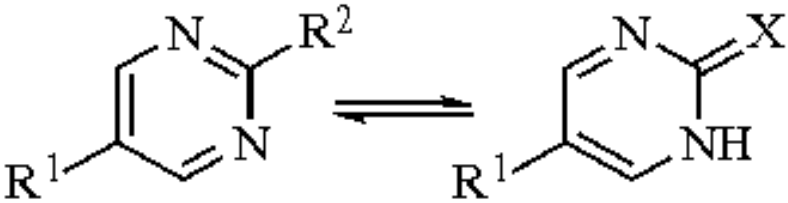

(1)

$R^2 = Me$ 50-70%

$R^2 = X = OH, SH, NR_2$ 25-90% $X = O, S$

The reaction of (**2**) or (**4**) with heterocyclic enamines such as 5-aminopyrazoles, -isoxazoles, or -isothiazoles (eq 2) yields 1*H*-pyrazolo[3,4-*b*]-,[7a] isoxazolo[5,4-*b*],[7b] or isothiazolo[5,4-*b*]pyridines.[7c] Intermediate heterocyclic aminoacroleins can be isolated. Vinylogous amidation of (**2**) and (**4**) with L-proline ester and cyclization of the aminoacroleins give 2,3-dihydro-1*H*-pyrrolizines.[8]

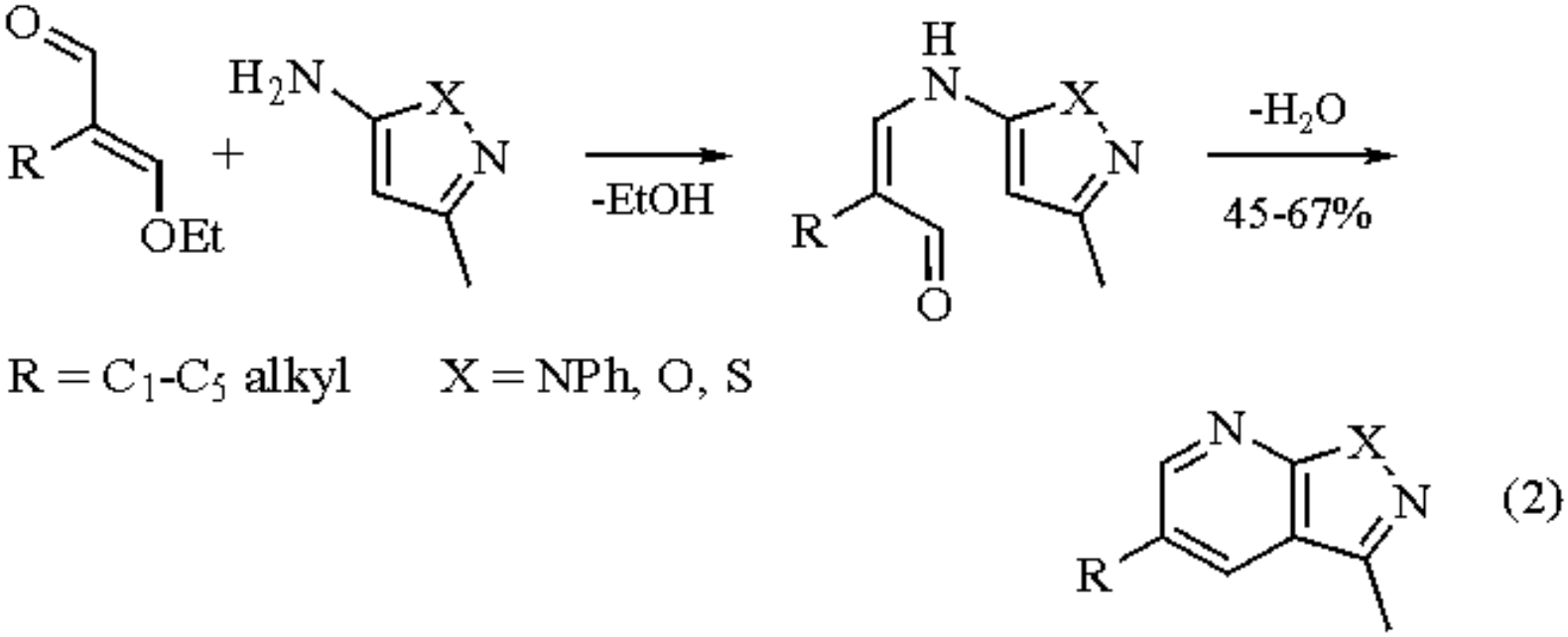

The macrocyclic 1,8-dihydro-1,4,8,11-tetraaza[14]annulenes are formed from 3-ethoxyacroleins and enediamines such as diaminomaleodinitrile (eq 3).[9a] Improvement of yields is achieved by the metal template effect, in which a metal cation coordinates the enediamine.[9b]

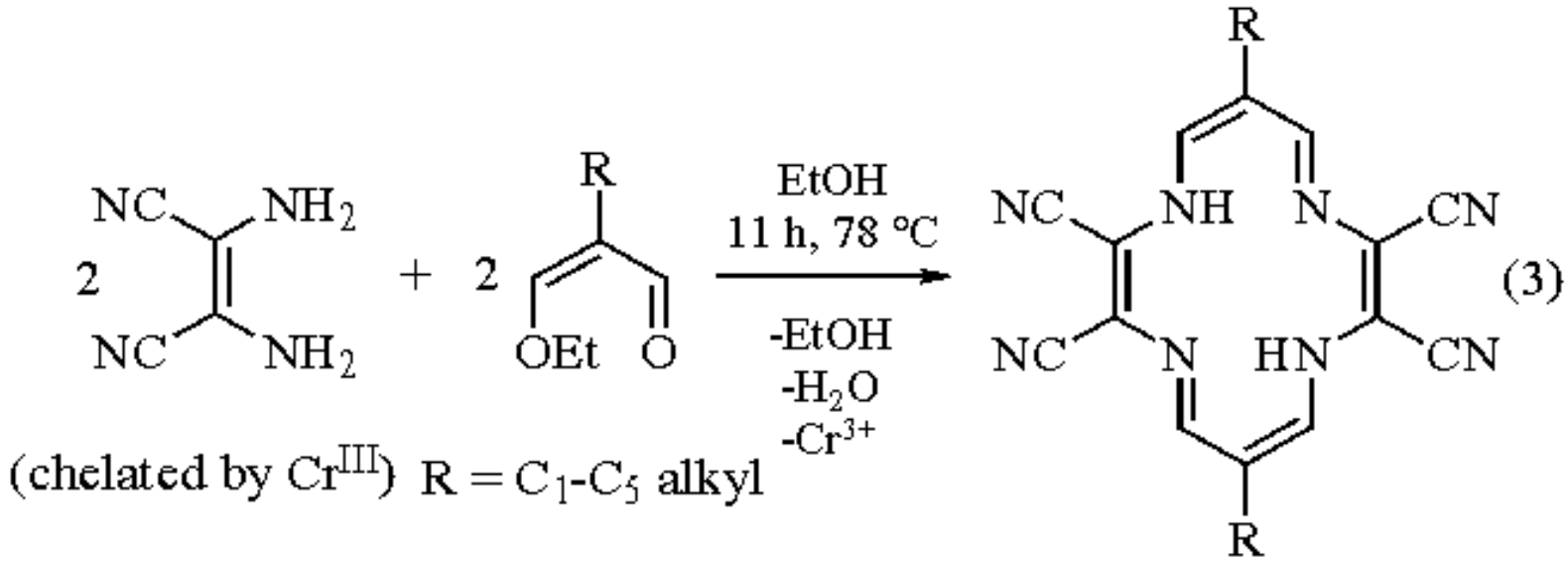

Reaction with Carbon Nucleophiles.

Alkylmagnesium halides add to (**2**) or (**4**) regioselectively in a 1,2-addition.[10] Hydrolysis of the intermediate γ-hydroxyenol ethers affords α,β-unsaturated aldehydes, resulting in the oxopropenylation of the Grignard reagent (eq 4).[2] The methoxy analog (**3**)[5b] and the reactive 3-trimethylsilyloxyacroleins[11] have also been used. Vinylic Grignard reagents afford conjugated polyenes.[12]

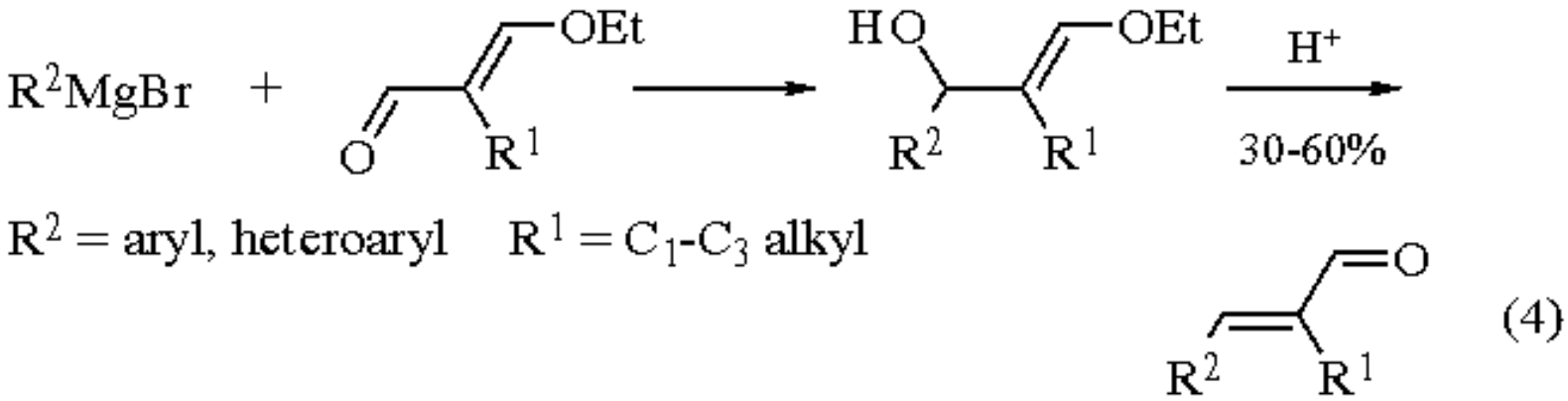

Nitrogen heterocycles with a lithiable α-methylimino group, such as 2-methylpyridine, and (**2**) or (**4**) yield labile heterocyclic γ-hydroxyenol ethers which cyclize with acids to compounds with a bridgehead nitrogen, such as 3-alkylquinolizinium salts (eq 5).[13] Substituted dihydroindolizinium and dihydrothiazolo[3,2-*a*]-pyridinium are obtained similarly.[14]

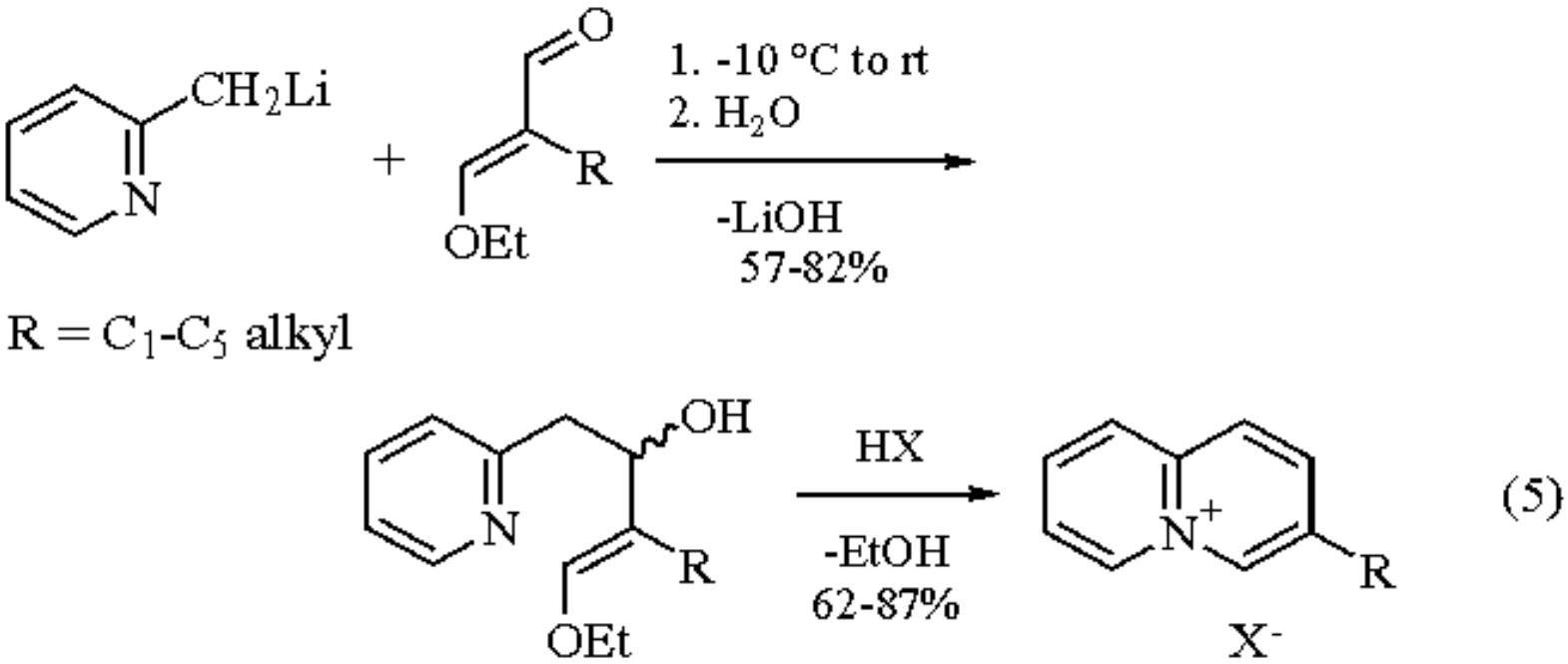

2-Alkyl-1-ethoxy-1,3-butadienes are obtained by Wittig alkenylation of (**2**) or (**4**)[15] (or (**3**)[5c]). Vinylogous transesterification of (**2**) with chiral 1-arylethanols and methenylation yields 3-aryloxy-1,3-dienes (ee 85-91%).[16a] These undergo Diels-Alder reactions with electron-deficient dienophiles. Addition to ***Isoprene*** (eq 6)[16a,b] gives an optically active terpene alcohol.

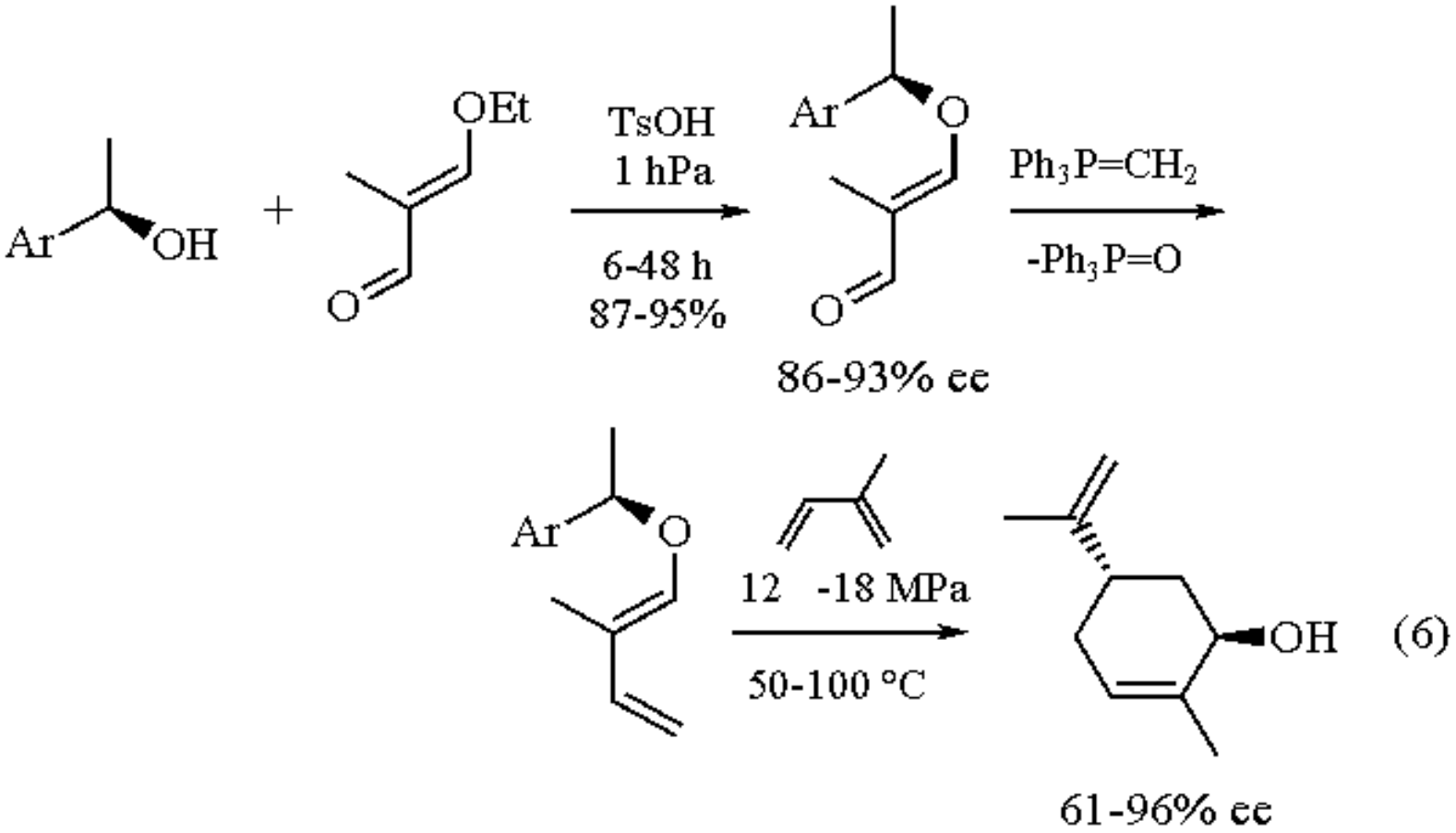

Related Reagents.

(Z)*-β-*Aminoacrolein; ***3-Ethoxyacrylonitrile***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Hydroxymethyleneacetate, Sodium Salt***; ***Malondialdehyde***; ***Methyl Diformylacetate***; ***Propargyl Aldehyde***.

---

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14. Böhme, R.; Rotscheidt, K.; Breitmaier, E. *S* **1989**, 109.
15. Potthoff, B.; Breitmaier, E. *CB* **1985**, *118*, 4646.
16. (a) Rieger, R.; Breitmaier, E. *S* **1990**, 697. (b) Zadel, G.; Rieger, R.; Breitmaier, E. *LA* **1991**, 1343.

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3-Ethoxyacrylonitrile

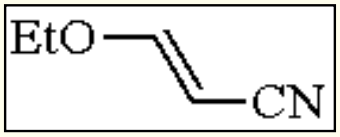

[61310-53-0] · C_5H_7NO · 3-Ethoxyacrylonitrile · (MW 97.12) (*E*)

[58243-08-6]

(bifunctional three-carbon electrophile; C_3N building block in various condensation reactions/cytosine synthesis;[1,2] polarized alkene for cycloaddition reactions[3])

Alternate Name: 3-ethoxy-2-propenenitrile.

Physical Data: bp 188-190 °C, 90-91 °C/19 mmHg; *d* 0.944-0.947 g cm^{-3}; *n*20D 1.454.

Form Supplied in: colorless liquid; commercially available.

Handling, Storage, and Precautions: keep cold; 3-ethoxyacrylonitrile is a lachrymator. Use in a fume hood.

Cyclocondensations.

One important condensation reaction of 3-ethoxyacrylonitrile involves a base-catalyzed cyclization with ***Urea*** to give cytosine (eq 1).[1] 3-Ethoxyacrylonitrile is obtained by fragmentation of isoxazole and subsequent ethylation.

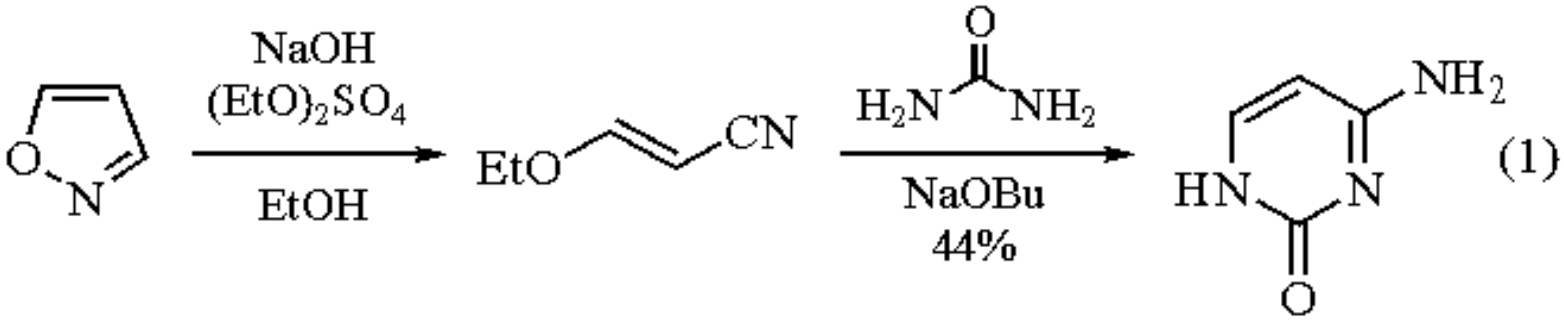

No catalyst is needed when 3-ethoxyacrylonitrile is condensed with aromatic (or aliphatic) amidines, affording 2-amino-2-arylpyrimidines.[2,4] The alternate ***2-Chloroacrylonitrile*** gives lower yields.[2]

The introduction of substituents in position 5 of the cytosine ring can be achieved by metalation of 3-

ethoxyacrylonitrile and subsequent alkylation.[5] Metalation with ***n-Butyllithium*** takes place regioselectively at the α-position.[6] The 2-lithio derivative reacts with activated primary bromides (***Allyl Bromide*** or ***Benzyl Bromide***) or straight chain primary alkyl iodides. Condensation with urea affords 5-alkylcytosines in moderate yields (eq 2).[5]

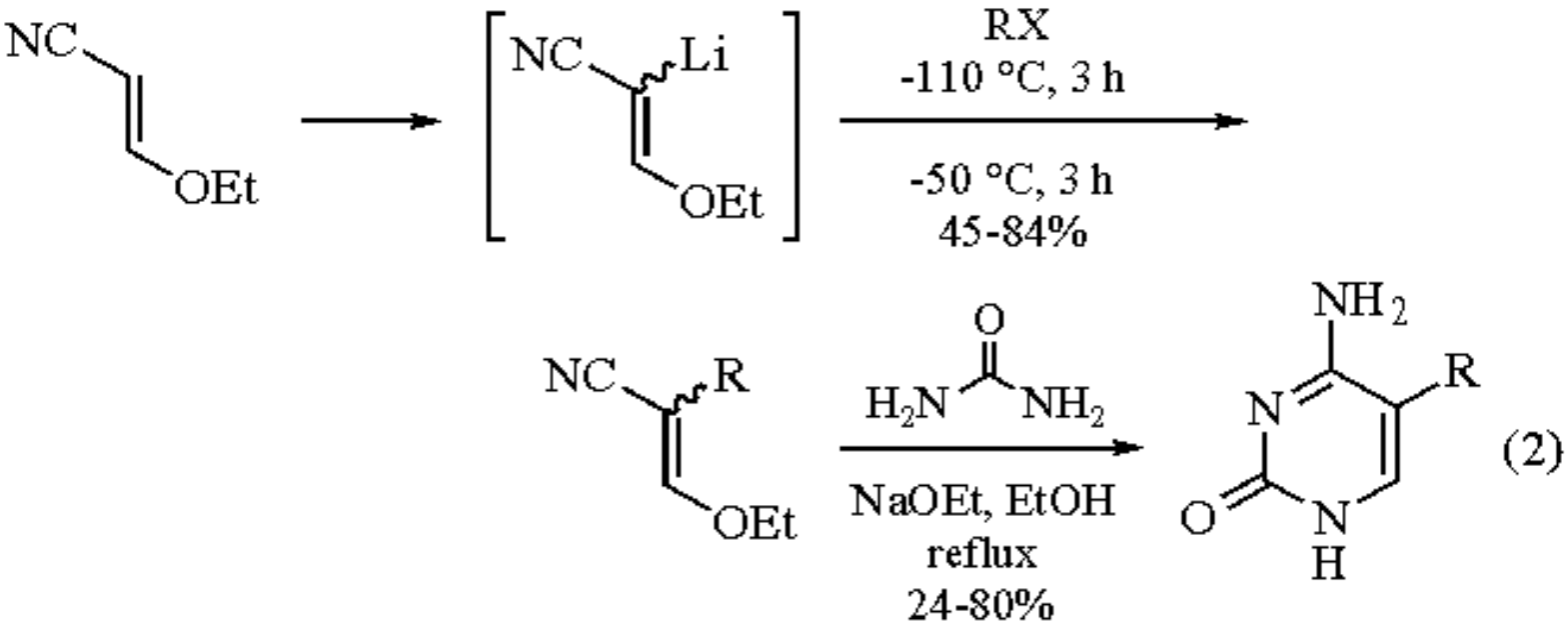

Other Cyclizations.

A benzimidazolium *N*-ylide undergoes 1,3-dipolar cycloaddition with 3-ethoxyacrylonitrile to give a benzopyrrolo[1,2-*a*]pyrazine derivative (eq 3).[7]

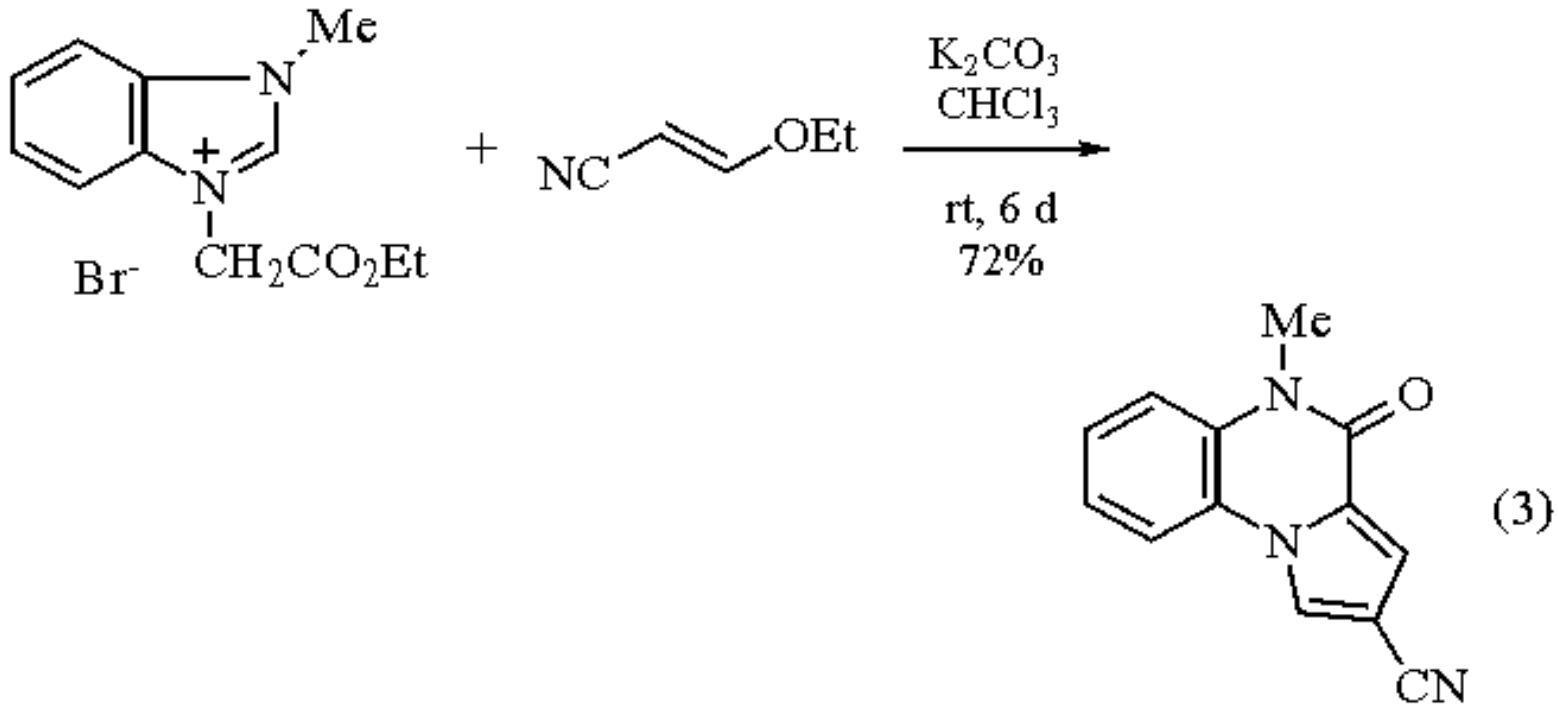

In a formal [3 + 2] cycloaddition, acylcarbenes add to conjugated nitriles. The acylcarbenes are produced from α-diazoaldehyde esters and can react, e.g. with 3-ethoxyacrylonitrile in the presence of catalytic amounts of

Dirhodium(II) Tetraacetate, to give a 2-substituted 4-ethoxycarbonyl-1,3-oxazole (eq 4).[8]

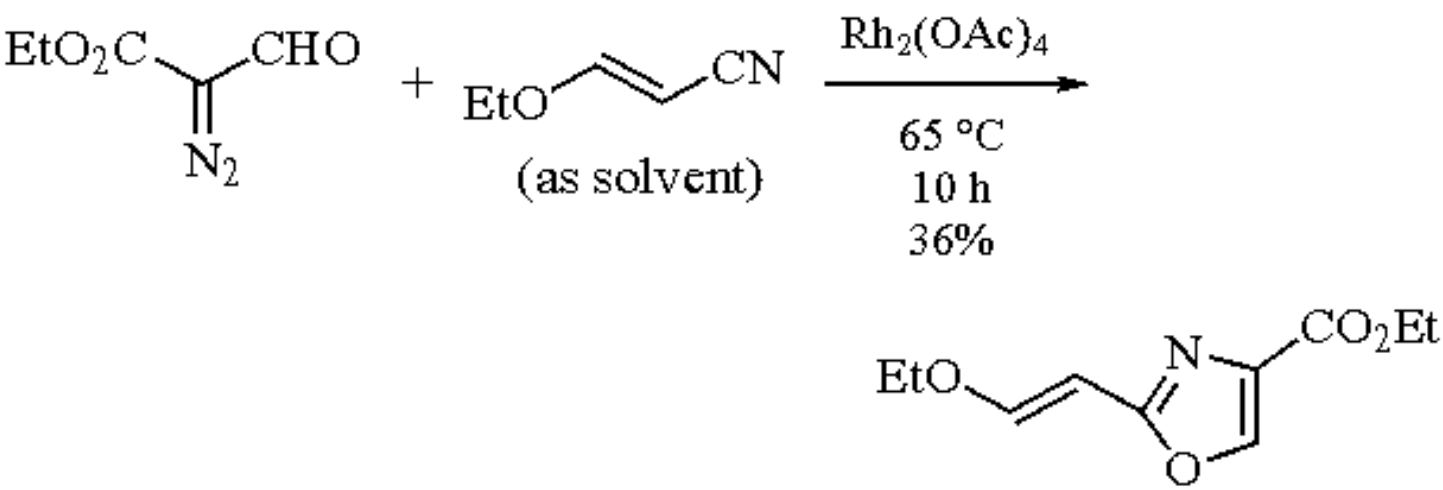

(4)

Photocycloadditions.

Ortho photocycloaddition with 4-cyanoanisole as the arene component and 3-substituted acrylonitriles are regiospecific. (*E*)-3-Ethoxyacrylonitrile yields predominantly a 1:1 adduct, a bicyclo[4.2.0]octa-2,4-diene derivative, after 24 h irradiation with 4-cyanoanisole in acetonitrile (eq 5).[3] No azocine is formed.

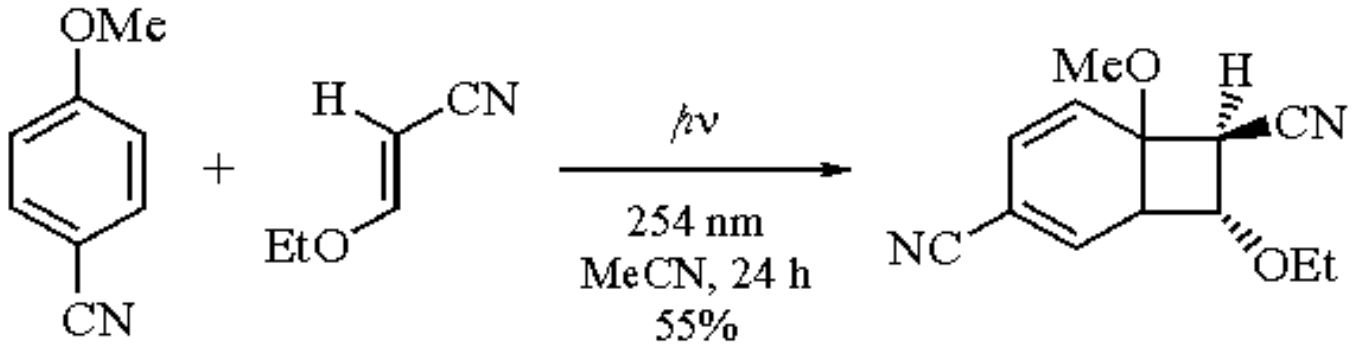

(5)

Ethylenes undergo photocycloadditions to 1,4-benzoquinone, yielding spiro-oxetanes (Paterno-Büchi reaction). Investigations were made with a variety of alkenes and electron-donor and -acceptor dienes.[9] While electron-donor dienes such as ***Ethyl Vinyl Ether*** give only very small yields of oxetane, the captodative alkene (*E*)-3-ethoxyacrylonitrile adds to 1,4-benzoquinone in 30% yield (equal amounts of the *cis* and *trans* isomer) (eq 6).

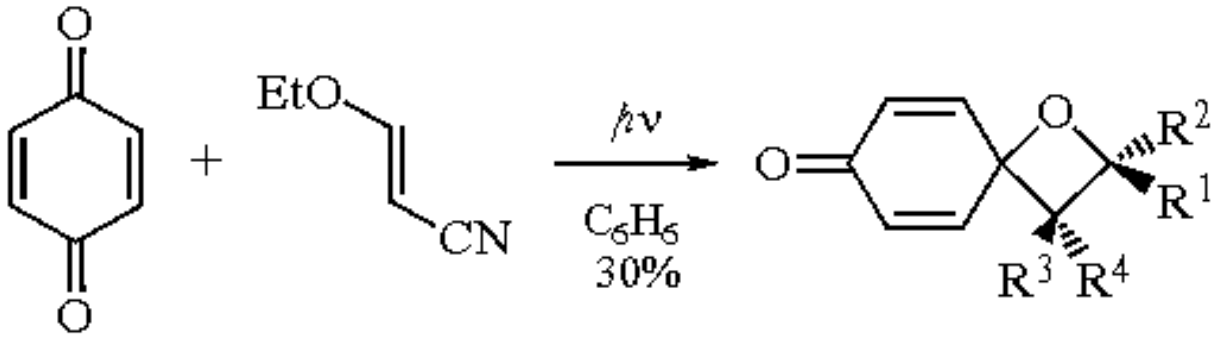

(6)

trans	*cis*
$R^1 = R^4 = H$	$R^1 = R^3 = H$
$R^2 = OEt$	$R^2 = OEt$
$R^3 = CN$	$R^4 = CN$

1:1

Similar photocycloaddition of (*E*)-3-ethoxyacrylonitrile to 1,4-naphthoquinone affords both *cis* and *trans* adducts and a small amount of a second *cis* isomer.[10]

Other Addition Reactions.

3-Ethoxyacrylonitrile can be used as the starting material for the synthesis of glyoxal mono(diethyl acetal). The nitrile is brominated to the bromo acetal with ***N-Bromosuccinimide***, which is converted into the cyano ester and the glyoxal acetal (eq 7).[11]

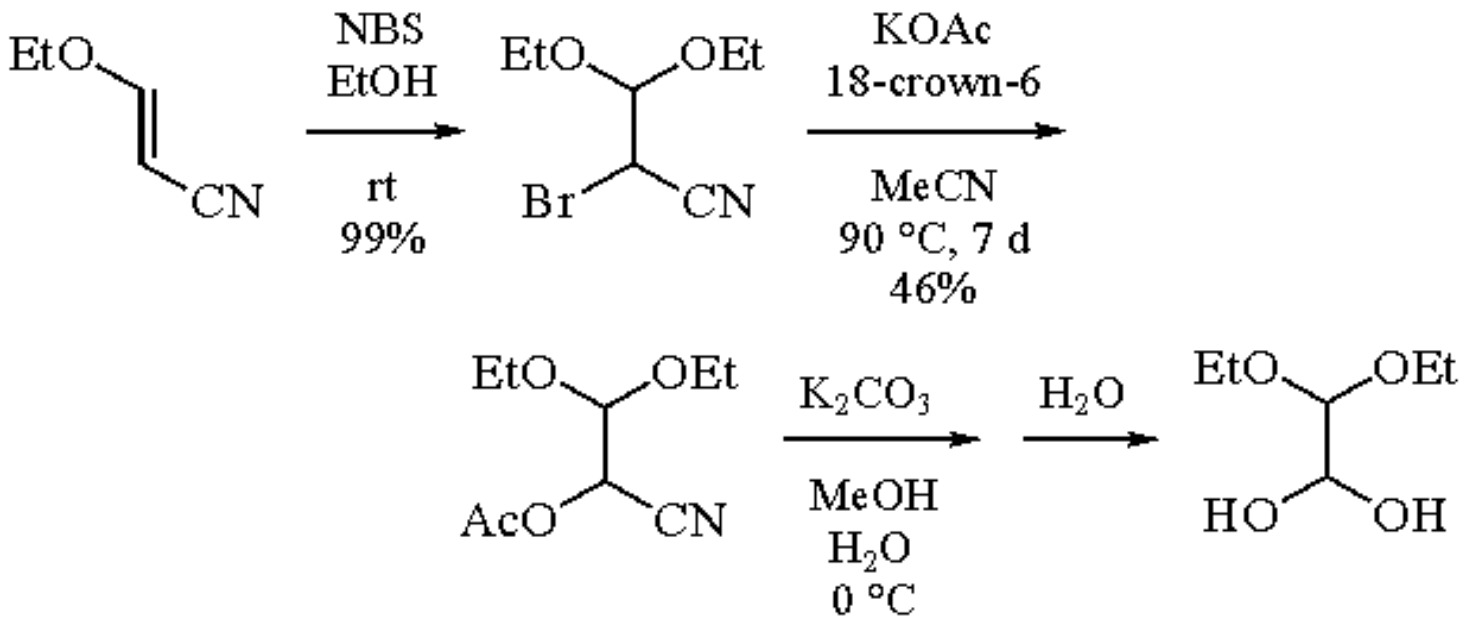

(7)

Related Reagents.

3-Ethoxyacrolein; ***Ethoxymethylenemalonitrile***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethylenecyanoacetate***.

1. Tarsio, P. J.; Nicholl, L. *JOC* **1957**, *22*, 192.
2. Singh, B.; Lesher, G. Y. *JHC* **1977**, *14*, 1413.
3. Al-Jalal, N.; Gilbert, A. *RTC* **1990**, *109*, 21.
4. Singh, B.; Laskowski, S. C.; Lesher, G. Y. *SL* **1991**, *2*, 549.
5. Smirnow, D.; Hopkins, P. B. *SC* **1986**, *16*, 1187.
6. Schmidt, R. R.; Speer, H. *TL* **1981**, *22*, 4259.
7. Matsuda, Y.; Yamashita, M.; Takahashi, K.; Ide, S.; Torisu, K.; Furuno, K. *H* **1992**, *33*, 295.
8. Connell, R. D.; Tebbe, M.; Helquist, P. *TL* **1991**, *32*, 17.
9. Bryce-Smith, D.; Evans, E. H.; Gilbert, A.; McNeill, H. S. *JCS(P2)* **1991**, 1587.
10. Bryce-Smith, D.; Evans, E. H.; Gilbert, A.; McNeill, H. S. *JCS(P1)* **1992**, 485.
11. Babler, J. H. *SC* **1987**, *17*, 77.

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2-Ethoxyallyl Acetate

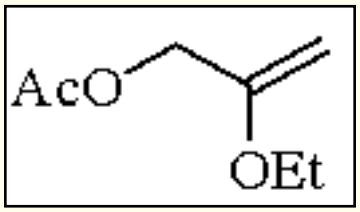

[76524-71-5] · $C_7H_{12}O_3$ · 2-Ethoxyallyl Acetate · (MW 144.17)

(preparation of enol ethers via the corresponding allylpalladium complexes;[1] cyclopentenone annulation[1])

Alternate Name: 3-acetoxy-2-ethoxy-1-propene.

Preparative Methods: by reaction of α-lithioethyl vinyl ether with ***Paraformaldehyde*** (40-50%) followed by acetylation (***Acetic Anhydride***, ***Pyridine***).[1]

Handling, Storage, and Precautions: use in a fume hood.

Preparation of Enol Ethers.

2-Ethoxyallyl acetate (**1**) is a useful reagent for the preparation of enol ethers by way of palladium-catalyzed allylic alkylations. Reaction of the π-allylpalladium intermediate generated from (**1**) with several types of nucleophiles has been studied. Aryl,[2] vinyl,[2] and enol stannanes[2,3] all give satisfactory reactions (eqs 1-3).

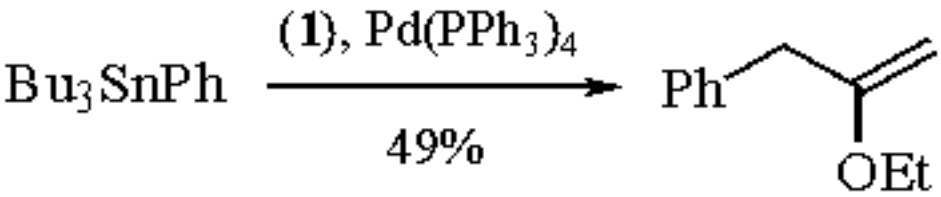

(1)

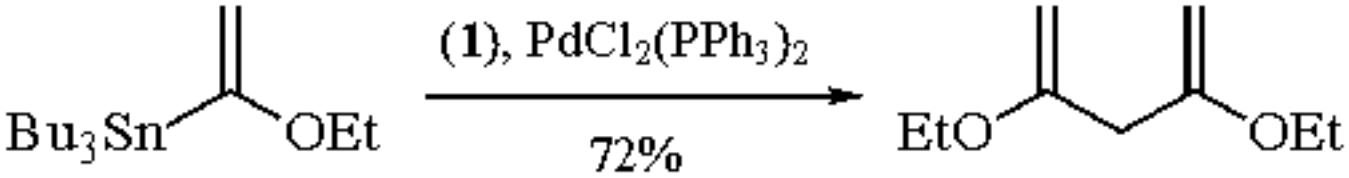

(2)

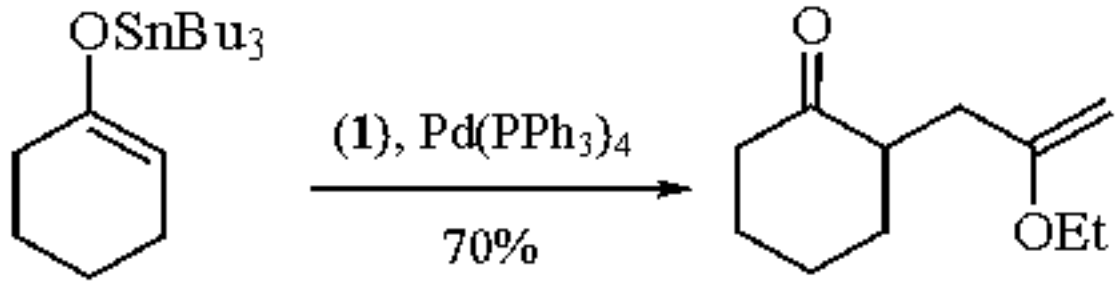

(3)

For enol stannanes where regioisomers are possible, the product obtained is that arising from reaction of the more stable enolate (cf. eqs 4 and 5).[3] Active methylene compounds, such as β-diketones or β-keto esters, can be alkylated in the presence of a base (eqs 6 and 7).[1]

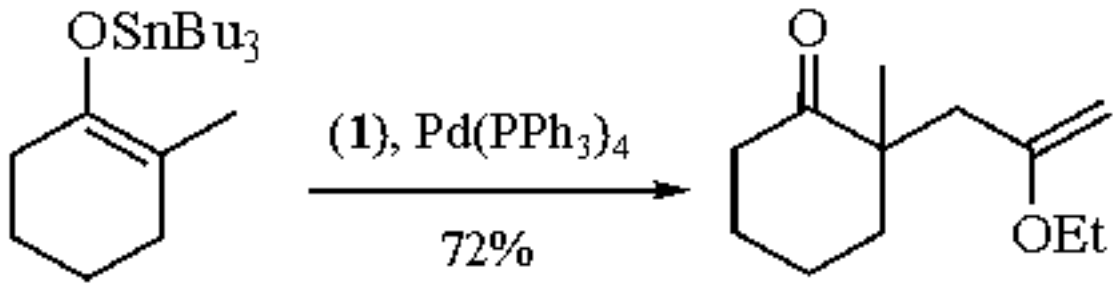

(4)

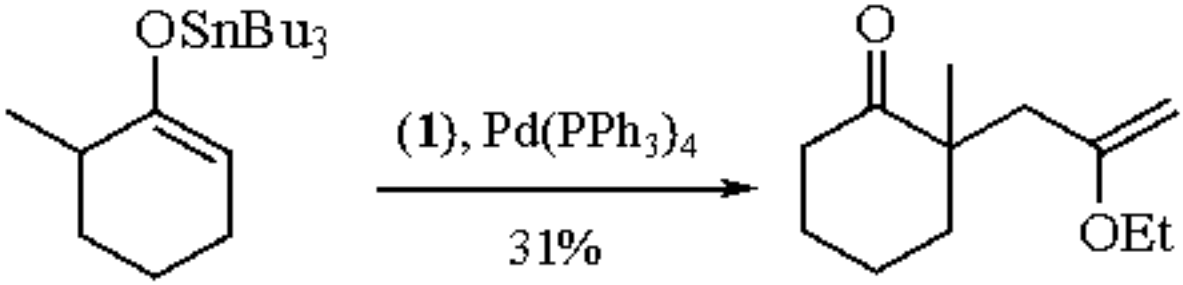

(5)

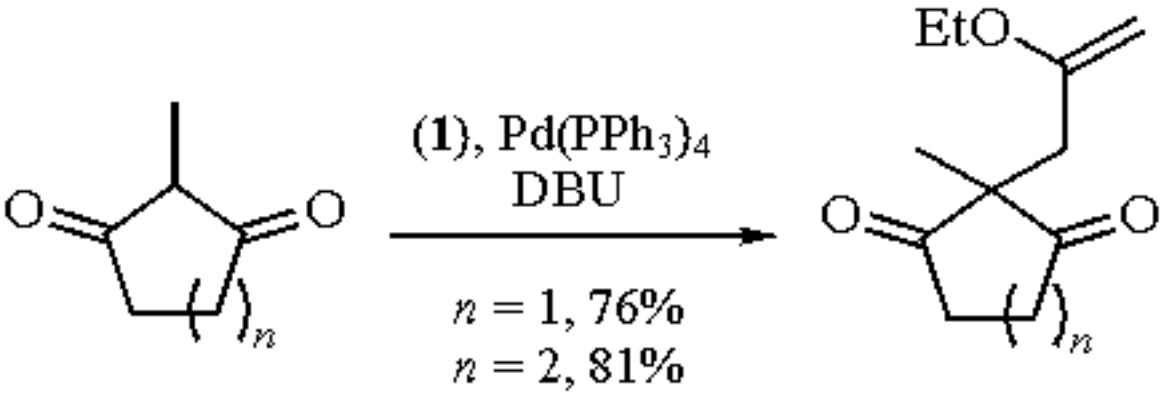

(6)

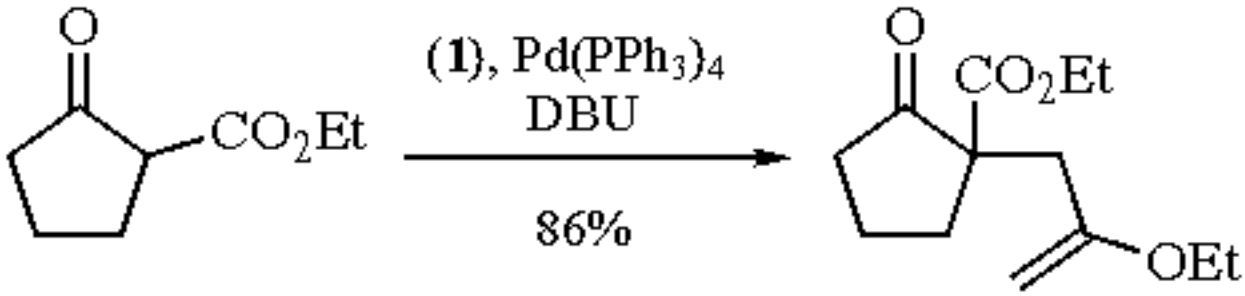

(7)

Cyclopentenone Annulation.[4]

The enol ethers arising from palladium-catalyzed allylic alkylations can be transformed into cyclopentenones. Several methods for cyclization have been developed. For simple ketones, acidic hydrolysis of the enol ether followed by base-promoted aldol condensation provides the annulated product (eq 8).[3] More complex ketones require the use of an intramolecular Wittig reaction to effect cyclization (eqs 9 and 10).[1] In the event, enol ether hydrolysis with ***N-Bromosuccinimide*** and H_2O provides the α-bromo ketone. Reaction with ***Triphenylphosphine*** yields a phosphonium salt which, upon treatment with base, undergoes cyclization. A useful application of this method is seen in the synthesis of several analogs of the Wieland-Miescher ketone (eq 9).[1]

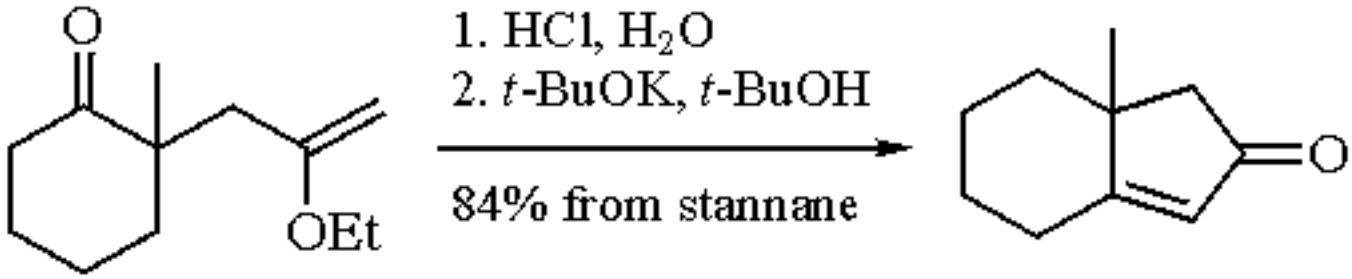

(8)

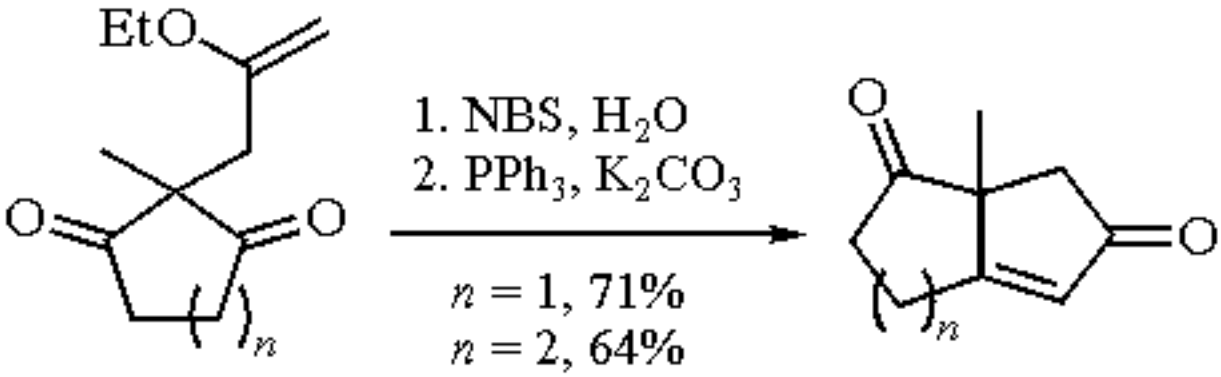

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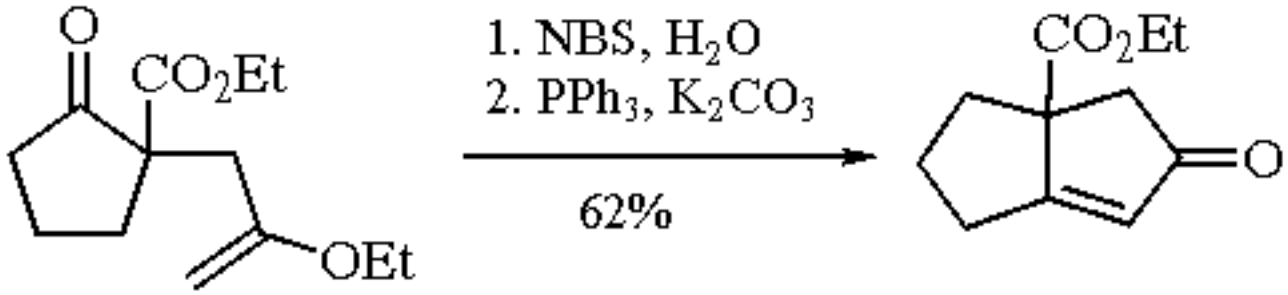

(10)

Related Reagents.

Bromoacetone; ***2,3-Dibromopropene***; ***2,3-Dichloropropene***; ***Ethyl Chloroformate***; ***2-Methoxyallyl Bromide***; ***2-Nitro-1-propene***; ***Tetrakis(triphenylphosphine)palladium(0)***.

---

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2. (a) Kosugi, M.; Ohashi, K.; Akuzawa, K.; Kawazoe, T.; Sano, H.; Migita, T. *CL* **1987**, 1237. (b) Kosugi, M.; Miyajima, Y.; Nakanishi, H.; Sano, H.; Migita, T. *BCJ* **1989**, *62*, 3383.
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4. For a review on cyclopentannulation methods, see: Ramaiah, M. *S* **1984**, 529.

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2-Ethoxycarbonylallyltrimethylsilane[1]

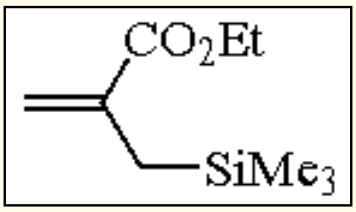

[74976-84-4] · $C_9H_{18}O_2Si$ · 2-Ethoxycarbonylallyltrimethylsilane · (MW 186.33)

(2-ethoxycarbonylallylation of aldehydes and acetals; the allylation products are useful precursors to α-methylene-γ-butyrolactones;[2] precursor of allyl cation equivalents for [3 + 2] and [3 + 4] cycloadditions[7,8])

Alternate Name: ethyl 2-(trimethylsilylmethyl)acrylate.

Physical Data: bp 35-40 °C/2 mmHg.

Solubility: sol common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Purification: by distillation.

Preparative Methods: a three-step synthesis from ***Diethyl Malonate*** has been reported.[2] *t*-Butyl and trimethylsilyl esters are also prepared by this method. Syntheses from ethyl diethylphosphonoacetate[3] and ethyl α-bromoacrylate[4] also have been reported, but the simplest procedure involves the reaction of ethoxalyl chloride with two equivalents of ***Trimethylsilylmethylmagnesium Chloride*** followed by treatment with ***Thionyl Chloride*** (53% yield).[5] The Ce^{III}-mediated reaction of trimethylsilylmethylmagnesium chloride with ***Diethyl Oxalate*** is also reported to give 2-ethoxycarbonylallyltrimethylsilane in 45% yield.[6]

Handling, Storage, and Precautions: the reagent can be stored in a glass bottle.

Reaction with Acetals.

The reaction of 2-ethoxycarbonylallyltrimethylsilane (**1**) with acetals proceeds smoothly in the presence of a Lewis acid such as ***Titanium(IV) Chloride*** to afford the corresponding ethoxycarbonylallylation products in good yield (eq 1).[2]

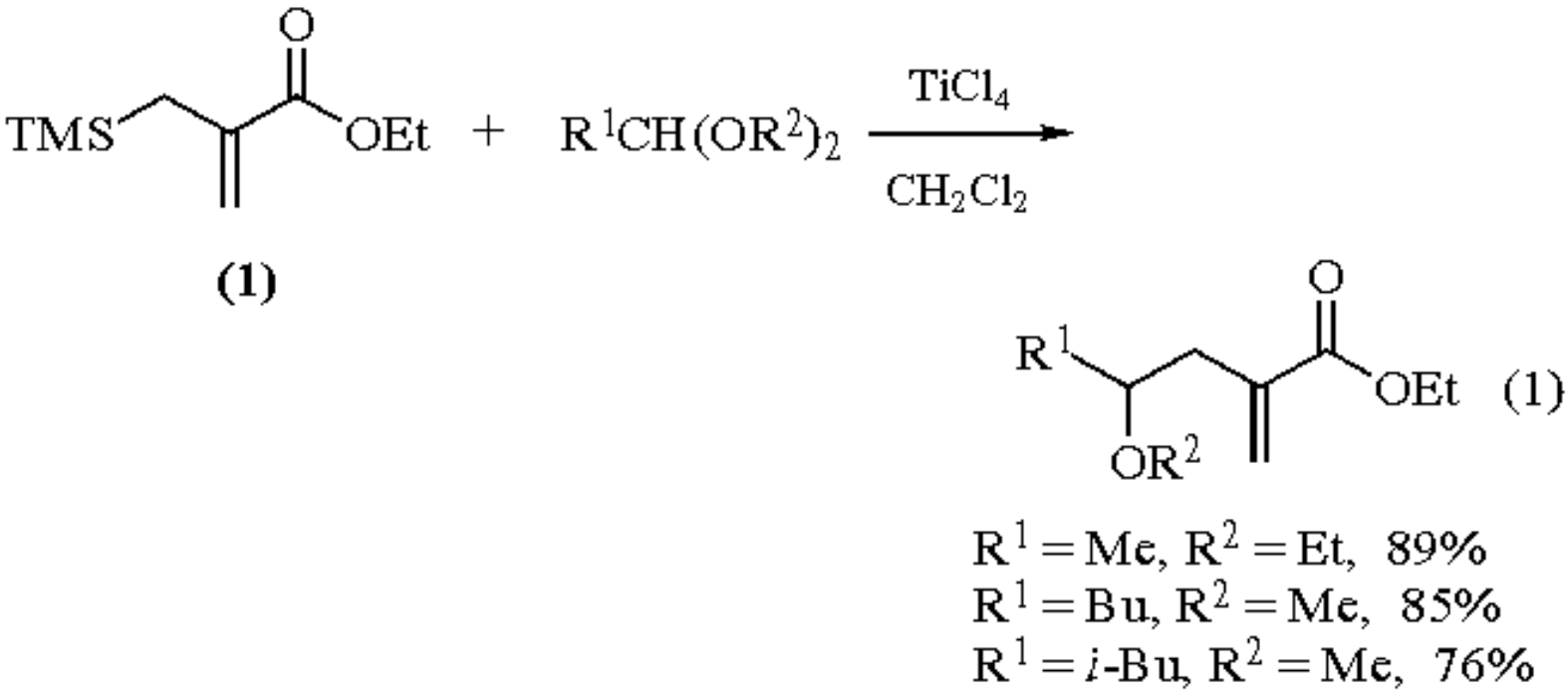

The resulting homoallyl ethers can be converted to the corresponding α-methylene-γ-butyrolactones by dealkylation with ***Iodotrimethylsilane*** (eq 2).

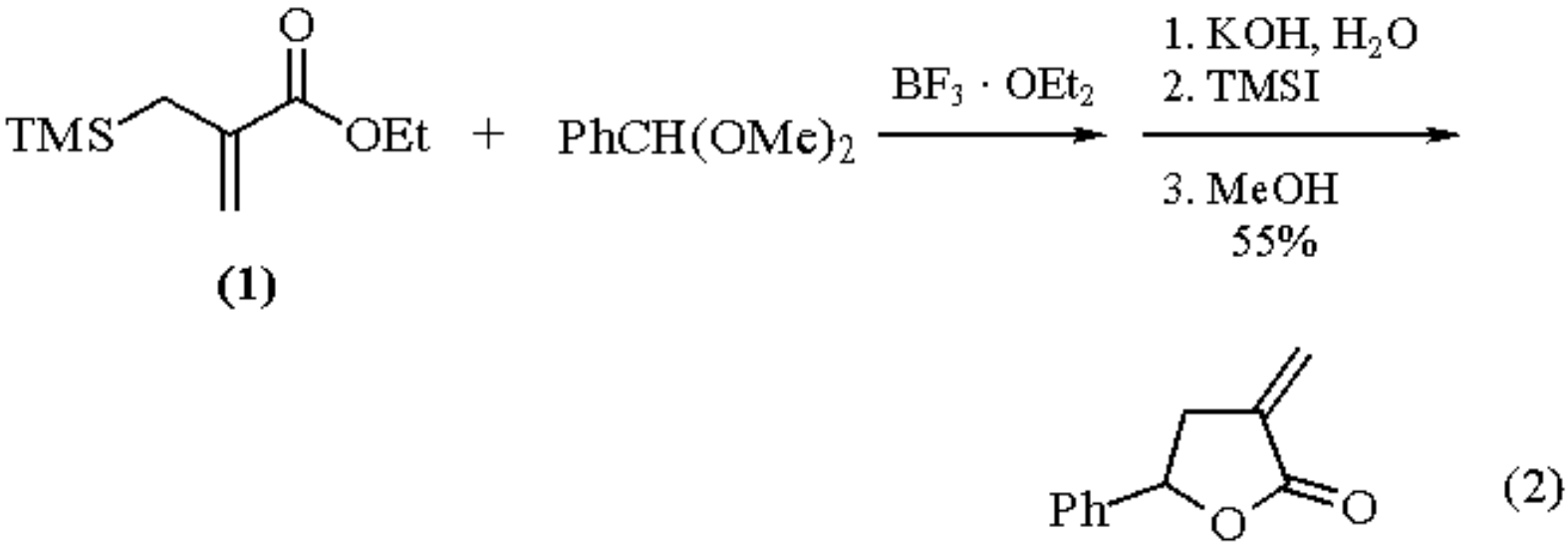

Reaction with Aldehydes.

The reaction with aldehydes in the presence of $TiCl_4$ leads to the formation of α-methylene-γ-butyrolactones directly but in low yield (eq 3).[2]

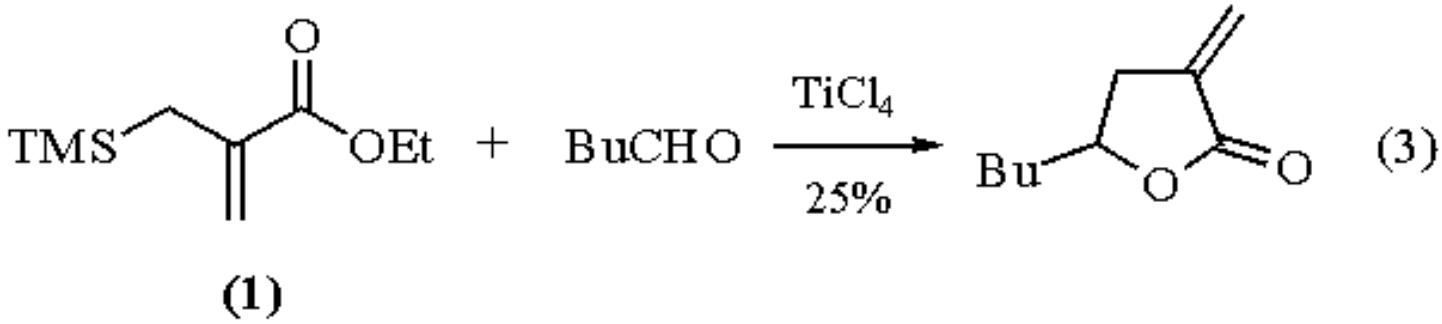

Preparation of 1-Acetoxy-2-trimethylsilylmethyl-2-propene.

Reduction of (**1**) with ***Lithium Aluminum Hydride*** gives 2-trimethylsilylmethylallyl alcohol, which is converted to 1-acetoxy-2-trimethylsilylmethyl-2-propene. When $LiAlD_4$ is used, the dideuterated compound is prepared (eq 4).[7] These acetates are used for the palladium-catalyzed cycloaddition with electron-deficient alkenes.

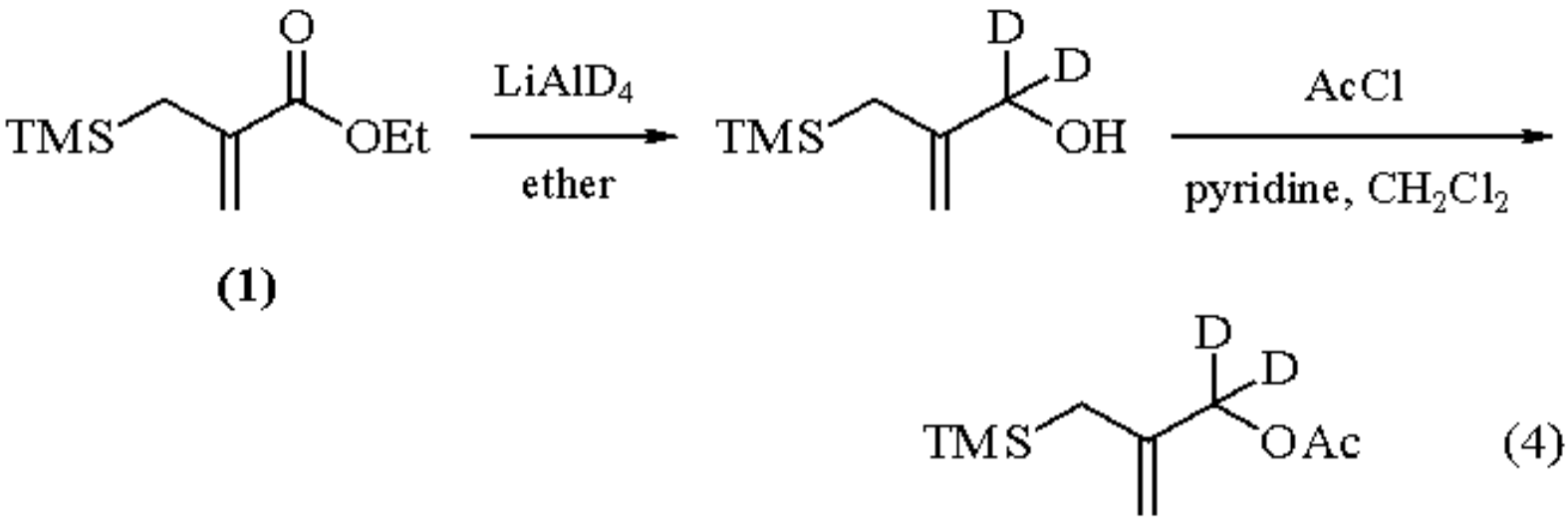

Preparation of Substituted 1-Trimethylsilylmethylallyl Alcohol.

The reaction of (**1**) with ***Methyllithium*** gives 1,1-dimethyl-2-trimethylsilylmethylallyl alcohol (eq 5). The trifluoroacetate derivative is useful for the generation of the 2-trimethylsilylmethylallyl cation (by reaction with ***Zinc Chloride***), which undergoes cycloaddition reactions with dienes.[8] The reaction of (**1**) with the di-Grignard reagent from 1,4-dibromobutane leads to cyclopentanol derivatives that also undergo cyclization reactions with dienes.[9]

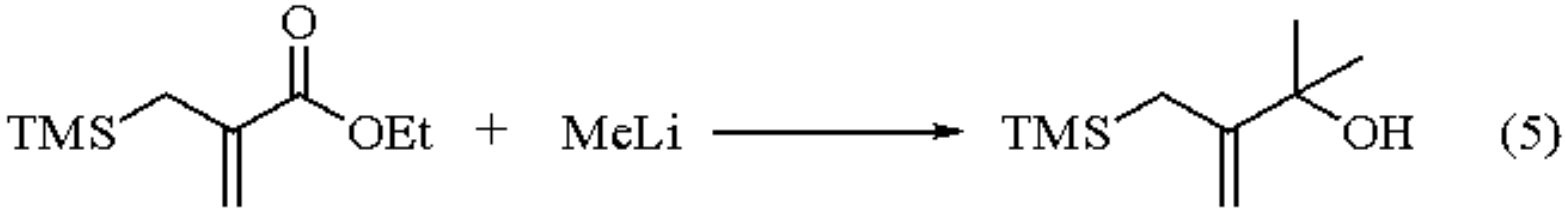

Chain Elongation of Aldonolactones.

2-Ethoxycarbonylallyltrimethylsilane is successfully applied to the chain elongation reactions of monosaccharides.[10] The *t*-butyl ester,[2] instead of the ethyl ester, is also used in the reaction (eq 6).

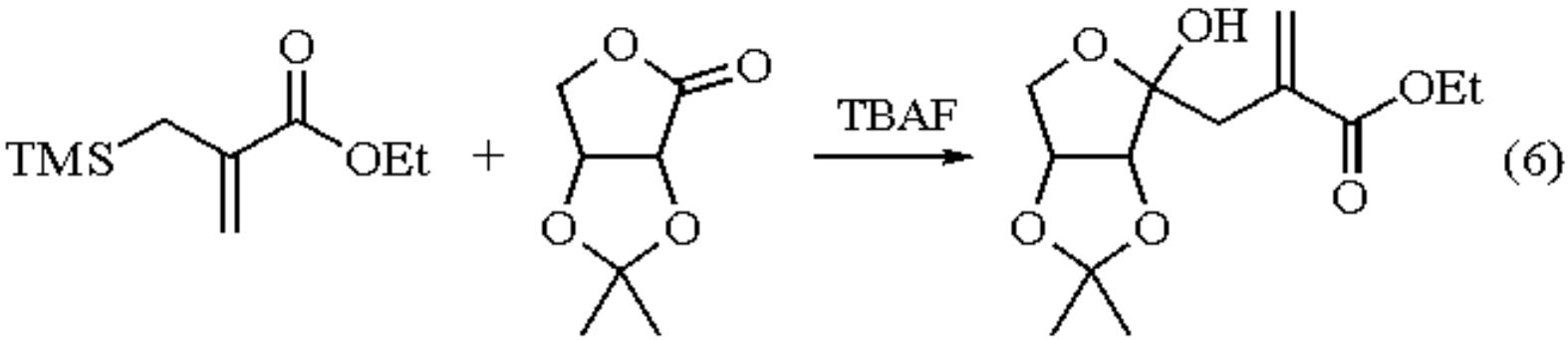

Related Reagents.

3-Acetoxy-2-trimethylsilylmethyl-1-propene; ***Allyltrimethylsilane***; ***3-Iodo-2-trimethylsilylmethyl-1-propene***.

---

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Tohoku University, Sendai, Japan

[1-(Ethoxycarbonyl)cyclopropyl]triphenylphosphonium Tetrafluoroborate

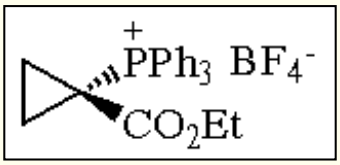

[52186-89-7] · $C_{24}H_{24}BF_4O_2P$ · [1-(Ethoxycarbonyl)cyclopropyl]triphenylphosphonium Tetrafluoroborate · (MW 462.24)

(used in annulation reactions with nucleophile-carbonyl pairs such as anions derived from β-dicarbonyls and imides)

Physical Data: mp 179-181 °C.

Solubility: sol chloroform; slightly sol DMSO, DMF, HMPT; insol diethyl ether.

Form Supplied in: white, nonhygroscopic crystalline solid.

Preparative Methods: prepared in 80% yield by treating commercially available ***Cyclopropyltriphenylphosphonium Bromide*** sequentially with ***Lithium Diisopropylamide*** and ***Ethyl Chloroformate***, followed by counterion exchange using sodium fluoroborate.[1]

Purification: recrystallization from chloroform-ether.

Carbocycle Synthesis.

The title reagent (**1**) is a geminally activated cyclopropane which reacts with a variety of carbonyl-containing carbon nucleophiles to afford carbocyclic products. This annulation process has been accomplished using anions derived from 1,3-diketones (eq 1),[1] β-keto esters (eq 2),[1,2] β-keto aldehydes (eq 3),[3] and β-keto phosphonates[4] to afford perhydroindans, spiranes, and cyclopentene-1-carboxylates. These reactions are most commonly conducted at 25 °C in HMPA but examples using DMSO (25 °C), DMF (25 °C), and THF (65 °C) as solvent have also been reported. The reactions involve ring opening of the cyclopropane followed by an intramolecular Wittig reaction of the resulting intermediate-stabilized phosphorane. The Wittig reaction occurs at the most reactive carbonyl group when dicarbonyl compounds are used (eqs 2, 3).

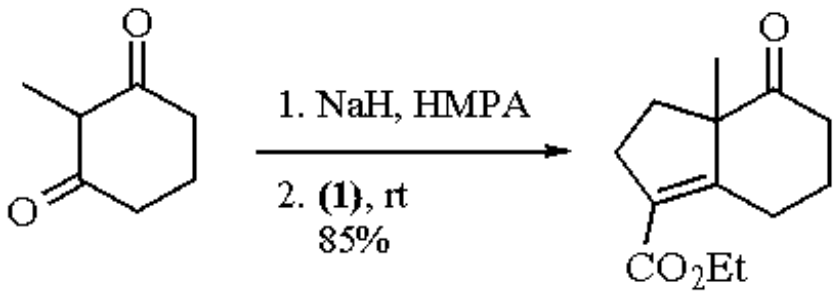

(1)

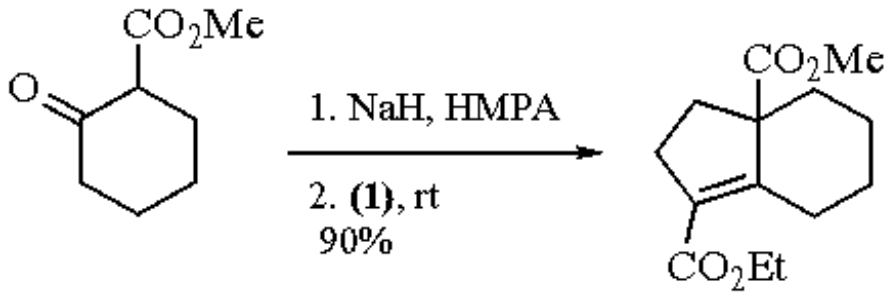

(2)

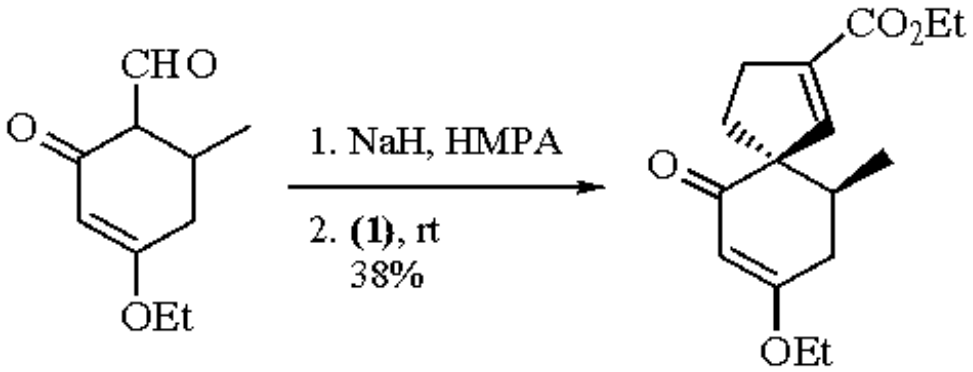

(3)

This annulation procedure has been used to prepare terpenoid materials, including spirovetivanes, steroids, and insect growth regulators.[3-5]

Heterocycle Synthesis.

Anions derived from imides (eq 4)[6-8] and carboxylic acids (eq 5)[9] react with (**1**) to afford dihydropyrroles and dihydrofurans. These processes have been used in the synthesis of pyrrolizidine and furoquinoline alkaloids.[6,9] Monothioimides give mixtures of products derived from Wittig reaction at both the carbonyl and thiocarbonyl groups.[6]

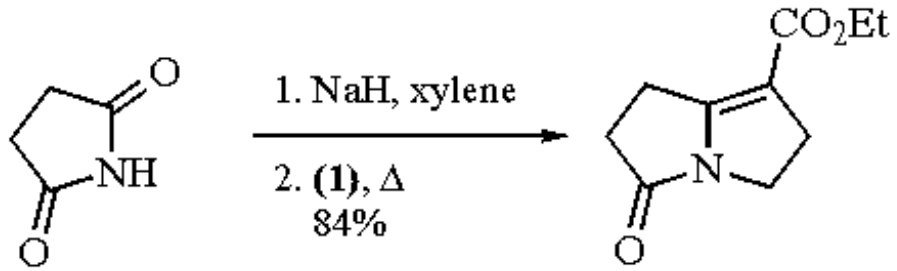

(4)

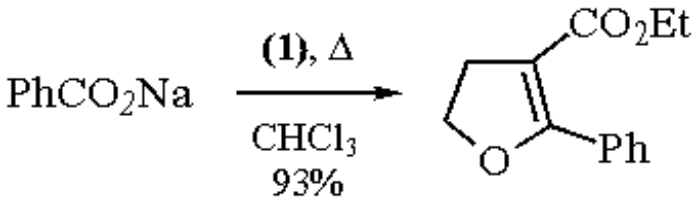

(5)

Heterocycles such as (**2**)-(**4**) have also been prepared from (**1**) and the appropriate nitrogen-, oxygen-, or sulfur-centered anions.[1,10] Intermediate stabilized phosphoranes have been characterized in several instances.[8,10]

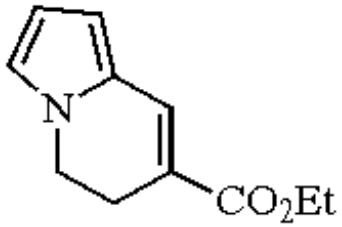

(2) 92%

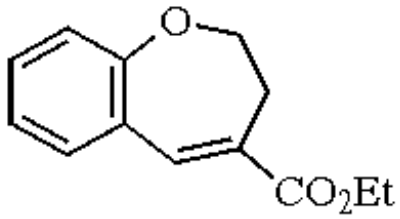

(3) 50%

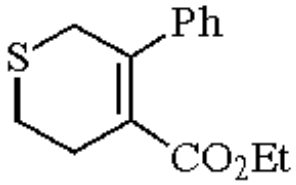

(4) 35%

Related Reagents.

[1-(Methoxycarbonyl)cyclopropyl]triphenylphosphonium tetrafluoroborate [*52186-91-1*][1] has seen little use and gave inferior yields in reactions with imide anions.[8] [1-(Ethoxycarbonyl)cyclobutyl]triphenylphosphonium tetrafluoroborate fails to give annulation products with the sodium salt of ethyl acetoacetate.[1] [1-(Phenylthio)cyclopropyl]triphenylphosphonium tetrafluoroborate [*58992-26-0*] has been shown to undergo some annulation reactions related to those reported for (**1**).[11] One example is shown in eq 6.[6]

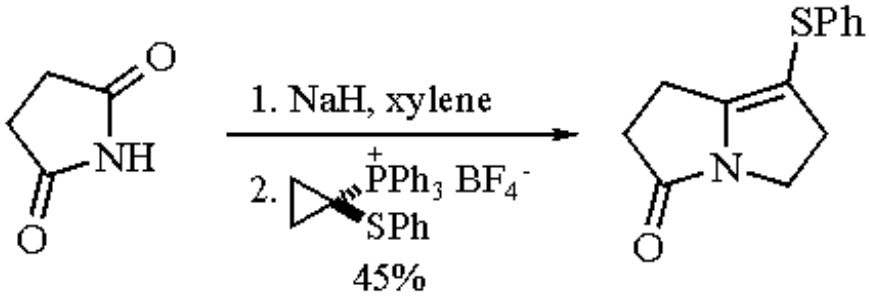

(6)

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Ethoxycarbonyl Isothiocyanate[1]

EtO_2C-NCS

[16182-04-0] · $C_4H_5NO_2S$ · Ethoxycarbonyl Isothiocyanate · (MW 131.49)

(highly reactive isothiocyanate for condensation and cyclization reactions to form thioamides, thioureas, and heterocycles[1])

Physical Data: bp 44-46 °C/10 mm Hg; *d* 1.160 g cm^{-3}.

Solubility: freely miscible in most organic solvents.

Form Supplied in: colorless to pale brown liquid.

Purification: distillation in vacuo.

Handling, Storage, and Precautions: exceedingly pungent odor, irritating to eyes and nose; store at 0 °C; slowly decomposed by water; reacts exothermically with alcohols and amines. This reagents should only be handled in a fume hood.

Thiourea Synthesis.

Ethoxycarbonyl isothiocyanate reacts with stoichiometric amounts of ammonia, primary, and secondary amines to afford the expected thioureas in high yield (eq 1).[1]

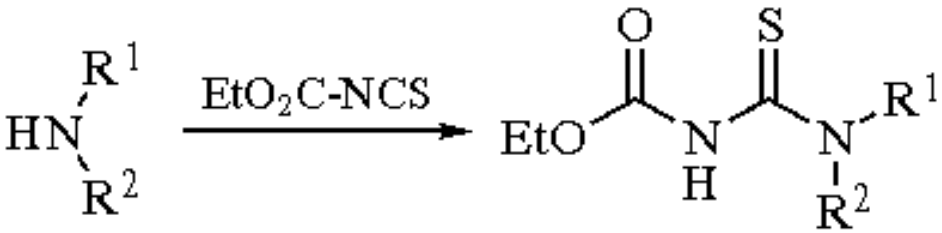

(1)

Synthesis of Thioamides.

Friedel-Crafts thioacylation of aromatics with ethoxycarbonyl isocyanate mediated by ***Aluminum Chloride*** gives moderate to good yields of arylthioamides or *N*-ethoxycarbonylthioamides, dependent on reaction conditions (eq 2).[2]

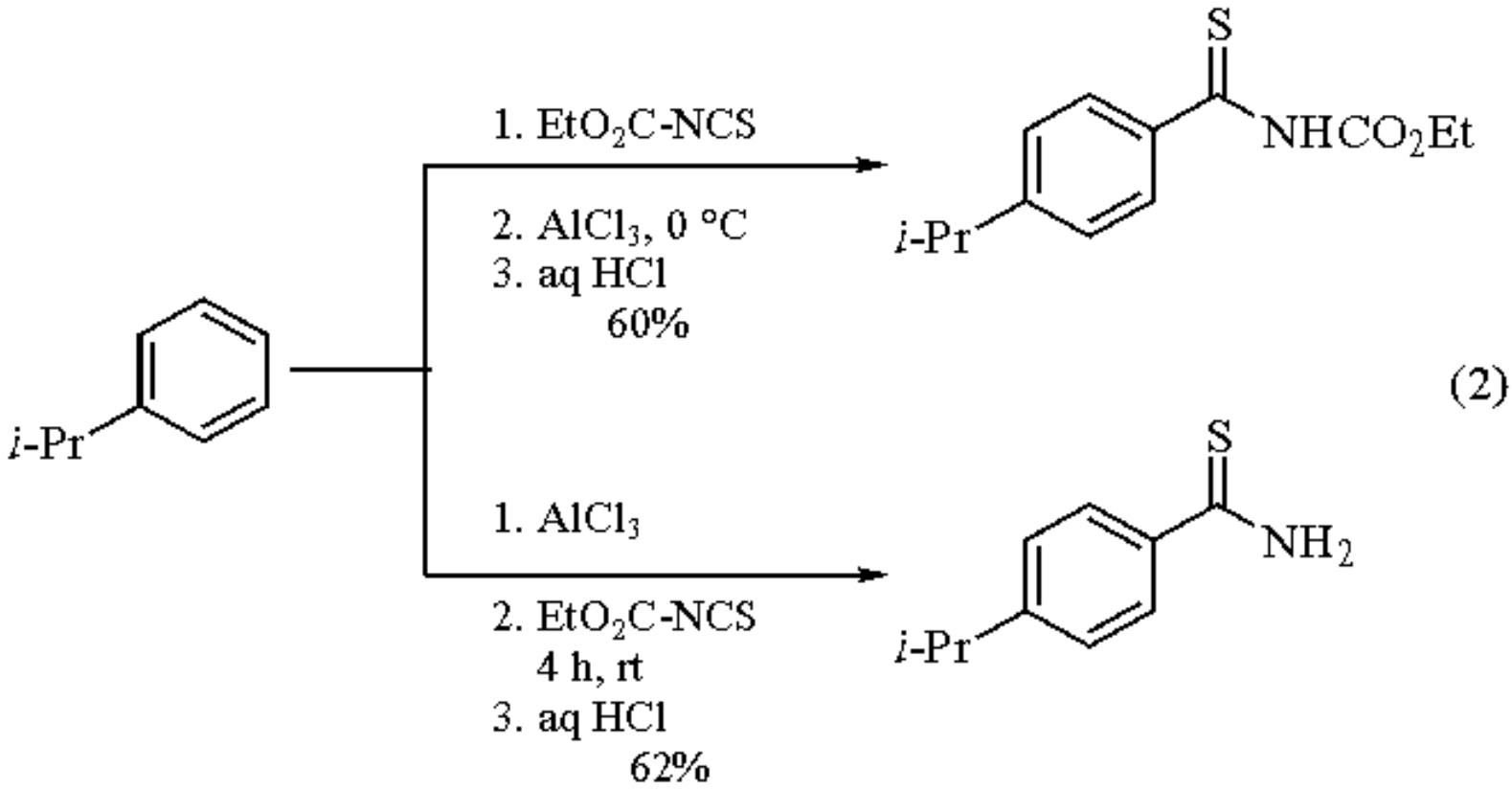

(2)

The thioamides synthesized by the reaction of cyclic or acyclic enamines with ethoxycarbonyl isothiocyanate can be isolated or carried on further to 4-thiouracils upon treatment with an additional primary amine (eq 3).[3,4]

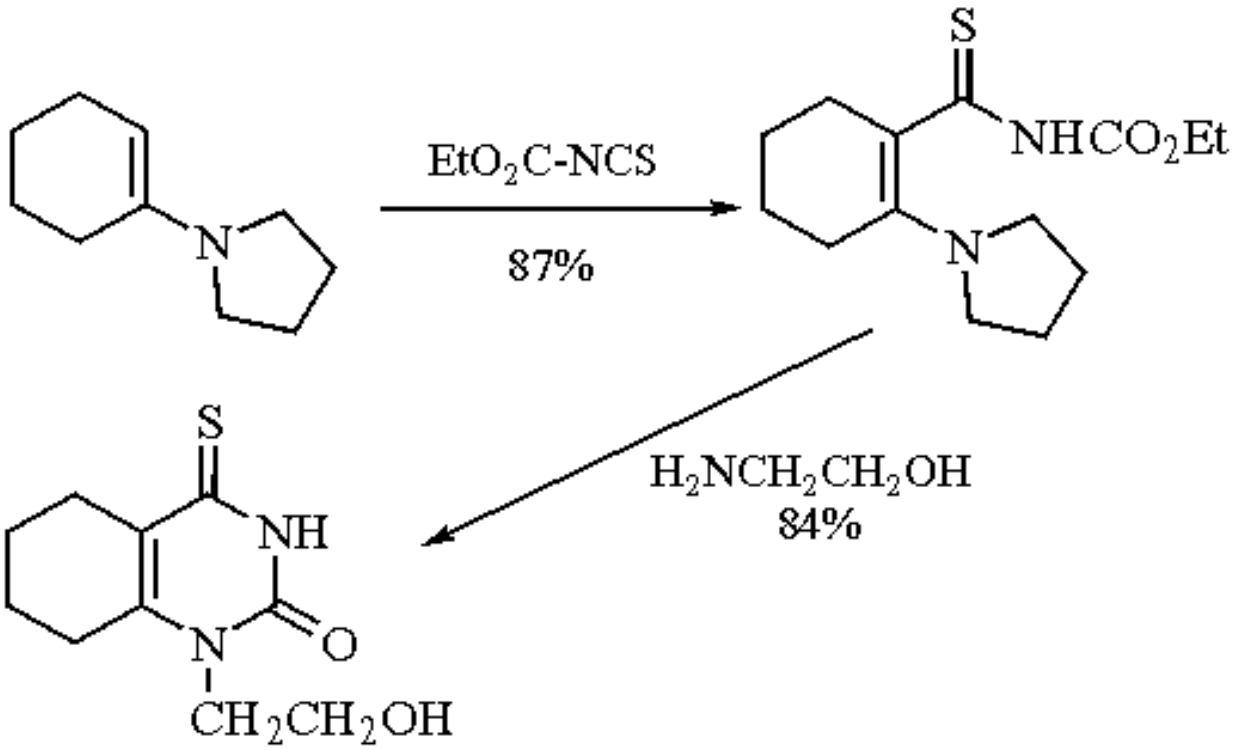

(3)

Synthesis of Heterocycles.

Ethoxycarbonyl isothiocyanate is sufficiently reactive for functionalization of urea nitrogens. Treatment of *N*,*N*´-disubstituted ureas with ethoxycarbonyl isothiocyanate followed by base-catalyzed ring closure and *S*-methylation provides a convenient synthesis of 1,3,5-triazine-2,4-diones (eq 4).[5]

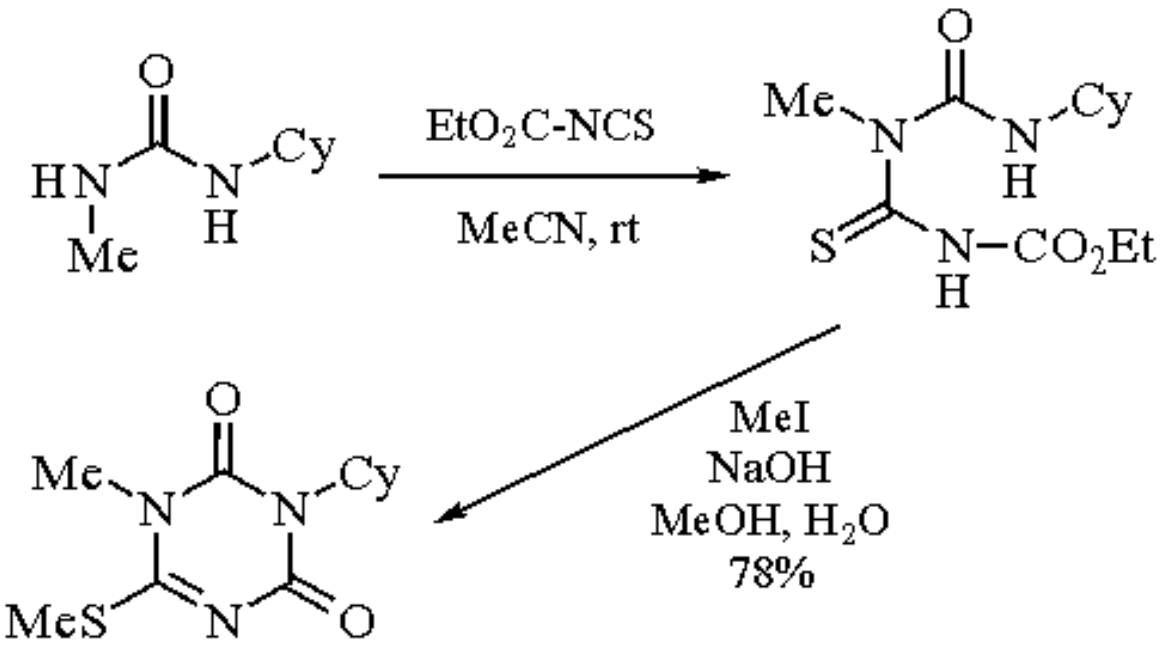

(4)

Ethoxycarbonyl isothiocyanate was used as a key starting point in a convenient and multigram synthesis of 1,2,4-oxadiazolidine-3,5-dione (eq 5), a bioisostere for the carboxylic acid group.[6]

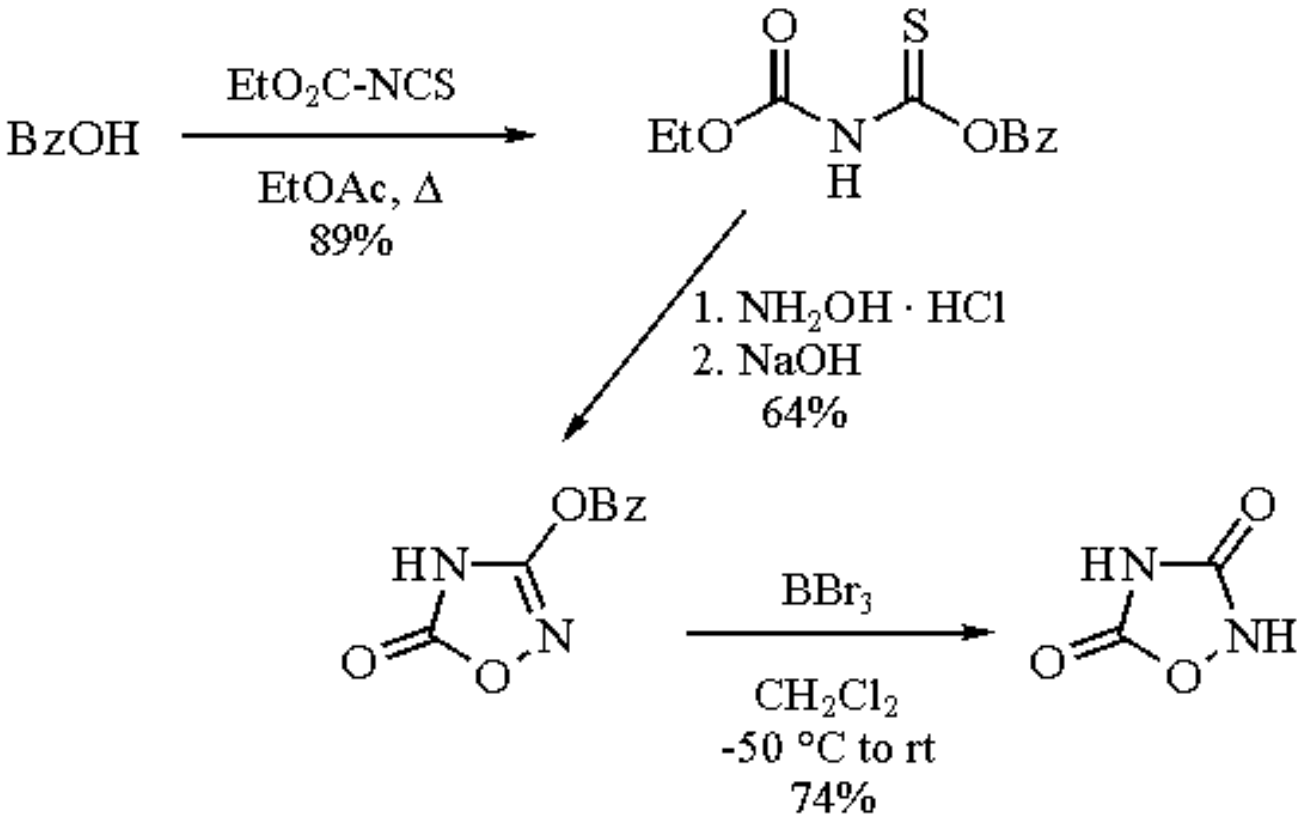

(5)

The synthesis of 5-amino-1,2,3-thiadiazoles can be achieved through [3 + 2] cycloaddition of ethoxycarbonyl

isothiocyanate with diazo ketones (eq 6).[7]

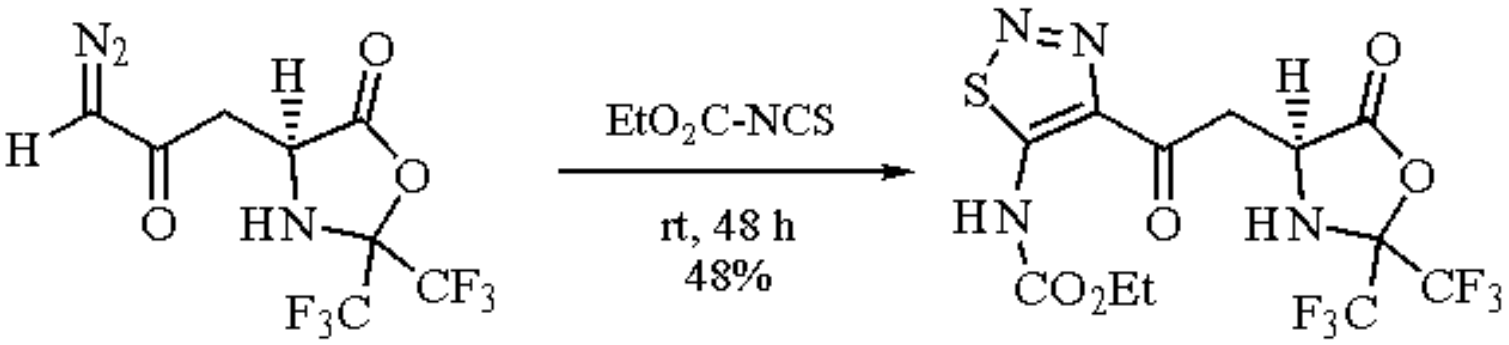

(6)

The reaction of 2-alkylamino[8] and 2-alkylhydrazino[9] aza-heterocycles with ethoxycarbonyl isothiocyanate has been used to generate interesting mesoionic species.

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Ethoxycarbonylmethylcopper[1]

EtO_2CCH_2Cu

[35756-99-1] · $C_4H_7CuO_2$ · Ethoxycarbonylmethylcopper · (MW 150.65)

(reagent for improved yields of allylation of ethyl acetate[2])

Preparative Methods: by the reaction of ***Ethyl Lithioacetate*** and ***Copper(I) Iodide*** in THF as a heterogeneous pale yellow solution at -110 °C or as a light brown homogeneous solution at -30 °C.

Handling, Storage, and Precautions: unstable above -30 °C; decomposes readily upon exposure to air or moisture. Use in a fume hood.

Characteristics.

Kuwajima and Doi[2] reported the preparation of ethoxycarbonylmethylcopper by the reaction of the lithium enolate of ethyl acetate with copper iodide in THF at -110 °C. Upon warming the mixture to -30 °C a light brown homogeneous solution was obtained. Oxidative dimerization of the ethoxycarbonylmethylcopper resulted in the formation of diethyl succinate in 73% yield. The copper enolate did not react with butyl bromide or tosylate and did not add to pentanal; however, reaction with cyclohexenyl bromide resulted in a 69% yield of the alkylated product (eq 1).

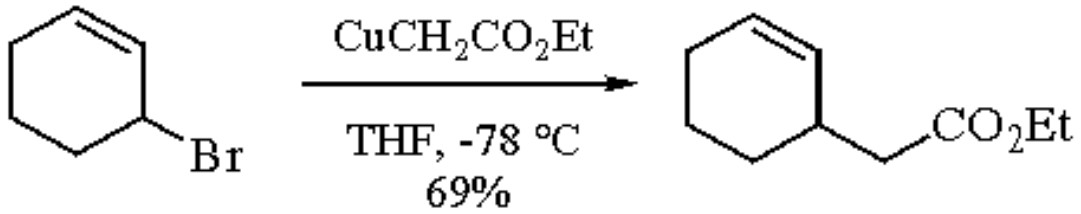

(1)

Amos and Katzenellenbogen[3] reported formation of a pale yellow heterogeneous reagent upon reaction of the lithium enolate of ethyl acetate and copper iodide at -78 °C, which turned dark brown upon warming to -30 °C. Oxidative coupling of the reagent prepared in this fashion also gave diethyl succinate, but in lower yield (29%). The nature of the species produced by reaction of the lithium enolate with copper iodide is not completely defined; however, the copper enolate exhibits dramatically different reactivity than the corresponding lithium enolate. The copper enolate appears to be a much softer nucleophile.

Reactions.

In the synthesis of sulfonium ion mimics of cationic intermediates involved in the squalene synthetase-catalyzed rearrangement of farnesyl pyrophosphate, alkylation of the lithium enolate of ethyl acetate with a thiosulfonate gave poor yields due to competing condensation reactions. Reaction of ethoxycarbonylmethylcopper and the thiosulfonate provided the desired product in reasonable yield (eq 2).[4] Selective displacement of the allylic halide of ***2,3-Dibromopropene*** has also been accomplished using the softer copper nucleophile (eq 3).[5]

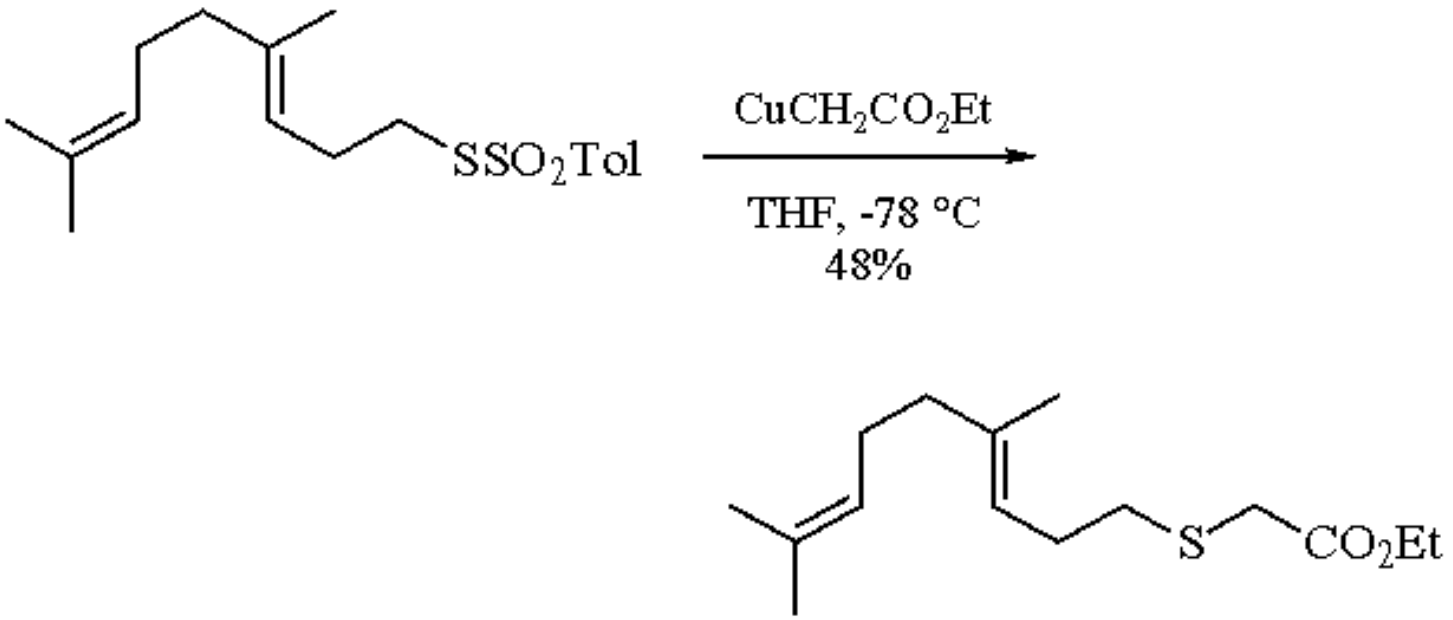

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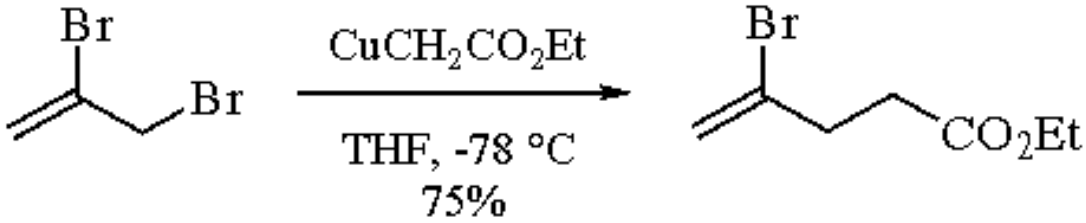

(3)

Reaction of ethoxycarbonylmethylcopper with propargylic mesylates resulted in the formation of the allene ester product by an S_N2' reaction while the corresponding lithium enolate provided only the alkynic product or did not react (eq 4).[3] In contrast to the reaction with the propargylic electrophile, reaction with most allylic electrophiles generally proceeds by direct substitution without allylic transposition. The synthesis of 4′, 8′, and 12′ nor analogs of geranylgeraniol was accomplished by direct displacement of allyl bromides with ethoxycarbonylmethylcopper.[6] Reaction of ethoxycarbonylmethylcopper with farnesyl bromide provided the ester in 97% yield; allyl chlorides may also be employed in the alkylation reaction. The synthesis of the sex pheromone of *Phtorimaea operculella* was achieved without any indication of competing S_N2' alkylation (eq 5).[7]

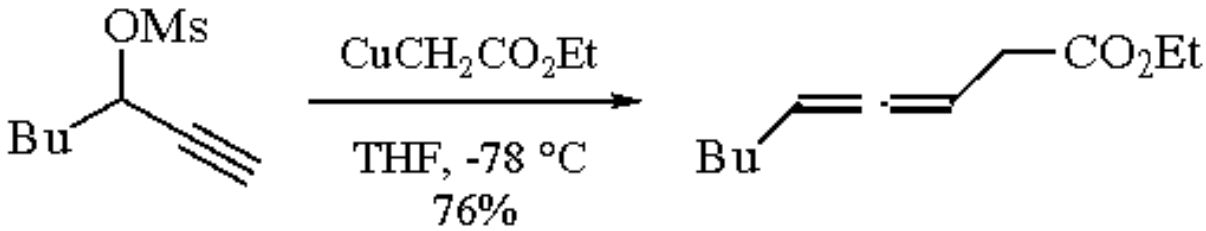

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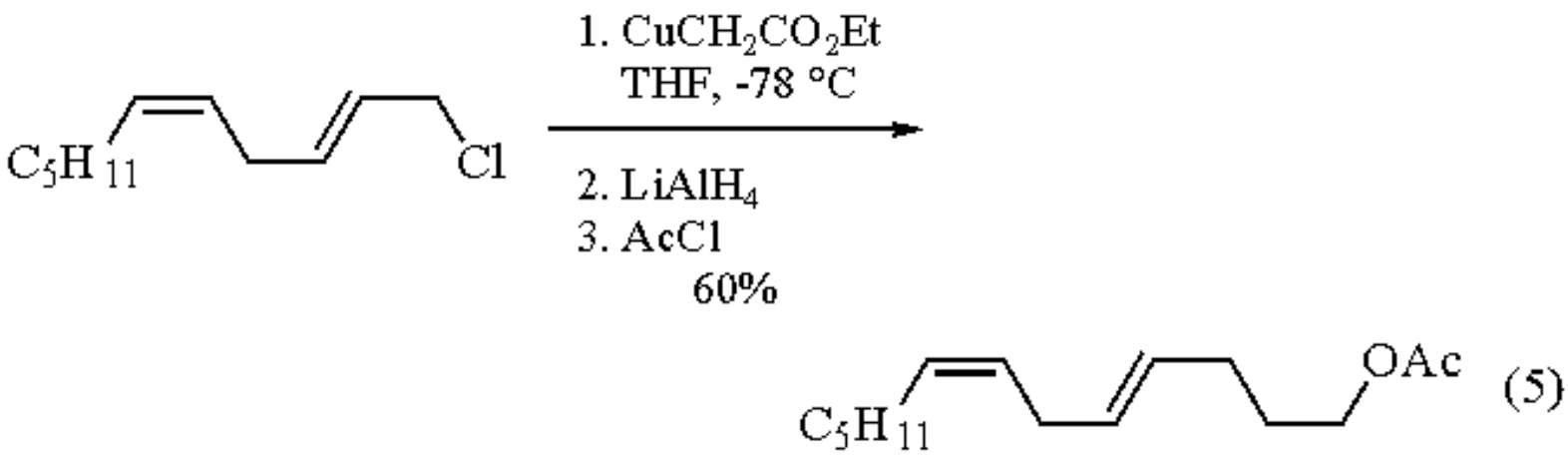

Regioselective 1,4-addition of ethoxycarbonylmethylcopper to cyclopentadiene monoepoxide has also been reported (eq 6).[8] There has been an exception to the predominant mode of α alkylation of allylic electrophiles. A general method for the regioselective synthesis of 2-alkenenitriles by the γ alkylation of 3-buten-2-one cyanohydrin diethyl phosphate included ethoxycarbonylmethylcopper as one of the nucleophiles.[9] A more reactive, stabilized copper derivative is produced from iododifluoroacetate and copper powder.[10] Ethoxycarbonyldifluoromethylcopper reacts with allyl, benzyl, alkenyl, alkynyl, and aryl halides.

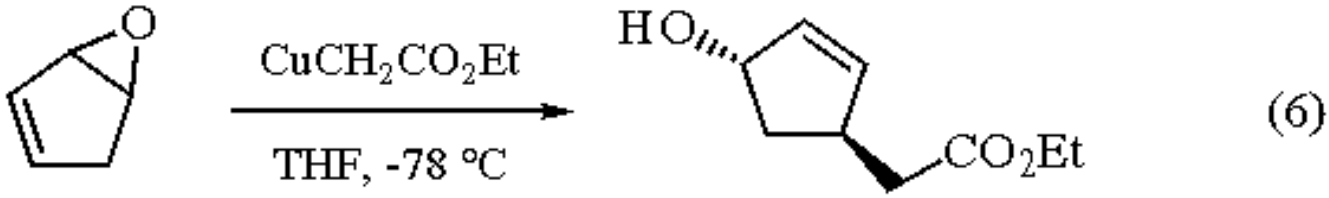

Related Reagents.

Cyanomethylcopper.

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Russell J. Linderman

Ethyl 2-Methyl-4-oxo-2-cyclohexene-1-carboxylate

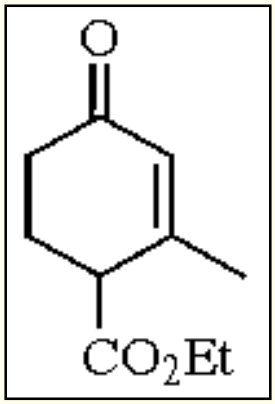

[487-51-4] · $C_{10}H_{14}O_3$ · Ethyl 2-Methyl-4-oxo-2-cyclohexene-1-carboxylate · (MW 182.22)

(a useful building block in natural product synthesis;[1-5] often alkylated in the 3-position[6])

Alternate Names: Hagemann's ester; 4-ethoxycarbonyl-3-methyl-2-cyclohexenone.

Physical Data: bp 268-272 °C; *d* 1.078 g cm^{-3}.

Form Supplied in: 90% technical grade liquid commercially available.

Preparative Methods: ethyl 2-methyl-4-oxo-2-cyclohexene-1-carboxylate[7] is typically prepared by the condensation of 2 equiv of ethyl acetoacetate with 1 equiv of formaldehyde in the presence of catalytic piperidine.[8] Aldehydes other than formaldehyde have been used to prepare 6-substituted compounds (eq 1).[9]

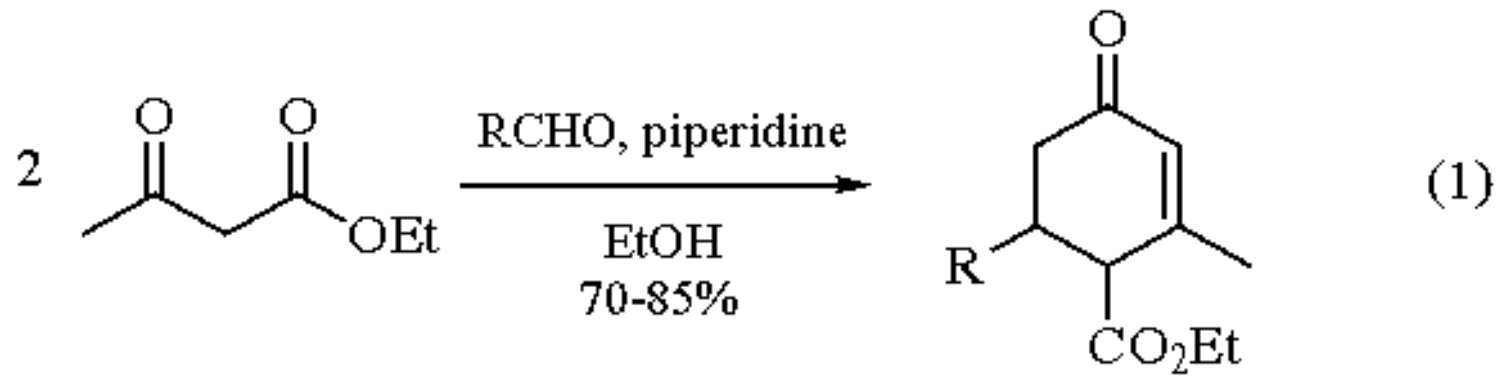

Cyclization of diketo esters proceeds in 50-75% yield using catalytic pyrrolidine and acetic acid (eq 2).[10]

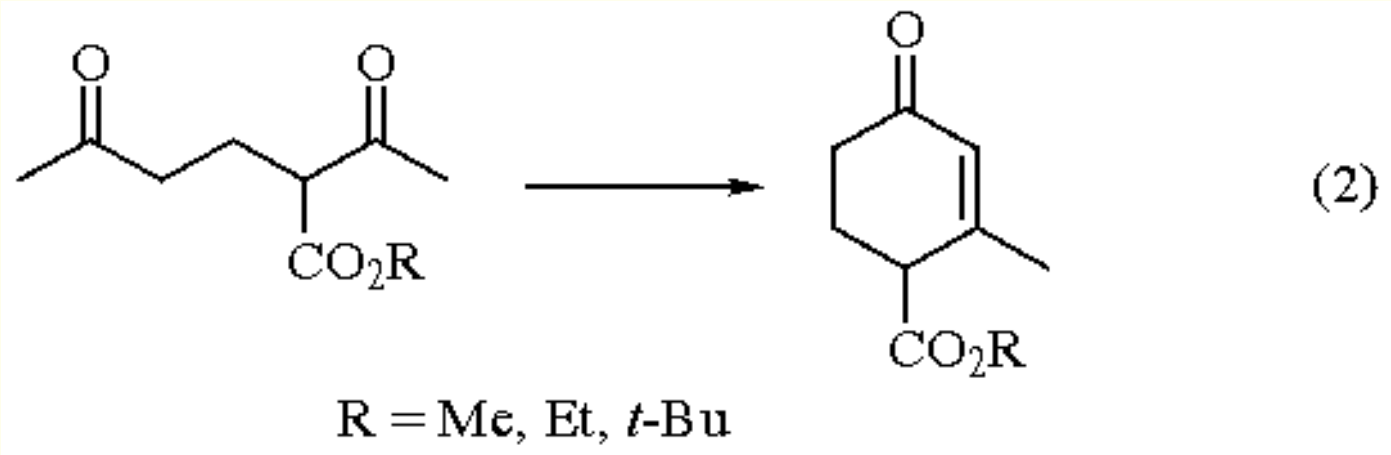

(2)

Natural Product Syntheses.

The title reagent (Hagemann's ester) serves, for example, as a starting material in the synthesis of (±)-α- and (±)-β-pinene,[1] yohimbine congeners,[2] vermiculine,[3] and other natural products.[4]

The 6-methyl derivative was employed in a total synthesis of (±)-agarospirol (epihinesol).[5] ***Lithium Aluminum Hydride*** reduction of its ethylene acetal followed by hydrolysis and concomitant dehydration afforded 3,5-dimethyl-4-methylene-2-cyclohexenone which underwent a 1,6-Michael addition with ***Diethyl Malonate***.

Alkylation of Hagemann's ester occurs predominantly at the 3-position, with a small amount of alkylation at the 1-position (eqs 3 and 4).[6]

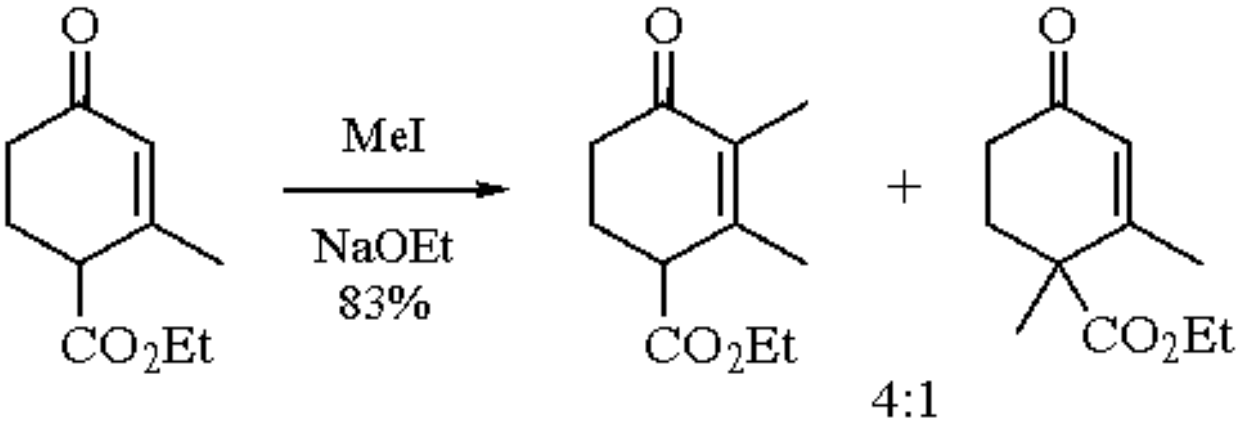

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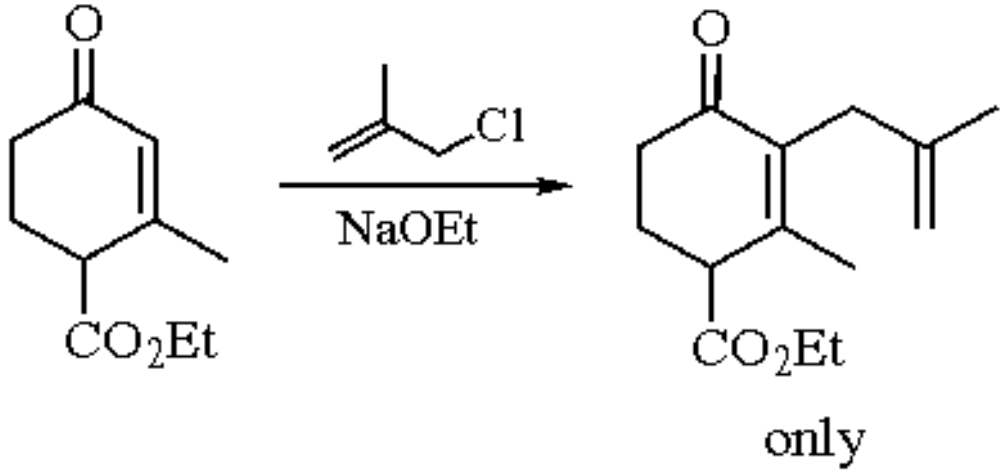

(4)

Reaction of Hagemann's ester with Michael acceptors such as ***Methyl Vinyl Ketone*** leads to C-1 and C-3 Michael adducts.[11]

Functionalization at C-1 is best achieved via the dienol ether or ester.[12] The ethyl dienol ether was prepared by treatment of Hagemann's ester with 2 equiv of diethyl sulfate and sodium hydride (eq 5).

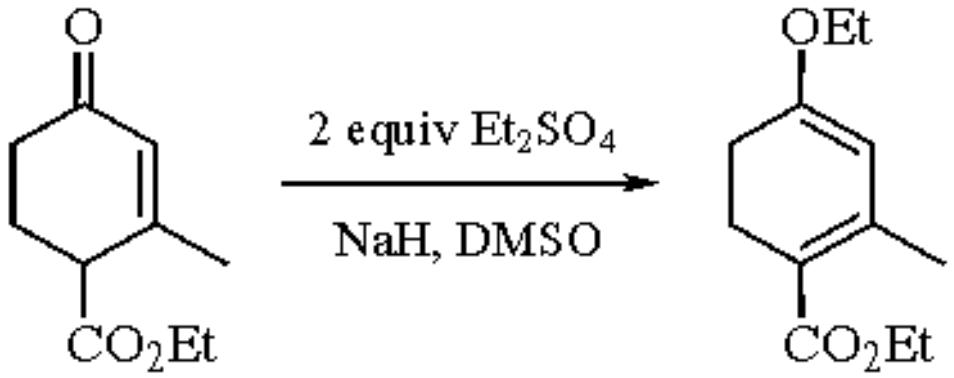

(5)

The ethyl dienol ether can be alkylated by a variety of electrophiles upon deprotonation with ***Lithium Diisopropylamide*** (eq 6). Other electrophiles used include ***Formaldehyde***, Michael acceptors, and ***Methyl Chloroformate***. All proceed in good to excellent yields.

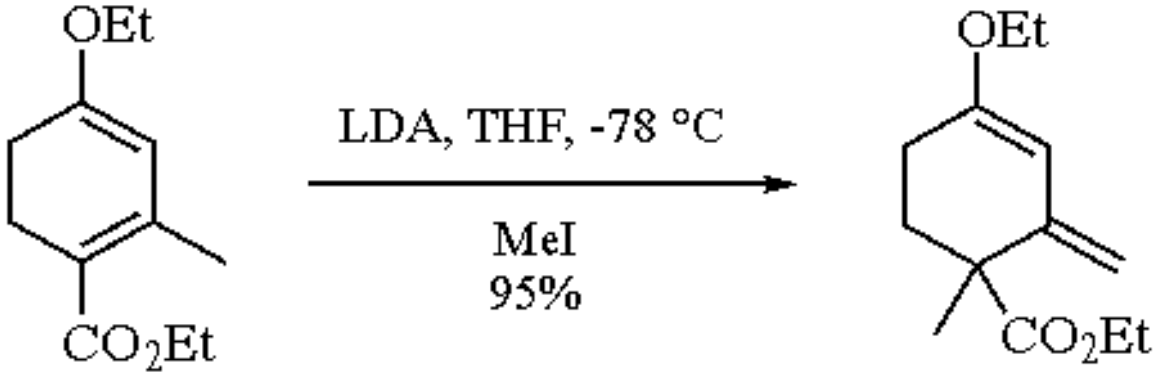

(6)

A regiospecific synthesis of substituted 1,3-cyclohexadienes uses Hagemann's ester and its derivatives as

starting material.[13] Borohydride reduction or Grignard reaction of the ketone carbonyl followed by saponification and dehydrative decarboxylation with *N*,*N*-dimethylformamide dineopentyl acetal gives various substituted 1,3-cyclohexadienes.

Related Reagents.

Ethyl Acetoacetate; ***Formaldehyde***; ***Iodomethane***; ***Methyl 6-Oxo-1-cyclohexenecarboxylate***; ***Methyl 3-Oxo-4-pentenoate***; ***Methyl Vinyl Ketone***.

---

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(Ethoxycarbonylmethylene)triphenylphosphorane[1]

$Ph_3P{=}CHCO_2Et$

[1099-45-2] · $C_{22}H_{21}O_2P$ · (Ethoxycarbonylmethylene)triphenylphosphorane · (MW 348.38)

(stabilized phosphorane reagent useful for Wittig alkenation reactions to give α,β-unsaturated ethyl esters on reaction with carbonyl compounds;[1] heterocyclic ring construction;[2-4] synthesis of cyclopropanes from epoxides[5])

Physical Data: mp 128-130 °C.

Solubility: sol EtOH (42 g 100 mL^{-1}), THF (13 g 100 mL^{-1}), and $CHCl_3$ (29 g 100 mL^{-1}); insol water (<0.5 g 100 mL^{-1}).

Form Supplied in: white crystalline powder.

Handling, Storage, and Precautions: no special handling or storage requirements are necessary. The use of carefully dried reagents leads to a lower rate of Wittig alkenation reaction.[6] The compound is stable in water (>3 h), and >99% stable in 0.5 N NaOH in MeOH-water (1:1) for at least 3 h.

Weakly Basic Phosphorus Ylide.

This phosphorane is readily prepared by deprotonation of ***(Ethoxycarbonylmethyl)triphenylphosphonium Bromide*** (pK_a 8.95-9.2), typically with ***Sodium Ethoxide*** or ***Sodium Hydroxide***.[7] Deprotonation of the phosphonium bromide produces a phosphorane in which the negative charge on the α-carbon is stabilized by d_π-p_π bonding to the phosphorus and also by the adjacent ethoxycarbonyl group. Additionally, NMR studies have shown that this reagent exists as a ca. 3:1 mixture of *cis*:*trans* ylide/enolates as shown in eq 1, with a barrier to rotation estimated at ca. 10 kcal mol^{-1} for the methyl ester.[6,8] The high proportion of negative charge on the oxygen is reflected in *O*-ethylation with ***Triethyloxonium Tetrafluoroborate*** at -78 °C to give a 3:1 mixture of *cis*:*trans* ethyl vinyl ethers.[6] The presence of small amounts of water or other proton sources facilitate the reaction of the phosphorane, presumably by reversibly protonating the α-carbon and lowering the barrier to rotation, allowing for more reactive ylide forms with single bond character between the α- and β-carbons (viz. *cis*- and *trans*-ylide structures).[6] For this reason, it is counterproductive to be overly concerned with removing traces of moisture in standard reactions involving this phosphorane.

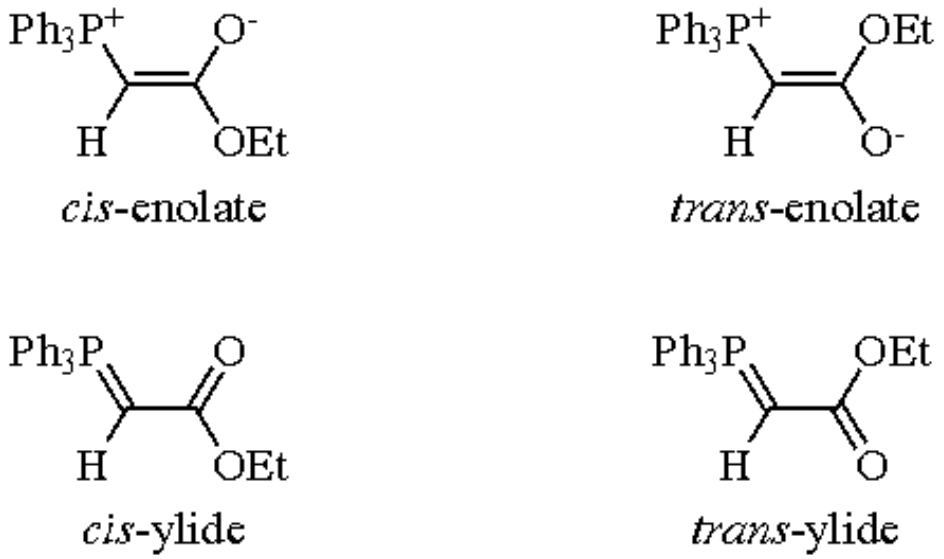

(1)

Wittig Alkenation Reactions.

This reagent is among those typically referred to as stabilized Wittig reagents, because of the extra negative charge stabilization by the ester functionality (see also ***(Methoxycarbonylmethylene)triphenylphosphorane***). As such, its basicity and reactivity is moderated relative to the nonstabilized alkylidenephosphoranes. If more reactive reagents are required, phosphonates such as $(EtO)_2P(O)CH_2CO_2Et$ can be employed in the Horner-Wadsworth-Emmons (HWE) alkenation procedure.[1] The phosphonate reagents have the added advantage that the phosphates obtained as side-products are easier to remove than triphenylphosphine oxide, the phosphorus-containing product of the phosphorane reactions. Although intermediates have not been observed in reactions of stabilized phosphoranes by spectroscopic techniques, the reaction mechanism would be expected to include a four-membered oxaphosphetane immediately prior to elimination to the alkene and triphenylphosphine oxide.[1a]

(Ethoxycarbonylmethylene)triphenylphosphorane reacts with the carbonyl groups of aldehydes,[9-26] ketones,[27-34] ketenes,[35-37] anhydrides,[39] imides,[40] and certain amides[41a,42] and esters[4,41] to insert the α,β-unsaturated ethyl ester (ethyl acrylate) functionality. The reaction has wide generality and has been extensively employed, especially en route to intermediates for further synthetic manipulation. Where the newly established double bond has stereochemistry, such as in reactions with aldehydes and unsymmetrical ketones, it is generally *trans* (*E*) in nature, although the (*E*:*Z*) ratio is influenced by a variety of factors, such as the nature of the aldehyde, solvent, and additives.

Reactions with Aldehydes.

There are numerous instances in which this reaction has been carried out in organic synthesis, and only a few representative examples are given here. In the synthesis of rapamycin, the aldehyde group was converted to the expected (*E*) ester, without significant epimerization or elimination of the α-mesyloxy or β-benzyloxy substituents, respectively (eq 2).[10a] The relatively low basicity of the phosphorane allows for mild transformations of this type, without affecting base-sensitive groups.

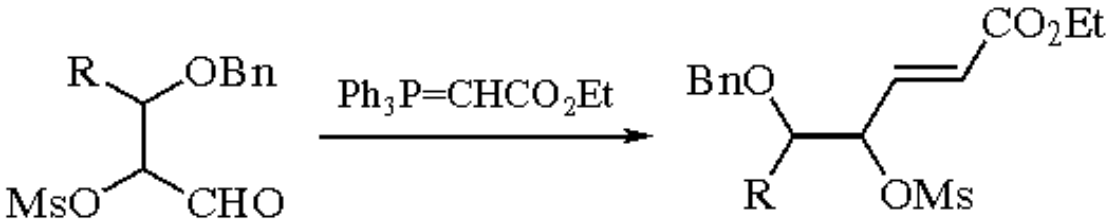

(2)

There are occasions when these mild conditions are preferred to the more basic conditions attendant to the HWE phosphonate reagent $(EtO)_2P(O)CHCO_2Et^-\ Na^+$. For example, in the preparation of a substrate for a quinolizine synthesis, the phosphorane produced the

desired acrylate ester, whereas use of the HWE reagent resulted in considerable amounts of premature ring closure to give a piperidine side product (eq 3).[10b]

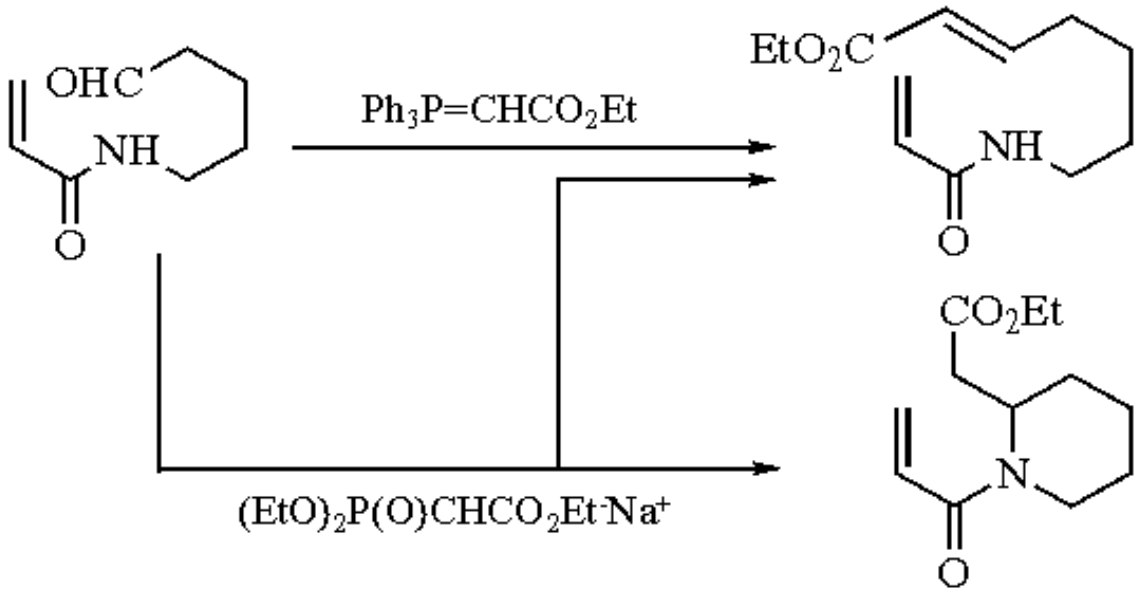

(3)

The alkenation reaction can be carried out by the in-situ generation of the phosphorane reagent by the use of ethylene oxide (eq 4).[11] The bromide counterion of the phosphonium salt opens the ethylene oxide, and the alkoxide which then forms deprotonates the α-carbon.

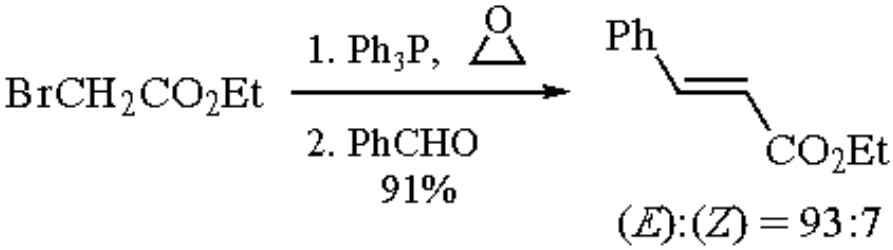

(4)

When the phenyl ligands on the phosphorus atom are replaced with alkyl groups, the relative proportion of (*E*) isomer increases.[12] For example, in reactions with benzaldehyde under the same conditions, $Ph_3P{=}CHCO_2Et$ and $Bu_3P{=}CHCO_2Et$ gave (*E*:*Z*) ratios of 89:11 and 95:5, respectively.[12] The placement of ferrocenyl ligands on the phosphorus also resulted in the same degree of (*E*) stereoselectivity,[13] but 2-furyl ligands produced more of the (*Z*) isomer in ethanol.[14] Rate studies on phosphoranes of type $(p\text{-}XC_6H_4)_3P{=}CHCO_2Et$ gave ρ values in the area of +2.5-3.0.[15] Bridged phosphorane species in which two of the phenyl ligands are attached via a divinyl spacer react slowly to give more (*Z*) isomer (24%) than use of the standard reagent (11%).[16]

Greater (*E*) selectivity is observed when the α-carbon is alkylated, such as in reactions of $Ph_3P{=}C(Me)CO_2Et$.[1,17] However, α-halogenation of the phosphorane and its use to prepare vinyl halides is less (*E*) selective (eq 5).[18]

(Ethoxycarbonylmethylene)triphenylphosphorane

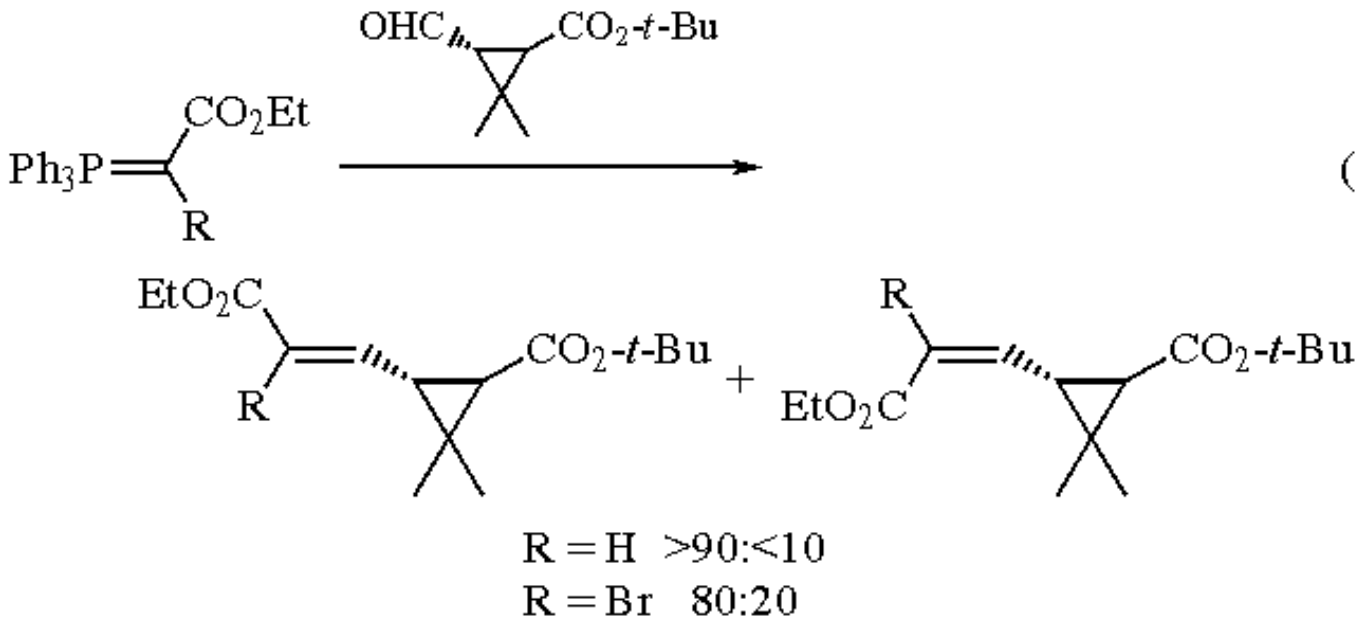

Generally, the formation of the (*E*) isomer is favored by the use of aprotic solvents in the absence of lithium salts,[1a] and the influence of solvent can often be remarkable. For example, reaction of the phosphorane with a sugar-derived aldehyde gave the corresponding acrylates with (*E*:*Z*) mixtures that varied from 86:14 (DMF) to 8:92 (MeOH; eq 6).[19]

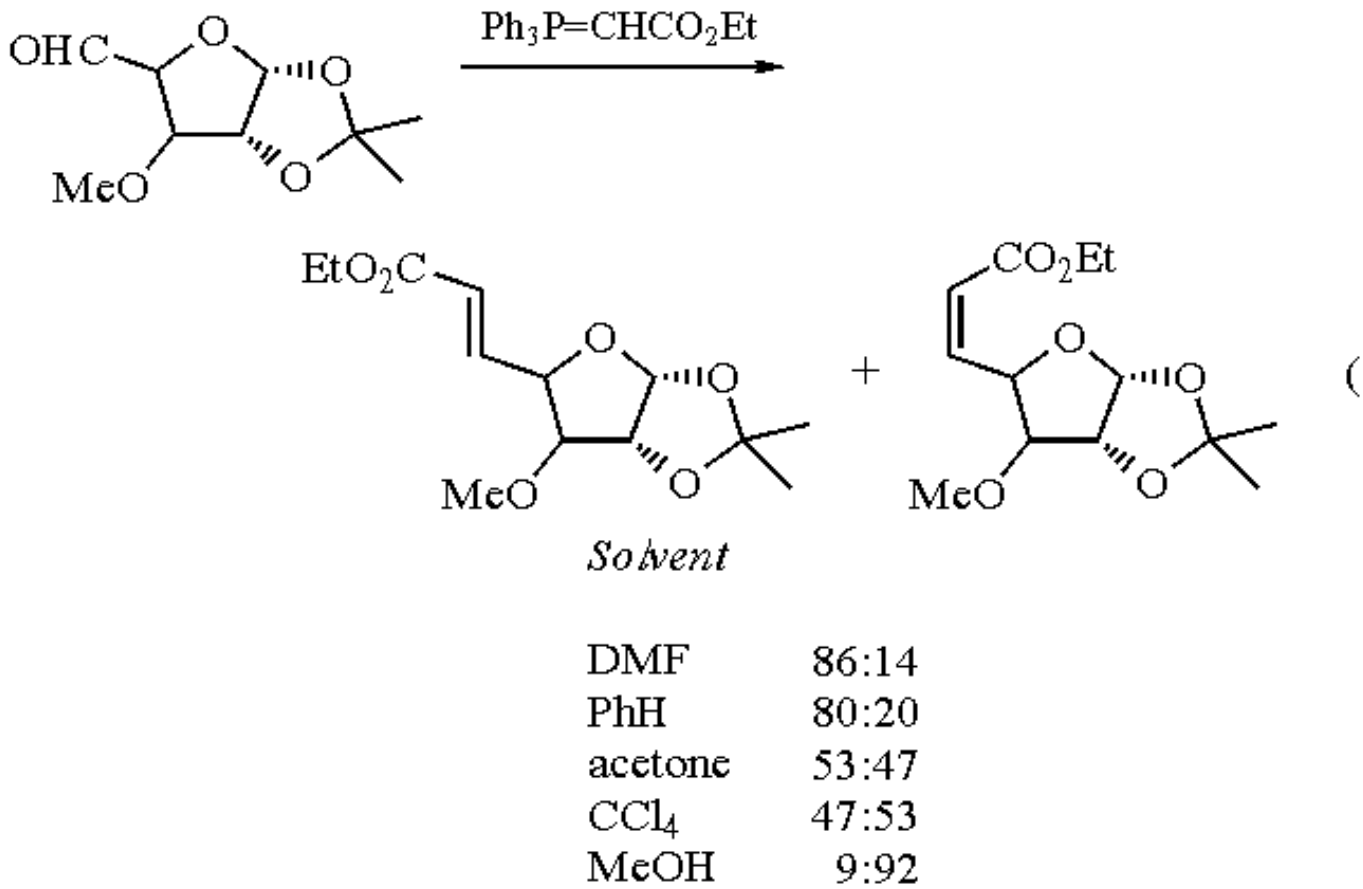

The high amounts of the (*Z*)-acrylate observed in eq 6 under certain conditions is characteristic of the reactions of α-alkoxy aldehydes, particularly in the presence of an additional β-alkoxy group and in an anhydrous alcoholic solvent.[1a] For example, treatment of isopropylideneglyceraldehyde with the phosphorane reagent in methanol at 0 °C[20] or 25 °C[21] gave the expected acrylates with an (*E*:*Z*) ratio of ca. 10:90. This effect has been observed repeatedly in reactions with carbohydrate-based aldehydes, as they bear multiple oxygenated sites. In the reaction of a fucose-derived hemiacetal (reacting in the aldehyde form) a ca. 1:2 mixture of (*E*:*Z*)

(Ethoxycarbonylmethylene)triphenylphosphorane

isomers formed (eq 7),[22] whereas reaction of 2-deoxyribose derivatives (lacking an α-alkoxy group) gave solely (*E*) acrylates.[23]

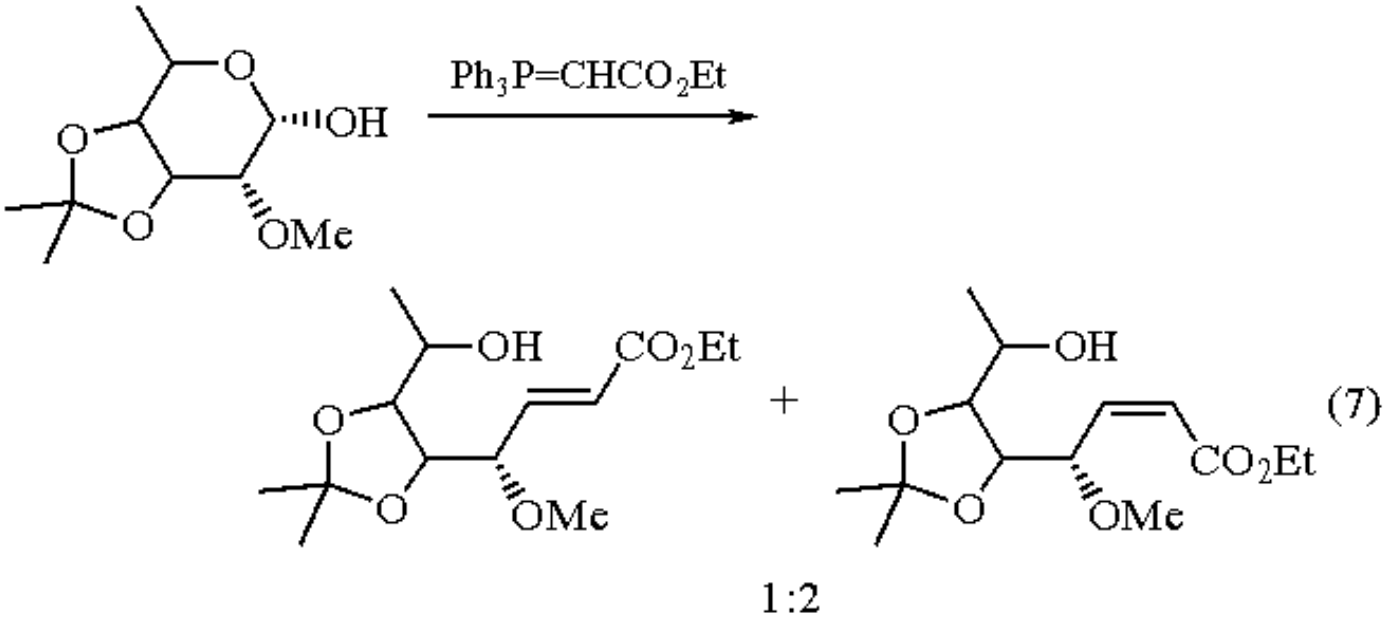

The reaction of sugar-derived hemiacetals with stabilized phosphoranes has provided an important starting point for the synthesis of key natural products such as the leukotrienes.[1c] Additionally, the hydroxyl group that remains from the hemiacetal can attack the β-carbon of the acrylate in a Michael fashion to form *C*-glycosides, useful as important synthetic intermediates, such as in the reaction of diisopropylideneallofuranose shown in eq 8.[24] The alkene product of the Wittig reaction can be isolated directly in some cases or the Michael closure can be so fast that only the *C*-glycoside products are detected. In certain circumstances, diene products formed by further elimination reactions are observed.[25] The nature of the ester group and the presence of free or masked hydroxyls on the sugar substrate are important determinants in whether cyclized or open chain products are isolated in these systems.[26]

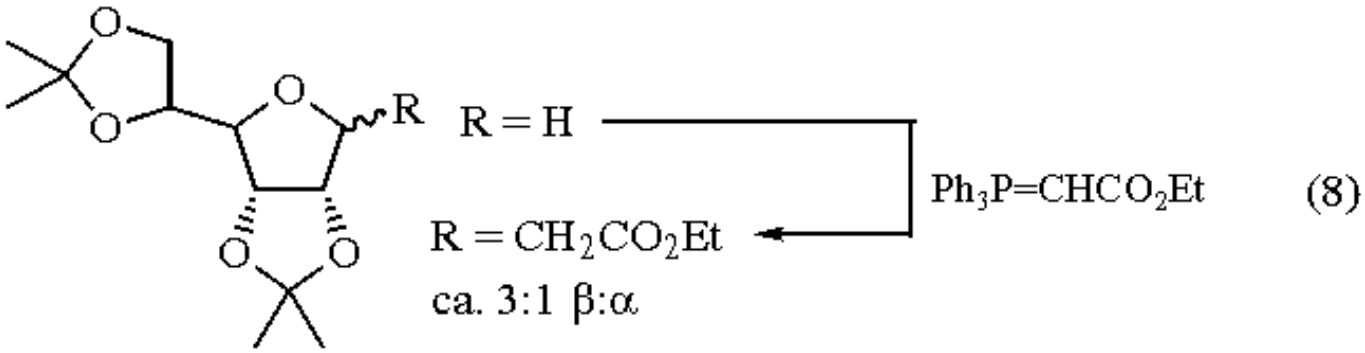

Reactions with Ketones.

Ketones can be unreactive partners in condensations with stabilized phosphoranes. These reactions can be enhanced by reaction at 9 kbar.[27] For example, alkenation with benzophenone gave an 82% yield of product at 50 °C after 35 h, whereas refluxing in xylene after 1 d at 1 bar resulted in only 10% product. In addition, the reaction with ketones can be facilitated by prolonged heating or mixing the two reactants together at high temperature without the use of solvent.[28] In other cases, the addition of small amounts of an acid catalyst (e.g. benzoic acid) increases the yield of reactions with hindered carbonyls (eq 9).[29] The acid may be acting by increasing the electrophilicity of the carbonyl or by enhancing the rate of exchange of the various ylide forms as discussed above.

(Ethoxycarbonylmethylene)triphenylphosphorane

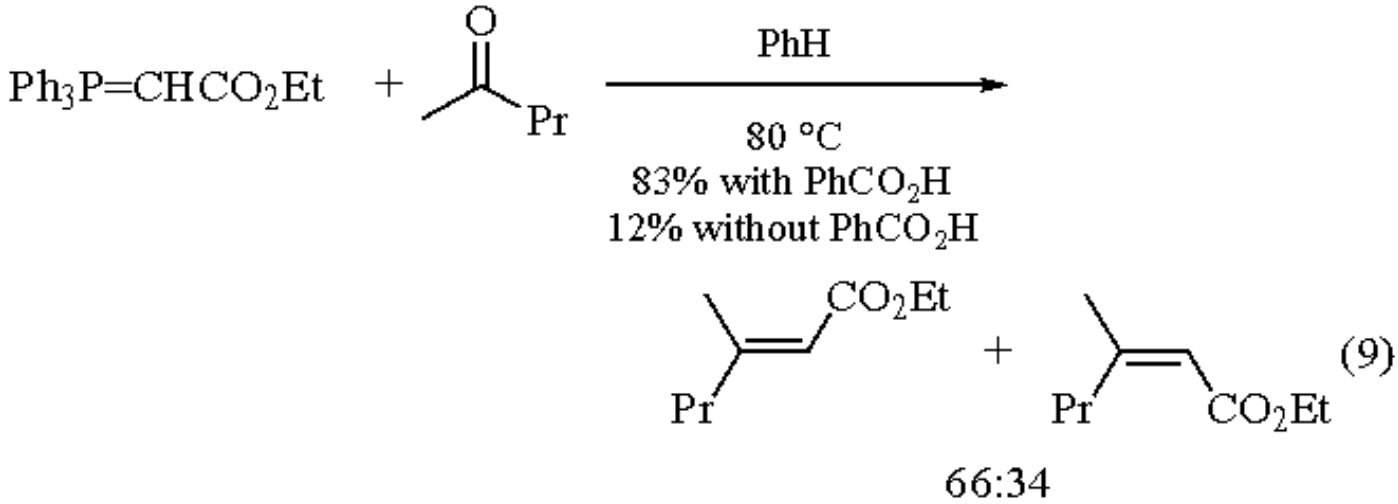

Keto sugars typically react very nicely with the phosphorane, often producing unexpected stereochemical outcomes. For example, the choice of a silyloxy or benzyl ether protecting group led to dramatically different mixtures of acrylates as shown in eq 10.[30] Alkoxy or hydroxy substituted ketones may actually react faster than their deoxy counterparts.[31]

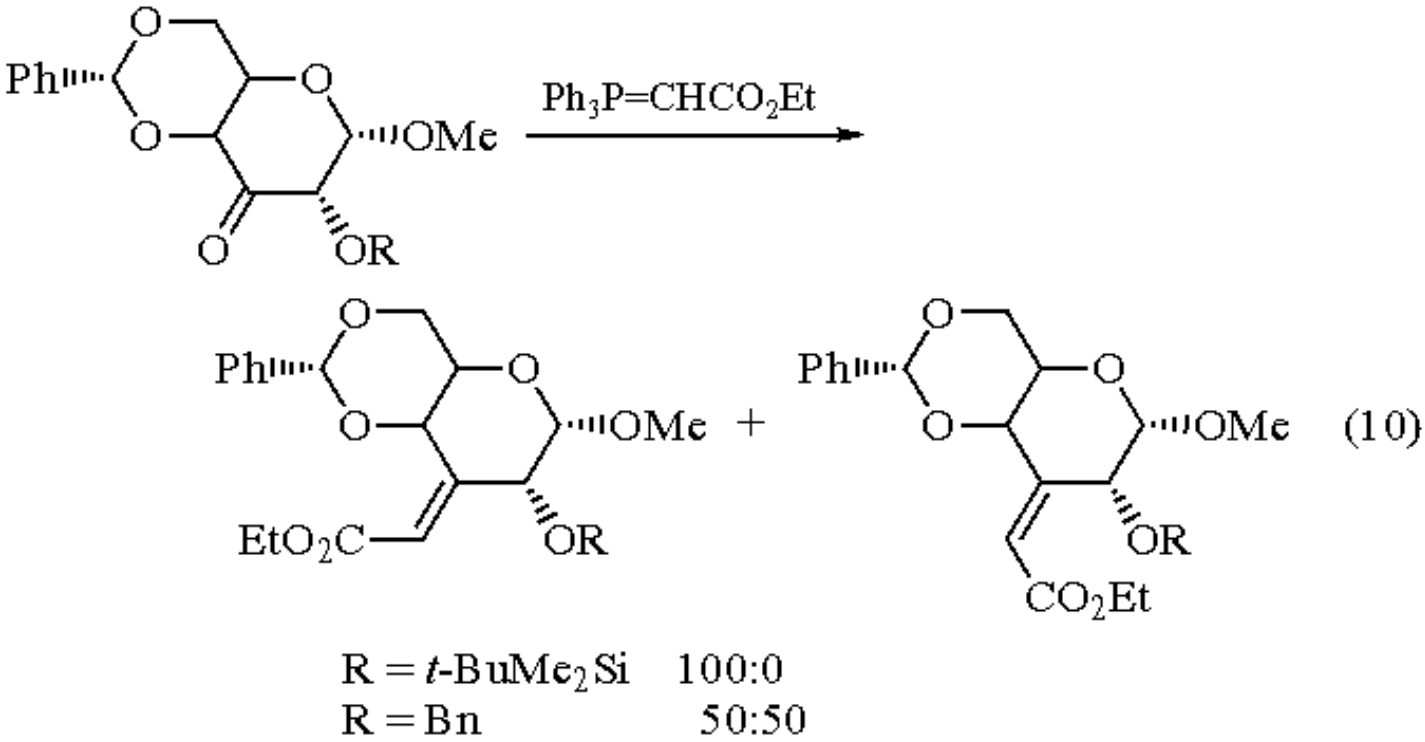

The use of a chiral carboxylic acid in reaction of the phosphorane and 4-methylcyclohexanone resulted in the expected ethyl acrylate with an enantiomeric excess (ee) of <10%.[32] However, the presence of a chiral host in the same sequence afforded the expected acrylate with an ee of 42% (eq 11).[33] There are only a few reported enantioselective Wittig alkenations, such as the use of bicyclic phosphonamide reagents, in which case as much as 90% ee is observed.[34]

(Ethoxycarbonylmethylene)triphenylphosphorane

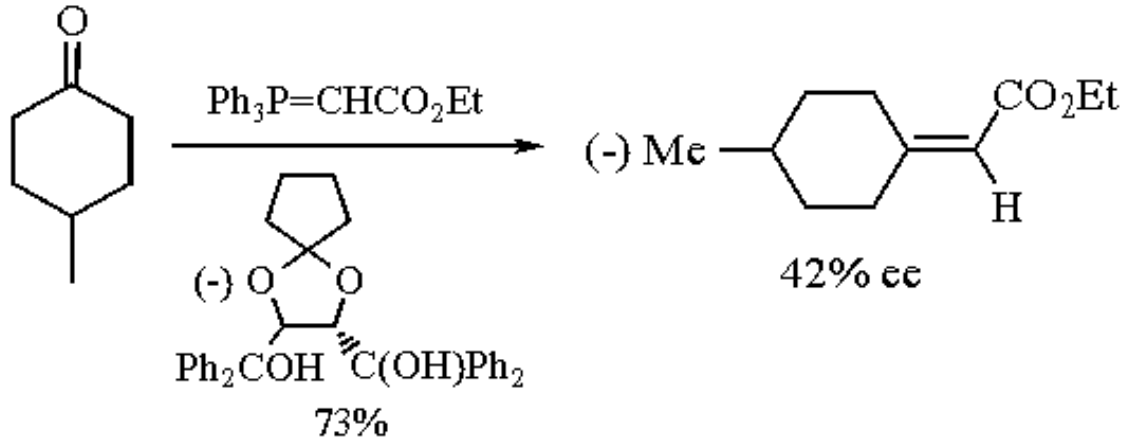

(11)

Reactions with Ketenes.

Reaction of an acyl halide with the phosphorane in the presence of 1 mol equiv of ***Triethylamine*** affords allenic esters via in-situ generation of a ketene from the acid halide, followed by a standard Wittig reaction (eq 12).[35] In a similar fashion, carboxylic acids, activated by triethylamine and ***2-Chloro-1-methylpyridinium Iodide***, generate ketenes which can be reacted with the stabilized phosphoranes to afford allenic carboxylate esters.[36] The reaction of silicon- and germanium-substituted ketenes ($Me_3MCH{=}C{=}O$) with the phosphorane also gives allenic esters, which rearrange to the alkynes Me_3MC&tbond;CCH_2CO_2Et upon distillation.[37]

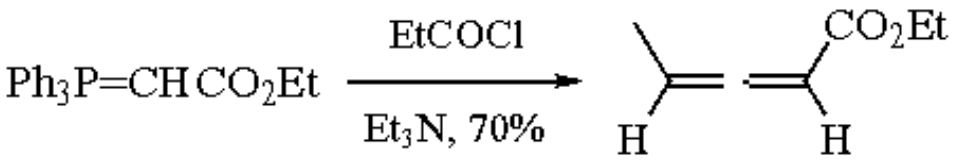

(12)

Allenes are also formed by the use of $Ph_3P{=}C{=}C(OEt)_2$, produced by treatment of $Ph_3P{=}CHCO_2Et$ with ***Triethyloxonium Tetrafluoroborate*** followed by base treatment.[38] Reaction with fluorenone gave the expected allene product, which dimerized immediately to a spirofluorene adduct.[38]

Reactions with Anhydrides and Imides.

Stabilized phosphoranes condense with anhydrides to yield enol lactones (see ***(Methoxycarbonylmethylene)triphenylphosphorane***).[39] Both the (*E*) and (*Z*) isomers can be obtained depending on the substrate, and also regioisomers are produced if the anhydride is unsymmetrical. There is predominant reaction at a site with weak steric hindrance (e.g. α-methyl) which changes to the less hindered carbonyl with added hindrance (α,α-dimethyl).[39] Imides also react to give *N*-vinyl amides in a similar manner.[40]

Reactions with Amides and Esters.

Certain reactive or suitably disposed esters[4,41] also react in a Wittig fashion to yield vinyl ethers, and some amides[41a,42] such as those in penicillin and clavulanic acid derivatives afford vinyl amines.

Alkylations, Acylations, and Related Processes.

Stabilized phosphoranes are sufficiently nucleophilic to be alkylated in order to construct more complicated reagents, particularly with reactive alkyl groups such as allyl, benzyl, and methyl.[1,43] Halogenation of the phosphorane leads to the α-halo derivatives, which give vinyl halides upon standard Wittig alkenations.[7c,44] The nucleophilic alkylation reaction of the phosphorane with a large

variety of substrates has been investigated, such as in the ring opening of *N*-methoxypyridinium salts[45] and the β-alkylation of alkyl propynoates.[46] Treatment of the phosphorane in the absence of an added electrophile leads to phosphaketene $Ph_3P{=}C{=}C{=}O$.[47] The phosphorane coordinates with organometallics to form stable complexes, and can occasionally participate in subsequent reactions of the organometallic complex.[48]

Acylation of the phosphorane provides diacylphosphoranes, which are often so highly stabilized and unreactive that they do not perform Wittig alkenations well.[1] However, flash vacuum pyrolysis (FVP) can afford either terminal alkynes or propargylic esters, depending on the conditions (eq 13).[49]

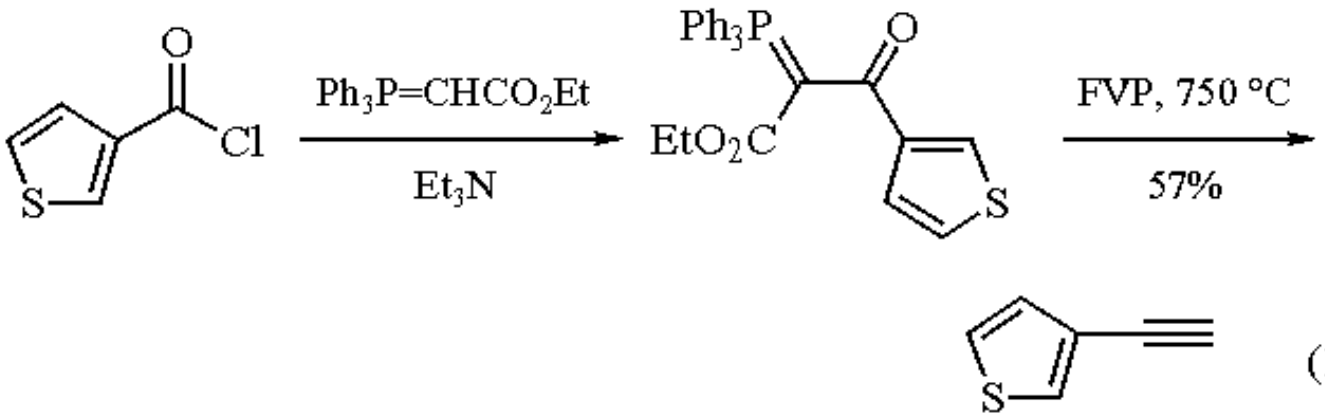

(13)

Heterocyclic Ring Formation.

Reaction of the phosphorane with azides gives phosphazenes, whereas similar treatment of $Ph_3P{=}C(Me)CO_2Et$ results in triazole formation via 1,3-dipolar cycloaddition of the azide to the enolate resonance form of the phosphorane (eq 14).[50] A similar cyclocondensation occurs with hydrazonyl chlorides to give 5-alkoxy substituted pyrazoles.[2]

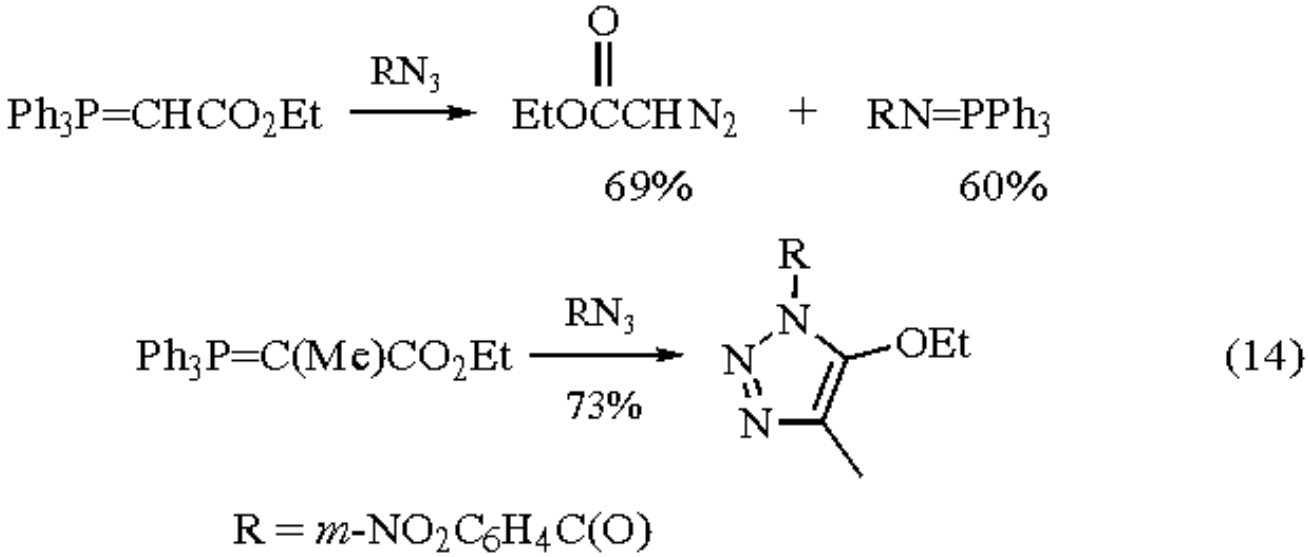

(14)

The combination of Wittig alkenation followed by further reaction of the α,β-unsaturated ester has resulted in the efficient preparation of several heterocyclic ring systems. In addition to the *C*-glycoside synthesis discussed earlier, pyrrolidines can be prepared in a similar Wittig/Michael sequence starting from α-hydroxypyrrolidine carbamates.[51]

Reaction of *o*-hydroxybenzaldehydes with the phosphorane is followed by condensation of the ester with the phenyl hydroxyl in a synthesis of coumarins (eq 15).[3,43,52]

(Ethoxycarbonylmethylene)triphenylphosphorane

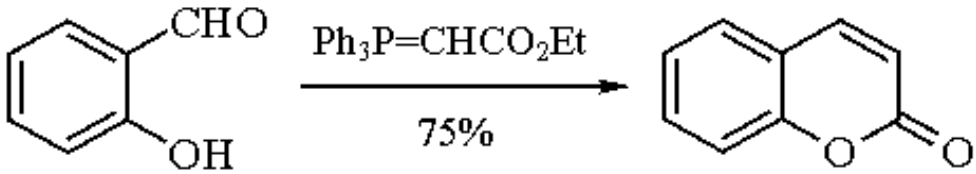

(15)

Nucleophilic Epoxide Opening.

Under rigorous conditions, oxiranes react with the phosphorane to give ethoxycarbonylcyclopropanes (eq 16).[5] The mechanism proceeds via nucleophilic opening of the epoxide, followed by attack of the alkoxide on the phosphorus, cleavage of the alkyl-phosphorus bond, and backside displacement of triphenylphosphine oxide. Normal Wittig alkenations of aldehydes with the phosphorane are sufficiently mild so as to not react with the epoxide functionality.

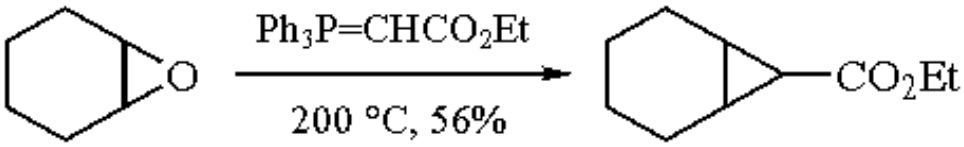

(16)

Oxidation.

Oxidation of the phosphorane yields symmetrical alkenes, or cyclic alkenes if bisylides are employed. This reaction was carried out originally using ***Triphenyl Phosphite-Ozone***;[53] however, a newer procedure using oxaziridines is a more general method.[54]

Formation of Thio- and Selenoaldehydes.

Treatment of the phosphorane with sulfur,[55] episulfides,[56] or selenium[57] results in formation of $Ph_3P{=}S$ or $Ph_3P{=}Se$ and $S{=}CHCO_2Et$ or $Se{=}CHCO_2Et$. These unstable thio- or selenoaldehydes can be trapped as their Diels-Alder adducts. In reaction with elemental sulfur or episulfides,[55,56] the symmetrical alkene ($EtO_2CCH{=}CHCO_2Et$) was formed by decomposition of the thioaldehyde. Treatment of thioaldehyde $S{=}CHCO_2Et$ with amines (e.g. ***Morpholine***) led to good yields of thioamides $R^1R^2NC(=S)CO_2Et$.[55a]

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Ethoxycarbonylmethyl Trifluoromethanesulfonate

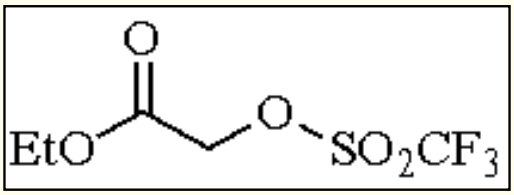

[61836-02-0] · $C_5H_7F_3O_5S$ · Ethoxycarbonylmethyl Trifluoromethanesulfonate · (MW 236.13)

(alkylation of sulfides,[1,3] amines,[2] and other nucleophiles;[3,4] in situ generation of ester-stabilized ylides via onium salt deprotonation[1,2,5-8])

Alternate Name: ethyl (2-trifluoromethylsulfonyloxy)acetate.

Physical Data: mp 22-23 °C.

Solubility: freely miscible with common organic solvents.

Form Supplied in: large colorless needles, refrigerator temperature; colorless liquid, room temperature.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$, δ) 1.35 (3 H, t, *J* = 7.0 Hz) 4.34 (2 H, q, *J* = 7.0 Hz) 4.98 (2 H, s).

Preparative Methods: from ***Ethyl Diazoacetate*** and ***Trifluoromethanesulfonic Acid***, or from ethyl glycolate and ***Trifluoromethanesulfonic Anhydride/Pyridine***.[3]

Purification: recrystallization from hexane at freezer temperatures.[3]

Handling, Storage, and Precautions: the reagent is a lachrymator. Like other moderately active alkylating agents, it should be treated as a potentially toxic agent. It can be stored for months under anhydrous conditions in the freezer as the frozen solid.

Onium Salt Formation.

The title reagent is used for the alkylation of sulfur or nitrogen compounds. It has an ca. 100-fold reactivity advantage over ethyl bromoacetate, and is a less potent lachrymator. It also has the advantage of the nonnucleophilic triflate counterion. The resulting ammonium or sulfonium salts are resistant to S_N2 dealkylation by the anion, a problem that

is often encountered with sulfonium bromides.[1] The initially formed onium salts are usually generated in situ and are treated with base to form the corresponding sulfonium or ammonium ylides. Synthetic applications focus on subsequent ylide fragmentation or rearrangement reactions.

Five-Center Ylide Fragmentation to Alkenes.

Alkylation of aminonitriles followed by deprotonation of the ammonium salt with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** results in the formation of unsaturated nitriles (eq 1).[2,5] The intermediate ammonium ylide (**1**) undergoes concerted α,α´-fragmentation. Good yields are obtained with aldehyde-derived aminonitriles (R^1 = H), but more highly substituted ylides (R^1 = alkyl) undergo competing homolytic C-N cleavage (Stevens rearrangement). Conversion of 2-dimethylaminocyclohexanone into cyclohexenone (68%) can be performed in the same way,[2] but fragmentation does not occur cleanly starting with unactivated amines $RCH_2CH_2NMe_2$. The five-center fragmentation is more facile using sulfides as starting materials (eq 2).[1,5] An activating group is not essential, but the five-center fragmentation is faster if an electron-withdrawing group is present at the α-carbon.[1]

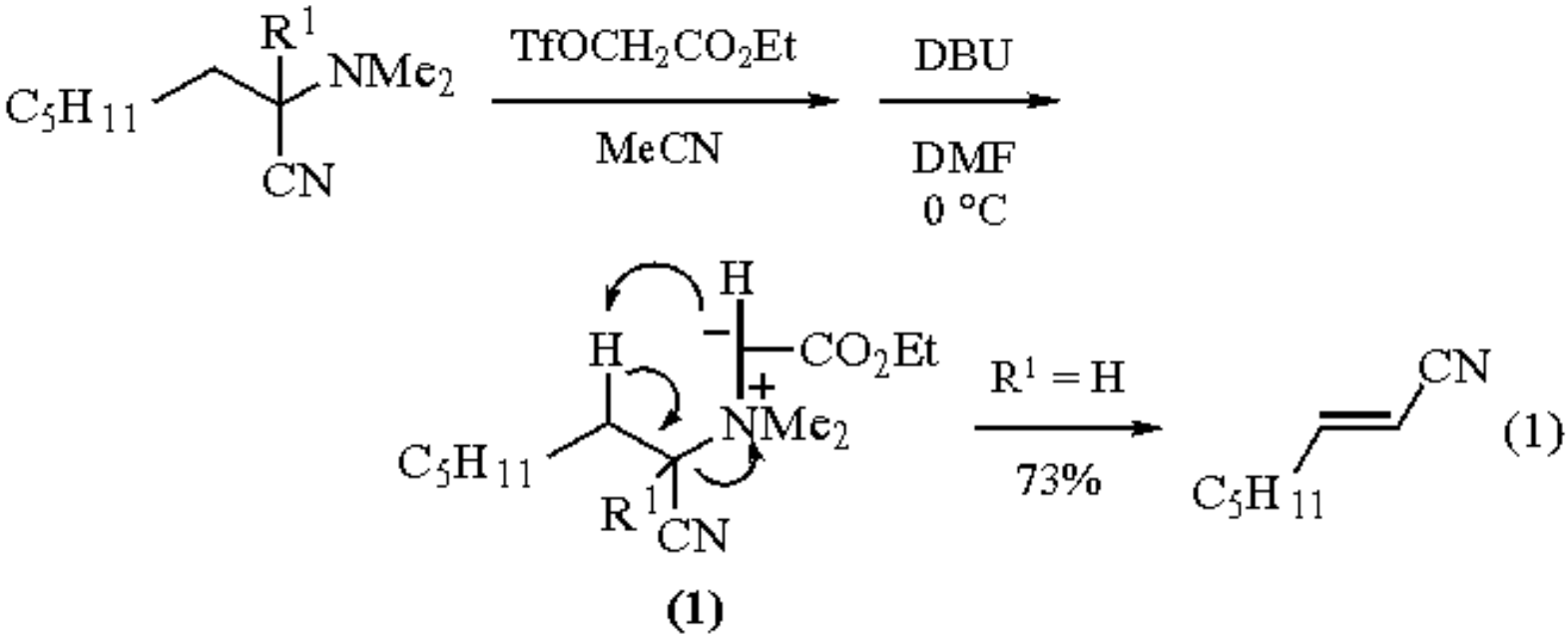

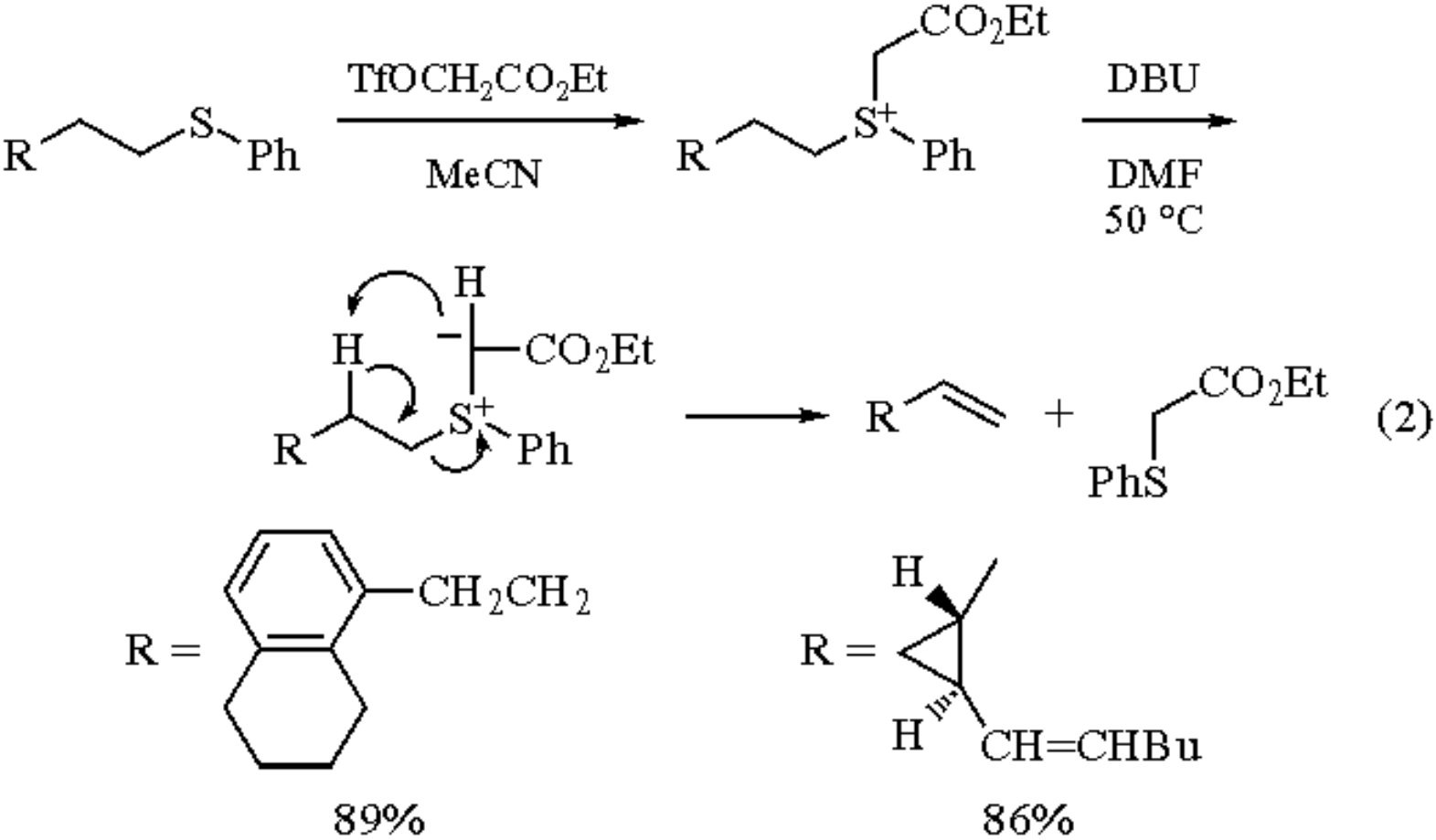

2,3-Sigmatropic Ring Expansion of Ylides.[6]

Medium ring sulfides or amines can be prepared from cyclic sulfides or amines having α-alkenyl or α-alkynyl substituents (eq 3).[6a] The intermediate onium salts are deprotonated with DBU, and the resulting ylides rearrange at room temperature or below. A similar ring expansion of a five-membered sulfide has been used in the early stages of a sulfur-based total synthesis of methynolide.[7].

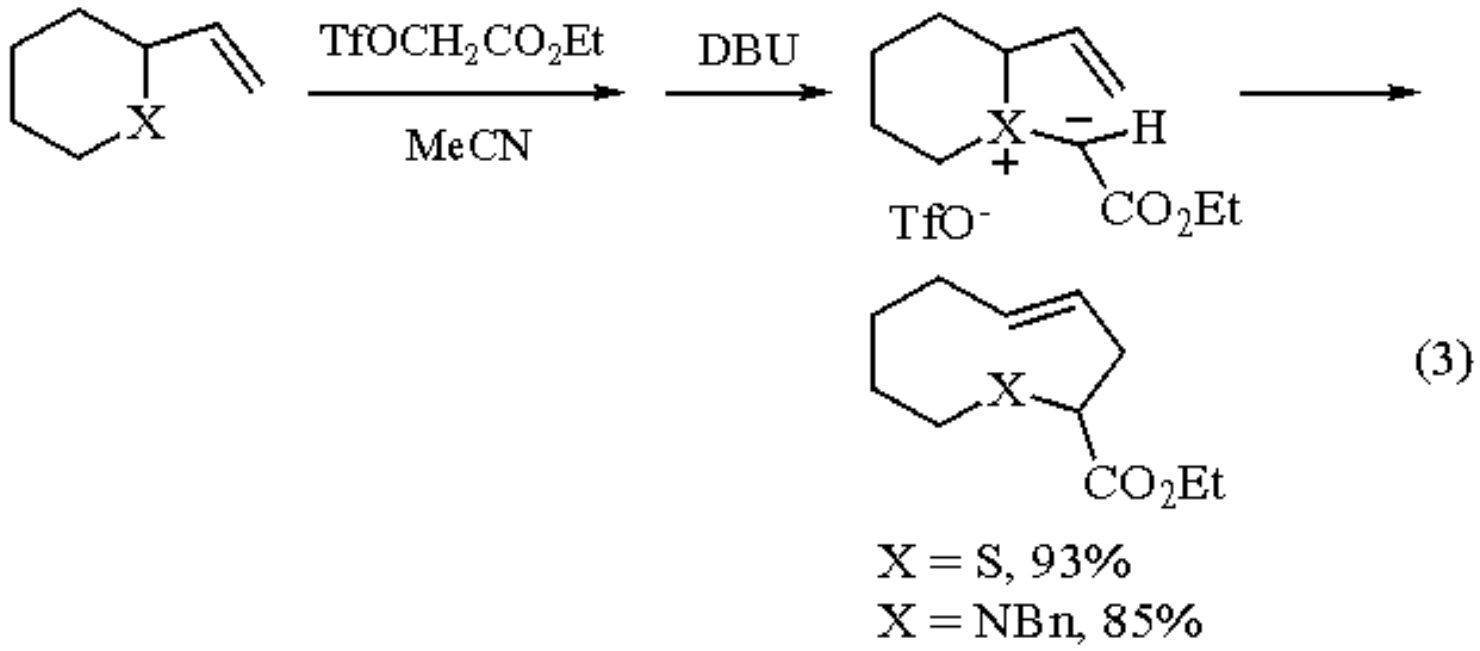

Keto Ester Synthesis by Sulfide Contraction.[8]

Thioamides are alkylated by ethoxycarbonylmethyl trifluoromethanesulfonate to give the salts (**2**) (eq 4). Treatment with a basic thiophile (**3**) results in the formation of a conjugated enamine (**5**) via the episulfide (**4**). Enamine hydrolysis with methanolic HCl affords the keto ester (**6**) (85% overall). A similar yield is obtained in this case using ethyl bromoacetate. However, the triflate has an advantage over the bromide if the α-methyl derivative is used.

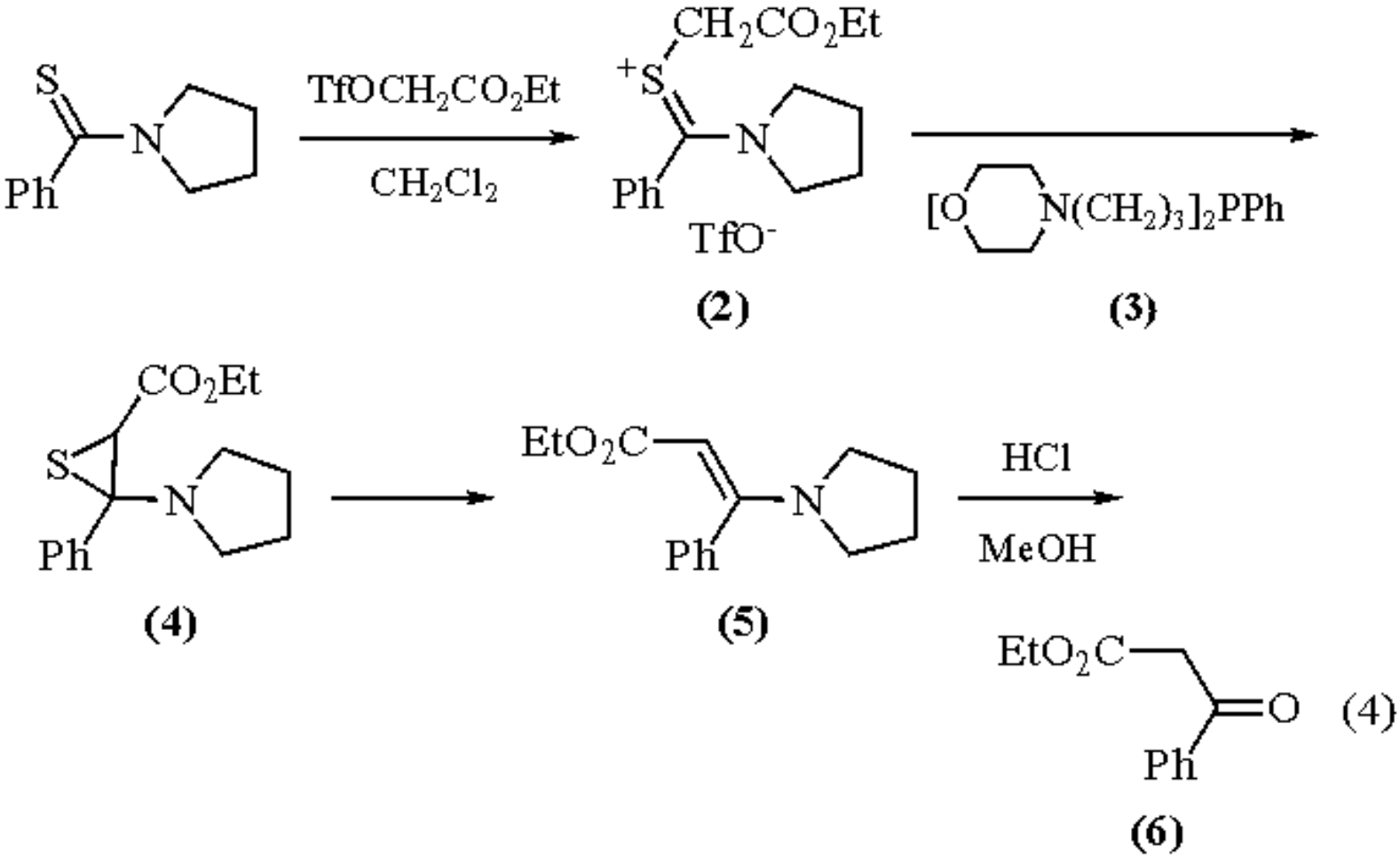

Miscellaneous Applications.

The title reagent has been used to alkylate imines.[4a,d,f] The reactivity advantage of the triflate by comparison with the α-bromo ester is increasingly important in more highly branched reagents such as $TfOCH(Me)CO_2R$.[4b,c,e] The latter can be used successfully in enolate alkylation reactions.

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(Ethoxycarbonylmethyl)triphenylphosphonium Bromide[1]

$Ph_3{+}PCH_2CO_2Et\ Br^-$

[1530-45-6] · $C_{22}H_{22}BrO_2P$ · (Ethoxycarbonylmethyl)triphenylphosphonium Bromide · (MW 429.30)

(precursor to $Ph_3P{=}CHCO_2Et$, a widely-used stabilized phosphorane;[2,3] Wittig reagent for the formation of α,β-unsaturated ethyl esters[2-4])

Physical Data: mp 158 °C (dec).

Solubility: sol water (10 g 100 mL^{-1}), EtOH (35 g 100 mL^{-1}), and $CHCl_3$ (55 g 100 mL^{-1}); insol THF (<1 g 100 mL^{-1}).

Form Supplied in: white, crystalline solid which can adopt a light pink tinge from dissociation of small amounts of HBr.

Handling, Storage, and Precautions: the compound is a mild irritant, due to the partial dissociation of HBr. Drying is not required for most synthetic applications. Storage at room temperature is adequate. Stable in water, but decomposes to triphenylphosphine oxide in 1.0 N NaOH ($t_{1/2}$ ca. 15 min).

Weakly Acidic Phosphonium Salt.

This compound is easily prepared by reaction of ***Triphenylphosphine*** and ethyl bromoacetate,[2,3] and has been mainly used as a precursor for $Ph_3P{=}CHCO_2Et$, formed by treatment with base (eq 1); see ***(Ethoxycarbonylmethylene)triphenylphosphorane*** and ***(Methoxycarbonylmethylene)triphenylphosphorane***).[2] The phosphorane is stabilized by both the ethoxycarbonyl group and d_π-p_π bonding to the adjacent phosphorus atom, and is a commonly employed Wittig alkenation reagent. The phosphonium bromide is somewhat acidic and can be deprotonated under weakly basic conditions (pK_a = 8.95-9.2).[5,6] Common bases employed are sodium alkoxides in alcohols,[3,4] aqueous sodium hydroxide,[7] and tertiary amines.[8]

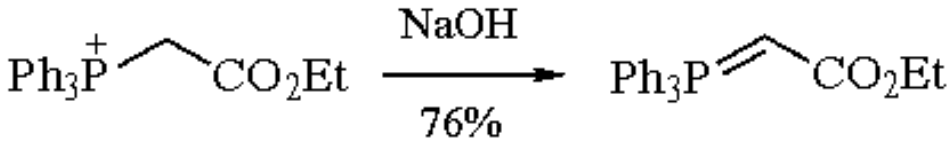

(1)

(Ethoxycarbonylmethylene)triphenylphosphorane has been generated in situ from the phosphonium bromide and utilized as

required, particularly during the first decade or so of general use of the Wittig reaction with aldehydes and ketones.[1-4] As an example, the phosphonium bromide was prepared from triphenylphosphine and ethyl bromoacetate and then treated with ***Sodium Ethoxide*** to form the phosphorane, which was reacted with α-fluoro ketones to afford α,β-unsaturated esters (eq 2).[4] The stereochemistry about the newly formed double bond in unsymmetrical alkenes is generally *trans* (*E*), as expected for reactions of stabilized phosphorus ylides, although there are many special conditions which enhance formation of the (*Z*) isomer.[1] (Ethoxycarbonylmethylene)triphenylphosphorane is now commercially available and can be stored without incident for prolonged periods, so that most chemists start with this reagent directly. The main advantage associated with the phosphonium bromide is that it is ca. 50% less expensive than the phosphorane on a molar basis. There is no special requirement for either the phosphonium bromide or the phosphorane to be absolutely dry when using them in Wittig alkenations, as trace amounts of water catalyze the reaction.[9] Large amounts of excess aqueous base hydrolyze the reagent, releasing triphenylphosphine oxide.

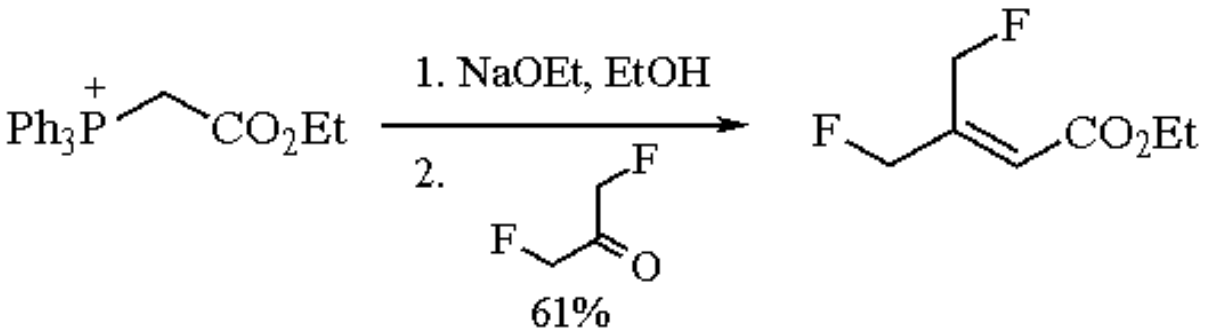

(2)

The phosphonium bromide can be prepared in situ and reacted directly with aldehydes in the presence of ***Ethylene Oxide*** (eq 3). The bromide counterion of the phosphonium salt opens ethylene oxide forming an alkoxide anion, which then deprotonates the α-carbon to form the phosphorane.[10]

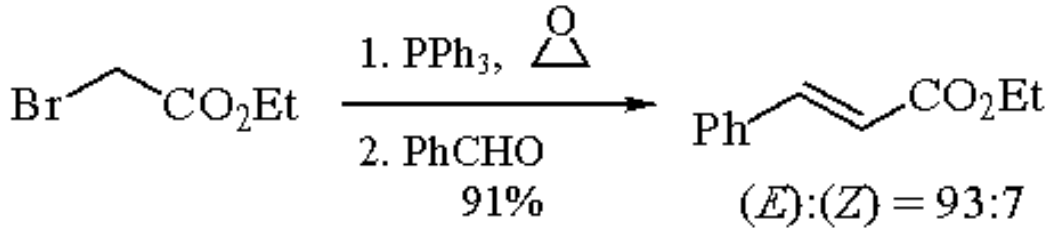

(3)

In addition to Wittig alkenations, the phosphonium bromide can be expected to substitute for (ethoxycarbonylmethylene)triphenylphosphorane in any of the other applications of the phosphorane, by in situ treatment of the phosphonium bromide with base.

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N-Ethoxycarbonylphthalimide

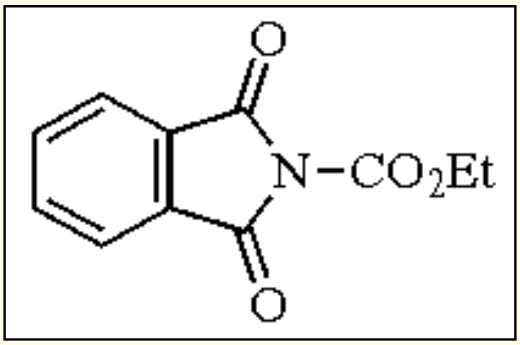

[22509-74-6] · $C_{11}H_9NO_4$ · *N*-Ethoxycarbonylphthalimide · (MW 219.20)

(phthaloylating agent selective for amines;[1] selective protection of amino acids[2] and amino alcohols[3])

Physical Data: mp 90-92 °C.

Solubility: sol DMF, benzene, THF, ether, chloroform; partially sol water, ethanol, isopropyl alcohol; insol petroleum ether.

Form Supplied in: crystalline (colorless).

Analysis of Reagent Purity: commercial material is >95% pure.

Preparative Methods: addition of ***Ethyl Chloroformate*** to a cold solution of ***Phthalimide*** and ***Triethylamine*** in DMF;[4] alkylation of potassium phthalimide with ethyl chloroformate.[5]

Purification: commercial product can be purified by recrystallization from ethanol, although some loss of material occurs due to ring opening. Synthetic material should be purified by the method of McArthur.[4] A 2 M solution of the crude material in chloroform is cooled overnight in a refrigerator and filtered to remove phthalimide. The solution is then concentrated to approximately 70% of the volume and an equal volume of petroleum ether is added. The crystals that form are collected and dried to give the desired *N*-ethoxycarbonylphthalimide.

Handling, Storage, and Precautions: no special handling conditions or precautions are required.

Phthaloylation of Amines.

The phthalimide protecting group has long been utilized for amines in organic synthesis.[6] While this group can be

introduced under a variety of conditions such as phthalic anhydride or ***Phthaloyl Dichloride***, these generally require drastic conditions and are not typically selective. The use of *N*-ethoxycarbonylphthalimide allows the phthaloylation of primary amines under mild conditions (eq 1).[7] Primary amines can be selectively protected in the presence of secondary amines (eq 2),[8] as well as amides and carbamates (eq 3).[9] The advantage of the phthalimido protecting group are its stability to both acid and mild base as well as the well known methods for selective removal with ***Hydrazine*** (eq 4)[10] or ***Phenylhydrazine*** (eq 5).[11]

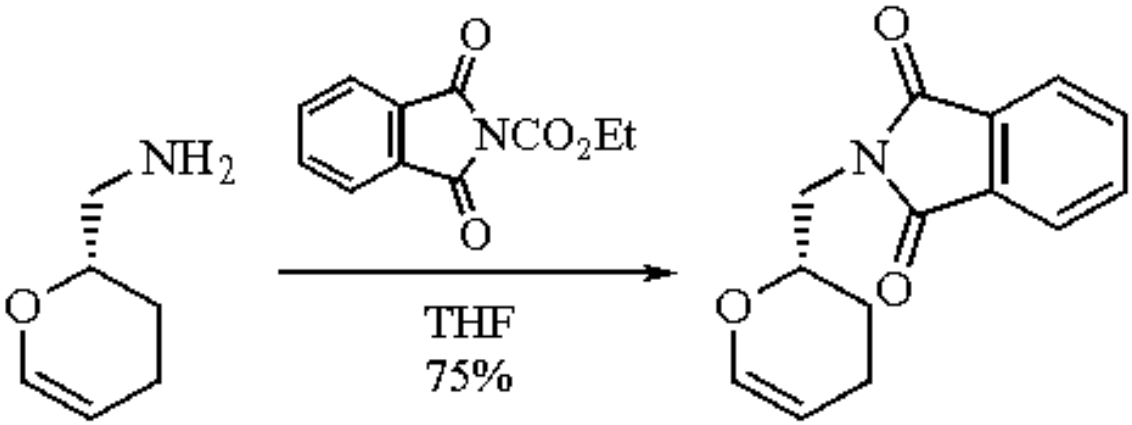

(1)

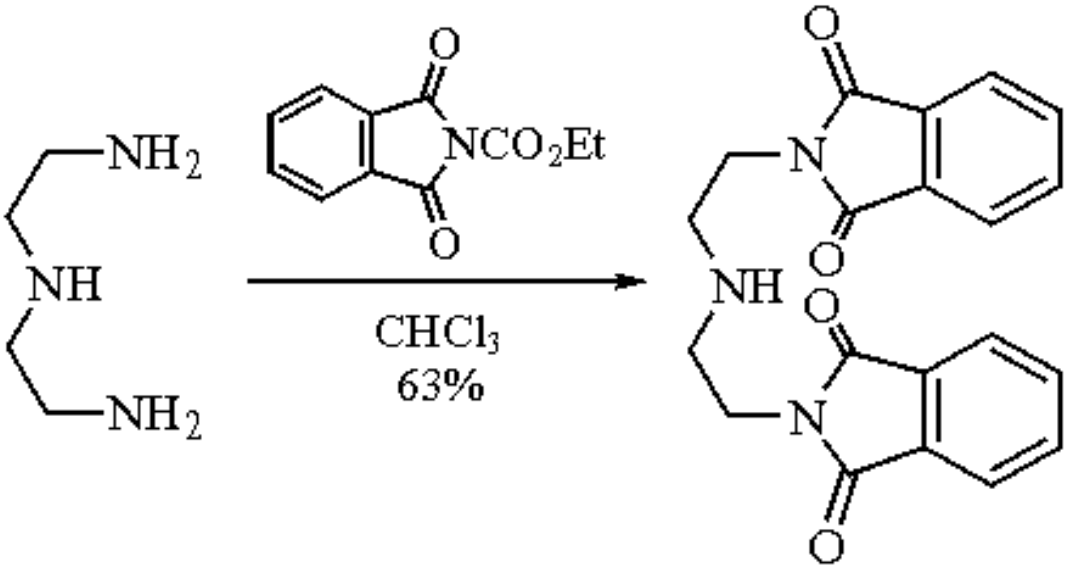

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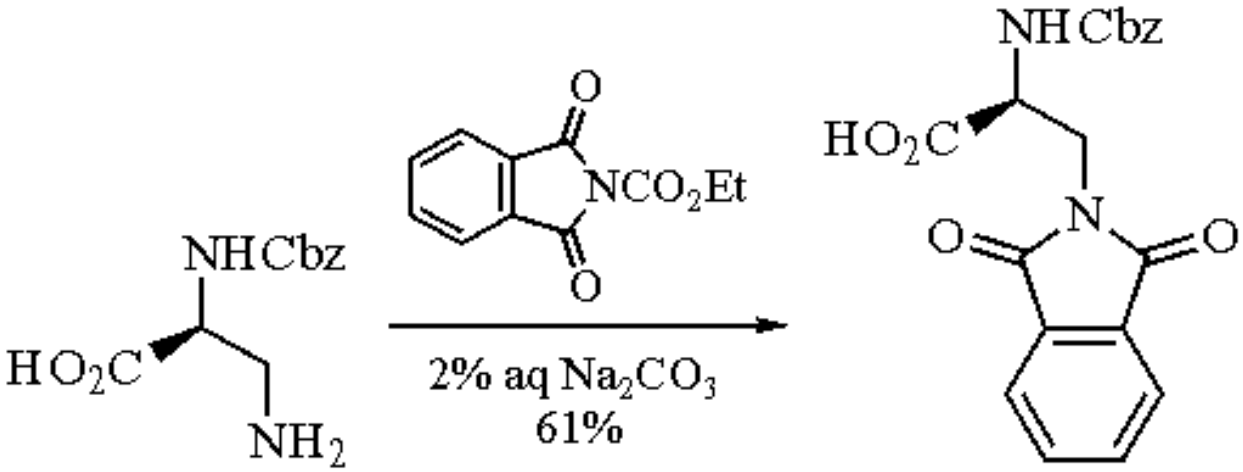

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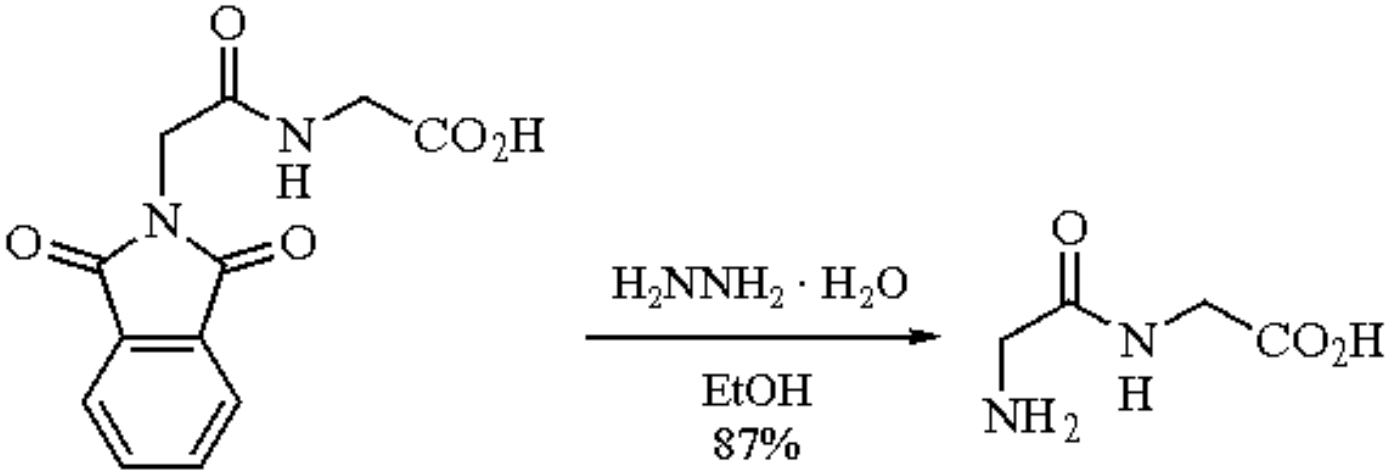

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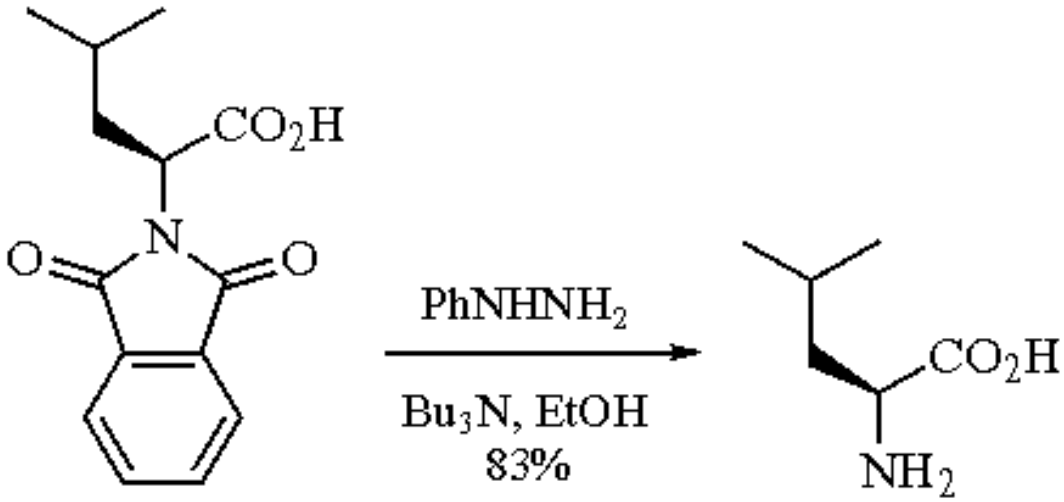

(5)

Selective Phthaloylation of Amino Acids.

In his attempt to develop a method for the selective amine protection of amino acids, Nefkens introduced *N*-ethoxycarbonylphthalimide.[5] He reported the protection of a variety of amino acids without racemization (eq 6).[2] These phthaloyl derivatives are typically highly crystalline, thereby facilitating purification. The phthaloylation of hindered amino acids such as valine could be achieved by initial deprotonation followed by protection in ethyl acetate (eq 7).[12] Recently, McArthur has shown that the aqueous conditions initially developed by Nefkens lead to the formation of undesired side products.[4] Heating *N*-ethoxycarbonylphthalimide in ethanol generates the corresponding carbamate (eq 8).[4] He has developed an alternative method for the phthaloylation of amino acids in THF that occurs in exceptional yields without racemization (eq 9).[1] These protections can be performed on amino acids with a variety of sensitive functionalities such as hydroxyl groups (eq 10)[2] or halogens without reaction at these centers (eq 11).[13]

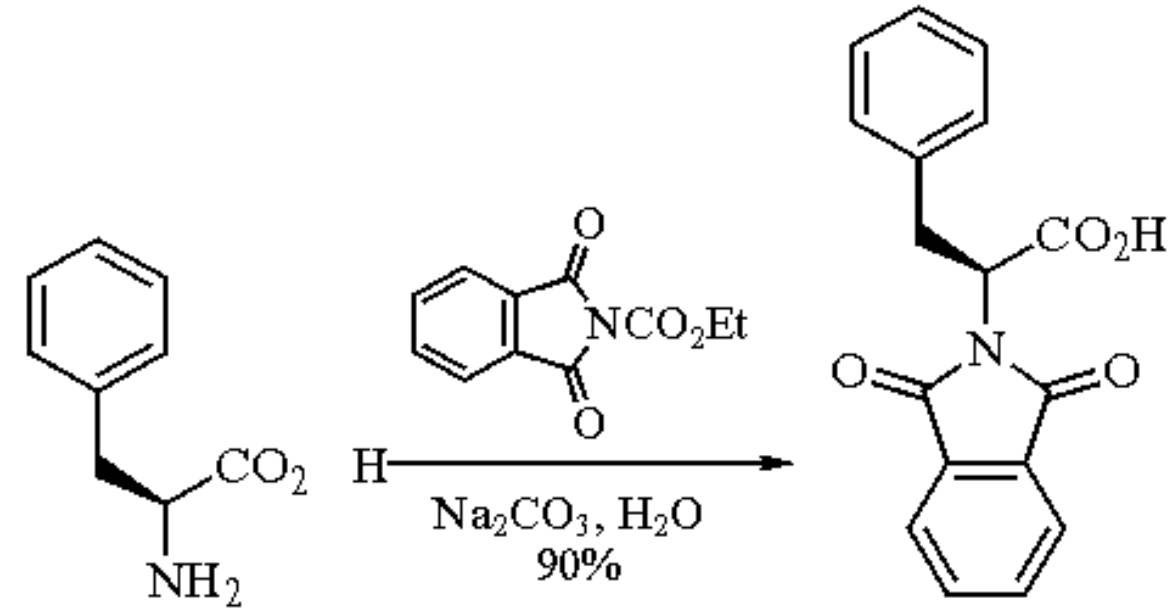
O
NCO2Et
O
CO2H
N
O
O
CO2
H
Na2CO3, H2O
90%
NH2

(6)

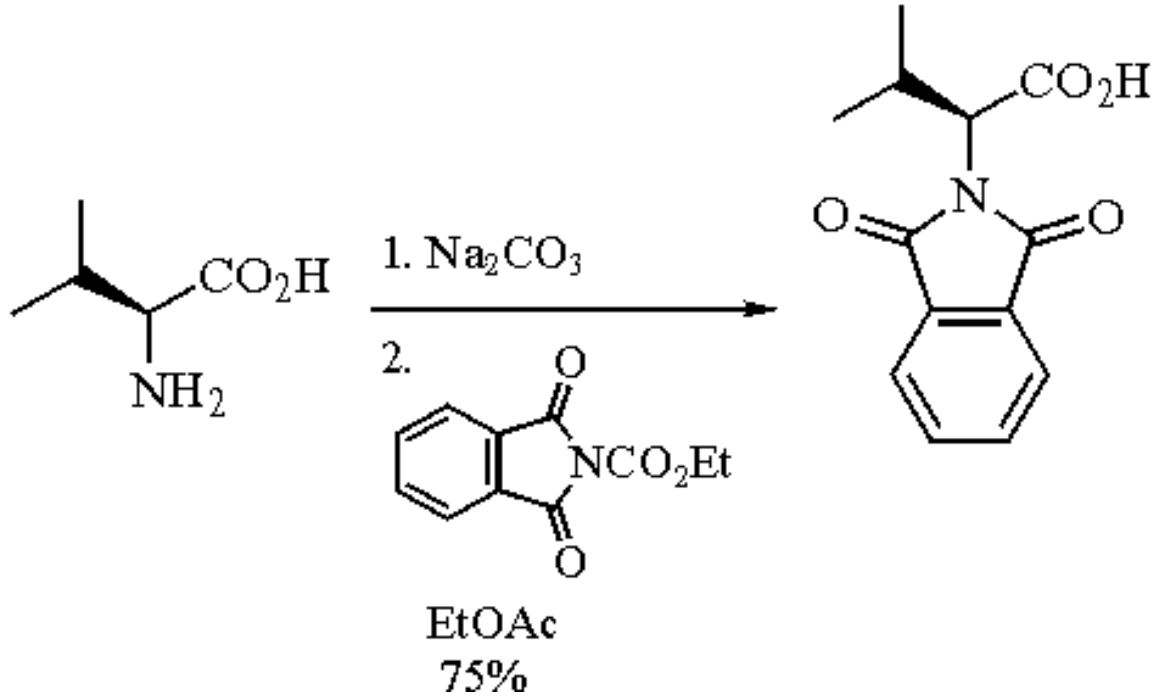
CO2H
N
O
O
CO2H
1. Na2CO3
2.
O
NCO2Et
O
NH2
EtOAc
75%

(7)

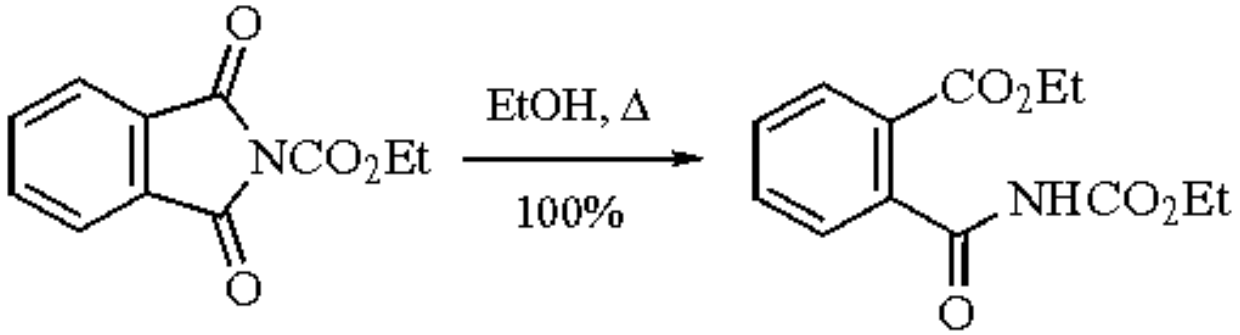
O
NCO2Et
O
EtOH, Δ
100%
CO2Et
NHCO2Et
O

(8)

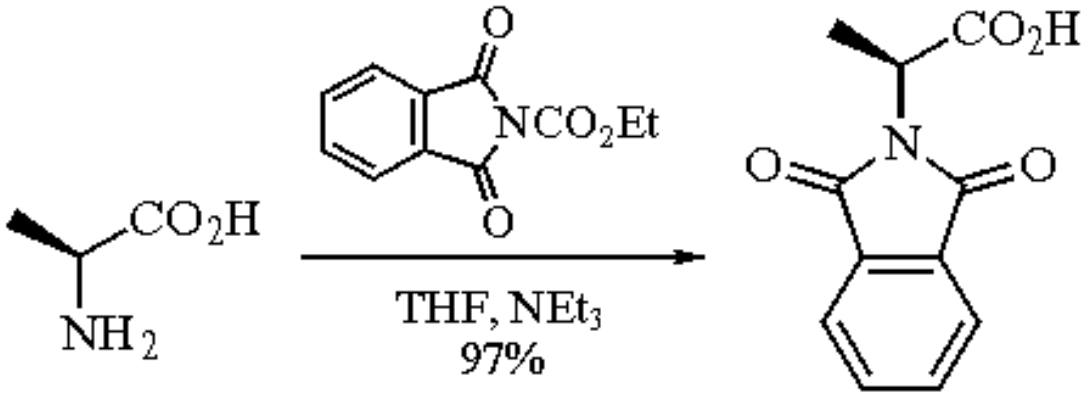

(9)

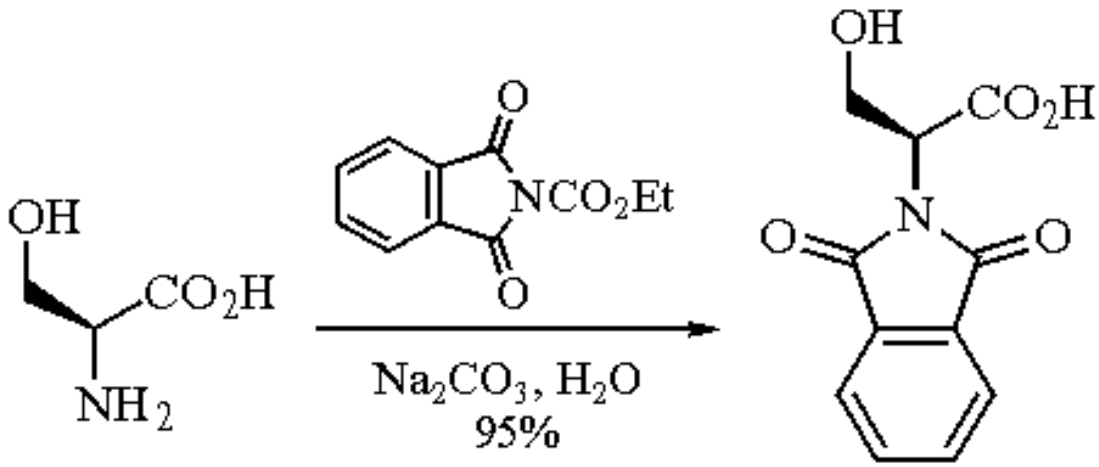

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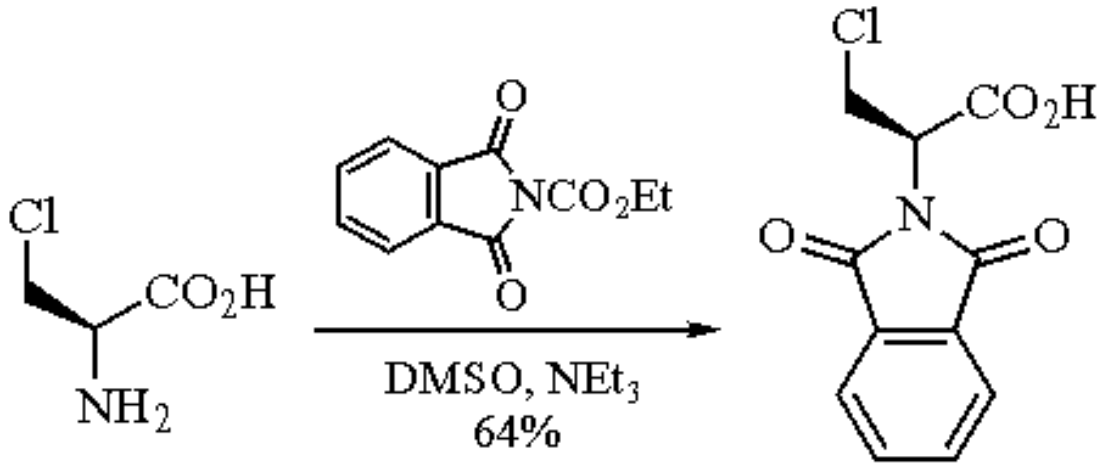

(11)

Phthaloylation of Amino Alcohols.

The use of *N*-ethoxycarbonylphthalimide to protect amino alcohols has also been demonstrated (eq 12).[3]

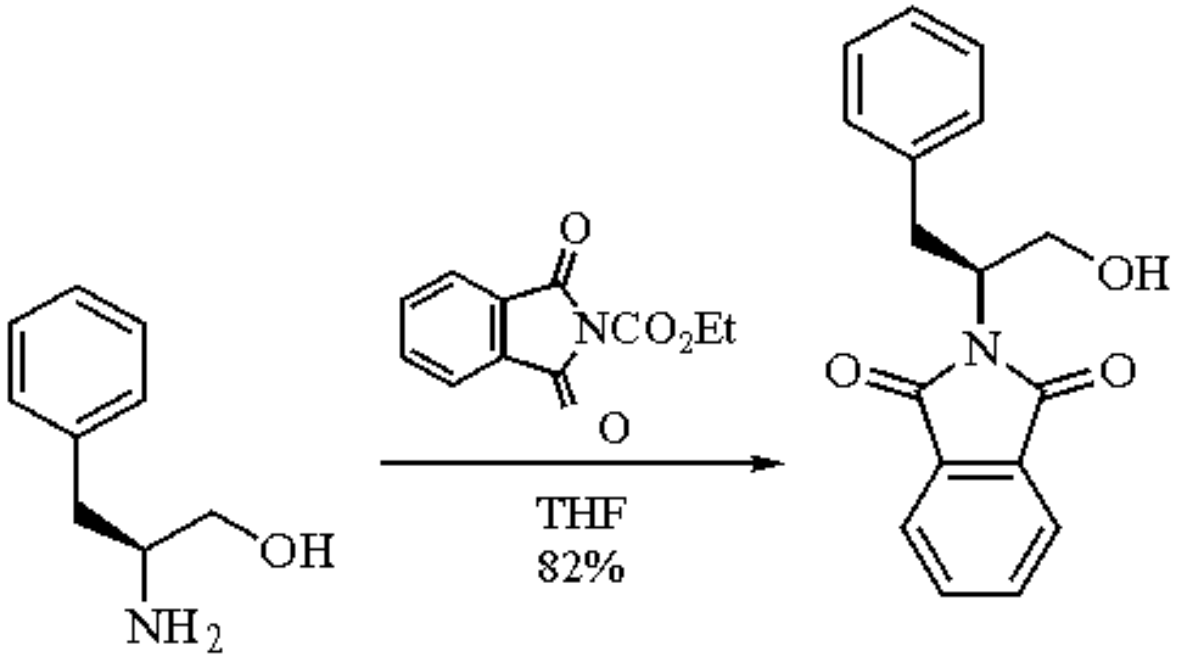

(12)

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1-Ethoxycyclopropanol[1]

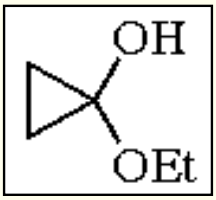

[13837-45-1] · $C_5H_{10}O_2$ · 1-Ethoxycyclopropanol · (MW 102.07)

(homoenolate formation, ring expansion to β-lactams and pyrrolines via 1-aminocyclopropanols, to cyclobutanones via 1-vinylcyclopropanols, and to cyclopentanones via 1-trimethylsiloxy-1-vinylcyclopropanes[1])

Physical Data: bp 60 °C/20 mmHg.

Solubility: sol usual organic solvents (ether, THF, CH_2Cl_2).

Preparative Methods: acyloin-type reaction of ethyl 3-halopropionates with highly dispersed ***Sodium*** (or ***Lithium***) in refluxing Et_2O in the presence of ***Chlorotrimethylsilane*** provides 1-ethoxy-1-trimethylsiloxycyclopropane in high yields.[2,3] Use of sonochemical activation simplifies the procedure.[4] Then, simple methanolysis (MeOH, $ClSiMe_3$) leads to the hemiacetal (eq 1).

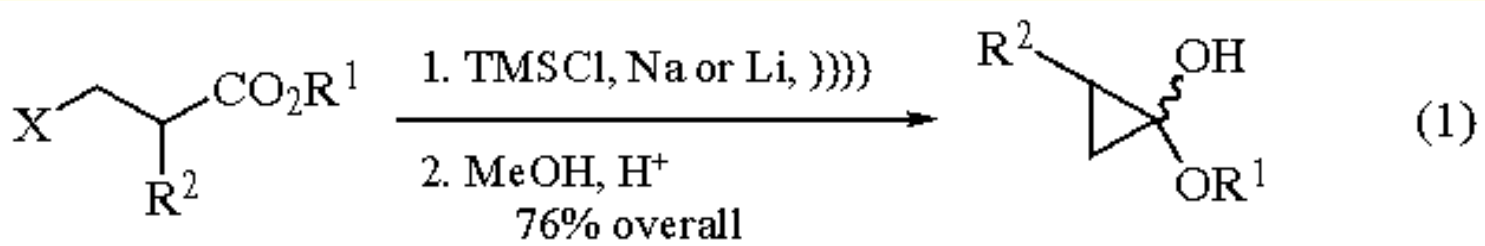

Cyclization of optically pure β-halo esters gives enantiomerically pure cyclopropanes at C-2 and a 1:1 diastereomeric mixture at C-1.[5]

Handling, Storage, and Precautions: can be kept unaltered for several months at 0 °C. On heating at 100 °C, or on standing in acidic solvents, it undergoes ring opening to ethyl propionate.

Preparation and Reactions of Isolable Metal Homoenolates.

With metals (Ti, Hg, Zn, Sn, Bi, Sb, Te, Nb, etc.), siloxycyclopropanes afford reactive homoenolate species which are stable enough for isolation and characterization.[1b] For instance, an exothermic reaction occurred with ***Titanium(IV) Chloride*** to provide fine violet needles of a titanium species in 89% yield (eq 2).[1b]

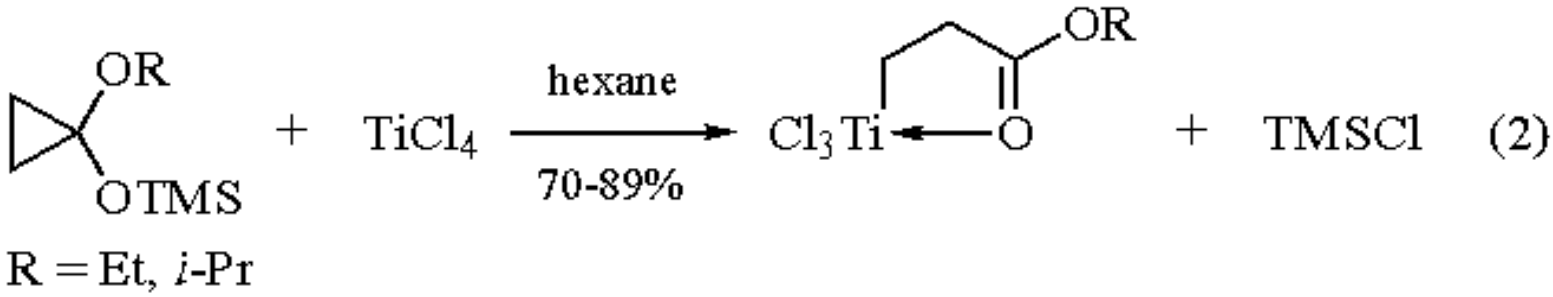

Many examples of carbon-carbon bond formation from metal homoenolates with various electrophiles have been reported. Thus reaction of zinc homoenolates with acid chlorides in ethereal solvents containing 2 equiv of HMPA produces γ-keto esters in high yield (eq 3).[6] Palladium catalysis accelerates the reaction.[7]

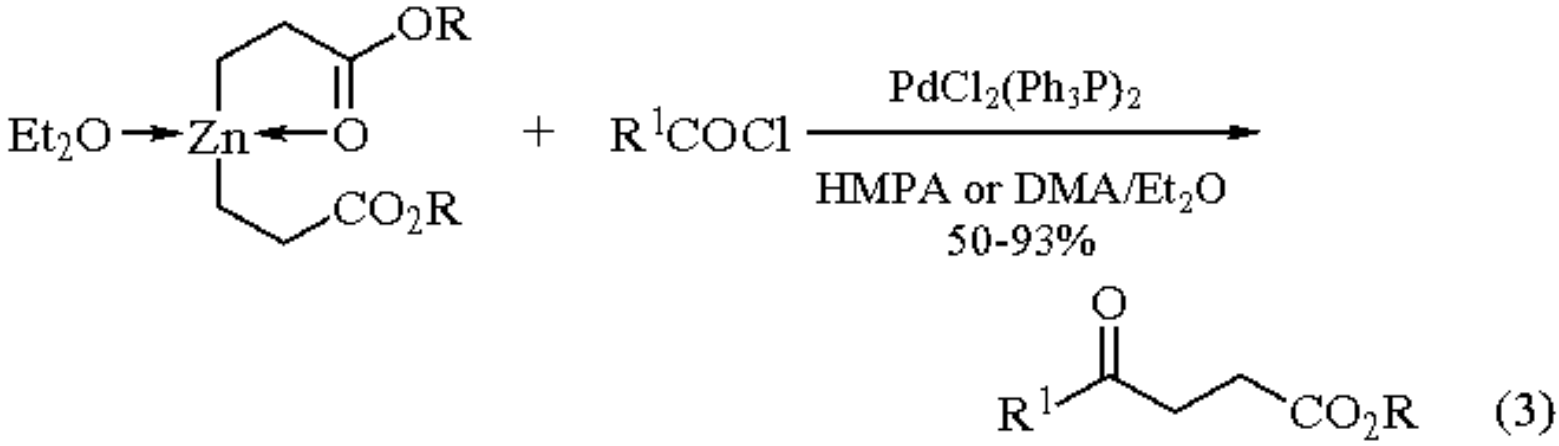

In a polar solvent, treatment of zinc homoenolates with Me_3SiCl results in cyclopropane formation.[1b] Palladium homoenolates, from siloxycyclopropanes and ***Palladium(II) Chloride*** or its phosphine complex, can also serve as useful reaction intermediates.[8]

Reactivity and Synthetic Applications.

Ring expansion of properly activated cyclopropanes is now one of the major methods of forming cyclobutane derivatives.[1] Thus, addition of vinylmagnesium halides to the cyclopropanone hemiacetal provides 1-vinylcyclopropanols,[9] which on simple heating at 100 °C in liquid phase or by reaction with a variety of electrophilic reagents (HBr, $PhCO_3H$, *t*-BuOCl, etc.), undergo quantitative C_3 -> C_4 ring expansion to substituted cyclobutanones, thus providing convenient intermediates for the creation of a wide range of structural building blocks (eq 4).[1a,c] For instance, Baeyer-Villiger oxidation leads to γ-butyrolactones,[10] and reaction with sodium azide in buffered acetone provides γ-lactams.[9]

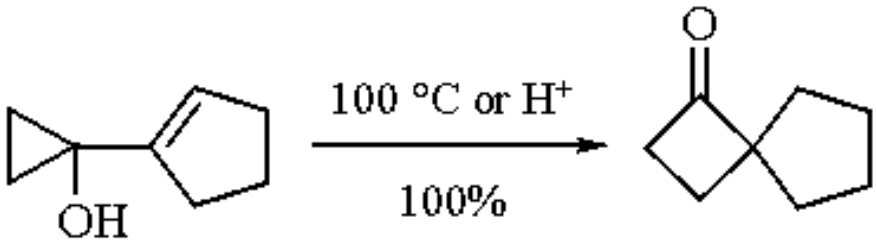

(4)

Conversely, *O*-silylation ($ClSiMe_3$, NEt_3, 5% DMSO)[11] affords 1-siloxy-1-vinylcyclopropanes, which undergo thermal vinylcyclopropane-cyclopentene rearrangement to 1-silyloxycyclopentenes exclusively (eq 5).[1]

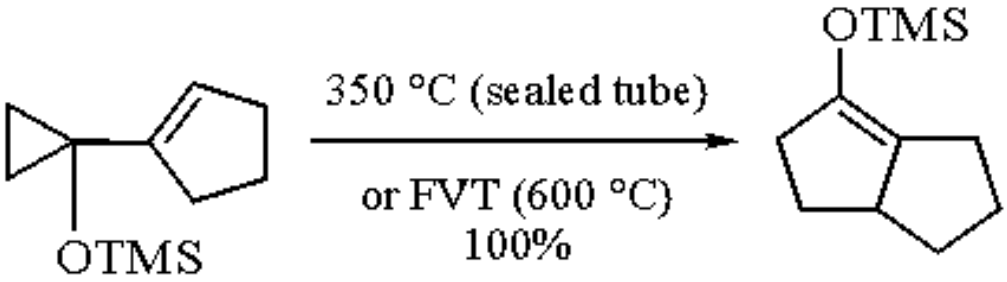

(5)

Acid or basic hydrolysis gives 2-substituted cyclopentanones. Alternatively, the generation of corresponding lithium enolates (***Methyllithium*** in Et_2O) followed by α-alkylation produces α,β-disubstituted cyclopentanone derivatives, which constitute the basic framework of several natural products of biological importance.[12] For instance, the total synthesis of (±)-11-deoxyprostaglandin E_2 has been performed from the cyclopropanone hemiacetal, via the thermal C_3 -> C_5 ring expansion of a suitable 1-butadienyl-1-trimethylsiloxycyclopropane (eq 6).[13]

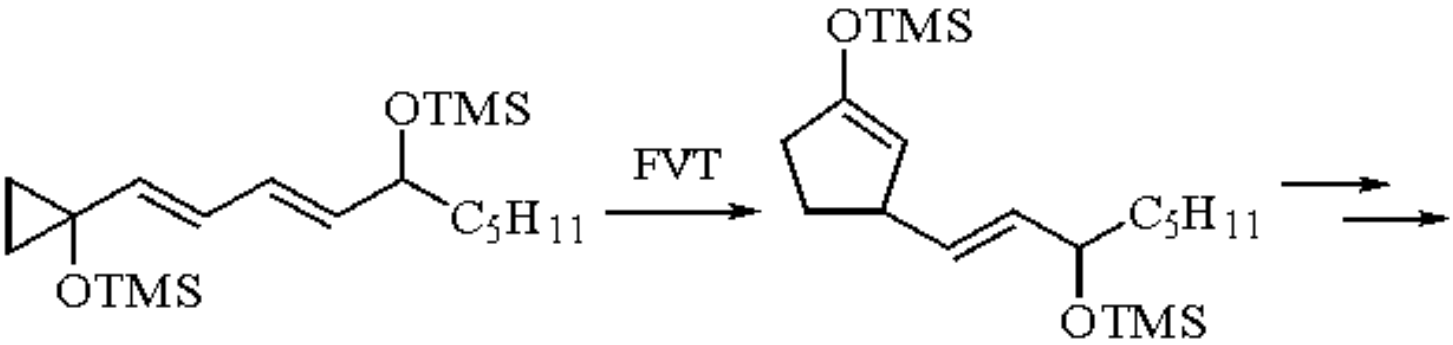

PGE_2 (6)

Reaction of enolates with the cyclopropanone hemiacetal magnesium salt led to substituted hydrazulenones.[14] β-Amino esters are formed on photolysis of ***Ethyl Azidoformate*** and 1-ethoxy-1-trimethylsiloxycyclopropane in MeCN.[15] Treatment of 1-alkoxy-1-siloxycyclopropane with a catalytic amount of palladium-phosphine complex in $CHCl_3$ under carbon monoxide atmosphere gives 4-ketopimelate.[8a] Arylation of siloxycyclopropanes by aryl triflates is effected by palladium catalysis.[8b] Inactivation of cytochrome P-450 by heteroatom-substituted cyclopropanes has been interpreted by the ring opening of a cyclopropanone hemiacetal to ethyl 3-hydroxypropionate.[16]

1-Vinylcyclopropyl sulfonates and allylically isomeric 2-cyclopropylidenethyl carbonate and acetate, which are readily available from the cyclopropanone hemiacetal, undergo regioselective palladium(0)-catalyzed nucleophilic substitutions. With stabilized anions Nu^1 (e.g. enolates of malonic esters or β-dicarbonyl compounds), the substitution

occurs *exclusively* at the terminal vinylic position providing cyclopropylidene derivatives; on the other hand, use of organometallic or hydride reagents Nu^2 (e.g. ***Phenylzinc Chloride***) entails tertiary substitution on the cyclopropane ring *exclusively* (eq 7).[17]

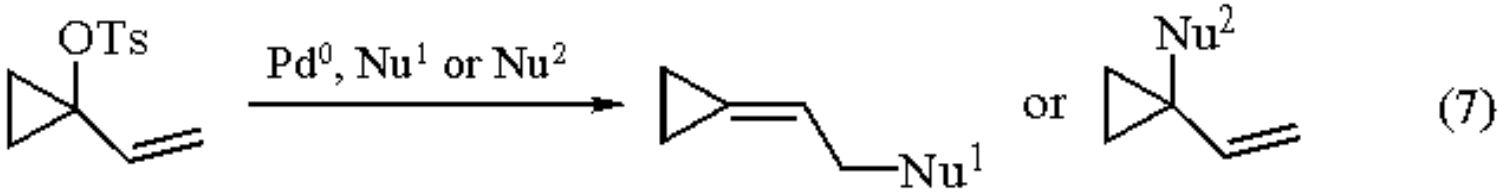

Related Reagents.

Cyclopropanone; ***Cyclopropenone 1,3-Propanediyl Acetal***; ***1-Ethoxy-1-(trimethylsilyloxy)cyclopropane***; ***1-(Tetrahydropyranyloxy)cyclopropanecarbaldehyde***.

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2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

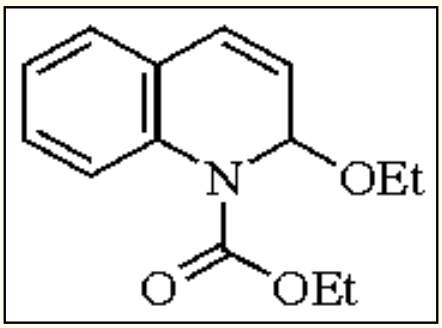

[16357-59-8] · $C_{14}H_{17}NO_3$ · 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline · (MW 247.29)

(activating agent used in peptide synthesis)

Alternate Names: ethyl 1,2-dihydro-2-ethoxy-1-quinolinecarboxylate; EEDQ.

Physical Data: mp 66-67 °C; bp 125-128 °C/0.1 mmHg.

Solubility: sol water, alcohol.

Form Supplied in: white powder; widely available and can be easily prepared.[1]

Peptide Synthesis.

In peptide synthesis, peptide bonds are created from the activated carboxylic group of a N^{α}-protected amino acid that is reacted with the nucleophilic free amino group of another amino acid (eq 1).

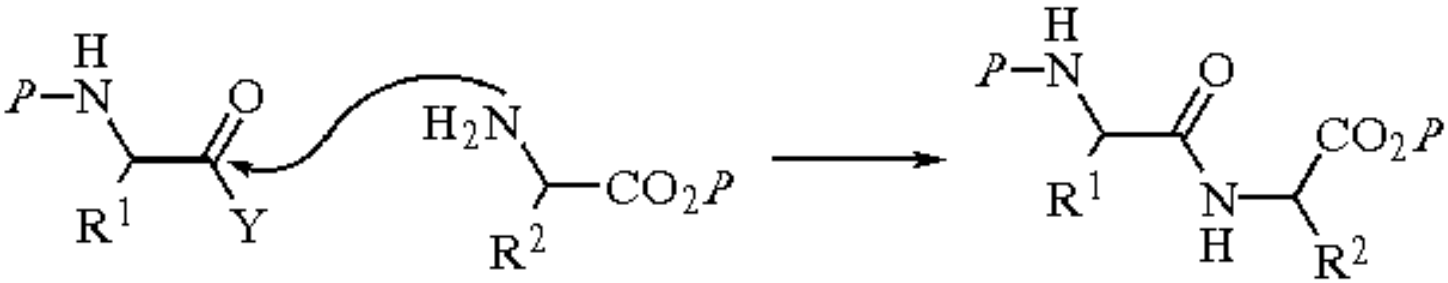

(1)

Activation of the carboxylic acid can be performed according to several strategies, leading mainly to two kinds of intermediates: active esters and acid anhydrides, which can be either symmetrical anhydrides or mixed anhydrides.

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

EEDQ is a reagent used in peptide synthesis for the mixed carbonic anhydride strategy. It allows a slow formation of unsymmetrical anhydrides under very mild conditions (eq 2).[2]

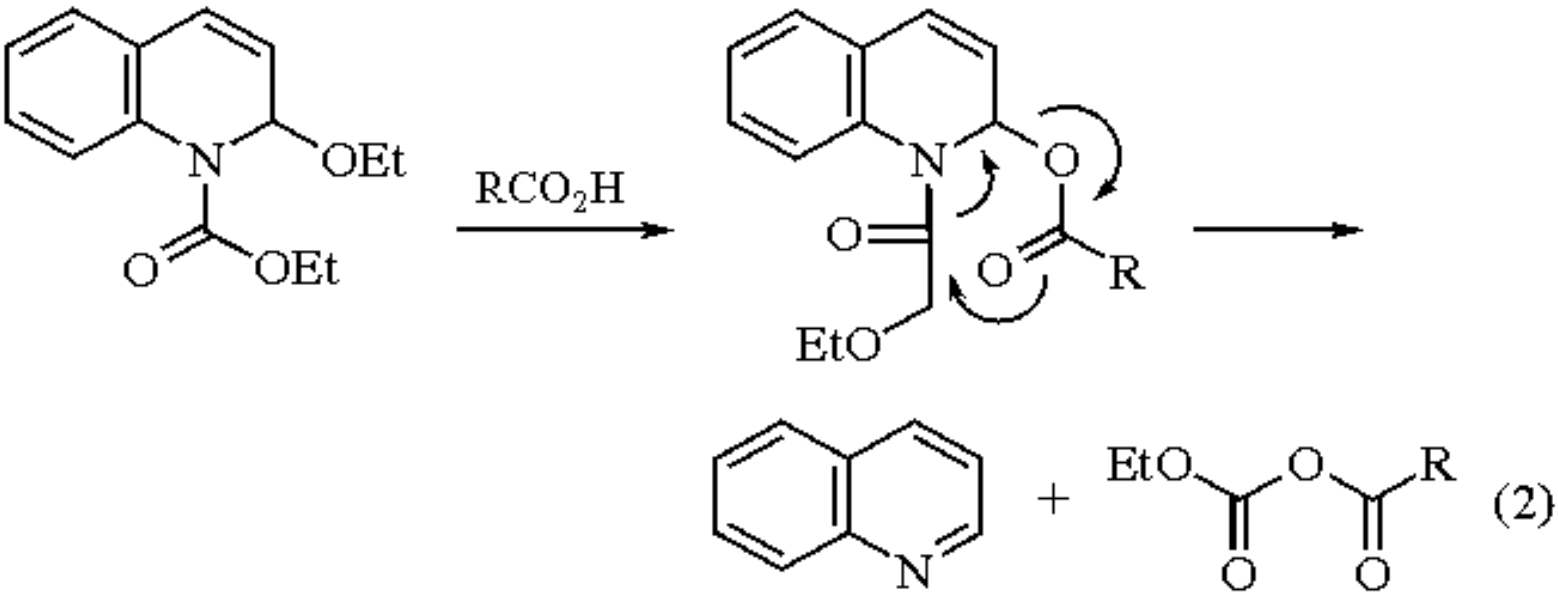

Faster reaction of the mixed anhydride with nucleophilic species reduces the extent of side reactions that occur with high concentration of the anhydride (eq 3).[3]

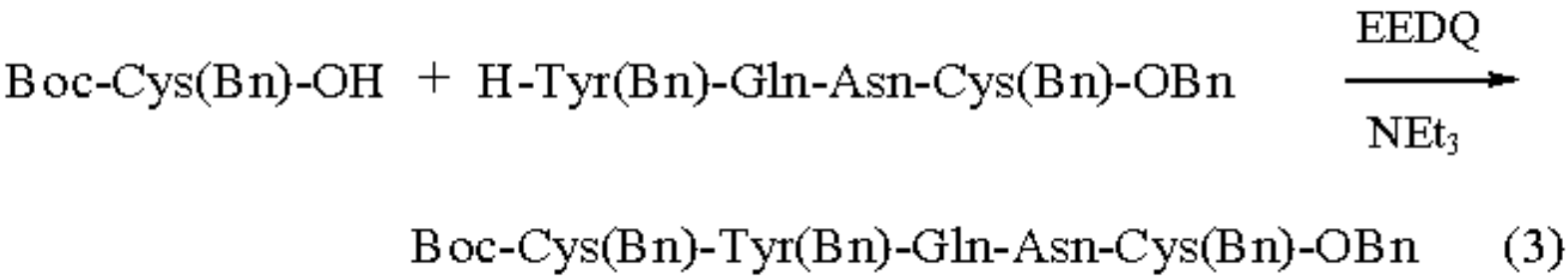

The tendency to racemization is limited to a small extent. Nevertheless, wrong-side attack, leading to the formation of urethane, is not suppressed (eq 4).[4]

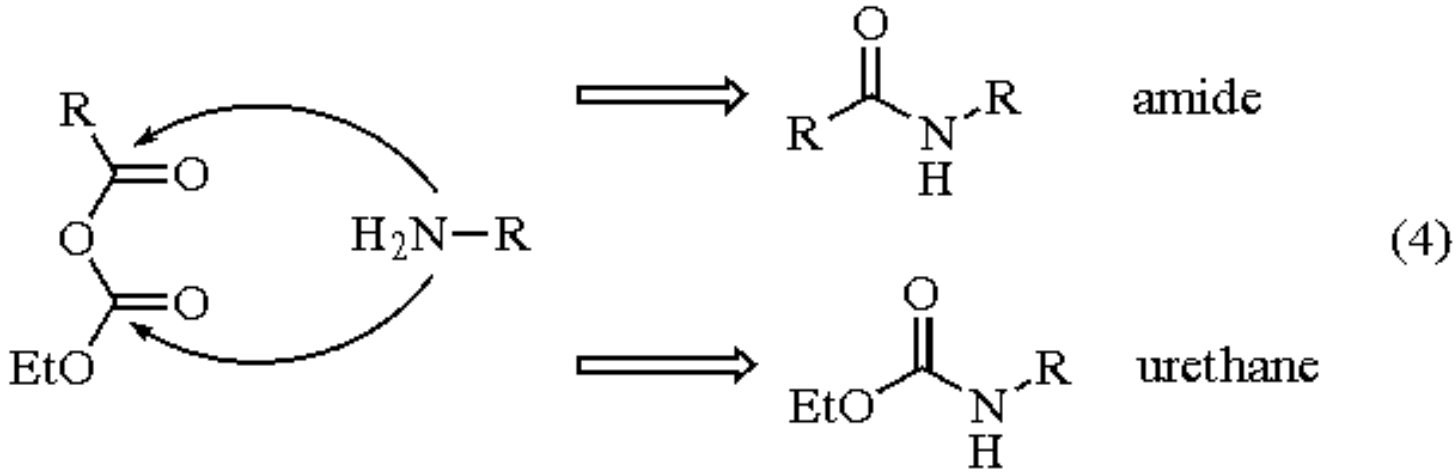

2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline

As best results had been obtained with mixed anhydrides of ***Isobutyl Chloroformate***, probably because the isobutyl group decreases the amount of urethane products, IIDQ (**1**), an analog of EEDQ, has been proposed for use in peptide synthesis.[5,6]

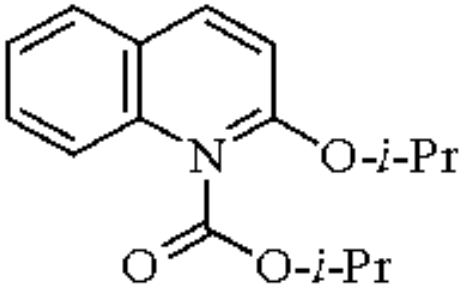

(1)

As another alternative, EEDQ has been linked to a polymeric support, providing a supported coupling reagent in high yield (eq 5).[7]

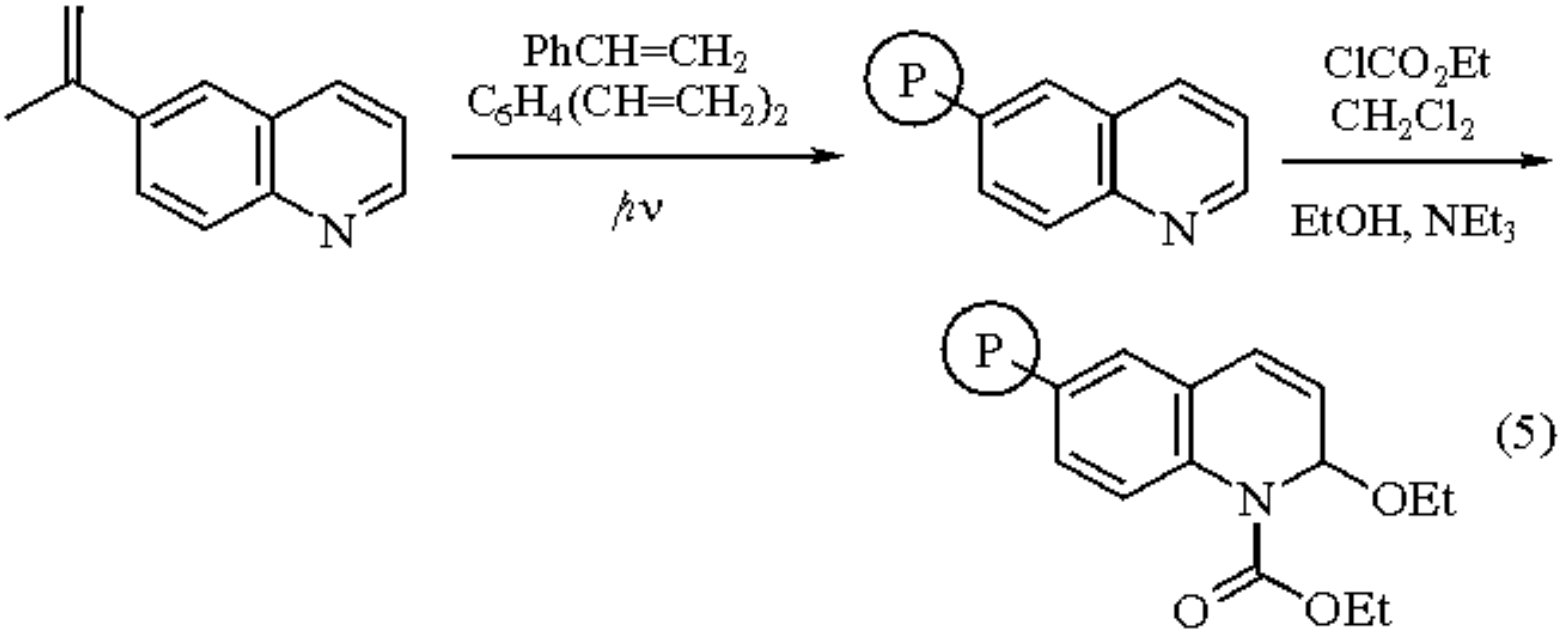

(5)

Coupling reactions mediated by this reagent occur cleanly in high yield and with a low degree of racemization, comparable with that observed with EEDQ itself.[8] Nevertheless, the use of EEDQ in peptide synthesis is rather limited, other coupling reagents being very much more popular. Examples are: the carbodiimides, mainly ***1,3-Dicyclohexylcarbodiimide*** and diisopropylcarbodiimide; the family of BOP reagents such as ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate***; uroniums such as ***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate*** (HBTU), or urethane *N*-protected carbonic anhydrides (UNCA), and active esters.

---

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3-(1-Ethoxyethoxy)propyllithium

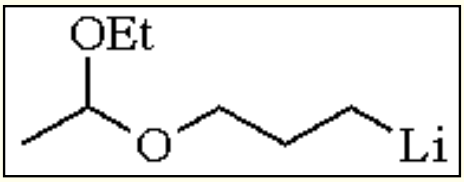

[37494-03-4] · $C_7H_{15}LiO_2$ · 3-(1-Ethoxyethoxy)propyllithium · (MW 138.14)

(nucleophilic organolithium reagent used as synthetic equivalent of 3-hydroxypropyl anion)

Solubility: normally prepared in diethyl ether and used in situ.

Handling, Storage, and Precautions: organolithium reagent sensitive to moisture; normally used immediately, but filtered 1 M solutions may be stored for months at -30 °C.

Nucleophilic Additions.

This reagent (referred to below as EEOPrLi), like the analogous Grignard reagent, is normally used in synthetic chemistry as a synthon for the 3-hydroxypropyl anion. The reagent, developed by Eaton for this purpose and first reported in 1972,[1] is normally prepared in ca. 1 M ethereal solution by treatment of the bromide with ***Lithium*** wire or shot at ca. -5 to -15 °C after initiation at room temperature. The cloudy solution may be used immediately, or may be passed through a sintered glass funnel to give a crystal clear solution which may be stored at -30 °C for months. At room temperature, slow decomposition occurs to give cyclopropane, among other products. The 3-(1-ethoxyethoxy)propyl bromide starting material may be prepared on a large scale by the dichloroacetic acid catalyzed solvent-free addition of acid-free 3-bromopropanol to ***Ethyl Vinyl Ether***.

Addition of the prepared reagent, unlike its Grignard counterpart,[1] takes place readily to ketones and aldehydes at 0 °C or lower under typical conditions for organolithium reagents. Treatment with aqueous acid or ***Pyridinium p-Toluenesulfonate*** after simple workup readily induces hydrolysis to liberate the free alcohol together with the volatile byproducts ethanol and acetaldehyde and without affecting the newly introduced tertiary alcohol. Heating with acid causes cyclodehydration to produce the tetrahydrofuran, while simple oxidation, for example with ***Chromium(VI) Oxide***, generates the γ-lactone.[1,2] These transformations are illustrated for cyclohexanone (eq 1).

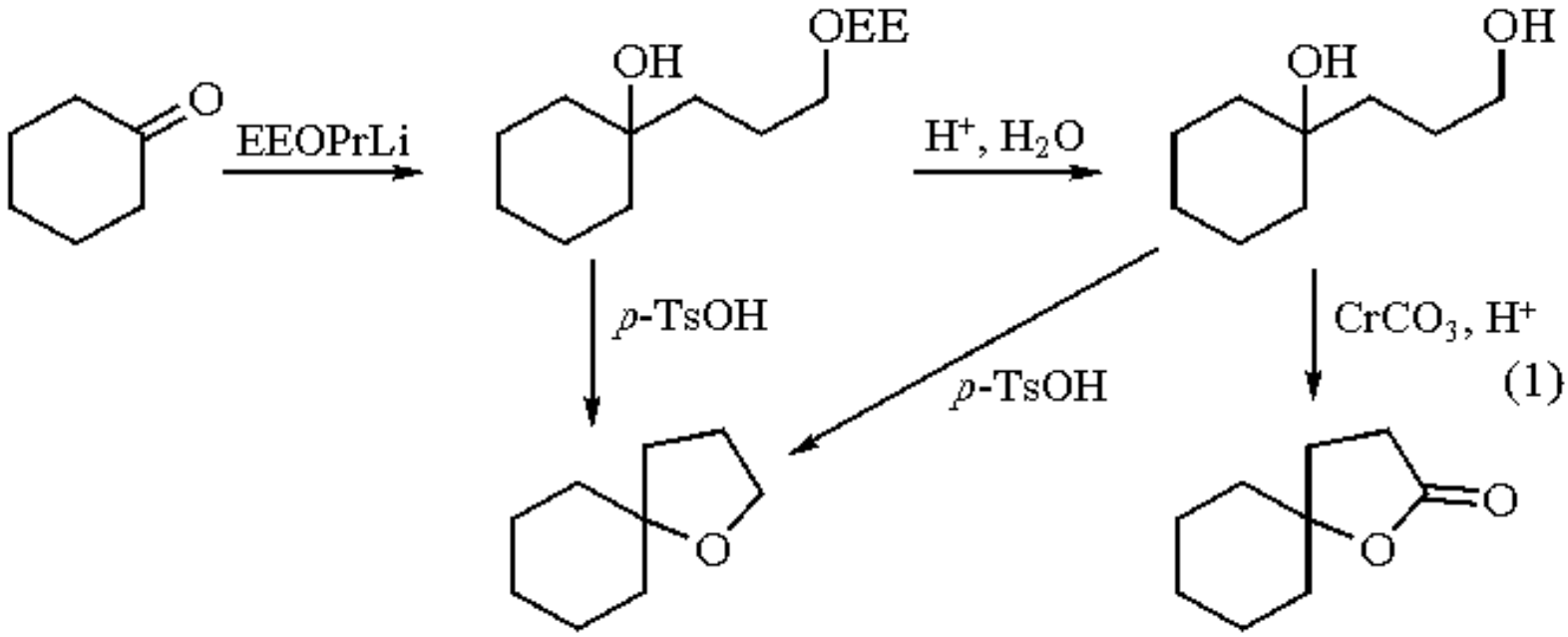

Eaton has used the addition to 2-octanone followed by hydrolysis and oxidation to the γ-lactone in his synthesis of dihydrojasmone (eq 2).[1]

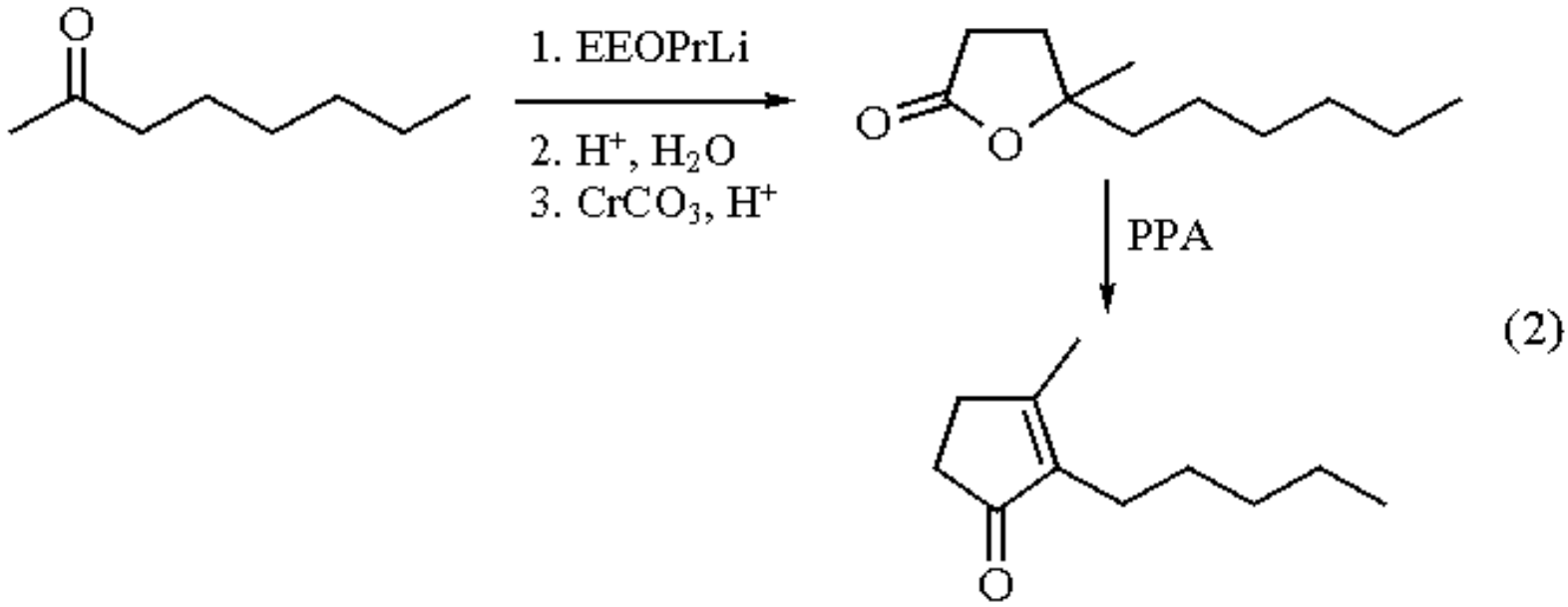

The reagent has also been shown to add to lactones, addition to γ-caprolactone followed by hydrolysis with HCl leading to cyclization to spiroacetals (eq 3).[3]

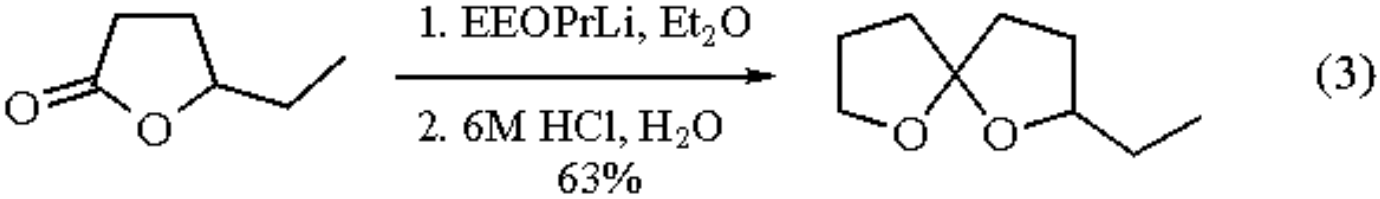

Addition to substituted pyridines takes place to give the 2-(3-hydroxypropyl) derivatives, both in rearomatized form

after aerial oxidation (eq 4)[4] and as the dihydropyridine by trapping with ***Ethyl Chloroformate*** (eq 5).[5]

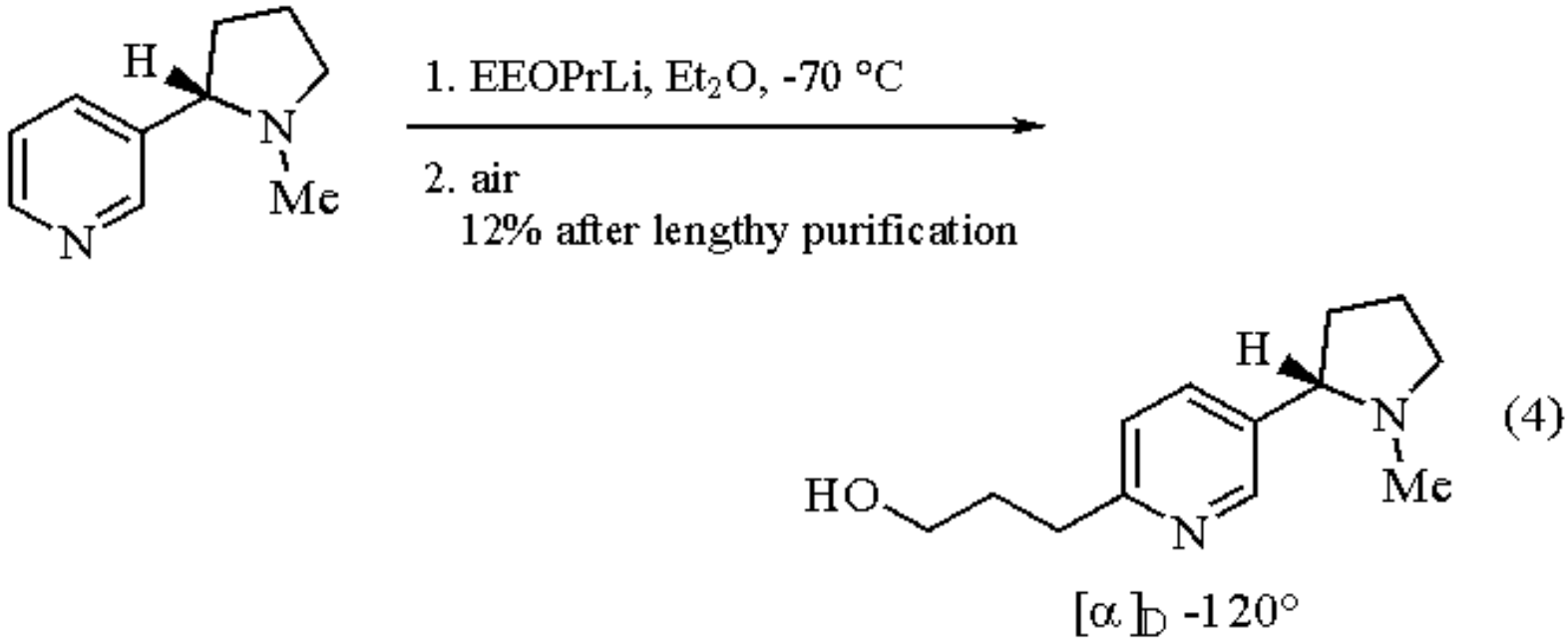

(4)

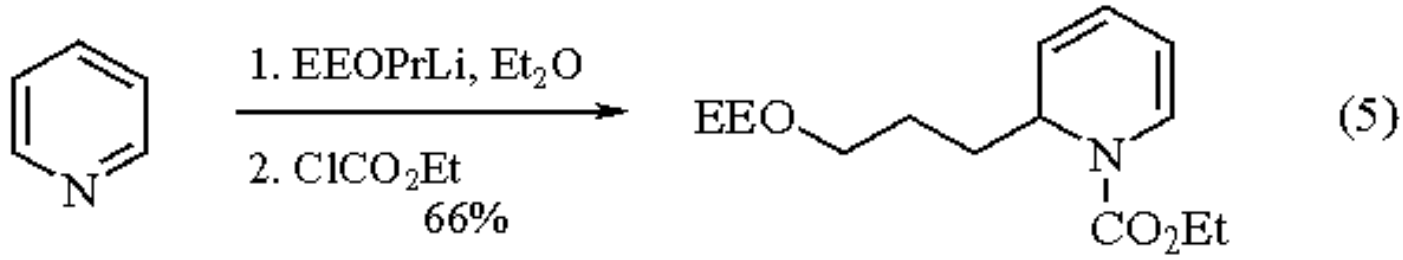

(5)

Epoxides are also successful electrophiles,[6] a reaction elegantly exemplified in a synthesis of brefeldin A in optically pure form. The synthesis involves addition of 3-(1-ethoxyethoxy)propyllithium to (*S*)-***Propylene Oxide*** and trapping of the alkoxide with ***Benzyl Bromide*** (eq 6).[7] Uncommonly for this reagent, the reaction is carried out in THF.

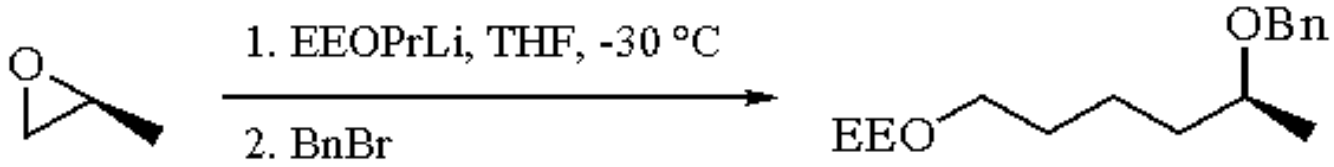

(6)

It is perhaps worth noting that 3-(1-ethoxyethoxy)propyllithium has also been used in the surface modification of poly(chlorotrifluoroethylene) films.[8] These authors comment that generation of the reagent in heptane solution is much more rapid than in ether.

The related dialkyl lithium cuprate reagent, also developed by Eaton,[1] undergoes efficient conjugate addition to α,β-unsaturated ketones at low temperature (e.g. eq 7).[9] Eaton has used this reaction to prepare a key intermediate in his synthesis of peristylane.[1,10] The cuprate reagent has also been shown to displace halide from primary alkyl iodides, as does the simple lithium reagent in the presence of catalytic quantities of Cu^{I}. This reaction was used to prepare gossyplure, the pink bollworm sex pheromone mixture (eq 8).[11]

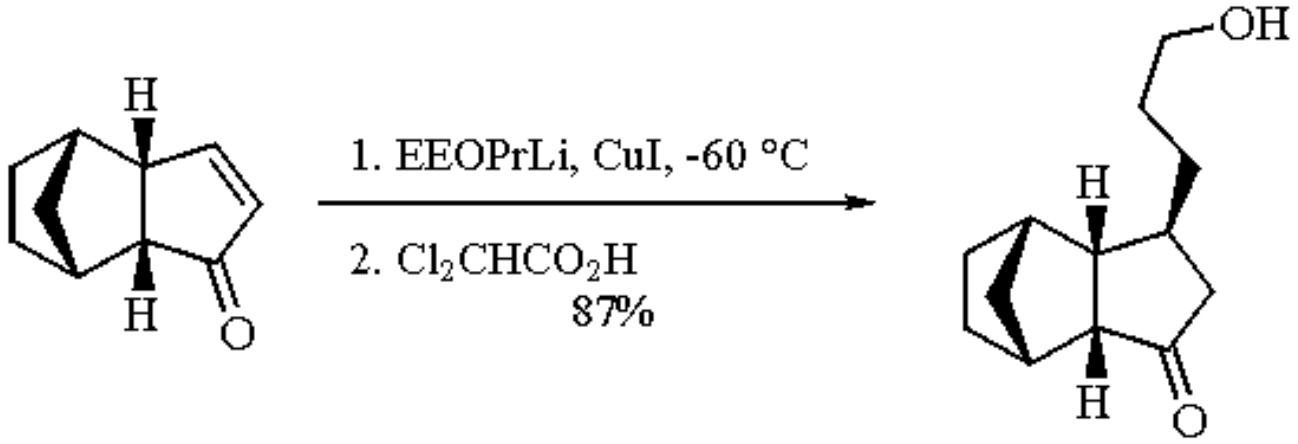

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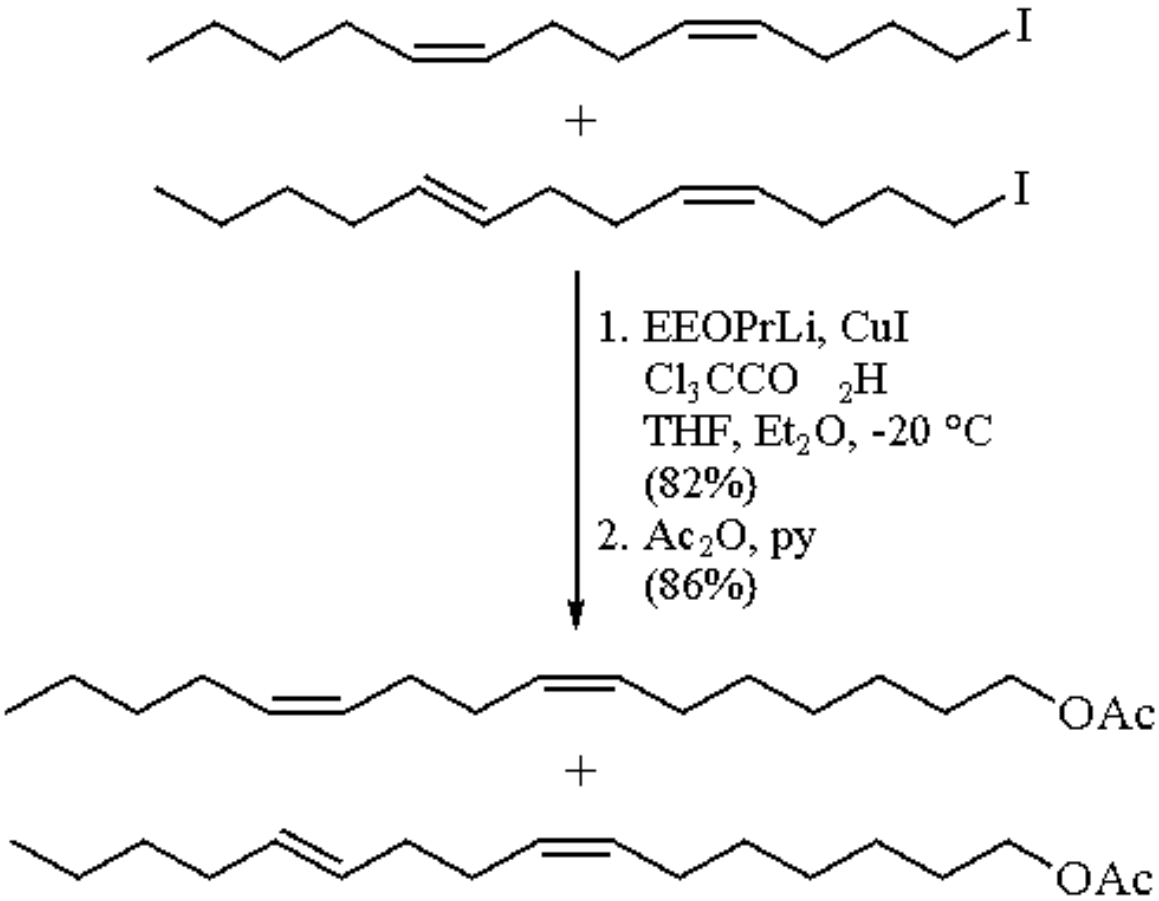

(8)

Related Reagents.

2-(2-Bromoethyl)-1,3-dioxane; ***3-Butenyl-1-magnesium Bromide***; ***(Diisopropoxymethylsilyl)methylmagnesium Chloride***; ***3-(1-Ethoxyethoxy)propylmagnesium Bromide***; ***1-Methoxyallyllithium***.

---

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3-(1-Ethoxyethoxy)propylmagnesium Bromide

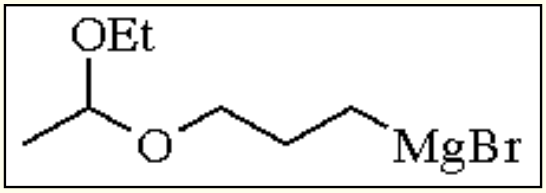

[86551-76-0] · $C_7H_{15}BrMgO_2$ · 3-(1-Ethoxyethoxy)propylmagnesium Bromide · (MW 235.41)

(nucleophilic Grignard reagent used as synthetic equivalent of 3-hydroxypropyl anion)

Solubility: normally prepared in THF and used in situ.

Handling, Storage, and Precautions: Grignard reagent sensitive to moisture; must be prepared in the cold and used immediately; tends to rearrange even below room temperature.

Nucleophilic Additions.

This reagent (referred to below as EEOPrMgBr), like the analogous organolithium reagent, is normally used in synthetic chemistry as a synthon for the 3-hydroxypropyl anion. The reagent was first prepared by Eaton in ethereal solution for this purpose in 1972,[1] but was indicated by him to be much less useful than the corresponding organolithium reagent. Following a 1976 report by Ponaras concerning preparation of another sensitive Grignard reagent oxygenated at the 3-position,[2] the reagent is now normally prepared in THF solution by treatment of the bromide with an excess of ***Magnesium*** while maintaining the temperature strictly below 25-30 °C; ***1,2-Dibromoethane*** is used to initiate the reaction if necessary. At room temperature the reagent tends to rearrange and is normally used at around 0 °C. The 3-(1-ethoxyethoxy)propyl bromide starting material may be prepared on a large scale by the dichloroacetic acid-catalyzed solvent-free addition of acid-free 3-bromopropanol to ***Ethyl Vinyl Ether***.[1] The value of the ethoxyethoxy group over the possible alternative tetrahydropyran is readily seen: after reaction of the organometallic species, hydrolysis to liberate the free alcohol takes place more readily, and the byproducts ethanol and acetaldehyde are both volatile.

Unlike its organolithium counterpart,[1] the reagent is not reported to add readily to ketones. The displacement of halides from primary bromides is, however, useful: in a report actually antedating that of Ponaras, the Grignard reagent is prepared at 0 °C in THF solution in 65% yield. Copper-catalyzed addition to 1-bromononane and subsequent hydrolysis of the acetal group using aqueous ***Trichloroacetic Acid*** gave 1-dodecanol in 52% isolated yield (eq 1).[3] In a later example not requiring copper catalysis, Shea prepared a functionalized diene by displacement of bromide from 2-bromomethyl-1,3-butadiene in THF at -10 °C followed by hydrolysis using ***Pyridinium p-Toluenesulfonate*** (eq 2).[4]

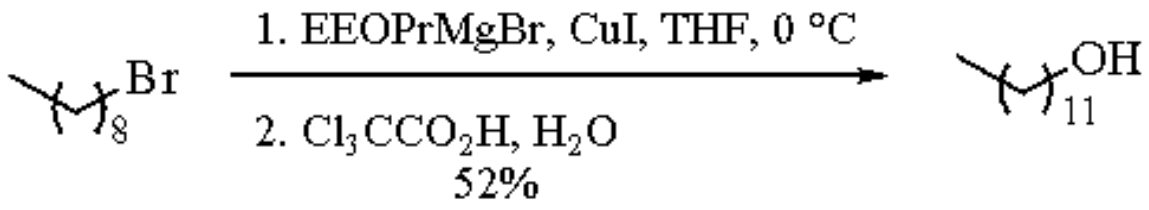

(1)

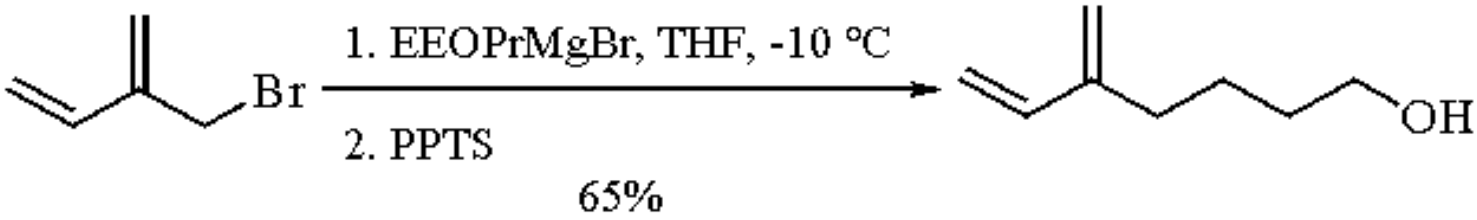

(2)

The reagent is also reported to undergo efficient reaction with β-alkoxy-α,β-unsaturated ketones.[5,6] For example, addition to 3-ethoxy-2-cyclohexenone in benzene-THF solution took place below 10 °C (eq 3). The authors comment that the corresponding organolithium reagent gives unsatisfactory yields. Very careful hydrolysis of the acetal to give the hydroxy ketone was necessary in order to avoid spirocyclization.[5]

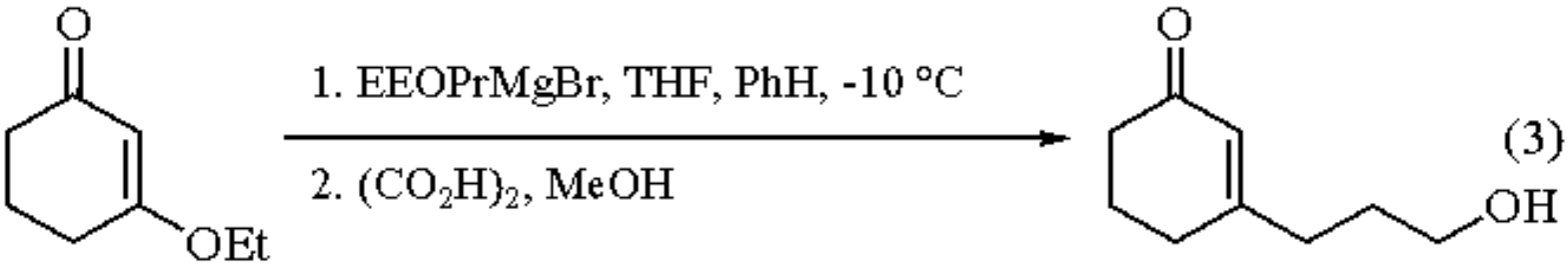

(3)

Particularly interesting is the addition of the reagent to an enantiomerically pure *N*-acylpyridinium salt to give the *N*-acylpyridone, subsequently used in an asymmetric synthesis of (+)-elaeokanines A and C (eq 4).[7]

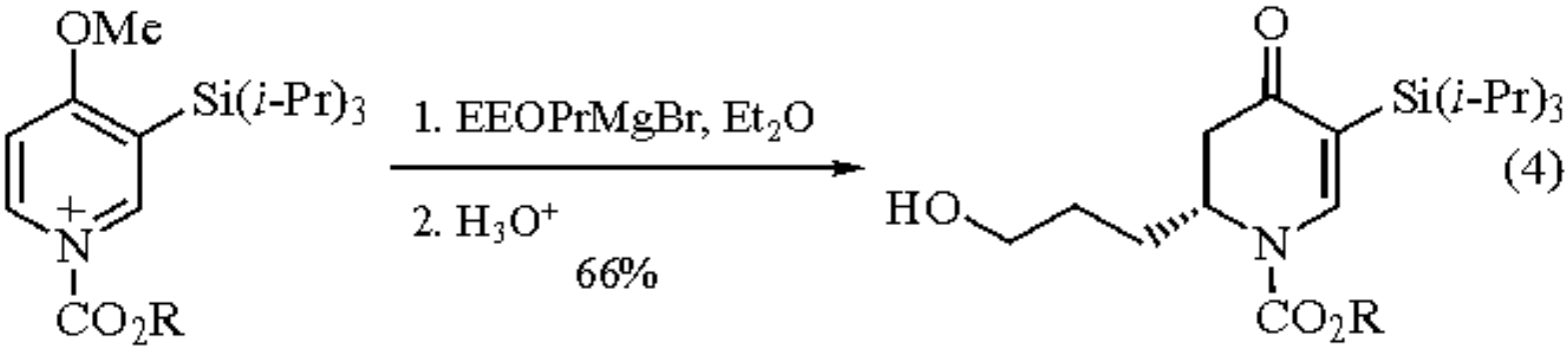

(4)

R = (-)-8-(4-phenoxyphenyl)menthyl

Related Reagents.

3-(1-Ethoxyethoxy)propyllithium; ***2-(2-Bromoethyl)-1,3-dioxane***; ***3-Butenyl-1-magnesium Bromide***.

---

1. Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *JOC* **1972**, *37*, 1947.
2. Ponaras, A. A. *TL* **1976**, 3105.
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4. Shea, K. J.; Wise, S. *TL* **1979**, 1011. Shea, K. J.; Wise, S.; Burke, L. D.; Davis, P. D.; Gilman, J. W.; Greeley, A. C. *JACS* **1982**, *104*, 5708.
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N-Ethoxymethyleneaniline[1]

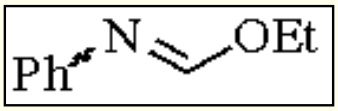

[6780-49-0] · $C_9H_{11}NO$ · *N*-Ethoxymethyleneaniline · (MW 149.19)

(preparation of aldehydes from Grignard reagents[2,3])

Alternate Name: ethyl *N*-phenylformimidate.

Physical Data: bp 87-88 °C/10 mmHg.

Form Supplied in: liquid, commercially available; best preparation is from ***Triethyl Orthoformate*** and aniline.[4]

Handling, Storage, and Precautions: store refrigerated under dry nitrogen.

Formylation Reagent.

Of the various older methods reviewed[1] for the synthesis of aldehydes from Grignard reagents, use of this imidate reagent was considered one of the best,[2] giving higher yields than ***Triethyl Orthoformate***.[1a] However, newer procedures have been developed that may yield superior results, e.g. treatment of Grignard reagents with ***Pentacarbonyliron***.[5] The reaction proceeds through the formation of the imine which is hydrolyzed to the aldehyde (eq 1).[2] Cyclohexane-1,3-dione also adds to the imidate, and upon hydrolysis of the intermediate 2-(phenylamino)methylene gives the 2-formylcyclohexane-1,3-dione.[6,7]

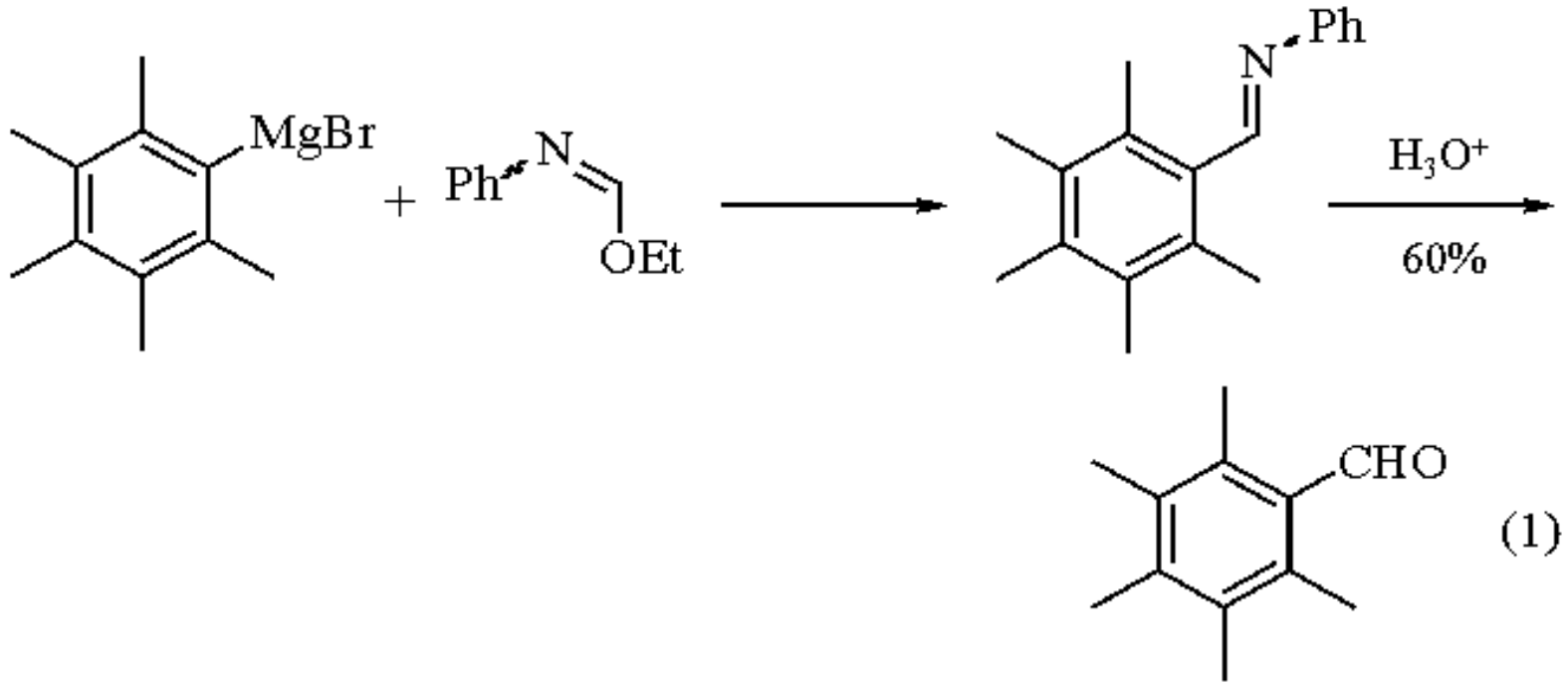

Formation of Ketones.

Recent reinvestigation of the above reaction has demonstrated that the reagent can also be utilized for the synthesis of a variety of ketones, by using 2 equiv of a Grignard reagent (80 °C) or alkyllithium (-30 °C).[8] This involves the addition of a second Grignard reagent or, preferably, an alkyllithium to the first-formed imine. Aqueous hydrolysis gives *N*-disubstituted methylaniline (ca. 100% yield) which is oxidized with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** to the Schiff's base; hydrolysis gives the ketone (eq 2).[8] This is not applicable to aliphatic ketones.

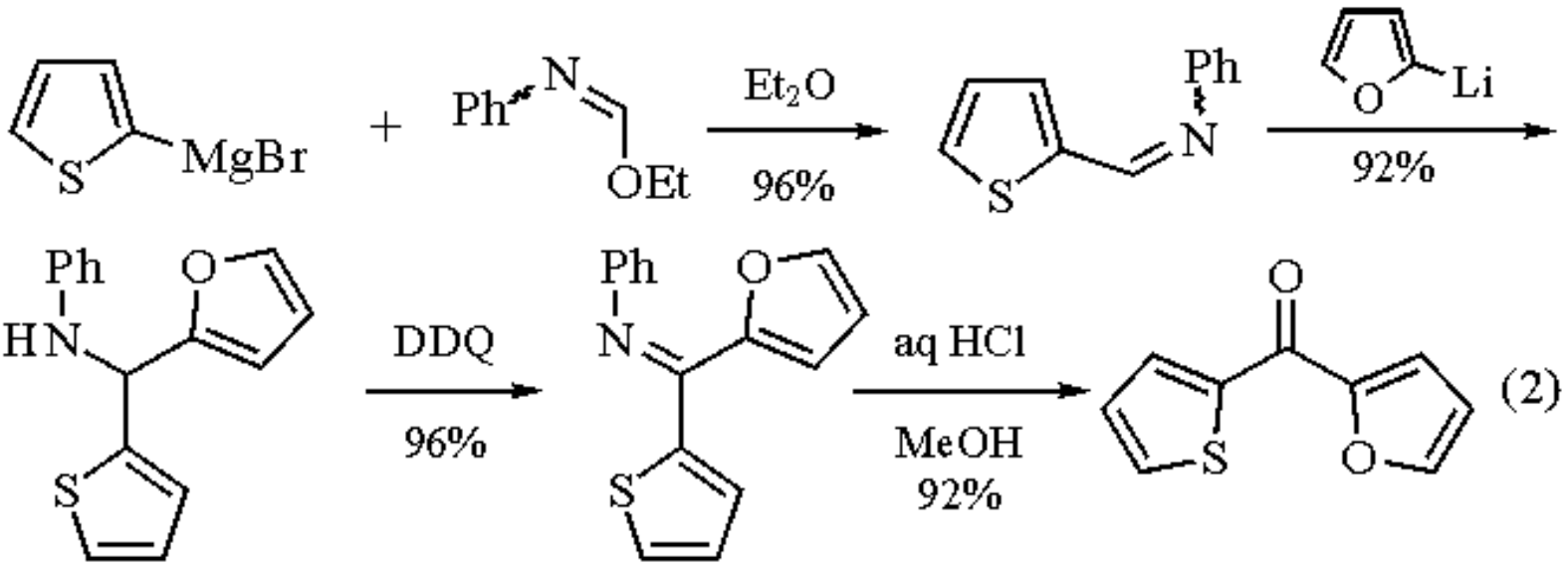

α,β-Unsaturated α-Substituted Aldehydes.

Condensation of ethoxymethyleneaniline with α-lithioalkylphosphonates gives, after treatment with ***Lithium Diisopropylamide***, lithio enaminoalkylphosphonates, which condense with aldehydes to give α,β-unsaturated α-

substituted aldehydes in moderate yield (eq 3).[9]

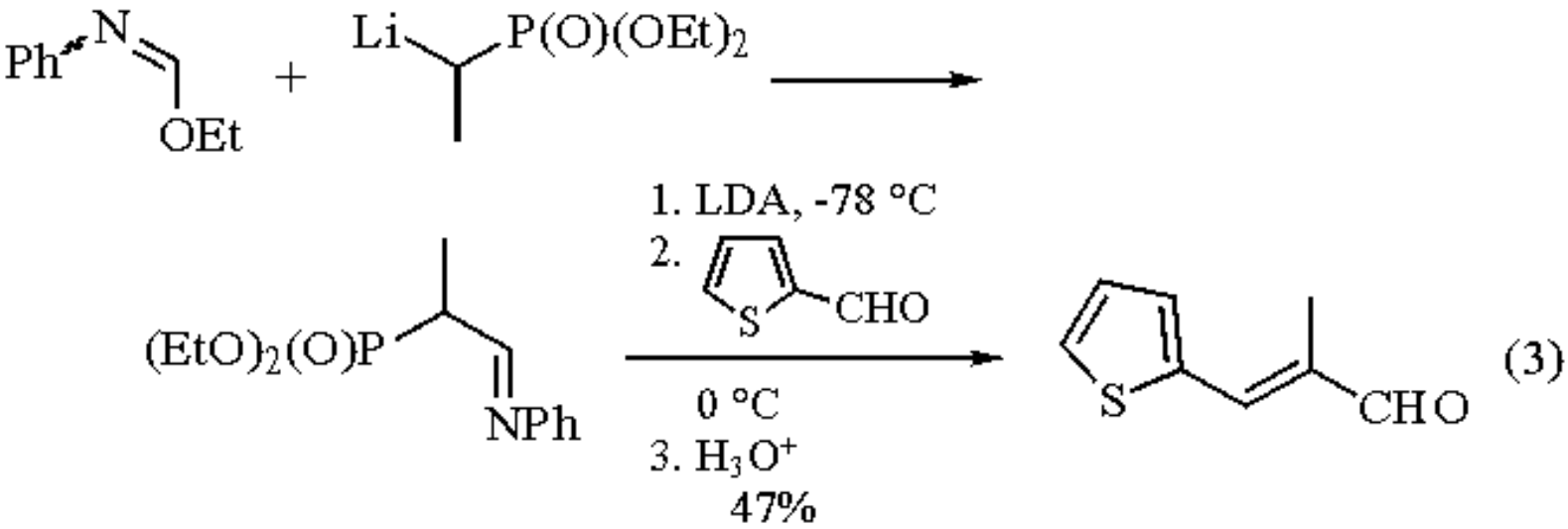

β-Lactams.

Treatment of α-substituted aliphatic acid chlorides with ethoxymethyleneaniline in the presence of ***Triethylamine*** generates only *trans* 1-phenyl-3-substituted 4-ethoxy-β-lactams in moderate to good yield.[10,11] The chromium carbene complex in eq 4 photochemically cyclizes with the imidate to give the same azetidinone (X = NBz_2) in good yield.[12]

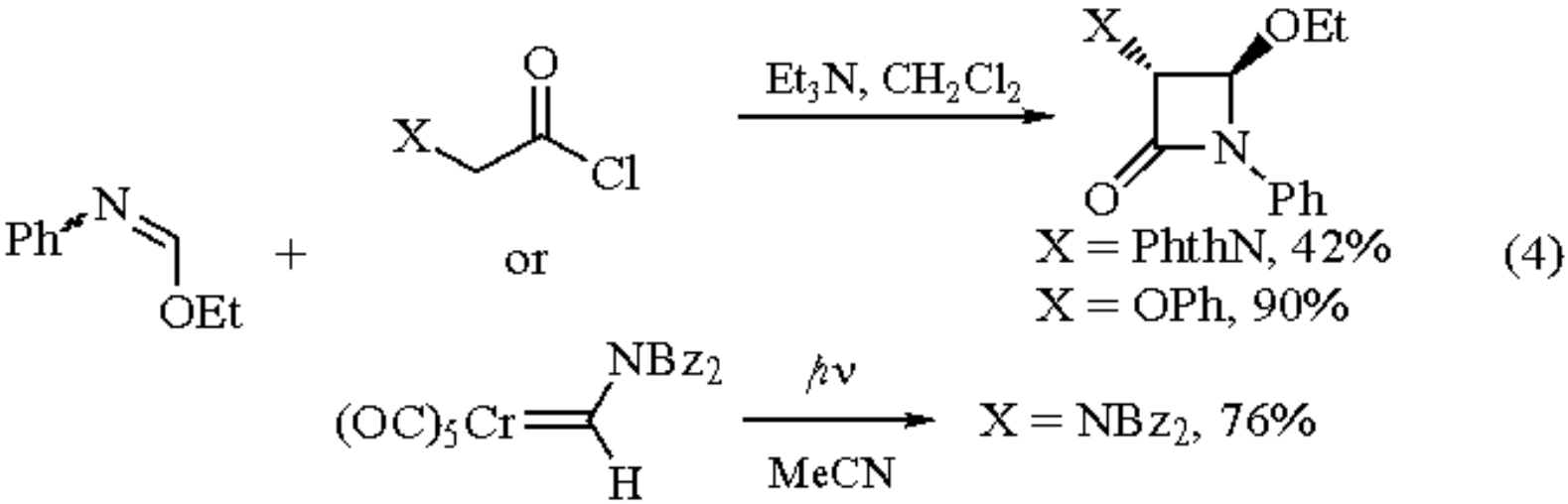

Related Reagents.

N,N-Dimethylformamide; ***N-Methyl-N-(2-pyridyl)formamide***.

---

1. (a) Roger, R.; Neilson, D. G. *CRV* **1961**, *61*, 179. (b) Kharasch, M. S., Reinmuth, O.; *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: Engelwood Cliffs, NJ, 1954. (c) Carnduff, J. *QR* **1966**, *20*, 169.
2. Smith, L. I.; Nichols, J. *JOC* **1941**, *6*, 489.

3. Monier-Williams, G. W. *JCS* **1906**, *89*, 273.
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5. Yamashita, M.; Miyoshi, K.; Nakazono, Y.; Suemitsu, R. *BCJ* **1982**, *55*, 1663.
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12. Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *JACS* **1987**, *109*, 1101.

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Ethoxymethylenemalonitrile[1]

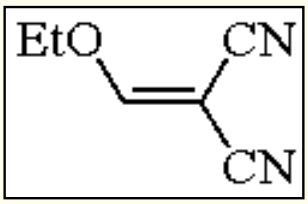

[123-06-8] · $C_6H_6N_2O$ · Ethoxymethylenemalonitrile · (MW 122.13)

(Michael acceptor for addition/elimination reactions;[2] synthesis of substituted benzene rings[3] and other aromatic heterocycles;[4] dipolarophile[5])

Alternate Name: EMMN.

Physical Data: mp 64 °C; bp 160 °C/12 mmHg.

Solubility: sol alcohols, THF, DMF, $CHCl_3$, CH_2Cl_2.

Form Supplied in: colorless crystalline solid; commercially available.

Analysis of Reagent Purity: mp, ^{1}H NMR, ^{13}C NMR, IR.

Preparative Methods: can be synthesized by the condensation of ***Triethyl Orthoformate*** and ***Malononitrile*** in the presence of ***Acetic Anhydride***.[6] Likewise, ethoxy[^{2}H]methylenemalonitrile can be made using $DC(OEt)_3$.[7]

Purification: by distillation under reduced pressure.

Handling, Storage, and Precautions: is classified as a strong sensitizing agent and should be handled with gloves and goggles in a fume hood. Avoid contact with eyes, skin, and clothes. Also, ethoxymethlenemalonitrile is a combustible liquid with a flash point of 155 °C. It should be stored in a cool, dry place.

Use as a Michael Acceptor.

Ethoxymethylenemalonitrile has been used as a Michael acceptor for a wide variety of nucleophiles such as alcohols,[8] amines,[9] anilines,[2] enamines,[10] ester enolates,[11] hydrazines,[12] imines,[13] pyrroles,[14] stabilized carbanions,[15] thiazoles,[16] and thiols[17] to name only a few. Usually, the Michael addition is accompanied by β-elimination of the

ethoxy group to give substituted methylenemalonitrile derivatives (eq 1). Some highly conjugated dithiolylidenebutenes can be synthesized in this manner (eq 2).[18]

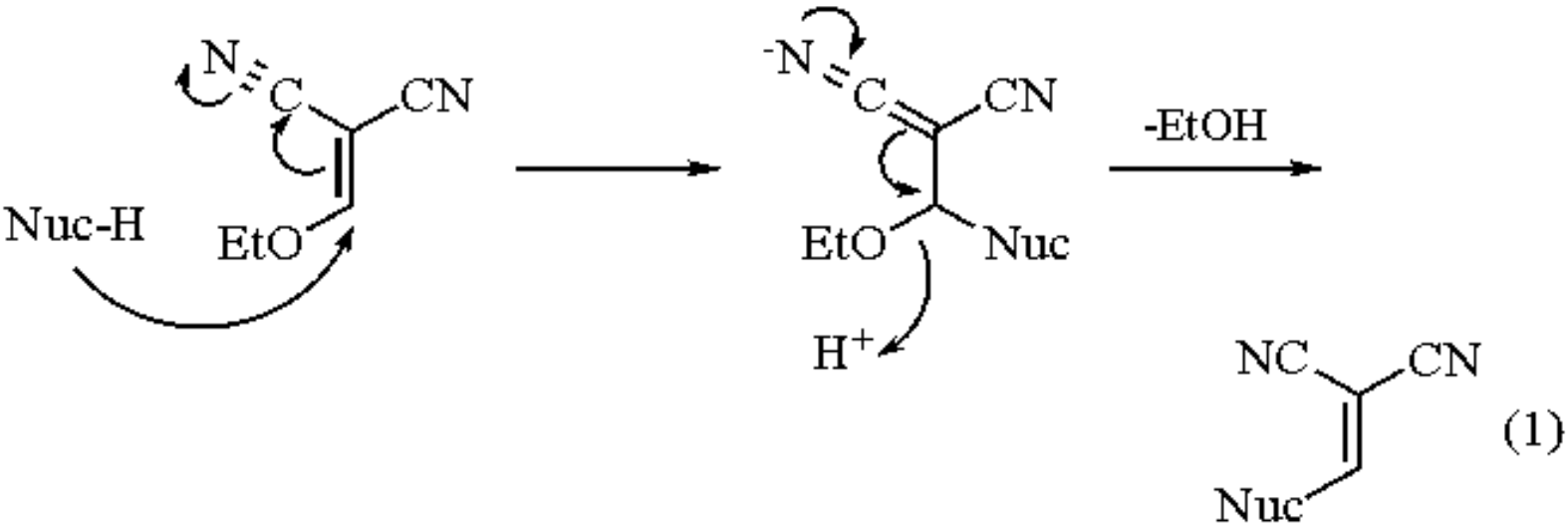

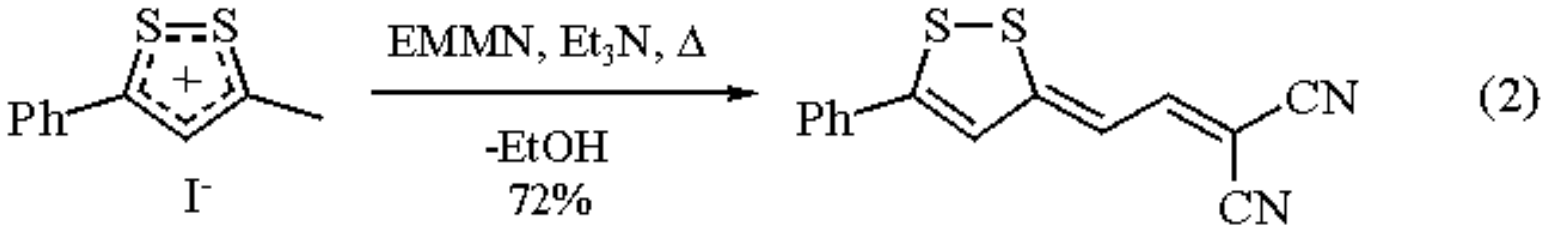

Treatment of EMMN with 2 equiv of ***Phenylmagnesium Bromide*** results in formation of the double Michael addition product (eq 3) following the customary addition/elimination sequence.[19]

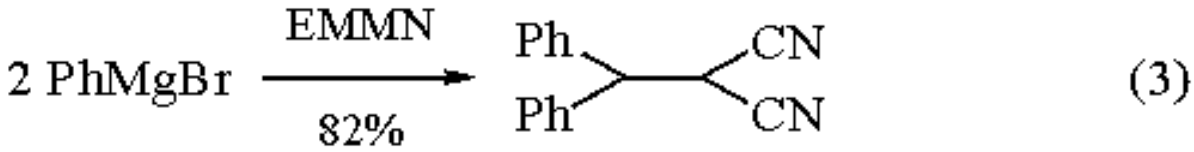

Use in the Synthesis of Aromatic and Heteroaromatic Derivatives.

Since the nitriles themselves offer yet another electrophilic site for reactivity, the addition/elimination adducts are often not isolated but are converted directly to a variety of aromatic (eq 4)[3] and heteroaromatic derivatives including pyridones (eq 5),[15] pyrimidines (eq 6),[20] thiophenes (eq 7),[17] pyrazoles (eq 8),[21] pyrones (eq 9),[22] and heterocyclic annulenes (eq 10).[23]

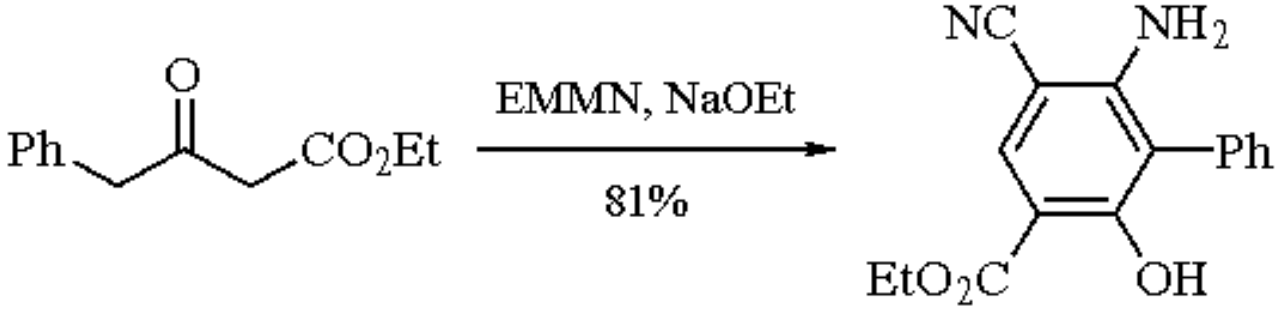

(4)

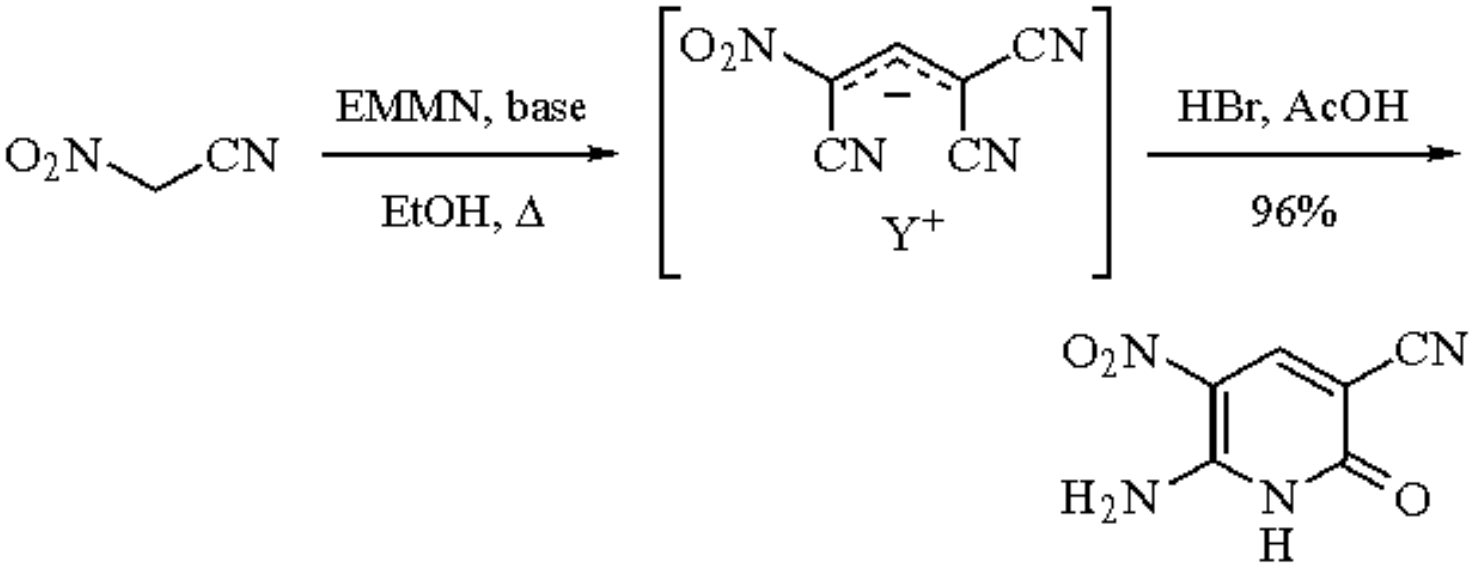

(5)

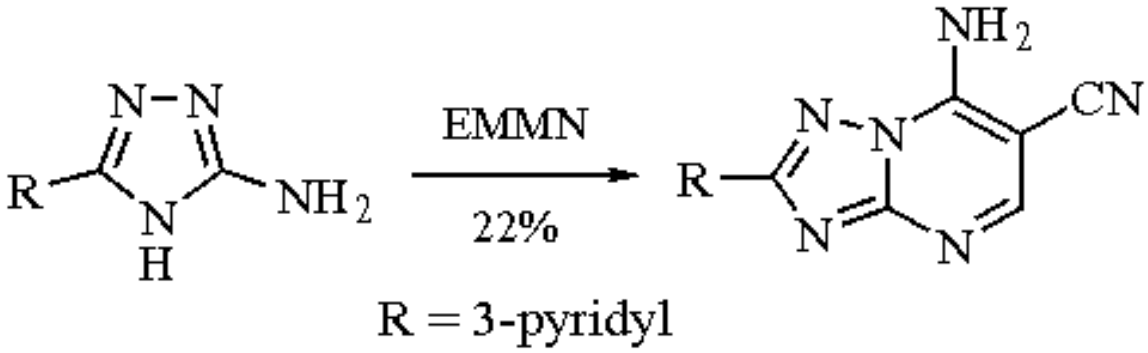

(6)

R = 3-pyridyl

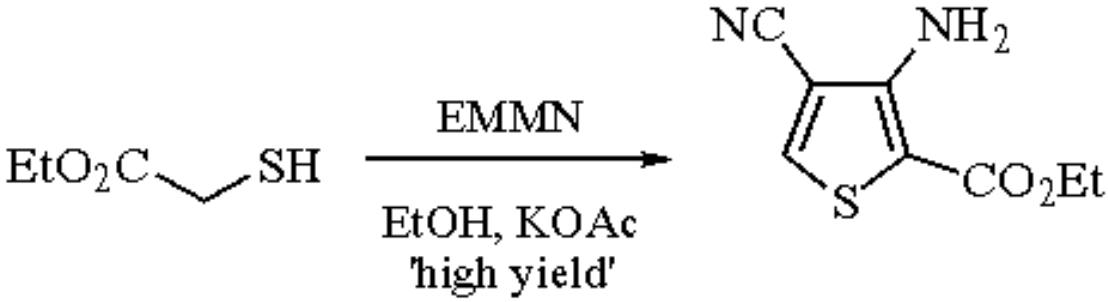

(7)

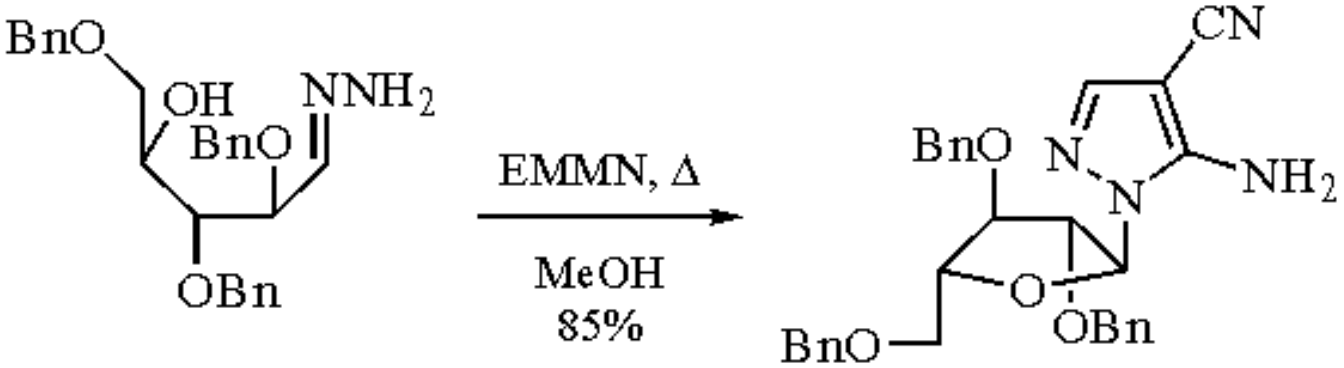
BnO
OH
NNH2
BnO
OBn
EMMN, Δ
MeOH
85%
CN
BnO
N
N
NH2
O
OBn
BnO

(8)

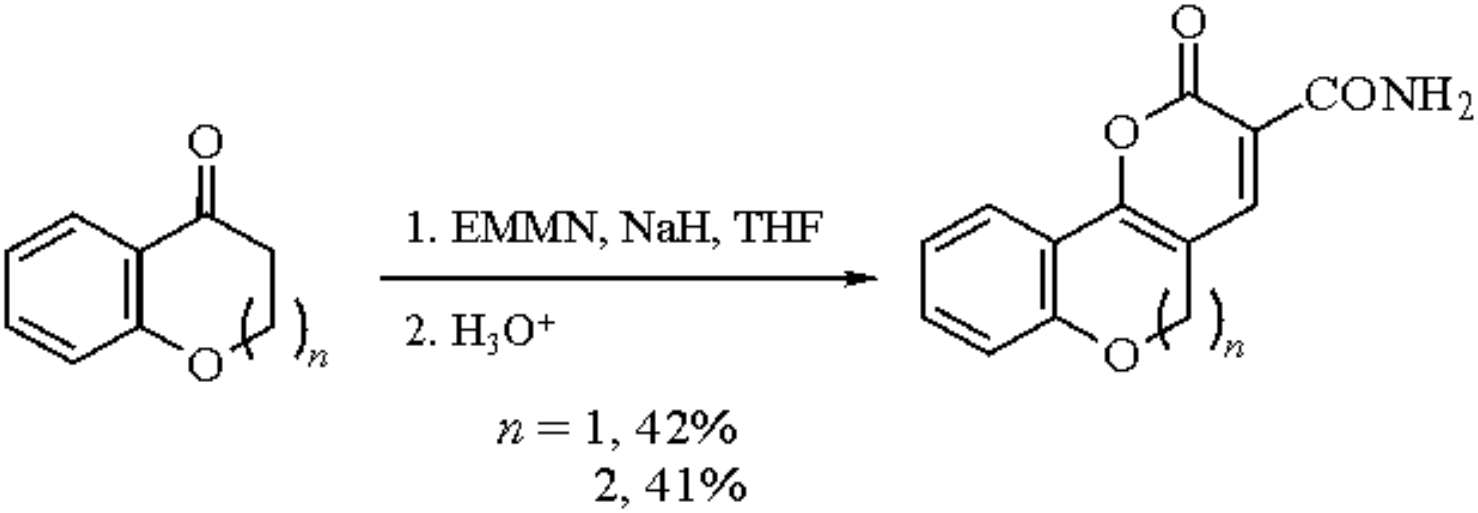
O
O
1. EMMN, NaH, THF
2. H3O+
O
CONH2
O
n
n = 1, 42%
2, 41%

(9)

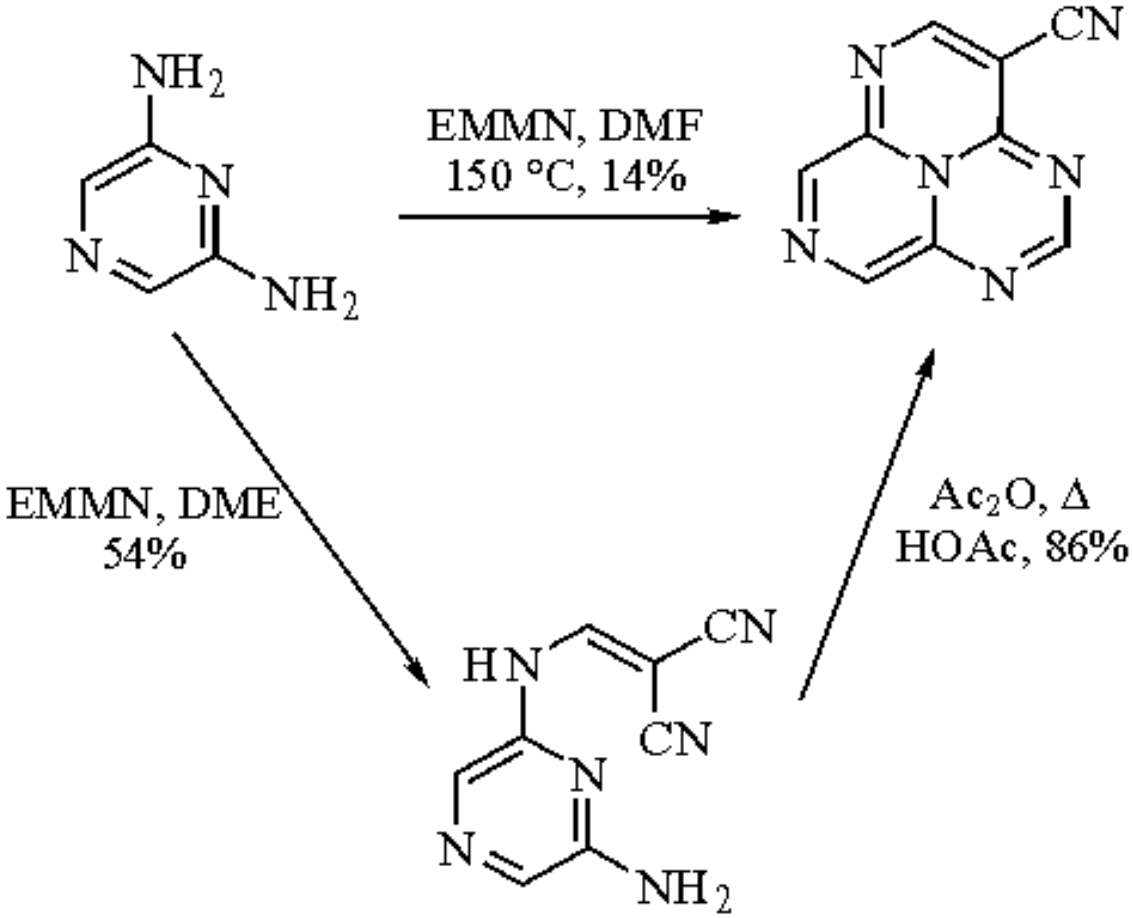
NH2
N
N
NH2
EMMN, DMF
150 °C, 14%
CN
N
N
N
N
N
EMMN, DME
54%
Ac2O, Δ
HOAc, 86%
HN
CN
CN
N
N
NH2

(10)

Other Uses.

EMMN has also been used in [3 + 2] dipolar cycloadditions (eq 11)[5] as well as an iron-mediated five-membered ring annulation (eq 12).[24]

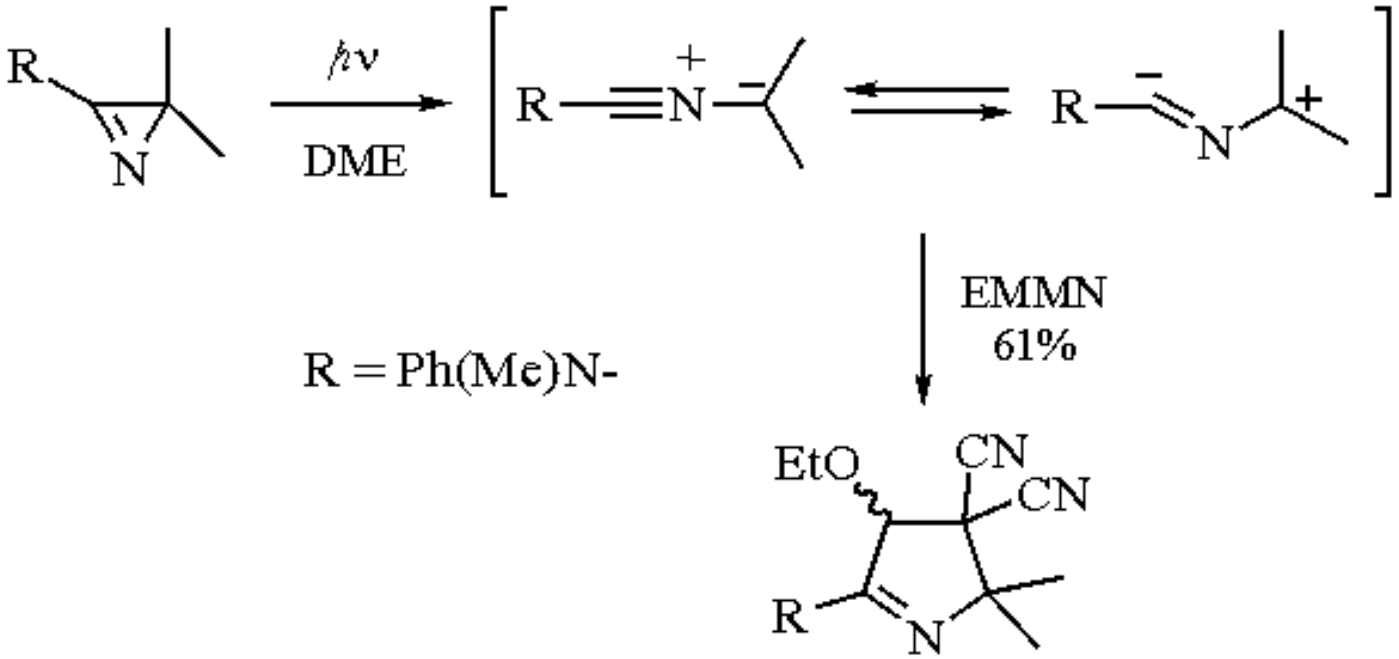

(11)

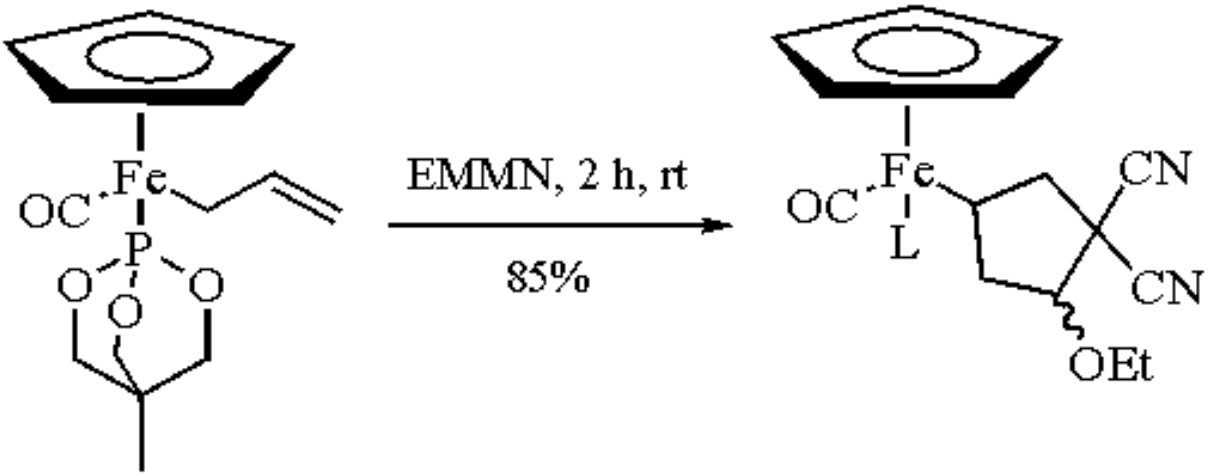

(12)

Related Reagents.

Diethyl Methylenemalonate; ***3-Ethoxyacrylonitrile***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethyleneacetoacetate***; ***Ethyl Ethoxymethylenecyanoacetate***; ***Malononitrile***.

---

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9. Taylor, J. B.; Tully, W. R. *JCS(P1)* **1976**, 1331.
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17. Saito, K.; Kambe, S.; Sakurai, A.; Midorikawa, H. *S* **1982**, *12*, 1056.
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19. Gupte, S. D.; Sunthankar, S. V. *JOC* **1959**, *24*, 1334.
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21. (a) Schmidt, R. R.; Guillard, W.; Heermann, D.; Hoffmann, M. *JHC* **1983**, *20*, 1447. (b) Acevedo, O. L.; Krawczyk, S. H.; Townsend, L. B. *JOC* **1986**, *51*, 1050.
22. Jaquet, M. C.; Bellassoued-Fargeau, M. C.; Graffe, B.; Maitte, P. *JHC* **1985**, *22*, 757.
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24. Rosenblum, M.; Waterman, P. S. *JOM* **1980**, *187*, 267.

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(3-Ethoxy-3-oxopropyl)iodozinc

I-Zn-$(CH_2)_n$-R

(n = 2; R = CO_2Et)

[104089-16-9] · $C_5H_9IO_2Zn$ · (3-Ethoxy-3-oxopropyl)iodozinc · (MW 293.43)

(organozinc reagents functionalized with ester, ketone, nitrile, amide, or halide functionalities, capable of C-C bond formation with a variety of organic electrophiles, e.g arylation, vinylation, ethynylation, acylation, allylation, Michael-type addition, and addition to carbonyl CO bonds)

Alternate Name: Tamaru's reagent.

Physical Data: dark powder; reagent prepared in situ (see below).

Analysis of Reagent Purity: aliquots of reactions in process can be checked by VPC or TLC after addition of 1 N HCl.[1c]

Preparative Methods: organozincs (**1**)-(**5**), possessing electrophilic functionality (ester, ketone, nitrile, amide, halide) in the same molecule, can be prepared in high reproducibility in mmol to mol scales by the direct reaction of the corresponding iodides and zinc metal. Four kinds of procedures have been reported. *Method A*:[1] reaction of ***Zinc/Copper Couple*** with an iodide in benzene containing 1.5-2 equiv of DMF or DMA at 60 °C for several hours. For the preparation of zincio ketone (**3**), the use of HMPA in place of DMF or DMA is essential.[2] For the preparation of β-zincio esters (**1a-c**) and β-zincio nitriles (**2a-c**), THF also may be used as solvent in place of benzene-DMF or DMA. *Method B*:[3] reaction of zinc/copper couple with an iodide in benzene-DMA (2.7 equiv) under sonication at 20-35 °C for 30 min. This method is applied to the preparation of (**1d**), characteristically possessing an acidic amide proton. *Method C*:[4] reaction of ***Zinc*** powder or foil, activated with ***1,2-Dibromoethane*** (4-5%) and ***Chlorotrimethylsilane*** (3%) in THF, with a primary iodide at 35-40 °C and with a secondary iodide at 25-30 °C in the same solvent (ca. 12 h). *Method D*:[5] reaction of zinc metal, prepared by a slow addition of ***Lithium Naphthalenide*** (2 equiv) to a THF solution of ***Zinc Chloride***, with an alkyl bromide at rt. The zinc powders produced by this method are very reactive and react even with vinyl bromides and aryl bromides (e.g. ethyl *o*- and *p*-bromobenzoates).

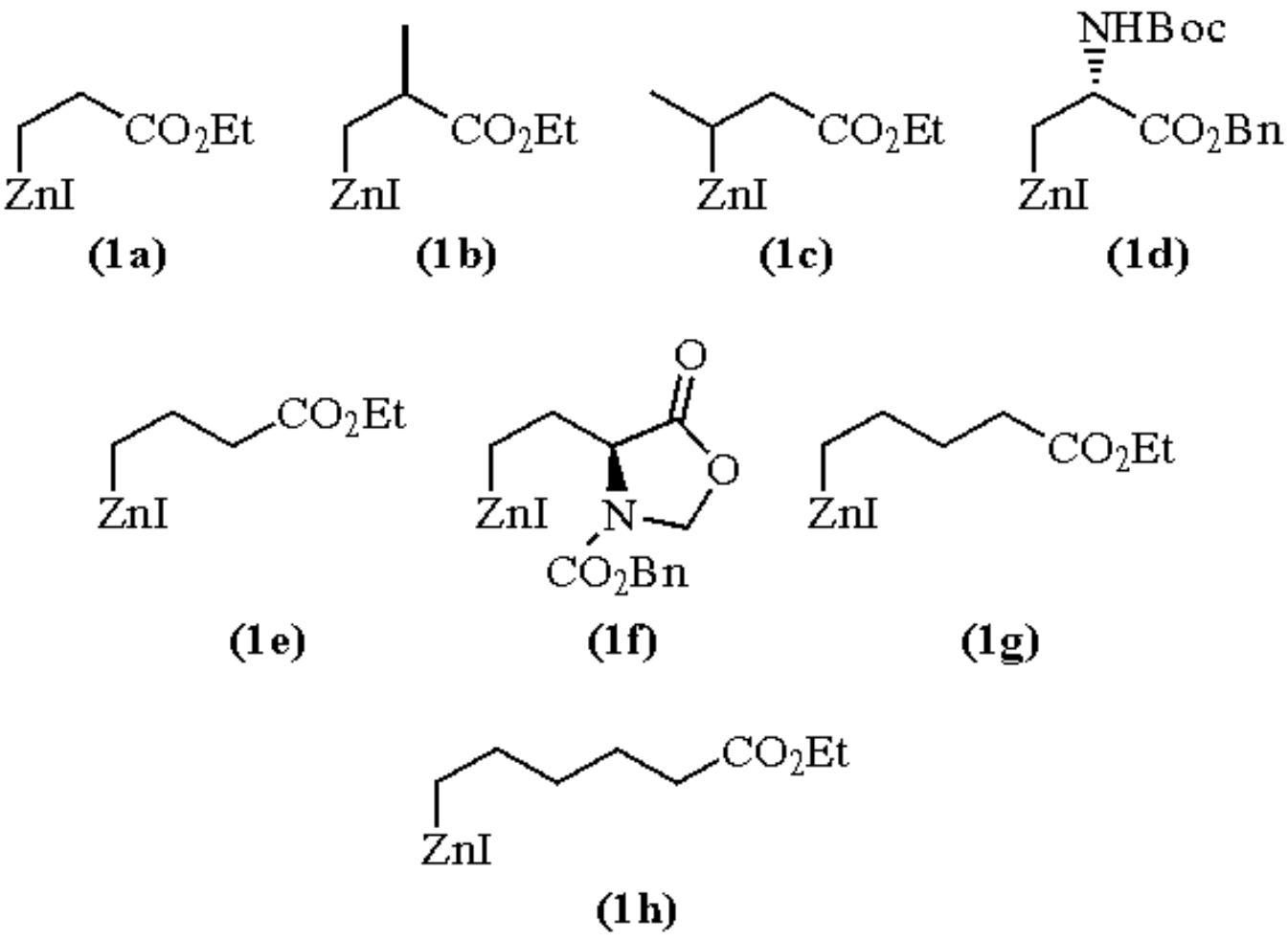

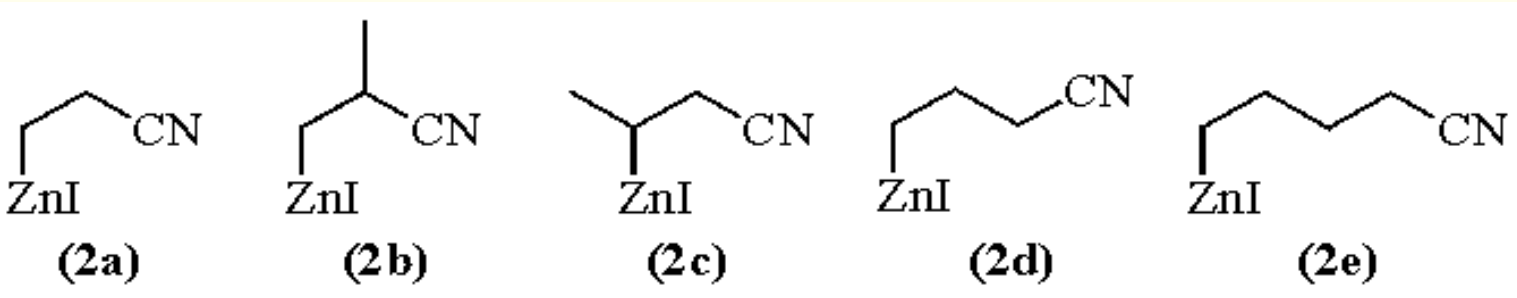

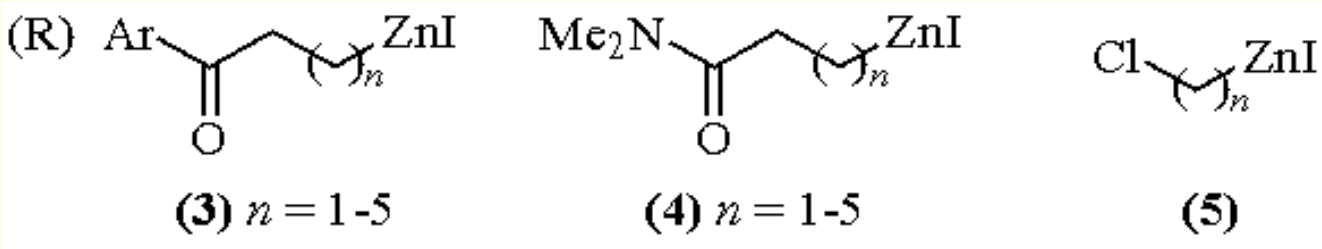

Handling, Storage, and Precautions: the iodozinc reagents can be prepared and handled like Grignard reagents, and may be stored at rt for ca. one week; however, freshly prepared samples are recommended. All reactions should be conducted in a well-ventilated fume hood.

Introduction.

(3-Ethoxy-3-oxopropyl)iodozinc

The title reagent is an example of a lower homolog in a series of functionalized organozinc reagents with the general structure depicted above. See Table 1 for selected examples of reagents discussed in this entry.

Table 1 Selected Functionalized Organozinc Reagents $I\ Zn\ (CH_2)_n\ R$

Compound	n	R	CAS number
(1a)	2	CO_2Et	[*104089-16-9*]
(1e)	3	CO_2Et	[*104089-17-0*]
(1g)	4	CO_2Et	[*109976-46-7*]
(1h)	5	CO_2Et	[*113274-32-1*]
(2a)	2	CN	[*121236-17-7*]
(2d)	3	CN	[*126761-11-3*]
(2e)	4	CN	[*142338-61-2*]
(3)	2	COPh	[*113274-38-7*]
	5	COPh	[*113274-37-6*]
(5)	4	Cl	[*112403-39-1*]

Reaction of Functionalized Organozincs.

As evident from their high functional group compatibility, organozincs show a very low reactivity toward most organic electrophiles. However, as discussed here, they can undergo C-C bond forming reactions with many electrophiles in the presence of an appropriate transition-metal catalyst or a Lewis acid. Some reactions of functionalized organocopper reagents,[6] derived from organozincs by transmetalation with a stoichiometric amount of CuCN.2LiCl (see ***Copper(I) Cyanide***) are discussed for comparison. For the reactions of bis(β-alkoxycarbonylethyl)zinc reagents, see Nakamura et al.[7]

Arylation, Vinylation, and Ethynylation.

Vinyl iodides, vinyl triflates, and aromatic iodides,[2,8] as well as aromatic bromides with electron-attracting substituents,[5] undergo coupling with organozincs in the presence of a catalytic amount of palladium (eqs 1-4). The vinylation (eq 3) proceeds with retention of configuration; the corresponding *trans*-iodide provides the *trans* coupling product exclusively in 71% yield.[8a] Arylation sometimes suffers from biaryl formation; for such cases, the use of the catalyst specified in eq 1 is recommended.[8a] The arylation tolerates an acidic amide proton (eq 2),[3,14c] and optically active phenylalanine derivatives are

obtained according to this procedure.[3] Organocopper reagents directly react with ethynyl iodides and bromides under mild conditions (eq 5).[9]

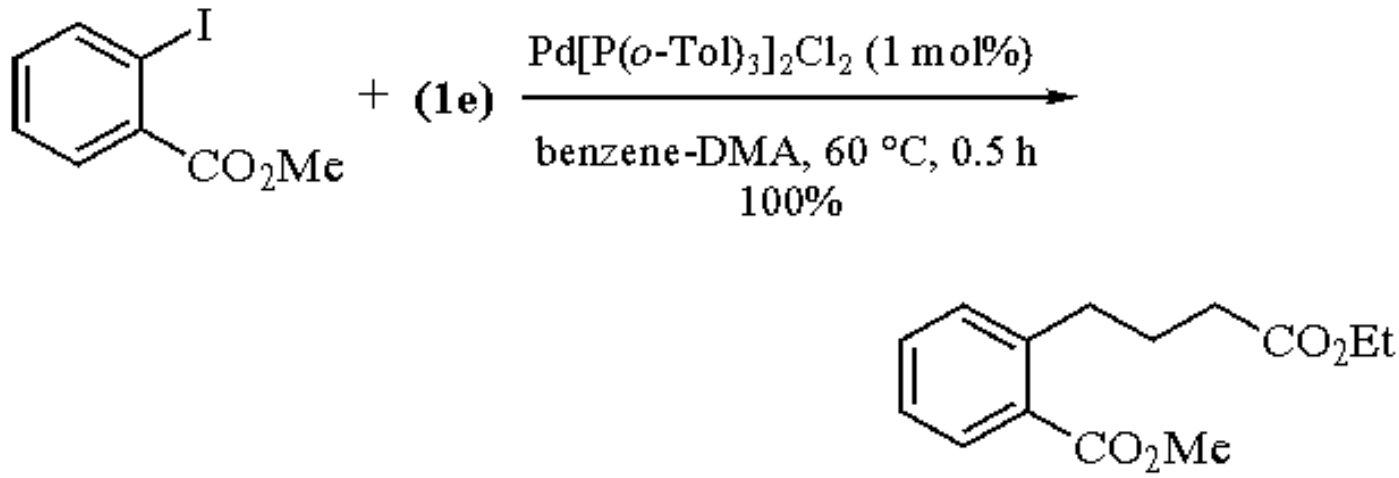

(1)

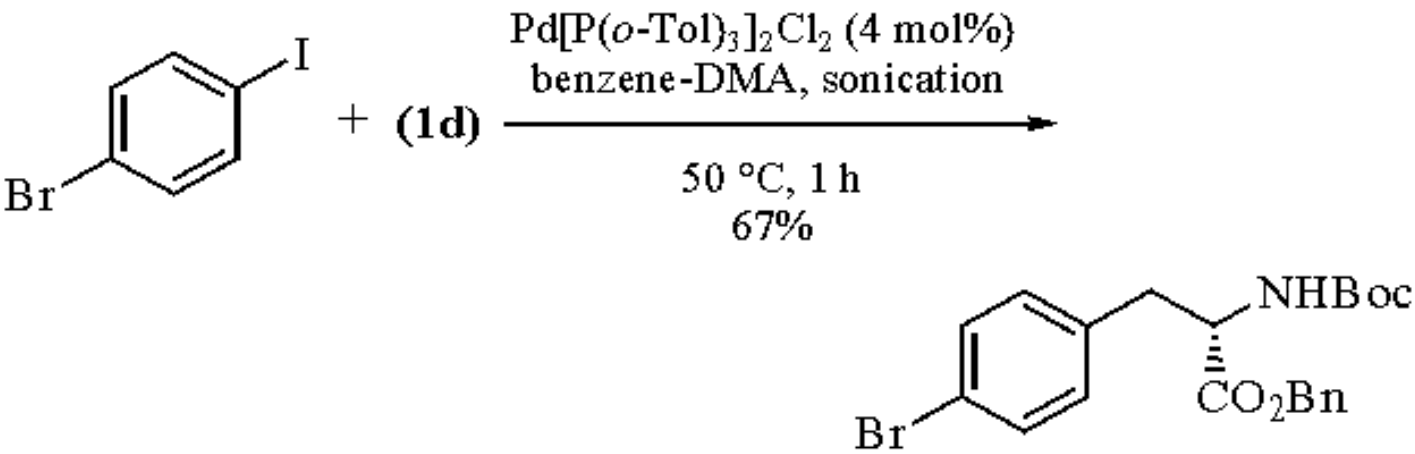

(2)

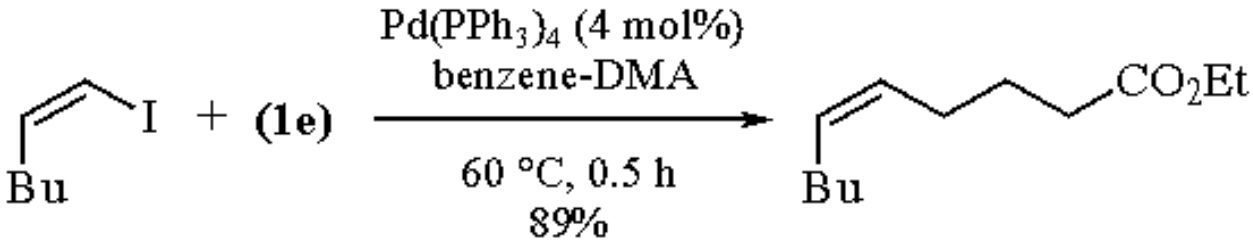

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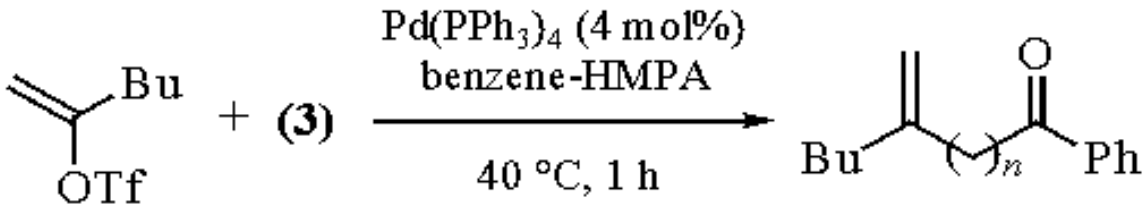

(4)

$n = 3$, 67%; $n = 6$, 74%

(3-Ethoxy-3-oxopropyl)iodozinc

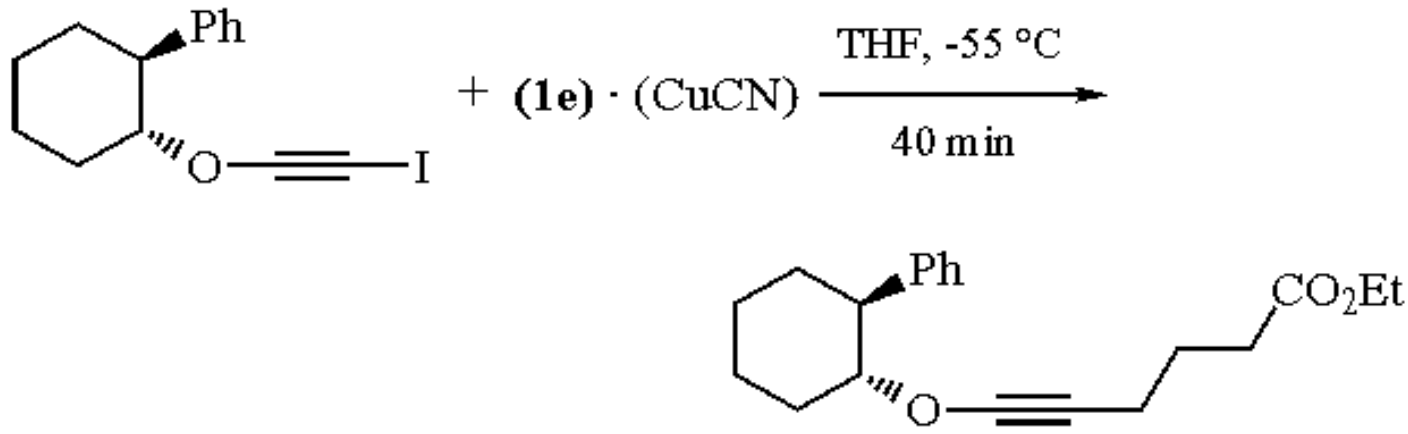

(5)

Acylation.

Organozinc iodides are so unreactive that they do not react smoothly even with highly reactive acid chlorides, e.g. yielding butyrophenone in 20% yield by the reaction of *n*-propylzinc iodide with ***Benzoyl Chloride*** in benzene-DMF at 70 °C for 4 h.[10] The acylation is greatly accelerated by a palladium catalyst (eqs 6 and 7)[1,2] or a stoichiometric amount of CuCN.2LiCl (eq 8).[4a,5,11] The reactions in eqs 6 and 7, and the three-component connection reactions of allylic benzoates, ***Carbon Monoxide***, and organozincs (eq 9),[12] may proceed via acylpalladium intermediates.

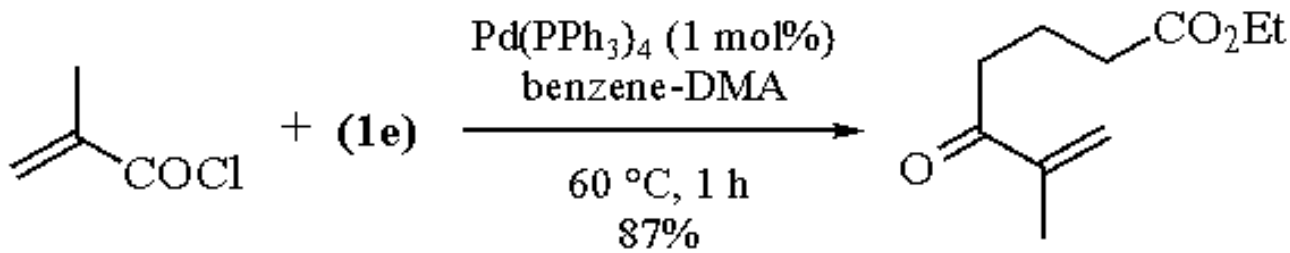

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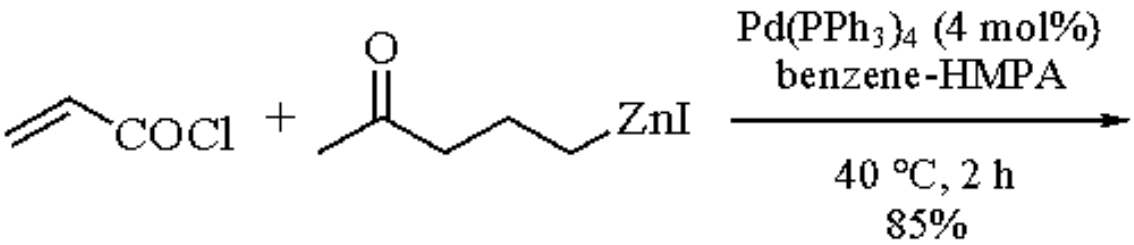

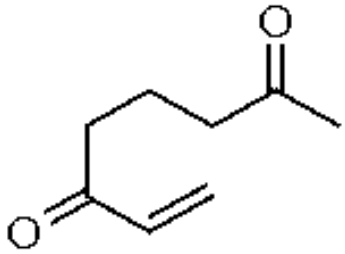

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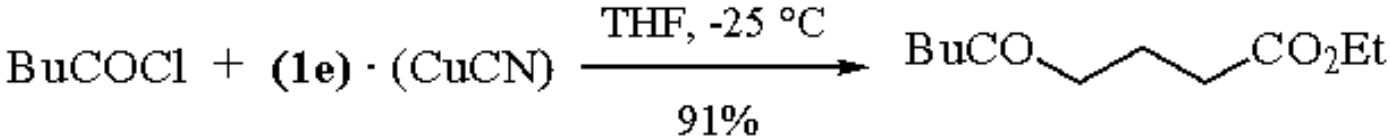

(8)

(3-Ethoxy-3-oxopropyl)iodozinc

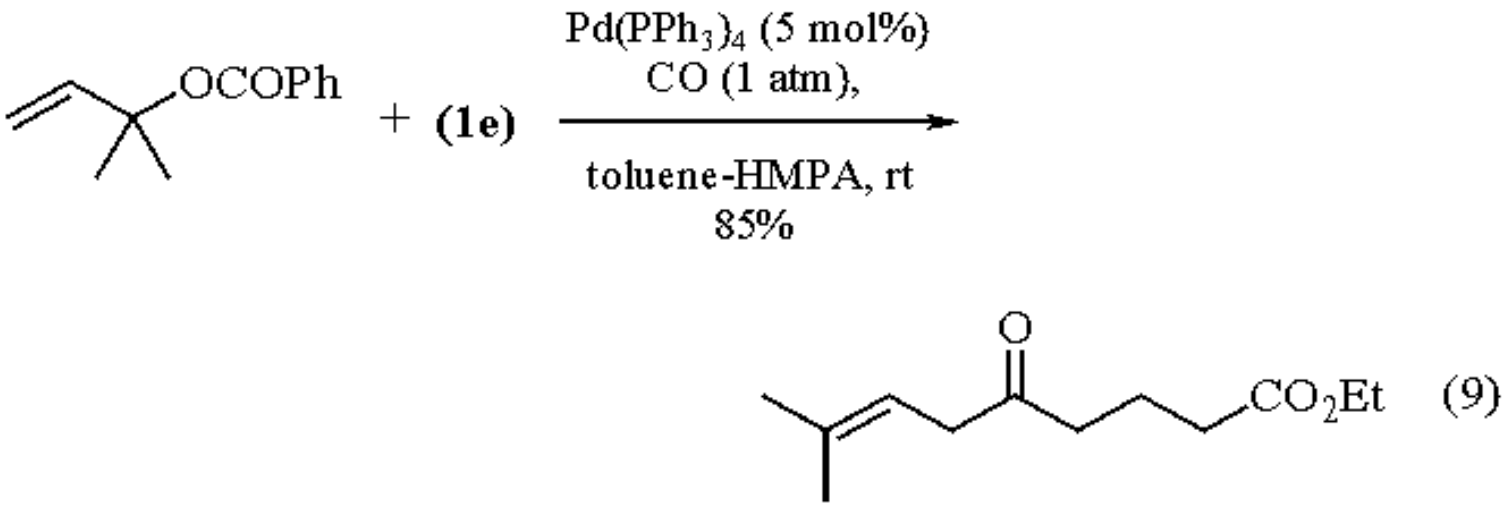

Addition to Activated Alkenes and Alkynes.

Conjugate addition of organozincs to α,β-unsaturated aldehydes, ketones, esters, and nitro compounds takes place smoothly in the presence of ***Chlorotrimethylsilane*** (2 equiv) and either a catalytic[13] or a stoichiometric amount of ***Copper(I) Cyanide***.[14] The retention of regiochemistry of the methyl substituent of (**1c**) (eq 11) is in contrast to the migration of the methyl group as observed for the reaction of (**1c**) with aldehydes (eq 18).[15] The reaction is not accompanied by racemization (eq 10)[13] and tolerates the acidic alkynic and amide protons (eq 12).[14c] Organozincs (e.g. **1a**, **1e**, **5**) nonselectively add to conjugated iminium salts in 1,2- and 1,4-fashion (eq 13),[16] while sorbaldehyde (2,4-hexadienal) undergoes a selective 1,4-addition reaction (vs. 1,2- and 1,6-additions) under the catalytic conditions shown in eq 10.[13]

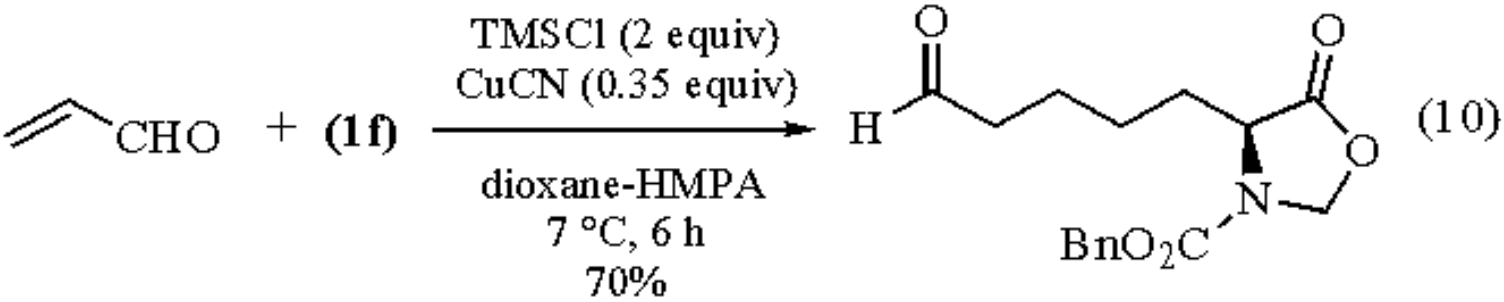

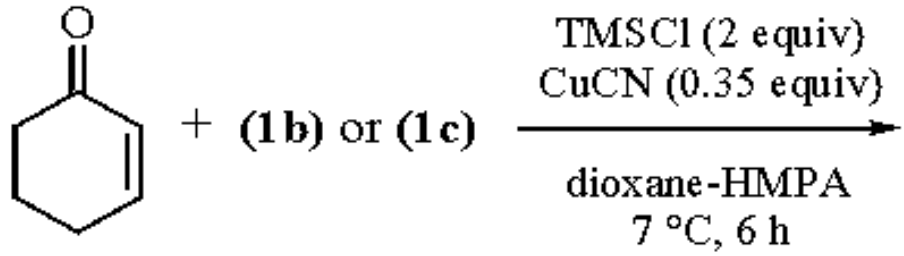

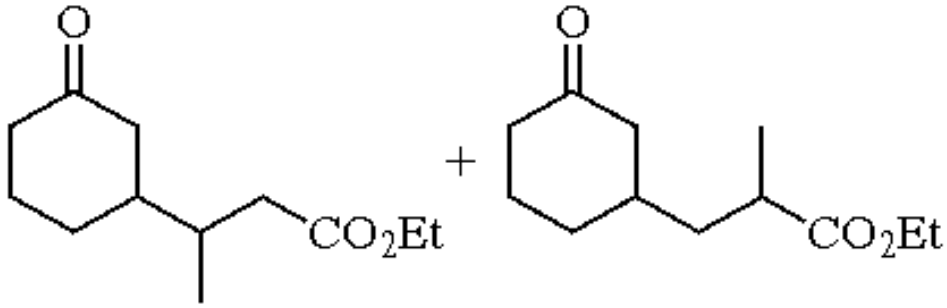

(11)

(78% from **(1c)**) (70% from **(1b)**)

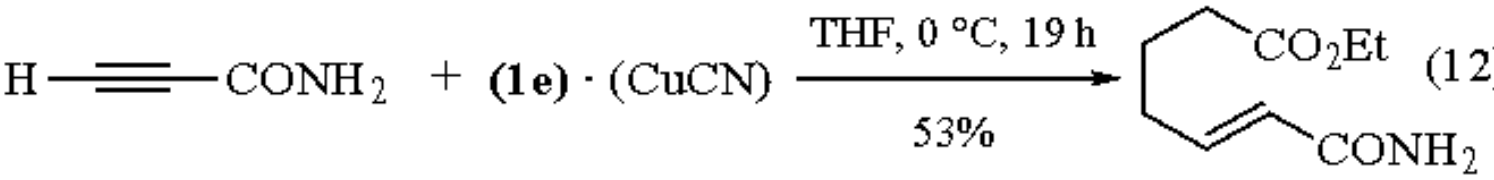

(12)

100% *E*

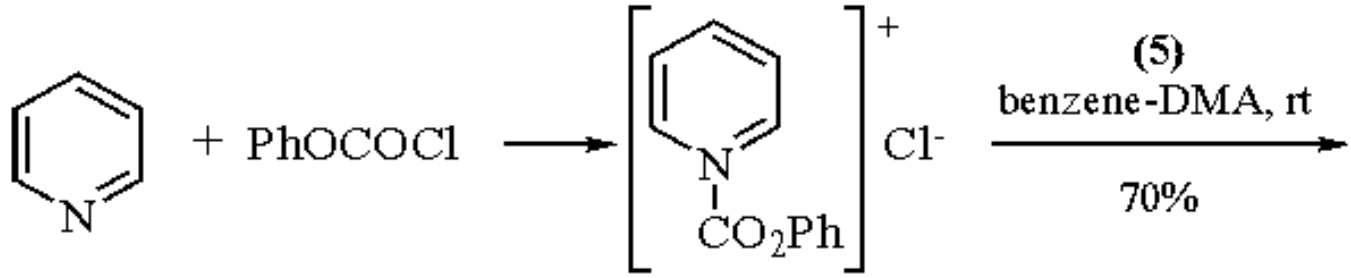

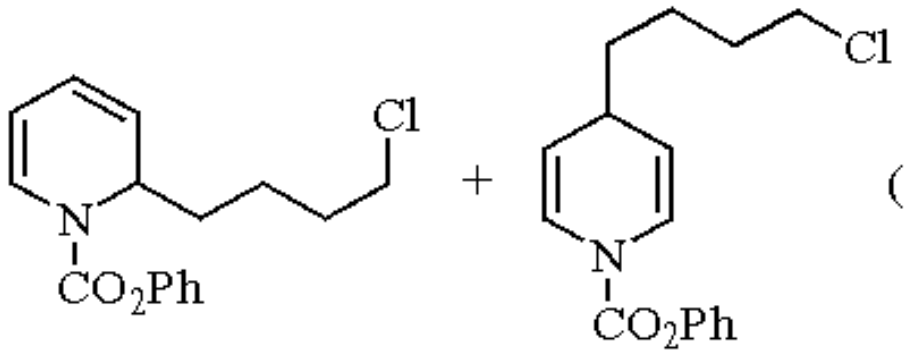

(13)

32:68

Allylation.

(3-Ethoxy-3-oxopropyl)iodozinc

Allylation of organozincs proceeds either catalytically (eqs 14 and 15)[17] or stoichiometrically (eqs 16 and 17)[14a] with respect to Cu^I salts. Generally, the stoichiometric reaction shows a higher regioselectivity (S_N2'/S_N2) and is applied to sequential double allylation reactions (eqs 16 and 17).[18,19]

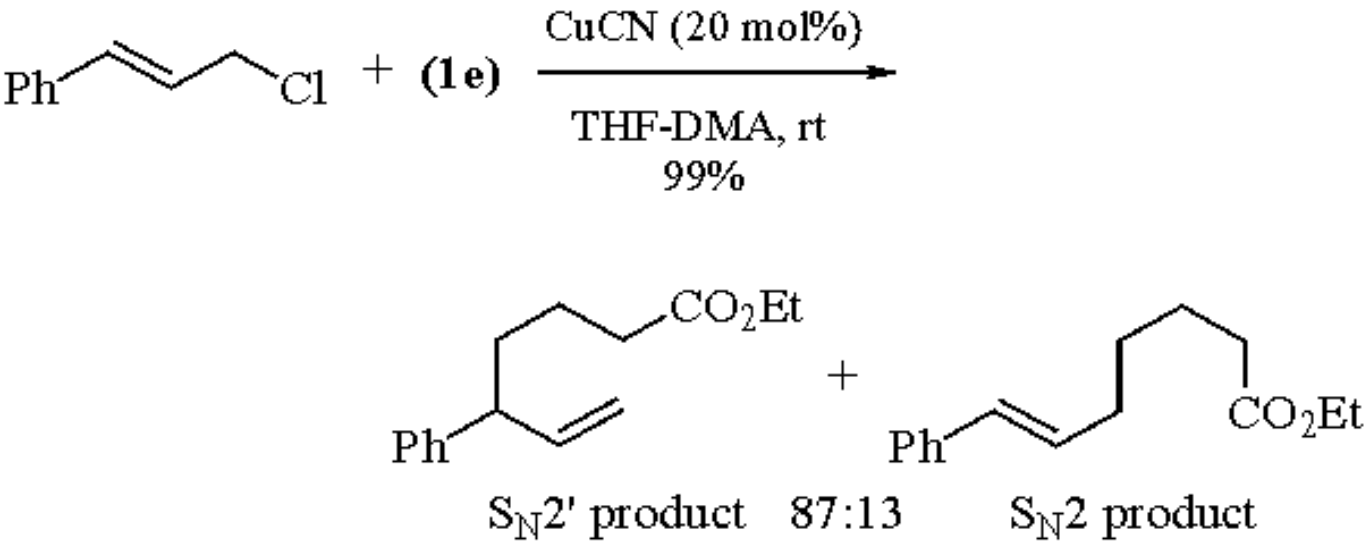

(14)

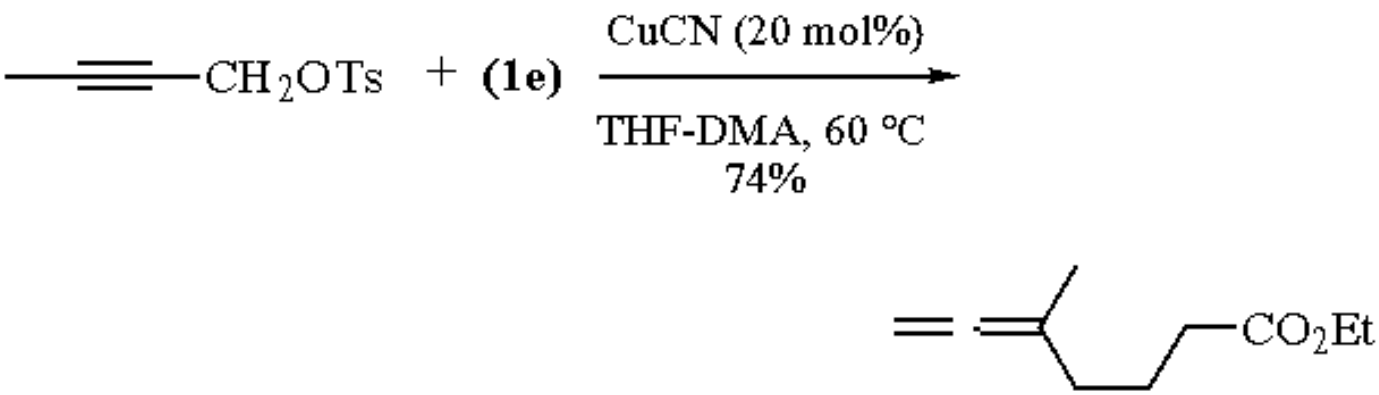

(15)

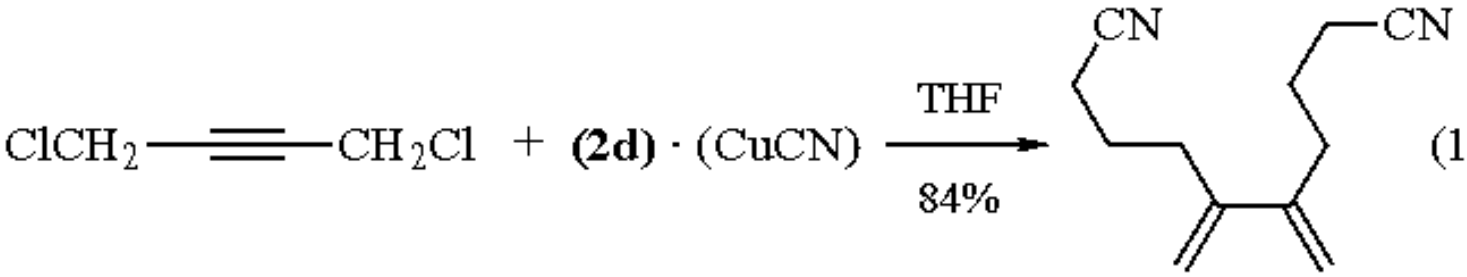

(16)

(3-Ethoxy-3-oxopropyl)iodozinc

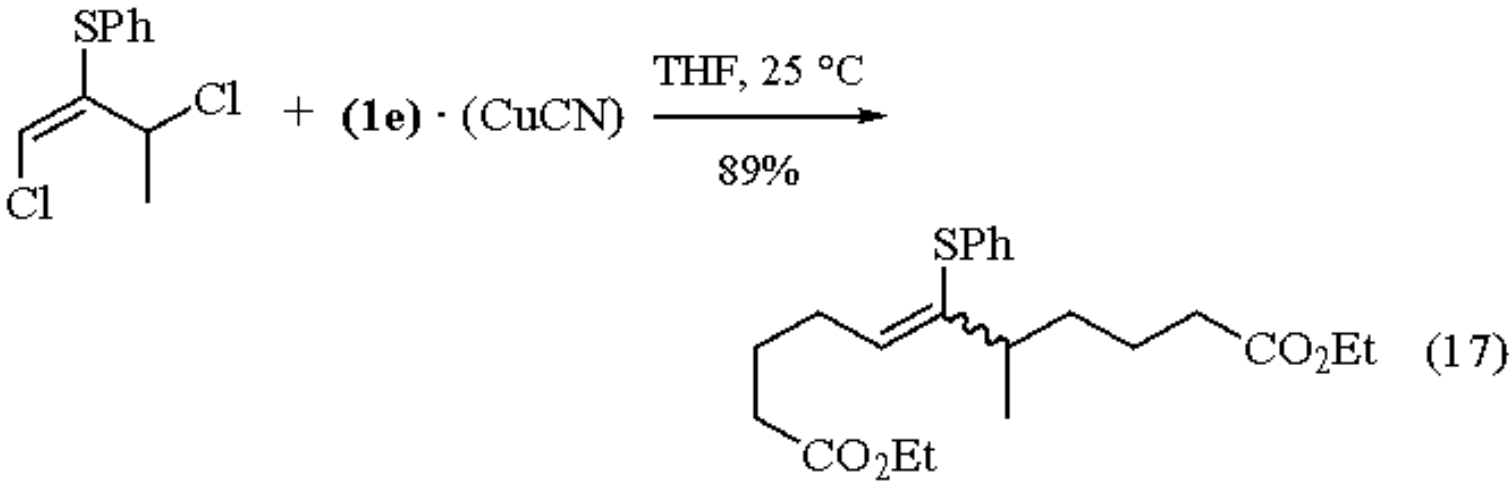

Addition to Carbonyls.

Functionalized organozincs react smoothly with aromatic aldehydes, but not with aliphatic aldehydes, in the presence of 2 equiv of chlorotrimethylsilane to give the alcohols in good yields (eqs 18 and 19).[15] Aliphatic aldehydes primarily provide the corresponding aldol products. Organocopper reagents may be sufficiently reactive toward both aromatic and aliphatic aldehydes in the presence of 2 equiv of ***Boron Trifluoride Etherate*** (eq 20).[20] Organotitanium reagents, prepared by the reaction of organozincs and ***Chlorotitanium Triisopropoxide***, are reactive toward aldehydes and ketones (eq 21).[21] Dialkylzincs (e.g. bis(γ-ethoxycarbonylpropyl)zinc) undergo an enantioselective addition to aldehydes in the presence of 2 equiv of ***Titanium Tetraisopropoxide*** and a catalytic amount of a chiral amide ligand.[22] In the presence of trialkylsilyl chloride and at elevated temperatures, β-zincio esters intramolecularly add to the ester carbonyl to provide allyloxysiloxycyclopropanes in moderate yields (eq 22).[23] These allyloxy derivatives are difficult to prepare according to Salaün's procedure.[24] The isomerization of (**1c**) to (**1b**) (eq 18) may involve cyclization similar to the one shown in eq 22.

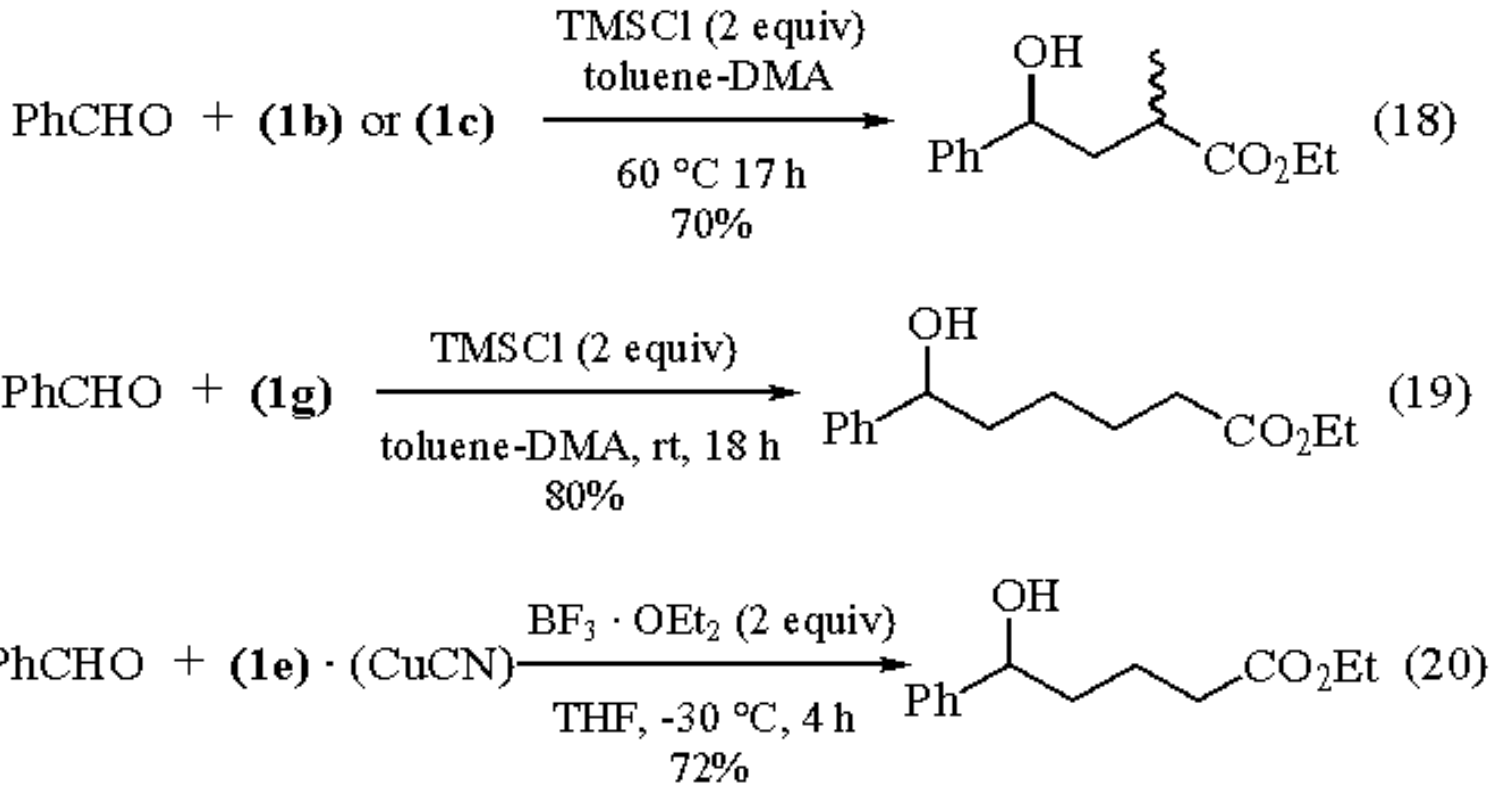

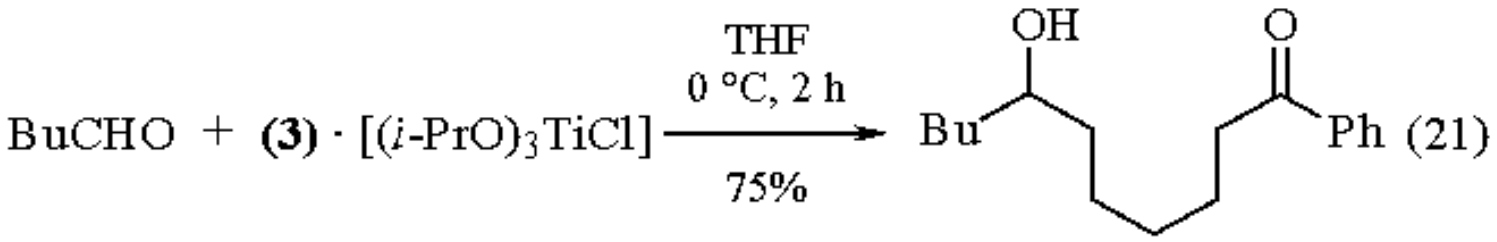

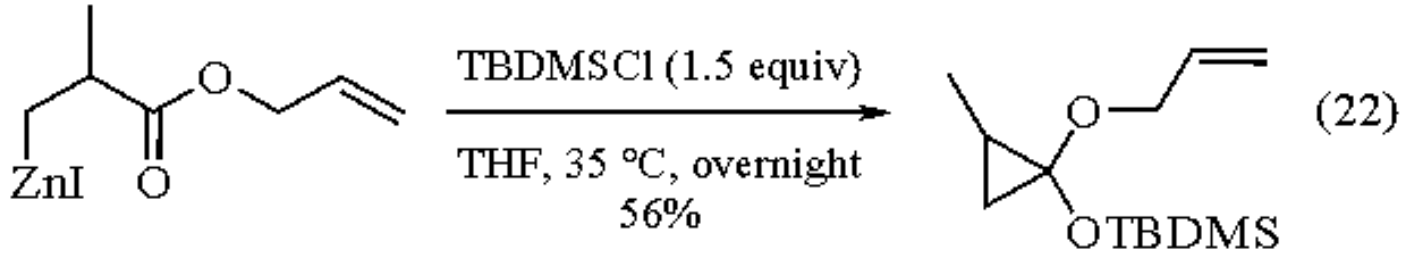

Related Reagents.

See also, for example, ***Ethyliodomethylzinc***, ***Ethylzinc Iodide***, ***2-Iodopropane***, ***Potassium Iodide-Zinc/Copper Couple***, and entries for zinc halides (and zinc combination reagents).

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1-Ethoxy-1-propene[1]

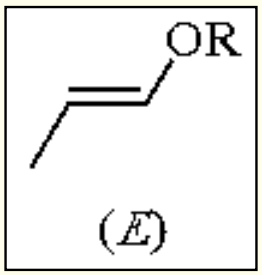

(**1**; R = Et)

[928-55-2] · $C_5H_{10}O$ · 1-Ethoxy-1-propene · (MW 86.15) (*E*)-(**1**)

[4696-26-8] (*Z*)-(**1**)

[4696-25-7] (*E*)-(**2**; R = Me)

[4188-69-6] · C_4H_8O · 1-Methoxy-1-propene · (MW 72.12) (*Z*)-(**2**)

[4188-68-5]

(condensation with acetals to give α,β-unsaturated aldehydes;[3] acyl anion equivalent;[4] [4 + 2][5] and [2 + 2][6] cycloaddition reactions; transvinylation to prepare allyl vinyl ethers[7])

Physical Data: (**1**) bp 69-71 °C; *d* 0.778 g cm^{-3}. (*E*)-(**1**) bp 75 °C. (*Z*)-(**1**) bp 69 °C. (*E*)-(**2**) bp 48.5 °C. (*Z*)-(**2**) bp 45 °C.[2]

Solubility: sol most common organic solvents; slightly sol water.

Form Supplied in: colorless, extremely flammable liquids, obtained as a mixture of (*E*)/(*Z*) isomers by the pyrolysis of the corresponding acetals over pumice or $NaHSO_4$.[2b,c] The (*E*)/(*Z*) isomers have been separated by fractional distillation[2b,8] and by preparative-scale gas chromatography.[6a] Pure (>97%) (*E*) isomers of propenyl ethers have been prepared by H_2-activated ***(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) Hexafluorophosphate*** catalyzed isomerization of allyl alkyl ethers.[9] 1-Ethoxy- but not 1-methoxy-1-propene is available commercially. 1-Ethoxy-1-propene is a skin irritant, moderately toxic by skin absorption, ingestion, and inhalation.[2c] Biological data on 1-methoxy-1-propene are unavailable. Use in a fume hood.

Condensation with Acetals.

Lewis acid-catalyzed condensations of 1-ethoxy-1-propene (**1**) with acetals give, after hydrolysis of the intermediate alkoxy acetals, α,β-unsaturated aldehydes and ketones.[3] Of the Lewis acids, ***Zinc Chloride*** and ***Boron Trifluoride Etherate*** are the most frequently used, although ***Montmorillonite K10*** can offer certain advantages, such as ease of workup.[10] In a study of the condensation of acetals with methyl vinyl ether in the presence of $BF_3.OEt_2$, the order of reactivity was found to be: acetals from α,β-unsaturated aldehydes > benzaldehyde acetals > methyl orthoformate > acetals from saturated aldehydes.[11] The enol ether-acetal condensation is exemplified by a synthesis of the C_{19} carotenal (**4**) from the C_{16} acetal (**3**) using (**1**) in the presence of $ZnCl_2$ (eq 1).[12]

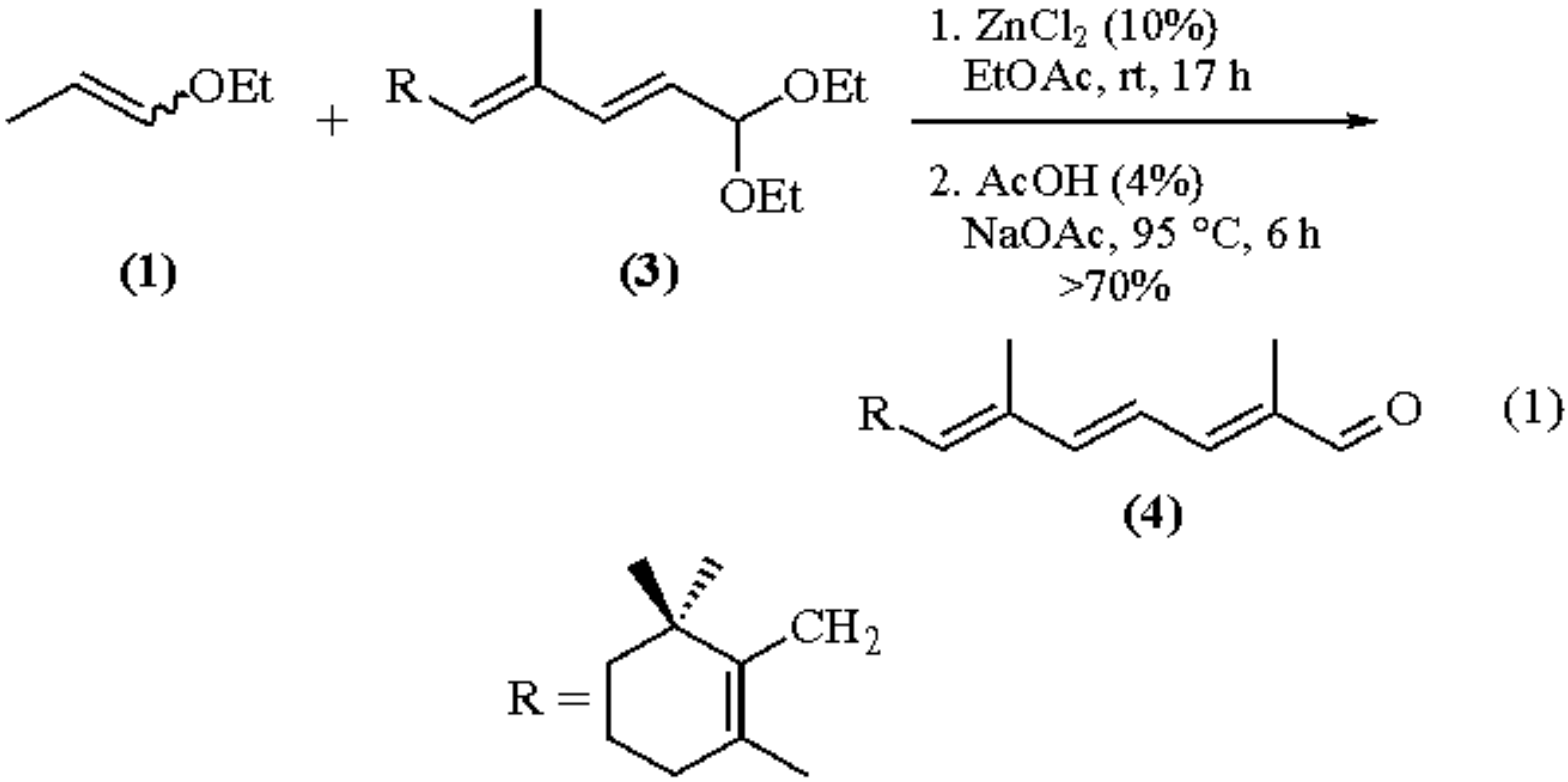

(1)

Acyl Anion Equivalent.

Deprotonation of the α-H of (**1**) with ***t-Butyllithium*** at -74 °C, in THF or in *n*-pentane/TMEDA, generates the highly reactive α-alkoxy vinyl derivative (**5**) (eq 2), related lithio derivatives of which are known to react with a variety of electrophiles.[4]

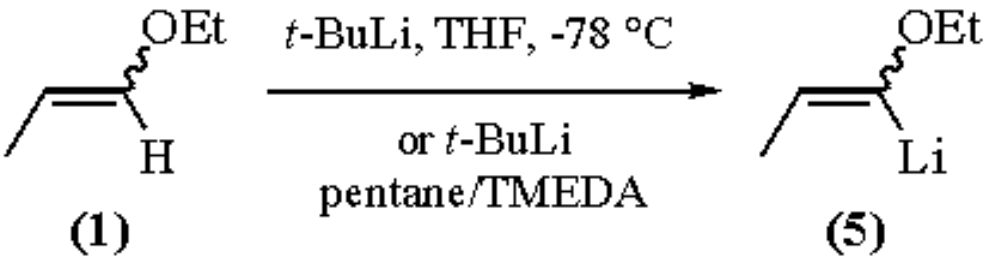

(2)

Cycloaddition Reactions.

Thermal [4 + 2] Addition.

1-Ethoxy-1-propene participates in a variety of inverse-electron-demand Diels-Alder reactions to give cycloadducts with high *endo* selectivity and retention of the dienophile alkene geometry. The (*E*) isomer reacts faster than the (*Z*) isomer, and improved reaction conditions include the use of high pressure and Lewis acid catalysis.[5] The cycloaddition of (**1**) to enals,[5] enones,[5] and α,β-unsaturated esters[13] is regiospecific, giving dihydropyrans in excellent yields, often with very high stereospecificity (eq 3).[14] Similarly, the thermal or pressure-promoted cycloaddition of (**1**) to *N*-sulfonyl-1-aza-1,3-butadienes produces tetrahydropyridines, generally in a highly stereospecific manner with predominant *endo* selectivity (eq 4).[15] Cycloaddition of (**1**) yields dihydrooxazines from nitrosoalkenes[16] or from azomethines,[17] and chromanes from quinone methides.[18]

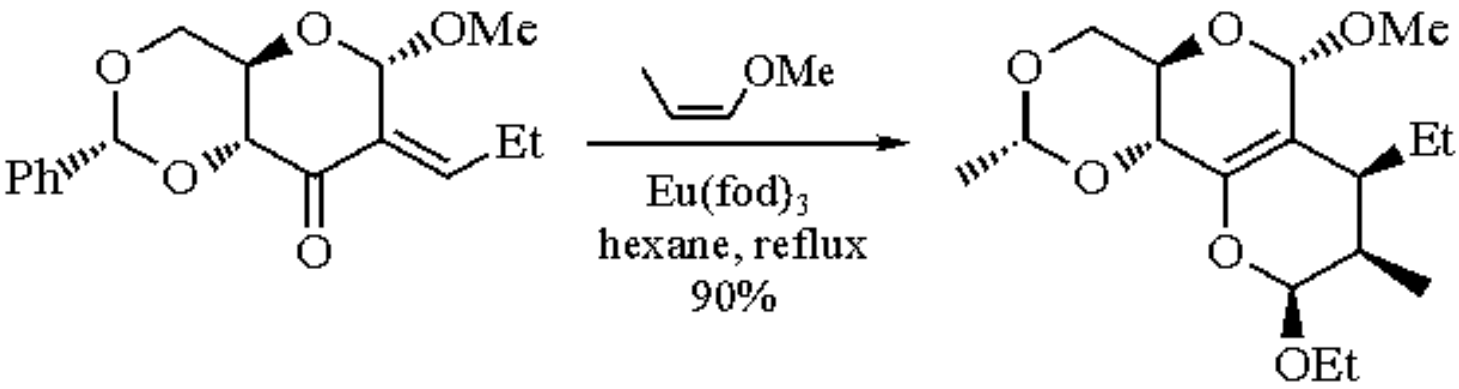

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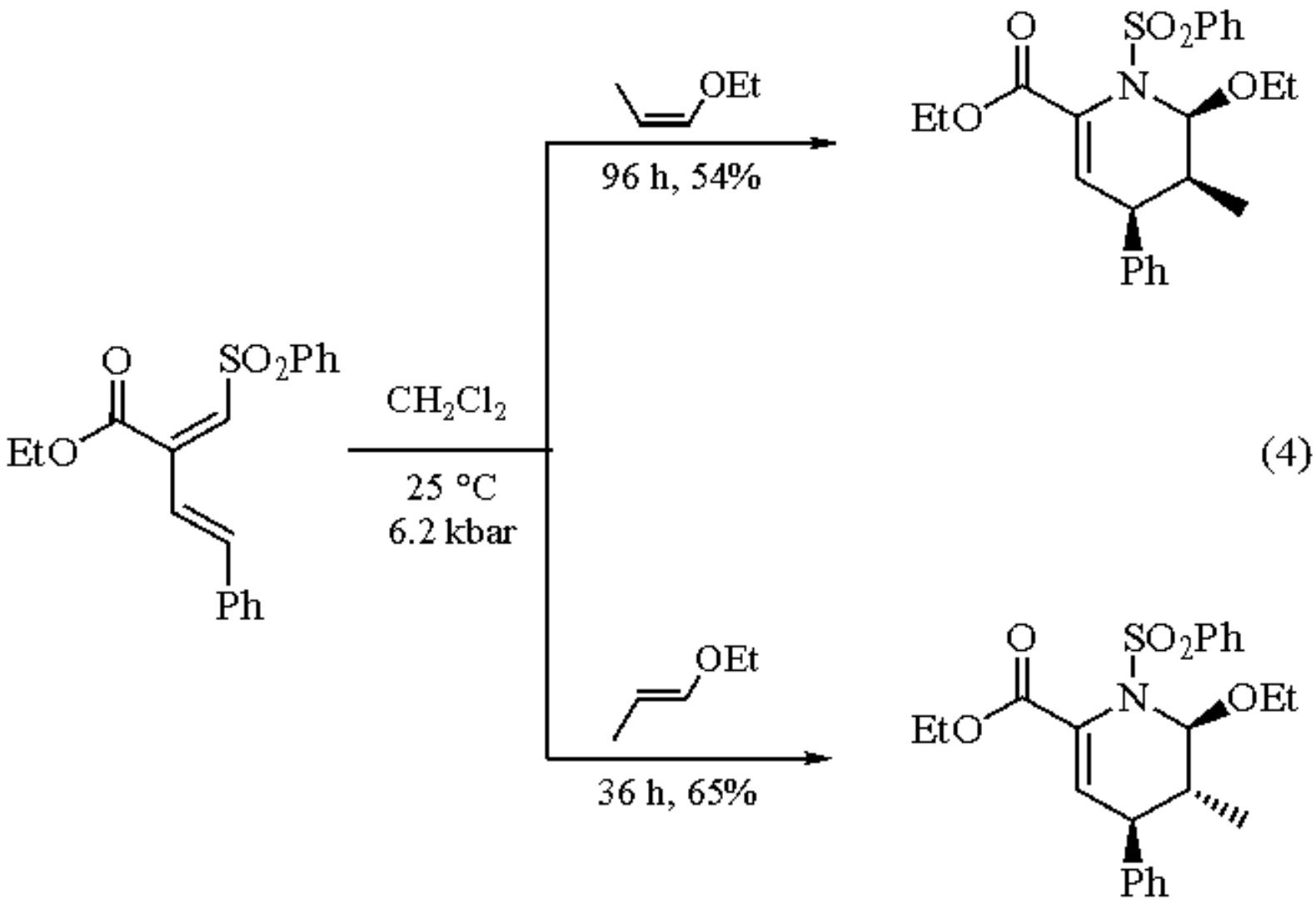

(4)

Thermal [2 + 2] Addition.

Electron-deficient alkenes react rapidly with (**1**) to give cyclobutane derivatives, with the (*Z*) isomer of (**1**) reacting faster than the corresponding (*E*) isomer. In general, stereoisomeric mixtures of products are obtained, which increase with solvent polarity (eq 5).[6] Ketenes give cyclobutanones (eq 6),[19,20] while *p*-tosyl isocyanate and *p*-tosyl isothiocyanate give *N*-tosyl azetidinone (eq 7)[20] and *N*-tosyl-2-thietaneimine (eq 8),[21] respectively, on cycloaddition with (**1**).

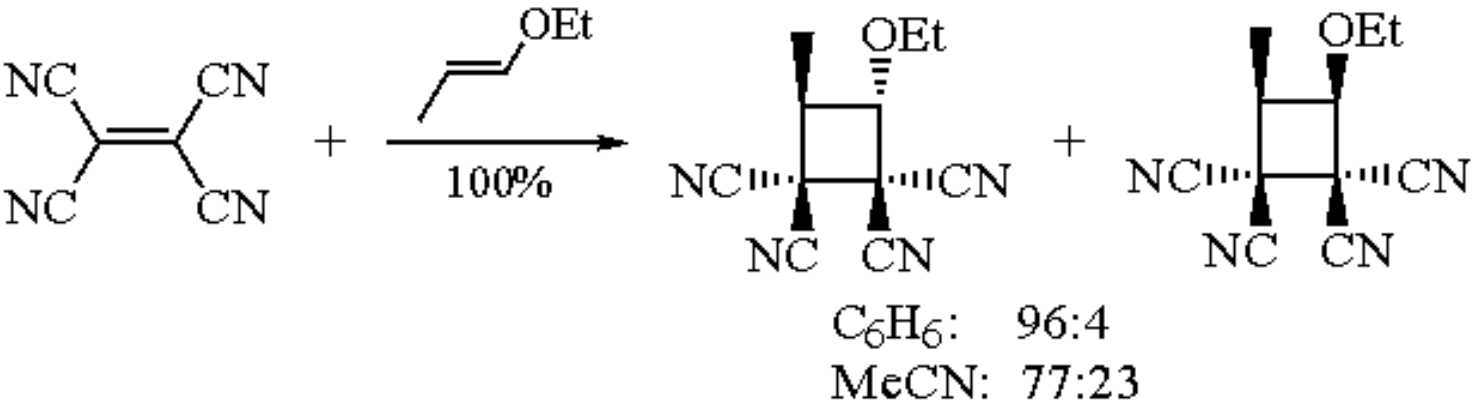

(5)

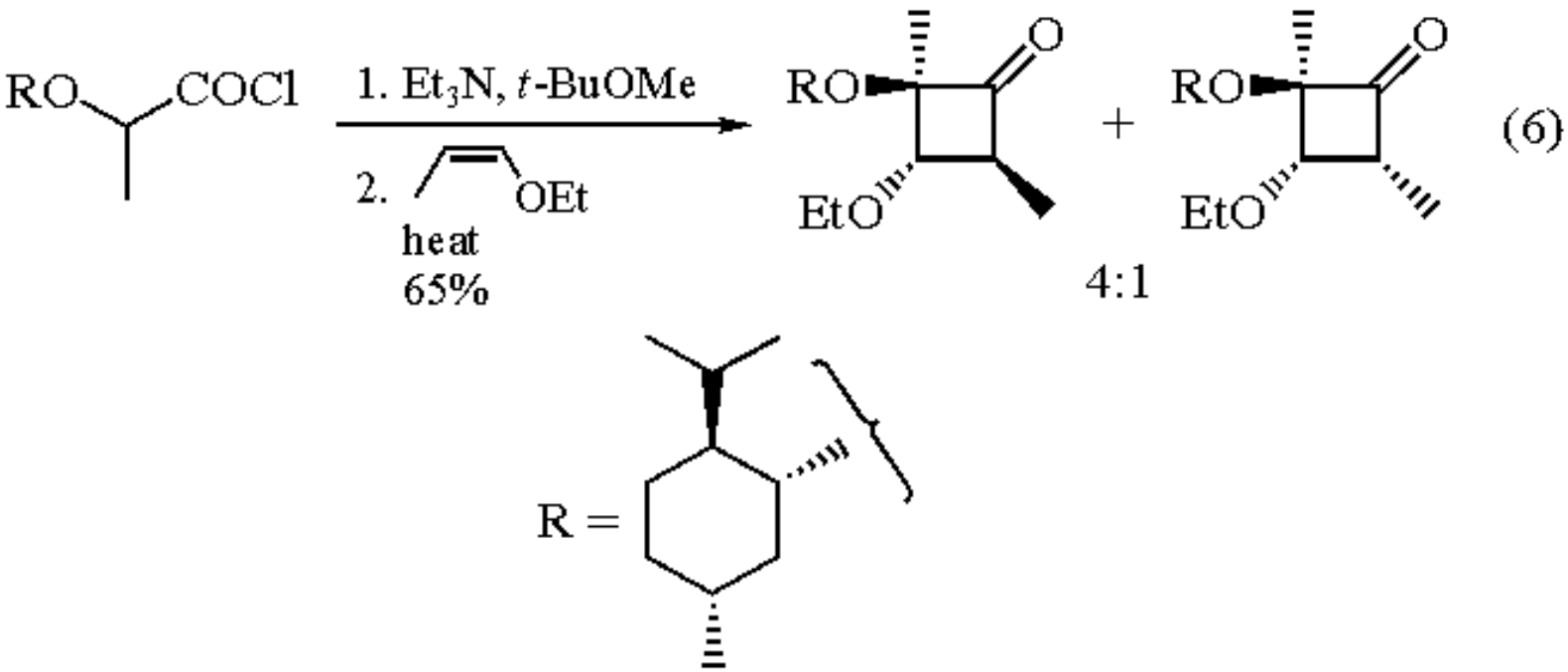

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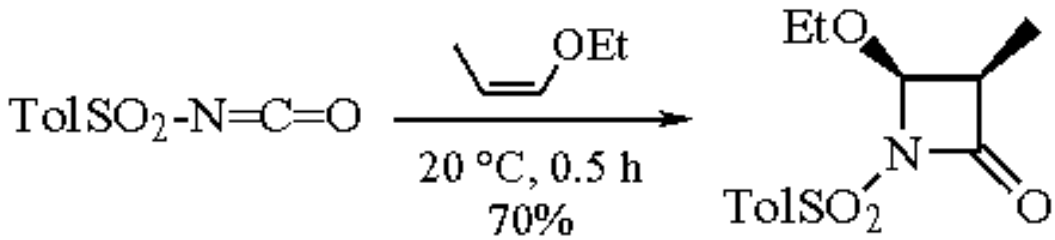

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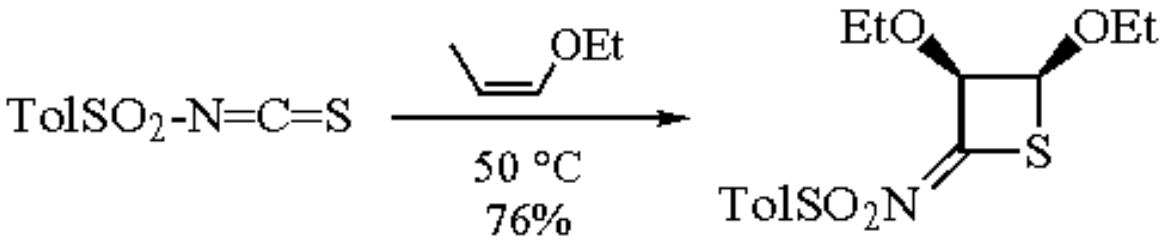

(8)

Photochemical Addition.

Photoaddition of vinyl ethers to α,β-enones produces alkoxycyclobutanes, and alkoxyoxetanes from aldehydes and ketones (see ***Ethyl Vinyl Ether***).[22] Although not with (**1**), extensive studies have been conducted on the cycloaddition of 1-methoxy-1-propene to acetone.[23]

Transvinylation.

In contrast to ethyl vinyl ether, (**1**) is rarely used in the transvinylation of alcohols. An example is the preparation of the aldehyde (**7**) in >51% yield by sequential transvinylation-Claisen rearrangement executed by heating an (*E*)/(*Z*) mixture of 1-ethoxy-1-propene with the allyl alcohol (**6**) in the presence of ***Mercury(II) Acetate*** (eq 9).[7]

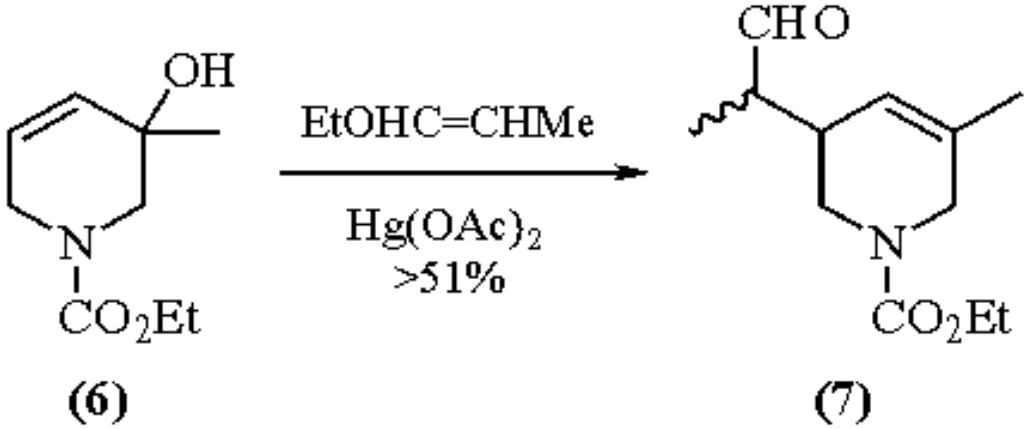

(9)

Related Reagents.

1-Ethoxyvinyllithium; ***Ethyl Vinyl Ether***; ***2-Methoxy-1,3-butadiene***; ***1-Methoxyvinyllithium***; ***Methylketene Dimethyl Acetal***; ***Propionaldehyde t-Butylimine***.

---

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(2-Ethoxy-1-propenyl)triphenylphosphonium Iodide

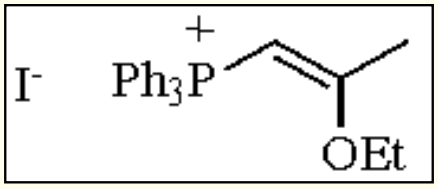

[62639-97-8] · $C_{23}H_{24}IOP$ · (2-Ethoxy-1-propenyl)triphenylphosphonium Iodide · (MW 474.29)

(precursor for 2-ethoxyallylidenetriphenylphosphorane, which is a three-carbon annulation reagent[1])

Physical Data: mp 163-165 °C.

Preparative Methods: by the condensation of ***Ethyl Iodide*** with 1-triphenylphosphoranylidene-2-propanone.[2]

Purification: recrystallization from methanol-ethyl acetate.

Handling, Storage, and Precautions: should be dried in vacuo for best results.

Annulation of Cyclohexanones.

Deprotonation of (2-ethoxy-1-propenyl)triphenylphosphonium iodide[1] with ***n-Butyllithium*** in hexanes gives 2-ethoxyallylidenetriphenylphosphorane (**1**) (eq 1).[2] This reagent has been used[2] to donate three carbon atoms in a [3 + 3] annulation of cyclohexenones onto enones for the construction of six-membered carbocyclic systems.[3]

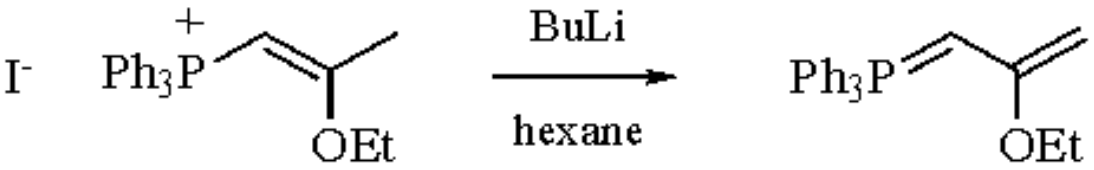

(1)

(1)

Thus the in situ generated ylide (**1**) reacts in a tandem Michael addition Wittig reaction with a variety of α,β-unsaturated ketones (**2**) to provide the 2-ethoxy-1,3-cyclohexadienes (**3**). These intermediates are subsequently hydrolyzed on workup with 1 N HCl to give the cyclohexenones (**4**) in 26-61% overall chemical yield (eq 2).[4] This reaction sequence has been used for the construction of monocyclic, fused bicyclic, and spiro bicyclic ring systems.[2]

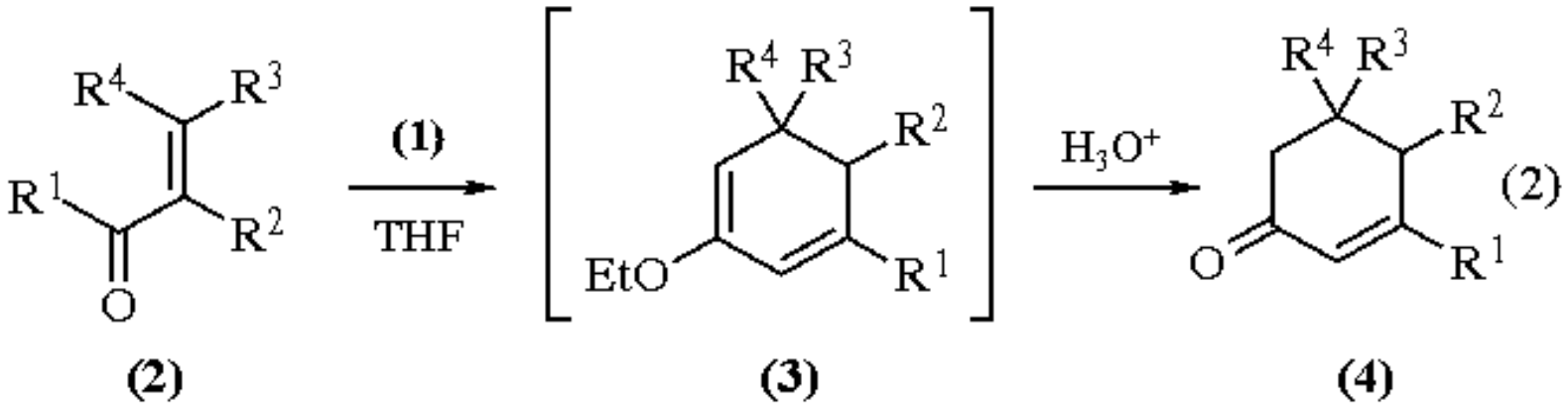

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Vertex Pharmaceuticals, Cambridge, MA, USA

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2-Ethoxypyridine 1-Oxide

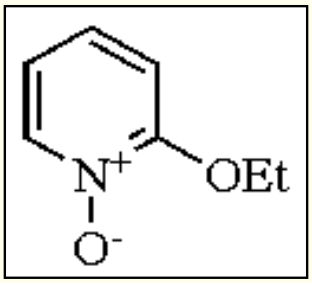

[3445-09-8] · $C_7H_9NO_2$ · 2-Ethoxypyridine 1-Oxide · (MW 139.16)

(acyl activating agent for peptide synthesis;[1] catalyst for phosphotriester bond formation[2])

Physical Data: mp 72-74 °C.

Solubility: sol ethanol, acetic acid.

Preparative Methods: from 2-ethoxypyridine and ***Hydrogen Peroxide***[3] or 2-chloropyridine 1-oxide and ethanolic ***Sodium Ethoxide***.[4]

Peptide Synthesis.[1]

Reacts with acid chlorides to give activated esters which can be condensed with amino acids, giving 1-hydroxy-2(1*H*)-pyridone as a water-soluble byproduct (eq 1). This is an advantage over coupling using ***1,3-Dicyclohexylcarbodiimide*** because of the easier separation of byproducts.

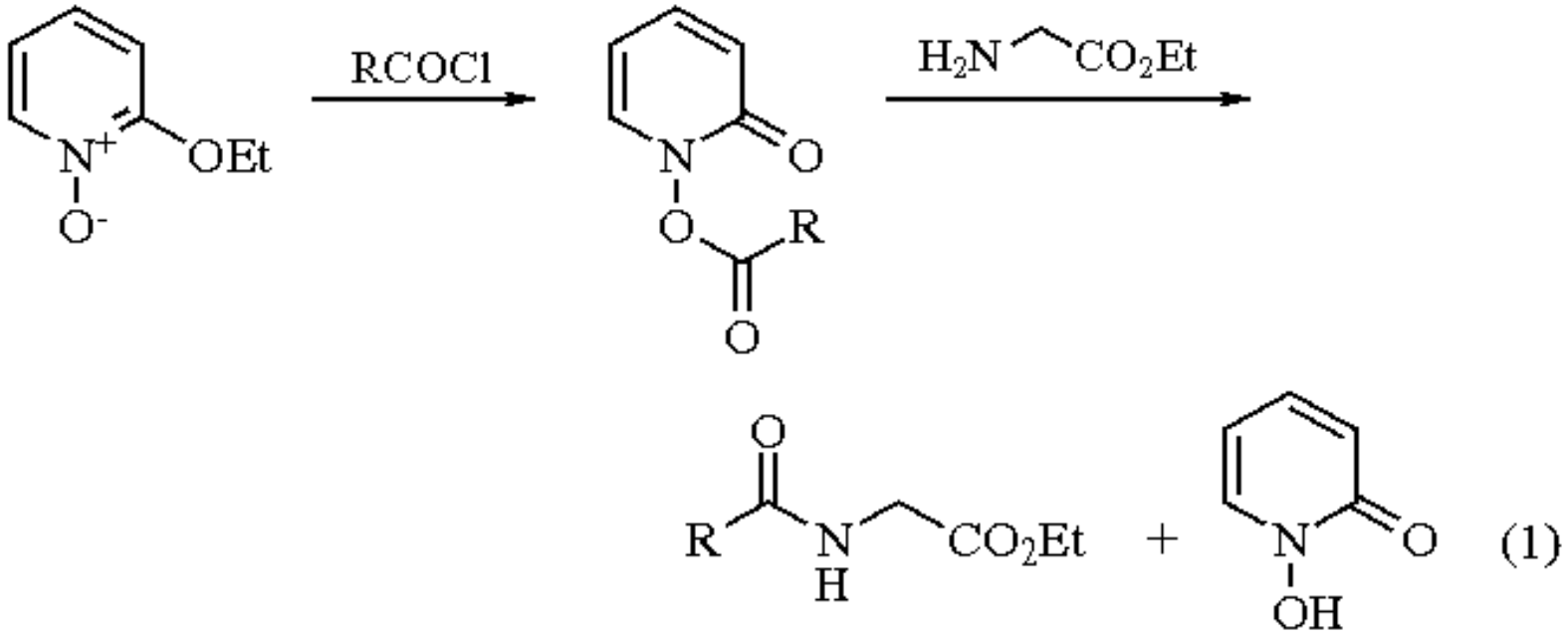

Phosphotriester Bond Formation.[2]

One of a range of oxygen-nucleophilic catalysts for phosphotriester bond formation which gives few byproducts. 4-Ethoxypyridine 1-oxide is even faster.[2]

---

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University of Cambridge, UK

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1-Ethoxy-4-tributylstannyl-1,3-butadiene[1]

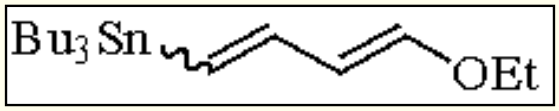

[66876-05-9] · $C_{18}H_{27}OSn$ · 1-Ethoxy-4-tributylstannyl-1,3-butadiene · (MW 386.91)

(reagent for the four-carbon homologation of aldehydes and ketones to dienals)

Physical Data: bp 120-130 °C/0.3 mmHg.[2]

Solubility: sol THF.

Preparative Methods: prepared as a mixture of (*E*) and (*Z*) isomers by the hydrostannation of 1-ethoxy-1-buten-3-yne with one equivalent of ***Tri-n-butylstannane*** and catalytic ***Azobisisobutyronitrile***.[2]

Purification: purified by distillation.[2]

Handling, Storage, and Precautions: organostannane reagents are potentially toxic;[3] their preparation and use must therefore be conducted wearing appropriate protective clothing in a well ventilated hood. The reagent should be stored under an inert atmosphere and protected from light and moisture.

Transmetalation.

Transmetalation of 1-ethoxy-4-tributylstannyl-1,3-butadiene (**1**) with one equivalent of ***n-Butyllithium*** at -78 °C proceeds smoothly to afford 1-lithio-4-ethoxy-1,3-butadiene (**2**).[2] This reagent reacts with aldehydes and ketones to yield the expected 1,2-adducts. Treatment of the resulting enol ethers with catalytic acid promotes the rearrangement to afford dienal products[2,4] (eq 1).[4a] Substrates which are sensitive to acidic environments can be converted to dieneals by treatment of the corresponding allylic mesylate with ***Triethylamine*** (eq 2).[5] This overall procedure provides (*E*,*E*)-dieneals in high geometric purity from aldehydes. Condensation of (**2**) with ketones affords mixtures of (*E*,*E*) and (*E*,*Z*) products.[2] Consequently, this reagent is of less synthetic utility for the homologation of ketones to geometrically pure (*E*,*E*)-dienals.

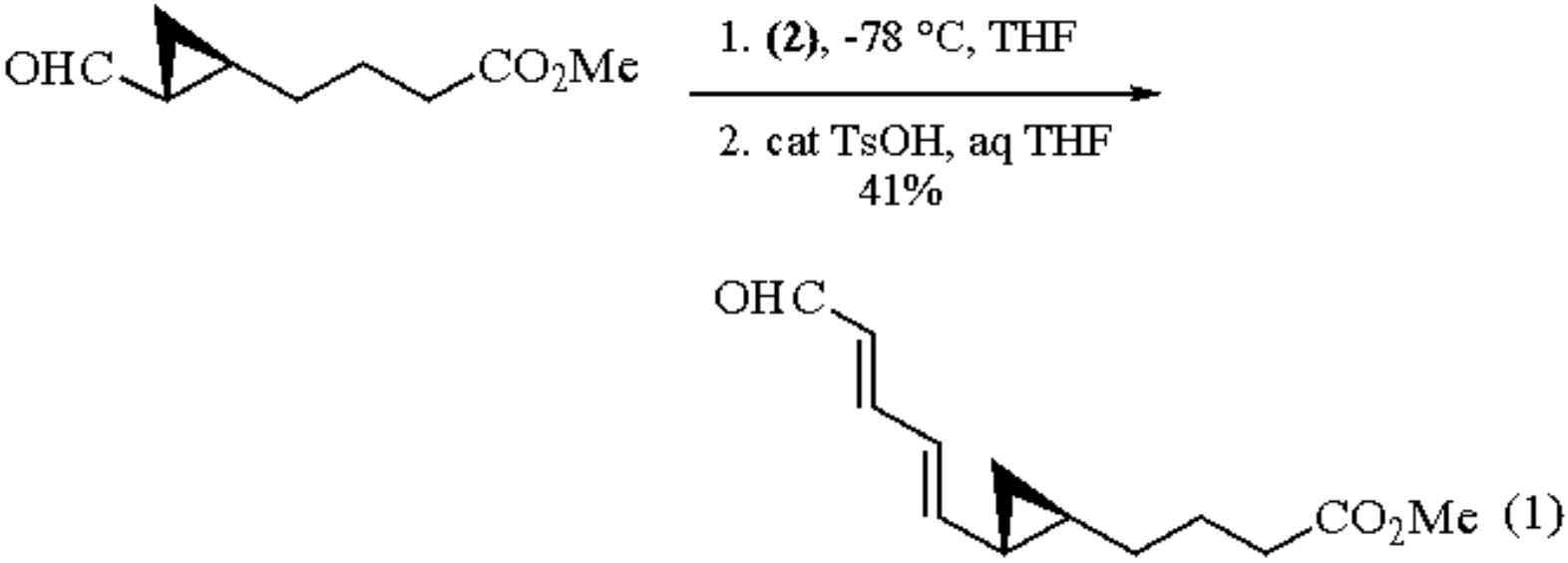

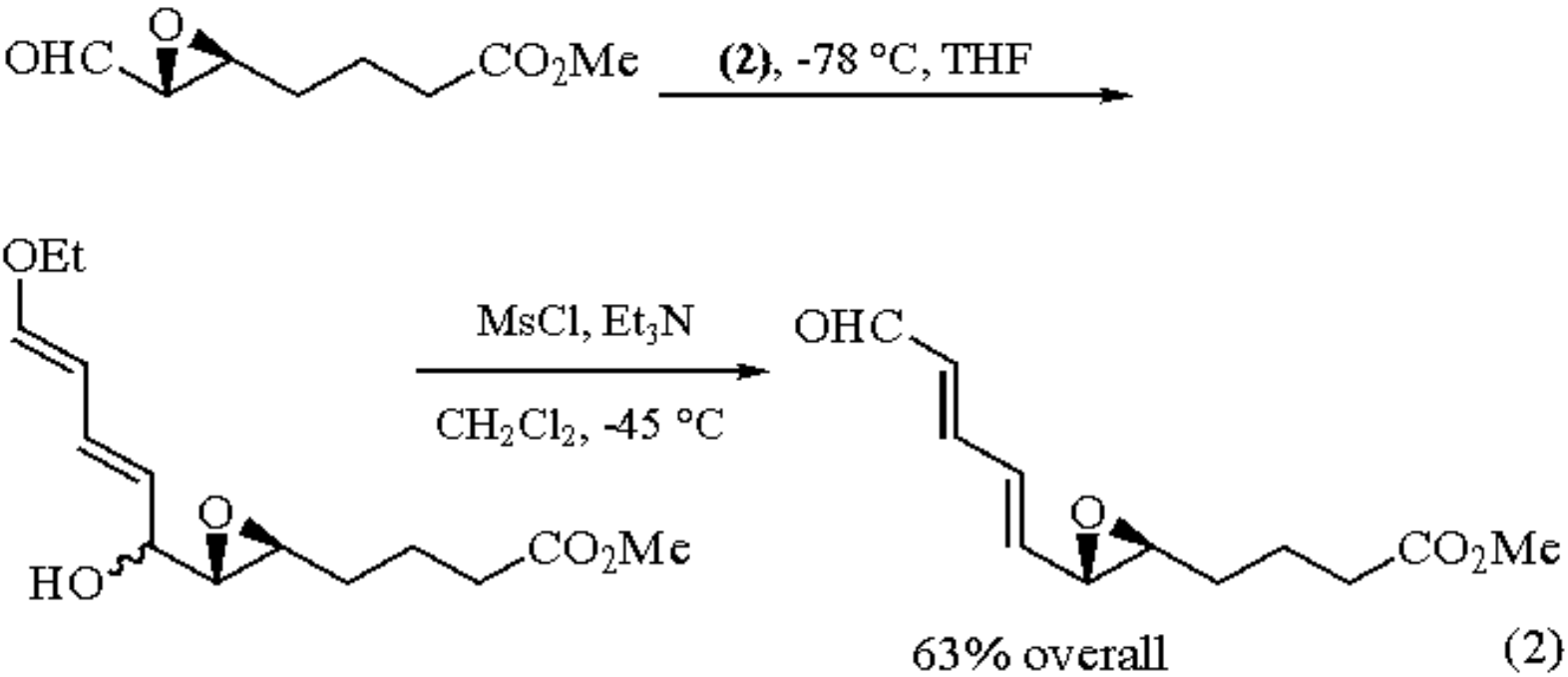

The iterative condensation of (**2**) provides an efficient method for the preparation of (*E*)-polyenals with high isomeric purity.[6,7] This approach was found to be superior to either the Wittig-Horner or Corey's lithio-*N*,*N*-dimethylhydrazone homologation procedures for the construction of geometrically pure hexenal (**3**) (eq 3).[6,7]

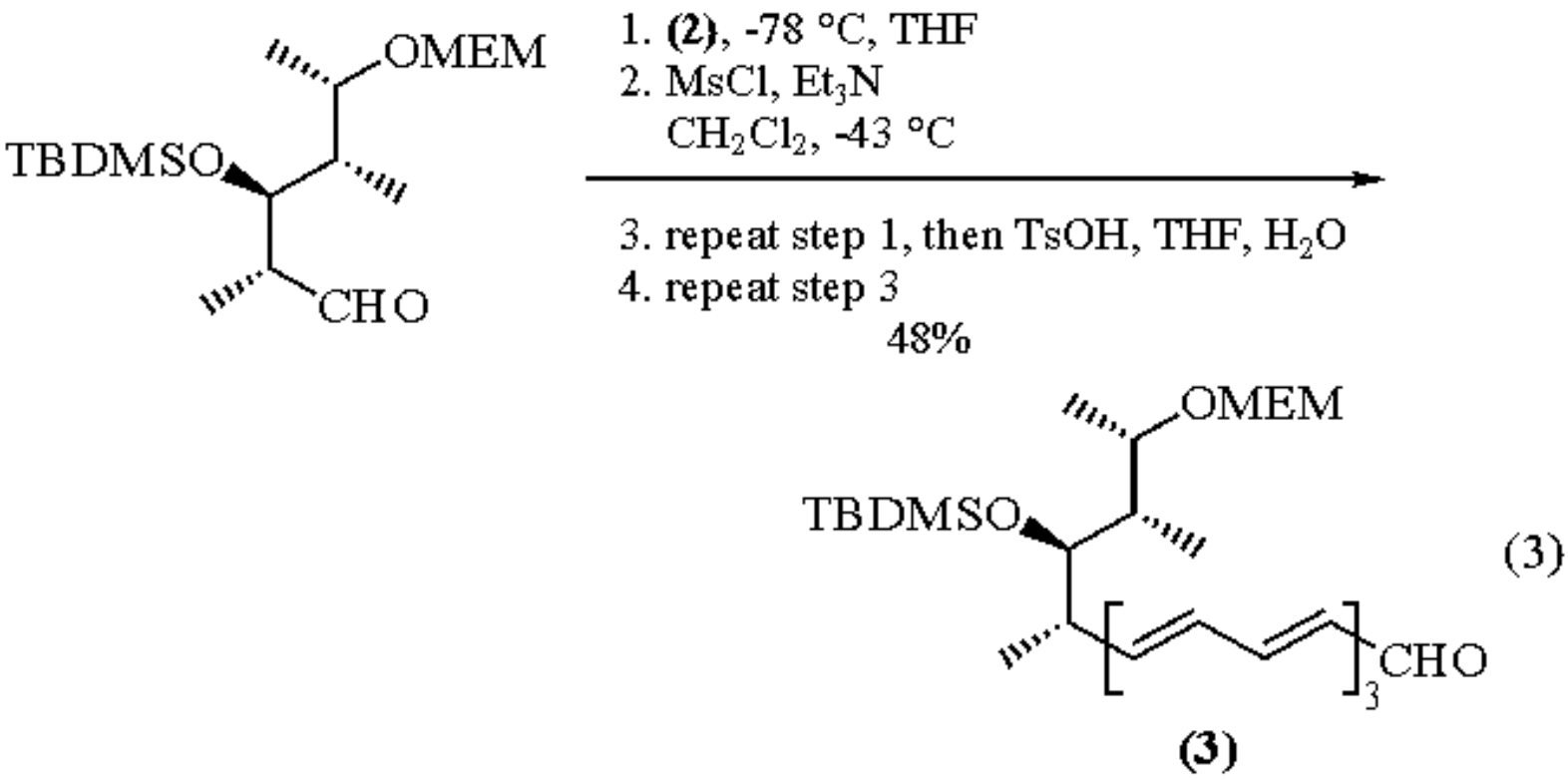

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1-Ethoxy-2-tributylstannylethylene[1]

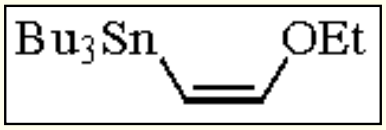

[64724-29-4] · $C_{16}H_{25}OSn$ · 1-Ethoxy-2-tributylstannylethylene · (MW 362.89)

(versatile synthon for acetaldehyde anion)

Physical Data: bp 110 °C/0.3 mmHg.[3a]

Solubility: sol THF, DMF, MeCN.

Preparative Methods: prepared in high yield by the reductive hydrostannation of ***Ethoxyacetylene*** with ***Tri-n-butylstannane***.[2,3a]

Purification: by distillation.[3a]

Handling, Storage, and Precautions: organostannane reagents are potentially toxic;[4] their preparation and use must therefore be conducted wearing appropriate protective clothing in a well ventilated hood. The reagent should be stored under an inert atmosphere and protected from light and moisture.

Transmetalation.

Treatment of 1-ethoxy-2-tributylstannylethylene (**1**) with ***n-Butyllithium*** proceeds quantitatively to afford (*E*)-2-ethoxyvinyllithium.[3] This reagent exhibits reactivity typical of vinyllithium reagents, affording entry into a variety of substituted enol ethers which are readily hydrolyzed to the corresponding acetaldehyde derivative.[3] For further discussion of this chemistry, see ***1-Ethoxyvinyllithium***.

Cross-Coupling Reactions.

Stille et al. pioneered the palladium-catalyzed cross-coupling reaction of organostannanes with a variety of electrophilic partners. These reactions proceed under mild conditions which are often compatable with typically sensitive functional groups.[1]

Aromatic halides, with the exception of phenols and unsubstituted anilines, couple smoothly with (**1**) to afford the corresponding (*Z*)-enol ether (eq 1).[5] Heteroaromatic halides and triflates also react smoothly with (**1**).[5,6] In several cases, mixtures of (*E*)- and (*Z*)-enol ethers were obtained with electron-deficient heteroaromatic substrates.[5b,6]

Coupling of (**1**) with an *ortho* heterosubstituted aromatic substrate followed by hydrolysis to the acetaldehyde and cyclization is a convenient and flexible method for the preparation of functionalized heterocycles (eq 2).[5b] Benzofurans, indoles, isocoumarins, pyranopyridinones, and pyrrolopyridines have been prepared using this sequence.[5b]

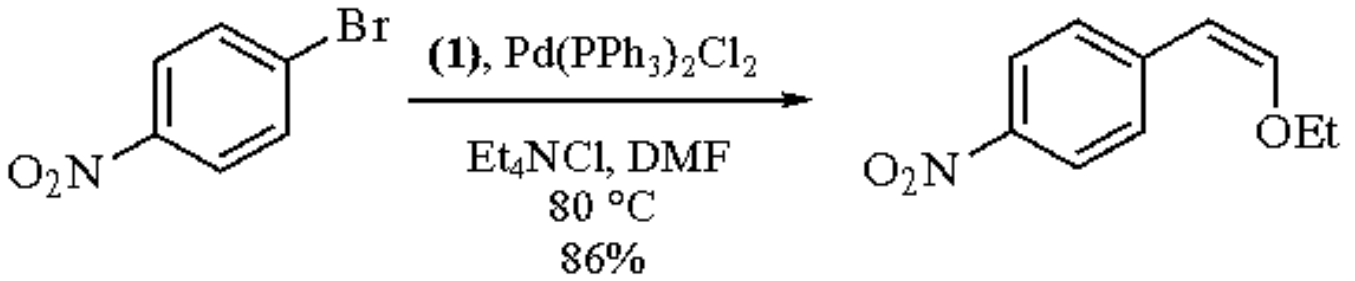

(1)

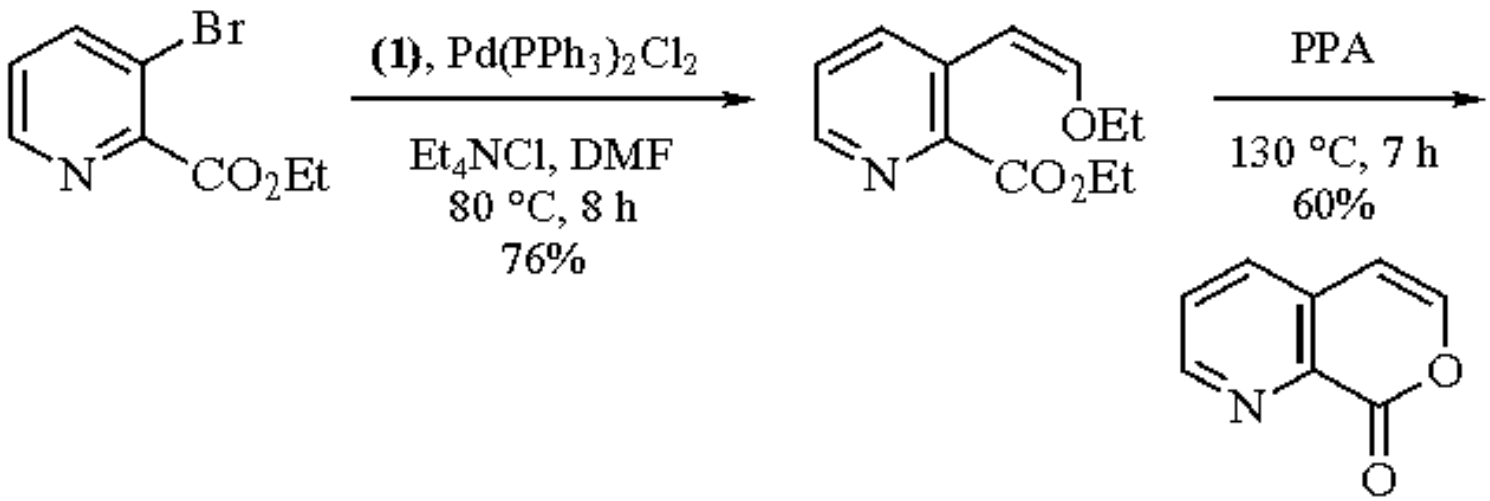

(2)

Palladium-catalyzed carbonylative coupling of (**1**) with aromatic iodides affords (*E*)-3-ethoxy-1-phenyl-2-en-3-ones in moderate yield.[7] Under similar coupling conditions the corresponding aryl bromides yield none of the expected product. Electron-deficient aromatic systems are poor substrates for this reaction. In such cases the rate of direct insertion of (**1**) is competitive with the carbonylative coupling reaction. For example, carbonylative coupling of (**1**) with 4-nitroiodobenzene afforded (*E*)-3-ethoxy-1-(4-nitrophenyl)prop-2-en-1-one and (*Z*)-2-ethoxy-1-(4-nitrophenyl)ethylene in 25% and 40% yields, respectively. Chromones and 4(1*H*)-quinolones have been prepared from these intermediates (eq 3).[7]

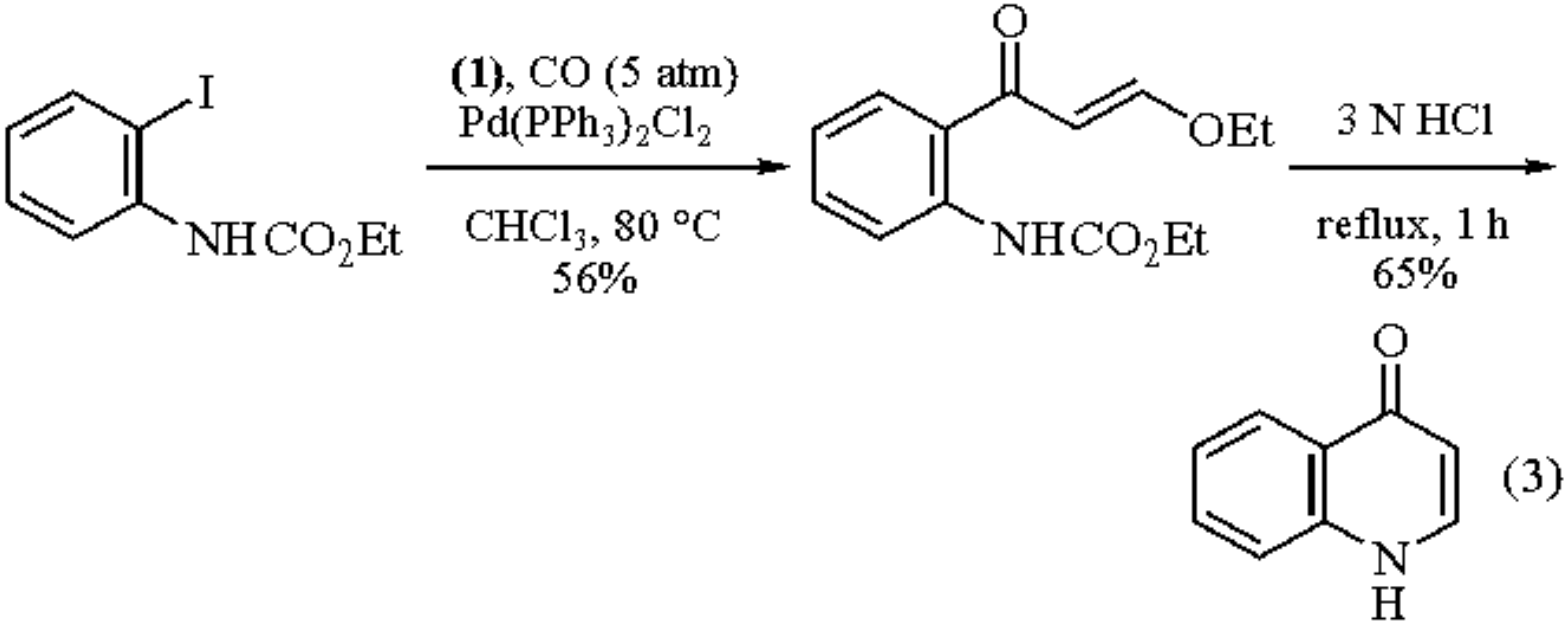

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Ethoxy(trimethylsilyl)acetylene

EtO-C&tbond;C-SiMe$_3$

[1000-62-0] · $C_7H_{14}OSi$ · Ethoxy(trimethylsilyl)acetylene · (MW 142.27)

(mild agent for conversion of carboxylic acids into carboxylic anhydrides;[1] dehydrative condensation agent for carboxylic acids and amines and alcohols;[2] trimethylsilylketene precursor;[3] 2π component in cycloaddition reactions[4])

Physical Data: bp 57 °C/34 mmHg; *d* 0.828 g cm^{-3}.

Solubility: insol H_2O; freely sol most common solvents.

Form Supplied in: colorless liquid; widely available.

Preparative Methods: by silylation of ***Ethoxyacetylene***.[1,3,5]

Handling, Storage, and Precautions: storable in a refrigerator for years without any polymerization or decomposition (one of the features that favors the use of this reagent over ethoxyacetylene for many applications).

Carboxylic Anhydrides.

Dehydration of carboxylic acids or dicarboxylic acids to the corresponding anhydrides is effected by using ethoxy(trimethylsilyl)acetylene (**1**). In general, a carboxylic acid is treated with 1.5 equiv of (**1**) in CH_2Cl_2, $ClCH_2CH_2Cl$, or MeCN at rt to 60 °C for 2 h to 1 d followed by concentration of the reaction mixture to give a pure anhydride in an almost quantitative yield (eq 1).[1] The only byproduct of this reaction is the neutral and volatile ethyl (trimethylsilyl)acetate. Use of ethoxyacetylene for this purpose has been limited because of its instability to heat, high volatility, and low reactivity with some carboxylic acids.[6] The reagent (**1**) resolves these problems and is especially effective for preparation of the carboxylic anhydrides with acid-sensitive functional groups such as (**2**)[1] and (**3**).[7] Suitably functionalized homophthalic anhydrides (**2**) and (**4**)[8] and their heteroaromatic derivatives (**5**)[9] are key intermediates for total synthesis of natural anthracyclines and their heteroaromatic analogs.

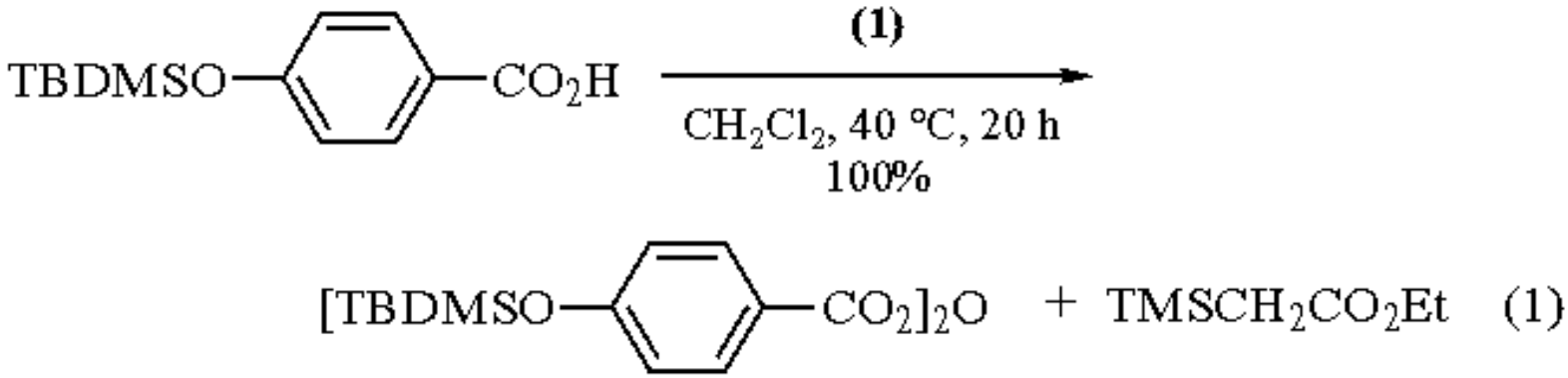

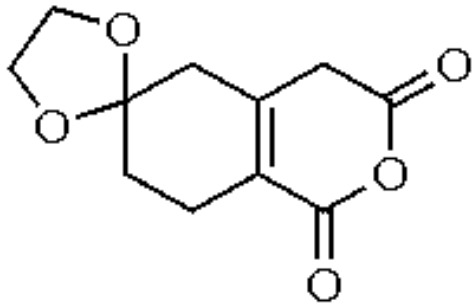

(2) 99%

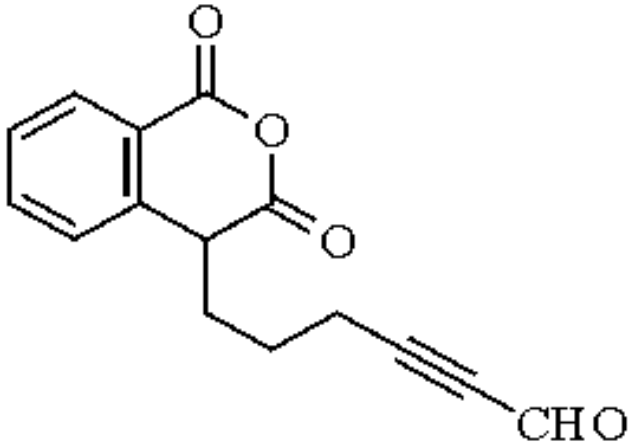

(3) 100%

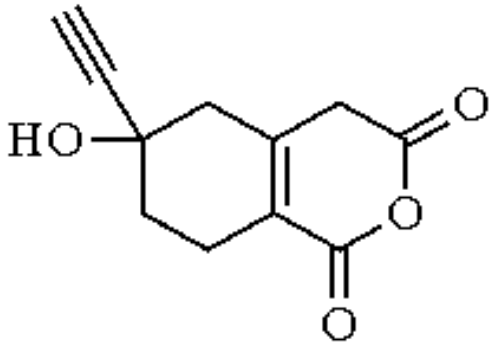

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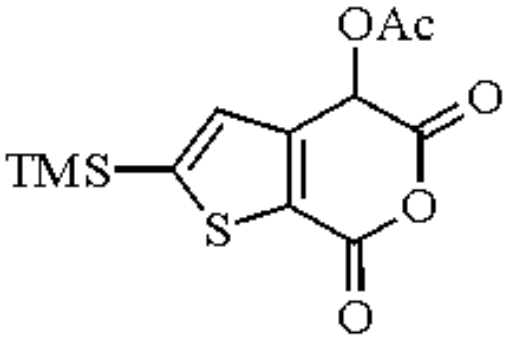

(5) 100%

Dehydrative Condensation of Carboxylic Acids with Amines and Alcohols.

In the presence of a mercuric catalyst, (**1**) causes dehydrative condensation of carboxylic acids with H-acidic materials such as amines and alcohols to give the corresponding amides, esters, lactones, and peptides in high yields.[2]

Preparation of (Trimethylsilyl)ketene.

Heating of (**1**) at 120 °C is a convenient method for preparation of ***Trimethylsilylketene*** (**6**) (eq 2).[3] This ketene is an easy-handling, storable, and distillable monomeric liquid, and is useful for acylation of sterically hindered alcohols and amines (eq 3). Other useful applications of (**6**) are represented in the preparation of α-silyl acetates,[10] α-silyl ketones,[11] α,β-unsaturated esters,[12] and silylallenes.[17]

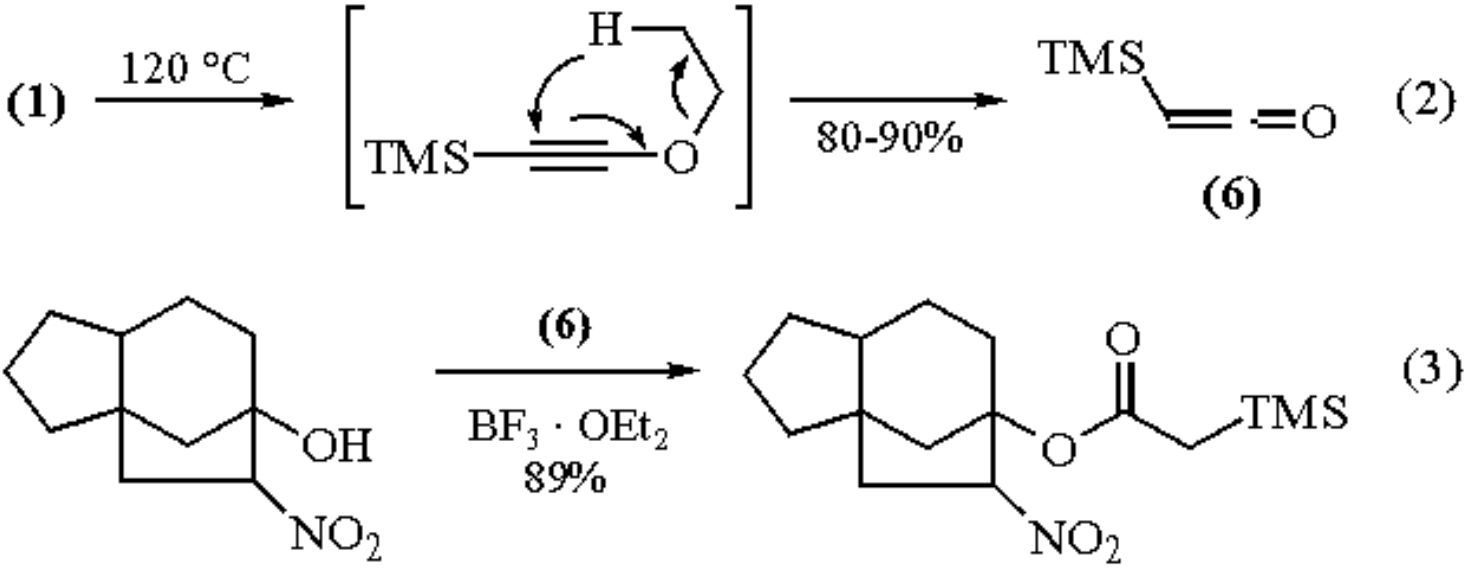

Cycloaddition Reactions.

Dichloroketene, *N*-sulfonylimines, ***Diazomethane***, and aroylketenes add to (**1**) to provide good yields of a cyclobutenone,[4] 2-azetines,[13] a pyrazole,[14] and 4-pyrones,[15] respectively. Cooligomerization of three molecules of (**1**) with one molecule of ***Carbon Dioxide*** proceeds in the presence of Ni^0 catalyst, giving a 2-pyrone derivative in 90% yield.[16]

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1-Ethoxy-1-(trimethylsilyloxy)cyclopropane

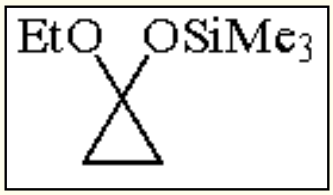

[27374-25-0] · $C_8H_{18}O_2Si$ · 1-Ethoxy-1-(trimethylsilyloxy)cyclopropane · (MW 174.32)

(preparation of 3-metallopropionates;[1] metal homoenolate precursor[2])

Physical Data: bp 50-53 °C/22 mmHg.

Solubility: insol H_2O.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: GLC, NMR.

Preparative Methods: for the synthesis of the parent and the 2-monoalkyl-substituted compounds, reduction of ethyl 3-chloropropionate with ***Sodium-Potassium Alloy*** alloy in the presence of ***Chlorotrimethylsilane*** in ether.[3] A recent modification using ultrasound irradiation is much more convenient and more widely applicable.[4] Other substituted derivatives are prepared by cyclopropanation of alkyl silyl ketene acetals with the Furukawa reagent (***Diiodomethane***/***Diethylzinc***).[5]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: moisture sensitive, yet, once purified by distillation, is stable for a long period of time in a tightly capped bottle at room temperature.

Stoichiometric Precursor of Metal Homoenolates.

The reaction of 1-alkoxy-1-trimethylsilyloxycyclopropane with a variety of Lewis acidic metal chlorides affords the 3-metallated propionate esters in good to excellent yield (see below).[1,6,7] For instance, the reaction of 1-ethoxy-1-trimethylsilyloxycyclopropane with one equivalent of ***Tin(IV) Chloride*** gives a 3-stannylpropionate, which further reacts with another equivalent of the cyclopropane to give a dialkylated tin compound (eq 1).

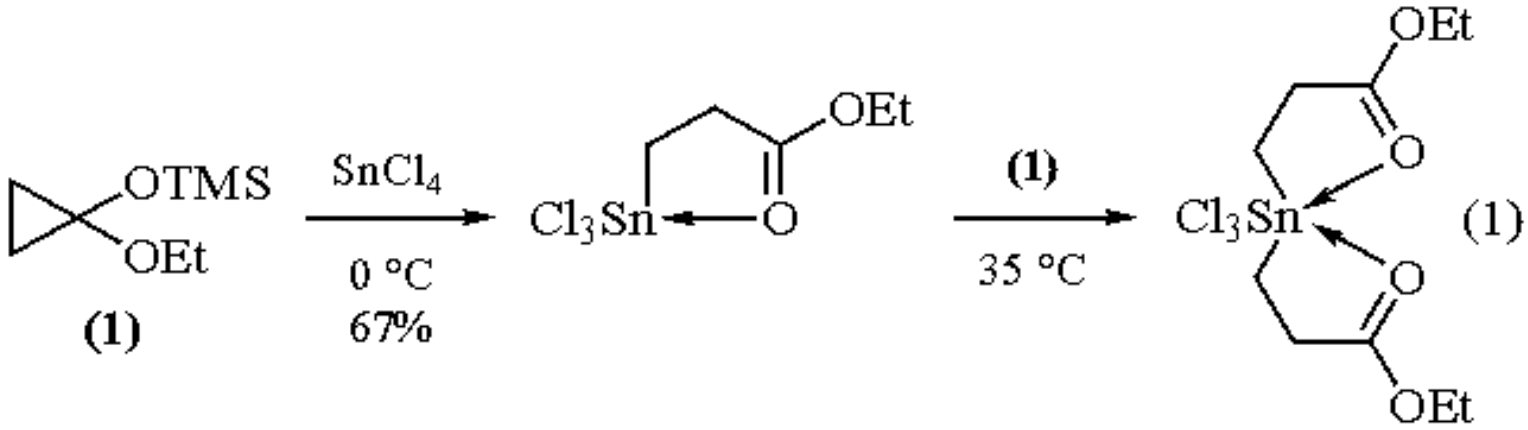

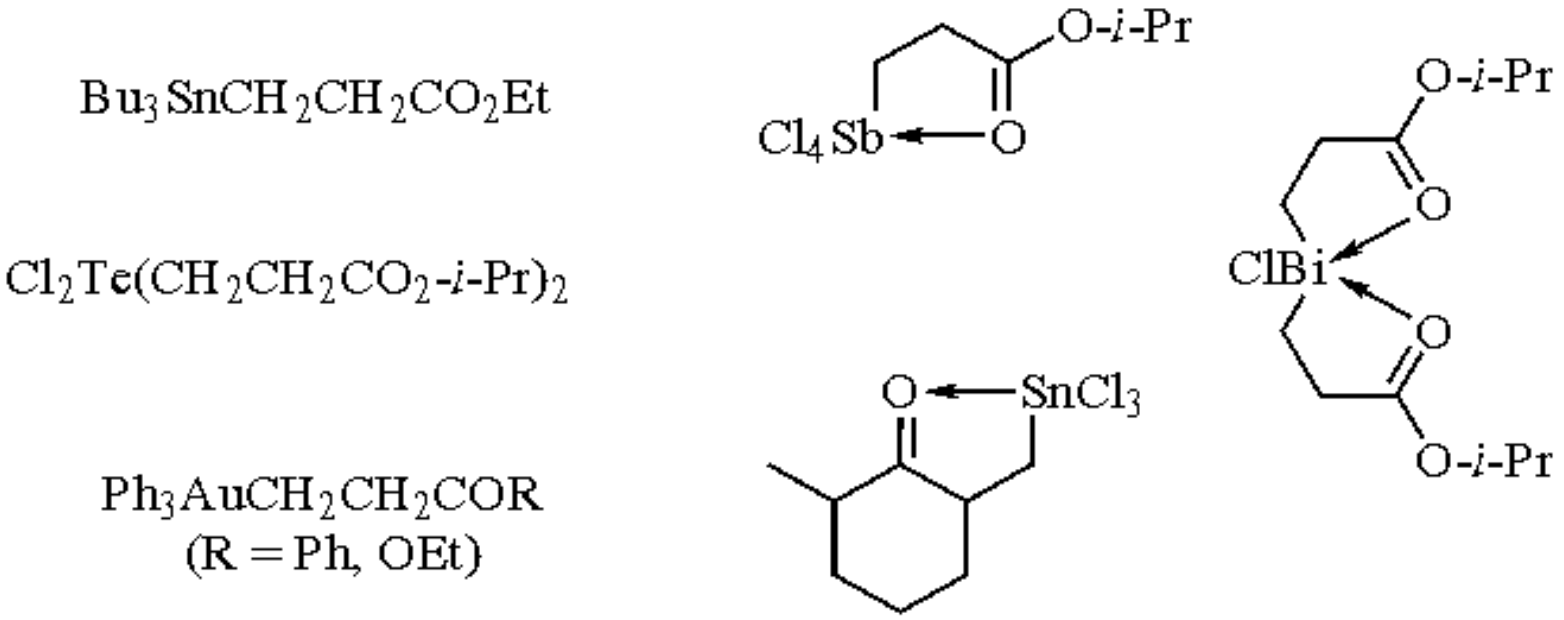

The reaction of the siloxycyclopropane with ***Titanium(IV) Chloride*** produces the titanium homoenolate (3-titaniopropionate) in good yield; this, however, is relatively unreactive (eq 2).[8] Addition of one equivalent of $Ti(OR')_4$ generates a more reactive $RTiCl_2OR'$ species, which smoothly reacts with carbonyl compounds below room temperature.[9] The γ-hydroxy ester adducts are useful synthetic intermediates and serve as precursors to γ-lactones and cyclopropanecarboxylates.[10] A useful variation involves the use of the cyclopropanecarboxylate ester as a functionalized homoenolate precursor to obtain levulinic acid derivatives (eq 3).[11]

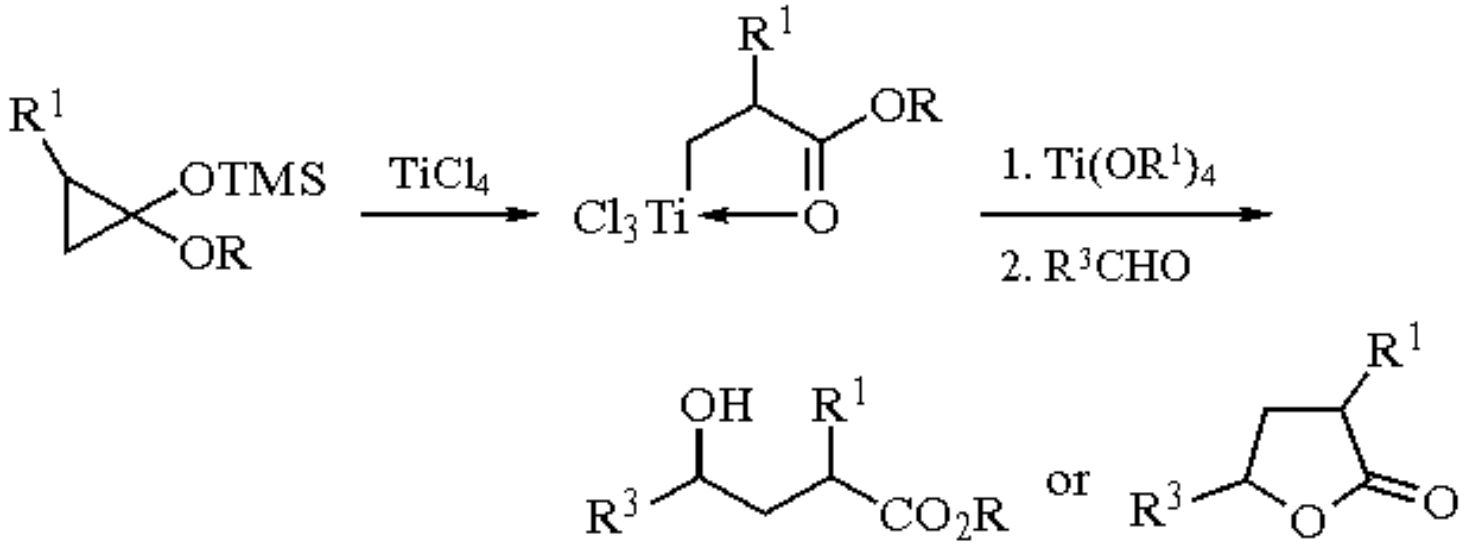

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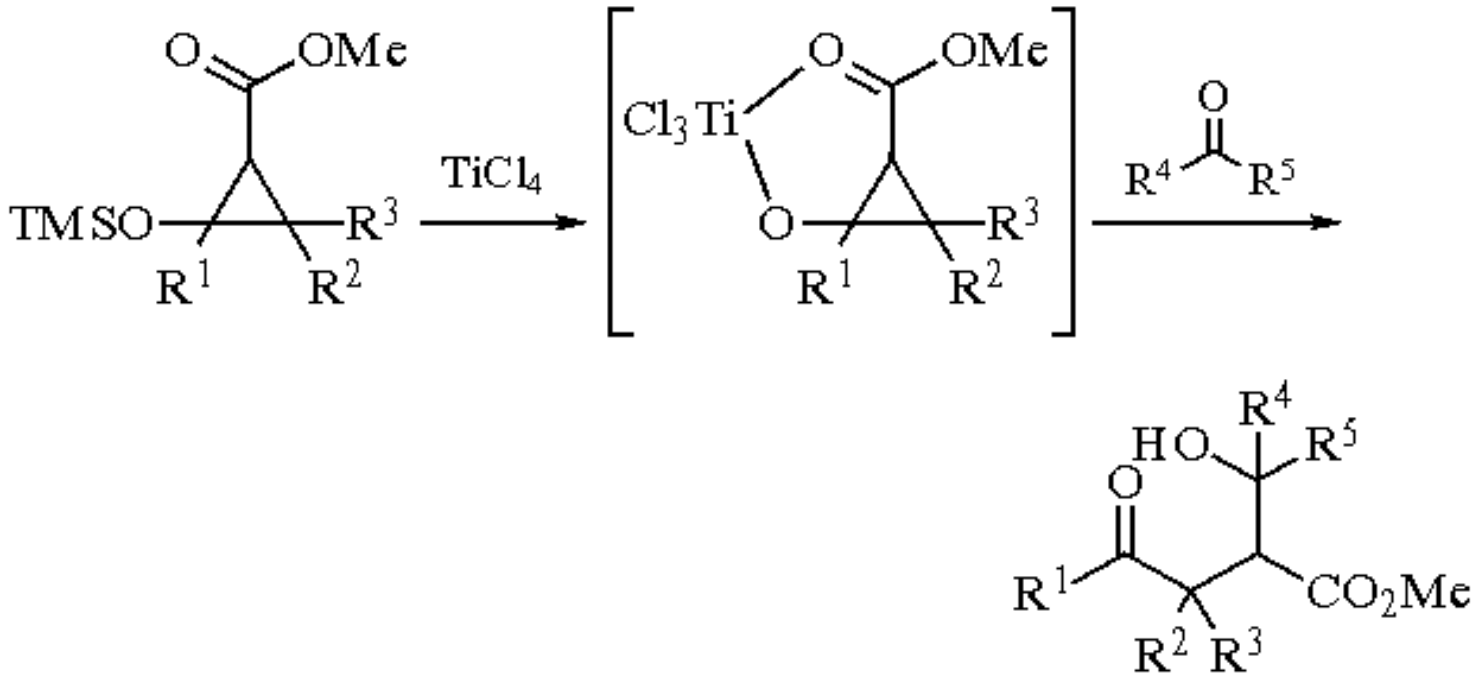

(3)

The zinc homoenolate prepared by the treatment of the siloxycyclopropane with ***Zinc Chloride*** is a versatile synthetic reagent (eq 4).[12] Reduction of 3-iodopropionate with activated ***Zinc*** also produces a zinc homoenolate species.[13]

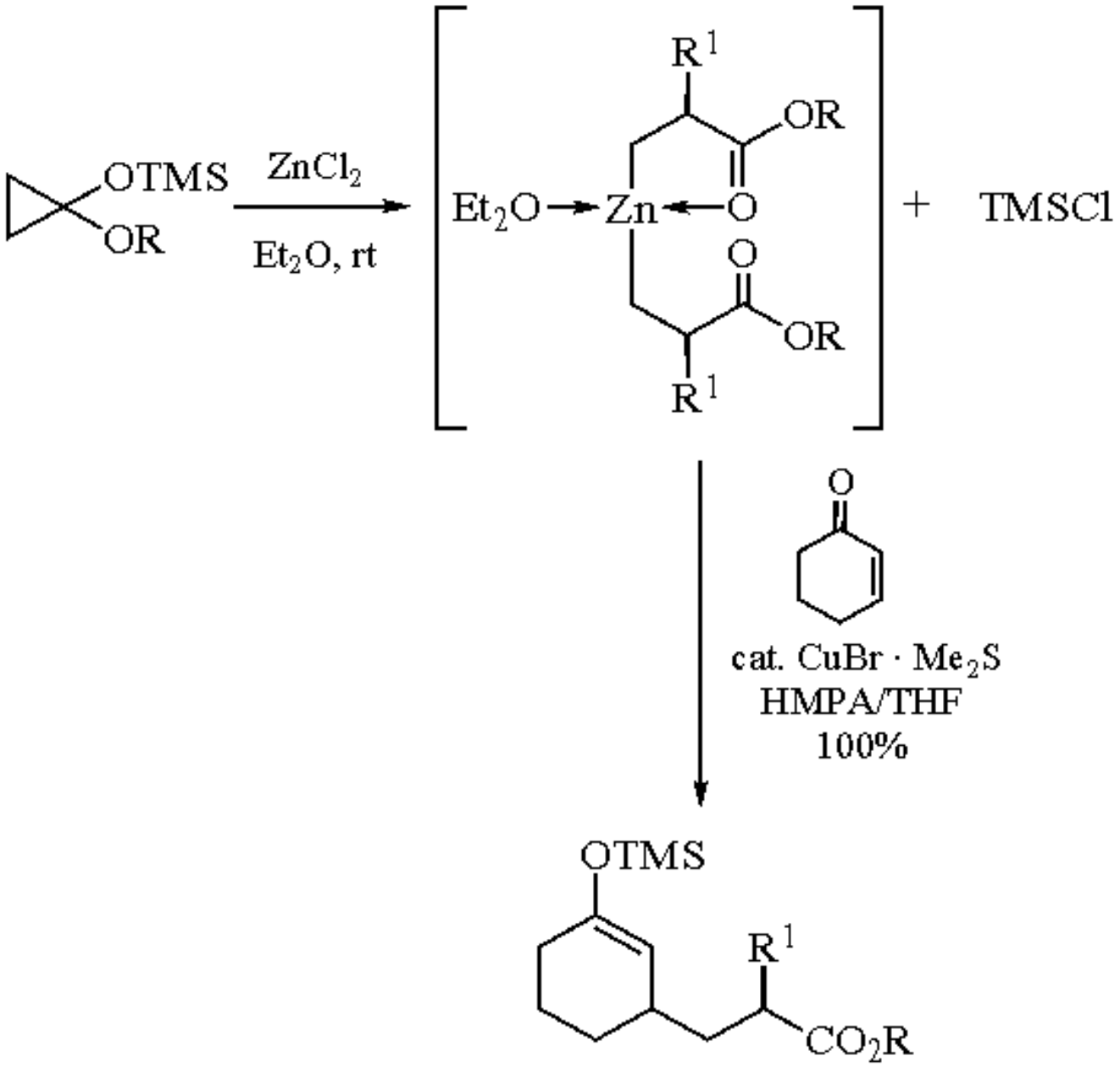

(4)

Treatment of the silyloxycyclopropane with $ZnCl_2$ followed by addition of an enone, HMPA, THF, and a catalytic amount of a Cu^I salt results in quantitative formation of a conjugate adduct as an enol silyl ether (eq 4). The chlorosilane, a byproduct, is essential for the conjugate addition of the copper homoenolate.[14,15] ***Boron Trifluoride Etherate*** promotes the copper-catalyzed conjugate addition reaction with a different stereochemical outcome.[16] A useful application of the conjugate addition reaction is a [3 + 2] synthesis of cyclopentenones, wherein the homoenolate acts as a 1,3-dipole equivalent (eq 5).[17]

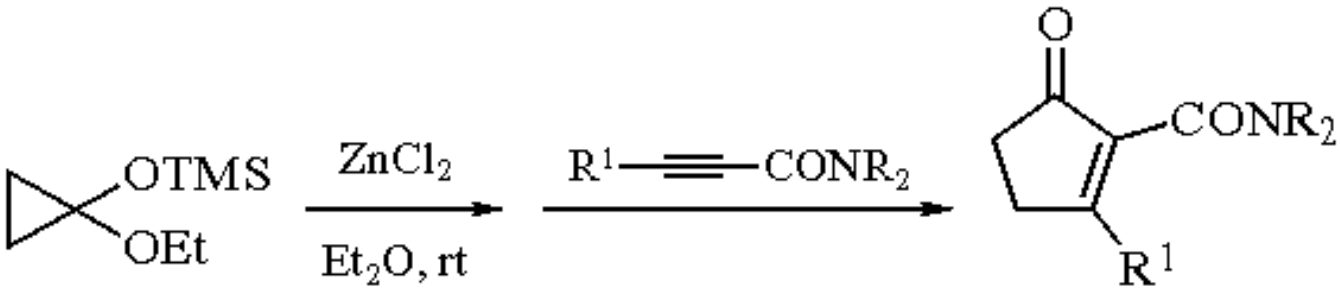

(5)

1-Ethoxy-1-(trimethylsilyloxy)cyclopropane

The zinc homoenolate undergoes copper-catalyzed allylation with allylic chlorides. The reaction is not only extremely S_N2' regioselective but stereoselective for δ-chiral allylic chlorides.[18] Arylation and vinylation of the zinc homoenolates proceed in the presence of a palladium-phosphine complex.[19] Similarly, palladium-catalyzed acylation reaction gives γ-keto esters (eq 6).

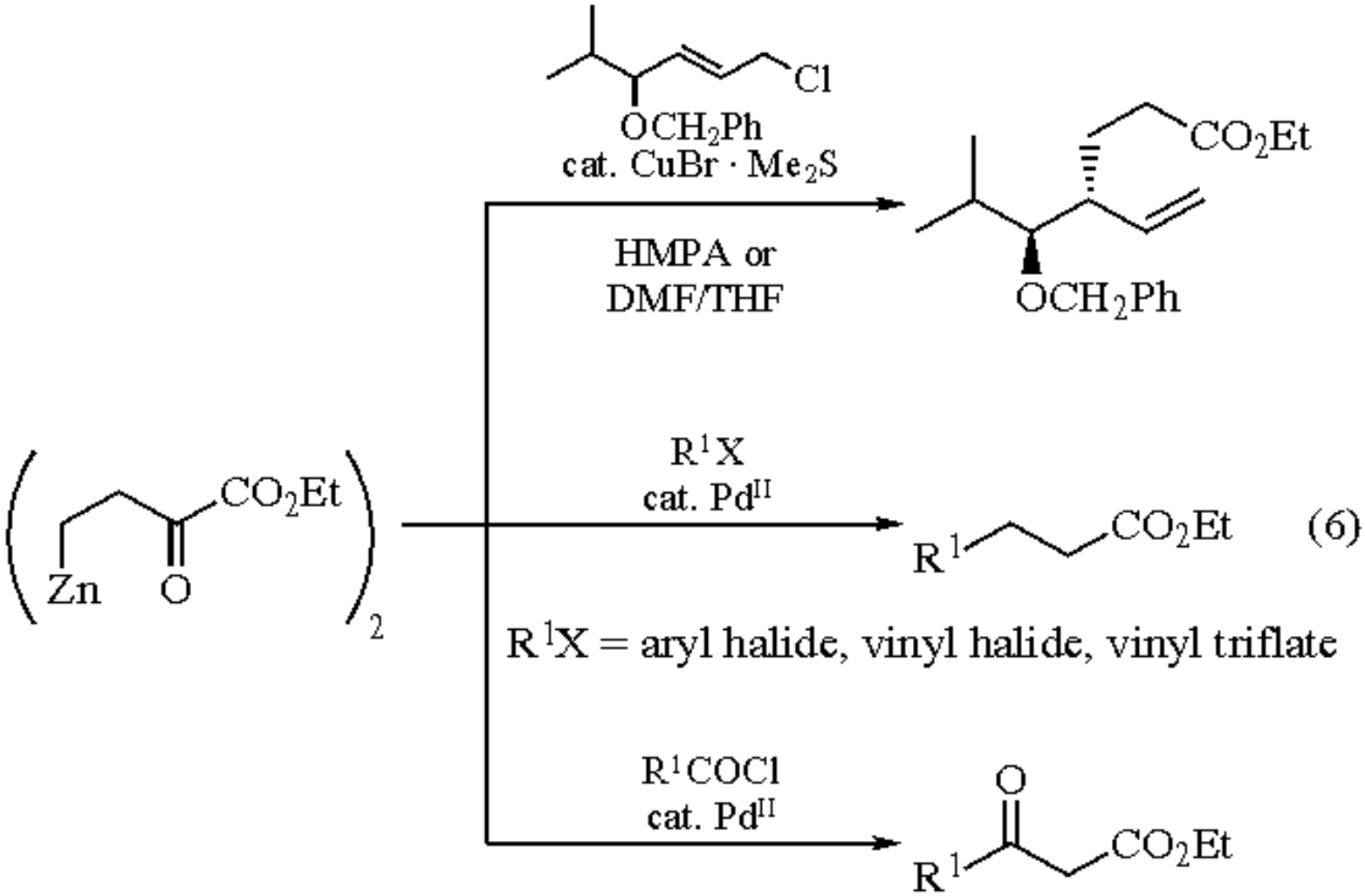

Catalytic Generation of Homoenolate Reactive Species.

Homoaldol reaction between the siloxycyclopropane and an aldehyde with a catalytic amount of ***Zinc Iodide*** in methylene chloride affords a γ silyloxy ester (eq 7).[18,20] Arylation[21] and acylation[22,23] of the silyloxycyclopropanes in the presence of a palladium catalyst take place via direct attack of an aryl- or acylpalladium intermediate on the C-C bond of the cyclopropane (eqs 8 and 9). The reaction is applicable not only to ester synthesis but also to ketone and aldehyde synthesis. Heating a chloroform solution of the silyloxycyclopropane in the presence of a palladium-phosphine catalyst under 1 atm ***Carbon Monoxide*** produces a γ-keto pimelate (eq 10).[24]

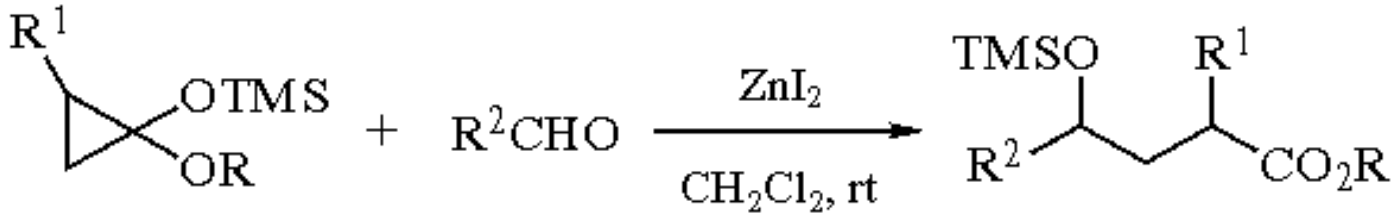

(7)

$R^1 = H, Me$

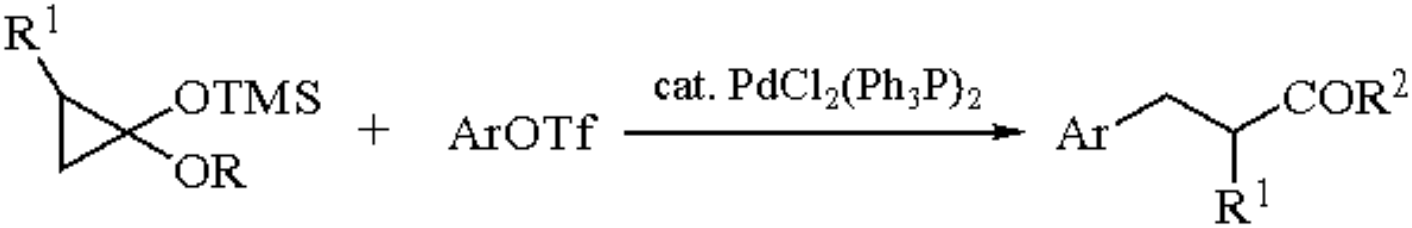

(8)

$R^2 = H$, alkoxy, alkyl, aryl

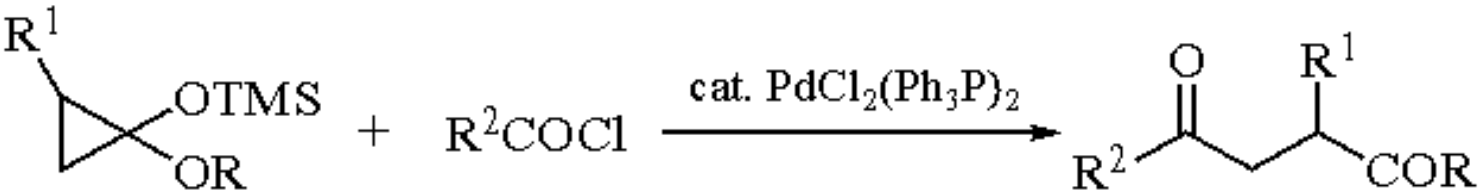

(9)

R = alkoxy, alkyl, aryl

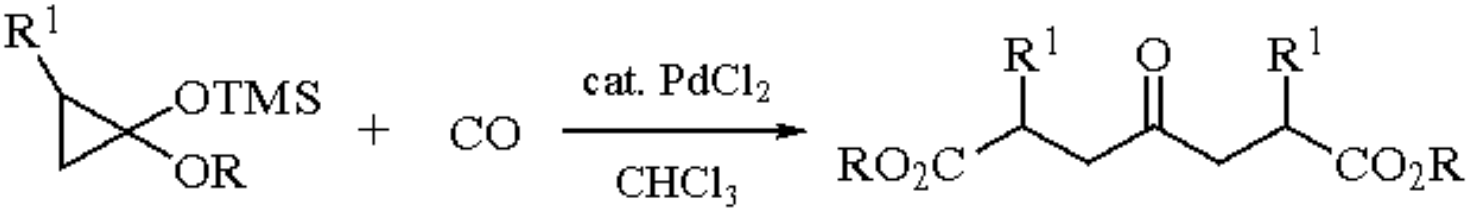

(10)

Precursor of Lithiocyclopropane.

Bromination of the silyloxycyclopropane with ***Phosphorus(III) Bromide*** produces 1-bromo-1-ethoxycyclopropane. Successive treatment of the bromide with ***t-Butyllithium*** and an enal affords a cyclopropylcarbinol, which undergoes acid-catalyzed ring enlargement to give 2-vinylcyclobutanone (eq 11).[25]

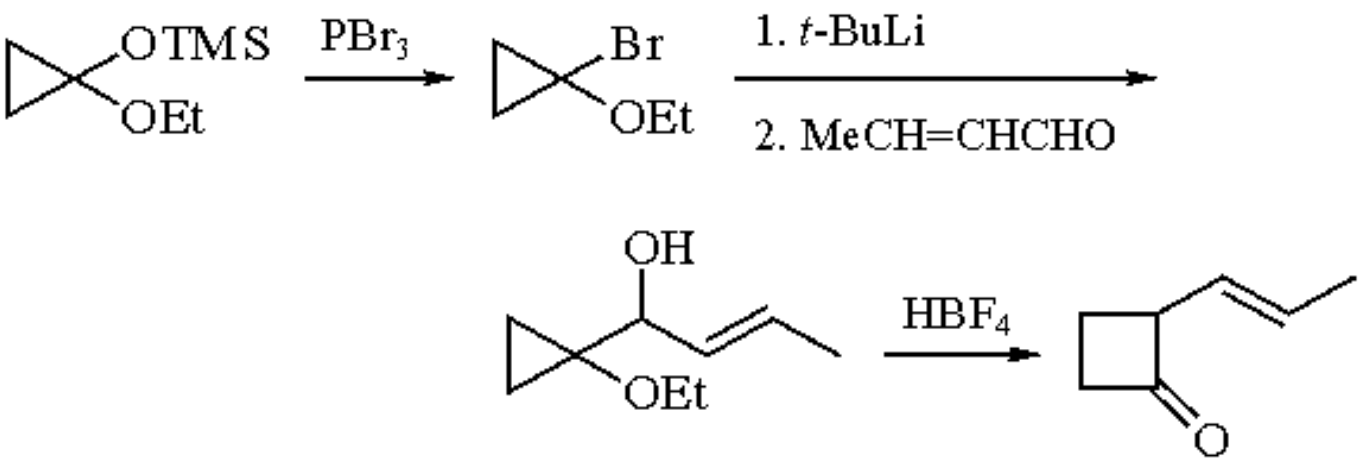

(11)

Reactions with Azidoformates.

Photolysis of an acetonitrile solution of the cyclopropane and ***Ethyl Azidoformate*** at rt gives a C-H insertion product (eq 12).[26] However, thermolysis of the same mixture in DMSO gives a 3-aminopropionate by insertion of nitrene into the cyclopropane ring (eq 13).[27]

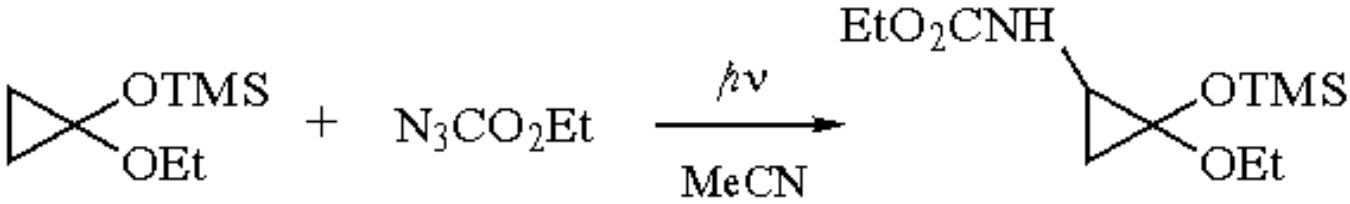

(12)

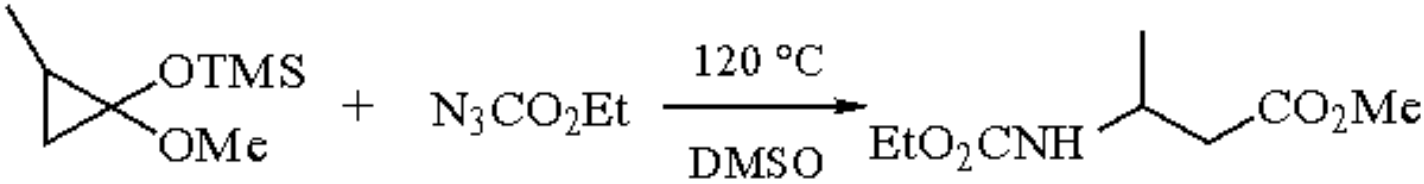

(13)

Cyclopropanone Hemiacetals and Their Use.

Mild alcoholysis of the silyloxycyclopropane gives a cyclopropanone hemiacetal. This compound serves as a stable equivalent of unstable cyclopropanones.[3] Treatment with two equivalents of alkynylmagnesium bromide gives a 1-ethynyl-1-hydroxycyclopropane (eq 14).[28]

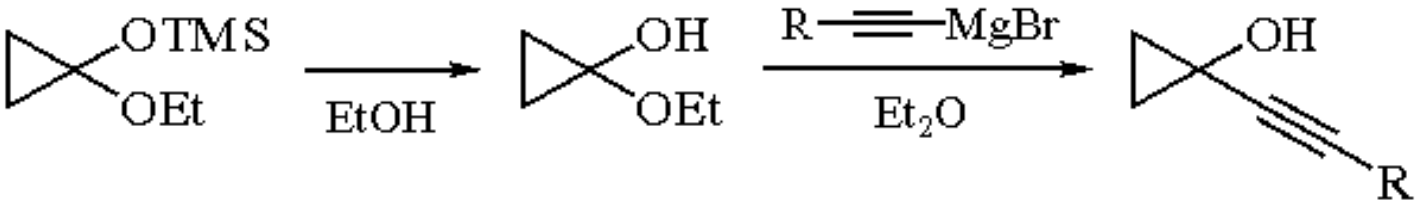

(14)

The cyclopropanol also serves as a source of homoenolate radical species. Treatment of a mixture of the cyclopropanol and an enol silyl ether with manganese(III) 2-pyridinecarboxylate in DMF gives a 1,5-dicarbonyl compound (eq 15).[29]

1-Ethoxy-1-(trimethylsilyloxy)cyclopropane

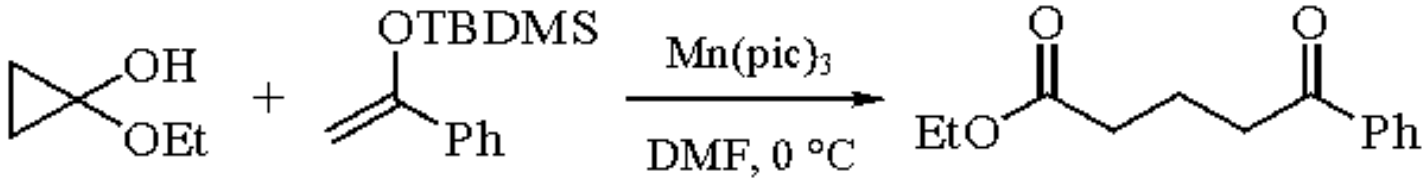

(15)

Strecker amino acid synthesis starting with the cyclopropanone hemiacetal provides a enantioselective route to a cyclopropane amino acid (eq 16).[30]

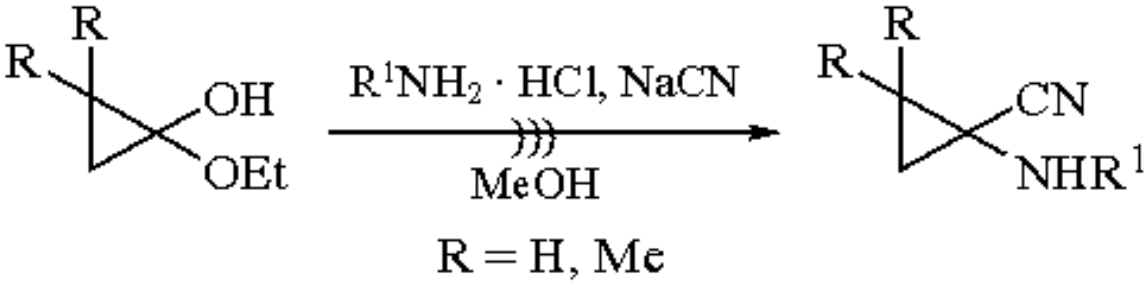

(16)

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(*Z*)-2-Ethoxyvinyllithium

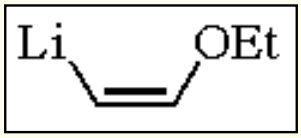

[64724-28-3] · C_4H_7LiO · (*Z*)-2-Ethoxyvinyllithium · (MW 78.04)

(equivalent of the anion of acetaldehyde in aldol condensation and alkylation)

Preparative Methods: proceeds smoothly by reaction of (*Z*)-1-ethoxy-2-tri-*n*-butylstannylethylene, prepared by hydrostannation of the commercially available compound ***Ethoxyacetylene***, with 1.1 equiv of ***n-Butyllithium*** in THF at -78 °C for 1 hr.[1,2] (*Z*)-2-Ethoxyvinyllithium can also be prepared by halogen-metal exchange between (*Z*)-ethoxyvinyl bromide and butyllithium in diethyl ether at -80 °C.[3]

Handling, Storage, and Precautions: (*Z*)-ethoxyvinyllithium is stable in THF up to -45 °C, in an ethylene glycol dimethyl ether/THF mixture (1:1) up to -35 °C, and fairly stable up to -30 °C.[3] (*E*)-2-Ethoxyvinyllithium is unstable even at -80 °C.

Addition to Carbonyl Compounds.

(*Z*)-2-Ethoxyvinyllithium offers a highly efficient route to α,β-unsaturated aldehydes from carbonyl compounds. Thus it reacts with aldehydes and ketones at -78 °C to produce allylic alcohols in good yields. The intermediate allylic alcohols are converted into α,β-unsaturated aldehydes under nonacidic conditions. Chromatography of the resulting allylic alcohols on silica gel or Florisil is sufficient to cause complete allylic rearrangement to the α,β-unsaturated aldehydes (eqs 1 and 2).[4,5]

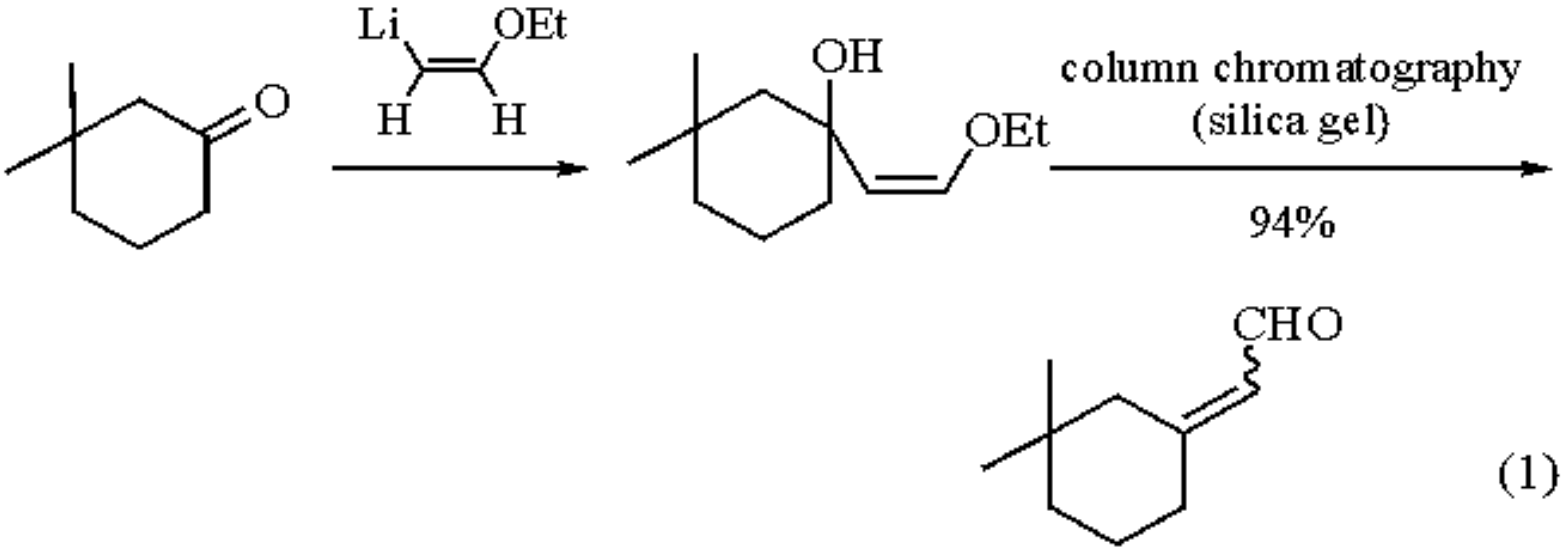

(1)

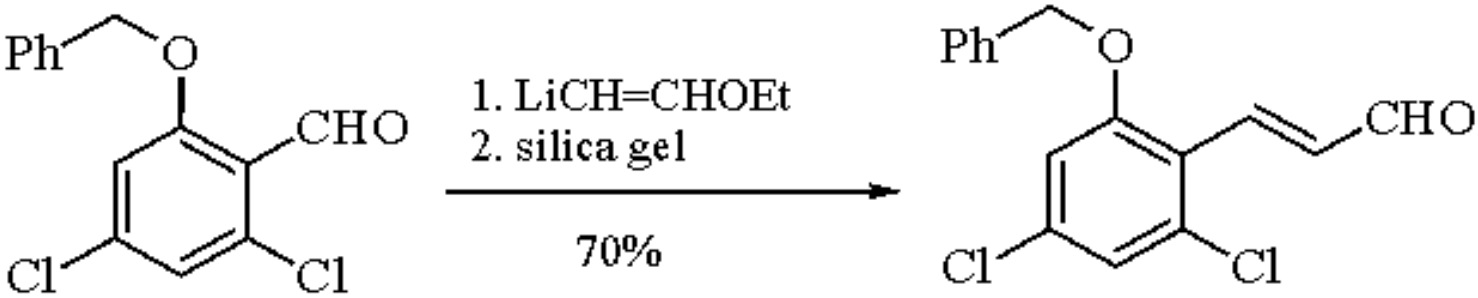

(2)

(*Z*)-2-Ethoxyvinyllithium can react with the hindered ketone (**1**), that is unreactive with either $(MeO)_2POCHLiCO_2Me$ or ***Ethyl Lithio(trimethylsilyl)acetate*** to form, after hydrolysis, an α,β-unsaturated aldehyde (eq 3).[6]

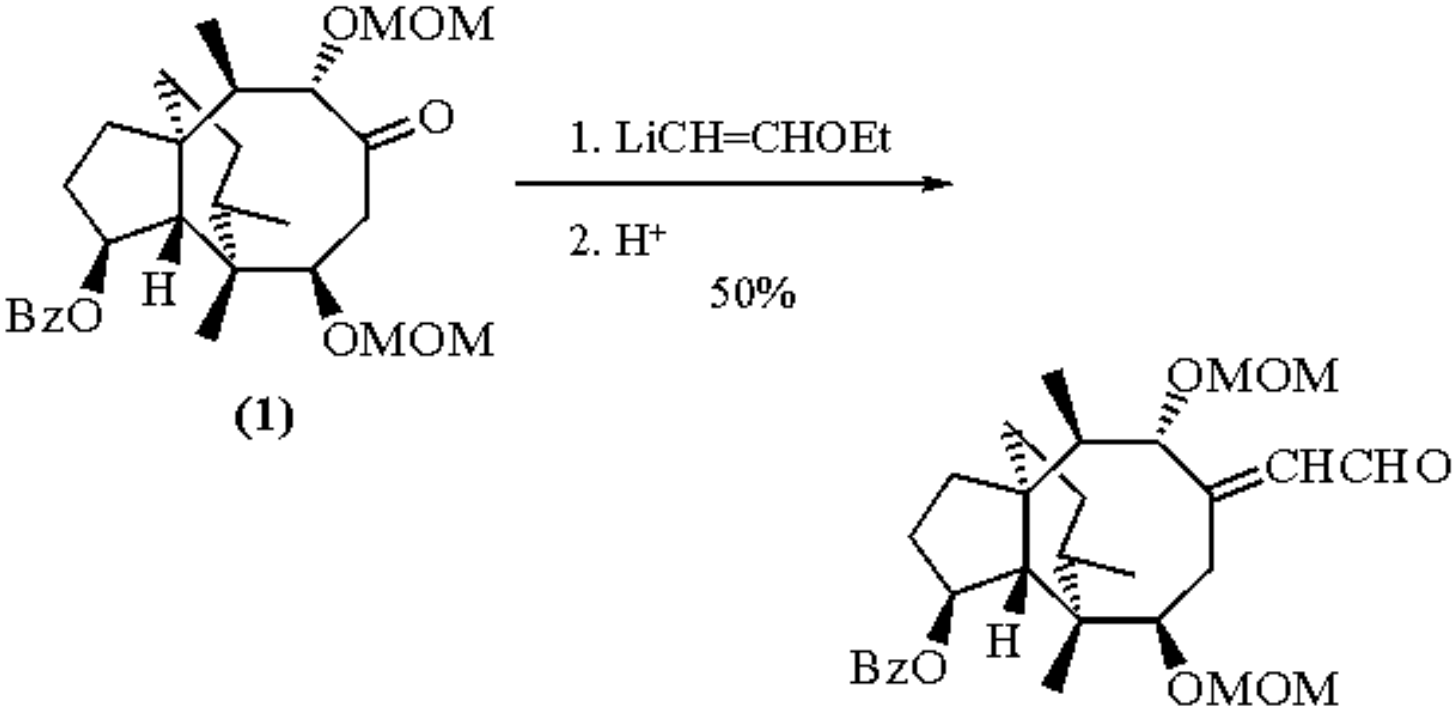

(1)

(3)

Addition of (*Z*)-1-ethoxyvinyllithium to the silyl ketone (**2**) and subsequent methylation provides the allenyl silyl ether (**3**) through C-O silyl migration and concomitant equilibration to allenyl anion (eq 4).[7]

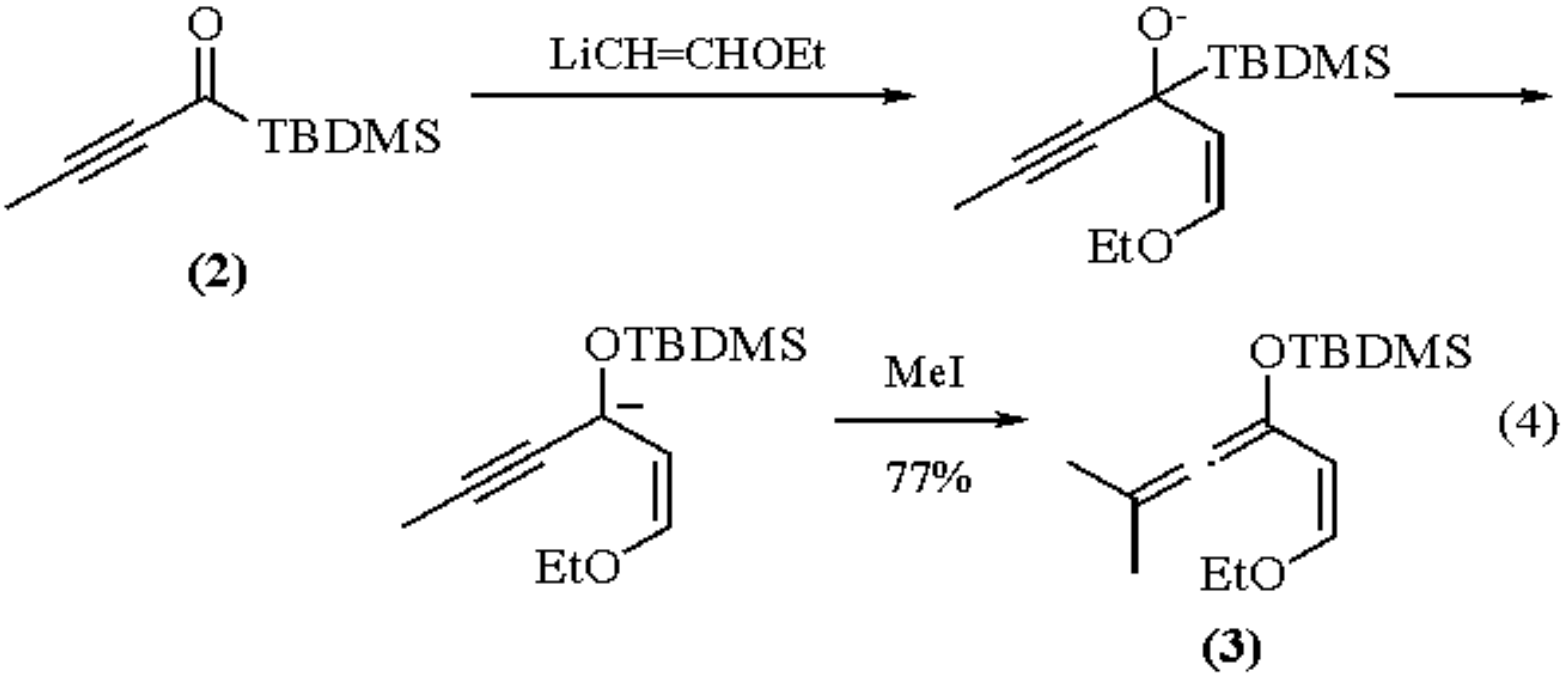

(4)

Alkylation.[1]

(*Z*)-2-Ethoxyvinyllithium reacts with alkyl halides to accomplish a two-carbon chain extension of halides to aldehydes. Alkylation of (*Z*)-1-ethoxyvinyllithium with 1-iododecane in THF at -78 °C requires ***Hexamethylphosphoric Triamide*** as cosolvent (1 equiv) (eq 5). The allylic halide geranyl bromide is more reactive and is smoothly alkylated without HMPA as cosolvent (eq 6). The resulting enol ethers are converted by mild acid treatment (3:2:1 acetic acid-THF-water, 40 °C) to carbonyl compounds in 95% isolated yields.

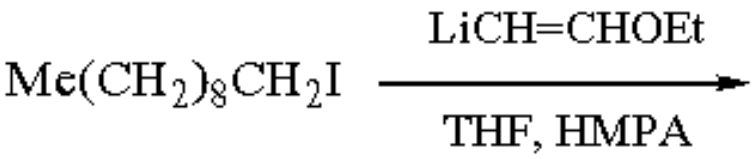

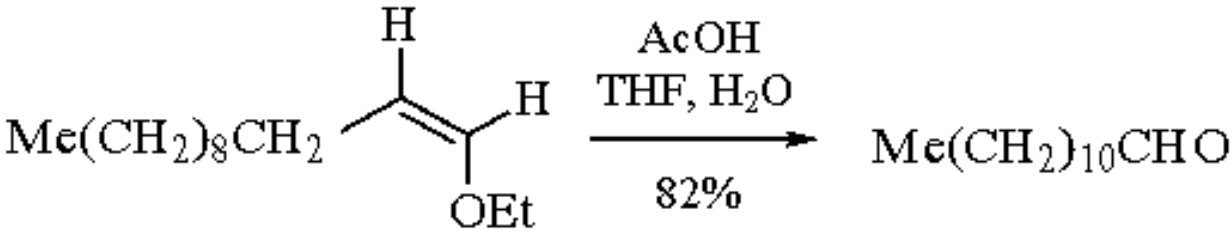

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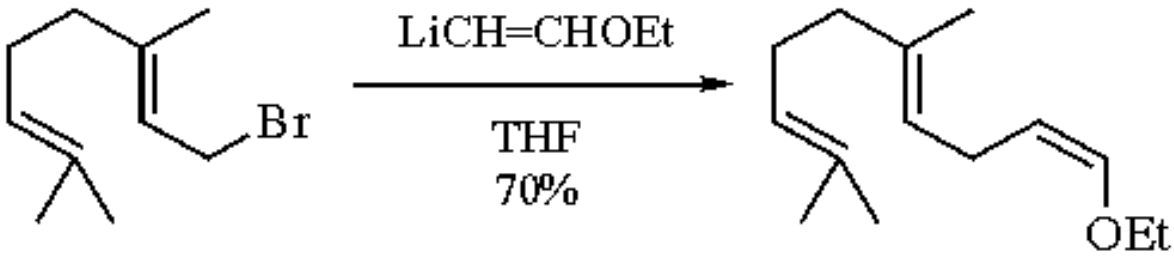

(6)

Vinylcuprate Reagent.[1]

Reaction of ***Copper(I) Iodide*** and ***Dimethyl Sulfide*** in THF with (*Z*)-1-ethoxyvinyllithium at -78 °C produces a red-brown soluble cuprate. It undergoes both conjugate addition with α,β-unsaturated carbonyl compounds (eqs 7 and 8) and direct displacement reaction with activated halides (eq 9).

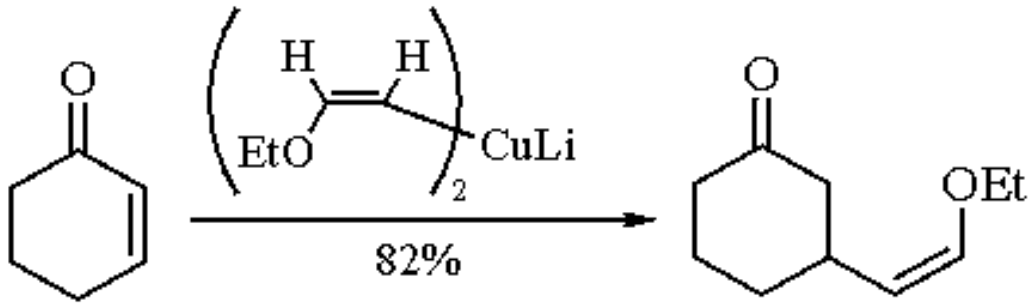

(7)

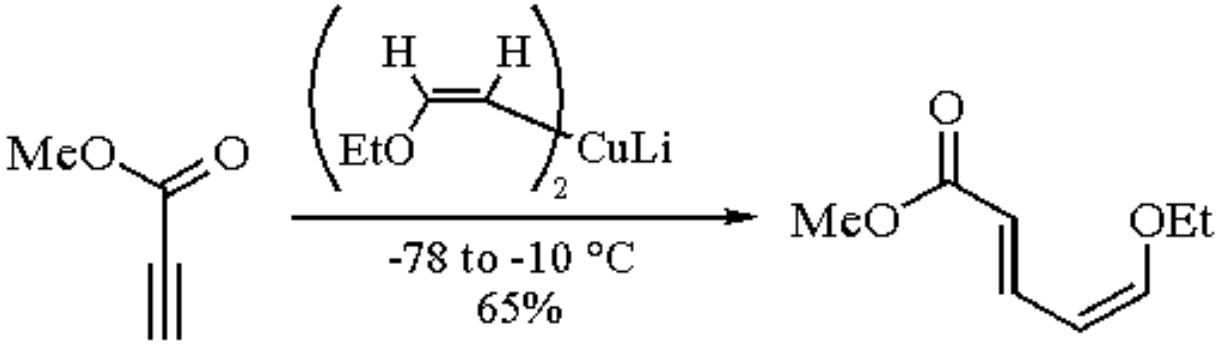

(8)

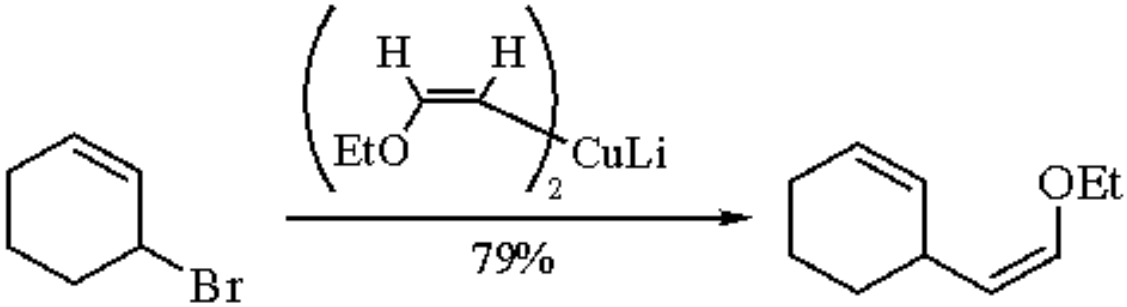

(9)

Related Reagents.

(*Z*)-[(Trimethylsiloxy)vinyl]lithium is prepared by halogen-metal exchange between (*Z*)-2-bromo-1-(trimethylsiloxy)ethylene and ***t-Butyllithium*** at -70 °C in ether. Condensation of (*Z*)-[(trimethylsiloxy)vinyl]lithium

with aldehydes and ketones occurs readily at -75 °C. Treatment of the products with dilute ***Hydrochloric Acid*** produces α,β-unsaturated aldehydes (eq 10).[8]

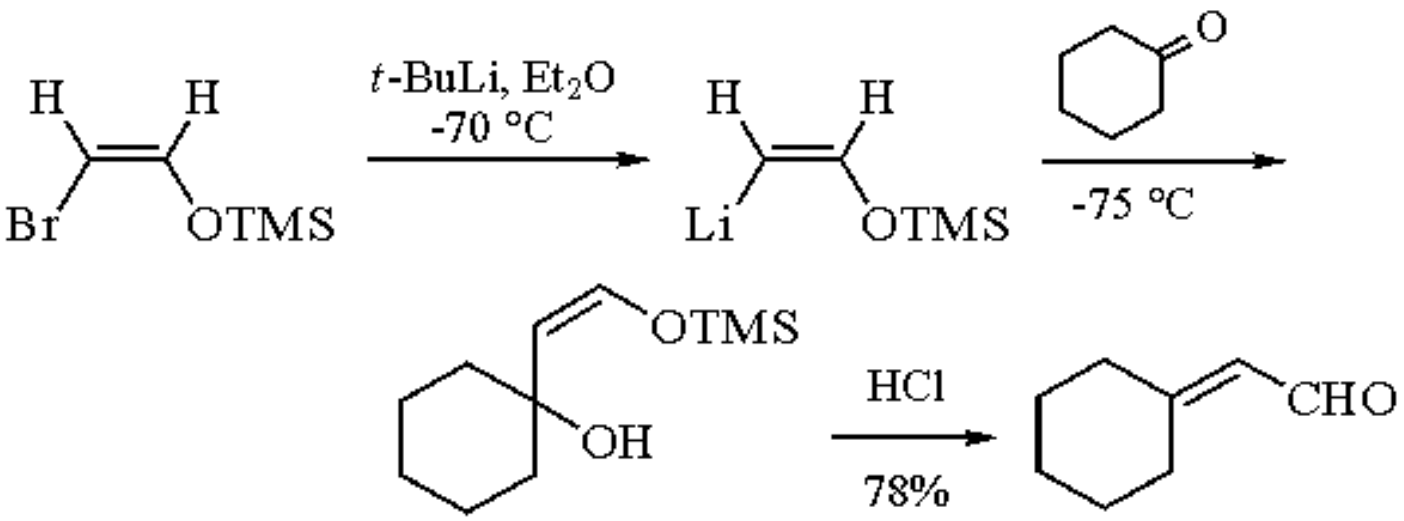

(10)

Transmetalation of the vinylstannane (**4**) (mixture of geometric isomers), available by treatment of 1-ethoxy-1-buten-3-yne with ***Tri-n-butylstannane*** and a catalytic amount of ***Azobisisobutyronitrile***, with *n*-butyllithium in THF at -78 °C proceeds smoothly. Condensation of the resulting lithium reagent with aldehydes and ketones produces dienols which transform into dienals by either silica gel chromatography or ***p-Toluenesulfonic Acid*** in aq THF (eq 11).[9]

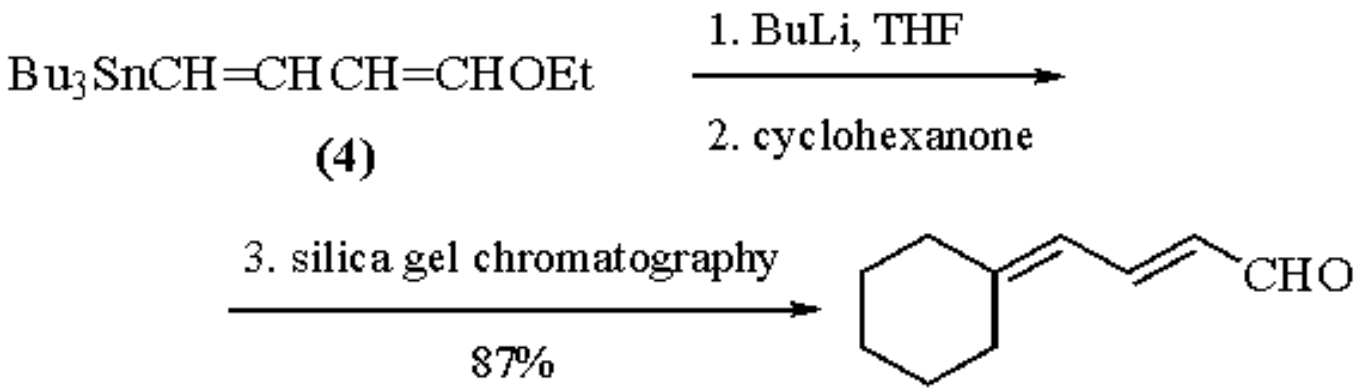

(11)

See also ***1,2-Dimethoxyvinyllithium 1-Ethoxyvinyllithium 5-Lithio-2,3-dihydrofuran 6-Lithio-2,3-dihydro-4H-pyran 1-Methoxyvinyllithium***

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1-Ethoxyvinyllithium[1]

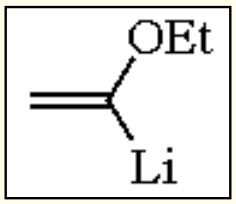

[40207-59-8] · C_4H_7LiO · 1-Ethoxyvinyllithium · (MW 78.04)

(reacts with aldehydes and ketones to form allylic alcohols;[1,2] adds to the carbon-nitrogen double bond of isoquinolinium salts;[3] reacts with chlorosilanes;[4] can add to conjugated sulfones[5])

Physical Data: ^{13}C NMR solution studies in THF have been reported.[6]

Solubility: sol THF.

Form Supplied in: prepared in situ and used directly.

Preparative Methods: prepared in situ under nitrogen by the reaction of ***Ethyl Vinyl Ether*** in anhydrous THF with ***t-Butyllithium***.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture.

Additions to Aldehydes and Ketones.

1-Ethoxyvinyllithium adds to benzaldehyde to yield an allylic alcohol (eq 1) which, upon acid hydrolysis, forms the α-hydroxy methyl ketone.[2] Reaction also occurs with ketones (eq 2).[7]

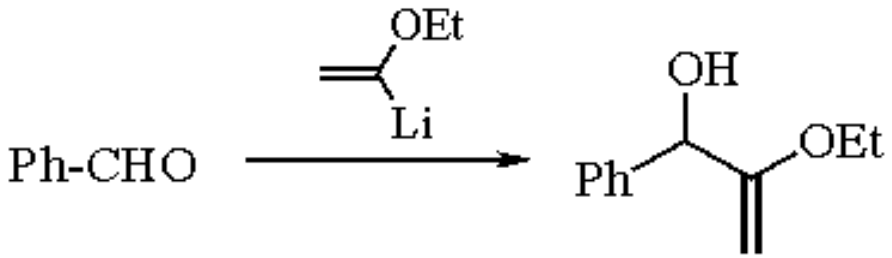

(1)

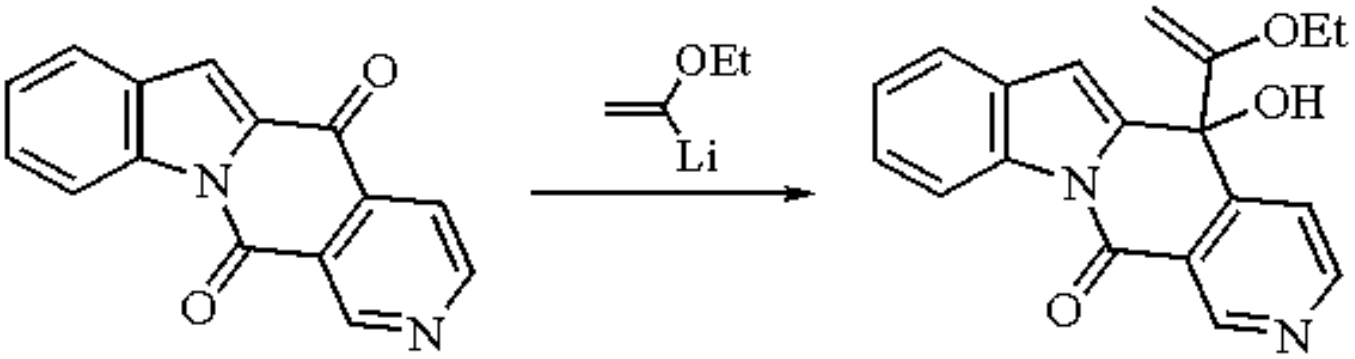

(2)

γ-Ethoxy dienones have been synthesized in good yields via the intermediate produced by the reaction of 1-ethoxyvinyllithium with 3-ethoxy-2-cyclohexenones.[8]

Addition of the reagent to a 2-dialkylaminocyclohexanone has been reported (eq 3).[9]

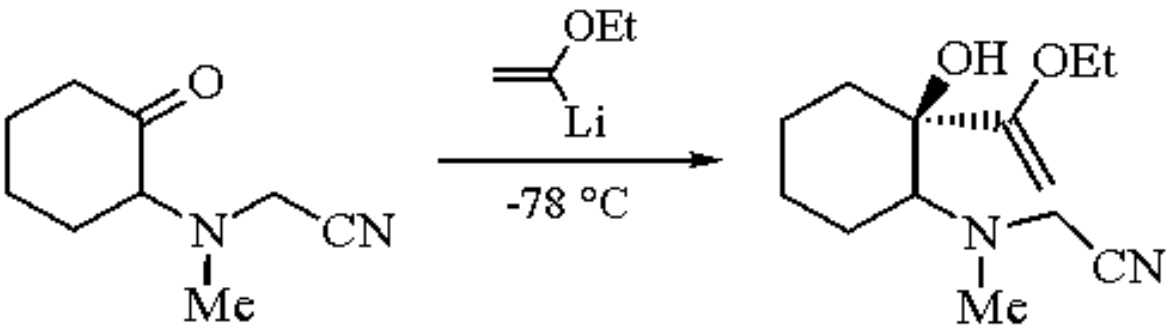

(3)

The reagent adds to conjugated enones at the carbonyl group (eq 4).[10-12]

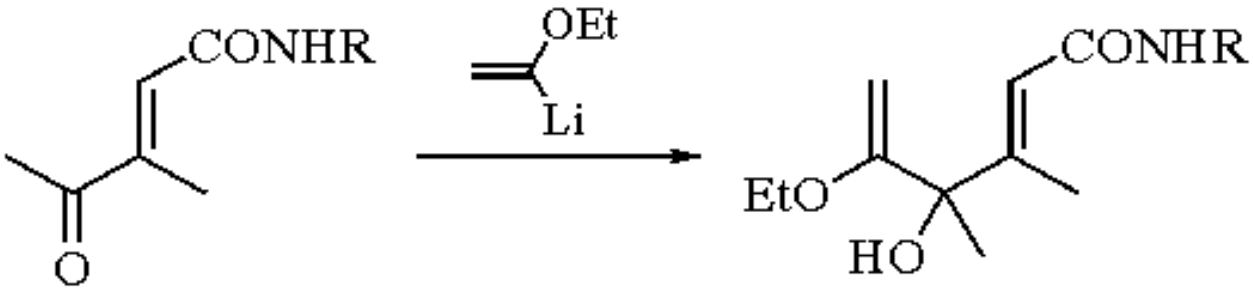

(4)

Addition of the reagent to an aldehyde in the total synthesis of nikkomycin B produced the vinyl ether, which was not isolated.[13] The reagent can also be used to prepare the corresponding cuprate, which adds 1,4 to enones.[14]

Addition to Carbon-Nitrogen Double Bonds.

The reagent adds cleanly to isoquinolinium salts (eq 5) to yield, after acid hydrolysis, the methyl ketone.[3]

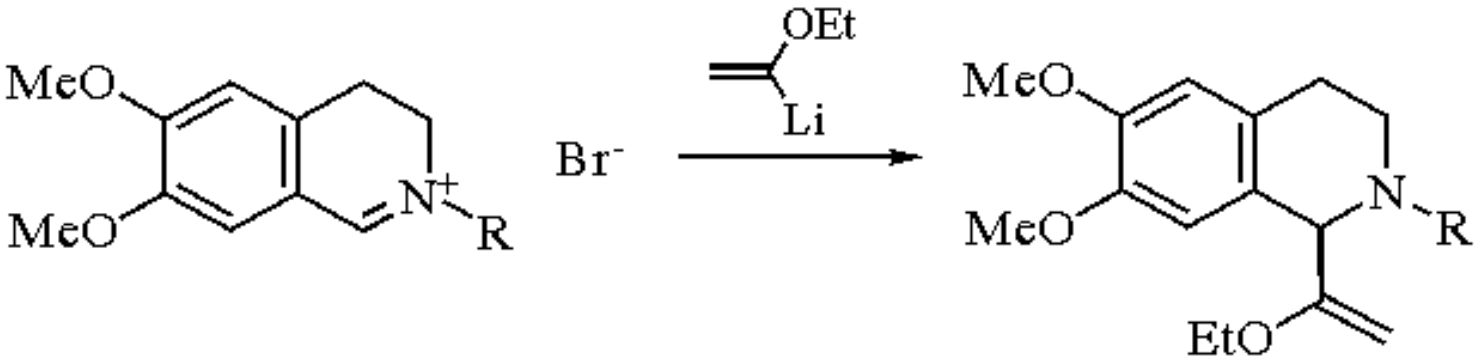

(5)

Reaction with Chlorosilanes.

Chlorosilanes react with 1-ethoxyvinyllithium[4,15] to yield, after acid hydrolysis, acylsilanes with overall yields of 19-31% (eq 6).[4]

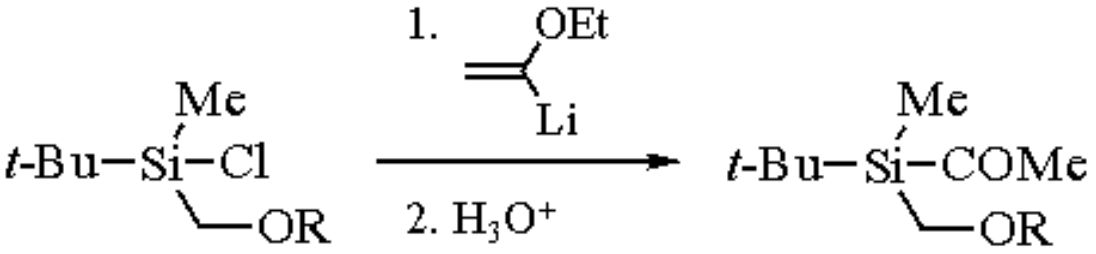

(6)

Addition to Conjugated Sulfones.

The reagent adds to conjugated sulfones at the β-carbon in good yields (eq 7).[5]

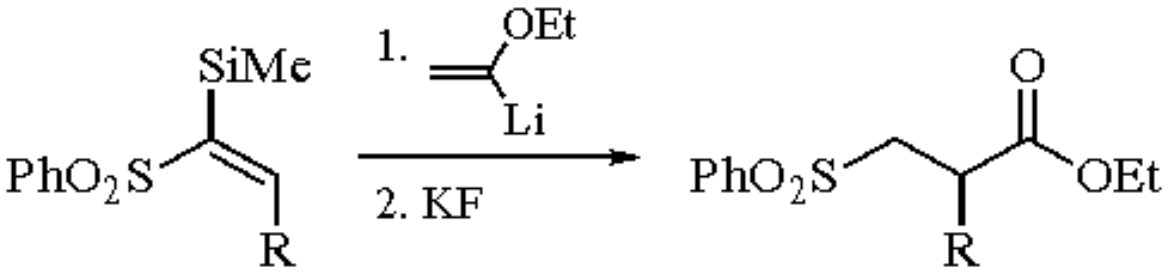

(7)

Related Reagents.

5-Lithio-2,3-dihydrofuran; ***6-Lithio-2,3-dihydro-4H-pyran***; ***1-Methoxyvinyllithium***.

---

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15. Cunico, R. F.; Kuan, C.-P. *JOC* **1985**, *50*, 5410.

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Ethyl Acetoacetate[1]

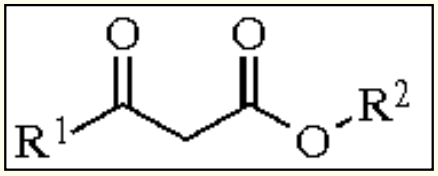

(**1**; R^1 = Me, R^2 = Et)

[141-97-9] · $C_6H_{10}O_3$ · Ethyl Acetoacetate · (MW 130.16) (**2**; R^1 = R^2 = Me)

[105-45-3] · $C_5H_8O_3$ · Methyl Acetoacetate · (MW 116.13) (**3**; R^1 = Me, R^2 = *t*-Bu)

[1694-31-1] · $C_8H_{14}O_3$ · *t*-Butyl Acetoacetate · (MW 158.22) (**4**; R^1 = Ph, R^2 = Et)

[94-02-0] · $C_{13}H_{16}O_3$ · Ethyl Benzoylacetate · (MW 192.29)

(three- or four-carbon nucleophile in alkylations,[2] conjugate additions,[3] and various condensation reactions[4,5])

Physical Data: (**1**) bp 180-181 °C; *d* 1.025 g cm^{-3}. (**2**) bp 169-170 °C; *d* 1.076 g cm^{-3}. (**3**) bp 71-72 °C/11 mmHg; *d* 0.961 g cm^{-3}. (**4**) bp 266-270 °C; *d* 1.113 g cm^{-3}.

Preparative Methods: ethyl, methyl, and *t*-butyl acetoacetates and ethyl benzoyl acetate are commercially available. A wide variety of acetoacetic esters may be prepared via alcoholysis of diketene[6] and ester exchange reaction of *t*-butyl acetoacetate.[7]

Handling, Storage, and Precautions: use in a fume hood.

Alkylations.

Alkylation at the α-carbon of ethyl acetoacetate via an alkali metal enolate and subsequent removal of the ester group by sequential hydrolysis and decarboxylation provides a classical synthesis of methyl ketones (eq 1).[8] The ambident reactivity of the acetoacetate anion often causes competing *C*- and *O*-alkylations.[9] The extent of *C* vs. *O* alkylation depends on the nature of the leaving group, metal counterion, and solvent.[10,11] In general, heterogeneous reaction conditions, less electropositive metal cations, e.g. lithium, nonpolar or protic solvents, and polarizable alkylating agents such as alkyl iodides and allylic, propargylic, and benzylic halides favor *C*-alkylation. Highly dipolar aprotic solvents, e.g. HMPA, and highly reactive alkylating agents such as alkyl sulfonates and sulfates tend to favor *O*-alkylation. Use of phase-transfer catalysis,[12] heating crystalline thallium(I) enolates with alkyl iodides,[13] and alkylation in the presence of ***Tetra-n-butylammonium Fluoride*** base (eq 2)[14] are among the methods that successfully avoid or minimize *O*-alkylation. While primary and unhindered secondary halides give good yields of *C*-alkylated products, tertiary halides undergo elimination

under anionic alkylation conditions. In such cases, alkylation may be achieved via reaction of the enol with cationic species (eq 3).[15]

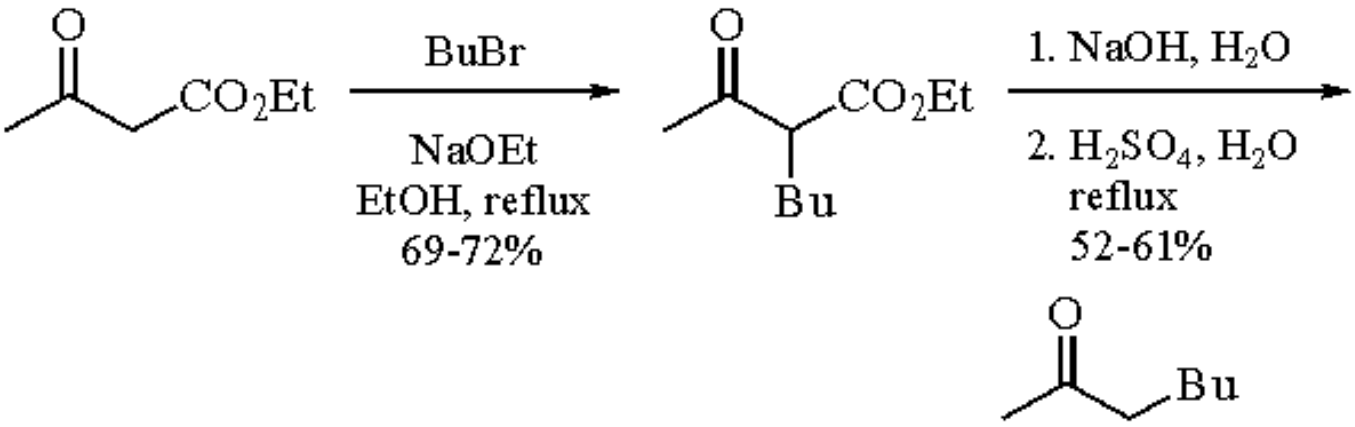

(1)

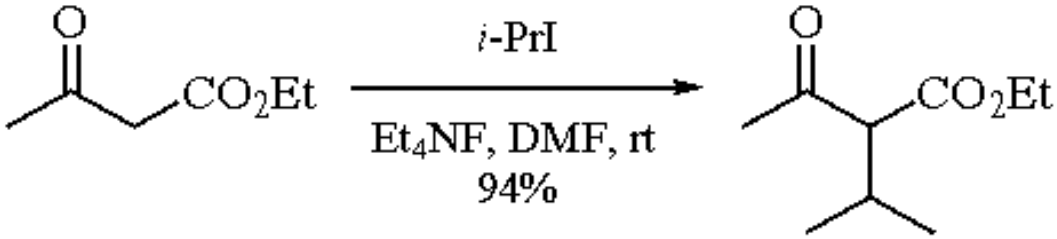

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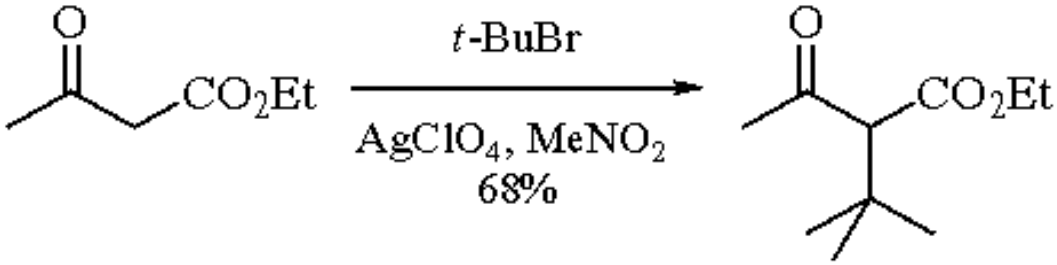

(3)

Metal coordinated alkenes react with acetoacetate anion, affording an alternative type of alkylation.[16] π-Allyl palladium species, catalytically generated by reaction of Pd^0 complexes with allylic acetates or halides, provide efficient *C*-allylation of the acetoacetate anion.[17] Alkylations with vinyl epoxides, allylic carbonates, and allylic carbamates via Pd^0 catalysis proceed without the need for an external base since the π-allylpalladium species in these systems are sufficiently basic to deprotonate acetoacetate in situ.[17] The regio- and stereoselectivities in alkylations with cyclic vinyl epoxides (eq 4)[18] are opposite to those observed under standard carbanion conditions.[19] A highly efficient Pd^0-catalyzed addition of methyl acetoacetate to 1,3-dienes can be achieved using ***1,3-Bis(diphenylphosphino)propane*** ligand (eq 5).[20]

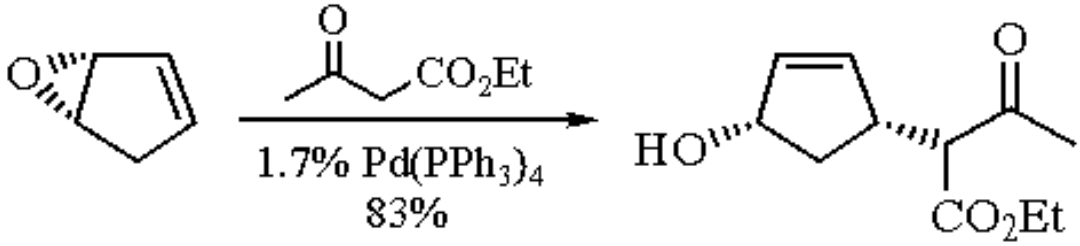

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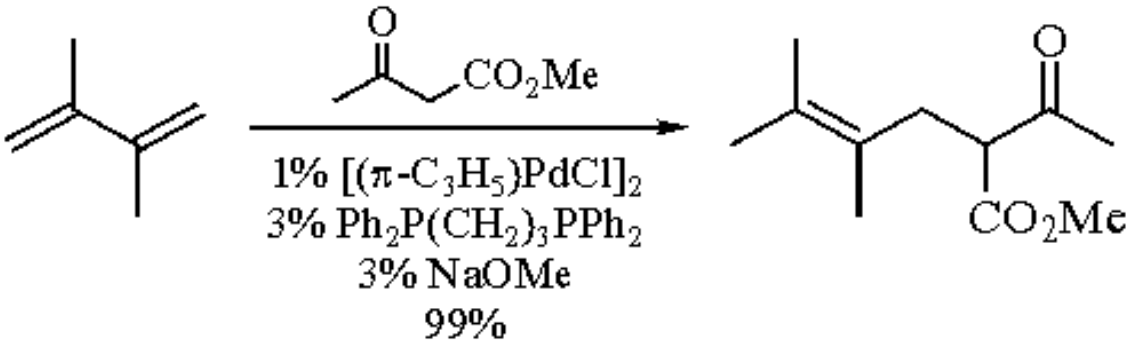

(5)

Manganese(III) Acetate promotes the radical addition of ethyl acetoacetate to enol ethers and subsequent oxidative cyclization to 1-alkoxy-1,2-dihydrofurans, which may be hydrolyzed to alkylated acetoacetate derivatives (eq 6).[21] The corresponding reaction with simple alkenes is less general.[22]

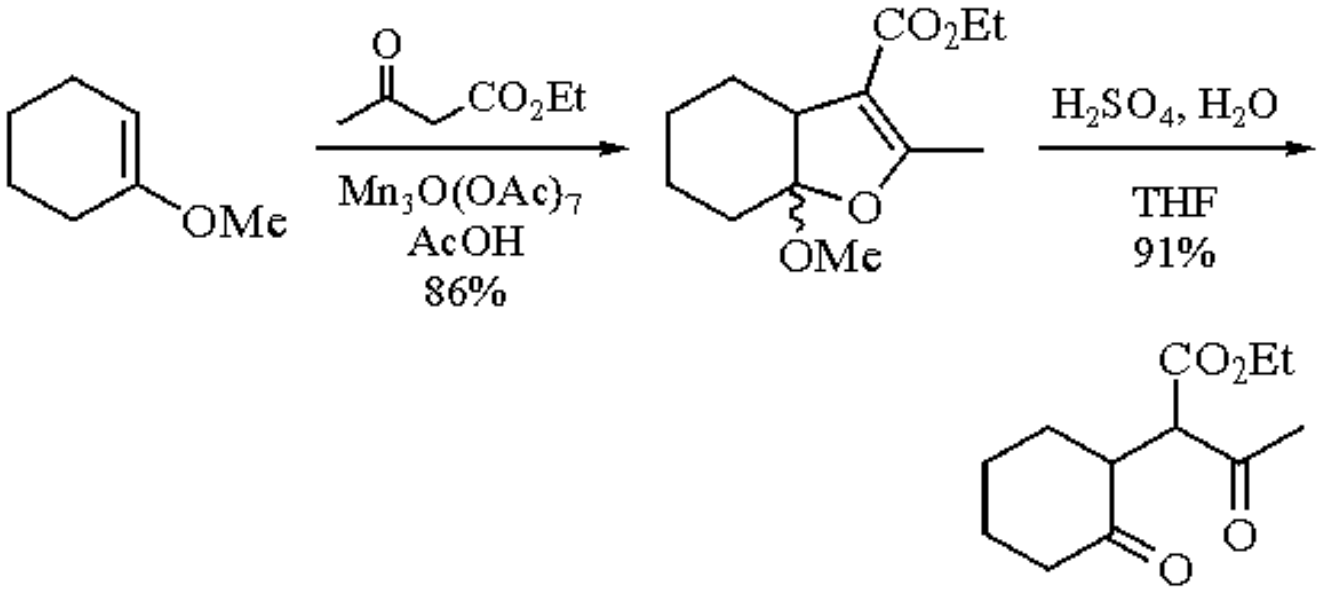

(6)

α,γ-Dianions of acetoacetates (see ***Methyl Dilithioacetoacetate***) can be generated by treatment with 1 equiv of ***Sodium Hydride***, followed by 1 equiv of ***n-Butyllithium***, or 2 equiv of ***Lithium Diisopropylamide*** in THF.[23] Reaction of the dianion with a variety of alkylating agents including alkyl halides (eq 7)[23] and epoxides (eq 8)[24] results in regioselective γ-alkylation.

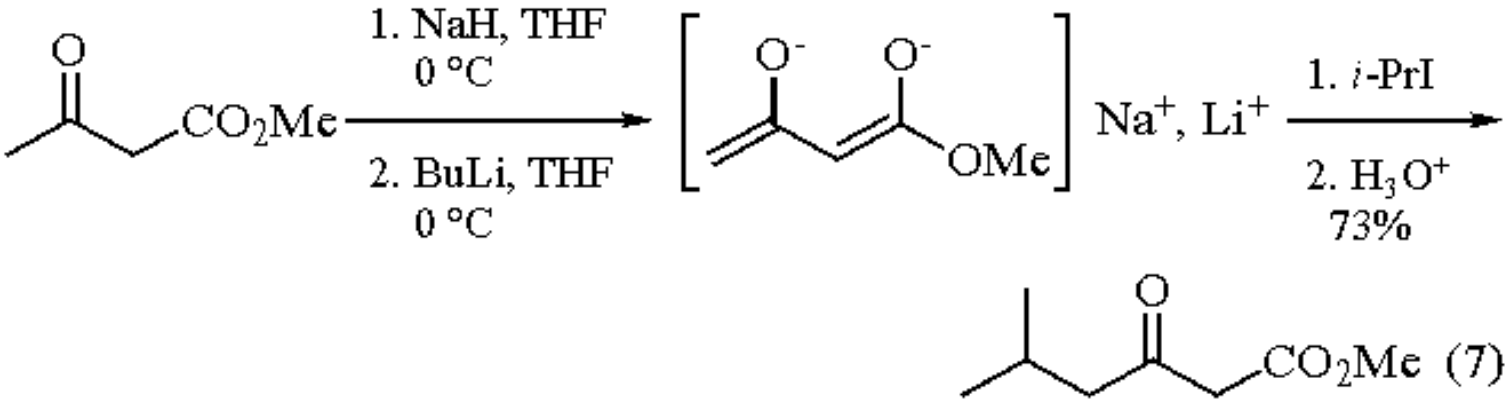

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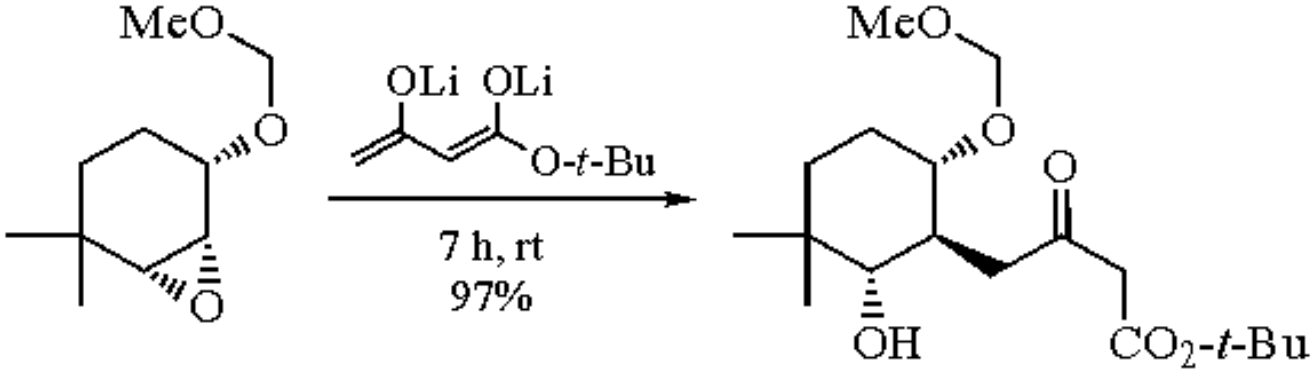

(8)

Acylations.

C-acylation at the α-carbon of ethyl acetoacetate may be achieved by reaction of the magnesio or sodio derivative with an acid chloride.[25] Acylation may also be performed efficiently in the presence of $MgCl_2$ and pyridine (eq 9).[26]

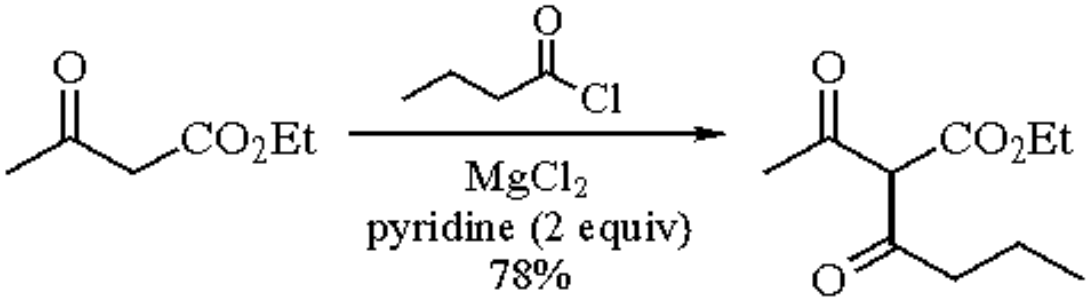

(9)

The dianions of acetoacetates undergo γ-*C*-acylation with esters.[27] Proton transfer occurs readily from product to the starting enolate. As a result, two equivalents of the dianion are needed to ensure complete conversion. This problem can be overcome by employing *N*-methoxy-*N*-methyl amides (see ***N-Methoxy-N-methylacetamide***) as acylating agents.[28] Addition of catalytic amounts of ***N,N,N´,N´-Tetramethylethylenediamine*** greatly improves the efficiency of acylation of dilithio ethyl acetoacetate (eq 10).[29] *N,N*-Dimethyl carboxamides can also be used as acylating agents in the presence of ***Boron Trifluoride Etherate***.[30]

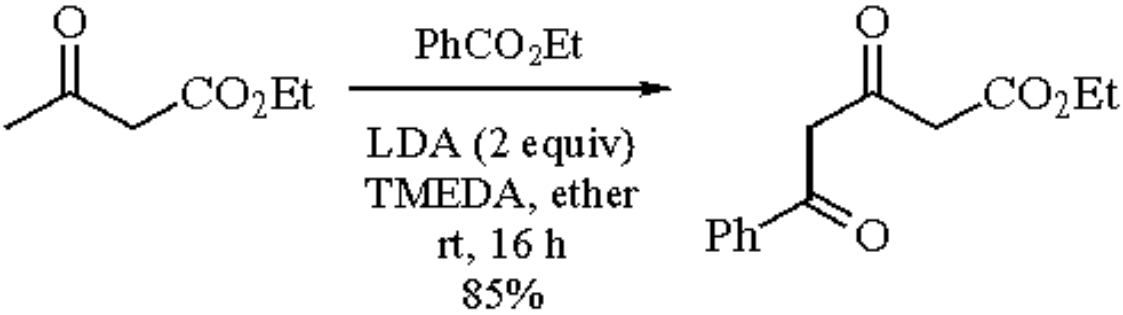

(10)

Carbonyl Additions and Condensations.

Knoevenagel condensation of acetoacetates with carbonyl compounds may be carried out using a wide range of catalysts and reaction conditions.[4] A particularly mild and efficient procedure involves the use of ***Titanium(IV) Chloride*** and pyridine in THF at low temperatures, which allows the condensation of ethyl acetoacetate with aliphatic, aromatic, and heteroaromatic aldehydes to produce α-alkylideneacetoacetates (eq 11).[31] The condensation of *t*-butyl acetoacetate with

aldehydes and subsequent cleavage of the *t*-butyl ester by heating with catalytic ***p-Toluenesulfonic Acid*** provides a convenient synthesis of α,β-unsaturated methyl ketones.[32] α-Alkyl-substituted acetoacetates can add to aldehydes; however, the adducts often undergo acyl cleavage under the reaction conditions to give α,β-unsaturated esters (eq 12).[33] The dianion of methyl acetoacetate reacts with aldehydes and ketones in the γ-position to give aldol adducts (eq 13).[34]

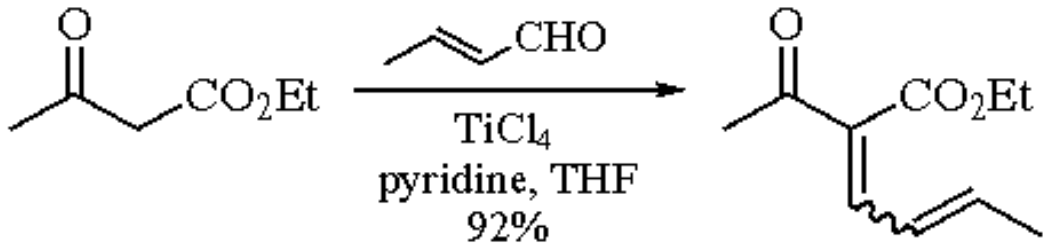

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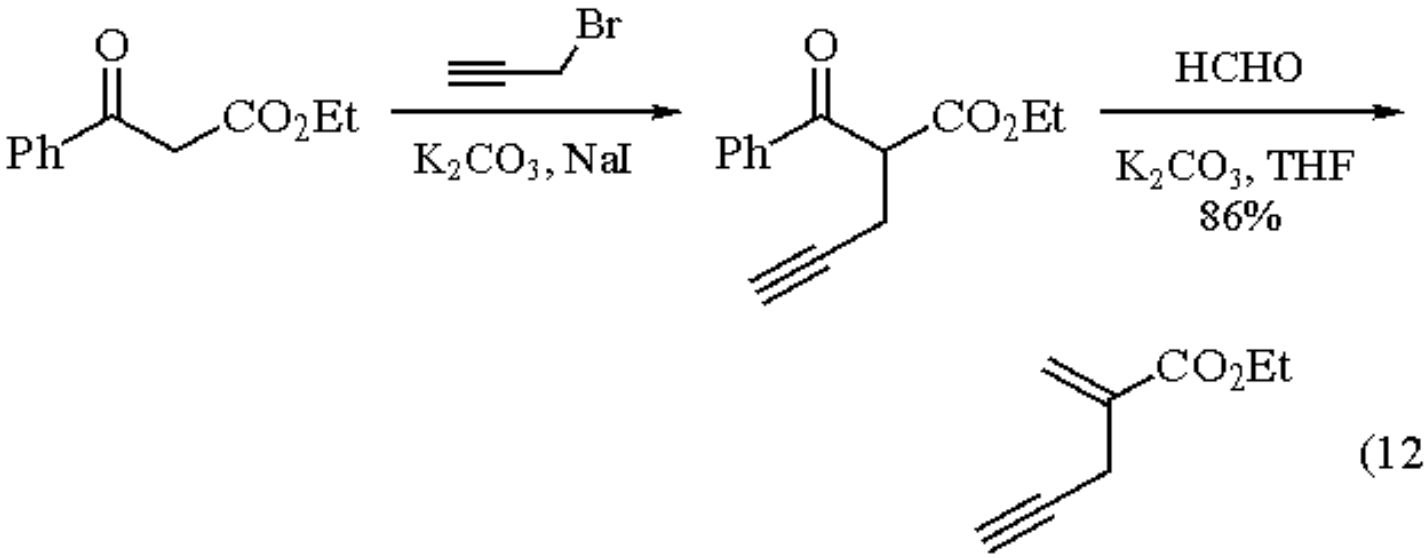

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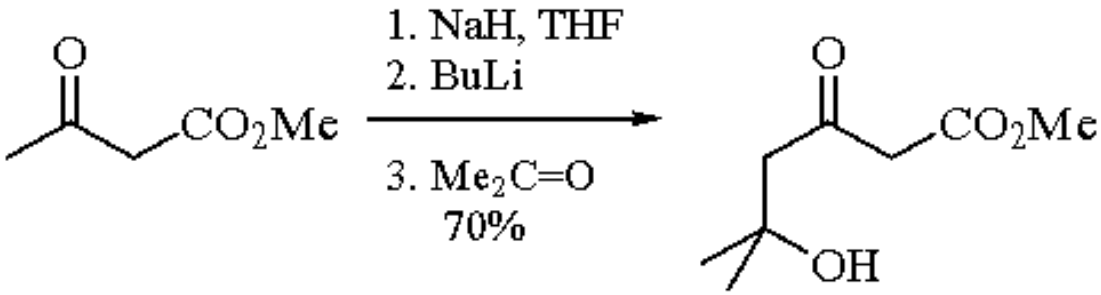

(13)

Conjugate Additions and Annulation Reactions.

A wide variety of activated alkenes, alkynes, and allenes participate in conjugate additions or Michael reactions with acetoacetates. α,β-Unsaturated ketones, esters, nitriles, aldehydes, lactones, sulfoxides, sulfones, and nitro compounds are among the more commonly used alkene acceptors.[3] Although conventional procedures employ strongly basic catalysts, neutral reaction conditions (eq 14)[35,36] are often used to overcome side reactions such as bis additions and self condensations.

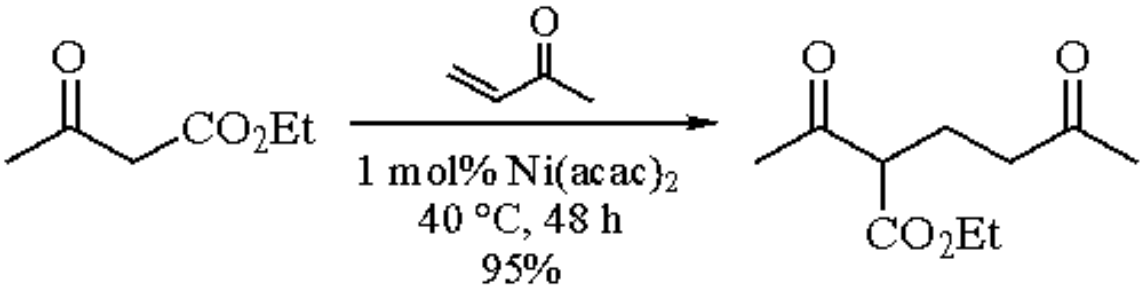

(14)

1,5-Diketones produced by the conjugate addition of acetoacetates to α,β-unsaturated ketones are useful in the synthesis of cyclohexenones via intramolecular aldol condensation.[37] A sequence of Knoevenagel condensation, Michael addition, aldol cyclization, and dealkoxycarbonylation may be carried in one pot using ethyl acetoacetate, an aliphatic aldehyde, and ***Piperidine*** catalyst (eq 15).[38] In general, however, annulation reactions of acetoacetates involve the Michael addition and the aldol cyclization as two separate steps (eq 16).[39]

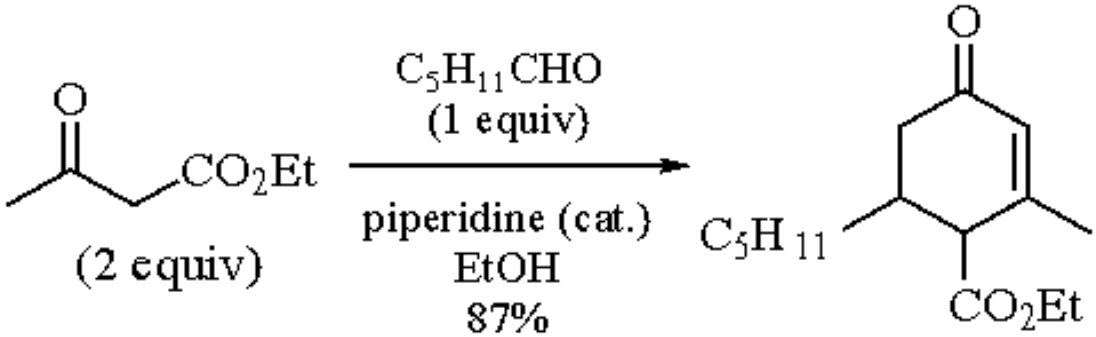

(15)

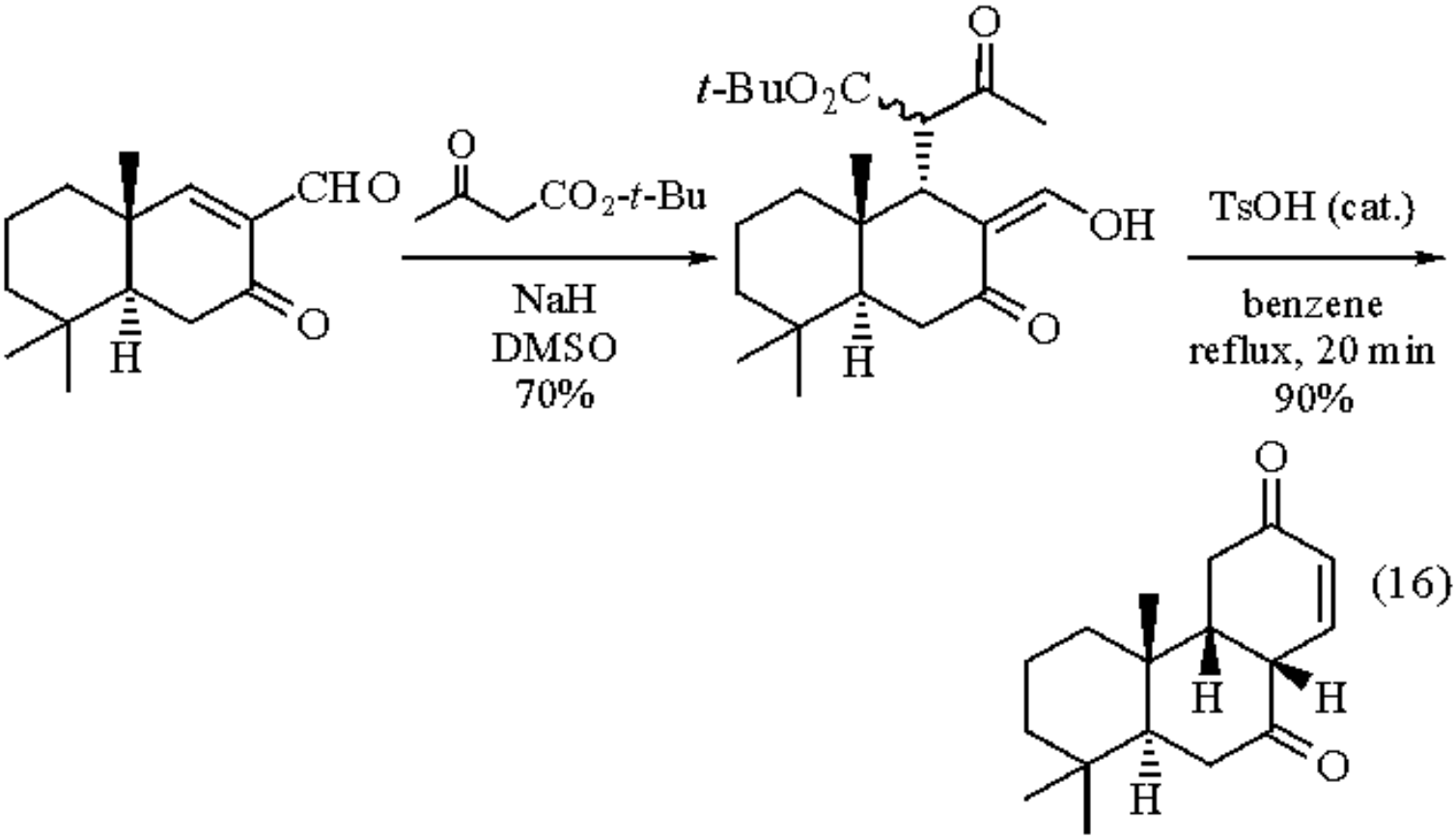

(16)

Trimethylsilyl Enol Ethers.

Successive silylation of methyl acetoacetate with ***Chlorotrimethylsilane*** gives the mono- and the bis(trimethylsilyl) enol ethers (eq 17),[40] which are useful as synthetic equivalents of acetoacetate in reactions with a variety of electrophiles. Lewis acid-catalyzed reaction of the mono(trimethylsilyl) enol ether with *N*-acylimines,[41] oxonium ions,[42] thianium ions[43] and vinyl iminium ions (eq 18)[44] gives α-*C*-alkylated acetoacetate derivatives.

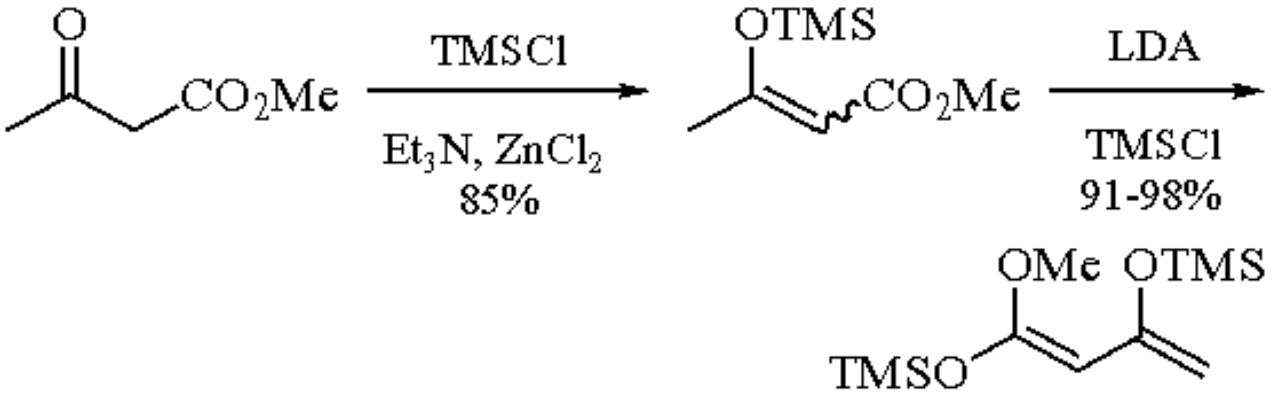

(17)

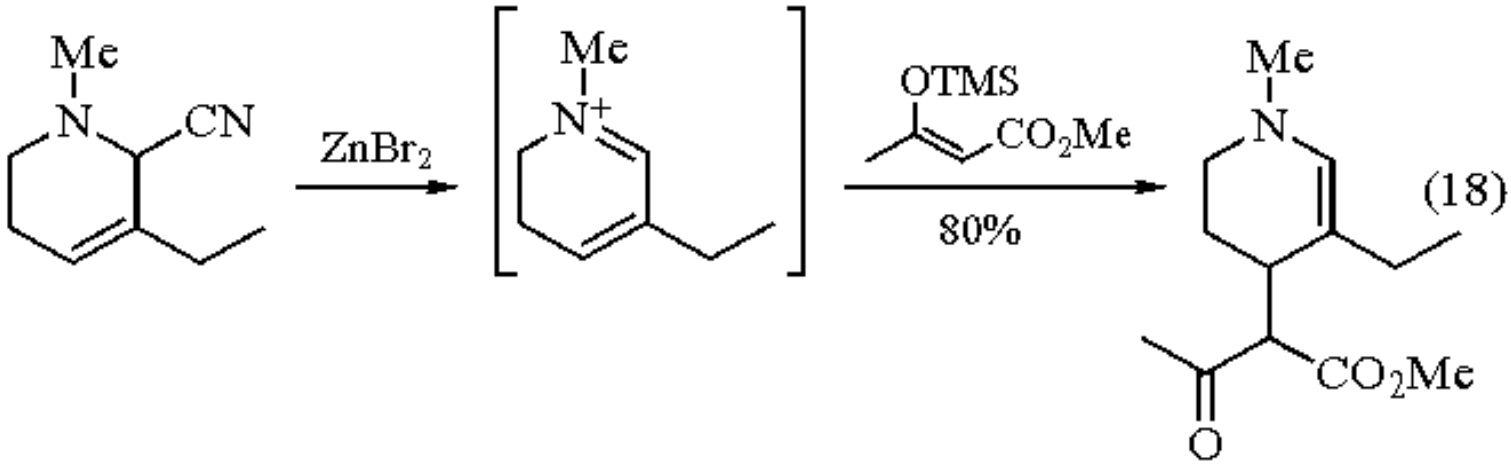

(18)

$TiCl_4$-catalyzed aldol addition of the bis(trimethylsilyl) enol ether of methyl acetoacetate to carbonyl compounds occurs exclusively in the γ-position.[45] Highly diastereoselective aldol additions can be achieved in reactions with α-alkoxy aldehydes (eq 19).[46] The bis(trimethylsilyl) enol ether may also be used as a 1,3-dianionic synthon for annulation with dicarbonyl electrophiles. Lewis acid-catalyzed annulation with α,α-dialkoxy ketones,[47] β,β-dialkoxy ketones,[40] and 1,4-keto aldehydes (eq 20)[48] allows the construction of five-, six-, and seven-membered ring systems, respectively.

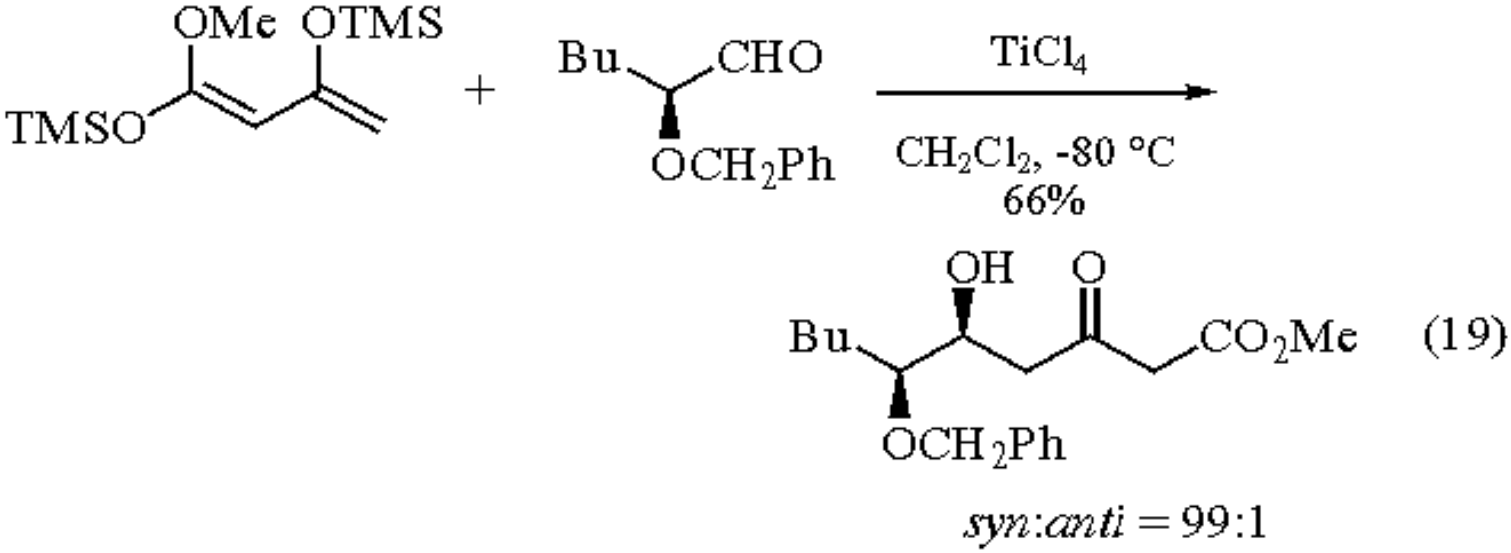

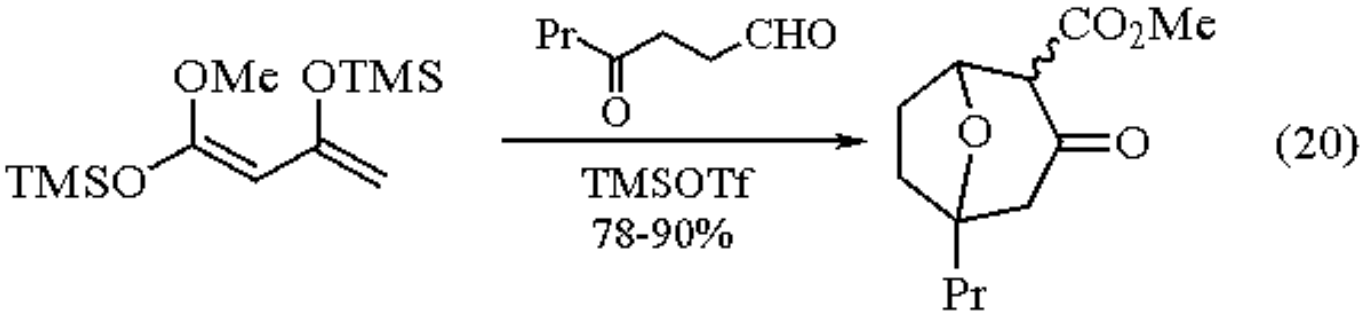

Asymmetric Reduction.

Highly enantioselective asymmetric hydrogenation of acetoacetates can be achieved using ***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***-ruthenium complexes (eq 21).[49] The resulting 3-hydroxybutanoates (see ***Ethyl 3-Hydroxybutanoate***) are versatile auxiliaries and building blocks for the synthesis of enantiomerically pure products. Racemic α-substituted acetoacetates may also be hydrogenated in high stereoselectivity via dynamic kinetic resolution.[50]

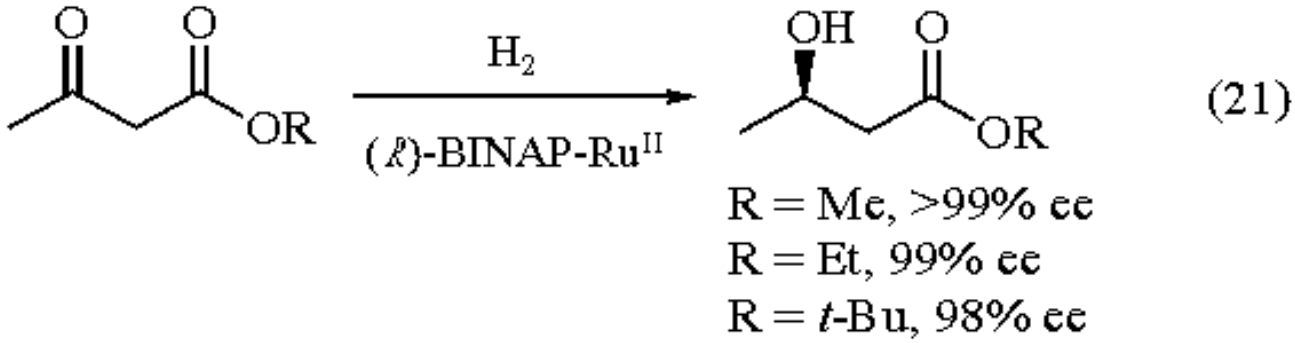

Heterocyclic Synthesis.

A wide variety of five- and six-membered heterocyclic systems may be derived by the cyclocondensation of acetoacetates with 1,2- and 1,3-bifunctional reagents wherein one or both of the functionalities are heteroatomic (Table 1). The regioselectivity in these cyclizations can often be altered by replacing acetoacetates with their enol ether or enamine derivatives.

Table 1 Heterocyclic Synthesis via Cyclocondensation of Ethyl Acetoacetate (and Analogs) with 1,2- and 1,3-Bifunctional Reagents

Bifunctional reagent	Heterocyclic products
Hydrazines[51]	pyrazolones
Hydroxylamines[52]	isoxazolones
Hydroxamoyl chlorides[53]	isoxazoles
Hydrazidoyl chlorides[53]	pyrazoles
a-Amino ketones[54]	pyrroles
a-Halo ketones[55]	furans
a-Hydroxy carbonyl compounds[4]	furanones
b-Hydroxy carbonyl compounds[4]	pyranones
Salicylaldehydes[4]	coumarins
o-Aminobenzaldehydes and *o*-aminoacetophenones[4,56]	quinolines
Ureas, thioureas, amidines and guanidines[57]	pyrimidines

The classical synthesis of coumarins via the von Pechmann reaction[58] involves the condensation of acetoacetates with phenols under acid catalysis (eq 22).[59] Chromones are produced when the phenol contains a deactivating group or the acetoacetates are α-substituted. The condensation of acetoacetates with anilines can give either 2-hydroxy- or 4-hydroxyquinolines, depending upon the reaction temperature.[60] In the Hantzch synthesis of symmetrical dihydropyridines, two equivalents of acetoacetates are condensed with aldehydes in the presence of ***Ammonia*** (eq 23).[61] A variation of the Hantzch synthesis for the preparation of unsymmetrical dihydropyridines involves the condensation of α-(alkylidene)acetoacetates with 3-aminocrotonate.[62]

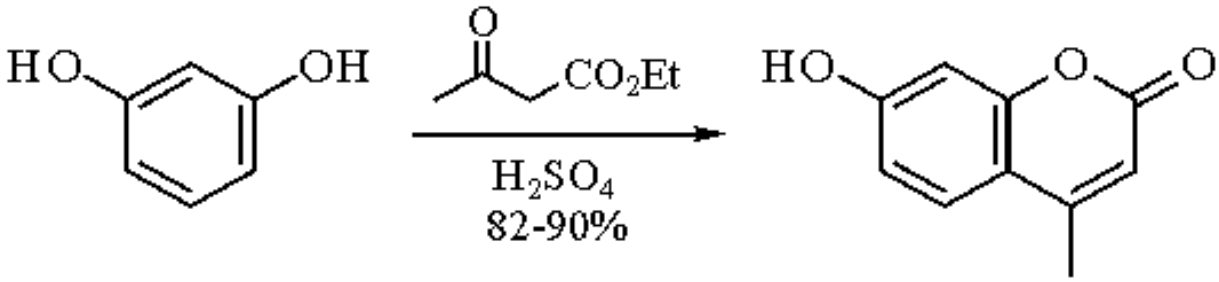

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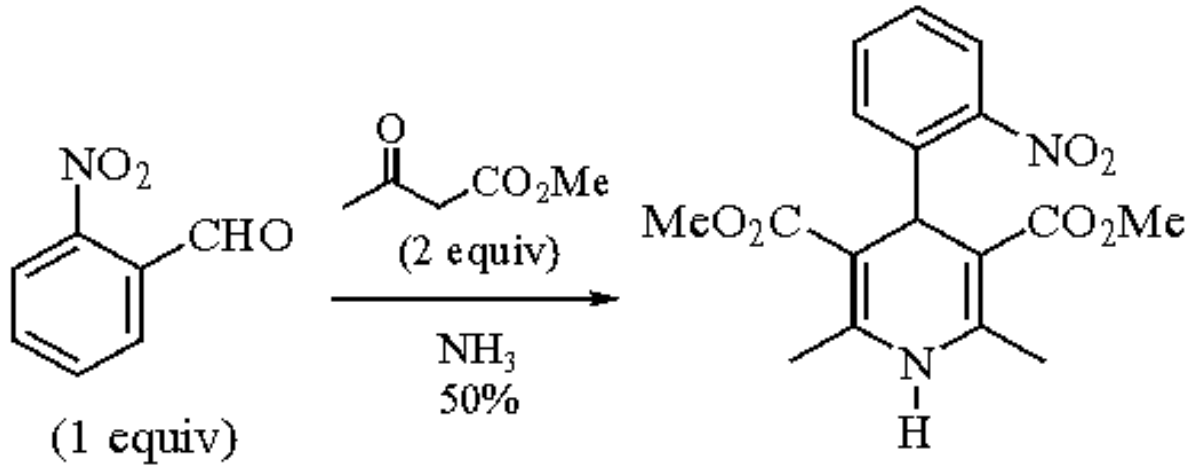

(23)

Related Reagents.

Acetoacetic Acid; ***Acetone***; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***N,O-Dimethylhydroxylamine***; ***Ethyl 4-Chloroacetoacetate***; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene***; ***N-Methoxy-N-methylacetamide***; ***Methyl Dilithioacetoacetate***.

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N-Ethylacetonitrilium Tetrafluoroborate

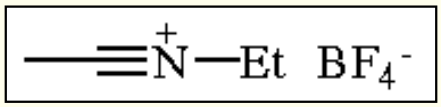

[462-35-1] · $C_4H_8BF_4N$ · *N*-Ethylacetonitrilium Tetrafluoroborate · (MW 156.91)

(reagent for the dehydration of aldoximes to nitriles[1])

Form Supplied in: needles; very unstable; not commercially available.

Preparative Methods: this salt can be prepared by *N*-alkylation of ***Acetonitrile*** with ***Triethyloxonium Tetrafluoroborate*** (eq 1),[2] or by *C*-alkylation of isocyanides.[1] The treatment of *O*,*O*,*O*-triethyl phosphorothioate with equimolar amounts of ***Nitrosonium Tetrafluoroborate*** in anhydrous acetonitrile gave the *N*-ethylacetonitrilium ion in moderate yield (eq 2).[3]

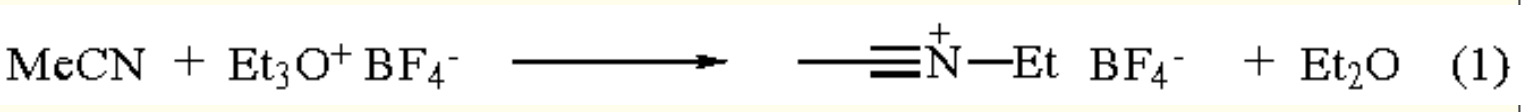

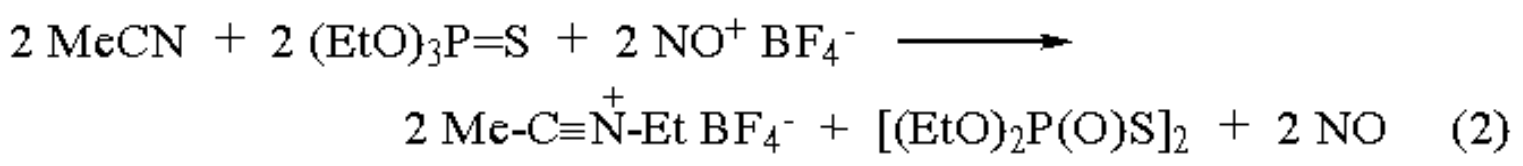

Handling, Storage, and Precautions: powerful alkylating agent similar to triethyloxonium tetrafluoroborate; treat with due caution.

Dehydration of Aldoximes.[1]

Nitrilium salts are very electrophilic and react readily with hydroxylic substances. They react with aldoximes (in MeCN for 8 h at 20 °C, 0.5 h at 80 °C) to give imino esters, which collapse to give the amide of the nitrilium ion and a nitrile (eq 3).[1] This reaction works well for a range of aromatic and alkyl R groups. The reagent compares favorably with the previous use of ***Trichloroacetonitrile*** for this transformation.[4]

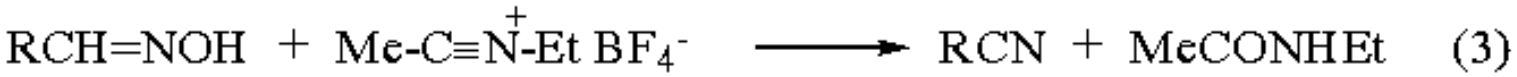

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Ethyl Acrylate[1]

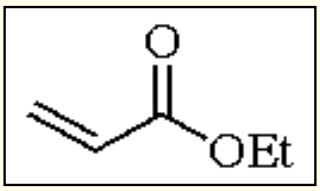

[140-88-5] · $C_5H_8O_2$ · Ethyl Acrylate · (MW 100.13) (Me ester)

[96-33-3] · C_3H_6O · Methyl Acrylate · (MW 58.09)

(two- and three-carbon alkylating and annulating reagent commonly used in cycloadditions,[2] conjugate additions,[3] tandem vicinal dialkylation reactions,[4] and Heck reactions[5])

Physical Data: mp -71 °C; bp 98-100 °C; *d*204 0.924 g cm^{-3}; *n*20D 1.4049.

Solubility: 2 g 100 mL^{-1} H_2O (20 °C); forms 45% aqueous azeotrope, bp 81 °C; sol EtOH, ether; forms 57% ethanol azeotrope, bp 76 °C.

Form Supplied in: &egt;99%; typically stabilized with 15-200 ppm hydroquinone monomethyl ether; widely available.

Purification: [6] commercial material should be washed repeatedly with aq dil NaOH to free it from stabilizers; alternatively, stabilizers can be extracted using inhibitor removal columns (commercially available). Follow by washing with saturated aq $CaCl_2$. Dry using $CaCl_2$, and distill under reduced pressure. Store the purified ester tightly capped in an amber container, refrigerated below 0 °C.

Handling, Storage, and Precautions: the compound is a cancer suspect agent. A highly flammable irritant, it has an acrid, lachrymatory, penetrating odor. It polymerizes upon standing; polymerization is accelerated by heat, light, or peroxides. Additionally, polymerization occurs upon distillation at atmospheric pressure. Pure material can be stored below -10 °C without polymerization. This toxic reagent should be handled in a fume hood and skin contact should be scrupulously avoided.

Introduction.

The chemical reactivity of the alkyl acrylates is dominated by the electron-deficient nature of the carbon-carbon double bond. The lower alkyl acrylates readily polymerize, and the resulting polymers find commercial application in surface coatings, varnishes, and printing inks.[7]

Cycloaddition Reactions.

Alkyl acrylates probably rival maleic anhydride as the most common dienophiles in Diels-Alder chemistry.[2] They undergo [4 + 2] cycloadditions with a wide variety of dienes and 1,3-dipoles such as nitrones[8] and *S*-methylides,[9] providing entry to functionalized carbocyclic and heterocyclic systems. Eq 1 illustrates the use of methyl acrylate in a sequential Diels-Alder-decarboxylative retrocycloaddition-Diels-Alder preparation of a bornene diester intermediate, which can be converted to barrelene.[10] Certain bulky Lewis acids preferentially coordinate to alkyl acrylates with sterically undemanding alkyl groups, activating them towards reactions with dienes and substantially increasing the stereoselection of the reaction for *endo* adducts (eq 2).[11] Lewis acid-catalyzed ene reactions[2] of acrylates can be used in stereoselective, three-carbon chain homologations, such as in the synthesis of chenodeoxycholic acid (eq 3).[12]

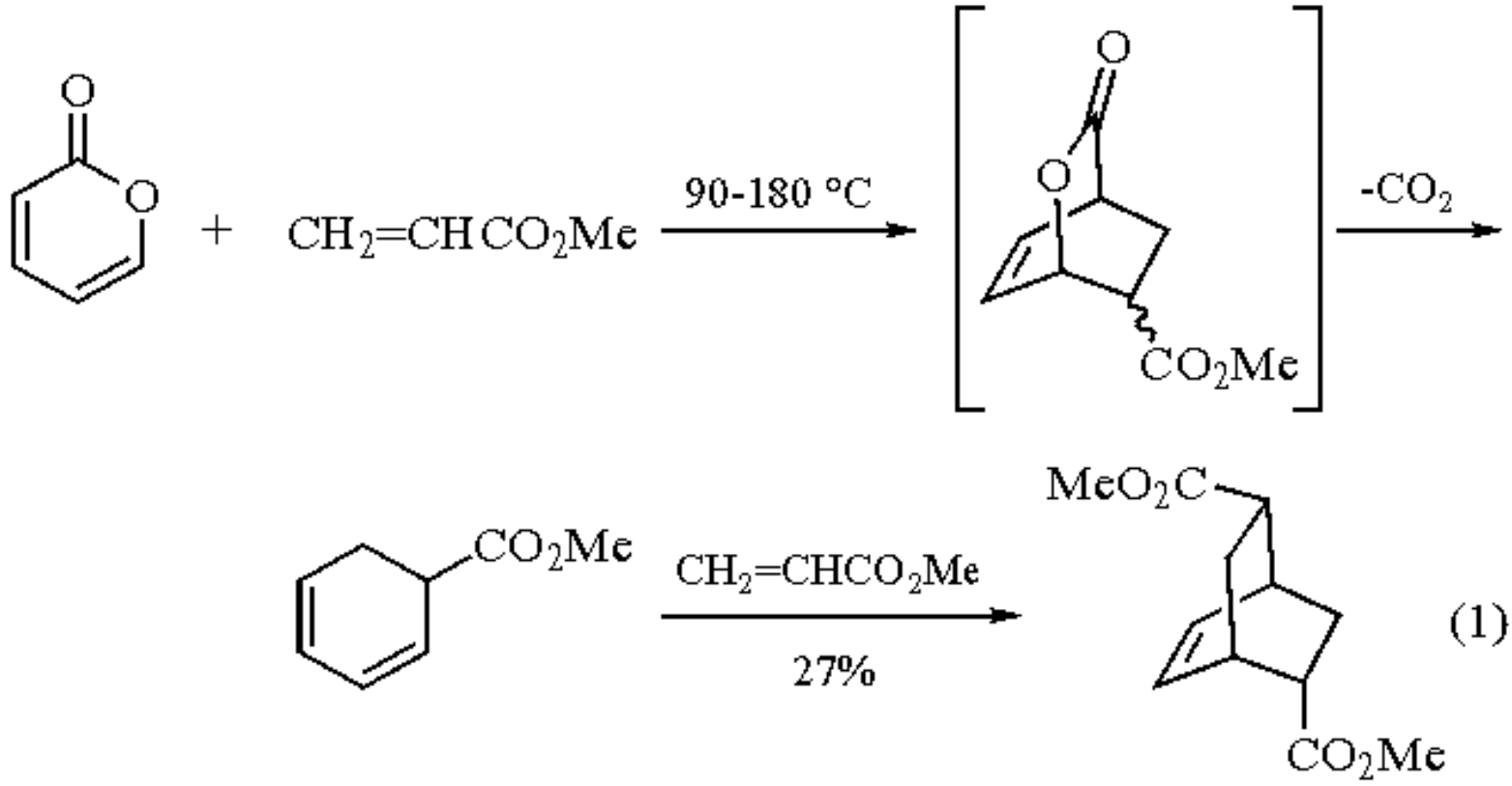

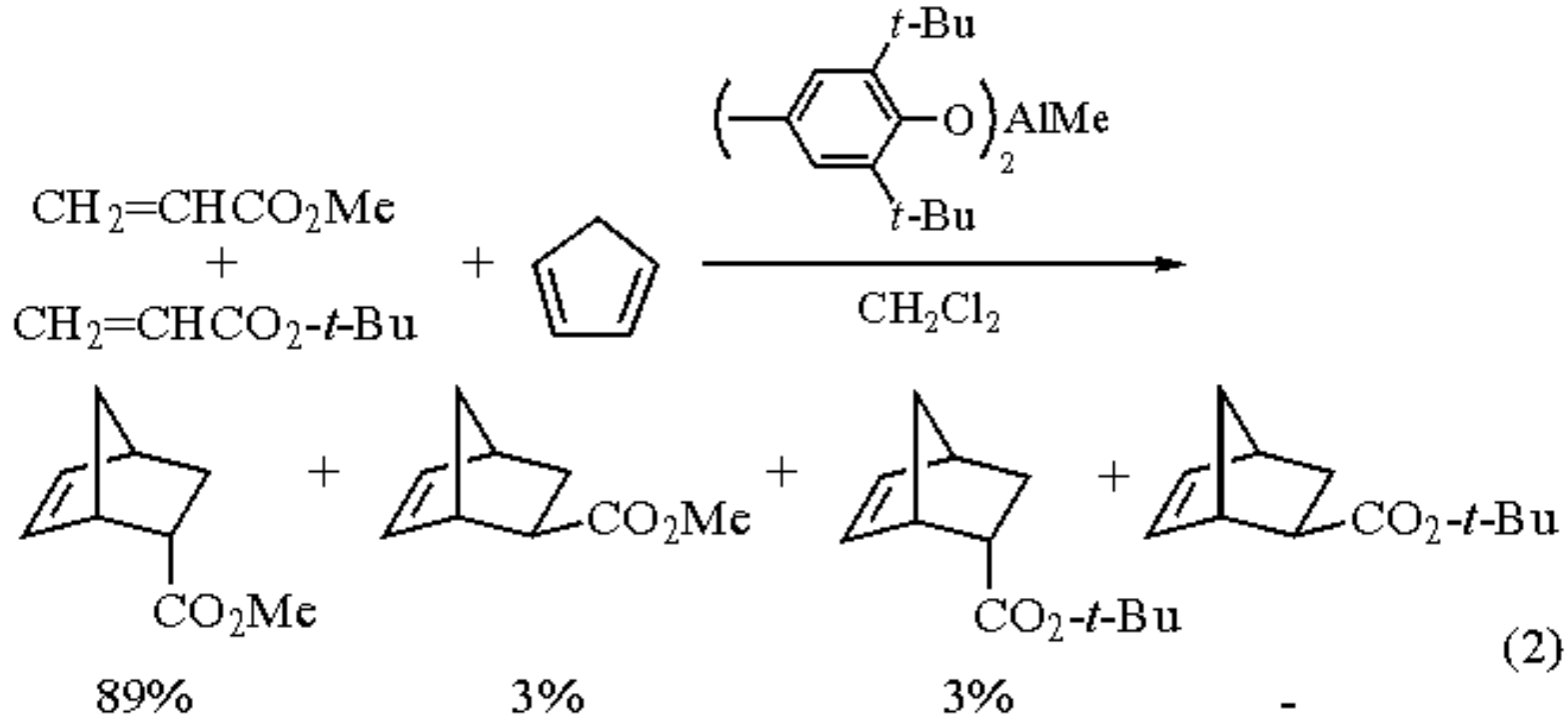

(2)

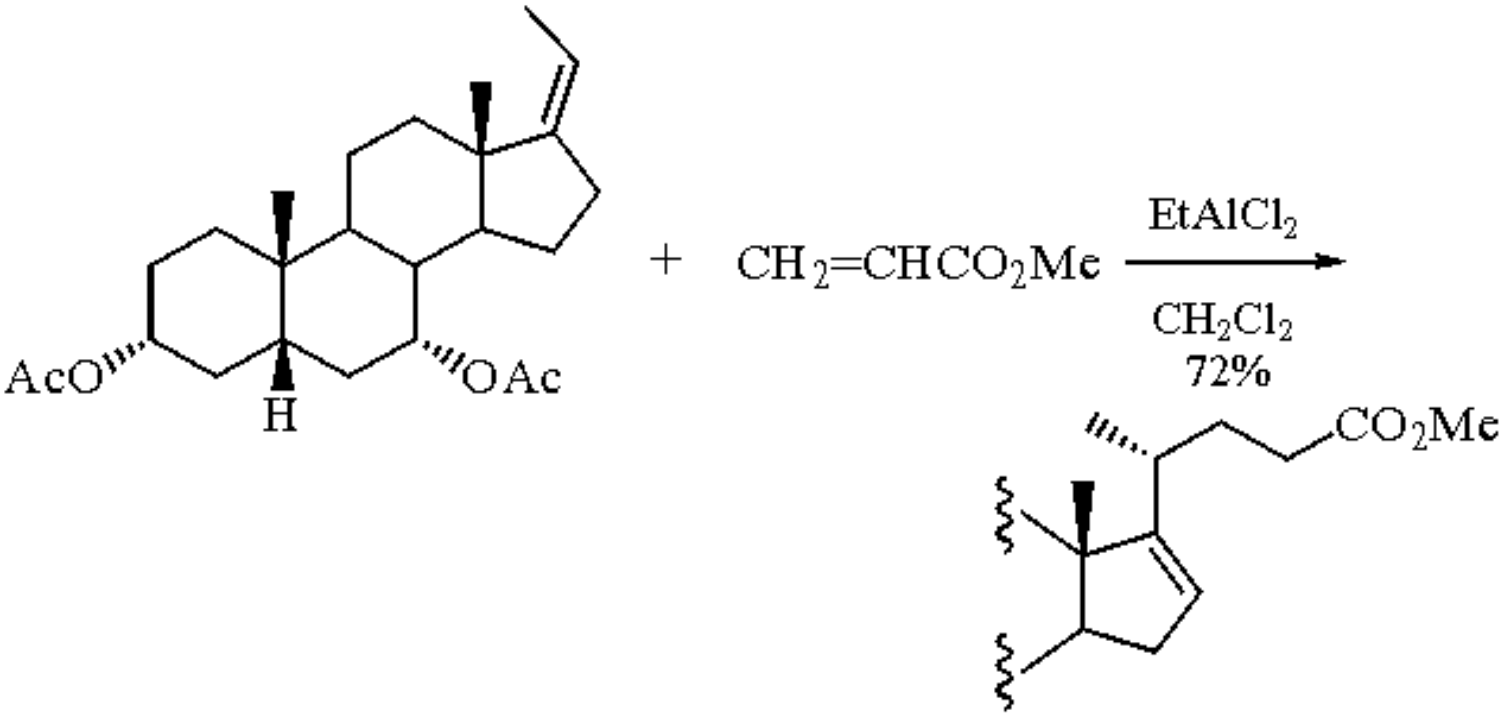

(3)

Conjugate Addition Reactions.

A large number of carbon nucleophiles undergo conjugate additions with alkyl acrylates, including cyanide, enolates, nitro-, sulfinyl-, and sulfonyl-stabilized carbanions, organocopper reagents, Grignard reagents, enamines, amines, thiols, and radicals.[3a,13] Performed under protic conditions, monobasic nucleophiles such as ***2-Nitropropane*** provide high chemical yields of β-substituted propionates (eq 4).[14] If the nucleophile is dibasic, 1:2 nucleophile:acrylate adducts form efficiently:[15] 3-amino-1-propanol provides a 1:2 adduct with ethyl acrylate (eq 5) that can be used to prepare azetidine.[16]

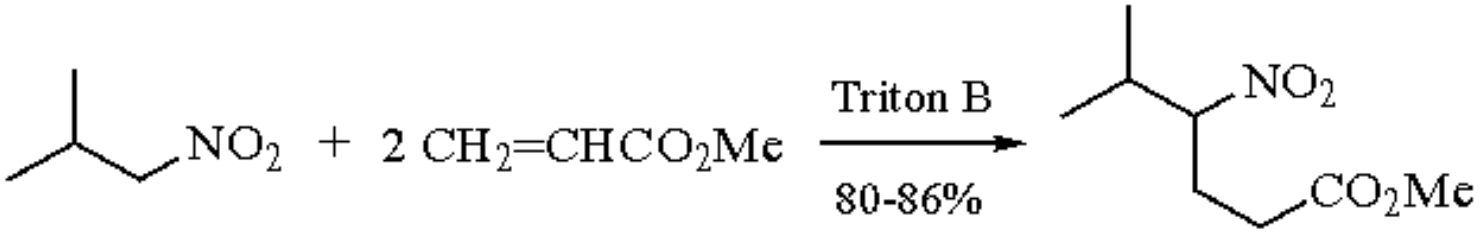

(4)

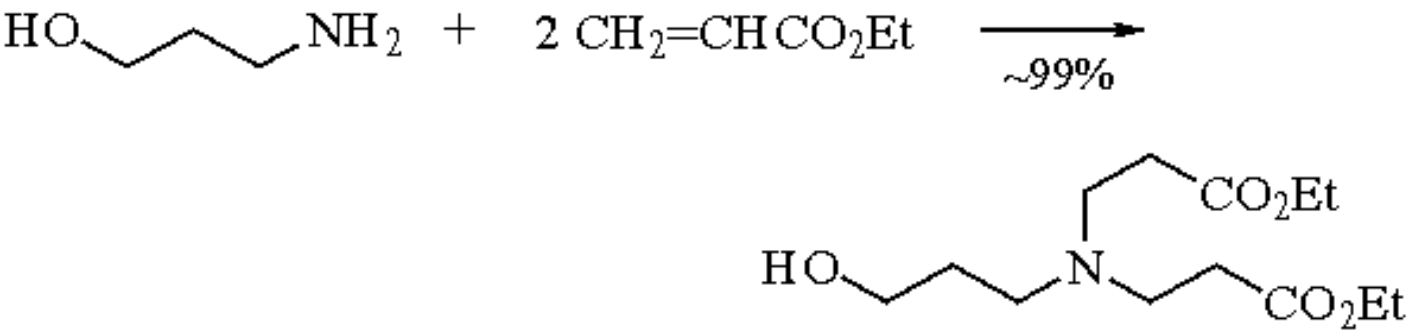

(5)

In aprotic solvents the ester enolate formed upon conjugate addition can be alkylated in the α-position; a large number of these tandem vicinal dialkylation reactions are known.[4] Most such reactions are initiated by Michael addition of an enolate to the acrylate substrate; in contrast, organocopper reagents have been used relatively rarely. This may be because of a lack of reactivity with lithium dialkylcuprates: the situation is substantially improved when higher order cyanocuprates are employed.[17] With proper choice of nucleophile, both 1:1 and 1:2 conjugate adducts can participate in subsequent annulation reactions, illustrated by the [3 + 3] annulation synthesis of glutethimide (eq 6).[18] In aprotic media, these Michael-ring closure (MIRC)[4] reactions can afford cyclized products directly, as in the [1 + 2 + 3][19] cyclohexanone synthesis of eq 7,[20] or upon workup, illustrated by the [3 + 3] synthesis of 6-methoxytetralone (eq 8).[21]

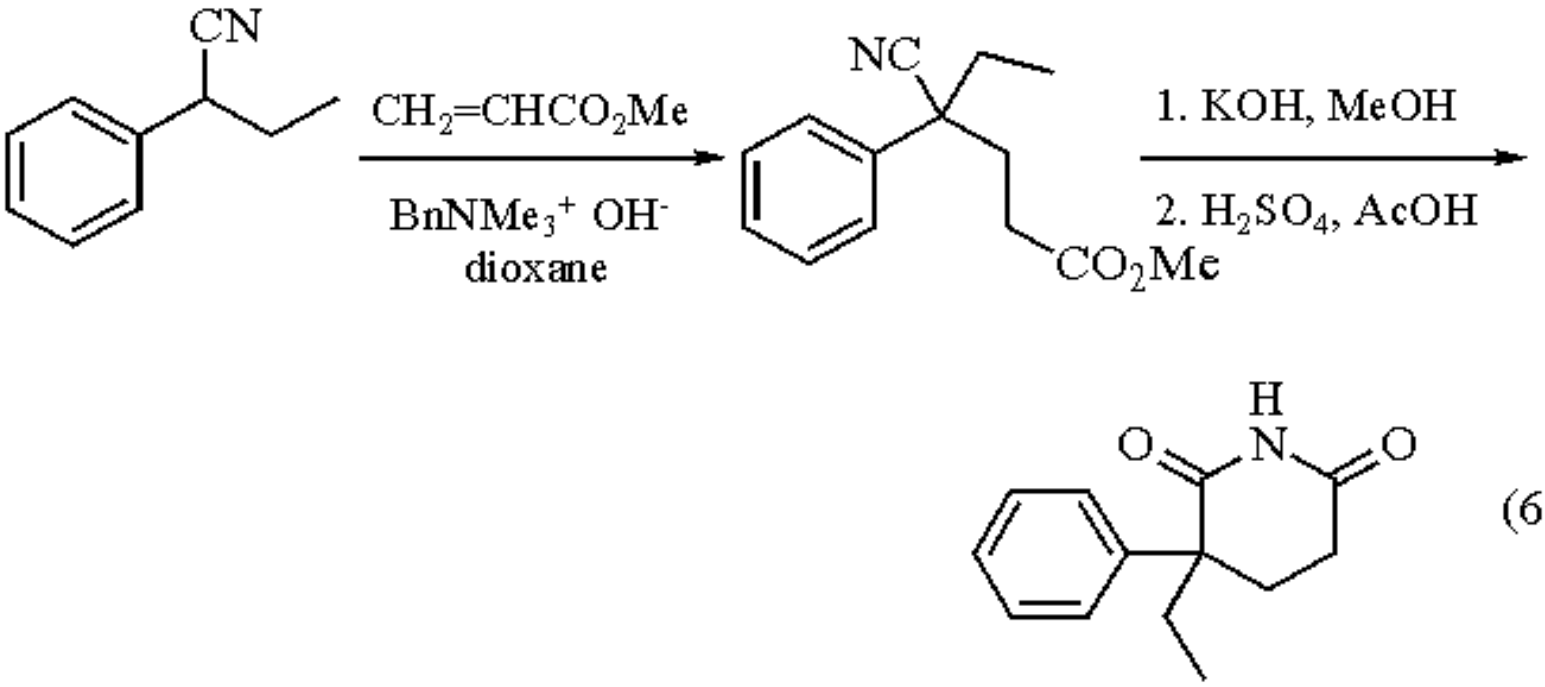

(6)

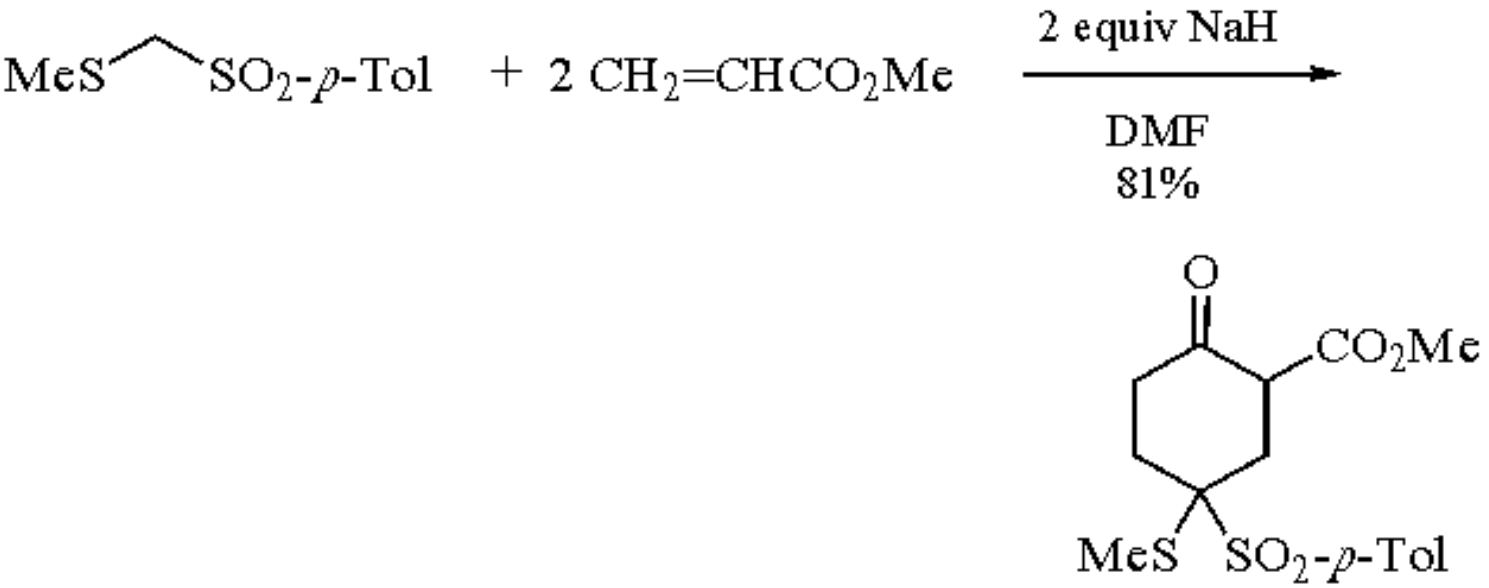

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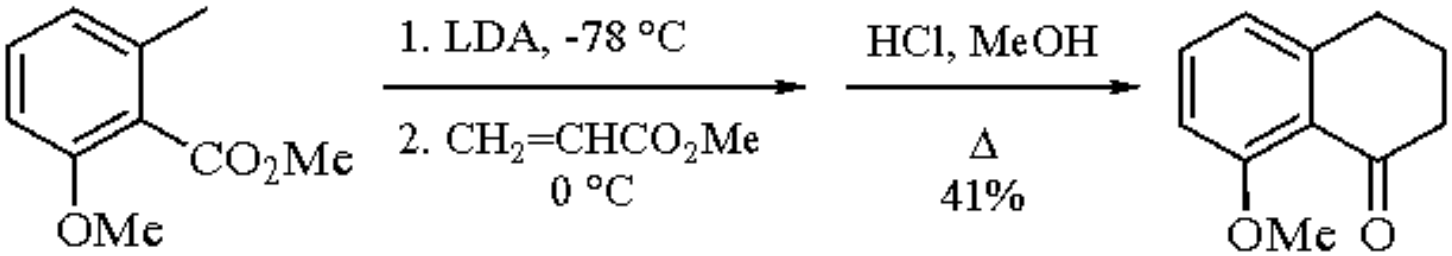

(8)

Radical conjugate additions are relatively straightforward to perform;[3a,22] typically, ***Samarium(II) Iodide*** is used as a one-electron transfer reagent to form the radical conjugate donor.[23] A simple MIRC-type synthesis of γ-lactones is initiated by conjugate addition of various ketyls to ethyl acrylate (eq 9).[24]

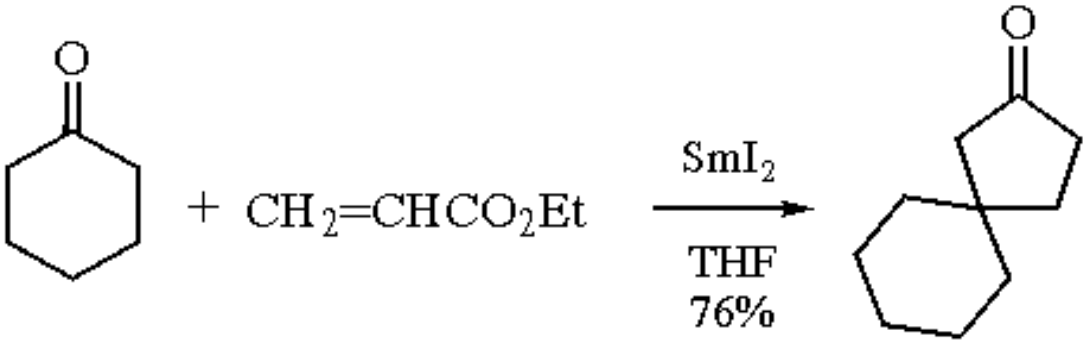

(9)

Vinylations of Organohalogen Compounds.

The Heck reaction provides a convenient route to various substituted acrylate derivatives.[5] While the substituting reagent may simply be a second molecule of alkyl acrylate, resulting in tail-to-tail dimerization for formation of dialkyl (*E*)-2-hexenedioates,[25] sp^2- and sp-hybridized halides are more commonly used.[26] A rapid, two-step, stereospecific synthesis of pellitorine is indicative of the efficiency of the method (eq 10).[27] The process is reliable and quite general, although anomalous products can form: the reaction of methyl acrylate and 2-bromobenzaldehydes provides, in addition to the expected β-substituted acrylate, unusual doubly substituted products (eq 11).[28]

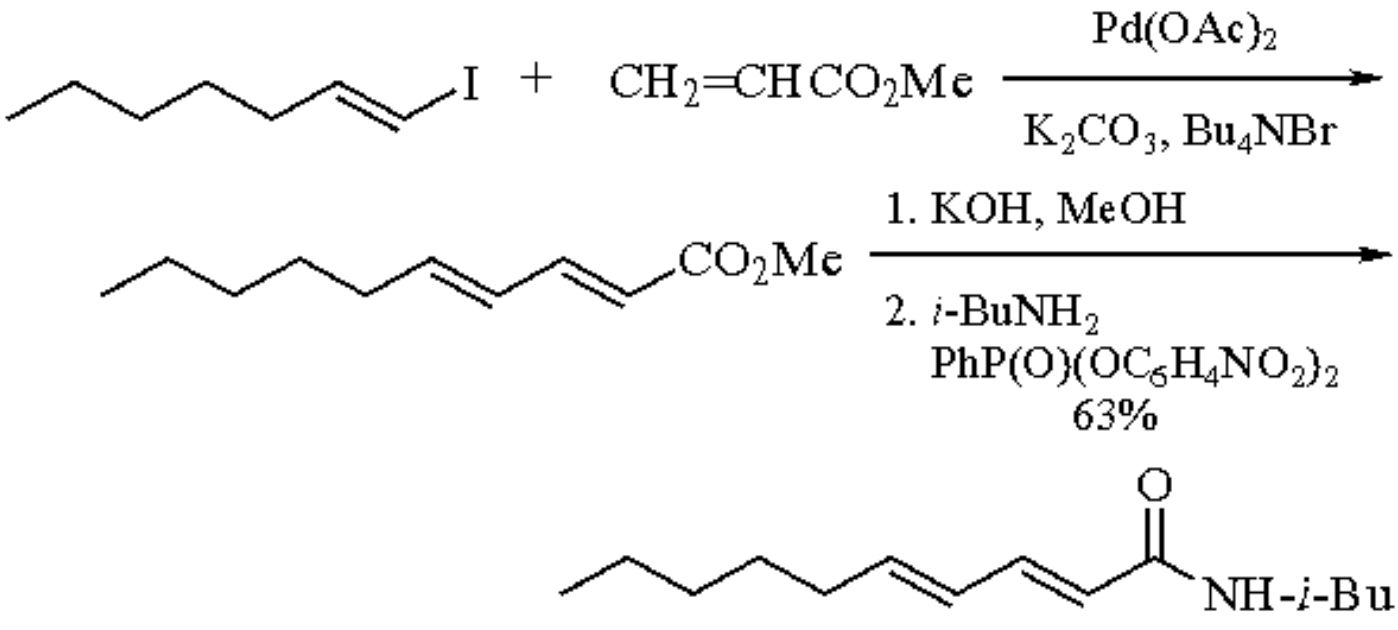

(10)

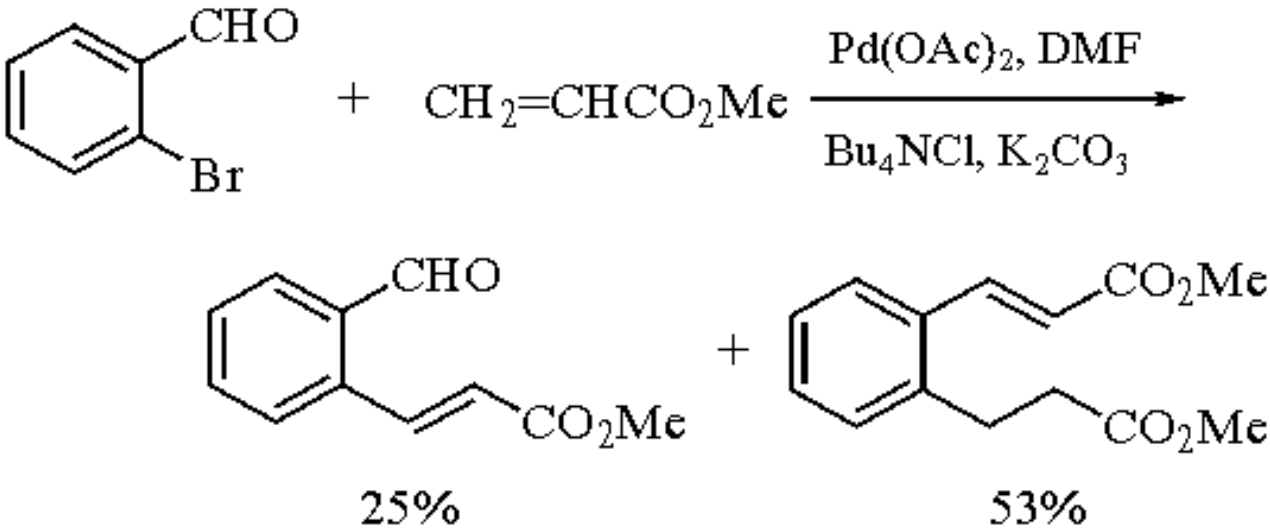

(11)

Other Reactions.

The carbon-carbon double bond of alkyl acrylates undergoes predictable electrophilic addition reactions:[29] the addition of ***Hydrogen Bromide*** to provide alkyl β-bromopropionates is typical (eq 12).[30] Transesterification[31] and hydrolysis[32] are accomplished via acid catalysis; concomitant polymerization can cause yields to be variable. Pyrolysis of ethyl acrylate at 590 °C yields ethylene and acrylic acid.[33]

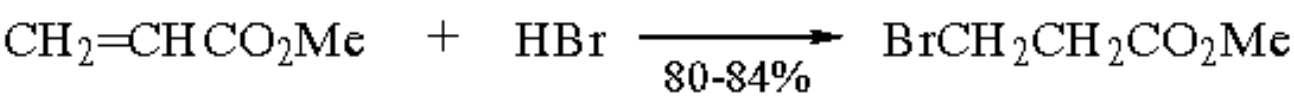

(12)

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Martin Hulce

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Ethylaluminum Dichloride[1]

$EtAlCl_2$

[563-43-9] · $C_2H_5AlCl_2$ · Ethylaluminum Dichloride · (MW 126.95)

(strong Lewis acid that can also act as a proton scavenger; reacts with HX to give ethane and $AlCl_2X$)

Alternate Name: dichloroethylaluminum.

Physical Data: mp 32 °C; bp 115 °C/50 mmHg; *d* 1.207 g cm^{-3}.

Solubility: sol most organic solvents; stable in alkanes or arenes.

Analysis of Reagent Purity: solutions are reasonably stable but may be titrated before use by one of the standard methods.[1e]

Form Supplied in: commercially available neat or as solutions in hexane or toluene.

Handling, Storage, and Precautions: must be transferred under inert gas (Ar or N_2) to exclude oxygen and water. Use in a fume hood.

Alkylaluminum Halides.

Since the early 1980s, alkylaluminum halides have come into widespread use as Lewis acid catalysts. These strong Lewis acids offer many advantages over traditional metal halide Lewis acids such as ***Boron Trifluoride***, ***Aluminum Chloride***, ***Titanium(IV) Chloride***, and ***Tin(IV) Chloride***. Most importantly, the alkyl group on the aluminum will react with protons to give an alkane and a new Lewis acid. Alkylaluminum halides are therefore Brønsted bases, as well as Lewis acids. The alkyl groups are also nucleophilic, and this is the major disadvantage in the use of these compounds as Lewis acids.

Pure, anhydrous Lewis acids do not catalyze the polymerization of alkenes or the Friedel-Crafts alkylation of aromatics by alkenes. Cocatalysts, such as water or a protic acid, react with the Lewis acid to produce a very strong Brønsted acid that will protonate a double bond. Therefore, use of strictly anhydrous conditions should minimize side reactions in Lewis acid-catalyzed ene, Diels-Alder, and [2 + 2] cycloaddition reactions. Unfortunately, it is difficult to prepare anhydrous, proton-free $AlCl_3$, BF_3, etc. Alkylaluminum halides are easily prepared and stored in anhydrous form and, more importantly, scavenge any adventitious water, liberating an alkane and generating a new Lewis acid in the process.

Using alkylaluminum halides, Lewis acid-catalyzed reactions can now be carried out under aprotic conditions. This is of value when side reactions can be caused by the presence of adventitious protons; it is of special value when acidic protons are produced by the reaction. In these cases, use of the appropriate alkylaluminum halide in stoichiometric rather than catalytic amounts gives high yields of products not formed at all with other Lewis acids. The Me_2AlCl-catalyzed ene reactions of aliphatic aldehydes with alkenes, which give homoallylic alcohol-Me_2AlCl complexes that react further to give methane and the stable methylaluminum alkoxides, is an example of this type of reaction (eq 1).[1h,2] Loss of methane prevents the alcohol-Lewis acid complex from solvolyzing or protonating double bonds.

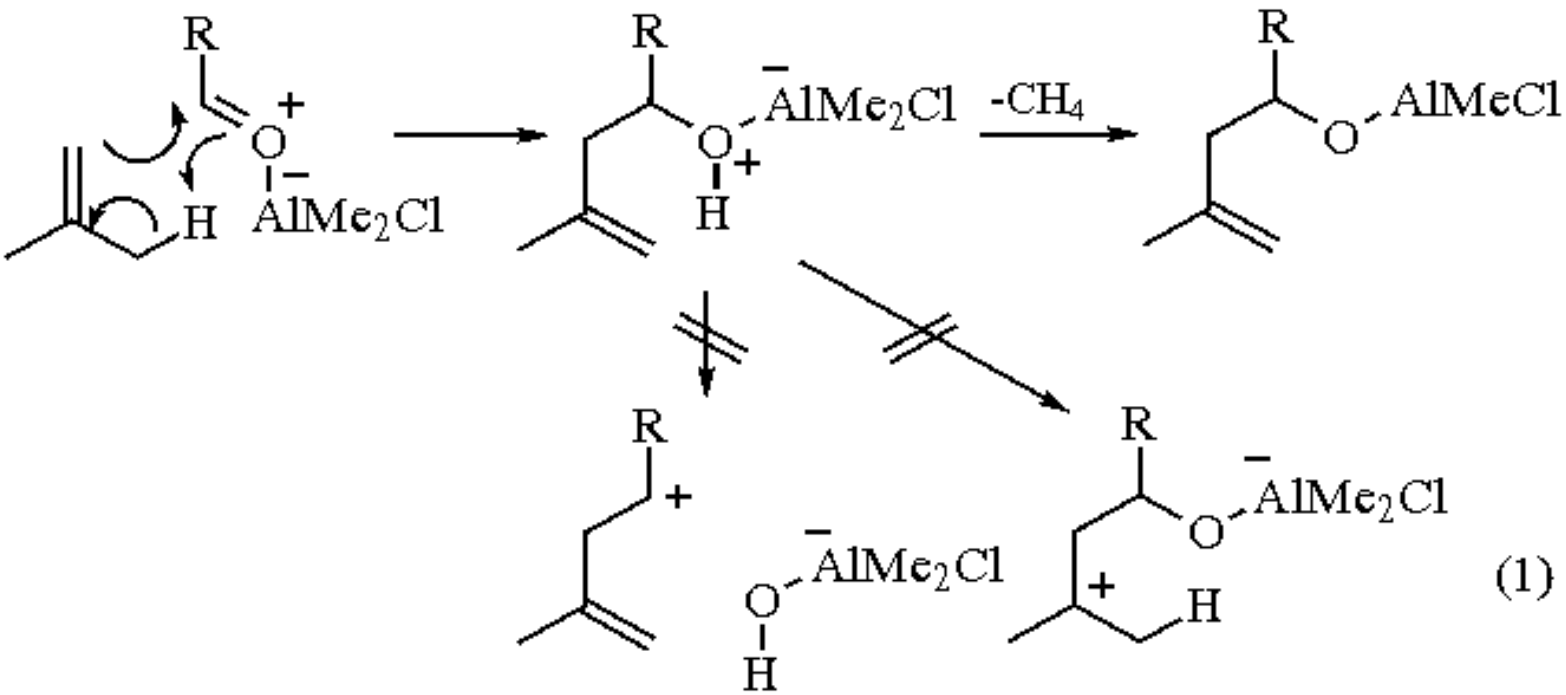

The alkylaluminum halides cover a wide range of acidity. Replacing chlorines with alkyl groups decreases Lewis acidity. $EtAlCl_2$ and ***Methylaluminum Dichloride*** are only slightly less acidic than $AlCl_3$. ***Diethylaluminum Chloride*** and ***Dimethylaluminum Chloride*** are substantially less acidic, and ***Trimethylaluminum***, Me_2AlOR, and $MeAl(OR)_2$ are even weaker Lewis acids. Alkylaluminum halides with fractional ratios of alkyl to chloride are also available. The sesquichlorides are commercially available. Other reagents can be prepared by mixing two reagents in the desired proportion. If no reaction occurs with the alkylaluminum halide, a stronger Lewis acid should be tried. If polymerization or other side reactions compete, a weaker Lewis acid should be used. The sequential ene and Prins reactions shown in eq 2 proceed cleanly with $Me_3Al_2Cl_3$.[3] Complex mixtures are obtained with the stronger Lewis acid $EtAlCl_2$ while the weaker Lewis acid Me_2AlCl reacts with ***Formaldehyde*** to give ethanol.

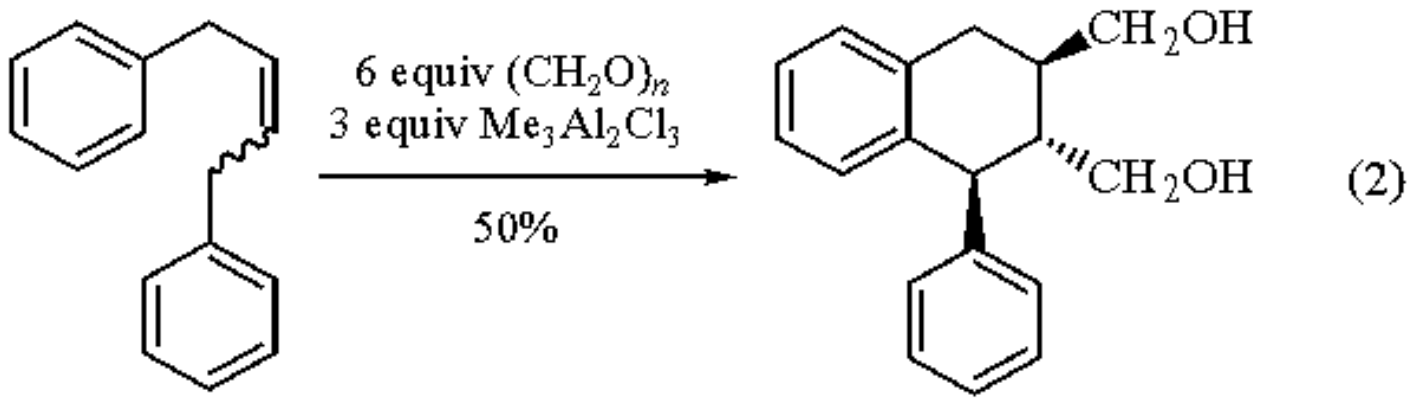

Use of more than one equivalent of Lewis acid will produce complexes that are formally 1:2 substrate Lewis acid complexes, but are more likely salts with a R_2Al-substrate cation and an aluminate anion.[4-6] This substrate in this salt is much more electrophilic and reactive than that in simple Lewis acid complexes.

These reagents are easier to use than typical inorganic Lewis acids. They are soluble in all organic solvents, including hexane and toluene, in which they are commercially available as standardized solutions. In general, alkane solvents are preferred since toluene can undergo Friedel-Crafts reactions. On a laboratory scale, these reagents are transferred by syringe like alkyllithiums and, unlike anhydrous solid Lewis acids, they do not require a glove bag or dry box for transfer.

While the Brønsted basicity of the alkyl group is advantageous, these alkyl groups are also nucleophilic. The addition of the alkyl group from the aluminum in the Lewis acid-reagent complex to the electrophilic center can be a serious side reaction. The ease of alkyl donation is $R_3Al > R_2AlCl > R_3Al_2Cl_3 > RAlCl_2$. When the nucleophilicity of the alkyl group is a problem, a Lewis acid with fewer alkyl groups should be examined. Addition of diethyl ether or another Lewis base may moderate the reaction if its greater acidity causes problems.

Ethylaluminum compounds are more nucleophilic than methylaluminum compounds and can donate a hydrogen as well as an ethyl group to the electrophilic center. Unfortunately, methylaluminum compounds must be prepared from ***Chloromethane***, while ethylaluminum compounds can be prepared much more cheaply from ***Ethylene***. Therefore ethylaluminum compounds are usually used unless the nucleophilicity of the alkyl group is a problem. Although the predominant use of alkylaluminum halides is as Lewis acids, they are occasionally used for the transfer of an alkyl group or hydride to an electrophilic center.

Eq 3 shows an unusual reaction in which the nature of the reaction depends on the amount, acidity, and alkyl group of the alkylaluminum halide.[6] Use of 1 equiv of Me_2AlCl leads to a concerted ene reaction with the side chains *cis*. Use of 2 equiv of Me_2AlCl produces a more electrophilic aldehyde complex that cyclizes to a zwitterion. Chloride transfer is the major process at -78 °C; at 0 °C, chloride transfer is reversible and a 1,5-proton transfer leads to an ene-type adduct with the side chains *trans*. Use of 2 equiv of $MeAlCl_2$ forms a cyclic zwitterion that undergoes two 1,2-hydride shifts to form the ketone. A similar zwitterion forms with $EtAlCl_2$, but β-hydride transfer leading to the saturated alcohol is faster than 1,2-hydride shifts.

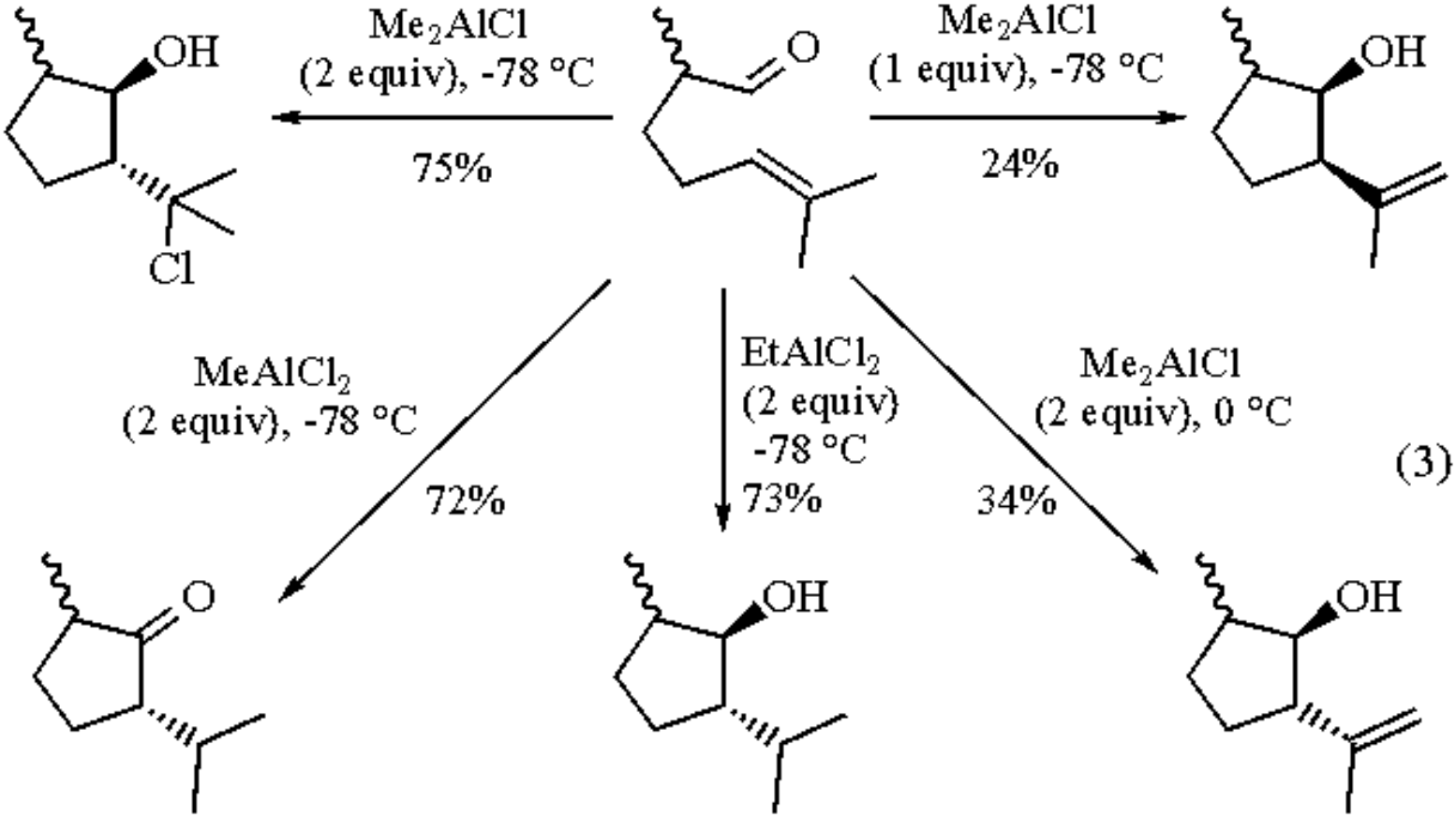

Catalysis of Diels-Alder Reactions.

$EtAlCl_2$ is a useful Lewis acid catalyst for Diels-Alder reactions. It is reported to be more efficacious for the Diels-Alder reaction of ***Acrolein*** and butadiene than either $AlCl_3$ or Et_2AlCl.[7] It is a useful catalyst for intramolecular Diels-Alder reactions with α,β-unsaturated esters (eq 4)[8] and aldehydes[9] as dienophiles. It has also proven to be a very efficient catalyst for the inter-[10] and intramolecular[11] asymmetric Diels-Alder reaction of chiral α,β-unsaturated acyl sultams (eq 5) and has been used to catalyze a wide variety of Diels-Alder reactions.[12]

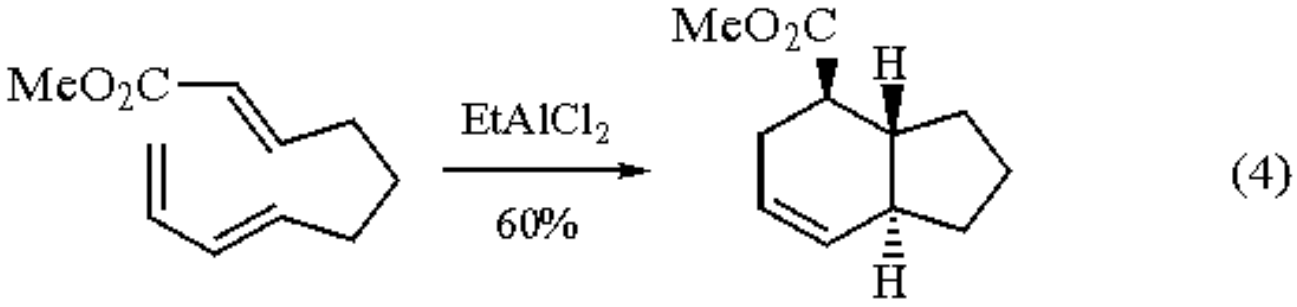

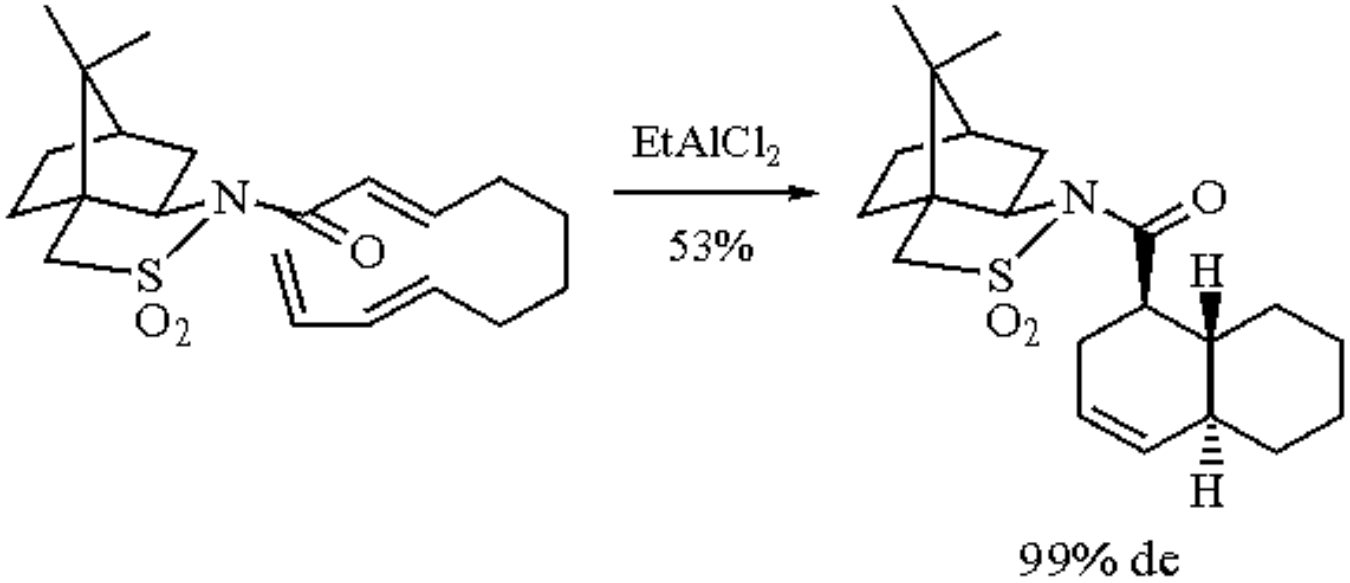

(5)

Catalysis of Ene Reactions.

Although $AlCl_3$ can be used as a Lewis acid catalyst for ene reactions of α,β-unsaturated esters,[13a] better results are obtained more reproducibly with $EtAlCl_2$. Ene reactions of ***Methyl Propiolate*** proceed in good yield with 1,1-di-, tri-, and tetrasubstituted alkenes (eq 6).[14] A precursor to 1,25-dihydroxycholesterol can be prepared by an ene reaction with methyl propiolate. Three equiv of $EtAlCl_2$ are needed since the acetate esters are more basic than methyl propiolate (eq 7).[15] *Endo* products are obtained stereospecifically with methyl α-haloacrylates (eq 8).[14] $EtAlCl_2$ has also been used to catalyze intramolecular ene reactions (eq 9).[16]

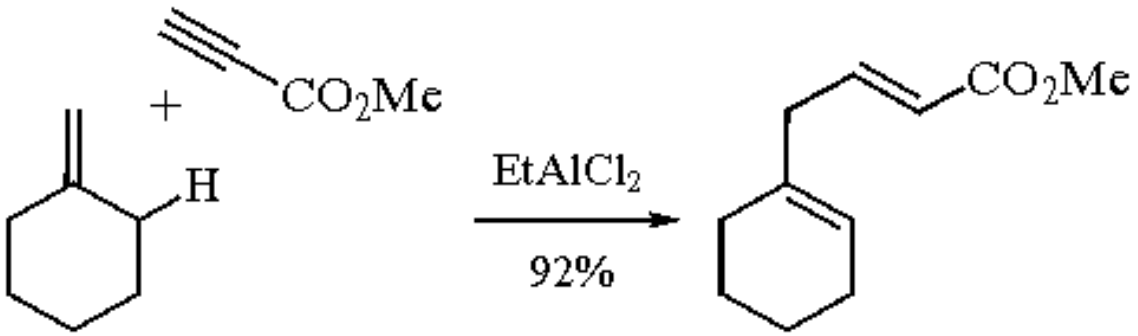

(6)

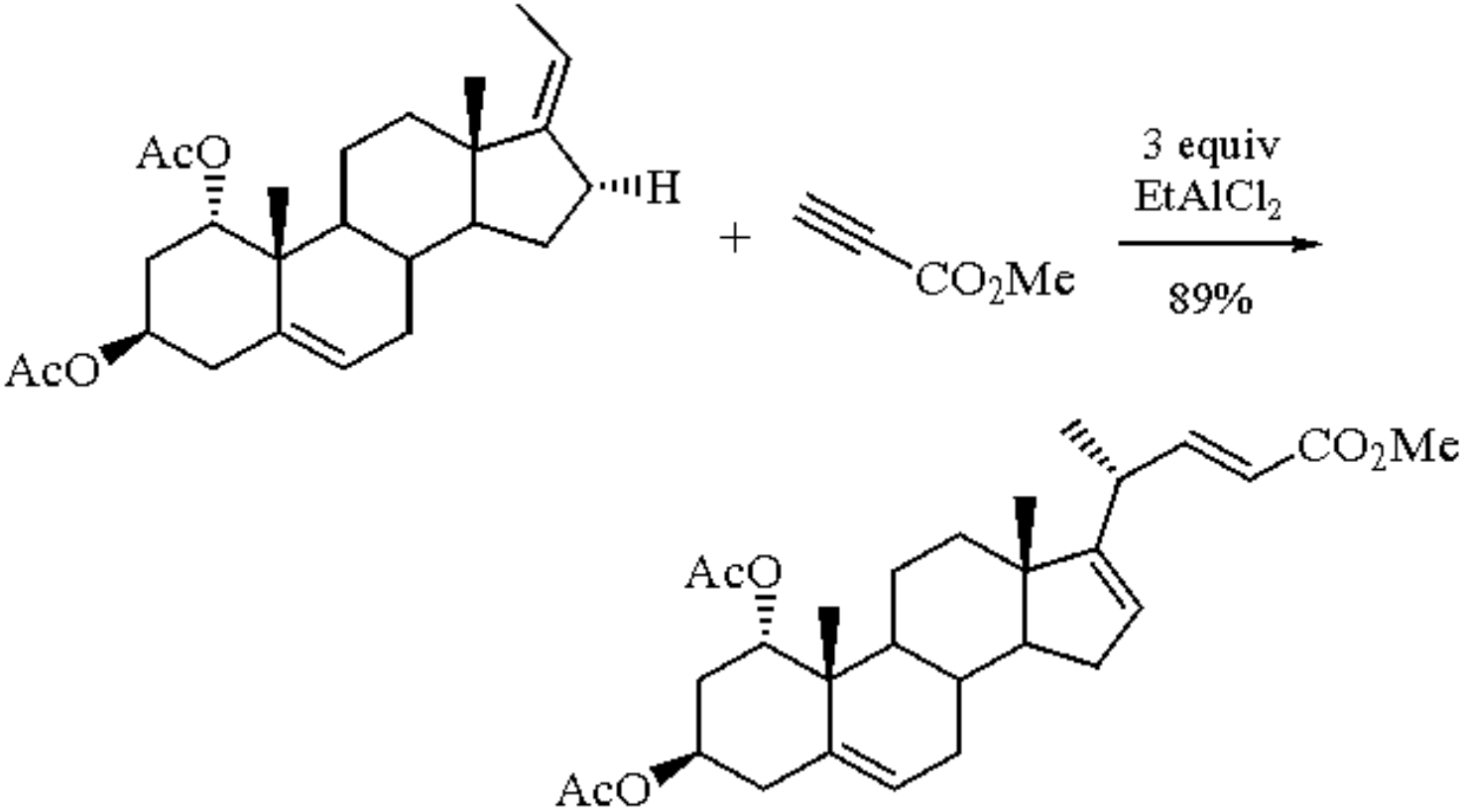

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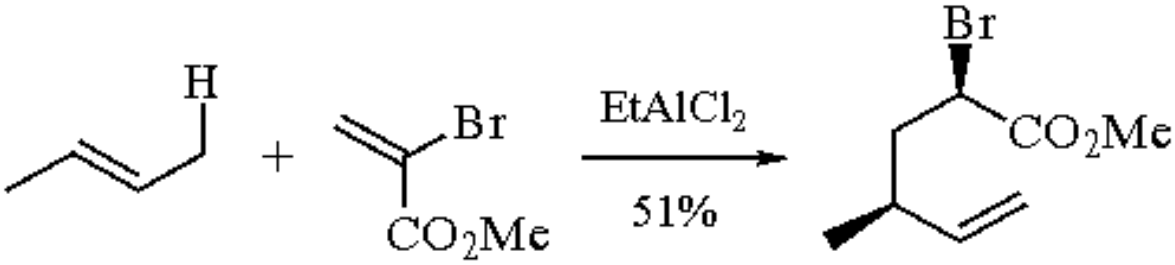

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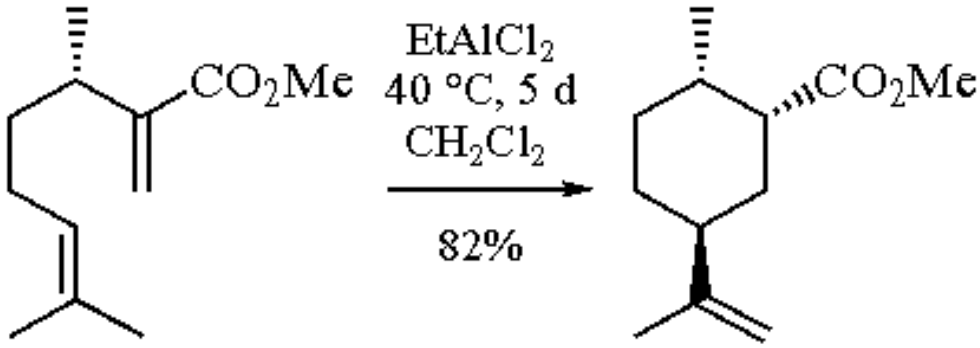

(9)

$EtAlCl_2$ is usually too strong a Lewis acid for ene reactions of carbonyl compounds.[13b,c] However, alkenes that contain basic sites that complex to the Lewis acid do not undergo Me_2AlCl-catalyzed ene reactions with formaldehyde. In these cases, $EtAlCl_2$ is the preferred catalyst.[17,18] The dienyl acetate shown in eq 10 reacts with excess ***Formaldehyde*** and $EtAlCl_2$ to provide the conjugated diene ene adduct that undergoes a quasi-intramolecular Diels-Alder reaction to afford a pseudomonic acid precursor. Me_2AlCl catalyzes the ene reaction of aliphatic aldehydes with 1,1-di-, tri-, and tetrasubstituted alkenes. Terminal alkenes are less nucleophilic, so the only reaction is addition of a methyl group to the aldehyde. $EtAlCl_2$, a stronger Lewis acid with a less nucleophilic alkyl group, catalyzes the reaction of aliphatic

aldehydes with terminal alkenes in CH_2Cl_2 at 0 °C to give 50-60% of the ene adduct.[18] Use of $EtAlCl_2$ as a catalyst affords the best diastereoselectivity in the ene reaction of dibenzylleucinal with ***Isobutene*** (eq 11).[19] $EtAlCl_2$ has also been used to catalyze intramolecular ene reactions of trifluoromethyl ketones.[20]

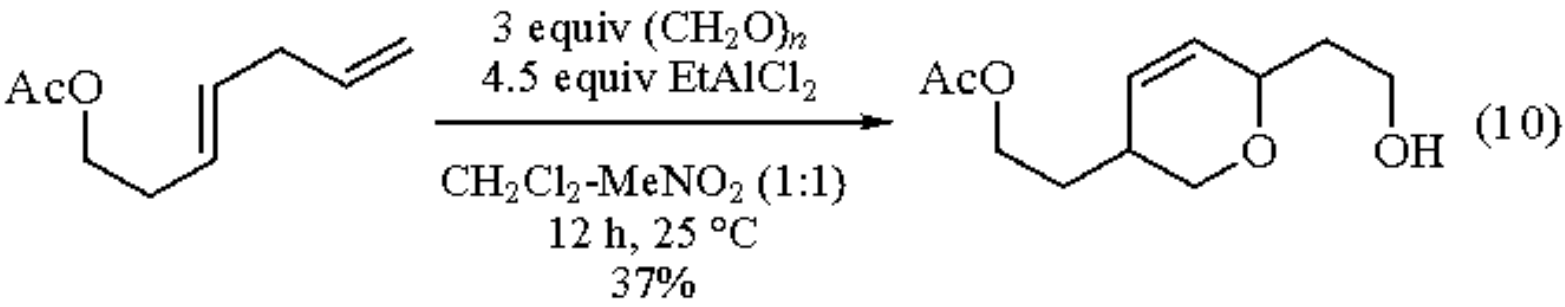

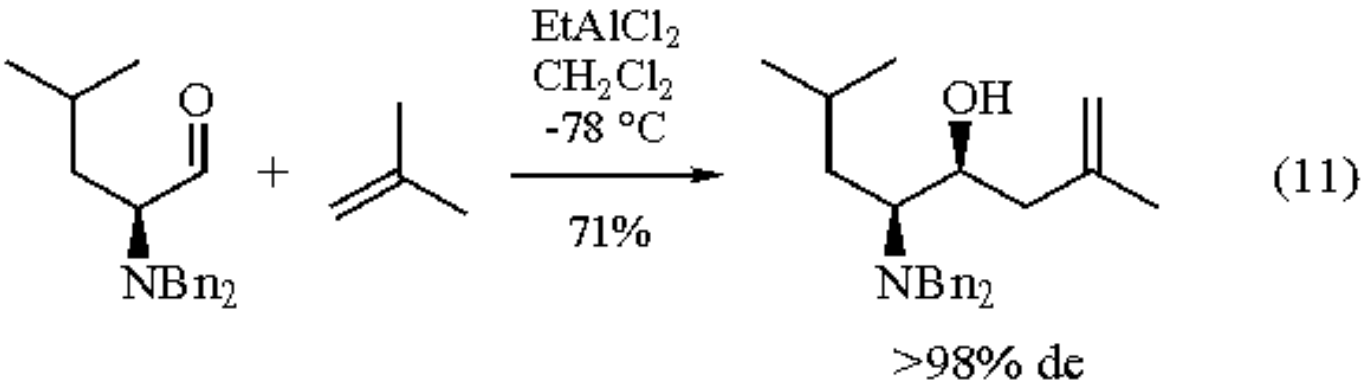

Catalysis of Intramolecular Sakurai Reactions.

$EtAlCl_2$ has been extensively used as a catalyst for intramolecular Sakurai additions. Enones (eqs 12 and 13)[21,22] have been most extensively explored. Different products are often obtained with fluoride or Lewis acid catalysis. $EtAlCl_2$ is the Lewis acid used most often although $TiCl_4$ and BF_3 have also been used. $EtAlCl_2$ also catalyzes intramolecular Sakurai reactions with ketones[23] and other electrophiles.[24] The cyclization of electrophilic centers onto alkylstannanes[25] and Prins-type additions to vinylsilanes[26] are also catalyzed by $EtAlCl_2$.

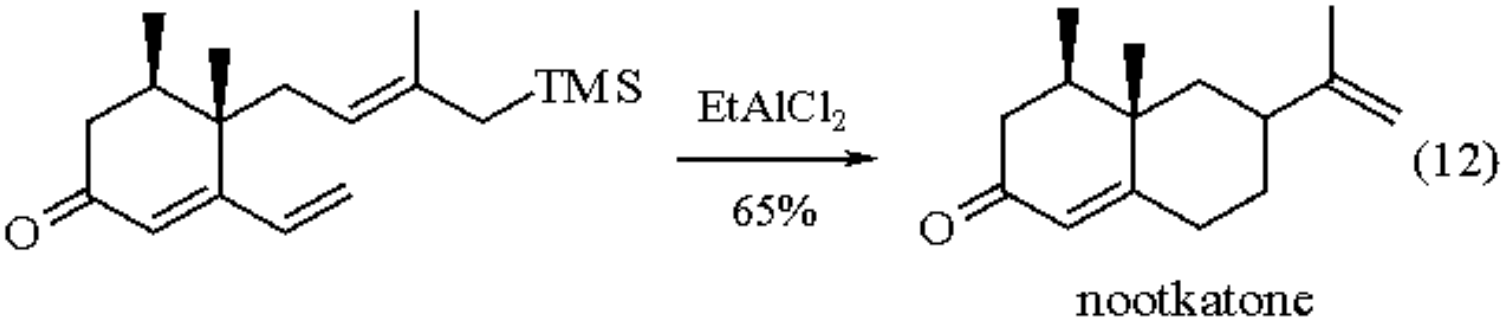

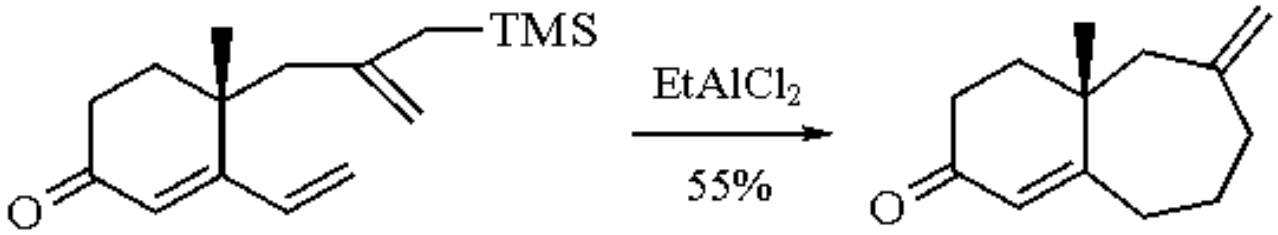

(13)

Catalysis of [2 + 2] Cycloadditions.

$EtAlCl_2$ catalyzes a wide variety of [2 + 2] cycloadditions. These include the addition of alkynes or allenes to alkenes to give cyclobutenes and alkylidenecyclobutanes (eq 14),[27] the addition of electron-deficient alkenes to allenyl sulfides (eq 15),[28] the addition of propiolate esters to monosubstituted and 1,2-disubstituted alkenes to form cyclobutene carboxylates (eq 16),[14b] and the addition of allenic esters to alkenes to form cyclobutanes.[29]

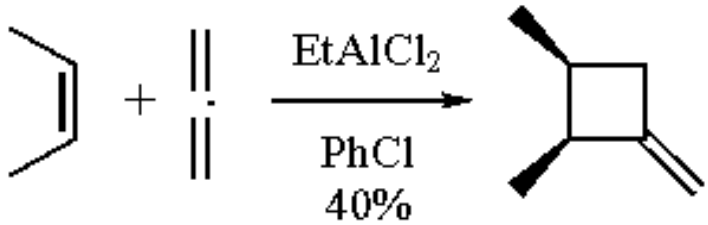

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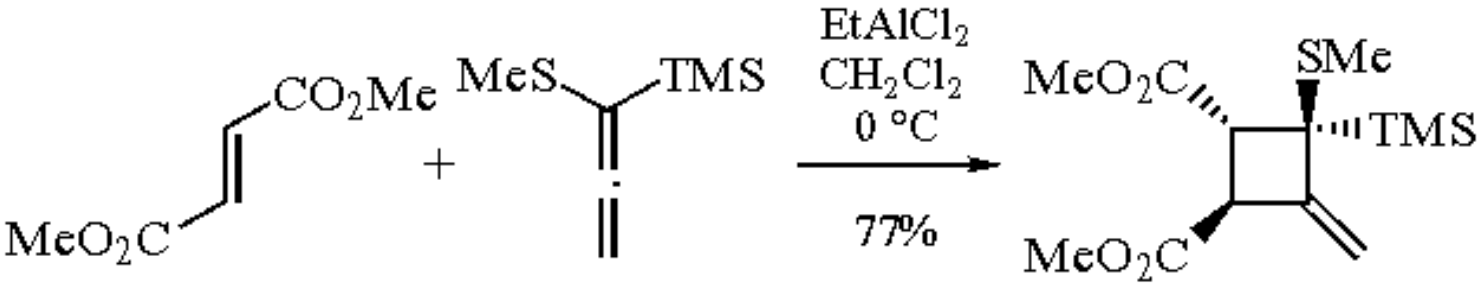

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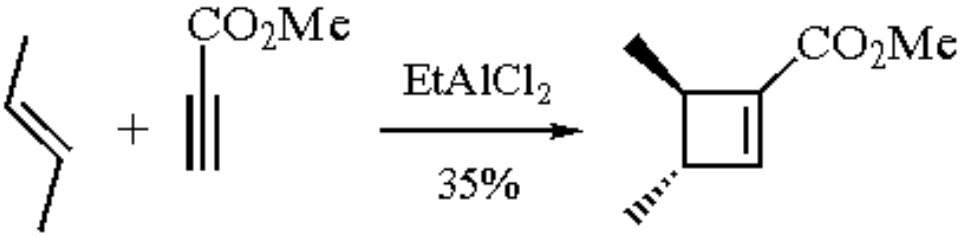

(16)

Generation of Electrophilic Cations.

$EtAlCl_2$ has proven to be a useful Lewis acid for inducing a wide variety of electrophilic reactions. It is particularly useful since an excess of the reagent can be used so that all nucleophiles are complexed to acid. Under these conditions, intermediates tend to collapse to give cyclobutanes or undergo hydride shifts to give neutral species. Reaction of the 1:2 ***Crotonaldehyde***-$EtAlCl_2$ complex with 2-methyl-2-butene at -80 °C affords a zwitterion that collapses to give mainly the cyclobutane. Closure of the zwitterion is reversible at 0 °C. Since there are no nucleophiles in solution, two 1,2-hydride shifts take place to give the enal (eq 17).[5] Intramolecular versions of these reactions are

also quite facile (eqs 18 and 19).[5,21] $EtAlCl_2$ promotes the ring enlargement of 1-acylbicyclo[4.2.0]oct-3-enes (eq 20).[30]

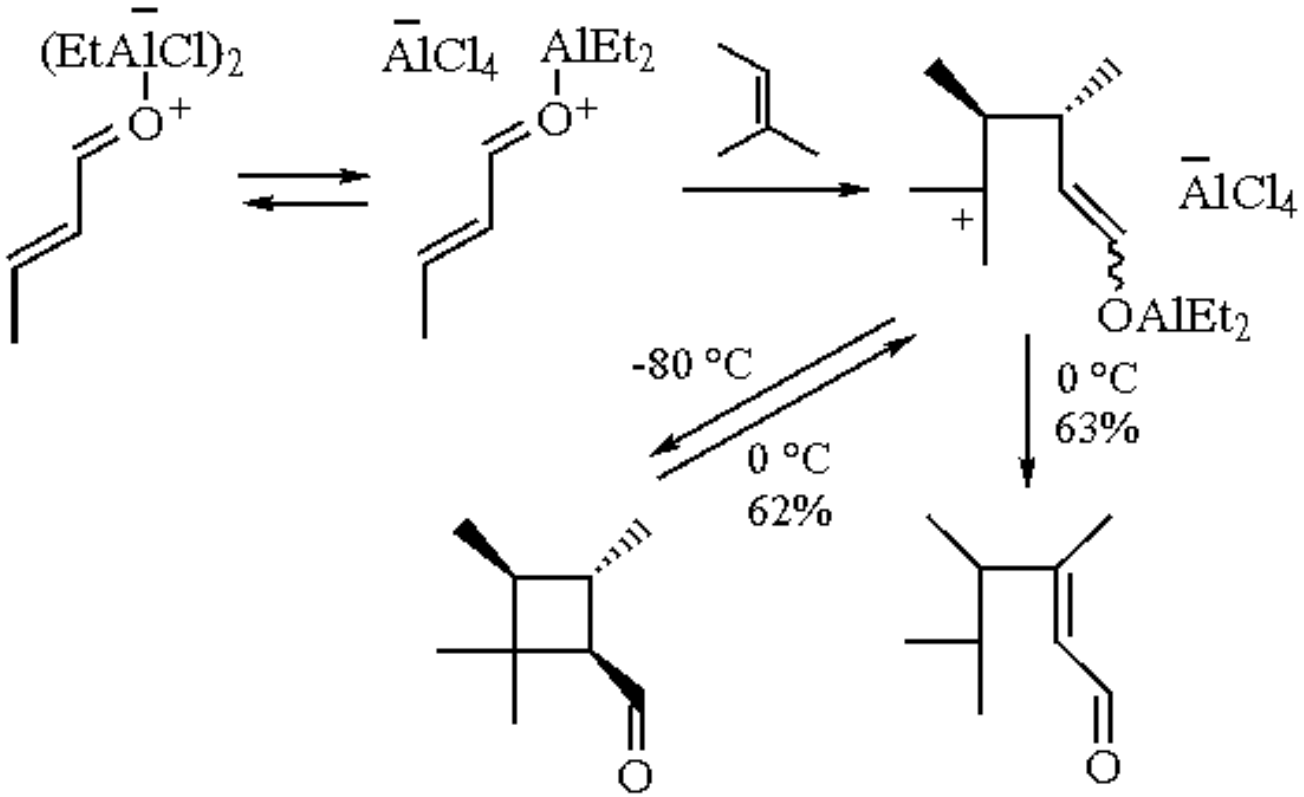

(17)

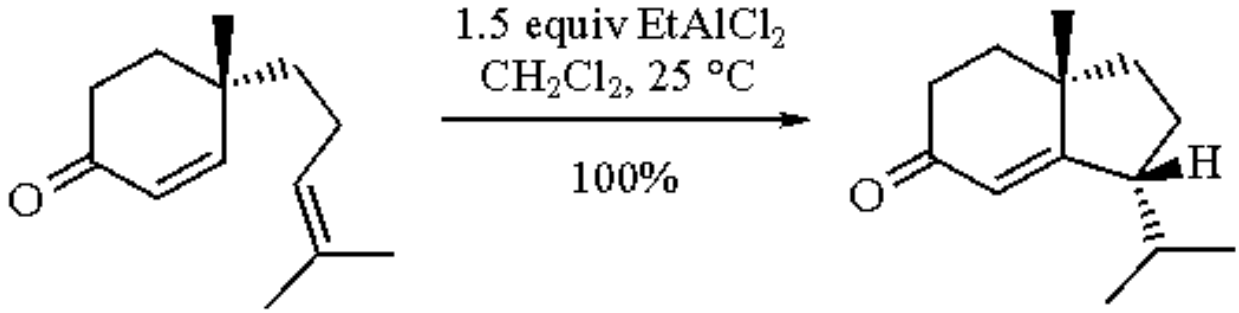

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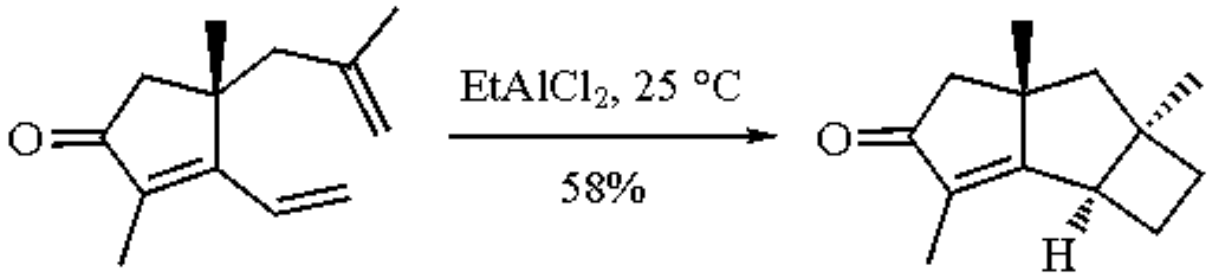

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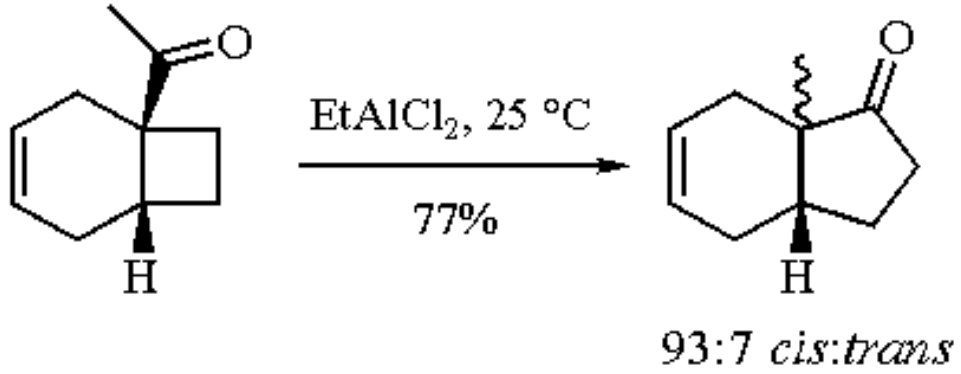

(20)

$EtAlCl_2$ catalyzes the Friedel-Crafts acylation of alkenes with acid chlorides,[31] the formal [3 + 2] cycloaddition of alkenes with cyclopropane-1,1-dicarboxylates (eq 21),[32] the Friedel-Crafts alkylation of anilines and indoles with α-aminoacrylate esters,[33] and the formation of allyl sulfoxides from sulfinyl chlorides and alkenes.[34] $EtAlCl_2$ induces the Beckmann rearrangement of oxime sulfonates. The cationic intermediates can be trapped with enol silyl ethers (eq 22).[35] $EtAlCl_2$ is the preferred catalyst for addition of the cation derived from an α-chloro sulfide to an alkene to give a cation which undergoes a Friedel-Crafts alkylation (eq 23).[36]

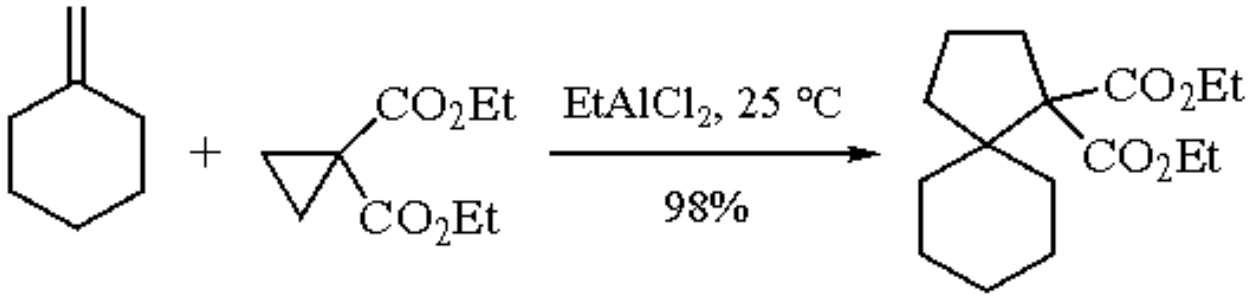

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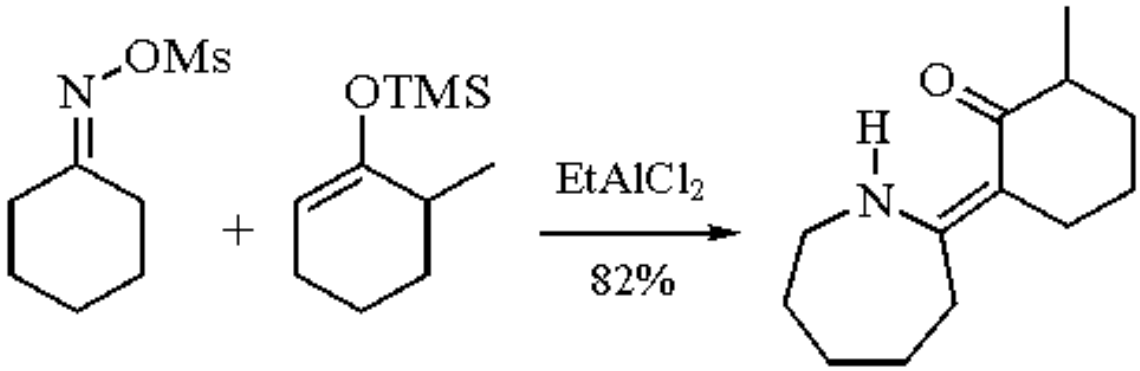

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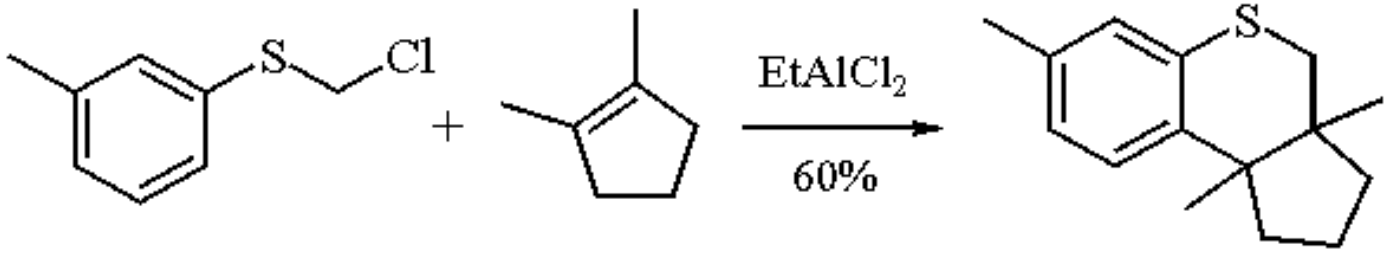

(23)

$EtAlCl_2$ reacts with aliphatic sulfones to generate an aluminum sulfinate and a cation that can be reduced to a

hydrocarbon by $EtAlCl_2$,[37] trapped with a nucleophile such as ***Allyltrimethylsilane***,[38] or undergo a pinacol-type rearrangement (eq 24).[39]

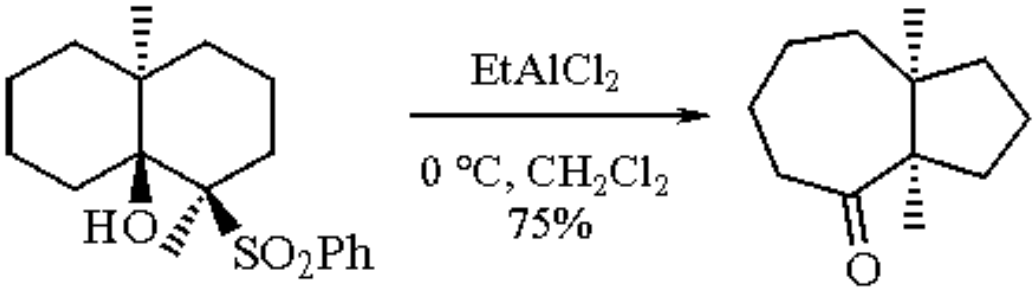

(24)

Elimination Reactions.

$EtAlCl_2$ induces elimination of two molecules of HBr from the dibromide to give the dihydropyridine (eq 25).[40] The usual base-catalyzed elimination is ineffective.

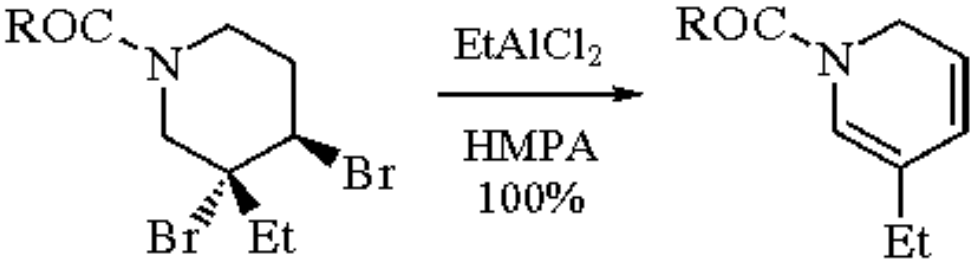

(25)

Nucleophilic Addition.

$EtAlCl_2$ has been used to activate conjugated systems toward attack of an external nucleophile or to transfer a hydride or ethyl group as a nucleophile. Addition of a cuprate to the chiral amide in the presence of $EtAlCl_2$ improves the diastereoselectivity, affording a >93:7 mixture of stereoisomers (eq 26).[41] Reaction of butyrolactones with $EtAlCl_2$ reduces the lactone to a carboxylic acid by opening to the cation and hydride delivery (eq 27).[42] Sulfonimidyl chlorides react with $EtAlCl_2$ at -78 °C to provide *S*-ethyl sulfoximines in 65-95% overall yield (eq 28).[43]

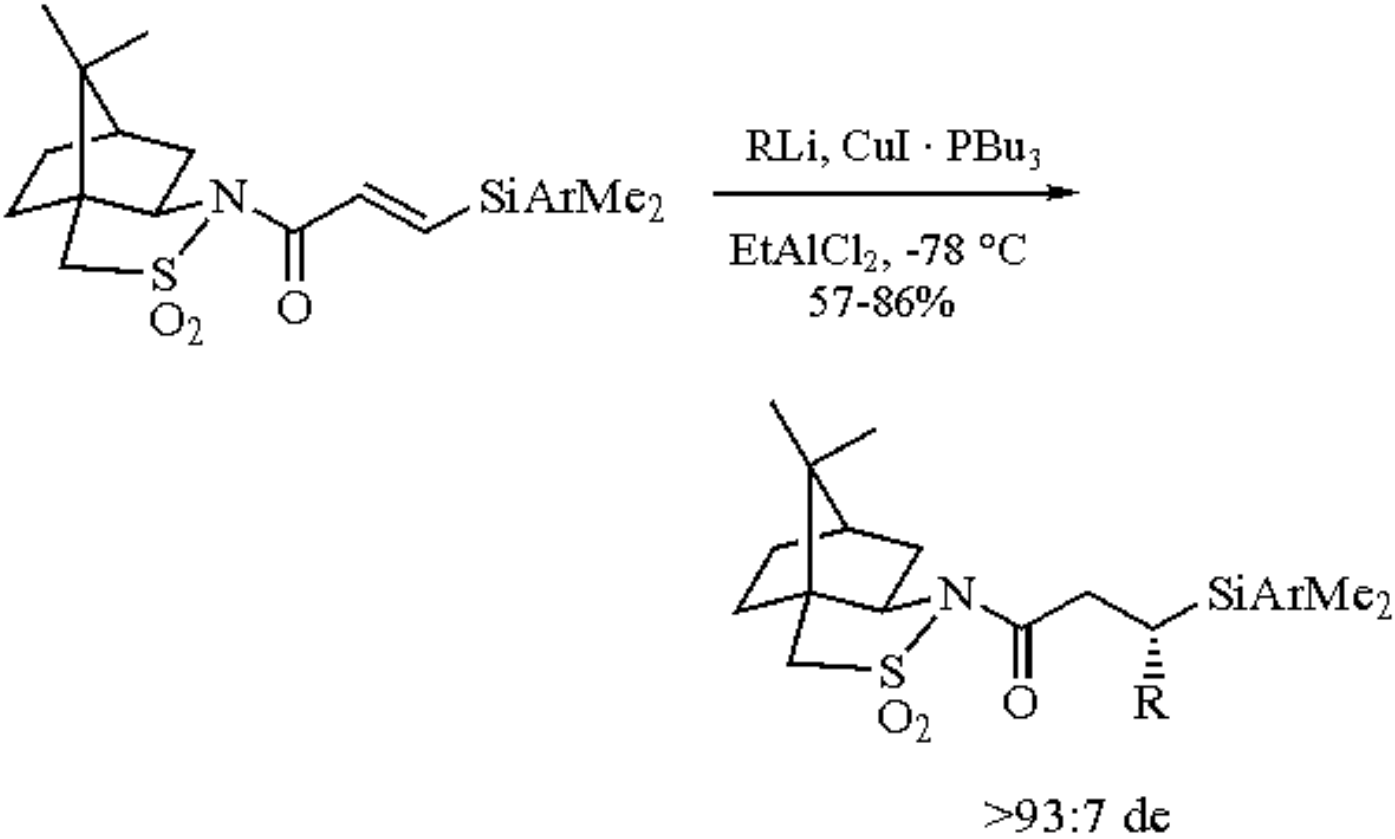

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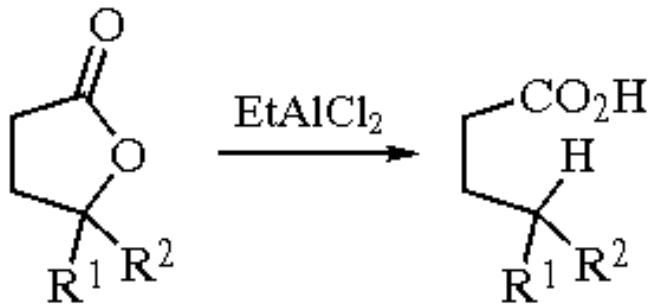

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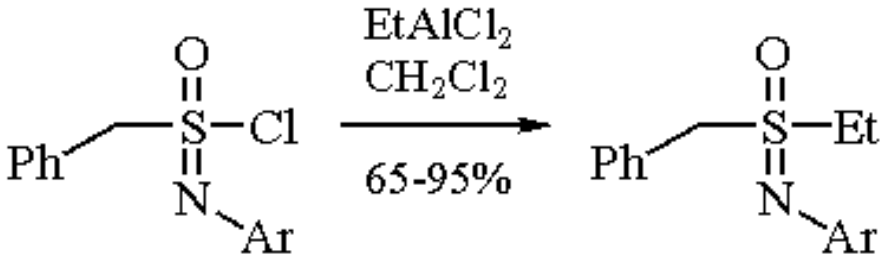

(28)

Modification of Carbanions.

Trimethylsilyl allylic carbanions react with aldehydes in the presence of $EtAlCl_2$ exclusively at the α-position to give *threo* adducts (eq 29).[44]

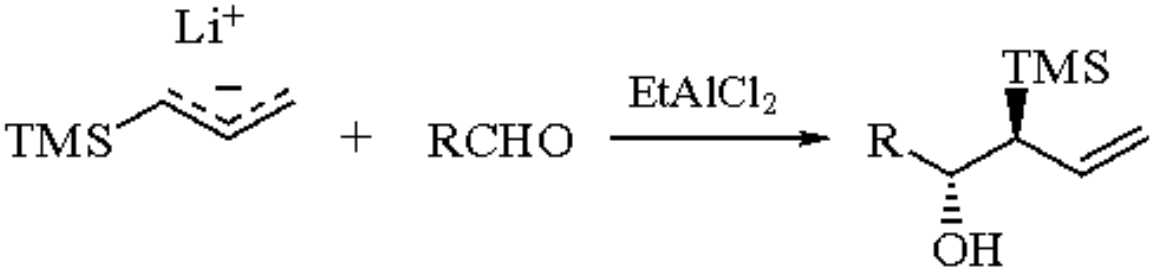

(29)

Related Reagents.

Diethylaluminum Chloride; ***Diethylaluminum Iodide***; ***Dimethylaluminum Chloride***; ***Dimethylaluminum Iodide***; ***Methylaluminum Dichloride***.

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Ethyl Azidoformate[1]

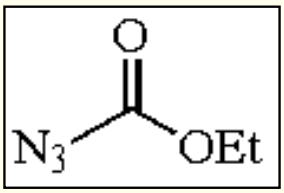

[817-87-8] · $C_3H_5N_3O_2$ · Ethyl Azidoformate · (MW 115.09)

(electron-deficient azide; can undergo cycloadditions with alkenes to yield triazolines;[1] generates ethoxycarbonylnitrenes on thermolysis and photolysis[1])

Physical Data: bp 40 °C/30.5 mmHg.

Solubility: sol ether, methylene chloride.

Preparative Methods: as reported by Lwowski and Mattingly.[27]

Handling, Storage, and Precautions: is potentially explosive and care should be taken when distilling or heating solutions of this compound. It has been stored in the cold, protected from light, for up to 3 months without any apparent deterioration. However, ethyl azidoformate is eventually hydrolyzed in the presence of moisture, leading to the formation of HN_3. Such long-stored samples can explode on handling (due to the HN_3) and it is therefore recommended that ethyl azidoformate be used immediately after preparation. The vapors of this compound are also toxic. The original literature should be consulted before preparation and use of this compound.[27] This reagent should only be handled in a fume hood.

Introduction.

Ethyl azidoformate is usually prepared by the reaction of ***Ethyl Chloroformate*** with ***Sodium Azide***. It is principally used for two broad classes of reactions: (a) the cycloaddition of the azide moiety to an unsaturated functionality, and (b) as a source of ethoxycarbonylnitrene. This reagent has limited synthetic utility primarily because of its thermal instability. Ethyl azidoformate and other azidoformates begin to decompose above 60 °C.[1b] The related methyl azidoformate also displays similar reactivity and will also be discussed wherever relevant.

Cycloaddition Reactions.

The cycloaddition reactions of azides to alkenes are generally believed to be concerted. Ethyl azidoformate is considered an electron-poor azide and reacts readily with electron-rich alkenes. The product of these reactions are Δ^2-triazolines. The triazolines derived from electron-poor azides are usually not stable and can lose nitrogen readily to give

the aziridines and/or imines even at room temperature.[1c] However, many triazolines have been isolated in good yields. If the desired products are the triazolines themselves, the cycloaddition reactions are synthetically useful only if they proceed readily well below the decomposition temperature of the parent azide. At higher temperatures, ethyl azidoformate decomposes to give the corresponding nitrene which can react in a variety of pathways. Also, at higher temperatures, triazoline decomposition occurs readily. Strained and/or electron-rich alkenes undergo cycloaddition readily at room temperature or below. Norbornene,[2] substituted norbornenes,[3] and other strained bicyclic systems give triazolines in high yields (eqs 1 and 2). The presence of functional groups such as primary amines on the alkene are known to interfere with the cycloaddition reaction.[4]

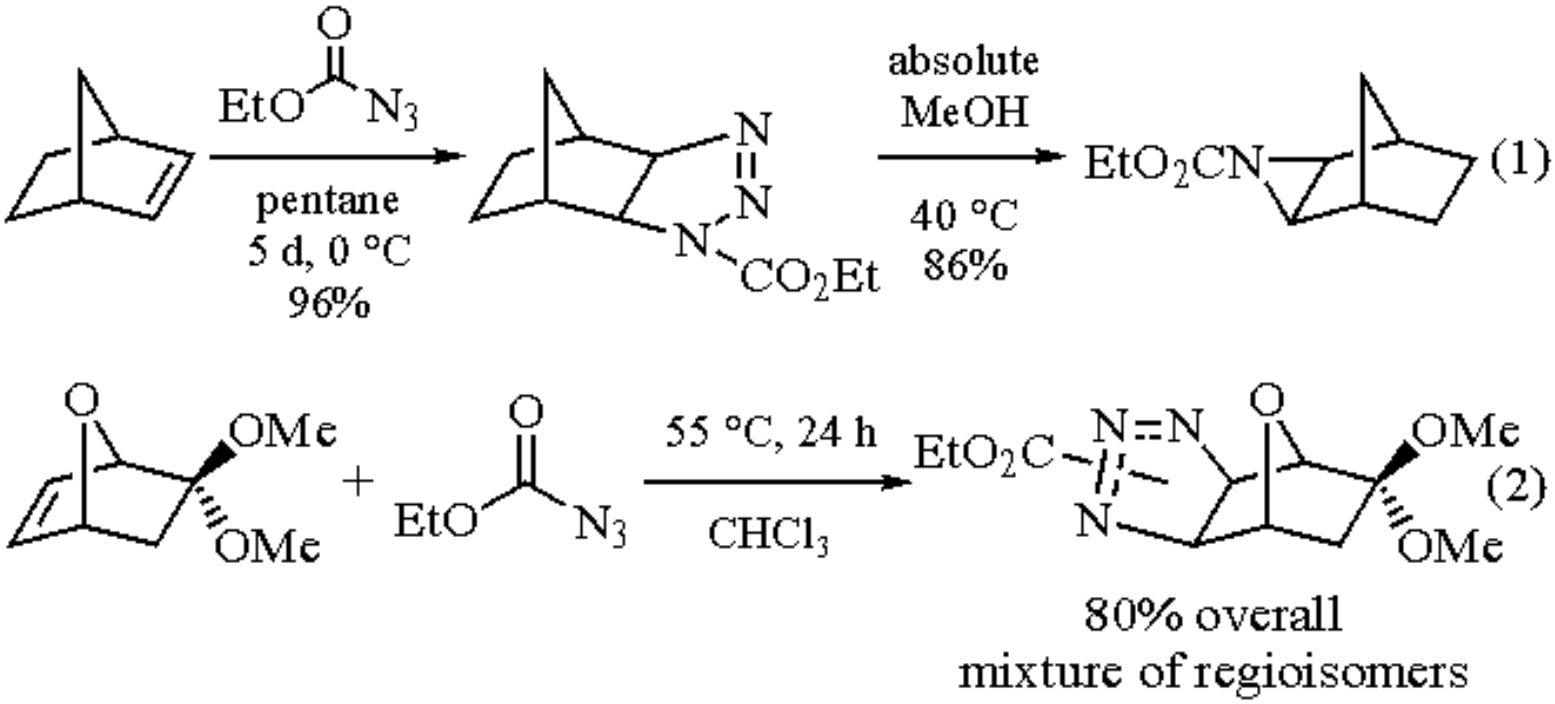

Cycloadditions with norbornenes usually proceed from the *exo* face, even in the case of a 7-substituted azanorbornene (eq 3),[5] although exceptions have been reported.[6] Unsymmetrical norbornenes exhibit poor regioselectivity (eq 2). The products of triazoline fragmentation under thermal conditions are not always predictable and both aziridines and imines can result, although there are occasional examples of good product selectivity. Other rearrangement products have also been observed (eq 4).[7] However, photolysis of triazolines generally gives the aziridines in good yields, which are free of other side-products (eq 5).[3] In many cases this thermolysis/photolysis route to aziridines is superior to the direct photolysis of ethyl azidoformate in the presence of an alkene. If aziridines are the desired products, the poor regioselectivity in the cycloaddition step is not a drawback since both regioisomeric triazolines lead to the same aziridine.

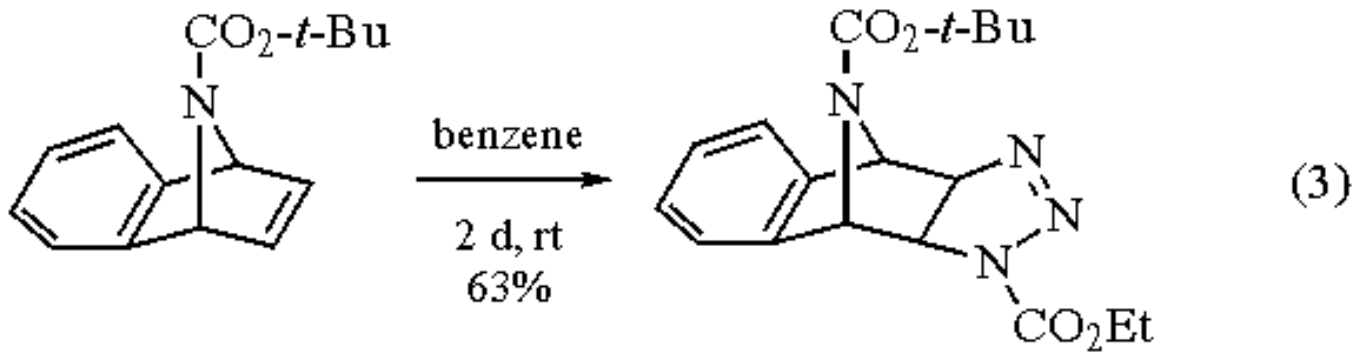

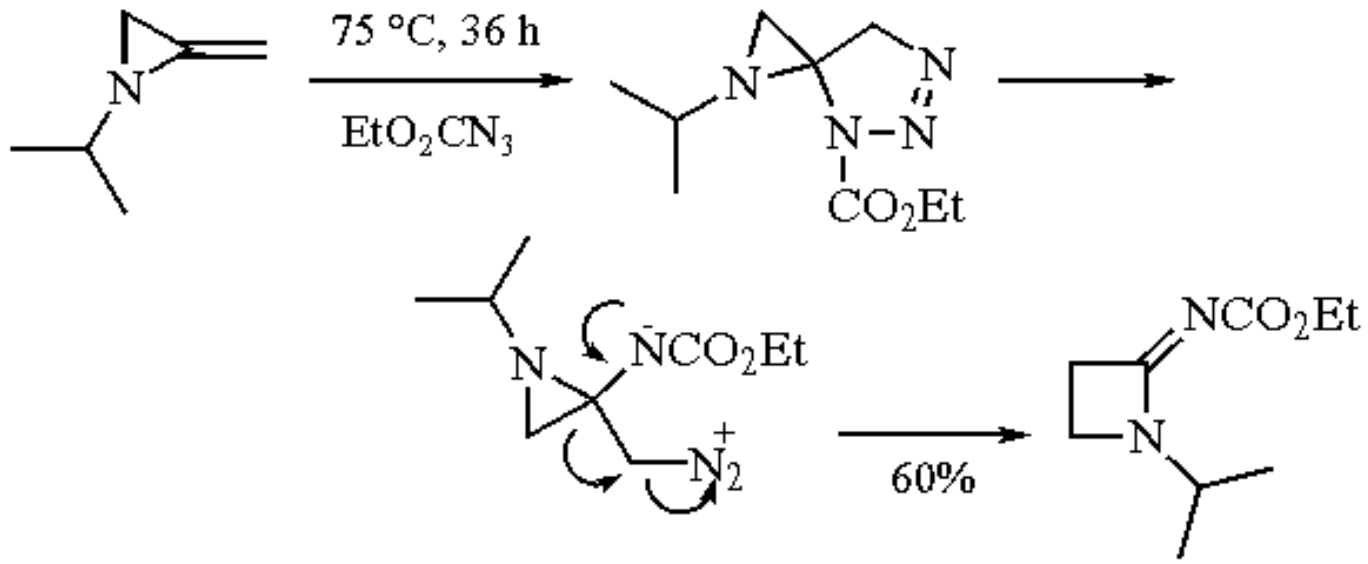

(4)

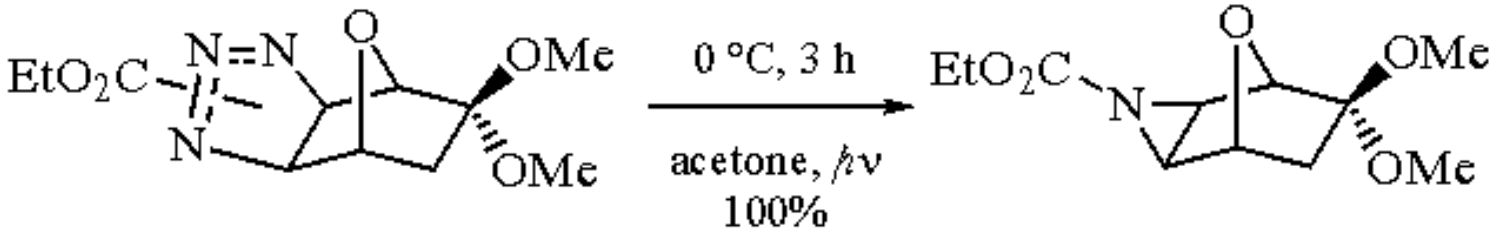

(5)

Cycloadditions of ethyl azidoformate with electron-rich alkenes are also expected to proceed readily, although few examples are known. The cycloadducts from the reaction of ethyl azidoformate with optically active enamines were subject to photolysis.[8a] α-Amino ketones were isolated in moderate yields, presumably derived from the ring opening of the initially formed aziridine (eq 6). Reaction of enol silanes with ethyl azidoformate has also been reported to give *N*-substituted α-amino ketones.[8b] However, under these conditions it is possible that the reaction may proceed through a nitrene intermediate.

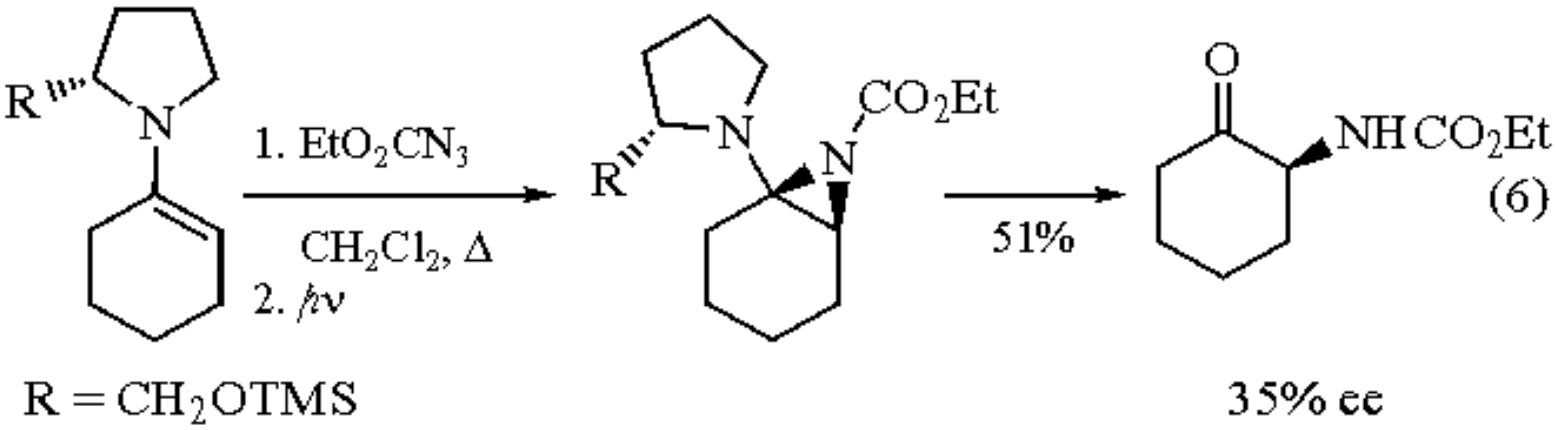

(6)

Cycloaddition of ethyl azidoformate to unactivated, unstrained alkenes usually requires elevated temperatures (70-120 °C). Under such conditions, nitrenes may be generated, leading to products derived from the fragmentation of triazolines. For example, reaction of ethyl azidoformate with tetramethylethylene (solvent) at 72 °C gave four products (eq 7).[9] The authors estimate that at least 60% of the aziridine was produced via the nitrene pathway.

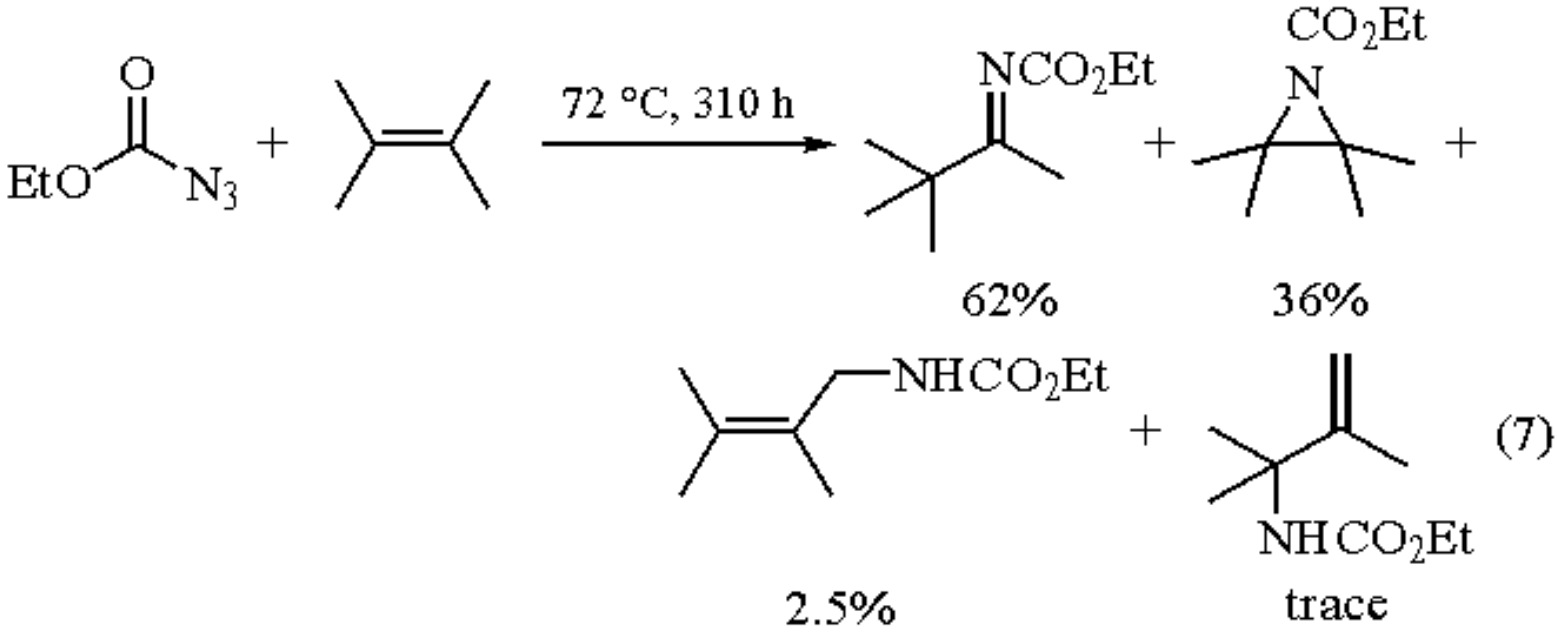

Cycloadditions of ethyl azidoformate with alkynes and other triple bonds have also been attempted. The reaction with *N*,*N*-diaminopropyne, a ynamine, and ***Ethoxyacetylene*** has been reported to proceed at room temperature to give triazoles, although no yields were given.[10] Reaction of ethyl azidoformate with tetramethylallene at 130 °C gave a 38% yield of the triazoline along with the oxazoline.[11] The latter is probably derived from a nitrene intermediate. The reaction of ethyl azidoformate with stabilized phosphorus ylides has also been reported to give the corresponding triazoles in excellent yields.[12]

Generation and Reactions of Nitrenes.

Photolysis of ethyl azidoformate gives rise to ethoxycarbonylnitrene. Curtius rearrangement of azidoformates to give isocyanates under photolytic conditions (the photo-Curtius rearrangement) is a minor pathway. Depending on the conditions of photolysis, the nitrenes generated can react from either the singlet or the triplet state and the reactivity of the two species can be different. Nitrenes undergo two major reactions, insertion into single bonds and addition across double bonds. In many cases, both reactions occur, limiting the utility. Other side products can also be formed. The synthetic application of intermolecular C-H insertion of nitrenes is severely limited because of the poor selectivity of the nitrenes for different types of C-H bonds.[13] Even intramolecular insertions of substituted azidoformates usually give a mixture of the possible insertion products and have hence found only rare application in synthesis.[14] Insertion of nitrenes into aromatic and heteroaromatic rings has found some preparative value. Irradiation of ethyl azidoformate in benzene with UV light gives good yields of the azepine (eq 8),[15] in contrast to the thermal process which gives a 40% yield.[16]

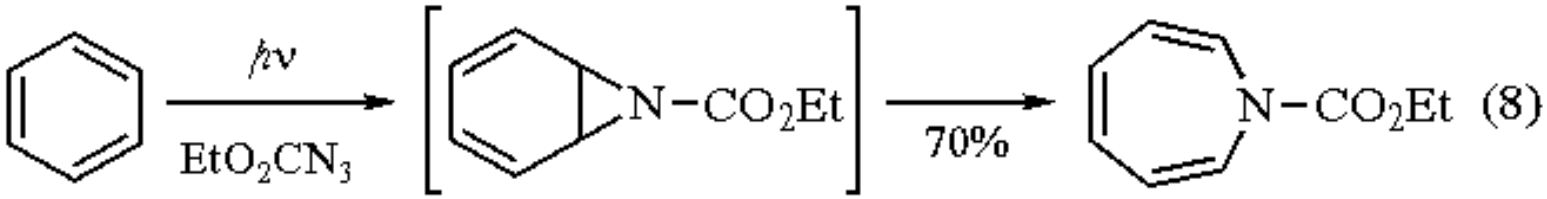

The addition of nitrenes to double bonds under photolytic conditions has found wider use. Singlet nitrenes add across alkenes stereospecifically. This reaction is applicable to many types of alkenes. Thus methoxycarbonylnitrene reacts

with a strained alkene, ***Methylenecyclopropane***, to give the azaspiropentane (eq 9).[17] Reaction of ethoxycarbonylnitrene with an unactivated alkene, ***3-Sulfolene***, gives the aziridine which on thermal decomposition yields a divinyl carbamate (eq 10).[18] Ethoxycarbonylnitrene has also been added to activated alkenes such as dihydropyrans[19] and optically active silyl ketene acetals.[20] In the latter case, the isolated products were *N*-carbonylethoxy α-amino esters, presumably formed by ring opening of the initial aziridine. Modest levels of asymmetric induction were obtained. In many cases the photolysis can be done below room temperature to minimize undesirable side reactions.

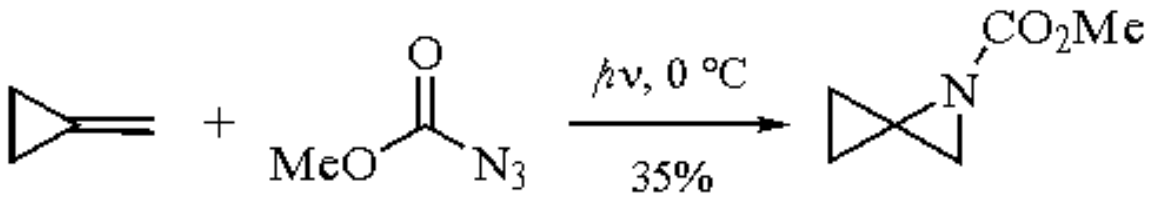

(9)

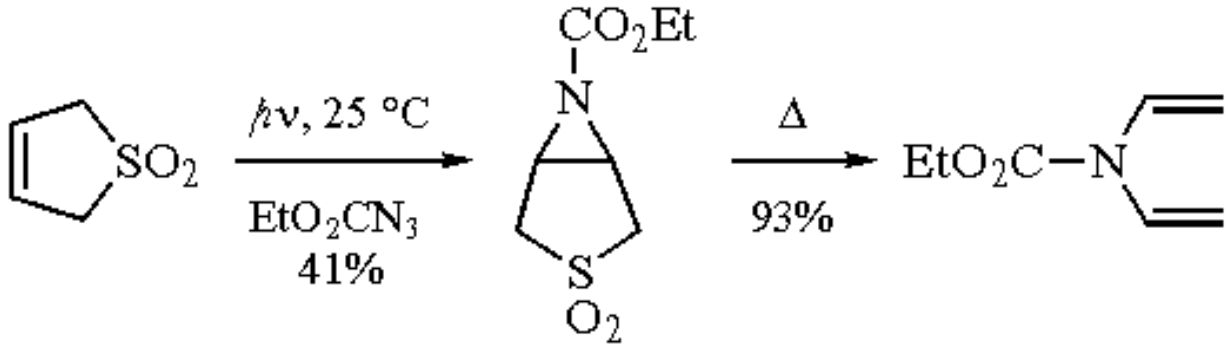

(10)

Ethoxycarbonylnitrene can also be generated from ethyl azidoformate by thermolysis, producing singlet nitrenes. Reaction of ethoxycarbonylnitrene with an electron-deficient alkene gives the aziridine in good yield (eq 11).[21]

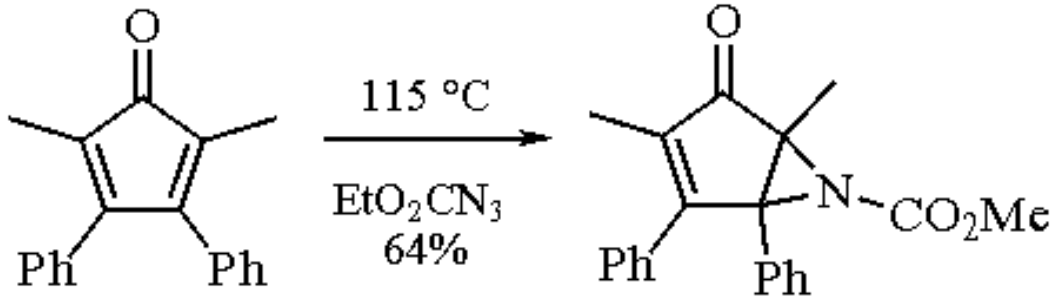

(11)

The reaction of ethoxycarbonylnitrene with ***Diphenylacetylene*** gives the corresponding oxazole in 33% yield (eq 12).[22] The mechanism of this reaction may proceed via a 1,3-dipole as shown or by a stepwise mechanism involving initial attack of the nitrene to produce a 1*H*-azirine. Aliphatic nitriles react in a similar manner under photolytic conditions to give the corresponding 5-ethoxyoxadiazoles.[23] The reaction of ethyl azidoformate with 1,1-dimethylallene under photolytic conditions has been reported to occur regioselectively at the more substituted double bond to give the the oxazoline.[11]

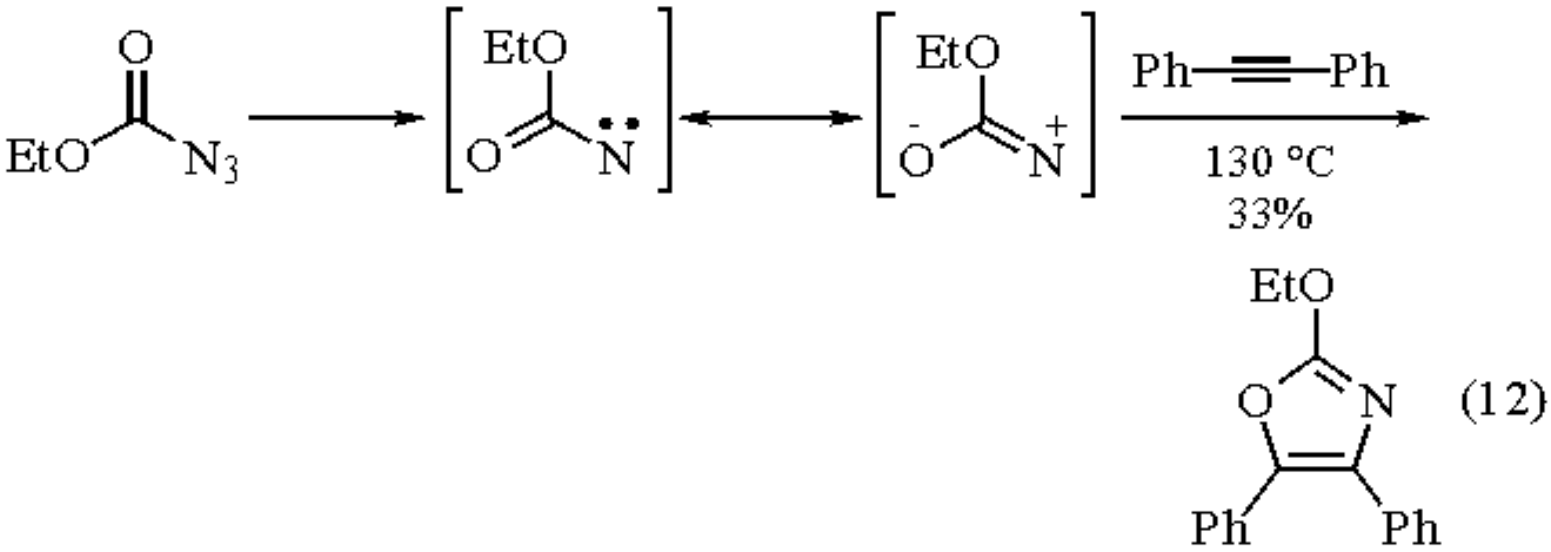

Photochemical addition of ethoxycarbonylnitrene to isocyanides leads to the corresponding carbodiimides in moderate yields, which on hydrolysis give ureas.[24] Addition of ethoxycarbonylnitrene to cobalt cyclopentadiene complexes has also been reported to give pyrroles, albeit in low yields.[25]

Other reagents such as ***p-Nitrobenzenesulfonyloxyurethane*** and *N*-ethoxycarbonyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine[26] have also been used as a source of ethoxycarbonylnitrene. The article on the urethane reagent should be consulted for further applications of ethoxycarbonylnitrene in organic syntheses.

Related Reagents.

t-Butyl Azidoformate; ***p-Nitrobenzenesulfonyloxyurethane***.

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N-Ethylbenzisoxazolium Tetrafluoroborate

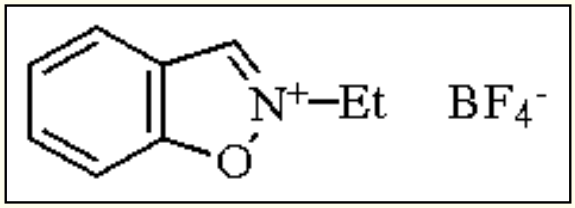

[4611-62-5] · $C_9H_{10}BF_4NO$ · *N*-Ethylbenzisoxazolium Tetrafluoroborate · (MW 234.99)

(peptide-coupling reagent;[1] reacts with a wide range of nucleophiles to give *o*-hydroxy-*N*-ethylbenzamido derivatives[2])

Physical Data: mp 109.5-110.2 °C.

Solubility: sol acetonitrile; slightly sol dichloromethane; sol aqueous acid (unstable above pH 4).

Form Supplied in: crystalline solid; commercially available.

Preparative Methods: ethylation of benzisoxazole with purified ***Triethyloxonium Tetrafluoroborate***.[2]

Handling, Storage, and Precautions: the salt is reported not to be hygroscopic, although it etches glass on long exposure to moist air; should be protected from light; reported to be an irritant.

Peptide Coupling.

N-Ethylbenzisoxazolium tetrafluoroborate (EBF) is used to couple amines and carboxylic acids in a two-stage procedure. Firstly, EBF reacts with the carboxylic acid to form an active phenolic ester. Secondly, the active ester reacts with the amine to form the peptide linkage (eq 1).[3] The procedure for the formation of the active ester employs a carefully buffered aqueous solution of the Cbz-protected aminoacid (or oligopeptide), to which an equal volume of ethyl acetate or dichloromethane is added, followed by 1.1 equiv of finely powdered EBF. The acylsalicylamide ester is isolated from the organic solvent and may be recrystallized. This product is stable to storage. This procedure does not suffer when used with the sterically demanding valine or proline residues. The active ester cleanly reacts with peptide amines in dipolar aprotic solvents, yielding the amide and *N*-ethylsalicylamide, which can be removed with alkali or carbon tetrachloride. The second step is, however, very slow, taking ca. 48 h at room temperature (roughly 20 times slower than the rate of *p*-nitrophenyl ester couplings[4]), and suffers from unwanted side-reactions (Brenner rearrangements[5]) in the presence of strongly basic amines such as triethylamine. More seriously, significant amounts (up to 1-2%) of epimerization may occur.[6]

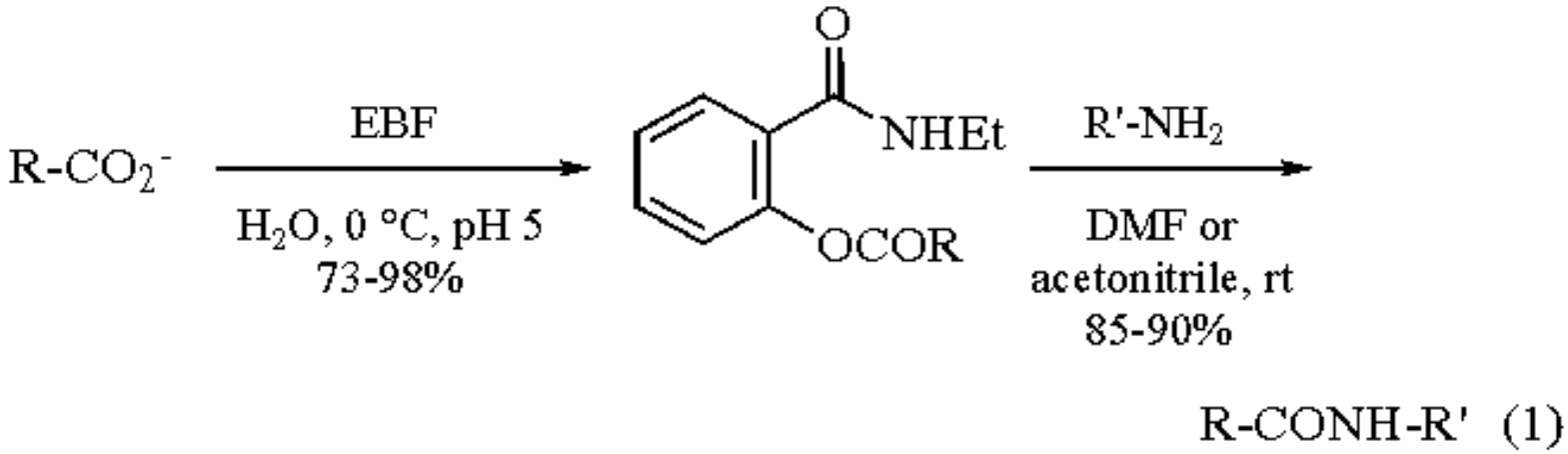

EBF has been used to prepare peptide cyclodimers in yields which compare favorably with other procedures.[1] For this method, intermediate Cbz-protected acylsalicylamide esters were hydrogenolyzed to form the free amines which then yielded the cyclodimers (eqs 2 and 3).

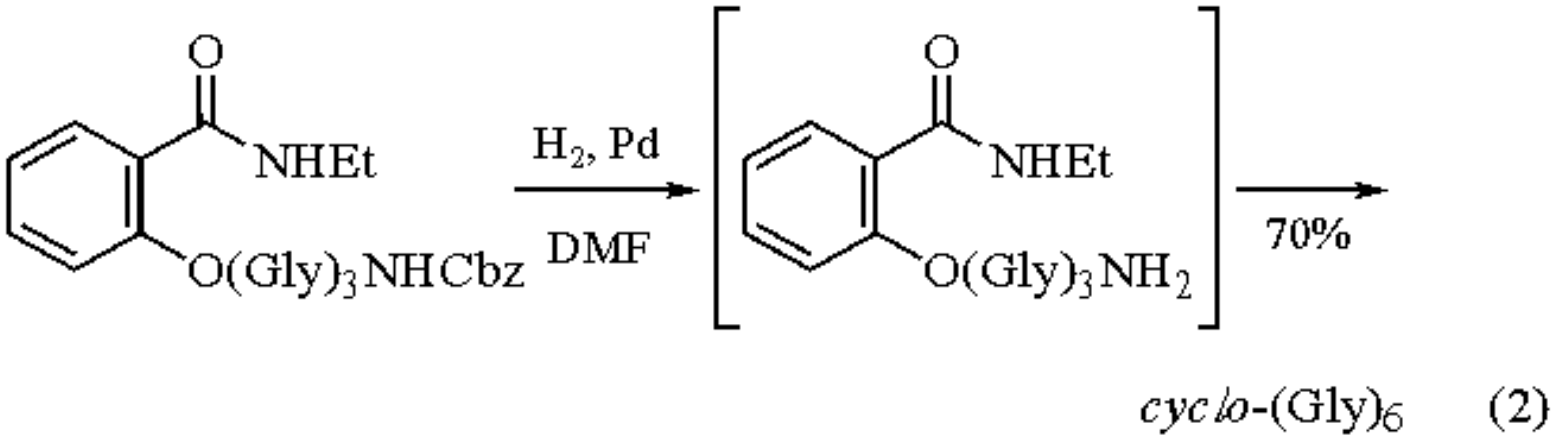

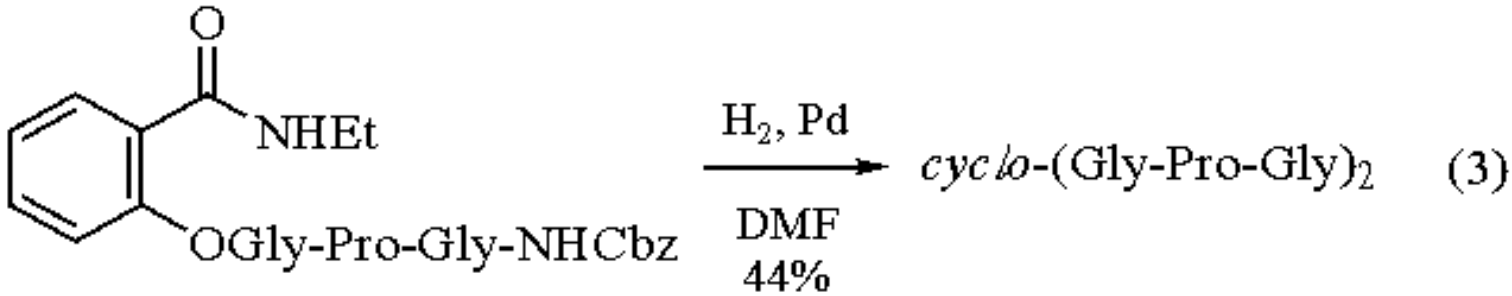

Peptide cyclotrimers have also been prepared in this manner.[7,8] After deblocking at nitrogen, a highly dilute solution of the resulting free amine in dry pyridine was stirred for 65 h at room temperature to give the cyclotrimer in an impressive 90% yield (eq 4).

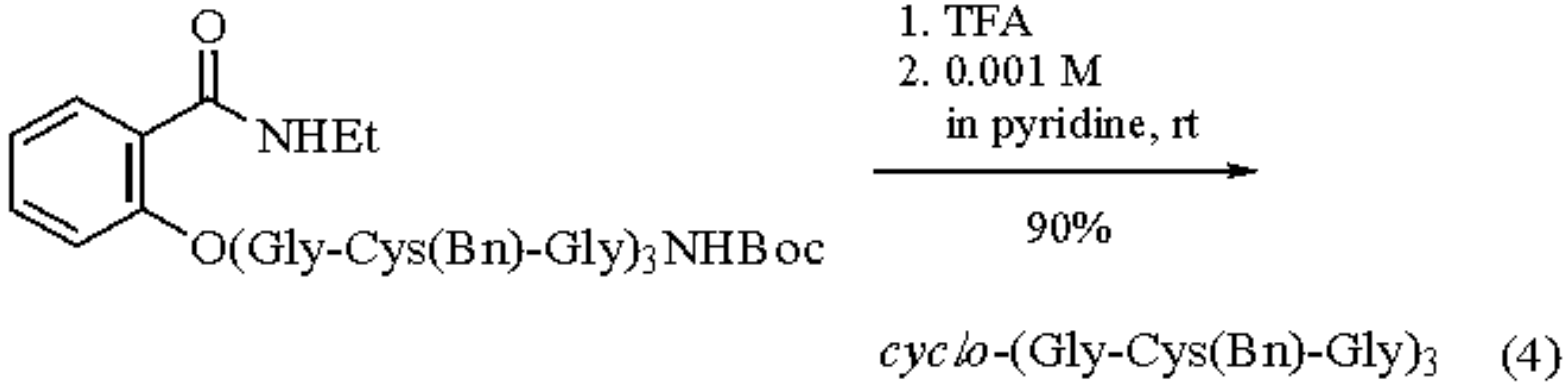

Detailed mechanistic studies indicate that the *N*-ethylbenzisoxazolium cation readily undergoes base-catalyzed elimination to form a transitory *N*-ethylbenzoketoketenimine (eq 5).[9]

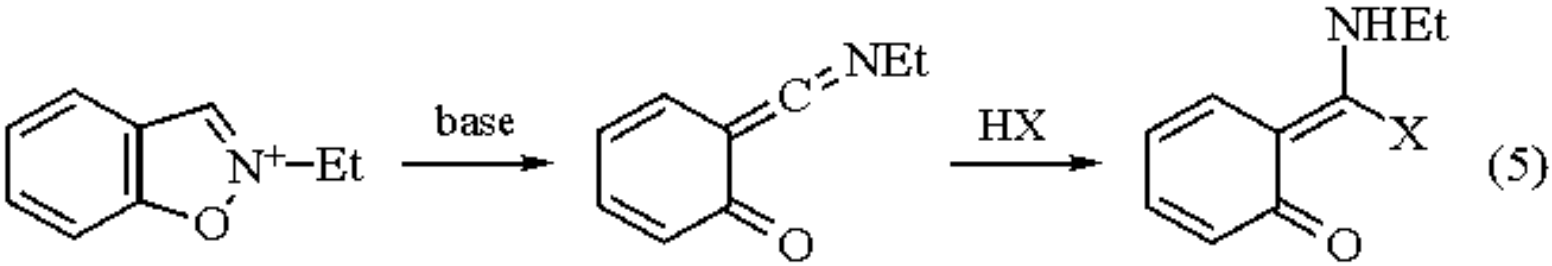

In the case of reactions with carboxylic acids (X = RCO_2), the initial addition product then rapidly rearranges to the active ester (eq 6).

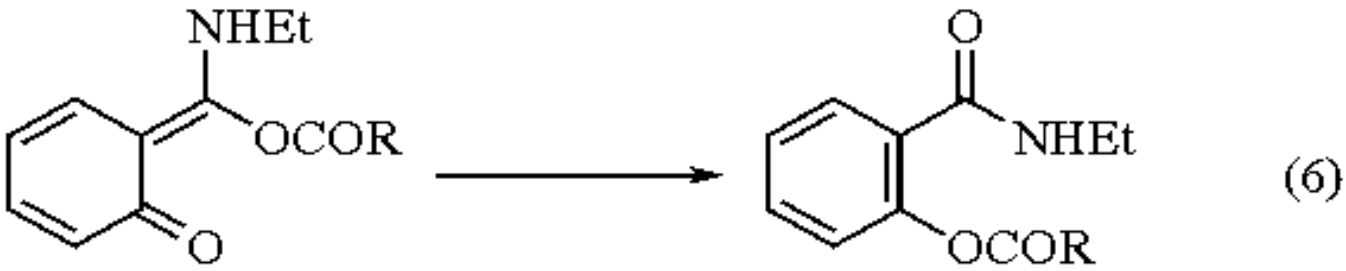

Several hydroxy-,[10] nitro-,[3] and chloro-substituted[11] *N*-ethylbenzisoxazolium cations have been studied in attempts to vary the reactivity of the intermediate active ester (see ***2-Ethyl-7-hydroxybenzisoxazolium Tetrafluoroborate***).

Reactions with Nucleophiles.

The *N*-ethylbenzisoxazolium cation reacts rapidly in aqueous solution with a range of nucleophiles, yielding *o*-hydroxy-*N*-ethylbenzimido derivatives. Hydrolysis proceeds smoothly in mild acid, but at pH above 7, polymeric material is obtained (eq 7).[2]

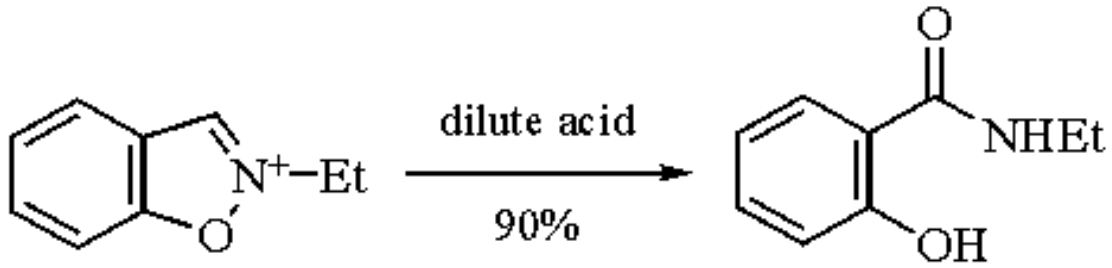

(7)

Treatment of EBF with aqueous solutions of simple nucleophiles (HS^-, F^-, CN^-) or with methanolic methoxide gives high yields of the benzimido derivatives (eq 8).

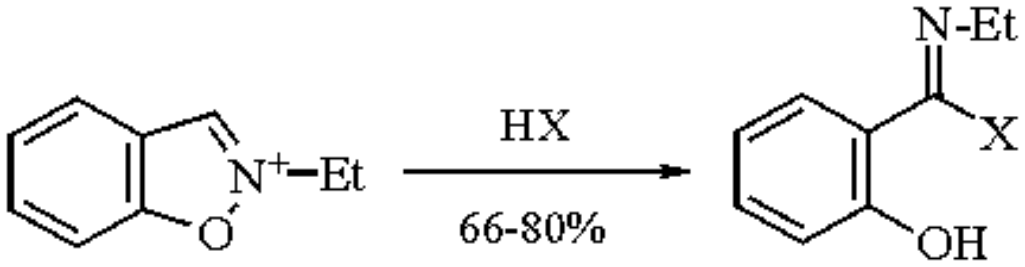

(8)

Reaction of EBF with cyanate, thiocyanate, and thiourea generates initial adducts which can undergo internal rearrangements. For example, the adduct of cyanate to EBF yields a cyclic urethane (eq 9); reaction with thiocyanate yields the analogous thiourethane.[2]

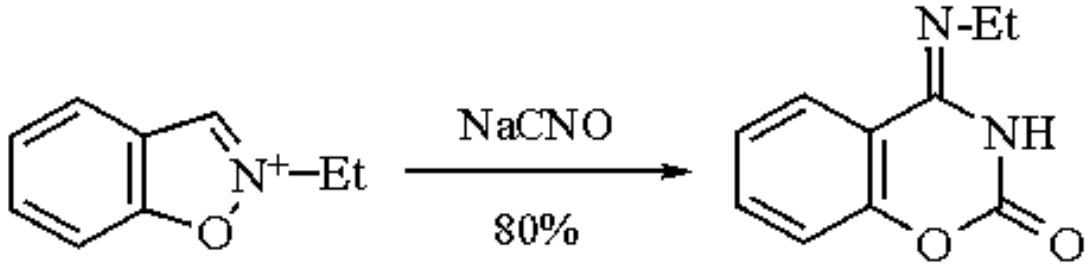

(9)

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11. Rajappa, S.; Akerkar, A. S. *CC* **1966**, 826.

Ross P. McGeary

Ethyl *N*-Benzylideneglycinate

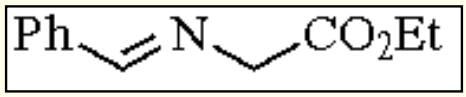

[40682-54-0] · $C_{11}H_{13}NO_2$ · Ethyl *N*-Benzylideneglycinate · (MW 191.23)

(α-amino acid synthesis)

Alternate Name: ethyl glycinate benzalimine.

Physical Data: pale yellow liquid; bp 65-75 °C/0.001 mmHg;[1] IR spectrum.[1]

Solubility: very sol most organic solvents; insol hexane.

Preparative Methods: condensation of ethyl glycinate with benzaldehyde.[1,2]

Handling, Storage, and Precautions: unstable to hydrolysis so that chromatographic treatment on silica gel produces ethyl glycinate and benzaldehyde.

α-Alkylated α-Amino Acid Synthesis.

Ethyl *N*-benzylideneglycinate has two acidic hydrogens at the α-position which can be metalated and then alkylated to give α-alkylated α-amino acids.[2-5] Iteration of this procedure produces α,α-dialkylated α-amino acids. The use of α,o-dihaloalkanes as alkylating agents opens a good entry to cyclic α-amino acids after hydrolysis (eq 1).[6-8] Alkylations using sterically bulky *t*-butyl α-halo esters result in unusual γ-alkylation to give β-amino esters after hydrolysis (eq 2).[9]

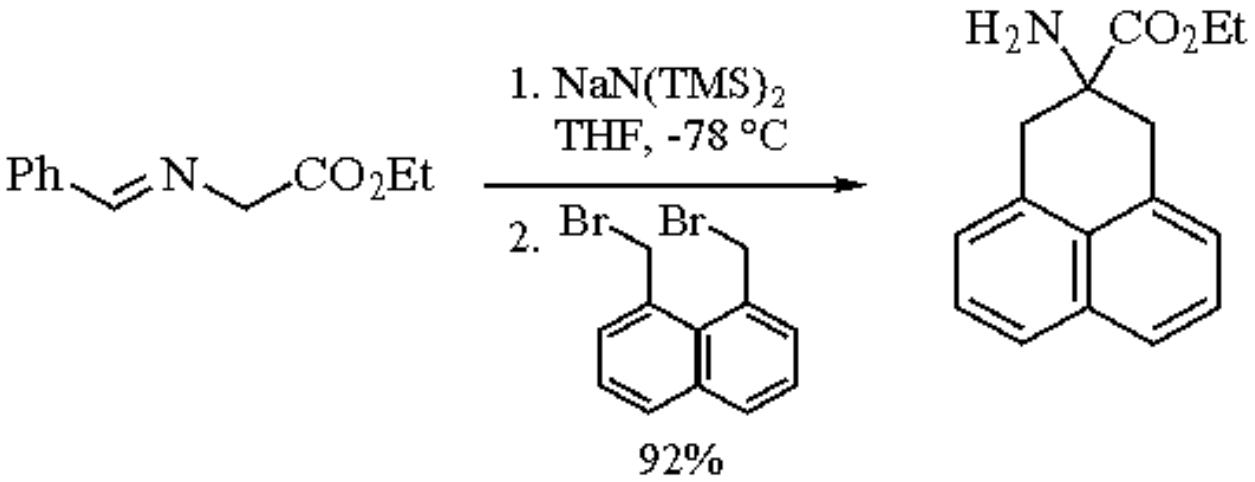

(1)

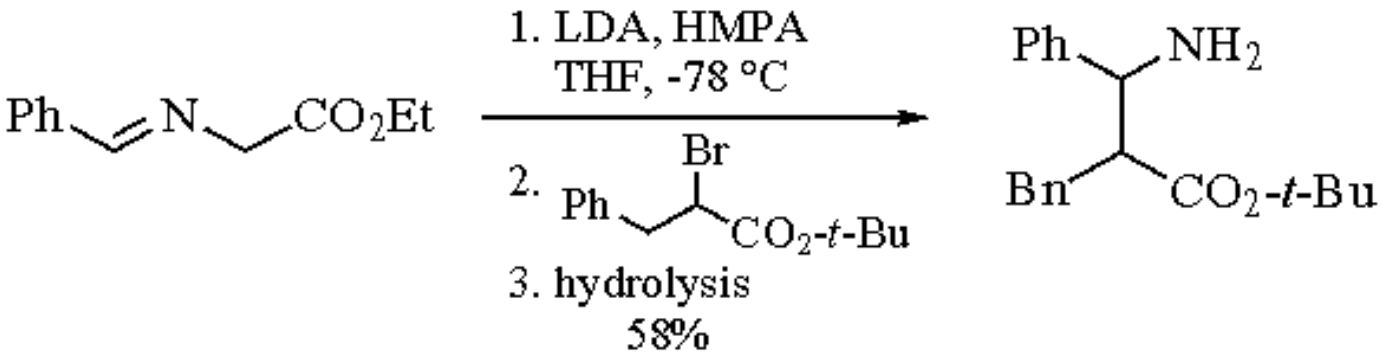

(2)

Stereoselective Pyrrolidine Synthesis.

Ethyl *N*-benzylideneglycinate can be reversibly lithiated on treatment with ***Lithium Bromide-Triethylamine*** in THF at room temperature and the lithiated species then undergoes exclusively *endo* selective cycloadditions to α,β-unsaturated carbonyl compounds to give pyrrolidine esters (eq 3).[10,11] The reactions with ketene dithioacetals followed by the elimination of thiol produce pyrrole or 2-pyrone derivatives, depending upon the reaction conditions (eq 4).[12]

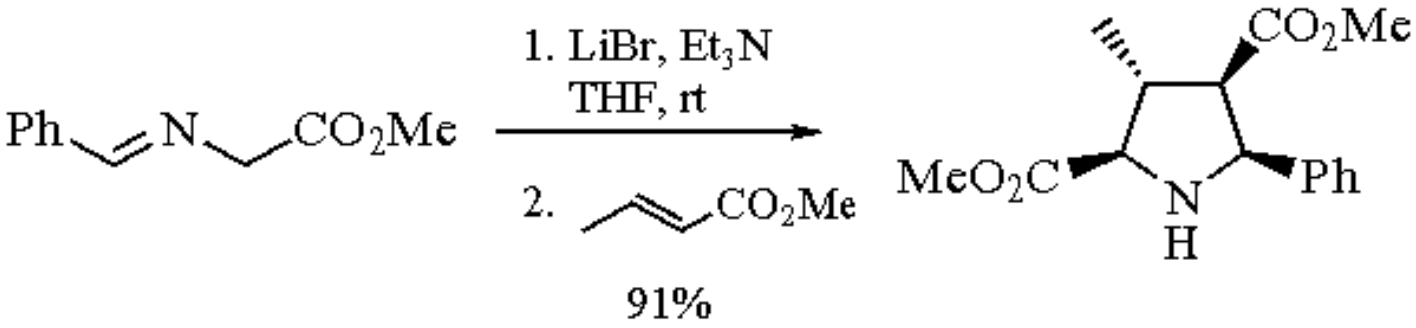

(3)

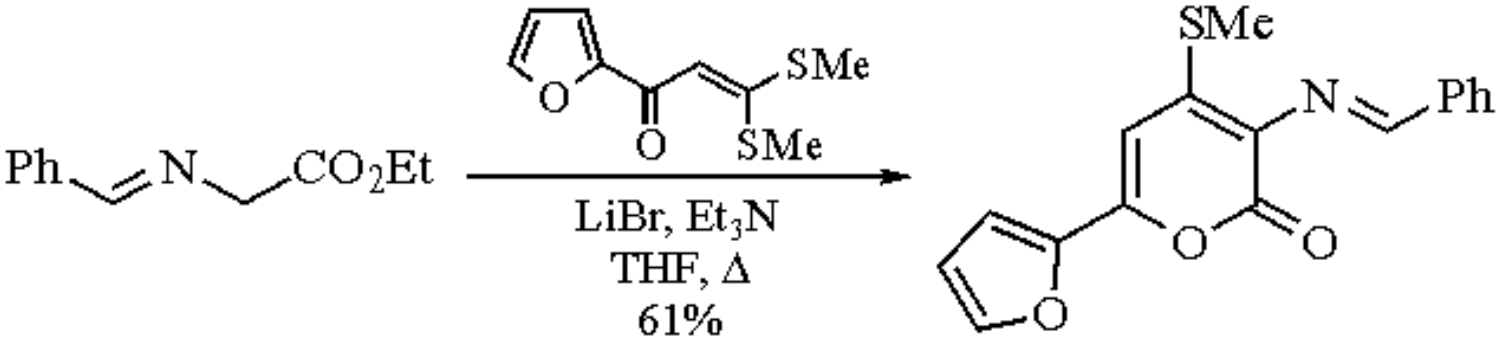

(4)

Glutamic Acid Synthesis.

Under catalyzed conditions, smooth Michael additions take place with α,β-unsaturated ester acceptors, offering a convenient and direct synthetic route to glutamic esters (eq 5).[13] Vinyl phosphonates can also serve as acceptor molecules.[14,15]

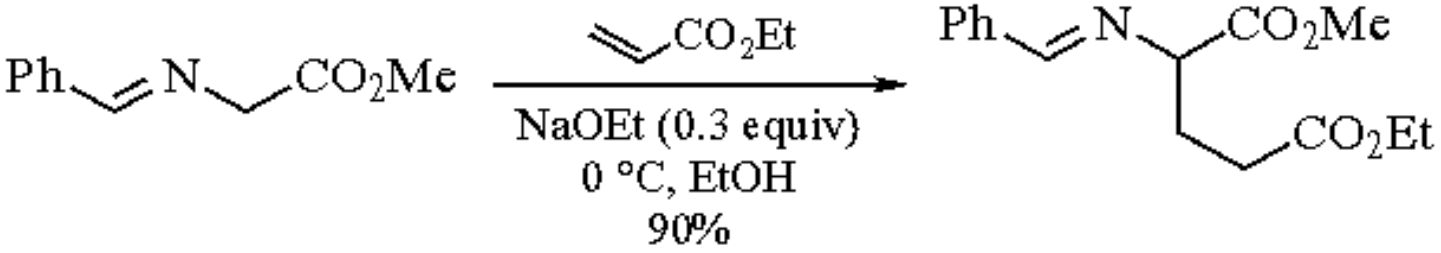

(5)

The C=N bond of ethyl *N*-benzylideneglycinate reacts with ketene or its equivalents to produce azetidinones.[1,16] When carboxylic acids are activated by interaction with trichlorocyanuric acid, azetidinones are formed (eq 6).[17] Stereoselective aldol reactions of the titanium (*Z*)-enolates of ethyl *N*-benzylideneglycinate are also known.[18]

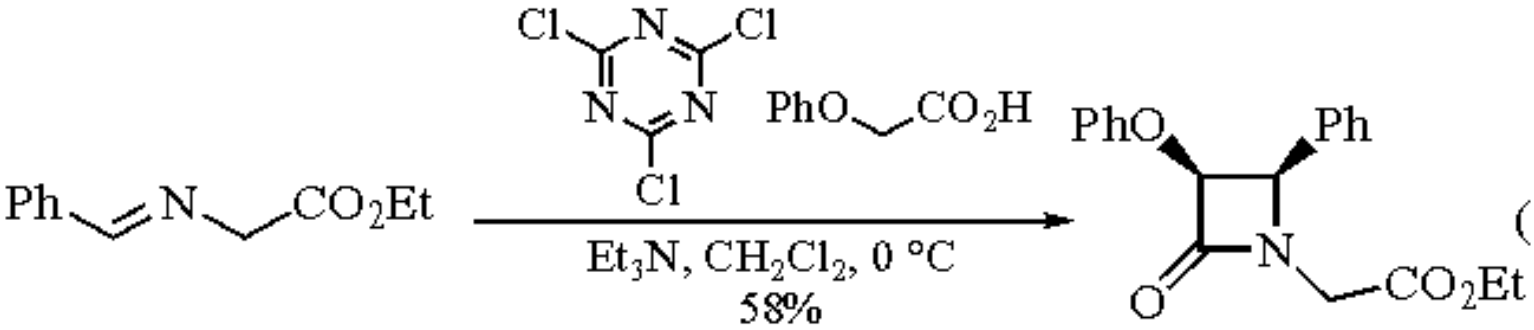

(6)

Related Reagents.

Ethyl N-(Diphenylmethylene)glycinate.

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Shuji Kanemasa

Ethyl 3-Bromo-2-(hydroxyimino)propanoate

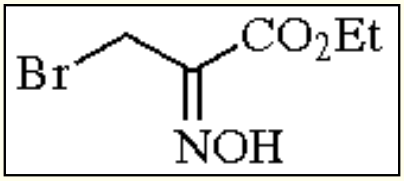

[73472-94-3] · $C_5H_8BrNO_3$ · Ethyl 3-Bromo-2-(hydroxyimino)propanoate · (MW 210.03)

(alkylating agent, especially useful for 3-substitution of indoles under mild conditions;[1] reacts with bases to give ethyl 2-nitrosopropenoate, an electron-deficient heterodiene[1,2])

Alternate Name: ethyl bromopyruvate oxime.

Physical Data: mp 78-79 °C.

Solubility: sol ether, dichloromethane, and most organic solvents.

Preparative Methods: reaction of ethyl 3-bromo-2-oxopropanoate (ethyl bromopyruvate) with hydroxylamine hydrochloride in methanol-chloroform gives the oxime (quantitative yield); it can be recrystallized from dichloromethane-hexane.[3,4] The compound has also been prepared using a two-phase system (water and chloroform).[5]

Handling, Storage, and Precautions: can be stored for several months in a refrigerator without deterioration. No specific toxicity data are available, but as a highly reactive alkylating agent it must be handled with appropriate precautions.

Alkylation of Indoles.

Indoles unsubstituted at the 3-position are alkylated by reaction with ethyl 3-bromo-2-(hydroxyimino)propanoate (**1**) and anhydrous ***Sodium Carbonate*** in dichloromethane at room temperature. The reaction has been carried out with a wide range of indoles, including indole-2-carbaldehyde and others with an electron-withdrawing substituent at the 2-position.[6] Adducts can usually be isolated in good yield when equimolar amounts of the indole and of the oxime are used. A side reaction which is sometimes troublesome is attack of a second mole of the alkylating agent at C-3 to give a 2:1 adduct, as in the example shown in eq 1.[7] This reaction can be suppressed by using the indole in excess.[8] Alkylation at other positions of the indole ring system is rare; minor products resulting from attack at the 2- and 5-positions have been observed with indoles bearing a dialkylamino substituent at C-4.[9]

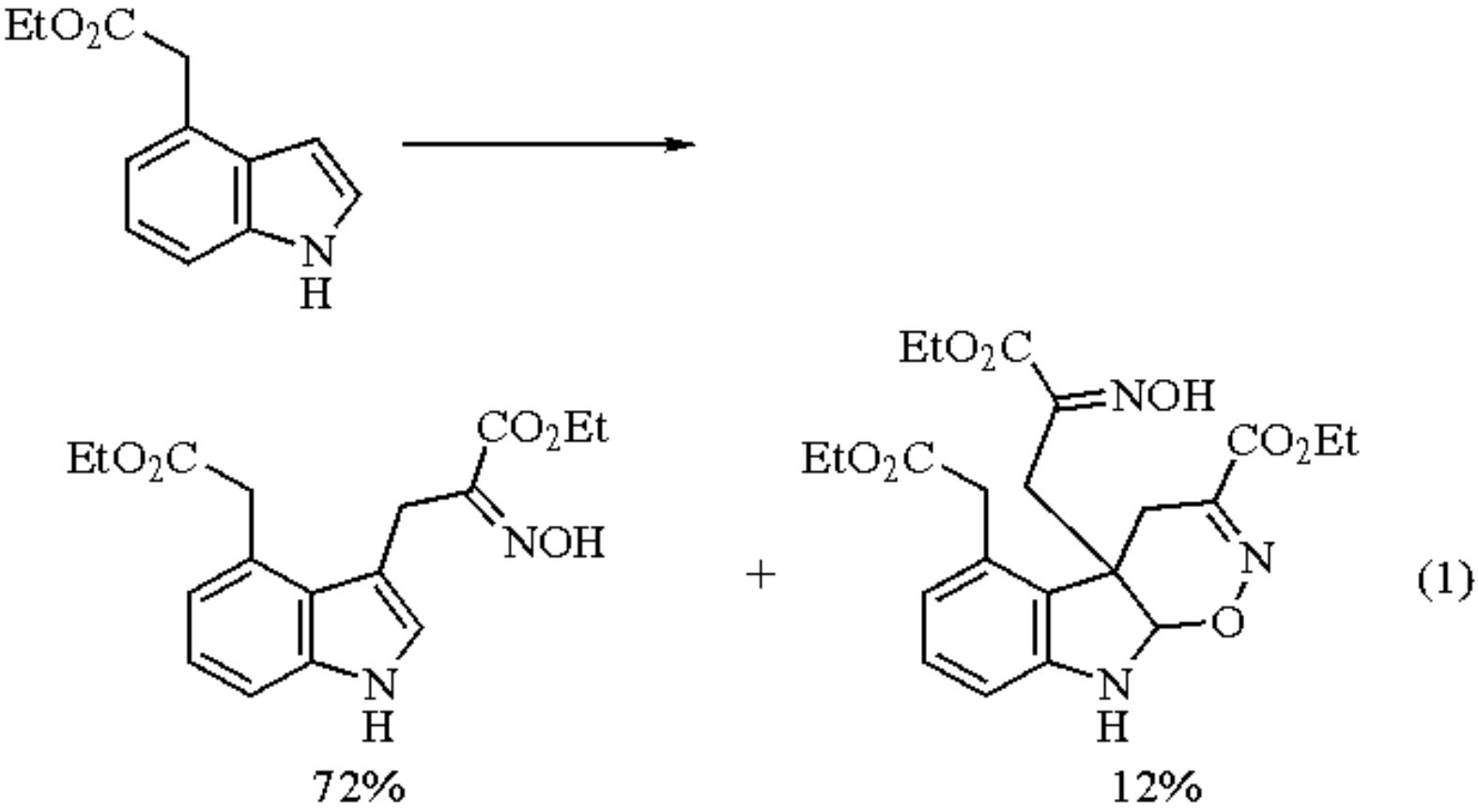

The oximes produced in these reactions have the (*E*) configuration,[8] as required by a mechanism involving cycloaddition of a transient nitrosoester, ethyl 2-nitrosopropenoate, to the indole followed by ring opening. The cycloadduct with 1-methoxyindole has been detected in solution; it rearranges to the oxime under mild conditions.[10]

With indoles bearing an alkyl or other electron-donating substituent at C-3, attack still takes place at the 3-position to give cycloadducts which can usually be isolated in high yield.[5,11] 3-(Alkylthio)indoles are an exception in that the products isolated result from migration of the alkylthio substituent to C-2.[12]

Alkylation of Other Heterocycles.

Pyrrole and 1-methylpyrrole are alkylated at C-2 by (**1**). 2,5-Dimethylpyrrole is also attacked at C-2, the product being a cycloadduct (eq 2).[13] Furan and 2,5-dimethylfuran similarly form cycloadducts.[5,14] With the nucleophilic heterocycles imidazole, pyrazole, and 1,2,4-triazole, products of *N*-alkylation are isolated.[15]

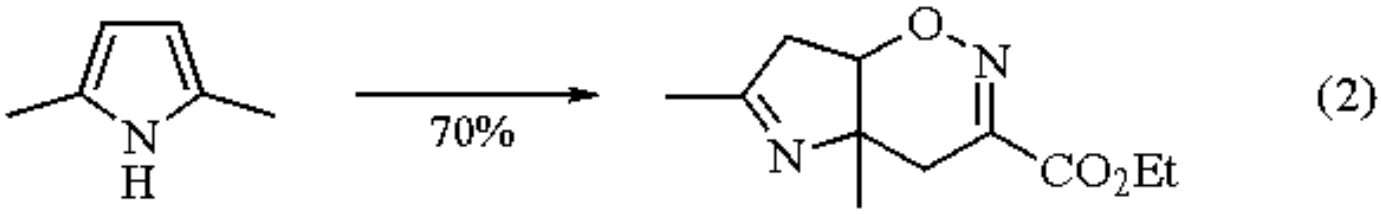

Formation of 5,6-Dihydro-4*H*-1,2-oxazines with Nucleophilic Alkenes.

Ethyl 2-nitosopropenoate, generated in situ from (**1**) and sodium carbonate, is an electron-deficient heterodiene which reacts with a wide range of electron-rich alkenes (eq 3). Cycloadducts have been formed in good yield with enamines,[16,17] enol ethers,[16,18] silyl enol ethers,[19] and allylsilanes.[20] The cycloaddition is regioselective and stereoselective; diastereoselective addition to a chiral enol ether has also been observed.[21] Conjugated alkenes such as indene and cyclopentadiene also form cycloadducts, but with simple alkenes such as 1-octene the yields are low.[5] Addition to methoxyallene takes place in good yield at the substituted double bond.[22] An example of cycloaddition to a C=N bond, in *N*-methyl-*N*-phenylbenzamidine, has also been reported.[23] The cycloadducts can be reduced to pyrroles[16,18,19] and pyrrolidines[17,18,24] and there are several reports of one-pot cycloadditions and in situ reductions.

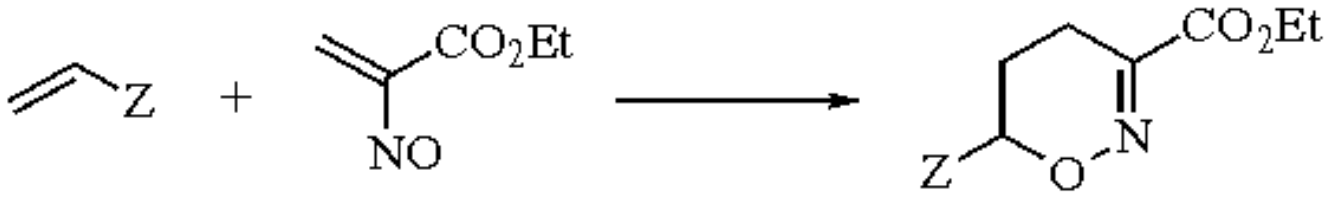

(3)

One special application of the reaction with enamines has been in the construction of the skeleton of *Vinca* alkaloids.[25]

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13. Gilchrist, T. L.; Lemos, A. *JCS(P1)* **1993**, 1391.
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Ethyl 2-(Bromomethyl)acrylate

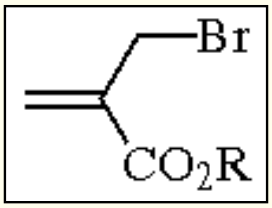

(R = Et)

[17435-72-2] · $C_6H_9BrO_2$ · Ethyl 2-(Bromomethyl)acrylate · (MW 193.04) (R = *t*-Bu)

[53913-96-5] · $C_8H_{13}BrO_2$ · *t*-Butyl 2-(Bromomethyl)acrylate · (MW 221.09)

(powerful allylic alkylating reagent[1-3] employed as its organozinc derivative to prepare α-methylene lactones[4] and lactams;[5] important source of functional acrylic monomers for polymerization[6,7])

Alternate Name: ethyl 2-(bromomethyl)propenoate.

Physical Data: R = Et, bp 40-41 °C/0.1 mmHg; R = *t*-Bu, bp 60-61 °C/0.1 mmHg.

Solubility: insol H_2O; sol ether, acetone, alcohol, THF, chloroform.

Form Supplied in: colorless liquid.

Preparative Methods: many preparations of these compounds have been described,[8] for example dehydrobromination of β,β´-dibromoisobutyric esters[9-11] or acid, or bromination of *t*-butyl or ***Ethyl* α-*(Hydroxymethyl)acrylate*** with ***Phosphorus(III) Bromide***.[12]

Handling, Storage, and Precautions: reputed to be lachrymatory, vesicatory, and toxic. Usual precautions of storage in darkness between 0 and 5 °C and handling with gloves under a well ventilated hood are recommended.

Electrophilic Alkylating Reagent.

The electrophilic reactivity of the allylic bromide moiety is increased by the presence of the carboxylate group (Michael acceptor) and the reagent can thus act as a powerful allylic electrophile. It can be coupled with various organometallic reagents, *gem*-dimetallic reagents[2,3] or O-,[13,14], S-,[15-17], N-, and P-nucleophiles (eq 1).[18,19]

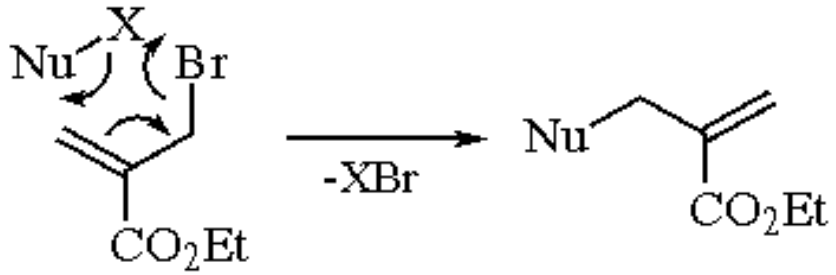

(1)

The alkylation with ***Cyanomethylcopper***[1] gave 89% yield of the corresponding 1-(3-cyanoethyl)acrylic ester, while π-2-(methoxyallyl)nickel bromide was tested as a source of 5-ethoxycarbonyl-5-hexen-2-one.[20] Palladium-catalyzed cross-coupling with vinyl- and aryltin[21] and vinylzirconium reagents[22] allowed the preparation of the corresponding 2-allyl- and 2-benzylacrylates. Coupling with functional zinc or zinc-copper organometallic derivatives[23-25] gives rise to various polyfunctional acrylic derivatives (eq 2).[26]

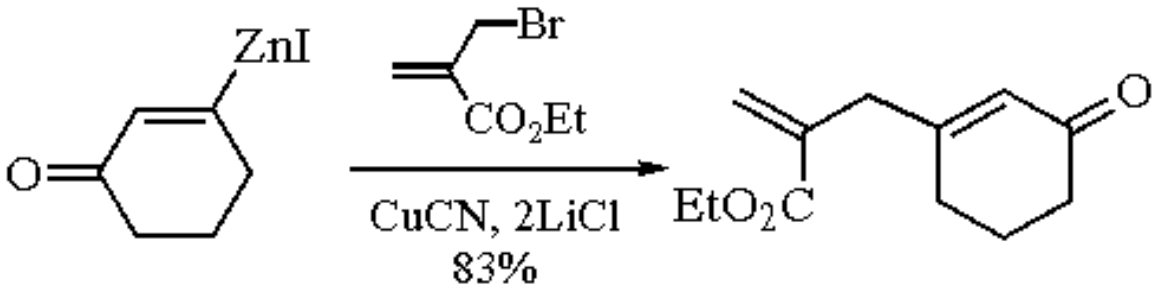

(2)

The allylation of other nucleophiles such as the enolates of cyclic 1,3-diketones[27] (or their enol ethers[28]), β-keto esters,[29] β-dimethylaminopropionates,[30] and bicyclic enolates[31] has been reported. Tandem alkylation-Michael addition with dienolates gives rise to cyclic or bicyclic compounds,[32] while tandem alkylation-Claisen condensations leads to the formation of functional α-methylenecyclopentanones (eq 3).[33]

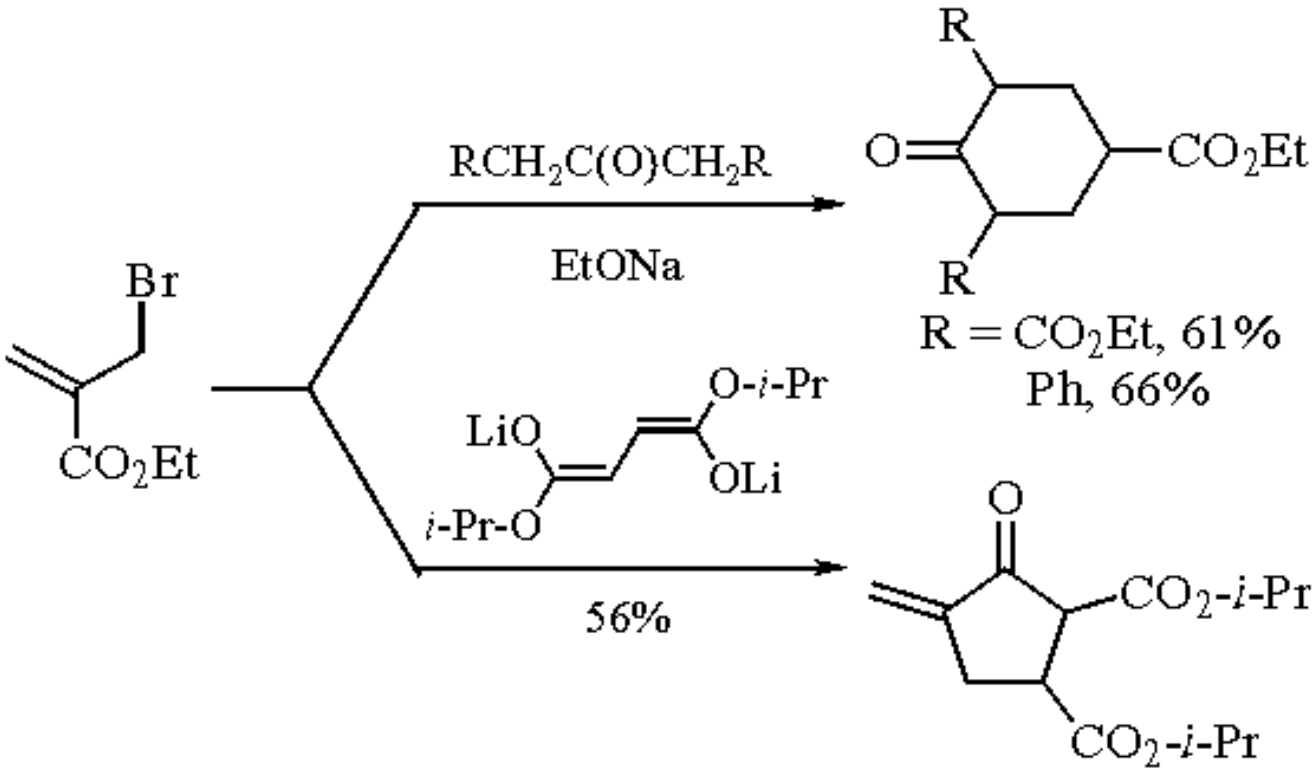

(3)

Alkylation of enamines[34] has been proposed as the first step in the synthesis of potential antitumor α-methylene δ-valerolactones.

Unsymmetrical organic sulfides containing the methacrylic ester group are produced under nonbasic reaction conditions.[35] Thio-Claisen rearrangement[36] took place via *S*-allylation with ethyl 2-(bromomethyl)acrylate (eq 4).

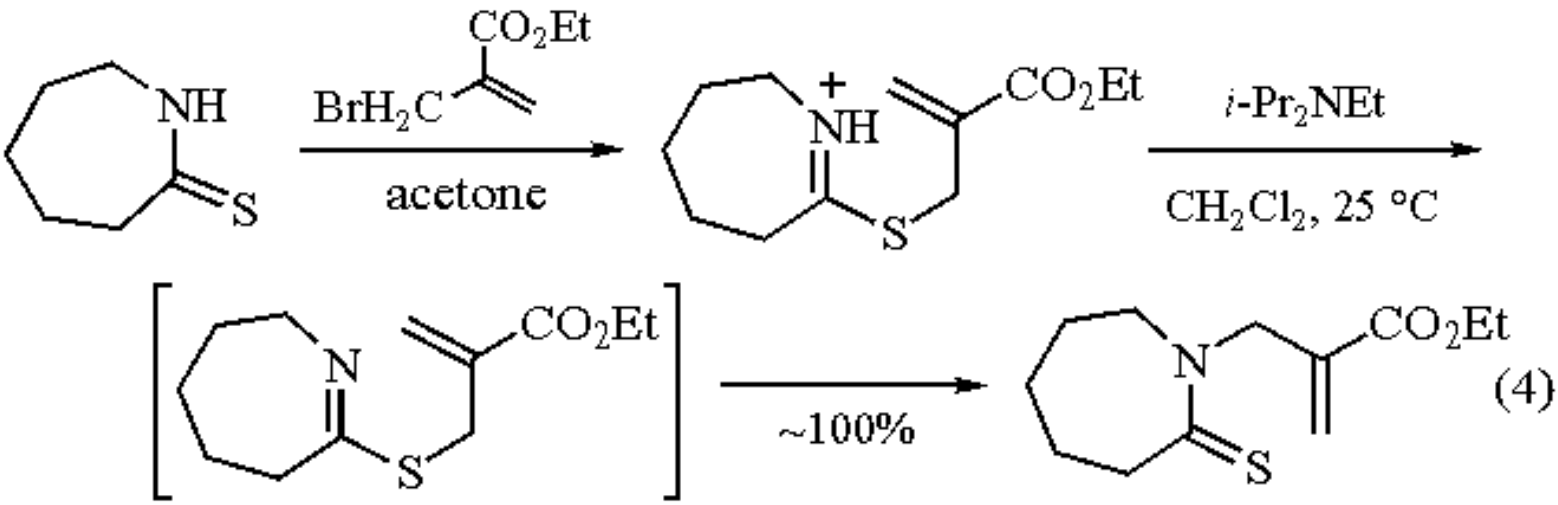

N-Allylation by ethyl 2-(bromomethyl)acrylate has been developed as key steps in the synthesis of bioactive molecules such as α-methylene-β-alanine,[37] or analogs of Iboga alkaloids.[38]

Synthesis of α-Methylene Lactones and Lactams.

One of the most important applications of ethyl 2-(bromomethyl)acrylate was found in a pseudo-Reformatsky reaction. First described by Ohler et al.,[4] this reaction leads to the formation of potential antitumor α-methylene-γ-lactones,[39,40] via an organozinc intermediate (eq 5).

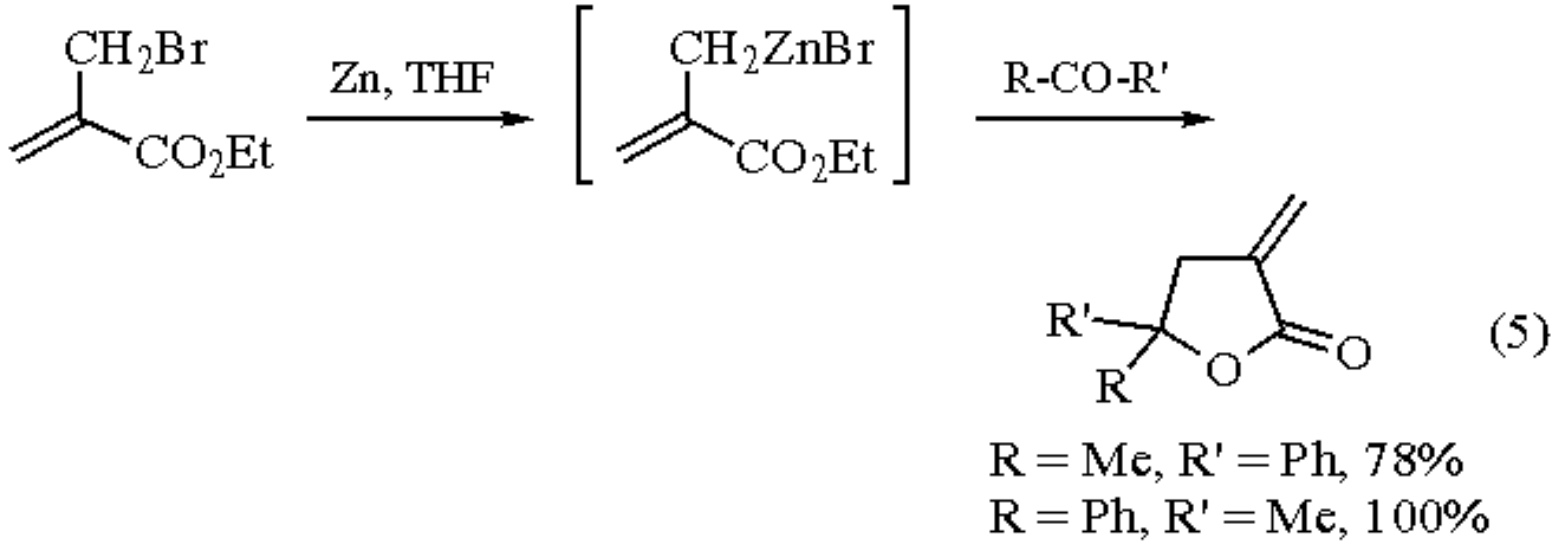

This reaction was extensively applied to various carbonyl compounds. 5-Mono- or 5,5-disubstituted α-methylene-γ-

lactones bearing a steroidal moiety,[41] nucleic acid bases,[42] furanose systems,[43] six-membered[44] or five-membered[45] heterocyclic groups, adamantyl groups,[46] and bornyl groups[47] have been prepared and evaluated as antineoplasic and allergenic[48,49] compounds. Bis-α-methylene-γ-lactones have been produced from dicarbonyl compounds.[50]

The Reformatsky reaction with imines leads to the corresponding less toxic α-methylene-γ-lactams.[5] Bis addition of the organozinc intermediate to acyl chlorides or nitriles before cyclization leads to the formation of new α-methylene-γ-lactones and lactams (eq 6).[51]

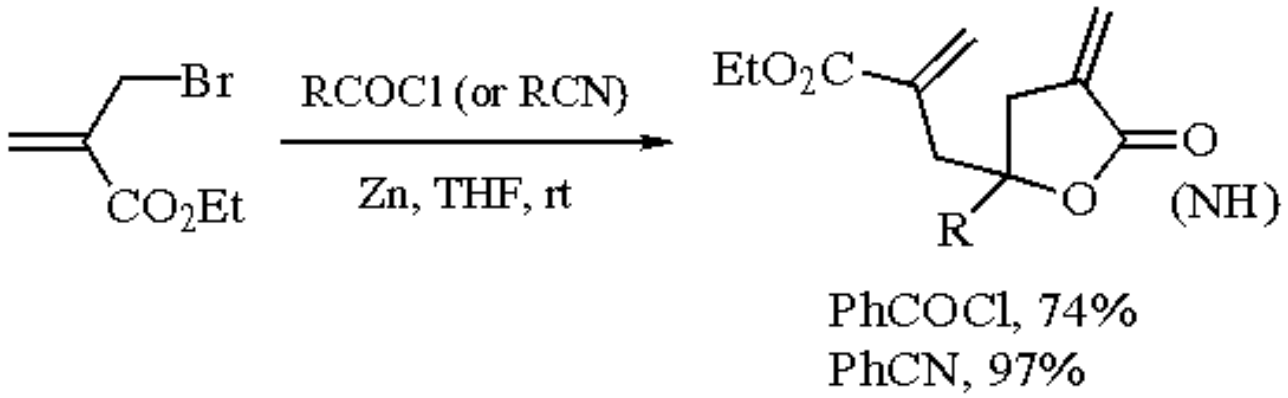

(6)

Attempts to improve the yield of the Reformatsky reaction included the use of ***Tin***,[52] tin-aluminum alloy,[53] ***Zinc*** dust in aqueous ammonium chloride solution,[54] or electrogenerated zinc.[55] Low valent metal halides (***Lithium Aluminum Hydride-Chromium(III) Chloride***)[56] and ***Tin(II) Chloride***[57] were found to undergo insertion into the carbon-bromine bond of 2-(bromomethyl)acrylates. Asymmetric induction from complex reagents made with $SnCl_2$, tartaric ester, and allylic bromides has been described.[58]

The preparation of intermediate organozinc derivatives of 2-(bromomethyl)acrylates[59] by direct action of zinc dust in THF (or DME) at controlled temperature allowed regio- and stereoselective condensations with polyfunctional electrophilic compounds without side reactions (eq 7).[60]

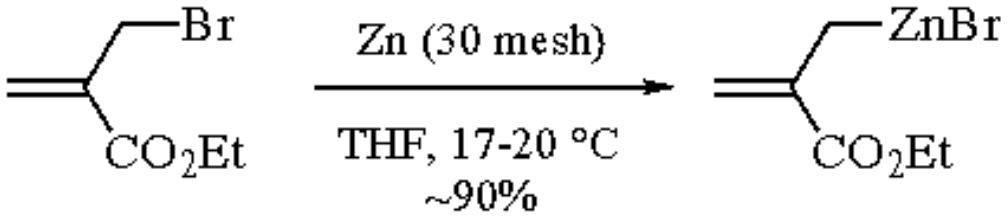

(7)

Their coupling with chiral imines, derived from α-amino esters[61] or β-amino alcohols,[62] leads to the formation of the corresponding α-methylene-γ-lactams (*R*,*R*) or (*S*,*S*) via a diastereoselective set of reactions (de > 95%).

Other organometallic reagents derived from ethyl 2-(bromomethyl)acrylate are known, such as organotin,[63] which allows palladium-promoted arylation, and organomercury,[64] for acylation reactions. Ethyl 2-(bromomethyl)acrylate/π-(allyl)nickel in DMF is a powerful selective nucleophilic reagent for haloaromatics[65] and iodoalkanes[66] (eq 8).

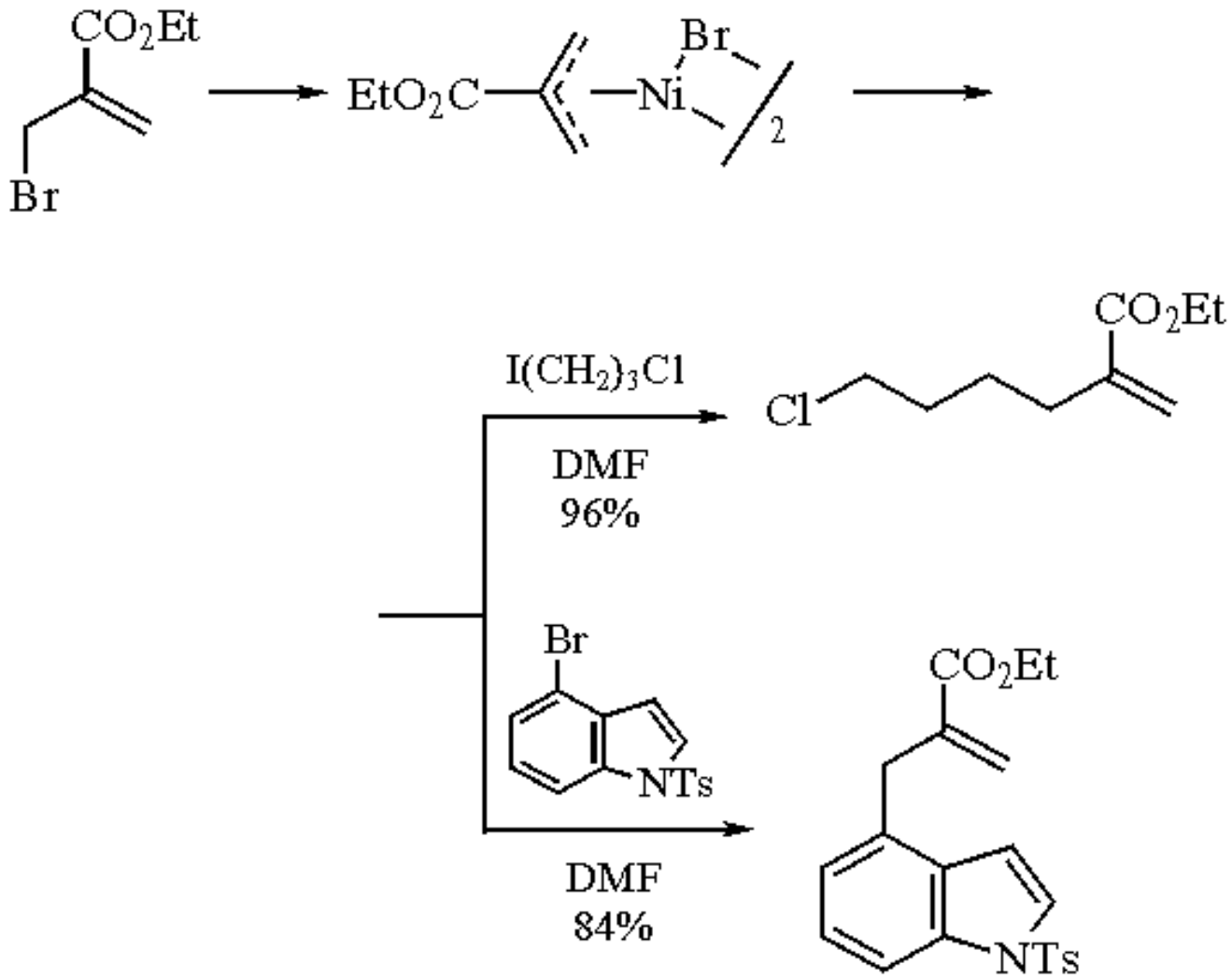

(8)

Polymer Chemistry.

Ethyl 2-(bromomethyl)acrylate also has an important place in polymer chemistry as a monomer[6] or as a source of functional monomers such as sulfur-containing acrylic compounds[67] or 6-*O*-methylallylgalactose intermediates for the preparation of poly(vinyl)saccharides.[7] It also has been employed as a chain-transfer agent.[68]

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Ethyl Bromozincacetate[1]

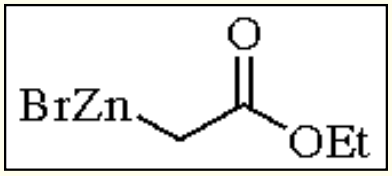

[5764-82-9] · $C_4H_7BrO_2Zn$ · Ethyl Bromozincacetate · (MW 232.37)

(chemoselective ester enolate reagent[1])

Alternate Name: Reformatsky reagent.

Preparative Methods: see below.

Handling, Storage, and Precautions: α-halo esters and α-halo ketones used for the preparation of Reformatsky reagents are lacrymators and should be used in a well ventilated hood; solutions of the reagent in ethereal solvents are stable at low temperatures for a few days. The reagent is prone to hydrolysis and must be handled in anhydrous solvents under an inert atmosphere.

Introduction.

The Reformatsky reagent shown in the above title is the historically first[5] and most widely used zinc ester enolate prepared by zinc insertion into an α-halo ester. However, the Reformatsky reaction can be taken as subsuming all enolate formations by oxidative addition of a metal or a low-valent metal salt into an activated carbon-halogen bond.[1] It is this mode of enolate formation which distinguishes the Reformatsky reaction from other fields of metal-enolate chemistry.

The reagent is dimeric in solution except in the most polar solvents;[2] X-ray analysis of $BrZnCH_2CO_2$-*t*-Bu.THF shows a dimeric unit in the solid state with the metal being bound to an sp^3 carbon atom.[3] In contrast, zinc enolates of ketones are *O*-metalated species.[4]

Performance and Reagent Preparation.

Originally,[5] the reaction was performed in a one-step fashion by adding a mixture of the halo ester and the electrophile (usually a carbonyl compound) to a ***Zinc*** suspension in an ethereal or hydrocarbon solvent. However, enolate formation and its reaction with electrophiles can be done successively. This two-step procedure has contributed to the advancement of the Reformatsky reaction, as electrophiles which would quarternize upon mixing with α-halo esters (e.g. azomethines) can be used under these conditions without problems. Moreover, the zinc enolates may be transmetalated prior to use in order to adapt their reactivity to electrophiles beyond the scope of classical Reformatsky reactions.[1]

Difficulties in initiating the reaction are avoided by the use of activated zinc samples.[1a,6] As they promote the reaction even at very low temperatures (Table 1), their use results in generally high yields, the suppression of undesirable side reactions, and an increase in diastereoselectivity. Less reactive donors such as α-chloro esters are equally suited when highly reactive metals are employed.[7] The improved reliability recommends metal-activation techniques for applications to natural product synthesis. Among the zinc samples described so far, finely dispersed and readily prepared zinc/silver on graphite[7] (see also ***Potassium-Graphite***) and zinc obtained by reduction of ***Zinc Chloride*** with ***Potassium Naphthalenide***, ***Lithium Naphthalenide***, or alkali naphthalenides are most effective (Table 1).[8] For large-scale experiments, the application of ultrasound[9] or of electrochemical support[10] for Reformatsky reactions is recommended.

Table 1 Comparison of the Reactivity of Different Zinc Samples for the Preparation of Ethyl Bromozincacetate followed by reaction with Benzaldehyde (A) or Cyclohexanone (B)

Reagent	Carbonyl compound	Solvent	T(°C)	t(min)	Yield (%)
Zinc dust	A	Benzene	+80	720	61
Zinc dust	B	Benzene	+80	[a]	56
Zn/Cu couple	A	THF	+66	60	82
Zn/Cu couple	B	THF	+66	60	82
Rieke Zn	A	Et_2O	+25	60	98
Rieke Zn	B	Et_2O	+25	60	95
Zn ultrasound	A	1,4-Dioxane	+25	5 300	98
$ZnCl_2/Li$[b]	A	Et_2O	0	30	95
$ZnCl_2/Li$[b]	A	Et_2O	- 78	30	56
Zn/Ag graphite	B	THF	- 78	20	92

[a] Reaction time not reported. [b] Zinc sample obtained by reduction of $ZnCl_2$ with commercially available lithium dispersion in Et_2O.[8e]

In contrast to other metal enolates, Reformatsky reagents are reasonably stable over a wide temperature range (from -78 °C to above 80 °C for short periods of time) and can be prepared in solvents greatly differing in polarity (most commonly employed are THF, DME, Et_2O, 1,4-dioxane, benzene, toluene, dimethoxymethane, DMF, or mixtures thereof; scattered reports using hexane, acetonitrile, CH_2Cl_2, $B(OMe)_3$, DMSO, and HMPA may be found).[1] The major path for their decomposition is loss of EtOZnBr with formation of ketene which immediately acylates an intact zinc enolate, thus leading to β-keto esters.[11] Reformatsky reagents are therefore usually freshly prepared and used without delay, although solutions

of $BrZnCH_2CO_2$-*t*-Bu in a number of solvents were reported to exhibit virtually unchanged reactivity after 4-6 days.[2]

Reformatsky Donors.

Ethyl bromoacetate is the most widely used halogen compound for zinc insertion but other short-chain 2-bromo esters work equally well under standard conditions.[1] The alcohol part of the ester plays only a minor role, and by its proper choice (e.g. *t*-butyl, TMS, tetrahydropyranyl bromo esters)[12] β-hydroxy acids can be readily obtained by zinc-induced reaction of these donors with carbonyl compounds followed by hydrolysis of the respective β-hydroxy esters initially formed. Allyl bromo esters on treatment with zinc undergo Claisen rearrangements to 4-alkenoic acids (eq 1).[13] As the chain length of the 2-bromo ester increases, or upon switching to the less reactive 2-chloro ester, the use of highly activated zinc samples and/or more polar solvent systems becomes obligatory in order to accomplish zinc enolate formation.[1]

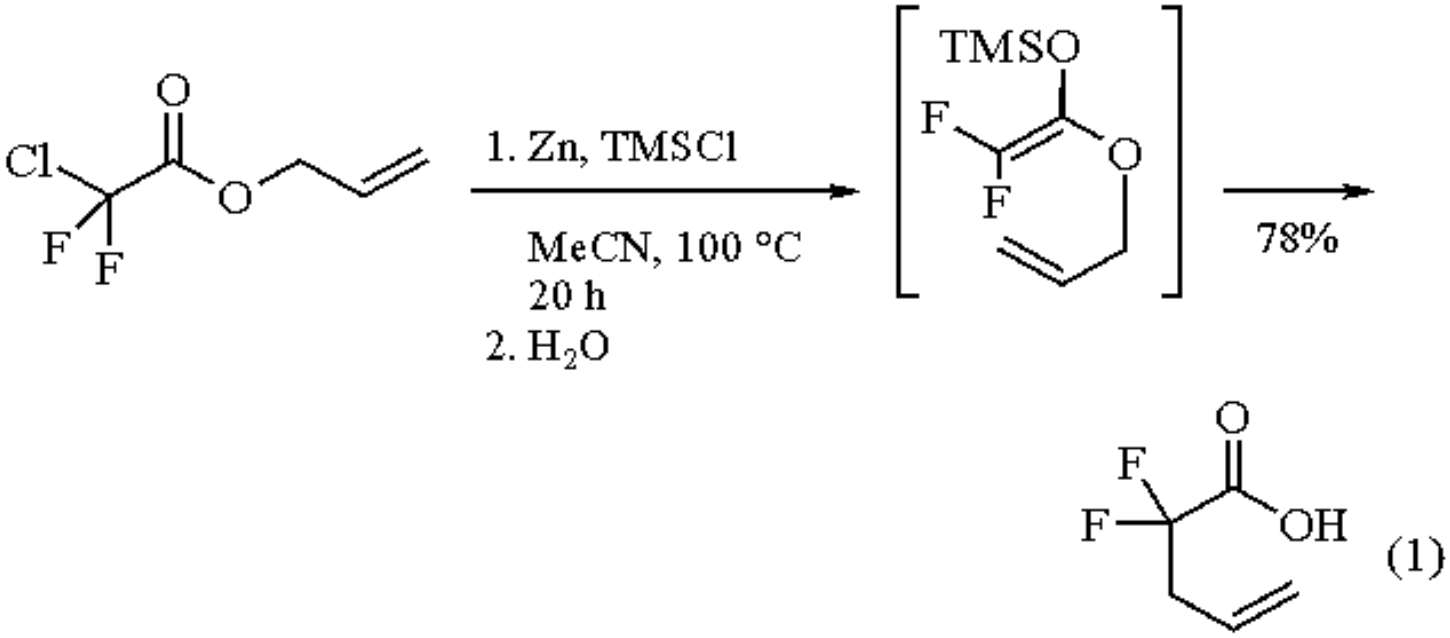

(1)

Bromo(chloro)difluoro esters and ketones show no peculiarities in their behavior and have found widespread applications in the synthesis of fluorinated natural product analogs (eq 2).[14] In contrast, dibromo-, dichloro-, and trichloroacetates tend to polymerize on reaction with zinc dust at reflux temperatures;[15] however, they can be selectively transformed with more appropriate reagent systems. Depending on the conditions used, they either afford glycidates (with Zn/Ag-graphite at -78 °C)[16] or 2-alkenoates (with Zn/***Diethylaluminum Chloride*** at 0 °C),[17] respectively, on reaction with carbonyl compounds (eq 3).

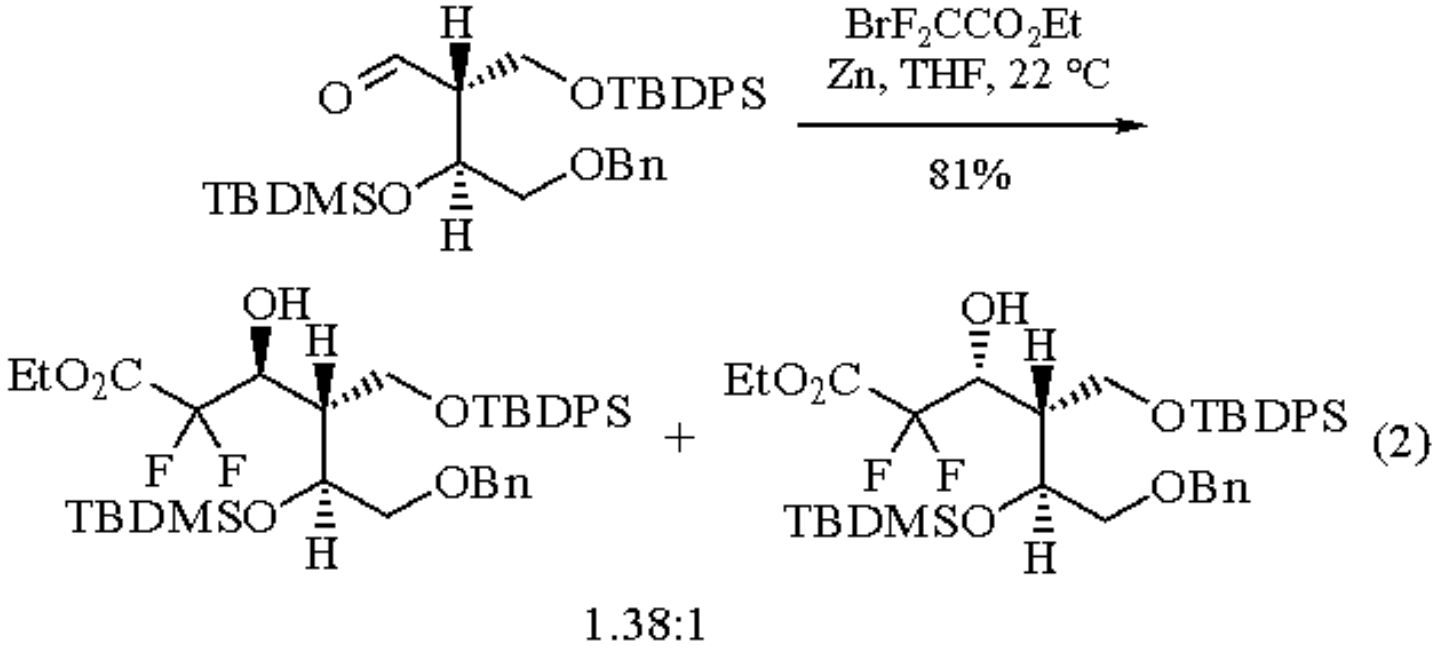

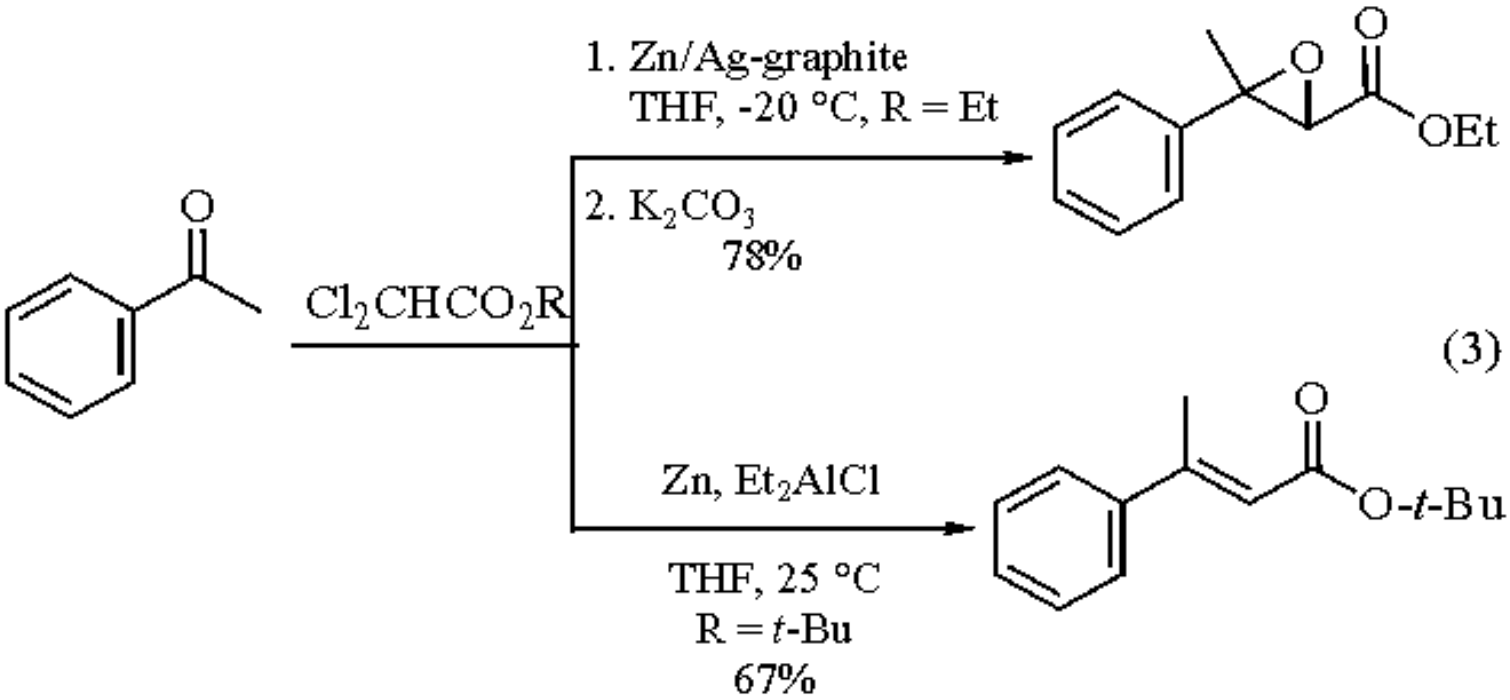

Haloacetonitriles and α-halo acetamides[1,18] are well suited as donors in Reformatsky reactions (eq 4). When *N*-methoxy-*N*-methylbromoacetamide is used (eq 5), the resulting products may be converted into β-hydroxy ketones by the Weinreb procedure.[19]

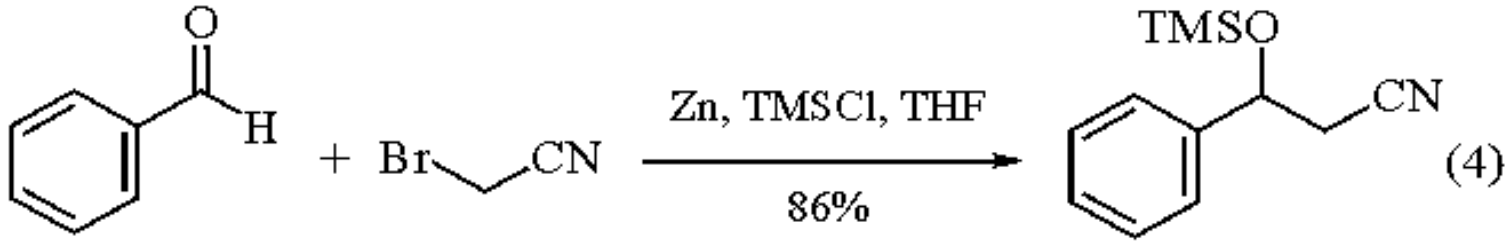

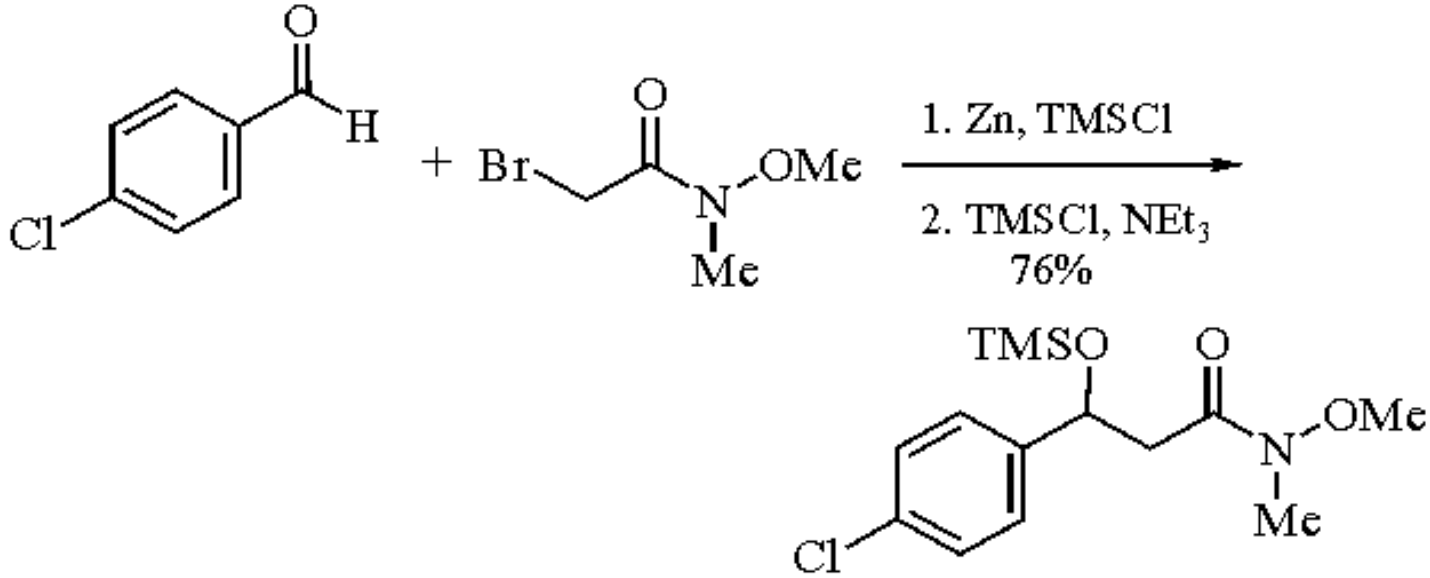

4-Bromo-2-butenoates as vinylogous bromo esters form ambident carbon nucleophiles upon treatment with zinc, which may either lead to α- or γ-substitution products on reaction with electrophiles. A set of conditions has been worked out that allows control of these pathways, with the polarity of the reaction medium and the temperature being the crucial parameters (eq 6).[20] The data suggest that kinetic control leads to α-products, whereas thermodynamic control affords the γ-substitution products.

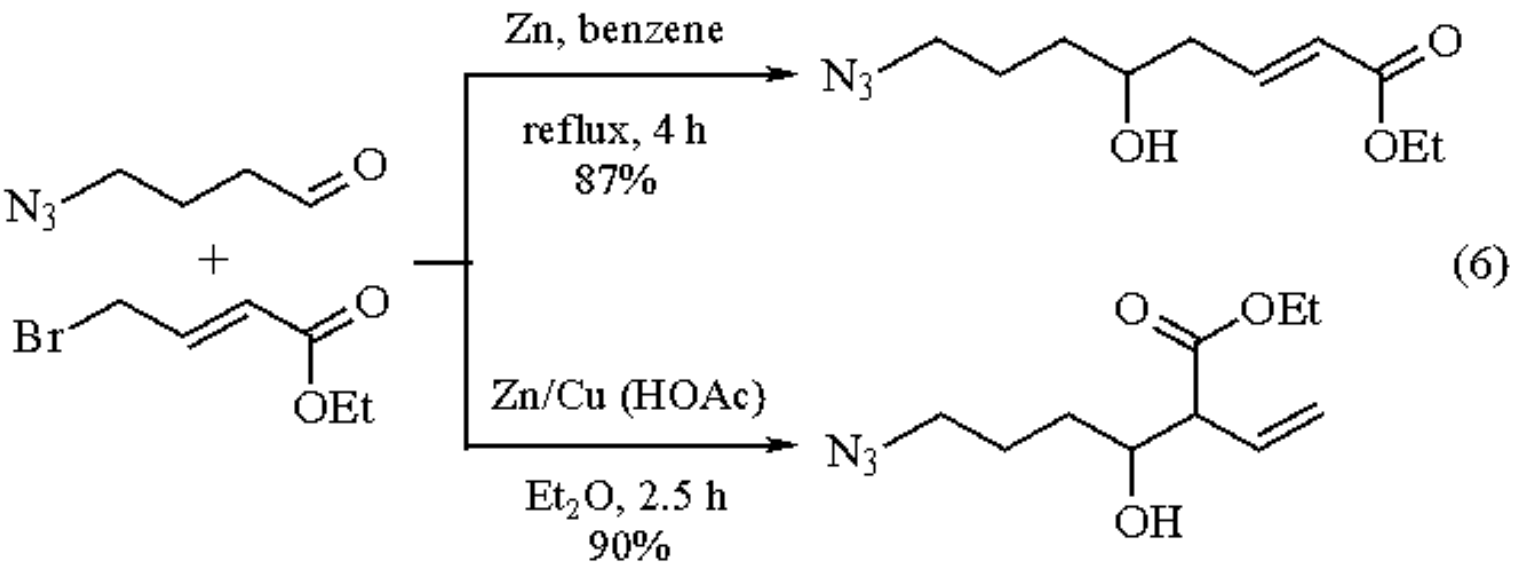

2-Bromomethyl-2-alkenoates react readily under allylic rearrangement with carbonyl compounds in the presence of zinc to form α-methylene-γ-lactones.[21] Because of the high biological relevance of that structural unit, this reaction has found widespread use in natural product synthesis,[22] both in an inter- (eq 7)[23] and intramolecular fashion (eq 8).[24] With diastereotopic ketones the stereoselectivity of the C-C bond-forming step may be significantly enhanced by using highly reactive Zn/Ag-graphite as promotor at very low temperatures.[25]

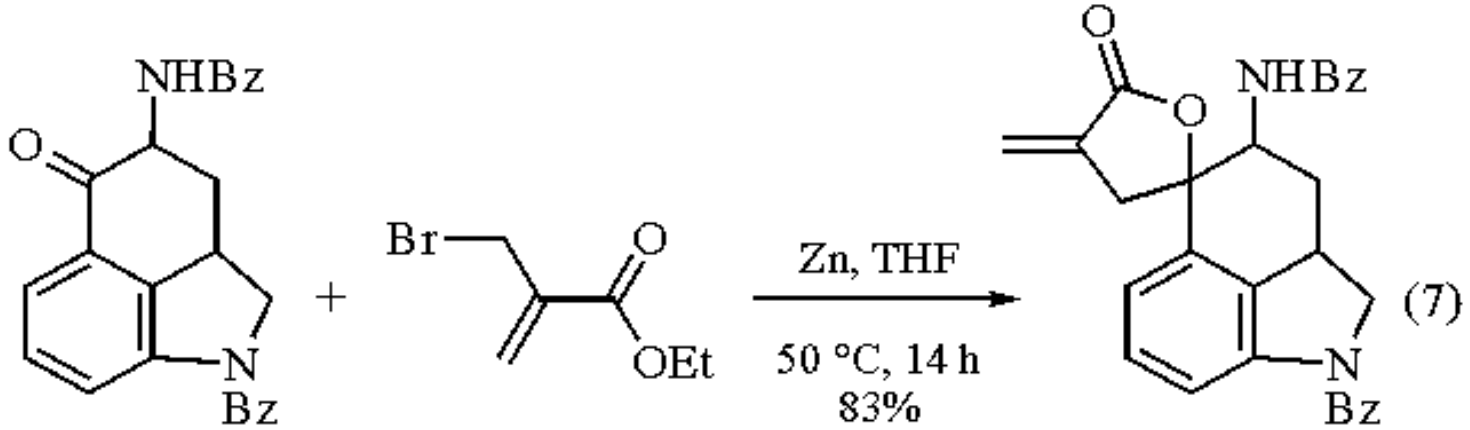

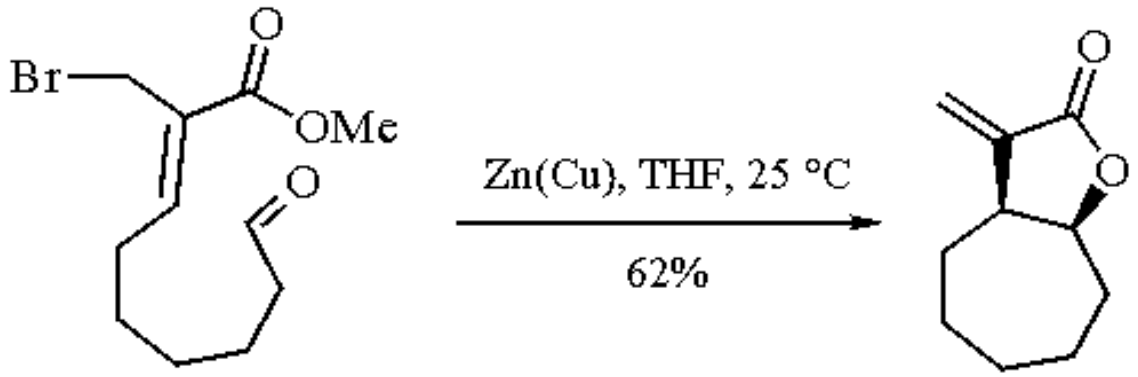

The particular advantages of the Reformatsky reaction are nicely illustrated by a recent total synthesis of (+)-pilocarpine.[26] Zinc insertion provides a reliable and regioselective access to monoenolates of succinic acid diesters, a difficult task with other methods of enolate formation (eq 9). Although some optimization was necessary in order to avoid undesirable side reactions (eliminations), dimethyl (2*S*,3*S*)-2-bromo-3-ethyl-1,4-butandioate could be transformed into the key intermediate of the pilocarpine synthesis in a highly selective manner and in excellent yield.

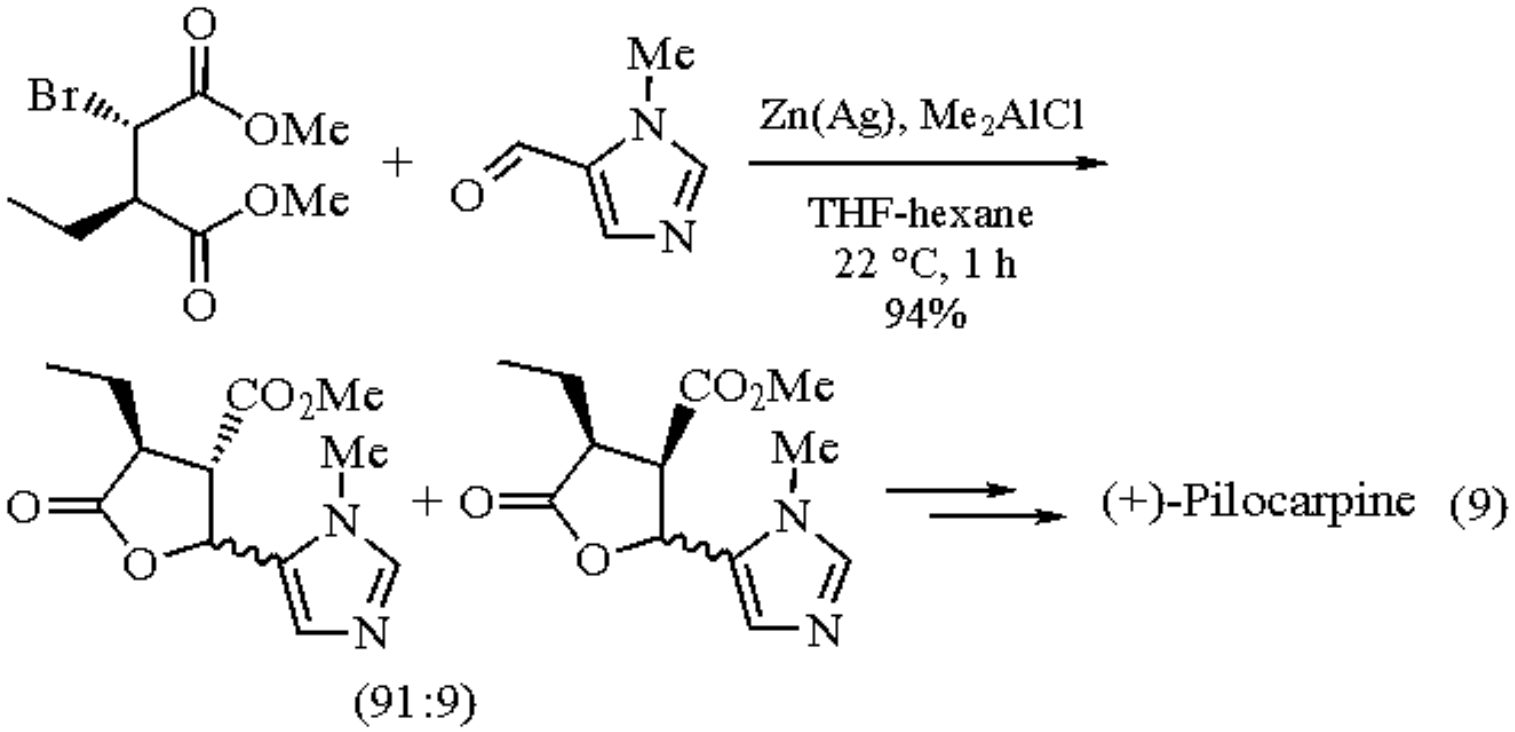

Electrophiles.

Zinc enolates of esters or ketones show moderate reactivity compared to the respective of alkali metal enolates. Hence, they exhibit higher degrees of chemoselectivity upon treatment with different electrophiles. For a long time, aldehydes and ketones have been the only relevant group of substrates for these reagents and they are still widely used.[1] Examples of Reformatsky reactions with carbonyl compounds of almost any class of natural products can be found in the literature. Highly hindered ketones as well as readily enolizable carbonyl compounds and even acylsilanes (eq 10)[27] are prone to nucleophilic attack. α,β-Unsaturated carbonyl compounds react regioselectively in a 1,2-addition manner with only very few exceptions to this rule. The latter can easily be explained by steric hindrance (eq 11)[4b,28] or peculiar electronic properties of the acceptor molecule, as in aroyl ketene *S,N*-acetals (eq 12)[29] or 1,3-diaza-1,3-butadiene[30] derivatives.

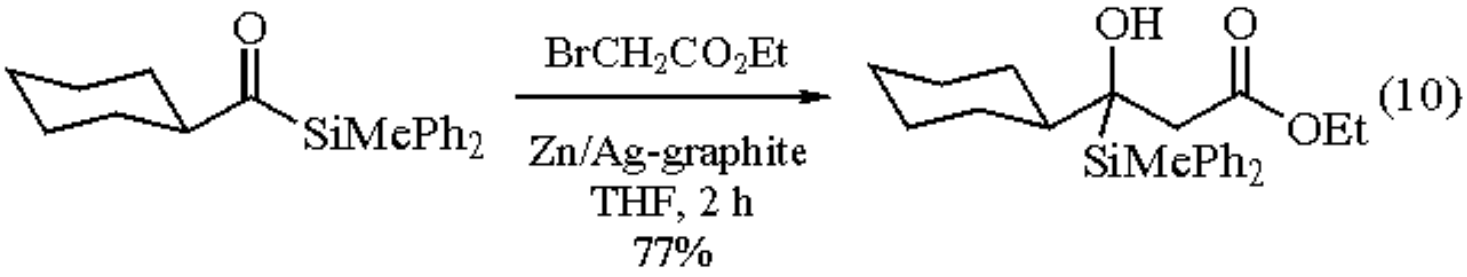

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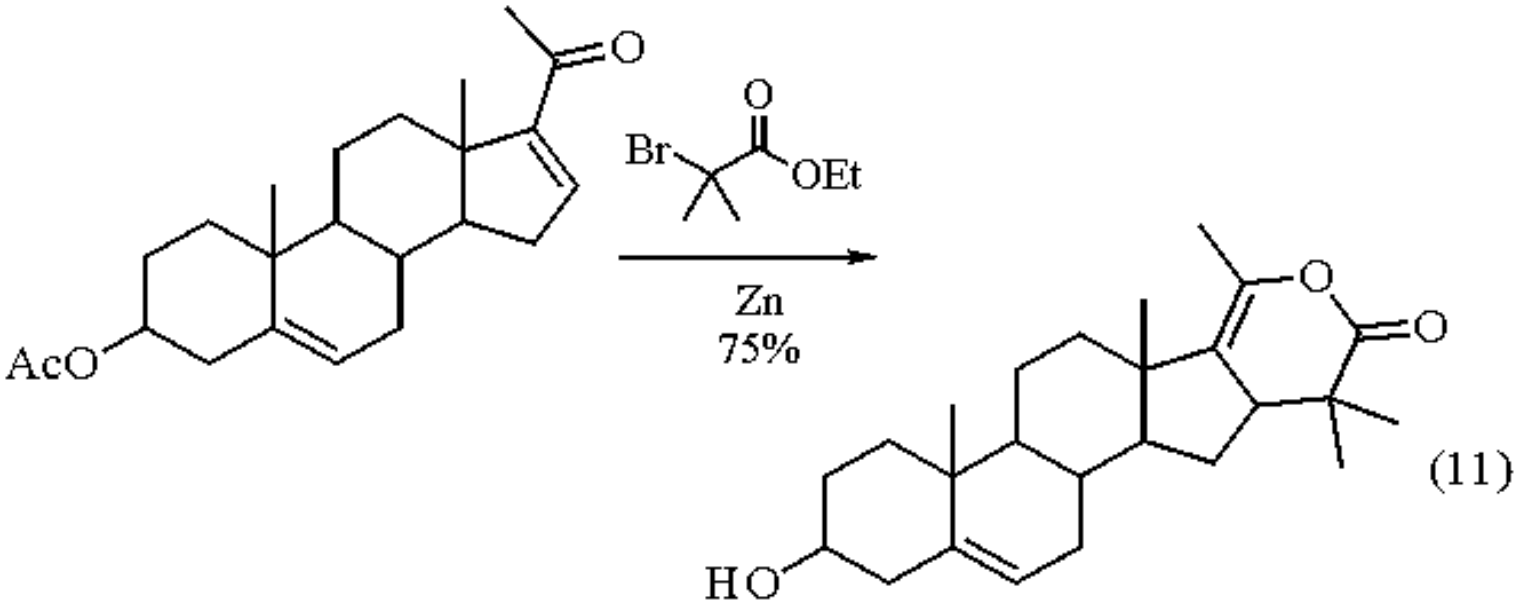

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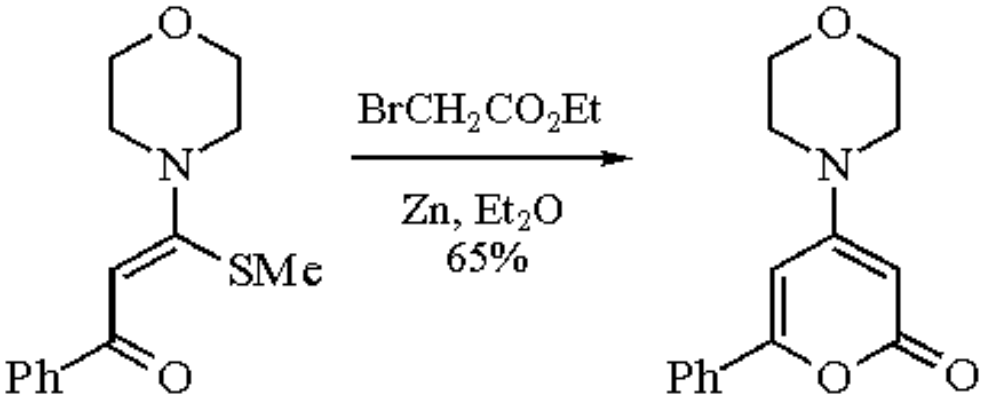

(12)

However, other kinds of electrophiles are also good acceptors for Reformatsky reagents, such as nitriles (sometimes called

the Blaise reaction) (eq 13),[31,4b] azomethines (preferably via the two-step procedure giving rise to β-lactams) (eq 14),[32] and carboxylic acid chlorides (with assistance of catalytic amounts of Pd^0 complexes) (eq 15).[31c,33] Alkylation of zinc ester enolates, however, is troublesome and restricted to short-chain alkyl iodides, allyl and benzyl halides in aprotic dipolar solvents.[2,34] Under transition metal catalysis they also react with aryl and alkenyl halides or triflates.[35] *C*-Silylation of the zinc enolates by ***Chlorotrimethylsilane*** is essentially confined to bromoacetate (eq 16)[36] and haloacetonitrile.[37]

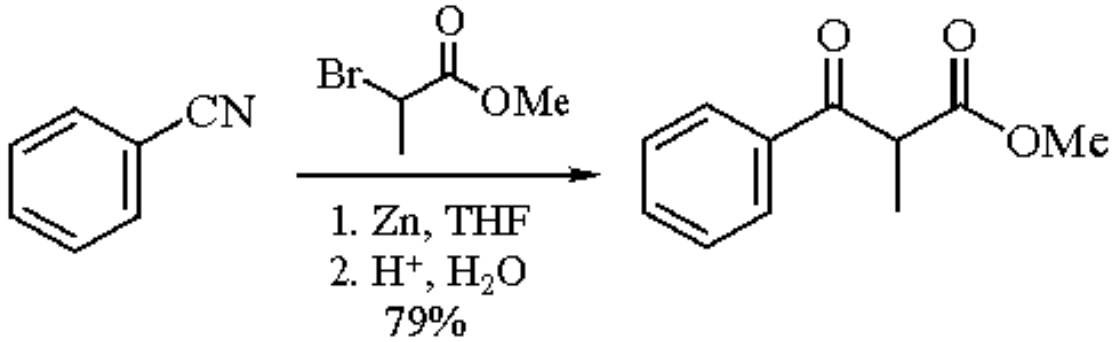

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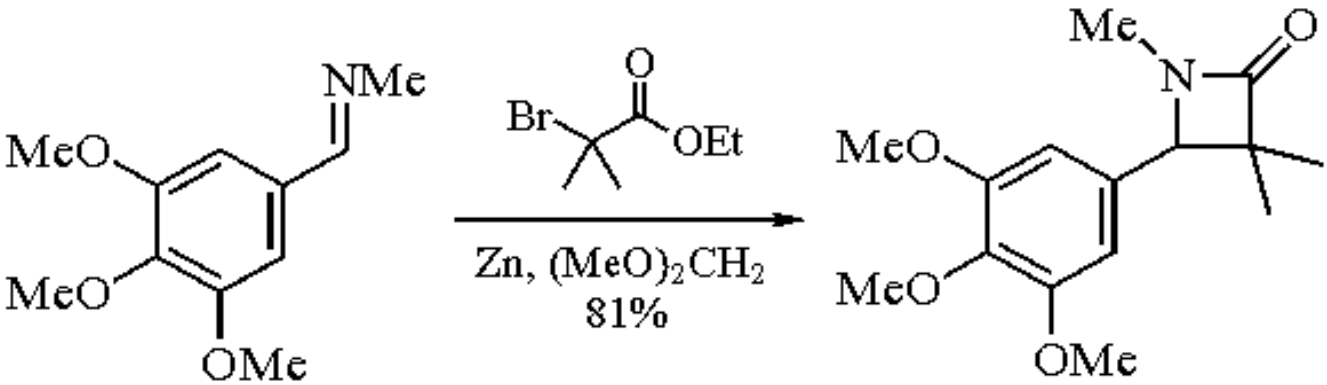

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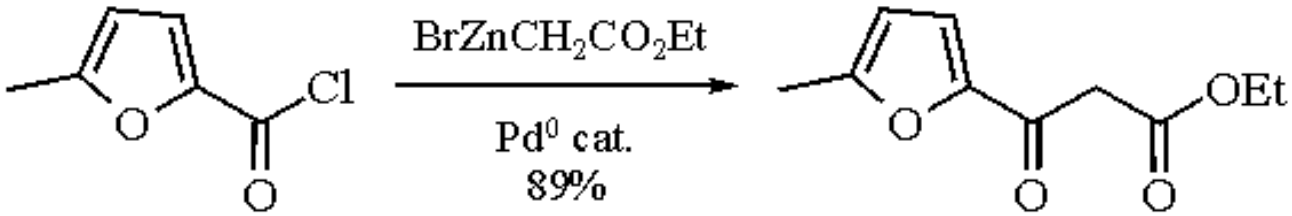

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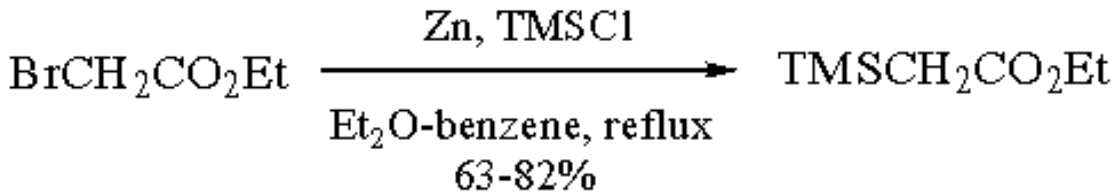

(16)

The slightly different reactivity of zinc enolates towards the aforementioned types of electrophiles allows chemoselective transformations of di- or polyfunctional substrates. Although in unsymmetrical diketones no differentiation among the carbonyl groups was reported, keto nitriles, keto amides, keto esters, or halogenated ketones may be attacked exclusively at the carbonyl group.[1]

Recent investigations show that 3-acyloxazolidin-2-ones or 3-acylthiazolidine-2-thiones constitute a promising group of acyl donors for zinc enolates (eq 17).[38] Different kinds of anhydrides (eq 18),[39] activated esters, and lactones,[40] including aldonolactones,[41] react smoothly with bromo esters under Reformatsky conditions. Particular emphasis is laid on the high

yield of β-amino esters by reaction of zinc enolates with different kinds of *N,O*-acetals and aminals (eq 19).[42] Oxocarbenium cations obtained by in situ activation of acetals with Lewis acids are equally suited as electrophiles in Reformatsky reactions (eqs 20 and 21).[43] A summary of reactions with electrophiles other than carbonyl compounds is given in the literature.[1]

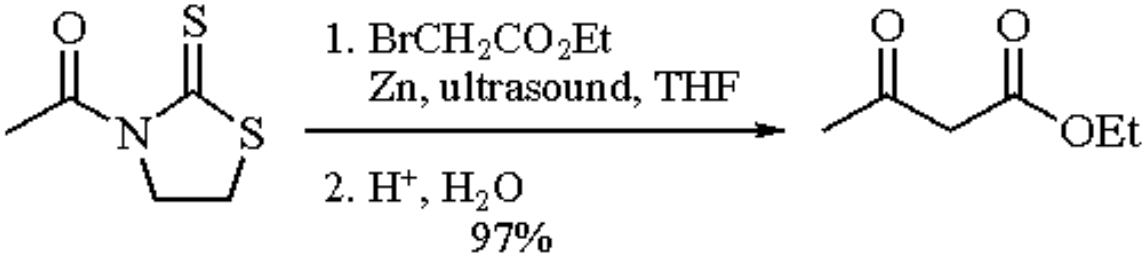

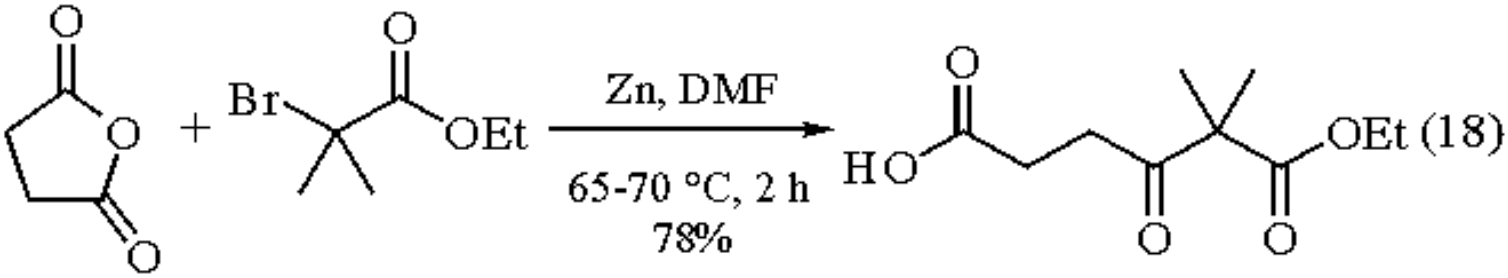

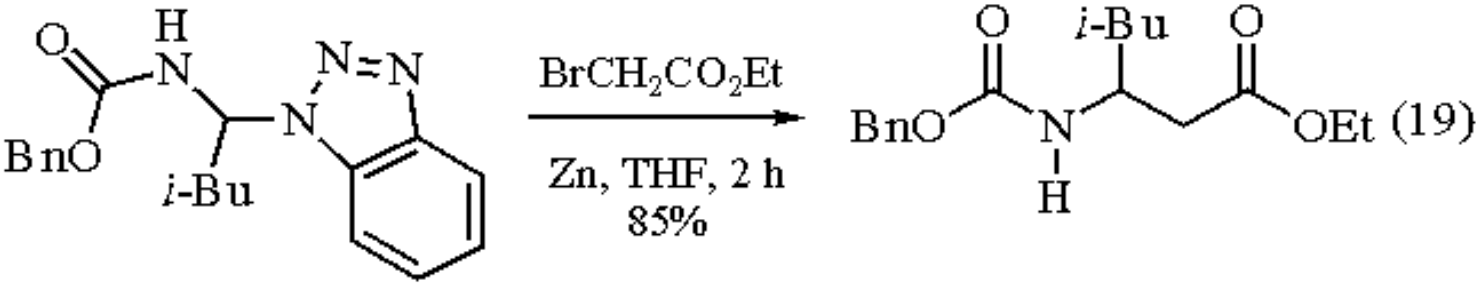

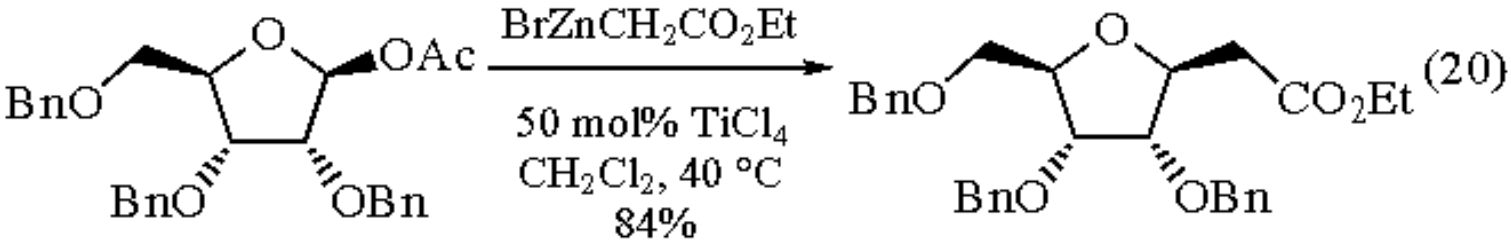

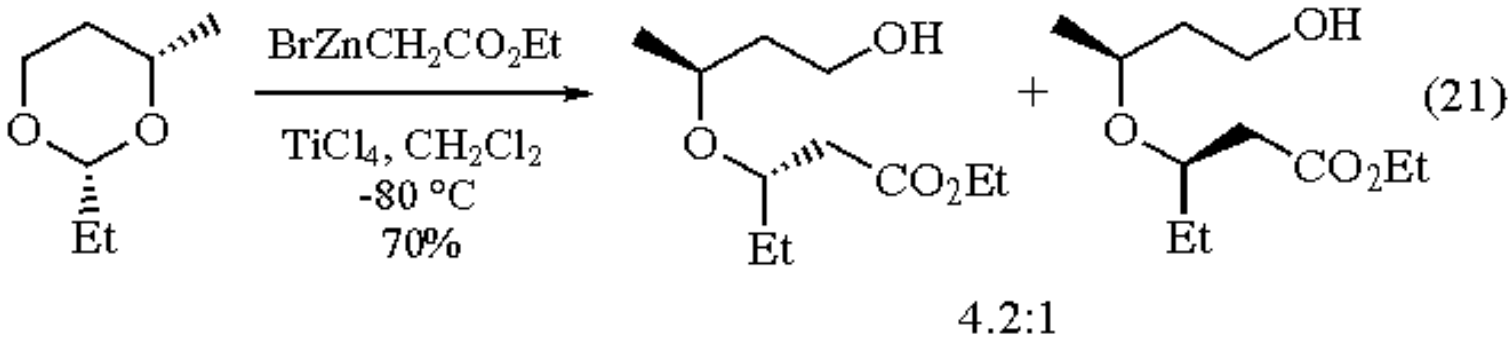

Intramolecular Reformatsky Reactions.

As the site of enolate formation is determined by the halogen moiety, Reformatsky reactions are well suited for intramolecular aldolizations. This is a major advantage since regioselective enolate formation by proton abstraction in polycarbonyl systems is a rather difficult task. Thus a homologous series of o-(α-bromoacetoxy)aldehydes has been cyclized to β-hydroxy lactones of ring size 13-16,[44] but smaller rings can also be formed in moderate to good yields.[45] This technique has been used in natural product synthesis (eq 22),[46] with the formation of the 11-membered ring of cyctochalasan being the most impressive example (eq 23).[47] Less conventional electrophiles such as nitriles[48] or imides[49] are equally well suited acceptors in entropically favored intramolecular reactions (eq 24).

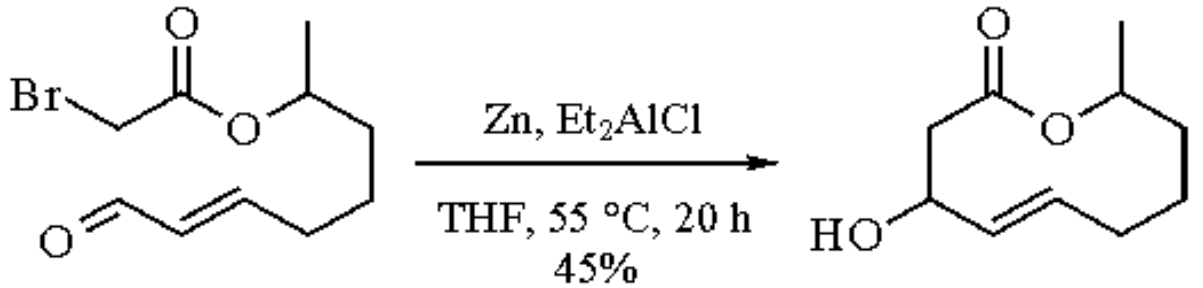

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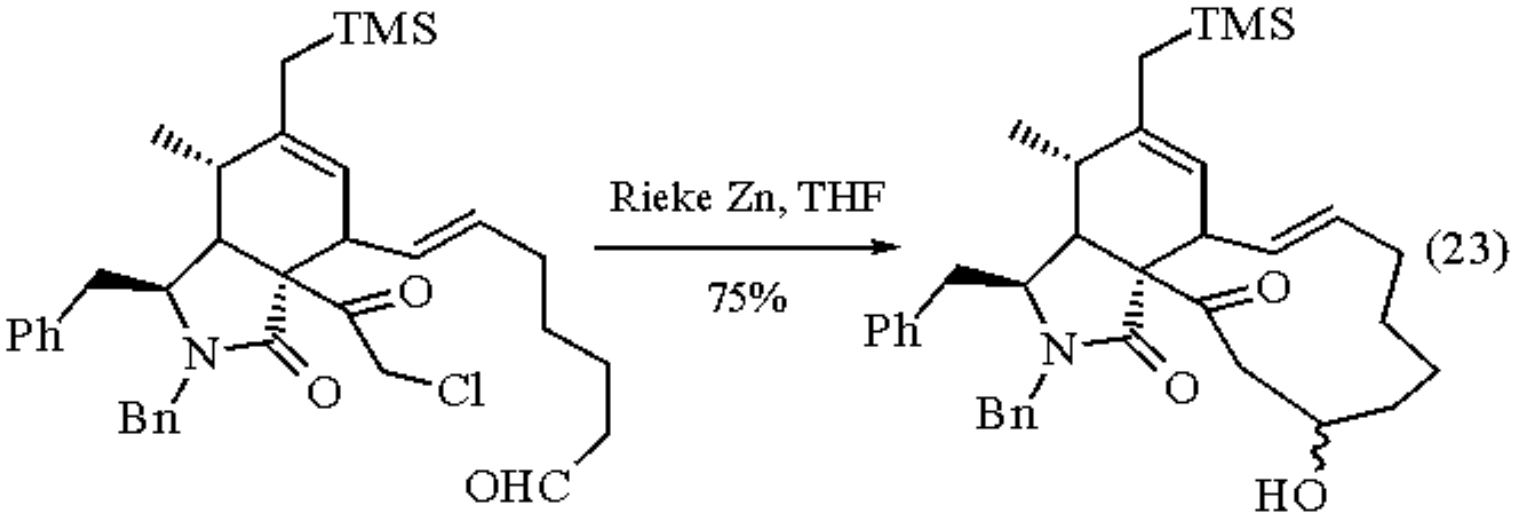

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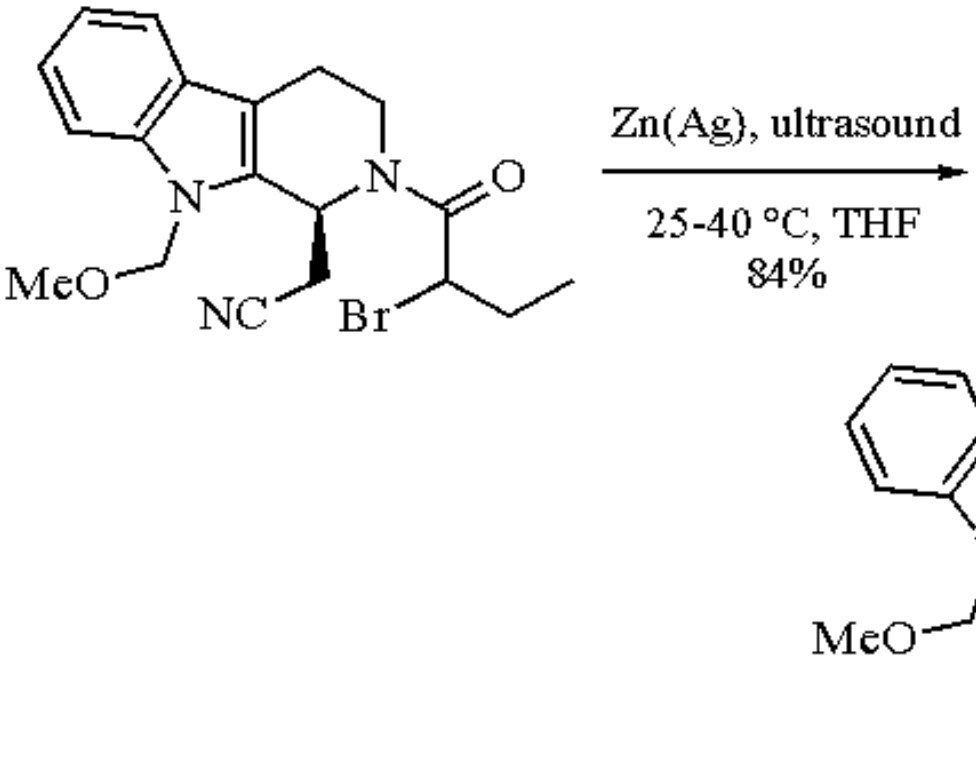

(24)

Samarium(II) Iodide as substitute for metallic zinc turned out to be highly advantageous in promoting such cyclizations with formation of normal-, medium-, and large-sized ring systems (eq 25).[50,51] Furthermore, high degrees of diastereocontrol may be exercised via the formation of rigid transition states with the strongly chelating Sm^{3+} counterion.[51]

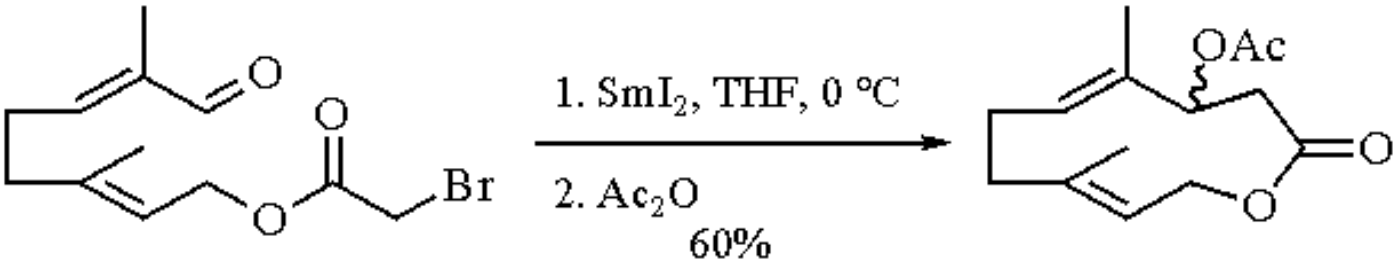

(25)

Tandem Reaction.

Due to their high tolerance towards different functional groups, zinc enolates are predisposed for reaction sequences. The selective formation of either a carbocyclic or a heterocyclic ring from nitriles bearing an additional halo or sulfonyloxy group within the molecule is an illustrative example of how to impose control on such reaction tandems (eq 26).[52] In this specific case, the hard-soft acid-base (HSAB) principle determines whether the intermediate zinc enamides are *N*-alkylated (X = OSO_2Me) or *C*-alkylated (X = Br). Moreover, *O*-TMS cyanohydrins serve for lactone syntheses in a one-pot procedure.[31c]

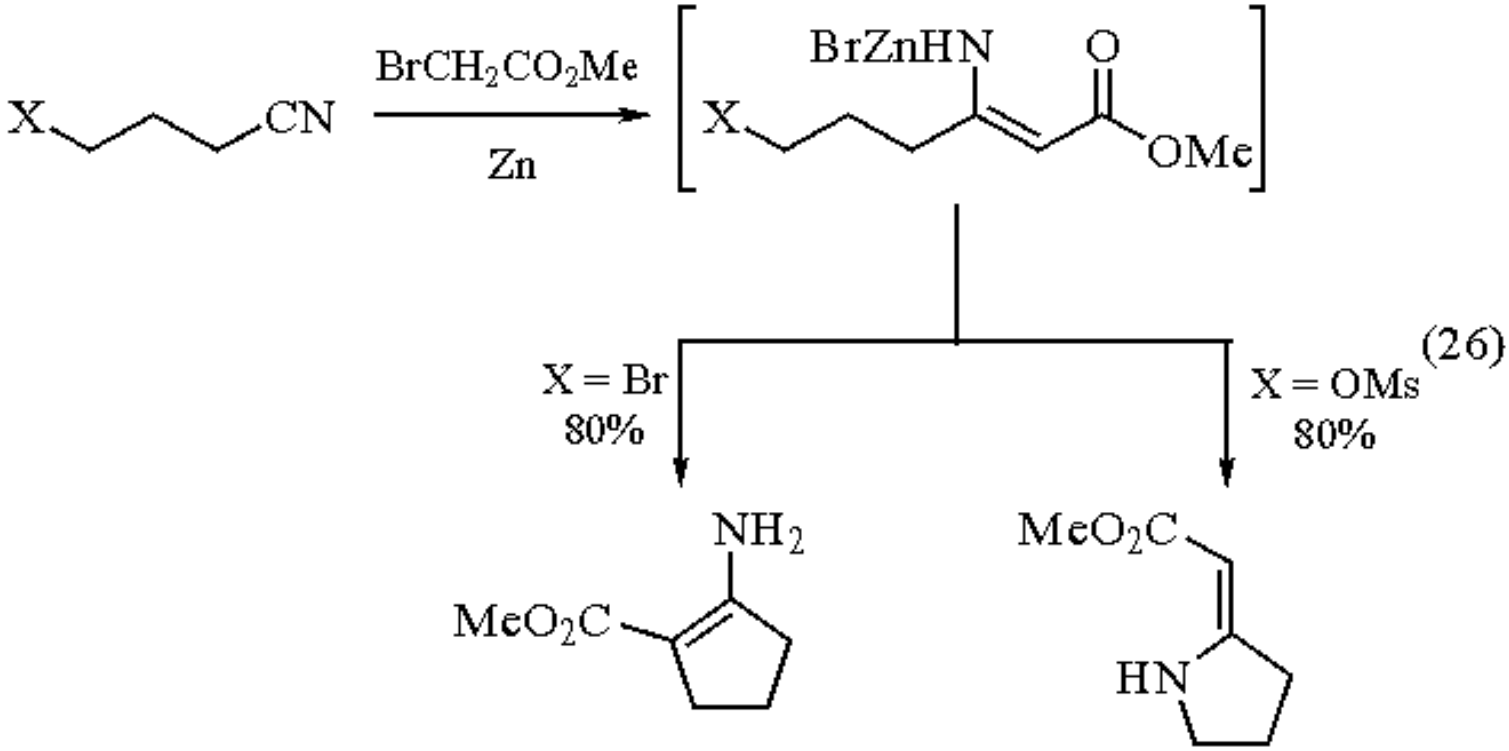

(26)

Under the rather drastic conditions of conventional Reformatsky reactions (reflux in ethereal or hydrocarbon solvents), the β-hydroxy esters formed may suffer subsequent dehydration in an unselective way. The use of α-silylated Reformatsky donors or of α-silyl ketones shows how to control the regioselectivity of the elimination step.[16,27a] Thus sequences of Reformatsky reactions followed by (in part spontaneous) Peterson eliminations determine the regiochemistry of the newly formed double bond (eqs 27 and 28). When bromo(trimethylsilyl)acetonitrile is used as donor, high to complete (*Z*) selectivity for the α,β-unsaturated nitriles obtained was reported.[53]

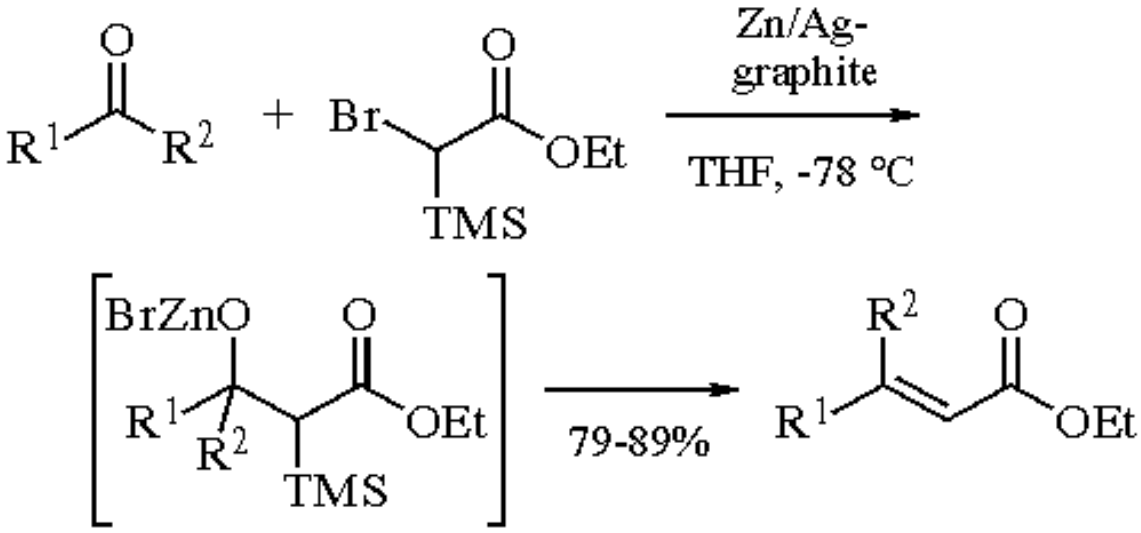

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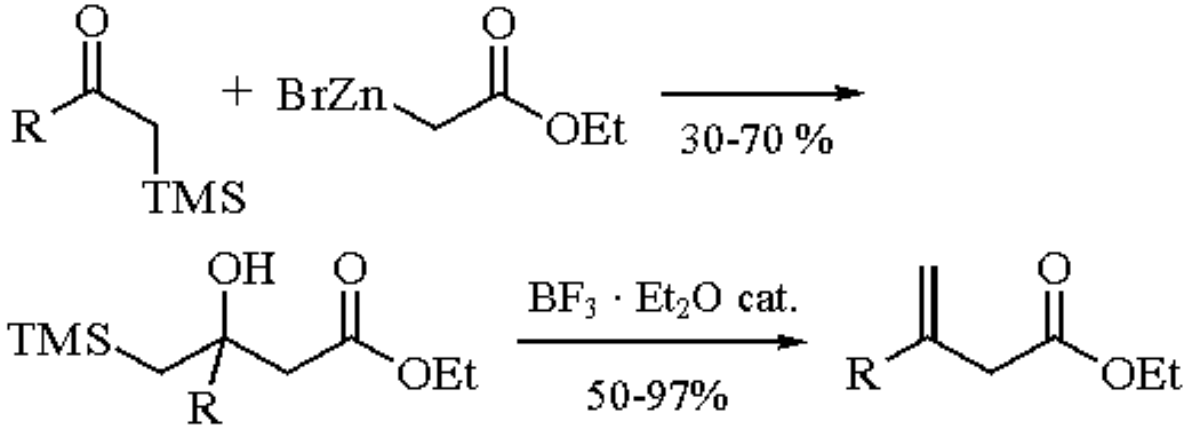

(28)

A sequence of an intramolecular Reformatsky reaction with a 2,5-dibromopentanoate donor, followed by etherification of the intermediate zinc aldolate with the terminal bromo group in the presence of HMPA, was ingeniously used to build-up the tricyclic skeleton of daphnilactone and related molecules starting from rather simple precursors (eq 29).[54]

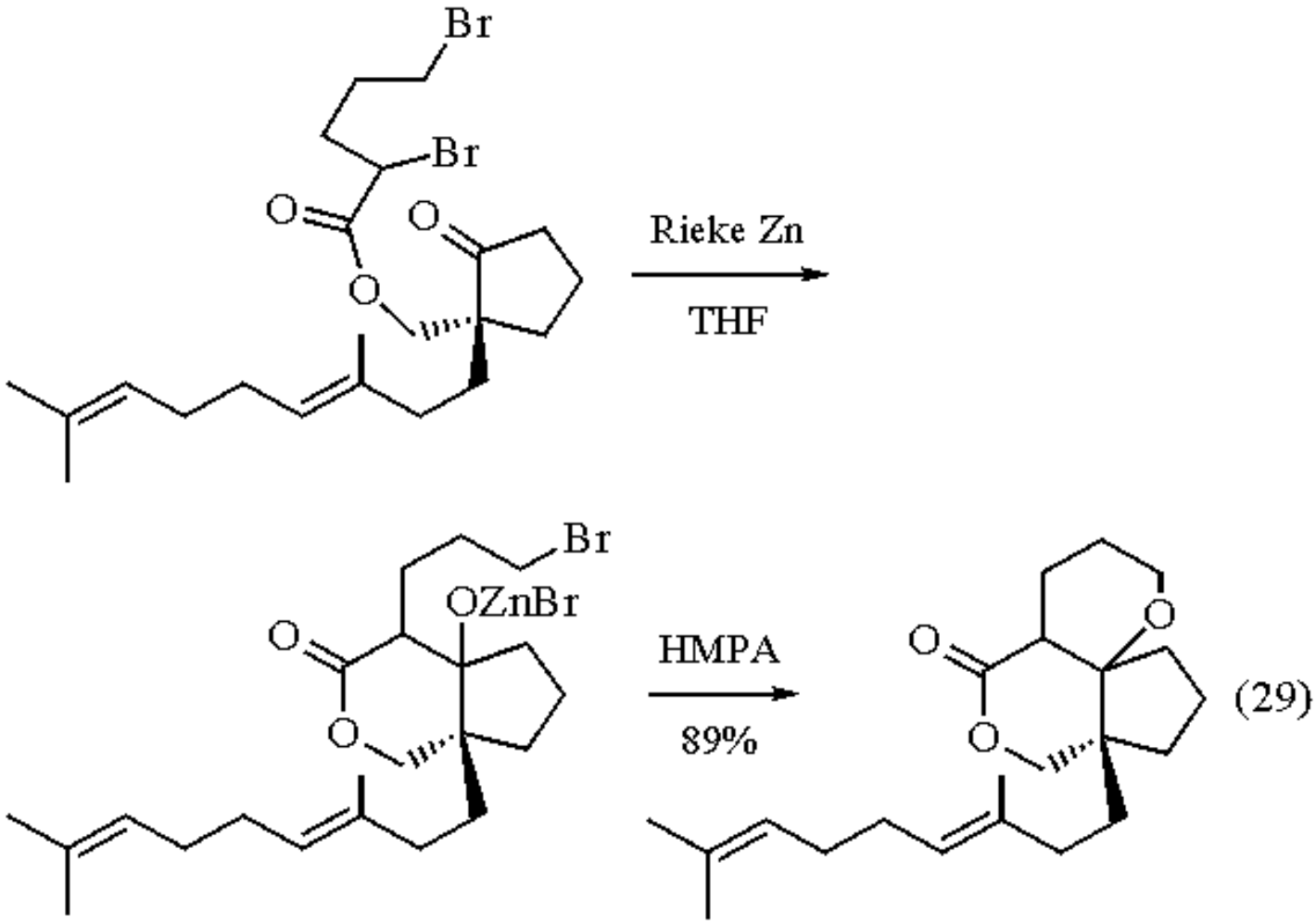

(29)

2-Oxoglycosyl bromides upon treatment with zinc give rise to carbohydrate intermediates with an umpoled anomeric center; the aldolate initially formed on reaction with excess ***Formaldehyde***, together with the residual ketone group on the sugar, trap a second aldehyde molecule with formation of a stable lactol ring (eq 30).[55]

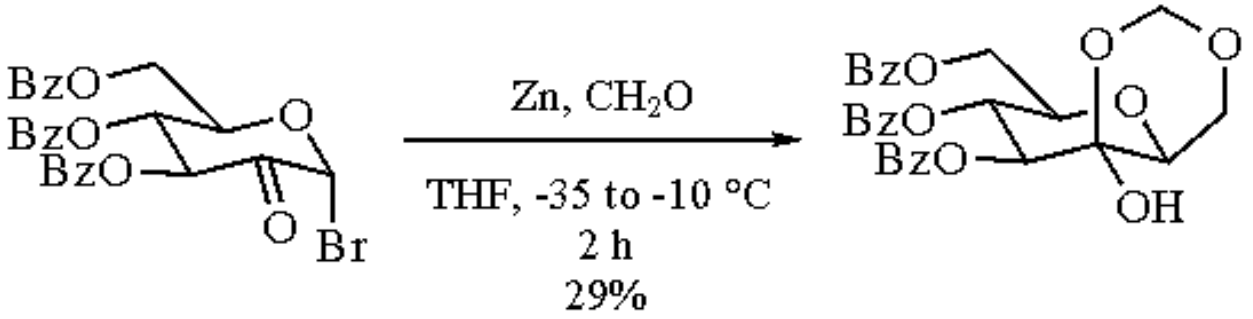

(30)

Stereoselectivity.

A general method for highly diastereo- and enantioselective Reformatsky reactions is still missing. Some of the approaches described so far take advantage of the known propensity of zinc(II) to bind to nitrogen donor atoms which may be present in either one of the substrates or in a ligand added to the reaction mixture. With amino carbonyl compounds as electrophiles, for example, highly stereoselective additions are usually observed, and a direct relationship between the complexing ability of the amino group (location, basicity of the N atom) and the de values for the products obtained has been established.[56] A nice illustration of how uncommon electrophiles can be used to prepare enantiomerically enriched products is the ring-opening of enantiomerically pure oxazolidines by zinc ester enolates to β-amino esters, proceeding with inversion of the configuration at the *N*,*O*-acetal carbon atom (eq 31).[57]

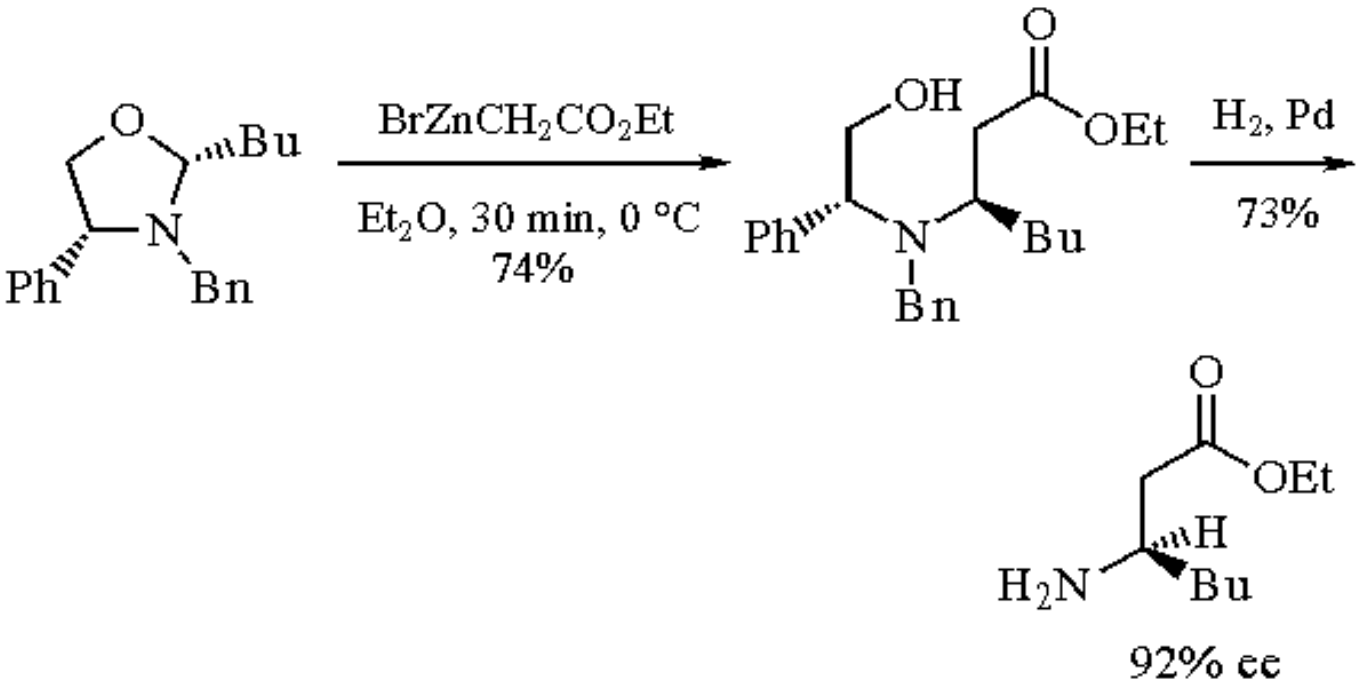

(31)

A means to achieve excellent diastereoselectivity in reactions of *ortho*-substituted benzaldehyde derivatives is the π-face selective attack of a zinc ester enolate on the corresponding tricarbonylchromium complexes (eq 32).[58]

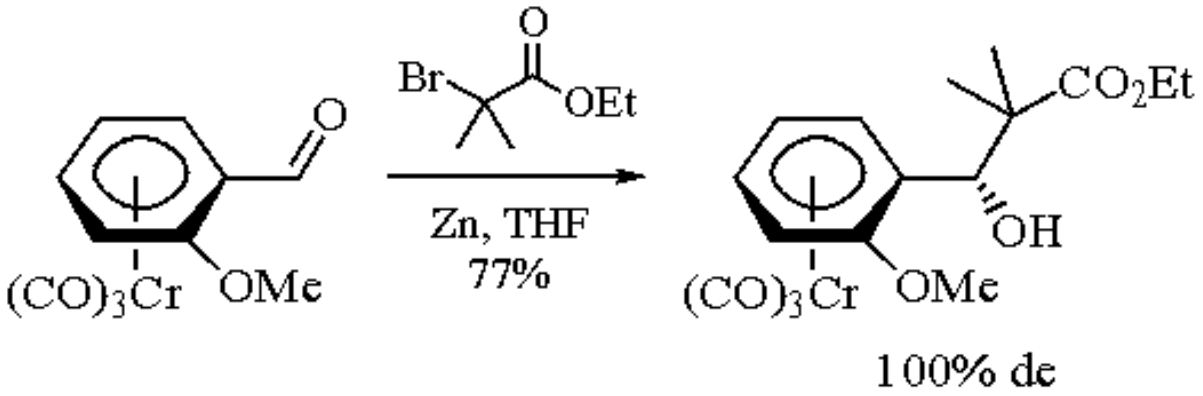

(32)

Preparatively useful degrees of diastereoselectivity have been observed with *N*-(α-bromoacyl)oxazolidinones[59] and/or with metals other than zinc exhibiting higher chelating abilities. For intramolecular reactions, SmI_2 served this purpose very well, because of the rigidity of a Sm^{3+}-chelated bicyclic transition state (eq 33).[51] An Evans-type auxiliary together with activated tin as promotor for the Reformatsky reaction have been employed in a diastereoselective approach to neooxazolomycin (eq 34).[60] With a few exceptions only, induction by chiral alcohol components in α-bromo esters is rather low[61] and until now hardly competitive with today's state of the art in aldol reactions.

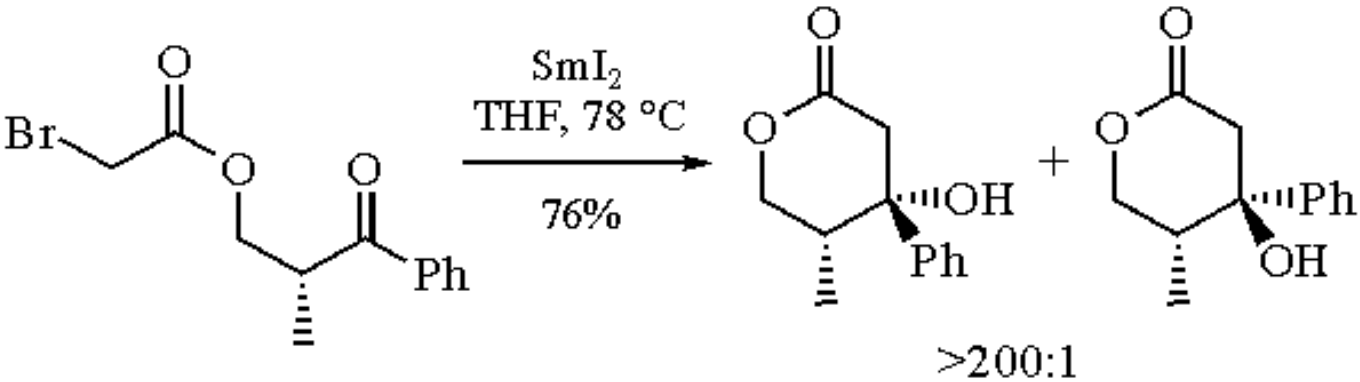

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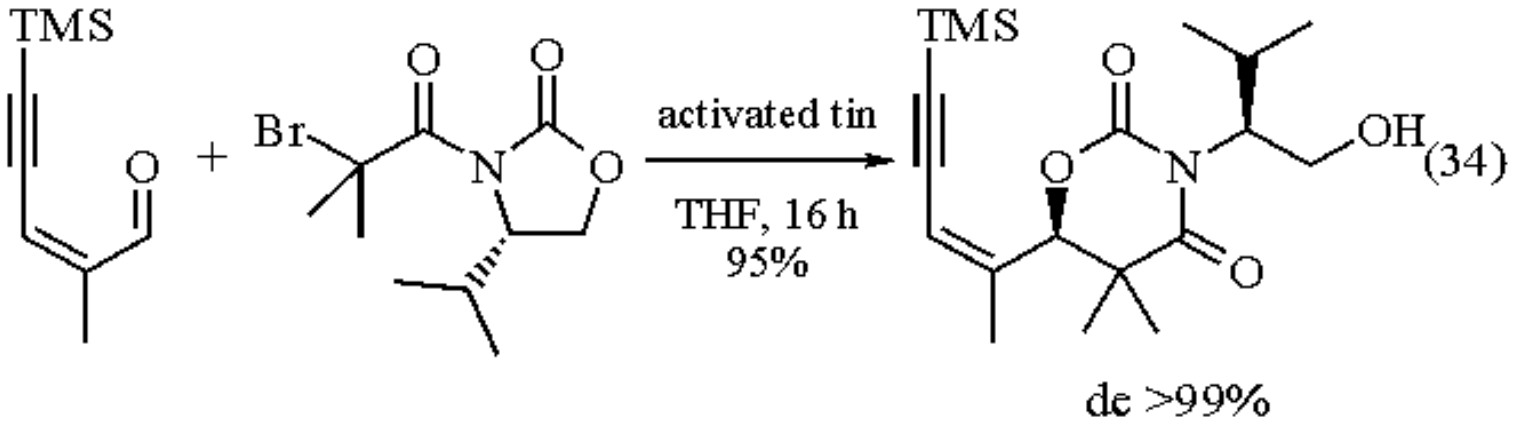

(34)

In addition to some early reports with (-)-spartein as chiral ligand,[62] promising results of enantioselective zinc- or indium-induced reactions of haloacetates with carbonyl compounds in the presence of chiral amines or amino alcohols as ligands to the metal have been published recently (eq 35).[63]

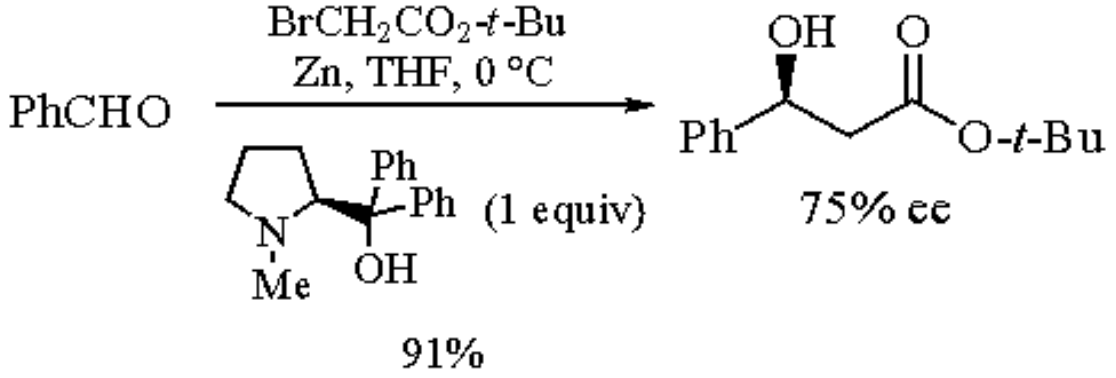

(35)

Substitution of Zinc by Other Metals.

Oxidative addition into an activated carbon-halogen bond with formation of enolates is by no means restricted to metallic zinc.[1] Low-valent metal salts of adequate reduction potentials such as ***Samarium(II) Iodide***[41d,64,50,51] or ***Chromium(II) Chloride***[65] are equally suited. A great deal of work has been carried out with more or less activated forms of ***Magnesium***,[66] ***Tin***,[67] ***Nickel***,[68] ***Cerium***,[69] ***Indium***,[70] manganese,[71] and cadmium[72] as promotors for Reformatsky-type reactions. Although in specific cases advantages such as increased diastereoselectivity could be drawn from their use, only SmI_2 and to some extent cerium and indium (both are effective with the more reactive α-iodo esters) show reasonable scope. Some representative examples are compiled in Table 2.

Table 2 Reformatsky Reactions with Substitutes for Zinc

Donor	Electrophile	Metal	T(°C)	t(h)	Yield (%)
$BrCH_2CO_2Et$[72]	Cyclohexanone	Cd[a]	35	24	100
ICH_2CO_2Et[70a]	Cyclohexanone	In	20	1.5	65
$BrCH_2CO_2Et$[69]	Benzaldehyde	Ce/Hg	20	17	49
ICH_2CO_2Et[69]	Benzaldehyde	Ce/Hg	0	3.5	81
$BrCH_2CO_2Et$[69]	Acetophenone	Ce/Hg	20	46	60
$BrCH_2CO_2Et$[67]	Benzaldehyde	Sn[b]	25	2	84
$BrCH_2COPh$[67]	Benzaldehyde	Sn	- 23	2	63
$BrCH_2CN$[68]	Benzaldehyde	Ni[c]	85	0.7	84
$BrCH(Me)CO_2Et$[64a]	Cyclohexanone	SmI_2	d	d	90
$BrCH_2COPh$[64b]	Benzaldehyde	SmI_2	20	1	75

[a] Rieke Cd. [b] Activated Sn obtained by reduction of $SnCl_2$; only 6%

[a] Rieke Cd. [b] Activated Sn obtained by reduction of $SnCl_2$; only 6% yield with commercial Sn dust in DMF. [c] Rieke Ni. [d] Not reported.

Related Reagents.

t-Butyl Chloroacetate; ***t-Butyl α-Lithioisobutyrate***; ***Dilithioacetate***; ***Ethyl Lithioacetate***; ***Methyl Bromoacetate***; ***Methyl 4-Bromocrotonate***; ***Methyl Chloroacetate***; ***Potassium-Graphite***; ***Zinc***; ***Zinc/Copper Couple***; ***Zinc-Graphite***; ***Zinc/Silver Couple***; ***Zinc-Zinc Chloride***.

---

1. (a) Fürstner, A. *S* **1989**, 571. (b) Rathke, M. W.; Weipert, P. D. *COS* **1991**, *2*, 277. (c) Rathke, M. W. *OR* **1975**, *22*, 423. (d) Shriner, R. L. *OR* **1942**, *1*, 1. (e) Gaudemar, M. *Organomet. Chem. Rev. A* **1972**, *8*, 183. (f) Nützel, K. *MOC* **1973**, *XIII/2a*, 805.
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Ethyl 4-Chloroacetoacetate[1]

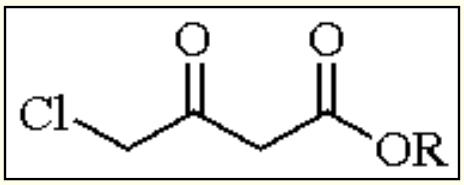

(**1a**; R = Et)

[638-07-3] · $C_6H_9ClO_3$ · Ethyl 4-Chloroacetoacetate · (MW 164.60) (**1b**; R = Me)

[32807-28-6] · $C_5H_7ClO_3$ · Methyl 4-Chloroacetoacetate · (MW 150.57) (**1c**; R = *i*-Pr)

[41051-20-1] · $C_7H_{11}ClO_3$ · Isopropyl 4-Chloroacetoacetate · (MW 178.63) (**1d**; R = *t*-Bu)

[74530-56-6] · $C_8H_{13}ClO_3$ · *t*-Butyl 4-Chloroacetoacetate · (MW 192.66)

(highly functionalized four-carbon building block for organic synthesis[1])

Physical Data: (**1a**) mp -8.5 °C; bp 95 °C/10 mmHg; fp 92 °C; *d* 1.212 g cm^{-3}. (**1b**) mp 14 °C; bp 50 °C/1 mmHg; fp 107 °C; *d* 1.287 g cm^{-3}. (**1c**) mp 10 °C; bp 64 °C/1.65 mmHg; fp 86 °C; *d* 1.152 g cm^{-3}. (**1d**) bp 101 °C/15 mmHg; fp 41 °C; *d* 1.130 g cm^{-3}.

Form Supplied in: the alkyl 4-chloroacetoacetates are colorless liquids.

Solubility: sol most organic solvents. The ethyl ester (**1a**) is 12% enolized in the pure liquid, and highly enolized (60% in CCl_4) in nonpolar solvents.[2]

Preparative Methods: the industrial production of the esters is made exclusively by chlorination of diketene followed by reaction of the intermediate acid chloride with the corresponding alcohol.[3]

Handling, Storage, and Precautions: these reagents are lachrymators of moderate toxicity; use in a fume hood.

Reactivity.

The 4-chloroacetoacetates with their four reactive carbon centers offer diverse synthetic possibilities, and their reactions may be subdivided into those occurring at the 1-, 2-, 3-, or 4-positions, and various combinations of these

with di- and trifunctional reagents to give ring formation.

Reactions at the 1-Position.

Reactions of nucleophiles at this position are of minor importance. Hydrolysis produces 4-chloroacetoacetic acid which on nitrosation gives 3-chloropyruvaldoxime, useful for the synthesis of 6-substituted pteridines.[4]

Reactions at the 2-Position.

Electrophiles readily react at position 2. Chlorination with ***Sulfuryl Chloride*** represents a good route for the synthesis of 3-chlorotetronic acid.[5] Nitrosation is best carried out under acidic conditions to form the (*Z*)-oxime (**2**). This may be isolated[6] or reacted directly in situ with thiourea to form the 2-aminothiazole (**3**) (eq 1),[7] which is an important intermediate for the side chain synthesis of many β-lactam antibiotics.

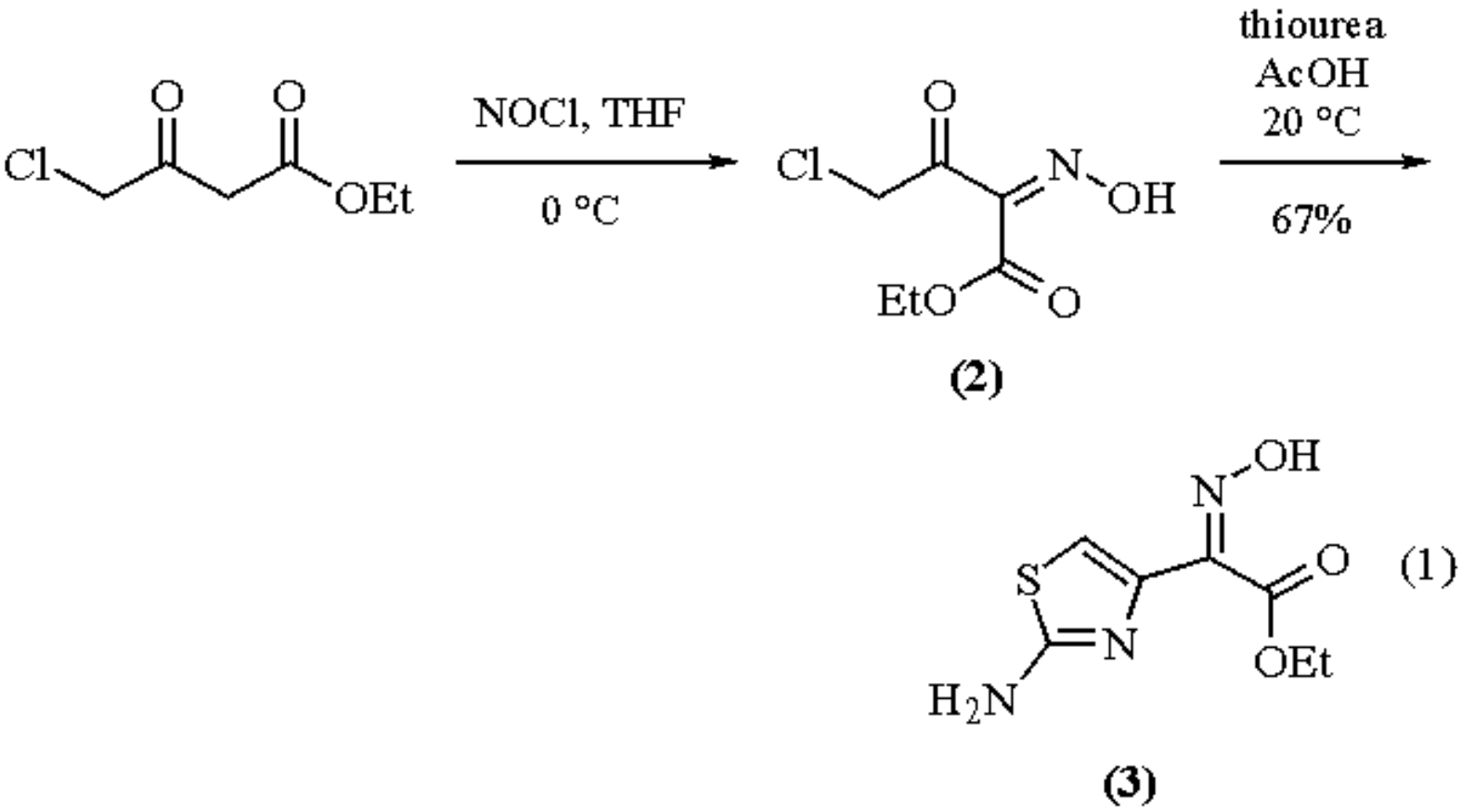

The combined effect of trimethyl orthoformate (see ***Triethyl Orthoformate***) and aniline results in the formation of the *N*-substituted methylene compound (**4**) (eq 2).[8]

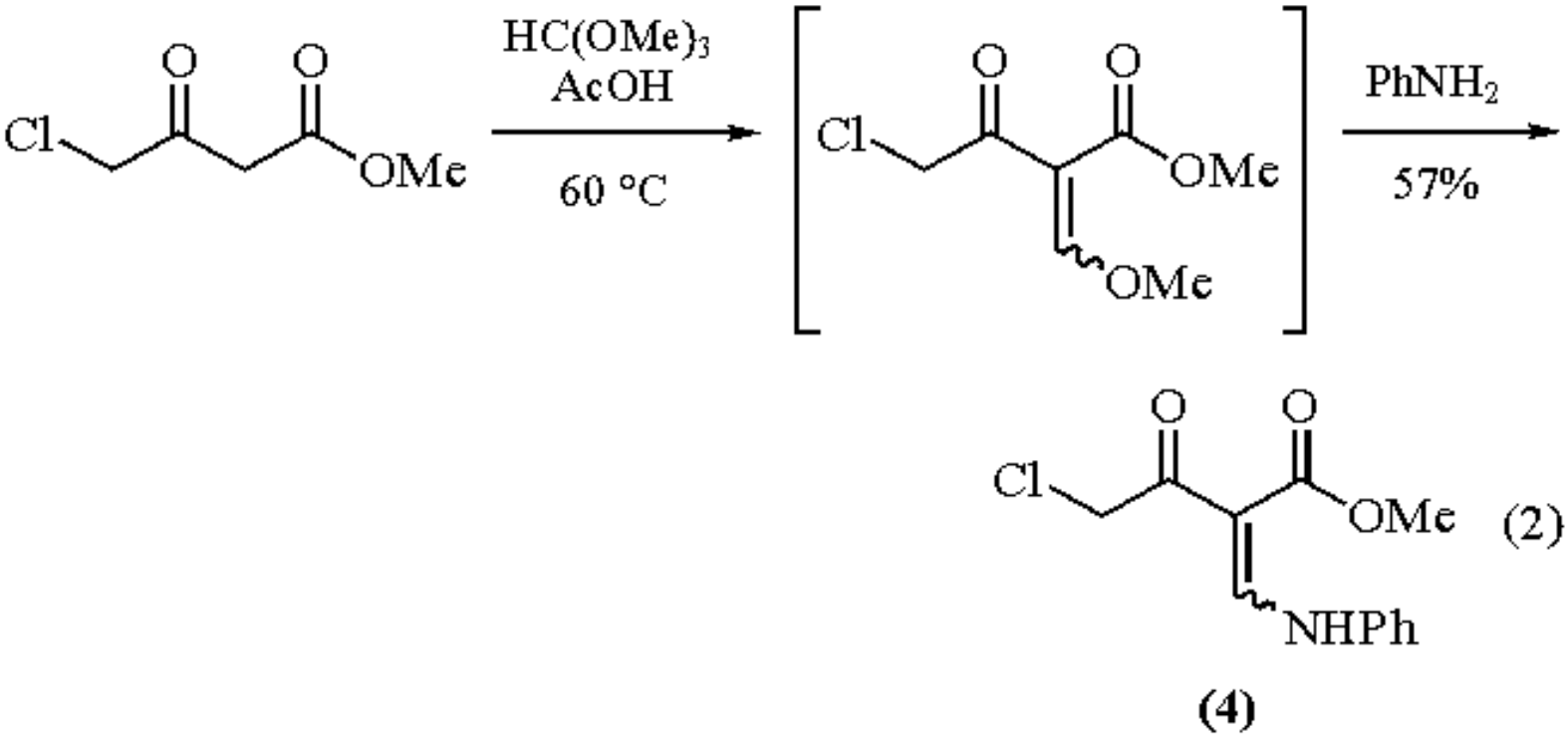

In the reaction with fluorosulfonyl isocyanate (see ***Chlorosulfonyl Isocyanate***), initial attack occurs at the oxygen atom and then at higher temperatures the enol-carbamate intermediate rearranges to give the 2-substituted product (**5**). This on further heating decarboxylates to yield the acetoacetamide (**6**) (eq 3),[9] useful for the preparation of acesulpham sweetener analogs.

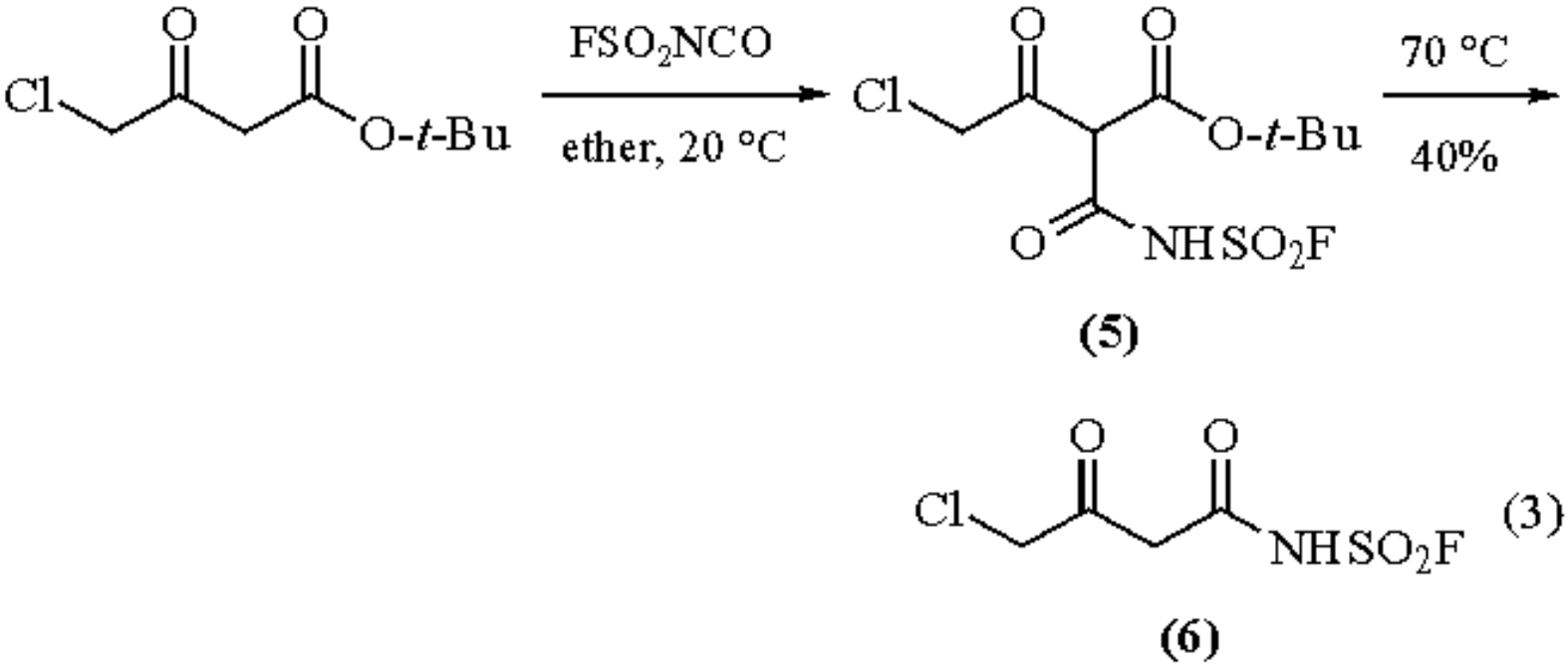

With less reactive electrophiles the enolate salt of (**1a**) is used (e.g. alkylation[10]). If deprotonation of (**1a**) (pK_a 9.7) is incomplete then dimerization occurs through intermolecular self-alkylation to give 2,5-dialkoxycarbonylcyclohexane-1,4-dione.[11] Aldehydes condense in the Knoevenagel reaction and the intermediate unsaturated ketones (**7**) are used in the Hantzsch synthesis of dihydropyridines (**8**) (eq 4).[12]

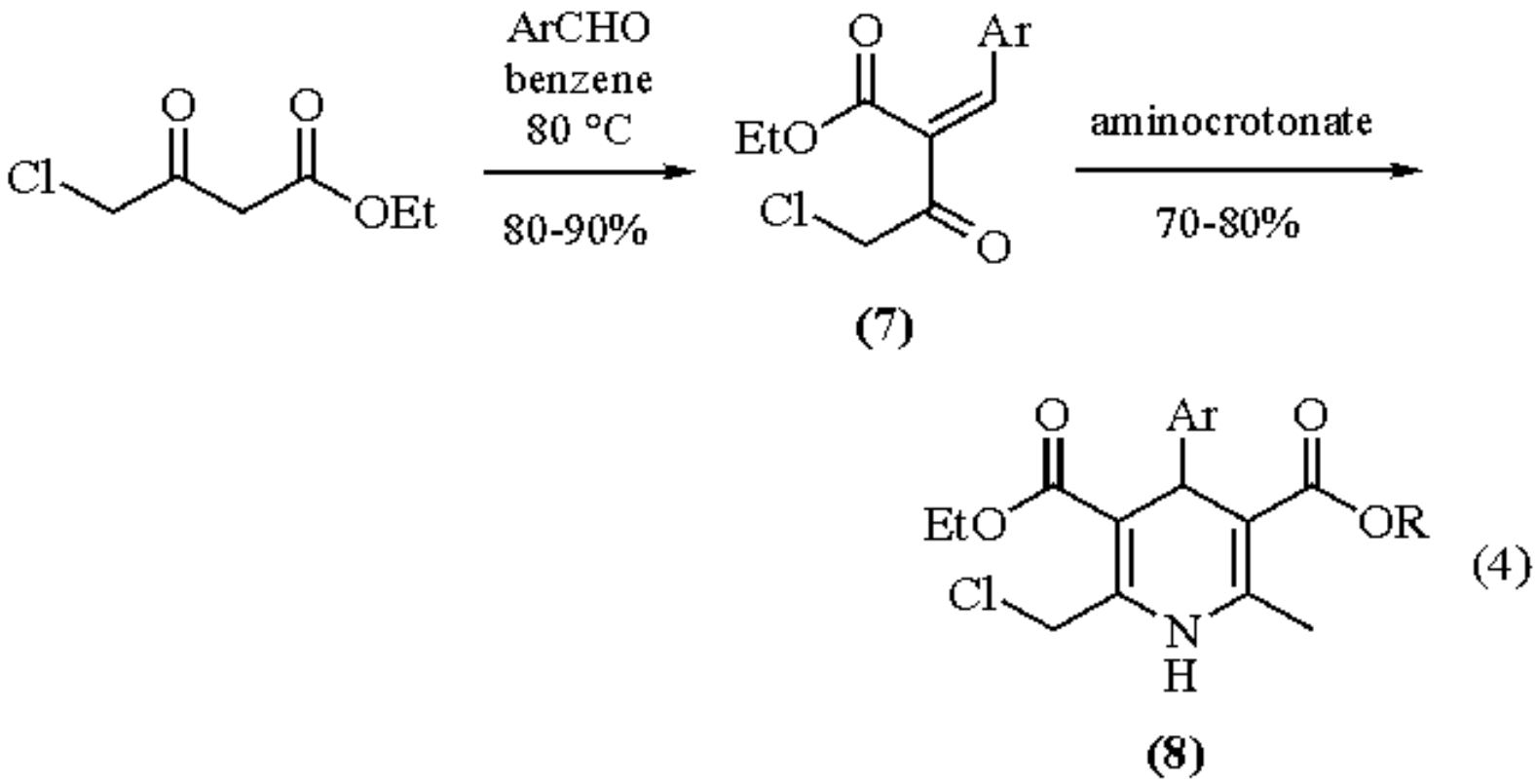

Reactions at the 3- and 4-Positions.

In general, soft nucleophiles react at position 4 and hard nucleophiles react at position 3. For selective reactions at position 4 it may be necessary to protect position 3.

Reactions at Position 4.

Aliphatic[13a] and aromatic[13b] thiolate anions and ***Potassium Thiocyanate***[13c] substitute readily, but with anionic oxygen nucleophiles the substitution is made on the acetoacetate enolate. The 4-*t*-butoxy derivative is used for the preparation of ethyl 4-*t*-butoxy-3-hydroxybutanoate (**9**), a versatile chiral building block (eq 5).[14]

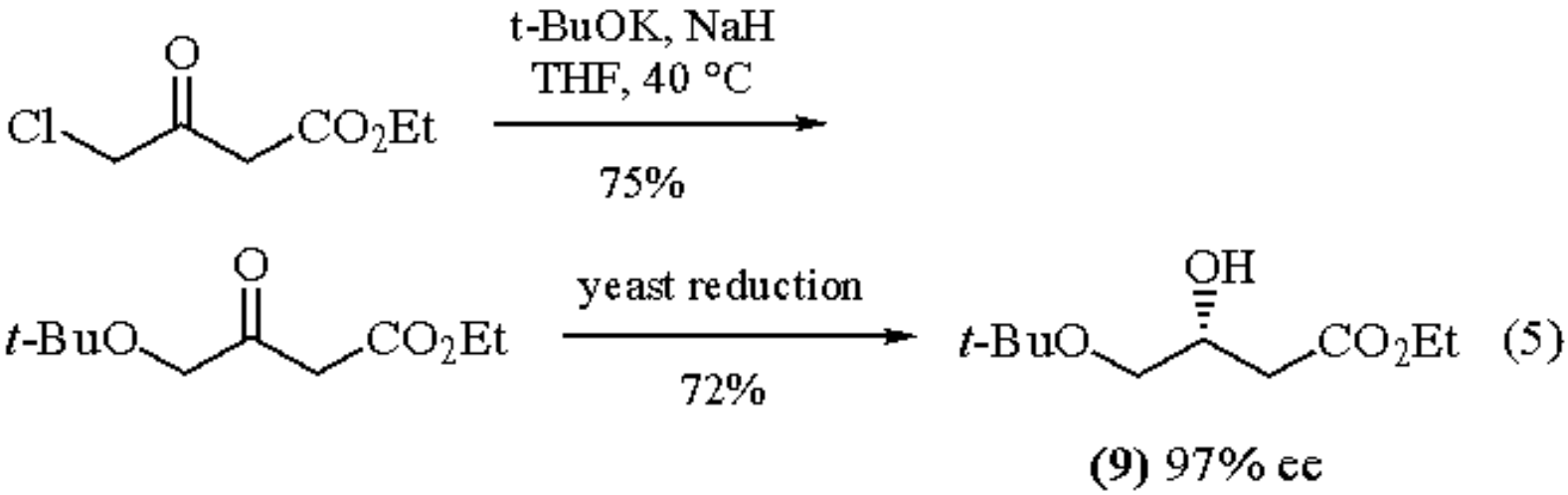

Substitution with tertiary amines proceeds readily, and the reaction with ***Trimethylamine*** provides a synthetic route to carnitine.[15] Substitution with primary and secondary amines is best made after protection of the 3-position.

Reaction at Position 3.

Asymmetric reduction of the keto group is accomplished using the Noyori process,[16a] which allows synthesis of either the (*R*)- or (*S*)-4-chloro-3-hydroxybutanoate more efficiently than with biological methods.[16b] After formation of the acetal (**10**), selective substitution with hydroxylamine at the 1-position gives a synthetic route[17] to the isoxazole pantherine (**11**) (eq 6).

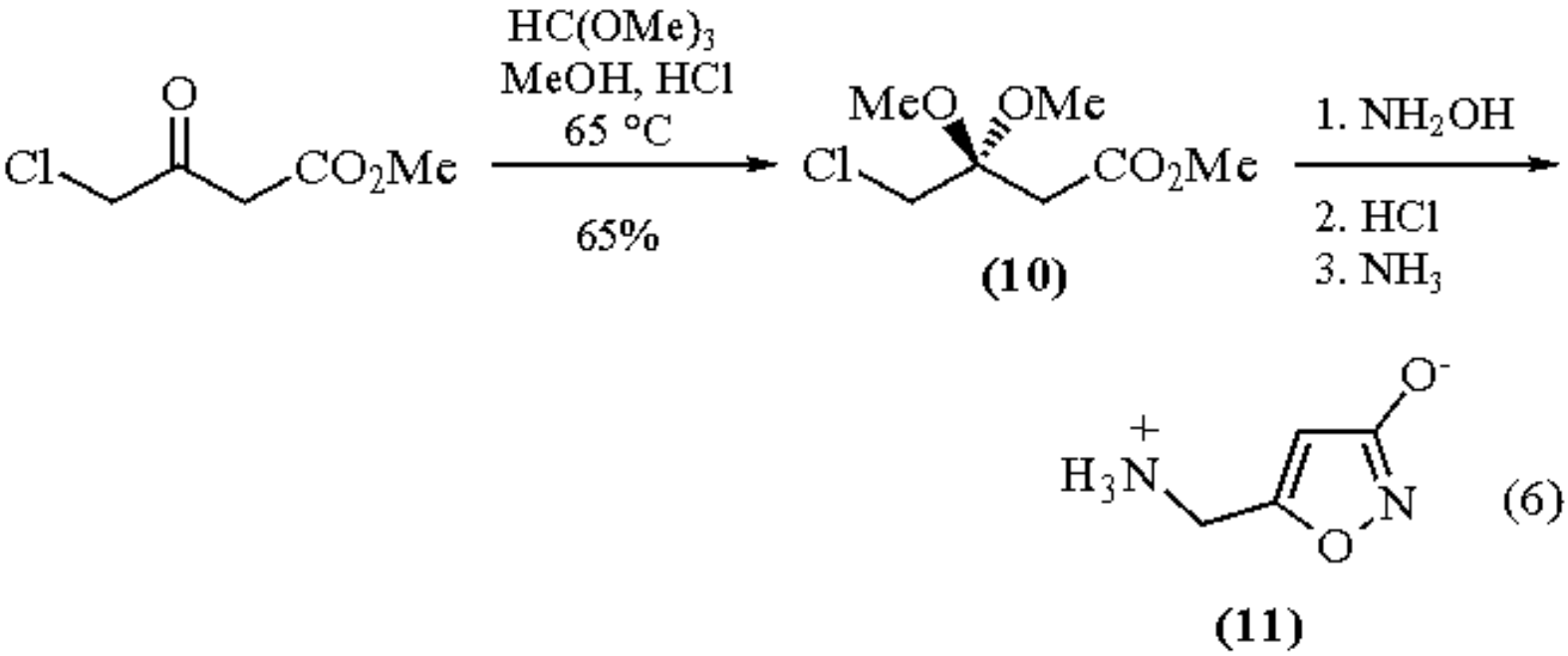

(6)

Acetal (**10**) can be directly converted to (*E*)-4-chloro-3-methoxy-2-butenoic acid ester (**12**). This compound is the reagent of choice for selective substitution at position 4.[18] With primary amines, cyclization to form tetramic acids (**13**) occurs (eq 7).

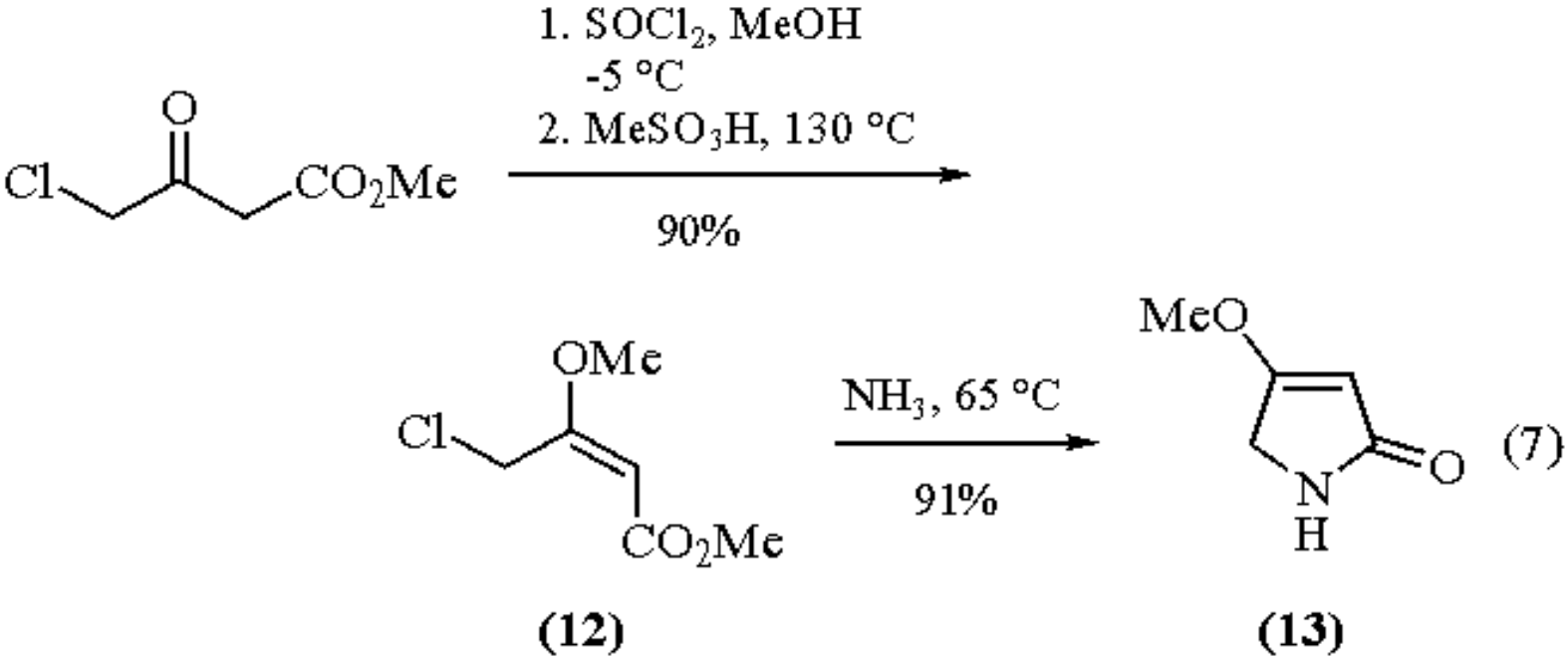

In contrast, the reaction of alkyl 4-chloroacetoacetates with weakly basic primary and secondary amines yields enamines;[19] the enamines from primary amines cyclize to give tetronic acids.[20] Enol ether (**12**) reacts with phosphites to produce Horner-Emmons reagents, useful for carbon chain extension after ylide generation with ***Sodium Hydride***.[18]

Ring-Closure Reactions.

When alkyl 4-chloroacetoacetates react with bifunctional reagents, various ring closures yielding heterocycles occur.

Retention of the Chloromethyl Group.

Cyclizations with hard dinucleophiles can occur between positions 1 and 3. Thus amidines yield pyrimidines[21] and carbamates give oxazinones.[23] In this category is the von Pechmann reaction with phenols, which produces coumarins.[22] Ring closure between positions 3 and 2 occurs with ***Chloroacetaldehyde*** under basic conditions to produce 3-alkoxycarbonyl-2-chloromethylfuran,[24] and the Hantzsch synthesis of dihydropyridines also falls in this category.

Loss of the Chloromethyl Group.

The reactions of alkyl 4-chloracetoacetate enolates with isocyanates and isothiocyanates give 2-aminofuranones[25] and 2-aminothiophenones,[26] respectively. Ring formation between the reactive 3- and 4-positions is well documented, whereby the soft nucleophilic center reacts at position 4. Amides, thioamides, and thiourea give the corresponding 4-oxazolyl- and 4-thiazolylacetic acid esters,[27] and 2-aminothiophenol produces a 3,4-dihydro-2*H*-1,4-benzothiazine.[28] Also, direct formation of an indole by reaction of an *N*-benzylaniline with (**1**) has been reported.[29]

Related Reagents.

Also available by bromination of diketene are the corresponding 4-bromoacetoacetates (methyl ester [*17790-81-7*]; ethyl ester [*13176-46-0*]), which find similar use in synthesis.[1] The 4-iodo- and 4-fluoroacetoacetates are known, but they are of minor importance. See also ***Acetoacetic Acid***; ***Diketene***; ***Ethyl Acetoacetate***; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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Barry Jackson

Lonza, Visp, Switzerland

Ethyl Chloroformate[1]

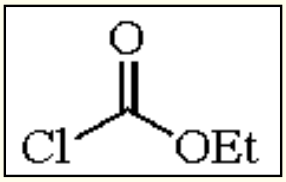

[541-41-3] · $C_3H_5ClO_2$ · Ethyl Chloroformate · (MW 108.52)

(for ethoxycarbonylation of a wide variety of nucleophiles including anions of carboxylic acids[4] and esters,[5] nitriles,[7] dithianes,[9] ketones, enamines,[10] imines,[11] sulfones,[12] cuprates,[13] stannanes,[14] Grignards,[15] alanes,[18] furans,[17] alkynes;[19] acylation of alcohols,[20,22] carbonyls,[23,25] amines, and aziridines;[27] cleavage of tertiary amines;[32] formation of mixed anhydrides[38])

Physical Data: mp -81 °C; bp 95 °C; *d* 1.135 g cm^{-3}.

Solubility: miscible with benzene, chloroform, diethyl ether, ethanol; insol water.

Form Supplied in: colorless liquid; widely available.

Purification: the liquid is washed with water then distilled at atmospheric pressure using an efficient fractionating column and $CaCl_2$ guard tube.[2]

Handling, Storage, and Precautions: slowly hydrolyzed by water to CO_2 and HCl; store at cool temperatures: pressure may develop within bottle; thermal decomposition to CO_2 and EtCl occurs; highly flammable (fp 2 °C); toxic by inhalation and skin absorption; lachrymatory, irritant; use in a fume hood.

Ethoxycarbonylation of Active Methylene Compounds.

Ethyl chloroformate[3] reacts with a wide range of nucleophiles. Enolates derived by deprotonation of aliphatic and aromatic carboxylic acids bearing at least one α-hydrogen with two equivalents of ***Lithium Diisopropylamide*** at low temperature in THF are ethoxycarbonylated to give the monoesters of malonic acids (eq 1).[4] The yields are highest for alkyl carboxylic acids at -78 °C.[5] Although higher yielding than with ***Diethyl Carbonate***, treatment of the α-lithiated esters with ***Carbon Dioxide*** frequently gives better yields of the malonates.[4,6] Mixed malonates, especially those derived from bulky alkyl esters, can be similarly prepared (eq 2).[5]

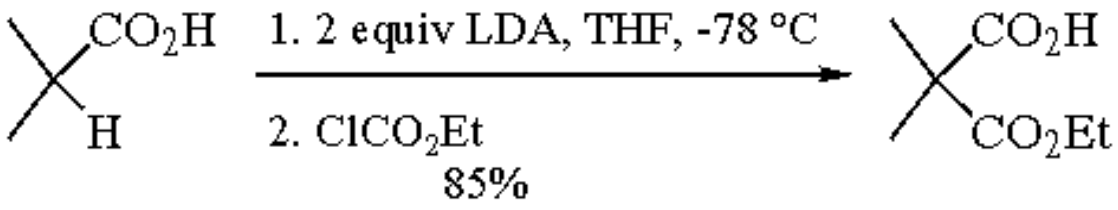

(1)

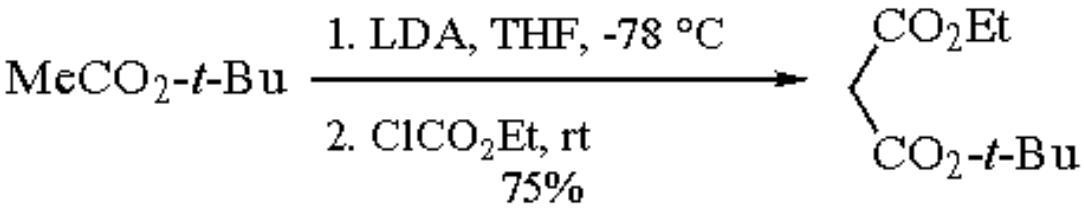

(2)

α-Lithionitriles are ethoxycarbonylated in good yield.[7] Acetals[8] and 1,3-dithianes[9] are effectively ethoxycarbonylated (eq 3) if ethyl chloroformate is used as a cosolvent to prevent side reactions. Ethoxycarbonylation of ketones is achieved when enamines are treated with ethyl chloroformate, in some cases giving comparable yields to those obtained using metal enolates.[10]

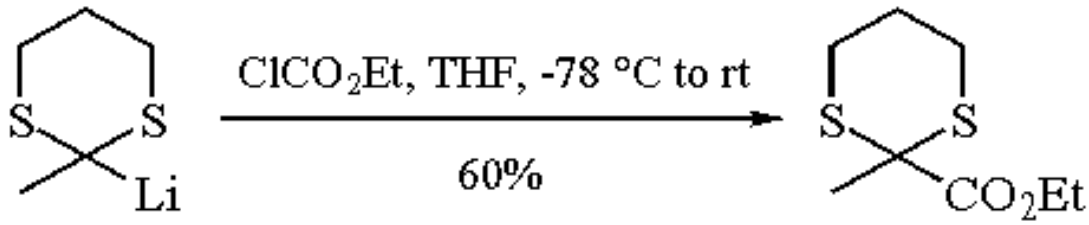

(3)

Enantioselective ethoxycarbonylation has recently been attempted[11] via deprotonation of *N*-benzylidenebenzylamine with two equivalents of a chiral lithium amide base and quenching with ethyl chloroformate; levels of asymmetric induction were low but higher than those obtained using other chloroformates (eq 4).

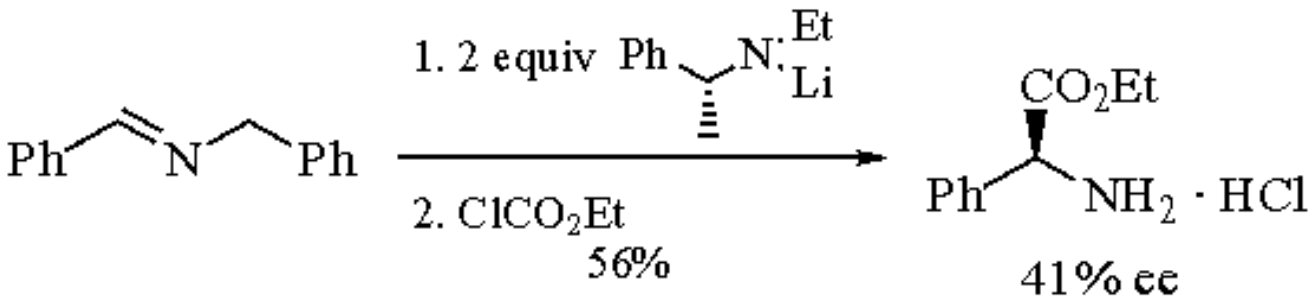

(4)

Ethoxycarbonylation of Vinyl Anions.

α,β-Unsaturated sulfones are α-ethoxycarbonylated (eq 5) on deprotonation with ***n-Butyllithium*** in THF at -78 °C and quenching with this reagent.[12]

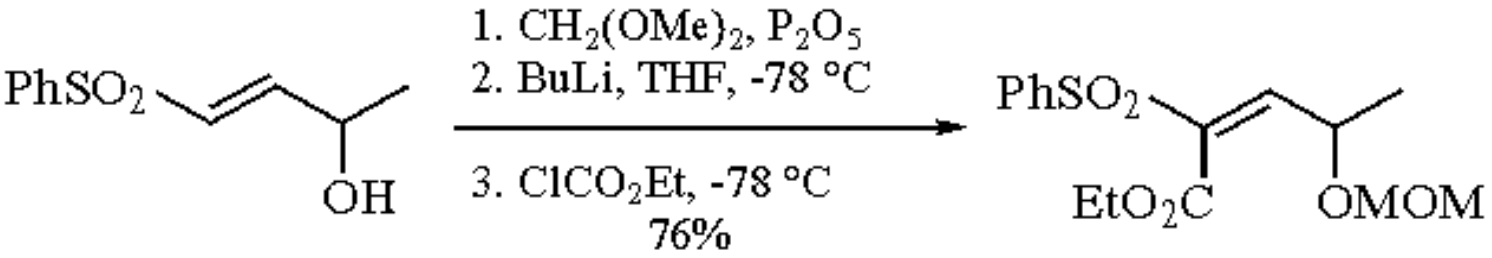

(5)

Vinyl cuprates under Pd^0 catalysis give α,β-alkenic esters (eq 6).[13] Aryl, vinyl, and heterocyclic stannanes[14] react smoothly under Pd^0 catalysis at 100 °C to give ethyl esters (eq 7) in good yields if the catalyst and chloroformate are added to the reaction mixture slowly. A wide variety of functionality on tin is tolerated but allylstannanes are generally low yielding. Use of isobutyl chloroformate improves the yields in these acylcarbonylations.

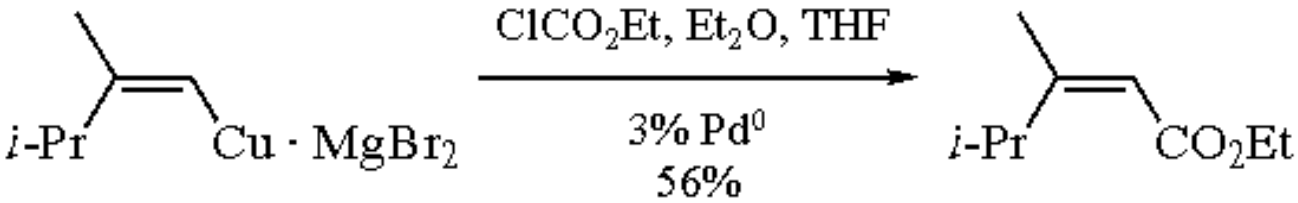

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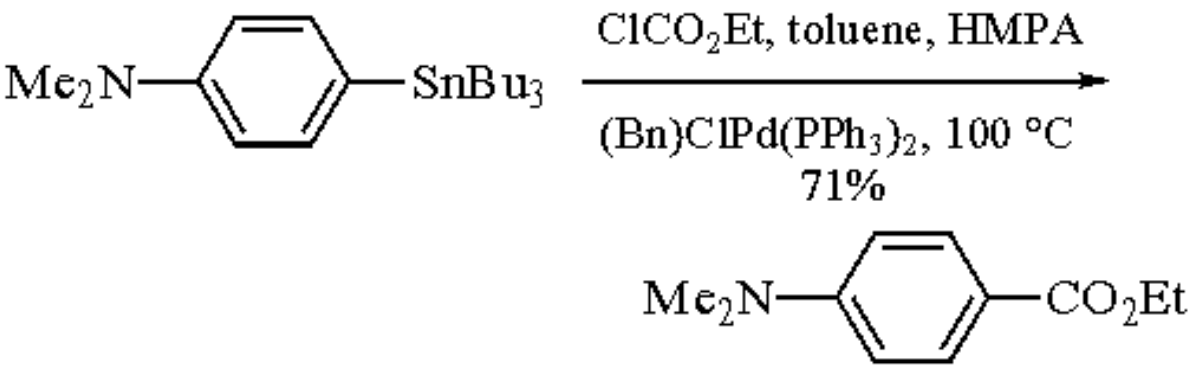

(7)

Ethyl esters are produced from Grignard reagents[15] if the organometallics are not present in excess. This is also the basis of the 5-ethoxycarbonylation of 2,4-dimethylpyrrole.[16] 2-Lithiofurans are ethoxycarbonylated in good yield (eq 8).[17]

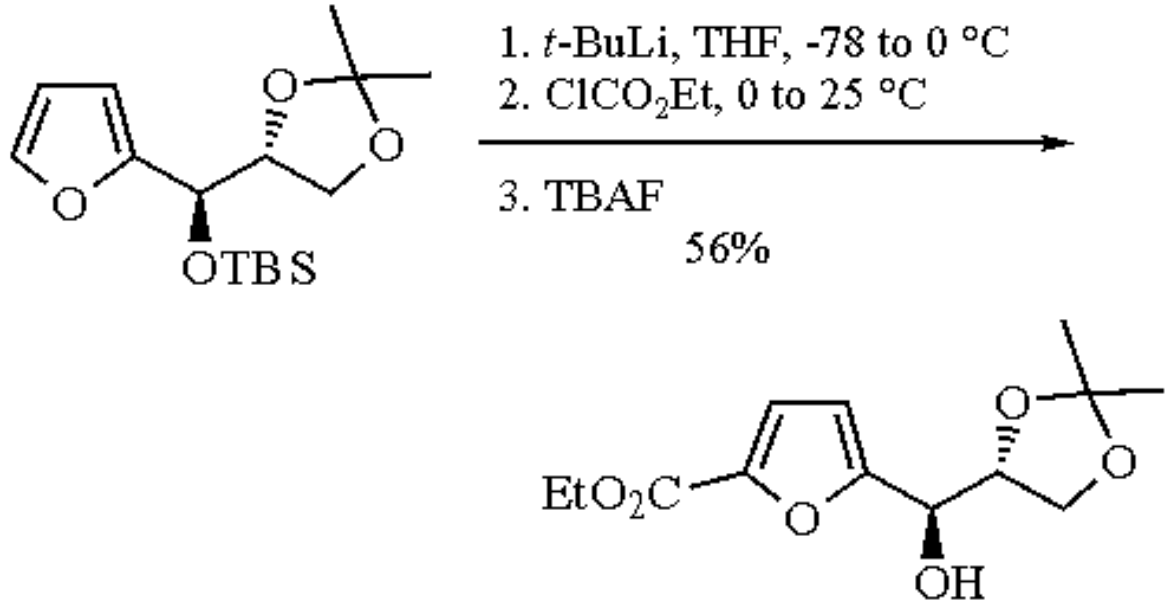

(8)

Trans-α,β-unsaturated esters can be prepared by ethoxycarbonylation of vinylalanes derived from terminal alkynes bearing primary, secondary, or tertiary alkyl substituents without the necessity of forming an intermediate ate complex (eq 9).[18] *Cis*-α,β-unsaturated esters result from ethoxycarbonylation of lithiated alkynes (eq 10)[19] followed by reduction over Lindlar catalyst.

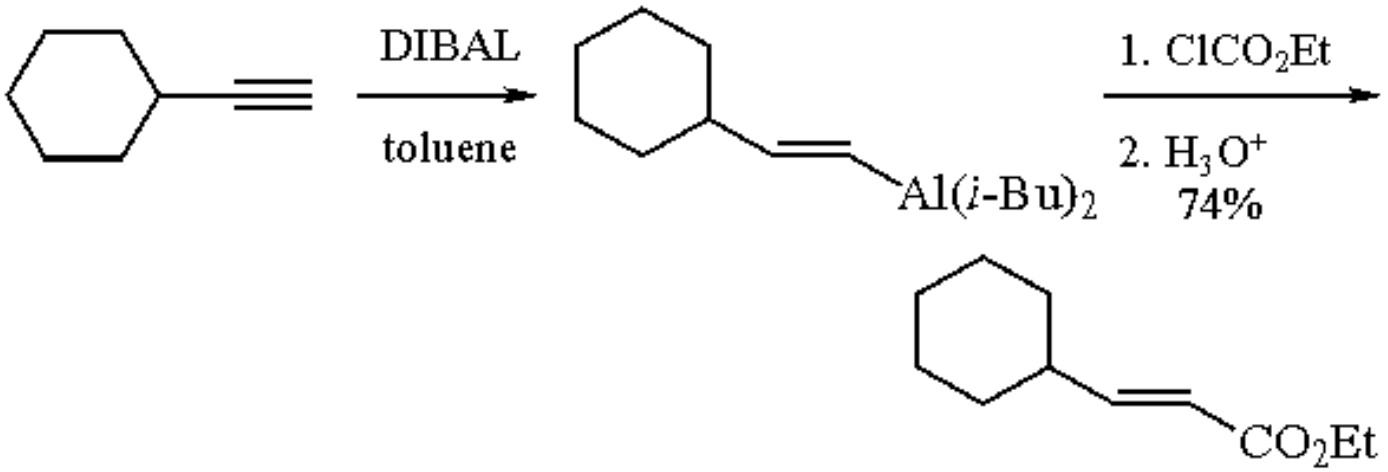

(9)

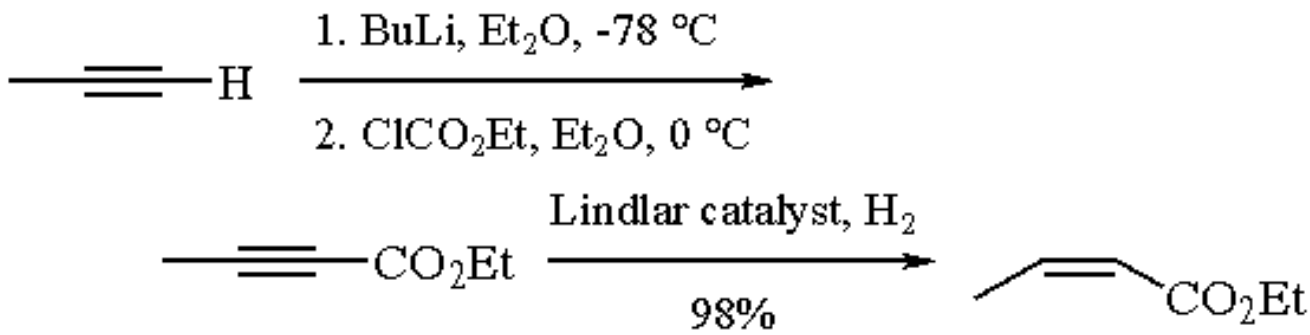

(10)

O-, *N*-, and *S*-Acylations.

O-Ethoxycarbonylation is observed in some instances. Aliphatic alcohols, phenols,[20] and cyanohydrins[21] react in the

presence of tertiary amines to give carbonates. Equatorial oriented steroid hydroxyls are selectively acylated in the presence of axial hydroxyl groups.[22] Enol carbonates (eq 11)[23] are readily derived from ketones by formation of the lithium enolate using ***Lithium 2,2,6,6-Tetramethylpiperidide*** in THF/HMPA at -78 °C followed by an ethyl chloroformate quench at room temperature. The use of HMPA prevents competitive *C*-acylation. LiTMP is necessary to avoid side reactions common with other amine-derived bases such as LDA. Sodium and potassium enolates are not useful, generally giving competitive *C*-acylation. This procedure avoids the use of classical methodology relying on the use of Hg^{II} salts.

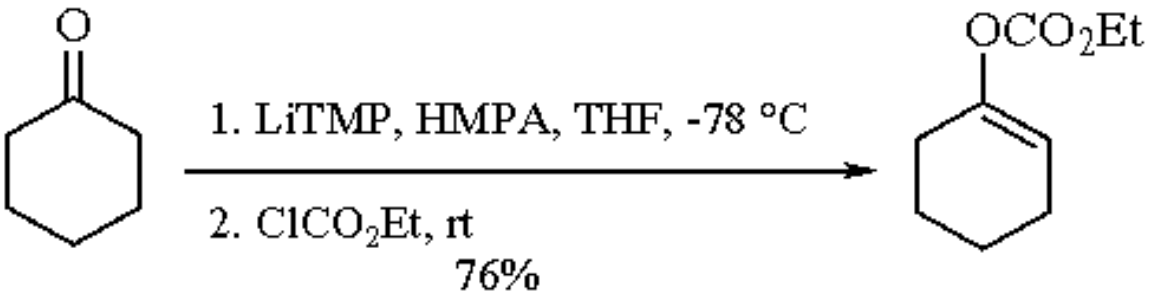

(11)

Trans-1-(1,3-butadienyl) carbamates[24] and carbonates[25] are useful dienes in Diels-Alder chemistry. The carbonates are produced when ***Crotonaldehyde*** (and its congeners) are deprotonated and treated at -78 °C with ethyl chloroformate (eq 12). Use of higher temperatures results in loss of some of the (*Z*) geometry. Similar treatment of crotonaldehyde imines affords the carbamates.

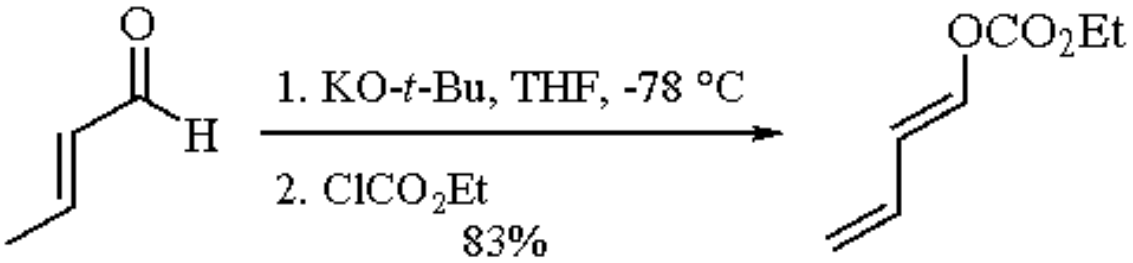

(12)

O-Ethylation occurs when the sodium enolates of α-formyl γ- and δ-lactones are refluxed in THF with ethyl chloroformate.[26]

N-Ethoxycarbonylation forms the basis of a variety of reactions of nitrogenous compounds. Aziridines form *N*-ethoxycarbonylaziridines which are converted, on heating, to allylic amines (eq 13).[27]

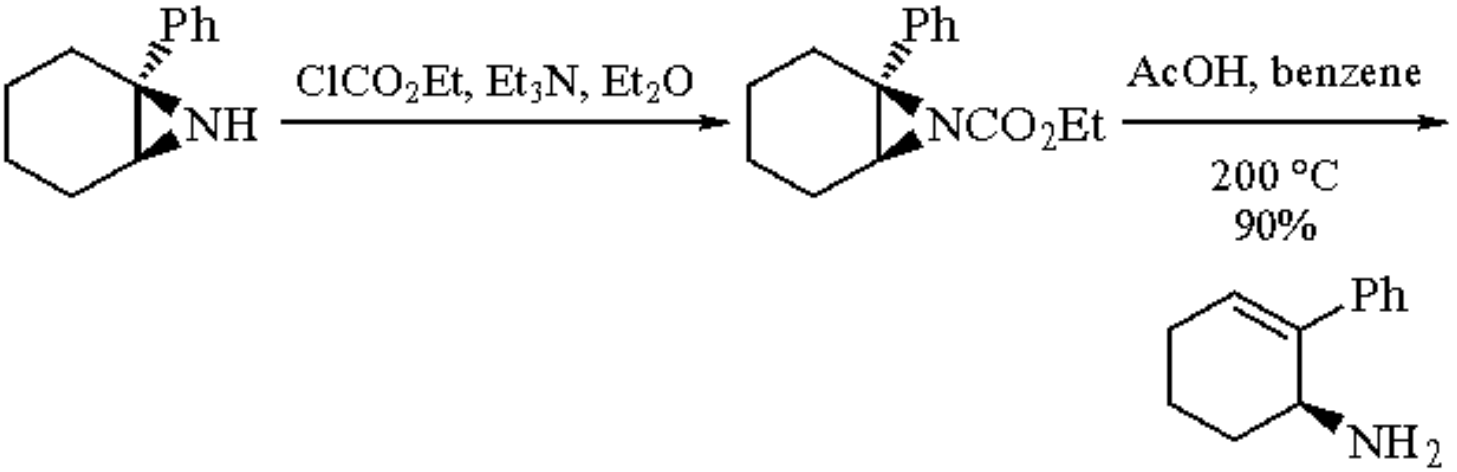

(13)

Tertiary amines may be cleaved by ethyl chloroformate in certain circumstances. *N*-Demethylation has been noted. For example, tropine acetate (eq 14) is readily converted to nortropine hydrochloride[28] on refluxing with ethyl chloroformate and subsequent acid-mediated hydrolysis of the intermediate urethane.

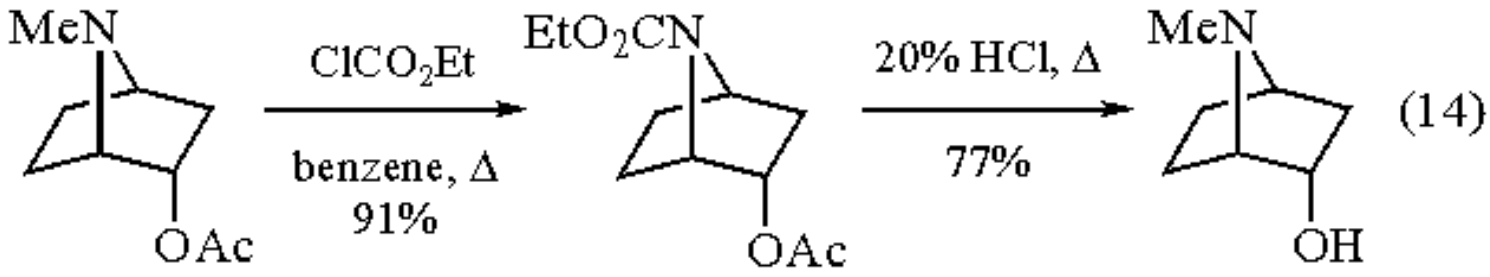

Reductive C-N bond cleavage has been demonstrated in more complex systems using ethyl chloroformate as a solvent.[29] Chlorination of corticosteroid cyclic ethers has been observed.[30] Tertiary aliphatic and alicyclic amines can be dealkylated.[31] Phenyl chloroformate, however, is usually regarded as the reagent of choice. In summary, deamination, demethylation, debenzylation, and deallylation of tertiary amines can all occur on treatment with ethyl chloroformate but the regioselectivities of these reactions are difficult to predict.[32]

Imides (e.g. phthalimide) are ethoxycarbonylated if the potassium salt is treated with ethyl chloroformate at 5-10 °C. At elevated temperatures (60-110 °C) the lithium salts are *N*-ethylated in high yield. *N*-Alkylation also occurs with other imide systems such as barbiturates, hydantoins, and succinimides.[33] Thiols give the corresponding monothiocarbonates.[34] Thioamides form ethyl imidates[35] and cyclic iminoethers[36] are obtained from thiolactams on mild warming with ethyl chloroformate. Sulfinic and sulfonic acids yield their ethyl esters.[37]

Mixed Anhydrides.

The preparation of mixed anhydrides from ethyl chloroformate and carboxylic acids enables coupling of peptides and amino acids.[38] This coupling procedure has largely been superseded by more effective methods relying on the use of superior reagents; see ***1,3-Dicyclohexylcarbodiimide*** (DCC) and ***1-Hydroxybenzotriazole*** (HOBT).

Ethyl chloroformate enables the one-step cyclization of peptides (eq 15),[39] yields generally being superior to those obtained if ***Bis(2,4-dinitrophenyl) Carbonate*** is used. However, ***Isobutyl Chloroformate***/*N*-methylmorpholine is now the reagent of choice for many solution-phase anhydride couplings.[40]

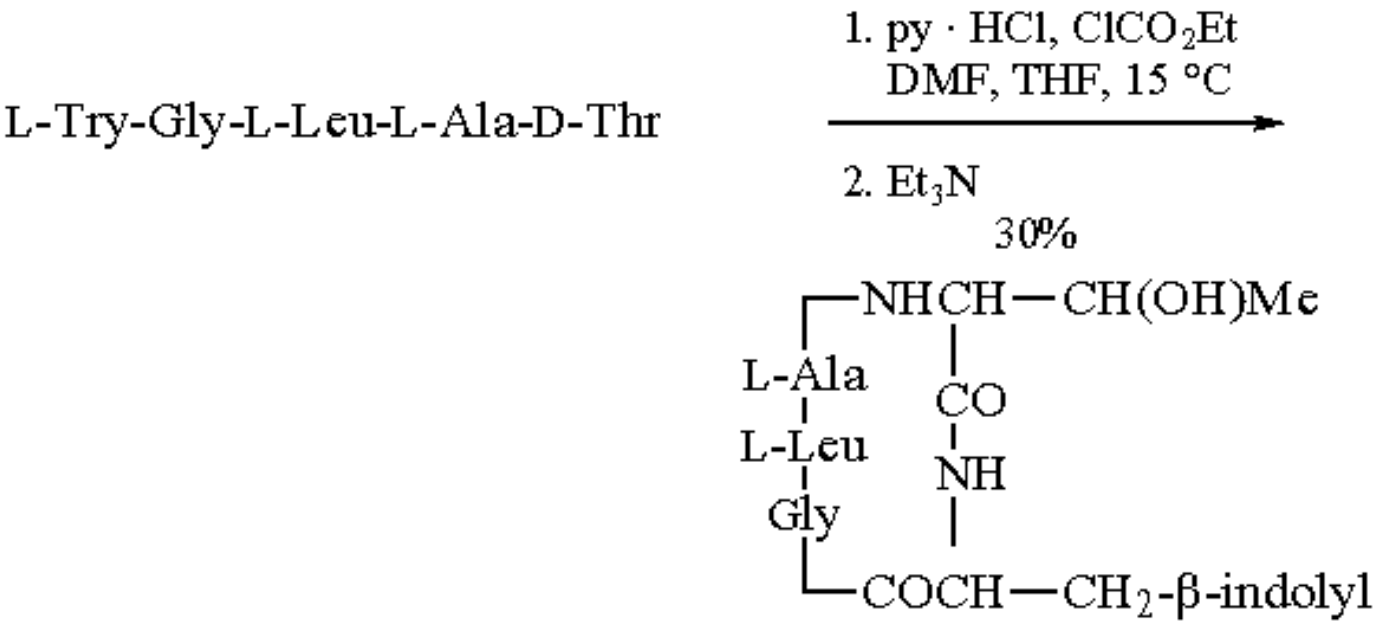

(15)

N-Protected amino acids and peptides are rapidly converted to the corresponding amino alcohols in high yields with complete retention of optical purity via reduction of the mixed anhydride by cold ***Sodium Borohydride*** in THF with dropwise addition of methanol (eq 16).[41] The disulfide bridges of cystine, the methyl and benzyl esters of o-carboxyl-protected glutamic and aspartic acids of peptides, and *N*-Cbz and *N*-Boc protection are compatible with the methodology. The anhydrides derived from ethyl chloroformate are superior to isobutyl and benzyl carbonates both in terms of yield and retention of optical purity.

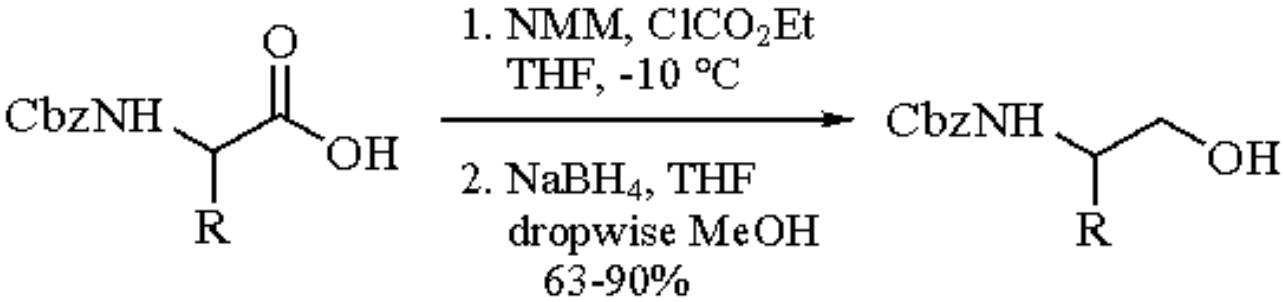

(16)

Carboxylic acid triethylamine salts yield mixed anhydrides which, when treated with ethoxymagnesiomalonic esters give the benzoylated malonate.[42] Alternatively, treatment of the mixed anhydrides with sodium tetracarbonylferrate(II) produces the aldehyde derived from the parent aliphatic or aromatic carboxylic acid in good yield.[43]

Formation of mixed anhydrides also provides the basis for the synthesis of acyl azides (eq 17)[44] and hence amines via the Curtius rearrangement. The azide ion is usually delivered to the most electrophilic carbonyl,[45] but steric considerations may be important. The method is applicable even to strained cyclopropyl- and cyclobutylcarboxylic acids.[46] ***Diisopropylethylamine*** (Hünig's base) has been mooted as a superior base for the formation of mixed anhydrides.[47]

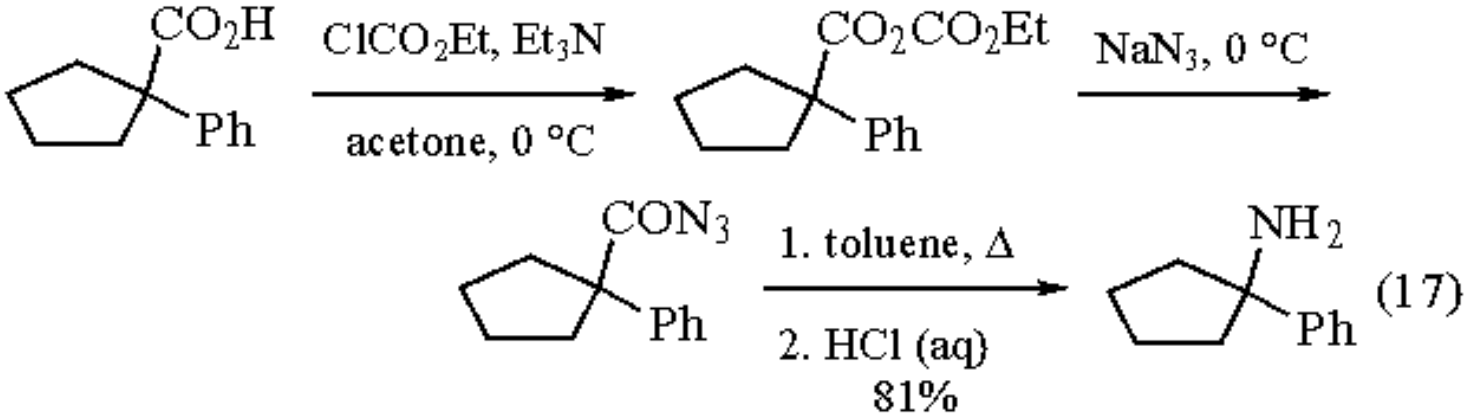

(*Z*)-Ethylenic mixed anhydrides are easily prepared without isomerization and react with vinyl cuprates (and other organometallics) under Pd^0 catalysis with >99% stereochemical control to give unsymmetrical divinyl ketones (eq 18).[13] Alternative routes via (*Z*)-ethylenic acyl chlorides produce (*E*/*Z*) mixtures.

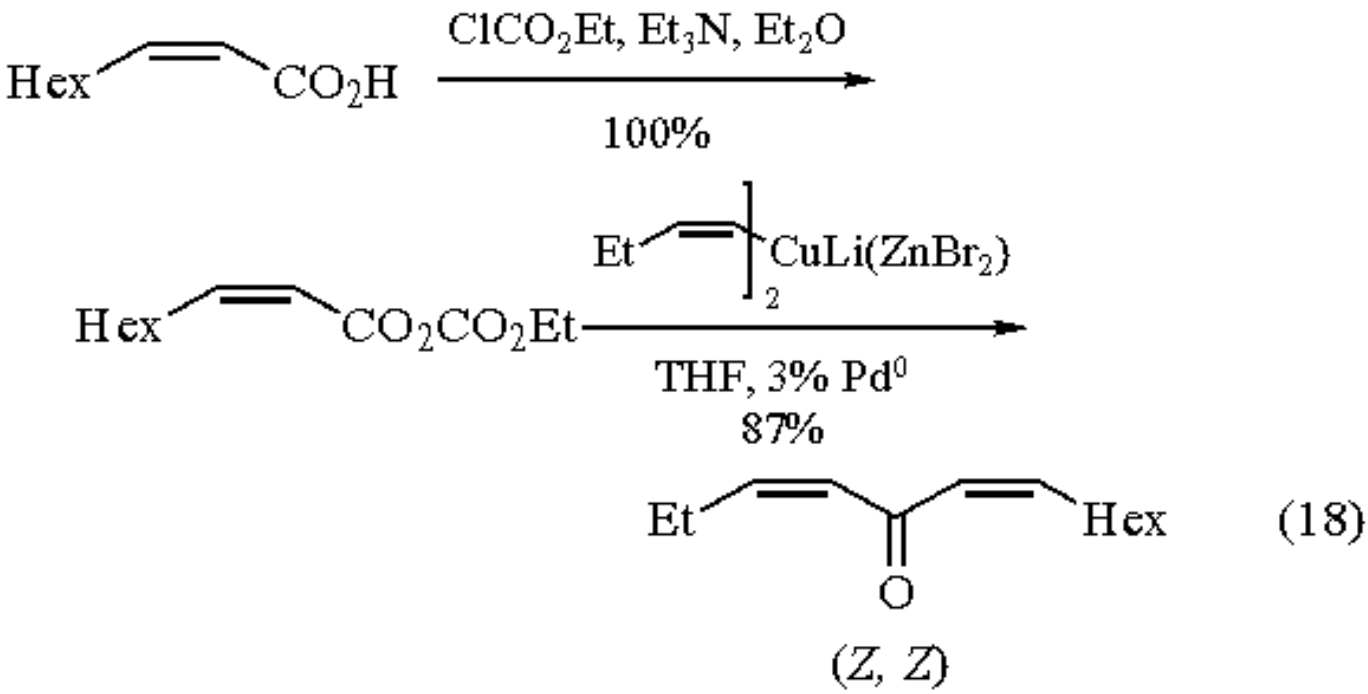

Miscellaneous.

β-Cyanoesters (eq 19)[48] are produced from β-amido acids providing that the acid and amide functionality are sufficiently close to enable formation of a cyclic intermediate.

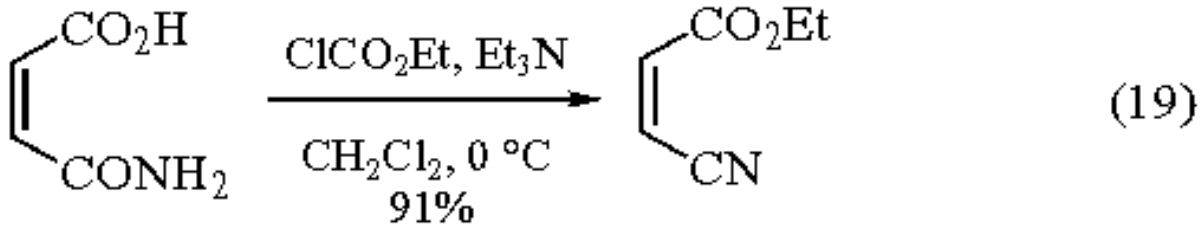

Aromatics undergo Friedel-Crafts alkylation in the presence of ***Aluminum Chloride***, probably due to the formation of

EtCl in situ.[49]

Ethyl chloroformate has been used to moderate reactivity in polymerizations. For example, PVC with good thermal stability is prepared in the presence of this reagent.[50]

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S-Ethyl Chlorothioformate

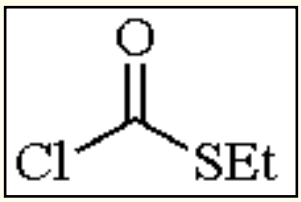

[2941-64-2] · C_3H_5ClOS · *S*-Ethyl Chlorothioformate · (MW 124.585)

(used in synthesis of carbothioate *S*-esters)

Physical Data: mp -60 °C; bp 132 °C; bp 39 °C/20 mmHg; *n*20D 1.4820; *d* 1.195 g cm^{-3}; fp 30 °C.

Solubility: sol DMF (17.9 g 100 mL^{-1}).

Form Supplied in: liquid; 95-98%, dependent on supplier.

Purification: two short-path distillations.

Handling, Storage, and Precautions: the liquid is flammable, moisture sensitive, harmful if swallowed and causes burns. It is also a lachrymator. Use in a fume hood.

Carbothioate *S*-Esters.

This reagent provides a superior procedure for the preparation of carbothioate *S*-esters. These are interesting synthetic intermediates, due to their activated carbonyl group,[1] and have, amongst other things, been used as a complexing reagent in some organometallic systems.[4] The previous method of Schotten-Baumann involves the reaction of a carboxylic acid with either ***Thionyl Chloride*** or ***Oxalyl Chloride*** followed by a thiol and base.[2] This has the disadvantage of introducing an acid chloride moiety into the substrate during the first step of the sequence with the consequent possibility of side reactions. The modified procedure involves the reaction of the sodium salt of the carboxylic acid with the reagent in DMF and pyridine, firstly at 0 °C and then at room temperature (eq 1).[3]

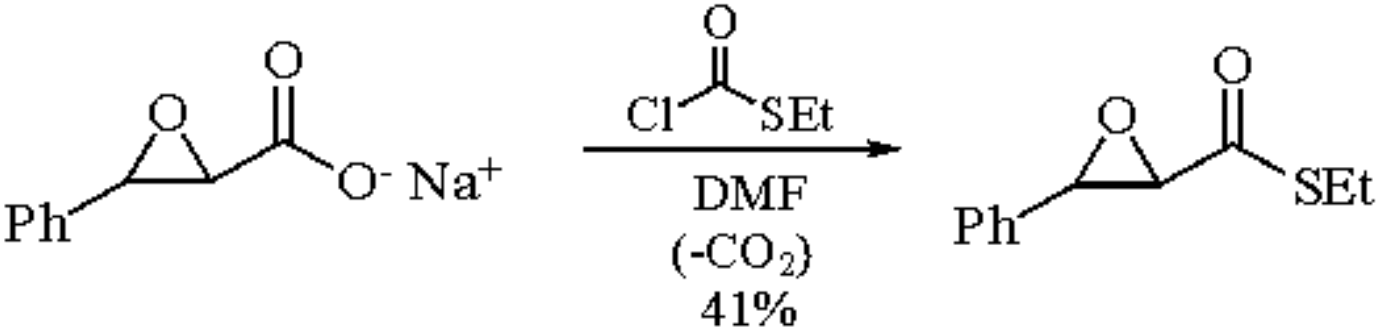

(1)

This reaction works considerably better if the *S*-phenyl ester is used instead (64%); with the same derivative, use of the lithium salt gave an improved yield over the sodium salt although no reaction of the *S*-ethyl ester with this cation was attempted.

Fungicidal carbanilates have have also been prepared using this method. Electron-donating *meta*-substituted phenyl(ethylthio-*N*-substituted amide)s were prepared, using a dichloromethane-pyridine solvent mixture.[5]

Tarbell et al. have studied the reaction of aromatic carboxylic acids with chlorothioformate *S*-esters to yield the corresponding mixed anhydrides.[6] Thermal decomposition of this gives the arenecarbothioate *S*-ester.

An alternative to forming carbothioate esters uses the *O*-ester isomer of ethyl chlorothioformate.[7] Treatment of dibutylethoxyphosphine in toluene with ethoxythiocarbonyl chloride gave 70-80% of the *S*-ethylcarboxydibutylphosphine oxide. This could then be reacted with benzylamine in isopropyl alcohol to give the benzylaminocarboxydibutylphosphine oxide.

α-Fluoro-β-thioester Esters.

An α-fluoro-β-thioester ester has been prepared in 57% yield using this reagent and some phosphorus chemistry.[8] ***Tri-n-butylphosphine*** and ethyl bromofluoroacetate were initially reacted in THF at rt; deprotonation with ***n-Butyllithium*** at -78 °C was followed by addition of the acid chloride; workup was with mild aqueous base to give $EtSC(O)CFHCO_2Et$.

α,β-Unsaturated Thiocarboxylates.[9]

Synthesis of α,β-unsaturated thiocarboxylates by Schaumann has been achieved by two different methods: *ipso* substitution of the silyl group in vinylsilanes or cyclopropylsilane by Lewis acid-activated *S*-ethyl chlorothiocarbonate;[10] and standard Horner-Emmons type alkenation.[11] With the former the best results were obtained with ***Aluminum Chloride***, rather than ***Titanium(IV) Chloride*** or ***Magnesium Bromide*** as catalysts, in dichloromethane at -60 °C and yields varied between 25% and 66% depending on the substrate. It is thus assumed that the reactive intermediate is the hard *S*-ethylcarbonyl cation; *S*-*t*-butyl, -

hexyl, and -cyclohexyl chlorothiocarbonates gave no substitution, due to cation breakdown, even with $AlCl_3$ at -78 °C, yielding instead the alkyl halide and carbonyl sulfide.[12] The workup was with saturated NH_4Cl (aq) followed by saturated $NaHCO_3$ (aq), brine, water, drying with $MgSO_4$ and distillation in vacuo, with added hydroquinone. More vigorous conditions were required with the cyclopropylsilane but no ring opening was observed. It appears that edge coordination of the cyclopropane to the electrophile is involved.[13]

The Horner-Emmons type reaction is a more general procedure and allows the use of the *S*-*t*-butyl, -hexyl, and -cyclohexyl chlorothiocarbonates, unlike the previously mentioned method. Yields for this one-pot reaction scheme were quite variable (21-81%). However, usually only the (*E*)isomer product was formed.

Other Reactions of *S*-Ethyl Chlorothioformate.

Bis(tributyltin) sulfide has been used as a sulfur transfer reagent under neutral and mild conditions with *S*-ethyl chlorothioformate; using 1 mol equiv in $CHCl_3$ at 110 °C for 12 h gave 97%, via GLC, of bis(*S*-ethylcarboxy) thioanhydride.[14]

A facile Rosenmund type reduction of acid chlorides, including the *S*-ethyl ester, with hypervalent silicon hydrides has been demonstrated.[15] Ethyl chlorothioformate was unreactive compared to most acid chlorides with this reaction, so a more efficient silane (**1**) had to be used; the yield of ethylthioformaldehyde was greater than 95% via NMR integration. In a continuation of this work, Corriu has also shown that reaction of the standard silane (**2**) with ***Phenyl Isocyanate*** yielded an adduct which, on addition of the reagent, gave the *N*-acylthioformamide EtSC(O)NPhCHO in 80% yield.[16] In addition the chlorosilane produced was readily recycled by reduction with ***Lithium Aluminum Hydride***. Only one paper previously existed on the preparation of *N*-acylthioformamides.[17]

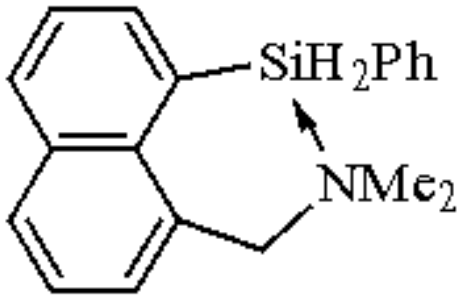

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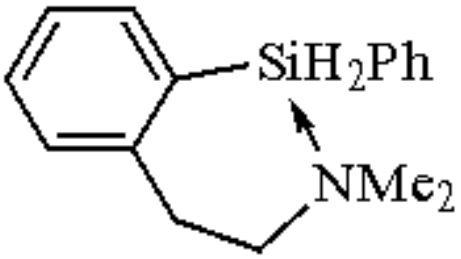

(2)

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Ethyl Crotonate[1]

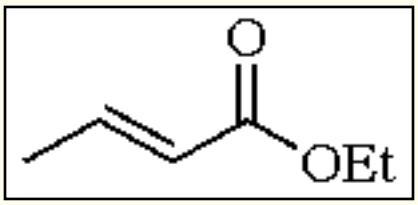

(*E*)

[623-70-1] · $C_6H_{10}O_2$ · Ethyl Crotonate · (MW 114.16) (*Z*)

[6776-19-8] (Me ester)

[623-43-8] · $C_5H_8O_2$ · Methyl Crotonate · (MW 100.13)

(alkylating and annulating reagent commonly used in cycloadditions,[2] conjugate additions,[3] tandem vicinal dialkylation reactions,[4] and Heck reactions[5])

Physical Data: bp 142-143 °C; *d*204 0.916 g cm^{-3}; *n*20D 1.425.

Solubility: insol H_2O; sol EtOH, ether, most other polar solvents.

Form Supplied in: typically furnished predominantly as the (*E*)-isomer; purity &egt;96%; widely available.

Preparative Method: the (*Z*)-isomer can be prepared by semihydrogenation of ethyl tetrolate in excellent chemical yield.[6]

Purification: commercial material can be washed with 5% aq Na_2CO_3, followed by aq saturated $CaCl_2$. Drying with $CaCl_2$ and distillation at atmospheric or reduced pressure provides the pure ester.[7]

Handling, Storage, and Precautions: should be stored tightly capped in an amber container and preferably refrigerated. Crotonates are flammable and corrosive, usually with a lachrymatory odor. This toxic reagent should be handled in a fume hood.

The chemistry of alkyl crotonates parallels that of the alkyl acrylates (see ***Ethyl Acrylate***), particularly in their use as dienophiles in cycloadditions[8] and in their conjugate addition reactions.[9]

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Ethyl Cyanoacetate

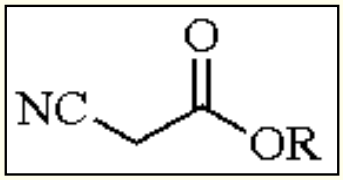

(R = Et)

[105-56-6] · $C_5H_7NO_2$ · Ethyl Cyanoacetate · (MW 113.13) (R = Me)

[105-34-0] · $C_4H_5NO_2$ · Methyl Cyanoacetate · (MW 99.10) (R = *t*-Bu)

[1116-98-9] · $C_7H_{11}NO_2$ · *t*-Butyl Cyanoacetate · (MW 141.19)

(reagent with a doubly activated methylene group for free radical cyclizations, for preparing heterocycles, for nucleophilic substitution reactions, for preparing α-alkylidene derivatives, and for carbocyclic ring formation)

Physical Data: R = Me, bp 204-207 °C; *d* 1.123 g cm^{-3}; R = Et, bp 208-210 °C; *d* 1.063 g cm^{-3}; R = *t*-Bu, bp 90 °C/10 mmHg.

Solubility: sol EtOH, ether.

Form Supplied in: liquid; widely available.

Preparative Method: ethyl and methyl cyanoacetate are conveniently prepared from cyanoacetic acid and the corresponding ***Triethyloxonium Tetrafluoroborate*** and trimethyloxonium fluoroborate.[1] *t*-Butyl cyanoacetate is prepared from cyanoacetyl chloride and *t*-butyl alcohol.[2]

Analysis of Reagent Purity: gas chromatography.

Handling, Storage, and Precautions: ethyl cyanoacetate is a lachrymator irritant. Methyl cyanoacetate is described as an irritant. Keep containers well closed. Inhalation should be avoided. Hydrogen cyanide or other low molecular weight cyano compounds may be liberated in event of overheating. Handle in a fume hood.

Condensation Reactions With Carbonyl Groups.

Ethyl cyanoacetate undergoes the Knoevenagel condensation[3] (or the Knoevenagel-Doebner modification) with aldehydes and ketones in the presence of β-alanine,[4] glycine,[5] ammonium acetate,[6,7] ***Piperidine***,[8] piperidine acetate,[8] bismuth trichloride,[9] ***Dihydridotetrakis(triphenylphosphine)ruthenium(II)***,[10] or weak bases.[11] The ammonium acetate-

catalyzed reaction of acetophenone and ethyl cyanoacetate affords ethyl (1-phenylethylidene)cyanoacetate (eq 1).[7] Condensation of ethyl cyanoacetate with propanal followed by reduction with hydrogen and palladium yielded ethyl butylcyanoacetate.[8] Ethyl cyanoacetate and other active hydrogen compounds can also be alkylated by alcohols in modest yields using the combination of ***Diethyl Azodicarboxylate*** and ***Triphenylphosphine***.[12]

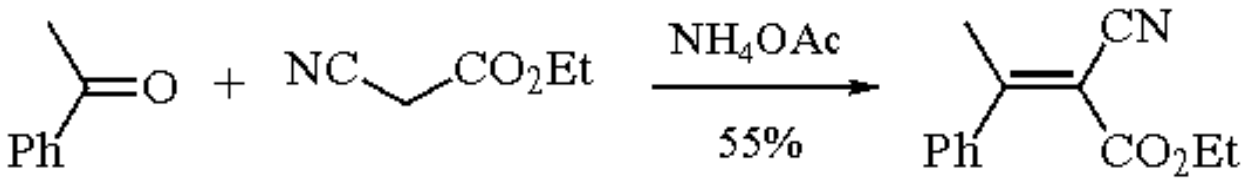

(1)

Reactions with α,β-Unsaturated Carbonyl Compounds.

Activated nitriles such as ethyl cyanoacetate react with α,β-unsaturated carbonyl compounds in the presence of dihydridotetrakis(triphenylphosphine)ruthenium to afford Michael adducts which can undergo an aldol cyclization stereoselectively to afford cyclohexanes (eq 2).[10] Ethyl cyanoacetate reacts with *p*-benzoquinone to afford diethyl α,α´-dicyano-2,5-dihydroxy-*p*-benzenediacetate which is hydrolyzed to 2,5-dihydroxy-*p*-benzenediacetic acid (eq 3).[13] Methacrylamides react with ethyl cyanoacetate in the presence of ***Cesium Fluoride***-tetramethoxysilane to form dihydropyridinones (eq 4).[14]

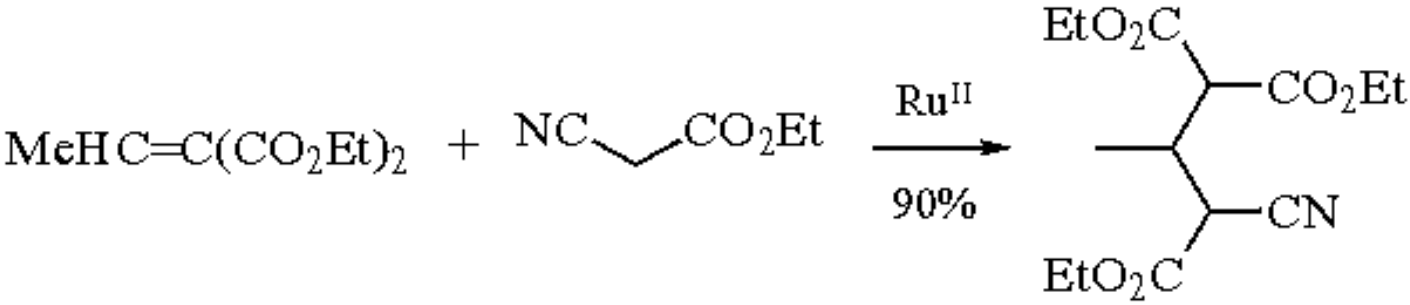

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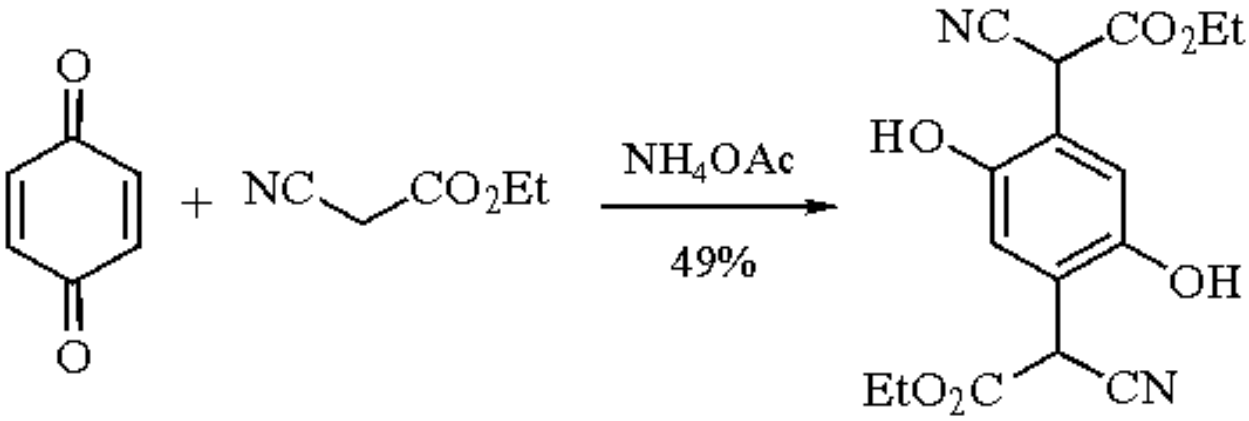

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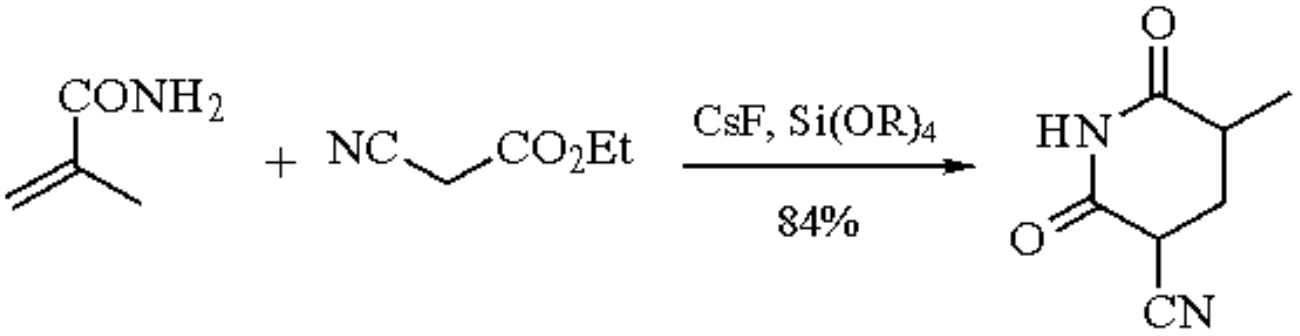

(4)

Synthesis of Cyclopropanes and Cyclopentanes.

1-Cyanocyclopropanecarboxylic acid (eq 5)[15] or 1-cyanocyclopentane-1-carboxylate[16] can be prepared by cyclocondensation (double alkylation) of ethyl cyanoacetate and ***1,2-Dibromoethane*** or ***1,4-Dibromobutane*** under phase transfer conditions. Ethyl cyanoacetate reacts (2 equiv) with alkenes (1 equiv) in the presence of ***Copper(II) Chloride*** and ***Copper(II) Acetate*** in DMF to afford *endo*- and *exo*-cyclopropane derivatives (yields based on the alkene) (eq 6).[17] Cyclopropanes were obtained under similar conditions from 1-decene and styrene. Use of dimethyl malonate in place of ethyl cyanoacetate gave lower yields of cyclopropanes.

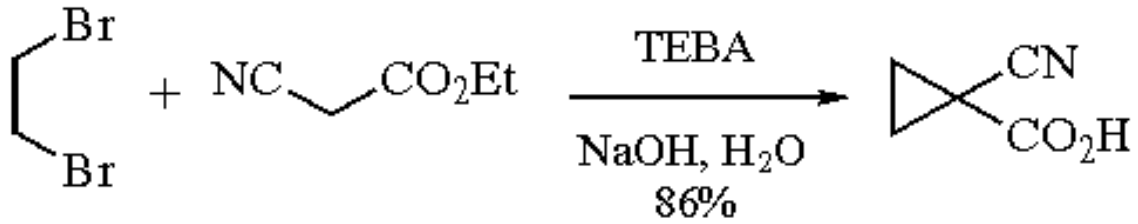

(5)

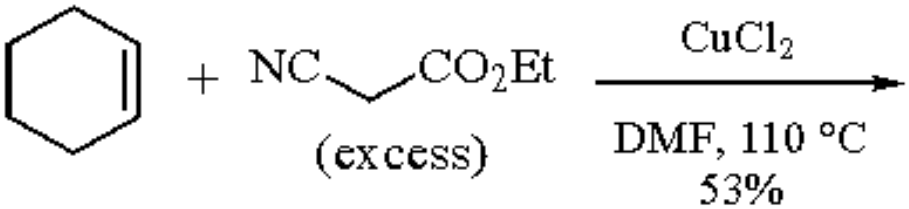

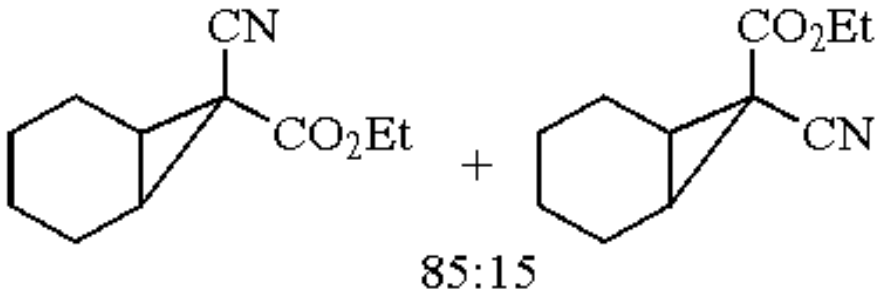

(6)

Alkylation Reactions.

Ethyl cyanoacetate undergoes nucleophilic aromatic substitution with hexafluorobenzene in DMF/***Potassium Carbonate*** to yield ethyl cyano(pentafluorophenyl)acetate which is converted to (pentafluorophenyl)acetonitrile.[18] Ethyl

cyanoacetate reacts with *o*,α-dichlorotoluene to afford ethyl 2-(*o*-chlorobenzyl)cyanoacetic acid which is an intermediate in the synthesis of 1-cyanobenzocyclobutene (bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile).[19] The nucleophilic substitution reaction of ethyl and *t*-butyl cyanoacetate with 3-bromochromone (eq 7) or 6-bromofurochromone affords the respective 3-substituted derivative,[20] presumably by an addition-elimination mechanism.

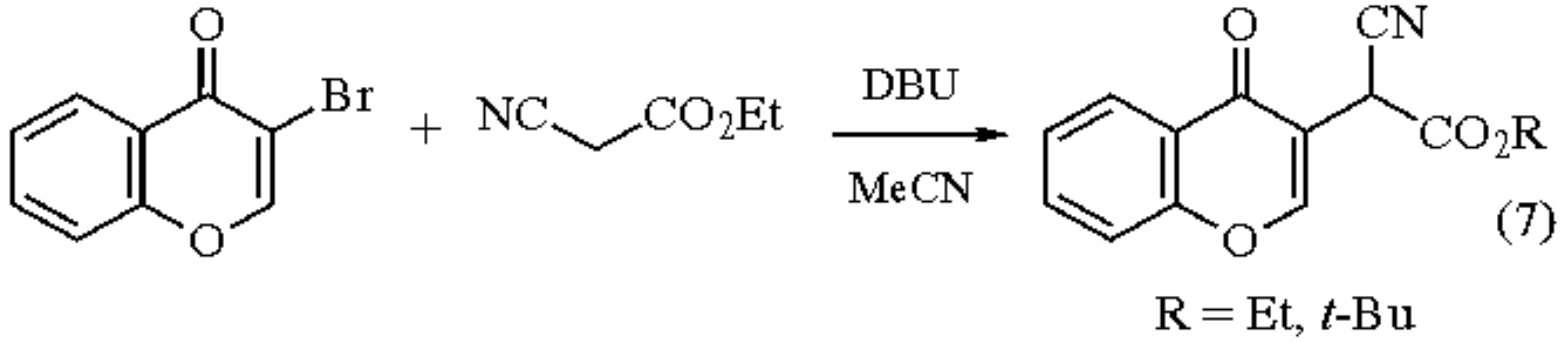

Radical Cyclizations.

Ethyl cyanoacetate reacts with the tosylate of (*E*)-4-hexen-1-ol to afford ethyl (*E*)-2-cyano-6-octenoate which yields 1-cyano-2-methylcyclohexanecarboxylate on treatment with ***Dibenzoyl Peroxide*** (eq 8).[21] Similarly, oxidative free radical cyclization of ethyl (*4E*,8-nonadien-1-yl)cyanoacetate in the presence of the co-oxidants Mn^{III} and Cu^{II} acetate afforded ethyl 1-cyano-2-[1-(1,4-pentadienyl)]cyclopentanecarboxylate (35%).[22] In the absence of Cu^{II} acetate or with benzoyl peroxide alone in cyclohexane, a mixture of the stereoisomers of methylhydrindane is formed (eq 9). The Mitsunobo reactions of 1,*n*-diols with ethyl cyanoacetate in the presence of triphenylphosphine and diethyl azodicarboxylate afford 1-cyano-1-cycloalkanecarboxylates (eq 10).[23]

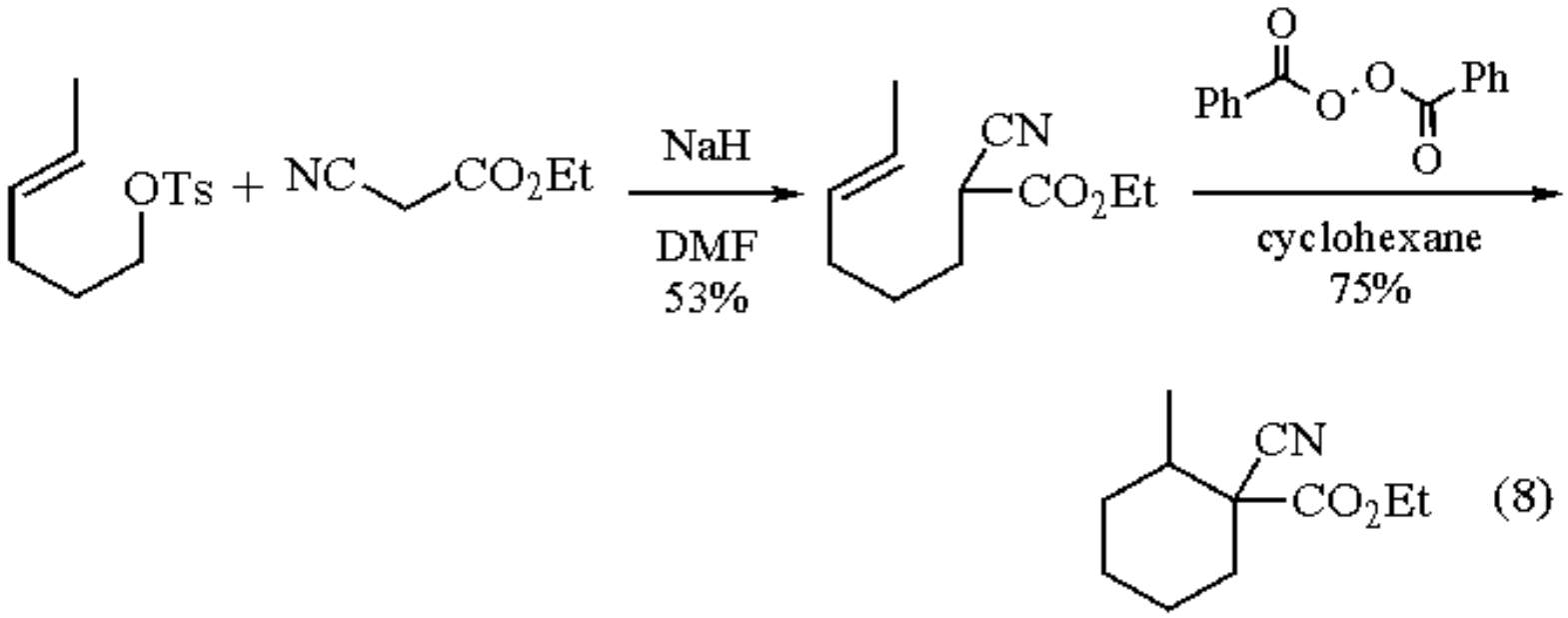

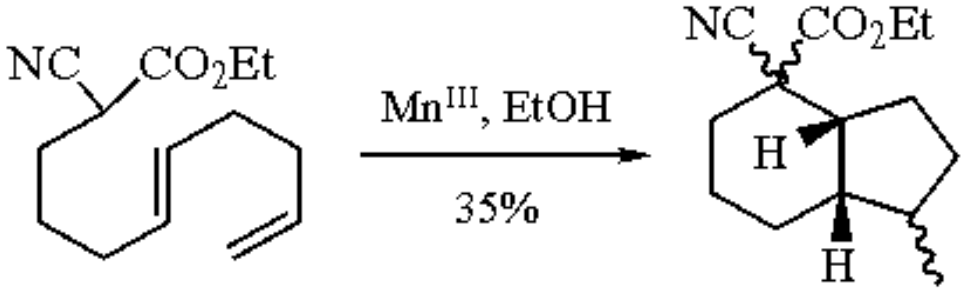

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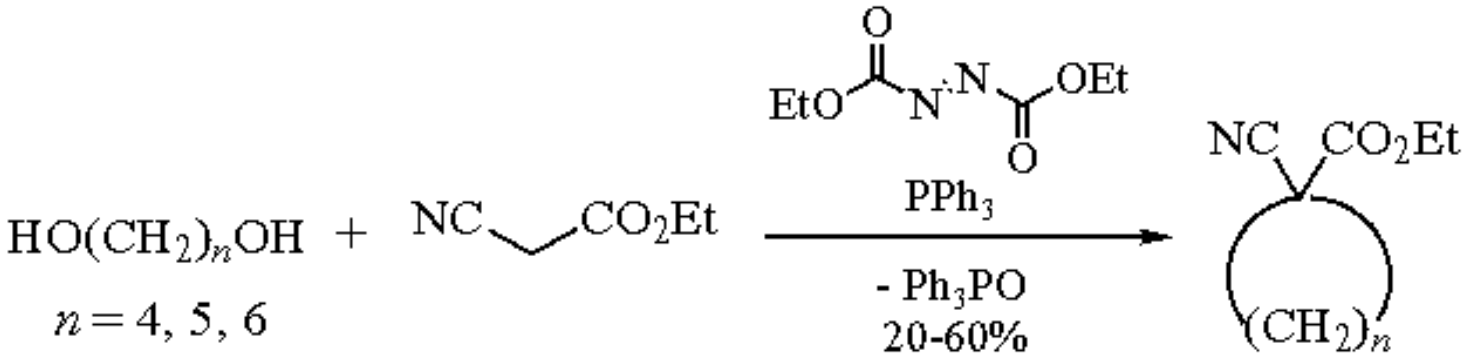

(10)

Synthesis of Heterocycles.

Reaction of 2-arylazirines and ***Hexacarbonylmolybdenum*** with ethyl cyanoacetate furnishes the *trans* disubstituted succinimides (eq 11).[24] Ethyl cyanoacetate condenses with butanone in the presence of ammonium acetate and ammonia to yield α,α´-dicyano-β-ethyl-β-methylglutarimide (70%), which can be converted to β-ethyl-β-methylglutaric acid.[25] Ethyl cyanoacetate reacts with aromatic and heterocyclic hydrazines to form 1-aryl-3-amino-5-pyrazolones (eq 12).[26]

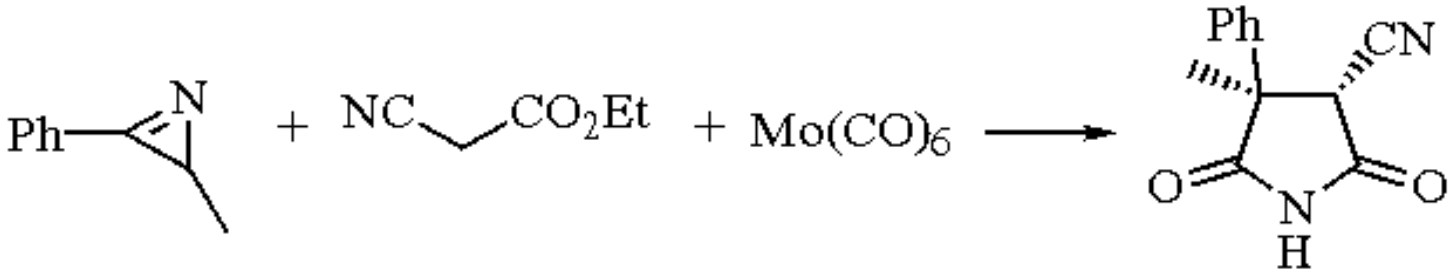

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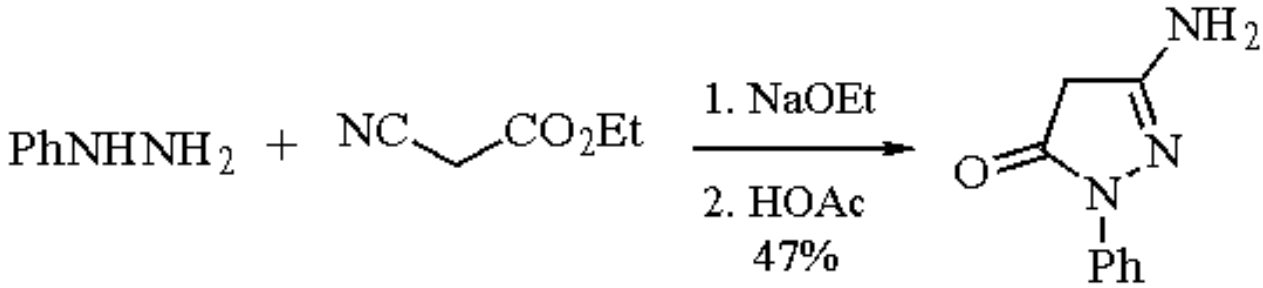

(12)

Ethyl cyanoacetate condenses with urea to form 2,6-dihydroxy-5-aminouracil (eq 13), which is the first step in a synthesis of 5,6-diaminouracil hydrochloride.[27] Similarly, thiourea and ethyl ethoxymethylenecyanoacetate afford 2-mercapto-4-amino-5-ethoxycarbonylpyrimidine and 2-mercapto-4-hydroxy-5-cyanopyrimidine.[28] Guanidine condenses with ethyl cyanoacetate to produce 2,4-diamino-6-hydroxypyrimidine.[29]

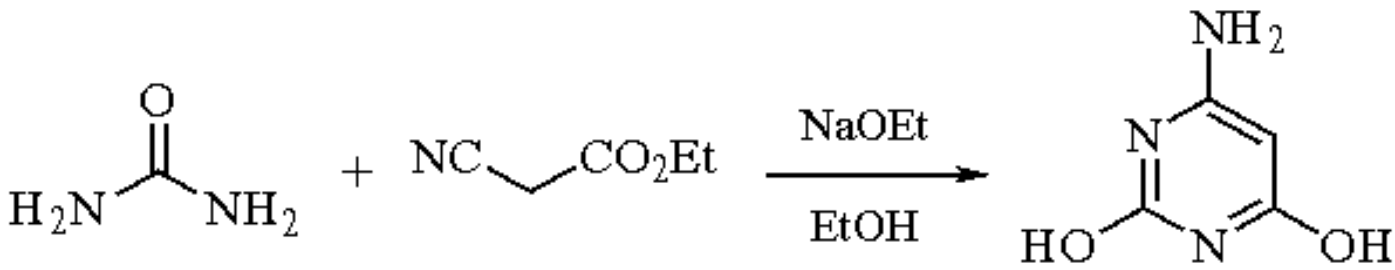

(13)

Other Applications.

Novel carbon-carbon bond formation of nonactivated alkenes with ethyl cyanoacetate has been developed by anodic oxidation using Mn^{II} and Cu^{II} diacetates to give selectively either ethyl cyanoalkanecarboxylates or cyanoalkenecarboxylates (eq 14).[30,31] Preparation of cyanomethyl ketone derivatives of *N*-acetylphenylalanine and *N*-acetylleucylphenylalanine is accomplished by condensation of the corresponding activated carboxylic acids and the carbanion of *t*-butyl cyanoacetate.[32] ***Malononitrile***, benzoylacetonitrile, and nitroacetonitrile are also reactive. Reaction of ethyl cyanoacetate and butanone in the presence of ***Potassium Cyanide*** and ***Acetic Acid***, followed by acidic hydrolysis and heat, affords α-ethyl-α-methylsuccinic acid.[33]

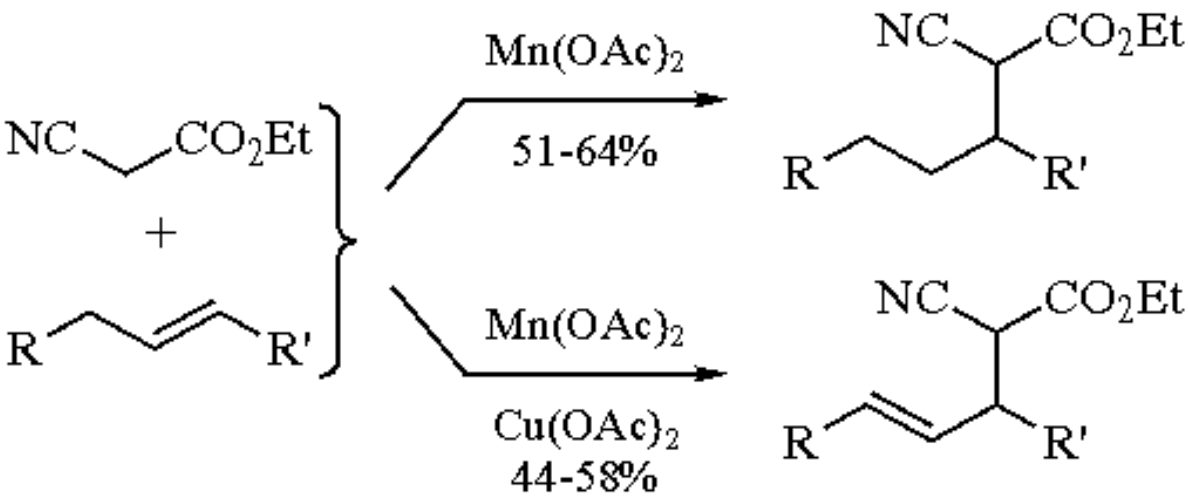

(14)

Related Reagents.

Acetonitrile; ***Cyanoacetic Acid***; ***3-Ethoxyacrylonitrile***; ***Ethyl Ethoxymethylenecyanoacetate***; ***Lithioacetonitrile***; ***Malononitrile***.

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Ethyl Diazoacetate[1]

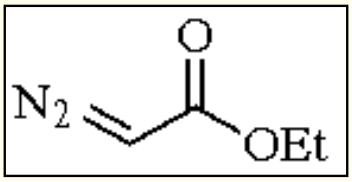

[623-73-4] · $C_4H_6N_2O_2$ · Ethyl Diazoacetate · (MW 114.10)

(for synthesis of cyclopropane- and cyclopropenecarboxylic acid derivatives,[1-3] β-keto esters,[4] and 2-substituted 2-diazoacetic esters,[5,6] for homologation of ketones[7-9])

Alternate Name: EDA.

Physical Data: mp -22 °C; bp 42 °C/5 mmHg 73 °C/80 mmHg, 141 °C/720 mmHg; *d*17.64 1.0852, *d*244 1.083 g cm^{-3}; *n*17.6D 1.4588, *n*25D 1.4616; volatile with steam, ether and benzene vapors.

Solubility: sol alcohol, acetone, benzene, ether, ligroin; slightly sol water.

Form Supplied in: yellow oil; commercially available from many suppliers; typical impurities include ethyl chloroacetate and solvents (CH_2Cl_2, ether).

Preparative Method: by the reaction of ***Sodium Nitrite*** with glycine ethyl ester hydrochloride.[5,6]

Handling, Storage, and Precautions: explodes when heated, or on contact with concentrated H_2SO_4 or HCl; decomposes under irradiation. The reagent has to be stored in a dark cold place. It is toxic and reactions involving the formation or reaction of this substance should be performed in well-ventilated fume hood and behind a safety shield. The chemist should wear a suitable face shield.

Cyclopropanation of Unsaturated Compounds.

The most useful method of preparation of many cyclopropanecarboxylic acids is catalytic decomposition of ethyl diazoacetate in the presence of alkenes (eq 1).[1-3,10-12]

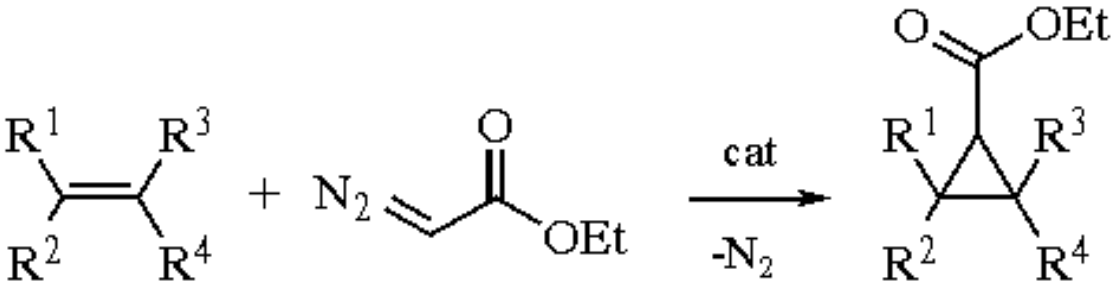

(1)

Addition of the transient ethoxycarbonyl carbenoid formed under catalytic decomposition of diazoacetate is *cis* stereospecific (eq 2).[1,13] The less sterically hindered cyclopropanecarboxylate usually predominates (eq 3).[1-3,11]

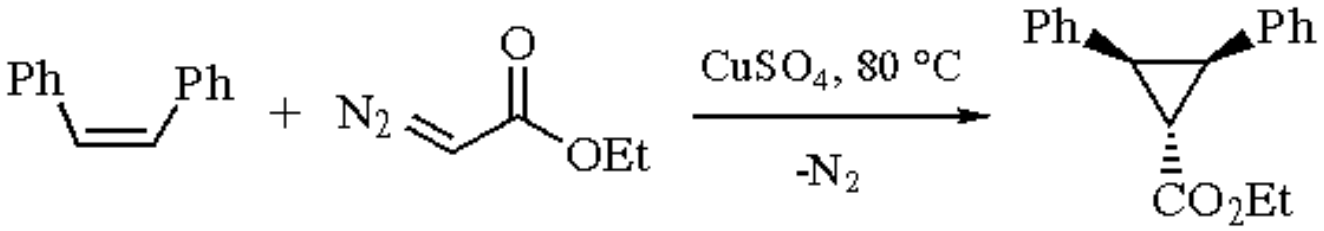

(2)

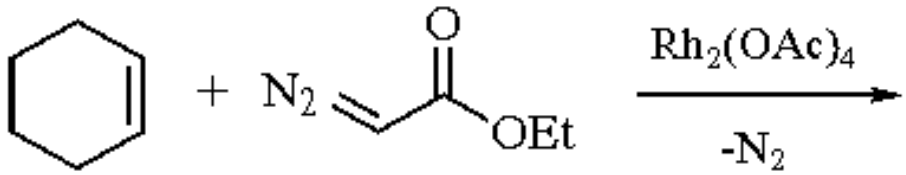

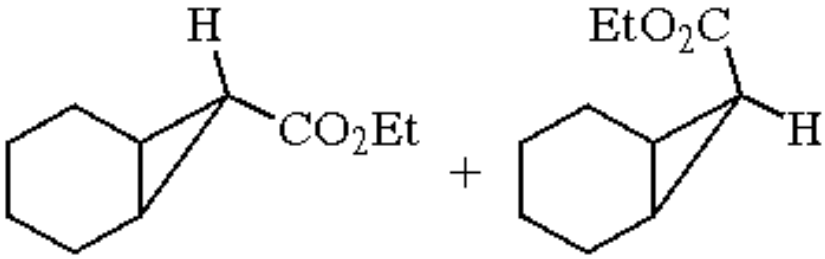

(3)

4.5:1

Decomposition of EDA with heterogeneous copper catalysts requires relatively high temperatures and gives moderate yields of cyclopropanecarboxylates.[1,2,14] Utilization of homogeneous catalysts such as ***Copper(I) Acetylacetonate*** increases the yields of cyclopropanes (eq 4). Rhodium(II) carboxylates (e.g. ***Dirhodium(II) Tetraacetate***) have been found to be even more effective, allowing the reaction to be carried out at room temperature or at even lower temperatures, with low concentrations of catalyst (0.5 mol %).[3,11] Rh^{II} complexes with chiral ligands have been used in stereocontrolled synthesis of chrysantemic and related acids.[2,15]

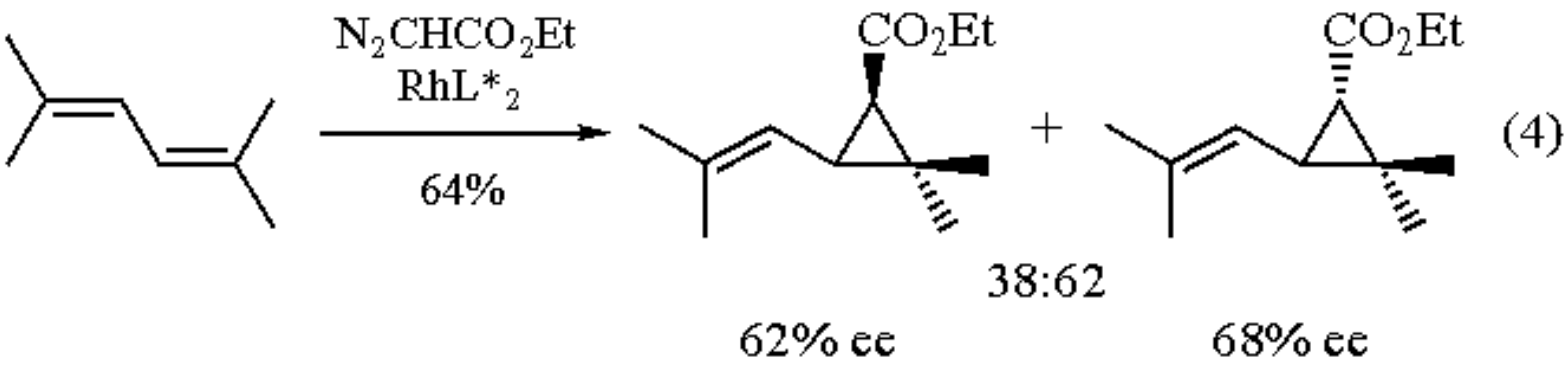

A wide variety of unsaturated compounds react with EDA in the presence of catalysts to give cyclopropanecarboxylates, for example polynuclear aromatic or heteroaromatic compounds,[1,2] enol ethers,[12] and ketene dialkyl acetals.[16] Catalytic cyclopropanation with EDA has also been used in the synthesis of bicyclobutanes,[1] triangulanes,[17] and other polycylic systems.[10,12]

Cyclopropene-3-carboxylate esters usually are prepared by rhodium-catalyzed decomposition of EDA and its analogs in the presence of alkynes. Target compounds can be obtained in a high yield even at room temperature from both terminal and disubstituted alkynes (eq 5).[1,18]

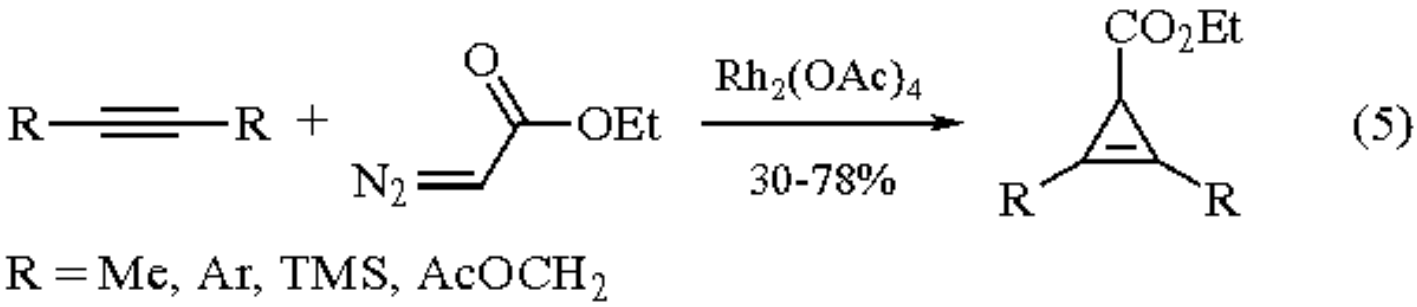

Copper catalysis requires a temperature of 90-140 °C and gives satisfactory yields of cyclopropene esters only in the case of disubstituted alkynes.[18] When double and triple bonds are both present in the same molecule, reaction takes place at both of them, a preference being shown for addition to the double bond.[1,6,19] Decomposition of EDA with chiral rhodium(II) compounds allows one to achieve high enantioselectivity in cyclopropene synthesis.[20]

Homologation of Ketones.

EDA is the most useful diazoalkane for homologation of cyclic and acyclic ketones without the formation of epoxides as byproducts. This reaction is catalyzed by ***Boron Trifluoride Etherate***,[7-9] ***Tin(IV) Chloride***,[21] or ***Triethyloxonium Tetrafluoroborate***.[2] The homologation is not regiospecific and usually gives a mixture of isomeric 2-keto esters, but insertion occurs preferentially at the less substituted side of the carbonyl group (eq 6).[8]

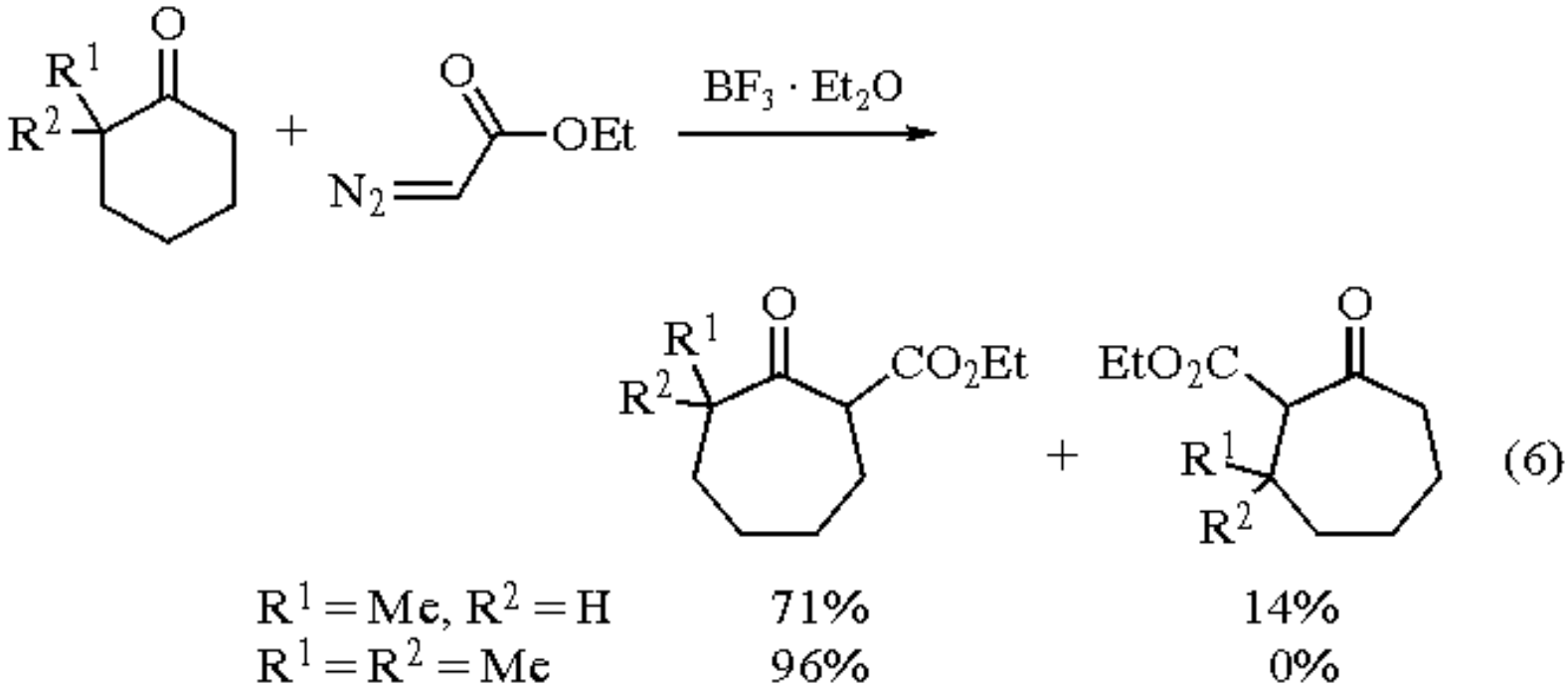

(6)

A procedure for regiospecific homologation of ketones was developed by using α-halo-substituted ketones. Treatment of the halo ketone with EDA is followed by removal of the halogen using ***Zinc*** followed by decarboxylation of the resulting β-keto ester (eq 7).[7,22]

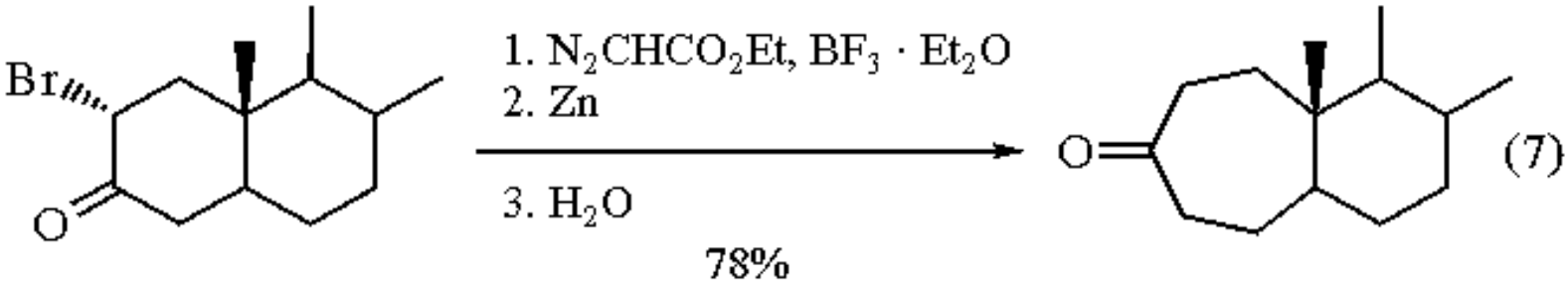

(7)

α-Diketones can be converted to β-diketones by reaction with EDA in the presence of ***Zinc Chloride*** followed by hydrolysis (eq 8).[23]

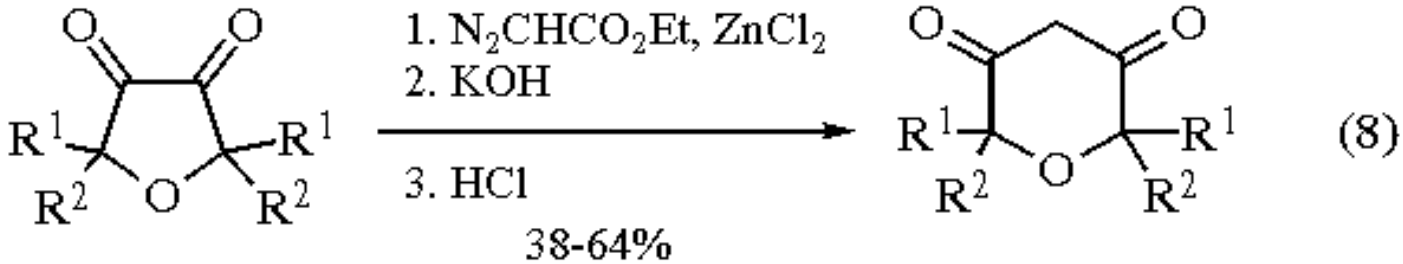

(8)

Synthesis of 2-Substituted Acetic Esters.

EDA reacts with trialkylboranes,[24] dialkylchloroboranes,[25] or alkyl(aryl)dichloroboranes[26] with loss of nitrogen to give, after hydrolysis, the homologated ethyl ester in a moderate to high yield. β,γ-Unsaturated carboxylic esters have

been obtained using this procedure (eq 9).[25]

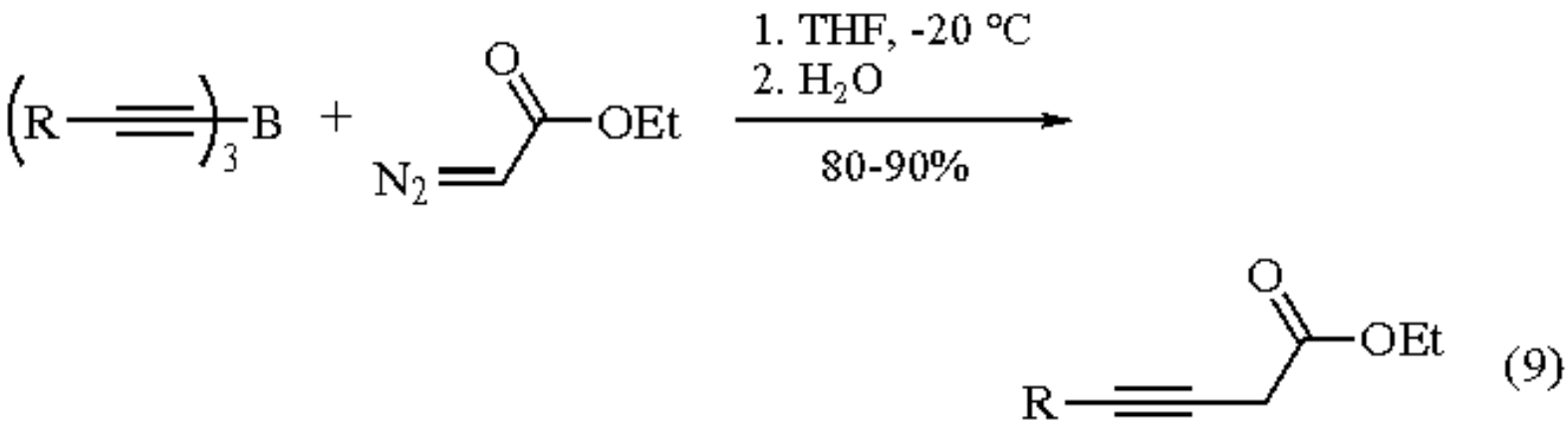

Homologated ethyl esters have also been prepared by insertion of ethoxycarbonylcarbene generated by catalytic decomposition of EDA in C-H,[12,27] C-O and C-S,[6] or Si-H bonds.[28] Ethyl 2-alkoxyacetates have been obtained in good yield by Rh^{II}-catalyzed decomposition of EDA in the presence of various alcohols.[29]

Ethyl Lithiodiazoacetate.

This reagent, which is stable only below -50 °C, can be prepared by treating EDA with ***n-Butyllithium*** in THF at -115 to -78 °C.[5] Reaction of ***Ethyl Diazolithioacetate*** with alkyl-, acyl-, and trialkylsilyl halides results in the formation of 2-substituted ethyl diazoesters (eq 10).[5,6,30]

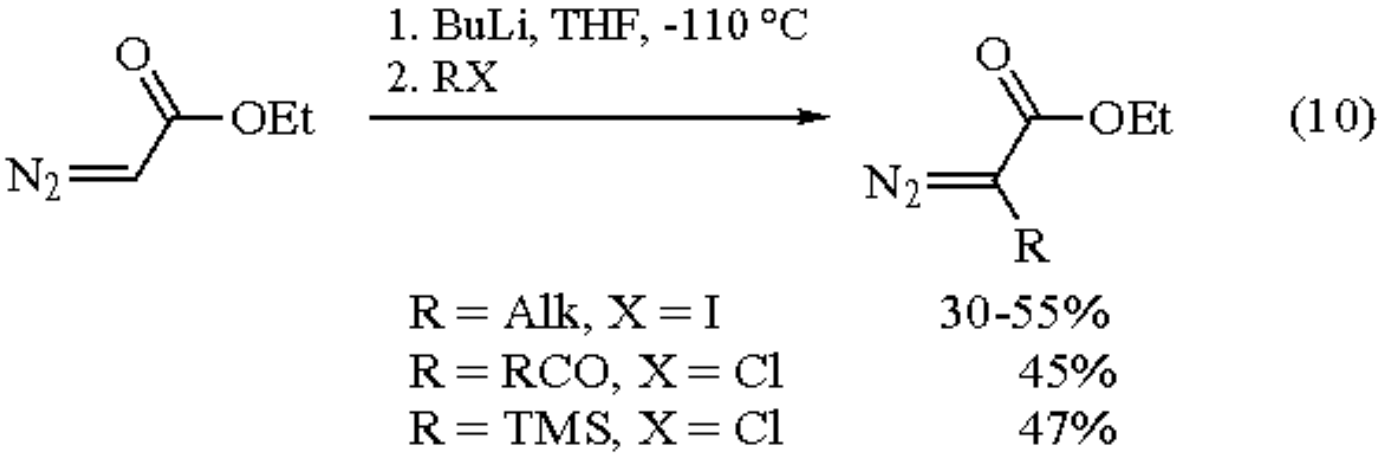

This reagent also reacts with carbonyl compounds, forming 2-diazo-3-hydroxy esters (eq 11).[5,6]

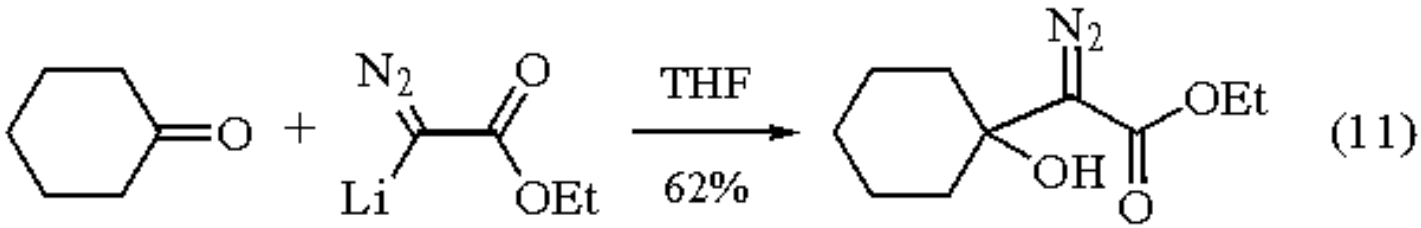

Transmetalation of ethyl lithiodiazoacetate gives access to silver, mercury, and tin derivatives of EDA.[5,6]

Cycloheptatrienes.

Thermal or photochemical decomposition of EDA in benzene and its derivatives leads to the formation of cycloheptatriene esters in moderate yields.[1,2] ***Dirhodium(II) Tetrakis(trifluoroacetate)*** has been recently reported to be a very effective catalyst for this reaction and increased the yields of cycloheptatrienes (eq 12).[31]

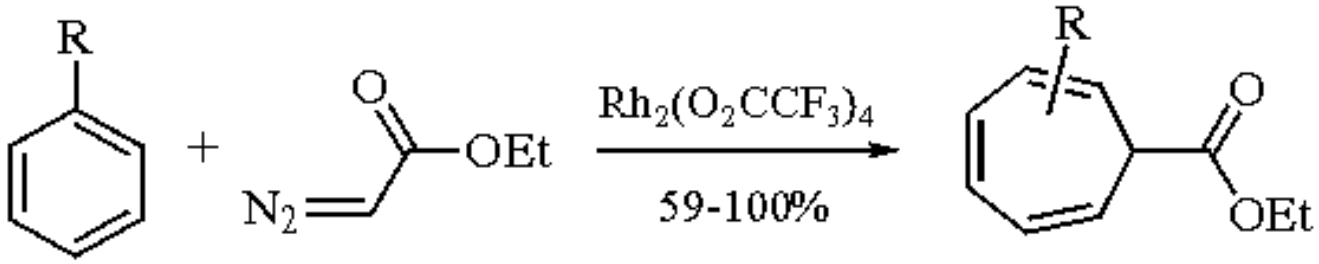

(12)

β-Keto Esters from Aldehydes.

In addition to methods of β-keto ester synthesis described above, these compounds can be prepared by the addition of EDA to aldehydes in the presence of ***Tin(II) Chloride*** (eq 13).[4]

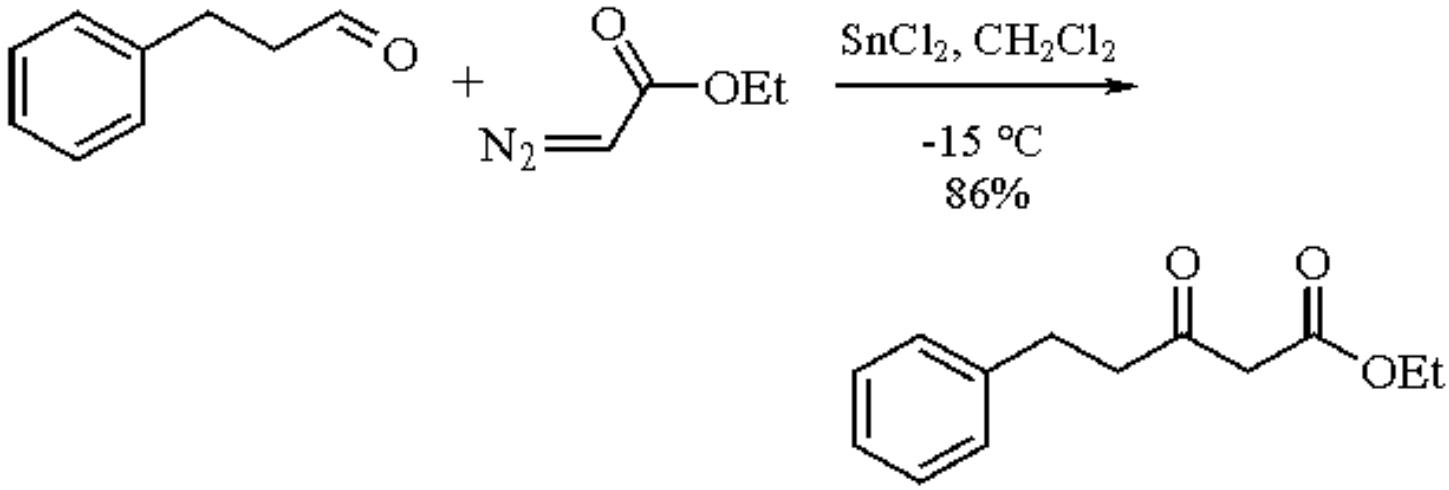

(13)

Ylide Rearrangements.

Catalytic decomposition of EDA in the presence of sulfides, tertiary amines, or iodides leads to formation of intermediate ylides which undergo Stevens rearrangement (eq 14).[2,3,6] Ylides bearing an allylic double bond give the products of a [2,3]-sigmatropic rearrangement (eq 15).[3,32]

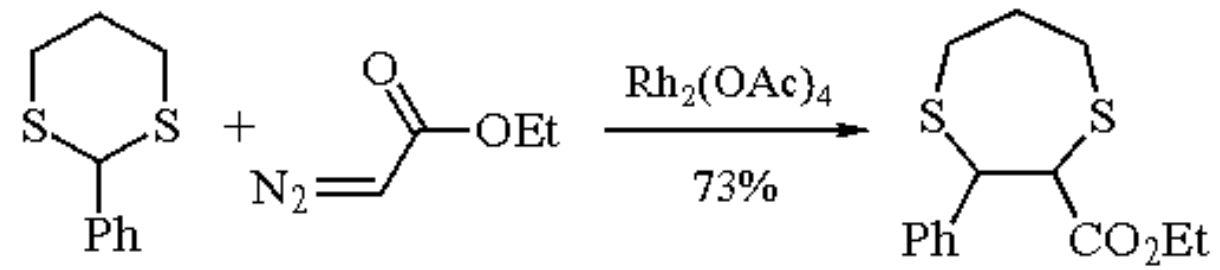

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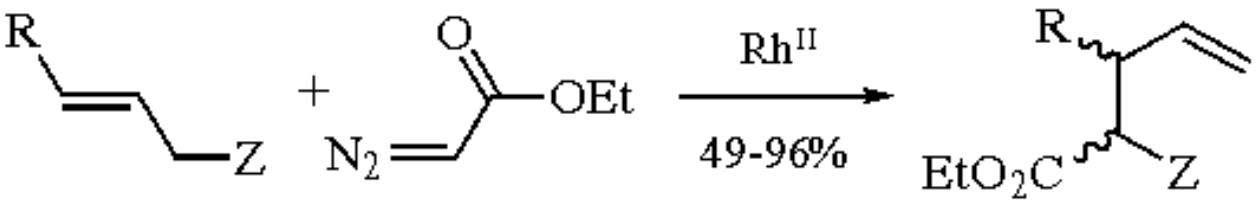

(15)

Dirhodium(II) Tetraacetate has been shown to be the most useful catalyst for this transformation.[3]

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Ethyl Diazolithioacetate[1]

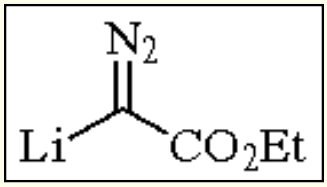

[55718-77-9] · $C_4H_5LiN_2O_2$ · Ethyl Diazolithioacetate · (MW 120.05)

(nucleophilic diazo species for preparation of substituted diazo esters,[2-9] β-keto esters,[3,6,10-12] acylalkynes,[13] and for carrying out one-carbon ring expansion reactions[14-16])

Alternate Name: ethyl lithiodiazoacetate.

Solubility: sol ether solvents.

Preparative Methods: prepared in situ by lithiation of ***Ethyl Diazoacetate*** using ***n-Butyllithium*** or ***Lithium Diisopropylamide***, or by transmetalation of $Hg[C(N_2)CO_2Et]_2$.

Handling, Storage, and Precautions: stable in solution only below -50 °C. Use in a fume hood.

Preparation of Diazo Esters.

Ethyl diazoacetate can be readily converted into a range of diazo esters by way of its lithio derivative. The lithium derivative can be prepared by transmetalation of diethyl mercuriobis(diazoacetate) with butyllithium at -70 °C,[2] or, much more conveniently, by lithiation of commercially available ethyl diazoacetate using butyllithium[2,3] or LDA.[4,5] The lithio derivative reacts with a range of electrophiles (eq 1) to give substituted diazoesters (Table 1). With carbonyl compounds, better yields are often obtained if butyllithium is added to the mixture of ethyl diazoacetate and carbonyl compounds;[3] acrolein undergoes exclusive 1,2-addition.[5,6] Similar condensations between ethyl diazoacetate and aldehydes (or ketones) can also be carried out in the presence of potassium hydroxide.[7]

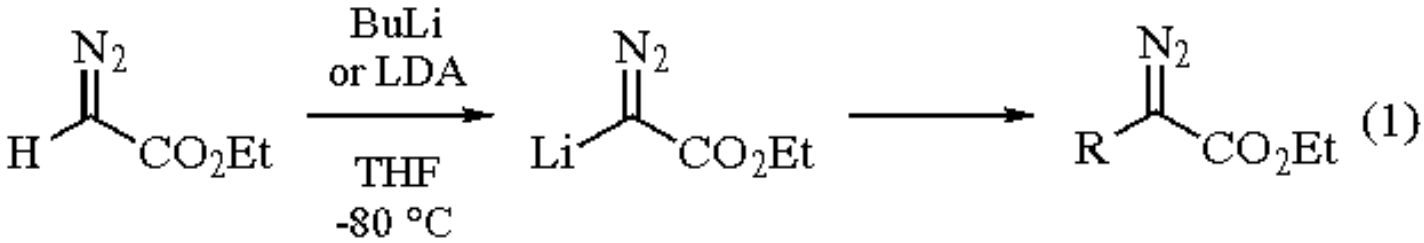

Table 1 Representative Examples of the Reaction of Ethyl Diazolithioacetate with Electrophiles

Electrophile	R	Yield (%)
Me_3SiCl[2]	Me_3Si	52
Bu_3SnCl[2]	Bu_3Sn	50
PhCOCl[2]	PhCO	45
PhCHO[2,3]	PhCH(OH)	41 (95)
$C_7H_{15}CHO$[4]	$C_7H_{15}CH(OH)$	68
$CH_2{=}CHCHO$[5,6]	$CH_2{=}CHCH(OH)$	87
PhCOMe[2,3]	PhCMe(OH)	50 (94)
MeCOMe[3]	$Me_2C(OH)$	93

Other carbonyl electrophiles such as six-membered lactones,[8] thiolactones,[9] and *N*-Boc lactams[8] also react with ethyl diazolithioacetate to give the corresponding diazo β-keto esters (eq 2), which in the case of the hydroxy and mercapto compounds can be recyclized to the corresponding seven-membered heterocycles by treatment with ***Dirhodium(II) Tetraacetate***.[8,9]

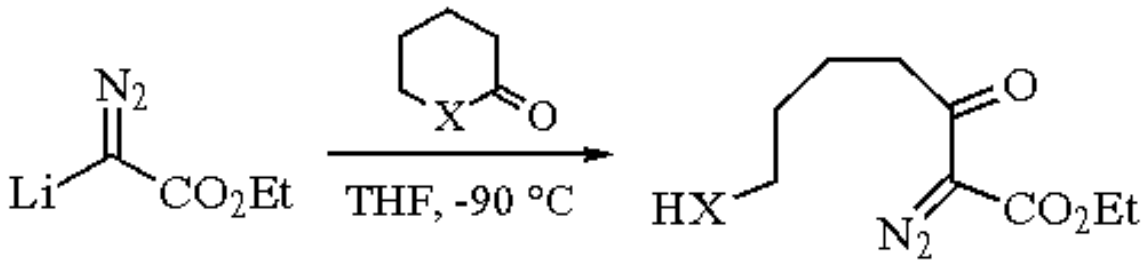

(2)

X = O 81%
X = S 58%
X = NBoc 60%

Preparation of β-Keto Esters and Related Compounds.

Addition of ethyl diazolithioacetate to aldehydes gives α-diazo-β-hydroxy esters (see above). Treatment of these with HCl,[3,10] rhodium(II) acetate,[11] or various other metal salts[12] results in loss of nitrogen and the formation of β-keto esters (eq 3). A variation on the reaction involves acetylation of the intermediate hydroxy diazo compound, followed by pyrolysis to give the enol acetate of the β-keto ester;[6] hydrogenation of the hydroxy diazo ester over palladium gives β-hydroxy esters (eq 3).[6]

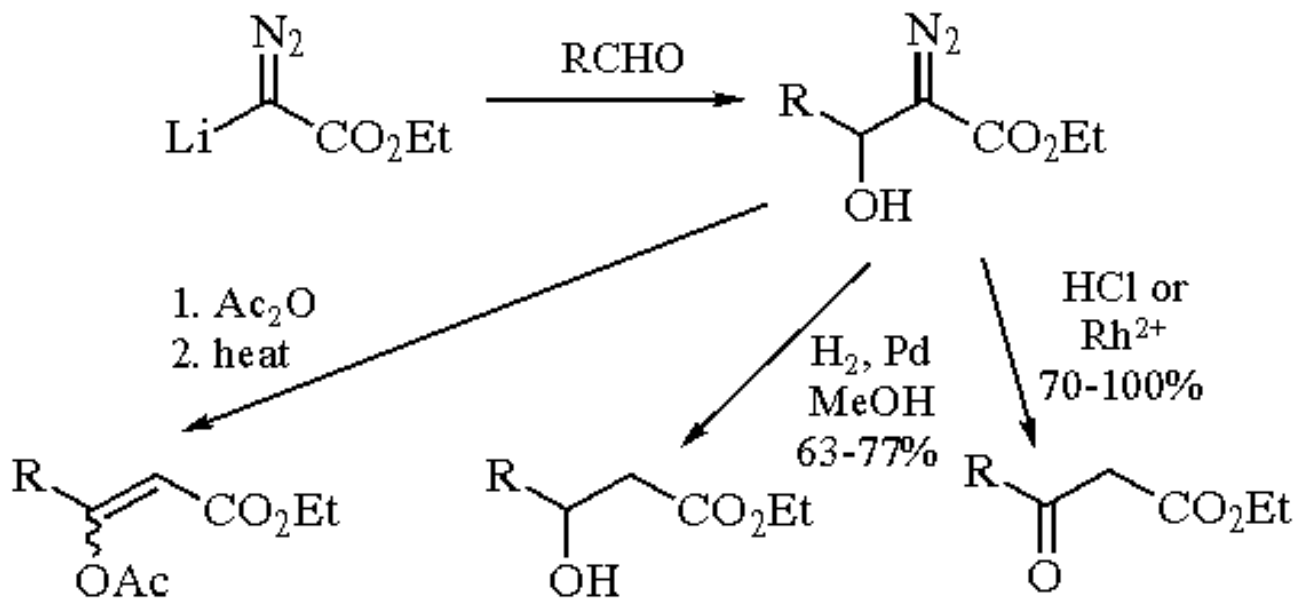

(3)

Preparation of Acylalkynes.

In contrast to the above reactions of α-diazo-β-hydroxy esters (eq 3), reaction of these species with ***Boron Trifluoride Etherate*** gives alkynic esters (eq 4).[13]

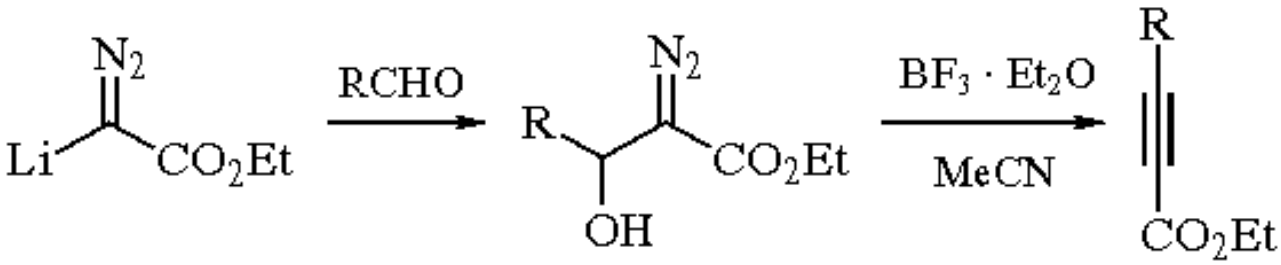

(4)

Ring Expansion Reactions.

The conversion of α-diazo-β-hydroxy esters derived from aldehydes into β-keto esters involves H-migration (eq 3); an analogous reaction of α-diazo-β-hydroxy esters derived from cyclic ketones would therefore result in a one-carbon ring expansion reaction. This has been successfully used for simple cyclic ketones (eq 5),[3] and for chromanones and their thio derivatives (eq 6).[14,15] Thiopyrylium salts can be similarly ring expanded.[16]

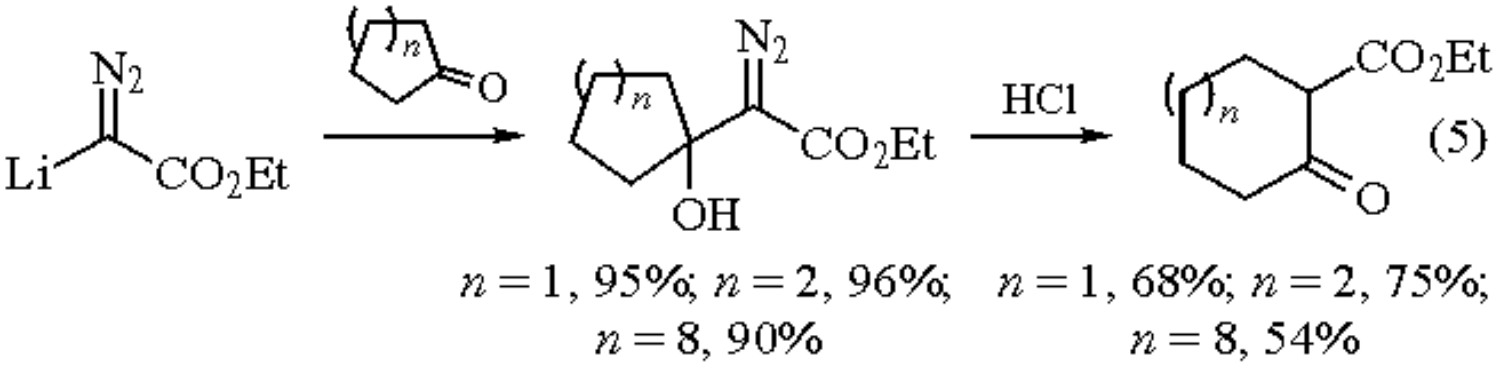

(5)

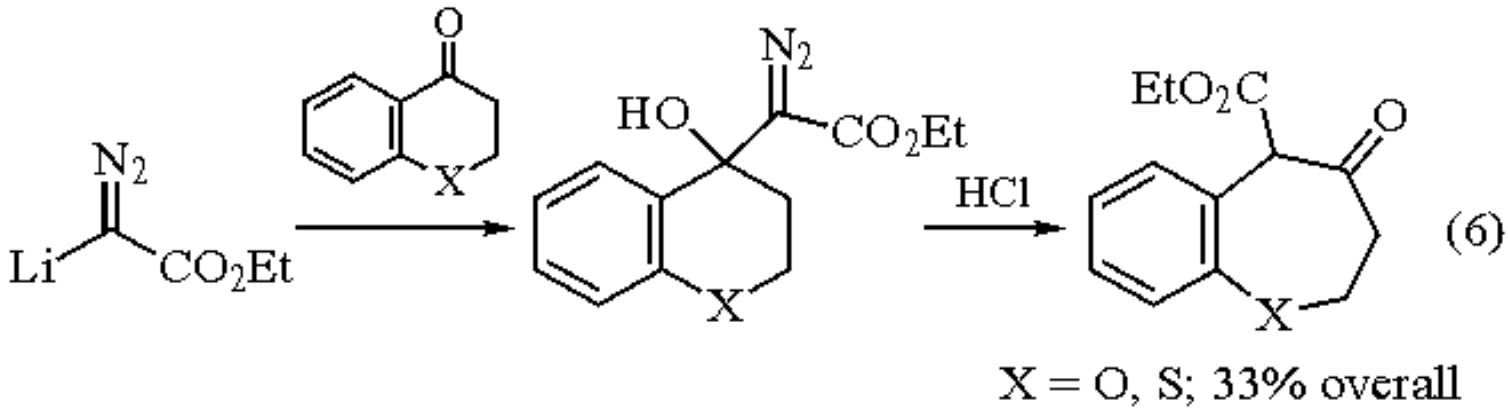

Related Reagents.

Other metalated derivatives of ethyl diazoacetate are known,[1] e.g. the silver derivative is readily converted into substituted diazo esters by alkylation (eq 7).[17]

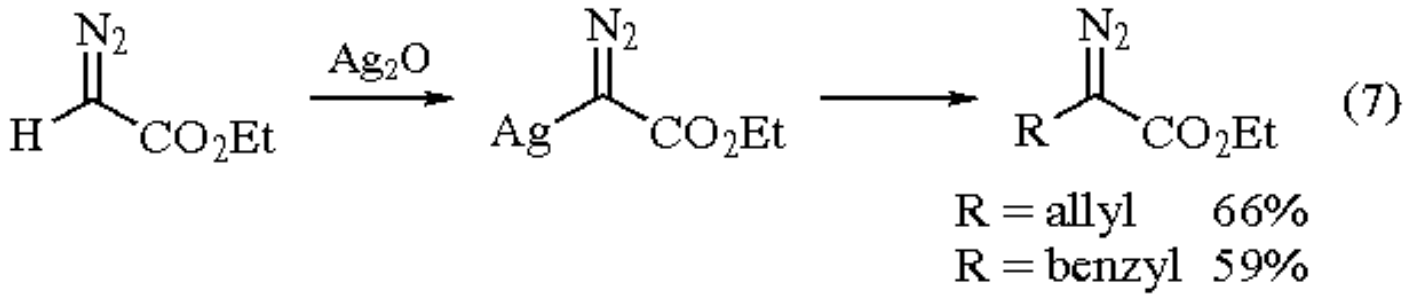

t-Butyl diazoacetate is also readily lithiated; quenching with lactones gives products entirely analogous to the ethyl ester (eq 2).[18]

Diazolithioacetone can be generated from ***Diazoacetone*** using butyllithium or LDA and participates in similar reactions to ethyl diazolithioacetate. Thus addition to aldehydes gives α-diazo-β-hydroxy ketones, treatment of which with rhodium(II) acetate gives β-diketones (eq 8),[19] or with boron trifluoride etherate to give acetylalkynes (cf. eq 4).[13]

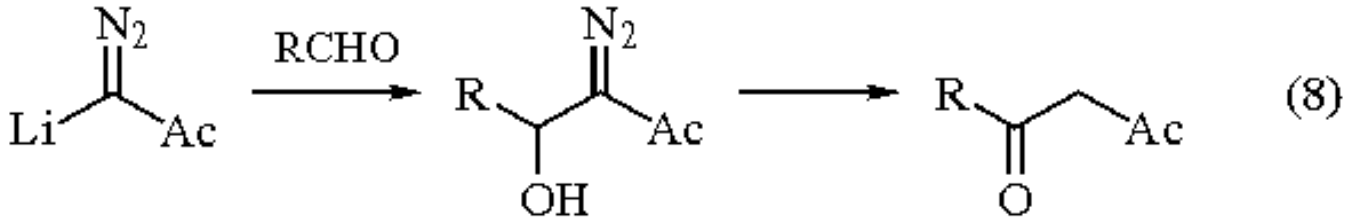

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Ethyl Dibromoacetate

Br_2CHCO_2Et

[617-33-4] · $C_4H_6Br_2O_2$ · Ethyl Dibromoacetate · (MW 245.90)

(used in preparation of α-bromo and α,α-dialkyl substituted esters;[1] undergoes Reformatsky/Darzens reactions with aldehydes and ketones[2])

Physical Data: bp 194 °C; 77 °C/12 mmHg; *d* 1.9025 g cm^{-3}.

Solubility: insol H_2O; sol hexane, ether, CH_2Cl_2, acetone, EtOAc, EtOH.

Form Supplied in: colorless to light yellow liquid; practical grade commercially available.

Handling, Storage, and Precautions: lachrymator; avoid inhalation of fumes. Handle in a fume hood.

Alkylation of Br_2CHCO_2Et with organoboranes in the presence of ***Potassium t-Butoxide*** or a hindered phenoxide base affords α-bromo esters or α,α-dialkyl substituted esters, depending upon the amounts of reagents employed and the reaction temperature (eq 1).[1] The phenoxide base (p*K* 11.7) minimizes self-condensation of both the starting material and the product. The procedure in eq 1 represents an attractive alternative to the classical malonic ester synthesis.[3]

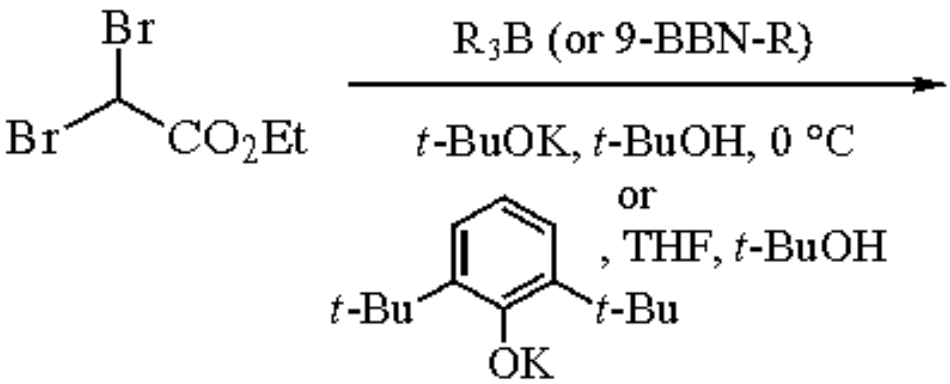

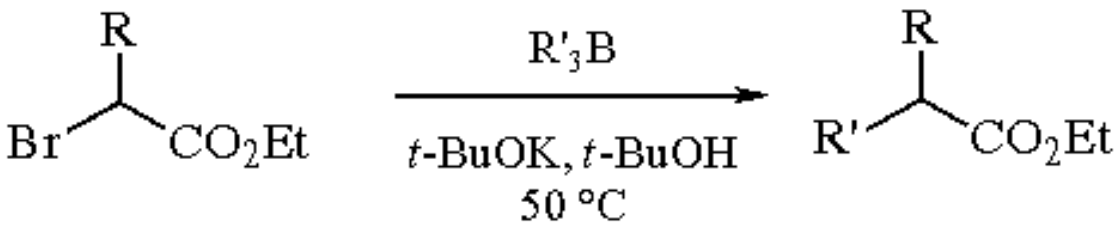

(1)

Reformatsky-type addition of Br_2CHCO_2Et to aldehydes or ketones at low temperature in the presence of zinc/silver-graphite provides α-bromo-β-hydroxy esters in excellent yield (eq 2).[2] Mild base treatment then yields the expected glycidic esters, while other transformations of the initial adduct have also been reported (eq 2).[4] The use of Zn/Ag-graphite represents a major improvement over the classical Reformatsky conditions,[5] which required the use of Zn, Mg, or Ca amalgams with Br_2CHCO_2Et to avoid reductive loss of the bromo substituent.[5] The Zn/Ag-C reagent has also been utilized with aldonolactones.[6] Modification of the Reformatsky-type zinc reagent by the addition of ***Diethylaluminum Chloride*** allows the isolation of α,β-unsaturated esters in moderate yield (eq 3),[7] an alternative to the Wadsworth-Emmons reaction.[8]

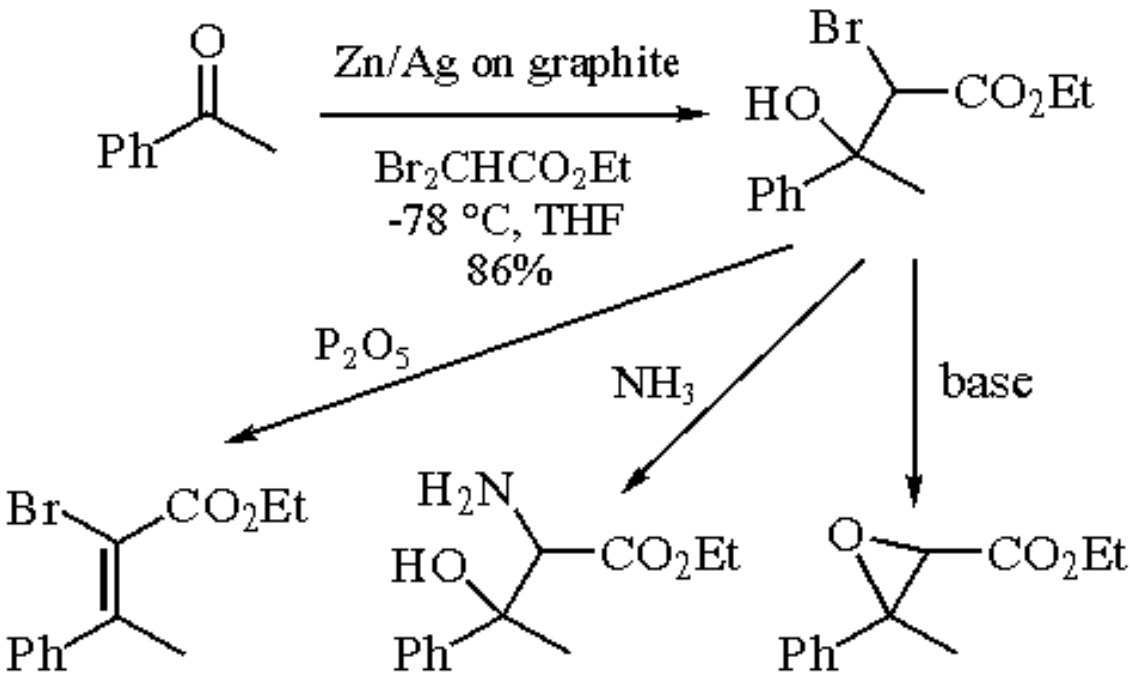

(2)

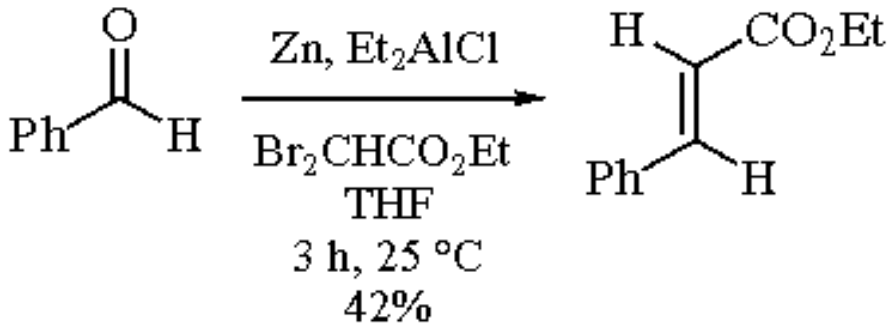

(3)

The ***Triethylborane*** catalyzed radical addition of Br_2CHCO_2Et to ketene acetals affords unsaturated 1,4-diesters in fair yield (eq 4),[9] although the generality of the reaction has not been explored.

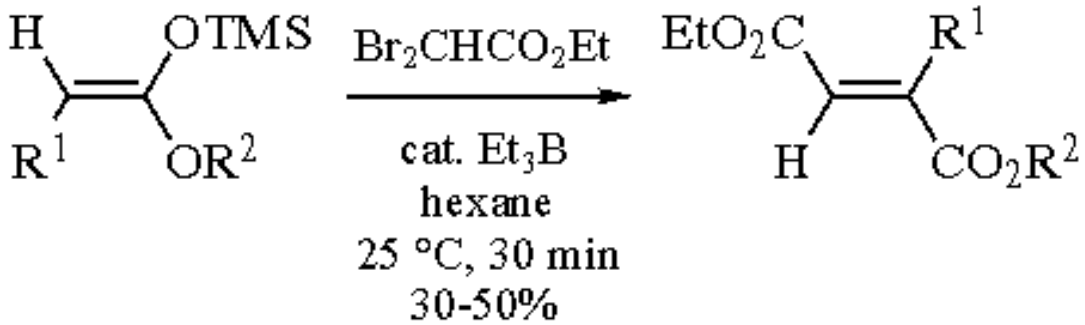

(4)

Under precisely controlled conditions (all reagents dispersed on sand), benzenethiolate displacement on Br_2CHCO_2Et provides the corresponding thioacetal (eq 5).[10] Further alkylation should provide a route to pyruvic acid derivatives.

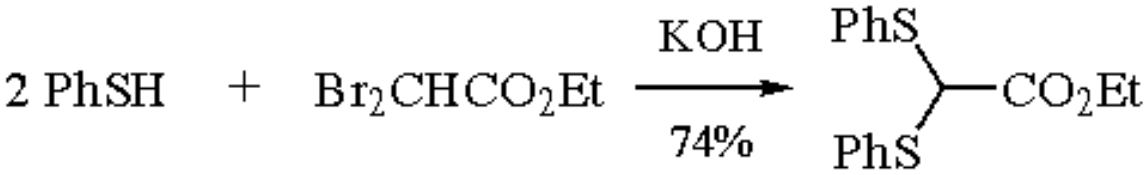

(5)

The ethoxycarbonylcyclopropanation of both simple alkenes (eq 6)[11] and alkylidenemalonates (eq 7)[12] with Br_2CHCO_2Et in the presence of copper powder or zinc has also been reported.

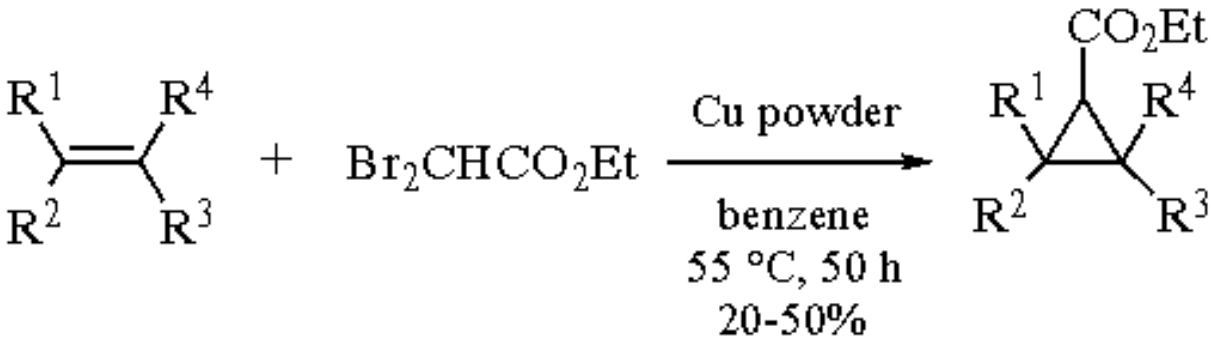

(6)

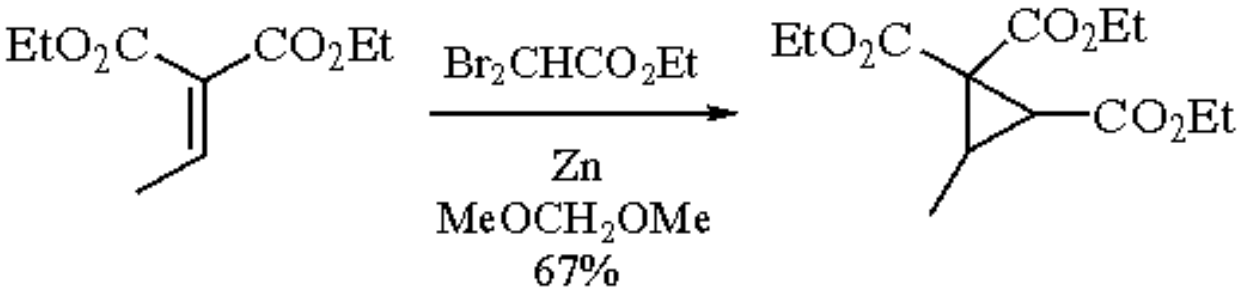

(7)

Related Reagents.

Dichloroacetonitrile; ***Methyl Dichloroacetate***.

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Ethyl 3,3-Diethoxyacrylate

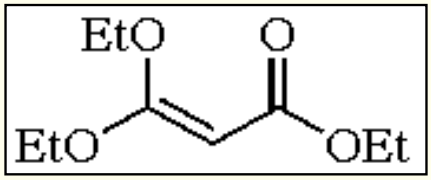

[32002-24-7] · $C_9H_{16}O_4$ · Ethyl 3,3-Diethoxyacrylate · (MW 188.25)

(used in cycloaddition reactions with cyclopentenones, 1-aza-1,3-butadienes, and alkynylalkoxycarbene metal complexes to give carbocyclic and heterocyclic compounds; undergoes [3,3]-sigmatropic rearrangement with allylic alcohols to give substituted allylmalonates.)

Physical Data: bp 122-123 °C/10 mmHg; *n*25D 1.4597.[1]

Solubility: sol organic solvents.

Handling, Storage, and Precautions: keep away from moisture. Handle in a fume hood.

Ethyl 3,3-diethoxyacrylate (**1**) is prepared[1] from ***Ethyl Cyanoacetate*** by the Pinner reaction.[2] It has been used in a variety of cycloaddition reactions. Head-to-tail regioselectivity in the [$_\pi$2 + $_\pi$2] photocycloaddition of (**1**) with cyclopentenones (**2**) to give the bicyclo[3.2.0]heptanones (**3**) was significantly better than that observed with methyl β-acetoxyacrylate. Treatment of the cycloaddition products (**3**) with ***Sodium Borohydride*** followed by ***p-Toluenesulfonic Acid*** gave the lactones (**4**).[3]

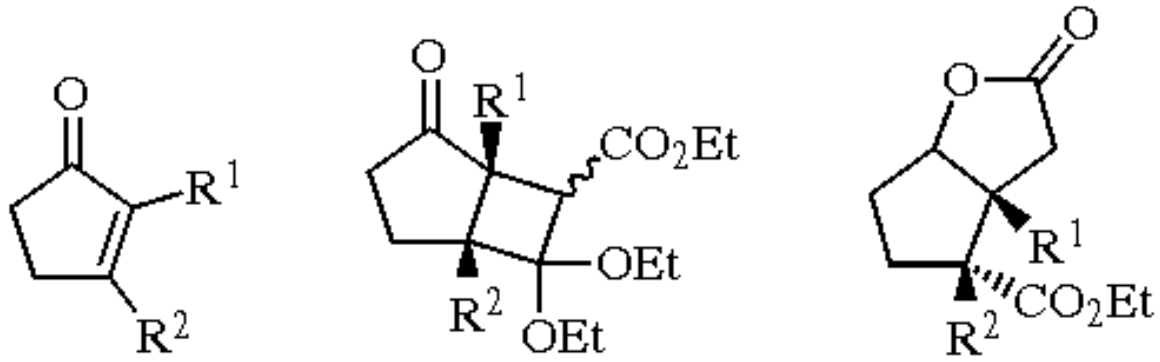

(2) **(3)** **(4)**

$R^1, R^2 = H, H; Me, H; H, Me$

Cycloaddition of the alkynylalkoxycarbene metal complexes (**5**) with (**1**) provided (**8**), via (**7**) and, presumably, (**6**).

Oxidation of (**8**) with ***Dimethyl Sulfoxide*** gave the 6-ethoxy-2*H*-pyrones (**9**).[4]

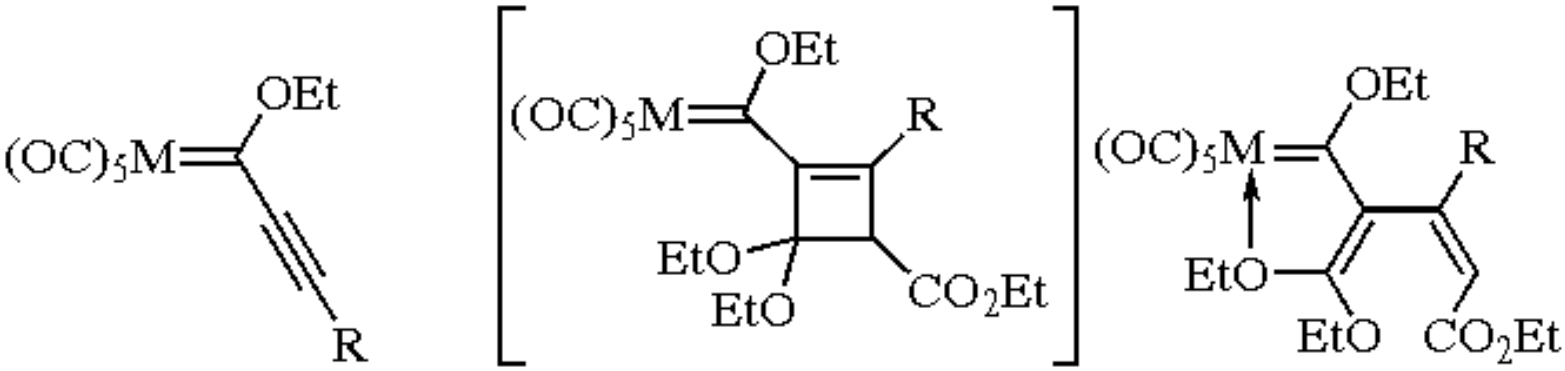

(5) **(6)** **(7)**

R = Ph, *t*-Bu; M = Cr, W

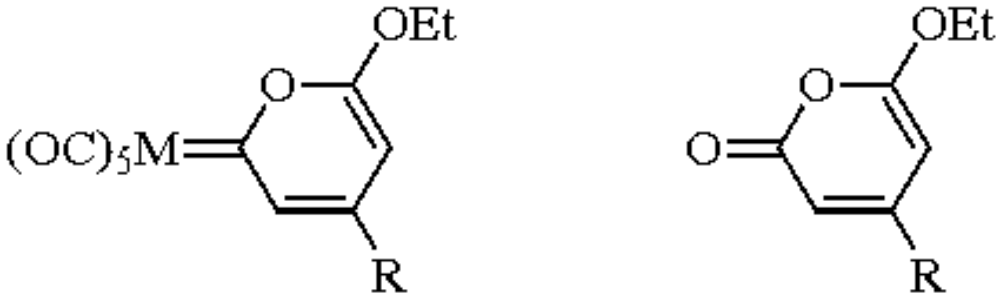

(8) **(9)**

Reaction of (**1**) and the 1-aza-1,3-butadiene (**10**) in a [4 + 2] cycloaddition reaction at 13 kbar (1300 MPa) provided (**11**), which was converted to the pyridine (**12**) by treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.[5]

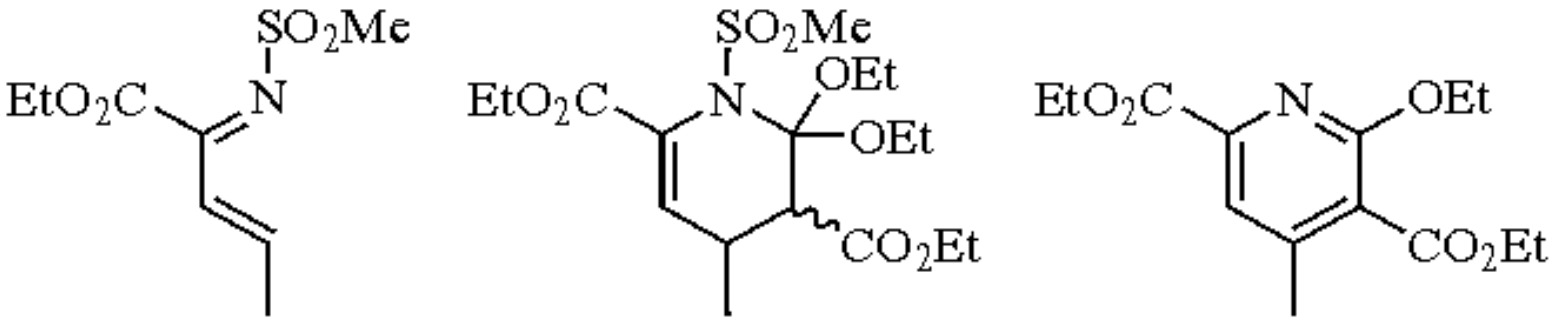

(10) **(11)** **(12)**

Raucher reported that the [3,3]-sigmatropic rearrangement of (**1**) with allylic alcohols (**13**) using a catalytic amount of ***2,4,6-Trimethylbenzoic Acid*** provides a convenient method for the regiospecific synthesis of substituted allylmalonate esters (**15**).[6] The alcohols examined were (**16**)-(**22**).

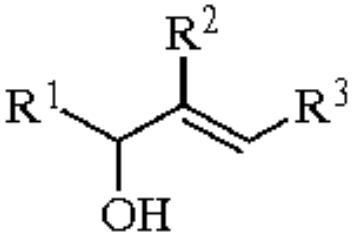

(13)

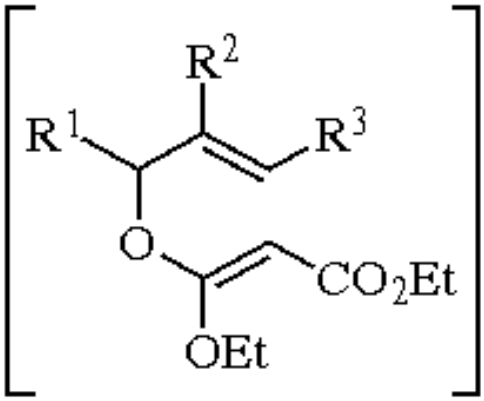

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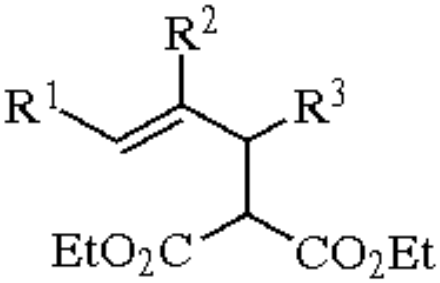

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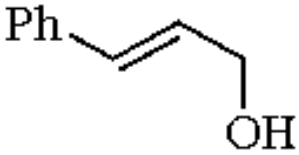

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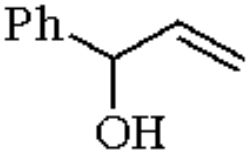

(17)

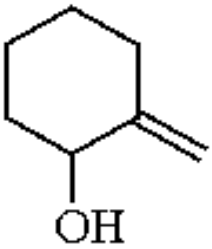

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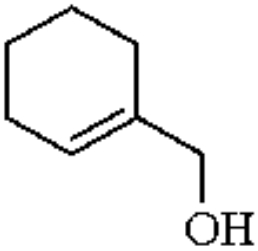

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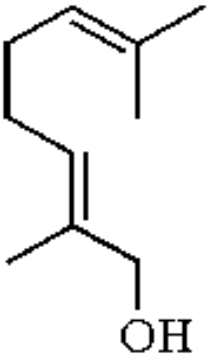

(20)

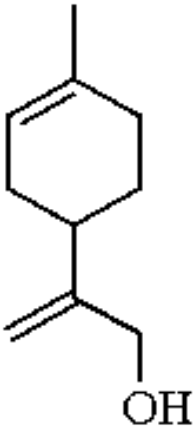

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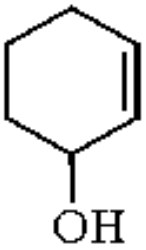

(22)

Trost reported that reaction of (**1**) and (**23**) with a catalytic amount of ***Pyridinium p-Toluenesulfonate*** at room temperature gave (**24**), an intermediate in a total synthesis of (-)-aspochalasin B.[7]

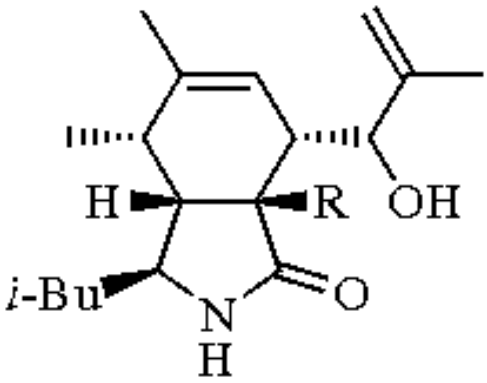

(23) R = $COCH_2SO_2Ph$

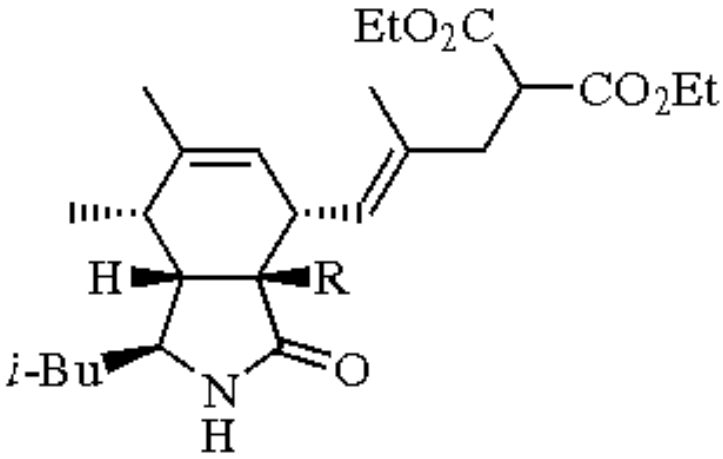

(24)

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl 3-Ethoxyacrylate***; ***Ketene Diethyl Acetal***; ***Methylketene Dimethyl Acetal***.

---

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N-Ethyl(diethoxyphosphinyl)methylketenimine

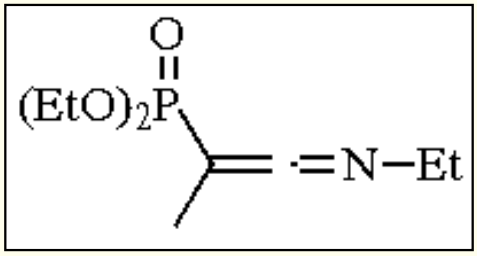

[73473-51-5] · $C_9H_{18}NO_3P$ · *N*-Ethyl(diethoxyphosphinyl)methylketenimine · (MW 219.25)

(ketenimine functionalized with a diethoxyphosphinyl group;[1] reacts with nucleophiles to give various phosphonates; an annulation reagent for the synthesis of heterocycles)

Physical Data: bp 86-90 °C/1 mmHg.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: IR: $\nu_{C=C=N}$ 2030 cm^{-1}.

Preparative Method: synthesized in 82% yield by the dehydration of diethyl (*N*-ethylcarbamoylethyl)phosphonate, which is prepared from *N*-ethyl-α-chloropropionamide and diethyl sodiophosphite (eq 1).

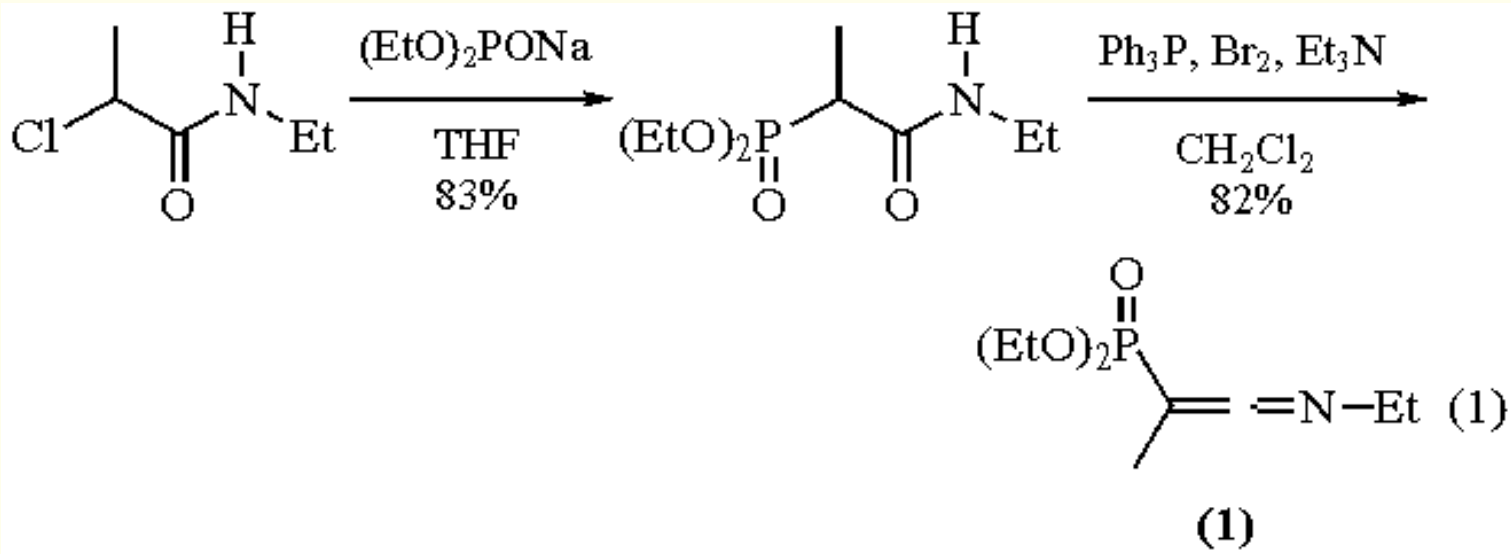

Handling, Storage, and Precautions: use in a fume hood.

Reaction with Nucleophiles and Use as an Annulation Reagent.[2]

Nucleophilic addition of ethanol, diethylamine, or hydrazoic acid to the title ketenimine (**1**) gives the imidate, amidine, or tetrazole with a phosphonyl residue, respectively, showing typical reactivity of ketenimines (eq 2).

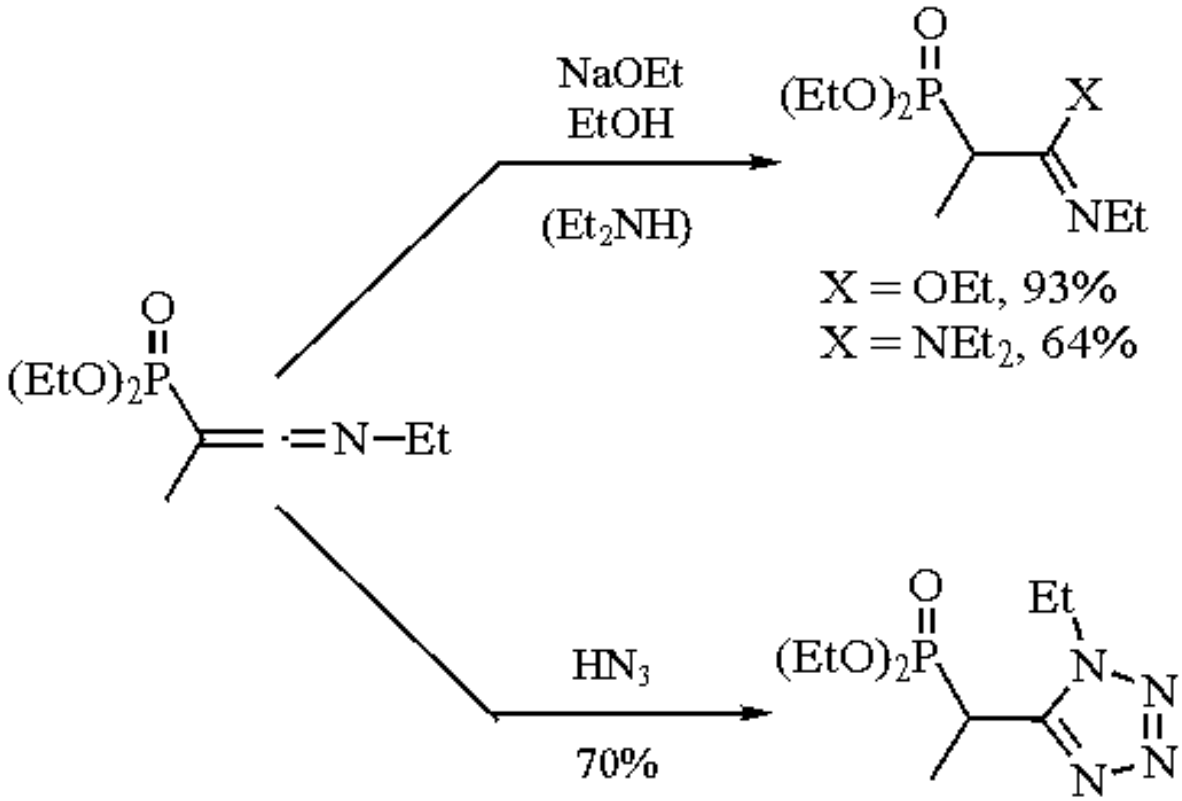

(2)

The reactions of (**1**) with sodium salts of salicylaldehyde, *o*-hydroxyacetophenone, α-formyl-β-naphthol, 2-formylpyrrole, and 2-acetylpyrrole in DMF give benzopyrans, naphthopyrans, and pyrrolizines with exocyclic imine groups (eqs 3 and 4). These annulation reactions occur via initial nucleophilic attack of the anionic species at the center carbon of the ketenimine followed by the intramolecular Horner-Emmons reaction as seen in the tandem Michael-Horner-Emmons reaction of vinylphosphonates.[3]

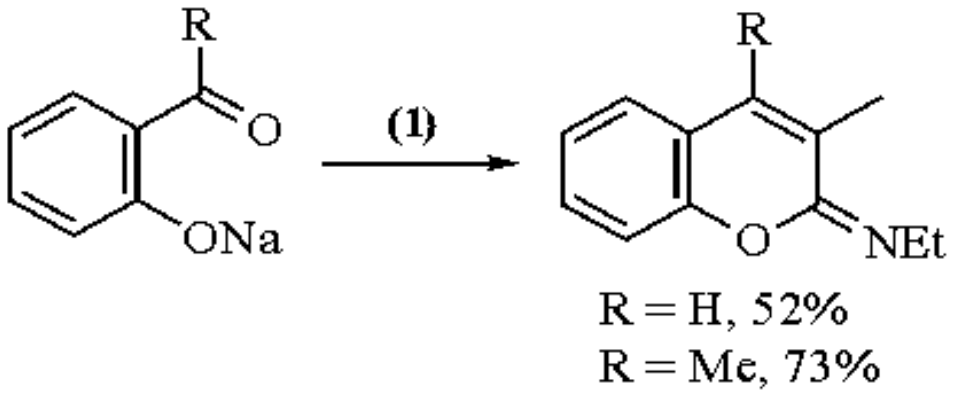

(3)

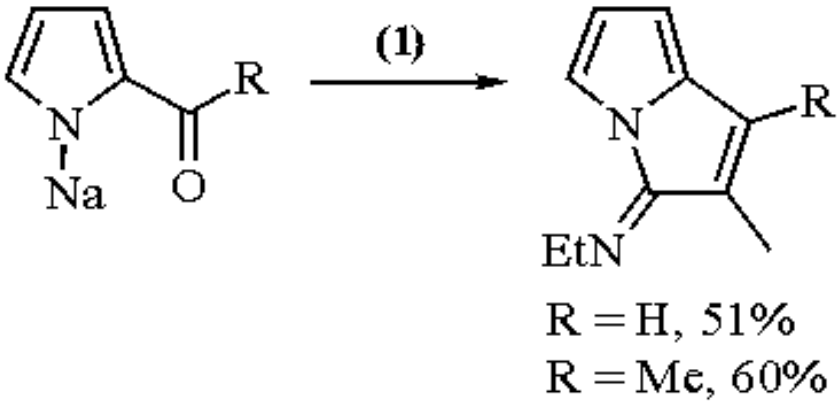

(4)

Related Reagents.

Trimethyl 2-Phosphonoacrylate; ***Tris(trimethylsilyl)ketenimine***.

---

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Ethyl 3,3-Diethoxypropanoate

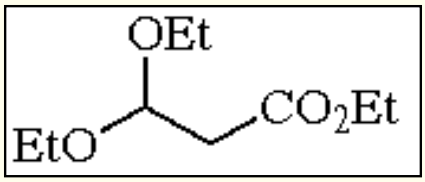

[10601-80-6] · $C_9H_{18}O_4$ · Ethyl 3,3-Diethoxypropanoate · (MW 190.27)

(synthesis of heterocycles; Pictet-Spengler reaction;[1] malonaldehyde monoacetal;[2] enantiomeric pure γ-amino-β-hydroxybutanoic acid[3])

Alternate Name: ethyl 3,3-diethoxypropionate.

Physical Data: bp 92-95 °C/15 mmHg; *d* 0.978 g cm^{-3}.

Solubility: sol water, diethyl ether.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: *n*20D = 1.4117.

Preparative Methods: can be obtained by treatment of 1,1,1-trichloro-4-ethoxy-3-buten-2-one with ethanol in the presence of catalytic amounts of ***Potassium Carbonate***. The trichloromethyl ketone is prepared from ***Ethyl Vinyl Ether*** and ***Trichloroacetyl Chloride***.[4]

Purification: fractional vacuum distillation through a short Vigreux column.

Handling, Storage, and Precautions: ethyl 3,3-diethoxypropanoate is the stable, protected derivative of the unstable 3-oxopropanoate. It can be stored at room temperature for several months without decomposition.

Ethyl 3,3-diethoxypropanoate is a useful starting material for the synthesis of heterocycles such as coumarins (eq 1),[5] isoxazoles,[6] pyrimidines,[7] porphyrins,[8] imidazolinones,[9] and thiadiazines (eq 2).[10] Also spermine metabolites,[11] steroids,[1] herbicides,[12] antihypertensives,[13] photographic sensitizers,[14] cephalosporins,[15] lycopodium alkaloids,[16] nucleic acids,[17] prostaglandin ($PGF_{2\alpha}$) precursor,[18] pentaerythriol[19] as well as related alcohols can be obtained from ethyl 3,3-diethoxypropanoate.

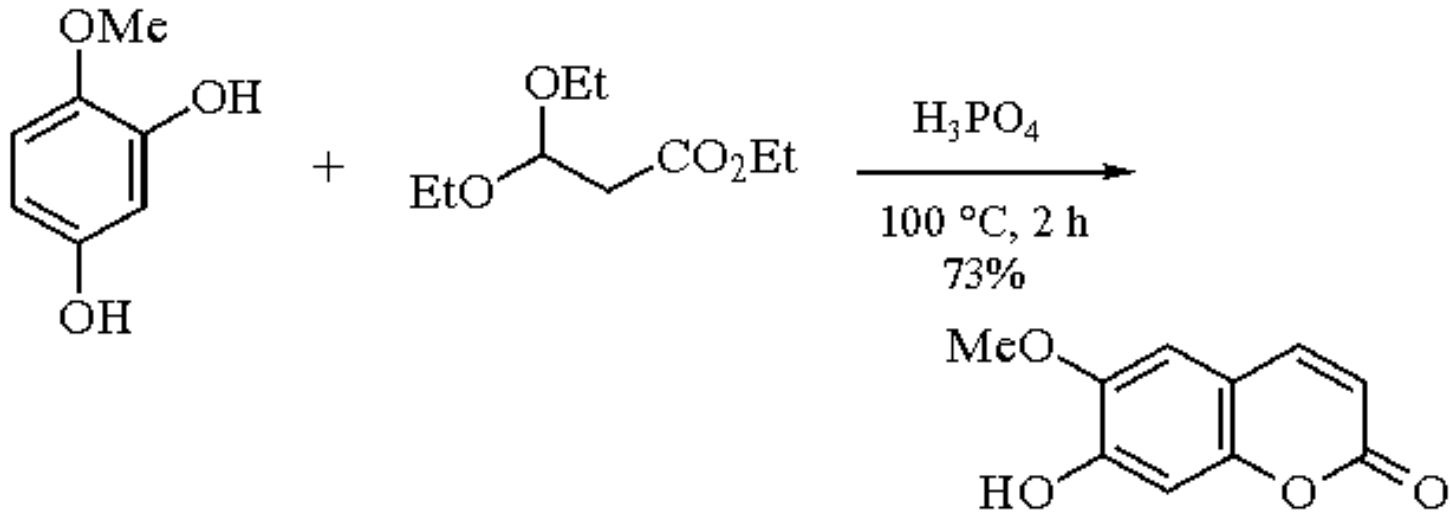

(1)

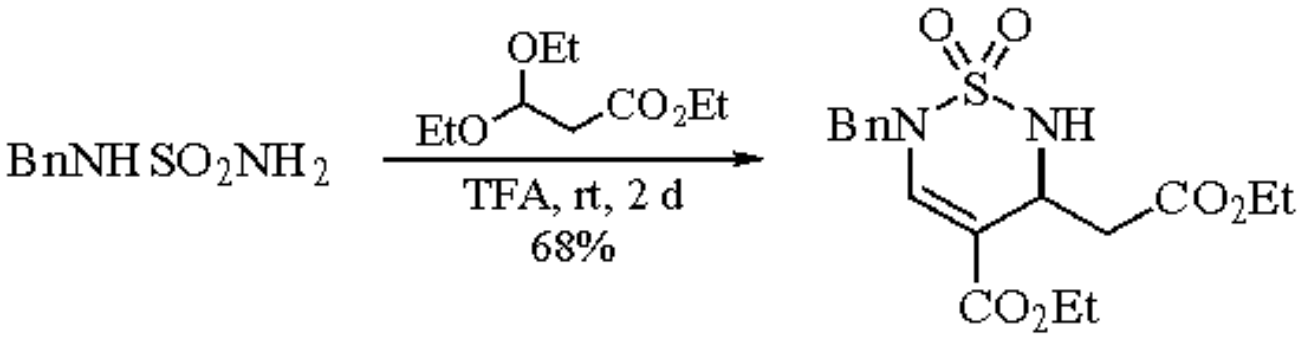

(2)

Ethyl 3,3-diethoxypropanoate can be used for Pictet-Spengler reactions (eq 3),[1] and various other condensation reactions.[5,8-10,20]

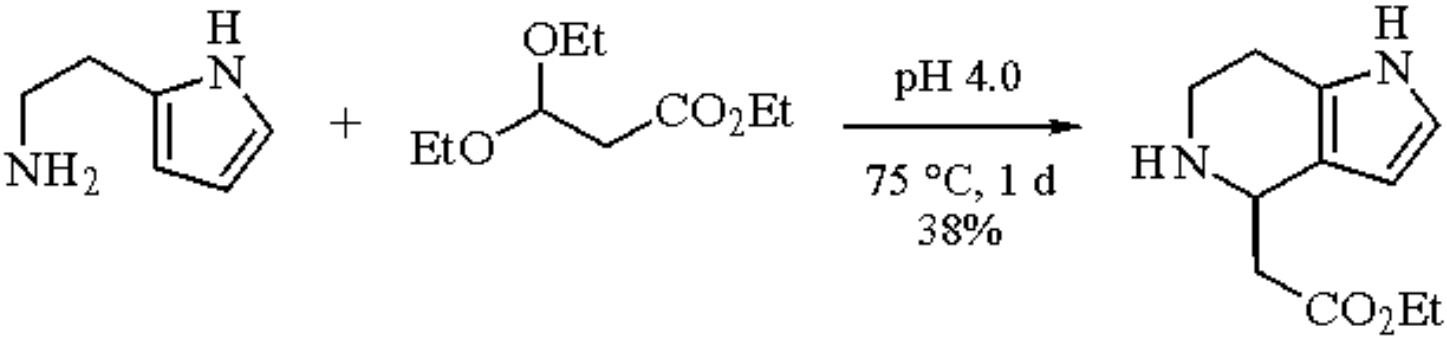

(3)

Different monoprotected malonaldehydes can be obtained from ethyl 3,3-diethoxypropanoate by transacetalization and reduction with ***Diisobutylaluminum Hydride***/Et_2O at -78 °C[2a,b] or with ***Lithium Aluminum Hydride*** followed by oxidation with ***Dimethyl Sulfoxide-Oxalyl Chloride***.[4] The malonaldehyde monoacetals were employed in the synthesis of dihydropyrans[21a] and secologanin derivatives[21b,c] by tandem Knoevenagel hetero-Diels-Alder reactions.[22] They can also be used in Wittig reactions with various phosphorus ylides, and in addition of Grignard reagents, carbanions generated from nitroalkanes, and other organometallic compounds.[2c] They are also valuable substrates for the synthesis of heterocycles such as pyrazoles, isoxazoles, and pyrimidines.[2c]

Ethyl 3,3-diethoxypropanoate is used for the total synthesis of both enantiomers of 3-amino-2-hydroxybutanoic acid (GABOB) by enzymatic kinetic resolution of its cyanohydrin acetate (eq 4).[3] As a substitute of ethyl 3,3-

diethoxypropanoate and the unstable 3-oxopropanoate, the stable 4,4,4-trichloro-3-oxobutanal may be used since the α,α,α-trichlorocarbonyl group can easily be transformed into an ester moiety with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** in the presence of an alcohol.[21a,b]

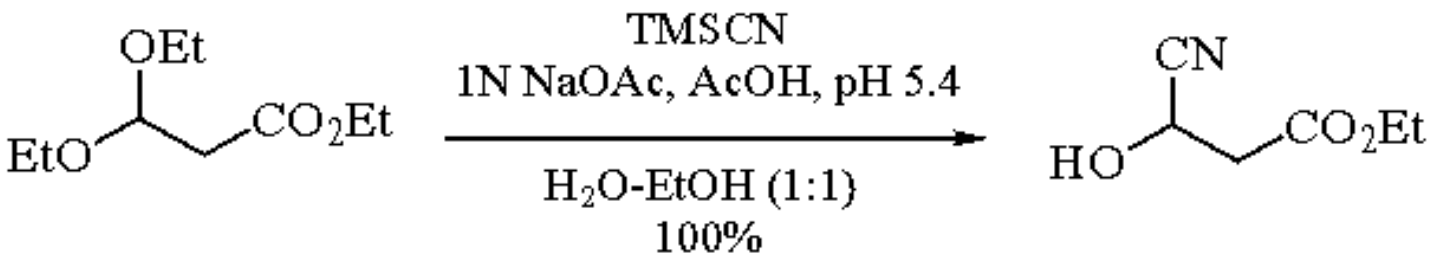

(4)

In addition, diformylacetates, which are useful educts for the synthesis of 1,4-dihydropyridines and NADH analogs as well as sugar derivatives (see ***Methyl Diformylacetate***), can be obtained from ethyl 3,3-diethoxypropanoate by formylation.

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***3-Ethoxyacrolein***; ***Ethyl Hydroxymethyleneacetate, Sodium Salt***; ***Malondialdehyde***; ***Methyl Diformylacetate***.

---

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Ethyl Difluoroiodoacetate

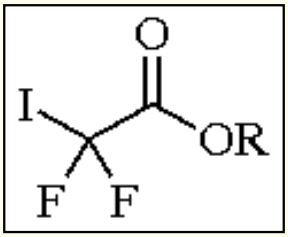

(R = Et)

[7648-30-8] · $C_4H_5F_2IO_2$ · Ethyl Difluoroiodoacetate · (MW 249.94) (R = Me)

[109872-87-9] · $C_3H_3F_2IO_2$ · Methyl Difluoroiodoacetate · (MW 235.92)

(useful for introduction of a CF_2CO_2R group)

Physical Data: R = Et, bp 70-72 °C/70 mmHg;[1] bp 72-74 °C/70 mmHg.[2]

Preparative Methods: prepared by the reaction of $FSO_2OCF_2CO_2Et$ with NaI (93%) (eq 1);[2] oxidation of $CF_2ICH{=}CF_2$ followed by esterification with EtOH (overall, 21% (eq 2);[3] by the addition of ICl to EtOCF = CF_2 followed by hydrolysis (overall, 44%) (eq 3);[1] and by the iodination of $XZnCF_2CO_2Et$ generated from $BrCF_2CO_2Et$ (available commercially) and Zn (58-73%) (eq 4).[4]

$$FSO_2OCF_2CO_2Et \xrightarrow{NaI} ICF_2CO_2Et \qquad (1)$$

$$CF_2Br_2 \xrightarrow{F_2C{=}CH_2} CF_2BrCH_2CF_2Br \xrightarrow{NaOH}$$

$$CF_2BrCH{=}CF_2 \xrightarrow{NaI} CF_2ICH{=}CF_2 \xrightarrow[2.\ EtOH]{1.\ KMnO_4} ICF_2CO_2Et \qquad (2)$$

$$F_2C{=}CFOEt \xrightarrow{ICl} ICF_2CFClOEt \xrightarrow{H_2SO_4} ICF_2CO_2Et \qquad (3)$$

$$BrCF_2CO_2Et \xrightarrow[2.\ I_2]{1.\ Zn} ICF_2CO_2Et \qquad (4)$$

Handling, Storage, and Precautions: handle in a fume hood

Reformatsky Reaction.

Treatment of difluoroiodoacetates with ***Zinc*** and aldehydes or imines gives the corresponding β-hydroxy-α,α-difluoro esters (eq 5)[5] and α,α-difluoro β lactams,[6] respectively. Alternatively, $BrCF_2CO_2Et$ could also be utilized as a precursor for this transformation.[7] Difluoroiodoacetates are converted to the 2,2-difluoroketene silyl acetal by the reaction with Zn and ***Chlorotrimethylsilane***. Subsequently, the silyl acetal reacts with α,β-unsaturated compounds to form the 1,4-addition product or a mixture of 1,4-addition and 1,2-addition products.[8]

$$ICF_2CO_2Et + RCHO \xrightarrow{Zn} RCH(OH)CF_2CO_2Et \qquad (5)$$

Formation and Reactions of the $CuCF_2CO_2R$ Reagent.

The copper reagent $CuCF_2CO_2R$ is prepared by the reaction of difluoroiodoacetate and ***Copper***. This copper reagent couples with a variety of halides including vinyl bromides and iodides, aryl and alkyl iodides, and allyl and benzyl bromides (eq 6).[9]

$$ICF_2CO_2R + Cu + RX \longrightarrow RCF_2CO_2R \qquad (6)$$

Radical Addition to Alkenes.

Addition of difluoroiodoacetates to alkenes has been initiated by Cu,[4,10] peroxide, and metallo complexes[11] to give the corresponding ester adduct, which could be reduced by ***Zinc/Nickel(II) Chloride***[4] to form the iodine-free α,α-difluoro ester (eq 7). More conveniently, the α,α-difluoro ester could be prepared from difluoroiodoacetates and alkenes in the presence of $Zn/NiCl_2.6H_2O$.[12] In this process, $Zn/NiCl_2.6H_2O$ behaves both as the radical initiator and the reducing reagent (eqs 7 and 8).

$$ICF_2CO_2R + H_2C{=}CHR' \xrightarrow{Cu} R'CHICH_2CF_2CO_2R \xrightarrow[NiCl_2 \cdot 6H_2O]{Zn} R'CH_2CH_2CF_2CO_2R \qquad (7)$$

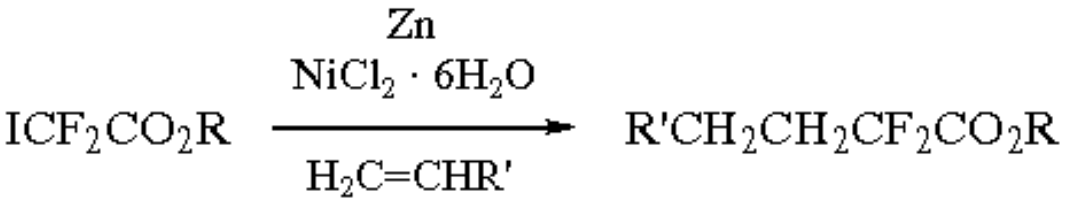

(8)

Related Reagents.

Chlorodifluoromethane; ***Dibromodifluoromethane***; ***Ethyl Bromozincacetate***; ***Methyl Bromoacetate***; ***Sodium Chlorodifluoroacetate***; ***Zinc***.

---

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1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride[1]

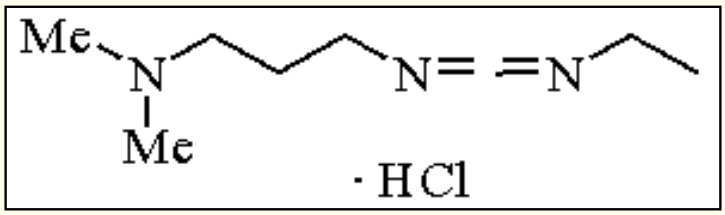

[25952-53-8] · $C_8H_{18}ClN_3$ · 1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride · (MW 191.74) (base)

[1892-57-5] (.MeI)

[22572-40-3]

(peptide coupling reagent;[1b,2] amide formation;[3] ester formation;[4] protein modification;[5] mild oxidations of primary alcohols[6])

Alternate Name: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; water-soluble carbodiimide; EDC; EDCI.

Physical Data: free base is an oil, bp 47-48 °C/0.27 mmHg; HCl salt is a white powder, mp 111-113 °C; MeI salt mp 97-99 °C.

Solubility: sol H_2O, CH_2Cl_2, DMF, THF.

Form Supplied in: commercially available as HCl salt and as methiodide salt that are white solids. Reagents are >98% pure; main impurity is the urea that can form upon exposure to moisture.

Analysis of Reagent Purity: IR: 2150 cm^{-1} (N=C=N stretch); urea has C=O stretch near 1600-1700 cm^{-1}.

Purification: recrystallization from CH_2Cl_2/ether.

Handling, Storage, and Precautions: EDC is moisture-sensitive; store under N_2 in a cool dry place. It is incompatible with strong oxidizers and strong acids. EDC is a skin irritant and a contact allergen; therefore avoid exposure to skin and eyes.

Peptide Coupling Reagent.

This carbodiimide (EDC) reacts very similarly to ***1,3-Dicyclohexylcarbodiimide*** and other carbodiimides. The advantage EDC has over DCC is that the urea produced is water soluble and, therefore, is easily extracted. Dicyclohexylurea is only sparingly soluble in many solvents and is removed by filtration which may not be as effective as extraction. A typical example of EDC for peptide coupling is shown in (eq 1).[2]

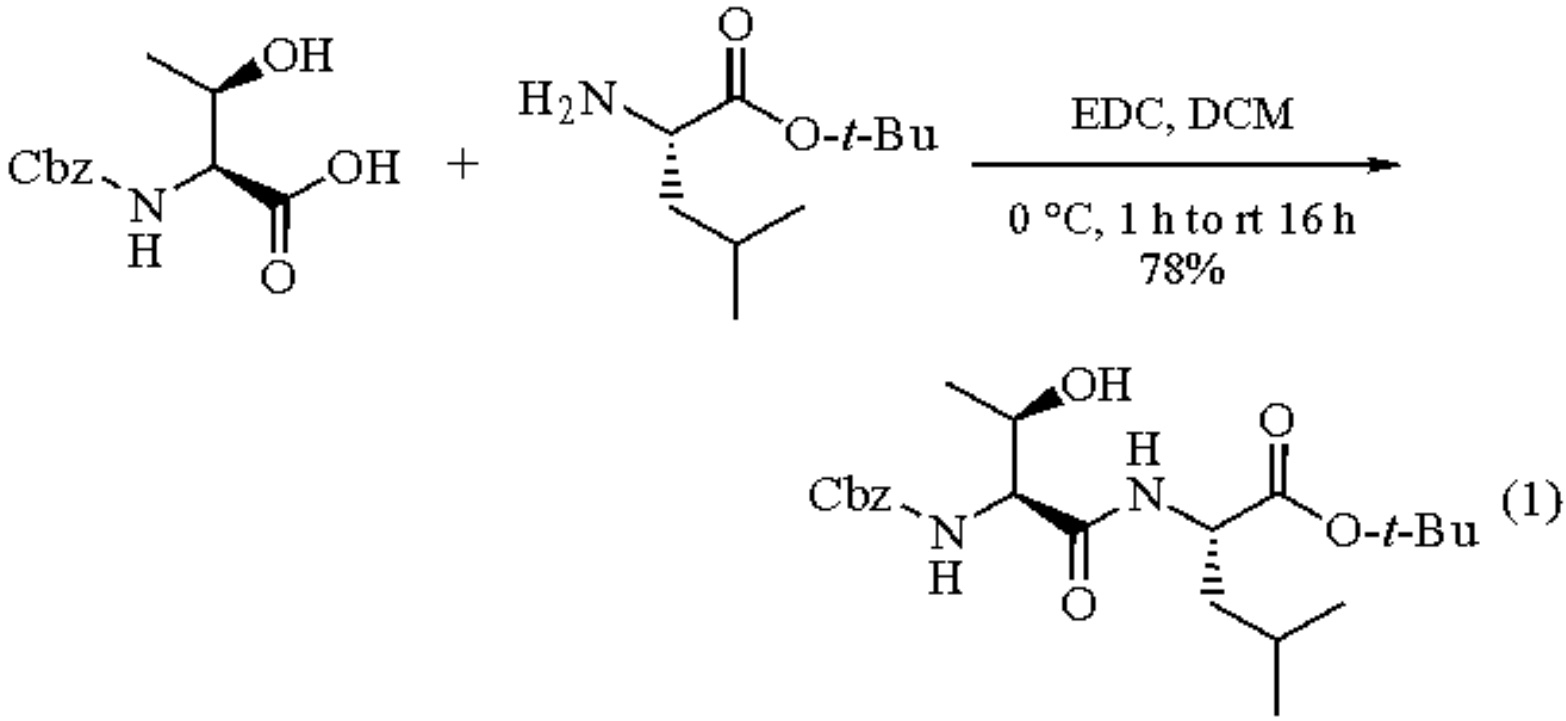

The problems associated with carbodiimide couplings are mainly from the *O*-acylisourea intermediate (**1**) having poor selectivity for specific nucleophiles. This intermediate can rearrange to an *N*-acylurea (**2**), resulting in contamination of the product and low yields. Additionally it can rearrange to 5(4*H*)-oxazolones (**3**) that tautomerize readily, resulting in racemization. Using low dielectric solvents like CH_2Cl_2 or additives to trap (**1**) minimizes these side reactions by favoring intermolecular nucleophilic attack on (**1**).[1b]

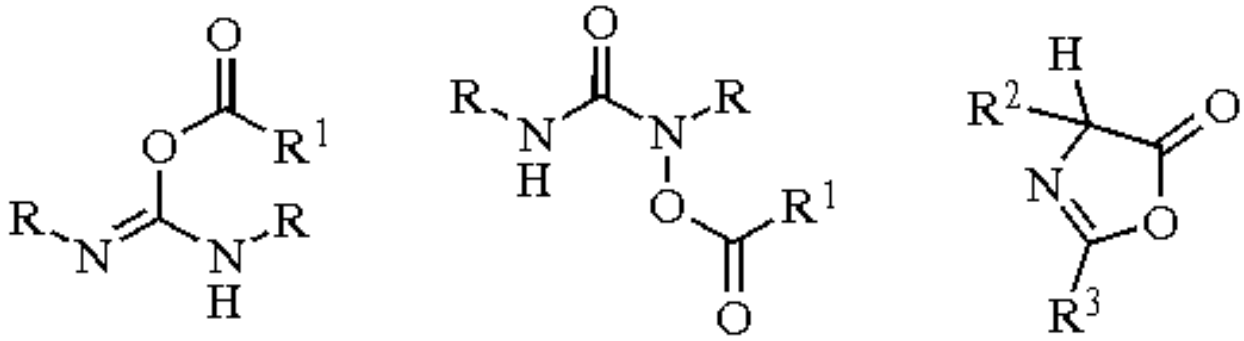

(1) (2) (3)

R = carbodiimide chain; R^1 = amino acid; R^2 = amino acid side chain; R^3 = NH protecting group

When low dielectric constant solvents are used, the carboxylic acid tends to dimerize, thus promoting symmetrical anhydride formation. This intermediate is stable enough to give good yields of the desired product. High dielectric solvents such as DMF retard acylation of amino acids, and *N*-acylurea can be a major byproduct.[1b] Unfortunately, many starting materials require polar solvents for dissolution.

Addition of trapping agents such as ***N-Hydroxysuccinimide***[7] and ***1-Hydroxybenzotriazole*** (HOBt)[8] reduce the extent of many side reactions, especially *N*-acylurea formation. Also, racemization is suppressed when these additives are present. The latter reagent eliminates the intramolecular dehydration of o-amides of asparagine and glutamine that occurs with carbodiimides (eq 2).[8,9]

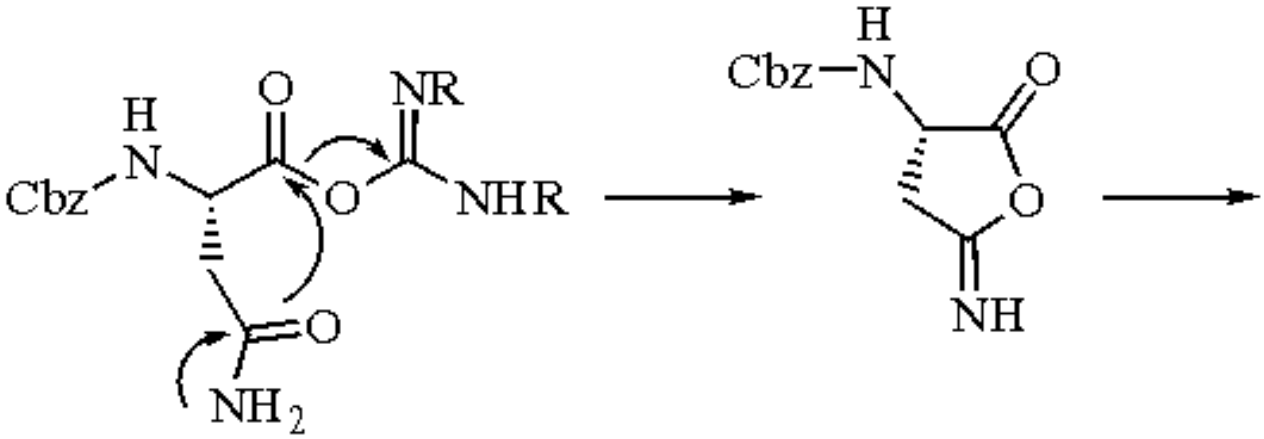

R = carbodiimide chain

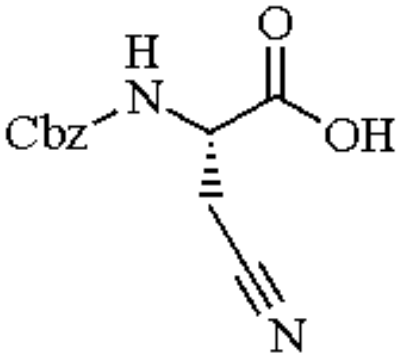

(2)

With EDC the addition of ***Copper(II) Chloride*** suppresses racemization to <0.1% compared to 0.4% with HOBt under ideal conditions.[10] Combinations of HOBt and $CuCl_2$ are also useful.[10b] The suggested stoichiometry for the highest optical purity and yield is 2 equiv of HOBt and 0.25-0.5 equiv of $CuCl_2$ in DMF.

A practical example of EDC's utility is the solution synthesis of human epidermal growth factor, a 53-residue protein.[11] This included several couplings of fragments ranging from three to six residues in length. All couplings were performed with EDC/HOBt in DMF or NMP. At the completion of the synthesis, no racemized material could be detected by HPLC.

Amide Formation.

Formylated amino acids and peptides are prepared in high yields by forming the acid anhydride (eq 3).[3] These products are pure without requiring chromatography or recrystallization.

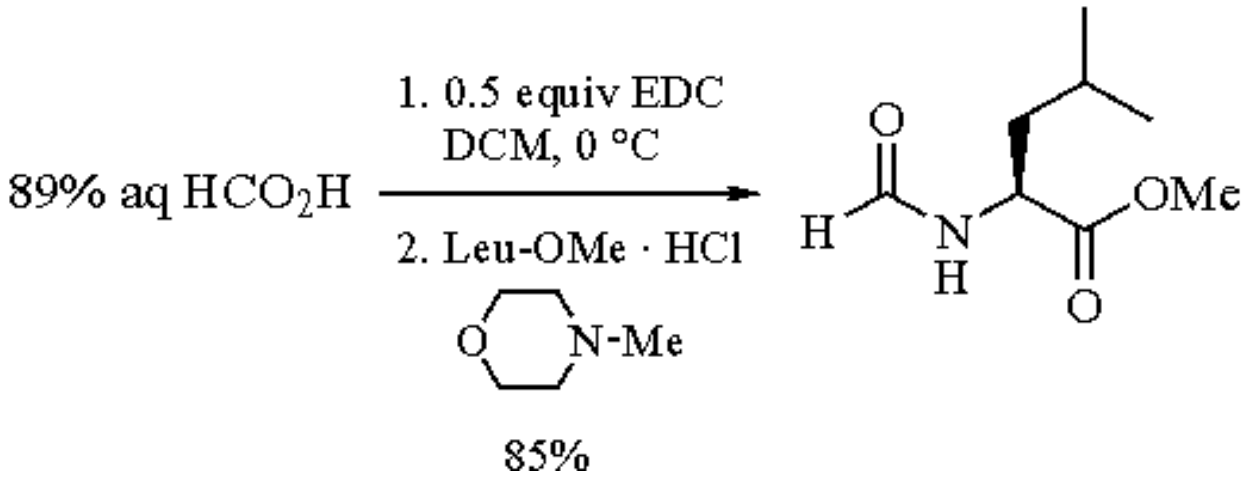

(3)

Another method for formylation of amines is with *p*-nitrophenyl formate, which usually gives products in high yield. However, removing the last traces of the *p*-nitrophenol is difficult.[12]

Treating carbon dioxide and amines with EDC gives symmetrical ureas (eq 4).[13] DCC with CO_2 at ambient pressure works equally well.

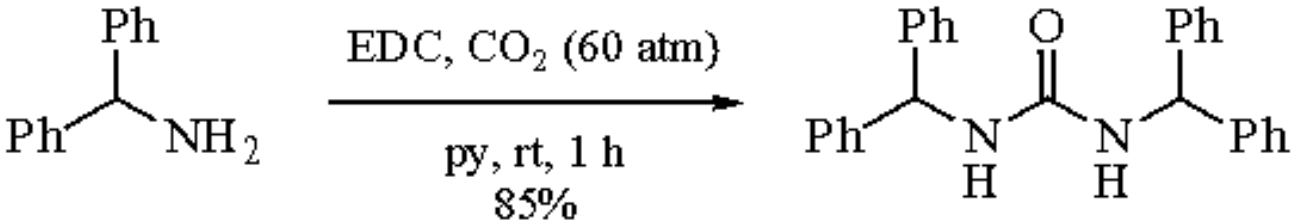

(4)

EDC facilitates the synthesis of xanthine analogs by condensing a diamine with water-soluble acids (eq 5).[14] The use of water as the solvent precludes the use of DCC in this case.

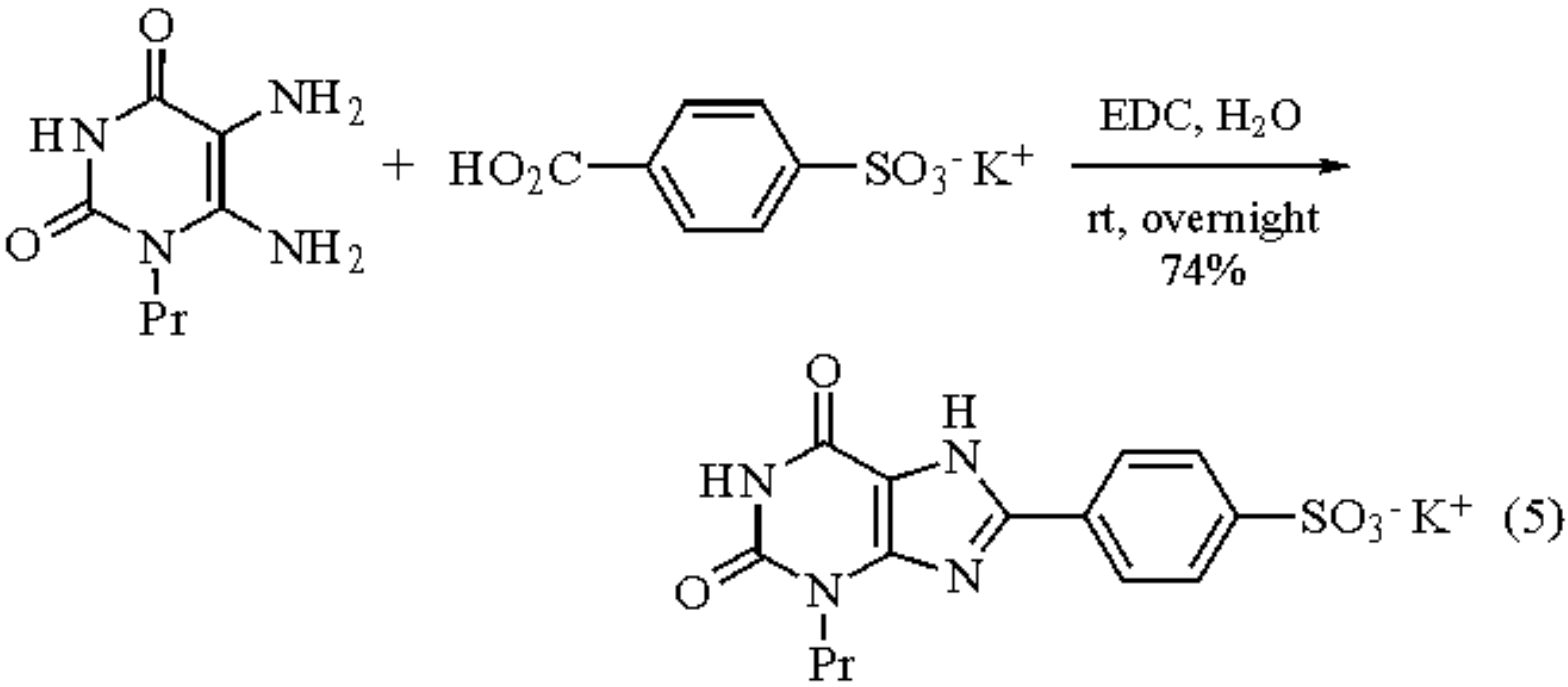

Ester Formation.

Esters of *N*-protected amino acids are prepared in high yield with EDC and ***4-Dimethylaminopyridine*** (eq 6).[4] DMAP causes extensive racemization if not used in a catalytic amount.[15] However, when esterifying the α-carboxyl of β- and γ-benzyl esters of aspartyl and glutamyl derivatives, extensive racemization was observed even with DMAP present in catalytic amounts. It is postulated that the side-chain esters contribute in some fashion to the lability of the α-H.

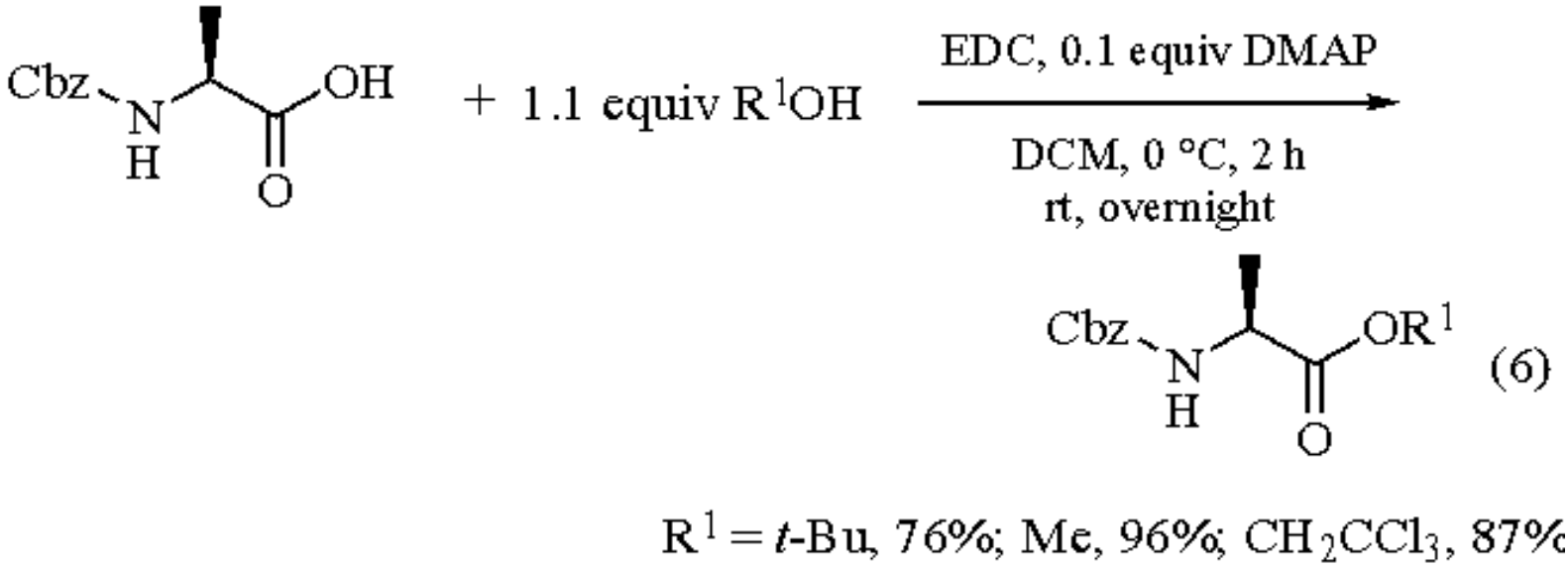

Carbodiimides including EDC are also useful in preparing active esters such as the *p*-nitrophenyl, pentafluorophenyl, and *N*-hydroxysuccinimide esters.[1b] Numerous additional methods have been reported.[16]

Protein Modification.

Carboxyl groups in proteins react with EDC, resulting in an activated group that can be trapped with a nucleophile such as glycine methyl ester.[5] The nucleophile can also be amino groups in the protein, causing cross-linking. Applications for carboxylate modification include determining which groups are buried versus exposed, and mechanistic studies for determining which carboxyl groups are essential for an enzyme's activity.

EDC is used extensively in cross-linking proteins to solid supports for affinity chromatography.[17]

Oxidation of Primary Alcohols.

One example of EDC substituting for DCC in the Pfitzner-Moffatt oxidation is shown in (eq 7).[6] The use of DCC in this example resulted in a difficult purification of the product and lower yields.

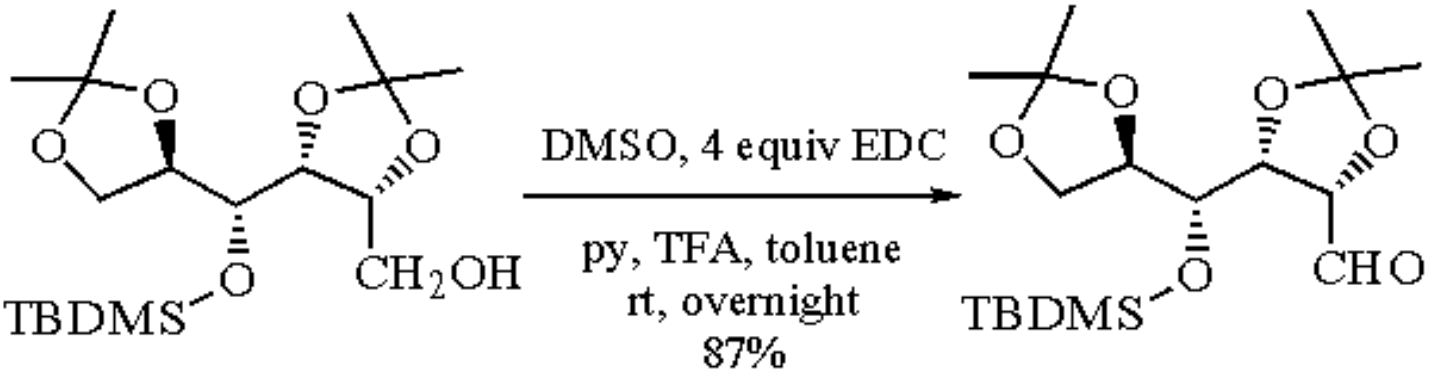

(7)

Miscellaneous Reactions.

EDC is a useful water scavenger as well. An example of this utility is given in (eq 8).[18] The carbodiimide is required in this reaction, but DCC does not work well in this transformation.

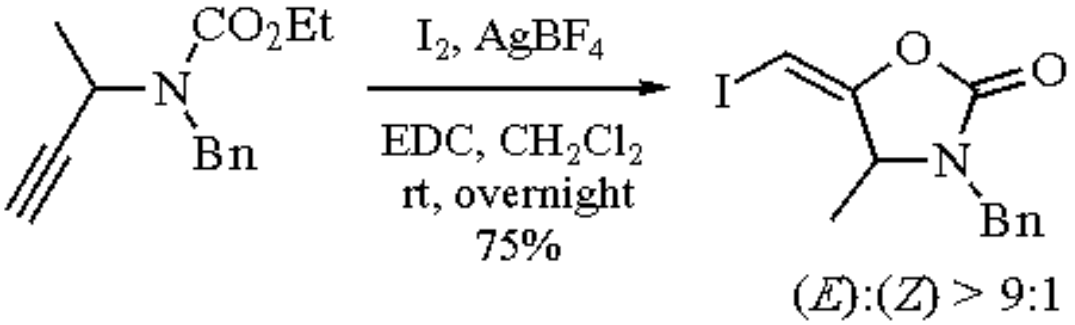

(8)

Another example of EDC having a marked improvement over DCC is the formation of cyanoguanidines (eq 9).[19] This was originally attempted with DCC, which gives poor yields even after extended reaction times. It is thought the positively charged nitrogen in EDC facilitates the C-S bond cleavage and since DCC lacks this atom the reaction goes slowly.

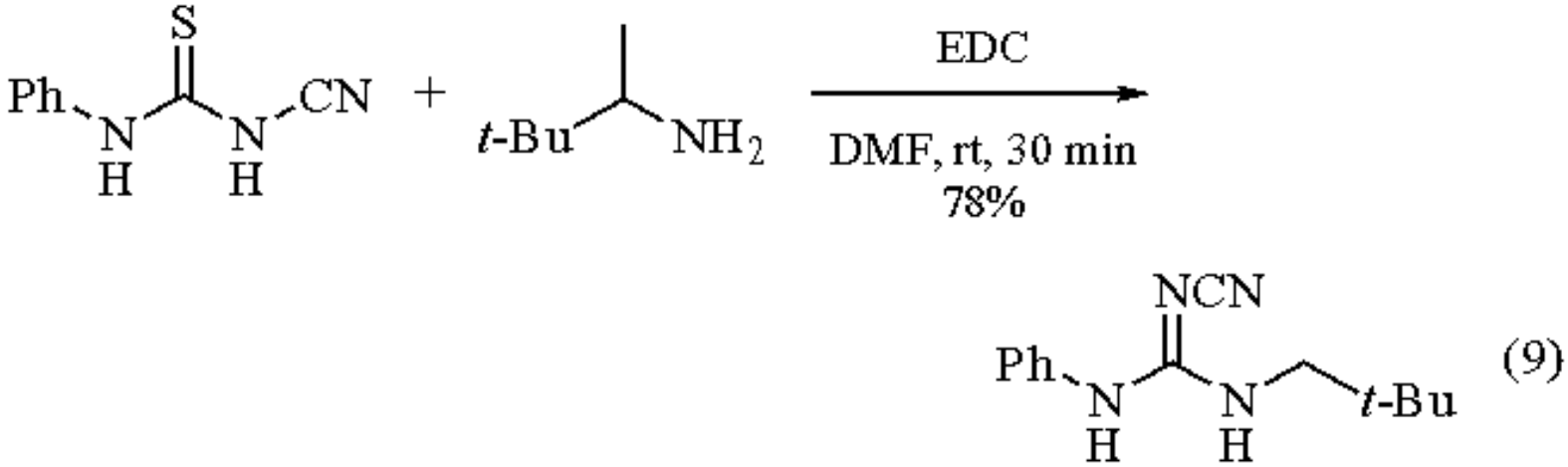

Pyrroles are formed when acetylenes undergo cycloadditions with *N*-acylamino acids in the presence of EDC.[20] An *N*-alkenylmunchnone azomethine ylide is generated in situ and is trapped by the dipolaraphile. Loss of CO_2 yields the pyrrole (eq 10).

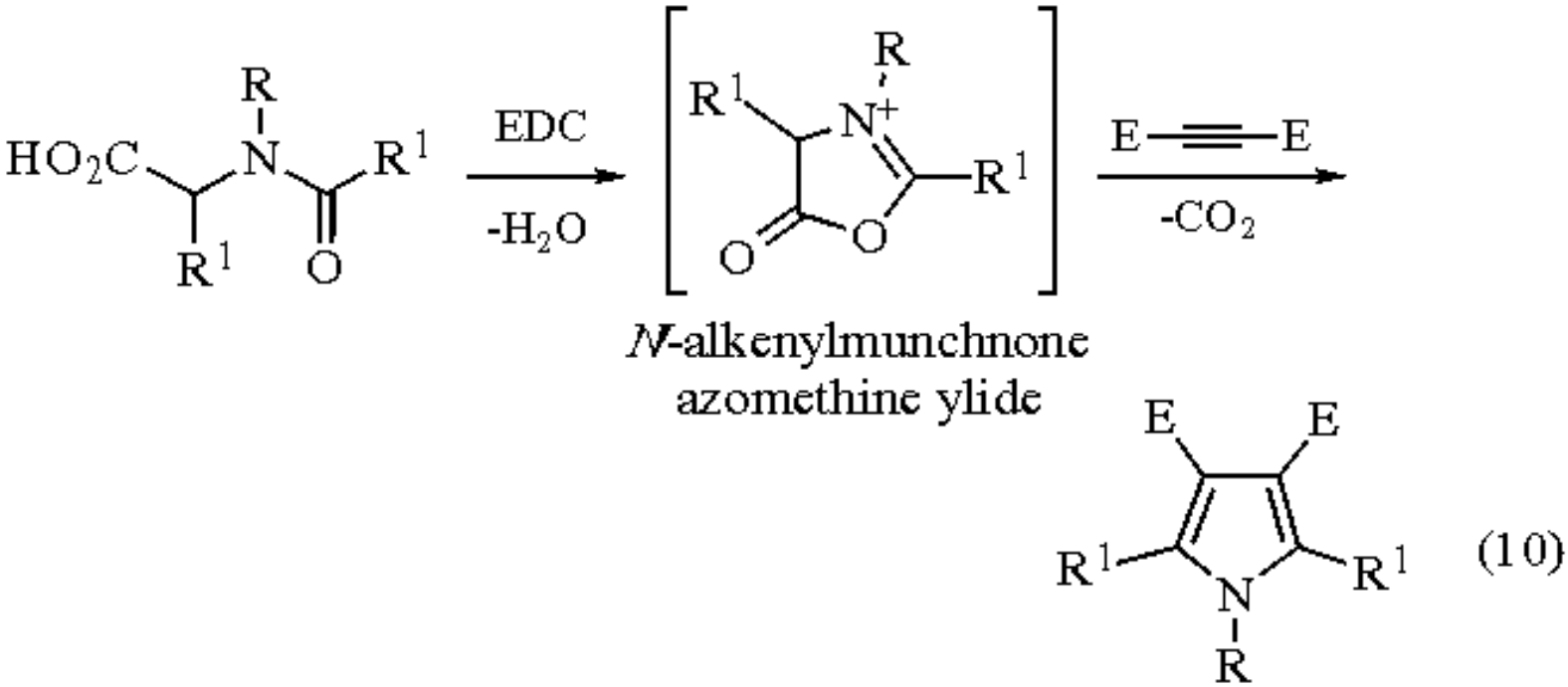

Related Reagents.

Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate; ***N,N´-Carbonyldiimidazole***; ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide***; ***1,3-Dicyclohexylcarbodiimide***; ***Diphenyl Phosphorazidate***; ***Di-p-tolylcarbodiimide***; ***N-Ethyl-5-phenylisoxazolium-3´-sulfonate***; ***1-Hydroxybenzotriazole***; ***Isobutene***; ***Isobutyl Chloroformate***; ***1,1´-Thionylimidazole***.

---

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Ethyl (Dimethylsulfuranylidene)acetate

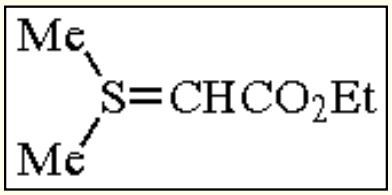

[7380-81-6] · $C_6H_{12}O_2S$ · Ethyl (Dimethylsulfuranylidene)acetate · (MW 148.25)

(stabilized sulfonium ylide reagent capable of reacting with a variety of electrophiles to produce substituted cyclopropanes, epoxides, enamines, and stabilized ylides, as well as other products[1])

Alternate Name: EDSA.

Physical Data: d 1.52 g cm^{-3}.

Solubility: toluene, benzene, CH_2Cl_2, acetone, THF, EtOH

Form Supplied in: not available commercially.

Preparative Method: synthesized in two simple steps (85% overall yield). An equimolar combination of ethyl bromoacetate and ***Dimethyl Sulfide*** is stirred in acetone at rt for three days, after which the precipitated sulfonium salt is isolated by filtration. The salt is then converted to the ylide by treatment with K_2CO_3/NaOH in $CHCl_3$/water.[1b]

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H), 3.9 (q, 2H), 2.7-2.8 (br s, 7H).

Handling, Storage, and Precautions: although the reagent is subject to moisture-induced and thermal decomposition, no report of hazard has been found. The presence of water gives rise to ester hydrolysis and quenching of the ylide to form the zwitterionic sulfonium carboxylate $Me_2{+}SCH_2CO_2^-$. Significant instability has also been noted at slightly elevated temperatures (35% decomposition at 80 °C in 3 h). Successful storage (several weeks) can be accomplished at -10 °C under anhydrous conditions.[1b]

Cyclopropanations.

A variety of electron-deficient alkenes react with this reagent in aprotic solvents to produce good yields of ethoxycarbonyl-substituted cyclopropanes (eq 1). EtOH and presumably other protic solvents allow alternative reaction pathways which seem to be dependent on proton transfer.[1c] The mechanism can be thought of as 1,4-addition followed by intramolecular ring closure with loss of dimethyl sulfide. In general, the reaction succeeds for double bonds activated by one or two strong electron-withdrawing groups (EWG) which may include CHO, COR, CO_2R, CN, and CF_3 (Table 1).[1b,2-8] The reaction is

stereoselective in favor of the *trans* product but in certain cases the selectivity is only marginal.

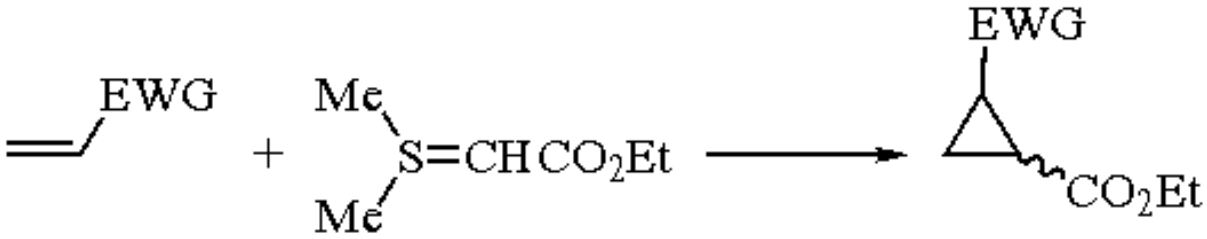

(1)

Table 1 Cyclopropanation Reactions with EDSA

Structure	Substitution	Yield (%)
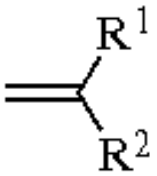	$R^1 = CHO$, $R^2 = H$	63[1b]
	$R^1 = CO_2Et$, $R^2 = H$	84
	$R^1 = COMe$, $R^2 = H$	87
	$R^1 = CHO$, $R^2 = Me$	86
	$R^1 = CO_2Me$, $R^2 = Me$	69
	$R^1 = CO_2Me$, $R^2 = CH_2CO_2Me$	89
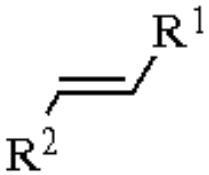	$R^1 = CHO$, $R^2 = Me$	50[1b]
	$R^1 = CO_2Et$, $R^2 = Me$	71
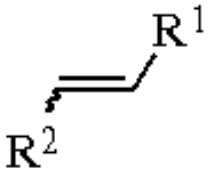	(*E*) $R^1 = CO_2Et$, $R^2 = CO_2Et$	91[1b]
	(*Z*) $R^1 = CO_2Et$, $R^2 = CO_2Et$	79
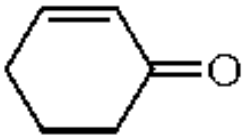		71[1b]
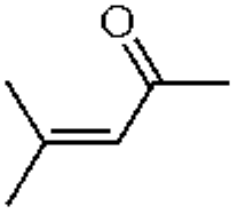		75[1b]

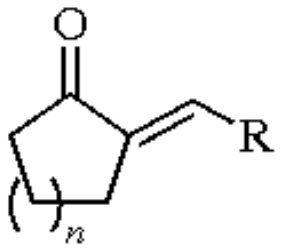	$n = 3$, R = Ph	-[2]
	$n = 3$, R = *i*-Pr	-
	$n = 2$, R = Ph	-
	$n = 2$, R = 2-furanyl	-
	$n = 3$, R = 2-furanyl	-
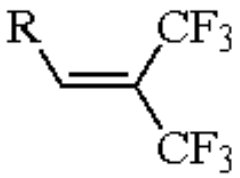	R = CH=CCl_2	42[3]
	R = CH(Cl)-*i*-Pr	75
	R = $CH(OEt)_2$	84
	R = CH(OCOMe)-*i*-Pr	87
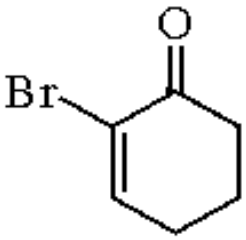		84[4]
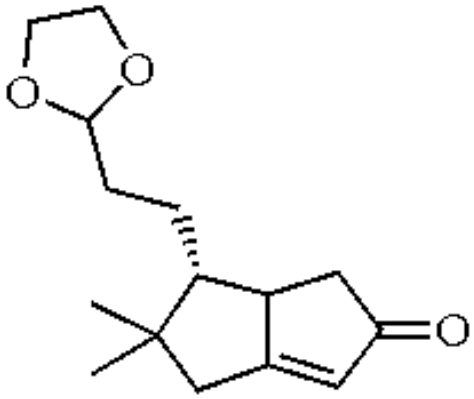	mixture of (*E*) and (*Z*)	72[8]
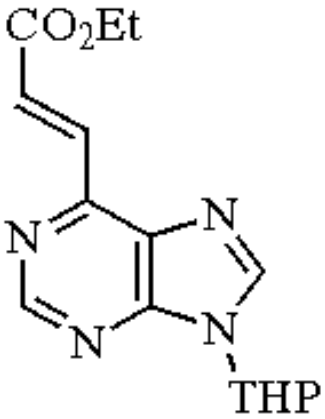	mixture of (*E*) and (*Z*)	90[5]

Ethyl (Dimethylsulfuranylidene)acetate

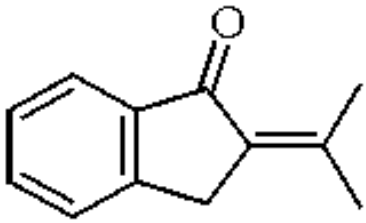

100[6]

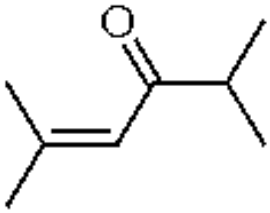

50[7]

Stabilized Sulfur Ylides.

Acid chlorides, anhydrides, and isocyanates acylate EDSA to generate good yields of stabilized sulfur ylides. In addition, alkynes conjugated with either ketones or esters react in a similar fashion (eq 2).[1e]

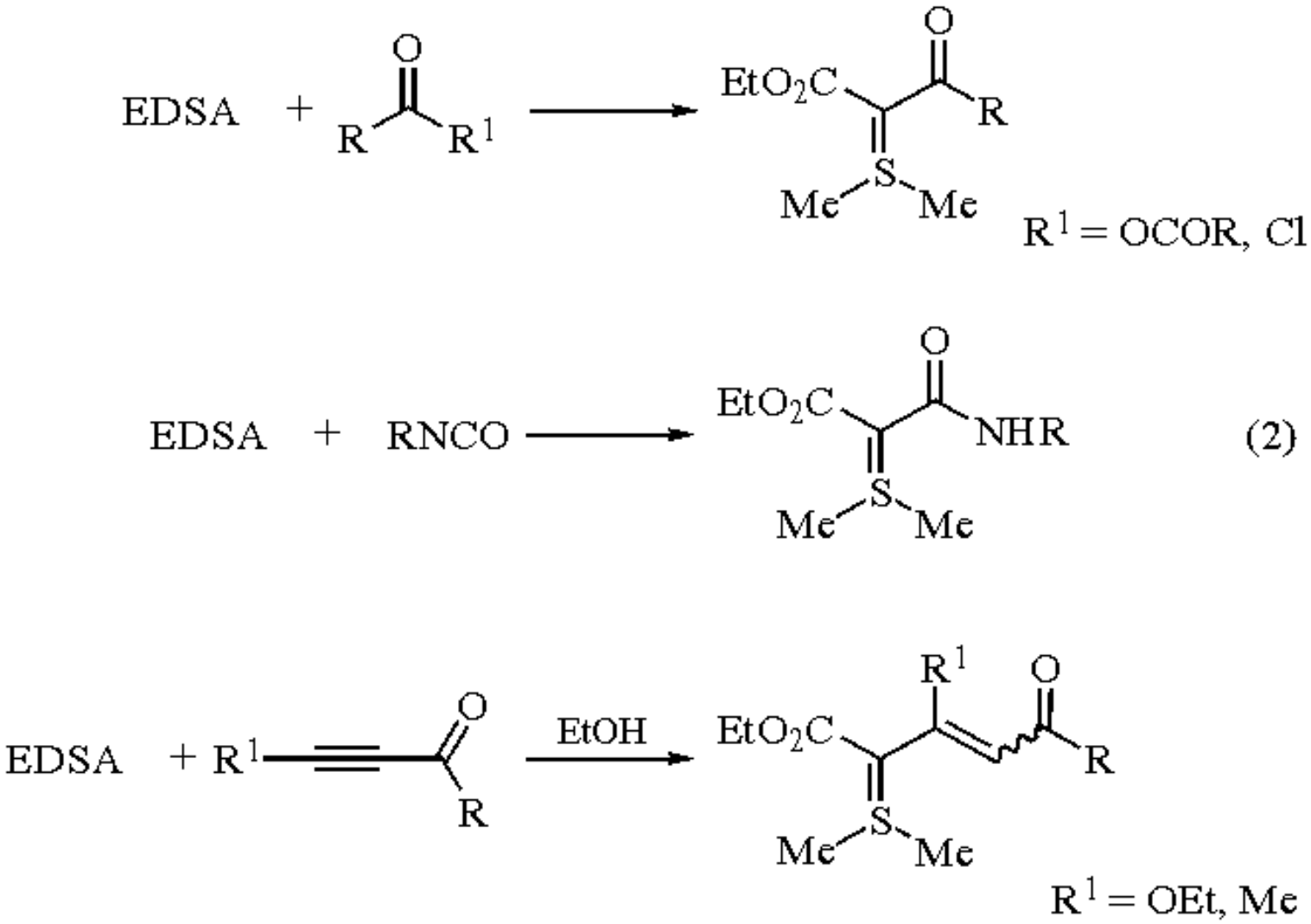

$R^1 = OEt, Me$

Epoxidations.

In contrast to ***Dimethylsulfonium Methylide***,[9] EDSA usually does not react with aldehydes or ketones in a 1,2-sense to generate epoxides. However, under certain conditions,[1e] electron-deficient carbonyls do undergo this reaction. Thus EDSA can be considered an alternative (albeit of limited scope) to α-haloacetic acid esters in the Darzens condensation (eq 3).[10]

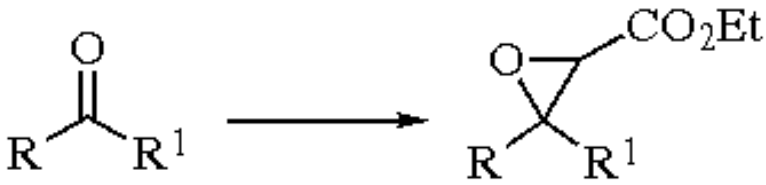

(3)

$R = Me, R^1 = COMe, 50\%$
$R = Ph, R^1 = COPh, 92\%$
$R = Me, R^1 = CO_2Et, 42\%$
$R = H, R^1 = CCl_3, 22\%$

Interestingly, the carboxylate salt of EDSA has been reported to epoxidize unactivated ketones.[11]

Alternative Reagents.

While ***Ethyl Diazoacetate***[12] also reacts with alkenes to provide good yields of ethoxycarbonyl substituted cyclopropanes, it can be differentiated from EDSA in two ways. In the first place, EDSA, requiring an electron deficient double bond, can be considered more selective. Secondly, in large scale reactions, ethyl diazoacetate carries a risk of explosion which EDSA does not have. Ethyl chloroacetate (or ***Methyl Chloroacetate***) under basic conditions accomplishes the same transformation as EDSA.[13]

Related Reagents.

Two similar carbonyl-stabilized dimethylsulfonium methylides (**1** and **2**) have been reported to function as cyclopropanating reagents in a fashion analogous to EDSA.[14]

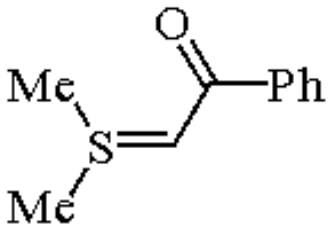

(1)

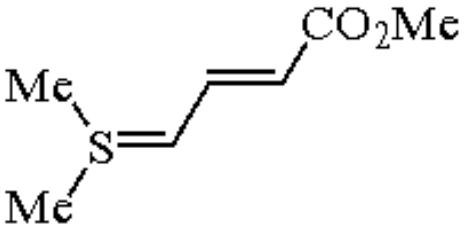

(2)

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Ethyl *N*-(Diphenylmethylene)-2-acetoxyglycinate

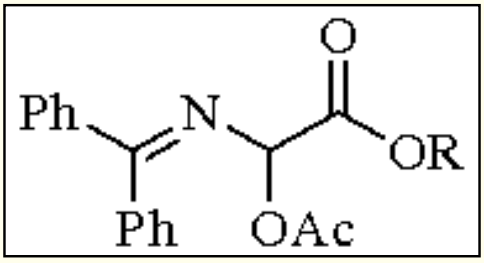

(R = Et)

[97611-55-7] · $C_{19}H_{19}NO_4$ · Ethyl *N*-(Diphenylmethylene)-2-acetoxyglycinate · (MW 325.36)
(R = Me)

[130551-77-8] · $C_{18}H_{17}NO_4$ · Methyl *N*-(Diphenylmethylene)-2-acetoxyglycinate · (MW 311.34)
(R = Bn)

[130946-34-8] · $C_{24}H_{21}NO_4$ · Benzyl *N*-(Diphenylmethylene)-2-acetoxyglycinate · (MW 387.43)

(glycine cation equivalent for amino acid synthesis)

Alternate Names: ethyl α-acetoxyglycinate benzophenone imine; O'Donnell's Schiff base.

Physical Data: R = Me, mp 102-103 °C; R = Et, mp 62-65 °C; R = Bn, mp 63-64 °C.

Preparative Methods: by bromination of ethyl *N*-(diphenylmethylene)glycinate in the presence of acetate (NBS, NaOAc, DMF).[1] The crude product can be purified by recrystalization. (Et_2O/hexane).

Handling, Storage, and Precautions: although stable at room temperature, the compound is normally stored under argon in the freezer. The hydrolysis product, benzophenone, can be detected either by TLC (EtOAc/hexane) or by NMR.

Complementary Synthons for Amino Acid Chemistry.

The acetate Schiff base ester can react as a glycine cation equivalent with a variety of nucleophiles to replace the acetate group. The resulting products are often difficult to prepare using the complementary anionic glycine

equivalent (see ***Ethyl N-(Diphenylmethylene)glycinate***) (eq 1).

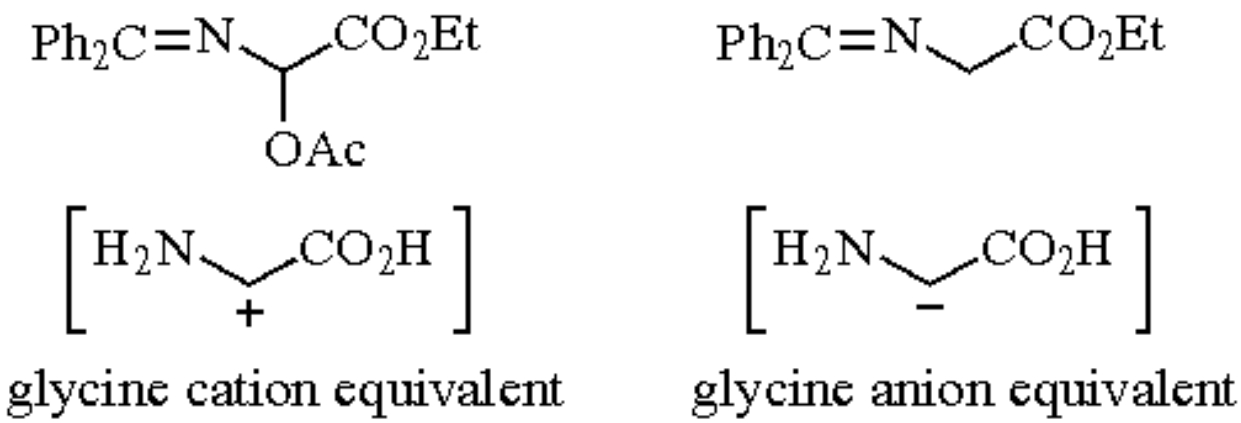

(1)

Reaction with Heteroatom Nucleophiles.

Reaction with alcohols (methyl, primary, secondary) or thiophenol replaces the acetoxy group with a new α-heteroatom group (eq 2). These products can themselves be used as cationic glycinates for further reaction with nucleophiles.[1]

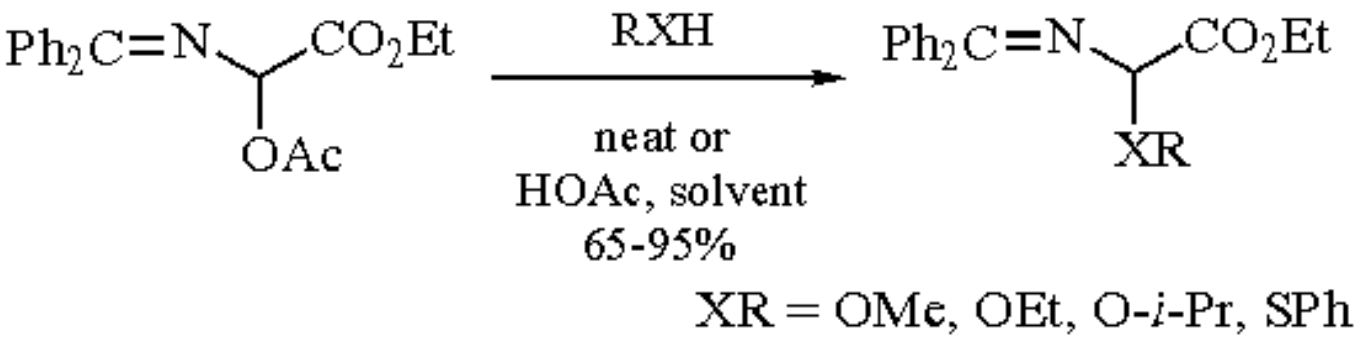

(2)

Reaction with Carbon Nucleophiles.

Reaction with higher order mixed cuprates results in α,β carbon-carbon bond formation (eq 3). This provides preparations of aryl and heteroaryl glycine derivatives as well as α-monosubstituted amino acids containing a β-quaternary center (e.g. *t*-butylglycine).[2]

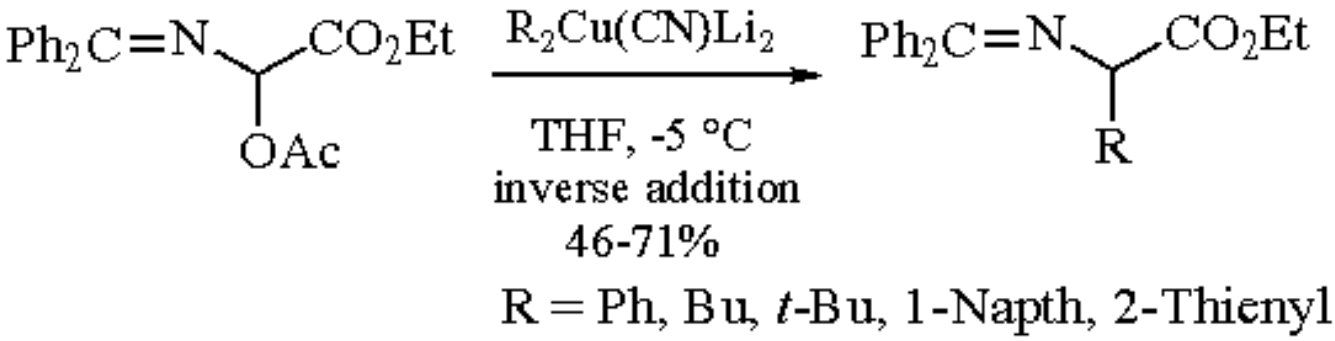

(3)

Neutral carbon nucleophiles such as activated aromatics or organosilicon reagents react in the presence of ***Titanium(IV) Chloride*** to yield aryl and heteroaryl glycines as well as γ,δ-unsaturated or γ-keto amino acid derivatives (eq 4).[3]

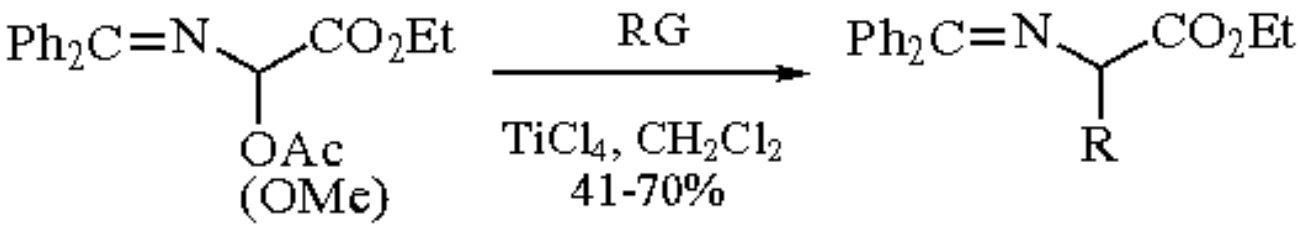

(4)

RG = ArH (active aromatics/heteroaromatics) or $CH_2{=}CHCH_2TMS$, $PhC({=}O)CH_2TMS$

Reaction with organoboranes allows for effective appendage of the amino acid substructure onto structures that can be converted into organoboranes (e.g. alkenes, organolithium reagents, aryl halides, hydrocarbons, etc.) (eq 5).[4]

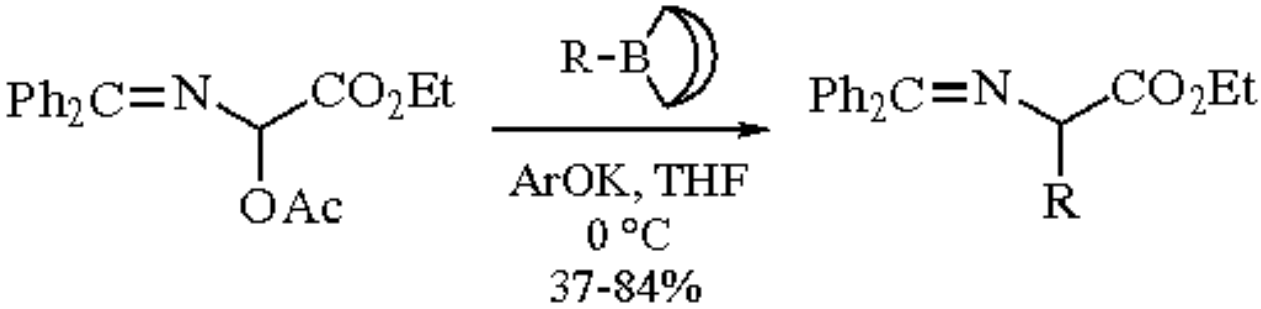

(5)

R = RCH_2CH_2, Cy, Ar, $ArCH_2CH_2$, *t*-Bu

Reaction of the methyl ester acetate Schiff base with anions of active methylene compounds (soft nucleophiles) in the presence of a Pd^0 catalyst results in carbon-carbon bond formation (eq 6). The reaction likely occurs through a 2-aza-π-allyl palladium complex.[5]

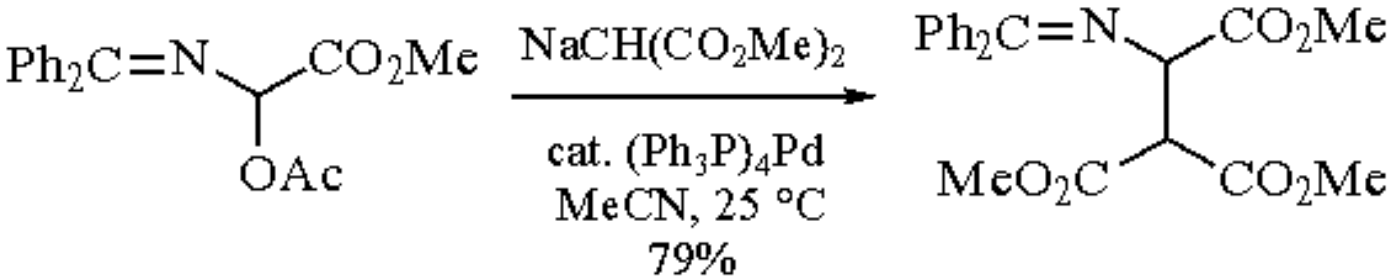

(6)

Related Reagents.

Benzophenone Imine; ***Methyl 2-Bromo-N-(t-butoxycarbonyl)glycinate***; ***N-***

(Diphenylmethylene)aminoacetonitrile; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Methyl Glyoxylate***; ***8-Phenylmenthyl Glyoxylate***.

---

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Ethyl *N*-(Diphenylmethylene)glycinate[1-3]

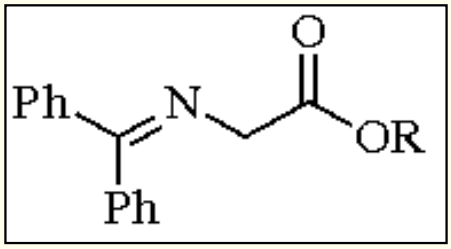

(R = Et)

[69555-14-2] · $C_{17}H_{17}NO_2$ · Ethyl *N*-(Diphenylmethylene)glycinate · (MW 267.33) (R = Me)

[81167-39-7] · $C_{15}H_{15}NO_2$ · Methyl *N*-(Diphenylmethylene)glycinate · (MW 253.30) (R = Bn)

[81477-91-0] · $C_{22}H_{19}NO_2$ · Benzyl *N*-(Diphenylmethylene)glycinate · (MW 329.38) (R = *t*-Bu)

[81477-94-3] · $C_{19}H_{21}NO_2$ · *t*-Butyl *N*-(Diphenylmethylene)glycinate · (MW 295.38)

(glycine anion equivalent for amino acid synthesis by phase transfer catalysis and other methods)

Alternate Names: ethyl glycinate benzophenone imine; O'Donnell's Schiff base.

Physical Data: R = Et, mp 51-52 °C; pK_a (DMSO) 18.7;[4] R = Me, mp 42.5-43 °C; R = Bn, mp 86.5-87 °C; R = *t*-Bu, mp 111-112 °C.

Form Supplied in: several are commercially available.

Preparative Methods: by transimination of ***Benzophenone Imine*** with alkyl glycinate hydrochloride (room temperature/CH_2Cl_2).[5] The crude product can often be used or it can be purified by recrystallization or flash chromatography.

Handling, Storage, and Precautions: the compounds are stable at room temperature, but they should be protected from moisture and acidic conditions (stored under argon or nitrogen). The hydrolysis product, benzophenone, can be detected either by TLC (EtOAc/hexane) or by NMR.

Amino Acid Synthesis by Catalytic Enantioselective Alkylation using Phase Transfer Catalysis.

Optically active α-amino acids are prepared in up to 66% enantiomeric excess (83:17 mixture of enantiomers) by

alkylation of the benzophenone imine of glycine *t*-butyl ester (R = *t*-Bu) under phase transfer catalysis (PTC) conditions using chiral catalysts derived from the *Cinchona* alkaloids. The ability to scale the reaction up and the possibility of preparing α-amino acids in high optical purity were demonstrated by the synthesis of 6.5 g of optically pure nonnatural 4-chloro-D-phenylalanine (eq 1) using the *N*-benzylated derivative of cinchonine. The enantiomeric L-amino acids are prepared by simply changing to pseudoenantiomeric catalysts derived from cinchonidine.[1] Use of optically active crown ethers (29% ee)[6] or optically active *vic*-diols as cocatalysts (4% ee)[7] has been reported.

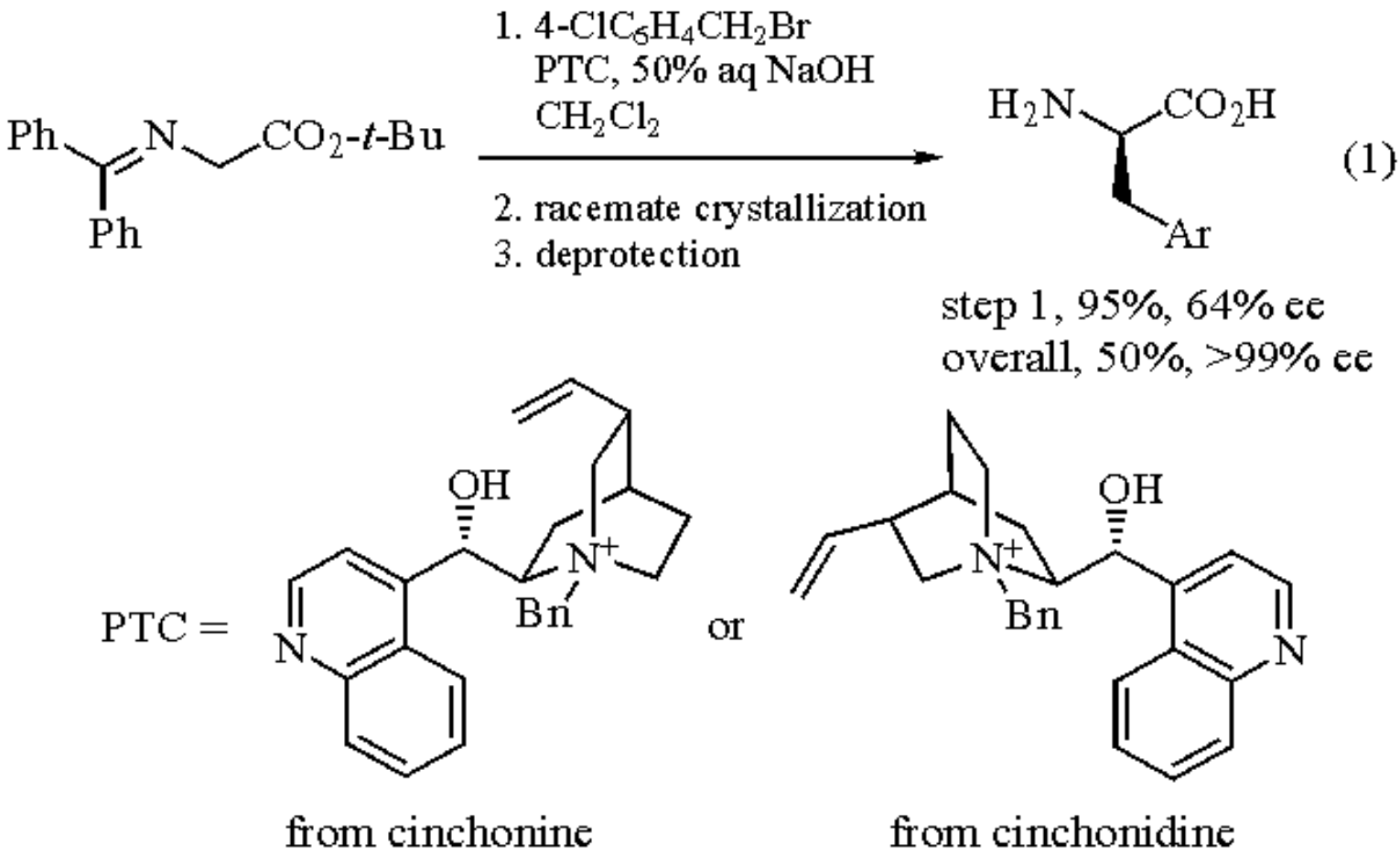

Other Preparations of Optically Active Amino Acid Derivatives.

Enzymatic resolution has been used to prepare optically pure α-amino acid derivatives following either enantioselective PTC alkylation[8] or racemic alkylation.[9-12]

Asymmetric synthesis involving alkylation of these and related Schiff base esters in the presence of either a chiral leaving group (up to 76% ee) or a chiral proton source (deracemization) (up to 70% ee) have been reported.[13]

Palladium Catalysis.

Pd^0 catalyzed alkylations of the anion of Schiff base esters leads to γ,δ-unsaturated,[14] γ-allenic,[15] cyclopropyl-containing,[16] or 1,3-diene-containing[17] amino acid derivatives. A catalytic, enantioselective allylation has been achieved in up to 68% ee by using chiral ligands in conjunction with Pd^0 catalysis (eq 2).[18,19]

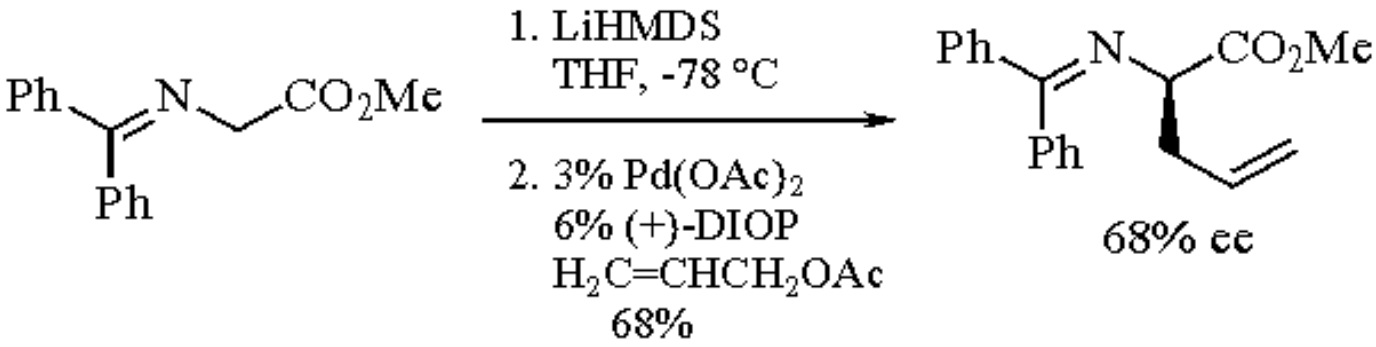

(2)

Other Alkylation Chemistry.

The benzophenone imines of glycine alkyl esters can be alkylated by a variety of different classes of alkyl halides (methyl, benzylic, allylic, propargylic, α-halo ester, primary, secondary) using either PTC or anhydrous conditions (Table 1).[20-22]

Table 1 Types of Amino Acid Side-Chains Produced by Alkylation of *N*-(Diphenylmethylene)glycinate Anions

Side-chain contains	Side-chain contains
^{11}C[23,24]	Cyclopropyl[16,25,26]
Cyclooctatetraenyl[11]	Boron[27]
Nitrogen[10,25,28–32]	Metal-binding (bipy)[8,33]
Photoaffinity label[34]	Nitroxide radical[35,36]
Phosphorus[37–40]	Oxygen[9,10,26,29,31,40–47]
Sulfur[9,39]	Selenium[48]
Fluoroalkyl[49]	Fluoro[12,30,34,50,51]
Halo (Cl, Br)[10,12,29]	

Other Reactions.

Michael additions,[44,52-55] aldol type reactions (eq 3),[56-60] imine additions,[61,62] acylation (both *N*-acylation[63] and *C*-acylation[64]), reaction with difluorocarbene,[65] and monoarylation[66-68] have been reported.

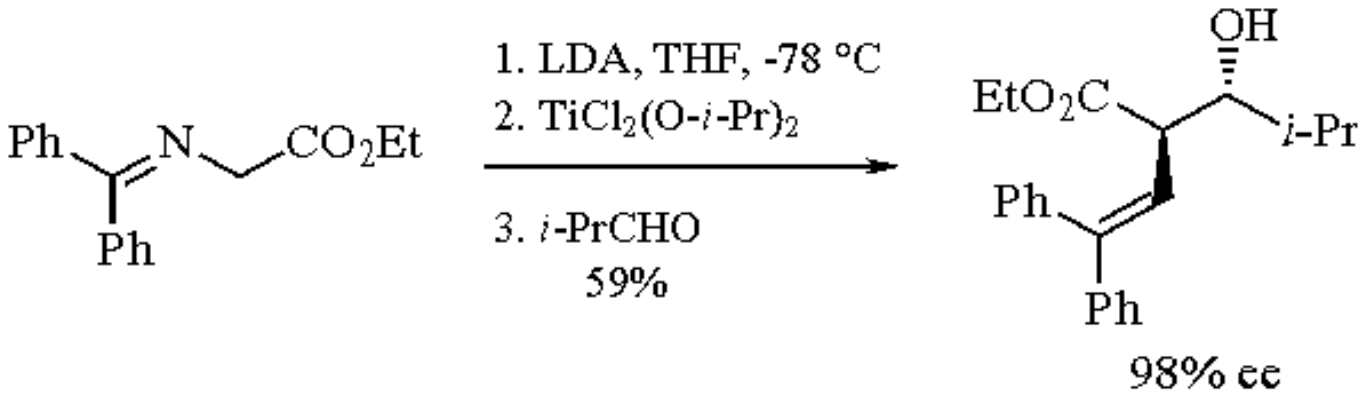

(3)

Related Reagents.

Benzophenone Imine; ***1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone***; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***; ***t-Butyl 2-t-Butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate***; ***N,N-Diethylaminoacetonitrile***; ***(2S)-(+)-2,5-Dihydro-2-isopropyl-3,6-dimethoxypyrazine***; ***N-(Diphenylmethylene)aminoacetonitrile***; ***Ethyl N-(Diphenylmethylene)-2-acetoxyglycinate***; ***Methyl N-Benzylidenealaninate***; ***Methyl α-Phenylglycinate***.

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Ethyl Diphenylphosphinite

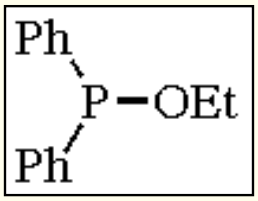

[1733-57-9] · $C_{14}H_{15}OP$ · Ethyl Diphenylphosphinite · (MW 230.26)

(amide and peptide formation from azides and carboxylic acids; Staudinger reaction)

Alternate Name: ethoxydiphenylphosphine.

Physical Data: d 1.066 g cm^{-3}.

Solubility: sol chloroform (50 mg mL^{-1}).

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: irritant; moisture sensitive; stored under N_2; needs refrigeration.

Peptide Synthesis.

The preparation of carboxylic amides via activation of the amino fragment through the Staudinger reaction[1] has been reported independently by Garcia[2] and Roberts.[3] The strategy involves the electrophilic addition of an azide to a phosphorus(III) center (**1**) followed by elimination of N_2 giving the iminophosphorane (**2**) (also known as phosphazene). Phosphorane (**2**) reacts with carboxylic acids to form amides (eq 1). While ***Triphenylphosphine*** (**1a**) and ethyl diphenylphosphinite (**1b**) have been used as phosphorus reagents, the latter has proven more advantageous. First, coupling with the carboxylic acid takes place at lower temperatures. Second, during the workup the phosphine oxide byproduct is hydrolyzed to diphenylphosphinic acid which is subsequently extracted out of the reaction mixture.

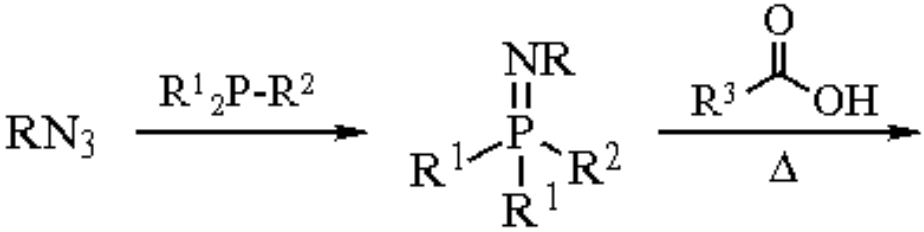

(1a) $R^1 = R^2 = Ph$
(1b) $R^1 = Ph;\ R^2 = OEt$

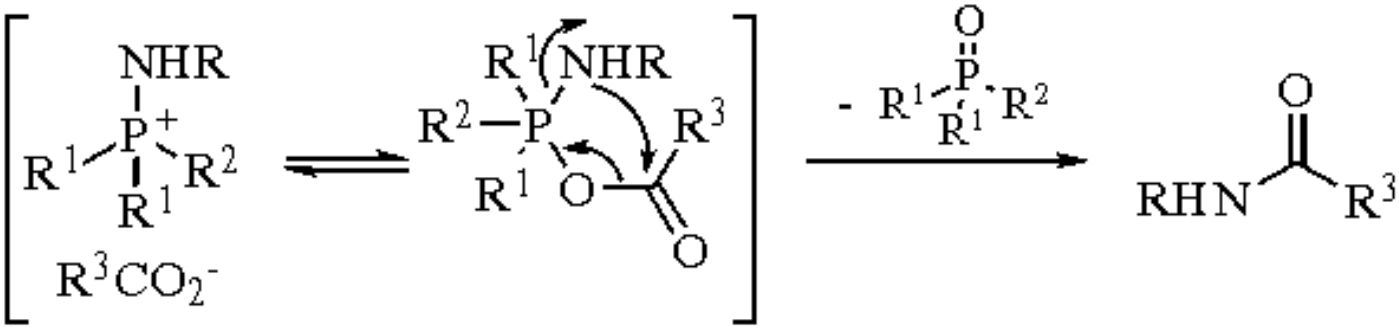

(1)

More recently, an approach to amide/peptide synthesis that bypasses the use of nonpolar solvents has been developed. This is based on the reduction of an azide to the corresponding amine in situ and in the presence of a preformed activated carboxyl component.[4]

Phosphoramide Synthesis.

A homolog of phosphinite (**1b**), namely methyl diphenylphosphinite (**3**), has been used in the synthesis of phosphoramides (eq 2).[5]

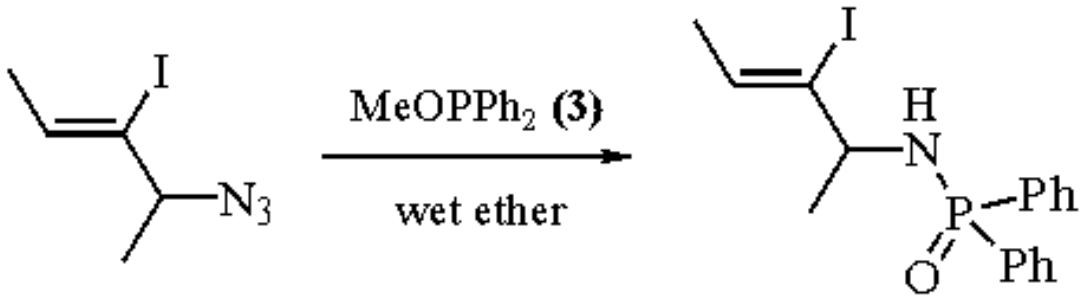

(2)

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Gerald B. Hammond

Ethyldiphenylsulfonium Tetrafluoroborate[1]

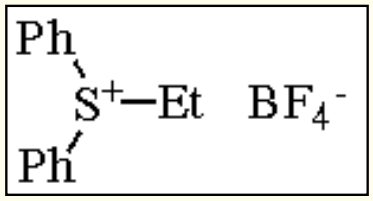

[893-69-6] · $C_{14}H_{15}BF_4S$ · Ethyldiphenylsulfonium Tetrafluoroborate · (MW 302.17)

(transformation of carbonyl groups to oxiranes;[2] α,β-unsaturated systems to α-cyclopropyl ketones;[3] a very powerful alkylating agent[4])

Physical Data: mp 76-77 °C.

Form Supplied in: not commercially available.

Preparative Methods: there are two common methods of preparation. The first involves adding ***Silver(I) Tetrafluoroborate*** to a solution of Ph_2S and ***Ethyl Iodide*** (5 equiv), and stirring the mixture for several hours (eq 1).[5]

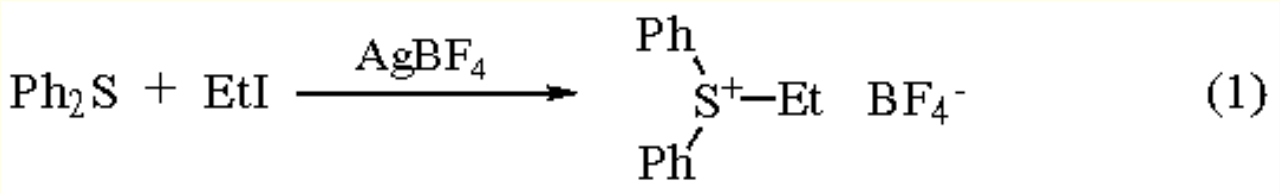

The second method is a relatively new and unique technique.[6] Under acidic conditions, the alkylation of aliphatic and aromatic sulfides has been carried out by using alcohols instead of alkyl halides (eq 2).

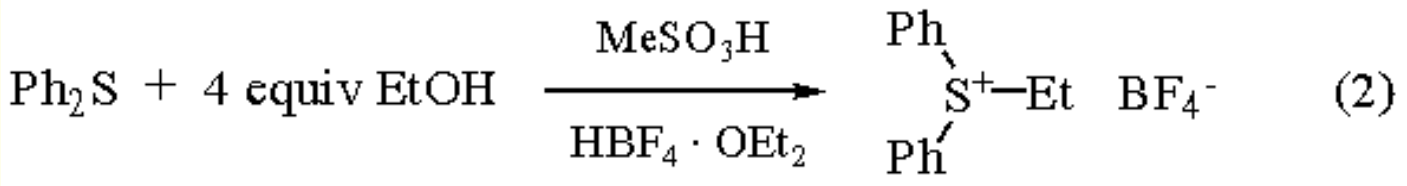

Carbonyl Additions to Form Oxiranes.

To a solution of ethyldiphenylsulfonium tetrafluoroborate in THF at -76 °C under nitrogen was added an appropriate alkyllithium, followed by 0.9 equiv of cyclohexanone. After stirring for 1 h and workup, the oxirane shown (eq 3) was obtained in good yield.[7]

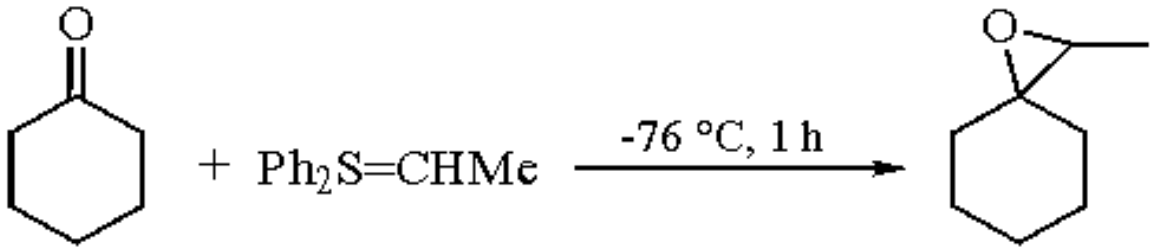

(3)

Reactions with α,β-Unsaturated Carbonyl Groups.

If the carbonyl group is α,β-unsaturated, reaction takes place at the alkene to form substituted cyclopropanes.[8] Meyers et al. have taken advantage of this and used ethyldiphenylsulfonium tetrafluoroborate to form 1,2,3-trisubstituted cyclopropanes (eq 4).[3]

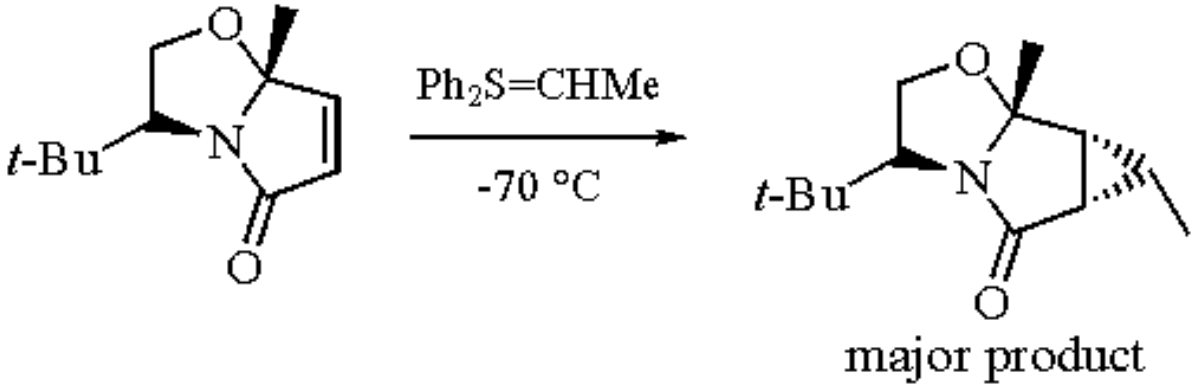

(4)

O-Alkylation of Carboxylates and Amides.

Ethyldiphenylsulfonium tetrafluoroborate acts as a very powerful alkylating agent and converts phosphoric diesters to phosphoric triesters (eq 5).[9] Ethyldiphenylsulfonium tetrafluoroborate also performs *O*-alkylation of amides[10] and carboxylate salts.[11]

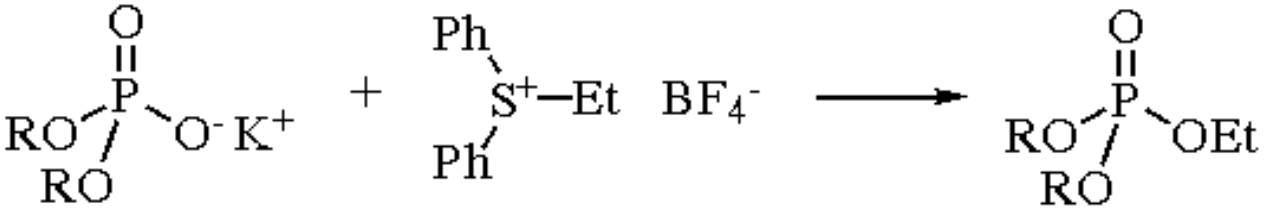

(5)

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Ethylene

$CH_2=CH_2$

[74-85-1] · C_2H_4 · Ethylene · (MW 28.06)

(used in photochemical and thermal cycloadditions, Friedel-Crafts and other alkylations, vinylation reactions, and as an alkene in electrophilic addition reactions)

Physical Data: mp -169 °C; bp -104 °C; vapor density 0.97; flammable gas.

Solubility: insol H_2O; sol THF, pet ether, benzene.

Form Supplied in: gas (lecture bottle); widely available.

Handling, Storage, and Precautions: store and use with adequate ventilation. Explosions involving ethylene have occurred: when mixed with aluminum chloride at 30-60 bar pressure in the presence of supported nickel catalysts, methyl chloride, or nitromethane; when mixed with trifluoromethyl hypofluorite without diluent; when reacted with chlorine, ozone, or nitrogen oxide; when passed through 5 Å molecular sieves.[1]

Photochemical Cycloadditions.

Ethylene has been utilized extensively in intermolecular [2 + 2] photocycloaddition reactions with enones.[2] Cyclohexenones (eq 1),[3] cyclopentenones (eq 2),[4] and functionalized enones (eqs 3 and 4)[5,6] undergo cycloaddition with ethylene in high yield.

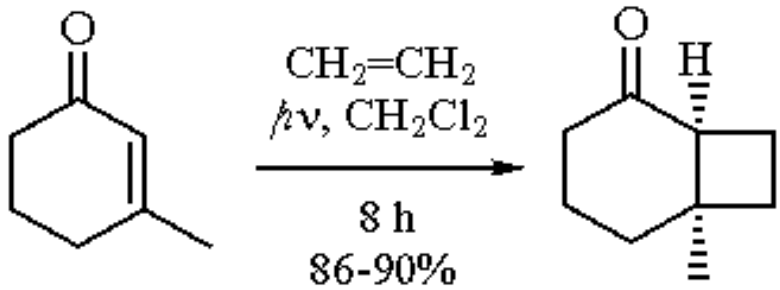

(1)

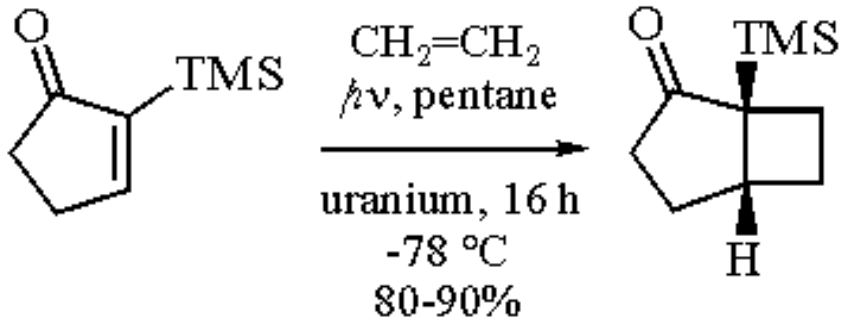

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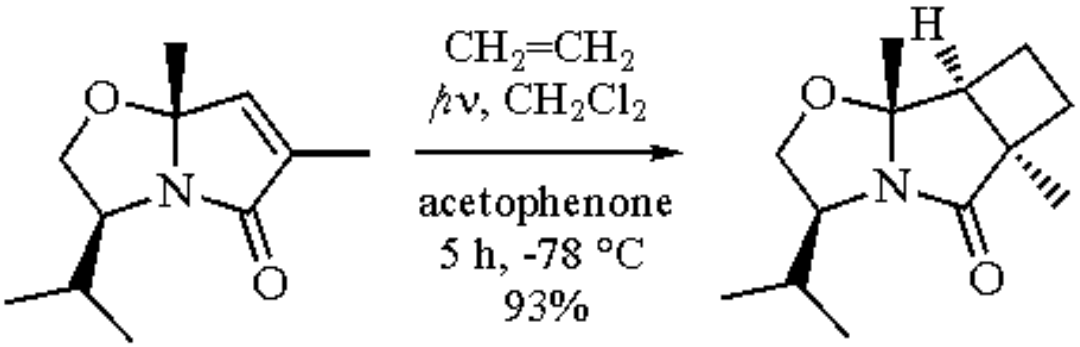

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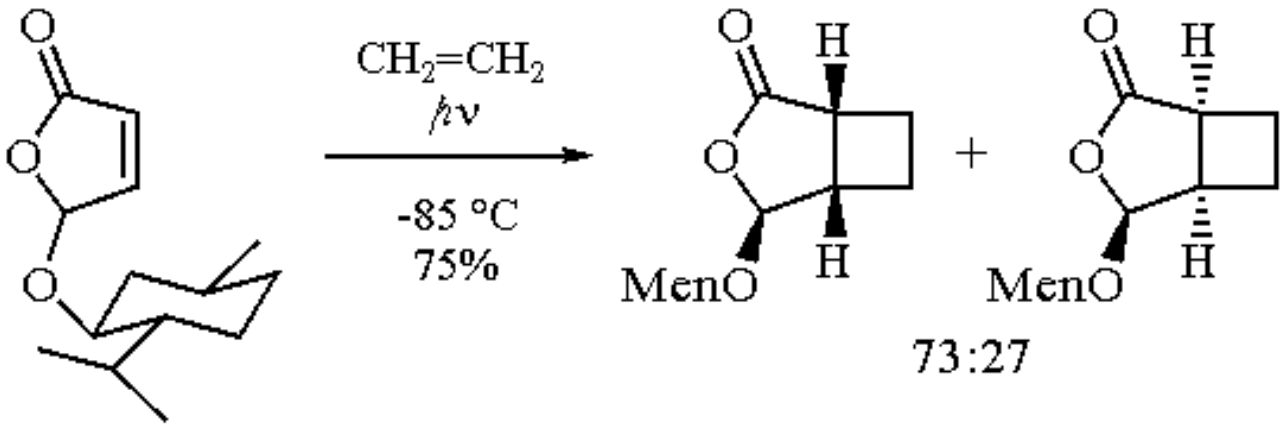

(4)

Thermal Cycloadditions.

Ethylene is a relatively poor dienophile but can be used in the Diels-Alder reaction with active dienes or under forced conditions such as high pressure (eqs 5-8).[7-9] Nitrone cycloadditions can also be carried out with ethylene under high pressure (eq 9).[10]

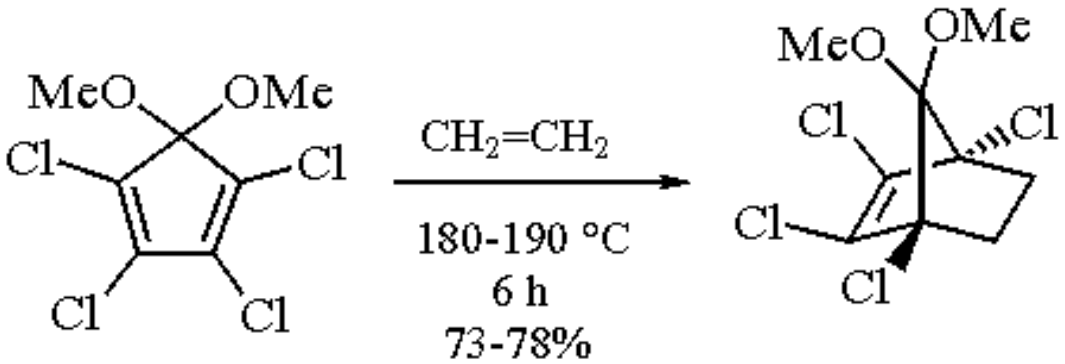

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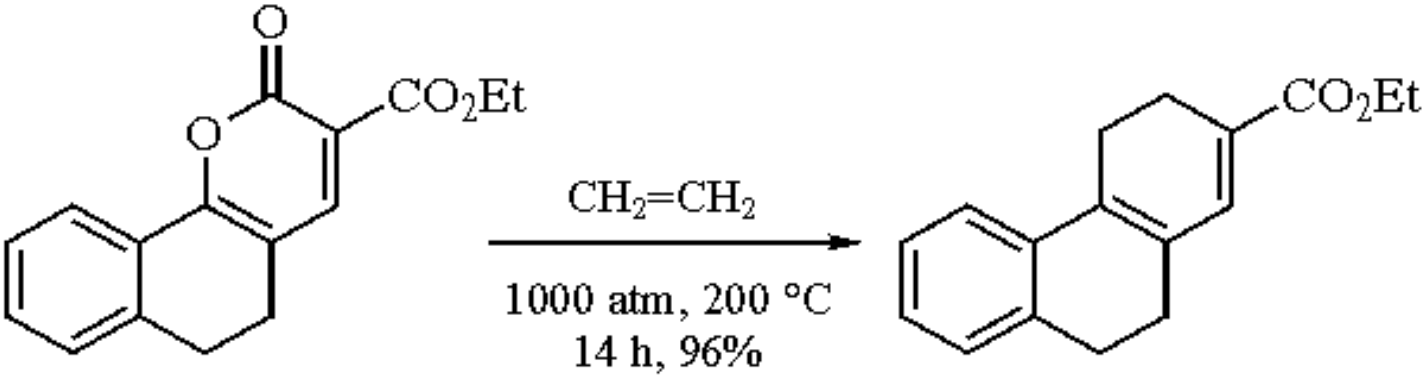

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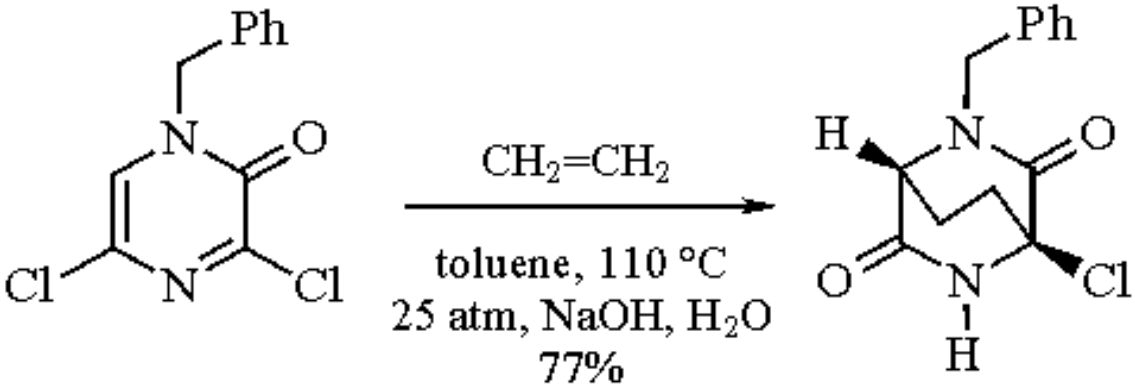

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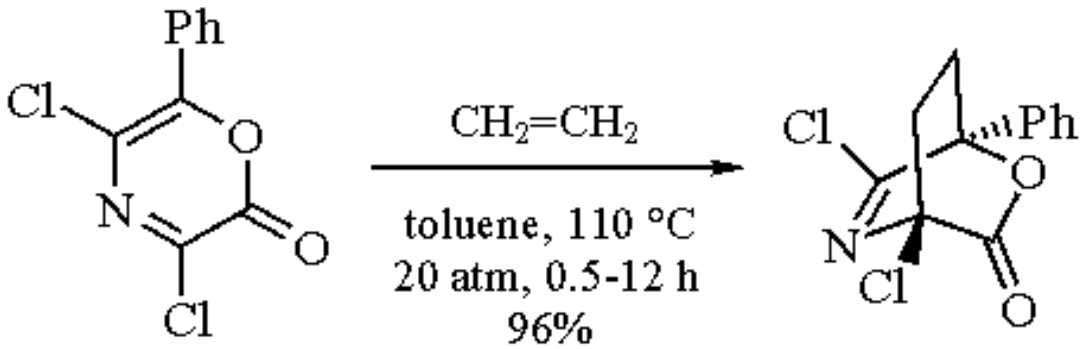

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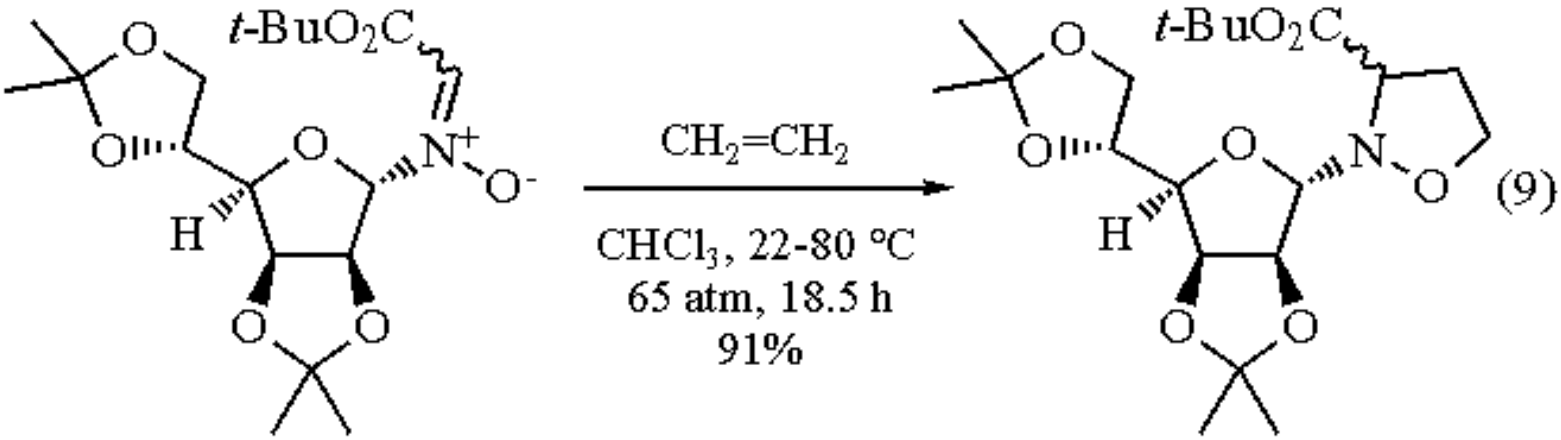

(9)

Friedel-Crafts Reactions.

Ethylene alkylates a variety of aromatic systems in the presence of Lewis acids (eqs 10 and 11).[11] 2-Tetralones can be

prepared from aromatic acetyl chlorides and ethylene in the presence of ***Aluminum Chloride*** (eqs 12 and 13).[12]

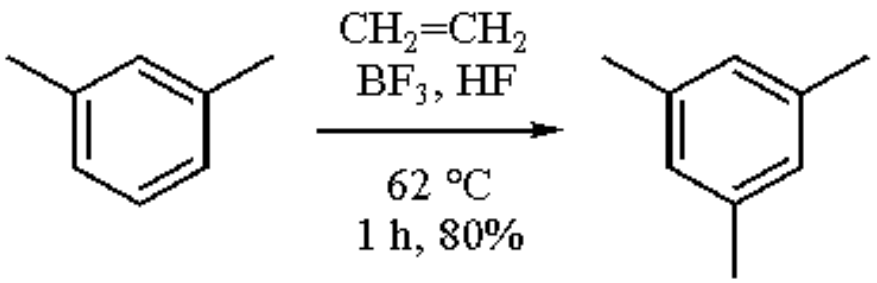

(10)

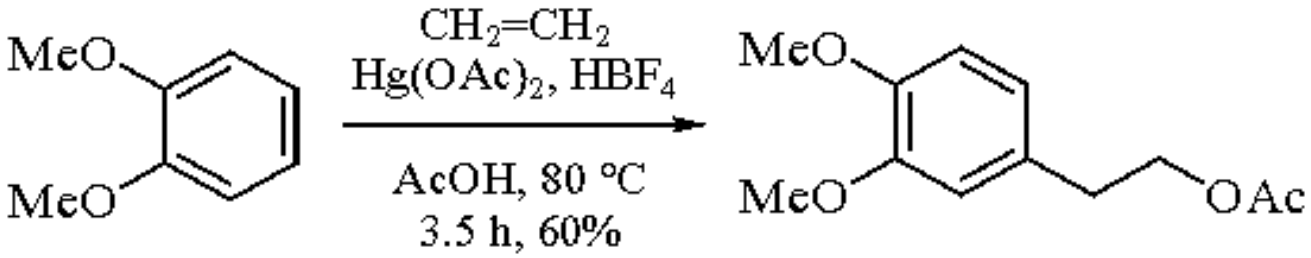

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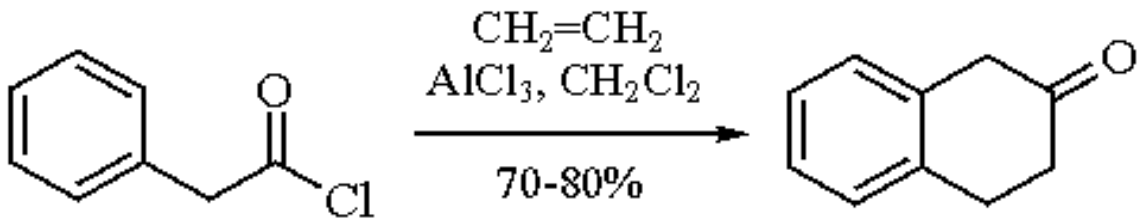

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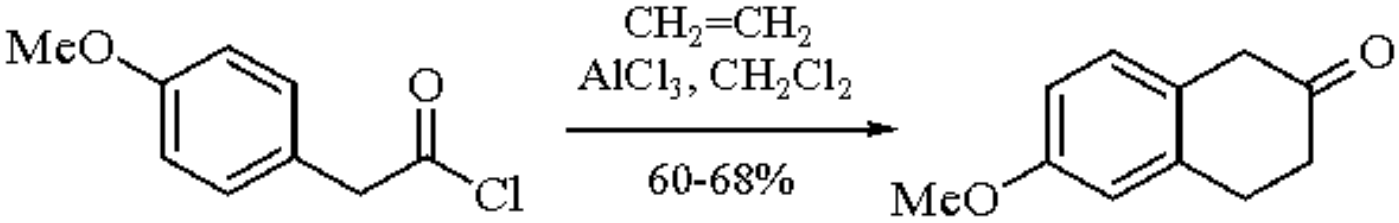

(13)

Ethylene reacts with aromatic acid chlorides (eq 14),[13] aliphatic acid chlorides (eqs 15 and 16),[14] and anhydrides (eq 17)[15] under Lewis acid catalysis to produce α,β-unsaturated ketones and 3-chloroethyl ketones. Ethylene also condenses with haloalkanes to effect a formal ethylene insertion (eqs 18 and 19).[16]

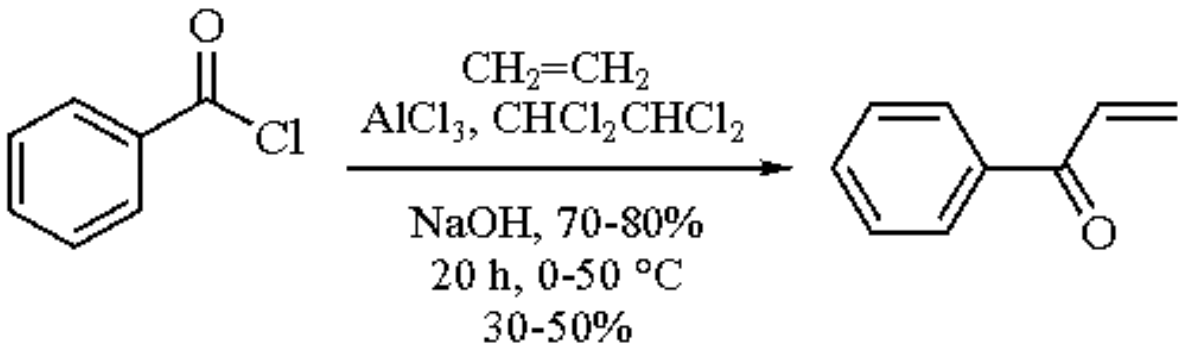

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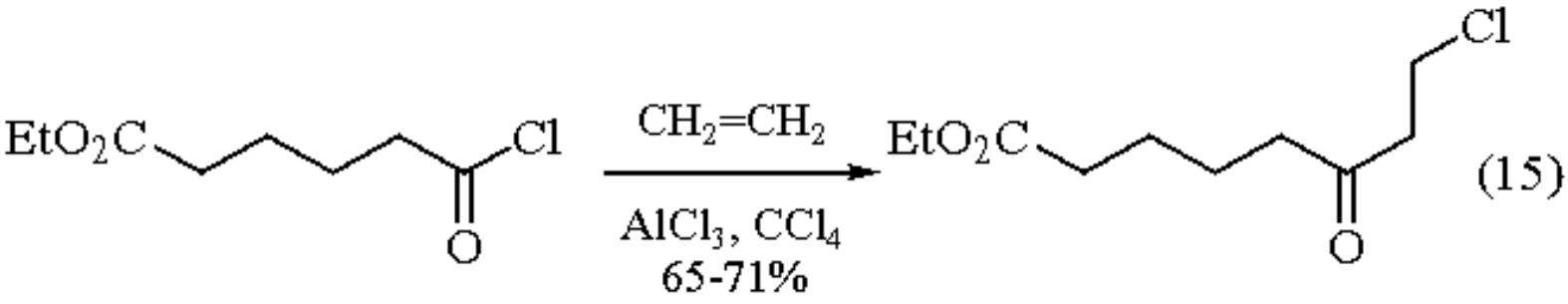

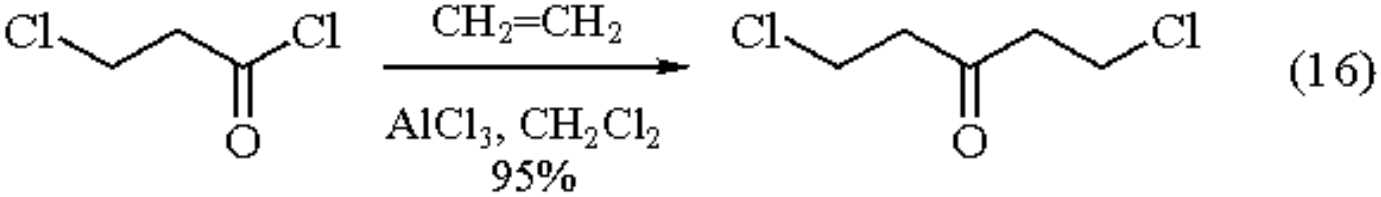

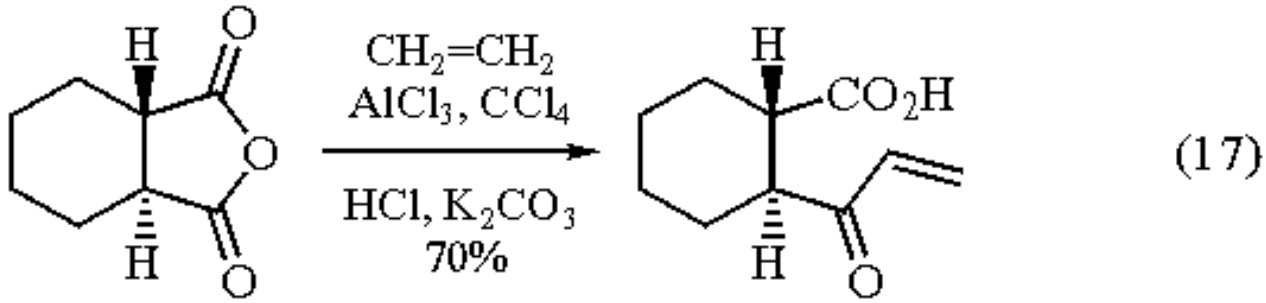

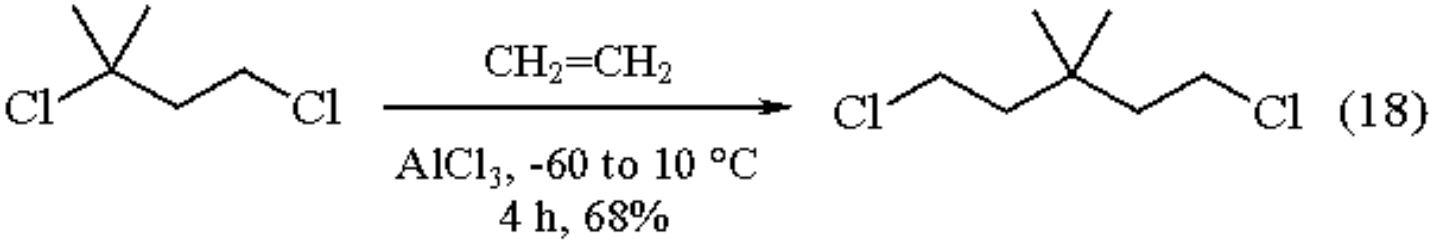

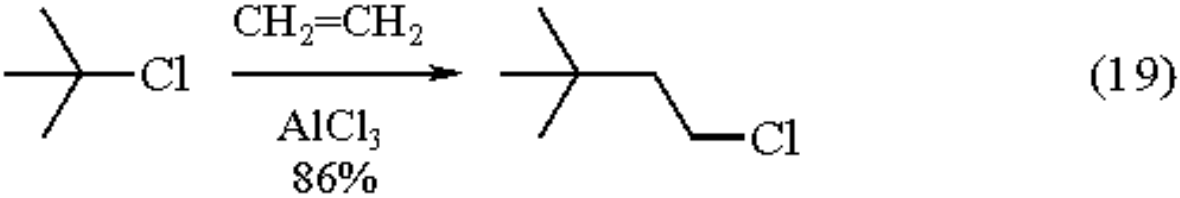

Other Alkylation Reactions.

Alkylbenzenes containing at least one benzylic hydrogen may be alkylated with ethylene in the presence of catalysts such as sodium or ***Potassium-Graphite*** (eqs 20 and 21).[17] Ethylene can alkylate aromatic rings *ortho* to heteroatoms using aluminum catalysts (eqs 22 and 23).[18]

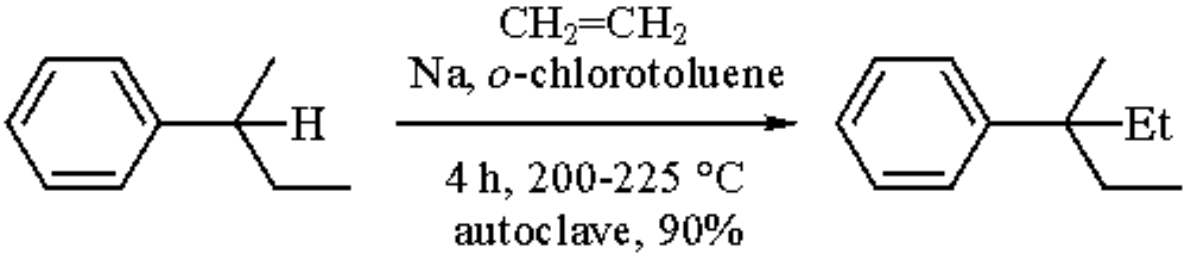

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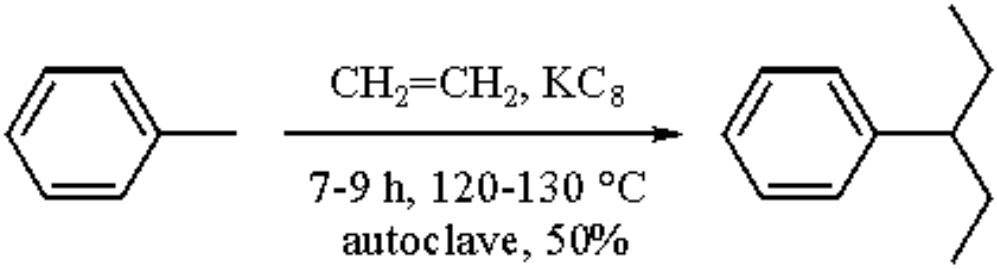

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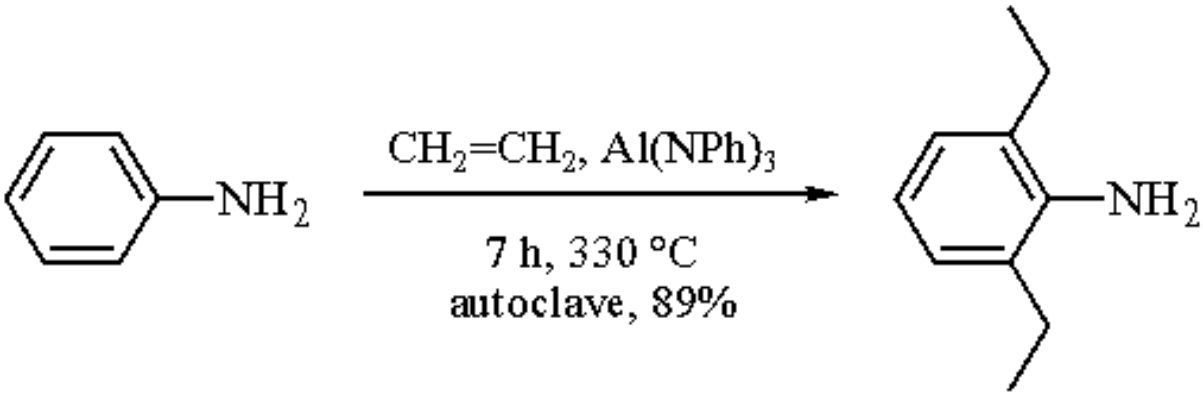

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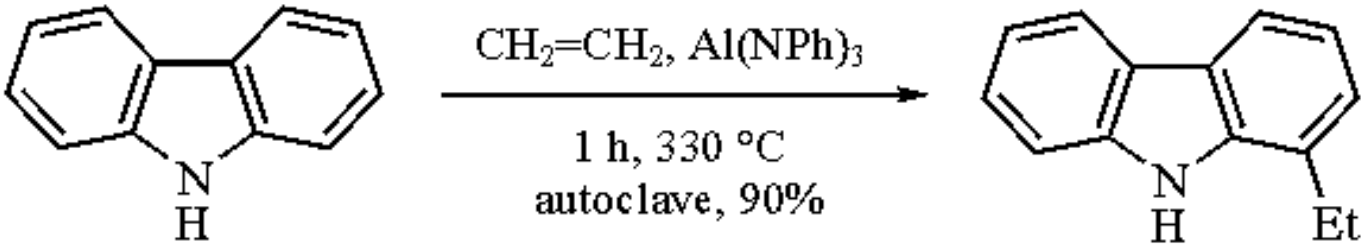

(23)

Organometallic Catalyzed Reactions and Heck Reactions.

Palladium-catalyzed oxidation of ethylene is an important industrial process. Ethylene is oxidized to vinyl acetate[19] by ***Palladium(II) Acetate*** in acetic acid and to acetaldehyde (the Wacker process).[20] In the presence of bis(acetonitrile)dichloropalladium(II), indoles are converted to vinyl indoles (eq 24).[21] Silyl enol ethers are alkylated by ethylene in the presence of ***Bis(benzonitrile)dichloropalladium(II)*** (eq 25).[22] Stabilized carbanions are also vinylated by ethylene with the assistance of $PdCl_2(MeCN)_2$ (eqs 26 and 27).[23] Substituted *o*-bromonitrobenzene derivatives react with ethylene to yield the corresponding indole derivative or vinyl derivative (eq 28).[24]

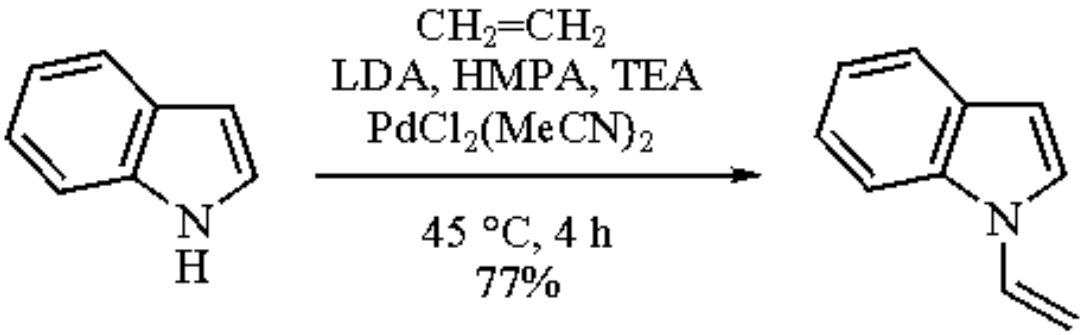

(24)

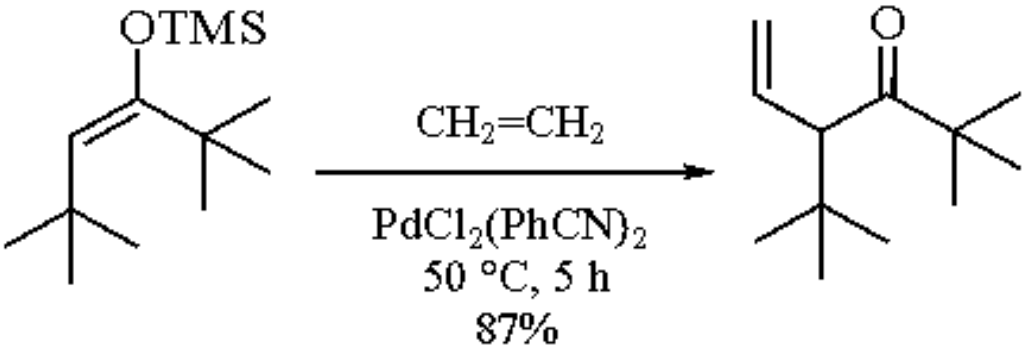

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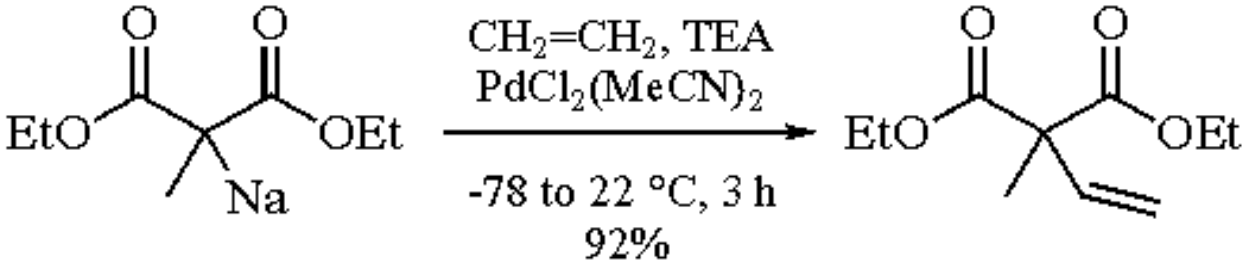

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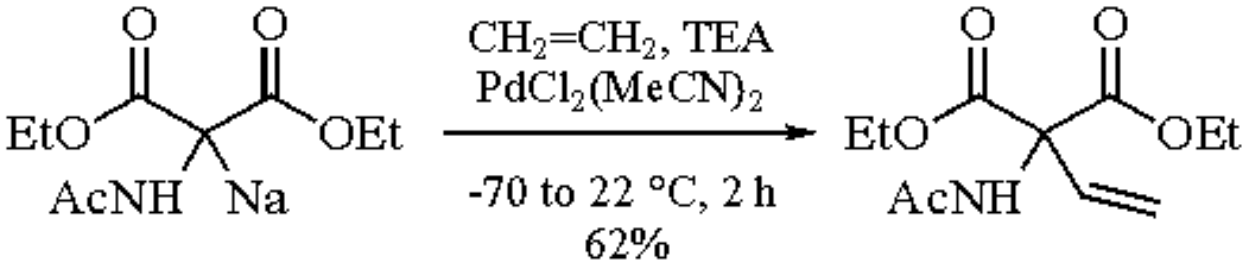

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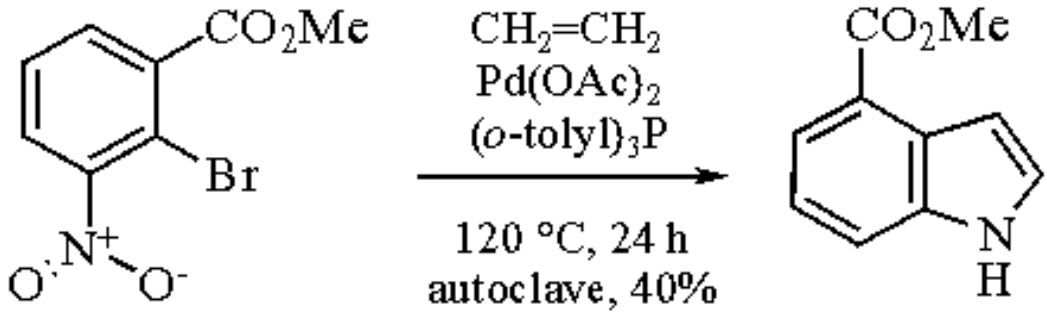

(28)

An efficient asymmetric hydrovinylation of cyclohexa-1,3-dienes catalyzed by nickel complexes in the presence of a chiral aminophosphine ligand has been reported (eq 29).[25] Acrylamides can be prepared through the reaction of isocyanates with ethylene in the presence of ***Bis(1,5-cyclooctadiene)nickel(0)*** (eq 30).[26] Bis(1,5-cyclooctadiene)nickel

also catalyzes the conversion of styrene to 5-phenyl-4-pentenoic acid (eq 31).[27]

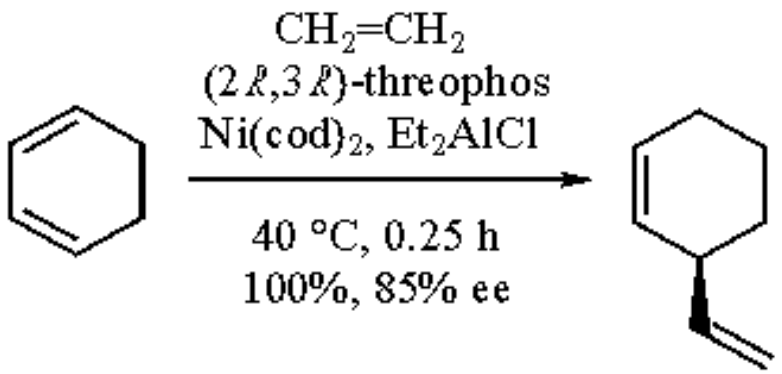

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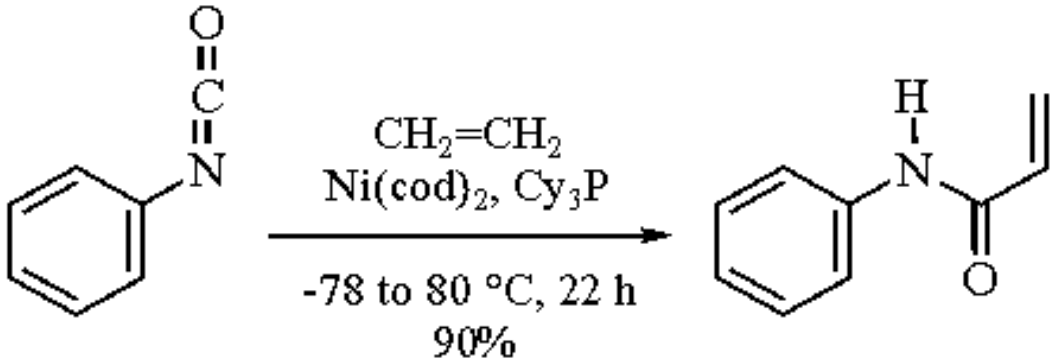

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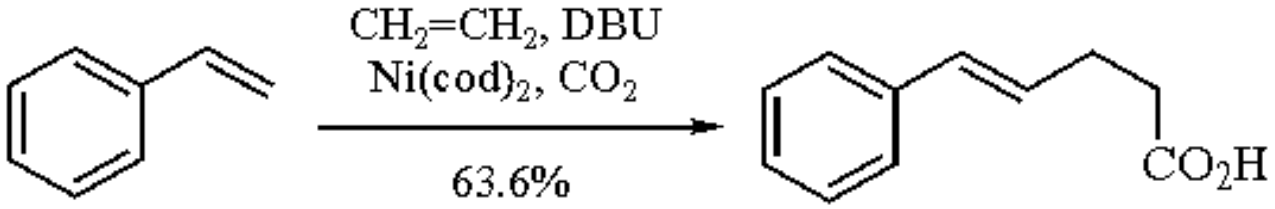

(31)

Rhodium catalysts (e.g. ***Dodecacarbonyltetrarhodium***) have also been used for carbonylation-alkylation reactions of alkynes with ethylene to form ketones (eq 32) and lactones (eq 33).[28]

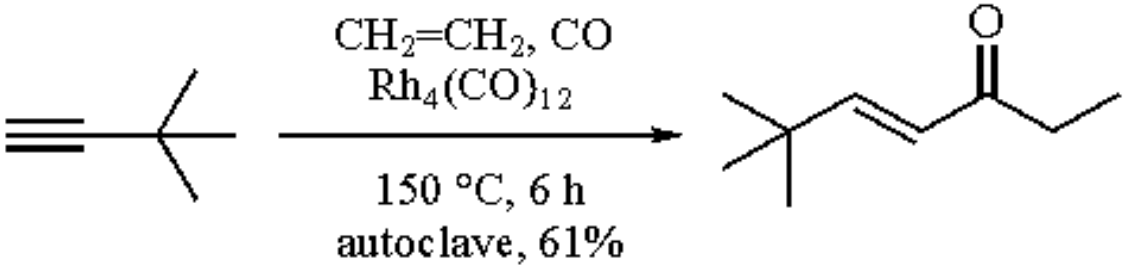

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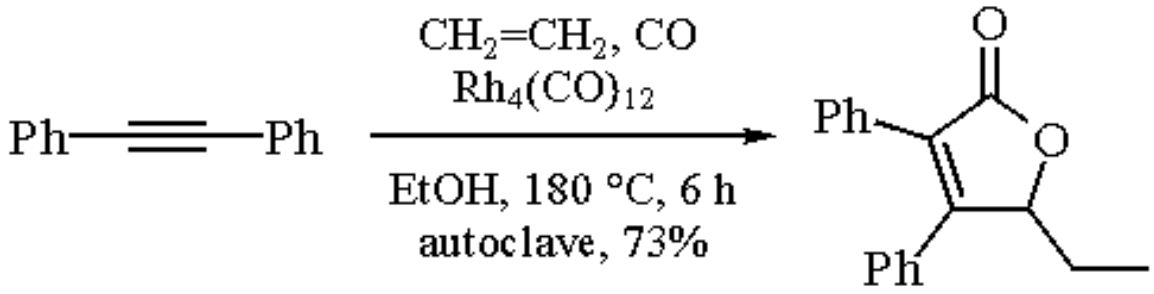

(33)

Other Organometallic Reactions.

Diallylic organozinc derivatives and allylic magnesium halides react with ethylene to afford the corresponding zinc or Grignard derivatives (eqs 34 and 35).[29] The conditions for the organozinc addition are milder than those needed for the Grignard addition. Secondary and tertiary alkyllithium reagents also add to ethylene to give primary alkyllithium reagents that are inert to further addition to ethylene (eq 36).[30] An example of an intramolecular addition of a lithium reagent generated from the addition to ethylene has also been reported (eq 37).[31] Ethylene can be deprotonated and added to benzaldehyde to obtain the allylic alcohol in high yield (eq 38).[32]

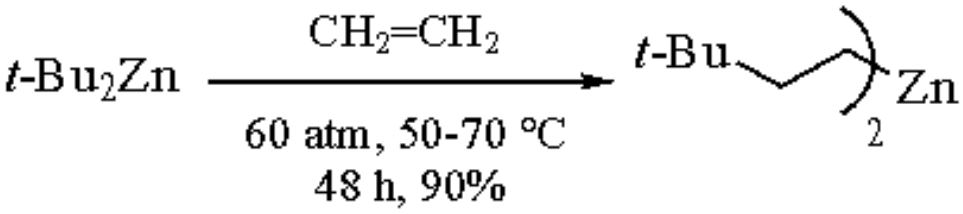

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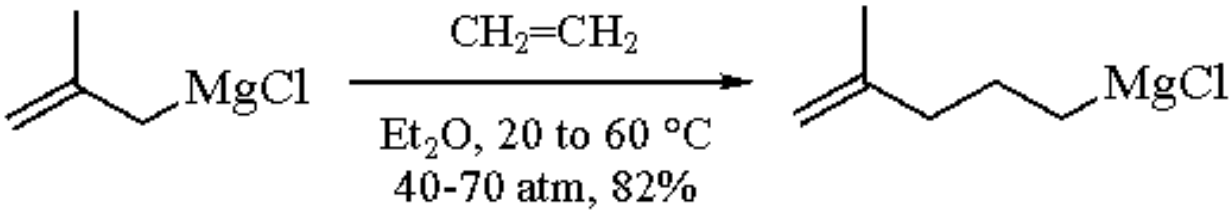

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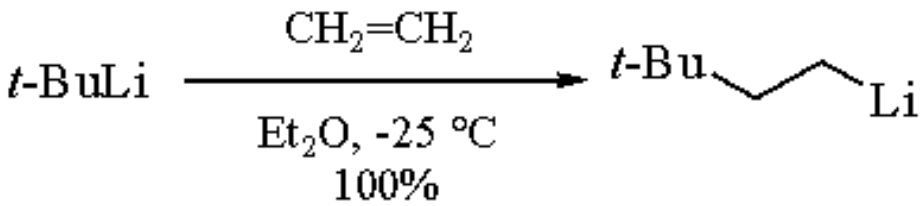

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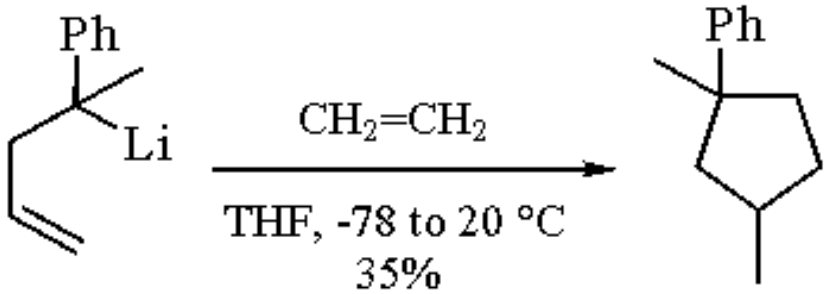

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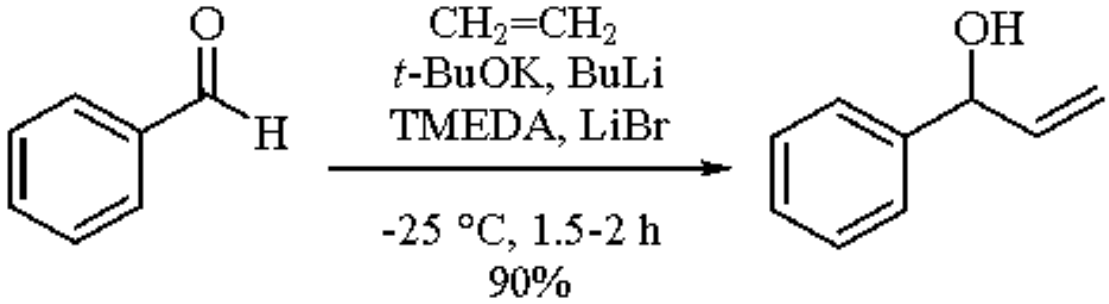

(38)

Alkene Polymerization.

Ethylene is used extensively in polymerization reactions (Ziegler-Natta). ***Titanium(IV) Chloride*** and ***Triethylaluminum*** catalyzed the conversion of ethylene to polyethylene (eq 39).[33]

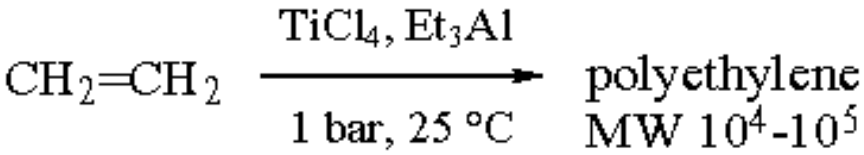

(39)

Miscellaneous Reactions.

Ethylene has been used in cycloadditions with ***Chlorosulfonyl Isocyanate*** to form 2-(2-chloroethyl)-3-oxoisothiazolidine 1,1-dioxides (eq 40).[34] Compared to other alkenes, ethylene provides substituted cyclopentenones with modest results under Pauson-Khand reaction conditions (eqs 41 and 42).[35] Perchlorovinylcarbene (formed from the thermal ring opening of tetrachlorocyclopropene) adds efficiently to form 1-chloro-1-(trichloroethenyl)cyclopropane (eq 43).[36] Electrophilic addition of sulfenyl chlorides and chlorine sulfate to ethylene provides chloroethyl sulfides (eq 44)[37] and chloroalkyl sulfonate (eq 45).[38]

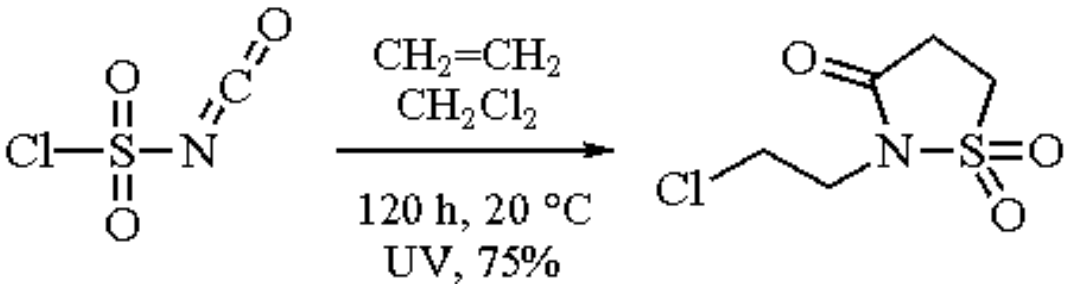

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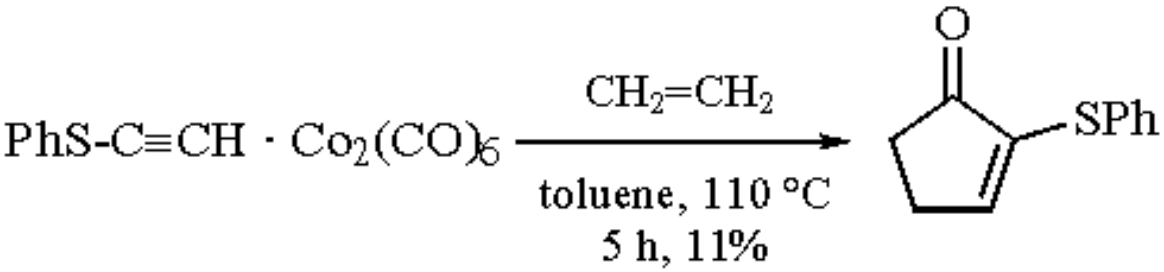

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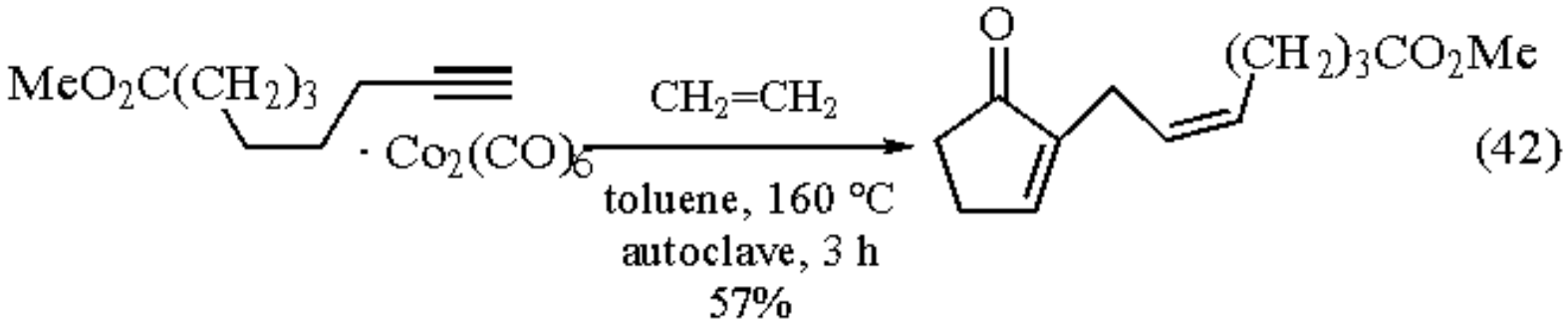

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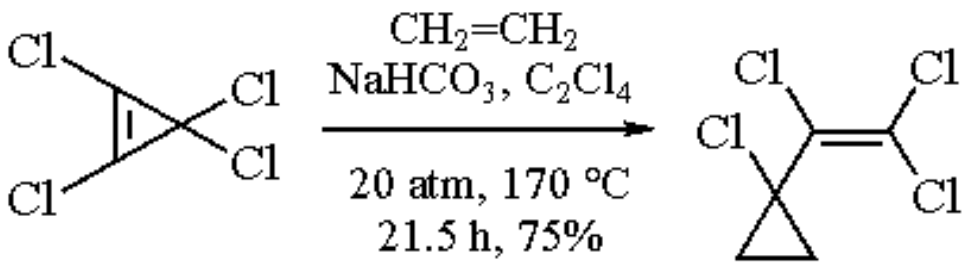

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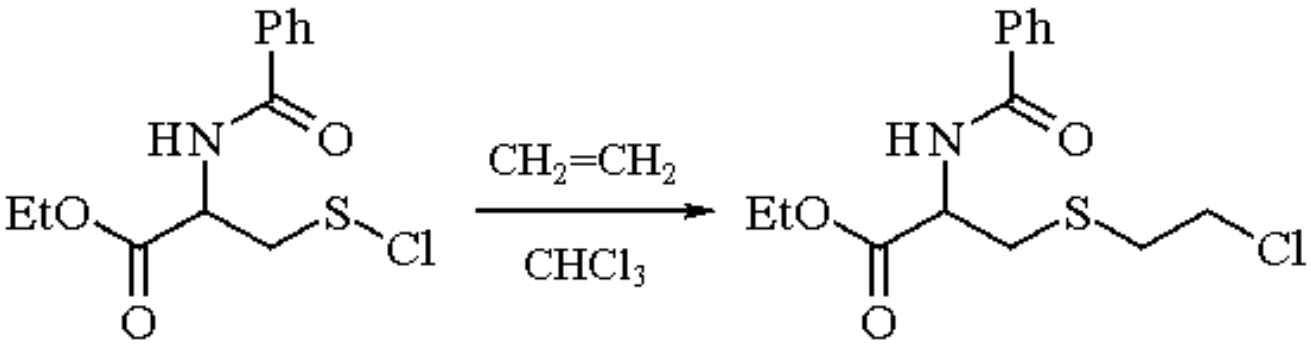

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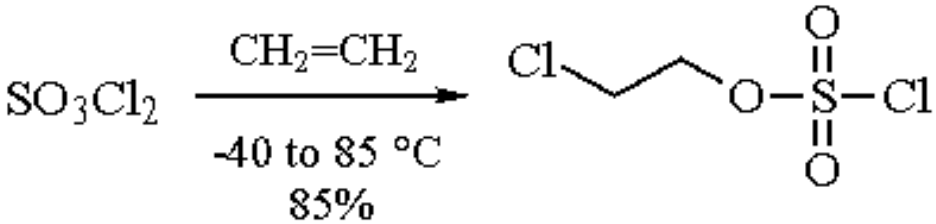

(45)

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(*R,R*)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]titanium (*R*)-1,1´-Bi-2,2´-naphtholate

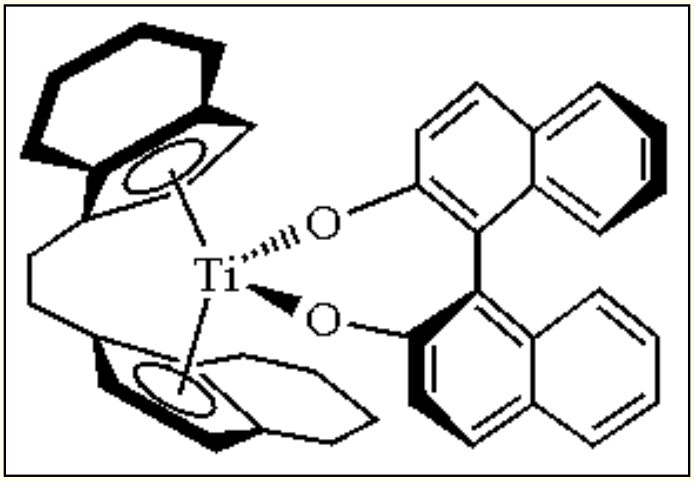

(*R,R,R*)

[143063-72-3] · $C_{40}H_{36}O_2Ti$ · (*R,R*)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]titanium (*R*)-1,1´-Bi-2,2´-naphtholate · (MW 596.64) (*S,S,S*)

[83417-93-0]

(precursor to a catalyst for the asymmetric reduction of unsaturated organic molecules[1])

Physical Data: mp 274.5-277 °C (dec); $[\alpha]_{578}$, -3700° (*c* = 0.45 mg cm^{-3} in $CHCl_3$).

Solubility: sol THF, benzene, toluene; slightly sol ether; very slightly sol hexane.

Preparative Methods: originally prepared and characterized by Brintzinger et al. from the corresponding dichloride derivative and ***(R)-1,1´-Bi-2,2´-naphthol***.[2] The dichloride is synthesized by reacting the dilithium salt of 1,2-bis(3-indenyl)ethane with ***Titanium(IV) Chloride*** followed by hydrogenation over ***Platinum(IV) Oxide***.[2] Since the original report, two improved procedures for its preparation have appeared.[3,1b]

Handling, Storage, and Precautions: the complex is air and moisture stable and can be stored indefinitely.

Catalyst Generation and Handling.

When complex (**1**) is allowed to react with 2 equiv of ***n-Butyllithium*** and 2.5-3 equiv of phenylsilane in THF under an inert atmosphere, an active reduction catalyst, complex (**2**), is formed (eq 1).

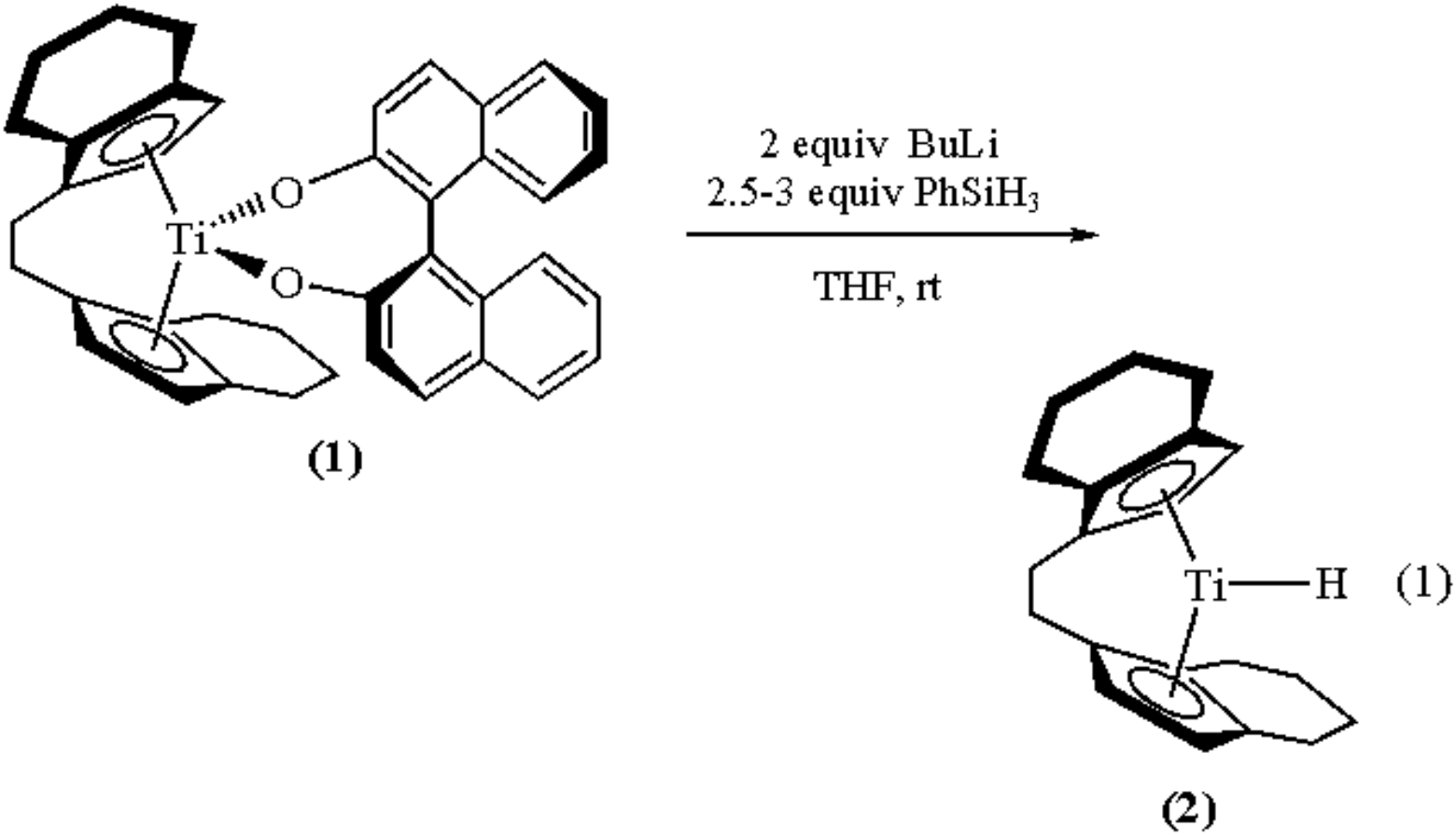

Complex (**2**) is believed to be a titanium(III) hydride and has not been isolated or characterized (no ^{1}H NMR signals for any titanium species are observable, probably as a result of the paramagnetic nature of the complex). This complex is extremely air sensitive and must be handled under rigorously oxygen-free conditions. Solutions of complex (**2**) are stable under inert atmosphere for at least 24 h and exhibit no sensitivity to light. For synthetic purposes it is most convenient to generate the active catalyst from complex (**1**) immediately prior to use.

Reduction of Unfunctionalized Alkenes.

The asymmetric reduction of trisubstituted alkenes with this system has recently been investigated.[4] It was shown that high ee's could be achieved in this reaction, although high pressures and long reaction times were necessary. As an example, *trans*-methylstilbene can be reduced at 2000 psi of hydrogen and 65 °C with excellent chemical and optical yield (eq 2). This represents the first catalyst system for the reduction of unfunctionalized, trisubstituted alkenes with good to excellent enantioselectivity.

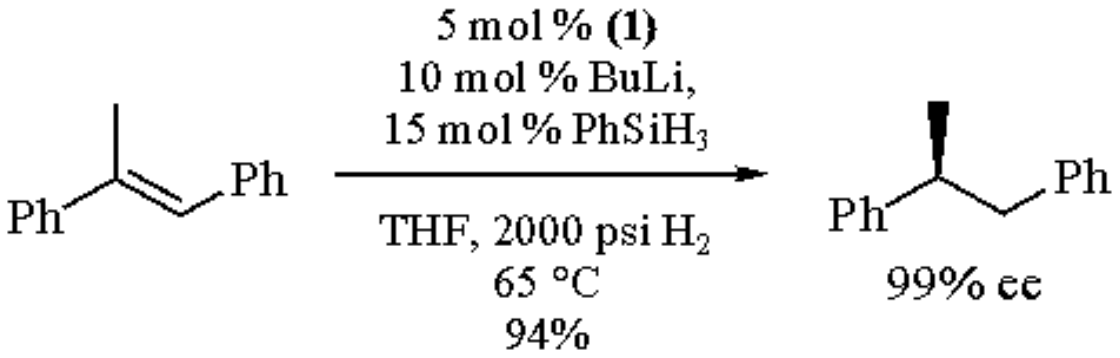

(2)

Reduction of Imines.

This catalyst system is very effective for the asymmetric hydrogenation of imines.[1b] For example, *N*-(1-cyclohexyl)ethylidenebenzylamine (as a mixture of *anti* and *syn* isomers) can be reduced in excellent yield and good enantiomeric excess (eq 3). The reaction must be conducted at high pressures in order to achieve maximum enantioselectivity. This effect was found for several acyclic imines.

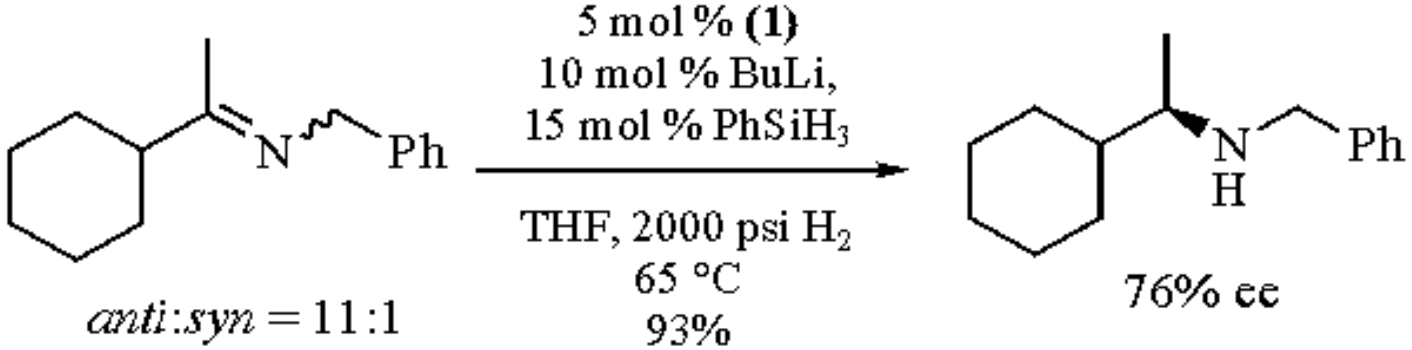

(3)

The reduction of cyclic imines with this system was found to proceed under much milder conditions.[5] For example, 2-phenylpyrroline was reduced at 80 psi of hydrogen to afford 2-phenylpyrrolidine in good yield and excellent enantiomeric excess (eq 4).

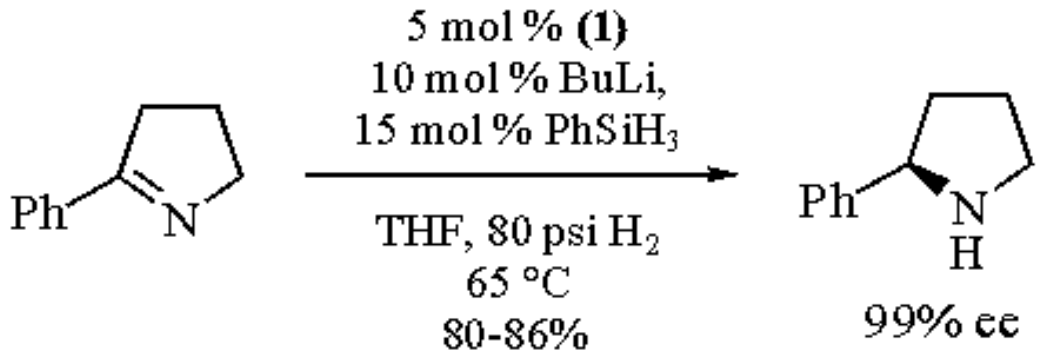

(4)

This reaction was found to be applicable to ring sizes of 5 to 7 (although more forcing conditions were required for six-membered rings) and was compatible with several functional groups. In all cases studied, ee's greater than 95% were observed. Among the functional groups investigated were acetals, silyl ethers, trisubstituted alkenes, and alcohols. Monosubstituted alkenes were completely reduced and disubstituted alkenes were partially reduced and isomerized under the standard conditions. The reaction has the practical advantage that the active catalyst can be generated in a Fisher-Porter bottle and the reaction can then be conducted in the same vessel. Thus no transfer of air-sensitive

materials is necessary.

Related Reagents.

(-)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]zirconium (R)-1,1´-Bi-2,2´-naphtholate; ***(±)-1,1´-Ethylenebis(4,5,6,7-tetrahydro-1-indenyl)zirconium Dichloride***.

---

1. (a) Buchwald, S. L.; Kreutzer, K. A.; Willoughby, C. A.; Grossman, R. B.; Berk, S. C.; Spaltenstein, E.; Gutierrez, A. PCT Int. Appl. 92 09 545. (b) Willoughby, C. A.; Buchwald, S. L. *JACS* **1992**, *114*, 7562.
2. Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *JOM* **1982**, *232*, 233.
3. (a) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *JOM* **1988**, *342*, 21. (b) Collins, S.; Kuntz, B. A.; Hong, Y. *JOC* **1989**, *54*, 4154.
4. Broene, R. D.; Buchwald, S. L. *JACS* **1993**, *115*, 12569.
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Christopher A. Willoughby

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(-)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]zirconium (*R*)-1,1´-Bi-2,2´-naphtholate[1]

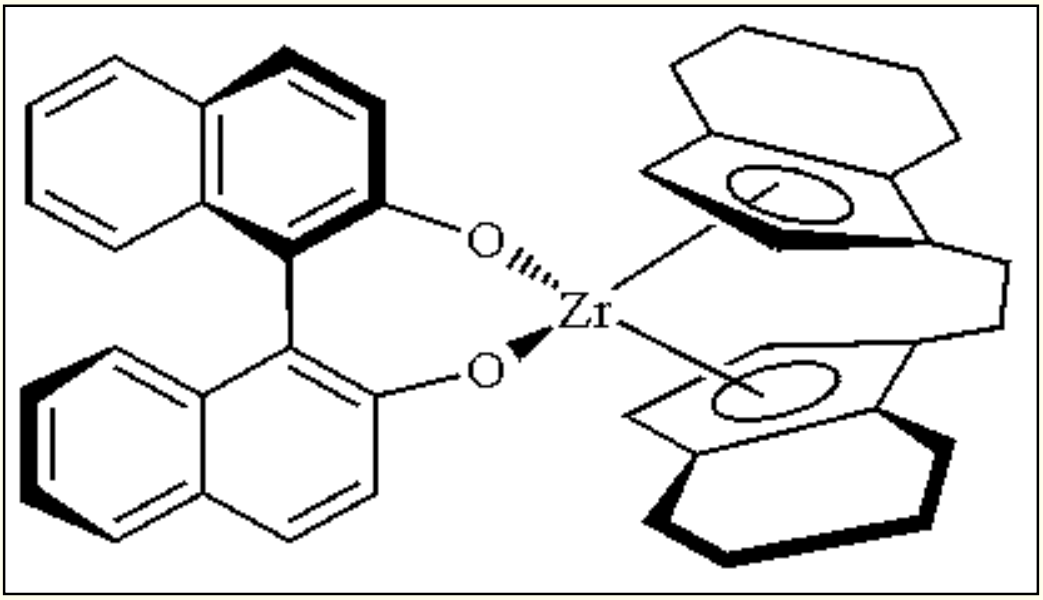

[133868-91-4] · $C_{40}H_{36}O_2Zr$ · (-)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]zirconium (*R*)-1,1´-Bi-2,2´-naphtholate · (MW 639.98)

(in combination with methylaluminoxane it is an enantioselective hydrogenating[2] and cyclopolymerizing agent;[3] reagent for the resolution of racemic ethylenebis(tetrahydro-1-indenyl)]zirconium dichloride[4])

Physical Data: [α]25436 -1761° (*c* 1.1, $CHCl_3$).

Preparative Methods: this reagent is an intermediate for the preparation of optically pure ethylenebis(tetrahydro-1-indenyl)zirconium dichloride.[4] That is, according to the procedure described for the kinetic resolution of ethylenebis(tetrahydro-1-indenyl)titanium dichloride with (*R*,*R*)- or (*S*,*S*)-binaphtholate,[5] 1 equiv of racemic ethylenebis(tetrahydro-1-indenyl)zirconium dichloride[6] can be resolved with 0.5 equiv of (*R*,*R*)-binaphthol in the presence of sodium metal in toluene to yield the optically active (*S*,*S*)-ethylenebis(tetrahydro-1-indenyl)zirconium dichloride and the (-)-[ethylenebis(tetrahydro-1(*R*)-indenyl]zirconium (*R*)-binaphtholate. The separated optically pure (-)-[ethylenebis(tetrahydro-1(*R*)-indenyl]zirconium (*R*)-binaphtholate can be easily converted to the corresponding optically pure zirconocene dichloride upon treating with HCl gas.

Catalytic Hydrogenation and Cyclopolymerization.

This zirconium reagent constitutes a homogeneous catalytic system (Ziegler-Natta catalyst) with methylaluminoxane (MAO) for the purpose of enantioselective hydrogenation[2] of alkenes or cyclopolymerization[3] of alkenic compounds to optically active polymers. In the hydrogenations, terminal alkenes substituted in the 2- or 3-positions and internal alkenes are hydrogenated with 23-65% ee in good yields. In the catalytic deuteration of styrene with this reagent, the *re*-face of styrene is deuterated in 65% optical purity (eq 1). This enantioselectivity in hydrogenation is opposite to propylene oligomerization with the same catalytic system. 1,5-Hexadiene is polymerized with this catalytic system in 91% enantioface selectivity to give poly(methylene-1,3-cyclopentane) (PMCP), which is inductive of a highly isotactic microstructure (eq 2). The absolute configuration of the polymer is tentatively assigned on the basis of the sign of the optical rotation of the model compound *trans*-(1*R*,3*R*) 1,3-dimethylcyclopentane.[3]

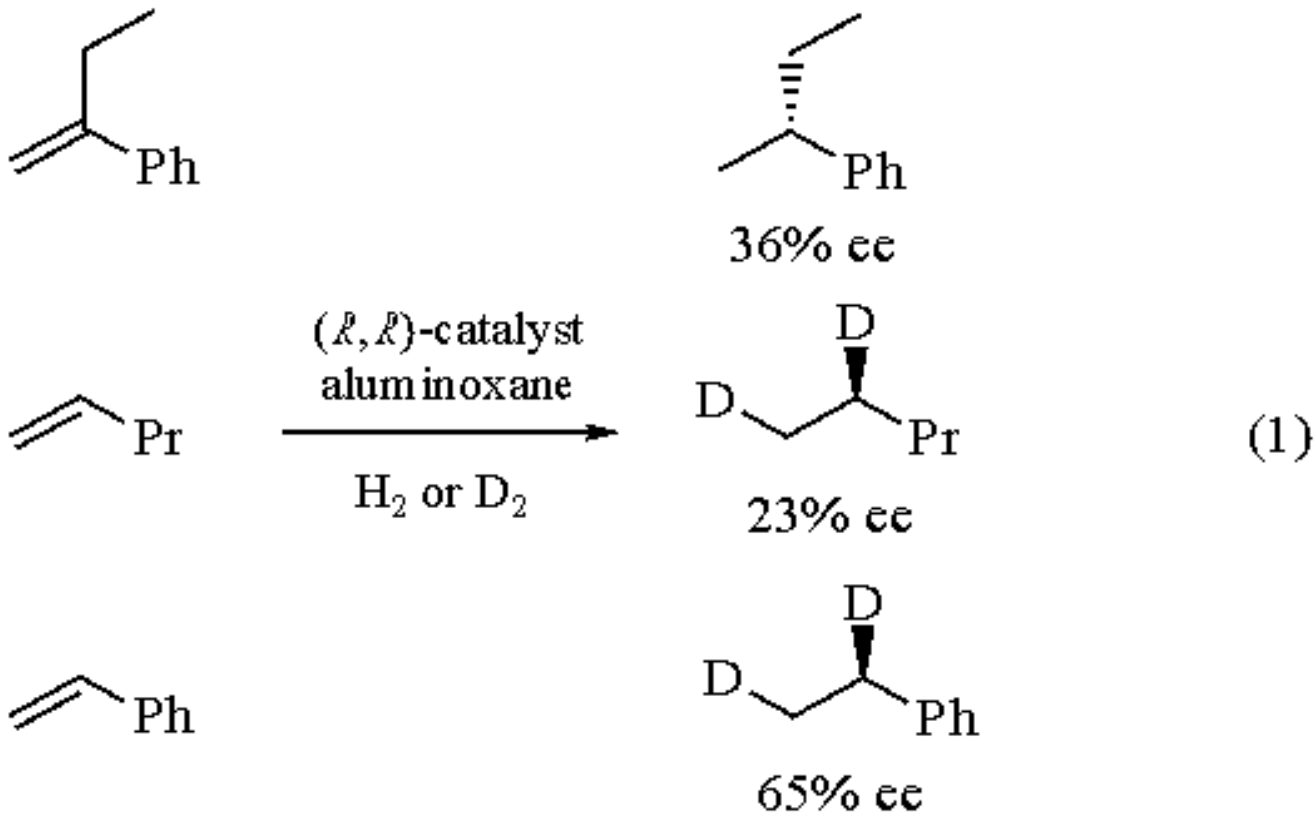

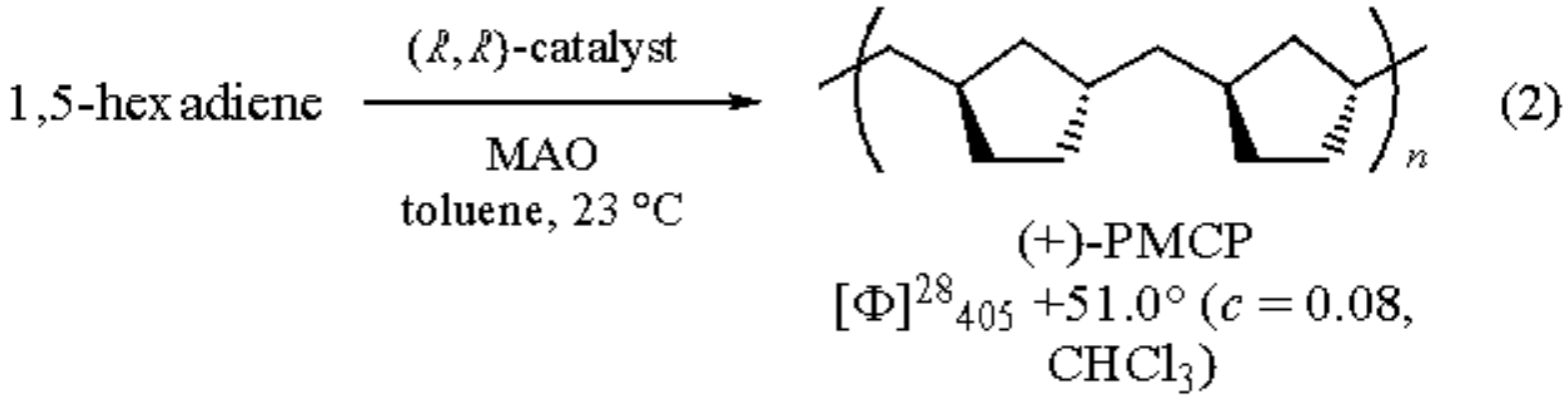

Related Reagents.

***(R,R)-[Ethylene-1,2-bis(η5-4,5,6,7-tetrahydro-1-indenyl)]titanium (R)-1,1´-Bi-2,2´-naphtholate*; *(±)-1,1´-Ethylenebis(4,5,6,7-tetrahydro-1-indenyl)zirconium Dichloride*.**

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4. (a) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *JACS* **1991**, *113*, 2321. (b) For the improved procedure of resolution, see; Schäfer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *JOM* **1987**, *328*, 87.
5. Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *JOM* **1982**, *232*, 233.
6. (a) Wild, F. R. W. P.; Wasiucionek, M.; Huttner, G.; Brintzinger, H. H. *JOM* **1985**, *288*, 63. (b) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *JOM* **1987**, *342*, 21. (c) Ewen, J. A.; Haspeslagh, L.; Atwood, J. L.; Zhang, H. *JACS* **1987**, *109*, 6544. (d) Grossman, R. B.; Doyle, R. A.; Buchwald, S. L. *OM* **1991**, *10*, 1501.

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(±)-1,1´-Ethylenebis(4,5,6,7-tetrahydro-1-indenyl)zirconium Dichloride

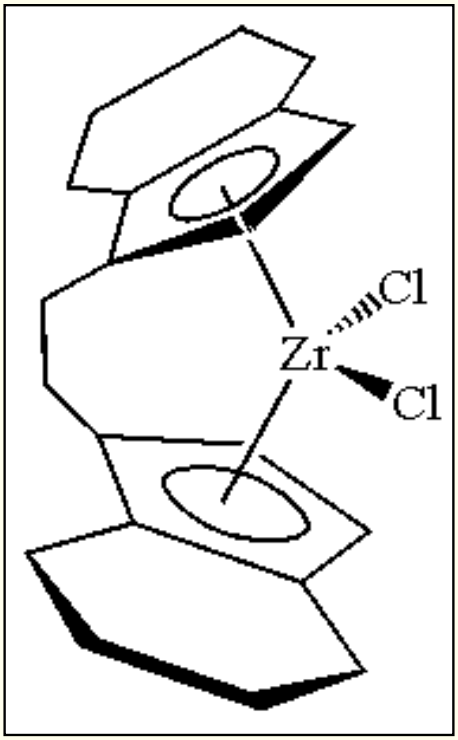

[112243-79-5] · $C_{20}H_{24}Cl_2Zr$ · (±)-1,1´-Ethylenebis(4,5,6,7-tetrahydro-1-indenyl)zirconium Dichloride · (MW 426.57)

(chiral metallocene complex for stereoselective alkene and silane polymerization;[1] asymmetric hydrogenation catalyst for alkenes;[2,3] reagent for the asymmetric synthesis of allylic amines;[4] asymmetric carbomagnesiation catalyst;[5] precursor to chiral Lewis acid catalysts[6])

Physical Data: d 1.616 g cm^{-3} (calc).

Solubility: insol hexanes, diethyl ether; sol CH_2Cl_2, $CHCl_3$, THF; slightly sol toluene.

Form Supplied in: crystalline white or pale yellow solid; not widely available.

Analysis of Reagent Purity: ^1H NMR and/or elemental analysis.

Preparative Methods: by hydrogenation of the corresponding racemic ethylenebis(η^5-indenyl)zirconium dichloride[7a] over PtO_2 or 5% Pt/C at 1000 or 50-500 psi, respectively. The indenyl precursor is generally prepared from 1,2-bis(3-indenyl)ethane and $ZrCl_4$ in THF solution via the dilithium[7b] or dipotassium salt[3] of the former compound. In the former case, racemic material can be obtained in pure form (40-50% yields),

whereas in the latter case the product (>70% crude) is contaminated with significant amounts of the *meso* isomer which can be removed by fractional crystallization from toluene. The racemate can be resolved on a gram scale by conversion to the (*S*)- or (*R*)-binaphtholate derivative.[4,8] Conversion, for example, of the (*S*,*S*)-binaphtholate derivative to the dimethylzirconocene derivative (MeLi, ether, or toluene) followed by treatment with either stoichiometric anhydrous dimethylamine hydrochloride (CH_2Cl_2) or anhydrous HCl (ether) provides optically pure material; $[\alpha]_{435}$ = +416°(*c* = 0.048 g 100 mL^{-1}, CH_2Cl_2).[8]

Purification: the racemate is best crystallized from hot toluene. Optically pure material, which is much more soluble, is best crystallized from hexanes/toluene.

Handling, Storage, and Precautions: the compound is air and moisture stable but is best stored for long periods of time (years) in a desiccator. No known toxic effects or safety hazards.

Introduction.

While primarily employed in the study of the stereoselective polymerization of alkenes and, to a lesser extent, dehydrogenative polymerization of silanes,[1] *rac*-$[CH_2(\eta^5\text{-}C_9H_{10})]_2ZrCl_2$ (**1**) has attracted increasing attention as a reagent and/or catalyst in organic synthesis.

Asymmetric Hydrogenation.[2,3]

In the presence of methylaluminoxane and hydrogen (or deuterium), the dimethyl derivative (**2**) of (*S*)-(+)-(**1**) effects the asymmetric hydrogenation or deuteration of alkenes in up to 65% ee (e.g. eq 1). While this level of asymmetric induction is modest, it should be noted that this is one of the few methods available for asymmetric hydrogenation of unfunctionalized alkenes. The sense of asymmetric induction is reversed from that observed in alkene polymerization; coordination and insertion of the alkenes occurs from the *re* enantioface.

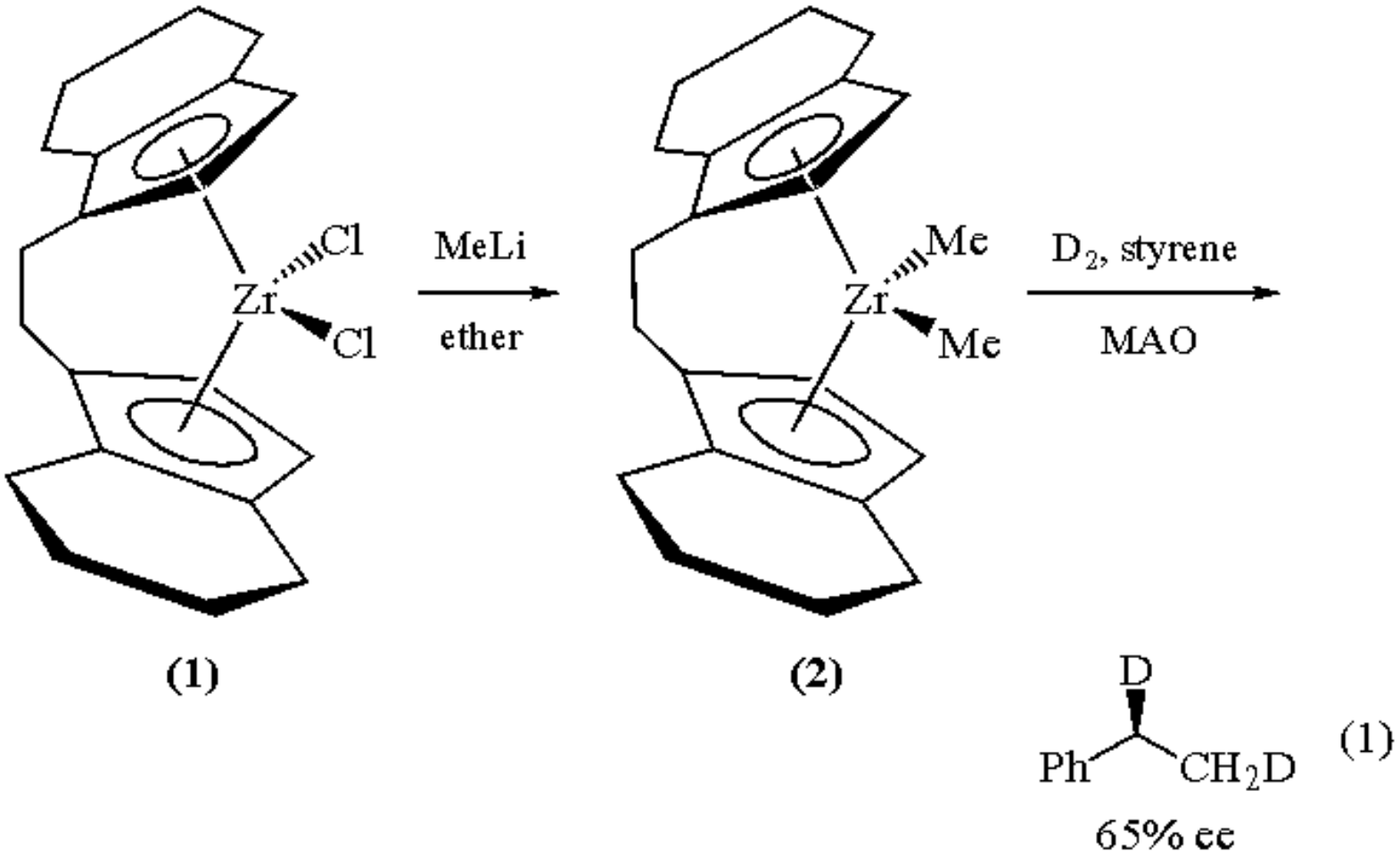

The active intermediate in these transformations is a cationic zirconium hydride complex generated in situ. More recent work has established that preformed cationic hydride complexes are equally effective.[3]

Asymmetric Synthesis of Allylic Amines.[4]

Optically pure (*S*)-(+)-(**1**) can be converted to the methyl triflate complex (**3**) via the dimethyl derivative (**2**). Reaction of (**3**) with lithium aryl amides at elevated temperatures generates, in situ, zirconaziridine intermediates which undergo facile insertion of alkynes to generate, on acidic workup, allylic amines in high optical purity (eq 2). Although this process requires stoichiometric amounts of (**2**), optically pure (**1**) can be recovered following workup with HCl/ether and recycled. Other substrates include alkenes and aldehydes and furnish saturated amines and β-amino alcohols, respectively, in high optical purity.

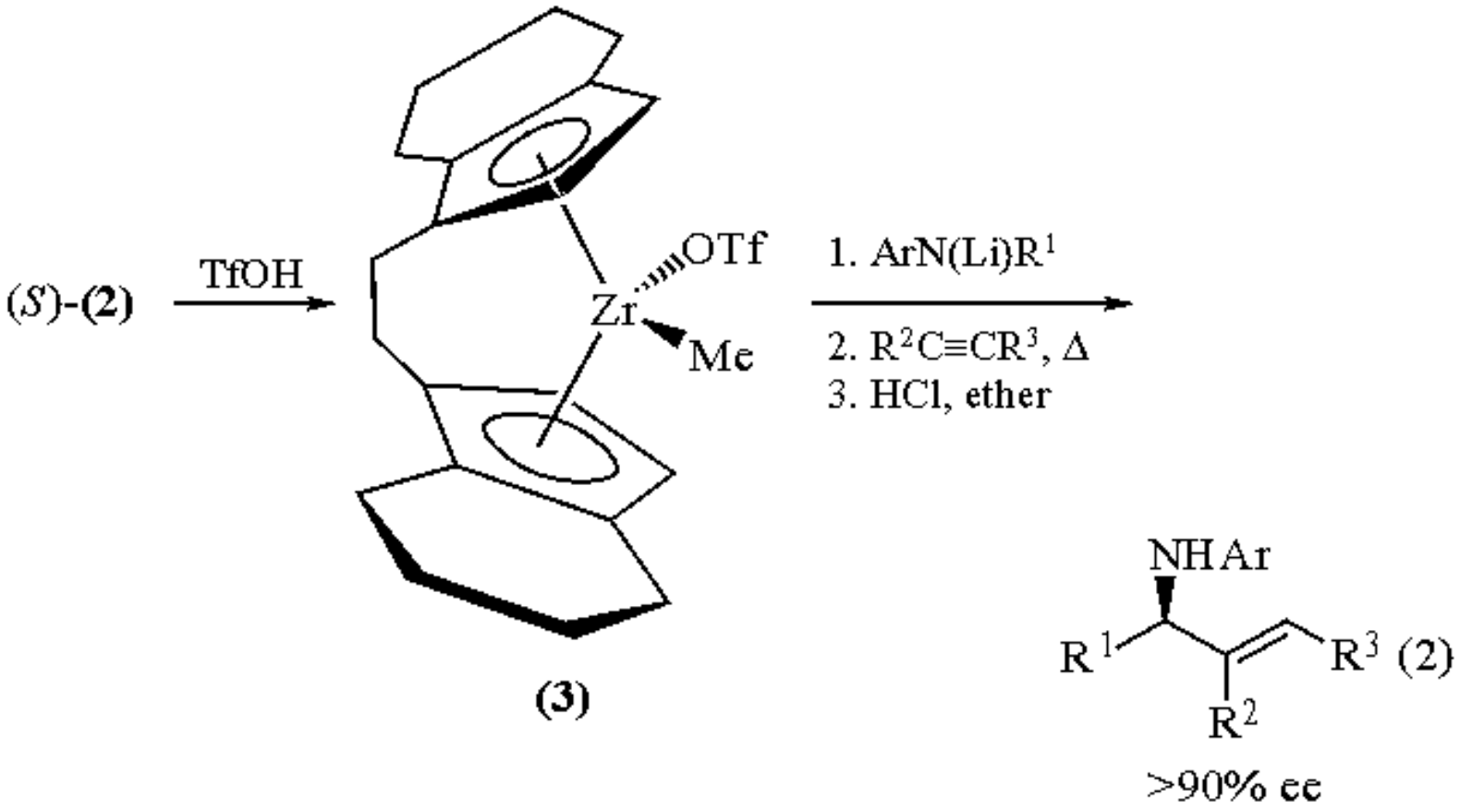

Asymmetric Carbomagnesiation of Alkenes.[5]

Complex (*S*)-(+)-(**1**) in the presence of alkyl Grigard reagents effects the catalytic carbomagnesiation of allylic alcohols or ethers in both a diastereo- and enantioselective manner. A mechanism involving an in situ generated metallacyclopropane complex has been invoked to rationalize the sense of asymmetric induction. For example, cyclic allylic ethers undergo carbomagnesiation with excellent levels of stereocontrol (eq 3).

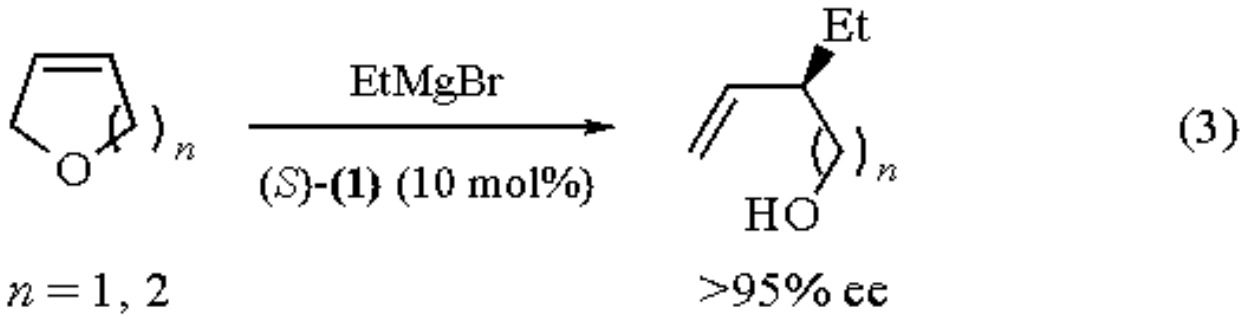

Asymmetric Lewis Acid Catalysts.[6]

Compound (**1**) has been transformed into the optically pure cationic alkoxide complex (**4**) via the intermediacy of the dimethyl derivative (**2**). Complex (**4**) is an effective catalyst for the Diels-Alder reaction of simple dienophiles with dienes (eq 4). With the dienophiles studied, the magnitude of the asymmetric induction is modest (<=55% ee) but the sense of asymmetry is consistent with a simple model for dienophile coordination to the metal center.

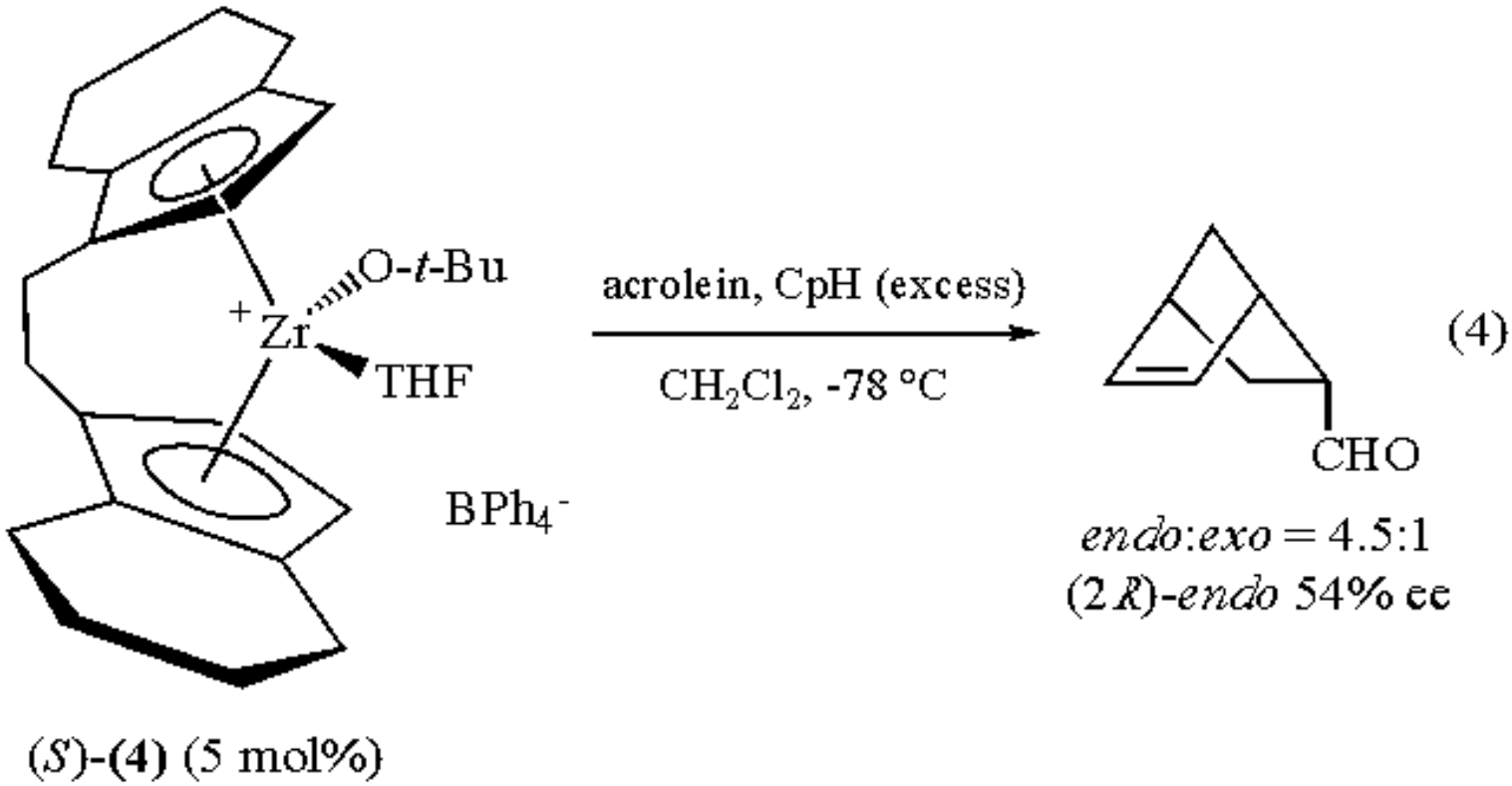

Related Reagents.

(-)-[Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)]zirconium (R)-1,1´-Bi-2,2´-naphtholate.

---

1. (a) Kaminsky, W.; Kuelper, K.; Brintzinger, H. H.; Wild, F. R. W. P. *AG* **1985**, *97*, 507. (b) Li, H.; Gauvin, F.; Harrod, J. F. *OM* **1993**, *12*, 575 and references therein.
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4. Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *JACS* **1991**, *113*, 2321.
5. (a) Morken, J. P.; Didiuk, M. T.; Hoyveda, A. H. *JACS* **1993**, *115*, 6997. (b) Hoyveda, A. H.; Morken, J. P. *JOC* **1993**, *58*, 4237.
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7. (a) Wild, F. W. R. P.; Wasiucionek, M.; Huttner, G.; Brintzinger, H.-H. *JOM* **1985**, *288*, 63. (b) Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *JOM* **1988**, *342*, 21.
8. An alternative procedure based on fractional crystallization of the bis((*R*)-*O*-acetylmandelate) derivatives has also been reported. Schaefer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H.-H. *JOM* **1987**, *328*, 87.

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Ethylenebis(triphenylphosphine)nickel(0)[1]

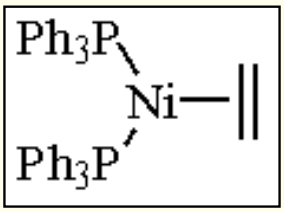

[23777-40-4] · $C_{38}H_{34}NiP_2$ · Ethylenebis(triphenylphosphine)nickel(0) · (MW 611.34)

(catalyzes vinylcyclobutene-cyclohexadiene rearrangement;[2] mild synthesis of [2^n]-cyclophanes;[3] stereospecific alkene dimerization catalyst;[4,5] cyclopropanation;[6] alkene oligomerization catalyst[7])

Physical Data: mp. 108-110 °C (dec); ^{1}H NMR δ (C_6D_6) 2.55 ppm (C_2H_4).

Solubility: very sol benzene, toluene; sparingly sol ether, pentane.

Form Supplied in: yellow crystalline solid; not commercially available.

Preparative Methods: most readily prepared in 75% yield from ***Nickel(II) Acetylacetonate***, ***Diethylaluminum Ethoxide***, and ***Triphenylphosphine***. In the presence of ***Ethylene*** the yields can be raised to >95% (eq 1).[8] Alternatively, ***Triethylaluminum*** may be employed in an ethylene saturated solution, yielding 85% of the complex.[9]

The reagent has also been prepared from ***Dichlorobis(triphenylphosphine)nickel(II)***, ***Zinc***, and ethylene (eq 2) or ***Nickel(II) Chloride***, zinc, PPh_3, and ethylene in yields of 80% and 71%, respectively.[10]

$$Ni(MeCOCHCOMe)_2 \xrightarrow[\substack{PPh_3,\ C_6H_6 \\ 75\text{-}98\%}]{Et_2AlOEt} (Ph_3P)_2Ni(C_2H_4) \qquad (1)$$

$$(Ph_3P)_2NiCl_2 \xrightarrow[\substack{THF \\ 80\%}]{Zn,\ CH_2{=}CH_2} (Ph_3P)_2Ni(C_2H_4) \qquad (2)$$

Purification: can be recrystallized from methanol at reduced temperatures.

Handling, Storage, and Precautions: is very air sensitive and should be stored under inert atmosphere,

preferably in a dry box.

The relatively weak nature of the ethylene-nickel interaction allows for the facile replacement with other coordinating ligands. Much of the chemistry of the catalyst is therefore attributed to this fact. In addition, a number of other related catalysts differ only by the nature of the phosphine ligands, thereby modifying some of its properties.[1]

Vinylcyclobutene-Cyclohexadiene Rearrangements.

Ethylenebis(triphenylphosphine)nickel(0) has been used as an isomerization catalyst for the ring expansion of vinylcyclobutenes to cyclohexadienes.[2,11] It also promotes the dechlorination of 1,2-dichlorides to the corresponding cyclobutenes. The reactions can be carried out independently, or direct conversion of the dichloride to the cyclohexadiene is also possible (eq 3). Conditions under which these transformations are carried out include thermolysis followed by oxidation of the resulting Ni^0 alkene complex to Ni^I and subsequent ring expansion, or preoxidation of the catalyst to Ni^I. Yields range from 40-50%. The presence of electron-withdrawing substituents on the cyclobutene system are required, whereas substitution on the vinyl group effectively lowers yields.

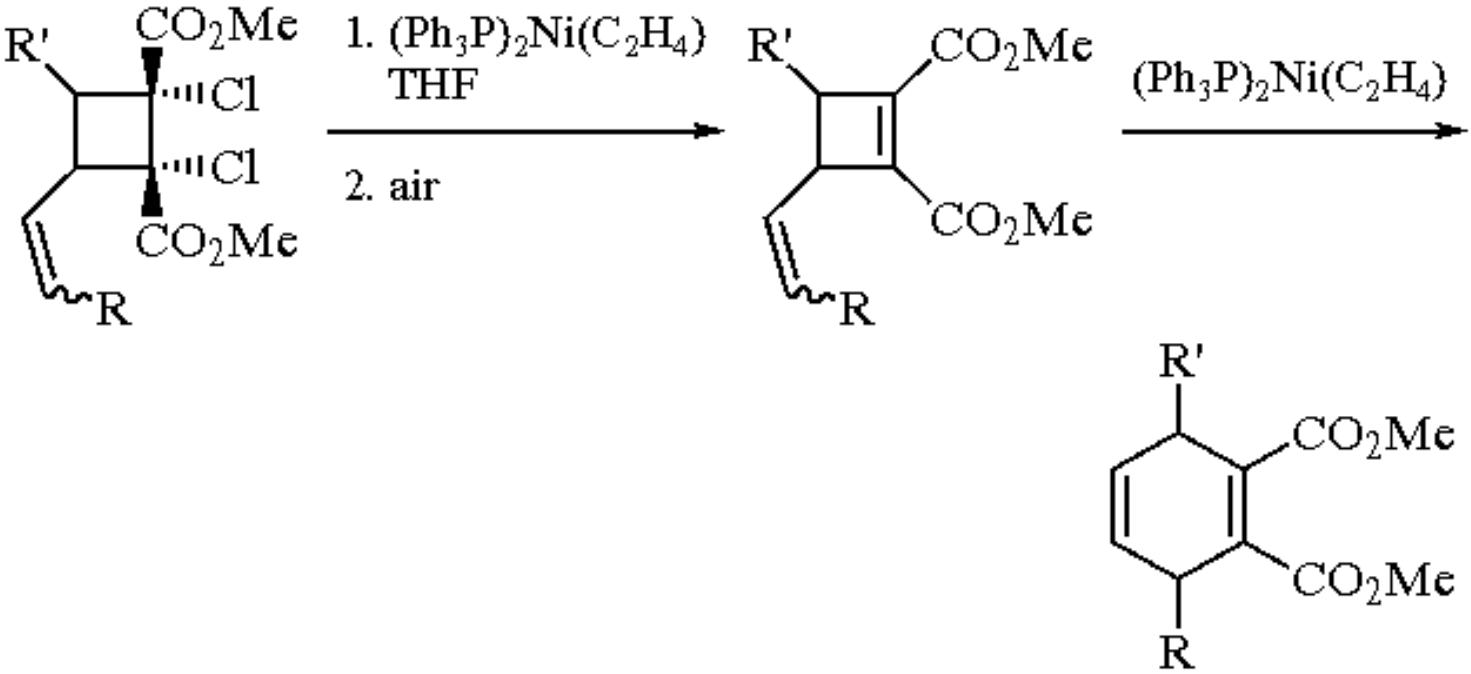

(3)

Preparation of Cyclophanes.

The reaction of halomethyl benzene derivatives with the catalyst results in oxidative addition to nickel, yielding the corresponding Ni^I or Ni^{II} benzyl complexes that have properties similar to nucleophilic Grignard species.[12,13] Appropriately, use of di-, tri-, to oligosubstituted aromatics results in the production of a variety of [2^n]-cyclophanes. For example, two equivalents of 1,2-bis(bromomethyl)benzene react with one equivalent of the catalyst to furnish the corresponding cyclophane in 66% yield (eq 4).[14]

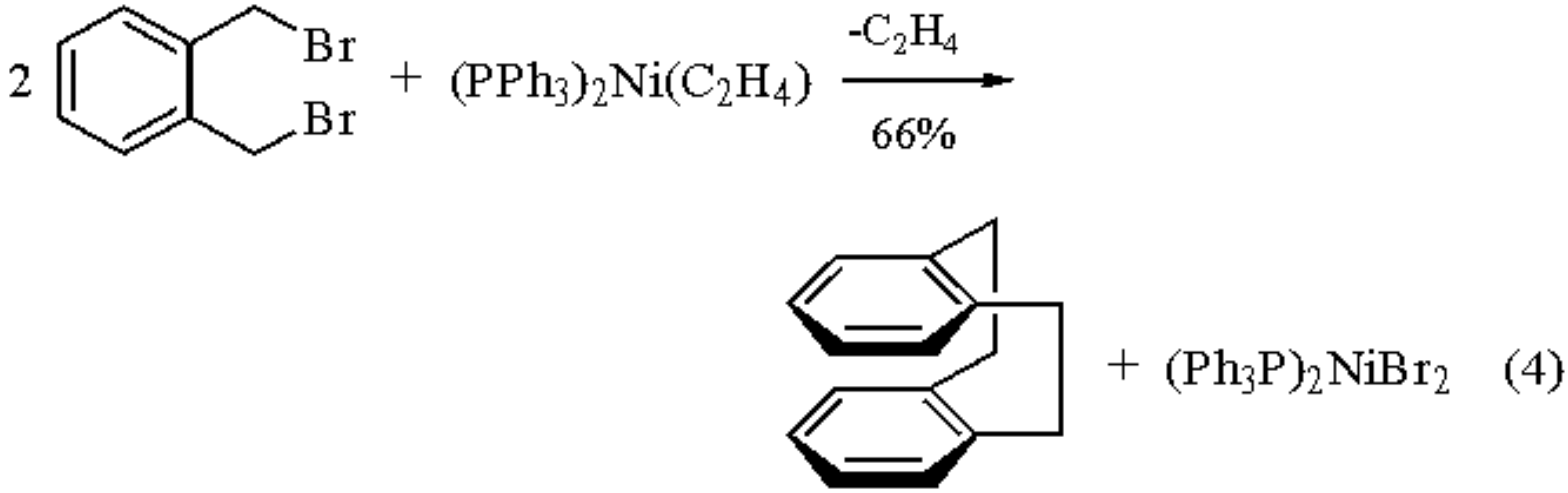

Other examples include the synthesis of [2^4](1,2,4,5)-cyclophane from 1,2,4,5-tetrabromomethylbenzene in 64% yield (eq 5).[14]

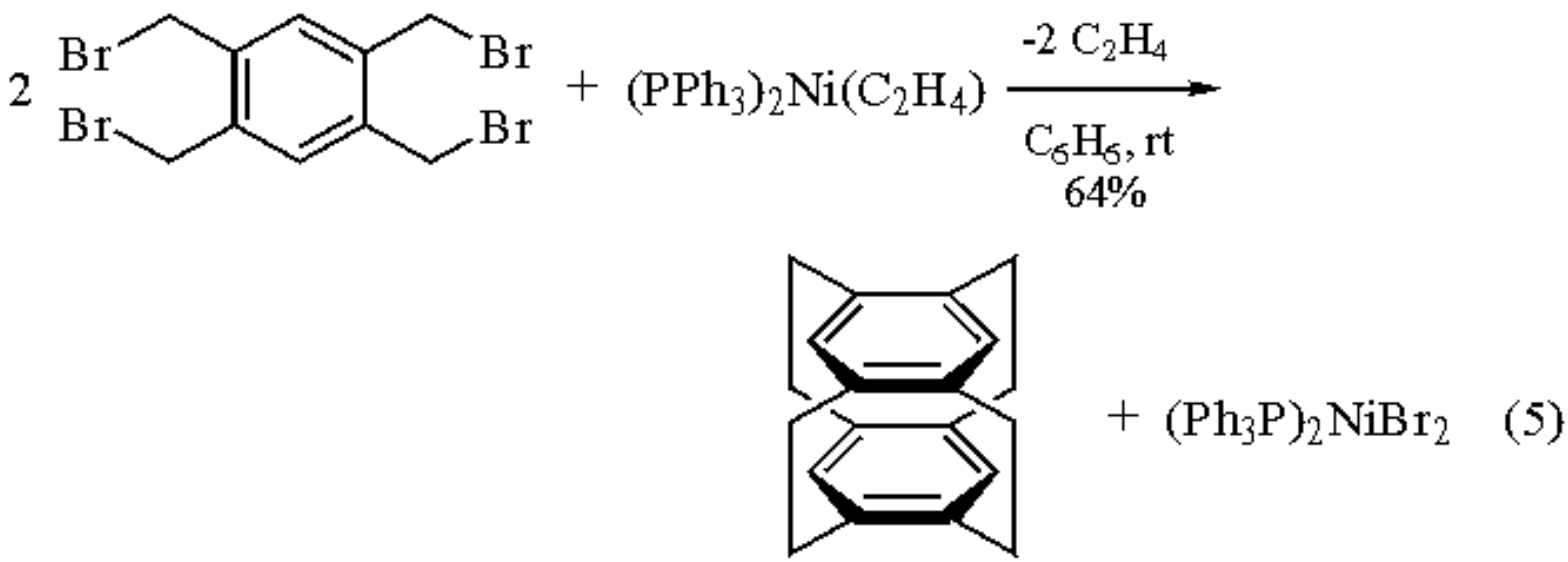

On a related note, the reaction of ethylenebis(triphenylphosphine)nickel(0) with 1,4-bis(chloromethyl)benzene in benzene at room temperature yields a variety of paracyclophanes including [2.2.2] (5%), [2.2.2.2] (20.3%), and [2.2.2.2.2] (8.1%).[3] These mild and efficient one-step preparations offer attractive alternatives to conventional syntheses that often employ reactive and corrosive alkali metals (Wurtz coupling) and/or multistep routes.[15]

Reaction with Alkenic and Allenic Compounds.

The catalyst can be utilized with a number of alkenes under either thermal or photochemical conditions to produce cyclobutane and other dimerized products. For example, irradiation of a toluene solution of 1,7-octadiene with ethylenebis(triphenylphosphine)nickel(0) followed by air oxidation yields stereospecifically *trans*-bicyclo[4.2.0]octane accompanied by oligomers (eq 6).[4] The reaction also works intermolecularly with monosubstituted alkenes, yielding the corresponding 1,2-*trans*-cyclobutanes (eq 7).

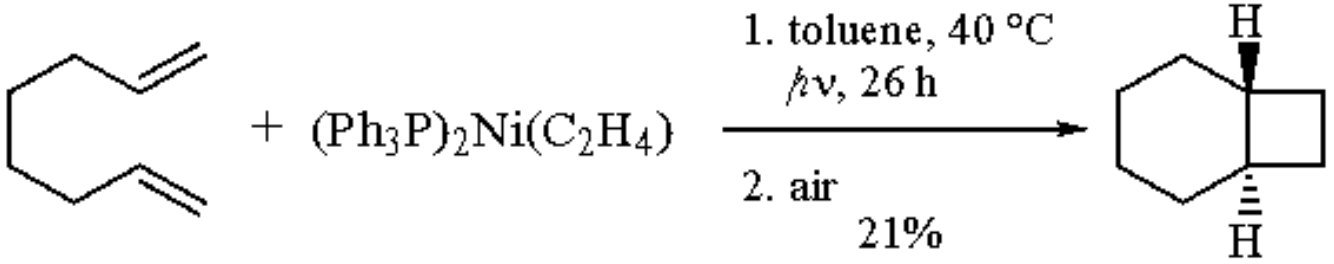

(6)

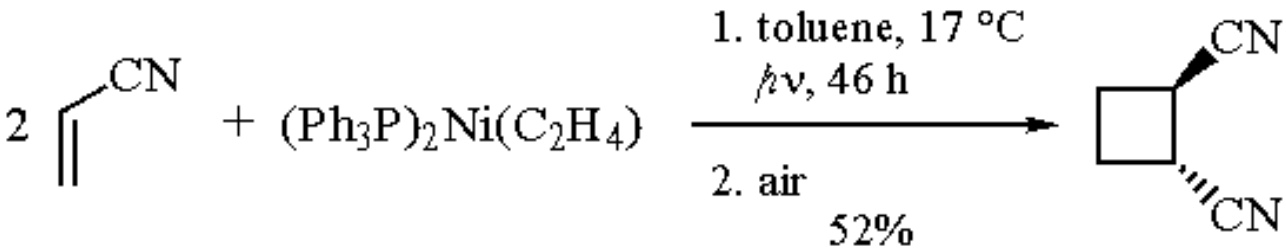

(7)

It is also possible to induce such alkene dimerizations thermally via well known nickelacyclopentane intermediates.[16] Treatment of such intermediates with a variety of reagents yields a number of useful organic products (eq 8).[5,17] Other catalytic ethylene dimerization systems include $(PPh_3)_2Ni(C_2H_4)$ embedded on an alumina surface.[18] A variety of cyclopropene systems can be cyclodimerized to the corresponding cyclobutane derivatives via oxidation of the intermediate nickelacyclopentane intermediates as well.[19,20]

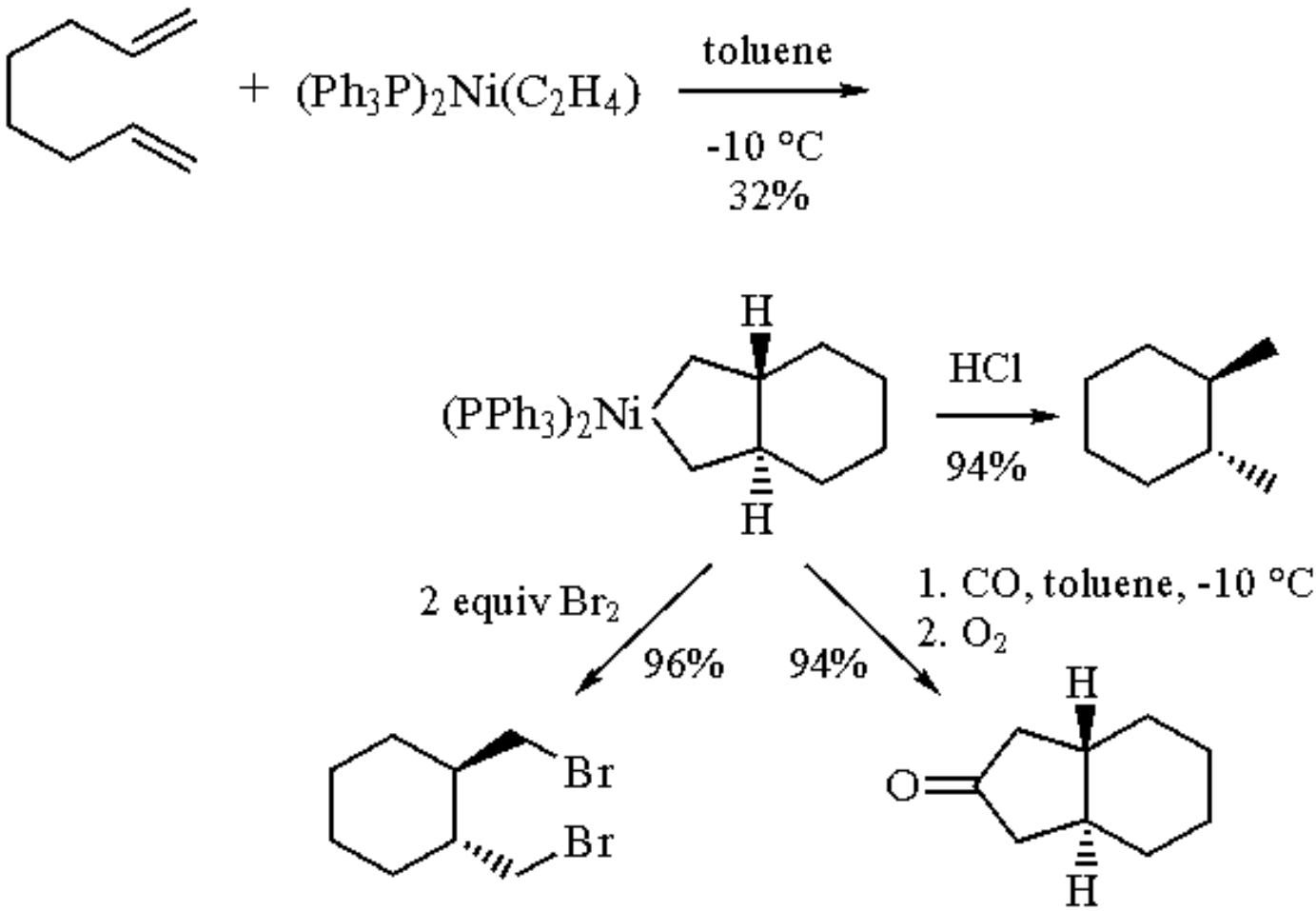

(8)

It has been found that a catalyst prepared from ethylenebis(triphenylphosphine)nickel(0) and ***Chloromethyl Methyl***

Sulfide acts as a cyclopropanation reagent for cyclooctene (eq 9).[6]

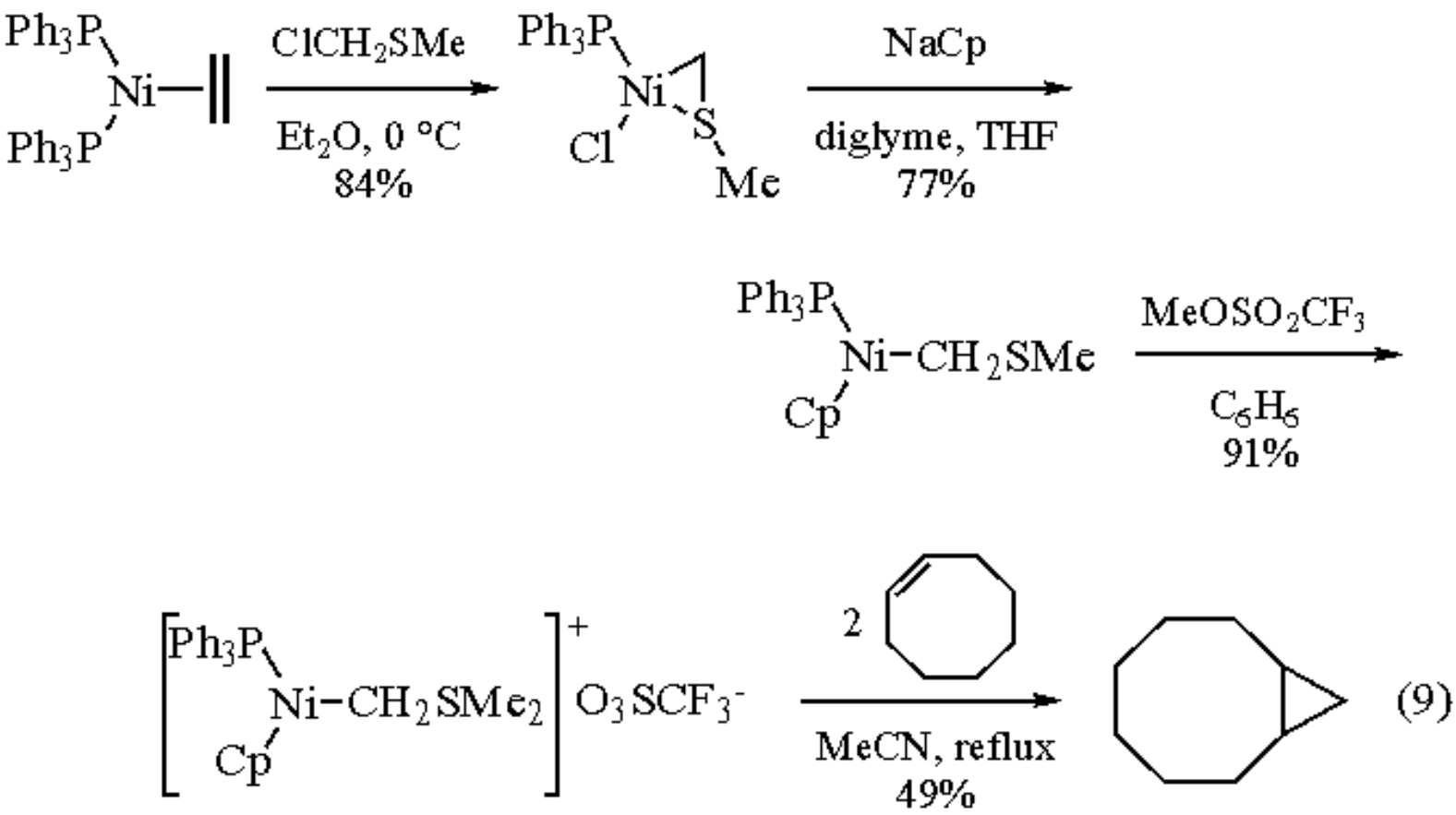

Another cationic complex which is active towards styrene oligomerization is derived from ***Benzyl Chloride***. Treatment of the intermediate η^3-coordinated cationic complex (0.09 mol %) with styrene at rt for 2 h forms oligomers with M_n = 850 and 67% isotactic content (eq 10).[21]

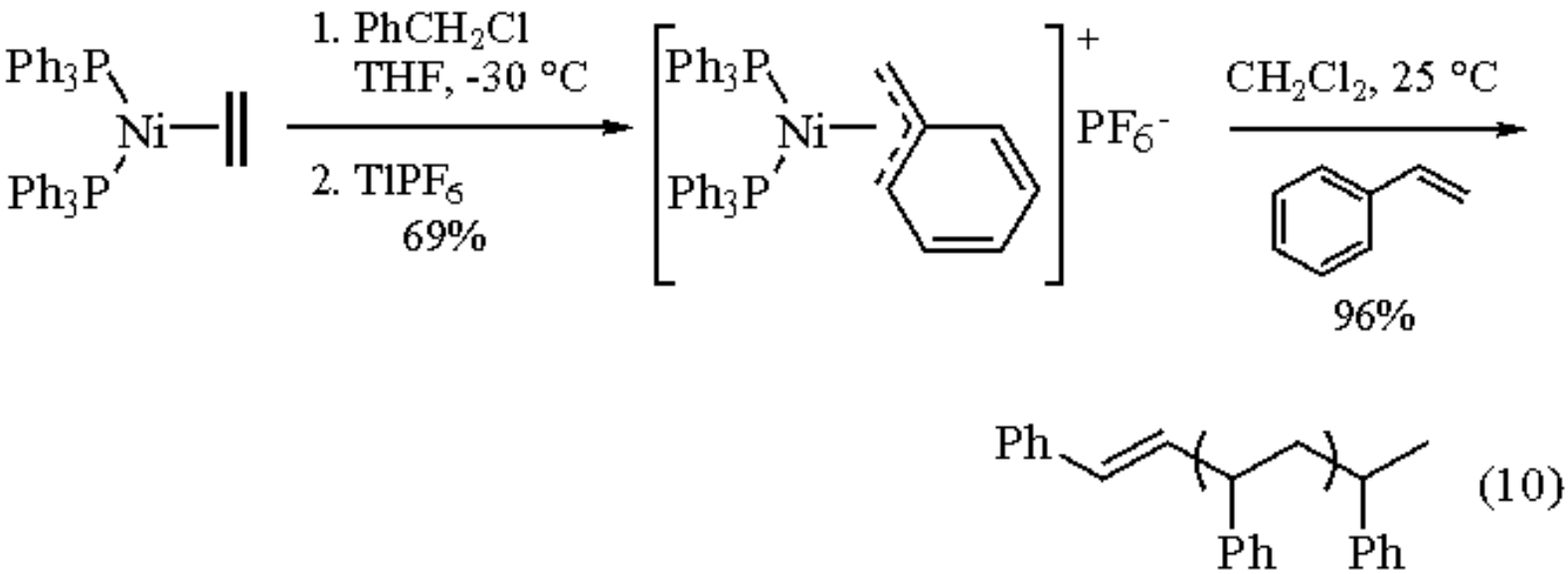

Isomerization and skeletal rearrangements[22] of alkenes are also promoted by the catalyst. For example, allylbenzene is quantitatively converted into *trans*-1-phenylpropene by a catalyst derived from ethylenebis(triphenylphosphine)nickel(0) and HCl (eq 11).[7]

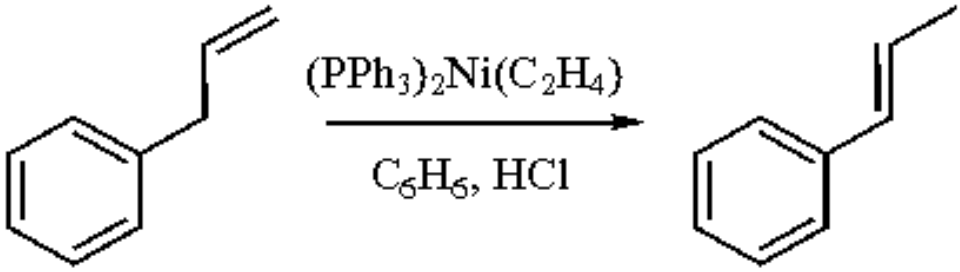

(11)

The catalyst (2.5 mol %) also reacts with allene at elevated temperatures to yield a mixture of the trimer, tetramer, pentamer, and higher oligomers (eq 12).[23] The related complex ***Bis(1,5-cyclooctadiene)nickel(0)*** also promotes a similar reaction.

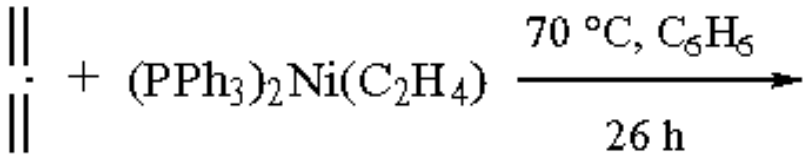

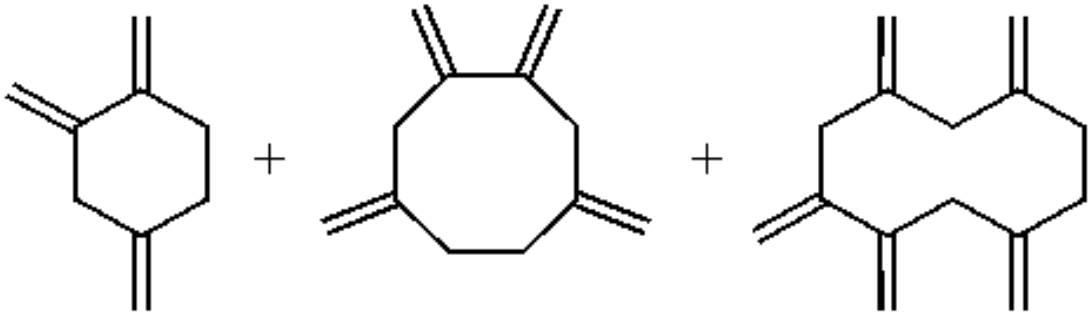

20% 53% 10%

(12)

Reaction with Isocyanates.

Ethylenebis(triphenylphosphine)nickel(0) reacts with alkenes (ethylene and propene) and isocyanates, producing isolable azanickelacyclopentanes which can be further converted into a variety of useful intermediates depending upon the conditions employed. Thus reaction with ***Phenyl Isocyanate*** and ethylene can yield amides or carbamides (eq 13).[24] Reaction with propene yields a mixture of regiosiomers. Related catalysts that also induce the desired transformations include (TPP)Ni(CDT) and $Ni(cod)_2$.[24]

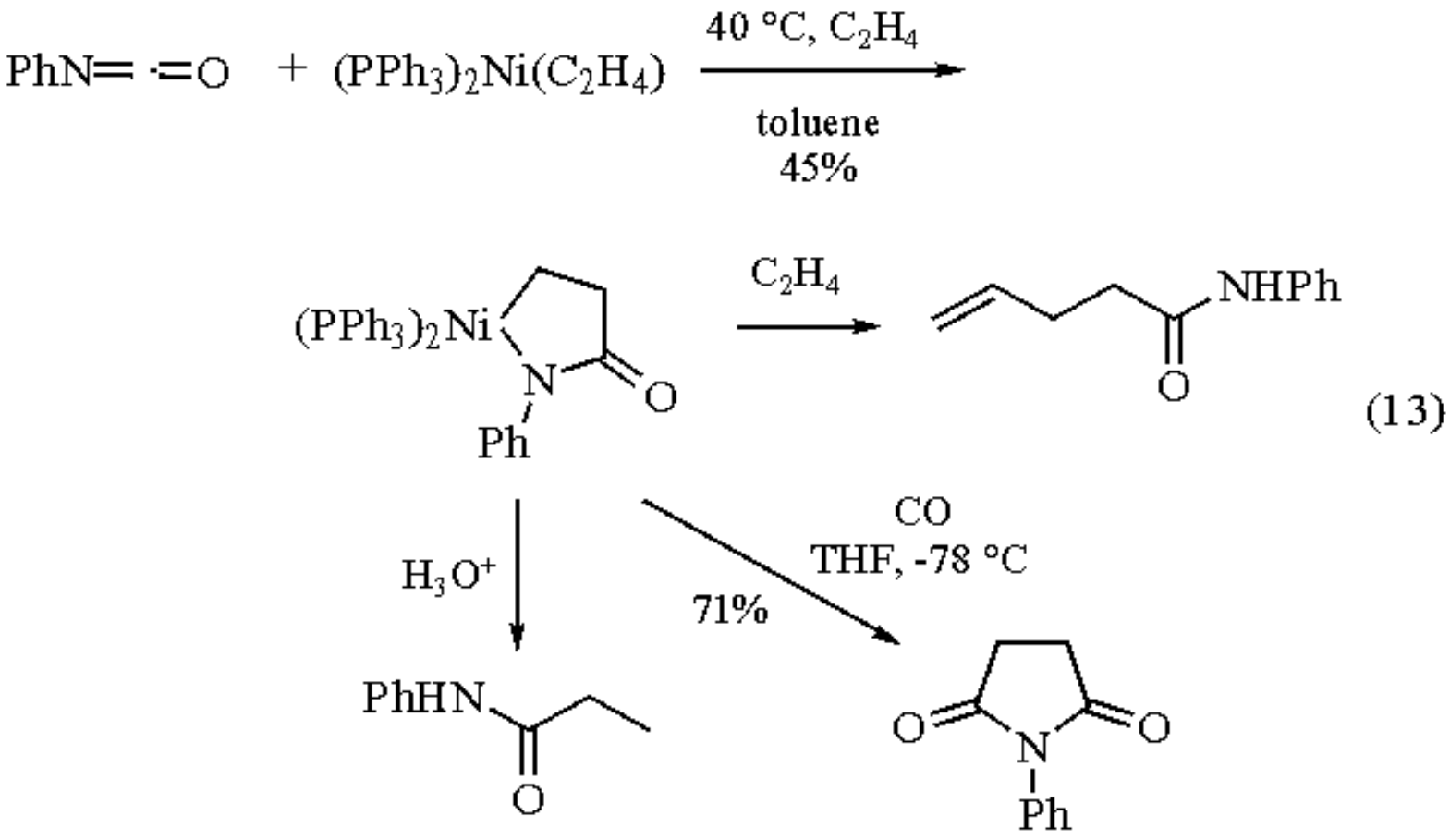

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Ethylenebis(triphenylphosphine)platinum(0)[1]

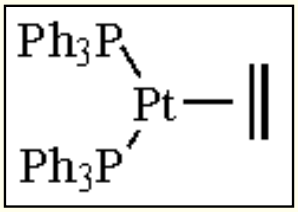

[12120-15-9] · $C_{38}H_{34}P_2Pt$ · Ethylenebis(triphenylphosphine)platinum(0) · (MW 747.73)

(nucleophilic metal species that readily undergoes ligand exchange with alkenes[2] and alkynes;[3] acts as an efficient hydrosilation catalyst;[4] oxidatively adds to activated C-X bonds[5] and some C-C bonds, enabling rearrangement to occur[6])

Physical Data: white solid, mp 126-128 °C (dec).

Solubility: sol benzene, THF, dichloromethane; insol alcohols.

Form Supplied in: commercially available as a white solid.

Preparative Methods: can be prepared by the reduction of $[Pt(PPh_3)_2(CO)_3)]$.PhH with ***Sodium Borohydride*** in ethylene saturated EtOH.[7]

Handling, Storage, and Precautions: the complex can be briefly handled in air and stored indefinitely under nitrogen. Platinum is reported to be of low toxicity.

Complexation with Alkenes.

The title reagent readily undergoes alkene ligand exchange, possibly via the unsaturated L_2Pt (L = Ph_3P) as the active species. Numerous platinum alkene complexes have been synthesized by this procedure.[2,3,8] Electron-deficient multiple bonds are generally more strongly bound, leading to more stable complexes. In some instances, alkene complexation is a preliminary to rearrangement of the carbon framework via the intermediacy of a σ bound organoplatinum species (eqs 1 and 2).[6,9]

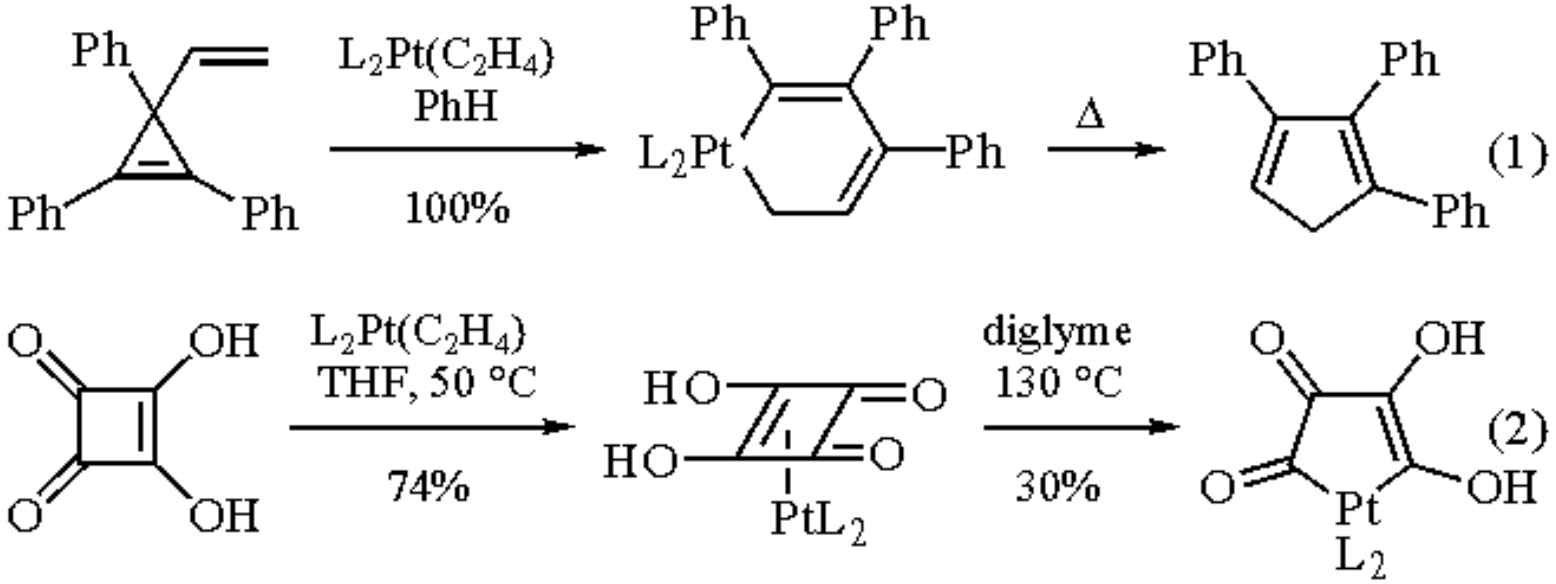

Hydrosilation.

The title reagent has been used to catalyze hydrosilation of a variety of functional groups, typically employing 2-4 mol % of catalyst.[10-14] In one example, a racemic silane and an alkyne provided a chiral vinylsilane.[10] Tanaka has used *o*-bis(dimethylsilyl)benzene to enable double silation of functional groups. The postulated intermediate formed from the catalyst and silane is a bis(silyl)platinum species (eq 3).[11] Aldehydes and ketones have been shown to add silicon across the C=O bond, whereas unsaturated carbonyl compounds undergo 1,2- or a 1,4-addition depending on the steric environment (eq 4).[12] Styrene reacts in a 1,1-fashion, presumably via a hydride shift, to afford the *gem*-disilyl derivative, whereas isoprene reacts in the more usual 1,2-mode (eq 5).[11] More recently, silicon polymers have been prepared by employing tetrakis(dimethylsilyl)benzene and diynes (eq 6).[3]

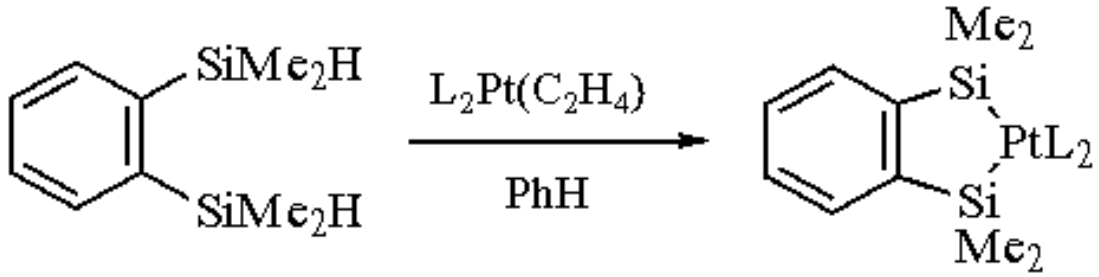

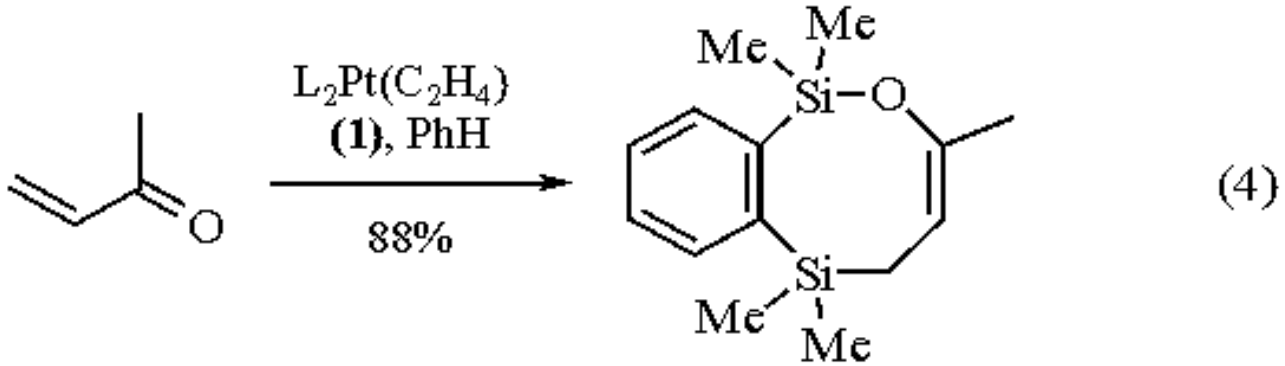

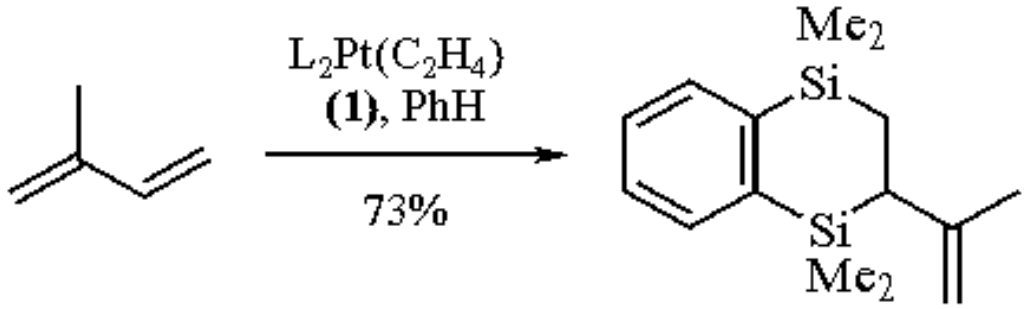

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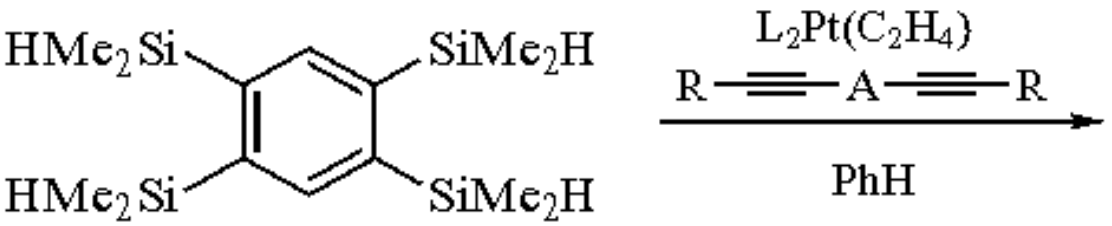

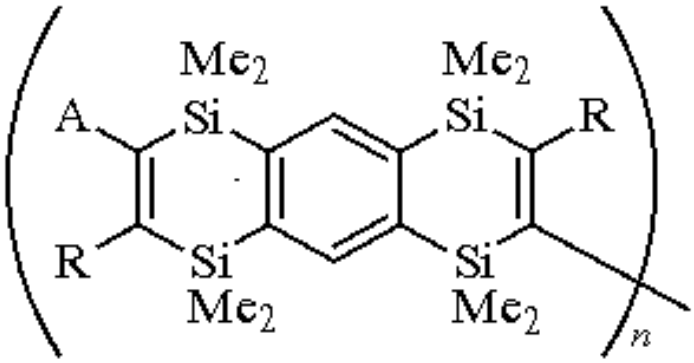

(6)

R = Hex, A = Ph, 78%
R = Ph, A = Fe(Cp)$_2$, 94%

Insertion into C-X Bonds.

Oxidative addition to alkyl,[13] allyl,[14] and alkenyl[15] C-X bonds (where X = leaving group) occurs readily. Inhibition of the insertions in the presence of radical scavengers suggests a radical mechanism.[13] The title reagent adds to *gem*-dihalomethanes to form stable complexes.[16] In the case of dichloromethane, photolysis is required before insertion occurs.[17] Addition to allylic C-X bonds occurs *anti* to the leaving group. This is postulated to be due, in part, to the electron-donating capacity of the triphenylphosphine ligands and the propensity of the complex to dissociate to form the more nucleophilic L_2Pt (eq 7).[14] An anomolous reaction is the insertion of platinum into the alkenyl C-Cl bond of 1,2-dichloropropene, as opposed to the expected insertion at the allylic position (eq 8).[18]

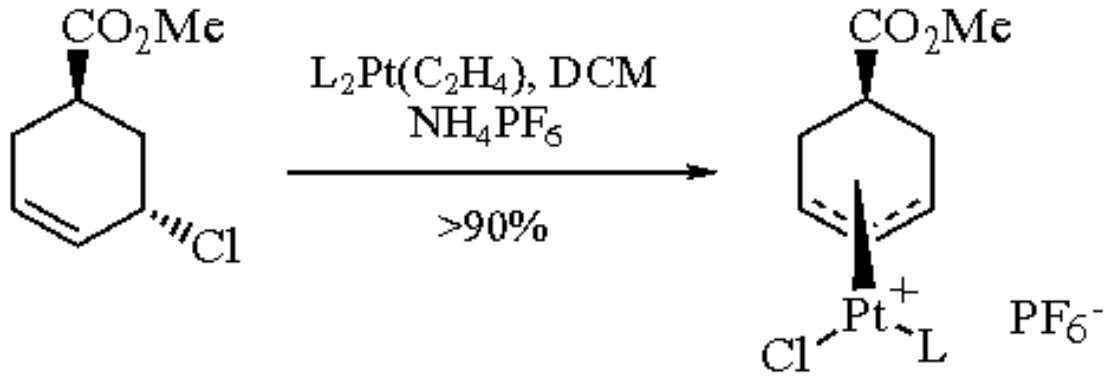

(7)

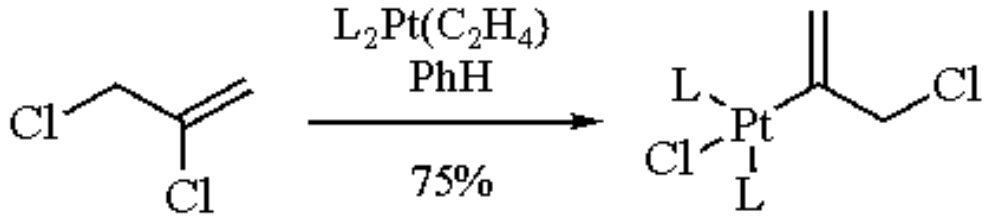

(8)

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Ethylene Chloroboronate[1]

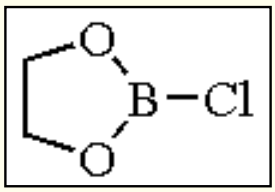

[1192-03-6] · $C_2H_4BClO_2$ · Ethylene Chloroboronate · (MW 106.32)

(mild Lewis acid, in combination with tertiary amines is a selective enolization reagent for ketones and thioesters;[2] the corresponding enolates show a high degree of regio- and stereocontrol in the aldol reaction[2])

Physical Data: viscous syrup at rt; bp 70-74 °C/1 mmHg; n_D^{20} 1.4640.

Solubility: insol *n*-pentane, diethyl ether; sol dichloromethane.

Analysis of Reagent Purity: (NMR) ^{11}B -31.20 ppm (monomer), -23.50 ppm (associated); ^{1}H 4.38 ppm; ^{13}C 65.79 ppm.

Preparative Methods: obtained by reaction of ***Ethylene Glycol*** with ***Boron Trichloride*** in CH_2Cl_2 (85% yield).[2a,3a,b]

Handling, Storage, and Precautions: should be used as prepared for best results. The viscous syrup should be handled under N_2 in the absence of moisture. 1.0 M Dichloromethane solutions of the reagent are stable for months when stored in the absence of moisture at -15 °C.

Regio- and Stereoselective Aldol Condensations.

Methyl, ethyl, and cyclic ketones react with ethylene chloroboronate (**1**) and ***Diisopropylethylamine*** at -78 °C to give the corresponding enolates (enolborates) with a high degree of regio- and stereocontrol.[2a-c] The selectivity is as follows: Me &egt; Et; Me > CH_2CH_2R; Me > CH_2CHR_2; Me >> CHR_2; Et >> CHR_2. Ethyl ketone derived enolborates are generated selectively with *Z*(O)-stereostructure (&egt;95%). An example is shown in (eq 1).

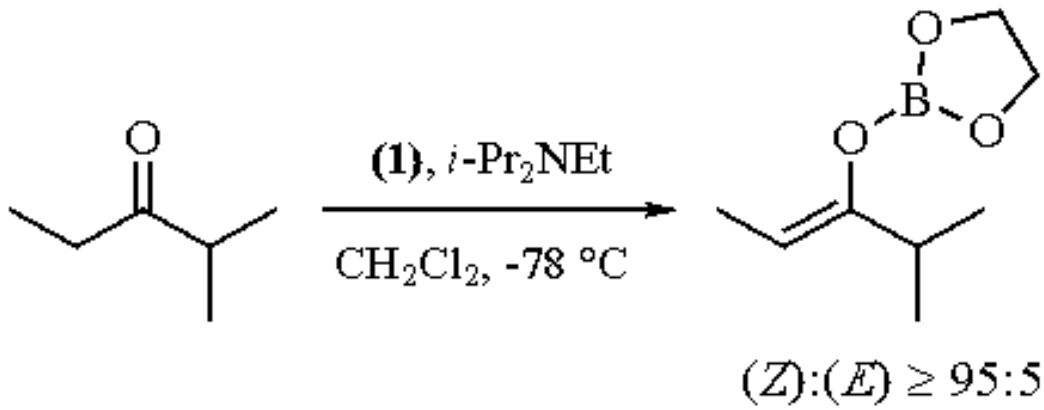

(1)

Reaction of enolborates with both aliphatic and aromatic aldehydes at -78 to -15 °C forms β-hydroxy ketones in good yield (60-90%) and with high *syn* diastereoselectivity (&egt;96:4) (eq 2).[1,2]

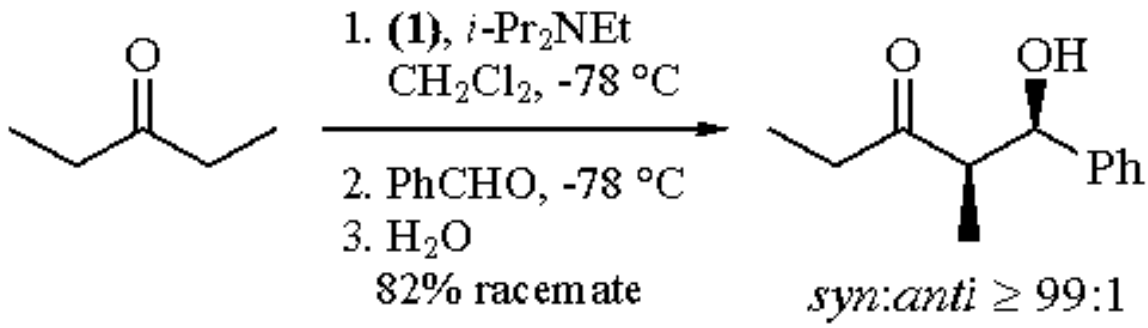

(2)

While *syn* selectivity from *Z*(O)-boron enolates is an expected result,[1b] much more surprising is the high *syn* selectivity observed with *E*(O)-enolborates, for example the enolate derived from cyclopentanone (eq 3).

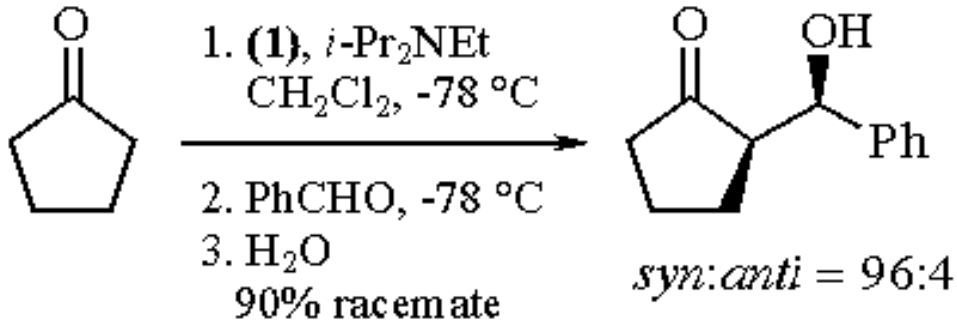

(3)

To explain the *syn* selectivity for reactions of both *Z*(O)- and *E*(O)-enolates derived from (**1**), a chair transition state for *Z*(O)-enolates and a boat transition state for *E*(O)-enolates were suggested.[2c,d] Computational studies on aldol reactions using *Z*(O)- and *E*(O)-enolborates, as well as enolborinates (-O-BR_2), provided a set of data which is consistent with the experimental results and further corroborates the proposed mechanism.[4] The following main conclusions are drawn. (i) The ground state conformations of the enolates are important in determining the different reactivities of *Z*(O)-enolborates and *E*(O)-enolborates, the latter being much more reactive that the former. (ii) *Z*(O)-Enolborates prefer chair transition states, while *E*(O)-enolborates favor twist-boat transition states. Both transition states lead to the formation of *syn* aldol products. (iii) In contrast, when enolborinates are used, bulky ligands at boron disfavor the twist-boat for the *E*(O)-enolates, resulting in the formation of *anti* isomers.[4]

Pinacol chloroboronate-derived enolborates are also stereoconvergent, giving high yields of the *syn* diastereoisomers irrespective of the enolate geometry (eq 4).[5]

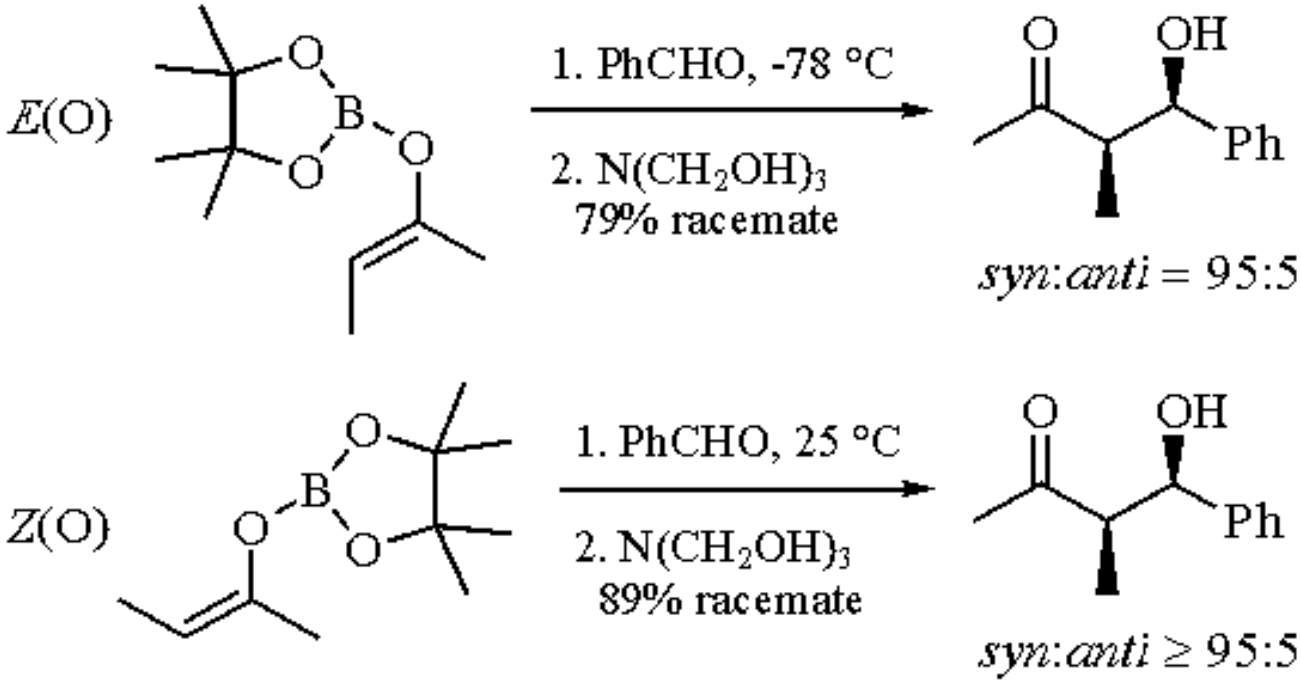

(4)

The enantioselective version of this reaction is also known, using chiral diols, but the ee's are modest (eq 5).[6]

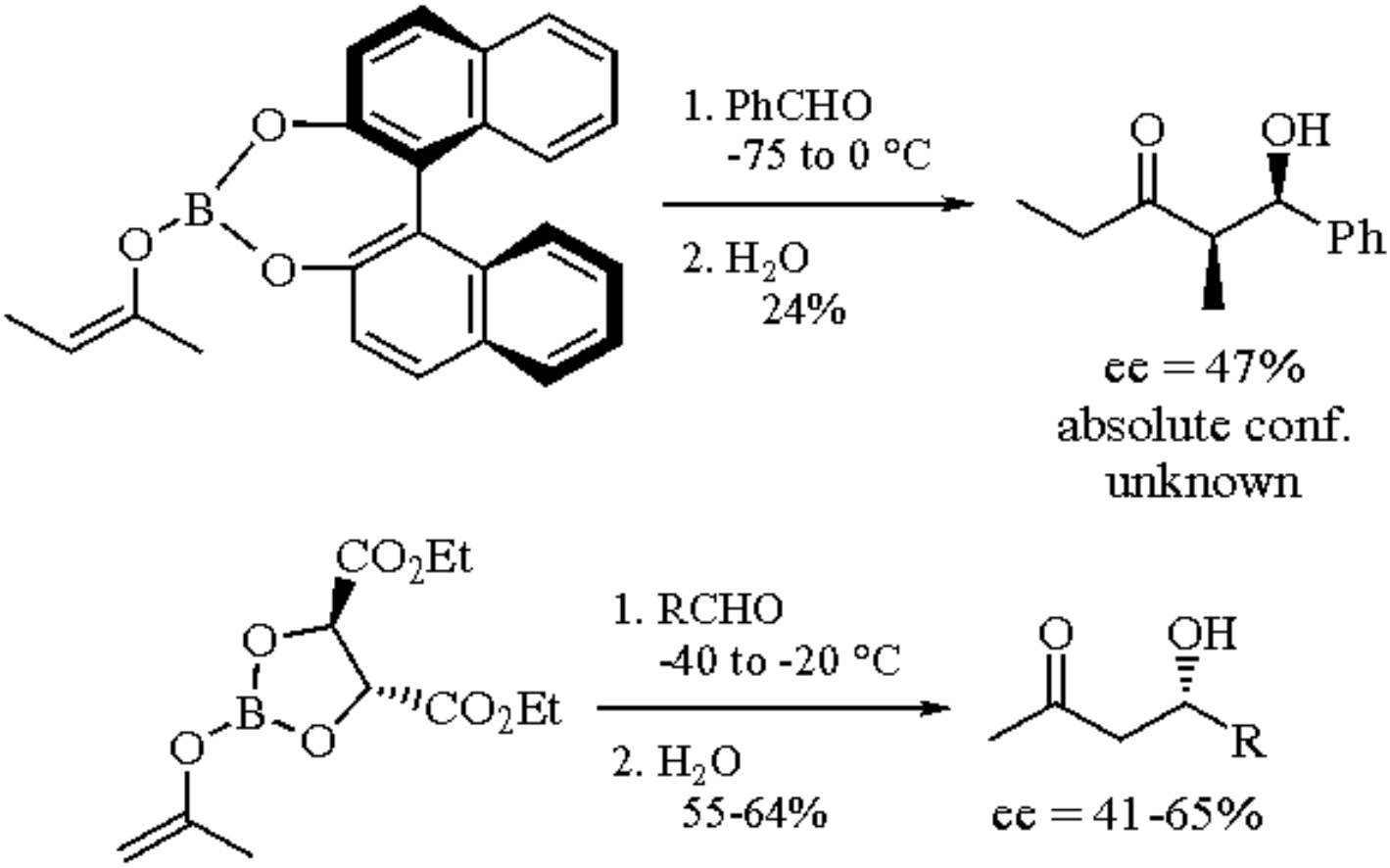

(5)

Reaction of phenyl thiopropionate with (**1**) and diisopropylethylamine provides the corresponding enolate, whereas esters give unsatisfactory yields. Enolization at -78 °C results in a 70:30 *Z*(O):*E*(O) enolate mixture, whereas the reaction at 25 °C furnishes an 18:82 mixture. However, both enolates react with aldehydes with high *syn* distereoselectivity. The addition to chiral aldehydes has also been studied (eq 6).[2d]

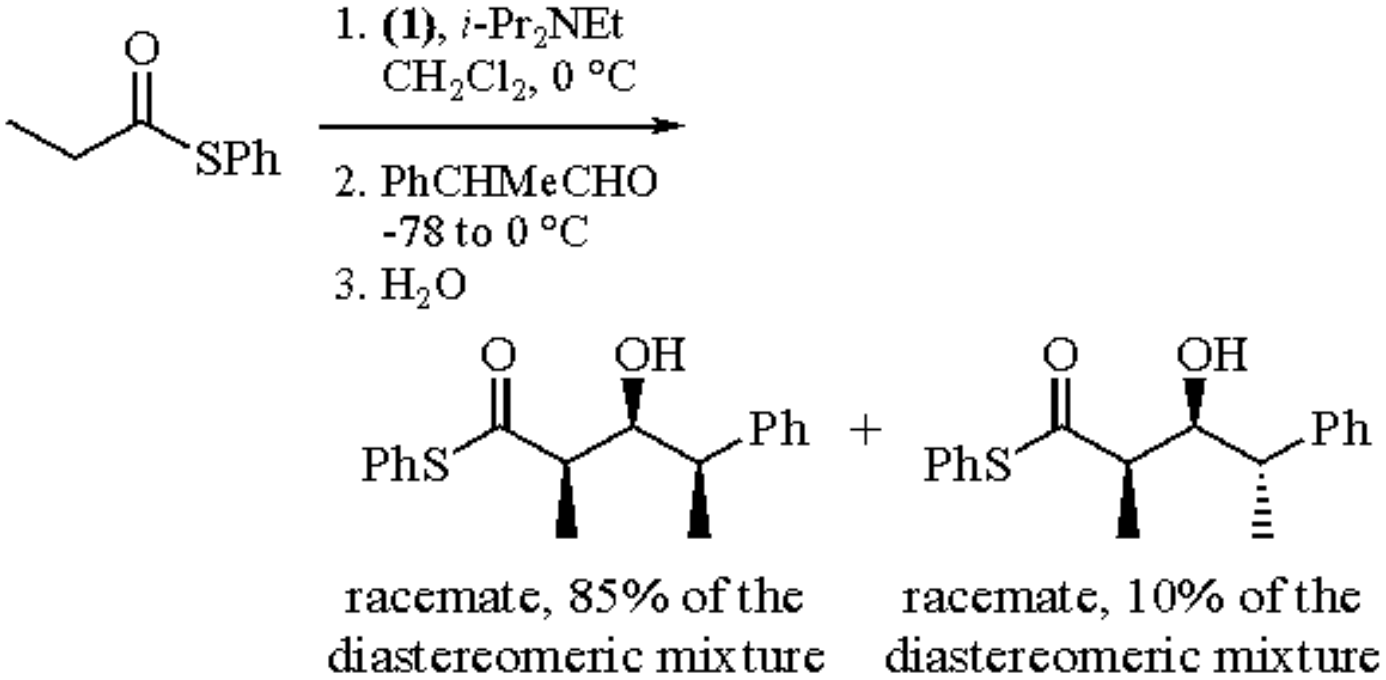

(6)

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4-Ethylenedioxybutyllithium

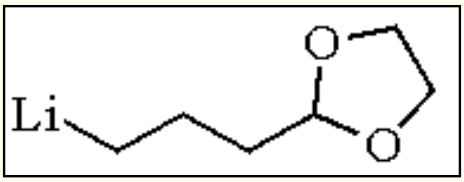

[129471-18-7] · $C_6H_{11}LiO_2$ · 4-Ethylenedioxybutyllithium · (MW 122.093)

(reagent used as a bis homoenolate equivalent for the production of aldehydes and lactones)

Preparative Method: solutions of the title compound can be obtained by treatment of a solution of chlorobutyraldehyde ethylene acetal (commercially available) in THF under inert gas with a solution of 2.4 equiv of ***Lithium Naphthalenide*** in THF at -78 °C for 7 h. Solutions are used directly.

Handling, Storage, and Precautions: the reagent is purported to be stable at -78 °C.

General Considerations.

This lithium reagent was reported for the first time in 1990 by Ramon and Yus[1] using the aromatic radical anion electron transfer technique (**1** -> **2**).[2] A variety of Grignard counterparts to the reagent are known and had seen extensive use prior to 1990. The advantage of the lithium reagent is its generation at low temperature because these reagents are quite basic and readily decompose at ambient temperatures.[3] However, the corresponding magnesium chloride can be prepared in high yield at room temperature in THF if the Grignard is prepared in high concentration (ca. 5 M).[4]

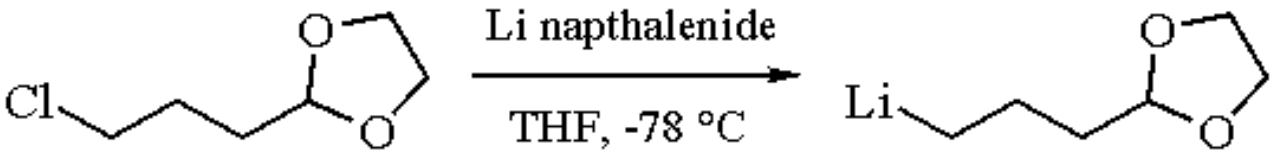

(1) (2) (1)

Reaction with Electrophiles.

The reagent (**2**) reacts with a variety of carbonyl-containing electrophiles at low temperature to provide adducts in moderate to good yield (eqs 2 and 3).

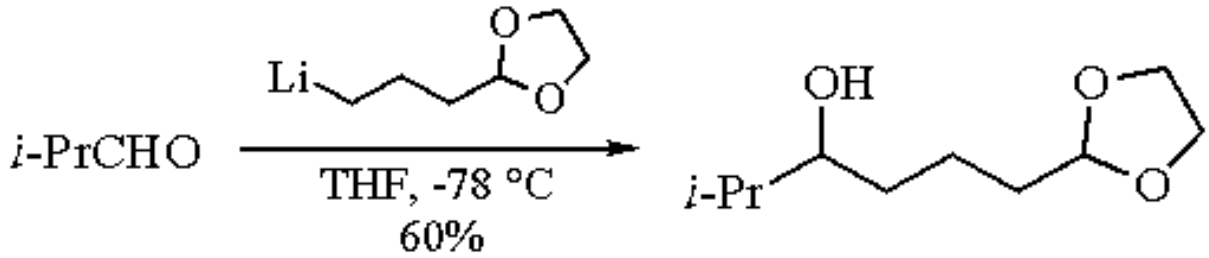

(2)

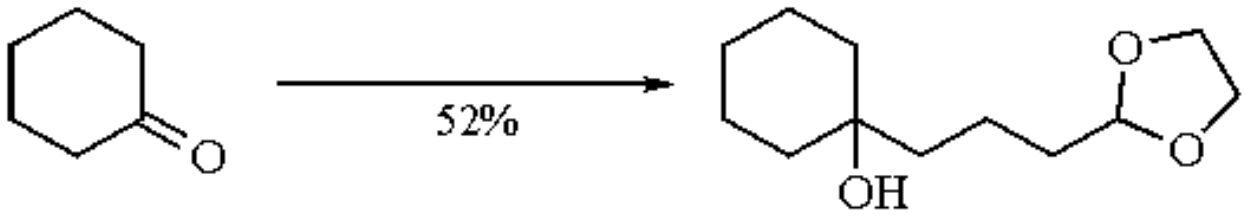

(3)

Reaction with aldehydes and ketones gives the corresponding alcohols while reaction with benzonitrile or the amides provides the protected keto aldehydes (eq 4). Reagent (**2**) also reacts with ***Phenyl Isothiocyanate*** and benzaldehyde phenylimine to give adducts. However, (**2**) does not react well with alkyl halides either by itself or in the presence of Cu^{I} salts. Further, reaction with nitriles and anhydrides results only in proton transfer, attesting to the basicity of the species.

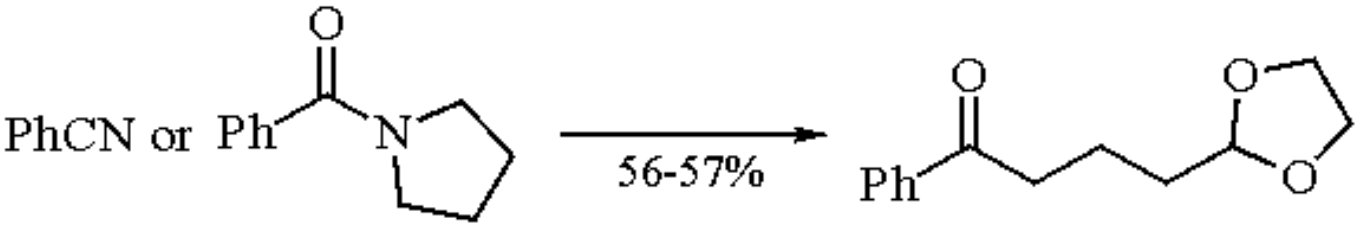

(4)

Treatment of (**2**) with a catalytic amount of CuBr-dimethyl sulfide complex (see ***Copper(I) Bromide***) allows conjugate addition to 2-cyclohexen-1-one to occur, resulting in the 1,4-adduct in 61% yield (eq 5).

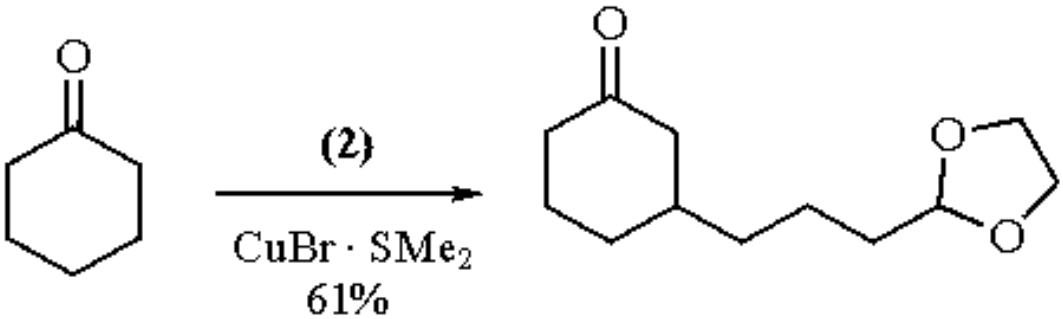

(5)

Synthesis of Tetrahydropyrans and δ-Lactones.[5]

Hydrolysis of the adducts of (**2**) and carbonyl compounds with acid affords cyclic hemiacetals. These can be oxidized with Cr^{VI} reagents to give δ-lactones in 30-60% overall yield from chloroacetal (**1**) (eq 6).

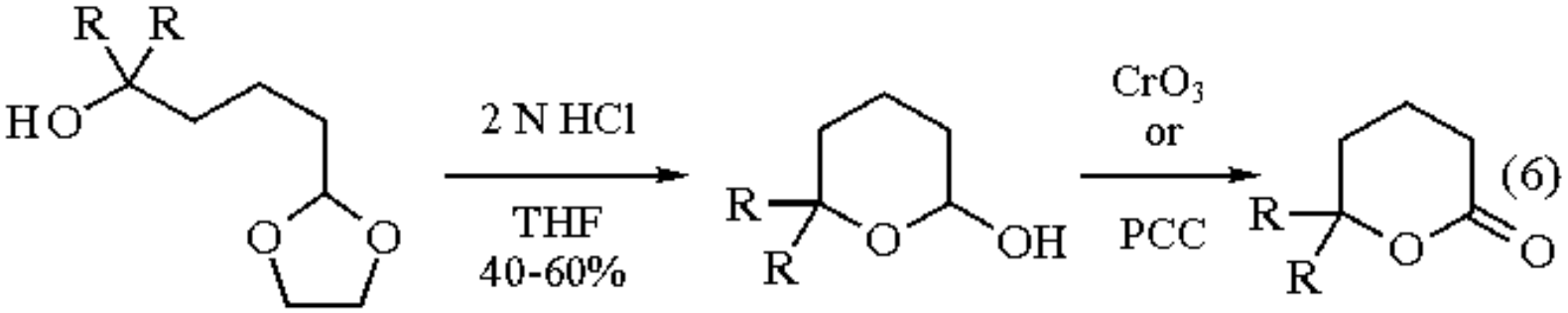

Synthesis of 6,8-Dioxabicyclo[3.2.1]octanes.

Reaction of (**2**) with α-trimethylsilyloxy aldehydes and ketones leads after hydrolysis to 6,8-dioxabicyclo[3.2.1]octanes, substructures found in the frontalin/brevicomin metabolite class (eq 7).[6]

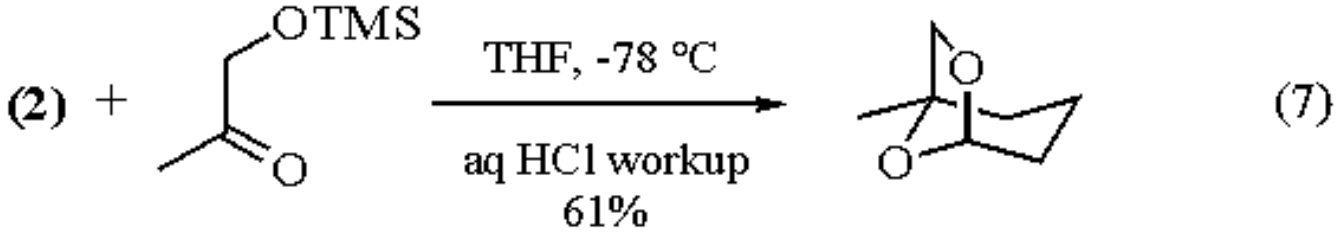

Related Lithium Reagents.

3-Butenyllithium (**3**)[7] has been used as a masked aldehyde bishomoenolate equivalent. Due to the amount of unmasking involved, however, this is not preferable to (**2**).

(3)

Related Reagents.

2-(2-Bromoethyl)-1,3-dioxane; ***3-Butenyl-1-magnesium Bromide***; ***4-Ethylenedioxybutylmagnesium Bromide***.

---

1. Ramon, D. J.; Yus, M. *TL* **1990**, *31*, 3763.
2. Cohen, T.; Bhupathy, M. *ACR* **1989**, *22*, 152.
3. Ramon, D. J.; Yus, M. *JOC* **1991**, *56*, 3825.
4. Forbes, C. P.; Wenteler, G. L.; Wiechers, A. *JCS(P1)* **1977**, 2353.
5. Ramon, D. J.; Yus, M. *TL* **1990**, *31*, 3767.
6. Ramon, D. J.; Yus, M. *JOC* **1992**, *57*, 750.
7. Mase, T.; Sodeoka, M.; Shibasaki, M. *TL* **1984**, *25*, 5087.

4-Ethylenedioxybutylmagnesium Bromide

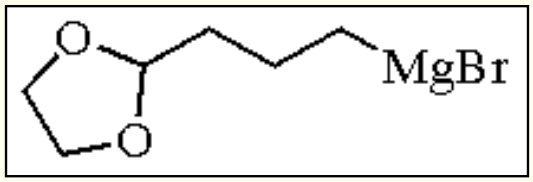

[91083-05-5] · $C_6H_{11}BrMgO_2$ · 4-Ethylenedioxybutylmagnesium Bromide · (MW 219.36)

(nucleophilic Grignard reagent used as a synthetic equivalent of the 4-oxobutyl anion)

Solubility: sol THF.

Handling, Storage, and Precautions: Grignard reagent sensitive to moisture; normally prepared in THF solution and used immediately.

Nucleophilic Additions.

This Grignard reagent and its magnesium chloride counterpart, like the analogous organolithium reagent, are employed in synthetic chemistry as synthons for the 4-oxobutyl anion; the Grignard reagents appear, however, to have been subject to much less widespread use than the organolithium reagent. They are normally used in THF as solvent. Both reagents are unstable under some circumstances, but the bromide may be readily prepared by stirring the bromoacetal precursor (ca. 2-3 M in THF) with crushed ***Magnesium*** turnings (1.5 equiv) at rt under a dry nitrogen atmosphere, with periodical external cooling.[1] For efficient formation, the chloride reagent is best prepared from a ca. 5 M solution of the chloroacetal in THF at below 30 °C.[2] Less concentrated solutions require higher temperatures, inevitably resulting in partial decomposition to the alkoxide of 2-cyclobutyloxyethanol.[2,3] The solutions of Grignard reagent are normally diluted with diethyl ether or THF before use.

Both reagents are effective nucleophiles. The bromide has been added to carbonyl groups, including those of α,β-unsaturated aldehydes,[4] and to cyanides without disruption of an adjacent aziridine unit (eq 1).[1] Copper-catalyzed conjugate addition to carboxymethyl alkynes also takes place; in this application the intermediate underwent Dieckmann-type cyclization, providing access to functionalized cyclopentenones (eq 2).[5] The more common chloride reagent undergoes acylation with anhydrides[6] and acid chlorides,[9] addition to carbonyl groups,[2] including those of α-chloro ketones,[7] and conjugate addition-elimination to β-alkoxy-α,β-unsaturated ketones.[8] Copper-catalyzed conjugate addition to α,β-unsaturated ketones is also reported,[9,10] hydrolysis and cyclization of the products leading to cyclohexenyl ketones (eq 3). The reagent is also reported to undergo addition to oxazolidines with concomitant ring cleavage (eq 4).[11]

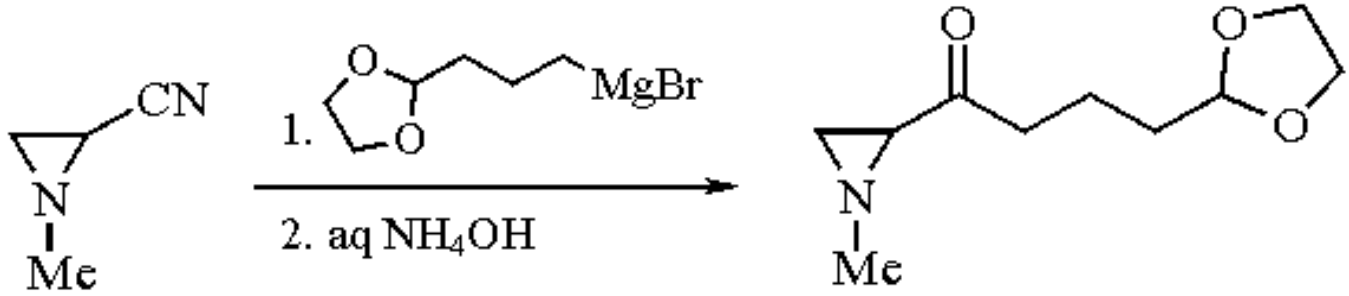

(1)

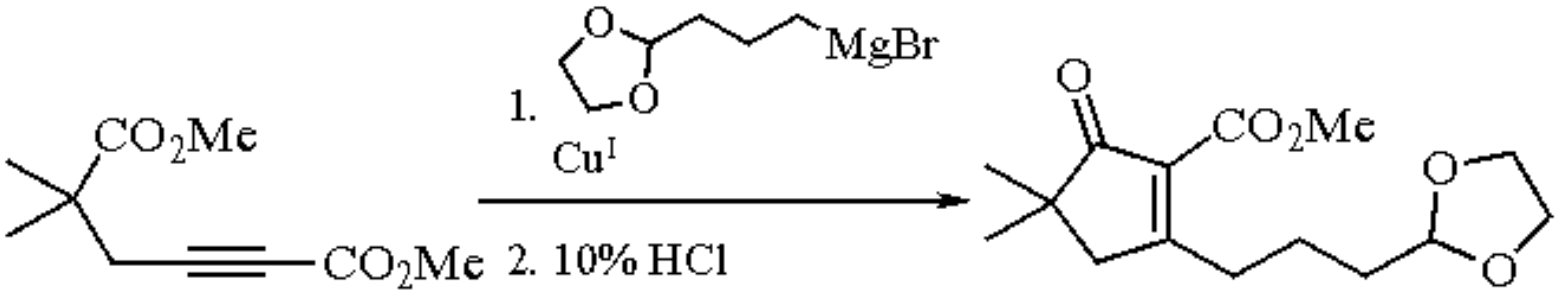

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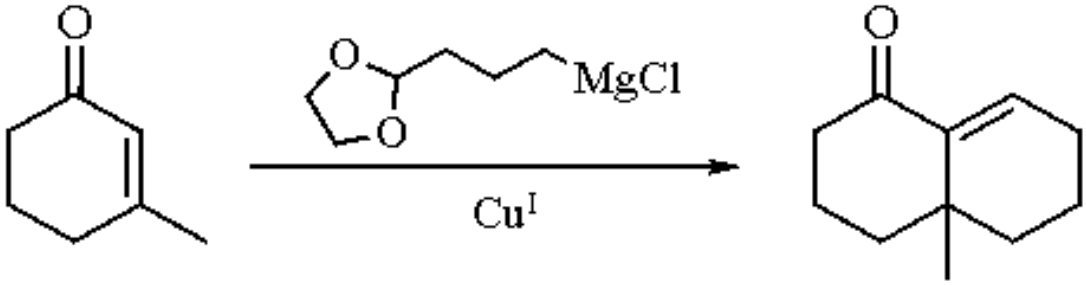

(3)

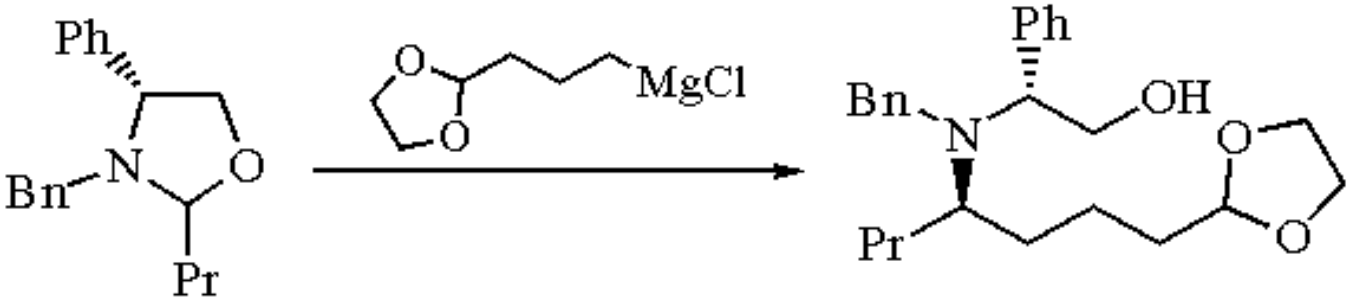

(4)

Related Reagents.

The functionally related organometallic reagents (**1**),[12] (**2**),[13] and (**3**)[14] have been prepared. See also ***2-(2-Bromoethyl)-1,3-dioxane***, ***3-Butenyl-1-magnesium Bromide***, and ***4-Ethylenedioxybutyllithium***.

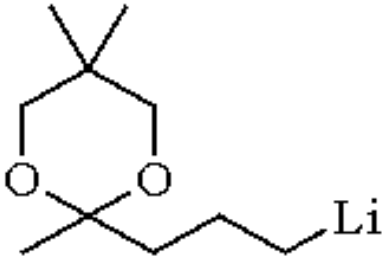

(1)

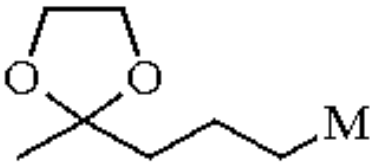

(2a) M = MgCl
(2b) M = Li

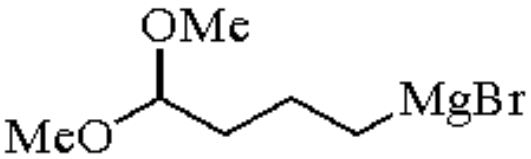

(3)

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1. Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. *JOC* **1985**, *50*, 4114.
2. Forbes, C. P.; Wenteler, G. L.; Wiechers, A. *JCS(P1)* **1977**, 2353.
3. (a) Feugeas, C.; Normant, H. *BSF(2)* **1963**, 1441. (b) Feugeas, C. *BSF(2)* **1963**, 2568; 2579.
4. Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *JACS* **1980**, *102*, 6889.
5. Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *JOC* **1984**, *49*, 3033.
6. van der Gen, A.; Wiedhaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *JACS* **1973**, *95*, 2656.
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8. Overman, L. E. *TL* **1975**, 1149.
9. Bal, S. A.; Marfat, A.; Helquist, P. *JOC* **1982**, *47*, 5045.
10. Abbott, R. E.; Spencer, T. A. *JOC* **1980**, *45*, 5398.
11. Higashiyama, K.; Nakahata, K.; Takahashi, H. *H* **1992**, *33*, 17.
12. Ryckman, D. M.; Stevens, R. V. *JOC* **1987**, *52*, 4274.
13. (a) Corey, E. J.; Balanson, R. D. *JACS* **1974**, *96*, 6516. (b) Ramón, D. J.; Yus, M. *JOC* **1991**, *56*, 3825.
14. Rigby, J. H.; McGuire, T. W. *TL* **1993**, *34*, 3017.

Philip C. Bulman Page & Andrew Lund

University of Liverpool, UK

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Ethylene Glycol[1]

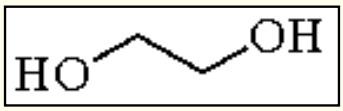

[107-21-1] · $C_2H_6O_2$ · Ethylene Glycol · (MW 62.08)

(formation of acetals;[1] stereoselective aldol reactions;[2] solvent for Diels-Alder reaction;[3] solvent for Fischer indole reaction;[4] preparation of tertiary alcohols from trialkylboranes[5])

Alternate Name: ethane-1,2-diol.

Physical Data: bp 197 °C; *d* 1.11 g cm^{-3}.

Solubility: completely sol H_2O, low MW alcohols, acetone; insol benzene, chlorinated hydrocarbons.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: harmful or fatal if swallowed. Prolonged or repeated breathing of vapor harmful. Causes eye irritation. May cause kidney and nervous system damage. Causes birth defects in laboratory animals. Use in a fume hood.

Acetal Formation.[1]

The dioxolane group is one of the most widely used protecting groups for carbonyl compounds. Dioxolanes are generally stable to bases, Grignard reagents, alkyl lithium reagents, metal hydrides, Na/NH_3, Wittig reagents, hydrogenation conditions, oxidants, and bromination and esterification reagents.[1] This wide range of stability has been especially useful in steroid synthesis.[6] The ease of formation of dioxolanes roughly follows the order: aldehydes > acyclic ketones and cyclohexanones > cyclopentanones > α,β-unsaturated ketones > α-mono- and disubstituted ketones >> aromatic ketones. Ketones generally require stronger acids than aldehydes, such as sulfuric, hydrochloric, or TsOH.[7-11] A typical protection procedure involves heating a benzene or toluene solution of the ketone and ***p-Toluenesulfonic Acid*** (eq 1).[9] Alternatively, a Lewis acid catalyst, such as ***Boron Trifluoride Etherate***[12-14] may be used (eqs 2 and 3).[13,14]

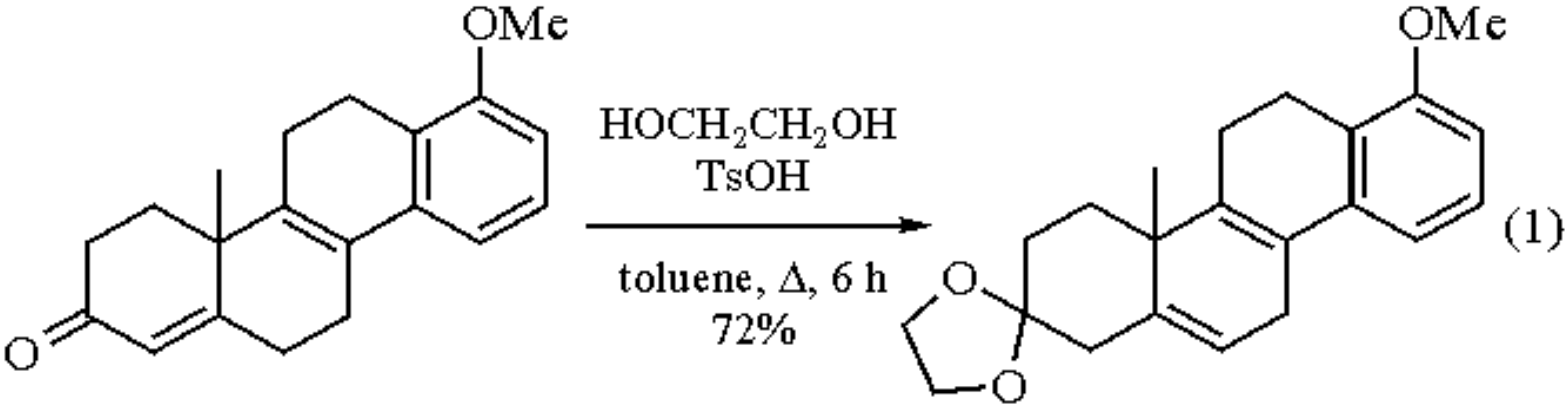

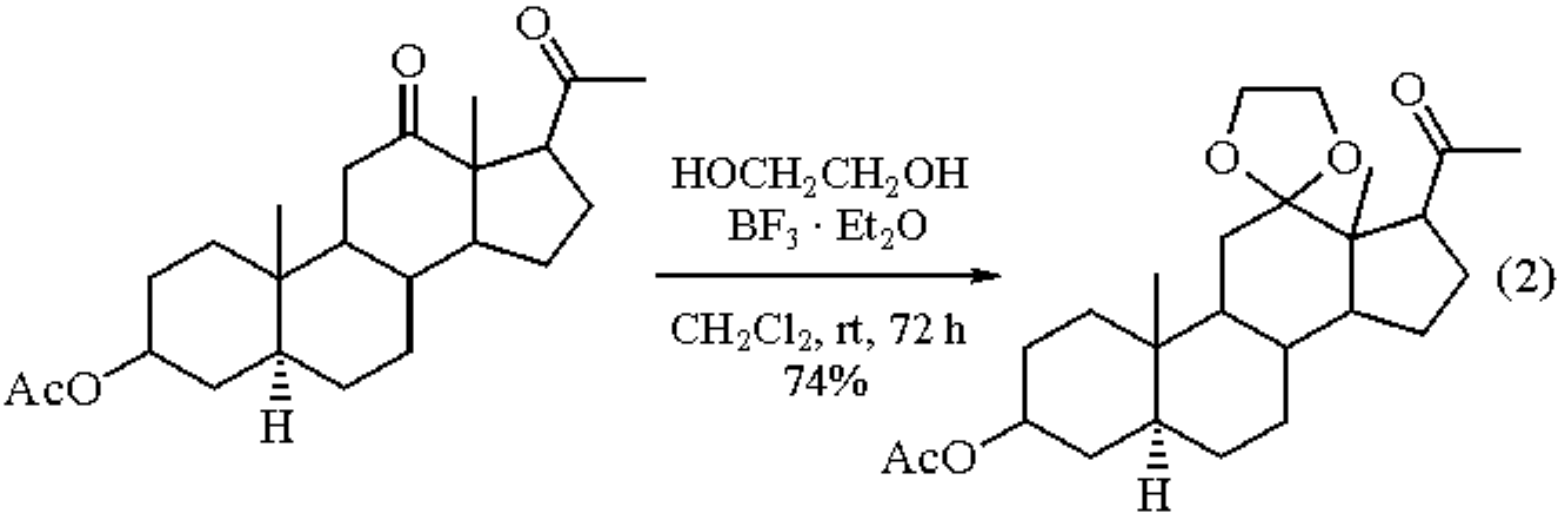

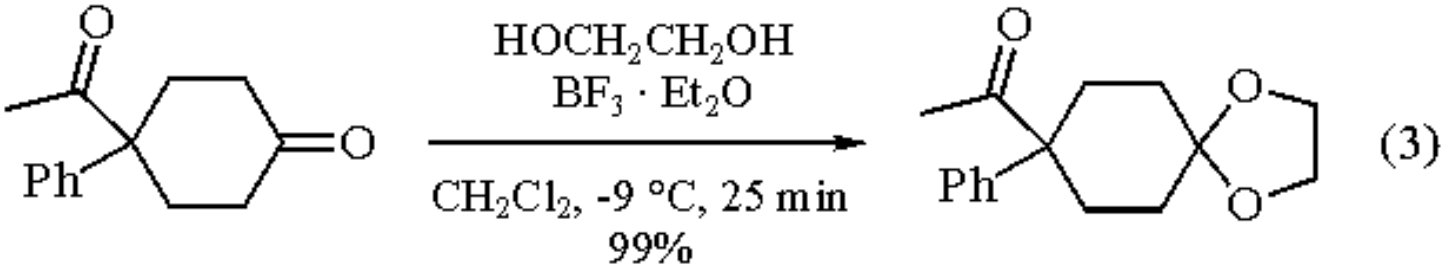

Water removal can be accomplished by using Dean-Stark distillation,[15] molecular sieves,[16] $CaSO_4$,[17] $CuSO_4$,[18] or water scavengers such as ***Triethyl Orthoformate***[19-21] or dialkyl sulfites (eq 4).[22]

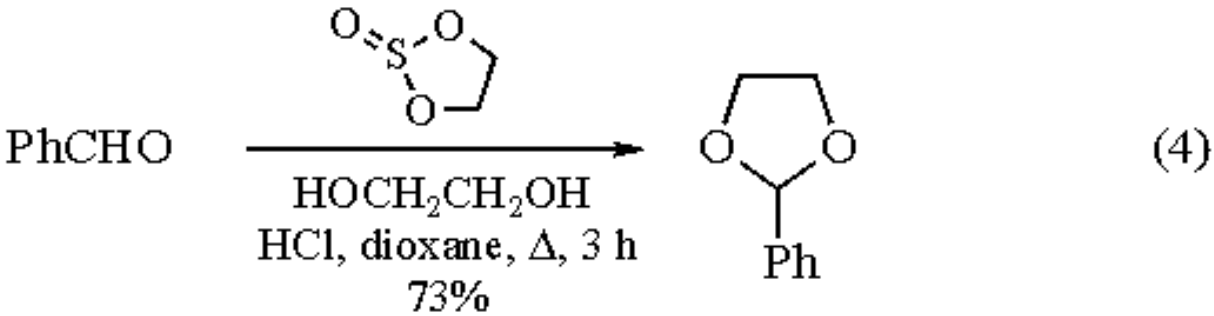

Compounds that are stable under strongly acidic conditions can be derivatized using a mixture of ethylene glycol and HCl (eq 5).[23,24]

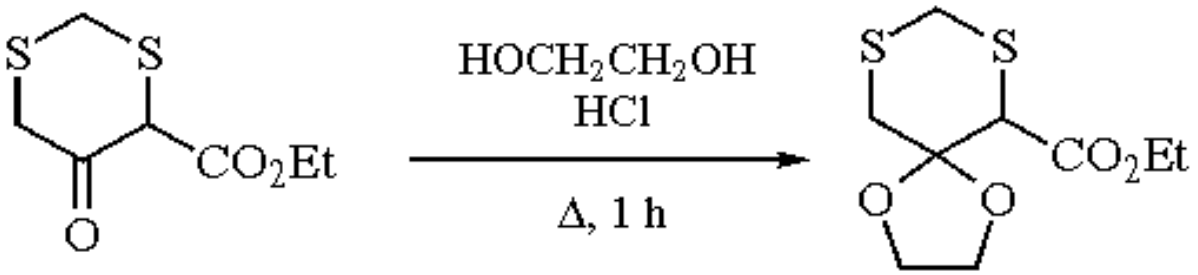

(5)

Many procedures have also been developed for acid-sensitive compounds. Use of either adipic[25] or ***Oxalic Acid***[26] gives good yields of sensitive steroid Δ^4-3-ethylene acetals. ***Selenium(IV) Oxide*** has also been used effectively for steroid acetalization (eq 6).[27]

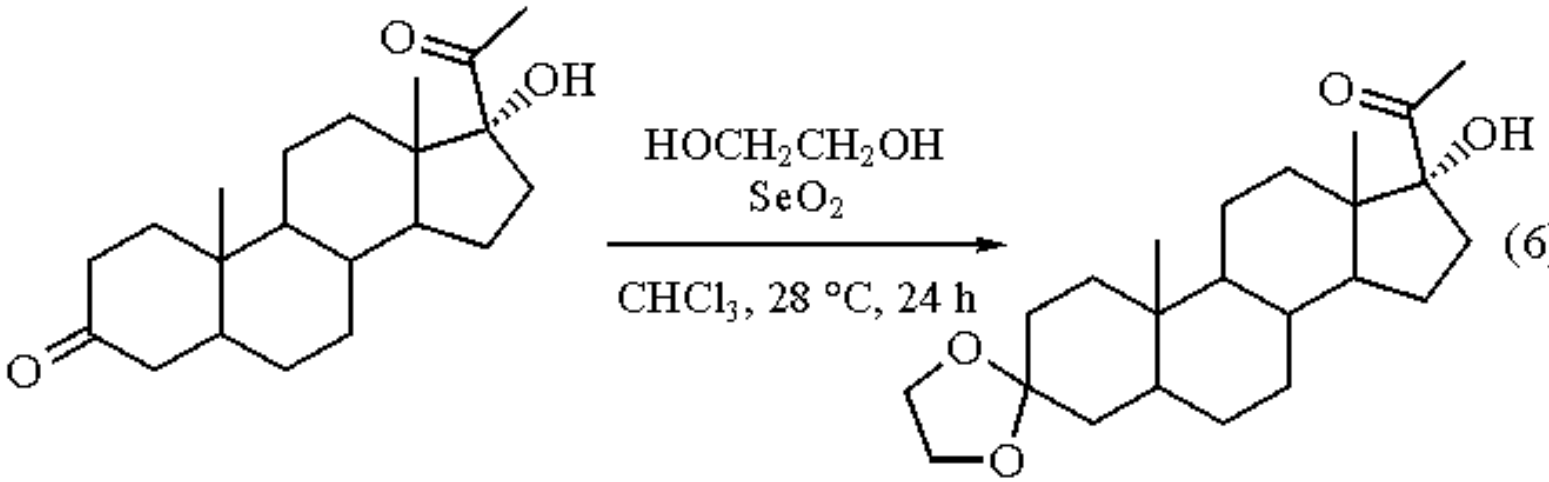

(6)

Pyridinium salts are mild catalysts for ethylene acetal formation.[28-31] ***Pyridinium p-Toluenesulfonate*** (PPTS) catalyzes acetal formation with less than 4% epimerization, whereas use of TsOH led to 34% epimerization (eq 7).[30]

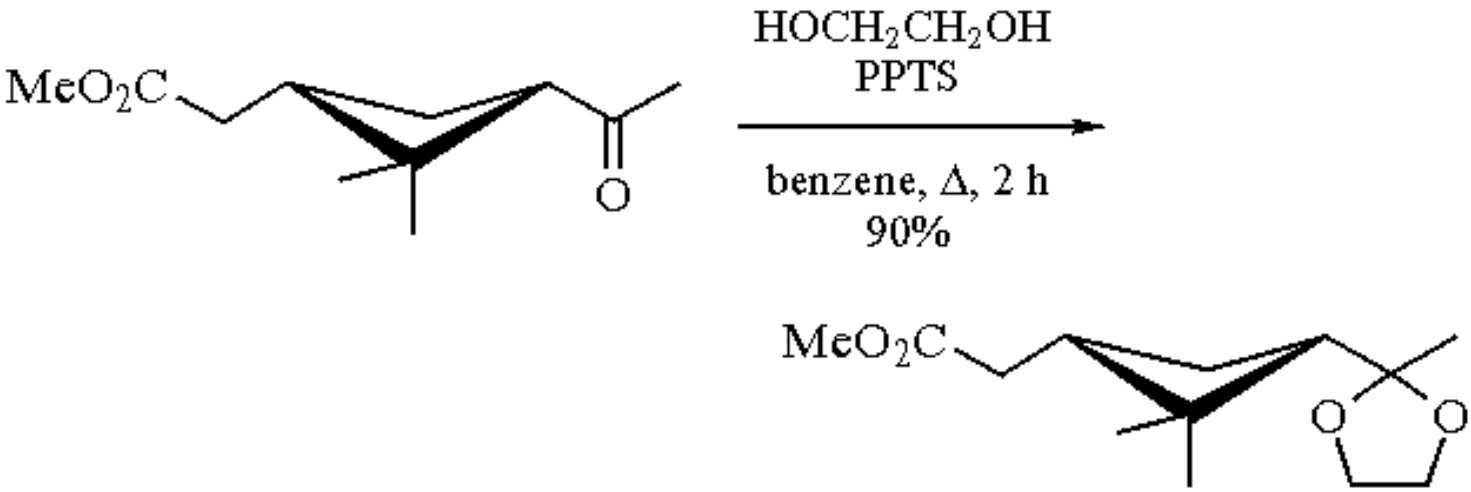

(7)

The use of a hindered pyridinium salt, such as ***2,4,6-Collidinium p-Toluenesulfonate*** (CTPS), allows acetalization of α,β-unsaturated ketones in the presence of saturated carbonyl systems (eq 8).[31]

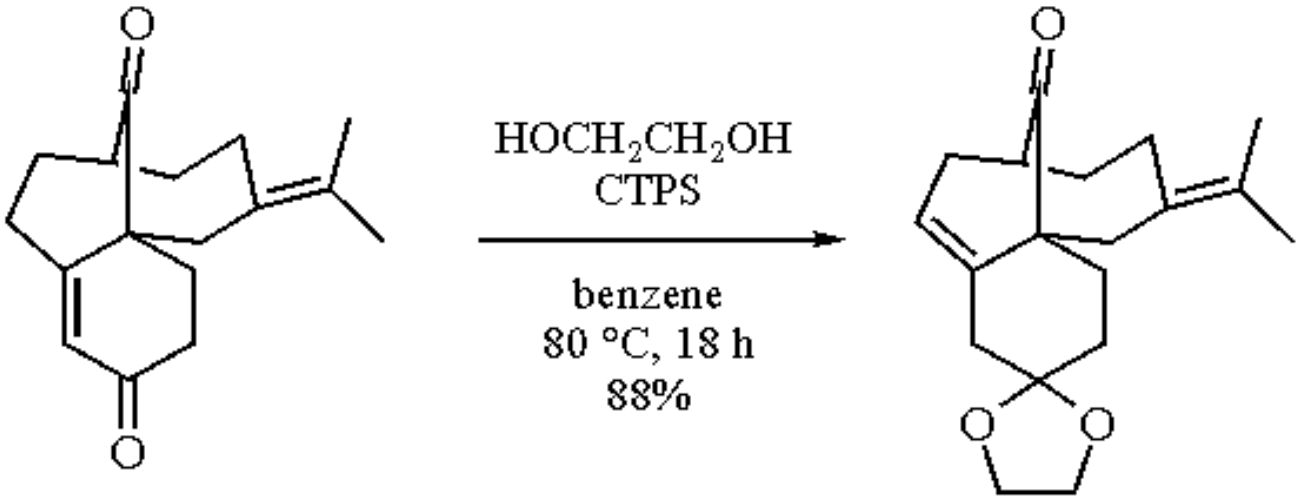

(8)

N,N-Dimethylformamide/Dimethyl Sulfate is another mild acetalization catalyst.[32] Metal catalysts, such as Rh complexes[33] and ***Palladium on Carbon***[1a] have also been used effectively (eqs 9 and 10). Ion-exchange resins offer significant advantages for the preparation of sensitive steroid acetals (eq 11).[34] An especially convenient method involves running a solution of the ketone and ethylene glycol through a column of Amberlyst.[35] Zeolites have also been used to prepare acetals.[36]

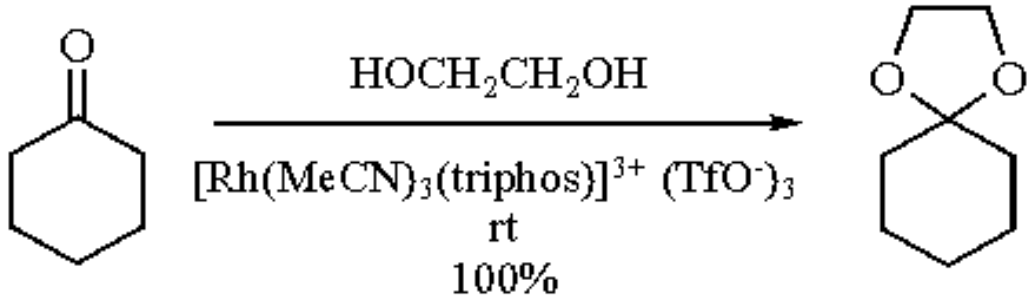

(9)

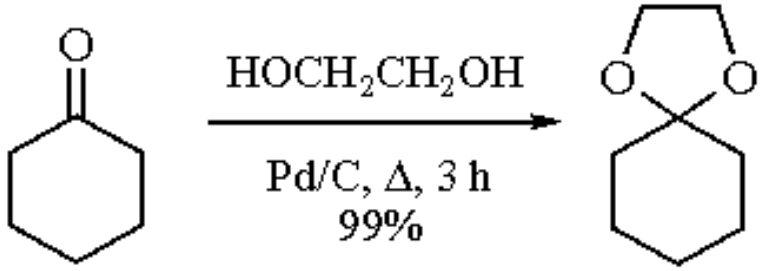

(10)

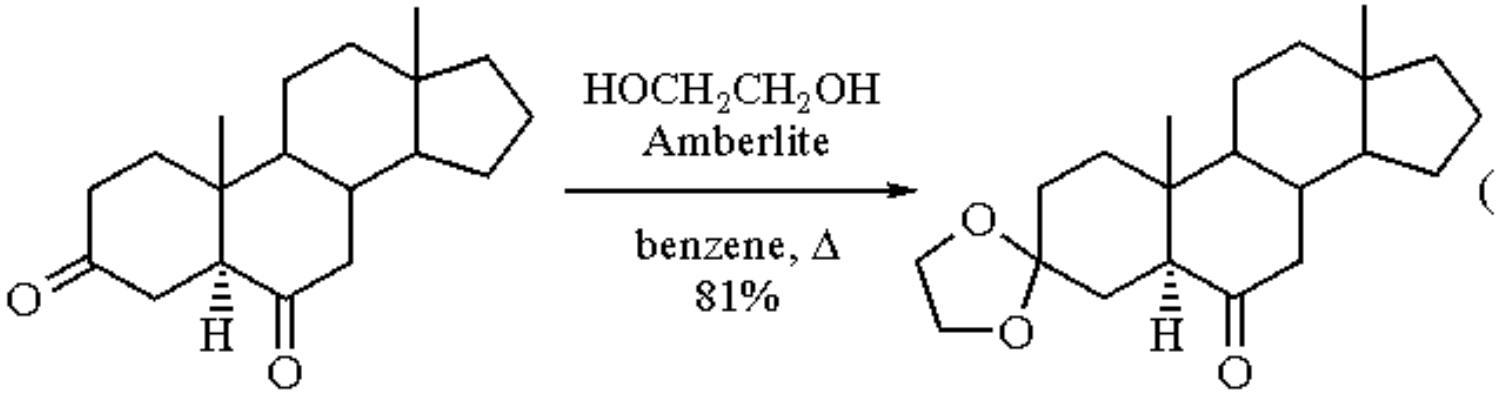

(11)

Ketones that react slowly under normal acetalization conditions can be converted into dioxolanes at high pressure (eq 12).[37] A procedure has also been developed for the dioxolanation of ketones in the presence of aldehydes using a bis-silyl ether of ethylene glycol (eq 13).[38] The selective acetalization of aldehydes in the presence of ketones has been accomplished using ethylene glycol and alumina or silica gel.[39]

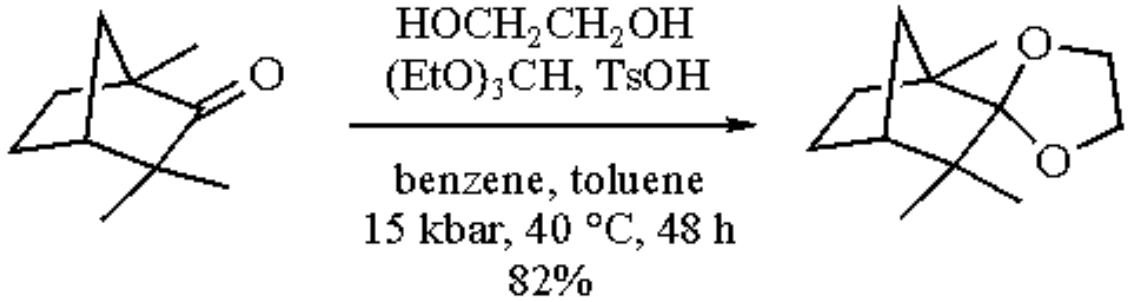

(12)

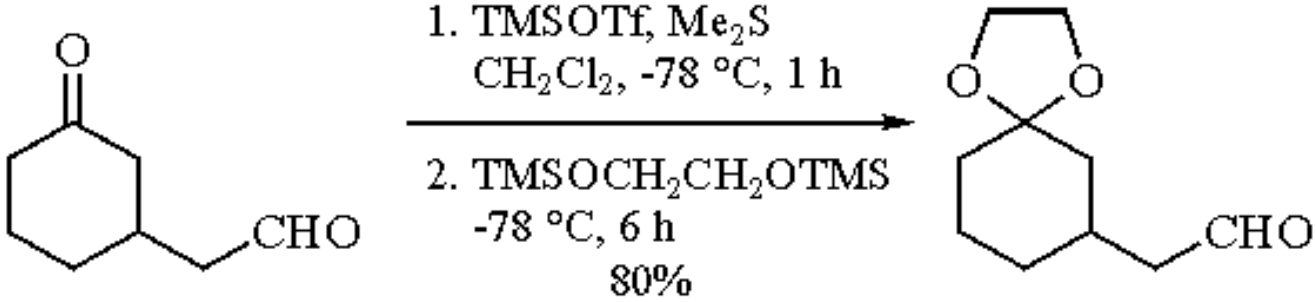

(13)

In addition to their use as protecting groups, dioxolanes have been employed as intermediates. One example is a ring expansion of cyclopentanones via Grob fragmentation of the acetal (eq 14).[40] A novel synthesis of glycerol from formaldehyde and ethylene glycol involves dioxolane intermediates.[41]

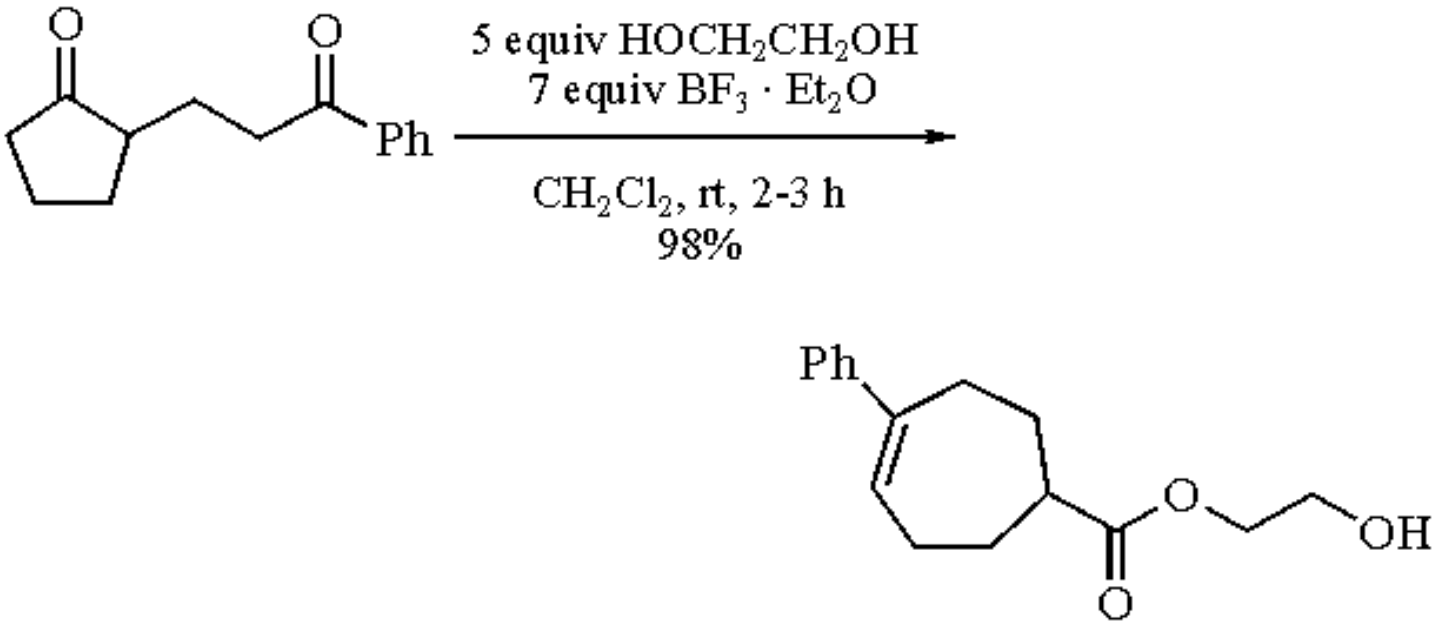

(14)

Dioxolane formation is not limited to aldehydes and ketones. Amide acetals have been prepared directly and by the alcohol interchange method (eq 15).[42]

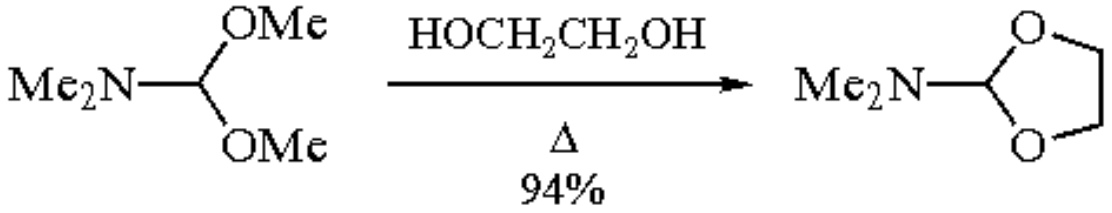

(15)

The interchange of carbonyl protecting groups can be quite valuable in organic synthesis. For example, replacing a thioacetal with an acetal would allow a subsequent oxidation or hydrogenation which is not possible in the presence of a sensitive sulfur-containing group. Reacting the thioacetal with $MeOSO_2F$, followed by treatment with ethylene glycol, achieves this transformation under mild conditions.[43] ***Ethylene Chloroboronate***, prepared from BCl_3 and ethylene glycol, has been used for stereoselective aldol reactions with aliphatic and aromatic aldehydes (eq 16).[2]

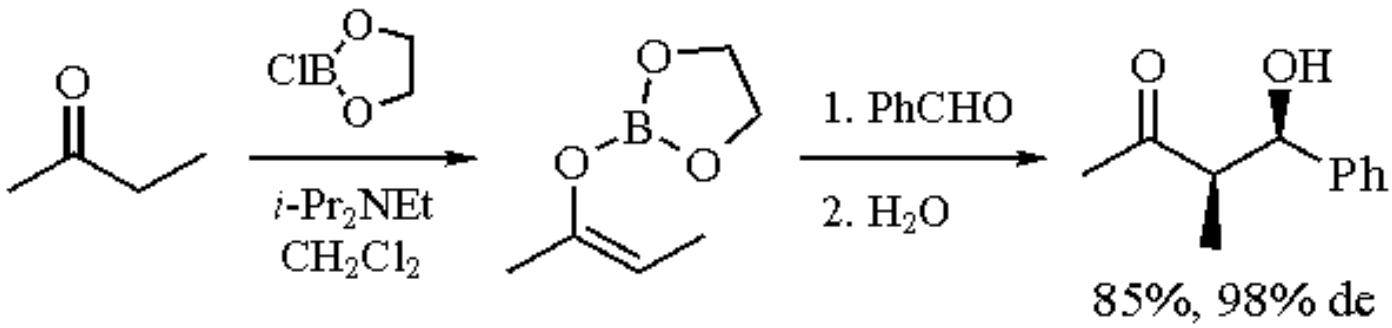

(16)

Solvent Effects.[1d]

Ethylene glycol is an excellent solvent for many reactions and its high boiling point (197.6 °C) and low freezing point (-13 °C) permit a wide range of operating temperatures. Both NaOH and KOH are very soluble in ethylene glycol. Examples are the hydrolysis of *t*-butylurea,[44] the dehydrochlorination of monovinylacetylene,[45] and the Wolff-Kishner deoxygenation.[46] Dehydroxylations of (*R*,*R*)-tartrates with ***Samarium(II) Iodide*** are best accomplished in ethylene glycol.[47] The conversion of alkyl bromides to alkyl fluorides has been carried out in ethylene glycol.[48] Removal of the acetonide group can be accelerated by substituting ethylene glycol for H_2O.[49] The Fischer indole synthesis can be performed without the addition of an acid catalyst by heating a phenylhydrazone in ethylene glycol.[4,50] Ethylene glycol has also been used as a substrate for the synthesis of indoles and other heterocycles.[51] The Ru complex catalyzed reaction of substituted anilines and ethylene glycol offers an alternative route to the indoles under milder conditions than conventional methods (eq 17).[51a,b]

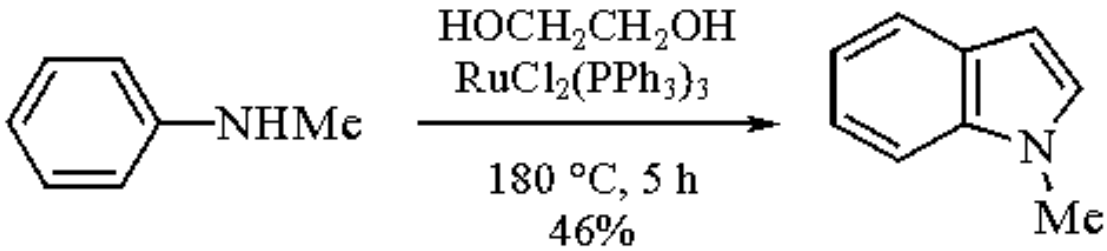

(17)

Ethylene glycol is superior to benzene, MeCN, DMSO, MeOH, and H_2O for the Diels-Alder reaction involving relatively hydrophobic dienes and dienophiles. The increased reaction rate in ethylene glycol is attributed to the improved aggregation of the diene and dienophile (eq 18).[3]

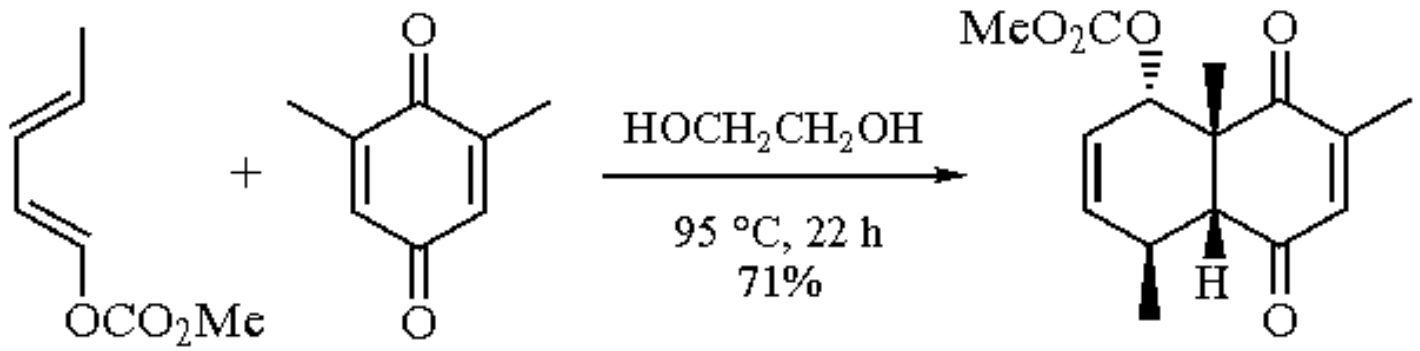

(18)

The synthesis of tertiary alcohols from trialkylboranes and CO at 100-150 °C has been improved in the presence of ethylene glycol[5,52-54] (eq 19).[54a] The purpose of the ethylene glycol is to trap the intermediate boronic anhydride, which can form a polymer that is difficult to oxidize.

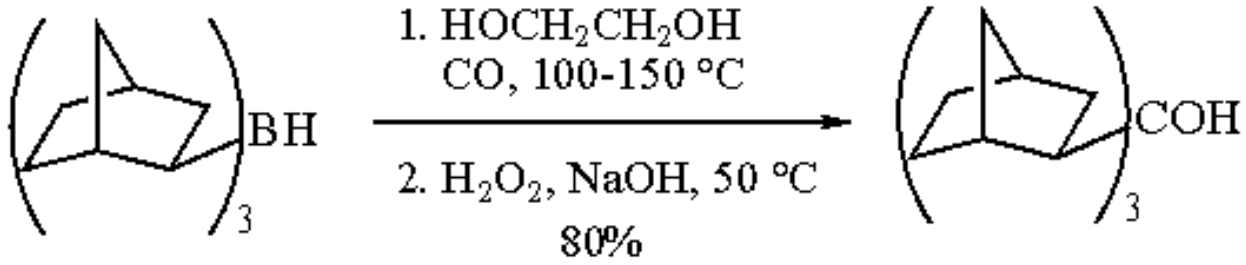

(19)

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Ethylenimine[1]

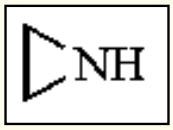

[151-56-4] · C_2H_5N · Ethylenimine · (MW 43.08)

(aminoalkylating agent[1])

Alternate Name: aziridine

Physical Data: mp -74 °C; bp 56.7 °C; *d* 0.829 g cm^{-3}.

Solubility: miscible with H_2O and virtually all organic solvents.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: highly toxic; causes inhalation hazard and skin burns. Use a laboratory hood and wear goggles and gloves. Aziridine is also highly flammable (flash point -11.1 °C, similar to that of benzene). Stable at rt if acid impurities are excluded. Usually stored over solid sodium hydroxide.

Introduction.

Many reactions of aziridines are similar to other cyclic amines. However, the strain present (113 kJ mol^{-1}) results in much easier ring-opening reactions by cleavage of C-N and occasionally C-C bonds.

Aziridines form quaternary ammonium salts with protons and Lewis acids, but these salts are usually reactive towards nucleophiles present in the reaction mixture. They are isolable using weakly nucleophilic solvents (like H_2O) and counterions[2] (perchlorate,[2a] tetrafluoroborate,[2b] trinitrophenylsulfonate,[2c] hydrogen sulfate, etc.). Aziridinium salts were formed at low temperatures from salicylic, glycolic, formic, acetic, benzoic, and dichloroacetic acids, but decomposed within a very short time.[1] Stable salts are obtained from dicarboxylic acids (oxalic,[3a] adipic, terephthalic, isophthalic, tetrachlorophthalic[3b]).

Aziridine forms coordination compounds by the donation of the unshared pair of electrons on the nitrogen atom to molecules or metal ions capable of accepting such electron pairs. The complex with BMe_3 is stable at 100 °C for several hours.[4] ***Boron Trifluoride Etherate*** cleaves aziridine rings readily,[5] but adducts with ***Trimethyl Borate*** and $B(OPh)_3$ are reasonably stable.[6] Labile metal ion-aziridine complexes have been made with Cu^{II}, Hg^{II}, Mn^{II}, Co^{II}, and Ni^{II}.[7] Some salts like Cr^{III}, Co^{III}, Pd^{II}, Pt^{II}, Rh^{I}, and Rh^{III} give inert complexes with aziridine.[7]

Nucleophilic Attack of the Aziridine Nitrogen on Carbon.

Stable HBF_4 salts are formed when trialkyloxonium fluoroborates are used for alkylation of aziridine.[1a] Problems with ring cleavage arise in the reaction of aziridine with alkyl or aryl halides (alkylation) and formation of quaternary ammonium salts. Ring cleavage can be avoided or reduced by using an excess of aziridine over alkyl halide.

Nucleophilic addition to β-alkenic carbons depends on the presence of acceptor groups to stabilize the transient partial negative charge on the α-carbon in the transition state. The reaction of aziridine with activated vinylic chlorides proceeds with retention of configuration.[8,9] Addition to activated alkynes is stereoselective (eq 1).[8] Only esters of alkyne mono-[9] and dicarboxylic acids[10] yield an excess of (*E*)-isomer. Other acceptor groups prefer the formation of (*Z*)-isomer.

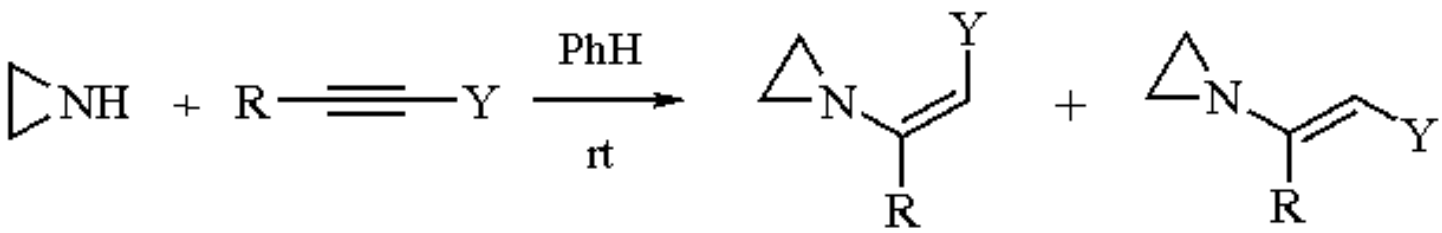

(1)

R = H; Y = CO_2Et	10:90
R = H; Y = Ts	>95:<5
R = H; Y = CN	93:7
R = H; Y = COPh	36:64
R = Y = CO_2Me	15:85
R = Y = CF_3	>95:<5

Ring Expansion of Aziridines.

Carbonylation gives β-lactams (eqs 2 and 3).[11] The insertion occurs with net retention of configuration and is quite regioselective. ***Carbon Monoxide*** inserts into either the more (catalyst ***Tetracarbonyl(di-μ-chloro)dirhodium***)[11a] or the less (catalyst ***Tetracarbonylnickel***)[11b] substituted C-N bond. The (*E*)-amidine formed by addition of aziridine to isocyanides (eq 4) rearranges to the imidazolines.[12]

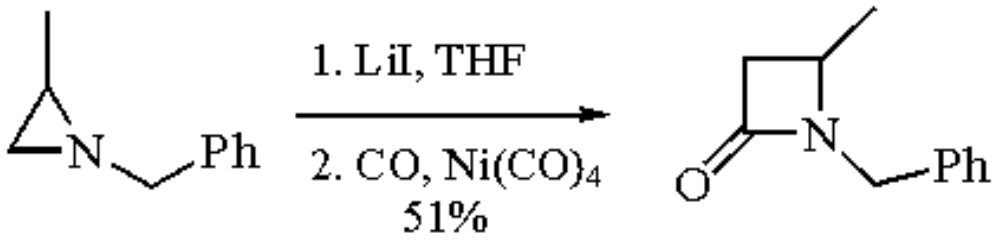

(2)

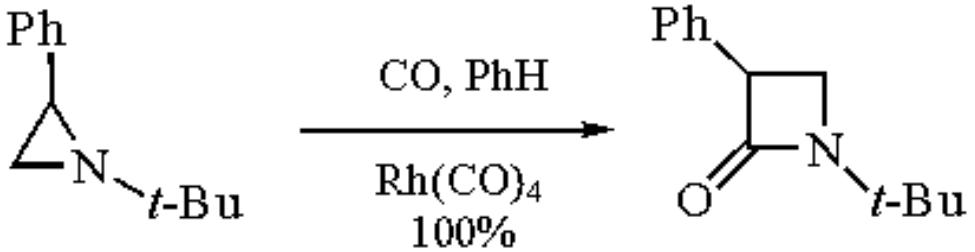

(3)

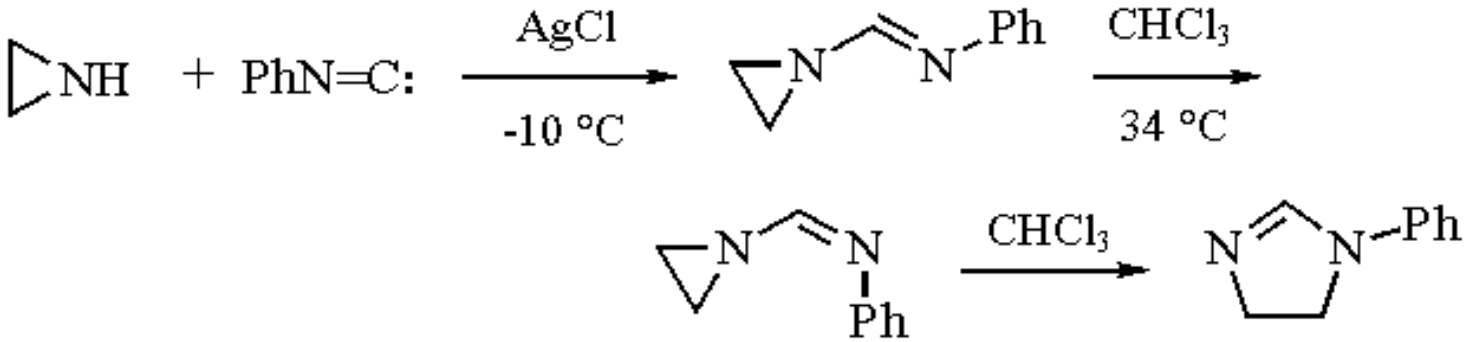

(4)

Aziridine is an excellent starting material for the synthesis of various heterocycles: 1,3-oxazolidines,[13] 1,3-thiazolidines,[13] dihydro-1,4-thiazines,[14] bicyclic pyrrolidines,[15] Δ^1-pyrrolines.[16] Moreover, it is a building block for various alkaloids: crinine, sendaverine, corgoine, reframidine, α-dihydrocaranone, and γ-lycorane.[1c]

Other Reactions.

N-Chloroaziridine is prepared by gas/solid chlorination[17] and used to prepare azirine by dehydrohalogenation. The larger cyclic imines (4-6 membered) are more stable and obtained in higher yields (eq 5).[17b] Various aza macrocycles can be formed by using aziridine as a construction unit, either by ring cleavage,[18a] or with aziridine in the side chain.[18b]

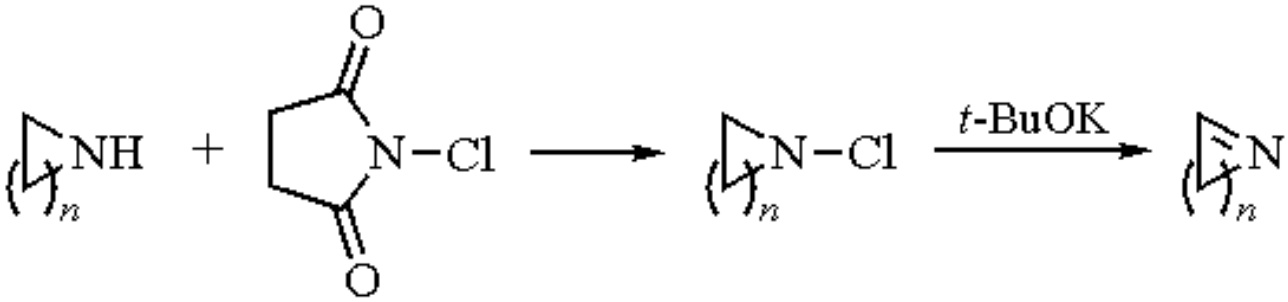

(5)

$n = 1$, 40%; $n = 2$, 96%; $n = 3$, 93%; $n = 4$, 90%

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Ethylene Oxide

[75-21-8] · C_2H_4O · Ethylene Oxide · (MW 44.05)

(electrophile; 2-hydroxyethyl equivalent)

Alternate Name: oxirane

Physical Data: bp 13.5 °C/746 mmHg; *d* 0.8824 g cm^{-3}.

Solubility: sol water and most organic solvents.

Form Supplied in: liquid, in 100 mL sealed tubes; gas, in 100 mL cylinders.

Handling, Storage, and Precautions: extremely flammable; vapors can detonate; possible carcinogen; use in a fume hood.

Nucleophilic Opening.

Ethylene oxide and epoxides in general have been the subject of extensive reviews.[1] Much of the chemistry involved with ethylene oxide revolves around the opening of the strained ring to form a 2-ethanol substituted moiety. The reagents employed have ranged from carbon nucleophiles, to alcohols and water, to amines.

Reaction with Organolithium Reagents.

The carbon nucleophiles can be classified by the type of organometallic reagent involved in the opening reaction of the epoxide. The reagent of choice for this transformation is an organolithium reagent.[2] Treatment of an ester lithium enolate with an excess of ethylene oxide affords a spirolactone (eq 1).[2a]

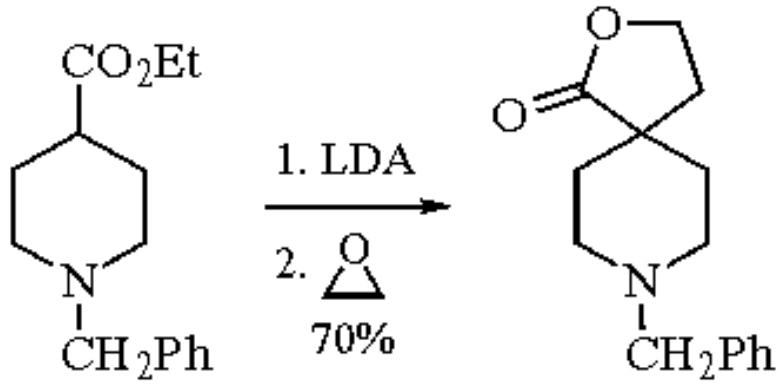

(1)

A lithio acetylide reacts with ethylene oxide in the presence of ***Boron Trifluoride Etherate*** (eq 2).[2c] While $BF_3.Et_2O$ has been used to increase the yields of epoxide openings with organolithium reagents,[3] the reaction solvent also plays an important role in obtaining high yields of ring-opened material with a lithio acetylide (eq 3).[2b] While ***t-Butyllithium*** readily metalates some epoxides, it only opens ethylene oxide.[4]

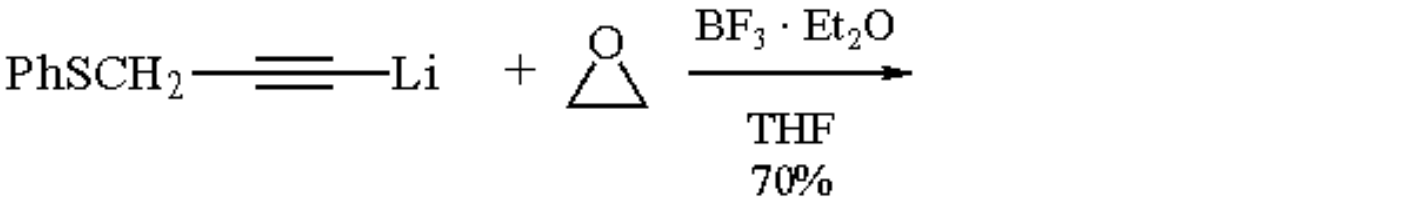

(2)

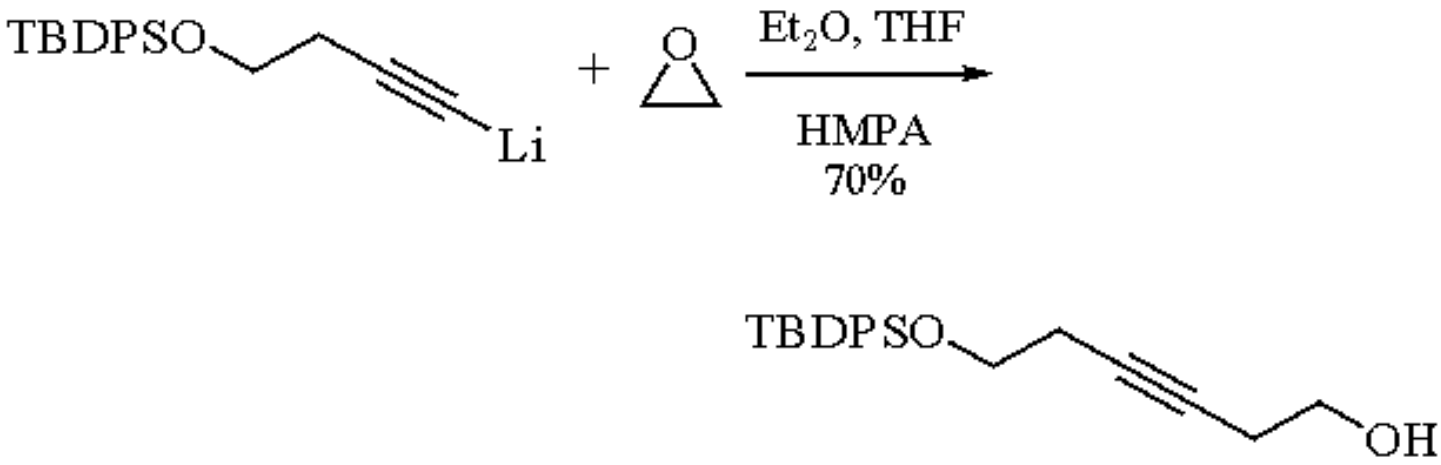

(3)

Reaction with Allylpotassium Reagents.

Isoprene has been metalated with ***Potassium Diisopropylamide*** (KDA). Employing this nonnucleophilic, strong base lessened polymerization and permitted the reaction of the allylpotassium reagent with ethylene oxide to form the homologated alcohol (eq 4).[5]

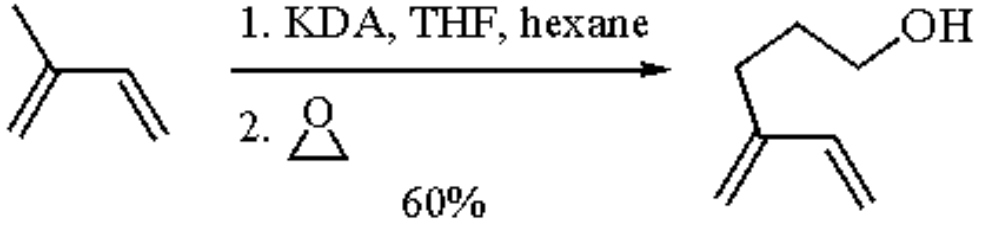

(4)

Reaction with Grignard Reagents.

Grignard reagents add with equal facility as organolithium reagents to ethylene oxide (eq 5).[6]

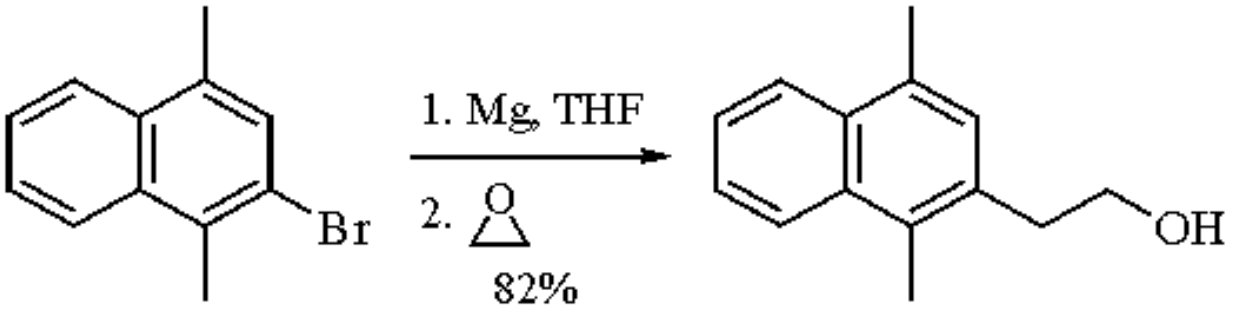

(5)

Reaction with Lithium Dialkylcuprates.

Lithium dialkylcuprates have long been known to react selectively and in high yield with oxiranes.[7] A number of more complex, modified cuprate reagents recently have been developed.[8] A vinylstannane was treated with the higher-order cuprate derived from ***Methyllithium*** and ***Copper(I) Cyanide*** and subsequent reaction with ethylene oxide afforded the homologated alcohol in 48% yield. The vinylstannane was also metalated with ***n-Butyllithium*** and reaction with 2-thienyl(cyano)copperlithium afforded the mixed higher-order vinyl cuprate that reacted with ethylene oxide in 38% yield. However, the authors found the easiest method for the formation of the homologated alcohol was to produce the mixed cuprate and treat it with ethylene oxide (eq 6).[8a]

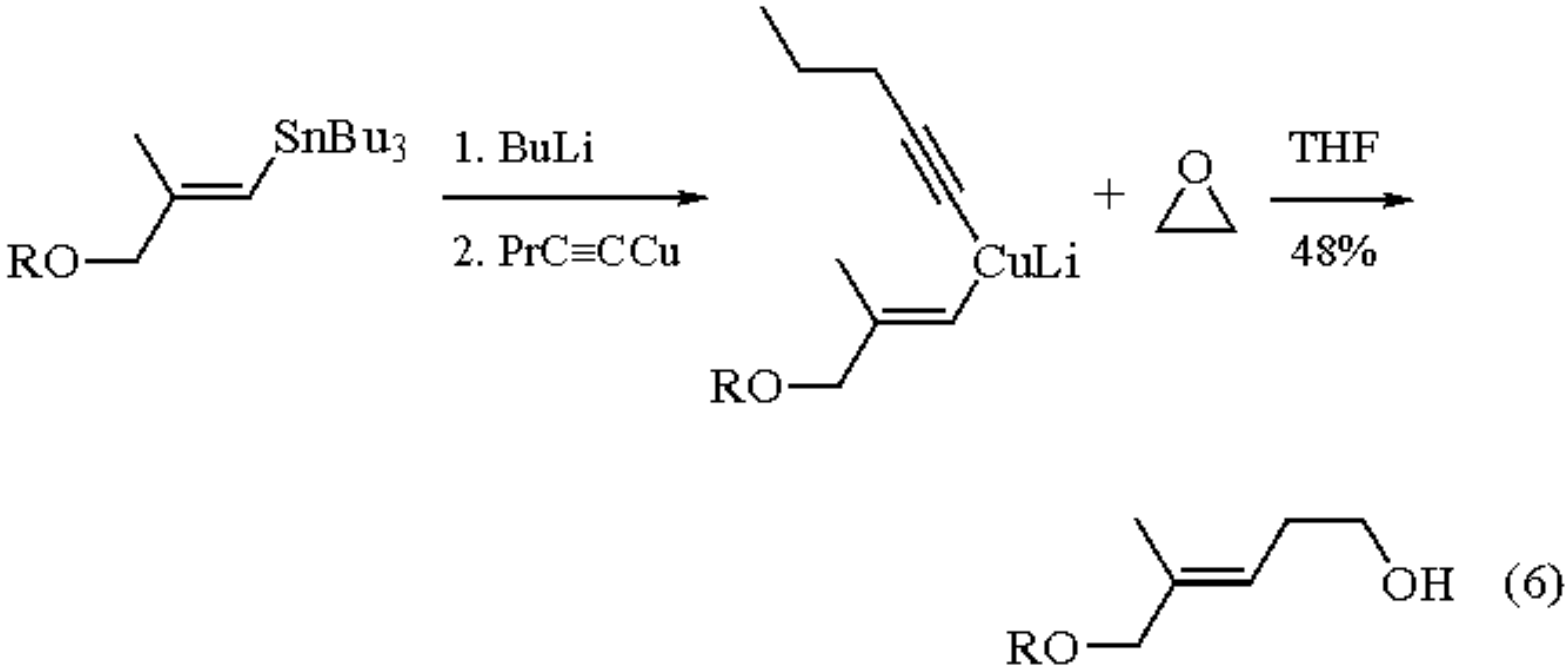

Reaction with Vinylaluminum Reagents.

Vinylaluminum reagents react with ethylene oxide, but lithium alanates react in even higher yield (eq 7).[9]

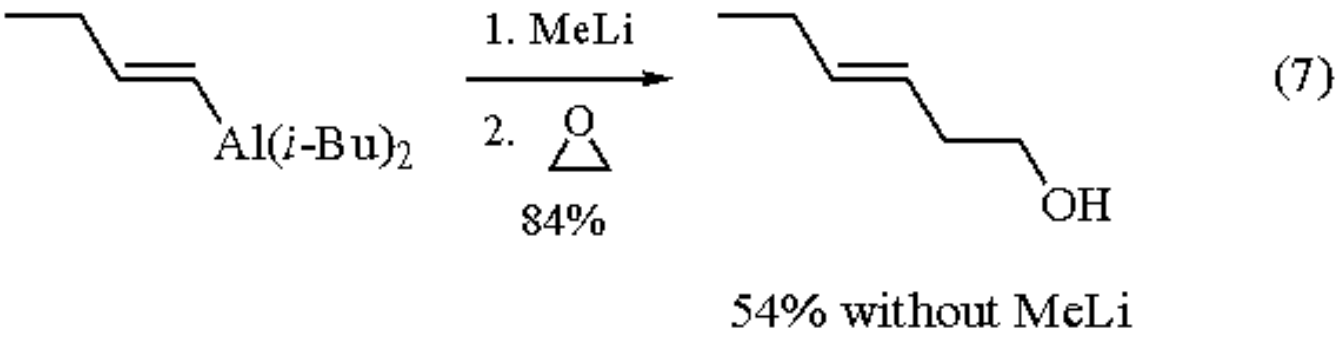

Reaction of Ylides.

A new β-oxidobenzyl ylide was formed by reacting lithium diphenylphosphide with ethylene oxide followed by reaction with ***Benzyl Bromide***. The reaction of these ylides with aldehydes afforded (*E*)-alkenes with good stereoselectivity (eq 8).[10] Another ylide formed from ethylene oxide undergoes a Wittig reaction with an aldehyde derived from (*R*)-limonene. The resulting alkene retains the ethanol moiety derived from ethylene oxide (eq 9).[11]

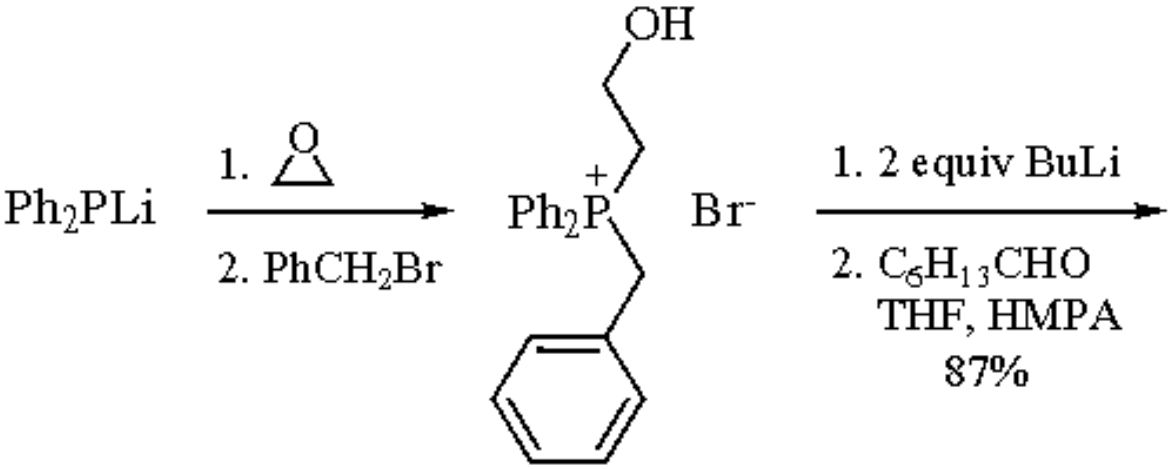

(8)

(*E*):(*Z*) = 85:15

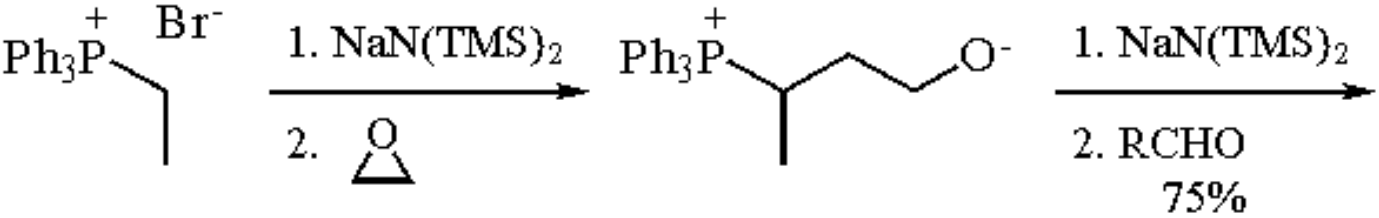

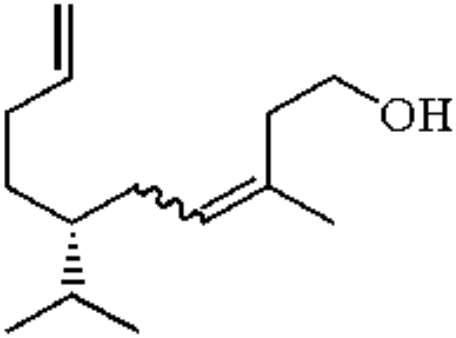

(9)

(*Z*):(*E*) = 67:33

Reaction with Amines.

Heteroatom-containing moieties add to ethylene oxide to form 2-substituted ethanol derivatives.[1] Amines add in this fashion to form 1,2-ethanolamines.[12] For instance, bubbling ethylene oxide through a solution of dimethylethylenediamine in methanol at 35 °C affords the corresponding alcohol (eq 10).[13]

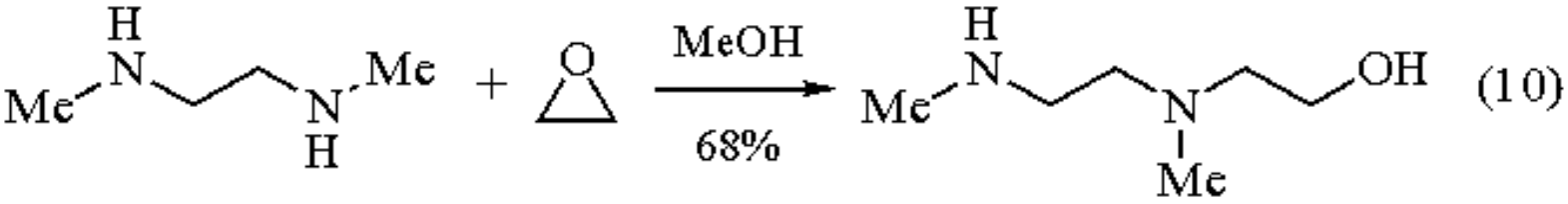

Reaction with Me_3SiI.

By reacting ethylene oxide with ***Iodotrimethylsilane***, a simple derivative is formed that is also useful as a two-carbon synthon in the preparation of pheromone components (eq 11).[14]

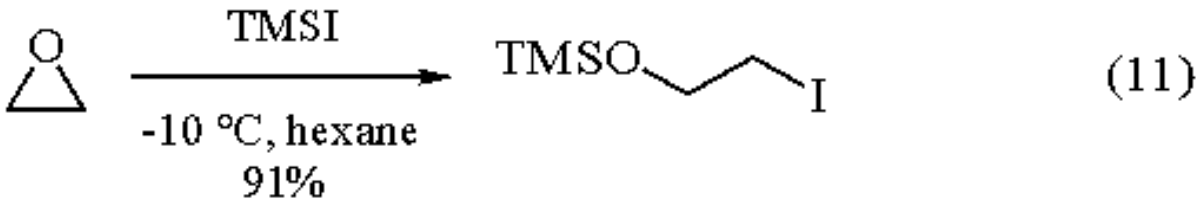

Reaction with Aldehydes.

A very facile method for the formation of acetals under essentially neutral conditions involves the reaction of ethylene oxide with aldehydes in an autoclave at 110-220 °C (eq 12).[15]

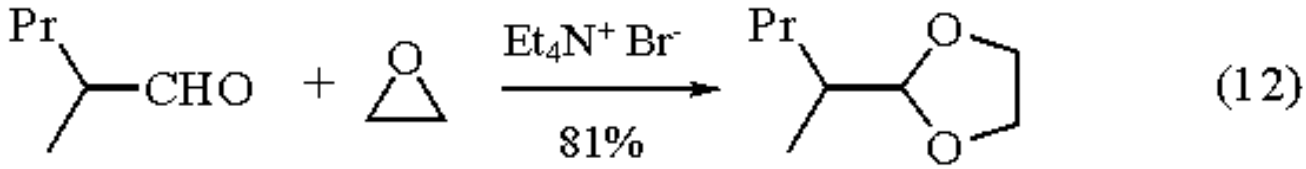

Related Reagents.

1,3-Butadiene Monoxide; ***Glycidol***; ***Isoprene Epoxide***; ***Propylene Oxide***.

---

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The Upjohn Company, Kalamazoo, MI, USA

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Ethylene Sulfide[1]

[420-12-2] · C_2H_4S · Ethylene Sulfide · (MW 60.13)

(mercaptoethylation reagent for primary and secondary amines[2])

Alternate Name: thiirane.

Physical Data: bp 55-56 °C; *d* 1.010 g cm^{-3}; n_D^{20} 1.4935.

Solubility: insol H_2O; sol most common organic solvents.

Form Supplied in: colorless liquid; commercially available, stabilized with 0.5% BuSH.

Analysis of Reagent Purity: by IR,[3a] ^1H NMR,[3b] and GLC.[4]

Preparative Methods: readily obtained from ethylene carbonate and ***Potassium Thiocyanate***.[5]

Handling, Storage, and Precautions: highly toxic,[6] flammable liquid; must be stored in a freezer to prevent gradual polymerization, which is promoted by mineral and organic acids, bases, aqueous ammonia, strong amines, and heavy metal salts. Stabilizers against polymerization: H_2S, alkyl and benzyl thiols, alkyl sulfides, and thioacetamide. Use in a fume hood.

Mercaptoethylation of Amines.

Ethylene sulfide is widely used for mercaptoethylation of primary and secondary amine groups in various organic compounds to obtain aminothiols themselves or to convert them into sulfur heterocycles. Aqueous ammonia causes only a rapid polymerization of ethylene sulfide and no cysteamine formation. The action of anhydrous ammonia has not been investigated. Efforts to obtain monomeric ethylene sulfide addition products to ***Hydrazine*** and ***Hydroxylamine*** failed.

Mercaptoethylation of amines by ethylene sulfide proceeds with opening of the episulfide ring by an S_N2 mechanism, the slow step being nucleophilic attack of the amine on the episulfide carbon atom followed by a rapid proton exchange between N and S atoms.[7] Strongly basic amines react more rapidly,[8] but high basicity promotes polymerization of ethylene sulfide as well.[9] The latter reaction may be suppressed by using nonpolar solvents (benzene, ether, THF,

dioxane) and an excess of the amine, which also prevents the formation of bis(mercaptoethyl) derivatives in the case of primary amines and further alkylation of product at sulfur (giving thioethers).[10] Heating favors the mercaptoethylation reaction and diminishes the polymerization.[11]

A substantial improvement of the earlier synthetic procedures is the gradual addition of the ethylene sulfide to a refluxing amine solution in benzene, which diminishes the polymerization to less than 1%.[2] This procedure with warm, but not refluxing, solution gives good yields even when stoichiometric amounts of reagents are used (eq 1).[12] Primary aliphatic amines may be mercaptoethylated near room temperature in aqueous media containing the amine-silver complex, which finally is decomposed by H_2S (eq 2).[13]

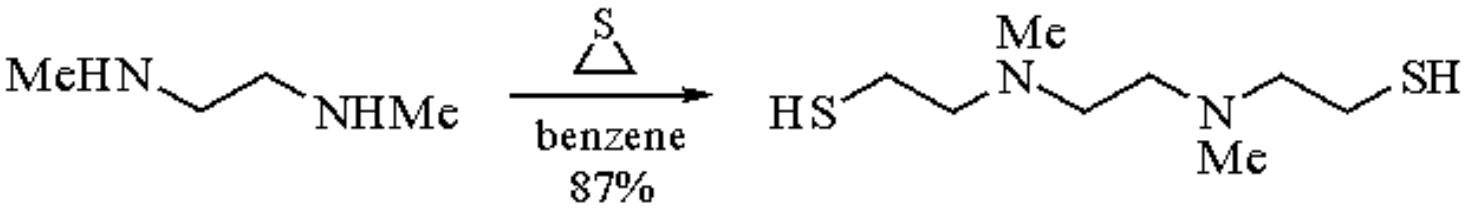

(1)

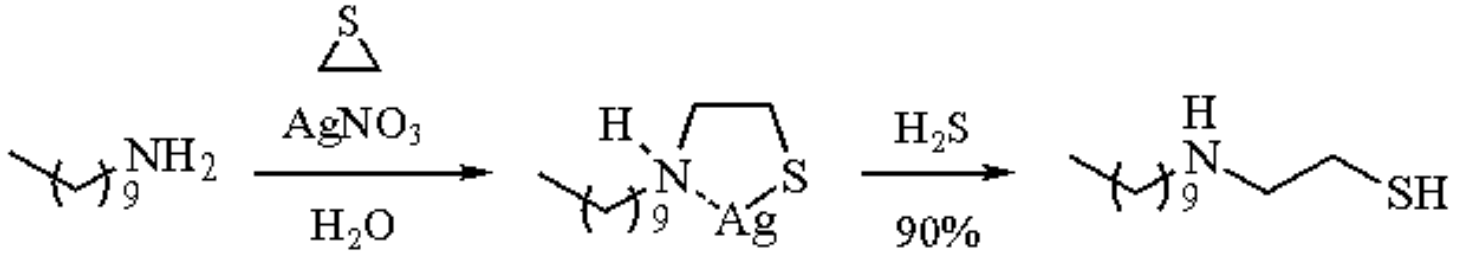

(2)

Weakly basic aryl amines,[8] esters of aminobenzoic acids,[14] and α-amino acids[15] require more drastic conditions (100-105 °C, sealed tube, alcoholic solutions or absence of solvent) for mercaptoethylation.

The preparation of bis(mercaptoethyl)amines by means of ethylene sulfide has been little investigated,[11,16] and reaction conditions have not been optimized. However, satisfactory yields of $HN(CH_2CH_2SH)_2$ (83%) and $N(CH_2CH_2SH)_3$ (72%) were obtained by slowly treating cysteamine with an excess of ethylene sulfide at rt in toluene followed by refluxing (24 and 36 h, respectively).[17]

Other Applications.

Other useful applications of ethylene sulfide for the synthesis of organosulfur compounds in excellent yields (>90%): $PhCH_2SCH_2CH_2Br$,[18] $PhSCH_2CH_2SH$,[19] $R_2AsSCH_2CH_2SCN$,[20] 1,4-dithiane,[21] 1,3-dithiolane-2-thione,[22] and a thiazolidine derivative of the C_{20} diterpenoid alkaloid lindheimerine by cyclocondensation of its N=C bond with ethylene sulfide.[23]

Related Reagents.

2-Mercaptoethanol.

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Ethyl 3-Ethoxyacrylate[1]

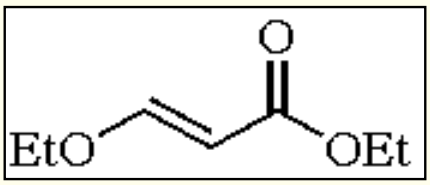

[1001-26-9] · $C_7H_{12}O_3$ · Ethyl 3-Ethoxyacrylate · (MW 144.17) (*E*)

[5941-55-9] (*Z*)

[40648-44-0]

(mono- and bifunctional three-carbon electrophile in acylation reactions;[2] various condensation reactions;[3] building block for heterocycles[1] and nucleoside synthesis[4])

Alternate Name: 3-ethoxy-2-propenoic acid, ethyl ester.

Physical Data: bp 195-196 °C, 85.5-86.5 °C/19 mmHg; *d* 0.993-0.998 g cm^{-3}; n_D^{20} 1.444-1.448.

Form Supplied in: colorless, sweet-smelling liquid, stabilized with 0.01% hydroquinone monomethyl ether; commercially available.

Handling, Storage, and Precautions: should be stored at 0-4 °C. It is a slight lachrymator and irritant. Use in a fume hood.

Reactions at the Double Bond.

Transetherification.

Ethyl 3-ethoxyacrylate and 3,3-diethoxypropionate undergo reversible interconversion in the presence of some acidic-type catalysts.[5] Thus the acrylate is converted into the propionate in the presence of ***Boron Trifluoride Etherate***; the propionate distilled with ethanol and a catalytic amount of sodium bisulfate affords the acrylate. Replacing ethanol by less volatile alcohols yields ethyl 3-alkoxyacrylates or ethyl 3,3-dialkoxypropionates[5] (eq 1). Similarly, thiols[5] and thiophenols[6] undergo transetherification reactions with ethyl 3-ethoxyacrylate and sodium bisulfate to give alkylthioacrylates.

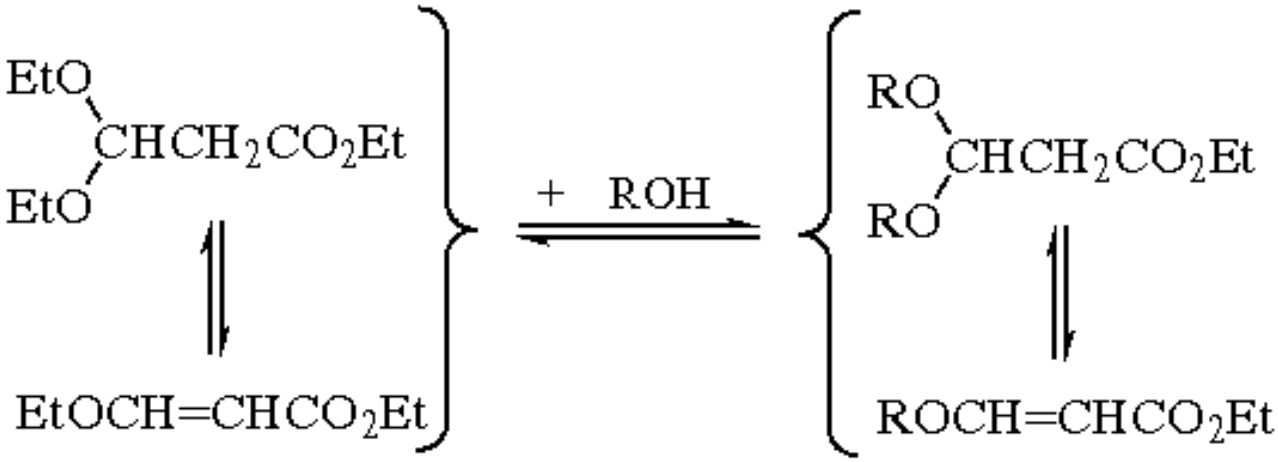

(1)

Addition.

Addition of allyl alcohols to ethyl 3-ethoxyacrylate using ***N-Bromosuccinimide*** as bromine donor yields ethyl 3-allyloxy-2-bromopropionates, which can be cyclized reductively to 3-ethoxycarbonyltetrahydrofurans with ***Chromium(II) Acetate*** (eq 2).[7]

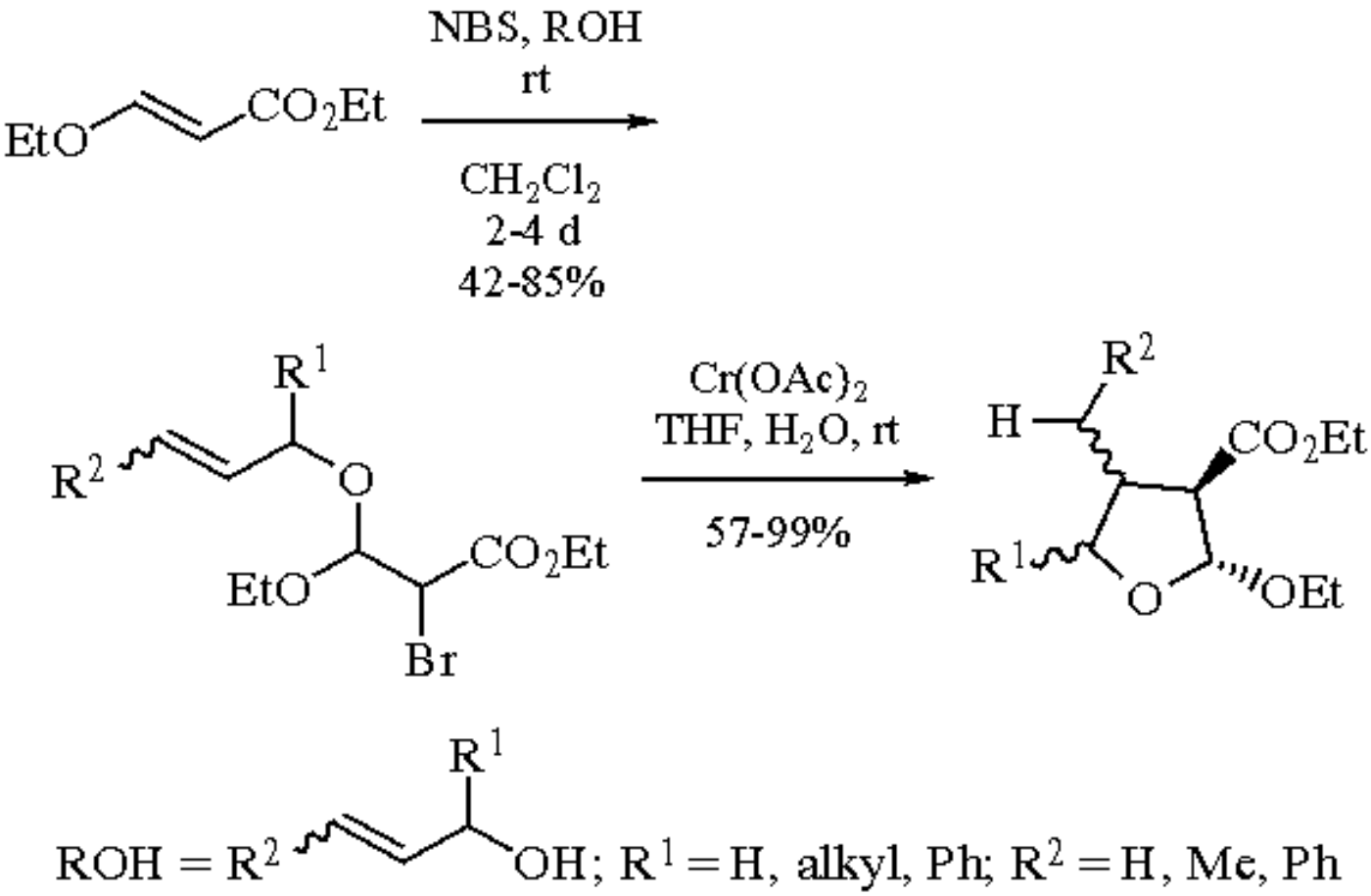

(2)

Other Substitutions.

β-Ethoxycinnamates are obtained in moderate yields by cross-coupling reaction of iodobenzenes with ethyl 3-ethoxyacrylate in the presence of ***Palladium on Carbon*** (eq 3).[8] 3-Iodopyridine and 3-iodoquinoline react similarly.[8]

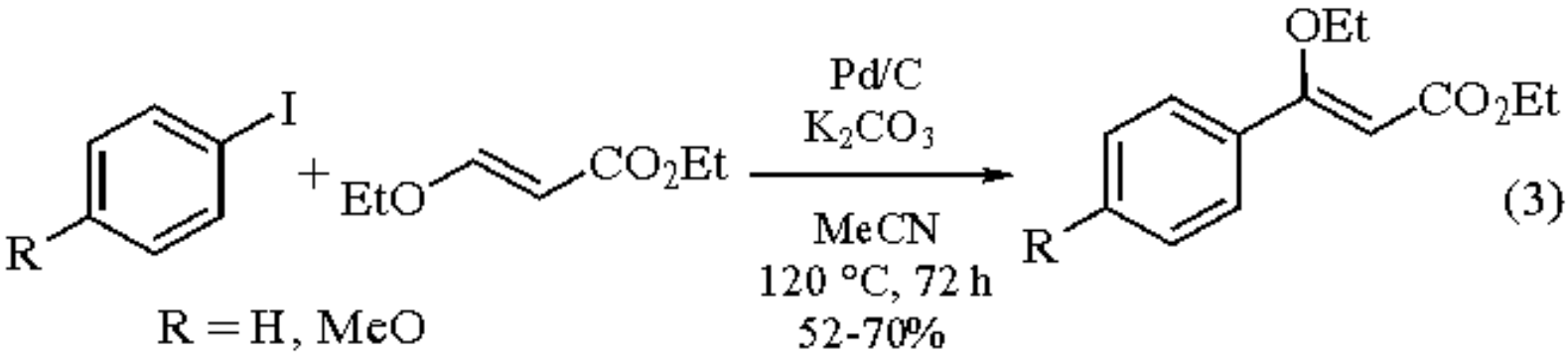

Carboxy Reactions and Subsequent Cyclization.

Ethyl 3-ethoxyacrylate is an important starting material in the synthesis of uracil nucleosides. In a three-step synthesis the ester is converted into the acid chloride, then to the acyl isocyanate which reacts with ammonia,[2a] aliphatic[2a] or aromatic amines[2a,9] to give β-ethoxyacryloylureas (cf. eq 4). These acylureas are cyclized in alkaline solution to the corresponding uracils. With acyl isothiocyanates, thiopyrimidones[2b] are obtained, while for the synthesis of thymines, 3-methoxy-2-methylacrylic acid is used.[2a] Carbocyclic analogs of uracil nucleosides are obtained when the amine component is a hydroxycyclopentylamine (eq 4).[4,10] The cyclization is catalyzed by acid.[4] Tetrahydroxycyclopentylamines may be also used.[11]

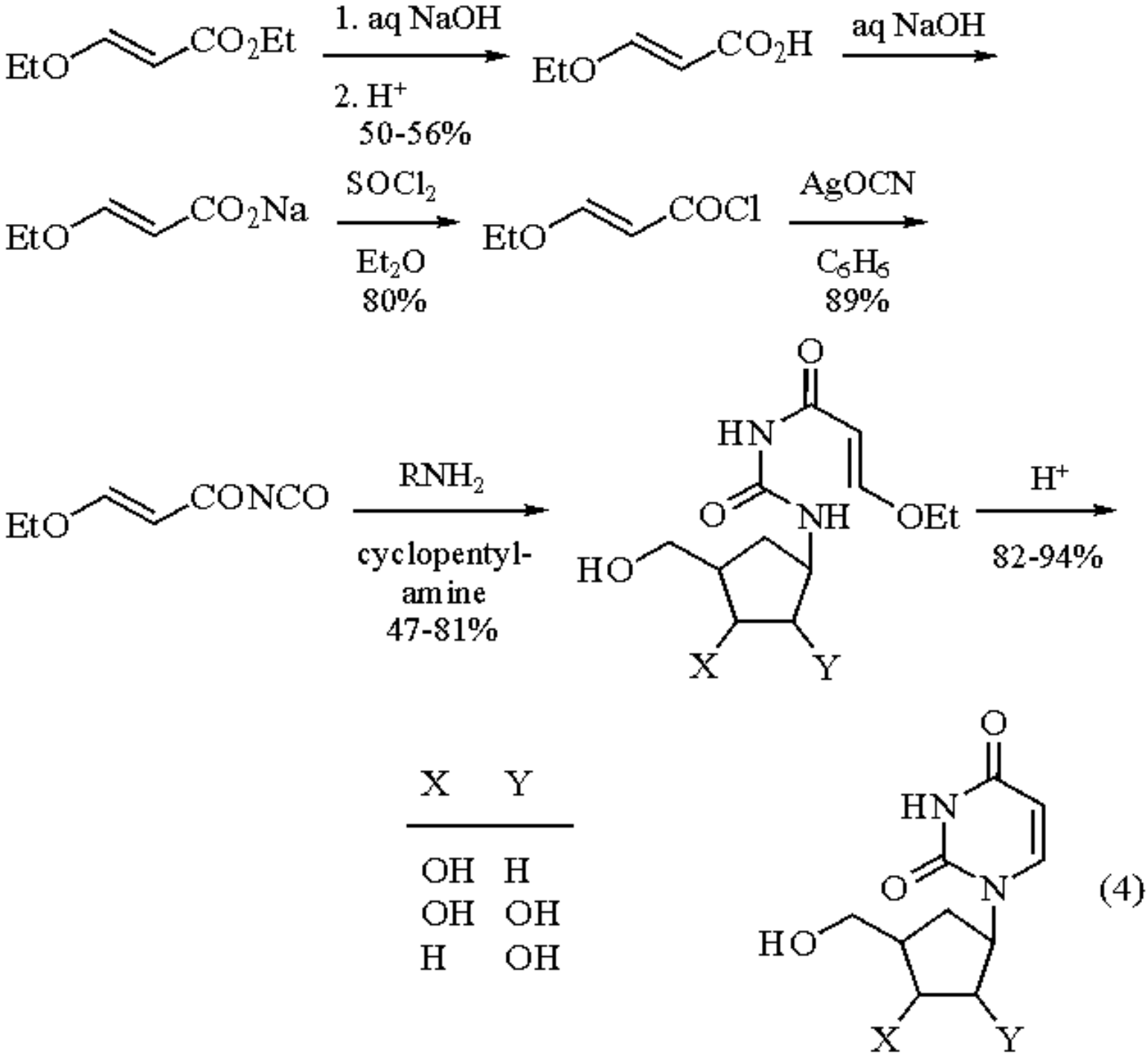

(4)

Other Cyclizations.

Aminoarabinose containing a 2´-amino-1,2-oxazoline ring reacts with ethyl 3-ethoxyacrylate directly to give the $O^{2,2'}$-anhydrouridine, although the yield is poor (24%).[12]

2-Substituted 4(3*H*)-pyrimidinones are obtained by reaction of ethyl 3-ethoxyacrylate with orthoesters and ammonia.[3] Ethoxyacrylate alone reacts with ammonia (mol ratio 2:1) to give ethyl 2(1*H*)-pyridone-5-carboxylate (eq 5);[3] excess of ammonia gives additional pyridine-3,5-dicarboxylate.

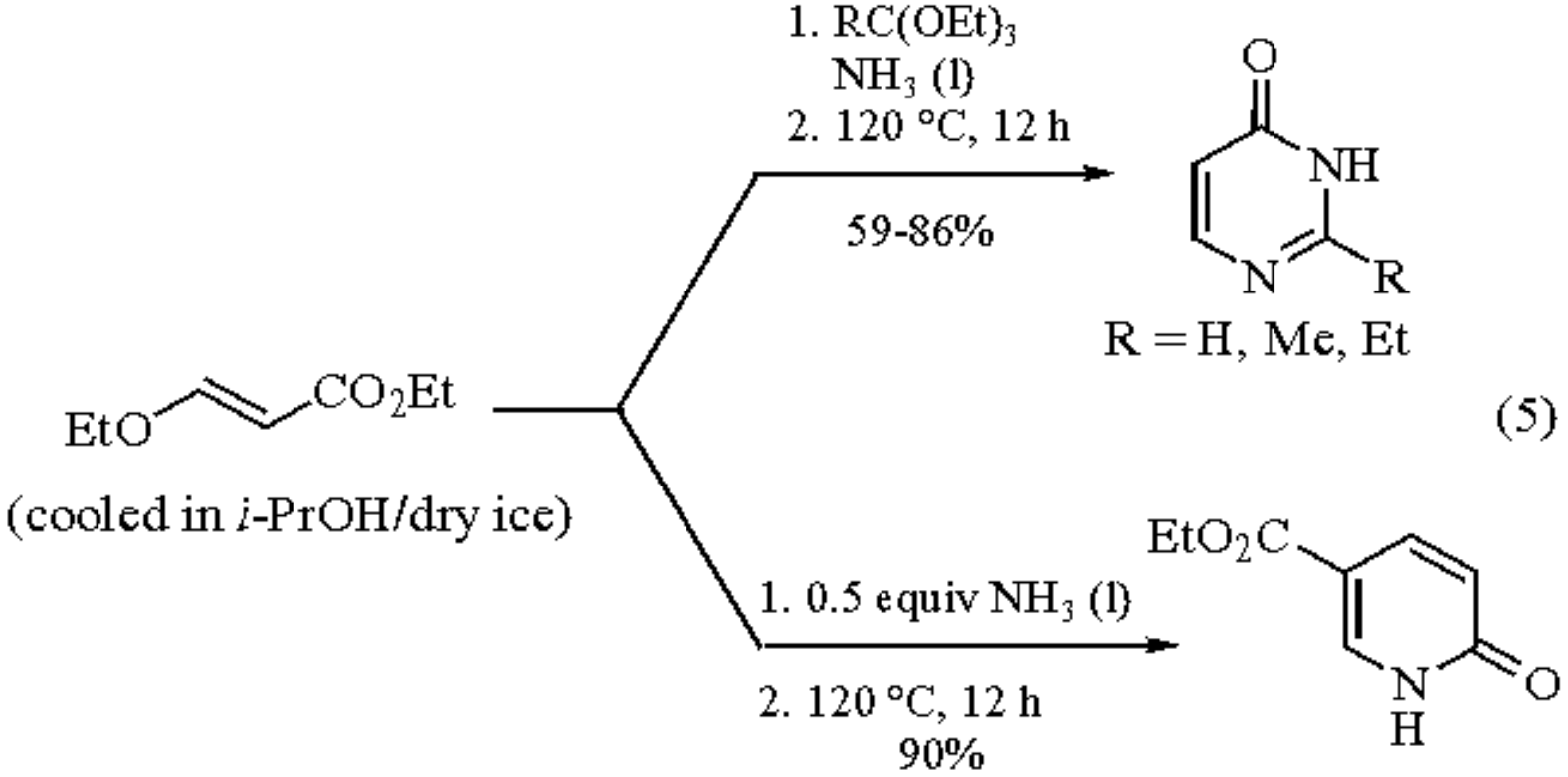

Condensation of 4,6-diamino-2-methylthiopyrimidine with ethyl 3-ethoxyacrylate in acetic acid yields 4-amino-2-methylthio-7-oxopyrido[2,3-*d*]pyrimidine, whereas a complex mixture is obtained with ethyl propiolate.[13]

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl Hydroxymethyleneacetate, Sodium Salt***; ***Methyl Diformylacetate***; ***Methyl Propiolate***.

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Roswitha M. Böhme

Ethyl Ethoxymethyleneacetoacetate

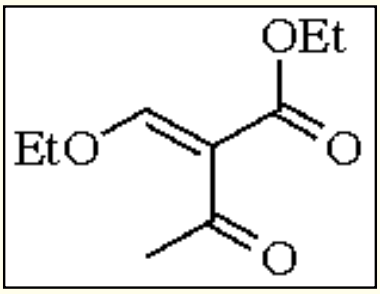

[3788-94-1] · $C_9H_{14}O_4$ · Ethyl Ethoxymethyleneacetoacetate · (MW 186.21)

(mono-, bi-, and trifunctional three-carbon electrophile in carbonyl reactions, cyclizations;[1] β-keto ester equivalent)

Physical Data: bp 265-266 °C, 149-151 °C/16 mmHg; *d* 1.067 g cm^{-3}; *n*20D 1.472-1.473.

Form Supplied in: colorless, viscous liquid.

Preparative Methods: obtained by heating ***Ethyl Acetoacetate*** with ***Triethyl Orthoformate*** in ***Acetic Anhydride***.[2a,b]

Handling, Storage, and Precautions: may be kept for a few weeks at 0 °C in the dark with addition of hydroquinone. The enol ether hydrolyses slowly in contact with water. Use in a fume hood.

Cyclization with Amino Nucleophiles.

Ethyl ethoxymethyleneacetoacetate (**1**) has three types of carbonyl groups, the labile ethoxy group (a masked aldehyde) being the most reactive. It will be substituted first by nucleophiles such as amino compounds. Amidines give aminomethylene derivatives, which cyclize to a substituted pyrimidine ring with a bridgehead nitrogen. 2-Aminopyridines condense with (**1**), the intermediates yielding 3-acetyl-4-keto-4*H*-pyrido[1,2-*a*]pyrimidine (eq 1).[1a] 5-Amino-4-cyanopyrazole and (**1**) cyclocondense to 6-ethoxycarbonyl-3-cyano-7-methylpyrazolo[1,5-*a*]pyrimidine.[1b] In a modified Gould-Jacobs reaction of amino heterocycles and (**1**), cyclization takes place at a carbon atom: 1-substituted 5-aminopyrazoles give 5-acetyl-1*H*-pyrazolo[3,4-*b*]pyridine derivatives.[3a,b] Similarly, acetyl-substituted isoxazolo[4,5-*b*]pyridines,[3c] thieno[2,3-*b*]pyridines,[4] thieno[3,2-*b*]pyridines,[4] 5*H*-[1]benzopyrano[3,4-*b*]pyridinones,[5a] and 3*H*-pyrano[3,2-*f*]quinoline[5b] are obtained from 5-aminoisoxazole, 2- or 3-aminothiophene derivatives, 3-aminocoumarin, and 6-aminocoumarin, respectively. 1,1,1-Tris(aminomethyl)ethane and (**1**) condense to form a hexadentate ligand for Co^{III} and Fe^{III}.[6]

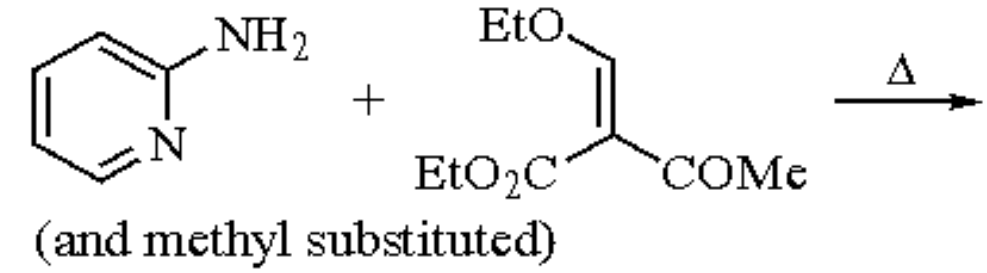

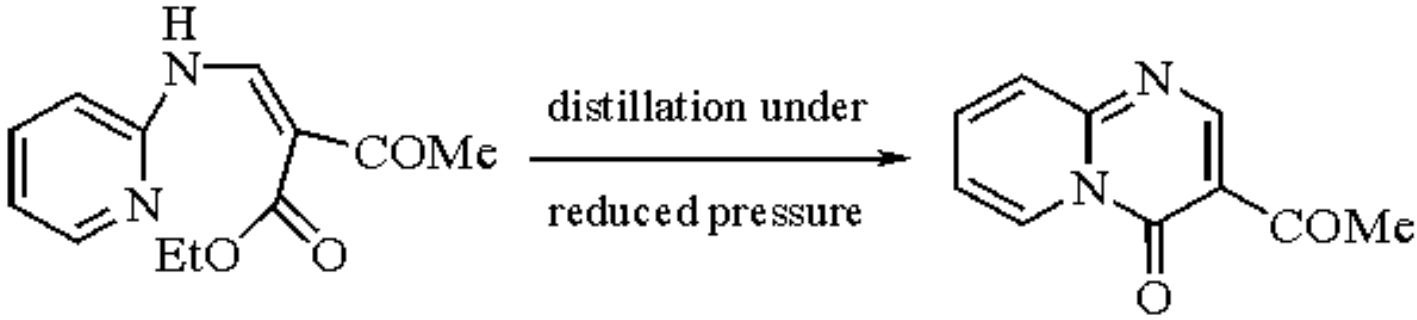

(1)

Reaction with Carbon Nucleophiles.

Compounds with acidic protons such as acetoacetate[7a] or malodinitrile[7b] behave as nucleophiles towards (**1**). 2-Methylpyridinium salts[8] and (**1**) give 1-alkyl-2-allylidenedihydropyridines (eq 2).

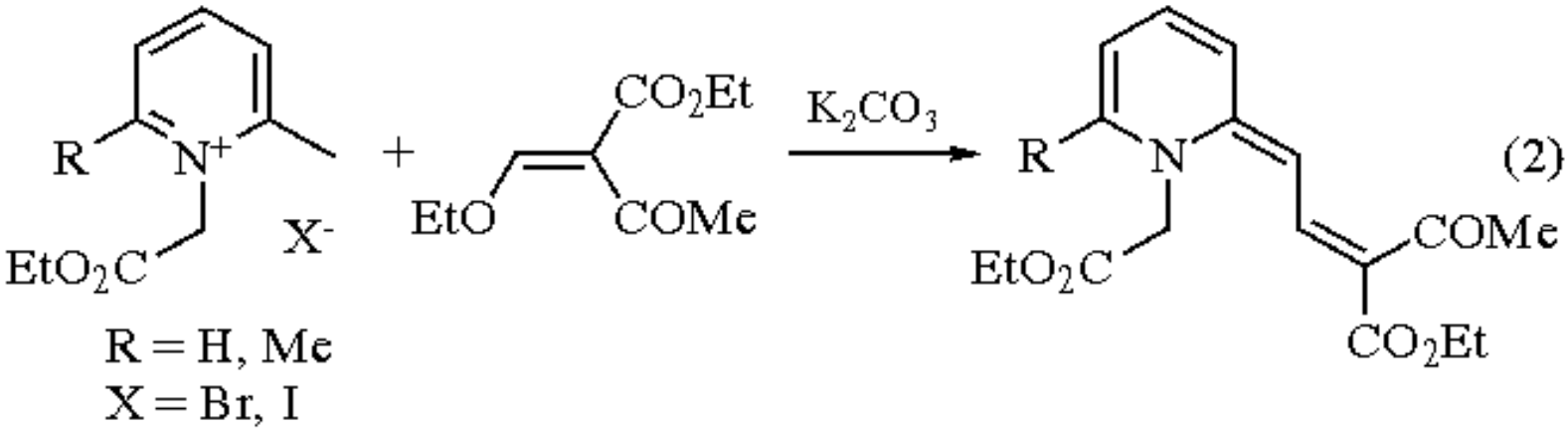

(2)

Dimethylsulfoxonium ylides as nucleophiles and (**1**) yield 4-ethoxycarbonyl-1,3-dimethylthiabenzene 1-oxide[9a] or a carbonylvinyl-stabilized sulfur ylide.[9b]

Related Reagents.

3-Butyn-2-one; ***Diethyl Ethoxymethylenemalonate***; ***Ethyl Acetoacetate***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethylenecyanoacetate***.

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Ethyl Ethoxymethylenecyanoacetate

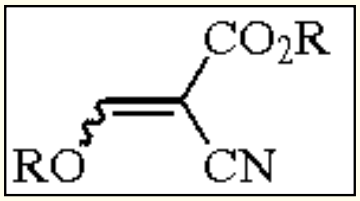

(R = Et)[5]

[94-05-3] · $C_8H_{11}NO_3$ · Ethyl Ethoxymethylenecyanoacetate · (MW 169.20) (*E*)

[42466-67-1] (*Z*)

[42466-69-3] (R = Me)[4,5]

[13974-74-8] · $C_6H_7NO_3$ · Methyl Methoxymethylenecyanoacetate · (MW 141.14) (*E*)

[55883-89-1] (*Z*)

[71363-40-1]

(push-pull alkene;[1] N-heterocycle synthesis; 1,3-dipolar cycloaddition;[2] 1,4-addition-elimination (Ad_N-E)[3])

Physical Data: R = Et, mp 51-53 °C; bp 190-191 °C/30 mmHg; subl. 25 °C/0.02 mmHg. R = Me, mp 88 °C; bp 185 °C/25 mmHg.

Solubility: slightly sol water; sol ethanol, diethyl ether.

Form Supplied in: white solid; widely available.

Preparative Methods: can be prepared from ***Triethyl Orthoformate***, ***Ethyl Cyanoacetate***, and ***Acetic Anhydride*** in the presence of ***Zinc Chloride*** (catalyst).[4]

Purification: recrystallization from ethanol and sublimation.

Handling, Storage, and Precautions: use in a fume hood.

Ethyl ethoxymethylenecyanoacetate is a valuable reagent in the synthesis of N-heterocycles. Pyrimidines (eq 1),[6] pyridines,[7] pyrazoles,[8] indolizines,[9] quinolizones, and pyridones[10] can be obtained. It is also used in the synthesis of

pyrones (eq 2).[11]

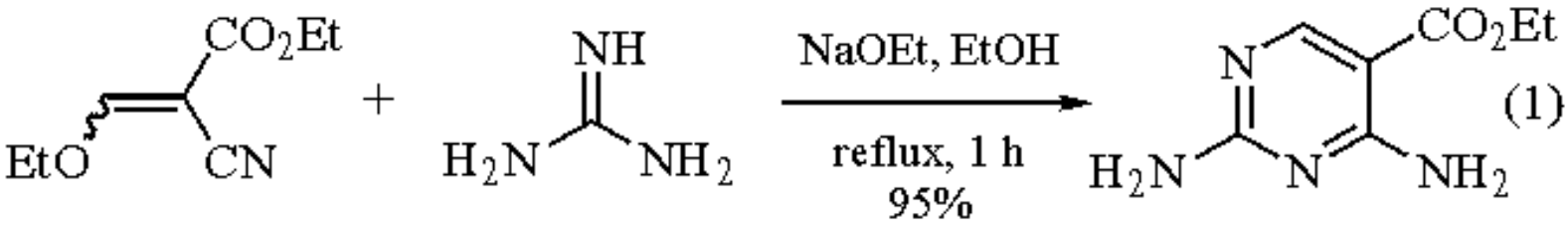

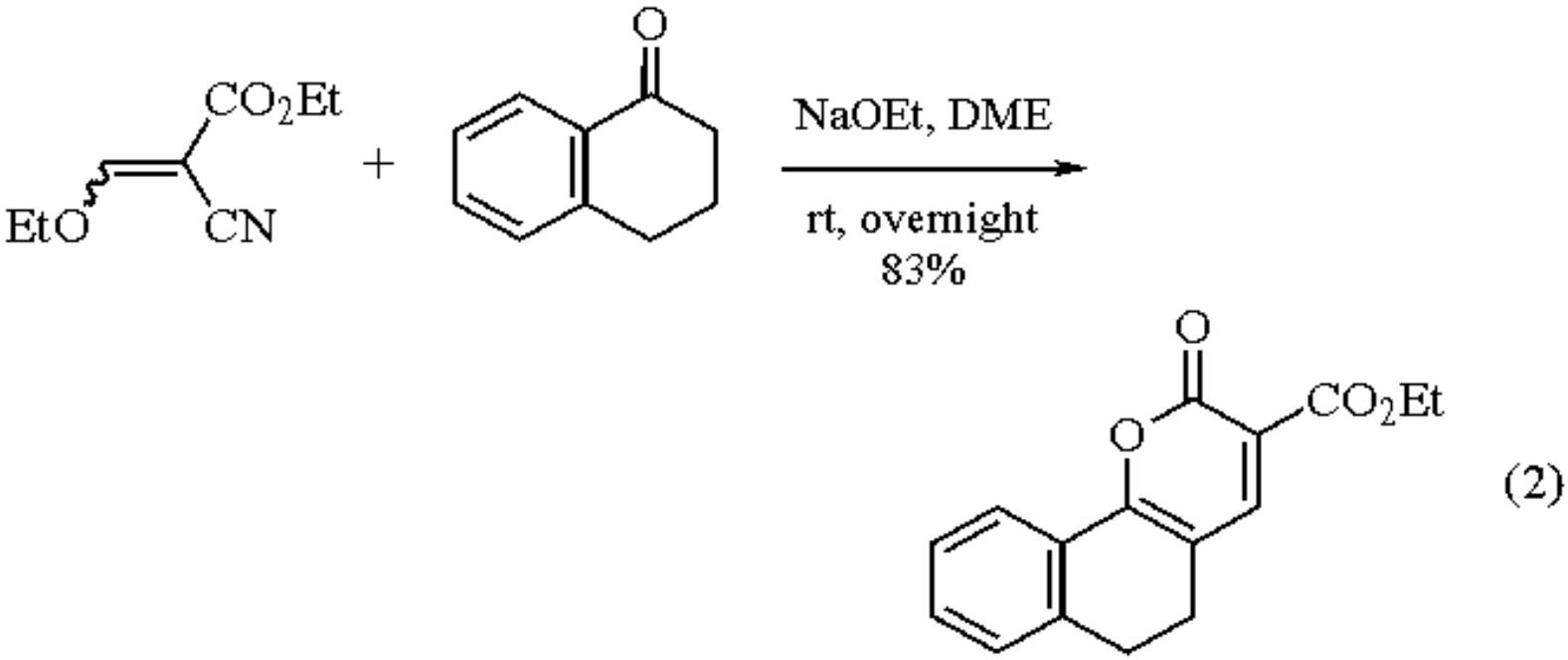

The [3 + 2] cycloaddition of ethyl ethoxymethylenecyanoacetate with cyclopropenone acetals[2a] (see also ***Diethyl Ethoxymethylenemalonate*** and ***Diethyl Ethylidenemalonate***), benzonitrilium isopropylide (eq 3)[2d] or diazo compounds[2b,c,12] leads to cyclopentenones, pyrrolines, and pyrazolines, respectively. Benzonitrilium isopropylide is generated in situ from a photoinduced cleavage of the corresponding 2*H*-azirine (eq 3).

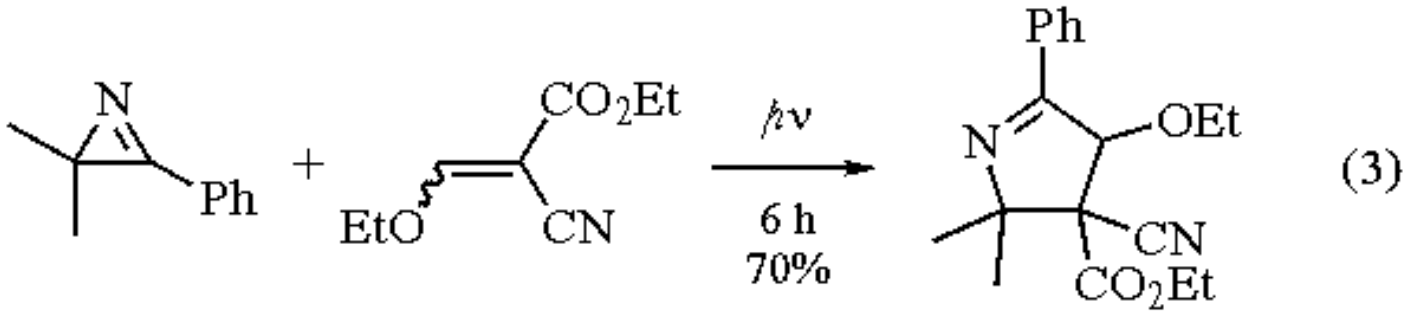

The ethoxy group of ethyl ethoxymethylenecyanoacetate can be substituted by various nucleophiles in an Ad_N-E mechanism. Malonates,[3f] enolates,[3b,c,g] quarternary salts of heterocyclic bases containing an active methylene group,[3d] amines,[3a,e] etc. were used as nucleophiles in this reaction.

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***3-Ethoxyacrolein***; ***3-Ethoxyacrylonitrile***; ***Ethoxymethylenemalonitrile***; ***Ethyl Cyanoacetate***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethyleneacetoacetate***.

---

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12. The photoinduced rearrangement or thermolysis of pyrazolines is used in the syntheses of cyclopropanes: see Ref. 2b, c.

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3-Ethyl-2-fluorobenzothiazolium Tetrafluoroborate[1]

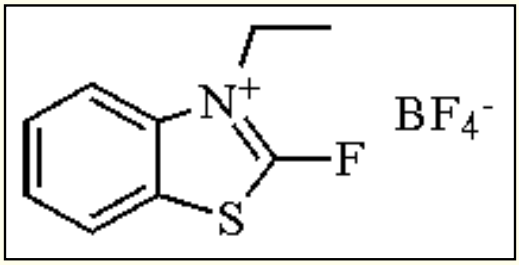

[60150-69-3] · $C_9H_9BF_5NS$ · 3-Ethyl-2-fluorobenzothiazolium Tetrafluoroborate · (MW 269.04)

(transformation of alcohols to alkyl halides;[2] optical inversion of secondary alcohols;[3] esterification of carboxylic acids;[4] cyclization of alcohols[5])

Solubility: insol CH_2Cl_2; reacts with alcohols.

Preparative Methods: treatment of 2-fluorobenzothiazole with Meerwein's reagent (***Triethyloxonium Tetrafluoroborate***).[1]

Handling, Storage, and Precautions: hygroscopic salt; handle cautiously, the toxicity of this reagent has not been reported.

Alkyl Halides.

2-Halobenzothiazolium salts react readily with alcohols to form an alkoxybenzothiazolium salt. This intermediate reacts with alkali metal halides to form alkyl halides in good yield (eq 1).[2]

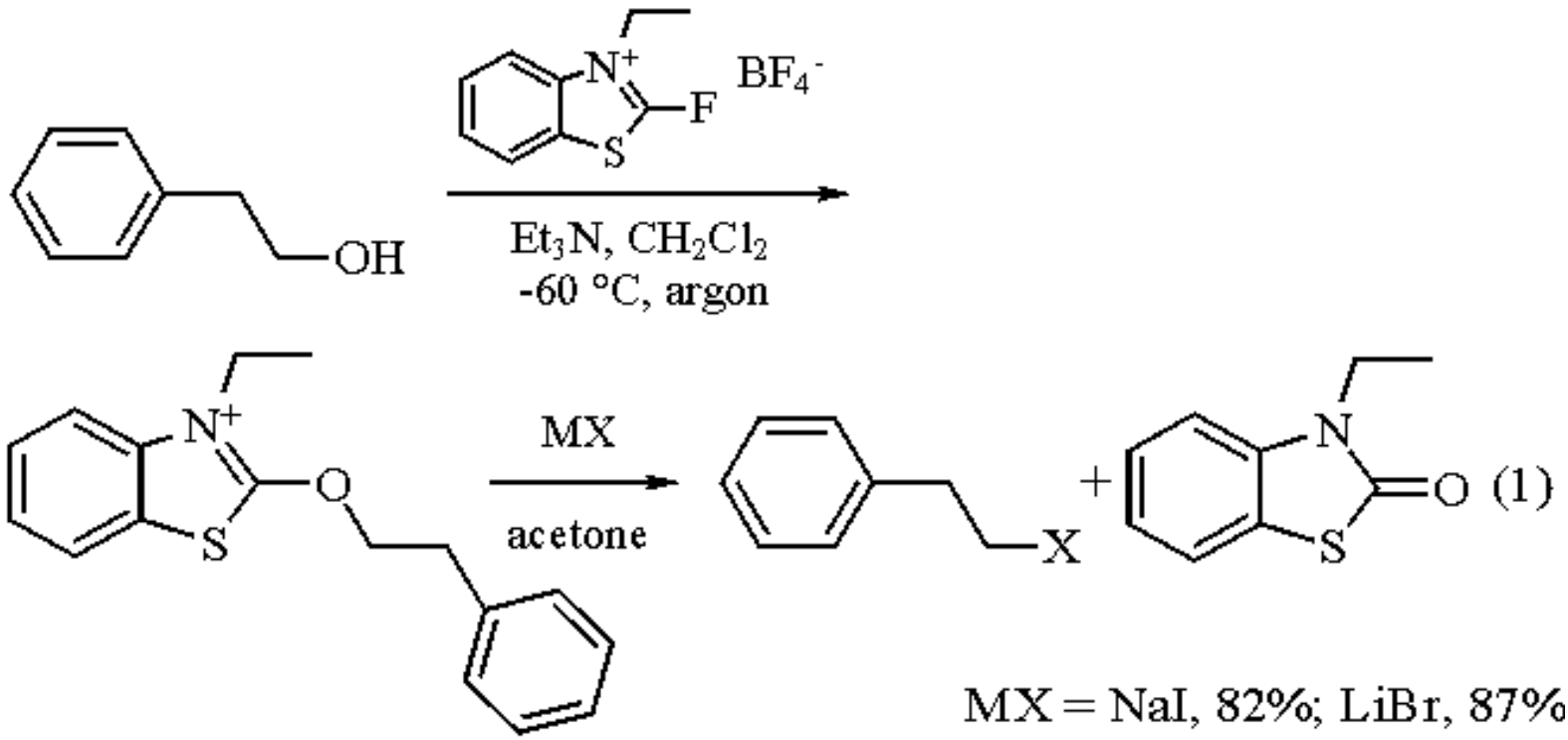

The general procedure is to suspend the benzothiazolium salt in CH_2Cl_2 and add the alcohol and ***Triethylamine*** dropwise. This is followed by addition of the alkali halide in acetone or DMF. Inverted alkyl halides are obtained with optically active secondary alcohols (eq 2).[2]

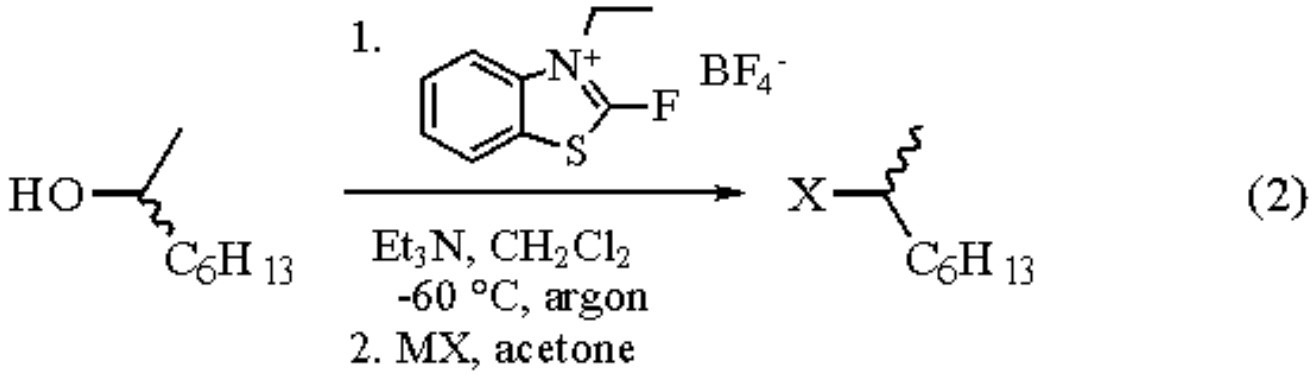

Alcohol config.	MX	Yield (%)
(*S*)	NaI	87 (*R*)
(*R*)	LiBr	64 (*S*)

There are a variety of ways to convert alcohols to halides. The most common is halogen acids HX or inorganic acid halides such as ***Thionyl Chloride***.[6] However, treatment of secondary alcohols with these reagents often gives rearranged products instead of the inverted alkyl halide.

A benzoxazolium salt (**1**) gives comparable yields with acyclic alcohols, and it gives good yields of the inverted halide

with cyclic alcohols (eq 3).[7] The benzothiazolium salt does not give satisfactory results for these types of alcohols (see also ***2-Chloro-3-ethylbenzoxazolium Tetrafluoroborate***).

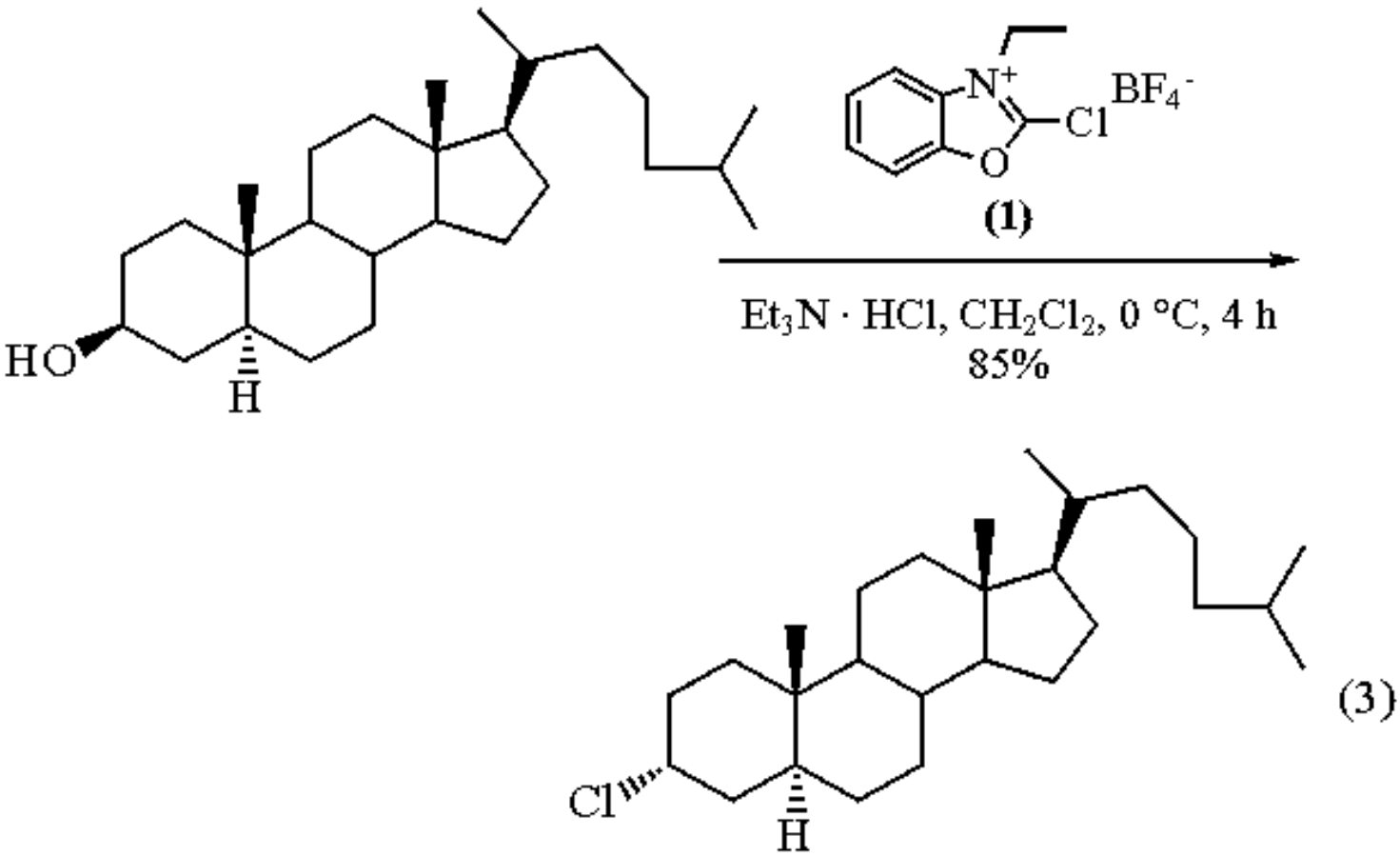

Inversion of Secondary Alcohols.

Reaction of alkoxybenzothiazolium salts with ***Trichloroacetic Acid*** gives esters with an inverted stereocenter. These are saponified under mild conditions to give the inverted secondary alcohol in good yield (eq 4).[3]

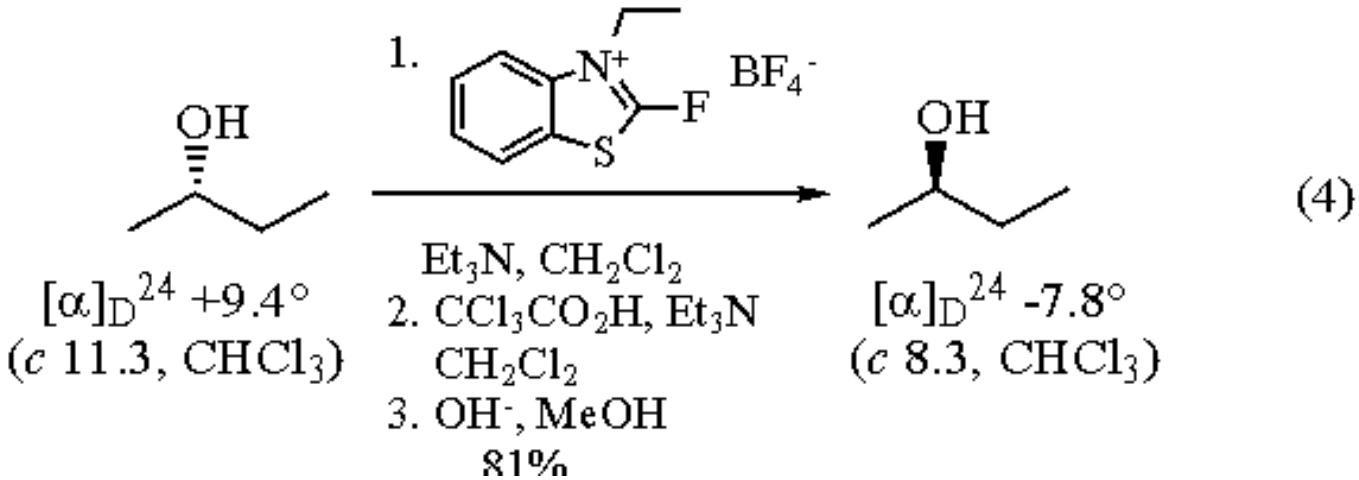

Another method often used for inverting secondary alcohols is the Mitsunobu reaction involving treatment of the alcohol with ***Triphenylphosphine*** and ***Diethyl Azodicarboxylate***.[8]

Ester Formation.

2-Halobenzothiazolium salts have been used to synthesize esters from carboxylic acids and alcohols (eq 5).[4] This is similar to (eq 4) except a more stable ester is formed when the trichloro substitution is avoided.

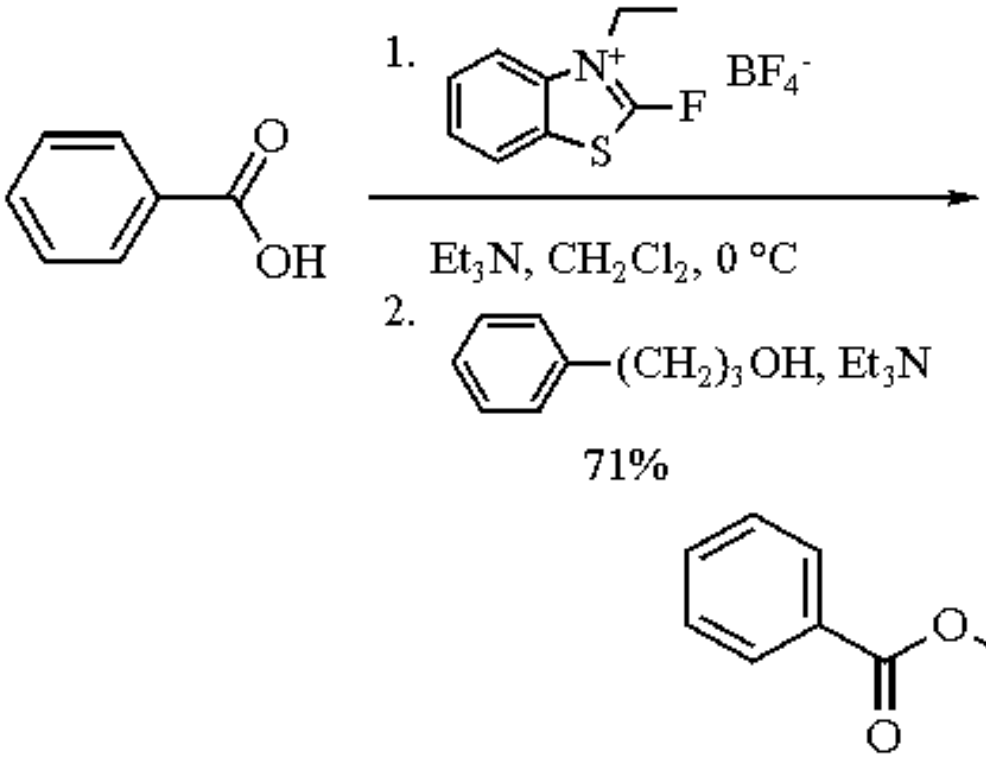

(5)

There are many useful reagents for synthesizing esters from carboxylic acids. Many of them are commercially available and are more practical than the benzothiazolium salts (see ***N,N´-Carbonyldiimidazole***, ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide***, ***1,3-Dicyclohexylcarbodiimide***, ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride***, and ***1,1´-Thionylimidazole***).

Cyclization of Alcohols.

A similar 2-fluorobenzothiazolium salt (**2**) has been used in the dehydrative cyclization of sesquiterpene alcohols (eq 6).[5]

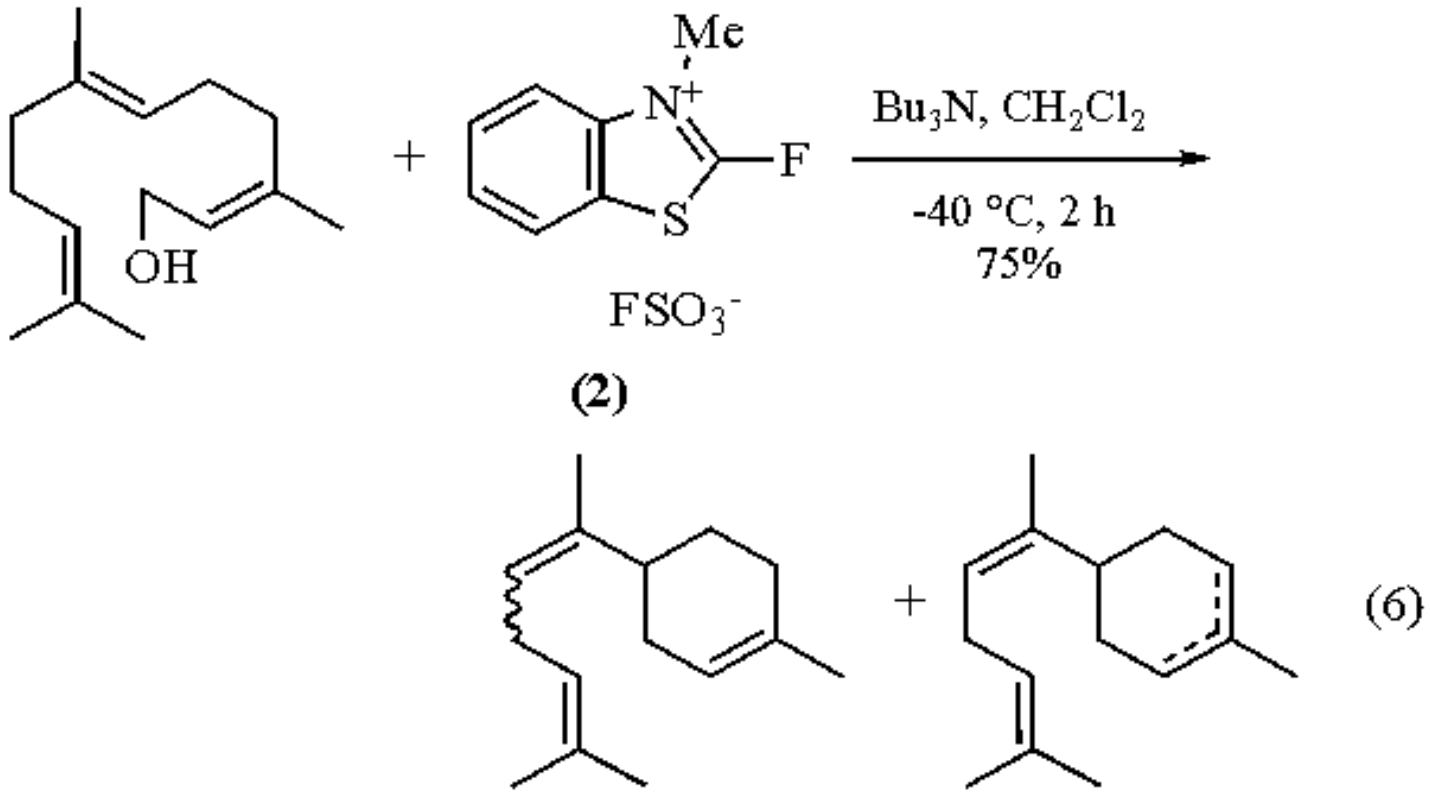

Presumably this would work similarly with the *N*-ethylbenzothiazolium salt. Yields of the desired products are lower when the reaction temperature is -78 °C. Compound (**2**) is the most effective reagent for this transformation. The benzoxazolium salt (**1**) gives about 45% of the desired products under similar conditions. The 2-fluoropyridinium salt (**3**) gives 58% of the desired products at -40 °C (see also ***2-Chloro-3-ethylbenzoxazolium Tetrafluoroborate***).

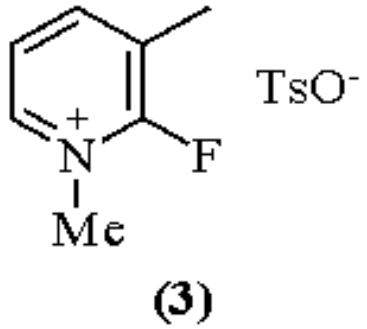

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Richard S. Pottorf

Ethyl Diethoxyacetate

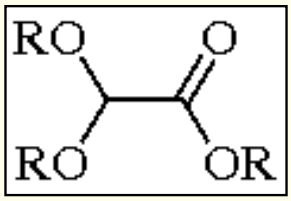

(R = Et)

[6065-82-3] · $C_8H_{16}O_4$ · Ethyl Diethoxyacetate · (MW 176.24) (R = Me)

[89-91-8] · $C_5H_{10}O_4$ · Methyl Dimethoxyacetate · (MW 134.15)

(lithium derivatives act as nucleophiles;[1-9] useful reagents for synthesis of heterocyclic compounds[1,3,10])

Alternate Name: ethyl glyoxylate diethyl acetal.

Physical Data: R = Et, bp 86-88 °C/16 mmHg; *d* 0.985 g cm^{-3}. R = Me, bp 67 °C/18 mmHg; *d* 1.096 g cm^{-3}.

Handling, Storage, and Precautions: these liquid compounds are moisture sensitive. They should be stored at low temperature.

Reaction of Lithium Derivatives.

A key step in a high yield total synthesis of (±)-4-isoavenaciolide is the conjugate addition of the lithium derivative of ethyl diethoxyacetate to a butenolide (eq 1).[1] Conjugate addition also occurs with 3-methoxy-2-cyclohexenone[2] and phenyl vinyl sulfoxide (eq 2).[3] However, reactions with α,β-enones mainly give the 1,2-addition products in many cases; exclusive conjugate addition is observed in the case of a 16-methylene-17-oxo steroid for steric reasons.[4] Obviously reactions with saturated ketones give the expected 1,2-adducts.[5,6]

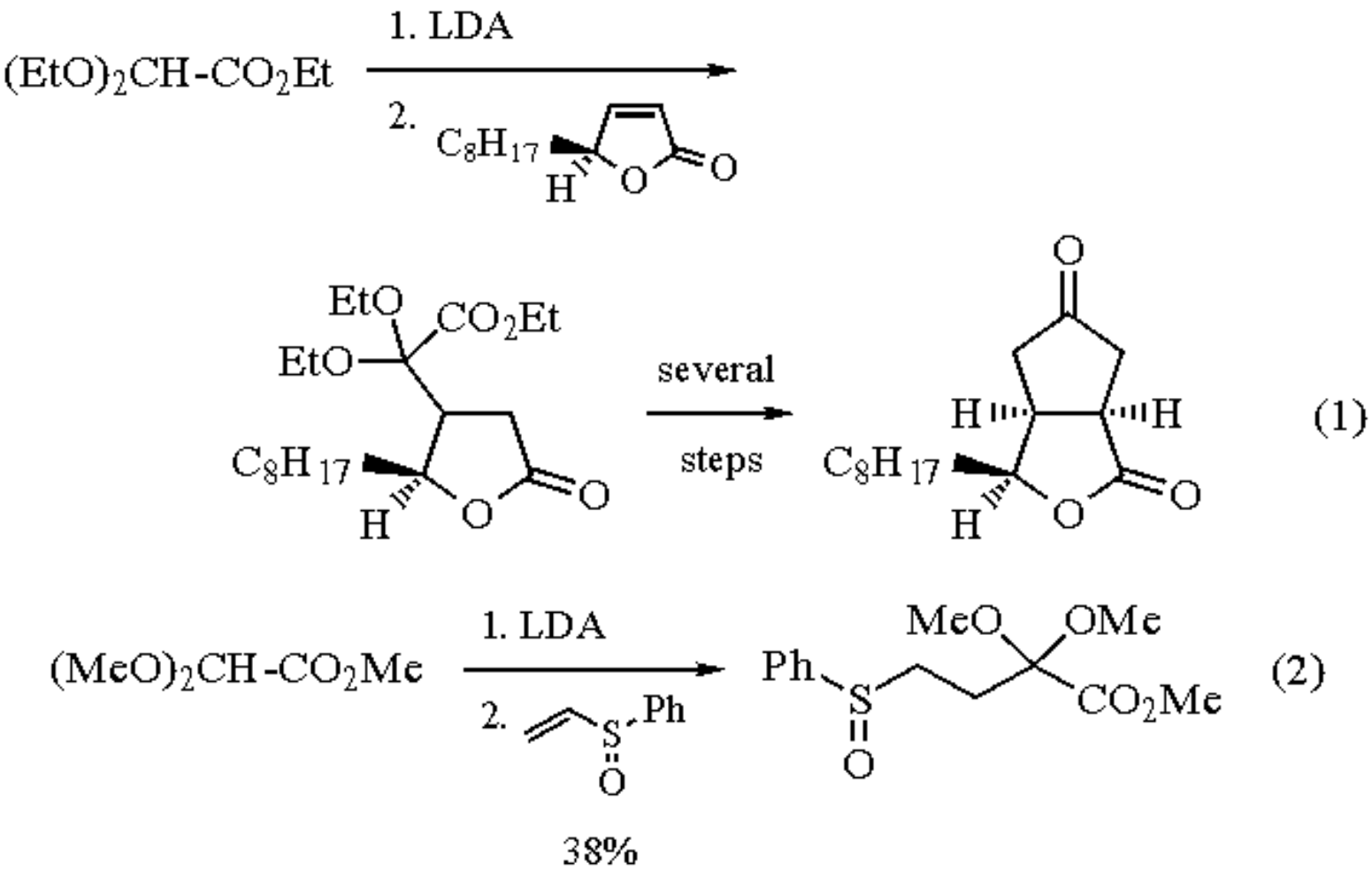

Alkylation with alkyl halides gives acetals of α-keto esters (eq 3).[7,8] The same reaction with 7-iodoheptanoic acid gives an intermediate for prostaglandins synthesis.[9]

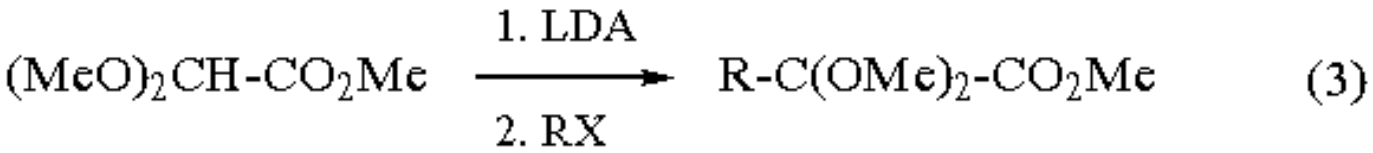

Synthesis of Heterocyclic Compounds.

Alkyl dialkoxyacetates are widely used in heterocyclic chemistry.[1,3,10] For instance, reaction of a lithium derivative with an α-iminocarbonyl compound gives the carbonyl addition product, precursor of 4-benzoyl-β-lactams (eq 4).[10a]

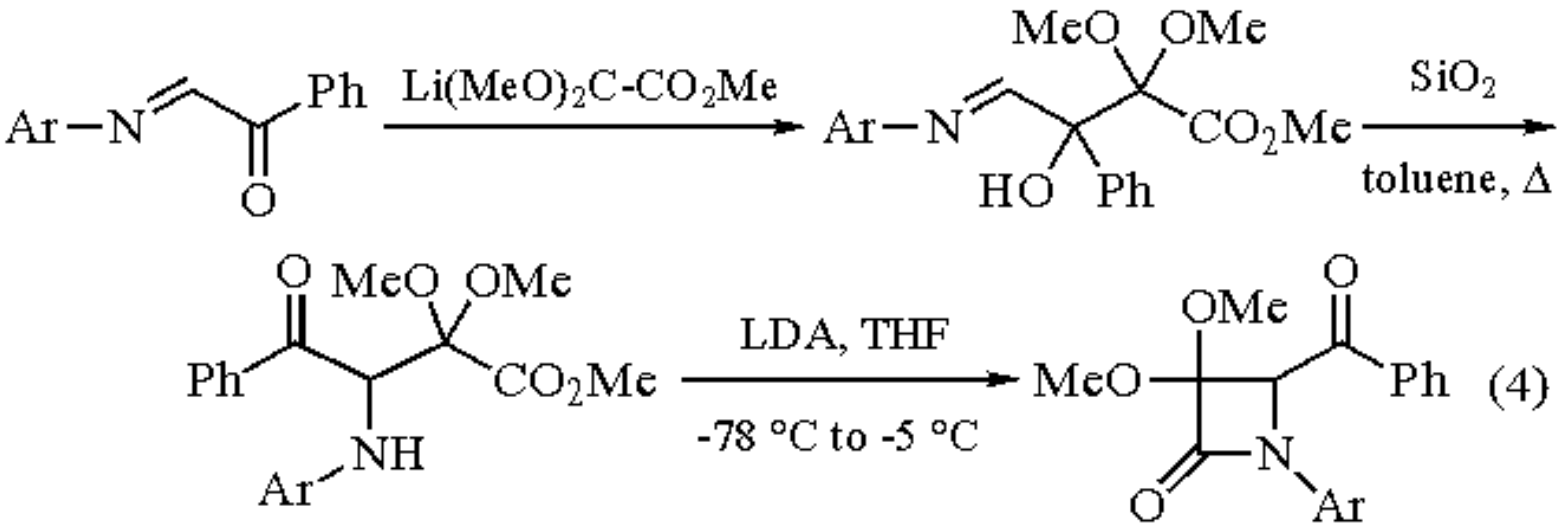

(4)

Substitution of a methoxy group of the acetal function of methyl dimethoxyacetate by a bromine using ***Triphenylphosphine Dibromide*** leads to an interesting reagent for synthesis of tetrahydroisoquinolines.[10b] Synthesis of 1*H*-1,2,4-triazole-3,5-dicarbaldehyde occurs according to eq 5.[10c]

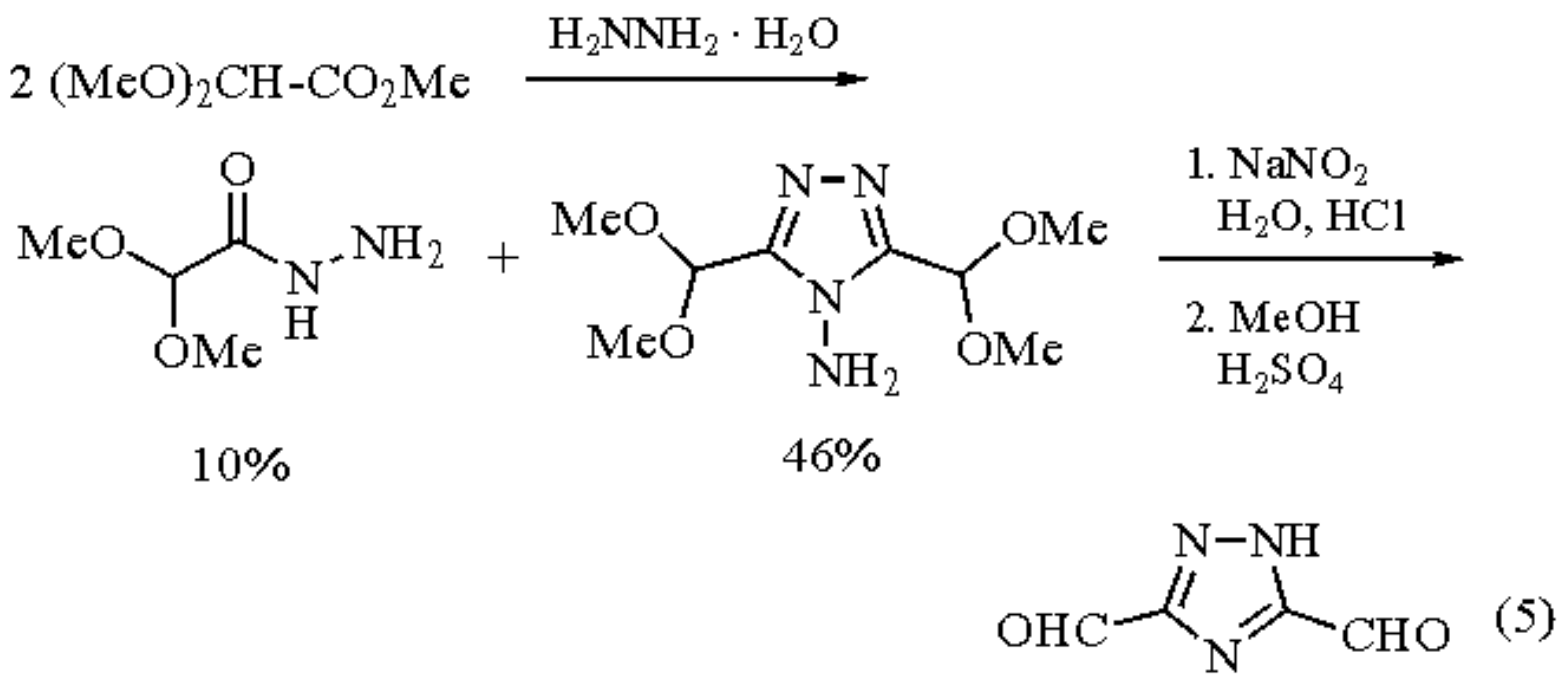

(5)

Reactions with Nucleophiles.

Tertiary alcohols are obtained by reactions with ***Ethynylmagnesium Bromide***[10d] and with ***Trimethylsilylmethylmagnesium Chloride*** and ***Cerium(III) Chloride***.[5] These alcohols are intermediates in syntheses of tin heterocycles[10d] and of 2-methylene-3-trimethylsilylpropionaldehyde (eq 6),[5] respectively. An organodimagnesium compound leads to the cyclic product (eq 7).[11]

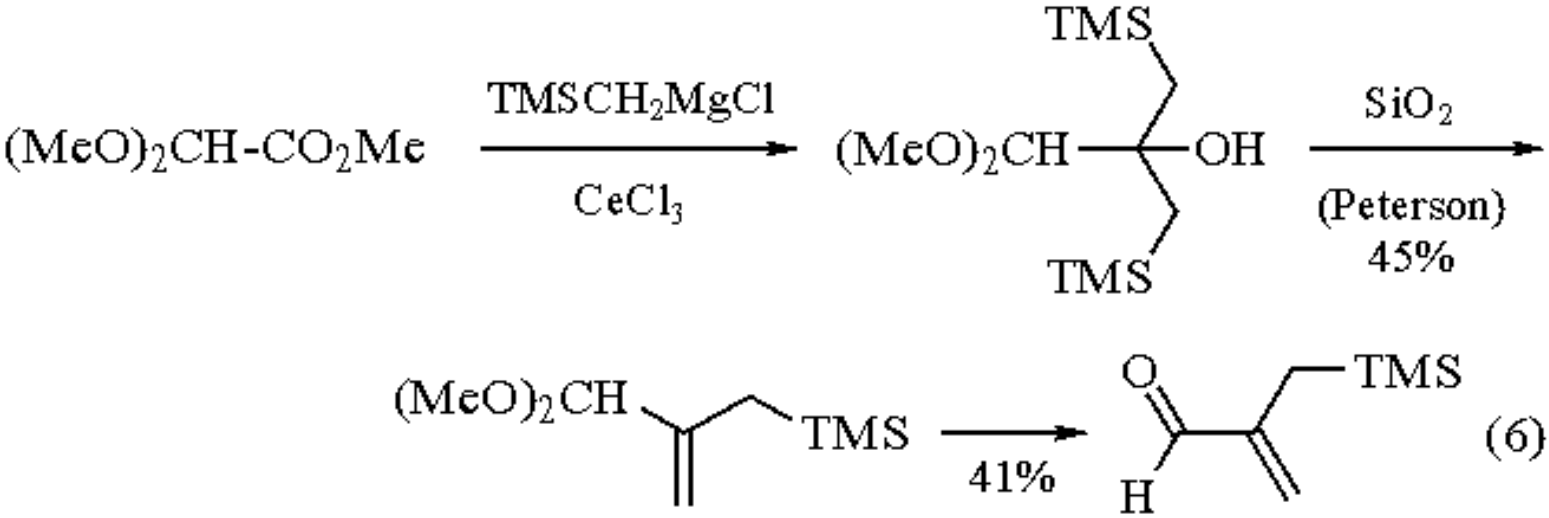

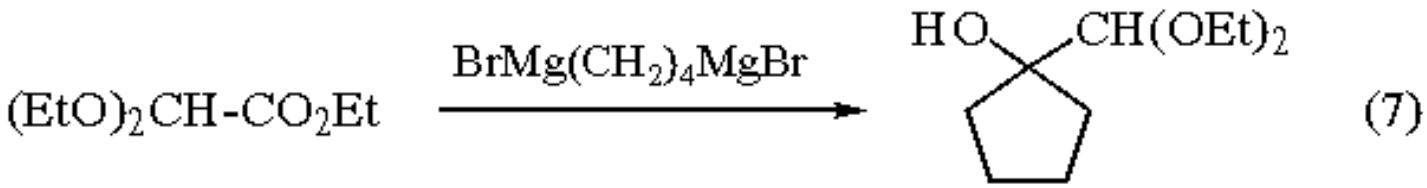

Ester[10f,12] or ketone[10e] enolates are also effective as nucleophiles in Claisen reactions. A similar result is obtained from dimsylsodium (eq 8).[13] However, ammonia gives an amide which leads to an interesting intermediate for synthesis of a polyheterocyclic antibiotic.[10g]

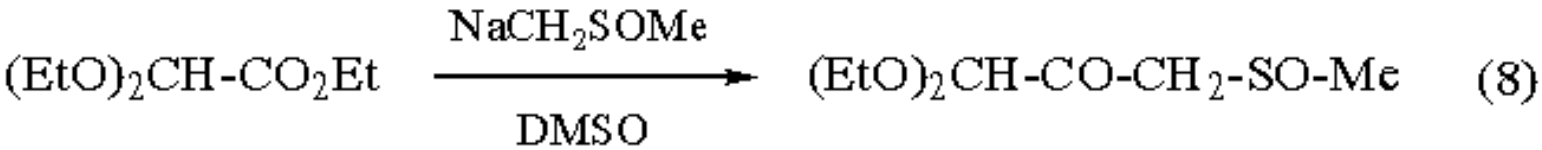

Preparation of Thioacetals.

Thioacetals are obtained by reaction with thiols[10i] or dithiols[14] which leads to a convenient synthesis of α-keto esters (eq 9).[14]

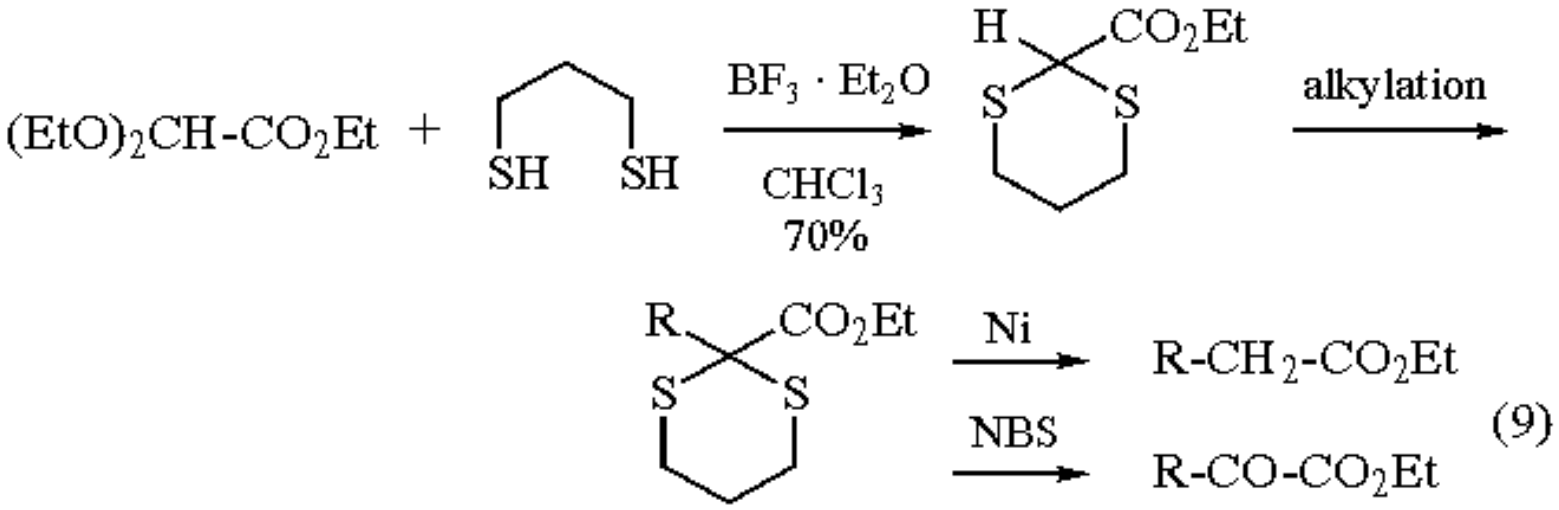

Reaction of Ylides.

Reaction with phosphonium ylides leads to other ylides which react with aldehydes and yield α,β-unsaturated carbonyl compounds (eq 10).[15]

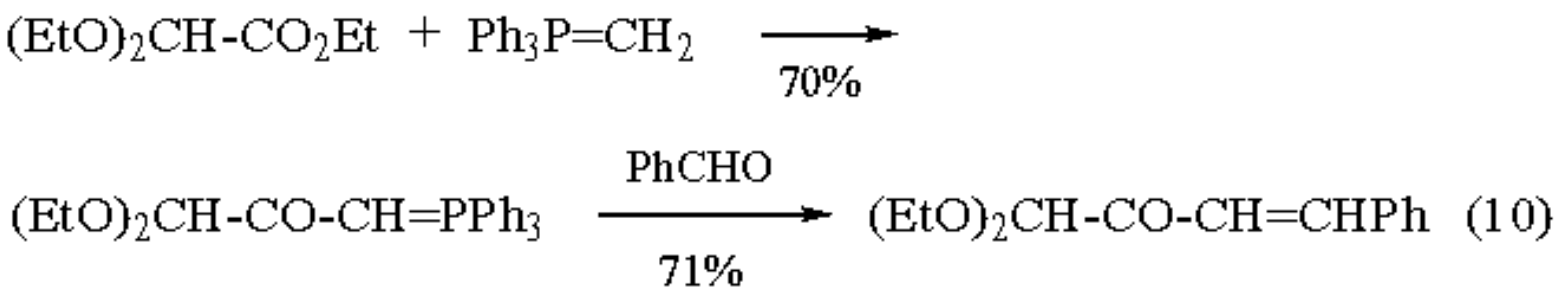

Formation of the Deacetalization Product.

Reactions with glyoxylic acid monohydrate lead to mixtures of hemiacetal and of alkyl glyoxylate hydrate. Dehydrations provide ethyl or methyl glyoxylate in a convenient way.[16]

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ethyl 3,3-Diethoxypropanoate***; ***Glyoxylic Acid Diethyl Dithioacetal***; ***Methyl Glyoxylate***.

---

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2-Ethyl-7-hydroxybenzisoxazolium Tetrafluoroborate

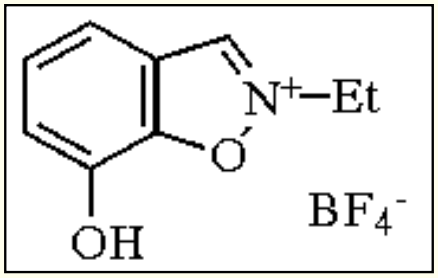

[16859-20-4] · $C_9H_{10}BF_4NO_2$ · 2-Ethyl-7-hydroxybenzisoxazolium Tetrafluoroborate · (MW 251.00)

(reagent for the formation of activated esters in peptide synthesis[1-3])

Physical Data: mp 137-138 °C.

Solubility: sol dipolar aprotic solvents and water.

Preparative Methods: from 2,3-dihydroxybenzaldehyde and ***Hydroxylamine-O-sulfonic Acid***, followed by treatment with ***Triethyloxonium Tetrafluoroborate*** (78% yield for the two steps).[1,3]

Handling, Storage, and Precautions: the salt is not hygroscopic or light sensitive but releases HF when exposed to moist air.

Peptide Synthesis.

The 2-ethylbenzisoxazolium cation has been studied as a peptide coupling reagent.[1] A reagent which reacted rapidly and efficiently with carboxylic acids to produce a stable but activated ester was required. This ester must then react efficiently with peptide amines without competitive hydrolysis or racemization. 2-Ethyl-7-hydroxybenzisoxazolium tetrafluoroborate was found to be the most satisfactory derivative to fulfill these criteria. Treatment of a peptide carboxylate salt with the title reagent in pyridine-water at pH 4.5-5.0 gives excellent yields of the ester product (eq 1) with a half life of the reaction of ca. 1-2 min. This ester is formed by attack at the iminium cation before migration of the acyl group to give the more stable *meta*-acyloxy substituted product containing a strong intramolecular hydrogen bond.

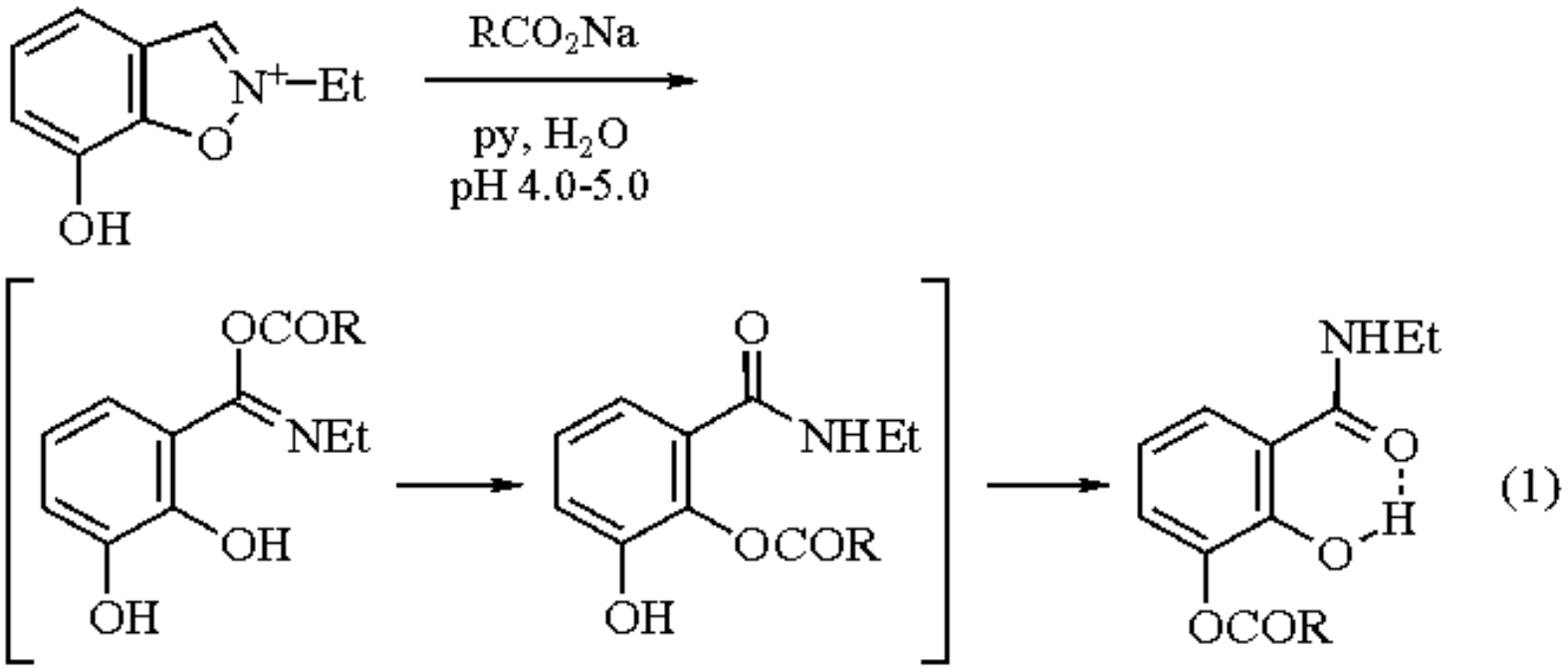

Coupling of the active ester with amines occurs rapidly in the presence of ***1,1,3,3-Tetramethylguanidine*** (TMG) (eq 2).[2] Racemization is minimized at 0-10 °C and above 0.05 M concentration. Reaction times for 90% reaction in DMSO at 22 °C range from 15 to 90 min. Hindered amino acids react more slowly, e.g. Val + Val having a reaction time of 4 h. Proline reacts very slowly (9 h for 90% completion with ZGly). A wide range of peptide couplings can be successfully achieved with the title reagent, which compares favorably with ***1-Hydroxybenzotriazole/1,3-Dicyclohexylcarbodiimide*** for peptide synthesis, particularly for the synthesis of small peptides.[3]

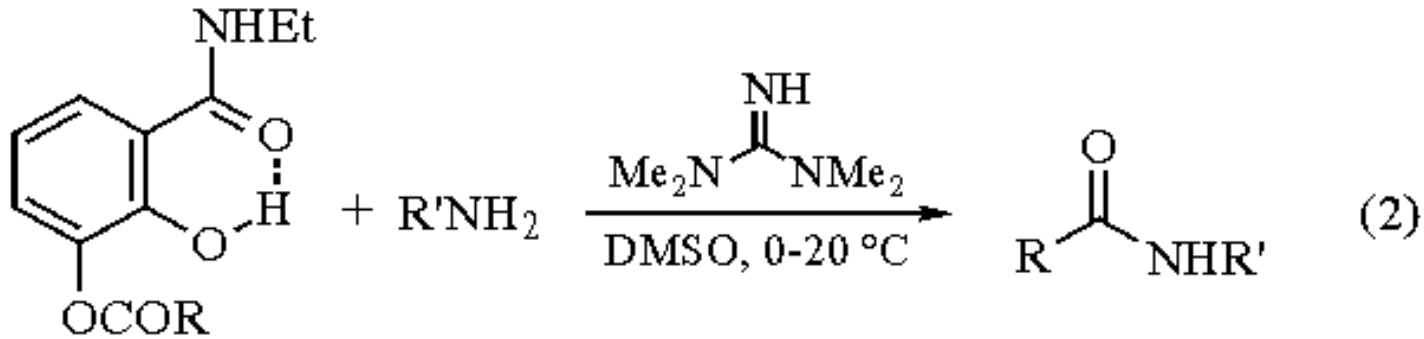

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University of Cambridge, UK

Ethyl 3-Hydroxybutanoate[1,2]

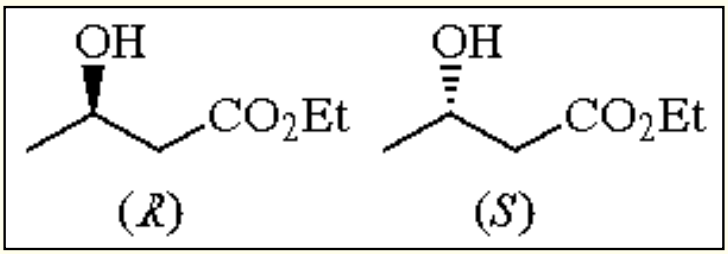

(*R*)

[24915-95-5] · $C_6H_{12}O_3$ · Ethyl 3-Hydroxybutanoate · (MW 132.18) (*S*)

[56816-01-4]

(chiral building block; stereoselective substitution of the dianion at C-2 by electrophiles[3])

Alternate Name: ethyl 3-hydroxybutyrate.

Physical Data: bp 71-73 °C/12 mmHg;[2] [α]20D +41.3° (*c* 1, $CHCl_3$) (97% ee);[4] [α]24D -43.6° (*c* 1.2, $CHCl_3$);[1] [α]24D -19.05° (neat) (100% ee).[1]

Solubility: sol common organic solvents such as ether, THF, *n*-hexane, CH_2Cl_2, EtOH, and also in water.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: NMR and optical rotation ($[\alpha]_D$).

Preparative Methods: reduction of ***Ethyl Acetoacetate*** with ***Baker's Yeast***[2,4-6] yields the (*S*)-(+) enantiomer; reduction with *Geotrichum candidum*[4,7] yields the (*R*)-(-) enantiomer. The (*R*)-(-) enantiomer was also prepared[1] by depolymerization of poly-(*R*)-3-hydroxybutyric acid (PHB). Both enantiomers can be prepared by chemical reduction using a ruthenium catalyst complexed with (*S*)- and (*R*)-BINAP, respectively.[8,9] The yeast reduction of ethyl acetoacetate has been varied: in petroleum ether (58%, 94% ee),[10] in the presence of ethyl chloroacetate (75%, 99% ee),[10,11] immobilized by magnesium alginate and under high concentration of Mg^{2+} ion (65%, 99% ee),[13] immobilized by calcium alginate in organic-water solvent system.[14]

Chemical reductions with ***Sodium Borohydride***-L-tartaric acid[15] ((*R*)-(-), 65%, 81% ee) and with a chiral oxazaphospholidine-borane complex[16] ((*R*)-(-), 80%, 99% ee) have been published.

Purification: the enrichment of the (*S*)-(+) enantiomer to 100% enantiomeric purity by means of the 3,5-

dinitrobenzoate has been described.[2,17]

Handling, Storage, and Precautions: should be stored in a refrigerator because of possible transesterification-oligomerization at room temperature.[2]

Dianion Alkylation.

β-Hydroxy carboxylates can be converted to their corresponding dianions through deprotonation of the hydroxy group and the α-carbon atom.[18,19] The so-formed double charged enolates are relatively stable species and can efficiently react with electrophiles in the α-position. The dianions of (3*R*)- and (3*S*)-ethyl 3-hydroxybutanoate were prepared[3,20] by lithiation with 2 equiv of ***Lithium Diisopropylamide*** in THF at -50 to -70 °C and 1 equiv of an alkyl halide was added, often in the presence of HMPA at -75 to 0 °C. The usual yield is 70-90%, and the stereoselectivity is generally better than 95:5 in favor of the *anti* isomer (eq 1).

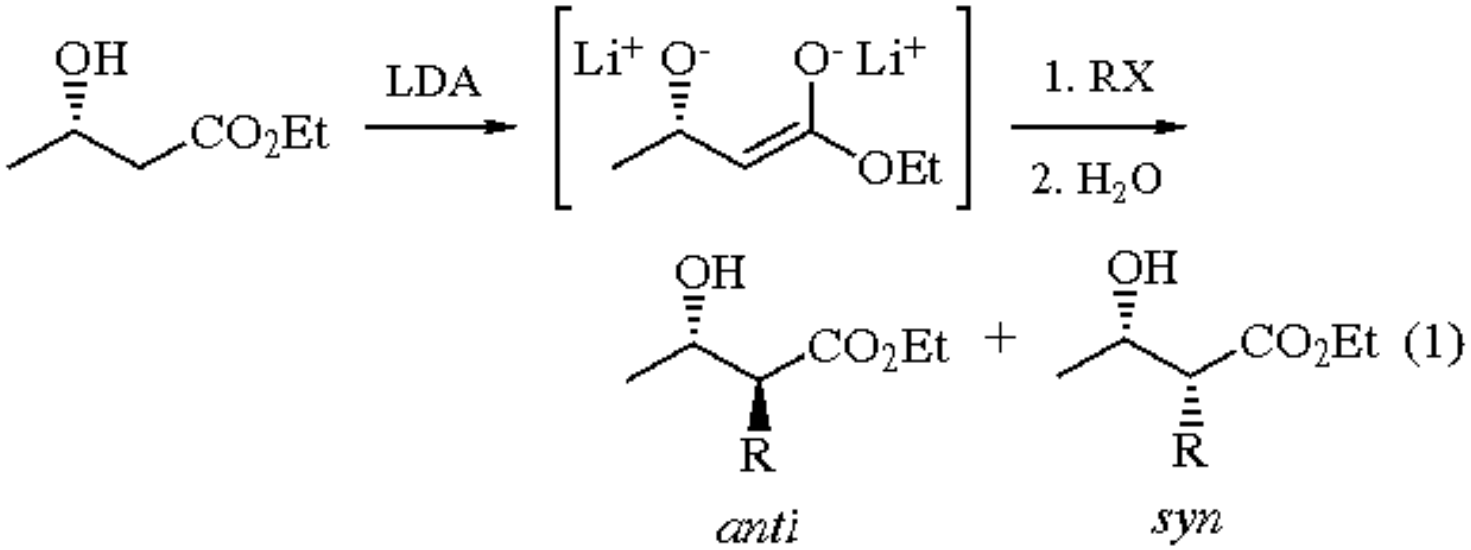

Alkylations with ***Iodomethane***,[3,21-24] ***Allyl Bromide***,[3,20] ***Benzyl Bromide***,[3] *n*-butyl bromide,[20] dimethylallyl bromide,[25] ***Benzyl Chloromethyl Ether***,[26,27] (*S*)-2-methylbutyl iodide,[29] and (benzene)$Mn(CO)_3^+PF_6^-$ [29] have been reported.

The mechanistic explanation for the ~20:1 stereoselection is the formation of a chelate as depicted in (**1**), where the approach of the electrophile is more favorable *anti* to the sterically more demanding Me (or alkyl) group.

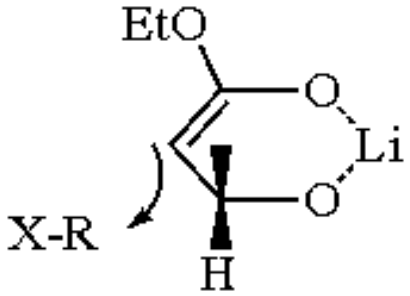

(1)

This method of dianion alkylation is an important and reliable preparative way to control the vicinal stereochemistry; the method is especially valuable, because both (*R*) and (*S*) starting materials are commercially available, although quite expensive, or may be easily prepared.

Dianion Amination.

The electrophilic amination has been carried out with the synthetic equivalent of [NH_2^+], i.e. ***Di-t-butyl Azodicarboxylate*** (TBAD) (eq 2).[30,31] The initially formed 94:6 mixture of the α-hydrazino-β-hydroxy ester was transformed into the α-amino-β-hydroxy derivative,[30] and was also used in the total synthesis of an amino sugar.[32]

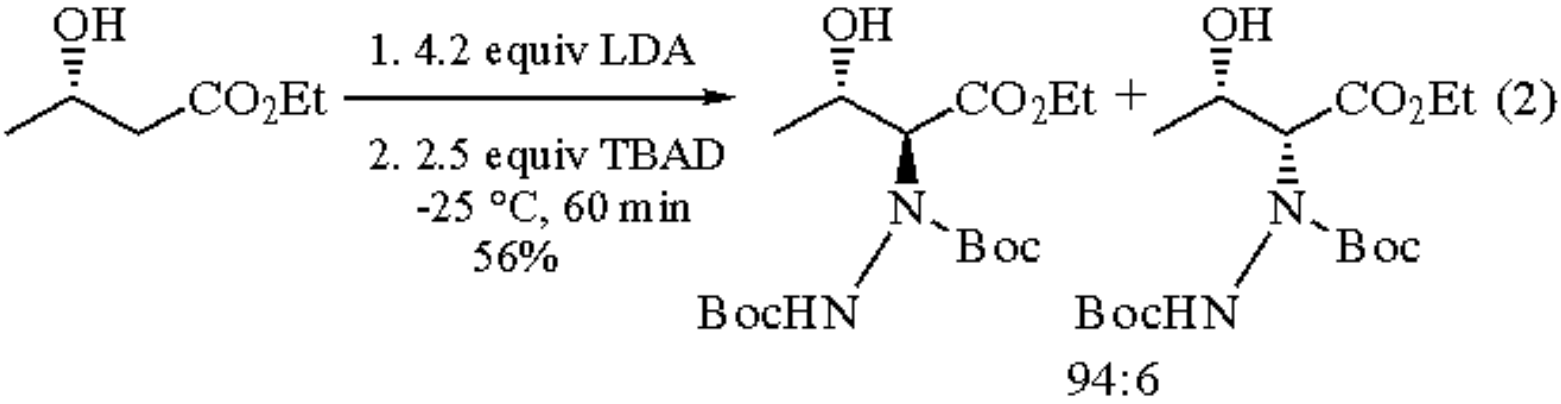

(2)

Reaction of the Dianion with Imines: Formation of β-Lactams.

The dianions of (*R*)- and (*S*)-ethyl 3-hydroxybutyrate have been added to different imines, yielding in one step the β-lactam, a precursor for, e.g. thienamycin (eq 3).[33-37]

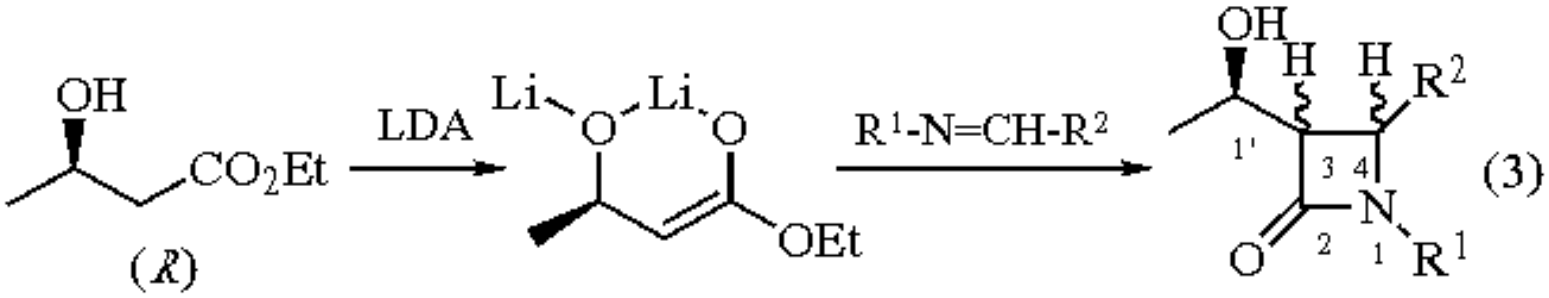

A very clean and highly stereoselective reaction has been achieved with the Zn/Li dianion and *N*-trimethylsilylphenylpropargylidene imine and the corresponding cinnamylidene imine (eq 4). Only one isomer was observed out of the four possible in yields of 85% and 78%, respectively.[38]

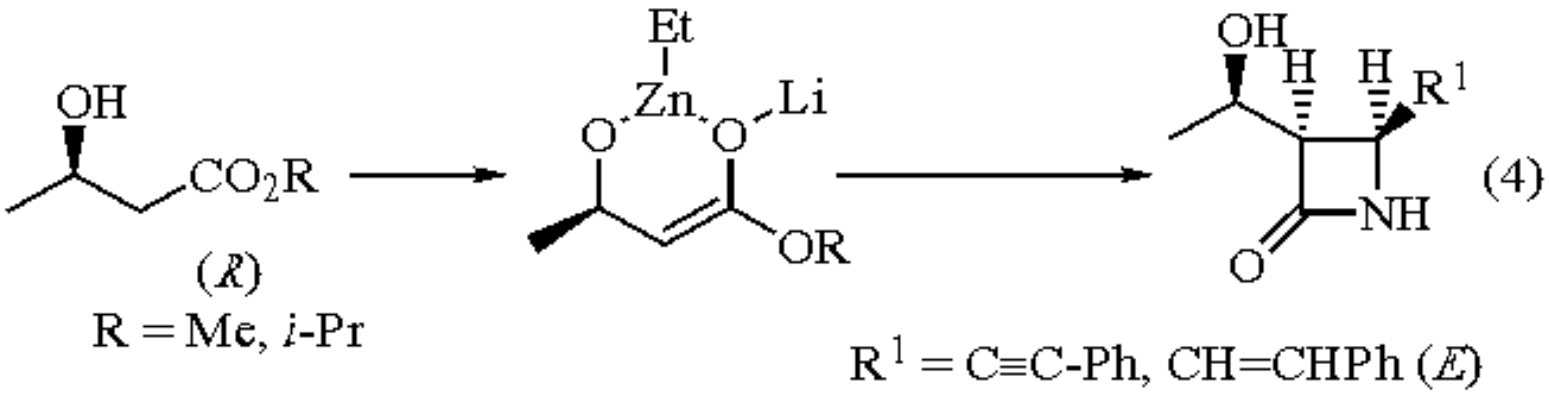

Other Esters and General Remarks.

The dianion chemistry of 3-hydroxy esters is of a very broad utility and synthetic importance.[39] Beside the cases above, a large variety of alkylations of 3-hydroxy ester dianions has been reported, e.g. (*S*)-dialkyl 2-hydroxysuccinate (malate)[40-42] and other examples.[3,43-45] It is of major importance to realize that a second alkylation allows the enantioselective preparation of a quaternary carbon center.[3,20,46-48] This is obviously also the case when cyclic analogs, such as (1*R*,2*S*)-ethyl 2-hydroxycyclohexanecarboxylates (eq 5), 95:5 de),[49] are alkylated by means of the dianion.[49-51]

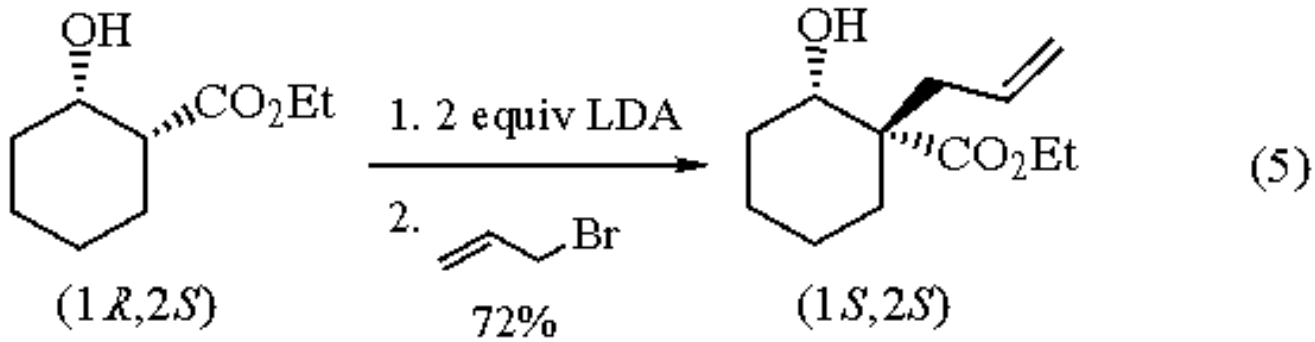

Related Reagents.

(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one; ***Di-t-butyl Azodicarboxylate***; ***Ethyl Acetoacetate***.

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Ethyl α-(Hydroxymethyl)acrylate[1]

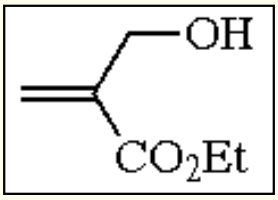

[10029-04-6] · $C_6H_{10}O_3$ · Ethyl α-(Hydroxymethyl)acrylate · (MW 130.16)

(important source of functionalized acrylic monomers for polymerization and copolymerization; intermediate in the preparation of α-(halomethyl)acrylates, methacrylates, and α-methylene lactones; powerful polyfunctional Michael acceptor)

Physical Data: bp 65-70 °C/1 mmHg; *n*20D = 1.4494.

Solubility: sol H_2O, ether, acetone, alcohol, THF, chloroform.

Preparative Methods: by hydroxymethylation of ***Ethyl Acrylate*** with aqueous ***Formaldehyde*** solution in the presence of tertiary amines (***Triethylamine***, ***1,4-Diazabicyclo[2.2.2]octane***),[3] under microwave radiation,[4] or by the Wittig-Horner reaction of ***Triethyl Phosphonoacetate*** with formaldehyde in the presence of aqueous ***Potassium Carbonate*** (eq 1).[5,6] Many side reactions have been found to occur with the first method and the mechanism involving the formation of ethers has been elucidated.[7] Carbonylation of propargyl alcohol to produce this reagent has also been described.[8]

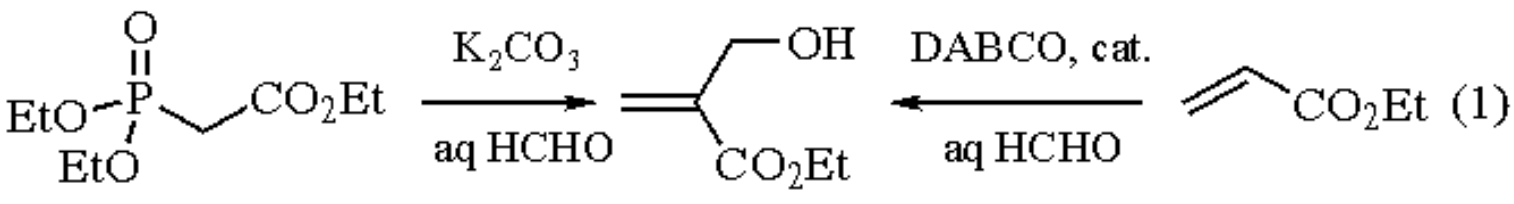

Purification: by distillation at reduced pressure.

Analysis of Reagent Purity: by GLC analysis (e.g. 2 m silica capillary OV-1 column); ^{1}H NMR (CCl_4) 4.20 (2H), 5.80 and 6.15 (2H); ^{13}C NMR ($CDCl_3$) 60.9, 124.8, 140.2, and 166.5.

Handling, Storage, and Precautions: is lachrymatory, vesicatory, and toxic.[2] This reagent should be handled with gloves in a well ventilated hood. Storage at 0 °C in the dark is recommended.

Preparation of Polymers.

Ethyl α-(hydroxymethyl)acrylate has been fully studied for polymerization as the pure compound,[9,10] as its derivatives (chloride,[11] trityl,[12] acetoxy,[13] disilyloxy[14]), as difunctional and multifunctional monomers capable of cyclopolymerization[15] and copolymerization with 2-vinyl-4,4-dimethylazlactone,[16] or as crosslinking agents with biepoxides.[17] It has found employment for the impregnation and in-situ polymerization in the manufacture of wood-polymer composites.[18]

Preparation of α-(Halomethyl)acrylates.

The corresponding bromide and chloride[11] have been prepared by reaction of ethyl α-(hydroxymethyl)acrylate with ***Phosphorus(III) Bromide*** and ***Thionyl Chloride***,[5] while the fluoride and iodide have been obtained by halogen exchange.[5]

Synthesis of Methacrylates and α-Methylene-γ-lactones.

α-(Hydroxymethyl)acrylate can act as a Michael acceptor and, in this way, it can add magnesium organocuprates without subsequent elimination giving rise to α-(hydroxymethyl)alkanoic esters (eq 2). In contrast, reaction of the acetoxy derivative with Grignard reagents in the presence of a catalytic amount of Cu^{I} salt leads to the formation of α-substituted acrylic esters (eq 3).[19]

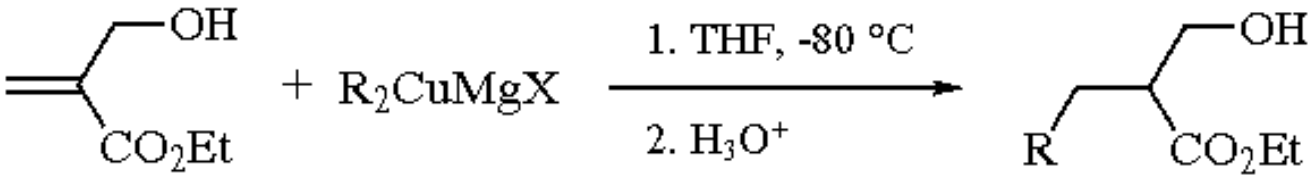

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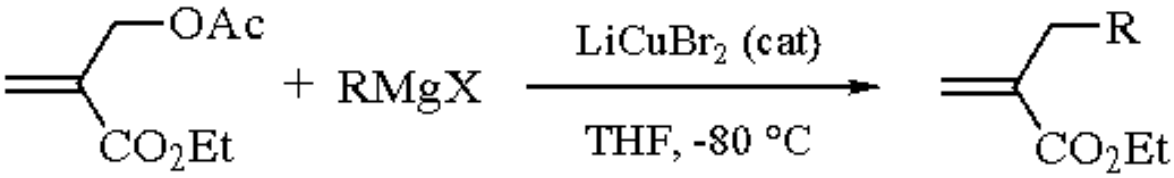

(3)

Palladium-catalyzed hydroxyalkylation of aldehydes and cyclohexanone by α-(hydroxymethyl)acrylate derivatives in the presence of ***Tin(II) Chloride*** and ***1,3-Dimethyl-2-imidazolidinone*** (DMI/H_2O) was shown to be a new route to α-methylene-γ-butyrolactones (eq 4).[20]

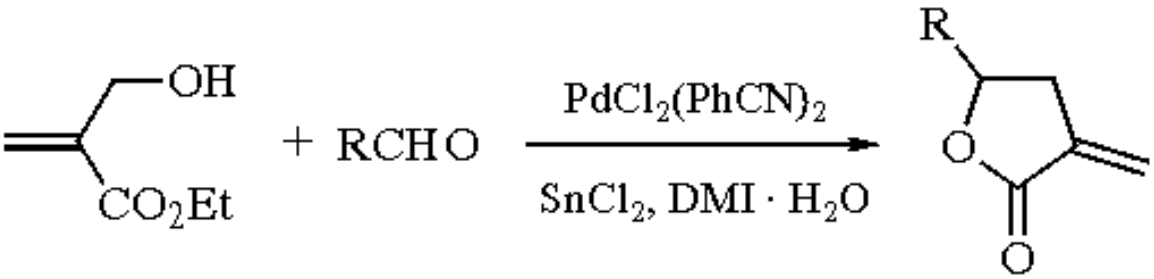

(4)

A new synthesis of α-(1-hydroxyalkyl)-β-lactams[21] by addition of primary amines to ethyl α-(hydroxymethyl)acrylate has been recently proposed (eq 5).

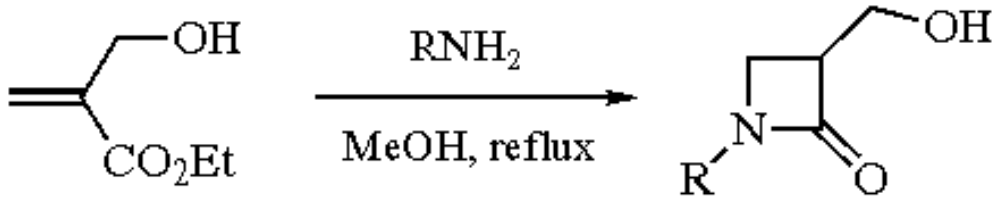

(5)

Bromine addition-dehydrobromination on ethyl α-(hydroxymethyl)acrylate resulted in the formation of α-(bromomethyl)glycidic ester (eq 6).[22]

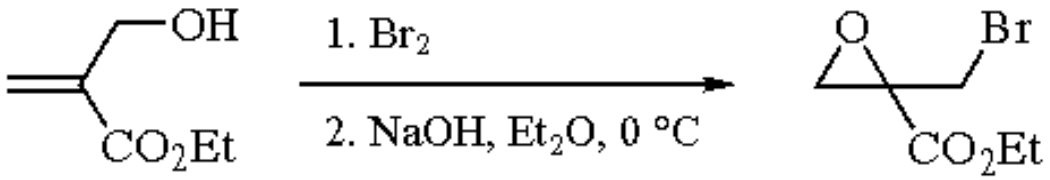

(6)

Ethyl α-(hydroxymethyl)acrylate was also employed as allyloxycarbonyl protecting group for amino acids in peptide synthesis[23] and used as an intermediate in the total synthesis of (±)-heptelidic acid.[24]

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Ethyl Hydroxymethyleneacetate, Sodium Salt

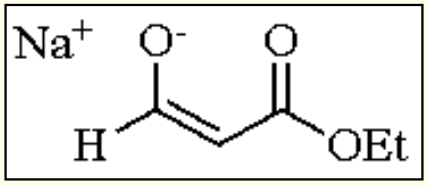

[58986-28-0] · $C_5H_7NaO_3$ · Ethyl Hydroxymethyleneacetate, Sodium Salt · (MW 138.11)

(a three-carbon β-dicarbonyl building block)

Alternate Name: ethyl formylacetate, sodium salt.

Solubility: sol H_2O and protic solvent; insol THF.

Preparative Methods: the material is usually prepared by the condensation of ethyl acetate and ethyl formate in the presence of a strong base such as ***Sodium Hydride***, sodium alkoxide, or ***Sodium*** metal (eq 1).[2-6]

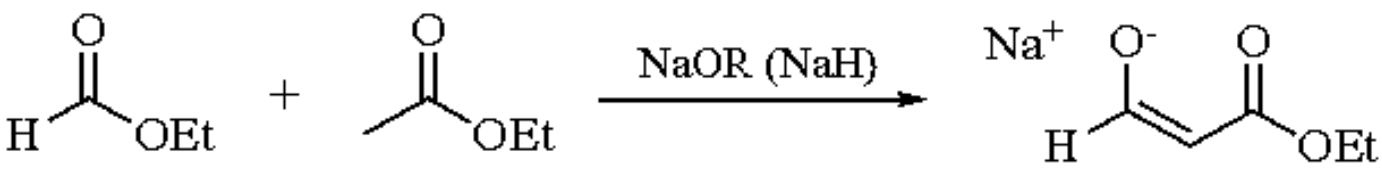

(1)

The condensation is accompanied by side reactions, and the white solid obtained is generally about 70% pure. Preparation under carbon monoxide pressure has been suggested to improve the yield and purity.[6] The compound has also been prepared by the careful hydrolysis of ethyl β-chloroacrylate.[7] The free acid (malonic semialdehyde) is easily oxidized in air,[1] and the various parent esters[8-10] are all subject to polymerization, although the *t*-butyl ester can be stored at -80 °C without deterioration for a month.[10a]

Handling, Storage, and Precautions: salts and free acid have limited stability[1] and should be prepared as needed; use in a fume hood.

Synthons.

Because the parent compound and its salts are unstable, a number of synthons have been prepared and investigated. As suggested in the references above, the various esters increase in stability as the bulk of the alkyl group increases. The enolate salt has been trapped as ethyl β-trimethylsilyloxyacrylate[11] and further elaborated as an equivalent of the sodium enolate. In similar manner, benzhydryl *N*-benzylaminoacrylate[12] has been used in reactions typical of the enolate salt.

Reactions.

Perhaps the most frequent use of ethyl hydroxymethyleneacetate is for the preparation of various 4-pyrimidinols, wherein the reagent provides the three-carbon piece in the principal synthesis of pyrimidines (eq 2).[6,13]

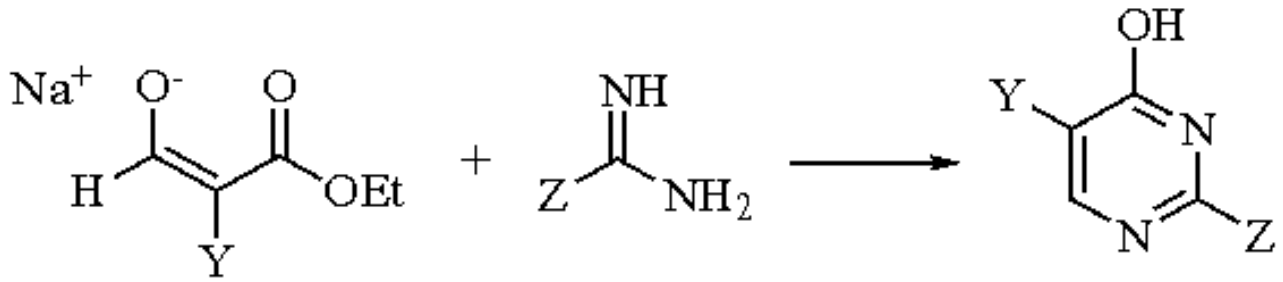

(2)

Y = H, R, OR, NR_2; Z = H, R, Ar, NR_2, OR, SR

The enolate has been used for the synthesis of variously β-substituted acrylates (**1**)[11,14,15] which have applications as stable synthons of the enolate. They have also served as dienophiles in electrocyclic reactions.[14]

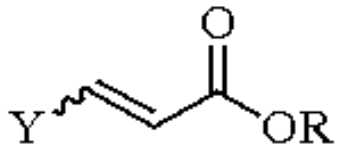

(1)

Y = OTMS, OAc, NR_2

1,1-Dialkylhydrazines yield the corresponding hydrazones.[16] The enolate can be alkylated on the central carbon to provide useful substituted building blocks. Condensation with acetone provides 4*H*-1,3-dioxin-4-ones, which have been brominated on C-6 (eq 3).[9] Xanthate formation on the central carbon provides an entry to 5-thiopyrazoles (eq 4).[17]

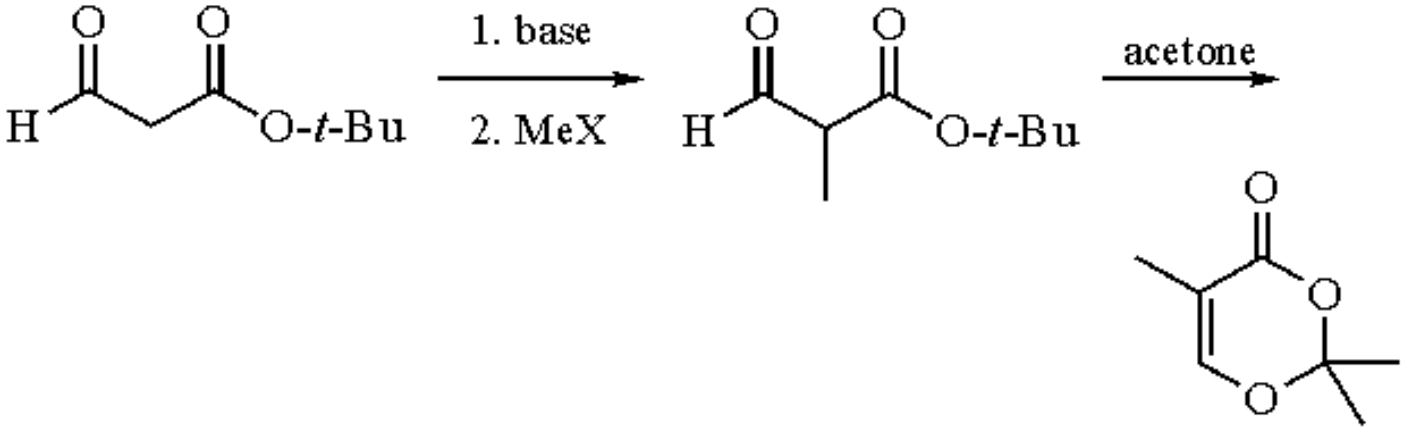

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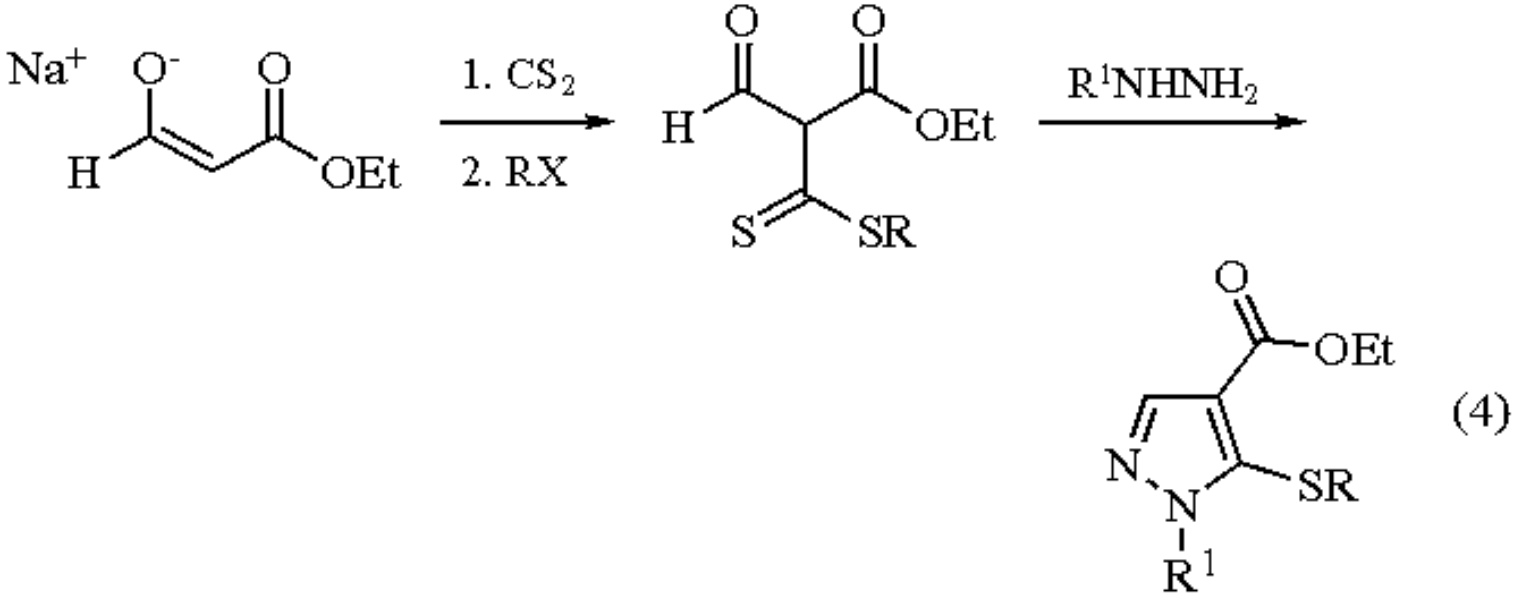

Reaction of substituted *t*-butyl esters with cysteine or penicillamine esters proceeds to thiazolidinylacetate esters. Subsequent Mukaiyama-Ohno cyclization diastereoselectively provides penam-3-carboxylic acid derivatives (eq 5)[8a,b] Oxapenams have been similarly prepared.[12]

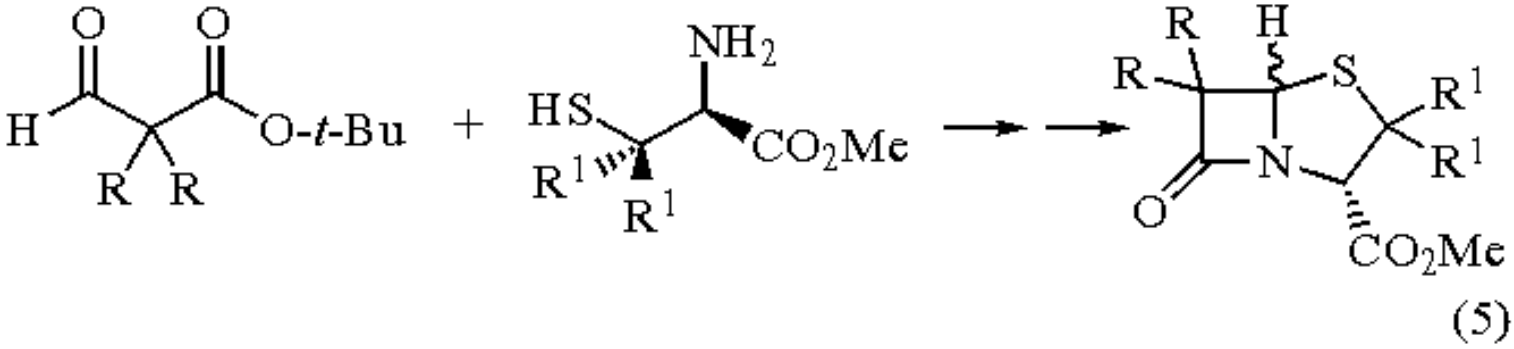

Related Reagents.

Diethyl Ethoxymethylenemalonate; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Ethoxymethyleneacetoacetate***; ***Malondialdehyde***; ***Methyl Diformylacetate***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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Ethyl Iodide[1]

[75-03-6] · C_2H_5I · Ethyl Iodide · (MW 155.97)

(esterification of carboxylic acids;[1] alkylation of amines,[6,8] alkoxides, thiolates[9] and enolates;[17,21] preparation of Grignard reagents[22])

Alternate Name: iodoethane.

Physical Data: mp -108 °C; bp 70-73 °C, *d* 1.941 g cm^{-3}.

Solubility: sol water (with decomposition), alcohol, most organic solvents.

Form Supplied in: heavy, clear, very refractive liquid; colorless when pure, becomes red on exposure to light and air due to iodine liberation; common impurities are ethanol and iodine.

Preparative Methods: prepared by reaction of ethanol and iodine in the presence of red phosphorus.

Purification: purified by shaking with dilute solution of sodium bisulfite or sodium thiosulfate until colorless; wash with water, dry ($CaCl_2$), and distill. May also be purified by passing through a column of silica gel or alumina followed by distillation.

Handling, Storage, and Precautions: store colorless solution over silver leaf or copper wire in brown bottle away from light. Avoid storing over mercury as ethylmercury(II) iodide, the byproduct of decomposition, is extremely poisonous. Harmful if swallowed, inhaled, or absorbed through the skin. Extremely harmful to mucous membranes, upper respiratory tract, eyes, and skin. Exposure can cause spasms, inflammation of contact area, coughing, nausea, and vomiting. Use in a fume hood.

Esterifications.

Ethyl iodide has seen widespread use as a reagent for conversion of carboxylic acids to ethyl esters.[1] The procedure involves treatment of a carboxylic acid with base followed by addition of ethyl iodide. The method is particularly useful with substrates containing acid-sensitive protecting groups. Conditions are varied: HMPA/NaOH (yields >95%),[2] DMSO/KOH (>90%),[3] $NaHCO_3$/DMF (>95%),[4] CsF/DMSO or DMF (92-100%).[5] The latter method was particularly useful in the direct conversion of organotin carboxylates, commonly employed to protect carboxylic acids in the presence of amines in peptide synthesis, to esters. The conversion proceeds in excellent yields (85-91%) at mild

temperatures with no racemization (eq 1).

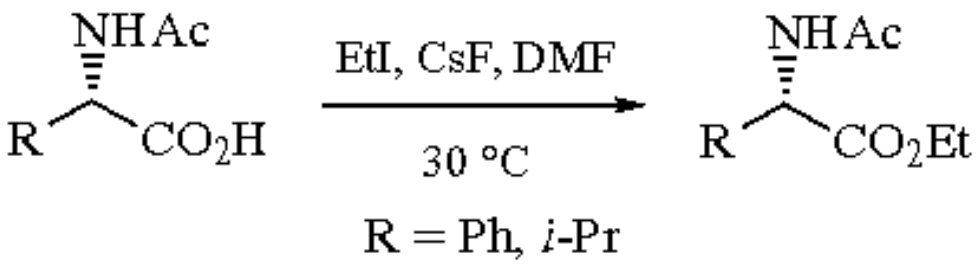

(1)

Heteroatom Alkylation.

Various heteroatoms react with ethyl iodide. *N*-Ethylamines, hydrazines,[6] and amides have been prepared. Secondary *N*-ethylamines were prepared by Katritzky et al. in 55-65% yield via the reaction of (**1**) with ethyl iodide followed by treatment with NaOH/H_2O (eq 2).[7]

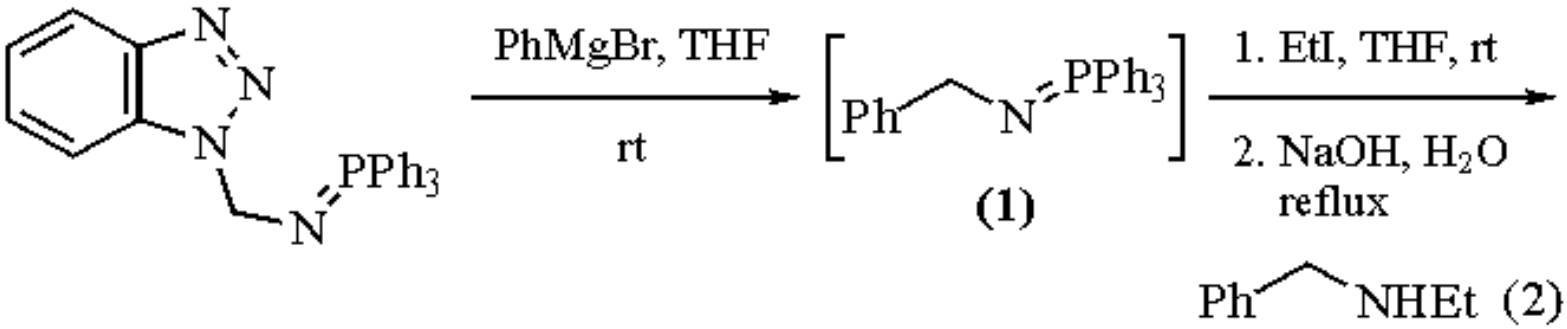

(2)

Pyrroles were *N*-ethylated (DMSO, KOH, 60% yield) during the synthesis of novel 2-azafulvenes.[8]

In a related reaction, thioethers were prepared in the presence of a Pt^{II} catalyst in 80-90% yield.[9] This reaction was developed as an alternative to the more traditional method demonstrated by Ono (DBU/benzene).[10] In a similar fashion, alcohols can be converted to the corresponding ethyl ethers.

C-Alkylations.

Alkylation of carbon nucleophiles with ethyl iodide is a convenient method for introducing an ethyl group at a carbon center. The substrates are treated with base (*t*-BuOK,[11] NaOEt,[12] *n*-BuLi,[13] NaHMDS,[14] LiHMDS,[15] LDA,[16] etc.) followed by quenching with ethyl iodide. The solvent is usually, but not limited to, THF or diethyl ether. Temperatures and reaction times vary depending on the specific substrate. Yields also vary but most appear to be good to excellent (>80%). A variety of compounds have been prepared including introduction of quaternary chiral centers at bridgehead positions (eq 3).[17]

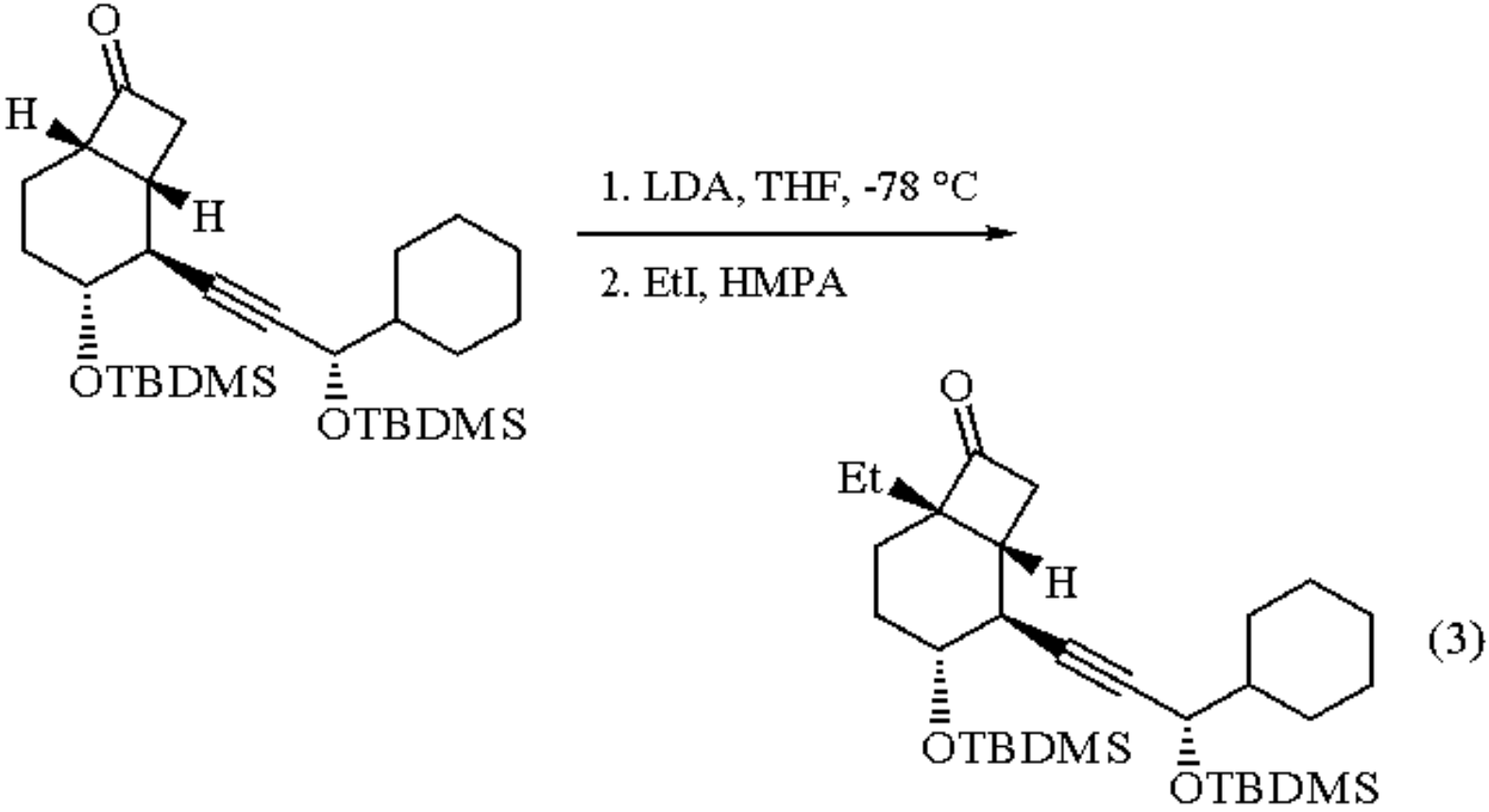

Asymmetric alkylation reactions have also taken advantage of the versatility of this reagent. Such chiral enolate systems as oxazolidinones,[18] dihydropyrimidinones,[19] camphorsulfonamides,[20] and chiral lactams[21] have been alkylated in high chemical and optical yields. Meyers et al. utilized chiral lactams in a general preparation of cyclohexenones bearing a tertiary or quaternary chiral center at the C-4 position (eq 4).[21]

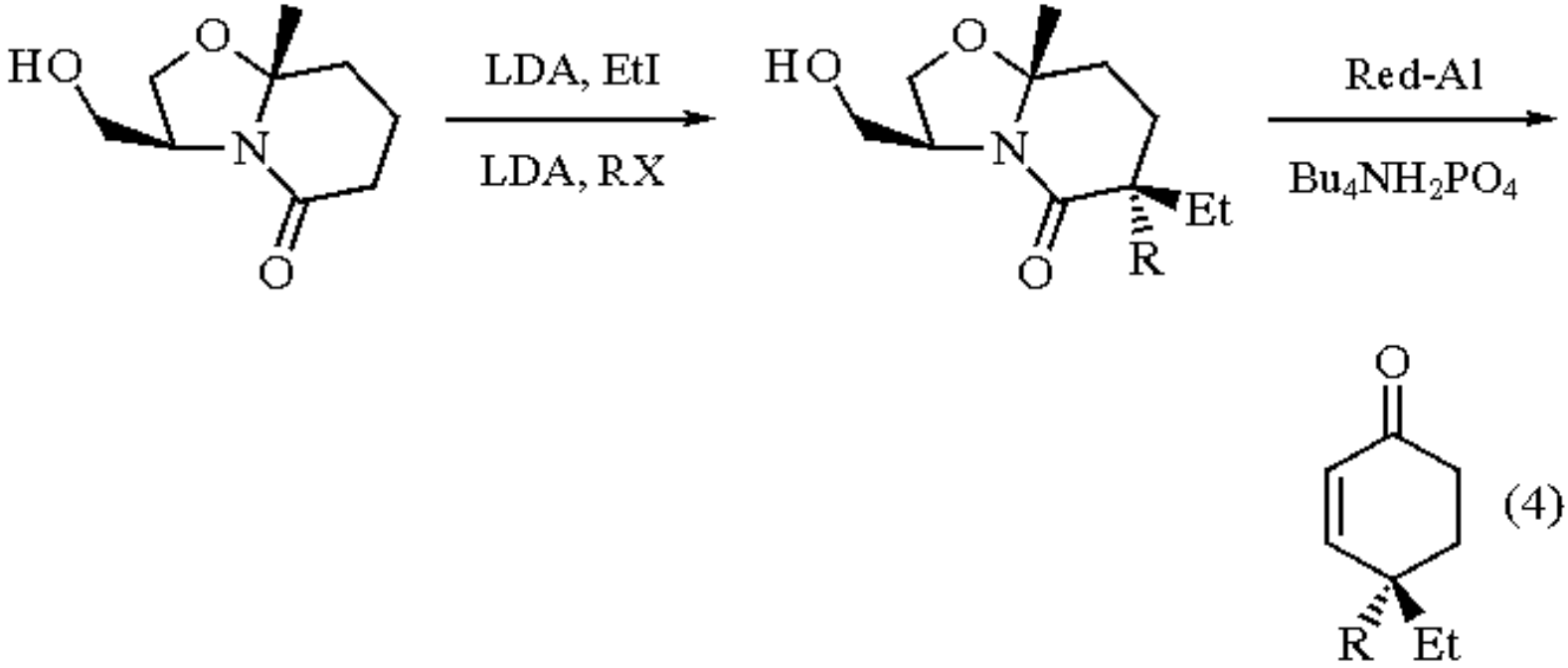

Grignard Reagent.

Conversion of ethyl iodide to its Grignard reagent proceeds easily (Mg, Et_2O, 0 °C). An example of the utilization of this reagent can be found in the synthesis of a debromoaplysin analog (eq 5).[22]

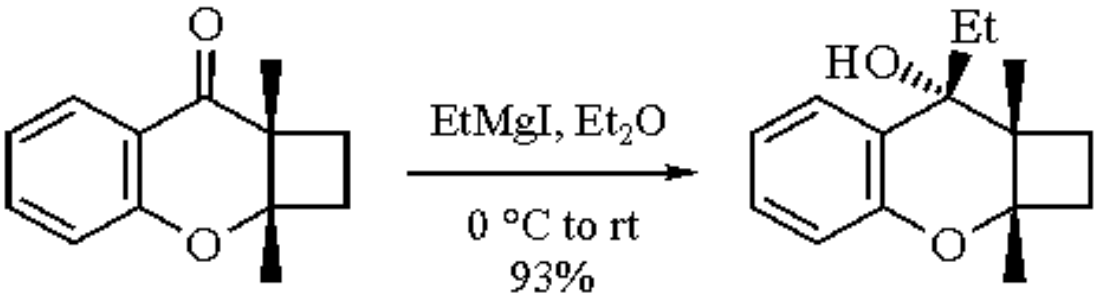

(5)

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Ethyliodomethylzinc[1]

ICH_2ZnEt

[33598-72-0] · C_3H_7IZn · Ethyliodomethylzinc · (MW 235.39)

(cyclopropanation reagent[1])

Alternate Name: Sawada reagent.

Preparative Methods: obtained by the reaction of ***Ethylzinc Iodide*** with ***Diiodomethane*** in ether at 30-35 °C[1] or by the reaction of diiodomethane with ***Diethylzinc***.[2]

Handling, Storage, and Precautions: decomposes slowly at room temperature; should be handled under nitrogen and in the absence of moisture.

Cyclopropanation Reactions.

Ethyliodomethylzinc (Sawada reagent) is a useful cyclopropanation reagent which gives, in many cases, better yields than the Simmons-Smith reagent[2,3] (see ***Ethylzinc Iodide*** and eqs 1 and 2).[1] Although formulated as ethyliodomethylzinc, the actual reagent may well be ***Iodomethylzinc Iodide***.[1] The difference of reactivity with the Simmons-Smith reagent may be due to the presence of different zinc salts and to the slightly different reaction conditions used for their generation. Contrary to the Furukawa reagent (CH_2I_2 and Et_2Zn, see ***Diethylzinc***), the Sawada reagent (CH_2I_2 and EtZnI) does not react well with enol ethers[1] and gives moderate yields in the case of α,β-unsaturated esters (eq 3).[1]

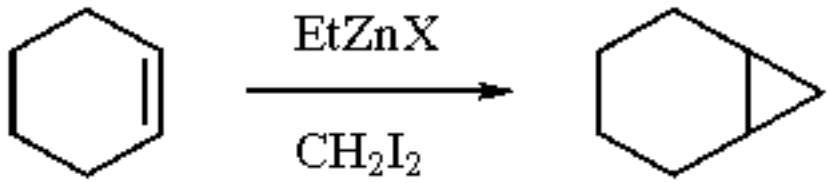

(1)

X = Et, Furukawa reagent, 79%
X = I, Sawada reagent, 92%

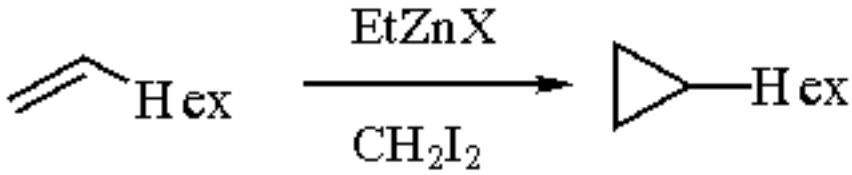

(2)

X = Et, Furukawa reagent, 60%
X = I, Sawada reagent, 77%

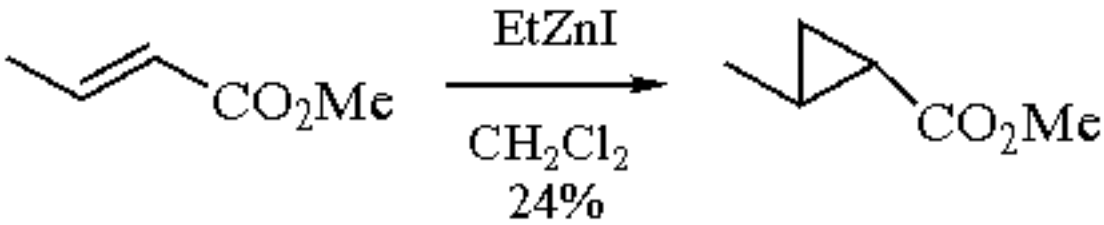

(3)

Interestingly, the polycyclic ketone (**1**) is efficiently converted to the corresponding cyclopropane derivative (**2**) in high yield (eq 4).[4] The related aluminum reagent prepared by the reaction of ***Trimethylaluminum*** and CH_2I_2 has proven to be a powerful cyclopropanation reagent (eqs 5 and 6).[5] Finally, ethyl iodomethylzinc allows the methylation of various phenols at high temperature (eq 7).[6]

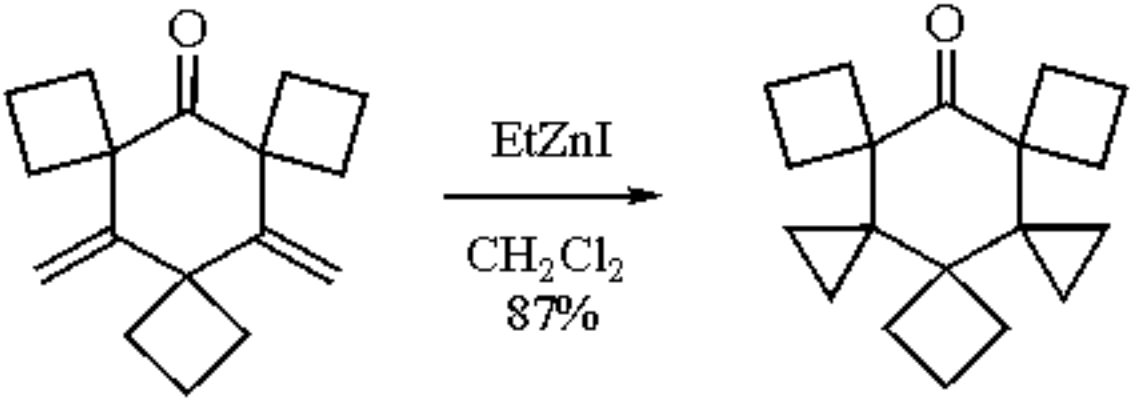

(4)

(1) **(2)**

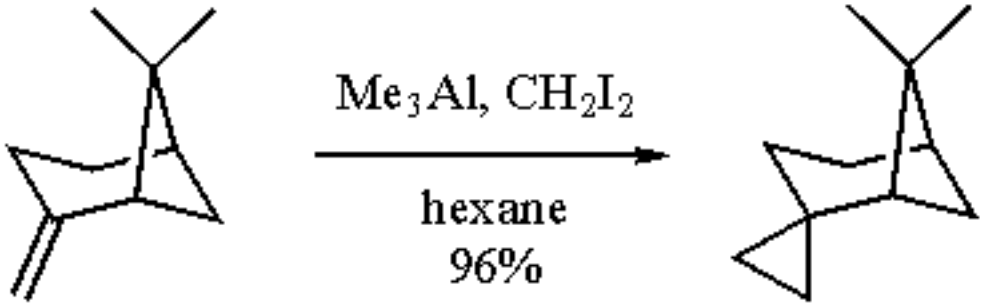

(5)

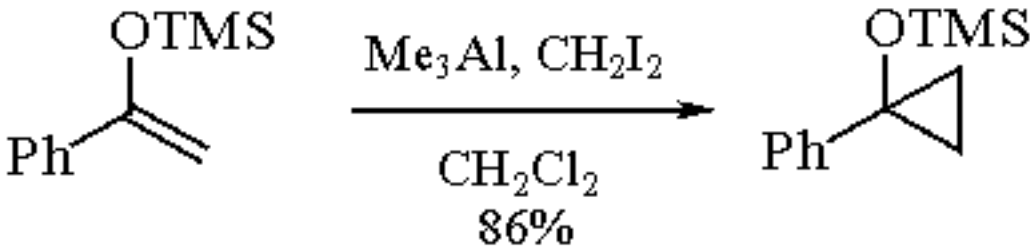

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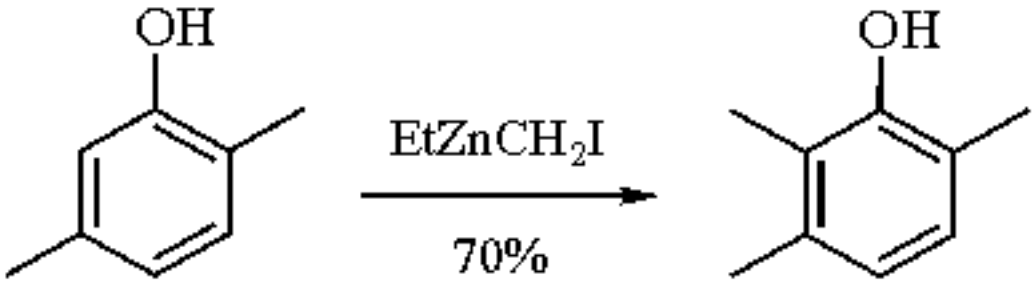

(7)

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Ethyl Isocyanoacetate[1]

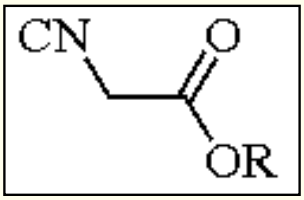

(R = Et)

[2999-46-4] · $C_5H_8NO_2$ · Ethyl Isocyanoacetate · (MW 113.14) (R = Me)

[39687-95-1] · $C_4H_6NO_2$ · Methyl Isocyanoacetate · (MW 99.11)

(heterocycle formation accompanied by cyclization onto the isocyano group;[1] forms stabilized carbanion for alkylations in amino acid synthesis;[1] α,α-additions to isocyano group and Passerini reactions[2])

Physical Data: ethyl ester, bp 89-91 °C/11 mmHg; methyl ester, bp 59-60 °C/3 mmHg.

Solubility: slightly sol H_2O; sol organic solvents.

Form Supplied in: yellow oils.

Preparative Methods: α-isocyanoacetate esters are most conveniently prepared by dehydration of the corresponding *N*-formylamino acid esters using ***Phosphorus Oxychloride*** in the presence of ***Triethylamine*** in CH_2Cl_2.[3]

Purification: by distillation.

Handling, Storage, and Precautions: isocyano compounds are generally quite sensitive to acids and immediately decompose to amine or formamide derivatives. They must be stored under N_2 at 0 to -20 °C. All operations should be performed in a well-ventilated fume hood because of the strong, disagreeable odor, and the equipment should be washed with acid after use.

Heterocycle Formation by Electrophiles.

Isocyanoacetates having hydrogen at the carbon flanked with two activating groups can easily form the carbanion. α-Metalated (anionic) isocyanoacetates, which are obtained by means of the usual bases in carbanion chemistry such as NaH, *t*-BuOK, *n*-BuLi, DBU, and Et_3N, permit attack of various electrophiles. The ambivalent nature of the isocyanide carbon atom allows nucleophilic cyclization to form heterocycles after addition to polar multiple bonds such as

carbonyl, imino, thioxo, nitrile, active alkene, etc. (eq 1).

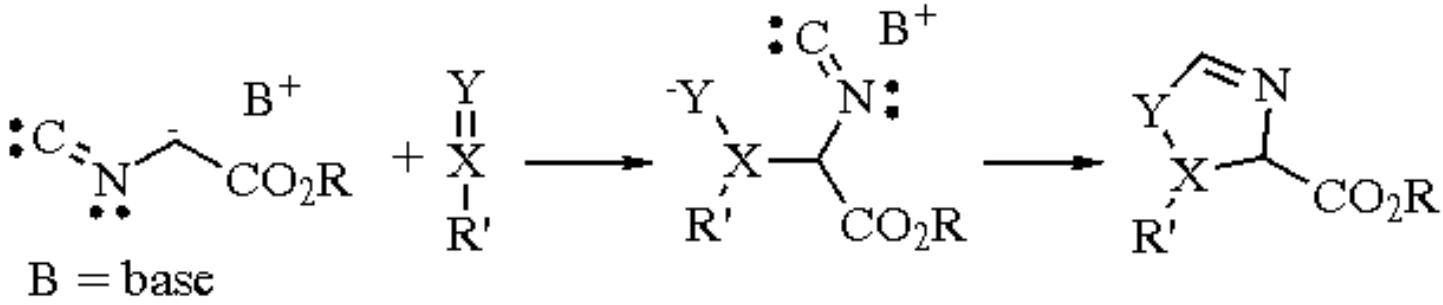

Reaction of α-anions from isocyanoacetate with acylating agents gives oxazole-4-carboxylates via cyclization of the enol form onto the isocyano group (eq 2).[4] 3-Amino-4-hydroxycoumarins and 2(1*H*)-quinolinones are synthesized by reactions with acetyl or salicyloyl chlorides[5] and benzooxazinones[6] followed by acid hydrolysis in a straightforward reaction. The addition of an arylsulfenyl chloride to the carbenoid carbon of ethyl isocyanoacetate followed by treatment with ***Triethylamine*** affords 2-arylthio-5-ethoxyoxazoles in situ (eq 3).[7] Reaction with nitriles in the presence of ***Potassium Hydride*** in diglyme affords 5-substituted imidazole-4-carboxylates[8] and reactions with Schiff bases (imino compounds) form imidazolines.[9]

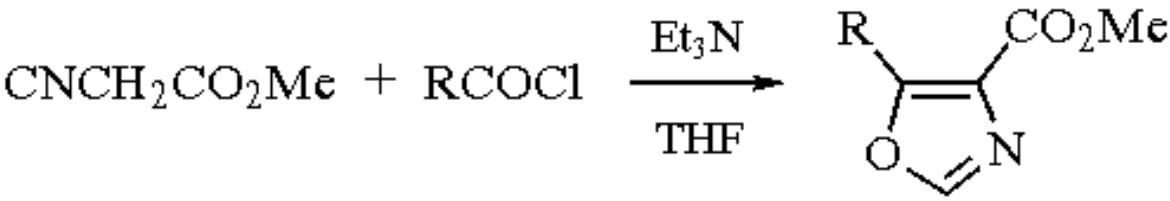

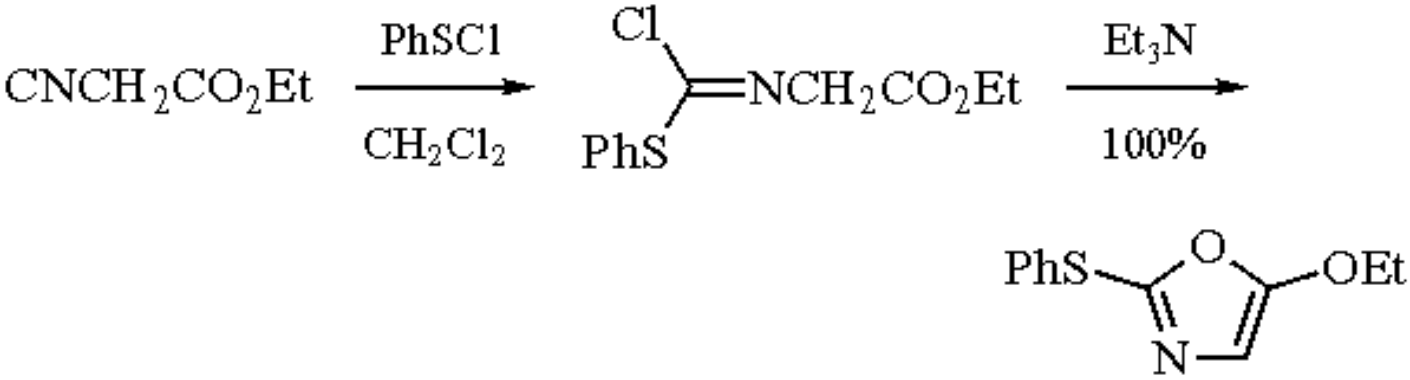

Ethyl isocyanoacetate reacts with ***Carbon Disulfide*** to give thiazolethiolates in the presence of ***Potassium t-Butoxide***, which provide 5-(methylthio)thiazole-4-carboxylates with ***Iodomethane*** (eq 4).[10]

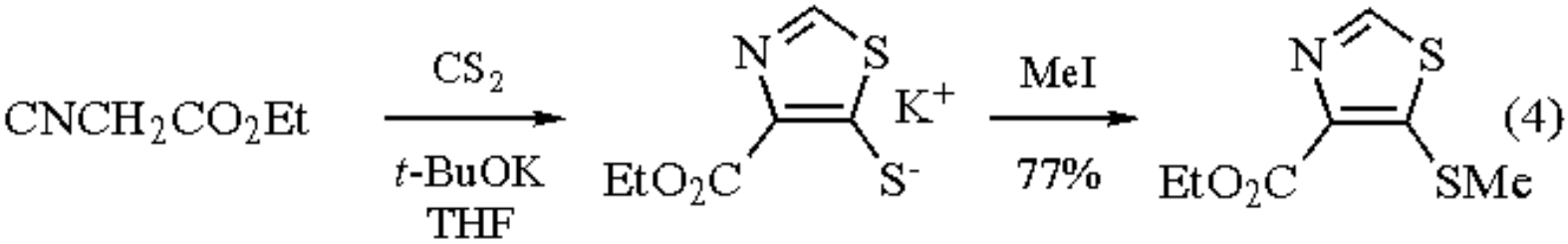

The coupling reactions with arenediazonium ions give 1-aryl-1*H*-1,2,4-triazole-3-carboxylates via cyclization of hydrazone compounds in the presence of sodium acetate in aq MeOH.[11] Condensation with heteroallenes such as isocyanates and isothiocyanates generates oxazole and thiazole skeletons, but the reactions give complicated products under various reaction conditions.[12] Michael addition proceeds easily with C-C bond formation, while α,β-unsaturated carbonyl compounds on heating to 70-80 °C provide pyrrolines accompanying further cyclization by insertion of the anion into the isocyano group.[13] When a nitroalkene is the Michael acceptor, 3,4-disubstituted pyrrole-2-carboxylates are obtained by cyclization and elimination of the nitro group (eq 5).[14]

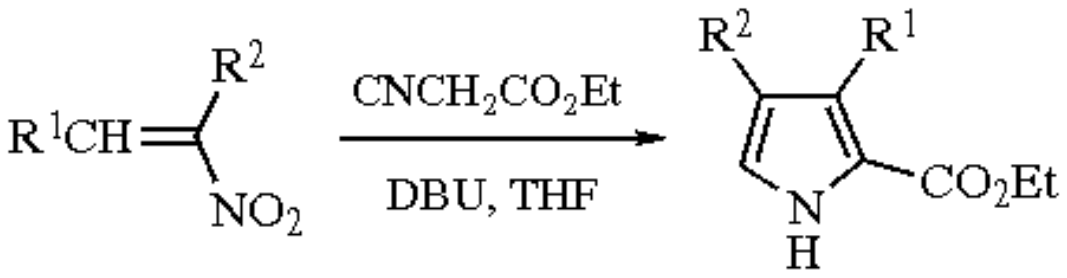

(5)

Reactions with Aldehydes and Ketones.

Reactions with carbonyl compounds as electrophiles afford many valuable products. For example, formylaminoacrylates are obtained in the presence of *t*-BuOK or NaH via isomerization of the oxazolinyl anion by proton shift from C-4 to C-2 followed by elimination (eq 6).[15] In the presence of NaCN in EtOH, *trans*-2-oxazoline-4-carboxylates are produced by protonation of the oxazolinyl anion.[16] The use of metal catalysts such as NiCl and Cu_2O also gives the oxazoline products. Especially, in the presence of a gold(I) complex (**1**) coordinated to a chiral ferrocenylphosphine ligand (**2**), oxazoline-4-carboxylates are formed with high enantio- and diastereoselectivity (eq 7).[17]

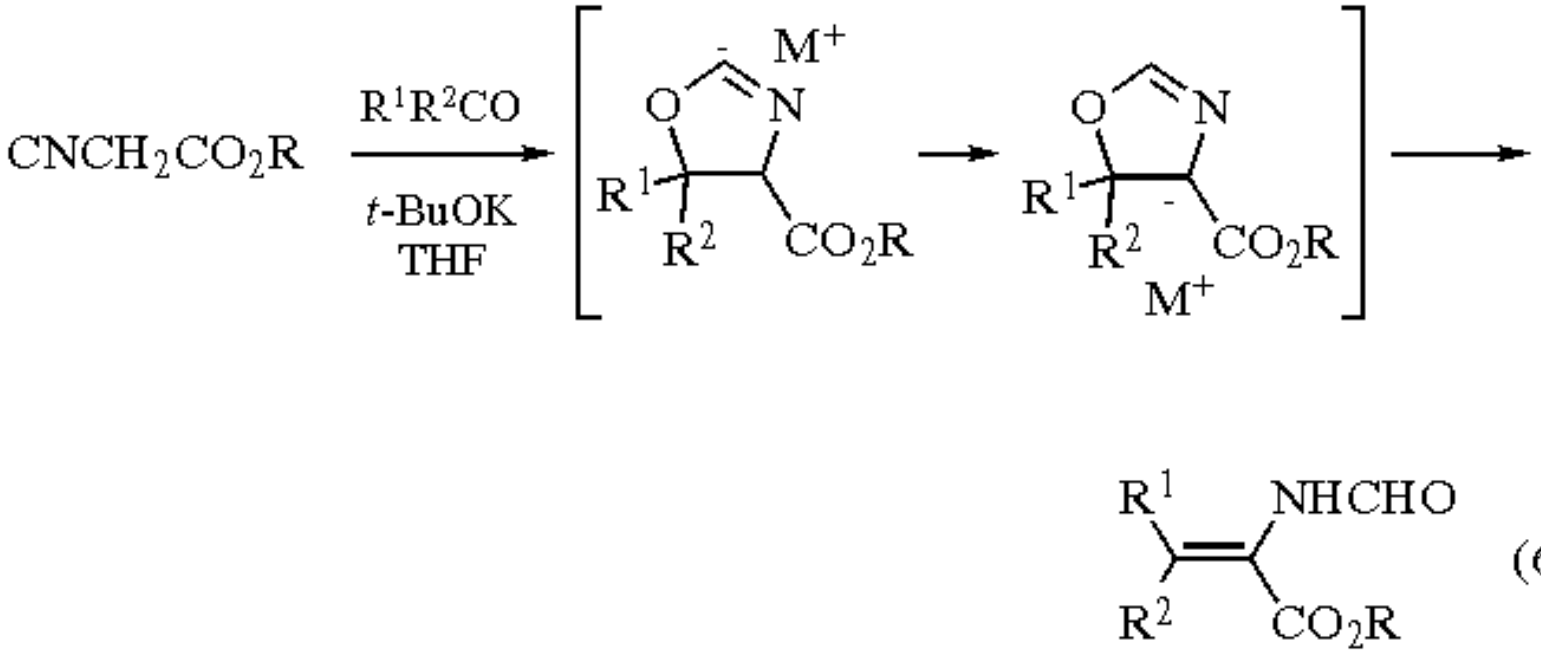

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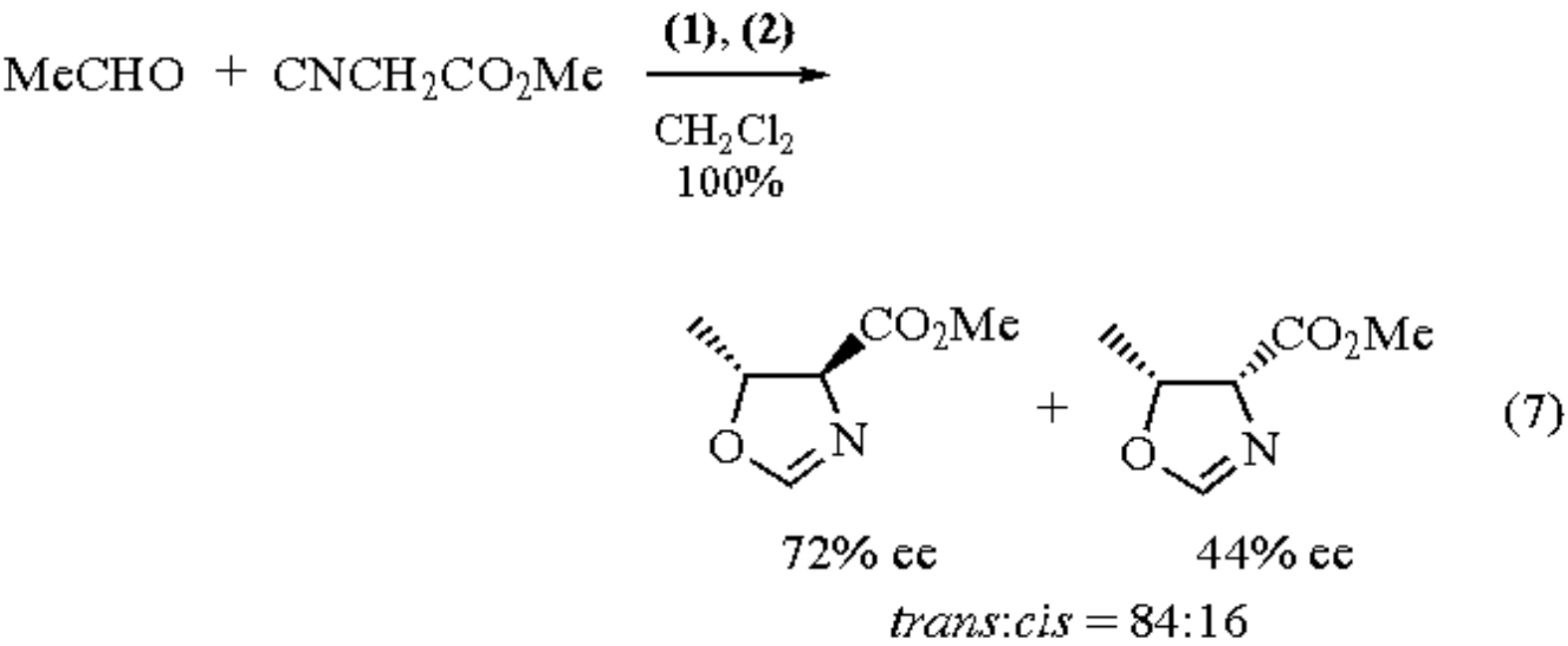

(1) **(2)**

Formamidine derivatives are also formed using pyrrolidine or piperidine as bases in MeOH by insertion of the bases into the isocyano group of α-isocyanoacrylate, which is proposed as an intermediate (eq 8).[18] The reaction with aldehydes in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** in THF affords pyrrole-2,4-dicarboxylates via Michael addition by another equivalent of methyl isocyanoacetate to the proposed intermediate, i.e. methyl isocyanoacrylates (eq 8).[19] Reaction with acetaldehyde in the presence of Et_3N in benzene affords methyl α-isocyano-β-hydroxybutyrate (eq 8).[20]

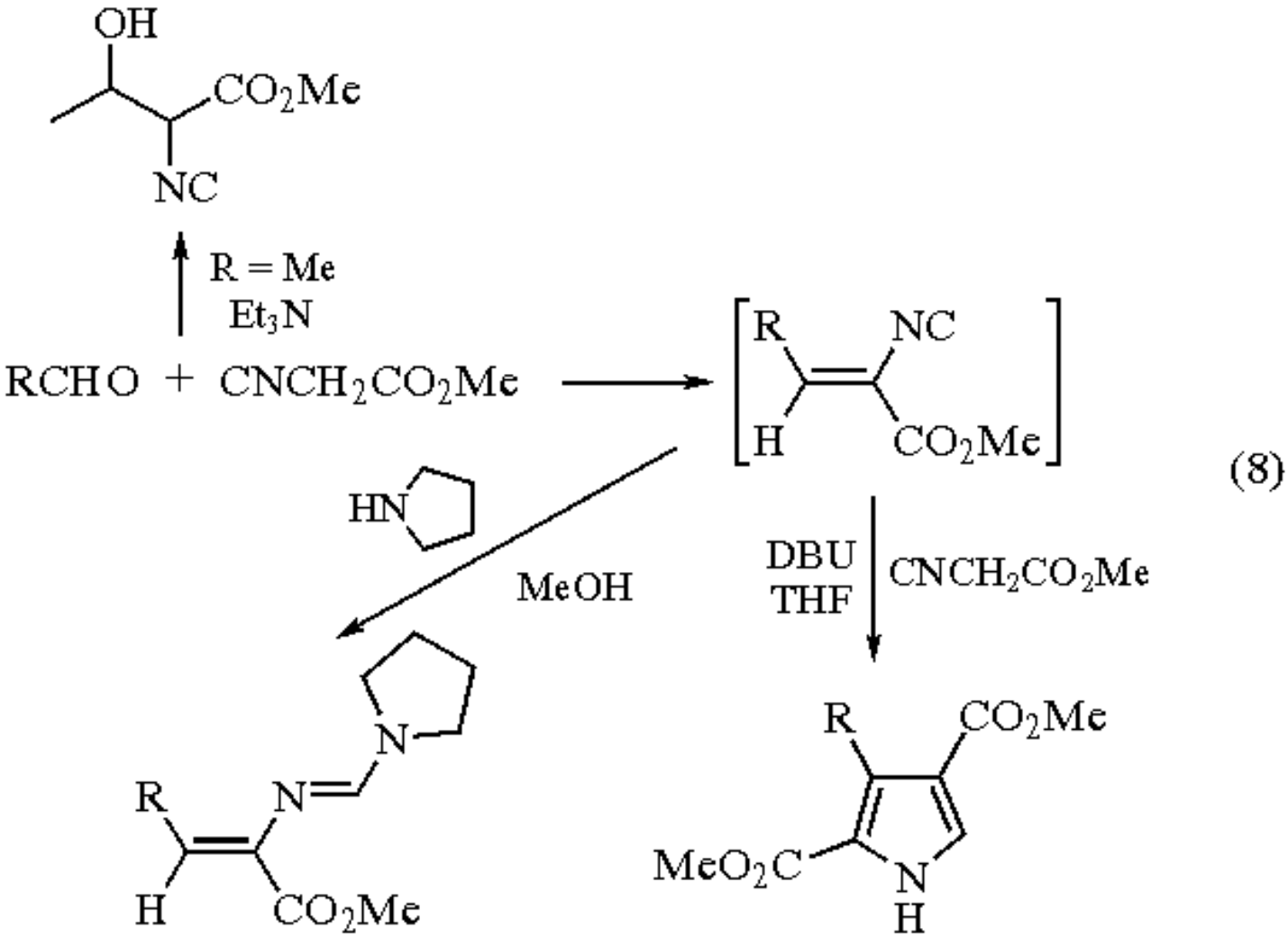

α-Activating Group for Amino Acids Synthesis.

Carbon-carbon bond formation at the α-carbon of α-isocyanoacetates by alkylation with carbon electrophiles provides a useful preparative method for the synthesis of various amino acid derivatives, since the isocyano group is easily converted to the amino group by acidification. Hence, isocyanoacetates are regarded as synthetic equivalents for α-activated amino acids (eq 9).[1]

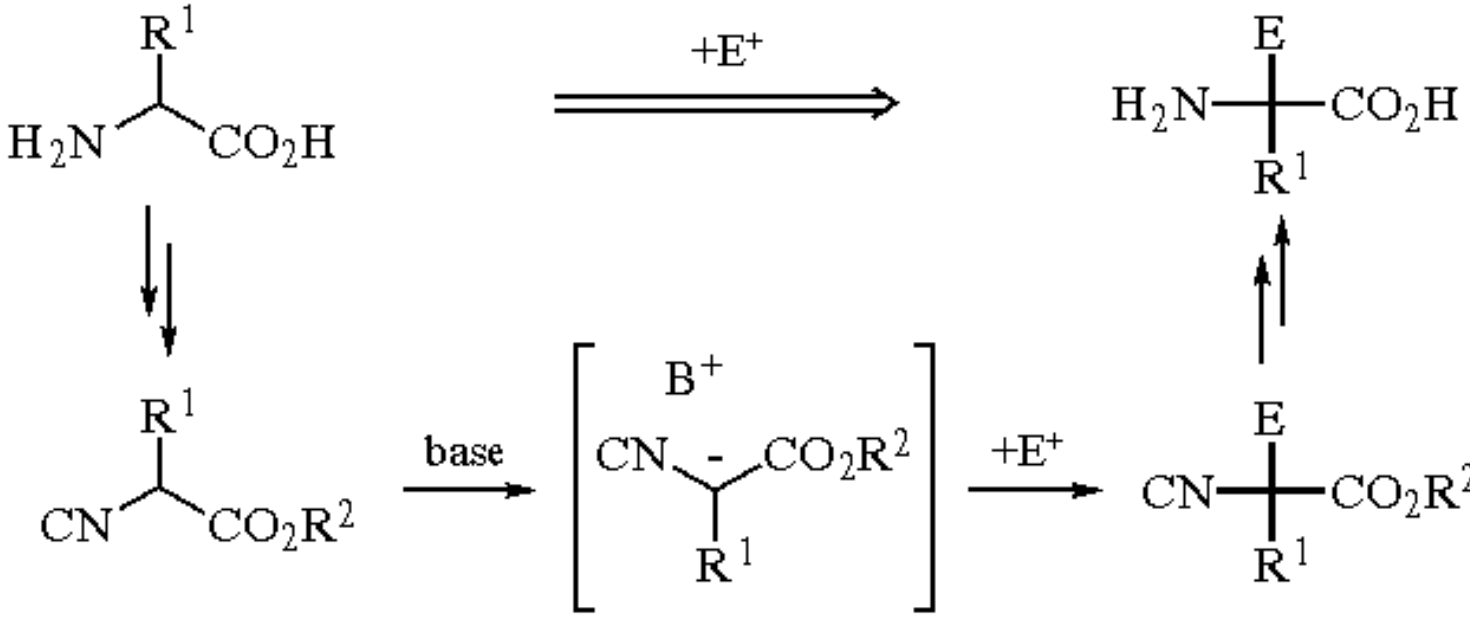

Reactions of α-metalated α-isocyanopropionate with alkyl halides and Michael acceptors followed by hydrolysis give α-methyldopa,[21] α-methylhistidine,[21] and α-methylglutamic acid.[22] Palladium-catalyzed allylation of ethyl α-isocyanopropionate with allyl acetate in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** affords α-allylalanine ethyl ester after acidification.[23] Furthermore, 2-oxazoline-4-carboxylates, which are accessed readily by reaction with aldehydes and ketones as described in the above section, are easily converted to β-hydroxy-α-amino acid derivatives by acid hydrolysis.[1] In the same way, oxazole-4-carboxylates obtained by reaction with acylating agents are hydrolyzed to give *C*-acylamino acid esters.[4]

Insertion into the Isocyano Group.

α,α-Additions to the isocyano group are well known reactions in catalytic chemistry.[24] Furthermore, the Passerini reaction, which provides α-acyloxycarboxamide from isocyano compounds, ketones, and carboxylic acids,[25] and the Ugi reaction (four-component condensation: 4CC)[26] are unique peptide synthetic methods. As an application of the 4CC, the reaction of 3-aryloxy-4,5-dihydroxypyrrole, which is an intramolecular condensation product of the aldehyde and amine components, with ethyl isocyanoacetate and benzoic acid affords *N*-benzoyl-β-aryloxyprolylglycinate (eq 10).[27]

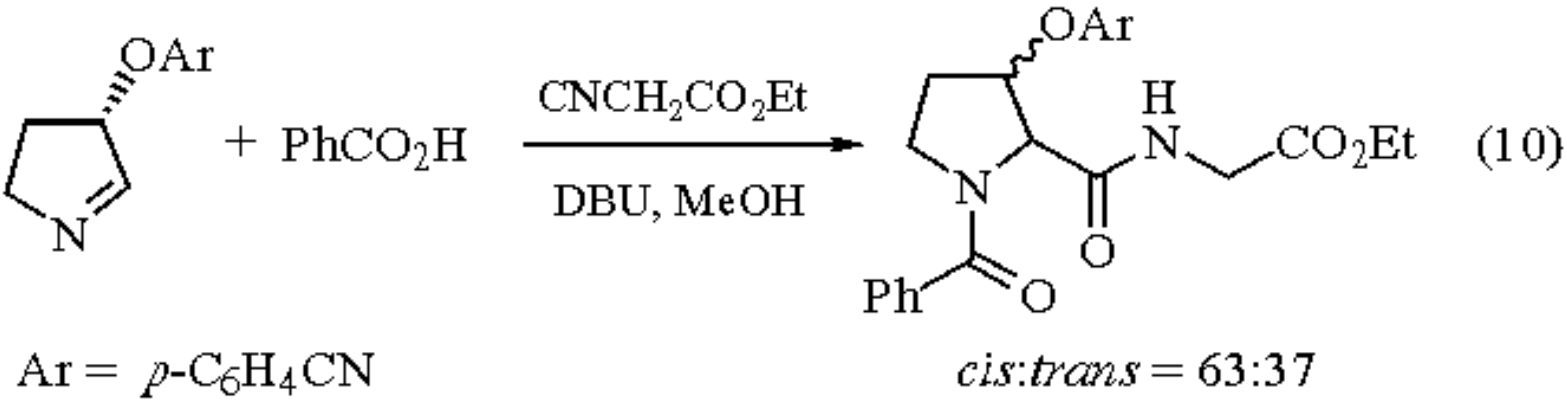

Related Reagents.

(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one; ***t-Butyl Isocyanide***; ***Diethyl Isocyanomethylphosphonate***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Phenyl Isocyanide***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***.

---

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(*S*)-Ethyl Lactate

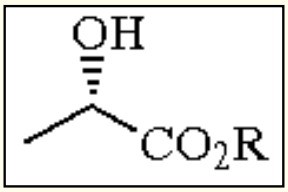

(*S*)-(R = Et)

[687-47-8] · $C_5H_{10}O_3$ · (*S*)-Ethyl Lactate · (MW 118.15) (*R*)-(R = Et)

[97-64-3] · $C_5H_{10}O_3$ · (*S*)-Ethyl Lactate · (MW 118.15) (*S*)-(R = Me)

[17392-83-5] · $C_4H_8O_3$ · (*S*)-Methyl Lactate · (MW 104.12) (*R*)-(R = Me)

[27871-49-4] · $C_4H_8O_3$ · (*S*)-Ethyl Lactate · (MW 104.12) (*R*)-(R = Bu)

[34451-18-8] · $C_7H_{14}O_3$ · (*R*)-*t*-Butyl Lactate · (MW 146.21)

(chiral pool reagent for synthesis; occasionally used as a chiral auxiliary)

Alternate Name: ethyl L-(-)-lactate.

Physical Data: (*S*)-(R = Et) bp 154 °C, 69 °C/36 mmHg, *d* 1.031 g cm^{-3};[20] (*R*)-(R = Et) bp 58 °C/20 mmHg, *d* 1.032 g cm^{-3};[20] (*S*)-(R = Me) bp 40 °C/11 mmHg, *d* 1.086 g cm^{-3};[25] (*R*)-(R = Me) bp 58 °C/19 mmHg, *d* 1.091 g cm^{-3};[20] (*R*)-(R = Bu) bp 77 °C/10 mmHg, *d* 0.974 g cm^{-3}.[27]

Solubility: sol water, alcohols, ethers, THF, and common organic solvents.

Form Supplied in: liquid; commercially available.

Use as a Chiral Pool Reagent.

(*S*)-Ethyl lactate has been extensively used as a chiral pool reagent, often via transformation into a diverse array of simple, enantiomerically pure analogs. Principal among these are a variety of *O*-protected (*S*)-2-hydroxypropanals (eq 1).

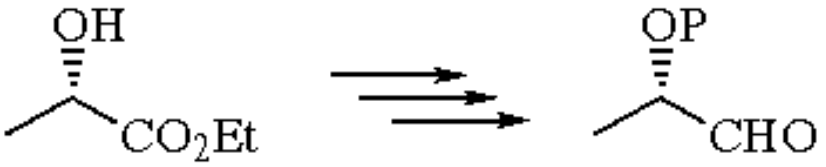

(1)

These have been prepared by various combinations of straightforward steps including ester to amide conversion, alcohol protection, direct reduction of the ester or amide to the aldehyde group, and reduction of the ester to the alcohol followed by reoxidation to the aldehyde. The sensitivity of the (*S*)-propanals to epimerization has been of paramount concern. One of the best procedures which avoids racemization and has been run on a preparative scale is noted (eq 2).[1]

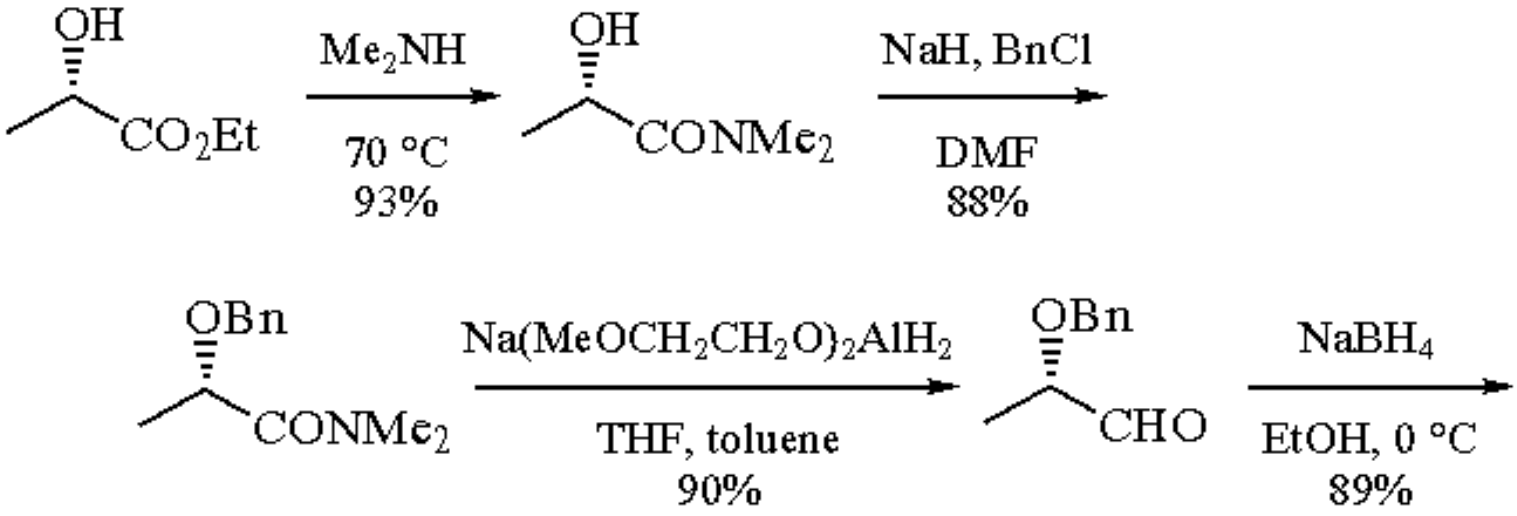

(2)

Subsequent reduction also affords (*S*)-2-benzyloxypropanol in 89% yield. NMR assay of the (*R*)- and (*S*)-Mosher esters indicated no racemization over the sequence. Synthesis via oxidation of (*S*)-benzyloxypropanol (eq 3) provides the benzyloxypropanal with <8% racemization.[2]

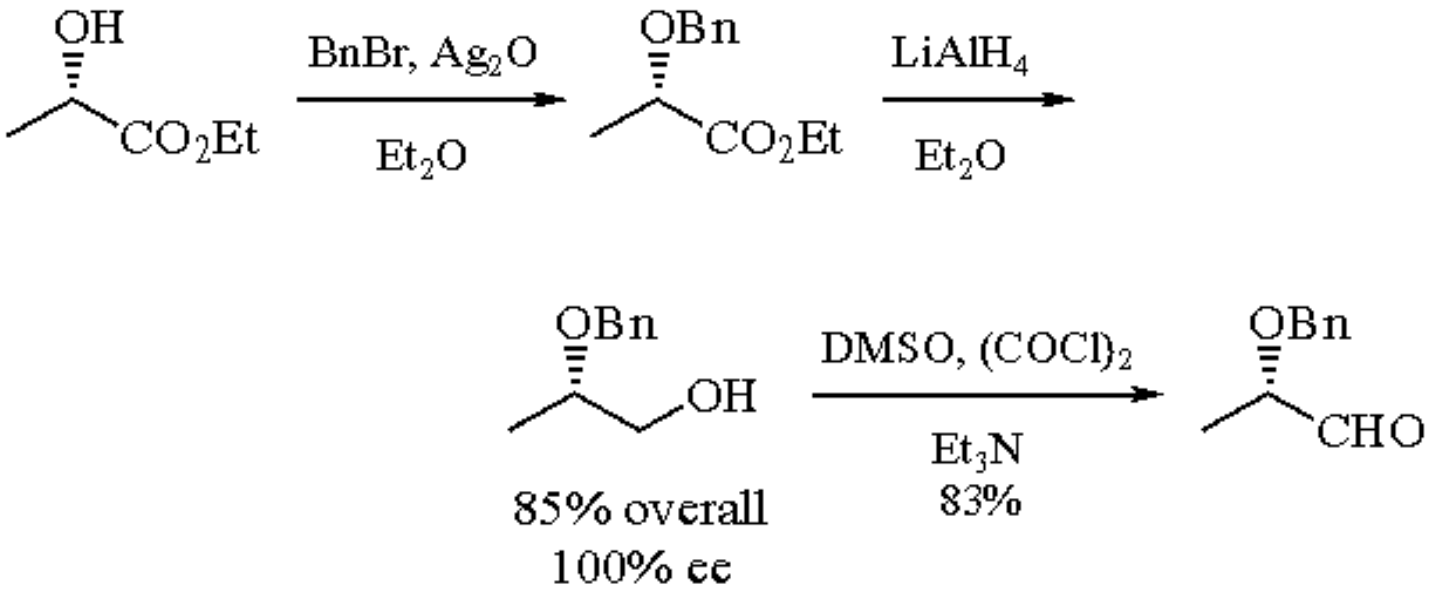

(3)

Attempted formation of the benzyl ether of (*S*)-ethyl lactate with NaH/BnBr results in considerable racemization (50-75% ee). This racemization is obviated by use of the amide analog noted in eq 2. ***Diisobutylaluminum Hydride*** has been used to convert the ester directly to the aldehyde employing the methoxymethyl,[3,4] benzyl,[2,5] 2,6-dichlorobenzyl,[6] *t*-butyldiphenylsilyl,[7] benzyloxymethyl,[8] THP,[9] trityl[10] and TBDMS[11] protecting groups. Protected (*S*)-2-hydroxypropanals have been used in synthetic studies relating to sugars,[12-15] amino sugars,[16] thiotetronic acids,[17] antimycin-A_3,[18] rhodinose,[19] aplysiatoxin via the (*R*)-lactate,[20] (-)-sarracenin,[21] and for preparation of enantiomerically pure 1-methyl-2-alkenyl-*N*,*N*-diisopropylcarbamates from the (*R*)- and (*S*)-lactates.[22]

(*S*)-Ethyl lactate has also been used as a ready source of (*S*)-propane-1,2-diol and (*S*)-methyloxirane (eq 4).[23,24] These compounds have been used for preparation of numerous natural products including nonactin,[25] sulcatol,[26] recifeiolide,[27] methyl-1,6-dioxaspiro[4,5]decanes, the pheromone components of *Paravespula vulgaris*,[28] and the rhynchosporosides.[29] The (*S*)-oxirane has also been used in the synthesis of chiral macrocyclic poly(ether diester)ligands.[30] A convenient procedure for preparation of the (*R*)-methyloxirane via mesylate activation, reduction, and internal inversion has been reported.[31]

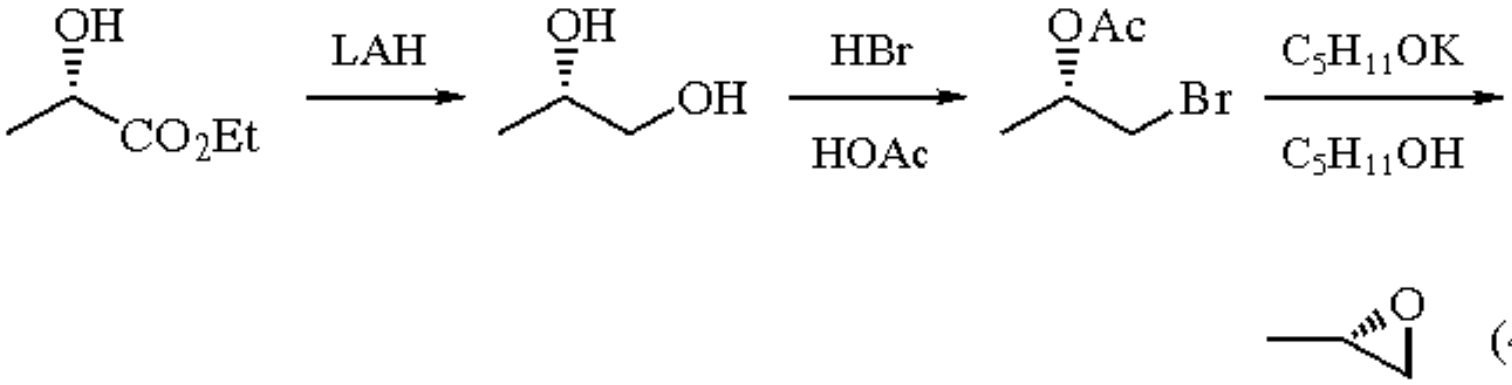

(4)

A variety of inverted analogs of (*S*)-ethyl lactate have been prepared by standard activation displacement procedures. Included are the (*R*)-propionyloxypropionate (mesylation/$EtCO_2Cs$-DMF);[32] azide (Mitsunobu conditions);[33,34] aryloxy ethers (mesylation/aryl oxide);[35] chloride ($SOCl_2$-DMF);[36] bromide (sulfonation/$MgBr_2$);[37] mercapto analogs (Mitsonobu conditions);[38,39] amino analogs (triflate/amine);[40] hydroxylamines;[41,42] and selenides.[43]

Protected (*S*)-ethyl lactate cleanly acylates methyllithium to afford the 2-butanone with essentially complete enantiomeric fidelity and in nearly quantitative yield. Various diastereoselective constructions were achieved by nucleophilic addition to the ketone (eq 5).[44] For example, addition of vinyllithiums, followed by acetal formation and Lewis acid-mediated rearrangement, provided a ready entry into the indicated 3-acyltetrahydrofurans.

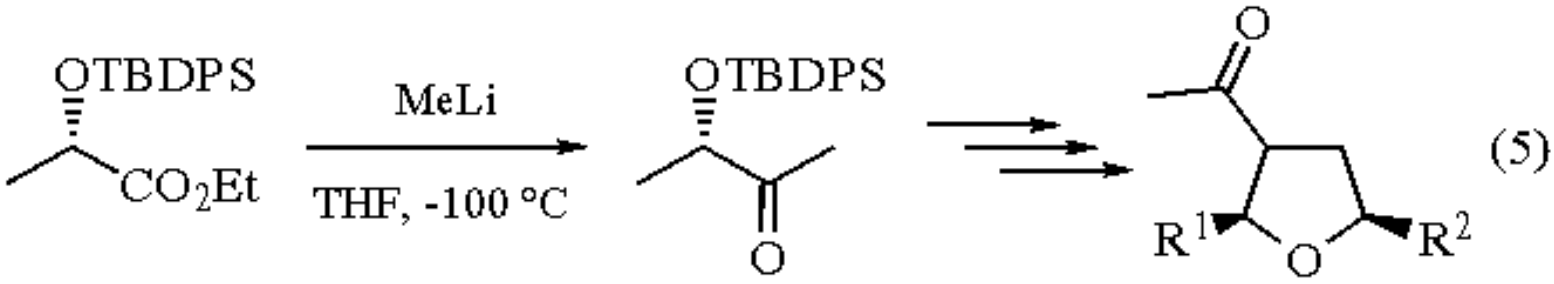

(5)

(*S*)-Ethyl lactate has been used to prepare (*S*)-2-methyloxetane in modest yield with <0.5% racemization by a series of standard transformations (eq 6).[45]

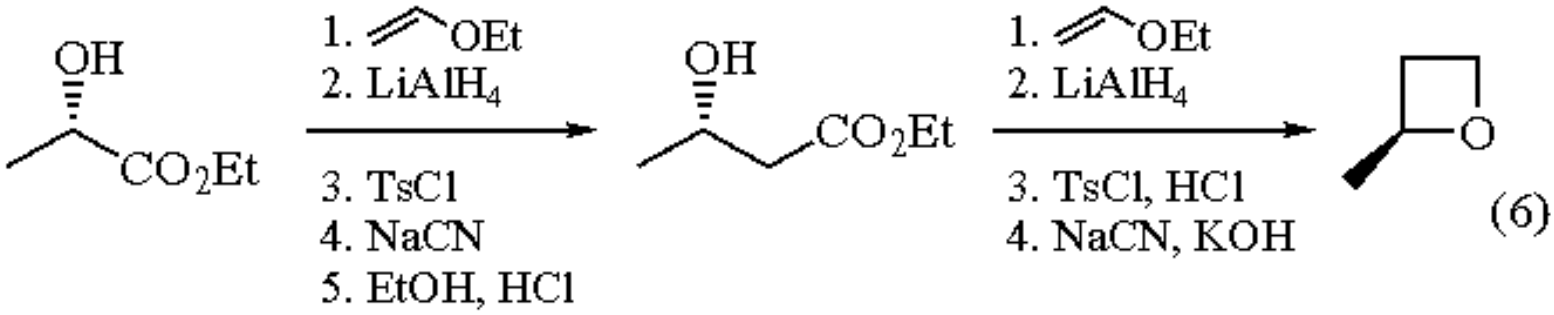

(6)

Other small chiral molecules have also been prepared by straightforward transformations (eq 7).[46]

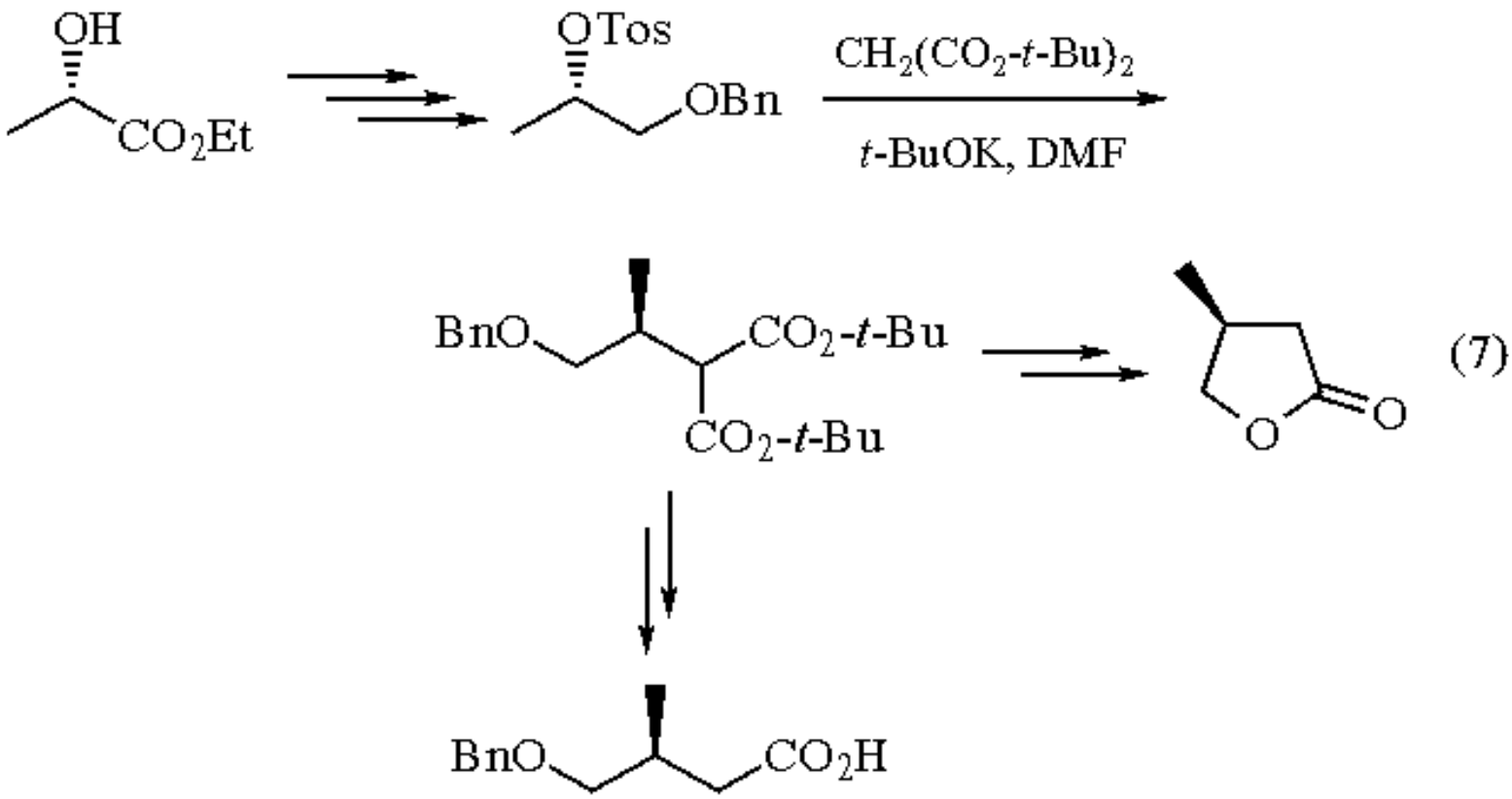

(*S*)-Ethyl lactate has also been used as a chiral fragment for numerous other studies. Included are synthetic efforts relating to salenomycin,[47] (-)-biopterin,[48] (+)-polyoxamic acid,[49] jaspamide,[50] the enantiomeric 2-pentanols,[51] pumilitoxin B,[52,53] D-ristosamine,[54] protomycinolide IV,[55] and tirandamycin.[56]

Use as a Chiral Auxiliary.

(*S*)-Ethyl lactate has been used as a chiral auxiliary in a variety of simple Diels-Alder reactions.[57-60] As the fumaric acid diester, the de employing cyclopentadiene can almost be completely reversed by addition of ***Titanium(IV) Chloride*** (eq 8).[61] In general, superior de values are achieved using ***(R)-Pantolactone*** in this context, and also for base-mediated addition to ketenes.[62]

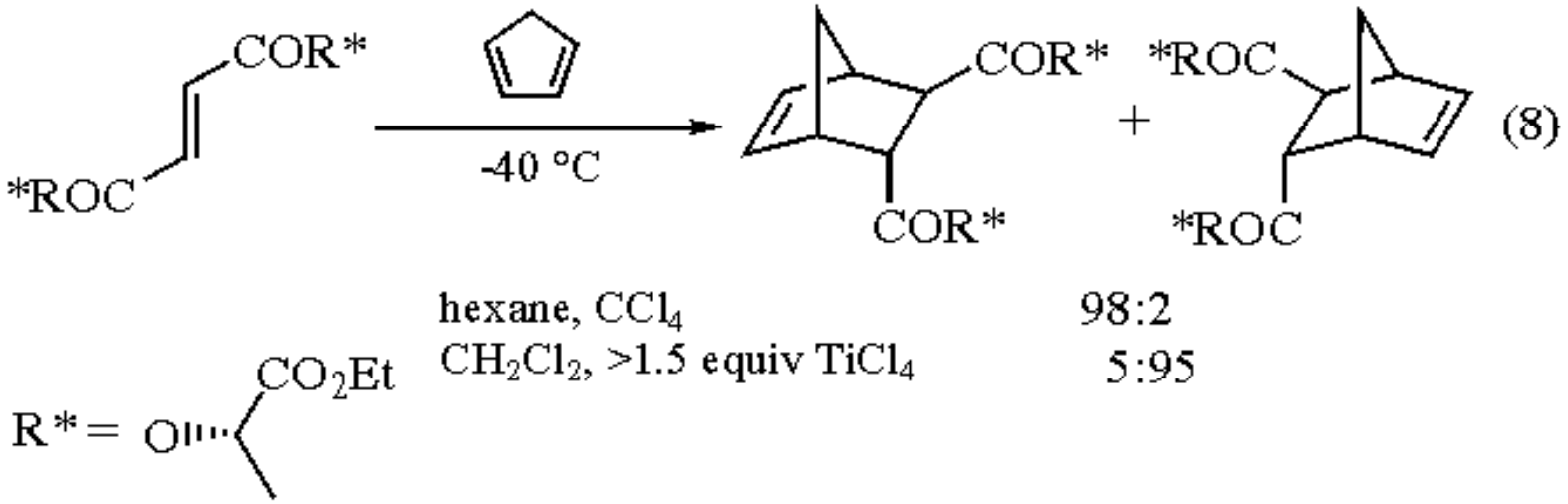

(*S*)-Ethyl lactate was used for diastereocontrol and asymmetric transmission in a sequential 2,3-Wittig-oxy-Cope rearrangement, affording product in 91% ee (eq 9).[63,64] Excellent asymmetric induction has also been noted in the Lewis acid-mediated ene reaction of (*S*)-ethyl lactate-derived intermediates (eq 10).[65]

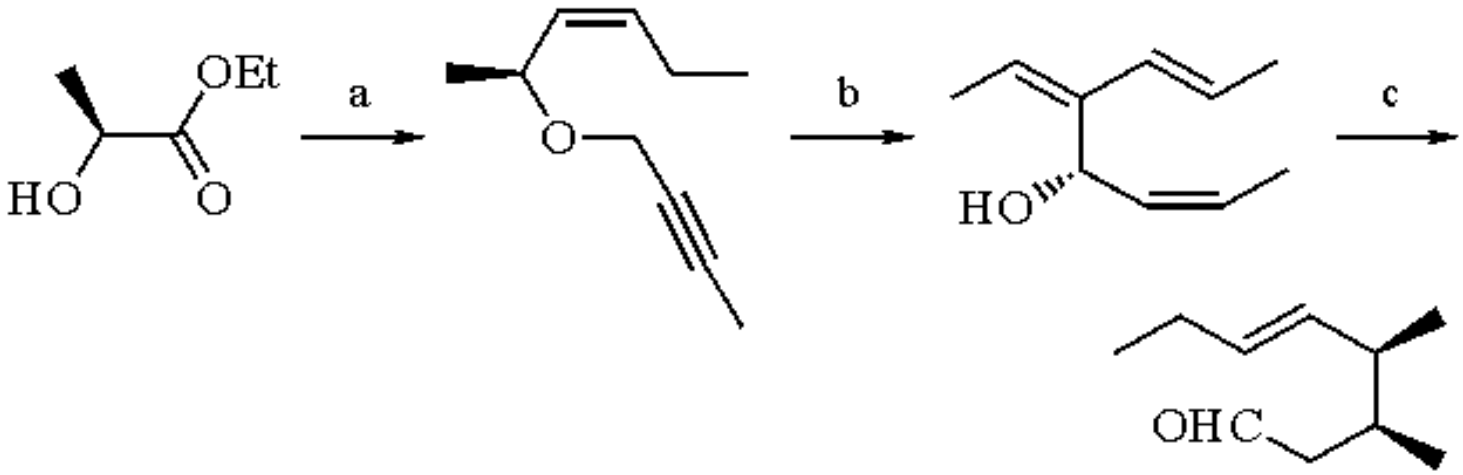

(9)

(a) $MeC{\equiv}CCH_2OC(=NH)CCl_3$, H^+, 85%; DIBAL, 82%; $PrPPh_3Br$, BuLi, -78 °C, 75%
(b) BuLi, -78 °C, 75%; H_2, P-2 Ni, 95%
(c) KH, 18-crown-6, 25 °C, 75%

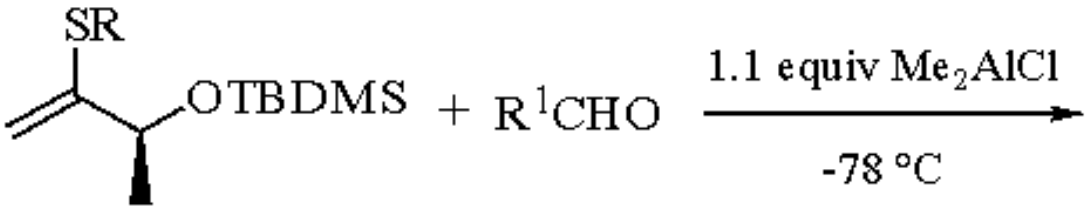

R = Et, Ph
$R^1 = C_6H_{13}$, aryl, styryl

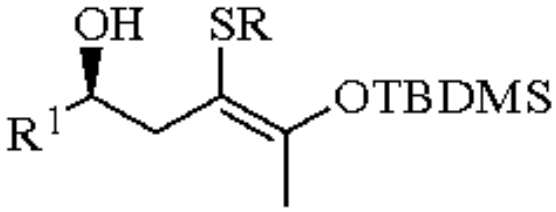

(10)

86-97% ee

(*S*)-Ethyl lactate has been used to enantioselectively protonate the indicated enolate at -100 °C to afford the (*R*)-ketone in 73% yield and 73% ee (eq 11).[66]

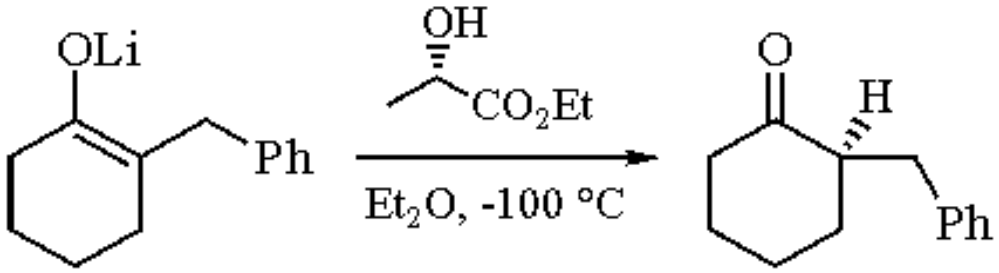

(11)

Applications to Products of Commercial Interest.

(*S*)-Ethyl lactate has been incorporated in chiral syntheses of (*S*)-2-arylpropionic acids, an important class of nonsteroidal anti-inflammatory agents, including ibuprofen and naproxen (eq 12).[67 -69] These syntheses, though elegant in concept, are unlikely to compete with existing industrial methods for production of the (*S*) enantiomers of these drugs.

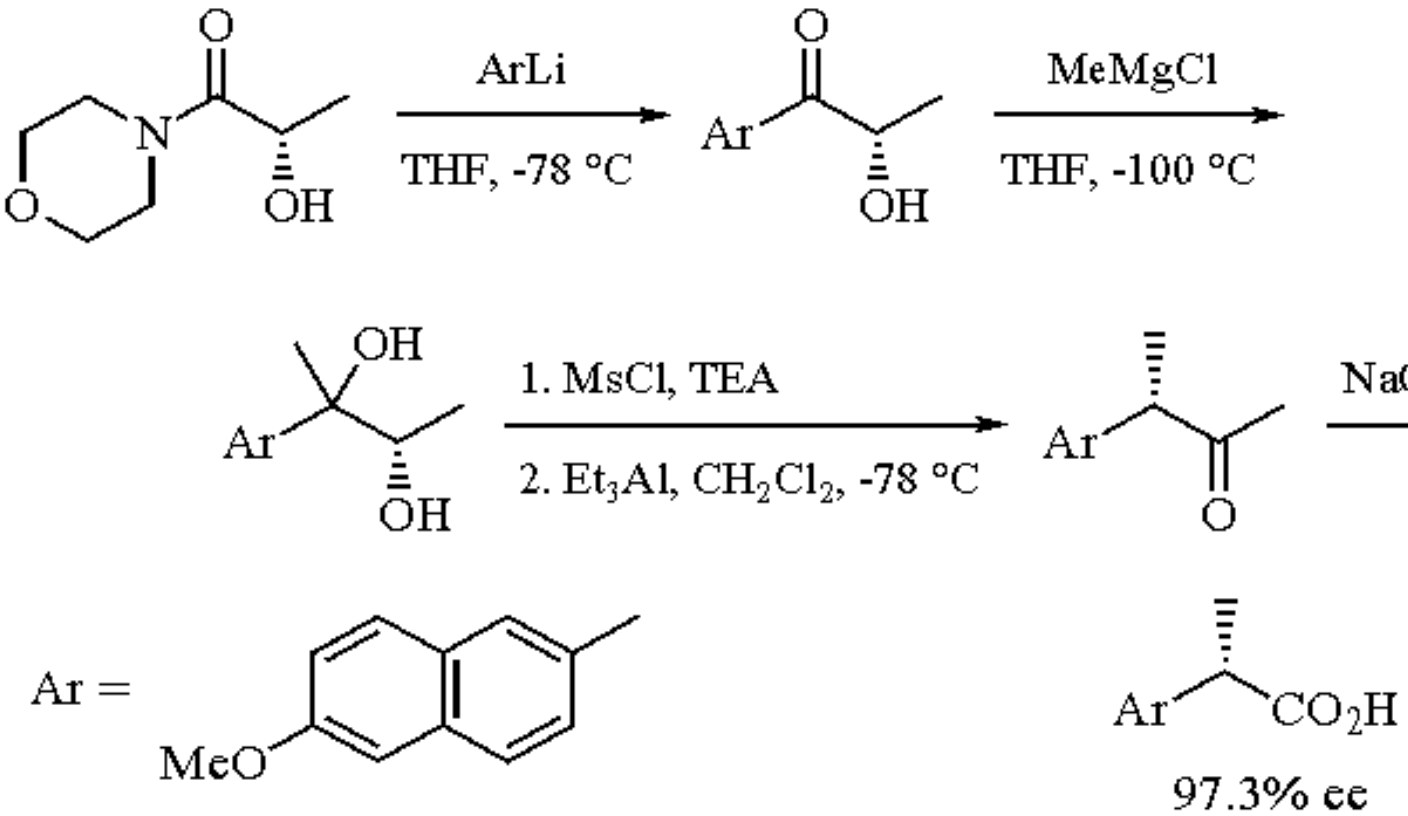

(12)

(*S*)-Ethyl lactate has also been used to synthesize the important 4-acetoxyazetidinone intermediate, crucial to numerous carbapenem syntheses. The key step in its use was the diketene addition to the (*S*)-lactaldehyde imine, which in the best case proceeded in 67% yield with a 10:1 ratio of diastereomers (eq 13).[70,71]

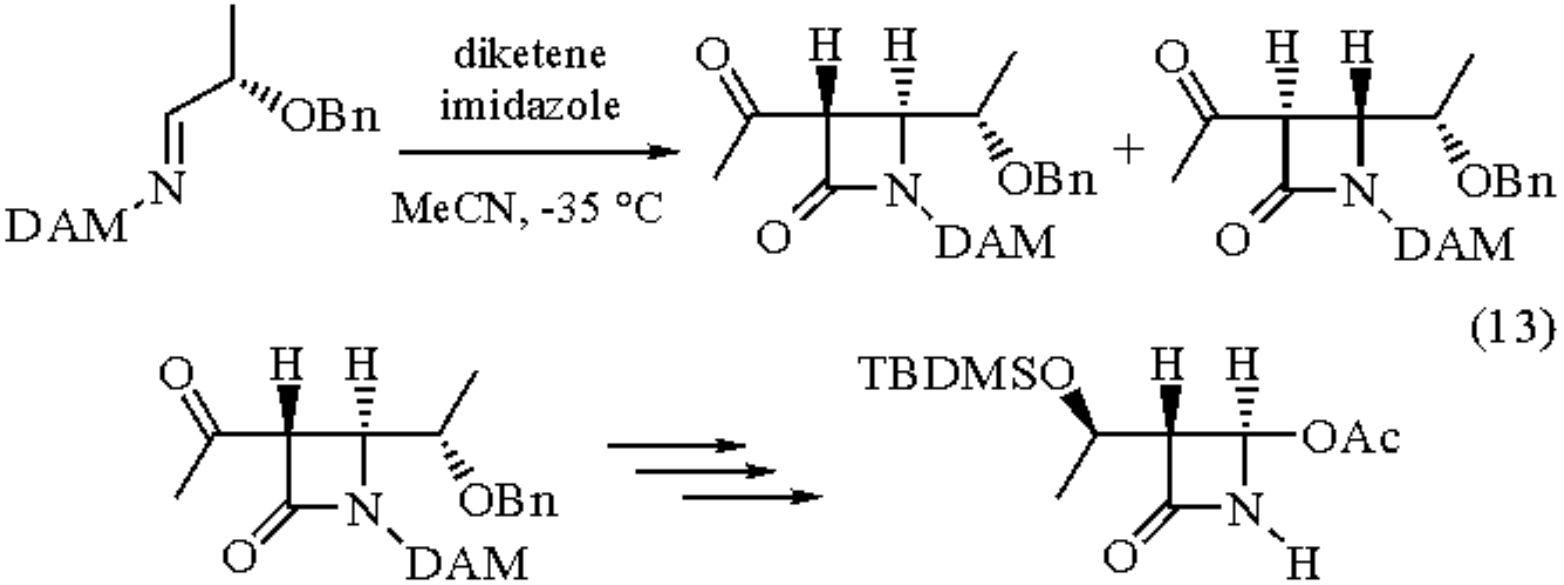

(13)

Other applications to β-lactam syntheses have been reported.[72-74]

Related Reagents.

Ethyl Mandelate; ***(R)-Pantolactone***.

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Ethyl Lithioacetate

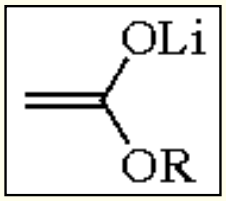

(R = Et)

[56267-15-3] · $C_4H_7LiO_2$ · Ethyl Lithioacetate · (MW 94.05) (R = Me)

[57570-85-1] · $C_3H_5LiO_2$ · Methyl Lithioacetate · (MW 80.02) (R = *t*-Bu)

[53503-61-0] · $C_6H_{11}LiO_2$ · *t*-Butyl Lithioacetate · (MW 122.11) (R = Bn)

[71010-30-5] · $C_9H_9LiO_2$ · Benzyl Lithioacetate · (MW 156.12)

(two-carbon nucleophile in ester enolate alkylation, condensation, conjugate addition, and transmetalation reactions)

Solubility: sol THF.

Form Supplied in: white solids.

Analysis of Reagent Purity: the ^1H and ^{13}C NMR spectra (C_6D_6/THF solutions) for *t*-butyl lithioacetate have been reported.[1]

Preparative Methods: solutions of lithioacetates are prepared by addition of the appropriate ester to a 1 M THF solution of ***Lithium Diisopropylamide*** maintained at -78 °C. Enolate formation is complete within 15 min and the solutions are normally used directly.[2] Enolization of *t*-butyl acetate in hexane produces a precipitate of amine-free enolate.[1,3] Solutions of the ester enolates are stable at -78 °C, but Claisen ester condensation products form rapidly at 25 °C, perhaps via a ketene intermediate.[4] This instability requires that reactions of the ester enolates be completed at as low a temperature as possible and is perhaps the major limitation to their use.

Alkylation Reactions.[5]

Alkylation of lithioacetates with primary organic halides generally occurs without significant problems of dialkylation or *O*-alkylation.[6] Typically, HMPA is added so that alkylation can be completed at low temperatures. Alkylation

procedures with α-chloroboronic esters,[7] α-halo esters,[8] triflates,[9] and halo epoxides[10] have been reported. In at least one case, alkylation with an epoxide has been achieved (eq 1).[11a] In the case of cyclohexene epoxide, the yield is improved by using the diethylaluminum derivative.[11b] Arylation or vinylation can be achieved by photostimulated reaction with aryl halides,[12] by means of a nickel catalyst,[13] and by reaction with arenetricarbonylchromium complexes (eq 2).[14]

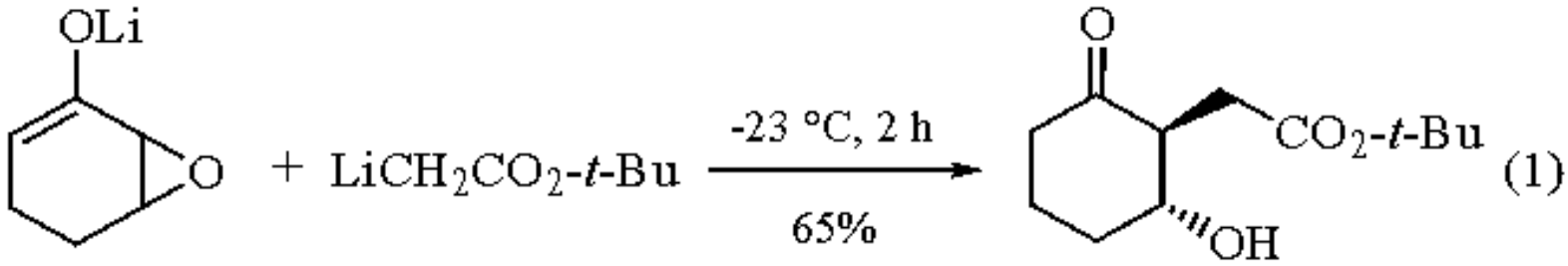

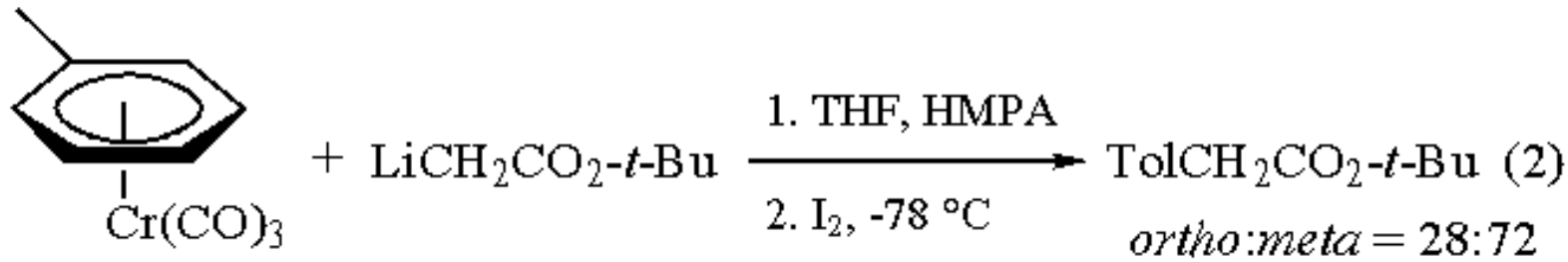

Aldol Condensations.[2]

Aldol condensations of lithioacetates usually proceed rapidly and stable lithium aldolates are obtained with both aldehyde and ketone substrates at -78 °C. If reaction mixtures are allowed to warm prior to quenching, lower yields of β-hydroxy esters may be obtained.[15] Diastereoselective reactions with a variety of chiral aldehydes have been reported.[2,16] Relatively high selectivity (13:1) is obtained with epoxy aldehydes (eq 3).[16a] Condensation of lithioacetates with imine substrates has been used to prepare β-lactams.[17]

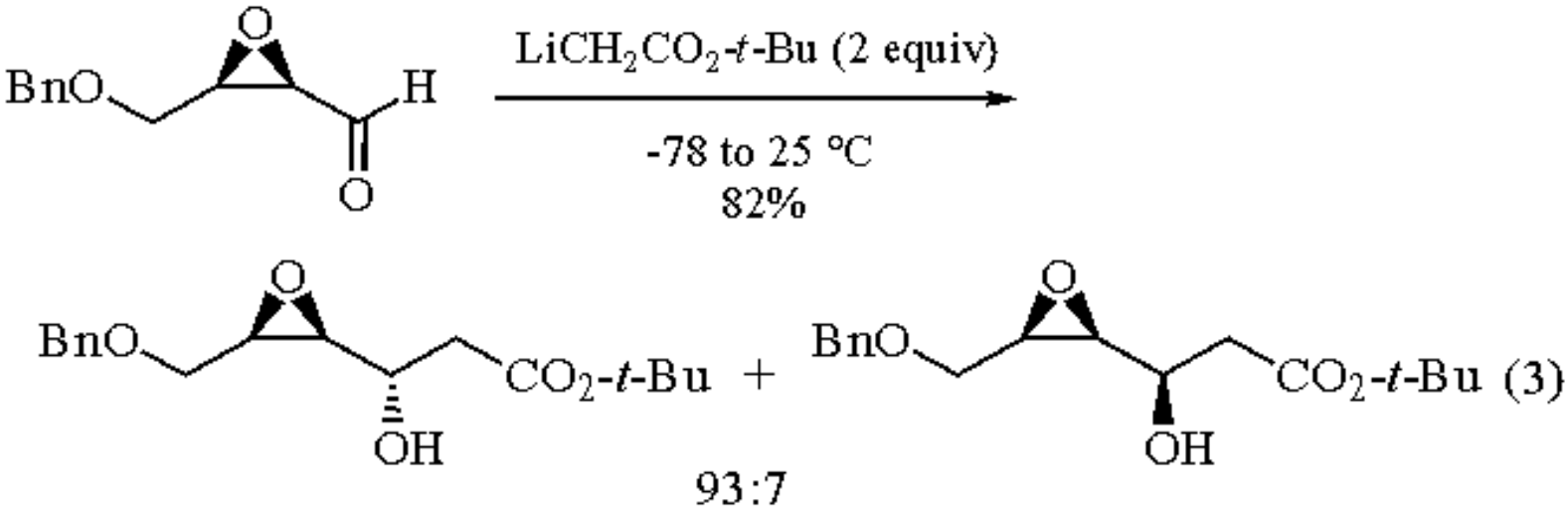

Acylation Reactions.[18]

The acylation of lithioacetates with a variety of acylating agents is possible, including esters,[19] acid chlorides,[20] acyl imidazoles,[21] anhydrides,[22] and thionolactones.[23] In most cases, yields are limited by proton exchange of the acidic β-keto ester product with the starting enolate. This is usually allowed for by using an excess of amide base,[20] or, more commonly, an excess of the lithioacetate (eq 4).[19a]

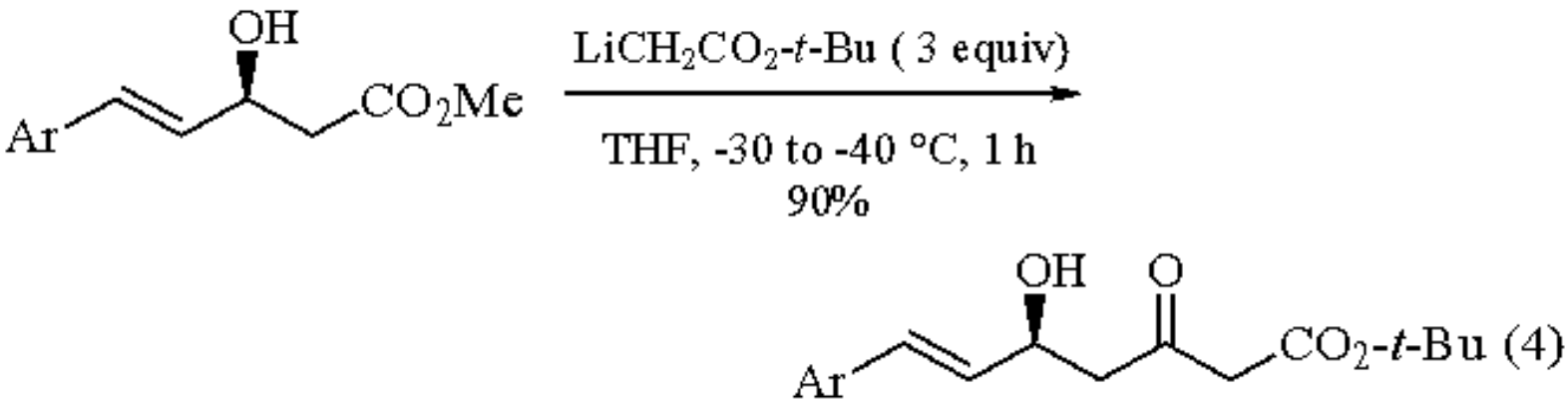

Conjugate Additions.[24]

Conjugate additions of lithioacetates to unsaturated esters,[25] thioamides,[26] acyl ylides,[27] sulfonium salts,[28] and ketones,[29] and to ketene thioacetal monoxides,[30] have been reported. Exceptionally bulky Lewis acids have been used to favor conjugate addition over carbonyl addition to unsaturated ketones.[31] The enolate product of conjugate addition reactions can be used for subsequent alkylation (eq 5)[32] or alkenation (eq 6)[25a] reactions.

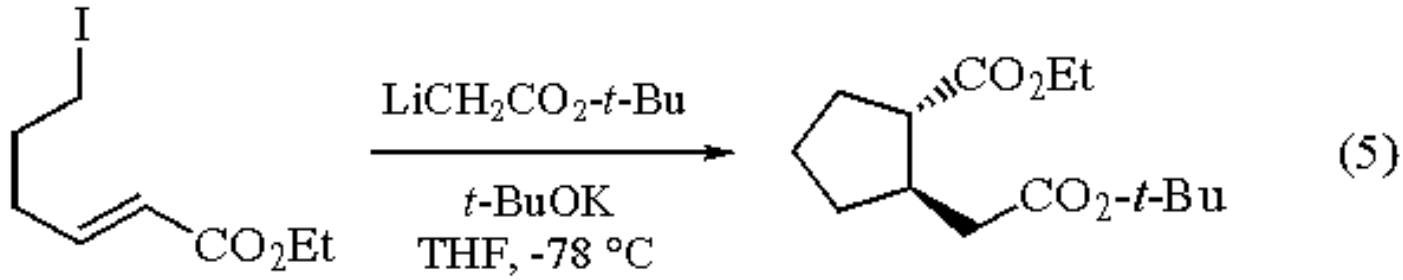

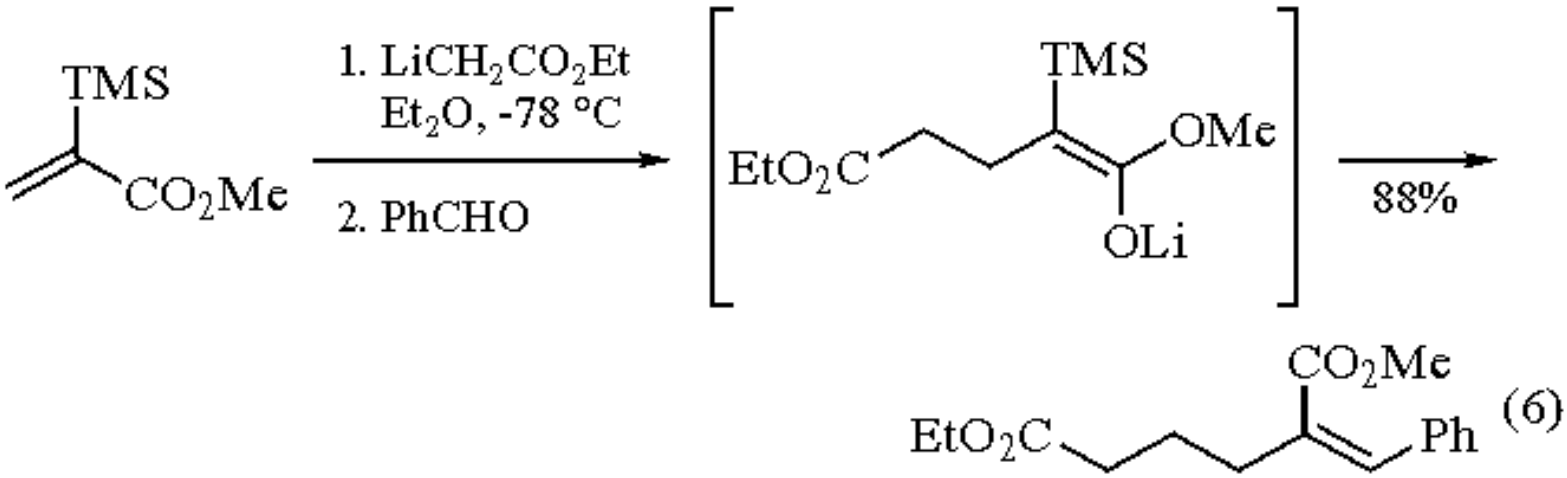

Transmetalation Reactions.

Lithioacetates have been transmetalated by a variety of metal compounds including ***Cerium(III) Chloride***,[33] ***Tri-n-butylchlorostannane***,[34] titanium alkoxides,[35] ***Diethylaluminum Chloride***,[11b] and complexes of nickel and palladium.[36] Reaction of lithioacetates with ***Chlorotrimethylsilane*** gives a mixture of *C*-silylated and *O*-silylated products (eq 7).[6]

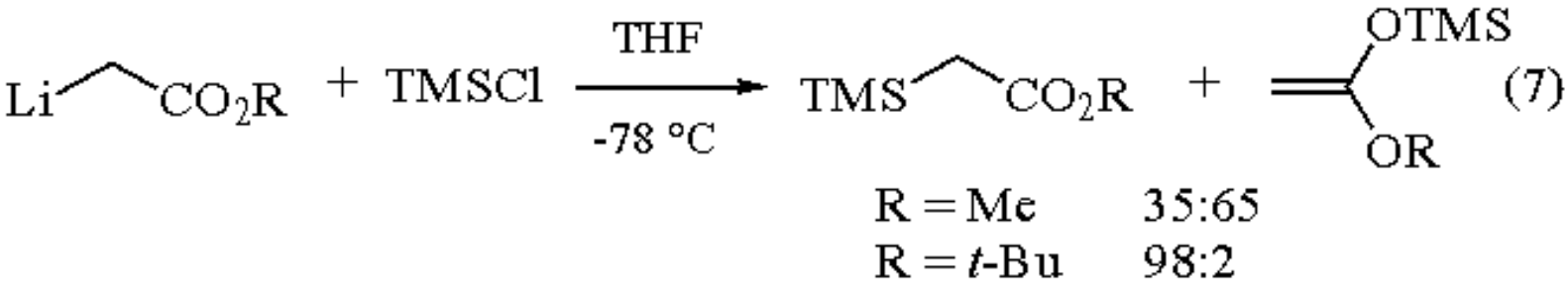

Related Reagents.

t-Butyl α-Lithiobis(trimethylsilyl)acetate; ***t-Butyl α-Lithioisobutyrate***; ***t-Butyl Trimethylsilylacetate***; ***Dilithioacetate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl Trimethylsilylacetate***; ***Phenoxyacetic Acid***.

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Ethyl Lithiopropiolate

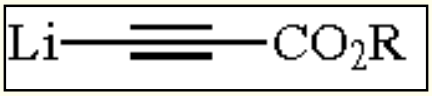

(R = Et)

[72036-30-7] · $C_5H_5LiO_2$ · Ethyl Lithiopropiolate · (MW 104.04) (R = Me)

[72036-29-4] · $C_4H_3LiO_2$ · Methyl Lithiopropiolate · (MW 90.01) (R = *t*-Bu)

[-] · $C_7H_9LiO_2$ · *t*-Butyl Lithiopropiolate · (MW 132.10) (R = $CH_2CH{=}CH_2$)

[109907-88-2] · $C_6H_5LiO_2$ · Allyl Lithiopropiolate · (MW 116.05)

(used in synthesis of alkynic alcohols by addition to aldehydes, ketones,[1] or epoxides[2])

Preparative Methods: by treating the alkyl propiolate (e.g. ***Methyl Propiolate***) with ***n-Butyllithium*** at low temperature.[1] An alternative method uses ***Lithium Diisopropylamide*** (LDA).[2]

Handling, Storage, and Precautions: alkynyllithium reagents are air- and moisture-sensitive. These reagents decompose above -78 °C. The ethyl derivative seems to be slightly more stable than the methyl compound. Ethyl and methyl propiolate should be handled with caution.

Synthesis of Propargyl Alcohols.

The lithium reagent rapidly adds to a variety of aldehydes and ketones to give the alkynic alcohols (eqs 1 and 2).[1] These products may be converted into γ-butenolides and γ-lactones.[3] The use of ***Cerium(III) Chloride*** provides higher yields in some cases (eq 3).[4]

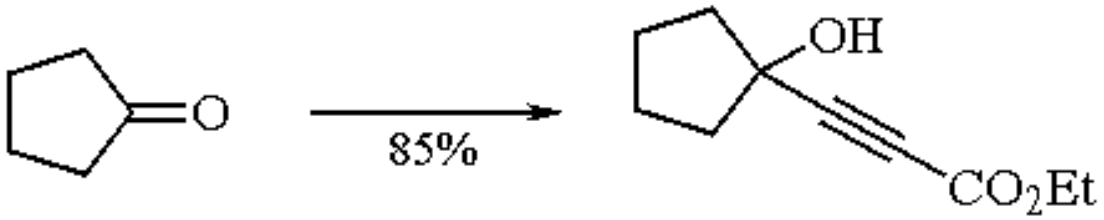

(1)

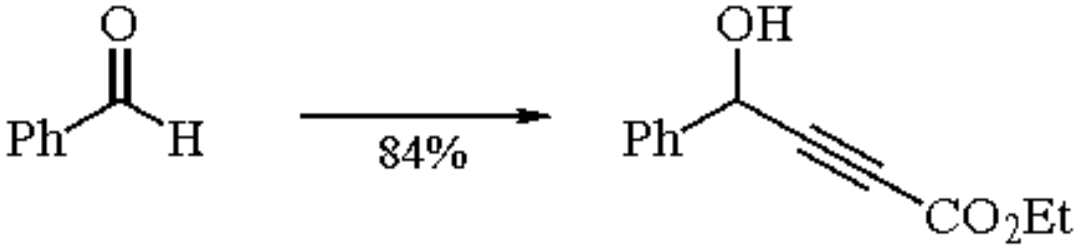

(2)

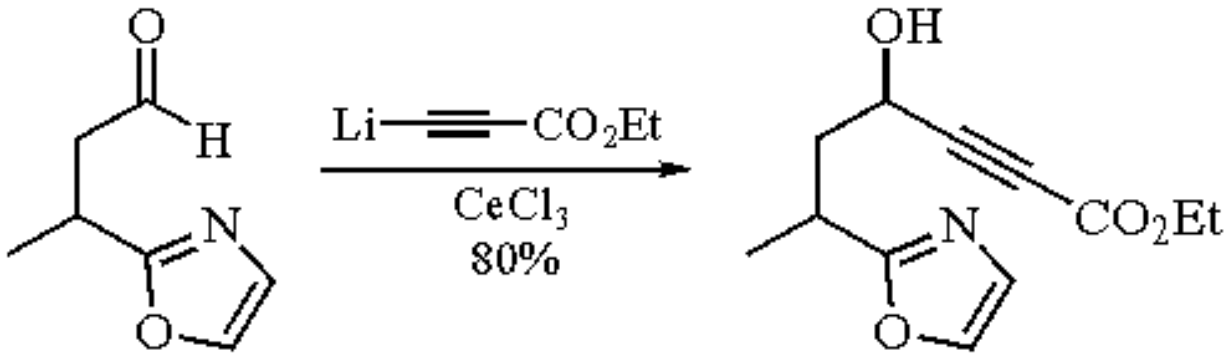

(3)

Synthesis of Homopropargyl Alcohols.

In the presence of ***Boron Trifluoride Etherate*** the reagent will open epoxides to provide homopropargyl alcohols (eq 4).[5] Allyl and *t*-butyl lithiopropiolates have been used in applications where an easily removable protecting group is required.[6]

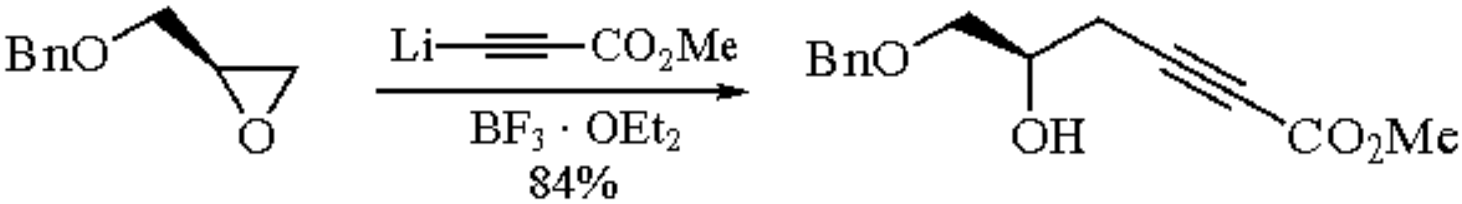

(4)

Related Reagents.

3,3-Diethoxy-1-propene; ***Lithium Acetylide***; ***Propynyllithium***; ***3-Tetrahydropyranyloxy-1-propyne***.

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M. Mark Midland

Ethyl Lithio(trimethylsilyl)acetate[1]

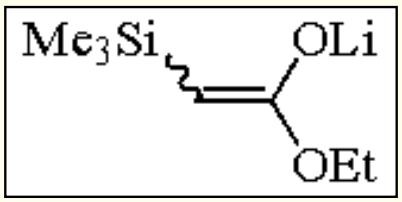

[-] · $C_7H_{15}LiO_2Si$ · Ethyl Lithio(trimethylsilyl)acetate · (MW 166.25)

(reacts with carbonyl compounds to give α,β-unsaturated esters[2])

Solubility: sol ethereal solvents; reacts with protic solvents.

Preparative Methods: available by reaction of ethyl trimethylsilylacetate with ***Lithium Diisopropylamide***, lithium isopropylcyclohexylamide, or lithium dicyclohexylamide in THF at low temperature.[1b,2]

Handling, Storage, and Precautions: as with any other organometallic agent, the reagent should be used under an inert atmosphere.

Peterson Alkenation.

The use of a Peterson approach for the preparation of α,β-unsaturated esters can hold a number of advantages over a Wittig reaction or one of its derivatives.[2] In addition to an easily removed byproduct, hexamethyldisiloxane, silyl esters can provide the desired α,β-unsaturated esters in moderate to good yields when a Wittig approach fails.[1a,3] Stereoselection can also be observed. In some cases, this can be increased by use of a magnesium enolate and acidic workup.[1a,4] While the analogous Wittig approach requires the use of a stabilized ylide and, hence, usually results in the formation of just the (*E*) isomer (or the thermodynamically more stable isomer) of the α,β-unsaturated ester product, the Peterson reaction can either provide a mixture of the isomeric product alkenes, or the (*Z*) isomer if selection is seen.[5] The stereochemical differences can be interpreted in terms of the Wittig reaction being under thermodynamic control, while the Peterson method is kinetically controlled. Thus stereochemical control during the addition of the silicon reagent can result in stereoselective formation of the α,β-unsaturated ester (eq 1).[6]

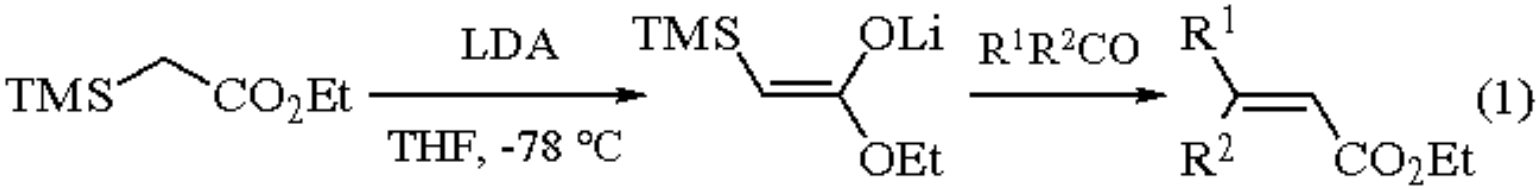

(1)

Alkylations.

Alkylation of the title enolate (**1**) with alkyl iodides in the presence of HMPA allows for the preparation of higher α-silyl esters.[7]

Ester enolate (**1**) can be alkylated by vinyl halides in the presence of a nickel catalyst to afford α-trimethylsilyl-β,γ-unsaturated esters. These products react with a wide variety of electrophiles in the presence of a Lewis acid to provide γ-subsituted α,β-unsaturated esters (eq 2).[8]

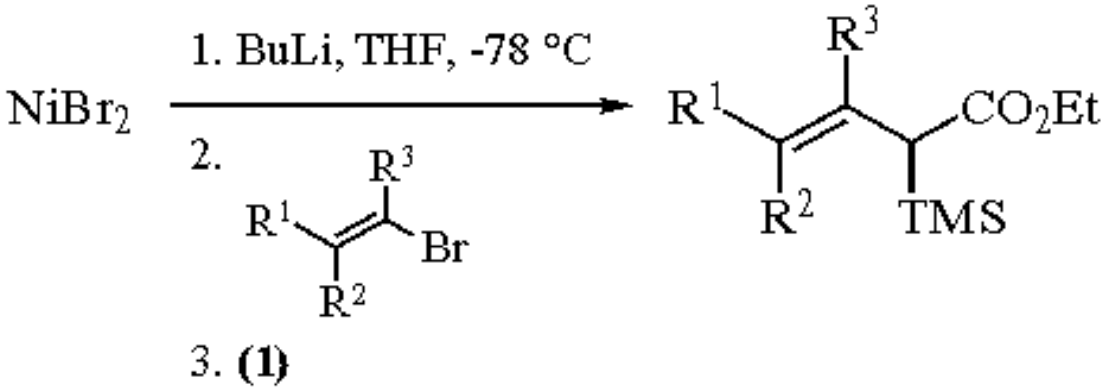

(2)

Other Electrophiles.

In addition to carbonyl compounds, ester enolate (**1**) also reacts with other electrophiles. With nitrones, the product is dependent upon the structure of the nitrone: α,*N*-dialkyl nitrones provide alkenes, while α-aryl-*N*-alkyl nitrones or α,*N*-diaryl nitrones usually give aziridines.[9] With the phenylhydrazone of a 1,2-dicarbonyl compound, reaction with (**1**) provides a convenient preparation of 3(2*H*)-pyridazinones (eq 3).[10]

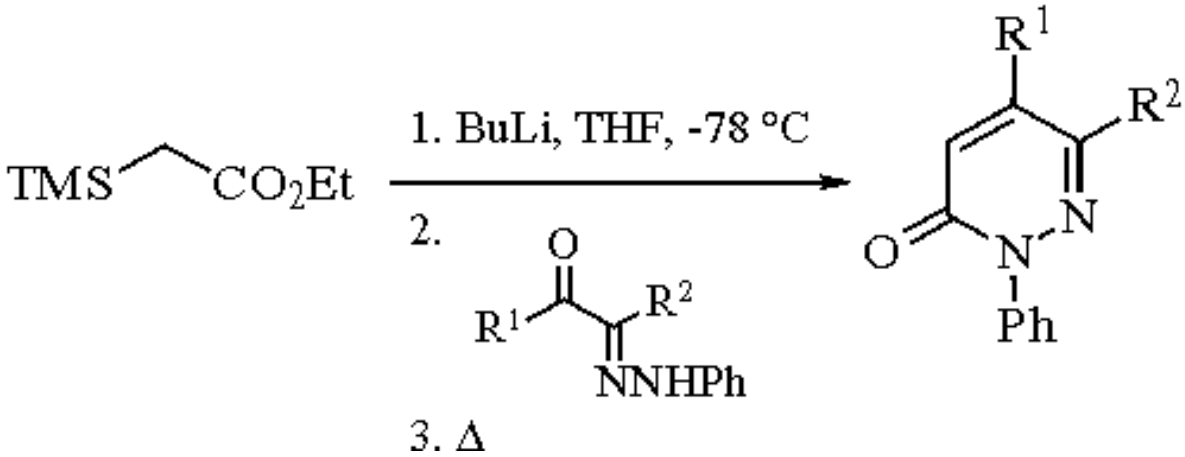

(3)

Analogs.

The ester enolates derived from methyl or *t*-butyl trimethylsilylacetate react in an analogous manner to ethyl ester (**1**) with carbonyl compounds.[1a,3,11] However, with the *t*-butyl ester the carbonyl reactant has to be an aldehyde as steric

problems result in enolization of ketonic substrates.[12] As with the ethyl ester, addition of the enolate to the carbonyl substrate may allow for stereochemical control of the resultant α,β-unsaturated ester geometry.[5c,13] In addition, the groups attached to silicon can be modified without substantial changes to the reactivity with carbonyl compounds.[14]

It is also possible to introduce additional functionality into the α-silyl ester. Thus *t*-butyl (trimethylsilyl)chloroacetate reacts with carbonyl compounds after ester enolate formation with LDA to form *t*-butyl α-chloro-α,β-unsaturated esters, although the elimination of the silyl moiety may have to be encouraged by the use of ***Thionyl Chloride***,[3,15] as it also is with the α-bromo analog.[16] A second silyl group, with its additional bulk, can allow for high stereoselection, although the outcome does depend on the metal counterion used in the enolate.[12,17]

Analogs of the ester enolate derived from higher carboxylic acids can also be prepared by the addition of an organometallic agent to ***Methyl 2-Trimethylsilylacrylate*** (**2**). The resultant ester enolate from the Michael addition can be used for a subsequent Peterson alkenation reaction when reacted with a carbonyl compound (eq 4).[18]

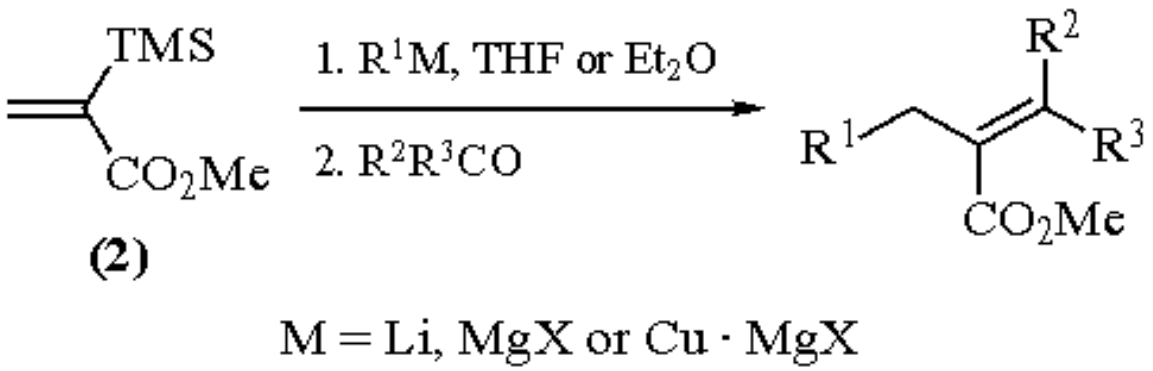

(4)

The sterically demanding *t*-butyl ester enolate reacts with acylimidazoles to provide β-keto esters (eq 5).[19]

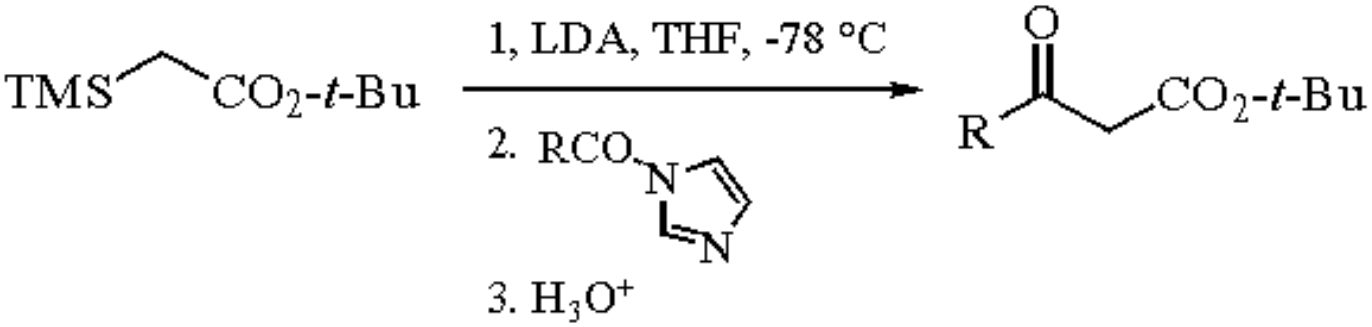

(5)

The ester enolates derived from the methyl or *t*-butyl esters react with lactones to yield vinyl ethers as a mixture of isomers (eq 6).[20]

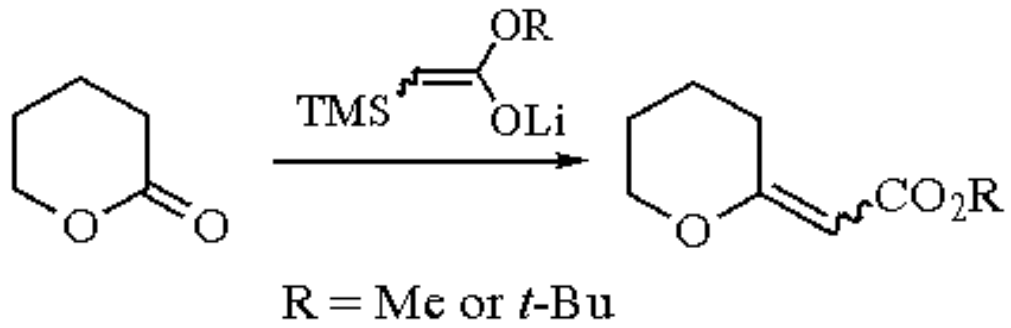

(6)

With cyclopentenone derivatives, 1,4-addition is observed for the ester enolates of methyl and *t*-butyl trimethylsilylacetate,[21] although 1,2-addition occurs with acyclic conjugated enals.[11,12] With a steroidal cyclopentenone substrate, both 1,2- and 1,4-addition were observed.[22] Conjugate addition is observed for the methyl ester with chiral vinyl sulfoxides. High enantioselectivity can be attained (eq 7).[23]

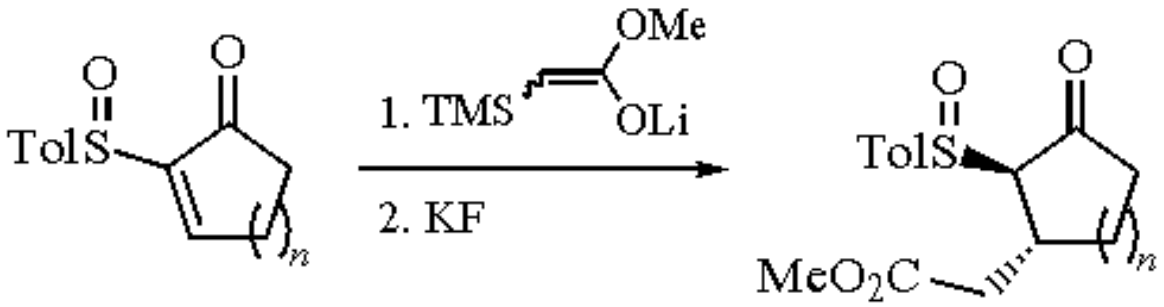

(7)

As with the ethyl ester, other ester derivatives can be alkylated through their lithium enolates.[24] Use of the menthyl ester provides a route to chiral silanes (eq 8).[25]

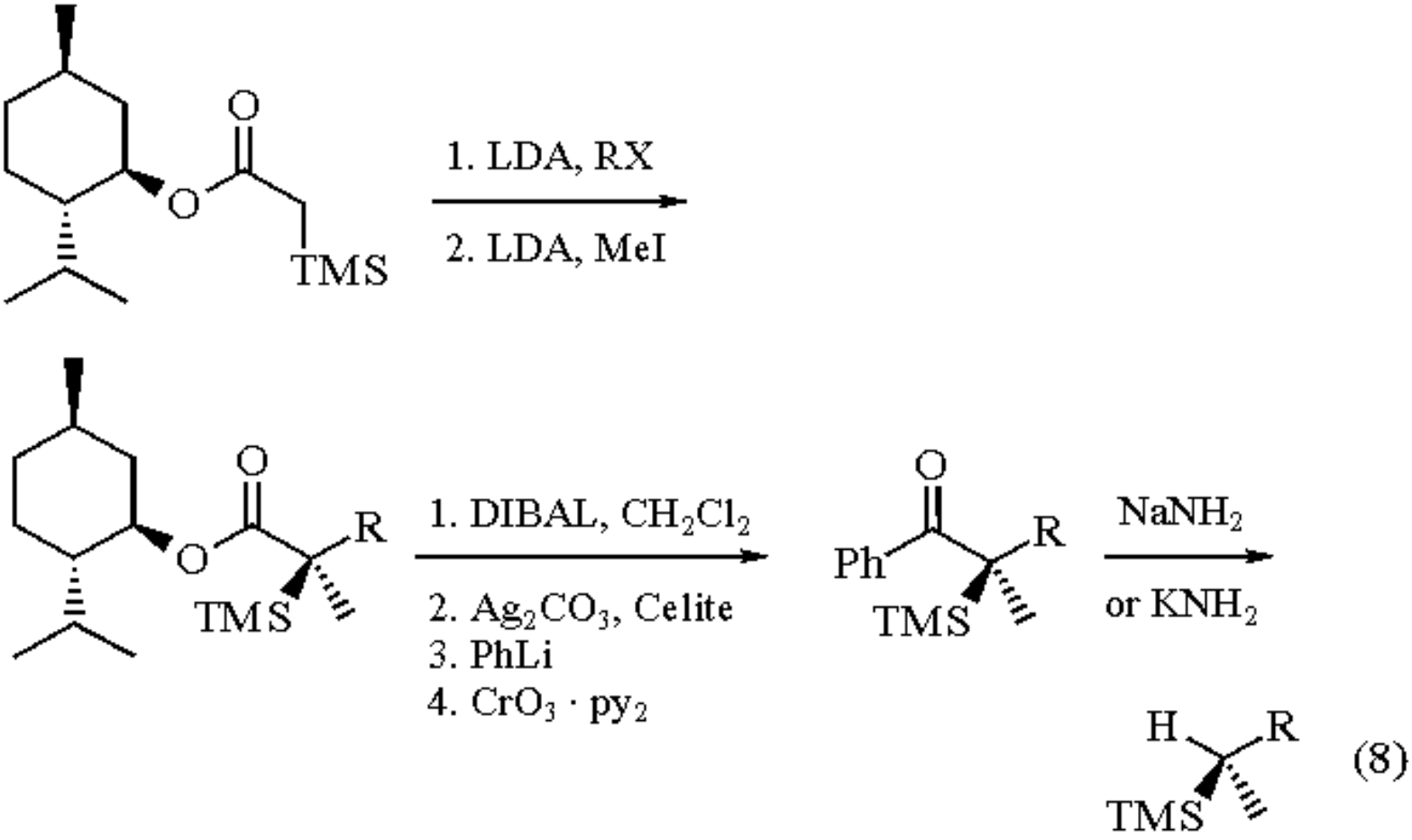

Related Reagents.

t-Butyl* α*-Lithiobis(trimethylsilyl)acetate; ***t-Butyl Trimethylsilylacetate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Ethyl Trimethylsilylacetate***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; Methyl (Methyldiphenylsilyl)acetate; ***Methyl 2-Trimethylsilylacrylate***; ***Triethyl Phosphonoacetate***; ***Trimethylsilylacetic Acid***.

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Ethyllithium[1]

EtLi

[811-49-4] · C_2H_5Li · Ethyllithium · (MW 36.01)

(organometallic reagent used in 1,2-[2] and 1,4-additions;[2a,b,3] synthesis of various transition metal complexes;[4] used as a base in the preparation of 2-bromofuran,[5a] with phenylallene to form terminal alkynes,[5b] as a catalyst in conjunction with TMEDA in the alkylation of amines with alkenes;[5c] used for the in situ preparation of lithium diethylcuprate,[2a,3b,6] and EtCu(CN)Li.BF_3[6])

Physical Data: mp 95 °C; sublimes at 80 °C/10^{-3} mmHg.

Solubility: sol hydrocarbons, THF, Et_2O.

Form Supplied in: approx. 1 M light brown solution in benzene.

Preparative Methods: prepared from alkyl halides and elemental lithium.[8a-e]

Purification: recrystallized from hexane[8e] or cyclohexane[8c,d] under argon at 4 °C to give a white solid.

Handling, Storage, and Precautions: the dry solid is extremely pyrophoric on exposure to air. Solutions are flammable, corrosive and react violently with water and should be used immediately. Storage for as little as one week at low temperatures can lead to up to one-half of the reagent being converted to ethane, ethylene, and the enolate of acetaldehyde.[3a,8a,d,e]

Nucleophilic Addition.

Ethyllithium is known to add as a nucleophile to α,β-unsaturated ketones in both a 1,2- and 1,4-manner. Addition of ***Hexamethylphosphoric Triamide*** (HMPA) enhances selectivity of 1,4-addition, as illustrated in eq 1. This selectivity is also affected by coordinating ability of the solvent. A general order for increasing 1,4-selectivity is EtLi (pet. ether) <= EtLi (Et_2O) <= EtLi (1 equiv HMPA) <= EtLi (2 equiv HMPA).[2a] Similar results were obtained for reactions with MVK, 2-cyclohexen-1-one, and 2-cycloocten-1-one.

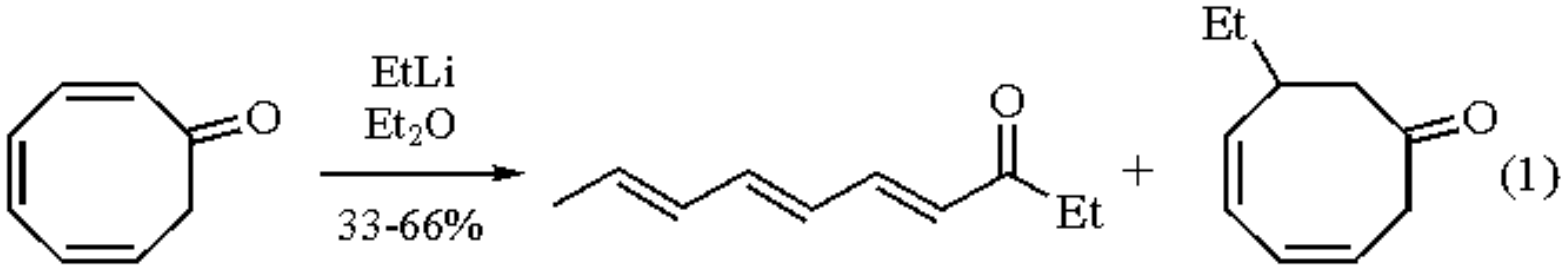

	1,2-addition, rearrangement	1,4-addition
EtLi	80%	20%
EtLi + HMPA (1 equiv)	24%	76%
EtLi + HMPA (2 equiv)	0%	100%

Ethyllithium undergoes nucleophilic addition with pyridine to afford exclusively the 1,2-adduct. When used in conjunction with diethylmagnesium, however, significant amounts of 1,4-adducts are observed (eq 2). This mixed organometallic system also provides enhanced 1,4-selectivity when reacted with 2-cyclohexen-1-one.[2b]

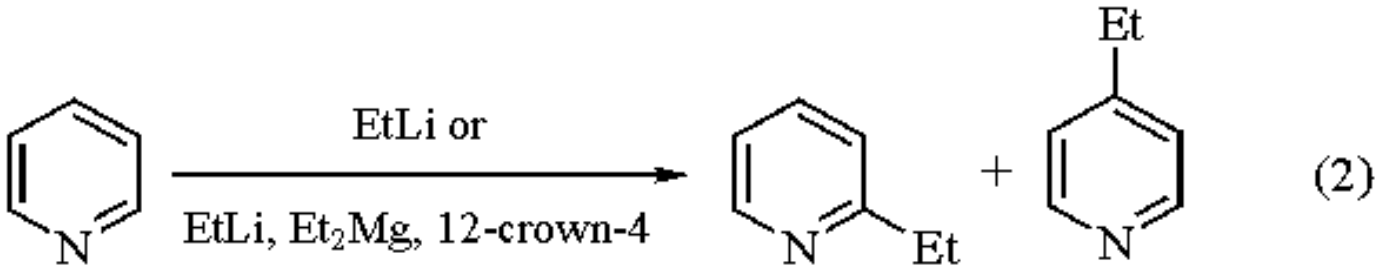

EtLi	100%	0%
mixed system	27%	54%

1,2-Addition of ethyllithium to triethyl phosphate is known to generate precursors for Horner reagents, as shown in eq 3.[2c,d]

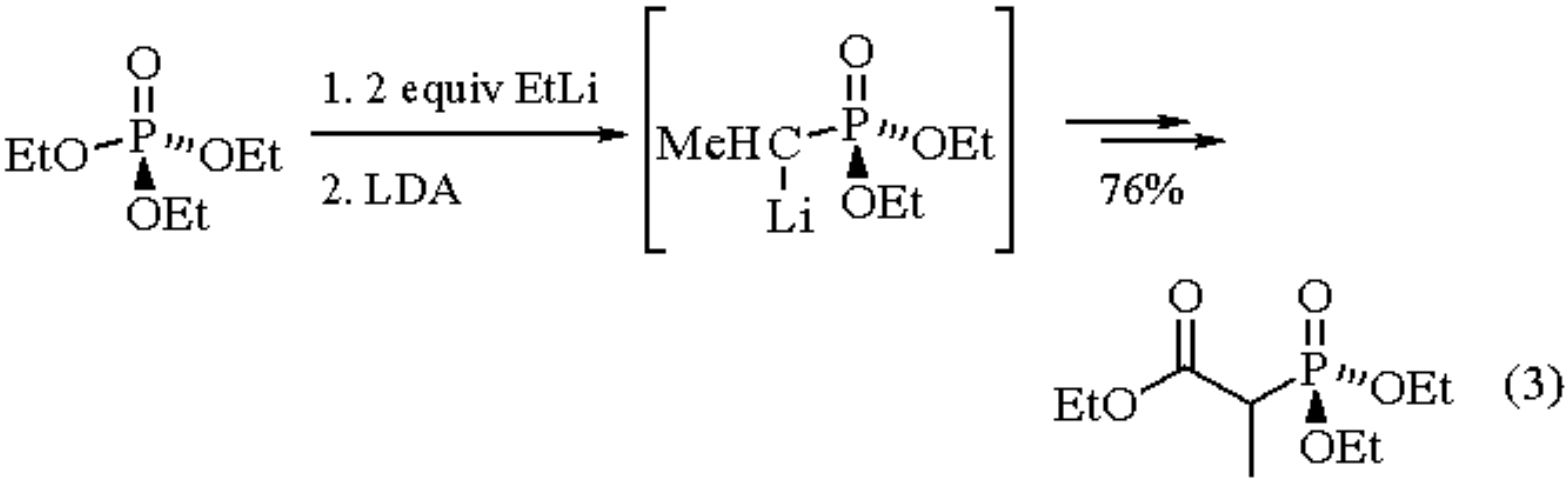

Addition to benzoquinone is exclusively 1,2- with the second addition favoring the *cis* isomer by a 4:1 ratio.[2e] Also

noted is 1,2-addition to amides followed by dehydration of the resulting aminal.[2f] Ethyllithium acts first as a base and then as a nucleophile in its reaction with aldehyde-*O*-alkyloximes. Ethyl ketones are prepared by their reaction with ethyllithium followed by hydrolysis of the imine (eq 4).[2g]

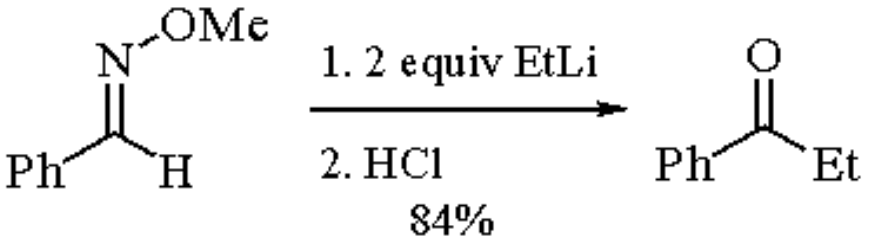

(4)

Azophilic 1,2-addition has been observed for the addition of ethyl- and *n*-butyllithium to fluorenimines.[2h] Superior diastereoselectivity to titanium and copper reagents is exhibited by EtLi in its 1,2-addition to acrolein dimer during chelation-free formation of the dihydropyranols illustrated in eq 5. Complementary selectivity is possible when other reagents are employed.[2i]

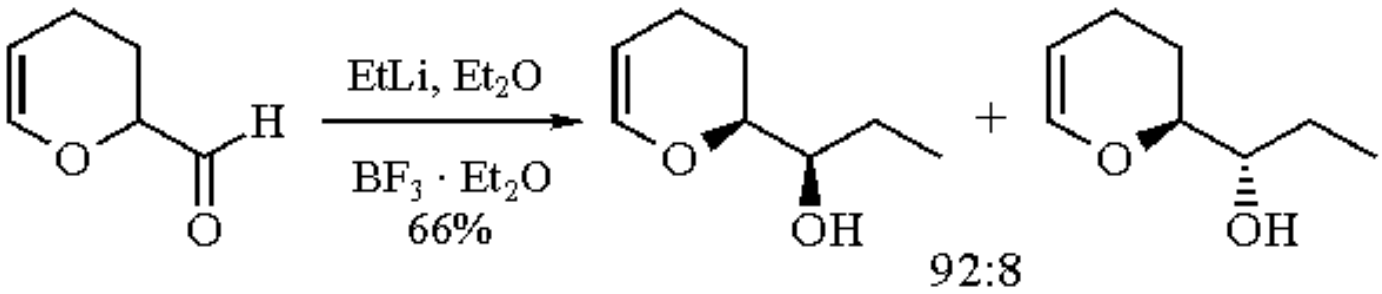

(5)

Metal-mediated asymmetric 1,2-nucleophilic attack by ethyllithium at C-2 (eqs 6 and 7) occurs exclusively *exo* to the $Fe(CO)_3$ group of (vinylketenimine)tricarbonyliron(0) complexes to give chiral quaternary centers of high optical purity.[2j]

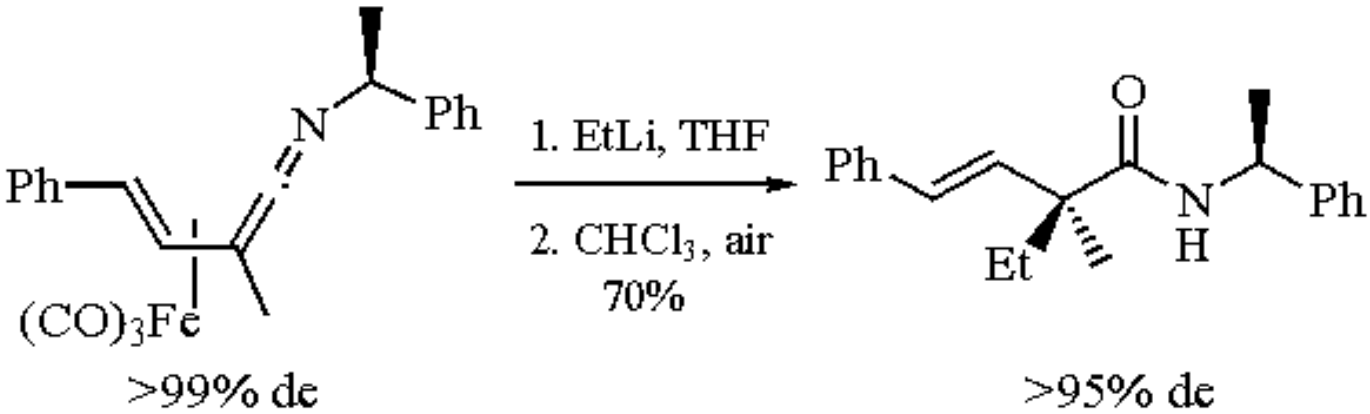

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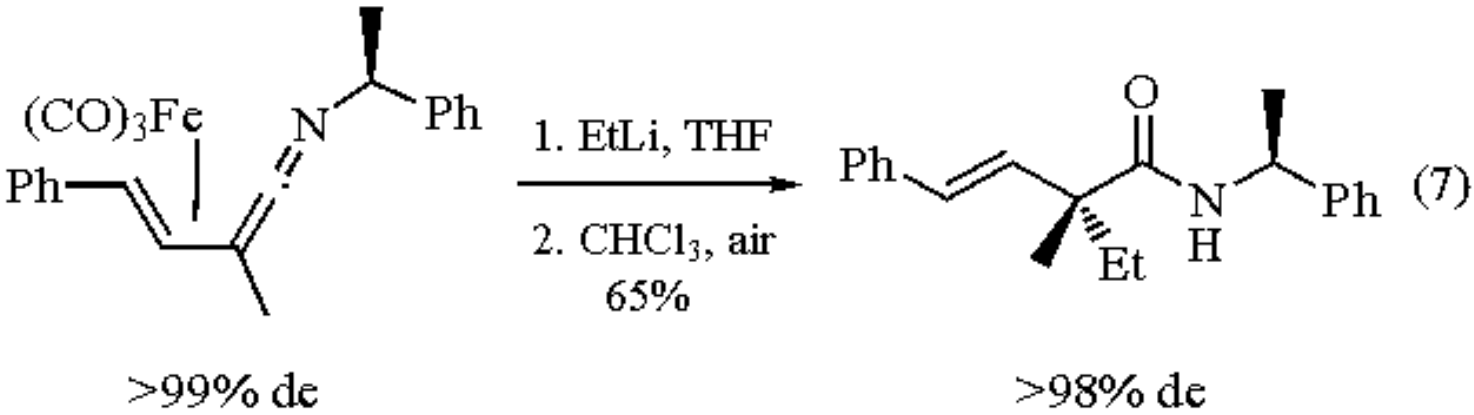

On the contrary, chelation-controlled 1,4-addition of ethyllithium to acylketene acetals with diastereoselective enolate trapping has been reported (eq 8).[3a,b]

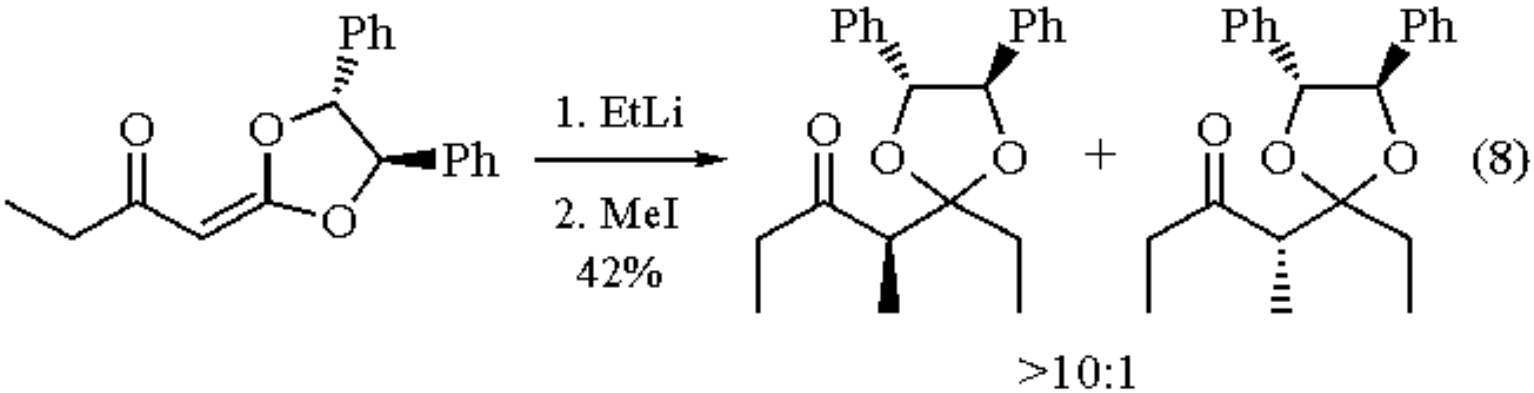

Similarly, tandem 1,4-additions of alkyllithium reagents to chiral aromatic and unsaturated oxazolines followed by electrophilic trapping with ***Iodomethane*** proceed in good yield and with excellent diastereoselectivity (eq 9).[3c]

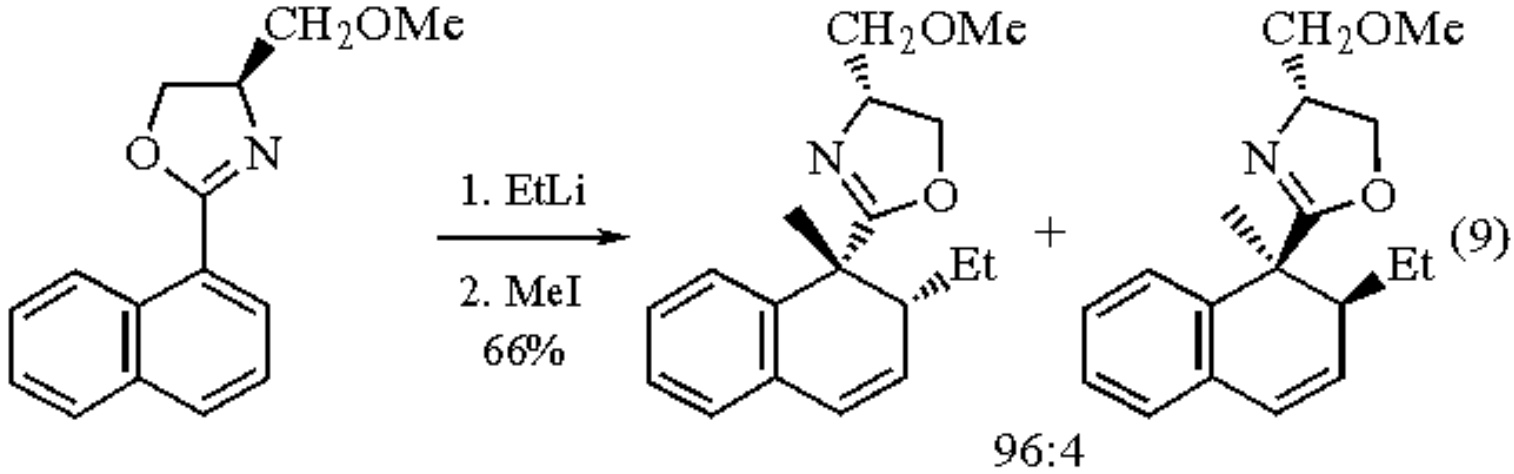

Synthesis of Organometallic Complexes.

Ethyllithium has been employed in the synthesis of ethylenic organometallic compounds,[4] including a Ziegler-Natta polymerization precursor complex that contains both an alkyl ligand and a coordinated alkene (eq 10),[4a] and a hydridobis(ethylene)rhenium(I) complex (eq 11).[4d]

$$HfCl_4 + 6\,EtLi + 2\,TMEDA \longrightarrow [Li(TMEDA)]_2[Hf(C_2H_4)Et_4] \quad (10)$$

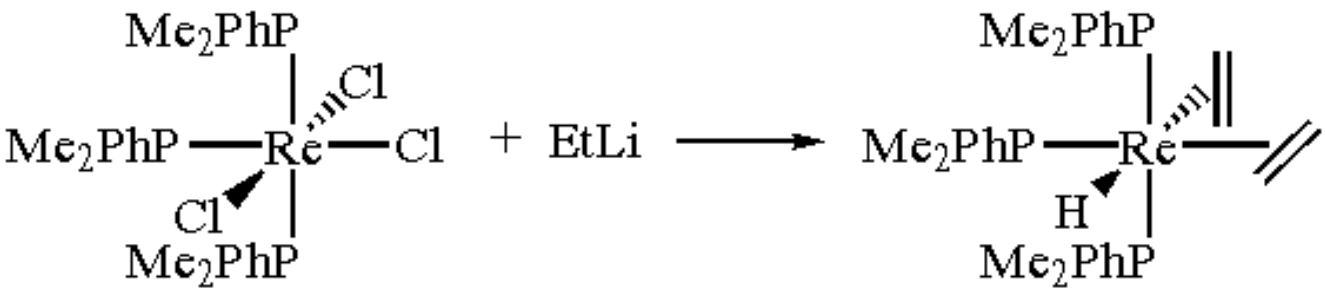

(11)

Use as a Base.

A clean procedure for the preparation of 2-bromofuran involves the lithiation of furan in diethyl ether followed by treatment with elemental ***Bromine*** (eq 12).[5a] Solutions of other alkyllithium reagents are impractical for this procedure due to the necessity of removal of less volatile solvents prior to their subsequent replacement by Et_2O.

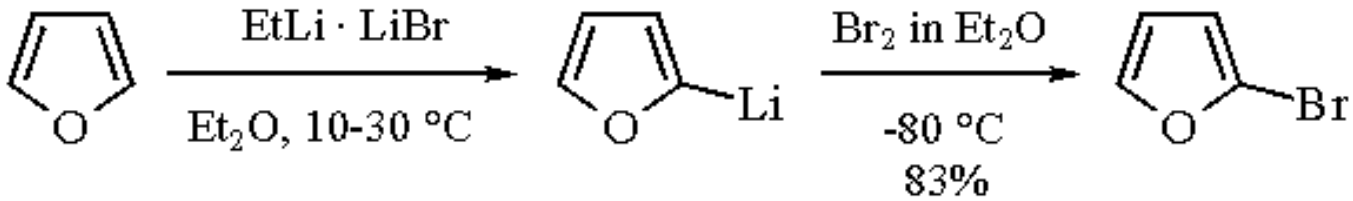

(12)

Reaction of phenylallene with two equivalents of ethyllithium followed by reaction with reactive electrophiles provides access to terminal alkynes (eq 13).[5b] The intermediate dianion readily undergoes alkylation exclusively at the sp^3 center.

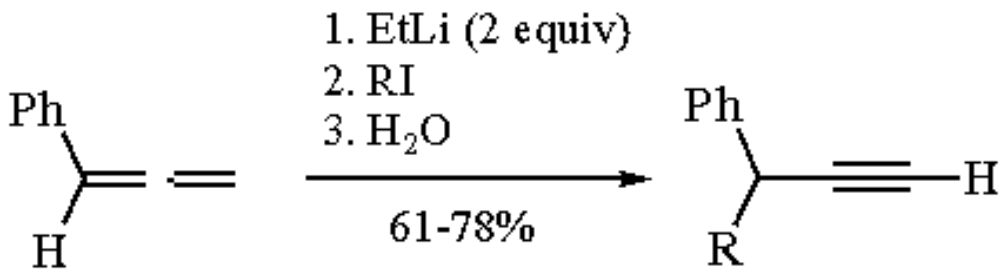

(13)

Ethyllithium serves as catalytic base in the alkylation of amines with alkenes in the presence of TMEDA.[5c]

Preparation of Other Reagents.

The in situ preparations of ***Lithium Diethylcuprate***[2a,6] and $EtCu(CN)Li.BF_3$[7] are widely documented. A chiral mixed ethylcuprate was used to produce (*R*)-(+)-3-ethylcyclohexanone with high selectivity (ee >95%) only when freshly prepared and recrystallized ethyllithium was used to make the reagent. Trace alkoxide contamination lowered the ee to

9%.[6b]

Related Reagents.

Diethylzinc.

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1. *FF* **1975**, *5*, 306. *FF* **1975**, *5*, 324. *FF* **1981**, *9*, 84. *FF* **1988**, *13*, 177.
2. (a) Ogawa, M.; Takagi, M.; Matsuda, T. *T* **1973**, *29*, 3813. (b) Richey, H. G., Jr.; Farkas, J., Jr. *OM* **1990**, *9*, 1778. (c) Tay, M. K.; About-Jaudet, E.; Collignon, N.; Teulade, M.-P.; Savignac, P. *SC* **1988**, *18*, 1349. (d) Teulade, M.-P.; Savignac, P.; About-Jaudet, E.; Collignon, N. *SC* **1989**, *19*, 71. (e) Alonso, F.; Yus, M. *T* **1991**, *47*, 7471. (f) Shibagaki, M.; Matsushita, H.; Kaneko, H. *H* **1986**, *24*, 2315. (g) Itsuno, S.; Miyazaki, K.; Ito, K. *TL* **1986**, *27*, 3033. (h) Dai, W.; Srinivasan, R.; Katzenellenbogen, J. A. *JOC* **1989**, *54*, 2204. (i) Singh, S. M.; Oehlschlager, A. C. *CJC* **1988**, *66*, 209. (j) Richards, C. J.; Thomas, S. E. *TA* **1992**, *3*, 143.
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Ethylmagnesium Bromide

EtMgBr

[925-90-6] · C_2H_5BrMg · Ethylmagnesium Bromide · (MW 133.28)

(ethyl group introduction; used for preparation of other Grignard reagents)

Solubility: sol diethyl ether (6.8 M L^{-1}), dibutyl ether (5.4 M L^{-1}), diisopropyl ether (1.0 M L^{-1}), THF (1.5 M L^{-1}), anisole (0.28 M L^{-1}).

Form Supplied in: 3.0 M solutions in diethyl ether (*d* 1.020 g mL^{-1}), 1.0 M solution in THF (*d* 1.010 g mL^{-1}) and 1.0 M solution in *t*-butyl methyl ether (*d* 0.841 g mL^{-1}).

Preparative Methods: details for preparation and determination of concentration are available.[1]

Handling, Storage, and Precautions: for preparation and use of EtMgBr the usual requirements for Grignard reagents must be considered (anhydrous ***Magnesium*** turnings and solvents, inert atmosphere). Reaction apparatus and bottles for storage of EtMgBr should be flushed with N_2 and protected from moisture. At the end of the reaction the BrMg derivatives can be decomposed by adding dil acid. If the reaction product is sensitive to acid, hydrolysis can be done with a saturated NH_4Cl solution.[1]

Reactions with Carbonyl Compounds.

EtMgBr with aldehydes produces secondary alcohols. Various aliphatic,[2] aromatic,[3] and allylic[4] aldehydes are transformed into corresponding hydroxy derivatives in 50-100% yield. Stereoselectivity of EtMgBr addition to the terminal or secondary aldehyde group is low; the Cram and anti-Cram isomers are formed in ratio 2:1 to 4:1. Unexpected anti-Cram selectivity is achieved in the MAD- or MAT-mediated alkylation of nonchelating α-chiral aldehydes (MAD = ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)***; MAT = ***Methylaluminum Bis(2,4,6-tri-t-butylphenoxide)***).[5] The Cram selectivity is enhanced (9:1) with addition of crown reagents;[6] nevertheless, Et_2Mg gives Cram isomers with greater selectivity than EtMgBr.crown. ***Hexamethylphosphoric Triamide*** as cosolvent also affects the stereochemistry of addition.[7]

Addition of EtMgBr to ketones (including cyclobutanone and macrocyclic ketones[8]) produces tertiary alcohols. The addition of ***Cerium(III) Chloride*** suppresses side reactions of enolizable ketones.[9] Stereoselectivity of the addition depends on ketone structure, solvent, temperature,[10] and reagents for stereoselective activation (eqs 1-3).[5,11]

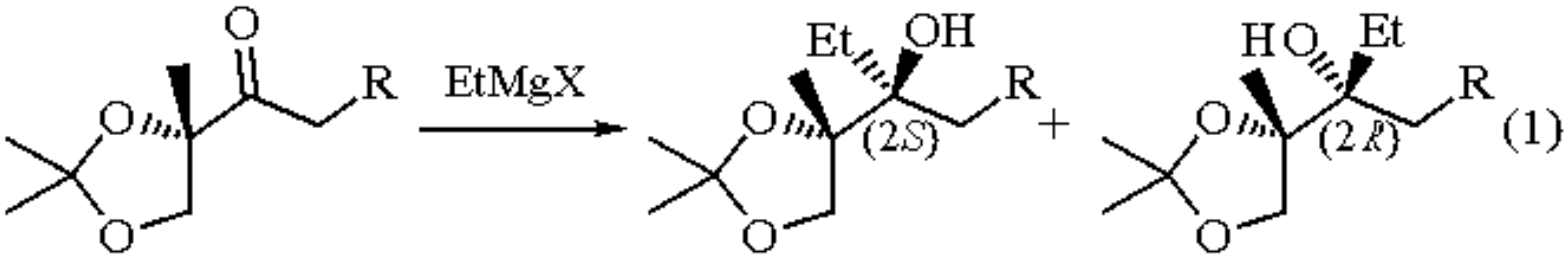

X	°C	Yield (%)	(2*S*):(2*R*)
I	-78	89	53:47
Br	-78	86	11:89
Br	0	94	3:97

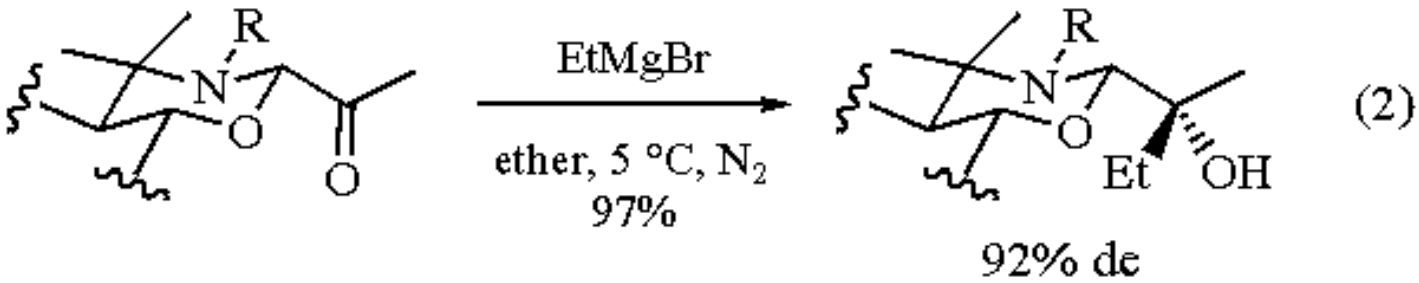

Highly stereoselective (92:8) addition to 2-acetyl-1,3-oxazine derivatives (eq 2)[12] is controlled by chelation to the oxygen rather than the nitrogen atom of the ring. Addition opposite to the 2-substituent side with formation of *cis*-cyclohexanols is predominant for 2-substituted cyclohexanones (eq 3).[13] 3-Substituted *N*-alkylpiperidin-4-one derivatives[14] react in a similar stereoselective manner. Addition to 4-*t*-butylcyclohexanones is nonselective: equal amounts of both equatorial and axial cyclohexanols are produced. The organoaluminum compound MAD[5] can be used for stereoselective activation to produce equatorial cyclohexanols exclusively.

In general, esters with an excess of Grignard reagent produce tertiary alcohols[15] (secondary alcohols from formic acid esters). In contrast, the one-pot synthesis of secondary alcohols from esters and EtMgBr/***Lithium Borohydride*** results from a slow addition of EtMgBr to the ester to provide a ketone intermediate which is reduced rapidly with $LiBH_4$ to form a secondary alcohol (eq 4).

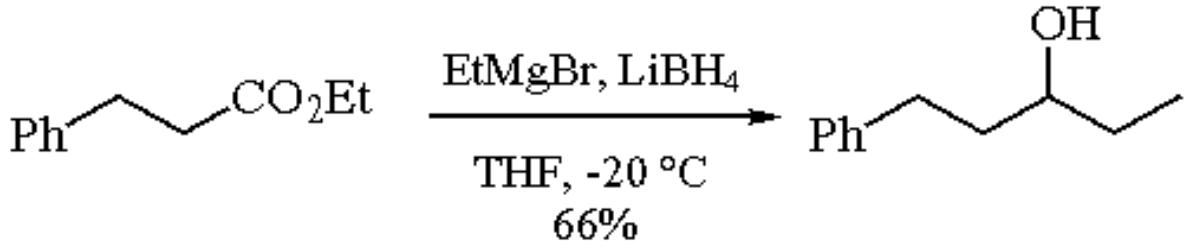

(4)

EtMgBr can be used for ester *O*-acyl bond cleavage and removal of common acyl groups[16] without affecting base-sensitive groups (silyl ether, halide, or phosphate) adjacent to the ester (eq 5). Debenzoylation of secondary alkyl esters requires excess of the reagent (up to 30 equiv). Interaction of alkyl esters with EtMgBr in the presence of ***Titanium Tetraisopropoxide*** results in hydroxy cyclopropane formation (eq 6). Ring opening produces an ethyl ketone.[17]

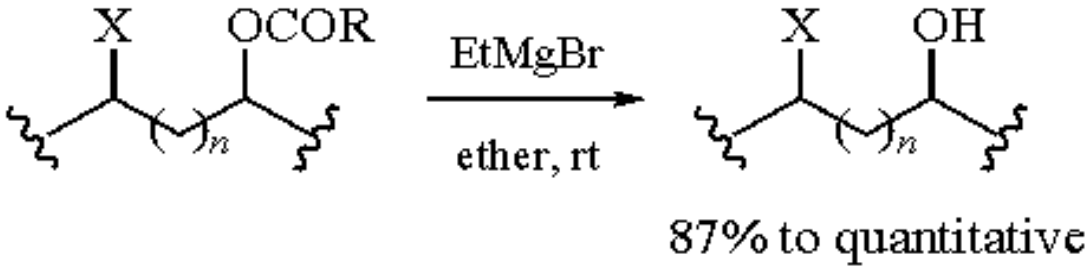

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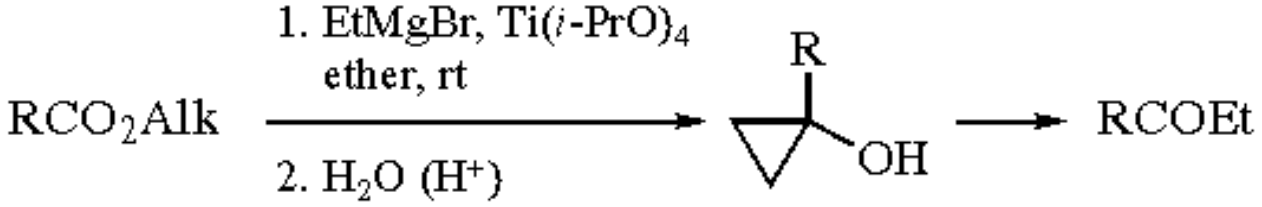

(6)

γ-Butyrolactone treated with EtMgBr in excess generates 4-ethylhexane-1,4-diol (eq 7).[18] α-Silylated derivatives of γ-butyro- and γ-valerolactone react with the Grignard reagent to give 2-substituted 4,5-dihydrofurans,[19] useful for the production of γ-keto acids (eq 8).

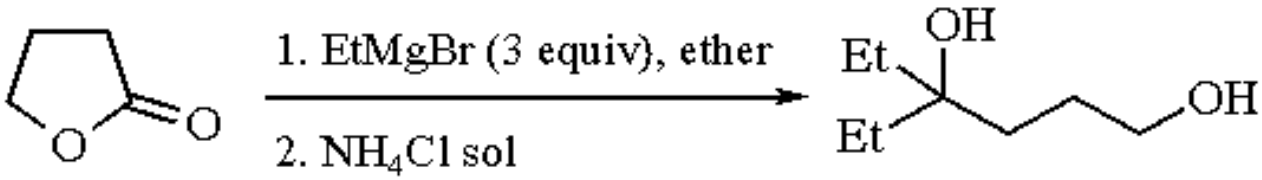

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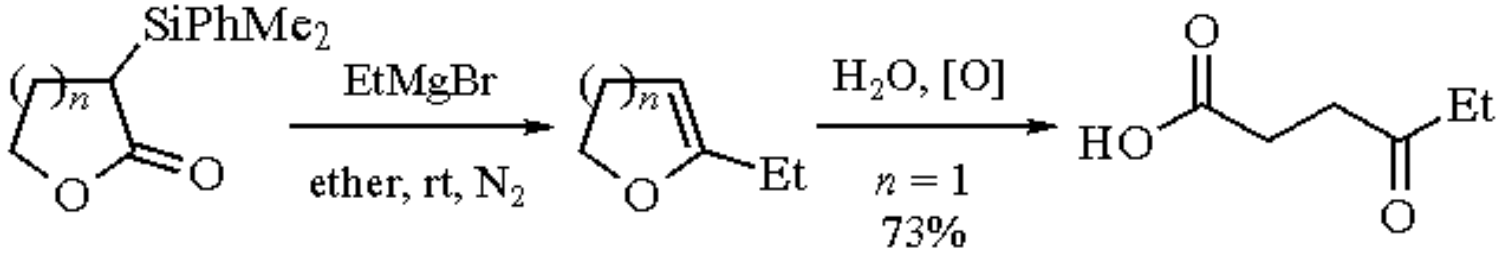

(8)

Halogenated 2-oxocoumarins react like γ-lactones, affording the ring-opening products and 4-ethyldihydrocoumarin derivatives (eq 9).[20] Lactone ring opening can be effected by EtMgBr in benzene, whereas in ether or THF the addition reaction is predominant.

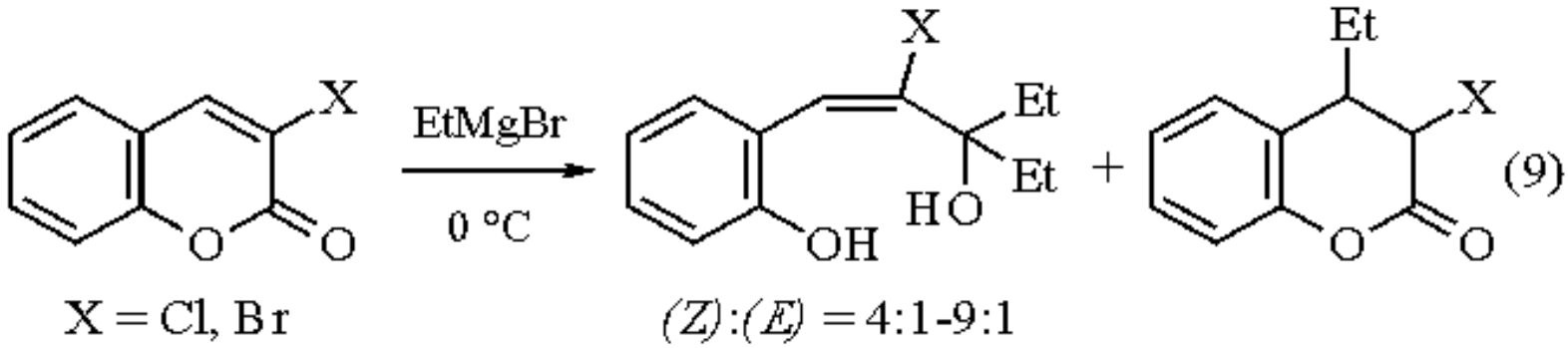

The reaction of ***Diketene***[21] with EtMgBr in the presence of the $NiCl_2${bis(diphenylphosphino)propane} complex gives 3-methylenepentanoic acid (eq 10).

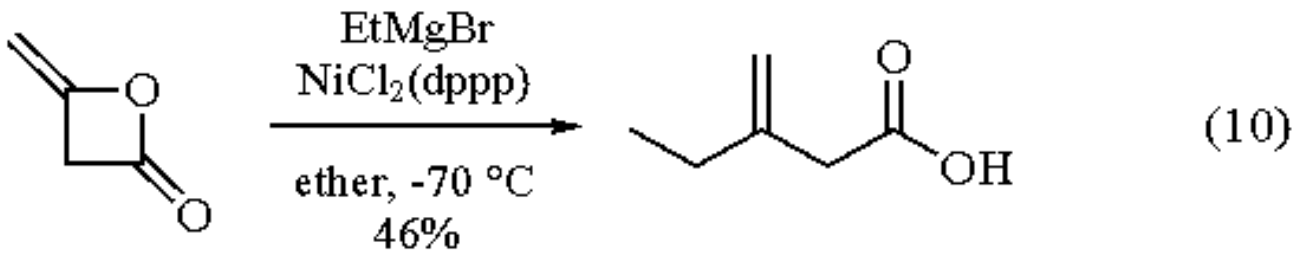

Acyl chlorides react with EtMgBr, affording ethyl ketones (eq 11). The reaction is applicable to acyl chlorides of high CH acidity.[22,23]

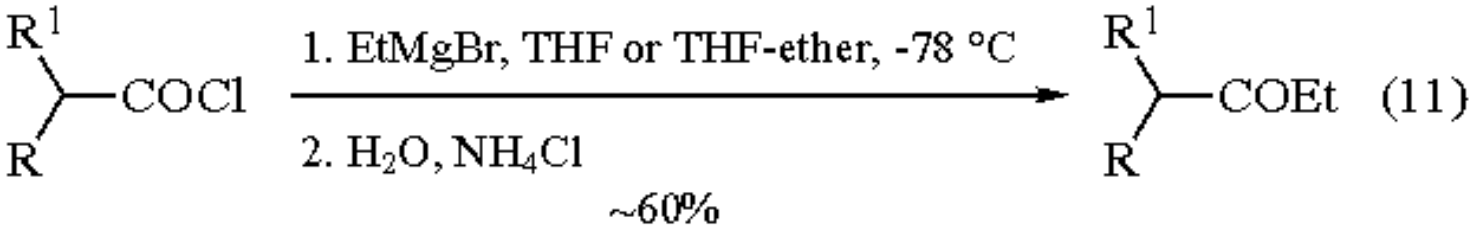

Cyclic anhydride reactions with EtMgBr can give products of anhydride ring opening[24] (eq 12), or the hydroxy acid formed may lactonize (eq 13).[25]

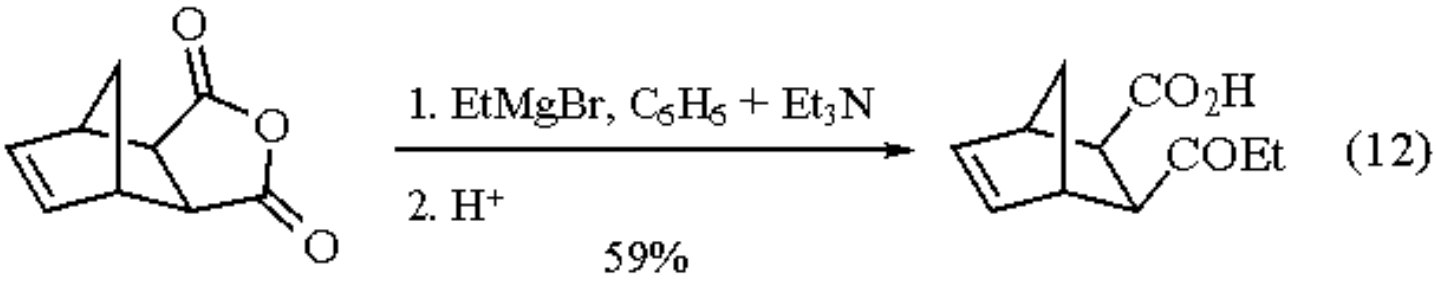

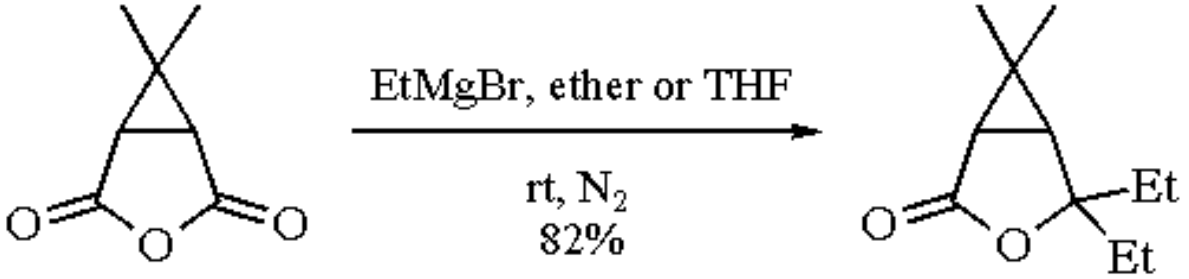

(13)

Interaction with C=C, C=N, and C&tbond;N Bonds.

The regioselectivity of EtMgBr addition to double bonds is determined by substrate structure. Regioselective 1,4-addition of EtMgBr to 2*H*-benzopyrans and 2-oxobenzopyran[26] is observed. Allenic[27] bonds and double bonds conjugated with azomethines[28] undergo 1,2-addition. Reactions with conjugated enynes[29] lead to both γ-alkynic (1,2-addition) and β-allenic (1,4-addition) compounds. Chiral zinc(II) complexes[30] catalyze the asymmetric 1,4-addition to α,β-unsaturated ketones. High stereoselectivity can be achieved in conjugate additions of γ-hydroxy enones[31] (eq 14). Preliminary complexation of EtMgBr with the alkoxide, followed by Et group transfer, results in formation of the *syn* product (*anti*:*syn* = 0:100).

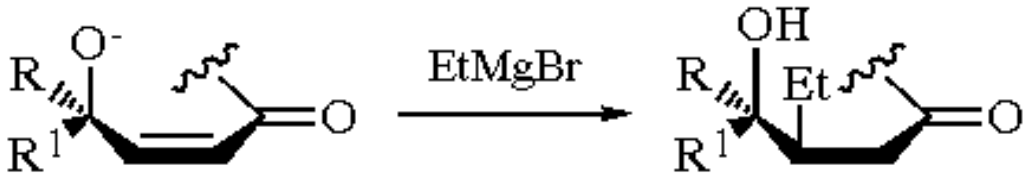

(14)

Several removable chiral auxiliaries have been used to achieve diastereoselective conjugate addition (eq 15).[32,33]

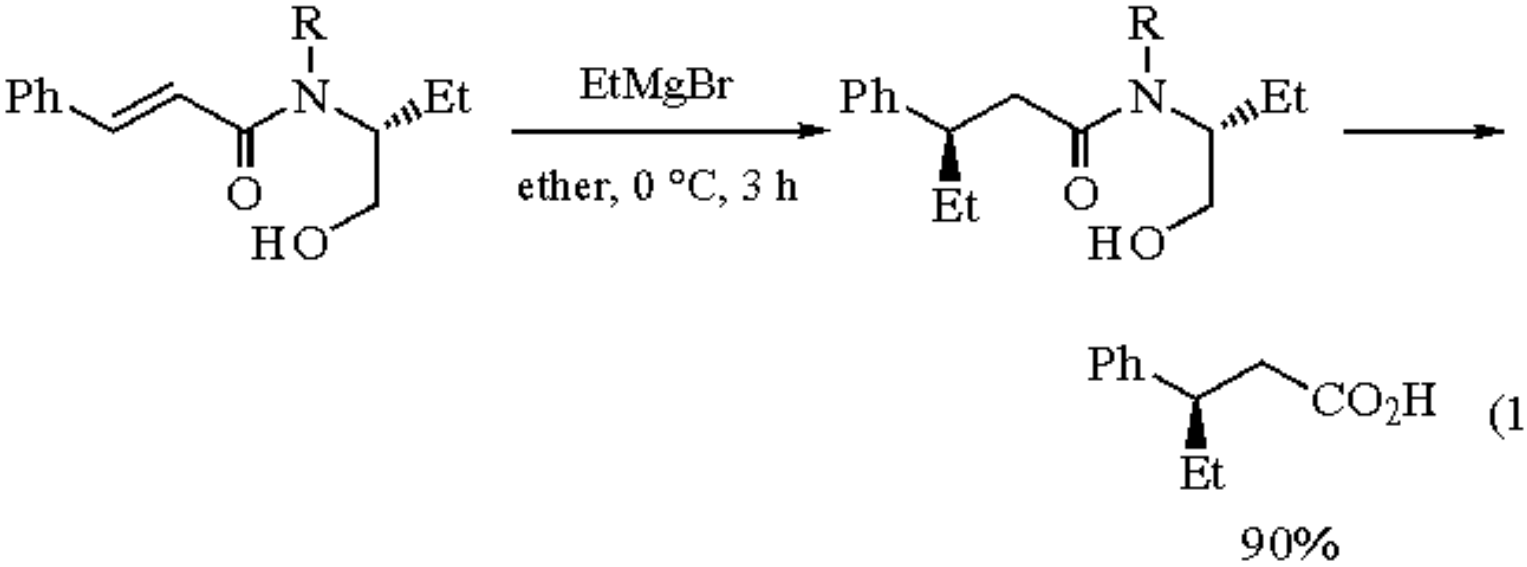

(15)

Interaction of α,β-unsaturated ketones[34] with EtMgBr followed by addition of ***Chlorotrimethylsilane*** forms β-ethyl enol silyl ethers.

Reaction with 2-substituted methyl acrylates[35] results in dimerization by conjugate addition (eq 16). Successive addition of EtMgBr and aldehydes to α-alkyl acrylates affords δ-lactones.[36] The diastereoselectivity of the product

increases with the bulkiness of aldehyde employed (eq 17).

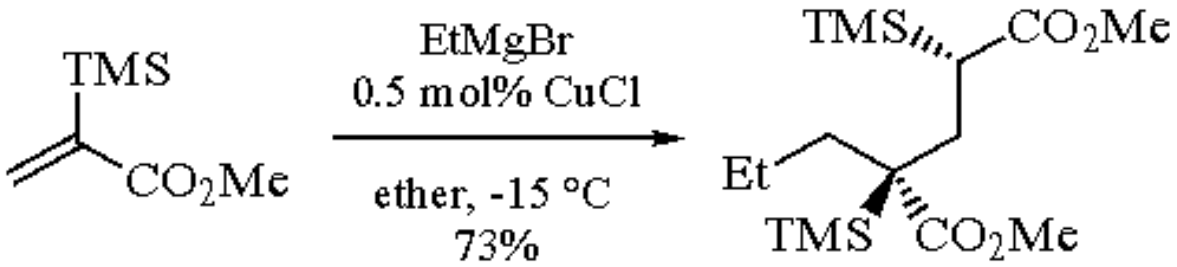

(16)

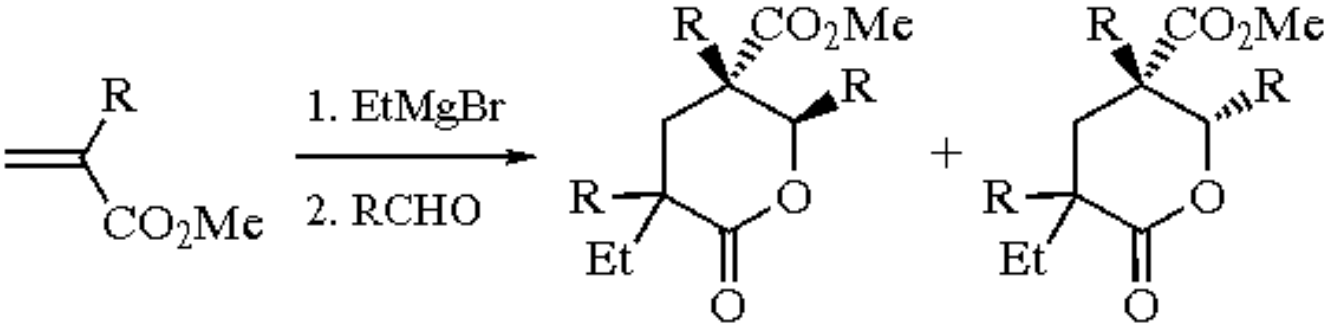

(17)

The copper-catalyzed reaction of EtMgBr with cyclic carbonates of vicinal diols[37] proceeds in S_N2' fashion and results in (*E*)-allylic alcohol formation with high diastereoselectivity (de >99%) (eq 18).

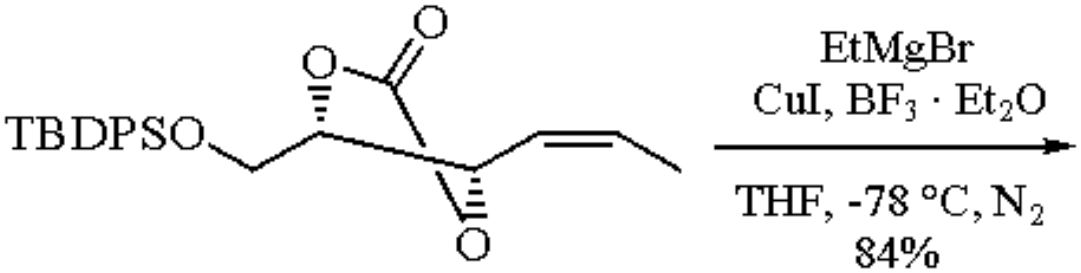

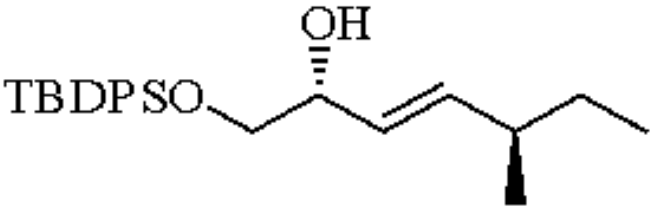

(18)

The interaction of EtMgBr with chiral *N*-enoylsultams[38] proceeds with Et group addition on the β-carbon in stereocontrolled fashion. Cross aldol condensation with the thioamide enolates forms predominantly the *threo* isomer (eq 19).[39]

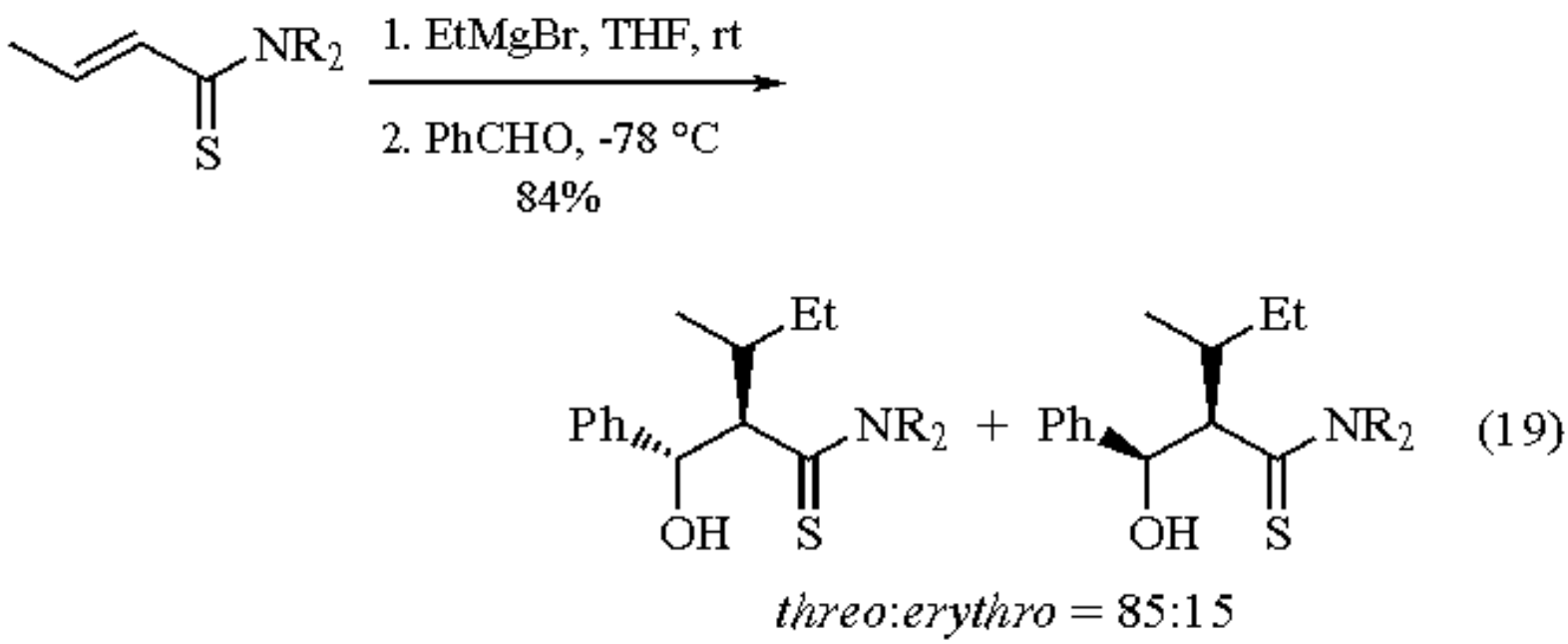

Reaction of EtMgBr with the endocyclic C=N bond of benzothiazine[40] or BF_3-complexed thiazolines[41] proceeds by 1,2-addition.[42] 1,4-Addition of EtMgBr to chiral α,β-unsaturated aldimines provides an asymmetric synthesis of aldehydes (eq 20).[43]

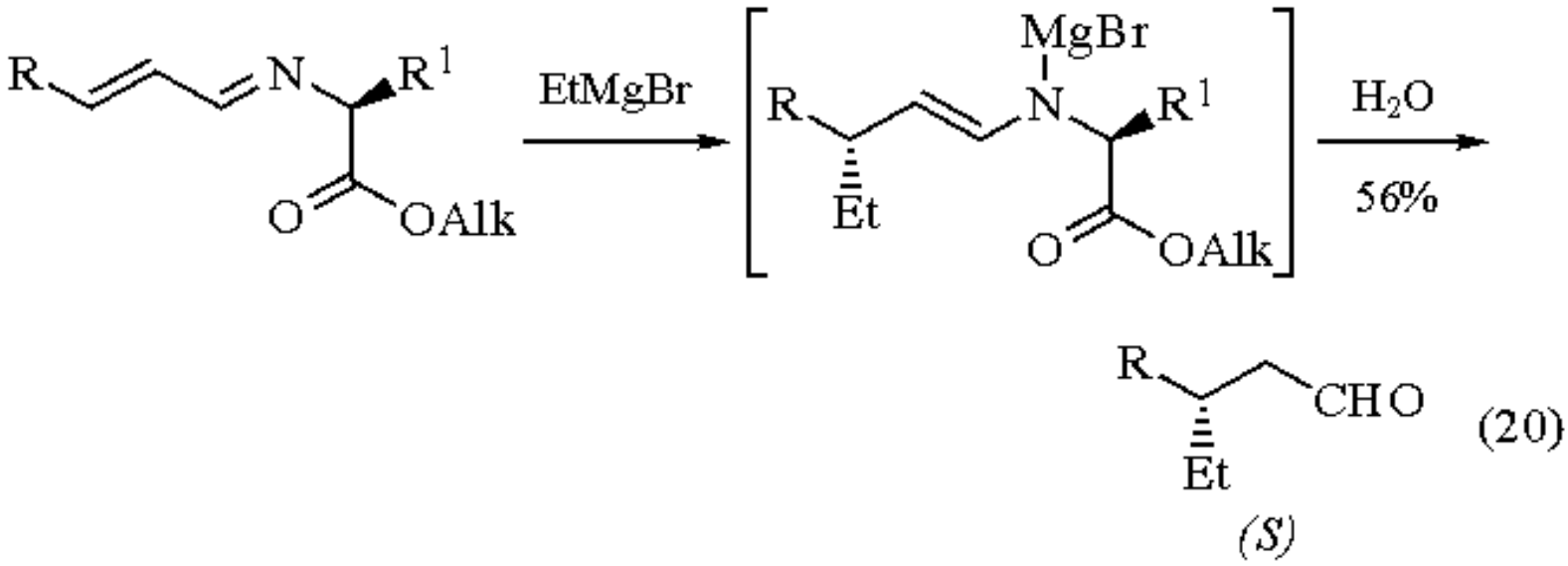

Crotonaldehyde oxime[44] with EtMgBr gives *threo* aziridines. Diazadienes[45] with EtMgBr give enediamines and/or tautomeric β-aminoimines in polar solvents; in nonpolar solvents, *C*-alkylation products can also be isolated.

Reaction of pyridinium salts with EtMgBr produces 4-ethyl-1,4-dihydro- and 2-ethyl-1,2-dihydropyridines in variable ratios (eq 21).[46] The presence of ***Copper(I) Iodide*** (5 mol %) favors 4-addition. When the 4-position is blocked, a regiospecific synthesis of 1,2-dihydropyridine may be feasible. The similar addition to the unsubstituted electrophilic position of the quinoline[47] ring is observed.

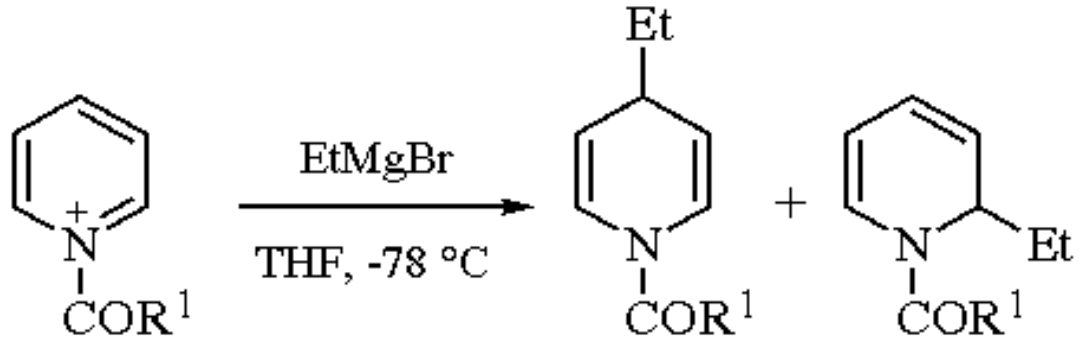

(21)

Addition of EtMgBr to nitriles forms ketimine-magnesium derivatives; hydrolytic workup gives ethyl ketones. Ketones are obtained from *p*-substituted benzonitrile,[48] 4-cyanomethylisoxazole, and isothiazole derivatives.[49] Treatment of cyanohydrin OTMS derivatives[50] with EtMgBr followed by hydrolysis affords α-hydroxy ketones. For sterically hindered cyano compounds,[51] forcing conditions are required (5 kbar).

Ketimine anions, generated by the reaction of nitriles with EtMgBr, are dimerized to form symmetrical azines[52] by ***Copper(I) Iodide*** and *t*-butyl peroxybenzoate (eq 22).

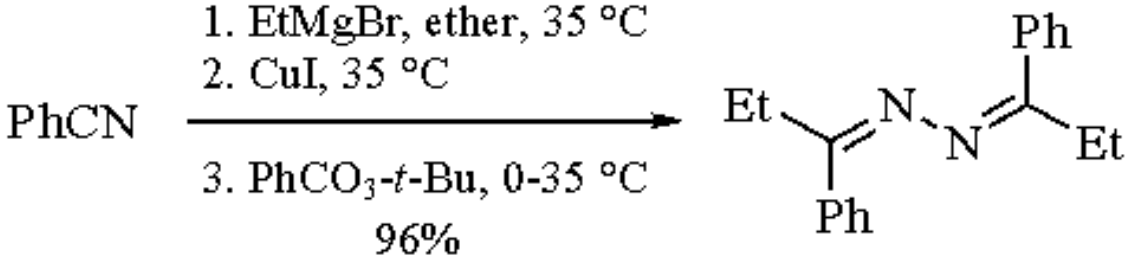

(22)

Reaction with Lactols, Acetals, and Aminals.

Ethylmagnesium bromide reacts with lactols to form secondary and tertiary alcohols, or the products formed from them (eq 23).[53] Such reaction can show interesting solvent effects, and can be highly diastereoselective (eq 24).[54]

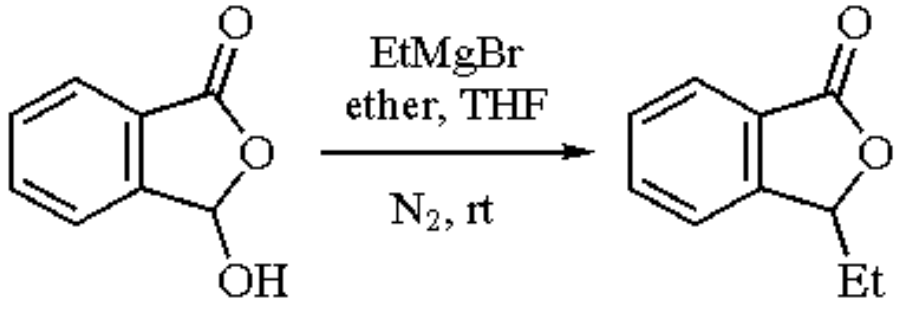

(23)

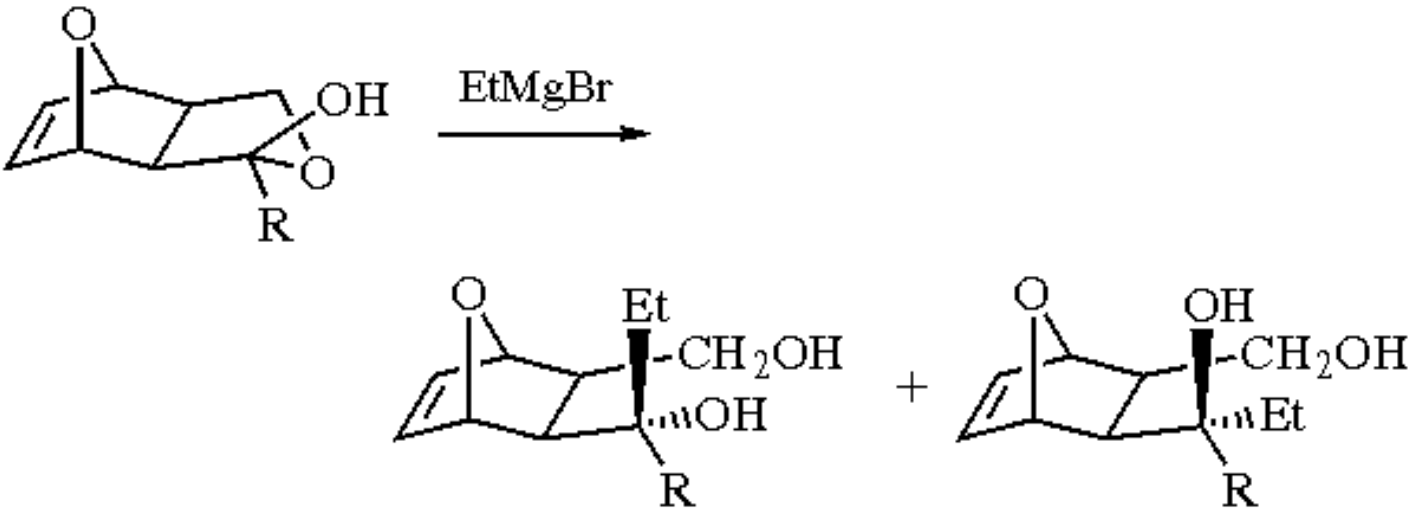

(24)

Reaction between EtMgBr and a mixed orthoester results in preferential substitution of a phenoxy group (eq 25).[55] The methoxy groups of *N*-dialkylformamide dimethyl acetal[56] can be easily substituted in a similar manner.

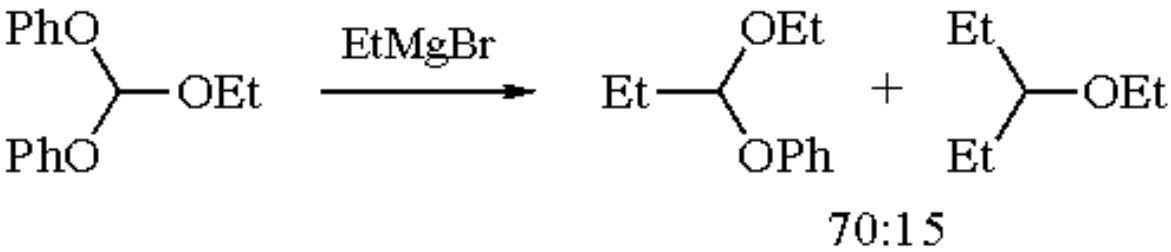

(25)

Dialkyl acetals derived from α,β-unsaturated aldehydes[57] afford the cross-coupling product with EtMgBr in the presence of ***Titanium(IV) Chloride*** (eq 26). The $TiCl_4$-catalyzed coupling of EtMgBr with cyclic chiral acetals[58] provide a convenient route for the preparation of chiral alcohols of high optical purity (eq 27).

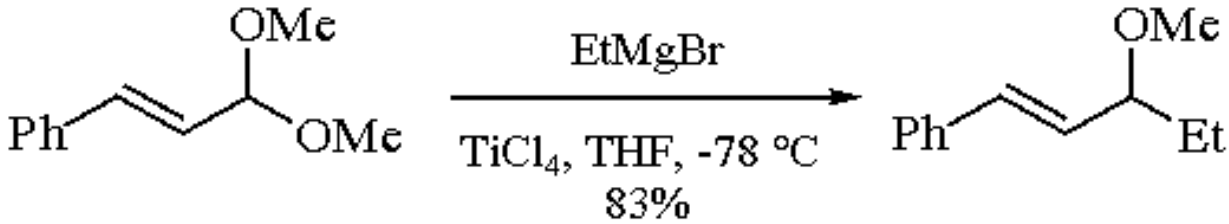

(26)

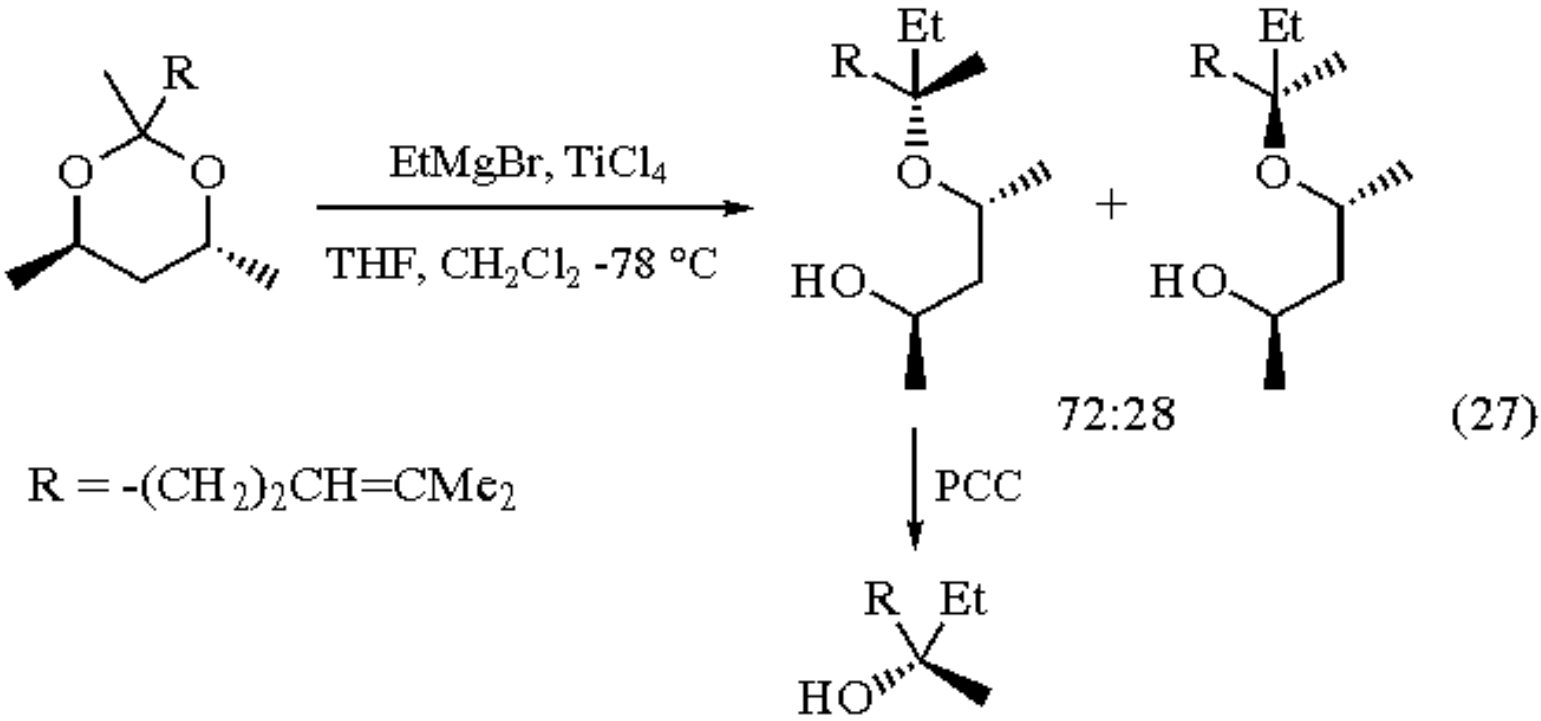

Reaction of dithiolane[59] derived from benzophenone with EtMgBr in the presence of a Ni catalyst proceeds in an unusual manner, with ethylidene coupling product formation (eq 28).

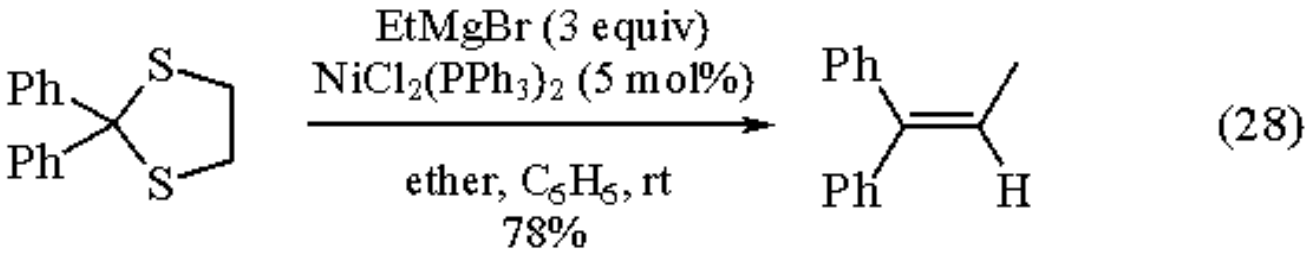

EtMgBr reacts with perhydrobenzooxazine derivatives[60] to provide primary amines in good chemical yield and with high enantiomeric excess. Diastereoselective ring opening of oxazoline[61] or oxadiazine[62] derivatives by EtMgBr is also observed.

Reaction with Epoxides.

Interaction of EtMgBr with (*S*)-(+)-***Epichlorohydrin***[63] and *trans*-1,2-epoxy-1,3-bis(trimethylsilyl)propane[64] proceeds with stereoselective opening of the oxirane ring.

Substitution at the sp^2 Carbon Atom.

The substitution of halogens in vinyl iodides and 2-bromo-1,4-benzodioxin, and the substitution of alkoxy groups of enol ethers,[65] are catalyzed by $NiCl_2$(dppp) or ***Tetrakis(triphenylphosphine)palladium(0)*** and proceed with retention of configuration when alkene derivatives are used. During reaction of (*E*)-(1-halo-1-alkenyl)boron esters[66] with EtMgBr the halogen substituent is replaced by the Et group with complete inversion of configuration at the vinylic center.

Substitution of the R^1R^2N group[67] is observed in the reactions of EtMgBr with diethylaminodinitrobutadienes or (3-dimethylamino-2-propenoyl)ketene dithioacetals (eq 29).

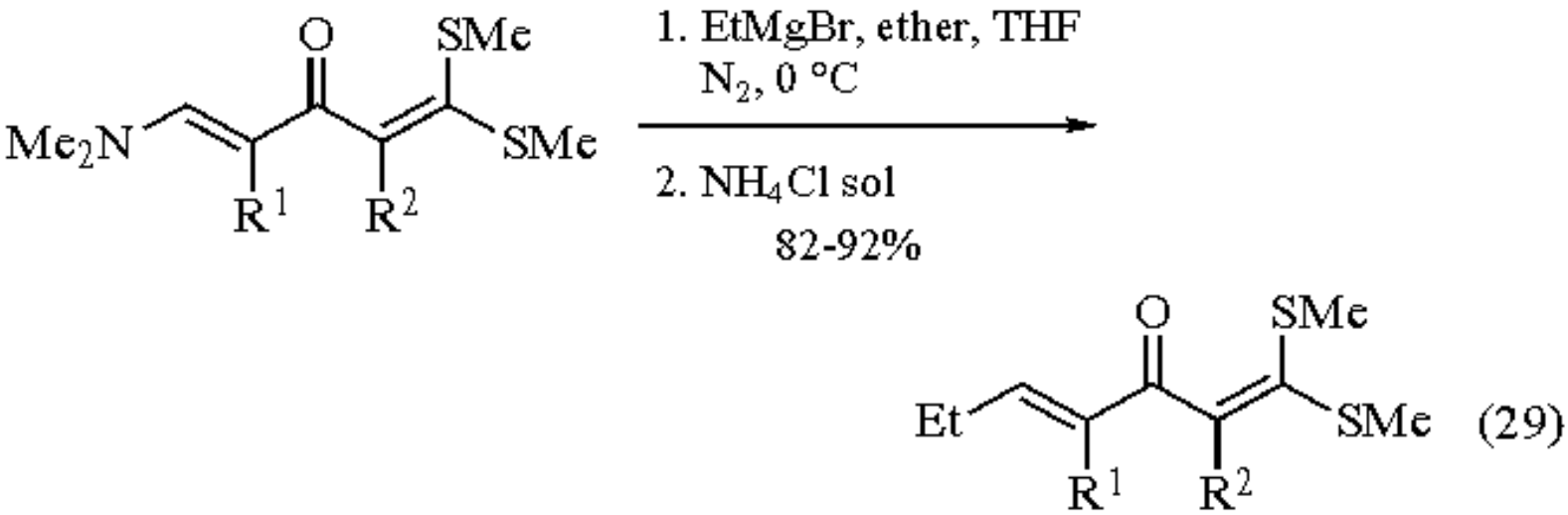

(29)

Ethylmagnesium bromide can give *ipso* substitution products with arenes and azines. When EtMgBr reacts with 2-methylsulfonyl-6-chloropyridine[68] the SO_2Me group is replaced; the chlorine atom is unaffected. An SET mechanism is probably involved, since 4-phenylsulfonylpyridine under the same conditions gives 4,4´-bipyridine. The replacement of pyrimidine 4-chloro substituents[69] by EtMgBr occurs in the presence of $NiCl_2$(dppp). The same types of catalysts, $PdCl_2$(dppf) and $PdCl_2$(dppb), are effective in the preparation of selectively monoalkylated benzenes.[70]

Substitution at Heteroatoms.

Nucleophilic cleavage of the 1,2-dithiolane S-S bond[71] by EtMgBr is a facile and selective route to mono-5-substituted 1,3-propanedithiols (eq 30). In the reaction of (1-chlorovinyl)diphenylphosphine oxide[72] with EtMgBr the chlorovinyl moiety is the leaving group.

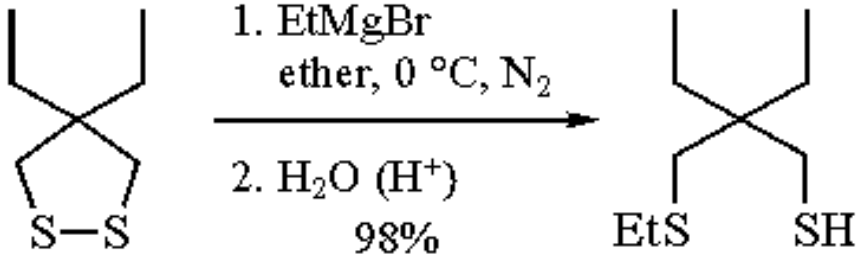

(30)

Ring opening of 1,2-propanediol cyclic sulfite[73] by EtMgBr affords a chiral sulfinate with high regio- and stereoselectivities (eq 31).

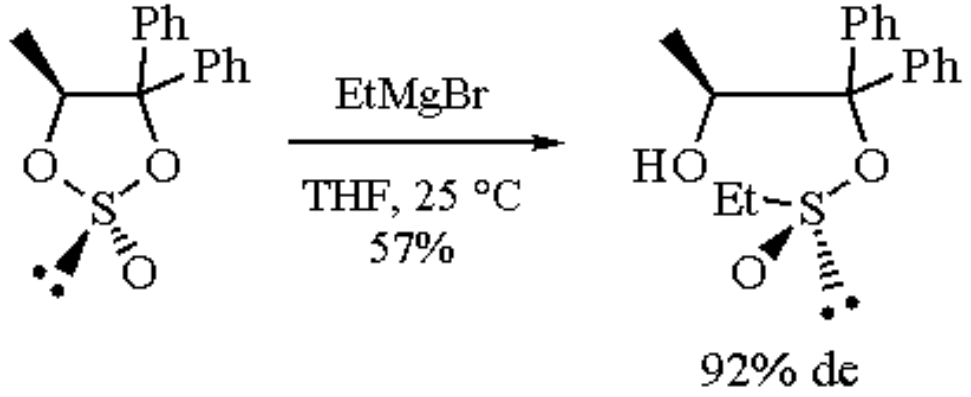

(31)

Ephedrine sulfinamides from oxathiazolidine derivatives[74] can be obtained in a similar way using Grignard reagents, but EtMgBr gives lower diastereoselectivity in the production of sulfinamides. Asymmetric synthesis of silicon compounds[75] is achieved by an EtMgBr substitution reaction at the Si atom.

Miscellaneous.

EtMgBr is used for the preparation of alkynic Grignard reagents[76] including γ-functional Grignard reagents[77] generated from propargylic alcohols (see ***Ethynylmagnesium Bromide***). Addition of EtMgBr in the presence of CuI to alkynic Grignard reagents affords vinylic magnesium reagents.[78]

EtMgBr is used for the preparation of 2-pyridylmagnesium bromide[79] and as a base[80] for carbanion generation. Highly regio- and stereoselective cycloaddition of reactive nitrones to magnesium alkoxides of allyl alcohols[81] is realized by use of EtMgBr (eq 32).

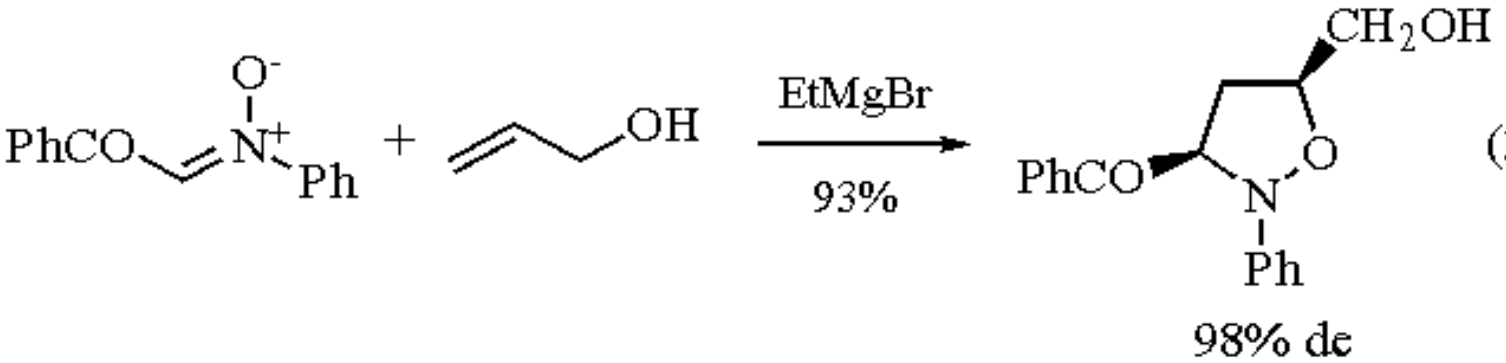

(32)

Trifluoroacetyltriphenylsilane reacts with EtMgBr to produce 2,2-difluoroenol silyl ether (eq 33).[82]

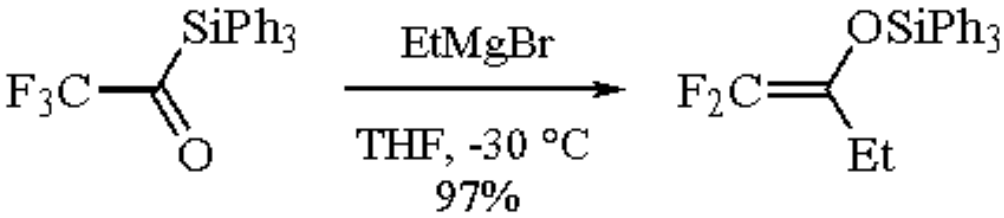

(33)

EtMgBr is also used for thione reduction[83] and preparation of alkyl isothiocyanates[84] and organozinc[85] compounds.

Related Reagents.

t-Butylmagnesium Chloride; ***Methylmagnesium Bromide***.

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Ethylmagnesium Bromide-Copper(I) Iodide[1]

EtMgBr + CuI

(EtMgBr)

[925-90-6] · C_2H_5BrMg · Ethylmagnesium Bromide-Copper(I) Iodide · (MW 133.28) (CuI)

[7681-65-4] · CuI · Ethylmagnesium Bromide-Copper(I) Iodide · (MW 190.45)

(used for preparing allenic,[2] alkenic,[2] and allylic alcohols;[3] reduces alkynes to alkenes;[4] reduces alkenyl sulfoxides to alkenyl sulfides[5])

Preparative Methods: prepared in situ under anhydrous conditions by reacting ***Ethylmagnesium Bromide*** (**1**) and ***Copper(I) Iodide*** (**2**) in varying molar ratios.

Handling, Storage, and Precautions: use in a fume hood.

S_N2' Alkylations: Preparation of Allenic, Alkenic, and Allylic Alcohols.

Allenic and alkenic alcohols have been prepared by reacting methoxy-substituted alkynyl and alkenic alcohols, respectively, with a preformed solution of ethylmagnesium bromide-copper(I) iodide (eqs 1 and 2).[2]

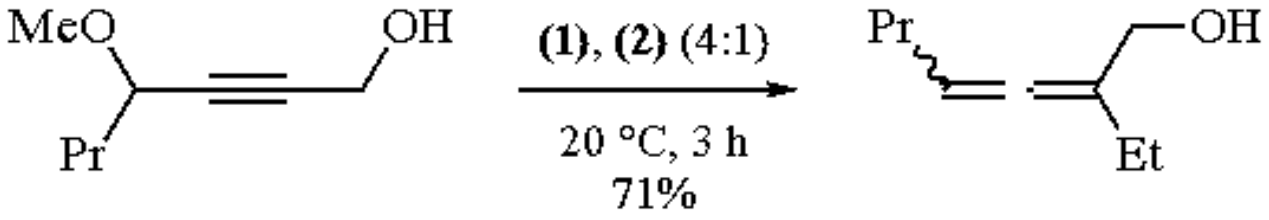

(1)

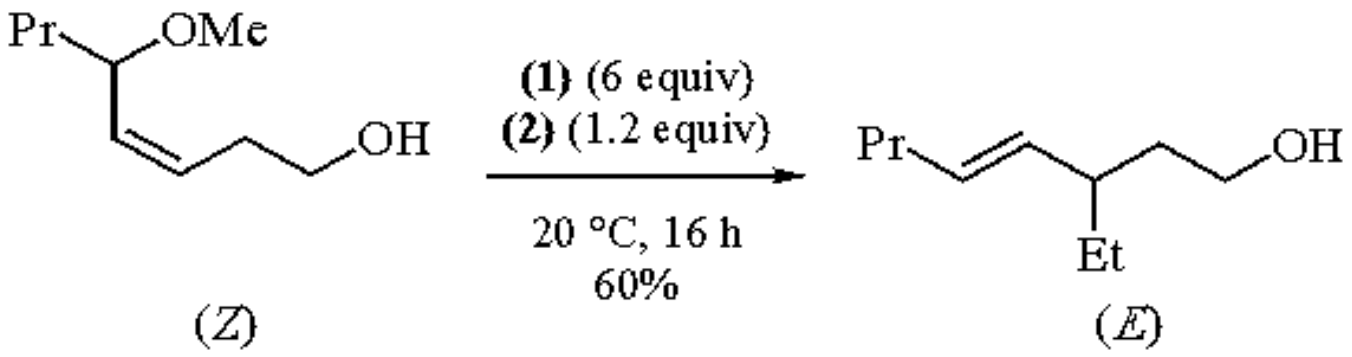

(2)

Kang et al.[3] used (**1**) and catalytic (**2**) in the presence of ***Boron Trifluoride Etherate*** to prepare a chiral allylic alcohol from a cyclic carbonate (eq 3). This conversion represents a 1,3-chirality transfer method.

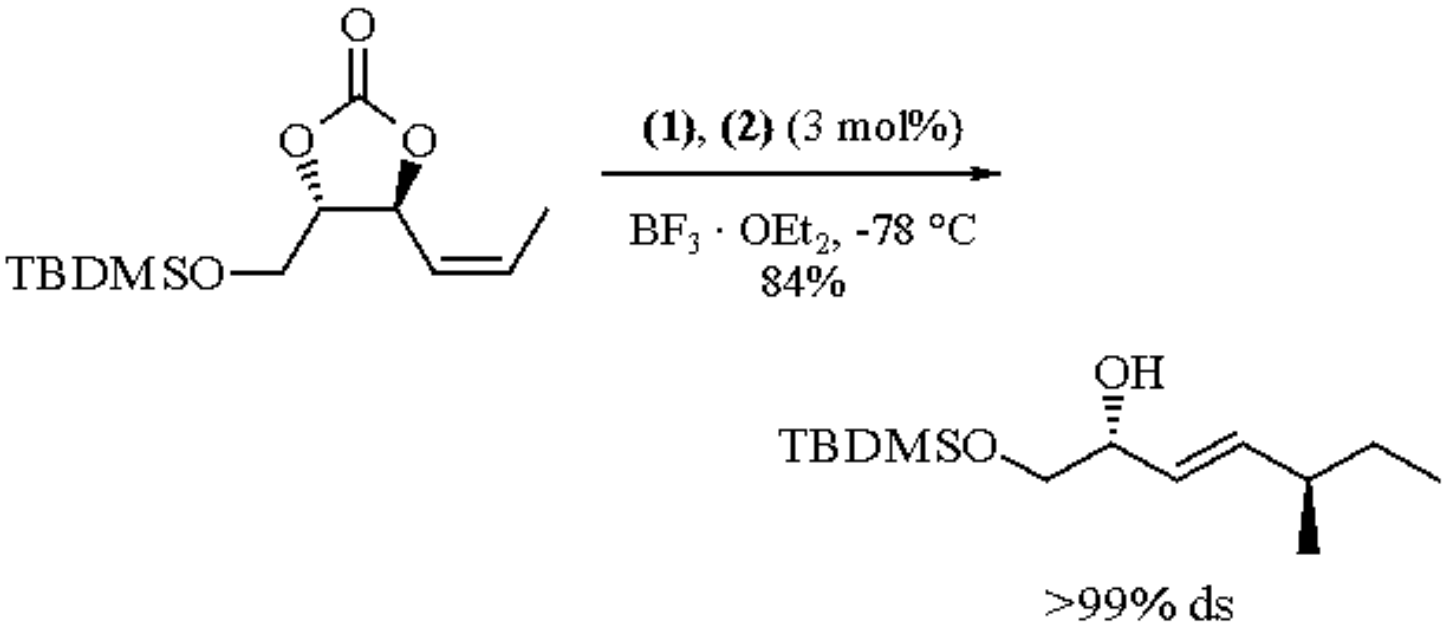

(3)

Reduction of Alkynes.

Alkynes are reduced to the corresponding *cis*-alkenes by treatment with excess (**1**) and (**2**) (2:1) at -30 °C in ether (eqs 4-6).[4]

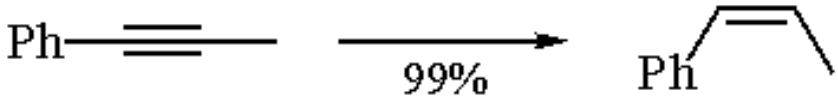

(4)

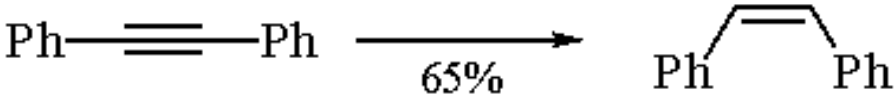

(5)

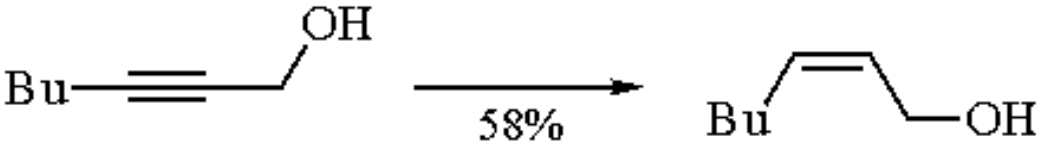

(6)

Reduction of Alkenyl Sulfoxides.

Treatment of α,β-unsaturated sulfoxides with (**1**) in the presence of catalytic (**2**) in ether at 0 °C affords the corresponding alkenyl sulfides with the original configuration about the vinyl group (eq 7).[5]

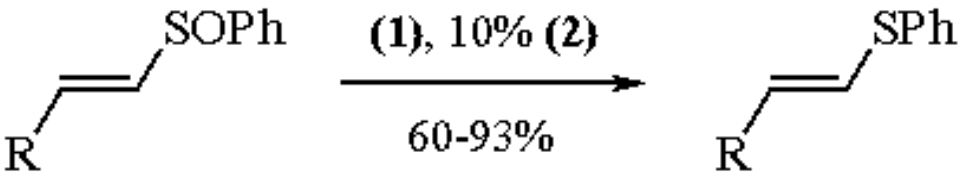

(7)

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Ethyl Malonate[1]

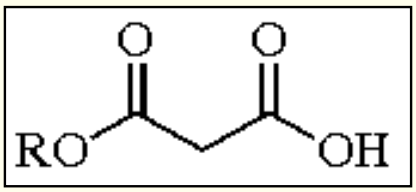

(R = Et)

[1071-46-1] · $C_5H_8O_4$ · Ethyl Malonate · (MW 132.13) (R = Me)

[16695-14-0] · $C_4H_6O_4$ · Methyl Malonate · (MW 118.10) (R = *t*-Bu)

[40052-13-9] · $C_7H_{12}O_4$ · *t*-Butyl Malonate · (MW 160.19) (R = Bn)

[40204-26-0] · $C_{10}H_{10}O_4$ · Benzyl Malonate · (MW 194.20)

(synthesis of β-keto esters[2,3] and esters[4])

Physical Data: R = Et, bp 110 °C/0.05 mmHg, *d* 1.189 g cm^{-3}. R = Me, bp 80 °C/0.15 mmHg, *d* 1.128 g cm^{-3}. R = *t*-Bu, bp 90 °C/2 mmHg. R = Bn, mp 49-52 °C.

Preparative Methods: ethyl malonate is commercially available, or it may be easily prepared[1] by acidification of the potassium salt of ethyl malonate, which is also commercially available or is readily obtained from ***Diethyl Malonate***.[1] Methyl and *t*-butyl malonates can be obtained from Meldrum's acid (***2,2-Dimethyl-1,3-dioxane-4,6-dione***) by treatment with the appropriate alcohol.[5,6] Methyl malonate has also been prepared from dimethyl malonate or from potassium methyl malonate.[7] Benzyl malonate has been prepared from ***Malonyl Chloride*** and benzyl alcohol,[8a] or from dibenzyl malonate.[8c,d]

Ethyl malonate (**1**) has been most widely utilized in the efficient one-step synthesis of β-keto esters.[3,9,10] Two different approaches have been taken in this regard, both of which take advantage of the facile decarboxylation which occurs when a *C*-acyl derivative of (**1**) is subjected to a mild acidic hydrolysis. In the first procedure, treatment of (**1**) with ***n-Butyllithium*** (2 equiv) results in the formation of the dianion (**2**), which readily undergoes *C*-acylation with various acid chlorides to provide β-keto esters in excellent yields following mild acidic workup (eq 1).[3a] This methodology has been applied in the synthesis of a variety of β-keto esters.[9] A related procedure involving a milder preparation of a dianion of (**1**) has also recently been reported.[10]

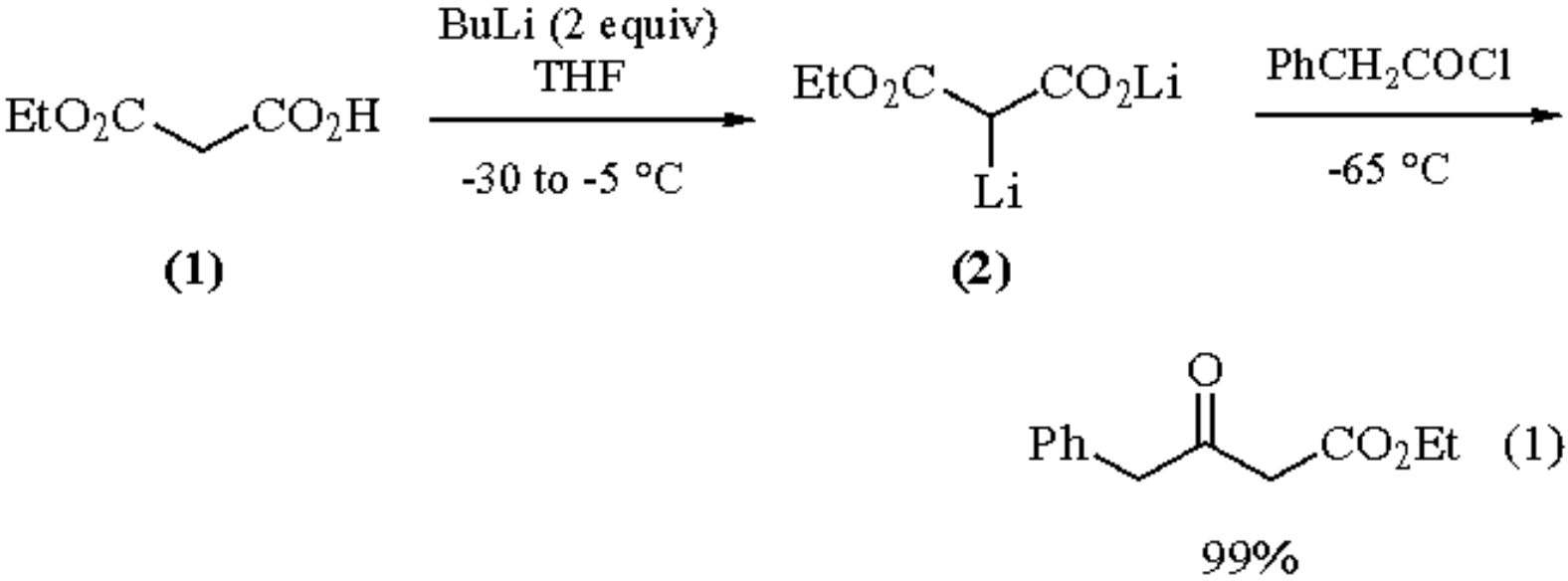

(1)

In a different approach, the neutral magnesium salt of methyl malonate (**3**), prepared from $Mg(OEt)_2$ and methyl malonate (2 equiv), adds smoothly to a variety of acylimidazoles, which are themselves obtained by prior derivatization of a carboxylic acid with ***N,N´-Carbonyldiimidazole*** (CDI) (eq 2).[3b] The β-keto ester is again obtained in a single step upon a mild acidic workup.

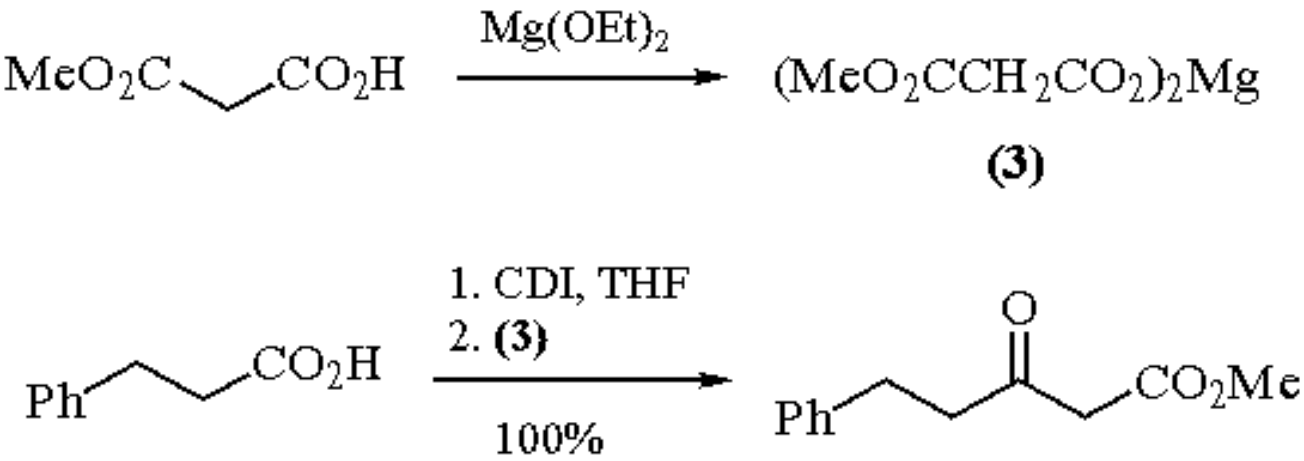

(2)

The corresponding magnesium salts of other malonate half-esters have been prepared and utilized extensively. The mildness and versatility of this procedure have made it the method of choice for the preparation of β-keto esters, as demonstrated by the numerous recent synthetic applications which have been reported.[11] For example, homologation of the acid (**4**) to keto ester (**6**), an important intermediate in the synthesis of thienamycin, was accomplished in 86% yield with the magnesium salt of *p*-nitrobenzyl malonate (**5**) (eq 3).[11a] This methodology has also been applied in the synthesis of β-keto esters from amino acids.[12]

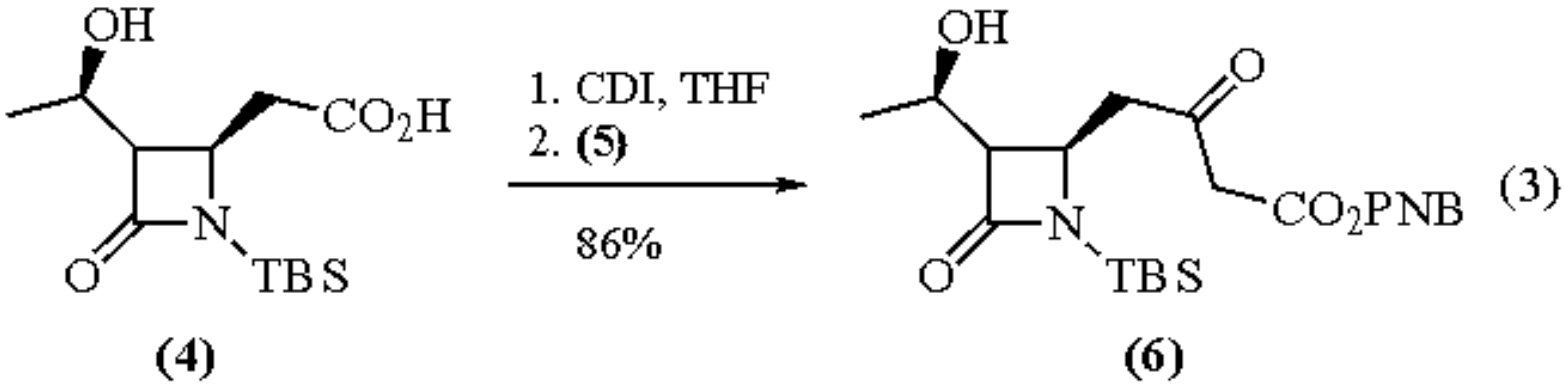

In a one-step alternative to the classical malonic ester synthesis, the dianion (**2**) has been alkylated with a number of alkyl halides. Subsequent decarboxylation leads to various esters in moderate yield (eq 4).[4]

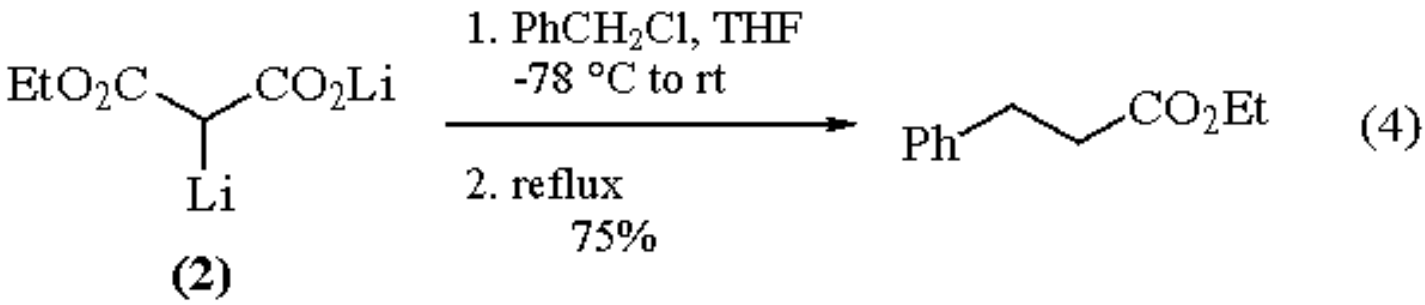

Ethyl malonate has been used in the preparation of cinnamic and acrylic acid derivatives under modified Doebner/Knoevenagel conditions.[13] Ethyl 2,4-pentadienoate has been prepared in a one-pot, high yielding application of this procedure (eq 5).[13a]

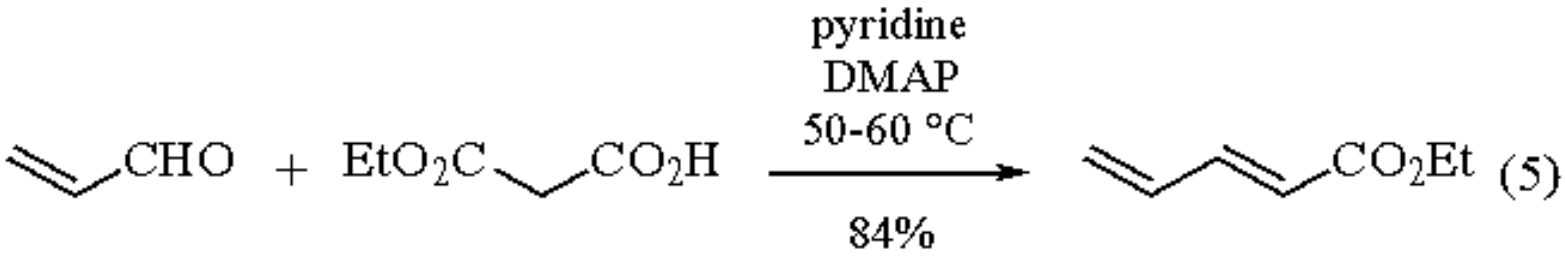

An intermolecular carbolactonization of alkenes with (**1**) in the presence of ***Manganese(III) Acetate*** has been employed in the preparation of various γ-lactones in good yields (eq 6).[14]

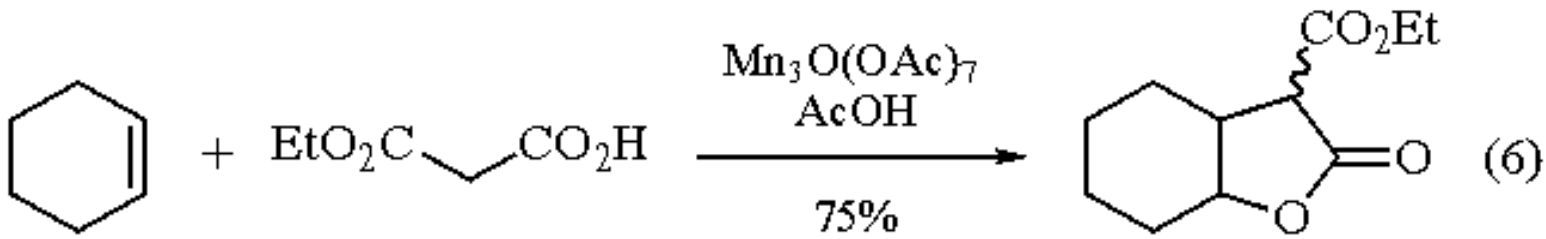

Activated derivatives of (**1**), such as the corresponding acid chloride or ***1-Hydroxybenzotriazole*** ester, have been utilized in the preparation of various mixed malonate esters or amides by reaction with alcohols or amines,

respectively.[8d,15]

Chiral monosubstituted[16] and disubstituted[17] derivatives of (**1**) are useful intermediates for the preparation of chiral synthons which have been applied in the synthesis of sesquiterpenes containing a quaternary chiral center (eq 7).[17a]

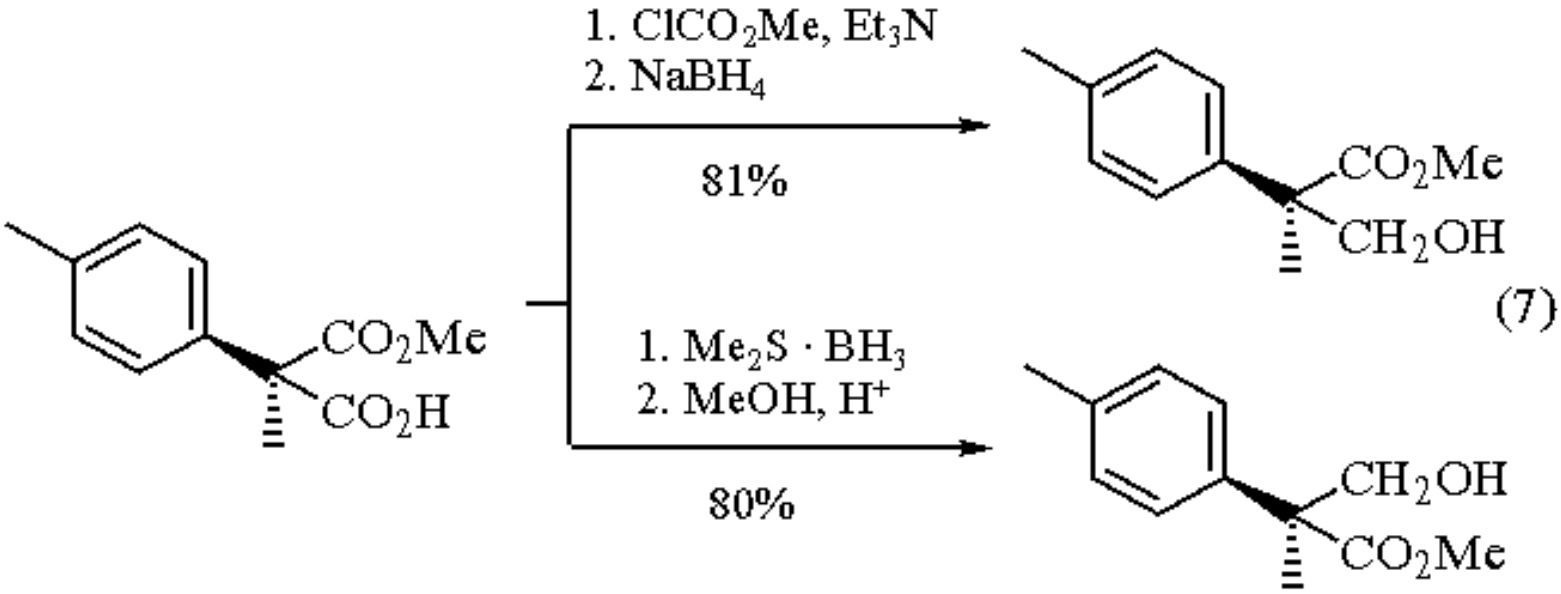

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Diethyl Ethoxymagnesiomalonate***; ***Diethyl Malonate***; ***Ethyl 3,3-Diethoxyacrylate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Methyl Magnesium Carbonate***; ***Malonic Acid***; ***Methyl Cyanoformate***.

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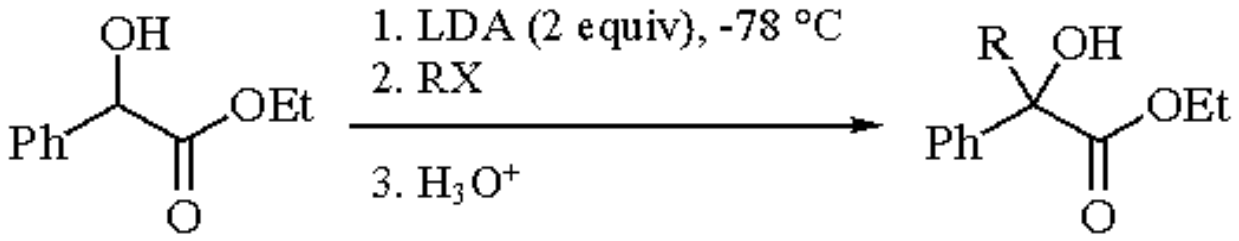

(1)

Mandelic acid esters are also useful chiral auxiliaries because both enantiomers are commercially available and inexpensive. For example, they serve as useful chiral auxiliaries in Diels-Alder reactions (de >95%) (eq 2)[3] and as precursors for chiral acetals.[7]

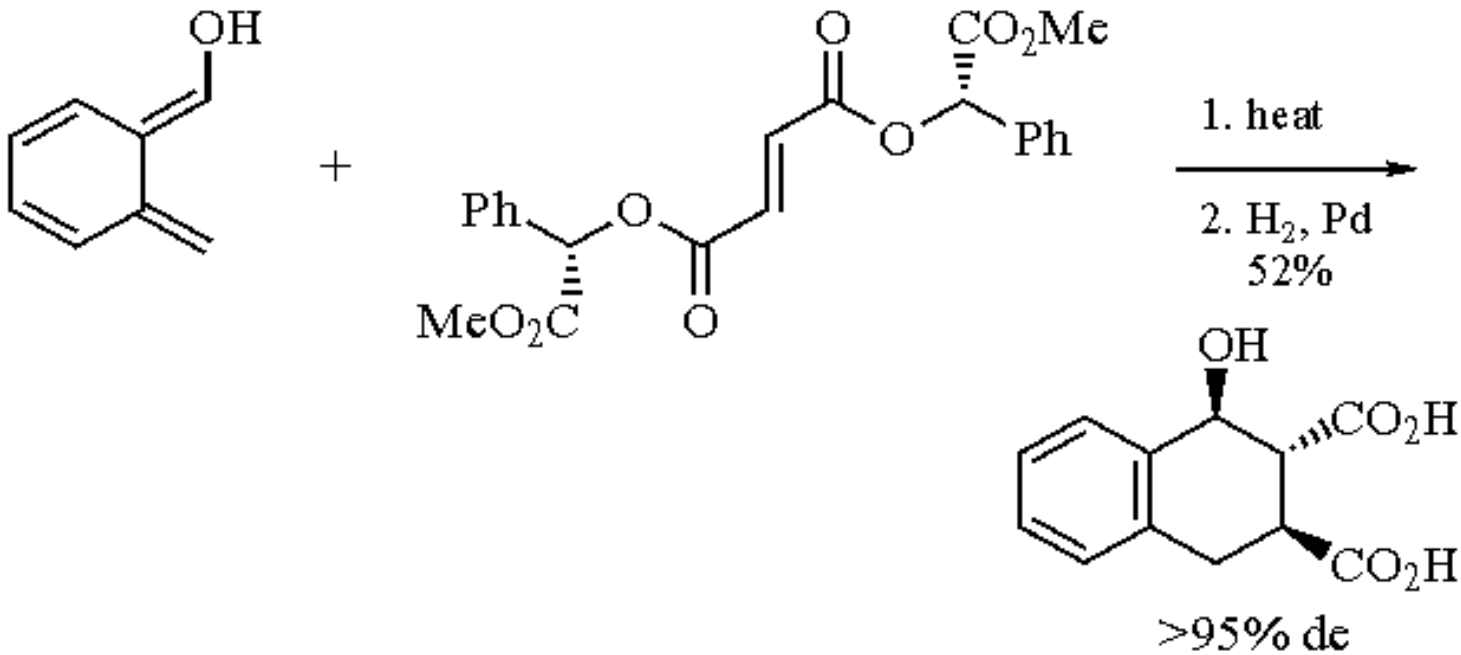

(2)

Optically active mandelic acid esters are also useful as derivatizing agents for NMR analyses of the enantiomeric purity of isotopically substituted carboxylic acids, alcohols, and amines through analysis of the corresponding derivatives using either the carboxyl group or the hydroxy group.[4]

Related Reagents.

Dilithioacetate; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Lithium Diisopropylamide***; ***Methyl O-Methyllactate***; ***Phenoxyacetic Acid***.

---

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7. Mash, E. A.; Arterburn, J. B.; Fryling, J. A.; Mitchell, S. H. *JOC* **1991**, *56*, 1088.

Ethyl Metaphosphate[1]

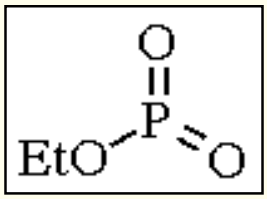

[4697-37-4] · $C_2H_5O_3P$ · Ethyl Metaphosphate · (MW 108.04)

(reagent used for phosphorylation of nucleophiles when generated in situ and used as a monomer[1])

Monomeric Metaphosphates.

The chemistry of metaphosphates has been reviewed.[1] Monomeric metaphosphates are highly reactive species and are typically prepared in situ via various fragmentation processes and then trapped with appropriate nucleophiles. For example, ethyl metaphosphate has been generated by photolytic[2] and thermal[3] fragmentation of ethyloxaphosphabicyclo[2.2.2]octene. The resulting reactive ethyl metaphosphate monomer can then be trapped with various alcohols to afford phosphate derivatives (eq 1). Another preparation involves the fragmentation of alkyl α-(oximino)benzylphosphonates using anhydrous HCl in the presence of various hydroxylic trapping agents.[4] An application for this methodology was demonstrated with the modification of silica gel for potential development of new phosphorylated chromatographic materials (eq 2).[5]

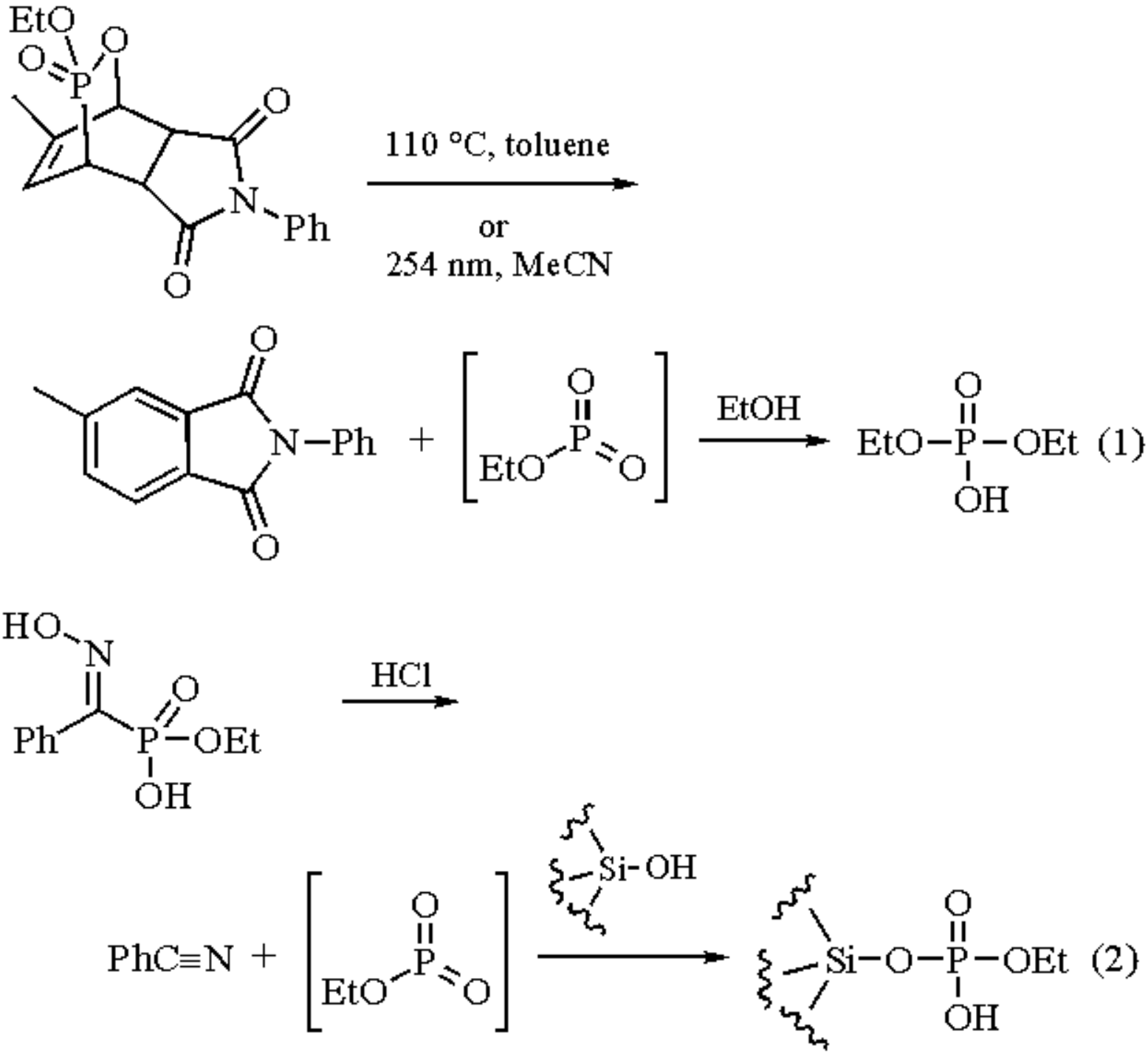

Metaphosphates are highly electrophilic species and also react with various activated aromatic compounds to afford products of electrophilic aromatic substitution,[3] as well as with epoxides to afford dioxaphospholanes.[6] Due to the highly reactive nature of monomeric metaphosphates, however, the use of these reagents for organic synthesis remains limited in scope.

Cyclic Tetramer of Ethyl Metaphosphate.

While the monomeric form of ethyl metaphosphate has only limited synthetic utility, the polymeric form commonly known as ***Polyphosphate Ester*** (PPE) has been used for a number of valuable synthetic

transformations including dehydrations,[7] Beckmann rearrangements,[8] Fischer indole synthesis,[9] and *N*-alkylation.[10] A convenient large scale preparation of PPE has been described by Cava and co-workers.[11] Thus, to a mixture of 300 mL of anhydrous diethyl ether in 150 mL of chloroform is added 150 g of phosphorus pentoxide. The mixture is warmed under reflux for 4 days. The resulting solution is filtered and the filtrate concentrated in vacuo at 40 °C to afford PPE as a clear colorless oil. Polyphosphate ester, sometimes referred to as ethyl polyphosphate or polyphosphoric ester, exists as a complex mixture of polymeric cyclic and acyclic esters. (**1**) shows the structure of the cyclic tetramer [*801-24-1*] (MW 432.14). Some applications of PPE in organic synthesis are described below.

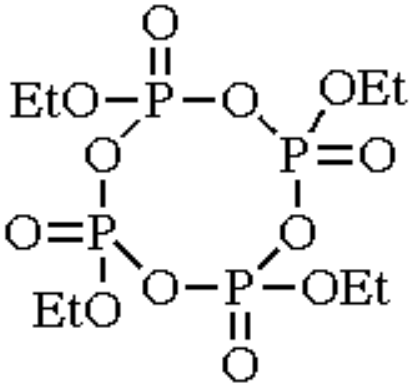

(1)

Dehydration Reactions.

PPE is commonly used to promote cyclodehydration reactions, such as the Bischler-Napieralski reaction. Thus, a key step in the synthesis of (±)-hernandine involves the cyclization of a secondary amide using PPE to afford the requisite dihydroisoquinoline (eq 3).[12] Another example of this reaction is the preparation of 5*H*-2-benzazepine analogs.[13] Polyphosphate ester is reported to be the reagent of choice for conversion of phenylpropylamines to the corresponding benzazepines (eq 4).

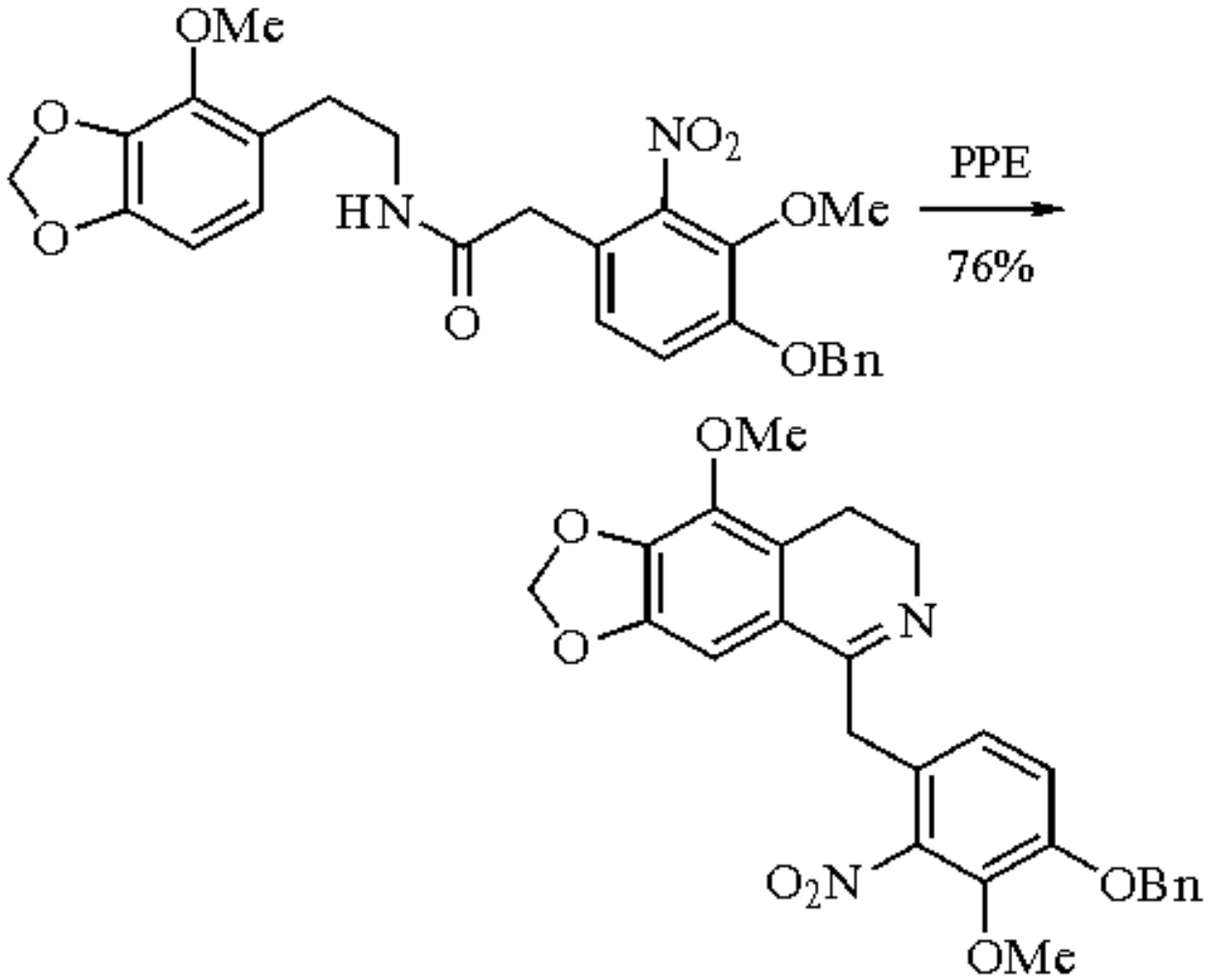

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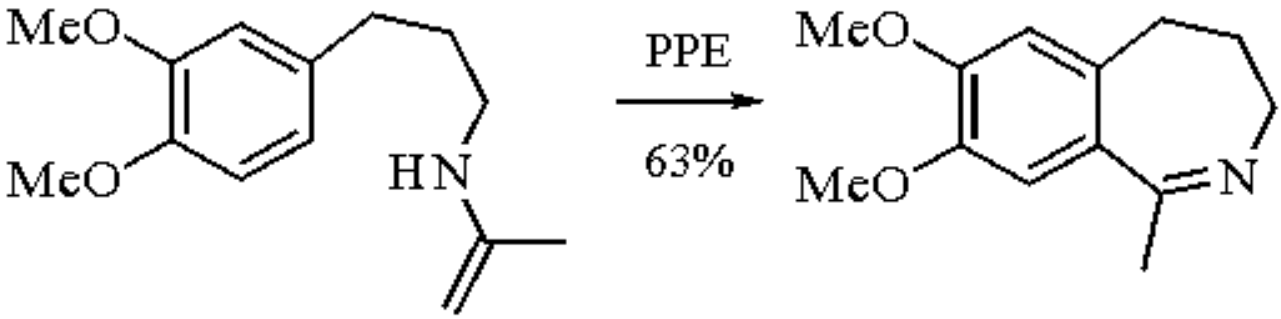

(4)

PPE has also been used for the preparation of 2-substituted benzimidazoles,[14] benzoxazoles, and benzothiazoles.[15] For example, condensation of *o*-aminophenol with acetic acid in the presence of PPE at 100 °C affords 2-methylbenzoxazole in 75% yield (eq 5).[15] Likewise, condensation of *o*-aminothiophenol with furan-2-carboxylic acid in the presence of PPE under refluxing chloroform gives 2-(2-furyl)benzothiazole in 64% yield (eq 6).[15] The preparation of the aforementioned benzazoles using PPE is reported to be superior to that using ***Polyphosphoric Acid*** (PPA). A general synthesis of 2,3-dihydro-4*H*-1,3-benzoxazin-4-ones based on the same protocol has also been reported. Thus condensation of a salicylamide with aldehydes or ketones using PPE affords good yields of the corresponding benzoxazinone (eq 7).[16]

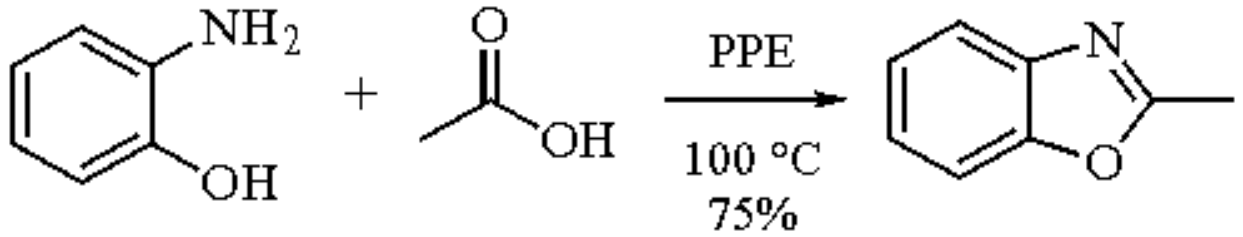

(5)

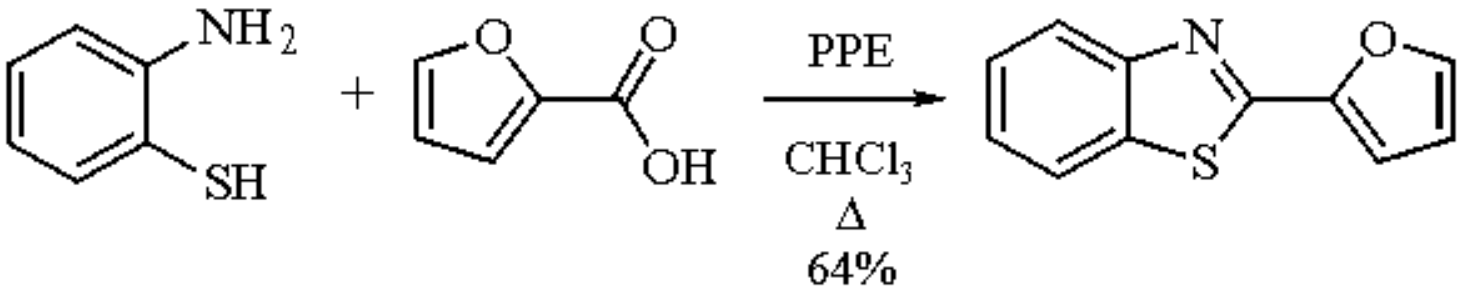

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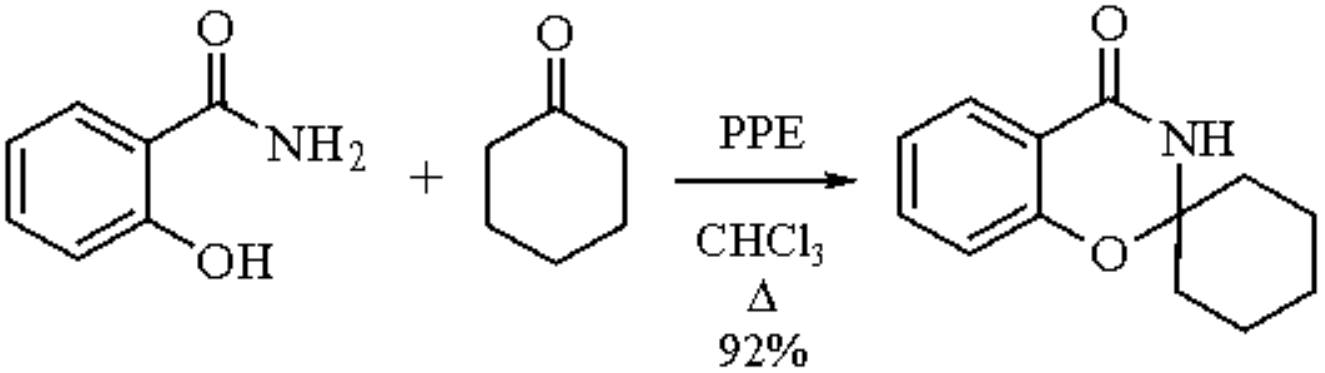

(7)

Cyclization via Friedel-Crafts acylation using PPE has also been reported. For example, the ring closure of substituted 2-(2-methoxycarbonylphenylamino)benzoic acids affords the corresponding 9-oxoacridan-4-carboxylic acids in excellent yield (eq 8).[17] Other examples involving the PPE activation or dehydration of carboxylic acid moieties include the conversion of carboxylic acids to nitriles[18,19] and the preparation of thioesters from acids.[20]

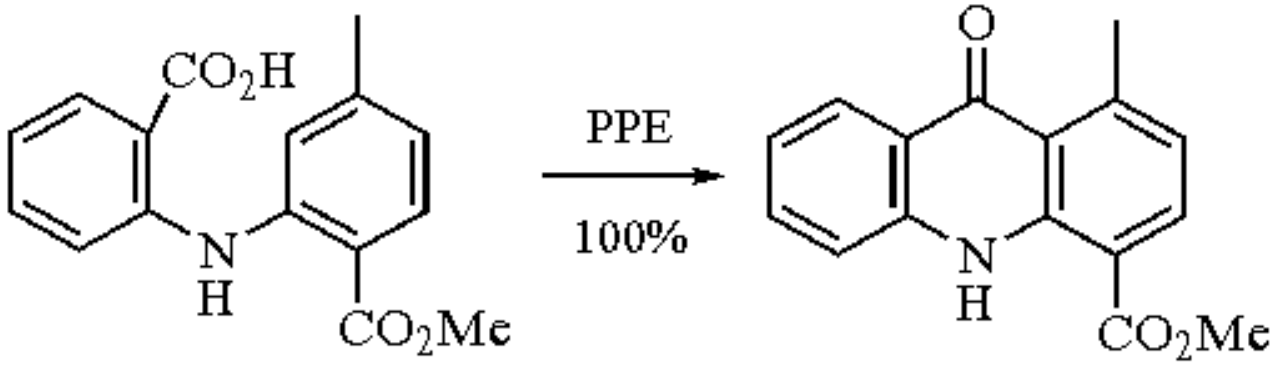

(8)

Beckmann Rearrangement and Fischer Indole Synthesis.

The use of PPE to effect certain rearrangements has also been reported. For example, the oxime derived from adamantanone readily undergoes the Beckmann rearrangement to afford the corresponding lactam in 65% yield (eq 9).[8] The procedure is reported to be superior to standard procedures which give primarily second-order Beckmann fragmentation products. The preparation of indoles via Fischer indole synthesis using PPE has also been described. For example, cyclohexanone phenylhydrazone undergoes rearrangement to the indole under mild conditions (eq 10).[9]

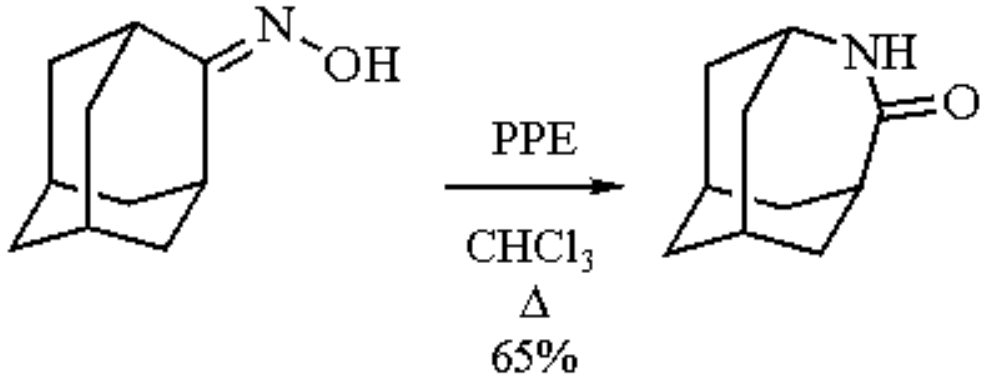

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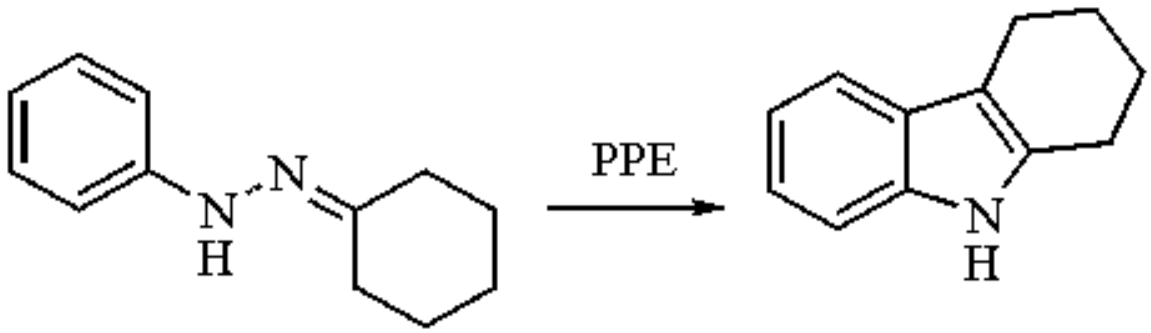

(10)

N-Alkylation.

PPE is also an effective alkylating agent for primary and secondary amines as well as for certain nitrogen containing heterocycles. The reaction usually occurs at temperatures higher than those typically used for the previously described transformations. Thus 2-aminobenzophenone *N*-(2-hydroxyalkyl)imines are conveniently *N*-alkylated and cyclocondensed at 160 °C to afford good yields of the corresponding benzodiazepine derivatives (eq 11).[10]

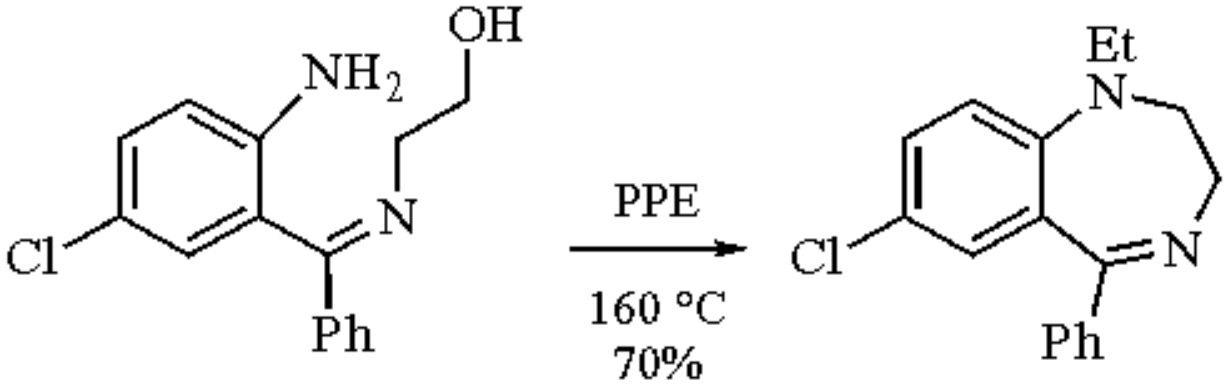

(11)

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Ethyl (Methyldiphenylsilyl)acetate[1]

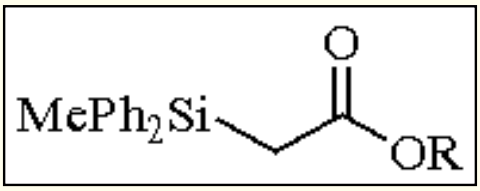

(R = Et)

[13950-57-7] · $C_{17}H_{20}O_2Si$ · Ethyl (Methyldiphenylsilyl)acetate · (MW 284.46) (R = Me)

[89266-73-9] · $C_{16}H_{18}O_2Si$ · Methyl (Methyldiphenylsilyl)acetate · (MW 270.43) (R = *i*-Pr)

[87776-13-4] · $C_{18}H_{22}O_2Si$ · Isopropyl (Methyldiphenylsilyl)acetate · (MW 298.49) (R = *t*-Bu)

[77772-21-5] · $C_{19}H_{24}O_2Si$ · *t*-Butyl (Methyldiphenylsilyl)acetate · (MW 312.52)

(vinyl 1,1-dication synthetic equivalent in reactions with Grignard reagents;[2] reagent for Peterson synthesis of α,β-unsaturated esters[3])

Physical Data: clear to light yellow liquids. R = Et, *n*25D 1.5381; R = *i*-Pr, *n*26D 1.5398; R = *t*-Bu, *n*24D 1.5324.

Preparative Method: whereas the direct silylation of the lithium enolate of an ester normally results in the formation of a mixture of the α-silyl ester and the corresponding silyl ketene acetal, the same reaction with ***Methyldiphenylchlorosilane*** gives exclusively the α-methyldiphenylsilyl ester.[2d,4] This direct *C*-silylation is the best general route to α-silyl esters.

Purification: best purified by silica gel chromatography. The esters can be distilled through a suitable short path apparatus.

Handling, Storage, and Precautions: the esters desilylate in acid or alkaline medium. They desilylate very slowly with water or alcohols under neutral conditions.

Alkene Synthesis.

The first synthetically successful conversion of an α-silyl ester to an alkene was accomplished by the reaction of ethyl trimethylsilylacetate with 2 equiv of the Grignard reagent formed from high purity ***Magnesium*** and a primary or aryl halide, followed by elimination of the β-hydroxy silane formed (eq 1).[2a] Although the same reaction has never been

reported for ethyl α-(methyldiphenylsilyl)acetate, use has been made of the ready *C*-methyldiphenylsilylation of the lithium enolates of esters to form ethyl α-alkyl-α-(methyldiphenylsilyl)acetates.[4a] These α-silyl esters react with primary or aryl Grignard reagents to provide, after elimination, trisubstituted alkenes (eqs 2-5).[2c,d] Improved results are often obtained when the first addition is carried out with a Grignard reagent and the second with an organolithium reagent. The use of a Grignard reagent followed by an organolithium reagent allows the preparation of mixed trisubstituted alkenes (eq 5). The stereoselectivity is excellent when the elimination step is accomplished under basic conditions, but only moderate when carried out under acidic conditions.

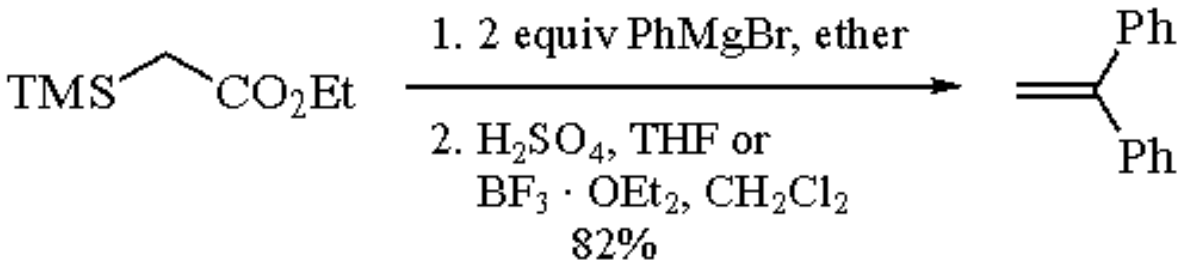

(1)

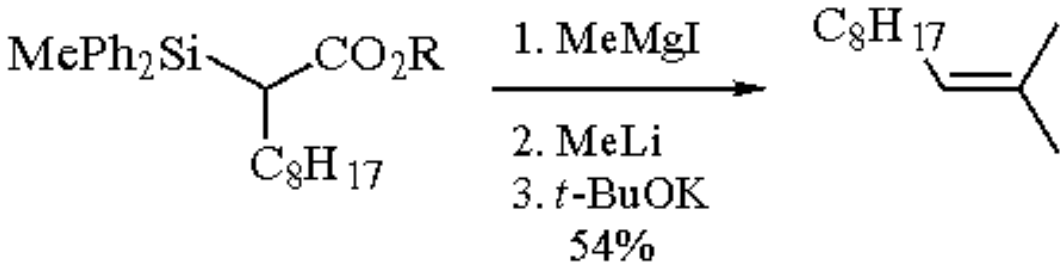

(2)

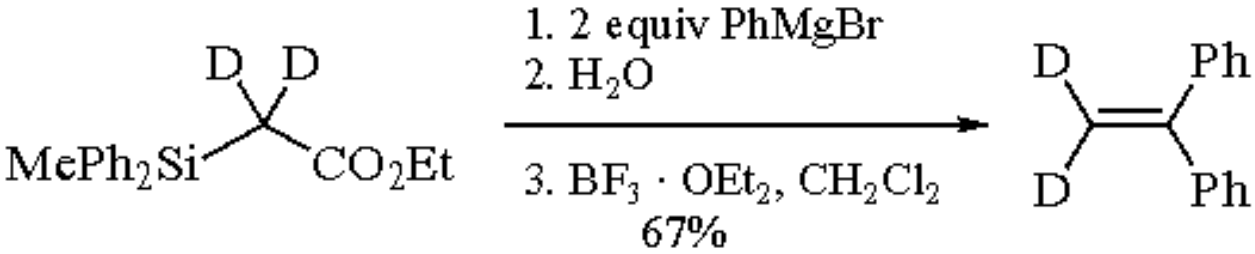

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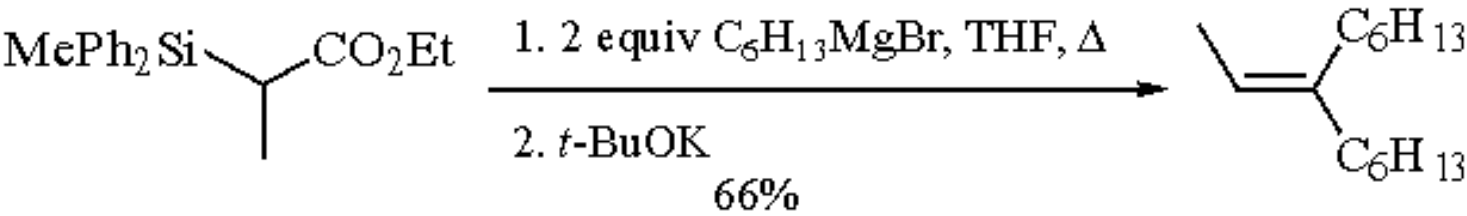

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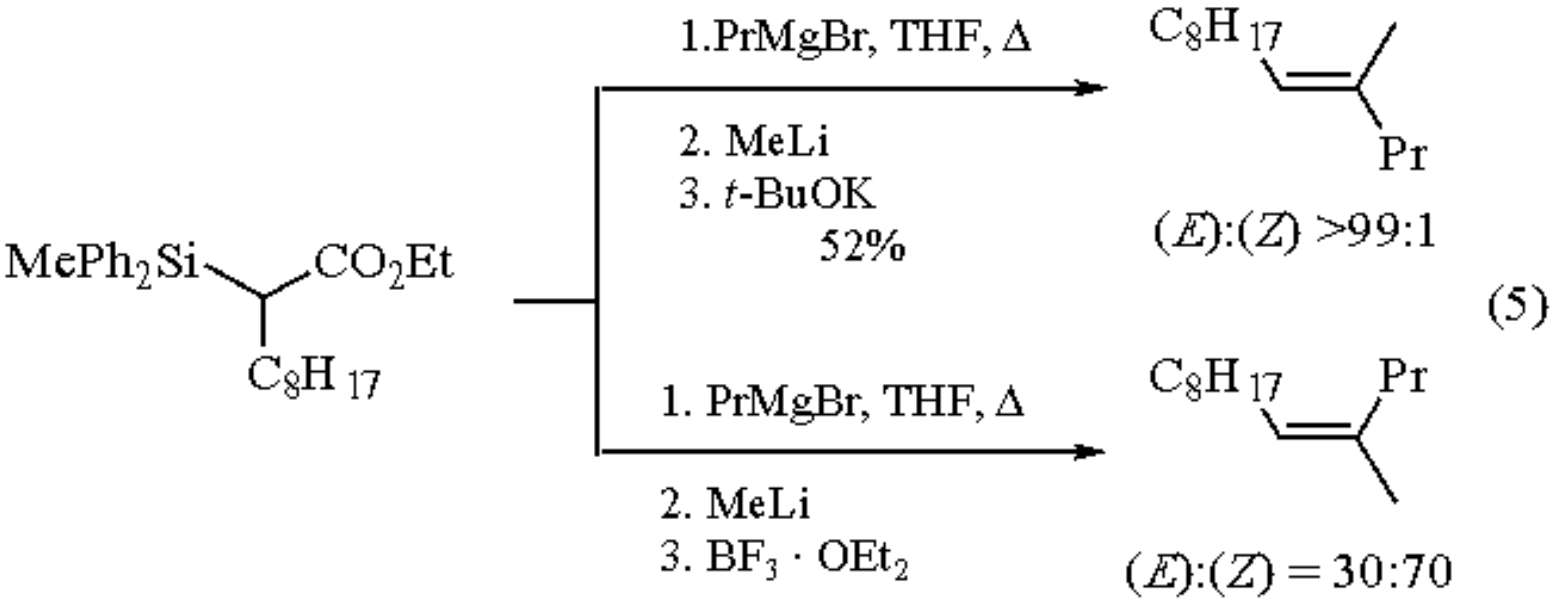

Tetrasubstituted alkenes can be prepared in an analogous fashion from α,α-dialkyl-α-(methyldiphenylsilyl)acetate, prepared by alkylation of the corresponding α-alkyl-α-silyl ester (eqs 6 and 7).[4b] These reactions are, however, strongly influenced by the steric demands of the highly substituted α-carbon and therefore tend to give ketones even with an excess of the Grignard reagent. Alkenes are obtained only with the Grignard/organolithium reagent combination, and even this sequence sometimes succumbs to steric strain. No reports of the use of cerium reagents in these transformations have appeared.

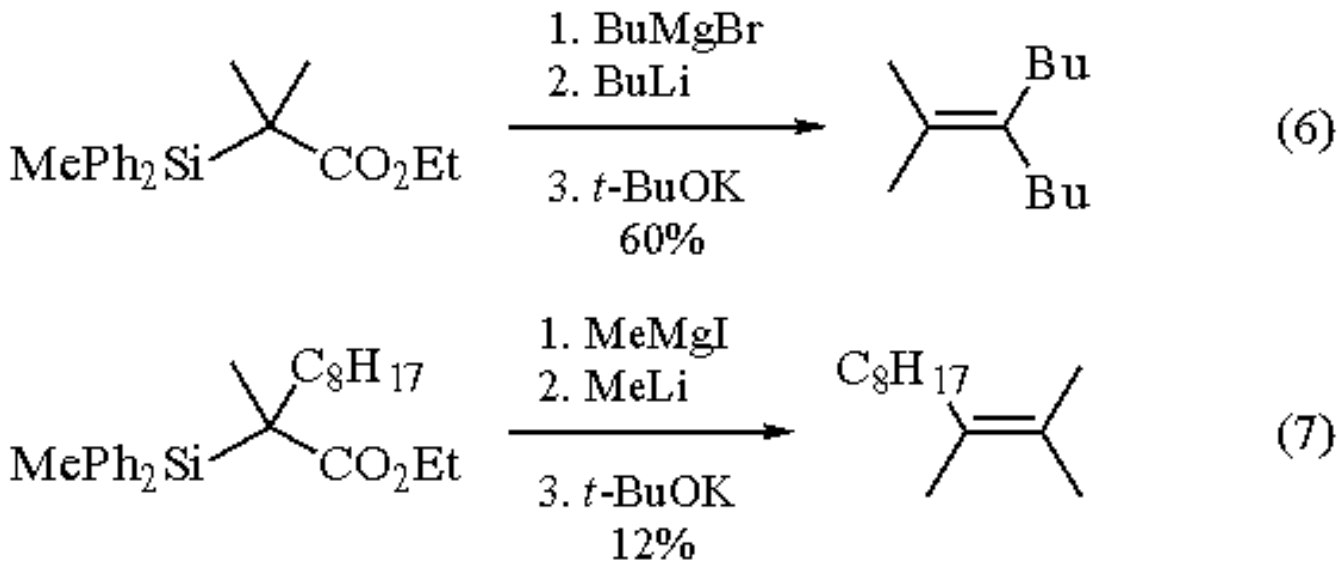

Synthesis of α,β-Unsaturated Esters.

Yamamoto and co-workers[3c] and others[3d,e] have shown that α-trimethylsilyl acetates effect Peterson alkenation of ketones and aldehydes. The lithium enolates of α-(methyldiphenylsilyl) esters react similarly with ketones and aldehydes to give α,β-unsaturated esters (eq 8).[3a,b] In the case of α-silyl acetates, no particular advantage of either the trimethylsilyl or methyldiphenylsilyl group over the other is apparent. In the case of α-substituted α-silylacetates, the methyldiphenylsilyl group has the distinct advantage of being directly prepared by methyldiphenylsilylation of the lithium enolate of the ester.[1b] The (*E*)/(*Z*) stereoselectivity of the α,β-unsaturated ester synthesis shows no correlation

with the steric bulk of the alcohol portion of the α-(methyldiphenylsilyl)acetates. However, the (*E*)/(*Z*) ratio is affected by the temperature and mode of addition. It appears that the elimination step in the process leads to a mixture of diastereomeric alkenes.[3a,b]

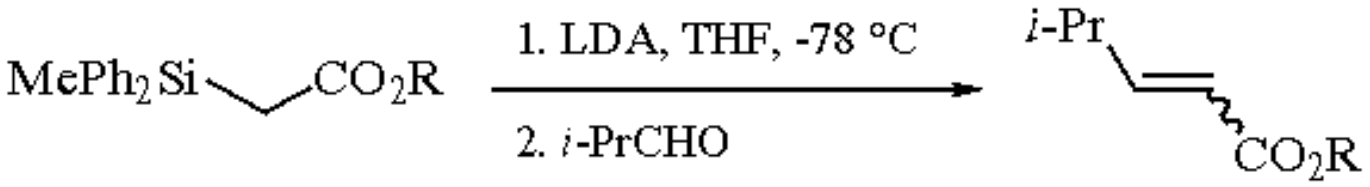

(8)

R = Et, *i*-Pr, *i*-Bu, (-)-menthyl

A Michael addition of the silyl enolate was employed in a short synthesis of (±)-methyl jasmonate from cyclopentenone (eqs 9 and 10).[5] This convergent scheme was carried out in three steps: conjugate addition of methyl α-(methyldiphenylsilyl)lithioacetate to cyclopentenone, alkylation of the resulting enolate with (*Z*)-1-bromopent-2-ene, and desilylation with ***Potassium Fluoride***. (±)-Ethyl jasmonate was prepared in a similar fashion. In the conjugate addition step, the α-(methyldiphenylsilyl)ester gave superior results to those obtained with the α-trimethylsilyl esters.

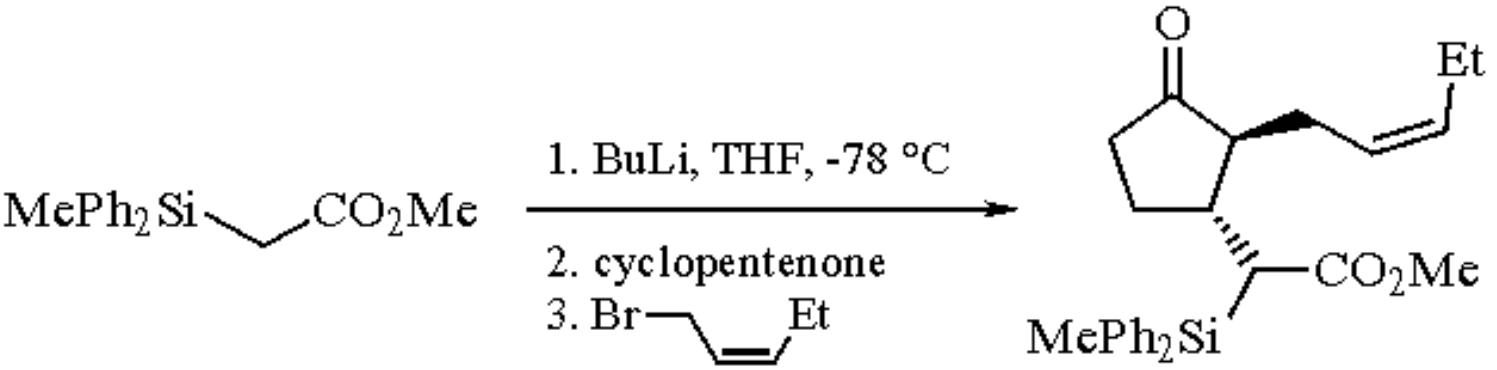

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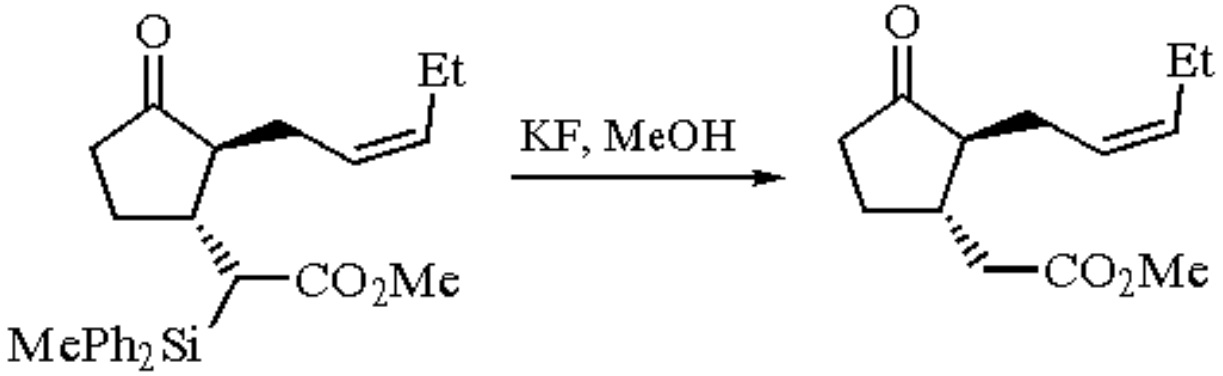

(10)

Related Reagents.

t-Butyl Trimethylsilylacetate; ***N,N-Dimethyl-2-(trimethylsilyl)acetamide***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***Ethyl Trimethylsilylacetate***; ***Trimethylsilylacetic Acid***; ***Trimethylsilylacetone***.

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Ethyl 2-(Methyldiphenylsilyl)propanoate[1]

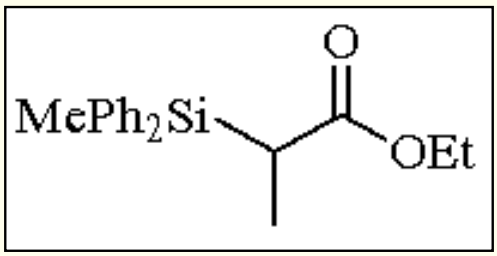

[77772-22-6] · $C_{18}H_{22}O_2Si$ · Ethyl 2-(Methyldiphenylsilyl)propanoate · (MW 298.49)

(precursor to 1,1-disubstituted 1-propenes;[1c,2] reacts with primary Grignard reagents to give 2-(methyldiphenylsilyl)-3-alkanones,[3] which in turn lead to regioselectively derived methyldiphenylsilyl enol ethers[4] or to 3-alkanones; reagent for the synthesis of α-methyl-α,β-unsaturated esters[5])

Alternate Name: ethyl 2-(methyldiphenylsilyl)propionate.

Physical Data: clear to pale yellow liquid; *n*24D 1.5407.

Preparative Method: whereas the direct silylation of the lithium enolate of an ester normally results in the formation of a mixture of the α-silyl ester and the corresponding silyl ketene acetal, the reaction of lithium ester enolates with methyldiphenylchlorosilane gives exclusively the α-methyldiphenylsilyl ester.[1b,c] This direct *C*-silylation is the best general route to α-silyl esters.

Purification: can be purified by silica gel chromatography, eluting with ethyl acetate/hexane (2:98 v/v), or by short path distillation.

Handling, Storage, and Precautions: this compound and other α-silyl carbonyl compounds are hydrolyzed under acidic or basic conditions to give the parent desilylated esters.

1,1-Disubstituted 1-Propenes.

The reaction of ethyl (methyldiphenylsilyl)propanoate (**1**) with primary or aryl Grignard reagents results in the formation of the α-silyl ketone or a 1,1-disubstituted 1-propene.[1c,2] For example, the reaction with ***Phenylmagnesium Bromide*** in refluxing THF for several hours leads to 1,1-diphenyl-1-propene in good yield (eq 1). In general, the more sterically demanding the Grignard reagent, the lower the yield of the alkene. The synthesis of alkenes from other more sterically hindered α-(methyldiphenylsilyl) esters requires a sequential reaction of the ester with a Grignard reagent followed by an organolithium reagent (eq 2).

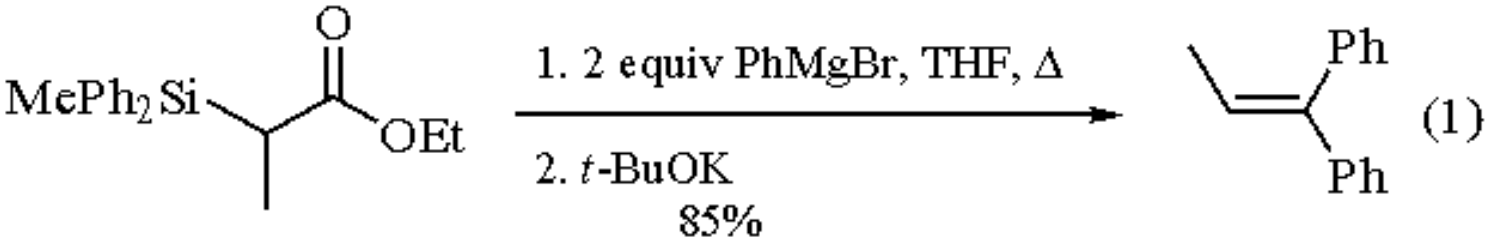

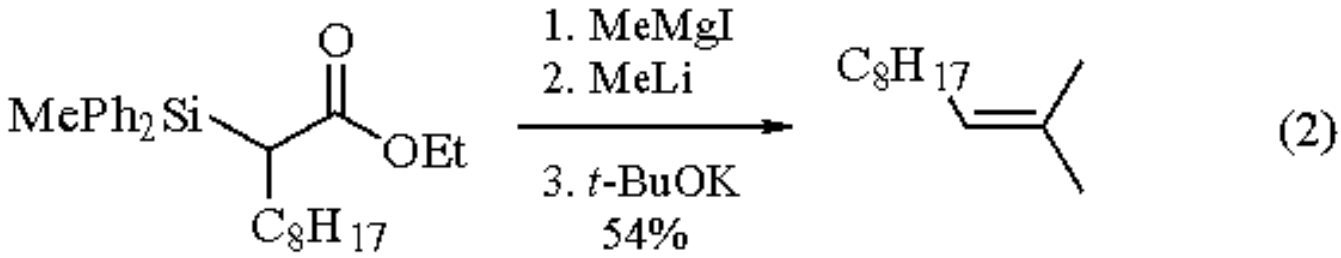

α-Silyl Ketones, Silyl Enol Ethers, and Ketones.

The reaction of (**1**) with Grignard reagents leads to the corresponding 2-(methyldiphenylsilyl)-3-alkanone (eq 3).[3] This reaction is favored when the acid portion of the ester is larger than propionyl. The reaction proceeds through formation of a magnesium enolate on the side of the α-silyl ketone opposite to that of the bulky methyldiphenylsilyl group (eq 4). The direct conversion of α-(methyldiphenylsilyl) esters to ketones can be accomplished by treatment of the ester with a Grignard reagent followed by protiodesilylation with ***Potassium Fluoride***/methanol (eq 5).

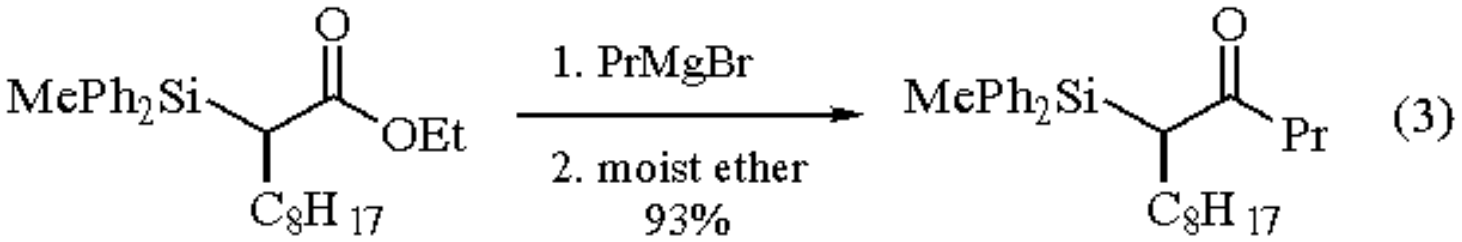

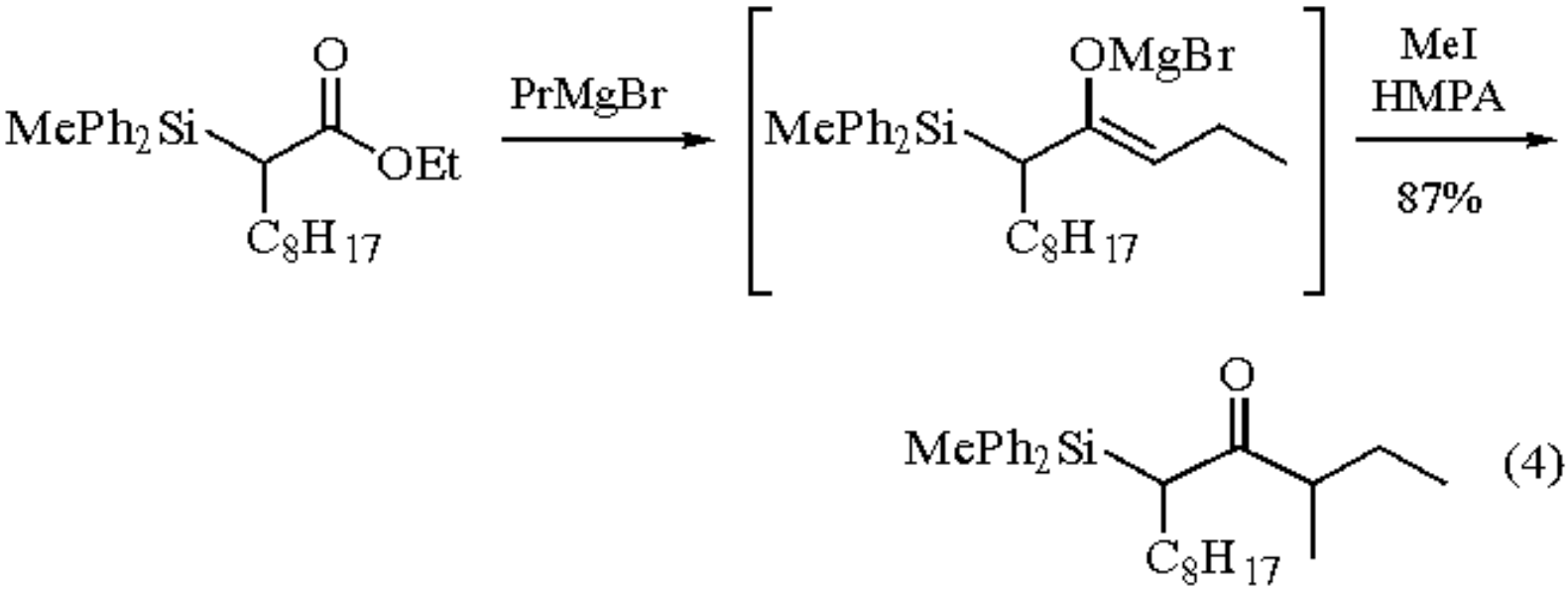

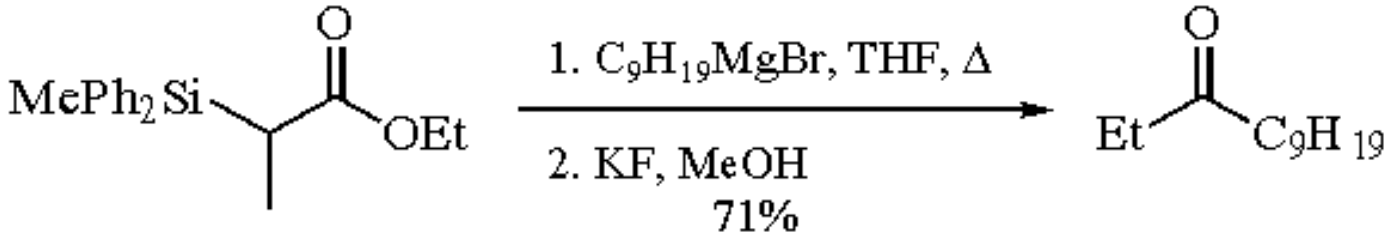

(5)

The α-(methyldiphenylsilyl) ketones isomerize to the corresponding silyl enol ether regioselectively simply by mild thermolysis at about 150 °C (eq 6). This reaction can also be done in a stereoselective fashion to give the (*Z*)-enol silyl ether when the thermolysis is carried out in acetonitrile (eq 7).[4]

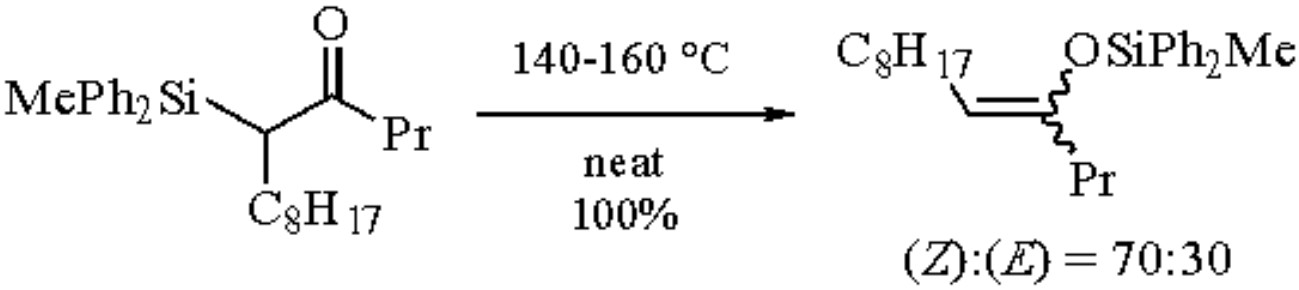

(6)

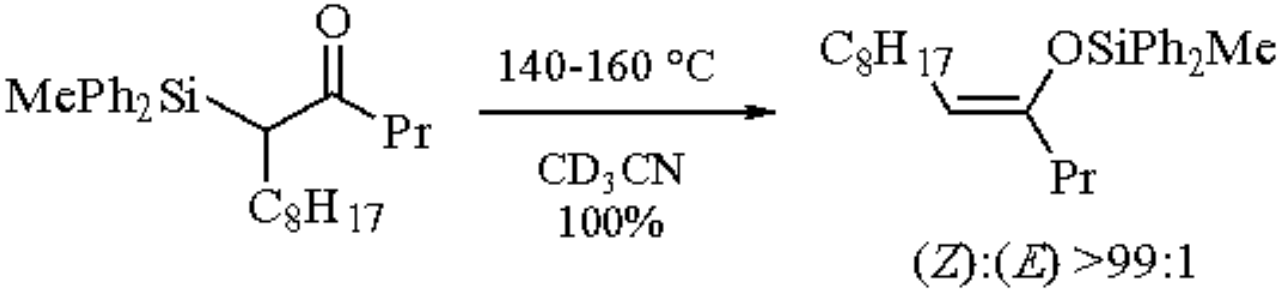

(7)

α-Methyl-α,β-unsaturated Esters.

Deprotonation of (**1**) and related compounds followed by reaction of the resulting enolate with aldehydes provides α-methyl(alkyl)-α,β-unsaturated esters in good yields.[5] The (*Z*) diastereomer predominates, with (*Z*)/(*E*) ratios between 90:10 and 79:21. Acrolein reacts in a similar manner, undergoing 1,2-alkenation to give a 77:23 mixture of (*Z*)- and (*E*)-ethyl 2-methyl-2,4-pentadienoates (eq 8).

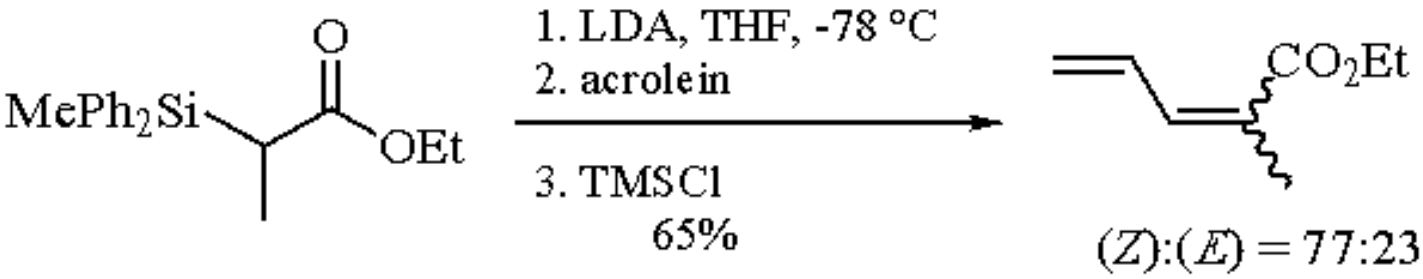

(8)

Related Reagents.

t-Butyl Trimethylsilylacetate; ***N,N-Dimethyl-2-(trimethylsilyl)acetamide***; ***Ethyl (Methyldiphenylsilyl)acetate***; ***Ethyl Trimethylsilylacetate***; ***Trimethylsilylacetic Acid***; ***Trimethylsilylacetone***.

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Gerald L. Larson

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Ethyl (Methylthio)acetate

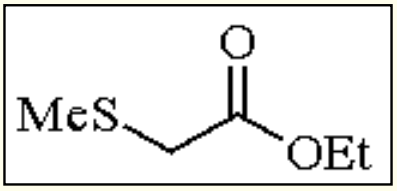

[4455-13-4] · $C_5H_{10}O_2S$ · Ethyl (Methylthio)acetate · (MW 134.22)

(addition to anilines; the chloride salt adds to anilines to give indolin-2-ones)

Physical Data: bp 70-72 °C/25 mmHg; *d* 0.905 g cm^{-3}.

Form Supplied in: oil; widely available.

Handling, Storage, and Precautions: water sensitive; protect from atmospheric moisture; stench.

Ethyl (methylthio)acetate can be treated with ***t-Butyl Hypochlorite*** in dichloromethane to give the methylsulfonium chloride[1] salt which reacts with anilines, via a Sommelet-Hauser type rearrangement of the intermediate azasulfonium salt, to afford *ortho* addition of ethyl (methylthio)acetate after treatment with ***Triethylamine*** and workup. This reaction is very mild and can be done in the presence of ketones, esters, and *N*-protected nitrogen groups. Treatment of the addition product with HCl gives 3-methylthioindolin-2-ones (eq 1).[2]

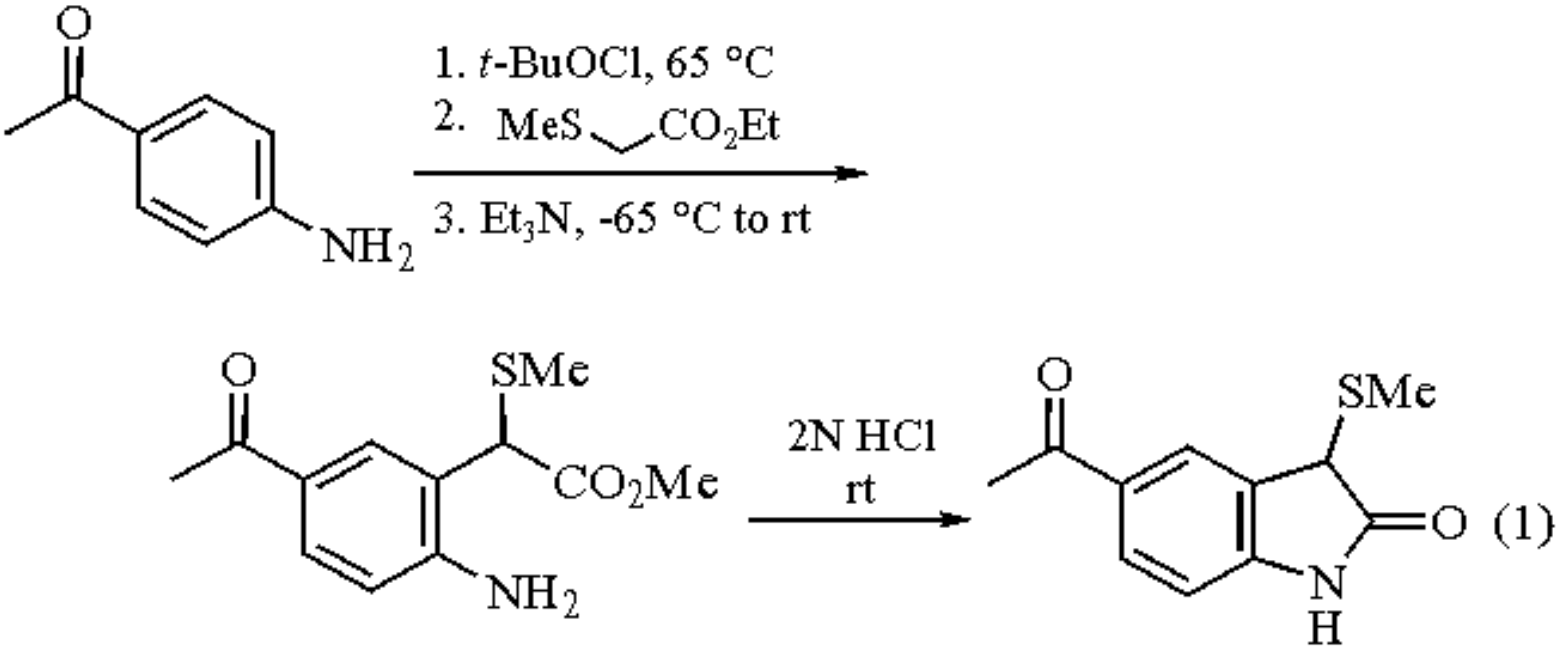

Oxidative removal of the methylthio group with ***N-Chlorosuccinimide*** in dichloromethane can be achieved to convert the methylthio group to a carbonyl group.[2] The reductive removal of the methylthio group is simply effected by the addition of commercially available ***Raney Nickel*** until the starting material has been consumed according to TLC analysis,[3] or by the use of ***Tin*** metal in ethanolic HCl.[4] Since alkylation of indolin-2-ones gives complex mixtures, ethyl (methylthio)acetate is also very useful for the preparation of 3-alkylindolin-2-ones. The methylthio group enables selective deprotonation with ***Sodium Hydride*** and quenching with reactive electrophiles,[3] such as ***Iodomethane*** and ***Benzyl Bromide***. Treatment with Raney nickel affords the alkylated indolin-2-ones (eq 2).

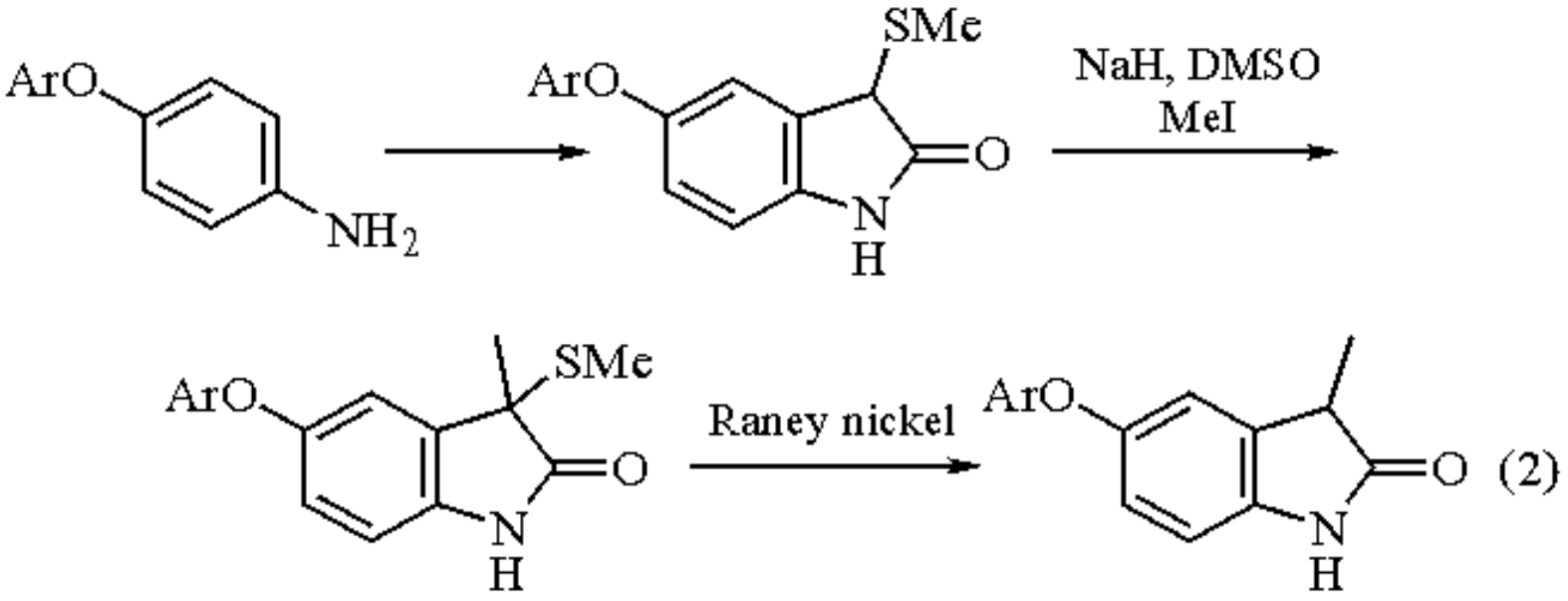

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Ethyl Nitroacetate

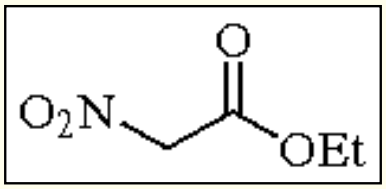

[626-35-7] · $C_4H_7NO_4$ · Ethyl Nitroacetate · (MW 133.12)

(alkylations;[3,5,6] Michael additions;[4] amidoalkylations;[7] Knoevenagel condensations;[8-11] palladium-catalyzed allylations;[12-14] α-alkoxyallylation;[15] generation of alkyl nitronates;[16,17] generation of hydroxynitrilium ions for synthesis of (*E*)-oximes;[18] synthesis of 4-hydroxy-2-isoxazolines;[19] oxidant for alcohols;[20] synthesis of α-amino esters[21])

Physical Data: bp 194-195 °C; *d* 1.203 g cm^{-3}; *n*20D 1.425.

Solubility: sol ethanol, diethyl ether.

Form Supplied in: colorless liquid; widely available.

Preparative Methods: from ***Nitromethane*** by self-condensation to produce methazonic acid, followed by dehydration to nitroacetonitrile, hydrolysis, and esterification.[22] Alternatively, it is accessible from ***Ethyl Acetoacetate*** by nitration; the resultant ethyl nitroacetoacetate is decomposed with ethanol.[23]

Purification: fractional vacuum distillation.

Handling, Storage, and Precautions: stable for at least six months if stored in the refrigerator.

C-Alkylation.

Due to its strong acidity (pK_a (DMSO) = 9.2),[24] ethyl nitroacetate (**1**) can easily be deprotonated by a number of weak bases or electrochemically at the cathode.[1] The anion typically reacts with alkyl halides, enones, acetates, carbonates, amines, and alcohols or it can be condensed with aldehydes, ketones, or imines.[2] Thus the sodium salt of ethyl nitroacetate (**1**) is alkylated with ***Benzyl Bromide*** (**2**) (eq 1).[3]

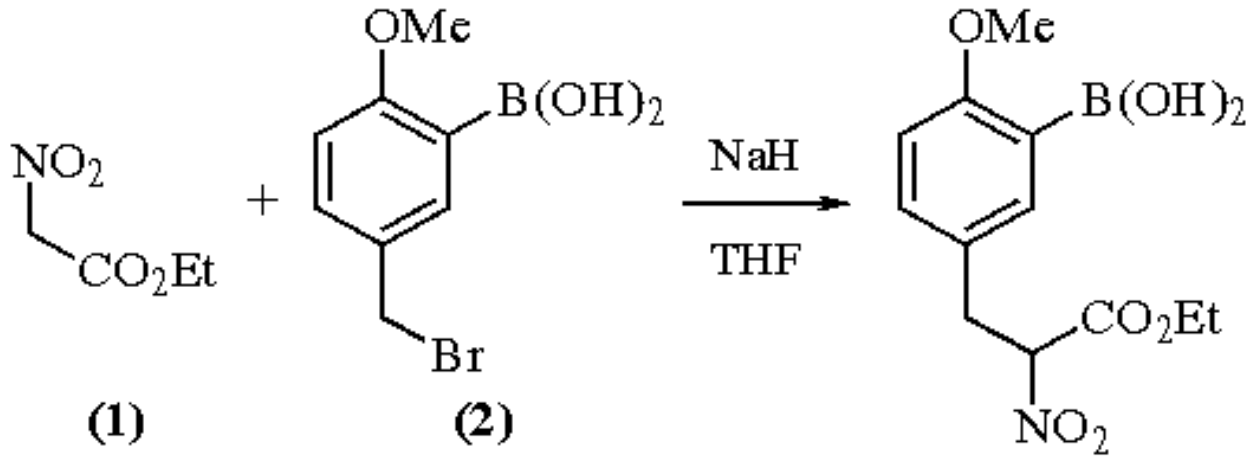

(1)

In a Michael addition, (**1**) reacts with 2-acetyl-1,4-dihydroxyanthracene-9,10-dione (**3**) in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (eq 2).[4] Aromatization of the Michael adduct (**4**) is achieved either by elimination of nitric acid with DBU in an inert atmosphere to form ester (**5**), or by oxidation of the quinone moiety in an air atmosphere to afford ester (**6**) (eq 2).

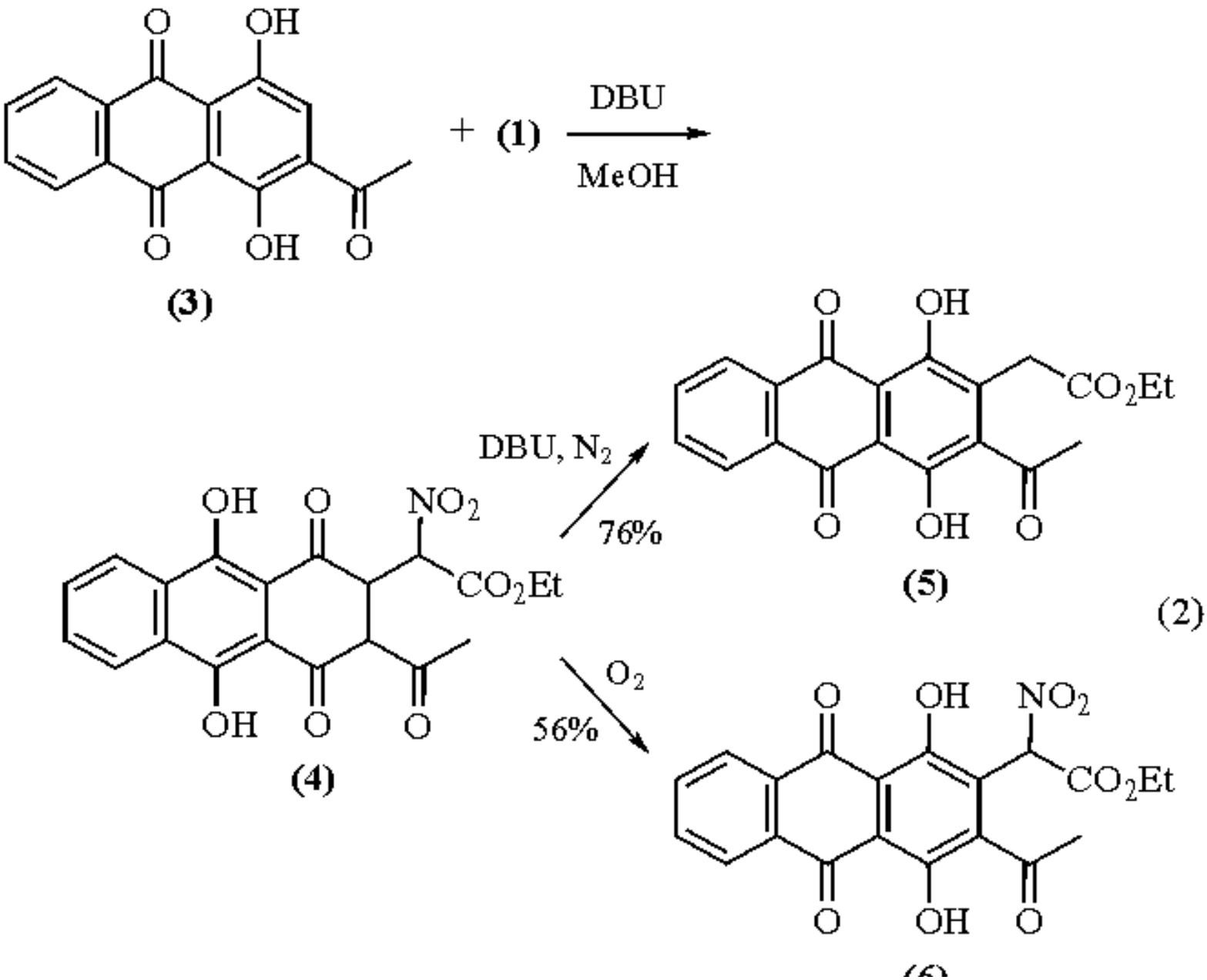

(2)

(6)

Ethyl nitroacetate can be alkylated by gramine in refluxing toluene in quantitative yield (eq 3).[5] Heating of (**1**) with trityl alcohol (**7**) and trichloroacetic acid gives ethyl 3,3,3-triphenyl-2-nitropropanoate (**8**) in 41% yield (eq 4).[6]

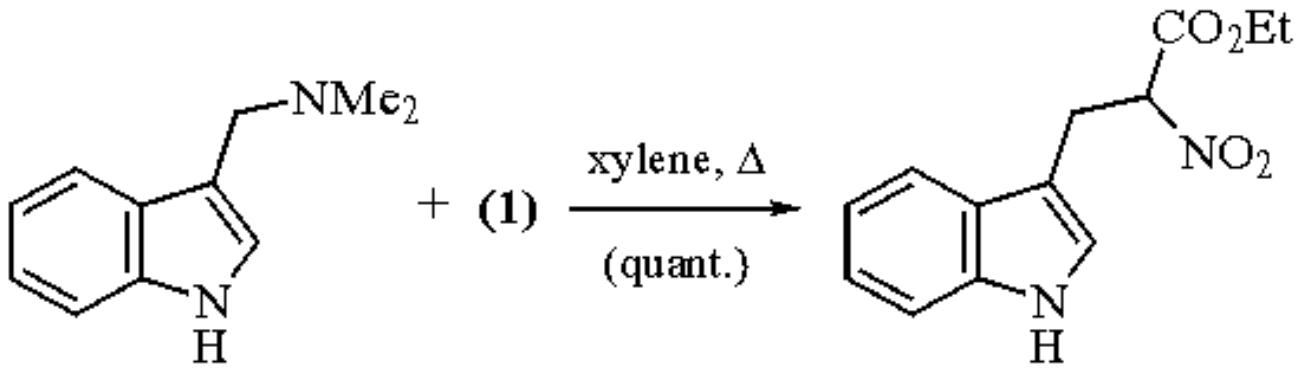

(3)

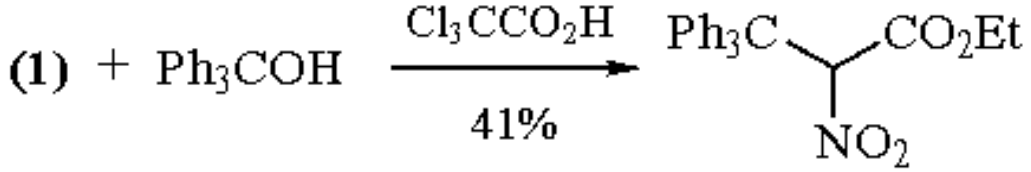

(4)

(7) **(8)**

N-(1-Benzotriazol-1-ylalkyl)amides (**9**) react with (**1**) under mild conditions to give rise to the α-amidoalkylation products (**10**) (eq 5).[7]

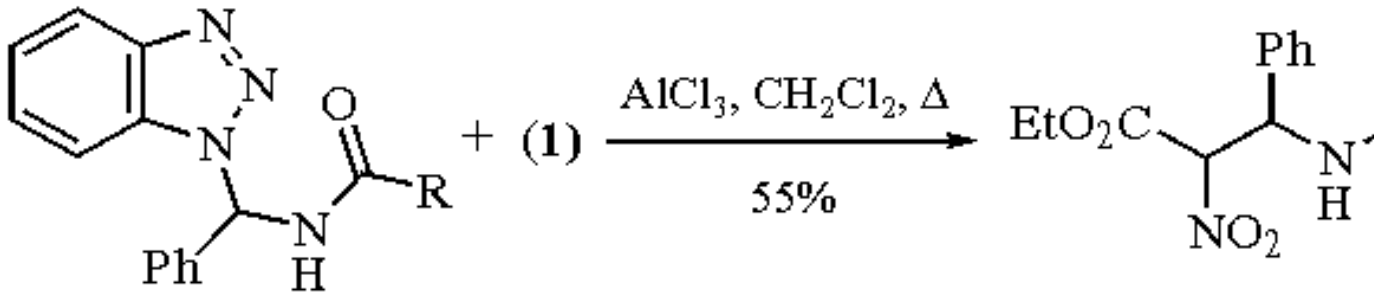

(5)

(9) **(10)**

Ethyl nitroacetate (**1**) undergoes Knoevenagel condensations[8] with aldehydes, ketones, and imines. Acid-base combinations like ***Titanium(IV) Chloride*/*Pyridine***[9] or ***Acetic Acid*/*Piperidine***[10] are particularly good catalysts for this reaction. Iminophosphate (**11**) is converted to the Knoevenagel product (**12**) upon exposure to the sodium salt of ethyl nitroacetate (eq 6).[11]

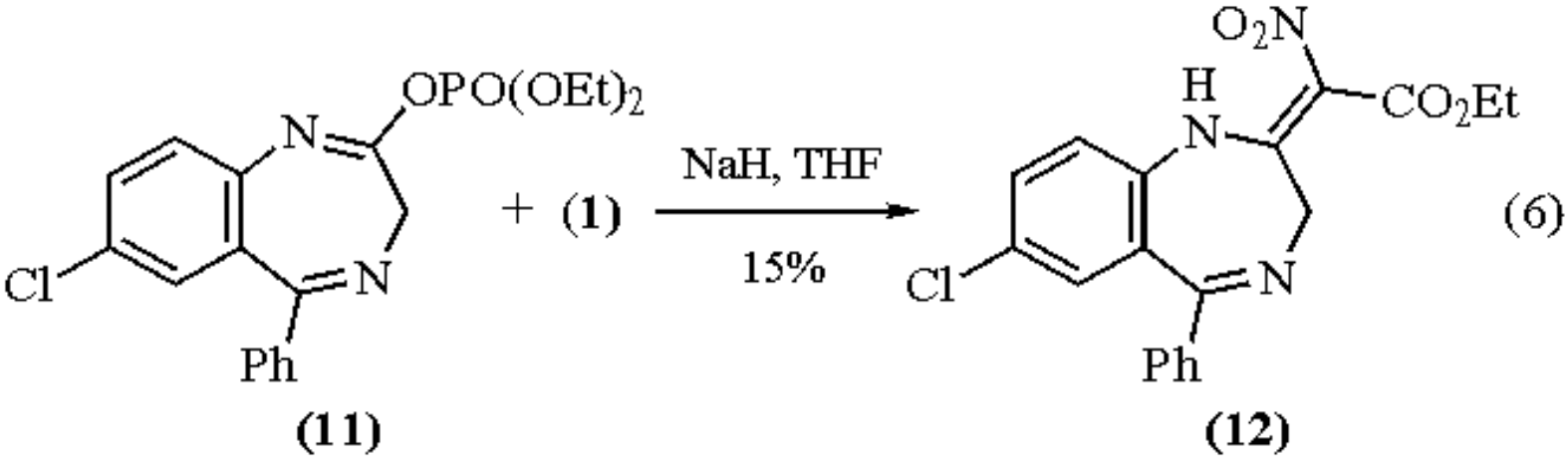

Under palladium catalysis, ethyl nitroacetate (**1**) reacts with allylic carbonates, acetates, and phenoxides to give the allylated compounds.[12] Thus *C*-glycopyranosides (**14**) are accessible from 2,3-unsaturated glycals (**13**) (eq 7).[13] The key step in the synthesis of the carbocyclic nucleoside carbovir is a Pd^0-catalyzed addition of (**1**) to the carbonate (**15**) followed by a Krapcho-deethoxycarbonylation (eq 8).[14] Both reactions are completely regio- and stereoselective.

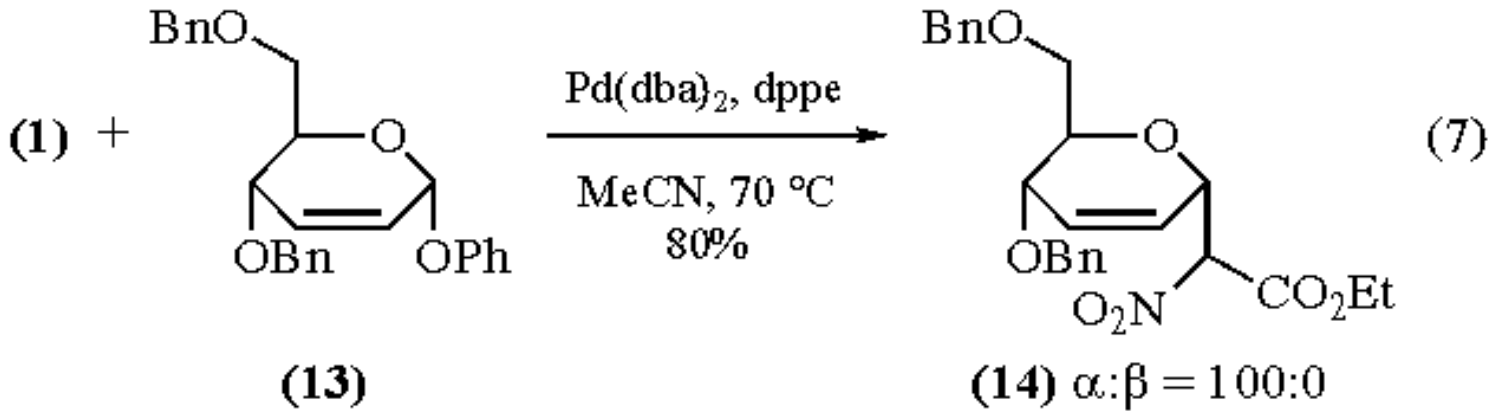

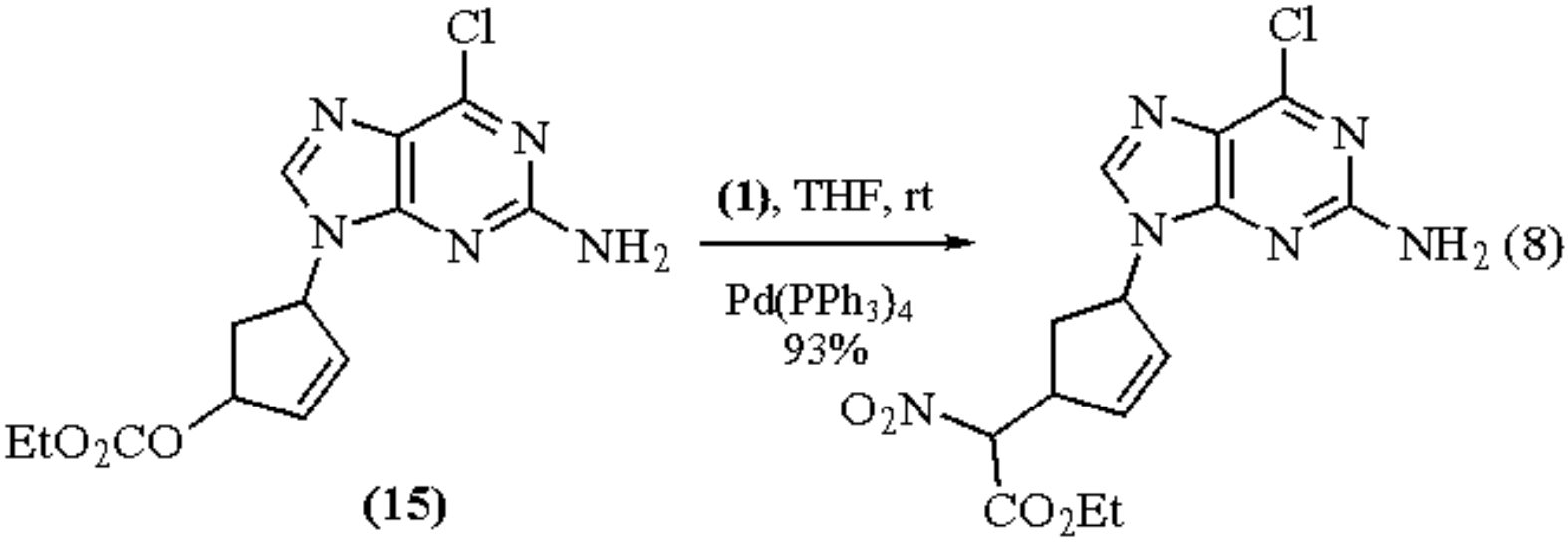

Ethyl nitroacetate (**1**) can be α-alkoxyallylated when treated with acetals (**16**) of α,β-enals.[15] The first step of the reaction is the formation of the Claisen system (**17**) which, when heated at 200 °C, undergoes the [3,3]-sigmatropic rearrangement, albeit in poor yield (eq 9).

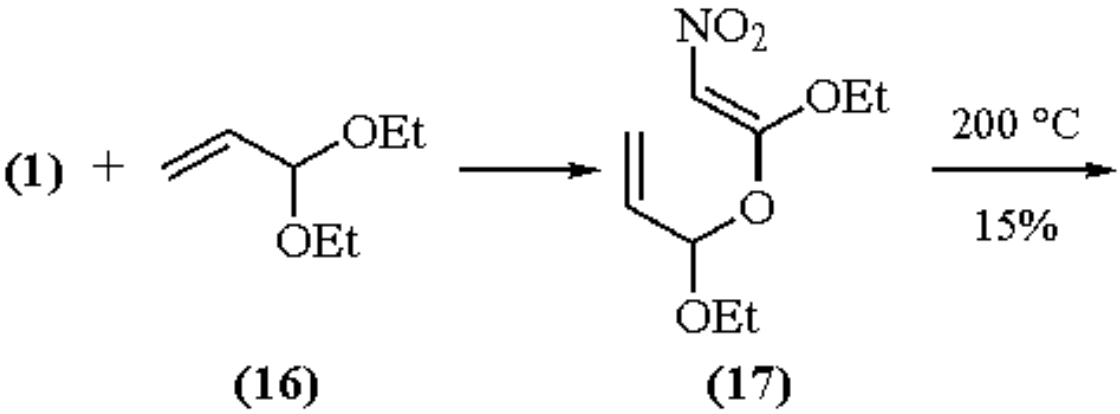

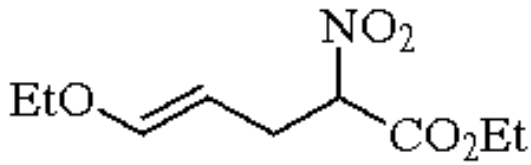

(9)

O-Alkylation.

Under Mitsunobu conditions, ethyl nitroacetate (**1**) reacts with alcohols by way of exclusive *O*-alkylation to afford alkyl nitronates (**18**) (eq 10).[16] These have been shown to be reactive 1,3-dipoles in cycloadditions with alkenes, alkynes, and hetero dipolarophiles.[2] Versatile heterocycles like isoxazolines are accessible by this transformation.[17]

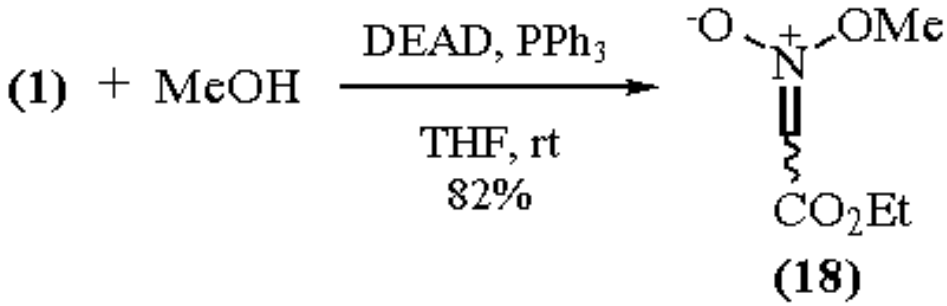

(10)

By the action of a strong acid like ***Trifluoromethanesulfonic Acid***, (**1**) is converted to the highly electrophilic hydroxynitrilium ion (**19**).[18] Aromatic compounds can easily add to (**19**) to furnish (*E*)-oximes (**20**) stereoselectively (eq 11).

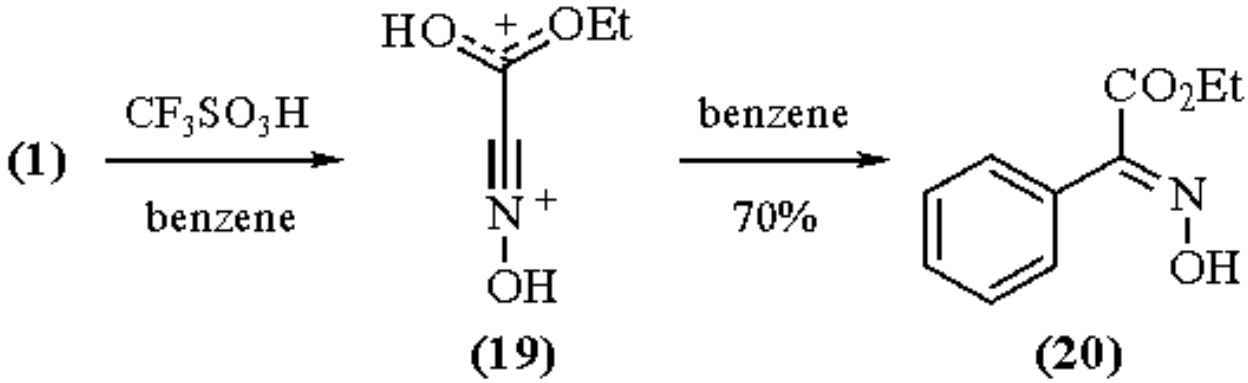

(11)

Ethyl nitroacetate (**1**) condenses with α-bromo aldehydes (**21**) in the presence of ***Alumina*** in a synthesis of 4-hydroxy-2-isoxazolines (**22**) (eq 12).[19] This reaction can be analyzed in terms of a nitroaldol-cyclization sequence. The primarily formed oxides (**23**) are reduced to the desired isoxazolines (**22**) with ***Trimethyl Phosphite*** (eq 12).

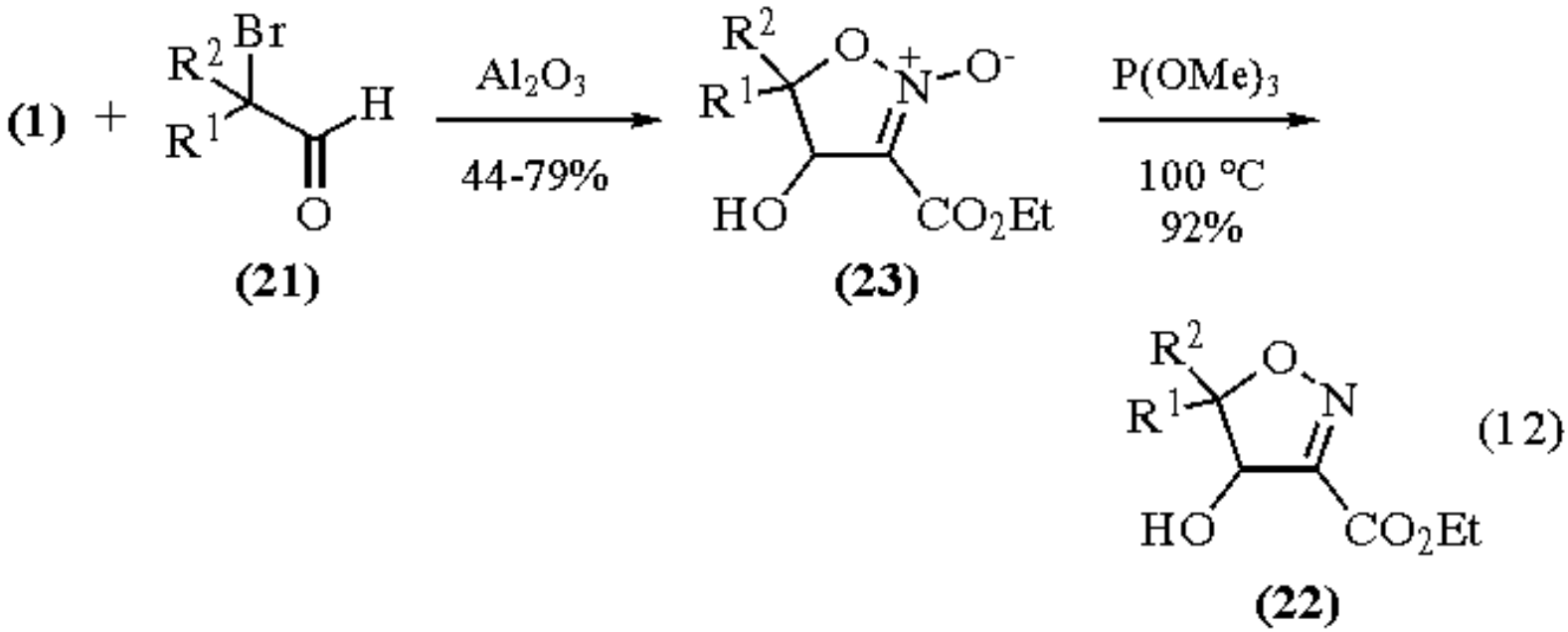

Oxidation.

A combination of ***Diethyl Azodicarboxylate***, ***Triphenylphosphine***, and ethyl nitroacetate (**1**) is an effective system for the oxidation of primary and secondary alcohols (eq 13).[20] Aldehydes and ketones are formed under neutral conditions. An *aci*-nitro ester (**24**) is the intermediate of the reduction and decomposes slowly when heated in THF (eq 13).

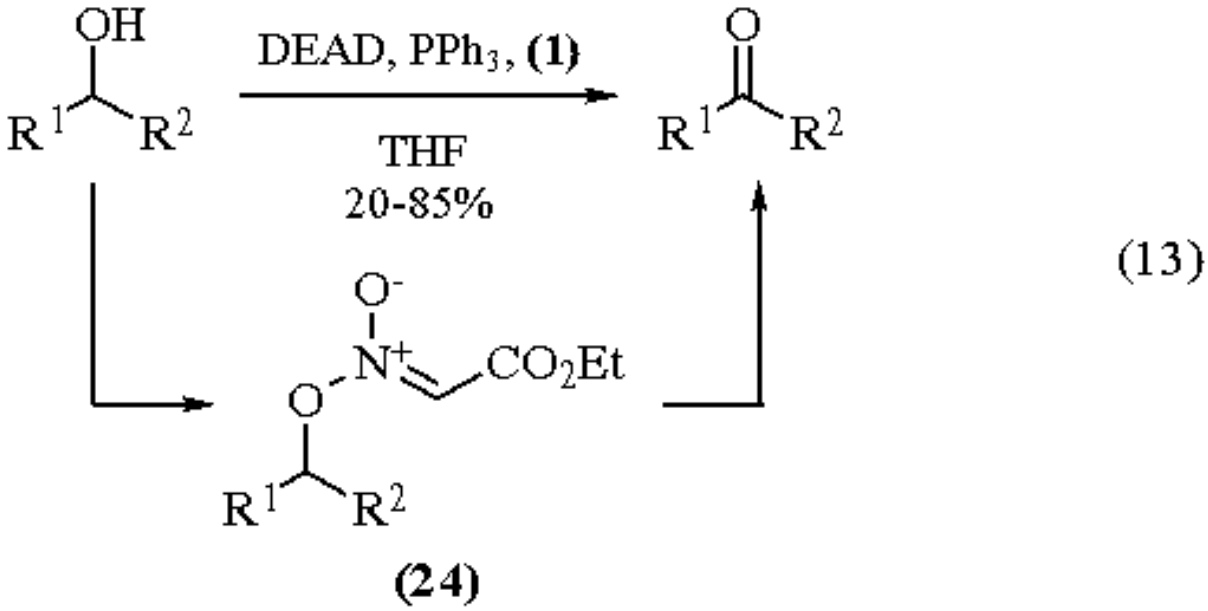

Ethyl glycinate (**25**) can be obtained via reduction of ethyl nitroacetate (**1**) using ***Ammonium Formate*** as a catalytic hydrogen transfer agent in a ***Palladium on Carbon*** suspension in methanol (eq 14).[21]

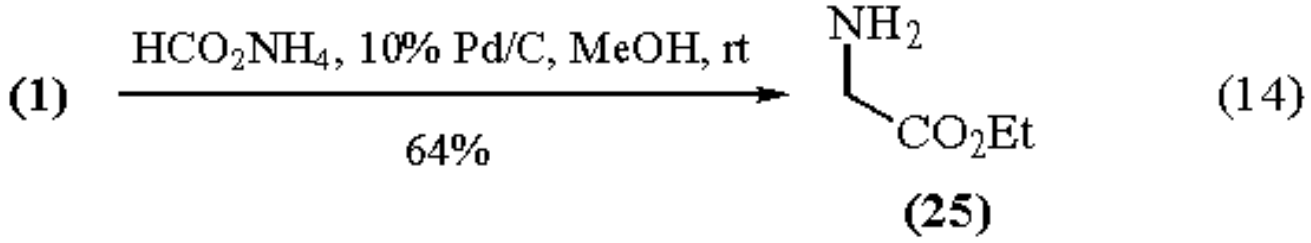

Related Reagents.

Methyl 4-Nitrobutanoate; ***Methyl 3-Nitropropanoate***; ***Nitromethane***; ***Phenylsulfonylnitromethane***.

---

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(3a*R*,7a*R*)-2-Ethyloctahydro-1*H*-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide

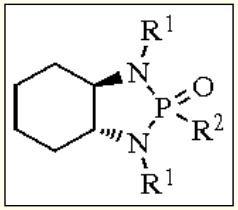

(**1**; R^1 = neopentyl, R^2 = Et)

[146397-34-4] · $C_{18}H_{37}N_2OP$ · (3a*R*,7a*R*)-2-Ethyloctahydro-1*H*-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide · (MW 328.54) (**2**; R^1 = Me, R^2 = allyl)

[146098-95-5] · $C_{11}H_{21}N_2OP$ · (3a*R*,7a*R*)-2-Allyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzodiazaphosphole Oxide · (MW 228.31) (**3**; R^1 = Me, R^2 = Et)

[91633-73-7] · $C_{10}H_{21}N_2OP$ · (3a*R*,7a*R*)-2-Ethyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzodiazaphosphole Oxide · (MW 216.30) (**4**; R^1 = Me, R^2 = Bn)

[146098-94-4] · $C_{15}H_{23}N_2OP$ · (3a*R*,7a*R*)-2-Benzyloctahydro-1*H*-1,3-dimethyl-1,3,2-benzodiazaphosphole Oxide · (MW 278.37) (**5**; R^1 = Me, R^2 = $CH_2CH{=}CHMe$)

[-] · $C_{12}H_{23}N_2OP$ · (3a*R*,7a*R*)-2-(2-Butenyl)octahydro-1*H*-1,3-dimethyl-1,3,2-benzodiazaphosphole Oxide · (MW 242.34) (**6**; R^1 = Bn, R^2 = Et)

[-] · $C_{22}H_{29}N_2OP$ · (3a*R*,7a*R*)-2-Ethyloctahydro-1*H*-1,3-dibenzyl-1,3,2-benzodiazaphosphole Oxide · (MW 368.50) (**7**; R^1 = Bn, R^2 = Pr)

[-] · $C_{23}H_{31}N_2OP$ · (3a*R*,7a*R*)-2-Propyloctahydro-1*H*-1,3-dibenzyl-1,3,2-benzodiazaphosphole Oxide · (MW 382.53) (**8**; R^1 = Me, R^2 = CH_2Cl)

[146983-74-6] · $C_9H_{18}ClN_2OP$ · (3a*R*,7a*R*)-2-(Chloromethyl)octahydro-1*H*-1,3-dimethyl-1,3,2-benzodiazaphosphole Oxide · (MW 236.71)

(chiral α-alkyl bicyclophosphonamides useful for the asymmetric synthesis of alkenes,[1-3] of α,α´-substituted phosphonic acids,[4] and of α-amino-α-substituted phosphonic acids,[5,6] and for asymmetric conjugate additions of *C*-allyl and *C*-crotyl groups to α,β-unsaturated carbonyl compounds[7])

Physical Data: (**1**) mp 110-111 °C; [α]25D -98.8° (*c* 1.10, $CHCl_3$). (**2**) mp 45-46 °C; [α]25D -51.1° (*c* 1.85, $CHCl_3$). (**3**) mp 55-56 °C; [α]25D -98.9° (*c* 1.48, $CHCl_3$). (**4**) mp 104-105 °C; [α]25D -109.6° (*c* 1.17, $CHCl_3$). (**6**) mp 153-154 °C; [α]25D -68.2° (*c* 1.18, $CHCl_3$). (**7**) mp 117 °C; [α]25D -66.0° (*c* 1.02, $CHCl_3$). (**8**) mp 84 °C; [α]25D -109.8° (*c* 1.0, $CHCl_3$).

Solubility: sol chlorinated and dipolar aprotic solvents, and hydrocarbon solvents in some cases. Gradual hydrolysis in protic media.

Form Supplied in: colorless crystalline or waxy solids.

Preparative Methods: [3] to a solution of (1*R*,2*R*)-*N*,*N*´-dineopentyl-1,2-diaminocyclohexane (1.37 g, 5.40 mmol) and triethylamine (2.3 mL, 48.5 mmol) in 25 mL of benzene is added ethylphosphoryl dichloride (0.89 g, 6.06 mmol). The suspension is heated to reflux for 80 h, the salts are filtered, and the filtrate is washed successively with 10% aq HCl (2 × 10 mL), aq saturated $NaHCO_3$, and water. Drying, evaporation, and chromatographic separation (EtOAc) gives the title compound (1.1 g, 62%) as a crystalline solid, mp 110-111 °C (hexanes). Single crystal X-ray analysis confirmed the structure. For an alternative synthesis of related compounds, see Kueller and Spilling.[8] Other 2-alkyl derivatives can be similarly prepared.[1-4]

Handling, Storage, and Precautions: crystalline reagents are stable when stored under argon at 0 °C for several months.

Asymmetric Alkenation of Alkylcyclohexanones.[1-3]

Anions of the reagents (**1**), (**4**), (**6**), and (**7**) add to alkylcyclohexanones in THF solution at -78 °C to give intermediate β-hydroxyphosphonamide adducts, which can be isolated and purified by chromatography. Treatment of the adducts with aq acetic acid leads to the corresponding alkylidene alkylcyclohexanes in good to excellent enantiomeric or diastereomeric excesses. The alkenes can also be obtained directly from the original reaction mixtures (aq AcOH quench), without isolation of intermediates. Except in the case of reagent (**1**), using the reagents prepared from (*R*,*R*)-1,2-diaminocyclohexane gives the (a*R*)-alkenes with 4-substituted alkylcyclohexanones and the (*E*)-alkenes with other analogs, based on a transition state that favors equatorial attack of the least encumbered face of the anion on the cyclohexanone derivative. For steric reasons, the reverse is observed with reagent (**1**).[3] Eq 1 illustrates a typical reaction and other examples of products are listed in Table 1 (enantiomeric excesses >99:1).[2,3]

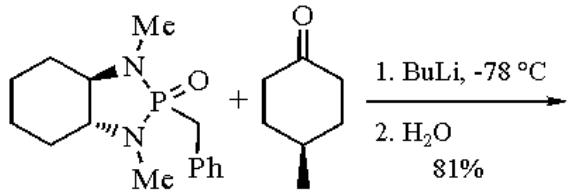

(R,R)-**(4)**

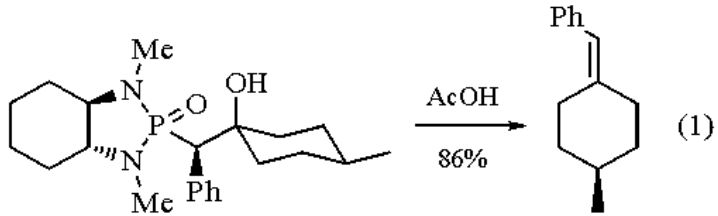

(1)

mp 131-133 °C, $[\alpha]_D$ -61.3° $[\alpha]_D$ -37.9°

Table 1 Products of Asymmetric Alkenation

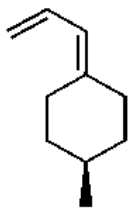

67%, $[\alpha]_{546}$ +42.3°

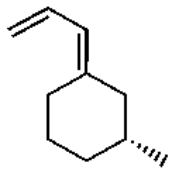

74%, $[\alpha]_{546}$ -41.9°

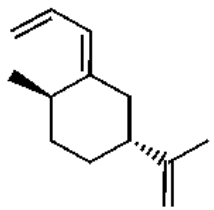

55%, 91:9

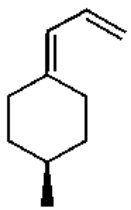

73%, $[\alpha]_{546}$ -42.7°

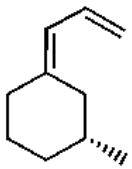

75%, $[\alpha]_{546}$ -141.6°

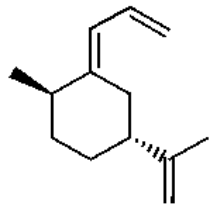

74%, $[\alpha]_{546}$ -155.9°

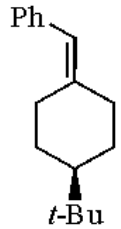

91%, $[\alpha]_D$ -33.3 °

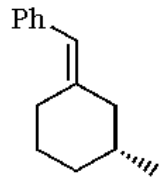

82%, $[\alpha]_D$ -72.0 °

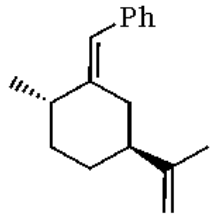

86%, $[\alpha]_D$ -86 °

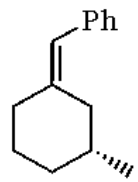

75%, $[\alpha]_D$ +30.3°

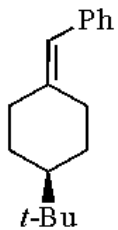

89%, $[\alpha]_D$ +32.3°

Kinetic Resolution.[2]

When the reacting partners allow for a high degree of stereodifferentiation in the transition state, it is possible to achieve asymmetric alkenation by kinetic resolution (eq 2). This is best done with α-alkyl substituted cyclohexanones and bulky anions such as that derived from (**4**). In a typical procedure, (±)-2-methylcyclohexanone (1 mmol) is treated with the anion of (**3**) (0.5 mmol, -78 °C, THF, 1 h; then AcOH, -> 25 °C, and workup), to give (*E*,2*S*)-(2-methylcyclohexylidene)benzene; [α]25D -86.4° (*c* 1, $CHCl_3$), and the (*Z*)-isomer (>98:2 by capillary GC; 63% based on the reagent).

(3aR,7aR)-2-Ethyloctahydro-1H-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide

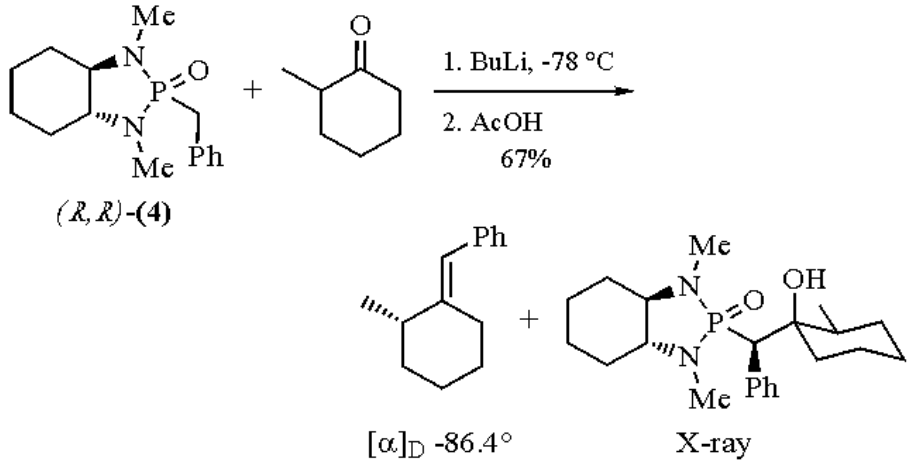

(2)

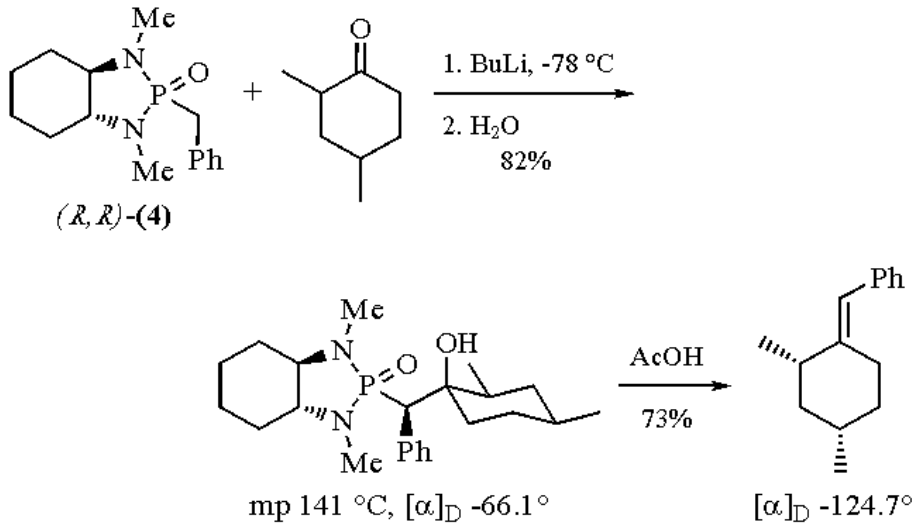

Sequential Asymmetric Alkenation and Ene Reactions.[3]

Treatment of a number of (alkylcyclohexylidene)ethane derivatives with chiral nonracemic α-benzyloxy aldehydes results in the formation of branched alkylcyclohexene derivatives via a highly stereocontrolled ene reaction. Based on a chelated transition state, it is possible to predict the disposition of the double bond and the chirality of two new stereogenic centers, as illustrated in eq 3. The newly created stereogenic center bearing a *C*-methyl group from the ene reaction leads to interesting substitution patterns in relation to the existing *C*-methyl group. Oxidative cleavage of the double bond leads to acyclic counterparts with predictable disposition and chirality (e.g. 1,6-dimethyl, 1,5-dimethyl, etc.).[3]

(3aR,7aR)-2-Ethyloctahydro-1H-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide

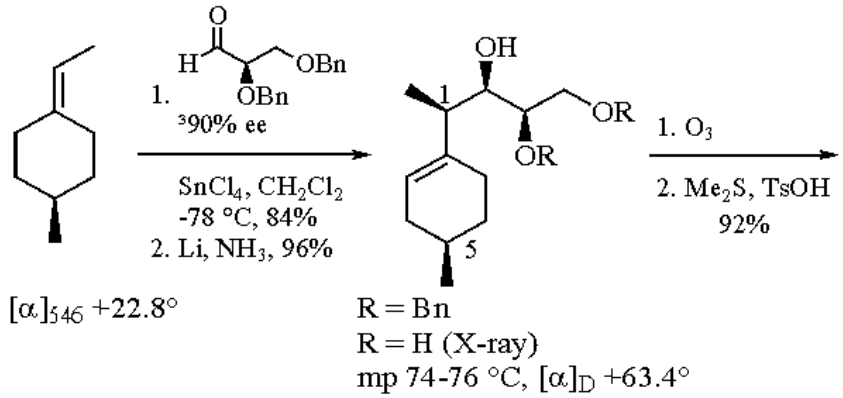

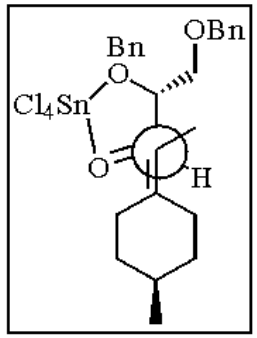

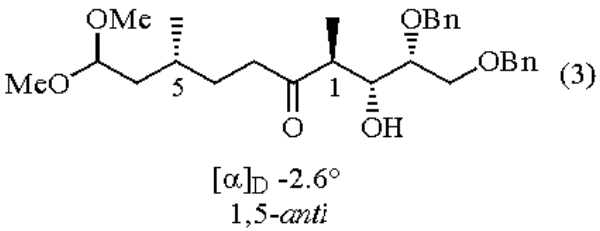

α-Substituted α-Alkylphosphonic Acids.[4]

In general, α-substituted phosphonamides can be transformed into the corresponding α-alkyl derivatives of very high diastereomeric purity by alkylation of the anions at -78 °C or lower (eq 4, Table 2). In most cases the approach of the electrophile is favored from the least hindered side of the anion, leading to highly enriched diastereomers. These products can be subsequently hydrolyzed to the corresponding phosphonic acids. A typical procedure is as follows. To a solution of (**3**) (1 mmol) in THF, is added ***n-Butyllithium*** (1.40 mmol at -78 °C), the temperature is lowered to -100 °C, and ***Allyl Bromide*** (1.15 mmol) is added. After stirring for 15 min, the reaction mixture is quenched with MeOH, and the solution processed as usual. Chromatographic purification gives the expected product as a crystalline solid (X-ray), mp 87-88 °C, [α]25D -91.5° (*c* 1.0, $CHCl_3$).

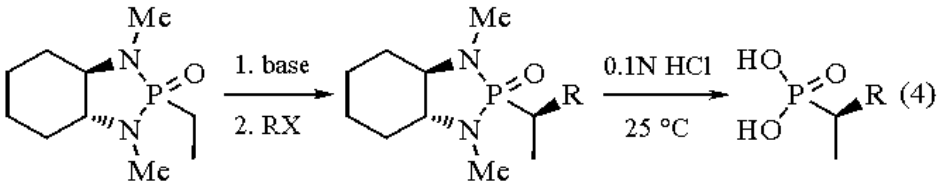

Table 2 Synthesis of a-Substituted a-Alkylphosphonic Acids

RX	Alkylation (- 100 °C)				Hydrolysis			
	Yield (%)	Ratio	Mp (°C)	$[a]_D^{25}$	Yield (%)	Mp (°C)	$[a]_D^{25}$	Config.
(*R*, *R*) Series								
EtI	76	95:5	95 96	- 81.5° (*c* 1.0)	90	54 57	+6.2° (*c* 1.0)	(*R*)
CH_2=$CHCH_2Br$	82	94:6	87 88	- 91.5° (*c* 1.0)	88	Oil	- 1.1° (*c* 1.75)	(*R*)
BnBr	83	97:3	95 97	- 35.2° (*c* 1.2)	86	122 125	+23.6° (*c* 2.2)	(*R*)
$TBDPSO(CH_2)_2I$	68	94:6	Oil	- 32.5° (*c* 1.03)	94	35	+7.0° (*c* 1.25)	(*R*)
$TBDPSO(CH_2)_3I$	71	98:2	Oil	- 35.5° (*c* 1.1)	92	Oil	+23.8° (*c* 1.1)	(*R*)
(*S*,*S*) Series								
EtI	70	5:95	92 95	+79.2° (*c* 1.0)	91	54 56	- 6.1° (*c* 0.9)	(*S*)
CH_2=$CHCH_2Br$	83	4:96	86 88	+91.0° (*c* 1.0)	88	Oil	+1.4° (*c* 1.4)	(*S*)
BnBr	84	4:96	96 97	+33.6° (*c* 1.0)	82	122 124	- 22.8° (*c* 1.0)	(*S*)

α-Chloro-α-alkylphosphonic Acids.[4]

The reagent is prepared from α-chloromethylphosphonyl dichloride and (*R*,*R*)- or (*S*,*S*)-*N*,*N*′-dimethyl-1,2-diaminocyclohexane as described above. Alkylation is done as described above (BuLi, THF, -100 °C, followed by isolation, then hydrolysis, 0.1N HCl, 25 °C). Eq 5 and Table 3 illustrate some examples.[4]

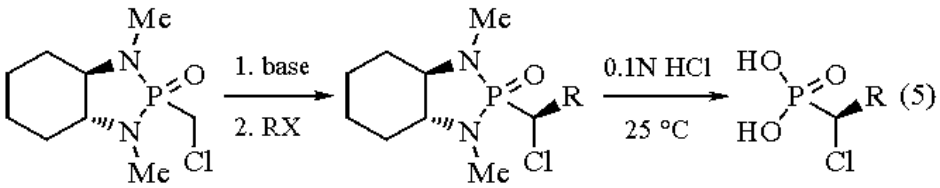

(3aR,7aR)-2-Ethyloctahydro-1H-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide

Table 3 Synthesis of a-Chloro-a-alkylphosphonic Acids

RX	Alkylation (- 100 °C)				Hydrolysis			
	Yield (%)	Ratio	Mp (°C)	$[a]_D^{25}$	Yield (%)	Mp (°C)	$[a]_D^{25}$	Config.
(*R*, *R*) Series								
MeI	87	90:10	75 76	- 99.6° (*c* 0.5)	95	35 38	+5.5° (*c* 1.0)	(*R*)
EtI	79	>99:1	123 125	- 69.0° (*c* 0.5)	98	109	+39.6° (*c* 1.2)	(*R*)
PrI	83	>99:1	131 133	- 62.0° (*c* 1.0)	97	87 88	+51.2° (*c* 1.0)	(*R*)
CH_2=$CHCH_2Br$	80	>99:1	136 137	- 71.5° (*c* 0.6)	Quant.	Oil	+32.0° (*c* 1.0)	(*R*)
BnBr	86	91:9	103 105	- 15.4° (*c* 1.0)	Quant.	104	+32.9° (*c* 0.9)	(*R*)
$TBDPSO(CH_2)_2I$	79	90:10	Oil	- 21.0° (*c* 1.3)	95	35	+21.9° (*c* 1.65)	(*R*)
$TBDPSO(CH_2)_3I$	76	90:10	56 58	- 34.0° (*c* 1.4)	88	Oil	+55.8° (*c* 1.1)	(*R*)

α-Amino-α-alkylphosphonic Acids.[5]

Treatment of iminodithiolane derivatives (eq 6) with ***Potassium Hexamethyldisilazide*** in THF (-78 °C) generates the corresponding anions which, when treated with various alkyl halides, give the corresponding α-alkyl derivatives in high diastereomeric excess. Unlike other α-substituted phosphonamides discussed above, the alkylation of the (*R*,*R*)-α-iminodithiolane derivative gives products with the opposite orientation of the new alkyl chain, which are normally expected from the enantiomeric (*S*,*S*) series. This has been rationalized based on the intermediacy of a potassium chelate involving the phosphoryl oxygen and the imino nitrogen atoms, thus exposing the other face of the anion.[5] Eq 6 illustrates a typical sequence and Table 4 lists some examples of α-amino-α-alkylphosphonic acids prepared using this sequence.

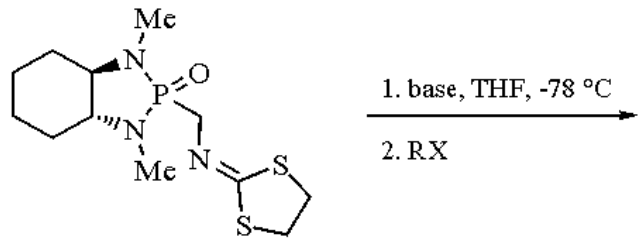

$[\alpha]_D^{25}$ -185.2° (*c* 1.02, $CHCl_3$)

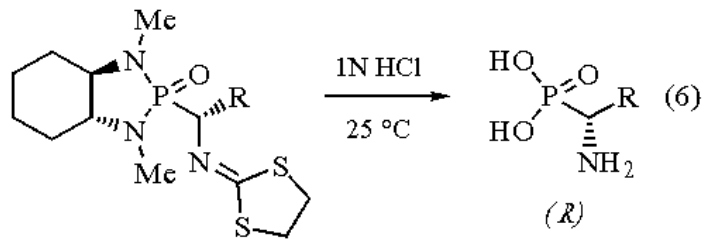

(6)

Table 4 Synthesis of a-Amino-a-alkylphosphonic Acids

RX	Alkylation (- 78 °C)				Hydrolysis				
	Yield (%)	Ratio	Mp (°C)	$[a]_D^{25}$	Yield (%)	Mp (°C)	$[a]_{578}$	ee	Config.
(*R*, *R*) Series									
MeI	74	90:10	134	- 183.6° (*c* 0.6)	82	278	- 12.9°	81%	(*R*)
EtI	73	95:5	137	- 189.0° (*c* 0.9)	84	277	- 19.2°	91%	(*R*)
PrI	76	>99:1	129	- 178.0° (*c* 0.7)	86	272	+8.5°	98%	(*R*)
CH_2=$CHCH_2Br$	82	>99:1	123	- 163.2° (*c* 1.0)	88	272	- 8.9°		(*R*)
i-BuOTf	77	95:5	136	- 183.0° (*c* 1.0)	81	288	- 21.6°	90%	(*R*)
BnBr	78	>99:1	140	- 148.6° (*c* 0.5)	87	268	- 47.6°	97%	(*R*)
HC° CCH_2Br	78	>99:1	125	- 137.2° (*c* 0.8)					
(*S*,*S*) Series									
MeI	75	8:92	139	+187.0° (*c* 1.0)	84	278	+14.3°	84%	(*S*)
BnBr	81	>1:99	142	+148.0° (*c* 0.75)	86	270	+50.9°	98%	(*S*)

α-Amino-β-aryl phosphonic acids are accessible from the addition of the anion of chloromethylphosphonamide (**8**) to *N*-arylimines, followed by hydrogenolysis of the aziridine derivative.[6]

Asymmetric Conjugate Addition of Allyl- and Crotylphosphonamides.[7]

The asymmetric *C*-allylation of α,β-unsaturated carbonyl compounds is a powerful tool for the functionalization of a carbonyl compound in the β-position. Since such a process normally leads to the corresponding enolate derivative when anionic reagents are used, there exists the possibility of trapping with an electrophile. Thus sequential addition and trapping can lead to vicinally substituted carbonyl compounds. Asymmetric allylation has been achieved previously with simple cycloalkenones using phosphorus[9] and sulfur[10] based reagents that must be prepared in diastereomerically pure form.

The anions of allyl- and crotylphosphonamides, (**2**) and (**5**) respectively, show excellent selectivity toward a variety of α,β-unsaturated compounds, affording the diastereomerically pure or enriched products. Quenching the enolates with various electrophiles gives vicinally substituted carbon centers. Oxidative cleavage of the phosphonamide moiety affords the equivalent of an acetaldehyde (α-methylacetaldehyde) anion 1,4-adduct to the original α,β-unsaturated carbonyl compound. Pertinent examples are shown in eq 7 and Table 5.

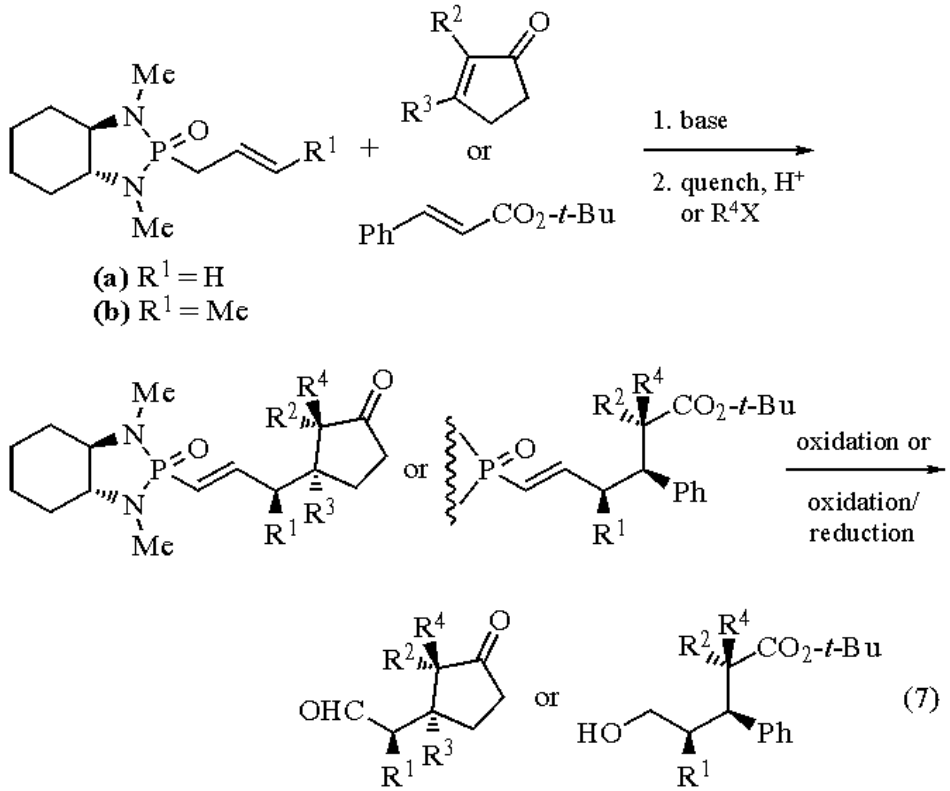

R^1, R^3 = H; R^2, R^4 = Me, alkyl, H
R^1 = Me, R^3 = H; R^2, R^4 = Me. alkyl, H (any combination)

Table 5 Asymmetric Conjugate Addition of Allyl- and Crotylphosphonamides

Entry	Reagent	Substrate	Product	Ratio	Yield (%)
1	**(2)**	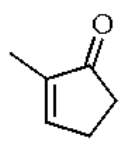	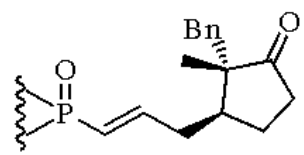 $[\alpha]_D$ +48.6° (*c* 1.20)	>99:1	80
2	**(2)**	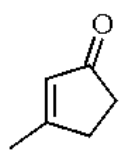	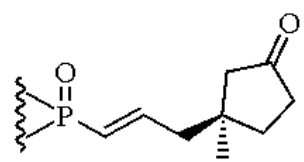		

(3aR,7aR)-2-Ethyloctahydro-1H-1,3-dineopentyl-1,3,2-benzodiazaphosphole Oxide

			$[\alpha]_D$ +17.4° (*c* 1.22)	99:5	75
3	**(5)**	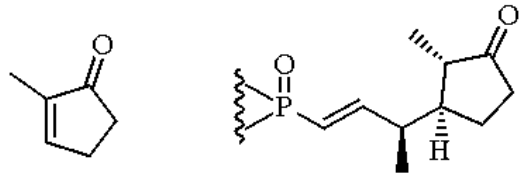	$[\alpha]_D$ +7.6° (*c* 2.00)	94:6	74
4	**(2)**	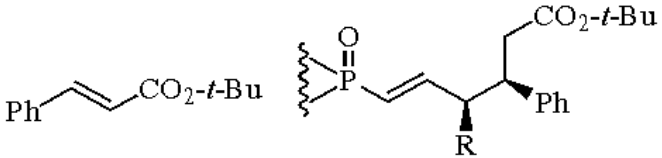	R = H, $[\alpha]_D$ -5.8° (*c* 1.90)	>99:1	80
			R = Me, $[\alpha]_D$ -1.9° (*c* 1.10)	>99:1	94
5	**(2)**	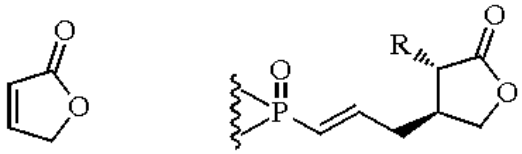	R = H, $[\alpha]_D$ -16.1° (*c* 1.00)	>99:1	93
			R = Bn, $[\alpha]_D$ -8.7° (*c* 0.80)	>99:1	67
6	**(5)**	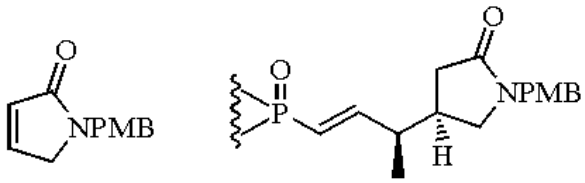	$[\alpha]_D$ -2.3° (*c* 2.20)	95:5	51

Conclusion.

The C_2 symmetry of (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexane, readily available from the racemic compound by resolution,[11] has served as a versatile chiral motif in the design of topologically unique stereodifferentiating reagents such as the phosphonamide anions described here. Several other applications of these reagents via anion chemistry, or simply based on the exploitation of other effects offered by their structures and heteroatom functionality, can be explored (catalytic processes, chiral ligands, etc.). The *N*,*N*′-disubstituted 1,2-diaminocyclohexane motif has also been remarkably versatile in other asymmetric processes such as the dihydroxylation of alkenes,[12] and a variety of other C-C bond-forming reactions.[13]

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O-Ethylperoxycarbonic Acid

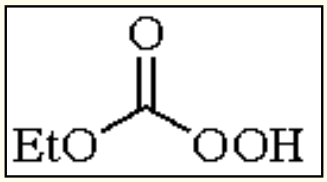

[70288-43-6] · $C_3H_6O_4$ · *O*-Ethylperoxycarbonic Acid · (MW 106.09)

(oxygen atom transfer reagent, useful for the epoxidation of alkenes)

Preparative Method: formed in situ by the reaction of aqueous ***Hydrogen Peroxide*** with ***Ethyl Chloroformate***.

Handling, Storage, and Precautions: generated in situ; not stable to storage.

Alkene Epoxidation.

The direct oxidation of an alkene to the corresponding epoxide is most typically accomplished by an organic peroxy acid or by metal-catalyzed oxygen atom transfer from a hydroperoxide.[1,2] Alternate methods based upon the utilization of hydrogen peroxide as the oxidant have also been developed, most notably by Payne.[3] Although H_2O_2 itself is not sufficiently reactive to epoxidize a nonconjugated alkene, its propensity for oxygen atom transfer can be markedly enhanced by placing the OOH moiety in conjugation with a multiple bond. Typical examples are peroxy acids (**1**) and peroxyimidic acids (**2**). The latter oxidant can be readily formed in situ by the addition of H_2O_2 to a nitrile. Acetonitrile,[3] benzonitrile,[3] and trichloroacetonitrile[4] have been employed as coreactants in the epoxidation of alkenes. ***Trichloroperoxyacetamidic Acid*** is a highly effective oxidant that is competitive with ***m-Chloroperbenzoic Acid*** on both a cost effective and reactivity basis. Acetoperoxyimidic acid has been scaled up for the synthesis of epoxides on a multimolar scale.[5]

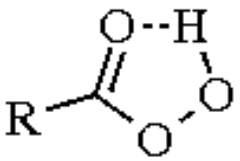

(1)

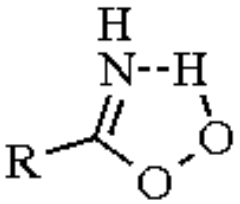

(2)

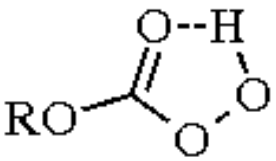

(3)

O-Alkylperoxycarbonic acids (**3**) can be formed in situ by the reaction of H_2O_2 with alkyl chloroformates.[6] Although dialkyl esters of peroxycarbonic acid ($ROCO_3R'$)[7a] and peroxydicarbonates $(ROCOO)_2$[7b] are stable isolable

compounds, an *O*-alkylperoxycarbonic acid (**3**) must be generated in situ. *O*-Benzylperoxycarbonic acid has been prepared from dibenzyl peroxydicarbonate and alkaline H_2O_2 in methanol.[8] This peroxycarbonic acid (**3**; R = Bn) is considerably less stable than a peroxycarboxylic acid (**1**) and has a half-life of about 61 h at room temperature in benzene. However, it is an effective oxidizing reagent and exhibits a reactivity toward (*E*)-stilbene that is intermediate between that of ***Perbenzoic Acid*** and *m*-CPBA in benzene.

The current procedure utilizes a biphasic solvent system that allows one to utilize the cost and safety advantages of aqueous 30% H_2O_2 and CH_2Cl_2 as a second phase. This two-phase system is ideal since the rate of epoxidation of alkenes is maximized in nonpolar solvents like CH_2Cl_2. *O*-Ethylperoxycarbonic acid (**4**) is produced at the interface by the reaction of H_2O_2 with ethyl chloroformate (eq 1). The epoxidizing reagent should be formed in the presence of a buffer to neutralize the HCl produced since the decomposition of the $-CO_3H$ functional group is catalyzed by both acids and bases. When Na_2HPO_4 is used as a buffer, the reaction medium is slightly acidic and the pH decreases from 6.8 to 4.5 during the course of the reaction. Alternatively, if alkaline conditions are desired because of an acid-sensitive functional group, Na_3PO_4 may be used as the buffer and the pH maintained between 9.5 and 8.8.[6] It should be recalled that aqueous 30% H_2O_2 is typically stabilized by a strong acid (e.g. H_2SO_4) and the solution is acidic. *m*-CPBA has also been used under biphasic conditions.[9]

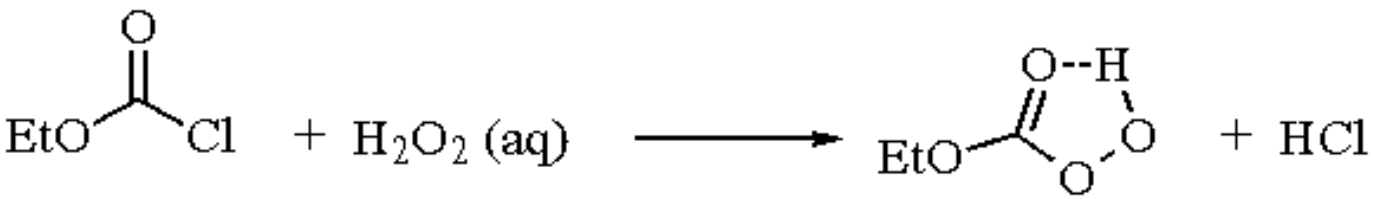

(1)

(4)

The overall procedure for alkene epoxidation with (**4**) is accompanied by the formation of two innocuous byproducts, carbon dioxide and ethanol (eq 2). Good to excellent yields of epoxides are obtained with a variety of alkenes, with the exception of 1-nonene. Terminal alkenes typically react more slowly with peroxy acids than more highly substituted double bonds.

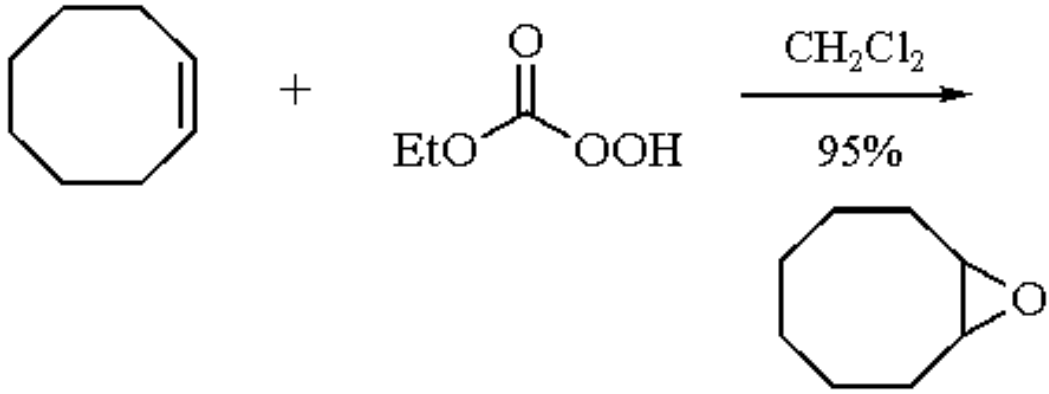

(2)

This synthetic procedure offers the advantage of the in situ generation of a relatively inexpensive oxidant under either mildly acidic or basic conditions. Reaction times vary from 3-24 h at room temperature. The products of oxidation are not contaminated with residual byproducts.

Related Reagents.

Peroxyacetimidic Acid; ***Trichloroperoxyacetamidic Acid***.

---

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N-Ethyl-5-phenylisoxazolium-3´-sulfonate[1]

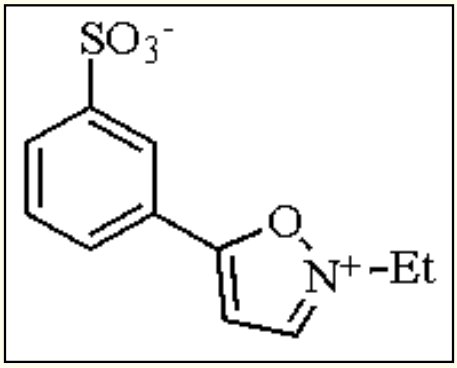

[4156-16-5] · $C_{11}H_{11}NO_4S$ · *N*-Ethyl-5-phenylisoxazolium-3´-sulfonate · (MW 253.30)

(coupling reagent for peptide synthesis;[2] protein modification;[3] reduction of carboxylic acids into alcohols[4])

Alternate Names: Woodward's reagent K; NEPIS.

Physical Data: mp 206-208 °C (dec); UV λ_{max} (ε) 283 nm (22 500) in 0.1 N HCl.

Solubility: insol MeCN, $MeNO_2$, DMF, CH_2Cl_2; sol H_2O.

Form Supplied in: crystalline, anhydrous zwitterion; widely available as 95% pure that may contain some of the *para* sulfonate derivative.

Analysis of Reagent Purity: material that is sufficiently pure has mp 206-208 °C.

Purification: dissolve in aqueous 1 N HCl and reprecipitate by the slow addition of acetone. After filtration and drying the reagent is a fluffy solid.

Handling, Storage, and Precautions: stable to light and temperature and nonhygroscopic. No extra precautions need to be observed.

Peptide Coupling Reagent.

Woodward's reagent K reacts with an *N*-protected amino acid, under mild conditions, in the presence of a tertiary amine to form an enol ester intermediate, e.g. (**1**). This enol ester acylates an amino acid ester or peptide to afford the elongated peptide derivative (eq 1). The isoxazolium salt is not soluble in organic solvents, but as it reacts with a carboxyl group in the presence of a tertiary amine the reaction mixture clears.

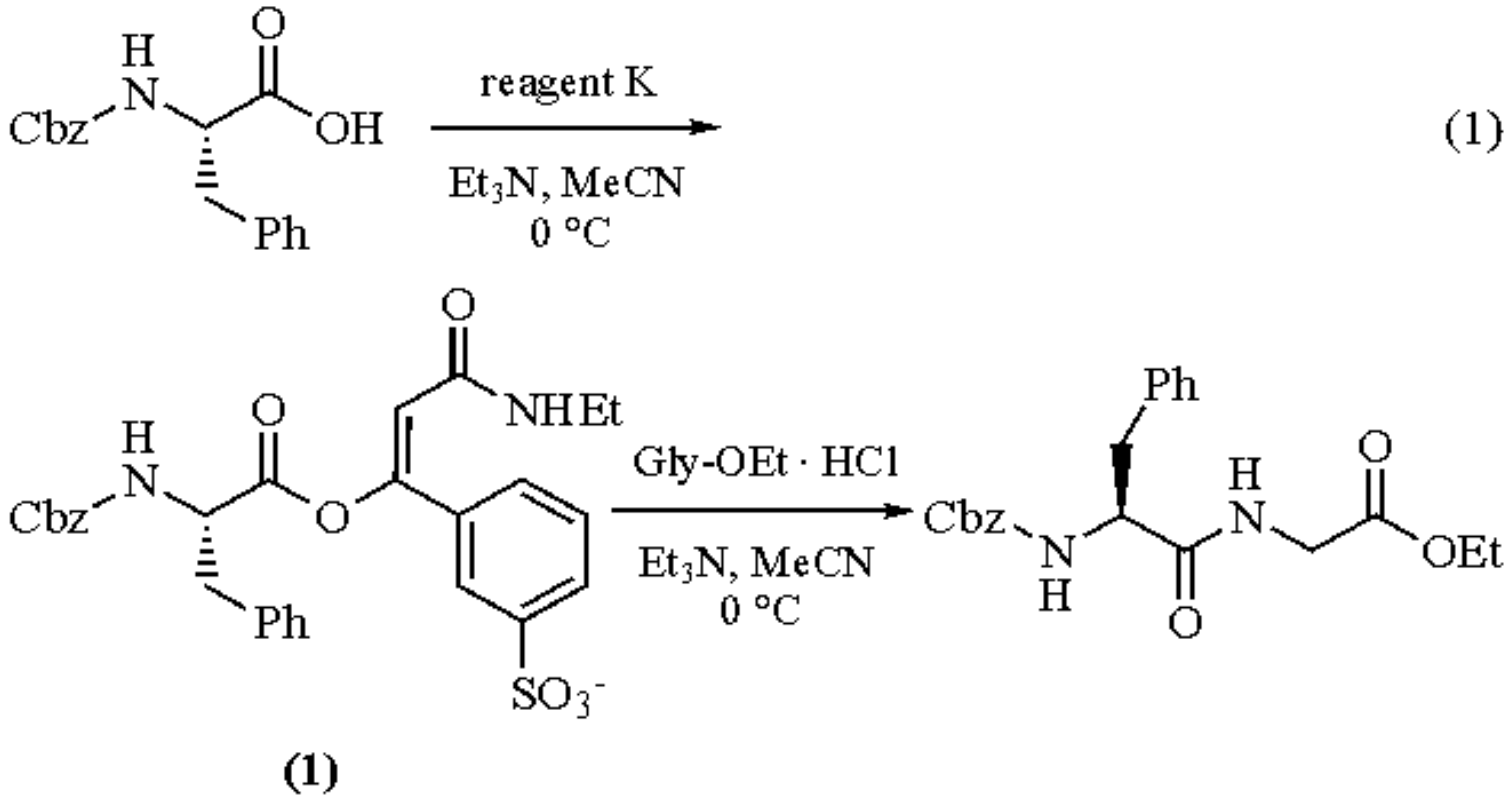

Examples of di- and tripeptide couplings abound with yields typically >80%; minimal purification steps are required since the byproducts are water soluble (eq 2).[2]

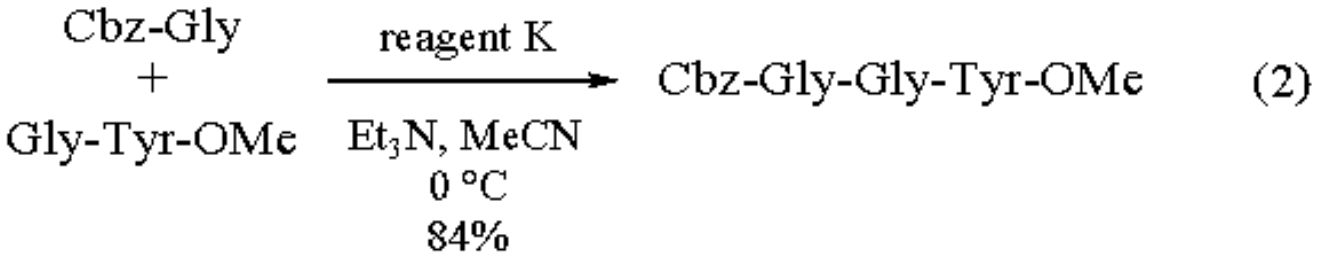

The recommended coupling procedure is to activate the carboxyl group in $MeNO_2$ or MeCN with vigorous stirring for 10 min at rt or 1 h at 0 °C. Then the amino ester, dissolved in $MeNO_2$ or MeCN, is added and the coupling allowed to go at rt for several hours.

Good yields are obtained in coupling asparagine and glutamine. With some coupling reagents the carboxamide of these residues can undergo an intramolecular dehydration when the α-carboxylate is activated to give a nitrile residue (**2**) in the peptide.[5] However, this byproduct has not been observed with reagent K.

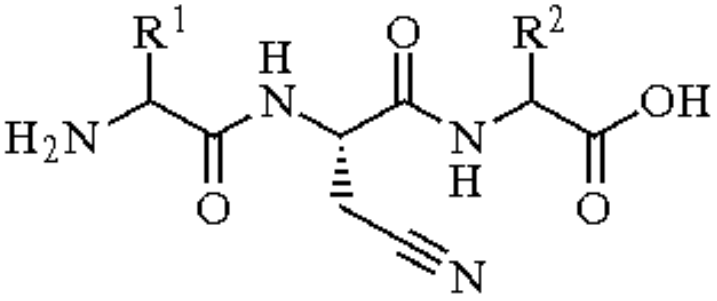

(2)

An additional advantage of reagent K is that when serine, threonine, etc., are activated their hydroxyl groups do not require protection.[6] For instance, the hydroxyproline tripeptide in eq 3 was obtained in good yield after crystallization.[2]

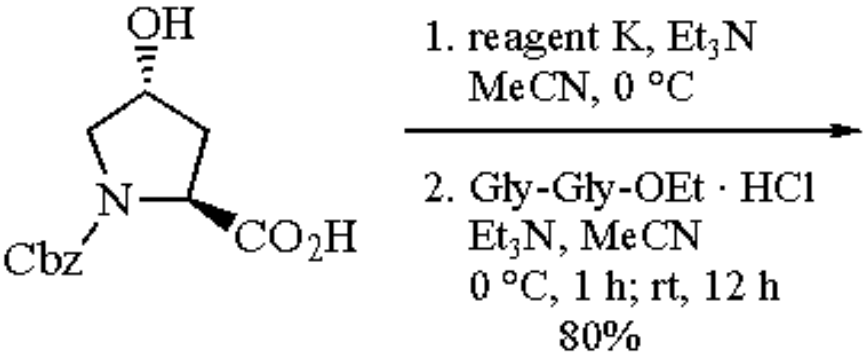

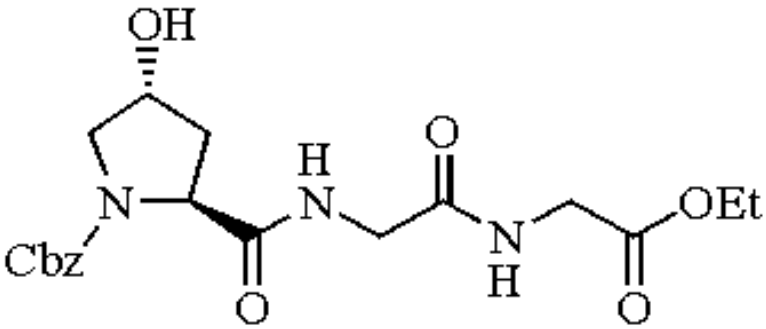

(3)

Several studies[7] on the extent of racemization with peptide coupling reagents have been published. This generally is a problem when performing a fragment condensation, but normally not a problem when the amino group is protected as a carbamate. For best control of the extent of racemization, accurate measurement of the tertiary amine is advised.[7b] The extent of racemization observed with reagent K is just a few percent for acylated amino acids,[7c] which is no worse than most coupling reagents except for the azide coupling procedure. There are some disadvantages of this reagent in peptide couplings. The most serious one is the limitation of solvents. Acetonitrile and nitromethane are the best for high yield, high optical purity products. However, many peptides are not readily soluble in these solvents. The next disadvantage is that the enol ester intermediate can rearrange to the imide side-product (**3**) which is difficult to remove.[1] Another problem with reagent K is its incompatibility with solid-phase peptide synthesis because of its poor solubility in organic solvents and relatively slow activation of carboxyl groups.[8]

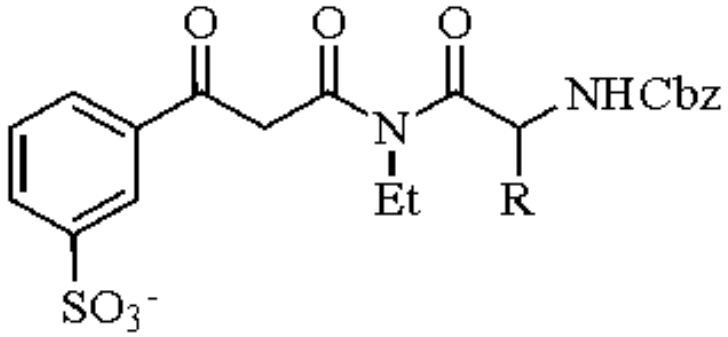

(3)

A good comparison of reagent K with other reagents is in the synthesis of a protected derivative of oxytocin (eq 4).[9] This product was further elaborated to give oxytocin. The results are compared with those for ***1,3-Dicyclohexylcarbodiimide*** and ***N,N´-Carbonyldiimidazole*** in Table 1.

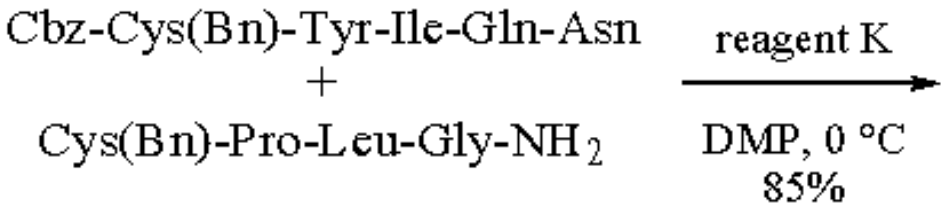

Cbz-Cys(Bn)-Tyr-Ile-Gln-Asn-Cys(Bn)-Pro-Leu-Gly-NH_2 (4)

Table 1 Comparison of Coupling Agents for Protected Oxytocin

Coupling method	Yield (%)	Mp (°C)	Biological activity[a]
DCC	80	225 230	81
CDI	70.5	225 230	50
Reagent K	85	240 242	134

[a] Units mg^{-1} in avian depressor activity for deprotected and oxidized nonapeptide.

An additional utility for reagent K is peptide cyclization.[10] The activation and cyclization steps are performed separately; therefore each can be carried out under the appropriate dilution conditions. This is advantageous when the carboxyl group activates slowly since it is in concentrated solution.

The isoxazolium salt has been used in the synthesis of other difficult peptide structures. A peptidoglycan has been obtained in good yield by this procedure (eq 5).[11]

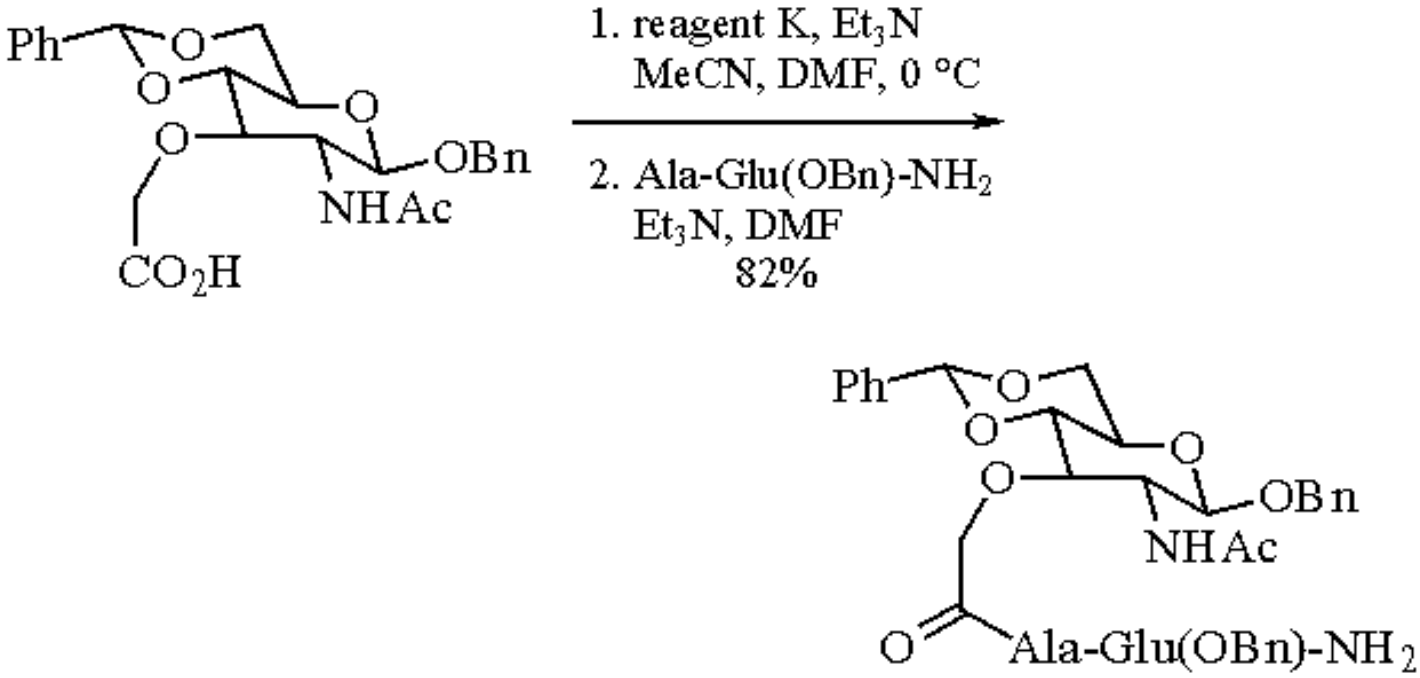

(5)

Additionally, this reagent has been used repetitively in the synthesis of a steroid-peptide adduct with a free hydroxyl group (eq 6).[12] Deprotection and another coupling with Cbz-Arg(N^G-nitro) gave the dipeptide-steroid adduct in good yield. In both couplings the steroid hydroxyl group was not acylated.

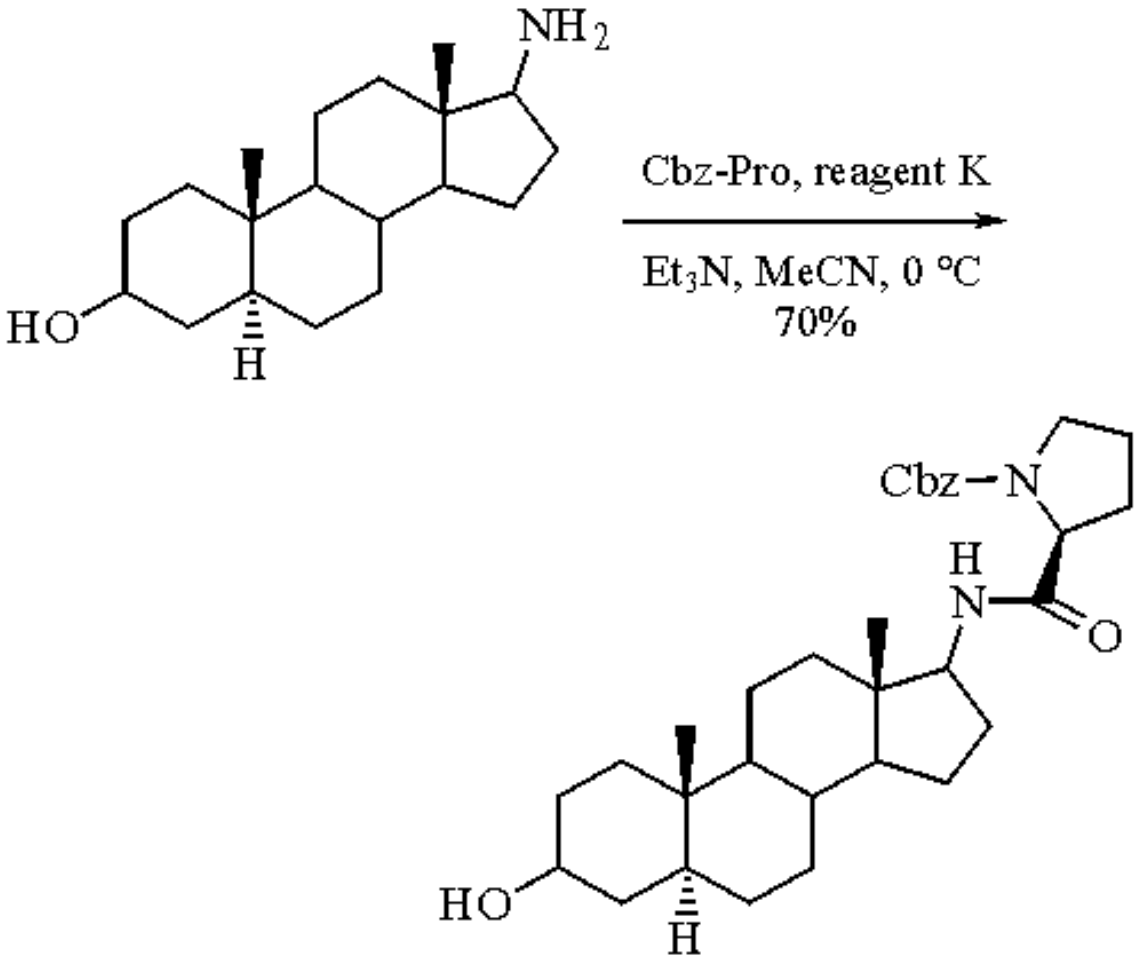

(6)

Protein Modification.

Since this reagent is water soluble and is reactive under aqueous conditions below pH 4.75, it can specifically modify carboxyl groups in proteins.[3,13] This has proven useful in determining essential carboxyl groups in various enzymes. The enol ester is stable enough to isolate the modified protein and tag with a nucleophile for eventual identification of the modified amino acid. Other reagents such as the water-soluble carbodiimides are also used extensively in these mechanistic studies. However, an advantage with reagent K is that the enol ester formed has a UV absorbance at 340 nm (E_{340} = 7000 M^{-1} cm^{-1});[14] thus the number of carboxyl groups modified can be quantified.

Reduction of Carboxylic Acids to Alcohols.

The conversion of carboxylic acids to alcohols occurs in a two-step process under mild conditions using reagent K with yields for simple alcohols ranging from 50-100%.[4] The reduction of a dipeptide (eq 7) suggests a potential utility in modifying carboxyl groups in proteins.

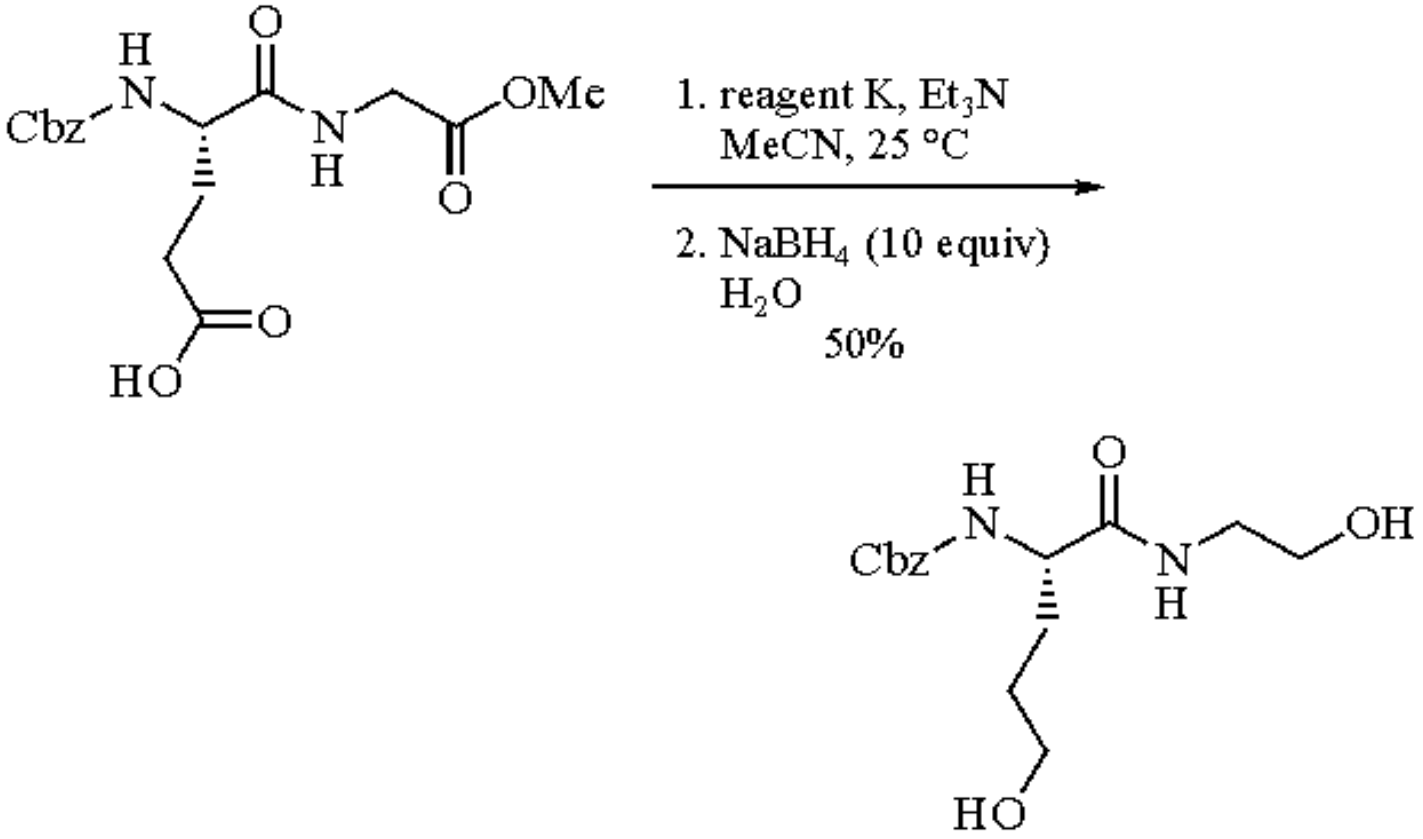

(7)

Another method[15] to obtain alcohols is to reduce the mixed carbonic acid anhydride prepared with ***Ethyl Chloroformate*** with an excess of ***Sodium Borohydride***. This method uses less costly reagents; thus it is more useful for synthetic transformations.

Miscellaneous Reactions.

Pantothenic acid has been coupled to a long chain amine with reagent K (eq 8).[16] This is another example of the nonreactivity of hydroxyl groups with the enol ester intermediate. Attempts to prepare this amide through the mixed anhydride procedure give low yields.

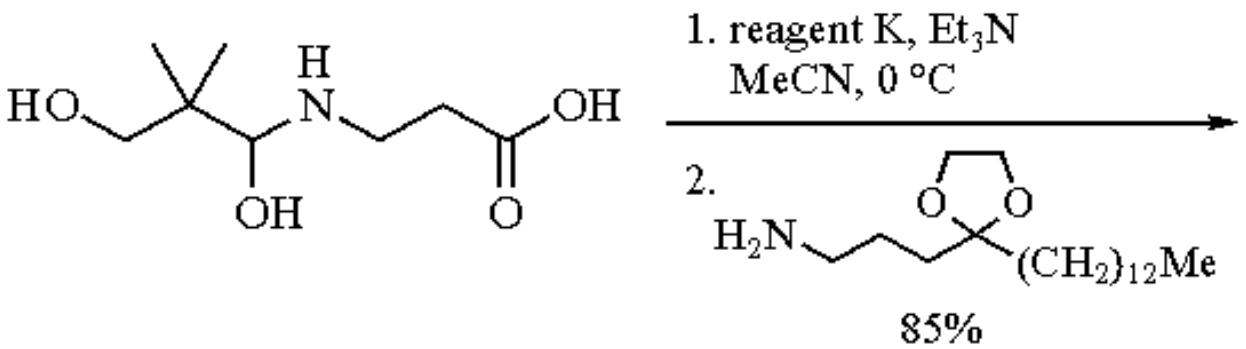

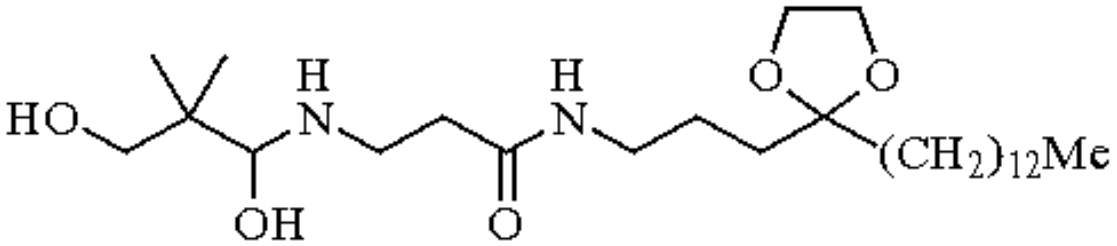

(8)

Reagent K may have utility in sequencing peptides and proteins from the *C*-terminus (eq 9).[17] The 2-thiohydantoin produced is used to analyze a peptide sequence upon cleavage of the thiohydantoin from the peptide. This mild procedure gives good yields with amino acids that have sensitive side chains such as serine and lysine. The original ***Acetic Anhydride*** procedure[18] for *C*-terminal sequencing does not work well with these amino acids; therefore this procedure is an improvement. Another activation reagent, hydroxysuccinimide esters of Fmoc-amino acids, fails to give the thiohydantoin.[17]

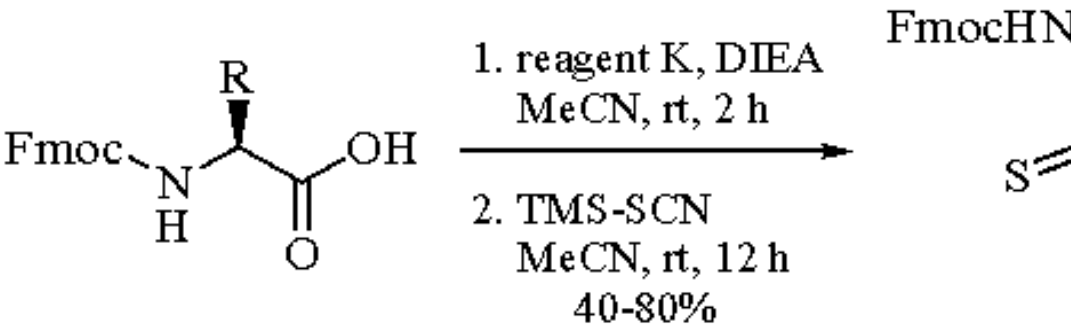

(9)

R = variety of amino acid side chains

Related Reagents.

Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate; ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide***; ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride***; ***Isobutyl Chloroformate***; ***p-Nitrophenol***; ***Pentafluorophenol***; ***1,1´-Thionylimidazole***.

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Ethyl (Phenylsulfinyl)acetate

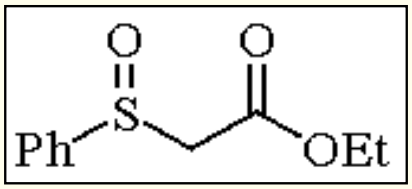

[54882-04-1] · $C_{10}H_{12}O_3S$ · Ethyl (Phenylsulfinyl)acetate · (MW 221.27)

(addition to aldehydes followed by thermal elimination gives 3-keto esters;[1] addition to carbonyl compounds followed by desulfurization gives 3-hydroxy esters;[2] aldehyde Knoevenagel condensation products undergo thermal rearrangement to give (2*E*,4*E*)-dienoate esters or 4-hydroxy-(2*E*)-enoate esters[3,4])

Physical Data: colorless liquid.

Analysis of Reagent Purity: microanalysis; ^{1}H NMR[2,3] and ^{13}C NMR[5] spectroscopy.

Preparative Methods: sodium thiophenoxide in ethanol is treated with ethyl bromoacetate and refluxed for 1 h, giving ethyl (phenylthio)acetate after distillation (bp 101-104 °C/0.4 mmHg), which is oxidized with sodium periodate or preferably sodium perborate[6] in water/methanol to afford the title compound as a colorless liquid.[3] Another method is by treatment of the anion of methyl phenyl sulfoxide with diethyl carbonate.[2]

Addition to Aldehydes to give 3-Keto Esters[1] and 3-Hydroxy Esters.[2]

When deprotonated with bases containing the lithium or sodium counterion ethyl (phenylsulfinyl)acetate exhibits poor reactivity and fails to undergo alkylation or nucleophilic addition. However, deprotonation of ethyl (phenylsulfinyl)acetate with 1 equiv of ***Ethylmagnesium Bromide*** in diethyl ether at 0 °C gives the magnesium salt as a milky precipitate, and addition of aldehydes results in the formation of alkyl-2-phenylsulfinyl-3-hydroxy esters. Thermal *syn* elimination of benzenesulfinic acid affords an enol which tautomerizes to the 3-keto ester (eq 1). Desulfurization of the addition product with ***Raney Nickel*** gives 3-hydroxy esters, the result of a formal addition of ethyl acetate anion to an aldehyde.

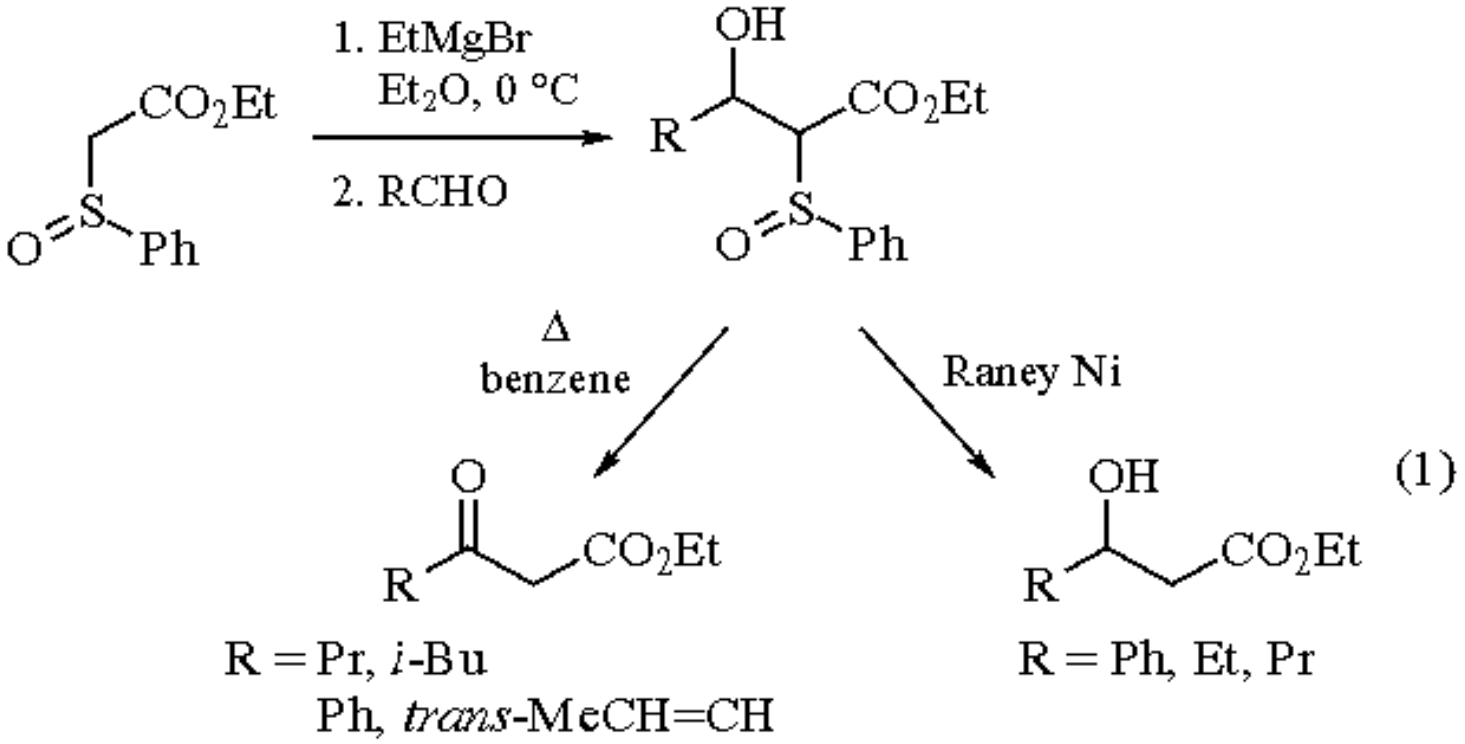

Preparation of (2*E*,4*E*)-2,4-Dienoate Esters or 4-Hydroxy-(2*E*)-enoate Esters.[3,4]

Ethyl (2*E*)-2-phenylsulfinyl-2-alkenoates can be prepared by treatment of the aldehydes with ethyl (phenylsulfinyl)acetate and a catalytic amount of ***Piperidine*** in acetonitrile. The resultant vinyl sulfoxide is treated with anhydrous ***Potassium Carbonate*** in refluxing xylenes; after 4 h the *trans,trans* dienoate is isolated in 59% yield as a 91:9 mixture of the *trans,trans* isomer to other isomers, as determined by GLC. A 12% yield of the 4-hydroxy-(2*E*)-enoate ester, presumably resulting from hydrolysis of the intermediate sulfenate ester, is also obtained. The vinyl sulfoxide product of the Knovenagel condensation is proposed to undergo a base-catalyzed deconjugation followed by a thermally induced [2,3]-sigmatropic shift to give the sulfenate ester which can either hydrolyze to give the hydroxyenoate or undergo another [2,3]-sigmatropic shift, eliminating the sulfoxide to give the dienoate. Use of anhydrous conditions favors the formation of the diene (eq 2).

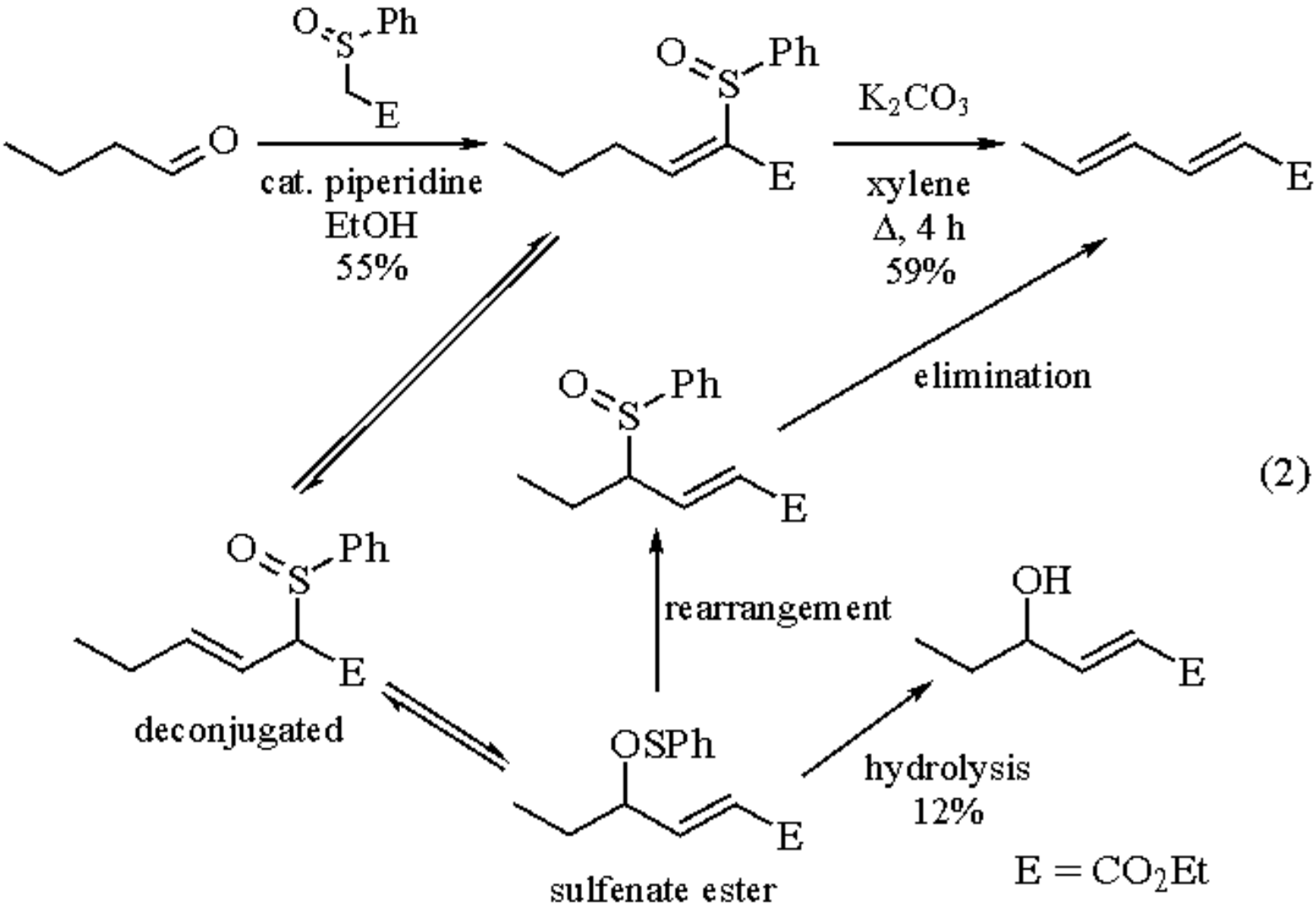

(2)

Treatment of an aldehyde with ethyl (phenylsulfinyl)acetate under prolonged Knoevenagel conditions using a catalytic amount of piperidine results in the formation, without isolation of intermediates of the hydroxy enoates.[7] This reaction has been used in the synthesis of (*R*)-patulolide (eq 3).[8]

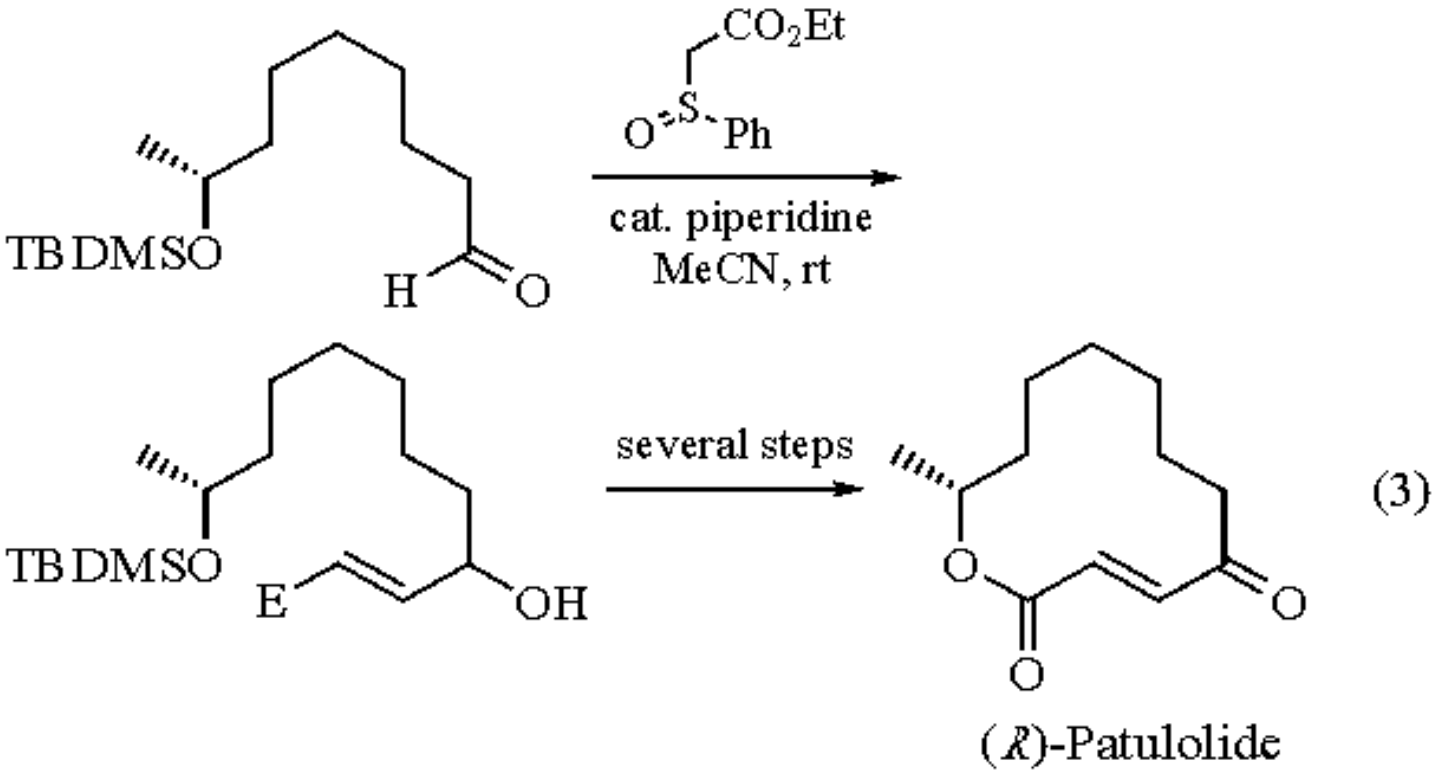

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Ethyl (Phenylsulfonyl)acetate

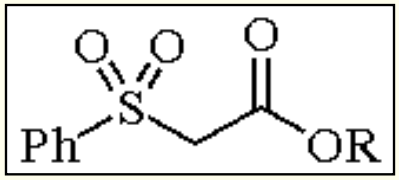

(R = Et)

[7605-30-3] · $C_{10}H_{12}O_4S$ · Ethyl (Phenylsulfonyl)acetate · (MW 228.27) (R = Me)

[34097-60-4] · $C_9H_{10}O_4S$ · Methyl Phenylsulfonylacetate · (MW 214.26)

(for introducing (ethoxycarbonyl)methyl and (phenylsulfonyl)methyl moieties)

Physical Data: R = Et, mp 41-42,[1] 42-43,[2] 45,[3] 47 °C;[4] bp 134-135 °C/0.01 mmHg. R = Me, bp 145 °C/0.01 mmHg.

Solubility: sol hot alcohol, benzene, diethyl ether; practically insol water.

Preparative Methods: prepared either by the substitution reaction of sodium benzenesulfinate[3] or Amberlyst A-26 benzenesulfinate[4] with ethyl chloroacetate or by reaction of the sodium salt of ethyl acetoacetate with benzenesulfonyl chloride.[5]

Utilization in Organic Synthesis.

The methylene group of ethyl (phenylsulfonyl)acetate (hereafter, abbreviated as EPSA) is more acidic than that of ethyl (phenylthio)acetate. Therefore EPSA generates a stable anion on its methylene carbon.[6] The Knoevenagel-type condensation with an aromatic aldehyde (eq 1),[7] the Michael-type addition to an α,β-unsaturated ester (eq 2),[8] the insertion reaction of a diazo compound,[9] and the condensation with DMF dimethyl acetal[10] can be applied to the chemistry of EPSA to give various phenylsulfonyl-containing compounds. The EPSA anion reacts with *N*-alkylisatoic anhydrides to yield phenylsulfonyl-substituted quinoline derivatives (eq 3).[11]

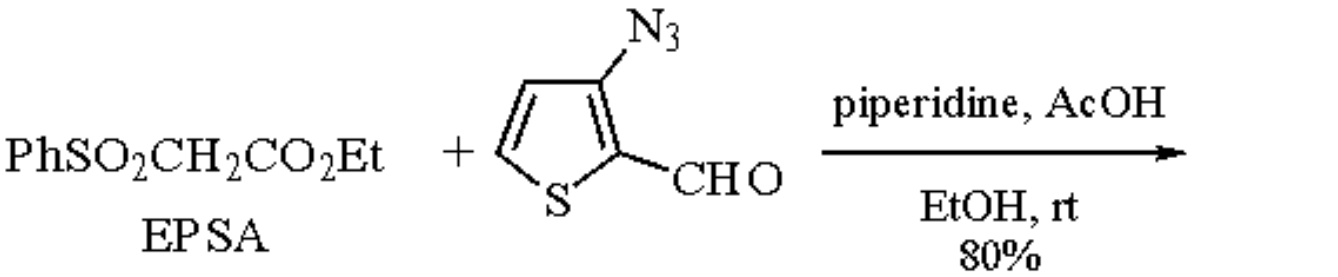

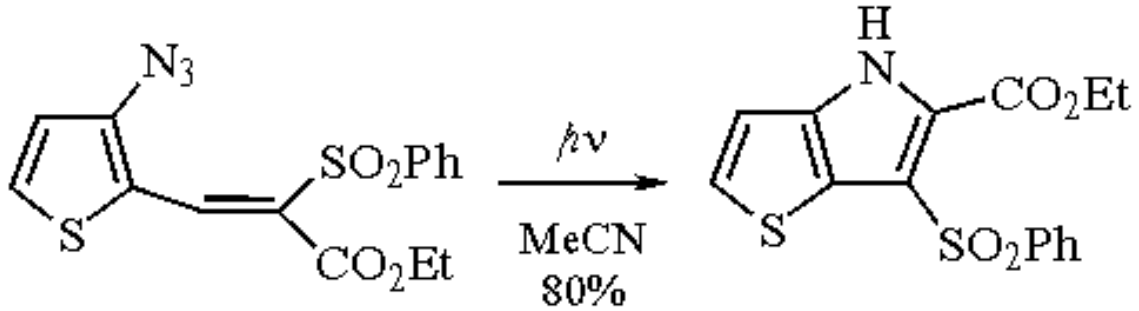

(1)

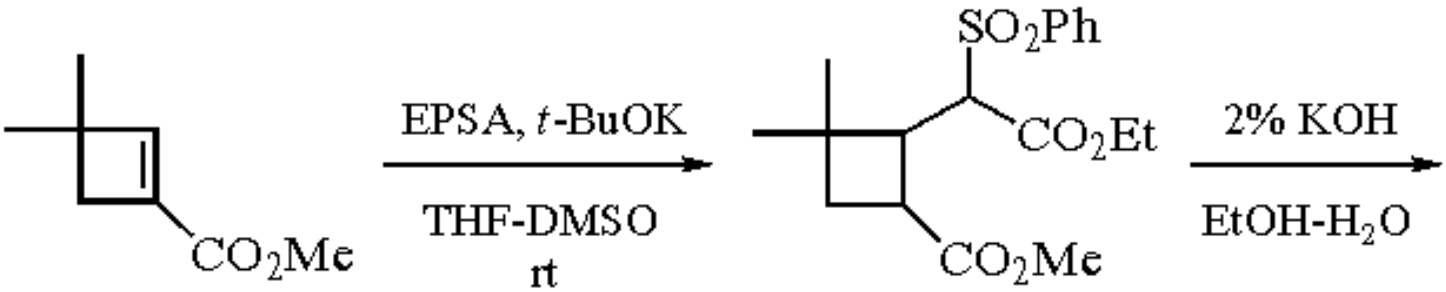

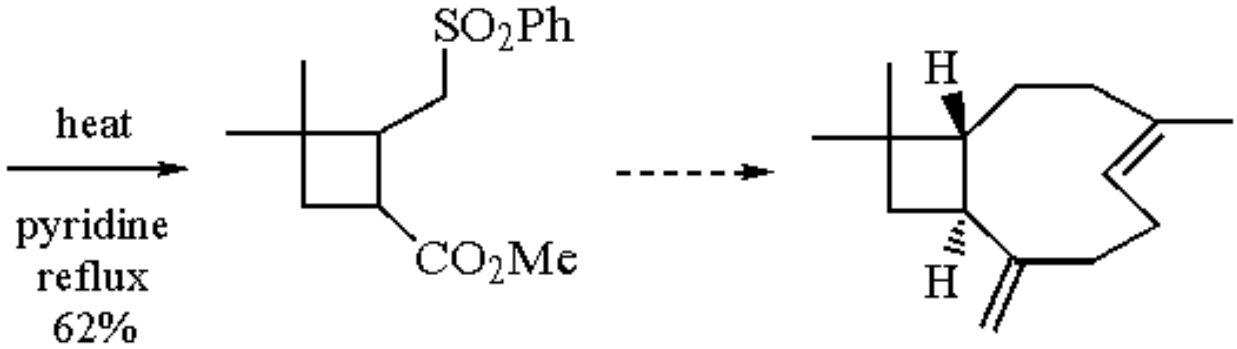

(2)

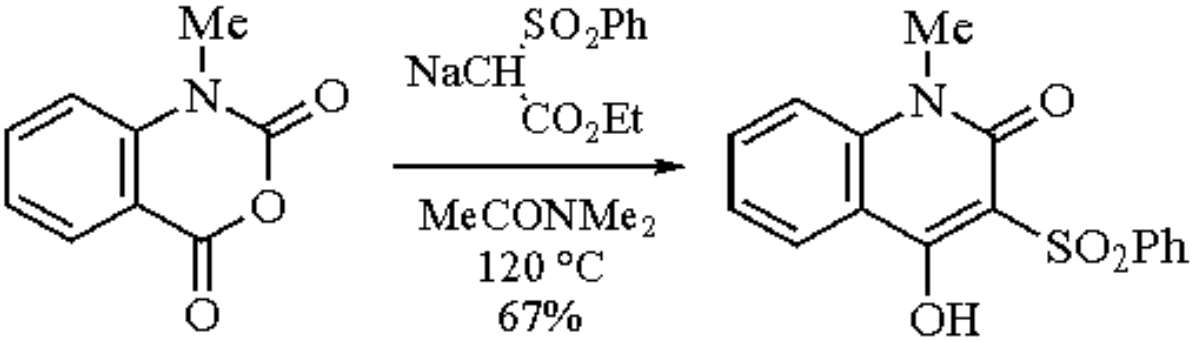

(3)

The anion of EPSA can react with an alkyl halide to give a mono- or dialkylated product (eq 4).[12,13] The most effficient method for alkylation of EPSA is the reaction of a π-allyl palladium complex with the EPSA anion (eq 5).[14] The introduced (ethoxycarbonyl)(phenylsulfonyl)methyl moiety is a synthetic precursor for many kinds of functionality

such as (ethoxycarbonyl)methyl, (phenylsulfonyl)methyl, hydroxymethyl, and formylmethyl.

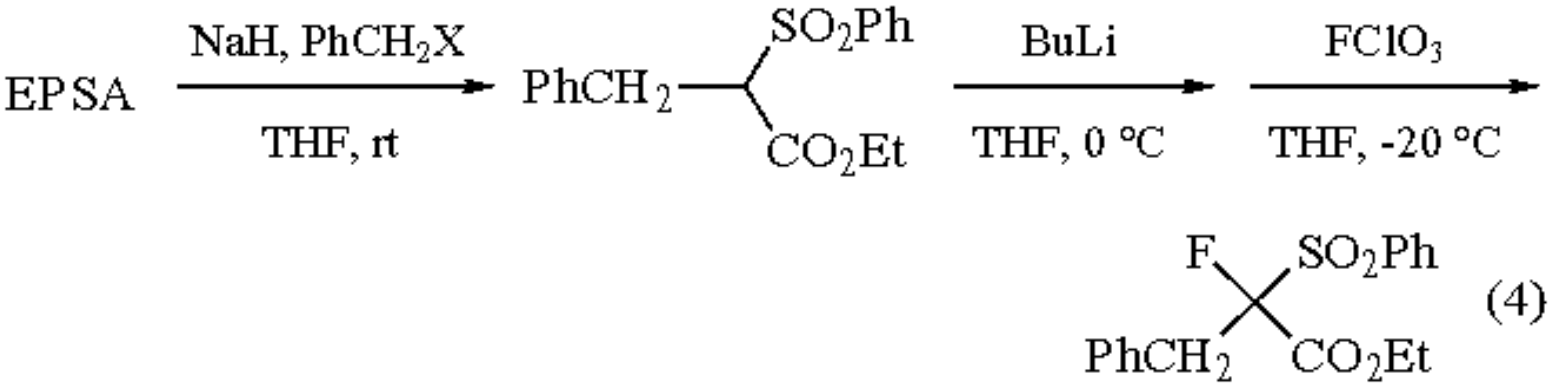

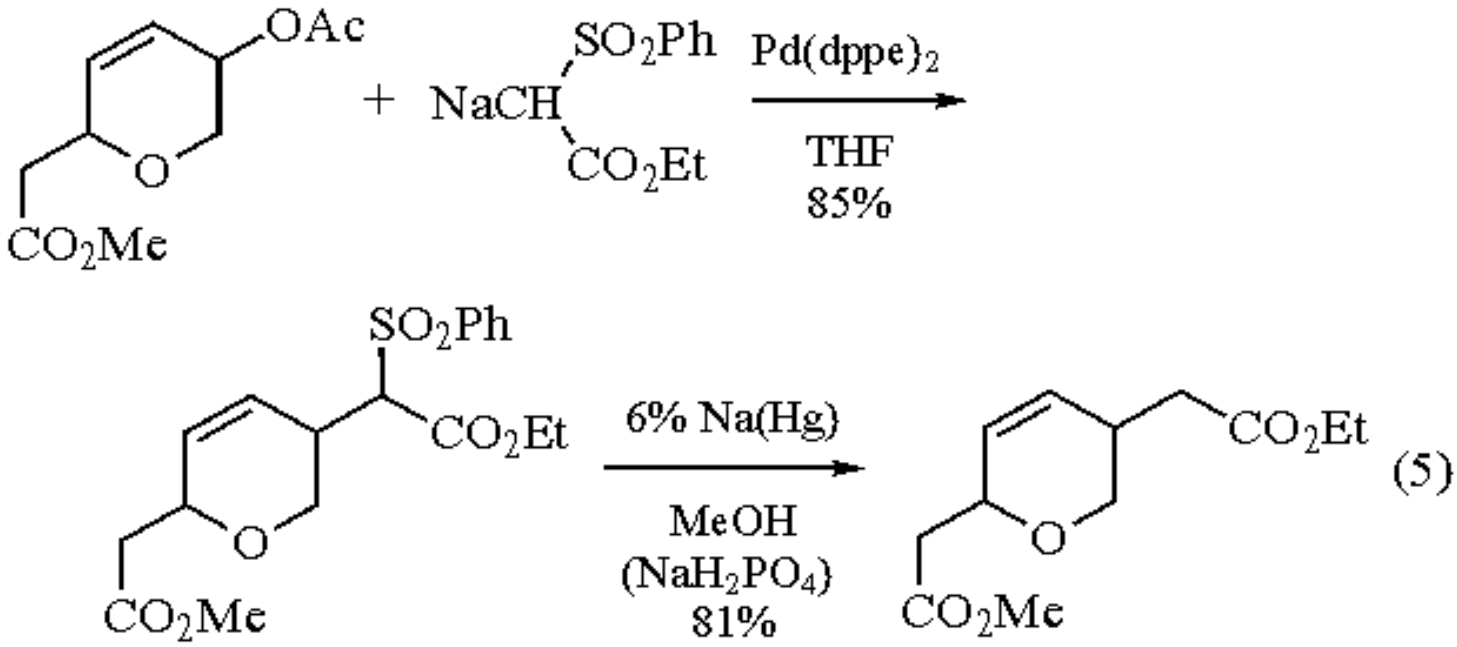

Synthetic Utilization of Methyl (Phenylsulfonyl)acetate as a Methyl Analog of EPSA.

Methyl (phenylsulfonyl)acetate (hereafter, abbreviated as MPSA) is prepared by the reaction of sodium benzenesulfinate with methyl chloroacetate in DMF.[15] In an analogous manner to EPSA, MPSA undergoes Michael-type addition to α,β-unsaturated lactones (eq 6)[16] or sulfones.[17]

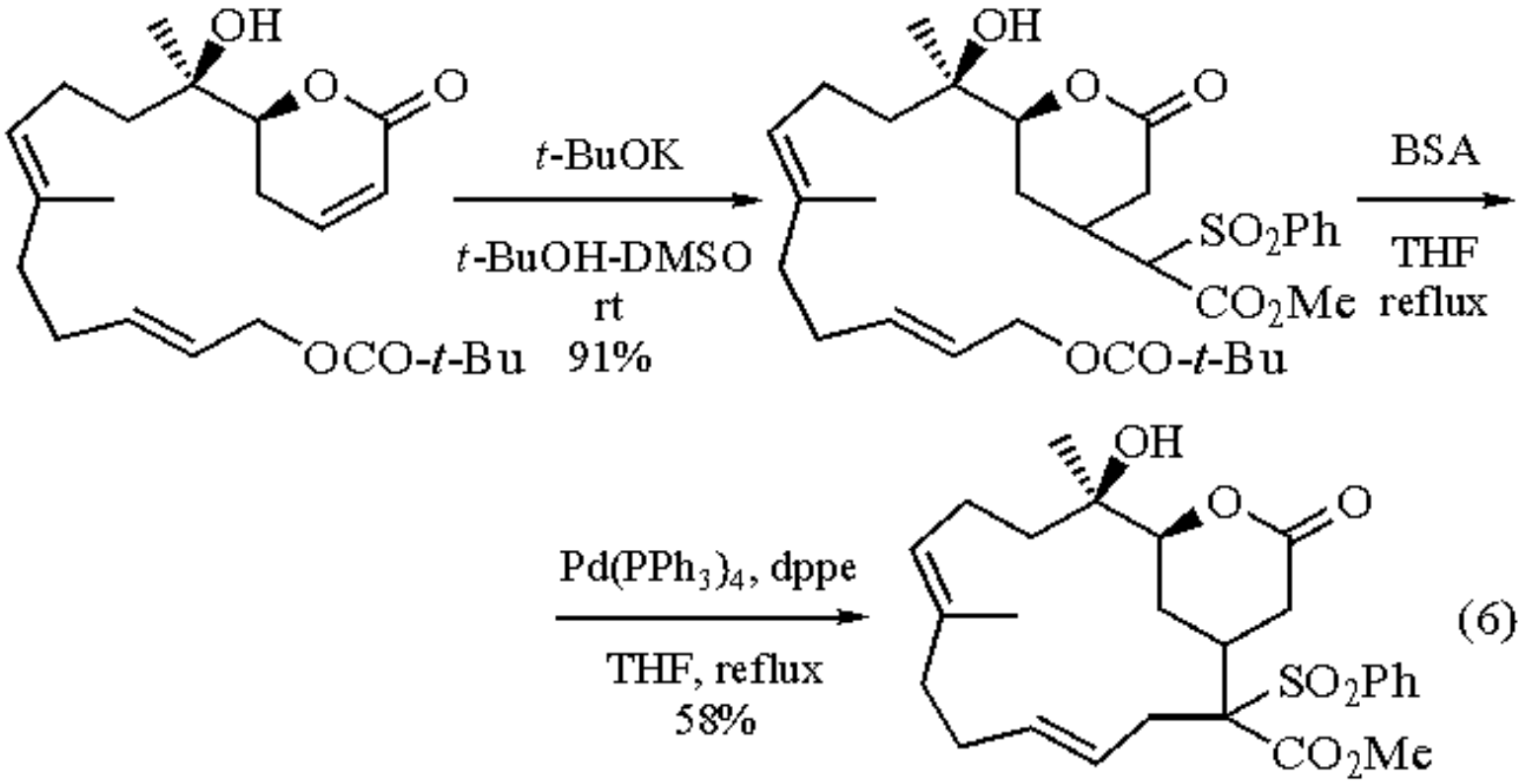

(6)

MPSA is also monoalkylated on the methylene carbon under a variety of conditions (NaOMe/MeOH,[18] NaH/THF,[19] NaH/DMF,[20-22] NaH/DMSO,[23] NaH/HMPA,[22] DBU/benzene[24]). The anion of MPSA reacts with a π-allyl palladium complex to provide a useful method for C-C bond formation between MPSA and allyl acetates (eq 7).[25] Other methods for generating π-allyl palladium complexes are also available (eqs 8 and 9).[26] The combination of these C-C bond formations serves as a synthetic method for constructing various cyclic compounds (eqs 6 and 10).[16,18,20-22,27]

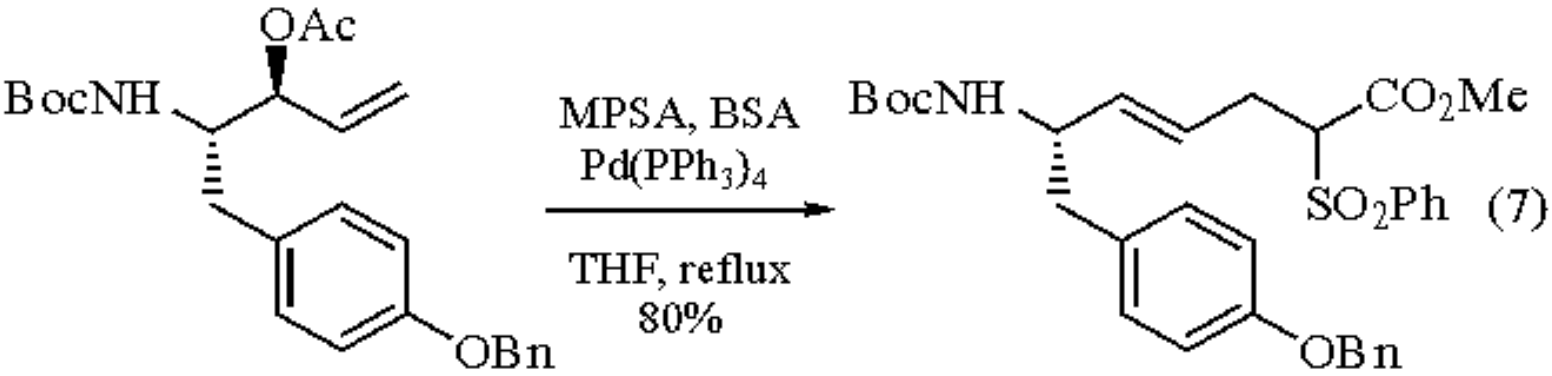

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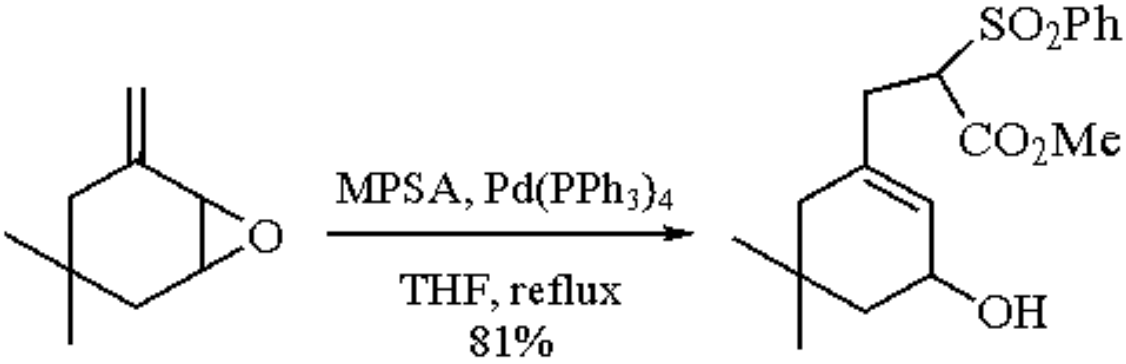

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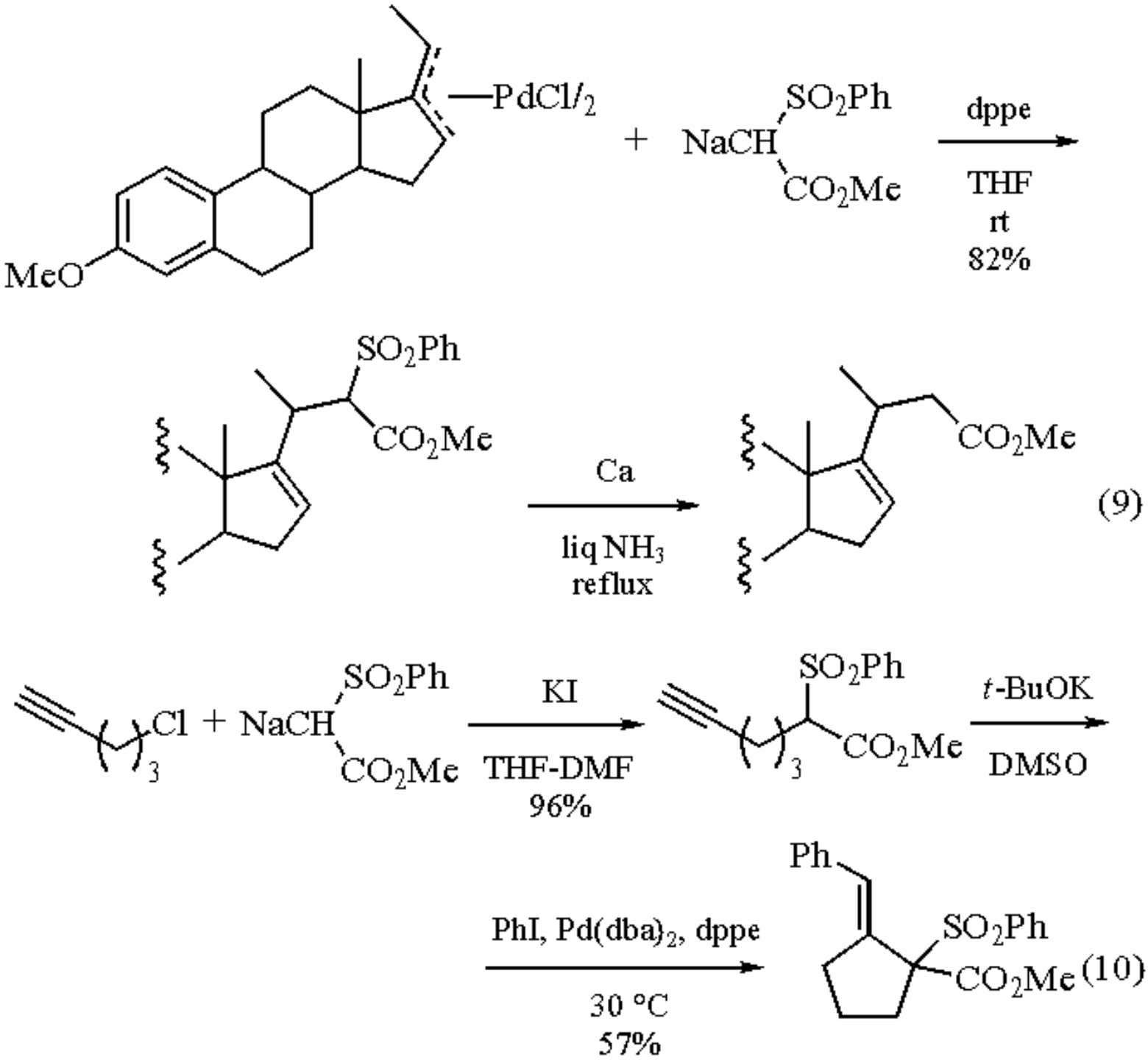

Iodo-substituted MPSA is utilized in an atom-transfer radical addition to an alkene. Thus the iodo derivative of allylated MPSA undergoes the atom-transfer radical cyclization with allylamine to form a bicyclo[3.3.0]octane (eq 11).[28]

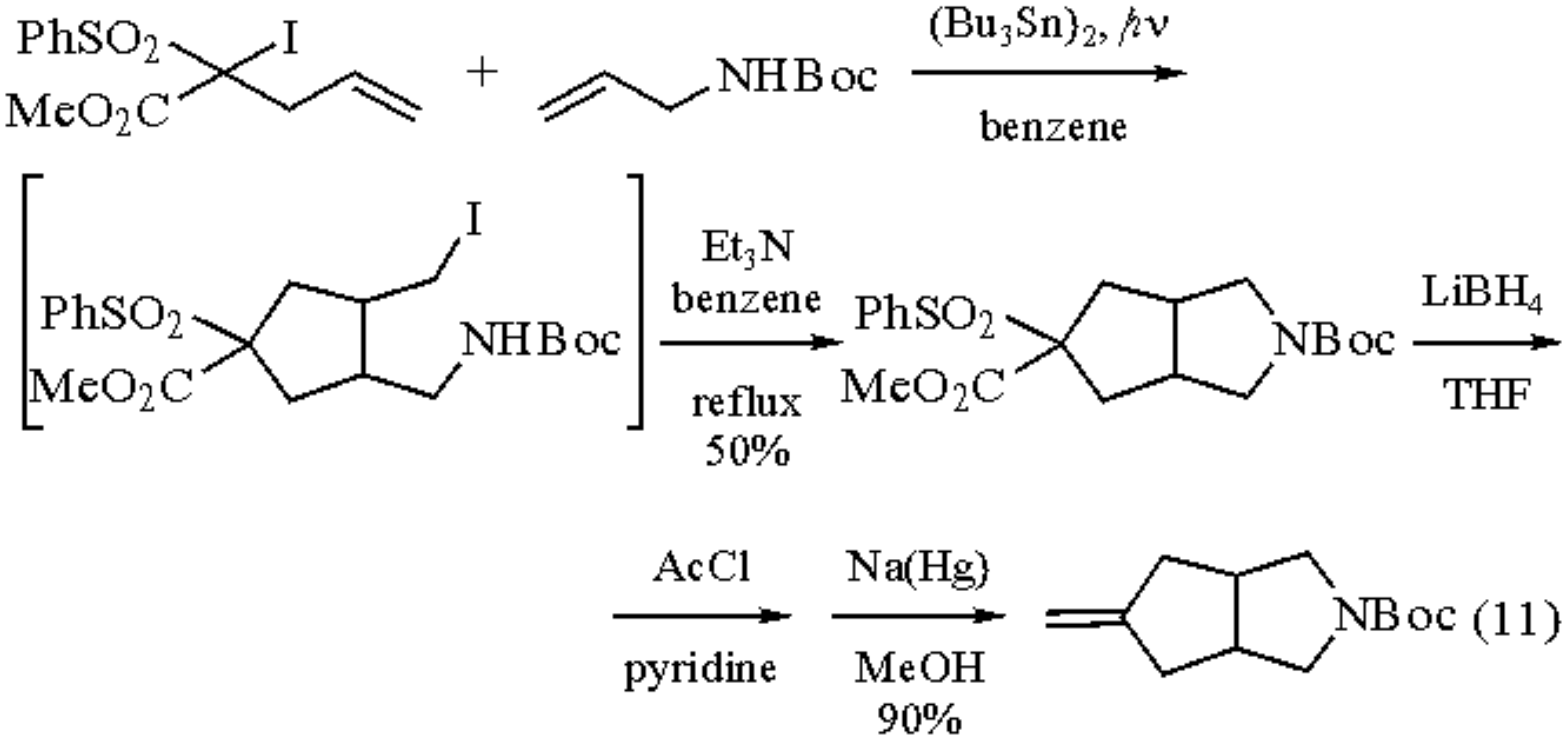

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Ethyl β-Phenylsulfonylpropiolate

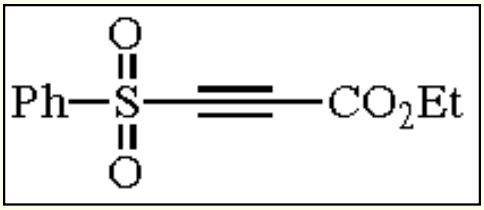

[80404-53-1] · $C_{11}H_{10}O_4S$ · Ethyl β-Phenylsulfonylpropiolate · (MW 238.28)

(dienophile[1,2] used in electrocyclic reactions, such as the Diels-Alder reaction; the adducts can be converted to substituted arenes)

Physical Data: lightly colored oil.

Solubility: sol most organic solvents.

Form Supplied in: prepared and used in situ.[1,3]

Analysis of Reagent Purity: based on spectral examination.[2]

Preparative Methods: Schultz and Shen[1] reported the first preparation of ethyl β-phenylsulfonylpropiolate (**1**) which involved ***m-Chloroperbenzoic Acid*** oxidation of methyl phenylthiopropiolate (**2**).[4] The latter is prepared from sequential treatment of ethyl propiolate with ***Lithium Diisopropylamide*** and phenyl phenylthiosulfonate (eq 1).[5] An alternate route to the synthesis of the corresponding methyl and *t*-butyl ester analogs of (**1**) has been recently reported.[3] Reaction of substituted alkynes with ***Mercury(II) Chloride*** and ***Sodium Benzenesulfinate*** produces a sulfonylmercury complex which under oxidative demercuriation conditions provides the desired β-phenylsulfonylpropiolate esters in modest yields.

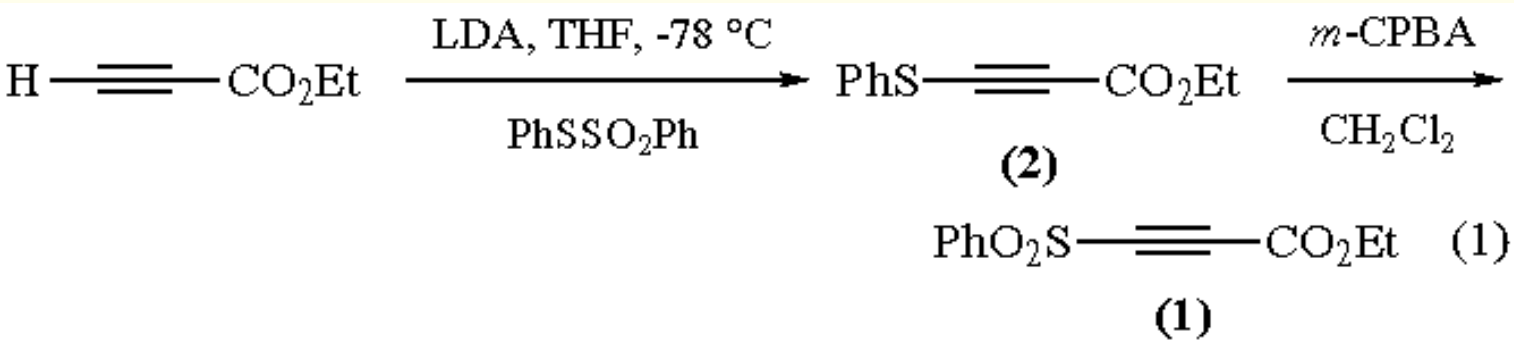

Handling, Storage, and Precautions: undergoes polymerization to a viscous dark substance on standing at rt; refrigeration and short-path silica gel filtration chromatography prior to use is recommended.[1]

Diels-Alder Reaction.

The reagent is a reactive dienophile; it undergoes essentially quantitative Diels-Alder addition to a variety of dienes including furan, 1,3-cyclohexadiene, and pyrrole (eq 2). Extremely high regioselectivity is observed for the addition of (**1**) with 1-substituted butadienes.

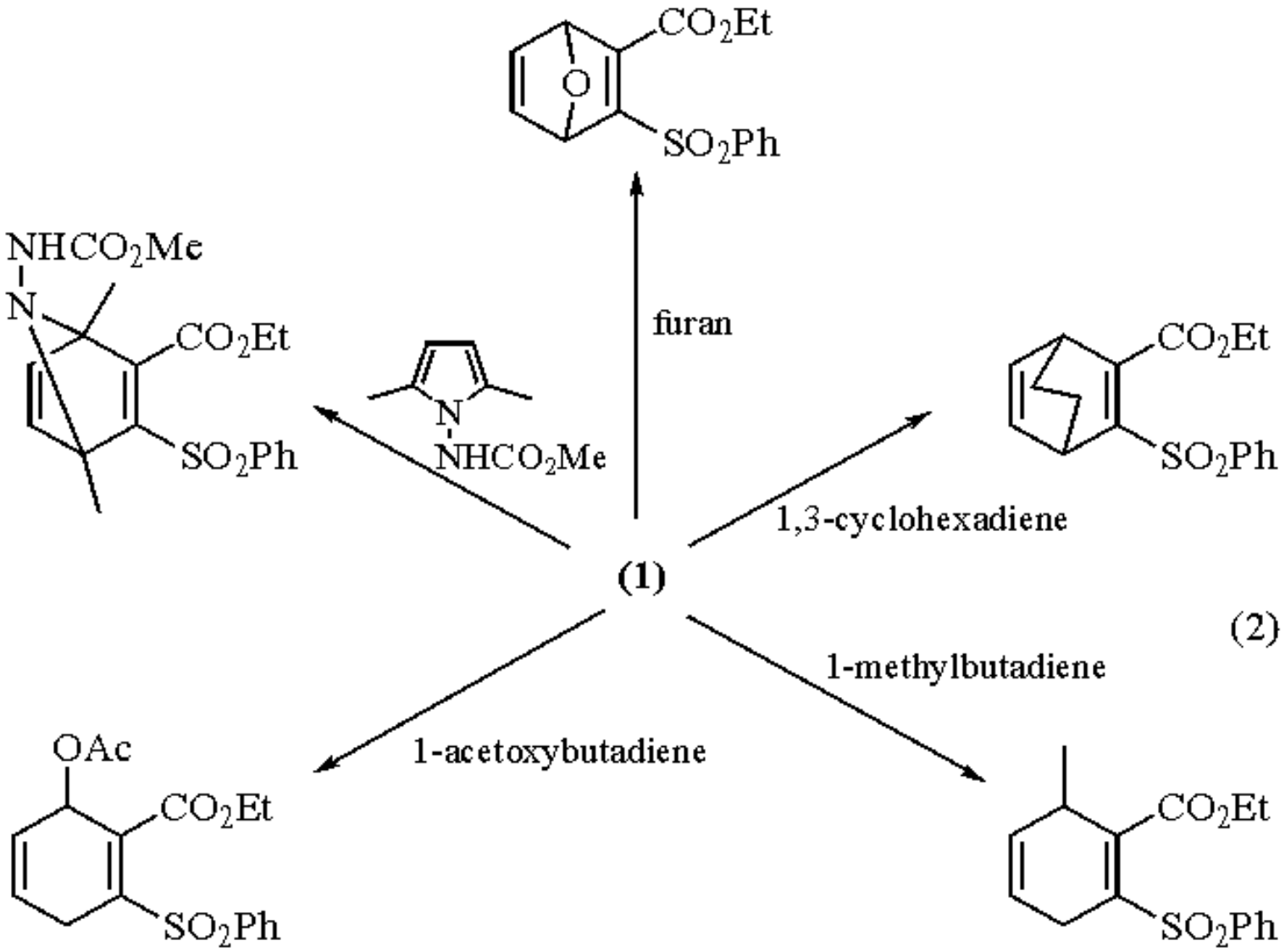

(2)

The synthetic utility of (**1**) for the preparation of substituted arene systems is exemplified in eq 3. Thus adduct (**3**) under benzenesulfinic acid elimination conditions provides benzoate (**4**). On the other hand, simple dehydrogenation of (**3**) gives aryl sulfone (**5**) in modest yield.[1]

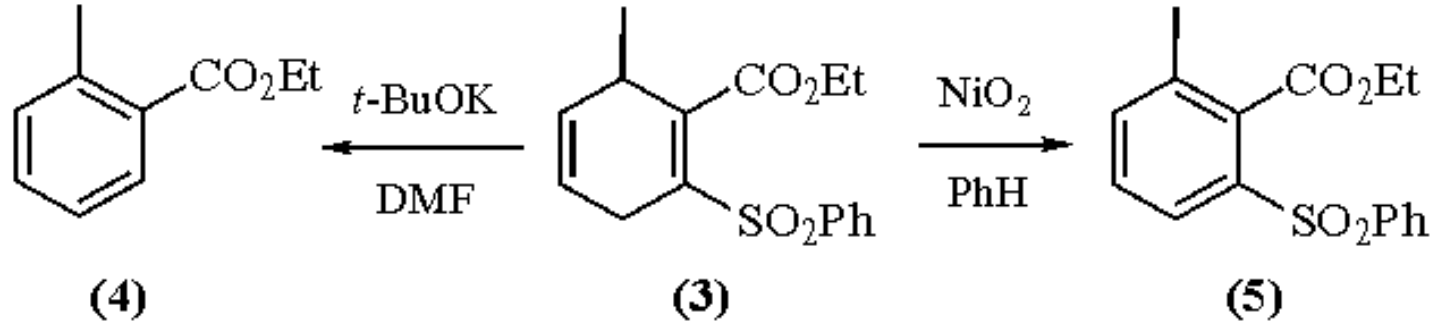

(3)

Methyl and ethyl β-phenylsulfonylpropiolates have been reported to participate in a [4 + 2] cycloaddition reaction with the vinyl and cross-conjugated porphyrin β,β´ double bonds of either ring A or B of protoporphyrin IX dimethyl ester in a regio- and stereospecific manner.[2] Corey et al., in their total synthesis of forskolin, utilized β-phenylsulfonylpropiolic acid as a dienophile for an intramolecular Diels-Alder reaction, wherein the alkyne unit is tethered to the required diene system through an ester moiety, to build the A/B ring system of the natural product.[6]

---

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Neelakautan Balasubramanian & Denis R. St. Laurent

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1-Ethylpiperidine

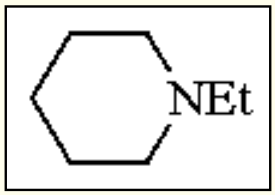

[766-09-6] · $C_7H_{15}N$ · 1-Ethylpiperidine · (MW 113.23)

(hindered nonnucleophilic amine used as base for the generation of tin enolates and aldol-like condensations;[1] aryl halide couplings; preparation of anhydrides)

Physical Data: bp 131 °C; fp 18 °C; *d* 0.824 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: liquid.

Handling, Storage, and Precautions: the liquid is corrosive and flammable. Bottles of 1-ethylpiperidine should be flushed with nitrogen or argon to prevent exposure to carbon dioxide. The vapors are harmful and care should be taken to avoid absorption through the skin. Use in a fume hood.

Aldol Condensations.

1-Ethylpiperidine is the base of choice for the in situ preparation of divalent tin enolates used in diastereoselective and enantioselective cross-aldol reactions (eq 1).[1] Preparation of the tin enolates involves treatment of a ketone with ***Tin(II) Trifluoromethanesulfonate*** in the presence of 1-ethylpiperidine. The aldol reaction is selective for the *erythro* diastereoisomer.[2]

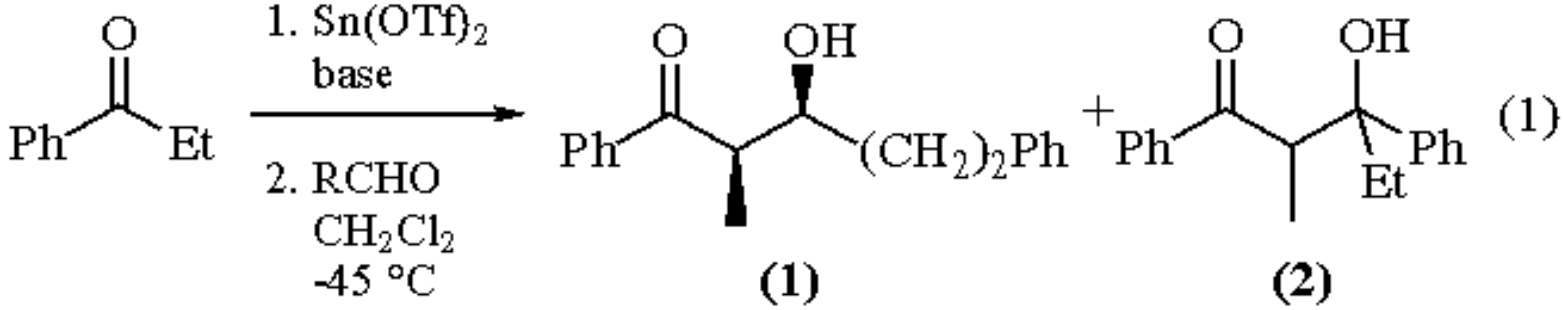

base	isolated yield (1)	(2)
N-methylmorpholine	22	65
N-ethylpiperidine	80	trace

Enantioselective cross-aldol reactions between ketone-derived tin enolates and aldehydes result from the addition of a chiral nonracemic diamine (eq 2).[3] The methodology is useful for cross-aldol reactions between two ketones (eq 3),[4] and aldol-like reactions involving acyl-2-oxazolidones,[5] acylthiazolidine-2-thiones (eq 4),[6] and enantiomerically enriched 4-substituted acylthiazolidine-2-thiones (eq 5).[7]

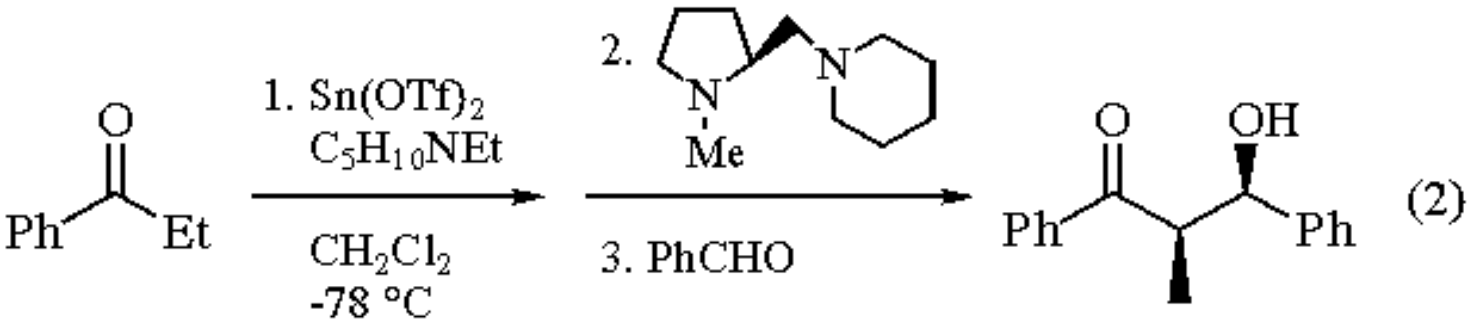

75%; *erythro*:*threo* = 6:1
erythro isomer = 80% ee

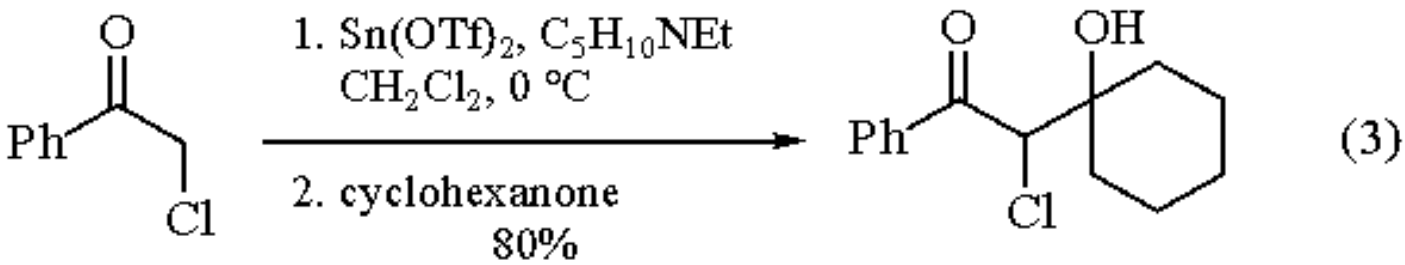

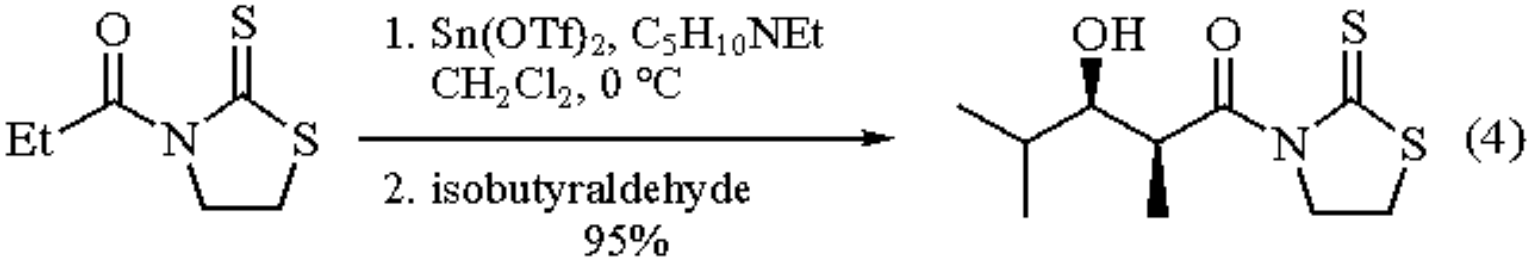

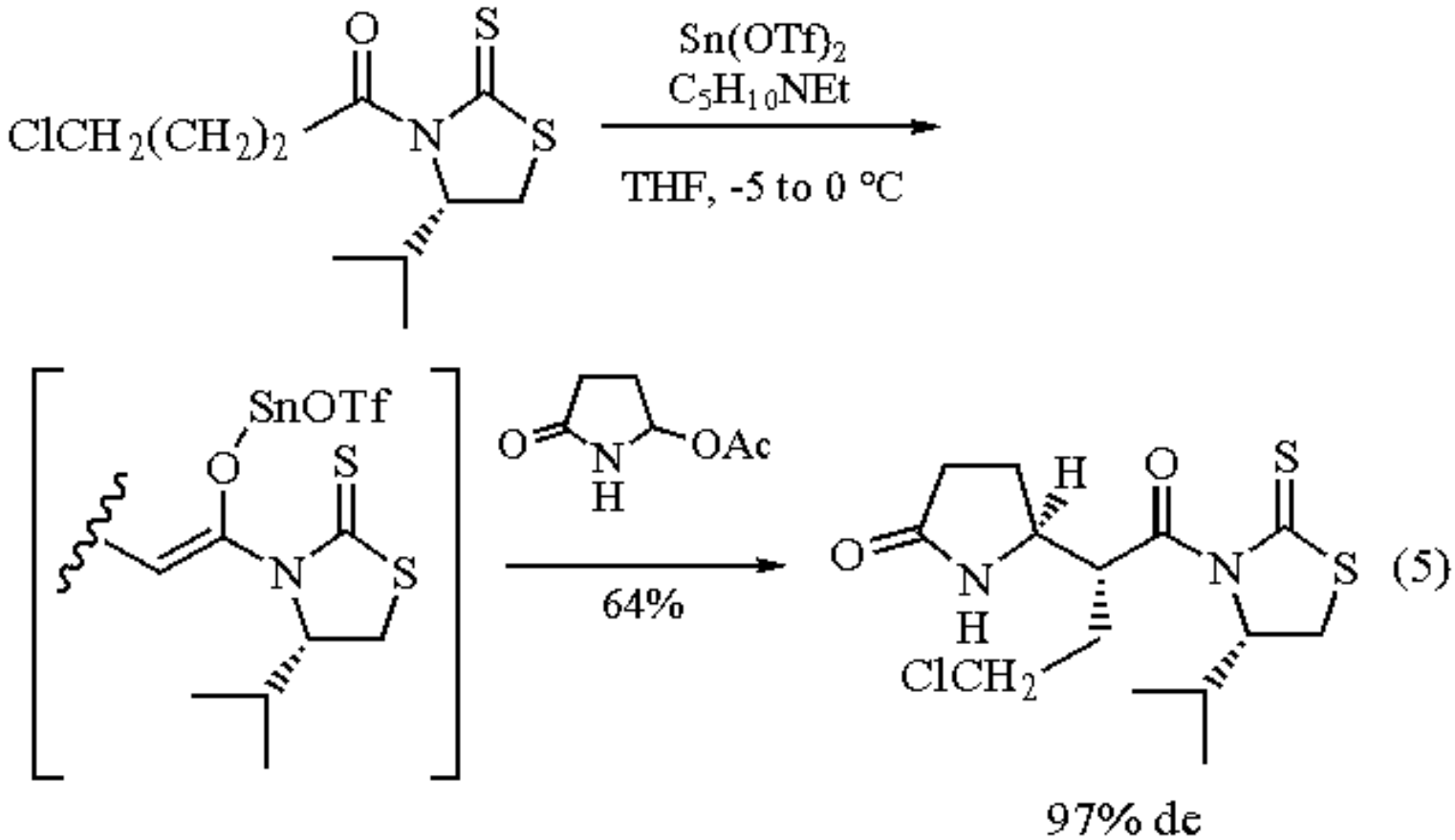

Preparation of Anhydrides.

The base is used in preparing symmetrical (eq 6)[8] and mixed carboxylic acid anhydrides which are used in amide or peptide synthesis (eq 7).[9]

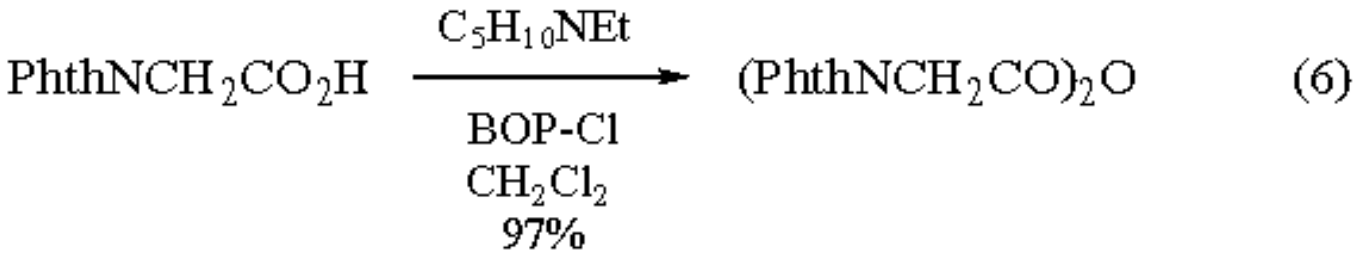

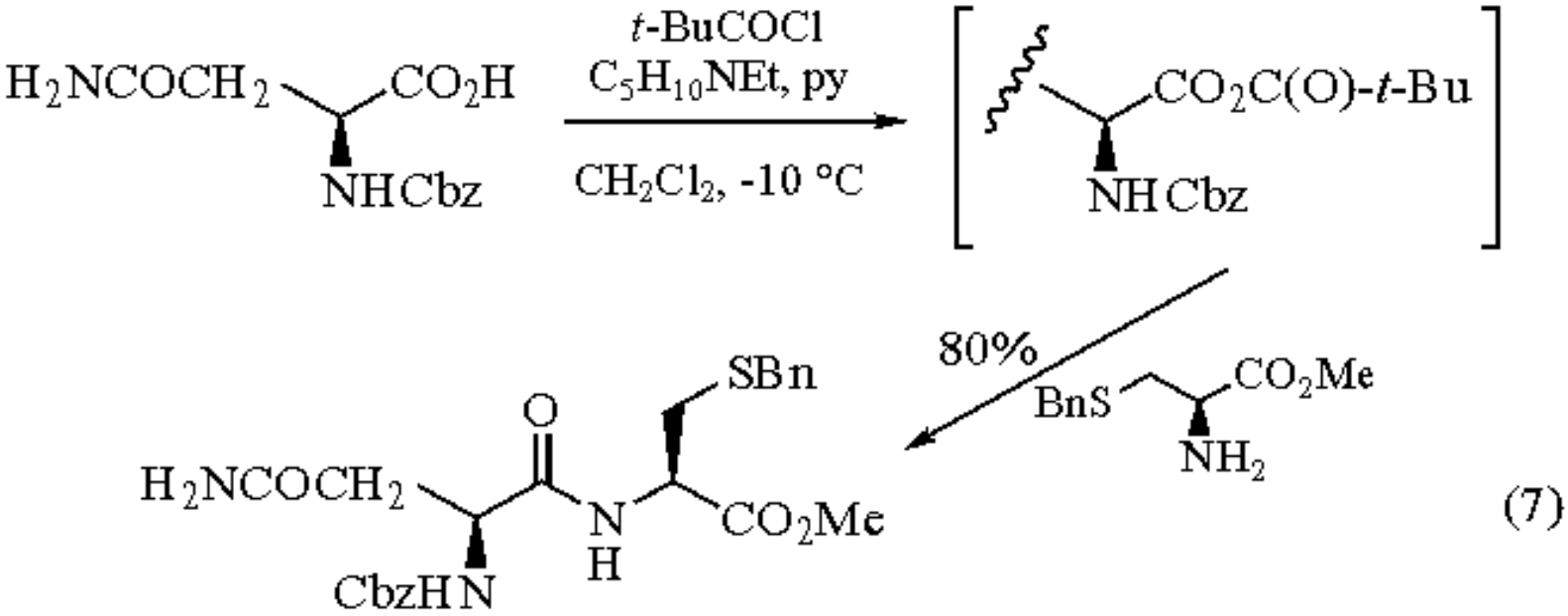

(7)

Aryl Halide Couplings.

Employment of ***Copper(I) Iodide*** and 1-ethylpiperidine as catalysts promotes coupling between aryl halides and alkynes (eq 8).[10]

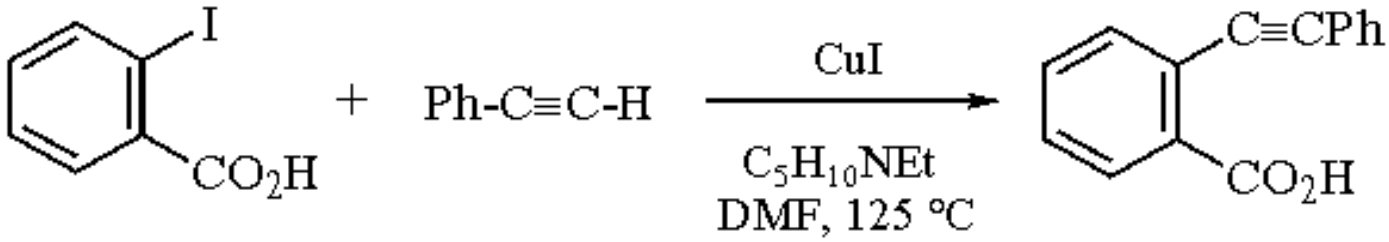

(8)

Esterifications.

Treatment of crotonyl chloride with 1-ethylpiperidine in ethanol yields ethyl vinylacetate, while use of 2,4,6-trimethylpyridine as base produces ethyl *trans*-crotonate (eq 9).[11]

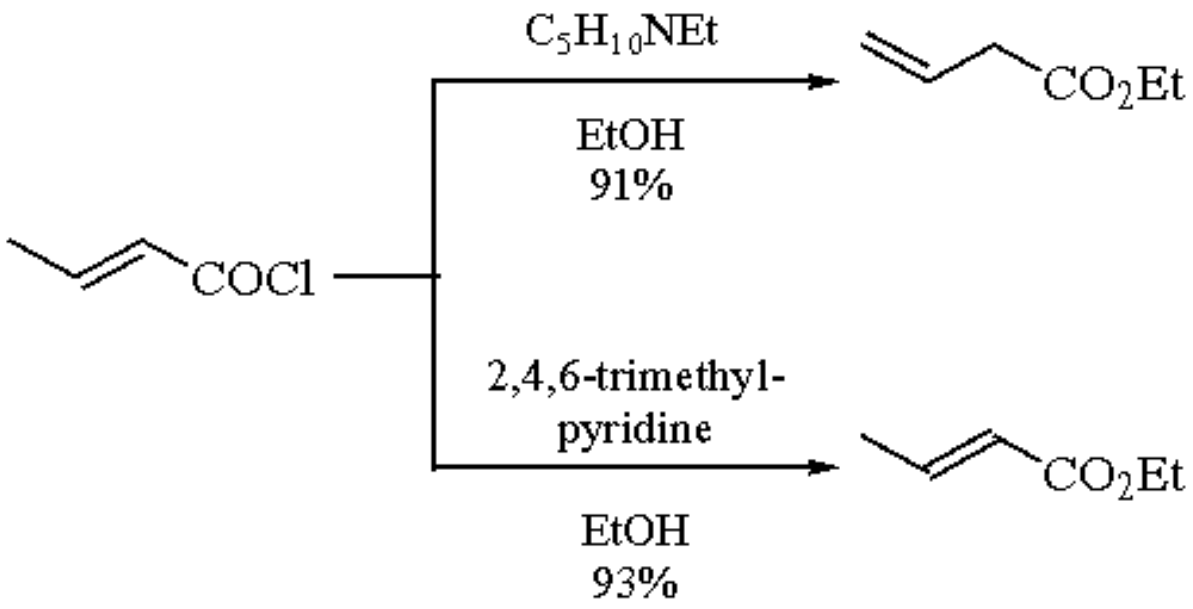

(9)

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Ethyl β-(1-Pyrrolidinyl)acrylate

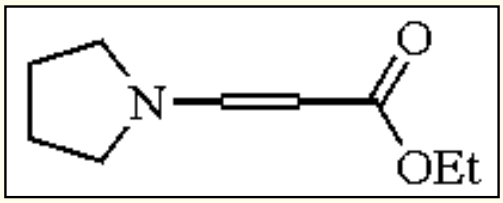

[53927-12-1] · $C_9H_{15}NO_2$ · Ethyl β-(1-Pyrrolidinyl)acrylate · (MW 169.25) (*E*)

[65651-80-1]

(precursor to β-vinyllithium derivative; reactions with electrophiles yield cyclopentenones, butenolides, maleic acid derivatives, and oxalacetic acid derivatives[1,2])

Physical Data: mp 41-43 °C; bp 80-105 °C/10^{-3} mmHg.[3]

Solubility: sol most organic solvents (ethanol, ethyl acetate, dichloromethane, chloroform, THF).

Form Supplied in: colorless solid.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, *J* = 7 Hz, 3 H, CH_3), 1.95 (m, 4 H, CH_2CH_2N), 3.30 (m, 4H, CH_2N), 4.16 (q, *J* = 7 Hz, 2 H, CH_2O), 4.50 (d, *J* = 12.5 Hz, 1 H, 2-H), 7.72 (d, *J* = 12.5 Hz, 1 H, 3-H); ^{13}C NMR δ 14.7 (CH_3), 25.3 (CH_2CH_2N), 4.88 (CH_2N), 58.5 (CH_2O), 84.6 (2-C), 169.2 (1-C); IR ($CHCl_3$) 1600 (C=C), 1665 (C=O) cm^{-1}; UV (EtOH) 287 nm (ε = 2600).[4]

Preparative Method: reaction of ethyl propiolate with pyrrolidine in acetonitrile at rt yields ethyl β-(1-pyrrolidinyl)acrylate in 55% yield as a colorless solid.[3,4]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: store under nitrogen protected from moisture.

Acrylates with functional groups (for instance, amino, hydroxy, mercapto moieties) in the β-position exhibit: (i) nucleophilic character at the α-position, permitting reactions with various electrophiles; (ii) electrophilic character at the β-position, enabling nucleophilic exchange reactions which can be employed for ring closure reactions; and (iii) CH acidity at the β-position (and/or α-position) which, for instance with strong lithiating agents, leads to direct β-lithiation, thus generating highly versatile functionally substituted vinyllithium derivatives.[5,6] Typical examples for ethyl β-(1-pyrrolidinyl)acrylate are shown below.

Reaction with Diazonium Salts.

The reaction of ethyl β-(1-pyrrolidinyl)acrylate with diazonium salts as electrophiles leads to the formation of iminium hydrazone derivatives (**1**) which can be isolated in 65-90% yields (eq 1). These products can be converted into imidazole derivatives by action of base (eq 2) or into cinnoline derivatives (eq 3), depending on the substituents of the aromatic ring.[7,8]

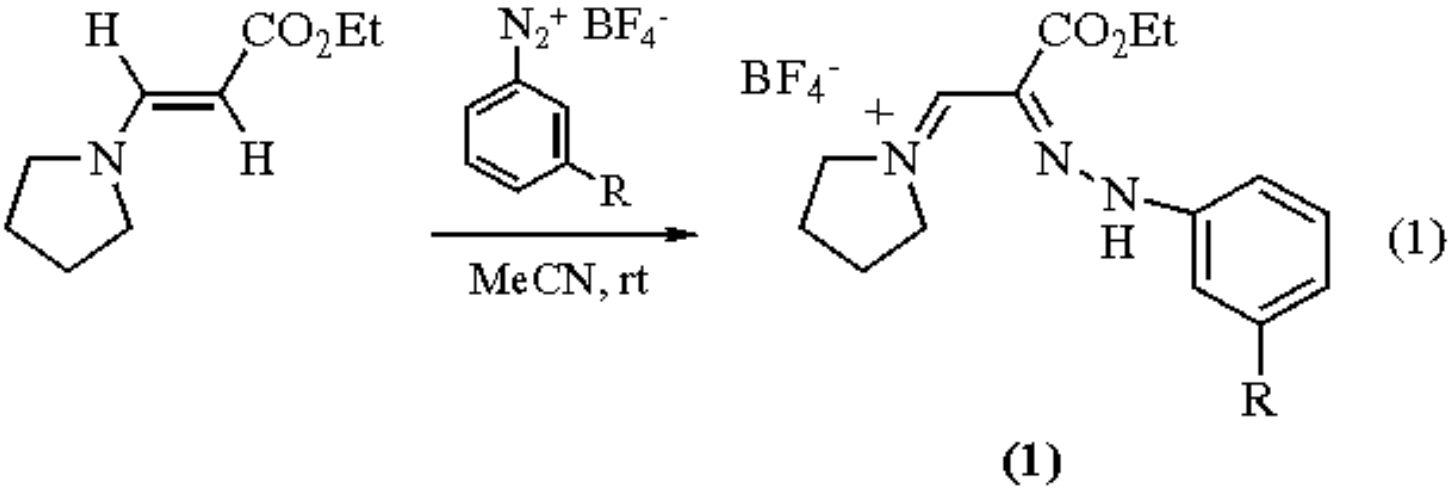

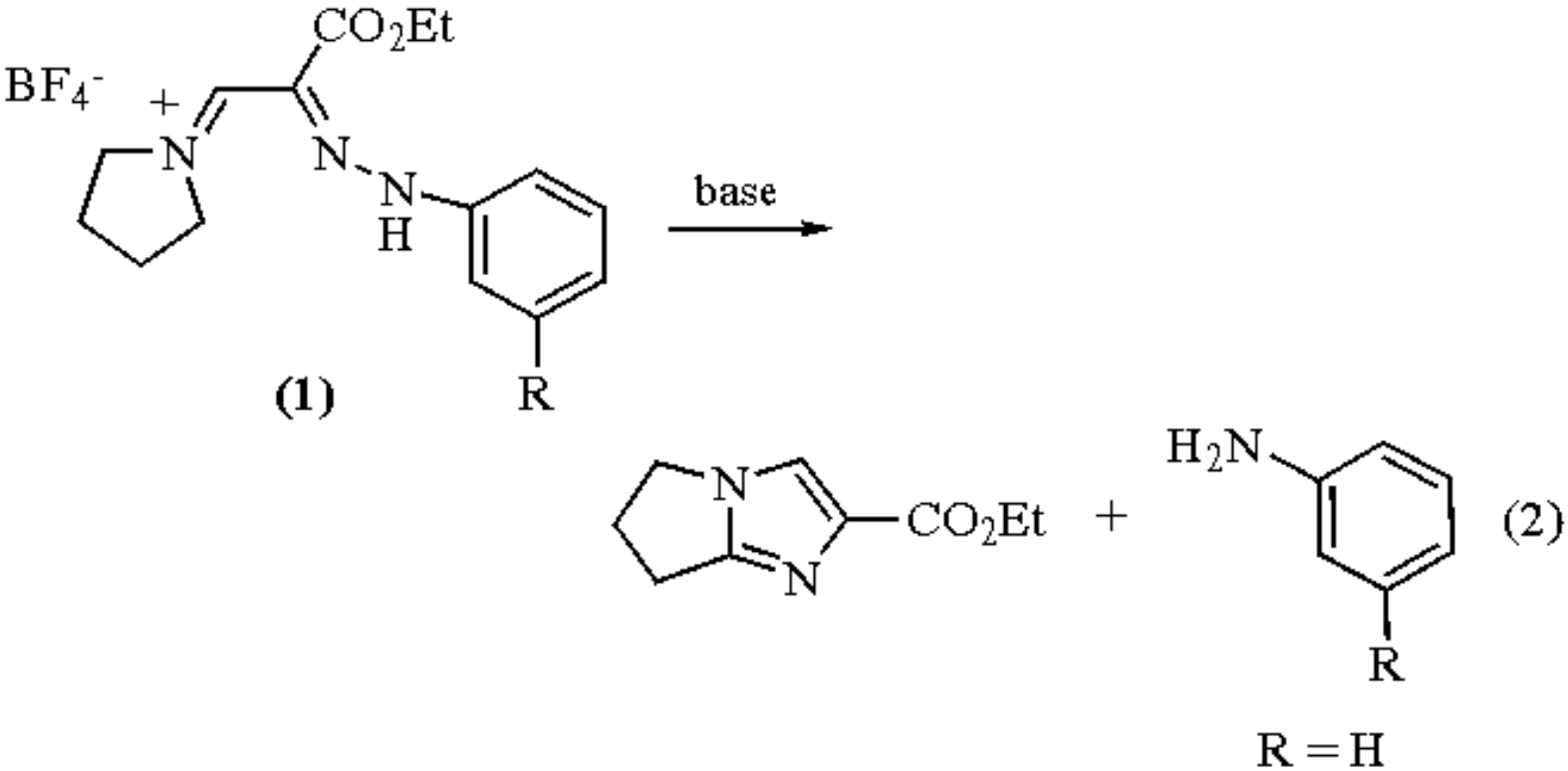

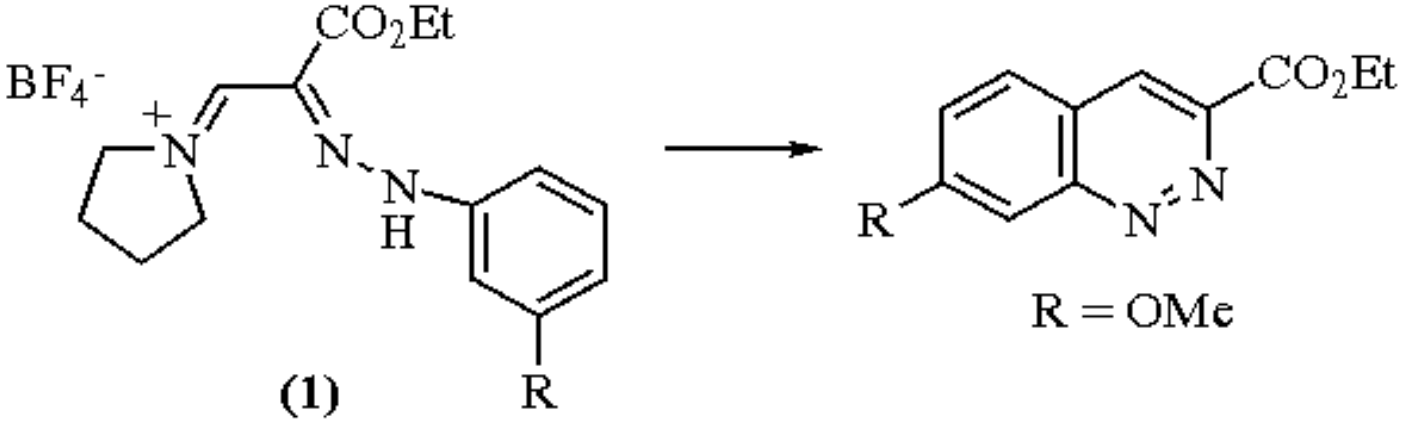

(3)

Reaction with α-Amino Carbonyl Compounds.

The reaction of ethyl β-(1-pyrrolidinyl)acrylate with α-amino carbonyl compounds as nucleophiles in refluxing ethanol proceeds via 1,4-addition followed by elimination to give transamination intermediates which cyclize immediately to yield 3-substituted pyrroles (eq 4).[9]

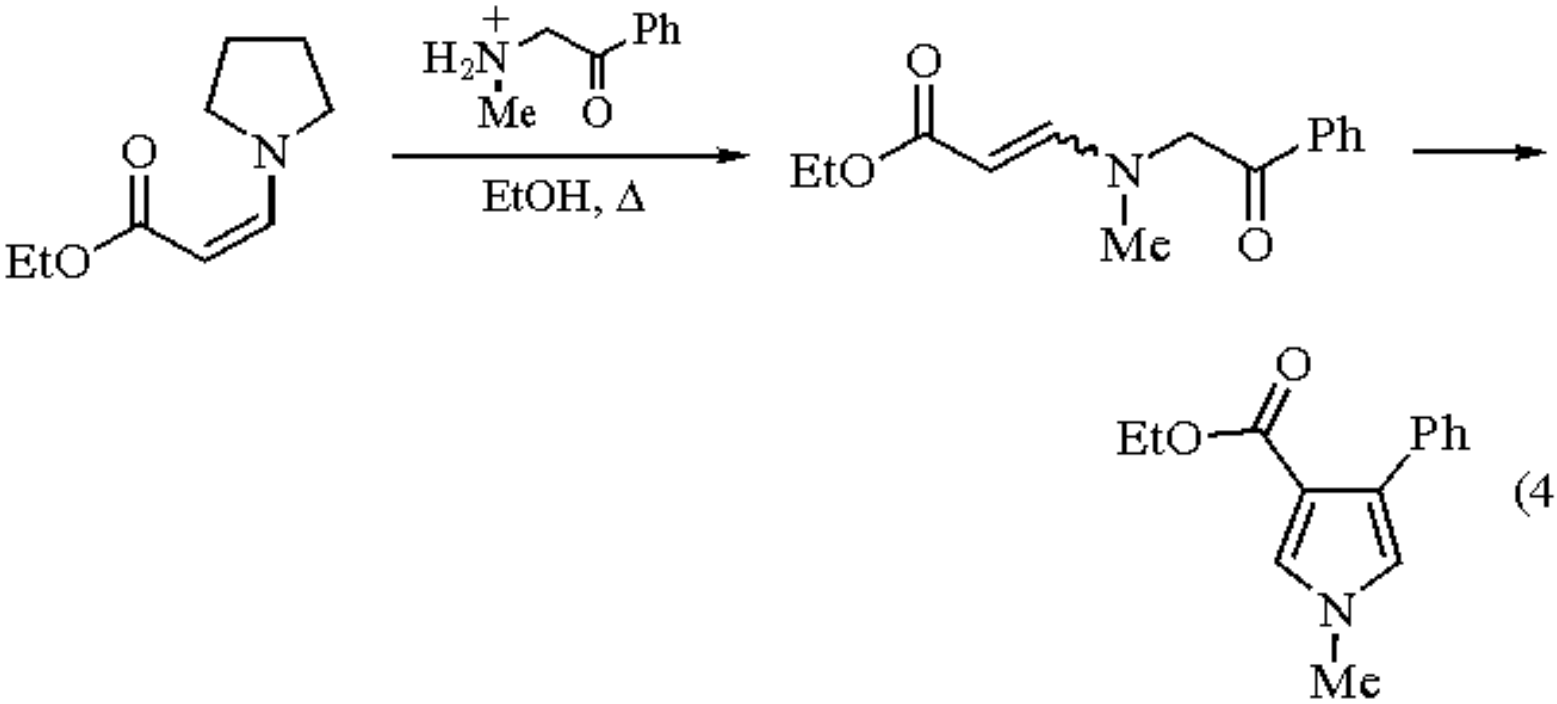

(4)

Vinylcarbanion Generation.

Ethyl β-(1-pyrrolidinyl)acrylate can be converted by direct lithiation with ***t-Butyllithium*** below -100 °C into a β-vinyllithium derivative (**2**) (eq 5), which can be used as a C_3 synthon for cyclization reactions. Reaction with acrylates, aldehydes, or ketones as electrophilic-nucleophilic species leads to functionally substituted cyclopentenones (eq 6) and butenolides (eq 7).[1] Many examples involving reactions with heterocumulenes have been reported.[2] For instance, addition of ***Phenyl Isothiocyanate*** or ***Phenyl Isocyanate*** yields, after cyclization, the thiomaleic anhydride derivative (eq 8) or the *N*-phenylmaleimide derivative (eq 9), respectively. Addition of alkyl isocyanates does not lead to cyclization, and oxalacetic acid derivatives are obtained (eq 10). Similarly, addition of ***Carbon Dioxide*** yields, after

hydrolysis of the enamine, an oxalacetate derivative (eq 11).

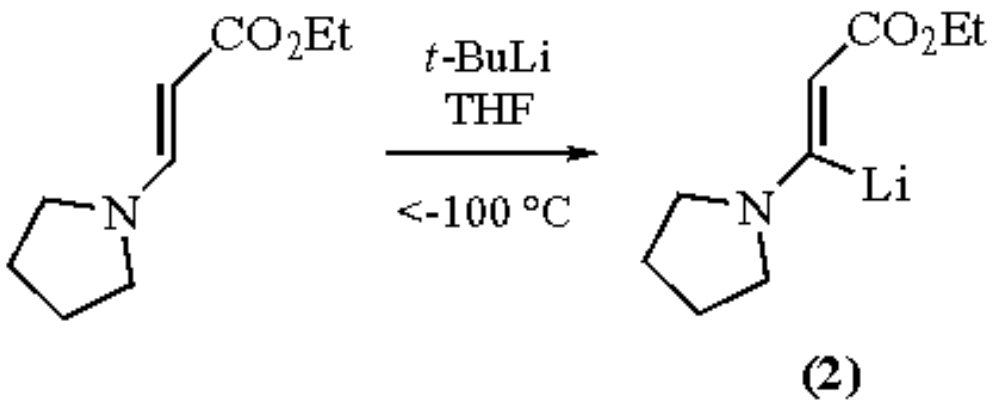

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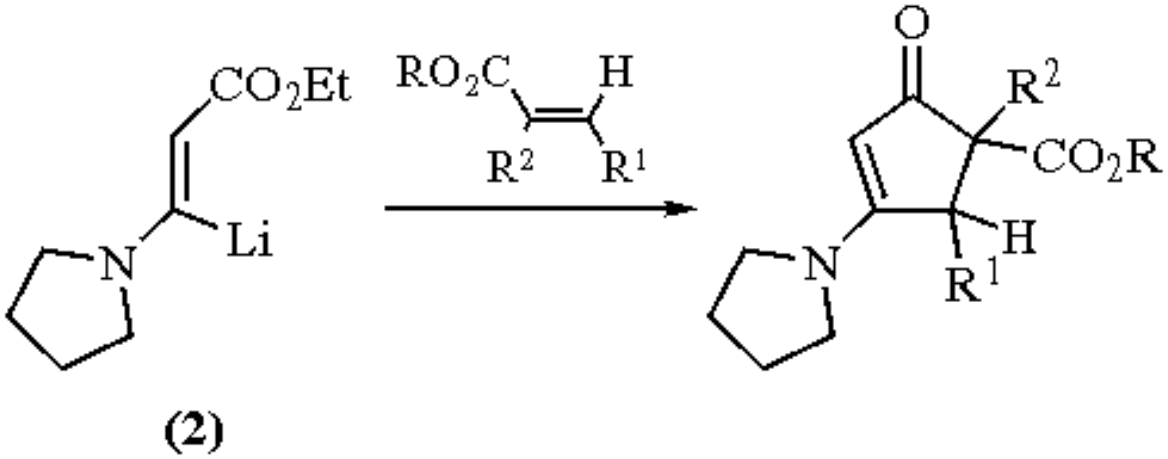

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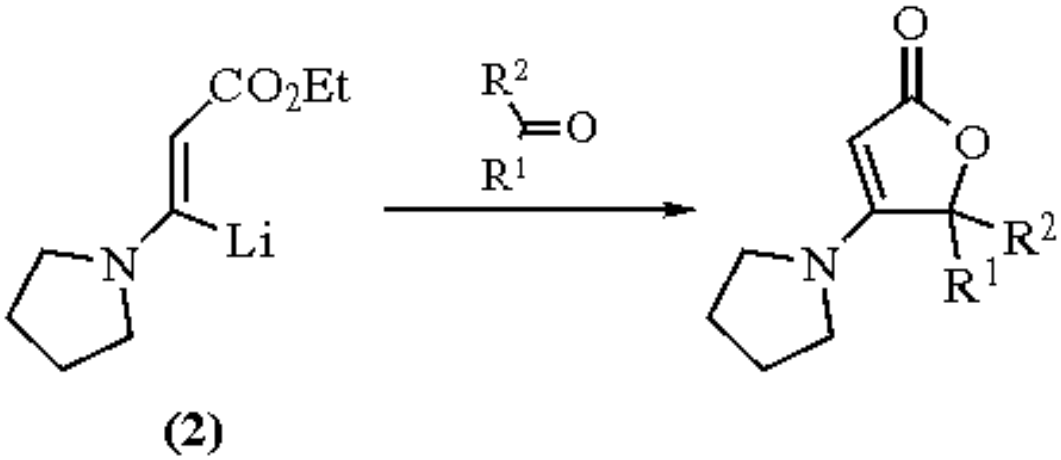

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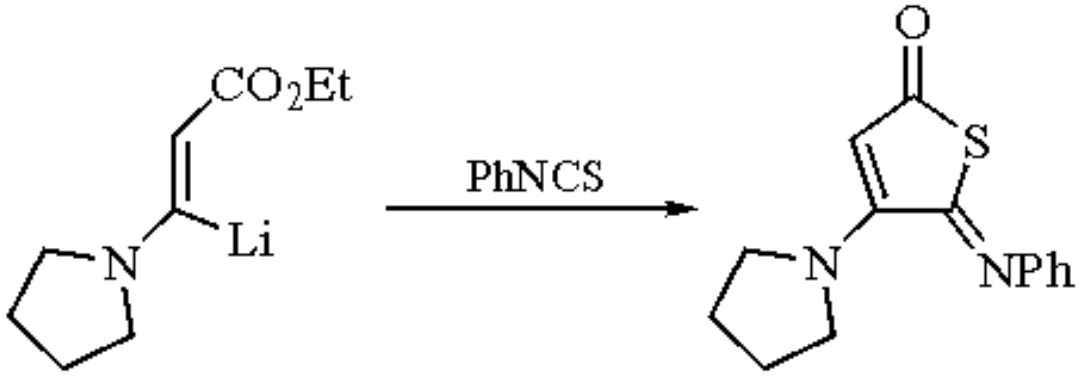
CO2Et
Li
N
PhNCS
O
S
NPh
N

(2) (8)

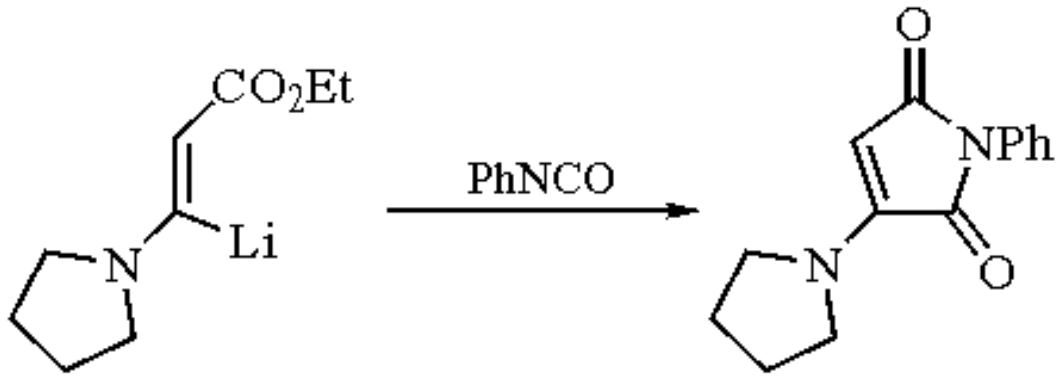
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Li
N
PhNCO
O
NPh
O
N

(2) (9)

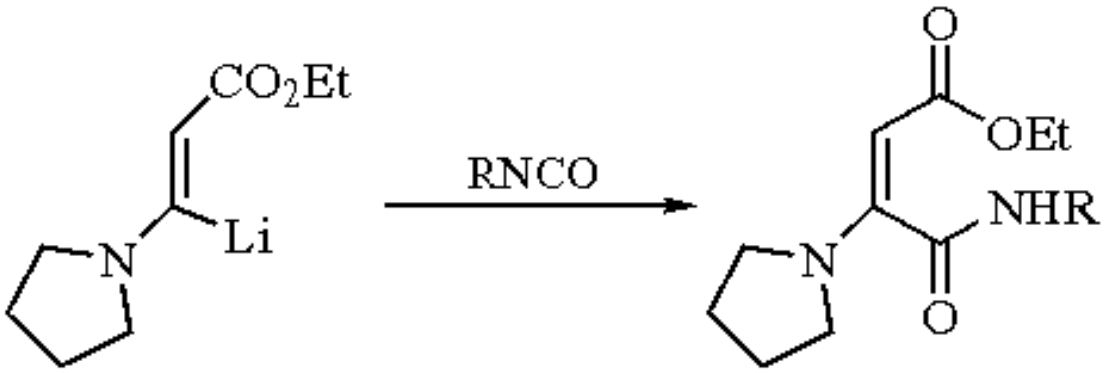
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RNCO
O
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NHR
O
N

(2) (10)

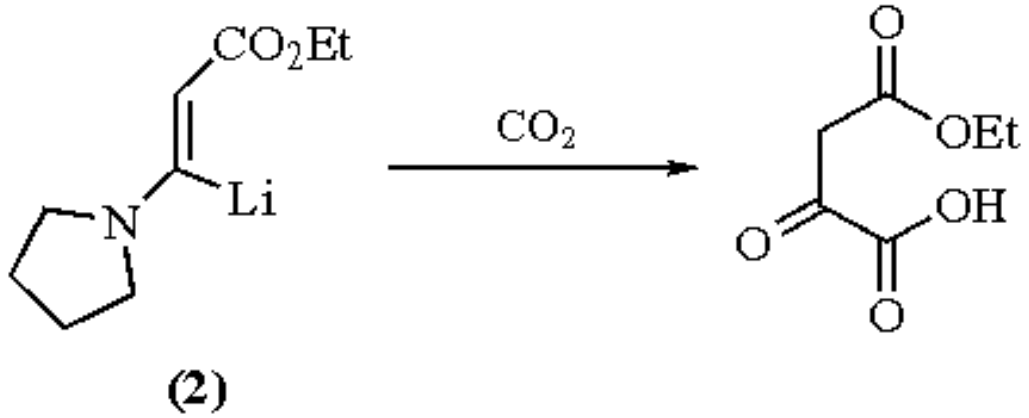

(11)

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Ethyl Pyruvate Diethyl Acetal

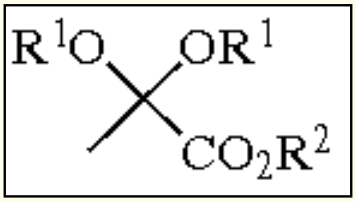

($R^1 = R^2 = Et$)

[7476-20-2] · $C_9H_{18}O_4$ · Ethyl Pyruvate Diethyl Acetal · (MW 190.27) ($R^1 = R^2 = Me$)

[10076-48-9] · $C_6H_{12}O_4$ · Methyl Pyruvate Dimethyl Acetal · (MW 148.18) ($R^1{}_2 = CH_2CH_2$, $R^2 = Et$)

[56624-93-2] · $C_7H_{12}O_4$ · Ethyl Pyruvate Ethylene Acetal · (MW 160.19)

(reactions with nucleophiles give various α-difunctional products;[1-8] useful reagents for synthesis of heterocyclic compounds;[8-10] several interesting results are obtained through transacetalizations[3,11-13])

Alternate Name: ethyl 2,2-diethoxypropanoate.

Physical Data: $R^1 = R^2 = Et$, bp 70-71 °C/10 mmHg; $R^1 = R^2 = Me$, bp 58-60 °C/13 mmHg; $R^1{}_2 = CH_2CH_2$, $R^2 = Et$, bp 70-76 °C/8 mmHg.

Preparative Methods: by acetalization of ethyl or methyl pyruvates (ROH, $HC(OR)_3$, HCl or TsOH or H_2SO_4; $HOCH_2CH_2OH$, TsOH, C_6H_6, Dean Stark).

Handling, Storage, and Precautions: should be stored at low temperature.

Reactions with Nucleophiles.

Reaction with organomagnesium compounds in HMPA leads to enolates of α-dicarbonyl compound monoacetals and then to α-keto acetals by hydrolysis. Therefore reactions require two molar equivalents of organomagnesium compounds (eq 1).[1] In several cases, an alcohol from ketone reduction is also formed; therefore the yield of the keto acetal is improved by oxidation of the crude product (eq 2).[1] Reduction of ethyl 2,2-diethoxypropanoate followed by oxidation of the resulting alcohol gives pyruvaldehyde diethyl acetal (eq 3).[1,2] Reactions with ketone,[3] ester,[4] and amide[5] enolates lead to Claisen condensation products (eq 4).[4] The nitromethane dianion (eq 5),[6] the lithium derivative of 1,3-dithiane,[7] and ammonia[8] also give substitution products.

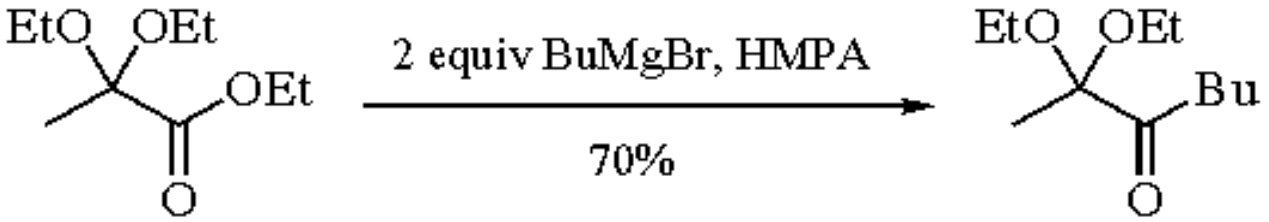

(1)

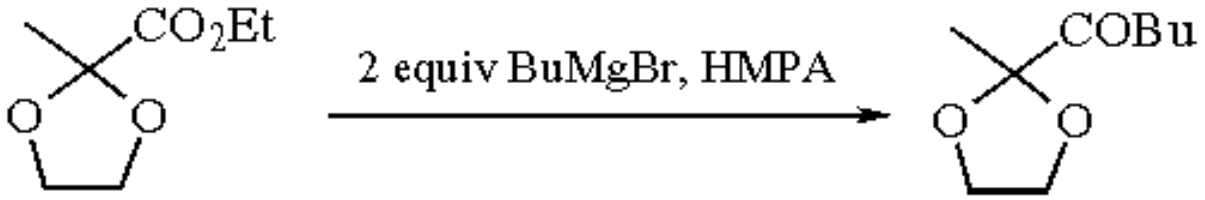

(2)

52%; 61% if the crude product is oxidized before isolation

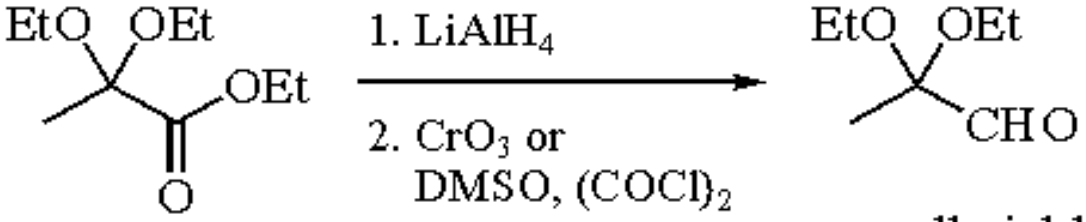

(3)

overall yield 43% or 87.4%

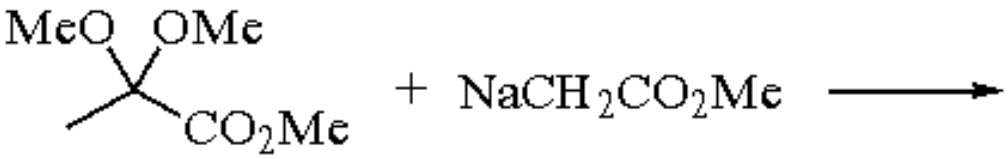

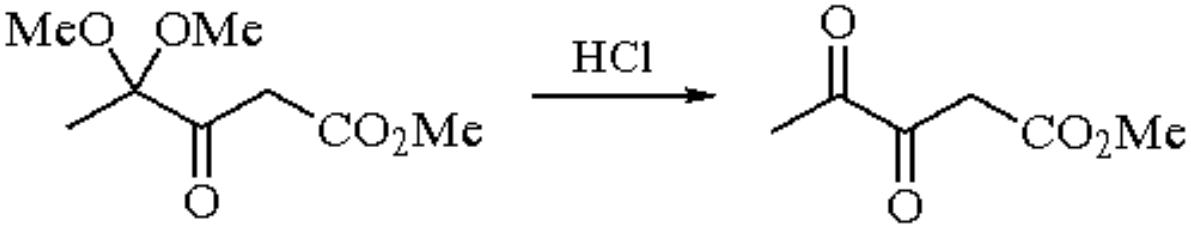

(4)

overall yield 80%

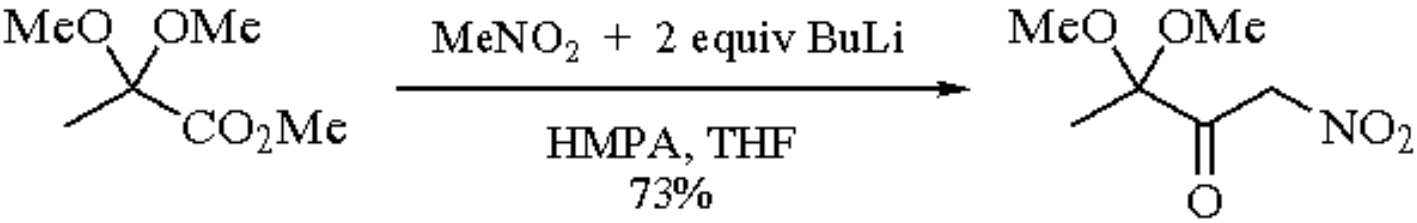

(5)

Synthesis of Heterocyclic Compounds.

Several syntheses of heterocyclic compounds using these reagents have been described.[8-10] For instance, 1-(3-methyl-1,2,4-oxadiazol-5-yl)ethanone has been prepared from 2,2-diethoxypropanamide (eq 6).[8]

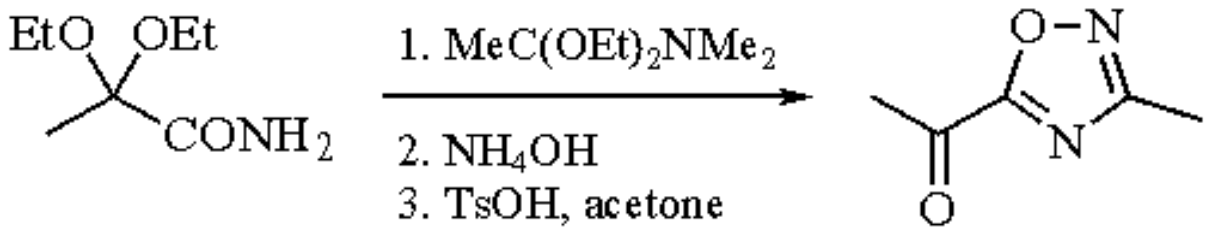

(6)

Transacetalization.

Claisen rearrangement of the diallyl acetal obtained from methyl 2,2-dimethoxypropanoate gives the γ,δ-unsaturated-α-keto ester, methyl 2-oxo-5-hexenoate, in good yield (eq 7).[11] Its preparation is thus possible on a large scale. The corresponding dibenzyl acetal is prepared by a similar way and leads to the benzyl alcohol elimination product in the presence of P_2O_5/DMF.[12,13] Intramolecular acetalization occurs after reaction of methyl 2,2-dimethoxypropanoate with the 2-methyl-1,3-cyclohexanedione dianion (eq 8).[3]

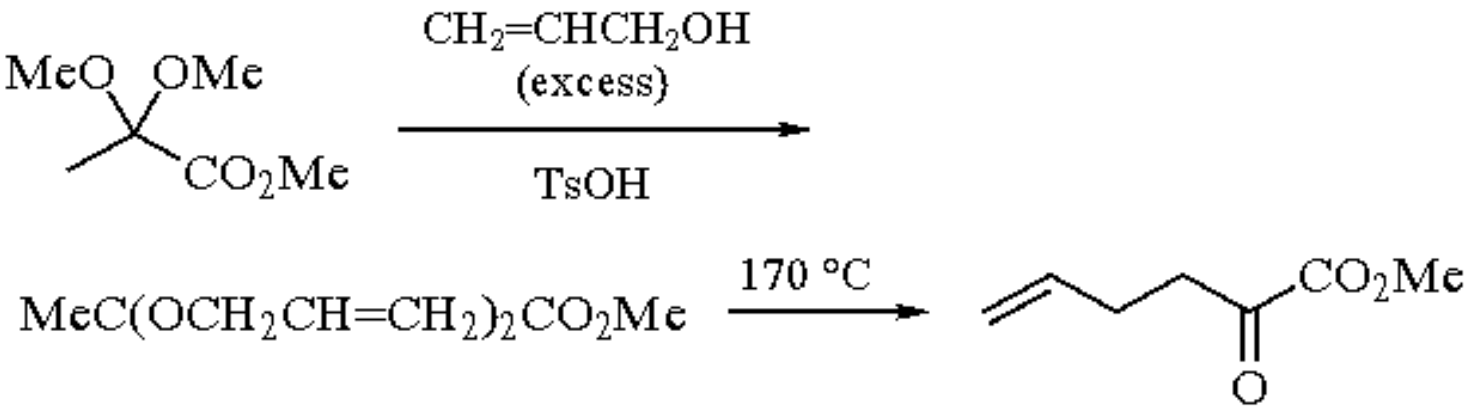

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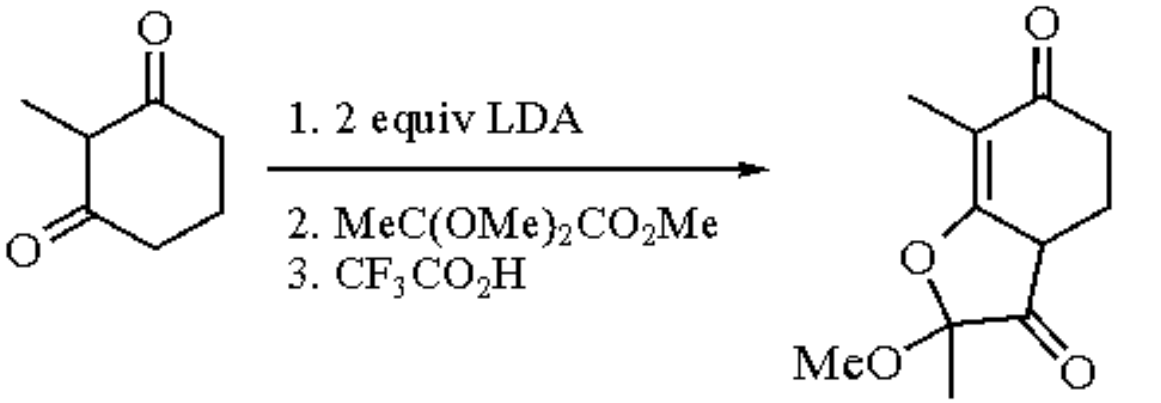

overall yield 61%

(8)

Alcohol Elimination.

In many preparative experiments, elimination of alcohol in acidic medium has been encountered.[12-15] Such an elimination product led to 2-methoxyacrylic acid (eq 9),[15] an intermediate for synthesis of the ergot alkaloids and related structures.

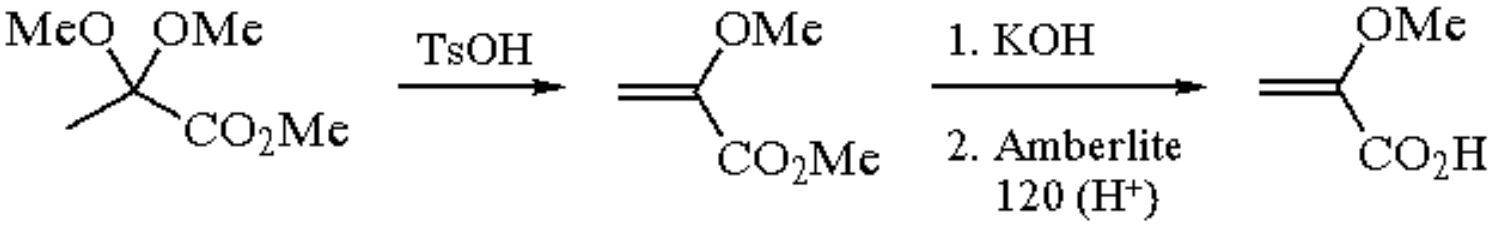

(9)

Related Reagents.

Ethyl Diethoxyacetate; ***Glyoxal Diethyl Acetal***; ***Pyruvaldehyde Diethyl Acetal***.

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Ethyl Trichloroacetate

CCl_3CO_2R

(R = Et)

[515-84-4] · $C_4H_5Cl_3O_2$ · Ethyl Trichloroacetate · (MW 191.44) (R = Me)

[598-99-2] · $C_3H_3Cl_3O_2$ · Methyl Trichloroacetate · (MW 177.41) (R = *i*-Pr)

[3974-99-0] · $C_5H_7Cl_3O_2$ · Isopropyl Trichloroacetate · (MW 205.47) (R = *t*-Bu)

[1860-21-5] · $C_6H_9Cl_3O_2$ · *t*-Butyl Trichloroacetate · (MW 219.50)

(convenient precursor of dichlorocarbene;[1a,2b] generates enolates that react with a number of electrophiles;[14b,19,22] effects addition reactions with alkenes[30,35-37])

Alternate Name: trichloroacetic acid ethyl ester.

Physical Data: R = Et, bp 168 °C, d^{20} 1.3836 g cm^{-3}; R = Me, bp 154 °C, d^{20} 1.4874 g cm^{-3}; R = *i*-Pr, bp 175 °C, d^{20} 1.3034 g cm^{-3}; R = *t*-Bu, bp 55 °C/7 mmHg, d^{20} 1.2363 g cm^{-3}.

Solubility: insol H_2O; miscible with alcohol, ether, benzene.

Form Supplied in: colorless liquid with odor resembling menthol; widely available. Purity 97-99%; typical impurity: CCl_3CO_2H <1%.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$) δ 1.4 (t, 3H, CH_3), 4.4 (q, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 13.7 (q, CH_3), 65.5 (t, CH_2), 90.0 (s, CCl_3), 161.5 (s, CO). IR (CCl_4) 1769 cm^{-1} (C=O).

Handling, Storage, and Precautions: combustible liquid; harmful and irritant. Incompatible with strong oxidizing agents and strong bases. Avoid prolonged or repeated exposure and contact with eyes, skin, and clothing. Keep tightly closed and store in a cool dry place. Use in a fume hood.

Carbene Precursor.[1a,2b]

The reaction of trichloroacetic acid esters with alkali metal alkoxides (RONa or ROK) generates dichlorocarbene (eq 1), which affords *gem*-dichlorocyclopropane adducts by cycloaddition reaction with various kinds of double bonds.

$$Cl_3CCO_2R + R'OM \longrightarrow R'OCO_2R + MCl + Cl_2C: \quad (1)$$

The alkyl trichloroacetate can be methyl, ethyl, or *t*-butyl[1b] and the alkoxide can be MeONa, EtONa,[1a] *n*-BuONa,[5b] or *t*-BuOK;[1b] the most usual combination is CCl_3CO_2Et and MeONa.[2b,7b] The best results are obtained by the use of excess (1.1 to 5 equiv) of both CCl_3CO_2Et and MeONa components in a nonpolar solvent with cooling. Reaction with the double bonds[1] of alkenes leads to *gem*-dichlorocyclopropane adducts in good yield (eq 2).[1a]

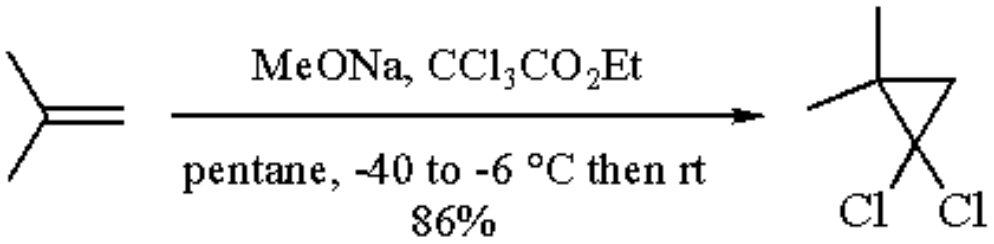

(2)

Such cyclopropanation is also realized with enol ethers[2] (eq 3)[2b] and enol thioethers.[3] The yields of adducts obtained with this carbene procedure are generally higher than those obtained by other methods: ($CHCl_3$, *t*-BuOK),[4] (CCl_3CO_2Na, pyrolysis),[5] and (*n*-BuLi, $CBrCl_3$).[6]

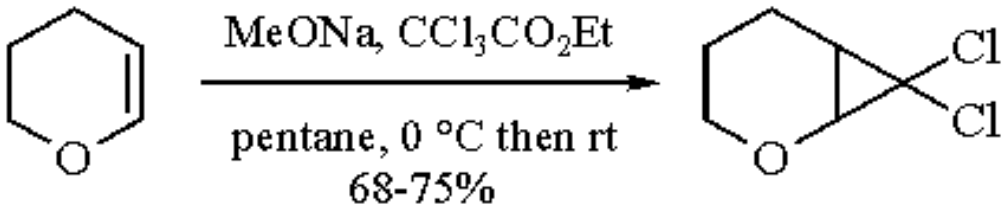

(3)

This carbene procedure has also been applied to the preparation of cyclic allylic and vinylic dichloro derivatives by ring enlargement from polycyclic alkenic compounds (eq 4).[7] The initially formed dichloro adduct rearranges spontaneously[7b-d] or by solvolysis in the presence of silver salts[7a] to provide dichloro compounds by ring expansion. In the norbornene series, such one-carbon-atom expansion leads to derivatives (**1**)-(**5**)[7b-d] in better yields than other methods of generating dichlorocarbene: ($CHCl_3$, *t*-BuOK),[8] (CCl_3CO_2Na, pyrolysis),[5] (CCl_3HgPh, pyrolysis),[9] and ($CHCl_3$, NaOH).[10]

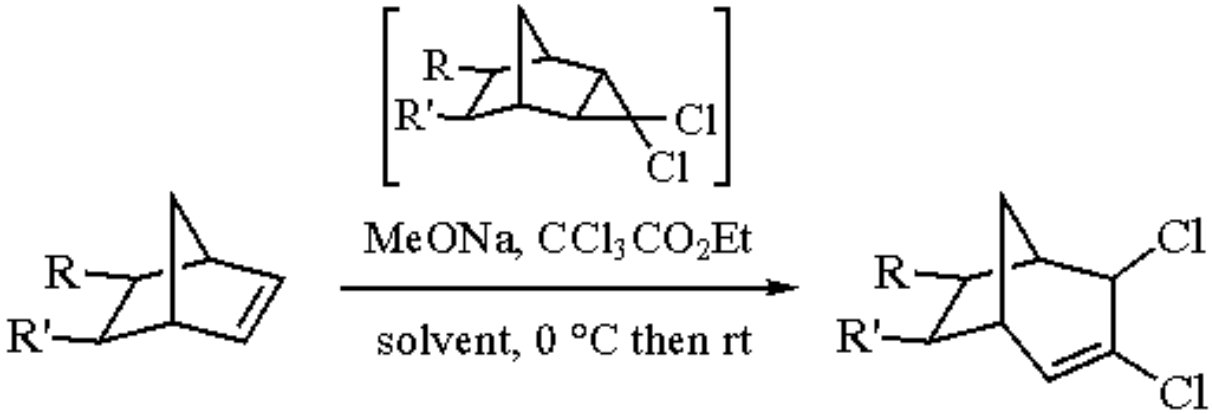

(4)

pet. ether **(1)** 74-88%,[7b] 4-45%[5,8,9]

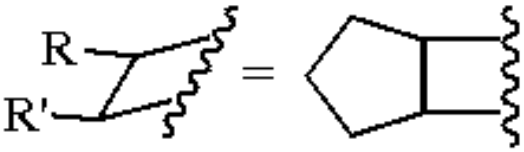

exo pet. ether **(2)** 50%[7c]

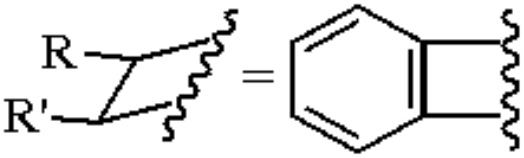

hexane **(3)** 96%[7d]

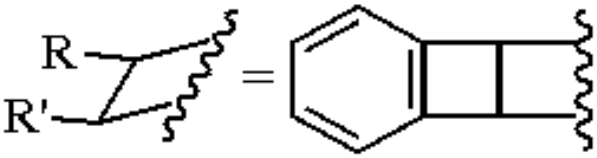

endo hexane **(4)** 97%, [7e] 50%[10]

exo hexane **(5)** 91%, [7e] 65%[10]

The mild reaction conditions further allow access, albeit in moderate yields, to *gem*-dichloro adducts that are difficult to obtain by other routes. Reactive substrates such as allenes,[11] unstable divinyl ethers[12] that undergo polymerization with other methods, or highly strained polycyclic compounds such as bicyclo[3.2.0]hept-1(5)-ene[13] give dichloro adducts (16-40%) by treatment with this reagent system.

Enolate Precursor.

gem-Dichloroenolates are generated from CCl_3CO_2Et by C-Cl bond cleavage. The lithium enolate[14] prepared by reaction of Me_2NLi (generated from ***Lithium*** metal solution in HMPA/THF) with CCl_3CO_2Et at -78 °C, reacts with electrophiles (H_2O, allyl halides, α-chloroalkyl ethers, aldehydes) to give moderate yields of α,α-dichloroacetate derivatives (E-CCl_2CO_2Et, 35-50%) by two-carbon homologation. Reformatsky-type reactions[15] proceeding via magnesium *gem*-dichloroenolates lead to reduced β-hydroxy esters from aldehydes and ketones (eq 5), albeit with little preparative value.

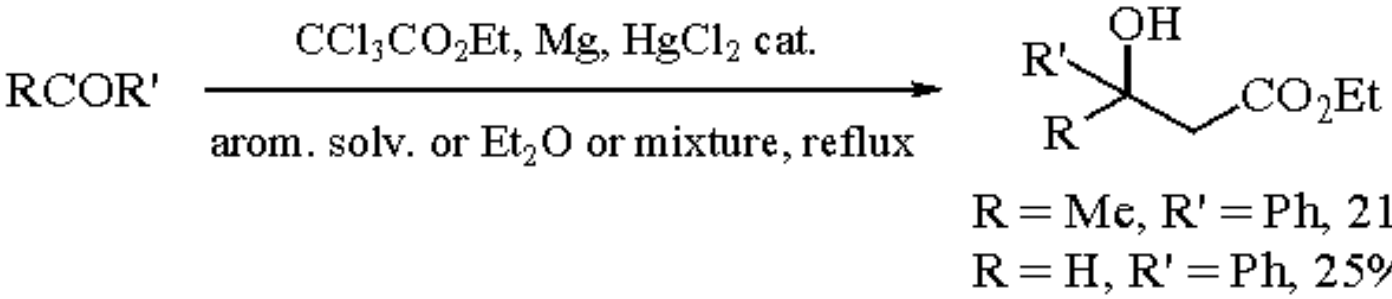

(5)

Better yields (42-79%) of nonreduced compounds can be obtained[14b,16] by preparing Mg enolates by halogen-metal exchange from *i*-PrMgCl and CCl_3CO_2Et in THF, at low temperature. Subsequent reaction of these enolates with various electrophiles (H_2O, aldehydes, ketones, carboxylic anhydrides, alkyl halides, and α-halo ethers) affords nonreduced adducts (eq 6).

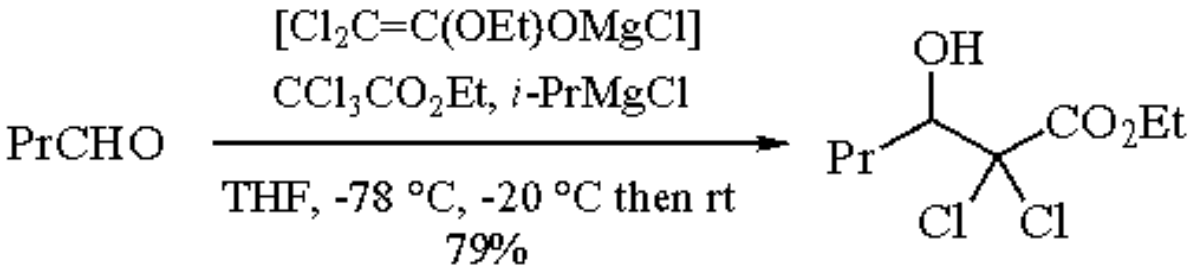

(6)

Reactions of D-glyceraldehyde[17a] and Boc-L-leucinal[17b] with the Mg enolates of methyl and isopropyl trichloroacetates (generated either by exchange with *i*-PrMgCl or by treatment of a phosphonium enolate (see below, eq 11) with $MgCl_2$) in THF at low temperature provide the corresponding α,α-dichloro-β-hydroxy alkyl esters (70% and 50%). The ratios of diastereoisomers are 70:30 for (3*R*,4*R*):(3*R*,4*S*) and (3*R*,4*S*):(3*S*,4*S*) respectively. By the same route, steroidal ketones lead to rearranged β-chloro-α-keto esters.[18]

The zinc dichloroacetate enolate (also called Reformatsky reagent) is prepared prior to use by reaction of CCl_3CO_2Et with ***Zinc*** metal in THF and it reacts with the same substrates as the Grignard reagent with comparable yields (22-81%) (eq 7).[19]

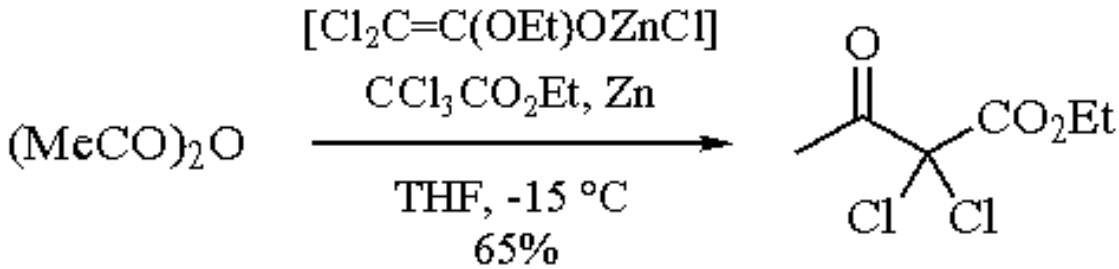

(7)

In the presence of a Lewis acid such as ***Diethylaluminum Chloride***,[20] the Zn enolate reacts with carbonyl compounds to give α-chloro-α,β-unsaturated esters by Knoevenagel-type reaction (51-91%, *Z* > *E*). A dimetalated species such as ClZnC(Cl)=C(OZnX)OEt is the assumed intermediate in this reaction, which constitutes an alternative to the Emmons-Wadsworth-Horner reaction.[21] This procedure has found use in the steroid field for the efficient preparation of α-chloro-α,β-unsaturated esters from ketones, with a two-carbon-chain extension (eq 8).[20b]

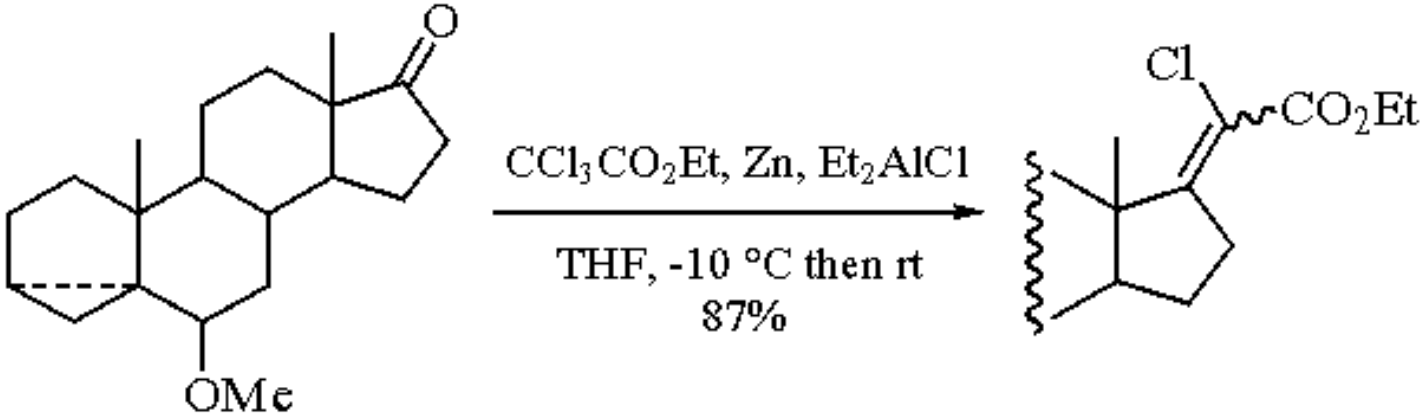

(8)

A phosphonium *gem*-dichloroenolate,[22,23] generated in situ by reaction of TDAP (trisdimethylaminophosphine) with CCl_3CO_2Et at low temperature, reacts with carbonyl compounds to give rise, depending on the stoichiometry and the nature of both solvent and substrate, either to α-chloroglycidic esters (eq 9)[22a,b] or to α-chloro-α,β-unsaturated esters (eq 10).[22c]

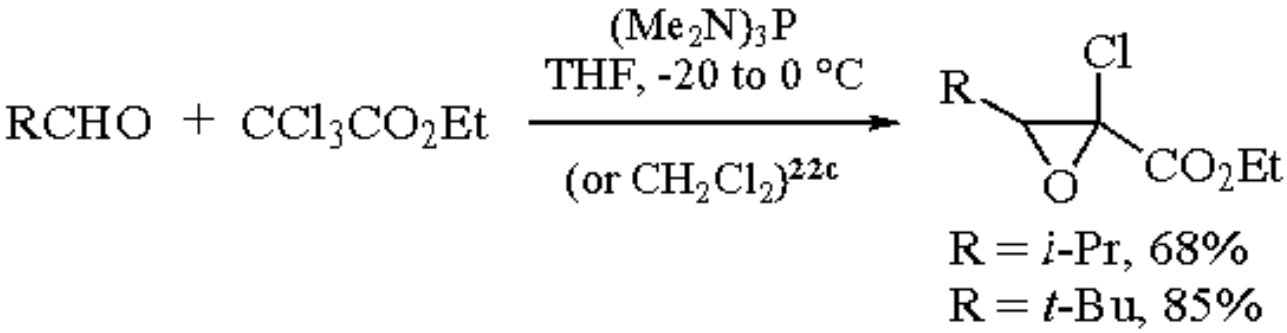

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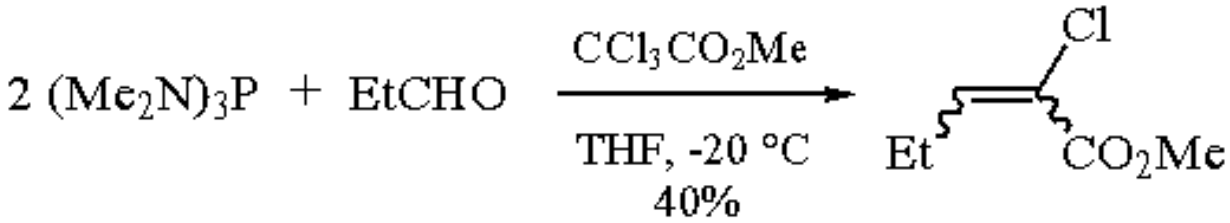

(10)

Depending upon both substrate reactivity and reaction conditions, mixtures[22b] of α-chloroglycidic and α-chloro-α,β-unsaturated esters could be formed, arising from path 1 or path 2 (eq 11). Glycidic esters derived from ketones very often undergo isomerization to β-chloro-α-ketoesters.[18,22a,b]

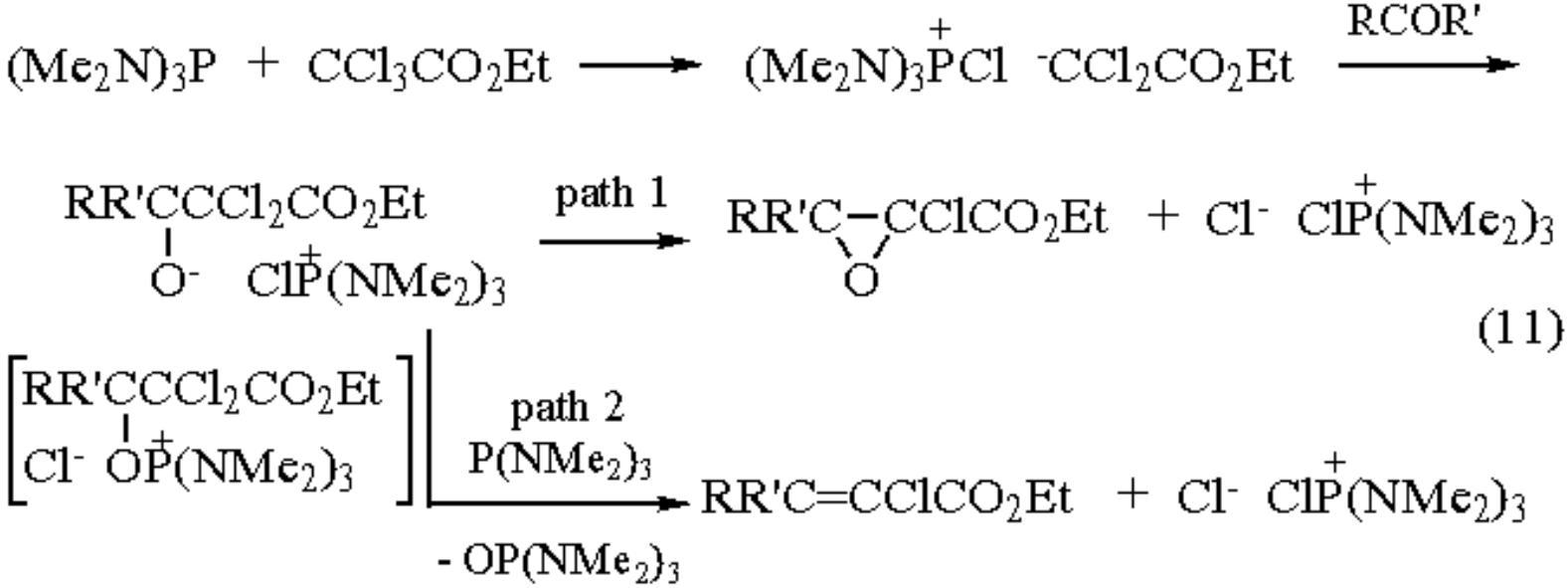

Methyl and isopropyl trichloroacetates have also been used[22b,c] for such transformations. Because of the different reactivity of the phosphine, the Ph_3P-CCl_3CO_2Me reagent system converts aromatic aldehydes into methyl α-chlorovinyl esters in good yields (60-74%, *E* > *Z*). Unlike $(Me_2N)_3P$ (path 2, eq 11), this reaction proceeds via the stabilized ylide, $Ph_3P{=}CClCO_2Me$.[24]

In a special case,[25] with $(Me_2N)_2P(OMe)$ as the P^{III} compound, the alkyl moiety of the phosphite part reacts with the initially formed enolate to provide a product with one-carbon extension instead of the expected phosphate from a Perkow reaction (eq 12).[26]

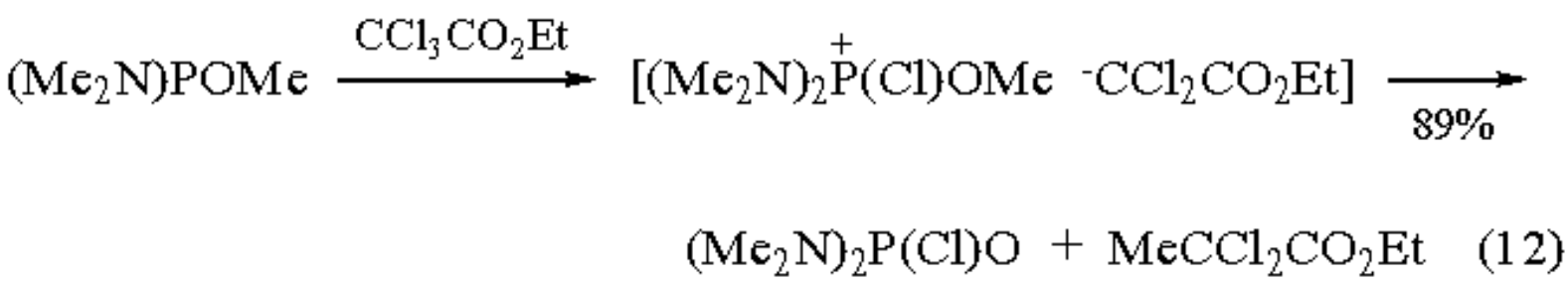

The ethyl dichloroacetate anion, cathodically generated[27] from CCl_3CO_2Et, adds to cyclic ketones.[27a] Rearrangement of the initially formed dichloro alkoxide affords α-chloro-β-keto esters with one-carbon ring expansion or the corresponding dehydrochlorinated ester (7-43%). Cycloaddition of such species with double bonds[27b] gives ethyl α-chlorocyclopropanecarboxylate (25-55%), expressing carbenoid properties.

Addition Reactions.

Double bonds undergo radical addition reactions with CCl_3CO_2Et (and other trichloroacetate esters) in the presence of various catalysts such as organic peroxides, UV irradiation, a redox system of copper salts, metal carbonyls, ruthenium salts-phosphine complexes, and palladium salts (eq 13).

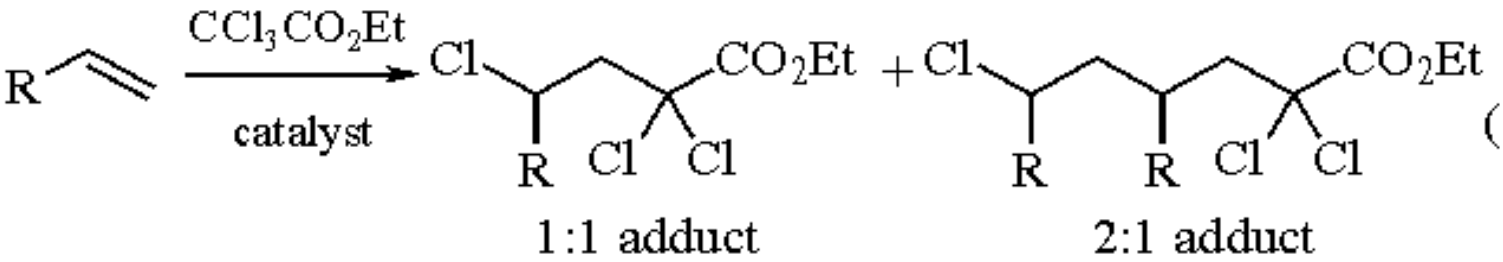

(13)

On prolonged heating in the presence of $(PhCO)_2O$, CCl_3CO_2Et adds to 1-alkenes to give ethyl 2-alkyl-2,2,4-trichloroacetates with two-carbon chain elongation from the starting alkene. Thus ethyl 2,2,4-trichlorononanoate is obtained from 1-heptene after 20 h under reflux in ~50% yield (purified) as a mixture with the 2:1 adduct.[28] This method affords mainly telomers of high molecular weight with vinyl monomers and only a low yield of the 1:1 adduct with other reactive alkenes such as styrene.[36]

The parent ester CBr_3CO_2Et adds readily in a 1,4-manner to 1,3-butadiene. This reaction is induced by UV irradiation and provides the 1:1 adduct quantitatively[29] (compare with eq 15). The use of copper salts as catalysts directs the reaction mainly towards the formation of the 1:1 adduct, but the yields of products still remain moderate (30-65%) (eq 14).[30]

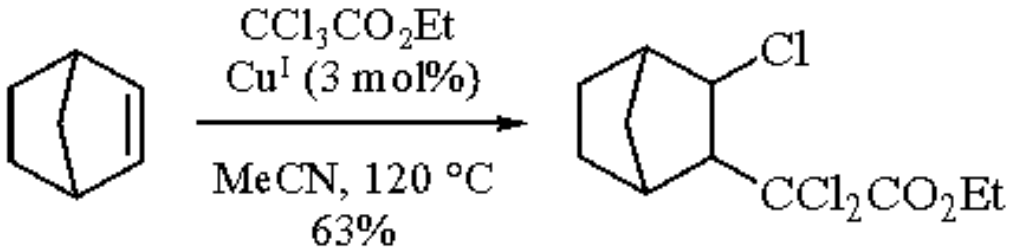

(14)

Telomerization, especially for 2:1 adduct formation from CCl_3CO_2Me and acrylic monomers with copper complex catalysis, has been studied.[31] The 1,4-addition reaction with 1,3-butadiene works well by redox catalysis with copper salts[32] (eq 15).[32b] The catalytic systems used make it possible to completely suppress polymer and telomer formation and to obtain the 1:1 adduct with good 1,4-selectivity, depending on the type of ligand on the copper complexes.

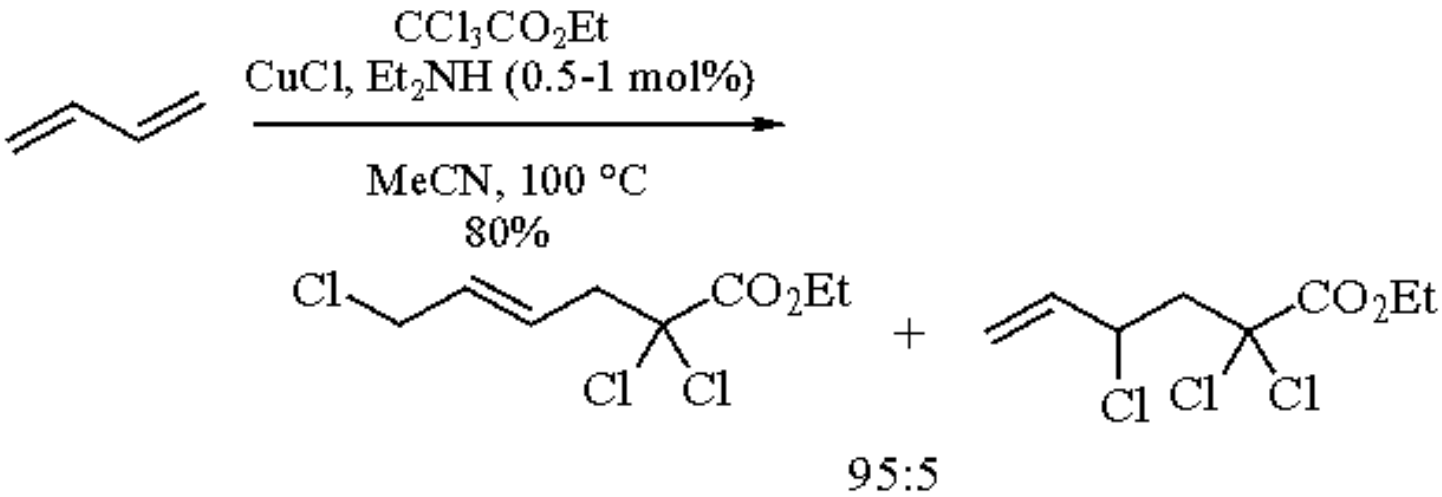

(15)

Microwave irradiation effects a 20-fold increase in rate in the reaction of CCl_3CO_2Et with styrene catalyzed by a CuCl/*i*-$PrNH_2$ complex (>90%, 15-40 min).[33] Under those conditions, but without microwave activation, the 1:1

adduct is formed exclusively with deactivated chloroethylenes (eq 16) and even with easily polymerizable alkenes such as styrenes.[34]

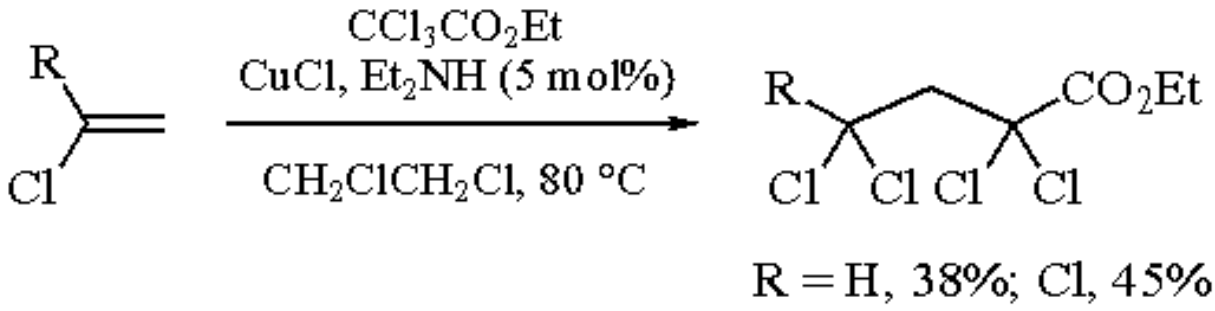

(16)

Reaction of CCl_3CO_2Me with 1-alkenes catalyzed by dinuclear metal carbonyls[35] ($Co_2(CO)_8$, $[CpMo(CO)_3]_2$, and $[CpFe(CO)_2]_2$) provides different results, depending on the catalyst nature. The Co catalyst gives methyl 4-alkyl-2,2,4-trichlorobutyrate (eq 17), while 4-alkyl-2,2-dichloro-γ-butyrolactone is the main product with the Mo (eq 18) and Fe catalysts. With benzene as the solvent the dichloro lactone (R = H, R´ = Me) is obtained almost exclusively.

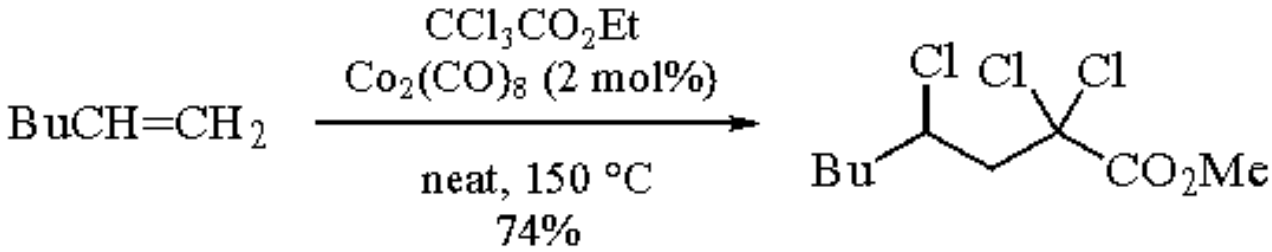

(17)

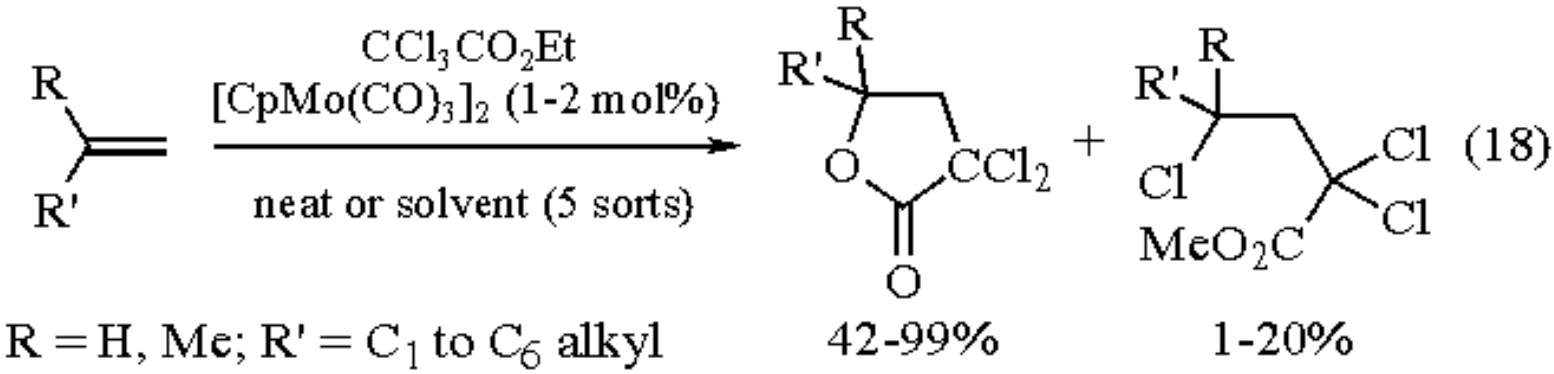

(18)

In the presence of ***Dichlorotris(triphenylphosphine)ruthenium(II)*** the reaction of CCl_3CO_2Et (or CO_2Me) with 1-alkenes leads to the formation of ethyl 2,2,4-trichloroalkanoates (eq 19)[36] in good yields, even with easily polymerizable alkenes such as styrene, acrylonitrile, methyl vinyl ketone, and methyl methacrylate.

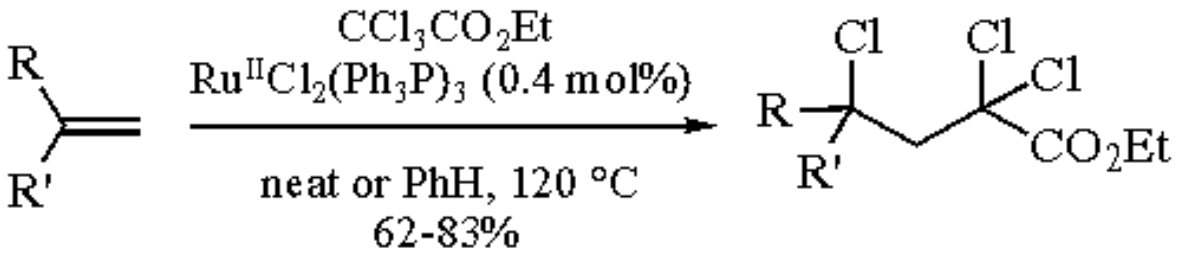

(19)

R = H, Me; R' = hexyl, phenyl, CN, Ac, CO_2Me

With CCl_3CO_2Me, 1-decene, and $Pd(OAc)_2$-Ph_3P as catalyst in the presence of base (AcONa or K_2CO_3) the addition reaction proceeds under milder conditions to afford the 1:1 adduct in good yield (eq 20). Unlike the reactions with previous catalysts, this reaction proceeds even at room temperature.[37]

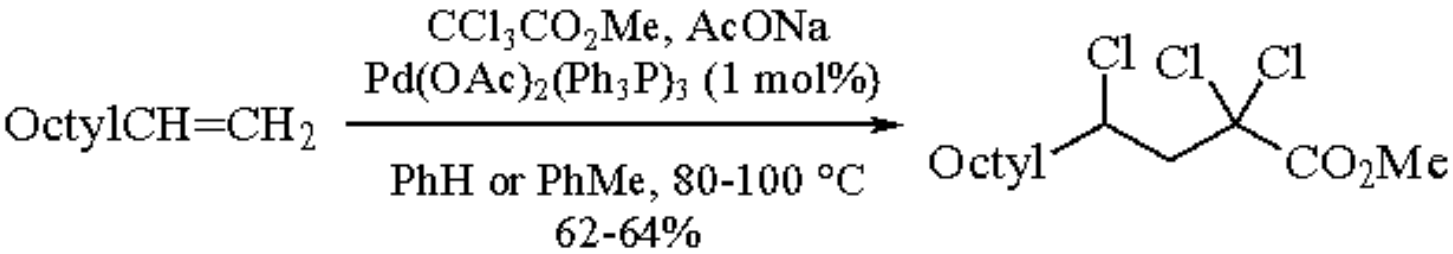

(20)

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Ethyl Trimethylsilylacetate[1]

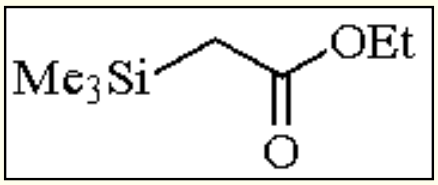

[4071-88-9] · $C_7H_{16}O_2Si$ · Ethyl Trimethylsilylacetate · (MW 160.29)

(silylating agent;[2] source of an ethyl acetate anion equivalent[3])

Alternate Name: ETSA.

Physical Data: bp 157-158 °C; *d* 0.876 g cm^{-3}.

Solubility: sol ethereal and chlorinated solvents; reacts with protic solvents.

Form Supplied in: liquid (>98%); commercially available.

Preparative Methods: available by a Reformatsky reaction from ethyl bromoacetate,[4] and by reaction of ***Trimethylsilylmethylmagnesium Chloride*** with ***Ethyl Chloroformate***.[5] An alternative approach requires the treatment of ethyl acetate with triphenylmethylsodium followed by ***Chlorotrimethylsilane***.[6] The use of a nitrogen base with ethyl acetate in THF followed by reaction with chlorotrimethylsilane results in a mixture of *C*- and *O*-silylation. The use of HMPA as additive in the reaction medium increases the amount of *O*-silylation to 90%.[7] Similar methods can be used to prepare analogs.

Handling, Storage, and Precautions: reacts with protic solvents to give the desilylated product.

Ethyl trimethylsilylacetate (**1**) is reactive to nucleophiles and readily undergoes desilylation reactions with acid or alkali, ethanol, and bromine (eq 1).[5,8]

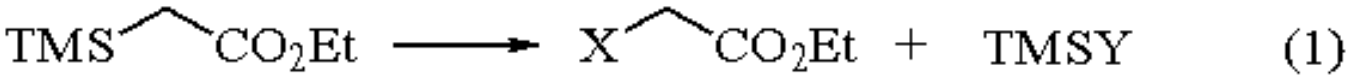

(1)

H_3O^+	X = H	Y = OTMS
HO^-	= H	= OTMS
HCl	= H	= Cl
Br_2	= Br	= Br
EtOH	= H	= OEt

Silylation Reactions.

In the presence of a catalytic amount of ***Tetra-n-butylammonium Fluoride*** (TBAF), ester (**1**) is a very efficient silylating agent for a wide variety of substrates including carbonyl compounds, alcohols, phenols, carboxylic acids, and alkynes.[2,9] With unsymmetrical ketones the kinetic enol ether is the preferred product.[2,10] Indeed, the use of (**1**) can provide superior selectivity to the use of hindered bases for enolate formation.[11] This is illustrated with a β,γ-epoxy ester which provides an entry to γ-keto-α,β-unsaturated esters (eq 2).[12] These silylation reactions of (**1**) can also be catalyzed by TBAF supported on silica.[13]

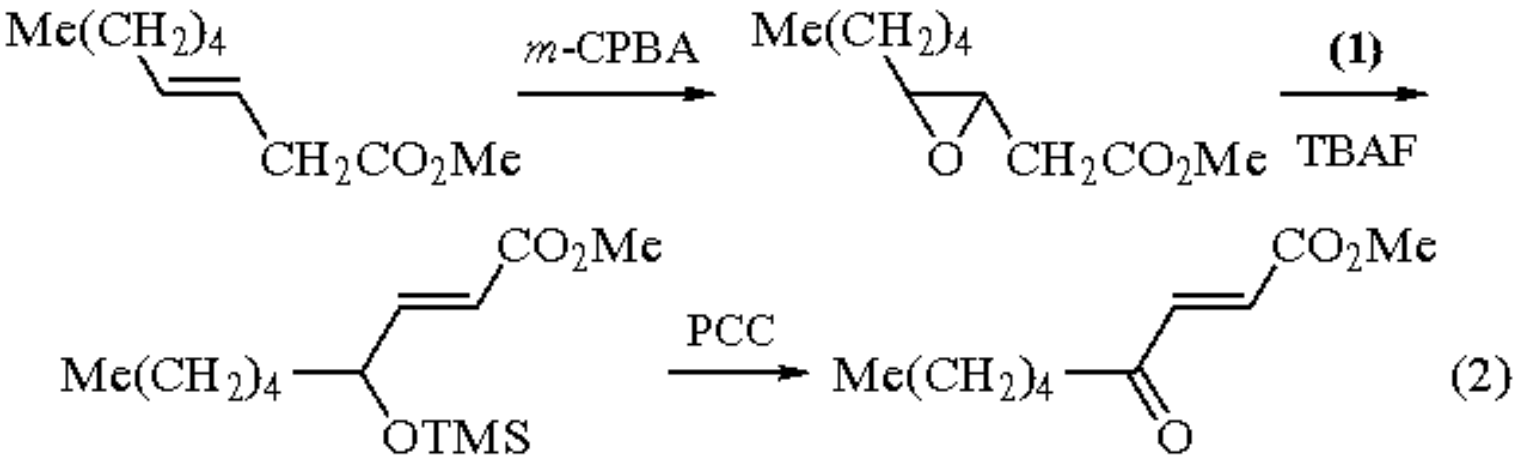

Alkylation Reactions.

The use of fluoride ion or a base catalyst allows reaction of the silyl ester (**1**) with electrophilic substrates (eq 3). Some of these reactions are similar to those of the ester enolate derived from ethyl acetate.[3,14,15]

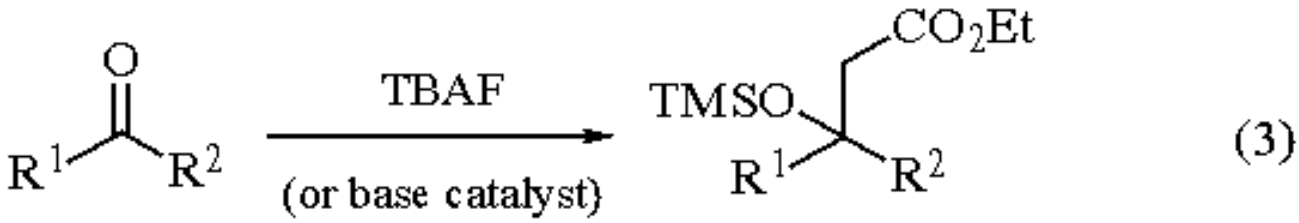

With conjugated enones a carbon-carbon bond is formed by a Michael addition with concomitant formation of the proximal silyl enol ether (eq 4).[16] In the presence of a Lewis acid, (**1**) undergoes conjugate additions with α,β-unsaturated carbonyl compounds (eq 5).[17]

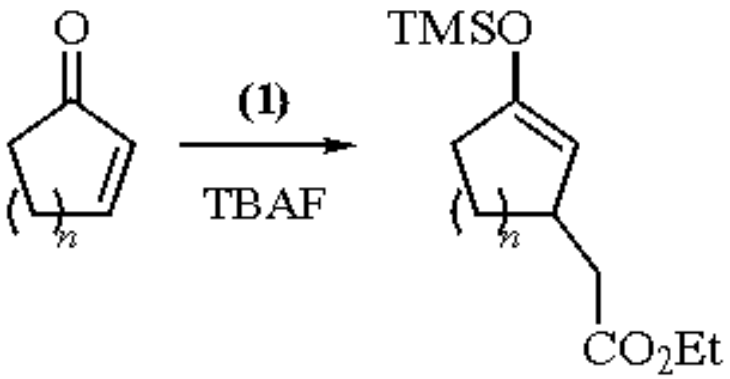

(4)

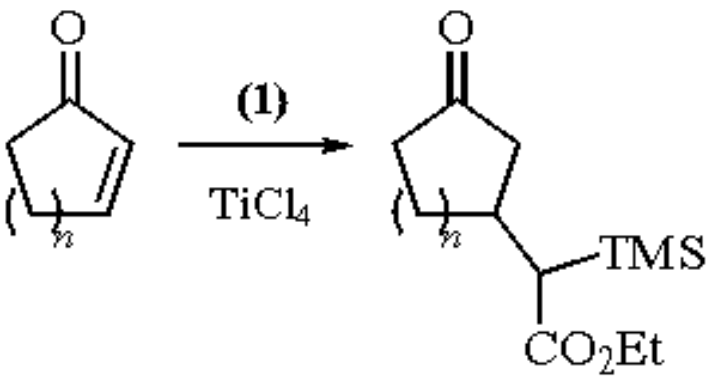

(5)

Nitroaromatic compounds react with (**1**) in the presence of ***Potassium Fluoride*** to provide an anionic σ-complex.[18] Subsequent oxidation with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** then provides ethyl arylacetates.[19] With an areneiron(I) complex, the alkylcarbonyl substituent from (**1**) is introduced on to the ring.[20]

Electrophilic Reactions.

Silylacetate (**1**) reacts with 2 equiv of a Grignard reagent to provide 1,1-disubstituted alkenes in good to excellent yield (eq 6), but this synthesis is limited to Grignard reagents that are not sterically demanding.[21]

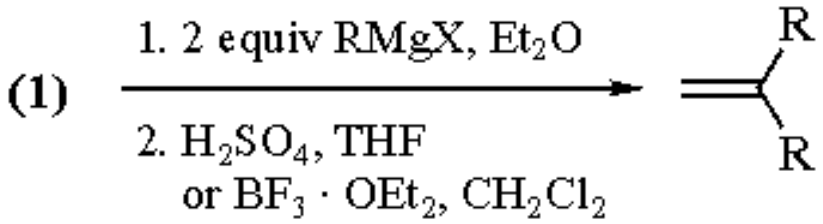

(6)

Analogs.

The methyl ester (**2**) undergoes similar reactions to the ethyl ester (**1**),[22] as do various silyl analogs.[23] These reactions

also include silylations with methyl trimethylsilylacetate in the presence of fluoride ion.[24,25]

Reaction of the lithium enolate of (**1**) followed by reaction with chlorotrimethylsilane provides ketene acetal (**3**). This enol reacts with aldehydes in the presence of a Lewis acid to provide (*Z*)-α,β-unsaturated esters (eq 7).[26] With conjugated enones, (**3**) undergoes conjugate addition when ***Titanium(IV) Chloride*** is used as catalyst (cf. eq 5).[27]

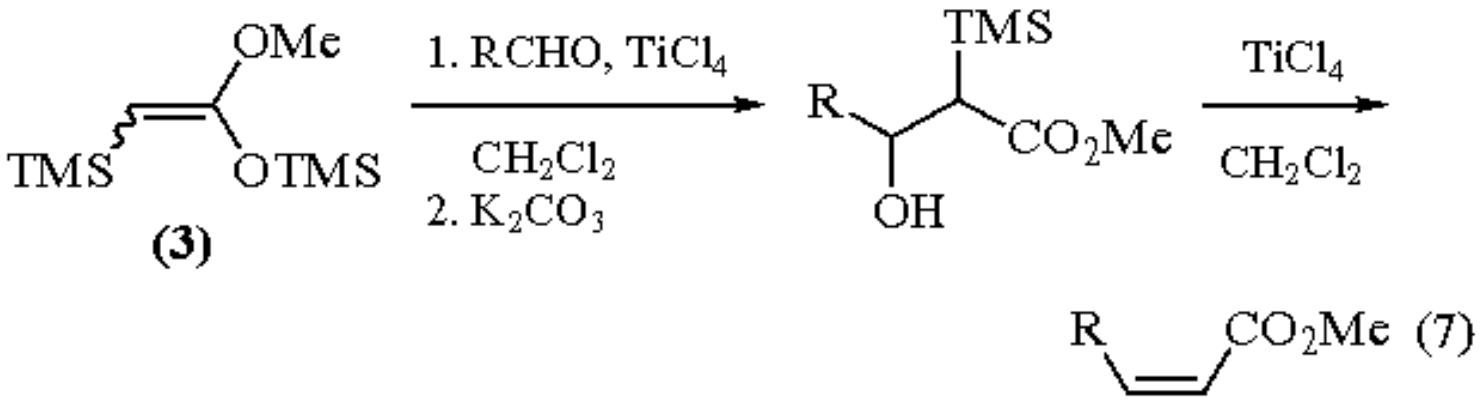

The use of ethyl diphenylmethylsilylacetate (**4**; R^1 = H) provides for some alternative methodology as the larger silyl group allows for the selective addition of only 1 equiv of Grignard reagent to afford the β-silyl ketone (eq 8).[28] The chemistry can also be extended to other carboxylic acid analogs. A number of approaches are then available for the preparation of ketones.[22,29,30]

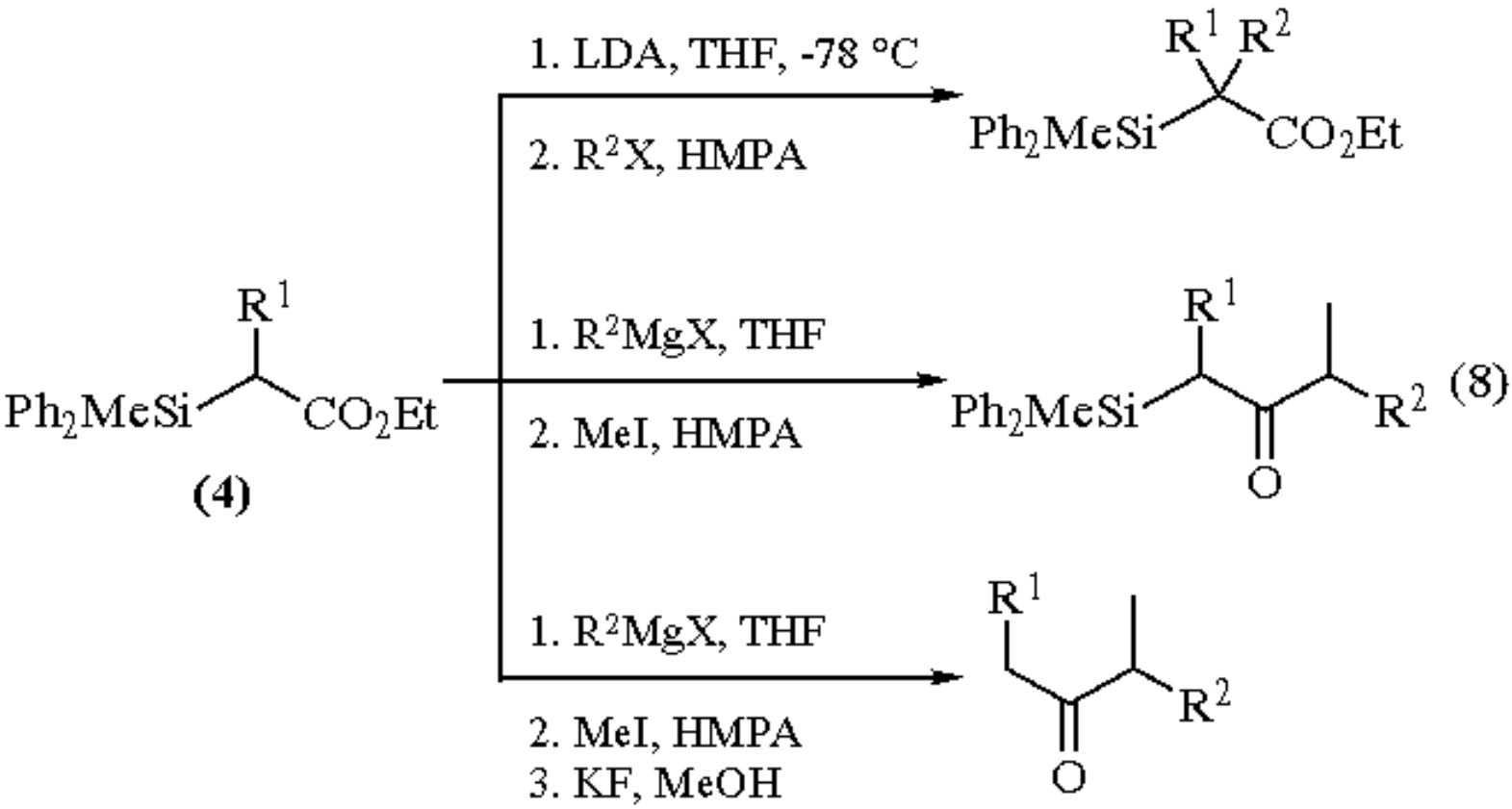

In addition to these enolate reactions, β-silyl ketones can be thermally isomerized to silyl enol ethers by a regioselective rearrangement (eq 9),[22,31] or treated with another Grignard reagent to provide alkenes through Peterson

alkenation reactions.[32]

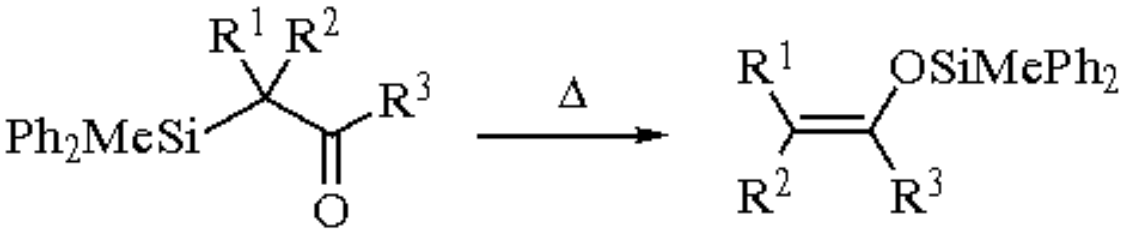

(9)

Many of the reactions of ethyl trimethylsilylacetate and its analogues involve the ester enolate; these are discussed in ***Ethyl Lithio(trimethylsilyl)acetate***.

Related Reagents.

t-Butyl α-Lithiobis(trimethylsilyl)acetate; ***t-Butyl Trimethylsilylacetate***; ***Dilithioacetate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; Methyl (Methyldiphenylsilyl)acetate; ***Trimethylsilylacetic Acid***.

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Ethyl Trimethylsilyl Malonate[1-3]

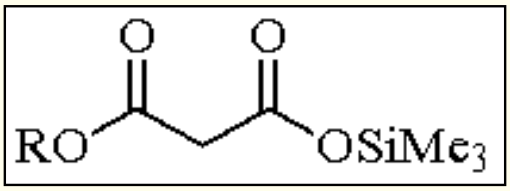

(R = Et)

[18457-03-9] · $C_8H_{16}O_4Si$ · Ethyl Trimethylsilyl Malonate · (MW 204.30) (R = Me)

[51849-23-1] · $C_7H_{14}O_4Si$ · Methyl Trimethylsilyl Malonate · (MW 190.27)

(synthesis of β-keto esters[1-3])

Physical Data: R = Et, bp 75 °C/0.5 mmHg, *d* 1.000 g cm^{-3}; R = Me, bp 105-110 °C/19 mmHg.

Preparative Methods: ethyl trimethylsilyl malonate is commercially available, or it may be easily prepared from the potassium salt of ***Ethyl Malonate***.[1,2,6] Methyl trimethylsilyl malonate has been prepared from *t*-butyl methyl malonate by treatment with ***Trimethylsilyl Trifluoromethanesulfonate***,[4] or from Meldrum's acid (***2,2-Dimethyl-1,3-dioxane-4,6-dione***) and methyl trimethylsilyl ether.[5] The preparation and use of *t*-butyl trimethylsilyl malonate has been reported, although it has not been isolated and characterized.[7,8]

Handling, Storage, and Precautions: the ethyl derivative is reported to be moisture sensitive.

Ethyl trimethylsilyl malonate is a useful alternative to other malonates in the synthesis of β-keto esters. Trimethylsilyl 2-lithio-2-ethoxycarbonylacetate (**1**) adds smoothly to a variety of acid chlorides to provide intermediates which undergo spontaneous decarboxylation upon aqueous hydrolysis at room temperature. However, since the first report of its preparation and use,[1] it has seen only limited application in organic synthesis. The reagent has been utilized in the synthesis of γ,δ-unsaturated β-keto esters (Nazarov reagents), which are themselves useful annulating agents.[2a] Ethyl trimethylsilyl malonate undergoes deprotonation with ***n-Butyllithium*** at low temperature to provide the lithio derivative (**1**). Treatment with crotonyl chloride furnishes ethyl crotonylacetate (eq 1).

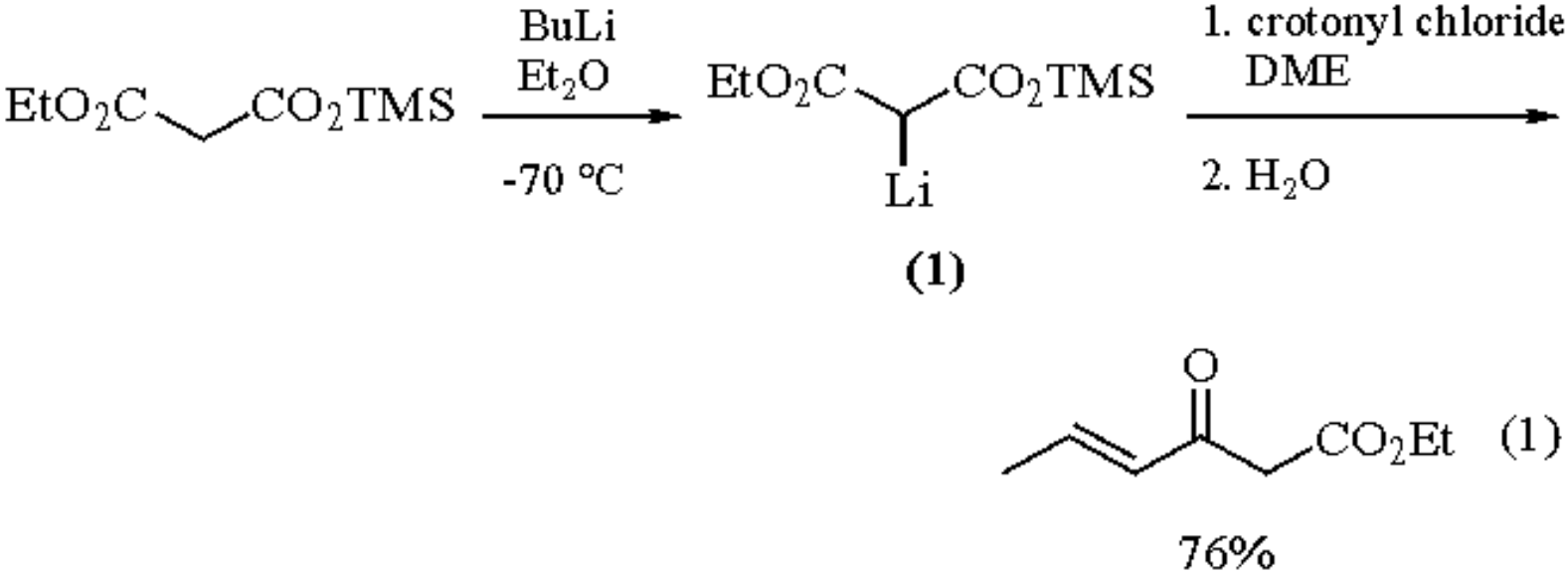

The scope of the reaction has been expanded to provide a general synthesis of β-keto esters. A variety of acid chlorides (alkyl, cycloalkyl, aromatic, and heteroaromatic) undergo the reaction (eq 2).[2b,9] The method is applicable to the preparation of bis-β-keto esters from diacid chlorides (eq 3).[2b]

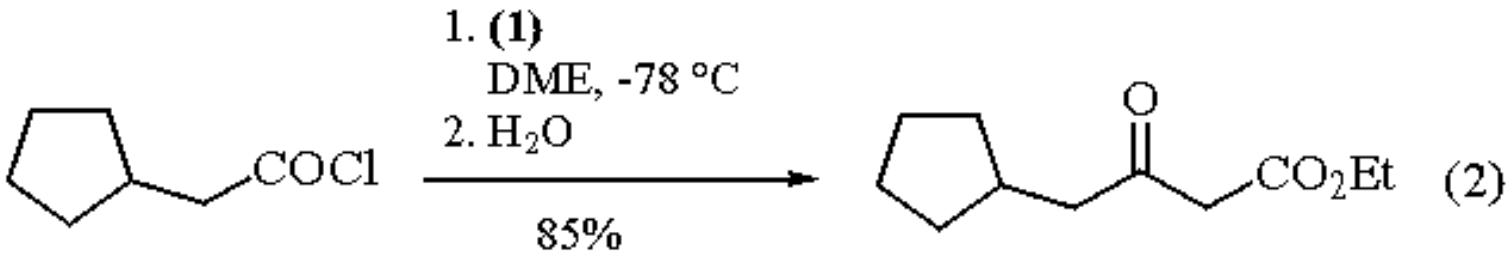

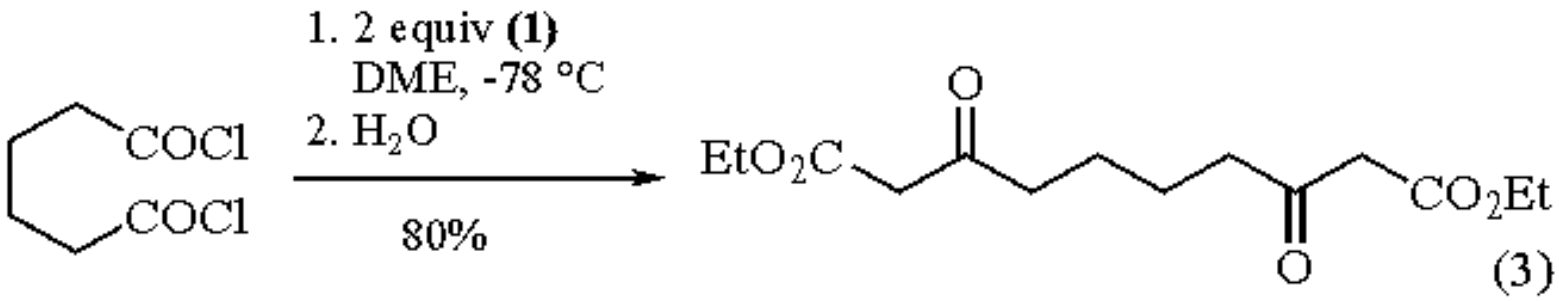

More recently, the mixed anhydride (**2**) has been shown to undergo efficient homologation under these conditions to give keto ester (**3**), a highly functionalized intermediate in the synthesis of members of the acomonine family of diterpene alkaloids (eq 4).[8]

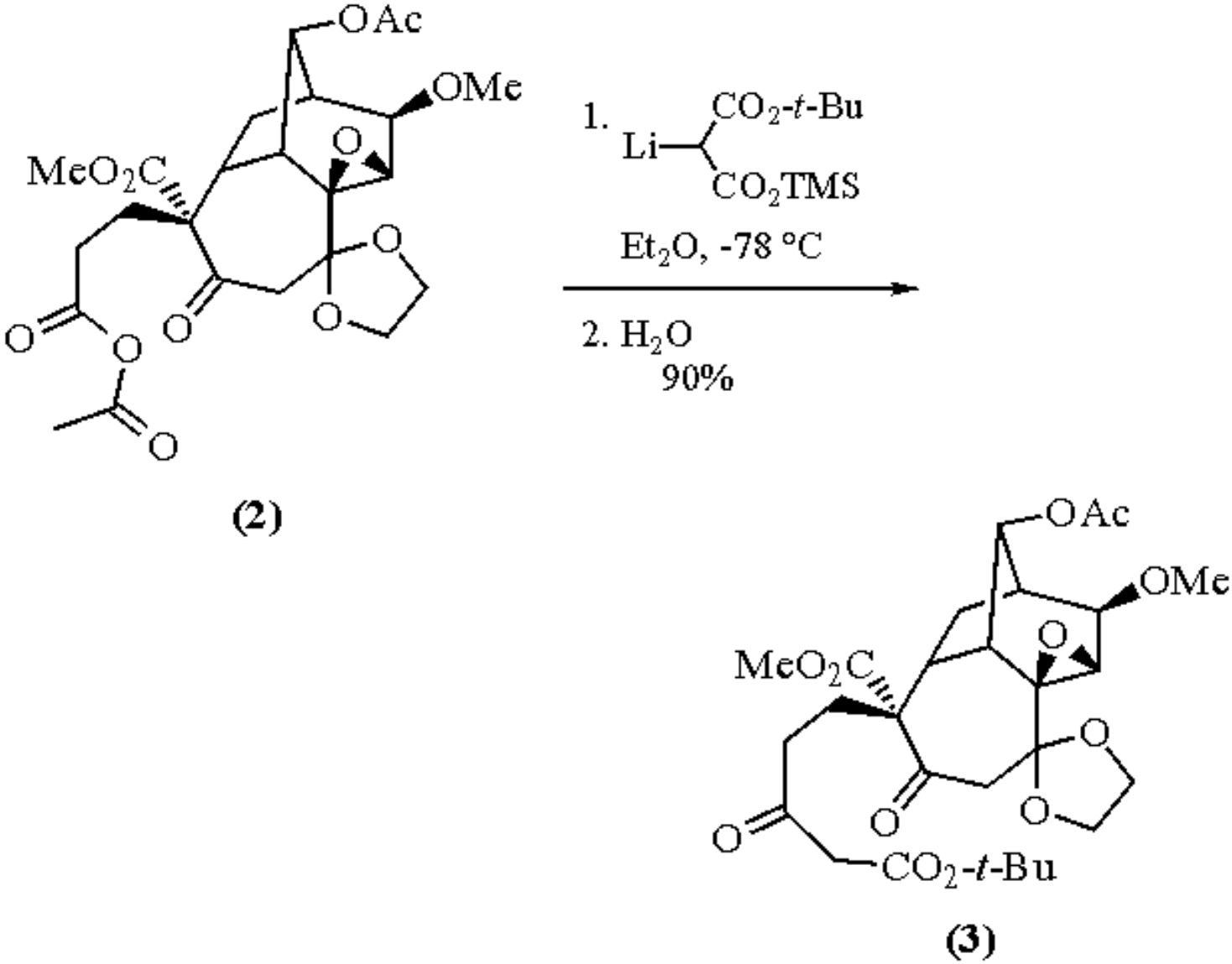

(4)

In the synthesis of corynomycolic acid derivatives,[10] a key β-keto ester intermediate has been prepared from a substituted malonate derivative (eq 5). In this case, higher yields are obtained when ***Lithium Diisopropylamide*** is employed in the deprotonation step instead of *n*-BuLi.

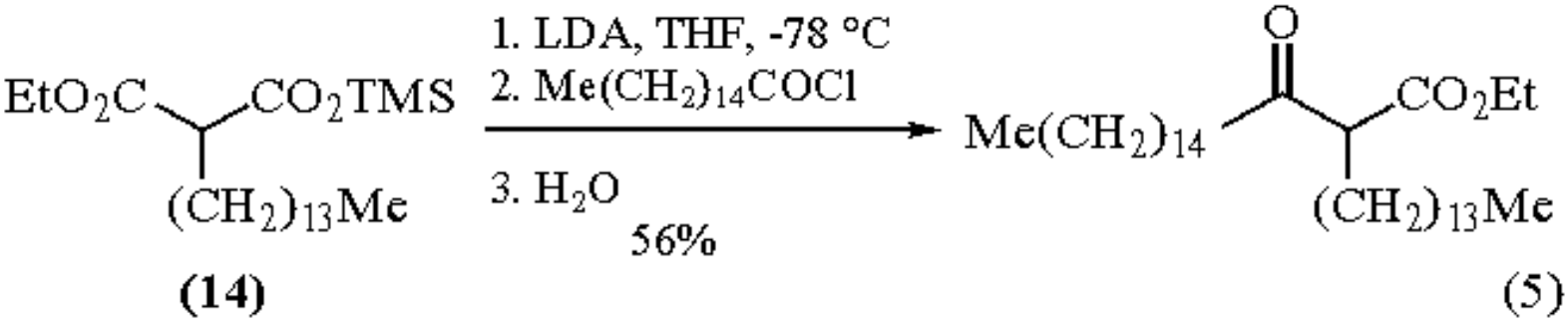

(5)

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Diethyl Ethoxymagnesiomalonate***; ***Diethyl Malonate***; ***Ethyl 3,3-Diethoxyacrylate***; ***Ethyl Malonate***; ***Magnesium Ethyl Malonate***; ***Malonic Acid***; ***Methyl Cyanoformate***.

1. Schmidt, U.; Schwochau, M. *M* **1967**, *98*, 1492.
2. (a) Pichat, L.; Beaucourt, J.-P. *S* **1973**, *537*. (b) Taylor, E. C.; Turchi, I. J. *OPP* **1978**, *10*, 221.
3. For a review of the synthesis of β-keto esters from malonates, see: Pollet, P. L. *J. Chem. Educ.* **1983**, *60*, 244.
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5. Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *TL* **1989**, *30*, 3073.
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7. Cambie, R. C.; Clark, G. R.; Jones, T. C.; Rutledge, P. S.; Strange, G. A.; Woodgate, P. D. *AJC* **1985**, *38*, 745.
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Ethyltriphenylphosphonium Bromide

$Ph_3{+}PEt\ X^-$

(X = Br)

[1530-32-1] · $C_{20}H_{20}BrP$ · Ethyltriphenylphosphonium Bromide · (MW 371.26) (X = Cl)

[896-33-3] · $C_{20}H_{20}ClP$ · Ethyltriphenylphosphonium Chloride · (MW 326.81) (X = I)

[4736-60-1] · $C_{20}H_{20}IP$ · Ethyltriphenylphosphonium Iodide · (MW 418.26)

(generation of the nonstabilized phosphorus ylide ethylidenetriphenylphosphorane for Wittig alkenation reactions[1])

Physical Data: Br, mp 209-210.5 °C;[2] Cl, mp ca. 235 °C (dec); I, mp 164-165 °C.

Form Supplied in: white to off-white solids; 98-99% (bromide; mp 206-208 °C), 98% (chloride), &egt;98% (iodide).

Preparative Methods: involves alkylation of triphenylphosphine with ethyl bromide, chloride, or iodide. The ethyl bromide reaction, performed in benzene at 135 °C in a pressure vessel for 20 h, gives an 89% yield of phosphonium salt (recrystallized from water and dried).[2]

Handling, Storage, and Precautions: may absorb moisture. Store in tightly sealed bottles in a dry place.

Ethylidene Transfer.

The most important synthetic reaction of the title phosphonium salts entails transfer of an ethylidene group, via ethylidenetriphenylphosphorane, to the carbonyl group of aldehydes and ketones in good yields.[1] This nonstabilized phosphorus ylide is prepared in situ by treatment of the phosphonium salt in a suitable dry solvent (e.g. THF, DMSO, toluene, *t*-butanol) with a reasonably strong base (e.g. sodium amide, potassium *t*-butoxide, sodium hydride, butyllithium, sodium hexamethyldisilazide, or dimsylsodium). The choice of base and solvent can significantly impact the yield and stereochemistry of the alkene products.[1,3] With standard aldehydes, the Wittig reaction affords (*Z*)-alkenes preferentially under most conditions. (*E*)-Alkenes are more likely to predominate in an alcohol solvent[3c,h] or by use of a lithium base;[3a,c-f] under lithium salt-free conditions in polar aprotic solvents, (*Z*) stereoselectivity is usually maximized (eqs 1-3).[3a-g]

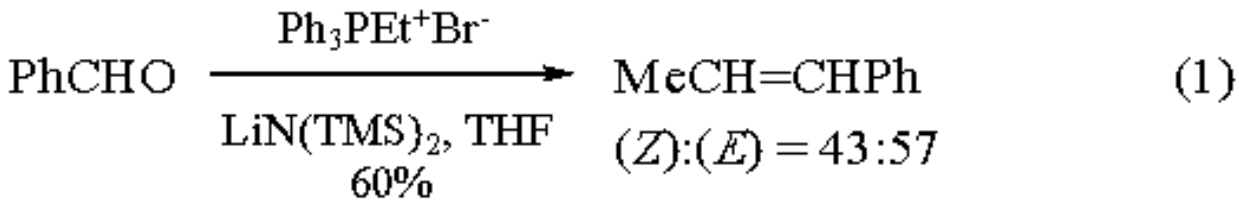

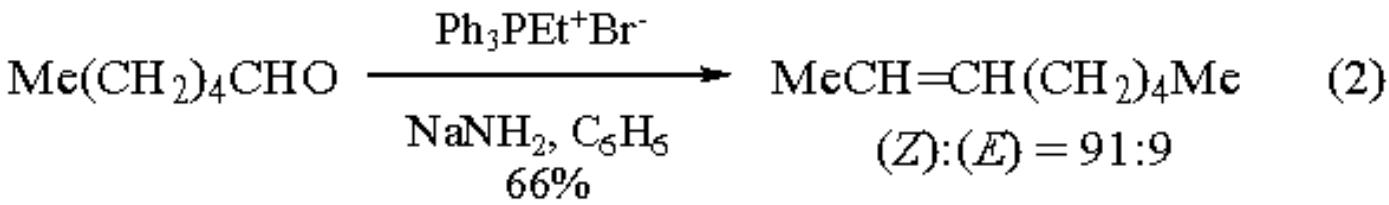

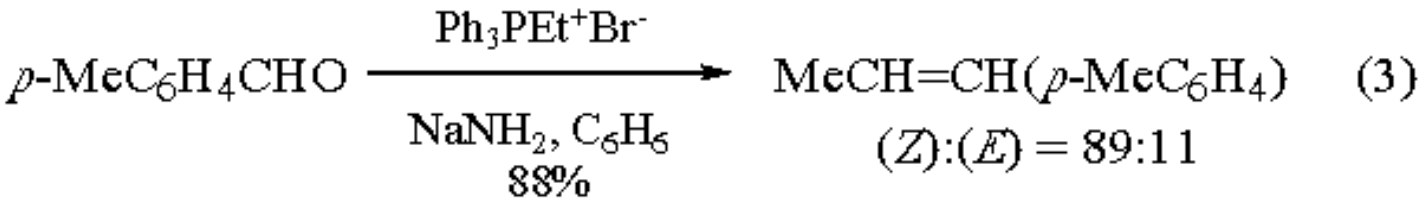

Unsymmetrical ketones with similar substituents on the carbonyl do not furnish good alkene stereoselectivity.[1b,c] When one of the groups is bulkier, such as with *i*-PrCOMe, ethylidenetriphenylphosphorane furnishes a (*Z*)/(*E*) ratio of ca. 9:1 under lithium-salt conditions.[4] The stereochemistry of ketone alkenation with ethylidenetriphenylphosphorane can be strongly influenced by certain substituents in the carbonyl component, especially an α-alkoxy substituent, which enhances (*Z*) stereoselectivity (eqs 4 and 5).[5] An α-amido substituent can also direct (*Z*) stereoselectivity (eq 6).[5e]

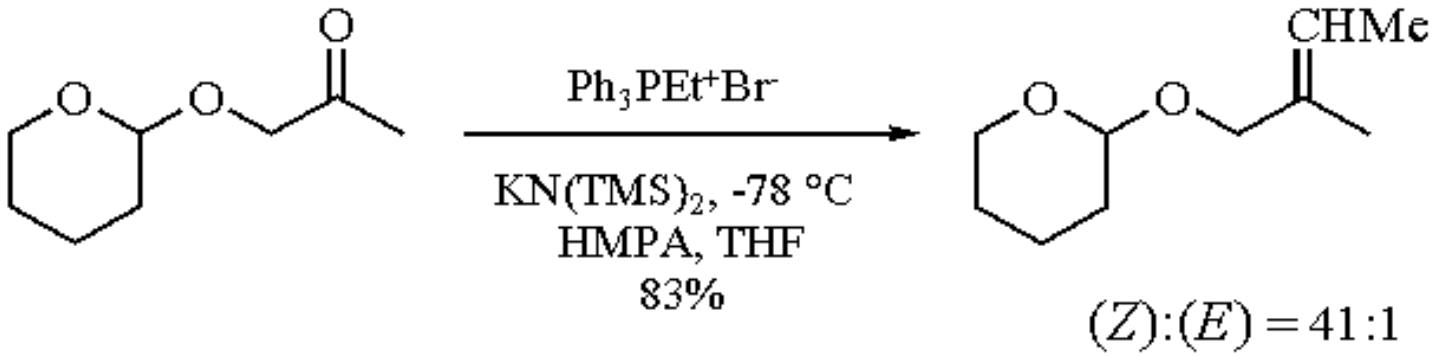

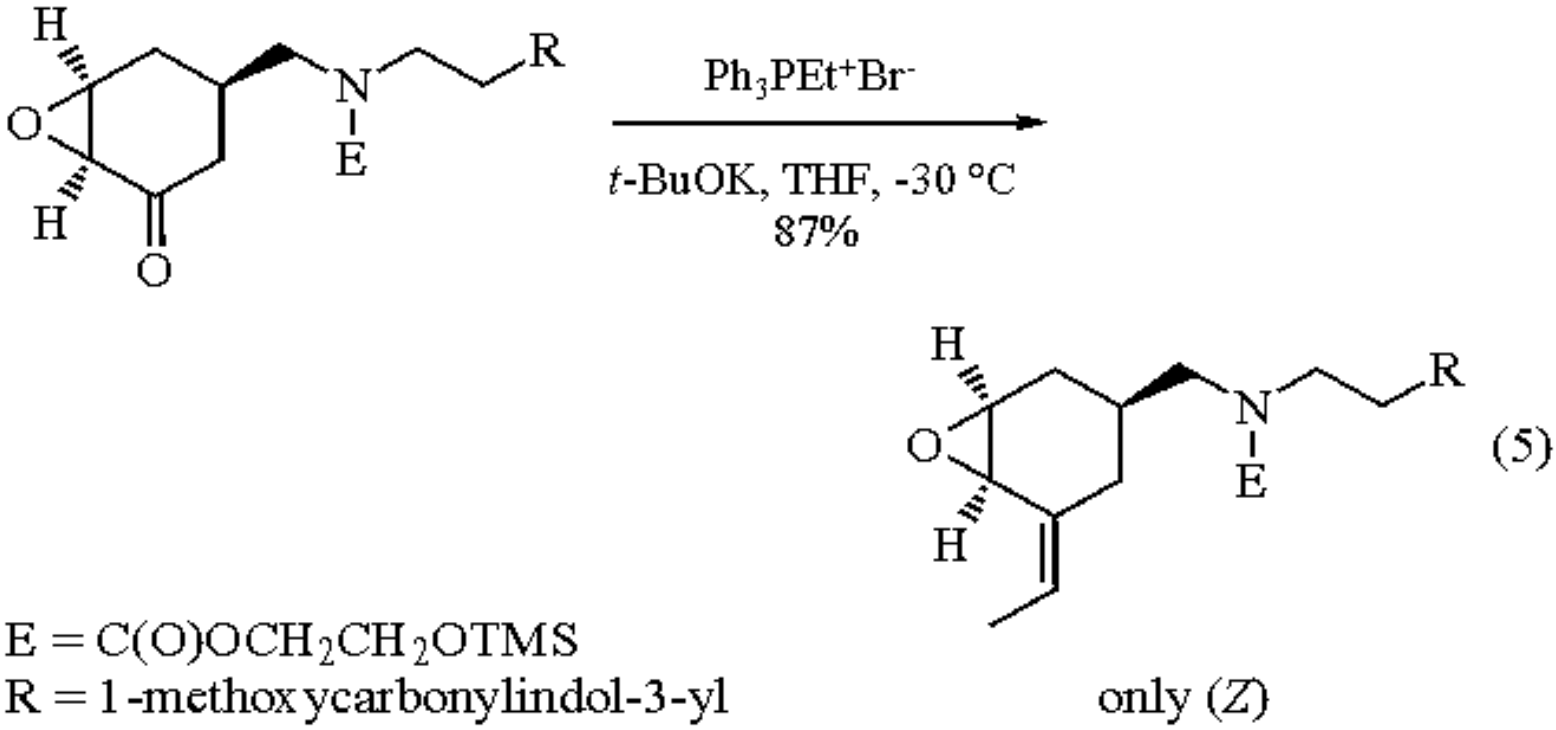

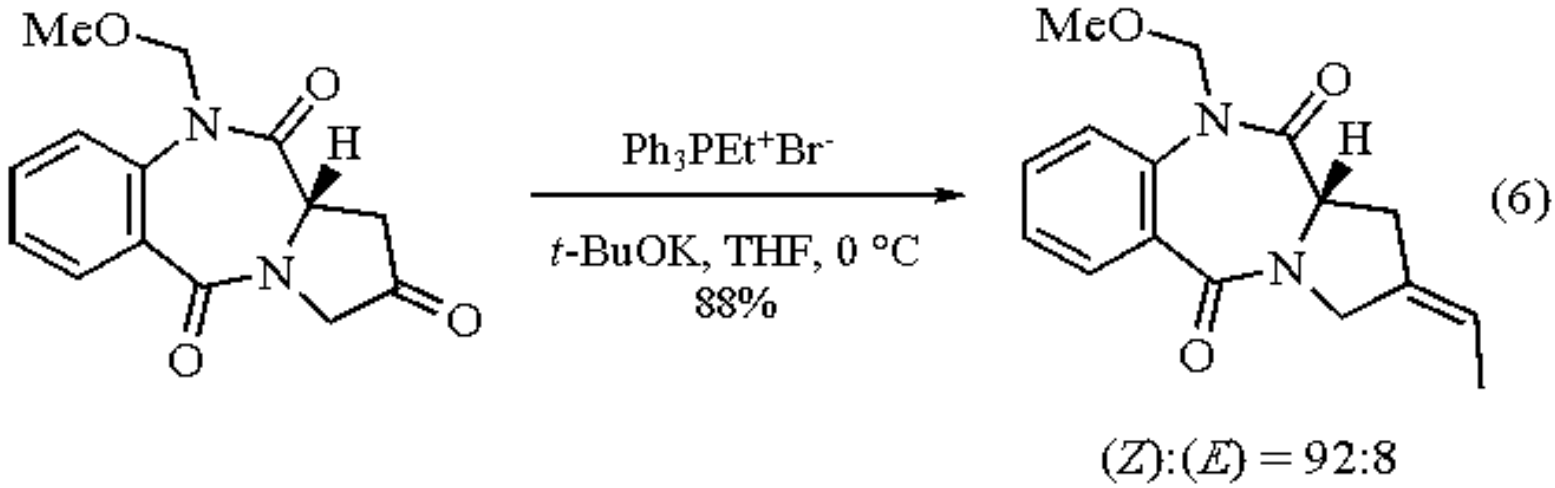

Schlosser has developed a modification of the Wittig reaction in which the intermediate adducts from condensation of ethylidenetriphenylphosphorane and aldehydes (betaines or oxaphosphetanes) are equilibrated by the addition of excess alkyllithium or phenyllithium.[3c,6] This allows the preparation of alkenes highly enriched in the (*E*)-isomer (eq 7),[6] and forms the basis for alkenation reactions with elaborated ylides, sometimes referred to as the SCOOPY reaction.[7,8]

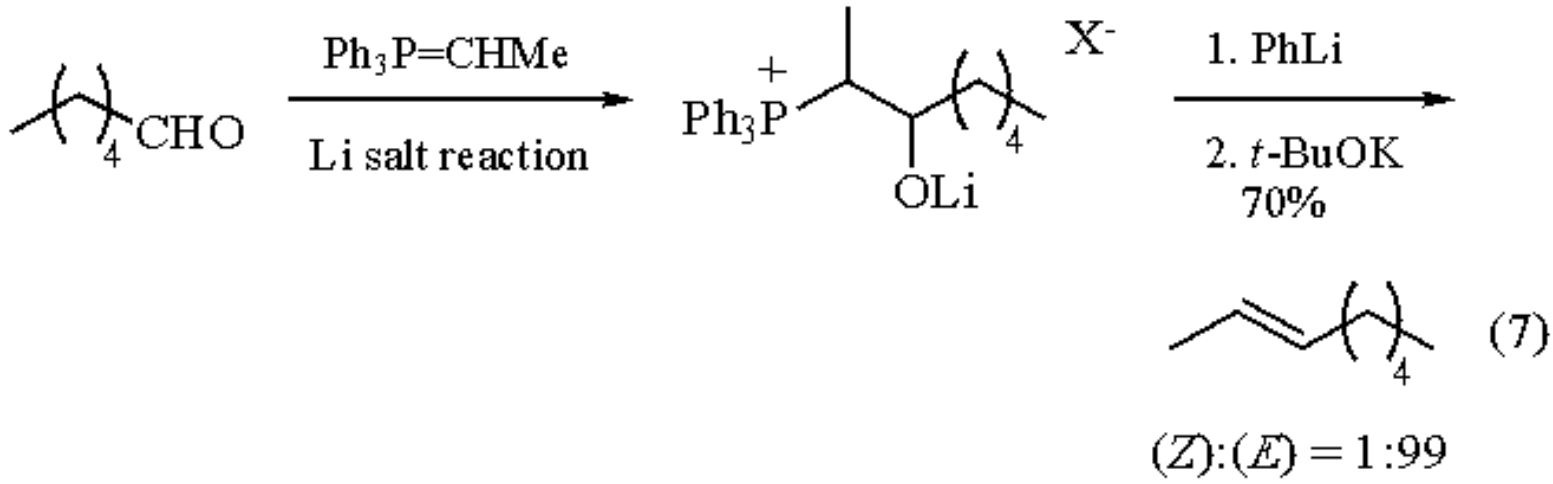

Elaboration of Ylides for Alkylidenation.

Ethylidenetriphenylphosphorane has been elaborated by electrophilic reagents into more complex phosphorus ylides, which can be effectively employed in subsequent alkenation chemistry. By using aldehydes as electrophiles, Schlosser and Corey independently developed useful stereocontrolled syntheses of various trisubstituted alkenes (eqs 8-10).[7,8] Intermediate β-oxido ylides were derivatized with electrophiles such as halogenating agents, reactive alkyl halides, aldehydes, and epoxides (SCOOPY reaction). Acylation of ethylidenetriphenylphosphorane can provide stabilized ylides for the synthesis of complex alkenes (eq 11).[9]

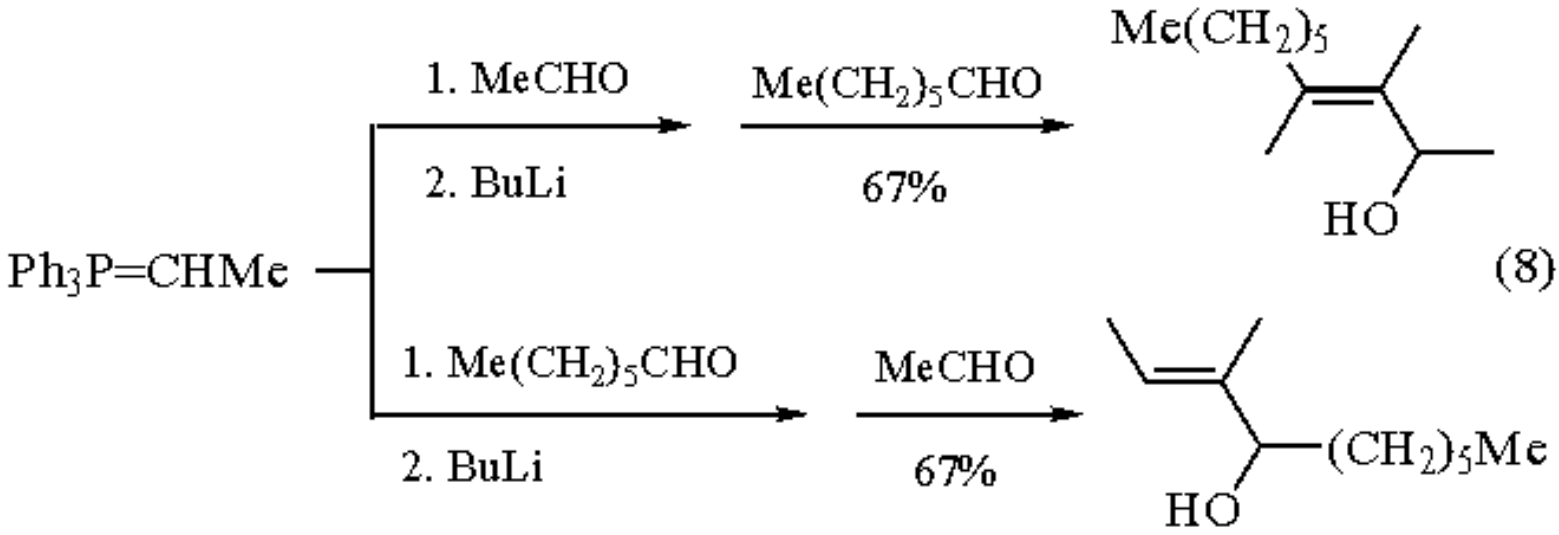

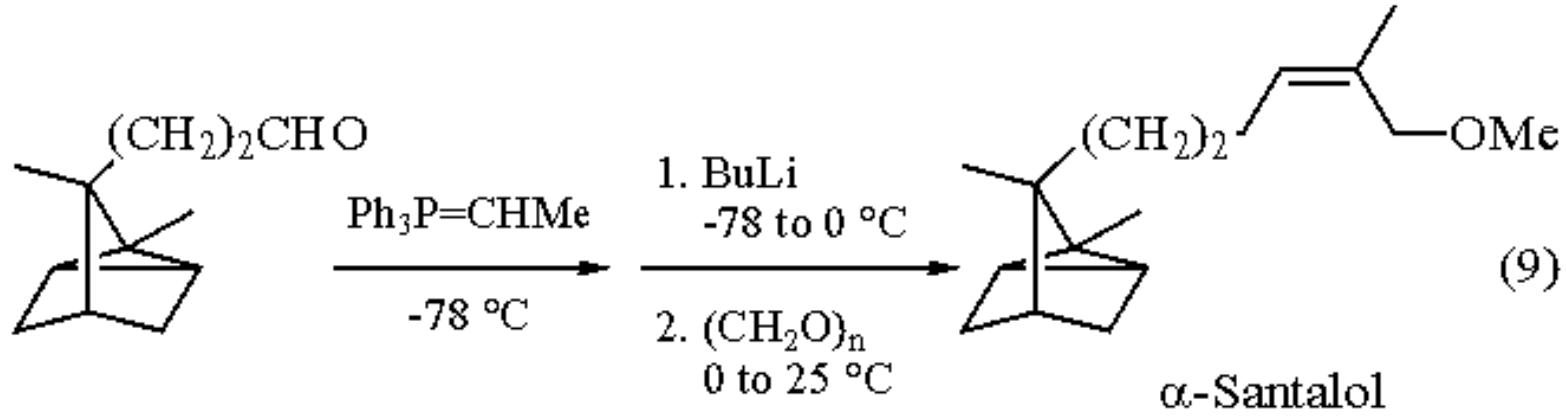
(CH2)2CHO
Ph3P=CHMe
-78 °C
1. BuLi
-78 to 0 °C
2. (CH2O)n
0 to 25 °C
(CH2)2
OMe
α-Santalol

(9)

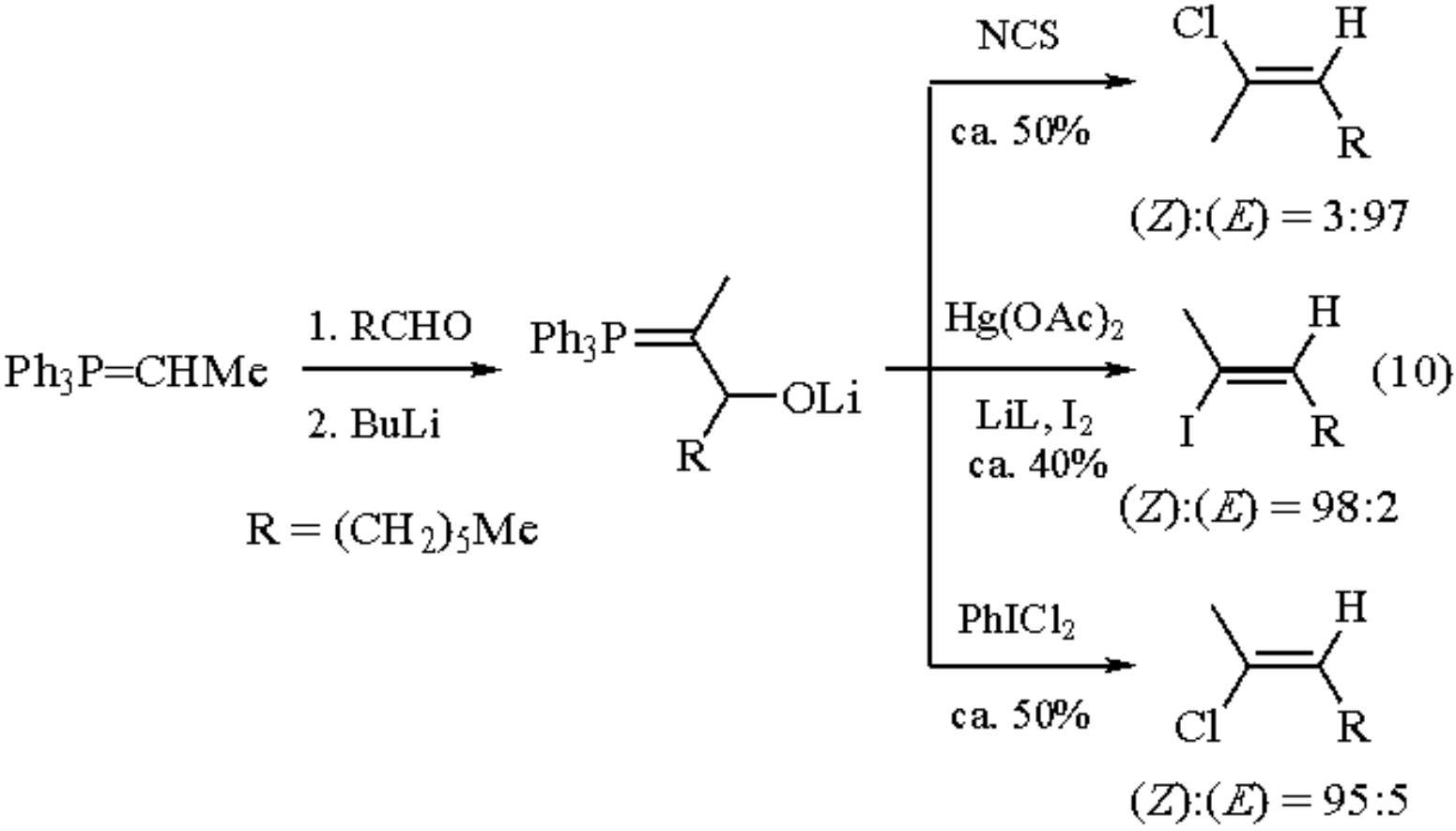
Ph3P=CHMe
1. RCHO
2. BuLi
R = (CH2)5Me
Ph3P
OLi
R
NCS
ca. 50%
Cl
H
R
(Z):(E) = 3:97
Hg(OAc)2
LiL, I2
ca. 40%
H
I
R
(Z):(E) = 98:2
PhICl2
ca. 50%
H
Cl
R
(Z):(E) = 95:5

(10)

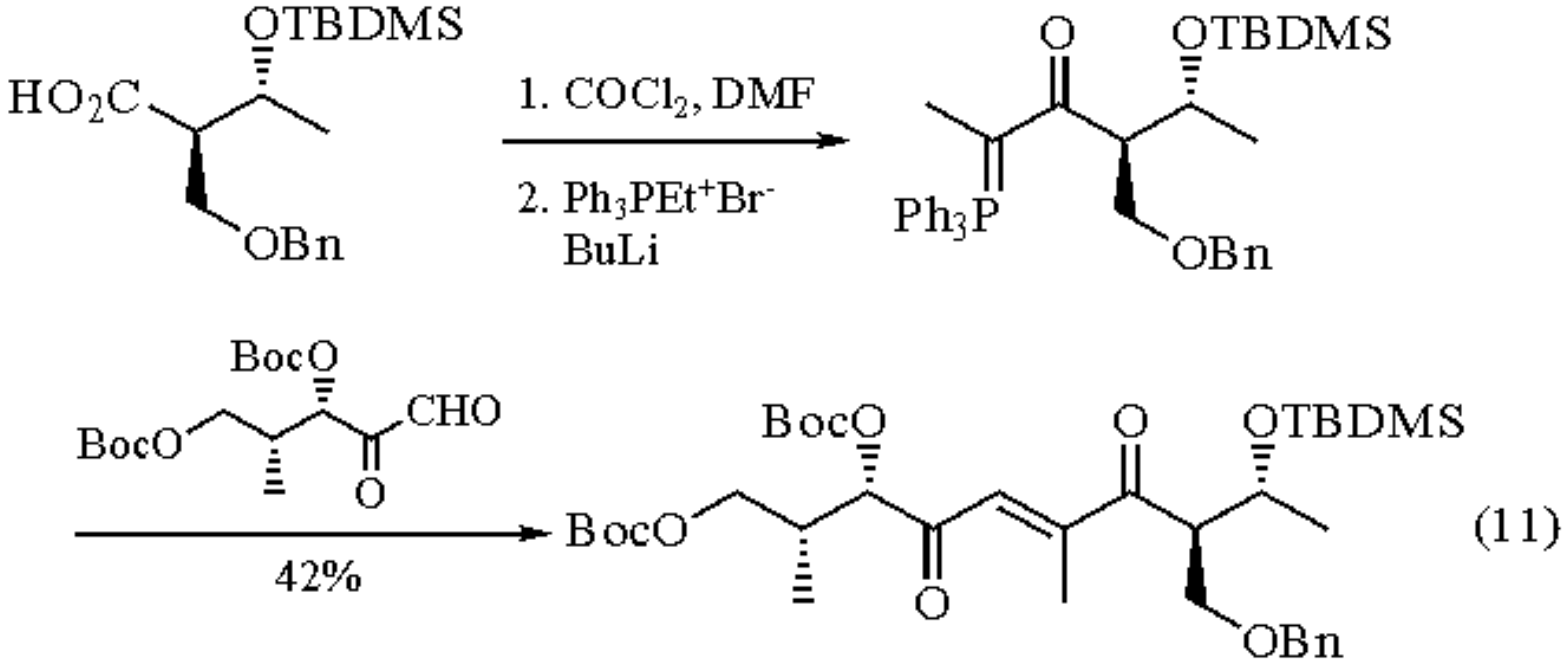

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1. For relevant reviews on the Wittig reaction: (a) Maryanoff, B. E.; Reitz, A. B. *CRV* **1989**, *89*, 863. (b) *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: New York, 1979. (c) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85. (d) Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1. (e) Maercker, A. *OR* **1965**, *14*, 270.
2. House, H. O.; Rasmusson, G. H. *JOC* **1961**, *26*, 4278.
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6. Schlosser, M.; Christmann, K. F. *AG(E)* **1966**, *5*, 126.
7. (a) Schlosser, M.; Christmann, K. F. *S* **1969**, 38. (b) Schlosser, M.; Christmann, K. F.; Piskala, A.; Coffinet, D. *S* **1971**, 29. (c) Schlosser, M.; Coffinet, D. *S* **1971**, 380. (d) Schlosser, M.; Coffinet, D. *S* **1972**, 575.
8. (a) Corey, E. J.; Ulrich, P.; Venkateswarlu, A. *TL* **1977**, 3231. (b) Corey, E. J.; Yamamoto, H. *JACS* **1970**, *92*, 226. (c) Corey, E. J.; Shulman, J. I.; Yamamoto, H. *TL* **1970**, 447. (d) Corey, E. J.; Yamamoto, H. *JACS* **1970**, *92*, 6636.
9. Ireland, R. E.; Wardle, R. B. *JOC* **1987**, *52*, 1780.

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Ethyl 4-(Triphenylphosphoranylidene)acetoacetate

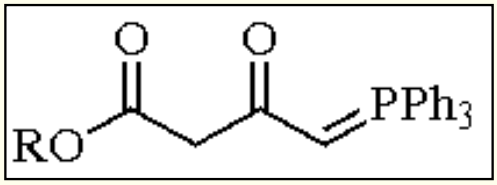

(**1**; R = Et)

[13148-05-5] · $C_{24}H_{23}O_3P$ · Ethyl 4-(Triphenylphosphoranylidene)acetoacetate · (MW 390.40) (**2**; R = Me)

[98815-59-9] · $C_{23}H_{21}O_3P$ · Methyl 4-(Triphenylphosphoranylidene)acetoacetate · (MW 376.37)

(Wittig reagent for the stereoselective synthesis of (*Z*)-enones;[1] annulation reagent for the synthesis of cyclohexenones[2])

Physical Data: R = Et, mp 105-106 °C; R = Me, mp 126 °C.

Solubility: insol cold ether and cold benzene; sol THF, CH_2Cl_2, and chloroform.

Preparative Methods: the title compound (**1**) and its methyl analog (**2**) are prepared in two steps from ethyl or methyl 4-chloroacetoacetates (see ***Ethyl 4-Chloroacetoacetate***), respectively, in 58-68% overall yield (eq 1).[3,4]

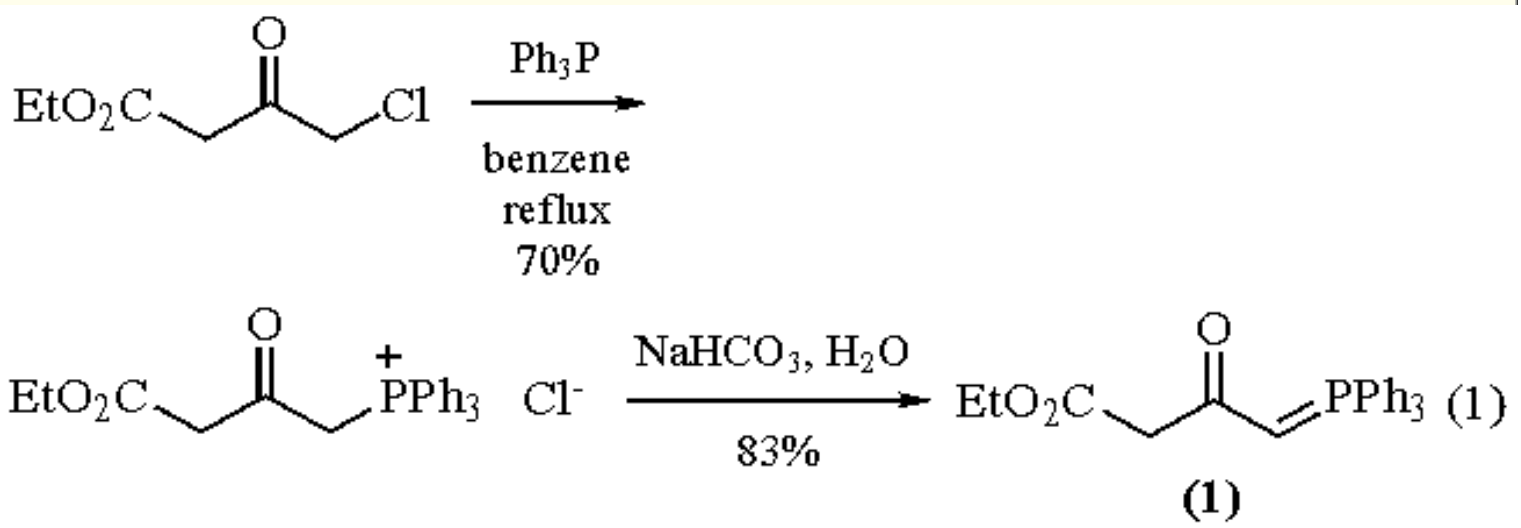

Wittig Reactions.

Under neutral conditions, reagent (**1**) exhibits only moderate reactivity in Wittig reactions with aldehydes and, like other stabilized Wittig reagents, generally produces (*E*)-enones (eq 2).[3,5] Although acid catalysis with ***p-Toluenesulfonic Acid*** or benzoic acid is known to effect rate acceleration, the reaction conditions are too destructive in the case of simple aliphatic aldehydes.[1,6] Wittig reaction of (**1**) with protected ribose derivatives provides *C*-glycosides (eq 3), which serve as precursors for the synthesis of *C*-nucleosides.[7,8]

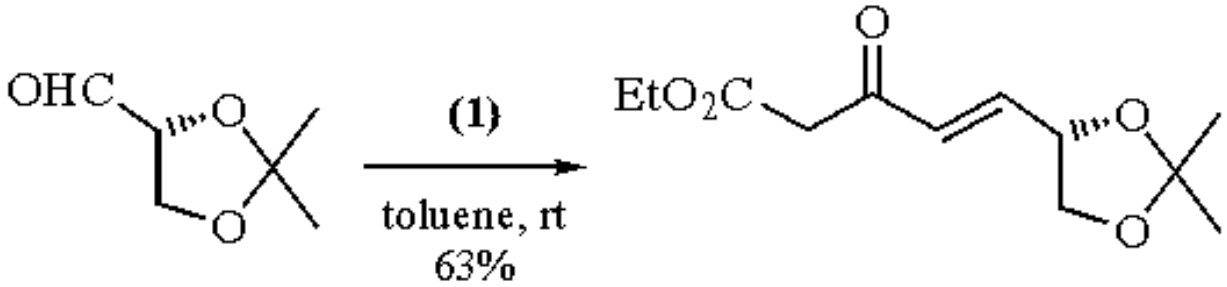

(2)

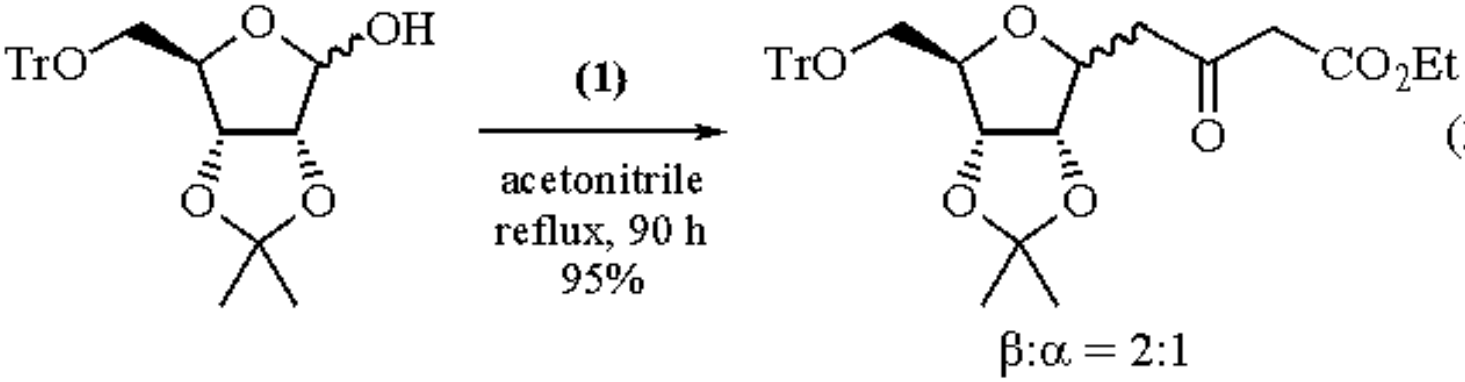

(3)

The in situ transformation of the carbonyl group in (**1**) into its enolate counterpart using ***Sodium Hydride*** activated by the addition of a few drops of water results in dramatic enhancement of reactivity of the ylide and reversal of stereoselectivity in Wittig reactions.[1] Under these conditions, a high degree of (*Z*) selectivity can be achieved in reactions with aliphatic straight-chain aldehydes as well as with α-branched aldehydes (eq 4).[1,9]

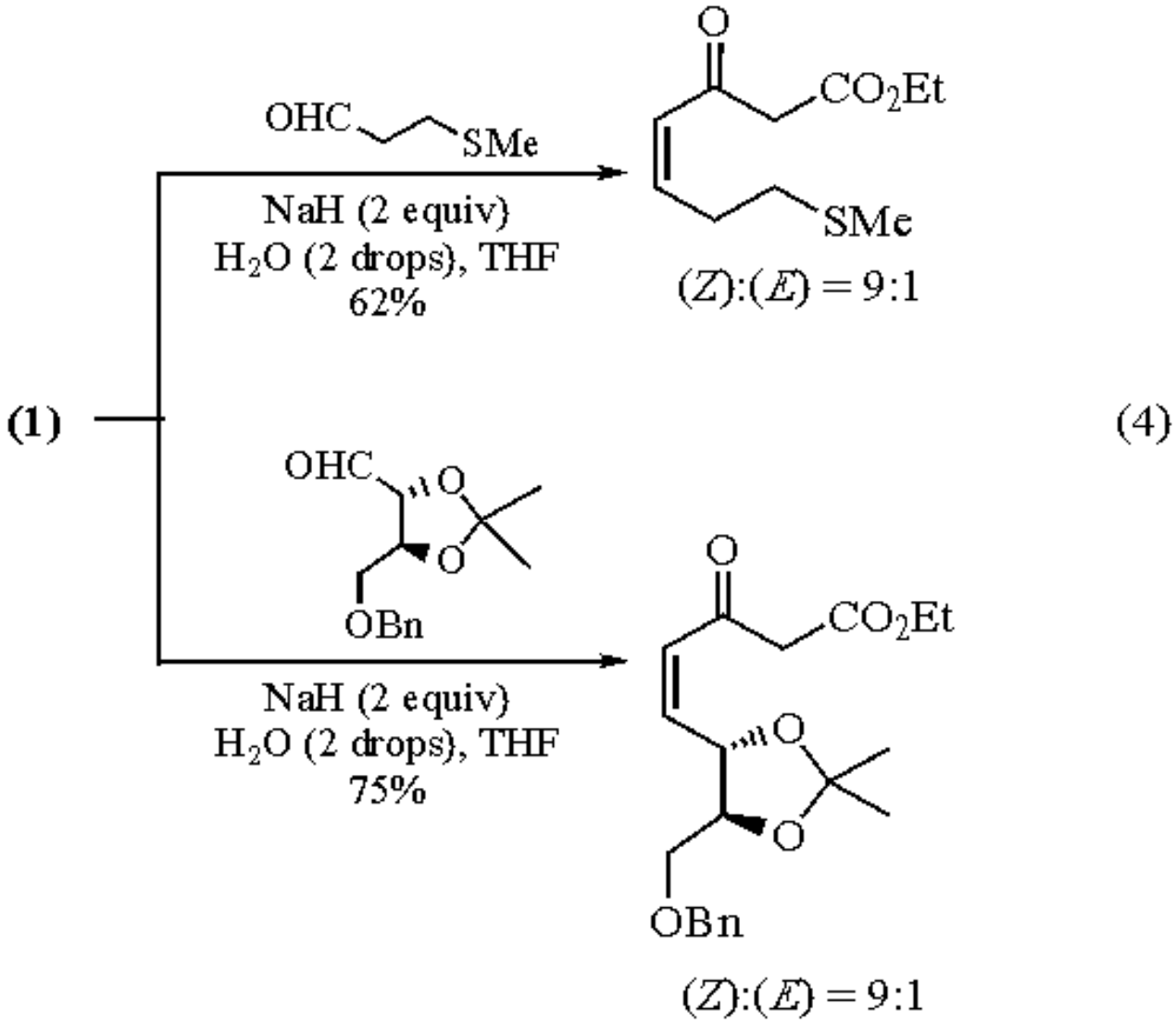

Annulation Reactions.

In the presence of an added base, a variety of α,β-unsaturated aldehydes participate in a [3 + 3] annulation reaction with reagent (**1**) to give cyclohexenones in modest yield (eq 5).[2,10] An excess of sodium hydride activated by a few drops of water is the most effective base for promoting this reaction. Dienals produce a mixture of products resulting from initial 1,2- and 1,4-reactivity under these conditions. However, the use of a catalytic amount of ***Potassium Hydride*** instead of water for the activation of sodium hydride improves the selectivity of cyclohexenone formation (eq 6).[11] Annulation reaction of a highly reactive trifluoromethyl enone with reagent (**2**) proceeds efficiently without any added base (eq 7).[12] The [3 + 3] annulation reactions of (**1**) and (**2**) provide useful alternatives to the commonly used [4 + 2] counterpart, the Robinson annulation, for the synthesis of cyclohexenones.

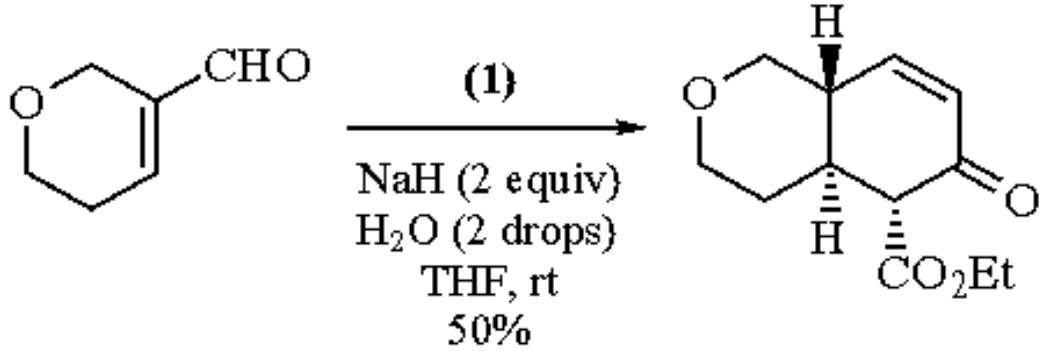

(5)

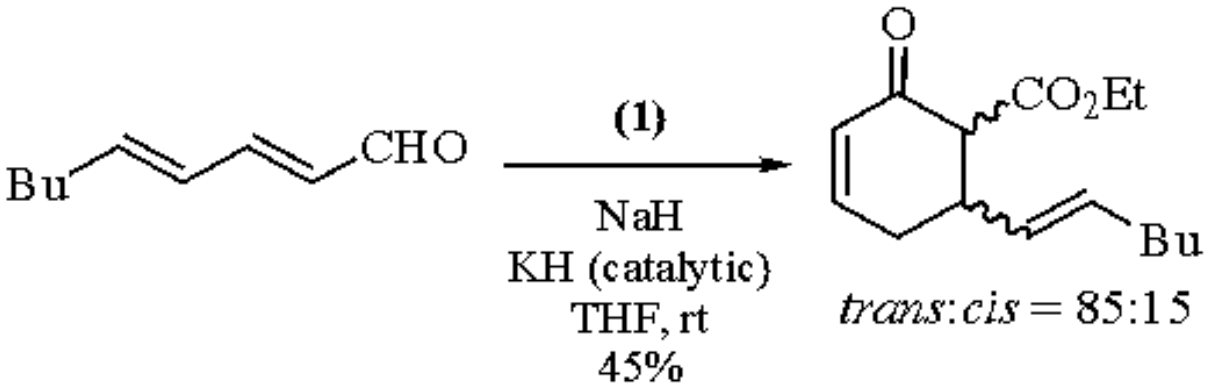

(6)

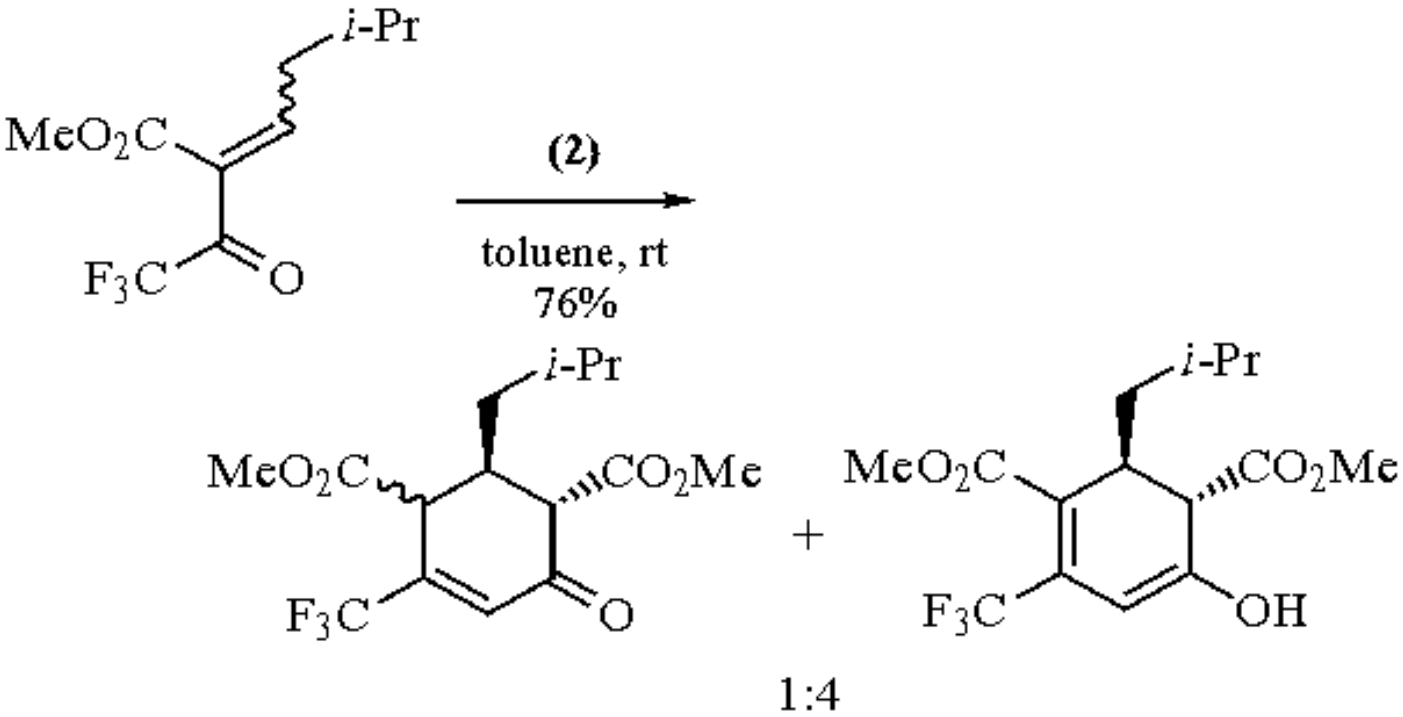

(7)

Related Reagents.

Ethyl Acetoacetate; ***Ethyl 4-Chloroacetoacetate***; ***Methyl Dilithioacetoacetate***; ***Methyl Vinyl Ketone***; ***Triphenylphosphine***.

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Shridhar G. Hegde

Monsanto Company, St Louis, MO, USA

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Ethyl Vinyl Ether[1]

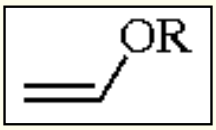

(R = Et)

[109-92-2] · C_4H_8O · Ethyl Vinyl Ether · (MW 72.12) (R = Me)

[107-25-5] · C_3H_6O · Methyl Vinyl Ether · (MW 58.09) (R = *n*-Bu)

[111-34-2] · $C_6H_{12}O$ · Butyl Vinyl Ether · (MW 100.18)

(protection of hydroxyl group; transvinylation, particularly to prepare allyl vinyl ethers for use in the Claisen rearrangement; condensation reactions; cycloaddition reactions)

Physical Data: R = Et, mp -115.8 °C, bp 35-36 °C, *d* 0.7589 g cm^{-3}; R = Me, mp -123 °C, bp 12 °C, *d* 0.7725 g cm^{-3} at 0 °C; R = *n*-Bu, mp -92 °C, bp 94 °C, *d* 0.7888 g cm^{-3}.[2]

Solubility: sol all common organic solvents; slightly sol water.

Form Supplied in: ethyl vinyl ether and *n*-butyl vinyl ether are colorless, extremely flammable liquids, while methyl vinyl ether is a colorless, extremely flammable gas. Ethyl vinyl ether is supplied stabilized with triethanolamine and methyl vinyl ether is supplied in stainless steel cylinders.

Purification: ethyl vinyl ether and *n*-butyl vinyl ether may be distilled from K_2CO_3 or Na if purification of the commercial materials is desirable.

Handling, Storage, and Precautions: all three compounds react *violently* with halogens and with strong oxidizing agents, and undergo rapid polymerization in the presence of acids. These vinyl ethers are lachrymatory and irritate the respiratory system; in particular, methyl vinyl ether can cause rapid suffocation if inhaled. Use in a fume hood.

Protection of the Hydroxyl Group.[3]

Acid-catalyzed reaction of primary and secondary alcohols with ethyl vinyl ether gives the α-ethoxyethyl (EE) group. Acids commonly used in the formation of the EE group include ***Trifluoroacetic Acid*** (eq 1),[4] anhyd ***Hydrogen Chloride*** (eq 2),[5] ***p-Toluenesulfonic Acid***,[6] and ***Pyridinium p-Toluenesulfonate*** (PPTS) (eq 3).[7] Whereas attempts to form the methyl or benzyl ether of the hemiacetal (eq 3), and reaction with DHP, result in decomposition, the

hemiacetal is successfully converted into the EE group with ethyl vinyl ether in the presence of PPTS (but not *p*-TsOH).[7] For extremely acid-sensitive substrates, ethyl vinyl ether generated in situ from 1-chloroethyl ethyl ether (MeCH(Cl)OEt) with $PhNMe_2$ in CH_2Cl_2 at 0 °C gives EE derivatives of primary, secondary, and some tertiary alcohols in excellent yields (eq 4).[8] Selective protection of a primary alcohol in the presence of a secondary alcohol with ethyl vinyl ether may be achieved at low temperatures (eq 5).[9] The EE group is more readily cleaved by acid hydrolysis than the THP ether, but is more stable than the 1-methyl-1-methoxyethyl ether.[3] In the case of the nucleoside (eq 2), which is subsequently converted into a nucleotide, the ethoxyethyl group is preferred to the THP group because of its ease of removal (5% HOAc, 2 h, 20 °C), with no detectable isomerization of the 3´-5´ nucleotide linkage.[5] Other methods of cleaving the EE group include 0.5N HCl in THF at 0 °C,[6] and PPTS in *n*-PrOH, where cleavage is possible in the presence of an acetonide group (eq 6).[10]

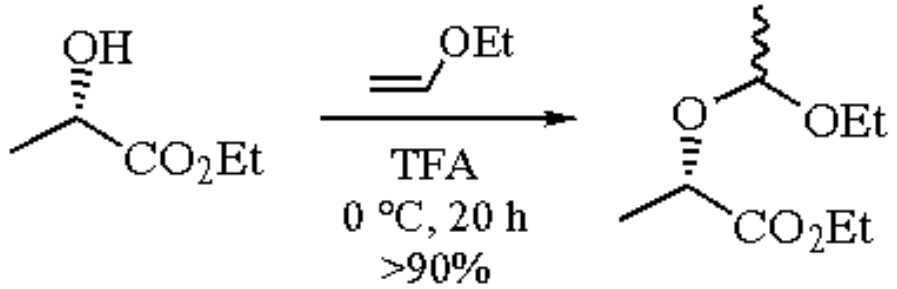

(1)

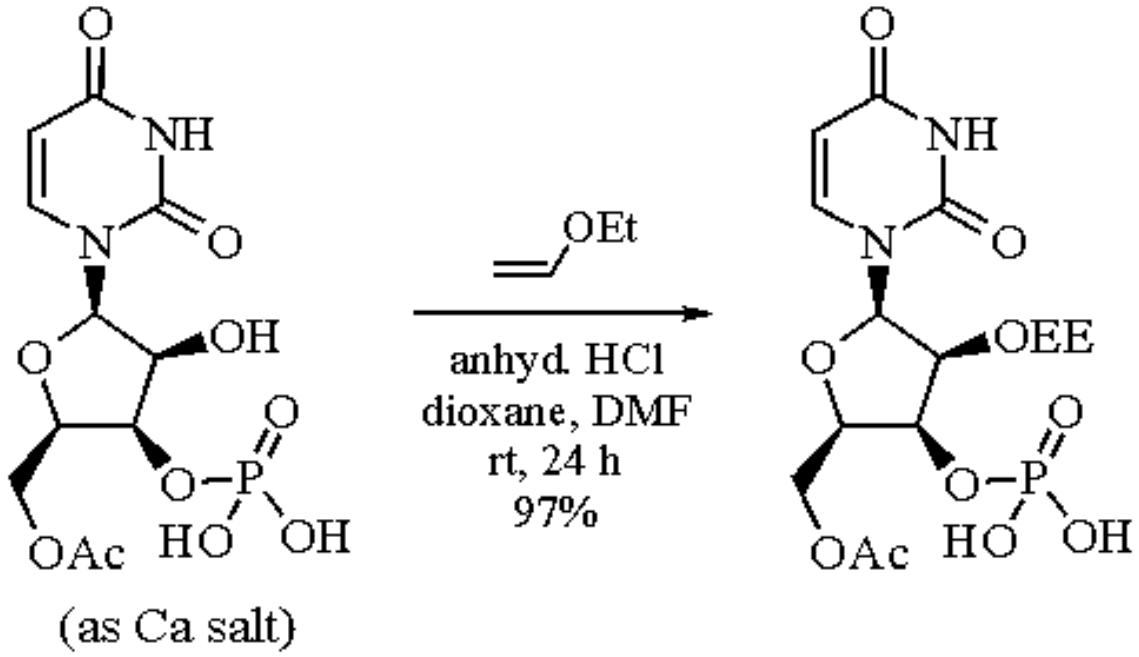

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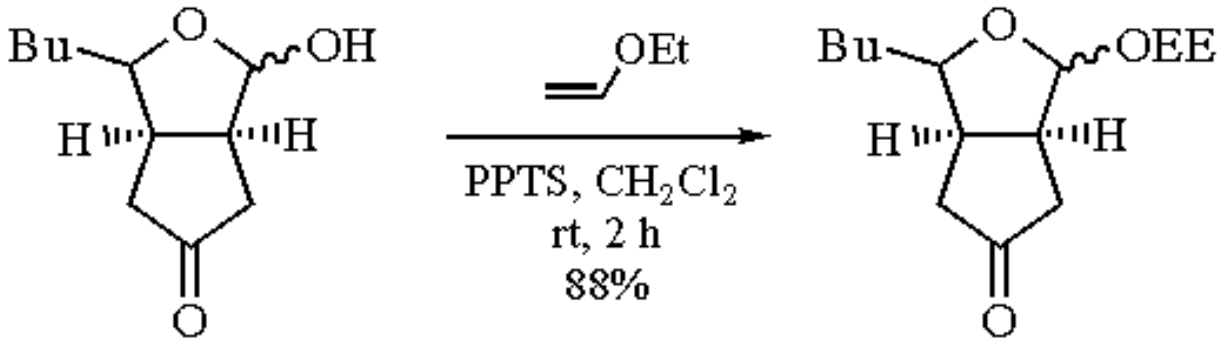

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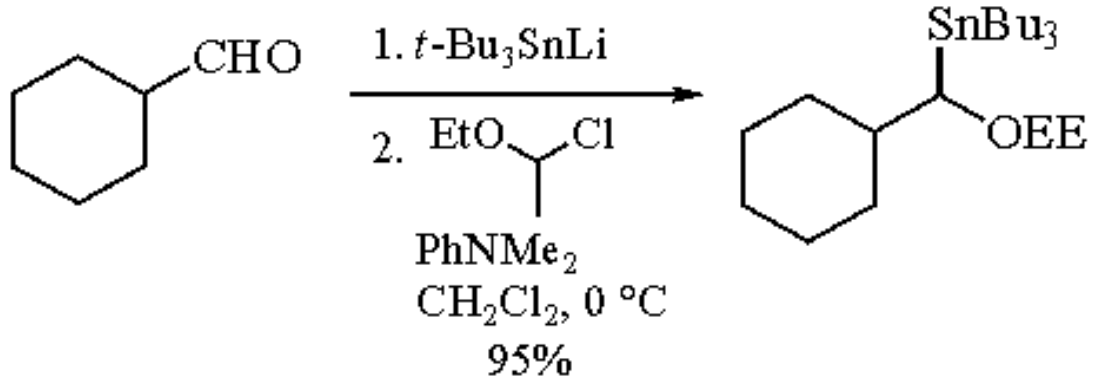

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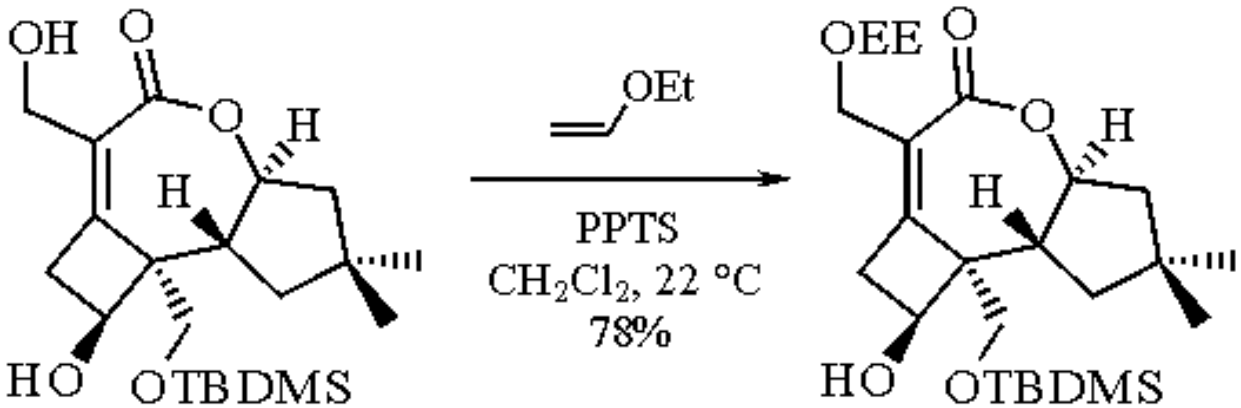

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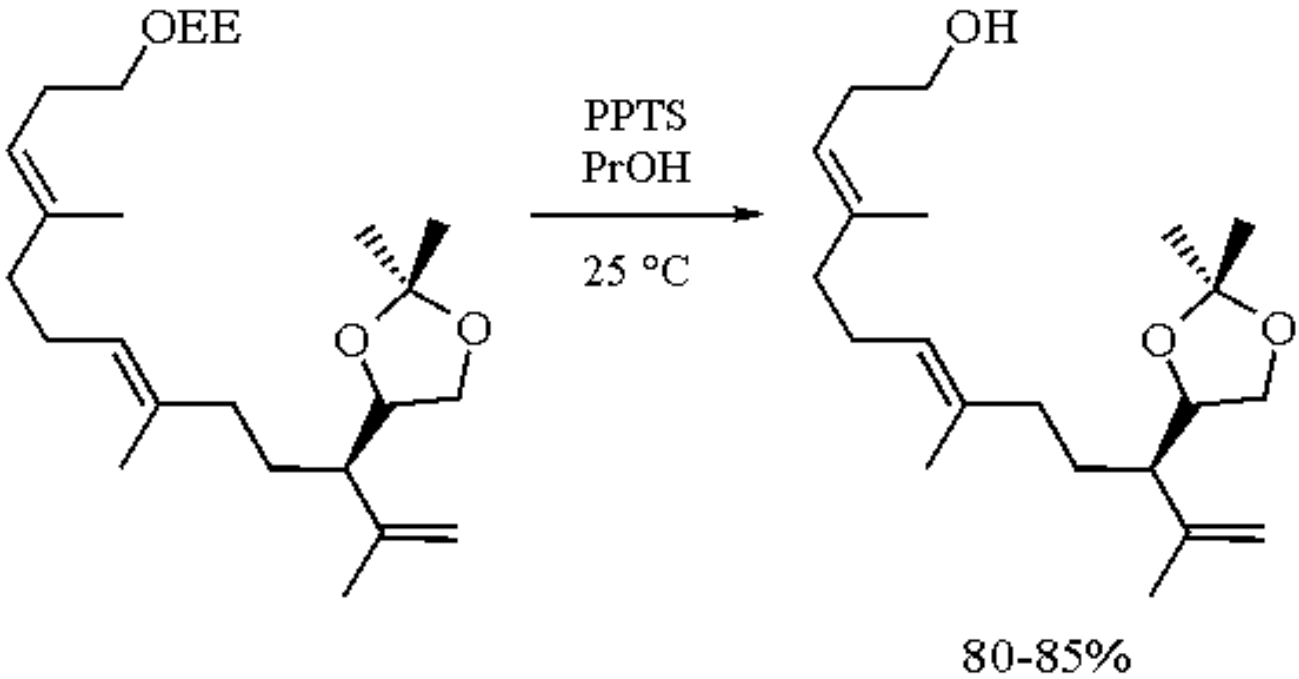

(6)

Augmenting its role as a protecting group, the EE group has been used to direct *ortho*-lithiation in suitably substituted aromatic ethers, yielding lithiated species that react rapidly with a variety of electrophiles, such as ***Carbon Dioxide***, to give the phthalide (eq 7).[11]

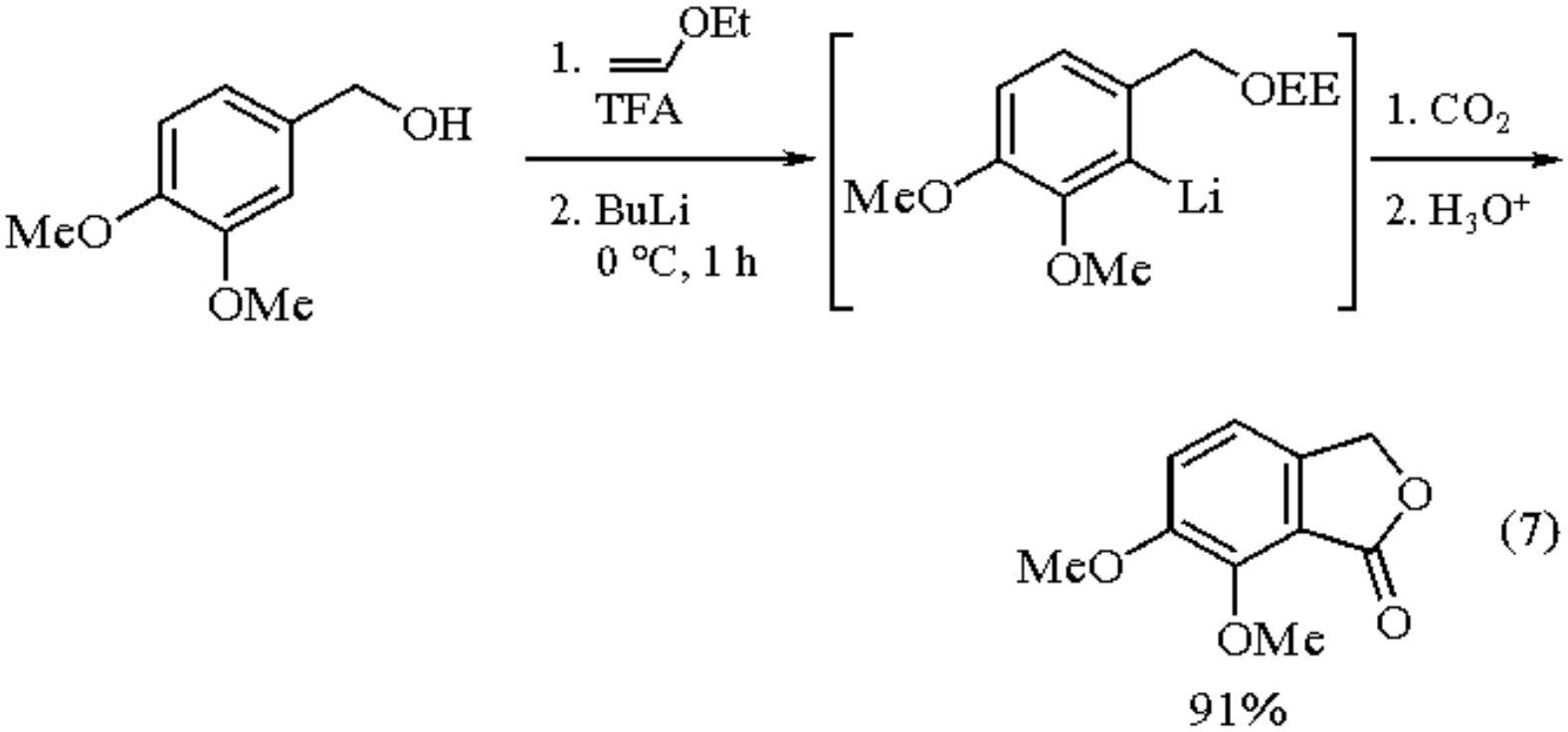

(7)

Transvinylation.

Acid-catalyzed transvinylation of allylic alcohols with ethyl vinyl ether gives allyl vinyl ethers, Claisen rearrangement[12] of which affords γ,δ-unsaturated aldehydes of varying complexity (eqs 8-12).[13,14,16-18] ***Mercury(II) Acetate*** (eq 8),[13] ***Phosphoric Acid*** (eq 9),[14] and *p*-TsOH[15] are frequently used to catalyze the transvinylation reaction, and the allyl vinyl ethers produced need not be isolated but may be subjected directly to the Claisen rearrangement, typically at 145-200 °C. $Hg(OAc)_2$, used in the transvinylation reaction, has been reported to effect the rearrangement at lower temperatures (eq 10).[16] Other examples illustrating the stereoselectivity of the reaction are given in eqs 11 and 12.[17,18]

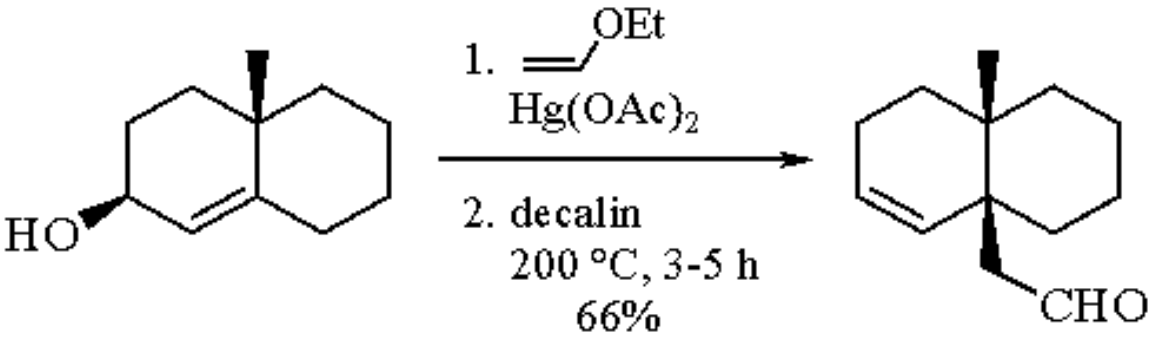

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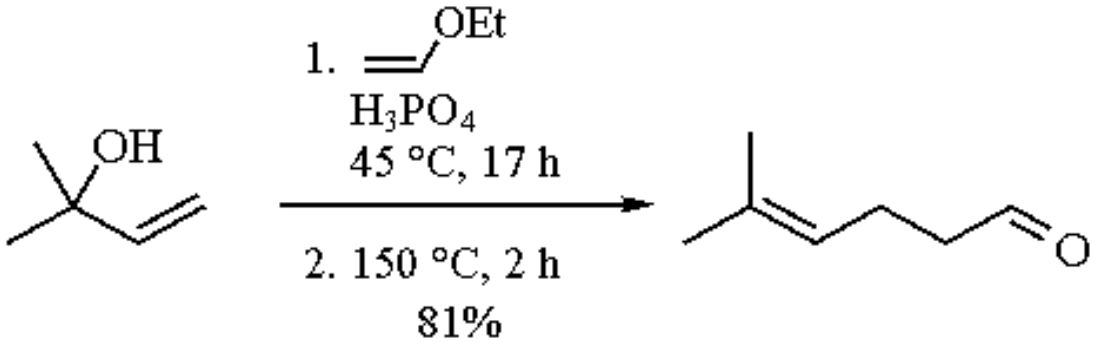

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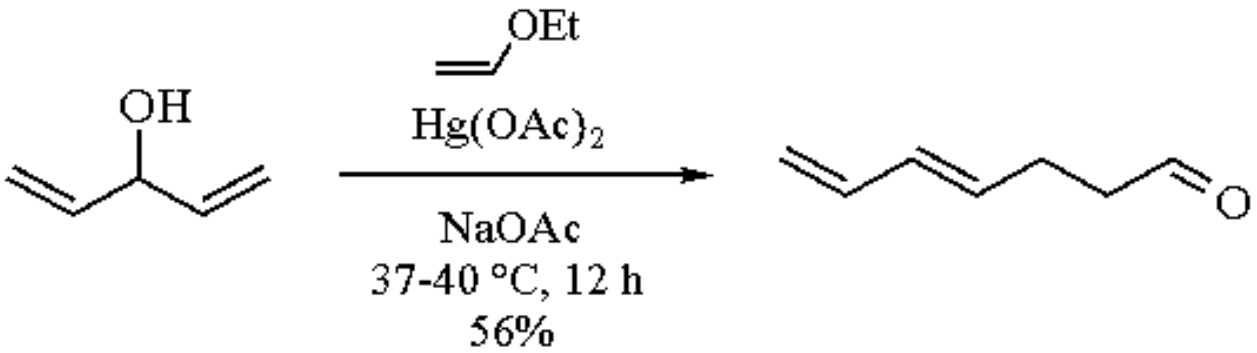

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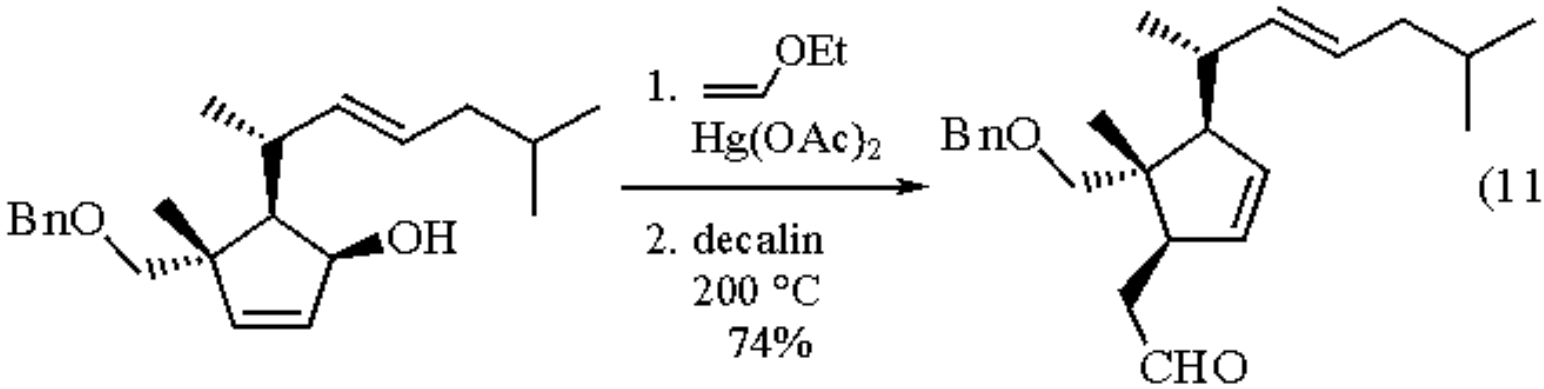

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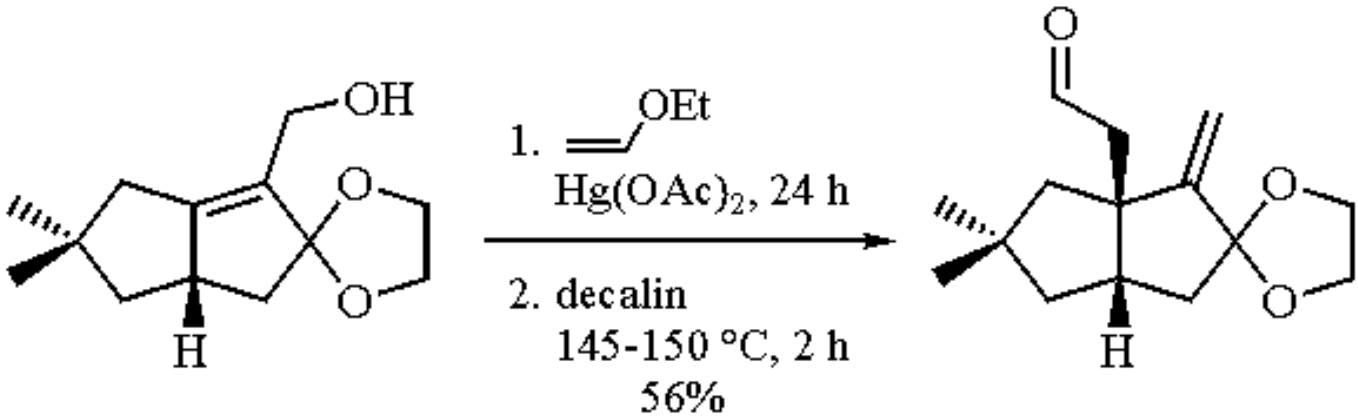

(12)

Condensation Reactions.

Acetal Condensations.

The acid-catalyzed condensation of ethyl vinyl ether with acetals derived from α,β-unsaturated aldehydes and ketones is an excellent method to lengthen a carbon chain by two carbon atoms, particularly of polyenals. In an industrial process for the manufacture of the C_{16} aldehyde (eq 13), the C_{14} acetal is reacted with ethyl vinyl ether in the presence of ***Zinc Chloride*** to give an alkoxy acetal, which, without isolation, is then hydrolyzed with moist acetic acid.[19] Longer conjugated carotenals have been synthesized by this method,[20] and montmorillonite K-10 clay (see ***Montmorillonite K10***) has been reported to be an excellent replacement for the Lewis acids normally used in the condensation.[21]

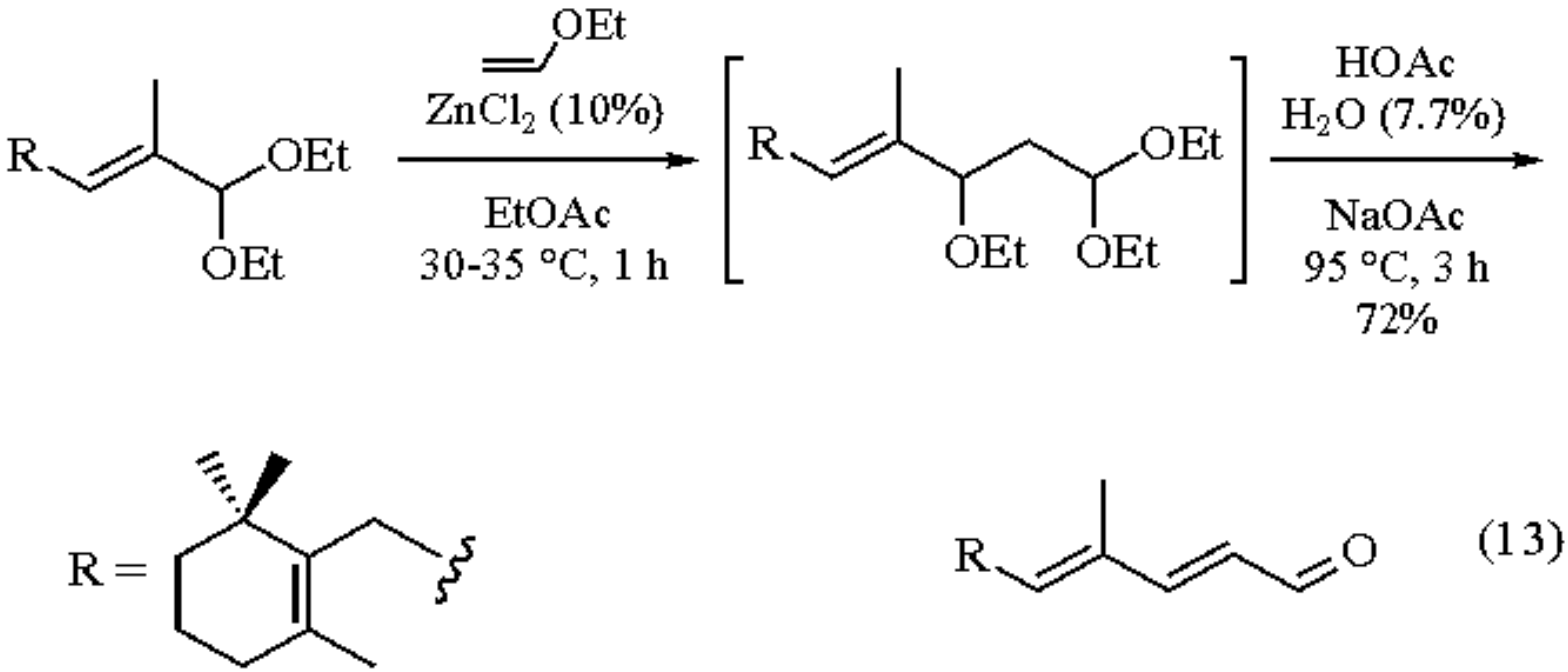

(13)

Acyl Anion Equivalents.[22]

The α-H of simple vinyl ethers can be deprotonated with strong bases, such as ***t-Butyllithium***, to give highly reactive α-alkoxyvinyllithium reagents (see also ***1-Ethoxyvinyllithium*** and ***1-Methoxyvinyllithium***). These react rapidly with various electrophiles, including aldehydes and ketones (eq 14),[23] and can undergo conjugate addition to α,β-unsaturated carbonyl compounds via the corresponding cuprates (eq 15).[24]

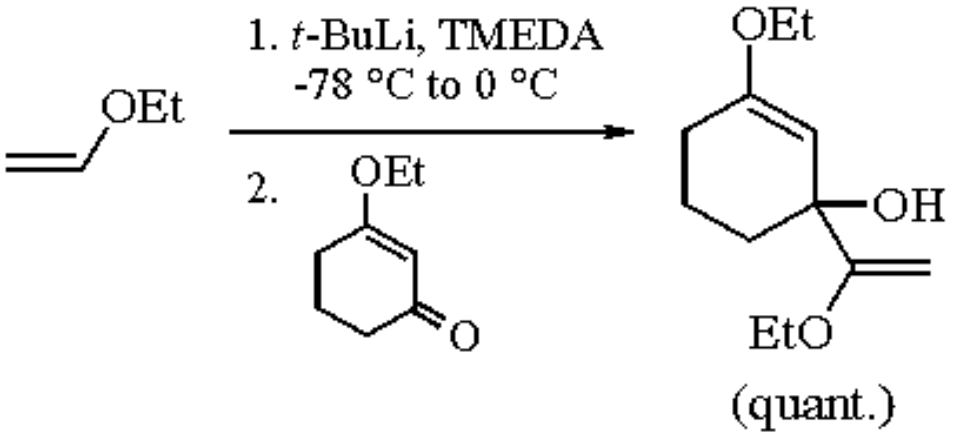

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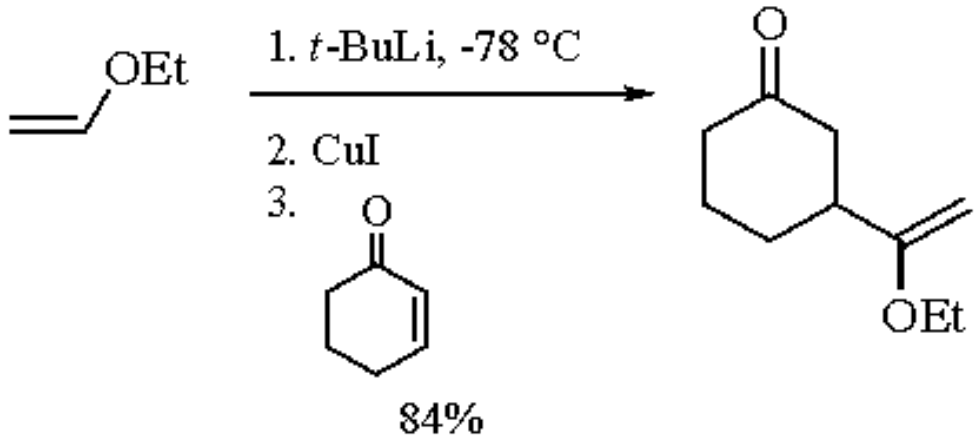

(15)

Cycloaddition Reactions.

Diels-Alder and Related Reactions.

Owing to their electron-rich nature, vinyl ethers participate in a number of inverse electron demand Diels-Alder reactions.[25] α,β-Unsaturated aldehydes and ketones react rapidly with vinyl ethers to give dihydropyrans (eq 16),[26] with high *endo* selectivity (eq 17),[27] the proportion of *endo* adduct being increased by conducting the reaction at low temperatures under pressure (eq 18).[28] Lewis acids can also catalyze these reactions and control the stereochemistry of cycloaddition.[25b,29] *o*-Quinone methides yield chromans (eq 19),[30] and imines give tetrahydroquinolines (eq 20).[31] Vinyl ethers react regio- and stereoselectively with isoquinolinium salts giving cycloadducts, which on hydrolysis afford tetralins in excellent yields (eq 21).[32] The cycloaddition of vinyl ethers with nitrones proceeds smoothly, giving, where relevant, isoxazolines with extremely high diastereoselectivity (eq 22).[33] Vinyl ethers react with nitroalkenes to give nitronate esters in moderate yields (eq 23),[34] but excellent yields of cyclobutane derivatives are obtained with tetracyanoethylene (eq 24).[35]

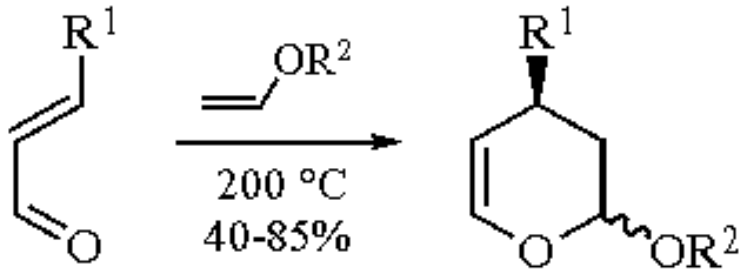

(16)

$R^1 = H, Me, Ph; R^2 = Et, Bu, Me$

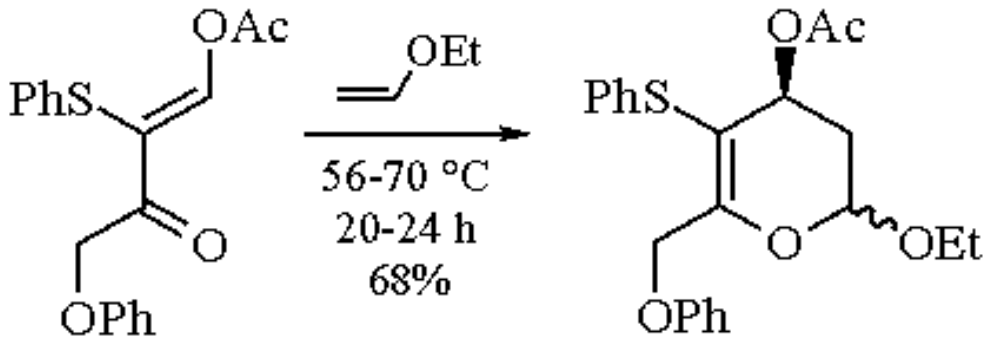

(17)

trans:*cis* = 12.5:1

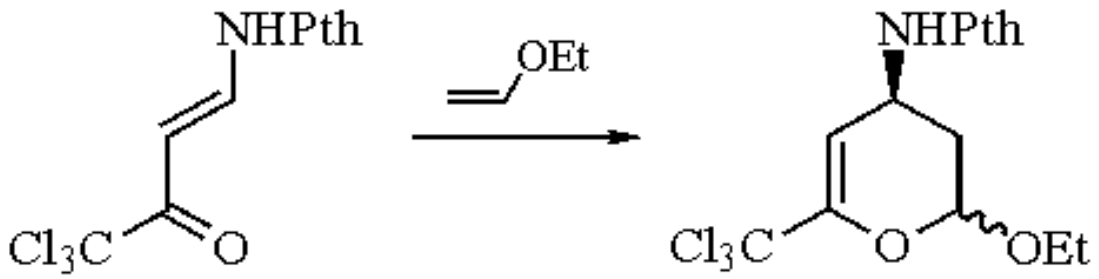

(18)

β-OEt:α-OEt

90 °C, 1 bar	1.67:1
0.5 °C, 6 kbar	13.6:1

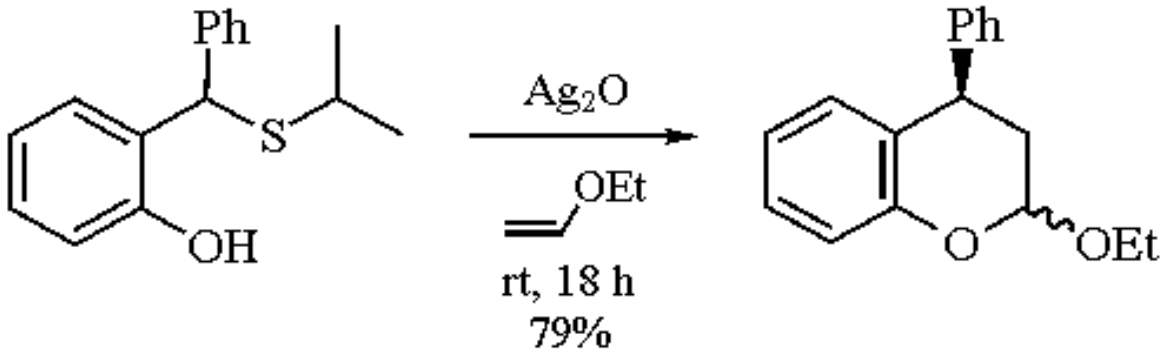

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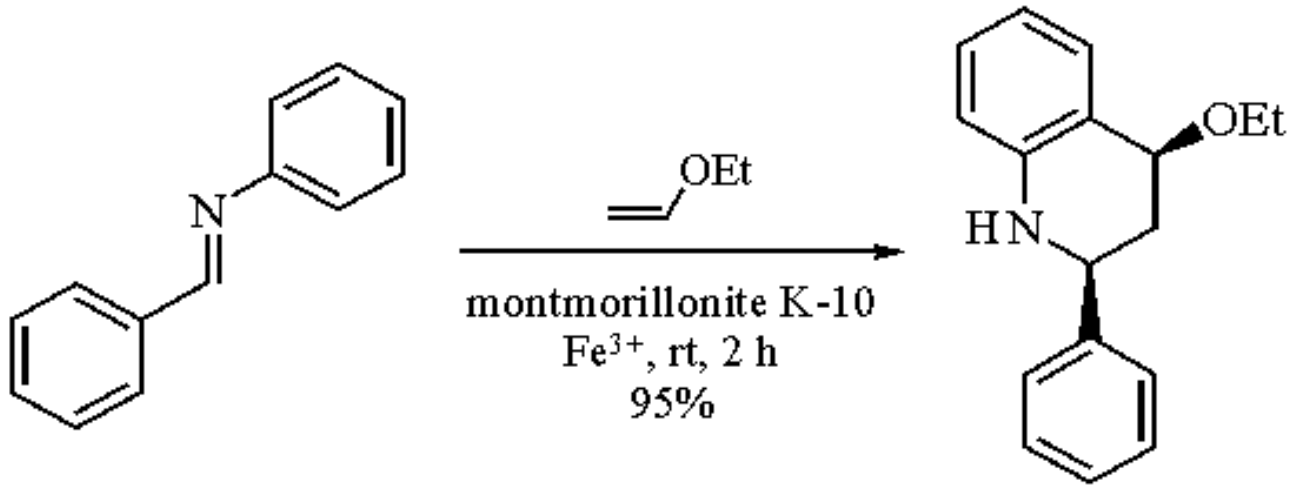

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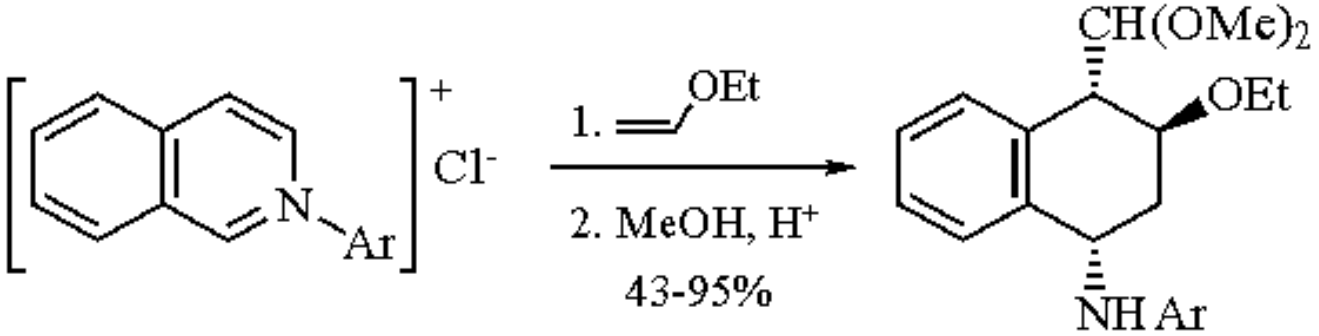

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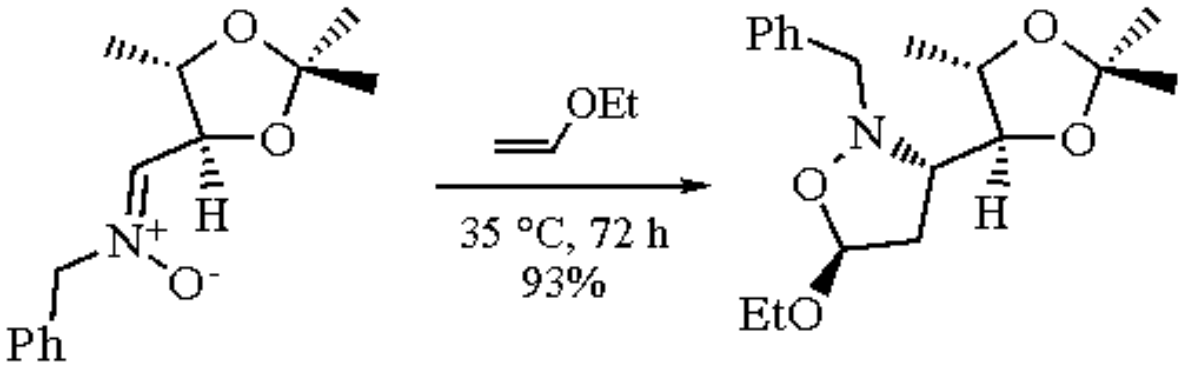

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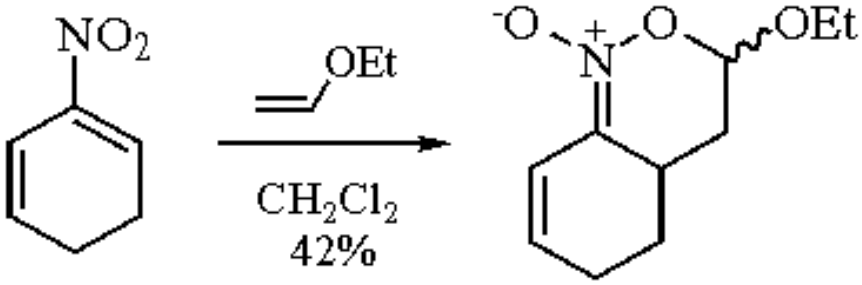

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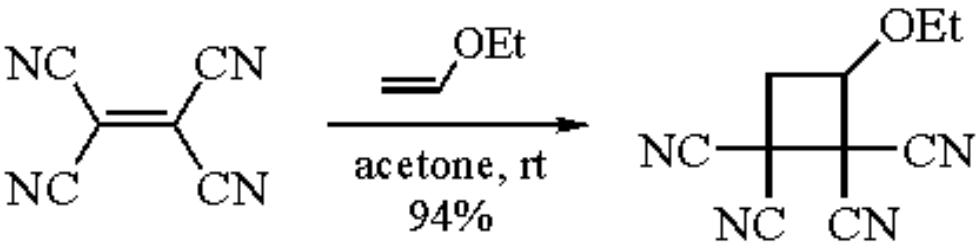

(24)

Photochemical.

Vinyl ethers undergo the Paterno-Büchi reaction with simple aliphatic and aromatic carbonyl compounds to give regioisomeric mixtures of alkoxyoxetanes, with a preponderance of the 3-alkoxy regioisomer (eq 25).[36] Photoaddition of vinyl ethers to enones produces alkoxycyclobutanes in excellent yields, with the alkoxy group orientated predominantly away from the carbonyl group (eq 26).[36] Vinyl ethers also undergo photoaddition to arenes, giving, with benzene, a mixture of *ortho*- and *meta*-cycloadducts in low yields; only the *exo* isomer is produced in the *ortho*-cycloaddition, whereas the *meta*-cycloaddition gives a mixture of regio- and stereoisomers (eq 27).[37]

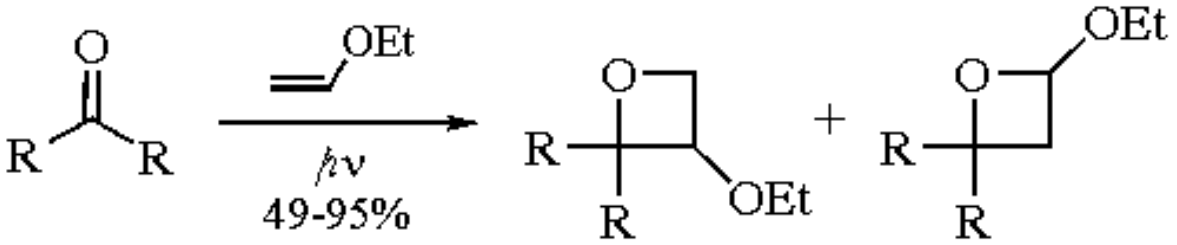

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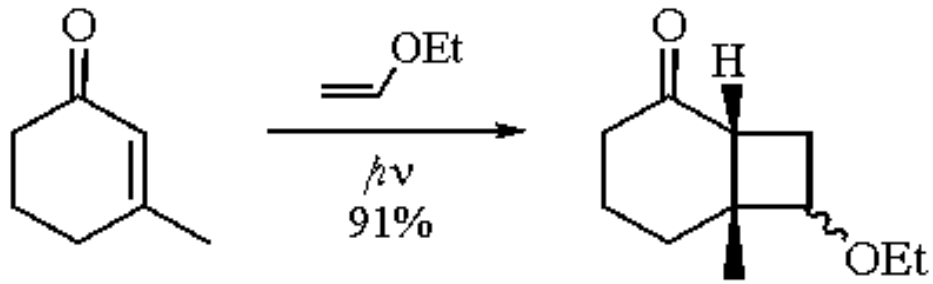

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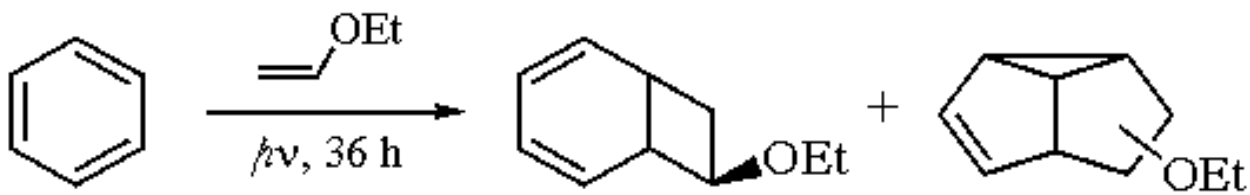

(27)

Related Reagents.

Acetaldehyde; ***Acetaldehyde N-t-Butylimine***; ***1-Ethoxy-1-propene***; ***2-Methoxy-1,3-butadiene***; ***Vinyl Acetate***.

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Ethylzinc Iodide[1]

EtZnI

[994-75-7] · C_2H_5IZn · Ethylzinc Iodide · (MW 221.36)

(used in combination with CH_2I_2 for the cyclopropanation of alkenes (Sawada reaction);[1] displays the typical reactions of an alkylzinc halide[2])

Physical Data: mp 98 °C dec; polymeric in the solid state, monomeric in ether, THF, and ethyl iodide.

Solubility: sol hexane, toluene, ether, THF, amines.

Form Supplied in: not commercially available.

Preparative Methods: by the reaction of commercially available ***Diethylzinc*** and ***Zinc Iodide*** in many solvents,[3] or directly from ***Ethyl Iodide*** and ***Zinc*** powder.[4]

Analysis of Reagent Purity: iodometric titration according to Job.[5]

Handling, Storage, and Precautions: ethereal solutions are stable for several months at 25 °C under an inert atmosphere, if contact with oxygen and moisture is avoided.

Cyclopropanation of Alkenes.

A wide range of alkenes and functionalized alkenes can be cyclopropanated by ***Diiodomethane*** and a ***Zinc/Copper Couple*** (Simmons-Smith reaction (see ***Diethylzinc*** and ***Iodomethylzinc Iodide***)).[1c] The easy insertion of zinc into diiodomethane leads to iodomethylzinc iodide[6] (ICH_2ZnI), which is the actual cyclopropanation reagent.[7] Diethylzinc[8] (Furukawa reaction) and ethylzinc iodide[9] (Sawada reaction) undergo a fast iodine-zinc exchange reaction with CH_2I_2, generating iodomethylzinc derivatives (eq 1). After the addition of an alkene, cyclopropanes are obtained in moderate to good yields (eq 2). A comparison between the three methods for generating iodomethylzinc-derived cyclopropanation reagents shows that the procedure using EtZnI often affords the best yields (Table 1).[9]

$$ICH_2ZnEt \xleftarrow[-\,EtI]{Et_2Zn} CH_2I_2 \xrightarrow[-EtI]{EtZnI} ICH_2ZnI \qquad (1)$$

(2)

Table 1 Comparison between the Simmons Smith,[10] Sawada,[9] and Furukawa[8] Cyclopropanation Procedures for Alkenes

Alkene	Yield (%) of the corresponding cyclopropane		
	Simmons Smith method[a]	Sawada method[b]	Furukawa method[c]
Cyclohexene	61	92	79
Styrene	32	78	76
1-Octene	70	77	60
Butyl vinyl ether		15	92
Methyl crotonate	9	24	

[a] Zn/Cu couple and CH_2I_2. [b] EtZnI and CH_2I_2. [c] Et_2Zn and CH_2I_2.

In some cases with the Sawada method the cyclopropanation succeeds, whereas the original Simmons-Smith procedure completely fails (eq 3).[10] The best experimental procedure consists of heating an excess of an ethereal solution of ethylzinc iodide (ca. 4 equiv) with diiodomethane (1.2 equiv) for an hour, adding the alkene (1.0 equiv) at 0 °C, and stirring the reaction mixture at 25 °C for several hours. Under these conditions, alkenylsilanes can be cyclopropanated in high yields (eq 4).[11]

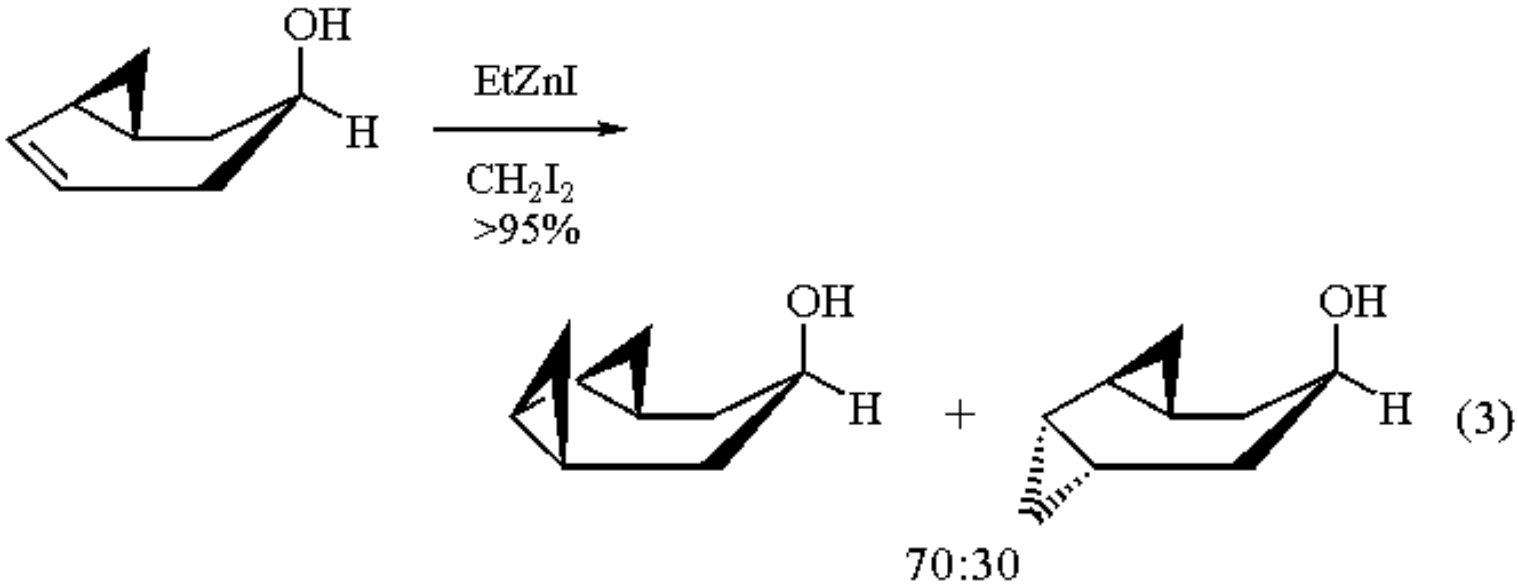

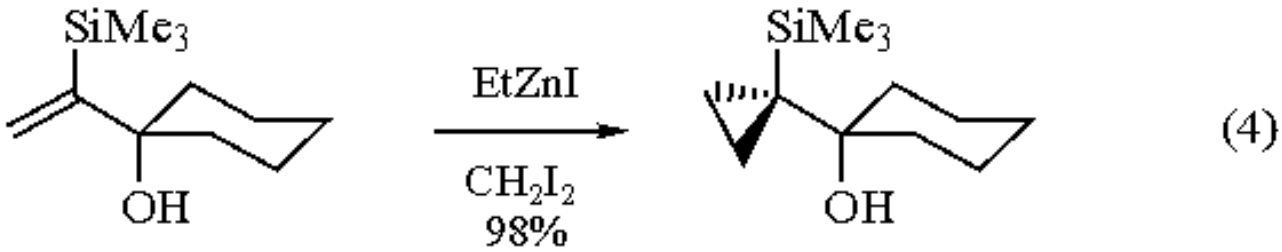

Other Uses.

Like other alkylzinc halides,[11] ethylzinc iodide adds to aldehydes,[4a] although in moderate yields due to its low reactivity. Far better results are obtained when the reactions are performed in the presence of Cu^I salts.[12] For example, reaction with cinnamyl chloride in the presence of catalytic ***Copper(I) Cyanide*** produces the allylated product (preferential S_N2' substitution) in satisfactory yield (eq 5).[13] Ethylzinc iodide has also been used for performing metathesis[14] and aldol condensation[15] reactions (eq 6), and as a polymerization[16] catalyst.

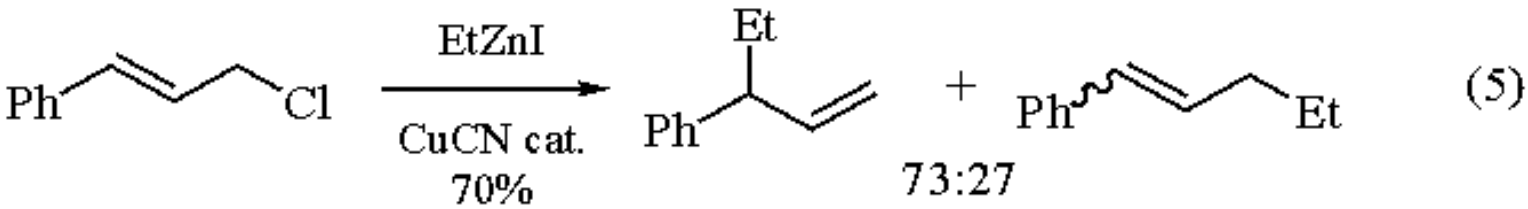

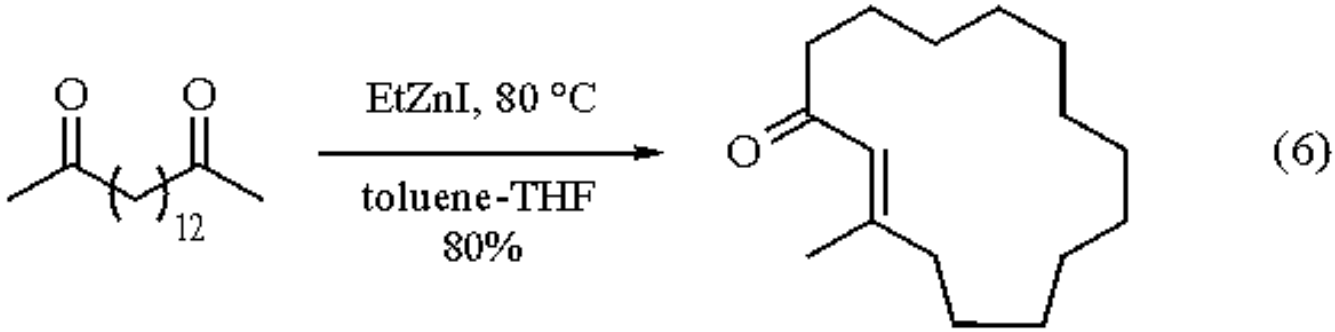

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Ethynyldimethylaluminum

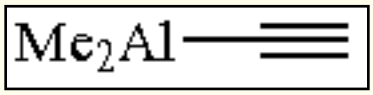

[66530-06-1] · C_4H_7Al · Ethynyldimethylaluminum · (MW 82.08)

(conjugate addition of ethynyl groups to enones[1,2])

Alternate Name: dimethylaluminum acetylide.

Solubility: sol ether.

Preparative Method: from ***Lithium Acetylide*** and ***Dimethylaluminum Chloride***.[1]

Handling, Storage, and Precautions: generated in situ and used directly.

Conjugate Addition of Acetylides to α,β-Enones.

Ethynyldimethylaluminum and its derivatives are useful reagents for the 1,4-addition of alkynyl groups to α,β-unsaturated ketones (eq 1).[1,2] The complex formed by reaction of ***Nickel(II) Acetylacetonate*** and ***Diisobutylaluminum Hydride*** (1:1) catalyzes the conjugate addition of the alkynyl unit of dialkylaluminum acetylides to both *s-cis* and *s-trans* enones. A low yield is obtained for direct addition of dimethylaluminum acetylide (R = H) to α,β-enones. This conjugate adduct is destroyed over a relatively short period of time in the presence of the nickel species due to side reactions involving the product, a terminal alkyne.

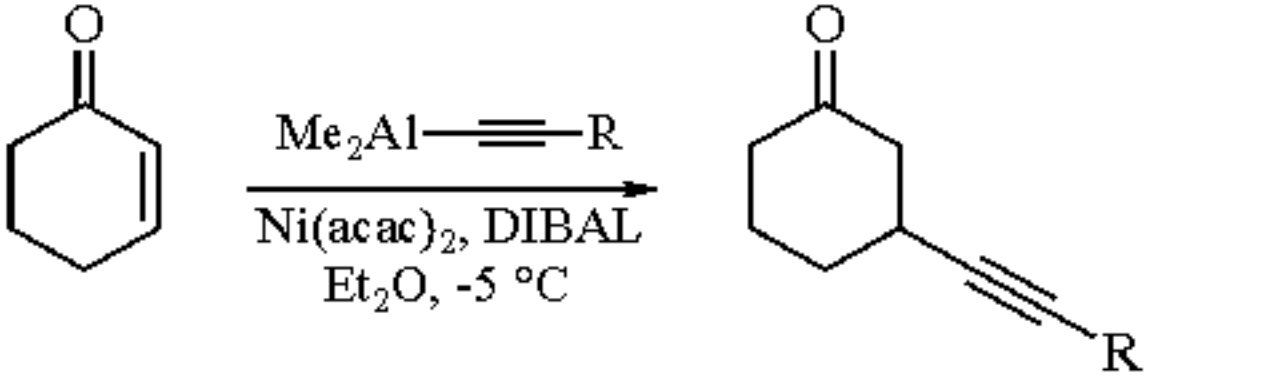

(1)

R = H, 15%; SiMe3, 80%

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Ethynylmagnesium Bromide

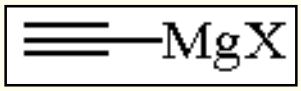

(X = Br)

[4301-14-8] · C_2HBrMg · Ethynylmagnesium Bromide · (MW 129.24) (X = Cl)

[65032-27-1] · C_2HClMg · Ethynylmagnesium Chloride · (MW 84.79)

(addition of acetylene to ketones;[1] preparation of TMSC&tbond;CH[2])

Preparative Methods: an *Organic Synthesis* preparation of ethynylmagnesium bromide[1] and chloride[2] from ***Acetylene*** and ***Ethylmagnesium Bromide*** or butylmagnesium chloride, respectively, is available. The use of butylmagnesium chloride instead of ethylmagnesium bromide is recommended[2] because of the greater solubility of the chloride.

Handling, Storage, and Precautions: ethynylmagnesium halides are air and moisture sensitive. They are usually used immediately after preparation.

Addition to Ketones and Aldehydes.[1]

Ethynylmagnesium bromide adds to ketones and aldehydes to give ethynyl carbinols (eq 1). The reagent is less prone to disproportionation to XMgC&tbond;CMgX than is monolithium acetylide. ***Lithium Acetylide*** provides the above product in 96% yield.[3] Ethynylmagnesium chloride also adds to aldehydes (eq 2).[4]

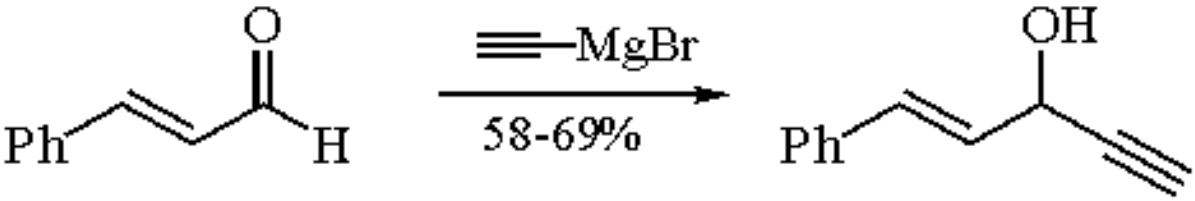

(1)

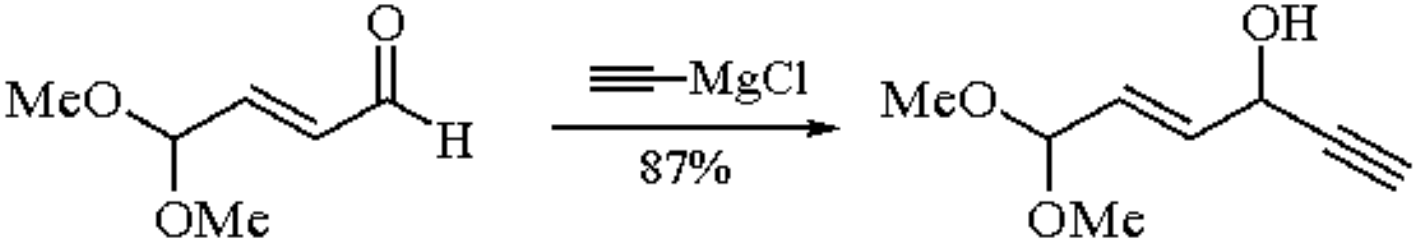

(2)

Preparation of TMS-acetylene.[2]

Treatment of ethynylmagnesium chloride with ***Chlorotrimethylsilane*** provides a good route to ***Trimethylsilylacetylene*** (eq 3).

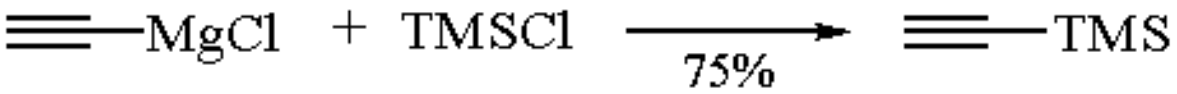

(3)

Related Reagents.

Lithium Acetylide; ***Lithium Chloroacetylide***; ***Lithium (Trimethylsilyl)acetylide***.

---

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β-Ethynyl-β-propiolactone[1]

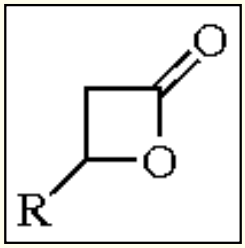

(R = CH&tbond;C-)

[59092-51-2] · $C_5H_4O_2$ · β-Ethynyl-β-propiolactone · (MW 96.09) (R = CH_2=CH-)

[7379-79-0] · $C_5H_6O_2$ · β-Vinyl-β-propiolactone · (MW 98.11)

(five-carbon homologating reagents for synthesis of dienoic and enoic acid derivatives)

Physical Data: R = ethynyl, bp 34-36 °C/3 mmHg; R = vinyl, bp 44-48 °C/4 mmHg.

Solubility: miscible with alcohol, acetone, ether, chloroform.

Form Supplied in: colorless oil.

Preparative Methods: by [2 + 2] cycloaddition of ketene with propynal (for β-ethynyl-β-propiolactone)[2a] and with acrolein (for the β-vinyl analog).[2b,c]

Handling, Storage, and Precautions: can be stored in the refrigerator for several months without noticeable changes. Cancer suspect reagent; β-ethynyl- and β-vinyl-β-propiolactone should be handled with due care.

β-Ethynyl-β-propiolactone.

Studies on the ring opening of β-ethynyl-β-propiolactone indicate that, under the influence of a catalytic amount of ***Palladium(II) Chloride*** in methanol or ethanol at room temperature, the ring opening takes place smoothly to give 3-alkoxy-4-pentynoic acids (eq 1).[2a] When the crude mixture is refluxed for a few hours, a quantitative esterification takes place.

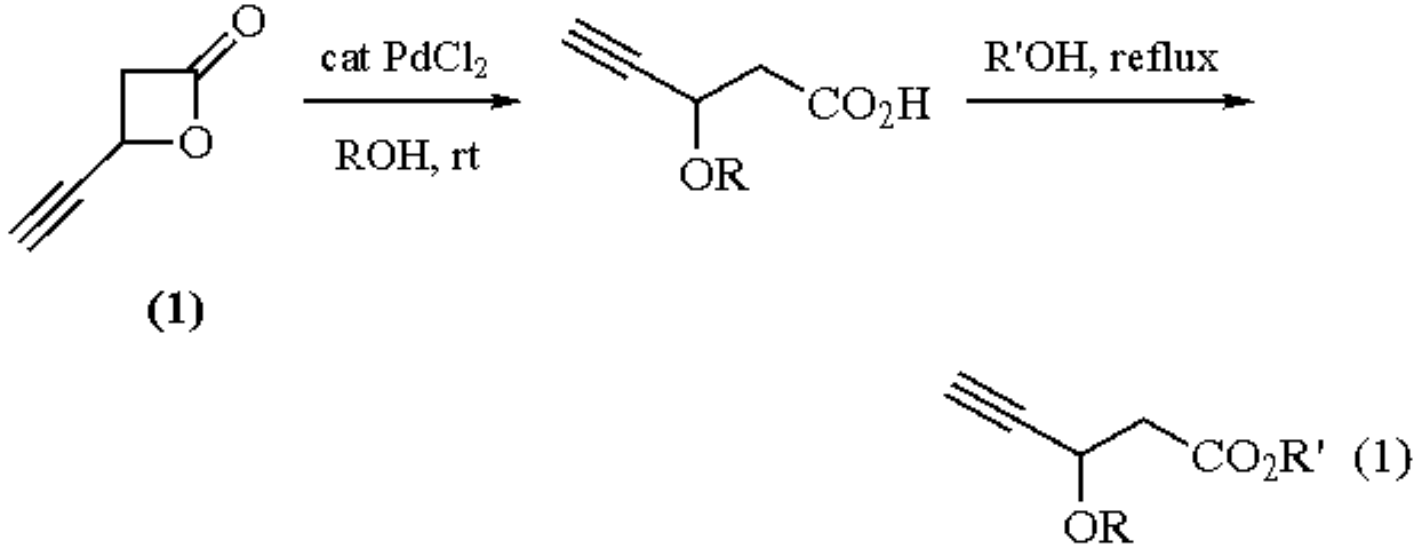

Regioselective attack at the terminal sp carbon is accomplished by the use of Grignard reagents in the presence of ***Copper(I) Iodide*** to give 3,4-alkadienoic acids (eq 2).[3] Results using a variety of Grignard reagents are summarized in Table 1. In the case of allylic metal reagents, diallylcuprate appears to be the reagent of choice.

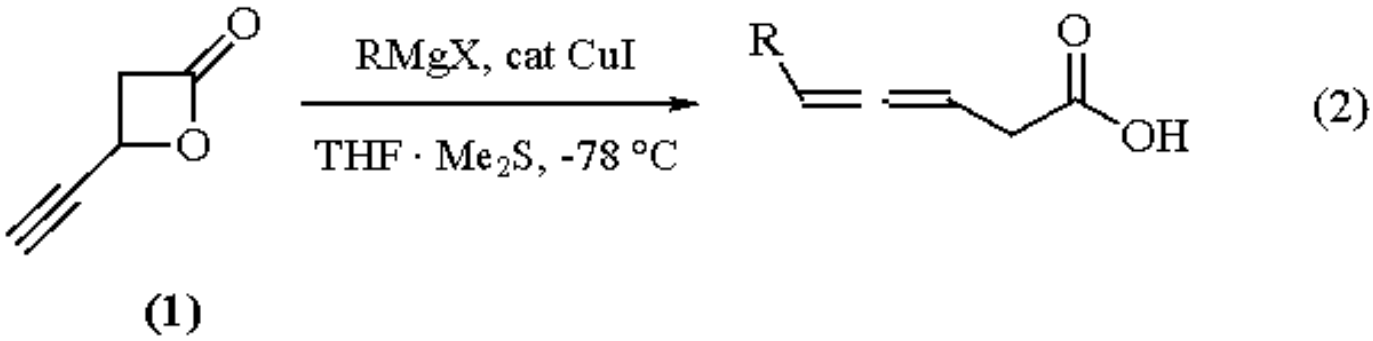

Table 1 Reaction of (**1**) with Grignard Reagents in the Presence of Copper(I) Iodide (eq 2)

RMgX	Yield (%)	RMgX	Yield (%)
MeMgBr	97	PhMgBr	78
BuMgBr	97	VinylMgBr	72
s-BuMgCl	90	AllylMgBr	11
t-BuMgCl	85	$(Allyl)_2CuMgBr$[a]	54

[a] In the absence of copper(I) iodide.

The application of this procedure to the synthesis of pellitorine is accomplished by the use of this ring opening followed by isomerization of the allenic double bond and amide formation (eq 3).[4]

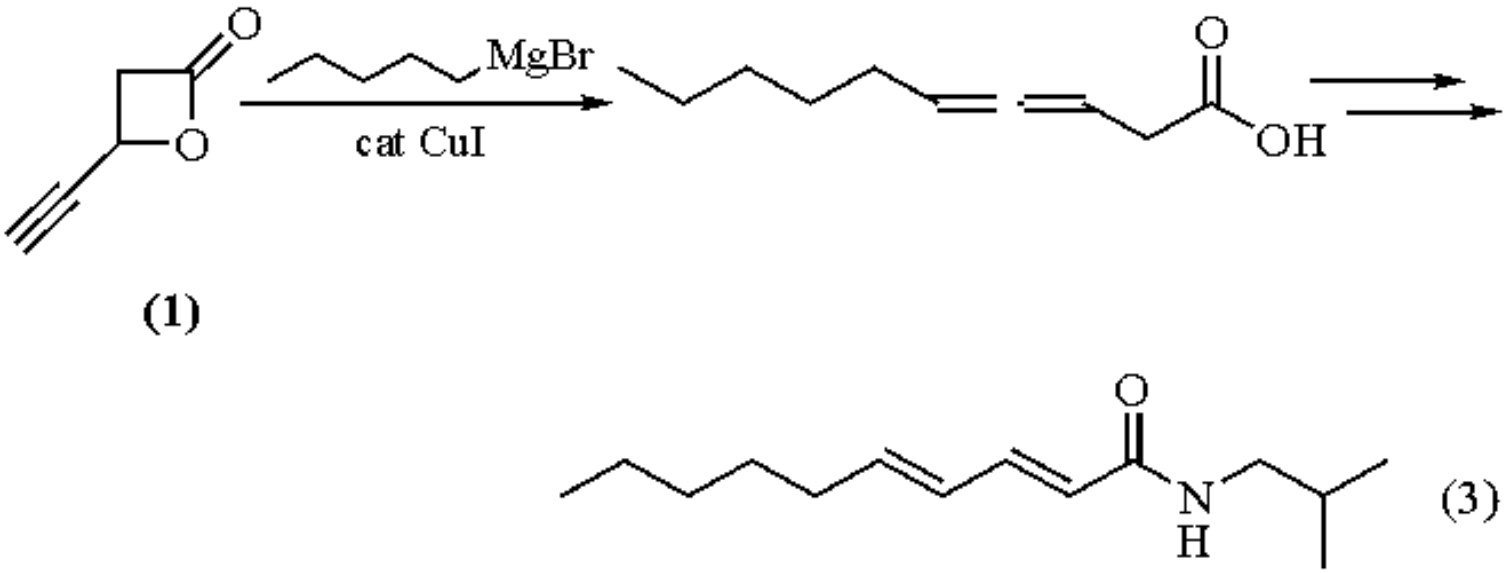

β-Vinyl-β-propiolactone.

The regioselectivity of the ring opening of the vinyl analog is dependent on the nucleophile used (eq 4). ***Sodium Methoxide***, a hard nucleophile, effects acyl-oxygen cleavage (path A), whereas methanol and benzylamine attack at the β-carbon to the carbonyl (path B), and a soft nucleophile such as ***Lithium Iodide*** or organocopper reagents favor path C.[5] In the case of organocopper reagents, the geometry of the resulting double bonds is (*E*) when the reaction is conducted at lower temperatures. Similar to the reaction with the β-ethynyl derivative, diallylcuprate seems to be a better reagent for allylation.[5,6] In addition to Grignard reagents, the regioselective ring opening proceeds with metalated *N*,*N*-dimethylhydrazone (**2**), an enolate equivalent, to give 7-oxo-3-alkenic acid,[7] whereas lithium dithioester enolate (**3**) effects the formation of 6-(methylthio)thiocarbonyl-(*E*)-3-alkenoic acid.[8]

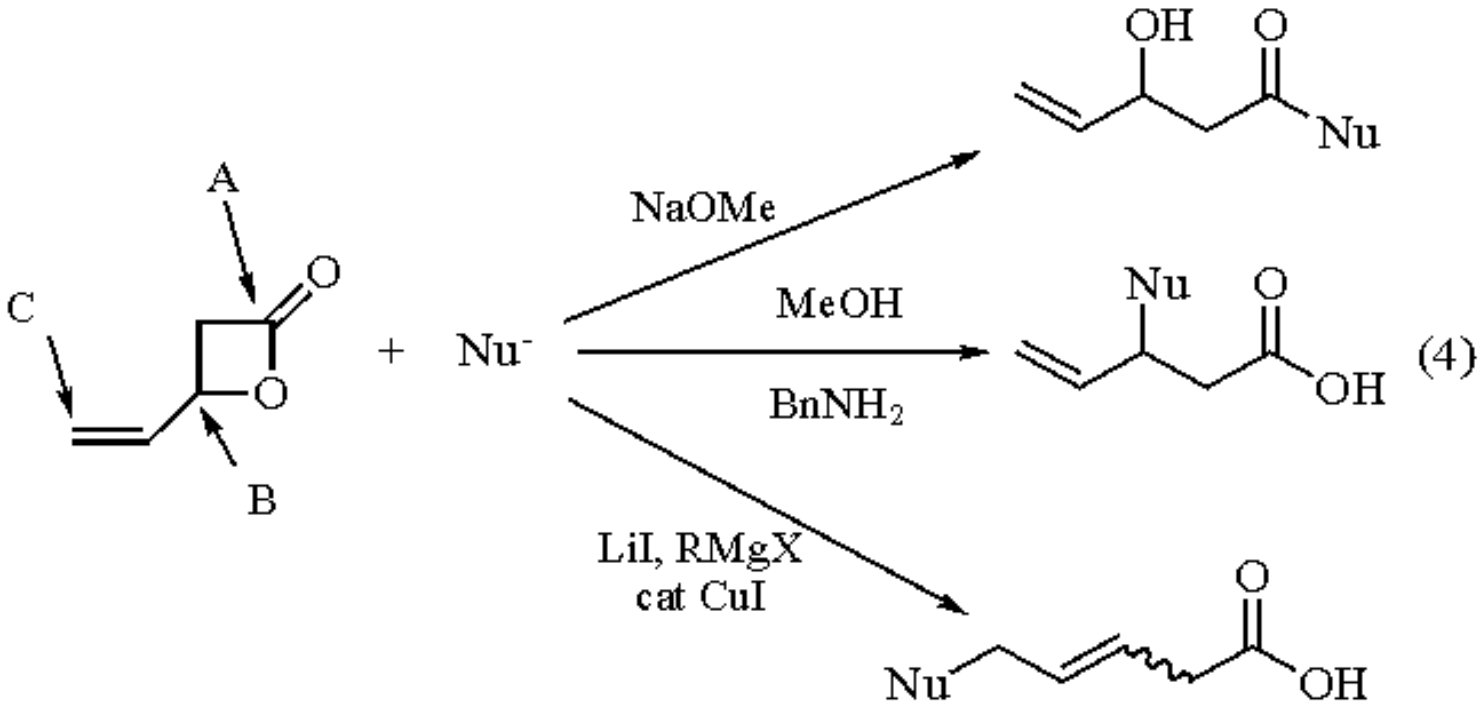

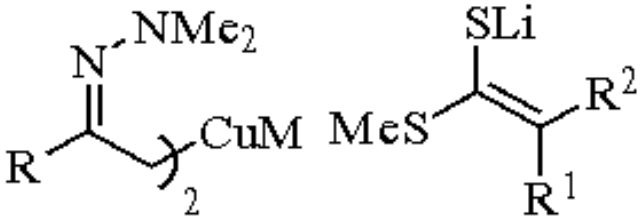

(2) **(3)**

Under the influence of a catalytic amount of $PdCl_2$ in methanol or ethanol at room temperature, the β-vinyl derivative also undergoes ring opening smoothly to give 3-alkoxy-4-pentenoic acids (eq 5).[2a]

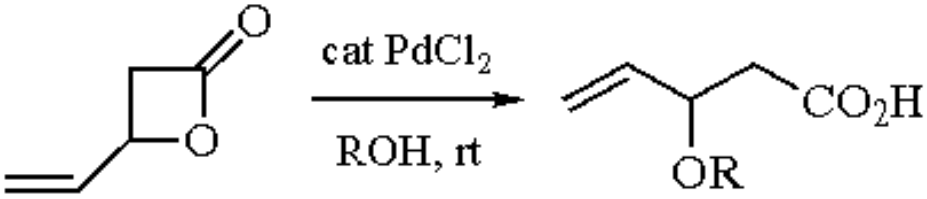

(5)

The reaction with ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) followed by sodium methoxide gives cyclopropylacetic acid (eq 6).[9]

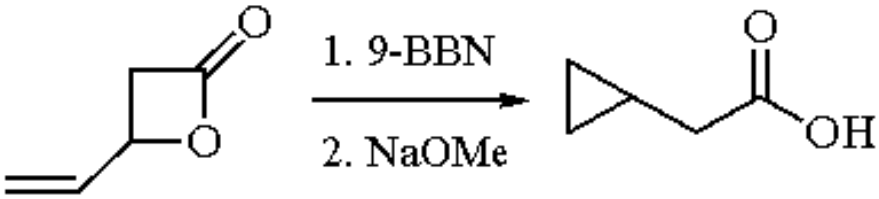

(6)

β-Vinyl-β-propiolactone serves as a useful C_5 unit for the syntheses of royal jelly acid (**4**), queen substance (**5**),[10]

recifeiolide (**6**), and pyrenophorin (**7**).[11]

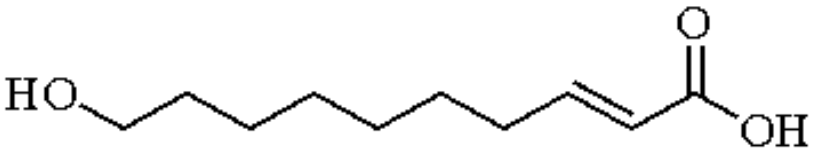

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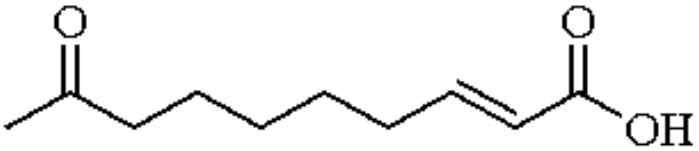

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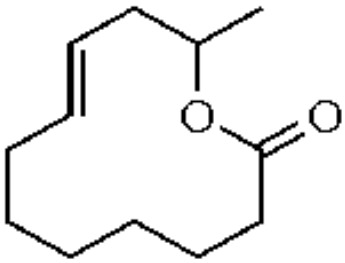

(6)

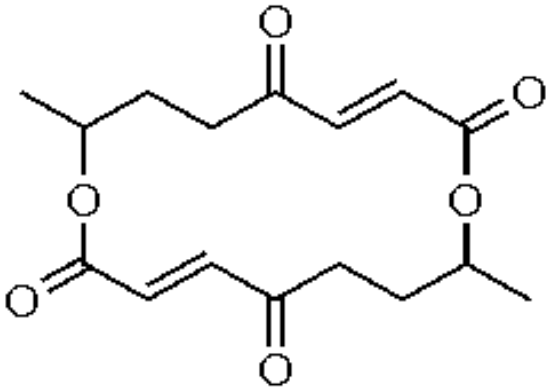

(7)

Related Reagents.

N-Benzyloxycarbonyl-L-serine β-***Lactone***; α,β-***Butenolide***; γ-***Butyrolactone***; ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***; β-***Methyl***-β-***propiolactone***; β-***Propiolactone***.

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Ethynyl *p*-Tolyl Sulfone[1]

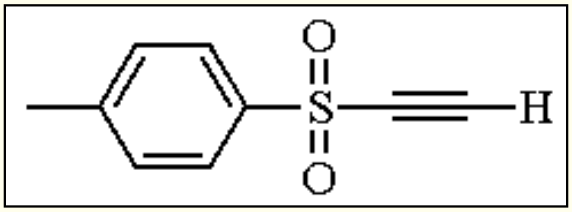

[13894-21-8] · $C_9H_8O_2S$ · Ethynyl *p*-Tolyl Sulfone · (MW 180.22)

(dienophile used in electrocyclic reactions such as dipolar cycloaddition,[2-4] Diels-Alder reaction,[5-7] and ene cyclization;[8] electron-poor Michael acceptor in conjugate additions;[9-17] undergoes direct displacement with organometallic complexes to give aryl- or alkylacetylenes[18])

Alternate Name: *p*-toluenesulfonylacetylene.

Physical Data: colorless crystals, mp 74-75 °C, mp 75 °C (hexane-ethyl acetate, 95:5).[19]

Solubility: sol most organic solvents.

Analysis of Reagent Purity: based on combustion and spectral examination.[19]

Preparative Methods: has been prepared by several groups over the years employing a variety of synthetic strategies including ethynyl Grignard addition to *p*-toluenesulfonyl fluoride,[20] dehydroiodination of (*E*)-2-iodo-1-tosyl-1-ethene,[21] oxidative elimination of β-[(4-methylphenyl)seleno]vinyl sulfone,[22] dehydrobromination of *cis*- and *trans*-2-bromovinyl 4-methylphenyl sulfone,[23] diazotization of 4-[(4-methylphenyl)sulfonyl]-5-aminoisoxazole,[24] and oxidation of ethynyl thioether.[25] The modified strategy commonly used today is an established Friedel-Crafts based procedure first performed by Bhattacharya et al.[26] but recently exploited by Waykole and Paquette (eq 1).[19] Its simplicity and mildness has shown it to be broadly useful since it bypasses the need for immoderate conditions encountered in the earlier strategies.[19]

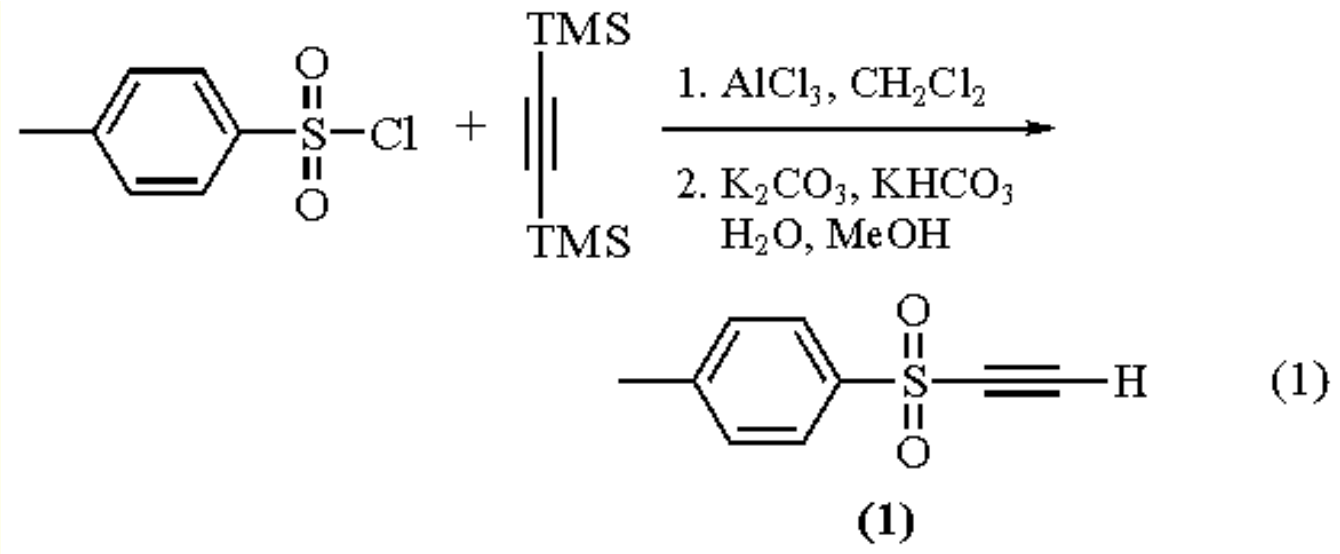

Purification: recrystallization readily removes an impurity formed by flash chromatography.

Handling, Storage, and Precautions: decomposition of the intermediate complex *p*-toluenesulfonyl chloride-aluminum chloride-bis(trimethylsilyl)acetylene with hydrochloric acid and ice is exothermic and due caution is recommended. Also, a nitrogen atmosphere is suggested throughout its preparation due to the hygroscopic nature of the reagents and intermediate(s) involved.[19]

Dipolar Cycloadditions.

Padwa and Wannamaker[2] have shown recently that ethynyl *p*-tolyl sulfone (**1**) undergoes a thermal 1,3-dipolar cycloaddition reaction with diazomethane (eq 2). Surprisingly, regioisomer (**2**) is formed in preference to *N*-methyl-4-(*p*-tolylsulfonyl)pyrazole, the expected isomer. Substitution of the acetylenic proton in (**1**) with the bulky trimethylsilyl group, however, furnishes only the expected regioisomer in quantitative yield following desilylation with fluoride. Further studies with 2-diazopropane led Padwa and Wannamaker to conclude that the difference in regioselectivity was primarily due to steric hindrance and not to an electronic effect.[2]

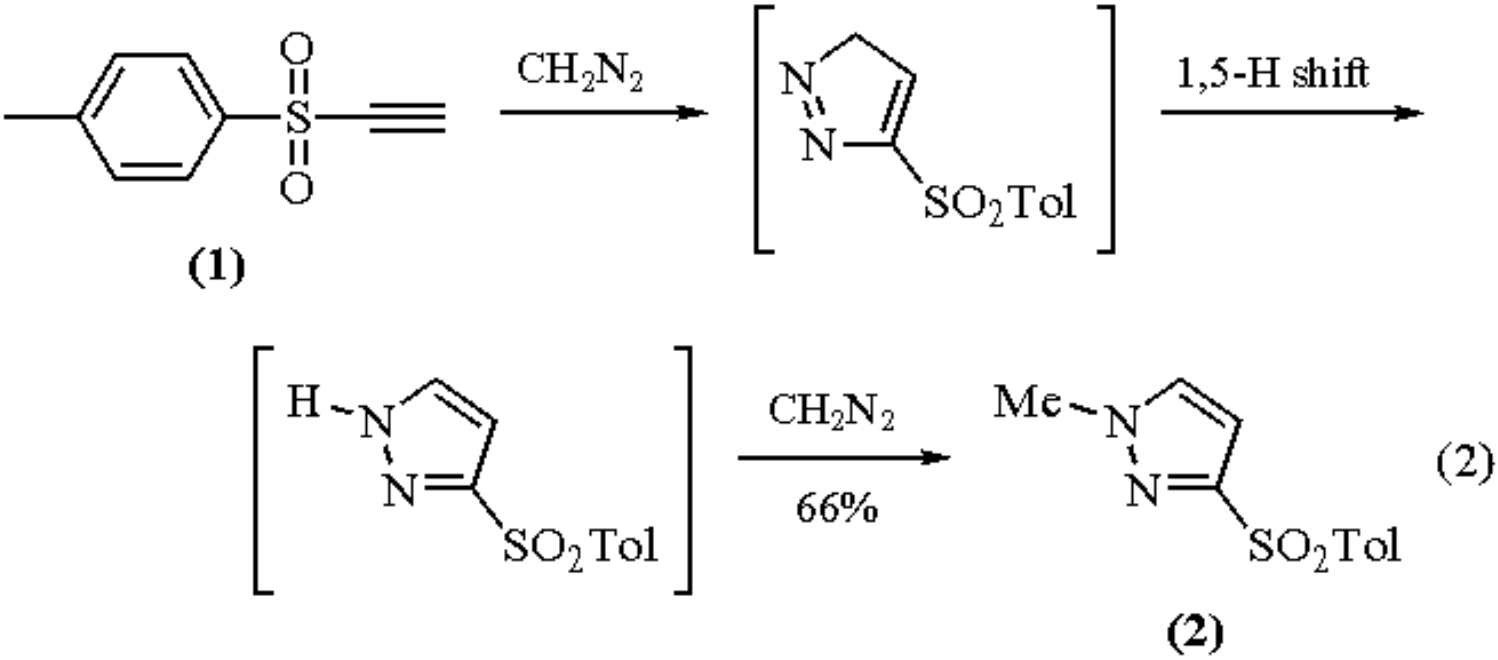

Heteroaromatic *N*-oxides and ylides are also suitable dipoles in this reaction.[3,4] For example, 4-chloropyridine *N*-oxide undergoes a smooth and clean cyclization with (**1**) in boiling toluene to yield 3-tosylfuro[3,2-*c*]pyridine (**3**) in 65% yield (eq 3).

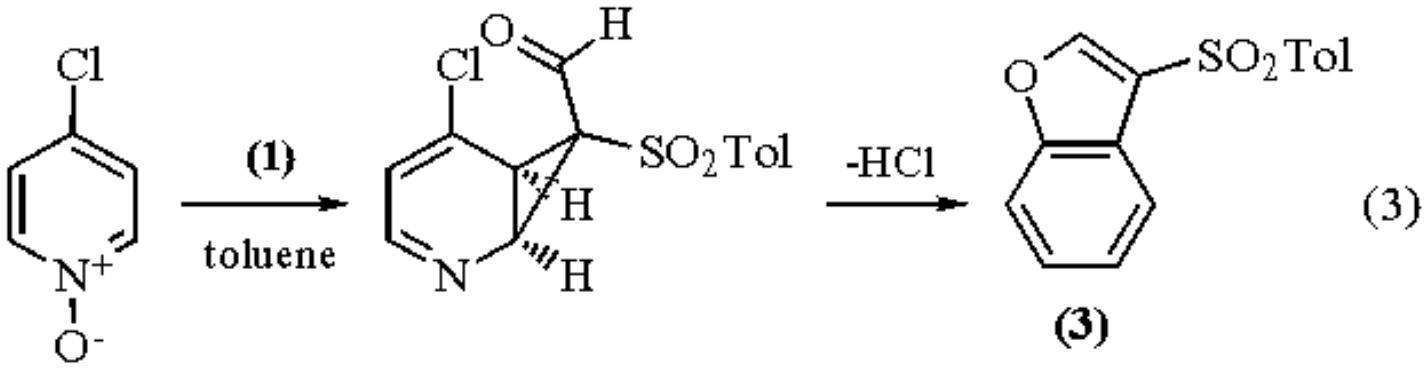

Diels-Alder Reactions.

The dienophilic properties of (**1**) in combination with the reductive elimination of the tosyl unit have made this compound a useful acetylene synthetic equivalent in various Diels-Alder reactions; it has a pivotal role in the synthesis of the elusive 7-azanorbornadiene (eq 4).[5] Cycloaddition is easily accomplished on a preparative scale in 60% yield by heating (**1**) with *N*-methoxycarbonylpyrrole. Desulfonation of (**4**) with 6% ***Sodium Amalgam*** in buffered medium affords a 42% yield of protected 7-azanorbornadiene (**5**), which is converted to the parent compound in two steps (72% yield). Notably, the first *C*-unsubstituted derivative, 7-tosyl-7-azanorbornadiene was synthesized by a laborious route by Prinzbach and Babsch;[27] however, cleavage of this protecting group was troublesome.[5]

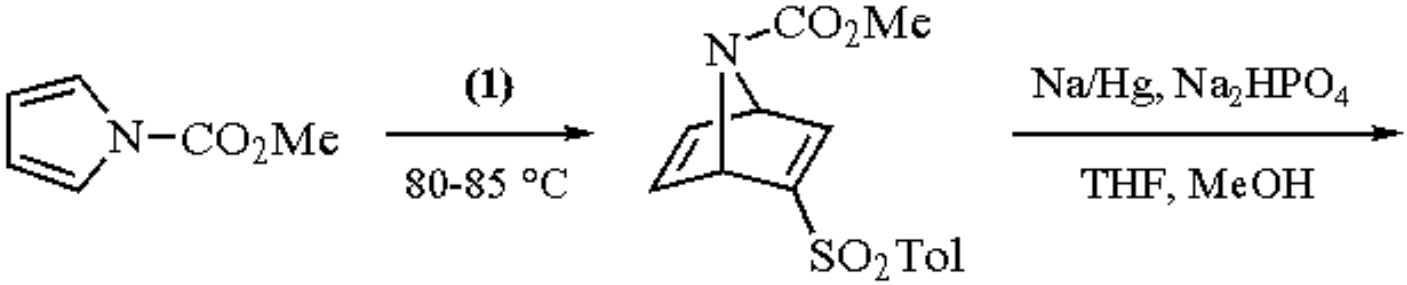

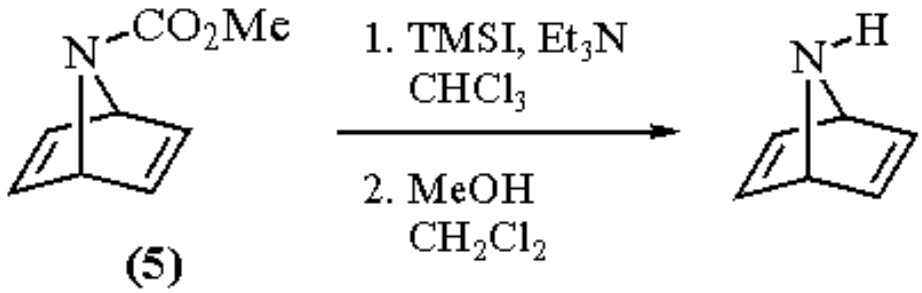

(4)

Another use of (**1**) as an acetylene equivalent is in its central role in the construction of the polyhedron [4]peristylane, which can be prepared in only 11 steps (eq 5).[6] Examples of Diels-Alder reactions between ethynyl *p*-tolyl sulfone and other dienes also exist.[7]

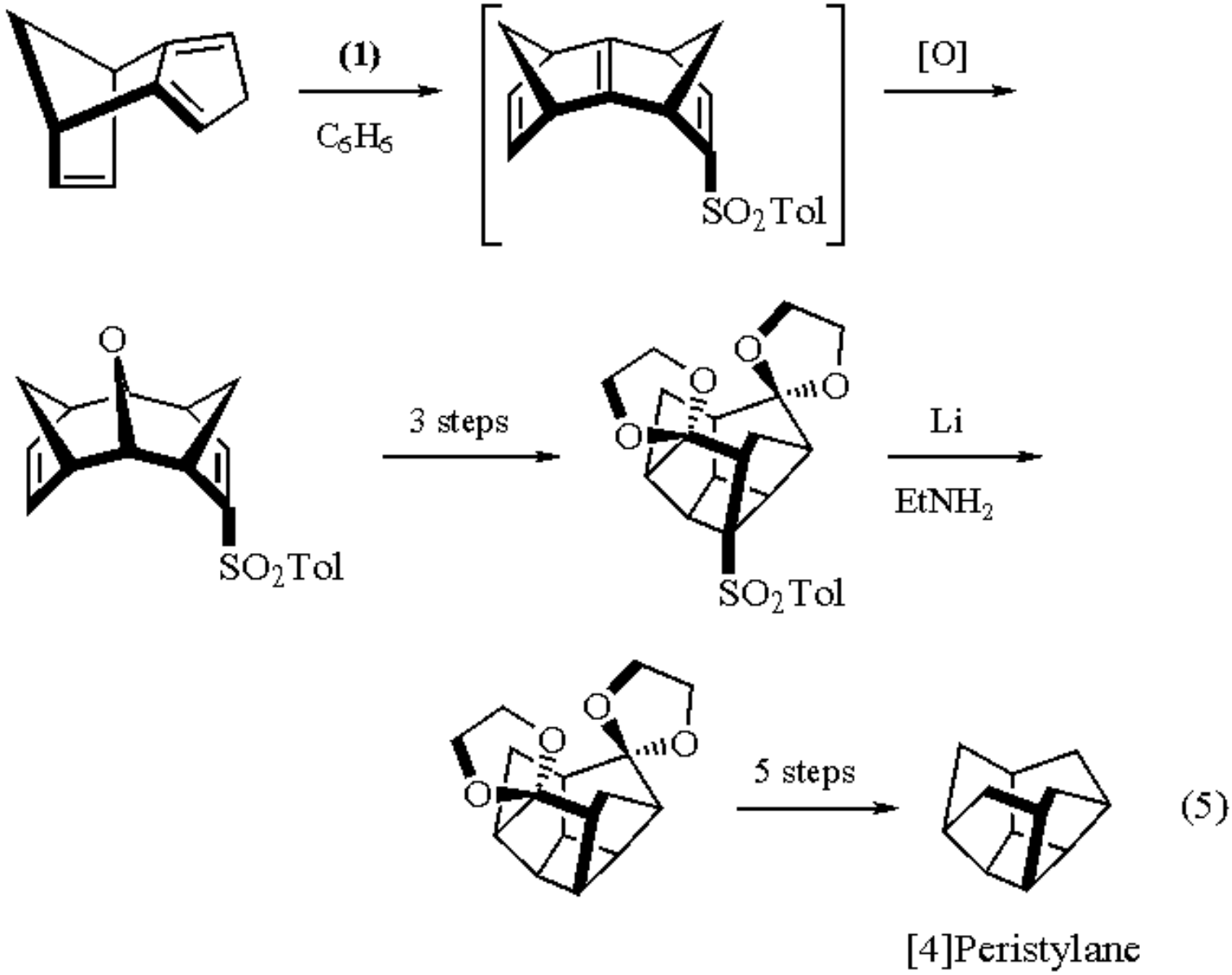

Ene Cyclizations.

Ethynyl *p*-tolyl sulfone has been shown by Snider et al.[8] to undergo a ***Ethylaluminum Dichloride***-catalyzed ene cyclization with alkenes to furnish a functionalized two-carbon fragment, a vinyl sulfone, which is a versatile synthon.[28] For example, 2,3-dimethyl-2-butene reacts with (**1**) in the presence of catalytic ethylaluminum dichloride to give dienyl sulfone (**6**) in 89% yield (eq 6). In general, these reactions proceed at 25 °C in aromatic solvents and are best for highly substituted, i.e. electron-rich, alkenes. Good yields of ene adducts are obtained from all alkenes with at least one disubstituted carbon.[8] Monosubstituted alkenes give low yields of adducts while 1,2-disubstituted alkenes give low yields of a mixture of ene product and cyclobutene byproduct.[8] The choice of ethylaluminum dichloride as catalyst appears to be optimal.

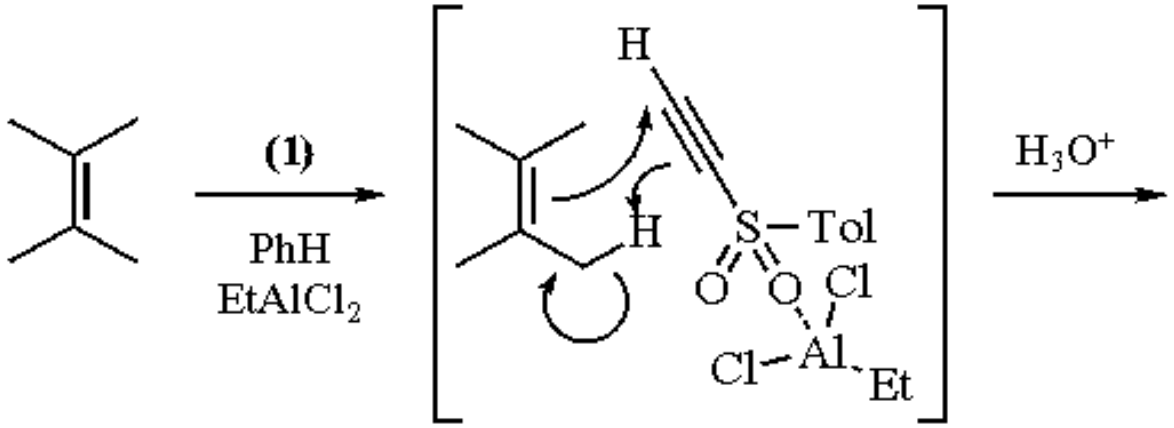

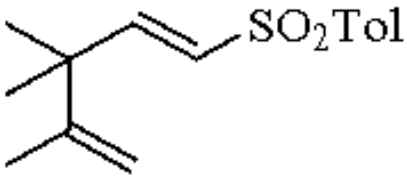

(6)

(6)

Conjugate Additions.

As a class of compounds, arylsulfonylalkynes behave as good Michael acceptors toward nucleophiles such as amines,[9] alkoxides,[10] thiolates,[11] hydroxylamines,[12] cuprates,[13] malonate anions,[14] and other enolates[15] (eq 7). Some examples are provided in Table 1.

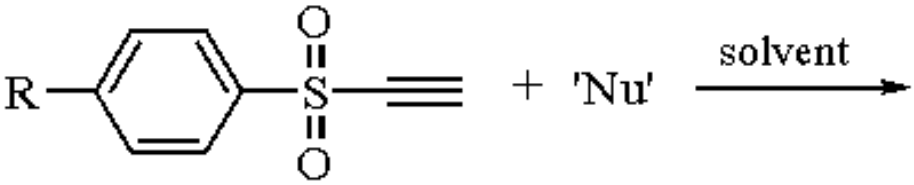

(1) or (7)

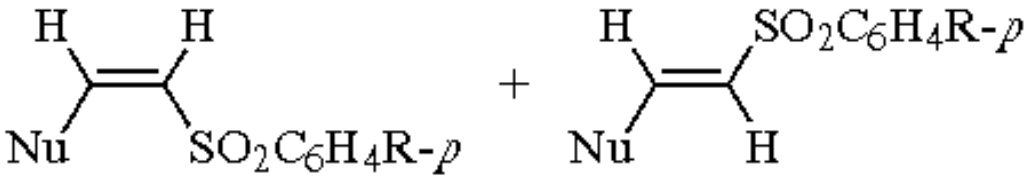

(7)

cis or (*Z*) *trans* or (*E*)

Table 1 Stereoselectivities Arising from Conjugate Addition Reactions (eq 7) between (**1**) (R = Me) or (**7**) (R = H) and Various Nucleophiles

R	Nucleophile (Nu)	Solvent	Yield (%)	Configuration (*Z*) (%)	Configuration (*E*) (%)
Me	*i*-Pr_2NH	EtOH	91	0	100
Me	Ethylenimine	EtOH	64	100	0
Me	PhONa	Neat	25	100	0
Me	*p*-MeC_6H_4SNa	MeOH	65	100	0[a]
				0	100[b]
H	(1*S*)-(+)-10-Mercaptoiso-borneol	MeCN	66	>95	<5
Me	Me_3NHOH	EtOH	63	NG	NG[c]
Me	CyNHOH	EtOH	51	NG	NG[c]
H	Me_2CuLi	Et_2O	70	0	100
H	*s*-Bu_2CuLi	Et_2O	80 90	22	78
H	*n*-$Bu(EtO_2C)_2CNa$	THF	85	>95	<5

[a] 2 h reaction time. [b] 144 h reaction time. [c] Not given.

Oxygen- and sulfur-containing anionic nucleophiles such as alkoxides and thiolates add kinetically in a *cis* fashion to yield the (*Z*)-isomer; however, over extended periods of time, isomerization to the more stable (*E*)-isomer can be accomplished via an addition/elimination pathway.[11a,29] Nevertheless, several different mechanistic pathways have been postulated and may be operative, depending on the nature of the substrate.[11a,29] Cuprates, in general, react to give almost exclusively (100-95%) the (*E*)-isomer at 0 °C, but at lower temperatures, such as -78 °C, the (*Z*)-isomer begins to make a minor (5-20%) contribution, perhaps through reactive intermediate (*E*) to (*Z*) isomerization.[13] In contrast, soft enolates like malonate anions give predominately the (*Z*)-isomer.[14] Owing to transition-state stabilization of the *cis* configuration, neutral nucleophiles like amines add stereospecifically in a *trans* manner to give (*E*)-isomer unless the adducts are capable of immonium-type resonance, in which case the addition is followed by an extremely rapid isomerization to the (*Z*) configuration.[9] Moreover, hydroxylamines also undergo conjugate addition to (**1**), but ensuing tautomerization provides nitrones usually as the main product.[12]

Dialkylaminoalkynes have been shown by Himbert and Kosack[16] also to react with (**1**) through its extended conjugation at room temperature to give 2-amino-5-(*p*-tolylsulfinyl)furans, which, if desired, can be thermally isomerized to maleic acid derivatives. *N*-Methyl-*N*-ethynylamine (**8**), for example, was stirred at rt with ethynyl *p*-tolyl sulfone to give (**9**) in 64% yield.[17] Isomerization of (**9**) in refluxing acetonitrile for 3 h gave almost exclusively the (*Z*)-maleate (**10**) (eq 8). The (*E*)-isomer was barely detectable by NMR spectroscopy.

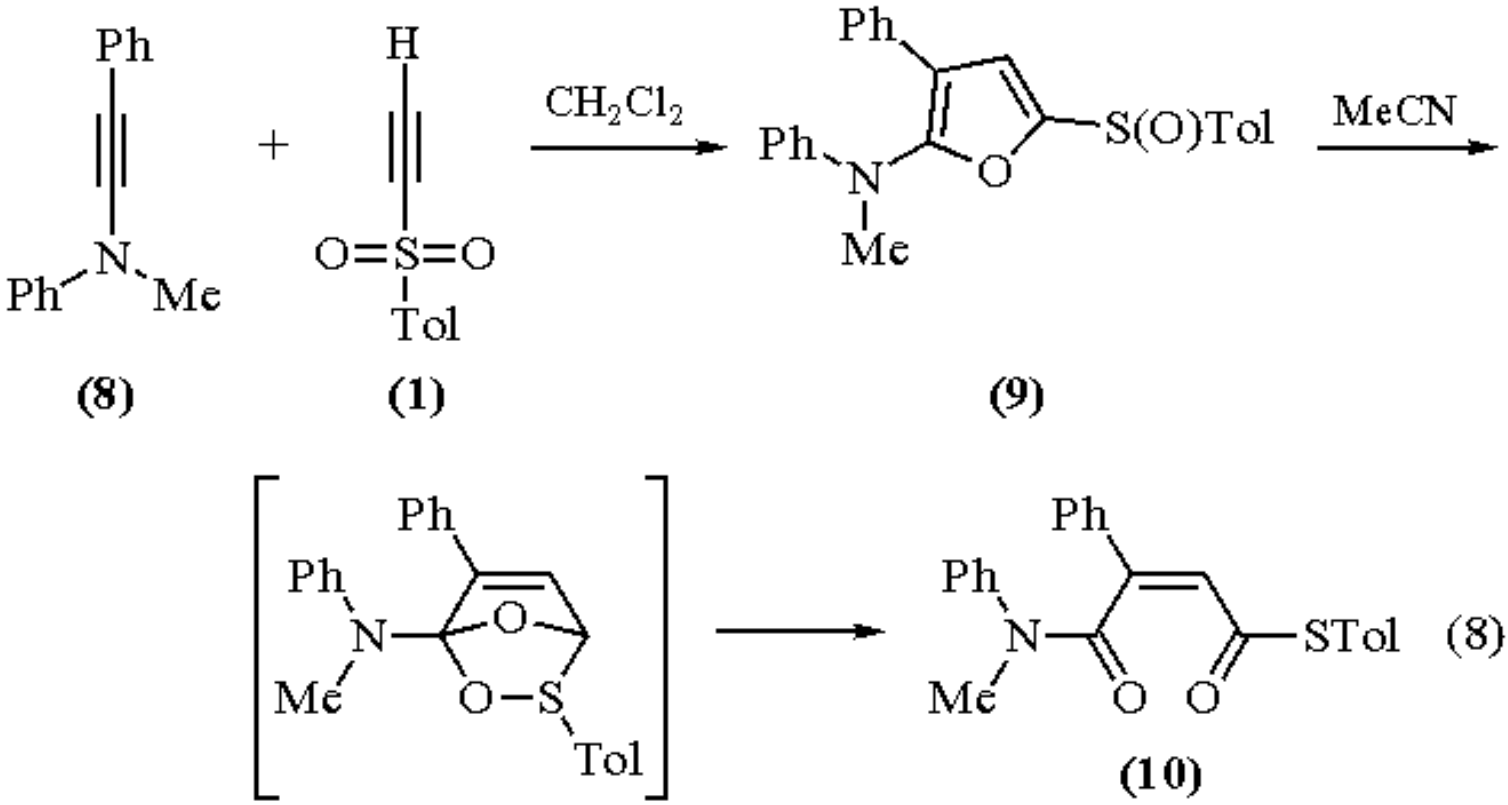

(8)

Direct Displacement.

Replacement of the arylsulfonyl group in substrates like (**1**) by various alkyl and aryl Grignard or lithium complexes has been reported.[17] The reaction is believed to involve initial attachment of the organometallic to the sulfonyl-bearing (α) carbon followed by expulsion of the arylsulfinate leaving group.[17] Such a transformation offers another synthetic route to aryl- or alkylacetylenes. As such, mesitylmagnesium bromide reacts with ethynyl *p*-tolyl sulfone to give mesitylacetylene (**11**) in 85% yield (eq 9).

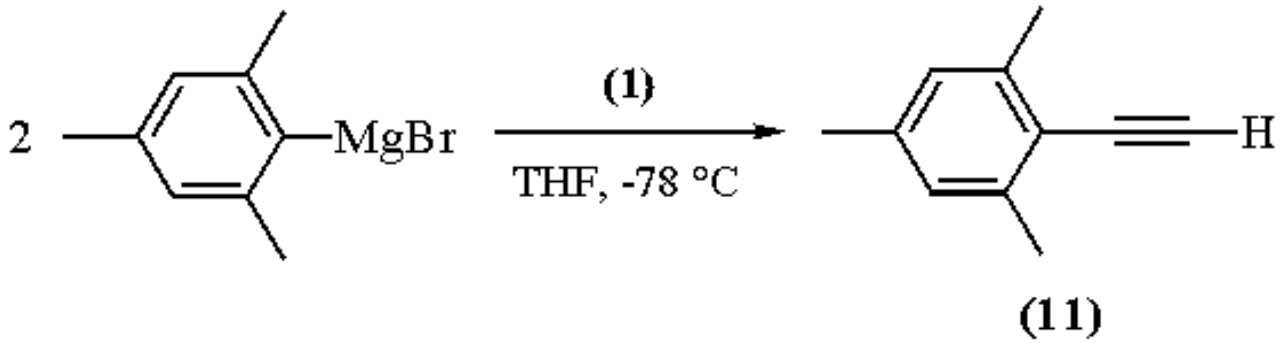

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Bristol-Myers Squibb Co., Wallingford, CT, USA

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Europium(III) Chloride[1]

$EuCl_3.6H_2O$

(anhydrous)

[10025-76-0] · Cl_3Eu · Europium(III) Chloride · (MW 258.32) (hexahydrate)

[13759-92-7] · $H_{12}Cl_3EuO_6$ · Europium(III) Chloride · (MW 366.41)

(member of a family of moderate Lewis acids capable of acting as catalysts in selected oxidative and reductive processes,[2-4] with particular utility in systems designed to exploit the chemistry of divalent and zerovalent reagents[2,4] and organometallic intermediates[5-7])

Alternate Name: europium trichloride.

Physical Data: mp 623 °C (dec); *d* 4.89 g cm^{-3}.

Solubility: anhydrous salt: sol dilute HCl; hydrolyzes in water to form oxychloride; sol alcohol and acetone; slightly sol in THF. Hydrate: sol water.

Form Supplied in: hydrated white crystalline solid which can be dehydrated to a yellow powder which intensifies in color upon heating; commercially available in both forms; readily recyclable; typically >99.9% pure with regard to total metallic impurities.

Preparative Methods: highest quality material is produced by reacting Eu_2O_3 at ca. 200 °C with the vapors of a suitable chlorinating agent (CCl_4 has been shown to work well).

Handling, Storage, and Precautions: hydrated salt is hygroscopic: keep tightly closed; hydration state may vary slightly; anhydrous salt should be handled and kept under nitrogen or argon; color modification to yellow-green may occur upon long-term storage under inert atmosphere.

Introduction.

The ability of selected lanthanide salts to promote an intriguing array of organic reaction mechanisms has led synthetic chemists to focus on key elements such as cerium,[8] lanthanum,[9] and samarium.[10] The relatively low cost of cerium and lanthanum reagents makes them particularly attractive for synthetic studies, whereas the use of samarium in organic synthesis features the unique chemistry of the Sm^{II} species, typically derived in situ or used in solution as the diiodide (see ***Samarium(II) Iodide***).[10,11] The other lanthanide species which form stable M^{II} oxidation states, ytterbium and

europium, have not been as extensively explored as synthetic organic reagents for a variety of reasons. In the case of europium, the primary factor has been material cost relative to the other lanthanides.

The accessibility of both Eu^{III} and Eu^{II} species has not been lost on researchers in various fields. Favorable thermodynamic parameters have been the basis for studies of new energy systems;[12] in the mid-1980s, investigation of solar energy conversion determined that both $SmCl_3$ and $EuCl_3$ (hydrated) catalyze the photogeneration of hydrogen in weakly acidic alcohol solutions, forming a variety of organic byproducts by a light-assisted solvent-to-ion single electron transfer.[13]

Hydroxymethylation.

Adapting hydrogen-generating Eu^{III}/Eu^{II} photoredox systems directly to organic photochemical reactions has shown limited synthetic promise. A radical mechanism governing the reaction of α-methylstyrene with a hydrogen atom and a hydroxymethyl radical was proposed for eq 1.[14] The formation of Eu^{II} ions as the key reactive intermediate for the reduction was confirmed by spectroscopic measurements.

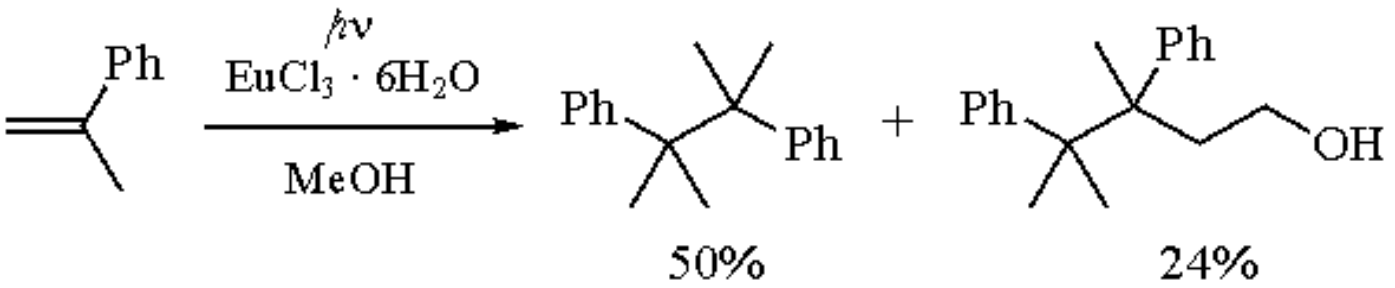

(1)

When 1,3-dimethyluracil is used as substrate, efficient regioselective hydroxymethylation takes place via an electron transfer mechanism (eq 2).[15] The Eu^{II} resulting from the oxidation of the alcohol becomes the primary light-absorbing species, promoting hydrogen generation. This chemistry was deemed pertinent to the photoinduced cross-linking of uracil and amino acids.

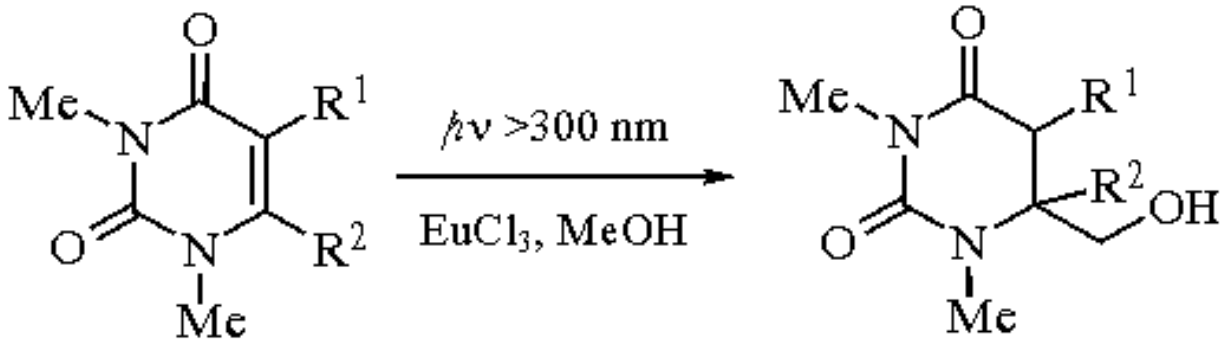

(2)

Further insights into the scope of this redox system came from a study of the reaction of various alkenes with methanol solutions of europium trichloride. The process has been described as a useful, general hydroxymethylation method.[16] The potential of this technique in more elaborate organic synthesis was explored in a study involving hydroxyalkylation and lactone formation of dialkyl malonates, where the europium species serves as photocatalyst and also as a condensation catalyst (eq 3).[17] A similar reaction carried out in ethanol produced a more complex array of products at a significantly reduced rate of reaction. Diethyl maleate undergoes photoconversion according to eq 4.

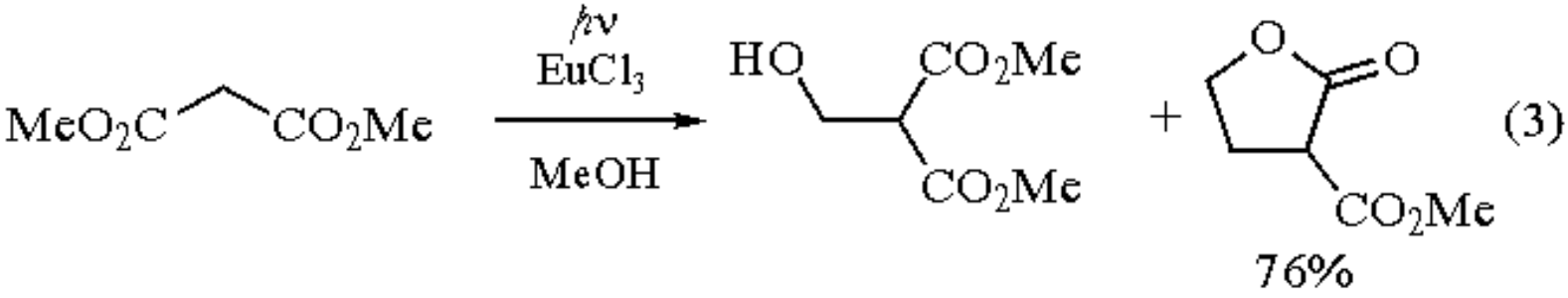

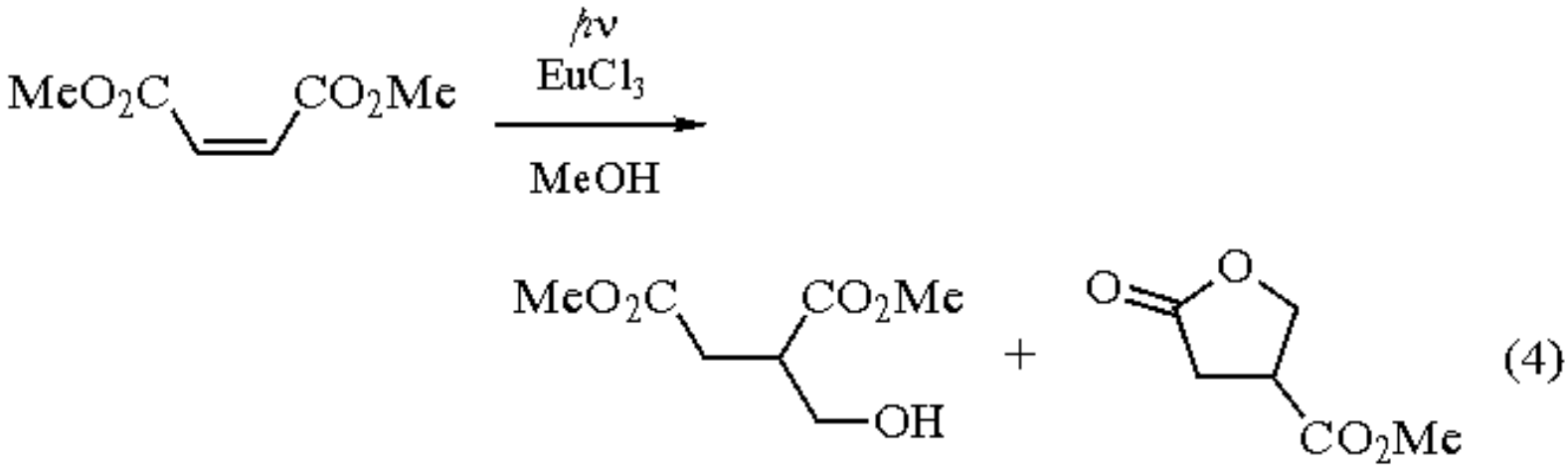

Lewis Acid Catalyst.

More recent literature surveys of organic reactions involving europium trichloride offer little beyond comparative studies of lanthanide chlorides as Lewis acid catalysts in classical organic syntheses such as Friedel-Crafts reactions. The efficiency of a variety of anhydrous lanthanide chloride catalysts relative to ***Aluminum Chloride*** in the benzylation of benzene follows the order $AlCl_3$ > $DyCl_3$ > $SmCl_3$ > $YbCl_3$ > $EuCl_3$.[18]

Transesterification of phosphate diesters is an area in which the catalytic activity of trivalent lanthanide ions appears to exceed that of transition metal ions.[19] In the reaction shown in eq 5, the observed order of activity was Tb^{III} > Gd^{III} > Yb^{III} > Eu^{III} > Nd^{III} based on apparent-second-order rate constants. The catalytic activity of Eu^{III} in phosphorus(V) nucleophilic displacement reactions has also been demonstrated in the cleavage of transfer-RNA, where relative rates of cleavage follow the order Eu^{III} > Pb^{II} > Zn^{II} > Mg^{II}.[20] In this case, favorable Lewis acid character rather than redox potential seems to be the dominant factor in metal ion catalyst efficiency.

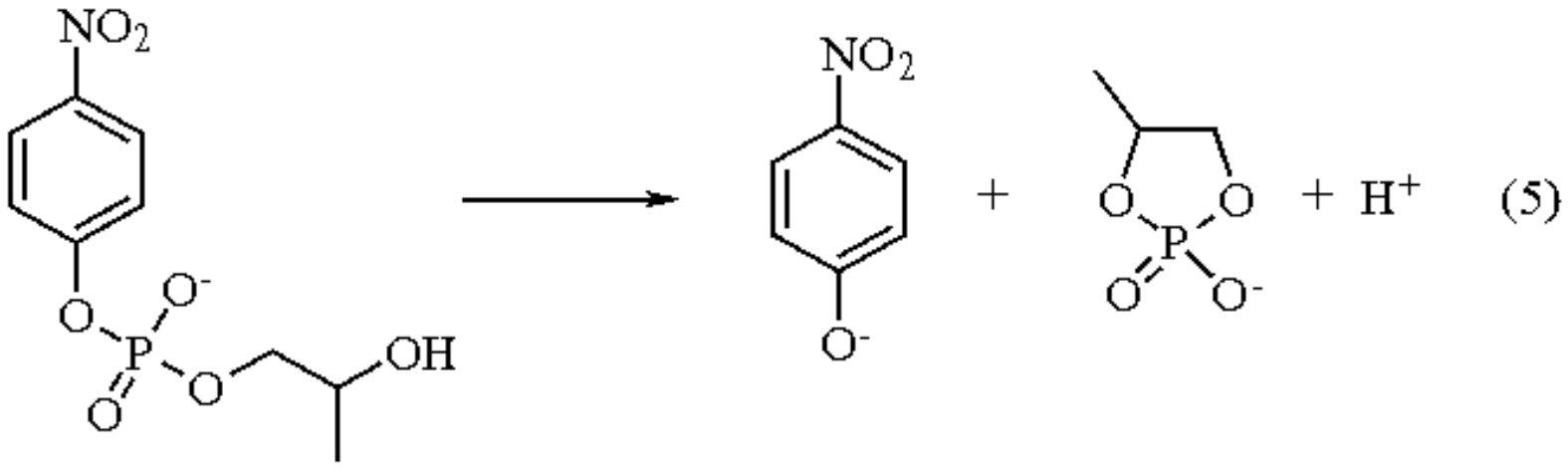

Overcoming the unfavorable economics of synthetic procedures involving europium species may depend upon the development of creative methods that combine europium's unique redox capabilities with the favorable Lewis acidity exhibited in selected bioinorganic processes. Otherwise, other lanthanide reagents will continue to dominate the attention of synthetic organic chemists.

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Ferrocene

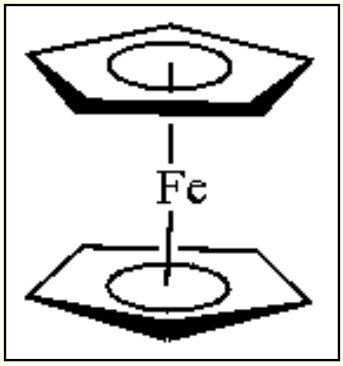

[102-54-5] · $C_{10}H_{10}Fe$ · Ferrocene · (MW 186.05)

(source of most substituted ferrocenes and hence precursor of substituted cyclopentadienes and cyclopentanes; the derived ferrocenium salts find use as mild oxidants; replacement of one ring by arenes yields cationic complexes which undergo nucleophilic addition and substitution at the arene ring, leading to substituted arenes)

Alternate Name: bis(cyclopentadienyl)iron.

Physical Data: mp 173-174 °C; sublimes slowly at room temperature, rapidly at 100 °C; bp 249 °C; *d* 1.49 g cm^{-3}.

Solubility: sol all common organic solvents; insol water.

Form Supplied in: deep orange crystals; widely available.

Handling, Storage, and Precautions: stable up to 470 °C; stable to alkalis and, in the absence of air, to strong, non-oxidizing acids; oxidized by air in the presence of strong acids and by many oxidizing agents, including HNO_3 and the halogens, reversibly forming the cation $(C_5H_5)_2Fe^+$.

Introduction.

Ferrocene[1,2] is a typically aromatic system and as such has a wide-ranging chemistry based on its substitution reactions. As a synthetic reagent its primary use is as a source of useful ferrocene derivatives themselves. These include sensors, which make use of the readily reversible oxidation of ferrocene and its derivatives, monomers for the synthesis of redox active polymers, compounds with nonlinear optical properties, and antianaemic agents. Ferrocene also serves as the source of cationic complexes of benzene derivatives, which are thereby rendered reactive towards nucleophiles. Although ferrocene derivatives can be cleaved to yield cyclopentane or cyclopentadiene derivatives, it has only rarely found use for this purpose.

With only the limits imposed by their facile oxidation, ferrocene derivatives undergo all the common functional group transformations of arenes. It is appropriate here to review only the principal direct substitution processes with emphasis on differences from the chemistry of benzenoid aromatics. These arise chiefly from the impossibility of effecting direct halogenation or nitration since all potential reagents oxidize ferrocene to the unreactive ferrocenium cation $[Fe(C_5H_5)_2]^+$. This cation itself is a very mild one-electron oxidizing agent which has frequently been employed to oxidize other organometallic species.

The ferrocenyl group, $C_5H_5FeC_5H_4$, is commonly abbreviated as Fc.

Electrophilic Substitution Reactions.

Ferrocene shows very high reactivity towards electrophiles, making it more closely comparable to phenol than to benzene. Thus it undergoes facile Vilsmeier formylation to the aldehyde (eq 1)[3] and Mannich-type aminomethylation (eq 2).[4] The aminomethylated product is frequently utilized in the form of its quaternary ammonium salt, $FcCH_2NMe_3^+ I^-$, which is highly reactive towards nucleophiles, readily undergoing S_N1-type reactions due to the high stability of α-ferrocenyl carbocations.[5] This stability also accounts for the basicity of the aldehyde which keeps it in the protonated form during the reaction depicted in eq 1, thereby preventing further substitution. This and similar examples show that electronic effects are transmitted to a substantial degree from the substituted to the unsubstituted ring. In the case of eq 2, disubstitution to yield 1,1´-bis(dimethylaminomethyl)ferrocene can be achieved under forcing conditions.[6]

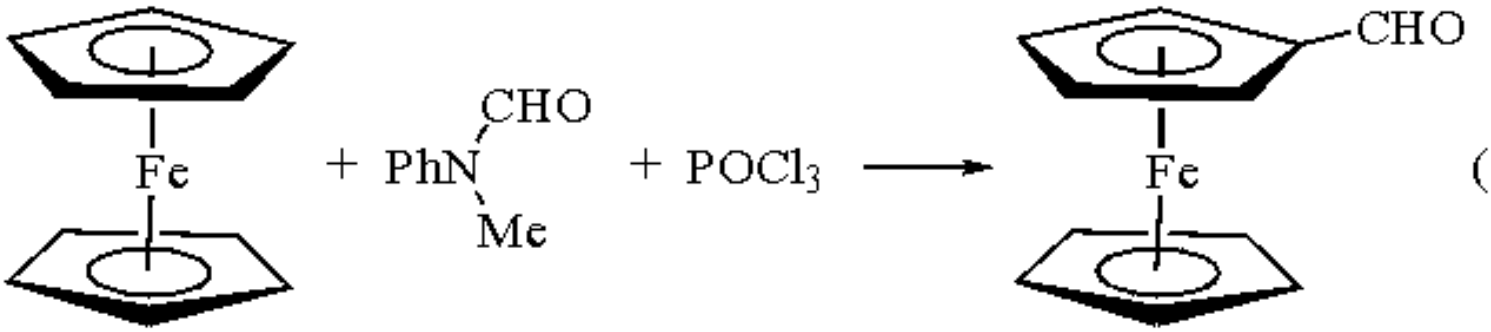

(1)

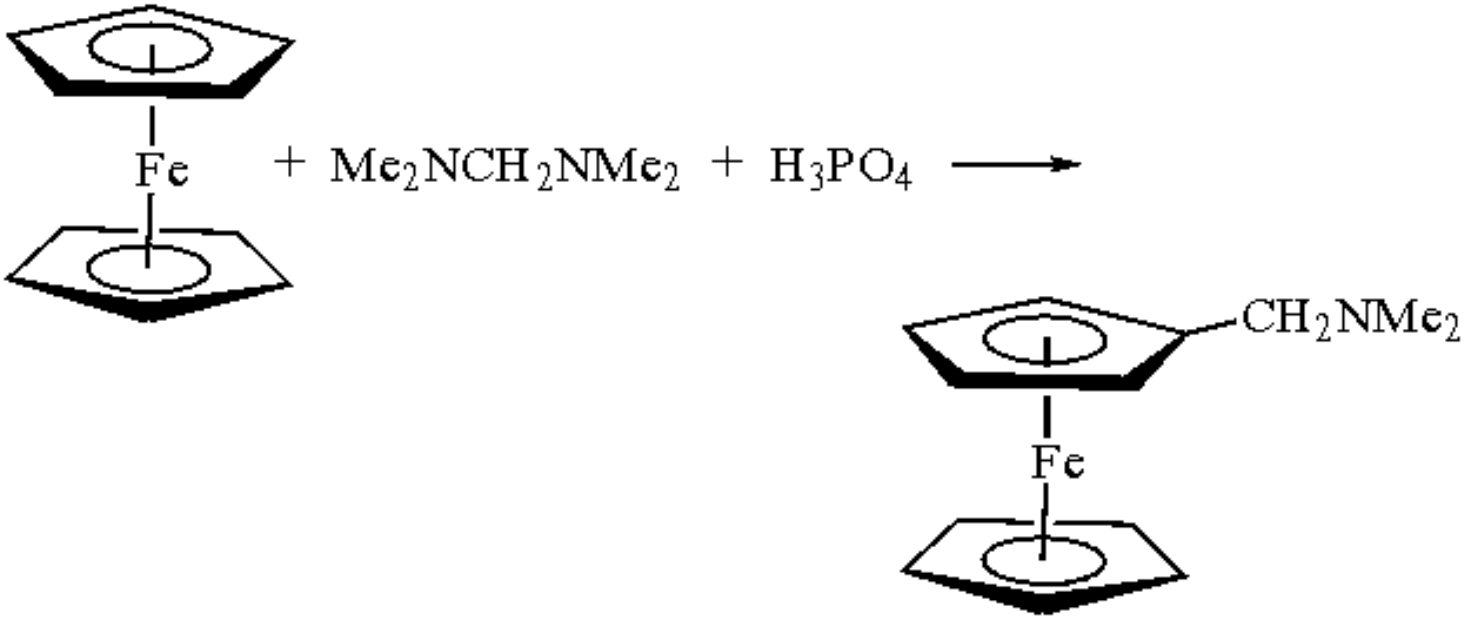

(2)

Friedel-Crafts acylation [with acid chlorides/$AlCl_3$ (eq 3) or acid anhydrides/BF_3] is readily regulated by the choice of reaction conditions to give mono- or disubstitution; the latter includes a very small amount of 1,2-disubstitution.[1] Column chromatography readily separates mixtures. Sulfonation, best done with ***Chlorosulfonic Acid***,[7] is more difficult to regulate (eq 4).

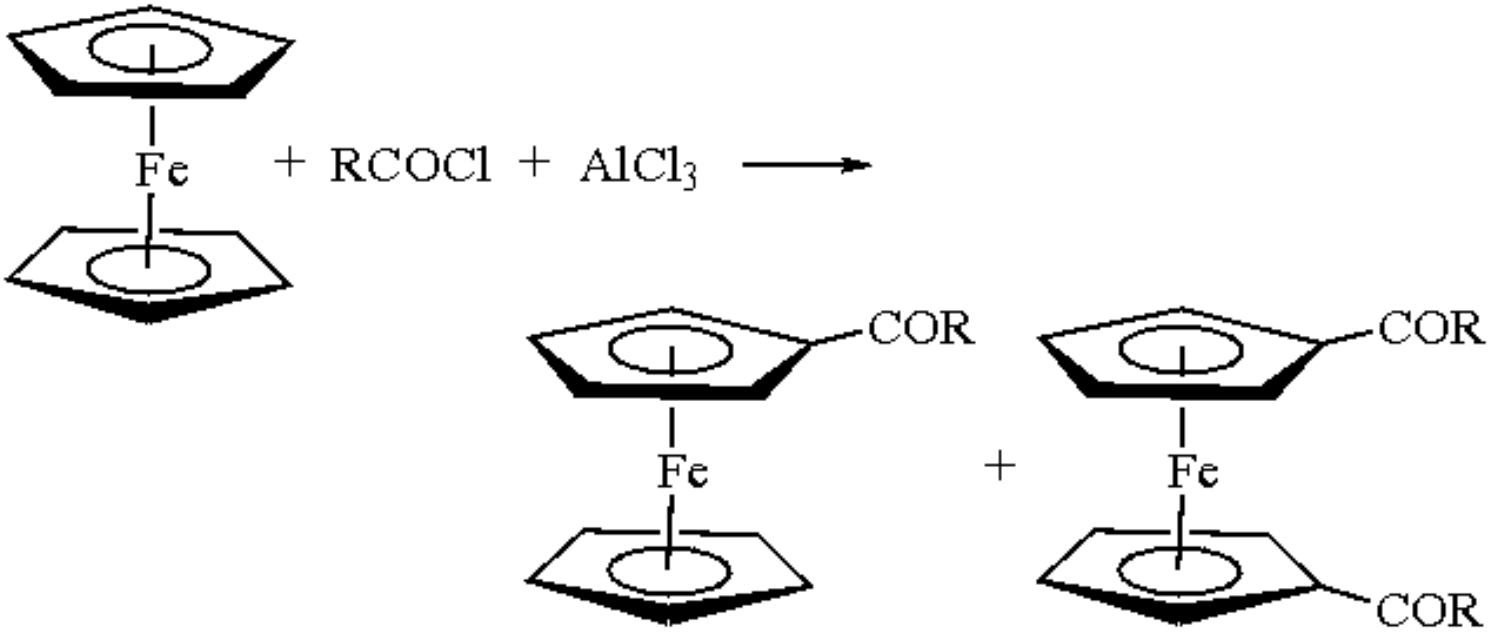

(3)

$$Cp_2Fe + ClSO_3H \xrightarrow{Ac_2O} FcSO_3H + Fe(C_5H_4SO_3H)_2 \qquad (4)$$

Arylation occurs when ferrocene is treated with arenediazonium salts and can likewise yield both mono- (eq 5) and 1,1´-disubstituted products; it has been shown to proceed via an initial electron-transfer step.[8]

$$Cp_2Fe + ArN_2^+ \longrightarrow FcAr + Fe(C_5H_4Ar)_2 + N_2 + H^+ \quad (5)$$

Most other simple ferrocene derivatives arise either by functional group transformations of the above products or via metallated compounds. Mercuration yields mixtures of mono- and bis(acetoxymercury) derivatives (eq 6), readily converted by ***Lithium Chloride*** or NaCl to the chloromercury derivatives and differing sufficiently in solubility to be fairly easily separated.[9] The chloromercury compounds in turn react with halogens, copper halides, or *N*-halosuccinimide to provide a good source of mono- and dihaloferrocenes.[10]

$$Cp_2Fe + Hg(OAc)_2 \longrightarrow FcHgOAc + Fe(C_5H_4HgOAc)_2 + HOAc \quad (6)$$

Lithiation is of wider use as well as more controllable. Whereas ***n-Butyllithium*** yields mixtures of mono- and 1,1´-dilithioferrocene (eq 7),[11] addition of ***N,N,N´,N´-Tetramethylethylenediamine*** leads almost exclusively to the dilithio derivative,[12] and replacement of *n*- by ***t-Butyllithium*** results in highly selective monolithiation.[13] Lithioferrocene in turn can then serve as the source of the haloferrocenes by reaction with polyhalocarbons or *p*-toluenesulfonyl halides, etc.,[10d,e] of nitroferrocene by reaction with, for example, alkyl nitrates (eq 8)[14a] or N_2O_4,[14b] of aminoferrocene by reaction with *O*-alkylhydroxylamines, e.g. eq 9,[15] and of ferroceneboronic acid by reaction with tributyl borate.[16]

$$Cp_2Fe + BuLi \longrightarrow FcLi + Fe(C_5H_4Li)_2 + C_4H_{10} \quad (7)$$

$$FcLi + RONO_2 \longrightarrow FcNO_2 + ROLi \quad (8)$$

$$FcLi + H_2NOCH_2Ph \longrightarrow FcNH_2 + PhCH_2OLi \quad (9)$$

The boronic acid is an alternative precursor of haloferrocenes and can similarly give acetoxyferrocene, both by reaction with copper salts (eq 10).[17] The acetate reacts with Grignard reagents to give hydroxyferrocene, but both this phenolic compound and aminoferrocene are very sensitive to oxidation and relatively little is known of their chemistry.

$$FcB(OH)_2 + CuX_2 \longrightarrow FcX \quad (10)$$

Lithiation also provides the principal route to 1,2-disubstituted ferrocenes since functionally substituted ferrocenes generally lithiate to yield 2-lithio derivatives at least as the kinetically favored products, as illustrated for (dimethylaminomethyl)ferrocene (eq 11).[11,18]

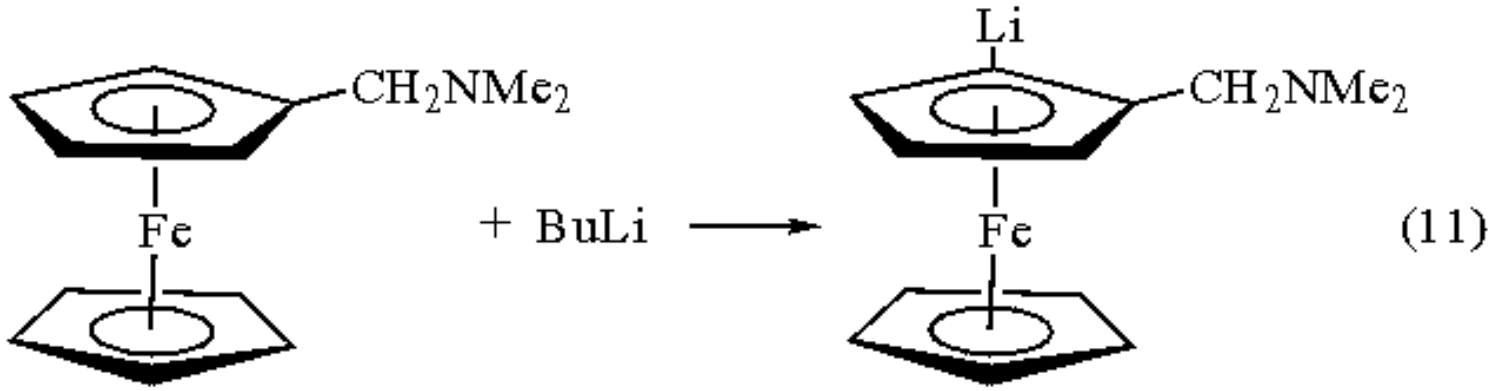

Formation and Uses of (Arene)cyclopentadienyliron Cations.

Replacement of one ring in ferrocene is the route chiefly used to obtain arenecyclopentadienyliron salts (eq 12);[19] they can also be obtained similarly from $CpFe(CO)_2Cl$. The reaction succeeds with a wide range of arene substituents and with polycyclic arenes. Electron-withdrawing substituents are preferentially retained,[19a,20] for example as in eq 13.[20]

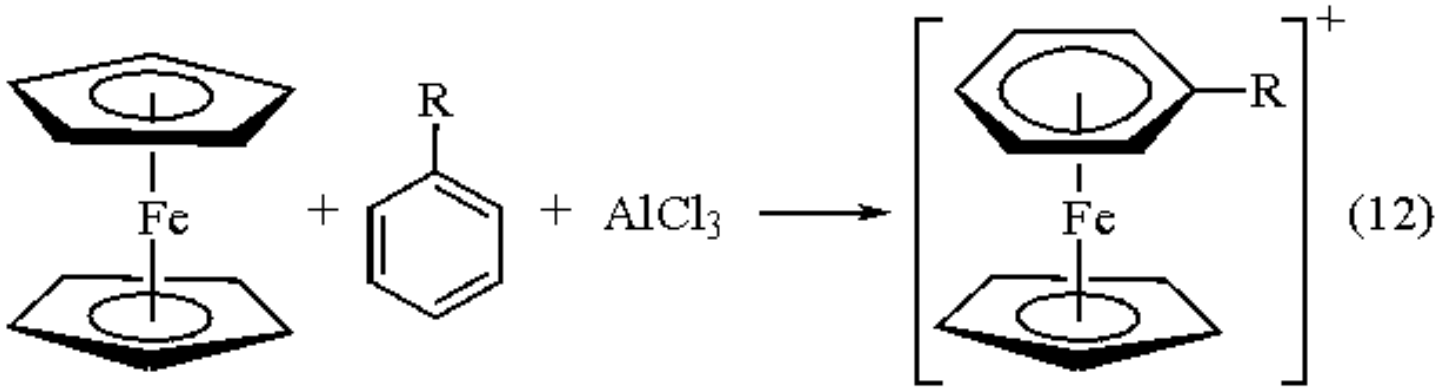

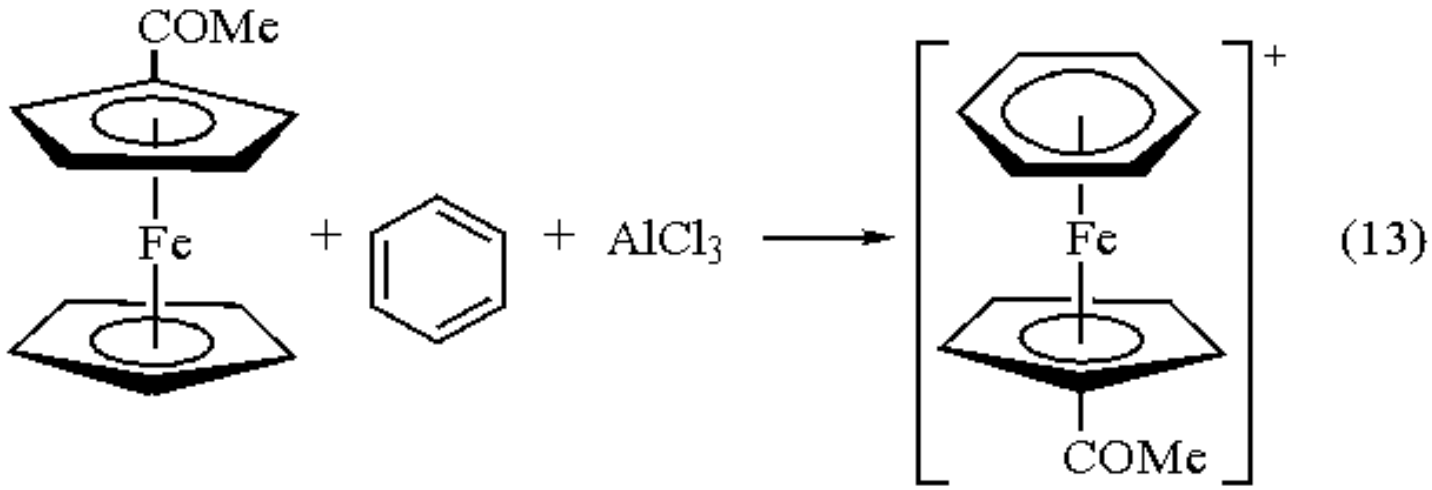

The synthetic value of these complexes arises from their reactivity towards nucleophiles (significantly greater than that of $(arene)Cr(CO)_3$, but less than that of $[(arene)Mn(CO)_3]^+$).[21a] Hydride and carbon nucleophiles add to give cyclohexadienyl complexes (eq 14),[22] whereas fluoro and chloro or nitro substituents are substituted by softer

nucleophiles (eq 15).[23] Halogen substituents on the five-membered ring are much more difficult to replace.[22f]

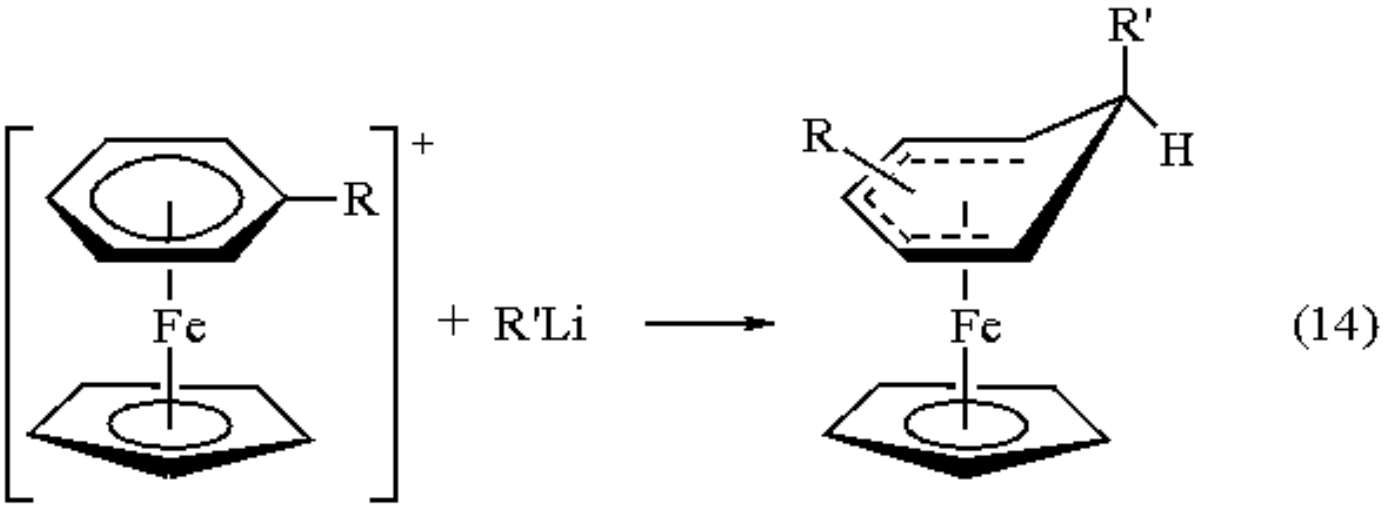

(14)

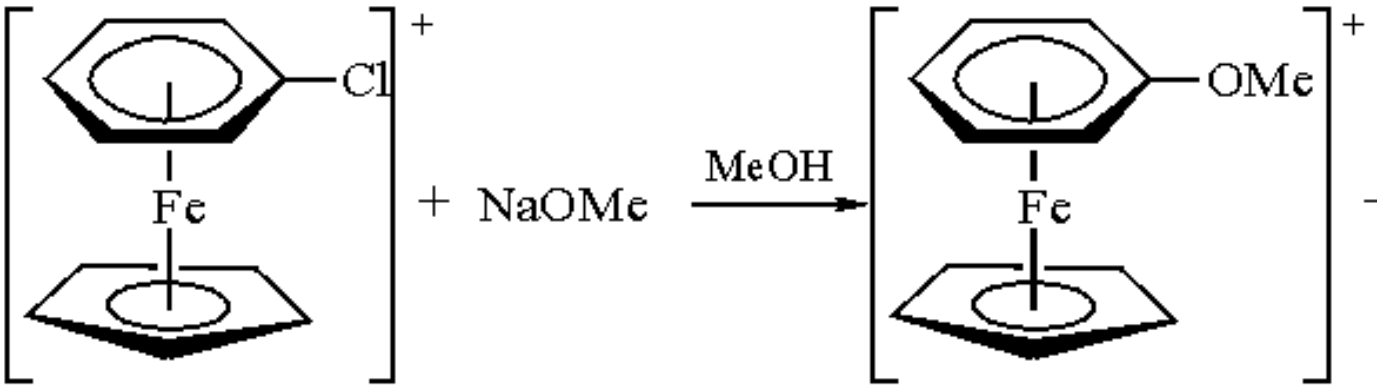

(15)

Directive effects on the addition (eq 14) can be roughly summarized by stating that electron-withdrawing groups direct the incoming nucleophile to the 2-position while donating groups direct to the 3-position with some addition at the 4-position; these effects are weaker than in electrophilic aromatic substitution, so that a methyl substituent allows nearly random addition of hydride to carbons 2, 3, and 4.[21]

The cyclohexadienyl groups can generally be rearomatized by reaction with ***N-Bromosuccinimide*** (eq 16)[24] or in some cases trityl salts,[24b] thus opening the way to further additions, but cyano, benzyl, malonyl, and similarly reactive *exo* substituents are cleaved by these reagents.

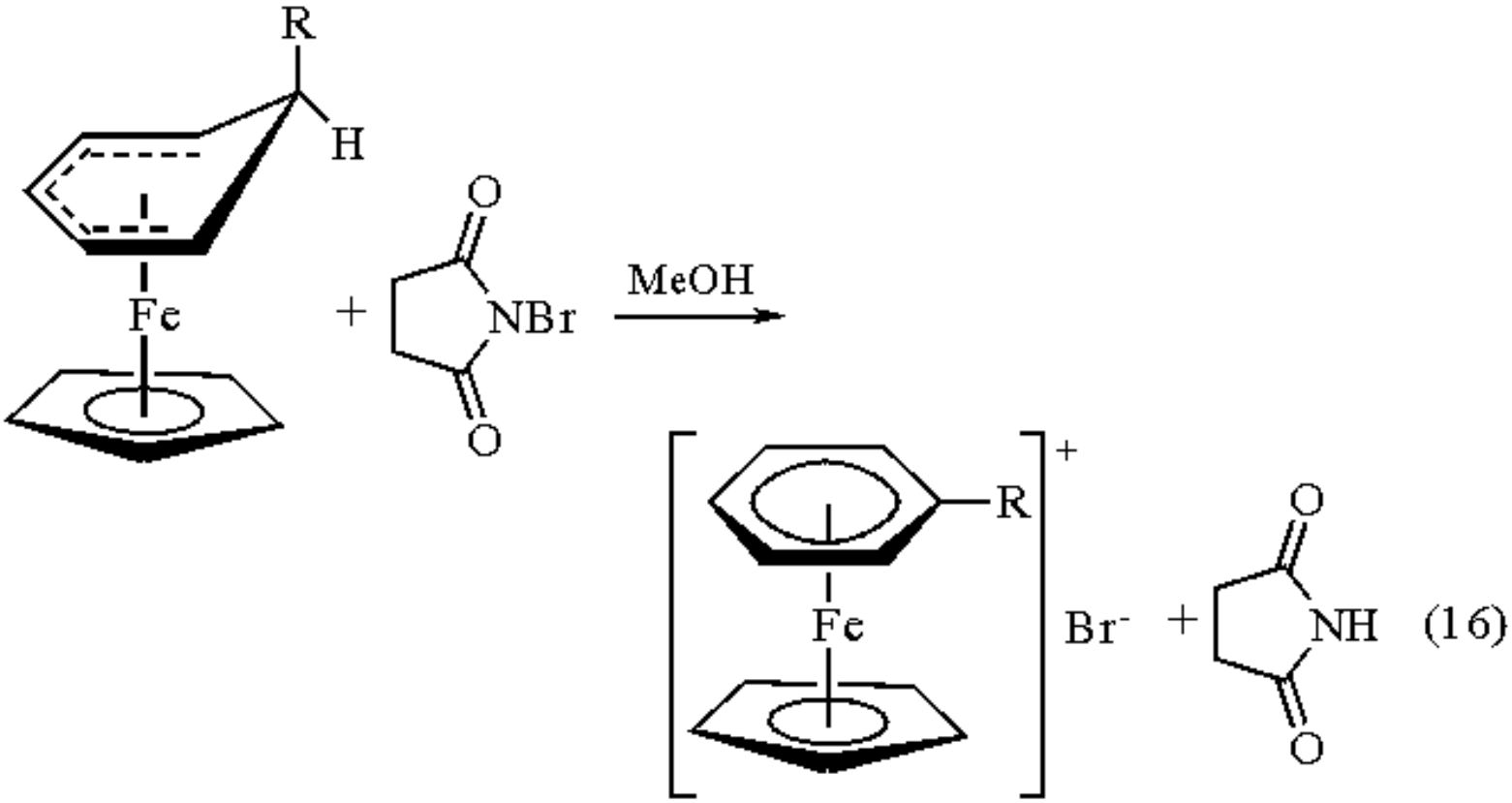

The acidity of α-hydrogens in (alkylbenzene)cyclopentadienyliron salts allows alkylation,[25,26] as exemplified for the hexamethylbenzene complex (eq 17).[25a] The intermediate methylenecyclohexadienyl complexes in such reactions have sufficient carbanionic character to act as nucleophiles in Michael-type addition (eq 18).[26]

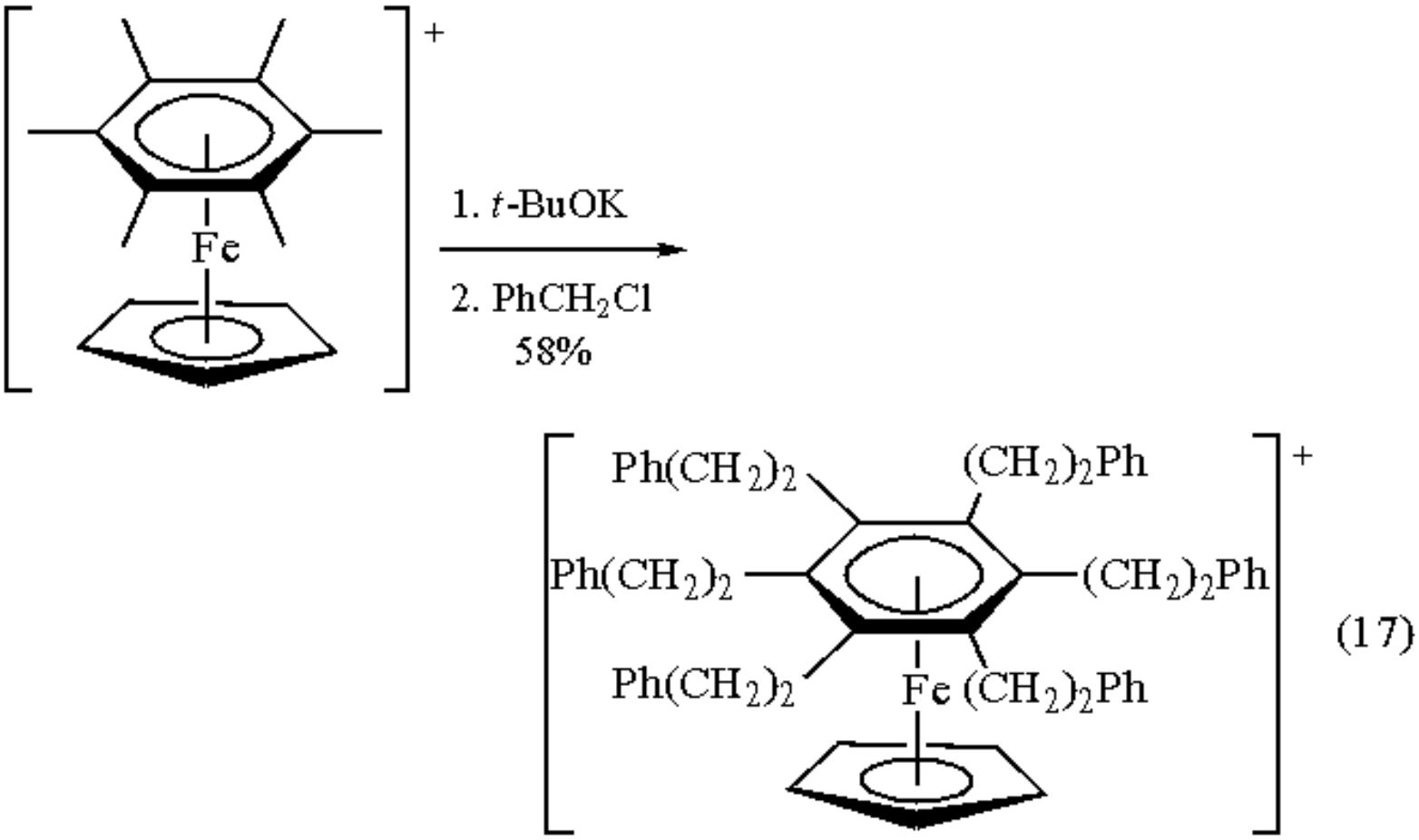
Fe
+
1. t-BuOK
2. PhCH2Cl
58%
Ph(CH2)2
(CH2)2Ph
Ph(CH2)2
(CH2)2Ph
Ph(CH2)2
Fe
(CH2)2Ph
+

(17)

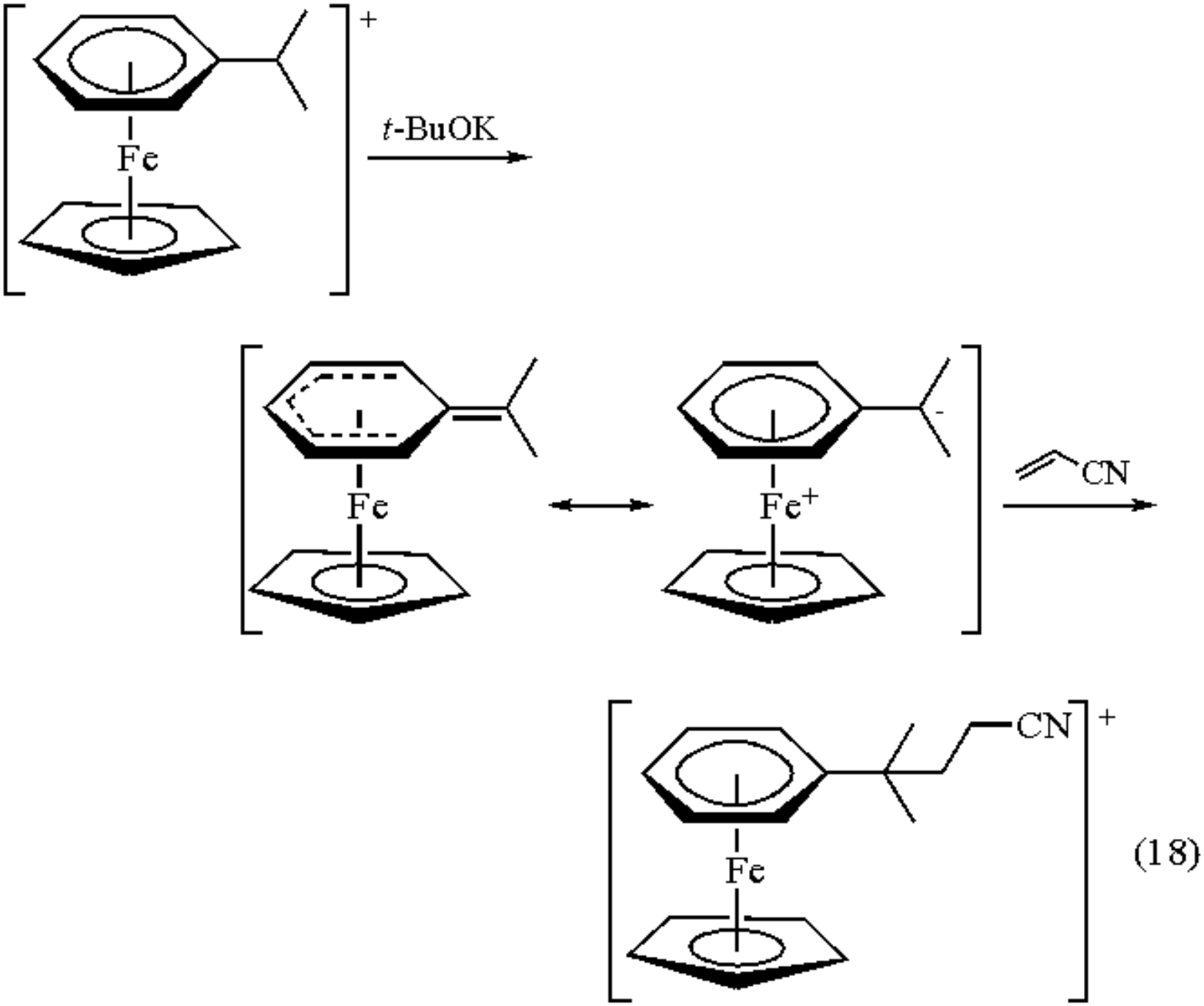

(18)

Side chains in these cations may also be oxidized, for example eq 19[27] and eq 20.[28]

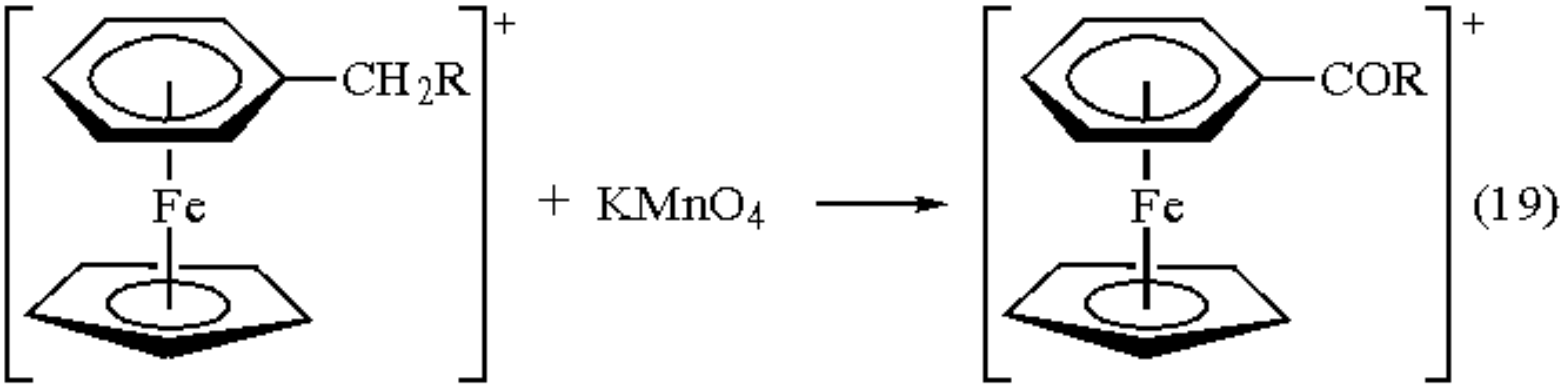

(19)

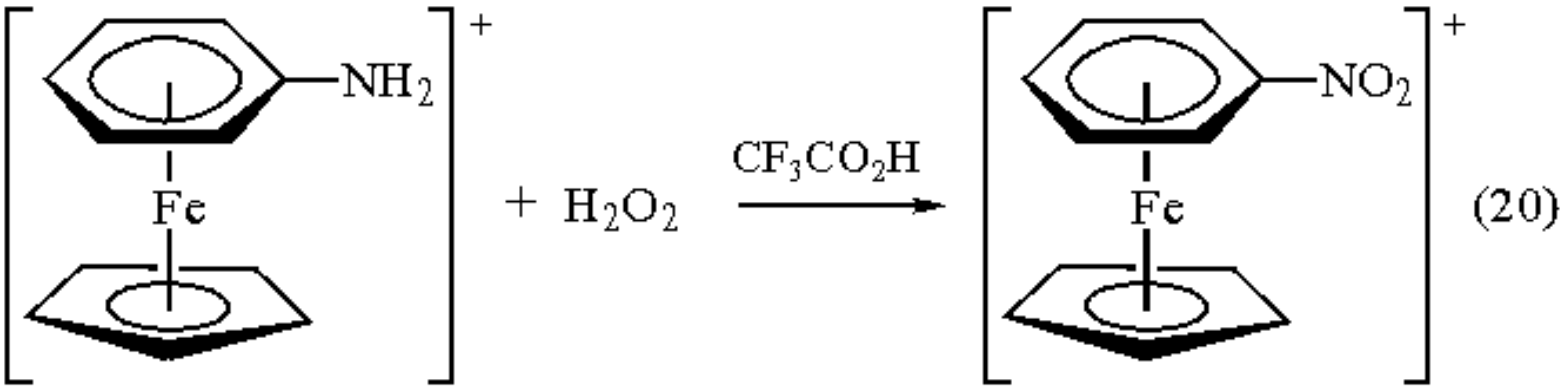

Cleavage of the complexes to recover substituted arenes has been achieved by thermolysis,[23a,29] photolysis,[30] electrochemical reduction,[31] and rather inefficiently by oxidation (directly from cyclohexadienyl precursors).[22] It is also known to occur by reaction with a wide variety of donor ligands including phosphines or phosphites (preferably with electron transfer catalysis or with photolysis),[32] nitriles,[33] and thioethers;[34] these reactions are widely used to prepare the corresponding salts (eq 21), but yields of recovered arenes are rarely reported.[33b]

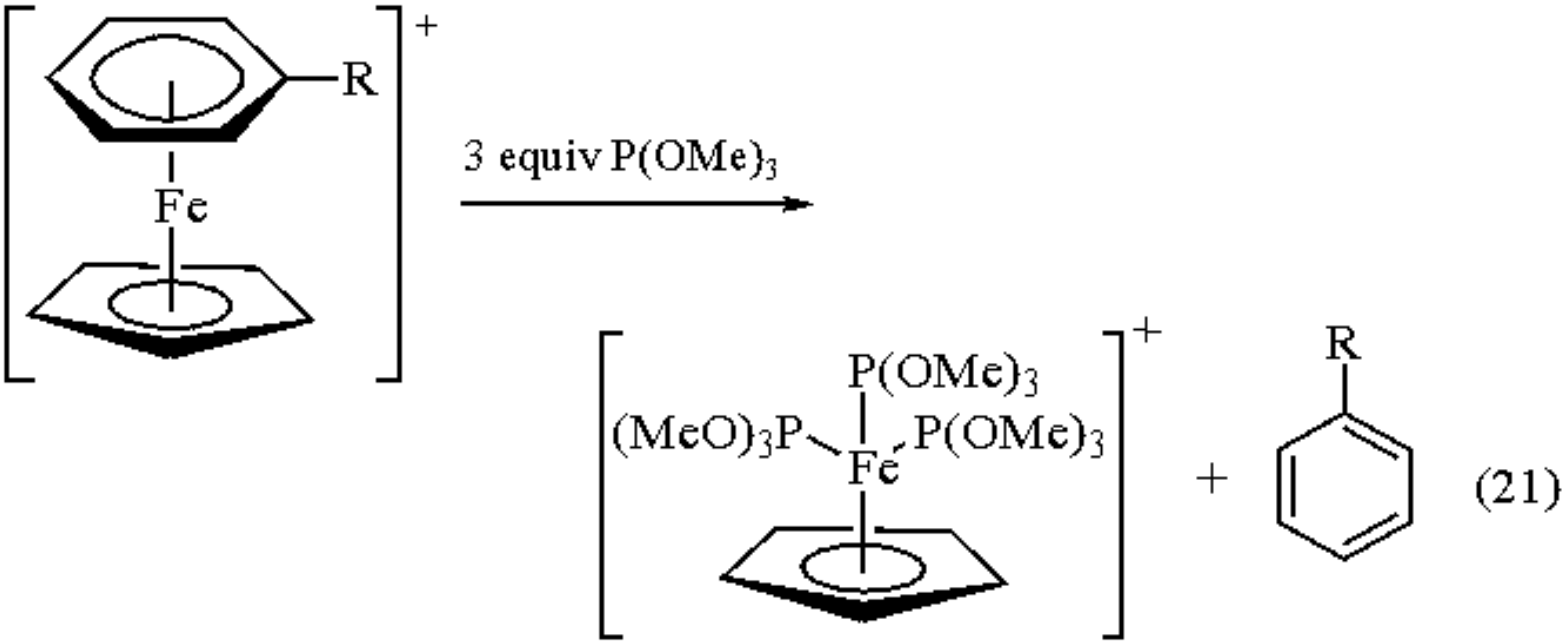

Heterocyclic syntheses employing this class of reaction are exemplified by eq 22[35] and eq 23.[29b]

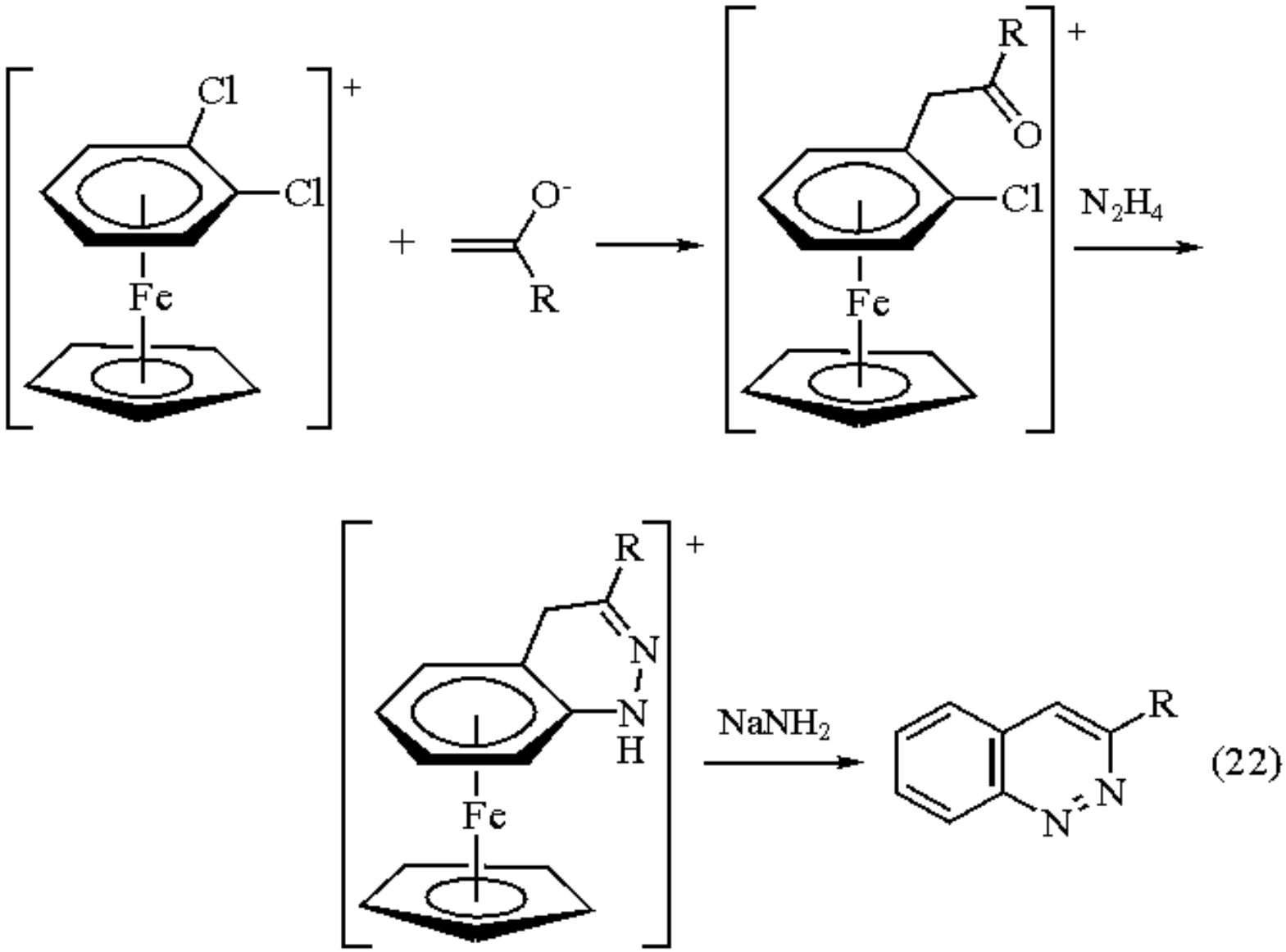

(22)

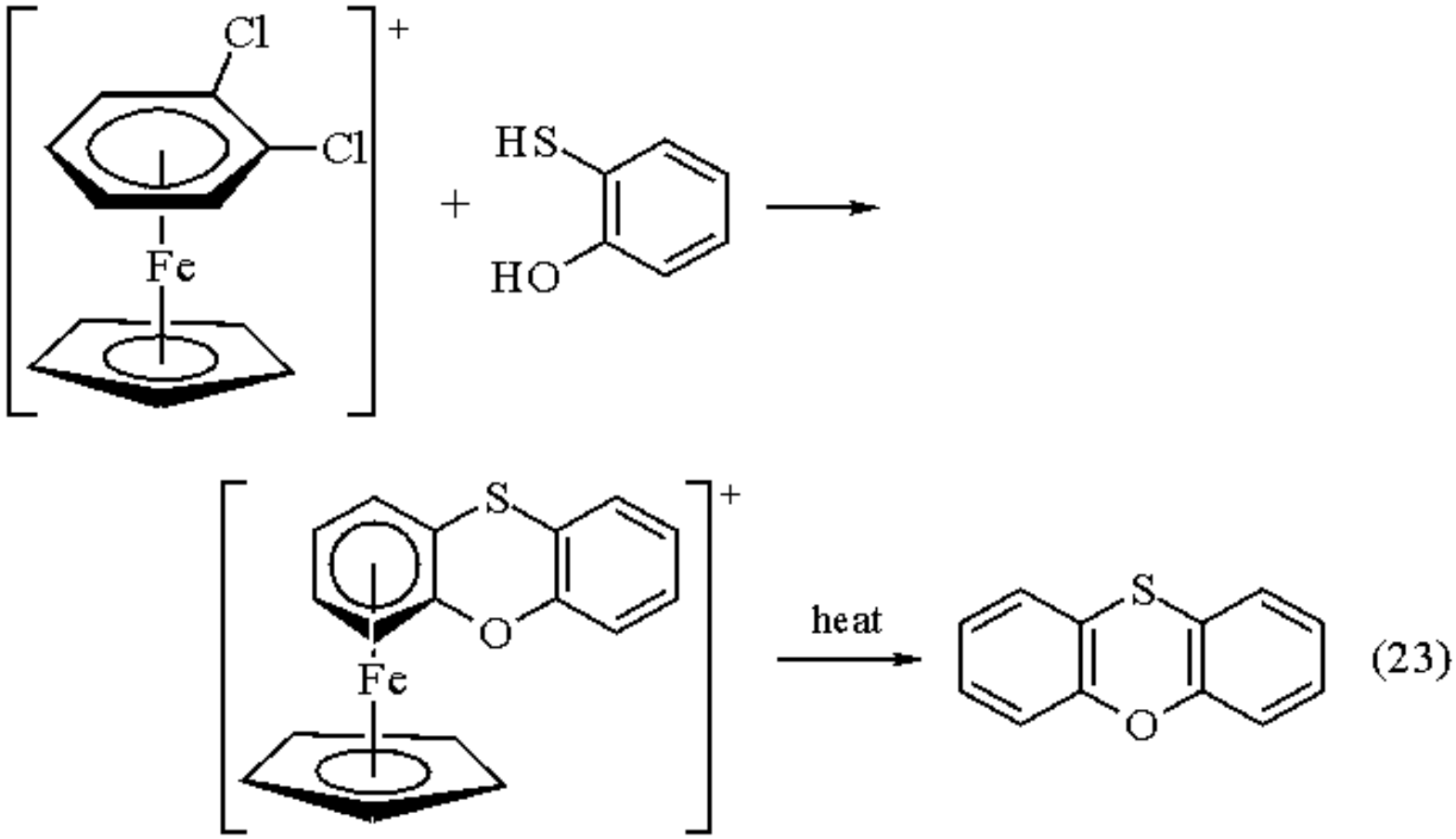

Cleavage of Ferrocenes.

Ferrocene resists hydrogenation under conditions which readily convert benzene to cyclohexane and has only been reduced (to metal and cyclopentane) at ca. 350 °C using a ***Raney Nickel*** catalyst.[36a] It is cleaved by an excess of ***Bromine*** to give pentabromocyclopentane;[36] neither of these degradations has been applied to derivatives.

Cleavage to metal and cyclopentadienide anion is achieved smoothly with lithium and amines (ethylamine).[37] A few substituted ferrocenes have been degraded by this method and the resultant lithium cyclopentadienides used to prepare new complexes. Thus the product of eq 2 was shown to yield 1,1´-bis(dimethylaminomethyl)ferrocene by the sequence shown in eq 24,[38a] although a better route to this product was described at the same time.[38b] A low yield of 1,1´-dimethoxyferrocene was obtained in similar fashion from methoxyferrocene.[38c] Tris- and tetrakis(cyclopentadienyl)methane have been generated via the tri- and tetralithium salts $(LiC_5H_4)_3CH$ and $(LiC_5H_4)_4C$ by ***Lithium-Ethylamine*** reduction of Fc_3CH and $Fc_3C(C_5H_5)$, respectively.[38d,e]

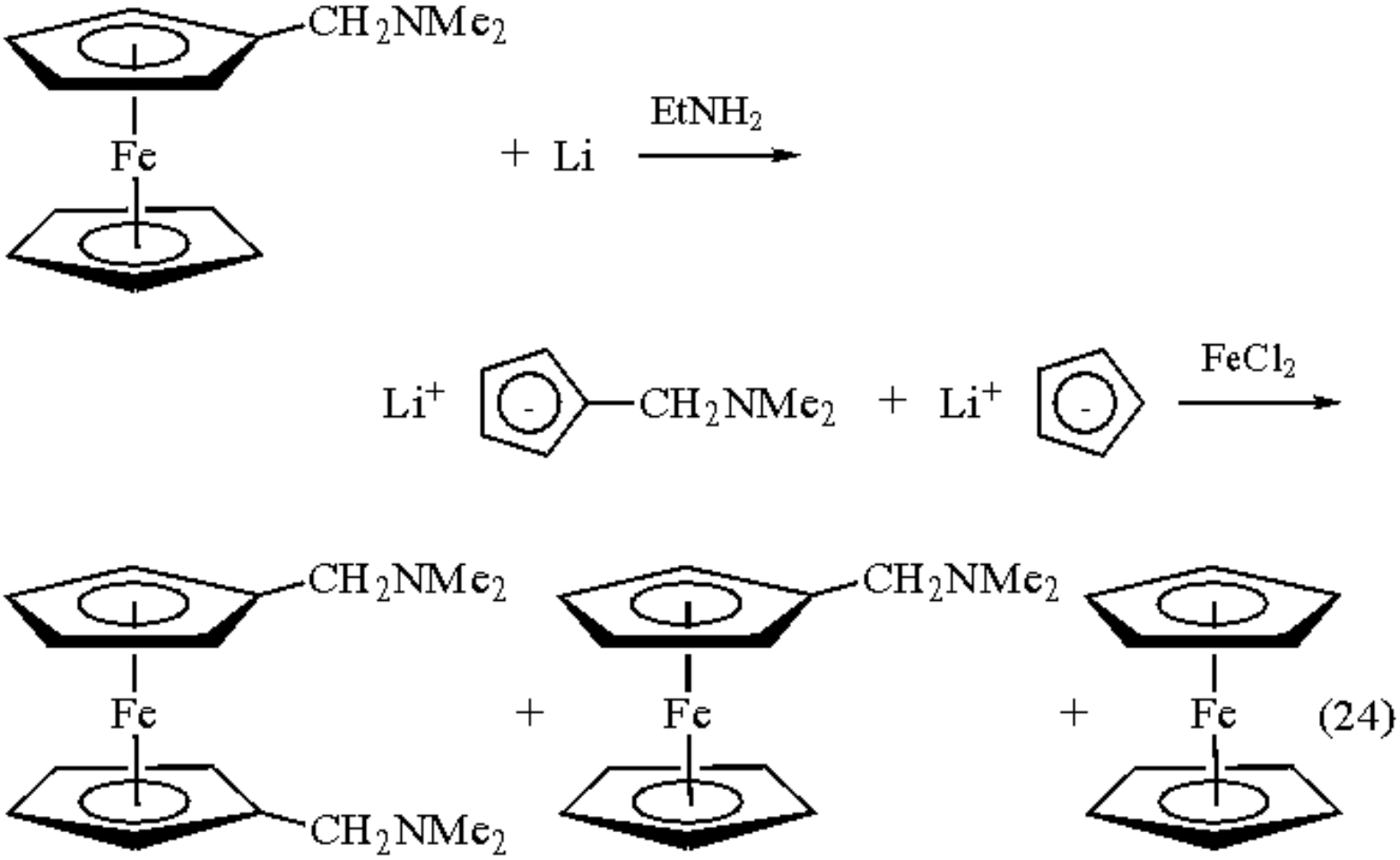

Despite the considerable stabilization of α-ferrocenyl cations, allowing their facile formation and in suitable cases isolation as stable salts, they are relatively easily cleaved, particularly on irradiation. That a partial positive charge at the 2-position suffices is exemplified by (2-pyridyl)ferrocene. After quaternization with ***Iodomethane***, this amine, which is readily obtained from ferrocenyllithium and pyridine,[39] is photolyzed in good yield in aqueous alkaline solution (eq 25).[40]

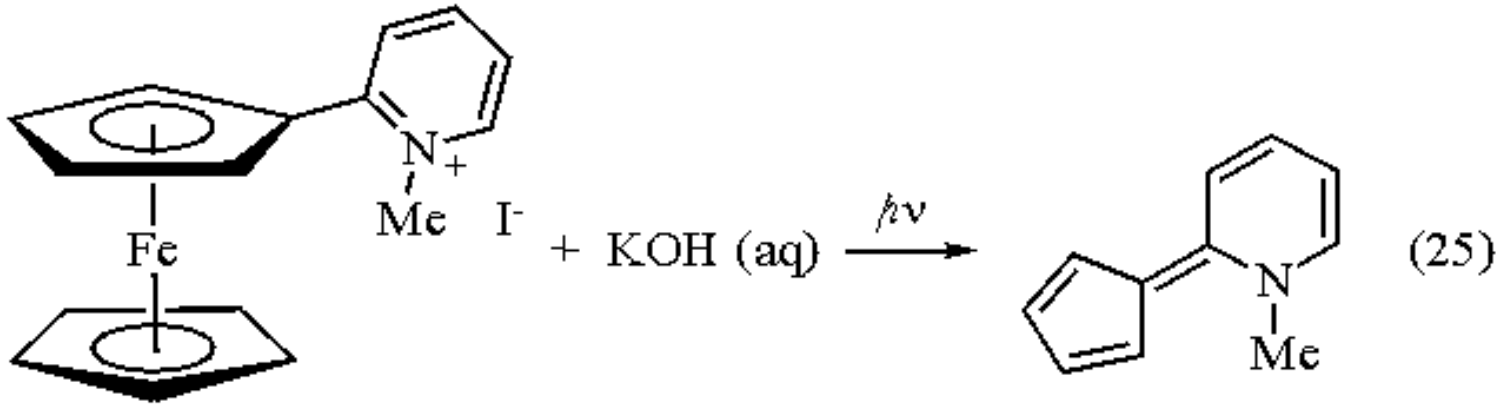

This route has been applied to fused ferrocenodihydropyridines (generated in four steps from [$FcCH_2NMe_3$]I) (eq 26).[41]

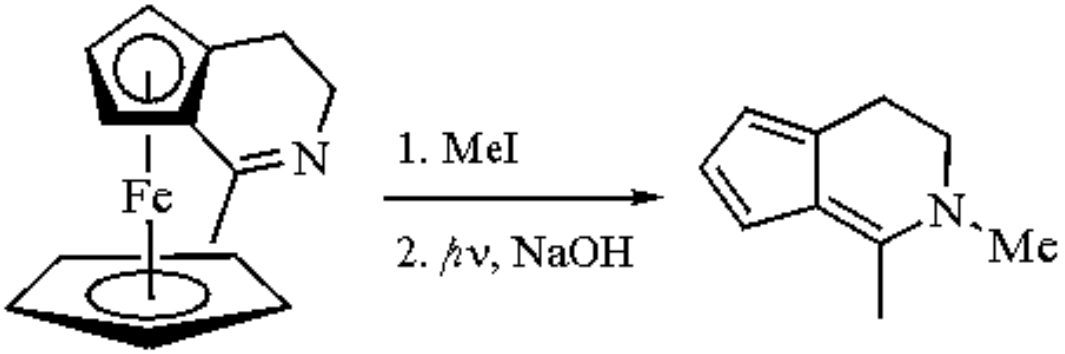

(26)

In an attempt to extend the latter example to tricyclic systems, appropriately substituted (amidophenyl)ferrocenes were prepared as precursors via arylation (eq 5) of ferrocene with 2-nitro- and with 2-cyanobenzenediazonium salts. The final Bischler-Napieralski type cyclization step appeared to proceed smoothly, but instead of the expected fused ferrocenes (isolated in low yield when *n* = 1) the metal-free heterocycles were the main products (eq 27);[42] i.e. cleavage had occured without quaternization even in the dark.

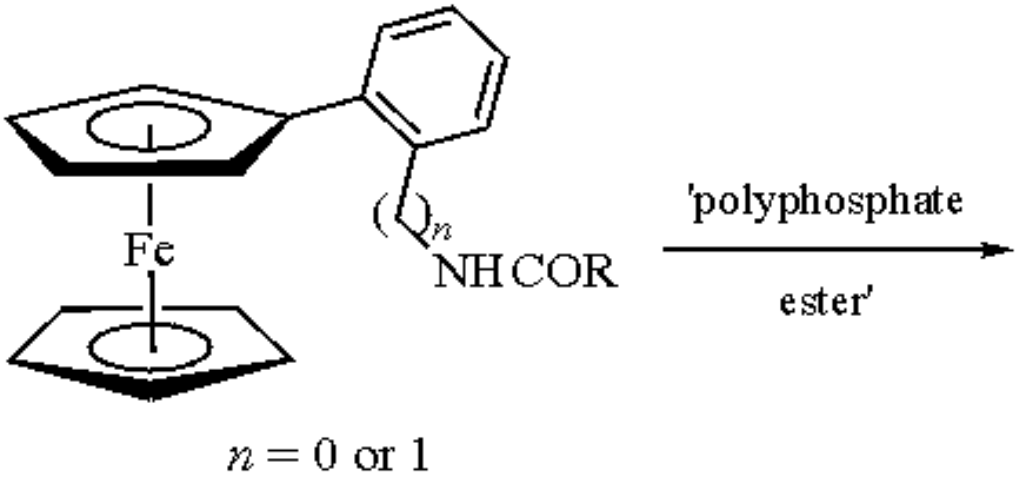

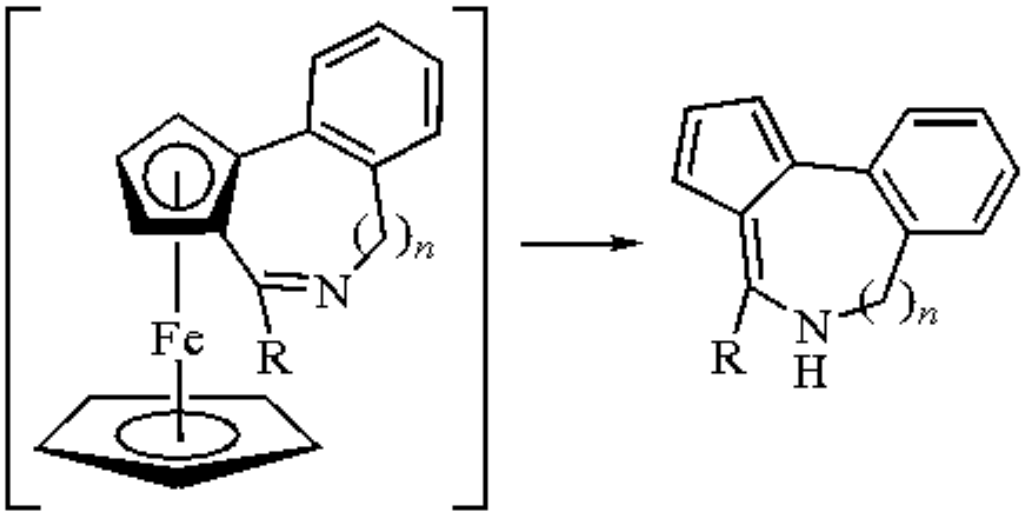

(27)

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9-Fluorenylmethyl Chloroformate[1]

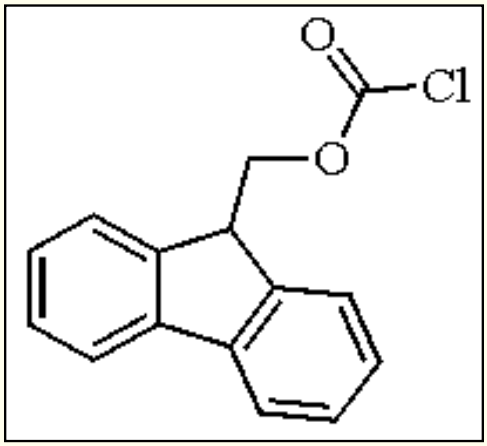

[28920-43-6] · $C_{15}H_{11}ClO_2$ · 9-Fluorenylmethyl Chloroformate · (MW 258.71)

(base-labile protecting group for primary and secondary amines;[3] used in peptide synthesis;[5] used for derivatization of amines and amino acids prior to HPLC analysis and fluorescence detection[13])

Alternate Names: 9-fluorenylmethoxycarbonyl chloride; FMOC-Cl.

Physical Data: mp 62-64 °C.

Solubility: sol organics (CH_2Cl_2, THF, dioxane); reacts with alcohols, amines, and water.

Form Supplied in: white crystalline solid; widely available.

Handling, Storage, and Precautions: FMOC-Cl is an acid chloride, and should be protected from moisture and heat. The reagent can evolve CO_2 (pressure!) upon prolonged storage; therefore bottles should be opened carefully. FMOC-Cl is harmful if swallowed, inhaled, or absorbed through skin, is corrosive, and is a strong lachrymator. Inhalation may be fatal. Use in a fume hood.

N-Terminus Blocking in Peptide Synthesis.

Solid-phase peptide synthesis based on base-labile FMOC protection[1] is rapidly augmenting and/or replacing older methods based on Boc and Z (Cbz) protection. The major advantage offered by the use of FMOC protection is that repetitive treatment with HF or CF_3CO_2H is no longer required for the deprotection steps. Most FMOC-protected amino acids are commercially available, although the search for orthogonal side-chain functional group protection continues.[2] FMOC protection is currently the method of choice for the synthesis of glycopeptides which carry acid-labile *O*-glycosidic bonds (eq 1).[3,5b,7]

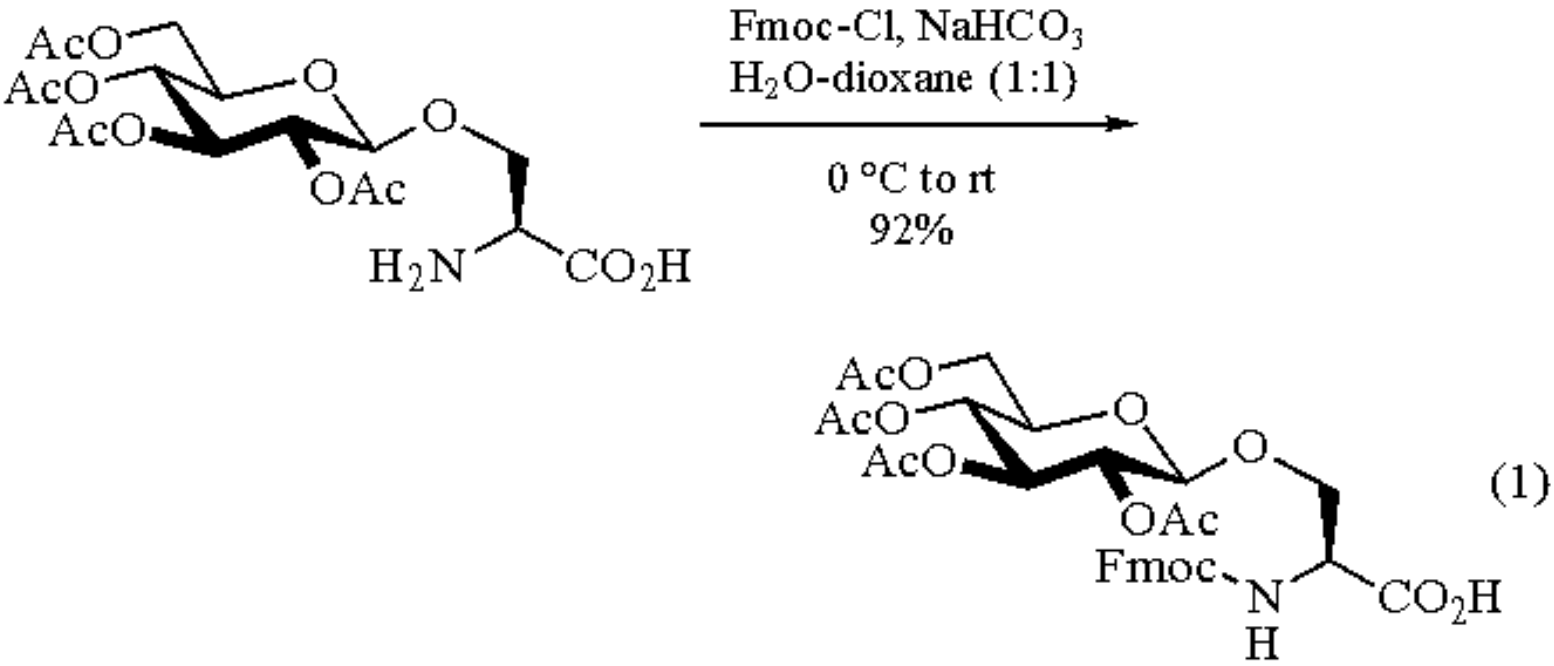

FMOC protection of amino acids is accomplished with Shotten-Bauman conditions (e.g. $NaHCO_3$/dioxane/H_2O or $NaHCO_3$/DMF), or with anhydrous conditions (e.g. pyridine/CH_2Cl_2) at room temperature or below (eq 1).[3a,4] A typical synthetic protocol for solid-phase peptide synthesis would involve coupling (eq 2), followed by deprotection with 20-30% ***Piperidine*** in DMF (eq 3), although other amines (e.g. 2% DBU, 10% Et_2NH, or 50% morpholine in DMF) have been used. Many workers no longer use the chloroformate ester FMOC-Cl (**1**), preferring the more shelf-stable carbonate FMOC-OSu (**2**) [*82911-69-1*],[5] or FMOC-pfp (**3**) [*88744-04-1*]. When used in the standard way,[4] FMOC-Cl (**1**) has been shown to promote the formation of FMOC-dipeptides in 3-7% yield, presumably via the mixed anhydride intermediate.[5a]

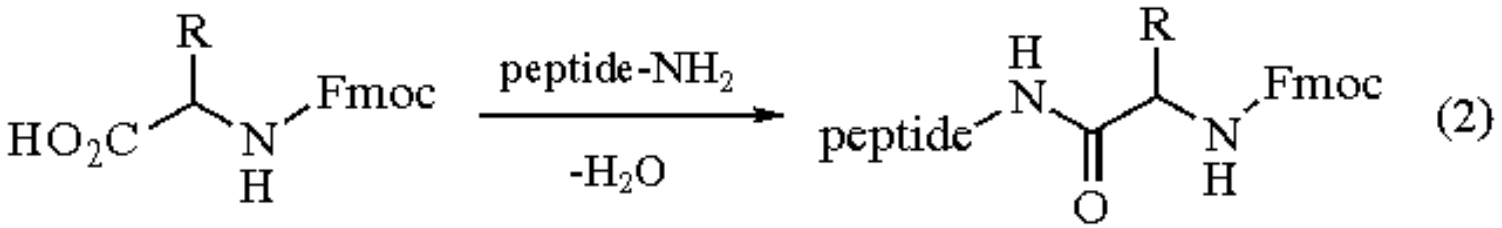

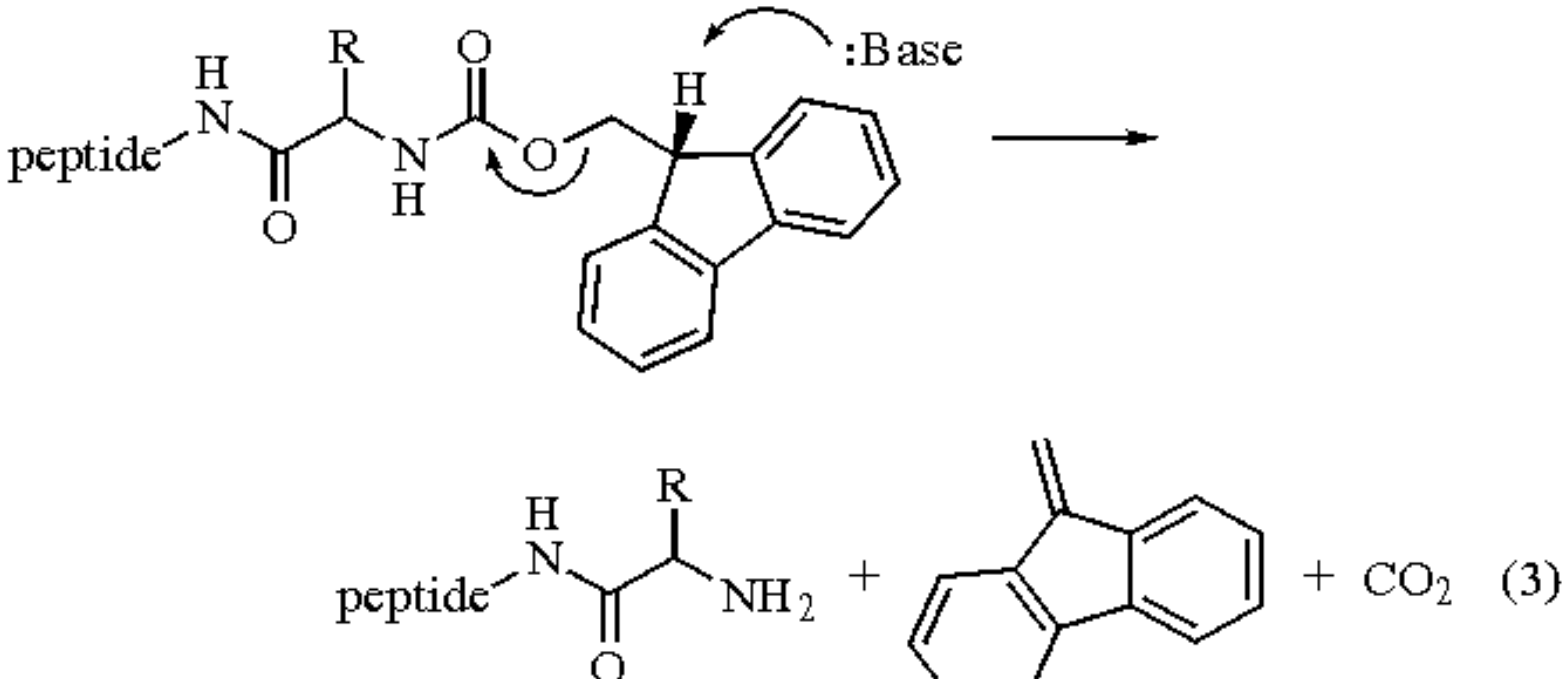

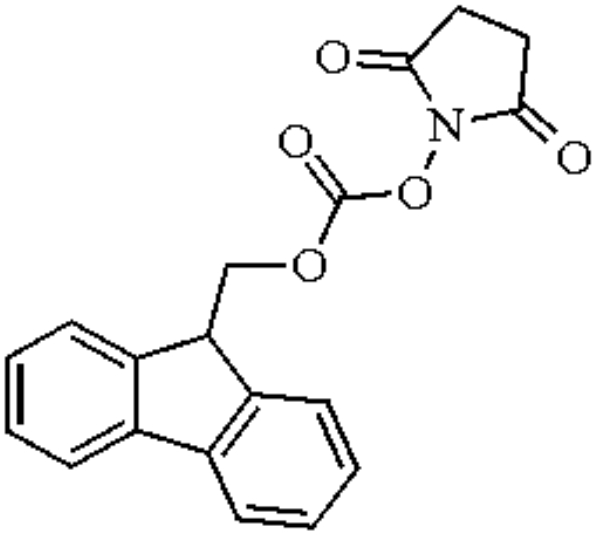

(2)

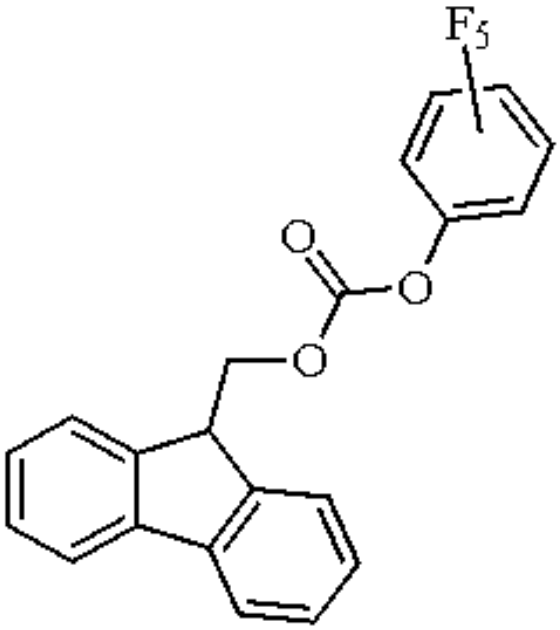

(3)

Use of FMOC-OSu (**2**) provides *N*-protected amino acids in comparable yields without the formation of the dipeptide impurities.[5] FMOC-pfp (**3**) has been used to prepare either FMOC-protected amino acids, or the corresponding pfp esters in one pot. Advantages of this reagent include supression of the dipeptide byproducts, as well as the production of the activated pfp esters using the same pentafluorophenol released during the *N*-protection step (eq 4).[6] This same *N*-protection/*C*-activation procedure has been used to produce serine glycosides (eq 5),[3b] and for the solid-phase synthesis of human intestinal mucin fragments (eq 6).[7] The use of FMOC-N_3 (**4**) is also claimed to reduce dipeptide formation during the protection step,[8] but the storage or use of potentially explosive oxycarbonyl azides cannot be recommended by this reviewer. Alternatively, the azide (**4**) may be generated in situ from (**1**).[4]

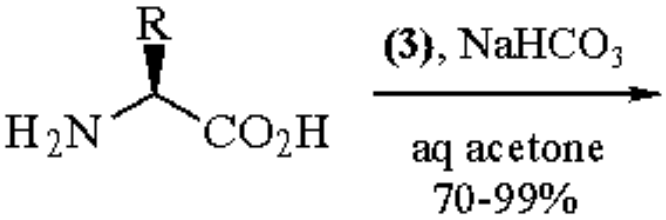
R
H2N
CO2H
(3), NaHCO3
aq acetone
70-99%

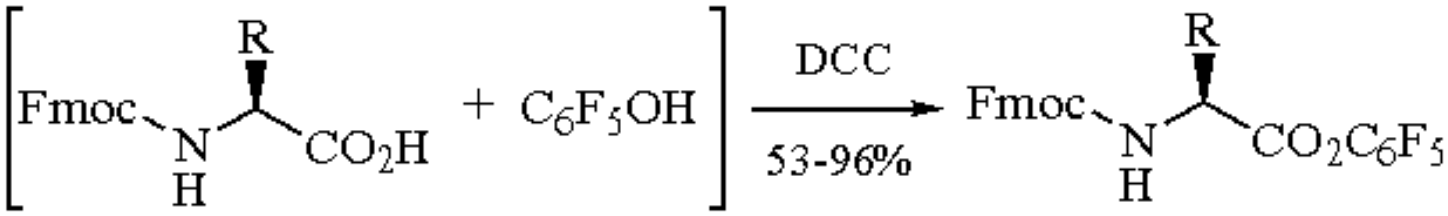
Fmoc
N
H
R
CO2H
+ C6F5OH
DCC
53-96%
Fmoc
N
H
R
CO2C6F5

(4)

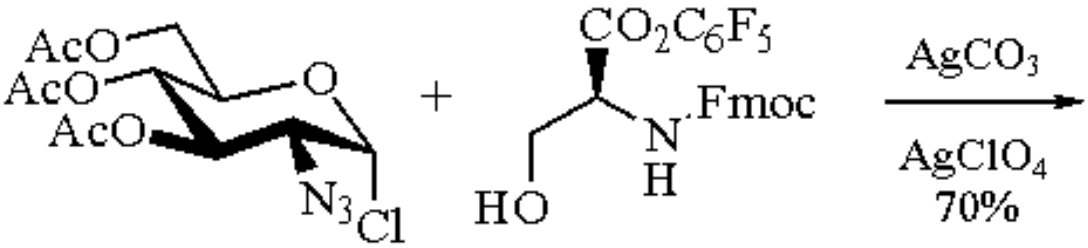
AcO
AcO
AcO
O
N3
Cl
+
CO2C6F5
Fmoc
N
H
HO
AgCO3
AgClO4
70%

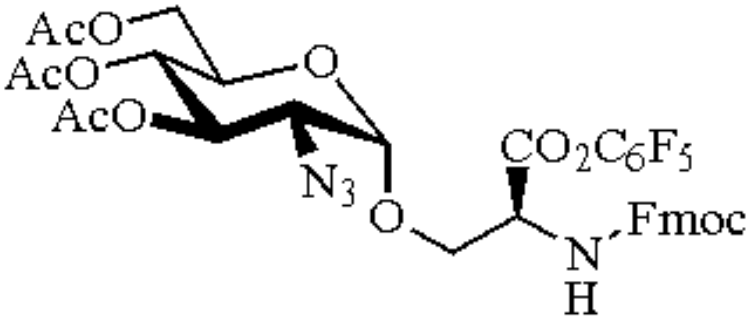
AcO
AcO
AcO
O
N3
O
CO2C6F5
Fmoc
N
H

(5)

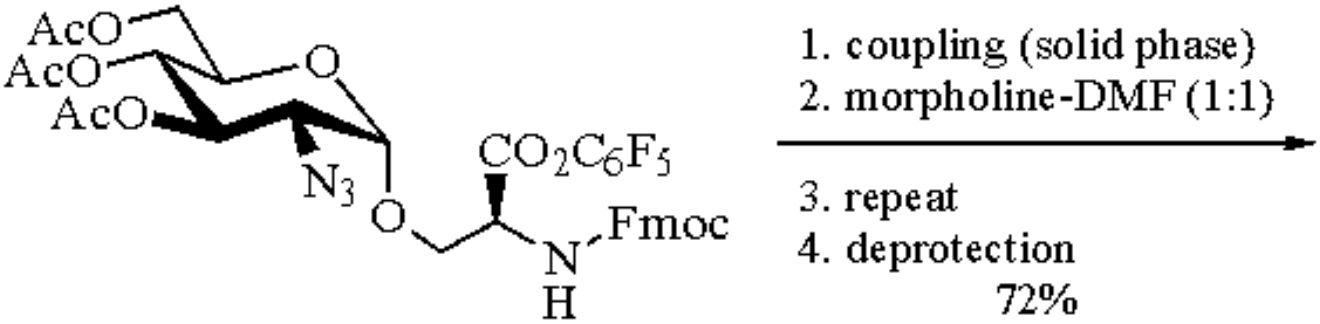
AcO
AcO
AcO
O
N3
O
CO2C6F5
Fmoc
N
H
1. coupling (solid phase)
2. morpholine-DMF (1:1)
3. repeat
4. deprotection
72%

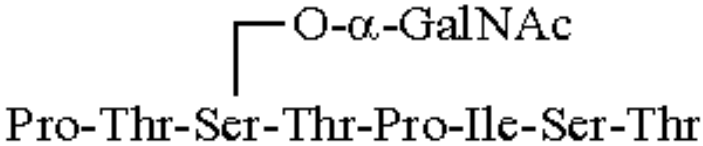
O-α-GalNAc
Pro-Thr-Ser-Thr-Pro-Ile-Ser-Thr

(6)

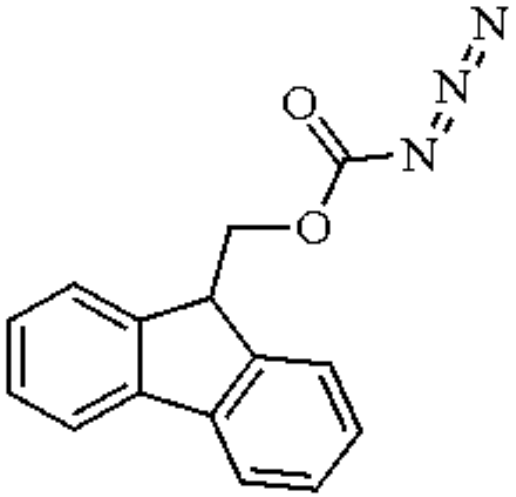

(4)

Fluorenylmethyl esters have been used for *C*-terminus protection in combination with FMOC *N*-terminus protection for solution-phase coupling of protected amino acids and peptide fragments. This permits simultaneous deprotection of both termini with Et_2NH/DMF (eq 7).[9]

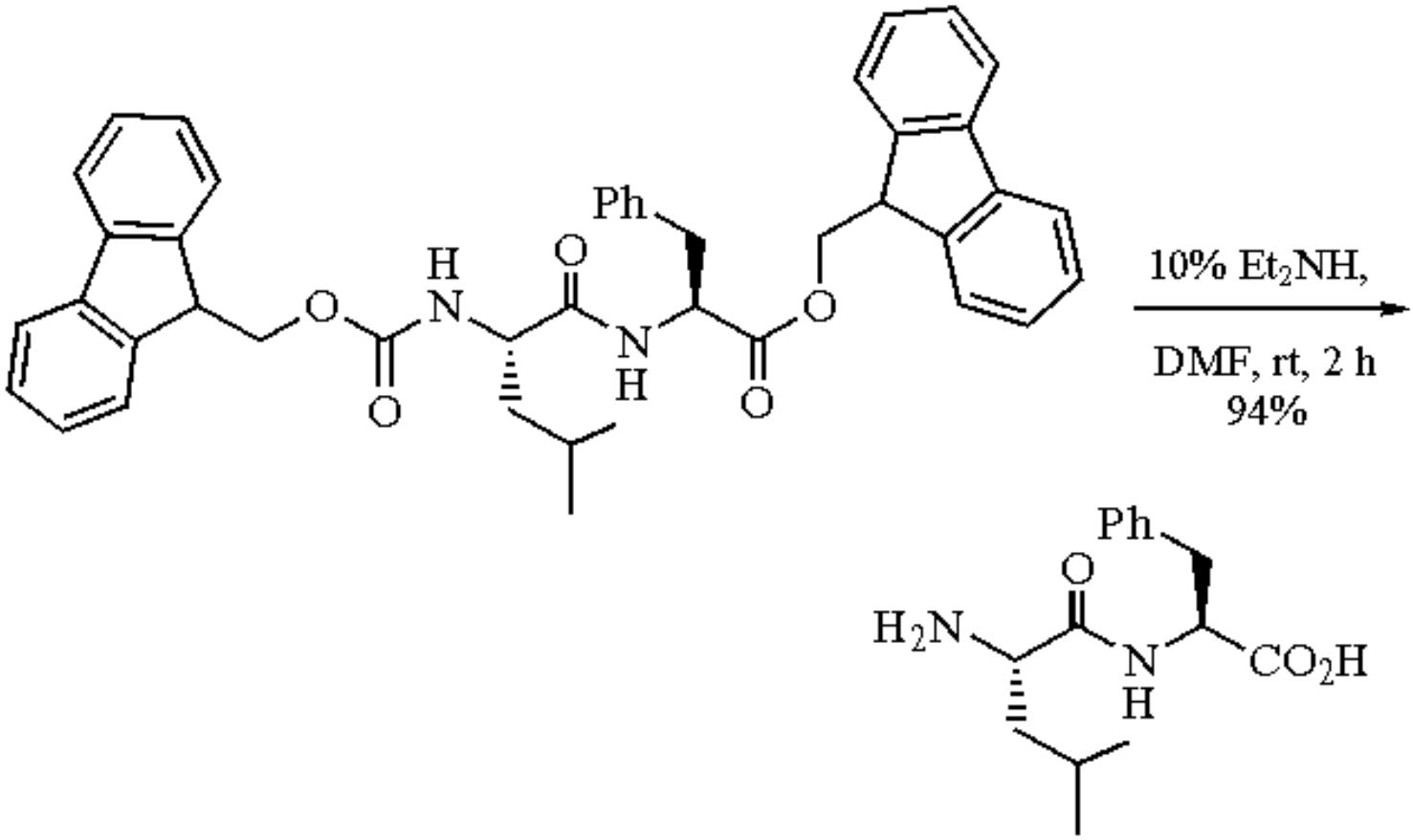

(7)

Amine and Hydroxyl Protection for Nucleosides, Carbohydrates, and Natural Products.

FMOC has been used to protect the amino groups on various nucleoside bases (adenosine, cytosine, guanine, and their 2-deoxy derivatives) for solid-phase oligonucleotide synthesis in a one-pot procedure.[10] ***Chlorotrimethylsilane*** in dry pyridine was used for transient protection of the 2´,3´,5´- or 3´,5´-hydroxyls, followed by the addition of FMOC-Cl, and hydrolytic workup of the TMS ethers to produce crystalline FMOC-protected nucleosides and 2-deoxynucleosides in good yield (eq 8). The FMOC group was removed from the heterocyclic bases with excess ***Triethylamine*** in dry pyridine.

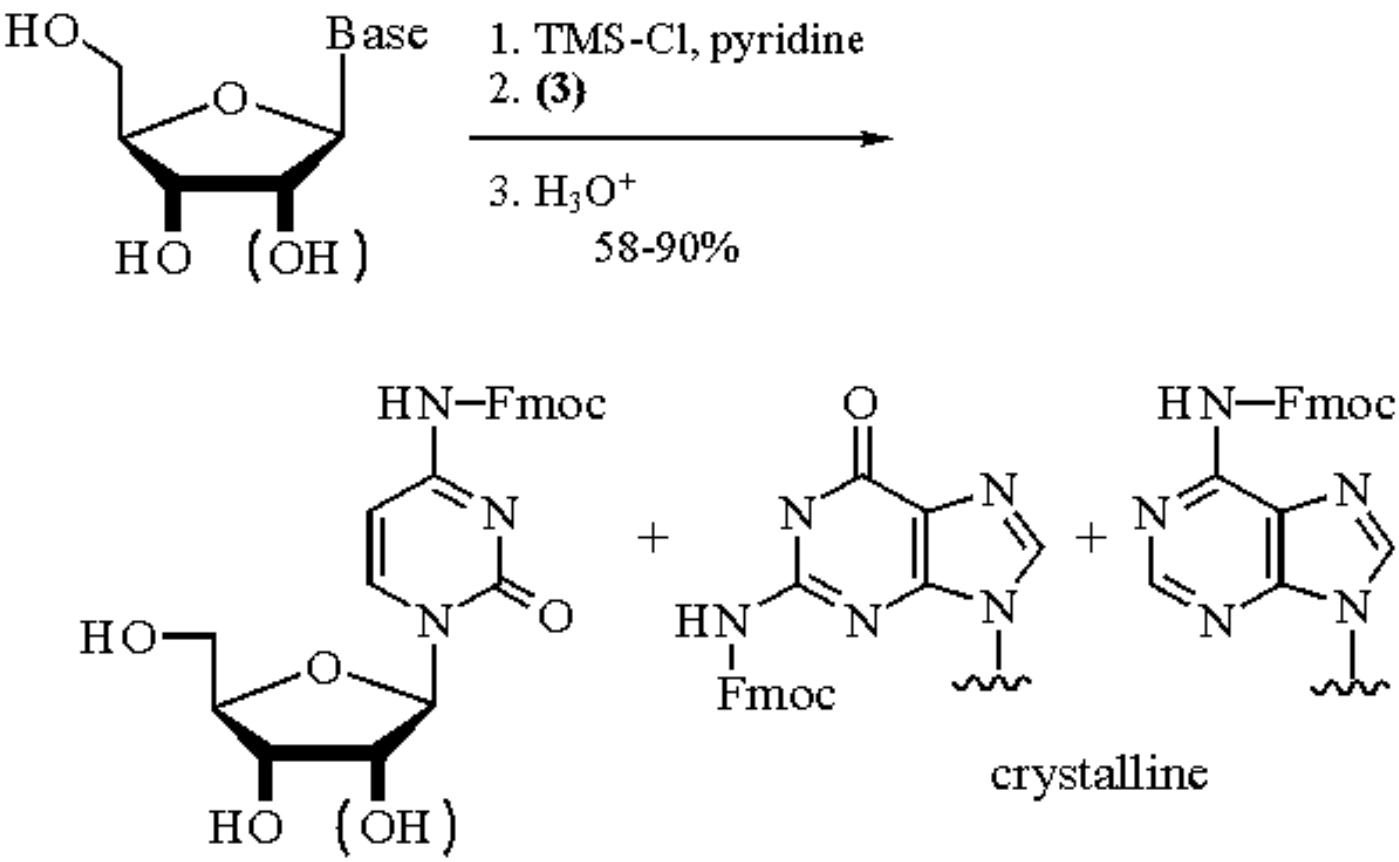

(8)

FMOC-Cl has been used for 3´,5´-hydroxyl protection of deoxyribose for the introduction of modified bases such as azacytidine using the classical Vorbrüggen reaction.[11] While the carbonate protecting groups do not alter the stereoselectivity of the *N*-glycoside formation, the FMOC groups can be removed under much milder conditions (Et_3N/pyridine) than the typical 4-methylbenzoyl group (eq 9).

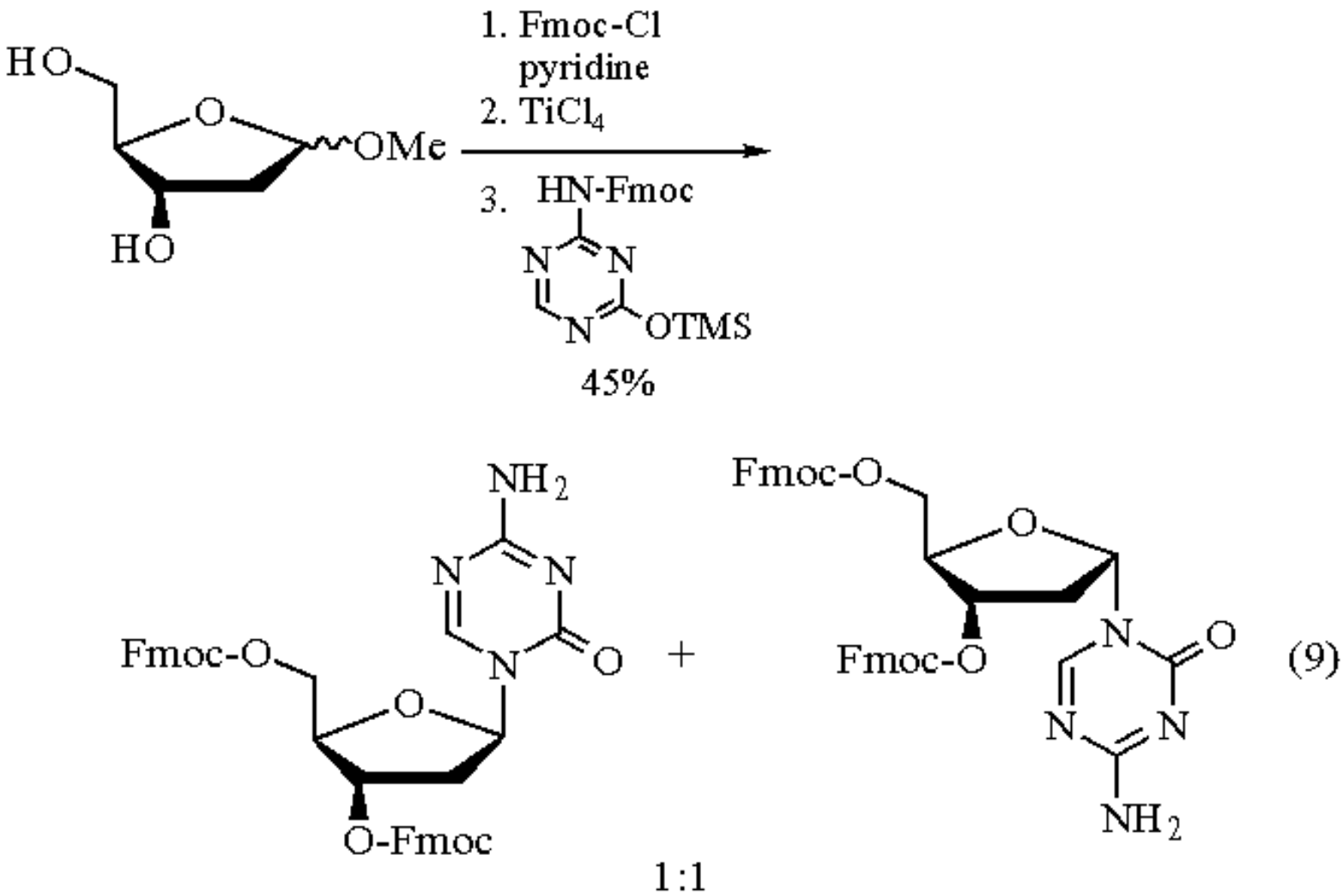

Perhaps the most impressive use of the FMOC group in the synthesis of natural products is provided by the key tetrasaccharide intermediate to calicheamicin.[12] The robust nature of this particular FMOC group is amply demonstrated by the fact that it survives 15 discrete reaction steps, including exposure to cat. NaH/$HOCH_2CH_2OH$, Br_2, EtN_3, K-Selectride, i-Bu_2AlH, and NaSMe (eq 10). Clearly, the use of FMOC protection is not limited to peptide synthesis.

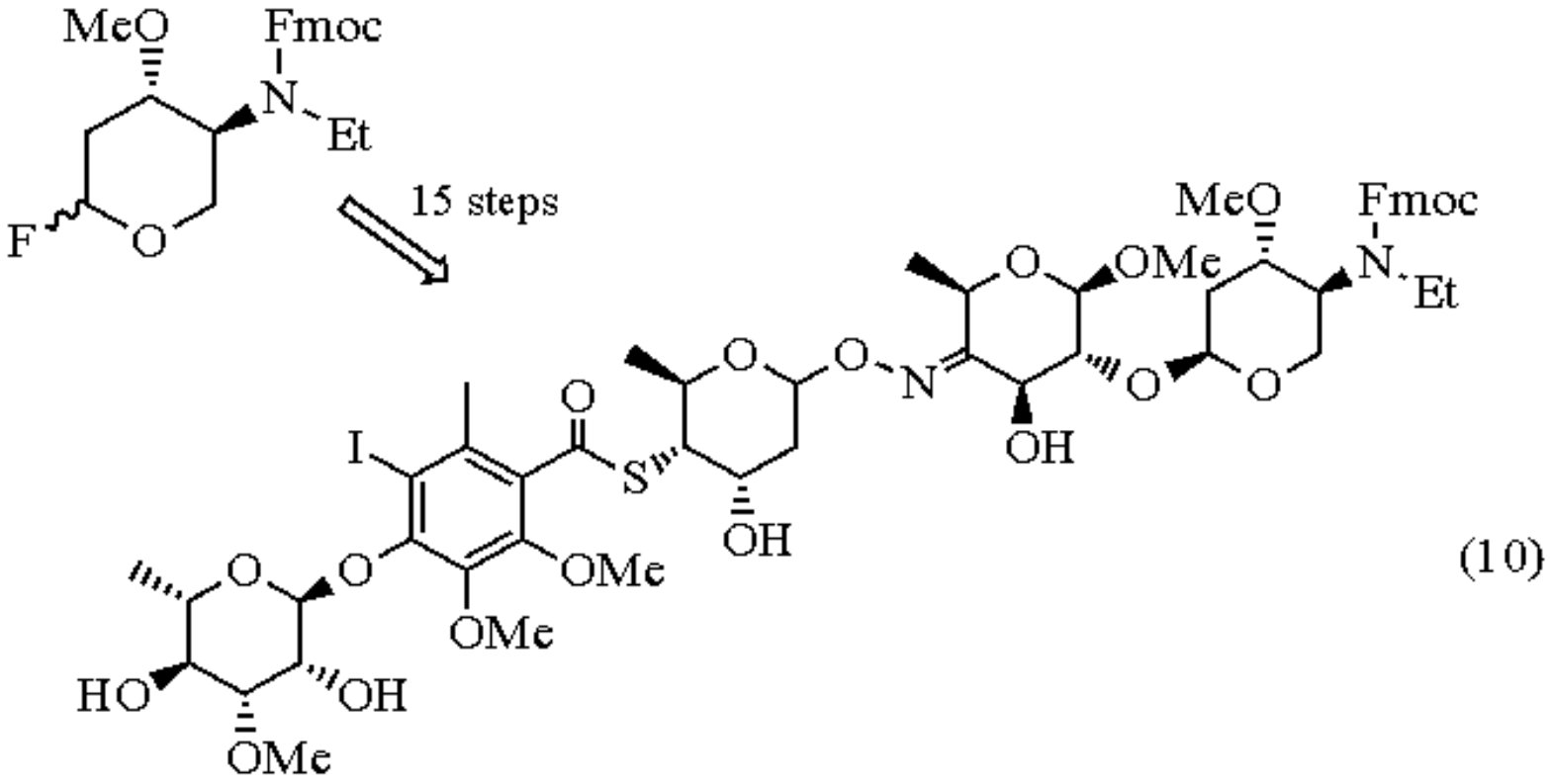

FMOC Derivatization for Fluorescence Detection and Analysis.

Derivatization of amino acids and other primary and secondary amines with (**1**) for HPLC analysis has been described. The chief advantage of this methodology is the high sensitivity due to the intense fluorescence of the fluorenyl moiety, but the FMOC also reduces polarity for faster elution from the column. Amino acids have been detected in concentrations as low as 26 femtomolar using a precolumn derivatization scheme.[13] FMOC derivatization of *lyso*-gangliosides in a two-phase Et_2O-H_2O system followed by chromatographic purification with fluoresence detection has also been reported.[14] Optically active 1-(9-fluorenyl)ethyl chloroformate (FLEC®) (**5**) is commercially available in both (+) [*107474-79-3*] and (-) forms for the analysis of racemates.

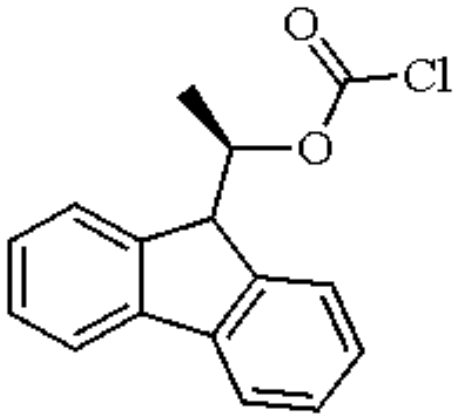

(5)

1. For illustrative procedures using FMOC and other protection schemes, see *The Practice of Peptide Synthesis*; Bodanszky, M.; Bodanszky, A., Eds.; Springer: Berlin, 1984.
2. (a) Histidine: Fischer, P. M. et al. *Int. J. Pept. Protein Res.* **1992**, *40*, 19. (b) Glutamate: Handa, B. K.; Keech, E. *Int. J. Pept. Protein Res.* **1992**, *40*, 66.
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Fluorine[1]

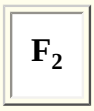

[7782-41-4] · F_2 · Fluorine · (MW 38.00)

(strong fluorinating agent and oxidizer; substitutes F for H in either radical[2] or electrophilic[2b,3] reactions; electrophilic substitution of F for other halides;[1c] adds to multiple bonds;[2b,4] oxidatively adds to centers of coordinative unsaturation;[5] used in synthesis of other (mostly electrophilic) fluorinating agents;[6] with aq MeCN, oxidizes tertiary H to alcohols,[7] alcohols to ketones,[8] ketones to esters,[8] aromatics to phenols or quinones,[9] amines to nitro derivatives,[10] and alkenes to oxiranes;[7,11] cyclotron-produced $^{18}F_2$ provides ^{18}F-labeled compounds for positron emission tomography[12])

Physical Data: mp -219.6 °C; bp -188.2 °C; vapor pressure at 77 K = 280 Torr.

Solubility: slightly sol $CFCl_3$, $CF_2ClCFCl_2$, $CHCl_3$, CH_2Cl_2, MeCN, perfluoroethers, perfluorocarbons; dec H_2O giving HF, O_2 and trace O_3, OF_2.[13]

Form Supplied in: faintly yellow compressed gas in steel cylinders at pressures of 160-400 psi, purity 97-99%; impurities HF, N_2, O_2, CF_4, SF_6, SiF_4; also in cylinders prediluted with inert gases.

Analysis of Reagent Purity: titration of Cl_2 liberated from NaCl, followed by GC for inert components; IR for HF. Rarely performed by user.

Preparative Methods: electrolysis of KF-HF mixtures.[14]

Purification: HF removed by passage through column of NaF pellets; other impurities removed only by cryogenic distillation.[15]

Handling, Storage, and Precautions: toxic; strong oxidizer. Pure fluorine should only be used by trained personnel! Prediluted F_2 is handled much more easily. Compatible materials: copper, brass, steel, stainless steel, nickel alloys (Monel, Inconel, Hastelloy), fluoropolymers (PTFE, FEP, PFA, Kel-F), *dry* glass. Vendors and handbooks[4a,14a,16] *must* be consulted for more detailed recommendations! Proper equipment cleaning and passivation are imperative to avoid ignition. Use fume hood, barricade, faceshield, leather gloves. Odor threshold: 20 ppb. TLV: 1 ppm. PEL: 0.1 ppm. IDLH: 25 ppm. Leaks easily detected with paper moistened with aq KI; monitors/detectors available. Use only fluorinated greases and oils for joints, bubblers, valve lubricants. Lubricate pipe threads with PTFE tape; permanent installations should be welded. Scrub effluent with soda lime, activated alumina, or 5-15% aq KOH. (More dilute base gives toxic OF_2; KF produced is more soluble than is NaF.) Users of solid scrubbers with vacuum pumps should consider an O_2-compatible pump fluid. NaF, aq base, and $CaCl_2$ are useful for workup of reactions producing HF. *Caution:*

Many things will burn in pure fluorine given enough (sometimes insignificant) activation energy; even many materials (PTFE, metals, concrete) not usually considered to be fuels can ignite in F_2.

Introduction of Fluorine.

Substitution of Fluorine for Hydrogen.

Perfluorination.

The chief processes for perfluorination of organic compounds are the low-temperature gradient (LaMar) and aerosol fluorination methods. The goal of these is generally complete fluorination and saturation while minimizing fragmentation (eqs 1 and 2)[2a,17] although certain functional groups can be preserved (eq 3).[18] Perfluorination can also be achieved using inert solvents (eq 4).[19]

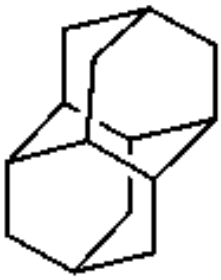

$$\xrightarrow[8\%]{F_2,\ NaF} \text{Perfluorodiamantane} \qquad (1)$$

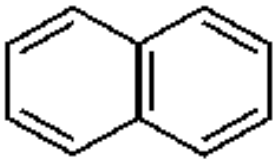

$$\xrightarrow{F_2} \text{Perfluorodecalin} \qquad (2)$$

$$Me_2C{=}O \xrightarrow[\text{Cu, -100 to -40 °C}\ 38\%]{F_2/He,\ NaF} (CF_3)_2C{=}O \qquad (3)$$

$$MeOC(CF_3)_2OCH_2(CF_2)_4H \xrightarrow[\text{FC-72 (3M)}\ 71\%]{F_2,\ UV,\ -10\ °C} CF_3OC(CF_3)_2OCF_2(CF_2)_4F \qquad (4)$$

NaF is sometimes added to trap the HF produced as $NaHF_2$. The above reactions are generally radical in character; complete fluorination sometimes requires photochemical polishing to provide larger concentrations of F&bdot; since the organic material becomes increasingly unreactive as fluorine substitution proceeds (see ***Cobalt(III) Fluoride***).

Polymer Surface Modification.

Direct fluorination with F_2 is used to convert polymers (e.g. coal-tar pitch)[20] to highly fluorinated materials. Fluorination also increases the activity of sulfonic acid catalyst resins in alkylation reactions[21] and, when used sparingly, increases the surface energy of polymers, producing improved adhesion.[22]

Electrophilic Fluorinations.

Despite fluorine's extreme reactivity, its use in selective and electrophilic replacements is not only possible but synthetically useful when mild conditions and solvents such as $CFCl_3/CHCl_3$ mixtures are employed. Fluorine excels at replacement of unactivated tertiary hydrogens and complete retention of configuration is observed. High selectivity for tertiary H is due to the higher degree of p character in tertiary C-H bonds over that in primary and secondary bonds,[23] and this also influences the relative reactivity of competing tertiary positions (eq 5).[2b] Nearby electronegative centers, for example, deactivate tertiary H in this reaction. In contrast, LaMar fluorination of alkylcyclohexanes leaves some tertiary H as the only H remaining in the molecule,[24] perhaps for steric reasons. Direct electrophilic aromatic substitution is rare although recent improvements have involved the directing effects of Lewis acids.[25] Heteroaromatics can also be fluorinated (eq 6).[26] Both aliphatic and aromatic substitutions are often facilitated by the use of organometallic derivatives[27] in place of the parent molecules (eq 7), and 1,3-diketones can be fluorinated in the form of silyl enol ethers (eq 8).[28] Fluorination of fullerenes has been a topic of recent interest.[29]

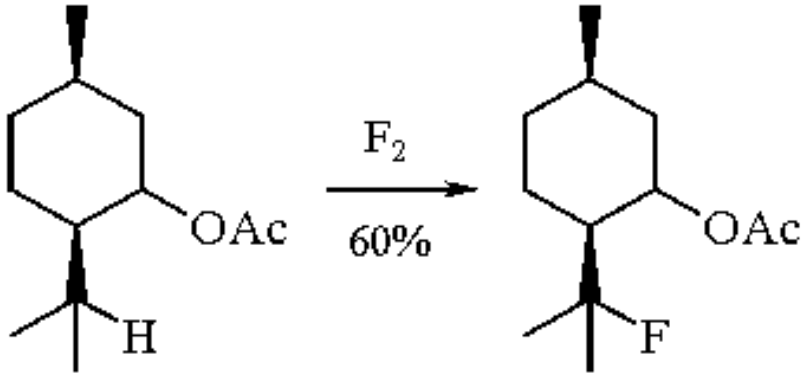

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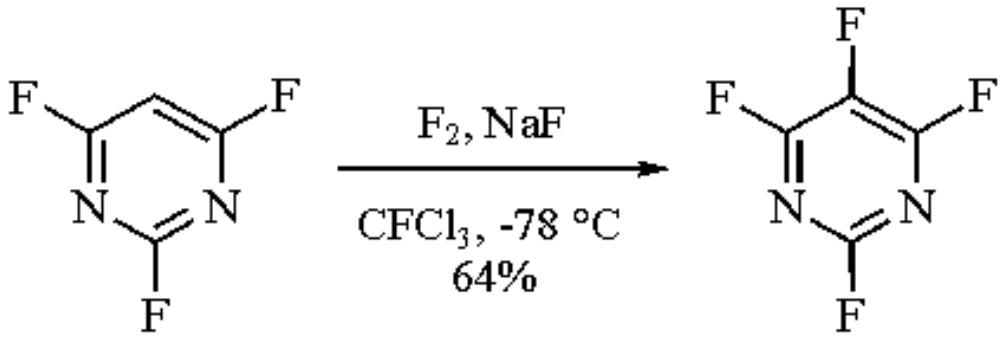

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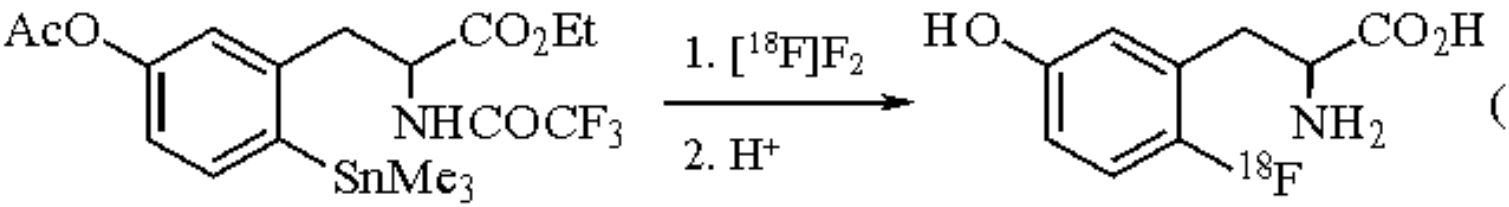

(7)

23% radiochem. yield

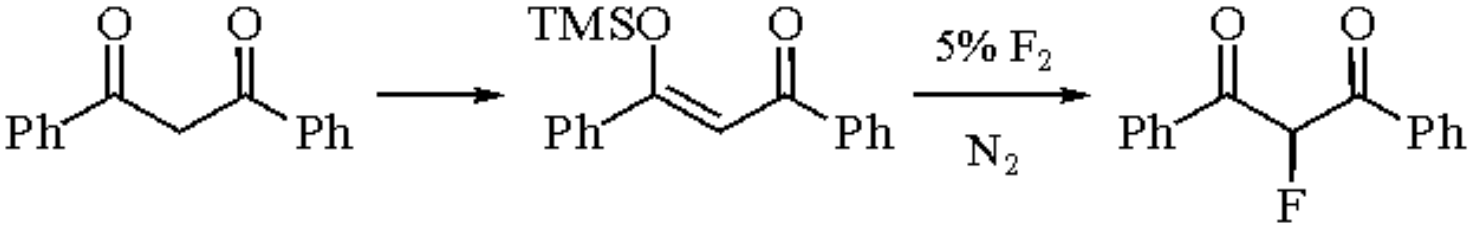

(8)

74% from silyl enol ether

Electrophilic Substitution of F for Other Halogens.

While fluoride ion is useful for nucleophilic displacement of other halides, molecular fluorine uses an electrophilic mechanism to achieve this (eq 9).[30] Substitution proceeds most effectively when the intermediate carbocation is stabilized. The reactivity of the starting organic halide increases with the atomic weight of the departing species: Cl < Br < I.

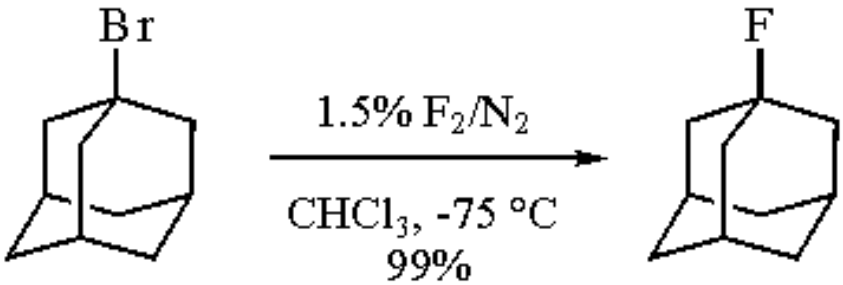

(9)

Addition to Multiple Bonds.

Alkenes.

Fluorine often adds smoothly in an electrophilic manner to alkenic double bonds, predominantly in *syn* orientation.[2b] Fluorine addition has even been applied to conversion of alkene impurities in HFC-134a (CF_3CH_2F) to more easily removed saturated products.[31] Many reactions which are formally replacement of vinylic H by F are addition reactions followed by dehydrofluorination (eq 10).[32] Under radical conditions, coupling of intermediate fluorocarbon radicals is often observed. Alkynes react to give tetrafluoro or difluoro products, depending on the conditions.[1b]

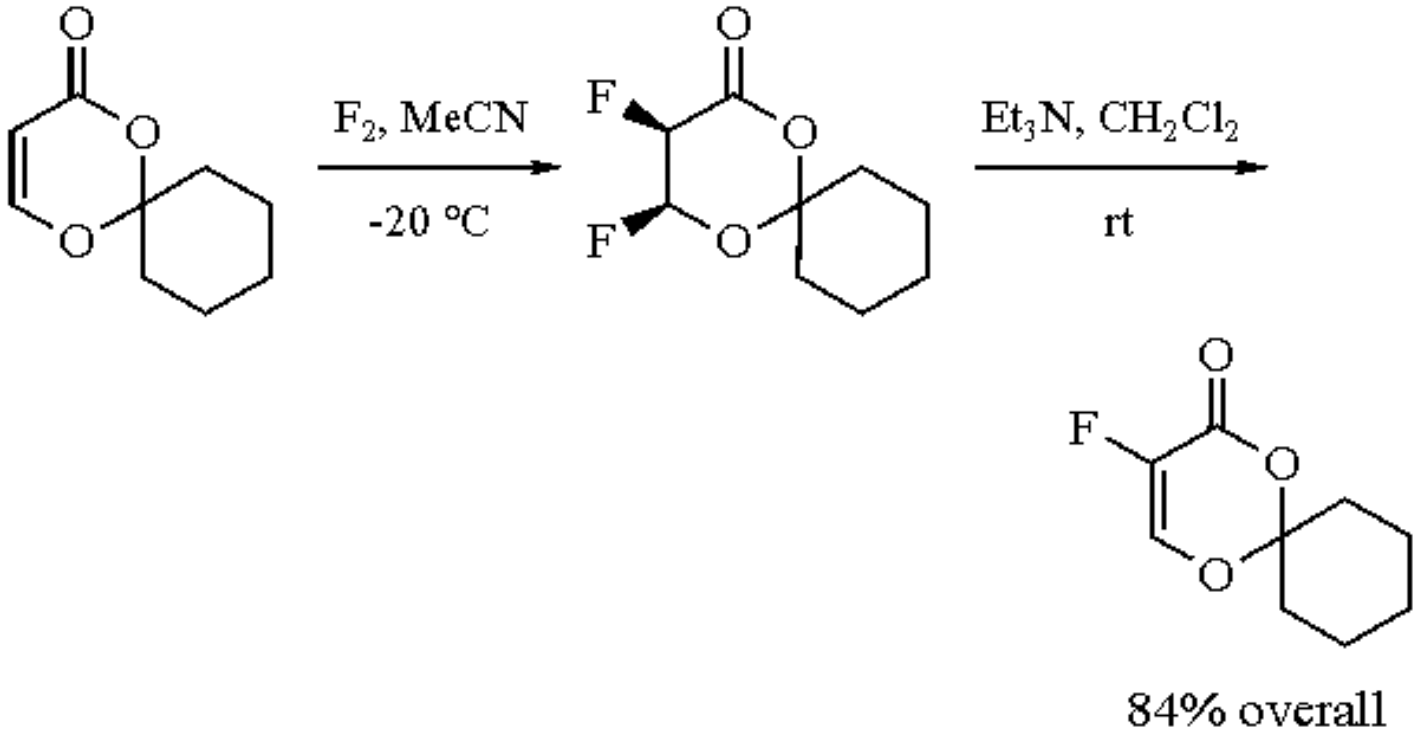

(10)

Imines.

Carbon-nitrogen double bonds react to form *N*-fluoro derivatives; for already highly fluorinated compounds, this is most often done with the aid of a metal fluoride catalyst (eq 11).[33] Subsequent dehydrofluorination is often observed if the vicinal proton is relatively acidic.[1b]

$$CF_3(CF_2)_5N{=}CF(CF_2)_4CF_3 \xrightarrow[\substack{22\ ^\circ C \\ 95\%}]{F_2,\ CsF} [CF_3(CF_2)_5]_2NF \qquad (11)$$

Carbonyls.

Such catalytic pathways are also used to add fluorine across carbonyl groups, forming fluoroxy compounds (hypofluorites) (eq 12).[34] Some hypofluorites have found use as electrophilic fluorinating agents in their own right (see, for example, ***Trifluoromethyl Hypofluorite*** and ***Acetyl Hypofluorite***).

$$CF_3C(O)CF_2Cl \xrightarrow[\substack{-196\ \text{to}\ -10\ ^\circ C \\ 80\%}]{F_2,\ CsF} CF_3CF(CF_2Cl)OF \qquad (12)$$

Oxidative Addition.

Fluorine is capable of oxidizing most elements to their highest valence state. In organic compounds, centers of coordinative unsaturation undergo oxidative addition with little fragmentation if conditions are mild. The sulfur(II) in thiols[5a] and sulfides, for instance, is transformed to sulfur(VI) in the form of $-SF_5$ or $-SF_4-$ groups (eq 13).[5b]

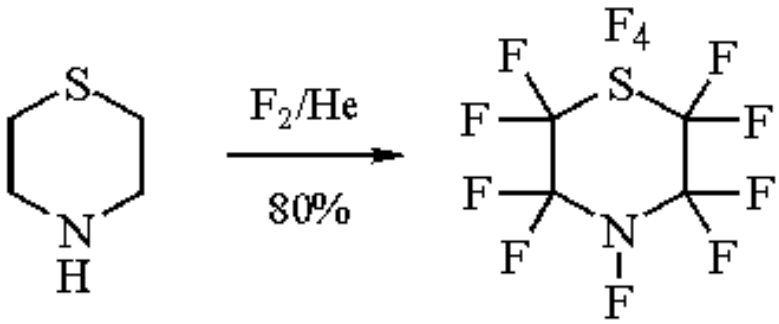

(13)

Preparation of Other Fluorinating Agents.

Most alternative electrophilic fluorinating agents are themselves prepared from elemental fluorine using variations of the reactions above, with extensions to substitution of H on N or O producing N-F or O-F bonds[6] (see for example, ***N-Fluoro-N-t-butyl-p-toluenesulfonamide***). Some hypofluorites such as MeOF[35] and *t*-BuOF[36] can be formed in situ and used to add RO-F across alkenic double bonds. Fluorination of diselenides can be used similarly[37] when conditions are mild enough to avoid oxidation. Oxidative addition is represented by the synthesis of reagents such as ***Xenon(II) Fluoride***, ***N-Fluoropyridinium Triflate***, *N*-fluoroquinuclidinium salts, and *N*-fluoro-1,4-diazabicyclo[2.2.2]octane salts.

Oxidations.

Fluorine reacts with aq MeCN to form HOF stabilized by solvent complexation.[38] The complex can act as an efficient oxidizing agent and and can be used for ^{18}O labeling.

Tertiary Hydrogen to Hydroxyl.

Fluorine can be used selectively to hydroxylate tertiary hydrogens due to the interaction of the highly electrophilic oxygen atom in the HOF/MeCN complex with the relatively electron-rich tertiary H-C bond (eq 14).[7] Experiments with *cis*- and *trans*-decalin show that the hydroxylation occurs with full retention of configuration.

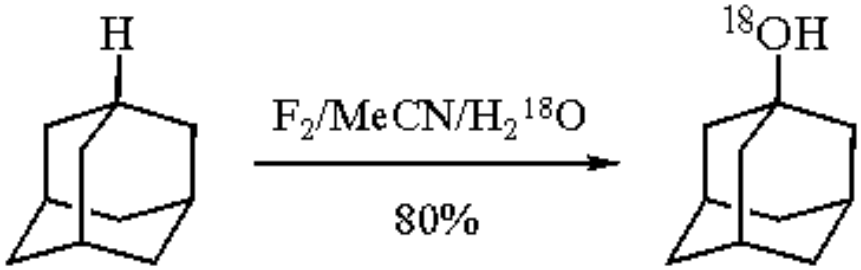

(14)

Alcohols to Ketones and Ketones to Esters.[8]

Oxidation of secondary alcohols with stabilized HOF yields ketones (eq 15); primary alcohols are less reactive. Ketones are converted to esters more slowly and with a larger excess of reagent (eq 16).

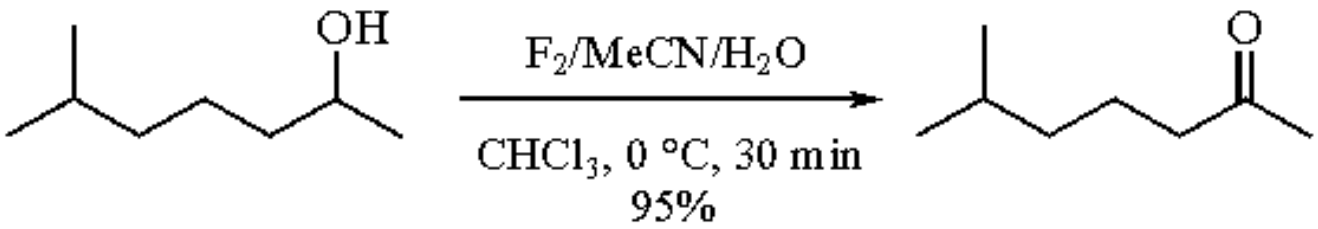

(15)

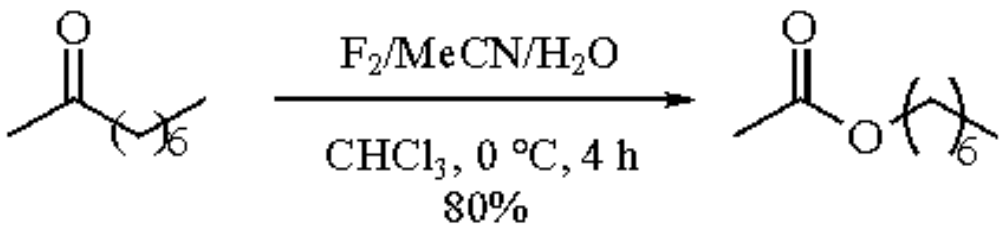

(16)

Aromatics to Phenols and Quinones.[9]

Aromatics and polynuclear aromatics are oxidized to the respective oxygenated derivatives. The reaction of mesitylene (eq 17) shows that phenols are likely intermediates to quinones. Quinones are quickly prepared in moderate yields (eq 18).

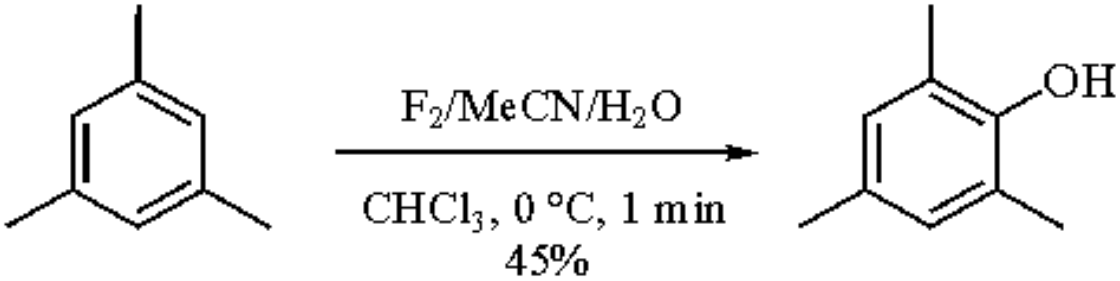

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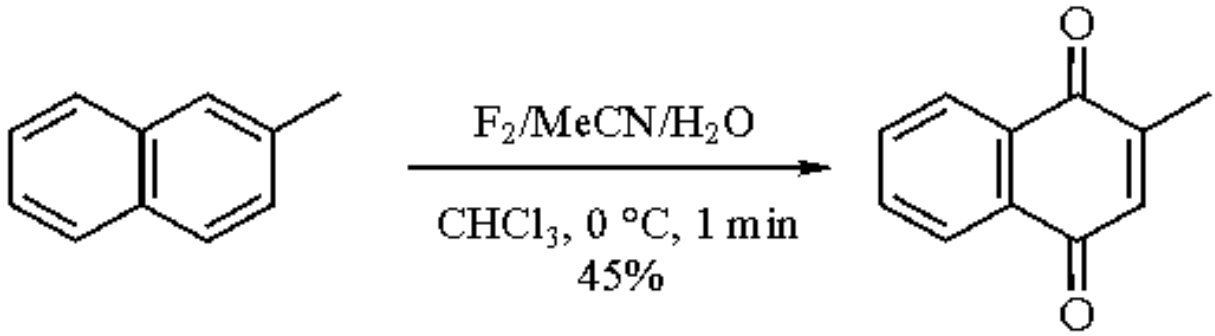

(18)

Amines to Nitro Compounds.

Primary aromatic[10a] and aliphatic[10b] amines are cleanly converted to nitro compounds without complications from other easily oxidized groups (eq 19).[10a] Amine salts are not reactive.[10b]

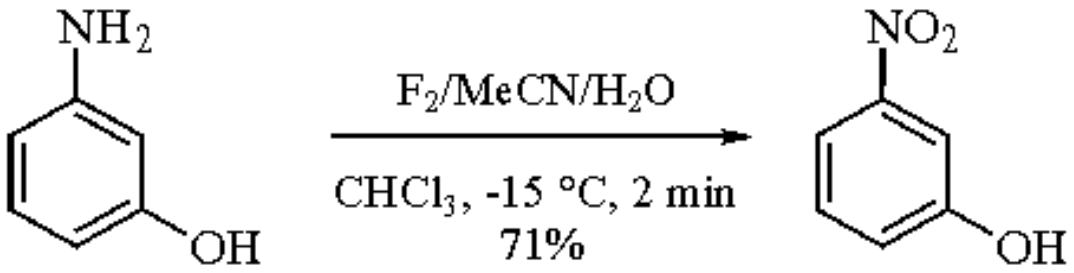

(19)

Alkenes to Oxiranes (Epoxides).[7,8,11]

Fluorine/aq MeCN readily epoxidizes electron-rich alkenes (eq 20).[7] More electron-deficient alkenes require a large excess of reagent and extended reaction time (eq 21).[7] Full retention of configuration is characteristic, since the oxides from *cis*- and *trans*-stilbene are exclusively *cis* and *trans*, respectively.[7] The epoxidation occurs preferentially over hydroxyl oxidation, as shown for dihydrocarveol (eq 22).[8] Dienes can form bis-epoxides (eq 23),[11b] or one double bond can react preferentially, given sufficient differences in electron density (eq 24).[11b] Other popular reagents such as ***m-Chloroperbenzoic Acid*** and ***Trifluoroperacetic Acid*** failed to react with *n*-$C_4F_9CH{=}CH_2$, which was epoxidized by the F_2/MeCN/H_2O system in 63% yield.[11b]

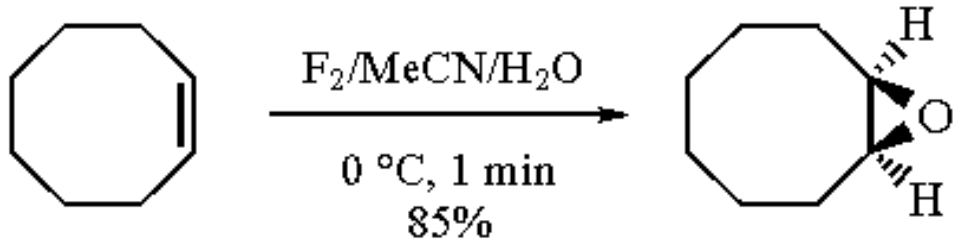

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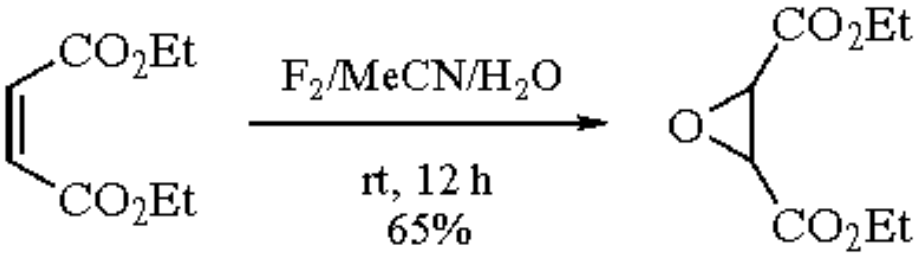

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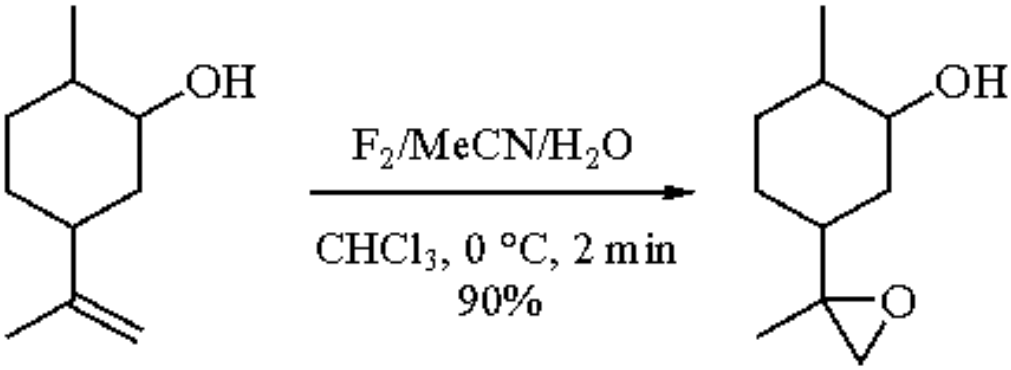

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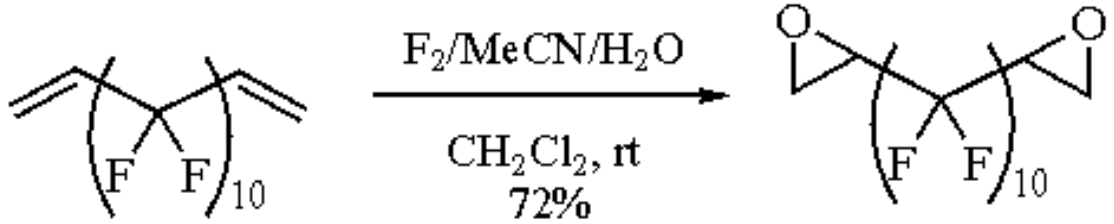

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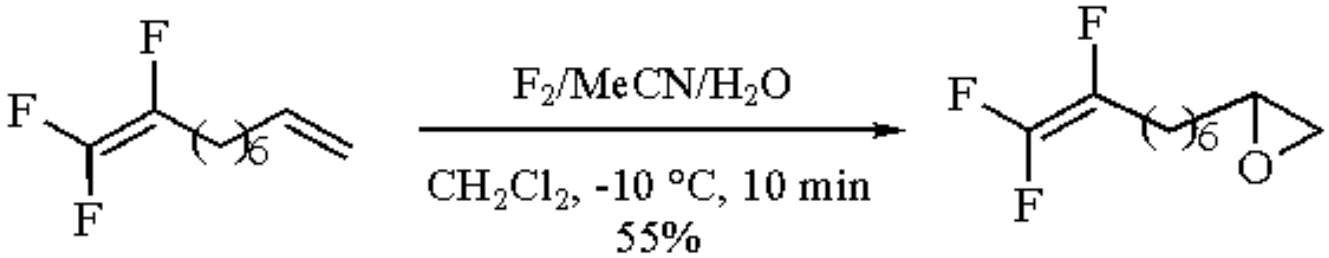

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N-Fluoro-*N*-*t*-butyl-*p*-toluenesulfonamide[1]

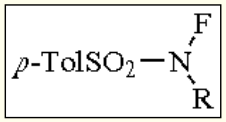

(**1**; R = *t*-Bu)

[88303-13-3] · $C_{11}H_{16}FNO_2S$ · *N*-Fluoro-*N*-*t*-butyl-*p*-toluenesulfonamide · (MW 245.35) (**2**; R = *exo*-norbornyl)

[88303-14-4] · $C_{16}H_{22}FNO_2S$ · *N*-Fluoro-*N*-norbornyl-*p*-toluenesulfonamide · (MW 311.46) (**3**; R = *endo*-norbornyl)

[88303-15-5] · $C_{16}H_{22}FNO_2S$ · *N*-Fluoro-*N*-*t*-butyl-*p*-toluenesulfonamide · (MW 311.46) (**4**; R = neopentyl)

[88303-17-7] · $C_{12}H_{18}FNO_2S$ · *N*-Fluoro-*N*-neopentyl-*p*-toluenesulfonamide · (MW 259.38)

(reagent for the fluorination of carbanions)

Physical Data: (**1**) mp 59-62.5 °C; (**2**) mp 54-60 °C; (**3**) mp 78-81 °C; (**4**) mp 58-62.5 °C.

Solubility: sol hexane, ether, THF, toluene.

Form Supplied in: white to light yellow solid.

Analysis of Reagent Purity: TLC, ^{1}H NMR.

Preparative Methods: a solution of the *N*-alkyl-*p*-toluenesulfonamide in $CFCl_3/CHCl_3$ (1:1) at -78 °C is treated with fluorine (1-5%) in nitrogen[2] (description of apparatus[3]).

Purification: flash column chromatography on silica gel.

Handling, Storage, and Precautions: solid can be stored in glass containers and is stable to moisture but becomes yellow at ambient temperatures over time with no significant change in fluorinating ability observed after several weeks. No significant decomposition was observed after freezer storage for one year. Reagent (**4**) decomposed with abrupt changes in temperature and pressure when heated above 180 °C in a closed pressure vessel.[4] These reagents should be handled in a fume hood.

Fluorination of Carbanions.

Treatment of a broad variety of carbanions with an *N*-fluoro-*N*-alkyl-*p*-toluenesulfonamide results in the transfer of fluorine from nitrogen to carbon. The carbanions can be generated under standard conditions and fluorinated in typical ether or hydrocarbon solvents.

Selection of a particular reagent is dependent upon the basicity of the carbanion and polarity of the solvent. For strongly basic carbanions, β-elimination of HF from reagents (**2**), (**3**), and (**4**) can become a major competing side reaction. Use of a nonpolar solvent or mixed polar/nonpolar system, where possible, can suppress elimination. Alternatively, reagent (**1**) can be used, although it is more difficult to prepare. The selection of type of base or counterion is generally a matter of convenience. Examples of typical carbanion fluorination reactions are included in Table 1.[2,5]

Table 1 Carbanion Fluorinations

Substrate	Base	Product	Reagent	Yield (%)	Ref.
$PhCH(CO_2Et)_2$	NaH	$PhCF(CO_2Et)_2$	**(4)**	81	2a, b
PhMgBr	-	PhF	**(1)**	50	2a, b
1-Naphthol	KH	2-Fluoro-1-naphthol	**(1)**	60	2a, b
Veratrole	BuLi	3-Fluoroveratrole	**(2)**	24	2b
Isobutyrophenone	KH	2-Fluoroisobutyrophenone	**(2)**	81	2a
Indene	KH	1-Fluoroindene	**(2)**	31	2a
2-Nitropropane	Bu_4NOH	2-Fluoro-2-nitropropane	**(1)**	83	2a, b
p-$TolSO_2NH$-*t*-Bu	BuLi	2-Fluoro-*p*-$TolSO_2NH$-*t*-Bu	**(2)**	55	2a, b
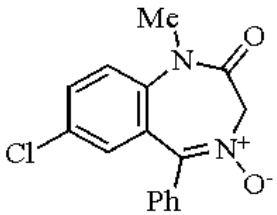	KH	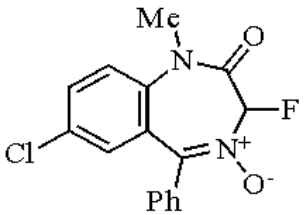	**(2)**	52	2a, b
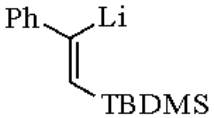	-	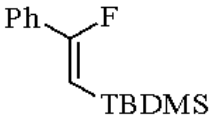	**(3)**	76	5

In addition, *N*-[^{18}F]fluoro-*N*-alkyl-*p*-toluenesulfonamides have been utilized as radiolabeling agents.[6]

Related sulfonamide-based fluorinating agents include *N*-fluoro-*N*-*t*-butylbenzenesulfonamide[7] and camphor-[8] and saccharin-based *N*-fluorosultams.[9] *N*-Fluoro-*N*-*t*-butylbenzenesulfonamide was utilized in the preparation of fluoroalkenes[7] and difluoroanthracenes[10] and is reported to have solubility advantages over the corresponding tolylsulfonamide at very low temperatures.[7] Camphor-based *N*-fluorosultams were utilized to enantioselectively prepare α-fluoro ketones.[8] The *N*-fluoro saccharin-based sultam has been used in a one-pot procedure in the synthesis of α,α-difluoro ketones.[11]

While the mechanism of fluorination by *N*-fluoro-*N*-alkyl-*p*-toluenesulfonamides has not been examined directly, studies utilizing the closely related sulfonamide-based saccharin-derived sultam suggest that the pathway involves direct nucleophilic attack on fluorine versus a radical or electron transfer mechanism.[12]

Following the development of the *N*-fluoro-*N*-alkyl-*p*-toluenesulfonamide reagents, *N*-fluorosulfonimides were prepared and demonstrated to be stable and effective fluorinating agents themselves. Thus *N*-fluorotrifluoromethylsulfonimide,[13] *N*-fluorobenzenesulfonimide,[14] and *N*-fluoro-*o*-benzenedisulfonimide[15] have found a number of applications. In addition to carbanions, the sulfonimide-based reagents can also directly fluorinate aromatics. This difference with the sulfonamides has been correlated with the relative potentials of the first one-electron reductions of their N-F bonds.[16] Similar increased reactivity has been observed with perfluoro-[*N*-fluoro-N-(4-pyridyl)]methanesulfonamide.[17]

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Fluorodimethoxyborane Diethyl Etherate

$(MeO)_2BF.OEt_2$

[367-46-4] · $C_6H_{16}BFO_3$ · Fluorodimethoxyborane Diethyl Etherate · (MW 166.03)

(electrophilic borylating agent, precursor of allylboronic esters)

Physical Data: bp 46-48 °C/760 mmHg.[1]

Solubility: sol common organic solvents (THF, Et_2O, toluene, CH_2Cl_2, etc.). The title compound is moisture sensitive and will hydrolyze when exposed to water.

Analysis of Reagent Purity: ^{1}H (δ 3.62 (br m, 4H), 3.51 (br s, 6H), 1.23 (6 H, t, *J* = 7.2 Hz)) or ^{11}B NMR.

Preparative Methods: by the disproportionation reaction of two moles ***Trimethyl Borate*** and one mole of ***Boron Trifluoride Etherate***. Distillation of the reaction mixture produces the title reagent as the diethyl etherate (76%).[1]

Purification: distillation.

Handling, Storage, and Precautions: reagent reacts with moisture and other protic solvents. It should be handled under an inert atmosphere in a well-ventilated hood. Contact with the eyes and skin should be avoided.

Fluorodimethoxyborane as an Electrophilic Borylating Agent.

The reagent has been used extensively as an electrophilic borylating agent in the synthesis of substituted allylboronic esters (eqs 1-5). Allyl anions used in these reactions include ***Allylmagnesium Bromide*** (eq 1),[2] crotylpotassium reagents (eqs 2-4),[1,3-5] and γ-alkoxyallyllithium reagents (eq 5).[6] The resulting allylboronate reagents undergo highly diastereoselective reactions with aldehydes (see ***Crotyldimethoxyborane***). The diastereoselectivity of these reactions depends on the isomeric purity of the reagent.[7]

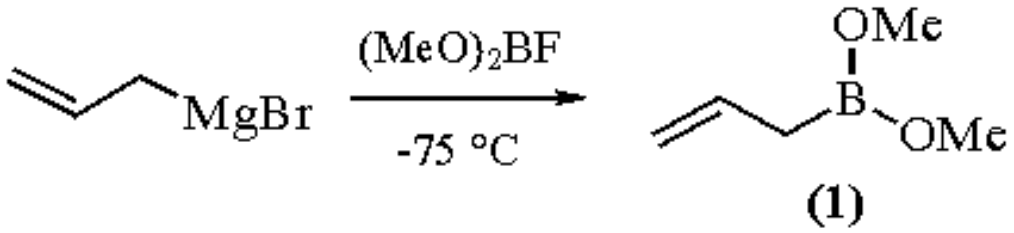

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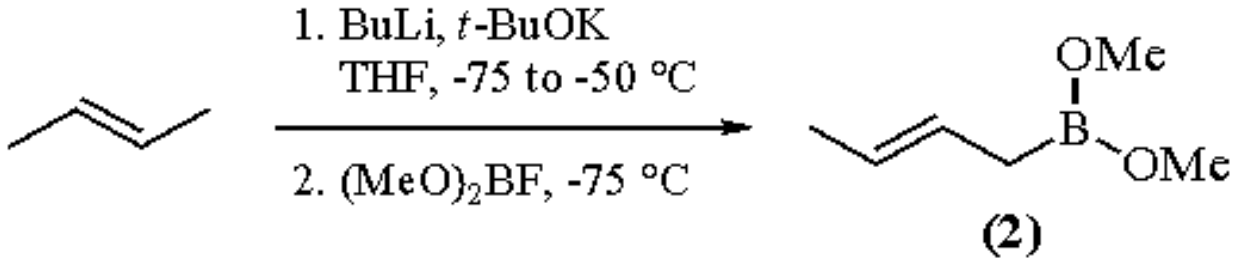

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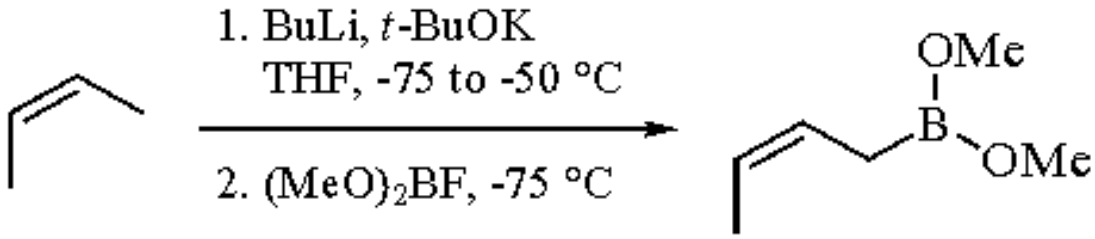

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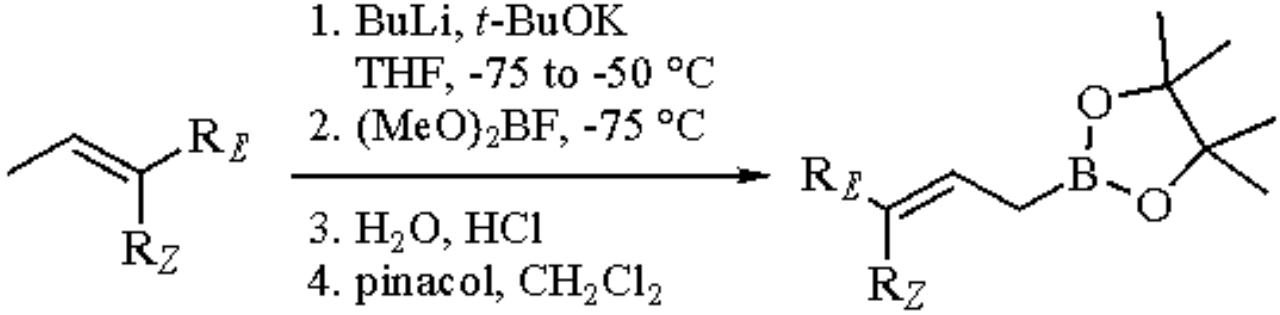

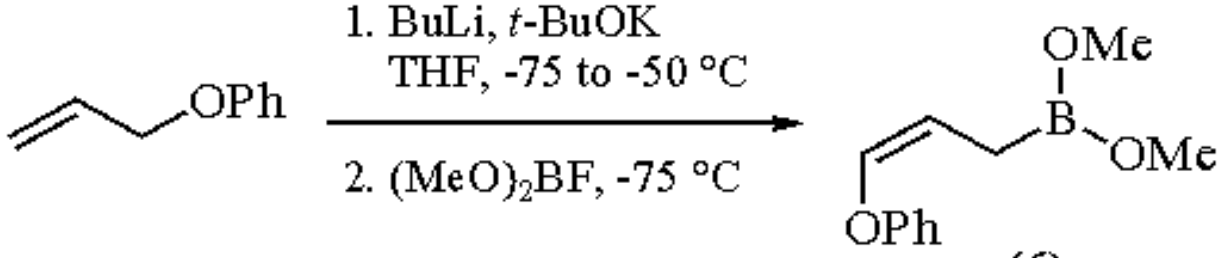

This procedure was used initially for the synthesis of the tartrate ester modified crotylboronates (**7**) and (**8**) (eq 6).[5] On scales up to 100 mmol, it was found that crotylboronates (**7**) and (**8**) were obtained in 70-88% yield with excellent

isomeric purity. However, as the scale increased to 200 mmol the yields fell to 14-35% and (**7**) and (**8**) were obtained with much lower isomeric purity. These problems have been attributed to the competitive formation of tricrotylborane.[5] Much more consistent results, particularly for large scale reactions (up to 400 mmol), have been achieved by using ***Triisopropyl Borate*** as the borylating agent. A similar improvement in yield has been reported for the preparation of the tartrate ester modified allylboronate (**9**) (eq 7).[2]

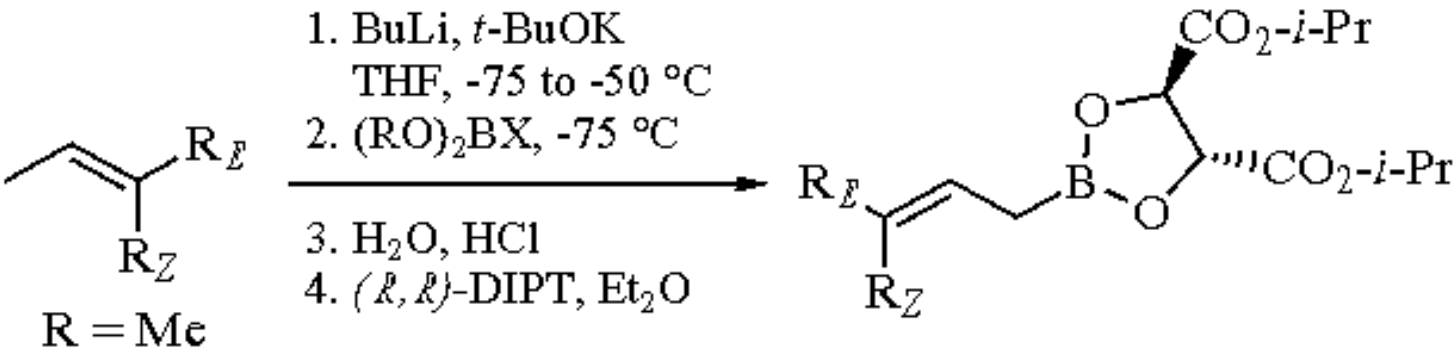

(6)

(7) 96% *(E)*
(8) 97% *(Z)*

Reagent	Scale (mmol)	$(RO)_2BX$	Yield (%)	Purity (%)
(7) *(E)*	[2]100	$(MeO)_2BF$	70-80	96-97 *(E)*
(7) *(E)*	200	$(MeO)_2BF$	35	94-97 *(E)*
(8) *(Z)*	[2]100	$(MeO)_2BF$	70-80	96-98 *(Z)*
(8) *(Z)*	200	$(MeO)_2BF$	14	92-95 *(Z)*
(7) *(E)*	425	$(i\text{-}PrO)_3B$	60	[3]98 *(E)*
(8) *(Z)*	200	$(i\text{-}PrO)_3B$	7032075	[3]99 *(Z)*

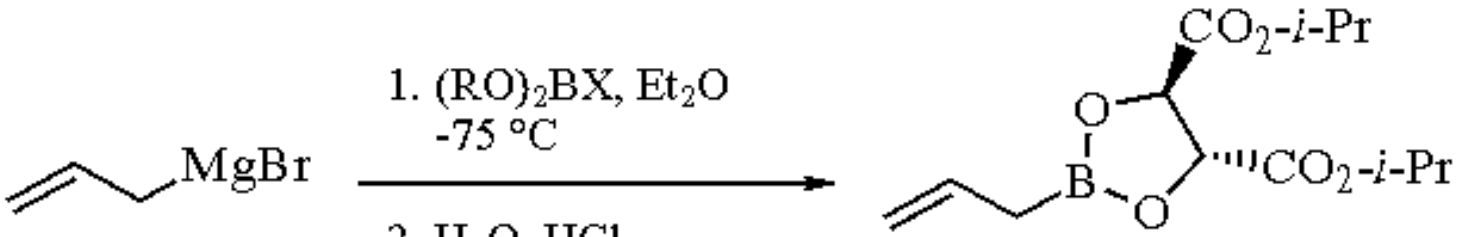

(7)

(9)

$(RO)_2BX$	Yield (%)
$(MeO)_2BF$	35-46
$(i\text{-}PrO)_3B$	65-76

A systematic study of the synthesis of alkyl boronic esters from the reaction of organometallic reagents and electrophilic borylating agents has been reported by Brown.[8] This study clearly identifies (i-PrO)$_3$B as the best reagent for these purposes. For example, the reaction of FB(OMe)$_2$ with ***Methyllithium*** gives only 10% yield of methylboronic ester and 28% of lithium tetramethylborate. However, treatment of triisopropyl borate with MeLi gives almost exclusively the methylboronic ester (&egt;98%) (eq 8).

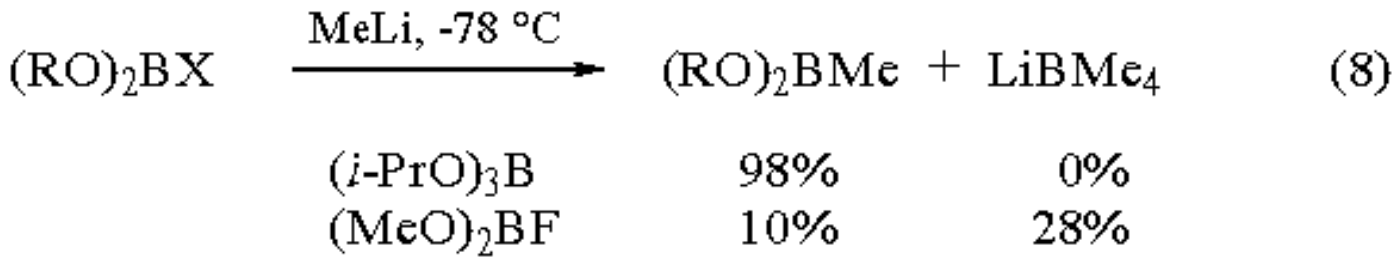

Fluorodimethoxyborane as a Precursor for the Synthesis of (δ-Hydroxy)allylsilanes.

Metalation of homoallylsilane (**10**) with ***n-Butyllithium*** and ***Potassium t-Butoxide*** followed by treatment of the resulting allyl potassium derivative with FB(OMe)$_2$ gives the (Z)-δ-(trimethylsilylmethyl)allylboronate exclusively, which is further oxidized by using basic peroxide to give the (Z)-allylsilane (**11**) (61% yield) (eq 9).[9]

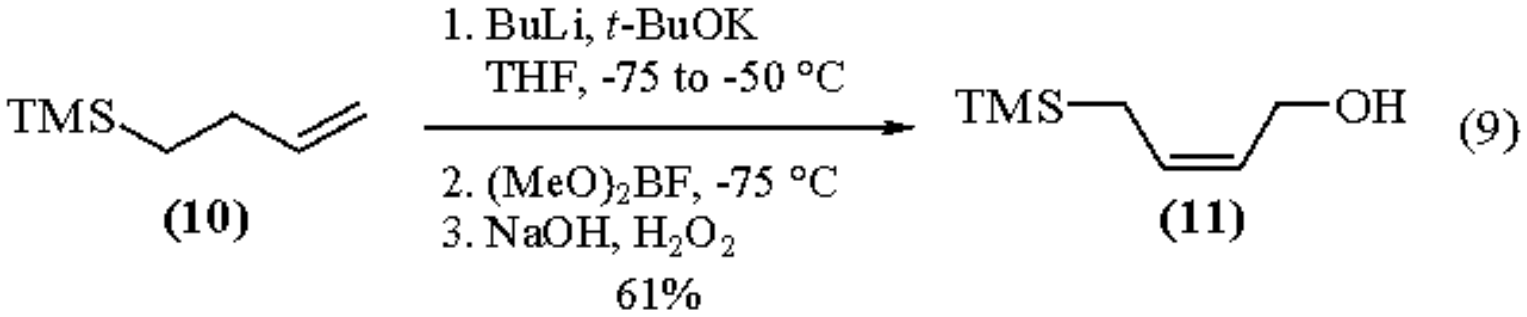

Related Reagents.

Triisopropyl Borate; ***Trimethyl Borate***.

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2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide

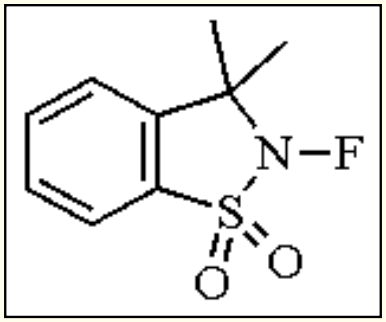

[124170-23-6] · $C_9H_{10}FNO_2S$ · 2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide · (MW 215.24)

(electrophilic fluorinating agent)

Alternate Name: N-fluoro-2,α-cumenesultam.

Physical Data: mp 115-117 °C.

Solubility: sol various organic solvents including THF, diethyl ether, CH_2Cl_2, acetonitrile.

Form Supplied in: white or slightly yellow solid, &egt;98% purity; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR.

Preparative Method: pressureless fluorination on a 100 g scale with F_2 in N_2 (F_2/N_2 10% v/v) in the presence of powdered NaF in $CHCl_3/CFCl_3$ (1/1 v/v) at -40 °C.[1,2]

Purification: flash chromatography (SiO_2, CH_2Cl_2) and/or crystallization from Et_2O/pentane.

Handling, Storage, and Precautions: handle and store at rt or below; protected from light, preferably under nitrogen or argon. Thermally stable up to 200 °C; decomposes exothermally above 200 °C. Reacts with easily oxidized compounds such as iodide or tetramethylphenylenediamine. This reagent should be handled in a fume hood.

Nitrogen-fluorine bond-containing compounds are among the most useful electrophilic fluorinating agents due to their easy access, their inherent stability, and the ease with which they can be handled. 2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (**1**) is one of the most thoroughly studied reagents, both from a preparative and a

mechanistic point of view.[1-8] There is evidence, both preparative and mechanistic, that direct nucleophilic attack at fluorine occurs. Electron transfer is a competing reaction, which leads to nonfluorinated products.[5,6,8]

Monofluorination of Enolates.

N-Fluorosultam (**1**) has been successfully used to prepare α-fluorocarbonyl compounds by electrophilic fluorination starting, for example, from disubstituted enolates derived from ketones, esters, and β-dicarbonyl compounds (eqs 1-3).[1] The related *N*-fluorosulfonamide reagents[9] give considerably lower yields due to the elimination of HF by proton abstraction from the carbon α to the nitrogen atom.[1]

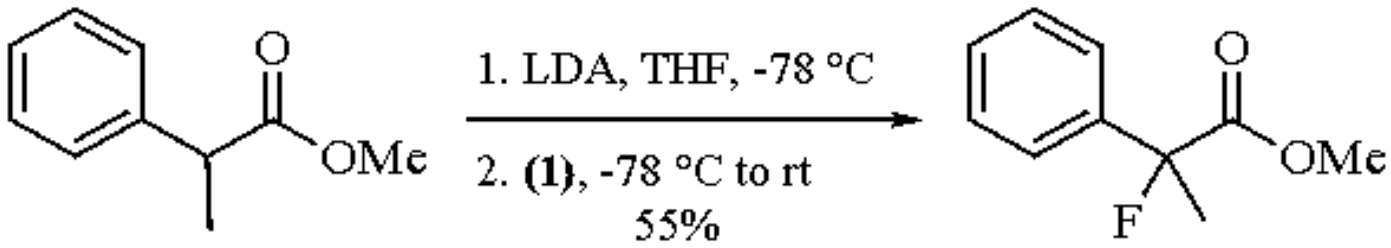

(1)

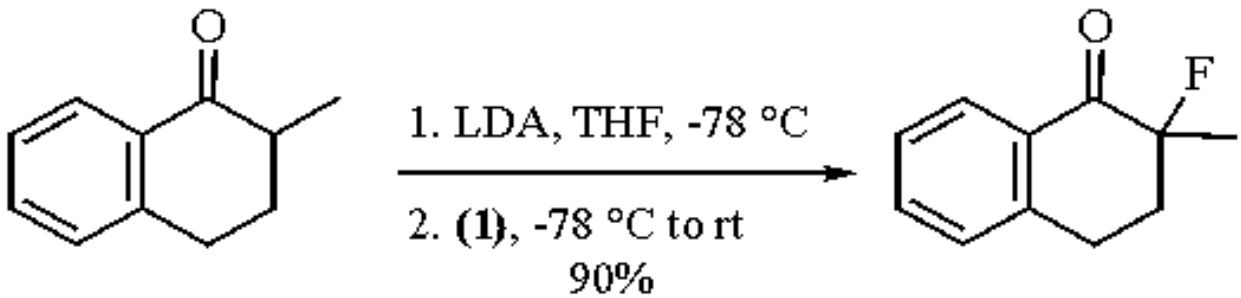

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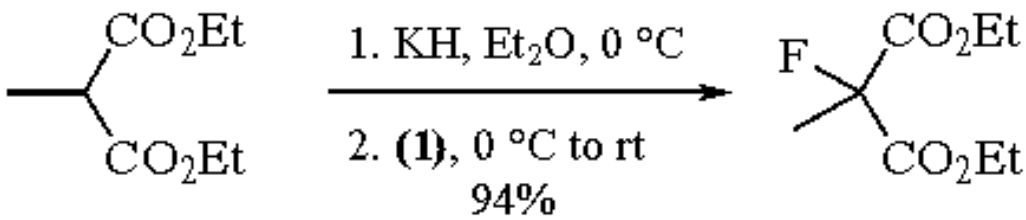

(3)

Monosubstituted enolates can be selectively monofluorinated using slightly more than 1 equiv of base and *N*-fluorosultam. The influence of the counterion is crucial and the selectivity decreases in the order Li > Na > K, although ***Potassium Hexamethyldisilazide*** often gives higher yields, especially with esters (eqs 4-6).[4]

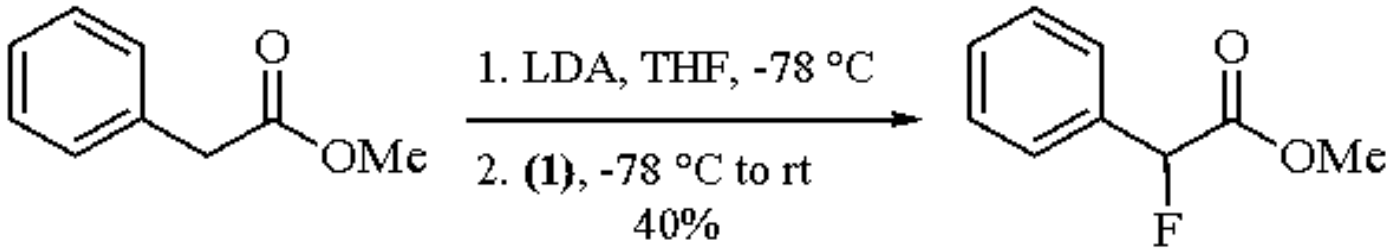

(4)

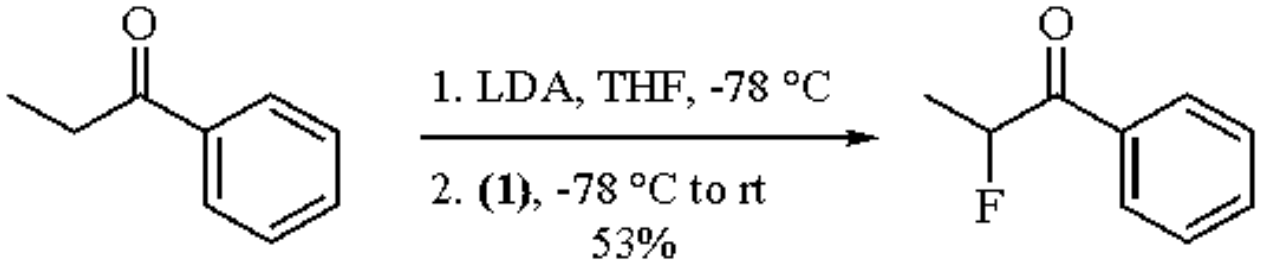

(5)

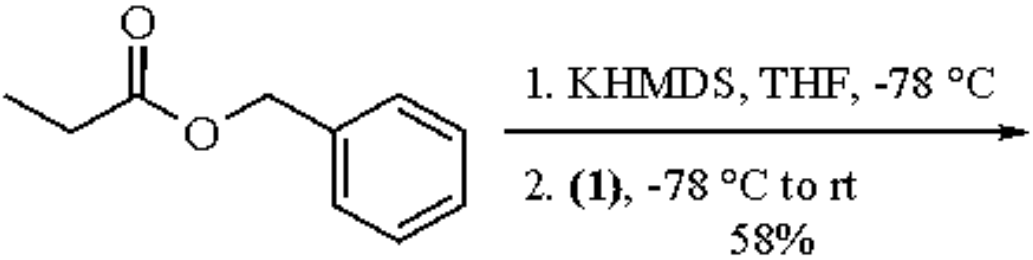

(6)

See also the related chiral *N*-fluorosultam reagents derived from camphor which allow for enantioselective fluorination with modest enantiomeric excesses (up to 75%).[10,11]

Double Fluorination of Enolates.

Double fluorination of monosubstituted enolates is achieved selectively in a one-pot procedure by adding the starting carbonyl compound to 2.4-3.6 equiv of base in THF at -78 °C followed by the addition of 2.6-3.6 equiv of the *N*-fluorosultam, and warming up to room temperatures. For this process, KHMDS and ***Potassium Diisopropylamide*** are the bases of choice (eqs 7-9).[4]

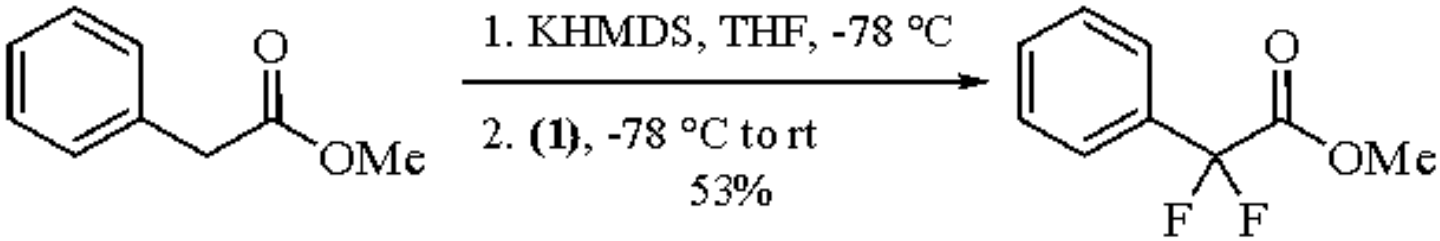

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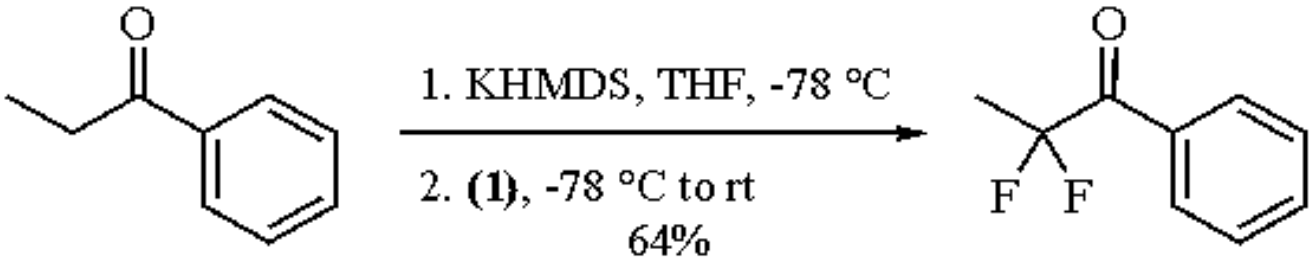

(8)

2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide

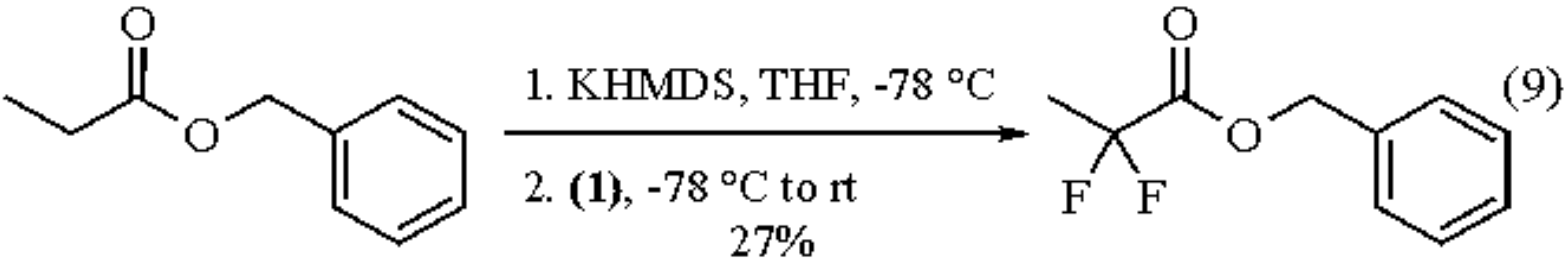

Fluorination of Organometallic Reagents.

Aryl fluorides can be prepared by reacting the corresponding aryllithium compound with (**1**) (eq 10). Grignard reagents give significantly lower yields, probably due to competing electron transfer reactions since radical-derived side products have been isolated and characterized (eq 11).[6]

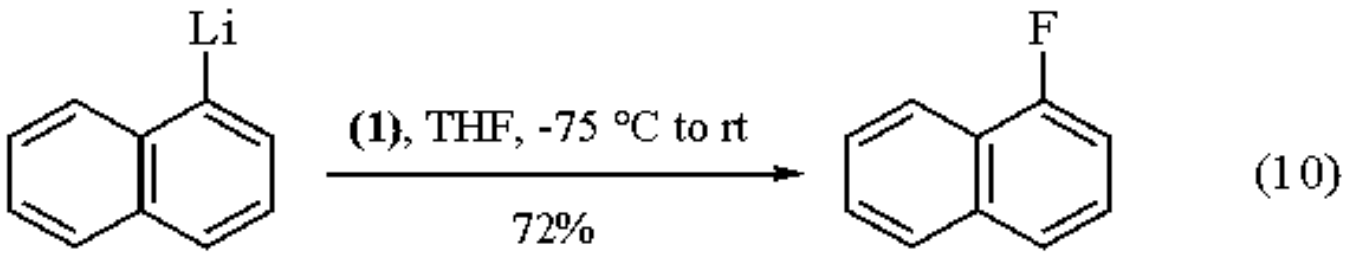

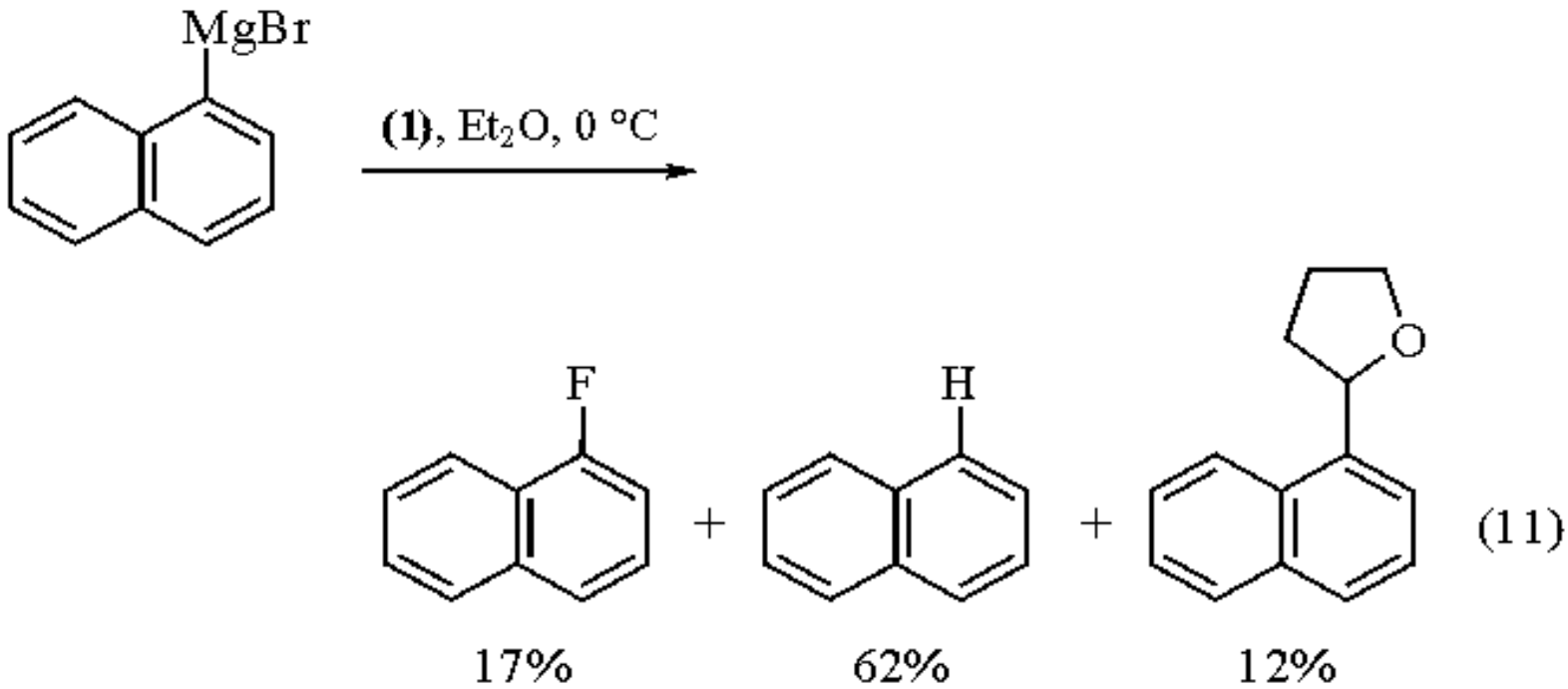

For a more reactive nitrogen-fluorine bond containing reagent, see ***N-Fluoro-N-(phenylsulfonyl)benzenesulfonamide***.[12]

---

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1-Fluoro-2,4-dinitrobenzene

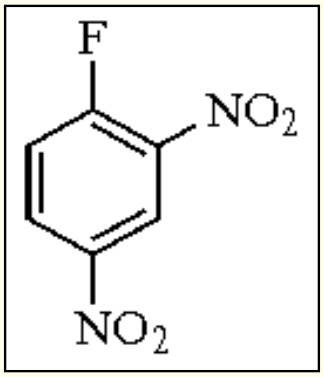

[70-34-8] · $C_6H_3FN_2O_4$ · 1-Fluoro-2,4-dinitrobenzene · (MW 186.10)

(identification of terminal amino acid residues in peptides;[1] amine protecting group;[4] deoxygenation of phenols;[11,12] thioamide protecting group[14])

Alternate Names: dinitrofluorobenzene; DNFB; Sanger's reagent.

Physical Data: mp 27.5-30 °C; bp 178 °C/25 mmHg; *d* 1.48 g cm^{-3}.

Solubility: sol benzene, Et_2O, EtOAc, acetone, DMF, propylene glycol.

Form Supplied in: 99% pale yellow crystals; widely available.

Purification: commercial sample can be recrystallized from diethyl ether.

Handling, Storage, and Precautions: stored at room temperature. Considered as highly toxic and cancer suspect agent. Use in a fume hood.

Peptide Analysis.

Sanger[1] developed an efficient method for the identification of the terminal amino acid residues in peptides and proteins using dinitrofluorobenzene. DNFB reacts at room temperature with the terminal amino functionality of the peptides in the presence of sodium bicarbonate and upon acid hydrolysis a dark yellow 2,4-DNP derivative of the terminal amino acid is liberated (eq 1). As the 2,4-DNP-amino acids produced are dark yellow in color, they may be estimated colorimetrically using the corresponding pure 2,4-DNP-amino acid as a standard. Partition chromatography or paper chromatography techniques can be used to separate the components; the DNP-amino acids provide visible yellow bands. DNFB is more widely used than dinitrochlorobenzene as the latter requires higher temperatures to react with amines especially in presence of sodium bicarbonate, which leads to hydrolysis of the protein. DNP derivatives of 4-

aminopentanoic acid[2] and 2,4-hexadiynylene esters of various amino acids[3] have been prepared for characterization purposes.

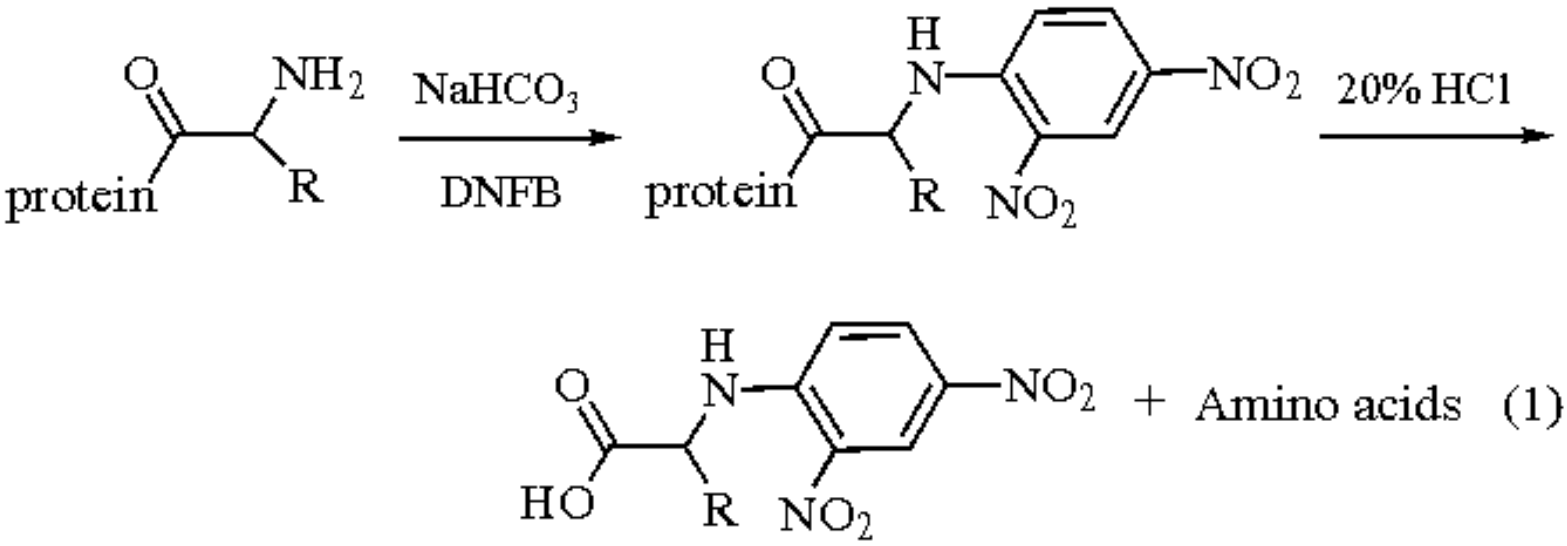

Amine Protection.

The use of DNFB for protection of amine functionalities in sugars during the synthesis of glycosides was first introduced by Lloyd;[4] the unprotected hexosamines gave poor yields in condensation reactions. Wolfrom[5] has used DNFB to install *N*-blocking groups in pyrimidine nucleoside synthesis from 2-amino sugars. DNP-D-glucosamine was prepared by treating 2-amino-2-deoxy-D-glucose hydrochloride with DNFB and sodium bicarbonate. After synthesis of the nucleoside the final deprotection was carried out by simply treating the DNP derivative with barium hydroxide to release the free amine (eq 2). Recently, Valli and co-workers[6] have shown that 2,4-DNP derivatives of some amines which are analogs of ranitidine, are good inhibitors of acetylcholinesterase.

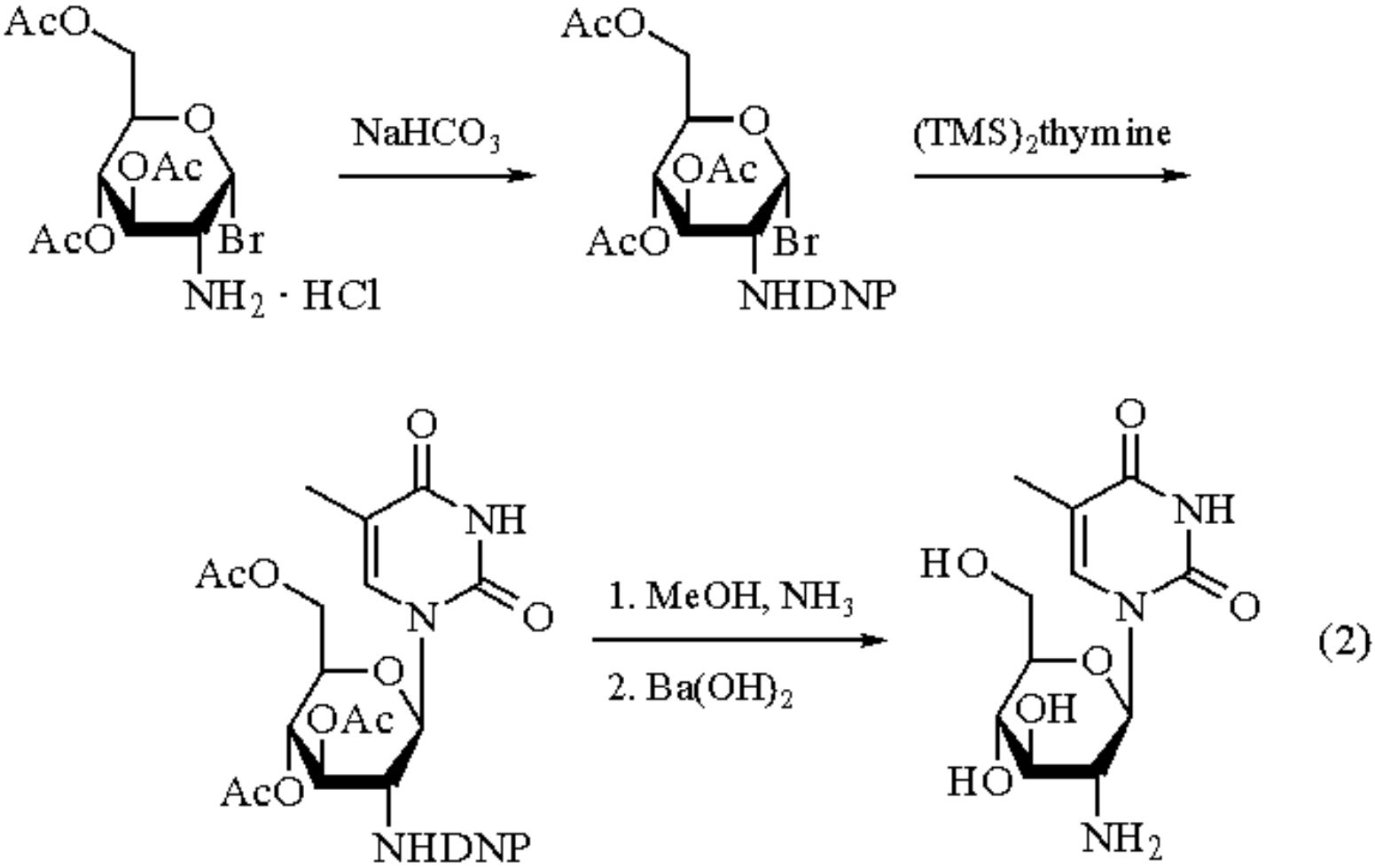

Derivatization of Phenols and Alcohols.

DNFB reacts with phenols under mild conditions in the presence of catalytic ***Triethylamine*** in acetone to give the corresponding 2,4-dinitrophenyl ethers as solid derivatives in high yields.[7] 2,4-Dinitrophenyl ether derivatives of alditols and *myo*-inositol have been prepared at room temperature using DNFB in DMF and triethylamine; the products are usually crystalline with sharp melting points.[8] 2,4-Dinitrophenyl ethers from neryl and geranyl alcohol were prepared with 1,4-diazabicyclo[2.2.2]octane and DNFB.[9]

Allyl Alcohols to Allyl Chlorides.

Allyl alcohols are converted to the corresponding allyl chlorides via 2,4-dinitrophenyl ether derivatives.[10] The allyl alcohol is treated with DNFB in the presence of triethylamine to yield the corresponding 2,4-dinitrophenyl ether, which in turn is treated with ***Lithium Chloride*** in HMPA to give the allyl chloride (eq 3).

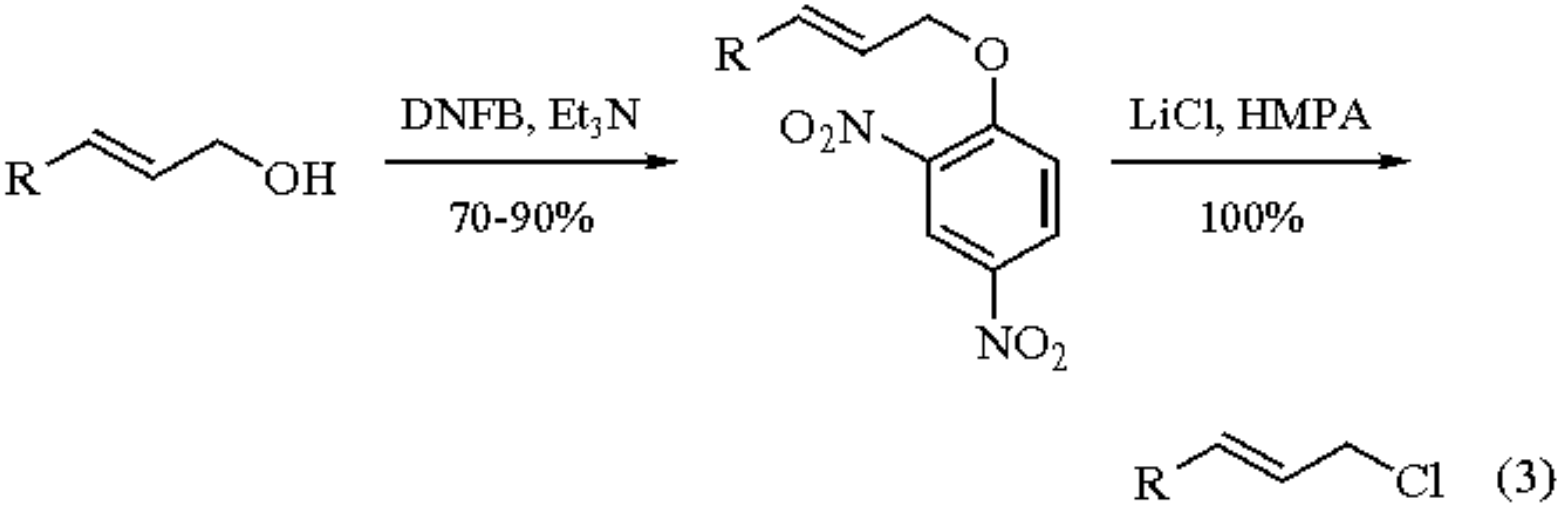

Deoxygenation of Phenols.

Pirkle[11] reported a method for the deoxygenation of phenols via the corresponding 2,4-dinitrophenyl ethers. The method was employed in their investigation of potential analgesic agents, morphinans and isomorphinans, derived from natural sources.[12] Treatment of the phenol derivative with DNFB in toluene-DMF using ***Sodium Hydride*** as catalyst gave the 2,4-dinitrophenyl ether in high yields. Catalytic hydrogenation to the 2,4-diaminophenyl ether followed by cleavage with ***Sodium-Ammonia*** gave the deoxygenation product in an overall yield of 93% (eq 4).

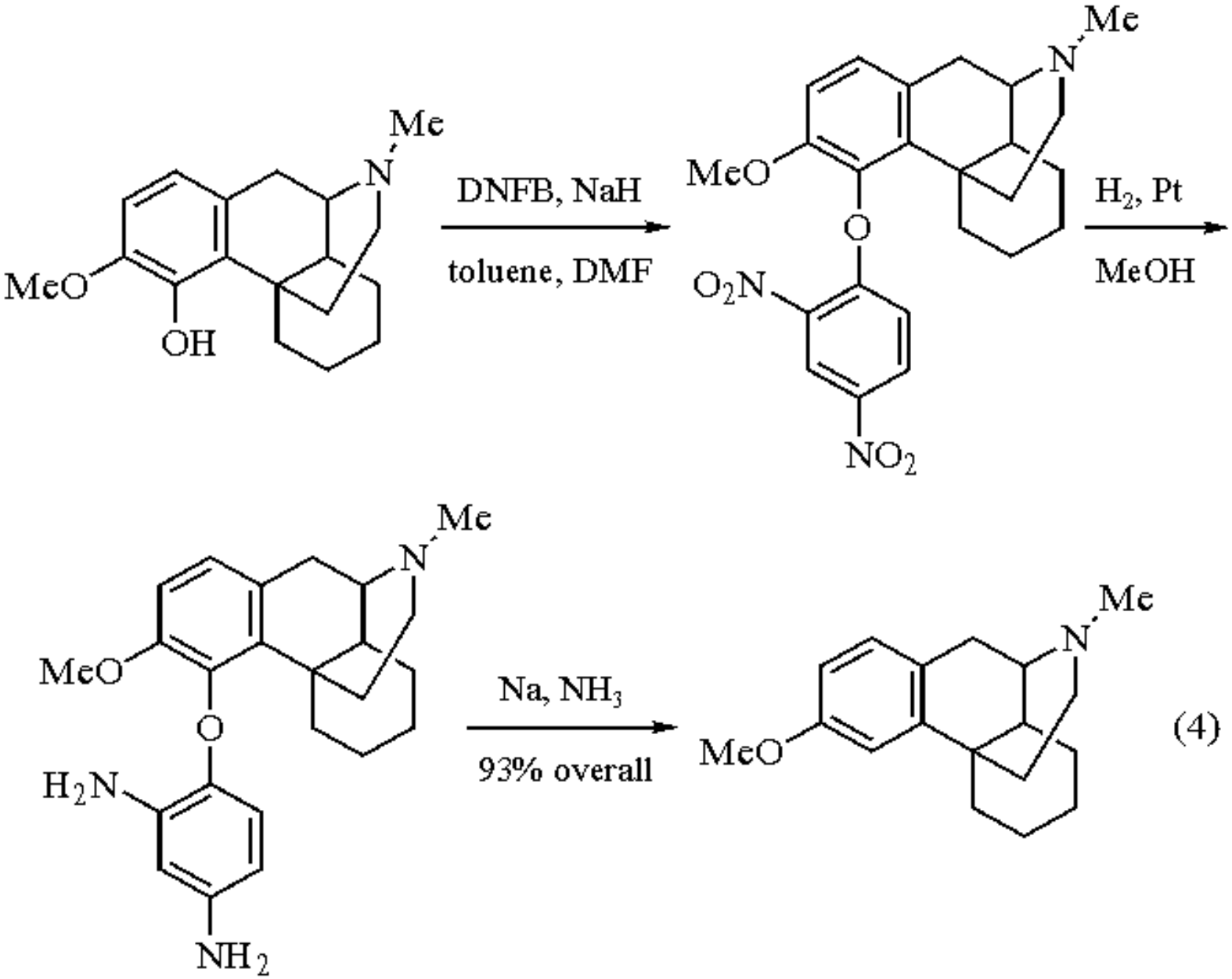

(4)

Degradation of Aldose Sugars.

2,4-DNP derivatives of aldose oximes are used in a Wohl degradation to obtain the next lower aldose sugars.[13] For example, D-glucose oxime when treated with DNFB in the presence of sodium bicarbonate provides the oxime aryl ether which decomposes to D-arabinose, 2,4-dinitrophenol, and hydrogen cyanide (eq 5).

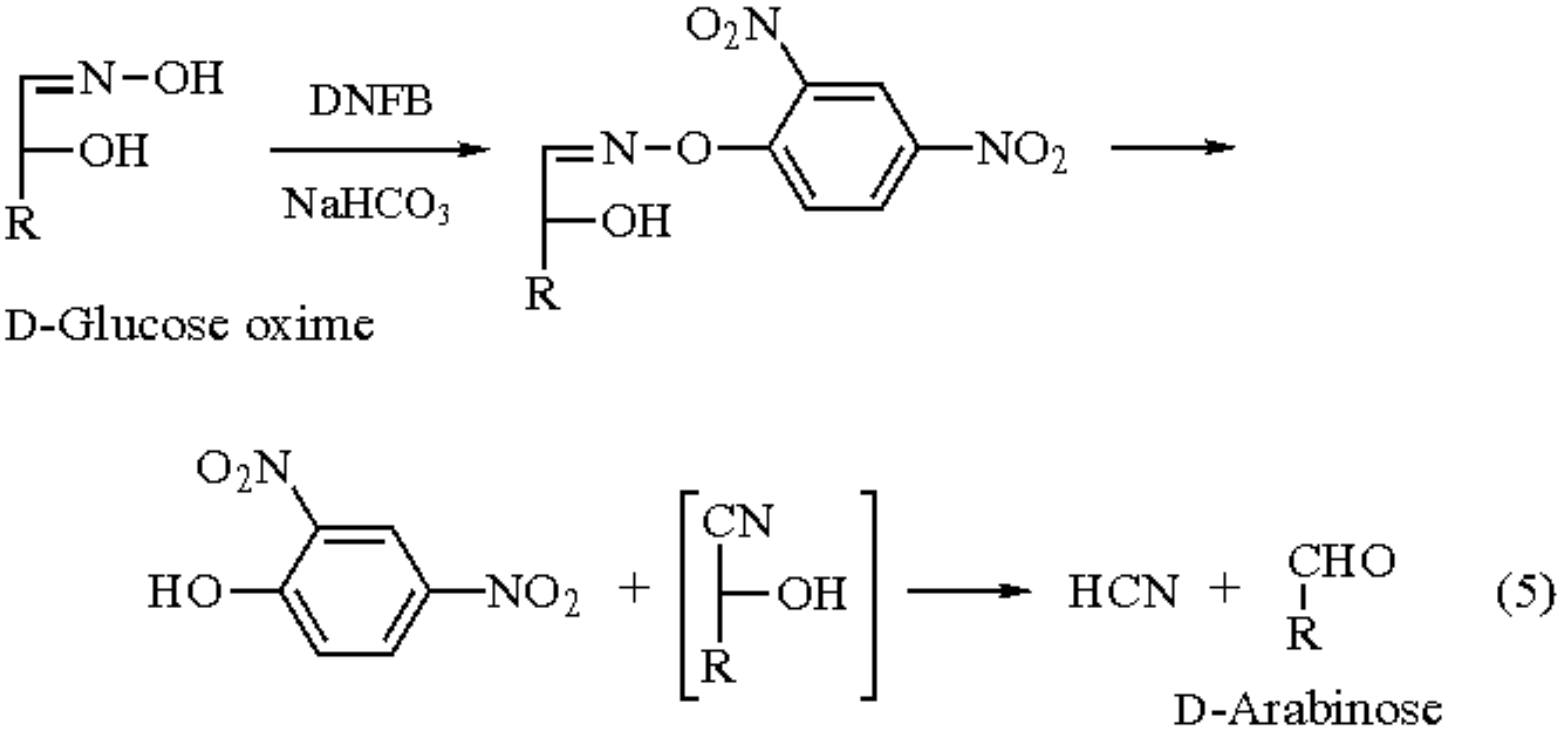

Thioamide Protection.

6-Thiodeoxyguanosine upon treatment with DNFB in the presence of triethylamine in acetonitrile give the *S*-2,4-DNP derivative.[14] Deprotection to thiocarbonyl can be achieved simply by treating with ***2-Mercaptoethanol*** at room temperature (eq 6). Such *S*-2,4-DNP functionalities can also be transformed to free amino, methylamino, methoxy, and oxo groups.

1-Fluoro-2,4-dinitrobenzene

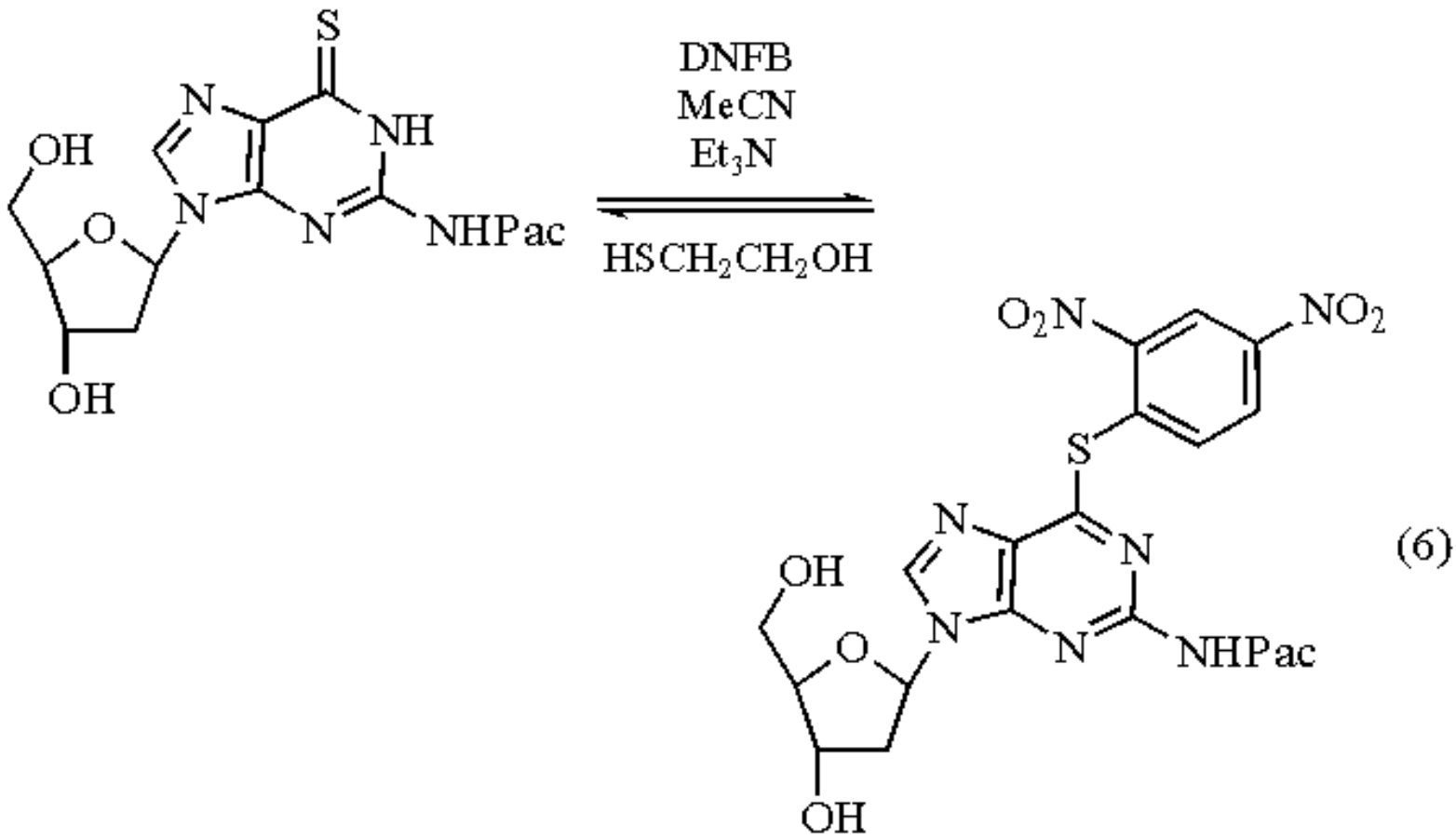

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Fluoromethylenetriphenylphosphorane

$Ph_3P{=}CHF$

[28096-33-5] · $C_{19}H_{16}FP$ · Fluoromethylenetriphenylphosphorane · (MW 294.32)

(can function for the introduction of =CFH into organic compounds)

Alternate Name: triphenylphosphonium fluoromethylide *[28096-34-6]*.

Preparative Methods: fluoromethylenetriphenylphosphorane is prepared in situ by the dehalogenation of fluoroiodomethyltriphenylphosphonium iodide with ***Zinc/Copper Couple*** in DMF,[1] or pregenerated by the dehydrohalogenation of fluoromethyltriphenylphosphonium iodide with ***n-Butyllithium***[1] or ***Phenyllithium***[2] at -78 °C. The precursor fluoromethyltriphenylphosphonium salt is prepared by the reaction of ***Triphenylphosphine*** with iodofluoromethane,[1] by the reaction of ***Methylenetriphenylphosphorane*** with $FClO_3$,[2] or by the reaction of hydroxymethyltriphenylphosphonium tetrafluoroborate with ***N,N-Diethylaminosulfur Trifluoride*** (DAST).[3]

Reaction with Carbonyl Compounds.

Reaction of the pregenerated ylide, fluoromethylenetriphenylphosphorane, with aldehydes and ketones at -78 °C gives the corresponding alkenes, RR´C=CHF, in 16-45% yields (eq 1). From aldehydes and asymmetrical ketones a mixture of *trans* and *cis* isomers was obtained in a 1:1 ratio.[2] A modification employs additional ***Potassium t-Butoxide*** in the above reaction sequence to achieve higher yields (28-69%) of RR´C=CHF.[1] Fluoromethylenetriphenylphosphorane could also be generated in situ. For example, treatment of fluoroiodomethyltriphenylphosphonium iodide with zinc-copper couple and aldehydes or fluorinated ketones in DMF gives the alkenes, RR´C=CHF, in 54-80% yields (eq 2).[1]

$$[Ph_3PCH_2F]^+\ I^- \xrightarrow[\text{-78 °C}]{\text{PhLi or BuLi}} [Ph_3P{=}CHF] \xrightarrow[\text{-78 °C}]{RC(O)R'} RR'C{=}CHF \qquad (1)$$

$$[Ph_3PCHFI]^+\ I^- + Zn(Cu) \xrightarrow[\text{DMF}]{RC(O)R'} RR'C{=}CHF \qquad (2)$$

R, R' = H, alkyl, aryl

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Fluoromethyl Phenyl Sulfide[1]

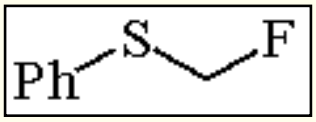

[60839-94-3] · C_7H_7FS · Fluoromethyl Phenyl Sulfide · (MW 142.21)

(synthesis of α-fluoro substituted sulfoxides[1] and sulfones[1e,2])

Physical Data: bp 60 °C/0.3 mmHg; n_D^{22} 1.5415.

Solubility: sol CH_2Cl_2, $CHCl_3$, MeOH.

Preparative Methods: there are several methods of preparation. The reaction of ***Chloromethyl Phenyl Sulfide*** with ***Potassium Fluoride*** and ***18-Crown-6*** gives fluoromethyl phenyl sulfide in good yield (eq 1).[1c] Alternatively, the compound can be prepared by reaction of methyl phenyl sulfoxide with ***N,N-Diethylaminosulfur Trifluoride*** (F_3SNEt_2, DAST) (eq 2),[1d,2,3] or with DAST and ***Antimony(III) Chloride*** (eq 3).[1e,f,4]

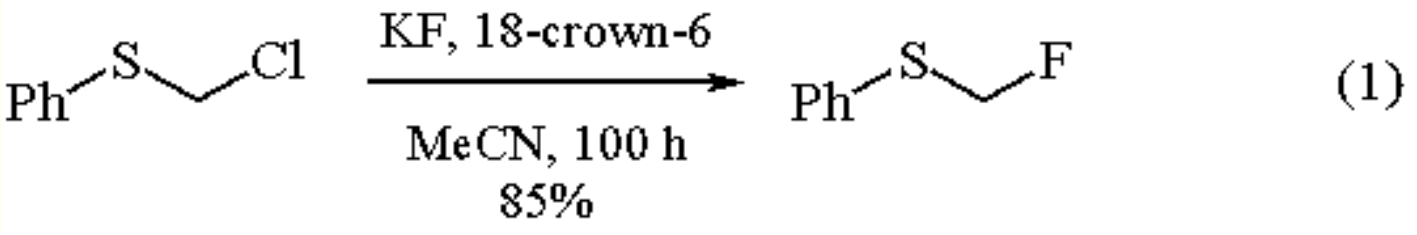

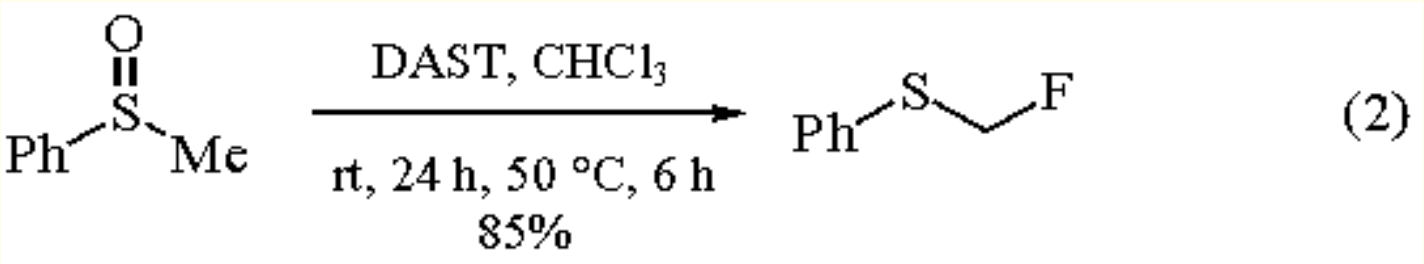

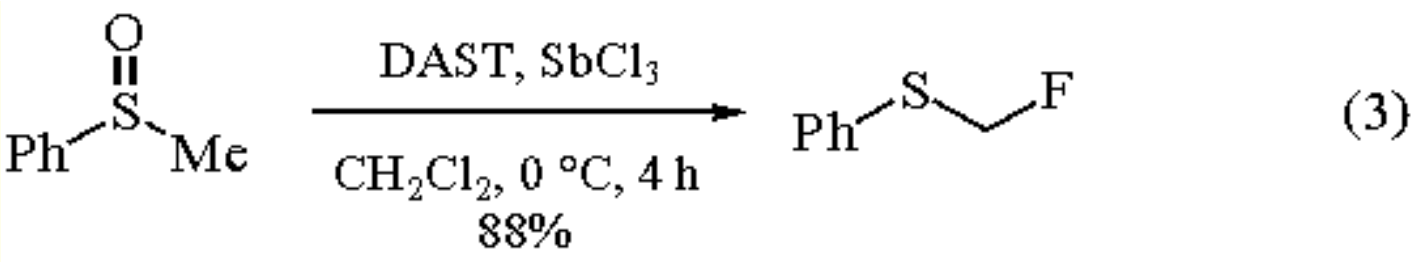

Direct α-fluorination of methyl phenyl sulfides can be performed by using DAST, antimony(III) chloride (eq 4),[1f] *N*-fluoro-2,4,6-trimethylpyridinium triflate (eq 5),[5] and ***Xenon(II) Fluoride***.[6] α-Fluorination of sulfides by an electrolytic process is also known. However, it has not been used widely in organic synthesis.[7]

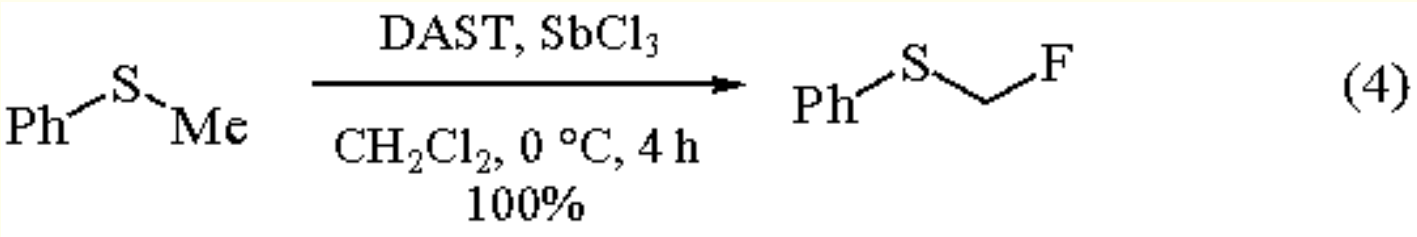

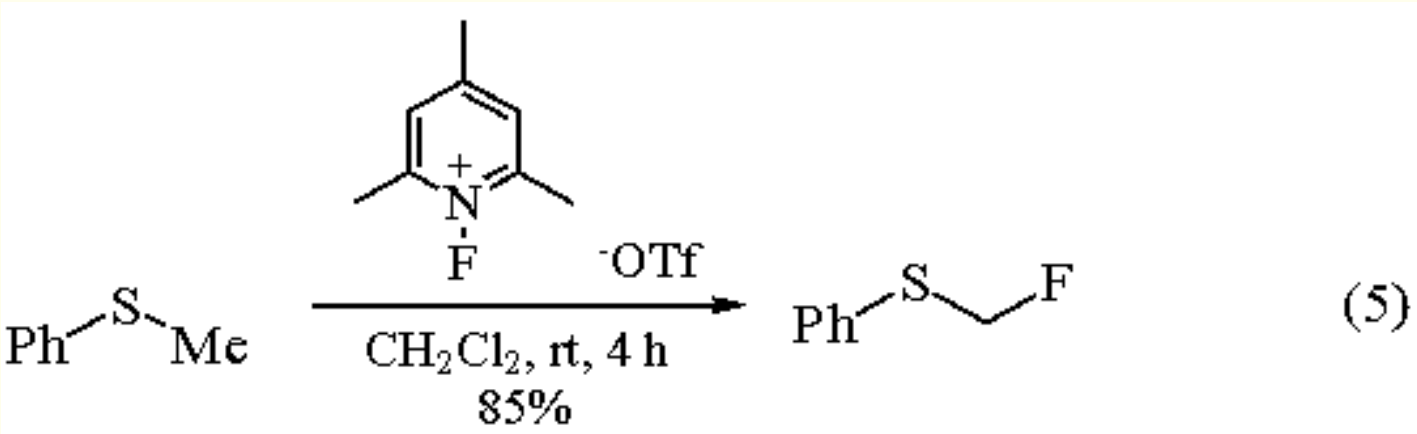

Of the methods reported, the routes shown in eqs 1-4 are more often used synthetically. α-Monosubstituted fluoromethyl phenyl sulfides are prepared from the reaction of the corresponding thioacetals with ***Mercury(II) Fluoride*** (eq 6).[8]

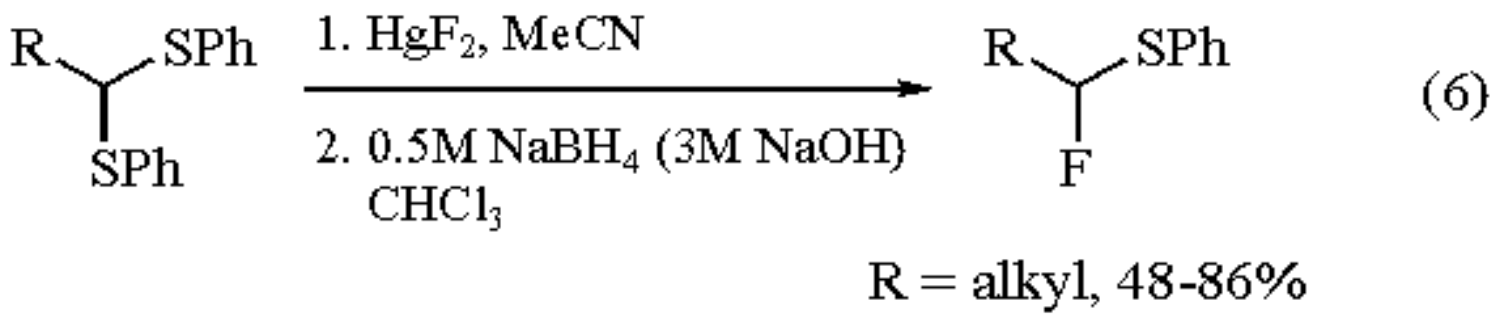

Handling, Storage, and Precautions: the compound should be used as soon as possible after

purification by distillation. Storing it at 5 °C overnight then warming it to room temperature causes polymerization. Handle in a fume hood.

Oxidation to Sulfoxides.

Fluoromethyl phenyl sulfide can be oxidized to ***Fluoromethyl Phenyl Sulfoxide*** by ***N-Bromosuccinimide***[1c] or one equivalent of ***m-Chloroperbenzoic Acid***[1d -f,3,4,8] (the latter method is the most convenient and most often employed) (eq 7).

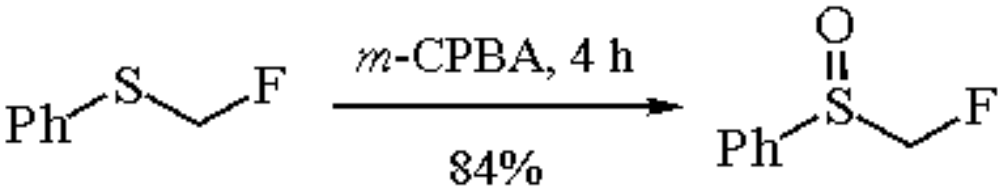

(7)

Oxidation to Sulfones.

Oxidation to ***Fluoromethyl Phenyl Sulfone*** is conveniently carried out by using two equivalents of *m*-chloroperbenzoic acid (eq 8).[1d,e,f,2,4b,d]

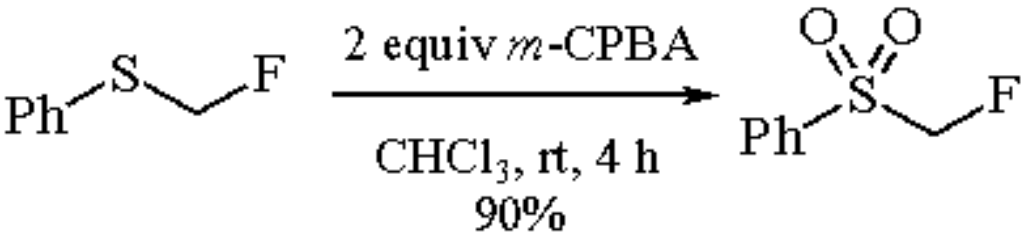

(8)

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Dalley, N. K. *JOC* **1991**, *56*, 6878.
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6. (a) Marat, R. K.; Janzen, A. F. *CJC* **1977**, *55*, 3031. (b) Zupan, M. *JFC* **1976**, *8*, 305.
7. (a) Brigaud, T.; Laurent, E. *TL* **1990**, *31*, 2287. (b) Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *JOC* **1990**, *55*, 6074.
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Fluoromethyl Phenyl Sulfone[1]

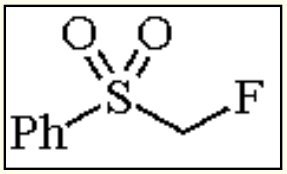

[20808-12-2] · $C_7H_7FO_2S$ · Fluoromethyl Phenyl Sulfone · (MW 174.21)

(synthesis of α-fluoro-α,β-unsaturated sulfones,[1b,d,2] vinyl fluorides[1b,d,2])

Physical Data: mp 50-51 °C (from MeOH).

Solubility: sol THF, $CHCl_3$, CH_2Cl_2.

Preparative Method: by the oxidation of ***Fluoromethyl Phenyl Sulfide*** with two equivalents of ***m-Chloroperbenzoic Acid*** (eq 1).[1b,c]

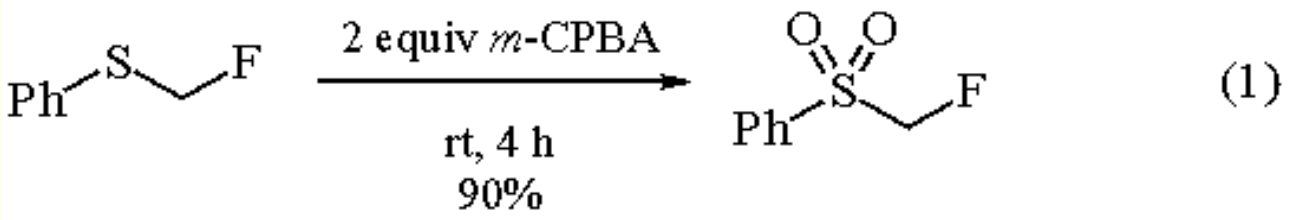

α-Fluoro-α,β-Unsaturated Sulfones and Vinyl Fluorides.

The reaction of phenylsulfonylfluoromethyllithium, generated by the reaction of fluoromethyl phenyl sulfone with ***n-Butyllithium***, with carbonyl compounds gives the α-fluoro-β-hydroxyphenylsulfonyl derivatives in good yields; upon dehydration with ***Methanesulfonyl Chloride***, these give the corresponding vinyl sulfones. Reductive desulfonylation with ***Aluminum Amalgam*** yields vinyl fluorides (eq 2).[1b] The overall process represents the use of fluoromethyl phenyl sulfone as a fluoromethyl Wittig equivalent. This method of preparation of vinyl fluorides is complementary to the existing few methods, e.g. the use of ***Fluoromethylenetriphenylphosphorane***[3] and ***Fluoromethyl Phenyl Sulfoxide***.[4]

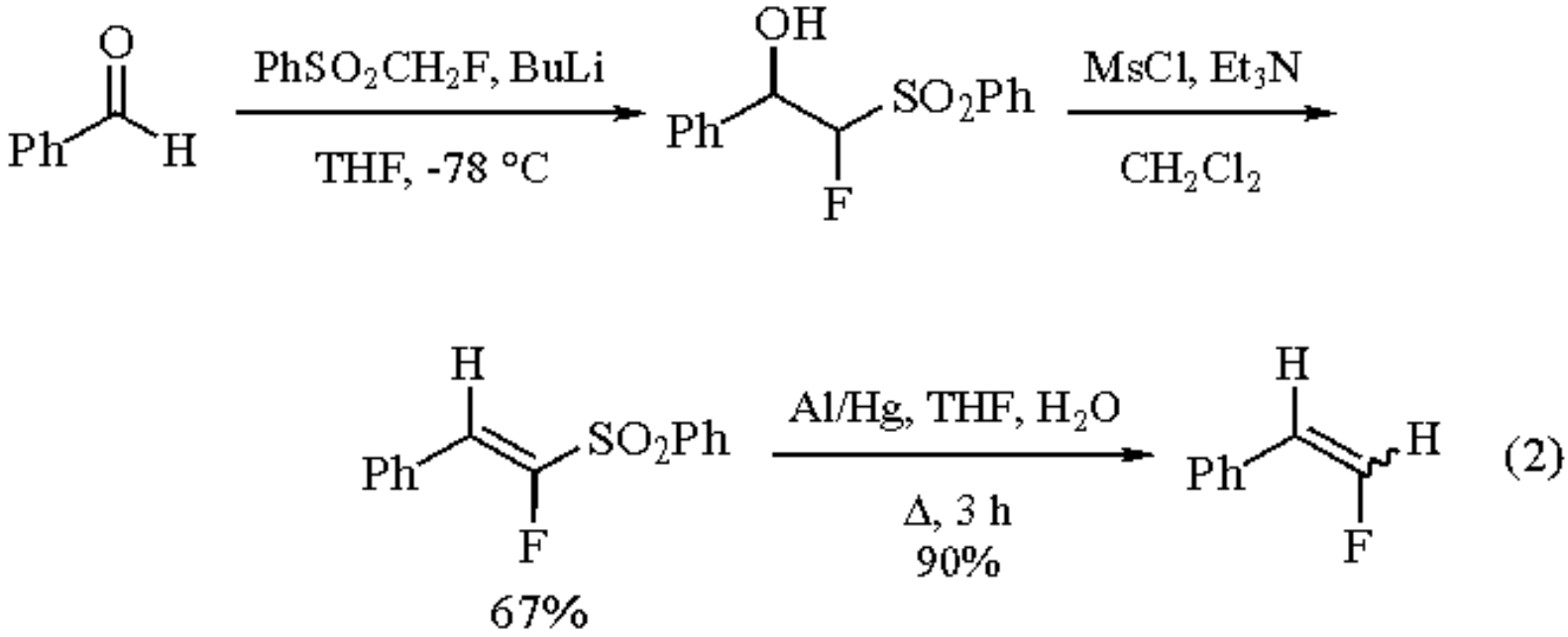

The Wittig-type reaction of the diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate carbanion, generated in situ from fluoromethyl phenyl sulfone with diethyl chlorophosphate and two equivalents of either ***Lithium Diisopropylamide*** or ***Lithium Hexamethyldisilazide*** at -78 °C, with carbonyl compounds gives α-fluoro-α,β-unsaturated sulfones in good to excellent yields (eq 3).[1d]

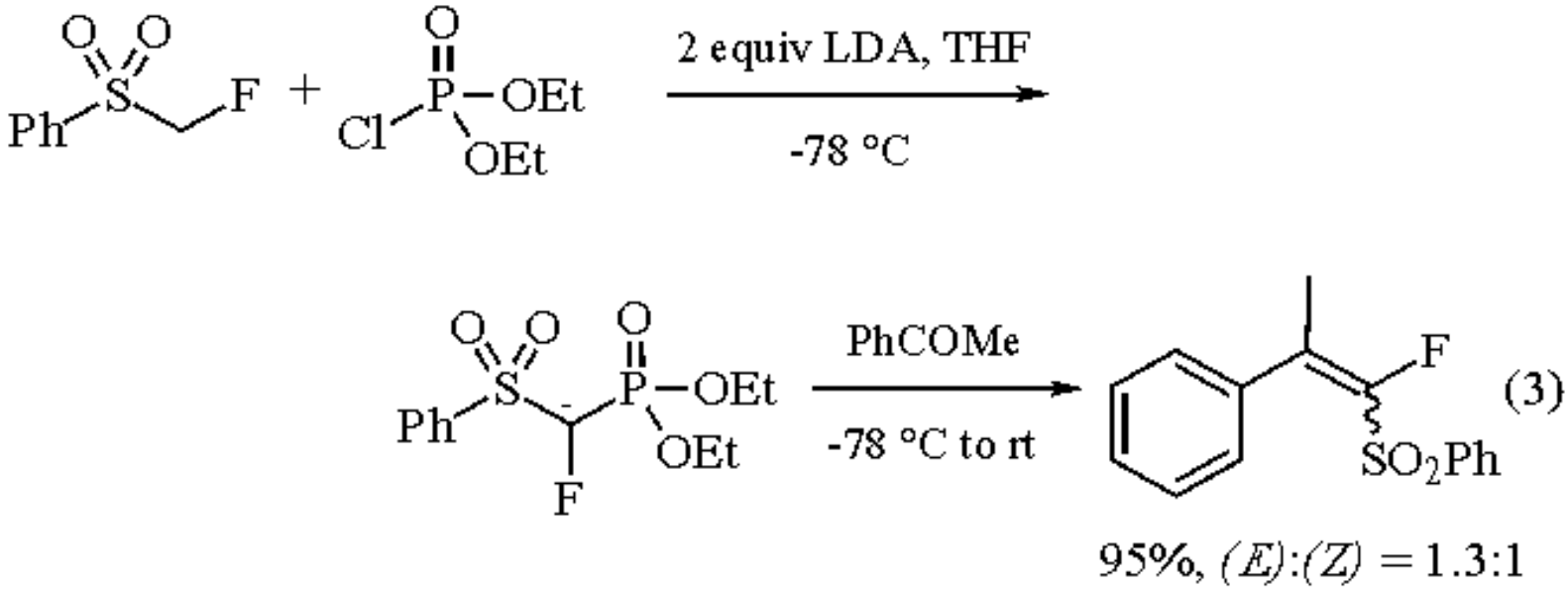

A similar Wittig reaction of 1-fluoro-1-(phenylsulfonyl)methanephosphonate carbanion is used in the synthesis of 2´-deoxy-2´-fluoromethylene nucleosides (eq 4).[2]

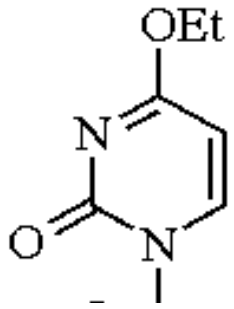

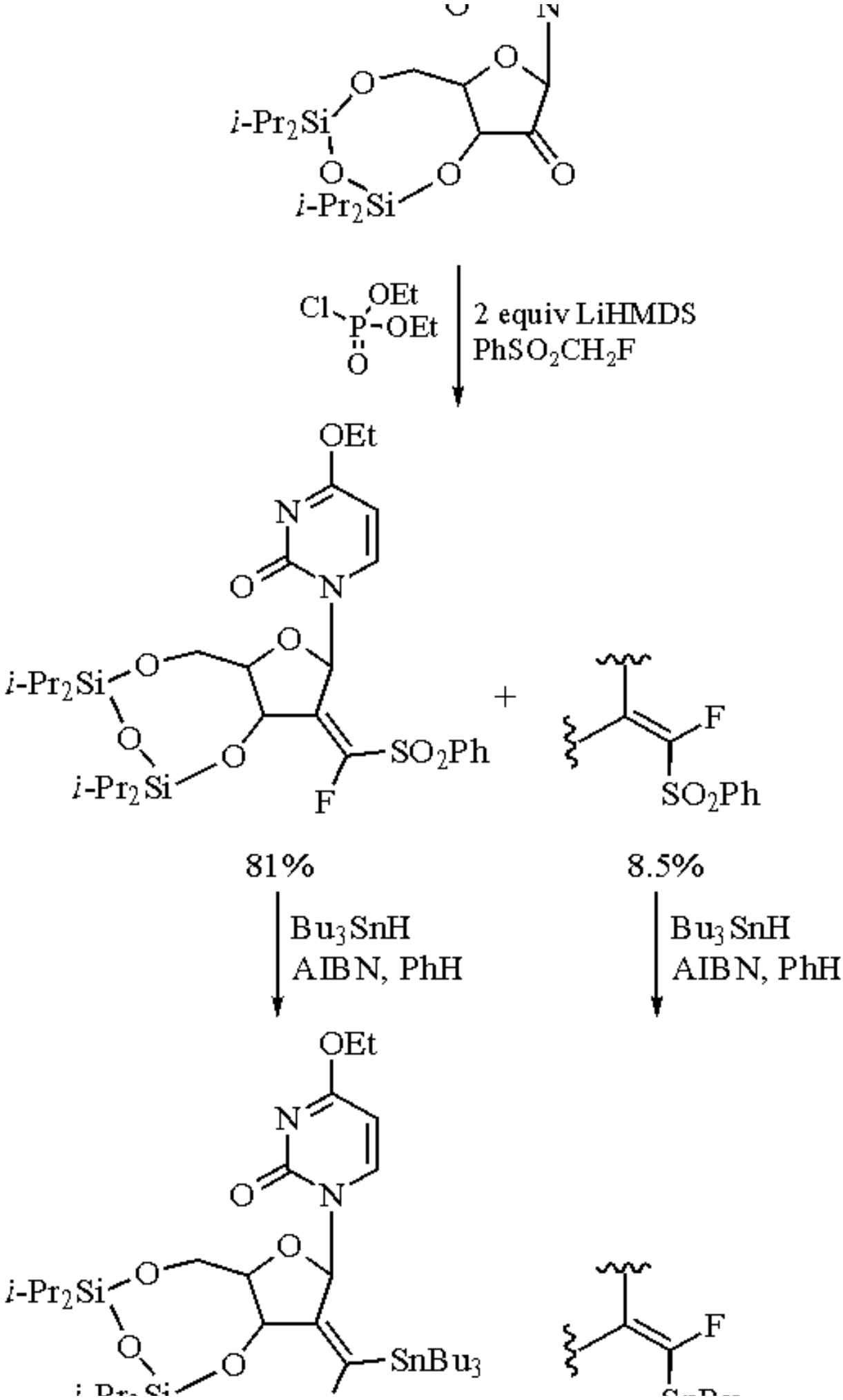
i-Pr2Si
i-Pr2Si
Cl
OEt
P
OEt
O
2 equiv LiHMDS
PhSO2CH2F
OEt
N
O
N
i-Pr2Si
i-Pr2Si
SO2Ph
F
+
F
SO2Ph
81%
8.5%
Bu3SnH
AIBN, PhH
Bu3SnH
AIBN, PhH
SnBu3
F

(4)

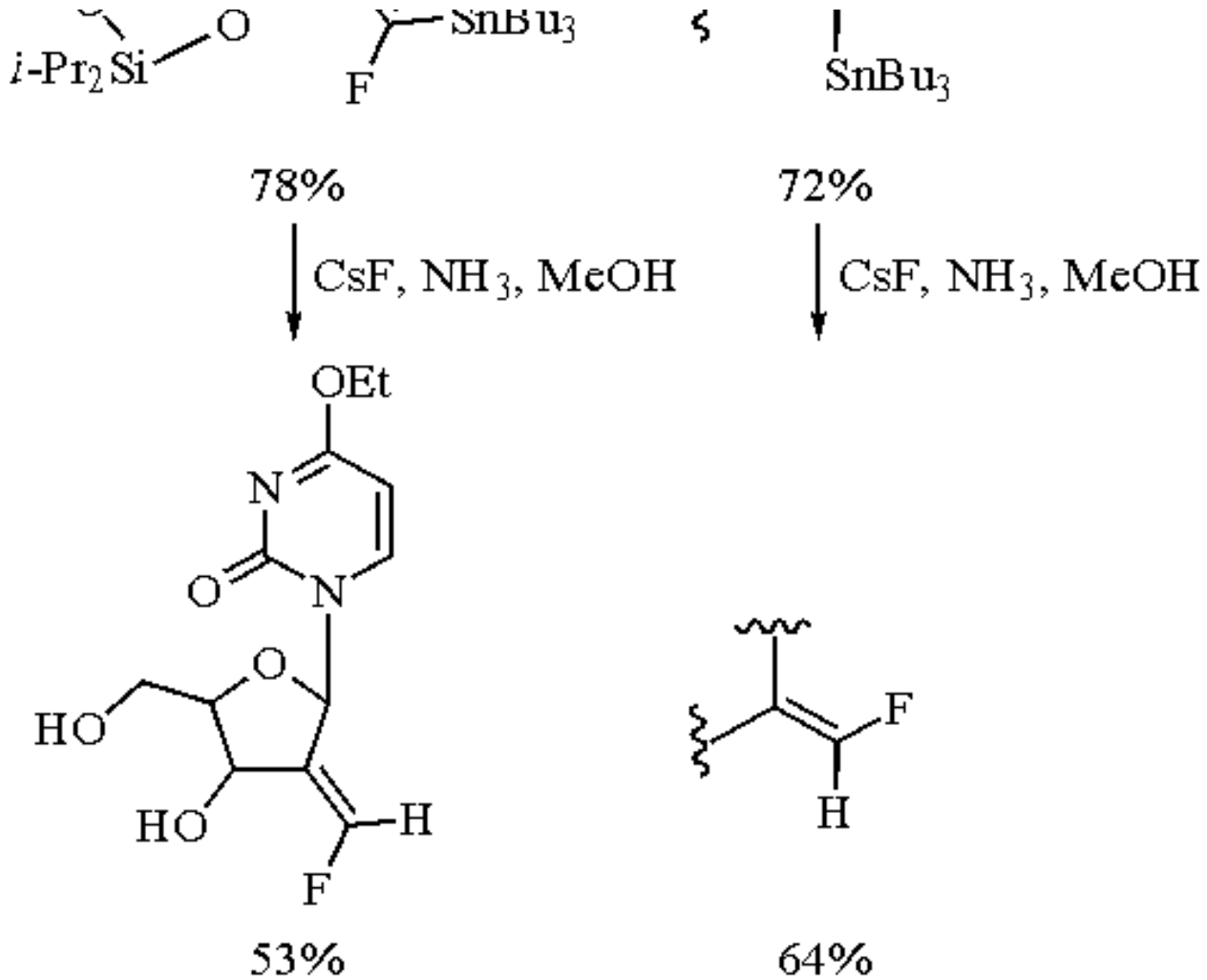

Diethyl 1-fluoro-1-phenylsulfonylmethanephosphonate can also be prepared by the direct fluorination of diethyl (phenylsulfonyl)methanephosphonate with ***Perchloryl Fluoride*** ($FClO_3$) (eq 5).[5] The Wittig reagent derived from it is used in the preparation of a number of alkylated α-fluorophenylsulfonyl derivatives and α-fluoro-α,β-unsaturated sulfones (eqs 6 and 7).[5] 1-Fluoro-1-(phenylsulfonyl)ethylene can also be prepared by the elimination of 2-chloro-1-fluoroethyl phenyl sulfone (eq 8).[6] Diels-Alder cycloadditions, Michael reactions (eq 9),[5] 1,3-dipolar cycloaddition (eq 10),[7] and radical addition (eq 10)[6] reactions of 1-fluoro-1-(phenylsulfonyl)ethylene have been demonstrated.

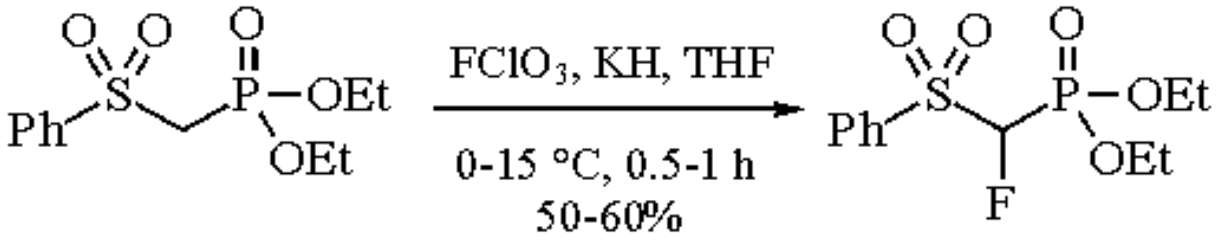

(5)

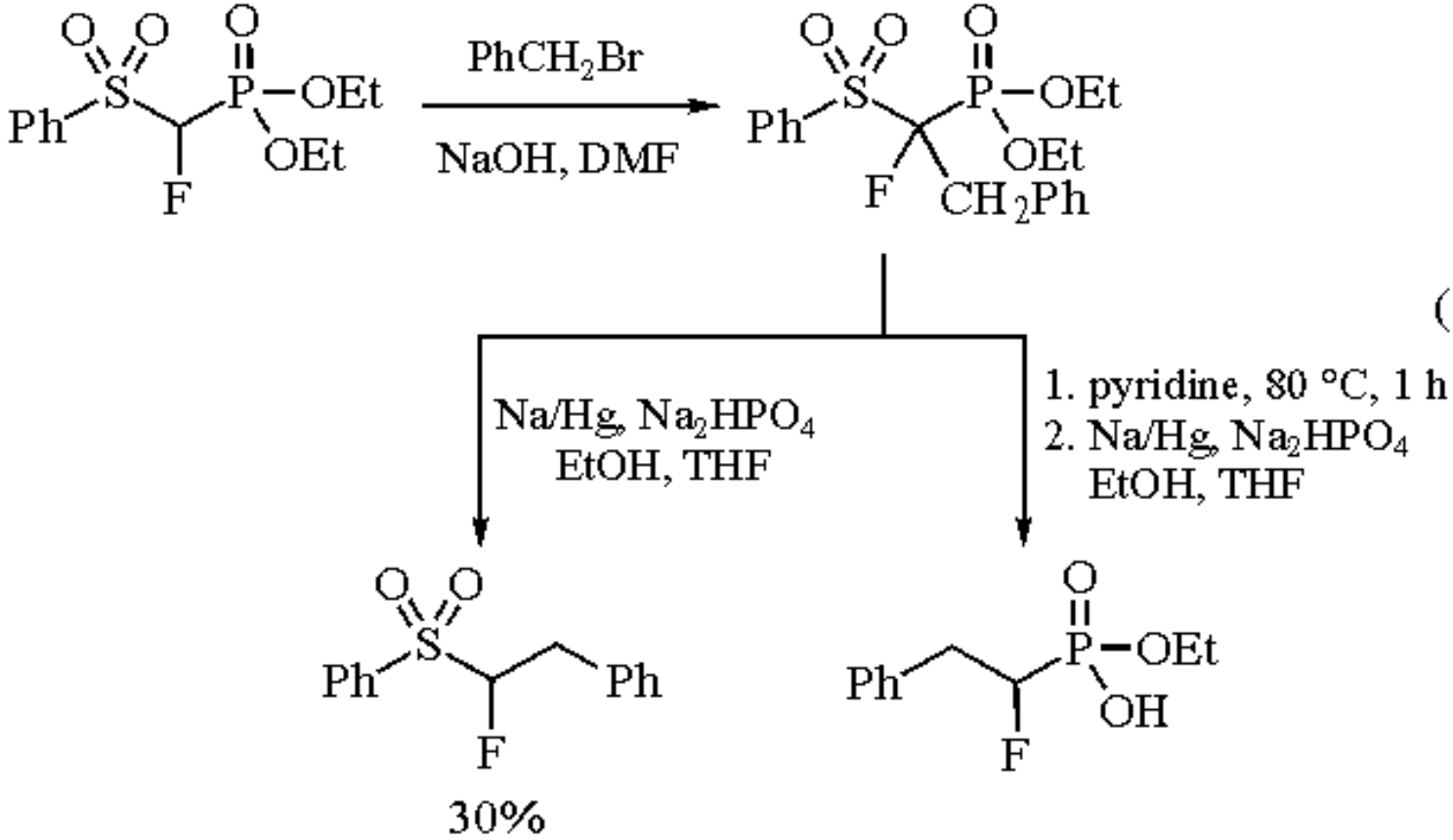
PhCH2Br
NaOH, DMF
Na/Hg, Na2HPO4
EtOH, THF
1. pyridine, 80 °C, 1 h
2. Na/Hg, Na2HPO4
EtOH, THF
30%

(6)

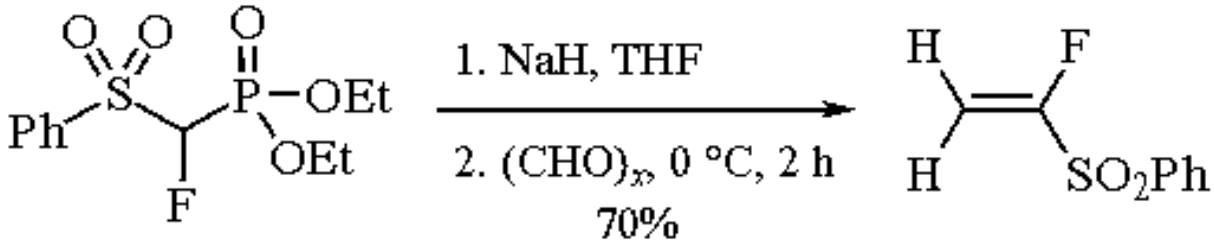
1. NaH, THF
2. (CHO)x, 0 °C, 2 h
70%

(7)

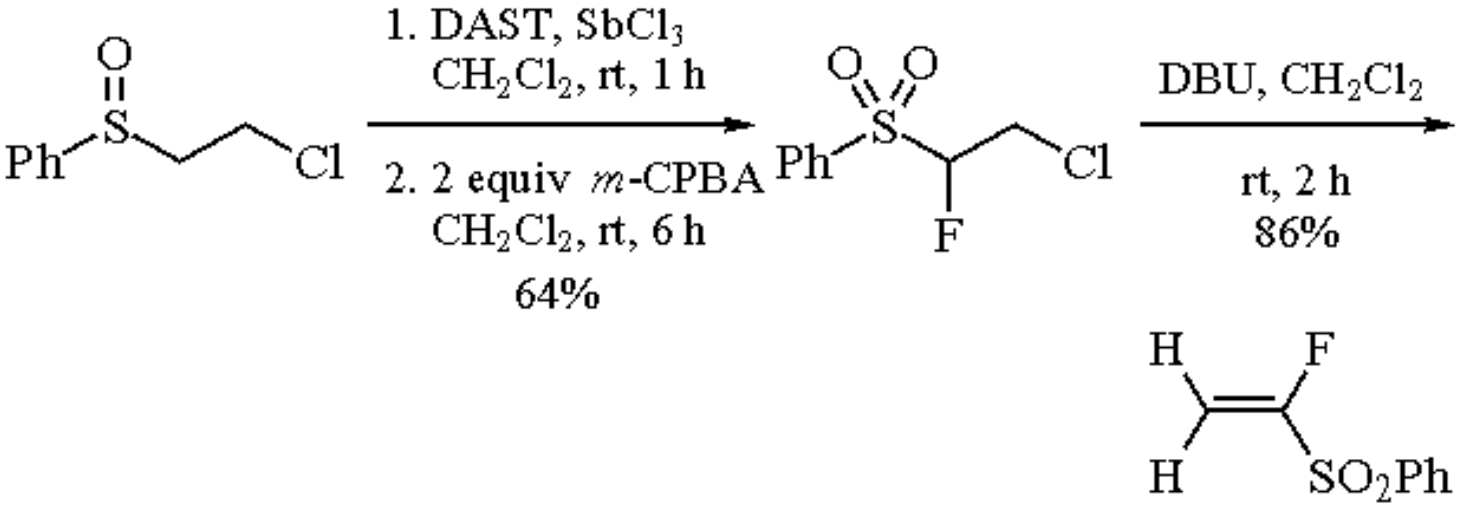
1. DAST, SbCl3
CH2Cl2, rt, 1 h
2. 2 equiv m-CPBA
CH2Cl2, rt, 6 h
64%
DBU, CH2Cl2
rt, 2 h
86%

(8)

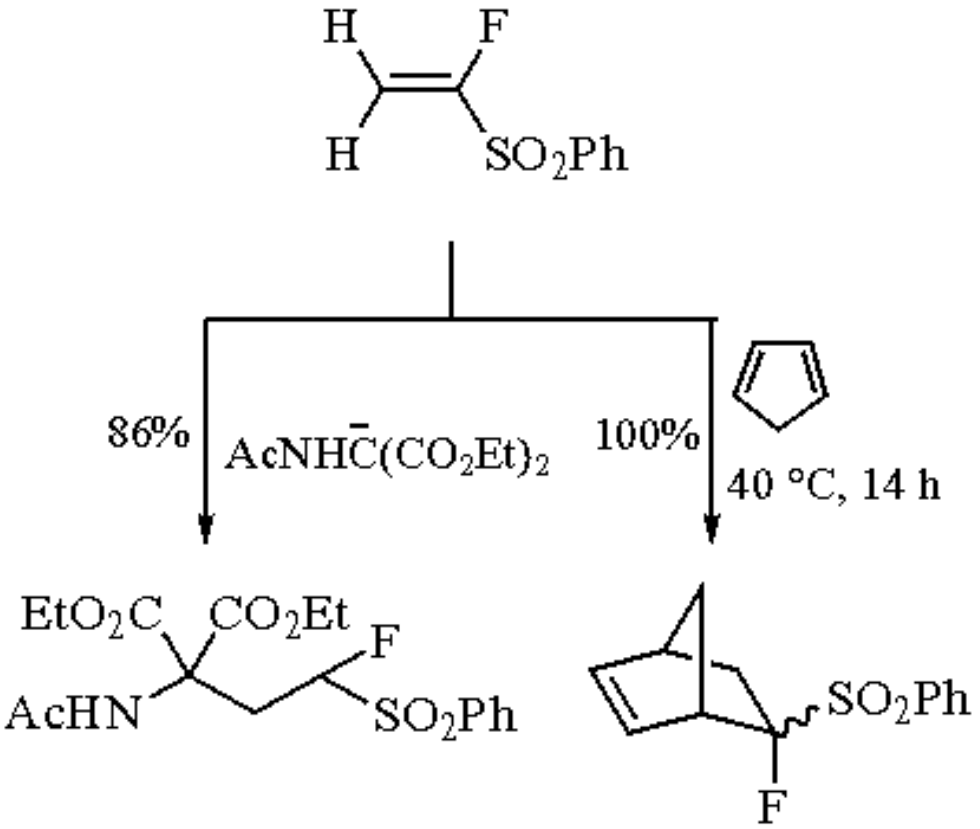
H
F
H
SO2Ph
86%
AcNHC(CO2Et)2
100%
40 °C, 14 h
EtO2C
CO2Et
F
AcHN
SO2Ph
SO2Ph
F

(9)

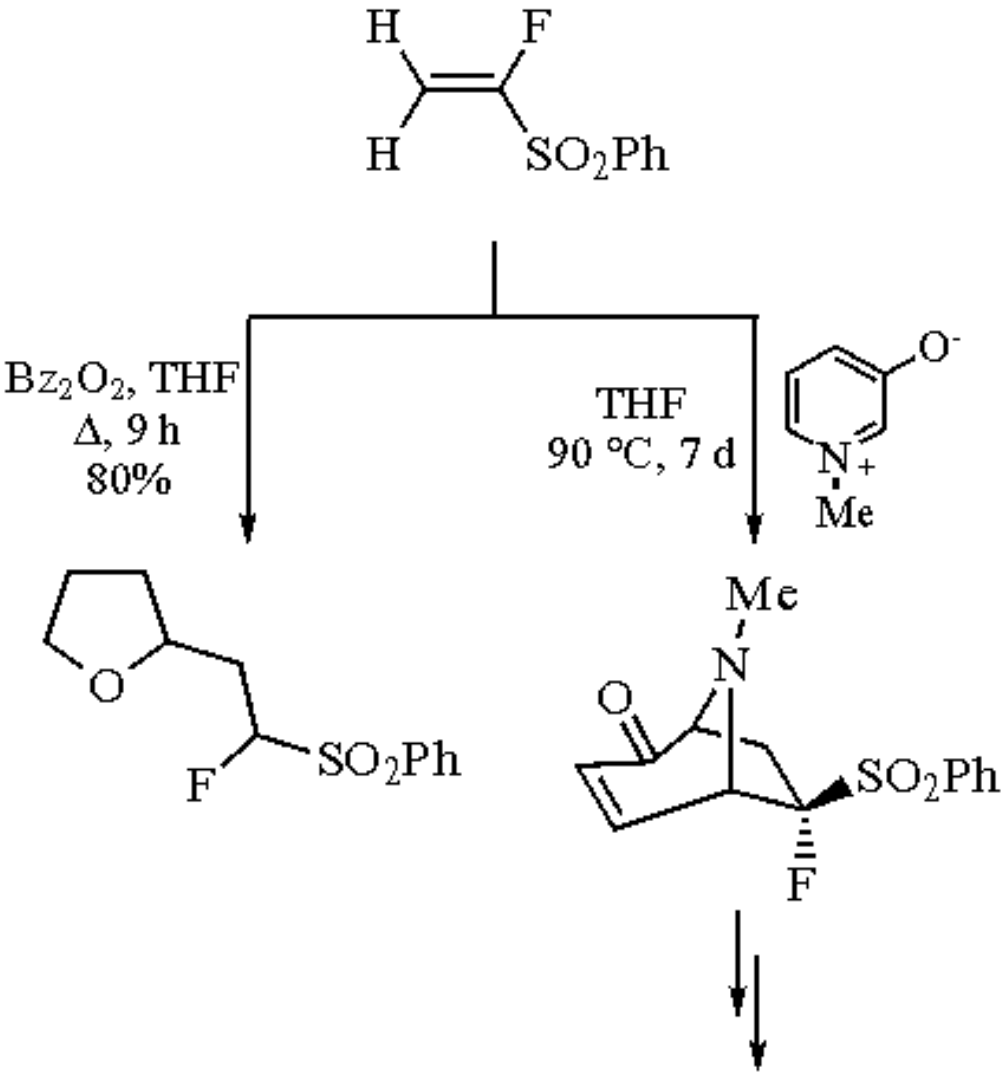
H
F
H
SO2Ph
Bz2O2, THF
Δ, 9 h
80%
THF
90 °C, 7 d
O-
N+
Me
O
F
SO2Ph
Me
N
O
SO2Ph
F

(10)

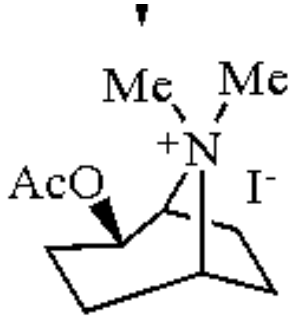

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1. (a) Schlosser, M. *T* **1978**, *34*, 3. (b) Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; LeTourneau, M. E. *CC* **1985**, 678. (c) McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. *JACS* **1985**, *107*, 735. (d) McCarthy, J. R.; Matthews, D. P.; Edwards, M. L.; Stemerick, D. M.; Jarvi, E. T. *TL* **1990**, *31*, 5449. (e) Robins, M. J.; Wnuk, S. F. *JOC* **1993**, *58*, 3800.
2. (a) Simpkins, N. S. *T* **1990**, *46*, 6951. (b) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *JACS* **1991**, *113*, 7439.
3. (a) Burton, D. J.; Greenlimb, P. E. *JOC* **1975**, *40*, 2796. (b) Bey, P.; Fozard, J.; Lacoste, J. M.; McDonald, I. A.; Zreika, M.; Palfreyman, M. G. *JMC* **1984**, *27*, 9. (c) McDonald, I. A.; Lacoste, J. M.; Bey, P.; Wagner, J.; Zreika, M.; Palfreyman, M. G. *JACS* **1984**, *106*, 3354. (d) Takeuchi, Y.; Nagata, K.; Koizumi, T. *JOC* **1989**, *54*, 5453.
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Fluoromethyl Phenyl Sulfoxide[1]

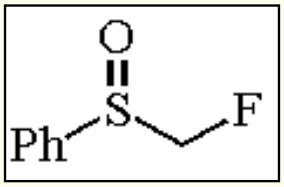

[65325-68-0] · C_7H_7FOS · Fluoromethyl Phenyl Sulfoxide · (MW 158.21)

(synthesis of fluoro ketones,[1b,2] fluoroalkenes,[2,3] and aziridines[4])

Physical Data: bp 75 °C/0.3 mmHg; *n*22D 1.5375.

Solubility: sol THF, CH_2Cl_2, $CHCl_3$.

Preparative Methods: by the oxidation of ***Fluoromethyl Phenyl Sulfide*** with either ***N-Bromosuccinimide*** or ***m-Chloroperbenzoic Acid*** (eq 1).[1c-f] Studies of the structure of fluoro(phenylsulfinyl)methyllithium, investigated by NMR, suggest that lithium is bound to oxygen, rather than to the α-carbon atom.[5]

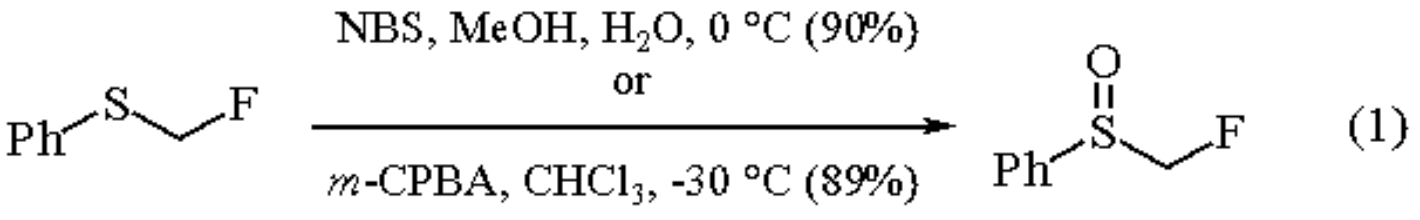

Purification: pure compound is obtained either by distillation or column chromatography on silica using hexane-ethyl acetate (1:4).

Handling, Storage, and Precautions: use in a fume hood.

Fluoro Ketones.

The reaction of fluoro(phenylsulfinyl)methyllithium, generated with ***Lithium Diisopropylamide***, with aldehydes gives the corresponding α-fluoro-β-hydroxy sulfoxides, which upon pyrolysis give fluoromethyl ketones (eq 2).[1b,2]

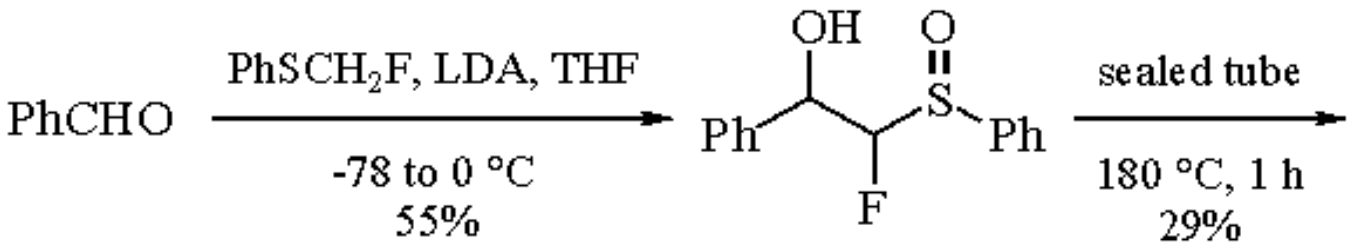

$PhCOCH_2F$ (2)

α-Fluoro-1,3-keto sulfoxides, prepared from the addition of alkylated α-fluoromethyl phenyl sulfoxide carbanion to aldehydes followed by Swern oxidation (***Dimethyl Sulfoxide-Oxalyl Chloride***), undergo desulfinylation with ***Ethylmagnesium Bromide*** to give α-fluoro ketones (eq 3).[6] Pyrolysis of the α-fluoro-1,3-keto sulfoxides gives α-fluoro-α,β-unsaturated ketones (eq 3).[6] Dienones can be prepared by this procedure and the product undergoes the Nazarov cyclization to give 2-fluoro-2-cyclopenten-1-one (eq 4).[6b]

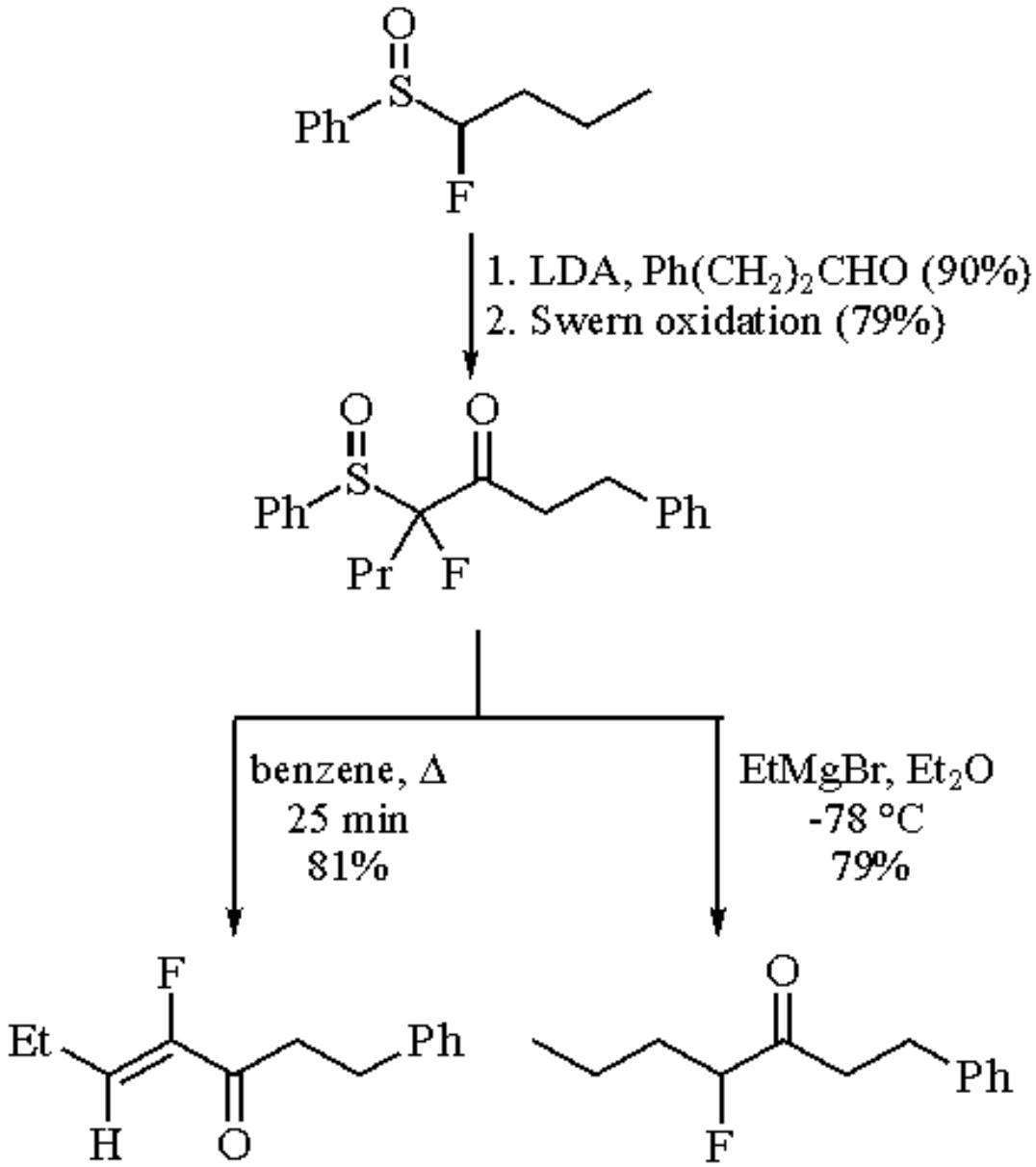

(3)

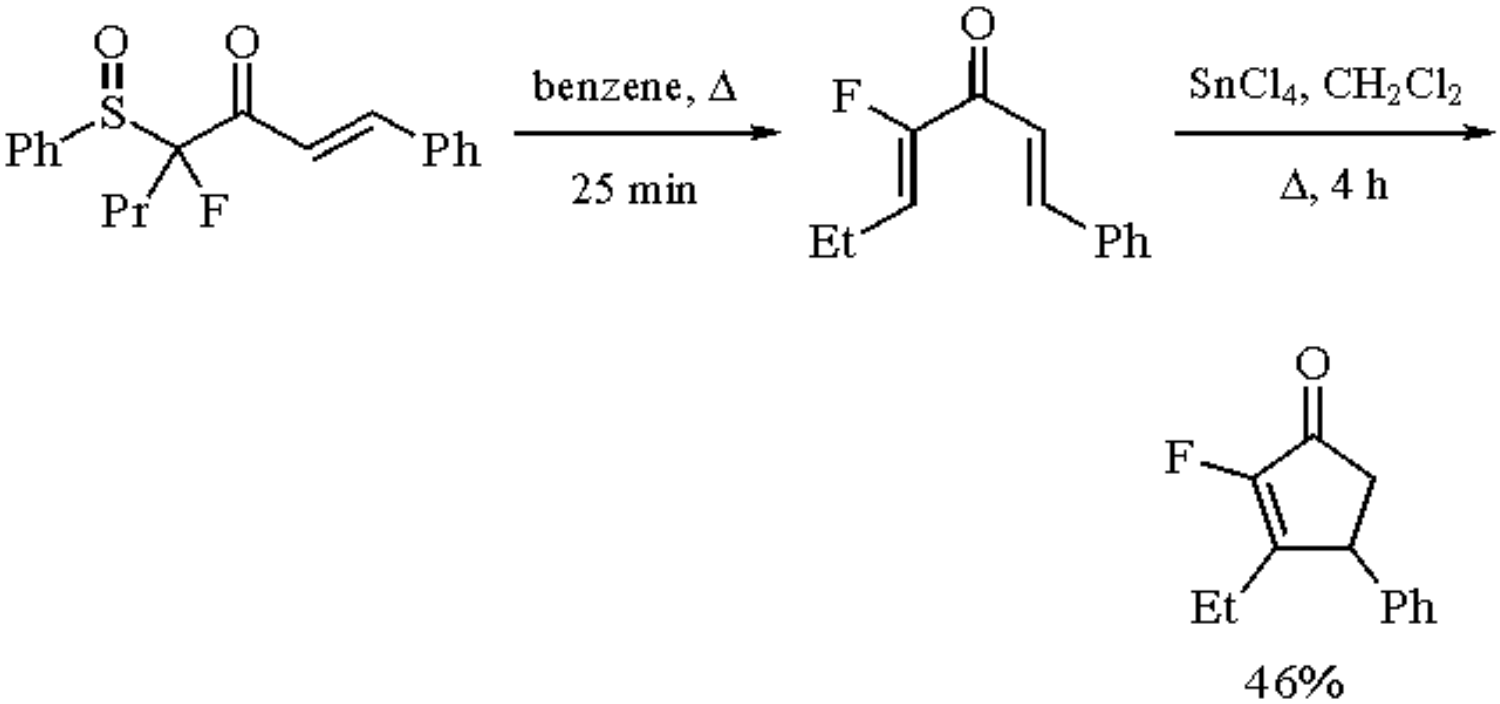

(4)

Fluoroalkenes.

Fluoro(phenylsulfinyl)methyllithium can be alkylated with alkyl iodides or reactive alkyl bromides to give monoalkylated products which upon pyrolysis afford vinyl fluorides (eq 5).[2] The addition of the α-fluoromethyl-*N*-methyl(phenyl)sulfoximine carbanion, derived from α-fluoromethyl phenyl sulfoxide, to carbonyl compounds gives α-fluoro-β-hydroxy(phenyl)sulfoximine adducts, which upon reductive desulfinylation with ***Aluminum Amalgam*** yield fluoroalkenes (eqs 6 and 7).[3c]

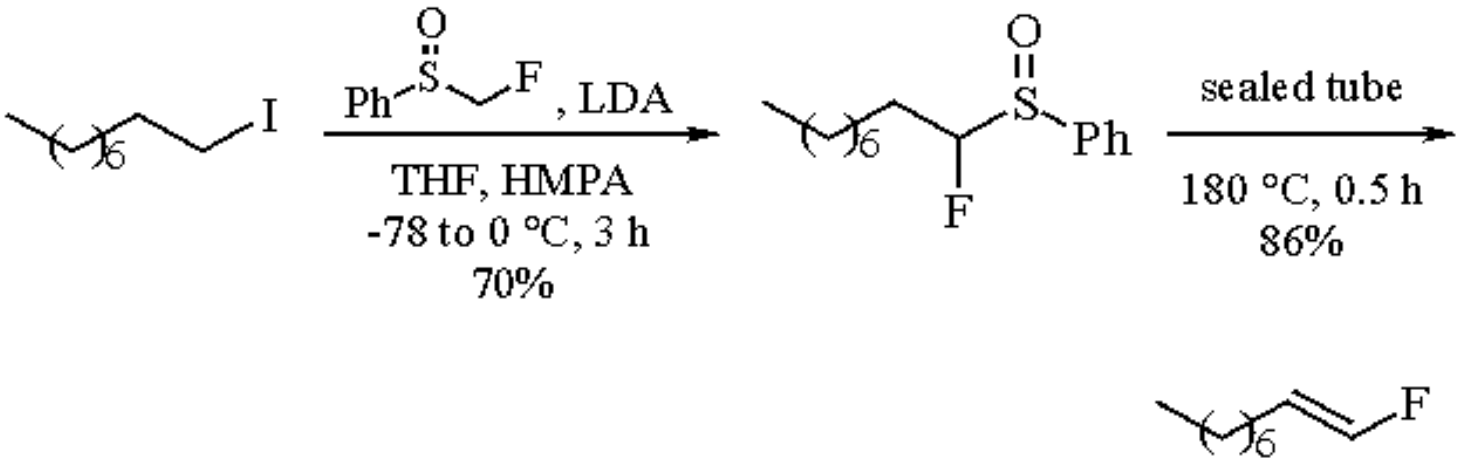

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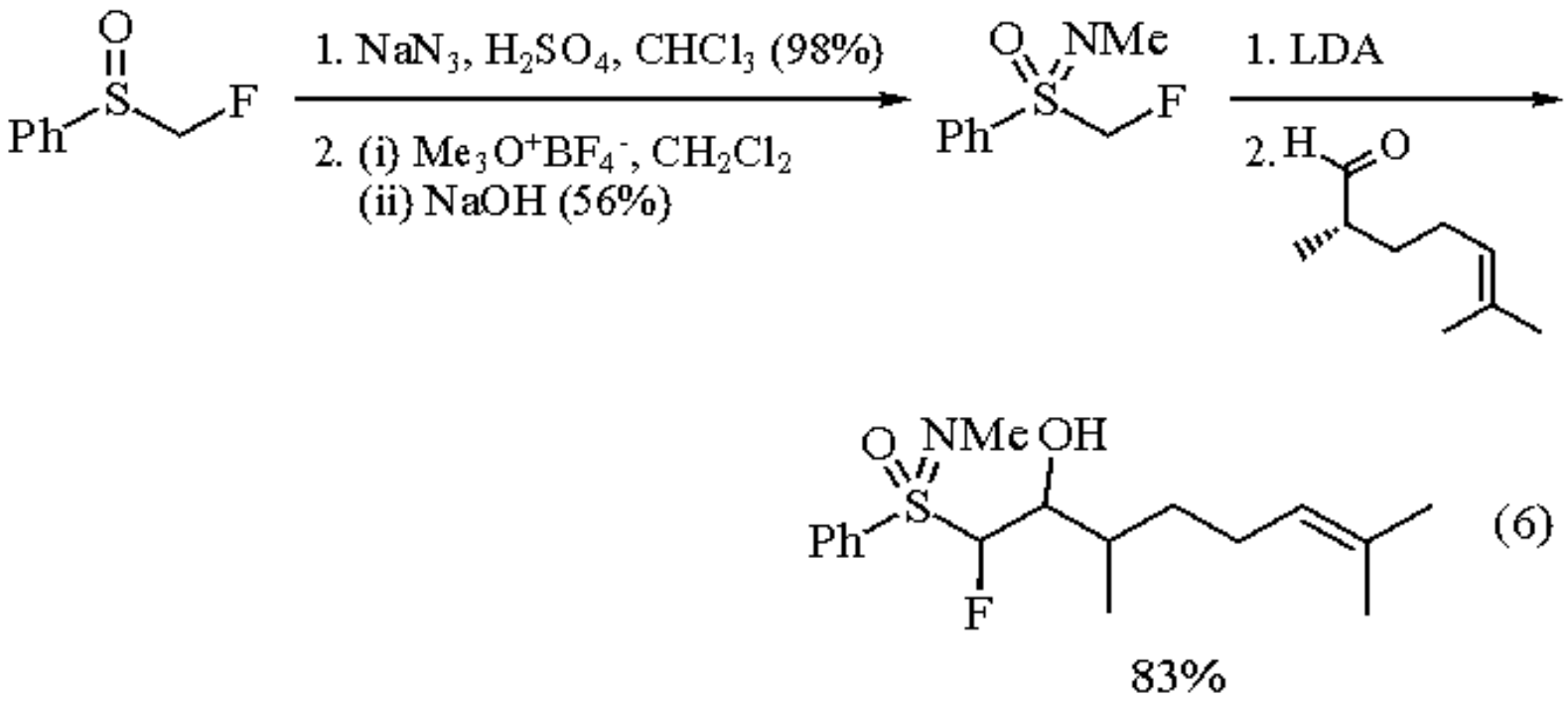

(6)

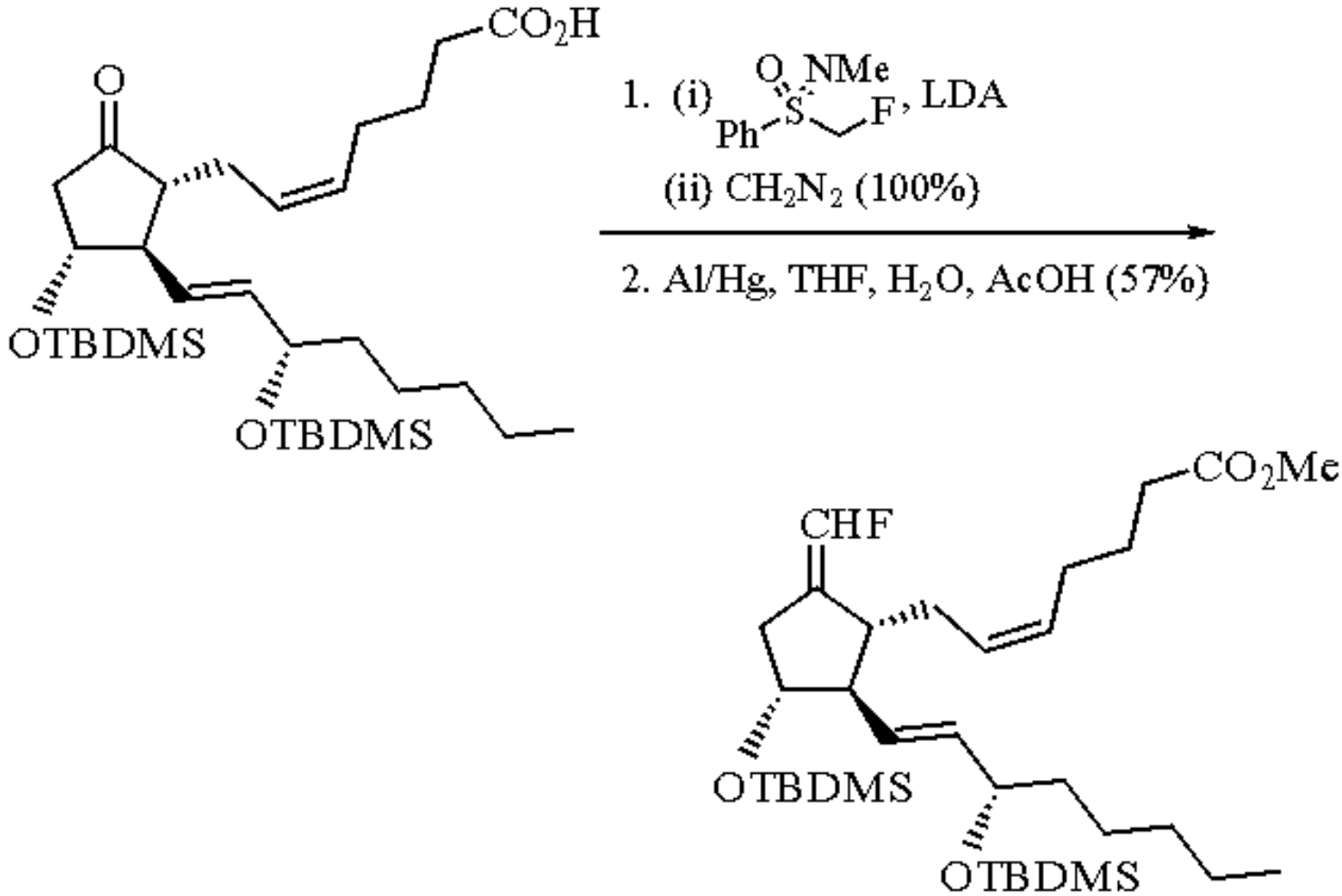

(7)

α-Substituted α-fluoro phenyl sulfoxides, prepared from thioacetals (eq 8)[3b] or from the corresponding sulfoxides, are used in the synthesis of fluoroalkenes (eqs 9 and 10).[3d,7]

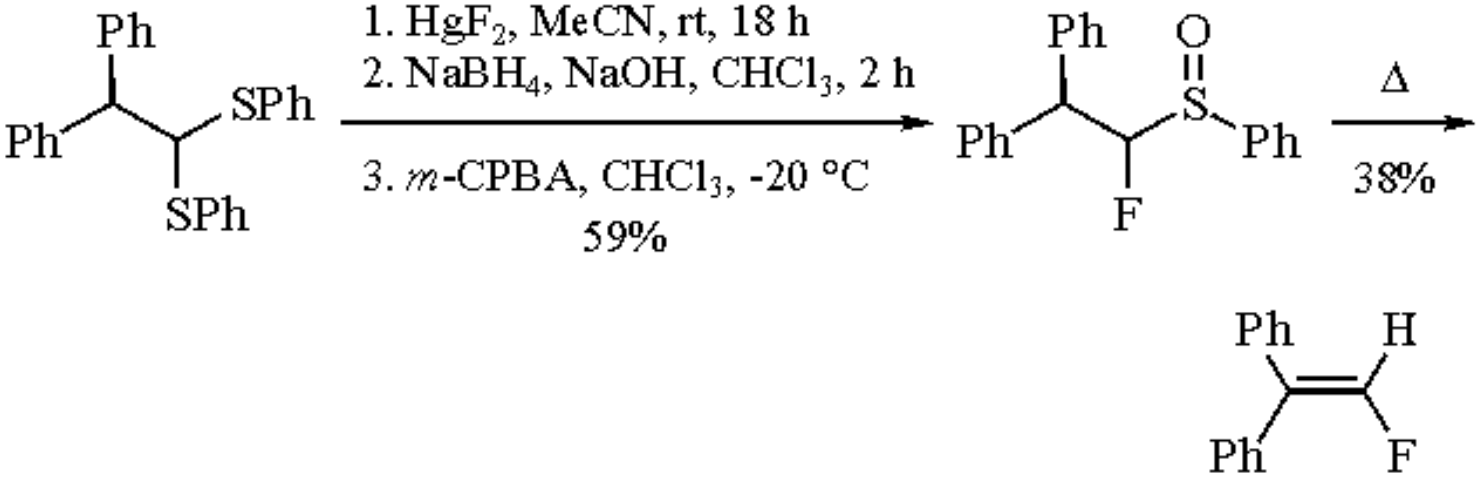

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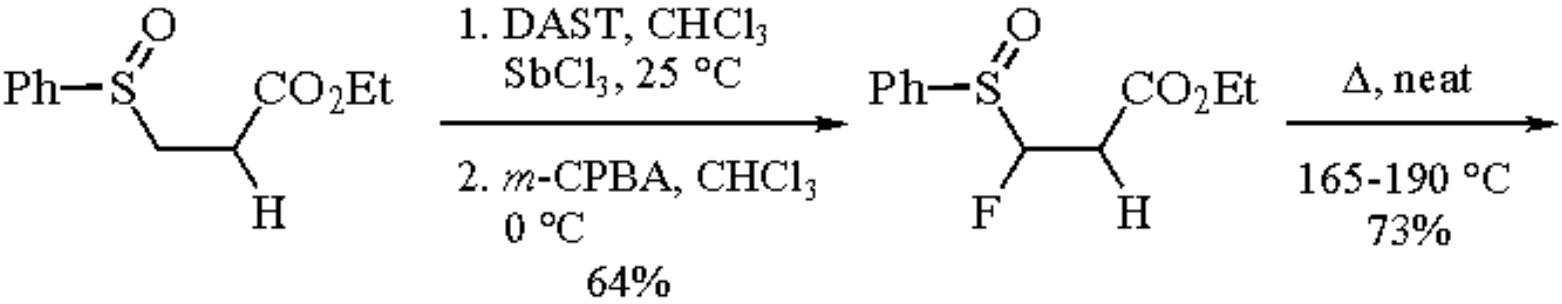

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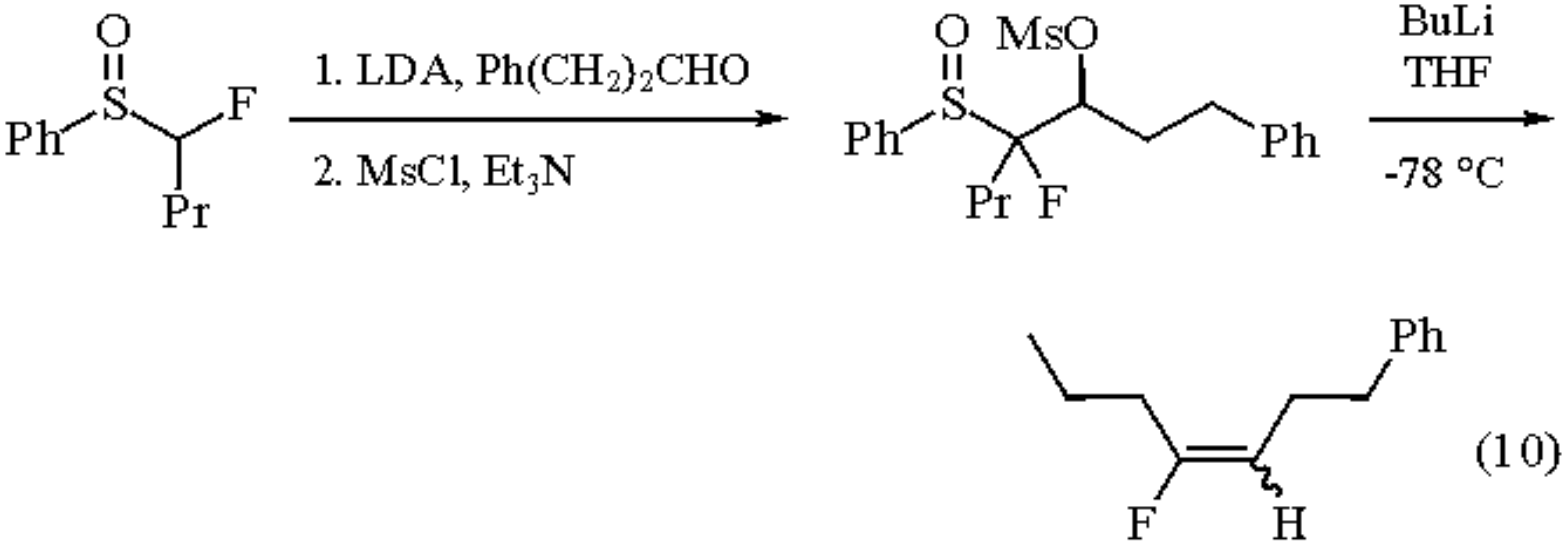

(10)

Fluoro(phenylsulfinyl)methyllithium adds to aryl imines to give phenylsulfinylaziridines as a mixture of isomers (eq 11). This method is complementary to the reaction employing chloro(phenylsulfinyl)methyllithium.[4]

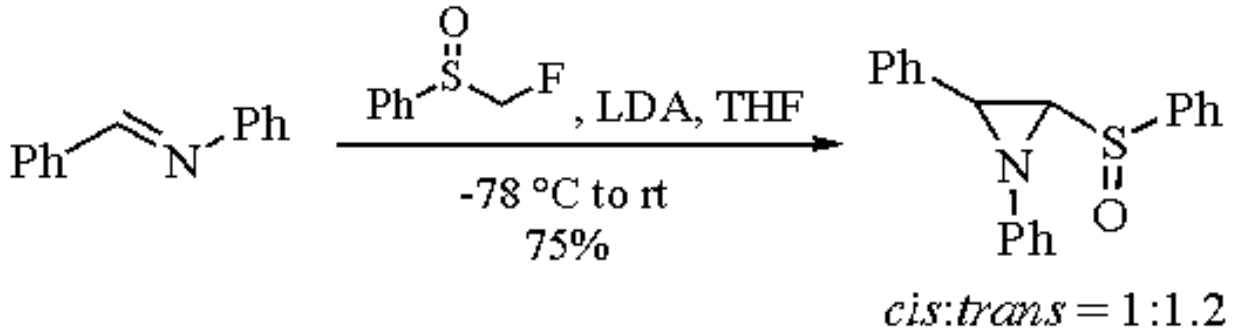

(11)

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1. (a) Schlosser, M. *T* **1978**, *34*, 3. (b) Rozen, S.; Filler, R. *T* **1985**, *41*, 1111. (c) More, K. M.; Wemple, J. *S* **1977**, 791. (d) McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. *JACS* **1985**, *107*, 735. (e) Wnuk, S. F.; Robins, M. J. *JOC* **1990**, *55*, 4757. (f) Robins, M. J.; Wnuk, S. F. *JOC* **1993**, *58*, 3800.
2. Reutrakul, V.; Rukachaisirikul, V. *TL* **1983**, *24*, 725.
3. (a) Burton, D. J.; Greenlimb, P. E. *JOC* **1975**, *40*, 2796. (b) Purrington, S. T.; Pittman, J. H. *TL* **1987**, *28*, 3901. (c) Boy, M. L.; Collington, E. W.; Finch, H.; Swanson, S.; Whitehead, J. F. *TL* **1988**, *29*, 3365. (d) Satoh, T.; Itoh, N.; Onda, K. I.; Kitoh, Y.; Yamakawa, K. *TL* **1992**, *33*, 1483.
4. Mahidol, C.; Reutrakul, V.; Prapansiri, V.; Panyachotipun, C. *CL* **1984**, 969.
5. Nájera, C.; Yus, M.; Hässig, R.; Seebach, D. *HCA* **1984**, *67*, 1100.
6. (a) Satoh, T.; Onda, K.; Itoh, N.; Yamakawa, K. *TL* **1991**, *32*, 5599. (b) Satoh, T.; Itoh, N.; Onda, K. I.; Kitoh, Y.; Yamakawa, K. *BCJ* **1992**, *65*, 2800.
7. (a) Krishnan, G.; Sampson, P. *TL* **1990**, *31*, 5609. (b) McCarthy, J. R.; Jarvi, E. T.; Matthews, D. P.; Edward, M. L.; Prakash, N. J.; Bowlin, T. L.; Mehdi, S.; Sunkara, P. S.; Bey, P. *JACS* **1989**, *111*, 1127. (c) Jarvi, E. T.; McCarthy, J. R.; Mehdi, S.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Sunkara, P. S.; Bey, P. *JMC* **1991**, *34*, 647.

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N-Fluoro-*N*-(phenylsulfonyl)benzenesulfonamide

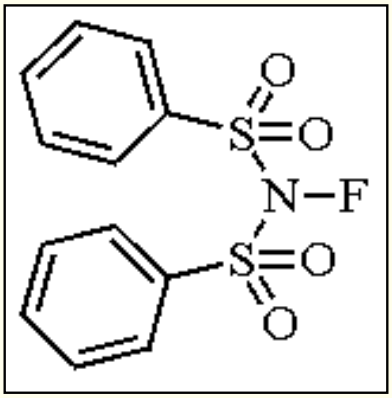

[133745-75-2] · $C_{12}H_{10}FNO_4S_2$ · *N*-Fluoro-*N*-(phenylsulfonyl)benzenesulfonamide · (MW 315.33)

(electrophilic fluorinating agent)

Alternate Names: *N*-fluorobenzenesulfonimide; *N*-fluorobis(phenylsulfonyl)amine; *N*-fluorodibenzenesulfonimide.

Physical Data: mp 114-116 °C.

Solubility: sol various organic solvents, including THF (0.24 g ml^{-1}), CH_2Cl_2 (0.40 g ml^{-1}), acetonitrile (0.25 g ml^{-1}), and toluene (0.09 g ml^{-1}).

Form Supplied in: white or slightly yellow solid, &egt;98% purity; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR.

Preparative Method: pressureless fluorination on a 0.2 mol scale with F_2 in N_2 (F_2/N_2 10% v/v) in the presence of powdered NaF in acetonitrile at -40 °C.[1]

Purification: flash chromatography (SiO_2, CH_2Cl_2) and/or crystallization from Et_2O.

Handling, Storage, and Precautions: handle and store at rt or below; protected from light, preferably under nitrogen or argon. Thermally stable up to 180 °C; decomposes exothermally at higher temperatures. Reacts with easily oxidized compounds such as iodide. This reagent should be handled in a fume hood.

Fluorination of Enolates and Silyl Enol Ethers.

N-Fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (**1**) can be used successfully to prepare α-fluorocarbonyl compounds starting from esters, ketones, or β-dicarbonyl precursors by electrophilic fluorination of the corresponding enolates (eqs 1-3) or silyl enol ethers (eq 4).[1] Diastereoselective fluorination of enolates with (**1**) has recently been reported.[7]

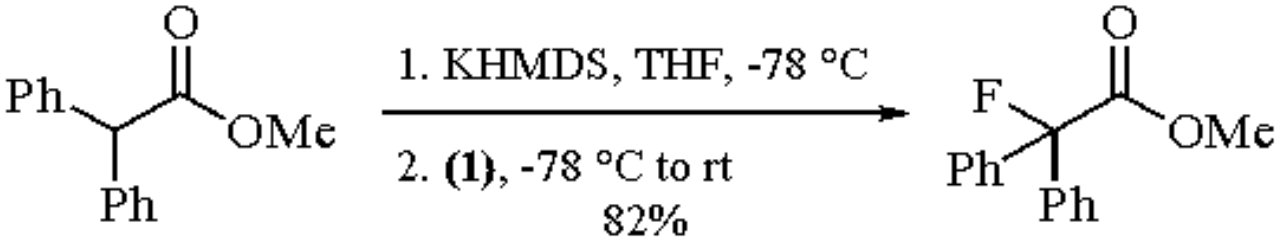

(1)

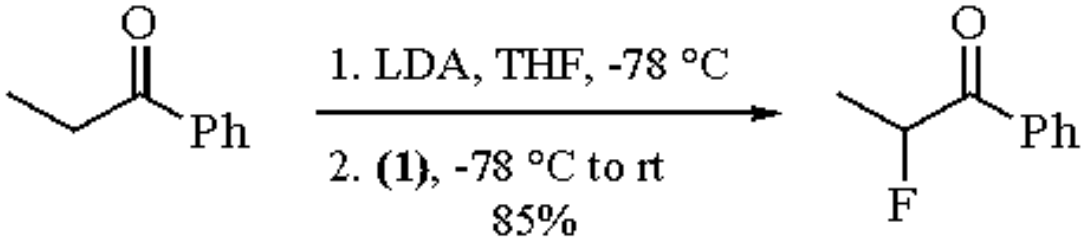

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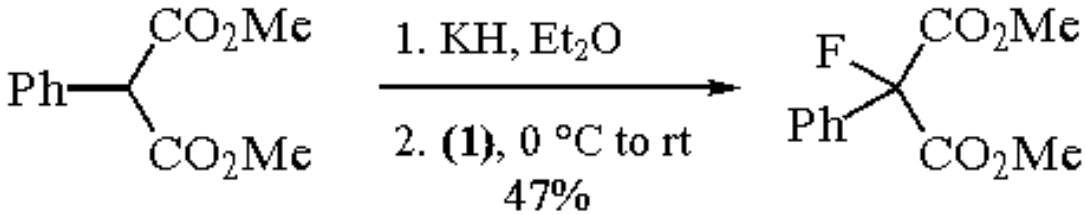

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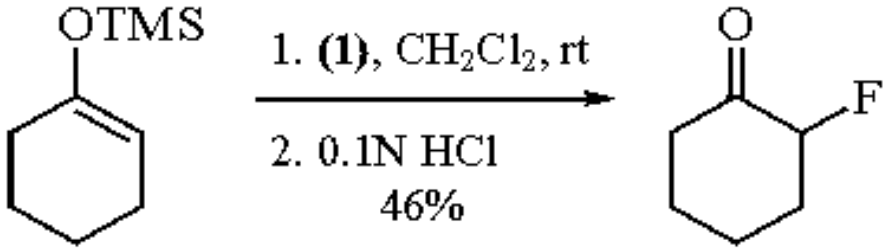

(4)

Fluorination of Organometallic Reagents.

Aryl and vinyl fluorides are conveniently prepared by reacting the corresponding lithium derivatives with (**1**).[1] For example, anthracenyllithium, generated from bromoanthracene with ***n-Butyllithium***, is fluorinated in THF at -78 °C (eq 5). 1-Phenyl-2-lithiopropene, obtained by reacting the corresponding iodoalkene with ***t-Butyllithium***, requires a lower reaction temperature (-105 °C, THF/Et_2O/pentane). This reaction affords the fluoroalkene with complete retention of configuration at the double bond (eq 6).

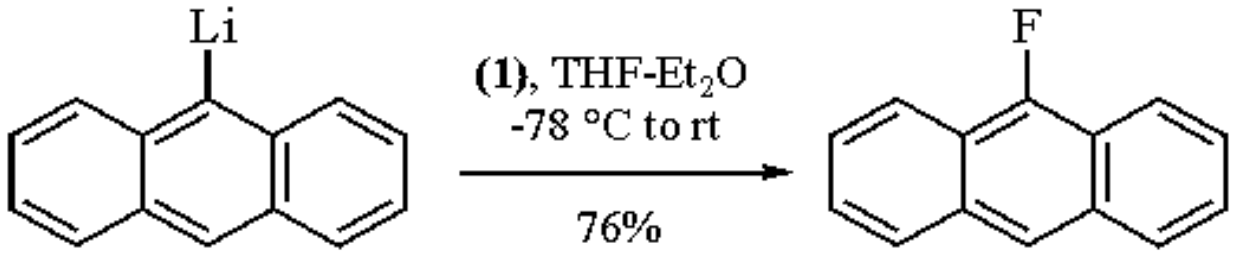

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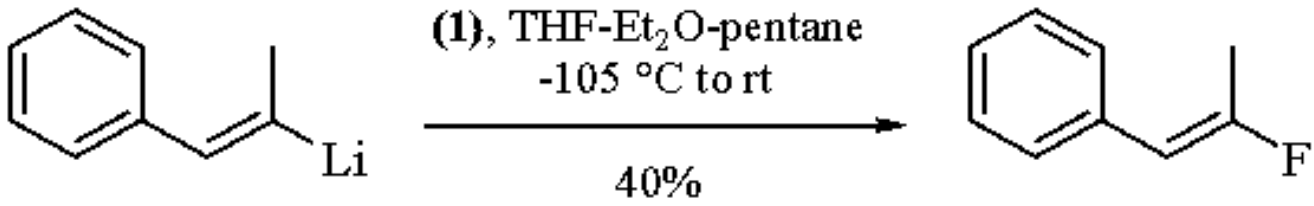

(6)

Fluorination of Alkyl Phosphonate Carbanions.

α-Fluoro- and α,α-difluoroalkyl phosphonates are prepared in good yields by electrophilic fluorination of phosphonate-derived carbanions (eqs 7 and 8).[2] The yields in the reaction strongly depend on the nature of the base, ***Potassium Diisopropylamide*** being the base of choice. α,α-Difluoroalkyl phosphonates are obtained in 54-70% yield from the corresponding monofluorinated precursors after deprotonation at low temperature (-90 °C). In situ double fluorination starting from alkyl phosphonates by using an excess of both base and (**1**) give only low yields (10-20%) of α,α-difluorinated products.

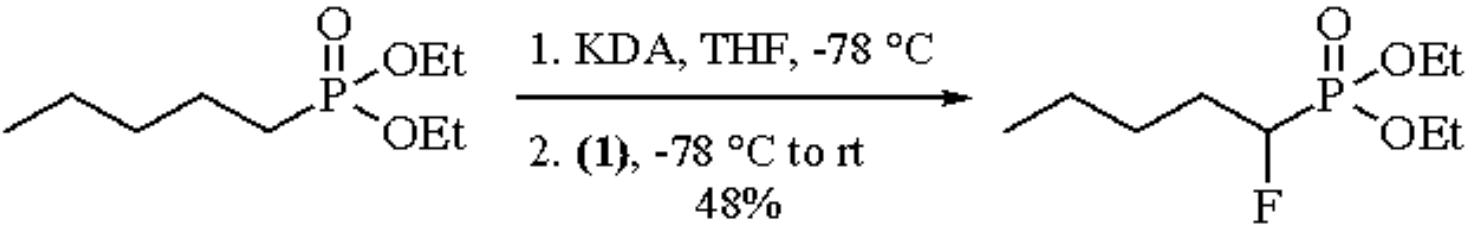

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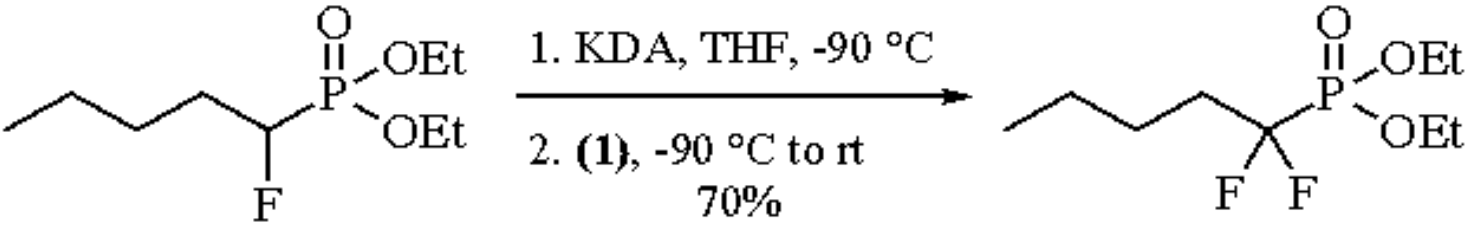

(8)

Electrophilic Addition to Aromatics.

Aromatic compounds are fluorinated with (**1**) by heating without a solvent to about 100-150 °C, or, for low-boiling compounds, up to reflux temperature.[1] Activated aromatics, such as anisole or *N*-acetylaniline, react smoothly, whereas toluene requires considerably longer reaction times and gives low yields (eqs 9-11). In all cases the regioselectivities are consistent with an electrophilic addition mechanism: *ortho* and *para* substituted products predominate over the *meta* isomers. (**1**) has recently been used in orthometalation-directed fluorination of aromatics.[8]

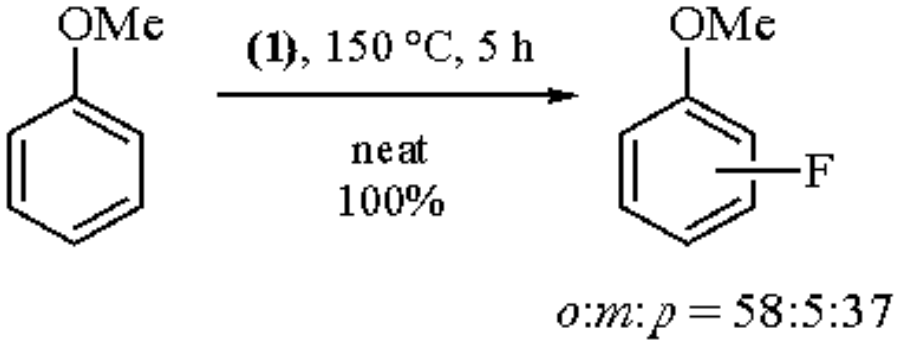

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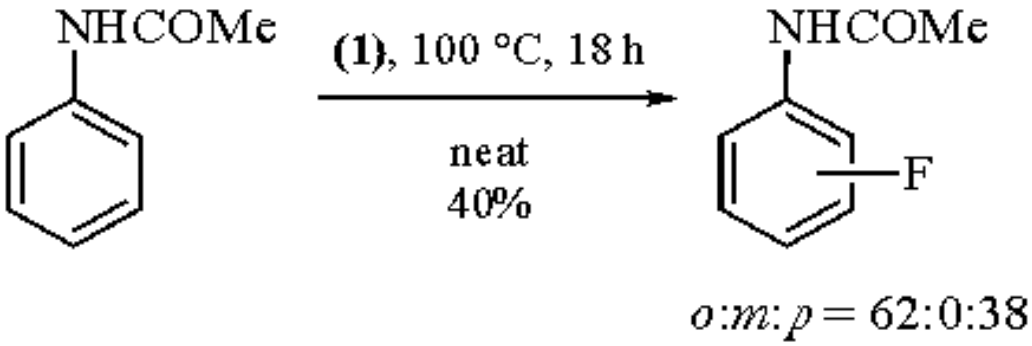

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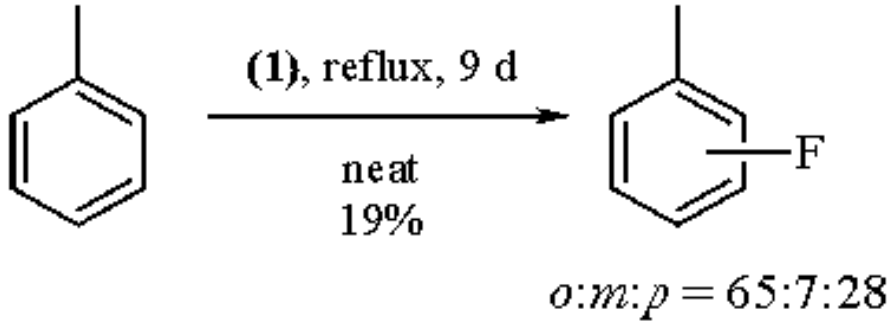

(11)

Related Reagents.

These include *N*-fluorobenzenedisulfonimide,[3] *N*-fluoroperfluoroalkane sulfonimides,[4] and ***2-Fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzisothiazole 1,1-Dioxide***.[5] For a review on electrophilic fluorinating agents, see German and Zemskov.[6]

---

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Edmond Differding

N-Fluoropyridinium Triflate[1]

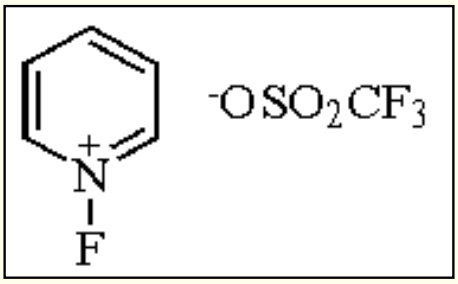

[107263-95-6] · $C_6H_5F_4NO_3S$ · *N*-Fluoropyridinium Triflate · (MW 247.17)

(fluorinating agent for many nucleophilic substrates)

Physical Data: mp 185-187 °C.

Solubility: sol polar solvents such as MeCN; 0.6 mg mL^{-1} in CH_2Cl_2; 1.7 mg mL^{-1} in THF; insol Et_2O.

Form Supplied in: white crystals; widely available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR, IR.[2]

Purification: recrystallization from MeCN-Et_2O at rt.[2]

Handling, Storage, and Precautions: nonhygroscopic and thermally stable. The reagent should be stored in a dry atmosphere protected from light. Handle in a fume hood.

Fluorination.[1]

N-Fluoropyridinium triflate (**1**) is an electrophilic fluorinating agent and is one of a series of *N*-fluoropyridinium triflates of differing strength. Typical related reagents include *N*-fluoro-2,4,6-trimethylpyridinium triflate (**2**), *N*-fluoro-3,5-dichloropyridinium triflate (**3**), *N*-fluoro-2,6-dichloropyridinium triflate (**4**), and *N*-fluoropentachloropyridinium triflate (**5**). The fluorinating power of these compounds varies in the order (**2**) < (**1**) < (**3**) < (**4**) < (**5**). The strongest reagent (**5**) smoothly fluorinates less reactive nucleophiles, while the mildest reagent (**2**) can be used satisfactorily for the more reactive nucleophiles. Reagents (**1**) and (**3**) fluorinate nucleophiles of intermediate reactivity. Because of this variation in strength, *N*-fluoropyridinium triflates fluorinate a wide range of nucleophiles including carbanions,[1] active methylene compounds,[1,3-6] sulfides,[7] enamines,[1] enol alkyl and silyl ethers,[1,8] vinyl acetates,[1] aromatics,[1,9-13] and alkenes.[1] In the following representative examples, *N*-fluoropyridinium triflate fluorinates enol silyl ethers (eq 1), alkyl enol ethers (eq 2), activated vinyl acetates (eq 3), and activated aromatics (eq 4).

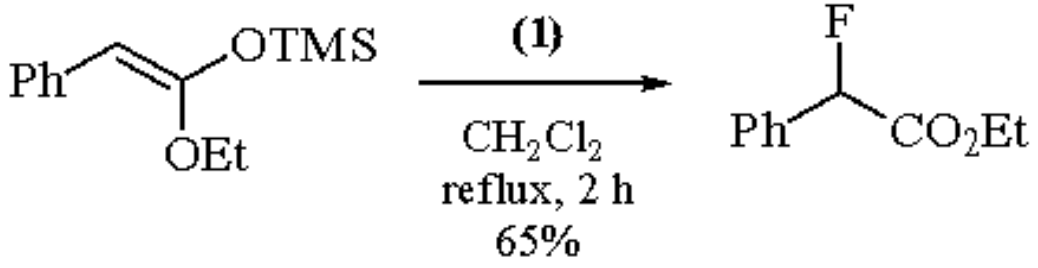
OTMS
Ph
OEt
(1)
CH2Cl2
reflux, 2 h
65%
F
Ph
CO2Et

(1)

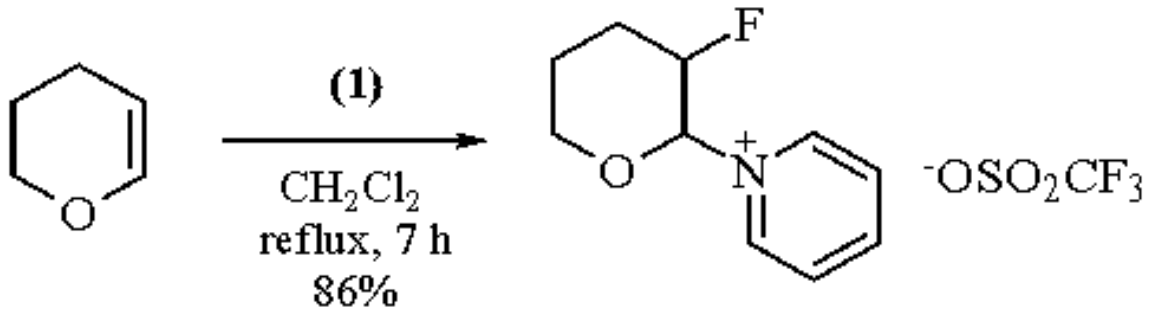
O
(1)
CH2Cl2
reflux, 7 h
86%
F
O
N
+
-OSO2CF3

(2)

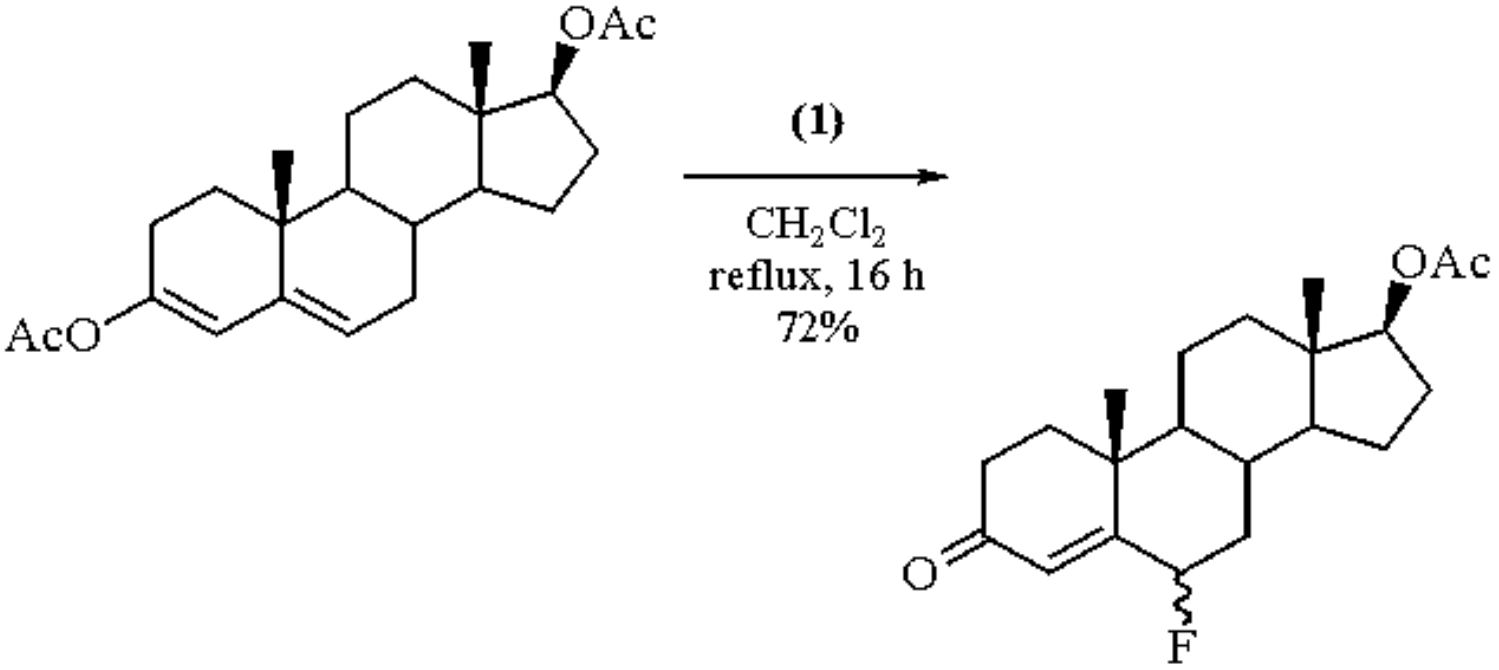
OAc
AcO
(1)
CH2Cl2
reflux, 16 h
72%
OAc
O
F

α:β = 1:2

(3)

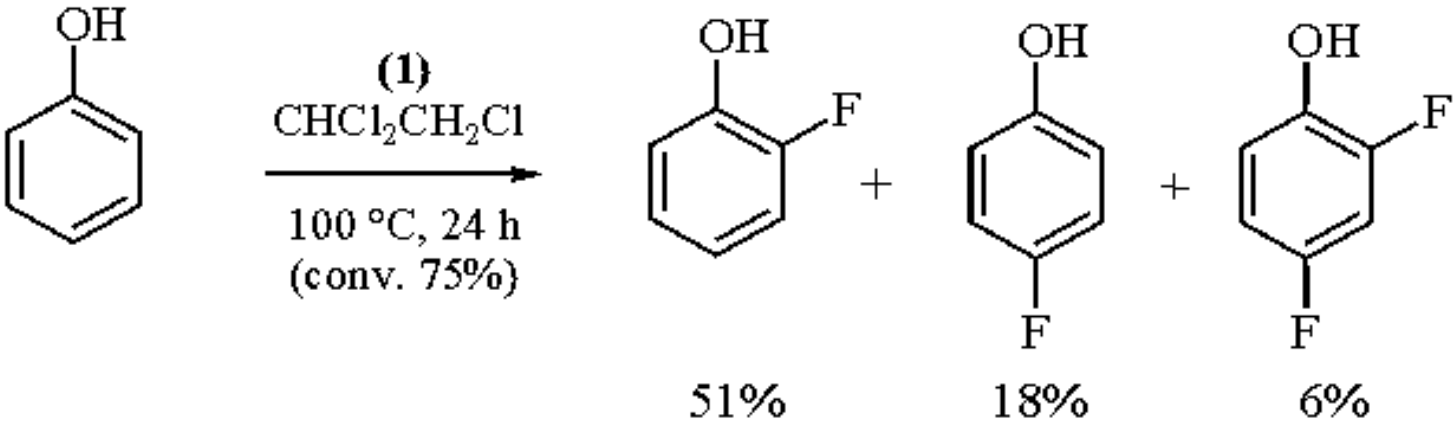
OH
(1)
CHCl2CH2Cl
100 °C, 24 h
(conv. 75%)
OH
F
+
OH
F
+
OH
F
F
51%
18%
6%

(4)

In some cases, *N*-fluoropyridinium triflate exhibits selectivity in the fluorination of silyl enol ethers. As shown in eq 5, a trialkylated enol silyl ether moiety is thus fluorinated preferentially.[1]

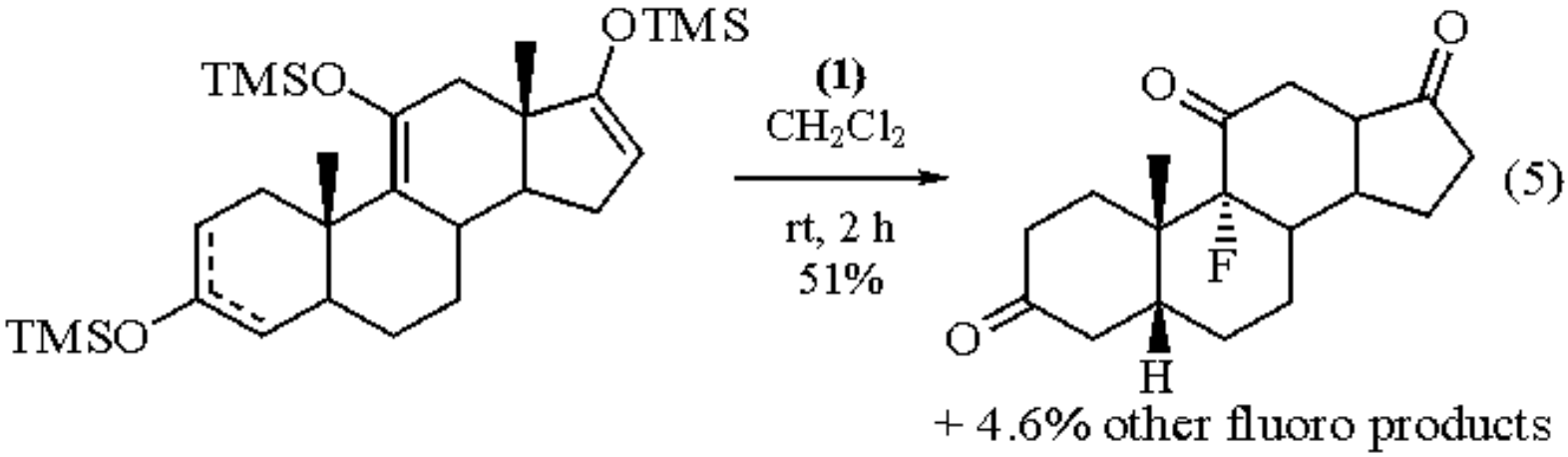

N-Fluoropyridinium triflates (**1**), (**2**), (**3**) and (**4**) are commercially available. A series of *N*-fluoropyridinium tetrafluoroborates[1,2,7] are also available. The triflates often give better yields because of better solubility in organic solvents.[1] Since (**3**), (**4**), and (**5**) readily decompose in water, exposure of these reagents to moisture should be avoided.

Selective Hydrolysis.

Efficient and selective hydrolysis of dithioacetals by (**2**) was reported.[14]

Related Reagents.

Other useful electrophilic fluorinating agents which are commercially available include ***Xenon(II) Fluoride***,[15] F-+N(CH_2CH_2)$_3$+N-CH_2Cl.2BF_4^- (**6**),[16] C_5H_5+N-F(C_5H_5N)$B_2F_7^-$ (**7**),[17] and ($PhSO_2$)$_2$NF (**8**).[18] XeF_2 is not suitable for large scale reactions because of its high cost. The scope of fluorination by each of these reagents (**6**)-(**8**) is also covered by the *N*-fluoropyridinium salts (**1**)-(**5**). ***Acetyl Hypofluorite*** ($MeCO_2F$), a useful electrophilic fluorinating agent, must be prepared in situ because of instability.[19] ***Perchloryl Fluoride*** ($FClO_3$) is a potentially explosive material.[20]

---

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18. (a) Differding, E.; Ofner, H. *SL* **1991**, 187. (b) Differding, E.; Duthaler, O. R.; Krieger, A.; Ruegg, G. M.; Schmit, C. *SL* **1991**, 395.
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Fluorosilicic Acid

H_2SiF_6

[16961-83-4] · F_6H_2Si · Fluorosilicic Acid · (MW 144.09)

(a fluoride source with both protic and Lewis acid properties providing efficient cleavage of silicon-oxygen bonds, e.g. silyl ether deprotection)

Physical Data: d 1.220 g cm^{-3} for a 25% aq solution.

Form Supplied in: 25% aq solution, clear and colorless. Upon dehydration, this reagent decomposes giving HF and SiF_4.

Handling, Storage, and Precautions: fluorosilicic acid is toxic and very corrosive. Like HF, this compound attacks glass and therefore must be stored in plastic containers. Use the same precautions as for aq HF solutions. Use in a fume hood.

Desilylation Reactions.

Fluorosilicic acid is a superior reagent for Si-O bond cleavage applications.[1] One of the common reagents used for desilylation is ***Hydrofluoric Acid***; however, significant problems can accompany its use. Standard protocols utilizing HF specify a large excess of the reagent, leading to low pH conditions which can decompose acid-sensitive substrates.[2] Hydrofluoric acid also lacks selectivity in removing silyl ethers. For example, a substrate which incorporates both a *t*-butyldimethysilyl (TBDMS) ether and a triisopropylsilyl (TIPS) ether will undergo cleavage of both protecting groups with little difference in cleavage rates. Of course, this is not problematic if the goal is to remove both groups; however, it is often desirable to remove one group selectively while retaining the other.

For the deprotection of silyl ethers, aq H_2SiF_6 is superior to aq HF. Fluorosilicic acid is a more potent cleaving agent than HF, allowing its use in stoichiometric or even catalytic quantities (eqs 1 and 2). The lower acid concentrations result in milder reaction conditions that are compatible with several acid labile moieties (see below).

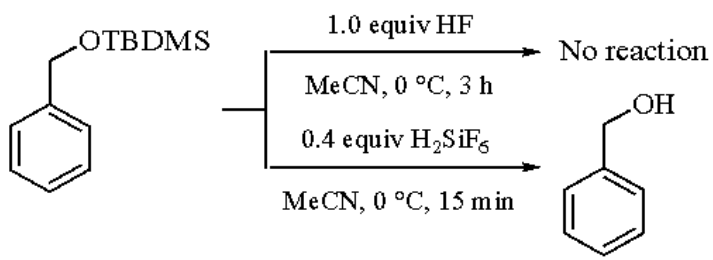

(1)

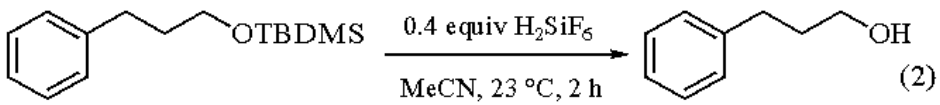

(2)

Fluorosilicic acid also has the unique ability to differentiate effectively between TBDMS and TIPS ethers, as seen in the competitive deprotection experiment in eq 3. The presence of bulky cosolvents, such as *t*-butanol, which serve as ligands to silicon, further enhance selectivity at the expense of reaction rate. The reaction time can be reduced by increasing the amount of H_2SiF_6; however, the accompanying increase in acid concentration precludes the use of acid-labile substrates.

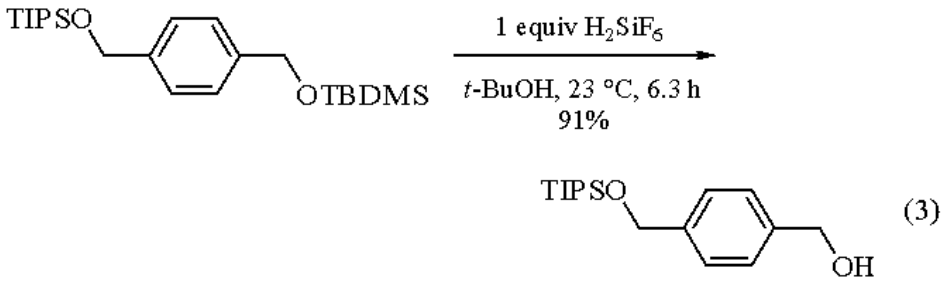

(3)

The optimal compromise between selectivity, reaction rate, and acid concentration is achieved by using a 90:10 acetonitrile-*t*-butanol solvent system. Under these conditions, selectivity is only slightly degraded and the reaction rate is relatively fast, so the amount of reagent can be reduced to 0.25 equiv (eq 4). Due to the lower acid concentration, certain acid labile groups are tolerated. In competitive deprotection experiments, Bn-O-TBDMS is deprotected in the presence of another acid labile protecting group (an example is shown in eq 5 for THP): MEM and MOM groups are 100% retained; THP (86%) and benzylidine derivatives (77%) are partially retained. An acetonide derivative is retained only to the extent of 16%.

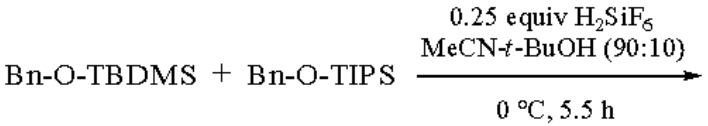

Bn-OH + Bn-O-TBDMS + Bn-O-TIPS (4)

1% 91%

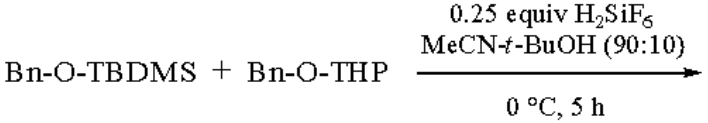

Bn-OH + Bn-O-TBDMS + Bn-O-THP (5)

1% 86%

The effects of increasing the steric bulk of the substrate at carbon were also probed. Compounds (**1**)-(**4**) (eq 6) were paired and used in competitive deprotection reactions, providing the results reported in Table 1. Excellent selectivity was observed in the deprotection of primary TBDMS vs. tertiary TBDMS, and secondary TBDMS vs. tertiary TBDMS derivatives. On the other hand, selectivity was only fair for primary TBDMS vs. secondary TBDMS, and secondary TBDMS vs. secondary TIPS ethers. As observed before, *t*-butanol provided greater selectivity than *t*-BuOH-MeCN solvent mixtures.

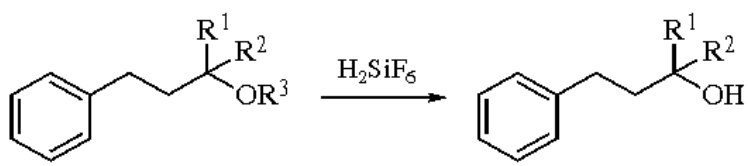

(6)

	R^1	R^2	R^3
(1)	H	H	TBDMS
(2)	H	Me	TBDMS
(3)	H	Me	TIPS
(4)	Me	Me	TBDMS

Table 1 Study of Substrate Steric Effects

Compd. A	Compd. B	Solvent[a]	Temp. (°C)	mmol H_2SiF_6	Time (h)	% A[b] (±2%)	% B[b] (±2%)	Selectivity
(**1**)	(**2**)	*t*-Butanol	25	0.500	3.3	4	62	58
(**1**)	(**2**)	90:10 MeCN *t*-butanol	0	0.125	3.0	4	52	48
(**1**)	(**4**)	90:10 MeCN *t*-butanol	0	0.125	3.0	0.3	100	100
(**2**)	(**4**)	90:10 MeCN *t*-butanol	0	0.250	8.0	2	99	97
(**2**)	(**3**)	90:10 MeCN *t*-butanol	0	0.250	24	2	65	63

[a] In each experiment, 0.5 mmol of compound A and compound B were dissolved in 5.0 mL of solvent. [b] Yields determined by GC analysis.

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Fluorosulfuric Acid

HSO_3F

[7789-21-1] · FHO_3S · Fluorosulfuric Acid · (MW 100.08)

(strong Brønsted superacid[1] used as catalyst and reagent for alkylation, isomerization, rearrangement, cyclization, cycloaddition, ring-opening polymerization, and fluorosulfonation; also widely used in generation of stable carbocations)

Alternate Name: fluorosulfonic acid.

Physical Data: mp -89.0 °C; bp 162.7 °C; *d* 1.743 g cm^{-3}.

Solubility: sol nitrobenzene, diethyl ether, acetic acid, ethyl acetate; insol carbon disulfide, carbon tetrachloride, chloroform. It dissolves most organic compounds that are potential proton acceptors.

Form Supplied in: colorless liquid; commercially available.

Handling, Storage, and Precautions: fluorosulfuric acid is highly toxic and corrosive and should always be handled in a fume hood with proper protection. It can be purified by distillation under anhydrous conditions using common glassware. When water is excluded, it may be handled and stored in glass containers, but containers should always be cooled before opening because HF gas pressure may have developed due to hydrolysis. For long-term laboratory storage, however, Teflon bottles are recommended.

Isomerization and Rearrangement.

Many hydrocarbons, especially terpenes, rearrange readily in fluorosulfuric acid, usually at low temperatures, with the intermediacy of carbocations.[2-15] Compared to conventional acid systems, the use of HSO_3F often alters the normal course of acid-catalyzed isomerization and rearrangement, since the carbocation intermediates formed during the reactions are stabilized in the superacid system. For example, treatment of 1,8-*p*-menthadiene (limonene) with HSO_3F gave α- and β-phellandrenes (eq 1)[14] which were not obtained by other weaker acid systems.

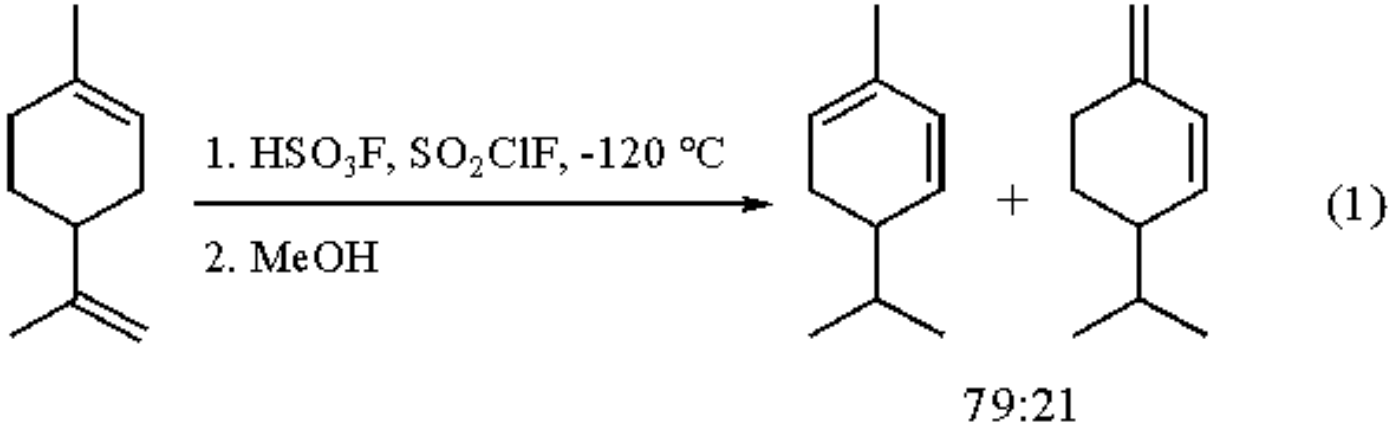

Longifolene rearranges to isolongifolene and other tricyclic derivatives in the presence of 50% ***Sulfuric Acid/Acetic Acid*** in dioxane, but both longifolene and isolongifolene rearrange to a variety of bicyclic products under the catalysis of fluorosulfuric acid (eq 2).[15]

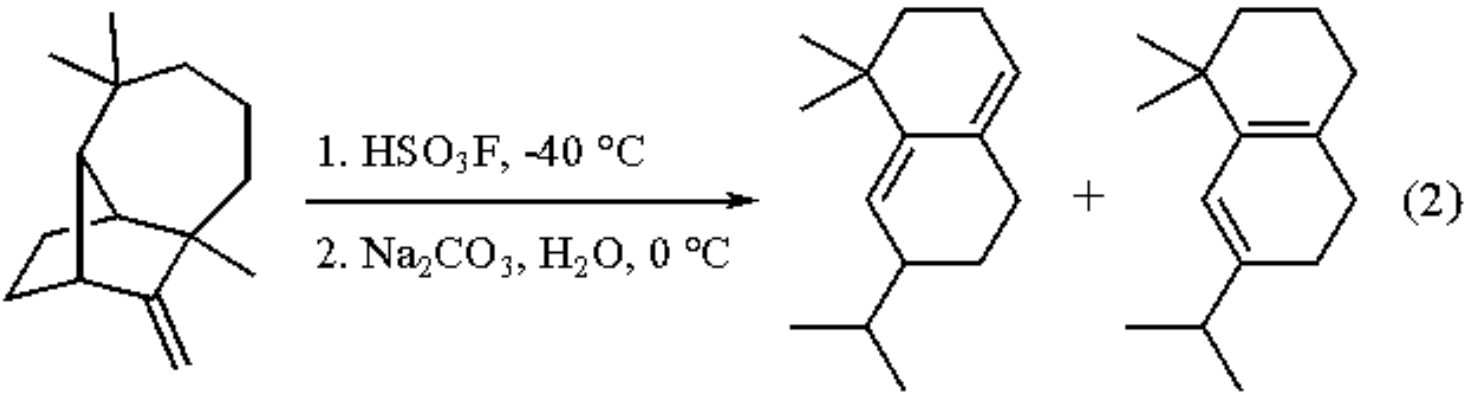

Temperature also plays an important role in determining the reaction pathway. Quenching of the reactions with bases or nucleophiles at specific temperatures can control the nature of the products.

Cyclization and Ring Opening.

Fluorosulfuric acid is a promising reagent in catalyzing intramolecular cyclizations at low temperature, giving better yields and higher degrees of structure selectivity compared to conventional acids. Monoterpenoids[16-21] and higher terpenoids[22-27] cyclize biomimetically by treatment with fluorosulfuric acid at low temperature (eq 3).[25]

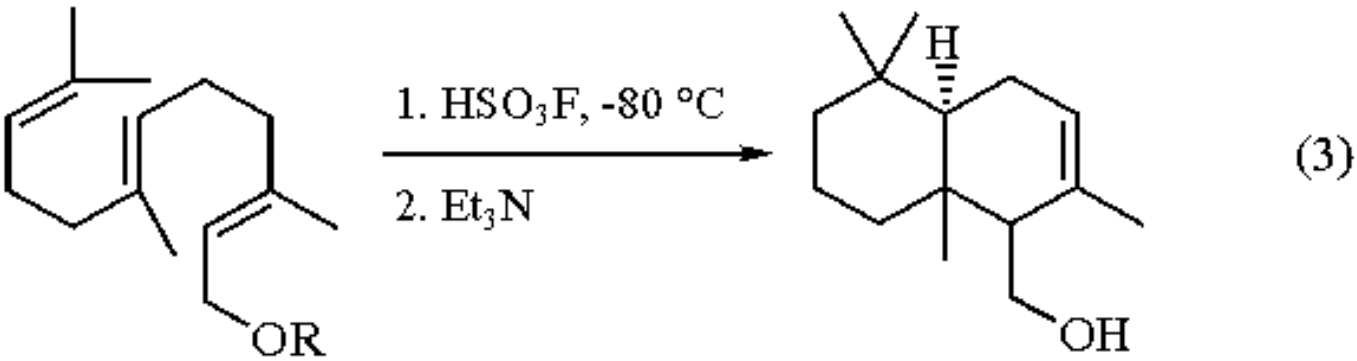

Trienols and dienols cyclize in a similar way, in the presence of an excess of fluorosulfuric acid in 2-nitropropane at -90 °C, to afford 74-87% yields of diastereoisomeric mixtures of odoriferous norlabdane oxides (eq 4).[27]

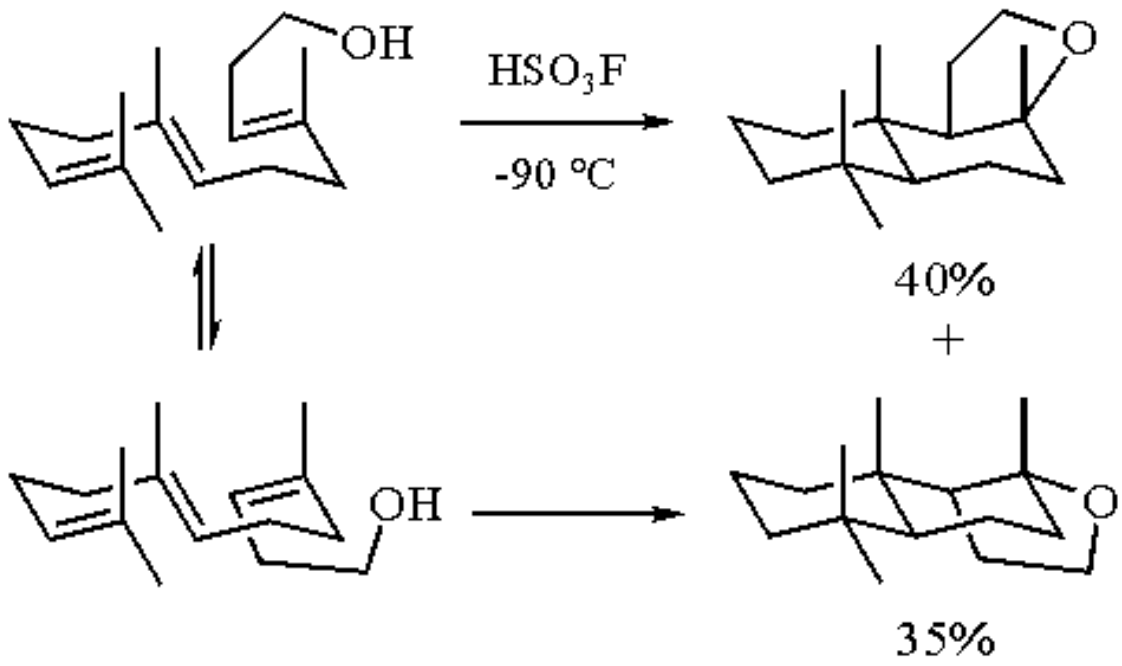

(4)

Cyclic ethers can be obtained by reacting unsaturated alcohols in fluorosulfuric acid.[28-33] Treatment of geraniol or nerol with HSO_3F at low temperature gave good yields (78 and 57%) of an iridoid ether (eq 5).[21,29b]

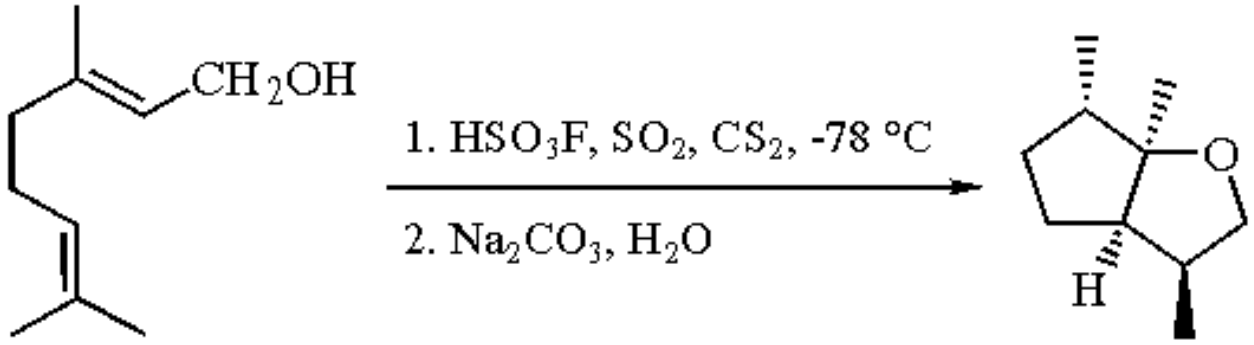

(5)

Benzyl carbinols react with fluorosulfuric acid through various reaction pathways[34-36] (rearrangement, dehydration, cyclization, ring expansion), depending on the substrate (eq 6).[34]

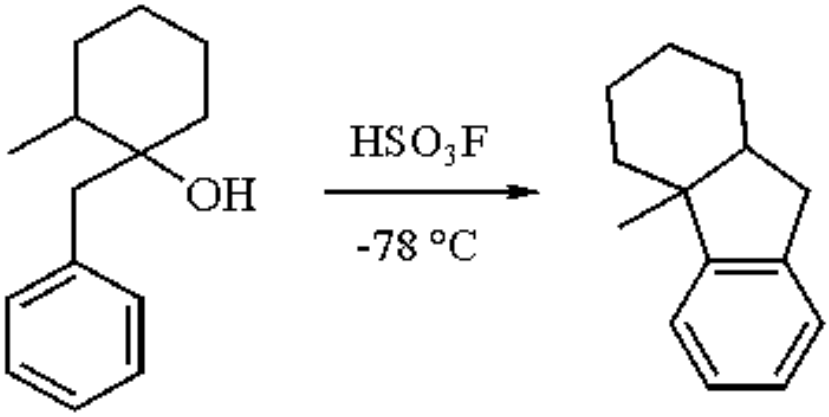

(6)

As opposed to cyclization, ring opening of a number of substituted nopinones occurred under fluorosulfuric acid catalysis to give 4-(2-propyl)cyclohex-2-enones (eq 7).[37] In industry, fluorosulfuric acid is used as an efficient catalyst to initiate the ring-opening polymerization of tetrahydrofuran.[38]

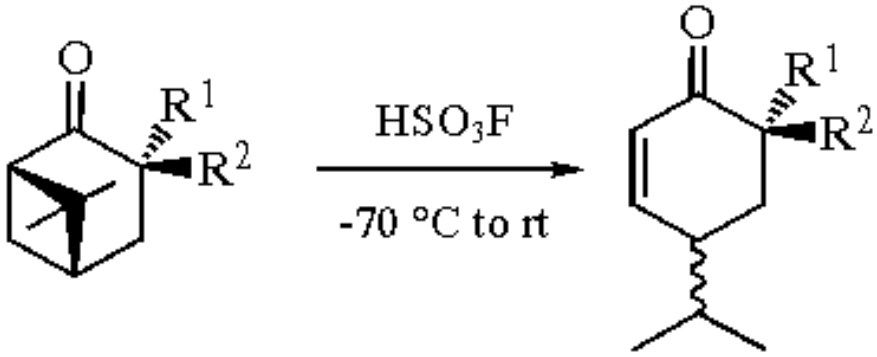

(7)

Cycloaddition.[39-42]

Triphenylpropynol reacts in HSO_3F with alkenes or dienes to give [4 + 2] or [2 + 2] cycloaddition products (eq 8).[42]

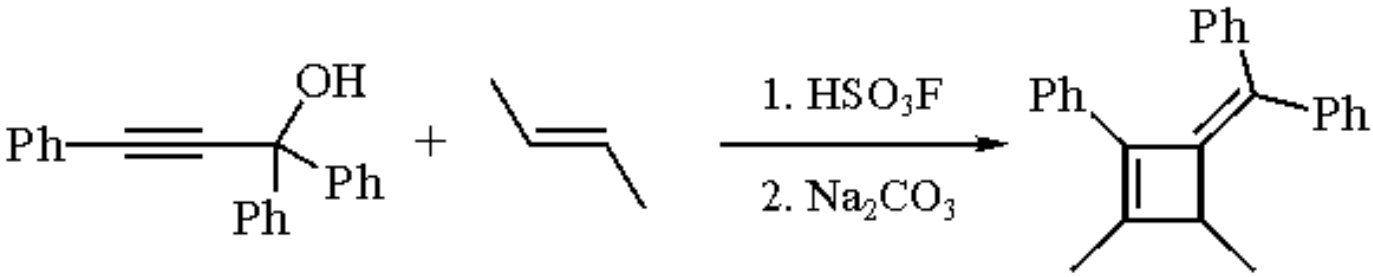

(8)

Formation of Fluorosulfates.

Alkyl fluorosulfates can be prepared by addition of fluorosulfuric acid to alkenes, haloalkenes, and cyclopropanes at low temperatures with good to moderate yields (50-95%) (eq 9).[43]

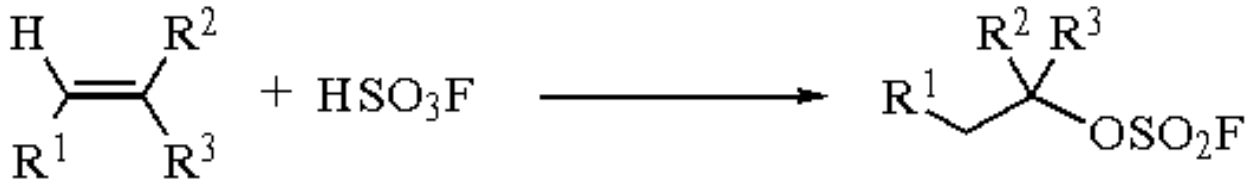

(9)

Fluorosulfonation.[44]

Aromatics react with HSO_3F in the presence of variable amounts of ***Antimony(V) Fluoride*** to give aromatic sulfonyl fluorides and diaryl sulfones (see ***Fluorosulfuric Acid-Antimony(V) Fluoride***).

Generation of Stable Carbocations.

Fluorosulfuric acid is the strongest known simple Brønsted acid, with an H_0 value[45] of -15.1 (compared to -12 for 100% sulfuric acid, -14.1 for ***Trifluoromethanesulfonic Acid***, and -15 for absolutely anhydrous ***Hydrogen Fluoride***).[46] The acidity of HSO_3F can be increased by the addition of Lewis acid fluoride (see ***Fluorosulfuric Acid-Antimony(V) Fluoride***). HSO_3F has low viscosity, high thermal stability, and a wide liquid range (250 °C from mp to bp). These advantageous properties make HSO_3F one of the most frequently used superacids for generating stable carbocations from the corresponding alcohols at low temperature.[1,47-50] Generally, neat HSO_3F or acid diluted with solvents such as SO_2, SO_2ClF, freons, and dichloromethane is suitable for the preparation of carbocations stabilized by aryl, cyclopropyl, vinyl, or other π systems. Representative examples are dicyclopropyl carbonium ions (eq 10),[47] cyanodiarylmethyl cations (nitrenium ions) (eq 11),[48] and the pyramidal $(CMe)_6^{2+}$ dication (eq 12).[49]

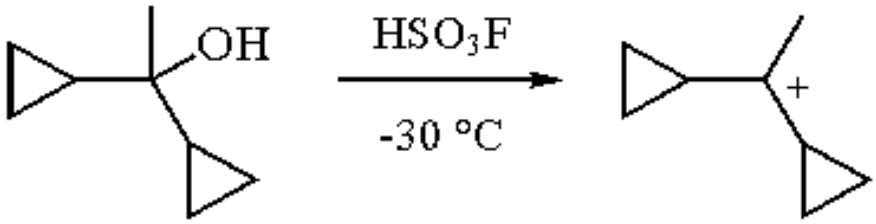

(10)

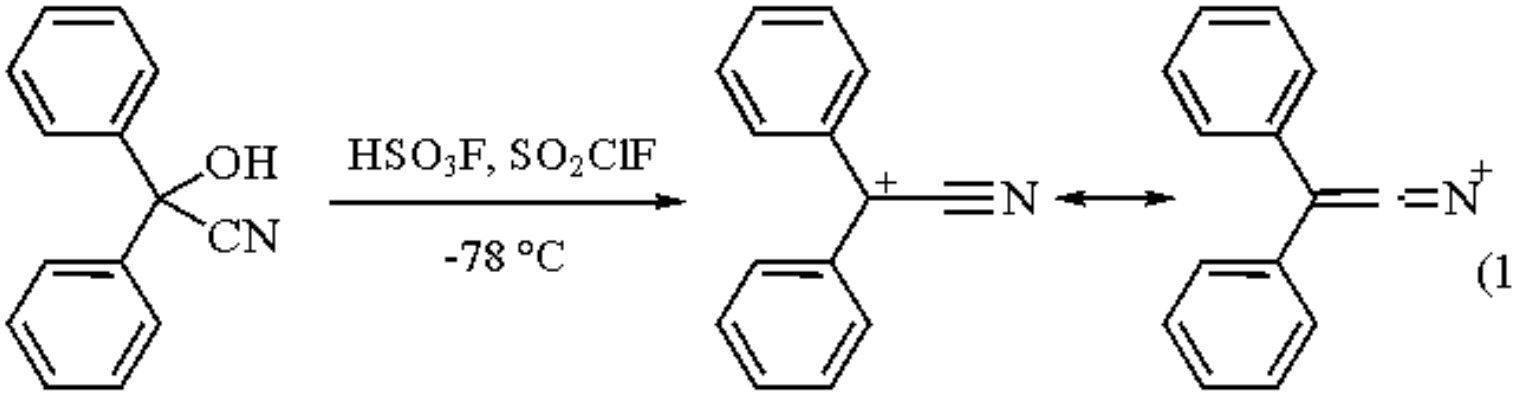

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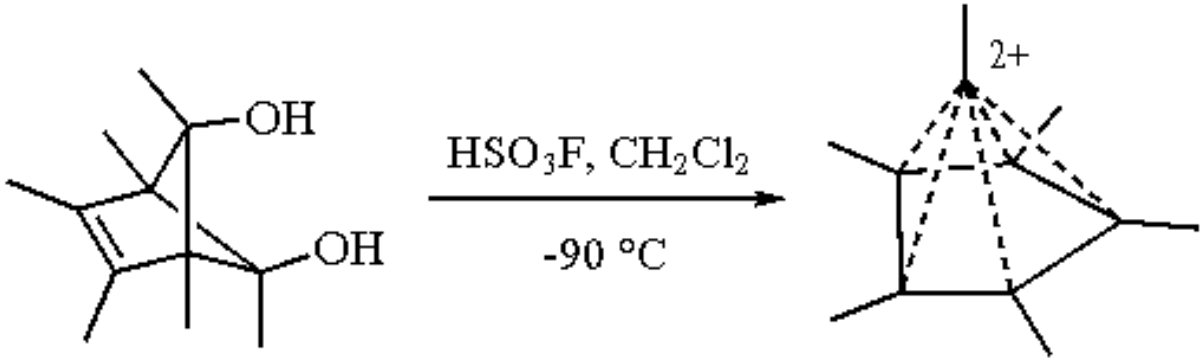

(12)

An intriguing cyclopropyl cation with a ferrocene substituent has been generated from its trimethylsilyl ether by eliminating trimethylsilyl fluorosulfate (eq 13).[51] 1,6-Methano[10]annulene undergoes protonation by HSO_3F in SO_2ClF to form the corresponding arenium ion (eq 14),[52] while benzenium ion generation needs a combination of HSO_3F and SbF_5.[53]

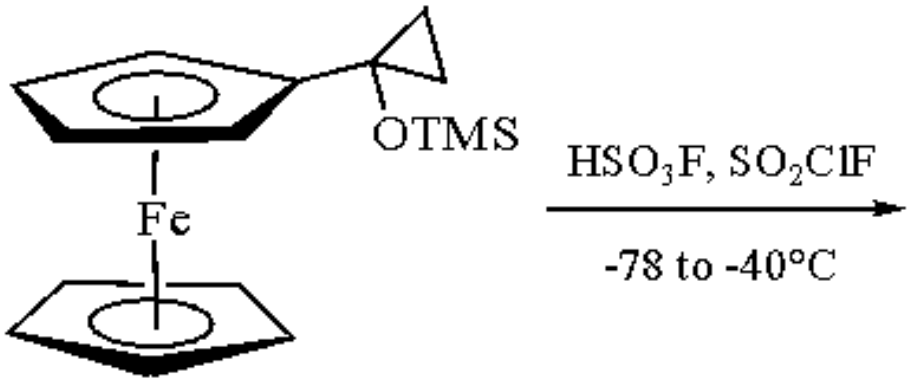

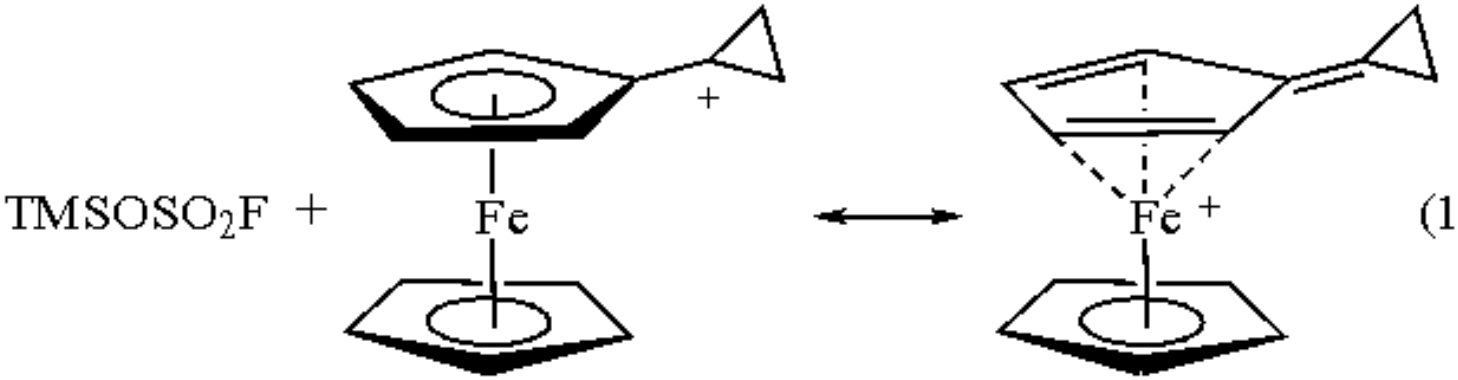

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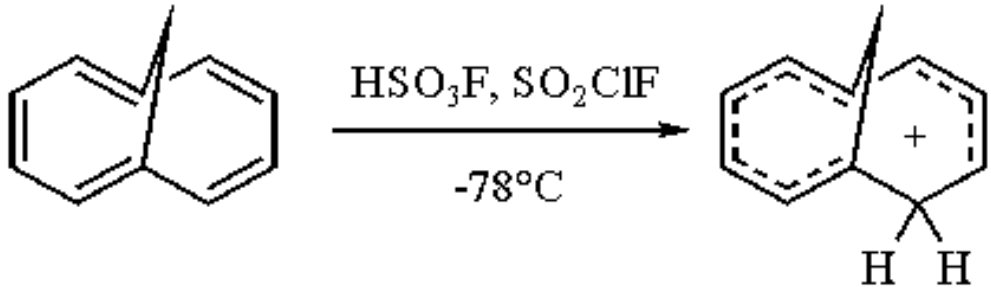

(14)

Related Reagents.

Fluorosulfuric Acid-Antimony(V) Fluoride; ***Hydrogen Fluoride***; ***Hydrogen Fluoride-Antimony(V) Fluoride***; ***Nafion-H***.

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Fluorosulfuric Acid-Antimony(V) Fluoride[1]

HSO_3F-SbF_5

[23854-38-8] · F_6HO_3SSb · Fluorosulfuric Acid-Antimony(V) Fluoride · (MW 316.83)

(a strong conjugate Brønsted-Lewis superacid system[1] widely used for the generation of stable carbocations and as catalyst and reagent for alkylation, isomerization, rearrangement, cyclization, oxyfunctionalization, formylation, sulfonation, and fluorosulfonation)

Alternate Name: Magic Acid®.

Physical Data: HSO_3F: mp -89.0 °C; bp 162.7 °C; *d* 1.743 g cm^{-3}. SbF_5: bp 149.5 °C; *d* 2.993 g cm^{-3}.

Solubility: sol SO_2ClF, liquid SO_2; solubilizes most organic compounds that are potential proton acceptors.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: HSO_3F-SbF_5 is prepared by mixing ***Fluorosulfuric Acid*** and ***Antimony(V) Fluoride*** at rt under dry nitrogen or argon atmosphere. The commercially available Magic Acid is a 50:50 mol % mixture of the two components. Magic Acid diluted in fluorosulfuric acid to various extents is also available. Commercial Magic Acid generally contains some HF in the form of conjugate acid.

Handling, Storage, and Precautions: Magic Acid is highly toxic, moisture sensitive, and corrosive, and should always be handled in a fume hood with proper protection. Glass is attacked by Magic Acid very slowly when moisture is excluded. Therefore, glassware may be used for handling and carrying out reactions involving Magic Acid. Teflon containers are recommended for long-term laboratory storage of Magic Acid.

Introduction.

Of all the superacids, Magic Acid is probably the most widely used medium for the study of stable long-lived carbocations and other reactive cations. The general rule is that the higher the acidity of the medium used, the more stable is the carbocation generated. The acidity of the fluorosulfuric acid-antimony pentafluoride system as a function of SbF_5 content has been studied.[2,3] The increase in acidity is very sharp at low SbF_5 concentration. The H_0 value changes from -15.1 for HSO_3F to -19.8 for a mixture containing 10% SbF_5.[2] The acidity continues up to the estimated value of H_0 = -26.5 for 90% SbF_5 content. The H_0 value for the 1:1 molar mixture of fluorosulfuric acid and antimony pentafluoride, known as Magic Acid®, is estimated to be about -23 by a dynamic NMR study.[3] The name Magic Acid originated in Olah's laboratory at Case Western Reserve University in the winter of 1966 when a piece of Christmas

candle was found to dissolve readily in this acid system, giving the sharp ^{1}H NMR spectrum of the *t*-butyl cation, a phenomenon considered by the research student involved to be magic.[1] A major reason for the wide application of Magic Acid compared with other superacid systems, besides its very high acidity, is probably the large temperature range in which it can be used. In the liquid state, it can be studied at temperatures as low as -160 °C (acid diluted with SO_2F_2 and SO_2ClF) and as high as 150 °C (neat acid).

Magic Acid has been employed as a high acidity medium for isomerization/rearrangement, alkylation, cyclization, carboxylation, formylation, oxyfunctionalization, and related reactions. It also serves as a fluorosulfonating/sulfonating agent for aromatics.

Generation of Stable Carbocations.

Thanks to its high acidity, Magic Acid can be used for the generation of such reactive carbocations as the *t*-butyl cation and other alkyl cations, while fluorosulfuric acid itself is suitable only for the generation of more stable cations such as aryl- or cyclopropyl-stabilized carbocations.

Carbocations and carbodications have been generated from a variety of precursors in Magic Acid systems.[4]

Carbocation Generation from Tertiary and Secondary Alcohols.[5-11]

A wide variety of aliphatic tertiary and secondary alcohols can be ionized to the corresponding alkyl cations by using Magic Acid. Formation of the *t*-butyl cation (eq 1)[5] and a cyclopropyl-stabilized dication (eq 2)[6] are representative examples. Primary (and some secondary) alcohols are protonated only at temperatures lower than -60 °C.[7] At more elevated temperatures they may cleave to give the corresponding carbocations, which, however, immediately rearrange to the more stable tertiary cations.[8,9]

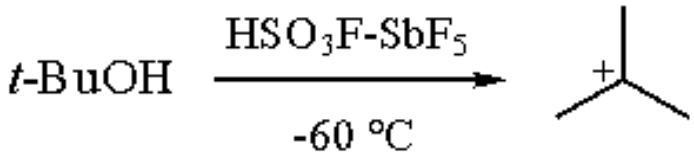

(1)

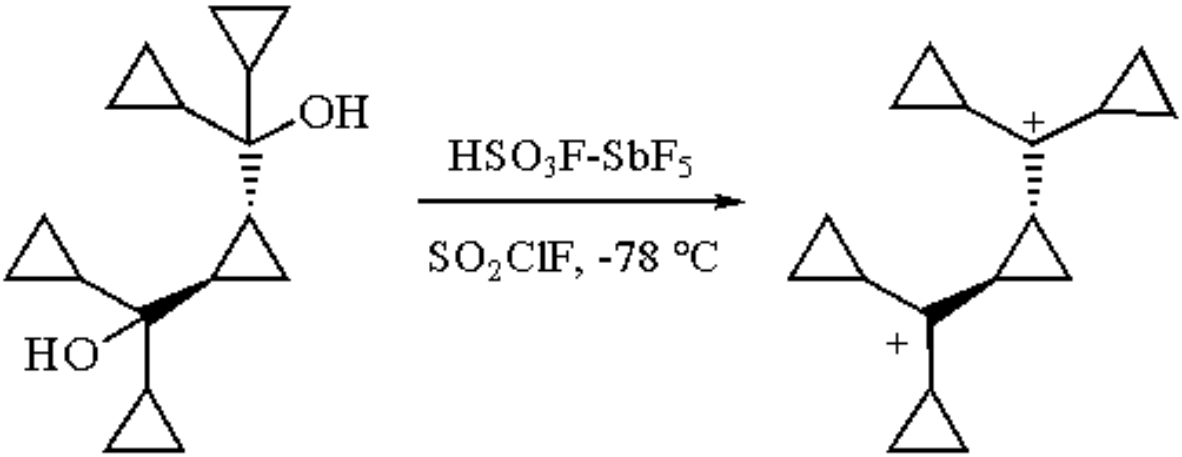

(2)

Similar to alcohols, aliphatic ethers,[12] thiols,[13] and sulfides are also protonated on oxygen or sulfur, respectively, at -60 °C in Magic Acid; carbocations are subsequently formed upon raising the temperature. Protonated sulfides, excluding tertiary alkyl, are resistant to cleavage up to +70 °C.[13]

Carbocation Generation from Alkyl Halides.

Alkyl chlorides, fluorides, and bromides are convenient and frequently used precursors for generation of alkyl cations in HSO_3F-SbF_5 systems.[14] It should be noted, however, that the HSO_3F-SbF_5 system is less suitable than SbF_5 for the generation of alkyl, especially secondary alkyl, cations from the corresponding alkyl halides (see ***Antimony(V) Fluoride***). Ionization of cyclohexyl chloride in Magic Acid is accompanied by isomerization, yielding the 1-methyl-1-cyclopentyl cation (eq 3).[8]

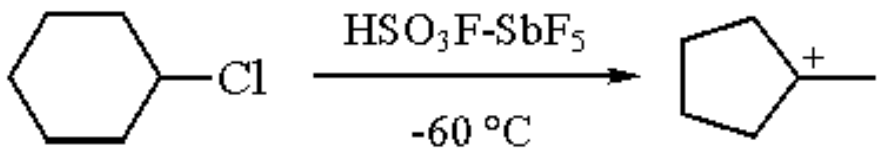

(3)

Carbocation Generation from Unsaturated Hydrocarbons.

Carbocations can be generated by protonation of unsaturated hydrocarbons such as alkenes and cycloalkenes,[8,11] cyclopentadienes,[15] benzenes and naphthalenes (eq 4),[16] pyrenes and cyclophanes,[17] unsaturated heterocycles,[18] and their derivatives with carbon-heteroatom multiple bonds,[1] including carbonyl and nitrile compounds and diazoalkanes (eq 5).[19] Compounds with two sites for protonation may undergo diprotonation to give dications in Magic Acid (eq 6).[15a]

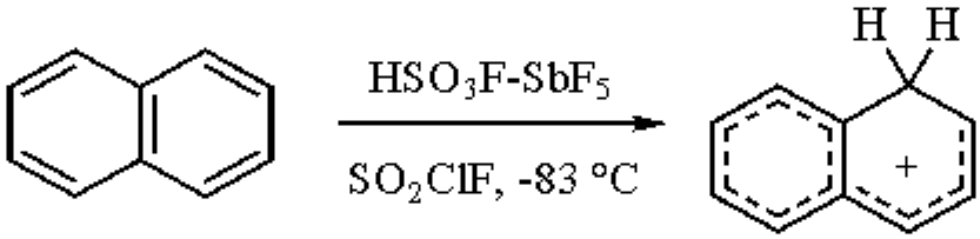

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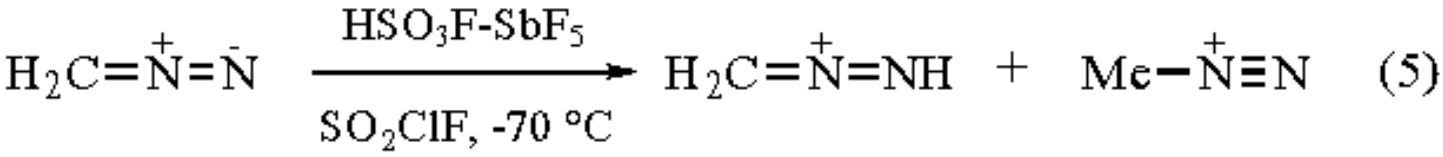

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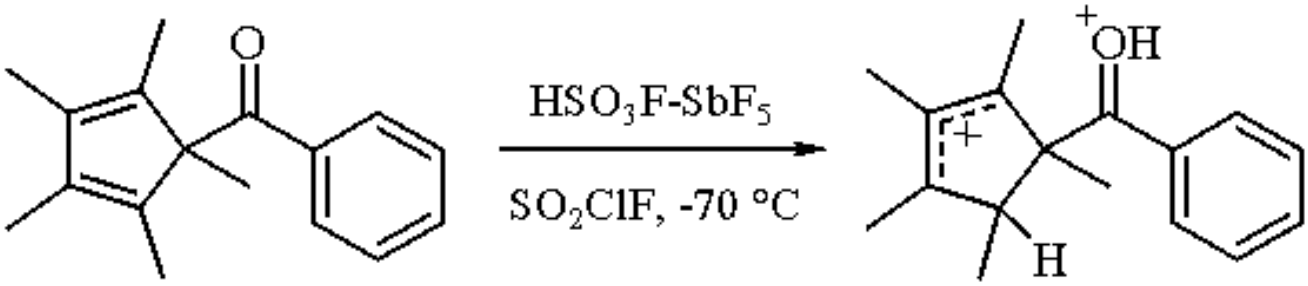

(6)

Carbocation Generation from Saturated Hydrocarbons.

Magic Acid, as a strong superacid, can abstract hydride from saturated alkanes, including straight-chain alkanes as well as branched and cyclic alkanes, at -125 to 25 °C to give alkyl cations.[6,20] For example, the 2-norbornyl cation is formed through protolytic ionization by dissolving norbornane in Magic Acid (eq 7).[20b]

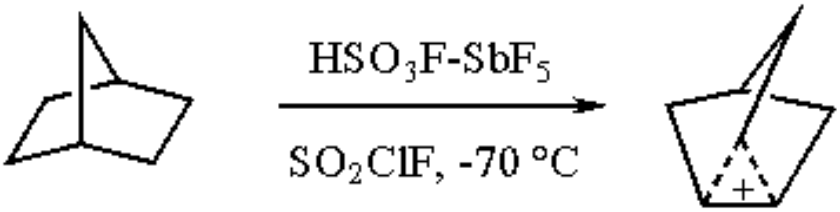

(7)

Carbocation Generation by Oxidation.

Oxidation of polycyclic arenes such as naphthacene and 1,2-benzanthracene (eq 8)[21] gives arene dications (see also ***Antimony(V) Fluoride***).

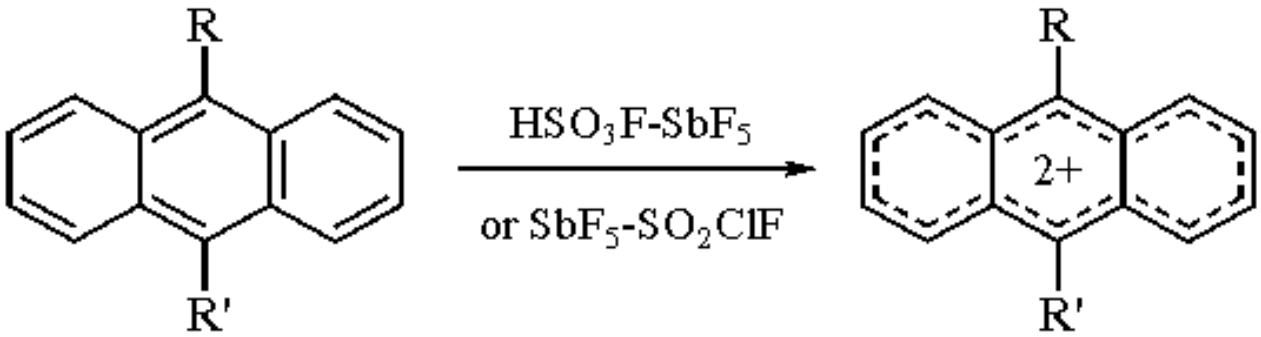

(8)

Isomerization and Rearrangement.

HSO_3F-SbF_5 is frequently used as a catalyst for the isomerization and rearrangement of terpenoids. The extremely high acidity of HSO_3F-SbF_5 allows the reaction to be carried out at temperatures as low as -100 °C and with improved selectivity.

In superacid, i.e. HSO_3F-SbF_5 or HF-SbF_5 systems, bicyclic phenols are isomerized to dienones in good yields (eq 9).[22] This is an unconventional isomerization process, in which the phenols lose their aromaticity to form nonaromatic

dienones. Similar phenol-to-dienone isomerization of estrones occurs with HSO_3F-SbF_5 as catalyst, accompanied by major dehydrogenation products (eq 10).[23]

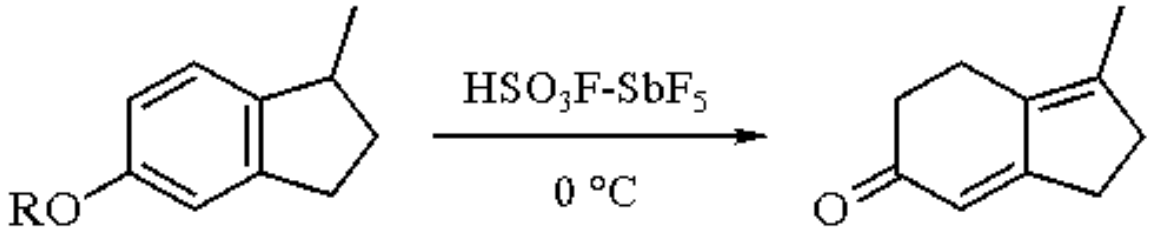

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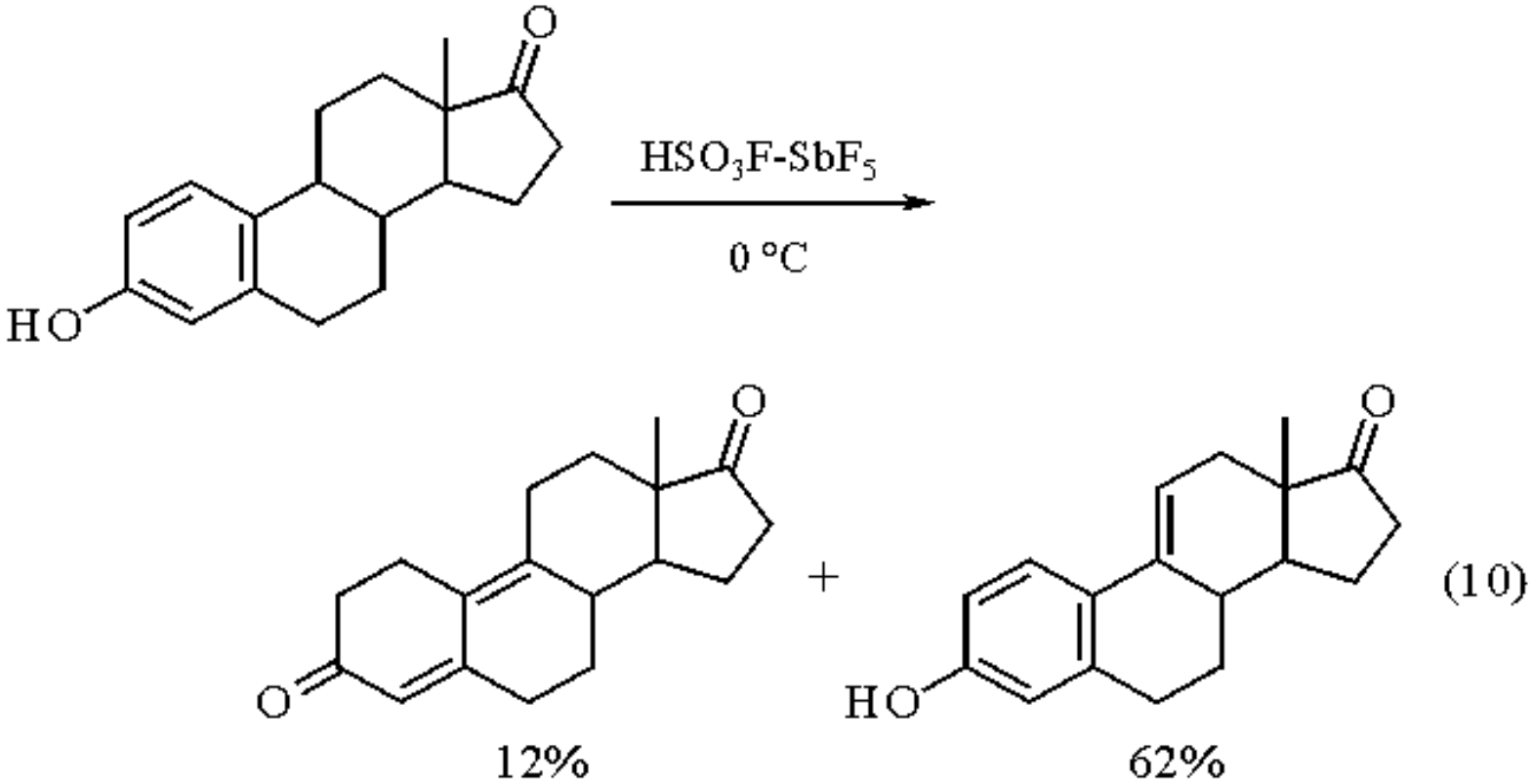

(10)

endo-Trimethylenenorbornane isomerizes to its *exo* isomer in quantitative yield at 0 °C under HSO_3F-SbF_5 catalysis (eq 11).[24] The isomerization will proceed further to adamantane when excess superacid is used (HSO_3F-SbF_5:substrate ratio = 1:3). For the rearrangement of trimethylenenorbornane to adamantane, HSO_3F-SbF_5 is, however, less efficient than CF_3SO_3H-SbF_5 or CF_3SO_3H-$B(OSO_2CF_3)_3$.[25]

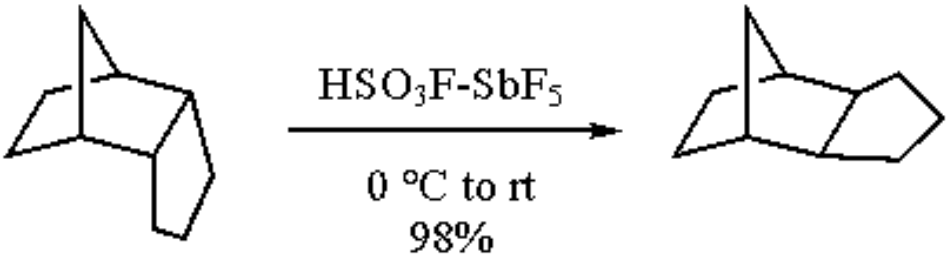

(11)

Alkylation.

Benzene, alkylbenzenes, and halobenzenes undergo alkylation with 2,2,4-trimethylpentane in the presence of HSO_3F-SbF_5 at temperatures as low as -30 °C with good selectivity (eq 12).[26]

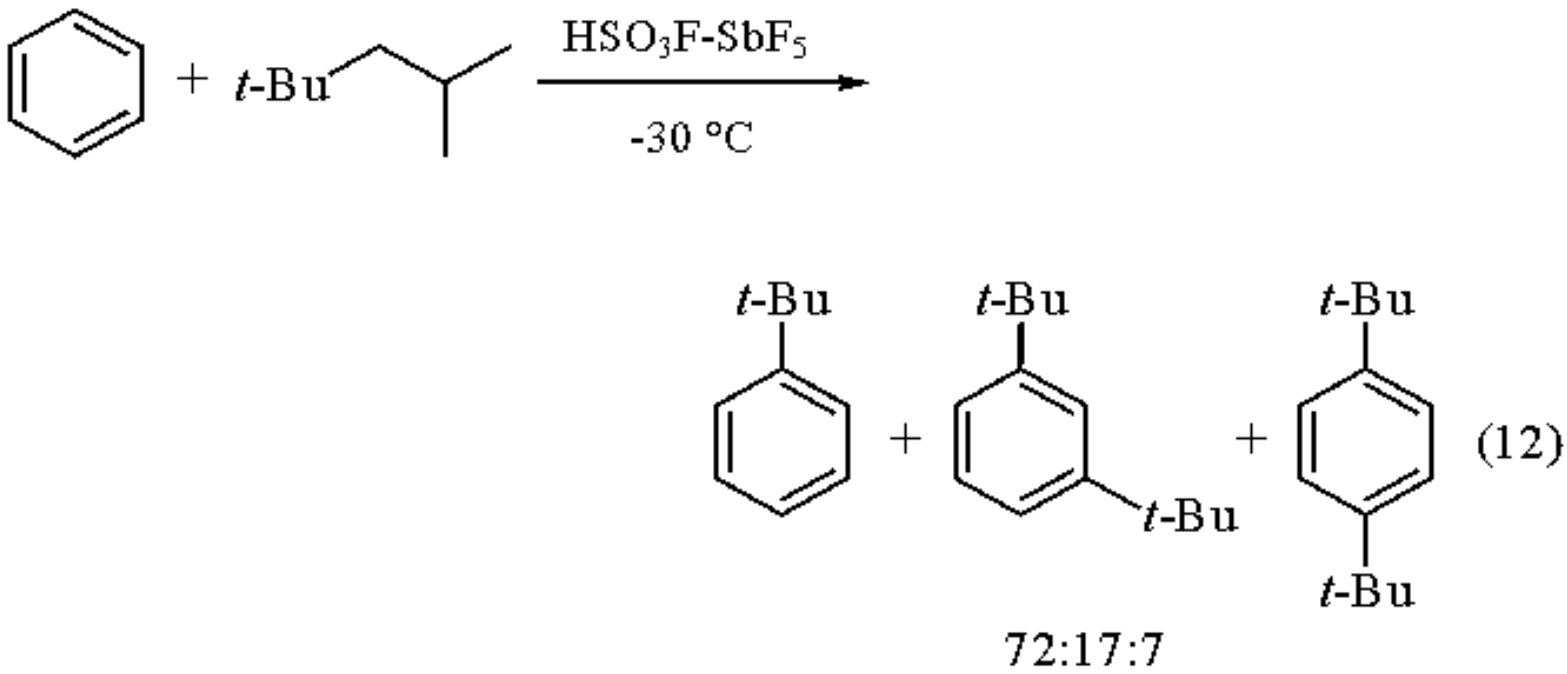

Cyclization.

HSO_3F-SbF_5 has been used as a high-acidity catalyst for the cyclization of acyclic isoprenoids at low temperatures. The reaction course and products of the cationic cyclization depend on the acidity of the catalyst and the structural differences in the substrates. Structural changes may also lead to dramatic changes in the reaction course and products. While geranate esters (eq 13)[27] and pseudoionones (eq 14)[28] are cyclized to monocyclic derivatives, geraniol or nerol (eq 15)[29] and geranylacetone (eq 16)[30] give bicyclic ethers.

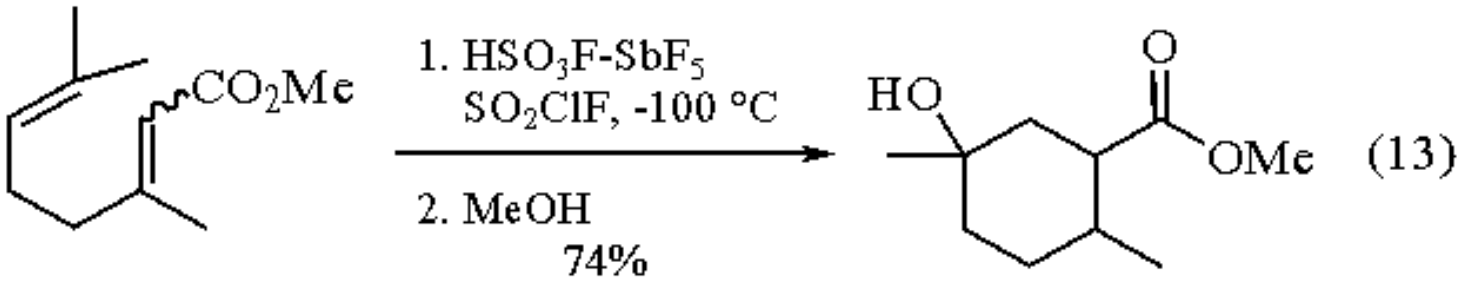

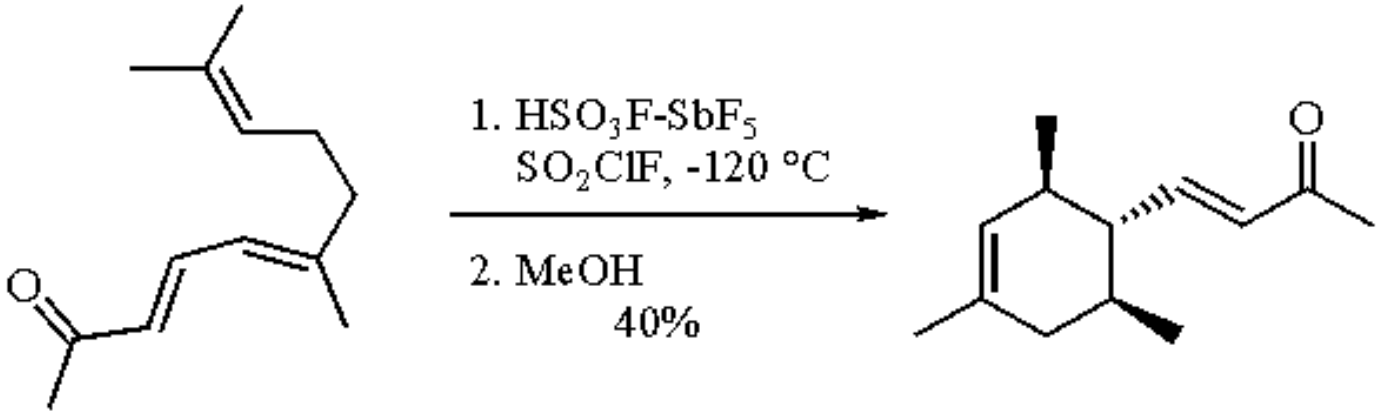

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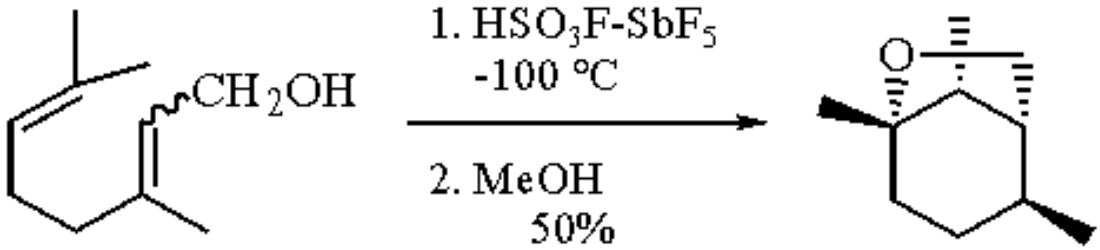

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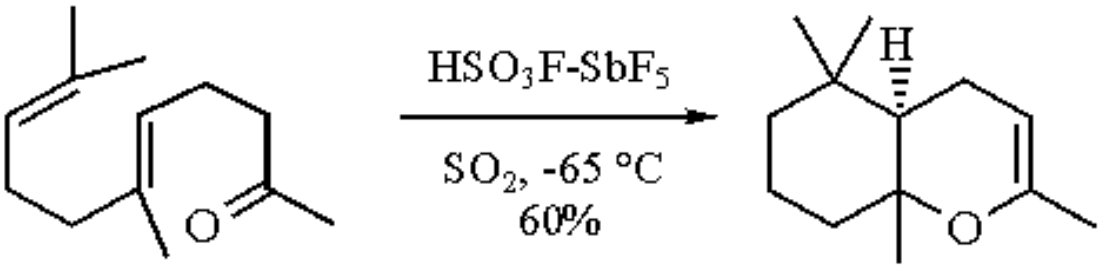

(16)

Sulfonation and Fluorosulfonation.

Aromatic compounds react with HSO_3F to give arenesulfonyl fluorides.[31] When the reactions are carried out in the presence of variable amounts of SbF_5, significant amounts of diaryl sulfones are obtained (eq 17).[32] In this example, the yields of arenesulfonyl fluorides decreased with increasing amounts of SbF_5. In contrast, the yields of diaryl sulfones first increased and then decreased with increasing amounts of SbF_5. The highest yield of diphenyl sulfone was obtained when the molar ratio of SbF_5:benzene was 1:1.5. Diaryl sulfones were also obtained in high yield from toluene, xylenes, and 1,2,4-trimethylbenzene under similar conditions. Sulfonation of fluoro-, chloro-, and bromobenzenes required higher molar ratios of SbF_5:arene (1:3.5) to obtain good yields of the corresponding diaryl sulfones.

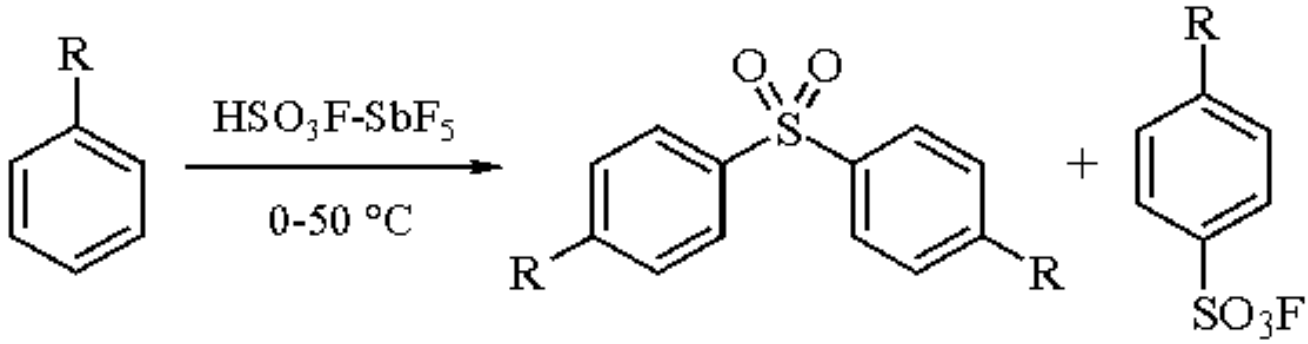

(17)

R = H	94%	4%
R = Me	95%	1%
R = F	83%	0%

Formation of Aromatic Sulfoxides.

By treatment with HSO_3F-SbF_5 (1:1) and ***Sulfur Dioxide***, alkylbenzenes, halobenzenes, and alkylhalobenzenes were converted to their corresponding diaryl sulfoxides along with small amounts of diaryl sulfides as minor products (eq 18).[33] In the absence of SO_2, aryl sulfone formation is the dominant process, although sulfoxide is also formed. Unsymmetrical (mixed) sulfoxides can be prepared by addition of one molar equivalent of an arene to the solution of the second arene and Magic Acid-SO_2 in Freon at low temperatures.

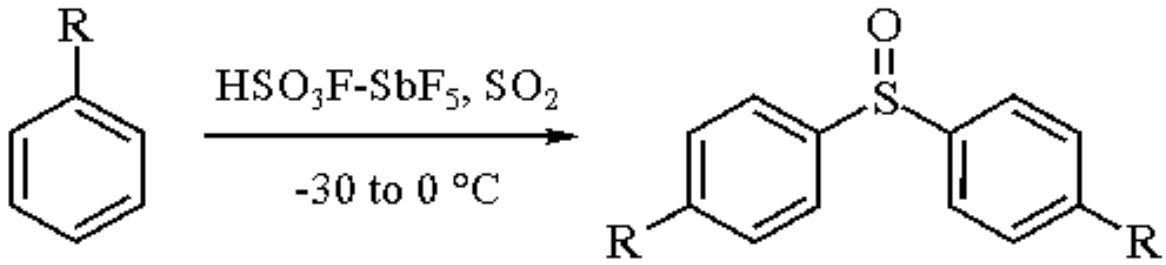

(18)

R = Me, 87%; F, 55%

Formylation and Carboxylation.

Formylation of aromatic compounds such as benzene, toluene, xylenes, mesitylene, indan, tetralin, and halobenzenes is achieved in HSO_3F-SbF_5 under atmospheric CO pressure at 0 °C (eq 19).[34] However, in the cases of alkylbenzenes, both formylation and sulfonation took place under these reaction conditions to give alkylbenzaldehydes and formylalkylbenzenesulfonyl fluorides, as well as small amounts of alkylbenzenesulfonyl fluorides and bis(alkylphenyl) sulfones. With benzene and halobenzenes, because of their lower reactivity only aldehydes were produced.

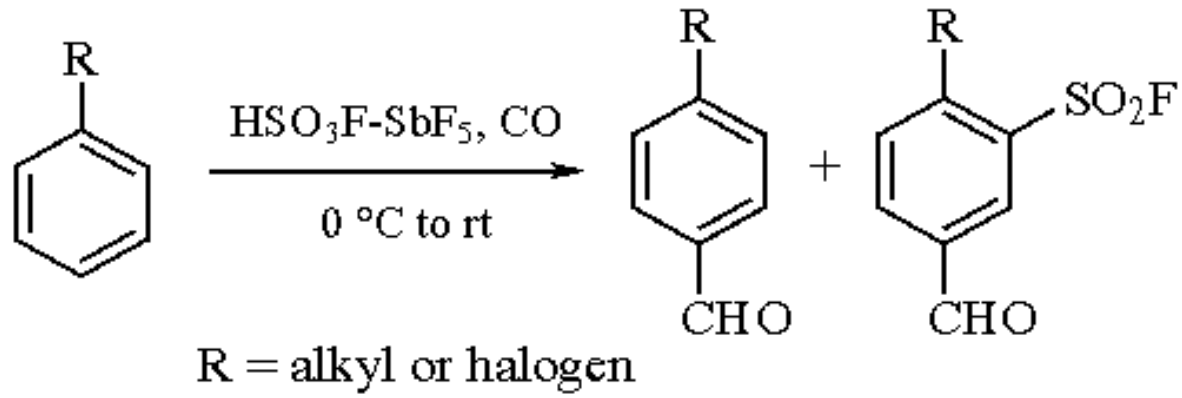

(19)

Saturated hydrocarbons, including branched and unbranched chain alkanes as well as cycloalkanes, react with carbon monoxide in the presence of ***Copper(I) Oxide*** in HSO_3F-SbF_5 to afford tertiary and secondary carboxylic acids in high yield (eq 20).[35] The reaction proceeds at 0 °C under 1 atm CO. In some cases the reaction involves cleavage of C-C bonds and isomerization of the intermediate carbocations.

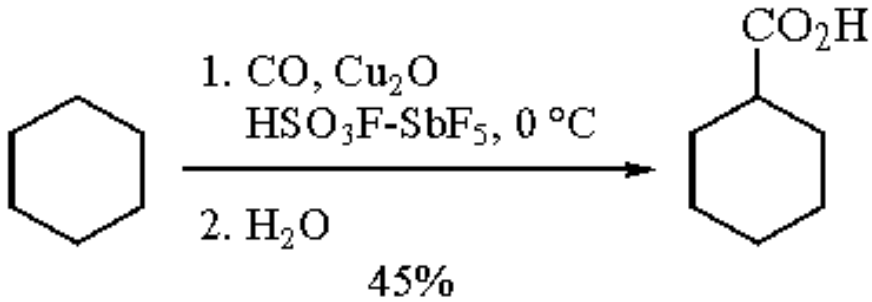

(20)

Oxyfunctionalization of Hydrocarbons.

When treated with ***Ozone***[36] or ***Hydrogen Peroxide*** (98%)[37,38] under Magic Acid catalysis, alkanes, including methane, ethane, butanes, and higher alkanes as well as haloalkanes,[39] undergo electrophilic oxygenation followed by carbon-to-oxygen alkyl group migration giving, via alkoxycarbenium ions, ketones and alcohols (eq 21). Aliphatic alcohols, ketones, and aldehydes react with ozone in Magic Acid solution to give bifunctional oxygenated derivatives such as diketones, hydroxyl ketones, and glycols (eq 22).[40] The relative reactivity of σ-bonds in alkanes with protonated ozone was found to be R_3C-H > $R_2(H)C$-H > $R(H_2)C$-H > C-C.[36]

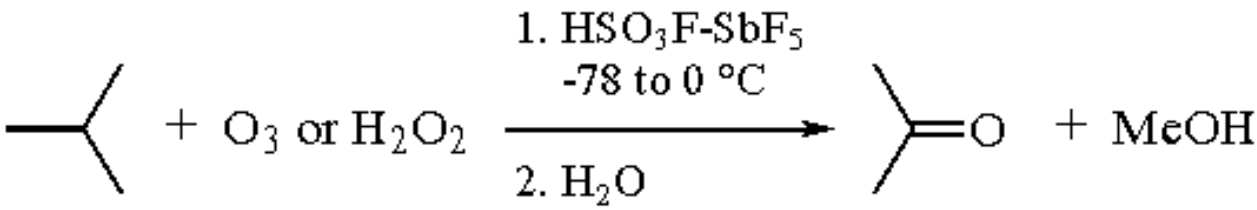

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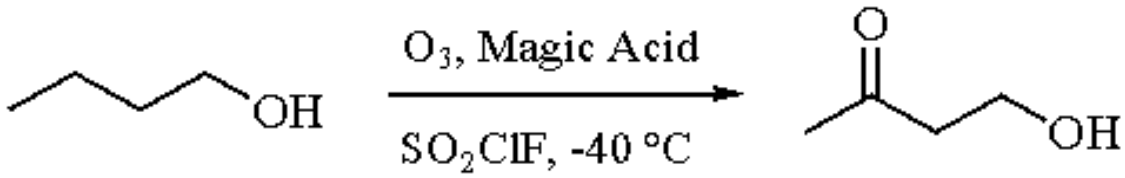

(22)

Aromatic compounds such as benzene, alkylbenzenes, and halobenzenes can be directly oxygenated with hydrogen peroxide in Magic Acid or other superacids, giving phenols (eq 23).[41] The phenols formed are protonated by the superacids and thus are deactivated against further electrophilic attack or oxidation. When naphthalene was treated with hydrogen peroxide in Magic Acid at -78 °C, 2-naphthol was obtained (92% regioselectivity) along with small amounts of dihydroxynaphthalenes (eq 24).[42] Unlike phenol derivatives, naphthols can be further hydroxylated with hydrogen peroxide in superacid systems to dihydroxynaphthalenes, since the unprotonated ring of the protonated naphthols can still be attacked by the electrophilic hydroxylating agent.

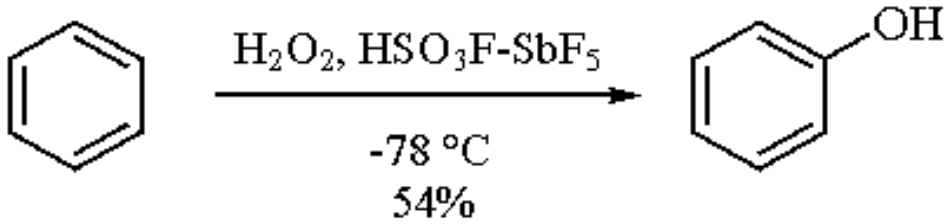

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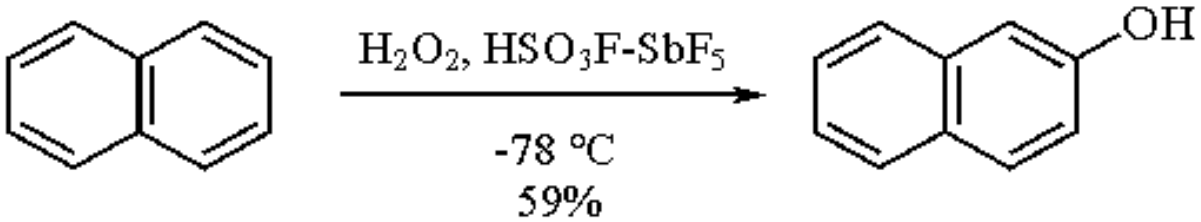

(24)

Miscellaneous Reactions.

In the presence of HSO_3F-SbF_5, ***Peroxydisulfuryl Difluoride*** ($S_2O_6F_2$) reacts smoothly with 1,1,2-trichlorotrifluoroethane at rt to give 1,2-dichlorotrifluoroethyl fluorosulfate (eq 25).[43] $S_2O_6F_2$ alone does not react with 1,1,2-trichlorotrifluoroethane even at 150 °C, while in the presence of HSO_3F the reaction occurs only at temperatures higher than 150 °C.

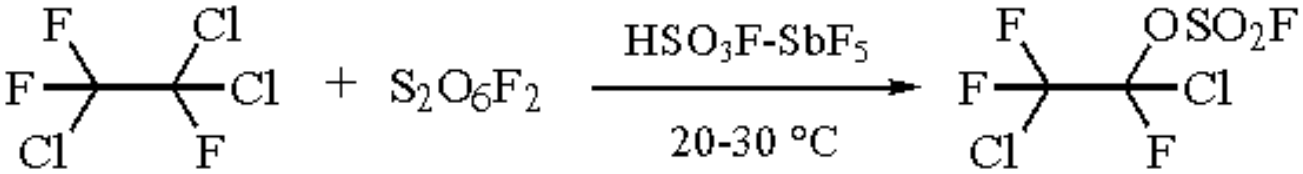

(25)

Polyfluoroarenes, such as *m*-$H_2C_6F_4$, *m*-$O_2NC_6F_4H$, *m*- and *p*-BrC_6F_4H, $(p\text{-}HC_6F_4)_2$, C_6F_5H, 1,3,5-$F_3C_6H_3$, and *m*-$FSO_2C_6F_4H$, have been thallated by ***Thallium(III) Trifluoroacetate*** in HSO_3F-SbF_5. The thallated products can be converted to polyfluoroiodoarenes by treatment with aqueous ***Sodium Iodide*** (eq 26).[44]

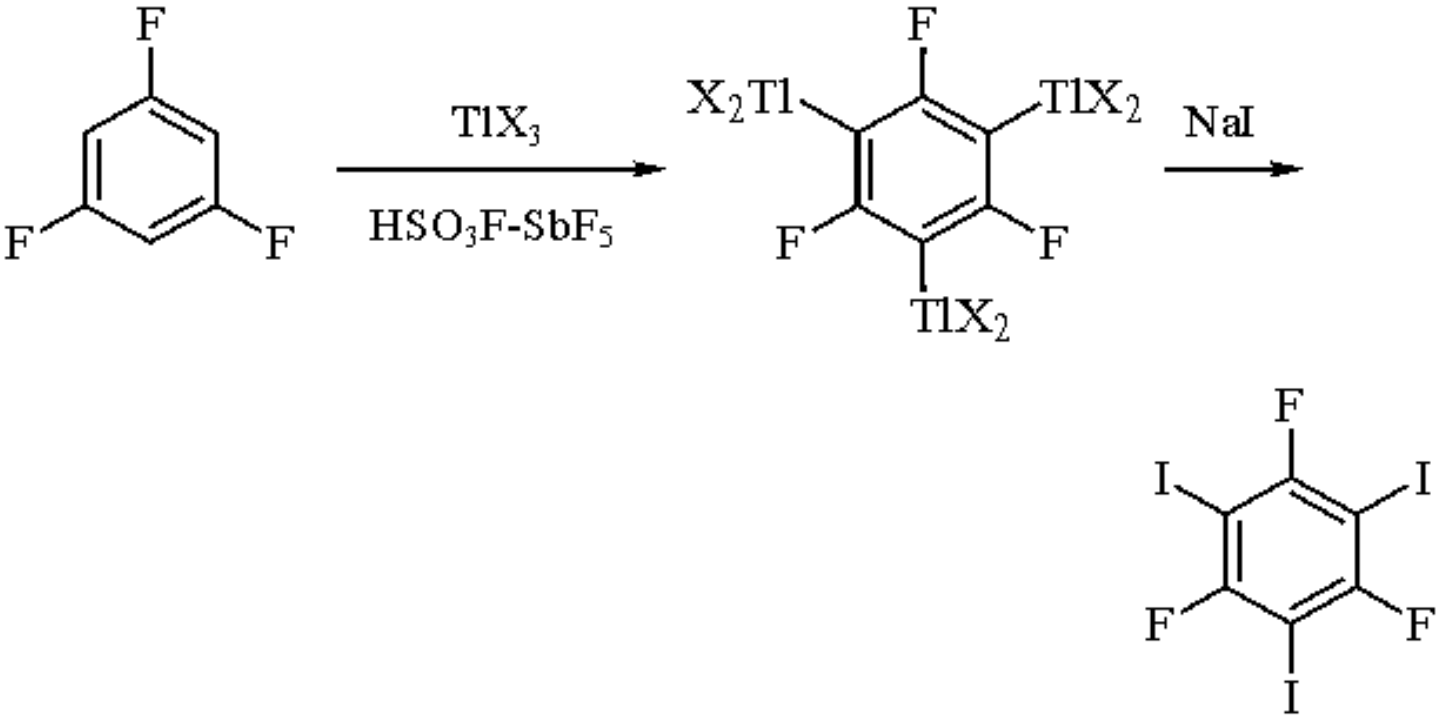

(26)

Although HSO_3F-SbF_5 is known to be a strong oxidizing system, it has been reported that octafluoroazoxybenzene was reduced by HSO_3F-SbF_5 at 20 °C to octafluoroazobenzene in quantitative yield (eq 27).[45] The mechanism of the process is still unclear.

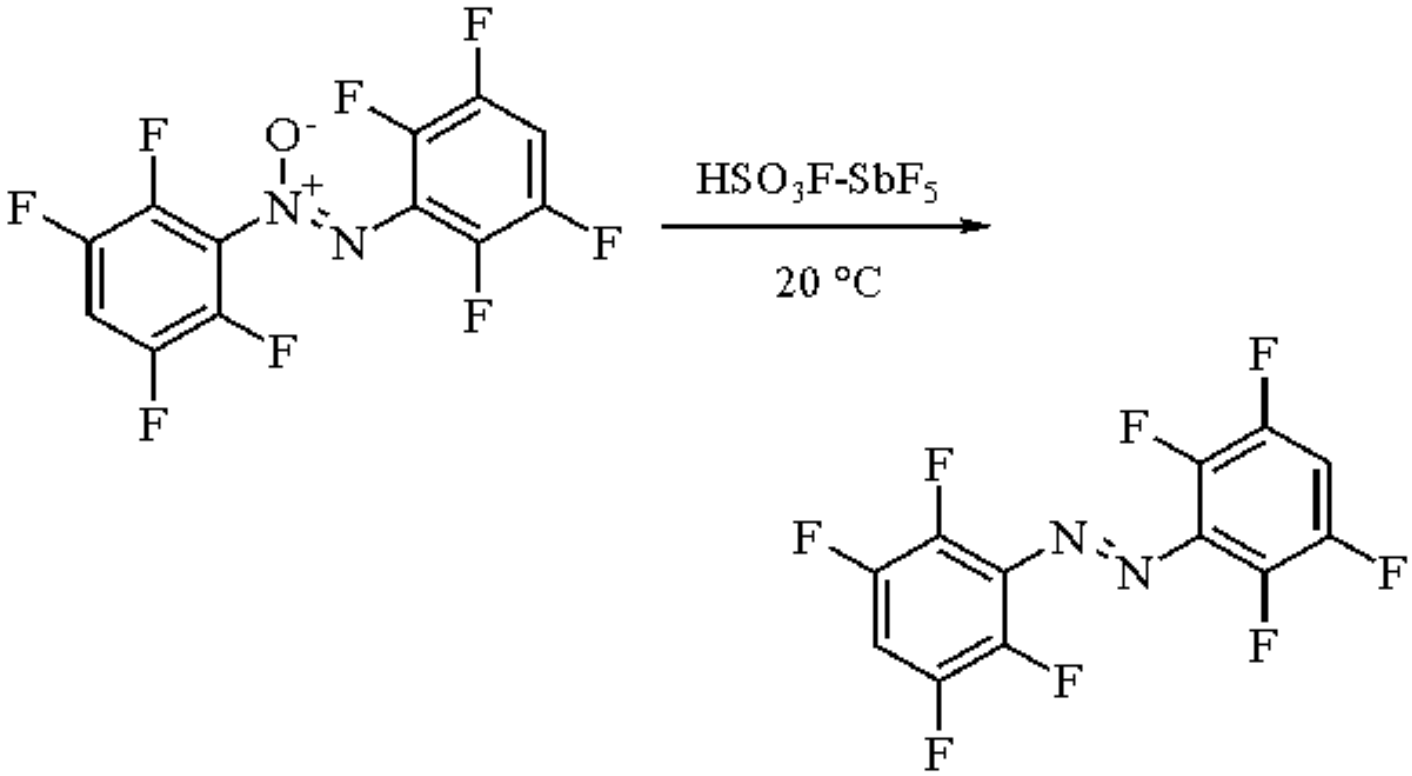

(27)

Isoalkanes are brominated by Br_2 in HSO_3F-SbF_5 to yield mono-, di-, and tribromoalkanes (eq 28).[46] Cleavage of C-C bonds occurs when isooctane is reacted under similar conditions, leading to butyl bromides.

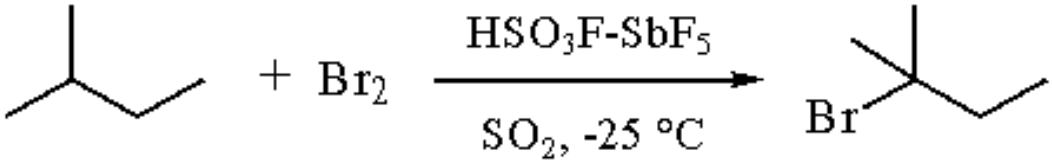

(28)

Fluorinative dediazoniation of an arenediazonium salt occurred at 0 °C in Magic Acid; (eq 29)[47] however, fluorosulfonation accompanied the dediazoniation.

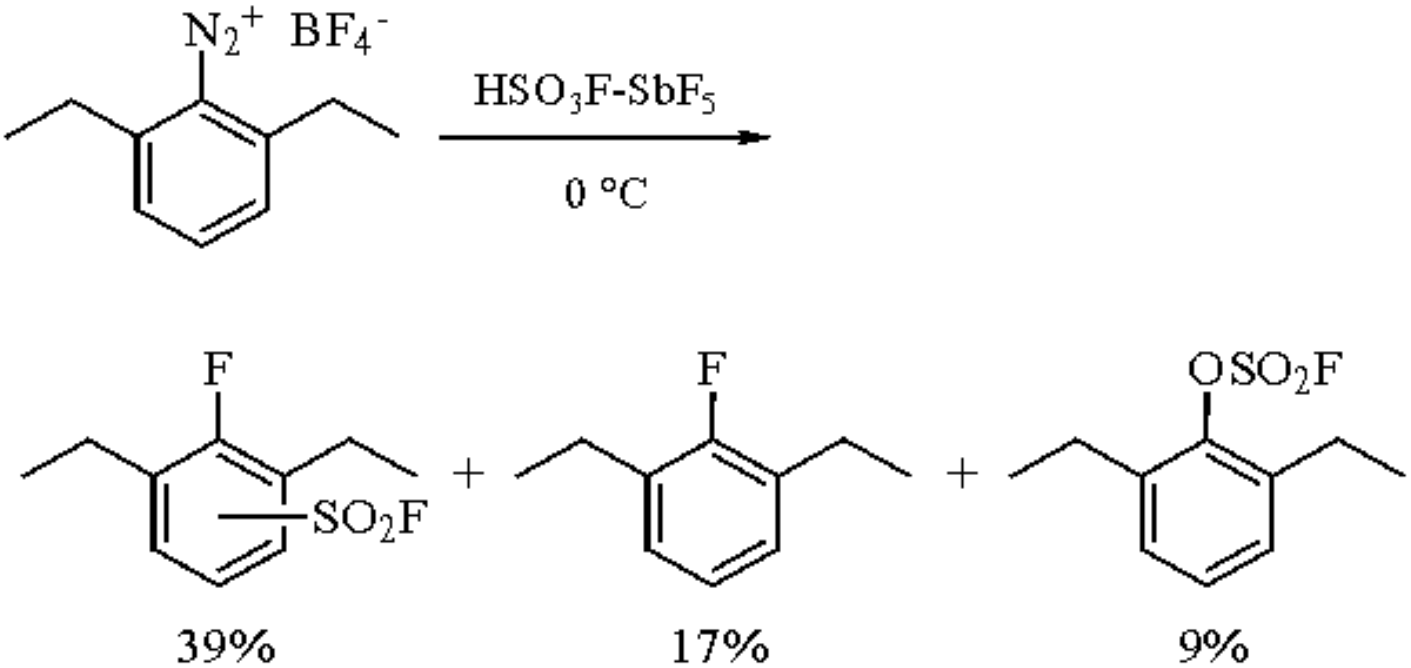

(29)

Related Reagents.

Antimony(V) Fluoride; ***Fluorosulfuric Acid***; ***Hydrogen Fluoride***; ***Hydrogen Fluoride-Antimony(V) Fluoride***.

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Fluorotributyl(methyl)phosphorane

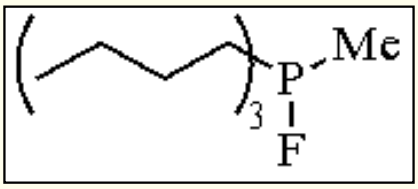

[36121-19-4] · $C_{13}H_{30}FP$ · Fluorotributyl(methyl)phosphorane · (MW 236.40)

(fluorinating reagent[1-3] and fluoride source for silicon displacement[1])

Alternate Names: tributyl(methyl)phosphonium fluoride; tributylfluoro(methyl)phosphorane.

Physical Data: bp 74-76 °C/0.1 mmHg;[4,5] mp 11-13 °C.[5]

Solubility: sol THF, diethyl ether, petroleum ether, benzene, cyclohexane.

Form Supplied in: not commercially available.

Preparative Methods: can be prepared in three steps from commercially available starting materials. Alkylation of ***Tri-n-butylphosphine*** with ***Iodomethane*** or ***Bromomethane*** gives a phosphonium salt[6] which yields tributylmethylenephosphorane after deprotonation with ***n-Butyllithium*** in ether and subsequent product distillation.[7] The tributylmethylenephosphorane is then treated with ***Hydrogen Fluoride*** or KHF_2, and purified fluorotributyl(methyl)phosphorane is obtained by distillation.[4]

Handling, Storage, and Precautions: water sensitive; best kept at -10 °C.[4]

Fluoride Formation.

Fluorotributyl(methyl)phosphorane has been used as a fluorinating reagent in the displacement reactions of alkyl bromides, chlorides, and tosylates.[1-3] For the fluoride displacement of benzyl chloride, fluorotributyl(methyl)phosphorane at -78 °C gives an 80% yield, whereas fluorotriethyl(methyl)phosphorane and fluorotrimethyl(phenyl)phosphorane give only a 20% yield.[1]

Fluorotributyl(methyl)phosphorane is a milder fluorinating reagent for sensitive functionality than ***Potassium Fluoride*** with a crown ether.[8] A bromoepoxide will undergo fluoride displacement with fluorotributyl(methyl)phosphorane but will decompose under KF-crown ether conditions (eq 1).[2]

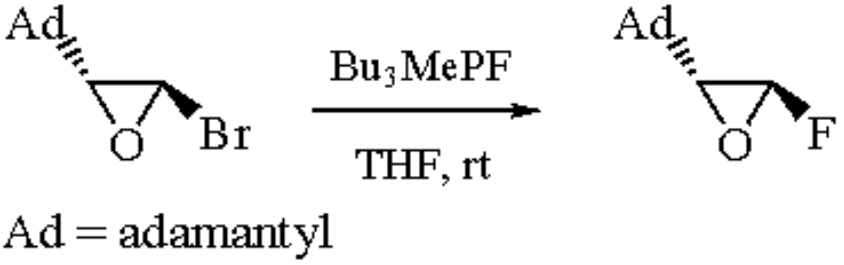

(1)

Secondary alkyl halides undergo elimination to afford alkenes; secondary alkyl tosylates give mixtures of alkyl fluorides and alkenes.[2,3] A comparison of fluorotributyl(methyl)phosphorane with other fluorinating reagents in the displacement of the secondary alcohol 2-hydroxyoctanol and derivatives thereof was made (eq 2).[3] The highest optical purity in the displacement reaction was obtained with fluorotributyl(methyl)phosphorane (X = OTs); however, this reagent also gave the most alkene (Table 1). ***(2-Chloro-1,1,2-trifluoroethyl)diethylamine*** (FAR) gave the best fluoride:alkene ratios. After publication of this comparison of fluorinating reagents, anhydrous ***Tetra-n-butylammonium Fluoride*** (TBAF) was shown to give a better fluorooctane yield (54%) and a higher optical purity than fluorotributyl(methyl)phosphorane (+14.2° vs. +13.6°).[9]

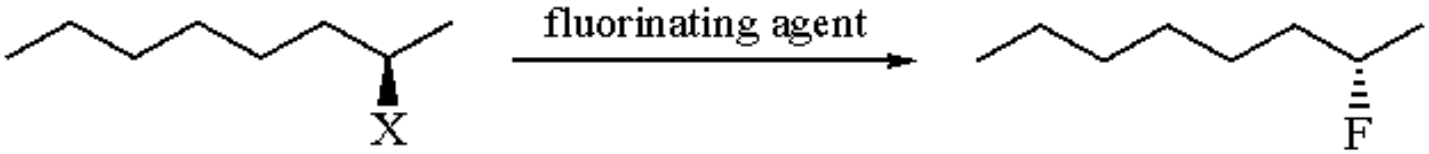

(2)

Table 1 Fluorinating Agents for S_N2 Displacement

Substrate	Reagent	Ratio (fluoro-octane: octenes)	Yield (%) (2-fluoro-octene)	Optical yield
(-)-$C_6H_{13}CH(OTs)Me$	Bu_3MePF	40:60	15	100
(+)-$C_6H_{13}CH(OTMS)Me$	$PhPF_4$	58:22	11	68
(+)-$C_6H_{13}CH(OH)Me$	FAR	78:22	40	88
(+)-$C_6H_{13}CH(OH)Me$	DAST[a]	48:52	23	98
(-)-$C_6H_{13}CH(OTs)Me$	KF	50:50	31	91

[a] DAST = *N,N*-diethylaminosulfur trifluoride

Aldol Condensation.

Fluorotributyl(methyl)phosphorane can act as a desilylating agent in the aldol condensation of the silyl enol ether of cyclohexanone with benzaldehyde (eq 3).[1] Similar yields are obtained with the more readily available TBAF.

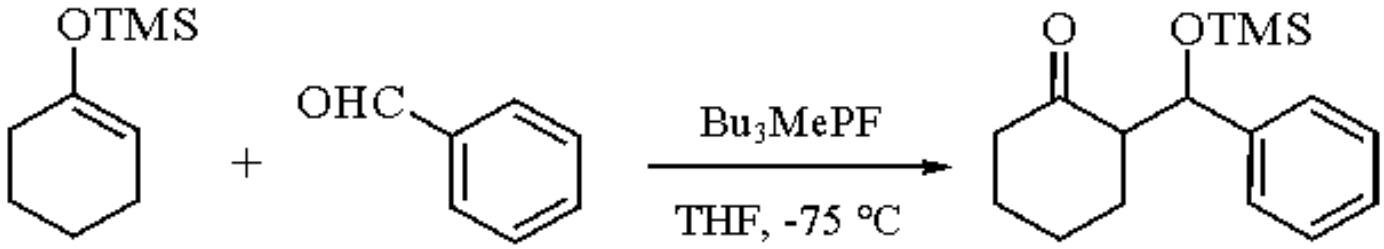

(3)

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Fluorotrimethylsilane

Me_3SiF

[420-56-4] · C_3H_9FSi · Fluorotrimethylsilane · (MW 92.21)

(capable of silylating ketones, alcohols, and terminal alkynes[3,4])

Alternate Name: TMSF.

Physical Data: bp 19 °C/730 mmHg.[1]

Solubility: sol most organic solvents.

Preparative Methods: from ***Chlorotrimethylsilane*** (TMSCl) by direct treatment with ***Hydrofluoric Acid***.[1,2] TMSF can also be generated in situ by reaction of ***Ethyl Trimethylsilylacetate*** (ETSA) and ***Tetra-n-butylammonium Fluoride*** (TBAF).[3]

Handling, Storage, and Precautions: typically generated in situ or used as prepared.

Ketones, alcohols, and terminal alkynes can be silylated in excellent yields using TMSF that has been generated in situ from ETSA and catalytic TBAF (eq 1).[3,4] Ketones silylated in this manner often show high regioselectivity as compared to those silylated with TMSCl.[3]

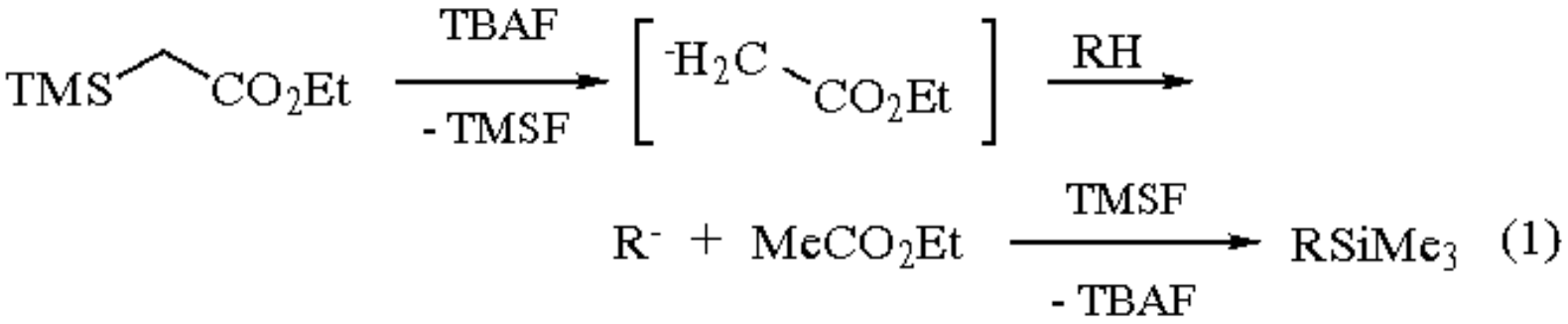

Addition of an aldehyde or ***N-Bromosuccinimide*** to the crude reaction mixture also afforded an aldol[3,4] or brominated product in good yield (eqs 2 and 3).[3]

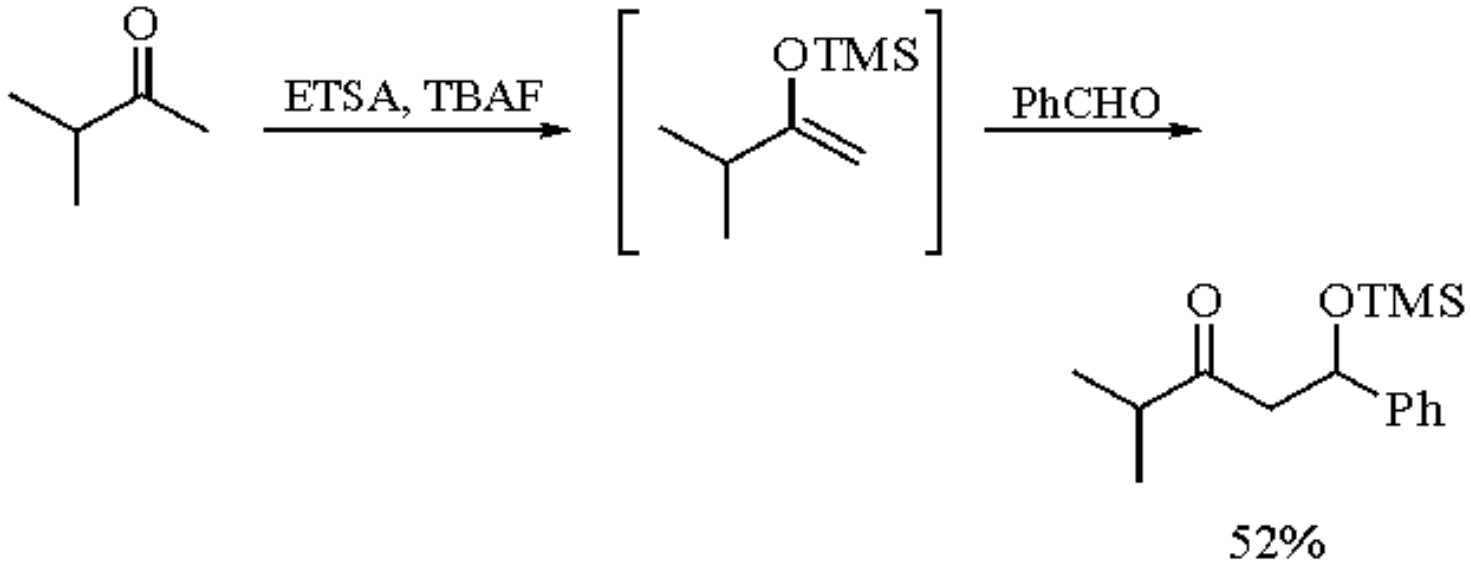

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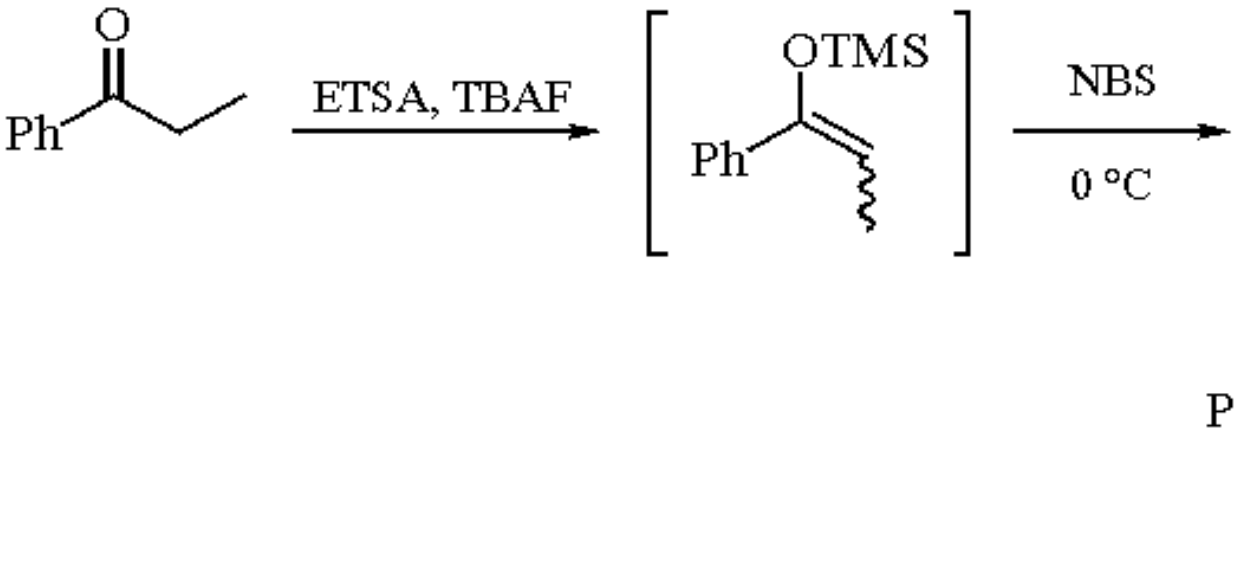

(3)

Carbonyl compounds possessing no acidic α-protons undergo a Reformatsky-type reaction under ETSA-TBAF conditions to afford β-siloxy esters which can then be hydrolyzed to β-hydroxy esters (eq 4).[3]

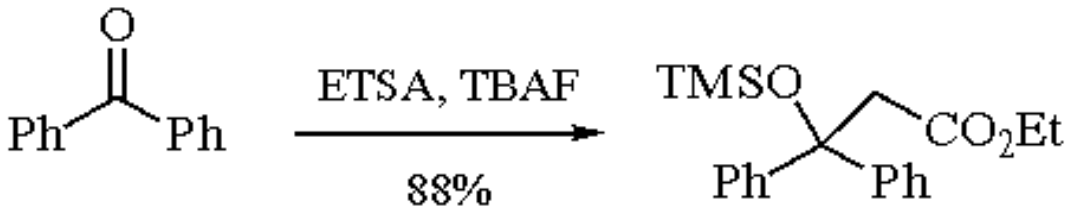

(4)

Related Reagents.

Trimethylsilyl Nonaflate.

1. Marans, N. S.; Sommer, L. H.; Whitmore, F. C. *JACS* **1951**, *73*, 5127.
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Formaldehyde

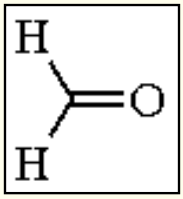

[50-00-0] · CH_2O · Formaldehyde · (MW 30.03) ($(CH_2O)_n$)

[30525-89-4] ($3CH_2O$)

[110-88-3]

(ene reaction;[1,2] Prins reaction;[1,3] enolate trapping;[4] alkylation; Mannich reaction; acetalization; condensation; reduction)

Alternate Names: paraformaldehyde; *s*-trioxane.

Physical Data: monomeric formaldehyde: mp -92 °C; bp -19.5 °C; *d* 1.067 g cm^{-3}. Paraformaldehyde: mp 163-165 °C (dec). *s*-Trioxane: mp 64 °C, bp 114.5 °C, *d* 1.17 g cm^{-3} (65 °C); sublimes readily.

Solubility: formaldehyde gas: v sol water, up to 55%; sol alcohol, ether. Paraformaldehyde: slowly sol cold water; readily sol hot water with evolution of formaldehyde; insol alcohol, ether. *s*-Trioxane: readily sol water (21.1 g/100 mL at 25 °C), alcohols, ether, acetone, chlorocarbons, aromatics; sl sol pentane.

Form Supplied in: 37% aqueous solution (with 10 to 15% methanol to prevent polymerization) known as formalin; colorless and pungent liquid. Paraformaldehyde: polymer as a white crystalline powder. *s*-Trioxane: crystalline solid.

Preparative Methods: dry formaldehyde may be generated by heating solid paraformaldehyde or by decomposing with barium peroxide; ethereal solutions of monomeric formaldehyde can be obtained by pyrolysis of paraformaldehyde at 150 °C in a special apparatus; can be generated in situ from trioxane by ***Methylaluminum Bis(2,6-diphenylphenoxide)*** (MAPH).[15]

Handling, Storage, and Precautions: reported to be storable for an extended period at -78 °C under argon (unchecked *OS* procedure);[5] irritating to mucous membranes; carcinogen; should be used only in a well-ventilated fume hood.

Ene Reaction.

Thermal ene reactions of paraformaldehyde with reactive 1,1-di- and trisubstituted alkenes occur at 180-220 °C.[6,7] β-Pinene, for example, is transformed into nopol upon reaction with formaldehyde at 180 °C (eq 1).[6] Extension of this reaction has been reported using acetic acid-acetic anhydride as solvent.[8]

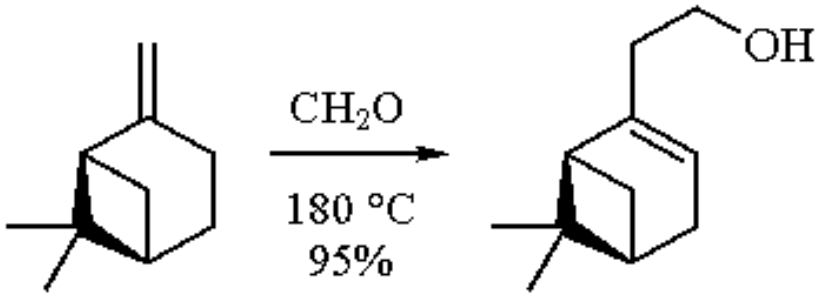

(1)

Lewis acids such as ***Tin(IV) Chloride***[9] and ***Boron Trifluoride Etherate***[10] can facilitate addition of formaldehyde to alkenes to afford ene adducts. Thus reaction with 2,6-dimethyl-2,5-heptadiene in the presence of $SnCl_4$ as catalyst provides lavanduol (eq 2).[11] The $BF_3.Et_2O$-promoted reaction with the ethylidene steroid shown in eq 3 takes place exclusively from the less hindered α-face to produce the ene adduct with the natural steroid configuration at C-20.[12]

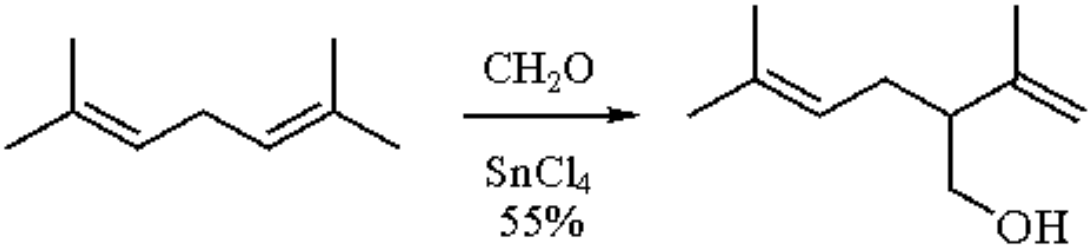

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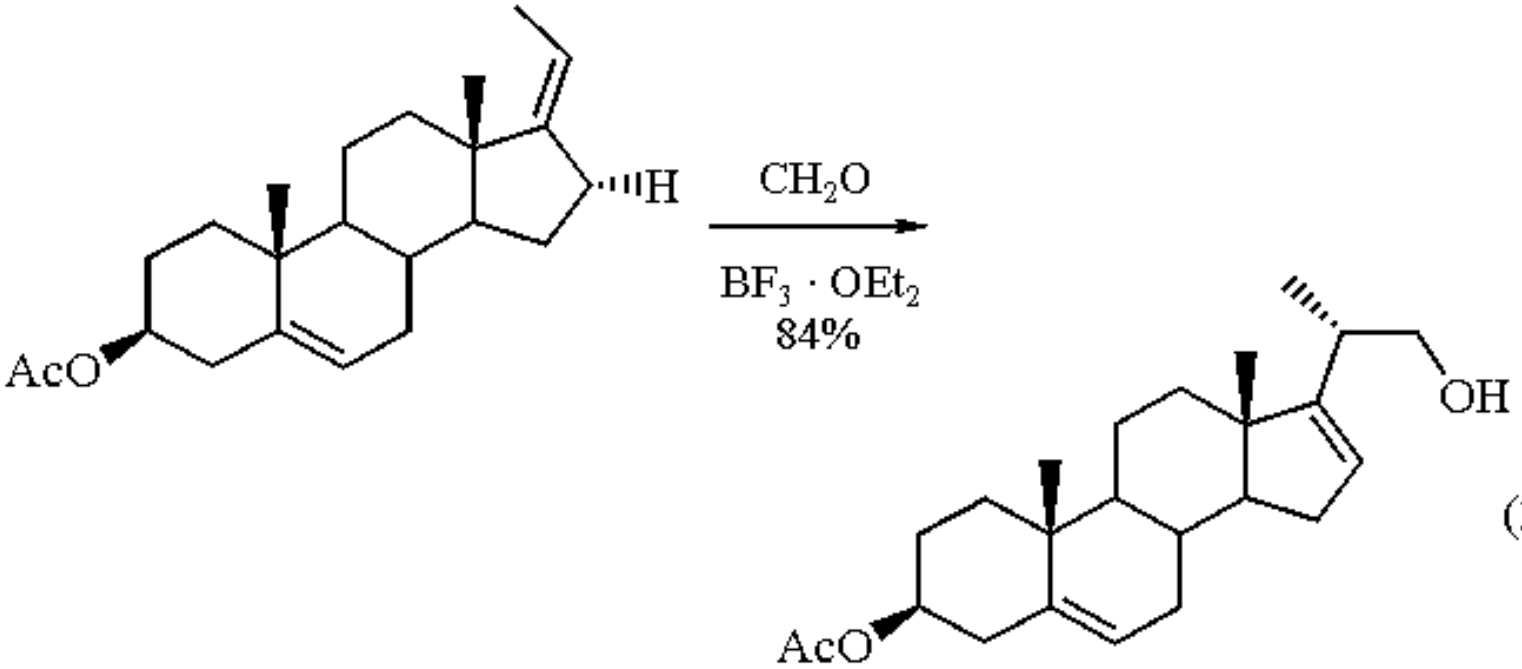

(3)

Organoaluminum reagents can also be utilized as promoters for ene reactions to give homoallylic alcohol ene adducts in high yield and selectivity, although γ-chloro alcohols are formed in some cases as byproducts.[13] ***Diethylaluminum Chloride***-induced ene reactions of formaldehyde with 1,4-dienes occur selectivity at the less deactivated terminal bond,

and subsequent quasi-intramolecular Diels-Alder reaction with formaldehyde as dienophile leads to the formation of a dihydropyran (eq 4).[14] The formaldehyde-dimethylaluminum chloride complex acts on terminal alkynes to afford α-allenic alcohols and (*Z*)-3-chloroallylic alcohols as byproducts in a 2:3 ratio (eq 5).[13b] The aluminum reagent MAPH complexed with formaldehyde, generated from trioxane, also reacts with various alkenes to furnish ene adducts with excellent regioselectivities (see ***Methylaluminum Bis(2,6-diphenylphenoxide)***).[15]

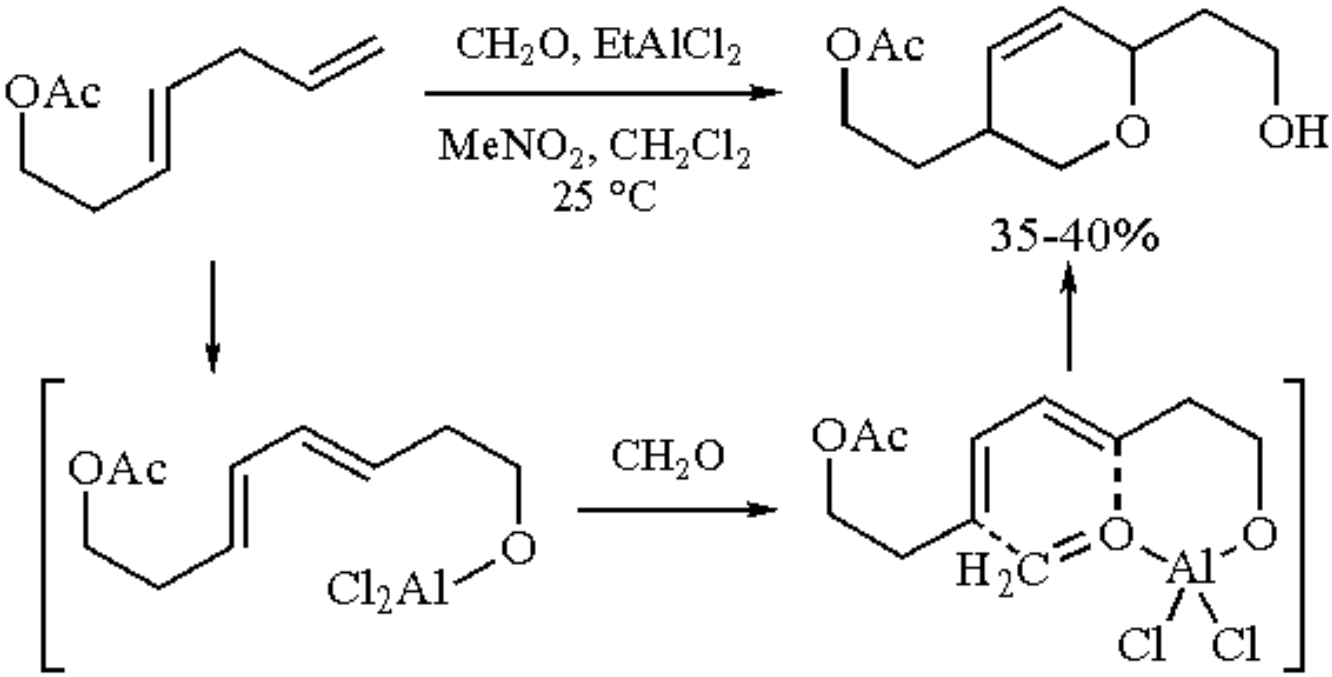

(4)

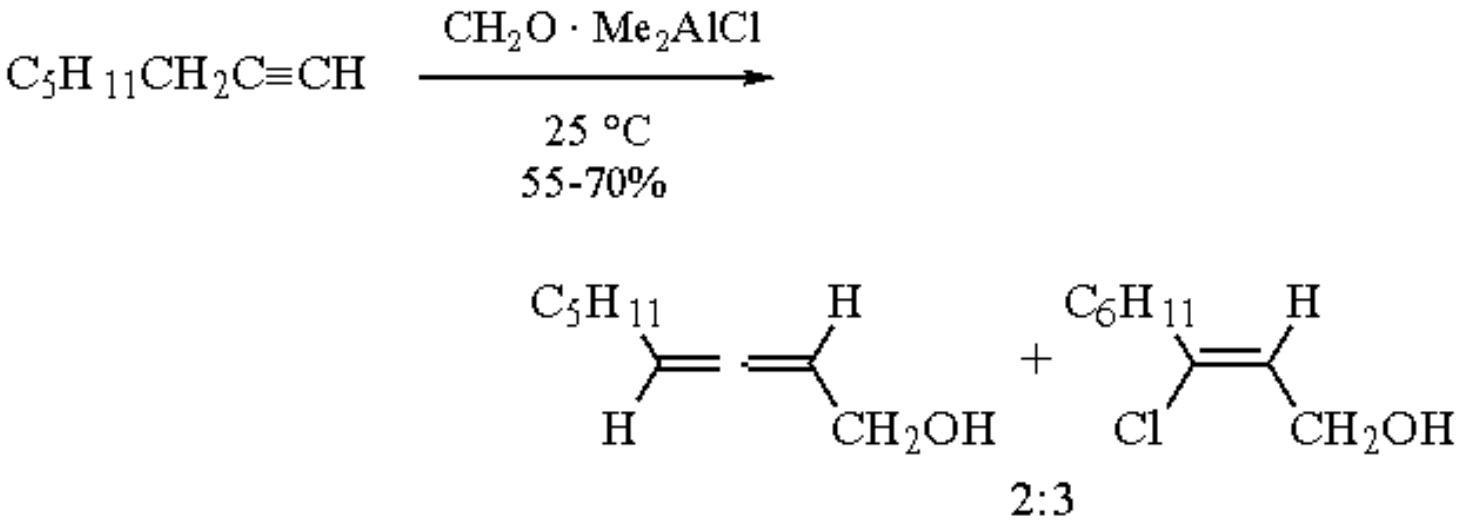

(5)

Prins Reaction.

The condensation of aldehydes and ketones with alkenes in the presence of Brønsted acids is usually called the Prins reaction. The main products of this alkene-aldehyde condensation, depending on experimental conditions, may be a 1,3-dioxane, a 1,3-diol, a homoallylic alcohol, or an α-chloro ether (see ***Formaldehyde-Hydrogen Chloride***).[3]

Various catalysts have been used in the Prins reaction, although in the synthesis of 1,3-dioxane, sulfuric acid seems to be the most efficient. Thus stirring a mixture of formalin, sulfuric acid, and styrene under gentle reflux gives 4-phenyl-

m-dioxane (eq 6).[16]

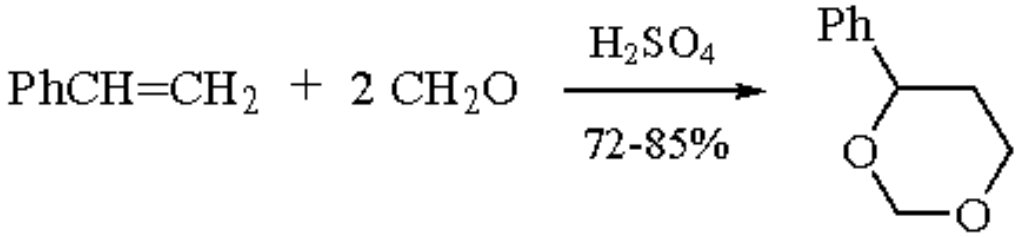

(6)

Prins reactions involving formaldehyde have been used to prepare prostaglandin intermediates. An example is the acid-catalyzed addition of formaldehyde to the unsaturated lactone in acetic acid at 60-80 °C to give a prostaglandin intermediate (eq 7).[17]

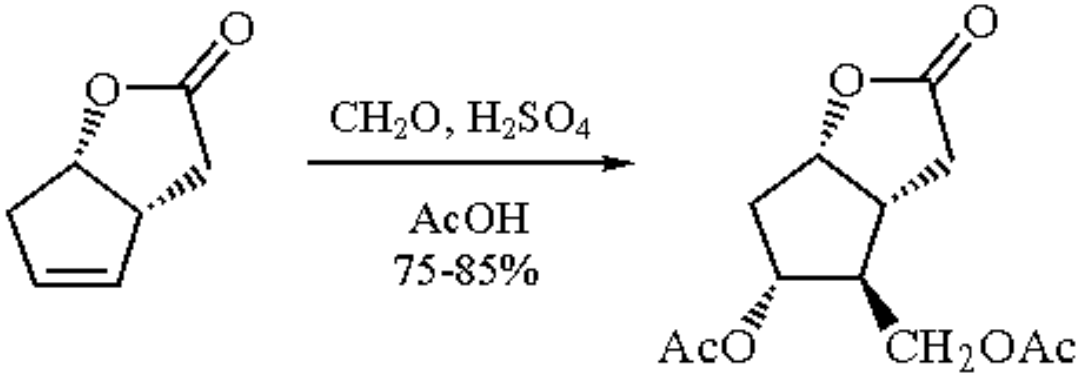

(7)

Reaction of a 1,4-diaryl-1-butene with paraformaldehyde catalyzed by a 1:1 mixture of ***Methylaluminum Dichloride*** and ***Dimethylaluminum Chloride*** resulted in cylization to form a 1-aryltetralin (eq 8). The mixed catalyst was found to be more effective than Me_2AlCl alone.[18]

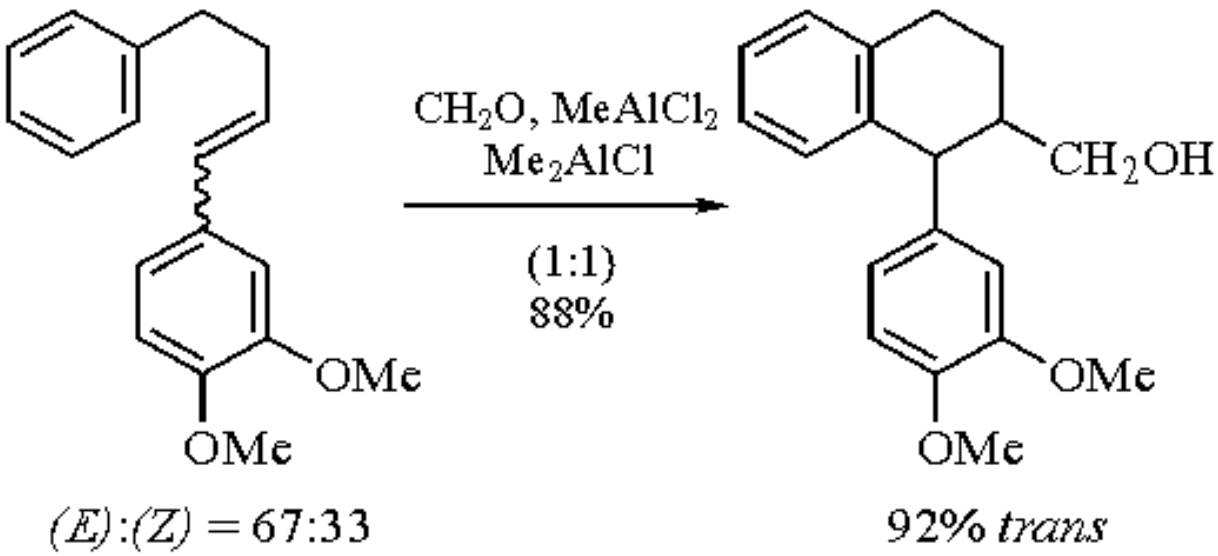

(8)

Enolate Trapping Reactions and Formation of α-Methylene Products.

Lactones when treated with ***Lithium Diisopropylamide*** in THF at -78 °C form enolate anions that react with gaseous formaldehyde to give the α-hydroxymethyl derivative. The product can be easily transformed to an α-methylene lactone by conversion to mesylate followed by treatment with refluxing pyridine (eq 9).[19] This method was used for bis-α-methylenation in the total synthesis of deoxyvernolepin, which contains a dilactone structure (eq 10).[20]

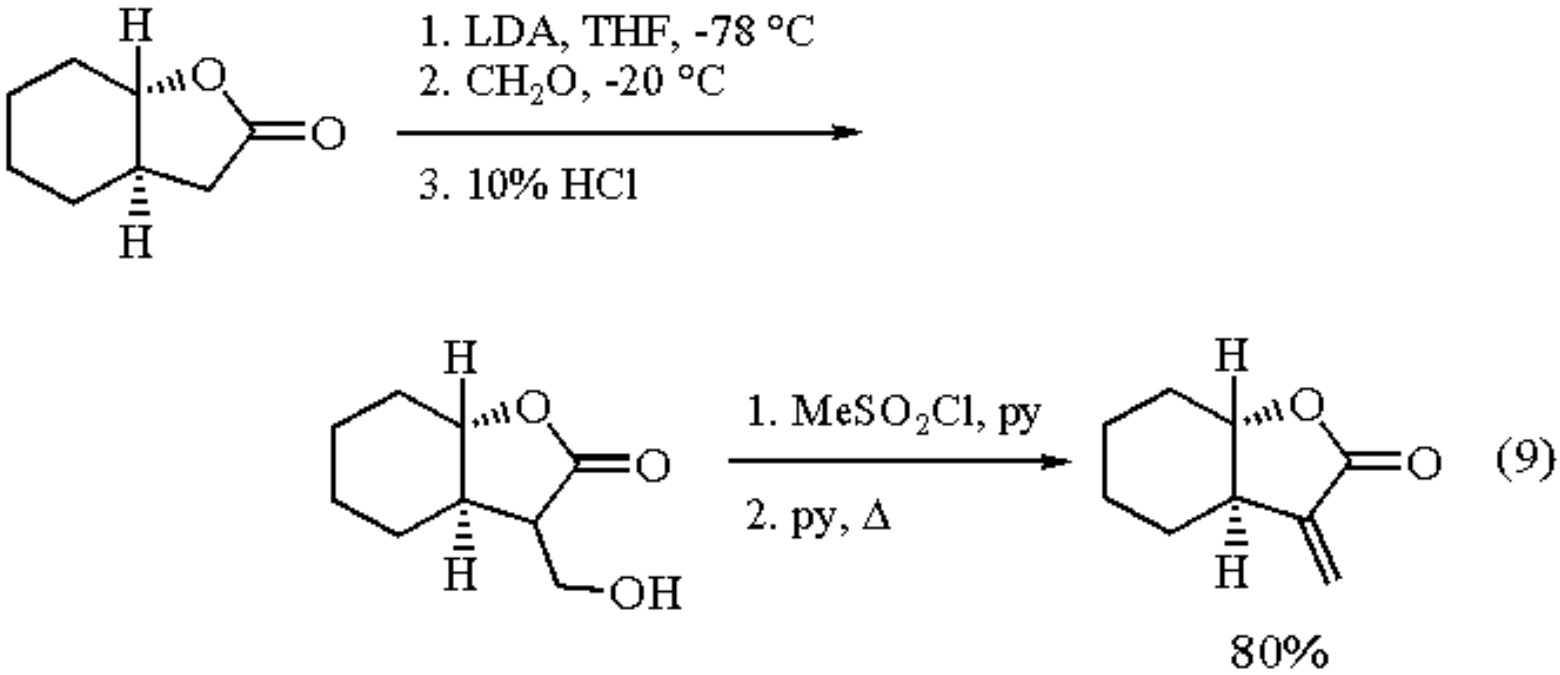

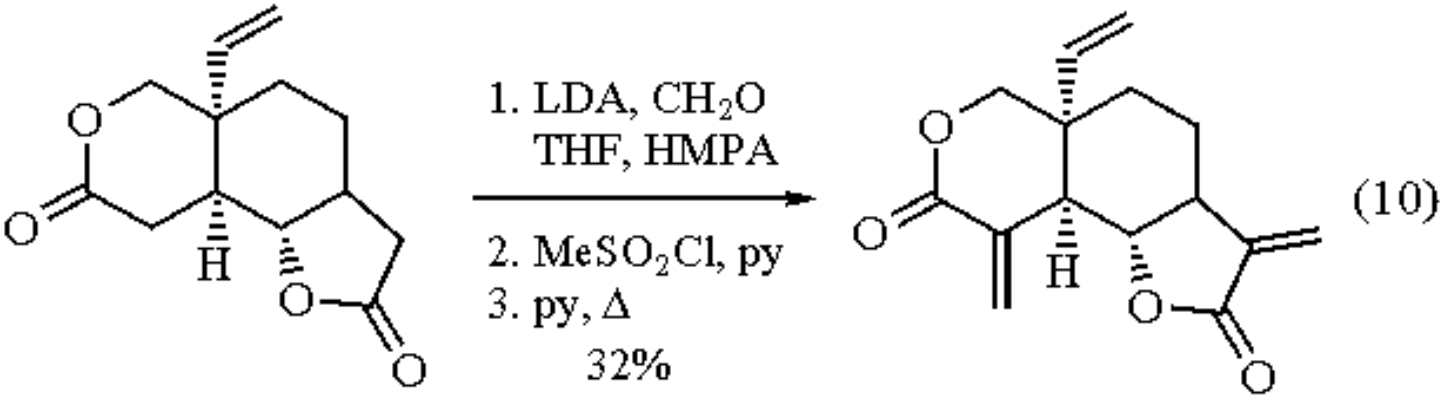

α-Thiobutyrolactones,[21] carboxylic acids,[22] sulfonyl-hydrazones,[23] enol phosphinites,[24] and α,β-enones[25] on treatment with lithium reagents and subsequent reaction with formaldehyde undergo the same reaction, providing aldol adducts.

α-Methylenation products can also result from reaction of the carbanion of α-alkyl β-keto esters or lactones with paraformaldehyde in THF, initially at -78 °C and followed by reflux (eq 11).[26]

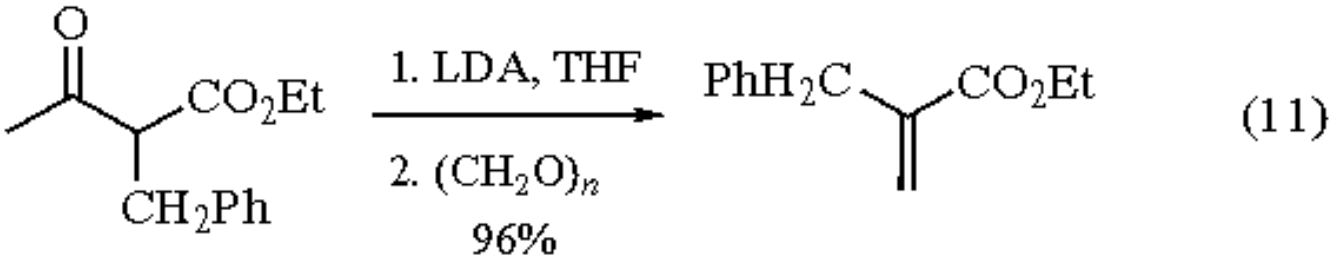

Δ^1-5α-Androsten-3-one in DMSO containing paraformaldehyde and $BF_3.Et_2O$ when heated resulted in formation of the 4-methylene ketone (eq 12).[27]

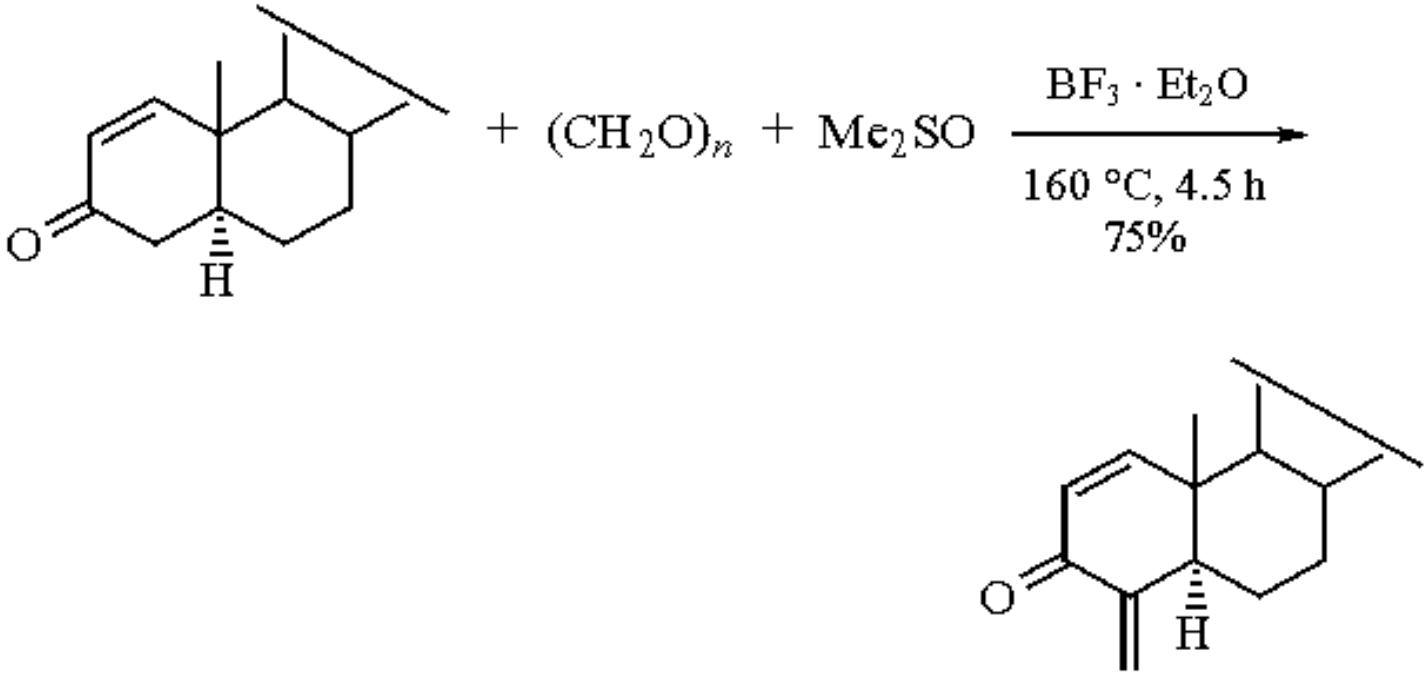

(12)

Reductive Methylation.

The classical method of dimethylation of primary amines or monomethylation of primary and secondary amines involves reaction with formaldehyde and ***Formic Acid*** (eq 13).[28]

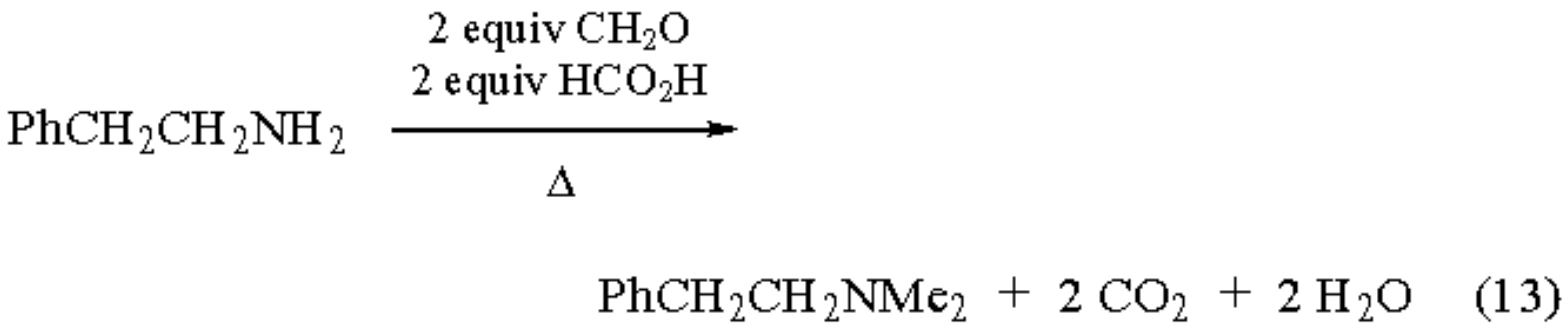

(13)

The use of either ***Sodium Borohydride***[29] or ***Sodium Cyanoborohydride***[30] in place of formic acid leads to the same reaction. However, $NaCNBH_3$ is usually the preferred reducing agent since the methylated amines can be formed without reduction of carbonyl compounds in the substrate.[31]

Potassium hydridotetracarbonylferrate prepared from ***Potassium Hydroxide*** and ***Pentacarbonyliron*** is likewise effective for the dimethylation of primary amines in ethanol under carbon monoxide at 20 °C (eq 14).[32] The use of a 1:1 molar ratio of amine and formaldehyde gives the monomethylated product.

$$PhNH_2 + 2\,CH_2O \xrightarrow[\text{CO, EtOH}]{KHFe(CO)_4} PhNMe_2 \qquad (14)$$

~100%

Carbonyl compounds having α-methyl or α-methylene groups also undergo methylation with formaldehyde in the presence of potassium or ***Sodium Tetracarbonylhydridoferrate*** (eqs 15 and 16).[33]

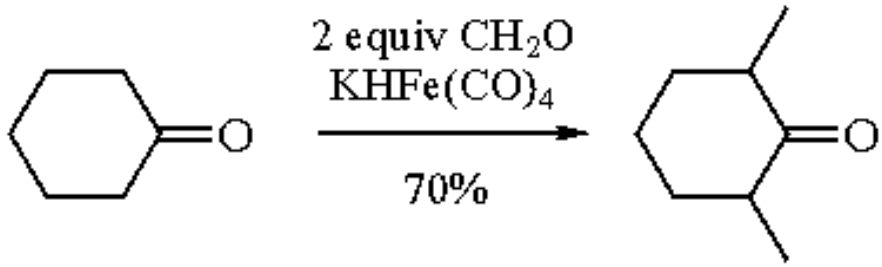

(15)

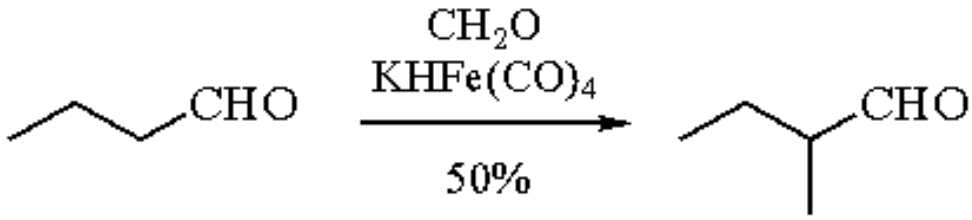

(16)

Ethyl *p*-nitrophenylacetate undergoes reductive methylation upon reaction with aqueous formaldehyde by catalytic hydrogenation with ***Palladium on Carbon*** (eq 17).[34]

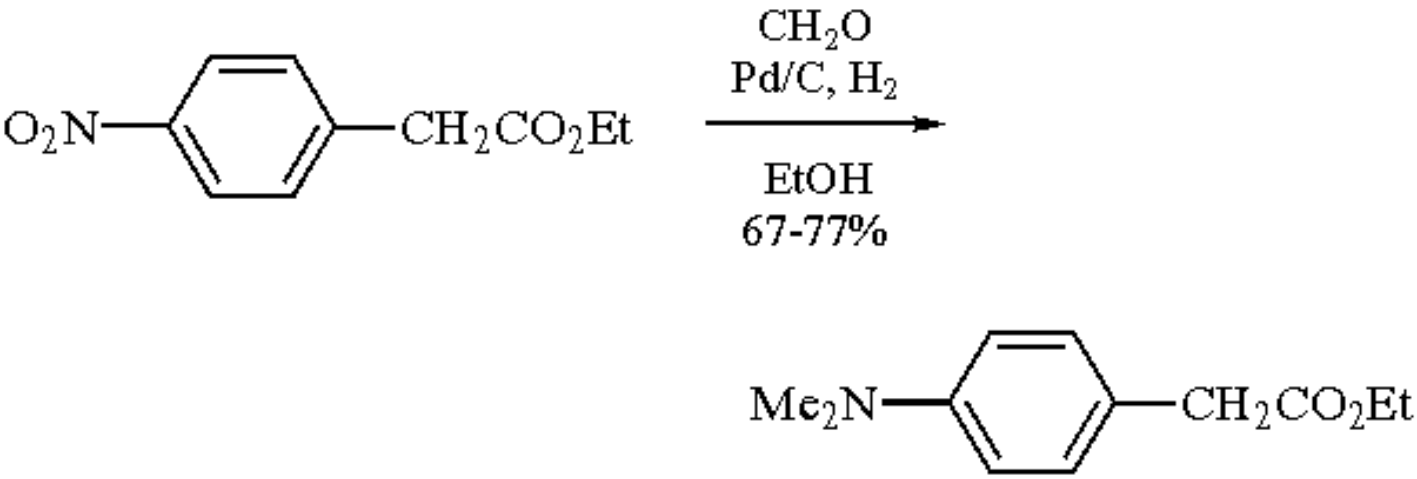

(17)

Hydroxymethylation.

Reaction of carbonyl compounds with formaldehyde in the presence of base results in the formation of hydroxymethylated products. For example, allyl β-keto esters react with formaldehyde and ***Potassium Carbonate*** to give the α-hydroxymethyl ketone in quantitative yield (eq 18).[35] Sugar aldehydes undergo the same reaction with K_2CO_3.[36]

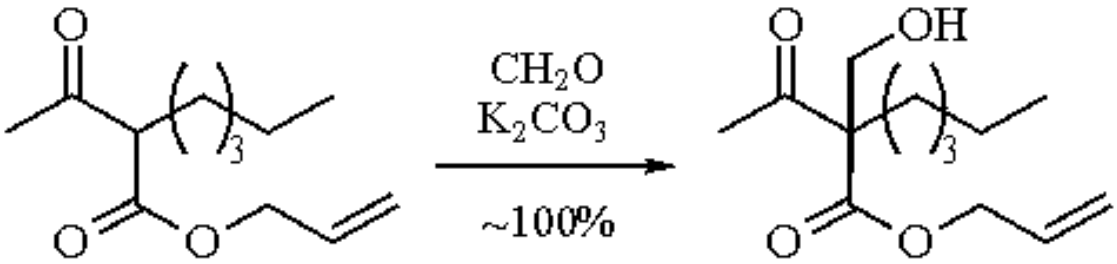

(18)

With a 2:1 ratio of formaldehyde and ***Diethyl Malonate*** and potassium bicarbonate as catalyst, the product is diethyl bis(hydroxymethyl)malonate (eq 19).[37]

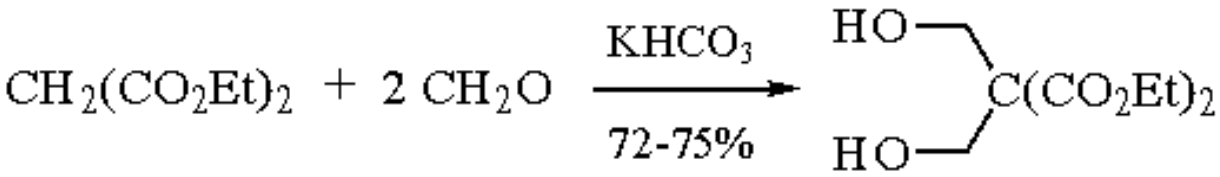

(19)

Nitriles possessing at least one α-aryl group can be hydroxymethylated using paraformaldehyde and Triton B (***Benzyltrimethylammonium Hydroxide***) in pyridine (eq 20).[38]

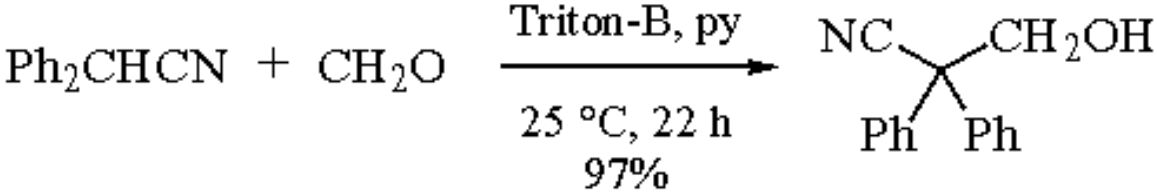

(20)

Chromium tricarbonyl complexes of methoxyalkylbenzenes in the presence of ***Potassium t-Butoxide*** and formaldehyde undergo regiospecific alkylation only at the *meta*-position with respect to the methoxy group (eq 21).[39]

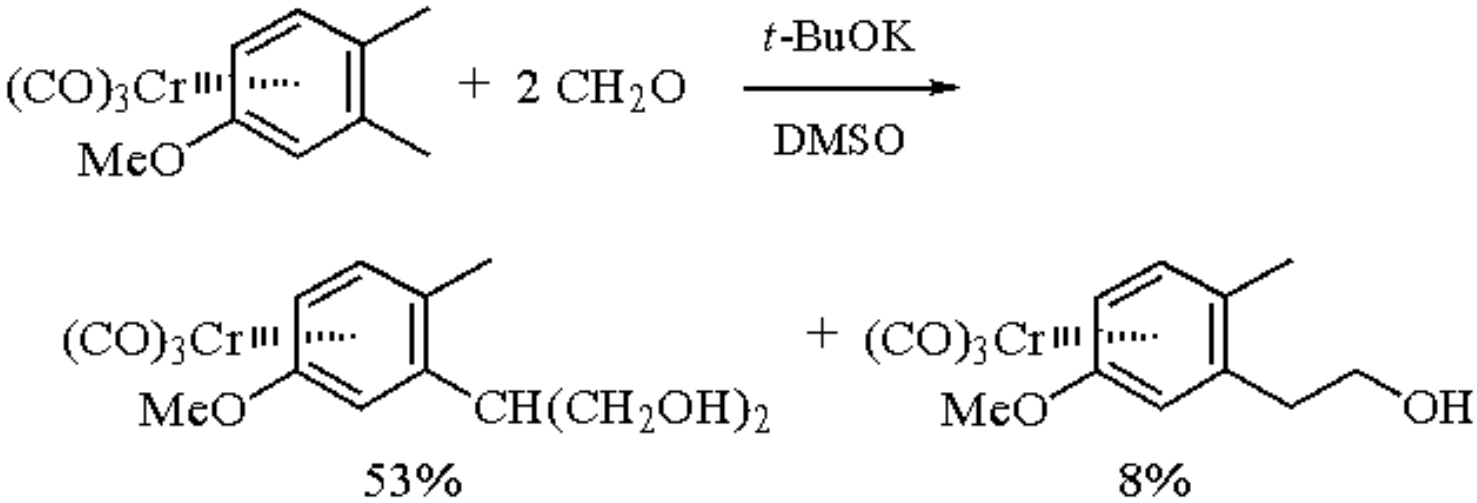

(21)

Reaction with Organometallic and Other Reagents.

Hydroxymethylation of Grignard reagents with formaldehyde can be represented by the synthesis of

cyclohexymethanol using cyclohexylmagnesium chloride.[40] ***Methylmagnesium Bromide***, in the presence of a nickel-aluminum catalyst, acts on 1-trimethylsilyl-1-octyne to provide a mixture of addition products which react with formaldehyde to give di- and trisubstituted vinylsilanes (eq 22).[41]

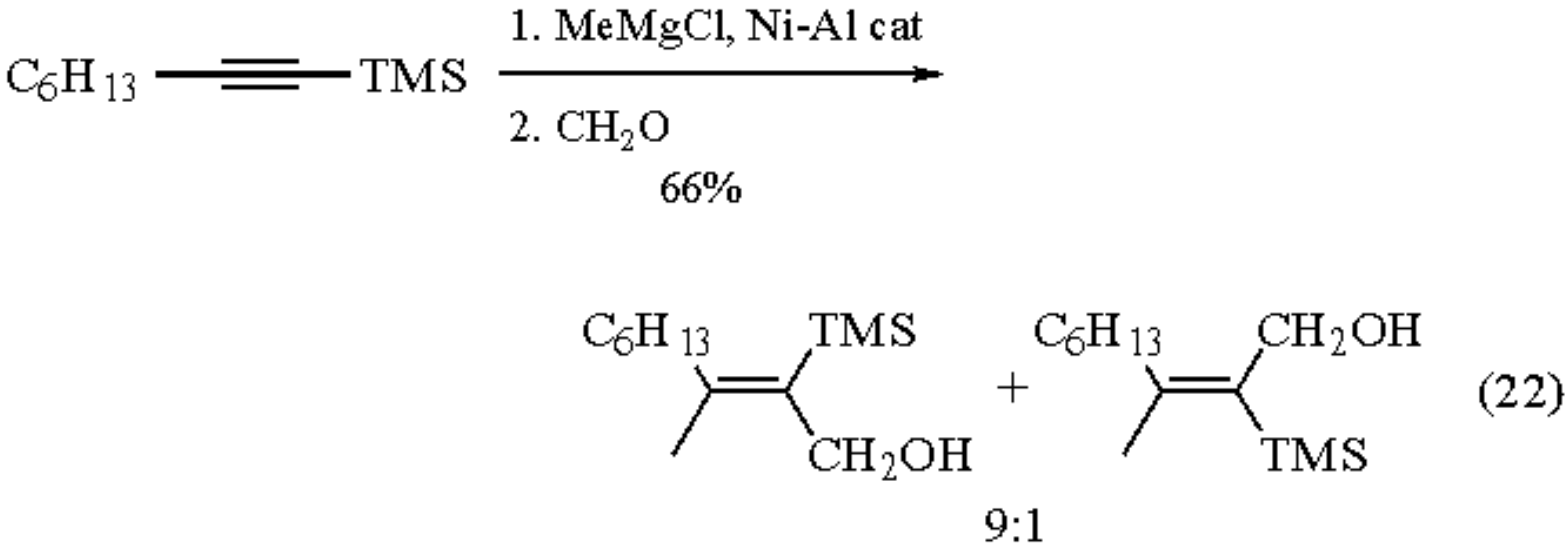

Boric Acid is a useful catalyst for the cyclocondensation of phenol with formaldehyde to give benzodioxaborin.[42] Phenylboronic acid, in combination with propionic acid, is found to be a more efficient catalyst.[43] Thus a high yield of dioxaborin is obtained in the reaction with a slight excess of phenylboronic acid, and the free hydroxymethylated phenol is liberated by an exchange reaction or by oxidation with ***Hydrogen Peroxide*** (eq 23).

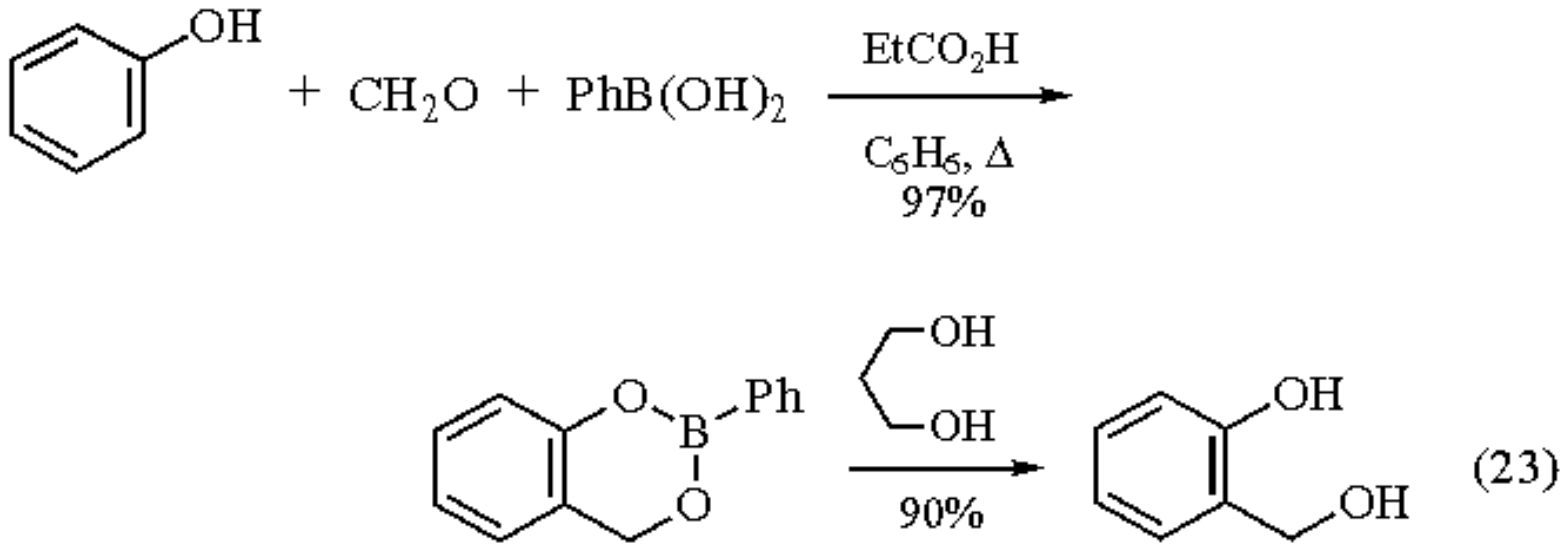

Silyl enol ethers of aldehydes and ketones react with trioxane in the presence of ***Titanium(IV) Chloride*** to give cross-aldol adducts in good yield (eq 24).[44]

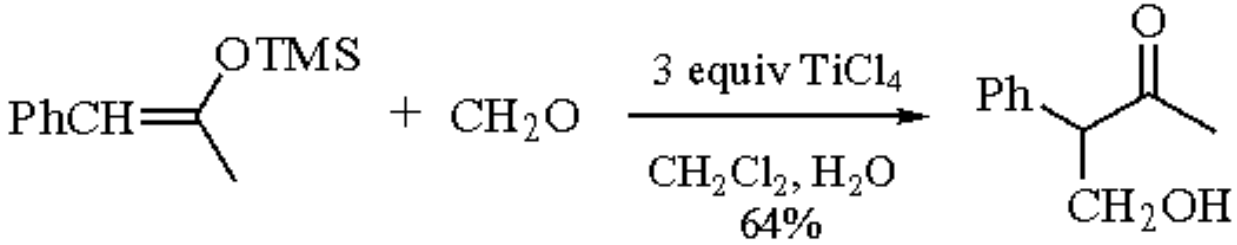

(24)

Ytterbium(III) Trifluoromethanesulfonate, a Lewis acid stable in aqueous media, is found to be effective in catalytic hydroxymethylation of silyl enol ethers with formalin (eq 25).[45]

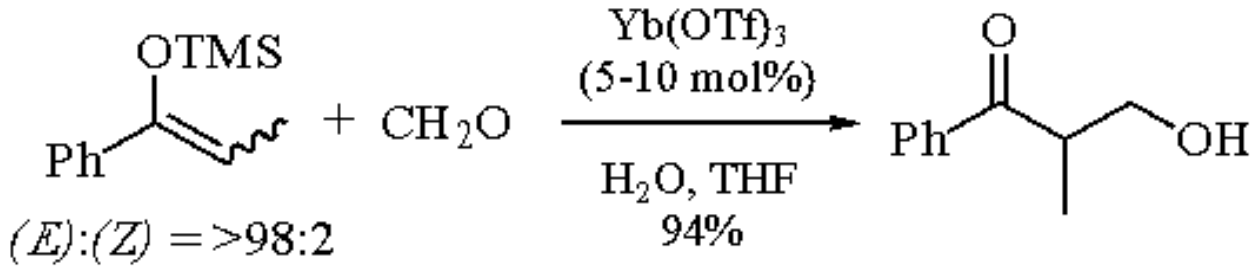

(25)

Synthesis of Heterocyclic Compounds.

Condensation of ***Ethyl Acetoacetate***, formaldehyde, and ***Ammonia*** in 2:1:1 molar ratio furnishes a 1,4-dihydropyridine which is the first step in the synthesis of 2,6-lutidine (eq 26).[46]

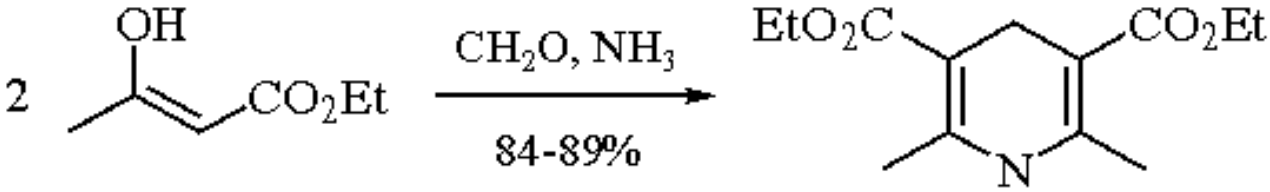

(26)

Symmetric trimers such as *sym*-trithiane[47] and hexahydro-1,3,5-tripropionyl-*sym*-triazine[48] are obtained from formaldehyde reactions. The former is synthesized by passing ***Hydrogen Sulfide*** into a mixture of formalin and concentrated HCl, while the latter is prepared by addition of trioxane in propionitrile to a mixture of propionitrile and concentrated H_2SO_4 (eqs 27 and 28).

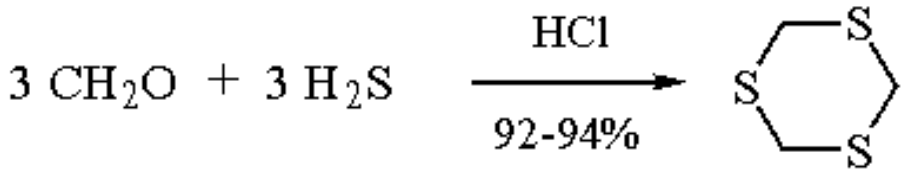

(27)

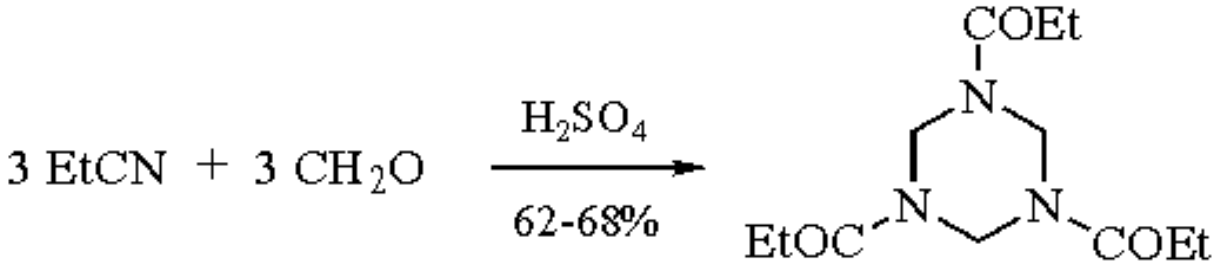

(28)

A general synthesis of piperidines involves the reaction of the acid salt of primary amines with allylsilanes and 2 equiv formaldehyde in H_2O. The iminium ion generated from the amine and formaldehyde reacts with the allylsilane to give a homoallyl amine, which then can form the second iminium ion and H_2O is captured to deliver the piperidinol (eq 29).[49]

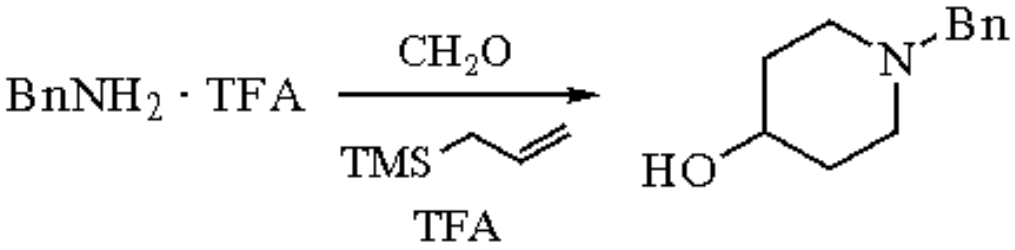

(29)

Cyclization of the alkynylamine *N*-benzyl-4-hexyn-1-amine with formaldehyde, ***Sodium Iodide***, and ***10-Camphorsulfonic Acid*** gives the iodomethylenepiperidine (eq 30).[50] In the absence of the iodide nucleophile, no cyclization is observed.

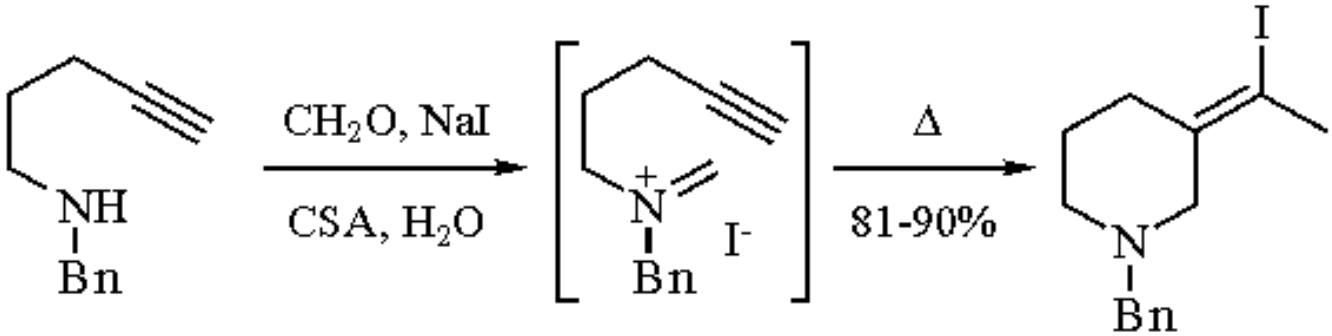

(30)

Reactions of (*E*)- or (*Z*)-vinylsilanes with an excess of paraformaldehyde and camphorsulfonic acid give the cyclized product with >98% retention of the double bond configuration of the starting reactants (eq 31).[51]

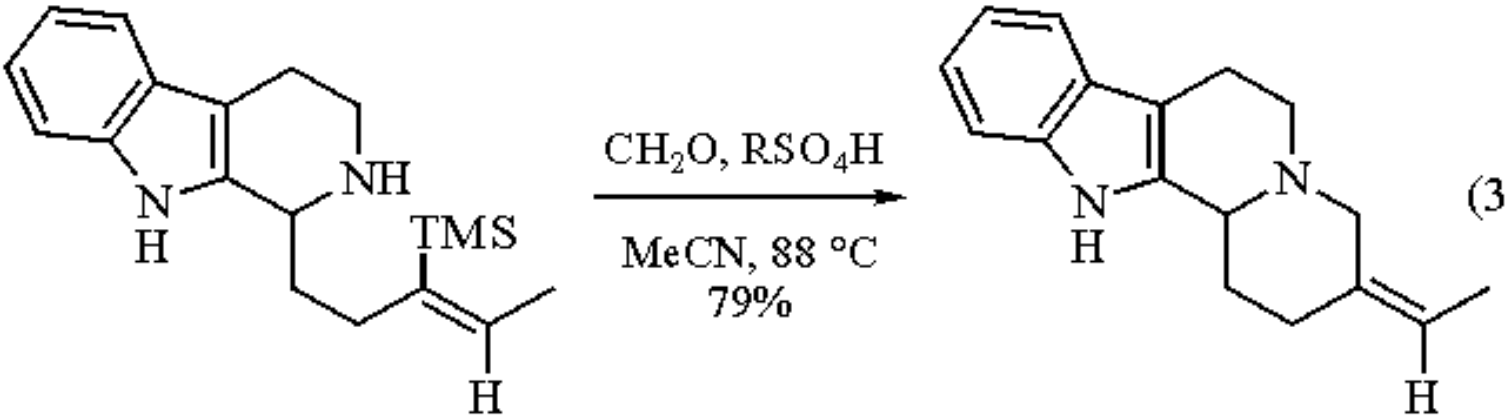

(31)

A series of imine condensations and chain cleavage occur when D-fructose is heated with ammonium hydroxide, basic copper(II) carbonate, and formaldehyde, which ultimately gives 4-hydroxymethylimidazole (eq 32).[52]

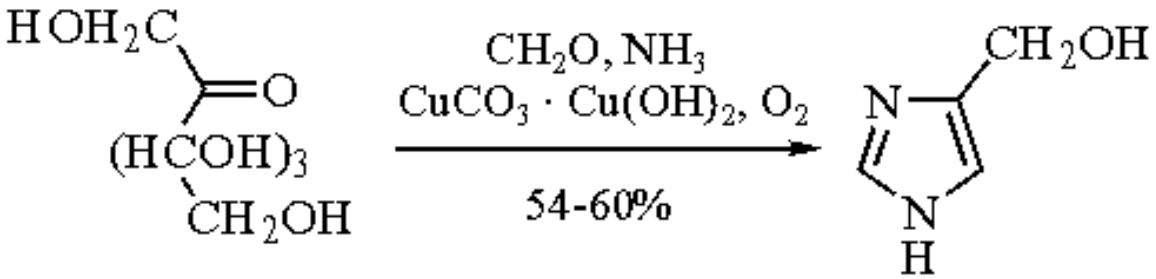

(32)

Condensation.

For the preparation of aurin tricarboxylic acid, solid ***Sodium Nitrite*** was added to concentrated sulfuric acid to produce nitrogen oxides, then salicyclic acid and formalin were added dropwise with vigorous cooling (eq 33).[53]

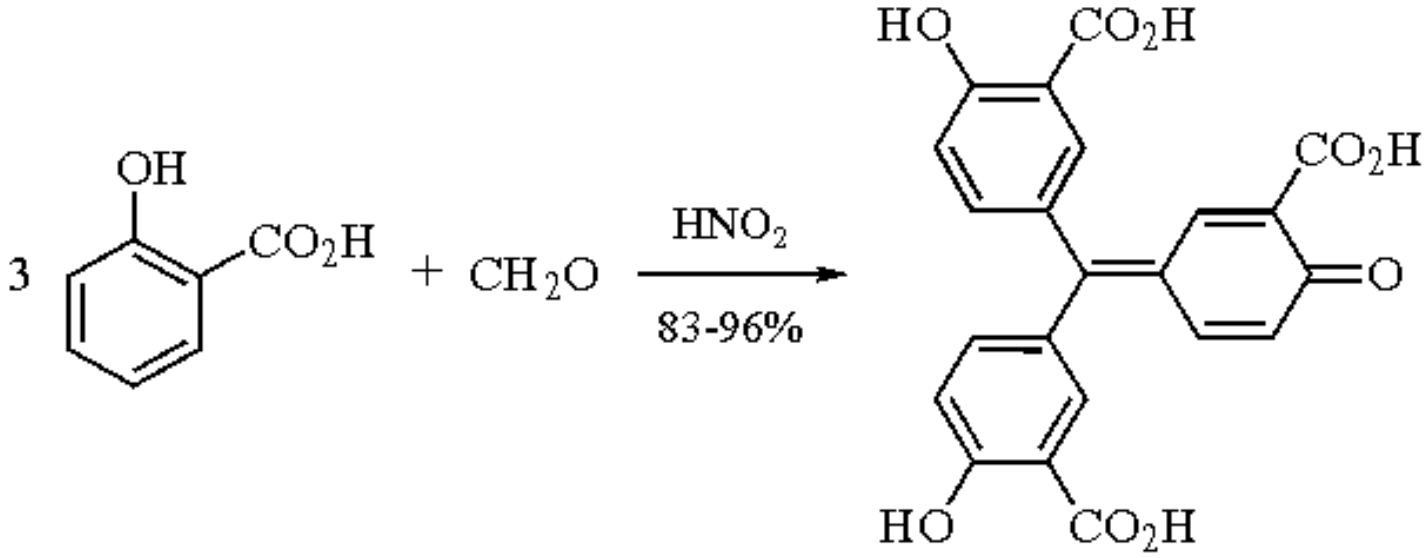

(33)

3,4-Diethylpyrrole can be converted to octaethylporphyrin by condensation with aqueous formaldehyde in benzene in the presence of ***p-Toluenesulfonic Acid***; the water is removed and the methylenepyrrole tetramer is oxidized with oxygen (eq 34).[54]

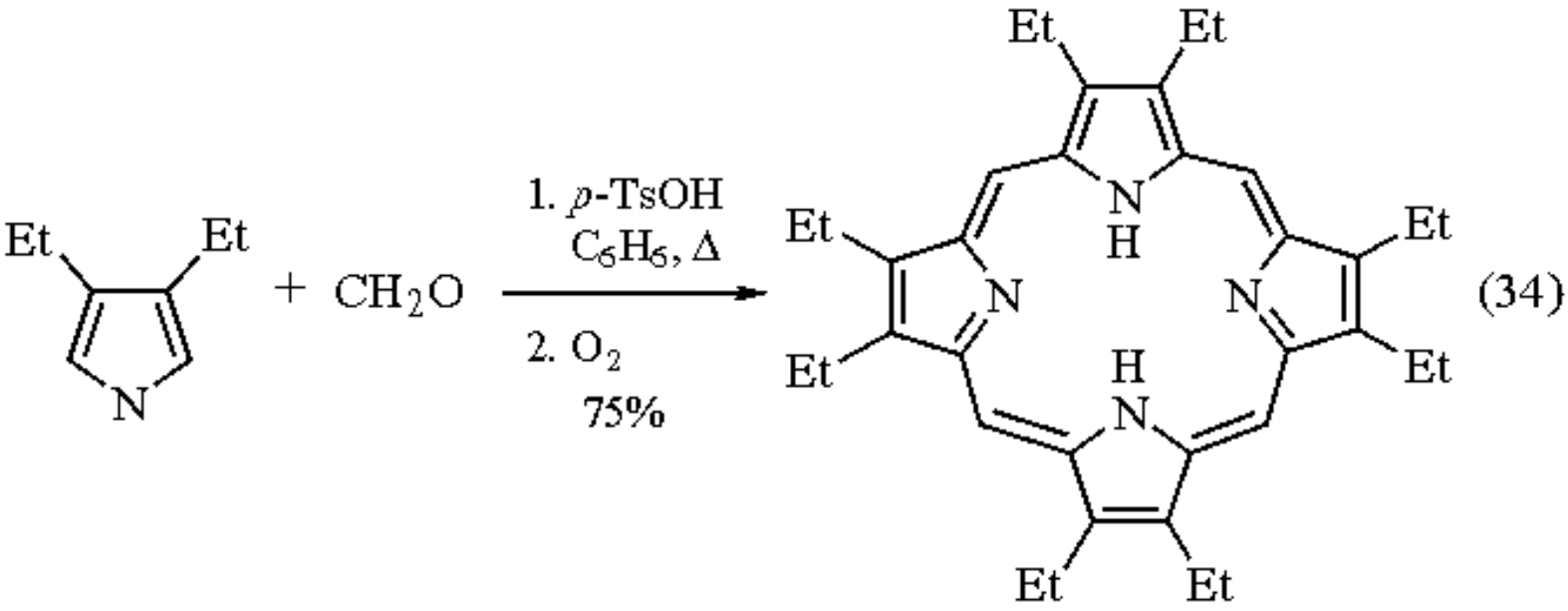

The synthesis of *p*-*t*-butylcalix[4]arene is a three-step process which involves initial reactions of *p*-*t*-butylphenol, formalin, and a base, followed by pyrolysis at a later stage (eq 35).[55] The procedure is limited to *p*-alkylphenols in which the *p*-alkyl group is highly branched at the position adjacent to the phenyl ring. A single-step procedure is also described for *p*-*t*-butylcalix[6]arene[56] and *p*-*t*-butylcalix[8]arene,[57] which requires a larger amount of base for the preparation of the hexamer.

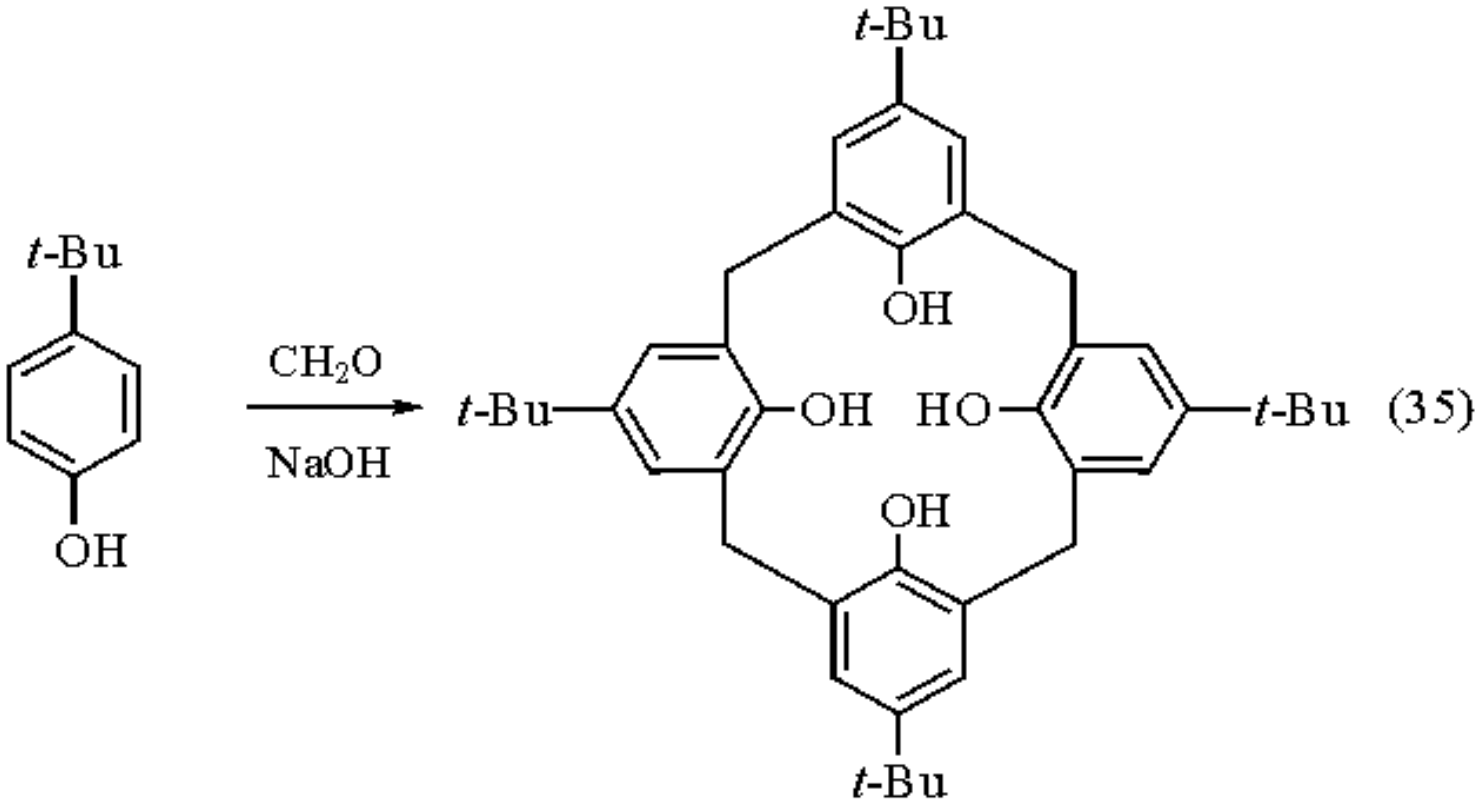

Acetalization.

1,3-Diols react with formaldehyde in an excess of alcohol under acid catalysis, such as *p*-TsOH or ion exchange resin,

to form cyclic acetals (eq 36).[58]

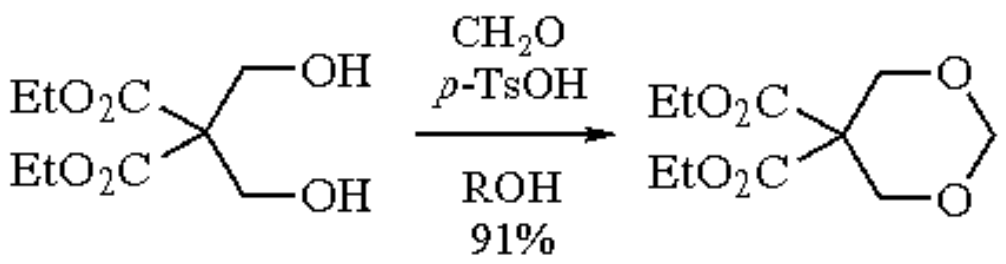

(36)

Cortisone, a steroid containing an α,α´-dihydroxyacetone side chain, is converted into the bismethylenedioxy derivative by stirring with chloroform, formalin, and concentrated HCl (eq 37).[59]

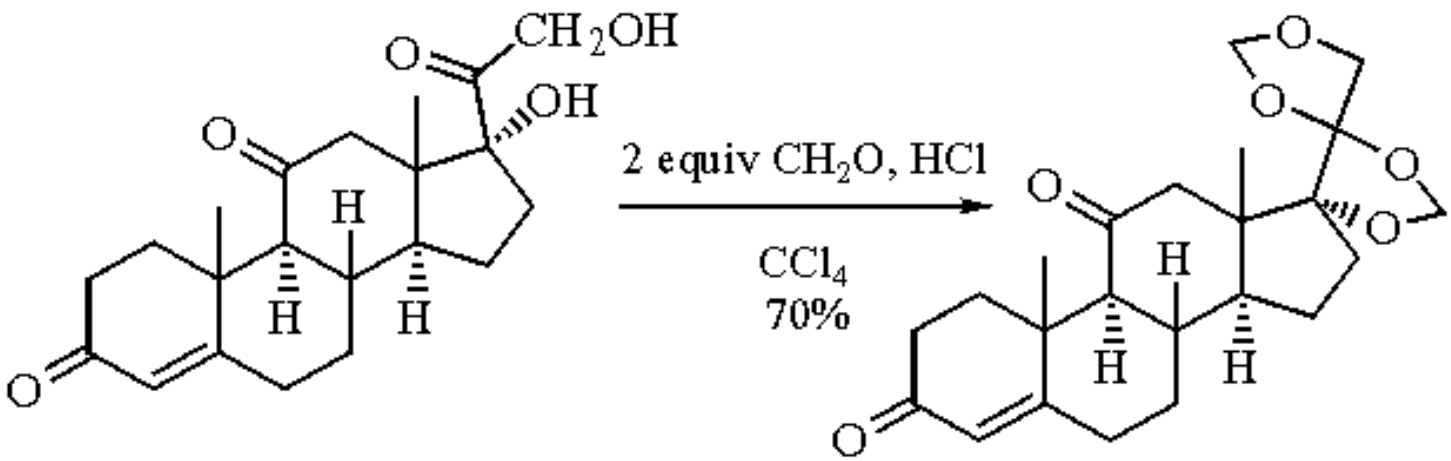

(37)

Cannizzaro and Related Reductions.

In the presence of calcium oxide and water, cyclohexanone reacts with 5 moles of paraformaldehyde to give the pentaol shown in eq 38.[60]

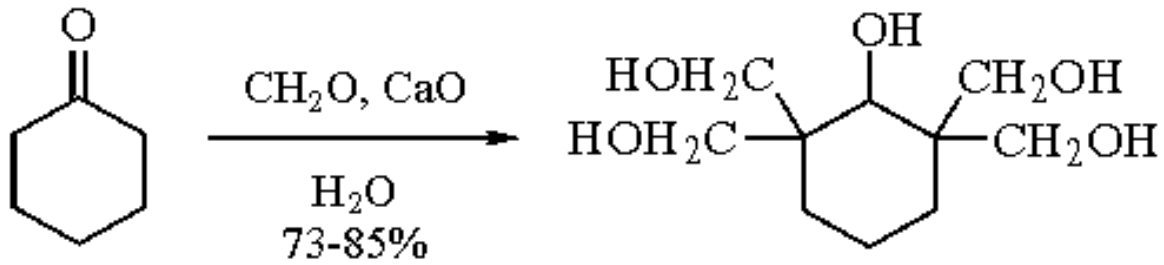

(38)

p-Tolylmethanol is formed in a Cannizzaro reaction involving *p*-tolualdehyde and formalin in aqueous KOH (eq 39).[61]

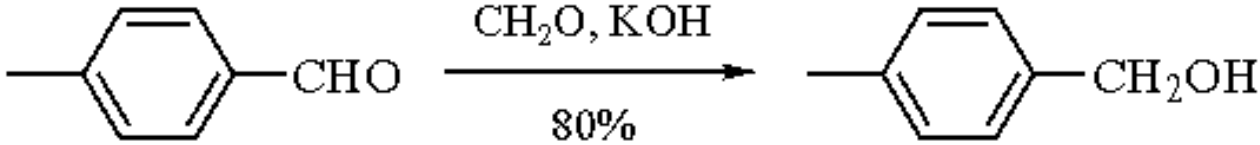

(39)

An interesting preparation of *p*-dimethylaminobenzaldehyde from *p*-nitrosodimethylaniline is accomplished by reaction

with dimethylaniline and 2 moles of formaldehyde in HCl solution. In the first step, one mole of formaldehyde is reduced and the other is oxidized to the formate level, furnishing the benzylidene derivative which is then hydrolyzed by exchange with formaldehyde (eq 40).[62]

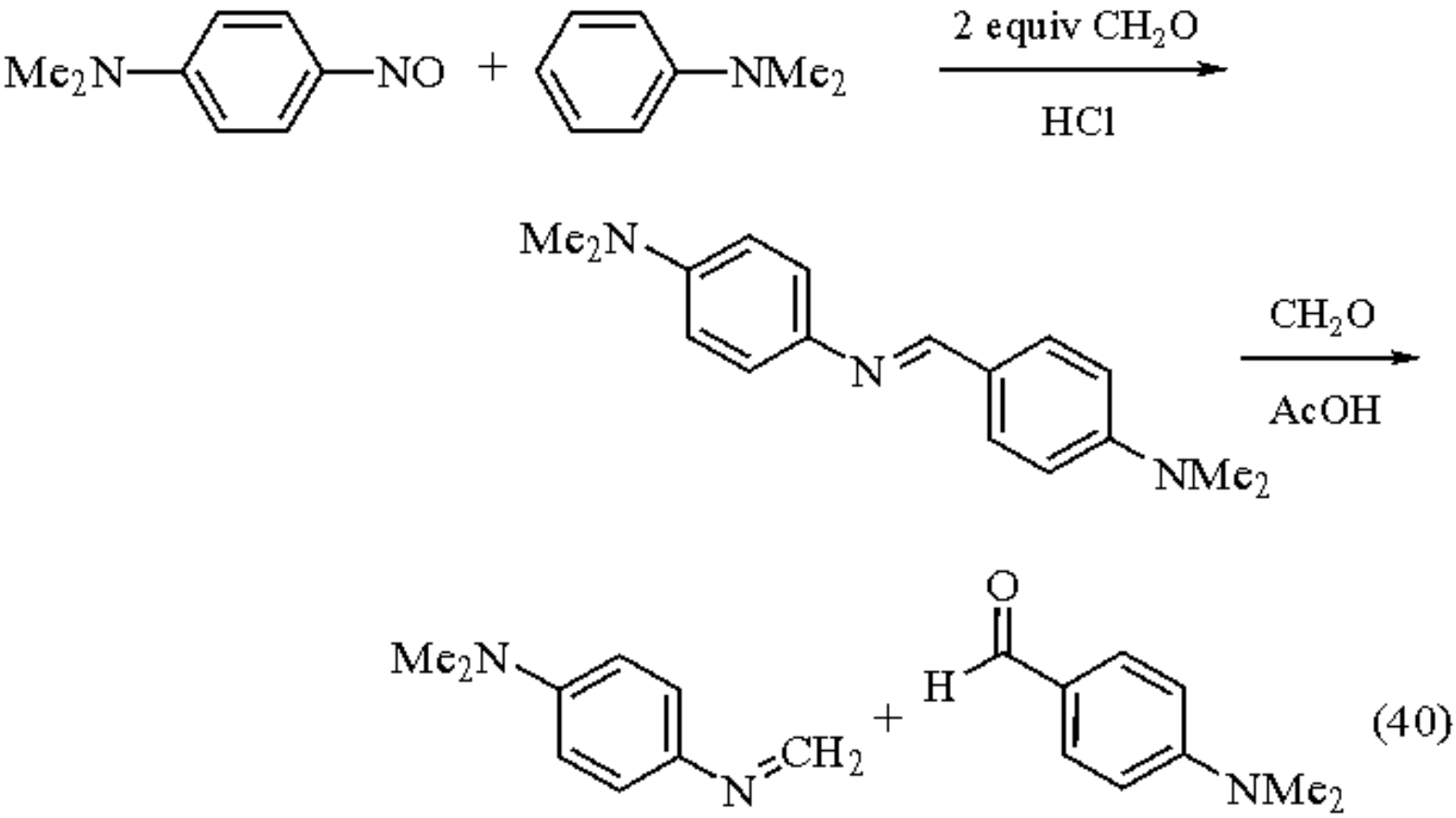

Other Reactions with Nitrogen Compounds.

A reaction involving a mixture of formalin, ammonium chloride, and aqueous ***Sodium Cyanide*** provides *N*-(methylene)aminoacetonitrile (eq 41).[63]

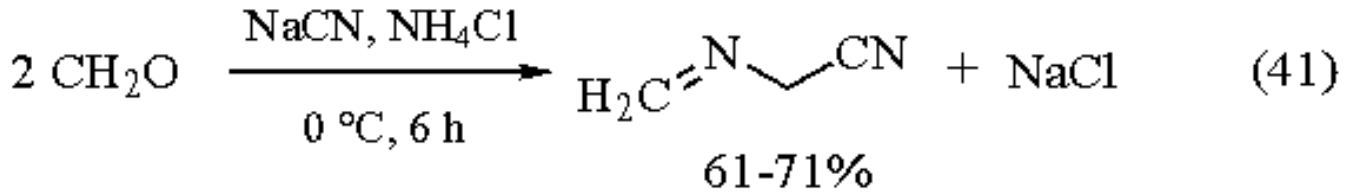

Diethylaminoacetonitrile is prepared by adding formalin to a solution of sodium bisulfate, thereby forming the addition compound which is stirred in diethylamine after cooling, and the aqueous solution of sodium cyanide is added (eq 42).[64]

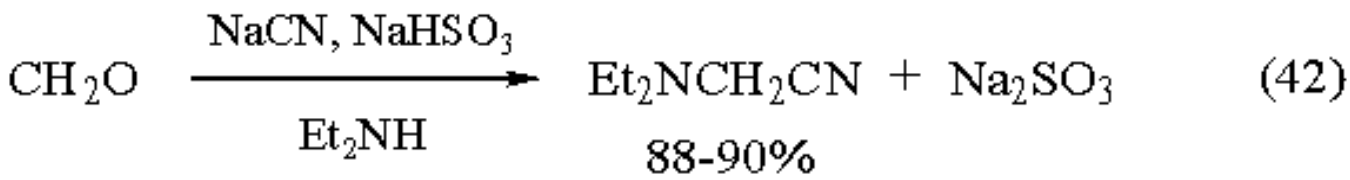

For the preparation of glycolonitrile, formalin is added to a stirred solution of ***Potassium Cyanide*** in water at 0-10 °C (eq 43).[65]

$$CH_2O \xrightarrow[0\text{-}10\ ^\circ C]{KCN,\ H_2O} \underset{76\text{-}80\%}{HOCH_2CN} + KOH \qquad (43)$$

For Mannich-type reactions involving formaldehyde, see ***Formaldehyde-Dimethylamine***.

Related Reagents.

Acetaldehyde; ***Formaldehyde-Dimethylamine***; ***Formaldehyde-Hydrogen Bromide***; ***Formaldehyde-Hydrogen Chloride***; ***Methylaluminum Bis(2,6-diphenylphenoxide)***; ***Sodium Cyanoborohydride***.

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Formaldehyde-Dimethylamine[1]

HCHO-R^1R^2NH

(HCHO)

[50-00-0] · CH_2O · Formaldehyde-Dimethylamine · (MW 30.03) ($(CH_2O)_n$)

[30525-89-4] · $(CH_2O)_n$ · Formaldehyde-Dimethylamine (R^1 = Me, R^2 = Me)

[124-40-3] · C_2H_7N · Formaldehyde-Dimethylamine · (MW 45.10) (R^1 = Me, R^2 = Me; HCl salt)

[506-59-2] · C_2H_8ClN · Formaldehyde-Dimethylamine · (MW 81.56) (R^1 = Bn, R^2 = H)

[100-46-9] · C_7H_9N · Formaldehyde-Benzylamine · (MW 107.17) (R^1 = Bn, R^2 = H; HCl salt)

[3287-99-8] · $C_7H_{10}ClN$ · Formaldehyde-Dimethylamine · (MW 143.63)

(reagent for aminomethylation of active methylenes,[1a-c] aromatic compounds,[1d] and nucleophilic alkenes,[1e,f] reagent for generation of methyleneiminium species capable of participating in [4 + 2][2] and [3 + 2][3] cycloadditions)

Physical Data: Me_2NH, bp 7 °C (also supplied as a 40 wt % solution in water); $Me_2NH.HCl$, mp 170-173 °C; $BnNH_2$, bp 184-185 °C, *d* 0.981 g cm^{-3}; $BnNH_2.HCl$, mp 262 °C.

Form Supplied in: amine HCl salts are widely available as white solids; HCHO is available as 37 wt % soln in water; paraformaldehyde $(CH_2O)_n$ is available as a white solid

Handling, Storage, and Precautions: amines are irritants and corrosive; HCHO is highly toxic and a cancer suspect agent; paraformaldehyde is a moisture-sensitive irritant which can be expected to give off HCHO. Use in a fume hood.

Mannich Aminomethylation.

The generation of reactive methyleneiminium salts (eq 1) from formaldehyde and primary or secondary amines (usually as HCl salts) defines the classical Mannich conditions under which a wide variety of nucleophilic species can be aminomethylated. Historically, the most common nucleophiles have been active methylene compounds[1a-c] with a pK_a of 20 or less (e.g. ketones, aldehydes, and malonates) and nucleophilic aromatic compounds.[1d] Recent examples of each

include the aminomethylation of a ketone in the synthesis of the alkaloid (±)-glaucine (eq 2)[4] and the aminomethylation of a phenol, which occurs regioselectively *ortho* to the hydroxyl group (eq 3).[5]

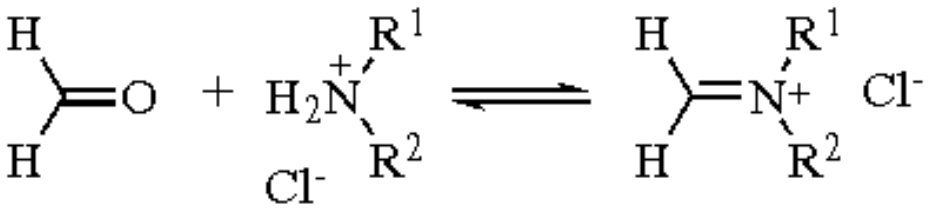

(1)

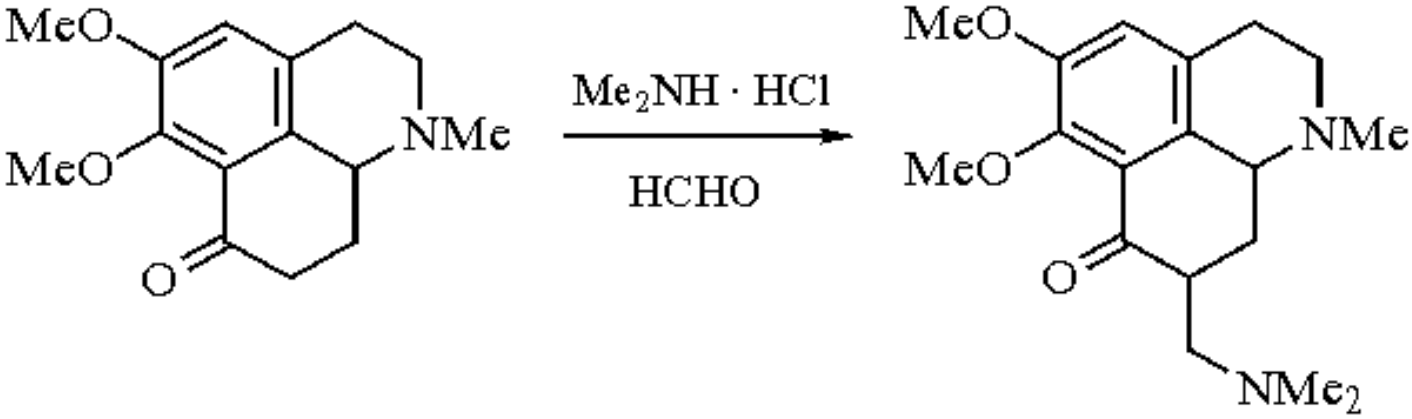

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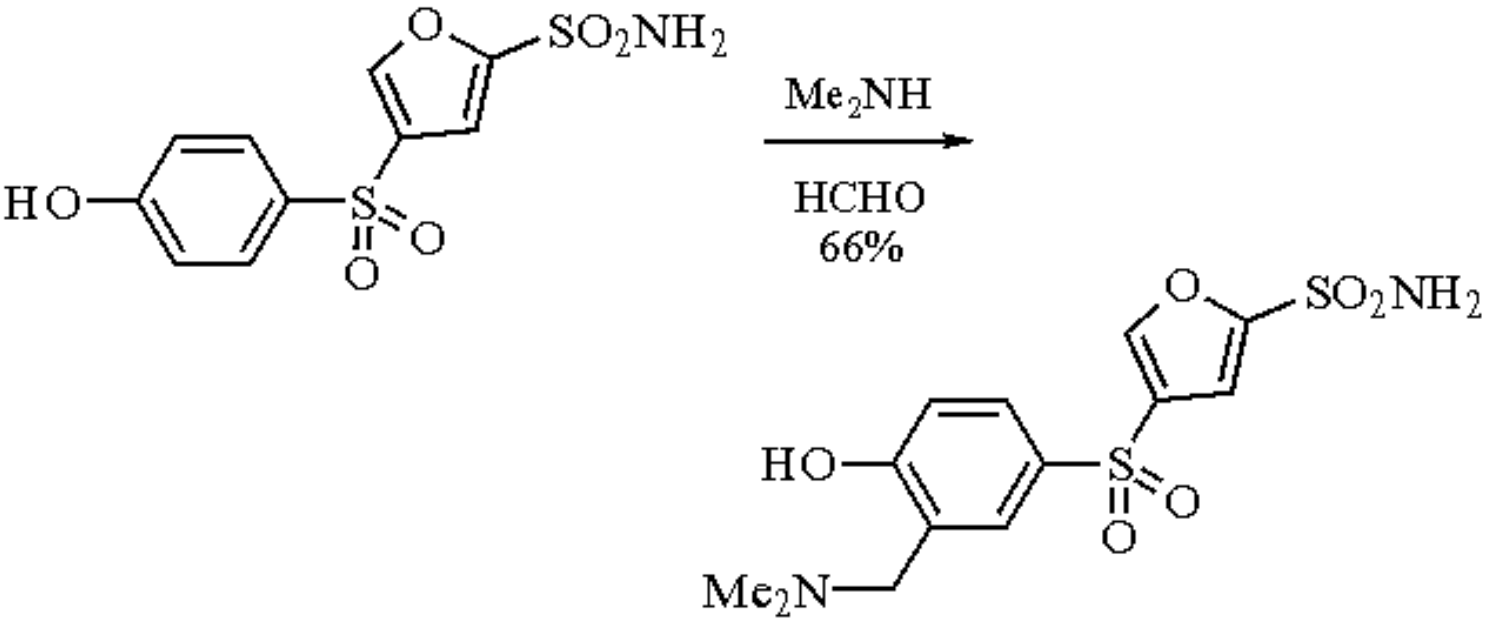

(3)

Aminomethylation of active methylene compounds is often accompanied by elimination of the amine, comprising one of the most useful syntheses of α-methylene carbonyl compounds.[1a-c] This methylenation procedure was recently incorporated into a cephalosporin synthesis (eq 4).[6] Formation of the double bond is also often accomplished separately by quaternization and base-induced elimination.

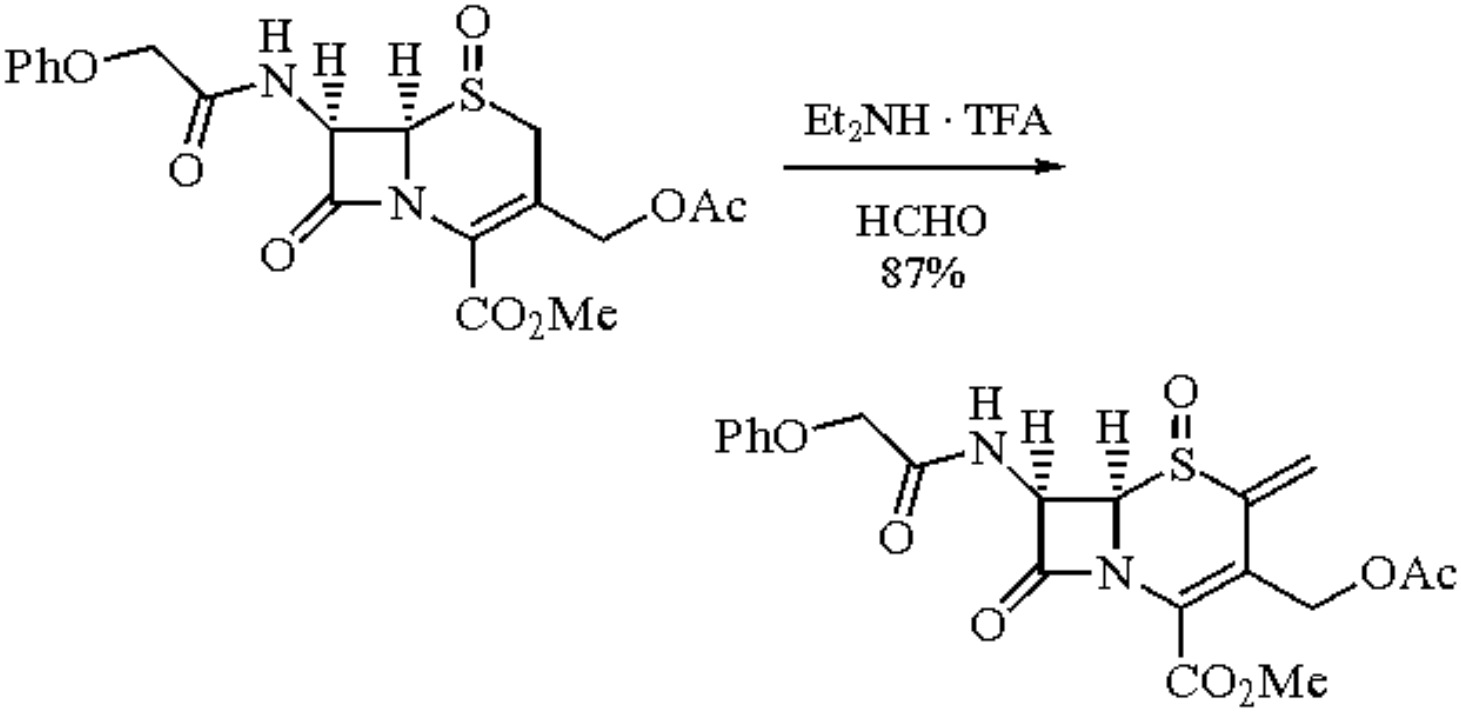

(4)

Methyleneiminium species are sufficiently reactive to be attacked by moderately nucleophilic alkenes.[1f,7-10] In most cases, this reaction is terminated by addition of an external nucleophile, such as halide or water, to the opposite terminus of the alkene.[9,10] However, the addition of an alkene to the methyleneiminium ion can also occur in the context of a pericyclic reaction. The elegant stereoselective pyrrolidine synthesis reported by Overman proceeds via a tandem aza-Cope rearrangement/Mannich condensation and has been incorporated into a number of alkaloid total syntheses.[1f] The method is exemplified in eq 5.[11] An unprecedented aza-ene reaction was also recently observed during an intramolecular reaction of an alkene with a methyleneiminium ion (eq 6).[12]

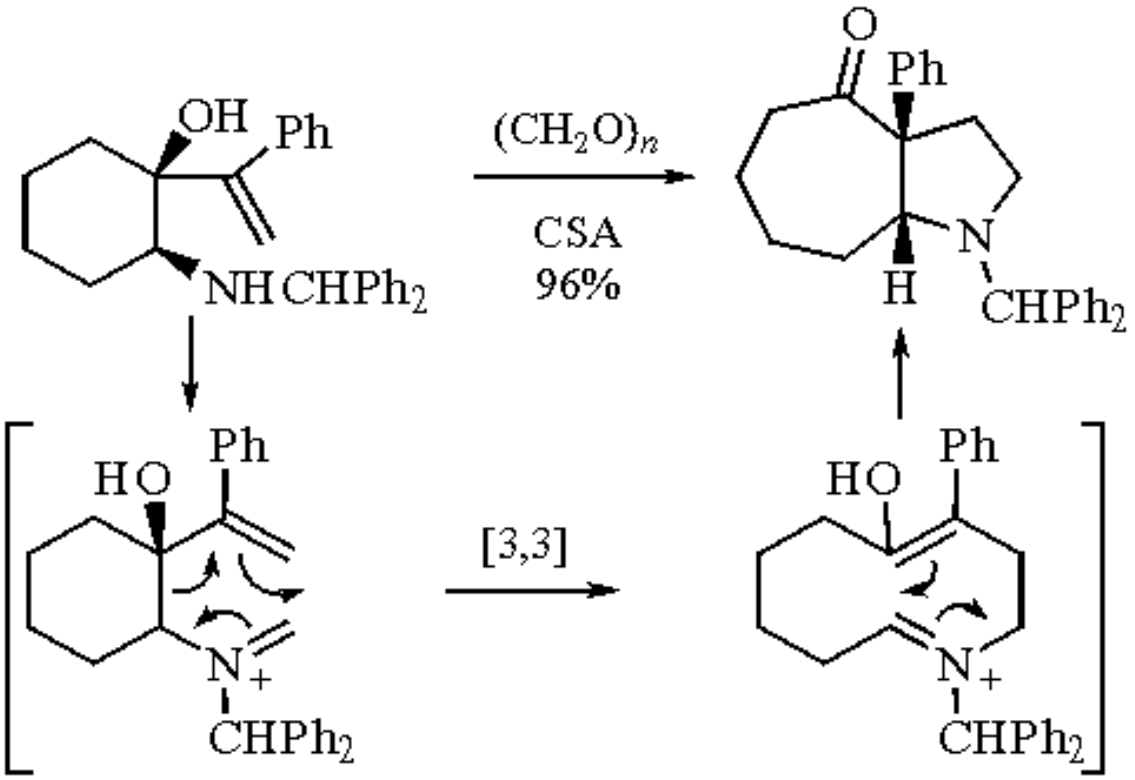

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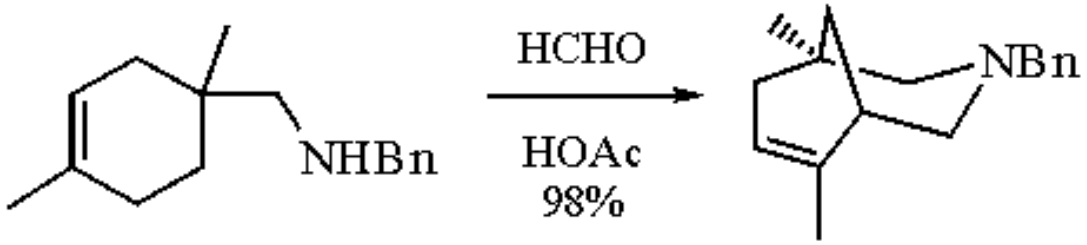

(6)

Terminal alkynes will condense with secondary amines and HCHO in the presence of Cu^{+} or Zn^{2+} catalysts to afford aminomethylalkynes[13] or allenes.[14] Overman has exploited the intramolecular trapping of methyleneiminium ions with alkynes coupled with nucleophilic addition to the incipient vinyl cations to effect the syntheses of pyrrolidines and piperidines possessing exocyclic substituted methylenes of defined stereochemistry (eq 7).[15] Apparently the success of this cyclization depends on the presence of an external nucleophile.

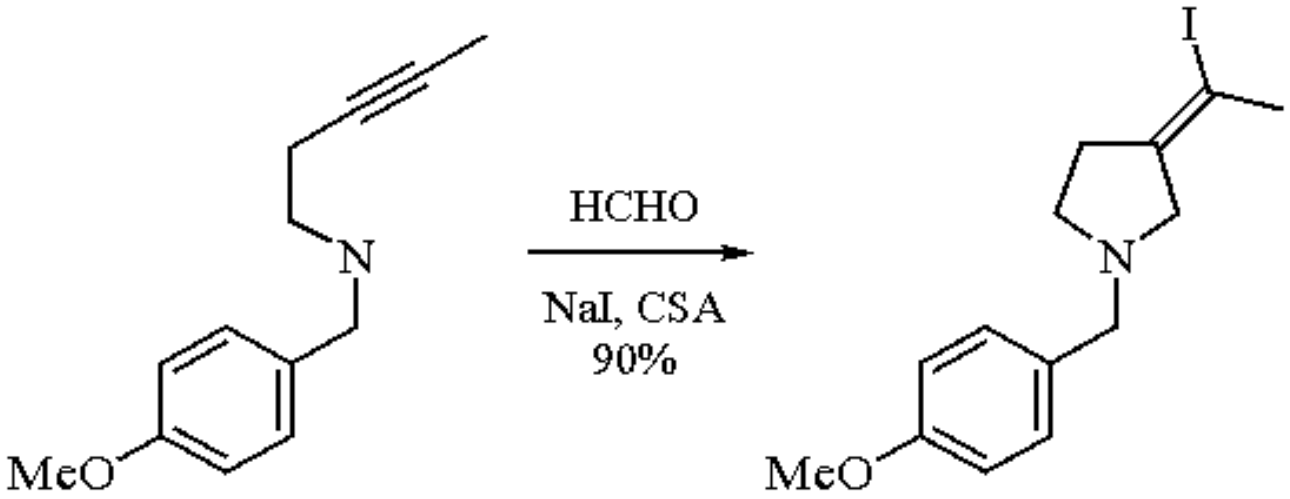

(7)

The enhanced nucleophilicity of allyl and vinyl silanes relative to alkenes renders them particularly susceptible to reaction with methyleneiminium ions. Grieco has demonstrated that allylsilanes and -stannanes react readily, both inter- and intramolecularly.[16] The resulting homoallyl amines may react further with formaldehyde, affording 4-hydroxypiperidines via the subsequent intramolecular addition of the terminal alkene to the methyleneiminium ion (eq 8).[16a] Vinylsilanes are particularly valuable nucleophiles in that they add intramolecularly in a stereospecific fashion to methyleneiminium ions (eq 9).[1f,17]

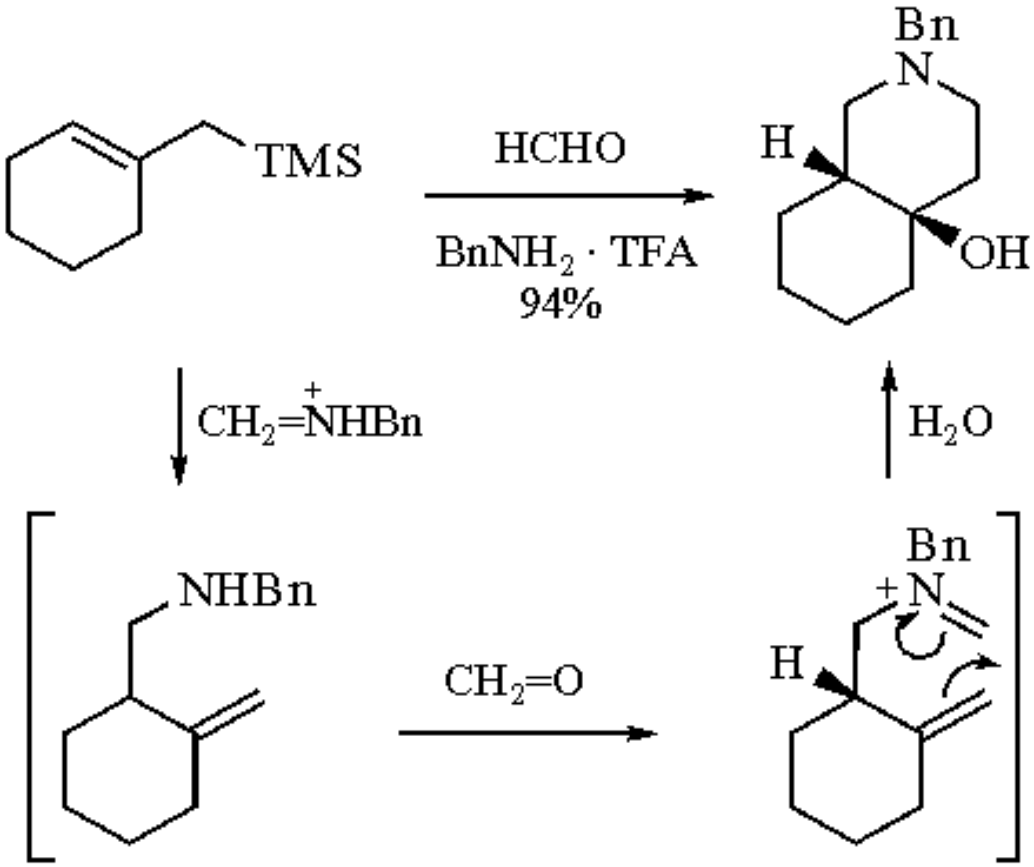

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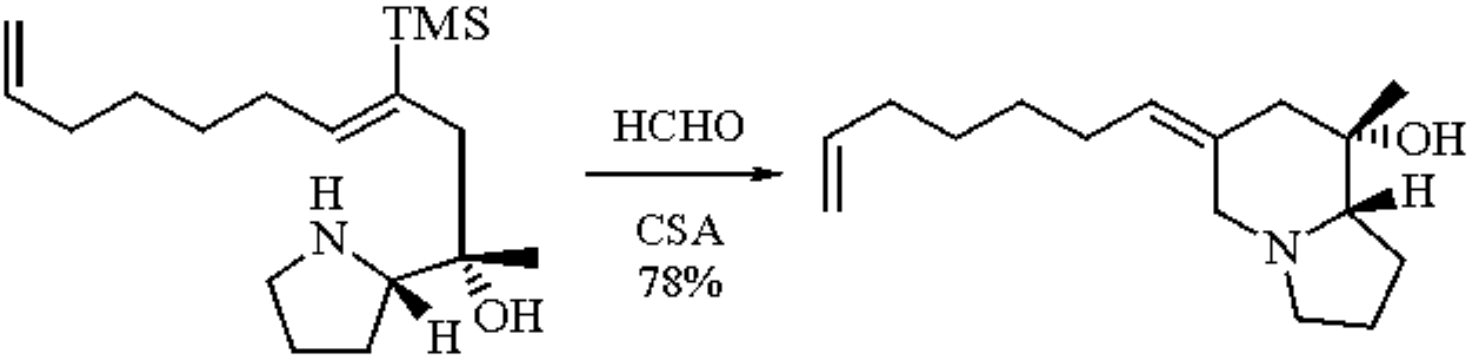

(9)

Cycloadditions.

Böhme first demonstrated that dimethylmethyleneiminium ion is reactive enough to participate as a dienophile in Diels-Alder reactions with 1,3-dienes.[18] More recently it has been reported that methyleneiminium ions generated in situ from primary amines and HCHO undergo this reaction as well (eq 10).[2] Diastereoselectivity has been noted when amines bearing asymmetrical groups are employed (eq 11).[2a,19]

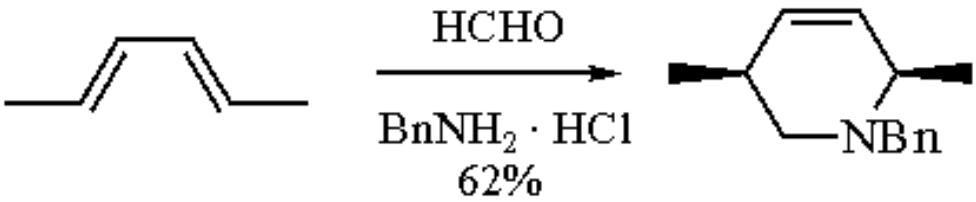

(10)

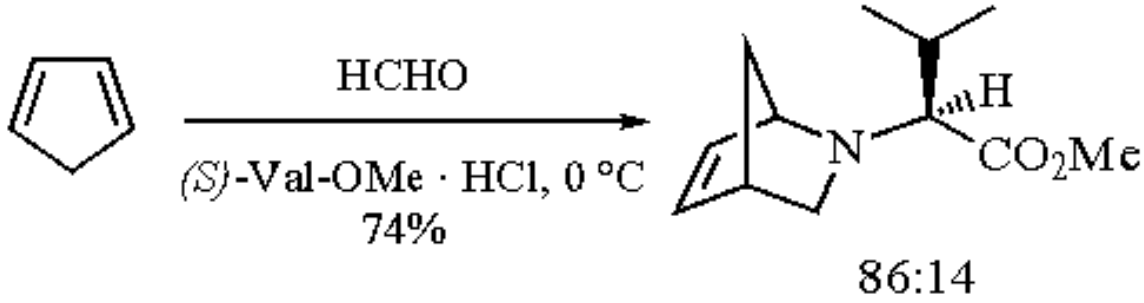

(11)

When HCHO is combined with a primary amine bearing an electron-withdrawing group (e.g. ester or nitrile) in the α-position, the resultant methyleneiminium ion can deprotonate at the α-carbon, generating an azomethine ylide capable of undergoing [3 + 2] cycloadditions with alkenic dipolarophiles.[3,20] A typical example is presented in eq 12.[20] This method suffers from a lack of regio- and stereoselectivity.

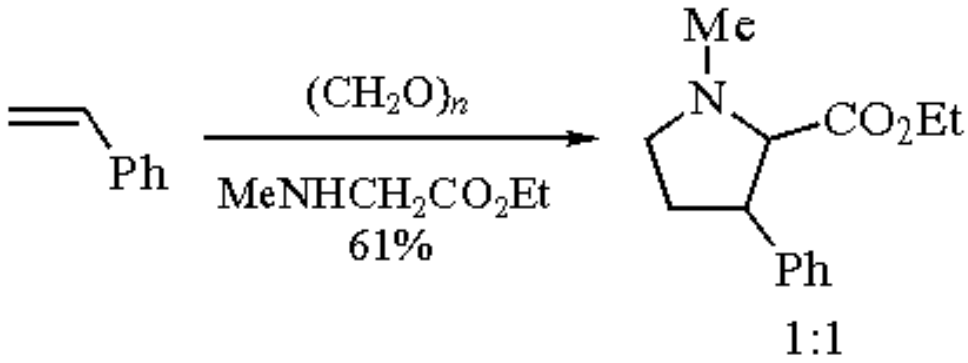

(12)

If the electron-withdrawing group is carboxyl, spontaneous decarboxylation occurs, comprising a remarkably mild and convenient generation of nonstabilized azomethine ylides.[21] Cycloaddition with various alkenes is stereospecific, providing 2,5-unsubstituted pyrrolidines (eq 13).[21b]

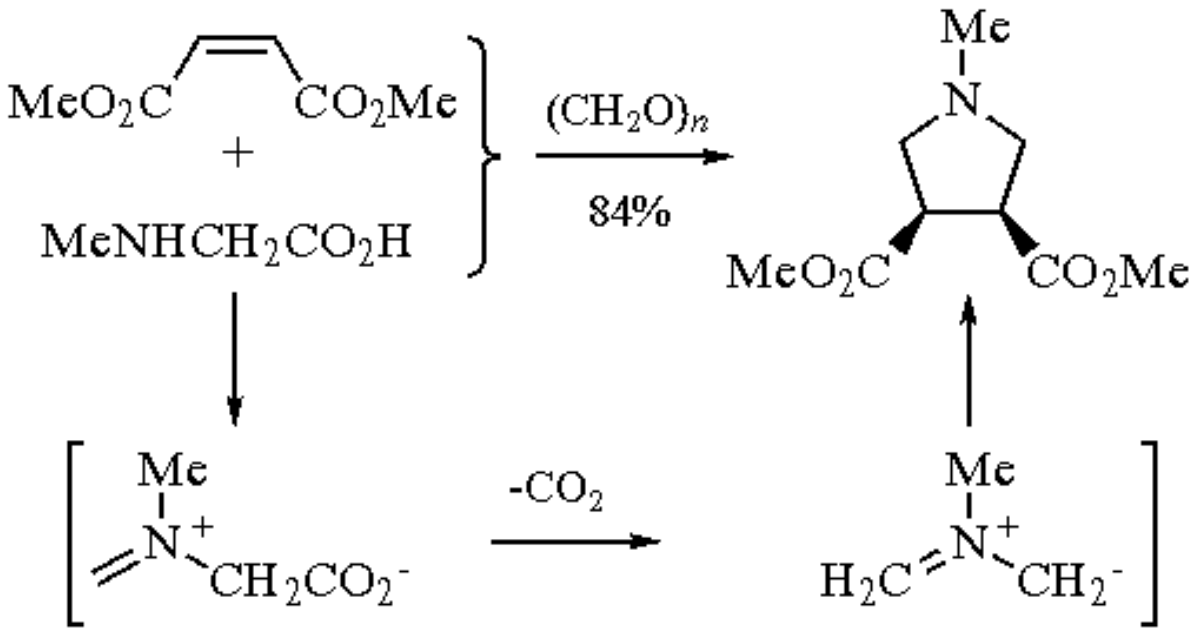

(13)

Related Reagents.

Dimethyl(methylene)ammonium Iodide; ***Dimethyl(phenylthiomethyl)amine***; ***Formaldehyde***; ***N-(Methylthiomethyl)piperidine***.

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Formaldehyde Dimethyl Thioacetal Monoxide[1]

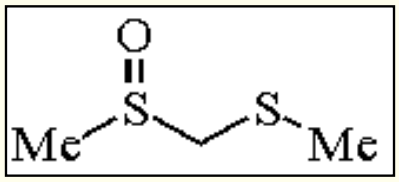

[33577-16-1] · $C_3H_8OS_2$ · Formaldehyde Dimethyl Thioacetal Monoxide · (MW 124.25)

(versatile synthetic reagent used for the production of aldehydes, ketones, α-keto carboxylates, α-amino acid derivatives, and arylacetic acid derivatives)

Alternate Names: methyl (methylthio)methyl sulfoxide (MMSO); formaldehyde dimethyl dithioacetal *S*-oxide; methyl methylsulfinylmethyl sulfide; (methylsulfinyl)methylthiomethane; bis(methylthio)methane *S*-oxide.

Physical Data: bp 222-226 °C; *d* 1.22 g cm^{-3} (20 °C); viscosity 11.78 cP (20 °C); refractive index (20 °C) 1.5524; specific heat (20 °C) 336 cal g^{-1} $°C^{-1}$; surface tension 37.04 dyn cm^{-1} (20 °C); dielectric constant (15 °C) 3.2; pK_a (DMSO) 29.0.[2]

Solubility: sol acetic acid, alcohol, THF, CS_2, CCl_4, $CHCl_3$, acetone, benzene, DMSO; slightly sol cyclohexane, hexane.

Form Supplied in: available as a colorless, clear liquid; commercially available.

Preparative Methods: substitution of chloromethyl methyl sulfoxide with sodium methanethiolate[3] or oxidation of formaldehyde dimethyl dithioacetal with hydrogen peroxide.[4]

Purification: distillation under a reduced pressure at a temperature below 100 °C.

Analysis of Reagent Purity: GC.

Handling, Storage, and Precautions: reagent decomposes slightly when heated under acidic conditions. It is stable in alkaline and neutral media. It is desirable to keep the reagent in a tightly sealed container over 4 Å molecular sieves.

Aldehyde and Ketone Synthesis.

The abstraction of a proton from MMSO with ***Sodium Hydride***, ***Lithium Diisopropylamide***, or ***Potassium Hydride*** affords a carbanion that readily reacts with a variety of electrophiles. Monoalkylation[5] employing alkyl halides or terminal epoxides,[6] followed by hydrolysis, yields the corresponding homologated aldehyde (eq 1). Dialkylation of this anion provides a pathway to symmetrical ketones.[7] The synthesis of cyclic ketones using this procedure has been effective in the production of both natural products (eq 2)[8] and theoretically interesting molecules.[9] It should be noted, however, that this method is not suitable for the synthesis of acyclic, unsymmetrical ketones as a protocol involving sequential alkylation with nonequivalent electrophiles failed.[10]

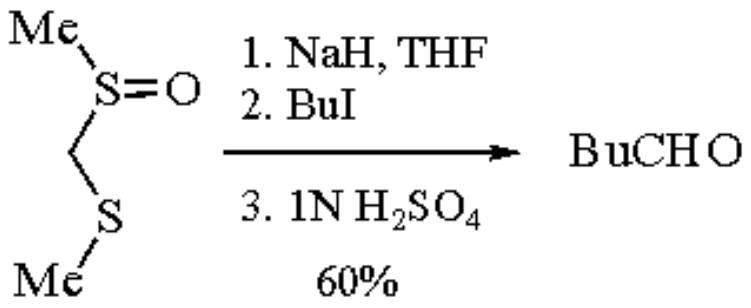

(1)

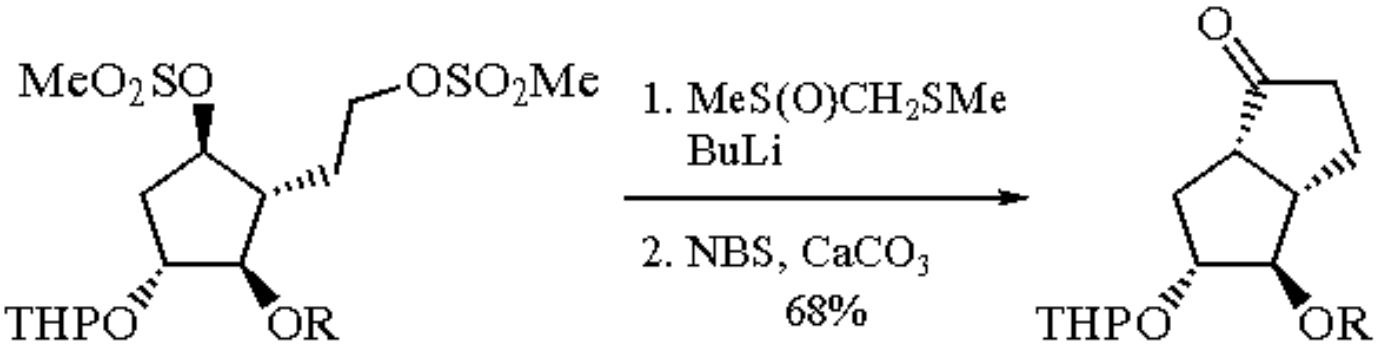

(2)

The addition of a Grignard reagent to MMSO, followed by hydrolysis of the intermediate dithioacetal, affords the corresponding aldehyde in moderate yield (eq 3).[11] This procedure is significant when compared to aldehyde formation through the use of ***1,3-Dithiane***. Since 1,3-dithiane requires an electrophilic coupling partner, the production of aromatic aldehydes is prohibited.

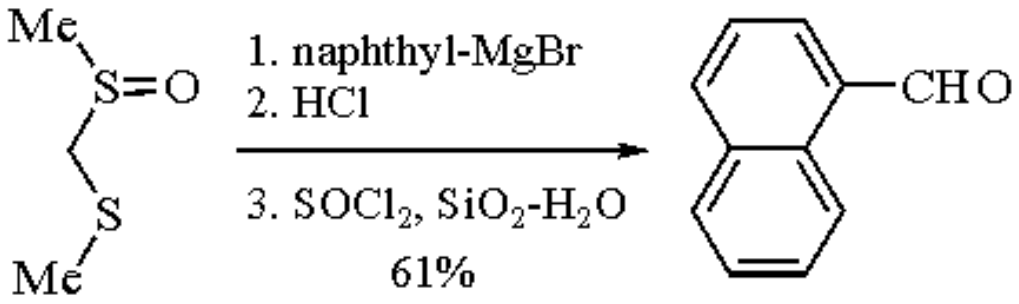

(3)

The anion of MMSO also reacts at activated sp^2 carbon centers. Michael addition proceeds efficiently when lithio MMSO is added to α,β-unsaturated carbonyl compounds.[12] The sodium anion of MMSO adds to 2-bromopyridine, displacing the bromide substituent (eq 4).[13] In both cases, hydrolysis of the coupled intermediate affords the corresponding aldehyde. Moreover, the lithium derivative of MMSO condenses efficiently with ketones to provide, after hydrolysis, the corresponding α-hydroxy aldehydes (eq 5).[14] The mild nature of the addition/hydrolysis sequence lends itself to the production of sensitive compounds. For instance, the aldehyde generated in eq 5 is difficult to prepare using certain other methods due to its lability toward both acid and heat.

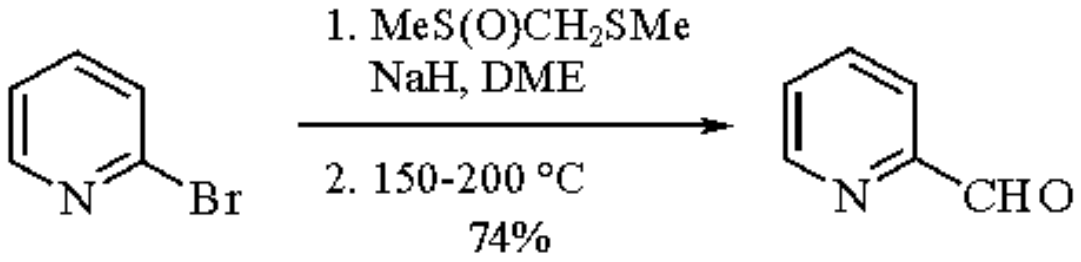

(4)

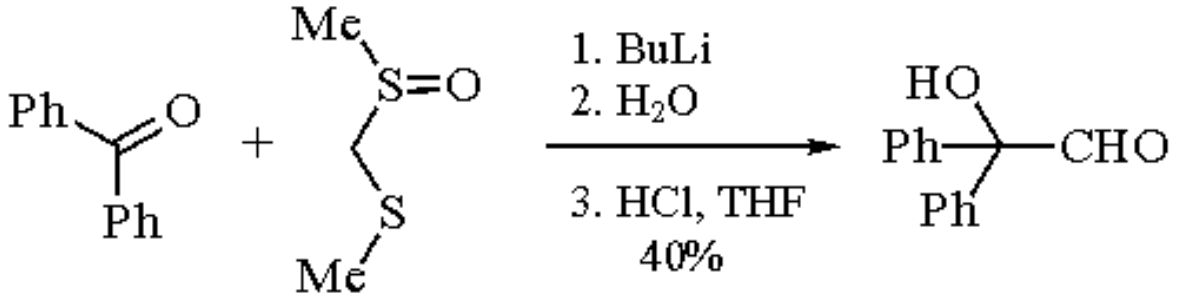

(5)

Synthesis of α-Keto Acid and α-Amino Acid Derivatives.

Nitriles react with MMSO in the presence of NaH to give enamino sulfoxides. These versatile intermediates can serve as precursors for both α-keto acids (eq 6)[15,16] and α-amino acids (eq 7).[15,17] Treatment of the enamino sulfoxide with ***Copper(II) Chloride*** in ethanol provides an α-keto ethyl ester. Acetylation of the intermediate enamino sulfoxide, followed by methanolysis and reductive desulfurization, affords protected α-amino esters.

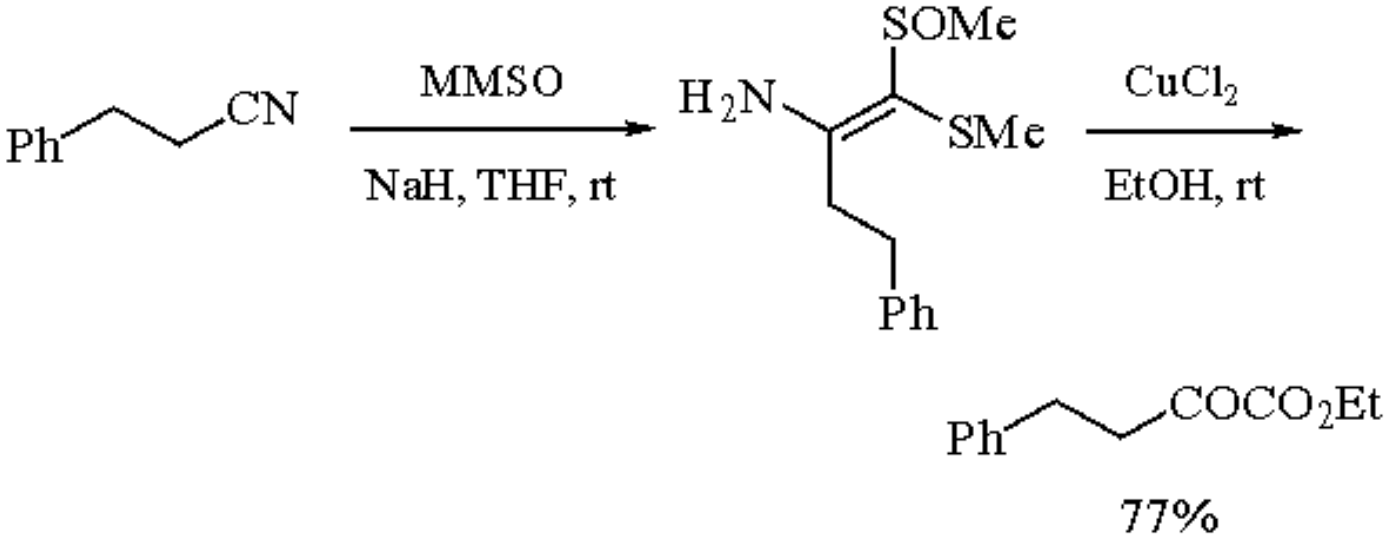

(6)

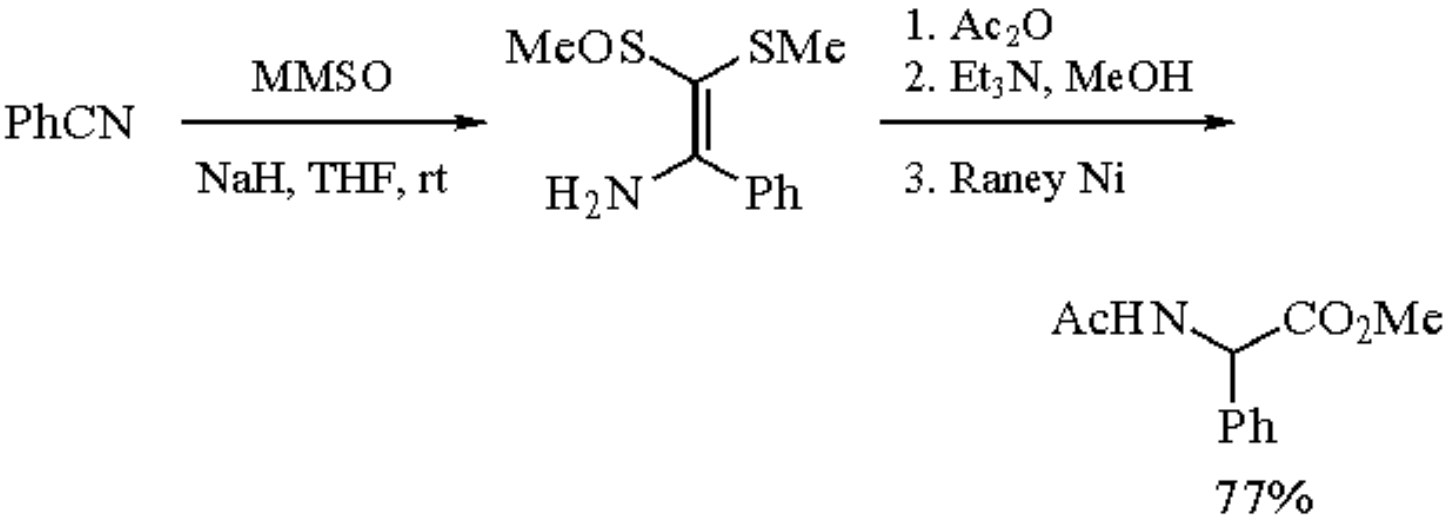

(7)

Synthesis of Arylacetic Acid Derivatives.

When a mixture of MMSO and an aromatic aldehyde is heated in the presence of a base, a Knoevenagel-type condensation results (eq 8). Reaction of the condensation products with HCl in an alcohol affords arylacetic esters.[18] In the case of electron-rich aromatic aldehydes, hydrolysis of the condensation product often generates the corresponding α-(methylthio)aryl acetate (eq 9). This undesired substrate can, however, be converted to the aryl acetate upon treatment with ***Raney Nickel***.[19] For acid-labile arylacetic acids, a two-step hydrolysis involving base can be employed.[20]

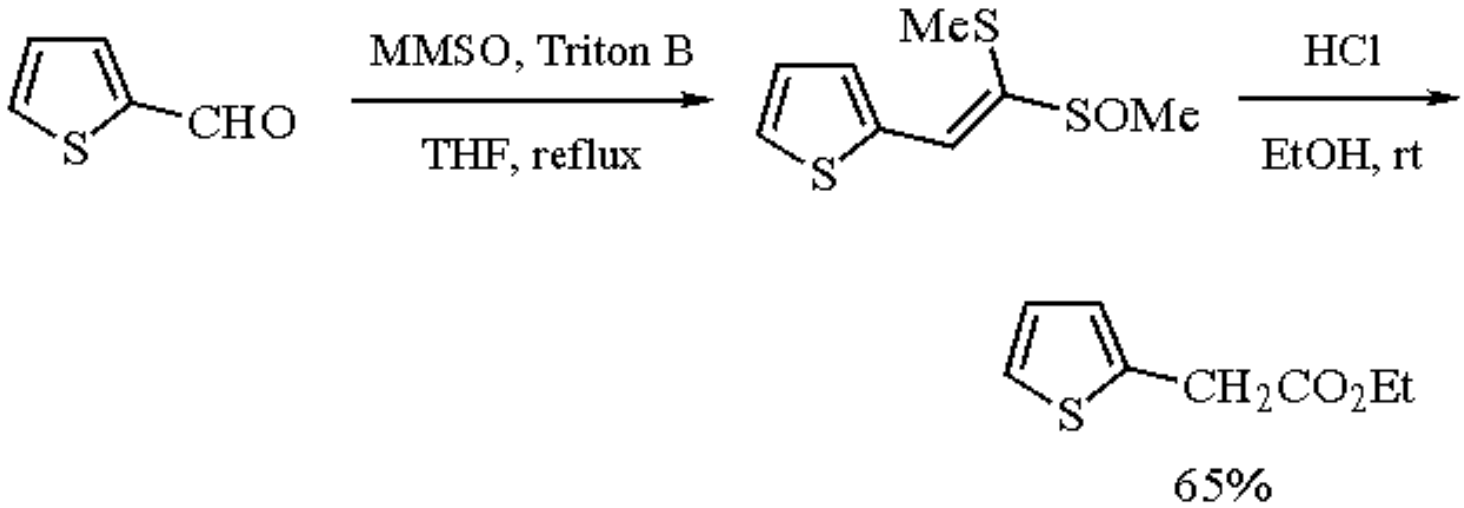

(8)

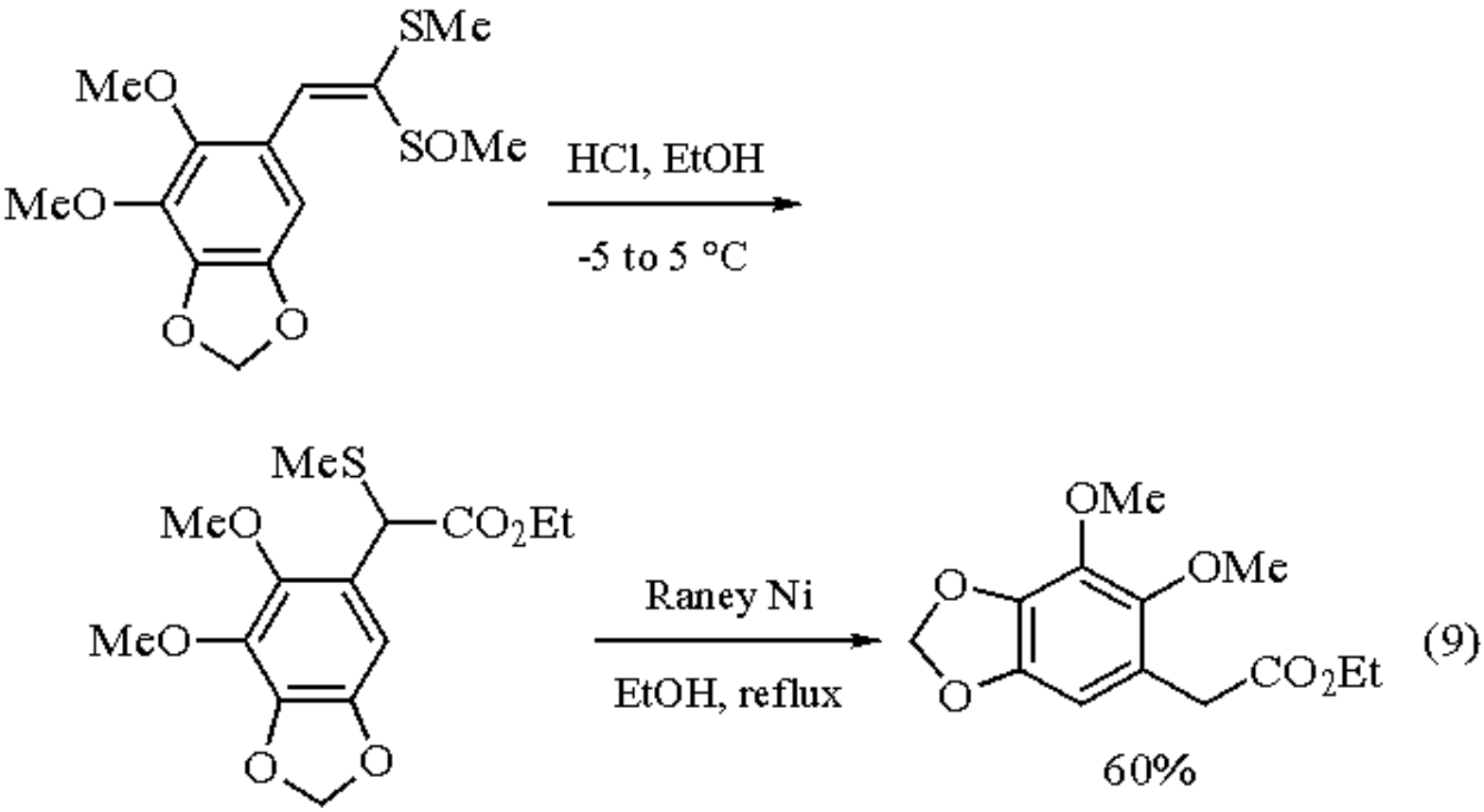

Friedel-Crafts Alkylation.

The α-thioalkylation of aromatic compounds can be carried out by subjecting the aromatic substrate to MMSO and a Lewis acid (eq 10).[21] Similar attempts employing chloromethyl methyl sulfide as the electrophile result in poor yields of the desired alkylated aromatics (35% as compared to the 90% in eq 10). ***Aluminum Chloride*** is the Lewis acid of choice, providing greater reproducibility than other catalysts that were examined. This method can be extended to heteroaromatic substrates. For example, thiophene and *N*-methylpyrrole are alkylated in 55% and 50%, respectively, when subjected to thioalkylation.

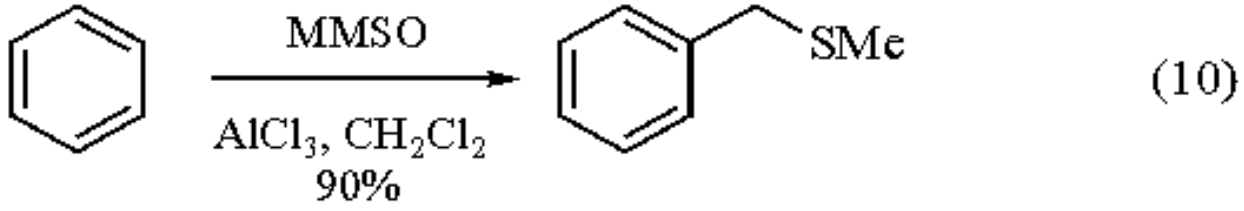

Heterocycle Addition.

The exposure of quinoxaline to the dianion of MMSO results in the production of an appended third ring (eq 11).[22] ***Dimethyl Sulfoxide***, participating in a similar process, affords annulated substrate in a slightly lower yield (51%). This reaction course is in contrast to the addition of a typical organometallic, such as a Grignard reagent, to quinoxaline. For this case, the 2-alkylquinoxaline is usually generated.

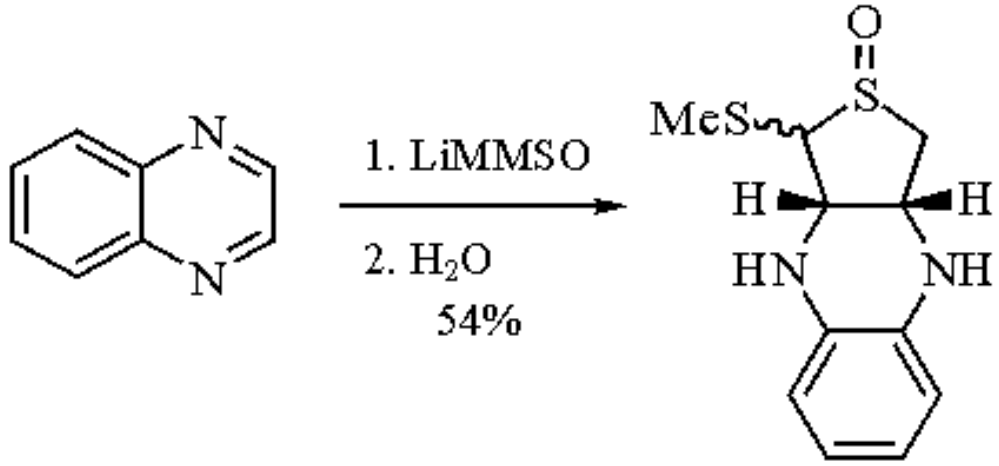

(11)

Ethyl Analog of MMSO.

Formaldehyde diethyl dithioacetal monoxide can be used in analogous synthetic applications,[10,23] although it is not commercially available.

Related Reagents.

N,N-Diethylaminoacetonitrile; ***N,N-Dimethyldithiocarbamoylacetonitrile***; ***(4aR)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin***; ***2-Lithio-1,3-dithiane***; ***Methylthiomethyl p-Tolyl Sulfone***; ***Nitromethane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***; ***2-(Trimethylsilyl)thiazole***.

---

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Formaldehyde-Hydrogen Bromide[1]

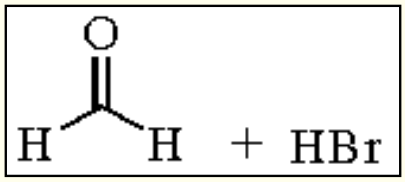

(HBr)

[10035-10-6] · BrH · Formaldehyde-Hydrogen Bromide · (MW 80.92) (CH_2O)

[50-00-0] · CH_2O · Formaldehyde-Hydrogen Bromide · (MW 30.03) ($(CH_2O)_n$)

[30525-89-4] ($3CH_2O$)

[110-88-3]

(conversion of alcohols to bromomethyl ethers; bromomethylation agent for aromatic compounds)

Physical Data: HBr (gas): mp -89.6 °C; bp -66.8 °C; *d* rel. to air 2.71; HBr (48 wt % in water): bp 124.9 °C; *d* 1.490 g cm^{-3}; HBr (30 wt % in acetic acid): *d* 1.354 g cm^{-3}. H_2CO (37 wt % in water): *d* 1.081-1.085 g cm^{-3}; bp 96-99 °C; paraformaldehyde ($HO(CH_2O)_nH$ *n* = 8-100): mp 120-170 °C (depending on degree of polymerization); trioxane: mp 61-62.5 °C; bp 114.5-115.5 °C.

Solubility: HBr: sol water, alcohols, polar organic solvents, acetic acid, propionic acid; H_2CO (as a monomer/polymer equilibrium mixture): sol water, alcohols, acetone, acids; paraformaldehyde: sol (depolymerizes) water, alcohols; insol acetone, ether; trioxane: sol water, alcohols, ethers, ketones, aromatic and chlorinated hydrocarbons.

Form Supplied in: HBr gas: 48 wt % in water (colorless), 30 wt % in acetic acid (colorless); H_2CO: 37 wt % aqueous solution (formalin) (colorless to slightly turbid; generally contains 10-15 wt % methanol as stabilizer); paraformaldehyde (white solid; contains 1-10% water); 1,3,5-trioxane (white solid).

Handling, Storage, and Precautions: HBr solutions turn yellow on storage as the result of bromine formation caused by air oxidation and exposure to light. HBr is highly toxic and corrosive and causes severe burns to eyes, skin, and mucous membranes. H_2CO has a pungent suffocating odor, has an irritant action on eyes and skin, is highly toxic, and a cancer suspect reagent. Combination of HBr and H_2CO may yield highly toxic bis(bromomethyl) ether (see carcinogenic ***Bis(chloromethyl) Ether***). Handle in a fume hood.

Bromomethyl Ethers.

Bromomethyl alkyl ethers, which are useful for bromomethylation of aromatic compounds,[1-5] are prepared by the reaction of an alcohol with an equimolar amount of paraformaldehyde and hydrogen bromide (eq 1).[1,2,4,6] Use of metal chloride Lewis acid catalysts in the bromomethylation of aromatics with bromomethyl ethers[2,3] sometimes gives chloromethylated compounds as well. Bromomethyl methyl and bromomethyl octyl ethers are commercially available.

$$ROH + H_2CO + HBr \xrightarrow{0\text{-}5\ ^\circ C} ROCH_2Br + H_2O \qquad (1)$$

Higher alcohols are reported to react more smoothly than lower alcohols.[4] The reaction is best performed at low temperatures[2,9] to suppress formation of dialkoxymethanes (acetalization of formaldehyde). Bromomethyl alkyl ethers, in particular those of lower alcohols, are sensitive to hydrolysis and best yields are therefore obtained when the water formed is efficiently removed from the reaction medium by using water-immiscible solvents such as CH_2Cl_2 or $CHCl_3$ and/or by addition of desiccating agents like $CaCl_2$.[1,2,6] The reaction is quantitative in the case of primary alcohols. Secondary, tertiary, and benzylic alcohols form the corresponding bromides as side products.[1c,2] Formation of toxic bis(bromomethyl)ether (from formaldehyde and HBr) is noted when an excess of formaldehyde with respect to the alcohol is used and/or for secondary, tertiary, or benzylic alcohols.[2] No information is available on the toxicity of bromomethyl alkyl ethers, but it is likely that they are as toxic (carcinogenic) as the corresponding chloromethyl ethers (see ***Formaldehyde-Hydrogen Chloride*** and ***Bis(chloromethyl) Ether***).[7]

Bromomethylation of Aromatic Compounds.

The combination formaldehyde-HBr is, in many cases, a suitable replacement for the more reactive but highly toxic bis(bromomethyl) ether and bromomethyl alkyl ethers in the bromomethylation of aromatic compounds (eq 2).[1,8-10]

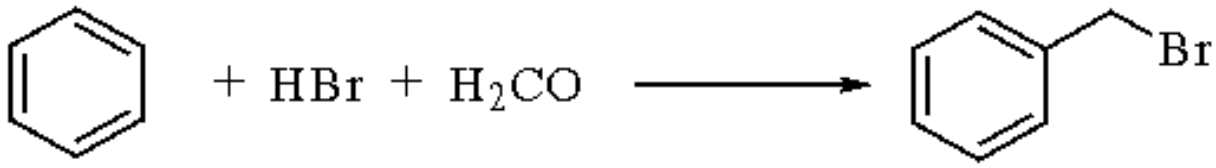

(2)

Bromomethylation is less well documented than chloromethylation (see ***Formaldehyde-Hydrogen Chloride***), but recipes for chloromethylation often can be adapted by substituting HBr for HCl.[1a,b,10,11] Among the catalysts employed are mild Lewis acids (***Zinc Chloride***, ***Tin(IV) Chloride***) and protic acids (***Sulfuric Acid***, ***Acetic Acid***), and often HBr by itself suffices.[1,3,6] Typical solvents are water, ether, chloroform, or (glacial) acetic acid. For aqueous systems, addition of a phase-transfer catalyst was found to improve rate and yield of the reaction.[9] Generally, product yields are high.

The source of formaldehyde in the reaction has been the aqueous solution,[1] paraformaldehyde,[1,8] or trioxane.[9] HBr can be introduced as a gas,[1,10] as an aqueous solution,[9] or in acetic acid solution.[8,12] It can also be generated in situ from sodium bromide and mineral acid.[1,13] The reactivity of the bromomethylating species is least in aqueous solvent systems and highest in anhydrous media containing $ZnCl_2$ or H_2SO_4. Benzene can only be bisbromomethylated by the anhydrous reagent.[13] The latter has a reactivity similar to bis(bromomethyl) ether, suggesting a common electrophile

(i.e. the bromomethyl carbenium ion, $^{+}CH_2Br$), whereas in water-containing media the less reactive hydroxymethyl cation ($^{+}CH_2OH$) is the electrophile.[3,4,11] Diarylmethane formation, i.e. condensation of the bromomethylated compound with the original aromatic compound, is the primary side reaction,[1] but this is less prevalent than in chloromethylation and is frequently absent.[8-10] Polycondensation with H_2CO may occur with phenols (Bakelite formation), but this side reaction is suppressed by the presence of electron-withdrawing groups or by esterification of the phenol group.[1a,c]

Bromomethylation is generally applicable to aromatic compounds such as benzene,[1,9] naphthalene (1-position),[10,13a] or anthracene (9,10-positions).[1] The reaction is faster with activated aromatics like alkylbenzenes (toluene,[9,13a] mesitylene,[8,9,12a] *t*-butylbenzene,[14] 1- or 2-methylnaphthalene[9a,10]), phenols (2- or 4-nitrophenol,[15a] 4-alkylphenol,[16b] 2-bromo-4-phenylphenol,[16b] 2-(3-bromo-5-phenylsalicyl)-4-*t*-butylphenol[16b]), alkoxy-[15b] or aryloxybenzenes[12c] (no ether cleavage observed). The reaction is retarded or even completely suppressed (in the case of aqueous media) by electron-withdrawing substituents like F,[14] Cl, Br,[13a] or CH_2Br.[8,9] In case of highly activated aromatics, the reaction is often difficult to stop after the introduction of one CH_2Br group and, for phenols in particular, bis-bromomethylation is observed.[16] For methylbenzenes the degree of bromomethylation can be controlled by adjusting the reaction temperature and/or the amount of reagent (e.g. selective mono-, bis-, or trisbromomethylation of mesitylene) (eq 3).[8,9]

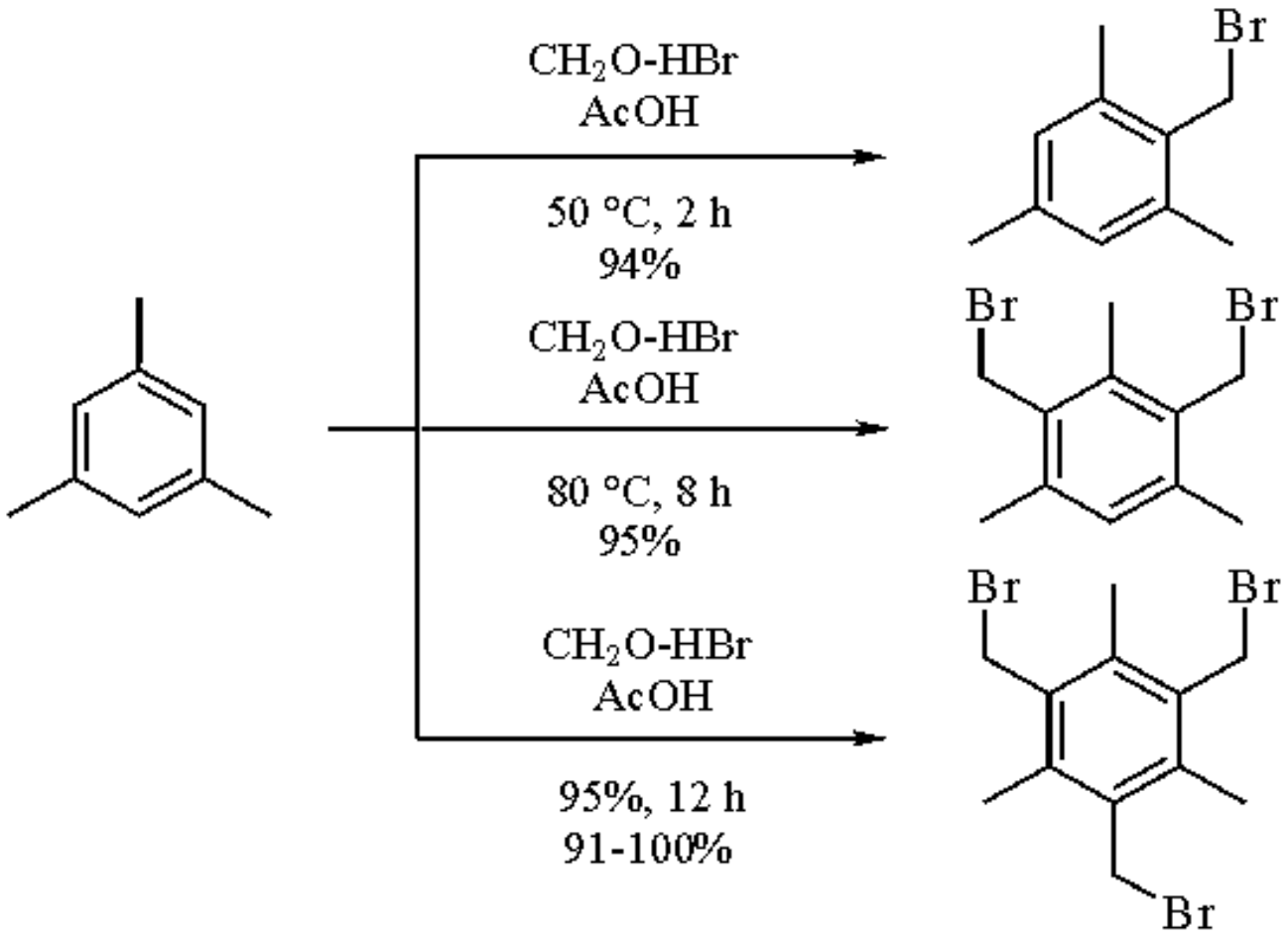

(3)

Related Reagents.

Bromomethyl Methyl Ether; ***Formaldehyde***; ***Hydrogen Bromide***.

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Formaldehyde-Hydrogen Chloride[1]

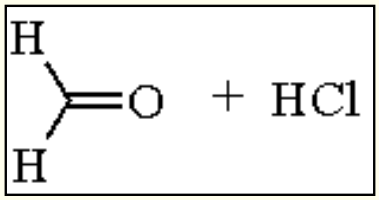

(CH_2O)

[50-00-0] · CH_2O · Formaldehyde-Hydrogen Chloride · (MW 30.03) (HCl)

[7647-01-0] · ClH · Formaldehyde-Hydrogen Chloride · (MW 36.46)

(chloromethylation of activated aromatics[1] and heteroaromatics,[1b] cyclophanes,[2] aromatic polymers;[1b,3] synthesis of chloromethyl ethers;[4,1a] lactones from phenylacetic acid[5])

Preparative Methods: formaldehyde is usually in the form of formalin or paraformaldehyde. For aromatic chloromethylation, solvents such as glacial acetic acid, CS_2, CCl_4, or chloroform are often employed, although heterogeneous chloromethylations using excess aromatic as solvent are numerous.[1b] A Lewis acid catalyst (often ***Zinc Chloride*** but a range of other Friedel-Crafts type catalysts have been reported), or a protic acid catalyst (usually ***Sulfuric Acid***, conc ***Hydrochloric Acid***, syrupy ***Phosphoric Acid***) is often necessary, especially if electron-withdrawing groups are present on the arene. Typically, a rapid stream of HCl is passed through the formaldehyde-substrate mixture in a suitable medium until no more gas is absorbed.

Handling, Storage, and Precautions: many chloromethylated compounds are lachrymatory. Chloromethyl ethers are carcinogenic. The reagents should be handled in a well-ventilated fume hood.

Chloromethylation Reaction.

Chloromethylation of arenes is a typical electrophilic aromatic substitution (ρ = -5).[1a] Alkylbenzenes like toluene and anisole give mixtures of *ortho*/*para* chloromethylated isomers and the proportion of *meta* always remains low (eq 1).

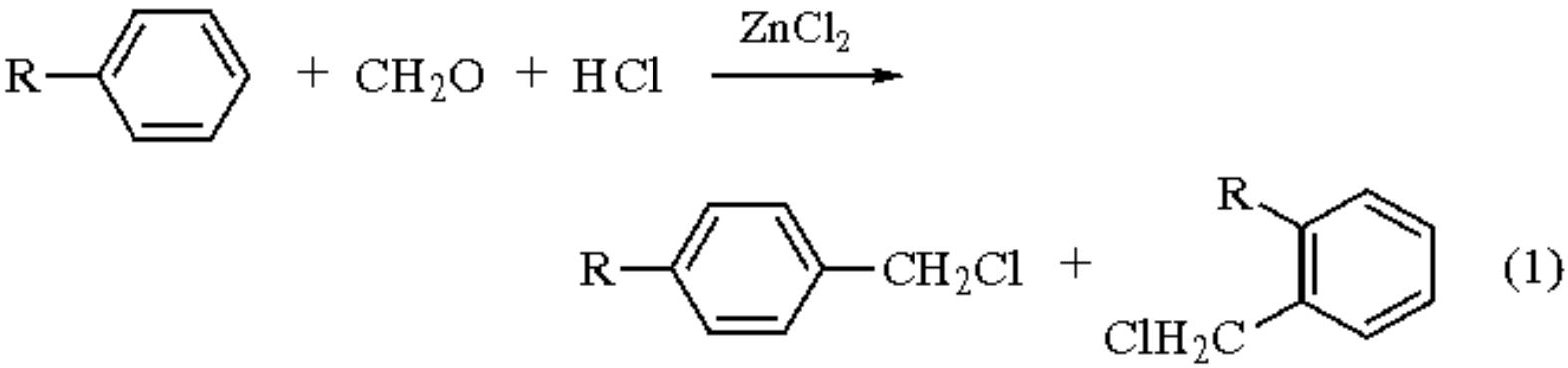

The reaction is facilitated by alkyl and alkoxy substituents and hindered by electron-withdrawing groups (halo, especially nitro). Increasing steric crowding of the substituent increases the *para* isomer at the expense of the *ortho*.[1a,1b] On the other hand, the proportion of *ortho* increases on going from fluorobenzene to iodobenzene.[1a,1b] Although substrate selectivities (K_T/K_B) are variable, depending on reaction conditions, isomer distributions do not change much.[6]

Bischloromethylated arenes are often observed as byproducts. Diarylmethane formation is a known side reaction in chloromethylation with CH_2O/HCl, especially with reactive arenes.[1] Use of $AsCl_3$ or As_2O_3 as a chloromethylation catalyst apparently inhibits this side reaction.[1a]

Whereas there seems to be general agreement that CH_2O/HCl is a chloromethyl alcohol equivalent, there is difference of opinion as to the exact nature of the chloromethylation electrophile.[1a] Thus $HOCH_2^+$ and CH_2Cl^+ have both been invoked.[1a,6] *O*-Protonated chloromethanol (**1**), which is observable in solution under persistent ion conditions,[7] has been suggested as a possible electrophile. Protonated formaldehyde (**2**) and chloromethylcarbenium ion (**3**) have also been proposed.[1a,6] When acetic acid is used as solvent for chloromethylation, chloromethyl acetate or its protonated form may serve as the actual electrophile.

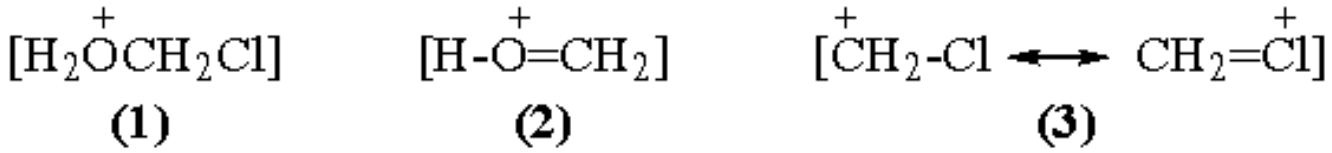

Bis(chloromethyl)ether (**4**) may be formed in situ in chloromethylation with CH_2O/HCl and it is likely that this could also act as the chloromethylating agent (eq 2). It is believed that (**4**) can become the chloromethylation reagent in reactions involving deactivated aromatics in the presence of protic acids, where its formation and further reaction effectively competes with direct chloromethylation via CH_2O/HCl.[1a] Environmental studies show that, under ambient conditions, (**4**) formation from CH_2O/HCl in moist air is insignificant.[8]

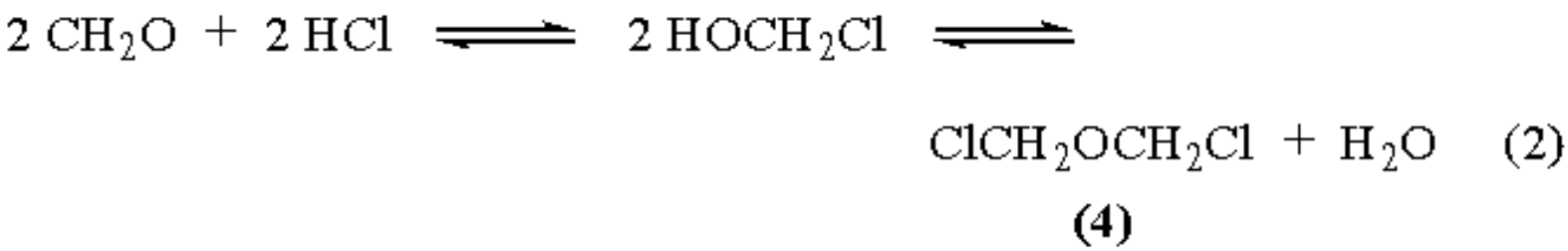

Scope and Limitations.

Alkylbenzenes such as toluene, xylene isomers, tri-, tetra-, and pentamethylbenzenes, ethyl-, isopropyl-, isomeric butyl-, and pentylbenzenes are all chloromethylated with CH_2O/HCl.[1b,1c] For example, mesitylene reacts with CH_2O/HCl (gas) in conc HCl solvent to give a 55-61% isolated yield of α^2-chlorodurene (eq 3).[9]

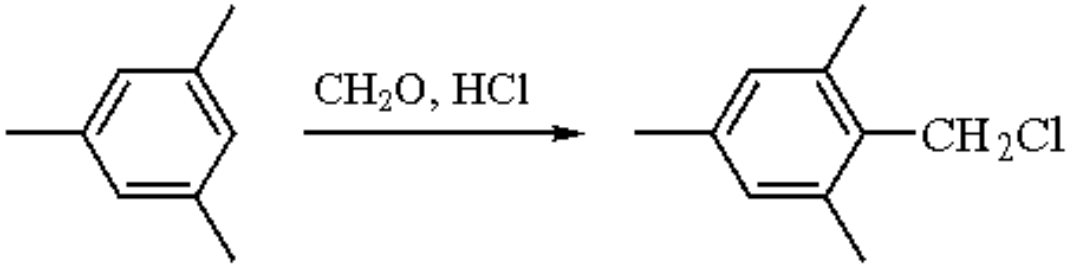

(3)

Biphenyl, diphenylmethane, indan, and tetralin also react.[1b] Whereas chloromethylations of halobenzenes are less efficient, haloalkylarenes are efficiently chloromethylated with CH_2O/HCl.[1b] The presence of nitro group(s) makes chloromethylation difficult unless activating substituents are present. With nitrobenzene and nitrotoluenes, the *meta* isomer is predominant.[1b] The higher reactivity of chloromethyl methyl ether makes it the reagent of choice for chloromethylation of nitroalkyl- and dihaloalkylbenzenes. In such instances, the reactions are often conducted in 60% H_2SO_4 (eq 4).[10]

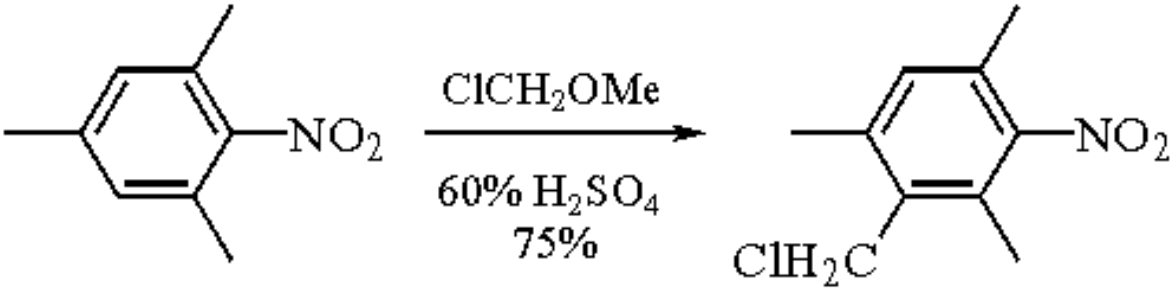

(4)

The CH_2O/HCl reagent is suitable for chloromethylation of various polycyclic aromatic hydrocarbons,[1b] as well as heterocyclic aromatic compounds.[1a,1b] Thiophene gives 2-(chloromethyl)thiophene in 40-41% isolated yield,[11] and 4-methylimidazole gives the 5-chloromethyl derivative (51-68%) (eq 5).[12]

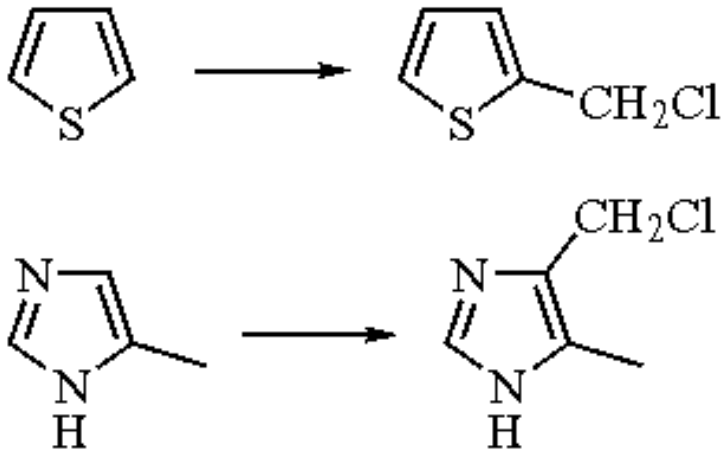

(5)

Phenols react readily with CH_2O/HCl but the initially formed product reacts further to give phenol-formaldehyde resin. Only if electron-withdrawing groups are present can the chloromethylation products be isolated.[1b]

Alkyl aryl ketones are chloromethylated at the side chain unless activating groups are present on the aromatic ring. It has been proposed that CH_2OH^+ attacks the enol tautomer.[1a] In the presence of activating groups, aromatic aldehydes and esters are chloromethylated. Otherwise, severe conditions are needed. *p*-Anisaldehyde chloromethylates in 90% yield with the CH_2Cl group entering *meta* to the formyl group (eq 6). Aryl alkyl sulfides and diaryl sulfides are usually ring chloromethylated in good yields.[1b]

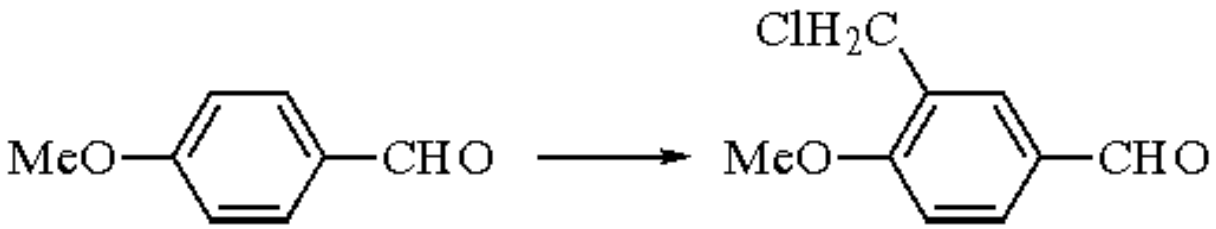

(6)

[2.2]Paracyclophane is chloromethylated with the CH_2O/HCl reagent. The presence of an acyl group in one ring assures pseudogeminal substitution by the chloromethyl group (eq 7).[2] This is a useful reaction for the synthesis of superphanes.

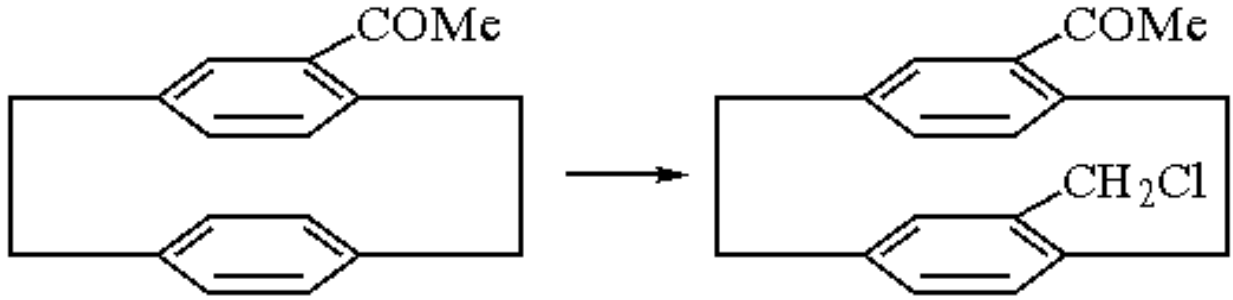

(7)

Chloromethylated phenethyl bromide is produced in >70% yield by chloromethylation with $CH_2O/HCl/ZnCl_2$ (75% *para*) and subsequently polymerized to chloromethylated styrene.[13] The patent literature contains numerous examples of chloromethylation of polymers (for example polystyrene, divinylbenzene/styrene copolymer, and polyoxyphenylenes) using the CH_2O/HCl reagent, although there is a larger tendency to use chloromethyl alkyl ethers instead.[4c,14]

Comparison with Other Chloromethylating Agents.

Because of the limitations that exist in chloromethylation of deactivated arenes, the more reactive ***Chloromethyl Methyl Ether*** and ***Bis(chloromethyl) Ether*** appear more suitable. However, these are carcinogenic and alternative routes have been sought.

Methoxyacetyl Chloride/Aluminum Chloride is suitable for chloromethylation of certain aromatics.[15] The methoxymethyl cation has been suggested as the electrophile (eq 8).

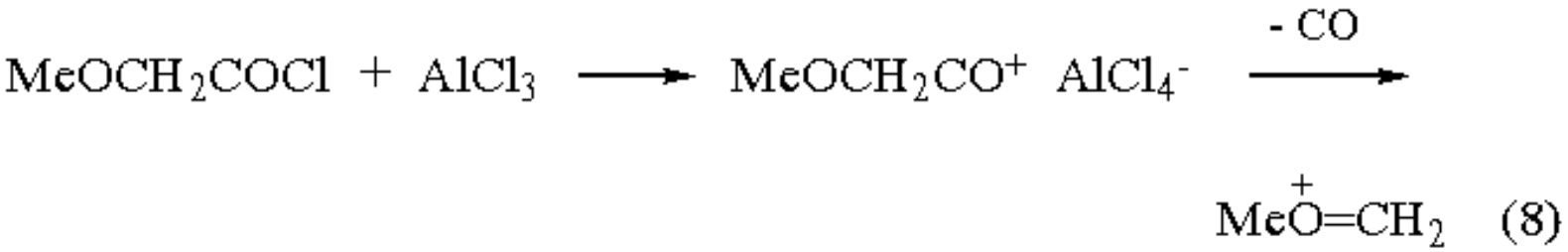

The less volatile long-chain halomethyl alkyl ethers prepared from alkanols and CH_2O/HCl in chlorinated solvents have been used successfully for the chloromethylation of arenes and polystyrene.[4c] The amount of (**4**) produced is quite low and depends on the ROH:CH_2O ratio.

1-Chloro-4-(chloromethoxy)butane and 1,4-bis(chloromethoxy)butane in combination with ***Tin(IV) Chloride*** or ***Zinc Bromide*** can be used for arene chloromethylation. Literature examples are limited to alkylbenzenes.[6,15] Yields are 43-60%, depending on the arene (eq 9).

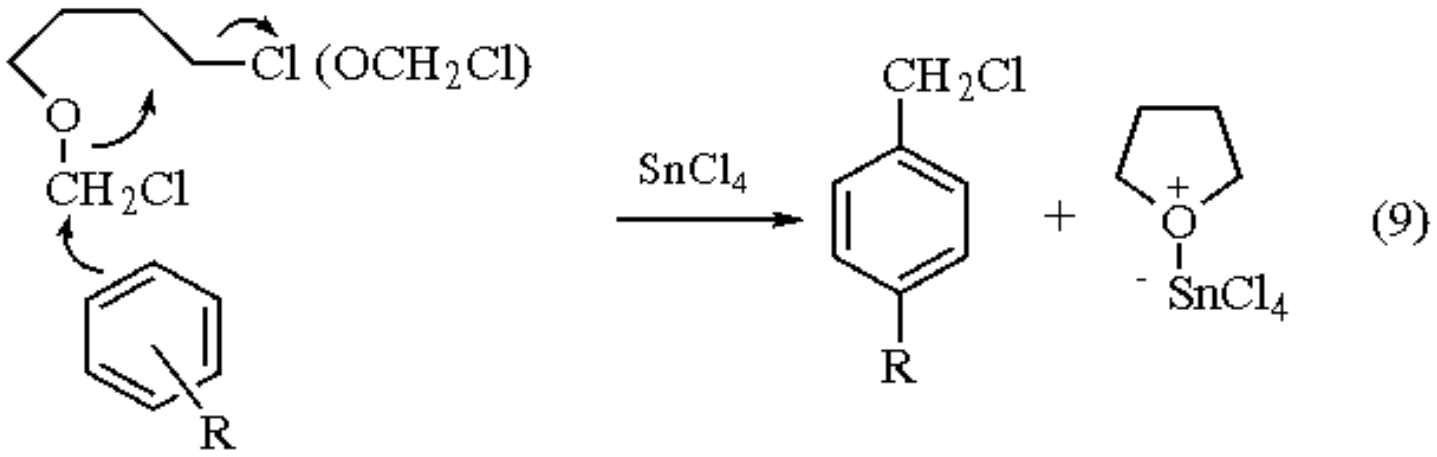

Synthesis of Chloromethyl Ethers.

Chloromethyl methyl ether can be prepared from MeOH/CH_2O/HCl in 86-89% isolated yield.[4a] The corresponding benzyl ether was obtained from $PhCH_2OH$ in 83% yield.[4b] Controlled addition of CH_2O to anhydrous MeOH or methylal saturated with HCl gas gives $ClCH_2OMe$ with little (**4**).[16]

Other Useful Reactions.

3,4-Dimethoxyphenylacetic acid reacts with CH_2O/HCl to give the corresponding lactone (eq 10).[5] Variations of this procedure are applicable to multi-ring compounds.[17] *sym*-Trithiane is formed by reaction of H_2S with CH_2O/conc HCl.[18] Long-chain thiols are chloromethylated with CH_2O/HCl to give $RSCH_2Cl$.[19]

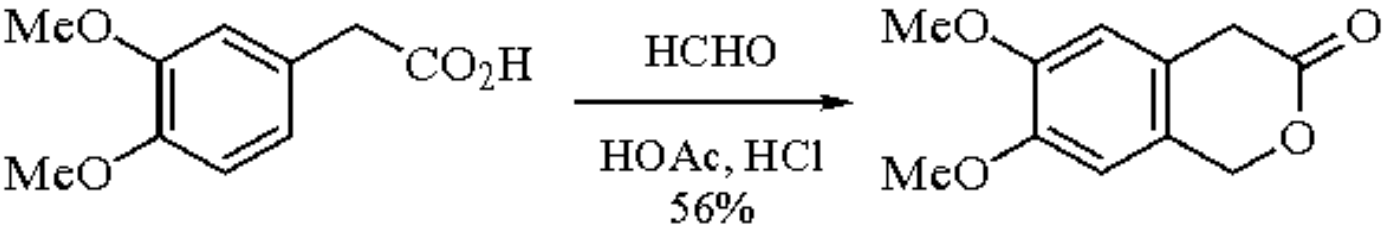

(10)

Related Reagents.

Benzyl Chloromethyl Ether; ***Bis(chloromethyl) Ether***; ***t-Butyl Chloromethyl Ether***; ***Chloromethyl Methyl Ether***; ***Chloromethyl Trimethylsilyl Ether***; ***Formaldehyde***; ***Formaldehyde-Hydrogen Bromide***; ***Hydrogen Chloride***; ***Methoxyacetyl Chloride***; ***Zinc Chloride***.

---

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Formaldoxime

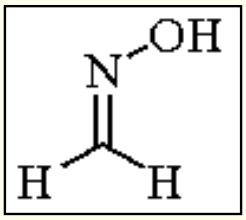

[75-17-2] · CH_3NO · Formaldoxime · (MW 45.05)

(formylation of arenes via diazonium salts;[1,2] 1,3-dipolar cycloaddition with electron-deficient alkenes and alkynes to form isoxazolidines[3])

Alternate Name: formaldehyde oxime.

Physical Data: mp 2.5 °C; bp 84 °C.

Solubility: frequently used in aqueous solution or in admixture with aqueous methanolic solution.

Form Supplied in: commercially available as hydrochloride.

Preparative Methods: reaction of 37% aqueous formaldehyde with hydroxylamine hydrochloride to which sodium hydroxide in 30% aqueous methanol is added (eq 1).[3-5] This procedure affords useful solutions of formaldoxime in aqueous methanol.[3] Alternatively, paraformaldehyde with hydroxylamine hydrochloride in the presence of sodium acetate in aqueous medium produces a 10% solution of formaldoxime.[2]

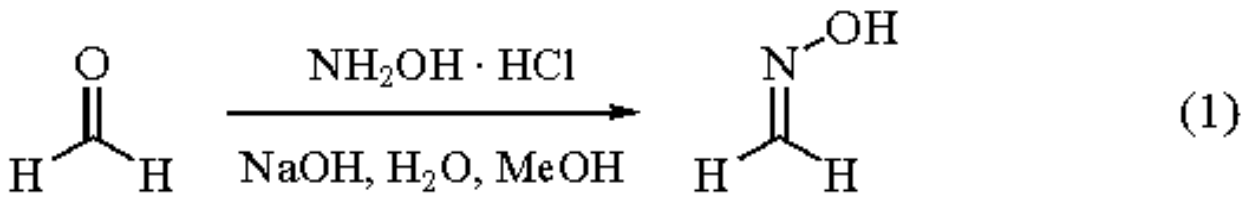

Handling, Storage, and Precautions: stable as hydrochloride; the oxime readily polymerizes at room temperature and is more stable in aqueous solution. Handle in a fume hood.

In the older literature, the trimer of formaldoxime is often reported, although this form was an open-chain polymer.[6] In contrast, *O*-acetyl and *O*-benzoyl derivatives of formaldoxime are cyclic trimeric compounds, i.e. derivatives of 1,3,5-trihydroxyhexahydro-1,3,5-triazine.[6] The hydrochloride $(CH_2NOH)_3$.HCl and other salts also exist as the cyclic trimer. They depolymerize into monomeric formaldoxime by neutralization. The cyclic trimer, which can be isolated, is water soluble and rearranges fast into the water-insoluble polymer. ^{1}H NMR spectra (D_2O) demonstrate equilibration

between the monomer and the trimer. At high pH, this equilibrium is completely shifted to the monomeric form.[6] The ^{13}C NMR chemical shift and ^{13}C-^{15}N coupling constant have been reported.[7]

Formylation of Arenes via Diazonium Salts.

Formaldoxime reacts with aromatic diazonium salts to give the corresponding substituted benzaldehyde oxime derivative, which is hydrolyzed in acid medium to afford aromatic aldehydes (eqs 2 and 3).[1,2] The net reaction constitutes the conversion of anilines into aryl aldehydes (eq 4).[3,8-12]

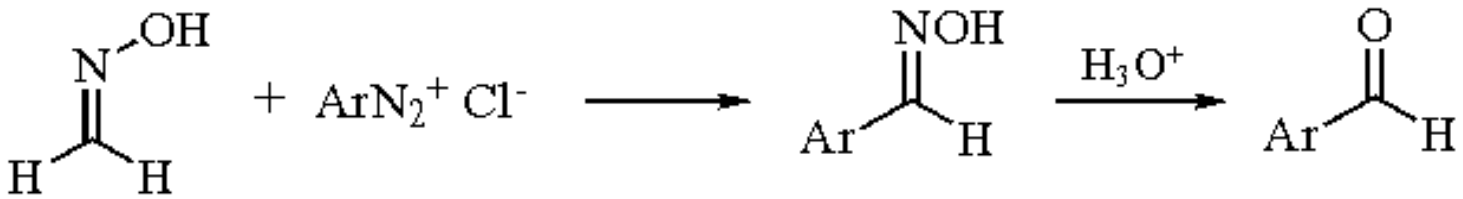

(2)

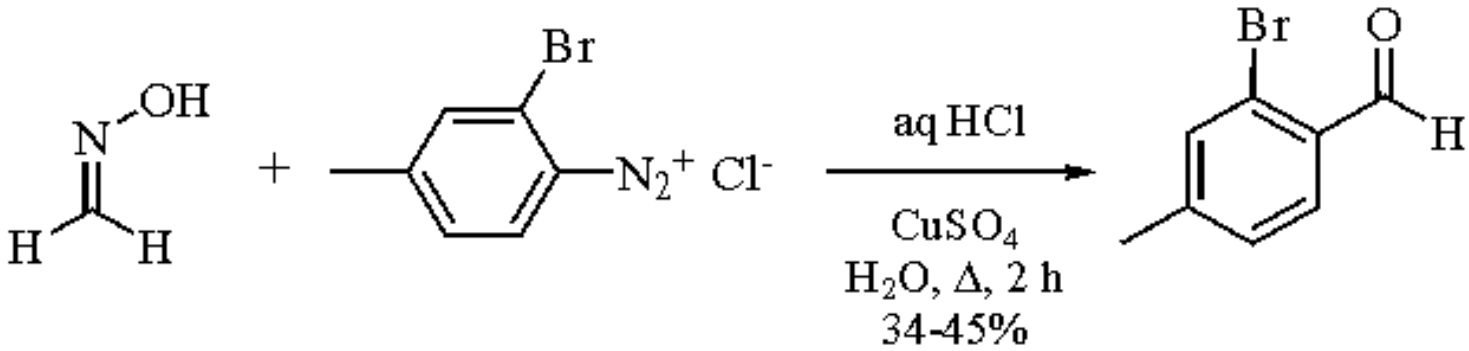

(3)

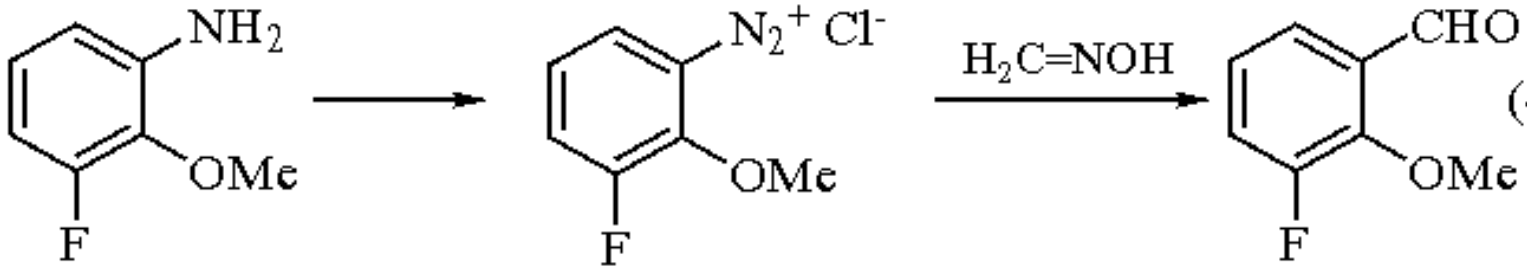

(4)

1,3-Dipolar Cycloaddition with α,β-Unsaturated Nitriles and Acrylates.

Formaldoxime acts as a 1,3-dipole in cycloaddition reactions with acrylonitrile (eq 5) and methyl acrylate (eq 6), affording functionalized isoxazolidines.[3] In both cases, the 1,3-cycloadduct is partially converted into the Michael adduct of the isoxazolidine with the α,β-unsaturated nitrile or acrylate. In contrast, acetaldoxime reacts with the same electron-deficient alkenes to give mixtures of regioisomeric isoxazolidines.[13]

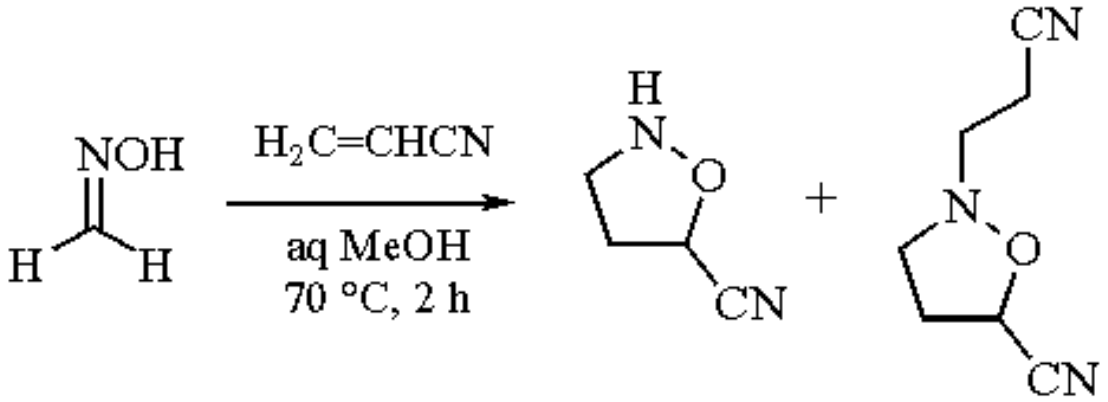

(5)

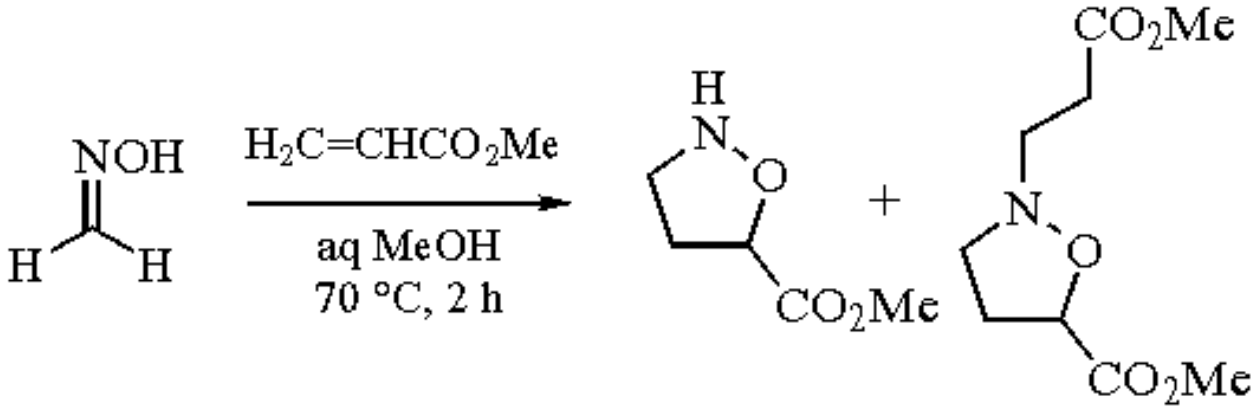

(6)

Cycloaddition with Propiolates.

The reaction of formaldoxime with ethyl propiolate (see ***Methyl Propiolate***) in 50% aqueous methanol leads to diethyl pyridine-3,5-dicarboxylate, during which a 1,4-dipolar cycloaddition mechanism is operative (eq 7).[3]

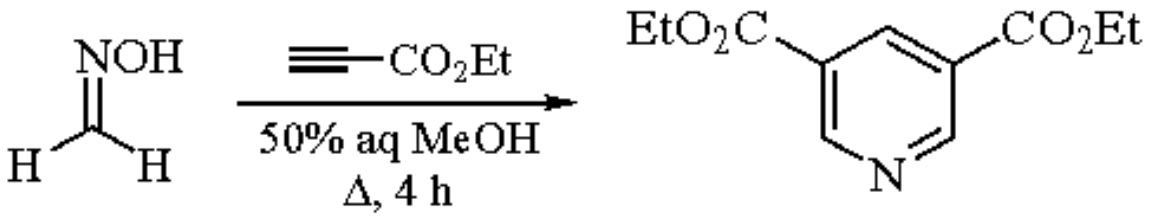

(7)

Additions of Carbanions Across the Carbon-Nitrogen Double Bond.

Formaldoxime undergoes addition of fluorodinitromethane in a biphase system of water-diethyl ether in the presence of sodium carbonate to afford 2-fluoro-2,2-dinitroethylhydroxylamine in moderate yield (eq 8).[14]

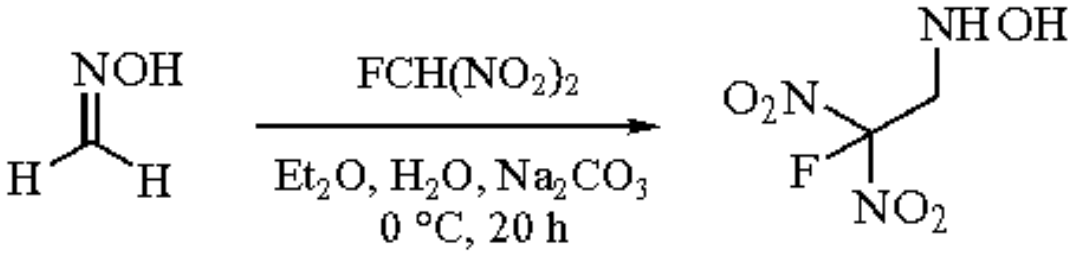

(8)

Related Reagents.

Acetaldoxime; ***Benzenediazonium Chloride***; ***Benzenediazonium Tetrafluoroborate***; ***Formaldehyde***; ***Hydroxylamine***; ***Methyl Propiolate***.

---

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Formamidine Acetate

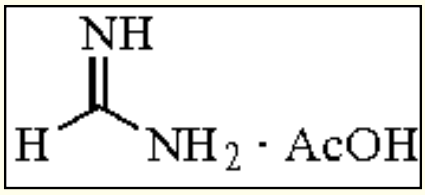

[40730-94-7] · $C_3H_8N_2O_2$ · Formamidine Acetate · (MW 104.13)

(condensing agent for the synthesis of pyrimidine[1] and imidazole[2] heterocycles)

Alternate Name: FA.

Physical Data: mp 162-164 °C.

Solubility: sol H_2O, hot alcohol.

Form Supplied in: white crystalline solid, widely available.

Handling, Storage, and Precautions: is nonhygroscopic and is stable on storage.

Synthesis of Pyrimidine Heterocycles.

The pyrimidine ring can be conveniently constructed by the reaction of unsaturated 2-aminonitriles (*o*-aminonitriles) with FA, as exemplified by the synthesis of 4-aminopyrimido[4,5-*d*]pyrimidine (eq 1)[2a] and 7-amino-2-(phenylamino)thiazolo[5,4-*d*]pyrimidine (eq 2).[3] 4-Amino-8-methyl-1,2,3-triazolo[1,5-*a*]-1,3,5-triazine is obtained from the reaction of 5-amino-4-cyano-4-methyl-4*H*-1,2,3-triazole with FA by translocative rearrangement (eq 3).[4] FA has also been widely used for the formation of fused pyrimidines in the synthesis of *C*-nucleosides (eqs 4 and 5).[5]

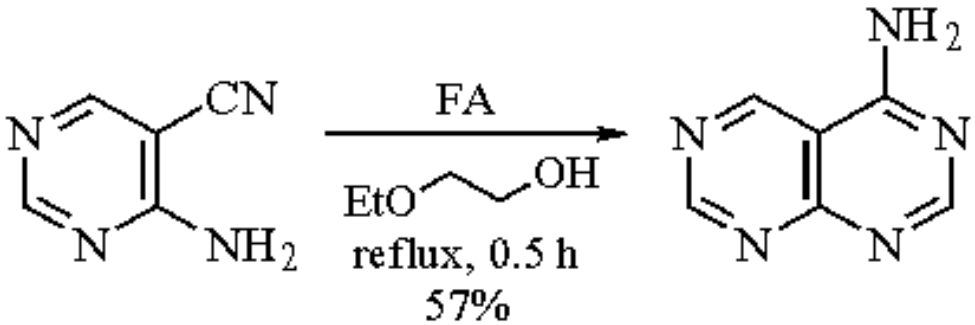

(1)

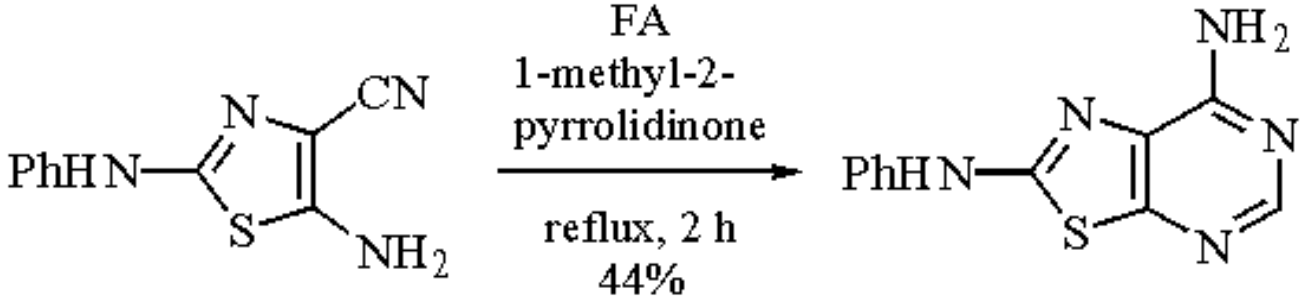
FA
1-methyl-2-
pyrrolidinone
reflux, 2 h
44%
PhHN
CN
NH2
N
S
NH2
N
N
N
S
N

(2)

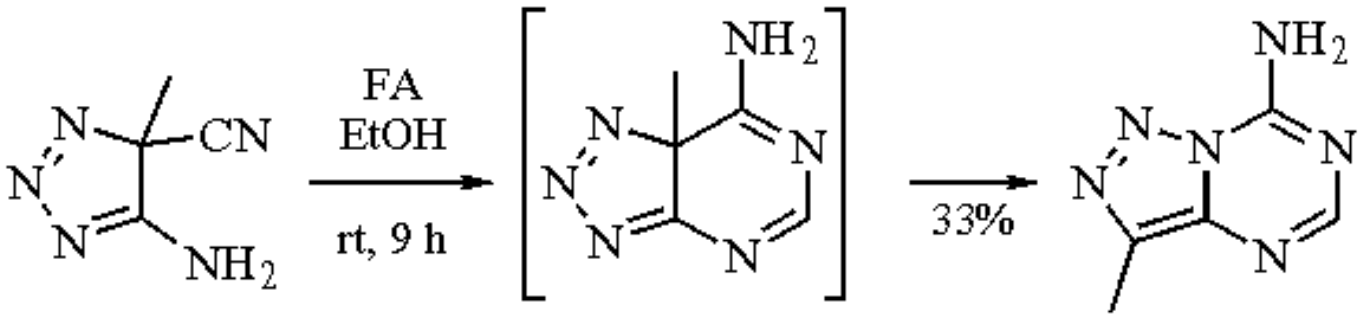
FA
EtOH
rt, 9 h
33%
N
CN
N
N
NH2
NH2
NH2

(3)

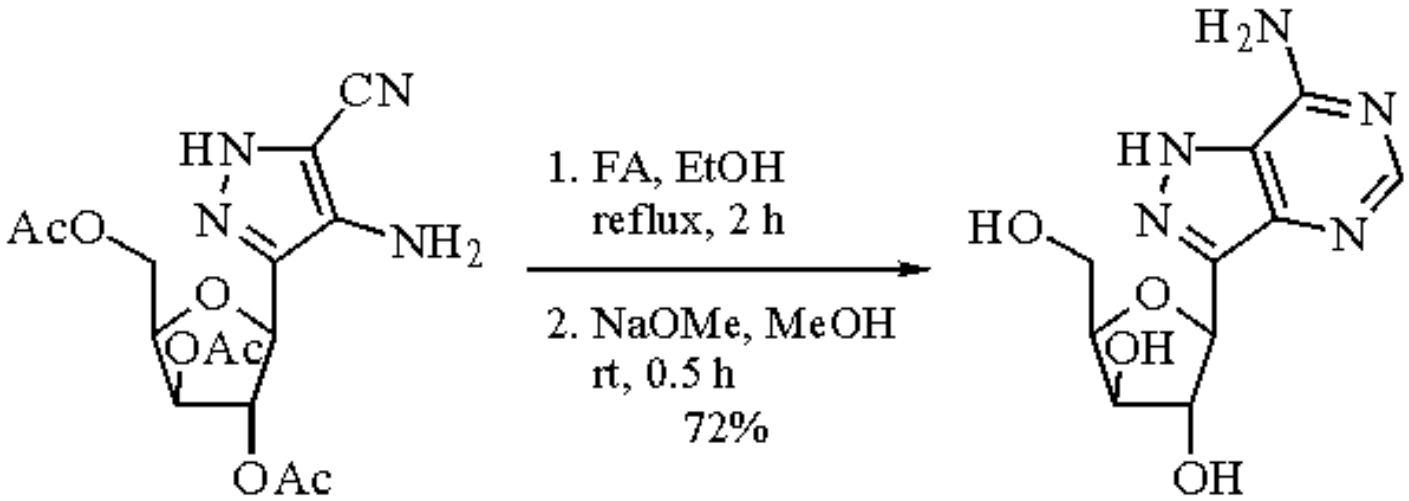
1. FA, EtOH
reflux, 2 h
2. NaOMe, MeOH
rt, 0.5 h
72%
CN
HN
N
NH2
AcO
O
OAc
OAc
H2N
N
HN
N
N
HO
O
OH
OH

(4)

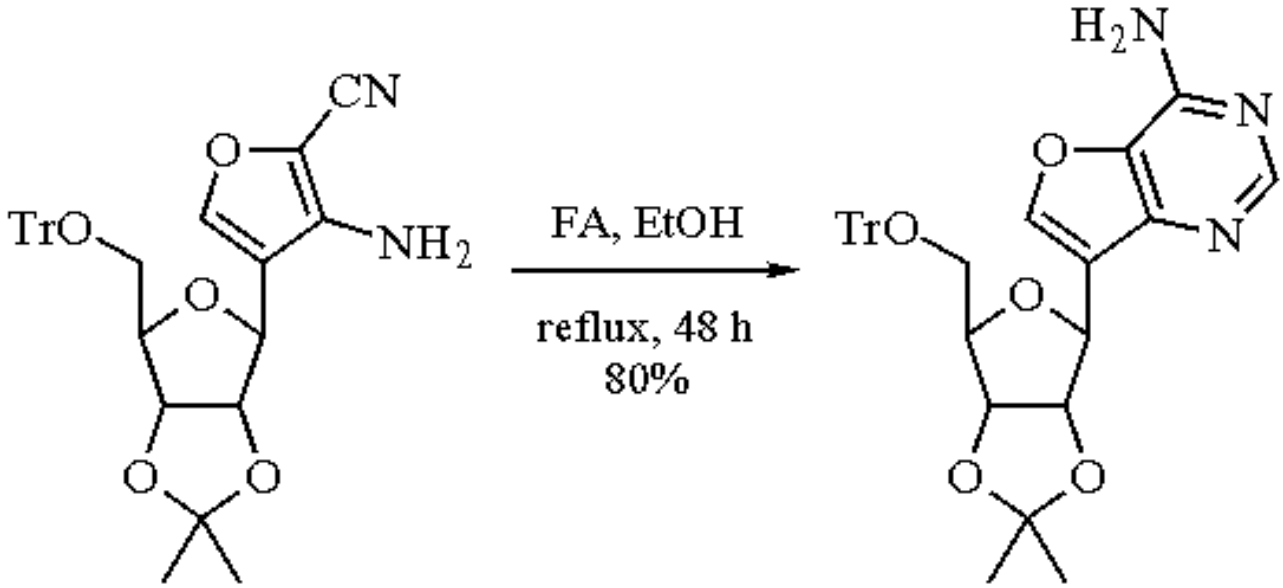
FA, EtOH
reflux, 48 h
80%
CN
O
TrO
NH2
O
O
O
H2N
N
O
TrO
N
O
O
O

(5)

Pyrimidones are obtained by the reaction of FA with 5,8-dihydroisatoic anhydride (eq 6)[6] or with *o*-amino esters (eq 7).[7] No aromatization or conjugation of double bonds in the product is observed in the former case (eq 6).

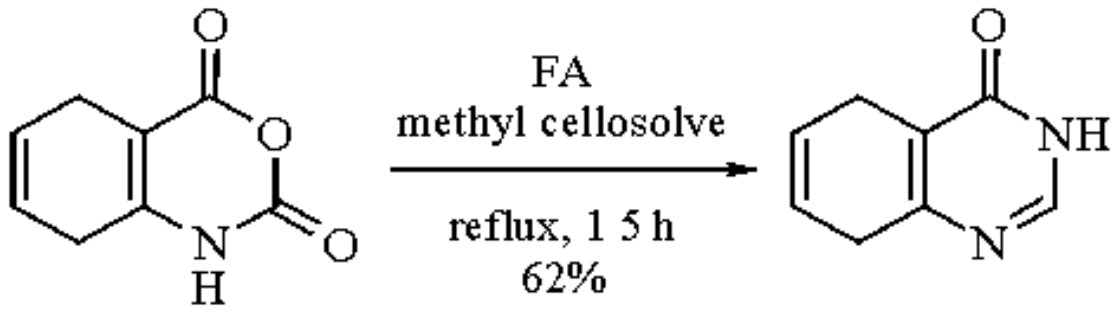

(6)

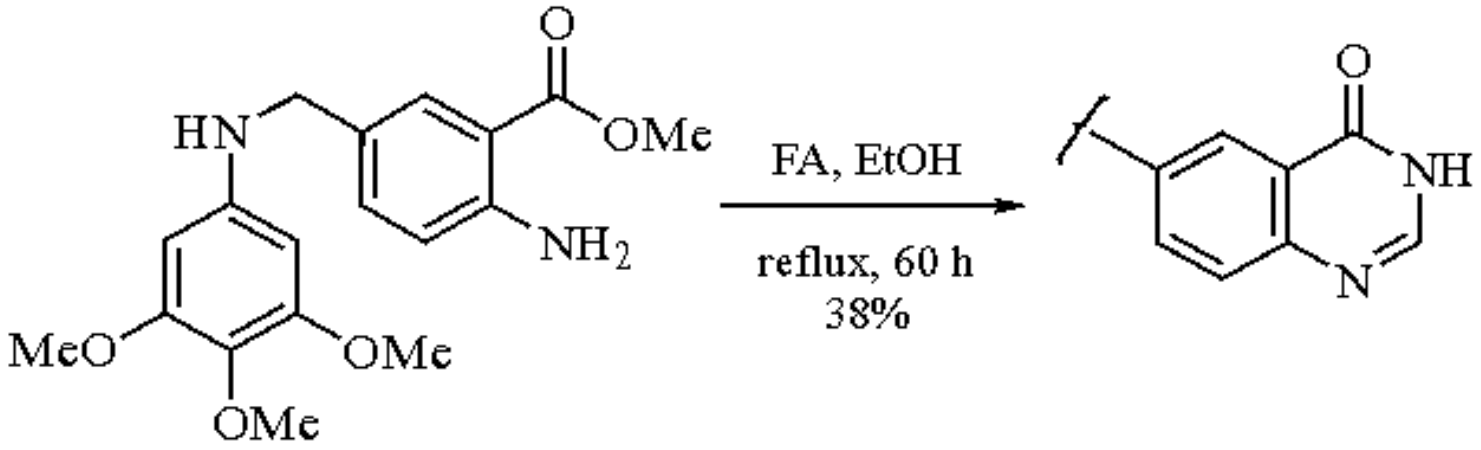

(7)

A dihydropyrimidine is obtained by the reaction of FA with mesityl oxide (eq 8).[8]

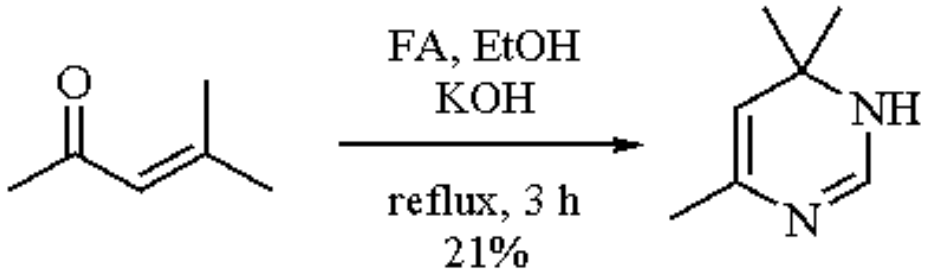

(8)

Synthesis of Imidazole Heterocycles.

FA has been used as a reagent providing a one-carbon fragment in the synthesis of a wide variety of imidazole derivatives.[2] The reaction conditions are often mild, and therefore it is the reagent of choice in the Traube synthesis of 9-glycosylpurines (eq 9).[9] Imidazoles have also been synthesized by the reaction of FA with α-chloro ketones (eq 10)[2e] and α-hydroxy ketones (eq 11).[10]

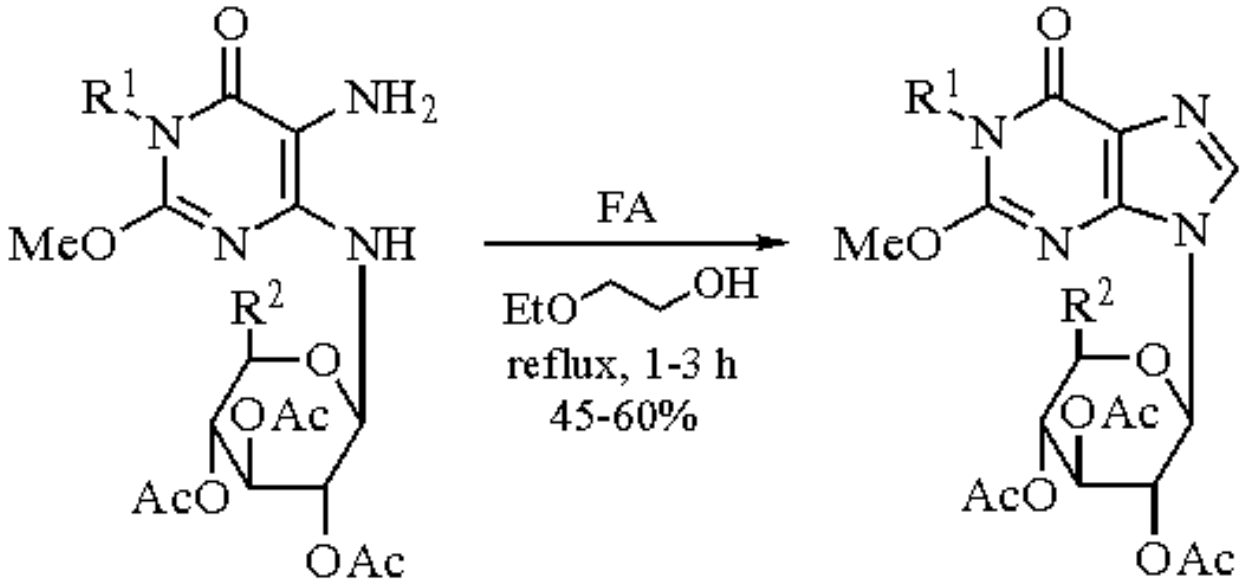

(9)

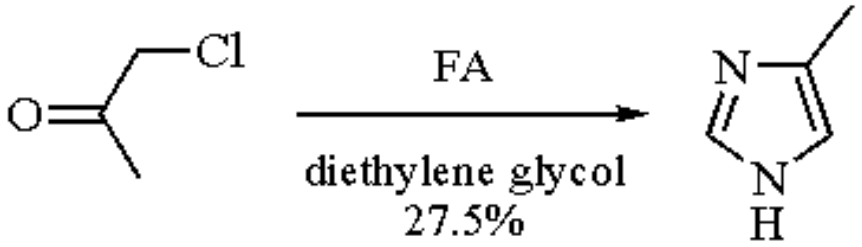

(10)

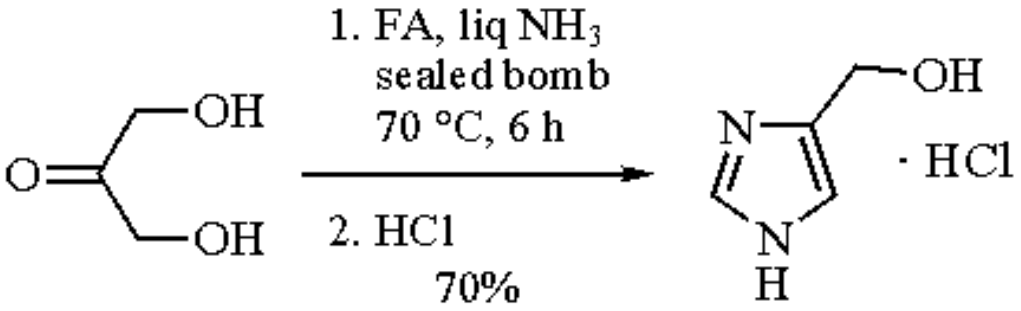

(11)

The trifluoromethyl group, which is usually inert in most reactions, can change the outcome of the condensation of FA with α-halo ketones if it is located at an α-position to the ketone group. For example, the reaction of FA with α-chloro-β-trifluoromethyl ketones gives 4-substituted imidazoles (eq 12). However, α-chloro-α´-trifluoromethyl ketones afford 5´-substituted 4-fluoro-6-chloromethylpyrimidines (eq 13).[11]

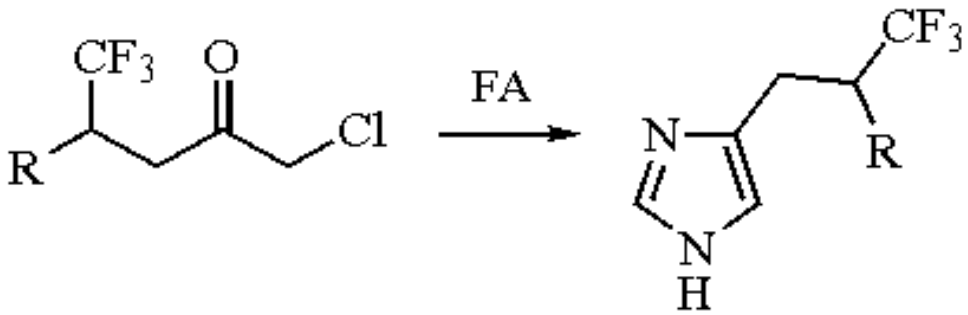

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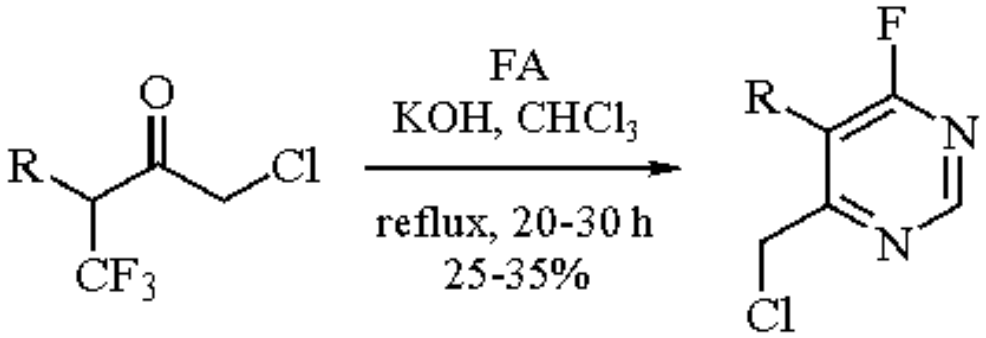

(13)

Similarly, the structure of the product obtained from the reaction of FA with azirines is highly dependent upon the substitution of the azirine ring (eq 14).[12]

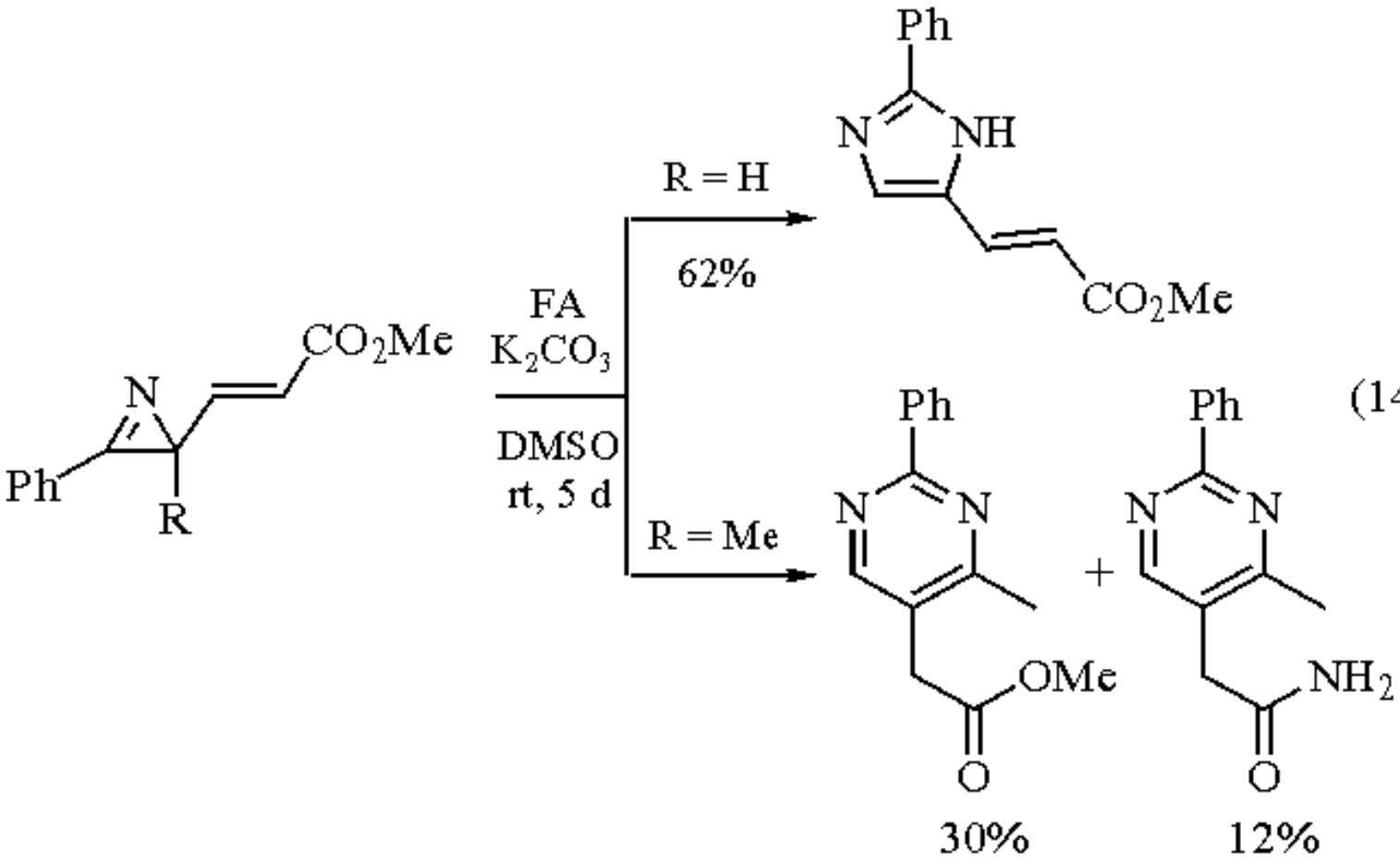

(14)

Advantages of Formamidine Acetate over Formamidine Hydrochloride.

It has been found that formamidine acetate could replace formamidine hydrochloride in syntheses previously reported using the latter. FA is nonhygroscopic and is stable on storage. FA, as the salt of a strong base and a weak acid, could often be used in most condensations without prior liberation of free formamidine. By contrast, formamidine hydrochloride is extremely deliquescent and cannot be used in most condensations but must be converted into the free base. The same restriction applies to the hydrogen methyl sulfate salt of formamidine; in addition, complications in synthesis may be anticipated from the fact that methyl hydrogen sulfate itself is an effective methylating agent.[2a]

Related Reagents.

Ammonium Formate; ***t-Butoxybis(dimethylamino)methane***; *N*-Cyclohexyl-*N´*,*N´*-dimethylformamidine; ***(S)-N,N-Dimethyl-N´-(1-t-butoxy-3-methyl-2-butyl)formamidine***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Ethyl Chloroformate***; ***Formic Acid***; ***Methyl Formate***; ***N´-t-Butyl-N-methyl-N-trimethylsilylmethylformamidine***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***; ***Triethyl Orthoformate***; ***Tris(dimethylamino)methane***; ***Tris(formylamino)methane***.

---

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Joginder S. Bajwa

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Formic Acid[1]

HCO_2H

[64-18-6] · CH_2O_2 · Formic Acid · (MW 46.03)

(formation of formate esters,[3] amides;[7] reductions;[10] transfer hydrogenation;[12] rearrangements[22])

Alternate Name: methanoic acid.

Physical Data: strongest of the simple organic acids; pK_a 3.77 (4.77 for acetic acid). Pure acid, mp 8.4 °C; bp 100.7 °C, 50 °C/120 mmHg, 25 °C/40 mmHg. Formic acid and water form an uncommon maximum boiling azeotrope, bp 107.3 °C, containing 77.5% acid. The dielectric constant of formic acid is 10 times greater than acetic acid.

Solubility: misc water in all proportions; misc EtOH, ether; mod sol C_6H_6.

Form Supplied in: commercially available as 85-95% aqueous solutions and as glacial formic acid, containing 2% water.

Analysis of Reagent Purity: formic acid is determined by titration with base. If other acids are present, formic acid content can be determined by a redox titration based on oxidation with potassium permanganate. Methods for analysis of trace organic and inorganic materials are presented.[2,23]

Purification: fractional distillation in vacuo; dehydration over $CuSO_4$ or boric anhydride.[24]

Handling, Storage, and Precautions: the strongly acidic nature of formic acid is the primary safety concern. Contact with the skin will cause immediate blistering. Immediately treat affected areas with copious amounts of water. Do not use dilute base solutions as a first treatment. Formic acid has a large heat of solution; the combined heat of neutralization and dilution will lead to thermal burns. Eye protection, gloves, and a chemical apron should be worn during all operations with concentrated formic acid. Volatile; vapors will cause intense irritation to mouth, nose, eyes, skin, and upper respiratory tract. Use of an appropriate NIOSH/MSHA respirator is recommended. Use in a fume hood.

During storage, glacial formic acid decomposes to form water and carbon monoxide. Pressure can develop in sealed containers and may result in rupture of the vessel. Ventilation should be provided to prevent the buildup of carbon monoxide in storage areas. Storage temperatures above 30 °C should be avoided.

Formic acid is incompatible with strong oxidizing reagents, bases, and finely powdered metals, furfuryl alcohol, and thallium nitrate. Contact with conc sulfuric acid will produce carbon monoxide from decomposition.

Formation of Formate Esters.

Formic acid will esterify primary, secondary, and tertiary alcohols in high yield (eq 1).[3] The reaction is autocatalytic due to the high acidity of formic acid. The equilibrium position of this reaction is closer to completion than for other carboxylic acids.

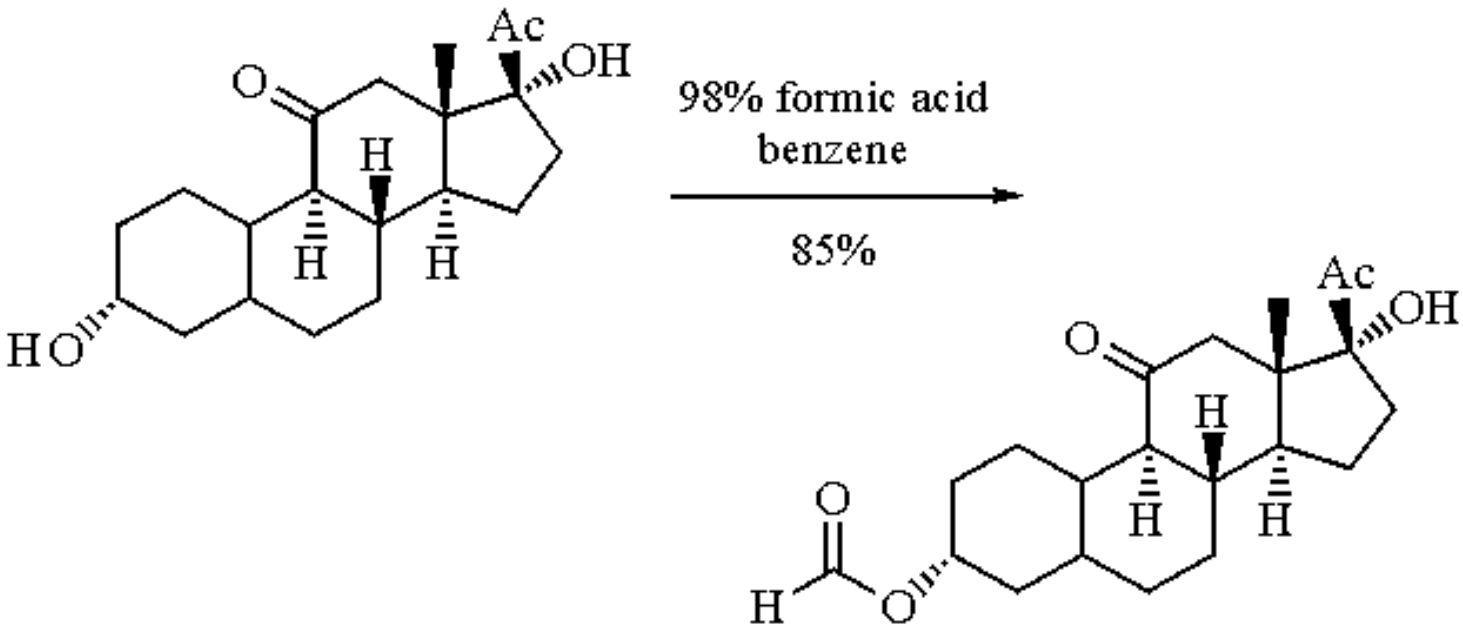

(1)

Formate esters can also be produced during acid-catalyzed rearrangements (eq 2),[4] by addition to alkenes (eq 3),[5] or by ***1,3-Dicyclohexylcarbodiimide*** coupling (eq 4).[6]

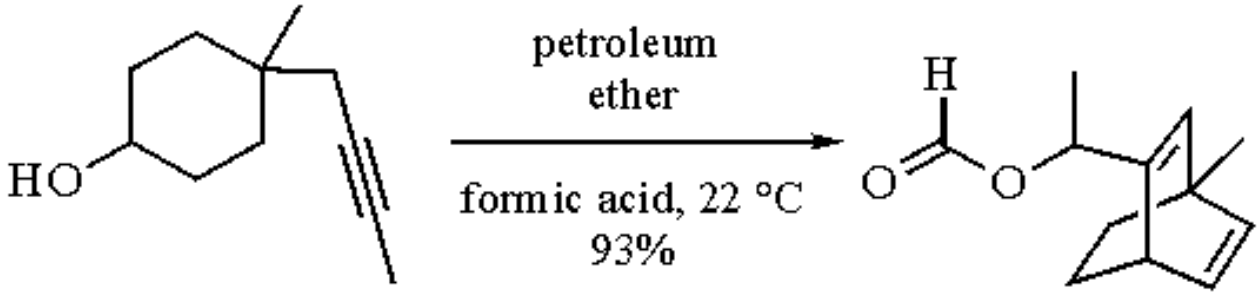

(2)

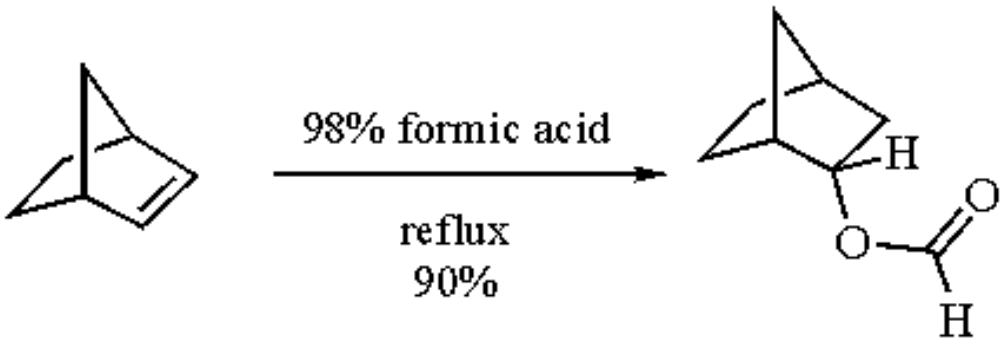

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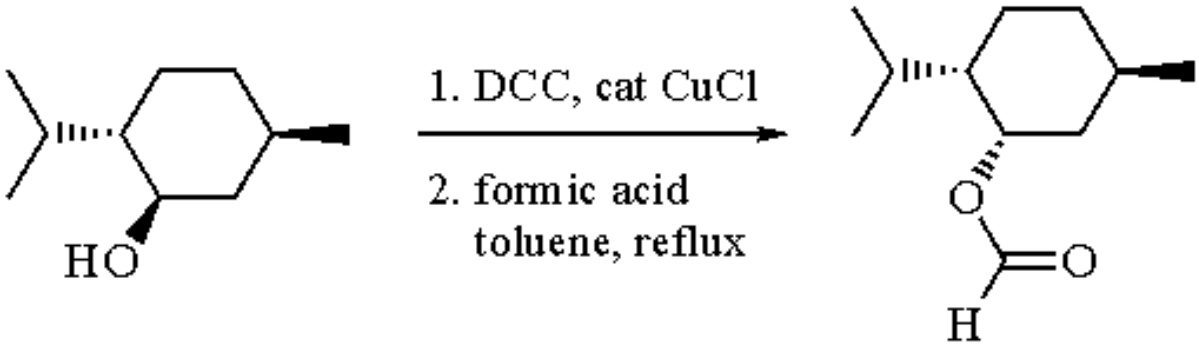

(4)

Formation of Amides.

Most amines react with formic acid to produce the expected amide in high yield.[7] Reaction with diamines is an important reaction for the formation of heterocyclic compounds, including benzimidazoles (eq 5)[8] and triazoles (eq 6).[9]

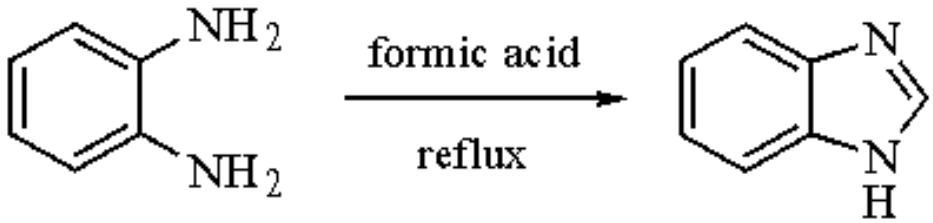

(5)

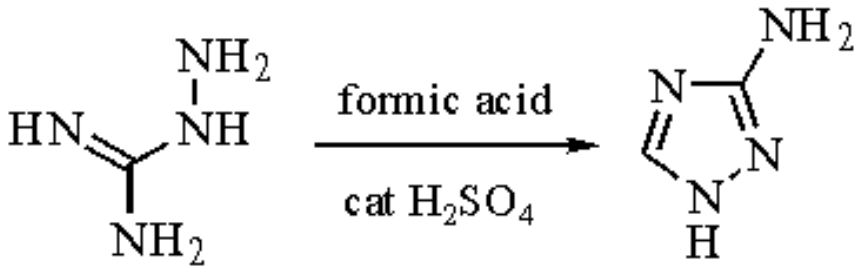

(6)

Reductions with Formic Acid.

Formic acid is unique among the simple organic acids in its ability to react as a reducing agent. Ketones are reduced and converted to primary amines by reaction with ammonia and formic acid (see ***Ammonium Formate***) (eq 7).[10] Ketones or aldehydes will react with formic acid and primary or secondary amines to produce secondary or tertiary amines (eq 8).[10a,11]

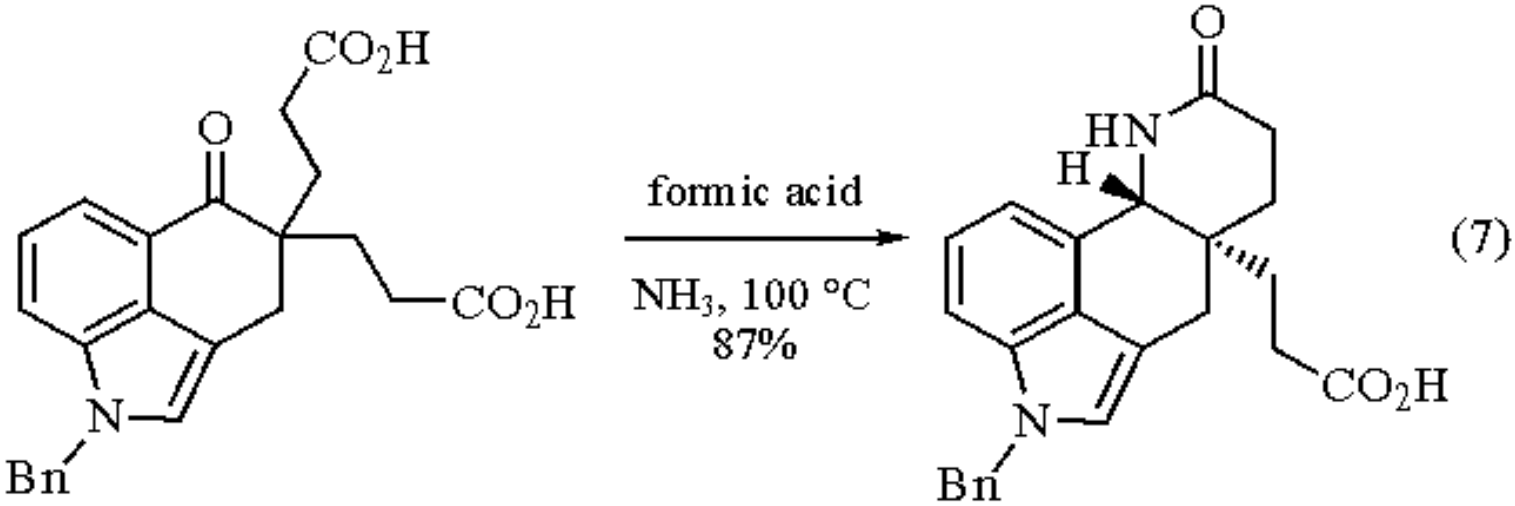

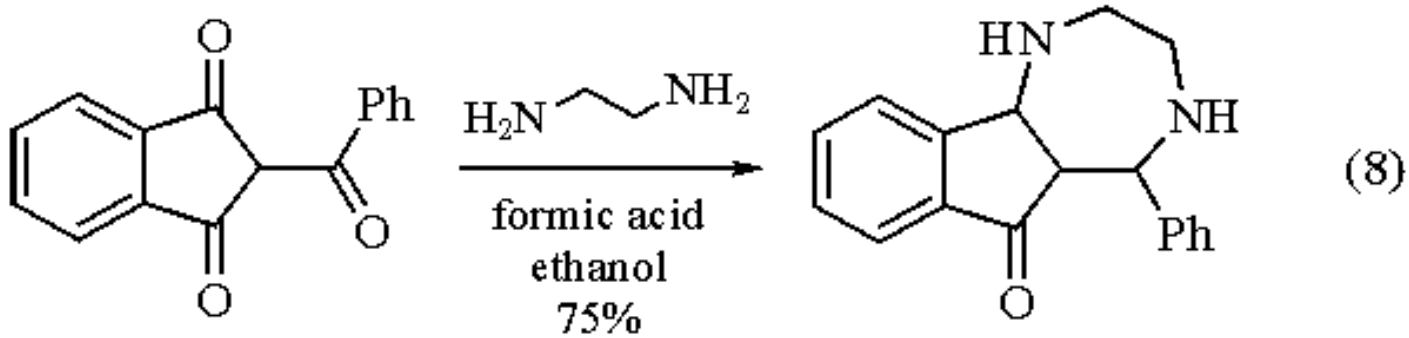

Catalytic Transfer Hydrogenation.[12]

Catalytic transfer hydrogenation uses a metal catalyst and an organic hydrogen donor as a stoichiometric reducing agent. This is a useful laboratory alternative to normal catalytic reduction, as the use of flammable hydrogen gas is avoided. Formic acid and amine formates are common hydrogen donors. Formic acid has been used to reduce α,β-unsaturated aldehydes and acids[13] to the saturated compounds (eq 9). Benzyl ethers (eq 10)[14] and benzyl amines (eq 11)[15] are cleaved by transfer hydrogenation with formic acid. A variety of nitrogen functions are reduced including the nitro group,[16] azo group,[17] hydrazines,[18] and enamines.[19] The resulting amines will be formylated under the reaction conditions; use of water or alcohol as solvent will limit formylation. If the reduction results in a suitable diamine, formylation will lead to heterocycle formation (eq 12).[16a] Aromatic halides are reduced to the aromatic hydrocarbon.[20] See also ***Palladium-Triethylamine-Formic Acid***.

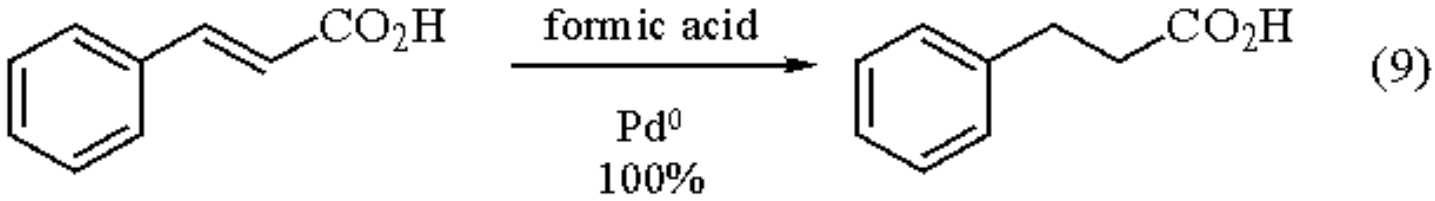

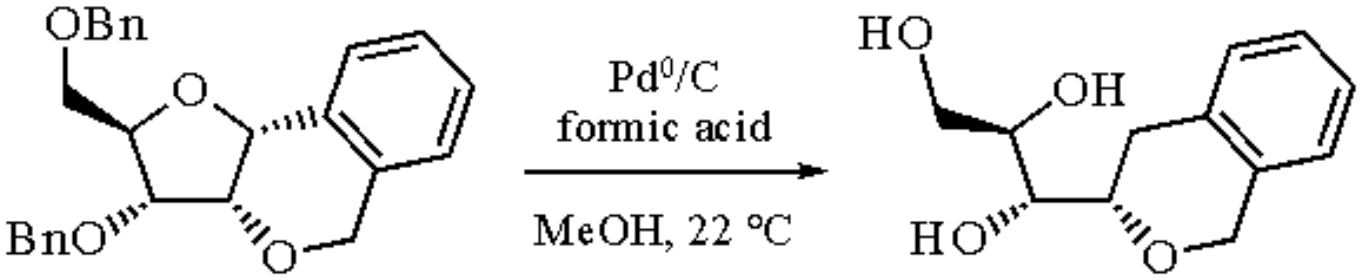

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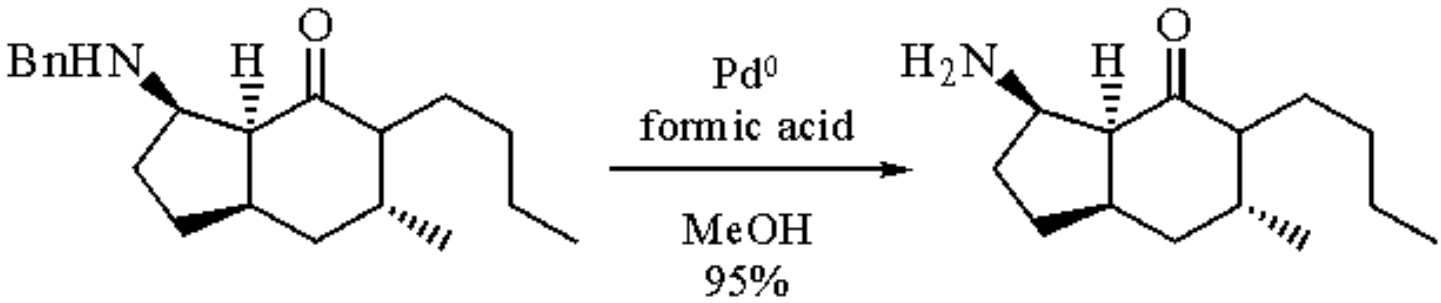

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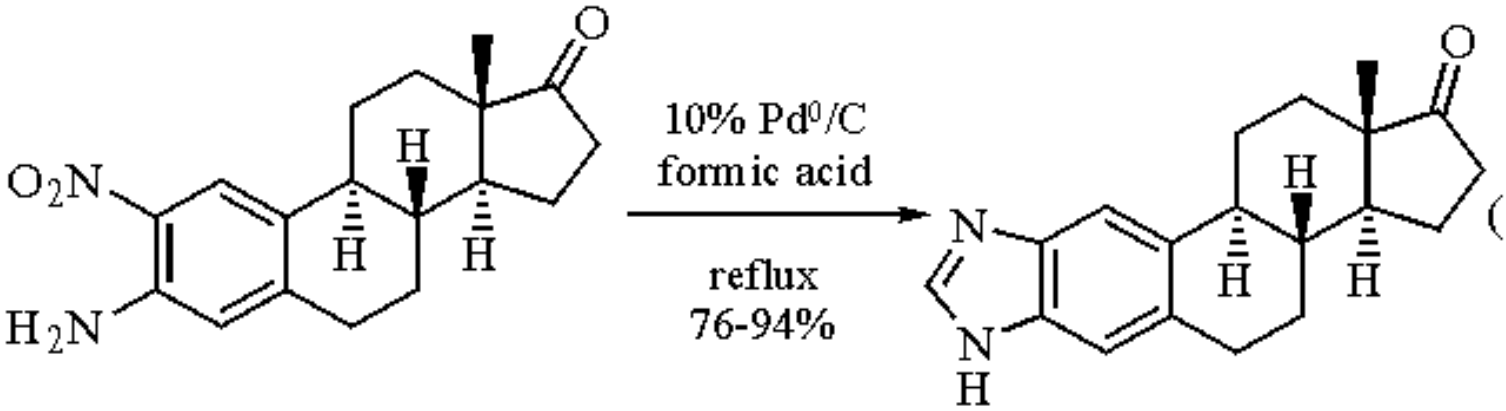

(12)

The Rupe Rearrangement.

Tertiary propargyl alcohols isomerize to α,β-unsaturated ketones in the Rupe rearrangement (eq 13).[21] The reaction has been reviewed.[22] Formic acid is the most common catalyst employed.

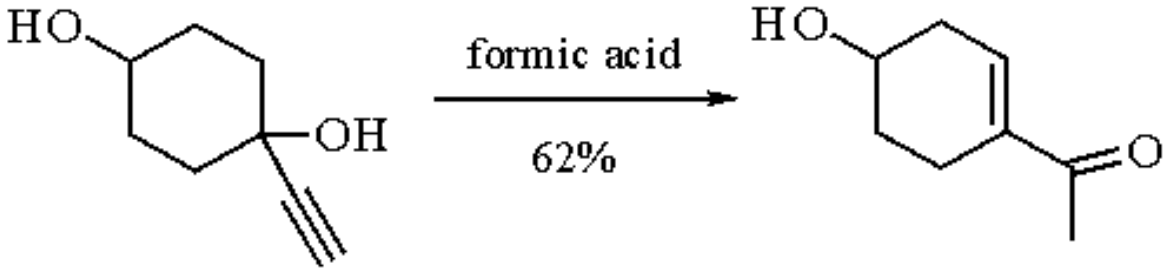

(13)

Related Reagents.

For uses of other carboxylic acids in synthesis, see ***Acetic Acid***, ***Acrylic Acid***, ***Glyoxylic Acid***, ***Oxalic Acid***, ***Methanesulfonic Acid*** and ***Trifluoroacetic Acid***.

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Formyl Chloride

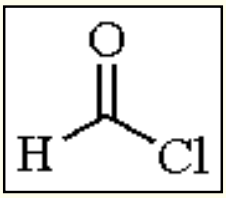

[2565-30-2] · CHClO · Formyl Chloride · (MW 64.47)

(Gatterman-Koch aldehyde synthesis;[1] conversion of alcohols to formate esters[2])

Physical Data: unstable at room temperature.

Preparative Methods: prepared by chlorination of ***Formic Acid*** at -78 °C[3] and by introduction of dry ***Hydrogen Chloride*** at -60 °C to a solution of ***N-Formylimidazole*** in chloroform.[4]

The procedure described by Gatterman and Koch[1] for the preparation of *p*-tolualdehyde calls for stirring a suspension of ***Copper(I) Chloride*** and ***Aluminum Chloride*** in toluene and passing in ***Carbon Monoxide*** and ***Hydrochloric Acid*** and hydrolyzing the resulting complex with ice. Formyl chloride was regarded as the transient intermediate (eq 1).

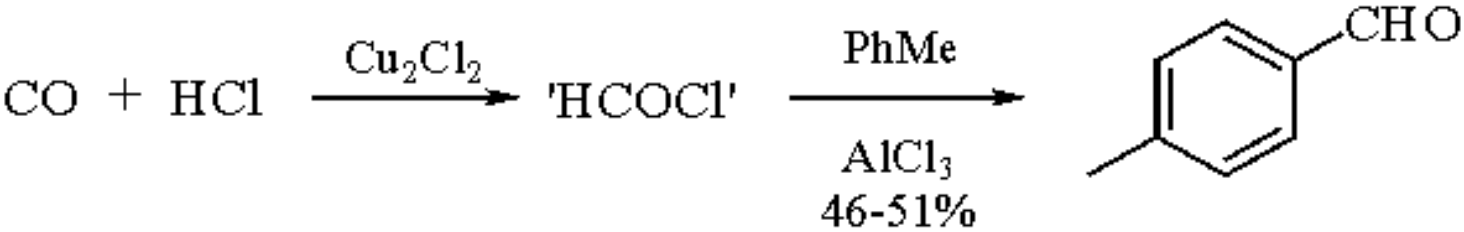

(1)

Treatment of 4-(1-hydroxyethyl)-3,7,7-trimethylbicyclo[4.1.0]hept-3-ene and its position isomers with ***Formic Acid*** and ***Thionyl Chloride*** gave in 65% yield the three double bond isomers of 4-(1-formyloxyethyl)-3,7,7-trimethylbicyclo[4.1.0]hept-3-ene (eq 2).[2]

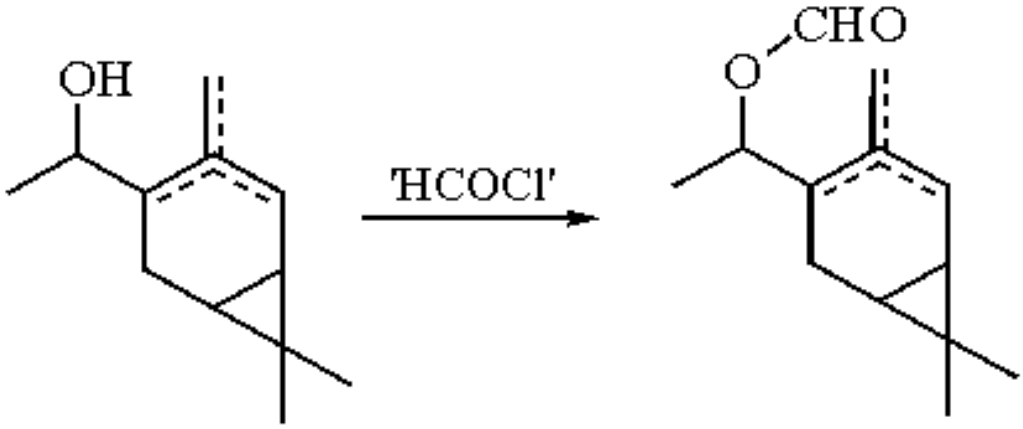

(2)

Related Reagents.

Formyl Fluoride.

---

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John C. Sih

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Formyl Fluoride[1]

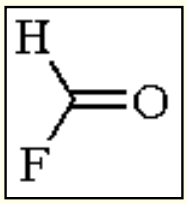

[1493-02-3] · CHFO · Formyl Fluoride · (MW 48.02)

(formylating agent for organic compounds[1])

Physical Data: bp -29 °C; mp -142 °C.

Preparative Methods: HCOF, one of the stable halides of formic acid, is generally prepared by combining ***Formic Acid*** with a fluorinating agent.[1] A variety of reagents such as ***Benzoyl Chloride***/***Potassium Fluoride***,[2] benzoyl fluoride,[3] benzoyl chloride/KHF_2,[4] cyanuric fluoride,[5] and tetramethyl-α-fluoroenamine[6] has been employed for this purpose. HCOF was also successfully prepared by reaction of ***Acetic Formic Anhydride*** with ***Hydrogen Fluoride*** at atmospheric pressure with continuous removal of formyl fluoride.[7] Combining benzoyl fluoride with sodium formate is another worthy procedure for its preparation.[5] Ozonolysis of 1,2-difluoroethylene and vinyl fluoride offers a potential new route to HCOF.[8] The best result among all the methods was achieved by fluorinating formic acid with tetramethyl-α-fluoroenamine.[6] A 100% yield was reported.

Handling, Storage, and Precautions: decomposes rapidly at room temperature into CO and HF.[1b] The reaction is autocatalytic since the HF formed initially catalyzes the decarbonylation. Therefore, acid-free HCOF should be stored at low temperature (of the order of -70 °C) under pressure over anhydrous sodium fluoride, which is able to absorb the hydrogen fluoride formed in decomposition. Use in a fume hood.

Formylation.

Formyl fluoride is used for Friedel-Crafts type formylation of arenes (eq 1). The best catalyst found for the reaction is ***Boron Trifluoride***.[3]

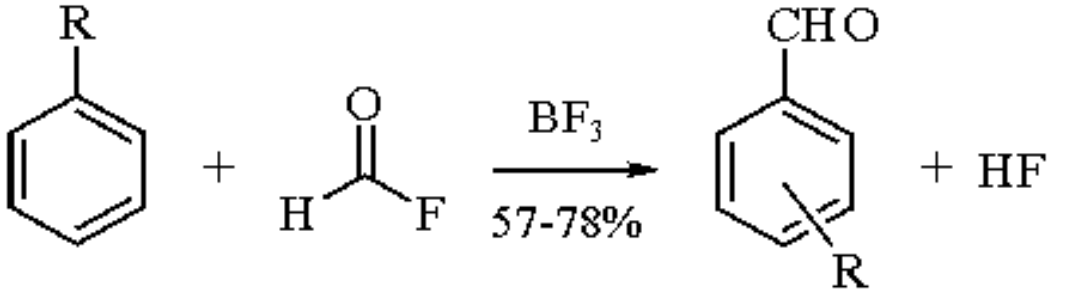

(1)

Formyl fluoride and BF_3 form a complex at low temperature, which has been isolated and characterized.[1b] ***Boron Trichloride*** and ***Boron Tribromide*** are also effective for the reaction; however, ***Aluminum Chloride*** and ***Aluminum Bromide*** were found to catalyze the decomposition of HCOF, giving lower yields of formylation products. If the aromatic substances are reactive and have a low freezing point, the reaction can be carried out by dissolving the HCOF neat in an excess of the cold arenes followed by saturation of the mixture with BF_3. When aromatic substrates are not sufficiently active to be formylated at low temperatures or have high freezing points, a solvent should be used. Solvents such as carbon disulfide or nitroalkanes are preferable for the reaction. The best results for such cases were obtained by passing HCOF and BF_3 gases simultaneously into the arenes at room temperature or higher. It is necessary to mention that HF and BF_3 should be removed from the reaction mixture as soon as the reaction is complete, since undesirable condensation reaction can occur with the aldehyde formed, which would decrease the yields.

Alkenes react in the presence of BF_3 with HCOF to give a β-fluoroaldehyde (eq 2).[1b] However, further reaction of the secondary C-F bond with BF_3 makes the isolation of pure products difficult.

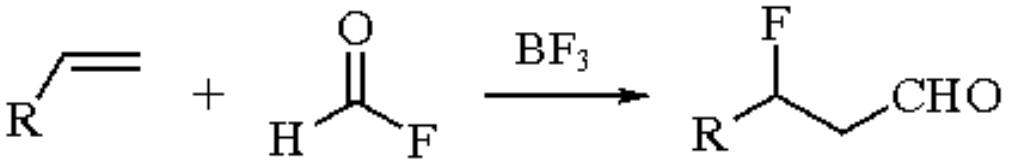

(2)

Formyl fluoride is also found to react with alcohols and phenols in the presence of a base (such as ***Triethylamine***) to form the corresponding formates (eq 3).[4] Primary and secondary aliphatic alcohols are formylated in 73-92% yield, while benzyl alcohols and phenol give 69% and 75% yields, respectively. Formyl fluoride reacts with carboxylic acid salts to yield the corresponding mixed carboxylic formic anhydrides (eq 4). Even the elusive formic anhydride can be prepared by the reaction at -78 °C. Oximes have also been formylated by HCOF.[9] This reaction has been employed to prepare 3-phenylethynyl-1,2,4-oxadiazole (eq 5).

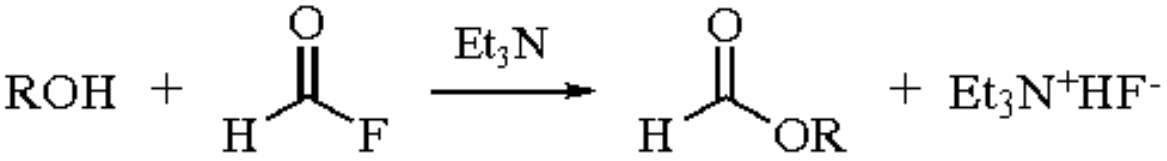

(3)

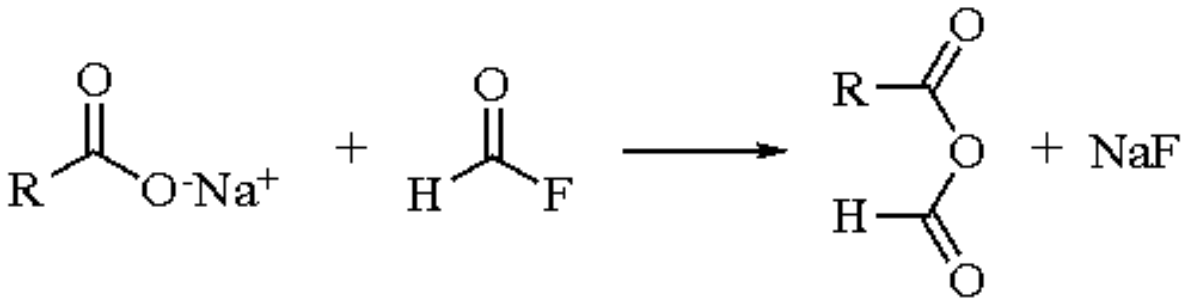

(4)

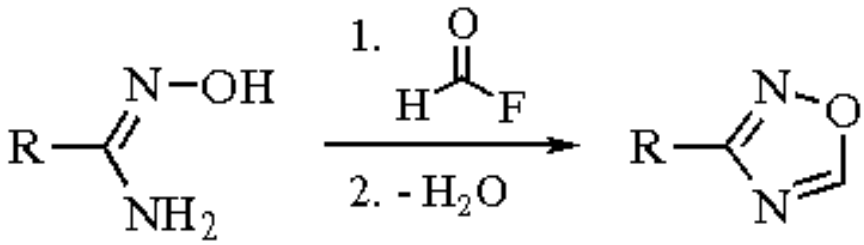

(5)

Reaction between HCOF and thiols yields thioformates in good yields (eq 6).[4]

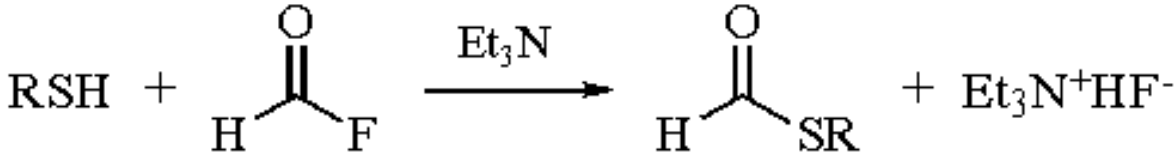

(6)

Formylation of amines can also be achieved.[1a] A large variety of primary and secondary amines react with HCOF to give *N*-alkylformamides in good to excellent yields (eq 7). However, reaction between tertiary amines and HCOF leads to elimination of carbon monoxide and formation of the amine hydrofluorides.

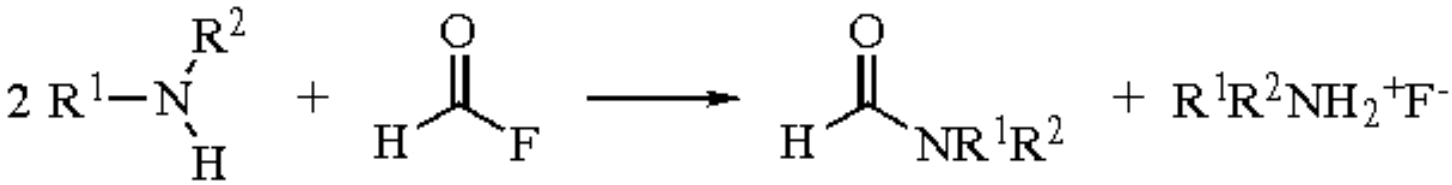

(7)

Related Reagents.

Acetic Formic Anhydride; ***Methyl Formate***.

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N-Formylimidazole

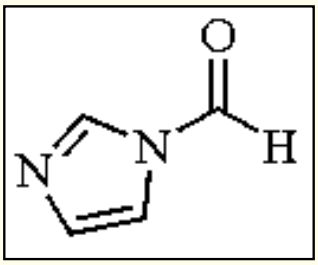

[3197-61-3] · $C_4H_4N_2O$ · *N*-Formylimidazole · (MW 96.10)

(active agent for formylation[1])

Alternate Name: 1*H*-imidazole-1-carbaldehyde.

Physical Data: mp 53-55 °C; dec 60 °C.[2]

Solubility: sol THF, acetone, chloroform; partially sol CCl_4, diethyl ether.

Preparative Method: a solution of 1.5 g (32 mmol) formic acid (98-100%) in 50 mL dry THF is added over a period of 15 min to a vigorously stirred suspension of 5.0 g (31 mmol) ***N,N´-Carbonyldiimidazole***[3] in 80 mL dry THF at rt. *N,N*-Carbonyldiimidazole dissolves rapidly and CO_2 is evolved. After 1 h the solvent is evaporated and the product is sublimed directly from the mixture, 35-40 °C/0.2 mmHg, to give 2.53 g (85%) of *N*-formylimidazole.[2]

Handling, Storage, and Precautions: like *N,N*-carbonyldiimidazole, *N*-formylimidazole is very sensitive to water. It should be kept sealed under an inert atmosphere.

Imidazole Reagents.

Like other derivatives of *N*-carbonyldiimidazole, *N*-formylimidazole is an activated form of formic acid, which can be used as a reactive intermediate in the synthesis of esters, amides, and isocyanides and for the formylation of Wittig reagents.[1] The high reactivity of carboxyimidazoles is due to the aromaticity of the imidazole ring. This exerts an electron-withdrawing effect on the exocyclic carbonyl bond, increasing the rate of nucleophilic attack at the carbonyl carbon. In most cases the freshly prepared reagent is used directly, without isolation. Good yields of products are usually obtained. *N,N*-Carbonyldiimidazole reacts with an equimolar amount of formic acid in THF or chloroform within a few minutes at rt to form *N*-formylimidazole (eq 1).

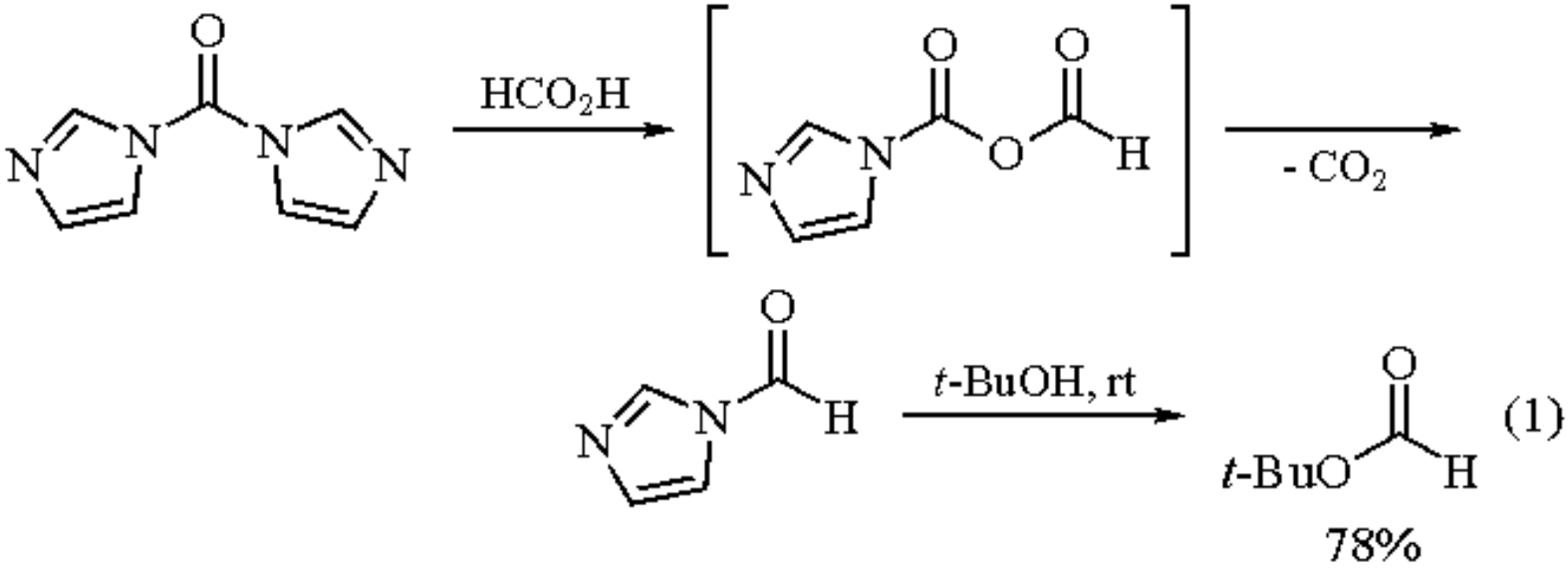

(1)

Reaction of this intermediate with a nucleophile leads directly to the desired product. One equivalent of alcohol in the presence of a catalytic amount of alcoholate (formed by addition of a base like ***Sodium Amide***[4] or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***[5]) yields the ester under mild conditions. Even sterically hindered alcohols like *t*-butanol react readily at rt (eq 1).[2] Under similar conditions, thioesters,[6] selenoesters,[6] and amides[2,7,8] can also be obtained. Triphenylphosphine-alkylidenes are readily *C*-acylated using 0.5 equiv of *N*-formylimidazole at rt in benzene or benzene/THF to give α-formyl derivatives.[9] Wittig reaction of these triphenylphosphine-α-formylalkylidenes leads to α,β-unsaturated aldehydes[10] (eq 2) or, after hydrolysis, to the aldehydes RCH_2CHO.

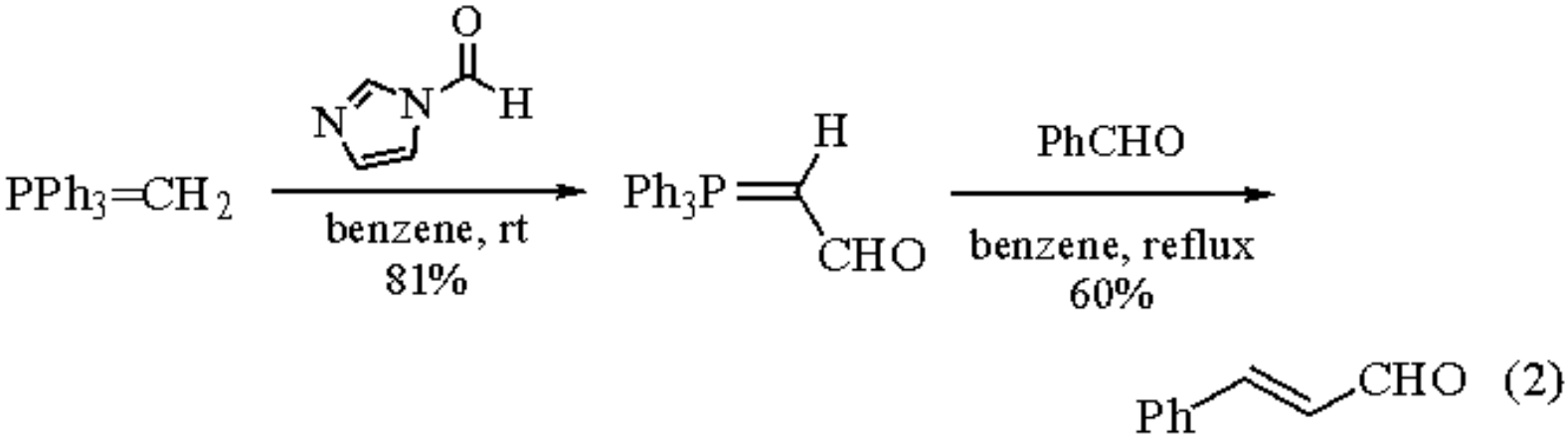

(2)

A simple synthesis of isoflavones with yields ranging from 60 to 76% was reported by Krishnamurty (eq 3). This involves the reaction between an *O*-hydroxydeoxybenzoin and *N*-formylimidazole whereby *C*-formylation at the benzylic position is followed by cyclization to the corresponding isoflavone.[11]

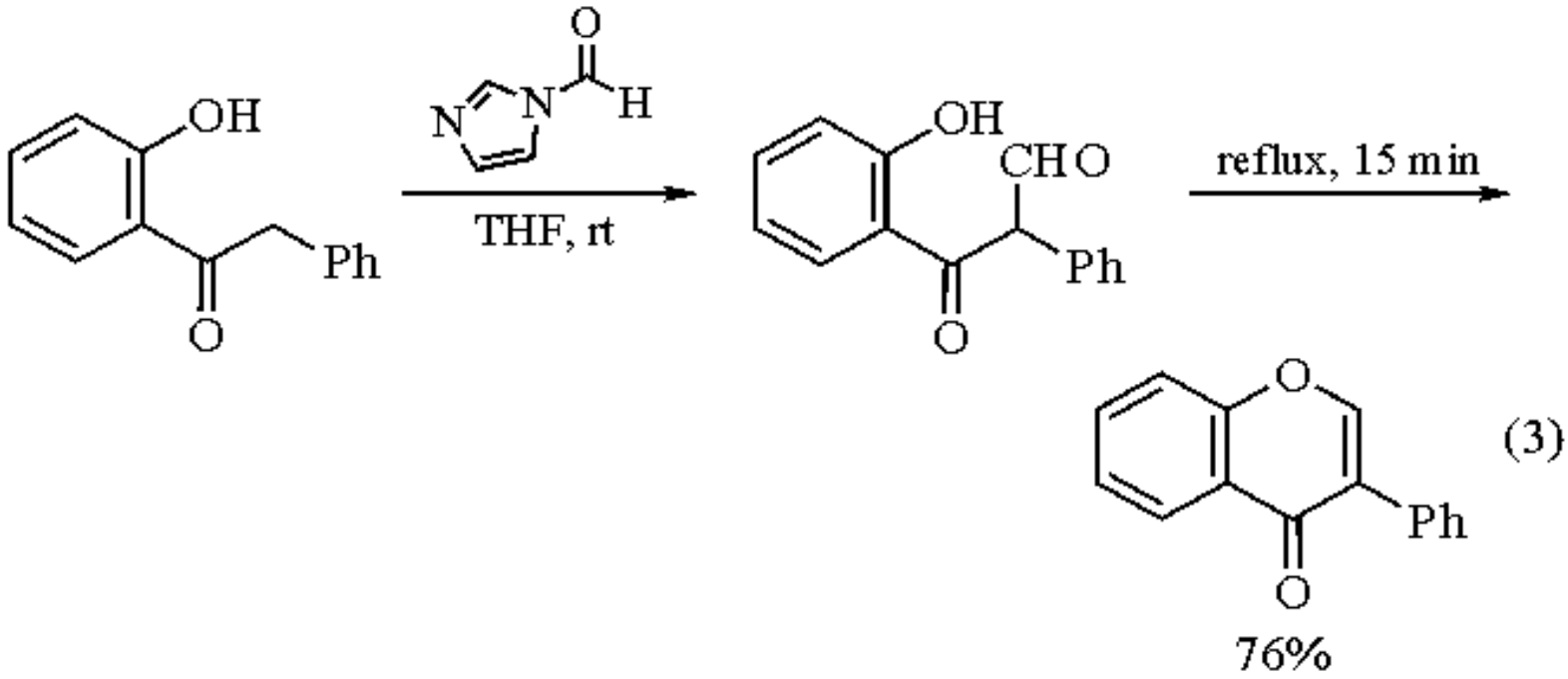

In the synthesis of substituted benz[*cd*]indoles (eq 4), *N*-formylimidazole was used to transform an amino group into an isocyanide group after dehydration of the resulting formamide with ***Phosgene***/***Triethylamine***.[12,13]

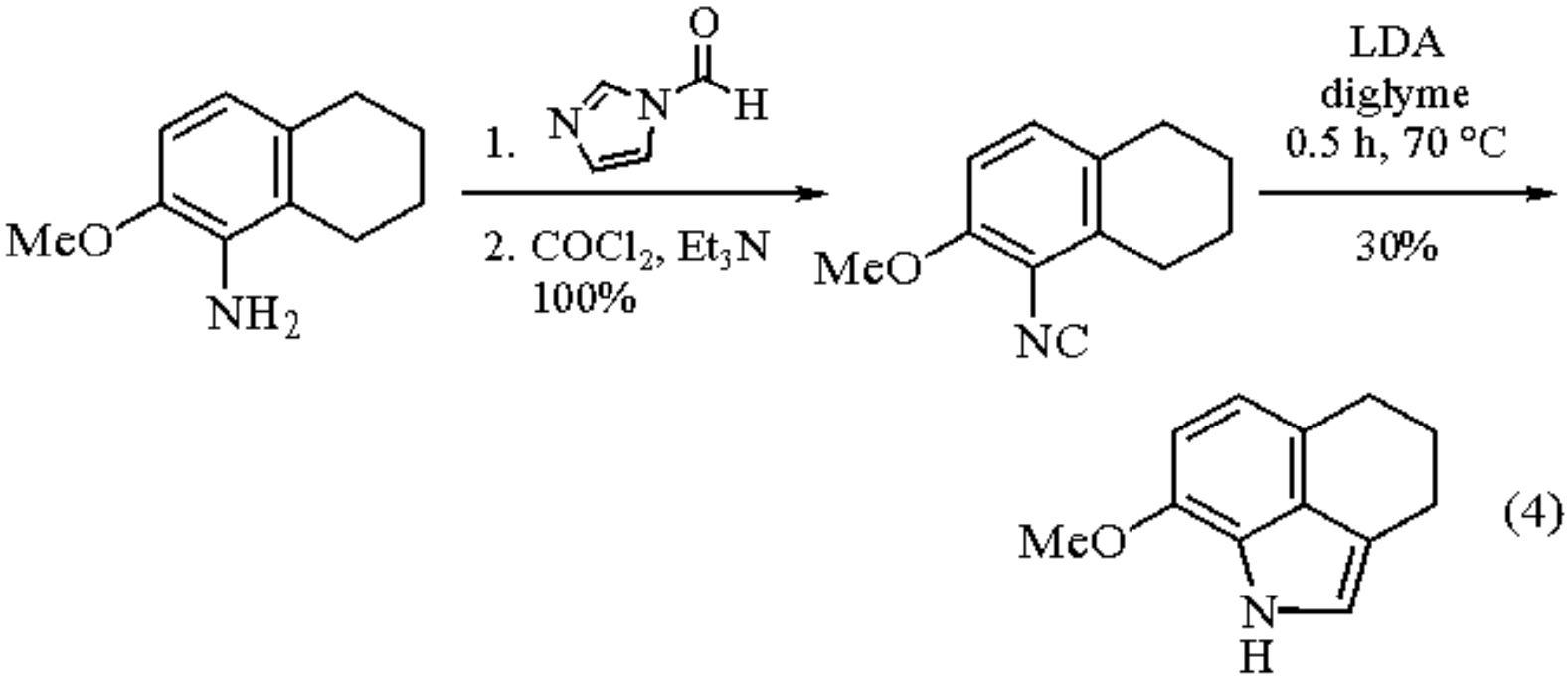

In organometallic chemistry, *N*-formylimidazole can act as a formylating reagent to produce formyl transition metal complexes. These can react with compounds of the type $Na_2M(CO)_4$ (M = Fe, Ru, Os) in THF or HMPA in the presence of a Lewis acid such as ***Trimethyl Borate*** to produce a mixture of $NaM(CO)_4CHO$ (e.g. sodium tetracarbonylformylferrate, sodium tetracarbonylformylruthenate, sodium tetracarbonylformylosmate) and $NaM(CO)_4H$. $NaM(CO)_4CRO$ is the product formed from the reaction with alkyl- and phenyl-*N*-acylimidazoles.[14]

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Maurus Marty

University of Neuchâtel, Switzerland

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Formylmethylenetriphenylphosphorane[1]

Ph_3P=CHCHO

[2136-75-6] · $C_{20}H_{17}OP$ · Formylmethylenetriphenylphosphorane · (MW 304.33)

(stabilized Wittig reagent used for the synthesis of α,β-unsaturated aldehydes from aldehydes; reagent for two-carbon chain homologation)

Alternate Name: (triphenylphosphoranylidene)acetaldehyde.

Physical Data: mp 187-188 °C (dec).

Form Supplied in: white solid, 97%; commercially available.

Preparative Methods: reaction of ***Chloroacetaldehyde*** and ***Triphenylphosphine*** affords formylmethyltriphenylphosphonium chloride, which furnishes the phosphorane reagent on treatment with ***Triethylamine*** in ethanol.[2]

Handling, Storage, and Precautions: unstable to moisture and acids. Keep dry.

(*E*)-α,β-Unsaturated Aldehydes.

This stabilized phosphonium ylide reacts with a wide variety of aliphatic and aromatic aldehydes to give α,β-unsaturated aldehydes, with a high predominance of the (*E*)-alkene.[2-5] This reagent has been applied in many areas of organic synthesis including natural products, carbohydrates, and heterocycles. Thus in the synthesis of swainsonine from D-mannose the chain-extended (*E*)-alkene (**2**) was prepared from the aldehyde (**1**) in good yield (eq 1).[6]

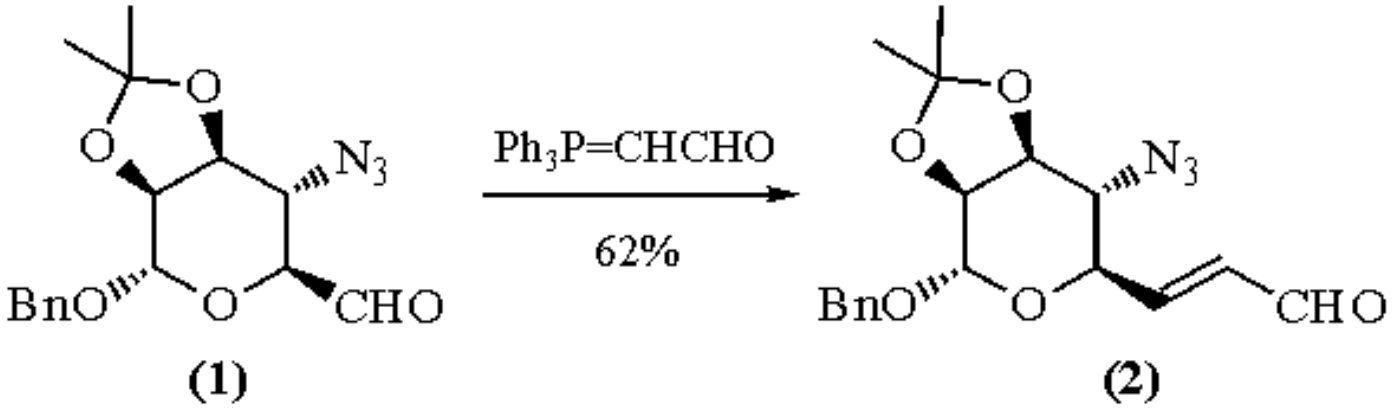

(1)

Tandem addition of the ylide has been successfully applied to the synthesis of (*E*,*E*)-dienyl aldehydes. For example, in the synthesis of natural leukotrienes, Rokach et al. converted epoxy aldehyde (**3**) to intermediate (**4**) en route to LTA_4 (eq 2).[7]

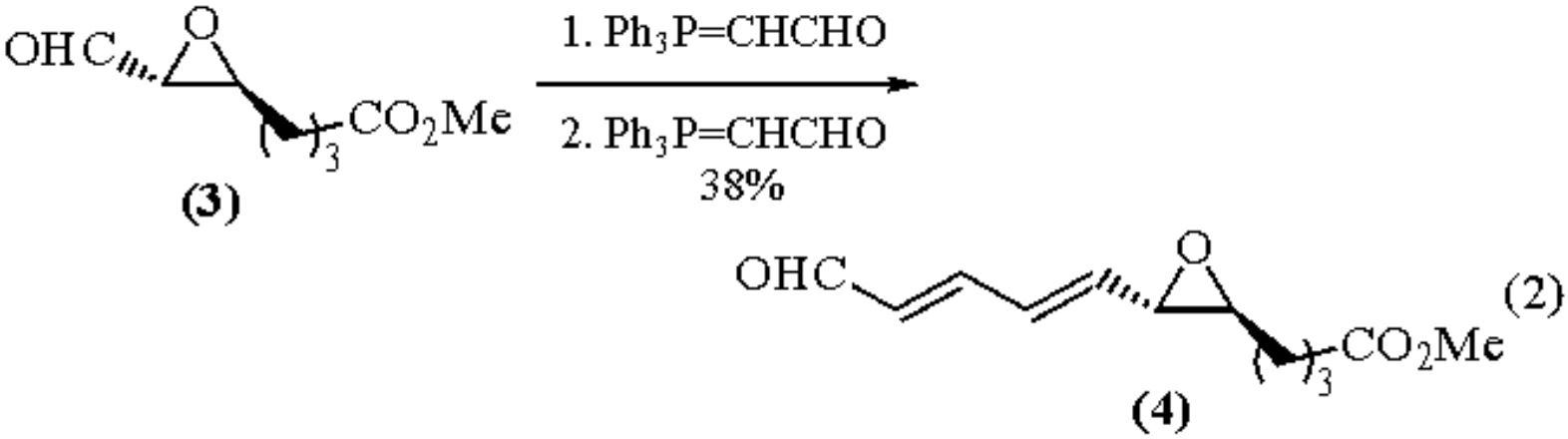

Reaction of the ylide with ketones is generally unsuccessful;[2] however, it has been reported to react with trifluoroacetone to give the expected trisubstituted alkene in low yield (eq 3).[8]

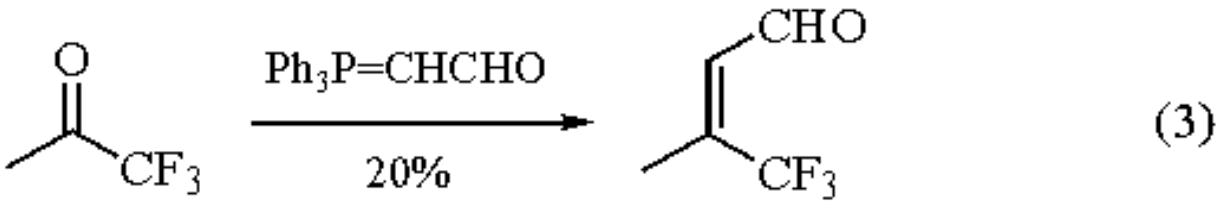

Alkenation with this ylide can be effected in good yield when a free hydroxyl group is present in the aldehyde substrate,[9,10] although a neighboring hydroxyl appears to detract from the normally high (*E*) stereoselectivity (eq 4).[10]

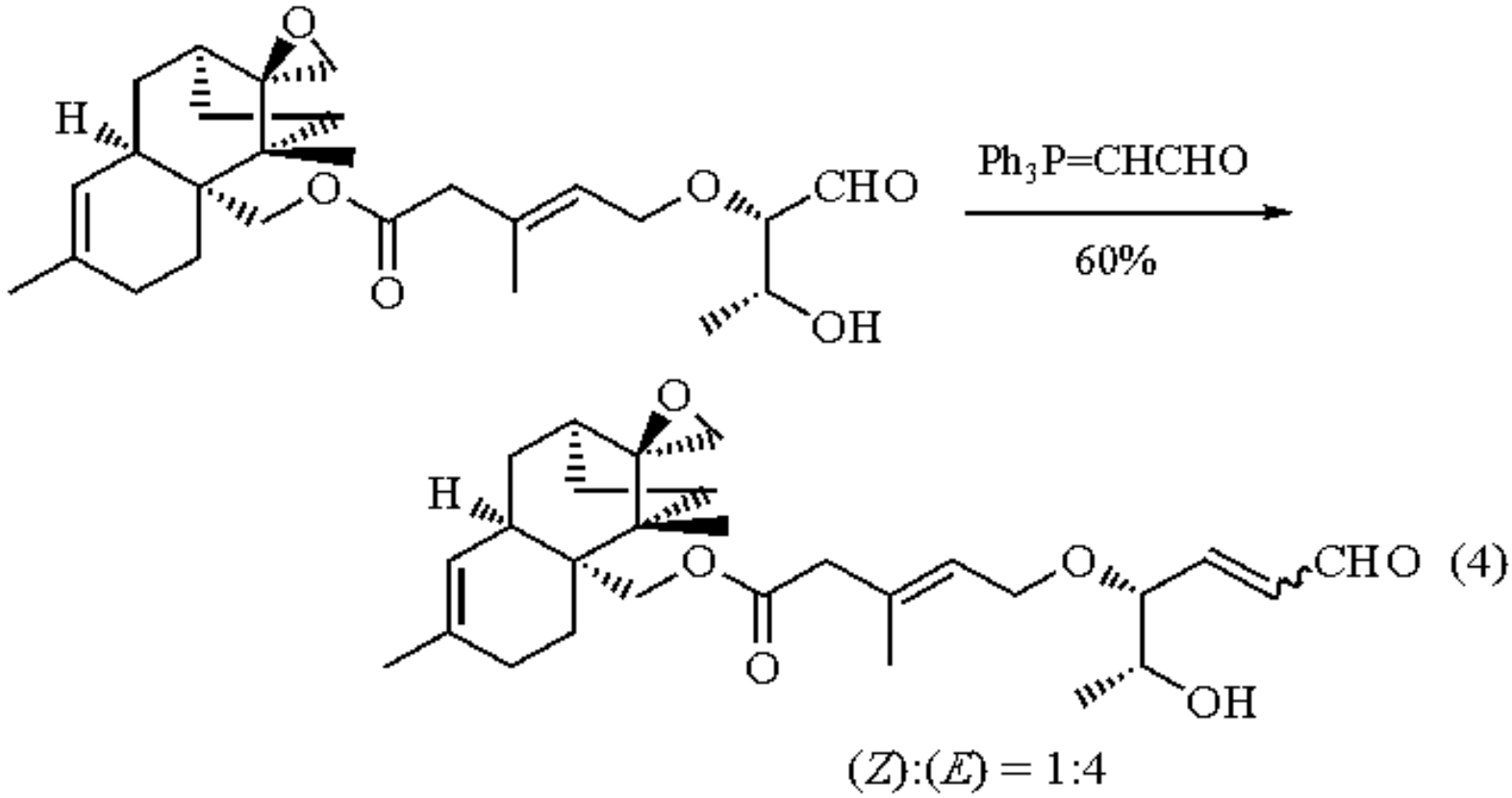

(*Z*)-α,β-Unsaturated Aldehydes.

In a complementary manner, Bestmann's group has shown that conversion of this ylide to a diethyl acetal in situ affords a new phosphorane that transforms aldehydes into α,β-unsaturated aldehydes with predominantly (*Z*) stereochemistry (86-97%).[11,12] The procedure involves treatment of the ylide with EtBr, followed by NaOEt, then addition of the aldehyde; the intermediate unsaturated diethyl acetals are hydrolyzed to obtain α,β-unsaturated aldehydes (eq 5). Higher yields of unsaturated diethyl acetals were usually realized by an alternative reaction sequence that employed a different base system: 1) EtBr; 2) sodium amide; and 3) ethanol.

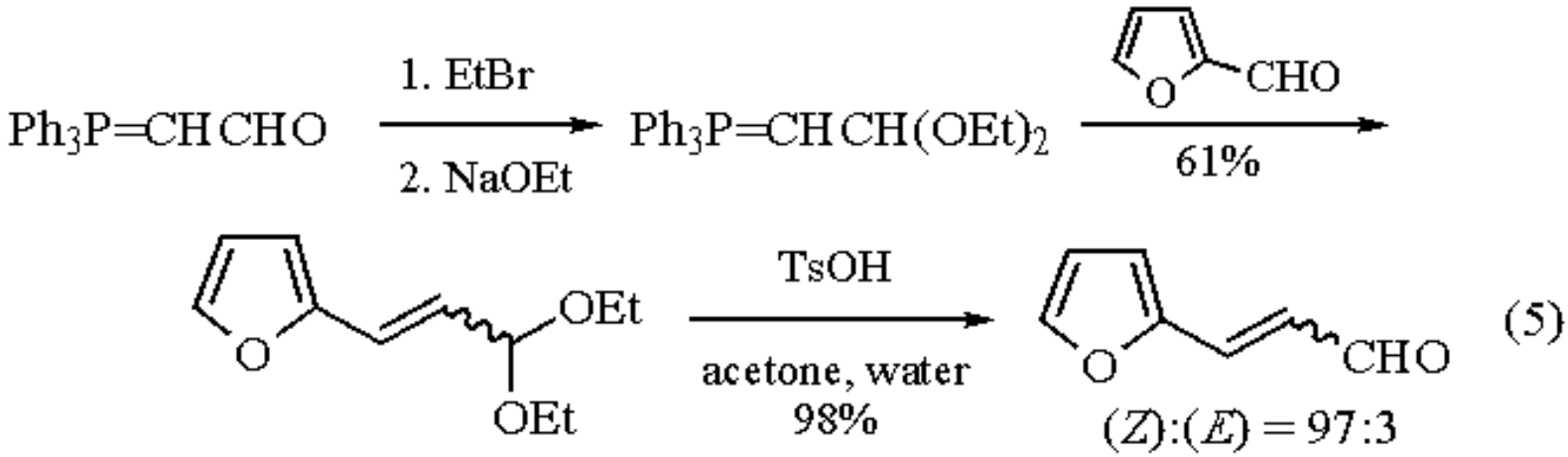

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N-Formylpiperidine

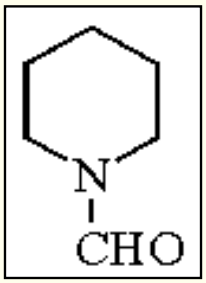

[2591-86-8] · $C_6H_{11}NO$ · *N*-Formylpiperidine · (MW 113.18)

(formylating agent for certain organometallics;[1] reacts with sulfur tetrafluoride/KF to give *N*-trifluoromethylpiperidine;[2] easily converted to reactive chloromethyleneiminium ions[3])

Physical Data: bp 222 °C; *d* 1.09 g cm^{-3}.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: IR, NMR.

Handling, Storage, and Precautions: toxic; irritant.

N-Formylpiperidine (**1**) is a good formylating agent for certain organometallics. Carbaldehydes can be obtained by reacting (**1**) with organolithium or Grignard reagents (eq 1).[1]

$$\mathrm{RM} \xrightarrow[72\text{-}96\%]{\textbf{(1)}} \mathrm{RCHO} \qquad (1)$$

$$\mathrm{M = MgX\ or\ Li;\ R = alkyl\ or\ aryl}$$

N-Trifluoromethylpiperidine will result on reaction of (**1**) with ***Sulfur Tetrafluoride*** and ***Potassium Fluoride*** (eq 2).[2]

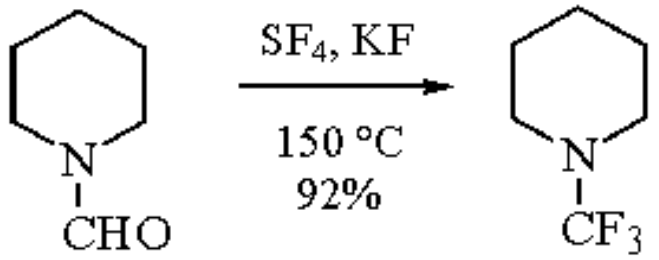

(2)

Chloromethyleneiminium ions with different counterions can be easily prepared from (**1**).[3] The chloromethyleneiminium ion generated from (**1**) reacts with thioamides to give various products depending on the reaction conditions (eqs 3-5).[4,5] *N,N*-Disubstituted thioamides undergo condensation to give thioenamides (**2**) (eq 3).[4] Under similar reaction conditions, primary thioamides yield either the nitrile (**3**) (eq 4) or the salt (**4**) (eq 5).[5]

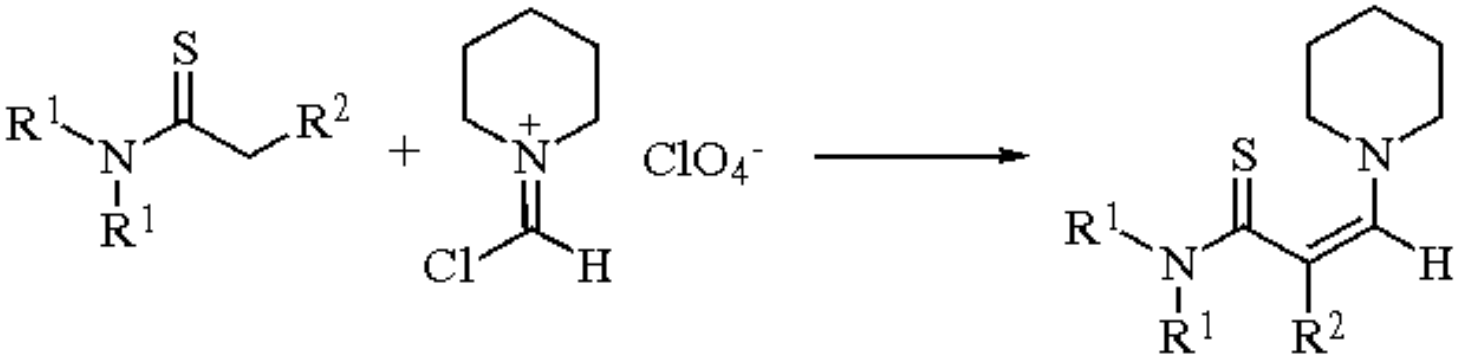

(2)

(3)

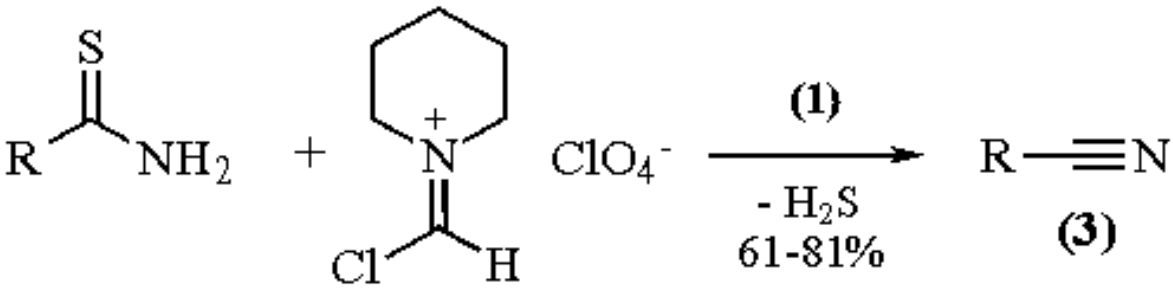

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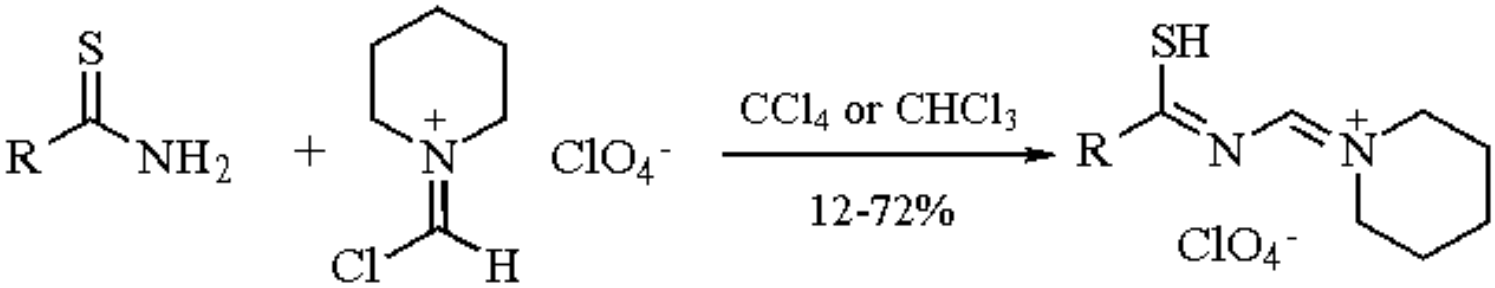

(4)

(5)

Related Reagents.

N,N-Dimethylformamide; ***N-Methylformanilide***; ***N-Methyl-N-(2-pyridyl)formamide***.

1. (a) Olah, G. A.; Arvanaghi, M. *AG(E)* **1981**, *20*, 878. (b) Hartman, G. D.; Halozenko, W.; Phillips, B. *JOC* **1985**, *50*, 2427. (c) Hartman, G. D.; Halozenko, W.; Phillips, B. *JOC* **1986**, *51*, 142. (d) Olah, G. A.; Arvanaghi, M. *OS* **1986**, *64*, 114. (e) Pflieger, P.; Mioskowski, C.; Salaun, J. P.; Weissbart, D.; Durst, F. *TL* **1988**, *29*, 6775. (f) Radinov, R.; Chanev, C.; Khaimova, M. *JOC* **1991**, *56*, 4793. (g) Flouzat, C.; Savelon, L.; Guillaumet, G. *S* **1992**, 842.
2. Dmowski, W.; Kaminski, M. *JFC* **1983**, *23*, 207.
3. Liebscher, J.; Knoll, A.; Hartmann, H.; Anders, S. *CCC* **1987**, *52*, 761.
4. Liebscher, J.; Abegaz, B. *S* **1982**, 769.
5. Liebscher, J. *S* **1982**, 1084.

Daniel L. Comins & Sajan P. Joseph

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Furan[1]

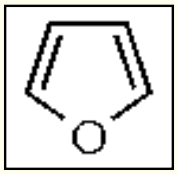

[110-00-9] · C_4H_4O · Furan · (MW 68.08)

(versatile four-carbon synthon;[1] aromatic heterocycle which exhibits reactivity towards various electrophiles[2] and electrophilic carbon radicals;[3] 2-monolithio[4a] or 2,5-dimetalated furan derivatives can be readily generated and transmetalated;[4] ene employed for [2 + 2] photochemical[1d,5] and [2 + 3] dipolar cycloadditions;[6] diene widely used for [4 + 2] Diels-Alder[1e] and [4 + 3] dipolar cycloadditions;[7] can be oxidized by a number of reagents such as singlet oxygen[8])

Physical Data: mp -85.6 °C; bp 31.4 °C; fp -35 °C; *n*20D 1.421;[9c] *d*204 0.9514 g cm^{-3}.[9a,b]

Solubility: sol ethanol, ether, benzene, acetone; slightly sol chloroform; insol water.[9a]

Form Supplied in: commercially available as a water-white liquid in >99% purity (GC); usually a trace of 2,6-di-*t*-butyl-*p*-cresol (BHT) added as an inhibitor of oxidation.

Purification: shaken with aq 5% KOH, dried with $CaSO_4$ or Na_2SO_4, then distilled under nitrogen, from KOH or sodium, immediately before use.[10]

Analysis of Reagent Purity: GC; IR (neat) 1592, 1485, 1380, 1172, 1061, 869, 744, 601 cm^{-1};[11a] ^1H NMR ($CDCl_3$) δ 6.39 (2H), 7.44 (2H);[11b,c] ^{13}C NMR ($CDCl_3$) δ 109.7, 142.8.[11d]

Handling, Storage, and Precautions: on EPA Extremely Hazardous Substances List; reported in EPA TSCA Inventory.[12] The vapors are anesthetic; can be absorbed through skin.[12] Use in a fume hood.

Electrophilic Substitution Reactions.

Synthesis of 2-Halo-, Acyl-, Cyano-, Sulfonyl-, and Carbonyloxyfurans.

Furan is an electron-rich, aromatic heterocycle which readily undergoes electrophilic substitution reactions with a wide range of electrophiles. Therefore furan serves as a convenient starting material for the preparation of various

substituted furans, including halo, acyl/formyl, cyano, and other heteroatom substituted furans.[1] The C-2 position is generally more susceptible than C-3 towards electrophiles, presumably due to the extended conjugation of the intermediate cation generated by the addition of an electrophile at the former. However, the ratio of the C-2/C-3 products appears to be highly dependent upon the type of electrophile and the reaction conditions. For example, acylation of furan with ***Acetic Anhydride*** and ***Tin(IV) Chloride*** in dichloromethane gives C-2/C-3 products in ratios of 6800 and 800 at 25 and 75 °C, respectively. However, the reaction with acetyl trifluoroacetate at 75 °C results in a C-2/C-3 product ratio of 6000.[13] The acetylation can also be achieved cleanly at the C-2 position in excellent yield with ***Acetyl p-Toluenesulfonate***.[14] Other electrophilic substitution reactions of furan at the C-2 position include: bromination (Br_2, DMF) (eq 1),[15] cyanation ($OCNSO_2Cl$, DMF),[16] Vilsmeier formylation (Me_2NCHO, $POCl_3$),[17] sulfonation (SO_3.py),[18] and carbonylation ($PdCl_2$,Hg^{2+}, Cu^{2+}/CO/ROH).[19]

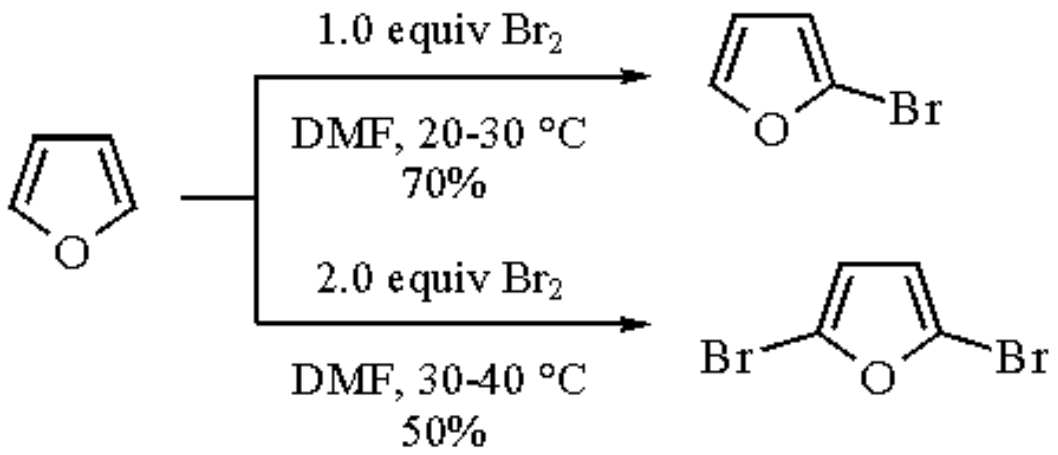

(1)

Synthesis of Alkylfurans.

Alkyl-substituted furans can be prepared by electrophilic substitution reactions of furan. For example, furan undergoes the Mannich reaction with aminals, α-amino ethers, and bis(alkoxymethyl)alkylamines under Lewis acid catalysis to give 2-(*N*,*N*-dialkylamino)methyl derivatives of furan (eq 2).[20] Furan can also add to the β-carbon of enones in the presence of ***Iodotrimethylsilane*** (eq 3).[21] In addition, Ag^+ has been reported to induce allylation of furan with 1,3-bis(phenylseleno)propene (eq 4)[22a] or cyclopropyl halides (eq 5).[22b] It should be noted that this Ag^+-catalyzed allylation of furan, illustrated in eq 4, has been shown to proceed with high stereoselectivity where the configuration of the stereochemically pure (*Z*)- or (*E*)-allylating agent is retained in the product.[22a] An arenecarbonylmolybdenum has been employed as a catalyst for the *t*-butylation of furan at C-2.[23]

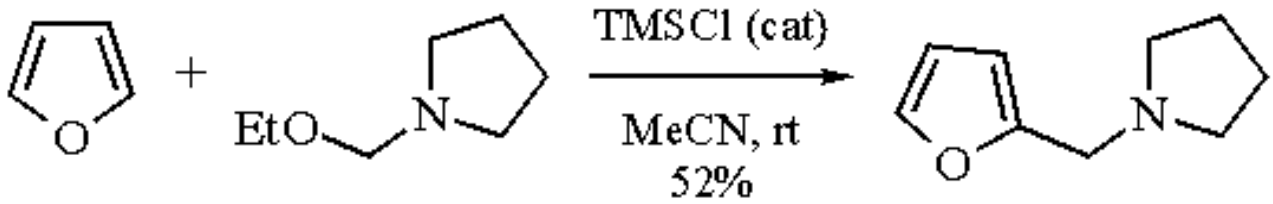

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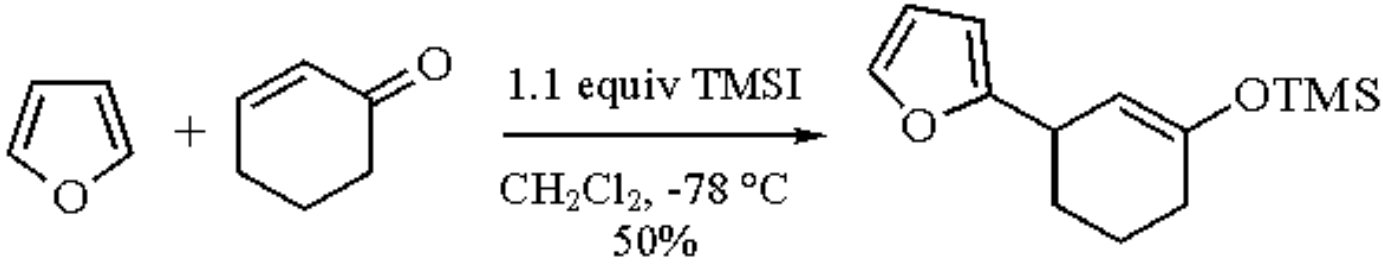

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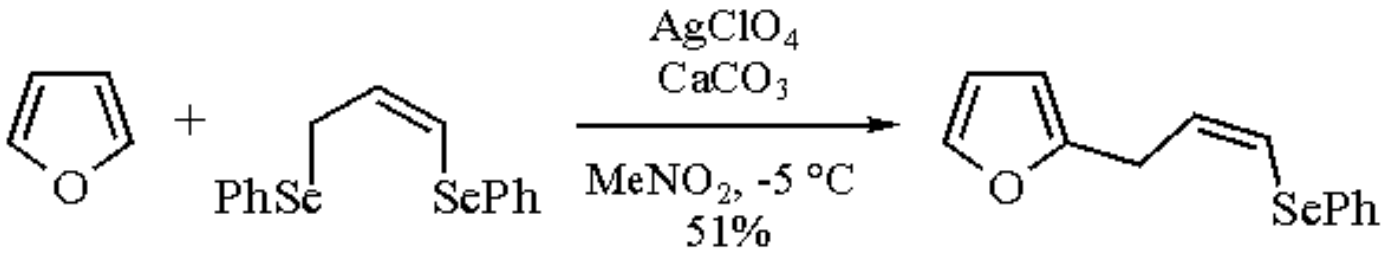

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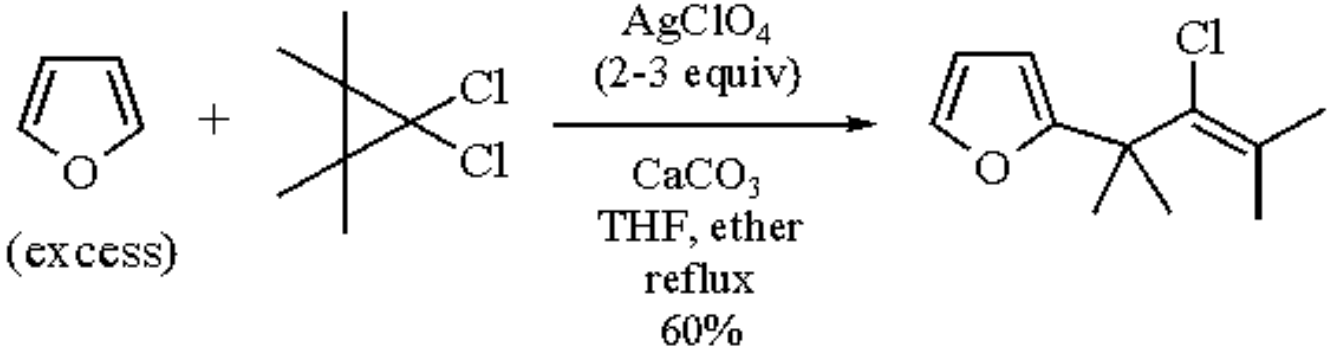

(5)

Radical-Mediated Substitution Reactions.

Furan undergoes substitution reactions with electrophilic carbon radicals to provide 2-alkyl substituted furans (eq 6).[3] These radicals are generated from dialkyl malonates with Ce^{4+},[3] triethyl methanetricarboxylate with Mn^{3+},[24a] Fe^{2+}/H_2O_2 in DMSO,[24b] or ethyl iodoacetate with triethylborane.[24c]

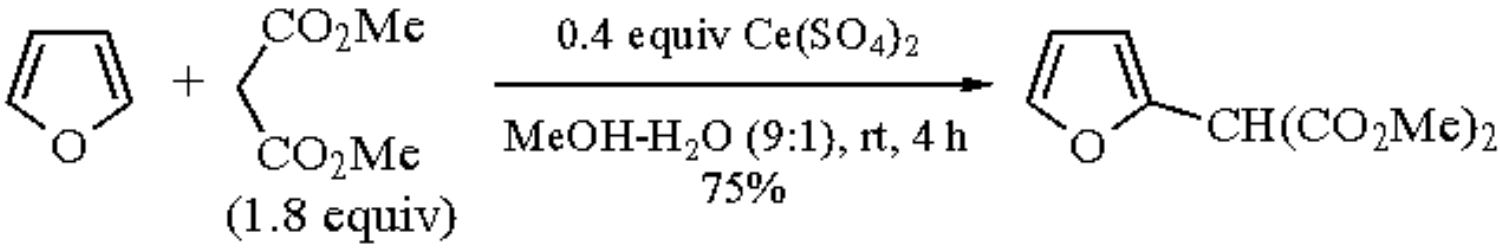

(6)

Cross-Coupling Reactions.

Two major types of cross-coupling reactions have been reported in conjunction with the synthesis of arylated furans. Thus the photochemical coupling of furan with 2-bromo- or -iodo- (eq 7)[25a] or 4-iodopyridine[25b] produces the corresponding coupled products in moderate yield. Other five-membered heterocycles such as thiophenes and pyrroles also undergo similar reactions.[25] Interestingly, the direct aryl coupling reaction of furan can also be achieved in the presence of a Pd^0 catalyst with aryl bromides bearing an electron-withdrawing group (moderate yield) or 1-naphthyl

bromide (low yield) at elevated temperatures (eq 8).[26a] It is noteworthy that although similar Pd^0-catalyzed cross-coupling reactions with a wide variety of aromatic, benzyl, and cinnamyl bromides can be effected using 2-lithio- or 2-furylzinc chloride in generally higher yield,[26b] these require prior generation of the organometallic reagent. While the use of the ***Palladium(II) Acetate-Copper(II) Acetate*** catalyst system results in facile alkenylation reactions of furan at the α-position with methyl acrylate and acrylonitrile, the yields of the reactions are generally low with frequent complication due to the formation of the 2,5-dialkenylated products.[27] However, if the $Pd(OCOPh)_2$-catalyzed reaction of furan with ethyl acrylate is carried out in the presence of *t*-butyl perbenzoate (postulated to act as a hydrogen acceptor), ethyl 3-(2-furyl)acrylate is obtained in 53% yield with virtually no formation of the dialkenylated product.[28]

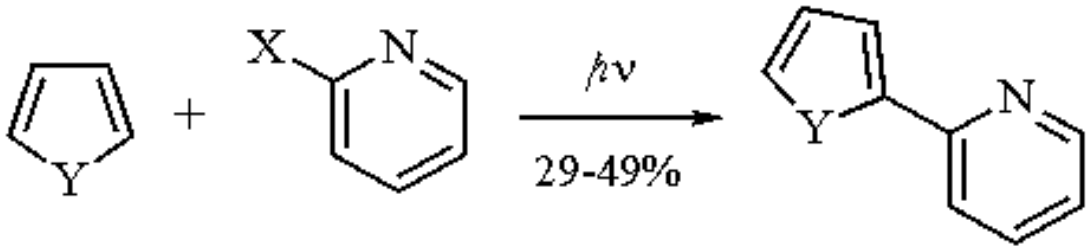

(7)

Y = O, NH, S, NMe
X = I, Br

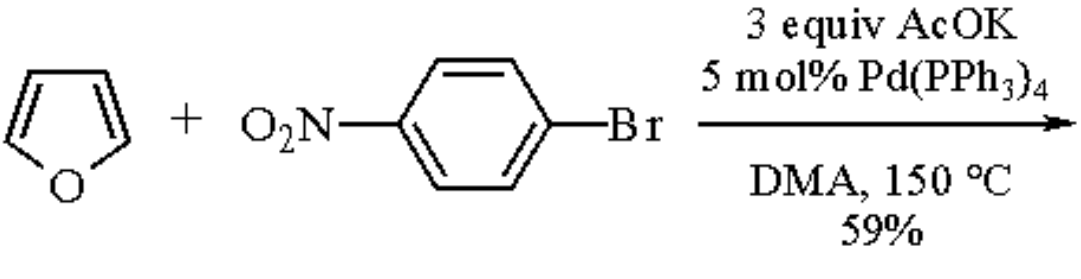

(8)

Organometallic Compounds.

Lithiated furans are presumably one of the most widely employed organometallic species in synthesis.[4a] Furan can be readily monolithiated at C-2 with ***n-Butyllithium*** and it can be dimetalated at C-2 and 5 either by careful control of reaction conditions using *n*-BuLi (to 2,5-dilithiofuran)[4b] or with the use of the Schlosser-Lochmann reagent (*n*-BuLi/BuOK)[29] (presumably to 2,5-dipotassiofuran) (eq 9).[4c] These metalated furans can react with a variety of electrophiles[4a] including TMSCl,[4a] CO_2,[4a] epoxides,[4a] ketones,[4a,30a] and aldehydes.[4a,30b] Additionally, 2-lithiofuran can also be readily transmetalated to the corresponding organometallic species such as organoboron ate complexes,[31a] lithium 2-furyltellurolate,[31b] and di(2-furyl)zinc (eq 10).[31c] Possibly the most useful of such C-2 organometallic furan species may be the higher-order cuprates, which can effectively undergo conjugate addition reactions at low temperatures onto enones (eq 11), as well as additions to epoxides and aldehydes, all under Lewis acid catalysis.[32]

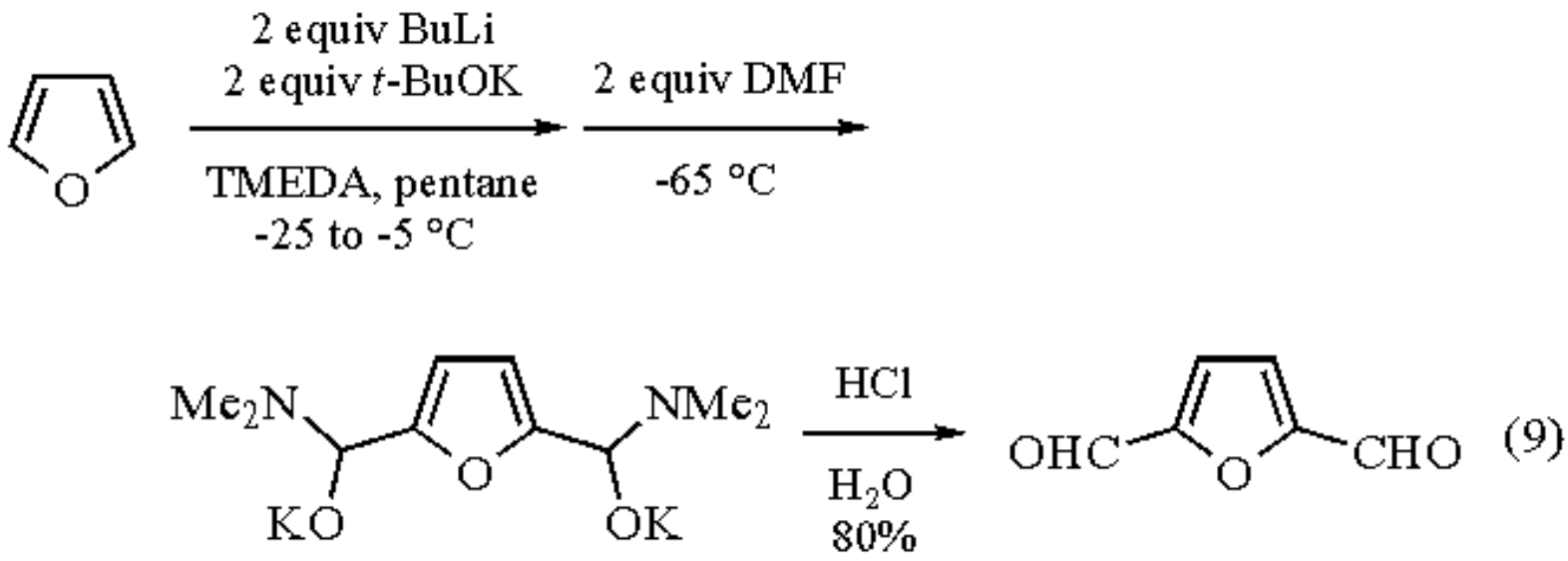

Cycloaddition Reactions.

Furan is known to undergo various types of cycloaddition reactions. It functions as an ene and participates in [2 + 2] and [2 + 3] cycloadditions under photochemical and thermal conditions, respectively. With an embedded cyclic conjugated diene system in it, furan also functions as a diene that undergoes various [4 + 2] and [4 + 3] cycloaddition reactions.[1]

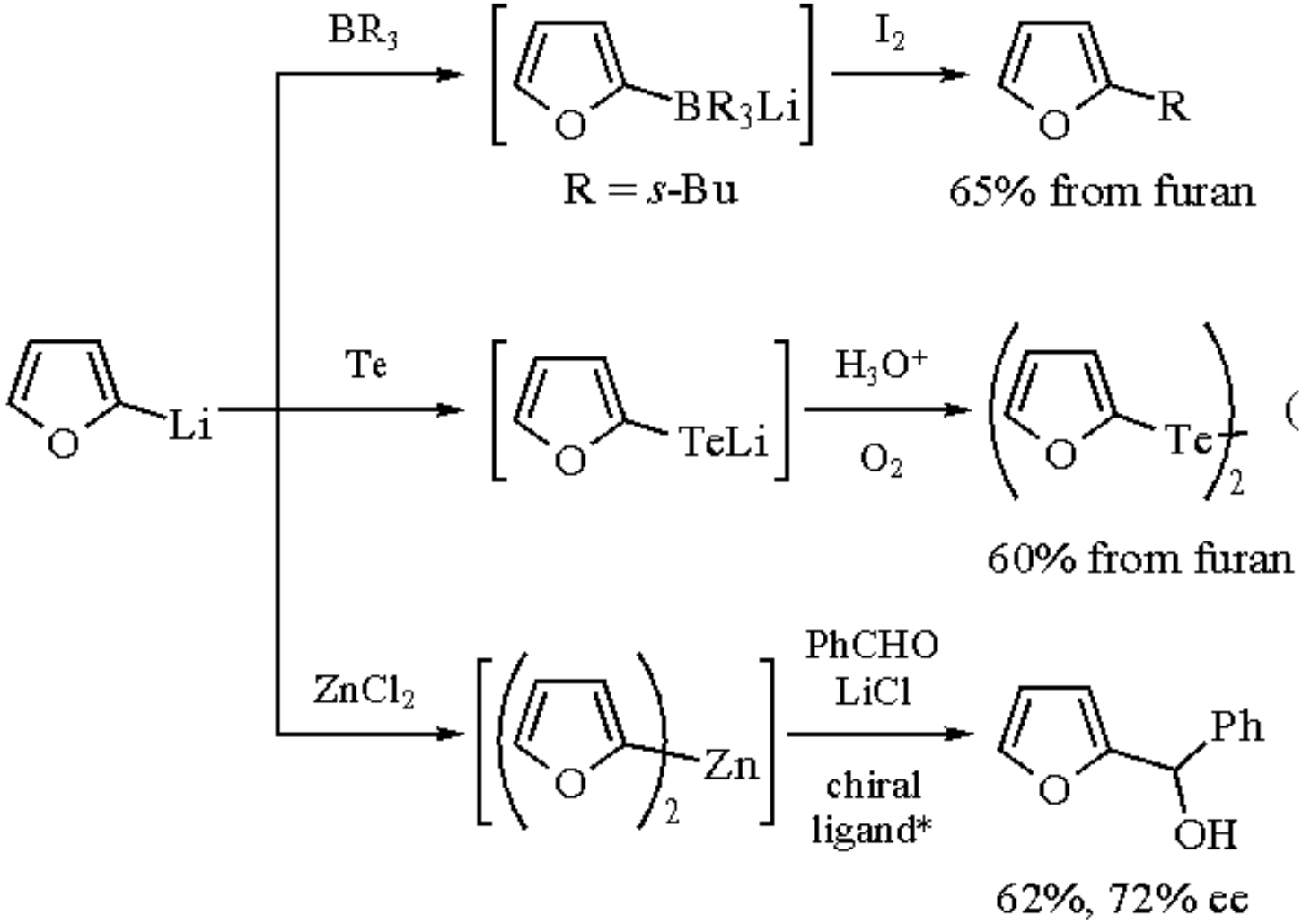

(10)

molar ratio: PhCHO:difurylzinc:chiral ligand:LiCl = 1:2.5:1:5

* (1*S*,2*R*)-(-)-*N*,*N*-dibutylnorephedrine

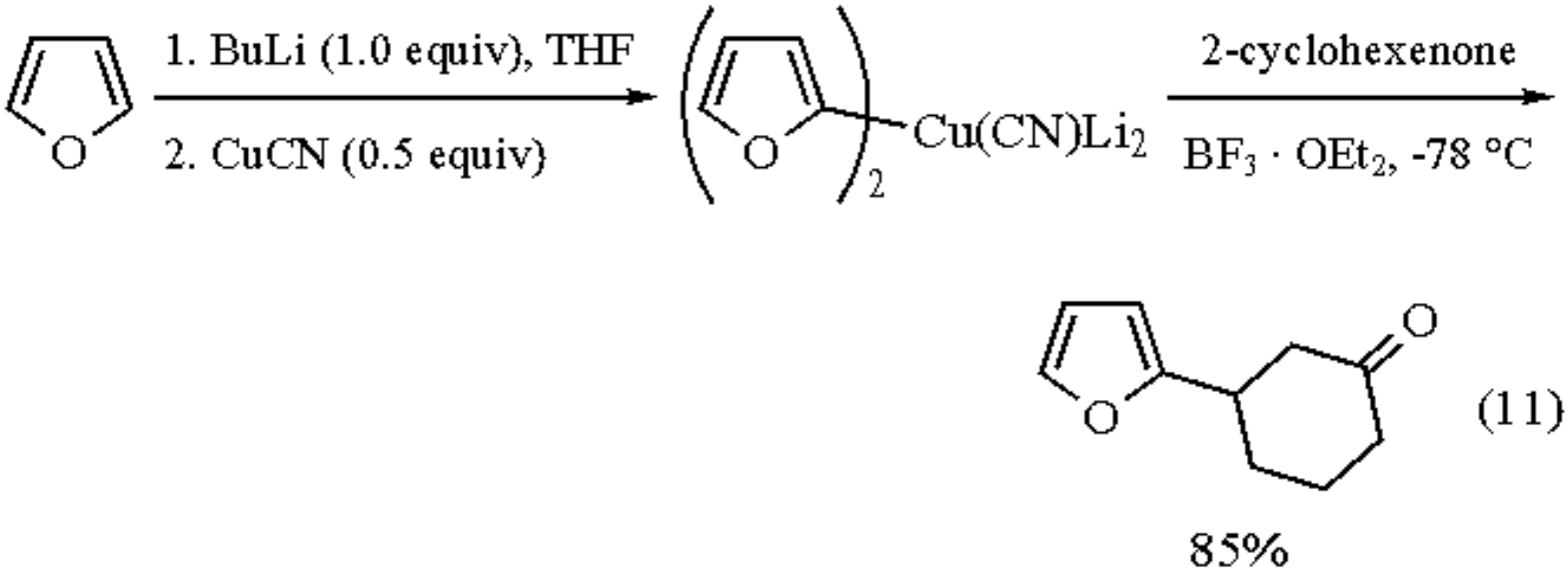

(11)

enone:cuprate equivalent:Lewis acid = 1:1.1:1.1

[2 + 2] Cycloaddition Reactions as an Ene.

It has been well established[5] that carbonyl compounds can be added to furan in a highly regioselective [2 + 2] fashion under photochemical conditions, providing relatively unstable 2,7-dioxabicyclo[3.2.0]hept-3-ene compounds (eq 12).[5c] These bicyclic oxetanes can be isomerized smoothly by acid treatment to 3-substituted furans (eq 12).[5c]

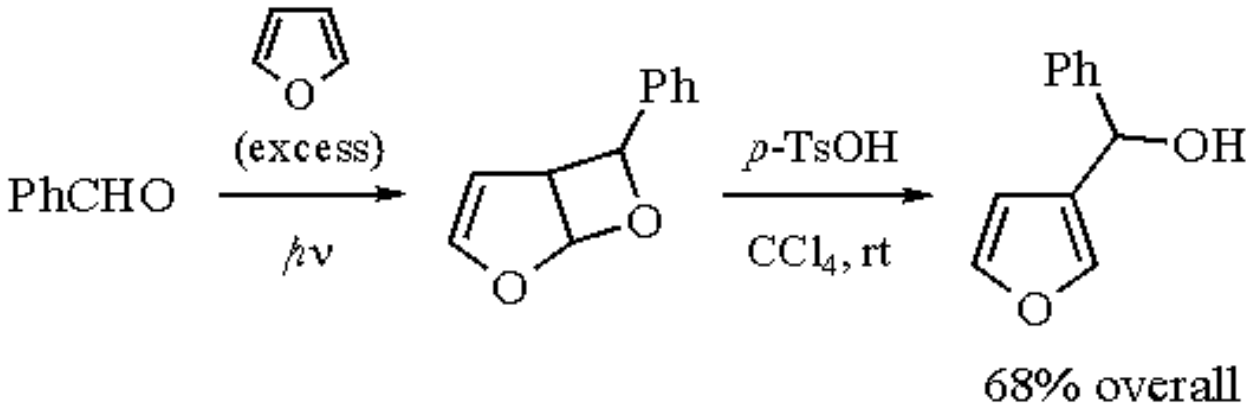

(12)

[2 + 3] Cycloaddition Reactions as an Ene.

Furan undergoes [2 + 3] cycloaddition reactions upon exposure to nitrile oxides generated in situ under high dilution conditions, giving rise to dipolar cycloaddition products in moderate yield (eq 13).[6] These regioselectively produced adducts have been employed in the synthesis of a number of amino-polyols including nojirimycin.[6a]

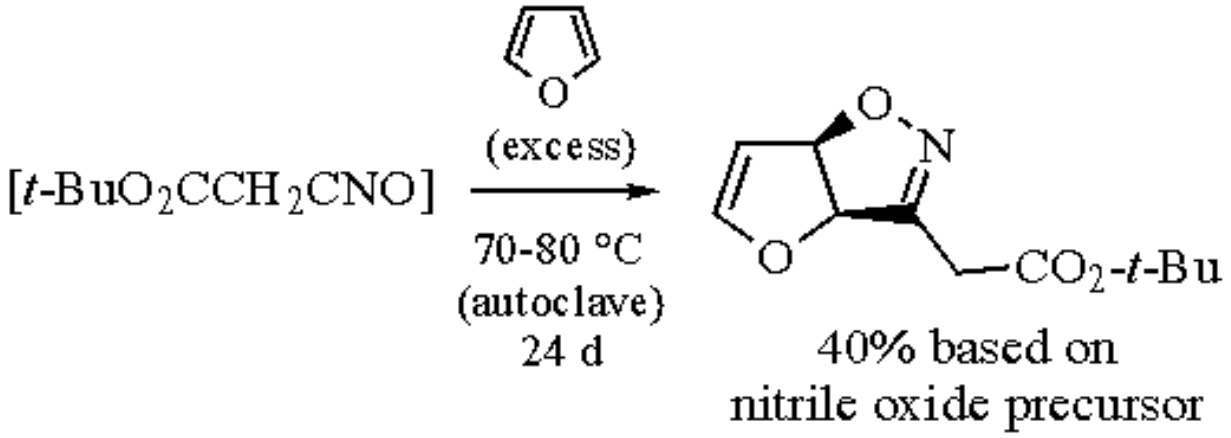

(13)

[4 + 2] Cycloaddition Reactions as a Diene.

The use of furan as a diene in intermolecular Diels-Alder reactions represents one of the most common applications of furan in synthesis, providing a highly versatile means for new C-C bond formation and for further synthetic manipulations.[1d,e] However, often these Diels-Alder reactions involving furan as a diene are sluggish, presumably due to its aromatic nature. Some otherwise difficult furan Diels-Alder reactions have been reported to be mediated by high pressure.[33] The initial report on the acceleration of furan Diels-Alder reactions with the use of catalytic quantities of the Lewis acid ***Zinc Iodide***[34] has been followed by similar observations of rate acceleration by a number of other

catalysts. These include $BF_3.OEt_2$,[35a] $Cu(MeCN)_4(BF_4)$,[35b] $Cy_3Sn(MeCN)_2SbF_6^-$,[35c] chromatography adsorbents,[35d] and K-10 bentonite clay doped with Fe^{3+} or $AlCl_3$.[35e] There is even a report describing observed acceleration of a Diels-Alder reaction between furan and maleic anhydride when the reaction is performed in an ultracentrifuge.[35f]

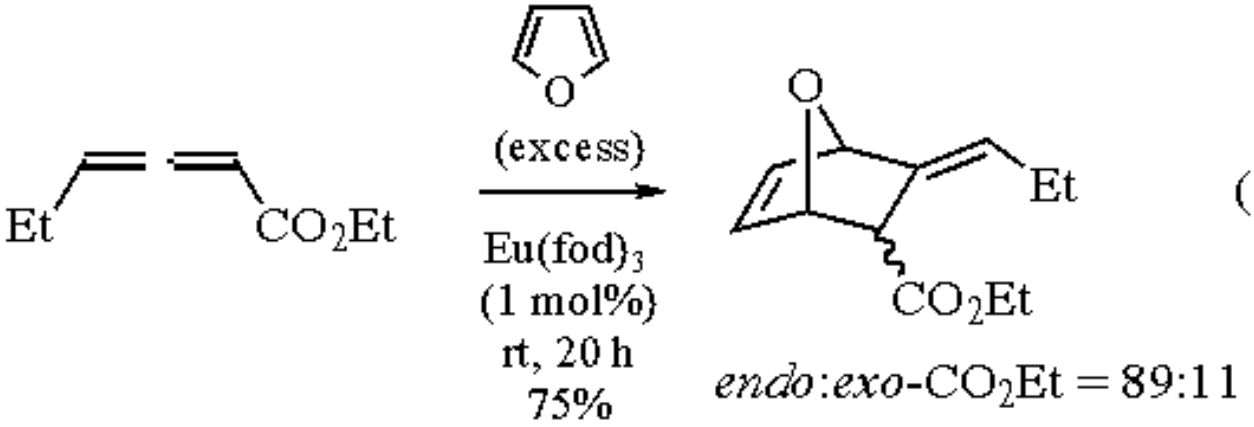

(14)

Furan has been shown to undergo Diels-Alder reactions with activated allenic compounds[36] with high regio- and stereoselectivity (eq 14).[36e] In addition, the Diels-Alder reactions with certain acetylenic compounds are also known.[37] Trapping of highly reactive arynes,[38] Dewar furans,[39] and strained bridgehead alkenes[40] with furan in a [4 + 2] Diels-Alder fashion is well documented. Particularly, reactions of furan with a variety of in situ-generated arynes followed by the aromatization of the 1,4-endoxide rings of the resulting cycloadducts constitute a well-established method for the synthesis of polyarenes (eqs 15 and 16).[38]

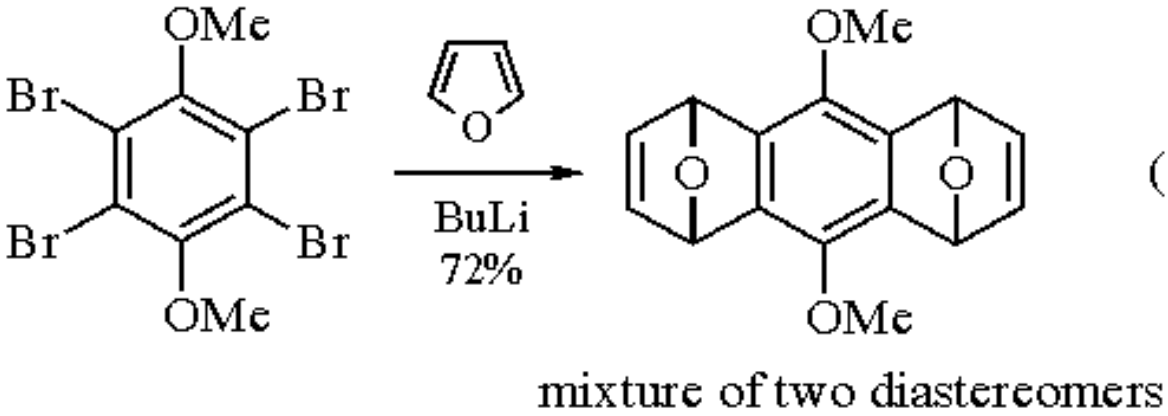

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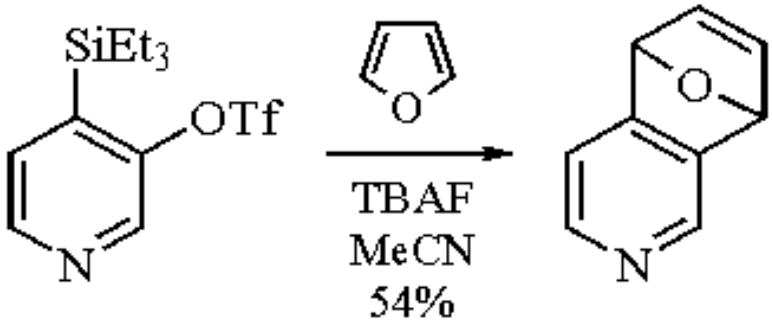

(16)

Asymmetric Diels-Alder reactions of furan with dienophiles have been developed for the synthesis of optically active 7-oxabicyclo[2.2.1]hept-5-ene derivatives, key intermediates for the synthesis of physiologically significant natural products. Diastereoselectivity is achieved with the use of a chiral oxazaborolidine as the catalyst (eq 17)[41a] or optically

active dienophiles[41b,c] (eq 18).[41b]

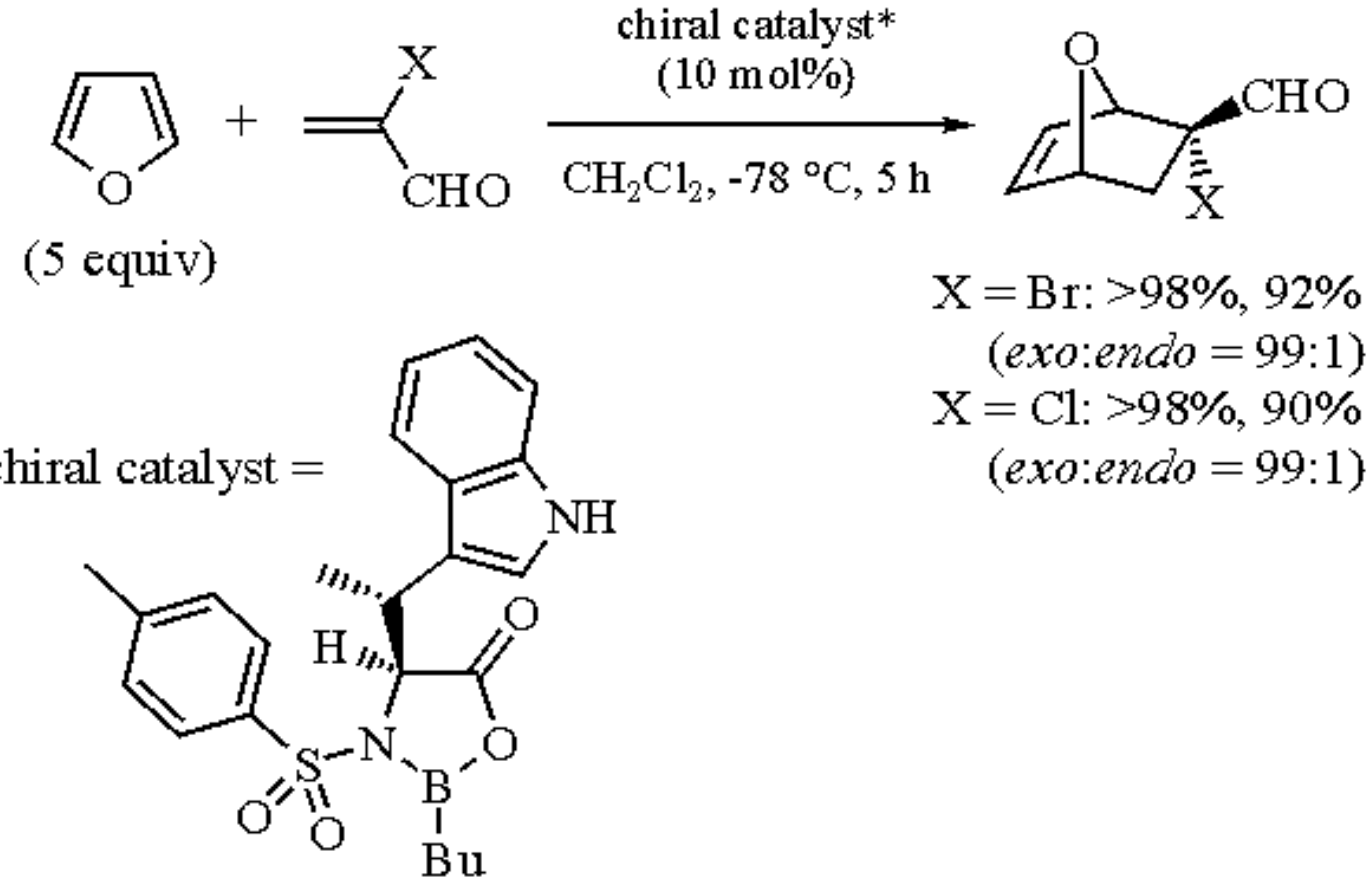

(17)

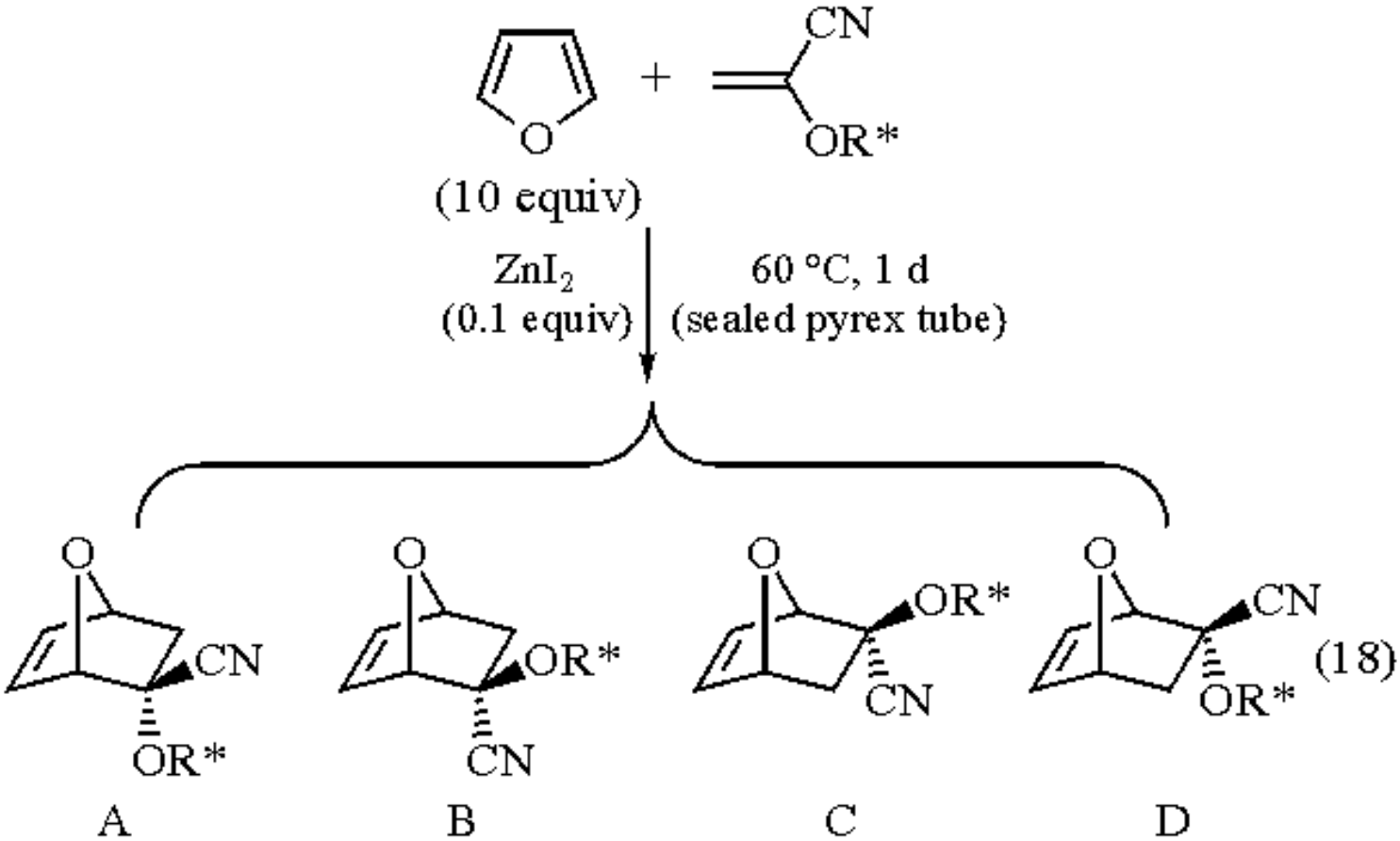

initial total yield = 58-60% with A/D:B/C = 65:35
D obtained in 29% yield in 98% purity after three recrystallizations

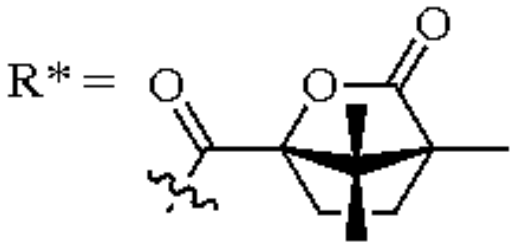

[4 + 3] Cycloaddition Reactions as a Diene.

Furan reacts with dipolar species generated from 2-oxyallyl cations generated from α,α´-polybromo ketones[7,42] or α,α-dialkoxy ketones (via their α´-enol TMS ethers)[43] to form 8-oxabicyclo[3.2.1]oct-6-en-3-ones (eq 19).[7,42] These [4 + 3] cycloadducts can be readily converted to cycloheptanones,[7] tropones,[7,43] highly substituted cycloheptane systems,[44] or even to substituted tetrahydrofuran compounds such as ribose.[7] Many of these have served as key synthetic precursors to a number of natural cyclic and acyclic compounds.[7,44]

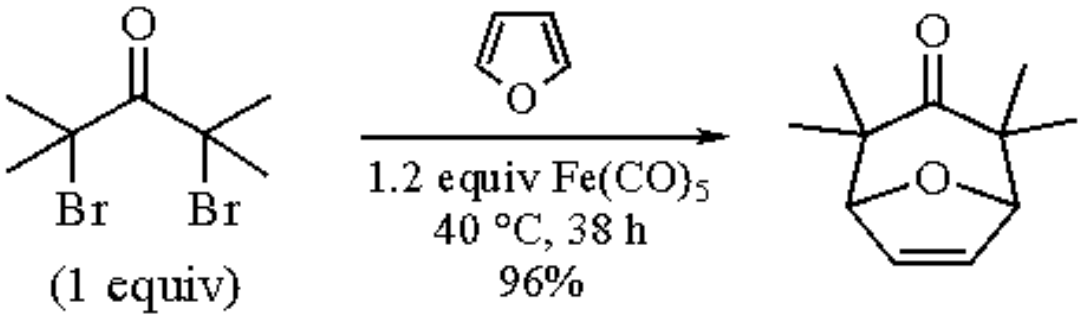

(19)

Oxidation Reactions.

Electron rich furan is readily oxidized by a number of oxidizing agents.[1b] One of the most frequently employed reagents for the oxidation of furan is singlet ***Oxygen***,[8,45a] generating the six-membered endoperoxide by a [4 + 2] cycloaddition reaction followed by its rearrangement or solvolysis to give rise to a variety of products.[45a,b] Treatment of furan with ***Dimethyldioxirane*** results in the formation of the extremely unstable malealdehyde through oxidative ring opening (eq 20).[45c] Under anodic oxidation conditions, furan produces 2-acetoxyfuran, which can be trapped by several kinds of electrophiles to form 4-substituted butenolides (eq 21).[45d]

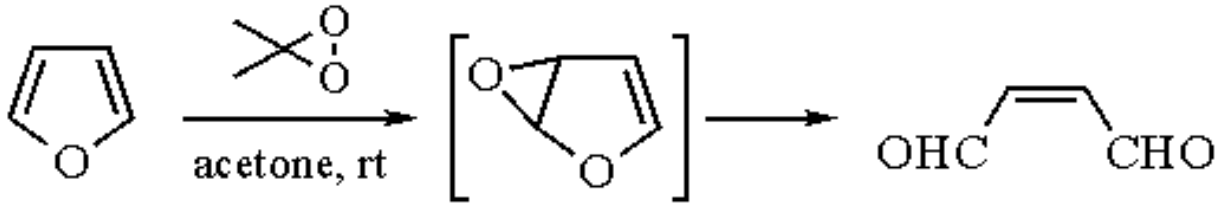

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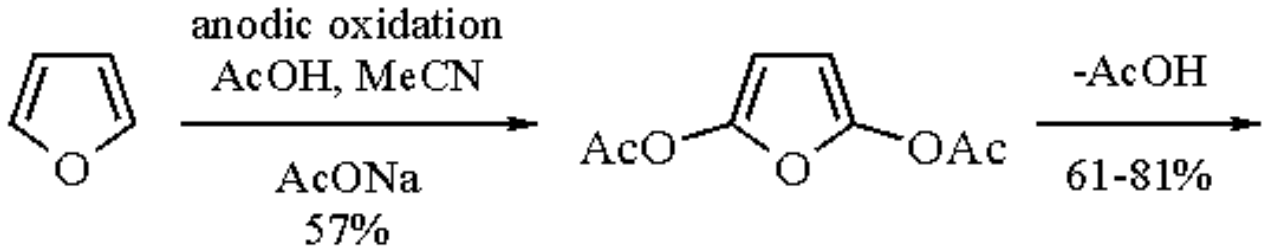

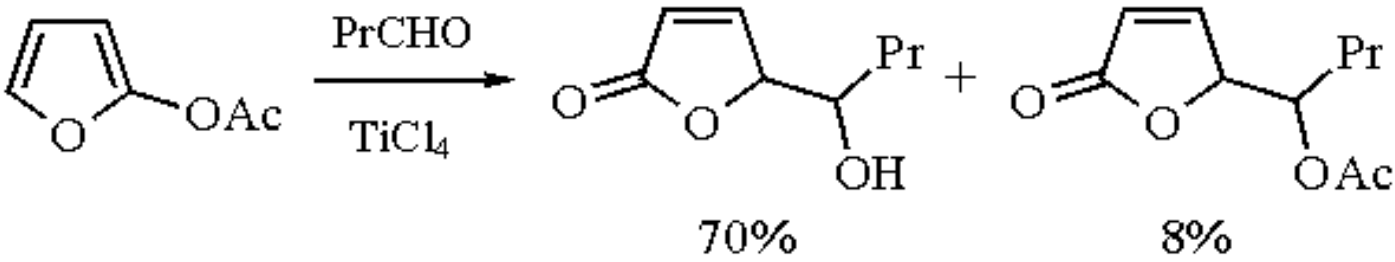

(21)

Carbenoid Reactions.

Other synthetically useful reactions include carbenoid addition to form 2-oxabicyclo[3.1.0]hex-3-ene systems.[46] The reaction of vinylcarbenoids with furan provides two products (eq 22).[47] These results may be rationalized invoking a nonsynchronous cyclopropanation mechanism that leads to two possible dipolar transition states.[47,48]

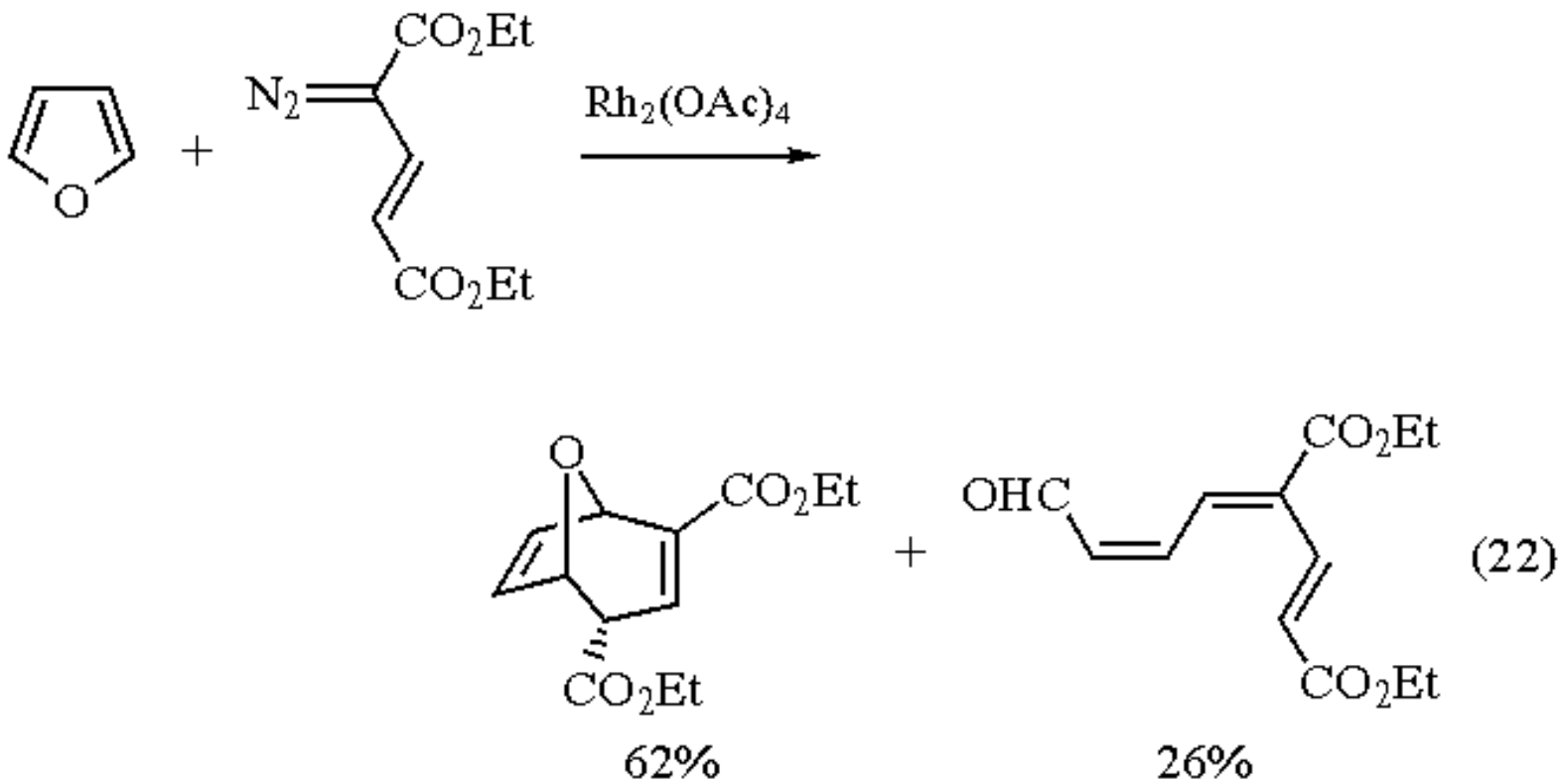

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Galvinoxyl[1,2]

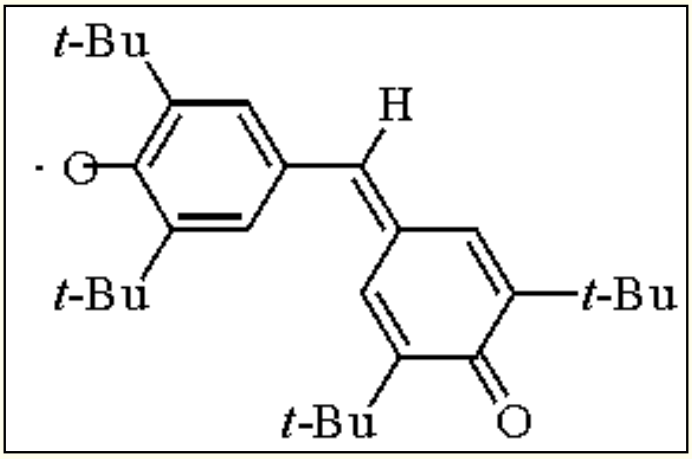

[2370-18-5] · $C_{29}H_{41}O_2$ · Galvinoxyl · (MW 421.70)

(stable radical and radical scavenger, extensively used as a mechanistic probe for radical chain processes;[2] used as an inhibitor to prevent undesired competitive radical paths in reactions[3,4])

Physical Data: mp 158-159 °C.

Solubility: sol organic solvents adequate for applications cited.

Form Supplied in: purple crystalline needles.

Handling, Storage, and Precautions: toxicological properties not investigated thoroughly. May be harmful by inhalation, ingestion, or skin absorption. Keep in tightly closed bottles away from oxygen in a refrigerator. Use in a fume hood.

Galvinoxyl is a stable phenoxy radical[5] which reacts with other radicals at a rate constant near the diffusion-controlled limit (eq 1). Scavenging of radicals leads to decolorization and colorimetric determination is a way of estimating the efficiency of radical formation. Galvinoxyl has been widely used as a probe in the study of organometallic[6] and radical[2] reaction mechanisms. A compilation of earlier work can be found in Kochi's monographs.[2,6]

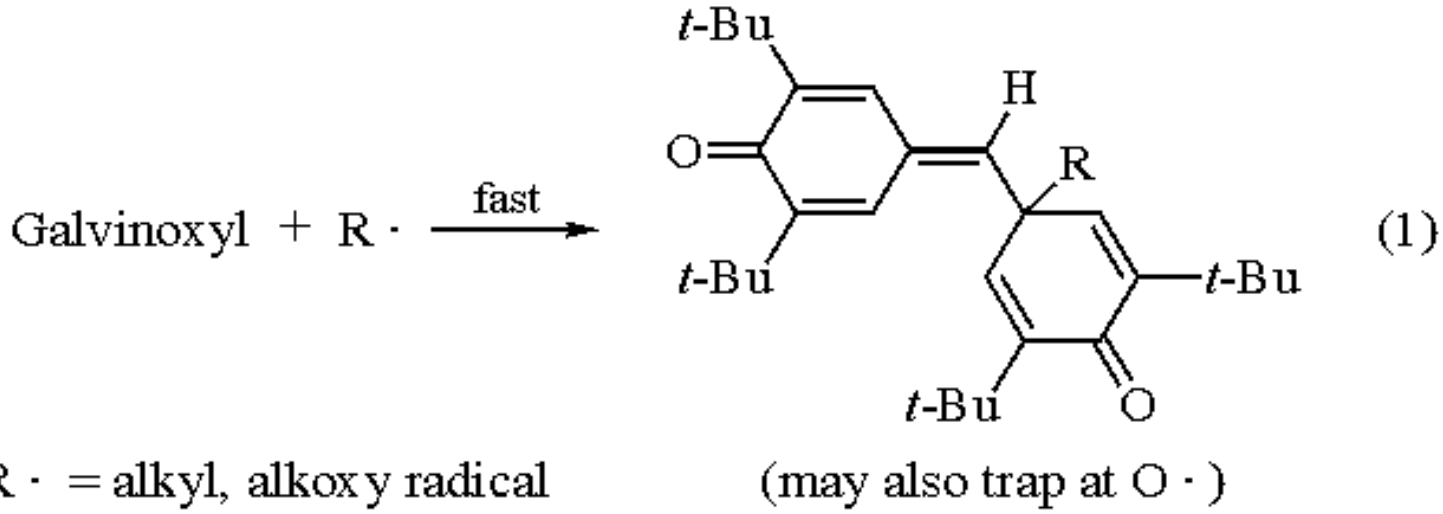

In a classical example, the inhibition of the addition of alkyl boranes to α,β-unsaturated carbonyl compounds was interpreted to mean a radical pathway for this reaction.[7] Other reactions that have been investigated recently, include addition of trialkylaluminum to enones,[8] Ru^{II}-catalyzed Kharasch-type additions of carbon tetrachloride to alkenes,[9] 2,3-dichloropropene-mediated homocoupling of aryl Grignards,[10] $S_{RN}1$ reactions,[11] carbonyl additions of acyltin reagents, and radical polymerization of styrene.

A recent example of the use of galvinoxyl to affect the course of a reaction is in the chemoselective reduction of the carbonyl group of α-bromo ketones with dibutyltin dihydride.[3] Without the the radical inhibitor the reduction of the α-bromo group took place.

A more general use of free radical inhibitors in organic synthesis is illustrated by the use of galvinoxyl in the synthesis of (*R*)-(+)-cyclohex-3-enecarboxylic acid via a Diels-Alder reaction. The major complication arising from the ***Ethylaluminum Dichloride***-mediated polymerizations (presumably through a radical mechanism) is suppressed by galvinoxyl (eq 2).[4]

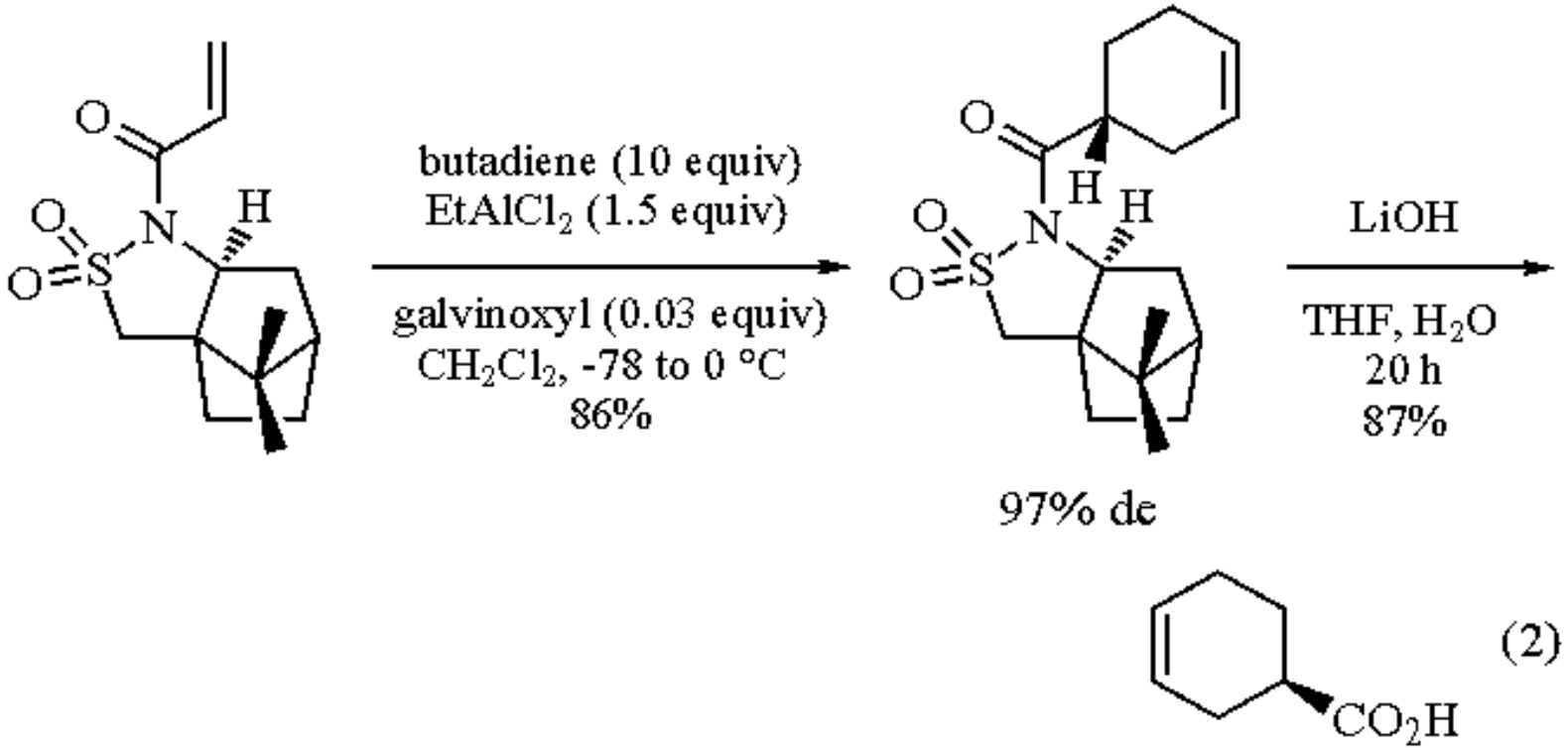

(2)

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Germanium Dichloride-Dioxane Complex[1]

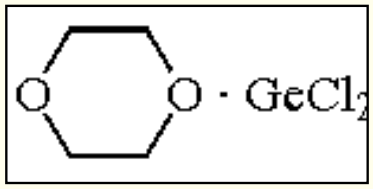

[28595-67-7] · $C_4H_8Cl_2GeO_2$ · Germanium Dichloride-Dioxane · (MW 231.60)

(germylene precursor; Lewis acid catalyst; insertion reactions; cycloadditions and polymerizations)

Physical Data: mp 176-178 °C.

Solubility: slightly sol Et_2O; sol THF.

Preparative Methods: a 100 mL flask equipped with a reflux condenser, nitrogen inlet, and gas outlet connected to a bubbling tower (for removing HCl) was charged with 21.8 g of germanium tetrachloride (0.102 mol), 18.7 mL of anhydrous 1,4-dioxane (0.220 mol), and 5 mL of hexane. To this solution at rt was slowly added 9.6 mL of 1,1,3,3-tetramethyldisiloxane (0.054 mol) through the condenser. The reaction mixture was heated at reflux for 8 h, cooled to rt, and filtered to remove a precipitated white solid via cannula. The solid was washed with three 20 mL portions of hexane, then dried in vacuo to give 14.5 g (63%) of the germanium dichloride-dioxane complex as a white solid.[2]

Handling, Storage, and Precautions: should be handled under nitrogen and stored in a refrigerator. Germanium is reputed to be of low toxicity. Use in a fume hood.

Germylene Precursor.

Germanium dichloride is a convenient starting material for the synthesis of germylenes with alkyl or heteroatom substituents, since the chloride ligands can be displaced by both lithium salts[3] and organolithium reagents.[4]

Lewis Acid Catalyst.

Germanium dichloride behaves as a Lewis acid toward aldehydes, and activates the carbonyl group to 1,2-addition by nucleophiles. For example, it catalyzes intramolecular ene reactions, as in the quantitative conversion of citronellal to isopulegol.[5] Germanium dichloride also catalyzes the conversion of aldehydes to β-keto esters with ***Ethyl Diazoacetate*** (see also ***Tin(II) Chloride***) (eq 1).[6] Finally, germanium dichloride has been used to promote self-condensation reactions with both carbonyl compounds and imines.[7]

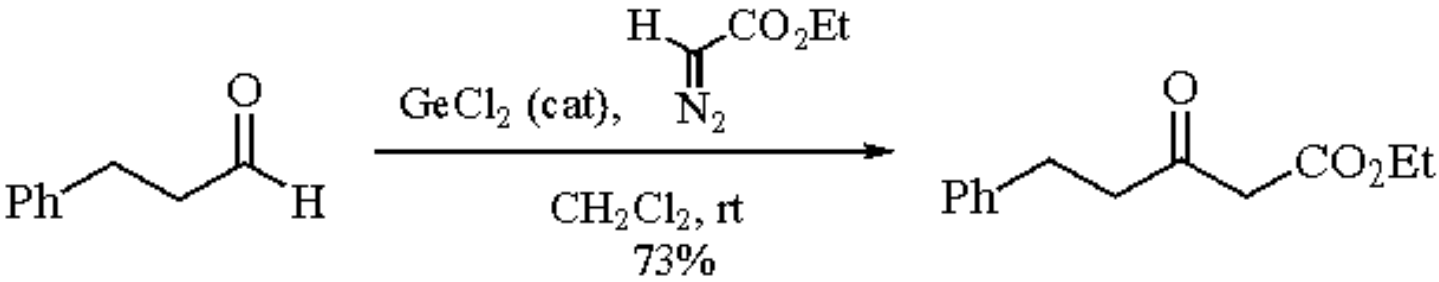

(1)

Insertion Reactions.

Germanium dichloride can insert into hydrogen-halogen, carbon-halogen, metal-halogen, metal-hydride, and metal-metal bonds.[1] Recently, it has been shown that germanium dichloride-dioxane reacts with aldehydes in the presence of alcohols to give α-alkoxygermanes.[5] Similar products are obtained when $GeCl_2$.dioxane is added to an acetal of a saturated aldehyde (eq 2). In both cases, the products of these insertion reactions were converted to more stable derivatives using ***n-Butyllithium***, methyl Grignard, or ***Lithium Aluminum Hydride***. Interestingly, the reaction of $GeCl_2$.dioxane with α,β-unsaturated aldehydes and acetals leads to γ-germyl enol ethers instead of α-alkoxygermanes (eq 3).[8] These γ-germyl enol ethers can be stereoselectively converted to tetrasubstituted tetrahydrofurans via reaction with aldehydes in the presence of ***Boron Trifluoride*** (eq 4).[5]

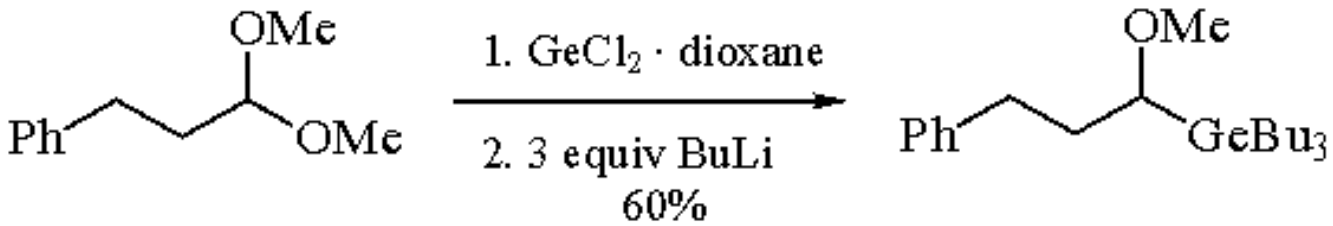

(2)

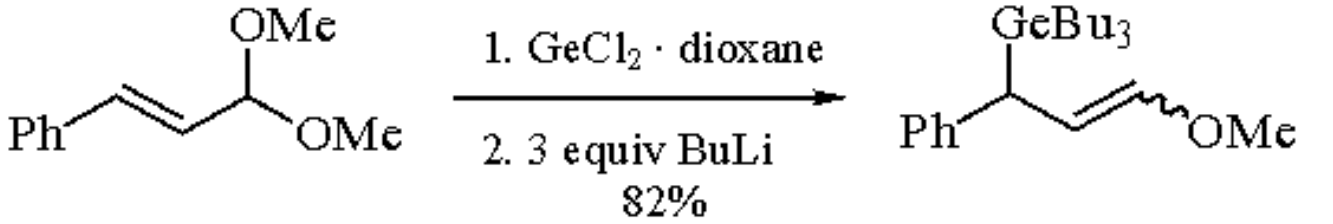

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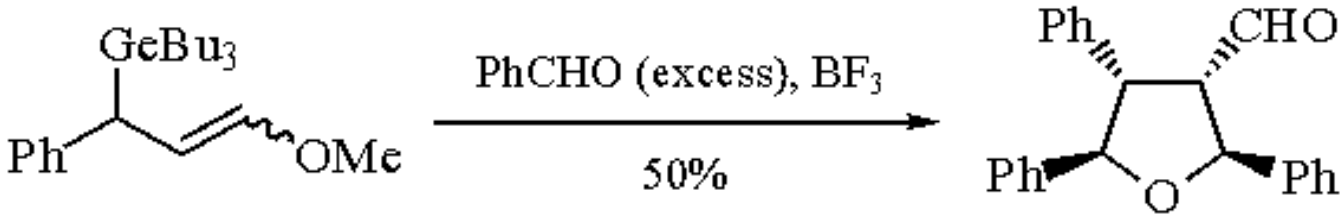

(4)

Cycloadditions and Polymerizations.

Germanium dichloride reacts with alkenes, alkynes, and other unsaturated organic molecules to give organogermanium polymers.[9] In the case of dienes, 1,4-cycloaddition products are obtained (eq 5).[10]

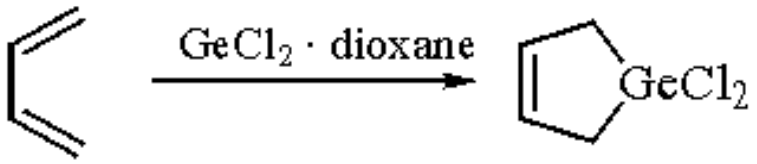

(5)

Related Reagents.

Allyltrimethylgermane; ***Ethyl Diazoacetate***; ***Tin(II) Chloride***; ***Trifluoromethanesulfonic Anhydride***.

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Glutaraldehyde

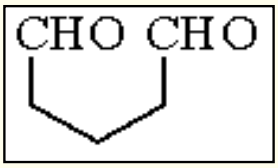

[111-30-8] · $C_5H_8O_2$ · Glutaraldehyde · (MW 100.13)

(useful annulating reagent for constructing heterocycles; most widely used in cross-coupling of proteins)

Alternate Name: pentanedial.

Physical Data: oil, bp 71 °C/10 mmHg; *n*25D 1.4338.

Solubility: very sol water, alcohol, ether.

Form Supplied in: 25 or 50% aqueous solution; commercially available.

Preparative Methods: in many cases, used as the commercial aqueous solution, but anhydrous glutaraldehyde can be obtained either by extraction of the aqueous solution by organic solvent followed by drying and distillation at reduced pressure,[1] or by preparation from 2-ethoxy-3,4-dihydro-2*H*-pyran.[2]

Handling, Storage, and Precautions: whereas aqueous glutaraldehyde solutions are stable, anhydrous glutaraldehyde has to be used immediately after distillation due to rapid polymerization. In ether solution, glutaraldehyde rapidly polymerizes even at low temperature.[3] Use in a fume hood.

2,6-Disubstituted Piperidines; Bicyclic Compounds.

The classical Robinson synthesis[2] of pseudopelletierine was the first example of a double Mannich reaction of glutaraldehyde (eq 1). It involved reaction of glutaraldehyde with methylamine and acetonedicarboxylic acid in a slightly acidic aqueous solution (for similar reactions, see also ***Succindialdehyde***).

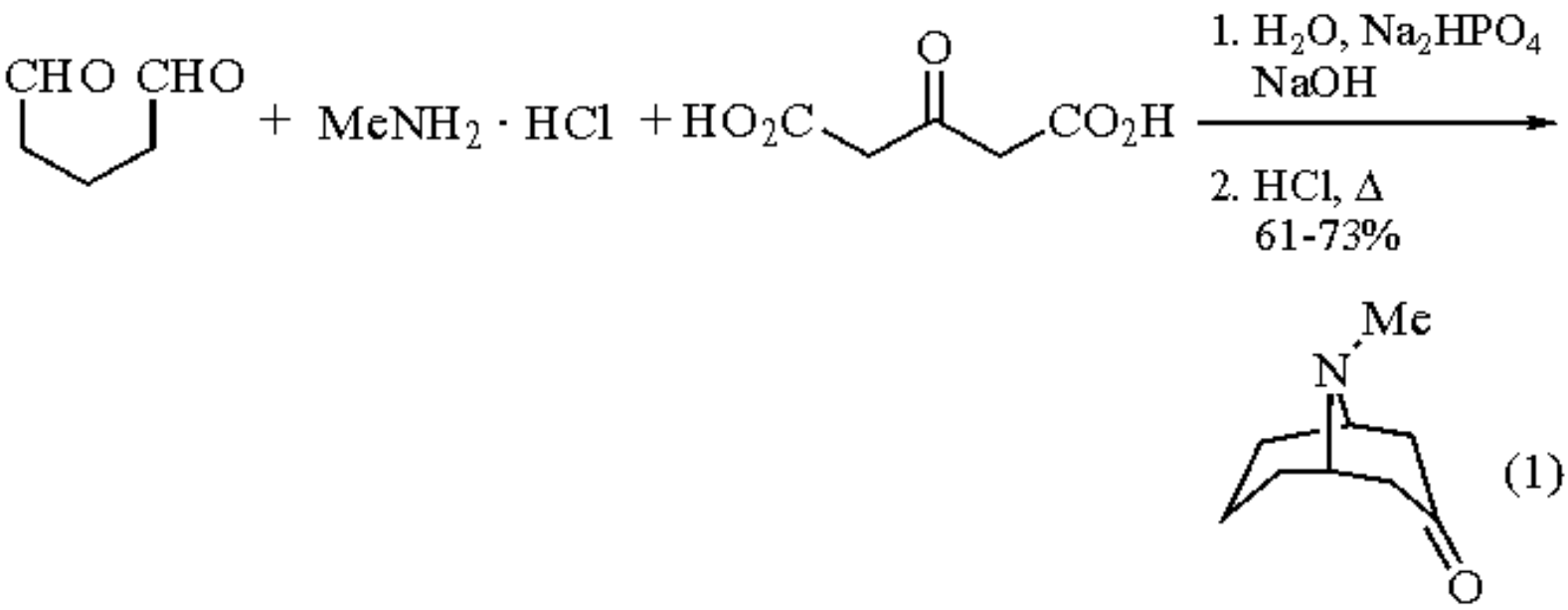

Synthesis of *cis*-2,6-diacetonylpiperidine has been reported using this methodology (eq 2).[4]

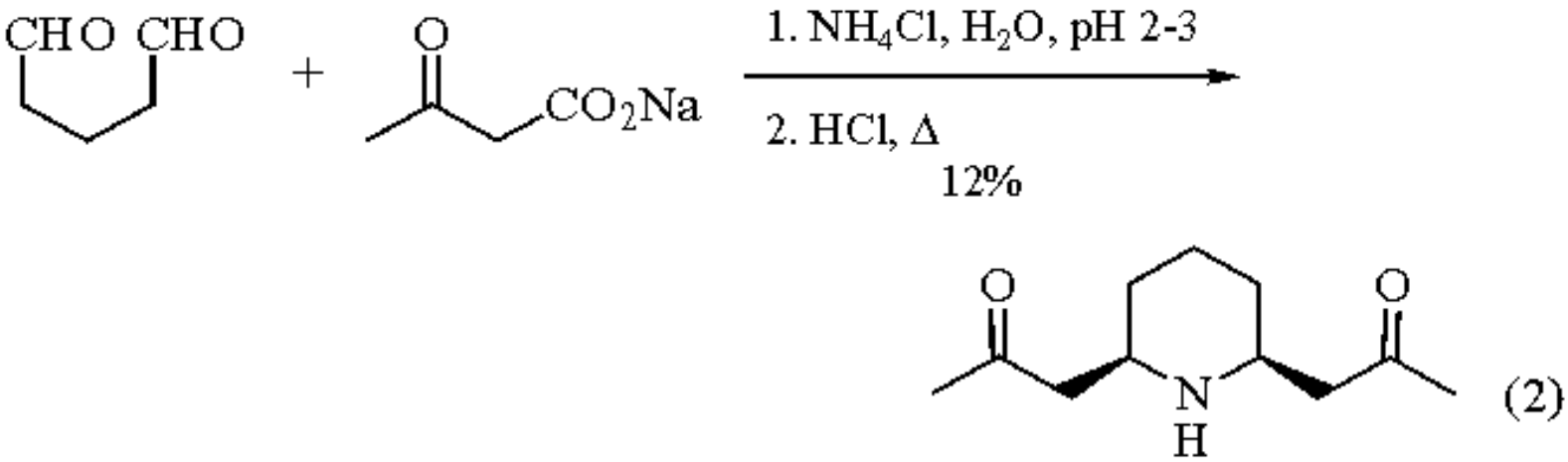

In the absence of a nucleophile, 1,4-dihydropyridine is formed (eq 3).[3]

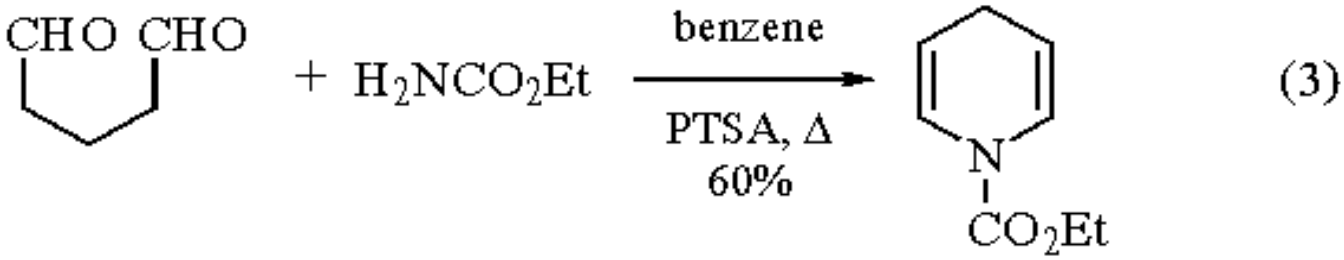

Stable equivalents of 1,4-dihydropyridine can also be obtained by the use of heteroatomic nucleophiles. The double condensation of glutaraldehyde with a chiral nonracemic amino alcohol in the presence of cyanide leads to the formation of a 2-cyano-6-oxazolopiperidine in an enantiomerically pure form and in 80% yield (eq 4).[5] This compound has proved to be a very useful tool for the asymmetric synthesis of piperidine derivatives and has been used largely in the asymmetric synthesis of alkaloids.[5b]

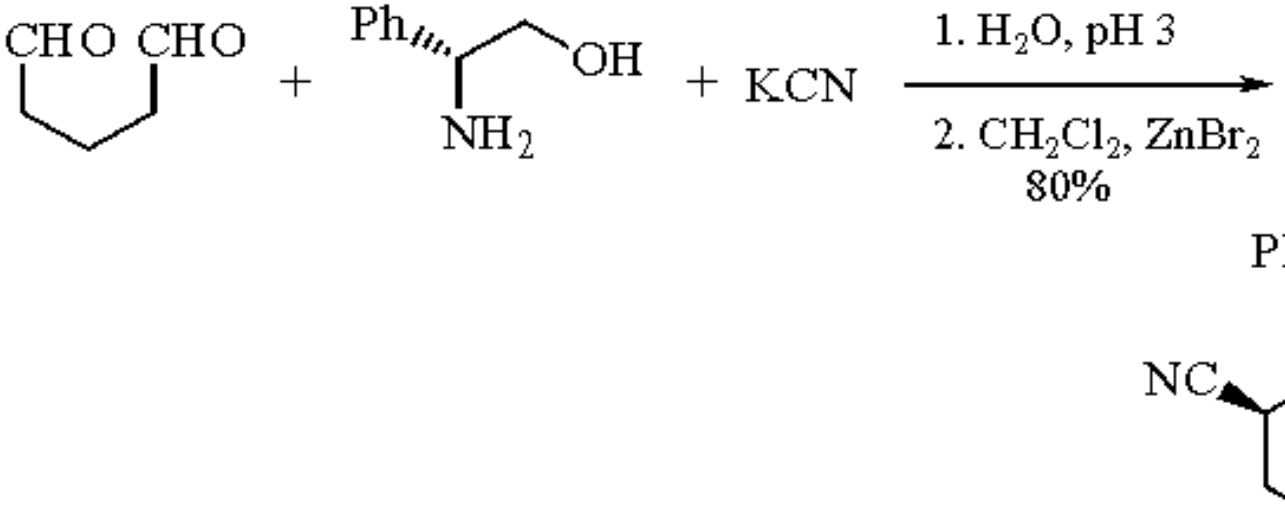

(4)

N-Substituted piperidines are obtained when glutaraldehyde reacts with primary amines in the presence of a reducing agent (reductive alkylation). The most popular reagent is ***Sodium Cyanoborohydride*** (eq 5),[6a] but other reagents are also efficient in this transformation.[6] This method is generally preferred to the condensation of a primary amine with 1,5-dihalogenopentane.

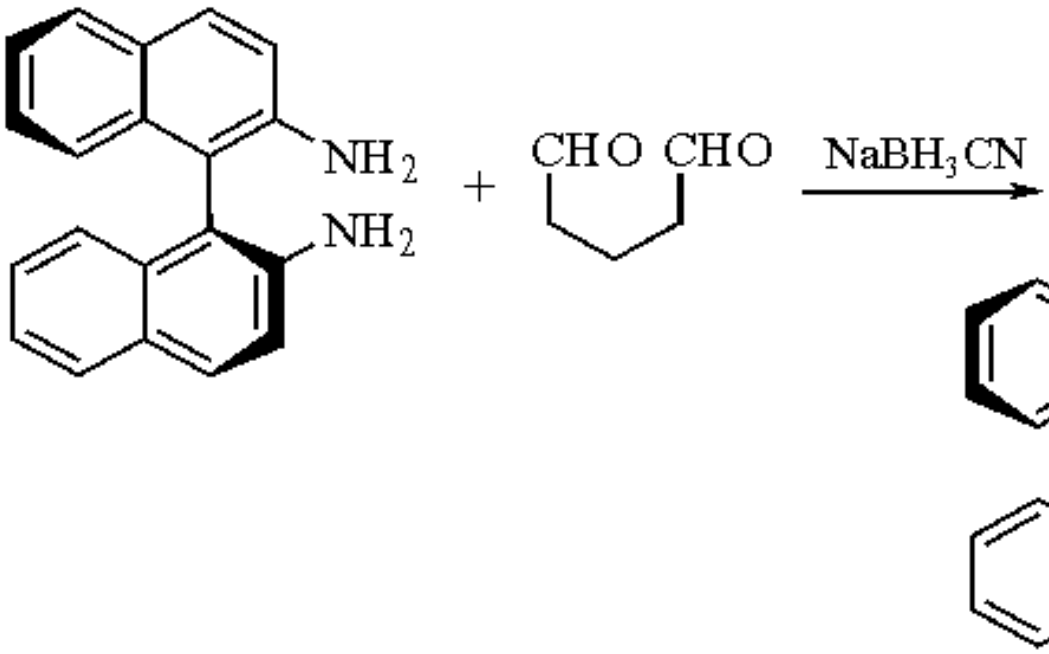

(5)

In the condensation of glutaraldehyde with tryptamine, one of the iminium salts can be trapped by the indole ring in a Pictet-Spengler reaction, and in the presence of ***Sodium Borohydride*** an indoloquinolizidine is obtained (eq 6).[7]

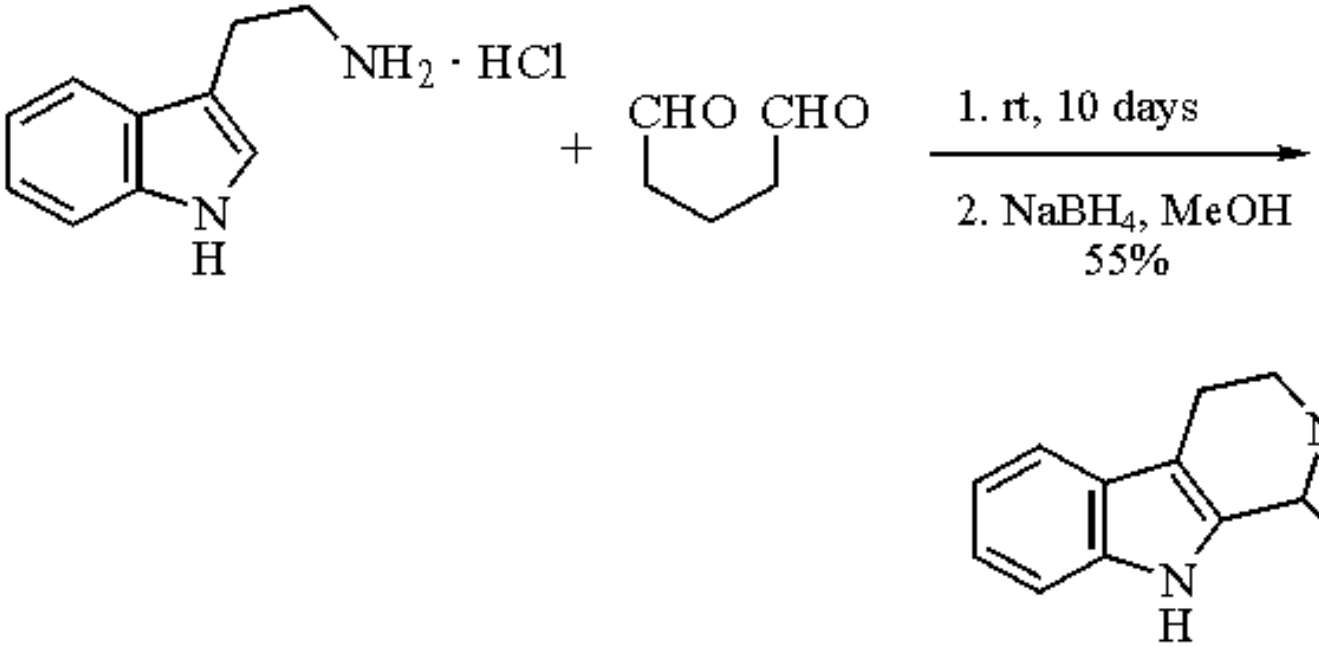

(6)

Other Uses.

Pyran derivatives can be prepared from glutaraldehyde, generally by monoalkylation with a carbon nucleophile,[1,8] as depicted in eq 7.

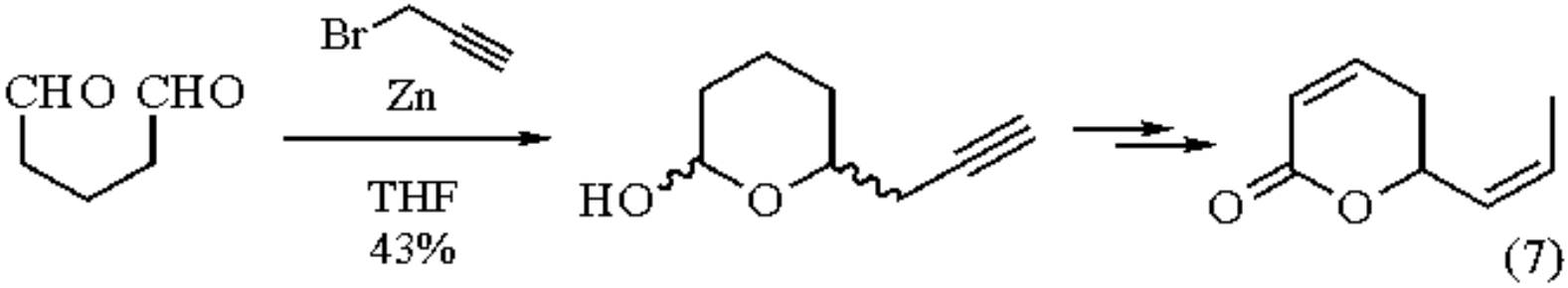

(7)

Active methylene compounds can add to glutaraldehyde to give cyclohexane derivatives (eq 8).[9]

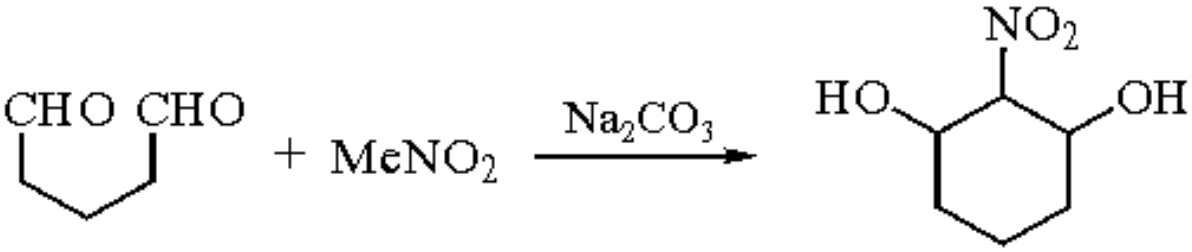

(8)

Glutaraldehyde monoacetals have been reported. Their preparations include the partial acetalization of glutaraldehyde and the partial hydrolysis of 2-ethoxy-3,4-dihydro-2*H*-pyran. These monoacetals are widely used in many organic syntheses and have been reviewed.[10]

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3. Foos, J. S.; Steel, F.; Rizvi, S. Q. A.; Fraenkel, G. *JOC* **1979**, *44*, 2522.
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6. (a) Kawakami, Y.; Hiratake, J.; Yamamoto, Y.; Oda, J. *CC* **1984**, 779. (b) Verardo, G.; Giumanini, A. G.; Favret, G.; Strazzolini, P. *S* **1991**, 447.
7. Gribble, G. W. *JOC* **1972**, *37*, 1833.
8. Fehr, C.; Galindo, J.; Ohloff, G. *HCA* **1981**, *64*, 1247.
9. (a) Lichtenthaler, F. W. *AG(E)* **1964**, *3*, 211. (b) González, F. S.; Diaz, R. R.; Garcia Calvo-Flores, F. A.; Berenguel, A. V.; Gimenez Martinez, J. J. *S* **1992**, 631.
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Glutarimide[1]

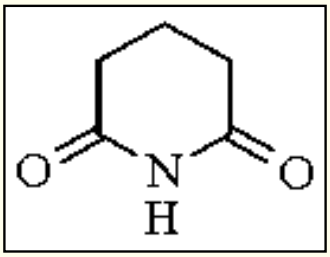

[1121-89-7] · $C_5H_7NO_2$ · Glutarimide · (MW 113.13)

(building block for synthesis of other heterocyclic compounds, especially via *N*-acyliminium cyclizations[2])

Alternate Name: 2,6-piperidinedione.

Physical Data: mp 163-165 °C; *d* 1.393 g cm^{-3}; dipole moment 2.58 D (dioxane, 30 °C); pK_a 11.43 (H_2O, 25 °C).

Solubility: sol H_2O, hot EtOH, boiling benzene; insol ether.

Form Supplied in: white solid.

Reactions at the Nitrogen Atom.

The direct reaction of glutarimide with a primary[3] or a secondary[4] alcohol, mediated by ***Triphenylphosphine*** and dialkyl azodicarboxylate (Mitsunobu reaction[5]) is the most widely used method for the *N*-alkylation (eq 1).[3] However, because of the tedious workup procedure (removal of Ph_3PO and $RO_2CNHNHCO_2R$), alkylation of alkali metal salts of glutarimide with primary halides or sulfonates is usually more convenient (eq 2).[6] The sodium salt is prepared by reaction with NaOMe in MeOH, followed by precipitation with ether. The alkali metal salts can also be generated from the metal hydride in DMF or HMPA, without isolation of the salt.

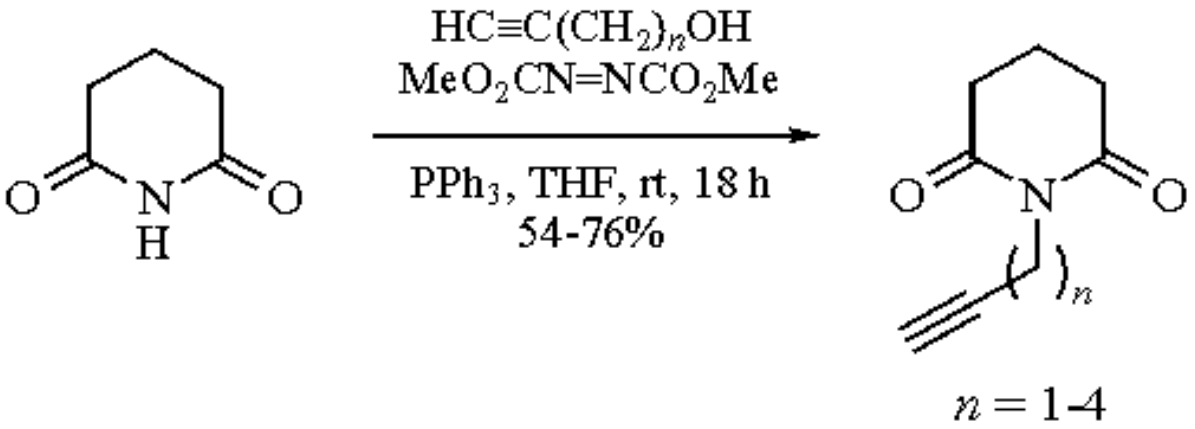

(1)

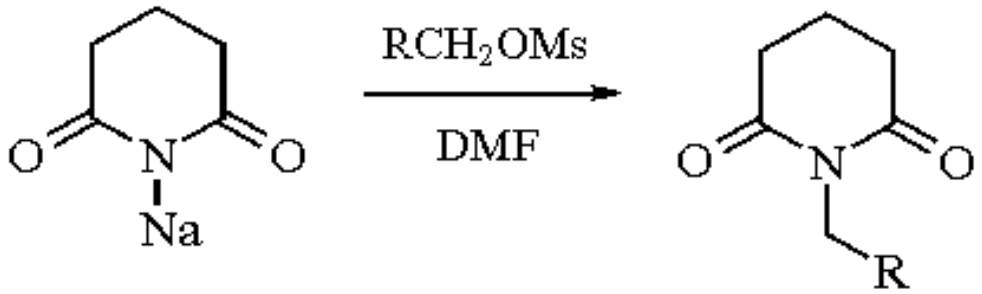

(2)

R = $CH_2C{\equiv}CCH_2TMS$, 84%; (*Z*)-$CH_2CH{=}CHCH_2TMS$, 83%

N-Alkylation of glutarimide in high yield is also possible by using primary chlorides, bromides, or tosylates under solid-liquid phase transfer conditions (***Potassium Carbonate***, 0.1 equiv ***18-Crown-6***, benzene or toluene, reflux).[7] Addition of 0.1 equiv ***Potassium Iodide*** increases the reaction rate for less reactive halides.

N-Alkenyl or *N*-alkynyl glutarimides are important intermediates for the synthesis of other heterocyclic systems; upon partial reduction to the hydroxylactam and treatment with acid, an *N*-acyliminium cyclization occurs.[2]

Reactions at the Carbonyl Group.

Addition of Grignard reagents (>2 equiv) to glutarimide gives rise to *t*-hydroxylactams (in equilibrium with the ring-opened keto-amide). In the case of alkenyl derivatives, *N*-acyliminium cyclizations to the 1-azaspiran derivatives are possible (eq 3).[8]

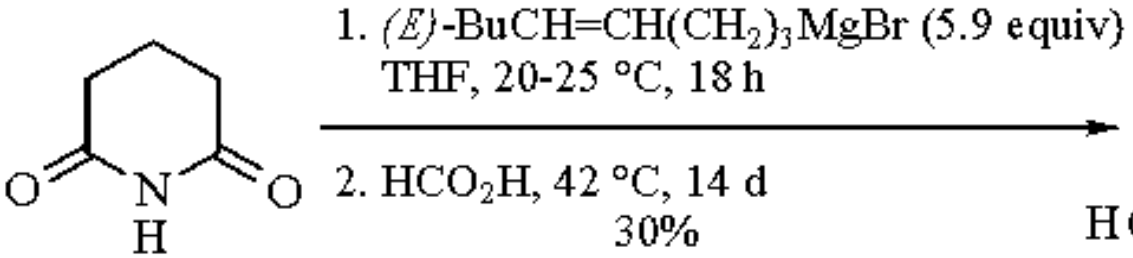

(3)

Reaction of sodium glutarimide with ***[1-(Ethoxycarbonyl)cyclopropyl]triphenylphosphonium Tetrafluoroborate*** leads to an indolizidine derivative via nucleophilic opening of the cyclopropyl ring and a subsequent intramolecular Wittig reaction (eq 4).[9]

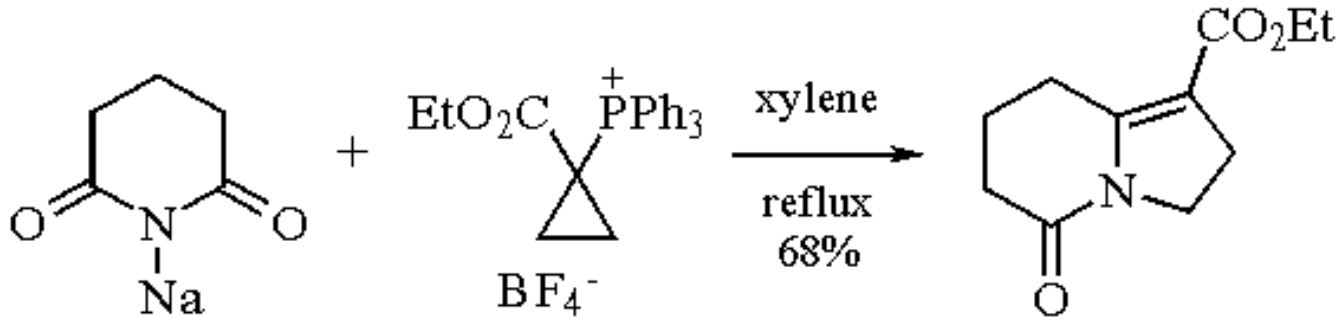

Reactions at the Carbon Atom next to the Carbonyl Group.

Disodium glutarimide in liquid ammonia can be alkylated or acylated with ***Benzyl Chloride***, benzophenone, or methyl benzoate to give the 2-substituted glutarimides[10] (e.g. eq 5).[11]

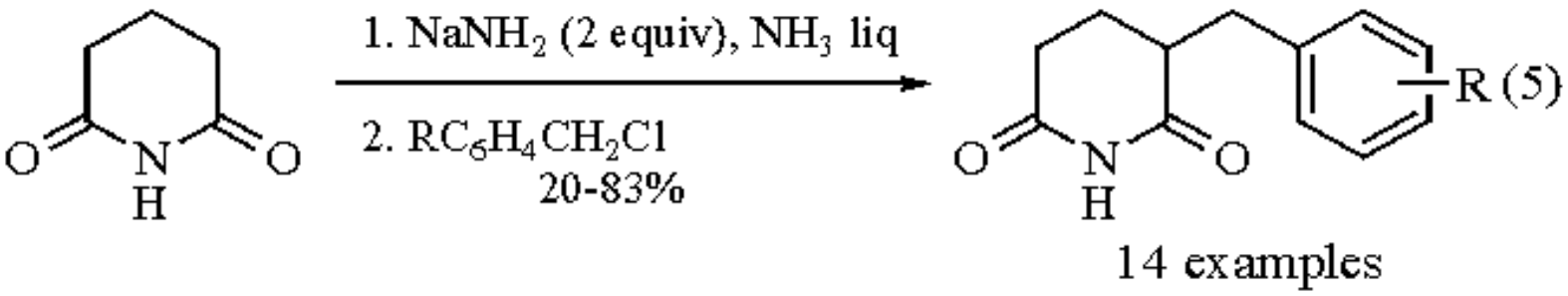

Related Reagents.

Diethyl Azodicarboxylate; ***[1-(Ethoxycarbonyl)cyclopropyl]triphenylphosphonium Tetrafluoroborate***; ***4-Phenylsulfonyl-3-buten-2-one***; ***Phthalimide***; ***Succinimide***.

---

1. Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *CRV* **1970**, *70*, 439.
2. (a) Speckamp, W. N.; Hiemstra, H. *T* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. *COS* **1991**, *2*, 1047.
3. Schoemaker, H. E.; Boer-Terpstra, T.; Dijkink, J.; Speckamp, W. N. *T* **1980**, *36*, 143.
4. Ent, H.; De Koning, H.; Speckamp, W. N. *H* **1988**, *27*, 237.
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9. Flitsch, W.; Russkamp, P. *LA* **1983**, 521.
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11. Goehring, R. R.; Greenwood, T. D.; Nwokogu, G. C.; Pisipati, J. S.; Rogers, T. G.; Wolfe, J. F. *JMC* **1990**, *33*, 926.

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Glycidol[1]

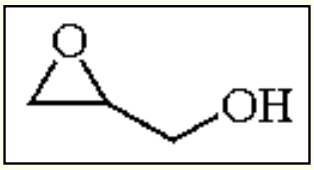

[556-52-5] · $C_3H_6O_2$ · Glycidol · (MW 74.08) (*R*)

[57044-25-4] (*S*)

[60456-23-7] (±)

[61915-27-3]

(versatile bifunctional, three-carbon synthon)

Alternate Name: oxiranemethanol.

Physical Data: mp -53 °C; bp 161-163 °C (dec), 30 °C/1 mmHg, 54 °C/8 mmHg, 114 °C/114 mmHg; *d* 1.115 g cm^{-3}; $[\alpha]_D$ +15° (neat, L-(+)-glycidol).

Solubility: insol aliphatic hydrocarbons; sol H_2O, acetone, THF, toluene, most other organic solvents.

Form Supplied in: racemic, (*R*), and (*S*) forms; all as colorless, neat liquids. Solid derivatives: phenyl isocyanate, mp 60 °C; α-naphthyl isocyanate, mp 102 °C.

Analysis of Reagent Purity: ^1H NMR.

Handling, Storage, and Precautions: neat samples of glycidol should be stored in the freezer to slow the process of self-condensation; when stored neat, glycidol should be checked for purity before use and will usually require purification, which can be achieved by distillation under reduced pressure; self-condensation is greatly reduced by storage of glycidol in solutions, e.g. 50-70% in toluene or dichloromethane; distillation of glycidol should be done behind a safety shield; care should be taken when using glycidol under acidic conditions (e.g. acetic acid) since acid catalyzes self-condensation; use in a fume hood.

Glycidol and Glycidol Derivatives.

Two excellent reviews of glycidol and glycidol derivatives are available. The first is a very thorough review of the properties and reactions of glycidol written by Kleemann and Wagner.[1a] In the second, the use of glycidol and glycidol derivatives as synthons, with a strong emphasis on nonracemic glycidol, is the subject of a superb review by Hanson.[1b]

Glycidol is a versatile three-carbon synthetic building block and its value is greatly expanded through derivatization of the hydroxyl group. The use in synthesis of derivatives such as *O*-aryl and *O*-arylmethyl (e.g. *O*-benzyl) ethers, sulfonates, carboxylates, and silyl ethers is integrated with those of glycidol for this review. In the following discussion, glycidol and derivatives are occasionally referred to collectively as glycidols. Also note that reactions of nonracemic glycidol are illustrated only with one enantiomer, but apply equally to use of both.

Glycidol, like all 2,3-epoxy alcohols, is susceptible to the Payne rearrangement when exposed to base. Payne rearrangement of (*R*)- or (*S*)-glycidol is degenerate; consequently racemization does not occur.

(*R*) and (*S*) are empirical designations of absolute configurations and in comparing glycidol and an *O*-substituted glycidol derivative having the same absolute configuration, the designation changes (see eq 1). For further discussion of this point, see Hanson's review.[1b]

Preparations.

Racemic glycidol, (*R*) and (*S*)-glycidol, and a number of derivatives of each are commercially available. Preparations of these materials are described in the literature and a selected listing follows: (*S*)-glycidol via asymmetric epoxidation[2] and enzymatic kinetic resolution;[3] *O*-benzyl glycidol,[4] *O*-trityl glycidol;[5] (*R*)-(-)-***Glycidyl Tosylate***;[6] (*R*)-(-)-glycidyl 3-nitrobenzenesulfonate (a derivative whose optical purity is enhanced by recrystallization);[6] (*R*)-(-)-glycidyl *p*-nitrobenzoate (see eq 1).[2,7]

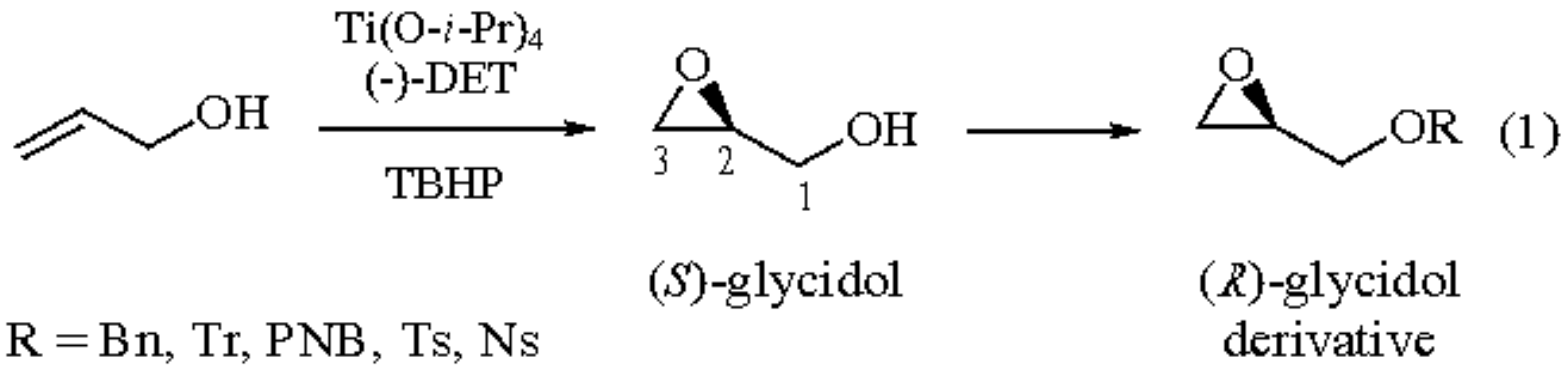

Reactions at C-1 of Glycidol.

A number of *O*-derivatives of glycidol are described in the preceding section and may be prepared directly from racemic or (*R*)- or (*S*)-glycidol. Alternatively, if carrying out the laboratory preparation of (*R*)- or (*S*)-glycidol, convenient in situ methods for derivatization have been developed.[2,7,8] Derivatization as *O*-sulfonate esters (e.g. tosylates) activates the C-1 position and permits displacement by nucleophiles. An example is displacement by phenolates to generate *O*-aryl glycidol ethers (see eq 2),[6] which find extensive use as intermediates in the synthesis of a variety of pharmacologically active agents (see additions of nitrogen at C-3, below).

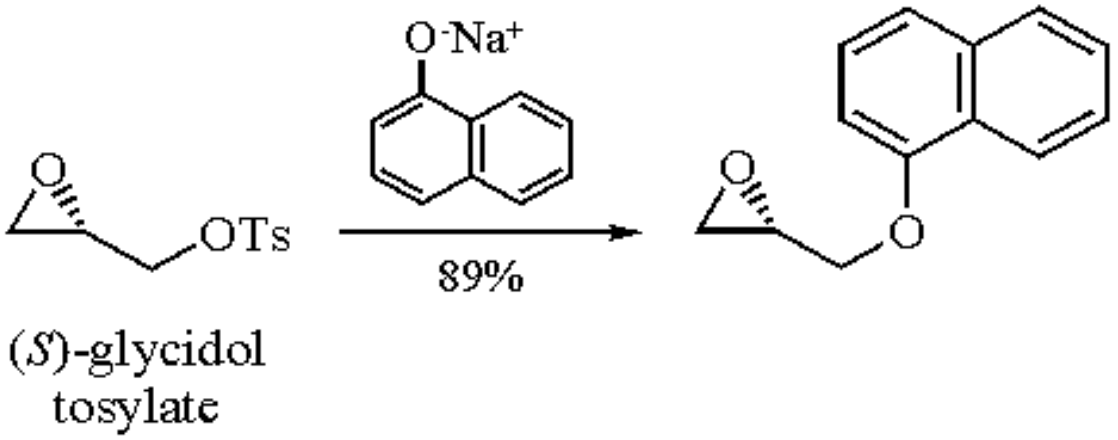

(2)

O-Aryl glycidol ethers can be prepared from glycidol by the Mitsunobu reaction with phenols (see eq 3)[9a] and are also made from direct displacement by glycidol on activated haloaryls.[9b]

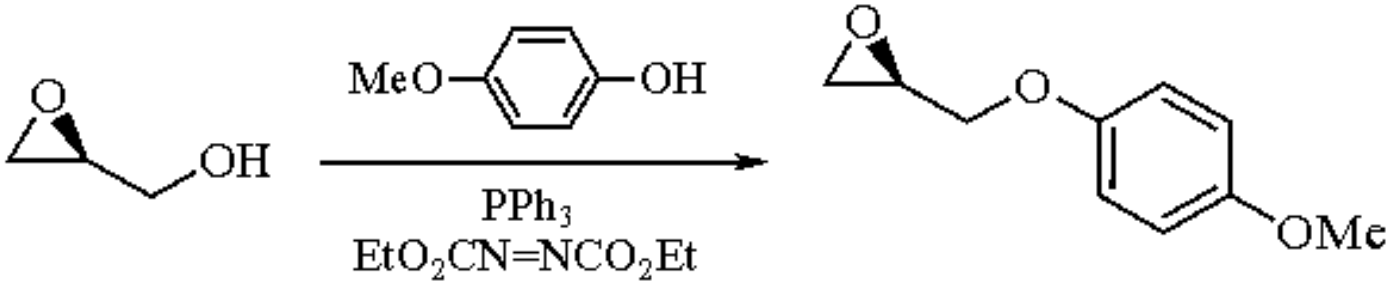

(3)

Addition of Hydrogen at C-3.

Both catalytic reduction of glycidol over Pd/C[10] and reaction with MeLi/CuBr$(PBu_3)_2$[11] give propane-1,2-diol as a consequence of addition of hydrogen at C-3. (*S*)-Glycidyl tosylate is reduced to (*S*)-propane-1,2-diol 1-monotosylate with ***Borane-Tetrahydrofuran*** and a catalytic amount of ***Sodium Borohydride***, as shown in eq 4.[6]

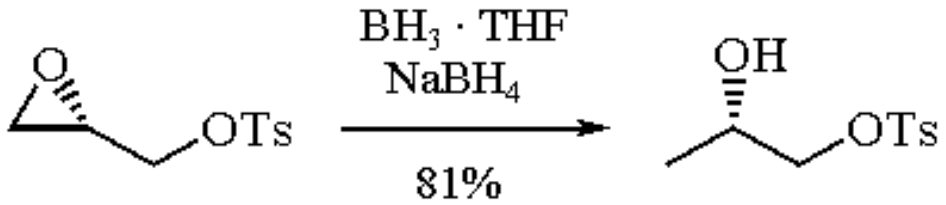

(4)

Nucleophilic Additions of Carbon at C-3.

One of the few reported additions of a carbon nucleophile to underivatized glycidol is that of diethyl sodiomalonate. The initial addition at C-3 is followed by lactonization between the C-2 hydroxyl group and one of the malonate carboxylic esters (eq 5).[12] Far more numerous are the additions of carbon nucleophiles to glycidol derivatives such as *O*-benzyl, *O*-phenyl, or *O*-tosyl glycidol. In addition to the examples included below, many others may be found in Hanson's review.[1b]

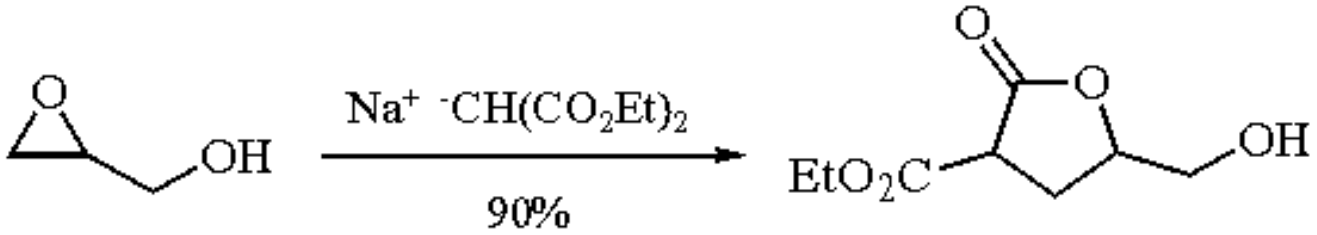

(5)

Single carbons can be added as cyanide using ***Acetone Cyanohydrin***,[6,7] diethylaluminum cyanide (eq 6),[6,7] or ***Lithium Cyanide***[13] or as methyl groups using an organocuprate (eq 7).[14] A single carbon may be added with dithiane salts and an example of addition of a substituted ***1,3-Dithiane*** to *O*-benzyl glycidol is shown in eq 8.[15]

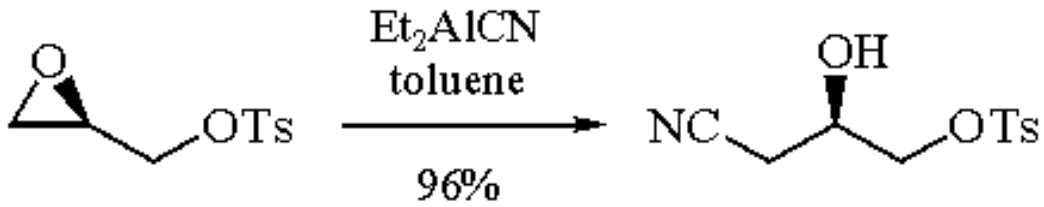

(6)

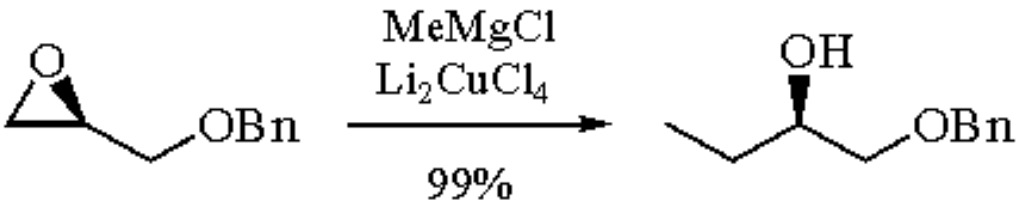

(7)

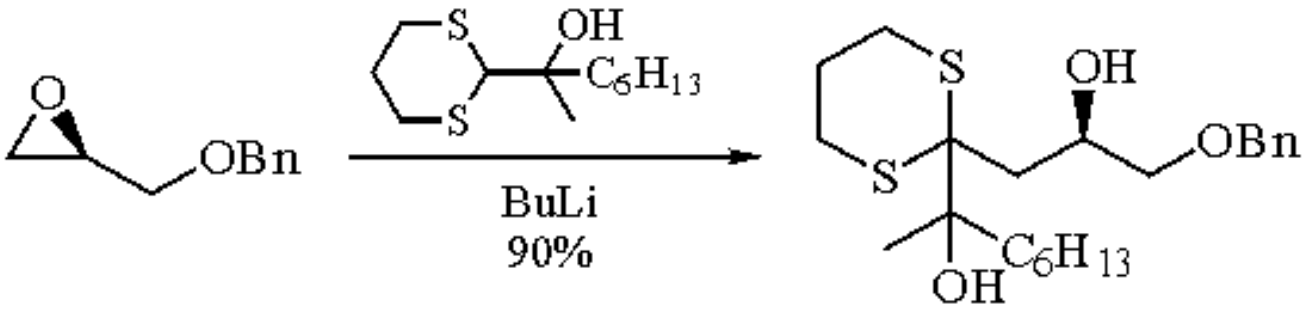

(8)

Other alkyl groups, alkenyl groups (eq 9), and aryl groups have been added to glycidol via organometallic reagents. The reactions with organometallic reagents often are sensitive to conditions and frequently are improved by the addition of Cu^{I} or Cu^{II} to the medium.[16] Alkynic salts add to glycidols, giving 3-alkynyl derivatives in yields which are generally good but which may be enhanced in some cases by the addition of a Lewis acid such as ***Boron Trifluoride Etherate*** to the reaction (eq 10).[17]

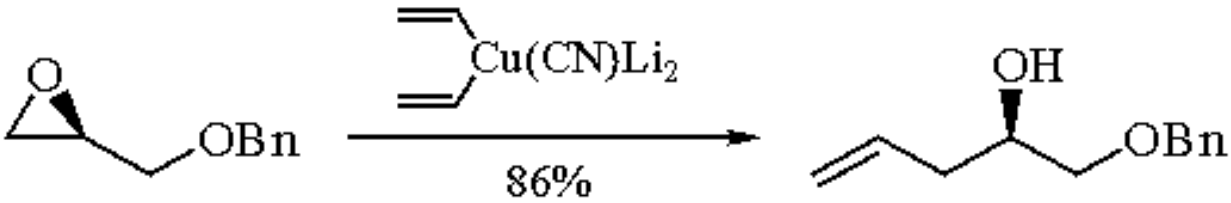

(9)

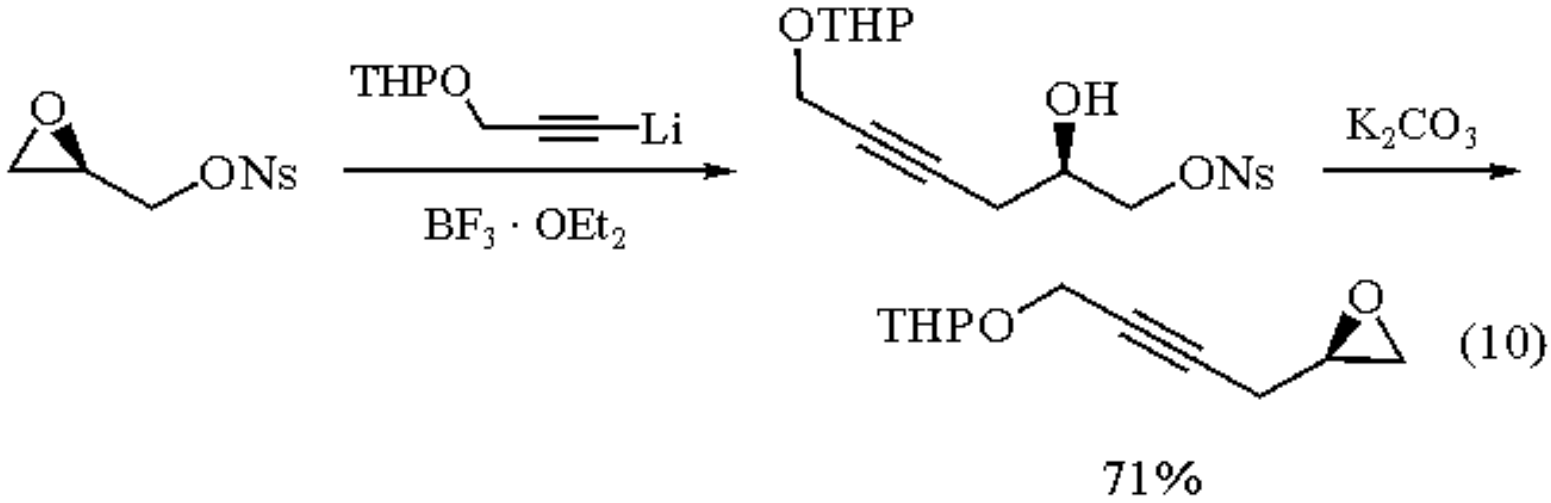

Opening at C-3 of glycidol sulfonates generates a 1,2-diol monosulfonate array which is ideally situated for closure under mildly alkaline conditions to a new epoxide group, as shown in eq 10 and also, below, in eq 18. Either the intermediate monosulfonate or the new epoxide present an activated electrophilic site for further synthetic transformations.

Carbon nucleophiles such as ester enolates and α-carboxylic acid anions add to glycidols by opening the oxirane ring and forming an intermediate C-2 alcohol. As shown above in eq 5, the intermediate can cyclize to a five-membered lactone via further reaction with the newly introduced carboxylic acid or ester.[18] Variations on the theme of intramolecular transformations following the initial addition to glycidol have been described. These include seven-membered lactone formation following addition of a sulfone-stabilized anion to *O*-benzylglycidol (eq 11),[19] and oxetane formation following addition of ***Dimethylsulfoxonium Methylide*** to glycidol (eq 12).[20]

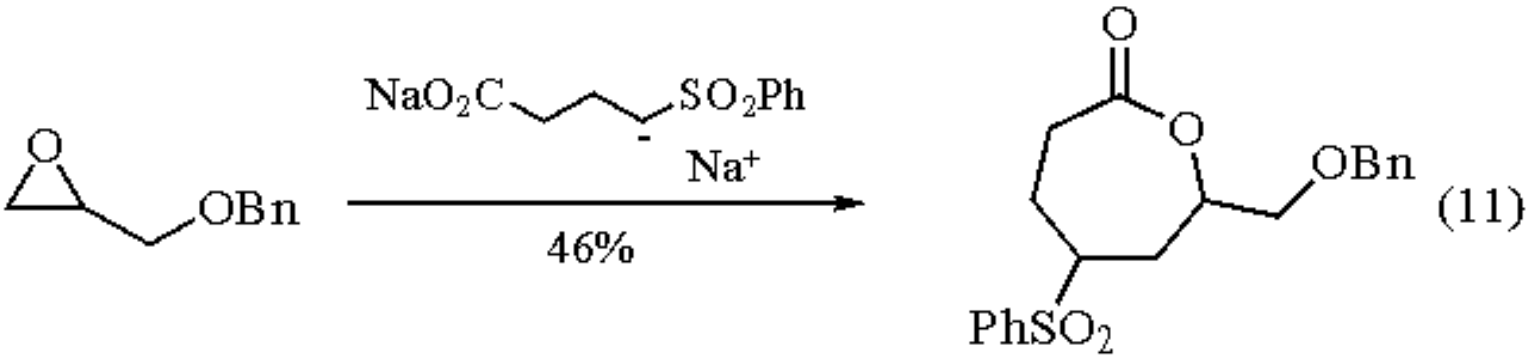

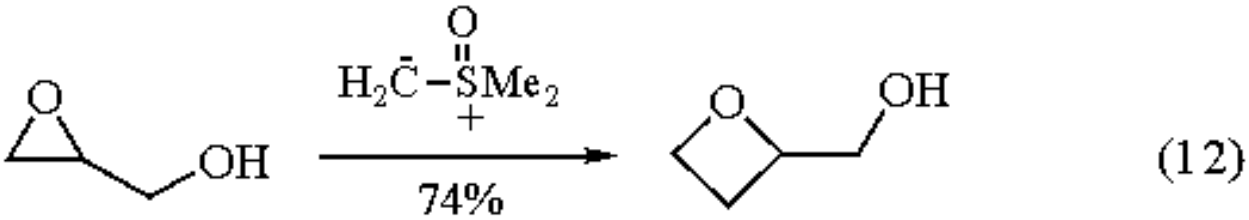

Other examples of carbon nucleophiles which have been added to a glycidol include the lithium salt of 1-trimethylsilyl-3-phenylthioprop-1-yne (eq 13),[21] the lithium salt of 1-phenylsulfonyl-2-trimethylsilylethane,[22] the lithium salt of pentacarbonyl(methoxymethylcarbene)chromium,[23] the dimsyl anion,[24] and the lithium salt of acetone dimethylhydrazone.[25]

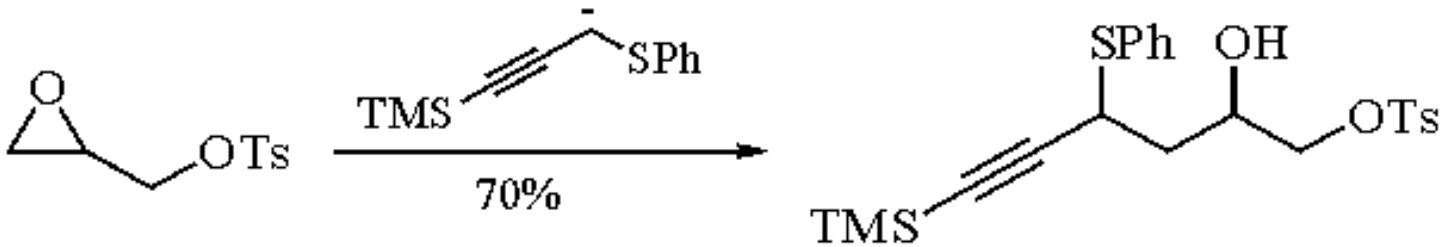

(13)

Nucleophilic Addition of Oxygen at C-3.

Addition of water to glycidol or a glycidol derivative produces glycerol or a substituted glycerol, respectively. The oxygen nucleophiles used most frequently for addition to glycidols are alcohols, phenols, and carboxylic acids and their close relatives. For glycidol itself, Kleemann and Wagner summarize extensive studies of additions of these classes of compounds.[1a] Very good yields of products are achieved with all three classes when acid or, preferentially, basic catalysts are added to the reactions. Careful analyses of the reaction products reveal that in addition to the primary opening of the oxirane at C-3, most reactions include small (2-10%) amounts of product derived from opening at C-2. Other byproducts can result from self-reaction of glycidol with the reaction products. Opening of glycidol with primary alcohols with 0.5% NaOH as catalyst yields 70% of the 1-*O*-alkylglycerol together with 3% of the 2-*O*-alkylglycerol.[1a] Opening with phenols and 0.03% NaOH gives 70-80% yields of 1-*O*- and 2-*O*-arylglycerols in ratios of 90-95:5-10.[1a] Glycidol generated in situ from hydrolysis of the *p*-nitrobenzoate ester with MeOH/H_2SO_4 reacts further at C-3 with the MeOH to give 1-*O*-methoxyglycerol (eq 14).[7]

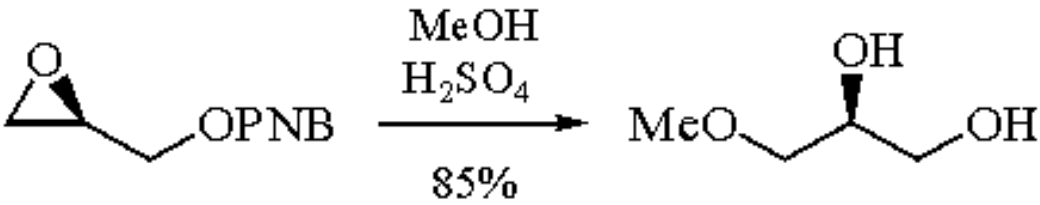

(14)

Lewis acid catalysis of additions to 2,3-epoxy alcohols often improves the regioselectivity of the ring-opening process.[26] $Ti(OR)_4$ catalyzed reaction of glycidol with primary alcohols gives 1-*O*-alkylglycerols in yields of 45-59%.[27] The addition of primary alcohols to (*R*)-glycidyl sulfonate esters give 1-*O*-alkylglycerol 3-sulfonates in yields of 73-89% when catalyzed with $BF_3.OEt_2$ (eq 15).[28] Non-racemic glycidol, generated by catalytic asymmetric epoxidation of allyl alcohol with $Ti(O\text{-}i\text{-}Pr)_4$ and a (+)- or (-)-dialkyl tartrate, undergoes ***Titanium Tetraisopropoxide*** assisted reaction in situ with sodium phenolates to generate 1-*O*-arylglycerols (eq 16).[8,29] The $BF_3.OEt_2$ addition of stearic anhydride to (*R*)-glycidyl tosylate gives (*R*)-1,2-distearoylglyceryl tosylate in 76% yield.[30]

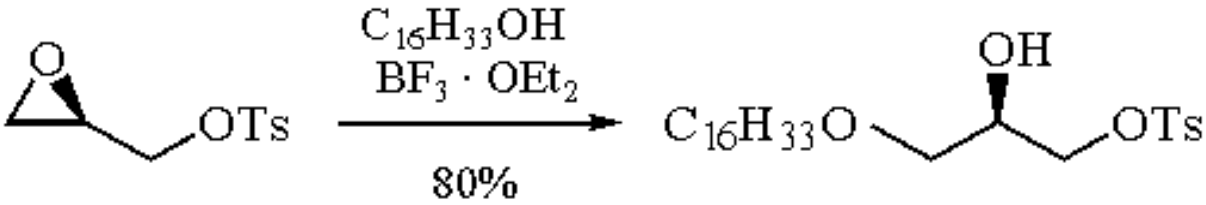

(15)

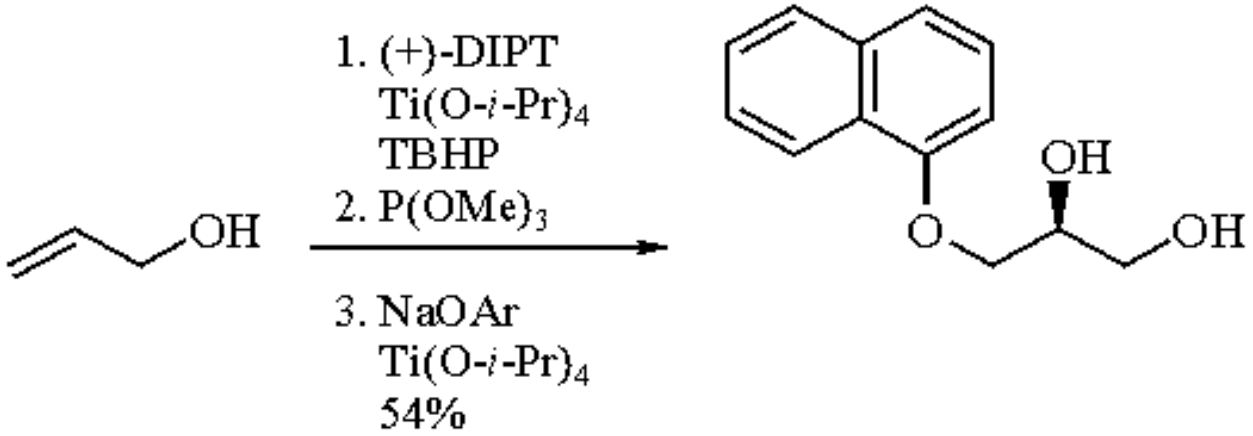

(16)

Examples of other oxygen nucleophiles that have been added at C-3 include phosphorylcholine (eq 17)[31] and ethyl *N*-hydroxyacetimidate (eq 18).[32]

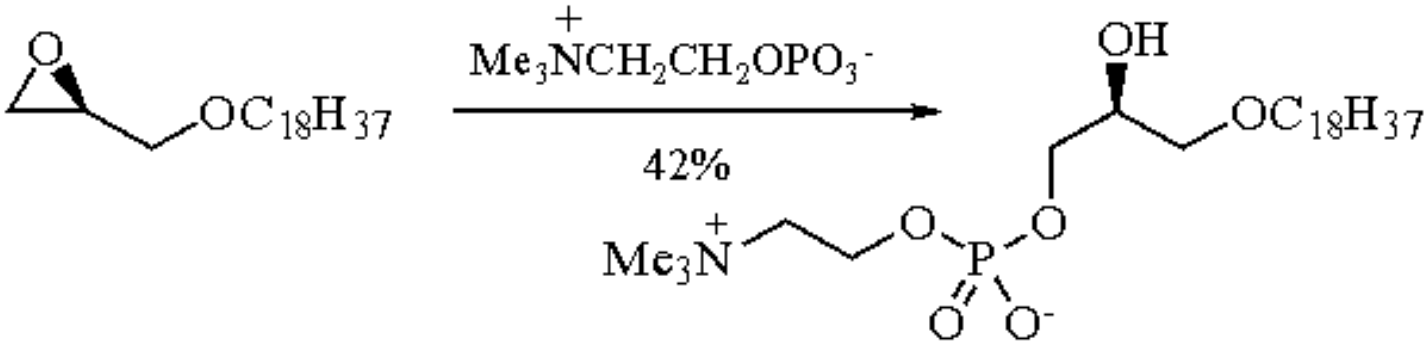

(17)

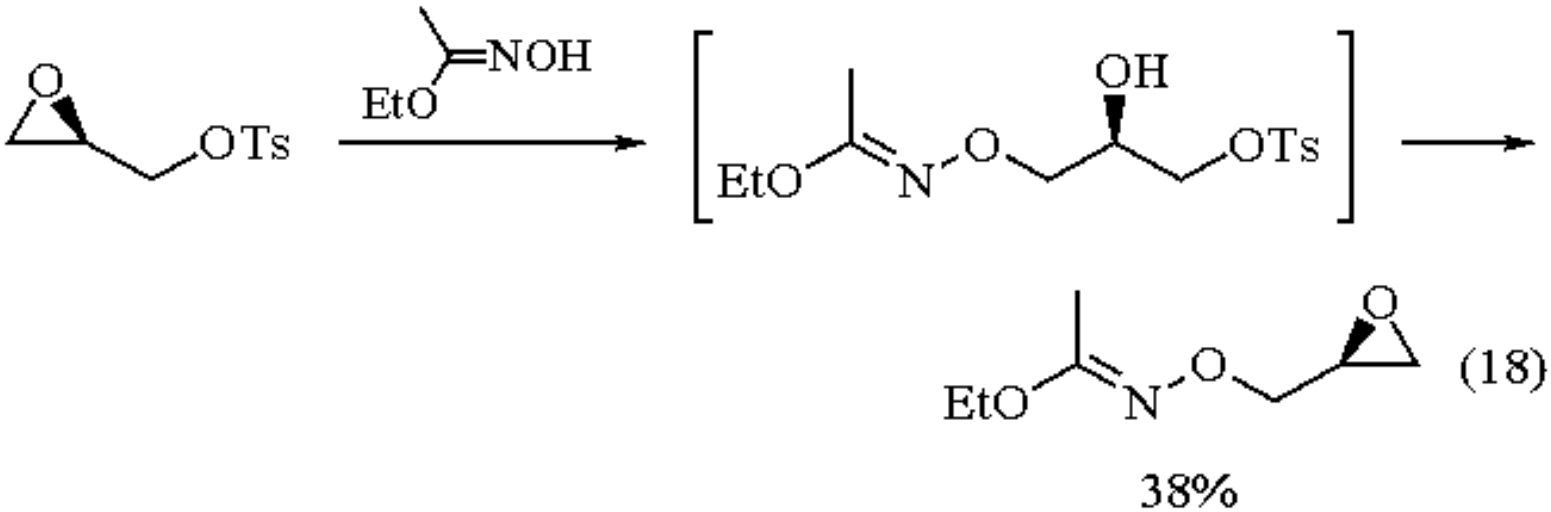

(18)

Nucleophilic Additions of Nitrogen at C-3.

Ammonia and amines add readily to glycidol and glycidol derivatives, giving the 1-aminopropane-2,3-diols (eq 19).[33] With ammonia and primary amines, an excess of the amine often is used to reduce the amount of addition by a second glycidol to the 1-aminopropane-2,3-diol. Secondary amines are used with glycidols in an equimolar ratio. Azide ion also opens glycidols at C-3. Ti(O-*i*-Pr)$_4$ or ***Aluminum Isopropoxide*** assisted openings with ***Azidotrimethylsilane*** have been examined with glycidol and a variety of derivatives[34] and give excellent yields of 3-azido-2-hydroxypropane 1-

O-derivatives (eq 20). ***Sodium Azide*** has also been used as a source of azide when combined with either ***Pyridinium p-Toluenesulfonate***,[7] NH_4Cl,[9,35] or ***Lithium Perchlorate***[36] to react with various glycidols.

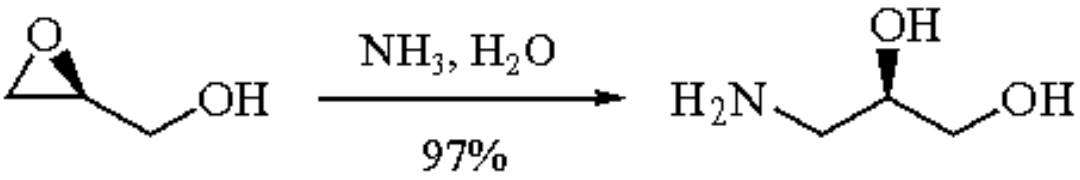

(19)

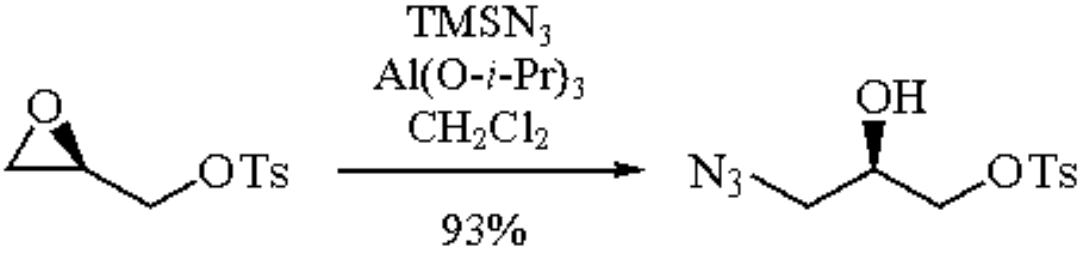

(20)

The opening of glycidols, especially of *O*-aryl glycidol ethers, at C-3 with amines has found extensive application in pharmaceutical research.[1b] A typical example is in the opening of *O*-(1-naphthyl)glycidol at C-3 with isopropylamine to generate the β-adrenergic blocking agent propranolol (eq 21).[29] A similar application is the addition of the 4-substituted piperazine to glycidol shown in eq 22.[37] With (*R*)- and (*S*)-glycidol now readily available, the synthesis of individual enantiomers or diastereoisomers of a pharmacological agent by methods such as those shown in eqs 21 and 22 becomes an attractive goal.

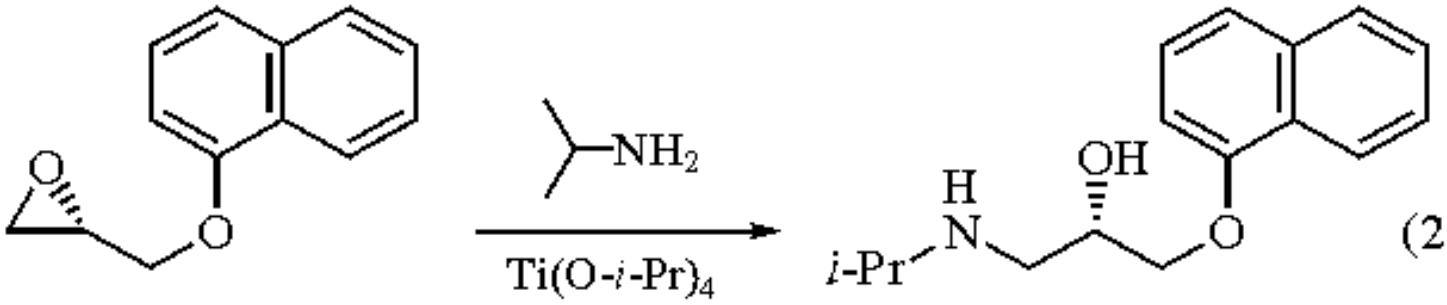

(21)

60% from
(*S*)-glycidol tosylate

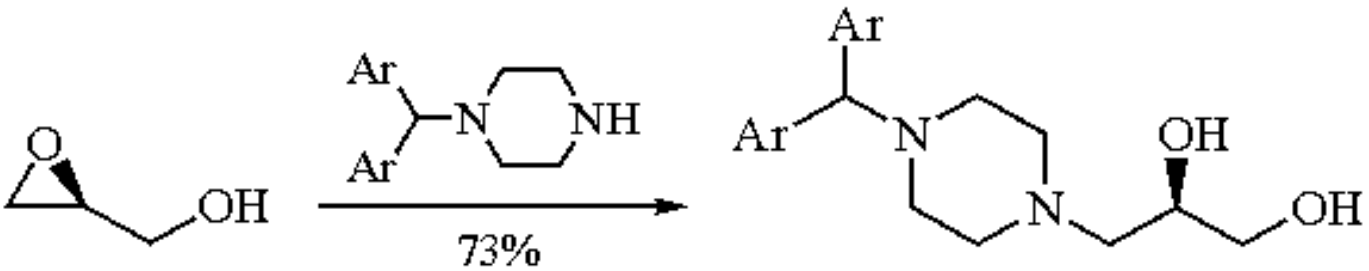

(22)

Other nitrogen nucleophiles added to glycidol include several heterocycles, an example of which is the addition of ***Imidazole***.[38] The iminodioxolane shown in eq 23 adds to glycidol and then undergoes further intramolecular cyclization to give a cyclic urethane.[39] ***Acetonitrile*** in a $BF_3.OEt_2$ catalyzed reaction adds to glycidyl tosylate to form

2-methyl-4-(tosyloxy)methyloxazoline (eq 24).[40] Dibenzylamine adds via an amidocuprate at C-3 of *O*-phenylglycidol to give 3-dibenzylaminopropane-1,2-diol 1-*O*-phenyl ether in 94% yield.[41]

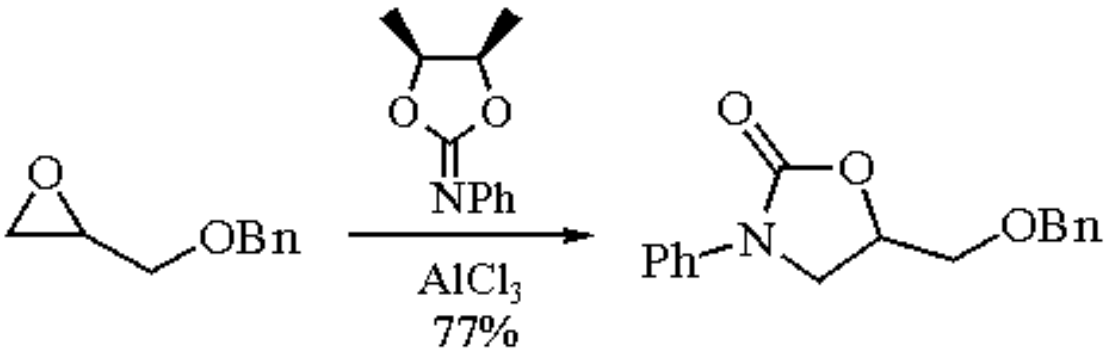

(23)

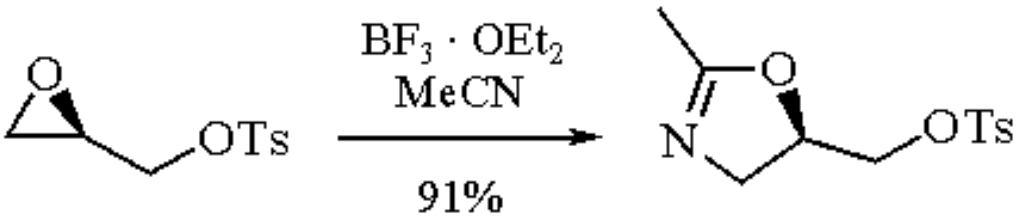

(24)

Additions of Other Nucleophiles at C-3.

The halogens (F, Cl, Br, and I) and sulfur are the other elements most frequently found in C-3 additions to glycidols. Fluoride has been added to both glycidol and various glycidol (see eq 25) derivatives using tetrabutylammonium dihydrogentrifluoride.[42] Several methods have been used for the other three halogens, including reaction with the lithium salts in THF[43] or with the ammonium salts and $LiClO_4$ in AcCN.[44] Chlorine has also been added via HCl[45] or with ***Benzoyl Chloride*/*Cobalt(II) Chloride***;[46] the latter reaction also adds the benzoyl group to give the 2-*O*-benzoate derivative (eq 26). Bromine has been added with dimethylboron bromide[47] and iodine has been added with ***Sodium Iodide*** in a NaOAc/HOAc/$EtCO_2H$ system.[7]

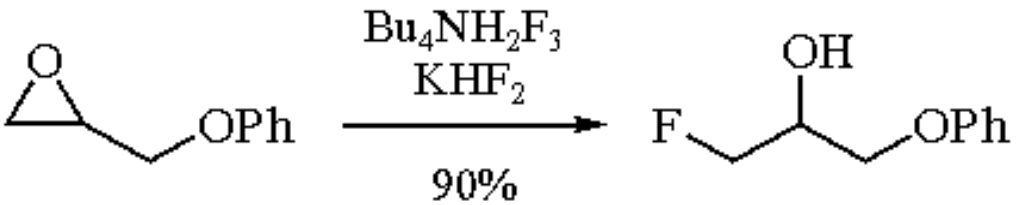

(25)

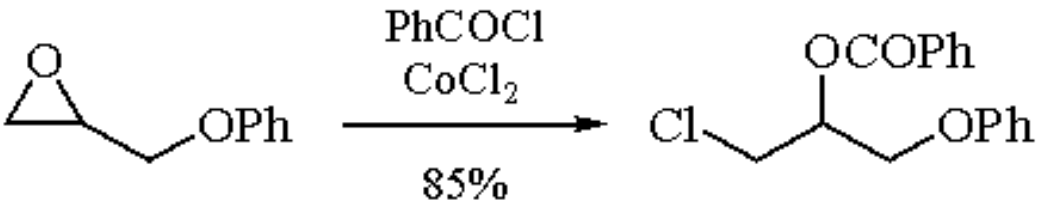

(26)

Most additions of sulfur to glycidols have been of arylthiolates and are performed under either acidic [$Ti(O\text{-}i\text{-}Pr)_4$ (eq 27),[8] $BF_3.OEt_2$[48]] or alkaline conditions.[7,49] $LiClO_4$[50] or $CoCl_2$[51] have also been used as catalysts for addition of aryl thiols. The additions of lithium alkylthiolates and of thiobenzoic acid to *O*-trityl glycidol have been reported.[5a]

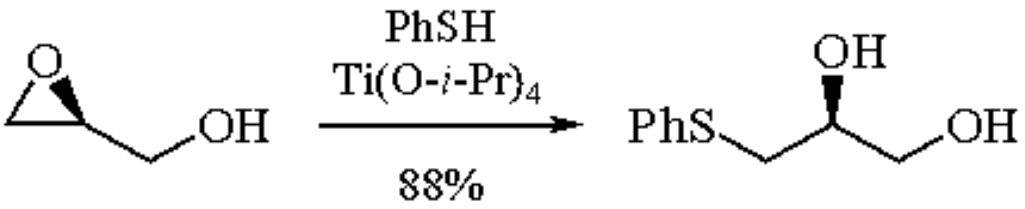

(27)

Oxidation of Glycidol.

Glycidol is oxidized to glycidic acid with ***Ruthenium(VIII) Oxide***.[52] Glycidaldehyde is a mutagenic compound that has been prepared in racemic form by epoxidation of ***Acrolein***[53] and in nonracemic forms by the degradation of mannitol.[54] Alternately, (*R*)- and (*S*)-glycidaldehyde may be prepared and handled more conveniently via asymmetric dihydroxylation of acrolein benzene-1,2-dimethanol acetal followed by conversion of the diol to an epoxide (see eq 28).[55]

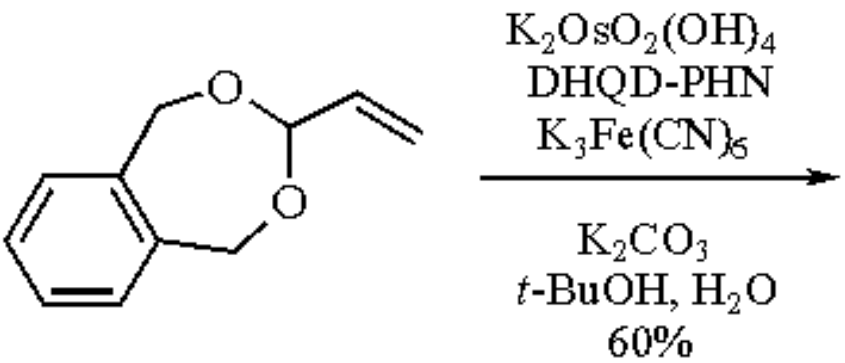

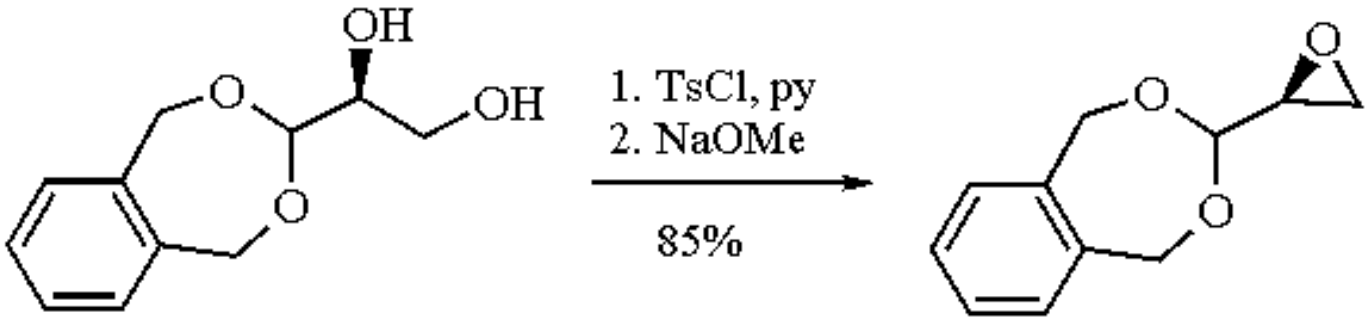

(28)

Miscellaneous.

Glycidol reacts with dinitrogen pentoxide (N_2O_5) in CH_2Cl_2 in the presence of $AlCl_3$, giving trinitroglycerine (73%).[56] A useful review describing numerous synthetic transformations of 2,3-*O*-isopropylideneglyceraldehyde, a three-carbon synthon related to glycidol, has been published.[57]

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Cortech, Denver, CO, USA

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Glycidyl Tosylate[1]

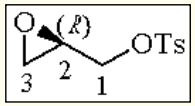

(*R*)-(-)

[113826-16-5] · $C_{10}H_{12}O_4S$ · Glycidyl Tosylate · (MW 228.29) (*S*)-(+)

[70987-78-9]

(chiral C_3 synthon;[2] undergoes regio- and stereoselective ring opening at C-3 with alcohols in the presence of $BF_3.OEt_2$,[3-8] Li_2CuCl_4-catalyzed Grignard reagents,[9,10] and carbanions (with[11] and without $BF_3.OEt_2$);[12-15] undergoes direct attack at the C-1 position by nucleophiles, including aryl oxides[9,16-26])

Physical Data: mp 47.5-48.5 °C; racemate mp 37.5-39 °C.[9] [α]25D (*S*) enantiomer (&egt;97% enantiomeric excess) +18.1° (*c* 2.1, $CHCl_3$),[9] (*R*) enantiomer (~94% enantiomeric excess) -17.0° (*c* 2.75, $CHCl_3$).[4]

Solubility: v sol chloroform, methylene chloride, and THF; insol hexane.

Form Supplied in: white solid; commercially available.

Analysis of Reagent Purity: enantiomeric purity can be assessed by the following procedures. *Procedure A* (no derivatization): Chiral HPLC on a Diacel OD column (10 µm, 0.46 × 25 cm); flow, 0.7 mL min^{-1}; 99:1 hexane-2-propanol; t_R: (*S*) enantiomer, 51.2 min; (*R*) enantiomer, 53.9 min.[27] *Procedure B*: the reagent is opened to the iodohydrin; the crude iodohydrin is esterified with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride; the resulting crude MTPA ester is analyzed by chiral HPLC and ^1H NMR.[28]

Preparative Methods: the title reagent (**1**) is obtained in 40% overall yield by the zeolite-modified Sharpless asymmetric epoxidation of allyl alcohol, using D-(-)-diisopropyl tartrate (DIPT) to obtain (*S*)-(**1**) and L-(+)-DIPT to obtain (*R*)-(**1**), followed by in situ low-temperature tosylation of glycidol.[28] Alternatively, (*R*)- and (*S*)-(**1**) can be prepared by direct sulfonylation of commercially available chiral ***Glycidol***. Note that the relative configuration of (*R*)-glycidyl tosylate is the same as that of (*S*)-glycidol.

Purification: multiple recrystallizations from 5:1 ether-petroleum ether, seeding (before refrigeration) each time with pure material.[28]

Handling, Storage, and Precautions: mutagenicity via reactions with biological nucleophiles has been assessed by using the Ames test in *Salmonella typhimurium* and by analysis of in vivo chromosomal aberrations.[29] (*S*)-(**1**) was more mutagenic than (*R*)-(**1**).[29] Use in a fume hood.

Displacement Reactions.

Aryl oxides attack (*R*)- or (*S*)-(**1**) at the C-1 position, displacing the tosylate group and affording aryloxymethyloxiranes (**2**) in good yield (see examples in Table 1). The latter react with amines in aqueous alcohol, yielding β-adrenergic blocking agents of high enantiomeric excess.[9] The regioselectivity for attack at the C-1 vs. C-3 position of (**1**) is very high, i.e. &egt;97:3 in DMF at rt[9] and 85:15 in refluxing acetone.[18] The ratio of C-1:C-3 attack on the related substrates, (*S*)-glycidyl 3- or 4-nitrobenzenesulfonate, by 1-naphthol in DMF at rt is >99.8:0.02.[9] A comparison of the C-1:C-3 product ratio obtained from several glycidyl arenesulfonates suggested that attack by aryl oxide nucleophiles at C-1 is enhanced when the electron deficiency of the leaving group is increased (see Table 1).[9]

Table 1 Alkylation of Phenolic Hydroxy Groups by **(1)**

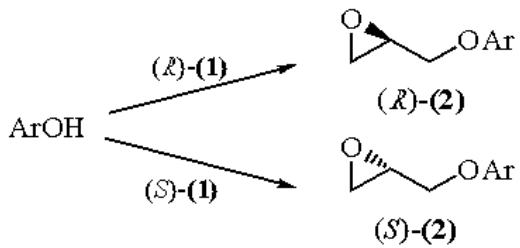

Reactant	Reagent	Conditions	Yield of glycidyl **(2)**	Ref
Phenol	(*R*)-**(1)** & (*S*)-**(1)**	NaH, DMF, 4.5-7 h	77-80	9, 16
$HOC_6H_4(CH_2)_2CO_2R$	(*S*)-**(1)**	K_2CO_3, DMF, 170 °C, 15 h	80	17
Methyl 4-hydroxy-3-methoxyphenylpropiolate	(*S*)-**(1)**	K_2CO_3, DMF, 70 °C, 1 h	82	17
3-Nitro-2-aminophenol	(*S*)-**(1)**	NaH, DMF, rt	70	18
2-Cyclopentylphenol	(*S*)-**(1)**	NaH, DMF, rt	86	9
1-Naphthol	(*R*)-**(1)** & (*S*)-**(1)**	NaH, DMF, rt	50-85	9, 19
8-Hydroxyisoquinoline	(*R*)-**(1)** & (*S*)-**(1)**	NaH, DMF, rt, 12 h	80	20
3-Acetyl-4-methoxy-1-naphthol	(*R*)-**(1)**	NaH, DMF, 50 °C, 4 h	75	21
4,8-Dibenzyloxy-6-methyl-1-naphthol	(*R*)-**(1)**	NaH, DMF, rt, 4 h	87	22
O^3-Benzyl-6β-naltrexol	(*R*)-**(1)**	KH, THF, 19 h	83	23
7-*O*-(3-*N*-Methyl-α-L-daunosaminyl)-β-rhodomycinone	(*R*)-**(1)**	heat	11	24

Reaction of ***Catechol*** with (*R*)- or (*S*)-(**1**) (***Potassium Carbonate***, DMF, 60 °C, 27 h;[25] or ***Sodium Hydride***, DMF, rt, 10 h[26]) affords (*S*)- or (*R*)-2-hydroxymethyl-1,4-benzodioxane in yields of 72%[25] and 18-21%[26] (eq 1).

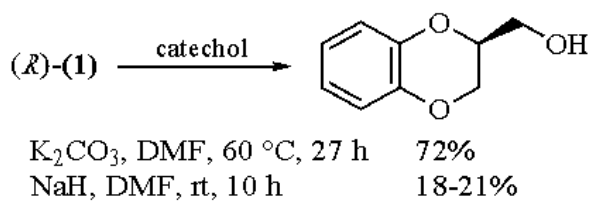

(1)

Ring-Opening Reactions.

Epoxide opening takes place at the C-3 position of (**1**) with a wide variety of nucleophiles, as summarized below.

Alcohols and Benzenethiol.

These react with (**1**) in methylene chloride or chloroform, generally at rt, in the presence of catalytic ***Boron Trifluoride Etherate*** (eq 2). The following alcohols have been used (yields in parentheses): benzyl alcohol (81-84%);[3b,4,8] 1-hexadecanol (80%);[3] $Cl(CH_2)_6OH$ (80%);[5] $Cl(CH_2)_{16}OH$ (85%);[5] methanol (100%);[7] $MeO_2C(CH_2)_5OH$ (89%).[6] Benzenethiol gives 3-phenylthio-2-hydroxy-1-tosyloxypropane in 81-83% yield.[3b] The 4-methylbenzene- and 3- nitrobenzenesulfonate derivatives of glycidol give exclusive formation of the C-3-opened product in the BF_3-mediated reaction,[3,4] whereas the *t*-butyldiphenylsilyl ether derivative of glycidol gives a regioselectivity (C-3 vs. C-2 isomer ratio) of 89:11 with benzyl alcohol, 93:7 with benzenethiol, and 90:10 with long-chain alcohols.[3b]

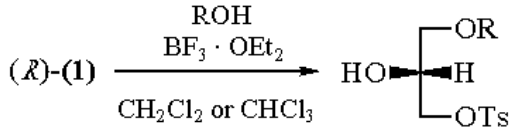

(2)

Halide and Azide Anions.

These also open the epoxide regioselectively at the C-3 position. Addition of Li_2CuBr_4 results in bromide addition at the C-3 position of *rac*-(**1**), forming 3-bromo-1,2-propane 1-*O*-tosylate in 70-76% yield in THF or acetonitrile at rt, or 1,3-dibromo-2-propanol in 82% yield in refluxing acetonitrile.[30] Hydrofluorination takes place with KHF_2 under solid-liquid phase transfer conditions, but the yield of fluorohydrin is very low (eq 3).[31] ***Azidotrimethylsilane*** adds in the presence of a Lewis acid catalyst (eq 3).[32] Addition of cyanide ion is achieved by using ***Diethylaluminum Cyanide*** in toluene.[9]

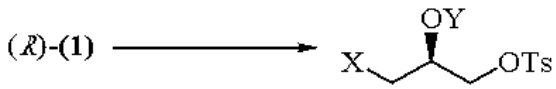

(3)

Hydrofluorination: KHF_2 (2 equiv), $Bu_4N^+ H_2F_3^-$ (1 equiv), 120 °C;
X = F, Y = H, 6%
Azide opening: $TMSN_3$ (1.5 equiv), cat. $Al(O\text{-}i\text{-}Pr)_3$, CH_2Cl_2, 1 d, 93%
or cat. $Ti(O\text{-}i\text{-}Pr)_4$, THF, 6 d, 76%

Addition of concentrated HCl to solid (*S*)-(**1**) at rt, followed by treatment of the ring-opened intermediate with sodium ethyleneglycolate, forms (*R*)-epichlorohydrin in 54% yield.[33a] The analogous reaction was carried out using (*S*)-glycidyl mesylate in 85%[33b] and 68% yield,[33c] and with *rac*-(**1**).[33d]

Carbanions.

These add to the C-3 position of (*S*)-(**1**), affording epoxides (**3**) after intramolecular displacement of the tosylate group and in situ ring closure of the ring-opened intermediate (eq 4). Deprotonation of oxirane (**3**) leads to rearrangement to cyclopropane derivatives.[11a,12,13]

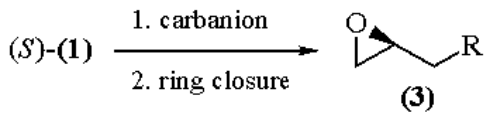

(4)

Lithium carbanion	Overall yield of **(3)** (%)
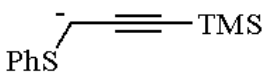	81
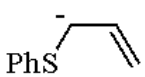	58
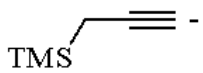	59
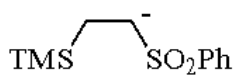	56
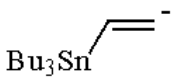	38

There are many examples of $BF_3.OEt_2$ promoted openings of (**1**) by carbanions, including sulfone-stabilized anions,[11a] vinylic anions,[11b] allylic anions,[14] and phosphonate-stabilized anions.[15] For example, the lithium anion of ***trans-1,2-Bis(tributylstannyl)ethylene*** opens (*S*)-(**1**) in the presence of $BF_3.OEt_2$ in THF at -78 °C, affording *trans*-1-(tributylstannyl)-5-tosyl-4-hydroxypent-1-ene in 50% yield; the latter is converted into oxirane (**3**) in 76% yield on treatment with powdered ***Sodium***

Hydroxide in monoglyme.[11b]

The carbanion derived from pentacarbonyl(methoxymethylcarbene)chromium(0) reacts with (*R*)-(**1**) in the presence of $BF_3.OEt_2$ to give a lactone in low yield after oxidation of the ring-opened intermediate.[14]

Lithium diethylmethanephosphonate adds to *rac*-(**1**) in the presence of $BF_3.OEt_2$ at -78 °C to afford a phosphonate ester in good yield (eq 5).[15]

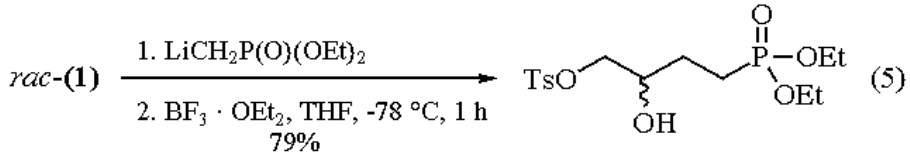

Organometallic Reagents.

The major product of the ***Dilithium Tetrachlorocuprate(II)***- or ***Copper(I) Iodide***-catalyzed Grignard reaction in THF or ether at low temperature arises from epoxide opening rather than from direct tosylate displacement (Table 2).[9,10]

Table 2 Copper-Catalyzed Grignard Reactions of **(1)**[9]

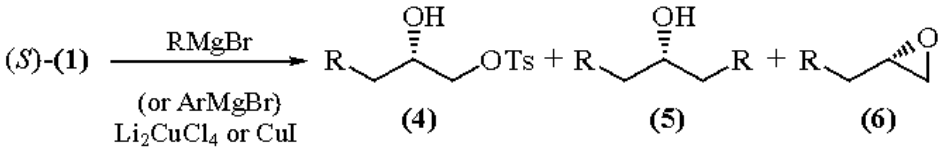

R	Conditions	Yields (%)		
		(4)	**(5)**	**(6)**
Ph	Li_2CuCl_4, -30 °C, THF	84	9	5
Vinyl	Li_2CuCl_4, -35 °C, THF	49	-	-
Bn	Li_2CuCl_4, -15 °C, THF	56	-	-
Hexyl	Li_2CuCl_4, -50 °C, THF	74	-	-
5-Hexenyl	Li_2CuCl_4, 20 °C, THF	44[b]	-	-
Mesityl	CuI, -25 °C, THF-Et_2O	90	-	-
Cy	CuI, -40 °C, Et_2O	69[a]	-	-

[a] *rac*-**(1)** was used. [b] Ref. 10.

Organolithium reagents add to (*R*)- and (*S*)-(**1**) as shown in eq 6.[9]

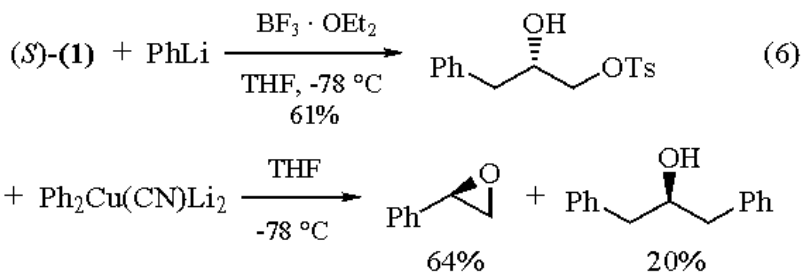

Hydride addition to (*S*)-(**1**) is achieved by use of BH_3 in THF with 0.05 equiv of ***Sodium Borohydride***, forming (*S*)-1-*O*-tosyloxy-2-hydroxypropane in 81% yield.[9]

Miscellaneous Addition Reactions.

Alkylation of MeC(OEt)=N-O$^-$ Na$^+$ with (*R*)-(**1**) gives (*S*)-*N*-(oxiranylmethoxy)ethanimidic acid ethyl ester in 34% yield.[34] Reaction of (*S*)-(**1**) with guanosine occurs at the N-7 position, giving (after deribosylation) (*S*)-7-(3-*O*-*p*-tolyl-2,3-dihydroxypropyl)guanosine in 56% yield.[35]

Fatty acid anhydrides react with (*R*)- and (*S*)-(**1**) in the presence of $BF_3.OEt_2$, giving a glyceryl tosylate with two identical fatty acid ester linkages in 76% yield.[36]

Reaction of (*S*)-(**1**) with acetonitrile at low temperature in the presence of $BF_3.OEt_2$ gives an oxazoline that is unstable at rt (eq 7).[9]

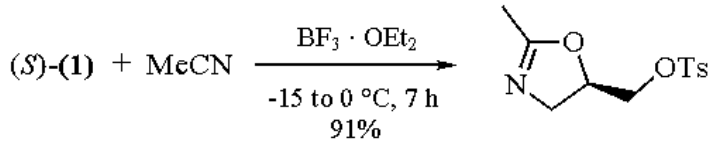

(7)

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2. For a review of recent syntheses of glycerolipids from (**1**) and other glycidyl derivatives and other precursors, see: Bittman, R. In *Phospholipids Handbook*; Cevc, G., Ed.; Dekker: New York, 1993; pp 141-232.
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Glyoxal

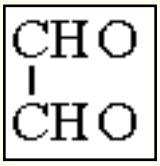

[107-22-2] · $C_2H_2O_2$ · Glyoxal · (MW 58.04)

(undergoes condensations and Wittig reactions to form carbo- and heterocycles)

Alternate Name: ethanedial.

Physical Data: yellow prisms, mp 15 °C; bp 50.4 °C/760 mmHg; *d*204 1.29 g cm^{-3}.

Solubility: sol water, ether, ethanol.

Form Supplied in: crystalline trimeric dihydrate $(OHC\text{-}CHO)_3.2H_2O$ [*4405-13-4*], which is nonhygroscopic; also supplied as a 40% aqueous solution which may contain polymerization inhibitors. An addition compound with $NaHSO_3$ serves as a nonaqueous form of glyoxal (monohydrate; *[517-21-5]*).

Purification: for most reactions, can be used without further purification. Anhydrous form should be freshly prepared.[1]

Handling, Storage, and Precautions: should be handled carefully to avoid exposure. Use in a fume hood.

Condensations.

Glyoxal (**1**) undergoes the Weiss-Cook reaction with dimethyl 1,3-acetonedicarboxylate in aqueous buffer at pH 8.3 and affords tetramethyl *cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (eq 1).[2] It undergoes a condensation reaction in methanol in the presence of ***Formic Acid*** with ***Formaldehyde*** and benzylamine in a stoichiometric ratio 1:2:4 and provides 2,4,6,8-tetrabenzyl-2,4,6,8-tetraazabicyclo[3.3.0]octane (eq 2).[3] Condensation of (**1**) with *N*,*N*´-diisopropylurea in aqueous HCl at rt

affords 2,4,6,8-tetraisopropyl-2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (eq 3).[4]

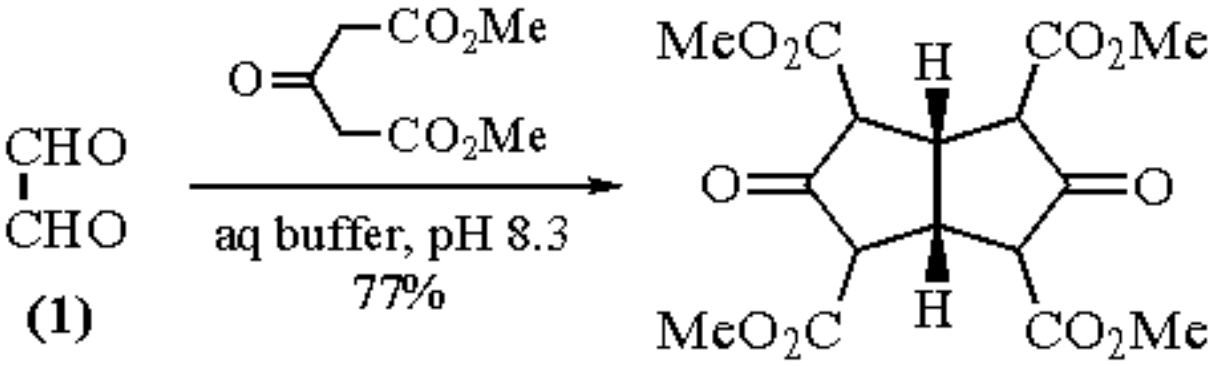

(1)

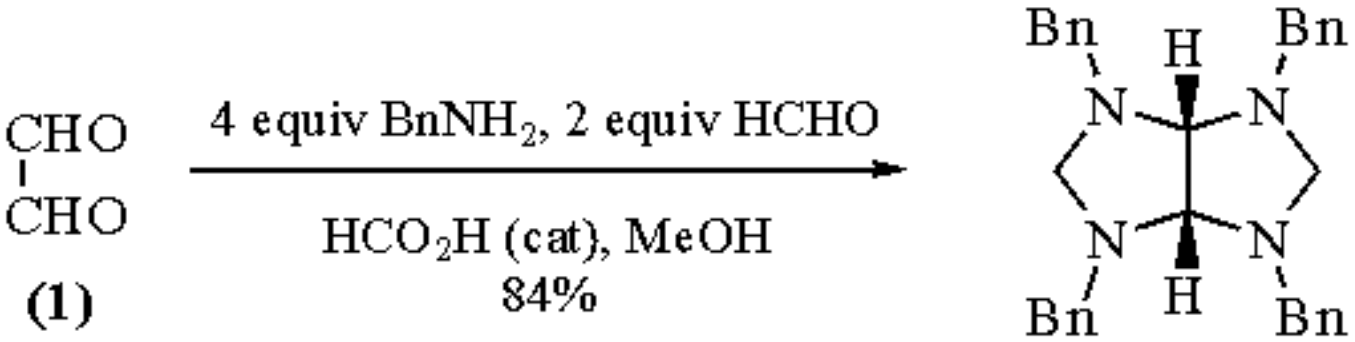

(2)

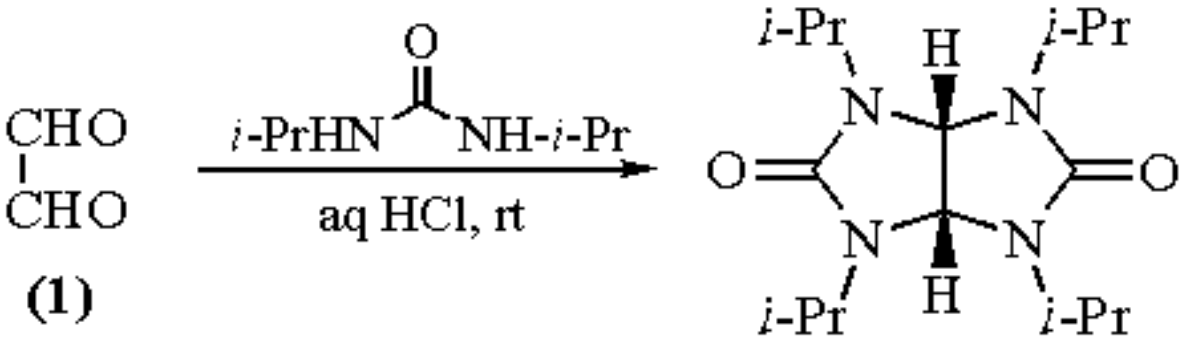

(3)

Glyoxal reacts with the (2,5)furano-4,4´-bis-(2-oxo-3-butyl) sulfide shown in eq 4 upon gradual addition of ***Sodium Methoxide*** in methanol to form 1,11-dioxo[3.3](2,5)furano(2,5)thiophenophane (eq 4).[5] Reaction of glyoxal with the nickel(II) complex of 1,5,8,12-tetraazadodecane followed by reduction with ***Sodium Borohydride*** and treatment with excess ***Sodium Cyanide*** affords 1,4,8,11-tetraazacyclotetradecane (cyclam) (eq 5),[6] a synthetically useful crown ether analog.

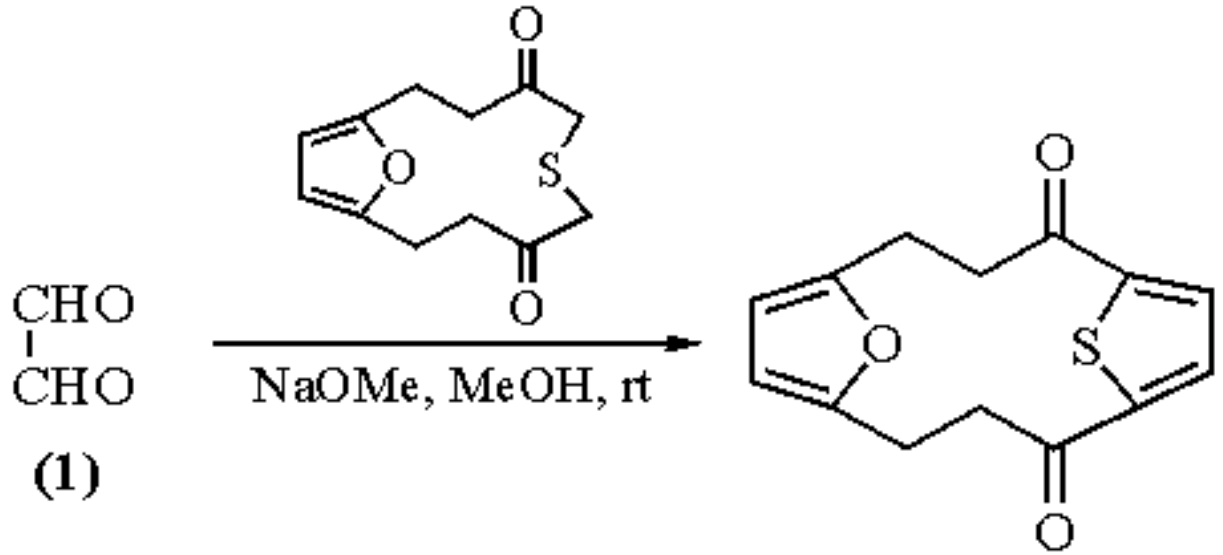

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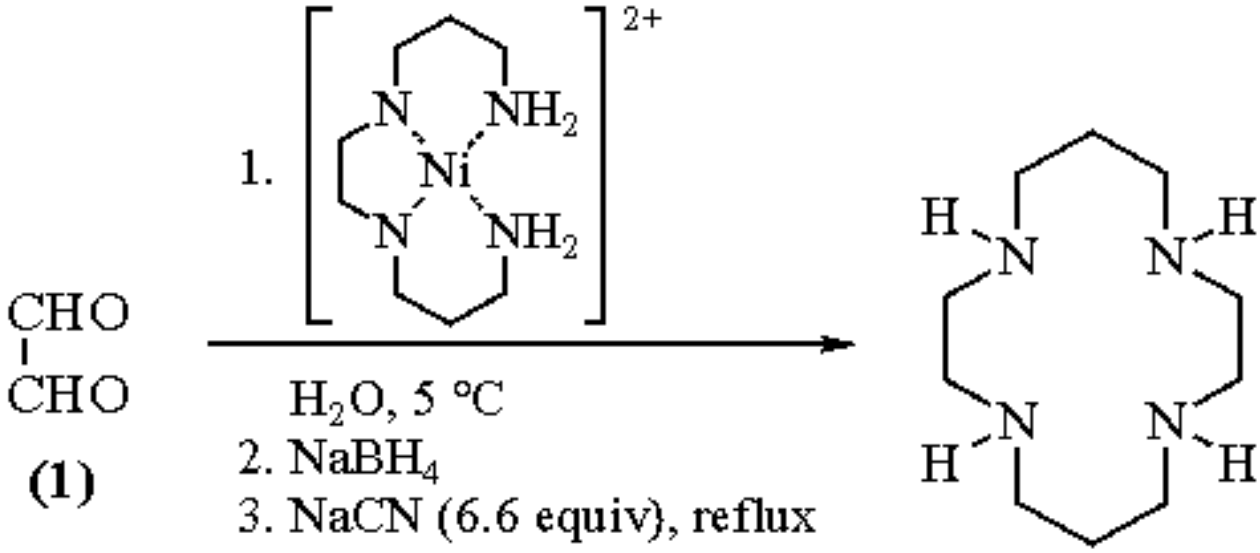

(5)

Condensation of glyoxal bisulfite with *o*-phenylenediamine in aqueous solution at 80 °C affords quinoxaline (eq 6).[7] Glyoxal also undergoes cyclocondensation upon heating with 3,4-diamino-1,2,5-thiadiazole and forms [1,2,5]thiadiazolo[3,4-*b*]pyrazine (eq 7).[8]

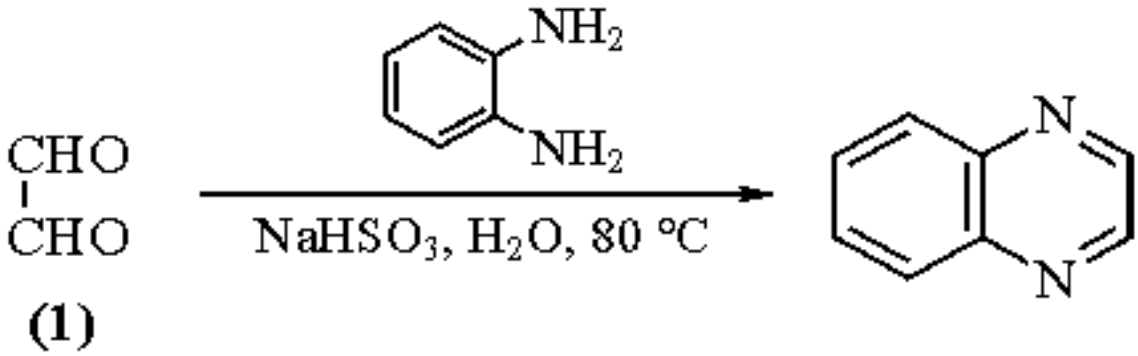

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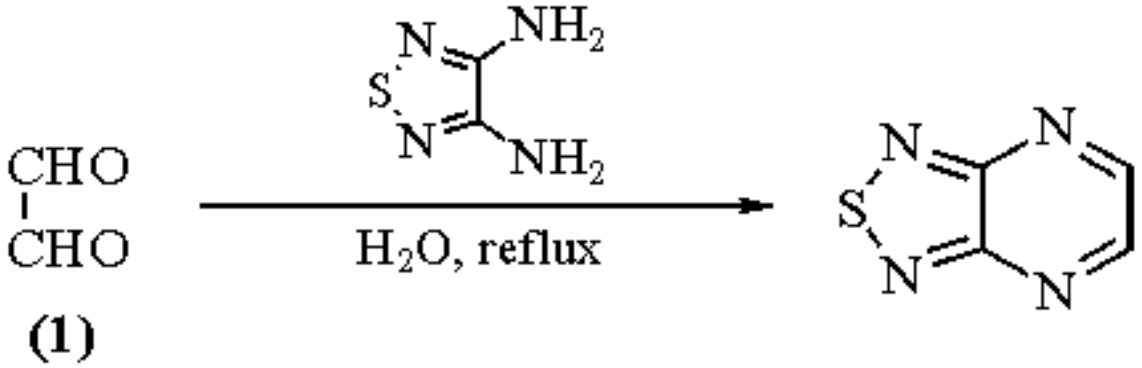

(7)

Wittig-Related Reactions.

Freshly prepared (dried) glyoxal,[1] when treated with phenacyltriphenylphosphorane, undergoes a Wittig condensation to form both the (*E*,*E*)- and (*E*,*Z*)-1,4-dibenzoyl-1,3-butadienes (eq 8).[9] A similar reaction of (**1**) with a bis-ylide [generated from 1,8-bis(bromomethyl)biphenylenetriphenylphosphonium salt and dimsylsodium] affords a complex mixture which contains 12% of the interesting cycloocta[*def*]biphenylene (eq 9).[10]

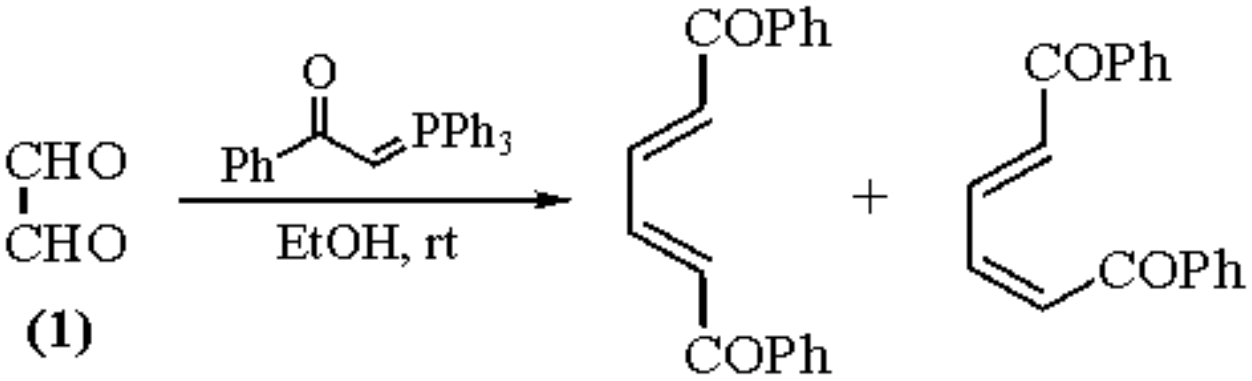

(8)

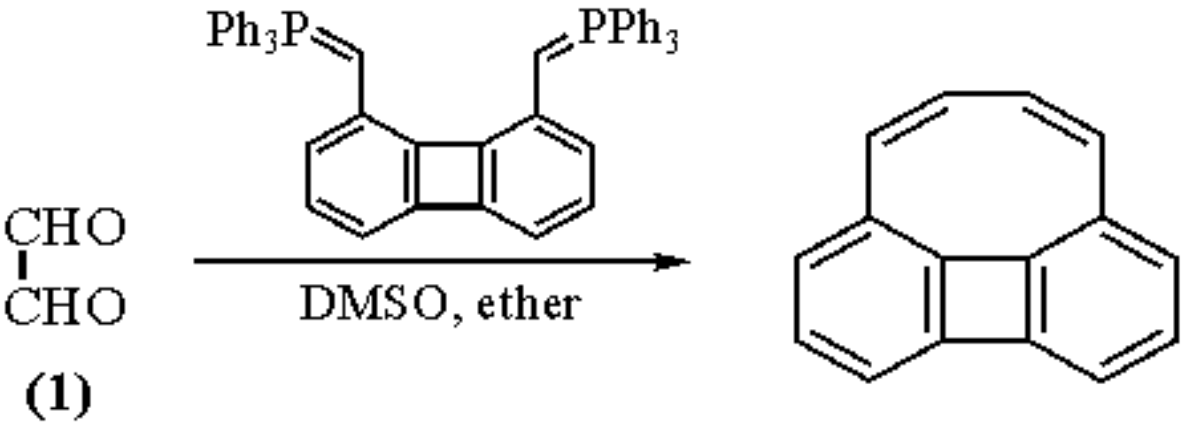

(9)

Aqueous glyoxal undergoes a Wittig-type condensation with the phosphorane generated from 1,3,4,6-tetrathiapentalene-2-(triphenylphosphonium) trifluoromethanesulfonate and triethylamine to form the mono-Wittig product 1,3,4,6-tetrathiapentalen-2-ylideneacetaldehyde (eq 10).[11] A similar reaction of (**1**)

with another phosphorane, derived by treating (4,5-dimethoxycarbonyl-1,3-diselenolyl)tributylphosphonium tetrafluoroborate with triethylamine in THF, affords 2-formylmethylene-4,5-dimethoxycarbonyl-1,3-diselenole (eq 11).[12]

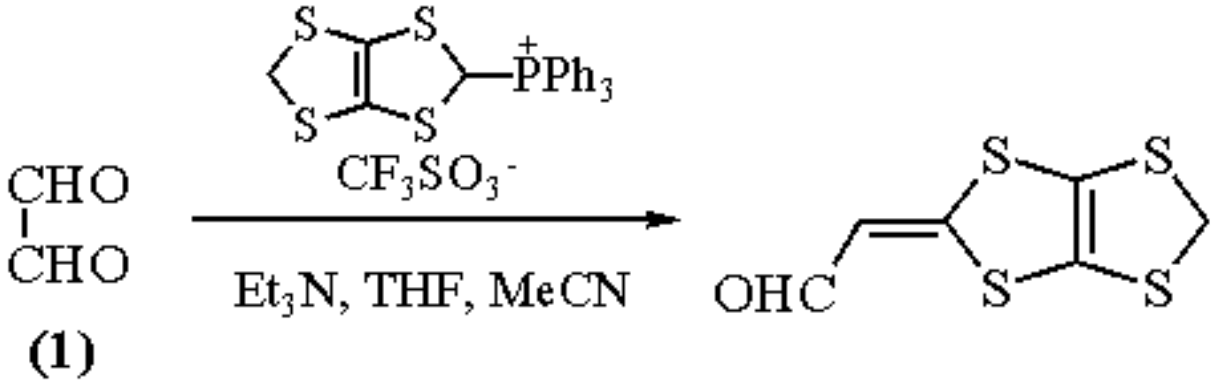

(10)

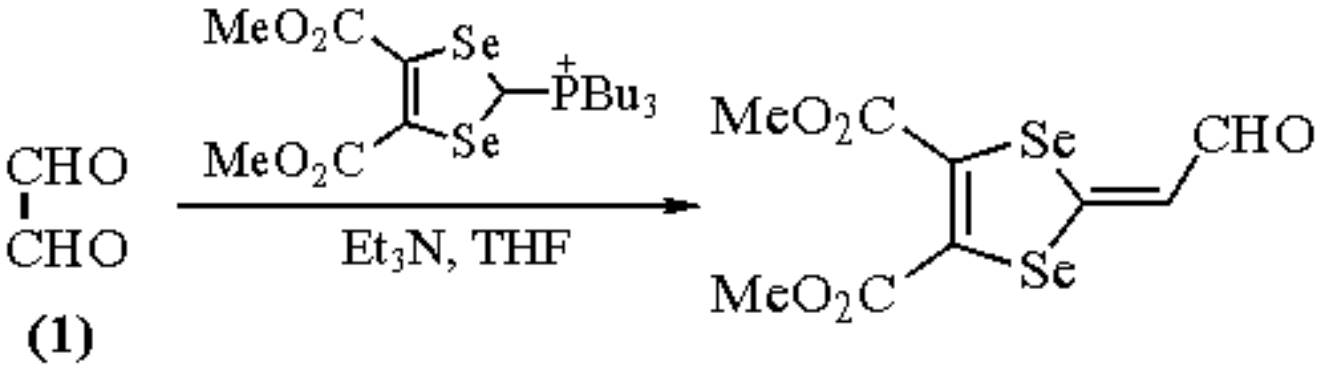

(11)

Glyoxal undergoes formic acid-catalyzed condensations with (*R*)-PhCHMeNH$_2$ or with (1*S*,2*S*,3*S*,5*R*)-3-(aminomethyl)pinane, individually, to form the corresponding diazadienes represented by eq 12.[13] Reaction of glyoxal with a dicarboxamide (see eq 13) in the presence of the phase-transfer catalyst benzyltributylammonium hydroxide, in $H_2O/CHCl_3$ containing sodium hydroxide, affords the bicyclic compound shown.[14]

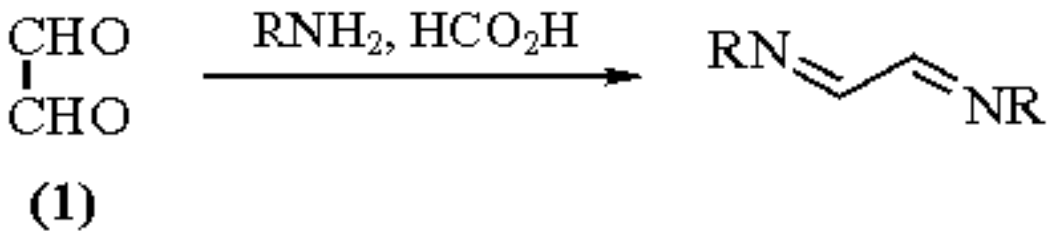

(12)

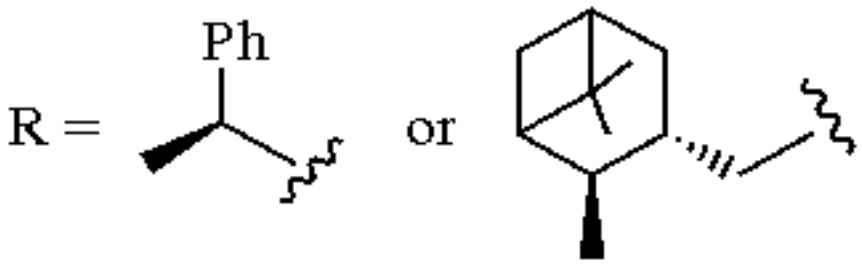

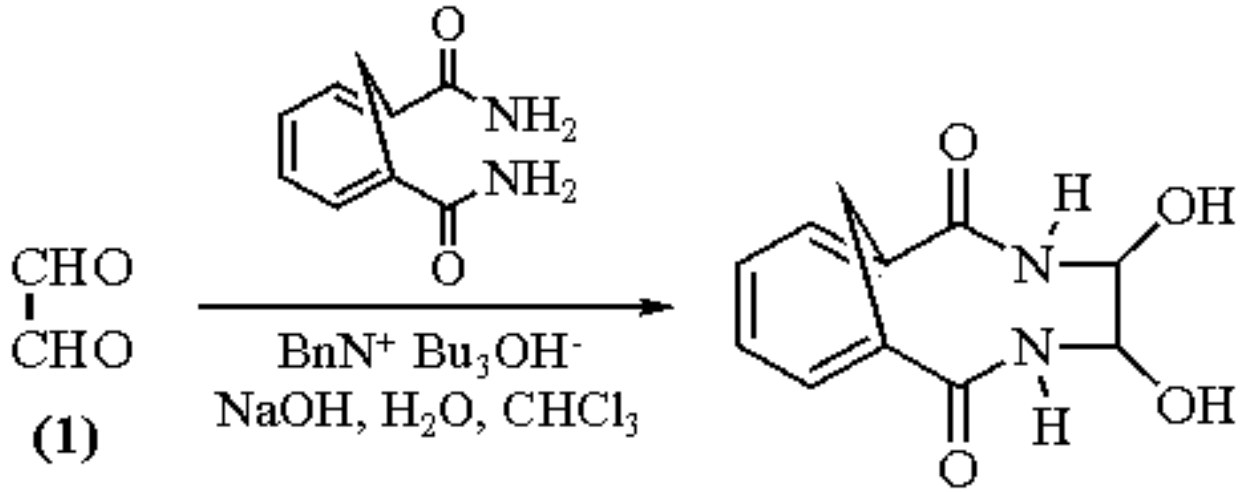

(13)

Powdered polymeric or monomeric glyoxal in dry benzene reacts with an ethereal solution of phenoxymagnesium bromide upon heating and directly produces the 2-hydroxyphenacyl alcohol (eq 14).[15] Reaction of glyoxal (obtained by concentration of 40% glyoxal) with gaseous HBr in methanol and dichloromethane at 0 °C affords 1,2-dimethoxy-1,2-dibromomethane which, upon treatment with sodium *t*-butoxide, undergoes dehydrobromination to yield 1,2-dimethoxyvinyl bromide (eq 15).[16]

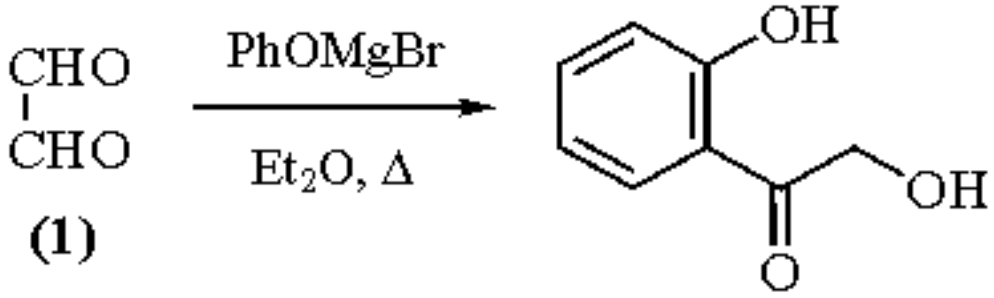

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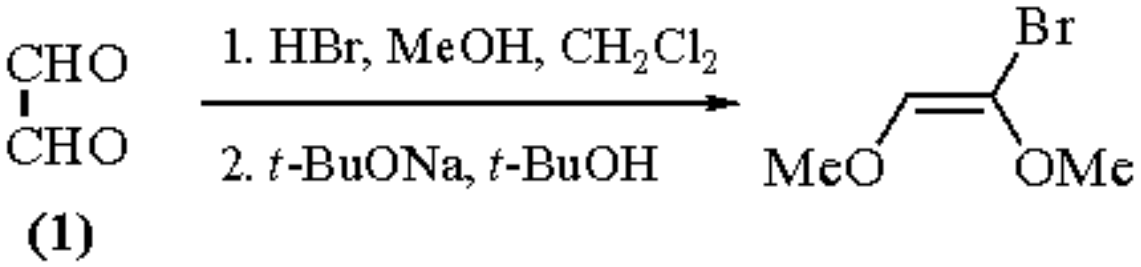

(15)

Reaction of glyoxal with 2-*t*-butyl-4-methylphenol in refluxing acetic acid in the presence of ***Hydrogen Chloride*** or ***p-Toluenesulfonic Acid*** as a catalyst affords 5-methyl-7-*t*-butyl-2(3*H*)-benzofuranone (eq 16).[17] Condensation of (**1**) with *N*-aryl substituted ureas produces the corresponding 1-aryl substituted hydantoins (eq 17).[18]

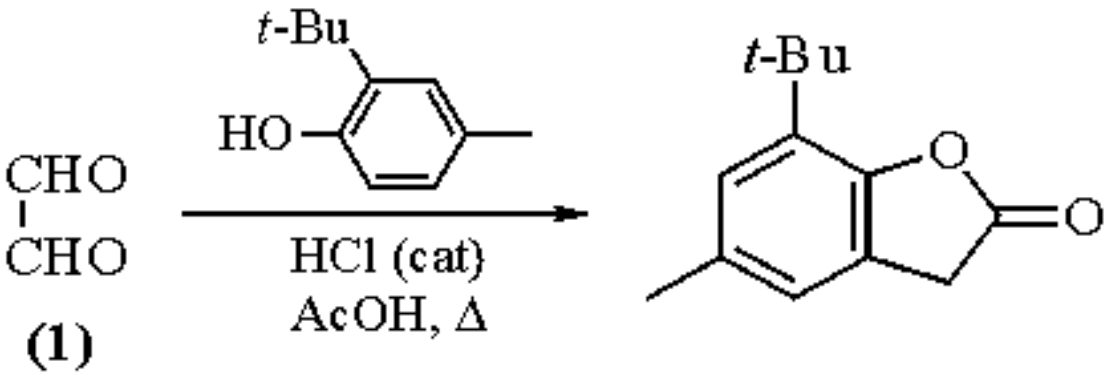

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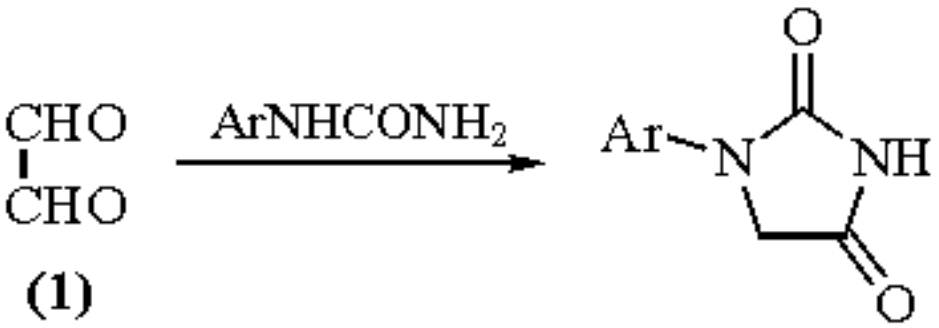

(17)

Glyoxal reacts with chiral *N*-homoallyl-β-amino alcohols in water-THF solution to produce an iminium ion which undergoes cyclization with complete stereoselectivity and affords the bi- and tricyclic alcohols[19] represented in eqs 18 and 19, respectively.

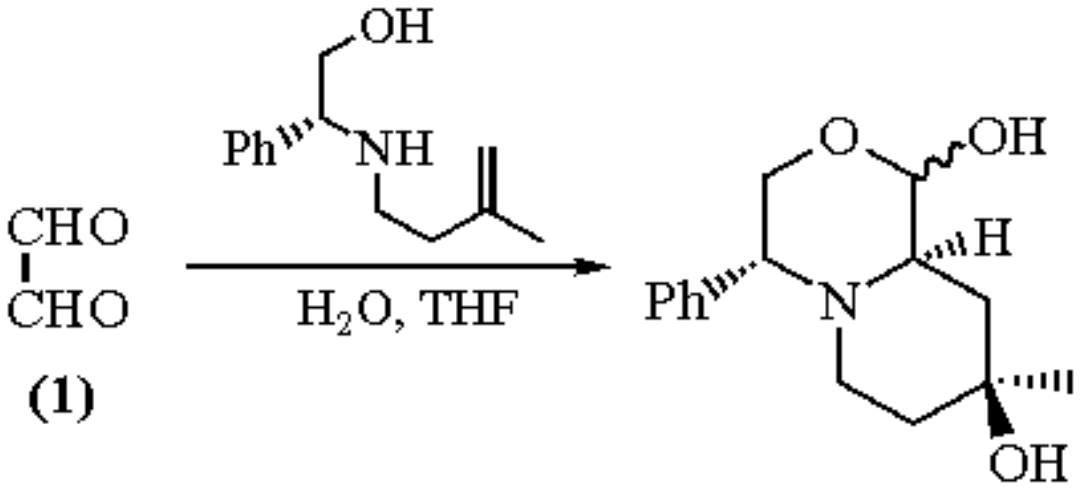

(18)

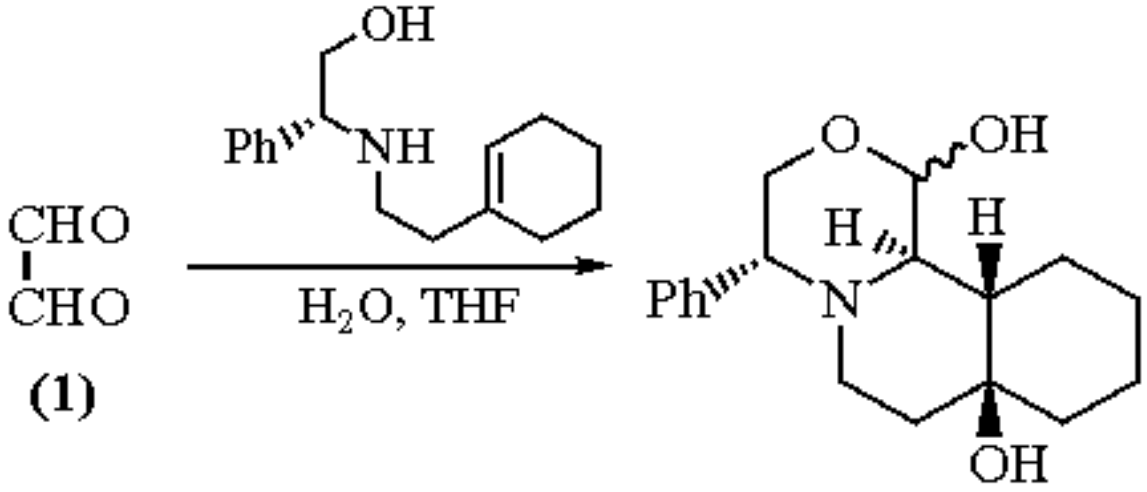

(19)

Related Reagents.

For uses of other dialdehydes in synthesis, see ***Malondialdehyde*** and ***Succindialdehyde***.

---

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Glyoxal Diethyl Acetal

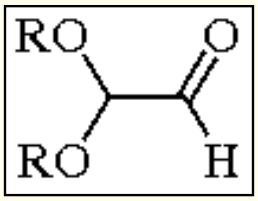

(**1**; R = Et)

[5344-23-0] · $C_6H_{12}O_3$ · Glyoxal Diethyl Acetal · (MW 132.16) (**2**; R = Me)

[51673-84-8] · $C_4H_8O_3$ · Glyoxal Dimethyl Acetal · (MW 104.11)

(reagents for preparation of α,β-unsaturated aldehydes[1-8] and heterocyclic compounds[1,9-12])

Alternate Name: diethoxyacetaldehyde.

Physical Data: (**1**) bp 50-55 °C/10 mmHg; (**2**) bp 60-90 °C/150 mmHg.

Form Supplied in: liquids; commercially available.

Preparative Methods: preparations usually involve either oxidative cleavage of glyceraldehyde acetals,[12-15] or reductive ozonolysis of acrolein[5,16] or crotonaldehyde[1] dialkyl acetals. Three new preparative procedures were recently reported.[17-19]

Handling, Storage, and Precautions: these compounds are moisture sensitive. They should be stored under inert gas and at low temperature.

Wittig Reactions.

Wittig or Horner-Emmons reactions yield α,β-ethylenic acetals.[1-8,10,14] Subsequent deacetalization, usually by moist silica gel, gives α,β-ethylenic aldehydes.[1-8] This approach was used in the synthesis of ethyl (2*E*,4*Z*)-decadienoate, a natural product from *Pyrus communis*, in which two of the three steps are Horner-Emmons reactions with dimethoxy- or diethoxyacetaldehyde and then deacetalization[20] (eqs 1-4).[3-5,8]

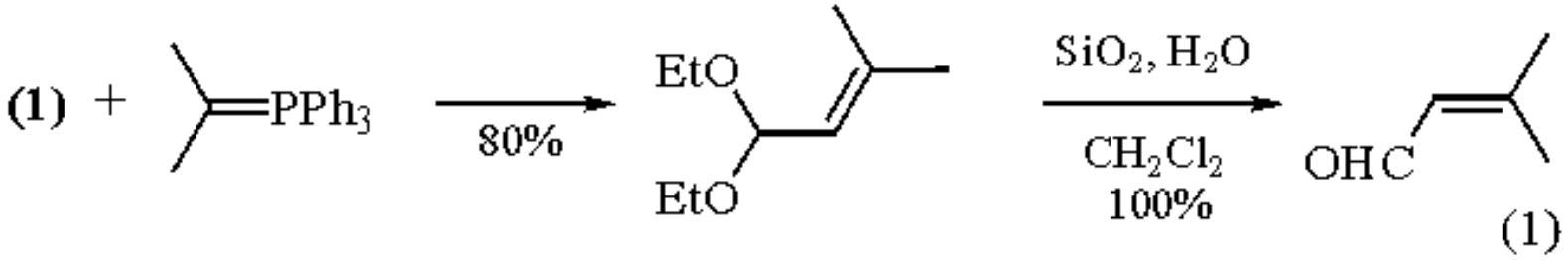

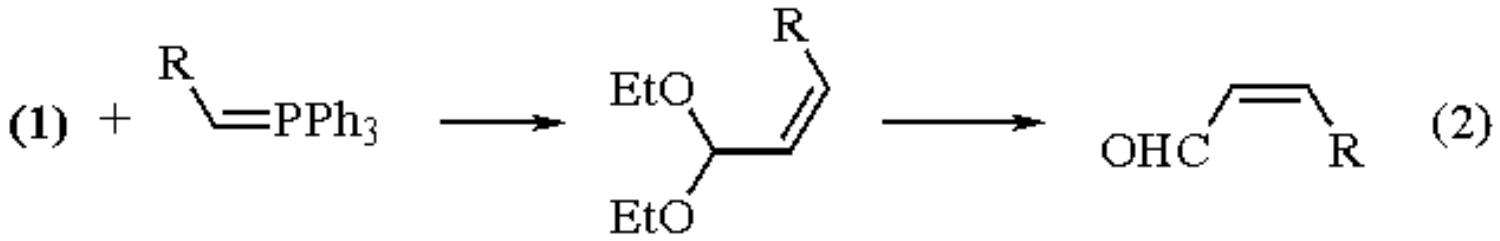

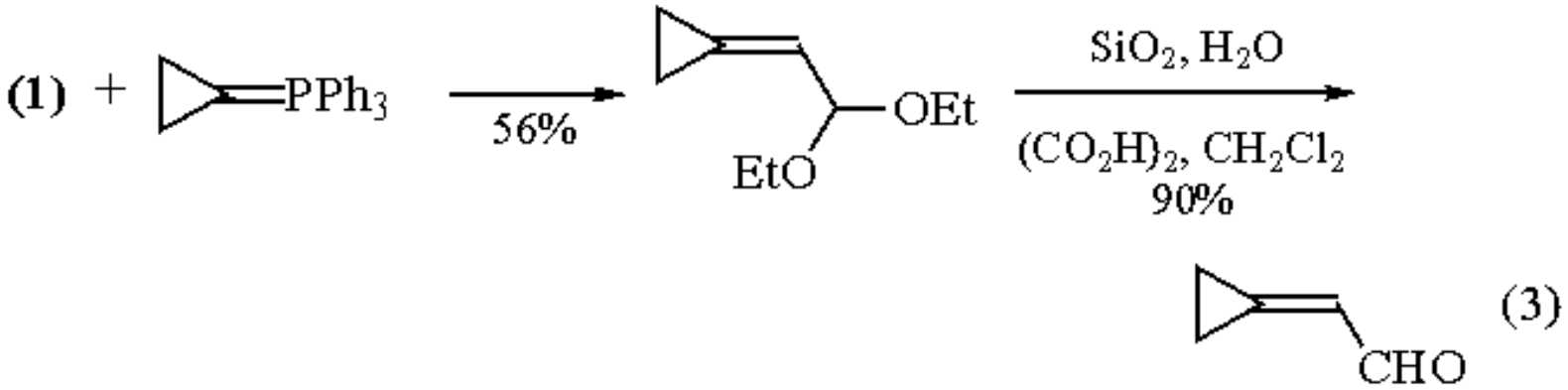

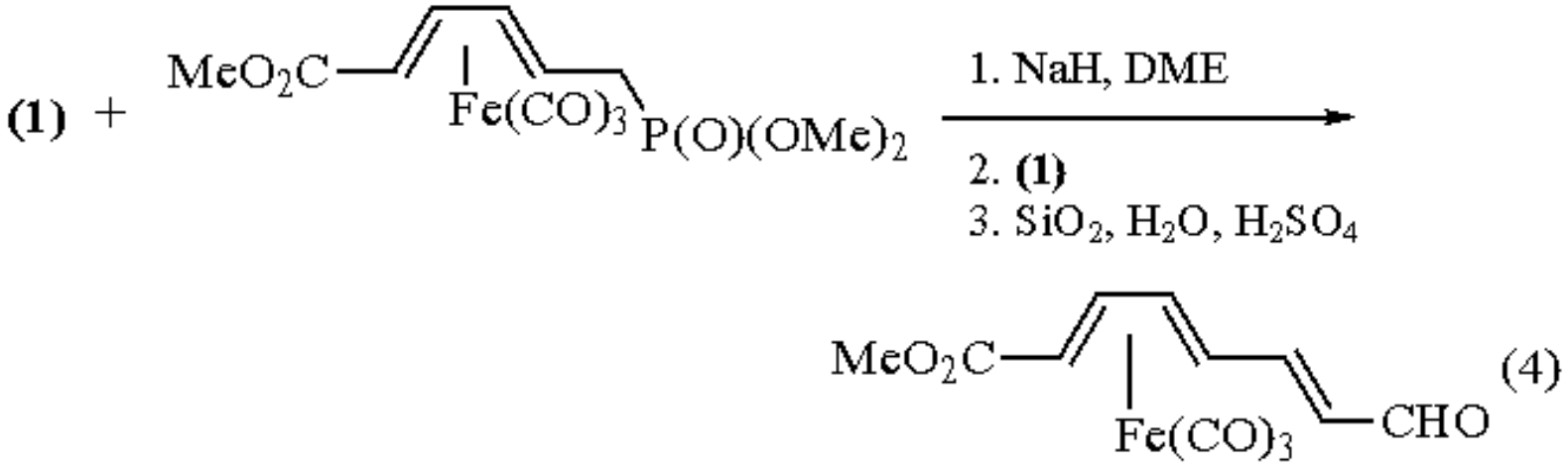

Synthesis of Heterocyclic Compounds.

Synthesis of complex alkaloids[9] and 4-methoxycarbonyl-α-pyrone (eq 5)[1] are based on successive reactions towards both functions of diethoxy-[9] or dimethoxyacetaldehyde.[1] Another possibility is the formation of heterocyclic compounds bearing an acetal function.[10-12] For instance, the Pictet-Spengler reaction between tryptophan derivatives and diethoxyacetaldehyde gives substituted tetrahydro-β-carbolines (eq 6).[11]

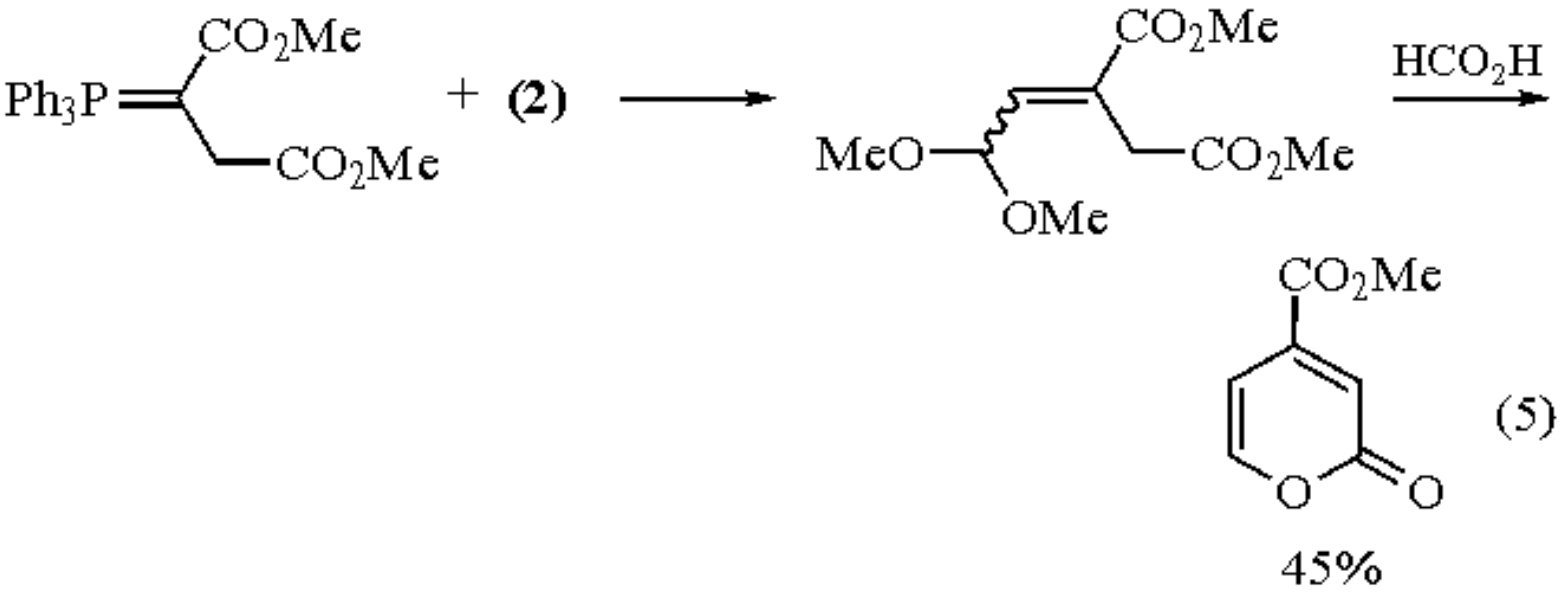

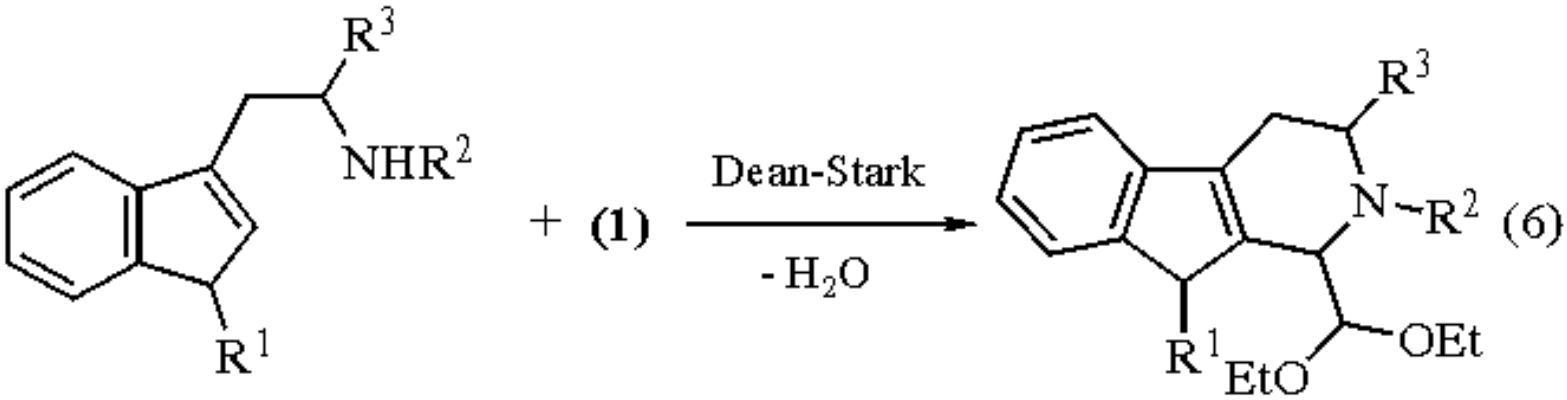

Reactions with Nucleophiles.

Organomagnesium[18a,21] and organolithium[17,22] compounds as well as metal hydrides[18a] lead to the expected acyloin acetals. As mentioned above, reaction of nitrogen compounds often leads to heterocyclic compounds; however, there are various other interesting possibilities.[18a,23] For instance, a novel synthesis of α-aminoaldehydes involves a substitution reaction between organomagnesium compounds and products obtained from benzotriazole, diethoxyacetaldehyde, and primary or secondary amines (eq 7).[23d]

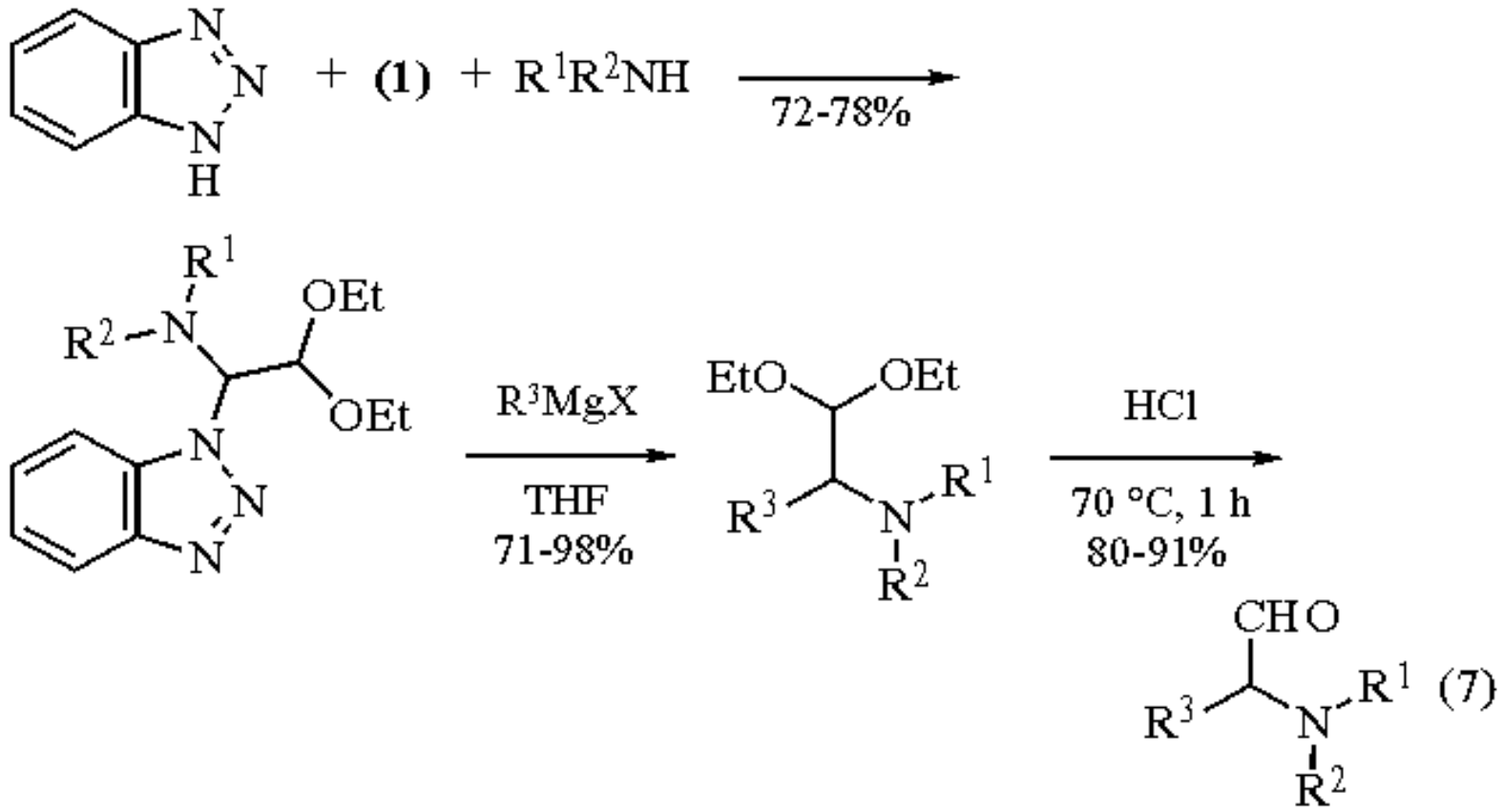

Other Reactions.

Dialkoxyacetaldehydes are also reagents for preparation of 1,4-dicarbonyl compounds[16] and of chiral α-hydrazono acetals.[24]

Related Reagents.

Pyruvaldehyde Diethyl Acetal; ***Ethyl Diethoxyacetate***; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl Lithioacetate***; ***Glyoxal***; ***Methyl Glyoxylate***.

---

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Glyoxylic Acid

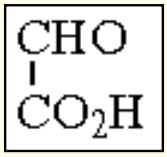

[298-12-4] · $C_2H_2O_3$ · Glyoxylic Acid · (MW 74.04)

(formaldehyde equivalent in Mannich reaction; reagent and its esters undergo a variety of additions, condensations, and Diels-Alder reactions)

Alternate Name: glyoxalic acid; oxoacetic acid.

Physical Data: deliquescent prisms; mp 98 °C (anhydrous), 50-52 °C (monohydrate); pK_a 2.32.

Solubility: sparingly sol ether, alcohol, benzene; v sol water.

Form Supplied in: crystalline solid as monohydrate [*563-96-2*] and in 50% aqueous solution.

Preparative Methods: glyoxylic acid is widely available, but the methyl, ethyl, and benzyl esters can be made easily from the ozonolysis of the corresponding maleate and fumarate esters.[1]

Purification: crystallized from water as the monohydrate.

Handling, Storage, and Precautions: corrosive and hygroscopic.

Mannich and Related Condensations.

Glyoxylic acid (**1**) has been extensively used in the Pictet-Spengler reaction to synthesize various β-carboline derivatives from the corresponding tryptamines (eq 1).[2] Reaction of glyoxylic acid and ***Hydroxylamine*** in water at pH 5 with excess $LiBH_3CN$ at rt affords α-hydroxyaminoacetic acid (eq 2).[3] The reagent reacts with an alkaline solution of *o*-methoxyphenol to form (*R*,*S*)-4-hydroxy-3-methoxymandelic acid (eq 3).[4] On the other hand, condensation of (**1**) with acetophenone gives 3-benzoylacrylic acid.[5]

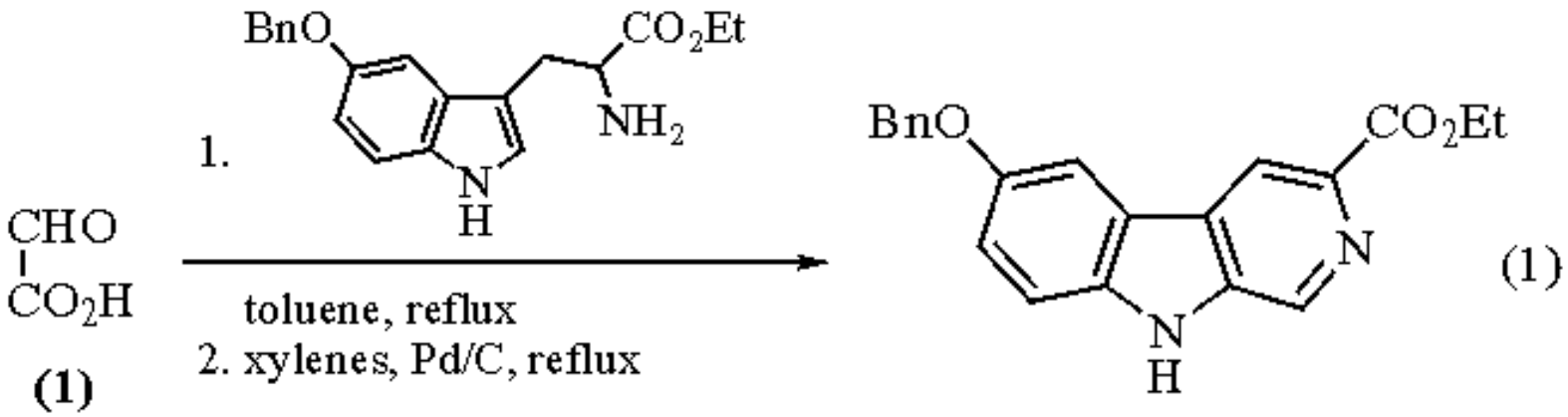

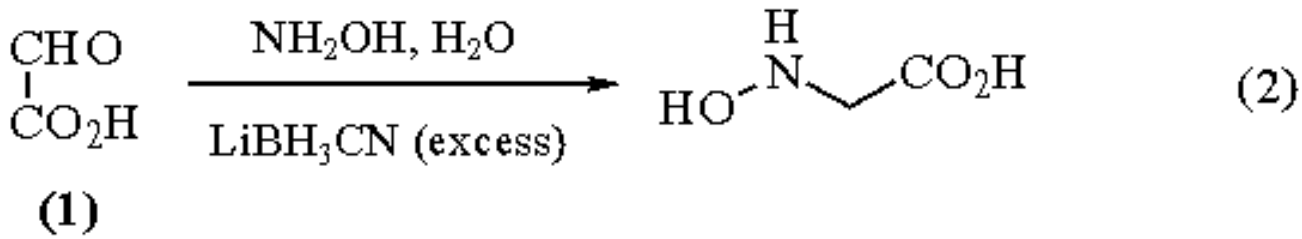

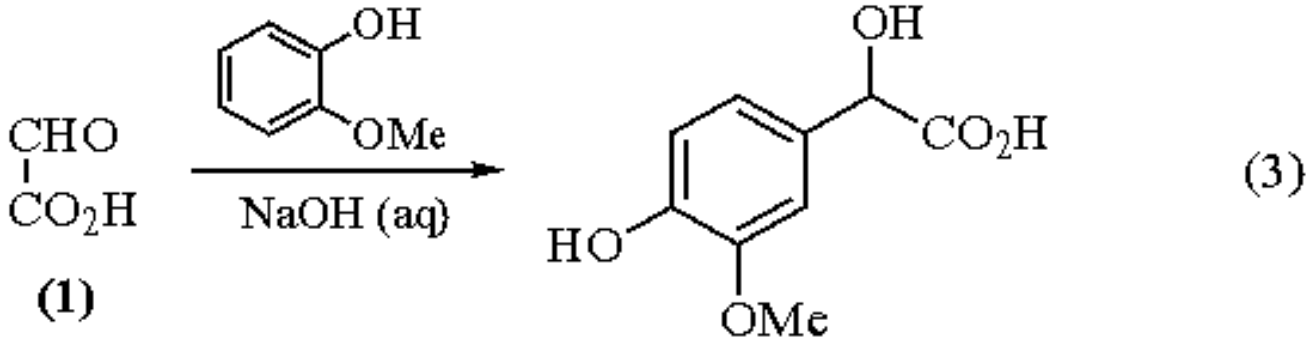

Treatment of glyoxylic acid with ethyl aminoformate followed by benzothiophene gives *N*-ethoxycarbonylbenzothienylglycine (eq 4) via the Mannich reaction.[6] Reaction of (**1**) with an alkyl- or arylamine in the presence of ***Pentacarbonyliron*** in alcoholic 1N KOH, under an atmosphere of carbon monoxide followed by HCl acidification affords the corresponding *N*-alkyl- or arylglycines (eq 5).[7] Treatment of the thioacetals of various ketones and aldehydes with (**1**) in acetic acid and hydrochloric acid at rt results in transthioacetalization and liberates the carbonyl compounds (eq 6).[8]

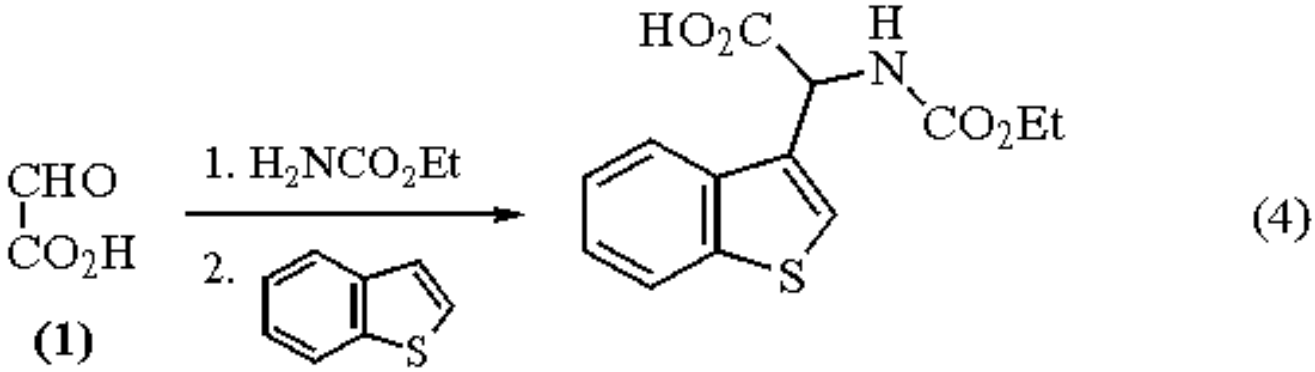

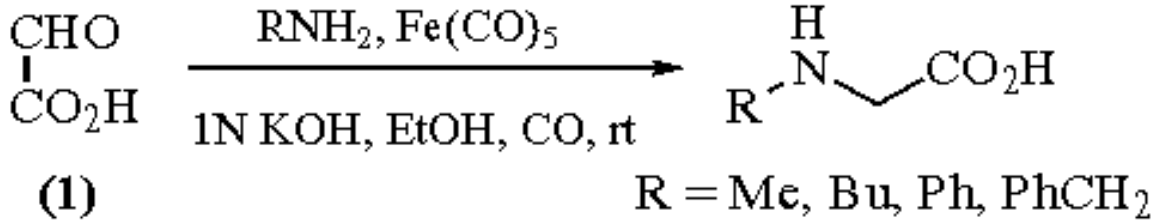

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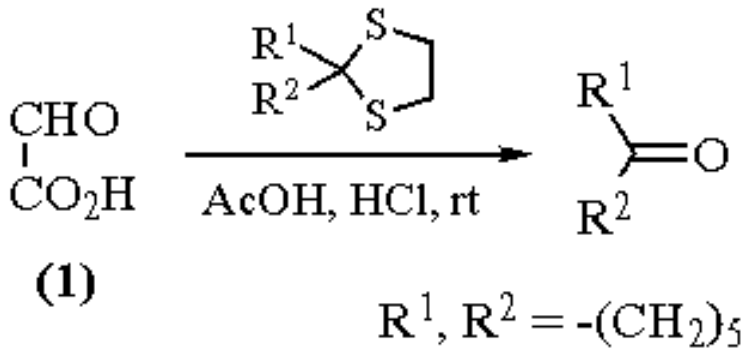

(6)

Glyoxylic acid, in the presence of 2N NaOH in ethanol, adds to 3-nitropropanal ethylene acetal to give 2-hydroxy-3-nitro-5-ethylenedioxypentanoic acid in quantitative yield (eq 7).[9] Reaction of *n*-butyl glyoxylate (**2**) with 1-morpholinocyclopentene in refluxing cyclohexane (Dean-Stark trap), followed by cooling and hydrolysis affords butyl 2-oxocyclopentylideneacetate (eq 8).[10]

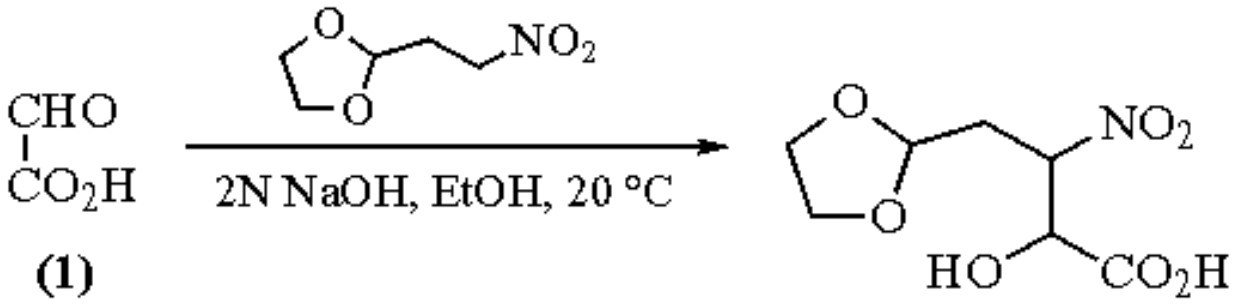

(7)

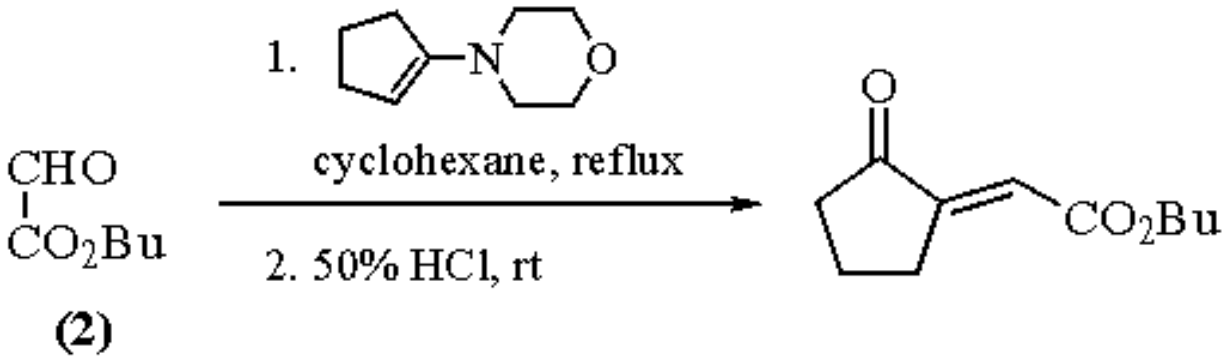

(8)

Treatment of methyl glyoxylate (**3**) with ***(S)-Proline*** in a 2:1 ratio in DMSO at 90 °C gives a diastereomeric mixture of oxapyrrolizidines (eq 9).[11]

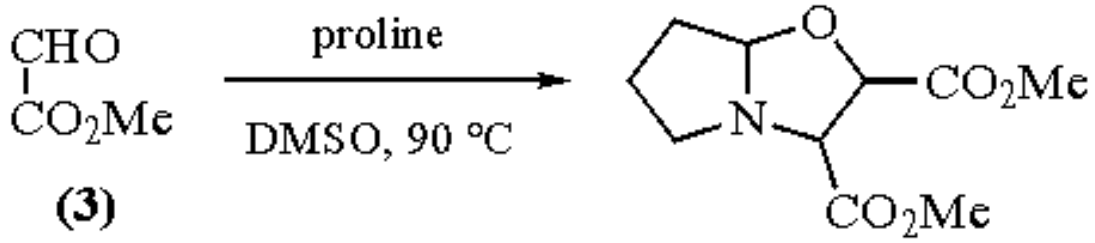

(9)

Diels-Alder Reactions.

Methyl or ethyl glyoxylates react with acylaza-Wittig reagents in refluxing benzene to produce the diacylimines, as shown in eq 10.[12] These are moderately reactive dienophiles for Diels-Alder reactions with various dienes, such as the Danishefsky diene[13a] or Cohen diene,[13b] to furnish the corresponding tetrahydropyridines.[12]

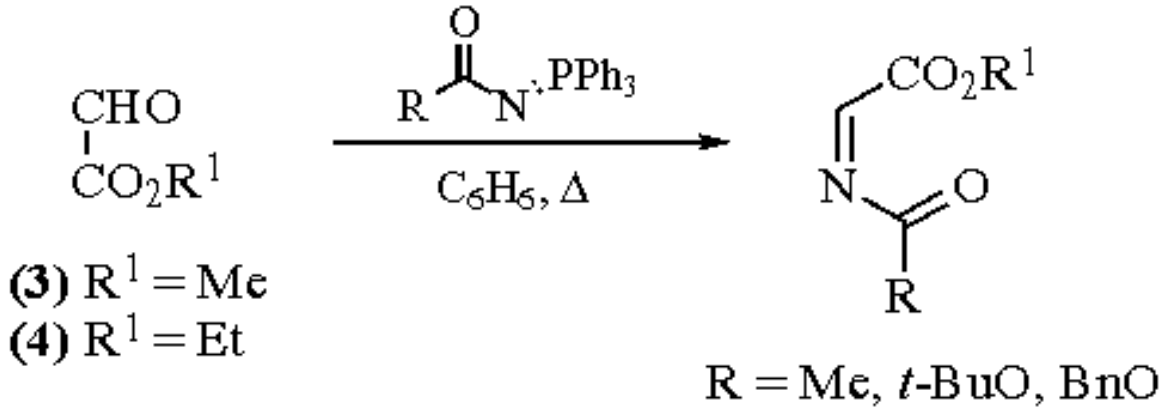

(10)

Methyl glyoxylate (**3**) itself undergoes a hetero-Diels-Alder reaction with the Danishefsky diene in refluxing benzene. Hydrolysis of the resultant adduct furnishes a 1:1 mixture of stereoisomers of 2-methoxy-6-methoxycarbonyl-5,6-dihydro-γ-pyrone (eq 11).[12] Similarly, reaction of methyl glyoxylate with 1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene, catalyzed by $Eu(fod)_3$ in CH_2Cl_2 at rt, regioselectively produces 2-methoxy-6-methoxycarbonyl-5,6-dihydro-γ-pyrone which, on subsequent hydrolysis with dilute aq HCl in refluxing benzene, produces 6-methoxycarbonyl-3-oxo-δ-lactone (eq 12).[14] Hetero-Diels-Alder reaction of *n*-butyl glyoxylate with 2-ethoxy-1,3-butadiene at 60 °C affords 4-ethoxy-6-butoxycarbonyl-5,6-dihydro-2*H*-pyran as the main adduct (eq 13).[15]

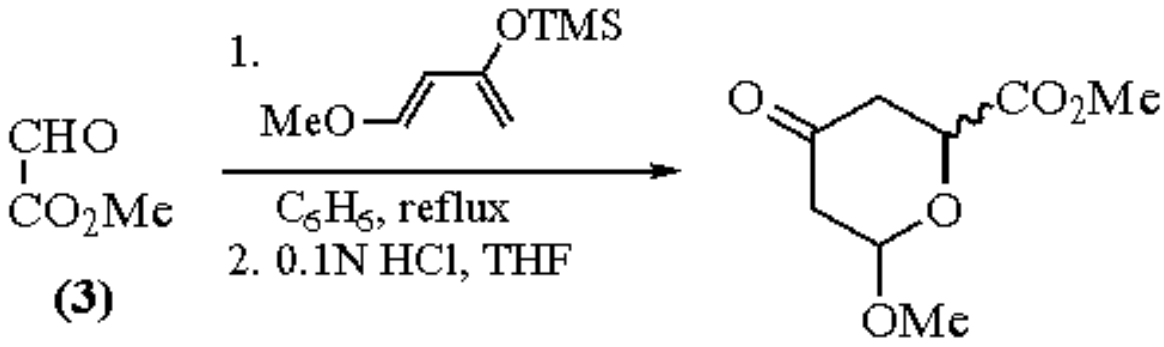

(11)

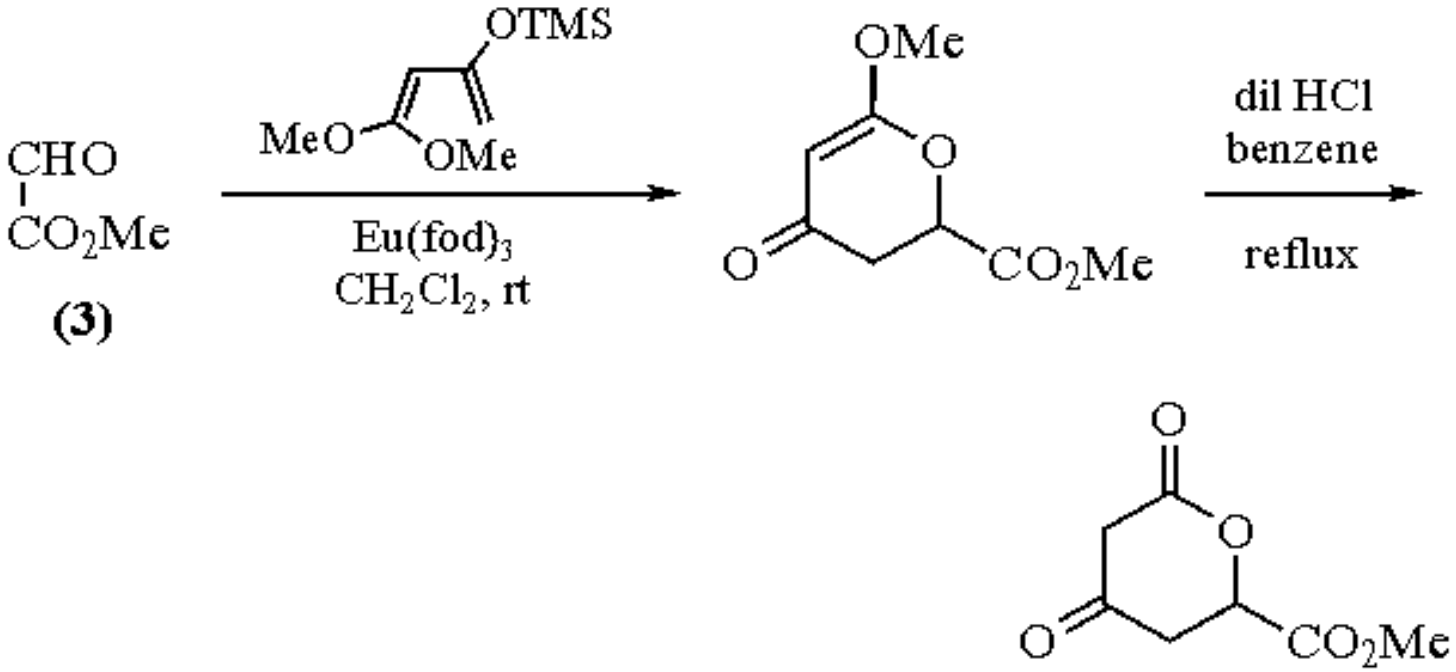

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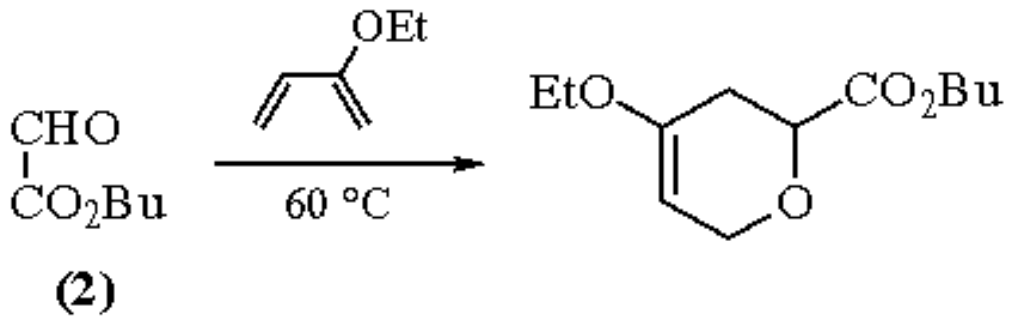

(13)

Butyl glyoxylate (**2**) undergoes an addition reaction with cyclohexene in the presence of ***Tin(IV) Chloride*** at 40-45 °C to produce butyl 2-hydroxy-2-(2-cyclohexenyl)acetate (eq 14).[16] Methyl glyoxylate undergoes an asymmetric carbonyl-ene reaction with isobutene catalyzed by a chiral titanium complex (generated in situ from ***(R)-1,1´-Bi-2,2´-naphthol*** (BINOL) and ***Dichlorotitanium Diisopropoxide*** over molecular sieves in methylene chloride) to produce (*R*)-methyl α-hydroxy-γ-methyl-4-pentenoate in high optical purity (eq 15).[17] Under similar reaction conditions, methyl glyoxylate (**3**) reacts with the symmetrical bis-allyl silyl ether shown in eq 16 to produce the corresponding α-hydroxy ester (>99% ee) through an asymmetric catalytic desymmetrization (eq 16).[18]

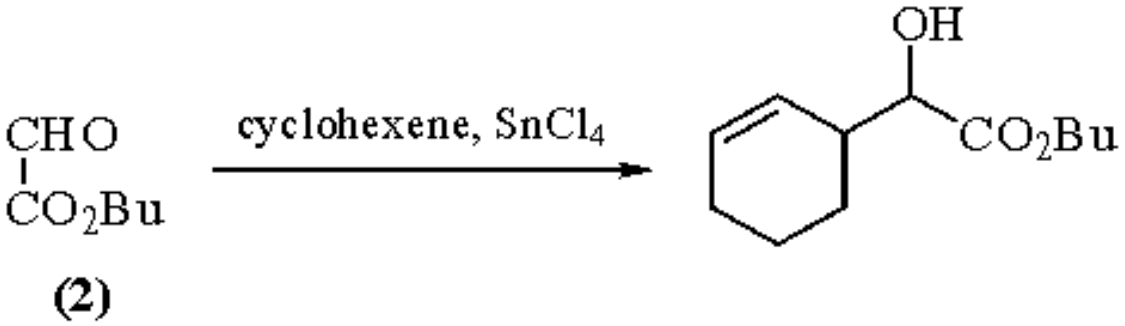

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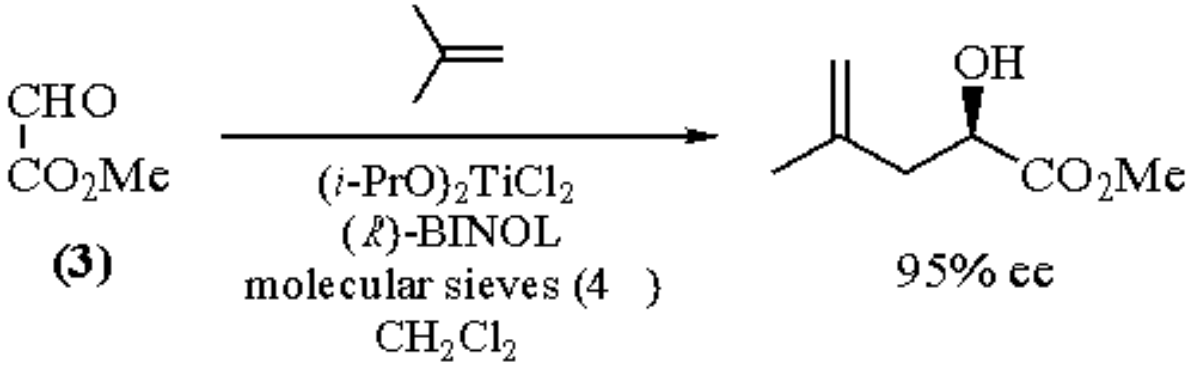

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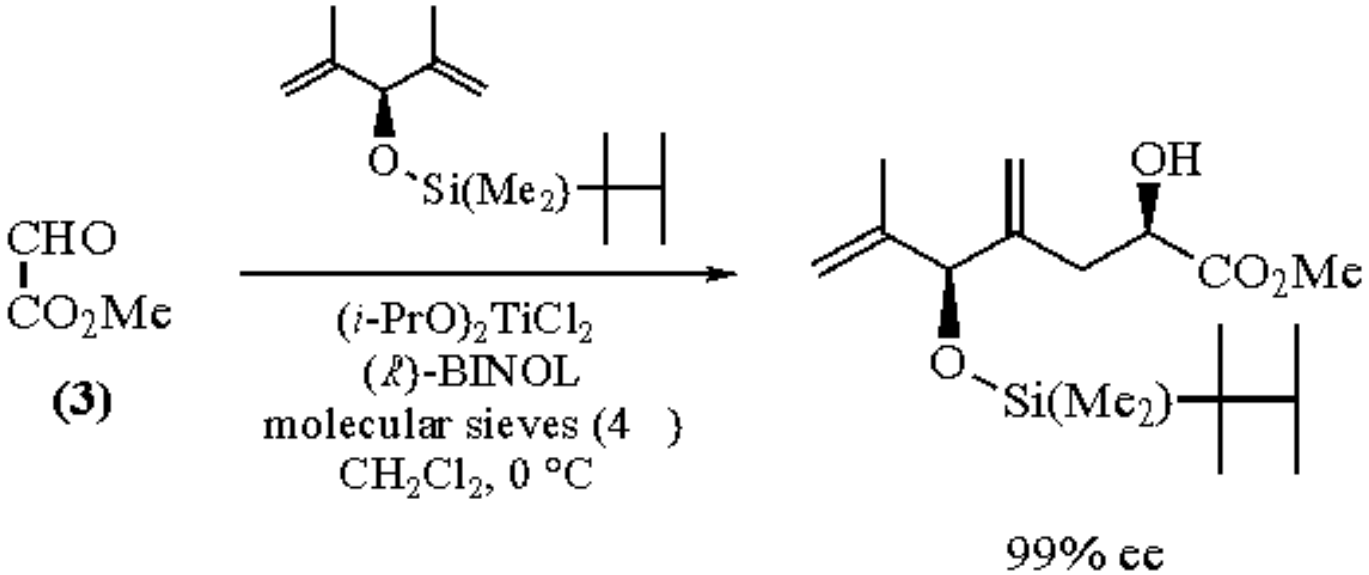

(16)

Reaction of methyl or ethyl glyoxylate with (*S*)-4-benzyloxypent-(2*E*)-2-enyl(tributyl)stannane in the presence of $SnCl_4$ at -78 °C produces (1*R*,5*S*,3*Z*)-5-benzyloxy-1-methoxycarbonylhex-3-en-1-ol with excellent diastereoselectivity (eq 17).[19] Ethyl glyoxylate (**4**) undergoes a [3 + 2] cycloaddition with 5-ethoxy-2-phenyloxazole in the presence of a Lewis acid catalyst (a 1:1 mixture of ***Titanium(IV) Chloride*** and ***Titanium Tetraisopropoxide***) to produce a mixture of *cis*- and *trans*-4,5-bis(ethoxycarbonyl)-2-oxazolines in an 84:16 ratio, whereas use of $SnCl_4$ reverses the selectivity and yields the same mixture in a 15:85 ratio (eq 18).[20]

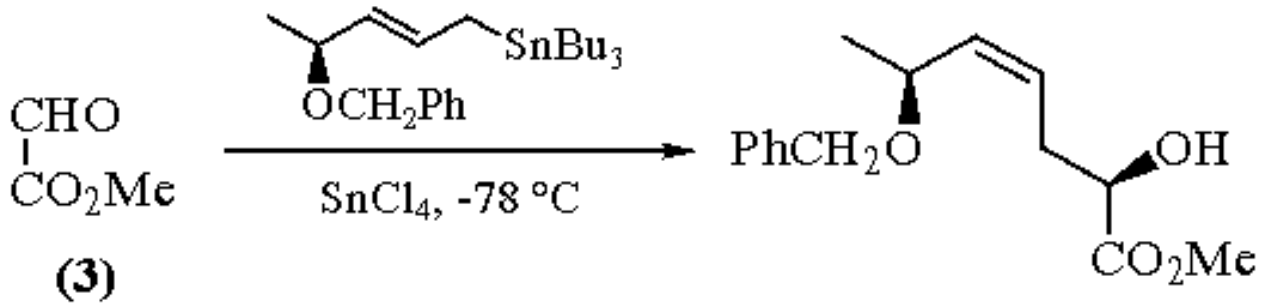

(17)

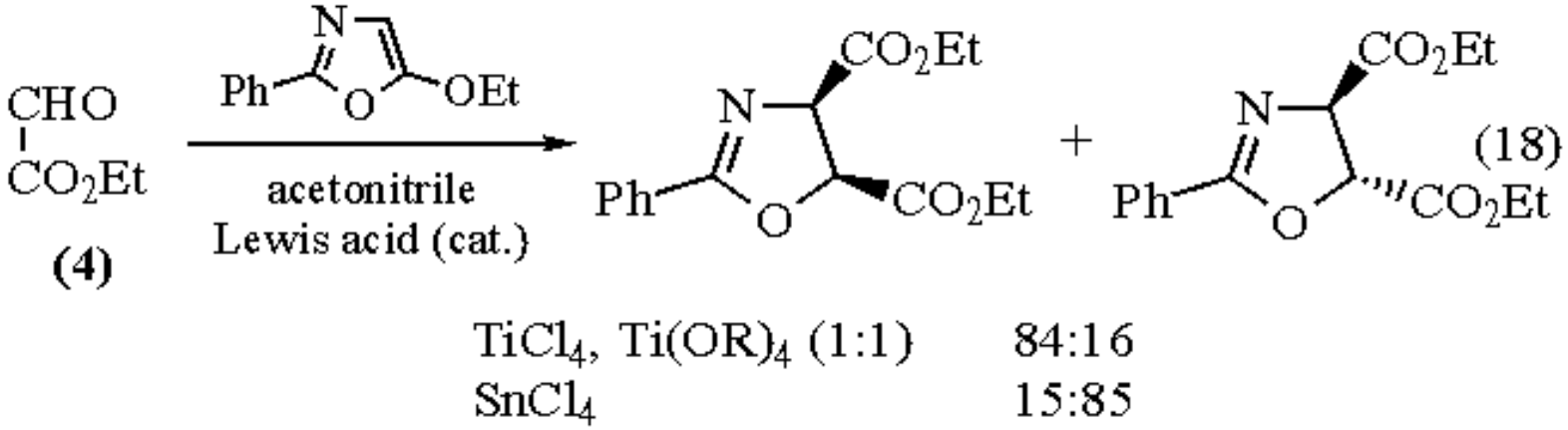

The imine derived from methyl glyoxylate and di-*p*-anisylmethylamine (DAM-NH_2)[21] reacts with ketene (generated in situ from the reaction of the corresponding alkanoyl chloride and triethylamine in refluxing hexane, benzene or methylene chloride) to afford the corresponding *cis*-4-methoxycarbonyl-β-lactams as single isomers (eq 19).[22]

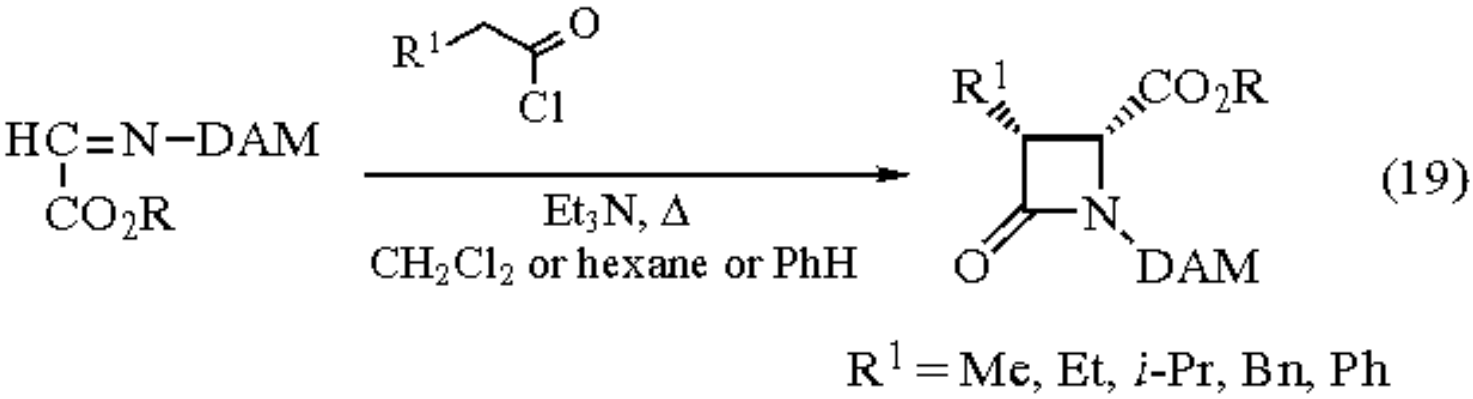

Related Reagents.

Formaldehyde.

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Glyoxylic Acid Diethyl Dithioacetal

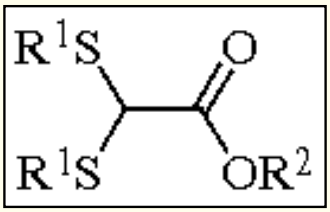

(**1**; R^1 = Et, R^2 = H)

[10490-06-9] · $C_6H_{12}O_2S_2$ · Glyoxylic Acid Diethyl Dithioacetal · (MW 180.32) (**2**; $R^1 = (CH_2)_2$, R^2 = H)

[5616-65-9] · $C_4H_6O_2S_2$ · Glyoxylic Acid Ethylene Dithioacetal · (MW 150.24) (**3**; $R^1 = (CH_2)_3$, R^2 = H)

[20461-89-6] · $C_5H_8O_2S_2$ · Glyoxylic Acid Trimethylene Dithioacetal · (MW 164.27) (**4**; R^1 = Et, R^2 = Me

[38564-39-5] · $C_7H_{14}O_2S_2$ · Methyl Glyoxylate Diethyl Dithioacetal · (MW 194.35) (**5**; R^1 = Et, R^2 = Et)

[20461-95-4] · $C_8H_{16}O_2S_2$ · Ethyl Glyoxylate Diethyl Dithioacetal · (MW 208.38) (**6**; $R^1 = (CH_2)_2$, R^2 = Et)

[20461-99-8] · $C_6H_{10}O_2S_2$ · Ethyl Glyoxylate Ethylene Dithioacetal · (MW 178.30) (**7**; $R^1 = (CH_2)_3$, R^2 = Me)

[56579-84-1] · $C_6H_{10}O_2S_2$ · Methyl Glyoxylate Trimethylene Dithioacetal · (MW 178.30) (**8**; $R^1 = (CH_2)_3$, R^2 = Et)

[20462-00-4] · $C_7H_{12}O_2S_2$ · Ethyl Glyoxylate Trimethylene Dithioacetal · (MW 192.33)

(α-keto equivalent; alkylation of the anions, aldol condensations, and both 1,2- and 1,4-additions to α,β-unsaturated compounds; thioketene and α-oxo dithioester precursor)

Alternate Name: (**1**) bis(ethylthio)acetic acid; (**2**) 1,3-dithiolane-2-carboxylic acid; (**3**) 1,3-dithiane-2-carboxylic acid.

Physical Data: (**1**) bp 110 °C/0.2 mmHg. (**2**) mp 90-91 °C. (**3**) mp 114.5-116 °C. (**4**) bp 125-127 °C/5 mmHg. (**5**) bp 70 °C/0.1 mmHg. (**6**) bp 105 °C/0.6 mmHg. (**7**) bp 102 °C/2 mmHg. (**8**) bp 75-77 °C/0.2 mmHg.

Preparative Methods: esters (**5**), (**6**), and (**8**) are available from commercial sources. The thioacetal acids may be prepared by thioacetalization of glyoxylic acid monohydrate[3] or by reaction on the appropriate

thiol(ate) with 2,2-dichloroacetic acid (or the diethyl acetal) directly[4] or under phase transfer[5] conditions using Aliquat 336. The esters may be obtained via similar exchange processes or via acid-catalyzed esterification of the corresponding acids.

General.

The most common usage of the above compounds is as α-keto acid equivalents via their corresponding anions (or dianions). There are differences in the reactivity and selectivity of these systems which depend on the nature of the thioacetal as well as the gegenion present in the reaction. Hydrolysis under a variety of conditions to the corresponding ketone[1] or reductive desulfurization[2] generally proceeds in excellent yields.

Alkylation.

The esters may be deprotonated with ***Sodium Hydride*** or comparably strong bases and the resulting anions subsequently alkylated with alkyl halides in good to excellent yields (eq 1).[4,6a,b] The reaction may also be carried out using phase transfer catalysis.[5] Opening of epoxides,[6c] cyclic sulfonates,[6d] and displacement of triflates[6e] also proceeds in good yields. The thioacetal acids may be converted into the corresponding dianion with ***Potassium Hexamethyldisilazide***. The dianions are readily alkylated in high yield by a wide variety of electrophiles (alkyl halides, tosylates, epoxides, *N*-tosylaziridines).[3]

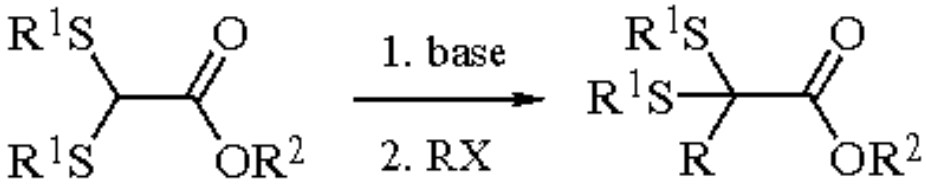

(1)

base: e.g. NaH, LDA, $KN(SiMe_3)_2$, K_2CO_3 (phase transfer)

1,4- and 1,2-Carbonyl Additions.

The anions of several of the esters undergo Michael addition with a wide variety of α,β-unsaturated compounds (aldehydes, ketones, esters, lactones, lactams, and nitroalkenes)[7] in high yields. The role of the gegenion is important in the regioselectivity of this addition (eq 2).[8] The reaction can also proceed under phase transfer[9a,b] (tetrabutylammonium hydrogensulfate) or crown ether (***18-Crown-6***) conditions.[9c] Trapping of the enolate resulting from conjugate addition to ketones with ***Formaldehyde*** provides a route to substituted lactones (eq 3).[10]

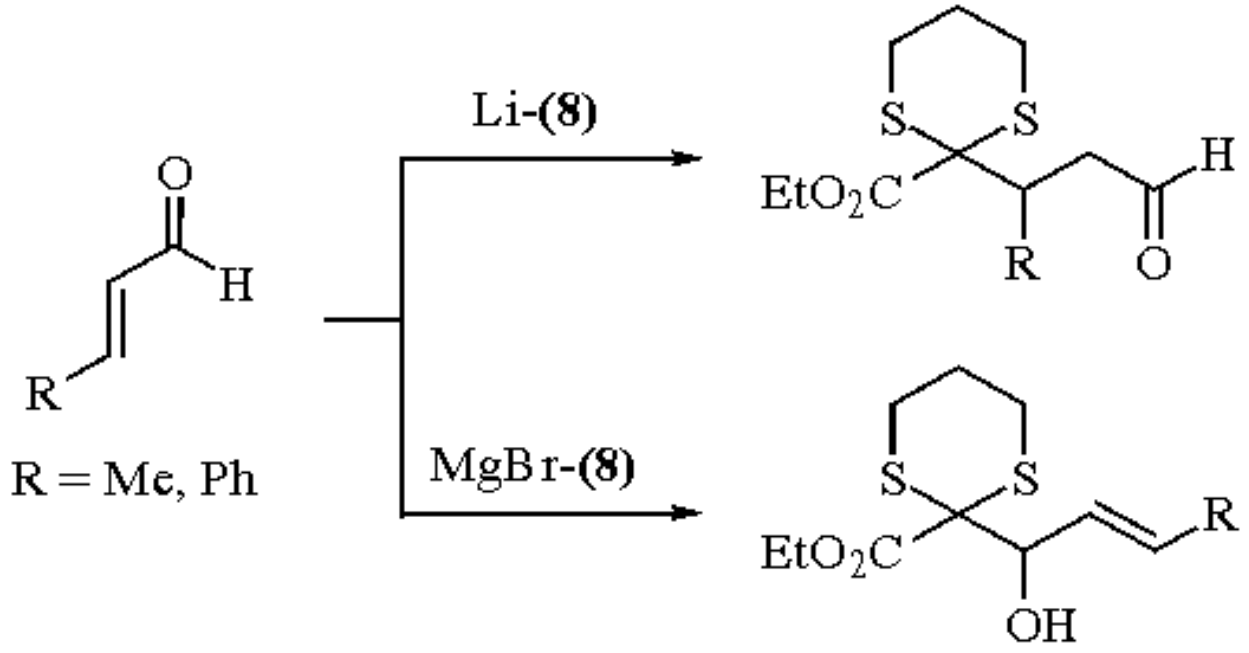

(2)

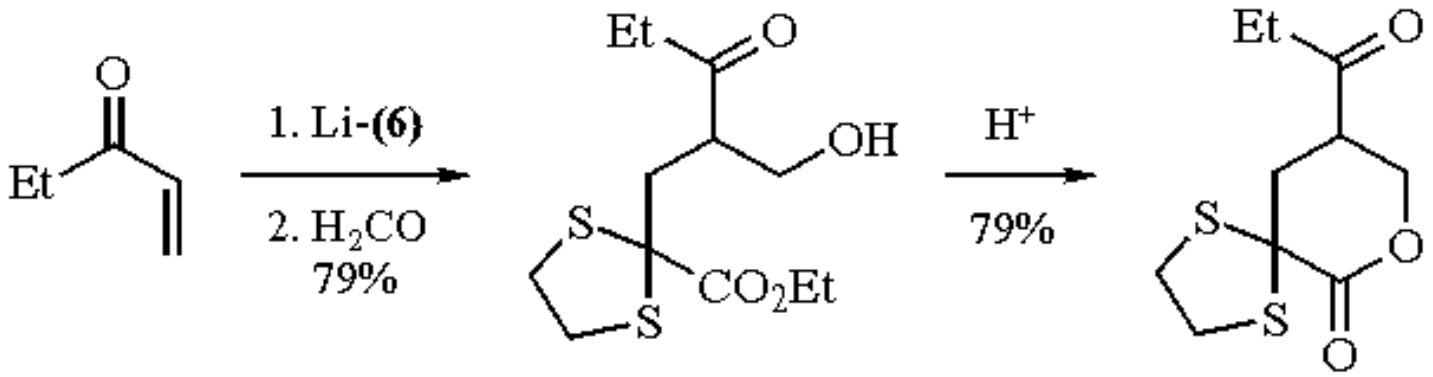

(3)

1,2,4-Benzenetriols may be prepared via a conjugate addition-cyclization-aromatization pathway (eq 4).[11]

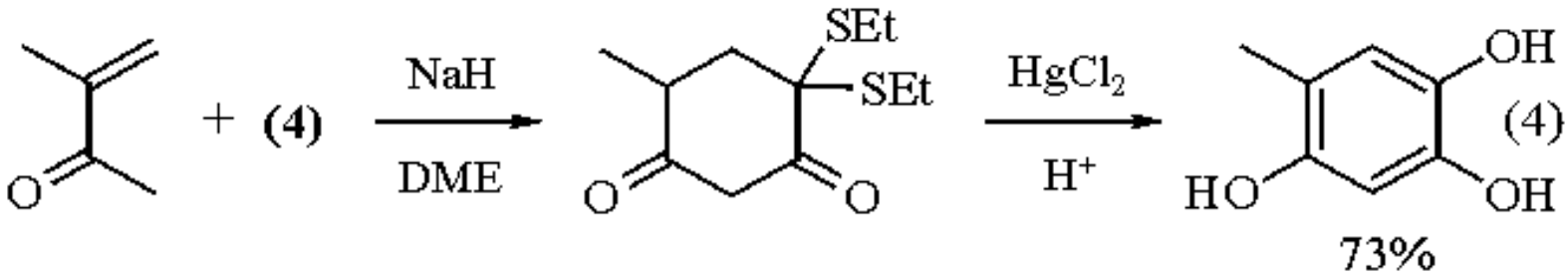

(4)

Aldol Condensation.

Condensation of the anions of esters (**6**), (**7**), and (**8**) with aldehydes has been reported.[8,12] The reaction can proceed with excellent diastereofacial selectivity (eq 5).[12a]

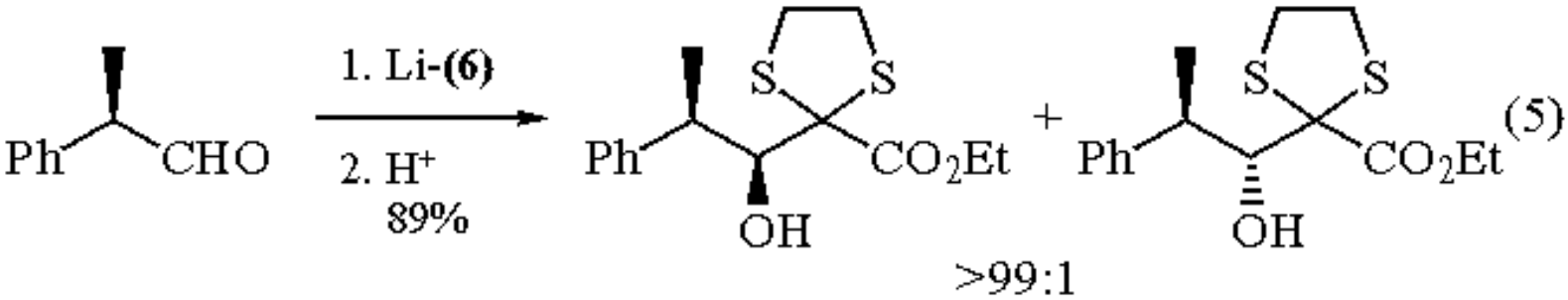

Miscellaneous.

Reactive intermediate species have been derived from several of the thioacetals. Reaction of aldehydes with the lithium anion of (**7**) in the presence of ***Trimethylacetyl Chloride*** with subsequent dealkoxycarbonylation forms ketene thioacetals (eq 6).[12c] In addition, reactions of the acid chlorides derived from (**2**) or (**3**) in the presence of base yield products consistent with the formation of a ketene intermediate (eq 7).[13]

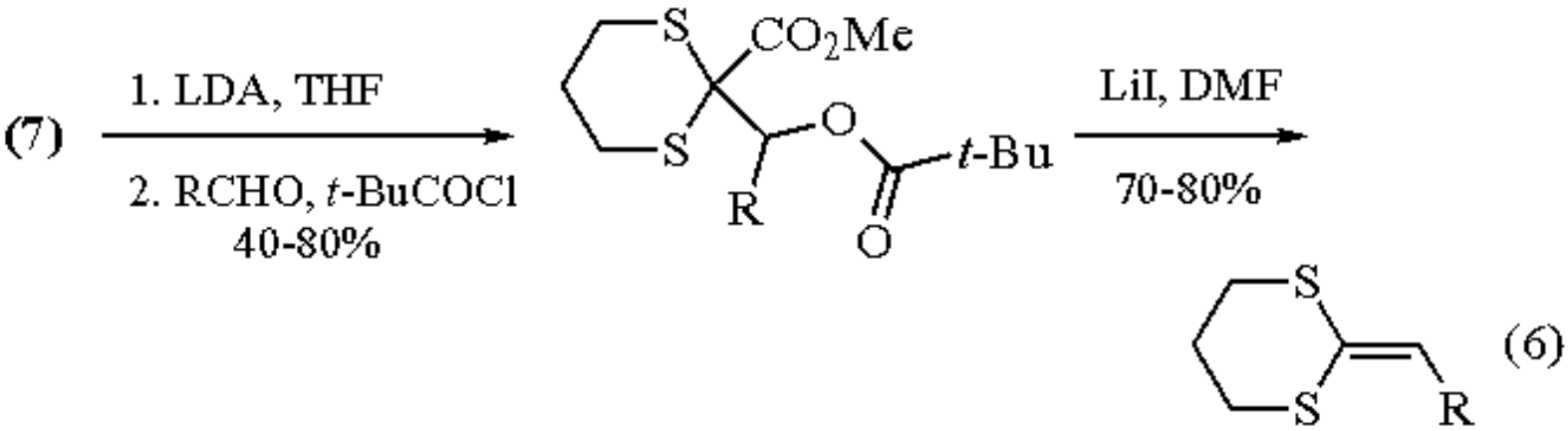

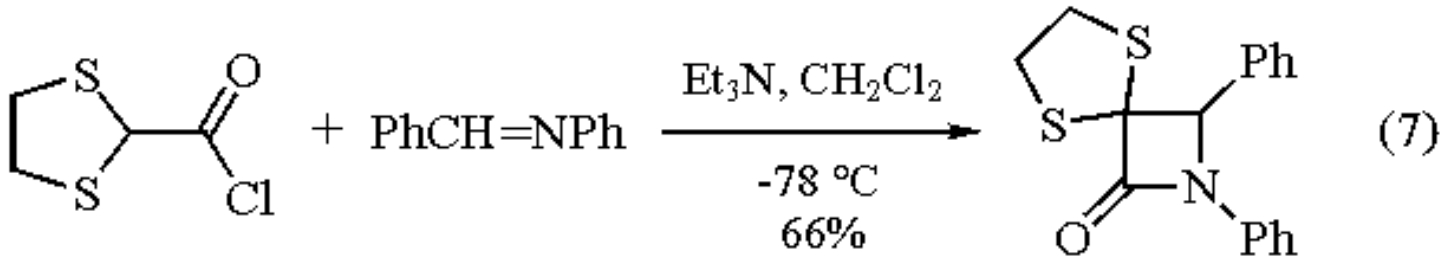

Retrocyclizations of *S*-alkylated derivatives of (**6**) yield α-oxo dithioester intermediates which react with alkenes in a Diels-Alder reaction (eq 8),[14] and cycloadditions with styrene derivatives and (**1**) yield 2-(ethylthio)butyrolactones.[15]

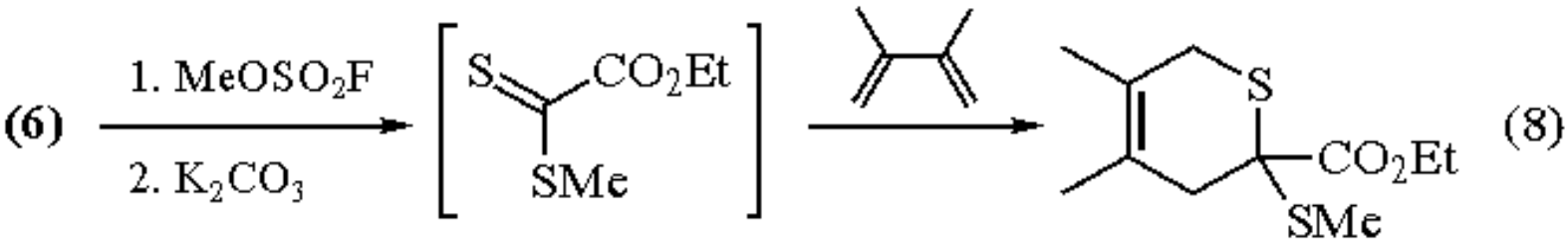

Ester (**6**) reacts with various dithiols in the presence of ***Trimethylaluminum*** to produce tetrathiafulvalenes in good yield (eq 9).[16]

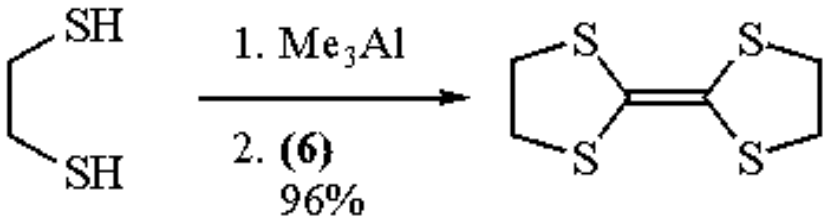

(9)

A chiral variant of (**8**) (menthyl ester) has served as an auxiliary (eq 10) in the condensation of aryl alkyl ketones with ***n-Butyllithium*** to produce chiral tertiary alcohols (70%, 55% ee).[17]

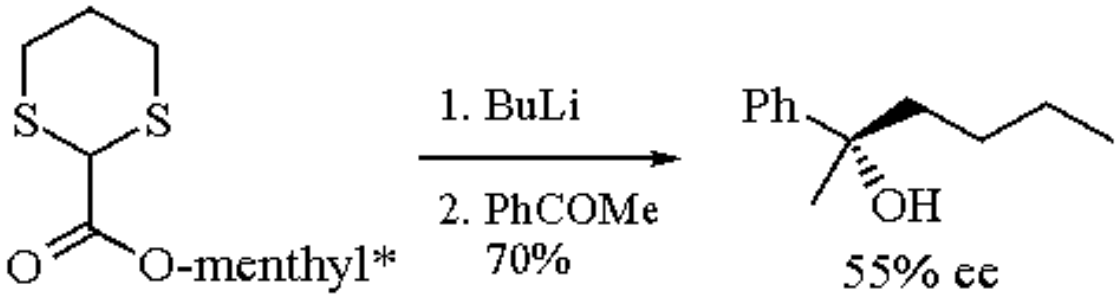

(10)

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***1,3-Dithiane***; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl Diethoxyacetate***; ***2-Lithio-1,3-dithiane***; ***Methyl Glyoxylate***; ***8-Phenylmenthyl Glyoxylate***.

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Glyoxylyl Chloride *p*-Toluenesulfonylhydrazone[1]

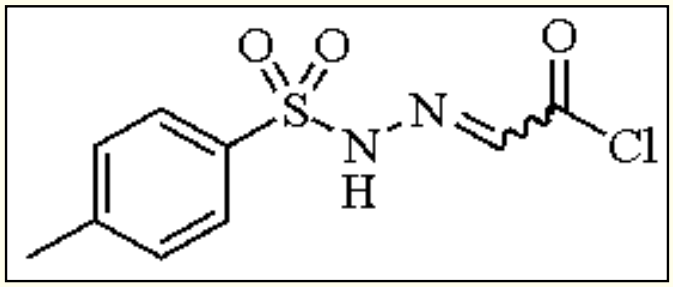

[14661-69-9] · $C_9H_{10}ClN_2O_3S$ · Glyoxylyl Chloride *p*-Toluenesulfonylhydrazone · (MW 261.73)

(synthesis of α-diazo esters and amides[2])

Physical Data: mp 103-110 °C (dec).

Solubility: sol methylene chloride, chloroform, THF, and warm benzene.

Preparative Methods: not commercially available; however, it can be prepared readily by the reaction of ***p-Toluenesulfonylhydrazide*** and ***Glyoxylic Acid***.[2]

Handling, Storage, and Precautions: anhydrous conditions are required; it is advisable to prepare the reagent freshly prior to use.

Introduction.

Glyoxylyl chloride *p*-toluenesulfonylhydrazone (**1**) is a versatile reagent for the synthesis of diazoacetyl esters and amides, which upon heating in the presence of a metal catalysts or irradiation generate reactive carbene intermediates.[1] Compound (**1**) undergoes reaction with alcohols to give the corresponding α-diazoacetyl esters under mild basic conditions. Typically, 2 equiv of ***Triethylamine*** are used in this reaction (eq 1). However, sulfinate species have been reported to contaminate the product.[1b] Corey and Meyers have shown that the formation of this undesired byproduct can be largely circumvented by the use of *N*,*N*-dimethylaniline instead of Et_3N (eq 2).[1b]

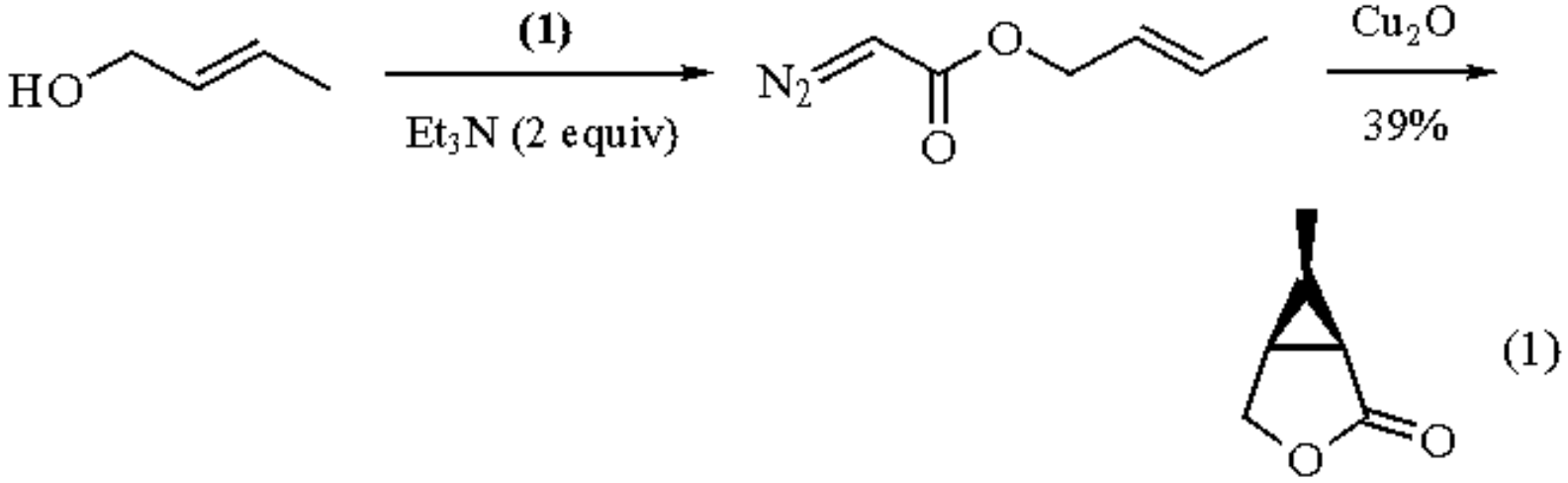

(1)

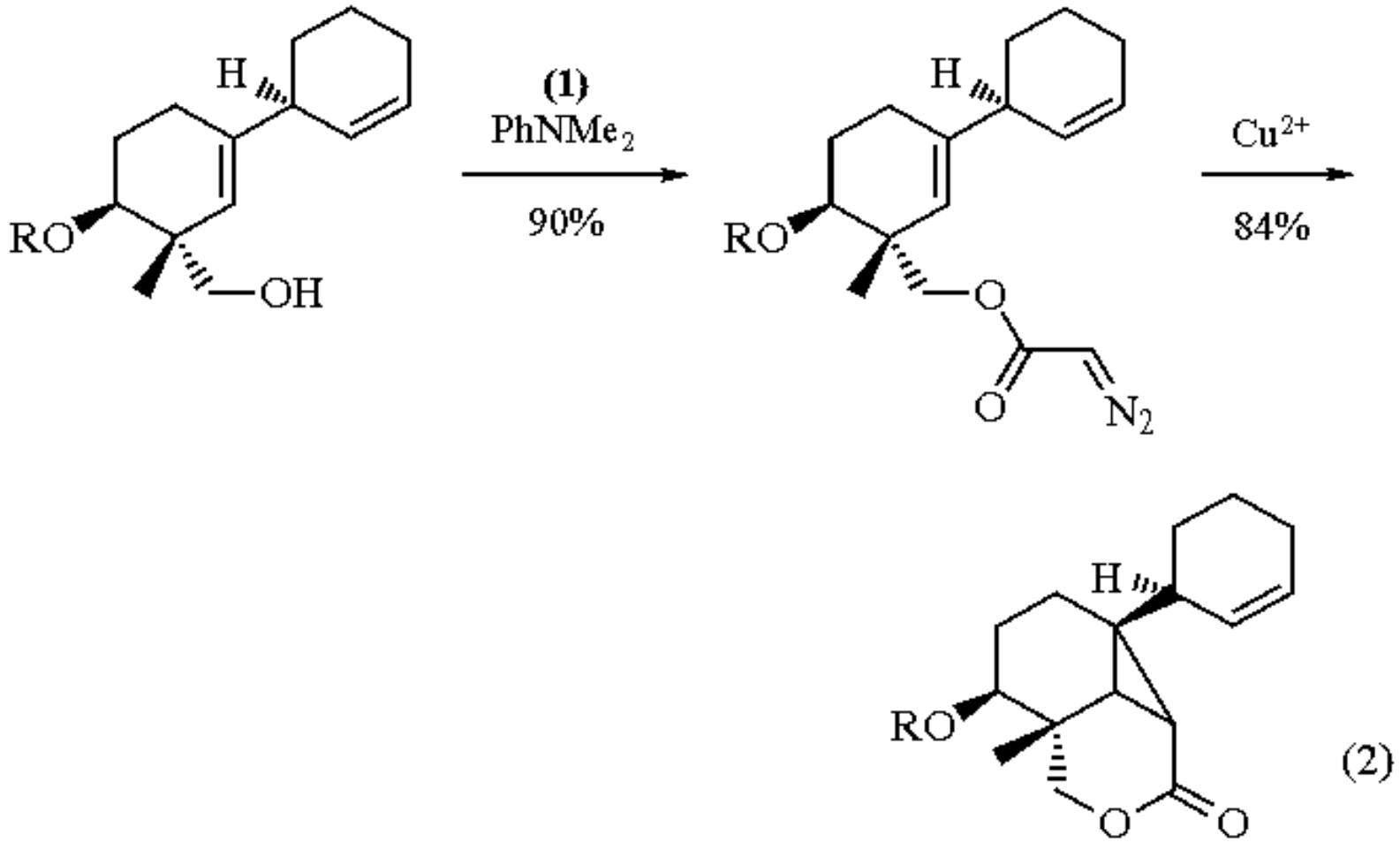

(2)

The existing alternative preparative methods for the α-diazo esters, such as diazotization of glycine esters,[3] pyrolysis of *N*-acyl-*N*-nitrosoglycine esters,[4] base-catalyzed cleavage of α-diazo-β-ketoacetates,[5] reactions of alkoxycarbonylmethylenephosphoranes with arenesulfonyl azides,[6] or acid-catalyzed decomposition of acetic esters with aryltriazene substituents,[7] all suffer from the disadvantage of being multistep synthetic procedures, and that at times harsh conditions (high temperature, strong acid or base) must be employed.

Intramolecular Cyclopropanation.

The resultant α-diazoacetyl ester from the reaction of (**1**) and an unsaturated alcohol undergoes cyclization in the presence of transition metals to give cyclopropyl derivatives (eqs 3, 4); the reaction proceeds via an intermediary carbene species.[1] Owing to the geometric constraints of the intramolecular cyclopropanation, the substituents and the product acquire all-*cis* configurations.[2] This is in contrast to the bimolecular cyclopropanation, which is unable to achieve sterochemical control, resulting in mixtures of products.

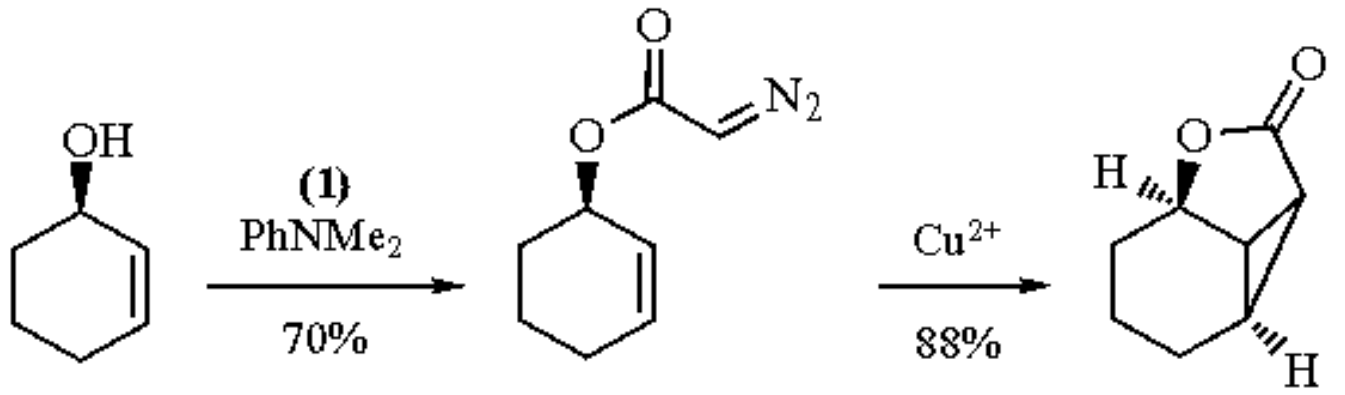

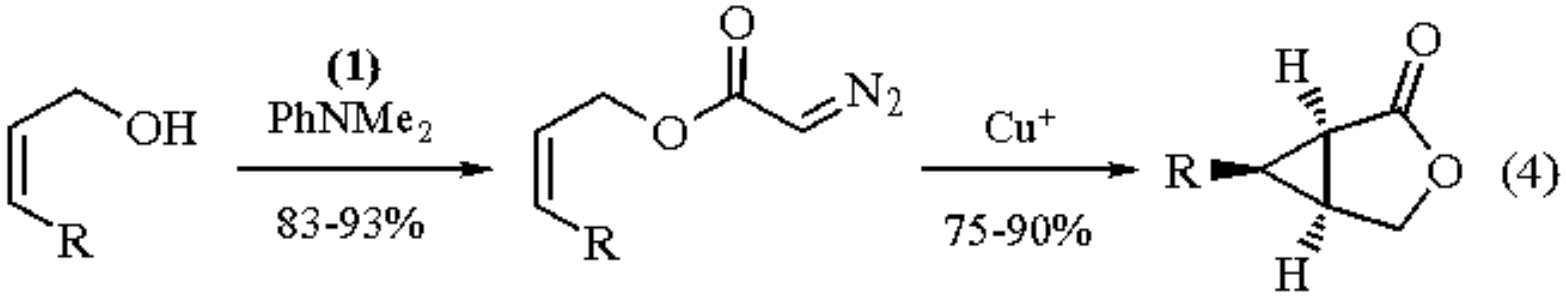

C-H and C-C Carbene Insertion Reactions.

Intramolecular carbene insertion at an unactivated bridgehead site is reported from an α-diazoacetyl ester precursor (eq 5).[8]

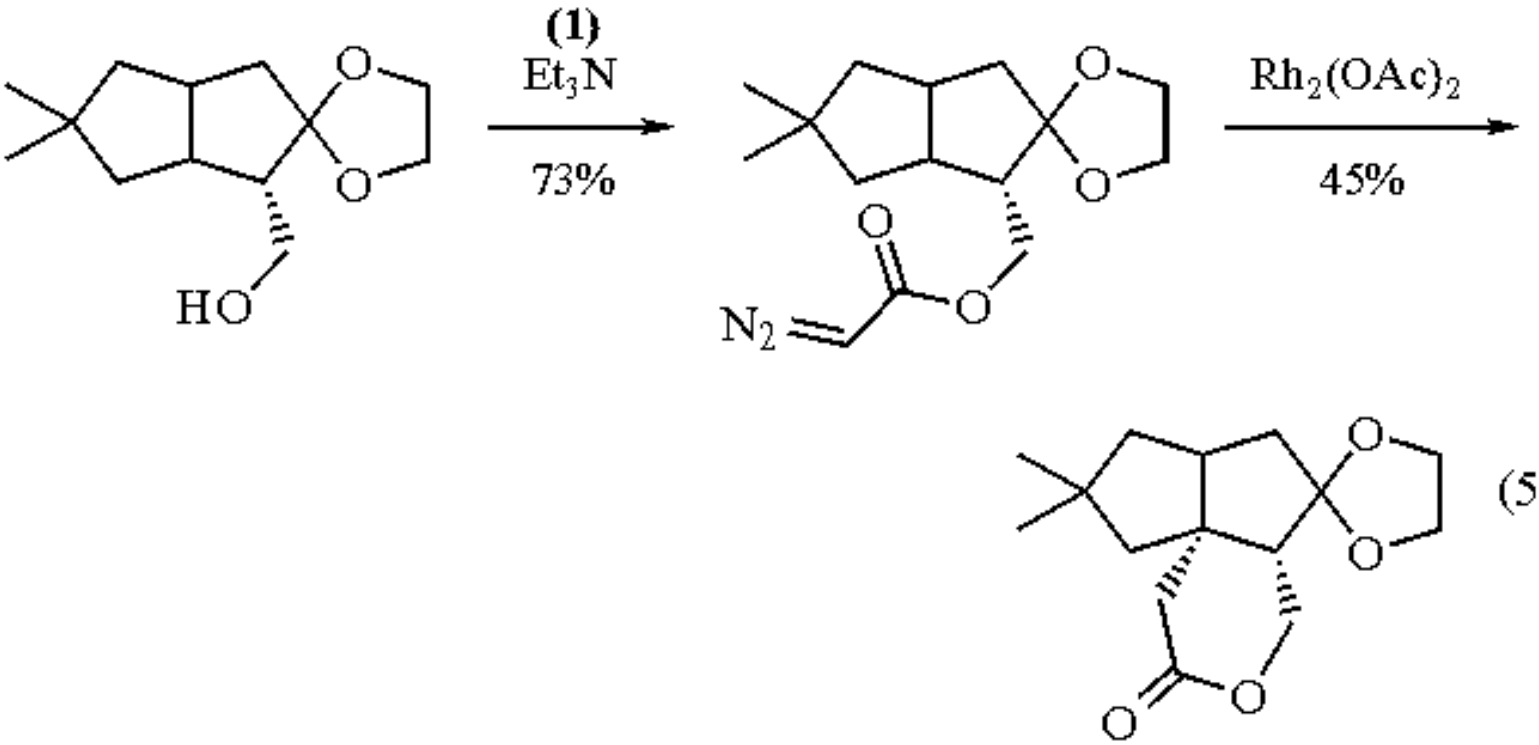

Decomposition of 6-(α-diazoacetamide)penicillanate in the presence of copper(II) or rhodium(II) in refluxing benzene resulted in the formation of a cycloheptatriene moiety (eq 6).[9]

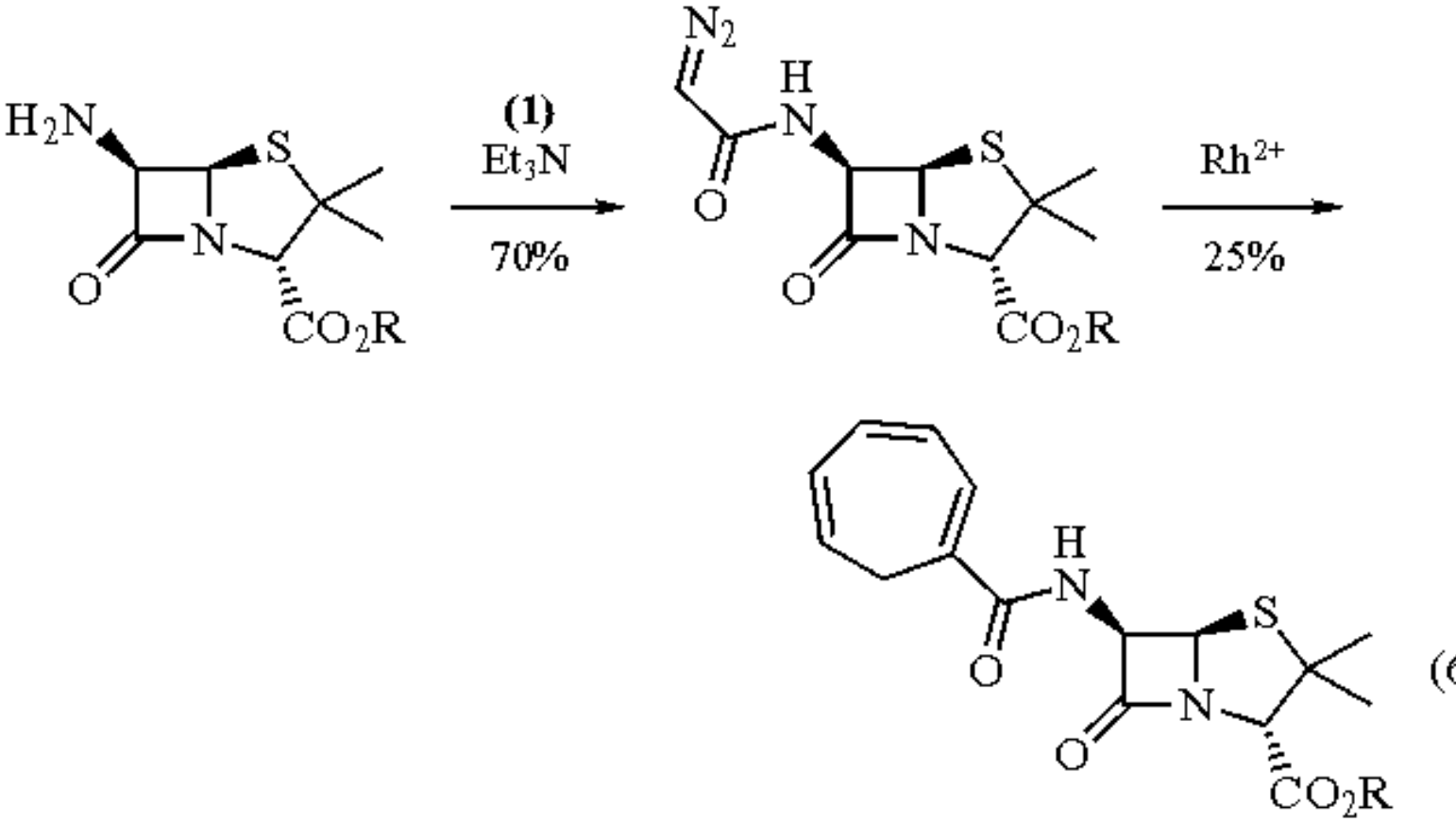

Photoaffinity Labels.

As an application of the carbene insertion reaction in structural studies of macrobiomolecules, radioactively labeled α-diazo esters have been used as photoaffinity labels.[10] Such esters are designed to bind specific targetted biological receptors (e.g. enzymes, membrane receptor proteins, nucleic acids, etc.). Photolysis of the complex generates the high-energy carbene species that inserts into C-H or X-H (X = a hetero atom) bonds in the receptor molecule readily at ambient temperature. In the absence of a facile insertion reaction, the resultant unquenched carbene may undergo Wolff rearrangement, thereby wasting a percentage of the reactive species for photoaffinity labeling.[11] The structures of a number of such biologically active molecules are shown in (**2**)-(**9**); these molecules are prepared typically by the reaction of reagent (**1**) with the corresponding alcohols in moderate to good yields.[10]

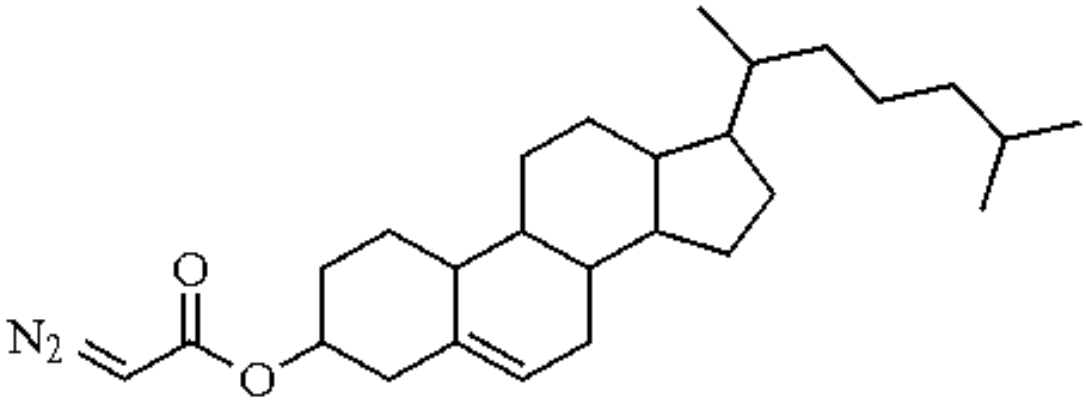

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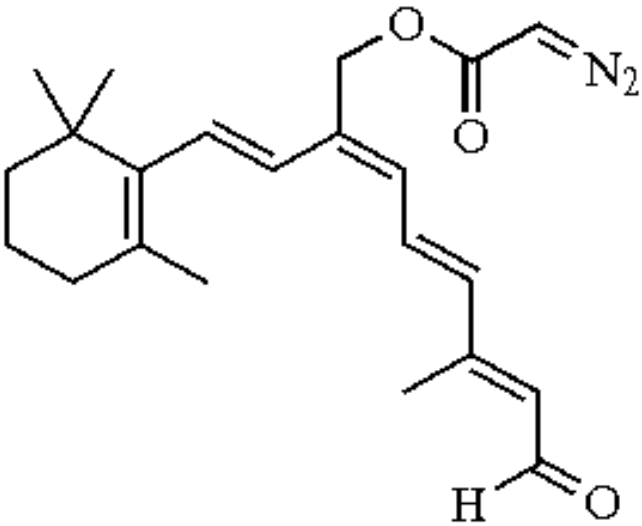

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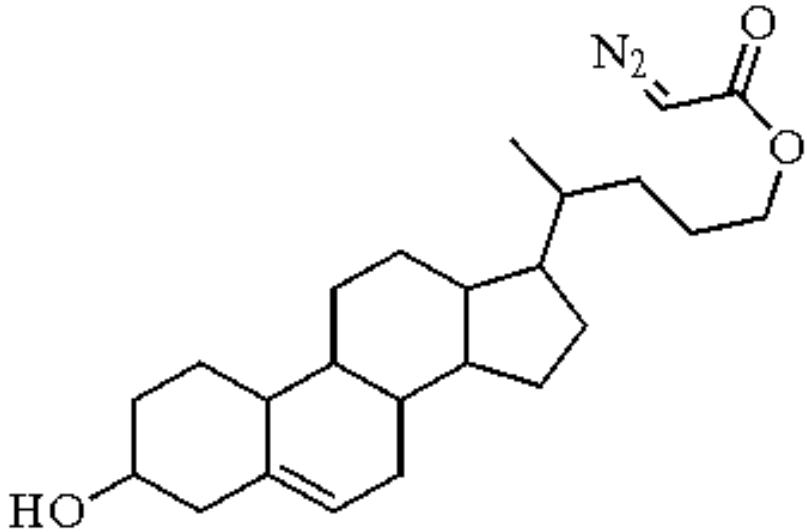

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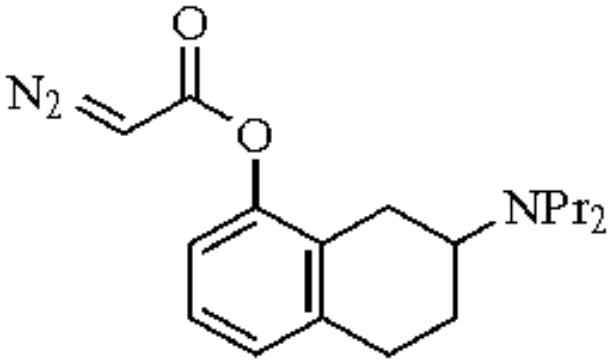

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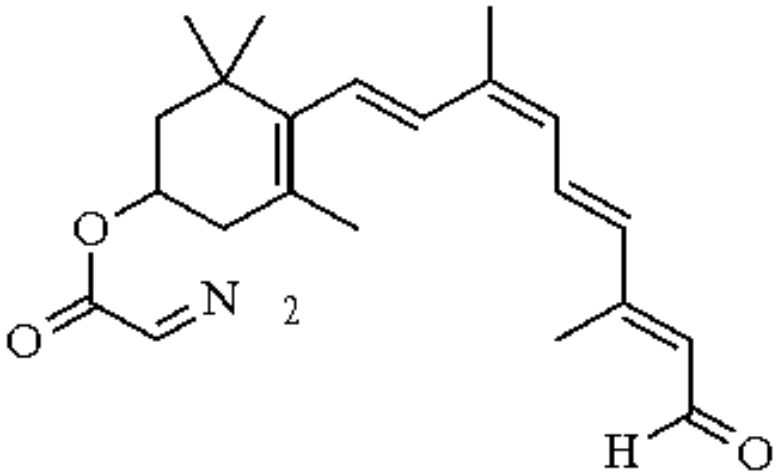

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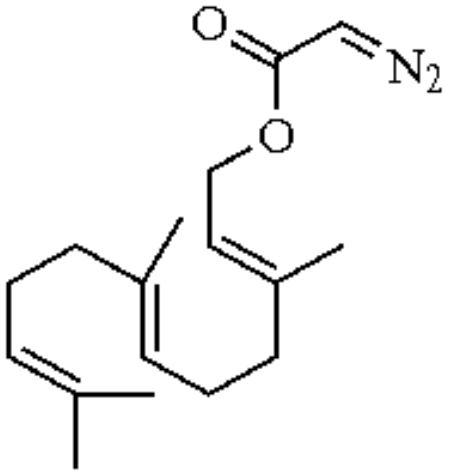

(7)

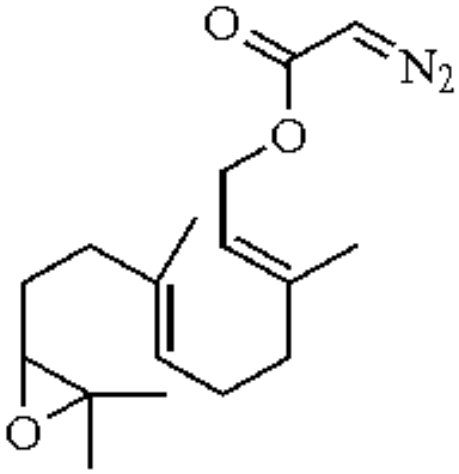

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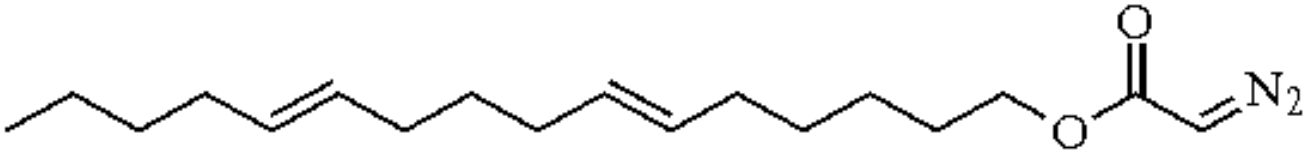

(9)

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Guanidine[1]

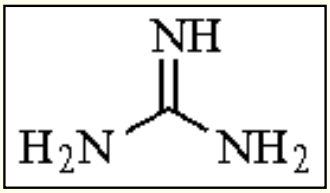

[113-00-8] · CH_5N_3 · Guanidine · (MW 59.09) (acetate)

[593-87-3] · $C_3H_9N_3O_2$ · Guanidine Acetate · (MW 119.15) (carbonate)

[593-85-1] · $C_3H_{12}N_6O_3$ · Guanidine Carbonate · (MW 180.21) (hydrochloride)

[50-01-1] · CH_6ClN_3 · Guanidine Hydrochloride · (MW 95.55) (nitrate)

[506-93-4] · $CH_6N_4O_3$ · Guanidine Nitrate · (MW 122.11) (sulfate)

[1184-68-5] · $C_2H_{12}N_6O_4S$ · Guanidine Sulfate · (MW 216.27) (thiocyanate)

[593-84-0] · $C_2H_6N_4S$ · Guanidine Thiocyanate · (MW 118.19)

(synthesis of heterocycles;[2] selective deacetylating agent;[3] synthesis of primary amines[4])

Physical Data: mp 48-49 °C; pK_a 13.6.

Solubility: free base readily sol alcohols, water; guanidinium salts of strong acids, e.g. HCl or HNO_3, sol water, DMF, alcohol; guanidinium carbonate water sol but virtually insol alcohol; guanidine acetate sl sol ether, while guanidine nitrate moderately sol acetone; guanidinium salts, in general, insol aliphatic or aromatic hydrocarbons.

Form Supplied in: commercially available salts include the acetate, carbonate, hydrochloride, nitrate, sulfate, and thiocyanate.

Preparative Methods: substituted guanidines can be prepared by several methods. The reaction of an *S*-alkylisothiourea with an amine is one of the oldest and most useful methods but it suffers from production of noxious side products, namely an alkanethiol.[7] An *O*-alkylisourea can also function in a similar manner,[8] although these reagents, generally, are not as reactive as the *S*-alkylisothioureas. Direct oxidation of ***Thiourea*** and substituted thioureas to sulfonic acids prior to reaction with amines avoids the problems of thiol production. The intermediate sulfonic acids are at least as reactive as the *S*-alkylisothioureas.[9] ***Cyanamide*** and substituted cyanamides react with amines or ammonium salts to produce guanidines.[10] This approach can be useful to prepare certain hindered guanidines, e.g. derivatives of ***t-Butylamine***.[11] Addition

of amines or ammonia to a disubstituted carbodiimide yields guanidines, but this method is limited by the availability of the carbodiimide.[11] Reaction of amines with either 1-guanyl-3,5-dimethylpyrazole nitrate[10] or 1-guanylpyrazole hydrochloride[12] affords good yields of substituted guanidines.

Handling, Storage, and Precautions: the free base is very hygroscopic and readily absorbs CO_2 from the air. It is liberated from a salt and used in situ. Hydrolysis occurs slowly at room temperature but more rapidly at elevated temperatures or in the presence of alkali to yield urea, then CO_2 and NH_3. Guanidinium salts of strong acids are stable to boiling water. Toxic fumes of NO_x are given off when guanidine is heated to decomposition. Use in a fume hood. Guanidine hydrochloride liberates toxic fumes of HCl and NO_x when heated to decomposition.[5] Guanidine nitrate is both a powerful oxidant and high explosive; *a warning cautioning against its preparation has been published.*[6]

Heterocycle Synthesis: Five-Membered Rings.

Synthesis of five-membered heterocycles proceeds well from guanidine and various bis-electrophiles. ***Glyoxal*** dihydrate condenses with monosubstituted guanidinium salts in aqueous solution to yield a mixture of *cis*/*trans* 1:1 adducts identified as 2-amino-4,5-dihydro-4,5-dihydroxy-1-substituted imidazolium salts.[13] Similarly, 1,1-disubstituted guanidinium salts react with 1-phenyl-1,2-propanedione in methanol to afford 2-(disubstituted amino)-4-hydroxy-4-methyl-4*H*-imidazoles, from which the corresponding imidazoles are available via catalytic hydrogenolysis.[14] A series of 2-amino-4-arylimidazoles has been prepared from cyclization of guanidine with an acetophenone using bromine as a condensing agent. Under these reaction conditions, the in situ generated phenacyl bromide reacts rapidly with guanidine to yield the product (eq 1).[15] When benzil is condensed with guanidine carbonate in ethanolic KOH, a good yield of 5,5-diphenyl-2-iminohydantoin is obtained. When 1-methylguanidine was used, this reaction afforded a 2.2:1 mixture of 5,5-diphenyl-2-methyliminohydantoin and 3-methyl-5,5-diphenyl-2-iminohydantoin (eq 2).[16]

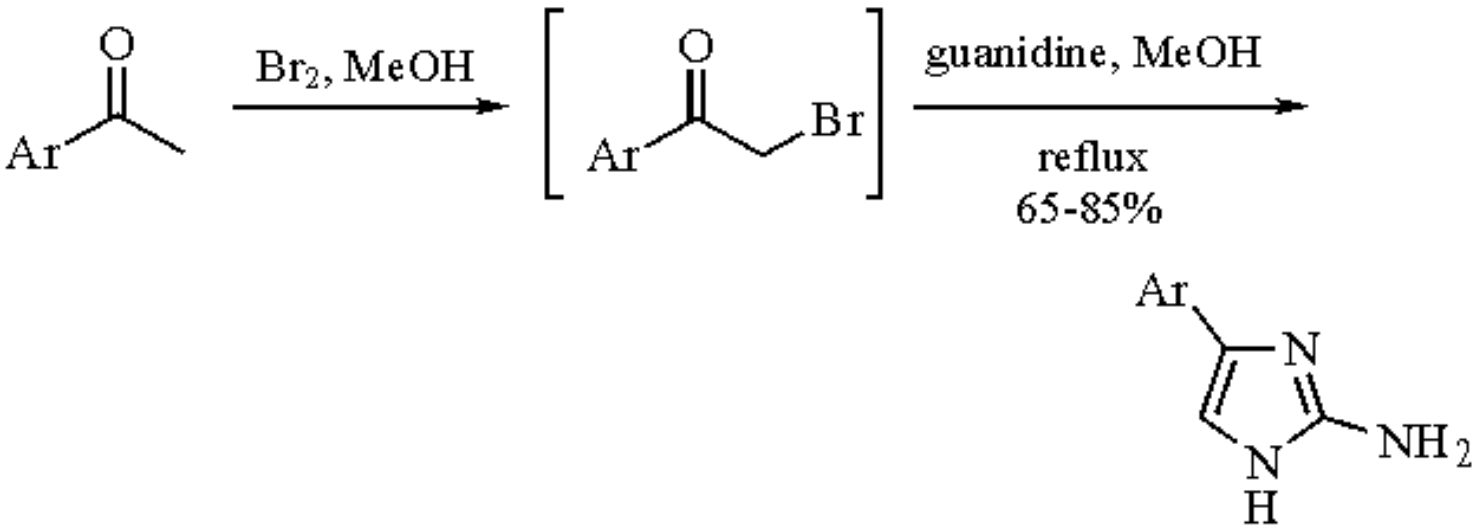

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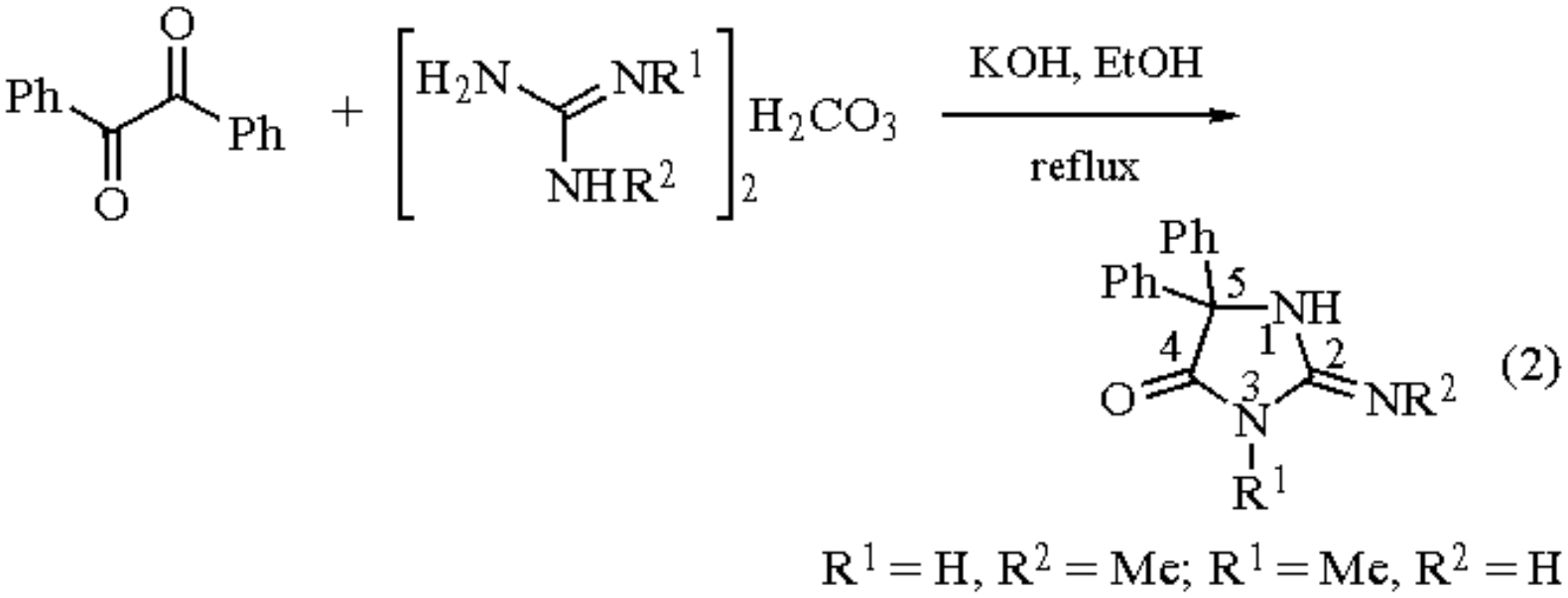

Guanidine ring-opening of 1-methylcarbamoylisatin afforded an α-keto acylguanidine which cyclized under the reaction conditions to produce a 3:2 mixture of the disubstituted quinazolin-2-one and the spirohydantoin, respectively (eq 3).[17]

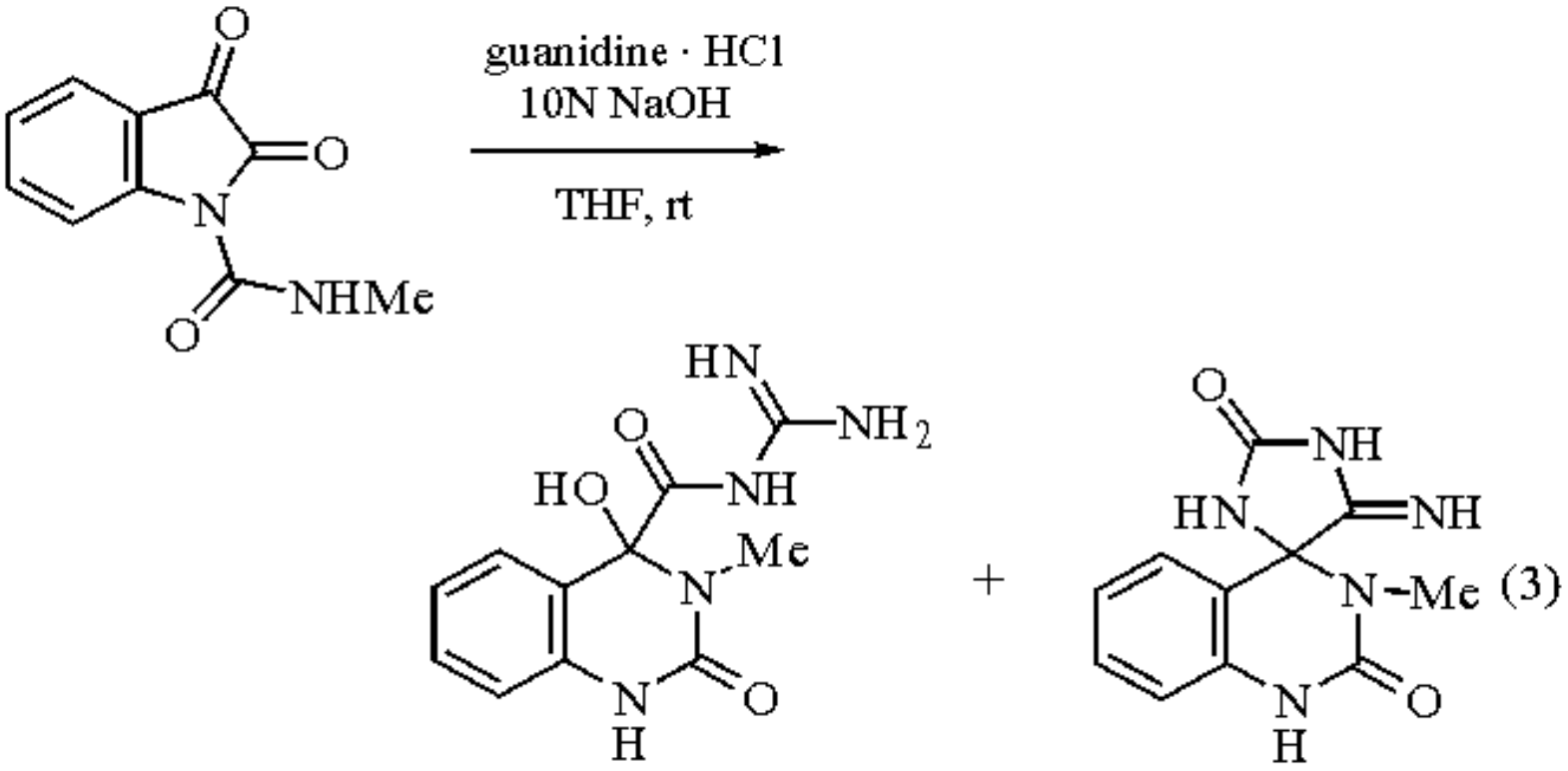

When 2,2-disubstituted propionitriles were cyclized with guanidine in DMF, a series of 5,5-disubstituted imidazolidine-2,4-diimines, including spiro analogs, were obtained.[18] ***Diethyl Oxomalonate*** and guanidine in ethanol give 2-amino-5-ethoxycarbonyl-5-hydroxy-4*H*-imidazolin-4-one in good yield (eq 4).[19] Use of isopropylguanidine affords the corresponding 2-isopropylamino derivative. L-Dehydroascorbic acid undergoes similar reactions. In this case the initially isolated products were refluxed in ethanol to effect dehydration as well.

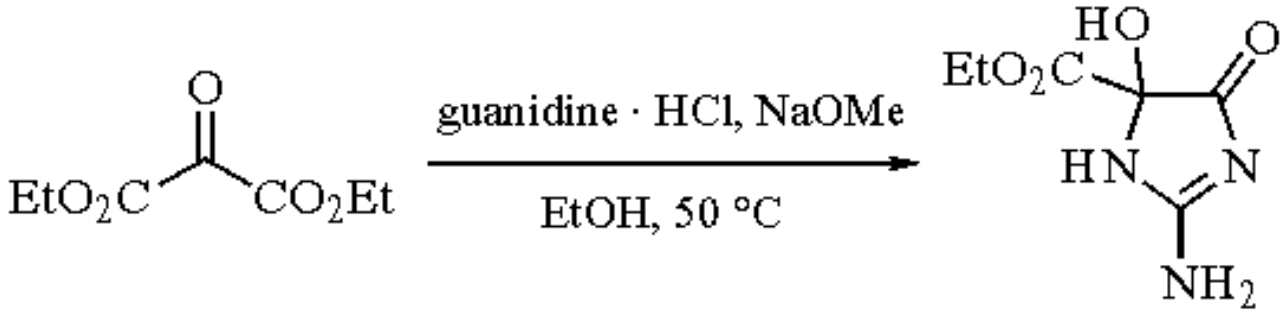

(4)

Heterocycle Synthesis: Six-Membered Rings.

Cyclization of guanidine with 1,3-bis-electrophiles is one of the oldest and most common methods available for the preparation of 2-aminopyrimidines.[1,2] Isocytosine (**1**) is readily prepared from reaction of guanidine sulfate and formylacetic acid, generated from malic acid under the reaction conditions (eq 5).[20] It can also be prepared by nucleophilic addition of guanidine to C-6 of 1,3-dimethyluracil, with subsequent ring cleavage and cyclization with loss of 1,3-dimethylurea.[21] The cyclization of guanidine with 1,3-diketones, leading to 2-amino-4,6-dialkyl substituted pyrimidines, is pH dependent with optimum conditions found to be pH 9-10.[22] Conjugate addition of guanidine to 1,3-bis(heteroaryl)-2-propenones followed by cyclization affords 2-amino-4,6-bis(heteroaryl)pyrimidines in good yields.[23]

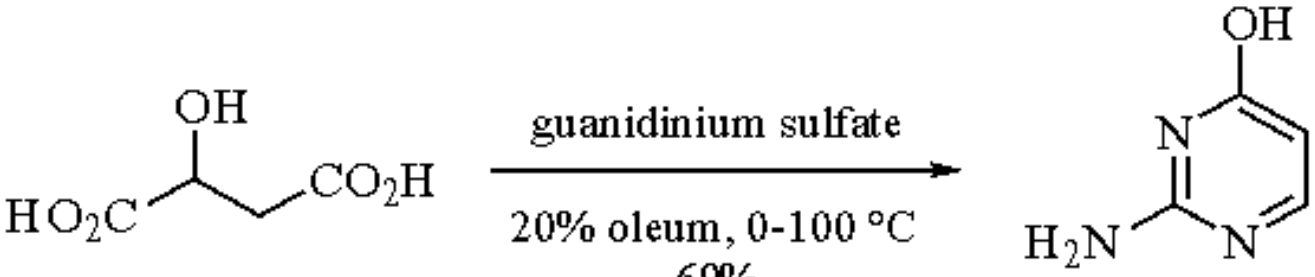

(1)

(5)

Condensation of cyanoacetic esters[24] or alkoxymethylene nitriles[25] with guanidine leads to 2,4-diaminopyrimidines in high yield. Cyclization of guanidine with ethyl acetamidocyanoacetate yields the expected 5-acetamidopyrimidine in high yield.[26] Extension of this methodology to reaction with diethyl ureidomalonate or 5-ethoxycarbonylhydantoin produced the 5-ureidopyrimidine analogs. The ureidomalonates did not react with ***O-Methylisourea*** or *S*-alkylisothioureas (see ***S-Methylisothiourea***).[27] The pyrimidines obtained from reaction of ***Ethyl Ethoxymethylenecyanoacetate*** with guanidine were greatly influenced by the stoichiometry of the reaction, with a fourfold excess of guanidine leading almost exclusively to (**2**) (eq 6).[28]

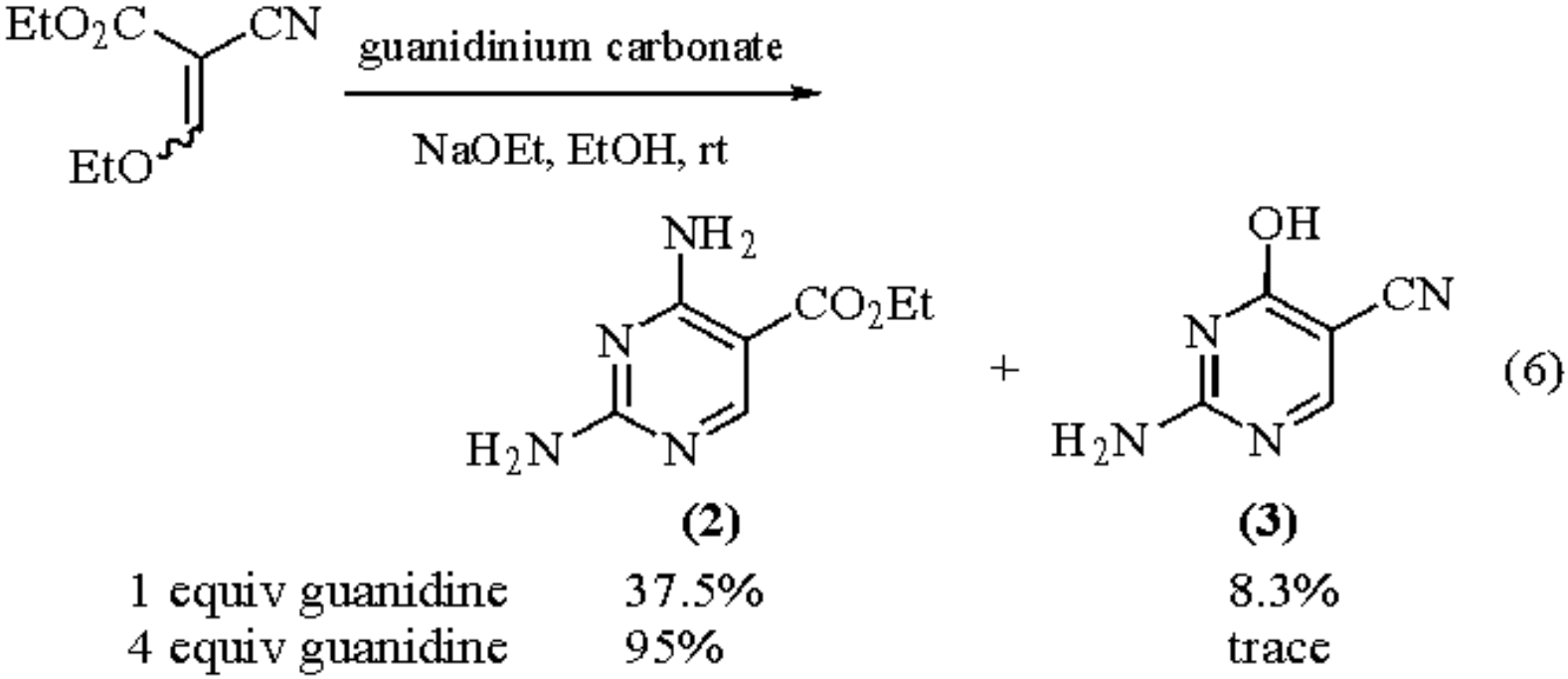

A simple, one-pot synthesis of 2-substituted 5-vinylpyrimidines involves cyclization of 1-vinylpiperidylacrolein (**4**) with amidines, including guanidine and 1,1-dimethylguanidine (eq 7).[29] Cyclization of acrylates and methacrylates with guanidine in *t*-butyl or isopropyl alcohol at room temperature provides a high-yield synthesis of the rather inaccessible dihydropyrimidines (eq 8).[30] With guanidine and methylguanidine the reaction proceeds in a few hours, whereas both 1,1- and 1,2-dimethylguanidine require 48 h and 1,2,3-trimethylguanidine is unreactive. No reaction was observed using methyl 3,3-dimethylacrylate. [$^{15}N_3$]Guanidine has been prepared and used to prove the mechanism for cyclization of heterocyclic *o*-aminonitriles to fused 2,4-diaminopyrimidines.[31]

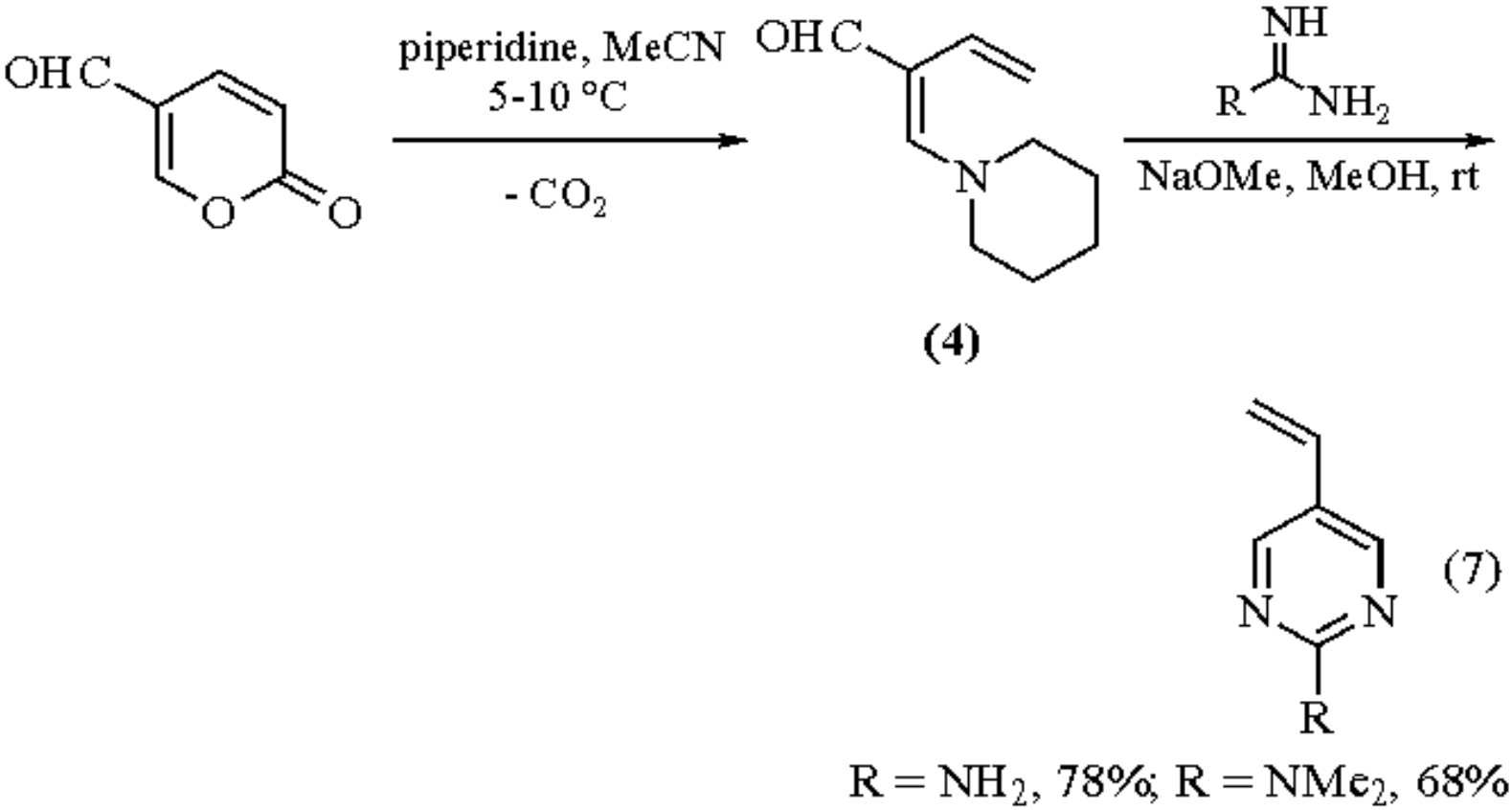

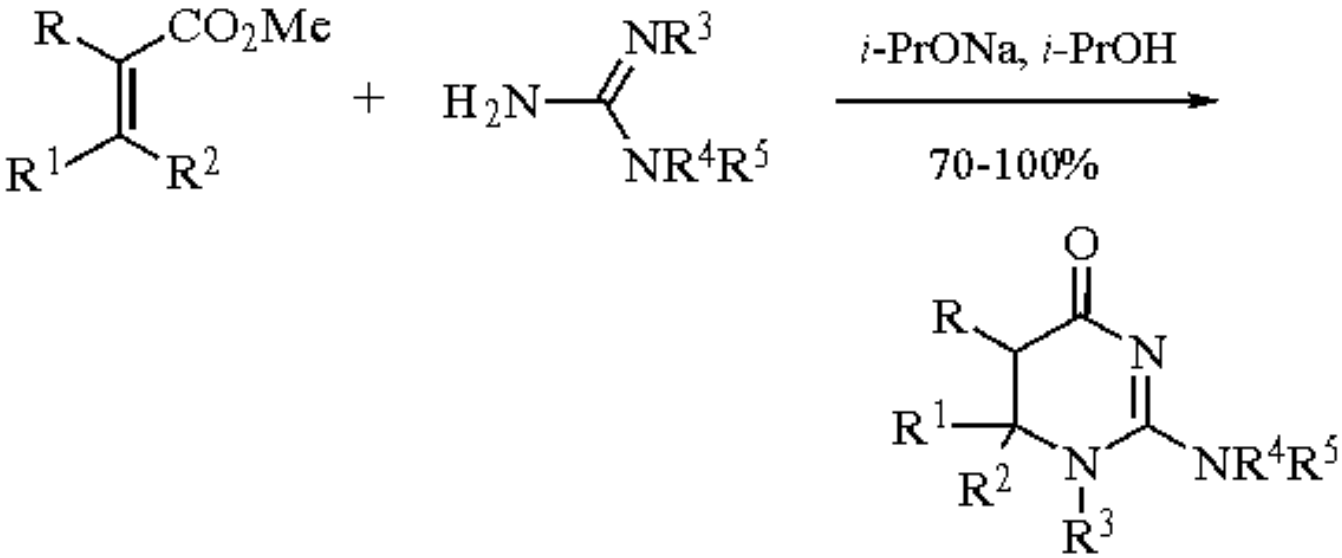

(8)

R = H or Me; $R^1 = R^2 = H$; R^3 = H, Me or Et; R^4, R^5 = H or Me

A general synthesis of 2-amino- and 2-substituted amino-1,3,5-triazines involves cyclization of the appropriate guanidine sulfate with ***Tris(formylamino)methane***, a precursor to *N*-formylformamidine, the actual species involved in the reaction (eq 9).[32] Best results were obtained using a 1:2 ratio of guanidine to tris(formamido)methane. To prepare 2,4-diamino-1,3,5-triazine, guanidine has been treated with *N*,*N*-dimethylformamide dimethyl acetal (see ***N,N-Dimethylformamide Diethyl Acetal***).[33] This method could be used to prepare 2,4-bis(alkyl)- and -(aryl)amino-1,3,5-triazines from the corresponding monosubstituted guanidine, although mixtures of products and modest yields were reported in some cases. Guanidine reacts with an azirineacrylate in DMSO via addition to C-2 followed by C-C bond cleavage to yield, ultimately, a trisubstituted 1,3,5-triazine (for R = H) after air oxidation (eq 10).[34]

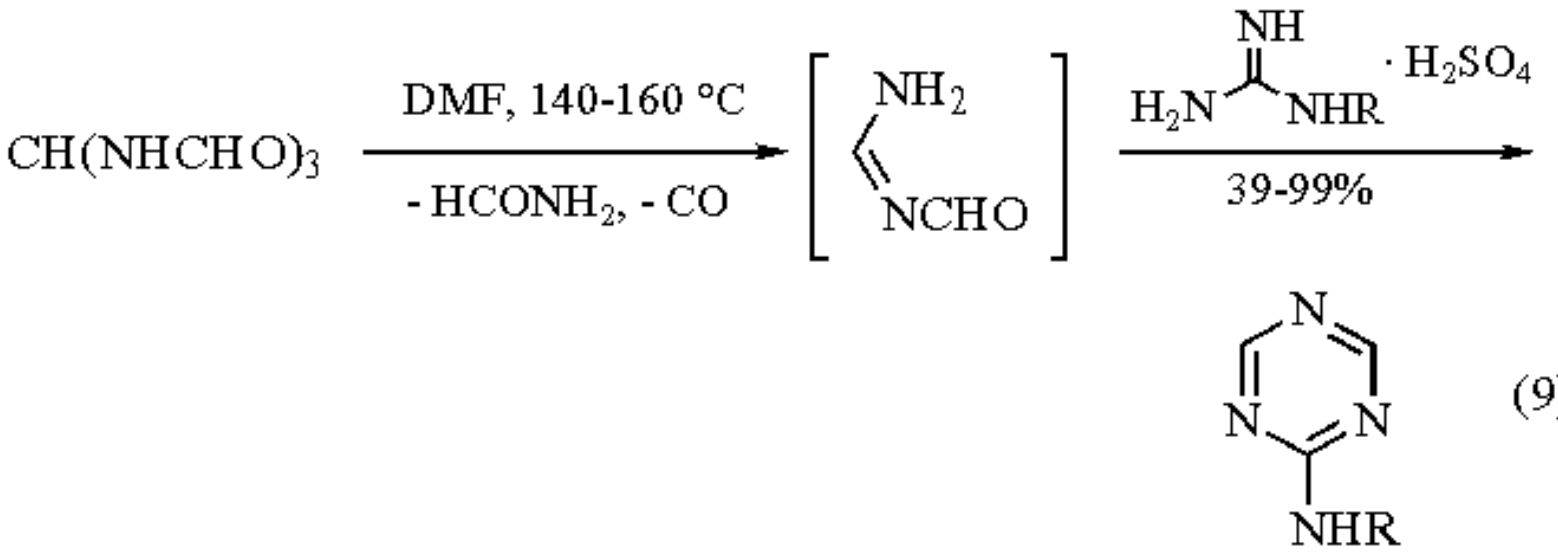

(9)

R = H, alkyl, aryl

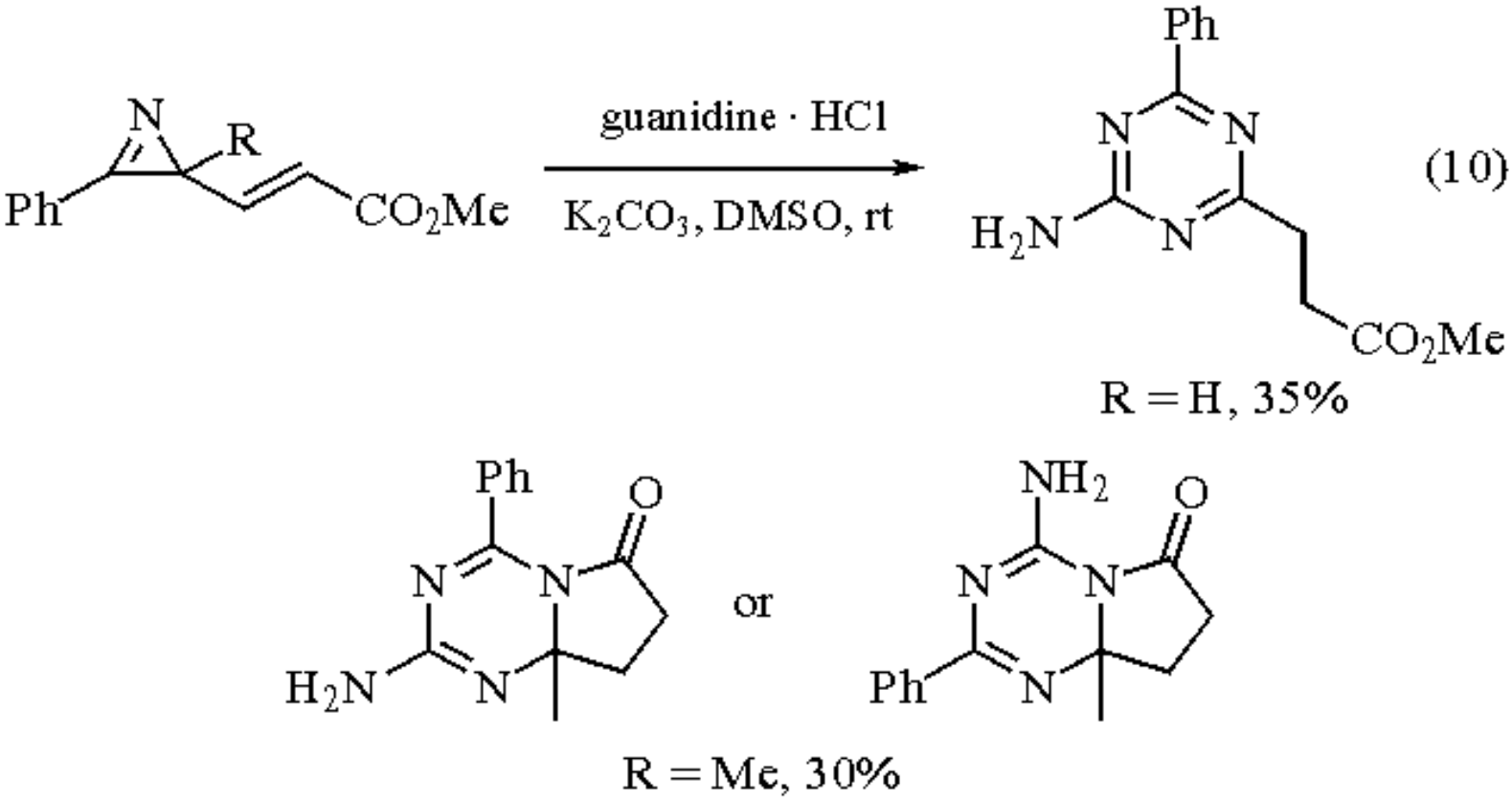

For R = Me, with oxidation no longer possible a bicyclic lactam was isolated, although it was not possible to distinguish between the regioisomers. In the presence of excess NaOMe, guanidine reacts with some benzaldehydes to produce 2,4-diamino-6-aryl-1,3,5-triazines.[35] These have been postulated to arise via an intramolecular oxidation-reduction of the initially formed bis-aldimine. Deuterium labeling studies and isolation of Cannizzaro reaction products support this hypothesis. Reaction of guanidine carbonate with a pyridinesulfonyl chloride gave a sulfonylguanidine, which was cyclized to 3-amino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**5**) (eq 11).[36] The 3-monoalkylamino analogs, evaluated as potassium channel openers, were prepared by amine displacement of the 3-methylmercapto derivative, presumably to avoid regioisomer formation expected using a monosubstituted guanidine.

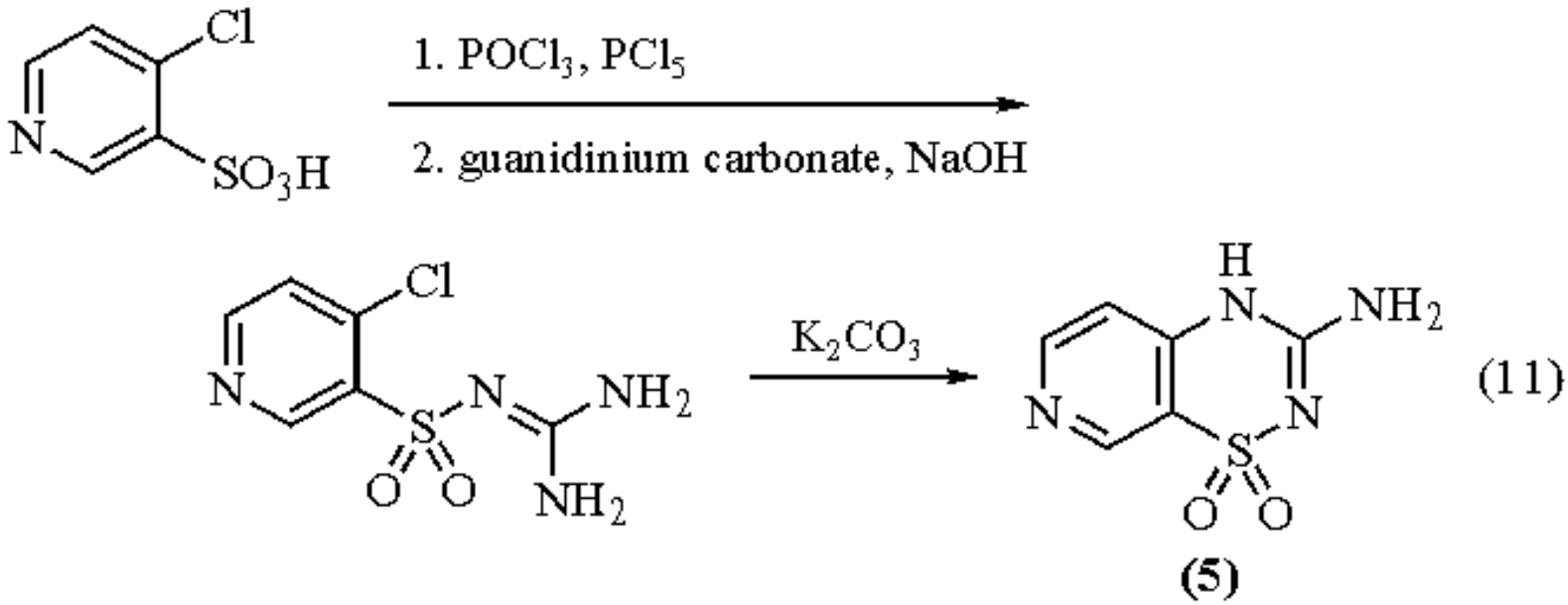

A key step in the synthesis of ptilocaulin (**7**), an antitumor antibiotic isolated from a marine sponge, is conjugate addition of guanidine to enone (**6**) with subsequent cyclodehydration (eq 12).[37] In an alternative approach, the tricyclic guanidine was prepared by guanylation of an amino ketone and subsequent cyclization.[38]

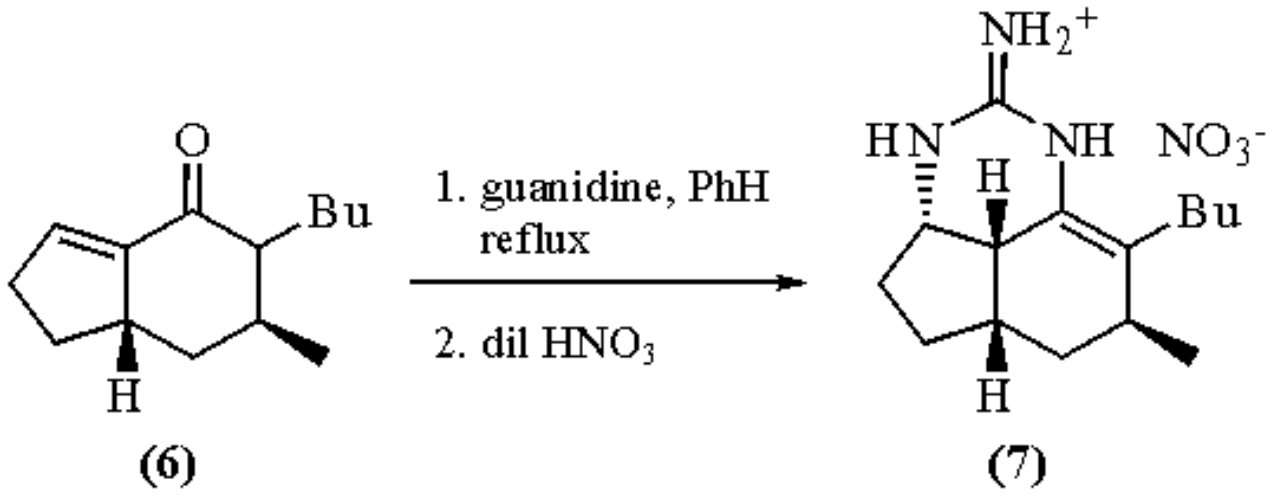

(12)

Selective Deacetylating Agent.

Guanidine selectively deacetylates phenolic acetates in the presence of benzylic acetates.[3] Acetamides, methyl esters, benzoates, and pivalates are stable to the reaction conditions. Peracetylated carbohydrates can be instantaneously and quantitatively deacetylated using a 1:1 molar ratio of carbohydrate to guanidine. The stereochemical integrity of the products was not described.

Synthesis of Primary Amines.

Treatment of primary bromides, allylic and benzylic halides with guanidine followed by base affords the corresponding primary amine.[4]

Miscellaneous.

Acylation of guanidine by α-amino esters produces amino acid acylguanidines which were explored as intermediates in peptide bond formation.[39] Guanidine has been used to effect both ester hydrolysis and epoxide ring opening in a single step.[40] Direct phosphorylation of guanidine can be accomplished in good yield using diisopropyl phosphite in CCl_4 in the presence of NaOH.[41] The reaction also works well with *S*-alkylisothioureas.

Related Reagents.

Aminoiminomethanesulfonic Acid; ***Formamidine Acetate***; ***S-Methylisothiourea***; ***O-Methylisourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

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Hexabutyldistannane[1]

Bu_3Sn-$SnBu_3$

[813-19-4] · $C_{24}H_{54}Sn_2$ · Hexabutyldistannane · (MW 580.20)

(source of tributylstannyl radicals; used in palladium-catalyzed tin-carbon bond formation; used for deoxygenation and desulfurization reactions)

Alternate Name: hexabutylditin.

Physical Data: bp 147-150 °C/0.2 mmHg, 198 °C/10 mmHg; *d* 1.1520 g cm^{-3}; *n*20D = 1.5120.

Solubility: sol most organic solvents.

Form Supplied in: colorless oil; readily available and not expensive.

Analysis of Reagent Purity: ^{119}Sn NMR recommended (δ -83 ppm, $^1J(^{119}Sn\text{-}^{119}Sn)$ 2748 Hz).[9]

Preparative Methods: various methods are available. The classical method uses ***Tri-n-butylstannane*** and either ***Bis(tri-n-butyltin) Oxide*** (0.5 equiv), tributyldiethylaminotin, or ***Tri-n-butyl(methoxy)stannane*** in yields of 90-98%.[2] Since hexabutyldistannoxane is commercially available and not air-sensitive, its use is preferable. A second method involving the stannoxane involves its treatment with metals (Mg, Na, K, Ti/K); the yields lie between 70 and 80%.[3]

It can also be obtained from ***Tri-n-butylchlorostannane*** and either lithium, sodium,[4] or magnesium,[5] from tributyltin chloride and ***Tri-n-butylstannyllithium***[7] (the latter from tributyltin hydride and ***Lithium Diisopropylamide***[6]), or by catalytic elimination of hydrogen from tributyltin hydride. This can be effected either by various bases[8a] or by palladium catalysts such as ***Tetrakis(triphenylphosphine)palladium(0)***.[8b]

Purification: reversed-phase flash chromatography using C-18.[10]

Handling, Storage, and Precautions: must be stored in the absence of oxygen, moisture, and light (preferably under argon). Highly toxic. Use in a fume hood.

Introduction.

General aspects of the preparation and chemistry of hexaalkyldistannanes are reviewed in the Houben-Weyl volume on organotin compounds (literature coverage up to 1977).[1]

The chemistry of hexabutyldistannane is determined by the weakness of the tin-tin bond and dominated by three aspects:

- 1)it dissociates on heating to give tributylstannyl radicals, which are of considerable importance in organic synthetic transformations;
- 2)under the influence of palladium catalysts it can be used for tin-carbon bond formation in the sense of either substitution reactions or addition reactions to multiply bonded systems;
- 3)it can readily take up oxygen or sulfur and can thus be used for deoxygenation and desulfurization reactions.

It can also be used for the preparation of other organometallic reagents via transmetalation.

Use as a Source of Tributylstannyl Radicals.

Thermolysis or photolysis of hexabutyldistannane generates tributylstannyl radicals; these can in turn be used to generate other synthetically useful radicals, for example carbon radicals from reactions with organic halides or sulfides.[11] This reaction has the advantage over generation of stannyl radicals from triorganotin hydrides in that the latter can act as powerful hydrogen donors and thus strongly influence subsequent reactions.

The distannane can also be used in less than stoichiometric amounts, the reactants being irradiated in the presence of a small amount of the distannane (generally 0.1-0.3 equiv). This so-called atom transfer method has been developed by Curran and also applied by other authors. Examples include the radical cyclization of α-iodo ketones (or esters with a suitably placed double bond) (eq 1),[12] annulation reactions of iodomalonates (eq 2),[13] cyclizations of unsaturated α-iodocarbonyls,[14] and radical cyclization of α-fluoro-α-iodo and α-iodo esters and amides (eq 3).[15] A novel cyclization of an iodoepoxide to a cyclopentanol possessing the hydrindane skeleton has also been reported (eq 4).[16] This type of reaction may be subject to a temperature effect; thus the cyclization of allylic α-iodo esters and amines proceeds much more efficiently at 80 °C than at 25 °C.[17]

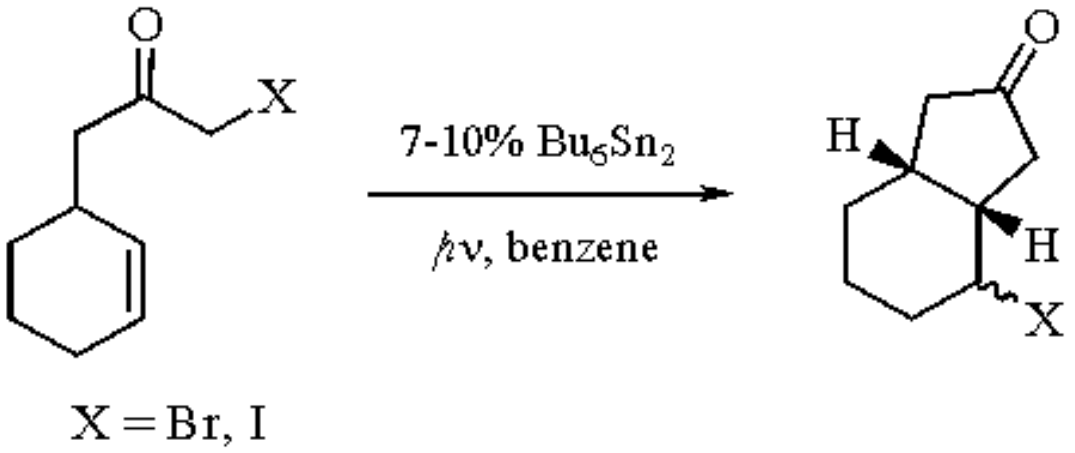

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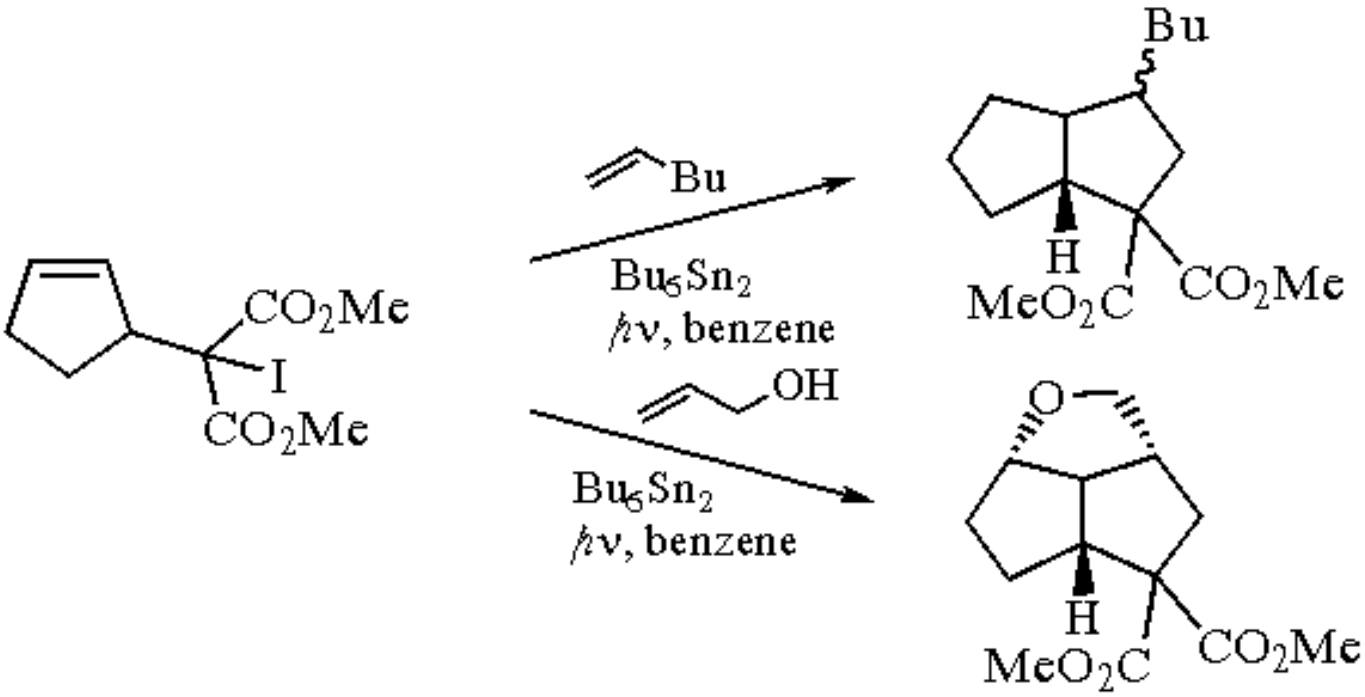

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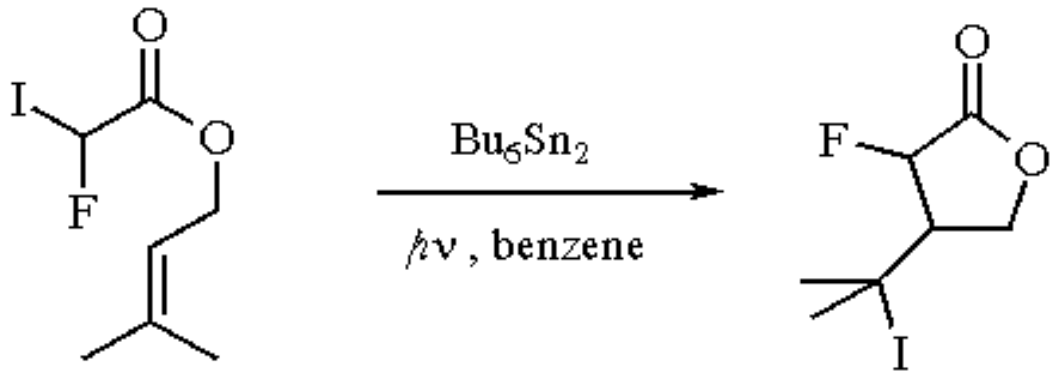

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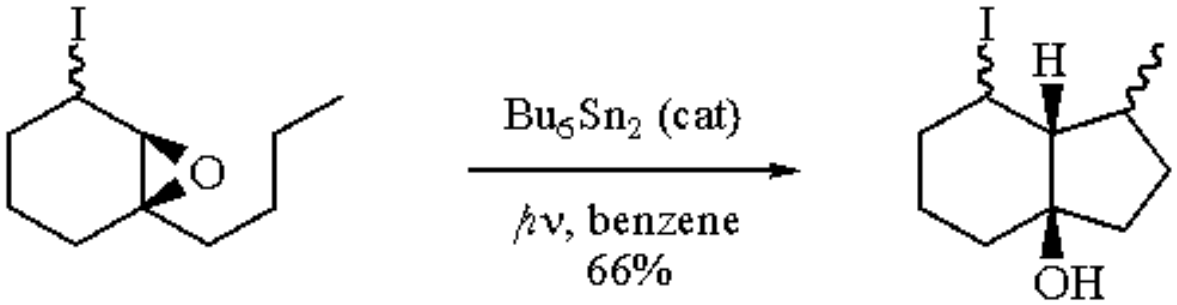

(4)

An in situ generation of nitrile oxides via photolysis of hexabutyldistannane has been reported (eq 5).[18]

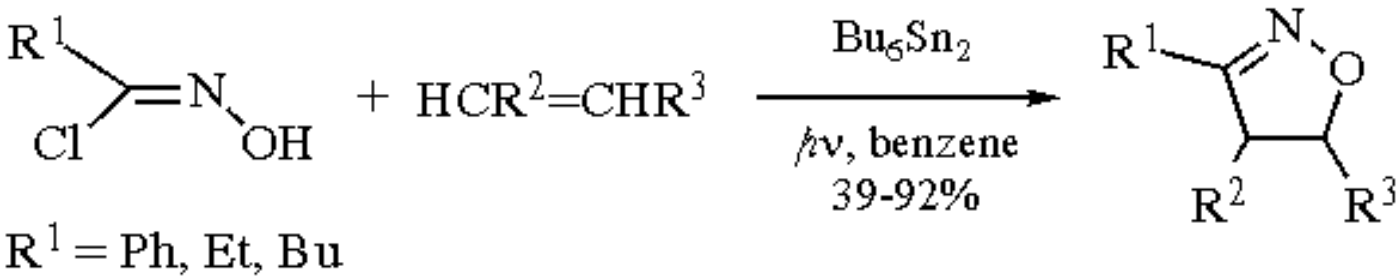

(5)

Palladium-Catalyzed Reactions.

These can be of two types, either substitution of a (generally halide) ligand by a tributylstannyl group or addition to multiple bonds. These reactions have been reviewed by Stille[19] and Mitchell.[20]

The substitution reactions provide a useful alternative to the conventional use of ***Tri-n-butylstannyllithium***, which is a very strong base. The halides used have mainly been aryl or heteroaryl halides, while ***Tetrakis(triphenylphosphine)palladium(0)***, dichlorobis(triphenylphosphine)palladium(II), and ***Bis(allyl)di-μ-chlorodipalladium***/***Tetra-n-butylammonium Fluoride*** have been employed as catalysts.

The synthesis of symmetrical biaryls has been described.[21] This principle has recently been applied in an intramolecular manner and extended to include more complex cyclization reactions. Thus as well as two (symmetrical or mixed) aryl and benzyl halide moieties, a combination of two aryl iodide moieties with a carbon-carbon double or triple bond can be used (eq 6).[22]

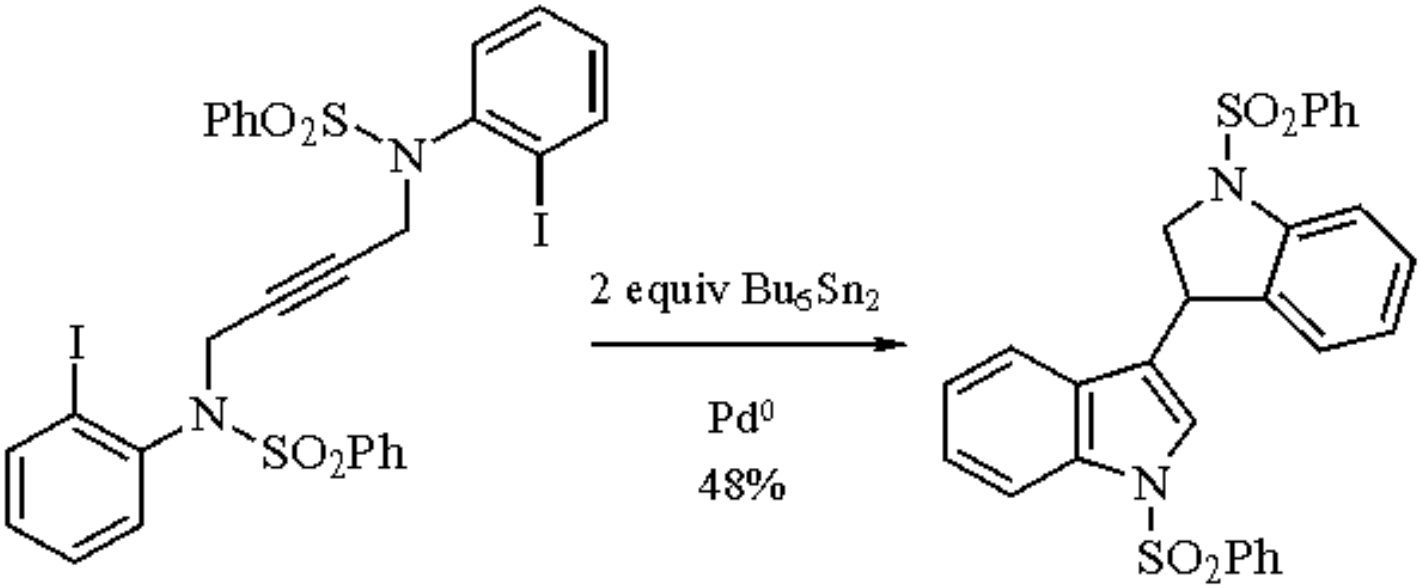

(6)

Unfortunately the reaction of Bu_6Sn_2 with acyl halides is not suitable for the preparation of tributylacylstannanes, in contrast to the corresponding reaction of ***Hexamethyldistannane***.[23]

A further interesting development is the use of three-component systems: a mixture of hexabutyldistannane, an allyl halide or carbonate, and a heteroaryl bromide leads to allylation of the heteroaromatic moiety; the catalyst used was the somewhat exotic ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***.[24] This method avoids the prior preparation of organotin reagents (eq 7).

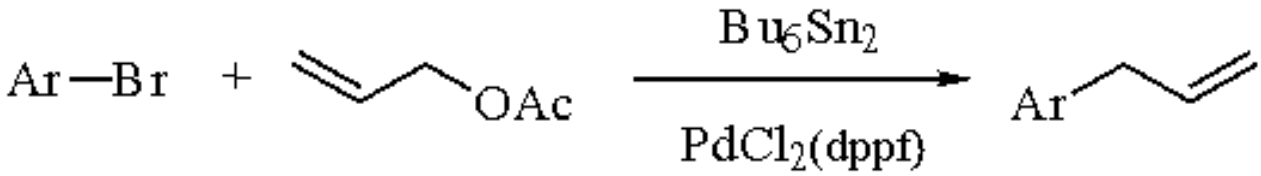

(7)

In the case of the addition reactions, hexabutyldistannane adds readily to a variety of allenes; it is often possible to

distinguish a kinetic and a thermodynamic product (eq 8).[25]

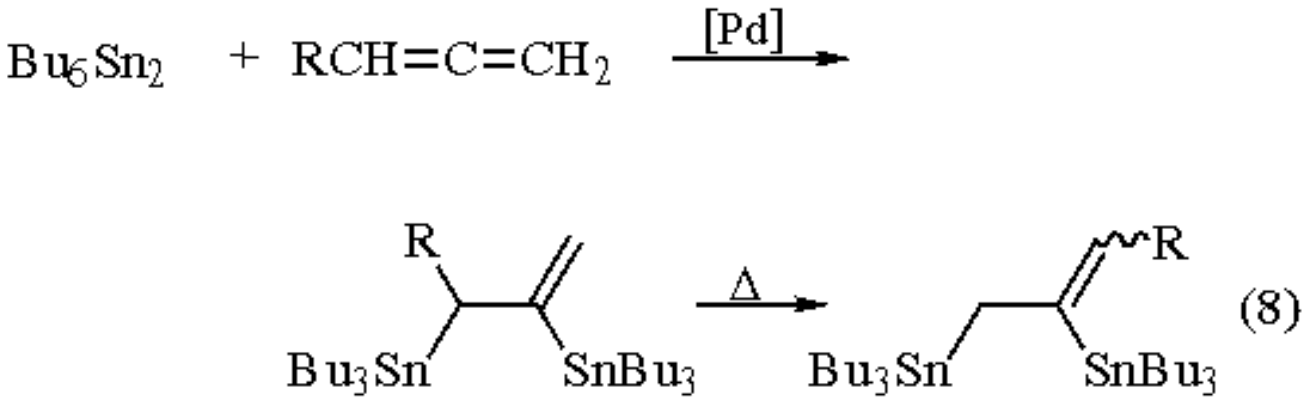

On the other hand, the addition to alkynes does not proceed in a quantitative manner at atmospheric pressure (in contrast to the behavior of hexamethyldistannane), though it can be forced to do so by the application of high pressure.[26]

Deoxygenation and Desulfurization Reactions.

The deoxygenation of amine oxides has been described,[27] as has the photo-desulfurization of 1,3-dithiole-2-thiones to give tetrathiofulvalenes.[28]

Use as a Source of Other Tributylstannylmetal Compounds.

Hexabutyldistannane can be cleaved by lithium metal[29] or a lithium alkyl (e.g. MeLi)[30] to give tributylstannyllithium. These methods cannot be recommended: Bu_3SnLi can be better obtained either in a one-step process from Bu_3SnCl and Li (via Bu_6Sn_2 which is not isolated) or from the reaction between Bu_3SnH and LDA[6] (see ***Tri-n-butylstannyllithium*** for details). Hexabutyldistannane can also serve as a source of stannylcuprates ($Bu_3SnCu(CN)Li$, $(Bu_3Sn)_2Cu(CN)Li_2$, $Bu_3Sn(R)Cu(CN)Li_2$).[31]

Use in Electron-Transfer Reactions.

It has been shown in a very recent development that Bu_6Sn_2 (and in addition Bu_4Sn) can take part in novel substitution reactions when allowed to react with pyridine derivatives.[32] Thus treatment of 4-cyanopyridine with Bu_6Sn_2 leads to a new type of *ipso* substitution accompanied by a substitution of the type observed when lepidine reacts with Bu_6Sn_2 and *t*-butyl bromide (eqs 9 and 10)

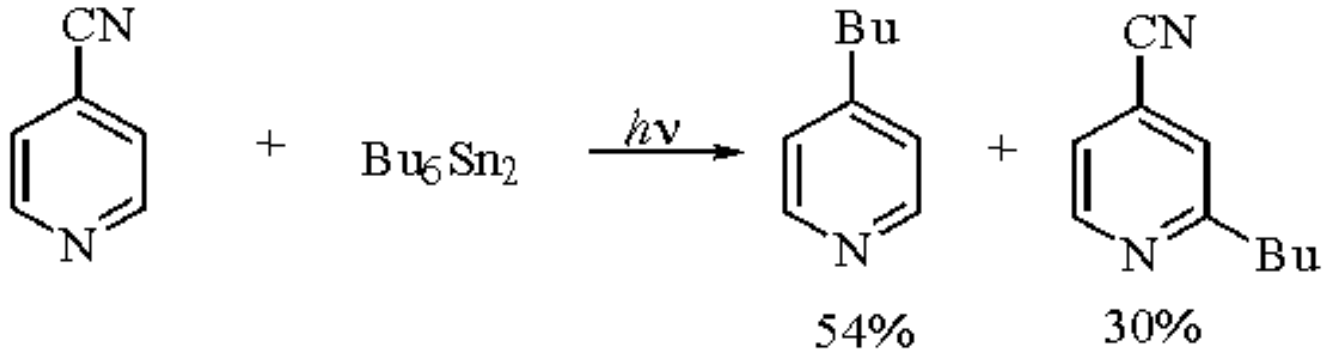

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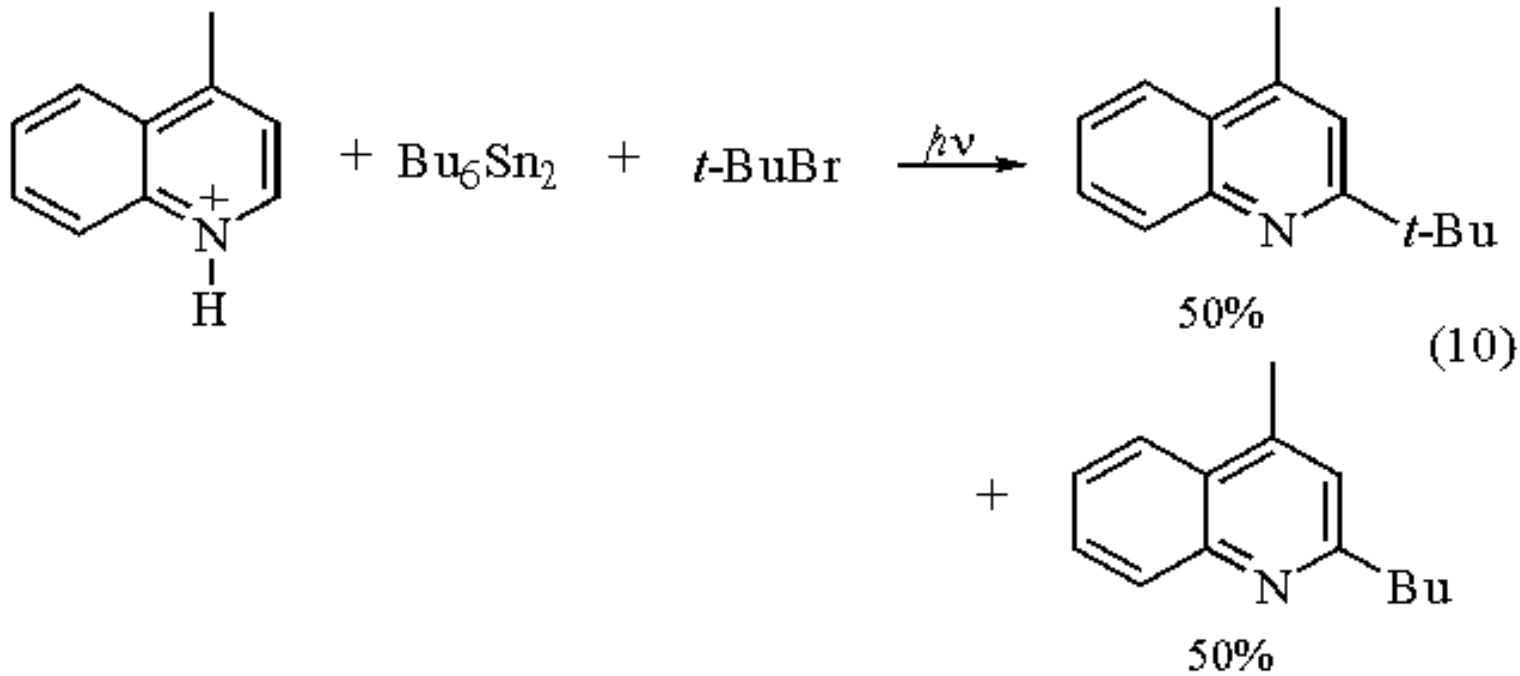

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Hexacarbonylchromium[1]

$Cr(CO)_6$

[13007-92-6] · C_6CrO_6 · Hexacarbonylchromium · (MW 220.06)

(catalyst for alkene isomerization, hydrogenation of 1,3-conjugated dienes, oxidation of allylic and benzylic positions; reagent for preparation of tricarbonyl(arene)chromium and Fischer carbene complexes)

Alternate Name: chromium hexacarbonyl.

Physical Data: sublimes at 50-80 °C; mp 154-155 °C (in sealed tube); *d* 1.77 g cm^{-3}.

Solubility: insol water, ethanol; slightly sol ether, $CHCl_3$.

Form Supplied in: white solid; widely commercially available.

Handling, Storage, and Precautions: highly volatile and must be stored and used in a well ventilated fume hood.

Oxidation.

Treatment of alkenes with ***t-Butyl Hydroperoxide*** in the presence of 0.5 equiv of $Cr(CO)_6$ or $Cr(CO)_x(MeCN)_y$ species in refluxing MeCN results in the oxidation of allylic methylene groups to give α,β-unsaturated ketones selectively in the presence of certain alcohols (eq 1).[2] Benzylic positions are also oxidized to phenyl ketone derivatives[3] under the same conditions (eq 2).

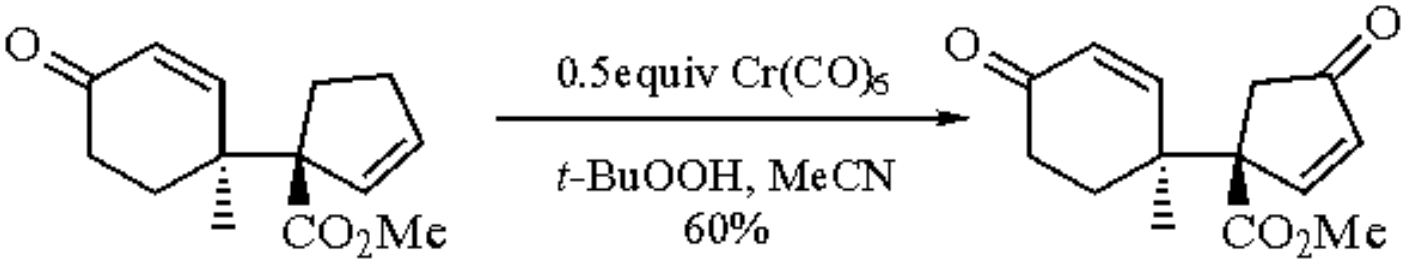

(1)

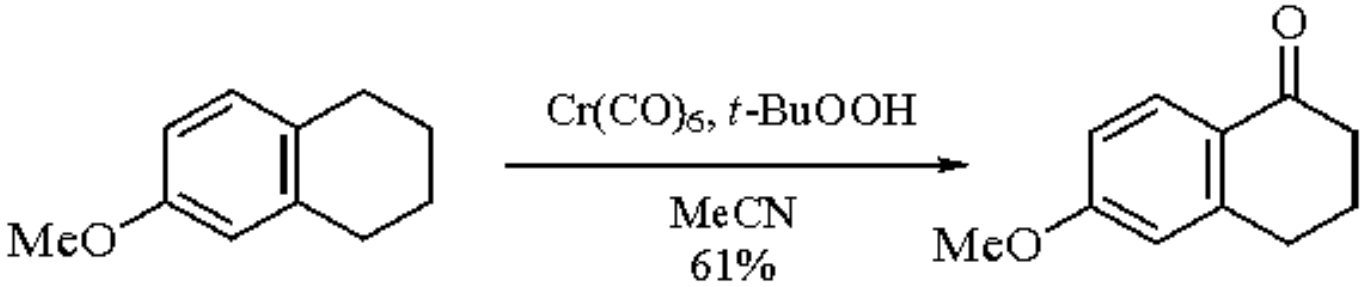

(2)

Hydrogenation and Isomerization of Dienes.

The catalytic behavior of (arene)$Cr(CO)_3$ complexes has been exploited in the homogeneous regioselective 1,4-hydrogenation of dienes to *cis*-alkenes.[4] Only 1,3-dienes that can easily achieve the less stable *s-cis* configuration to undergo this catalytic hydrogenation (eq 3). Similar catalytically active species $Cr(CO)_3H_2$(diene) (**1**) can be generated photochemically from $Cr(CO)_6$ or from kinetically thermally labile π-bonded ligated complexes (naphthalene, anthracene, MeCN) in coordinating solvents (THF, acetone, dioxane) under milder conditions (eq 4).[5] This regioselective hydrogenation of dienes can be applied to the total synthesis of complex natural products (eq 5) such as carbacyclin, cyanopcarbacyclin, and deplanchein.[6] 1,4-Hydrosilylation of dienes is also achieved to produce (*Z*)-allyltrimethylsilanes[7] under these conditions. The (arene)chromium complexes are superior catalysts for stereoselective hydrogenation of alkynes to (*Z*)-alkenes, and in addition, cisoid α,β-unsaturated enones and imines can be reduced.[8]

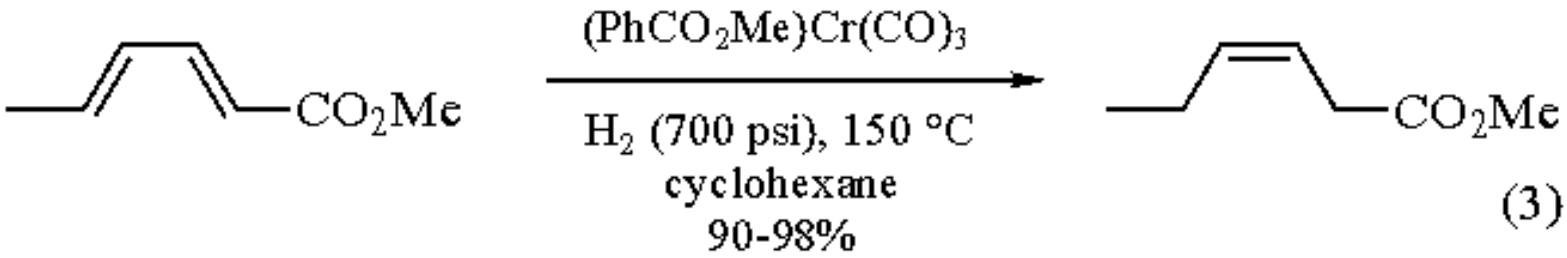

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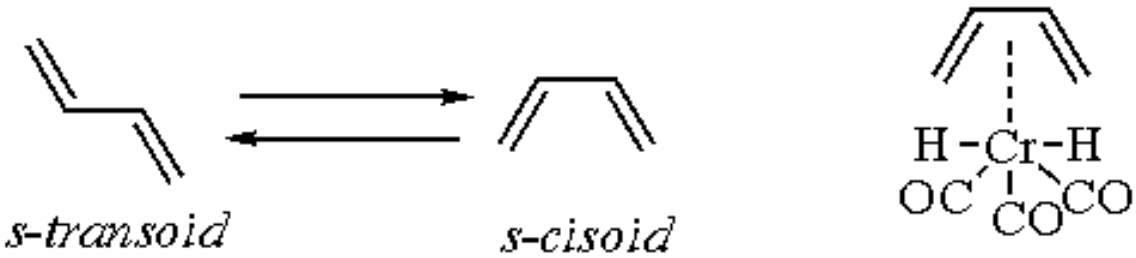

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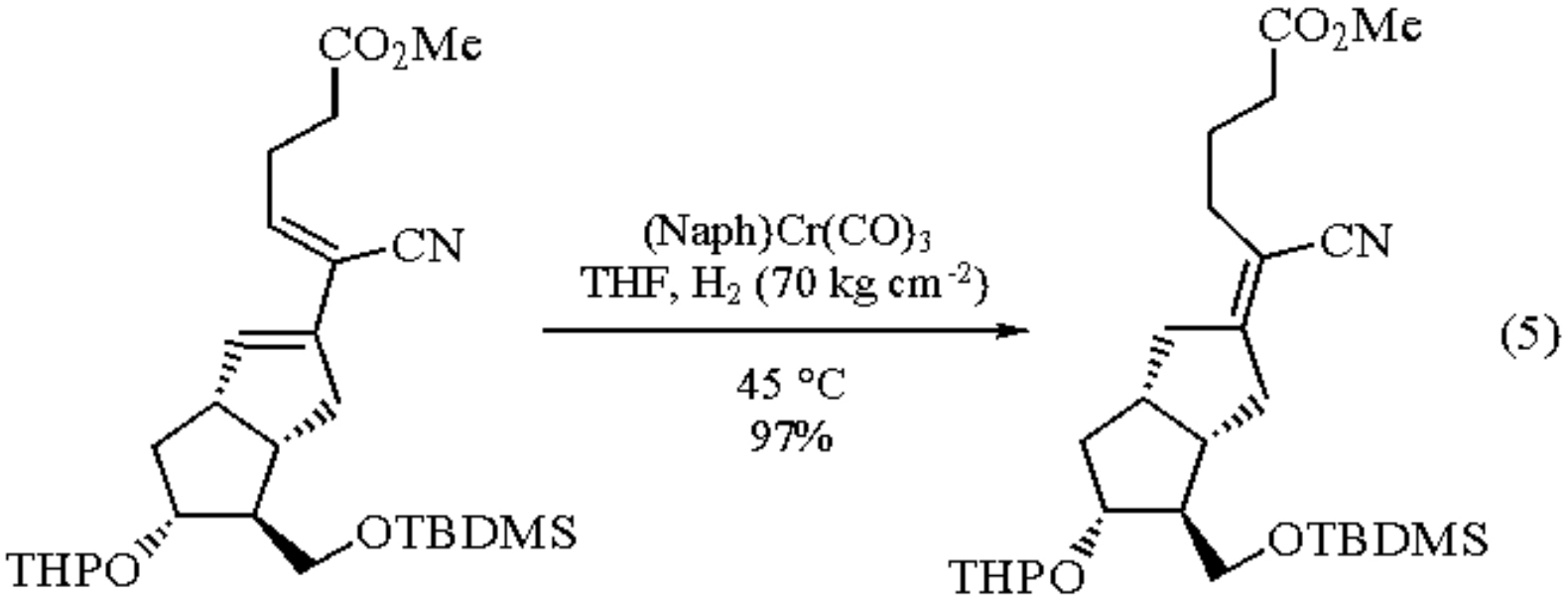

Chromium hexacarbonyl offers a highly regioselective method for the isomerization of cisoid 1,3-dienes to transoid dienes (eq 6).[9] (Naphthalene)chromium tricarbonyl catalyzes isomerization of silyloxymethylbutadiene derivatives to silyl dienol ethers in quantitative yields via a U-shaped pentadienyl intermediate (eq 7).[10]

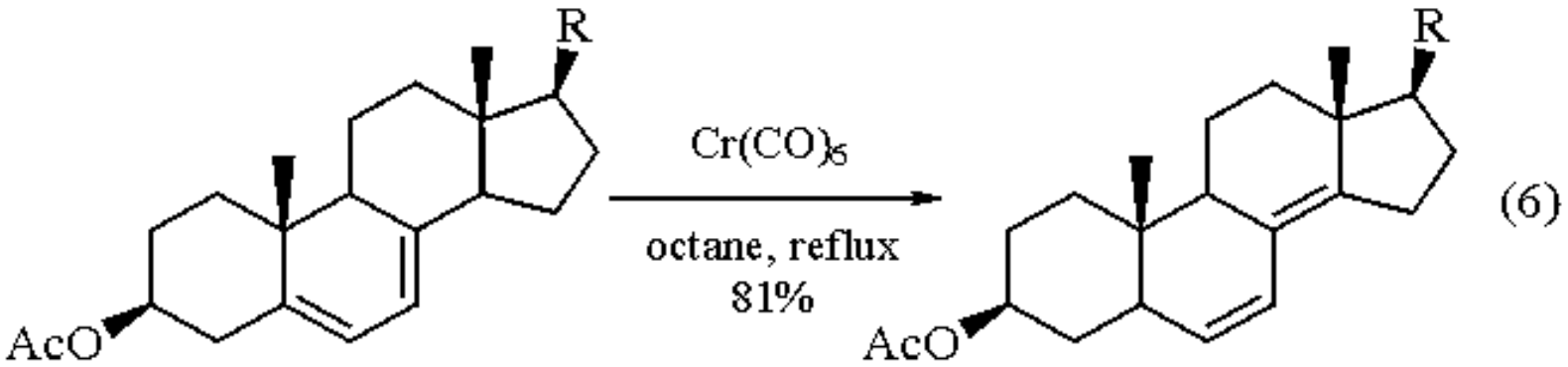

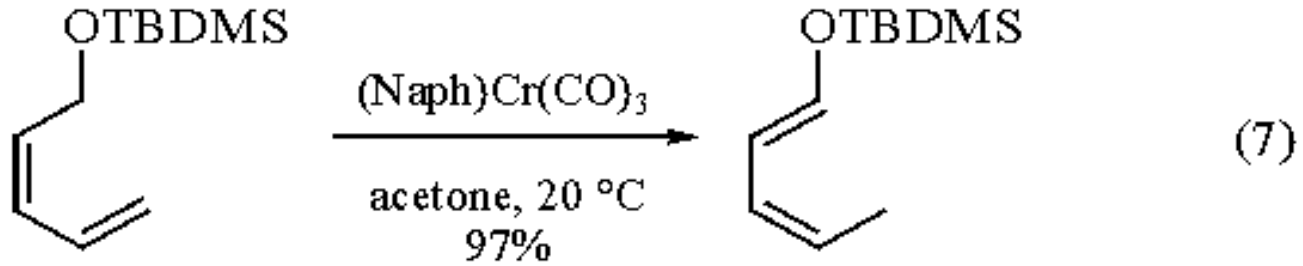

(Arene)Cr(CO)$_3$ Complexes.

Complexation of an arene ring to the chromium tricarbonyl unit is easily accomplished by simple heating with $Cr(CO)_6$ or by ligand transfer with $Cr(CO)_3L_3$.[1,11] The significant properties of (arene)chromium complexes in organic synthesis are as follows: nucleophilic substitution to arene ring; enhancement of acidity of aromatic hydrogen; enhancement of acidity of benzylic hydrogen; enhancement of solvolysis at the benzylic position; and steric hindrance of the $Cr(CO)_3$ group.

Nucleophilic Substitution.[1]

Some carbon nucleophiles add to tricarbonyl(arene)chromium complexes to yield anionic η^5-cyclohexadienyl complexes (**2**) (eq 8), which give the substituted arenes via decomplexation by oxidation with iodine. Protolysis of the intermediate cyclohexadienylchromium complexes (**2**) generate cyclohexadienes, and reaction with electrophiles generates either the arene chromium complexes or produces the acylated species.

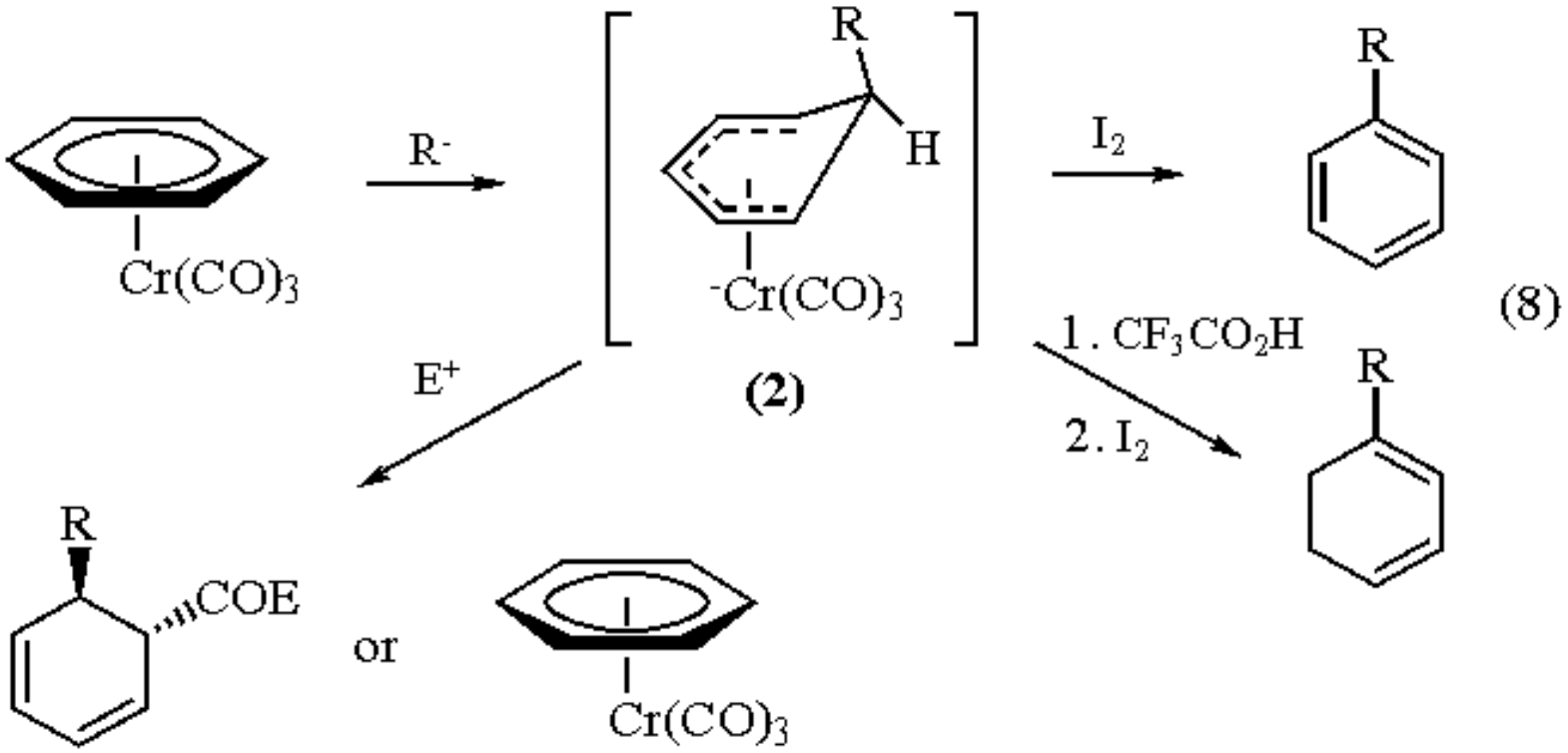

(8)

With substituted aromatics, the following regioselectivity for nucleophilic substitution is generally observed (eq 9); alkoxy substituents strongly direct to the *meta* position, and trimethylsilyl groups ensure *para* substitution.[12] Alkylation of the chromium complexes of indoles and benzofurans takes place at the C-4 or C-7 position, depending on the steric effect of the C-3 substituent.[13] Intramolecular nucleophilic alkylation can also be achieved; the products formed depend on chain length, reaction conditions, and other substituents on the aromatic ring (eq 10).[14] With an (anisole)chromium complex, 3-substituted cyclohexenone derivatives can be obtained by the protolytic cleavage of the intermediates (eq 11).[17] A combination of the intramolecular alkylation with protolysis gives an elegant synthesis of the spiro sesquiterpenoids acorenone and acorenone B (eq 12).[15,16]

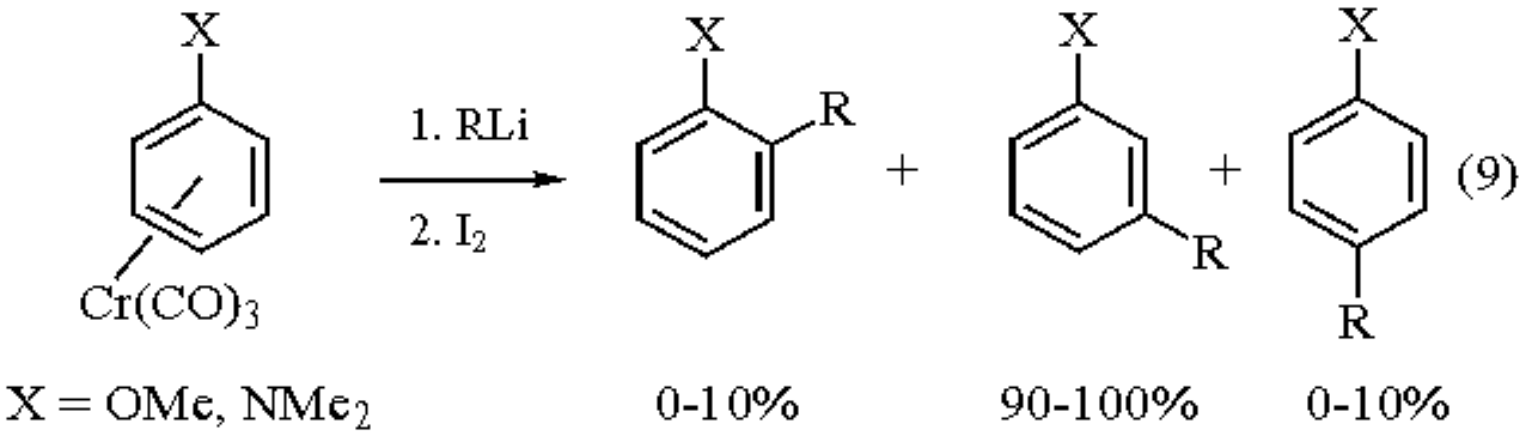
X
Cr(CO)3
1. RLi
2. I2
X
R
+
X
R
+
X
R
(9)
X = OMe, NMe2
0-10%
90-100%
0-10%

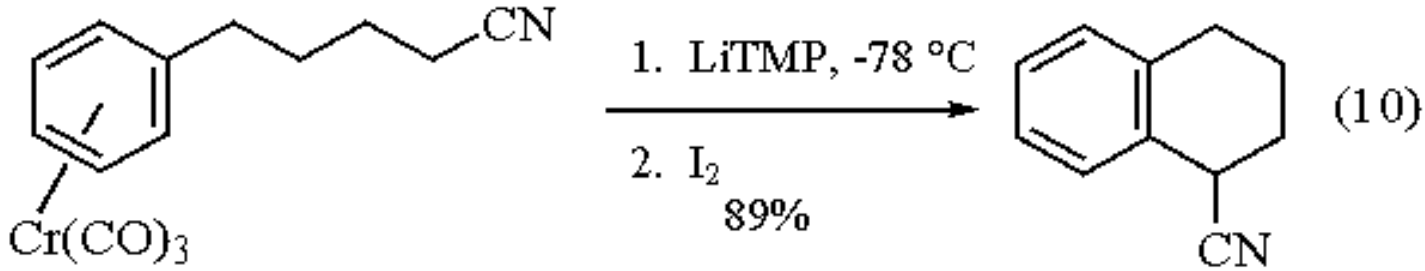
CN
Cr(CO)3
1. LiTMP, -78 °C
2. I2
89%
CN
(10)

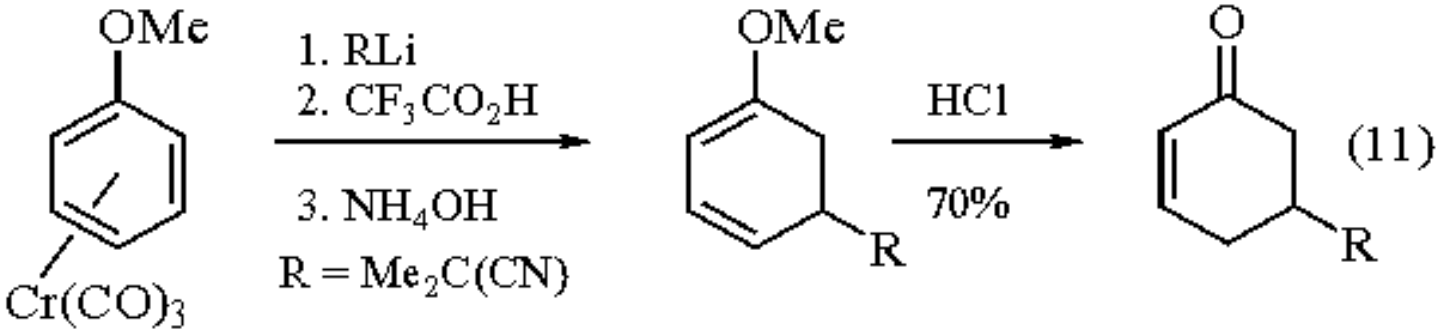
OMe
Cr(CO)3
1. RLi
2. CF3CO2H
3. NH4OH
R = Me2C(CN)
OMe
R
HCl
70%
O
R
(11)

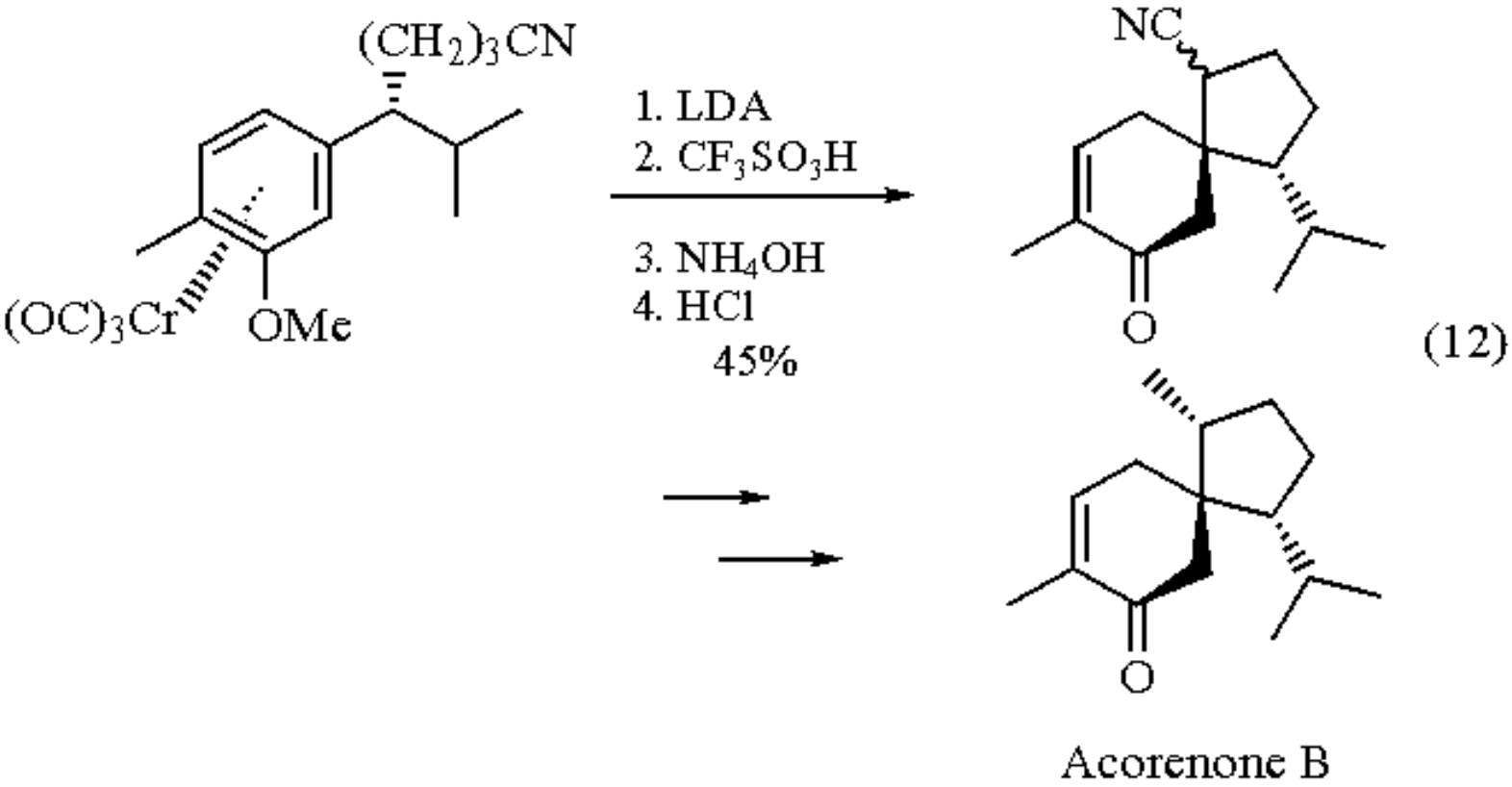

Reaction with a range of electrophiles regenerates the (arene)chromium complexes under reversible conditions, but electrophilic attack upon the cyclohexadienyl complex formed under irreversible conditions from dithiane carbanions produces *trans* addition products (eq 13).[17]

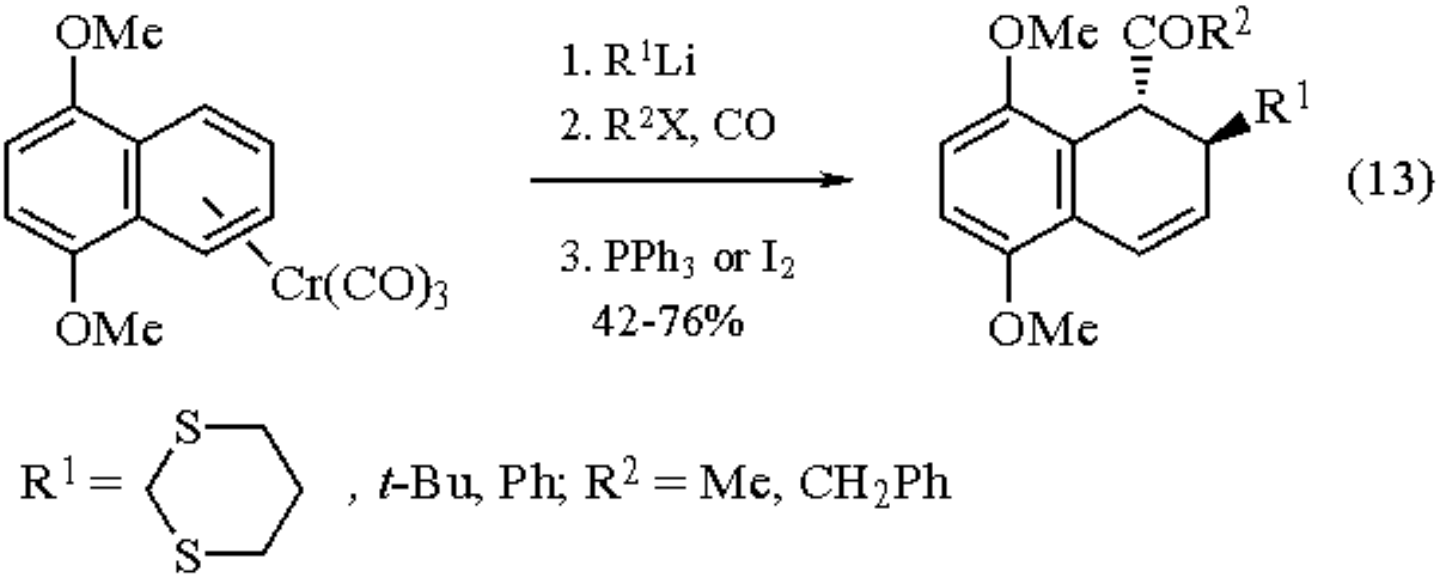

Lithiation.

With anisole, fluorobenzene, and chlorobenzene chromium complexes, lithiation always occurs at an *ortho* position of the substituents under mild conditions (eqs 14 and 15).[18] Protected phenol or aniline chromium complexes with sterically bulky substituents produce *meta* lithiation exculsively.[19] The lithiated position of some (arene)chromium

complexes (**3**) differs from that of the corresponding chromium-free compounds (**4**).[20]

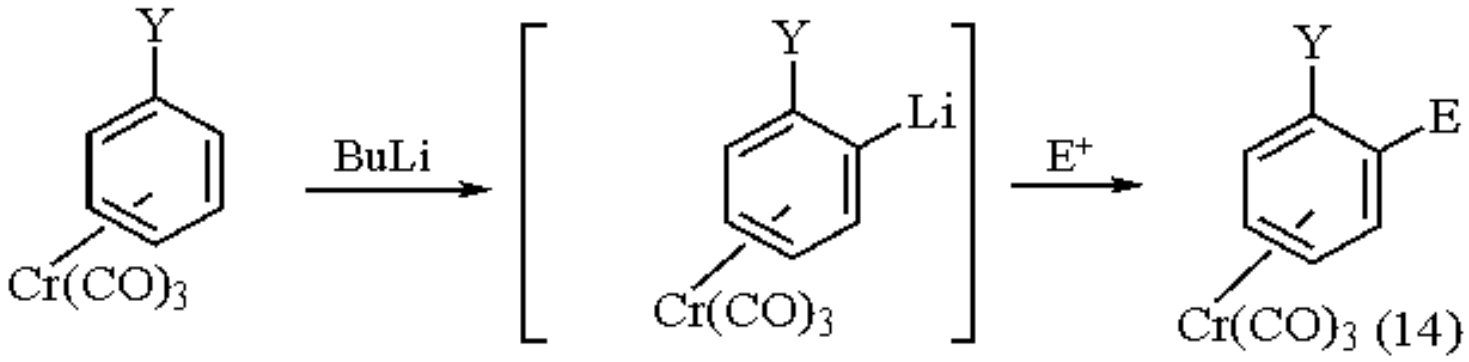

Y = H, OMe, F, Cl; $E^+ = CO_2$, MeX, TMSCl, aldehydes, ketones

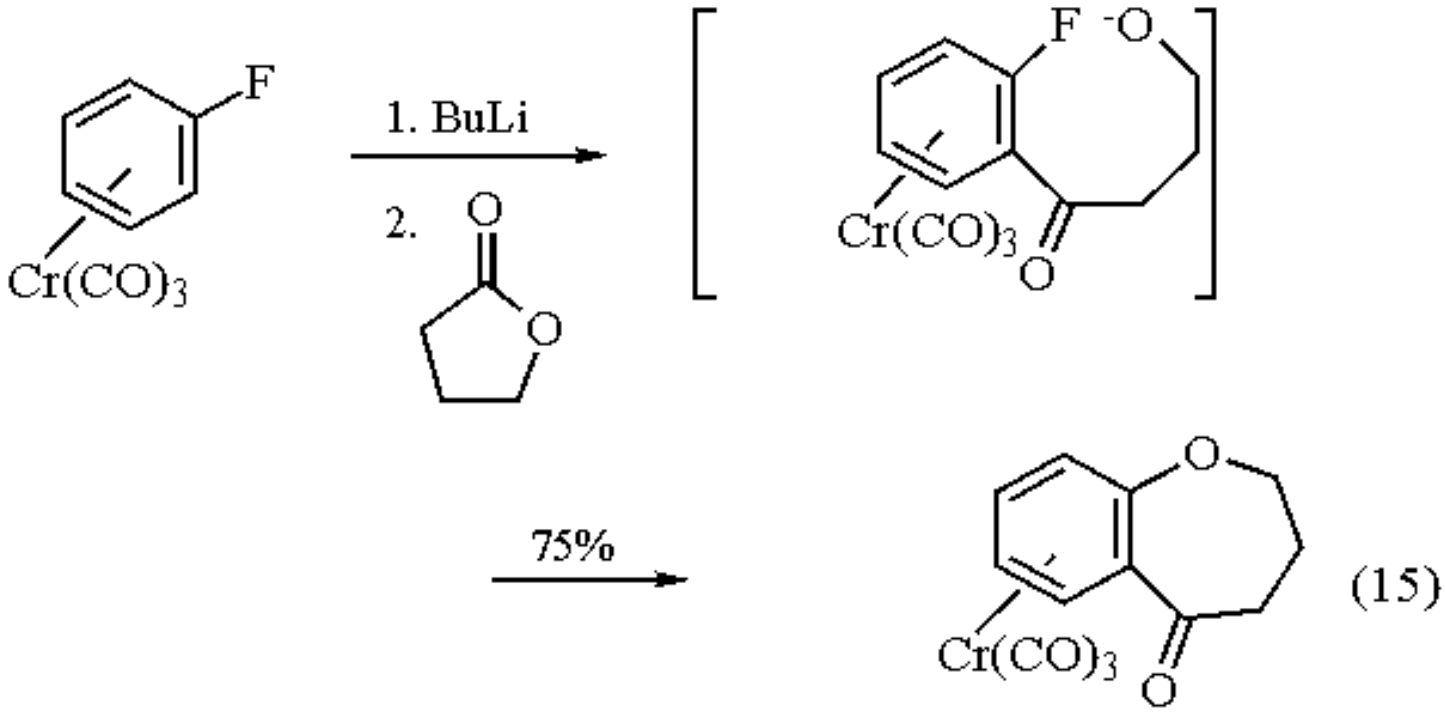

(3) **(4)**

Activation of the Benzylic Position.

Both chromium complexed carbanions and carbocations are stabilized at the benzylic position.[21] Dialkylation of alkyl halides at the benzylic position occurs via stabilized carbanions under mild conditions (eq 16).[22] Regio- and stereoselective products are obtained via the benzylic carbanions, depending on the conformation of the tricarbonyl group to the arene (eq 17).[22] (Styrene)chromium complexes stabilize negative charges at the benzylic position by addition of nucleophiles to the β-position, giving bifunctionalization products by trapping with electrophiles (eq 18).[23]

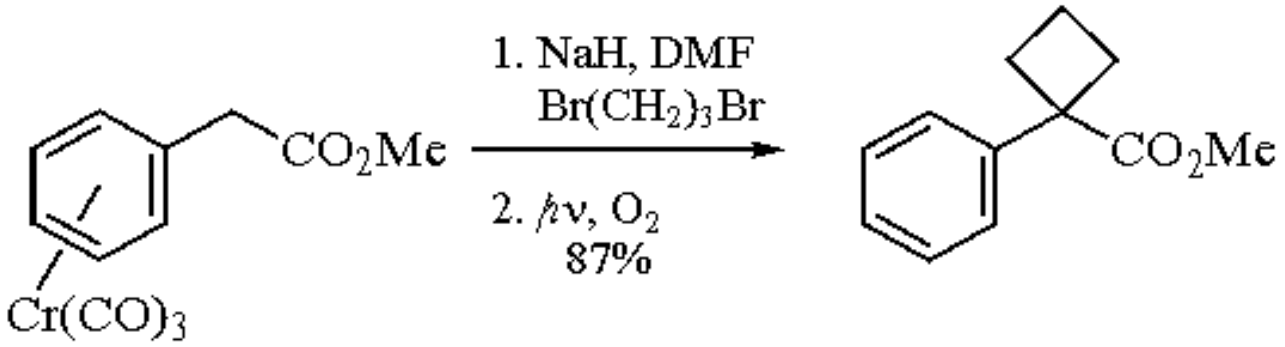

(16)

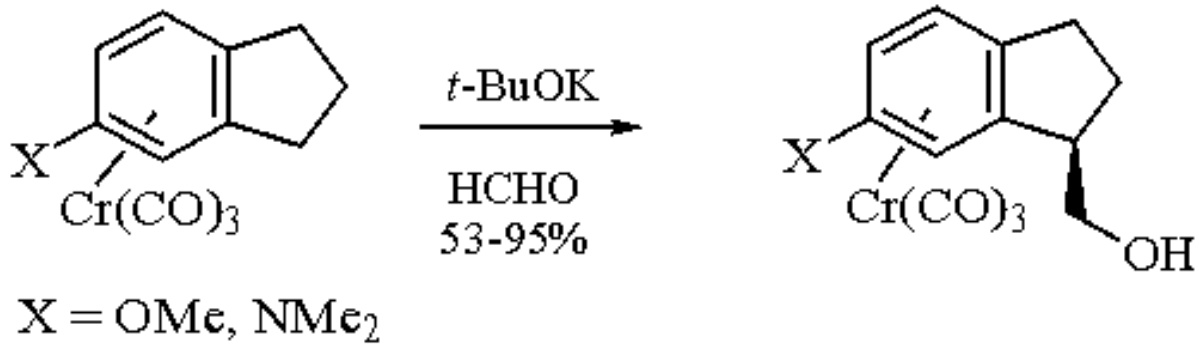

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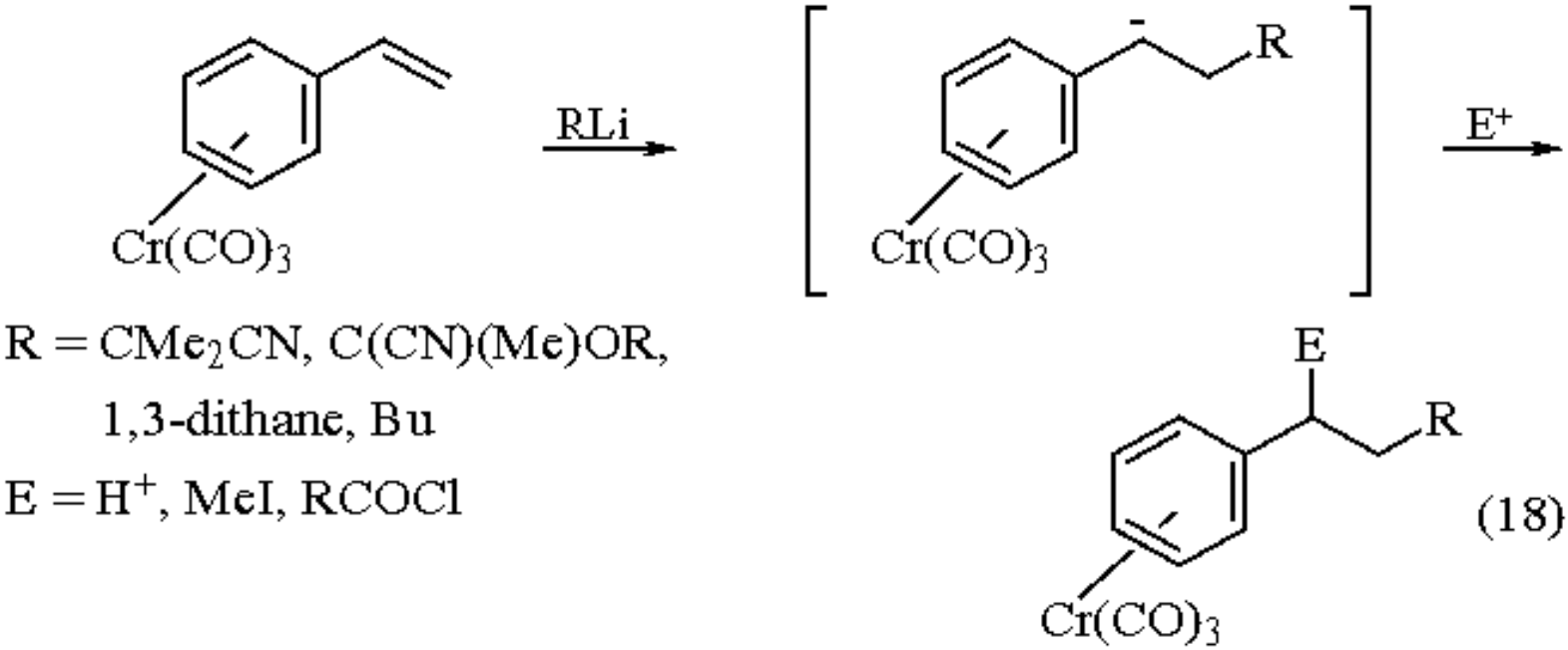

(18)

Tricarbonylchromium stabilized benzylic carbocations can be captured by a large variety of nucleophiles,[24] such as alcohols, amines, thiols, nitriles, trimethylsilyl enol ethers, allylsilanes, electron-rich aromatics, dialkylzincs, and

trialkylaluminums (eq 19). The relative stereochemistry formed during these reactions via carbocations in acyclic systems proceeds with net retention.[21b,c,25] Friedel-Crafts acylation of (styrene)chromium complexes has been explored via the benzylic cations (eq 20).[26] Tricarbonylchromium-stabilized oxonium ions are also utilized for steroselective carbon-carbon bond forming reactions (eq 21).[27]

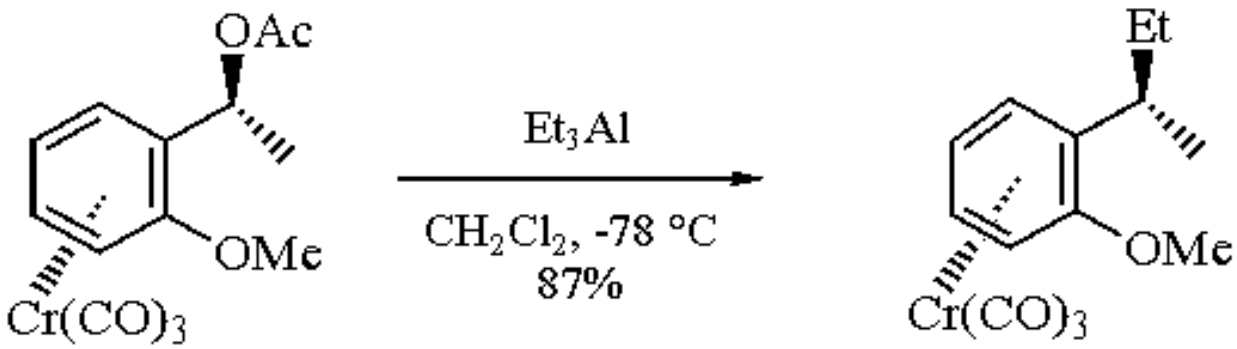

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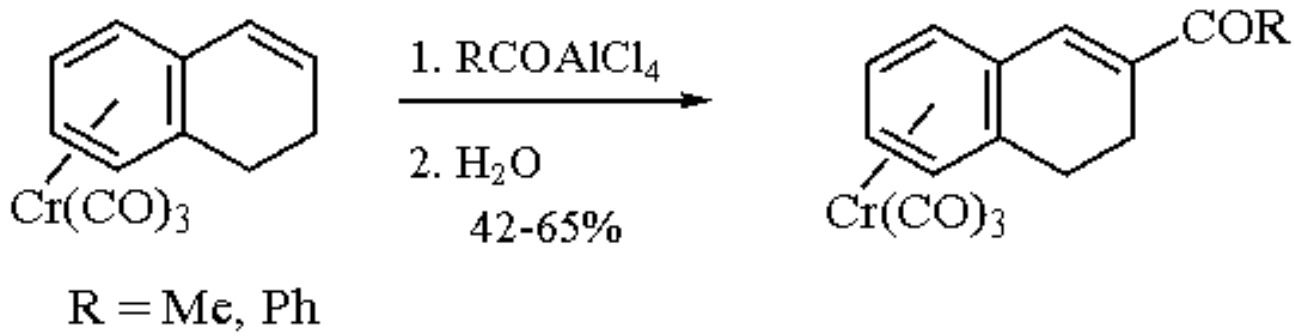

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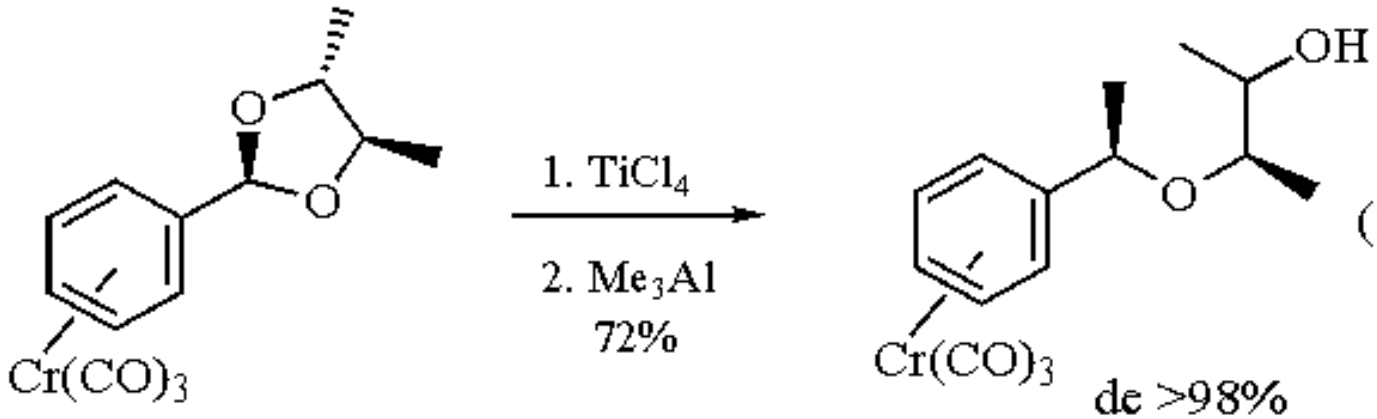

(21)

Steric Effect of the $Cr(CO)_3$ Group.[1]

A feature of (η^6-arene)chromium complexes is the steric interference offered to the approach of reagents, which occurs exclusively from the *exo*-face at the reactive center in cyclic chromium complexes (eq 22).[28] Even in the (acyclic arene)chromium complexes, such as *o*-substituted benzaldehyde and phenyl alkyl ketones with electron-donating *ortho* substituents (OMe, Me, F), addition of nucleophiles to the chromium complexed benzylic carbonyl group proceeds stereoselectively, giving one diastereomeric complex predominantly (eq 23).[29] A Friedel-Crafts reaction produces predominantly an *exo*-substituted complex (eq 24).[30]

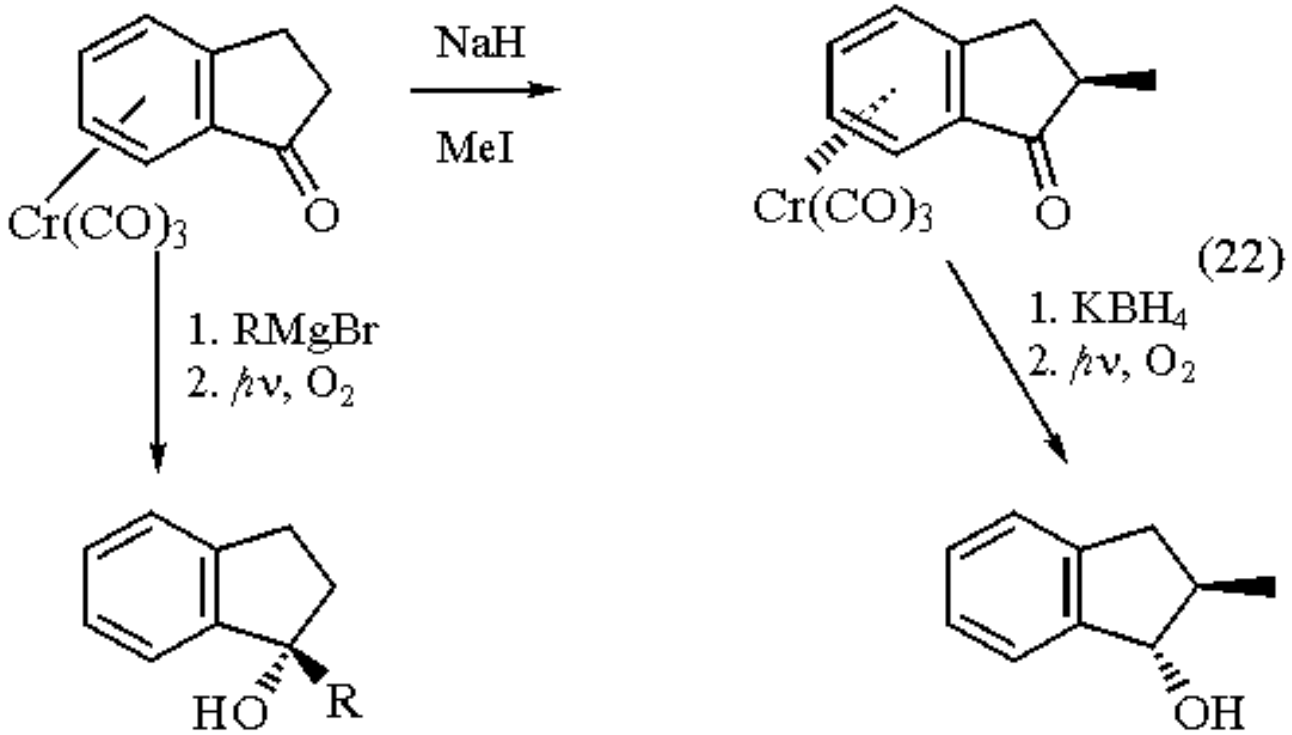

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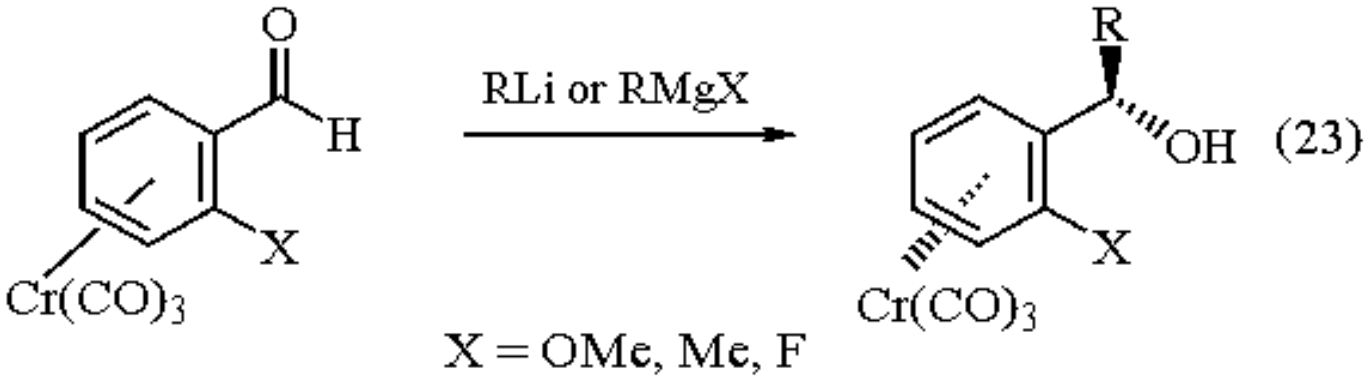

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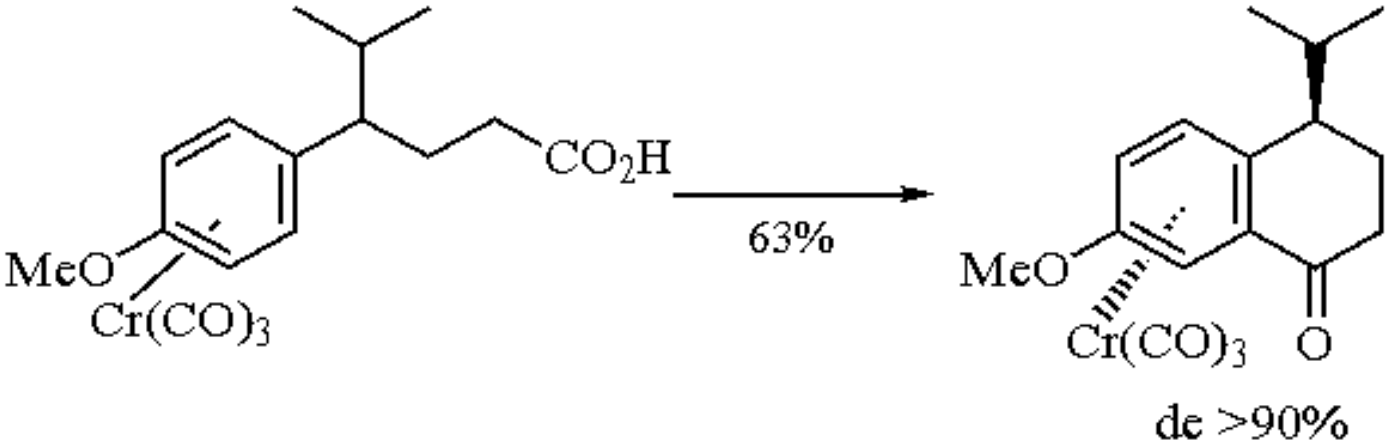

(24)

A 1,2 or 1,3 unsymmetrically disubstituted arene is prochiral and therefore the corresponding chromium tricarbonyl compounds are chiral.[31] (Substituted arene) complexes with amine, carboxyl, and formyl groups at the *ortho* position are resolved into optically active chromium complexes through corresponding diastereomeric adducts (eq 25).[32] Biocatalysts also perform the kinetic resolution of racemic chromium complexes (eq 26).[33] The optically active

chromium complexes can be prepared by diastereoselective *ortho* lithiation[34] of the chiral benzaldehyde or acetophenone acetal complexes, and diastereoselective chromium complexation[35] of the chiral *ortho*-substituted benzaldehyde aminals (eq 27). Catalytic asymmetric cross-coupling of *meso* (1,2-haloarene)chromium complex produces chiral monosubstituted complexes.[36] The chiral (arene)chromium complexes can be used as ligands in asymmetric reactions.[37]

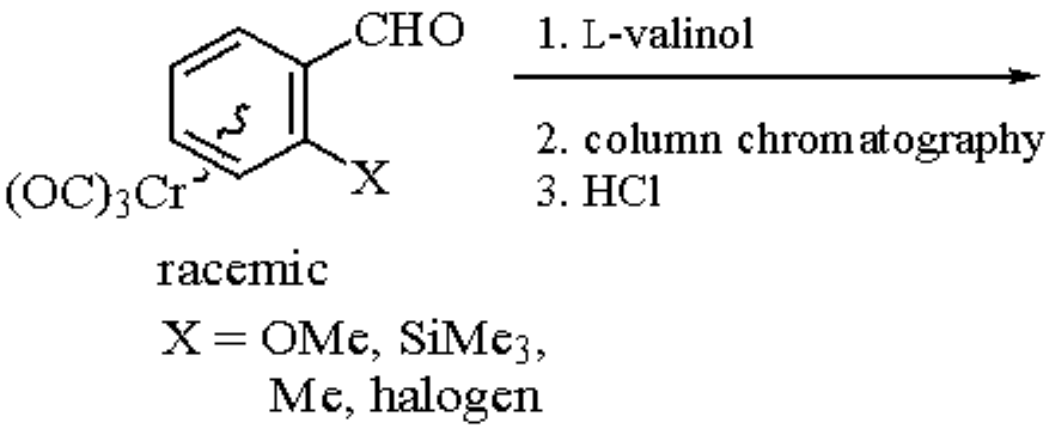

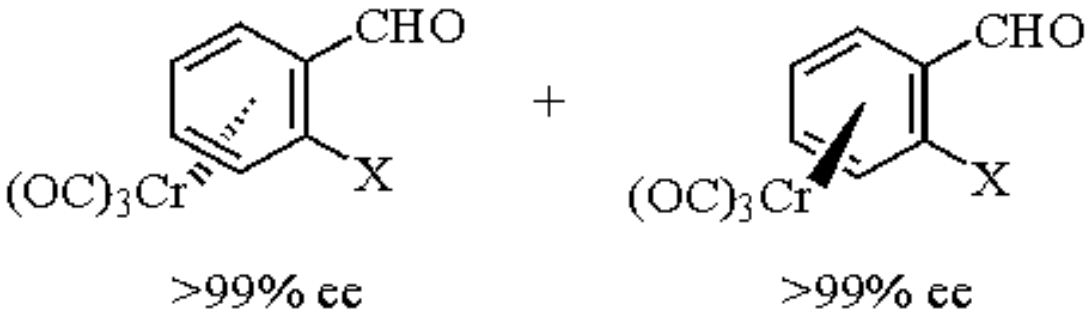

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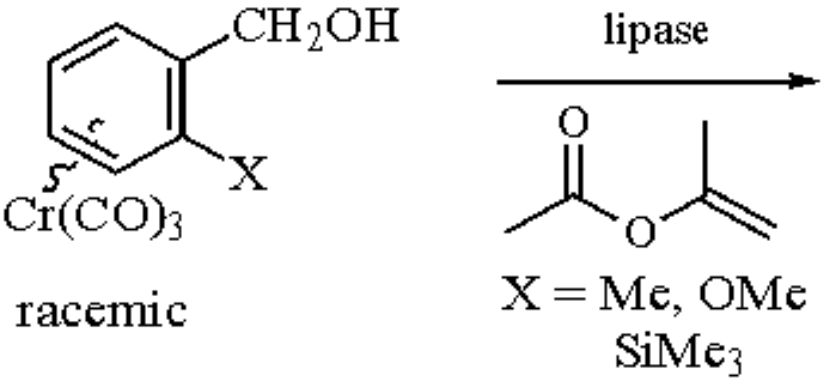

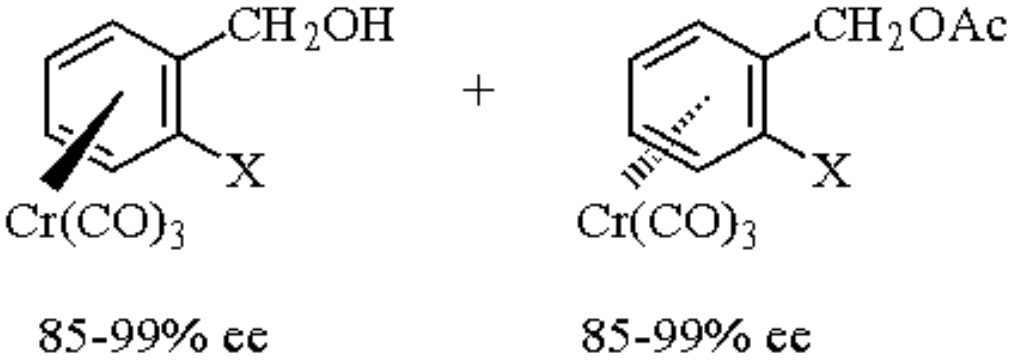

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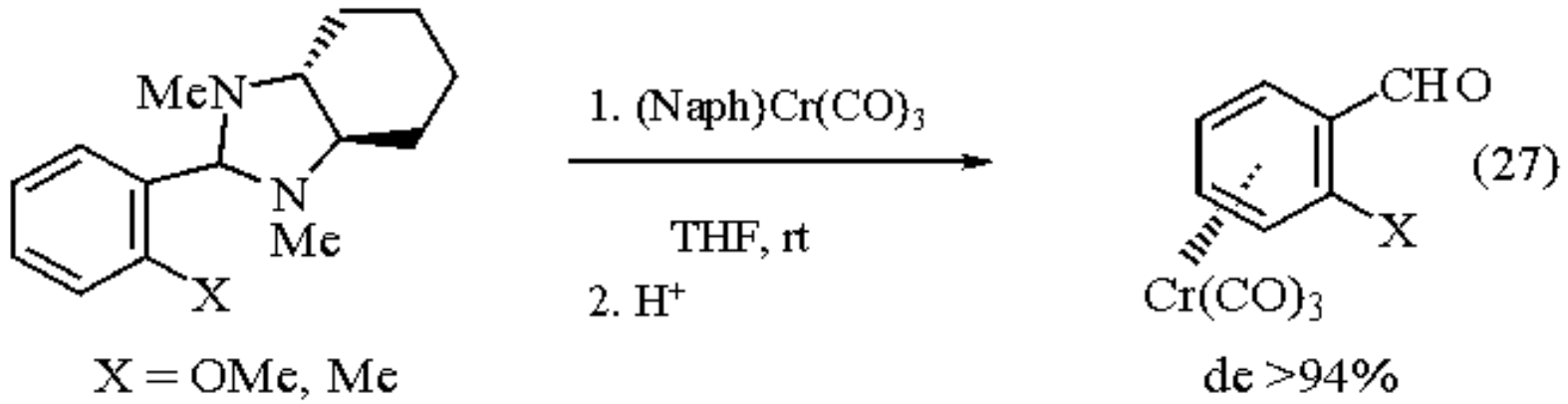

(27)

Related Reagents.

(η6-Benzene)tricarbonylchromium; ***Dodecacarbonyltriiron***; ***Pentacarbonyliron***.

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Hexacarbonylmolybdenum

$Mo(CO)_6$

[13939-06-5] · C_6MoO_6 · Hexacarbonylmolybdenum · (MW 264.00)

(starting material for many organomolybdenum compounds and reagents;[1] can be used as catalyst for catalytic allylations[2] and epoxidations)

Alternate Name: molybdenum hexacarbonyl.

Physical Data: mp 150 °C (dec); *d* 1.96 g cm^{-3}.[3]

Solubility: only very slightly sol most organic solvents; slightly sol THF, diglyme, MeCN.

Form Supplied in: white crystals; commercially available.

Handling, Storage, and Precautions: indefinitely stable at rt under nitrogen or argon. The crystals can be handled in air for short periods with no significant decomposition. Prolonged exposure to air produces some oxidation to a blue oxide. The compound readily sublimes and purification is effected conveniently by sublimation under static vacuum, which yields large crystals of pure material. In most cases, the material can be used as supplied. Owing to the high vapor pressure of the solid, caution should be taken to avoid accidental breathing of the vapor or ingestion of this potentially toxic material; however, $Mo(CO)_6$ is relatively innocuous compared to the high toxicity of liquid metal carbonyls. Many reactions involve displacement of carbon monoxide; hence they should be carried out in an efficient fume hood.

Organomolybdenum Complexes.

Hexacarbonylmolybdenum is the starting material for many organomolybdenum compounds and reagents. It is more readily available and less expensive than its other Group 6 counterparts. Although (arene)molybdenum carbonyl complexes are known, the chemistry of (arene)chromium carbonyl complexes has been better developed. The chemistry of importance to organic synthesis often involves molybdenum carbonyl complexes with cyclopentadienyl or other ligands and this chemistry has been more fully developed than that of chromium or tungsten. Although direct reactions of potential ligands occur with $Mo(CO)_6$, a typical organomolybdenum synthesis would begin by displacing three of the carbonyl ligands with a donor solvent while heating under vigorous reflux (eq 1) to yield a more reactive tricarbonyl intermediate. Displacement of carbonyl groups by other ligands occurs much more readily with $Mo(CO)_6$ than with ***Hexacarbonyltungsten***. For example, the reaction depicted in eq 1 is typically complete within 2 h, whereas the tungsten analog may still only be partially substituted after several days. UV irradiation or use of higher

boiling nitriles also increases the rate of displacement.

$$Mo(CO)_6 + \text{excess } MeCN \longrightarrow Mo(CO)_3(MeCN)_3 + 3\ CO \quad (1)$$

Oxidative additions of allylic halides occur to yield Mo^{II} species which usually contain η^3-allylic moieties.[3] Typical reagents and catalysts are then formed by the addition of lithium cyclopentadienide[3] or bisphosphines[4] (eqs 2-4).

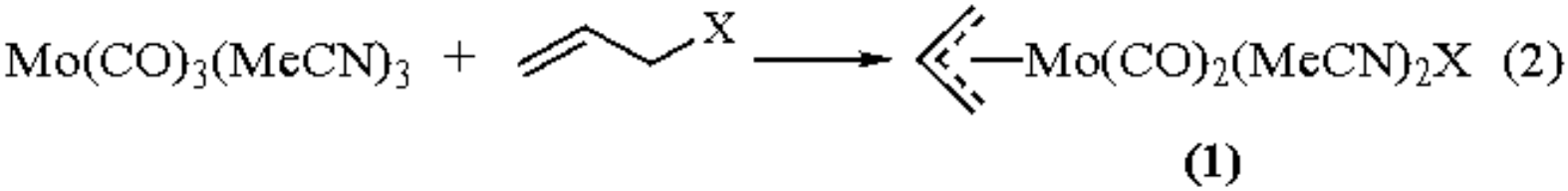

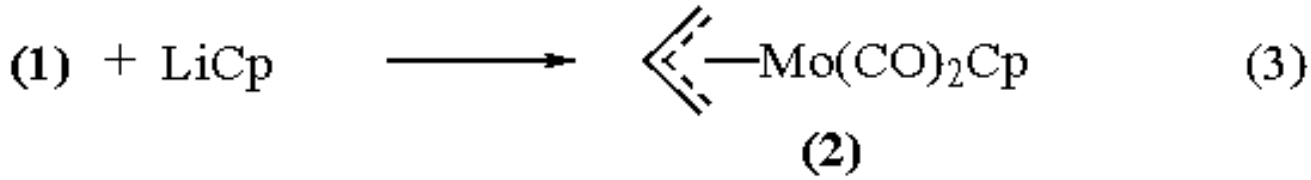

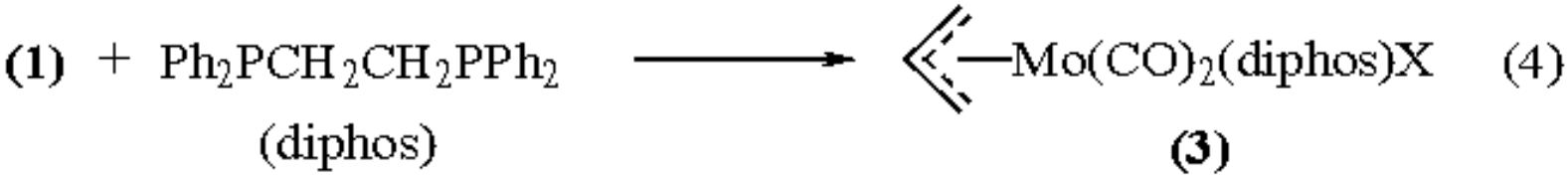

Another convenient starting material is the dimer $[CpMo(CO)_3]_2$, which can be obtained by heating $Mo(CO)_6$ with high-quality cyclopentadiene dimer under reflux,[5] or the air oxidation of $CpMo(CO)_3H$ (not very reproducible),[6] or quite reliably by the oxidation of $CpMo(CO)_3^-$ with ***Iron(III) Sulfate*** (eqs 5 and 6).[7] Although the $CpMo(CO)_3^-$ anion, prepared as in eq 5, is often used directly in the preparation of $CpMo(CO)_3R$ by reaction with alkyl halides, it is more often prepared by reduction of dimer (**5**) with ***Sodium Amalgam*** in THF or by treatment with ***Lithium Triethylborohydride***.[8]

$$CpH + NaH \xrightarrow{THF} NaCp \longrightarrow Na[CpMo(CO)_3] \quad (5)$$

(4)

$$2\ Na[CpMo(CO)_3] + 2\ Fe^{3+} \longrightarrow [CpMo(CO)_3]_2 \quad (6)$$

(5)

Regiochemistry of Allylic Alkylations.

The reaction of the dimethyl malonate anion with an allylic acetate is catalyzed by $Mo(CO)_6$ and several complexes which are readily derived from it. Trost and Lautens[2] have carried out an extensive study of the regiochemistry of these catalytic reactions. A number of these reactions can be carried out stoichiometrically on isolated η^3-allylmolybdenum complexes.[2,4] The mechanism of the catalytic reaction is generally presumed to involve nucleophilic attack on an η^3-allyl intermediate formed via oxidative addition to a Mo^0 complex.[9] One of the classic examples is the reaction of crotyl acetate with an enolate (eq 7).[10]

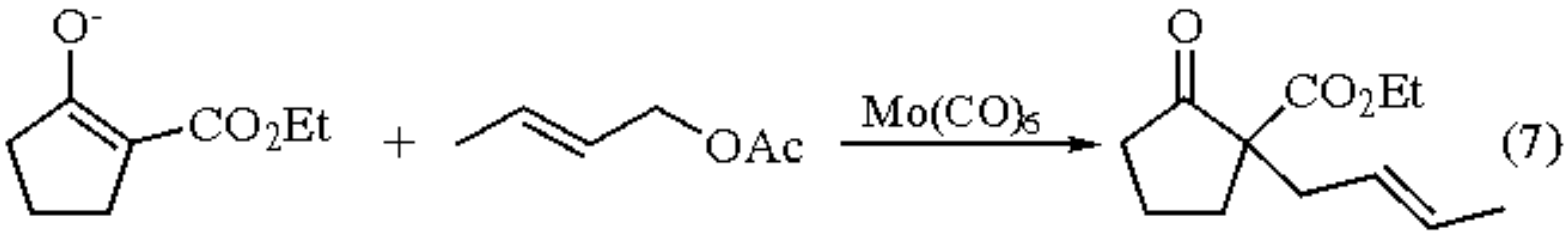

The regiochemistry of the reaction can be drastically influenced by the ligands on molybdenum and this can provide useful syntheses for regioisomers that might not be available via the more commonly used palladium catalysts. For example, with some nucleophiles the preferred regioisomer for $Mo(CO)_6$ is the reverse of that obtained with a Pd^0 catalyst in eq 8.[2] The $Mo(CO)_6$ catalyst yields a ratio of (**6**):(**7**) of 15:85, whereas ***Tetrakis(triphenylphosphine)palladium(0)*** yields a ratio of 100:0. The $Mo(CO)_4$(2,2´-bipyridyl) catalyst shows better regioselectivity than $Mo(CO)_6$, however, and yields exclusively (**7**). Generally the palladium routes give additions at the least substituted terminus, whereas $Mo(CO)_6$ will often give a greater fraction of addition to the more substituted terminus. This generalization for molybdenum catalysis can vary substantially with nucleophiles, as seen in eq 7.

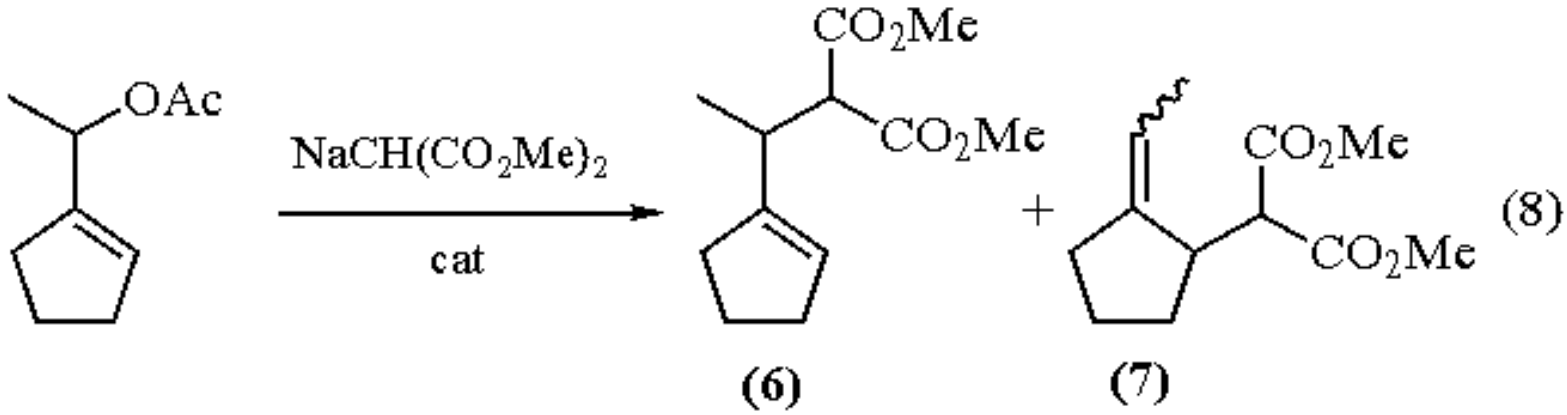

Another reaction which shows this reversal of regiochemistry between Mo and Pd reagents is the conversion of allylic acetates to allyltrimethylsilanes (eq 9).[11] The palladium-catalyzed reaction gives a ratio of (**8**):(**9**) of 61:39; whereas the $Mo(CO)_6$-catalyzed reaction gives a 0:100 ratio. The molybdenum-catalyzed reaction is also effective with carbonates and provides a route for α-allylation of ketones (eq 10).[12]

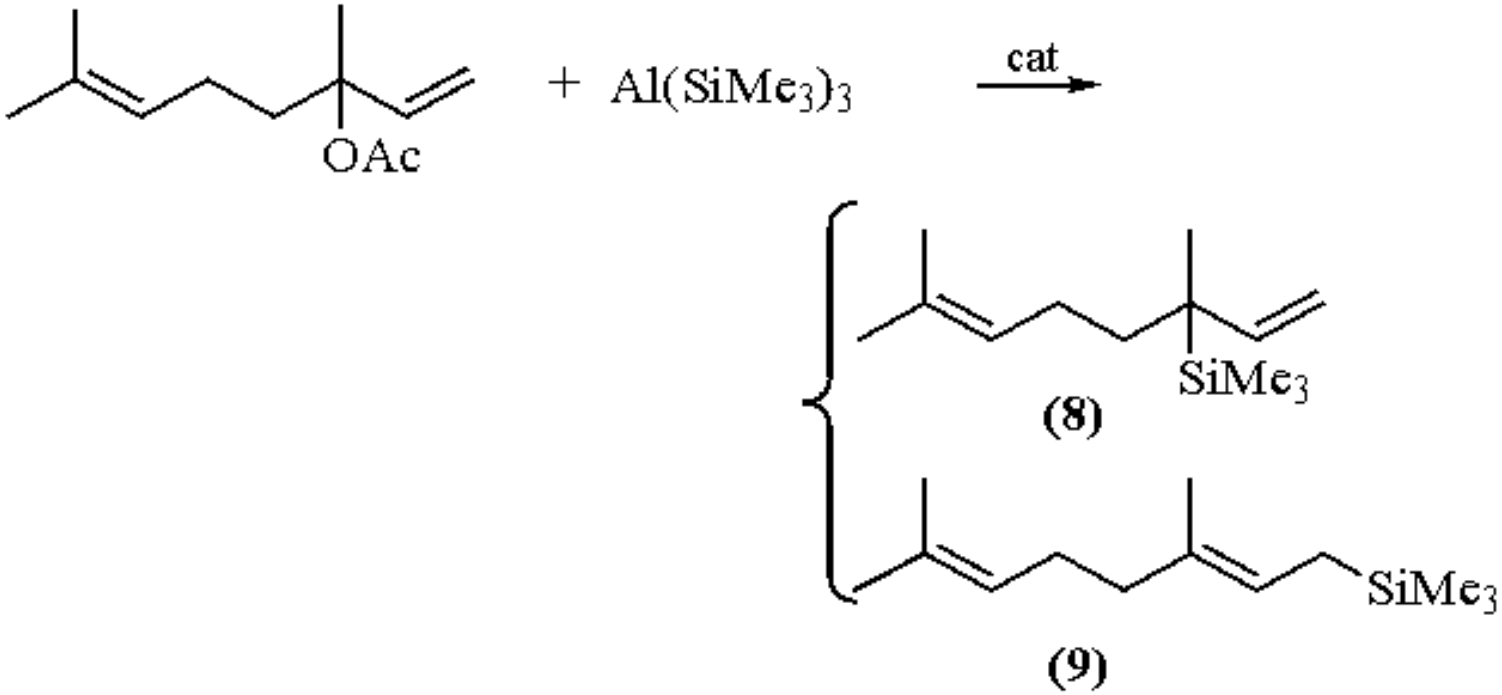

(9)

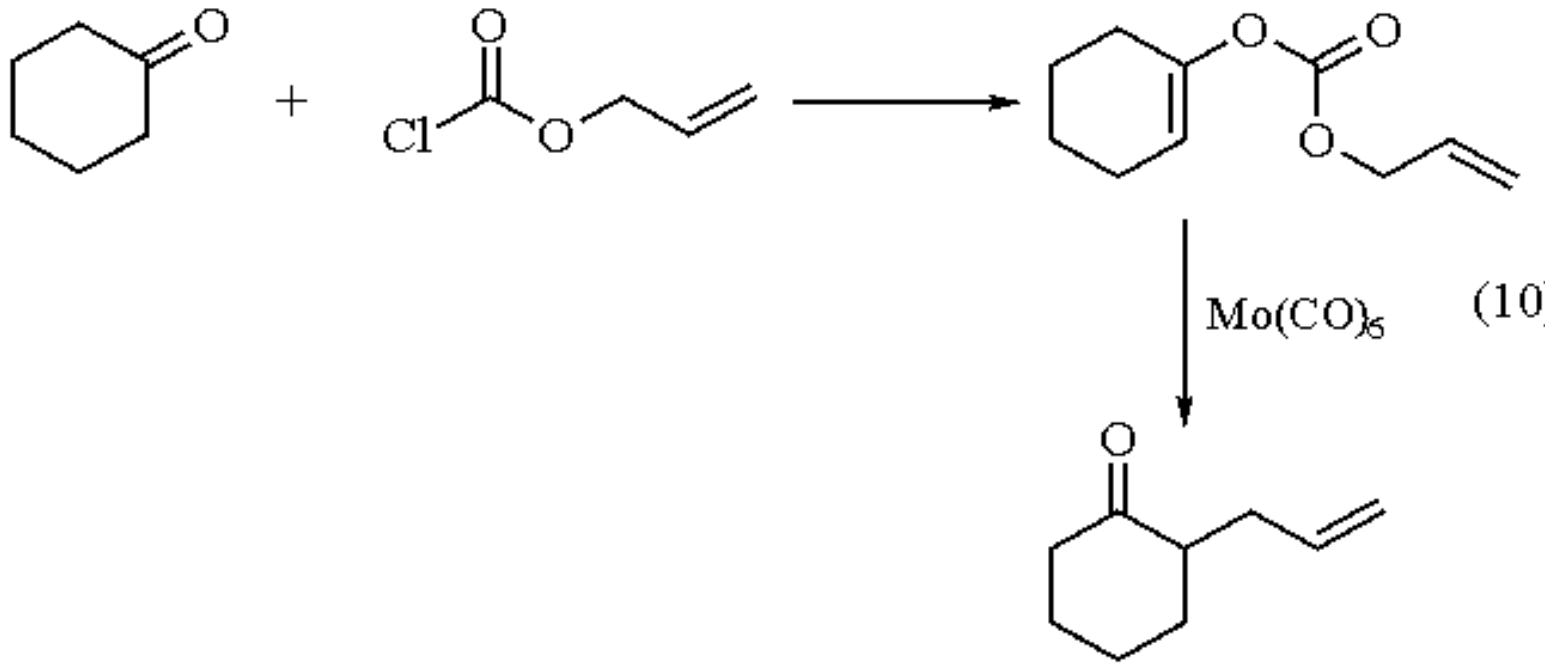

(10)

Although the reaction is stoichiometric, the Mo-catalyzed alkylation of an allyl sulfide results in desulfenylative allylation. The regiochemistry of the addition correlates with the original position of sulfur (eqs 11 and 12).[13]

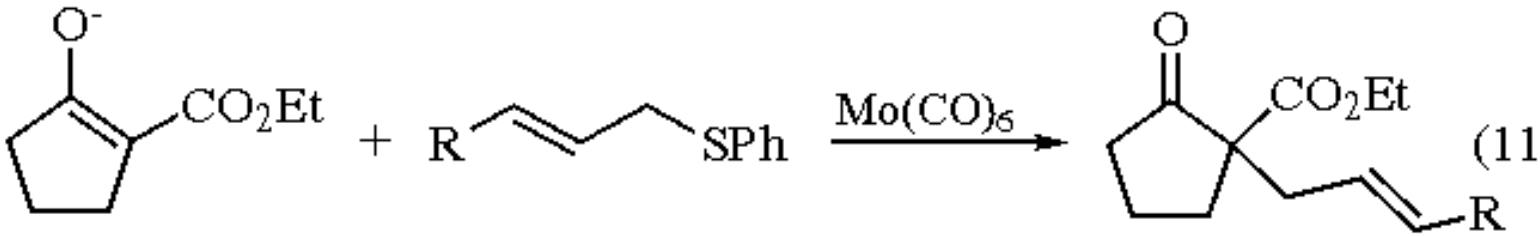

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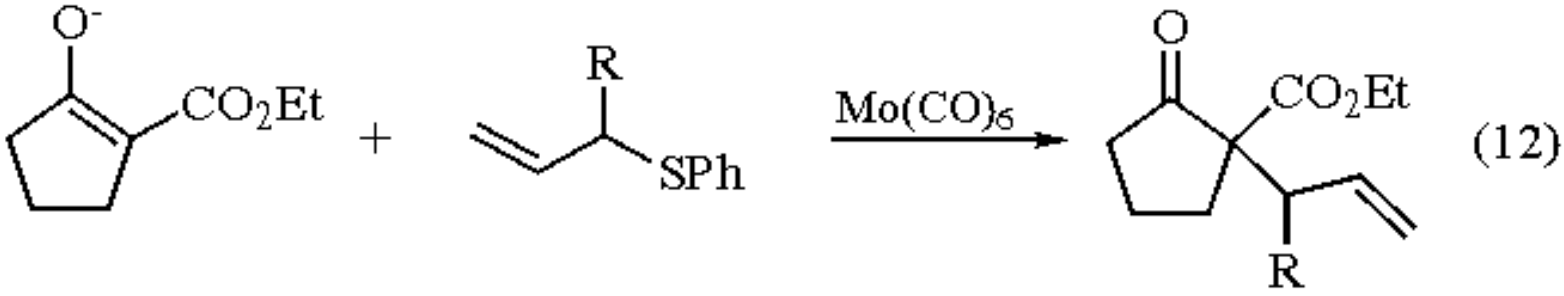

Allylic alkylations catalyzed by Pd^0 complexes[14,15] and $Mo(CO)_6$[2,16] occur with net retention of configuration. This is consistent with double inversion, i.e. inversion in forming the η^3-allyl complex and nucleophilic attack *trans* to the metal. The use of chiral nonracemic allylic acetates in Pd-catalyzed reactions has shown that the first step involves inversion.[17] Thus the double inversion mechanism appears to be general for Pd^0. Net retention is also consistent with a double retention mechanism and this may occur in some molybdenum-catalyzed reactions, as suggested by the observation that addition of (*R*)-(*E*)-4-acetoxy-5-methyl-2-hexene to $Mo(CO)_3(MeCN)_3$ occurs with retention.[18] On the other hand, net inversion has been observed in a stoichiometric reaction.[18]

Hydrogenations and Reductions.

Although precious metal catalysts are more often used for hydrogenations, $Mo(CO)_6$ can function as a hydrogenation[19] or transfer hydrogenation catalyst.[20] However, some of the more synthetically useful reactions are those hydrogenations effected by hydrosilanes using catalytic amounts of $Mo(CO)_6$ that provide selective reductions of unsaturated ketones, esters, amides, and nitriles (eq 13).[21]

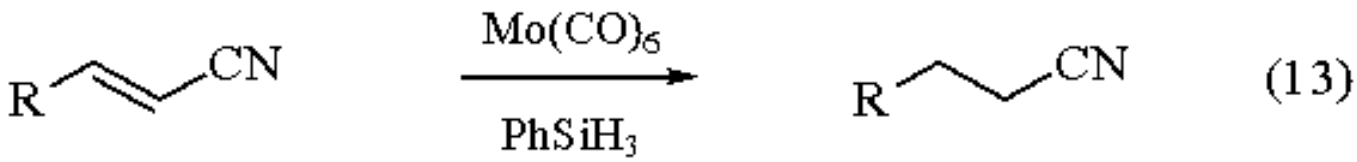

The low oxidation state of molybdenum in the hexacarbonyl complex gives it reductive capabilities which provide a route for dehydrosulfurization (eq 14).[22] The reaction of alkyl or aryl sulfonyl chlorides with excess (10-30%) $Mo(CO)_6$ in anhydrous tetramethylurea provides a route to disulfides (eq 15).[23]

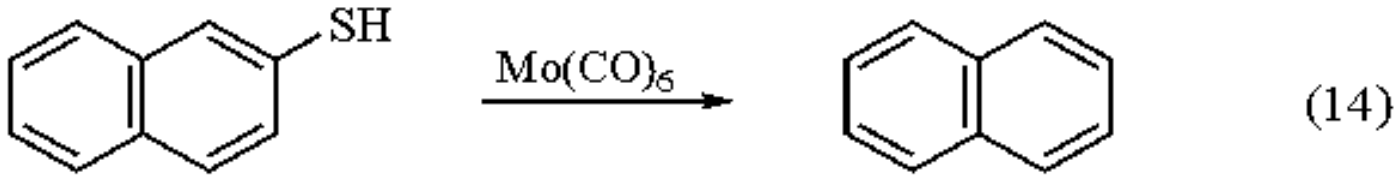

The oxidative addition of halides to Mo^0 provides an alternate route for dehalogenation of α-halocarbonyl compounds.[24] For α-halo ketones, partitioning between the methyl ketone and the aldol product (eq 16) depends upon

the catalyst.[25] For $Mo(CO)_6$ in 1,2-dimethoxyethane the methyl ketone is formed as the major, if not the only, product. Use of $Mo(CO)_3(NCMe)_3$ with 2-chloroacetophenone allows stabilization and isolation of η^3-allylmolybdenum adducts of condensation of two and three acetophenone units (eq 17).[26]

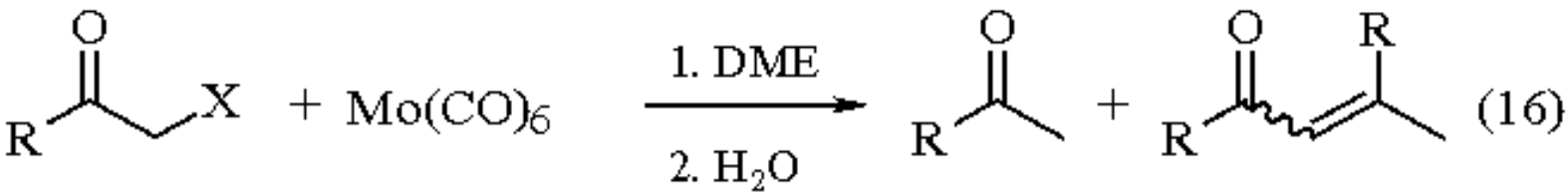

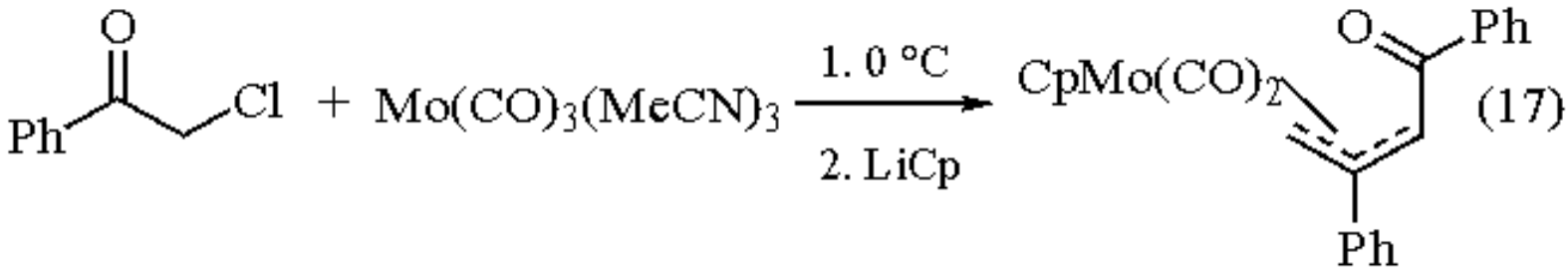

Epoxidations and Oxidations.

Molybdenum carbonyl can be used as an alkene epoxidation catalyst in conjunction with ***t-Butyl Hydroperoxide***.[27,28] It provides a convenient route for monoepoxidation of 1,5-cyclooctadiene (eq 18).[27] This approach can be useful for epoxidation of enol ethers,[29] which complements approaches using peracids or ***Tetracarbonylnickel***, a far more toxic metal carbonyl.[30] This approach also provides a route to larger ring lactones, such as 6-ketononanolide (eq 19).[31] The molybdenum is oxidized to a peroxy species in these reactions. In the absence of *t*-BuOOH, however, epoxides can rearrange to aldehydes in the presence of catalytic amounts of $Mo(CO)_6$ (eq 20).[32] The $Mo(CO)_6$/*t*-BuOOH system also allows selective oxidation of a secondary alcohol to a ketone in the presence of a primary alcohol (eq 21).[33] The selectivity is improved upon addition of cetylpyridinium chloride.

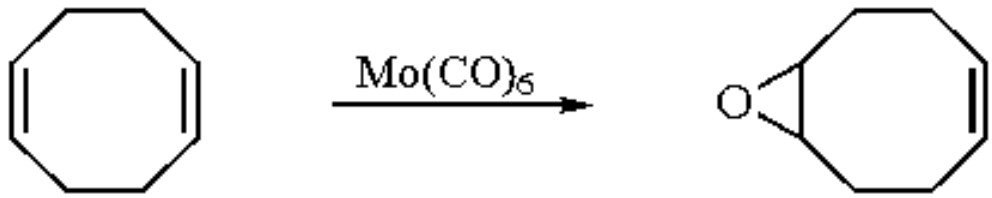

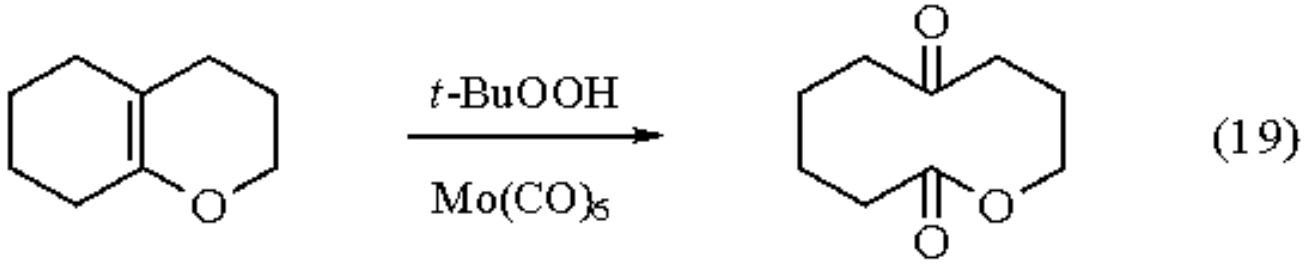

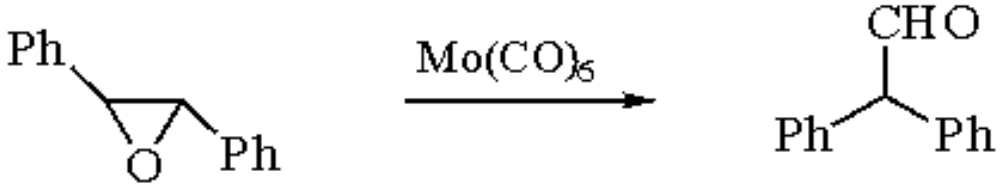

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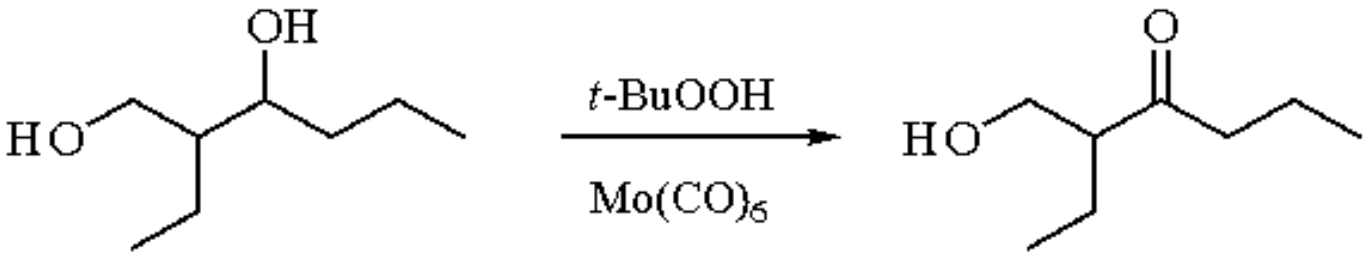

(21)

Ring Formation and Opening.

Ring closures in (**10**) have been effected by $Mo(CO)_6$ (eq 22)[34] to form benzocyclobutenones in a stoichiometric reaction. Stabilization of a metallocyclobutene intermediate provides a route to α-naphthols from arylcyclopropenes (eq 23) in a catalytic reaction; however, nearly molar equivalents of $Mo(CO)_6$ increase the yield and the rate substantially.[35]

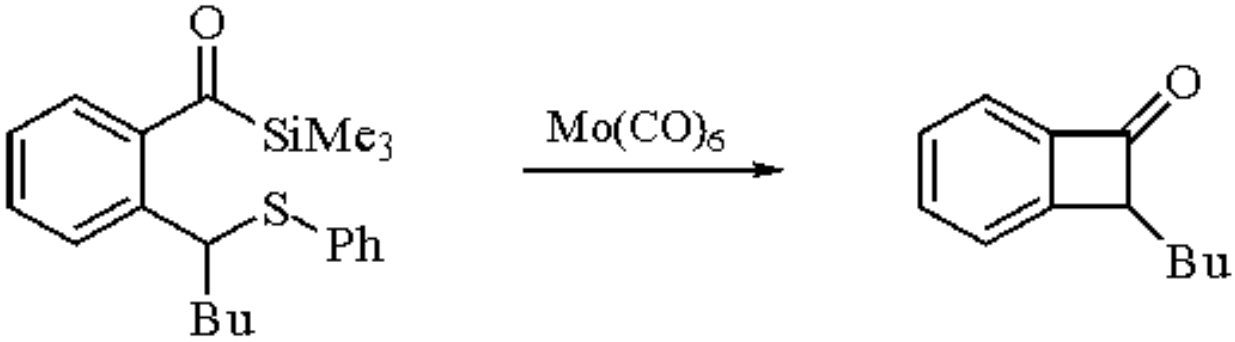

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(10)

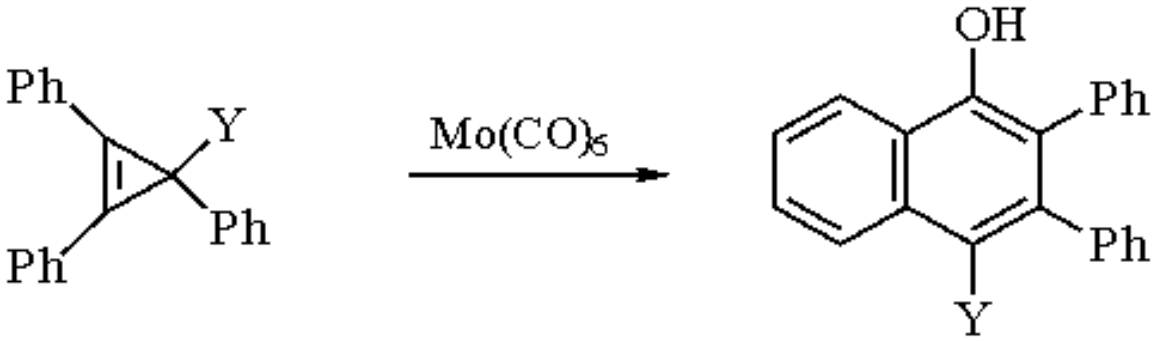

(23)

There are other examples of stabilization of carbene intermediates by molybdenum which are useful in heterocyclic synthesis. Pyrroles have been prepared from α-azidostyrene (eq 24)[36] and 2,5-pyrrolidones have been prepared from azirines and diethyl sodiomalonate (eq 25).[37] Although the reaction can be carried out with SbF_5, $Mo(CO)_6$ also

catalyzes cyclopropane formation for diazo additions to electron-deficient alkenes (eq 26).[38] The (*E*):(*Z*) ratio ranges from 0.7 to 2.2, depending on R^1 and R^2.

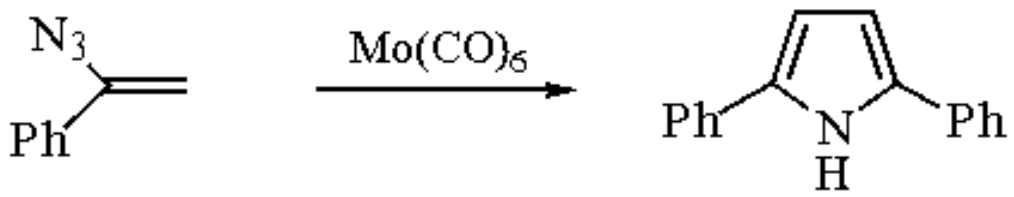

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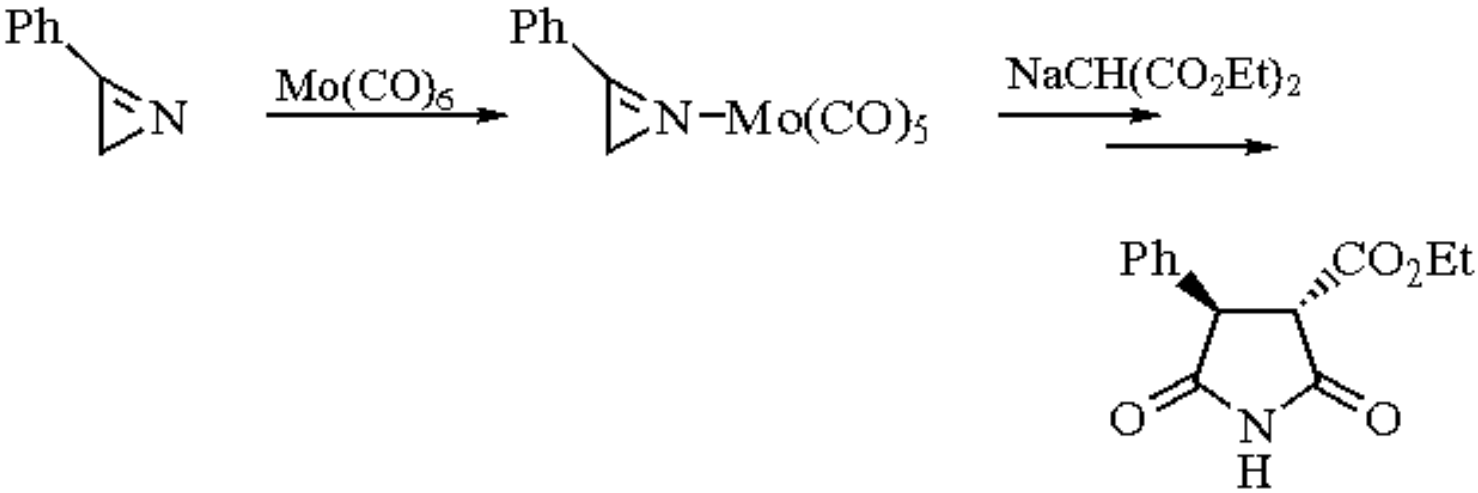

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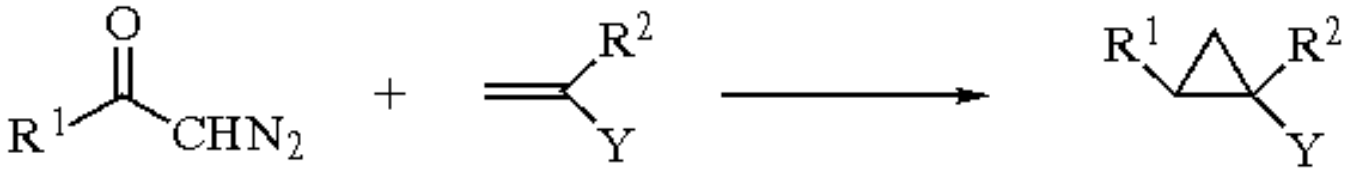

(26)

The N-O bond is easily cleaved by $Mo(CO)_6$ and this provides a route for conversion of oxime acetates to ketones (eq 27).[39] Ring openings of isoxazoles[40] and isoxazolines[41] provide routes to β-amino-α,β-unsaturated ketones (eq 28) and β-hydroxy ketones (eq 29). This is also a key step in an asymmetric synthesis of α-aminocarboxylic acids from 1-alkoxy-3-siloxy-2-aza-1,3-dienes which has been published recently (eq 30).[42] The acyl nitroso intermediate is generated in situ via oxidation of a hydroxylamine.

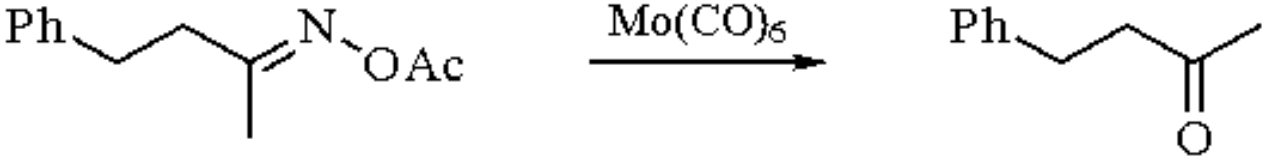

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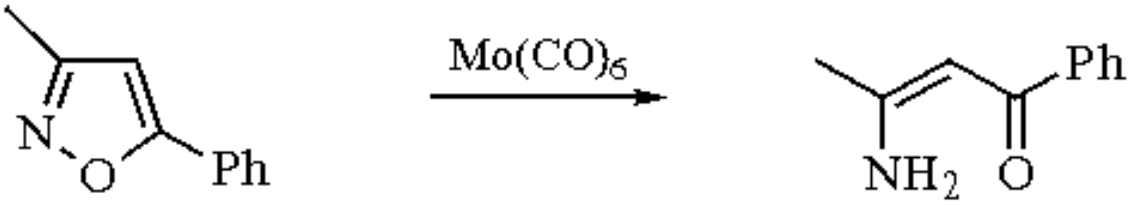

(28)

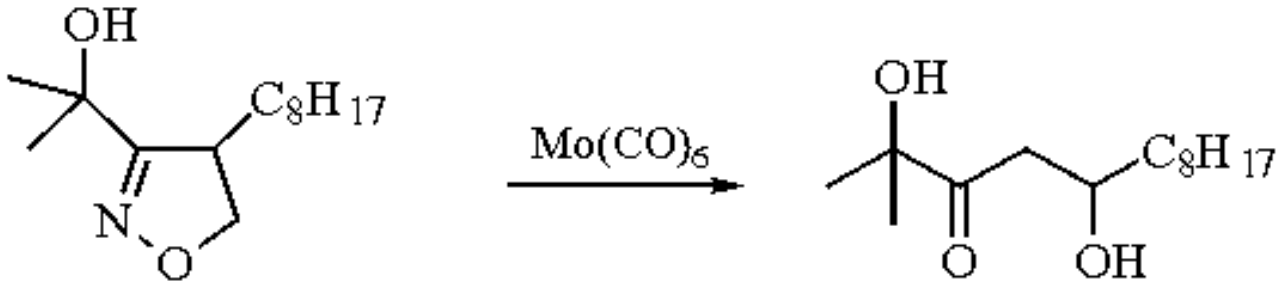

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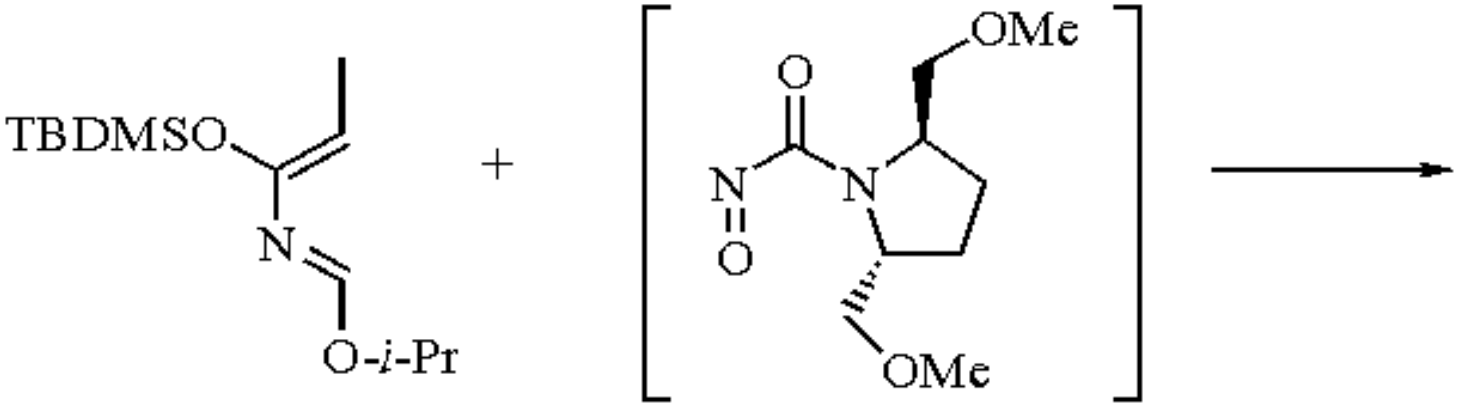

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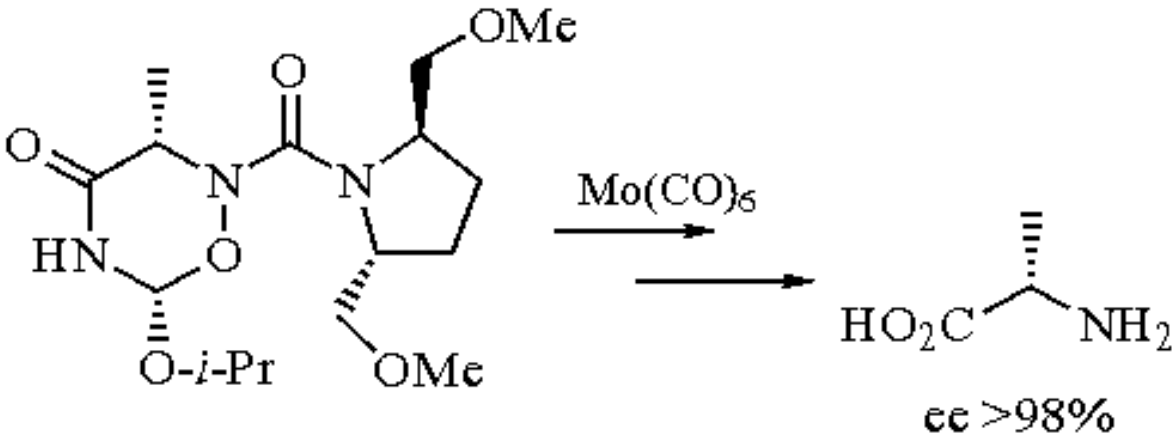

Other Organomolybdenum Reagents.

Recent reviews[43,44] have covered some of the extensive chemistry of organomolybdenum reagents derived from $Mo(CO)_6$, which allows stoichiometric regioselective and stereoselective C-C bond formation. Control of regiochemistry by differences in electronic character of the nitrosyl and carbonyl ligands can be observed in nucleophilic additions to $[CpMo(NO)(CO)(allyl)]^+$ complexes.[45] The stereogenic center at molybdenum has been resolved, which allows the preparation of chiral alkenes in high enantiomeric purity.[45] $[CpMo(CO)(dienyl)]^+$ systems, such as ***Dicarbonyl(cyclohexadiene)(cyclopentadienyl)molybdenum Tetrafluoroborate***, provide routes for stereocontrolled multiple functionalization of cyclohexene rings.[43,46] $CpMo(CO)_2$(2*H*-pyran) cations derived from the chiral pool have allowed enantioselective transformations for replacement of the pyran carbonyl group by two different substituents.[47] CpMo(NO)(halide)(crotyl) complexes, such as ***Bromo(crotyl)(cyclopentadienyl)(nitrosyl)molybdenum***, are useful reagents for stereocontrolled synthesis of β-methyl homoallyl alcohols via crotyl addition to aldehydes.[48] These reagents and their methallyl analogs have been

resolved and yield products of high enantiomeric purity, comparable to those obtained with crotyltitanium, crotylboron, and crotylboronate reagents. The molybdenum reagents have advantages in ease of separation of products and resistance to moisture.

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Hexacarbonyltungsten

$W(CO)_6$

[14040-11-0] · C_6O_6W · Hexacarbonyltungsten · (MW 351.91)

(desulfurization[1] and dehalogenation[2] of organic compounds; alkene metathesis catalyst[3])

Alternate Name: tungsten hexacarbonyl.

Physical Data: dec. 150 °C; bp 175 °C.

Solubility: slightly sol alcohol, benzene, ether.

Form Supplied in: white crystals; commercially available.

Purification: recrystallized from diethyl ether or sublimed in vacuo at 65-70 °C. For most purposes, hexacarbonyltungsten is used without further purification.

Handling, Storage, and Precautions: highly toxic.

Desulfurization Reactions.

Treatment of sulfides or thiols with hexacarbonyltungsten leads to cleavage of the carbon-sulfur bond. Reactions proceed readily if the sulfur is in the benzylic position. For example, reaction of methyl 2-naphthylmethyl sulfide (**1**) with hexacarbonyltungsten in refluxing chlorobenzene provides dimeric compound (**2**) and the reduced compound 2-methylnaphthalene (**3**) (eq 1).[4] The reaction is thought to proceed via tungsten-induced homolytic cleavage of the carbon-sulfur bond. The resulting benzylic radical then either undergoes radical-radical coupling or hydrogen abstraction.

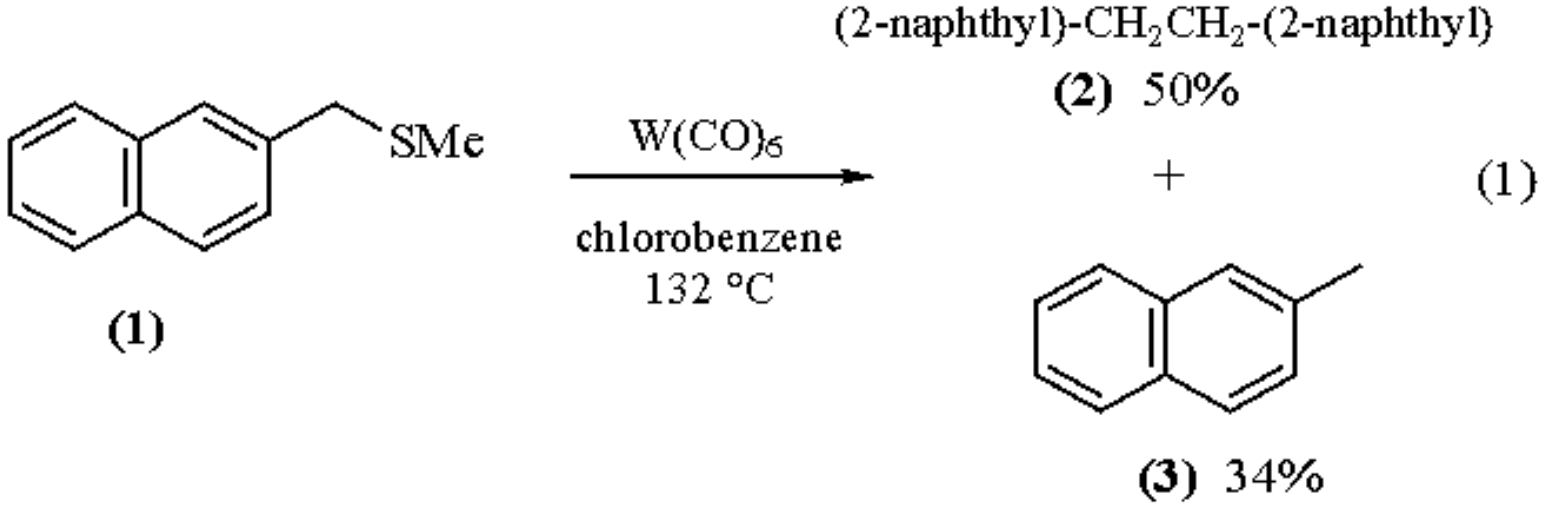

Desulfurization of dithioacetals by hexacarbonyltungsten results in dimerization and alkene formation (eq 2). Dithioacetals derived from ketones, aldehydes, and ketenes (eq 3) are all effective in this transformation. The reaction is believed to involve a carbene intermediate, which undergoes dimerization. In cases where the dimerization is inhibited by steric effects, a sizable amount of the thioketone (**7**) is observed (eq 4).[5] The mechanism for thioketone formation involves tungsten-induced homolysis of the carbon-sulfur bond, followed by elimination of ethylene. In addition, the alkene (**10**) was also observed and results from a C-C insertion of the carbene intermediate (**8**).

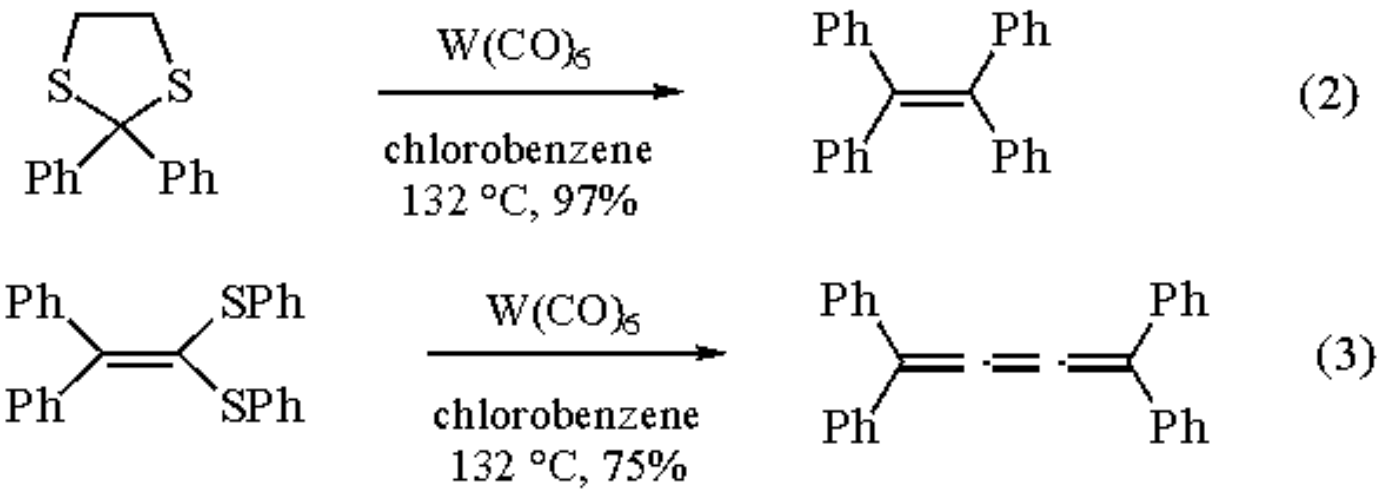

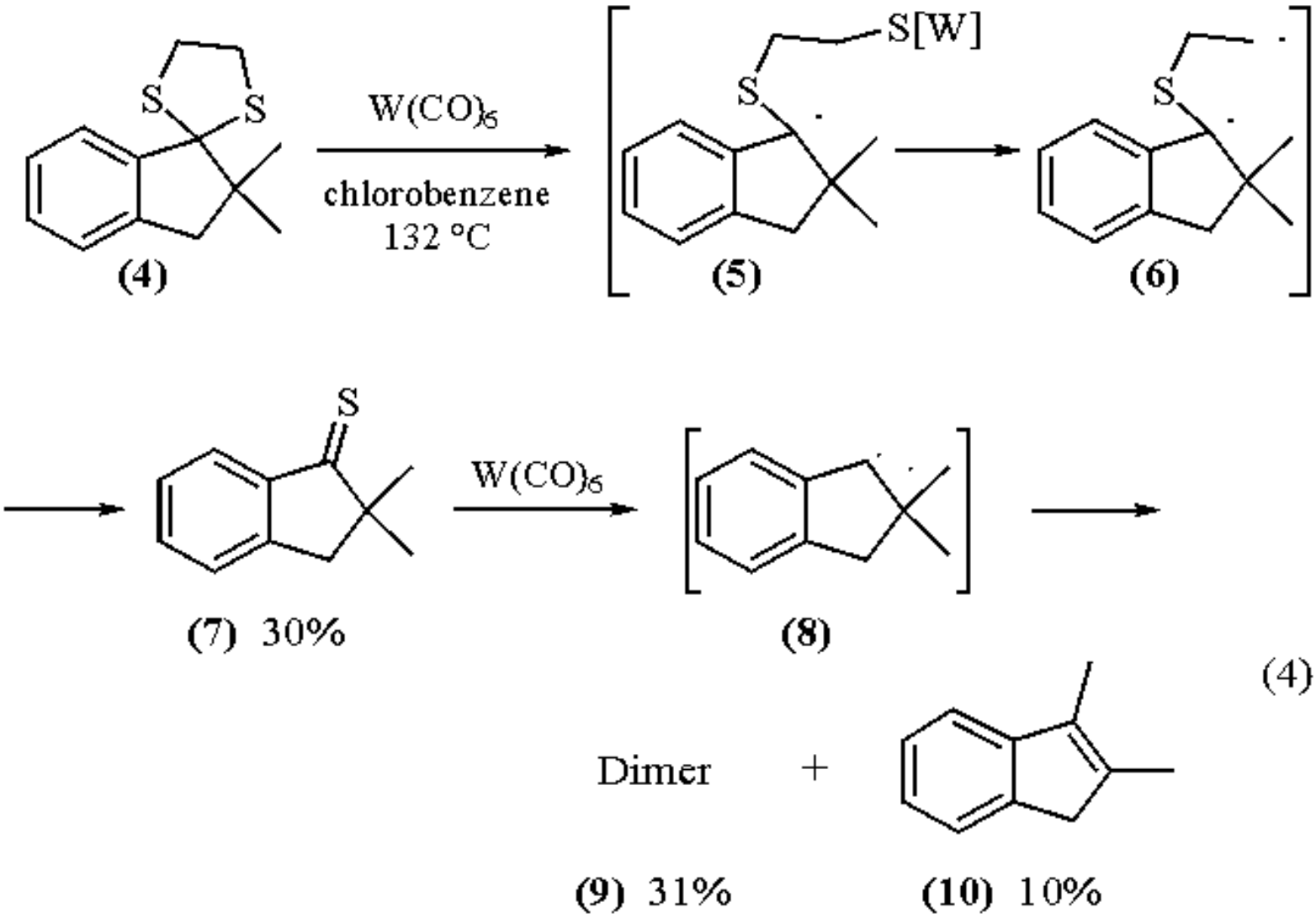

(4)

Dehalogenation-Dimerization of Geminal Dihalides.

Treatment of geminal benzylic dihalides with hexacarbonyltungsten leads to dehalogenation-dimerization (eq 5).[2] The reaction proceeds through a carbene or carbenoid intermediate, and leads to the more stable alkene stereoisomer. This transformation can also be effected using ***Tungsten(VI) Chloride*** and ***Lithium Aluminum Hydride***. Benzylic alcohols undergo deoxygenation-dimerization under similar conditions (eq 6).

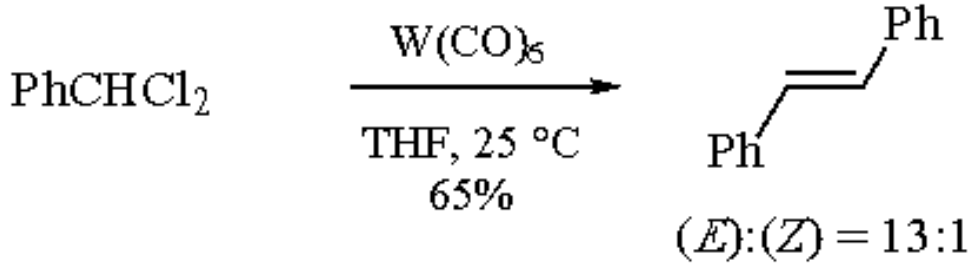

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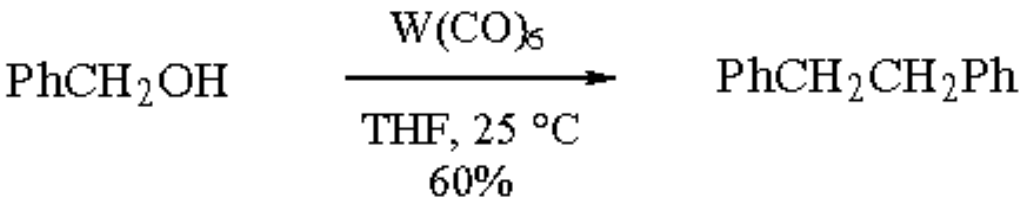

(6)

Alkene Metathesis.

Irradiation of 2-pentene in the presence of hexacarbonyltungsten in carbon tetrachloride solution leads to a 2:1:1 mixture of 2-pentene, 3-hexene, and 2-butene (each compound is predominantly the *trans* isomer) (eq 7).[3] The true alkene metathesis catalyst is generated from irradiation of hexacarbonyltungsten in carbon tetrachloride, and has not been unequivocally determined.[6]

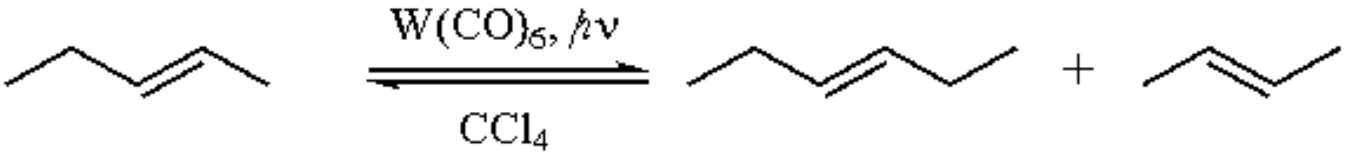

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Hexachloroacetone

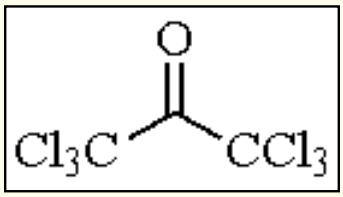

[116-16-5] · C_3Cl_6O · Hexachloroacetone · (MW 264.73)

(chlorination of enamines;[1] preparation of trichloroacetamides[2,3] and trichloroacetates[4,5] under neutral conditions; conversion of allyl[6] and cyclopropylcarbinyl[7] alcohols to the corresponding chlorides)

Alternate Name: hexachloro-2-propanone.

Physical Data: bp 66-70 °C/4 mmHg; mp -30 °C.

Solubility: sol CH_2Cl_2, $CHCl_3$, benzene.

Form Supplied in: commercially available as a liquid in 98-99% purity.

Analysis of Reagent Purity: GC, HPLC.

Purification: distillation.

Handling, Storage, and Precautions: is highly toxic and is suspected to be mutagenic. This reagent should be handled in a fume hood.

Chlorination of Enamines.

Hexachloroacetone rapidly reacts with enamines in THF at -78 to 0 °C to give, after acid hydrolysis, good yields of the corresponding α-chloroketones.[1] The reagent does not affect enol ethers, alkenes, or thioethers at rt.

This reagent is reported to provide cleaner products than Cl_2 or NCS in the chlorination of cyclohexanone enamines. For example, treatment of cyclohexanone enamines with hexachloroacetone followed by acid hydrolysis cleanly gives α-chlorocyclohexanone, whereas use of ***N-Chlorosuccinimide*** results in formation of substantial amounts of dichlorinated ketone byproduct. Direct chlorination of the ketone can also be problematic. Treatment of 2-methylcyclohexanone with ***Chlorine*** gives 2-chloro-2-methylcyclohexanone as the major product, plus *cis*- and *trans*-6-chloro-2-methylcyclohexanone along with 2,6-dichloro-2-methylcyclohexanone.

This reagent can exhibit different regioselectivity from other chlorinating agents. For example, the pyrrolidine enamine of 2-methylcyclohexanone reacts with hexachloroacetone to produce a 9:1 mixture of 6-chloro-2-methylcyclohexanone and 2-chloro-2-methylcyclohexanone (eq 1),[1] whereas ***Sulfuryl Chloride*** gives 2-chloro-2-methylcyclohexanone as the predominant product.

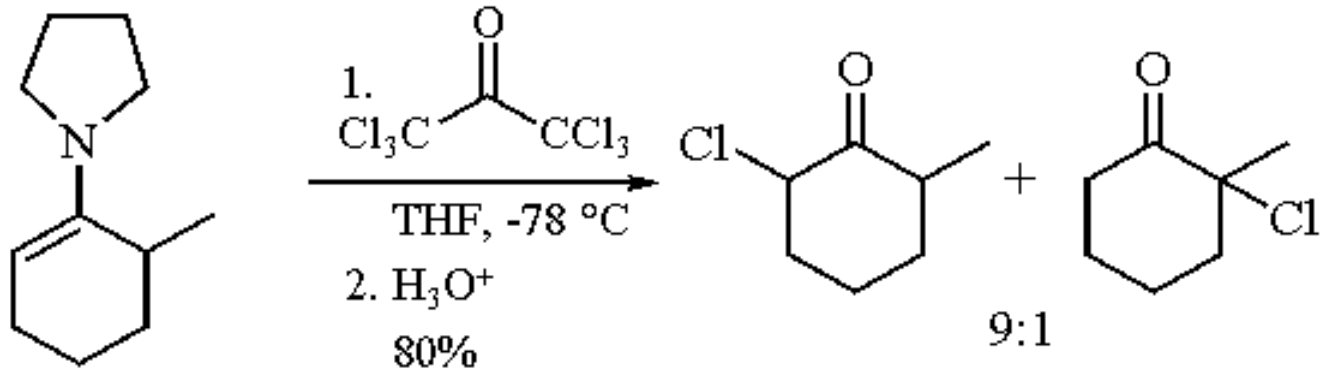

(1)

Trichloroacetylation of Alcohols and Amines.

Hexachloroacetone reacts under neutral conditions with dipeptides at rt in DMSO to produce the corresponding trichloroacetamides in high yield.[2] No reaction with the carboxylic acid functional group is observed (eq 2).

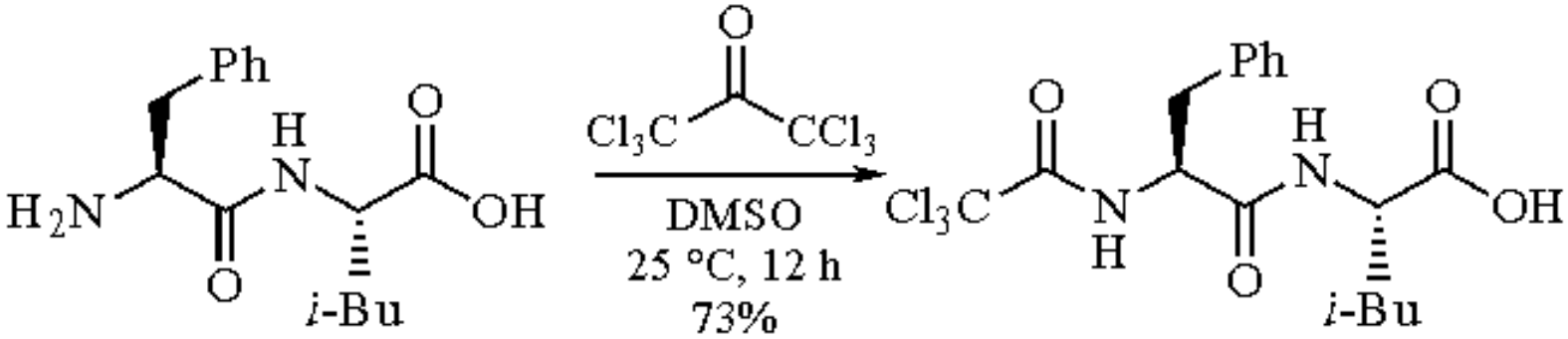

(2)

With modification of the reaction conditions, a number of alkyl, aryl, and heteroaryl amines can be efficiently trichoroacetylated using this reagent.[3]

Hexachloroacetone in the presence of a strong hydrogen bond acceptor such as DMF will convert alcohols into the corresponding trichloroacetates in high yield (eq 3).[4] This reaction is sterically sensitive, and thus can be used to selectively acylate less hindered hydroxy groups.[5]

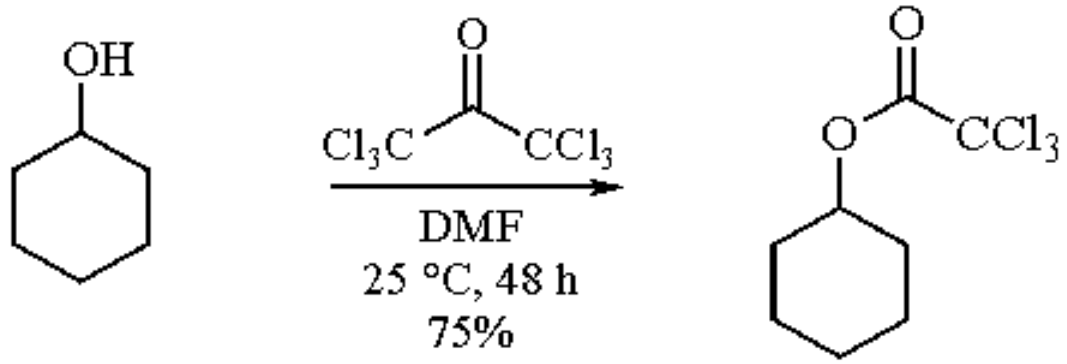

(3)

Chlorination of Allyl and Cyclopropylcarbinyl Alcohols.

Hexachloroacetone reacts with allyl and cyclopropylcarbinyl alcohols in the presence of ***Triphenylphosphine*** to produce the corresponding chlorides. With primary and secondary allyl alcohols, the reaction proceeds to give mostly unrearranged allyl chloride with retention of double bond stereochemistry and inversion of configuration at the hydroxy-bearing carbon (eq 4).[6] Tertiary allylic alcohols predominantly give rearranged products. This reagent system is a useful substitute for ***Triphenylphosphine-Carbon Tetrachloride*** in preparing volatile allyl chlorides that are not easily separable from CCl_4.

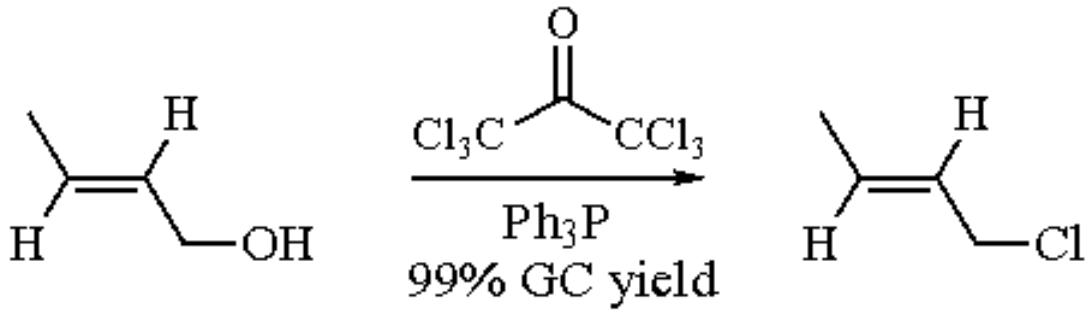

(4)

Cyclopropylcarbinyl alcohols react with hexachloroacetone in the presence of triphenylphosphine to give high yields of cyclopropylcarbinyl chlorides that are free of homoallylic rearrangement products (eq 5).[7]

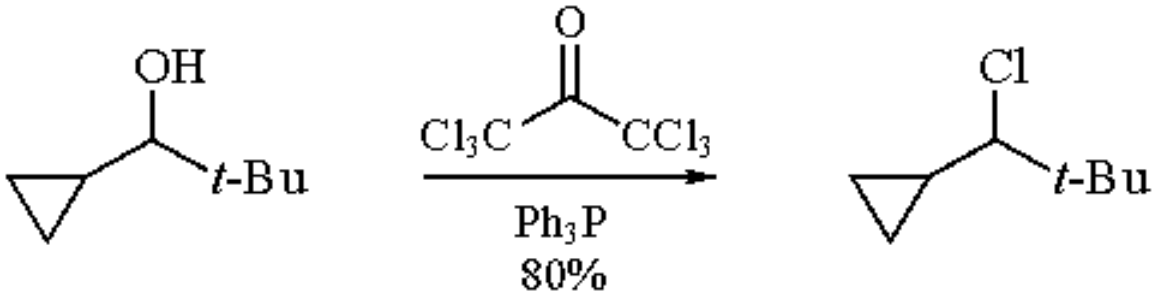

(5)

Related Reagents.

Triphenylphosphine-Hexachloroacetone.

1. (a) Laskovics, F. M.; Schulman, E. M. *TL* **1977**, 759. (b) Laskovics, F. M.; Schulman, E. M. *JACS* **1977**, *99*, 6672.
2. Panetta, C. A.; Casanova, T. G. *JOC* **1970**, *35*, 2423.
3. (a) Bew, C.; de Joshi, V. O.; Gray, J.; Kaye, P. T.; Meakins, G. D. *JCS(P1)* **1982**, 945. (b) Rudavskii, V. P.; Khaskin, I. G. *UKZ* **1967**, *33*, 391 (*CA* **1967**, *67*, 63 963).
4. Freedlander, R. S.; Bryson, T. A.; Dunlap, R. B.; Schulman, E. M.; Lewis, C. A., Jr. *JOC* **1981**, *46*, 3519.
5. Haines, A. H.; Sutcliffe, E. J. *Carbohydr. Res.* **1985**, *138*, 143.
6. (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *TL* **1977**, 2999. (b) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *JOC* **1979**, *44*, 359. (c) Magid, R. M.; Talley, B. G.; Souther, S. K. *JOC* **1981**, *46*, 824.
7. Hrubiec, R. T.; Smith, M. B. *JOC* **1984**, *49*, 431.

George D. Maynard

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2,3,4,5,6,6-Hexachloro-2,4-cyclohexadien-1-one[1]

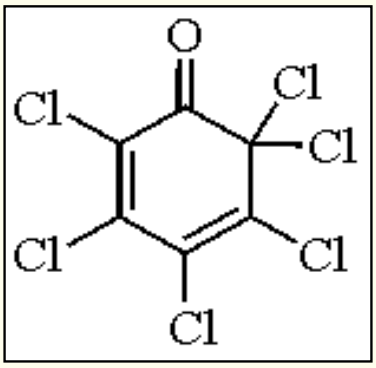

[21306-21-8] · C_6Cl_6O · 2,3,4,5,6,6-Hexachloro-2,4-cyclohexadien-1-one · (MW 300.76)

(regioselective chlorination of ketones[2] and phenols;[3] α´-chlorination of α,β-unsaturated ketones[3])

Physical Data: mp 50-51 °C.

Solubility: sol dichloromethane, methanol, ethanol, DMF.

Form Supplied in: crystalline material; commercially available.

Preparative Method: chlorination of the sodium salt of pentachlorophenol at 0 °C (eq 1).[2,4,5]

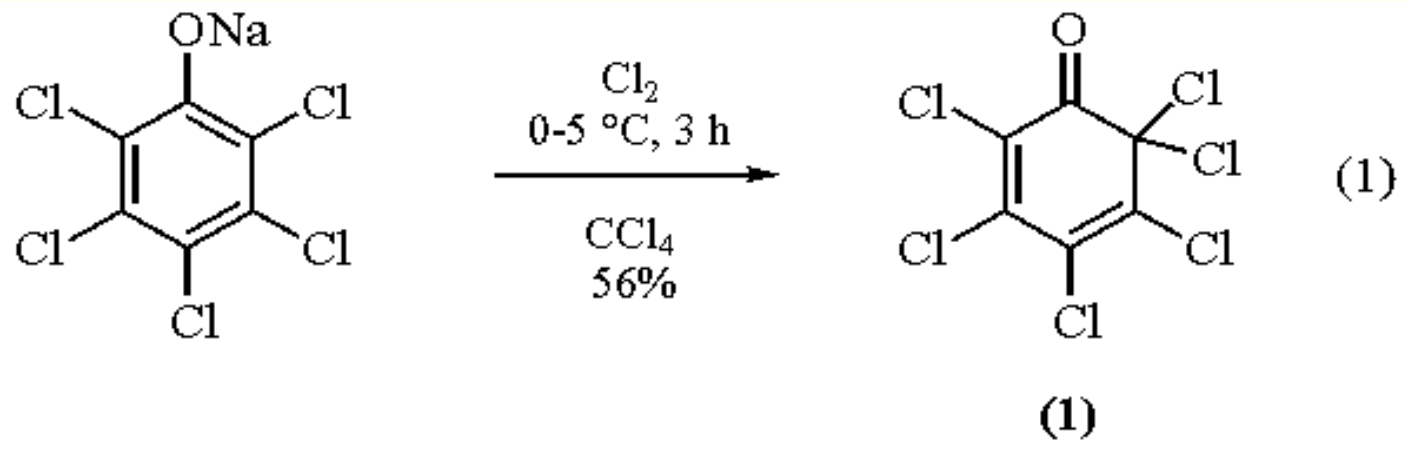

Analysis of Reagent Purity: mp, ^{13}C NMR.[6]

Handling, Storage, and Precautions: keep in a dark vessel, well protected from light to prevent isomerization (see below). The reagent should always be handled in a well-ventilated fume hood.

Regioselective *ortho*-Chlorination of Phenols and Naphthols.

The chlorination of phenol with 1 equiv of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one (**1**) in CCl_4 under irradiation of a 100 W mercury lamp gave rise to 2-chlorophenol and 4-chlorophenol in a 92:8 ratio (eq 2).[5] Similar selectivity was obtained for 4-methylphenol, which by direct chlorination with chlorine leads to mono-, di-, and trichloro derivatives, in addition to some oxidation products. Irradiation may not be necessary, as similar results are obtained on chlorination of phenols with this reagent in dichloromethane (sometimes in the presence of 25% DMF) at rt.[3,7]

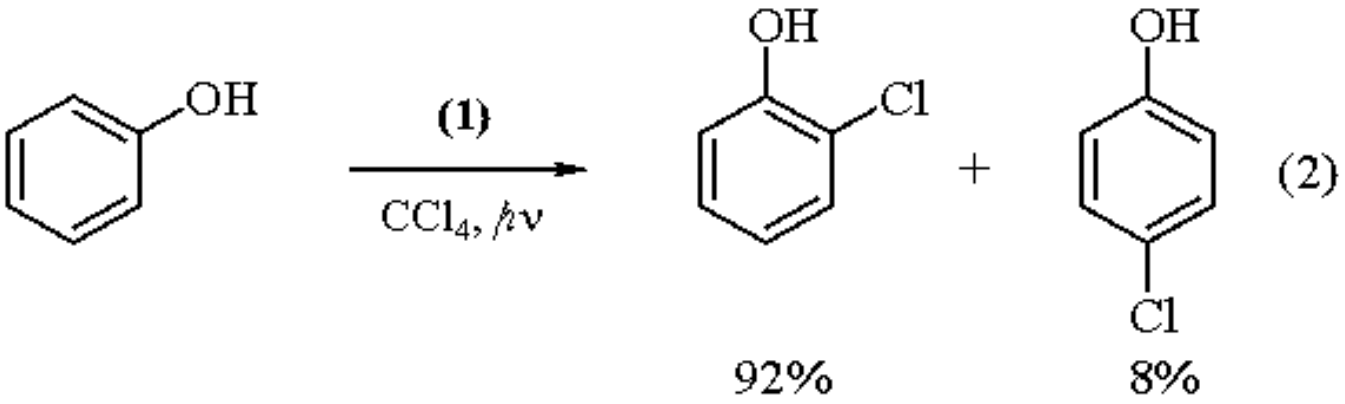

The ability of this reagent to effect regioselective *ortho*-chlorination of phenols has been ascribed to charge transfer interactions and hydrogen bonding with the substrate (eq 3). The reagent can differentiate between phenols and phenolic ethers (eq 4).[7] It should be stressed that the isomeric reagent 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one gives *p*-chlorination of phenols by similar complexation.[3,7] Naphthols are chlorinated by 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one to give *o*-chloronaphthols with even better selectivity than for phenols (eq 5).[8] Regioselective *ortho*-chlorination of naphthols substituted with alkoxy groups is cleanly achieved (eqs 6 and 7).[3,8] Again the isomeric 2,3,4,4,5,6-hexachloro derivative affords *p*-chlorinated naphthols preferentially.[8]

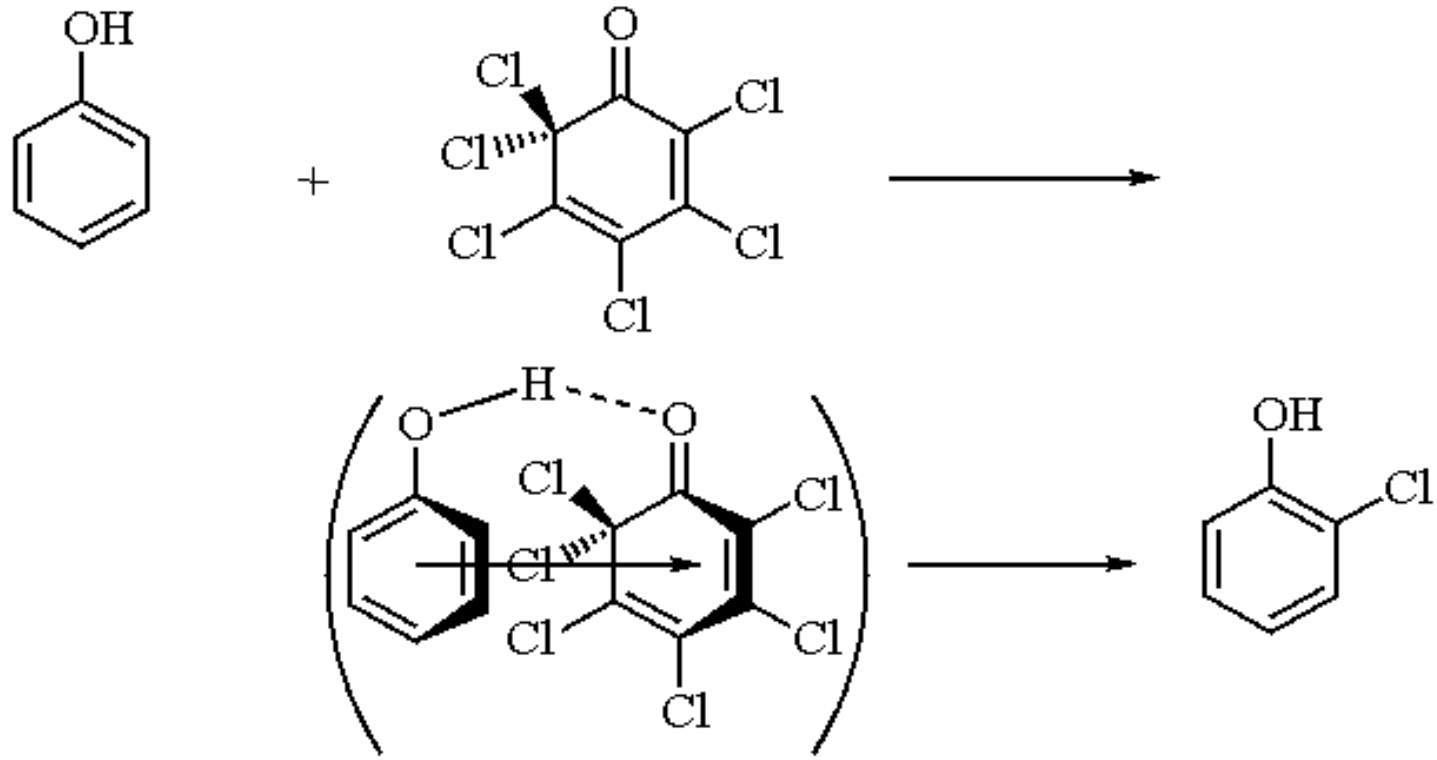
OH
O
Cl
Cl
Cl
Cl
Cl
Cl
H
O
O
OH
Cl

(3)

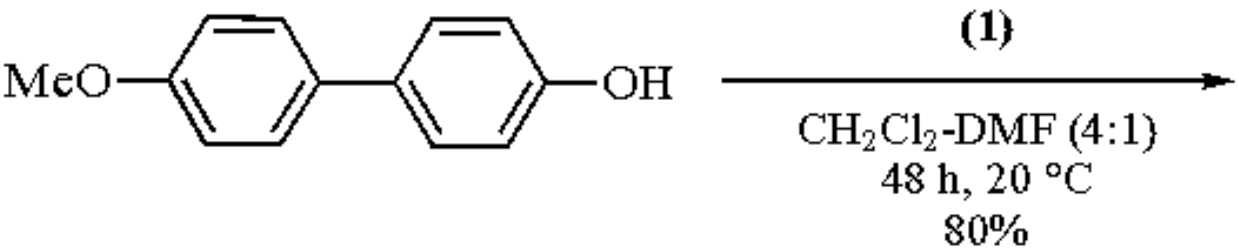
MeO
OH
(1)
CH2Cl2-DMF (4:1)
48 h, 20 °C
80%

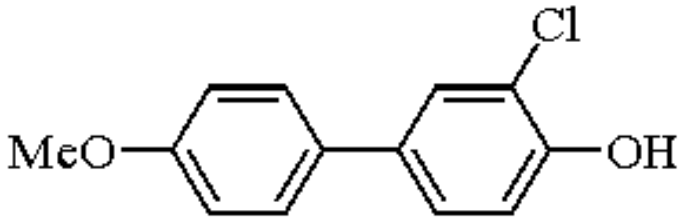
Cl
MeO
OH

(4)

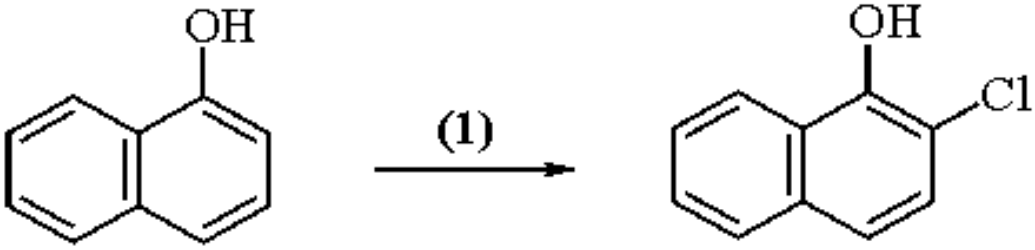
OH
(1)
OH
Cl

(5)

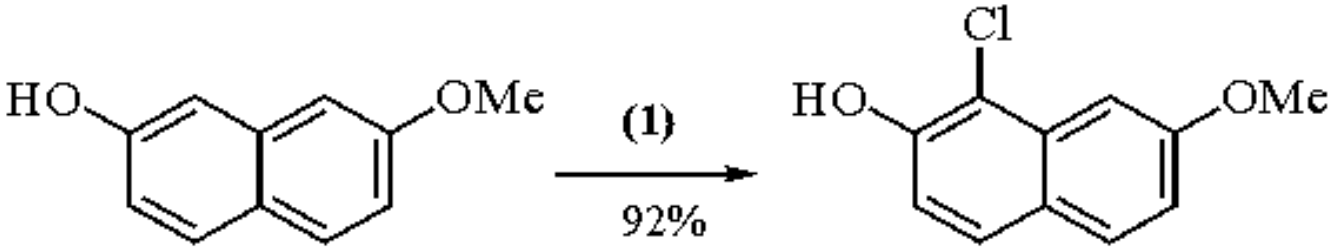

(6)

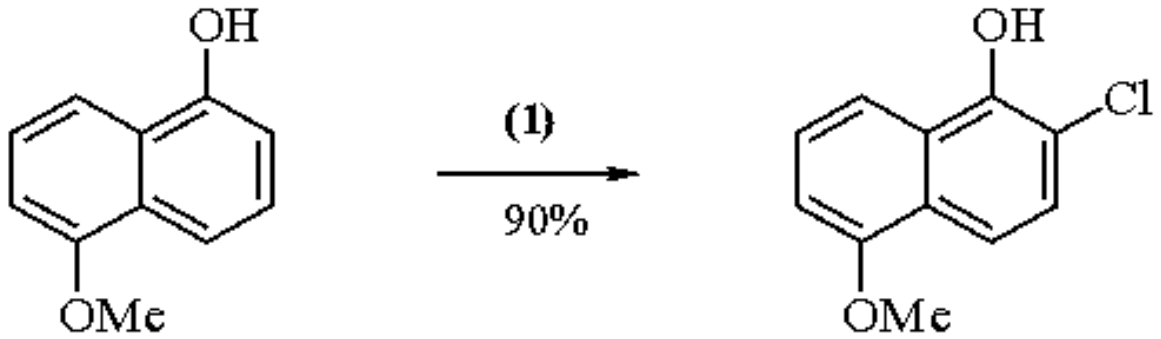

(7)

Selective α-Chlorination of Alkyl Aryl Ketones.

Enol derivatives of ketones can participate in donor-acceptor interactions with 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one. The presence of an electron-rich aromatic ring is a necessary prerequisite for complex formation and the resulting α-chlorination. Aliphatic ketones do not form sufficiently stable complexes with the chlorinating reagent, and thus are not chlorinated.[2] However, alkyl aryl ketones react smoothly with the reagent in ethanol at reflux to give high yields of 1-chloroalkyl aryl ketones (eqs 8-11).[2,3] Chlorination of the aromatic nucleus is not observed in reactions of *p*-hydroxy aromatic ketones (eqs 9 and 10).

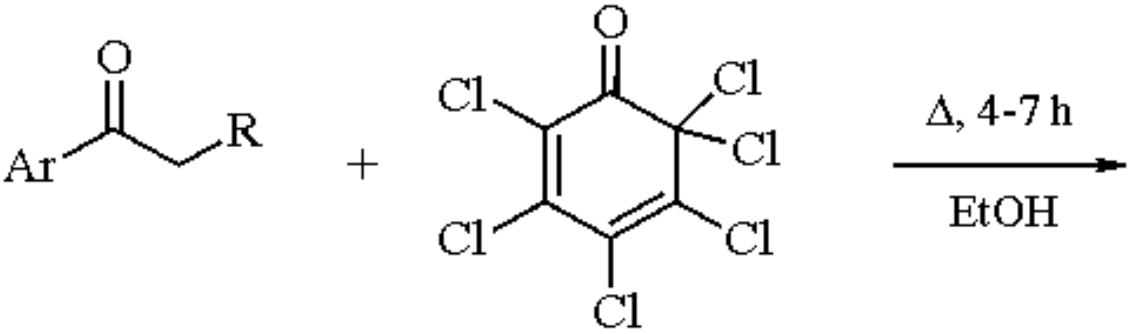

(8)

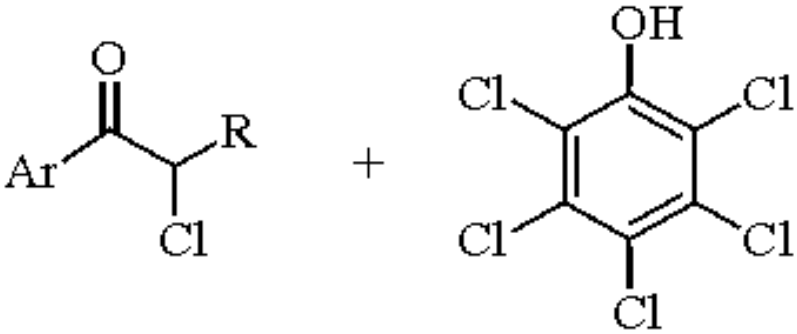

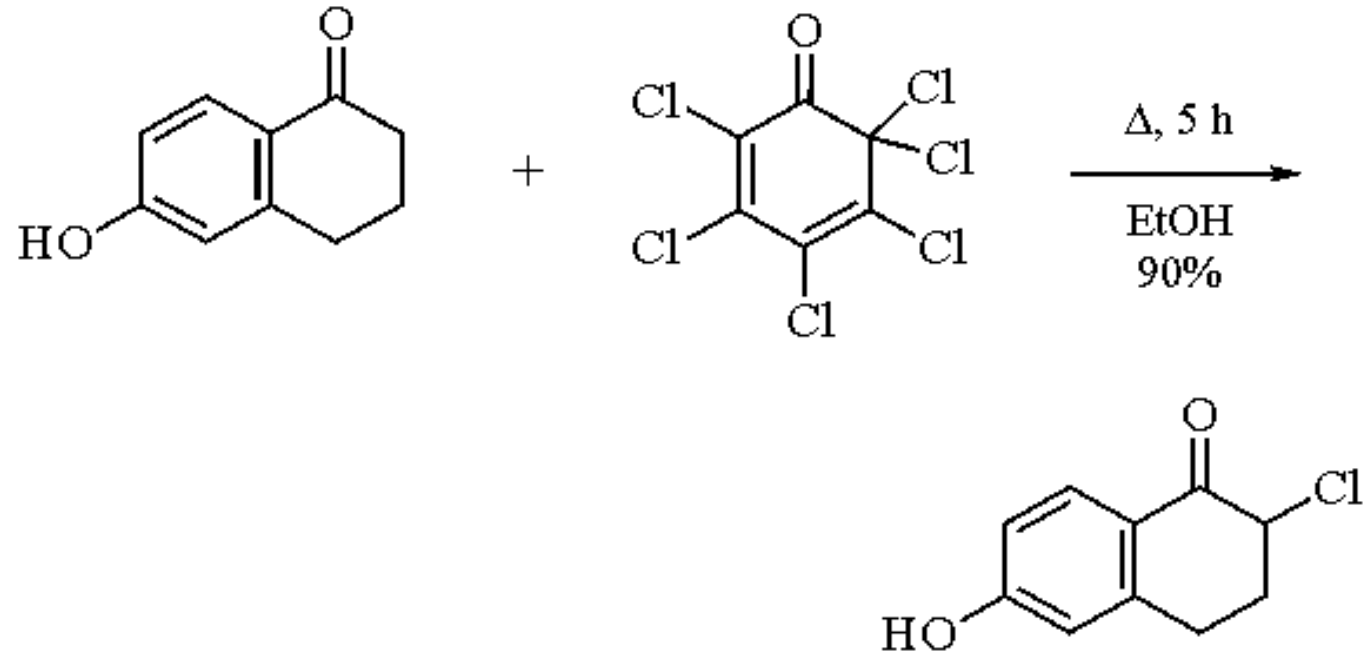

(9)

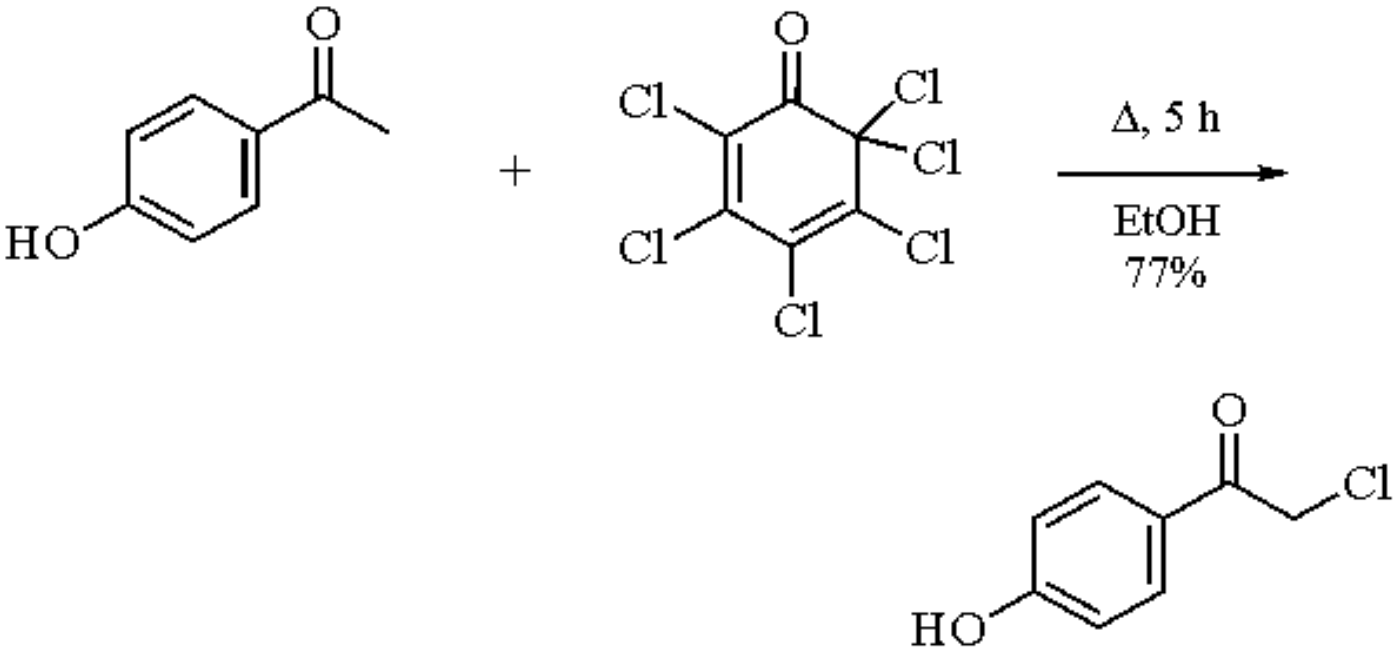

(10)

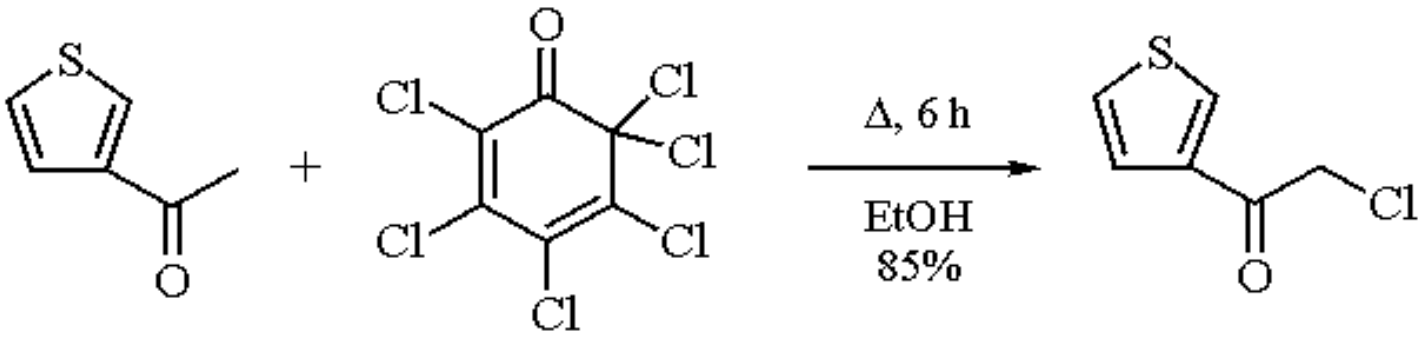

(11)

In DMF, however, selective chlorination of the aromatic system again takes precedence (eq 12).[9]

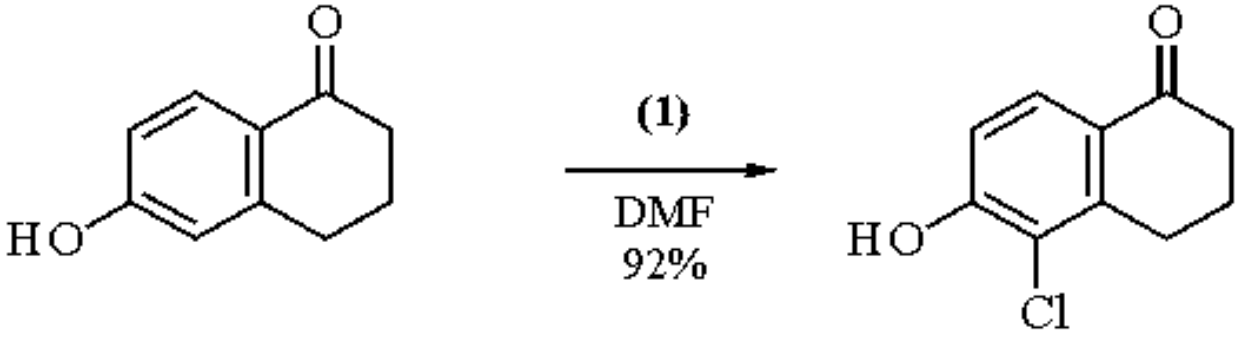

(12)

α,β-Unsaturated ketones are monochlorinated by this reagent at the α´-position (eq 13).[2,3]

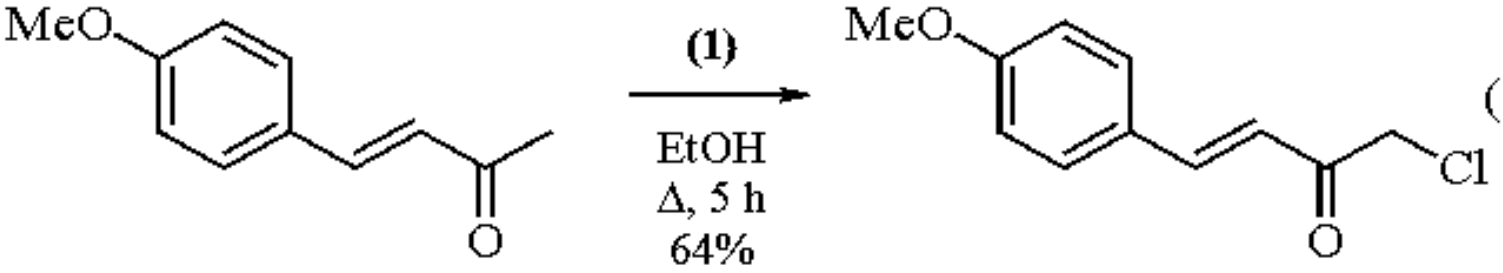

(13)

Isomerization.

Care should be taken to avoid isomerization of 2,3,4,5,6,6-hexachloro-2,4-cyclohexadien-1-one to 2,3,4,4,5,6-hexachloro-2,5-cyclohexadien-1-one, because the regiochemical course of chlorinations with this reagent is different.[3,5,7] The former reagent rearranges to the latter by treatment with acid or ***Aluminum Chloride***, by heating, or upon irradiation.[5]

---

1. Lemaire, M.; Guy, A.; Hoa, H. A.; Guetté, J.-P. *Janssen Chim. Acta* **1987**, *5*, 3.
2. Guy, A.; Lemaire, M.; Guetté, J.-P. *S* **1982**, 1018.
3. Lemaire, M.; Guy, A.; Guetté, J.-P. *BSF* **1985**, 477.
4. Denivelle, L.; Fort, R. *BSF* **1956**, 1834.
5. Guy, A.; Lemaire, M.; Guetté, J.-P. *CC* **1980**, 8.
6. Hawkes, G. E.; Smith, R. A.; Roberts, J. D. *JOC* **1974**, *39*, 1276.
7. Guy, A.; Lemaire, M.; Guetté, J.-P. *T* **1982**, *38*, 2339.
8. Guy, A.; Lemaire, M.; Guetté, J.-P. *T* **1982**, *38*, 2347.
9. Lemaire, M.; Guy, A.; Guetté, J.-P. *CR(2)* **1984**, *299*, 693.

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Hexachlorodisilane[1]

Cl_3Si-$SiCl_3$

[13465-77-5] · Cl_6Si_2 · Hexachlorodisilane · (MW 268.88)

(deoxygenation and desulfurization of phosphine oxides, phosphine sulfides, and amine oxides; reducing agent for nitro groups and sulfur diimides)

Physical Data: bp 144-145.5 °C; *d* 1.562 g cm^{-3}.

Solubility: sol $CHCl_3$, CH_2Cl_2, benzene, THF; reacts violently, producing toxic fumes, with H_2O, alcohols.

Form Supplied in: neat as clear colorless liquid.

Handling, Storage, and Precautions: neat liquid and solutions react violently with water and protic solvents to produce HCl gas. Avoid contact with strong bases. Hexachlorodisilane is corrosive and should be handled and stored in a tightly sealed vessel under N_2. Store cool. Vapor ignites in air when heated. Avoid prolonged and repeated exposure. Use in a fume hood.

Deoxygenation and Desulfurization.

Hexachlorodisilane has been shown to effect the stereospecific reduction of phosphine oxides to phosphines with inversion of configuration (eq 1),[2] although short reaction times are required to prevent chemical racemization of the phosphine products under the reaction conditions. This protocol complements ***Trichlorosilane*** which, under appropriate conditions, reduces phosphine oxides with retention of configuration.[2,3] Reductions of bridged bicyclic phosphine oxides[4] and cyclic halophospholene oxides[5] by hexachlorodisilane have also been reported.

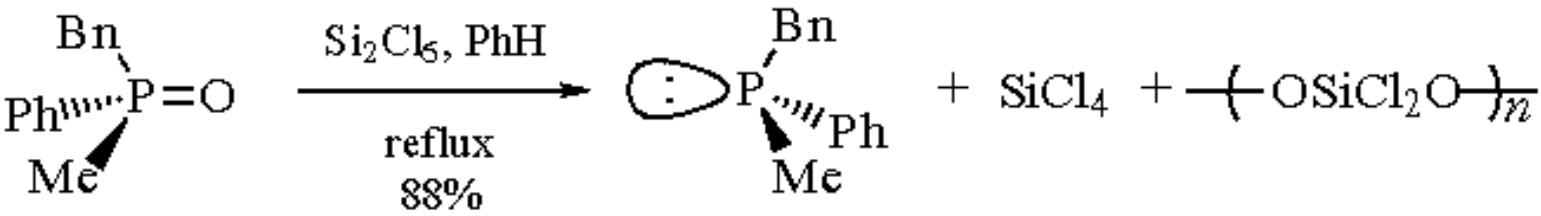

(1)

In contrast to the deoxygenation of phosphine oxides by hexachlorodisilane, desulfurization of phosphine sulfides by this reagent occurs stereospecifically with *retention* of configuration (eq 2).[6]

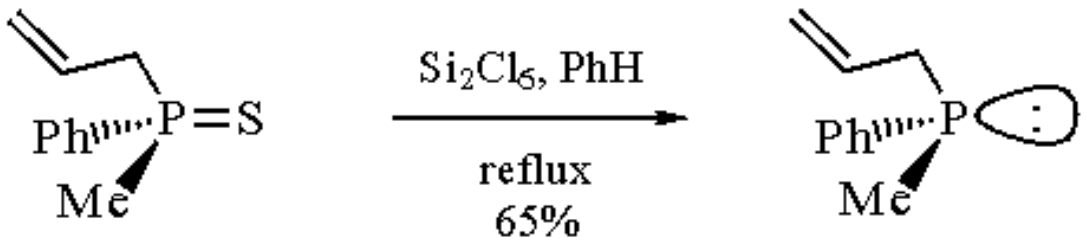

(2)

Quinuclidine *N*-oxide was reduced by hexachlorodisilane (eq 3).[2] Likewise, azo oxide,[7] azo dioxide,[8,9] and sulfoxide deoxygenations[2] by the reagent were also reported. Treatment of aryl nitro compounds with hexachlorodisilane afforded products which suggested the possibility of a nitrene intermediate being involved (eq 4).[10] Other disilanes were evaluated in the study, including hexamethyl- and hexaphenyldisilane, pentamethylphenoxy- and pentamethylphenyldisilane, as well as novel benzodisilacyclopentane (**1**).

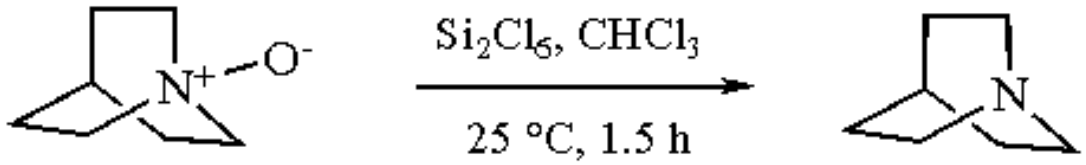

(3)

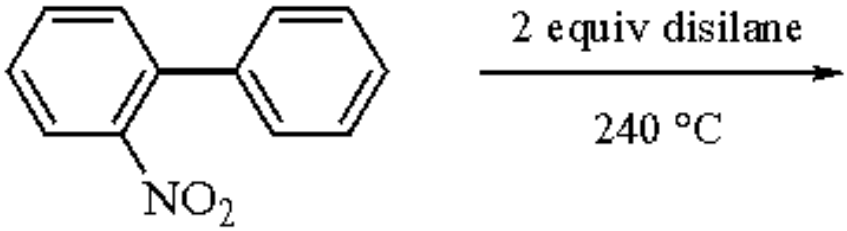

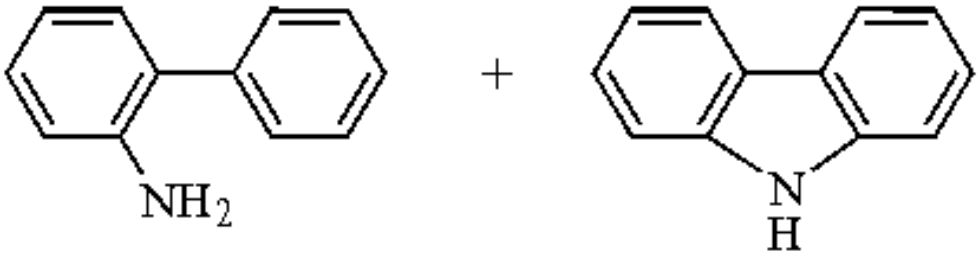

(4)

$SiCl_6$	47%	10%
(1)	1%	71%

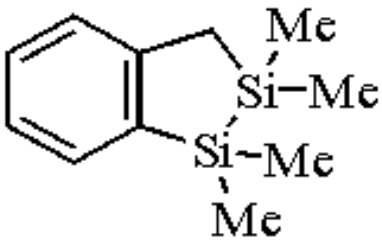

(1)

Quinoxaline 1,4-dioxide derivatives were reduced by hexachlorodisilane to give the corresponding quinoxalines (eq 5).[11] Also evaluated in the study were the reducing agents ***Iodotrimethylsilane***, ***Trifluoroacetic Anhydride-Sodium Iodide***, and ***Titanium(IV) Chloride-Zinc*** dust. Hexachlorodisilane, for its convenience and efficiency, was recommended by the authors as the reagent of choice for this transformation.

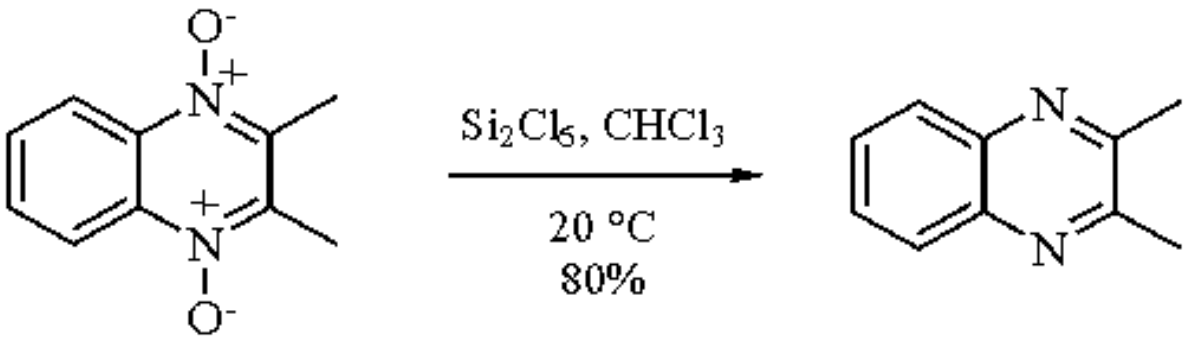

(5)

Dehydroxylation occurred upon treatment of the alkoxide of a 1-hydroxyimidazole derivative with hexachlorodisilane (eq 6).[12] In the same report it was observed that nitrones are deoxygenated upon treatment with hexachlorodisilane, while C=N reduction occurs to yield hydroxylamines with ***Trichlorosilane*** (eq 7).

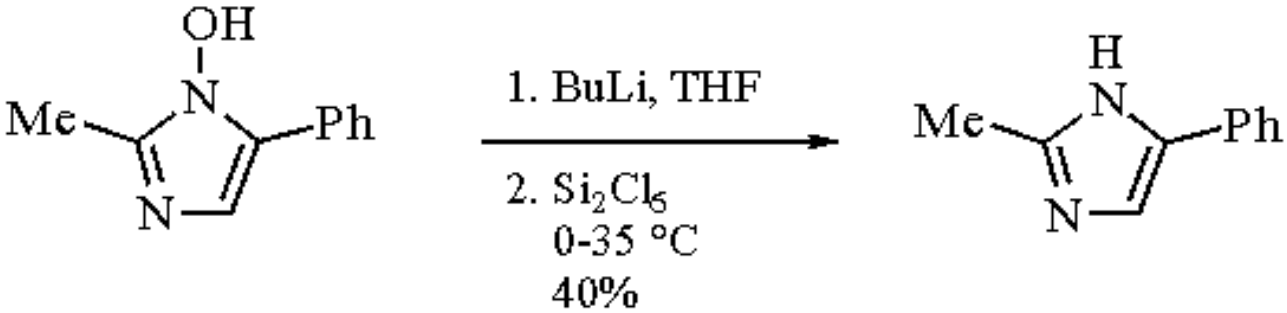

(6)

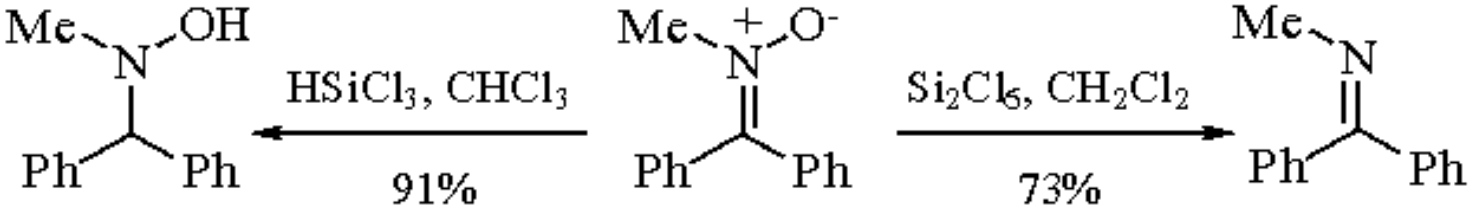

(7)

(Trichlorosilyl)phosphane Synthesis.

Chlorophosphanes or (trimethylsilyl)phosphanes are converted to trichlorosilylphosphanes upon treatment with hexachlorodisilane (eq 8).[14]

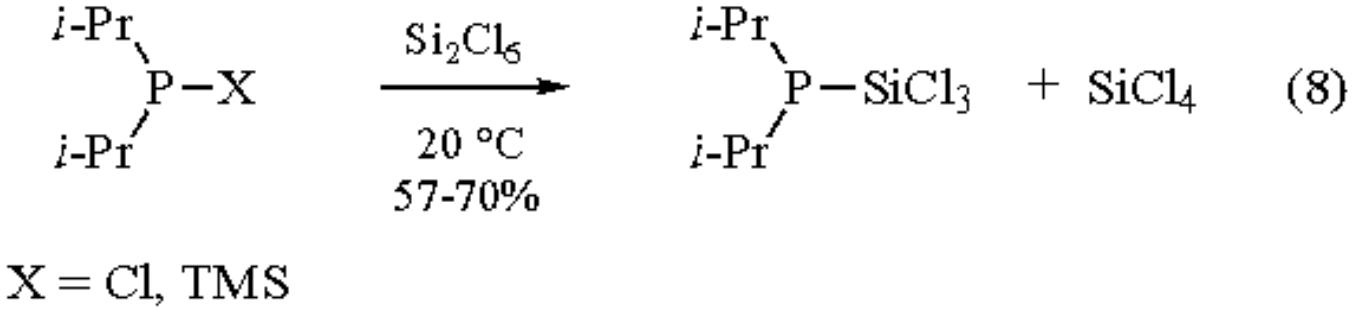

Sulfur Diimide Reduction.

N-Trichlorosilyldiaminosulfanes were prepared upon treatment of sulfur diimides with hexachlorodisilane (eq 9).[13] Likewise, the corresponding *N*-dichloromethylsilyldiaminosulfanes resulted by substituting 1,2-dimethyl-1,1,2,2-tetrachlorodisilane for hexachlorodisilane.

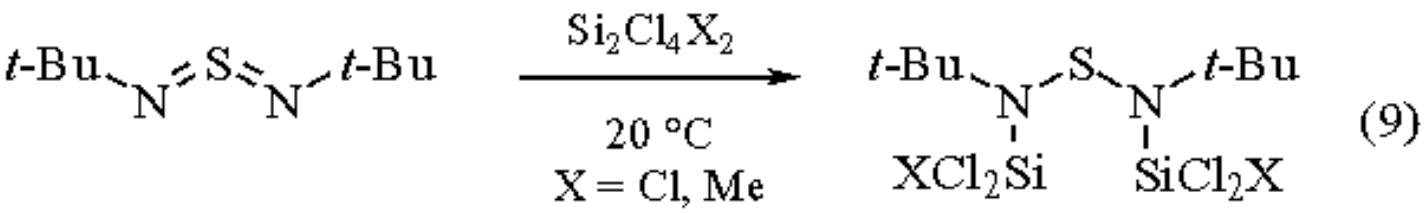

Related Reagents.

Trichlorosilane.

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Hexachloroethane

Cl_3C-CCl_3

[67-72-1] · C_2Cl_6 · Hexachloroethane · (MW 236.72)

(mild chlorinating agent;[1,2] versatile reagent in organophosphorus chemistry[3-5])

Alternate Name: perchloroethane.

Physical Data: mp 190-195 °C (sublimes); *d* 2.091 g cm^{-3}; rhombohedric crystals from EtOH.

Solubility: insol H_2O; sol organic solvents.

Form Supplied in: white solid; widely available.

Purification: steam distillation, then recrystallization from 95% EtOH.[20]

Handling, Storage, and Precautions: cancer suspect agent; irritant. Use in a fume hood.

Chlorination of Carbon Compounds.

Hexachloroethane is a formal source of electrophilic chlorine in the chlorination of nucleophiles.[1,2] The reagent can conveniently be used in large-scale reactions.[6] THF[7-11] is the solvent of choice for chlorination of aryllithiums (eqs 1 and 2).

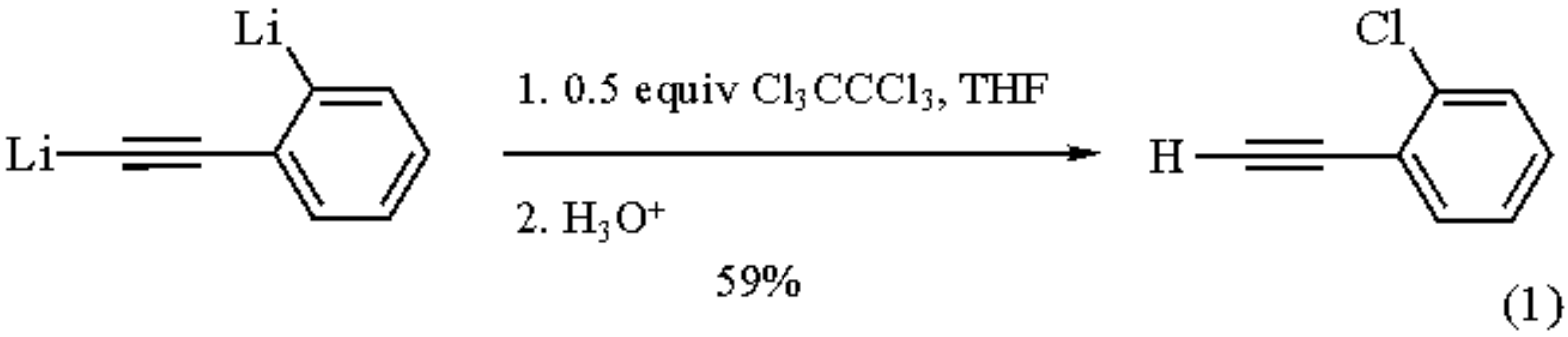

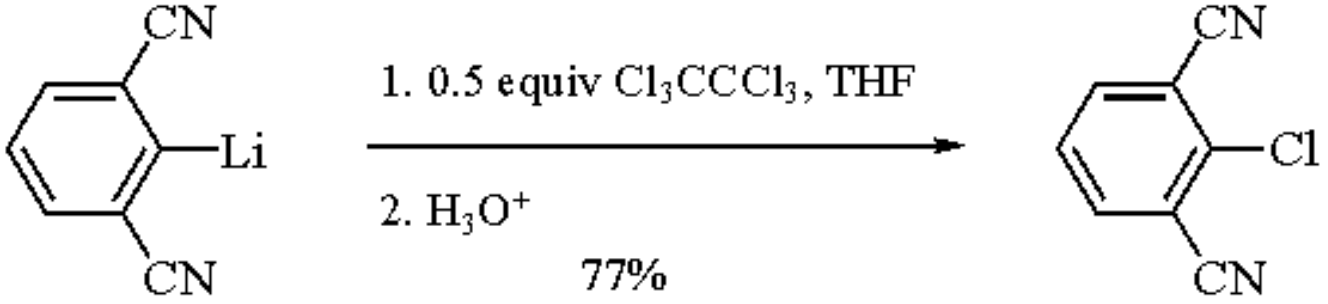

(2)

The reactions with Wittig reagents (eq 3) are usually conducted in ether,[12] and sulfoximine derivatives are chlorinated by Cl_3CCCl_3 in DMF.[13] Phase-transfer conditions are recommended for chlorination of allyl sulfones (eq 4)[14,15] and benzyl and benzal chlorides (eq 5).[6]

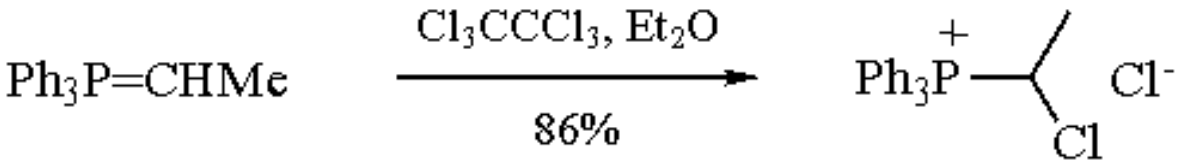

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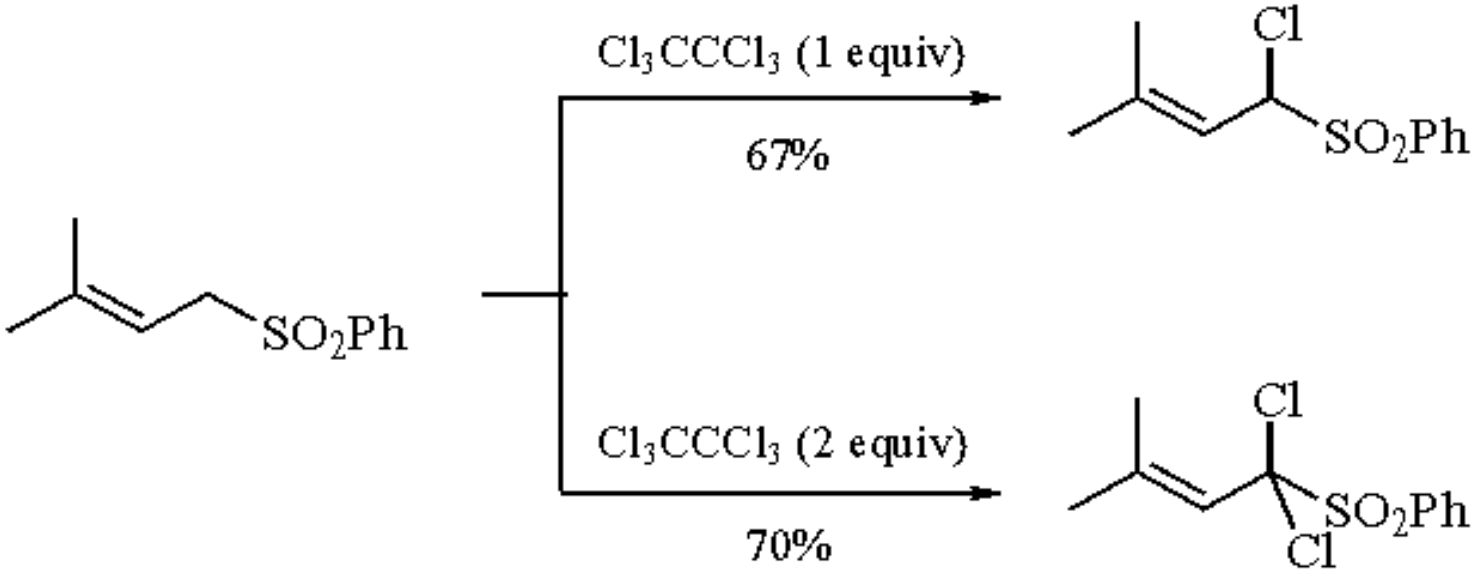

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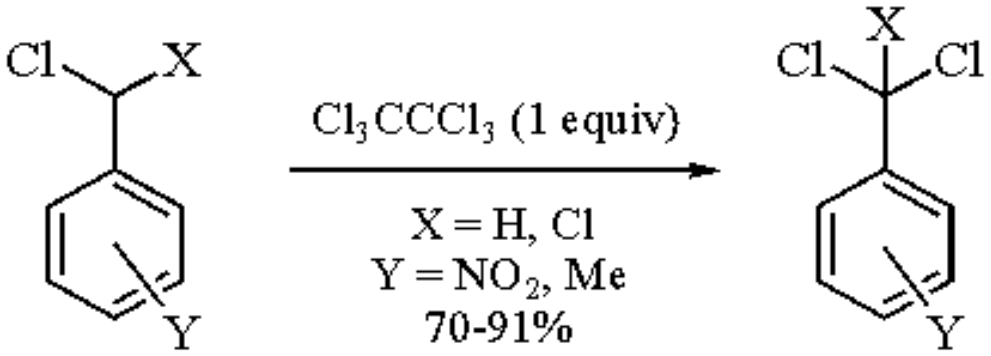

(5)

In a typical reaction, a mixture of equimolar amounts of the substrate and Cl_3CCCl_3, dichloromethane, 50% aq NaOH, and a catalytic amount of tetrabutylammonium bromide (TBAB) is stirred at rt.[15] The phase-transfer catalysis can be aided by sonication in the synthesis of *gem*-bromochlorocyclopropanes by the reaction of an alkene,

Bromoform, and Cl_3CCCl_3 in the presence of powdered ***Sodium Hydroxide***.[16]

Reactions with Organophosphorus Compounds.[3-5]

The important applications of Cl_3CCCl_3 in organophosphorus chemistry are the syntheses of 1-chloro-2-phenyl-2-(trimethylsilyl)-1-phosphaethylene (eq 6),[3,4] tetraphosphacubanes (eq 7),[17] and *trans*-1,2,4,5-tetraphosphatricyclo[3.1.0.0^{2,4}]hexane (eq 8).[18]

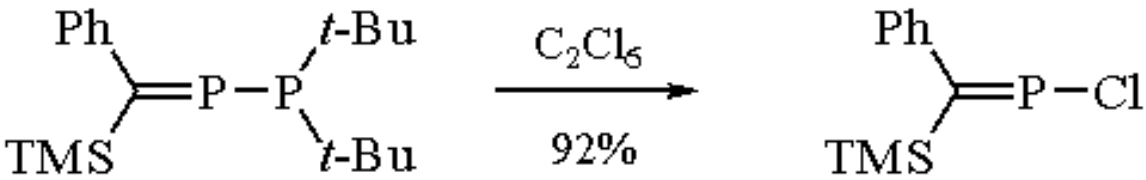

(6)

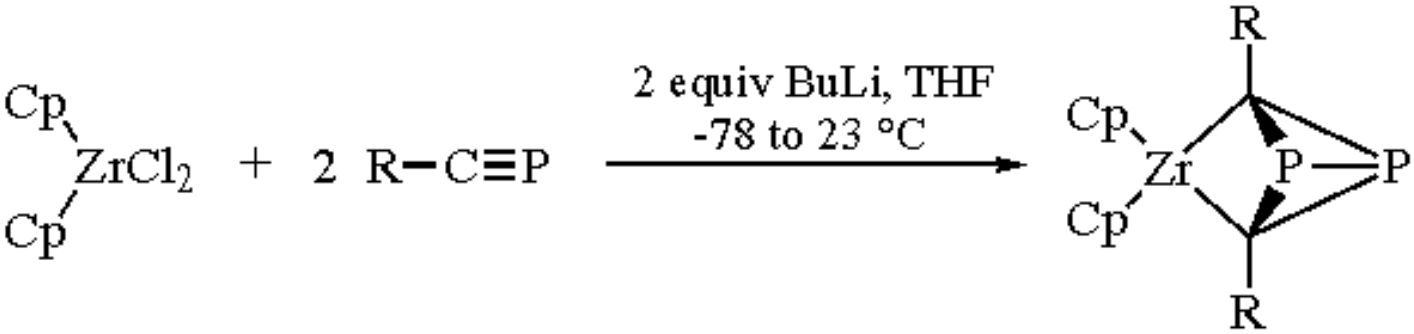

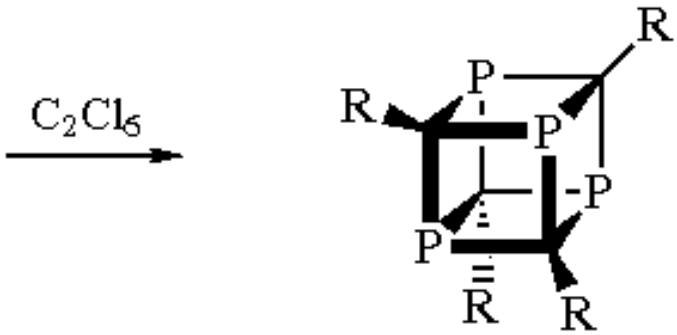

(7)

R = *t*-Bu, 70%;
CMe$_2$Et, 75%;
adamantyl, 30%

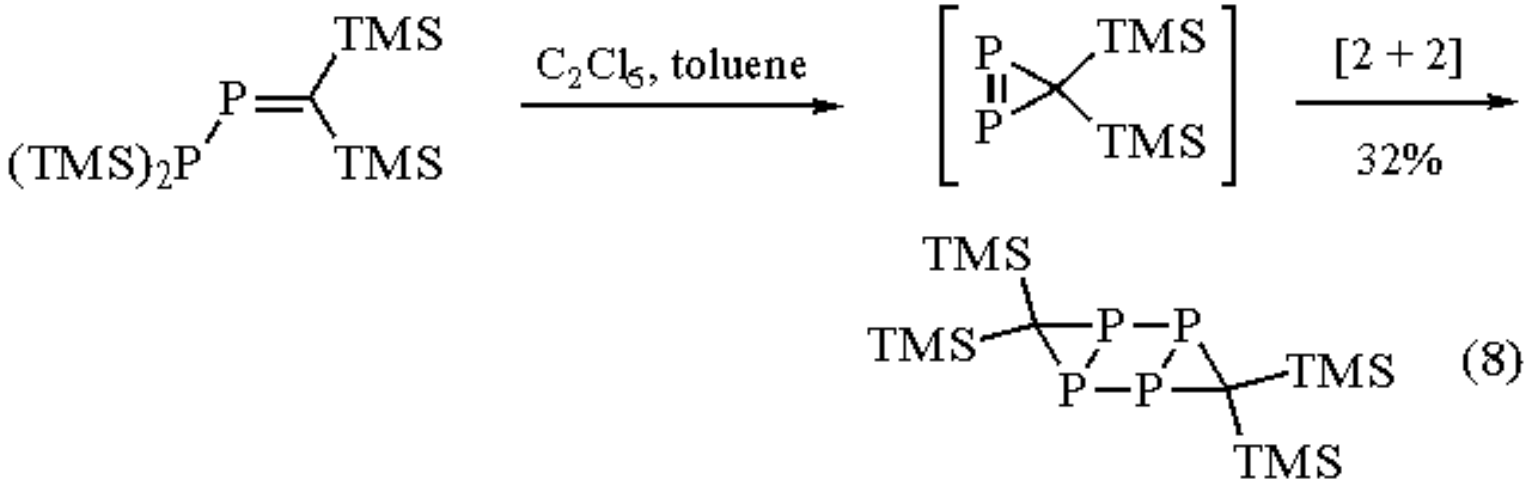

A combination reagent, ***Hexamethylphosphorous Triamide***-Cl_3CCCl_3-***1-Hydroxybenzotriazole***, has been used in the synthesis of oligopeptides containing arginine.[19]

Related Reagents.

t-Butyl Hypochlorite; ***Chlorine***; ***Chlorine-Chlorosulfuric Acid***; ***Dimethyl Sulfide-Chlorine***; ***Chlorine Fluoroxysulfate***; ***Chlorine-Pyridine***; ***N-Chlorosuccinimide***; ***Dichlorine Monoxide***; ***Phosphorus(III) Chloride***; ***Sulfuryl Chloride***.

---

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Hexadecacarbonylhexarhodium[1]

$Rh_6(CO)_{16}$

[28407-51-4] · $C_{16}O_{16}Rh_6$ · Hexadecacarbonylhexarhodium · (MW 1065.62)

(catalyst for hydrogenation of alkenes, hydroformylations of alkenes; reducing agent for aldehydes, ketones, and nitro groups; catalyst for carbenoid reactions of diazo compounds)

Physical Data: mp 235 °C;[2] IR (KBr) CO 2073, 2026, 1800 cm^{-1}.[3]

Solubility: sol methanol, ethanol, acetone; slightly sol toluene, benzene, hexane.

Form Supplied in: black crystals.

Preparative Methods: from ***Rhodium(III) Chloride***[5] or from ***Pentacarbonyliron*** and $RhCl_3.3H_2O$.[4]

Catalytic Hydrogenation of Alkenes.

Alkenes are catalytically hydrogenated to alkanes in the presence of $Rh_6(CO)_{16}$,[5] although the reaction is slow in the absence of a ligand such as ***Triphenylphosphine***. Considerable improvement is seen by binding the catalyst to a phosphine-funtionalized polystyrene.[6] In the presence of phosphines, $Rh_6(CO)_{16}$ has been found to be a mild, effective catalyst for the hydrogenation of alkenes.[7] Cyclohexene, for example, can be quantitatively reduced to cyclohexane. Asymmetric hydrogenations have been performed in the presence of ***(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane*** [(+)-DIOP]. *N*-Acylenamine (**1**) was converted to (+)-*N*-acylphenylalanine (**2**) in 40% ee (eq 1) using $Rh_6(CO)_{16}$ and (+)-DIOP.[8] A wide variety of quinolines and isoquinolines have been reduced to 1,2,3,4-tetrahydroquinolines and *N*-formyl 1,2,3,4-tetrahydroisoquinolines in excellent yields under water-gas shift conditions.[9]

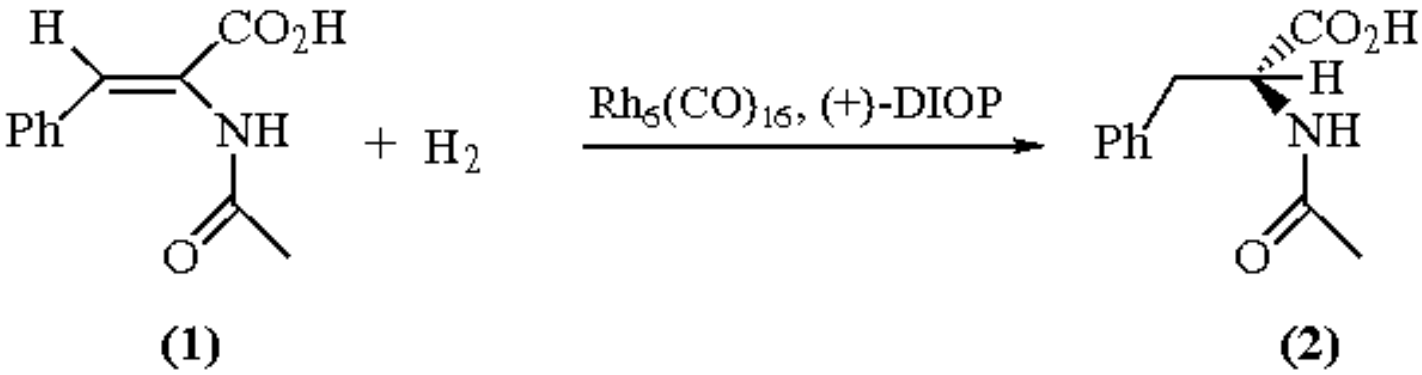

(1)

Hydroformylation.

Alkenes undergo hydroformylation to give aldehydes in good yields with $Rh_6(CO)_{16}$ when used as either a homogeneous catalyst or supported on zeolites,[10] to yield mixtures of normal and isoaldehydes.[11] Fluorinated alkenes, however, are hydroformylated with a high degree of selectivity (eq 2), with iso to normal aldehyde ratios of 97:3.[12] Hydroformylations also occur with $Rh_6(CO)_{16}$ under water-gas shift conditions to give mixtures of iso and normal aldehydes,[13] but these conditions have been reported to effect reduction of the resulting aldehydes to alcohols at extended reaction times.[14]

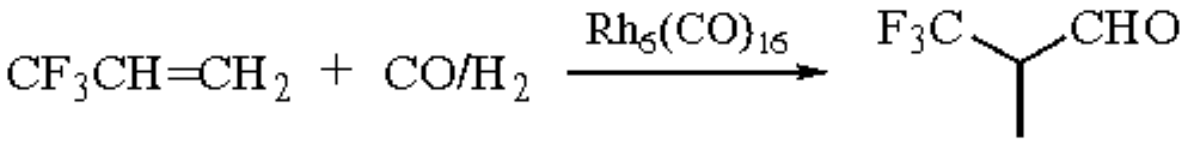

(2)

Reductions of Aldehydes, Ketones, and Aromatic Nitro groups.

Aldehydes and ketones are reduced under water-gas shift conditions to give alcohols in excellent yields.[15] Aromatic nitro compounds are reduced to anilines under similar conditions.[16] *o*-Nitrostyrenes have been converted to indoles (eq 3) in moderate (68%) yields.[17]

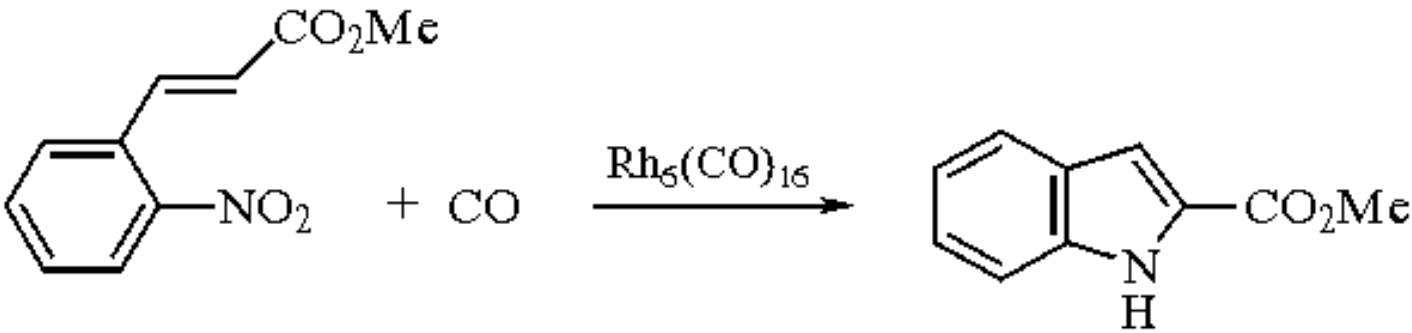

(3)

Reductive Amination.

Primary, secondary, and tertiary amines can be produced in good yield by the reaction of aldehydes and ketones with ammonia or amines in the presence of a catalytic amount of $Rh_6(CO)_{16}$ at 100-300 atm synthesis gas (CO/H_2 = 1:1).[18]

Metal Carbene Transformations.

$Rh_6(CO)_{16}$ has been found to be an efficient catalyst for dinitrogen extrusion from diazo carbonyl compounds to generate electrophilic metal carbenes that react with allyl sulfides, amines, or iodides to give ylides which undergo [2,3]-sigmatropic rearrangement to form homoallylic sulfides, amines, and iodides (eq 4) in good yield.[19] These carbenes can also react with alkenes to give cyclopropanes in good yields.[20]

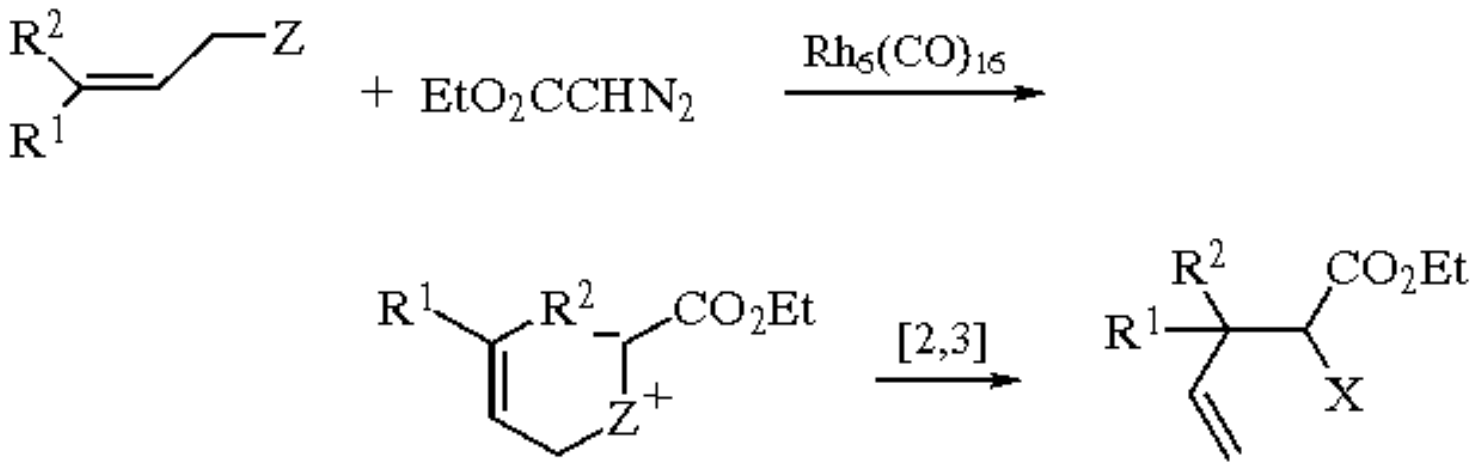

(4)

Decarbonylation of Formate Esters.

Formate esters are decarbonylated at 200-220 °C in 2-methoxyethanol in the presence of 1 mol % $Rh_6(CO)_{16}$ to give alcohols in 69-94% yield.[21] The reaction is effective in decarbonylating secondary as well as primary formate esters, producing only small amounts of alkenes as byproducts.

Related Reagents.

Dirhodium(II) Tetraacetate; ***Dodecacarbonyltetrarhodium***; ***Tetracarbonyl(di-μ-chloro)dirhodium***.

---

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N-[(Hexadecyloxy)sulfonylethyl]-*N,N,N*-trimethylammonium Fluorosulfate[1]

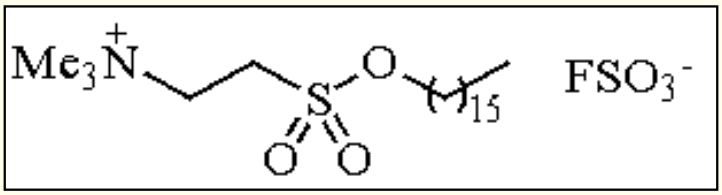

[66143-52-0] · $C_{21}H_{46}FNO_6S_2$ · *N*-[(Hexadecyloxy)sulfonylethyl]-*N,N,N*-trimethylammonium Fluorosulfate · (MW 491.81)

(alkyl transfer agent[1,2])

Alternate Names: 2-[(hexadecyloxy)sulfonyl]-*N,N,N*-trimethylethanaminium fluorosulfate; hexadecyl [2]betylate fluorosulfate.

Physical Data: white solid.[2]

Solubility: sol H_2O, MeOH, organic solvents (e.g. DME, toluene), two-phase H_2O-organic solvent mixtures.[2]

Analysis of Reagent Purity: [2]betylates show a characteristic signal (typically a broad singlet) at ~3.7 ppm in the ^1H NMR spectrum.[2]

Preparative Methods: [2]betylates (**3**) are prepared[2] from alcohols by the sequence ROH -> (**1**) -> (**2**) -> (**3**) (eq 1). Vinylsulfonyl chloride is easily made by the action of ***2,6-Lutidine*** or cold ***Triethylamine*** on 2-chloroethanesulfonyl chloride,[3,4] which is obtained commercially or made from sodium 2-hydroxyethanesulfonate (sodium isethionate) and ***Thionyl Chloride*** with a catalytic amount of DMF.[5]

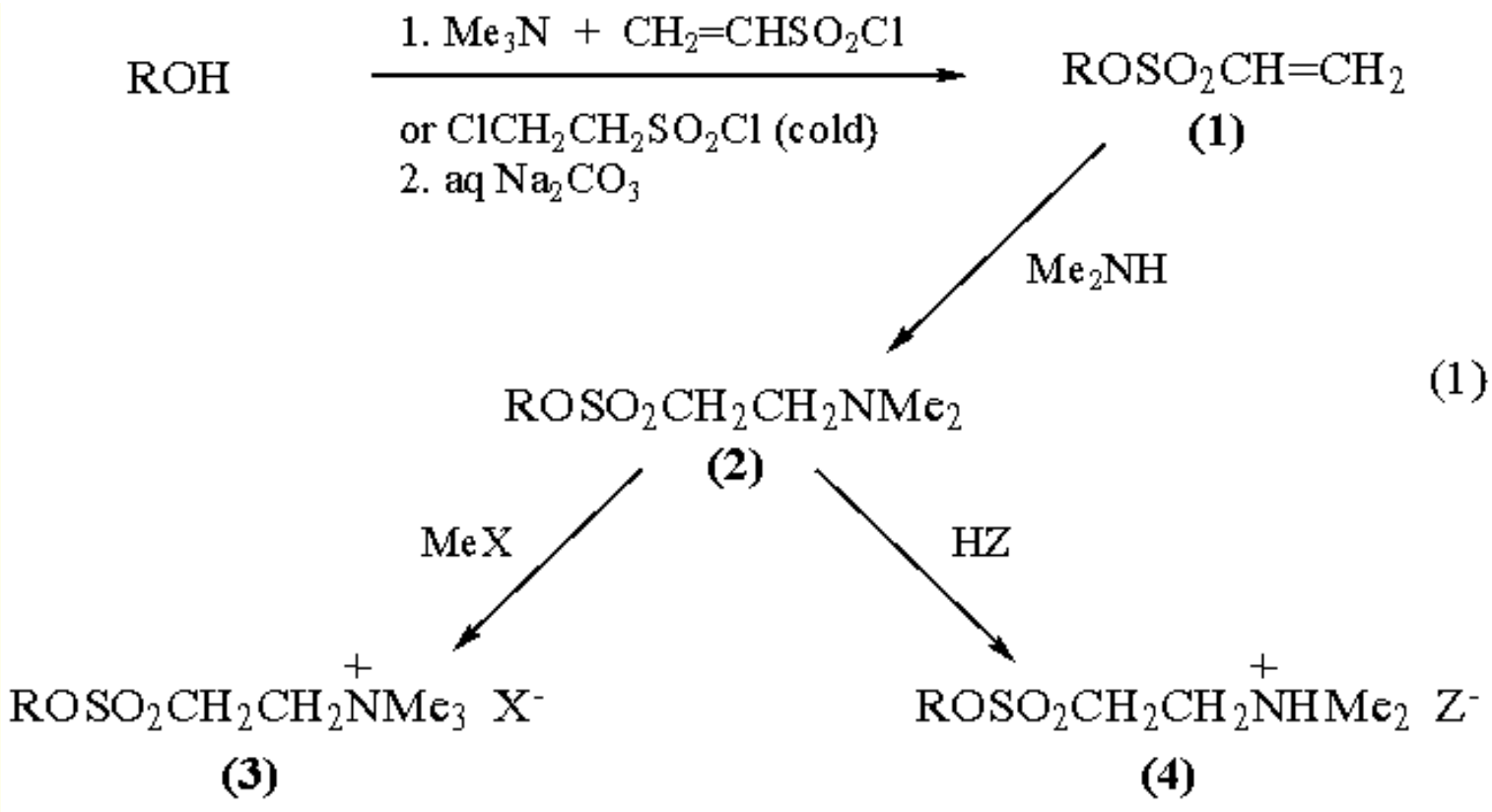

(1)

Handling, Storage, and Precautions: [2]betylates (**3**) are usually prepared as needed, but may be stored under dry conditions for extended periods.

Alkyl Transfer Intermediates.

Betylates [$Me_3{+}N(CH_2)_nSO_2OR\ X^-$] are useful intermediates, enabling an alcohol to transfer its alkyl group to a variety of nucleophiles to form a wide array of products (eq 2). (The byproduct in these reactions is a betaine; hence the nickname betylate.)

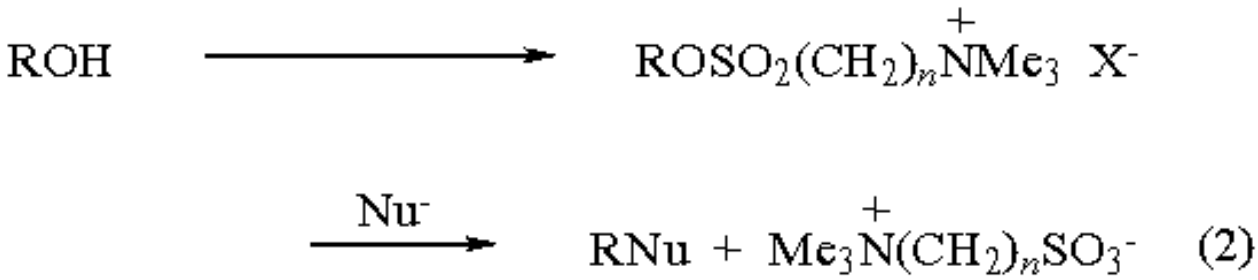

(2)

Of the various betylates, those with n = 2 ([2]betylates) offer the most serviceable combination of ease of preparation and handling, and general reactivity under neutral or acidic conditions. [0]Betylates (n = 0) are extremely reactive and not usually isolated;[6] [3]- and [4]betylates (n = 3, 4) are less conveniently made than [2]betylates, but can be used in much more basic media.[2]

The title compound and related alkyl [2]betylates react readily (rt, 0.5-24 h) with a wide variety of water-soluble nucleophiles (***Sodium Azide***, ***Sodium Thiocyanate***, KBr, NaCl, KNO_3, ***Thiourea***, Na_2SO_3 and ***Sodium Thiosulfate***), either

in water or in such two-phase aqueous-organic mixtures as CH_2Cl_2-H_2O, to give the alkyl transfer products (azide, thiocyanate, bromide, etc.) in fair to excellent yields. Other tested alkyl groups include butyl, 1-methylheptyl, 3-phenylpropyl, and docosyl.[2]

The nucleophile may be made the counterion of the betylate cation (by ion extraction or with an ion-exchange resin); the salt so obtained may lead to a substrate-reagent ion-pair (SRIP) reaction,[2] as in eq 3. Nu^- in eq 3 may be not only I^-, SCN^-, picrate, and formate, but also ClO_4^-, FSO_3^-, $CF_3SO_3^-$, $CH_2{=}CHSO_3^-$, etc., yielding the alkyl perchlorate, fluorosulfate, triflate, or vinylsulfonate in fair to excellent yields.[2] SRIP reactions also take place with norbetylates (**4**), produced by addition of the conjugate acid of the nucleophile to the alkyl 2-(dimethylamino)ethanesulfonate (**2**).[2]

$$RO\overset{+}{S}O_2CH_2CH_2NMe_3\ Nu^- \xrightarrow{\Delta} RNu + Me_3\overset{+}{N}CH_2CH_2SO_3^- \qquad (3)$$

SRIP reactions at a chiral secondary center go with complete inversion of configuration. (*S*)-(+)-2-Iodooctane was obtained in high optical purity (i.e. without subsequent racemization by I^-) from (*R*)-1-methylheptyl [2]betylate iodide.[2] (*R*)-2-Octanol was converted into both (*S*)-2-bromooctane and (*R*)-2-bromooctane by the sequence shown in eq 4.[2]

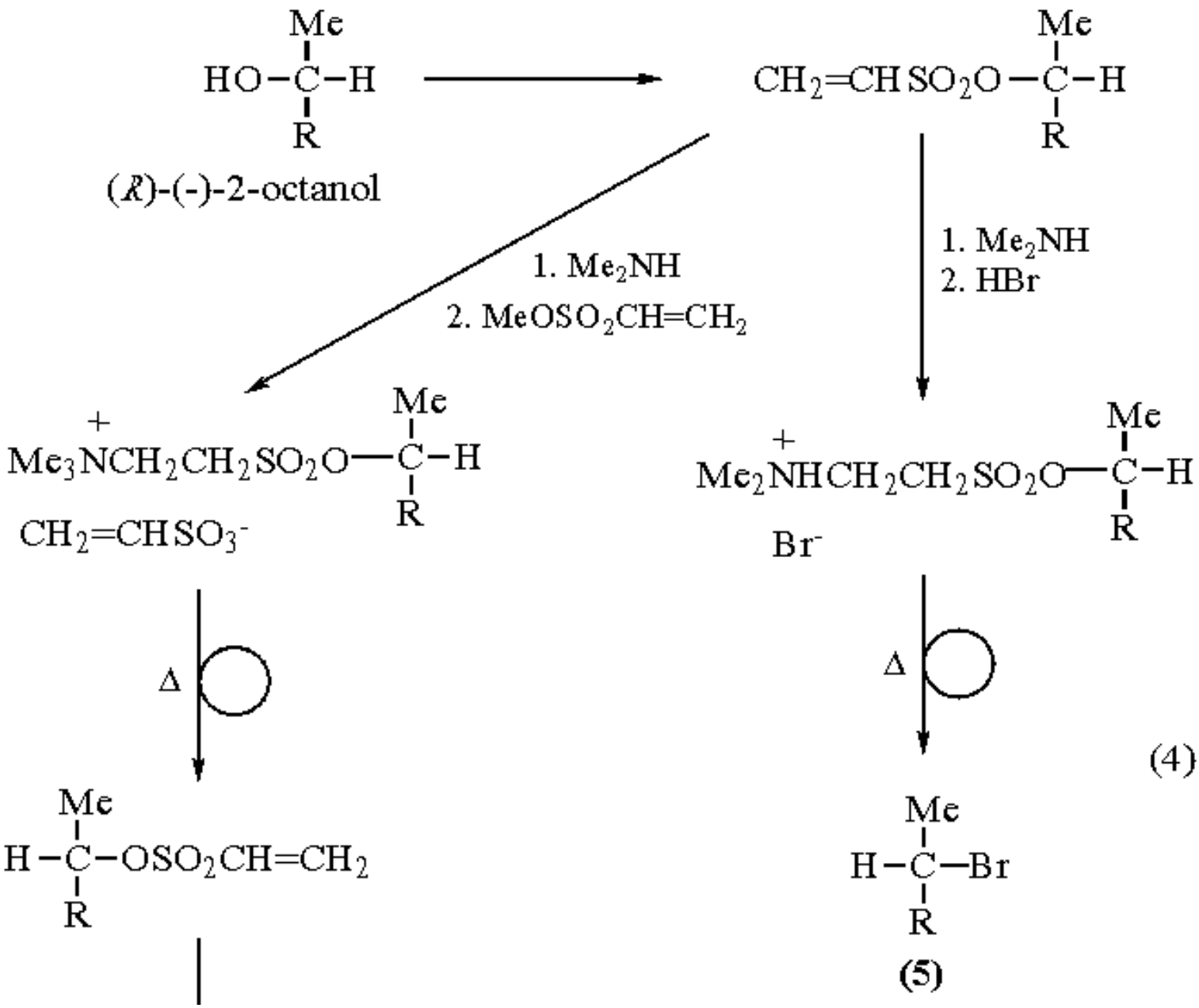

(4)

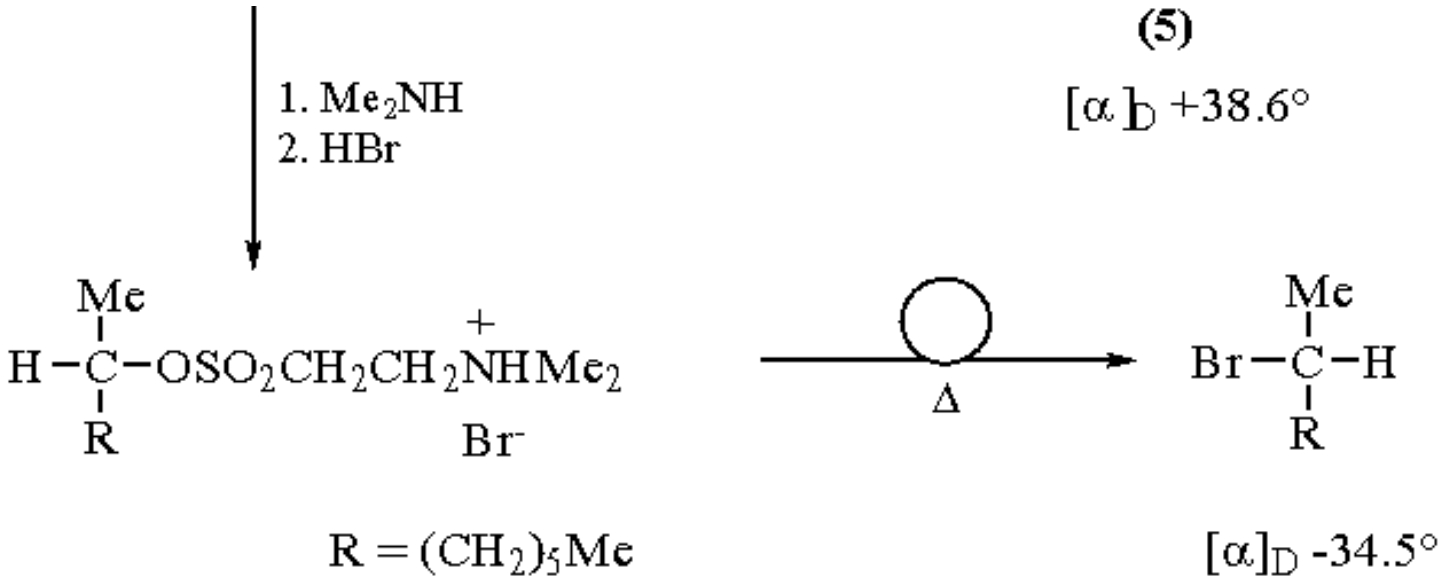

The betylate procedure was found[7] to be valuable for introducing the isobutyl group to make (**5**) (eq 5).

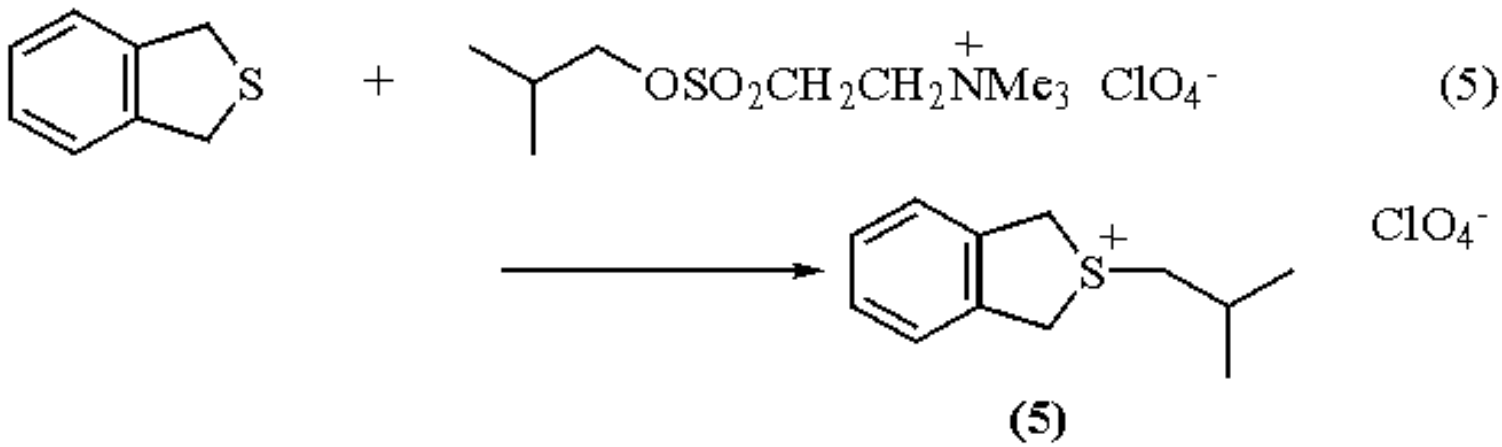

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James F. King

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2*H*-Hexafluoropropyl Azide

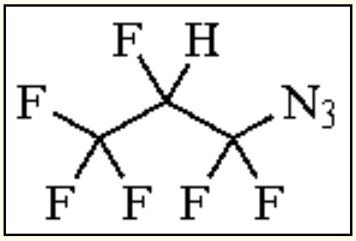

[2991-70-0] · $C_3HF_6N_3$ · 2*H*-Hexafluoropropyl Azide · (MW 193.07)

(mild fluorinating reagent for oxidative fluorination of P^{III} compounds[1-3])

Alternate Name: hexafluoroazidopropane.

Physical Data: bp 51-53 °C.

Solubility: insol water; sol most organic solvents.

Preparative Methods: readily prepared from hexafluoropropene (CF_2=$CFCF_3$) and ***Sodium Azide*** in alcohols.[1,4] Synthesis of up to 134 g has been described.[1]

Handling, Storage, and Precautions: easily handled and stored (several months in dark glass vessel at rt), provided due care is taken: avoid sharp strikes and heating. Explosions have not been reported, but a protective shield should always be used. Use in a fume hood.

Fluorination.

The reaction of $CF_3CHFCF_2N_3$ with various P^{III}-containing substrates results in oxidative fluorination (eq 1).[1-3] Usually the reactions are performed without solvent, the highly volatile CF_3CHFCN byproduct (bp 39-41 °C) being easily removed. The reaction has been applied to fluorophosphites, trialkyl phosphites, halophosphines, amidophosphites, and hydrophosphoryl compounds.

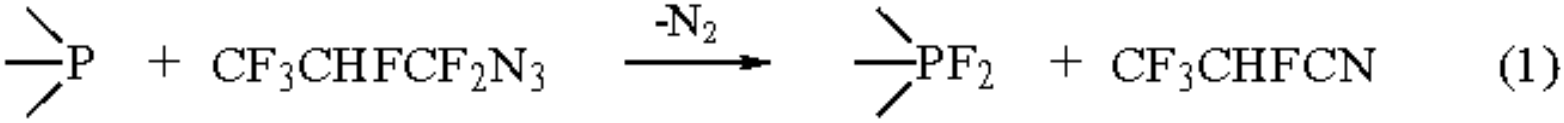

An unusual Arbuzov rearrangement was observed in the case of alkyl difluorophosphites, $ROPF_2$. If R = isobutyl or neopentyl, rearrangment to a corresponding tertiary group is observed (eq 2).[1]

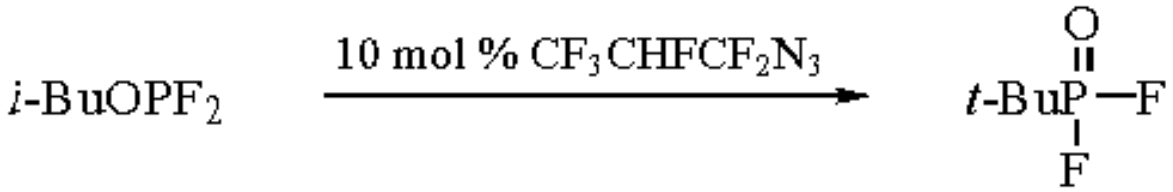

(2)

Other Properties.

The azide decomposes slowly under heat or UV irradiation to give 3*H*-hexafluoro-2-aza-1-butene (eq 3).[5]

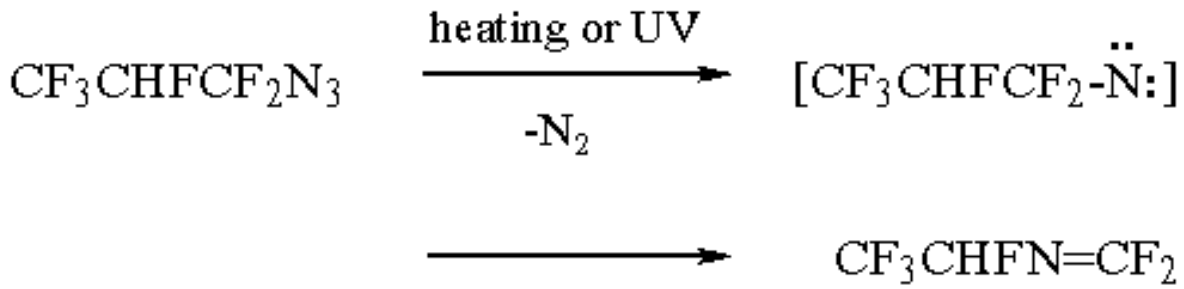

(3)

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Hexa-μ-hydrohexakis(triphenylphosphine)hexacopper[1]

$[(Ph_3P)CuH]_6$

[33636-93-0] · $C_{108}H_{96}Cu_6P_6$ · Hexa-μ-hydrohexakis(triphenylphosphine)hexacopper · (MW 1961.16)

(chemo- and stereoselective conjugate reduction;[2,3] catalytic, hydride-mediated, reduction of enones and ketones;[4] reduction of alkynes and propargyl alcohols to *cis*-alkenes[5])

Alternate Name: triphenylphosphine copper hydride hexamer.

Physical Data: mp 111 °C (dec).[1b]

Solubility: sol benzene, toluene, THF (~1 g/10 mL); reacts with CH_2Cl_2 and $CHCl_3$.

Form Supplied in: bright red crystals to dark red powders; commercially available.

Analysis of Reagent Purity: assay by means of hydrogen evolution.[1b] ^1H NMR spectroscopy (deaerated benzene-d_6) shows ligated and, if present, free Ph_3P.

Preparative Method: prepared by hydrogenolysis of Ph_3P-stabilized ***Copper(I) t-Butoxide***,[1c,d] which can be generated in situ from *t*-BuONa and ***Copper(I) Chloride***.[1e]

Purification: Ph_3P is removed by recrystallization from benzene layered with hexanes or acetonitrile under anaerobic conditions, or by trituration with deaerated hexanes or acetonitrile.[1e]

Handling, Storage, and Precautions: has an indefinite shelf life if stored under an inert atmosphere; can be handled briefly in the air without harm and is stable toward water. The reagent is highly air sensitive in solution; thus only rigorously deoxygenated solvents should be used. For bench top manipulation, transfer of the bulk reagent to a Schlenk tube that can be easily opened under a purge of inert gas and evacuated and backfilled after each use is recommended.

Stoichiometric Reductions.

$[(Ph_3P)CuH]_6$ provides stoichiometric conjugate reduction of α,β-unsaturated ketones,[2,3] esters,[2a,3a] aldehydes,[2c] nitriles,[6a] sulfones, and sulfonates.[3b] The reagent is highly chemoselective. Isolated alkenes, carbonyl groups, halogens, and typical oxygenated functionality are not reduced under the reaction conditions (eq 1).[2,3]

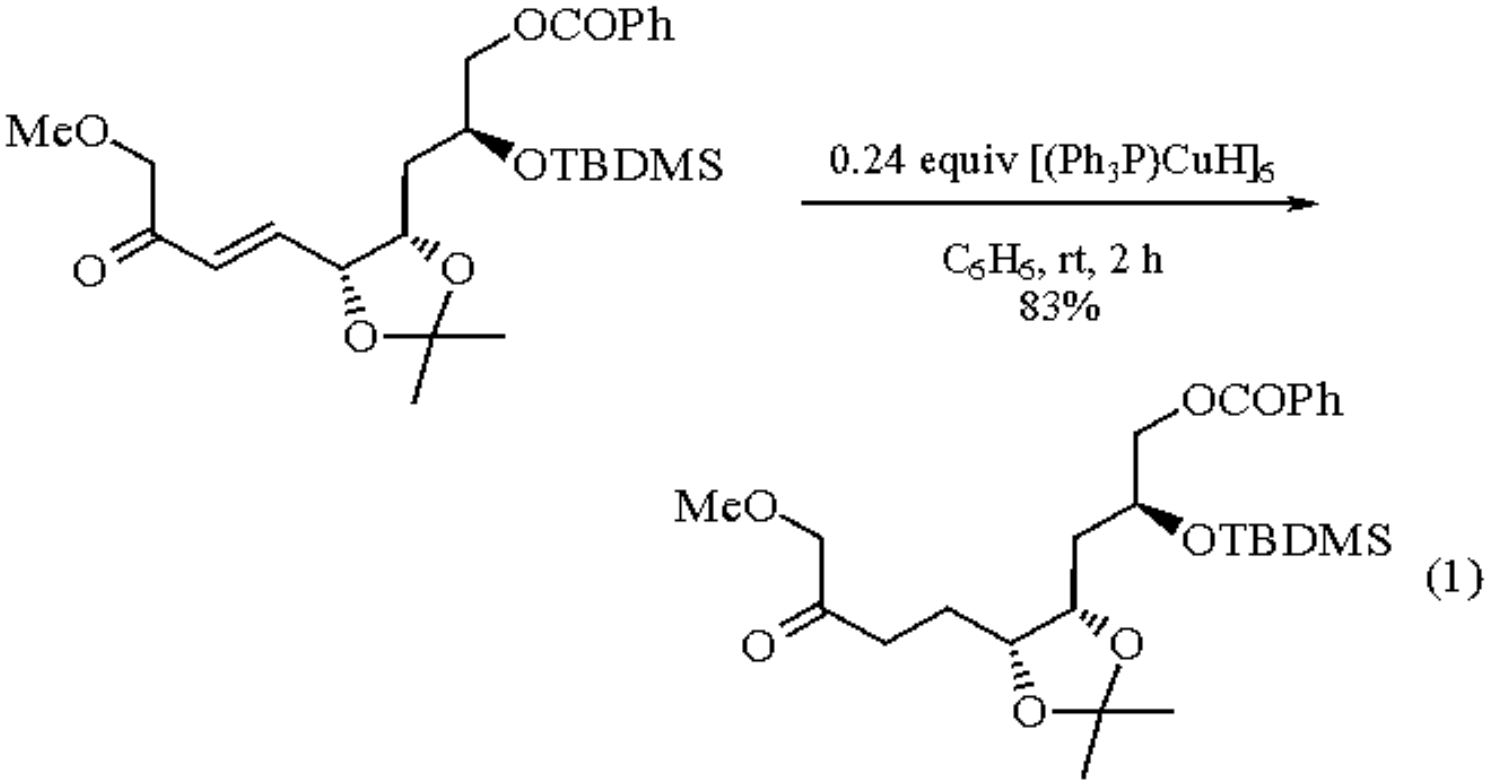

When reducing substrates that are prone to aldol and Michael type reactions, it is advisable to include 5-20 equiv deaerated water in the reaction medium to hydrolyze the intermediate copper enolate. However, reductions run in wet solvents or in the presence of a chlorotrialkylsilane require a slight excess of the reagent to completely consume starting material (0.18-0.5 equiv $[(Ph_3P)CuH]_6$).[2,3]

Initial 1,2-reduction is not competitive and further reaction of the carbonyl product resulting from conjugate reduction is generally only observed with enals. Over-reduction is prevented by running the reactions in the presence of a chlorotrialkylsilane (eq 2).[2c] Both ketone and aldehyde enolates are thus trapped as their corresponding silyl enol ethers. Alternatively, in the presence of water and excess hydride, some enals can be completely reduced to the saturated alcohol.[2c]

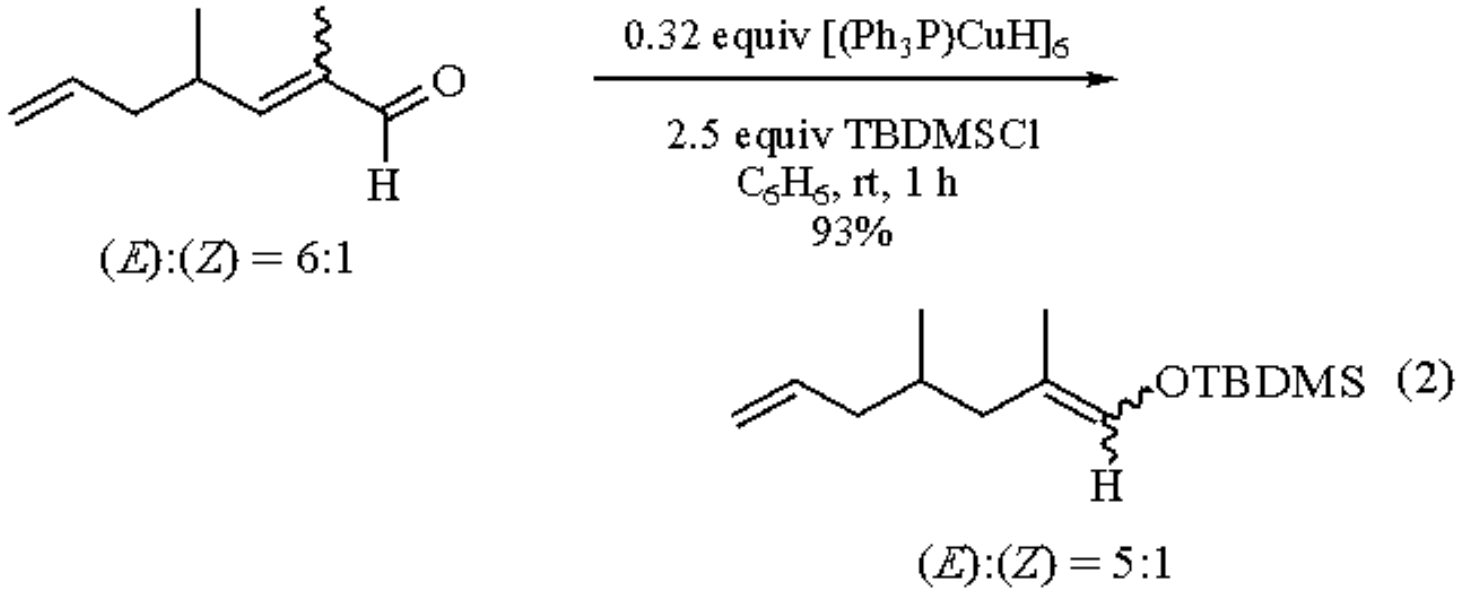

Stoichiometric reductions are performed at rt in wet deaerated benzene or THF at or below the solubility limit of the reagent.

Starting material may remain during reduction of sterically demanding substrates, especially at higher dilution (eq 3).[6b] Performing such reductions as concentrated suspensions and/or by adding the reagent dropwise to a heated solution of the substrate can help alleviate this difficulty as well as shorten the reaction time.

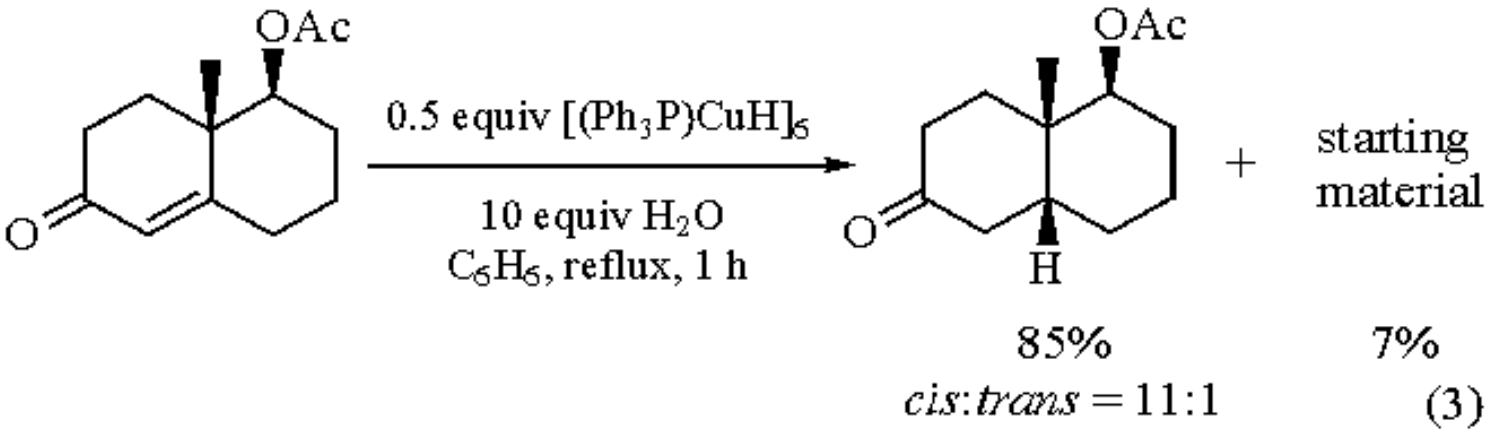

Aside from offering broad chemoselectivity and complete regioselectivity, the reagent is highly stereoselective, delivering hydride to the less hindered face of the substrate (eqs 3 and 4).[2a,b,3] The selectivity exhibited towards 3,5-dimethylcyclohexanone (eq 4) is superior to that observed using either Boeckmans' hydridocuprate (9:1)[7a] or catalytic hydrogenation (15:1).[2a] The *cis* selectivity obtained when reducing tetra- and hexahydronaphthalen-6(7*H*)-ones (eq 3) parallels that observed with catalytic hydrogenation[8] and exceeds the selectivity observed when similar substrates are reduced with hydridocuprate reagents.[7] High selectivity for the *cis* A/B ring juncture is also observed when reducing 3-keto-$\Delta^{4,5}$ steroidal enones.[6b,9]

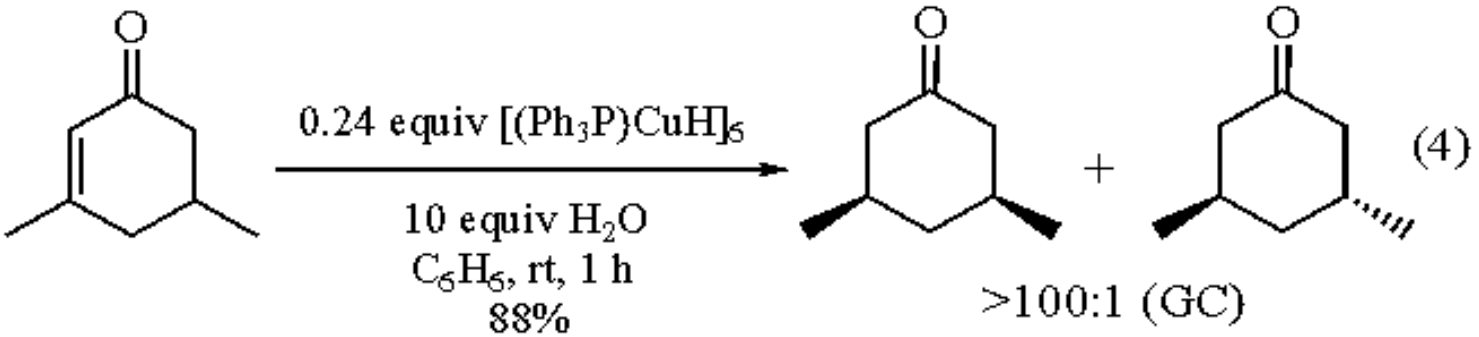

$[(Ph_3PCuH]_6$ is also compatible with γ-heteroatom-substituted enones (eqs 5 and 6).[2b] Conjugate reduction of such compounds without elimination of the γ-substituent is significant as they can suffer hydrogenolysis during catalytic hydrogenation[10] or elimination during reductions where electron transfer is mechanistically relevant.[11]

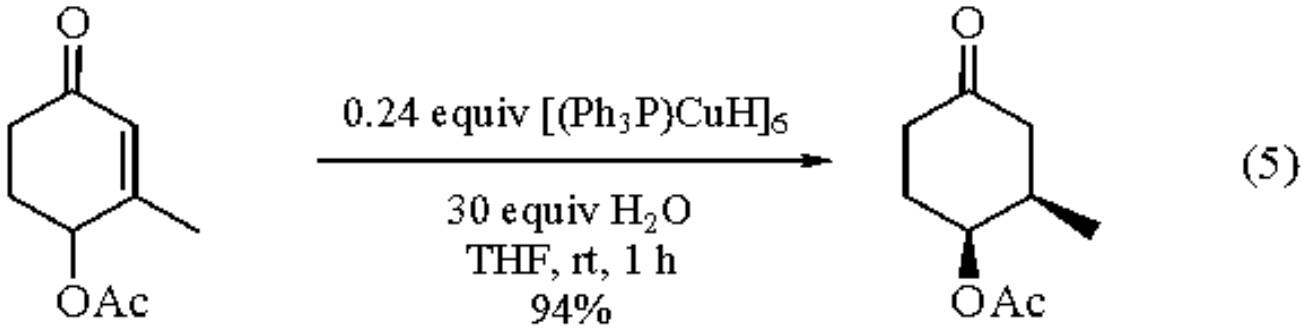

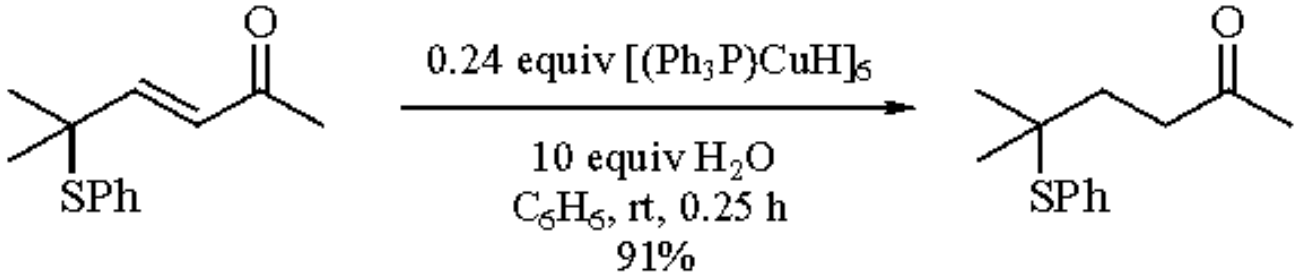

(6)

Conjugate reduction of β-heteroatom substituted enones is not straightforward.[12] However, endocyclic vinylogous esters[6b] and amides[3c] react under chlorotrialkylsilane-mediated conditions (eq 7) suggesting that they are reduced through the oxonium and iminium ion, respectively. All efforts to reduce exocyclic vinylogous esters and amides such as 3-substituted cyclohex-2-en-1-ones were unsuccessful.[6b]

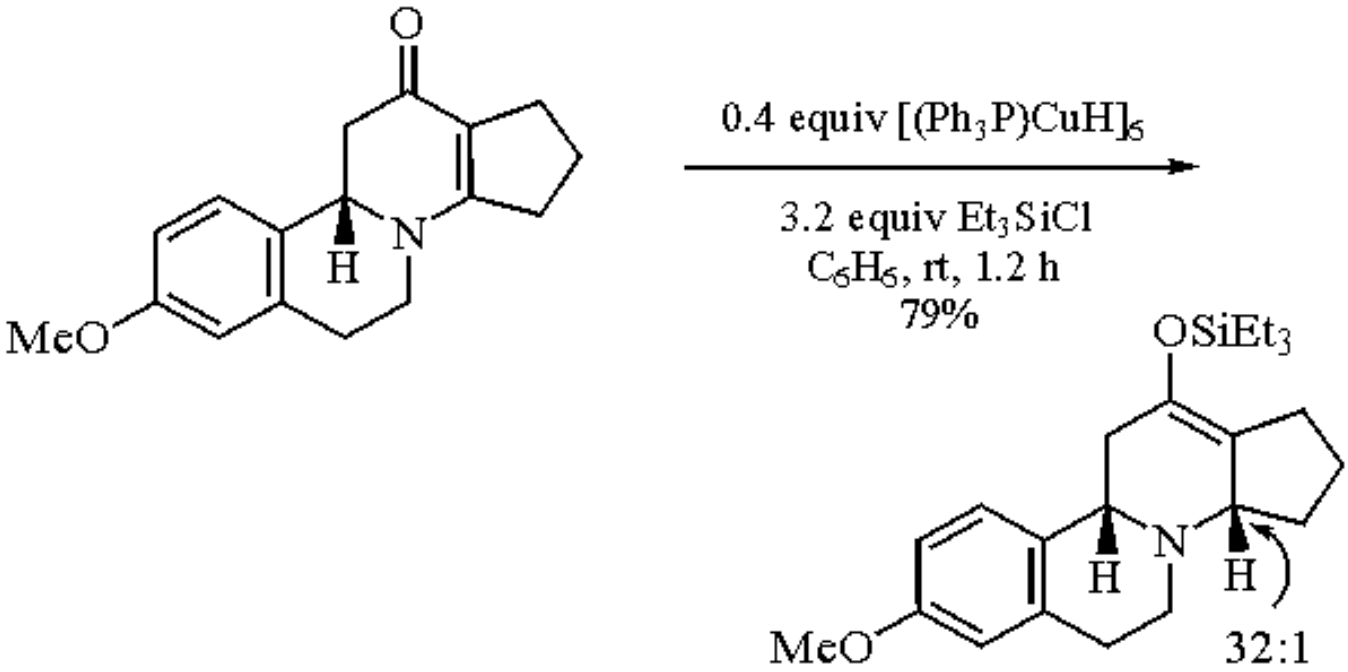

(7)

The workup requires exposure of the reaction to air and dilution with ether and/or hexanes. Addition of a small amount of silica gel facilitates decomposition of the copper containing byproducts. After being stirred under air for at least 1 h, the mixture is filtered through silica gel and purified by column chromatography. Alternatively, free Ph_3P can be removed from products of similar polarity by oxidation with 5% NaOCl. The resulting phosphine oxide is then removed by simple silica gel filtration. Isolation of the silyl enol ethers requires exposure of the reaction to air and dilution as outlined above, with the usual precautions taken when chromatographing these compounds.

Hydrometalation of Alkynes.

$[(Ph_3P)CuH]_6$ reduces alkynes (eq 8) and propargyl alcohols (eq 9) to the *cis*-alkene.[5] Complications include overreduction (<=10%) with some substrates and partial fragmentation of unprotected secondary and tertiary propargyl alcohols. As with enone reductions mediated by $[(Ph_3P)CuH]_6$, alkyne reduction is concentration dependent, can be promoted by using higher temperatures, and benefits from the presence of water in the reaction medium.

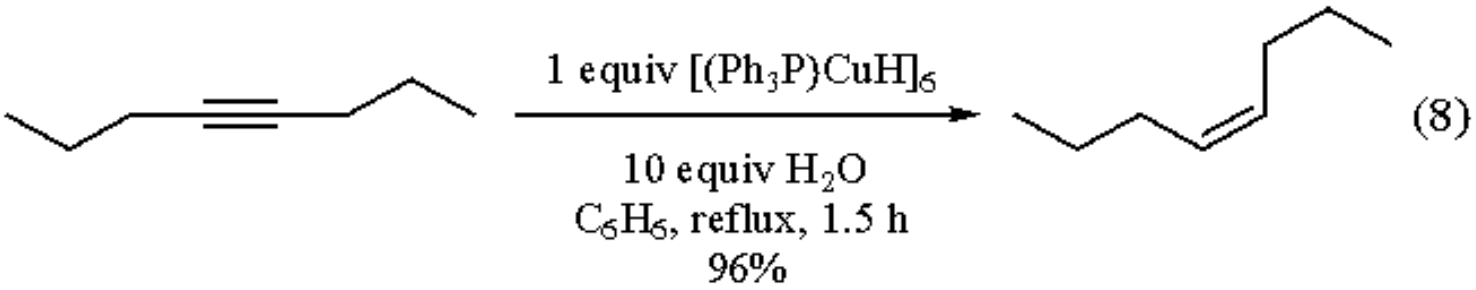

(8)

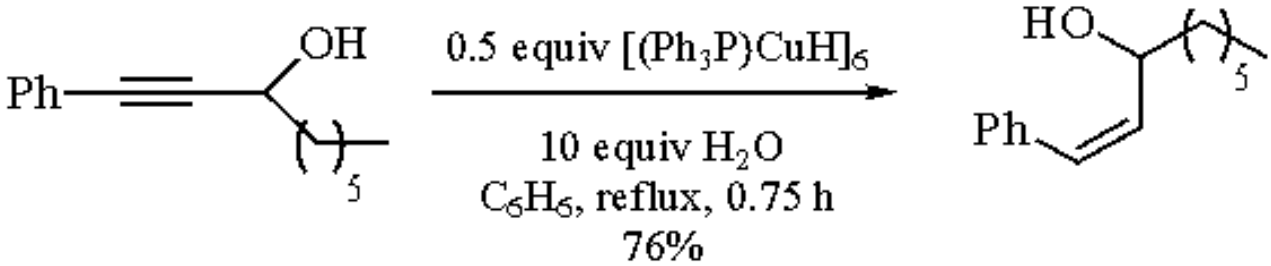

(9)

Catalytic Reductions.

The presumed copper(I) enolate formed during conjugate reduction heterolytically activates H_2, allowing the reductions to proceed catalytically in copper.[4] In the presence of excess Ph_3P (4-6 equiv per Cu) and H_2 pressure (200-1000 psi) the catalytic enone reduction can be reasonably controlled, providing either conjugate reduction or complete reduction to saturated alcohol, depending on reaction conditions.[4] While work to provide a synthetically useful catalytic enone reduction continues, a practical catalytic reduction of ketones under one atmosphere of H_2 has been developed (eq 10).[6b] The catalytic reducing system is prepared simply by adding Me_2PPh (6-10 equiv per Cu) to $[(Ph_3P)CuH]_6$ followed by *t*-BuOH (10-20 equiv per Cu) and the reducible substrate (10-100 equiv per Cu) in dry, deaerated benzene (0.4-0.8 M in substrate) under an inert atmosphere. The solution is then subjected to one freeze-pump-thaw-degas cycle and an atmosphere of H_2 is admitted as the solution thaws. Alternatively, the catalyst can be prepared by substituting ***Copper(I) Chloride*** and NaO-*t*-Bu for $[(Ph_3P)CuH]_6$. Me_2PPh is superior to numerous other tertiary phosphines screened. This catalyst is quite robust, allowing the reactions to be monitored by TLC and displaying sustained turnover, as indicated by reduction of fresh substrate added to a completed reaction. The chemoselectivity is comparable to that of $[(Ph_3P)CuH]_6$ with the exception that this catalyst does reduce ketones effectively but reacts with enones to give mixtures of saturated and allylic alcohols. The reduction of cyclic ketones proceeds mainly by axial delivery of hydride, with stereoselectivity exceeding ***Sodium Borohydride*** and ***Lithium Aluminum Hydride*** in many cases (eq 11).[6b,13]

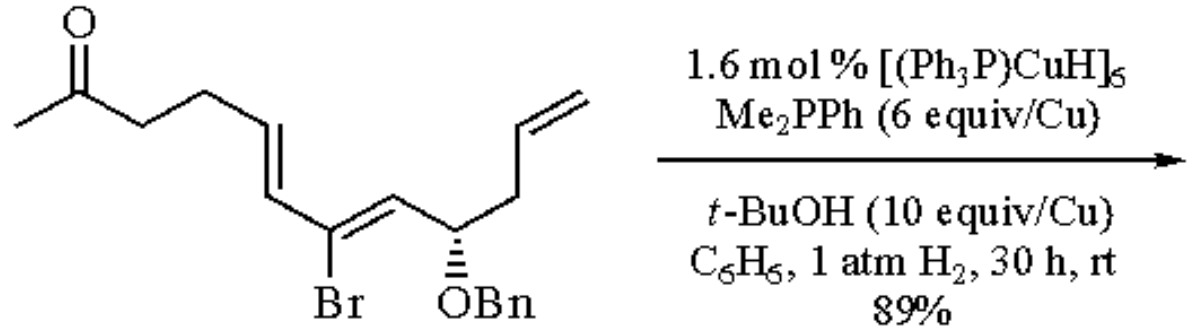

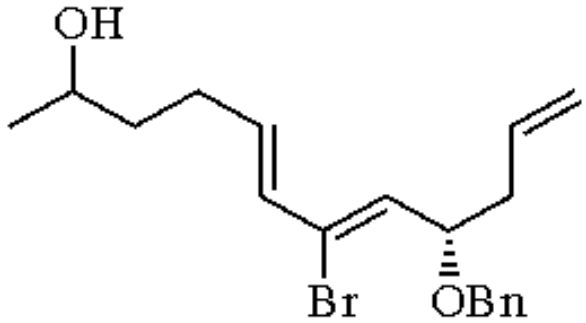

(10)

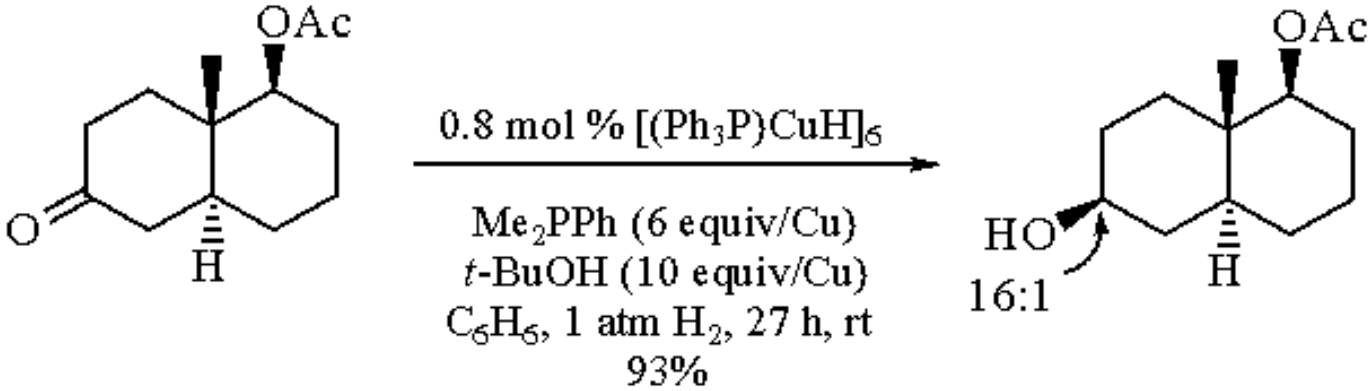

(11)

Related Reagents.

Lithium n-Butyl(hydrido)cuprate.

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9. Hydrogenation of 3-keto-$\Delta^{4,5}$ steroidal enones over Cu^0/Al_2O_3 also gives the *cis* A/B ring juncture, but with lower selectivity: Ravasio, N.; Rossi, M. *JOC* **1991**, *56*, 4329.
10. (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic: New York, 1979; pp 235-250. (b) Rylander, P. N. *Hydrogenation Methods*; Academic: London, 1985; pp 148-183.
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(2*S*)-(2α,3β,8aβ)-Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5*H*-oxazolo[3,2-*a*]pyridin-5-one

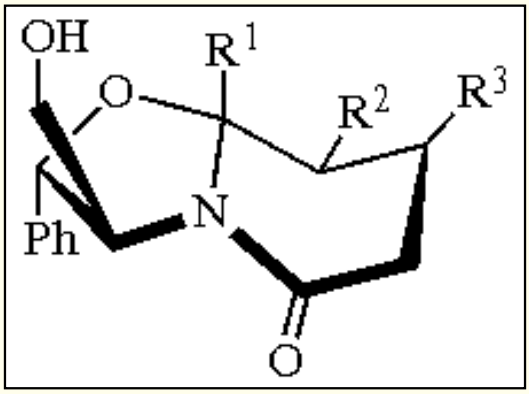

(2*S*)-(**1**; R^1 = Me, R^2 = H R^3 = H)

[116950-01-7] · $C_{15}H_{19}NO_3$ · (2*S*)-(2α,3β,8aβ)-Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5*H*-oxazolo[3,2-*a*]pyridin-5-one · (MW 261.35)

[101979-96-8] (2*S*)-(**2**; R^1 = Et, R^2 = H, R^3 = H)

[101979-99-1] · $C_{16}H_{21}NO_3$ · (2*S*)-(2α,3β,8aβ)-Hexahydro-3-(hydroxymethyl)-8a-ethyl-2-phenyl-5*H*-oxazolo[3,2-*a*]pyridin-5-one · (MW 275.38) (2*S*)-(**3**; R^1 = Me, R^2, R^3 = C_4H_4 (benzo))

[127998-41-8] · $C_{19}H_{19}NO_3$ · (2*S*)-(2α,3β,8aβ)-Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5*H*-oxazolo[3,2-*a*]pyridin-5-one · (MW 309.39)

(chiral templates for the synthesis of enantiopure 4,4-dialkyl-2-cyclohexenones, 6,6-dialkyl-2-cyclohexenones, and 4,4-dialkyl-1(4*H*)-naphthalenones[1])

Physical Data: (**1**) mp 98-99 °C; [α_D] +13.5°. (**2**) mp 83-85 °C; [α_D] +12.6°. (**3**) mp 91 °C; [α_D] +166.7°.

Preparative Methods: the chiral bicyclic lactams are easily procured via condensation of commercially available (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol and the appropriate δ-keto acid (eq 1).[1,2] Similar bicyclic lactams have been prepared from other amino alcohols and have been extensively utilized in the stereocontrolled formation of quaternary carbon-carbon bonds.[1,3]

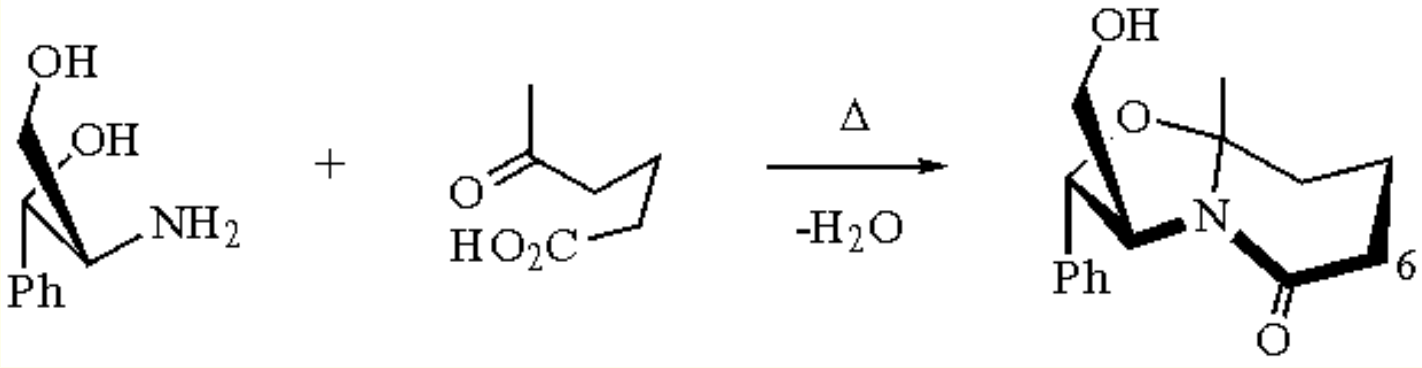

Handling, Storage, and Precautions: no special precautions are warranted.

These compounds can be alkylated twice at the 6-position in a stereocontrolled fashion (eq 2).[4,5] Treatment of the unsubstituted bicyclic lactam with ***Lithium Diisopropylamide*** and reaction of the enolate anion with an alkyl halide affords the monosubstituted product. The epimeric mixture is treated again with LDA and a second alkyl halide to give the dialkylated bicyclic lactam. The initial epimeric mixture is used directly in the second alkylation since this subsequent step proceeds via a planar enolate. It is the second alkylation that dictates the final diasteromeric ratio. The order of addition also affects the final ratio.[4] Inverting the order of addition provides the antipode at position 6, although the highest diastereoselectivity is observed when the larger electrophile is added last.[6] The monoalkylated bicyclic lactam can also be prepared by condensation of the amino alcohol and the appropriately substituted keto acid.[1]

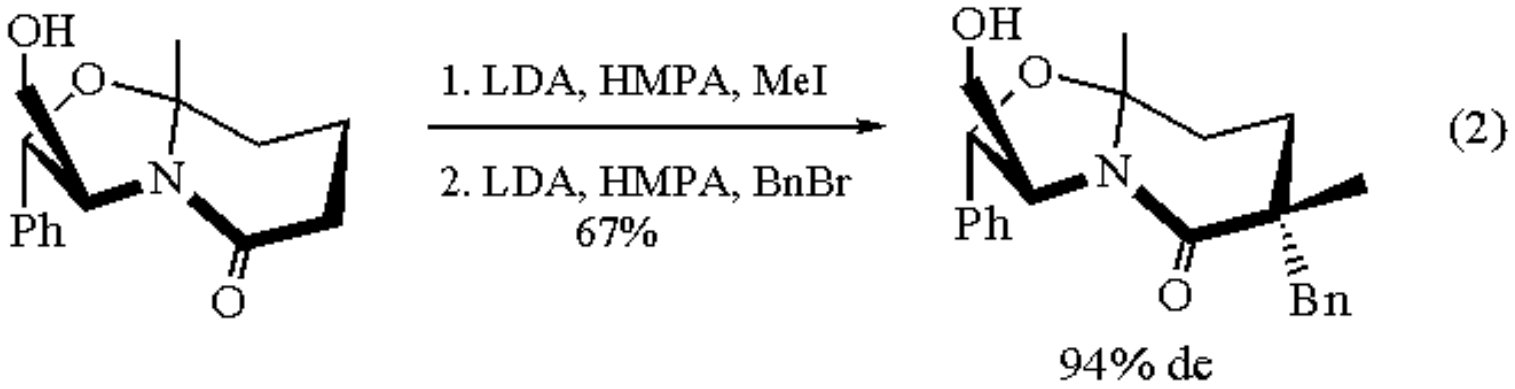

These compounds can be partially reduced to the carbinol amine, and then hydrolyzed and cyclized to afford the enantiomerically pure 4,4-dialkyl-2-cyclohexenones (eq 3).[4]

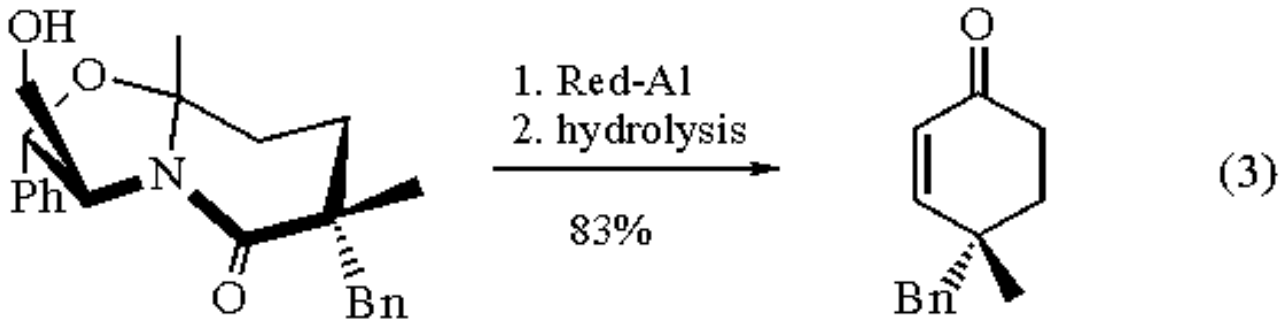

In addition, Grignard addition to the lactam followed by hydrolysis of the bicyclic lactam affords either 3,4,4- or 2,6,6-trisubstituted 2-cyclohexenones, depending upon the hydrolytic conditions employed (eq 4).[6]

(2S)-(2alpha,3beta,8abeta)-Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5H-oxazolo[3,2-a]pyridin-5-one

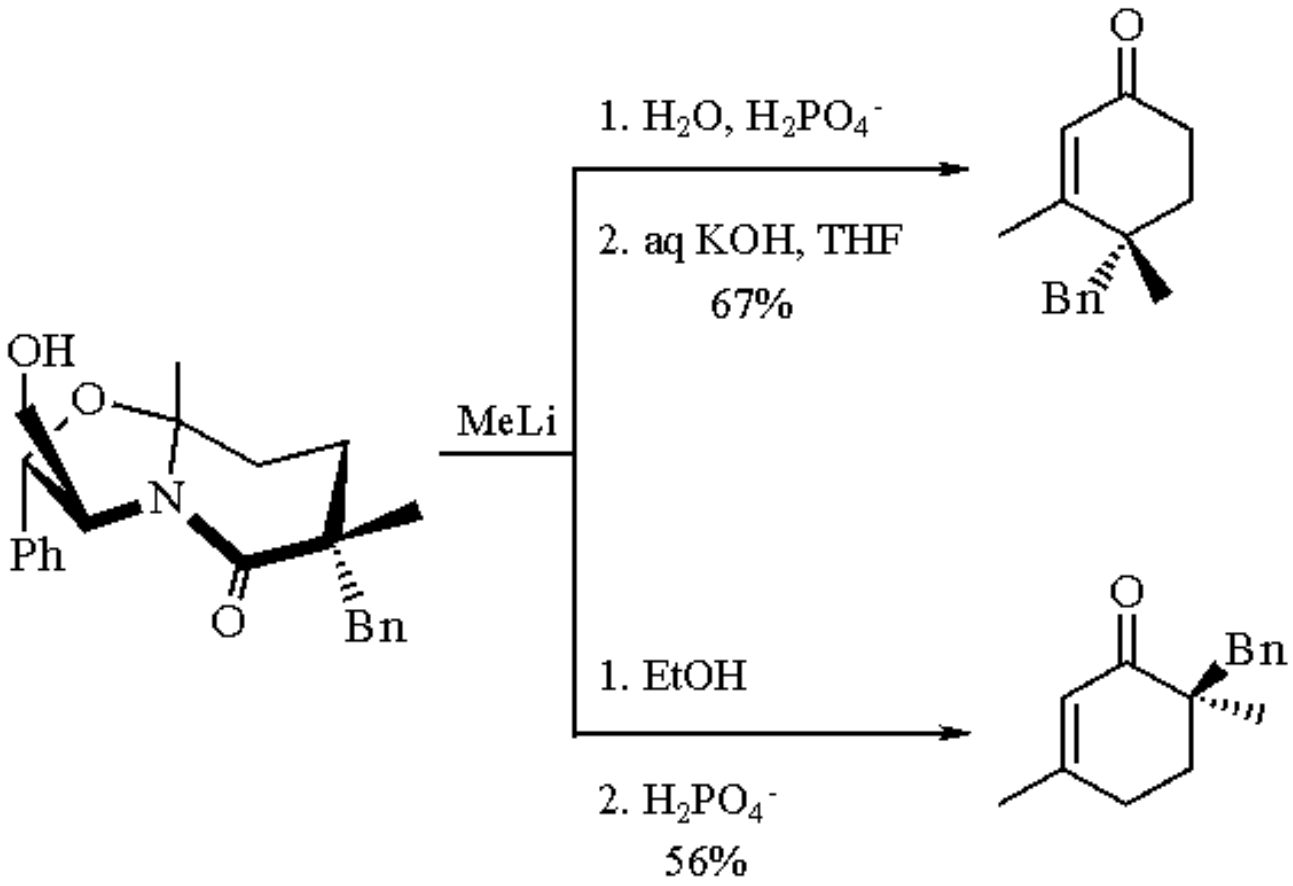

(4)

Similar manipulations with a dialkylated benzo tricyclic lactam lead to the corresponding 4,4-dialkylnaphthalenones (eq 5).[7]

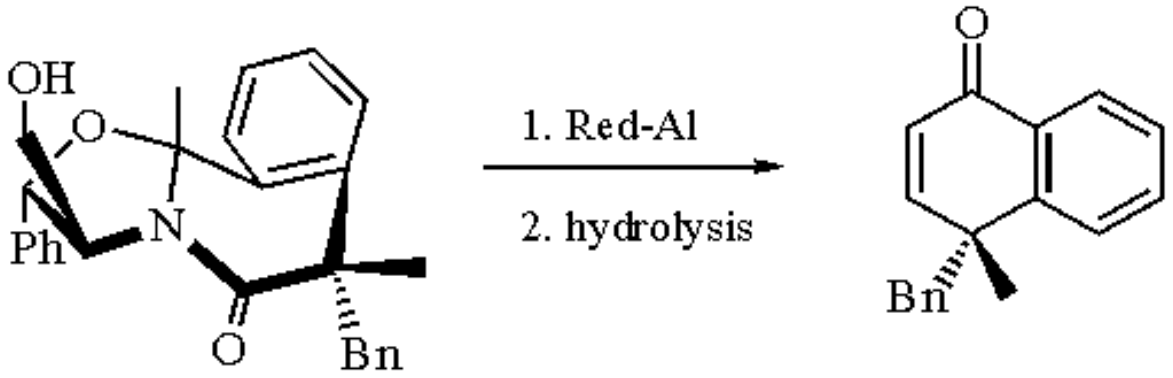

(5)

Related Reagents.

(S)-1-Amino-2-methoxymethylpyrrolidine; ***trans-2,5-Bis(methoxymethyl)pyrrolidine***; ***10,2-Camphorsultam***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***α-Methyltoluene-2,α-sultam***; ***(3S,cis)-Tetrahydro-3-isopropyl-7a-methylpyrrolol[2,1-b]oxazol-5(6H)-one***.

---

1. Romo, D.; Meyers, A. I. *T* **1991**, *47*, 9503.

2. Meyers, A. I.; Berney, D. *OSC* **1993**, *8*, 241.
3. (a) Other amino alcohols have been used to prepare bicyclic lactams such as the title reagent. These bicyclic lactams have served as precursors to a variety of enantiomerically pure compounds that possess a quaternary stereocenter, such as 2,2-dialkyl keto acids, cyclopropanes, cyclobutanes, cyclopentenones, cyclohexenones, indanones, naphthalenones, and 3,3-disubstituted dihydronaphthalenes. For an extensive review on the utility of chiral, nonracemic bicyclic lactams, see Ref. 1.
(b) A valinol-derived bicyclic lactam has been used to prepare 4,4-disubstituted 2-cyclohexenones: Meyers, A. I.; Hanreich, R.; Wanner, K. T. *JACS* **1985**, *107*, 7776.
4. Meyers, A. I.; Lefker, B. A.; Wanner, K. T.; Aitken, R. A. *JOC* **1986**, *51*, 1936.
5. Meyers, A. I.; Berney, D. *JOC* **1989**, *54*, 4673.
6. Meyers, A. I.; Lefker, B. A. *T* **1987**, *43*, 5663.
7. Wünsch, T.; Meyers, A. I. *JOC* **1990**, *55*, 4233.

Todd D. Nelson & Albert I. Meyers

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(4a*R*)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin

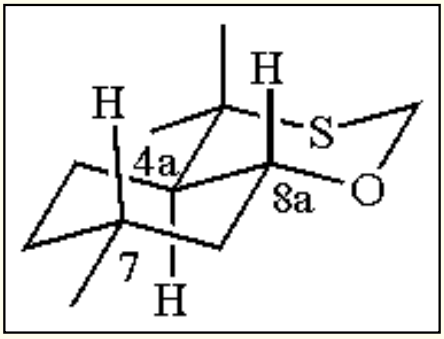

(4a*R*)-(4aα,7α,8aβ)

[79618-03-4] · $C_{11}H_{20}OS$ · (4a*R*)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4*H*-1,3-benzoxathiin · (MW 200.38)

[59324-06-0]

(useful chiral auxiliary for asymmetric synthesis of tertiary[1] and secondary[2] alcohols[3])

Physical Data: mp 37-38 °C; bp 70-94 °C/0.1 mmHg (for diastereomeric mixture).

Solubility: very sol most organic solvents at 20 °C; slightly sol pentane at 0 °C; insol H_2O.

Preparative Method: prepared in three steps from optically pure (+)-pulegone (eq 1).[4]

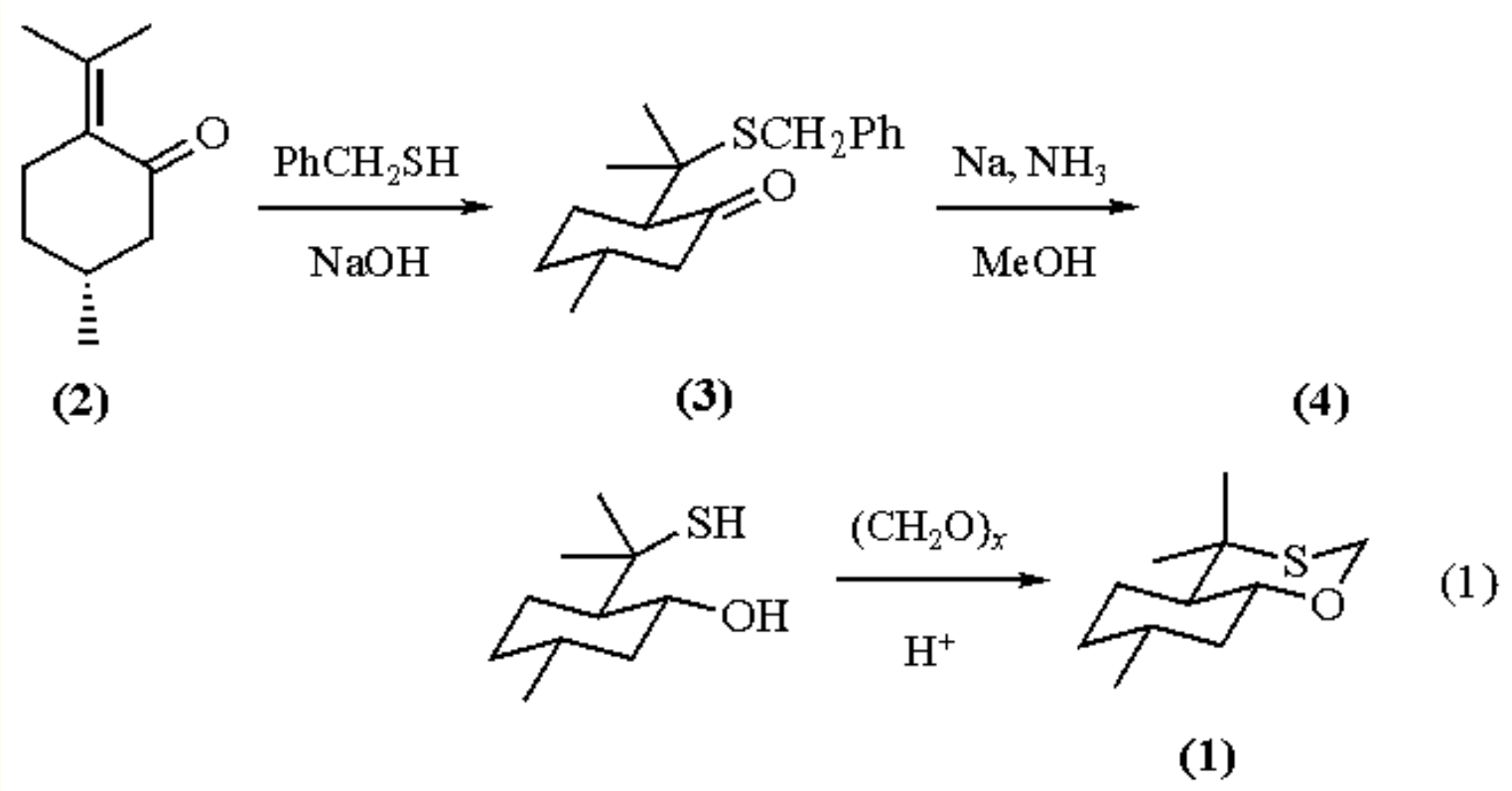

Handling, Storage, and Precautions: refrigerated storage is recommended. Use in a fume hood.

Asymmetric synthesis via the title reagent (**1**) is the result of two highly stereoselective reactions. The first involves the reaction of 2-lithio-1,3-oxathiane (**5**), with an aldehyde to give exclusively the equatorial addition product (**6**) (this reaction typically shows little aldehyde facial selectivity) (eq 2). The selectivity is due to the greatly enhanced stability of the equatorial lithium species (**5**) as compared to the axial isomer, a result of the stereoelectronics of the conformationally rigid oxathiane.[5] Swern oxidation of the resulting carbinols allows the preparation of 2-acyloxathianes as single stereoisomers in high yield.[6] Direct acylation of (**5**) has been achieved recently in selected cases by reaction with nitriles[7] or α-heteroatom-substituted esters.[8] Acyloxathianes (**7**) have also been prepared by acylation of the cuprate (**8**) (obtained from (**5**) and 0.5 equiv ***Copper(I) Iodide***) with acid chlorides (eq 3).[9]

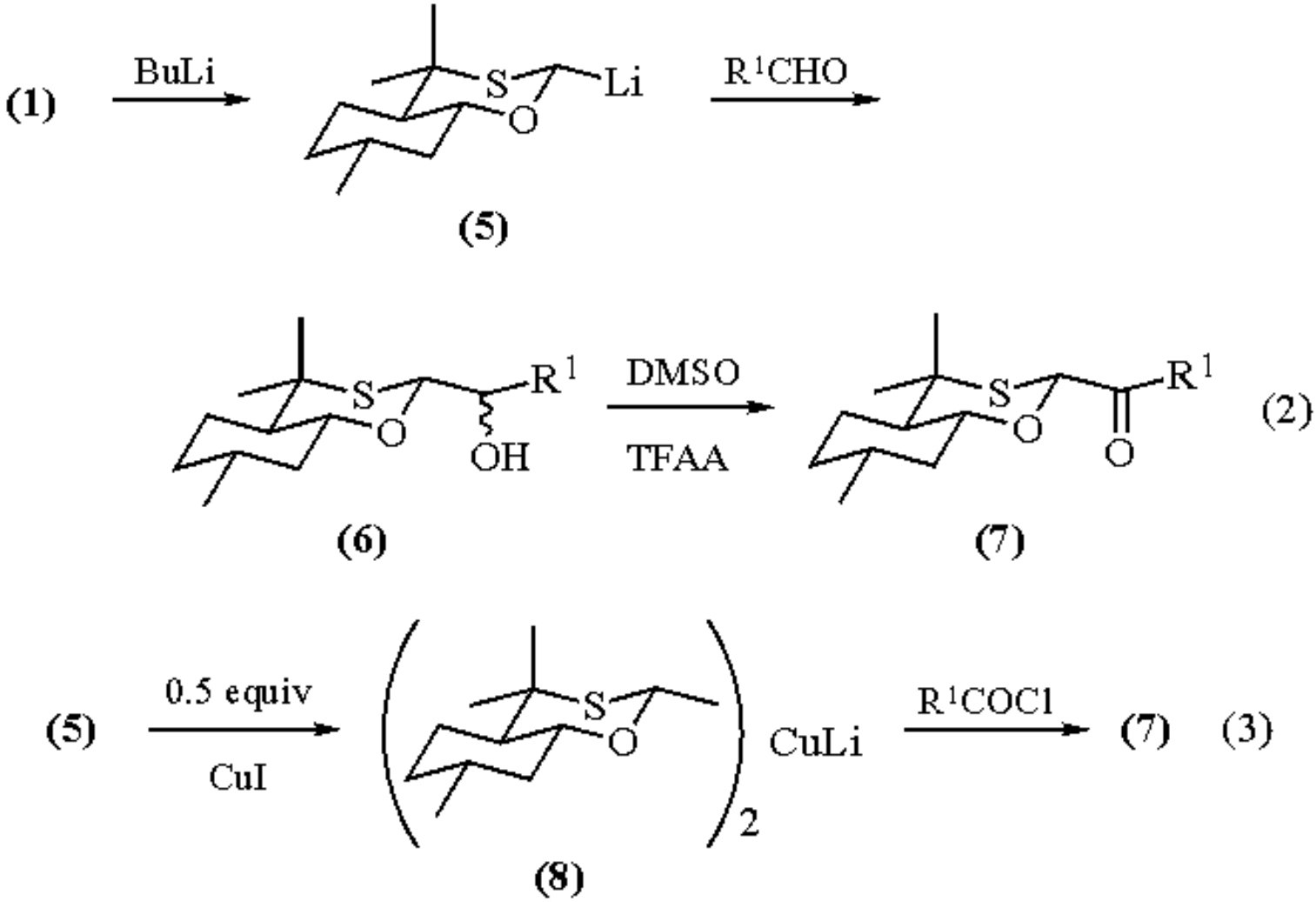

The ketones (**7**) undergo highly stereoselective additions with Grignard reagents to give tertiary alcohols or can be reduced stereoselectively to secondary alcohols. In the case of Grignard reactions, the addition generally shows very high selectivity, typically >9:1, often >95:5 (**9**):(**10**) (eq 4).[10] The major isomer is that predicted to be formed by Cram's chelate rule.[11,12] The kinetics of Grignard reactions with α-alkoxy ketones have been measured by Eliel et al.[13] and these studies strongly support the intermediacy of a chelate structure.

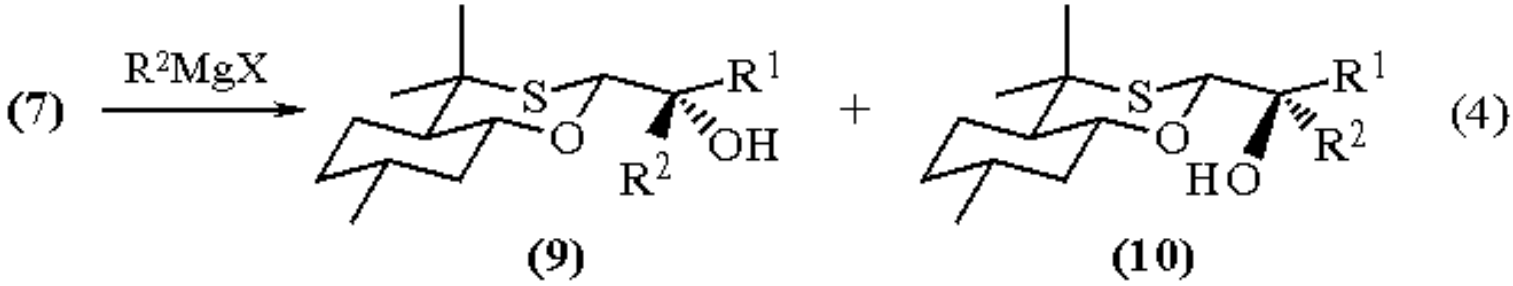

When the R group of ketone (**7**) contains a heteroatom capable of competing with the oxathianyl oxygen for magnesium chelation, a sharp decrease or reversal in the selectivity has been observed (eq 5).[14] The selectivity was restored when the heteroatom (in this case oxygen) was rendered incapable of chelation by protection with a bulky silyl group.

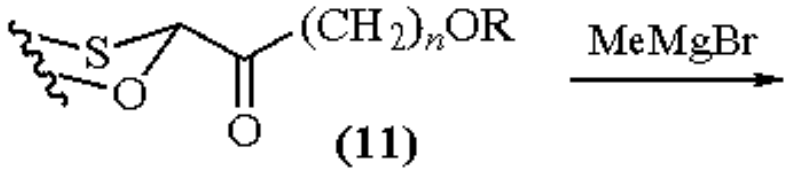

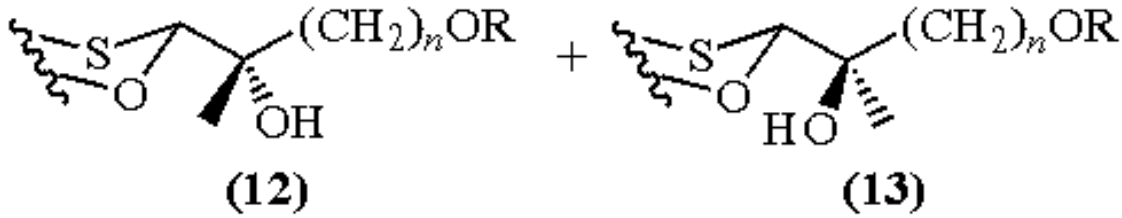

(5)

n	R	(12) (%)
1	CH_2Ph	38
2	CH_2Ph	42
3	CH_2Ph	82
1, 2	$Si(i\text{-}Pr)_3$	98

Ketones having a heteroatom (O or S) at a second adjacent chiral center have also been studied.[15] High selectivity in the addition of a Grignard or lithium reagent was obtained in many cases, but the sterochemical outcome was found to depend on the configuration of the additional center, the organometallic reagent, and the heteroatom substituent (eq 6).[15]

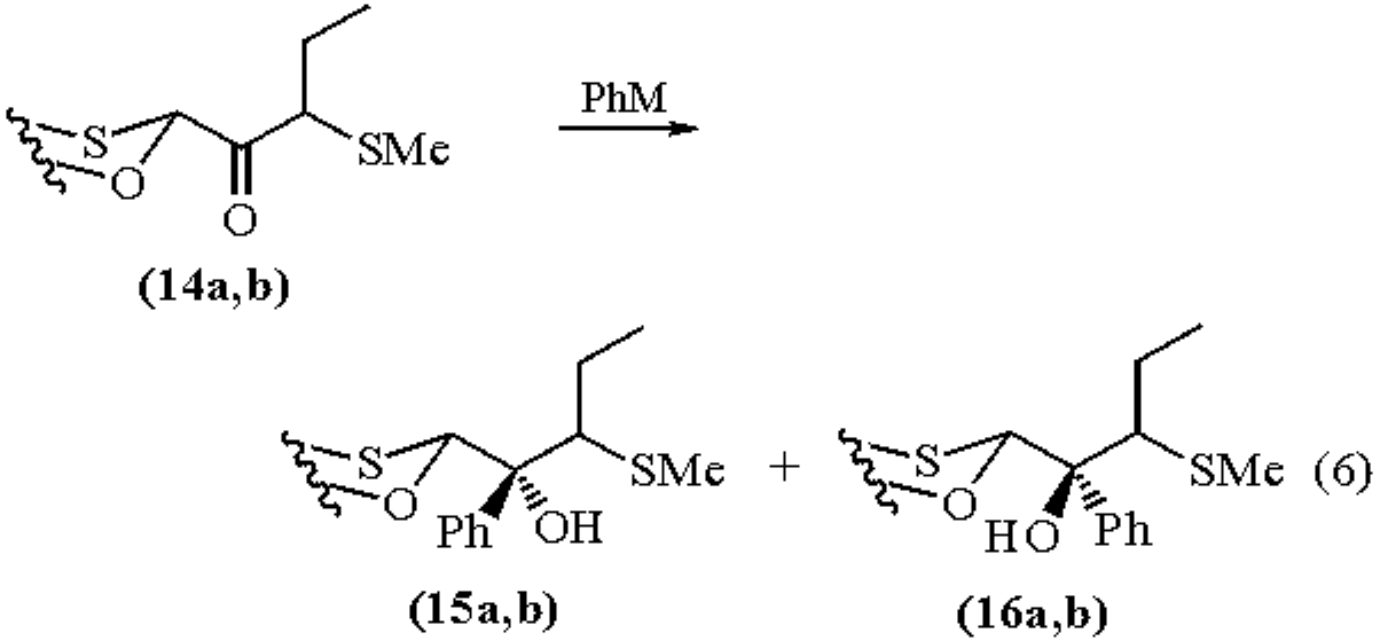

Side chain configuration	M	(15):(16)
(*R*)	Li	53:47
(*R*)	Mg	100:0
(*S*)	Li	0:100
(*S*)	Mg	100:0

Ytterbium-mediated additions of alkynyllithium or -magnesium reagents to (**7**) have also been reported to show high selectivity, but for the opposite diastereomer (**10**) (eq 4) from that obtained in Grignard reactions.[16]

Hydride reductions of (**7**) can be controlled to give either the (*R*) or (*S*) secondary hydroxy compound with good selectivity by choice of the reducing agent. ***Lithium Tri-s-butylborohydride*** (L-Selectride®) provided the (*S*)-alcohol (according to Cram's chelate rule) and ***Diisobutylaluminum Hydride*** (DIBAL) gave the (*R*)-carbinol in excess (eq 7).[2] The DIBAL results were rationalized in terms of the open-chain Cornforth dipole model.[17]

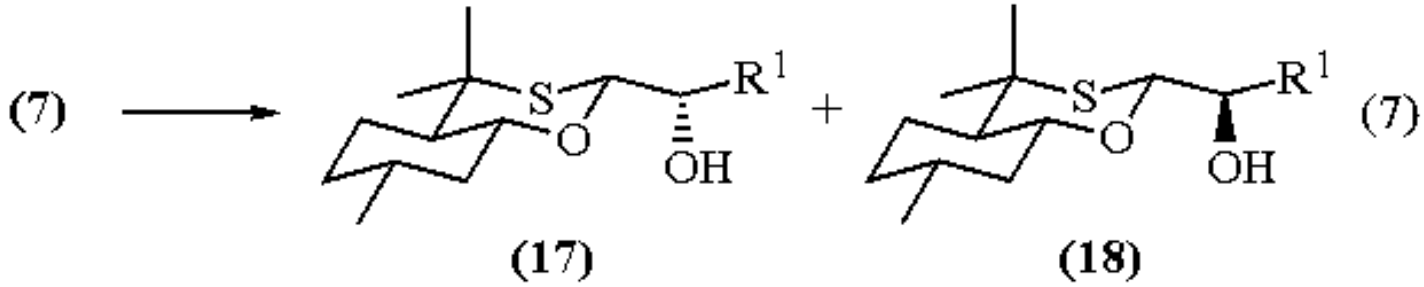

R^1	Reducing agent	(17):(18)
Me	L-Selectride	21:79
Me	DIBAL	78:22
n-Hex	L-Selectride	11:89
n-Hex	DIBAL	87:13
i-Pr	L-Selectride	67:33
i-Pr	DIBAL	88:12
Cy	L-Selectride	52:48
Cy	DIBAL	89:11
t-Bu	L-Selectride	22:78
t-Bu	DIBAL	81:19

Hydrolysis of the 1,3-oxathiane moiety has been accomplished under mild conditions (0 °C, 5 min) by the use of ***N-Chlorosuccinimide-Silver(I) Nitrate***.[18] This oxidative hydrolysis produces α-hydroxy aldehydes in good yields and, in addition, two diastereomeric sultines (**19**) (eq 8).[1] The use of ***Iodine***-$AgNO_3$ for the oxidative hydrolysis of 1,3-oxathianes has also recently been reported.[19] The tertiary α-hydroxy aldehydes are easily oxidized directly to the acids (***Sodium Chlorite***)[20] or methyl esters (MeOH, I_2, KOH)[21] or are conveniently reduced to the diols by direct reduction of the hydrolysis mixture with ***Sodium Borohydride***. The secondary α-hydroxy aldehydes could likewise be reduced to the glycols without racemization; however, oxidation required protection as the benzyl ether prior to hydrolysis. The sultines (after chromatographic separation) are reduced to the hydroxy thiol (**4**) by ***Lithium Aluminum Hydride***.

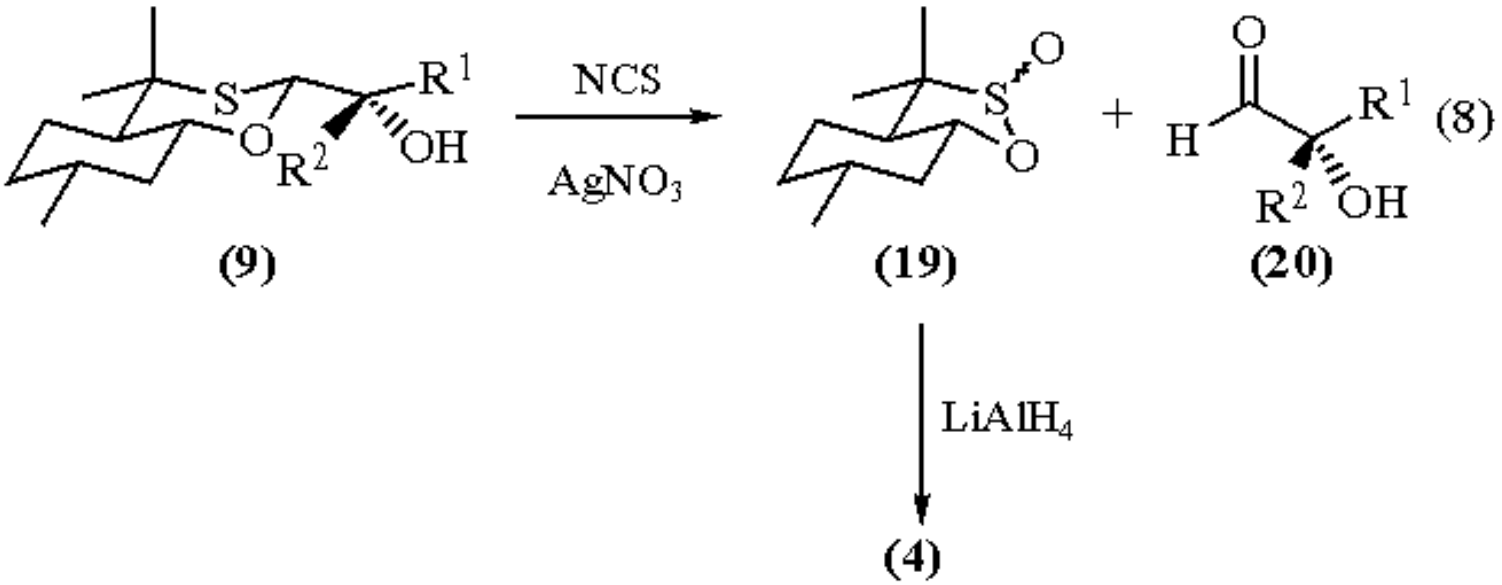

Advantage has been taken of the fact that the diastereomers (**9**) and (**10**) are often easily separated by silica gel chromatography, particularly when both enantiomers of a compound are desired in pure form. Nonselective addition of (**5**) to 2-hexanone followed by chromatographic separation of the diastereomeric carbinols and hydrolysis of each gave both (+)- and (-)-2-hydroxy-2-methylhexanal in optically pure form.[22]

Hydroxy thiol (**4**) likewise has been used to resolve dimethyl 4-oxocyclopentane-1,2-dicarboxylate by crystallization of the mixture of the derived oxathianes. This provided the (*R*,*R*) enantiomer in >99% purity (eq 9).[23]

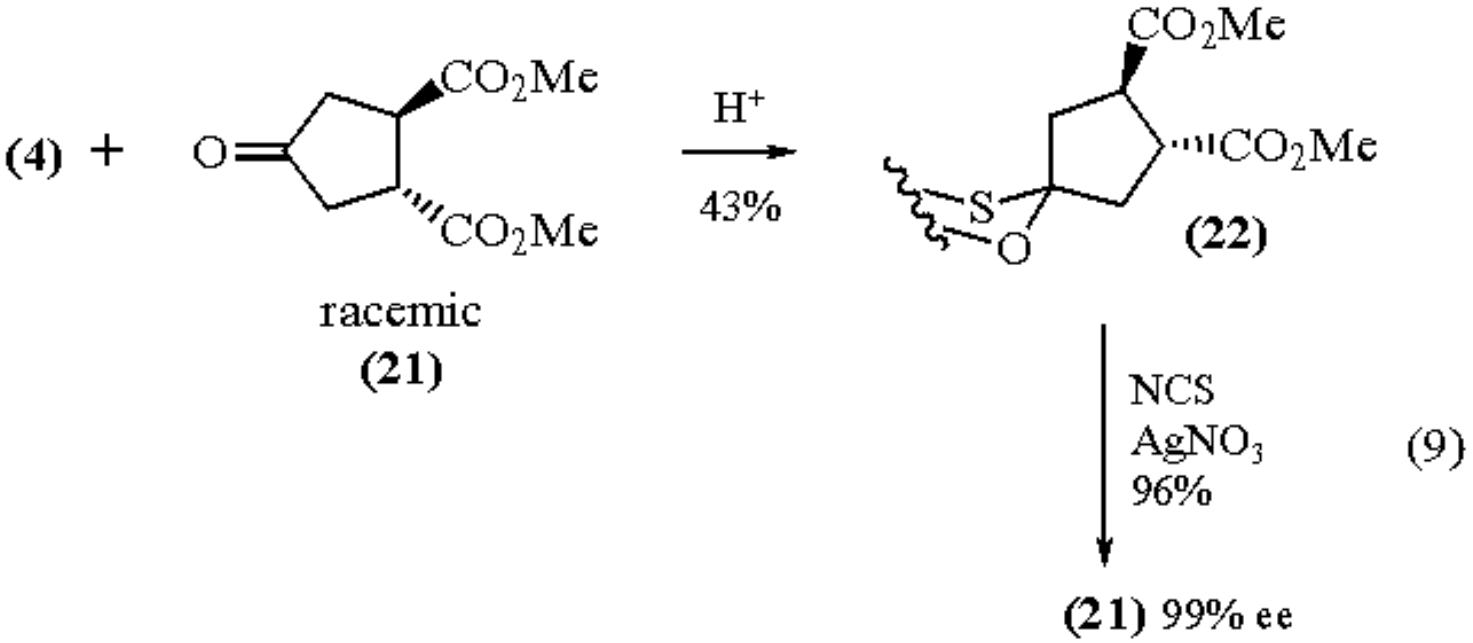

An interesting 1,4-addition to the vinyl sulfone derivative of a related 1,3-oxathiane[24] has also been reported (eq 10).[25]

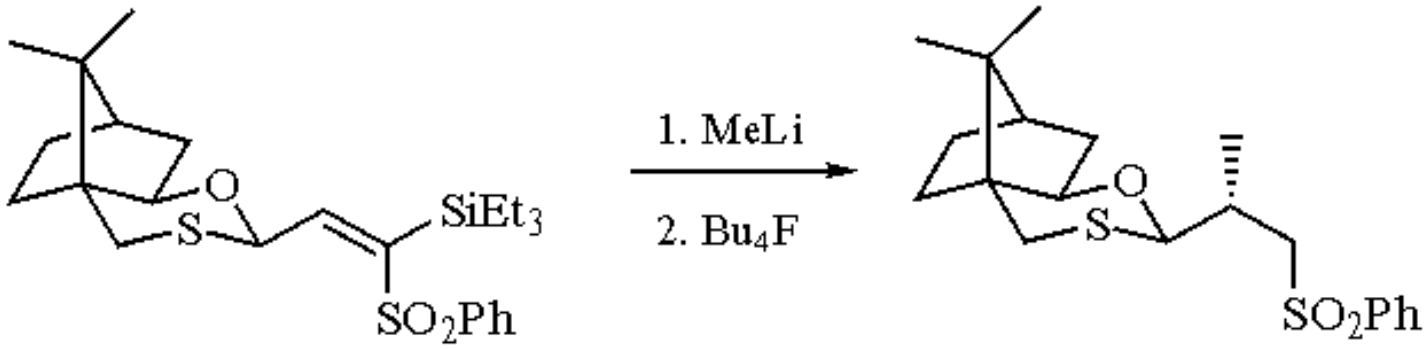

(23) (24)

The use of stoichiometric, covalently bound chiral auxiliaries as a method of asymmetric synthesis is generally impractical and cannot compete with catalytic methods on a commercial scale. However, at the laboratory scale, the oxathiane method provides a predictable method to obtain a desired enantiomer with high selectivity. Since the intermediate compounds prior to hydrolysis are diastereomeric, they are easily separated (often by crystallization) and thus enantiomerically pure compounds are readily obtained.

Related Reagents.

Benzothiazole; ***Carbon Monoxide***; ***N,N-Diethylaminoacetonitrile***; ***N,N-Dimethyldithiocarbamoylacetonitrile***; ***2-Lithio-1,3-dithiane***; ***Methylthiomethyl p-Tolyl Sulfone***; ***2-(Trimethylsilyl)thiazole***.

---

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1,1,1,3,3,3-Hexakis(dimethylamino)-1λ^5,3λ^5-diphosphazenium Fluoride

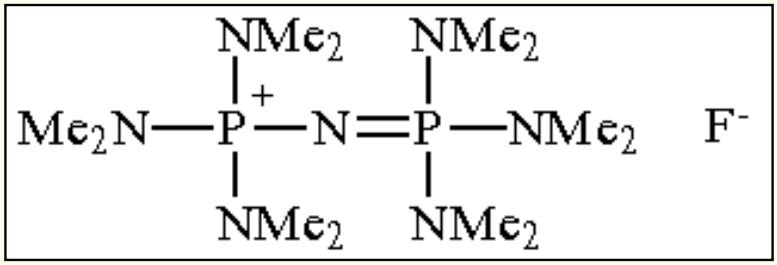

[137334-99-7] · $C_{12}H_{36}FN_7P_2$ · 1,1,1,3,3,3-Hexakis(dimethylamino)-1λ^5,3λ^5-diphosphazenium Fluoride · (MW 359.49)

(anhydrous stable organic fluoride salt; source of homogeneous, extremely basic solutions of naked fluoride ions of unprecedented reactivity and selectivity in E2 elimination reactions;[1] readily cleaves C-Si bonds, generating extremely reactive naked carbanions[1])

Alternate Name: P_2-F.

Physical Data: mp ca. 152 °C (dec); *d* 1.193 g cm^{-3}.

Solubility: very sol benzene, fluorobenzene (with partial deactivation); sol with deactivation in protic solvents, acetonitrile, DMSO; sparingly sol toluene, dioxane, HMPA, THF; reacts rapidly with partially halogenated alkanes and slowly with CCl_4.

Form Supplied in: commercially available as a 0.5 M solution in benzene.

Preparative Methods: a solution of 1,1,1,3,3,3-hexakis(dimethylamino)-1λ^5,3λ^5-diphosphazenium tetrafluoroborate[1] (12.8 g, 30.0 mmol) in anhydrous MeOH (20 mL) is treated with a solution of KF (1.83 g, 31.5 mmol, dried for 12 h at 240 °C in a high vacuum) in cold MeOH (25 mL) under N_2 and stirred vigorously for 10 min. The KBF_4 is removed by suction. The flask is then equipped with a glass-covered stirring bar, the solution concentrated in vacuo at 40-50 °C bath temperature, purged with N_2, and anhydrous *i*-PrOH (5 mL) is added. This sequence is repeated twice. The flask is then fitted to the cold trap of a (diffusion pump) vacuum apparatus, connected by a 10-mm flow cross-section stop-cock. The solution is concentrated in vacuo with stirring, the bath temperature being brought to 80 °C within 1 h and kept for 1 h at 80 °C and 1 h at 100 °C. For the following operations, rigorous exclusion of moisture (glove box) is essential. The completely solidified product is scratched from the surface of the flask and dried for 1 h at 120 °C. The product is slurried in absolute THF (20 mL), larger lumps are crushed with a pestle, the crystals filtered off with a D4 glass suction filter, washed with absolute THF (15 mL) and dried in a high vacuum, providing 9.7 g (90%) of colorless crystals, 98-99% in naked fluoride by titration; ca. 1% of

inorganic material can be removed by filtration of the benzene solution.

Analysis of Reagent Purity: ^{1}H NMR (benzene-d_6) δ 2.60; by titration in benzene with solid HPF_6 salt of 1,8-bis(dimethylamino)naphthalene, with triphenylmethane as indicator.

Handling, Storage, and Precautions: store and handle so as to rigorously exclude moisture. It is thermally stable up to ca. 100 °C and insensitive to dry oxygen.

E2 Eliminations.

P_2-F is the first reported, soluble source of naked fluoride.[1d] For substrates that tolerate its high basicity (P_2-F deprotonates DMSO in equilibrium), it is one of the most effective E2 elimination bases known. Due to formation of FHF^-, 2 mols are required for elimination of 1 mol of acid. Workup of reaction mixtures is achieved by precipitation of the salts formed with ether or benzene, by extracting the product from aqueous solution with diethyl ether or hydrocarbons, or by filtration over silica gel. All halides of the cation can be converted to tetrafluoroborates by precipitation from aqueous solution with $NaBF_4$.

Very high selectivity (low nucleophilicity) and very high reactivity are the main advantages of P_2-F over conventional bases. In general, reactivity is only slightly reduced when heterogeneous conditions are employed[1d,2] (e.g. THF, eq 1). These conditions have the advantage of slowing down double bond migration considerably. However, reaction of primary alkyl fluorides at rt is rapid only in a homogeneous benzene solution, affording a largely equilibrated mixture of alkenes.[2] Other primary alkyl halides react in THF at -78 °C, affording isomerically pure 1-alkenes[1d] (eq 2) (see also ***Potassium t-Butoxide***).

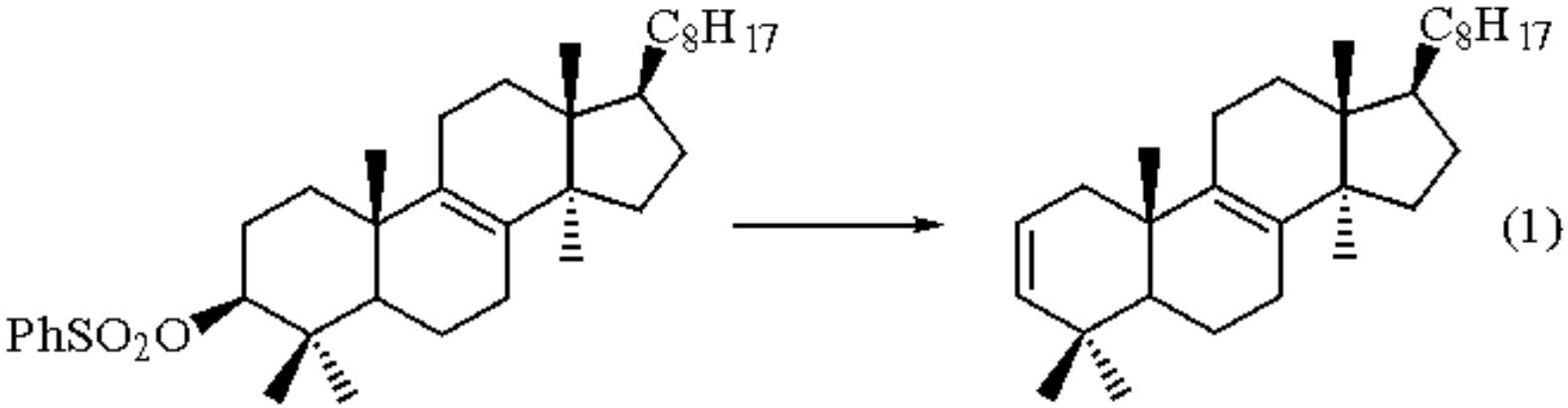

(1)

3 equiv P_2-F, THF, 25 °C, 30 min	99%
3 equiv P_2-F, benzene, 25 °C, 10 min	99%
3 equiv KO-*t*-Bu, THF, DMSO, 80 °C, 4 d	75%
10 equiv $Me_4N^+F^-$, THF, 65 °C, 4 d	< 5%

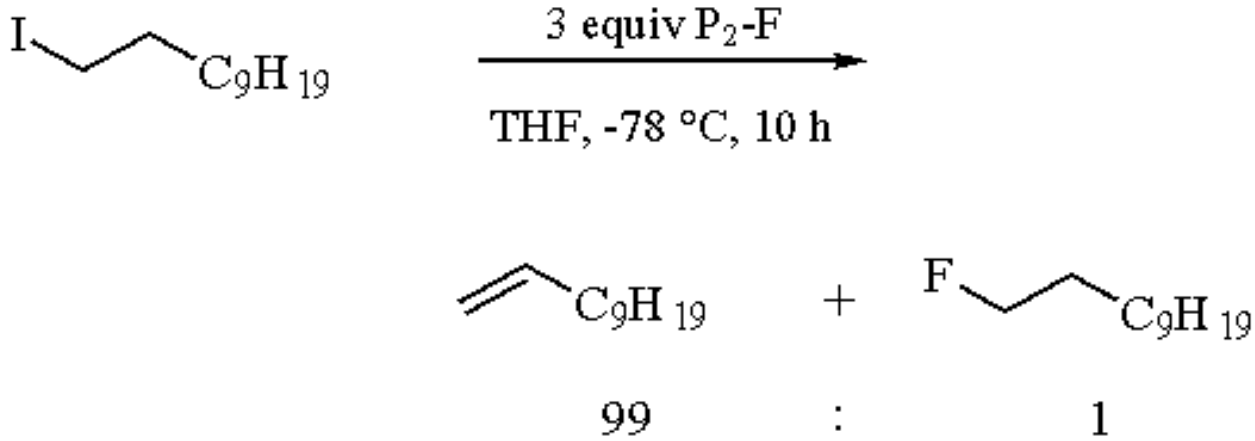

(2)

Strongly shielded protons are readily attacked,[3] even when other bases fail completely (eq 3).

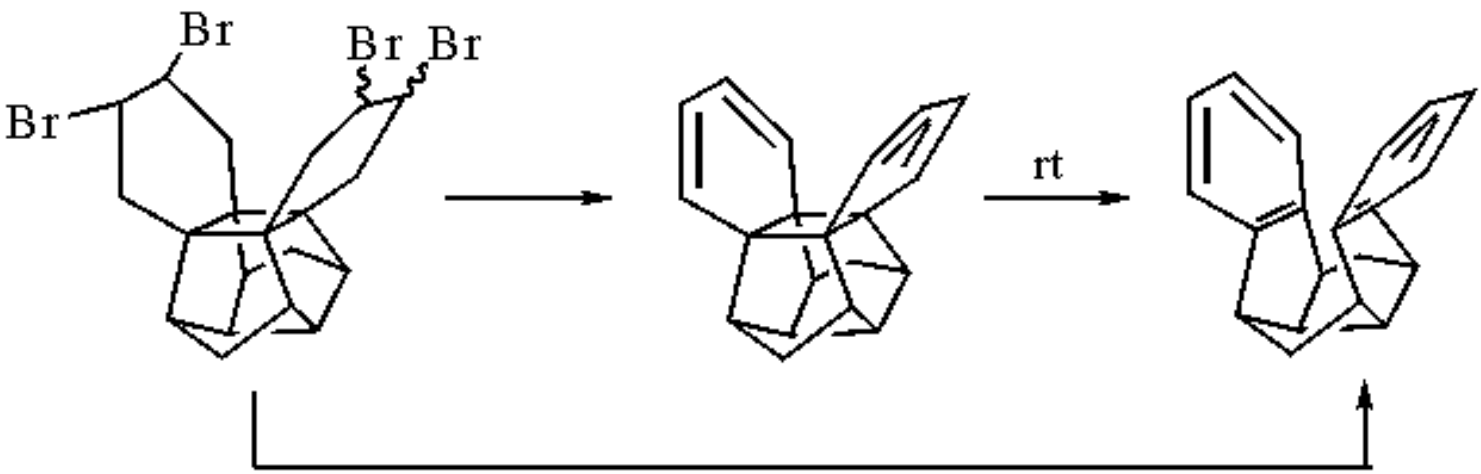

(3)

P_2-F, benzene, 5 °C, 5 min	80%	12%
KO-*t*-Bu, THF	0%	<1%
LiCl, DMF	0%	12%

Highly strained alkenes like dodecahedrene[4] are formed with great ease (eq 4) in almost quantitative yield.

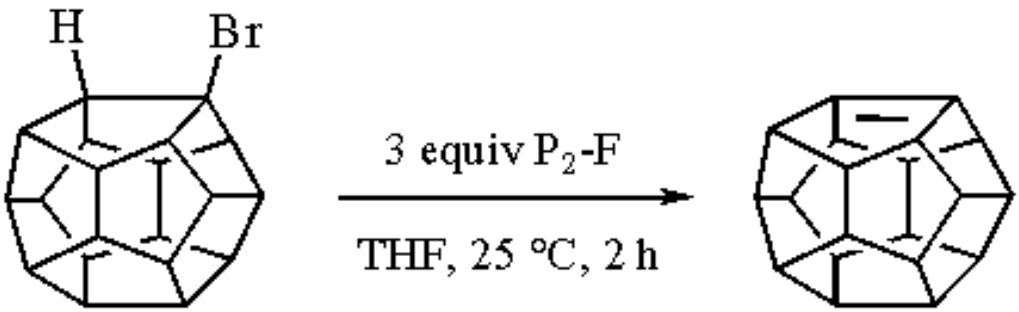

(4)

Epoxides are isomerized to allylic alcohols under relatively mild conditions (eq 5).[2] The stereochemistry differs considerably from that of the reaction with ***Lithium Diethylamide***, with *trans*-diaxial elimination predominating.

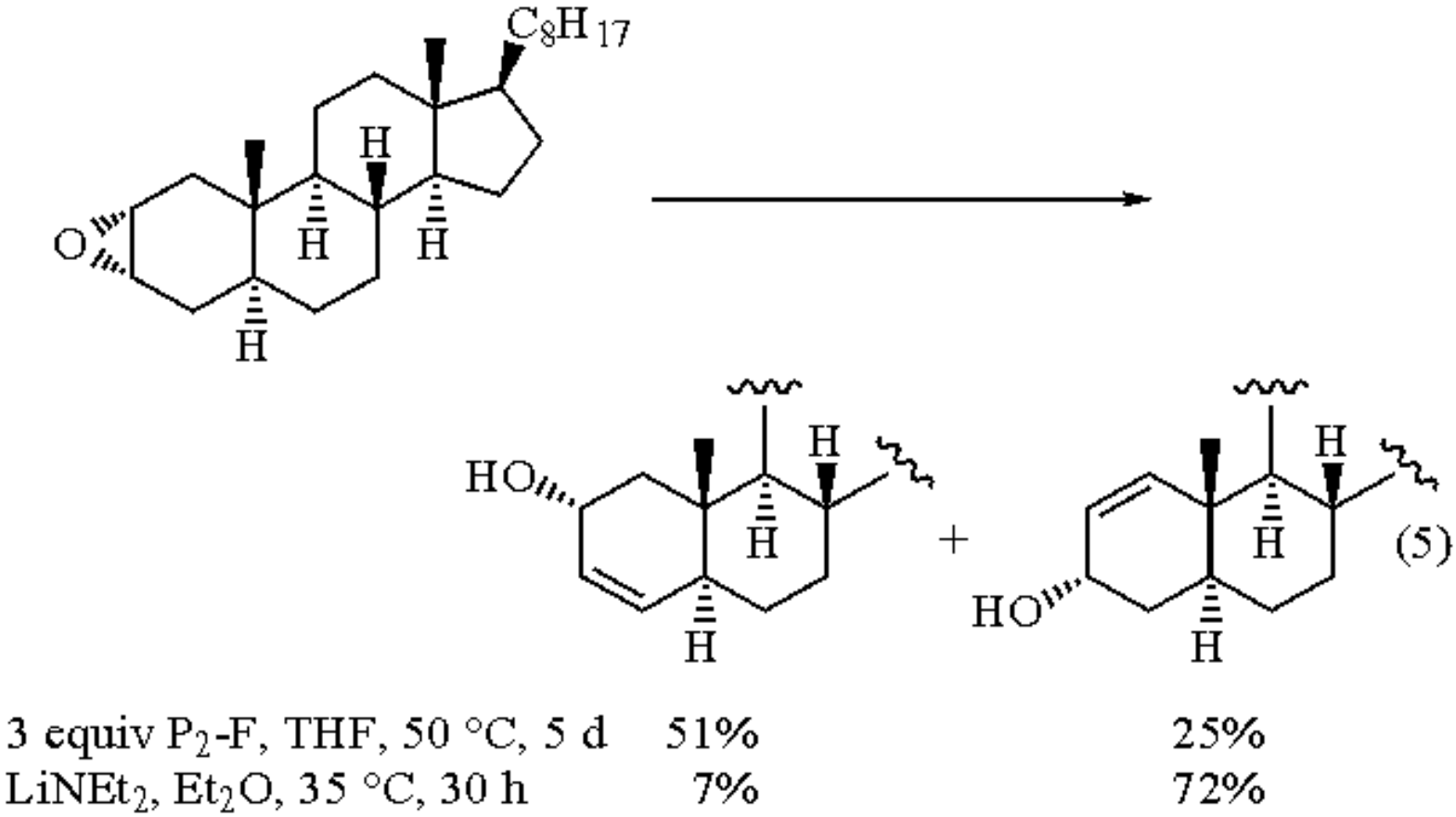

In benzene solution, unactivated aryl halides afford mixtures of regioisomeric aryl fluorides,[2] presumably via arynes, but only with higher phosphazenium fluorides[2] is partial reduction to the arene effectively suppressed.

Cleavage of Carbon-Silicon Bonds.

Allylsilanes are cleaved at -78 °C, forming naked allyl anions, which can be alkylated in situ (eq 6).[1d]

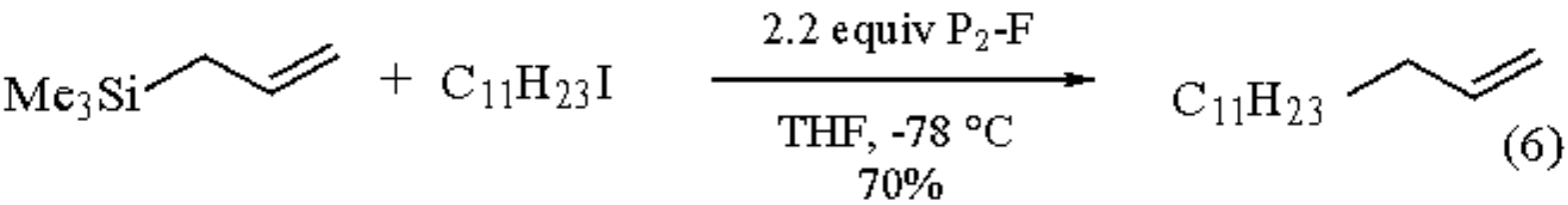

Related Reagents.

Phosphazene Base P_4-t-Bu.

---

1. (a) Most efficacious procedure: Link, R.; Schwesinger, R. *AG(E)* **1992**, *31*, 850; compare also: (b) Marchenko, A. P.; Shaposhnikov, S. I.; Koidan, G. N.; Kharchenko, A. V.; Pinchuk, A. M. *ZOB* **1988**, *58*, 2230; (c) Schwesinger, R.; Schlemper, H. *AG(E)* **1987**, *26*, 1167; (d) Schwesinger, R.; Link, R. *AG(E)* **1991**, *30*, 1372.

2. Schwesinger, R.; Link, R., unpublished.
3. Wollenweber, M.; Pinkos, R.; Leonhardt, J.; Prinzbach, H., *AG(E)* **1994**, *33*, 117.
4. Prinzbach, H.; Sackers, E.; Weiler, A., unpublished.

Reinhard Schwesinger

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Hexamethyldisilane

Me_3Si-$SiMe_3$

[1450-14-2] · $C_6H_{18}Si_2$ · Hexamethyldisilane · (MW 146.42)

(silylating or reducing reagent in combination with a Pd catalyst or a nucleophile)

Physical Data: bp 112-114 °C; *d* 0.729 g cm^{-3}.

Solubility: sol common organic solvents; insol H_2O.

Form Supplied in: oil; commercially available.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$-Me_4Si) δ 0.045 (s).

Preparative Methods: by standard synthesis.[1]

Purification: grossly impure sample (25% impurities) is purified by repeated spinning band distillation. This lowered the impurity level to 500 ppm. The main impurity is identified as 1-hydroxypentamethyldisilane.

Handling, Storage, and Precautions: stable to H_2O and air; flammable liquid; irritant. Readily oxidized by oxidants such as halogen and peroxide. Use in a fume hood.

Trimethylsilyl Anion.

Treatment of hexamethyldisilane (**1**) with an alkyllithium, metal alcoholate, or fluoride ion generates the trimethylsilyl anion (**2**) (eq 1).[2] Reaction of (**2**) with aryl halides gives trimethylsilylarenes in 63-80% yields along with reduced products (ArH, 4-27%).[3] ***Tetra-n-butylammonium Fluoride*** (TBAF) catalyzed reaction of Me_6Si_2 with butadienes gives 1,4-disilyl-2-butenes (15-81% yield) with high (*E*) selectivity.[4]

$$\underset{\textbf{(1)}}{Me_3Si\text{-}SiMe_3} \xrightarrow[\text{or } F^-]{\text{RLi, ROM}} \underset{\textbf{(2)}\ M = Li, Na, K, Bu_4N}{Me_3Si^-\ M^+} \qquad (1)$$

Aliphatic aldehydes react with Me_6Si_2/TBAF in HMPA to afford 1-trimethylsilyl-1-alkanols (**3**), whereas aryl aldehydes give pinacols (**4**) under the same conditions (eq 2).[5]

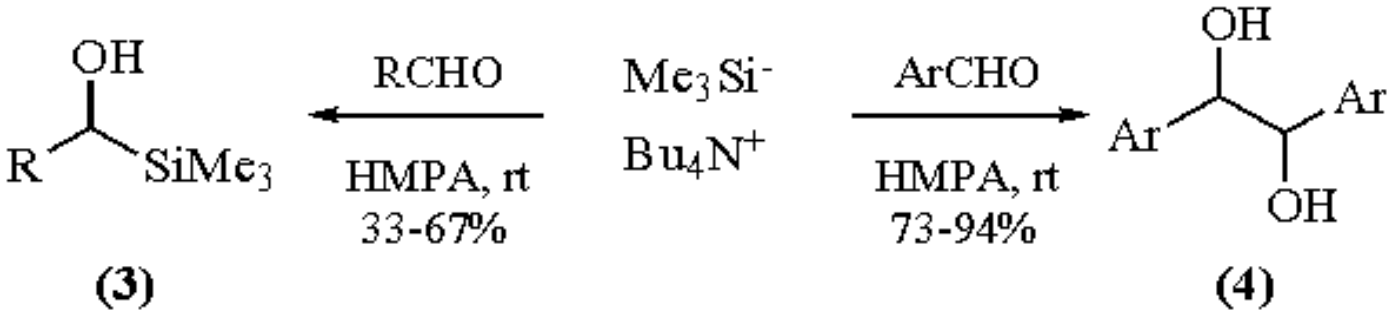

(2)

The trimethylsilyl anion adds to α,β-unsaturated ketones in a 1,4-manner to give β-silyl ketones. This reaction has been applied to the synthesis of carbacyclin.[6]

α-Diketones (**5**) react with Me_6Si_2 in the presence of $PdCl_2(PMe_3)_2$ or $Pt_2(dba)_3$-$P(OCH_2)_3CEt$ to give the corresponding 1,2-bis(trimethylsilyloxy)ethylenes (**6**) (eq 3), while α-keto esters (**7**) provide pinacol 2,3-bis(trimethylsilyl) ethers (**8**) (eq 4).[7] The regio- and stereoselectivities are moderate (62:38-87:13).

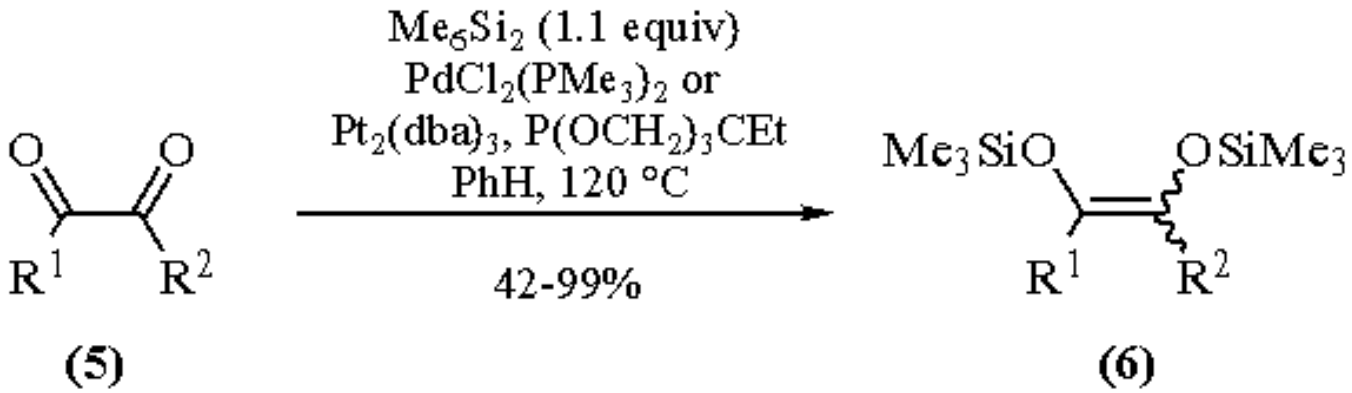

(3)

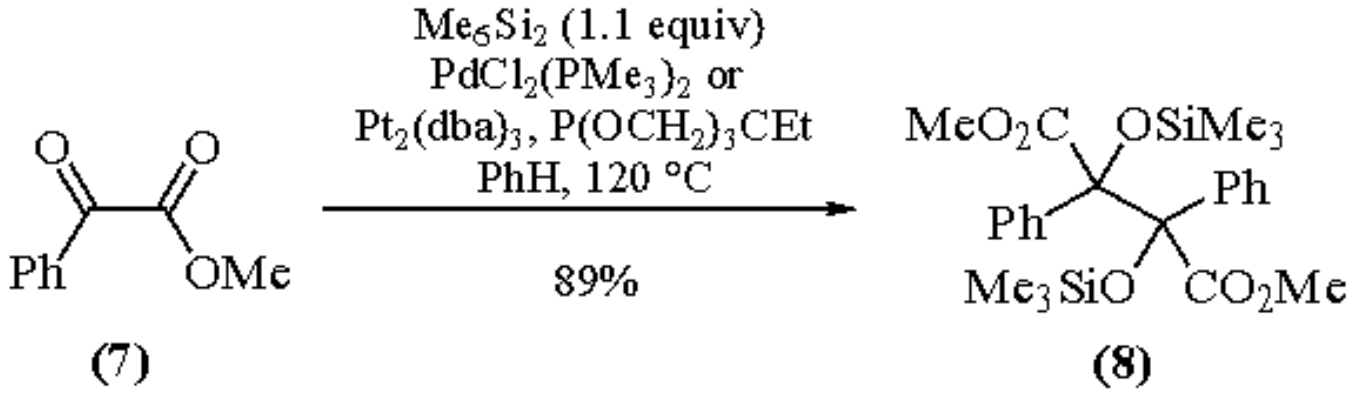

(4)

Allyl alcohols are converted into allylsilanes (**11**) with ***n-Butyllithium*** and Me_6Si_2 (eq 5). Here, the in situ generated lithium allyl alcoholates (**9**) first react with Me_6Si_2 to produce trimethylsilyllithium and trimethylsilyl allyl ethers (**10**), which subsequently react in an S_N2' manner to give the products. Similarly, the lithium alcoholates generated from α,β-unsaturated aldehydes (or ketones) and an alkyllithium, or alternatively from ketones and vinyllithium, can be

converted into the corresponding allylsilanes.[8]

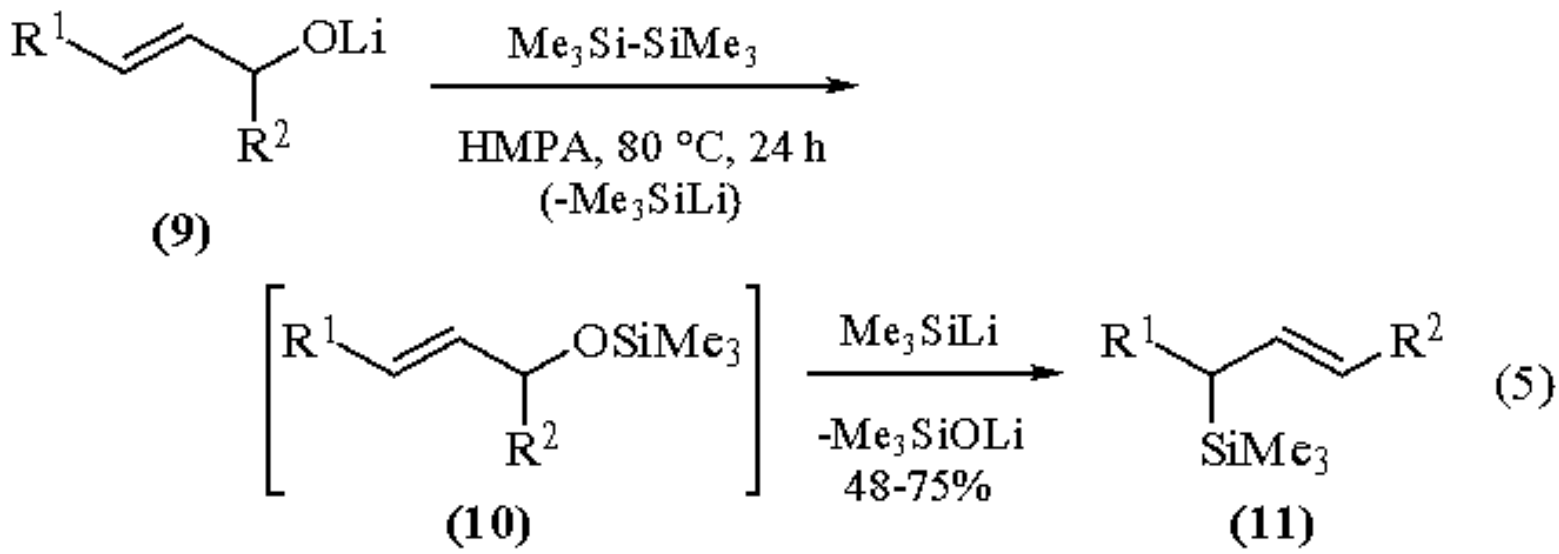

Palladium-Catalyzed Coupling Reaction with Organohalides.

In the presence of ***Tetrakis(triphenylphosphine)palladium(0)***, vinyl halides (**12**) are converted to the corresponding vinylsilanes (**13**) with the aid of Me_6Si_2 and ***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate*** (TASF) in 53-92% yields with high chemoselectivity and stereospecificity (eq 6).[9] Similarly, aryl-, benzyl-, and allylsilanes are obtained from the corresponding halides in 57-100, 8-48, and 52-93% yield, respectively.[10] Allyl esters also are transformed by Pd-catalyzed reaction of Me_6Si_2 into allylsilanes.[11]

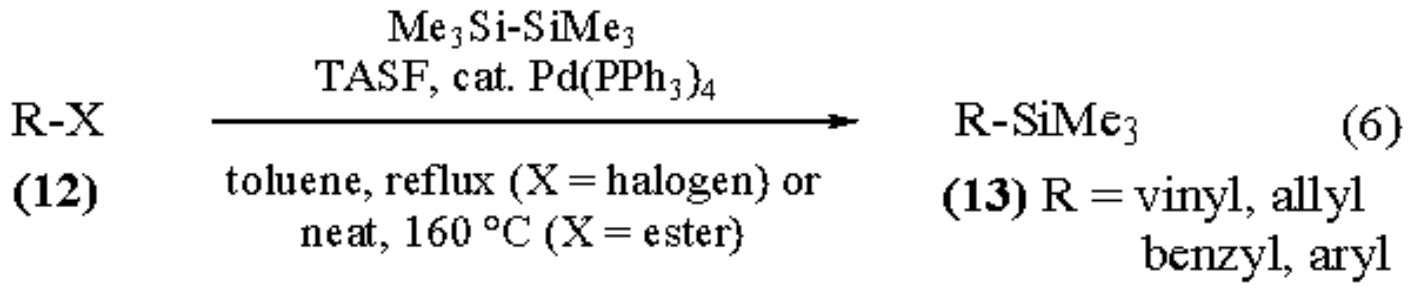

Intermolecular Disilylation of Alkynes.

Intermolecular disilylation of 1-alkynes (**14**) are promoted using ***Palladium(II) Acetate-1,1,3,3-Tetramethylbutyl Isocyanide*** at reflux[12] or $Pd(dba)_2$-$P(OCH_2)_3CEt$ at 120 °C[13] to give (*Z*)-1,2-bis(trimethylsilyl)alkenes (**15**) in yields up to 91% (eq 7). Internal alkynes are unreactive. The latter catalyst system allows 1-alkynes to insert between the Si-Si bonds of poly[*p*-(disilanylene)phenylene] and poly(dimethylsilylene).

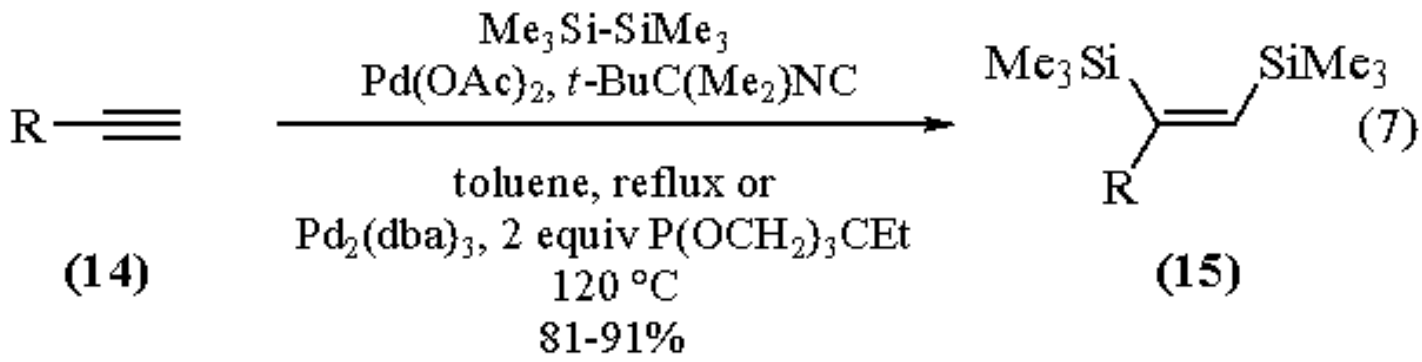

Silyl Vinyl Ethers.

Enolizable ketones (**16**) are readily transformed to silyl vinyl ethers (**17**) by the action of disilane and a catalytic amount of ***Sodium*** in HMPA (eq 8).[14] The regioselectivity of the silyl vinyl ether formation depends on the structure of the ketones.

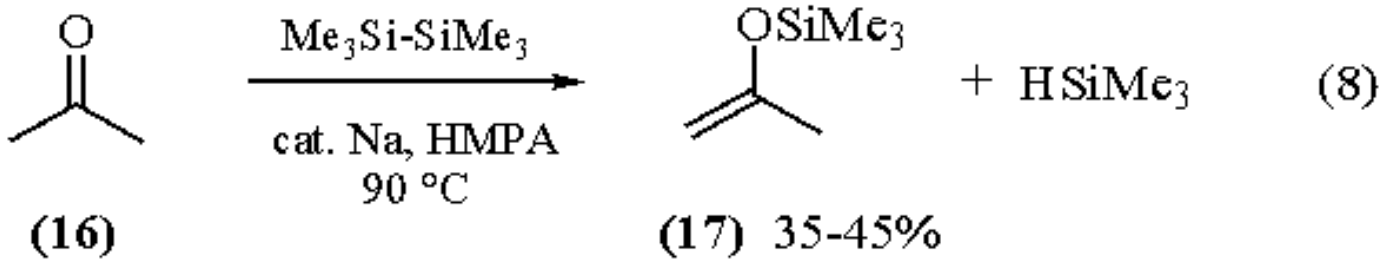

Reductive Coupling of Acyl Halides.

Electron-deficient aromatic acid chlorides (Ar_W-COCl; **18**) are converted into biphenyls (**19**) by the dichlorobis(triphenylphosphine)palladium(II) catalyzed reaction of Me_6Si_2 in mesitylene at 165 °C (eq 9).[15] Arylsilanes are produced as byproducts, but these are switched to major products with $(ClMe_2Si)_2$.[16] In contrast, aromatic acid chlorides (Ar_D-COCl; **20**) bearing an electron-donating group give acylsilanes (**21**) upon catalysis with ***Bis(benzonitrile)dichloropalladium(II)-Triphenylphosphine*** (eq 10).[17]

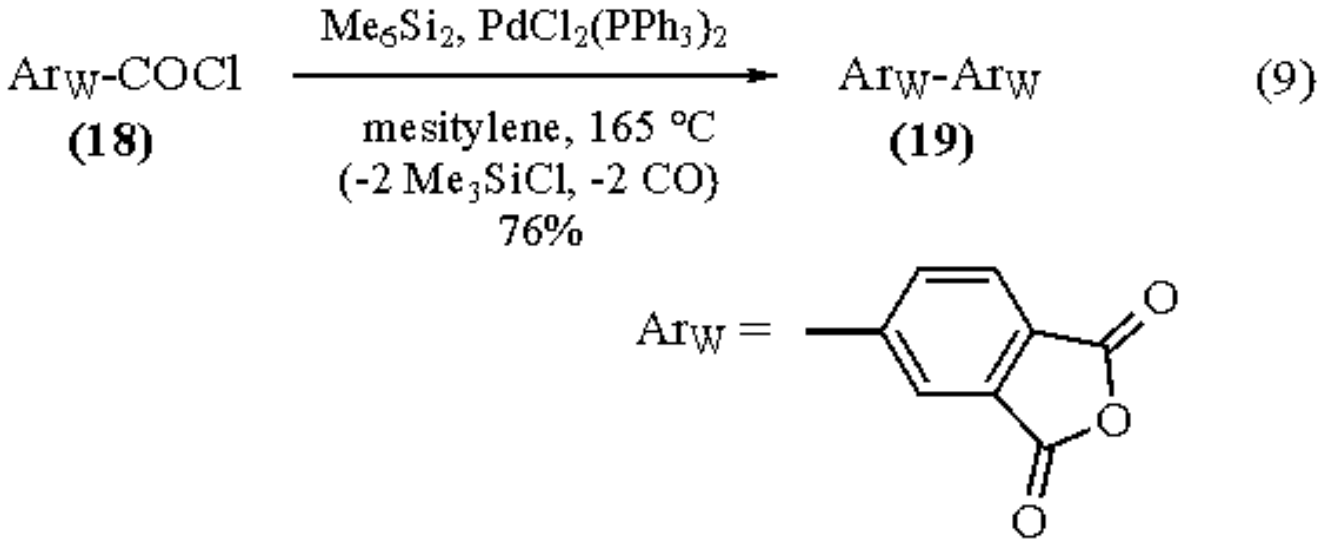

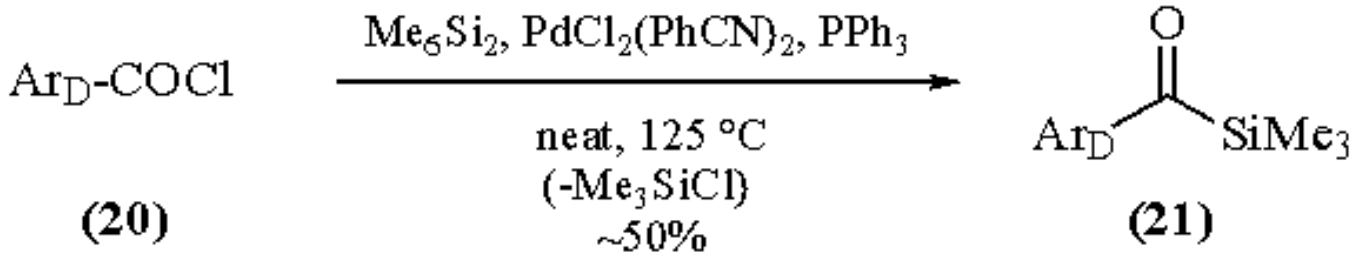

(10)

Reduction of α-Halo Carbonyl Compounds and α-Halo Nitriles.

A halogen substituent on the carbon next to a carbonyl or cyano group is reduced with Me_6Si_2 in the presence of $Pd(PPh_3)_4$ catalyst (eq 11). In the case of α-halo ketones, oxy-π-allyl(trimethylsilyl)palladium intermediates are proposed.[18]

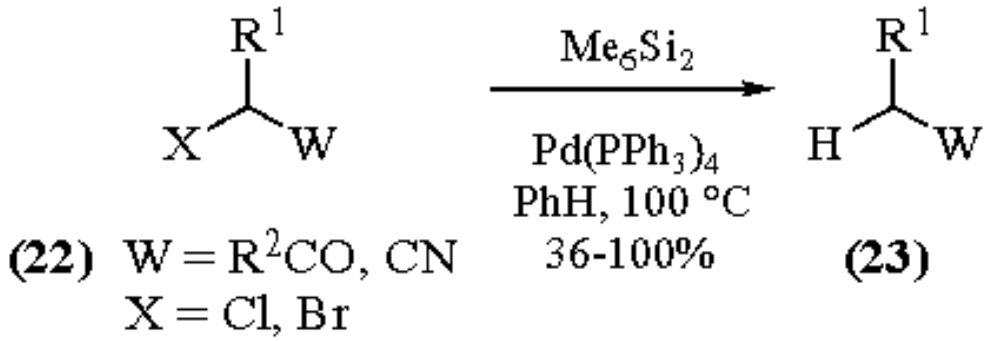

(11)

Palladium-Catalyzed Insertion of Isocyanides into Si-Si Linkage.[19]

A mixture of Me_6Si_2, aryl isocyanide (**24**), a catalytic amount of ***Palladium(II) Acetate*** and toluene is heated to reflux to give disilylformaldehyde imines (**25**) (eq 12). This reaction is applied to the insertion of the isocyanide unit into all the Si-Si linkages of (tetradecamethyl)hexasilane (**26**) to give oligomeric silylimines (**27**) (eq 13).

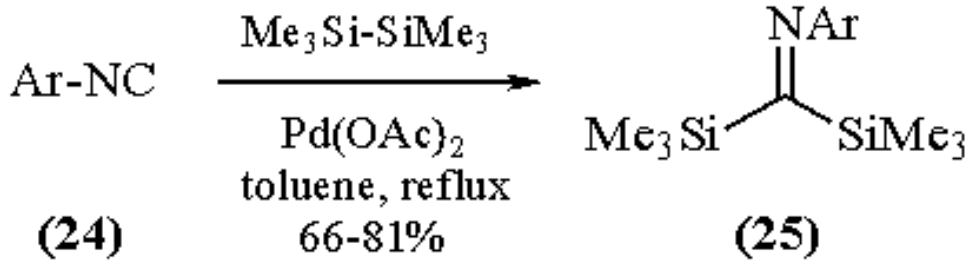

(12)

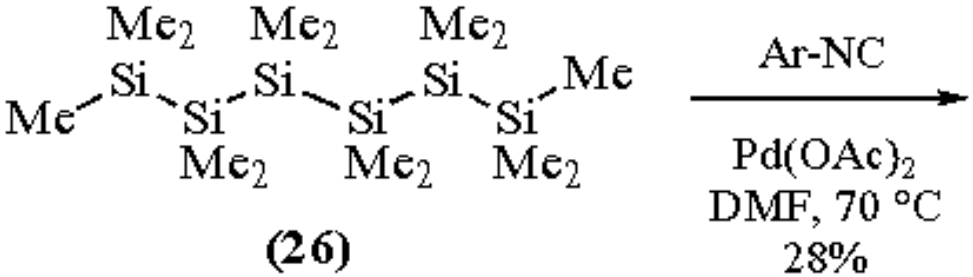

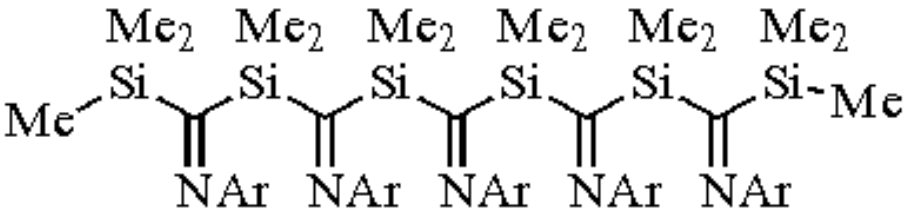

(13)

(27) Ar = 2,6-xylyl

Alkyl Bromides from Alcohols.

Alkyl bromides (**29**) are obtained in high yields by the reaction of the corresponding alcohols (**28**) with Me_6Si_2 and ***Pyridinium Hydrobromide Perbromide*** (eq 14).[20] The substitution reaction is very fast for tertiary, allylic, and benzylic alcohols, but very slow for primary and secondary alcohols. Inversion of configuration is observed with secondary alcohols.

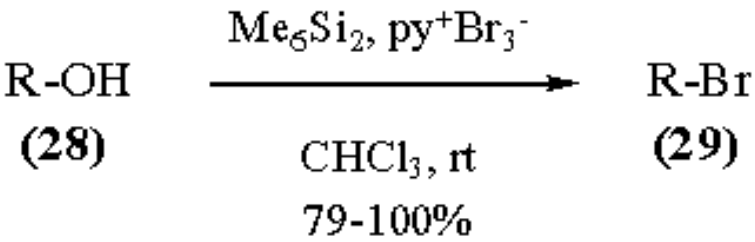

(14)

Reductive Silylation of *p*-Quinones.

Me_6Si_2 in combination with a catalytic amount of ***Iodine*** converts *p*-quinones (**30**) into 1,4-bis(trimethylsiloxy)arenes (**31**) in almost quantitative yields (eq 15).[21] The products are a protected form of quinones, which are regenerated by oxidation with ***Pyridinium Chlorochromate*** (PCC).[22]

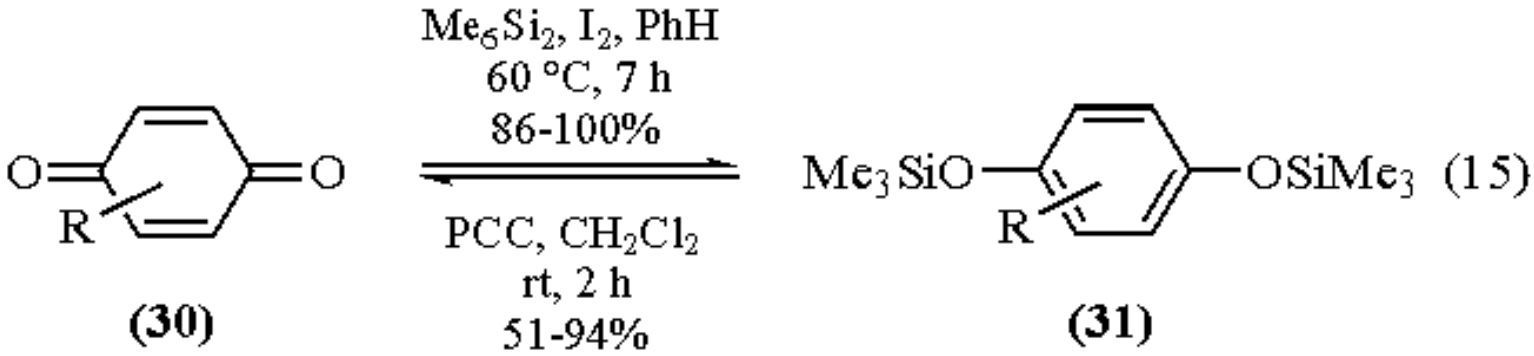

Reductive Coupling of *gem*-Dichloroalkanes.[23]

The reaction of *gem*-dichloroalkanes (**32**) with Me_6Si_2 proceeds smoothly in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give dimerized alkenes (**33**) in fairly good yields (eq 16). The (*E/Z*) ratio of the products is moderate. R^1-CCl_2-$SiMe_3$ also reacts with Me_6Si_2 in the presence of Pd catalyst to yield (*E*)-$R^1(Me_3Si)C{=}CR^1(SiMe_3)$ quantitatively.

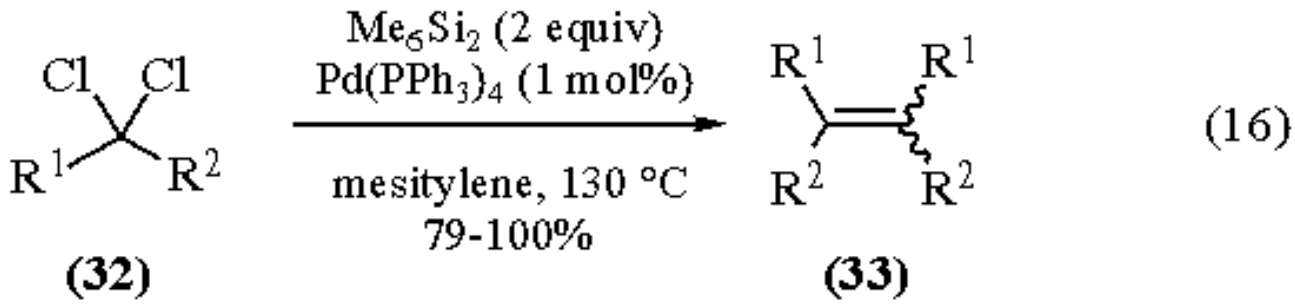

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Hexamethyldisilazane

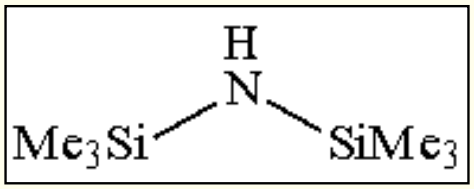

[999-97-3] · $C_6H_{19}NSi_2$ · Hexamethyldisilazane · (MW 161.44)

(selective silylating reagent;[1] aminating reagent; nonnucleophilic base[2])

Alternate Name: HMDS.

Physical Data: bp 125 °C; *d* 0.765 g cm^{-3}.

Solubility: sol acetone, benzene, ethyl ether, heptane, perchloroethylene.

Form Supplied in: clear colorless liquid; widely available.

Purification: may contain trimethylsilanol or hexamethyldisiloxane; purified by distillation at ambient pressures.

Handling, Storage, and Precautions: may decompose on exposure to moist air or water, otherwise stable under normal temperatures and pressures. Harmful if swallowed, inhaled, or absorbed through skin. Fire hazard when exposed to heat, flames, or oxidizers. Use in a fume hood.

Silylation.

Alcohols,[3] amines,[3] and thiols[4] can be trimethylsilylated by reaction with hexamethyldisilazane (HMDS). Ammonia is the only byproduct and is normally removed by distillation over the course of the reaction. Hydrochloride salts, which are typically encountered in silylation reactions employing chlorosilanes, are avoided, thereby obviating the need to handle large amounts of precipitates. Heating alcohols with hexamethyldisilazane to reflux is often sufficient to transfer the trimethylsilyl group (eq 1).[5] Completion of the reaction is indicated by either a change in the reflux temperature (generally a rise) or by the cessation of ammonia evolution.

$$HN(TMS)_2 + 2\,ROH \xrightarrow{\Delta} 2\,ROTMS + NH_3 \qquad (1)$$

Silylation with HMDS is most commonly carried out with acid catalysis.[5] The addition of substoichiometric amounts

of ***Chlorotrimethylsilane*** (TMSCl) to the reaction mixtures has been found to be a convenient method for catalysis of the silylation reaction.[5,6] The catalytically active species is presumed to be hydrogen chloride, which is liberated upon reaction of the chlorosilane with the substrate. Alternatively, protic salts such as ammonium sulfate can be employed as the catalyst.[7] Addition of catalytic ***Lithium Iodide*** in combination with TMSCl leads to even greater reaction rates.[8] Anilines can be monosilylated by heating with excess HMDS (3 equiv) and catalytic TMSCl and catalytic LiI (eq 2). Silylation occurs without added LiI; however, the reaction is much faster in the presence of iodide, presumably due to the in situ formation of a catalytic amount of the more reactive ***Iodotrimethylsilane***.

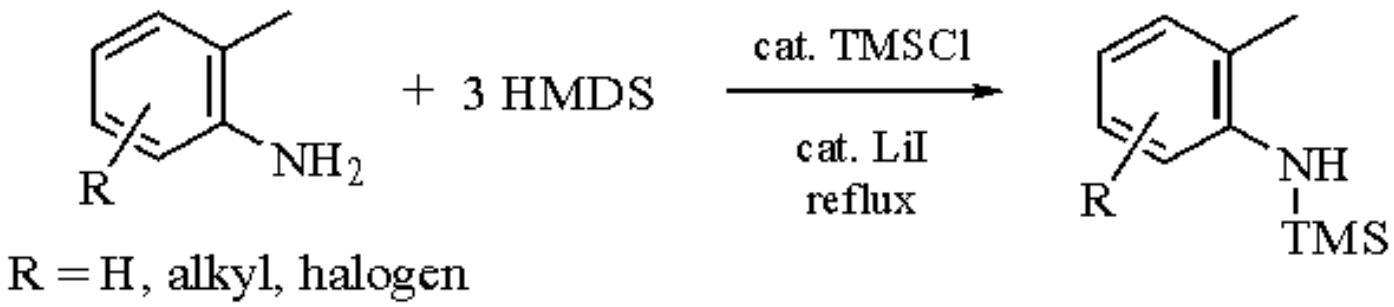

(2)

Hexamethyldisilazane is the reagent of choice for the direct trimethylsilylation of amino acids, for which TMSCl cannot be used due to the amphoteric nature of the substrate.[9] Silylation of glutamic acid with excess hexamethyldisilazane and catalytic TMSCl in either refluxing xylene or acetonitrile followed by dilution with alcohol (methanol or ethanol) yields the derived lactam in good yield (eq 3).[10]

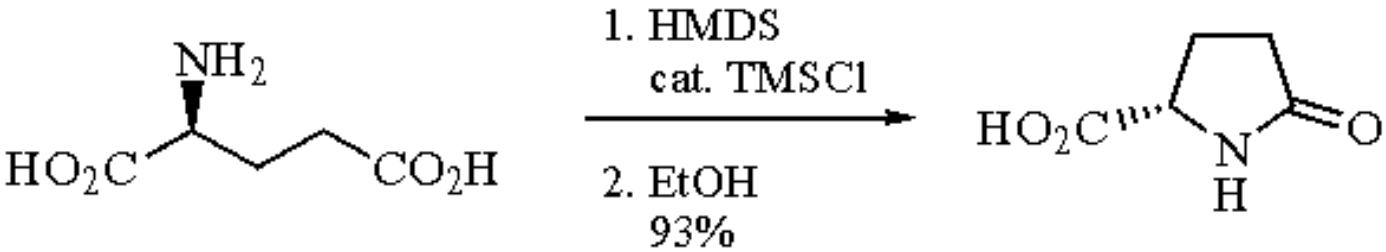

(3)

The efficiency of HMDS-mediated silylations can be markedly improved by conducting reactions in polar aprotic solvents. For example, treatment of methylene chloride solutions of primary alcohols or carboxylic acids at ambient temperatures with HMDS (0.5-1 equiv) in the presence of catalytic amounts of TMSCl (0.1 equiv) gives the corresponding silyl ether and the trimethylsilyl ester, respectively (eq 4).[1] *N*-Silylation of secondary amines occurs in preference to primary alcohols when treated with 1 equiv of HMDS and 0.1 equiv TMSCl (eq 5). The silylation of secondary amines cannot be effected in the absence of solvent.[5] Secondary and tertiary alcohols can also be silylated at ambient temperatures in dichloromethane with HMDS and TMSCl mixtures; however, stoichiometric quantities of the silyl chloride are required. Catalysis by ***4-Dimethylaminopyridine*** (DMAP) is necessary for the preparation of tertiary silyl ethers.

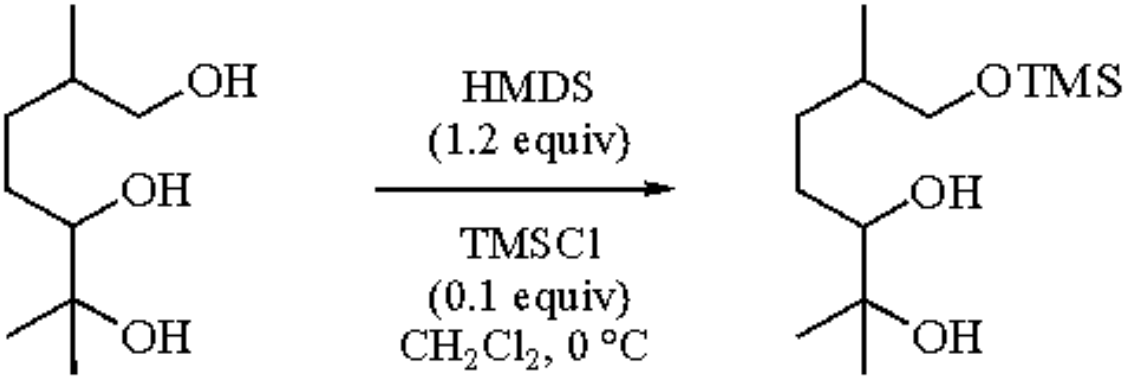

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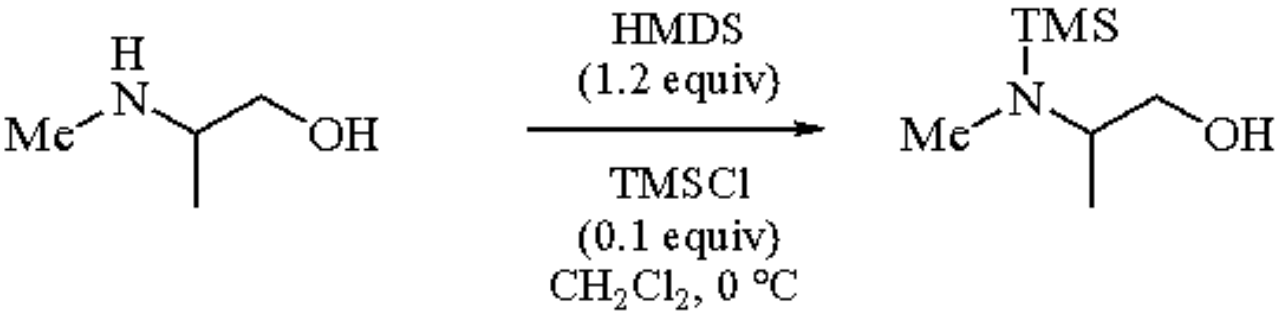

(5)

DMF is a useful solvent for HMDS-induced silylation reactions, and reaction rates 10-20 times greater than those carried out in pyridine have been reported.[11] DMSO is also an excellent solvent; however, a cosolvent such as 1,4-dioxane is required to provide miscibility with HMDS.[12]

Imidazole (ImH) catalyzes the silylation reaction of primary, secondary, and tertiary alkanethiols with hexamethyldisilazane.[12] The mechanism is proposed to involve the intermediacy of ***N-(Trimethylsilyl)imidazole*** (ImTMS), since its preparation from hexamethyldisilazane and imidazole to yield 1-(trimethylsilyl)imidazole is rapid.[13] The imidazole-catalyzed reactions of hexamethyldisilazane, however, are more efficient than the silylation reactions effected by ImTMS (eq 6 vs. eq 7) due to reversibility of the latter. Imidazole also catalyzes the reaction of HMDS with ***Hydrogen Sulfide***, which provides a convenient preparation of hexamethyldisilathiane, a reagent which has found utility in sulfur transfer reactions.[14]

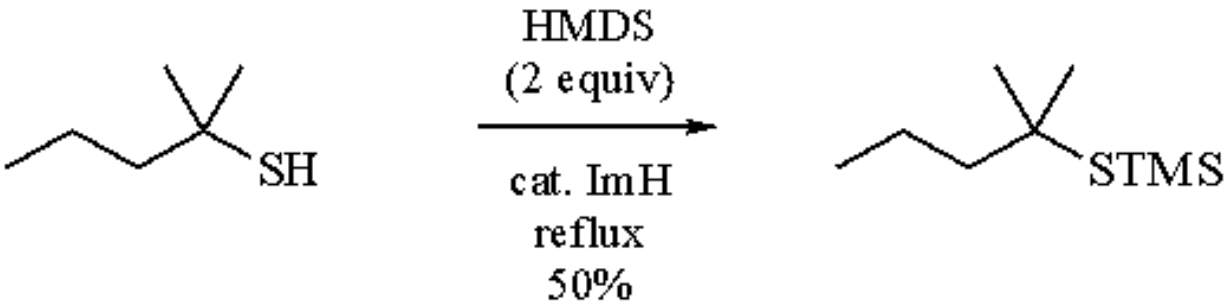

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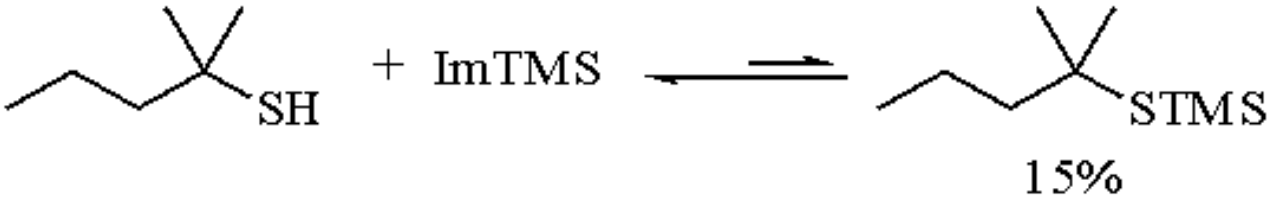

(7)

Silyl Enol Ethers.

Silylation of 1,3-dicarbonyl compounds can be accomplished in excellent yield by heating enolizable 1,3-dicarbonyl compounds with excess HMDS (3 equiv) and catalytic imidazole (eq 8).[15]

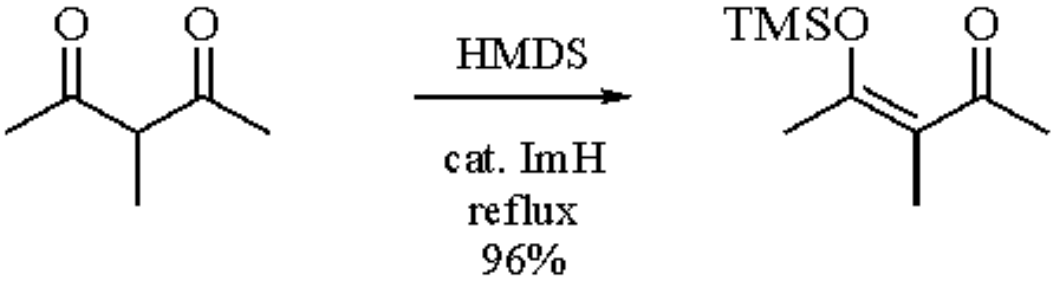

(8)

In combination with TMSI, hexamethyldisilazane is useful in the preparation of thermodynamically favored enol ethers (eq 9).[16] Reactions are carried out at rt or below and are complete within 3 h.

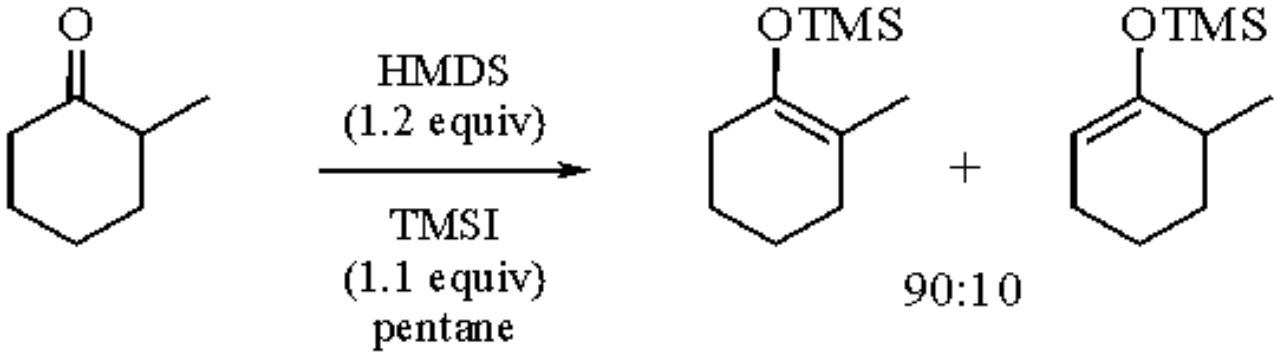

(9)

Related thermodynamic enolization control has been observed using metallated hexamethyldisilazide to give the more substituted bromomagnesium ketone enolates.[17] Metallation reactions of HMDS to yield Li, K, and Na derivatives are well known and the resulting nonnucleophilic bases have found extensive applications in organic synthesis (see ***Lithium Hexamethyldisilazide***, ***Potassium Hexamethyldisilazide***, ***Sodium Hexamethyldisilazide***).[2]

Amination Reactions.

Hexamethyldisilazane is a useful synthon for ammonia in amination reactions. Preparation of primary amides by the reaction of acyl chlorides and gaseous Ammonia, for example, is not an efficient process. Treatment of a variety of acyl halides with HMDS in dichloromethane gives, after hydrolysis, the corresponding primary amide (eq 10).[18] Omitting the hydrolysis step allows isolation of the corresponding monosilyl amide.[19]

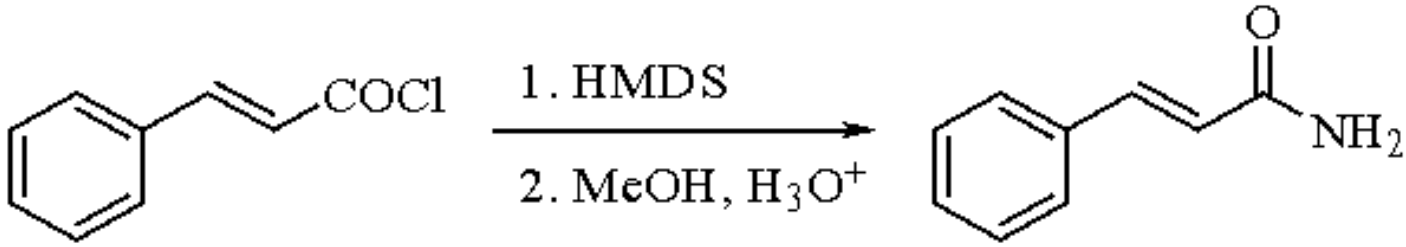

(10)

Reductive aminations of ketones with HMDS to yield α-branched primary amines can be effected in the presence of ***Titanium(IV) Chloride*** (eq 11).[20] The reaction is successful for sterically hindered ketones even though HMDS is a bulky amine and a poor nucleophile. The use of ammonia is precluded in these reactions since it forms an insoluble complex with $TiCl_4$.

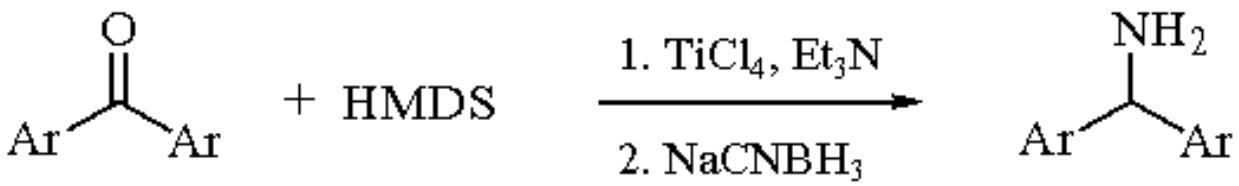

(11)

The reaction of phenols with diphenylseleninic anhydride and hexamethyldisilazane gives the corresponding phenylselenoimines (eq 12).[21] The products thus obtained can be converted to the aminophenol or reductively acetylated using ***Zinc*** and ***Acetic Anhydride***. The use of ammonia or tris(trimethylsilyl)amine in place of HMDS gives only trace amounts of the selenoimines.

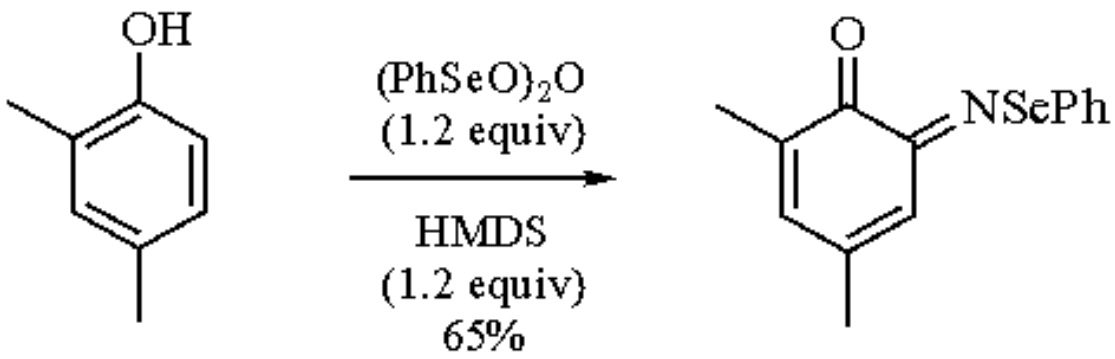

(12)

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Hexamethyldisiloxane

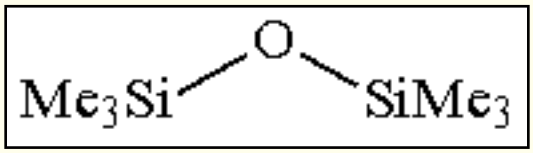

[107-46-0] · $C_6H_{18}OSi_2$ · Hexamethyldisiloxane · (MW 162.42)

(silylating agent for carboxylic acids[1,2] and alcohols;[3] used in preparation of aroyl chlorides;[4] precursor for a variety of trimethylsilyl derivatives[5])

Alternate Names: bis(trimethylsilyl) ether; bis(trimethylsilyl) oxide.

Physical Data: mp -59 °C; bp 101 °C/760 mmHg; *d* 0.764 g cm^{-3}.

Solubility: sol organic solvents such as toluene, chloroform.

Form Supplied in: colorless liquid; available in NMR (99.5%+) and technical (98 or 99%) grade; available in research and commercial quantities.

Analysis of Reagent Purity: ^1H NMR 0.49 ppm; ^{13}C NMR 1.94 ppm (in $CDCl_3$).

Handling, Storage, and Precautions: skin irritant. Incompatible with strong acids, strong bases, and oxidizing agents. Use in a fume hood.

Silylation of Carboxylic Acids.

Alkanoic and aromatic carboxylic acids can be readily silylated with hexamethyldisiloxane.[1] The reaction is carried out under acid catalysis (usually sulfuric acid) and azeotropic removal of water (eq 1). The rate of reaction is strongly influenced by the acidity of the carboxylic acid and increases with increased acidity. This method avoids the use of an amine and thus simplifies isolation of the product because it does not have to be separated from an amine hydrochloride. A limitation is the need for a solvent which allows for azeotropic removal of water.

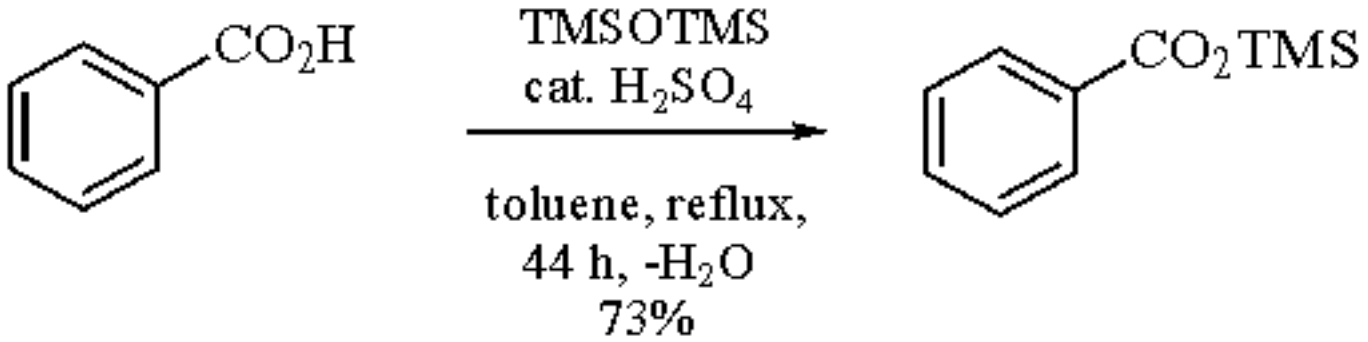

(1)

An alternate silylation procedure employs ***Zinc Chloride*** as the catalyst and uses the carboxylic acid anhydride as starting material for the preparation of the silyl ester (eq 2).[2] A limited number of examples (benzoic and acetic anhydrides) of this reaction have been published. Distillation is the preferred method for isolation of the product.

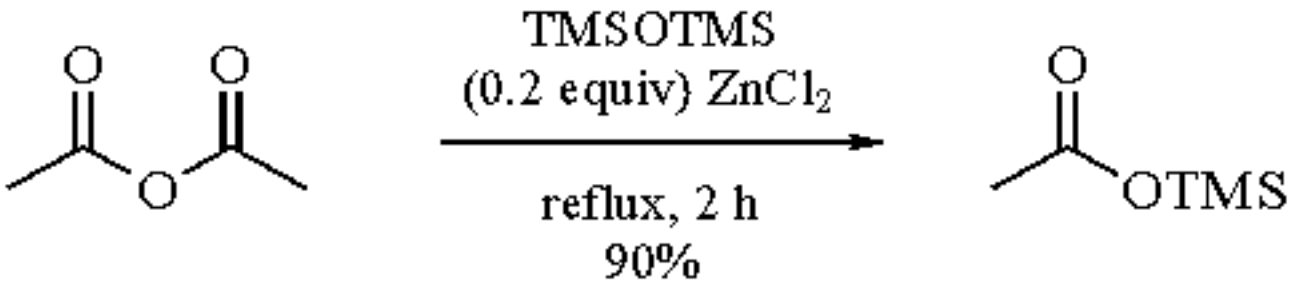

(2)

Silylation of Alcohols.

Pyridinium p-Toluenesulfonate can be used as the catalyst in the silylation of primary and secondary alcohols and phenols (eq 3).[3] Even alcohols sensitive to acid-catalyzed rearrangements can be successfully silylated under these conditions. Continuous removal of the water generated during the reaction is necessary and is achieved via the use of a Soxhlet extractor filled with 4Å molecular sieves.

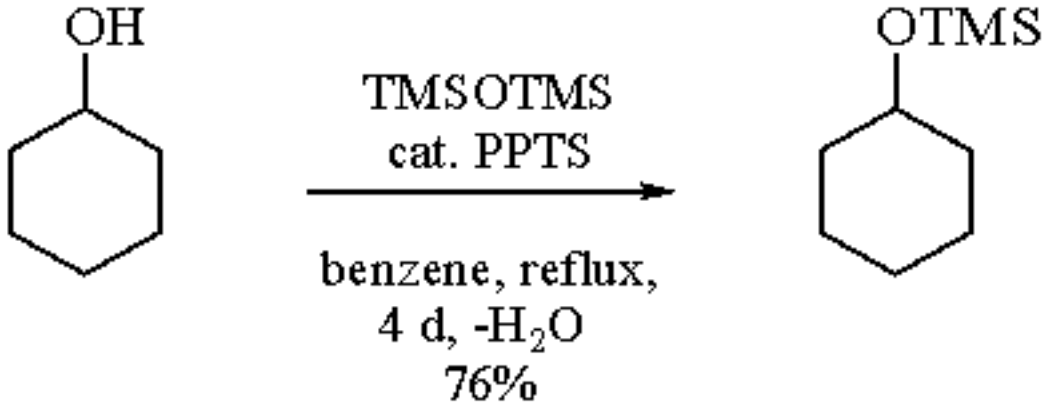

(3)

A special case for the preparation of a phenyl silyl ether involves ultrasound irradiation of benzenediazonium fluoroborate in the presence of hexamethyldisiloxane.[6]

Preparation of Aroyl Chlorides.

Substituted benzylidene chlorides (trichloromethylarenes) can be converted to the corresponding substituted benzoyl chlorides (aroyl chlorides) with hexamethyldisiloxane in the presence of a catalytic amount of ***Iron(III) Chloride*** (eq 4).[4] These mild reaction conditions offer a distinct advantage over procedures which employ inorganic oxides and high temperatures to achieve the transformation.[7]

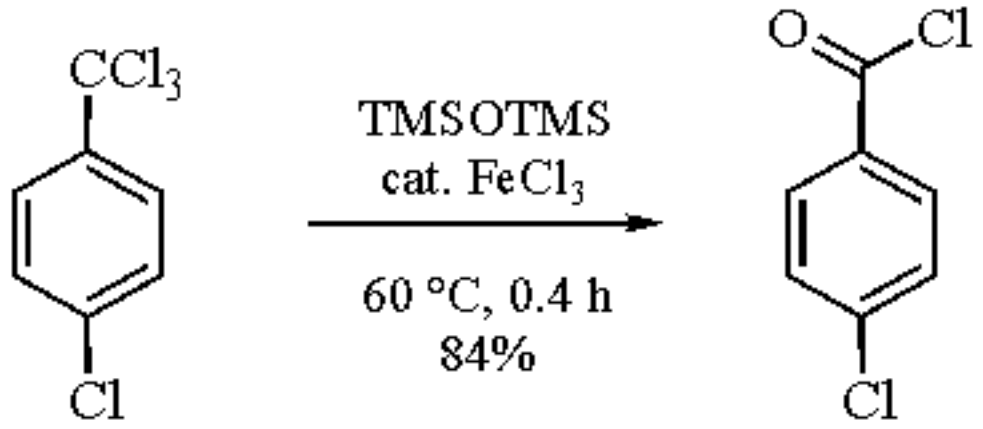

(4)

Preparation of Other Trimethylsilyl Derivatives.

Hexamethyldisiloxane has been used as an inexpensive starting material for the preparation of numerous synthetically useful trimethylsilyl derivatives. Examples include ***Fluorotrimethylsilane***,[5a,b] ***Bromotrimethylsilane***,[5c] and ***Iodotrimethylsilane***,[5d,e] as well as polyphosphoric acid trimethylsilyl ester (PPSE).[5f]

Related Reagents.

N,O-Bis(trimethylsilyl)acetamide; ***N,N´-Bis(trimethylsilyl)urea***; ***Chlorotrimethylsilane***; ***Hexamethyldisilazane***; ***N-(Trimethylsilyl)imidazole***.

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Hexamethyldistannane[1]

Me_3Sn-$SnMe_3$

[661-69-8] · $C_6H_{18}Sn_2$ · Hexamethyldistannane · (MW 327.66)

(palladium-catalyzed substitution and addition reactions)

Physical Data: colorless oil, bp 62-63 °C/12 mmHg, 182 °C/756 mmHg; mp 23 °C; *n*20D = 1.5321.

Solubility: sol most organic solvents.

Form Supplied in: colorless oil; readily available but highly expensive.

Analysis of Reagent Purity: ^{119}Sn NMR recommended (δ -109 ppm, $^1J(^{119}Sn\text{-}^{119}Sn)$ 4404 Hz).[8]

Preparative Methods: although the preparation from ***Trimethylstannane*** and trimethyl(diethylamino)stannane affords an excellent yield (95%), it has the disadvantage of requiring two extremely air-sensitive starting materials.[2] Better methods involve the use of ***Chlorotrimethylstannane*** with either ***Lithium*** or ***Sodium***,[3] or ***Trimethylstannyllithium*** (the latter from trimethylstannane and ***Lithium Diisopropylamide***[4]).[5] Catalytic elimination of hydrogen from trimethylstannane also affords hexamethyldistannane and can be effected either by various bases[6a] or by palladium catalysts such as ***Tetrakis(triphenylphosphine)palladium(0)***.[6b] This latter method can be recommended. The preparation of hexamethyldistannane starting from bis(trimethylstannyl) sulfide has also been described.[7]

Handling, Storage, and Precautions: the compound must be stored in the absence of oxygen, moisture, and light (preferably under argon). Very highly toxic. Use in a fume hood.

Introduction.

General aspects of the preparation and chemistry of hexaalkyldistannanes are reviewed in the Houben-Weyl volume on organotin compounds (literature coverage up to 1977).[1]

The chemistry of hexamethyldistannane is determined by the weakness of the tin-tin bond. The main reaction of synthetic importance is its use in palladium-catalyzed substitution reactions or addition reactions to multiply bonded systems.

While, in analogy to ***Hexabutyldistannane***, Me_6Sn_2 dissociates on heating to give trimethylstannyl radicals, these are generally no longer used in organic synthetic transformations because of the toxicity of methyltin compounds and their cost. Me_6Sn_2 can also be used in transmetalation reactions, leading to the formation of other trimethylstannylmetal reagents.

Palladium-Catalyzed Reactions.

These can be of two types, either substitution of a ligand (generally halide) by a trimethylstannyl group or addition to multiple bonds. These reactions have been reviewed by Stille[9] and Mitchell.[10]

The substitution reactions provide an extremely useful alternative to the conventional use of ***Trimethylstannyllithium***, which is a very strong base. The halides used have mainly been aryl or heteroaryl halides, while ***Tetrakis(triphenylphosphine)palladium(0)***, dichlorobis(triphenylphospine)palladium(II), and ***Bis(allyl)di-μ-chlorodipalladium-Tetra-n-butylammonium Fluoride*** have generally been employed as catalysts. In more recent developments, couplings involving enol triflates[11] and aryl triflates[12] have been described.

The first example of a *cine* substitution was observed when a vinylstannane derived from a camphor triflate and hexamethyldistannane was allowed to react with bromobenzene (eq 1).[13]

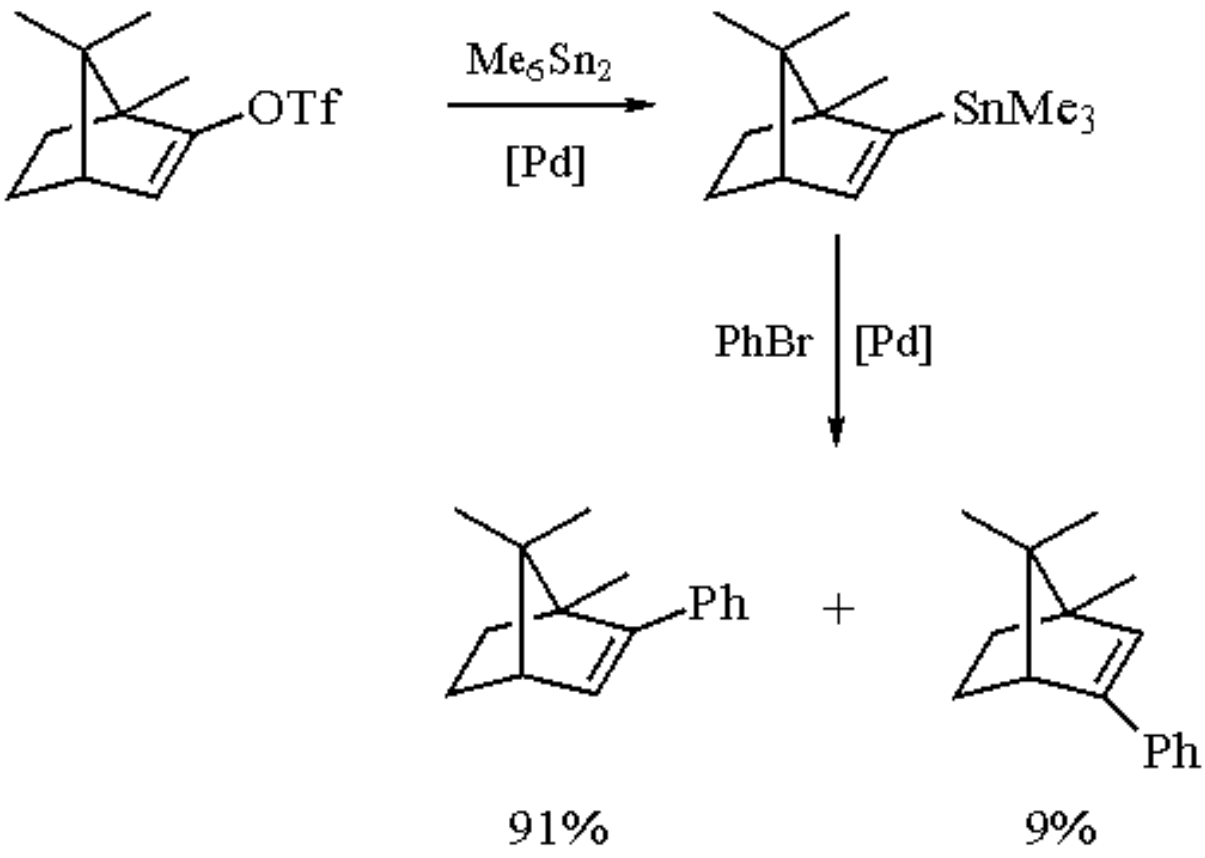

(1)

The synthesis of symmetrical biaryls (using Bu_6Sn_2) has been described.[14] This principle has recently been applied in an intramolecular manner and extended to include more complex cyclization reactions; hexamethyldistannane can be used as an alternative to hexabutyldistannane. Thus as well as two (symmetrical or mixed) aryl and benzyl halide moieties, a combination of two aryl iodide moieties with a carbon-carbon double or triple bond can be used (eq 2).[15]

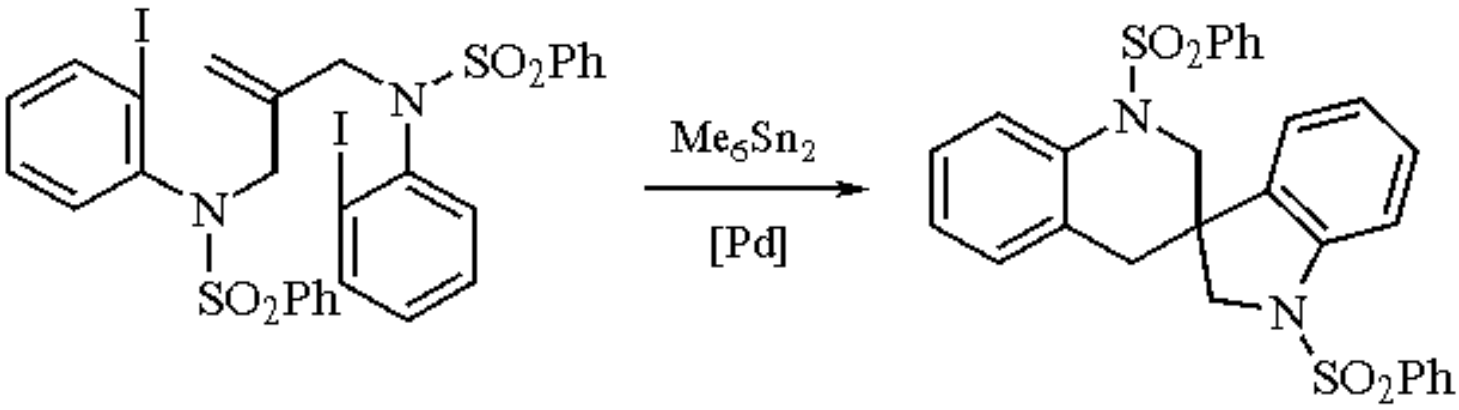

(2)

The reaction of Me_6Sn_2 with acyl halides provides an excellent method for the preparation of trimethylacylstannanes (eq 3).[16]

$$Me_6Sn_2 + RCOCl \xrightarrow{[Pd]} Me_3SnCOR + Me_3SnCl \quad (3)$$

In the case of the addition reactions, hexamethyldistannane adds readily to a variety of allenes to give 2,3-distannyl-1-propenes; it is often possible to distinguish a kinetic and a thermodynamic product (eq 4).[17]

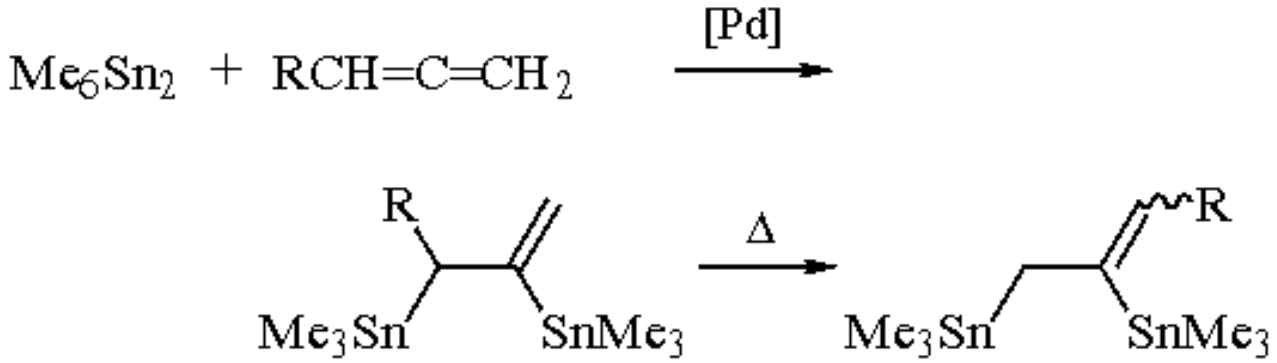

(4)

The addition to 1-alkynes proceeds in a quantitative manner at atmospheric pressure to give (*Z*)-1,2-distannylalkenes, which can in some cases undergo photochemical isomerization to afford the corresponding (*E*)-products in quantitative yields (eq 5).[18]

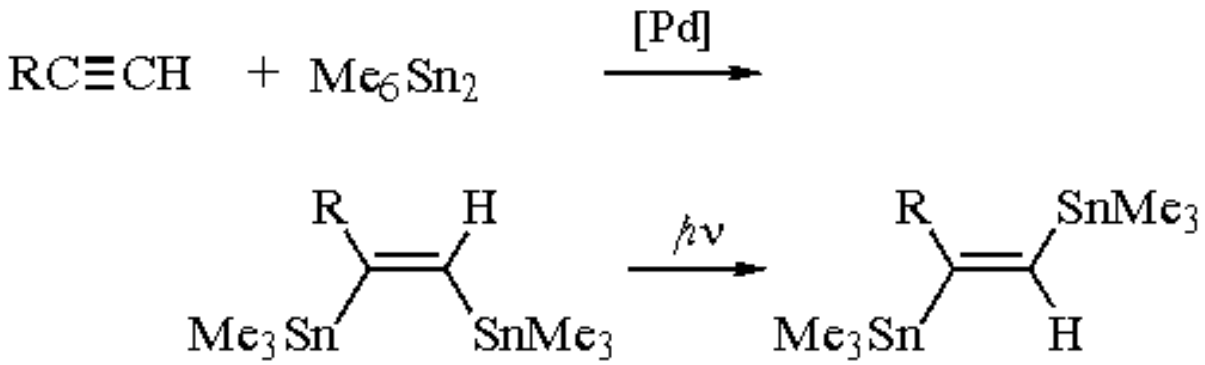

(5)

The presence of various functional groups is tolerated; thus the preparation of trimethylstannyl-substituted

allylglycine derivatives[19] and (*Z*)-4-trimethylstannyl-1,3-butadienes[20] (via the enones) have been described (eqs 6 and 7). The first tris(trimethylstannyl)ethylenes were obtained by using a more active precatalyst system.[21]

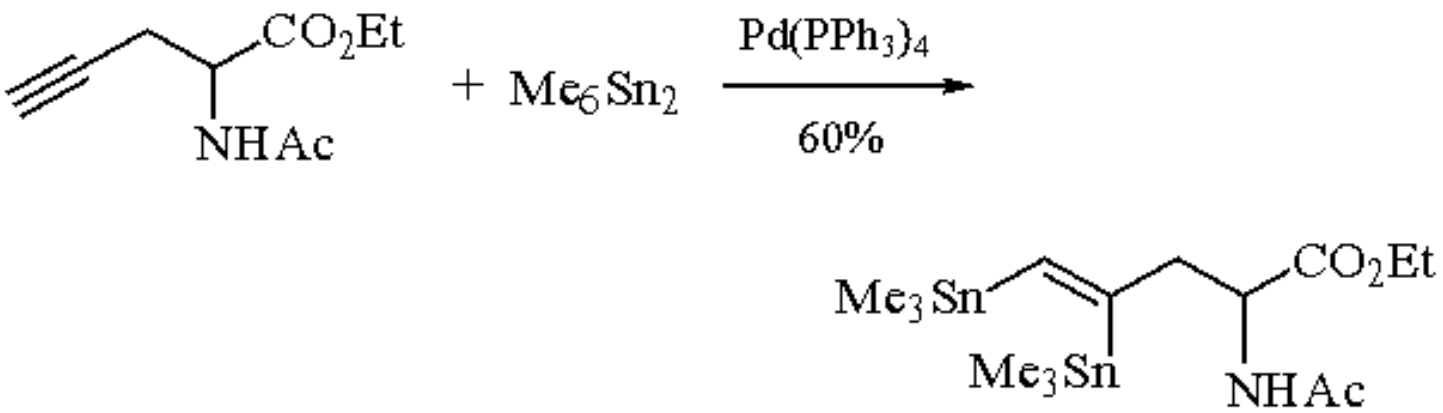

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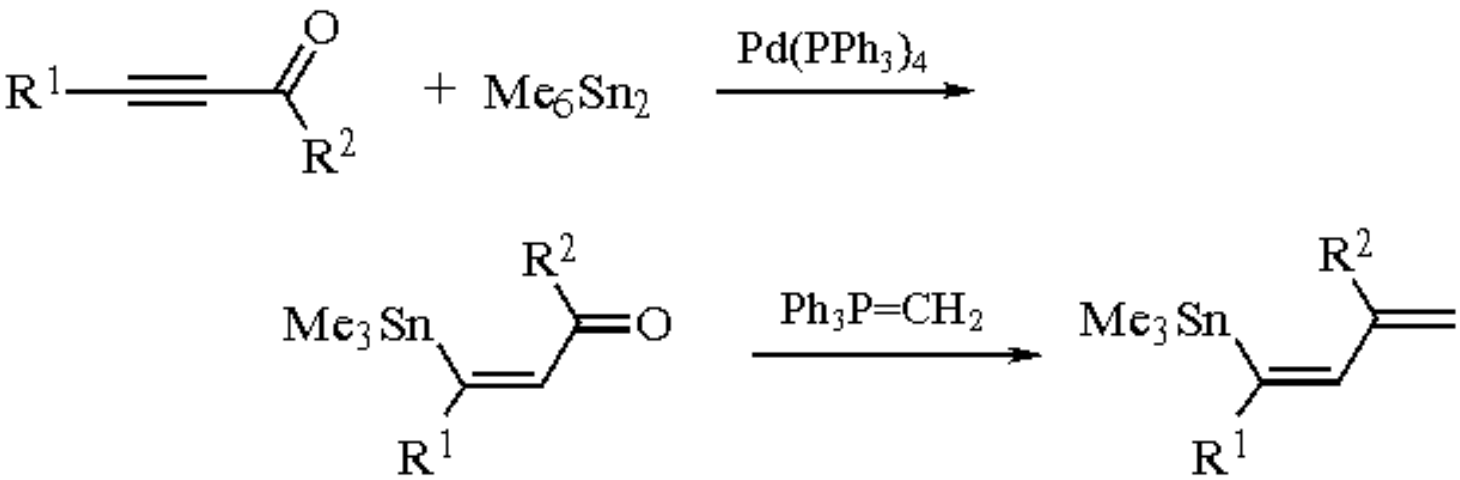

(7)

In spite of the development of new catalyst systems, additions to nonterminal alkynes remain a virtually unsolved problem. Two groups have described the addition of hexamethyldistannane to 1,3-dienes; depending on the reaction conditions, the products are either (*Z*)-1,4-bis(trimethylstannyl)-2-butenes[22] or the products of addition/dimerization (eqs 8 and 9).[23]

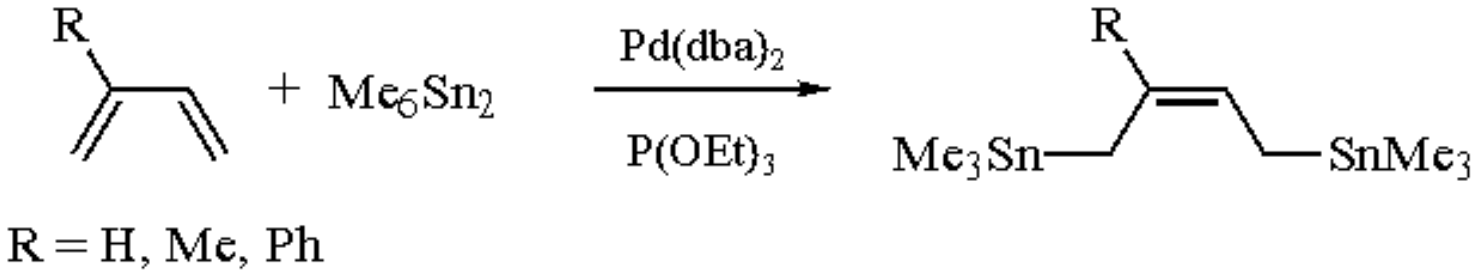

(8)

R = H, Me, Ph

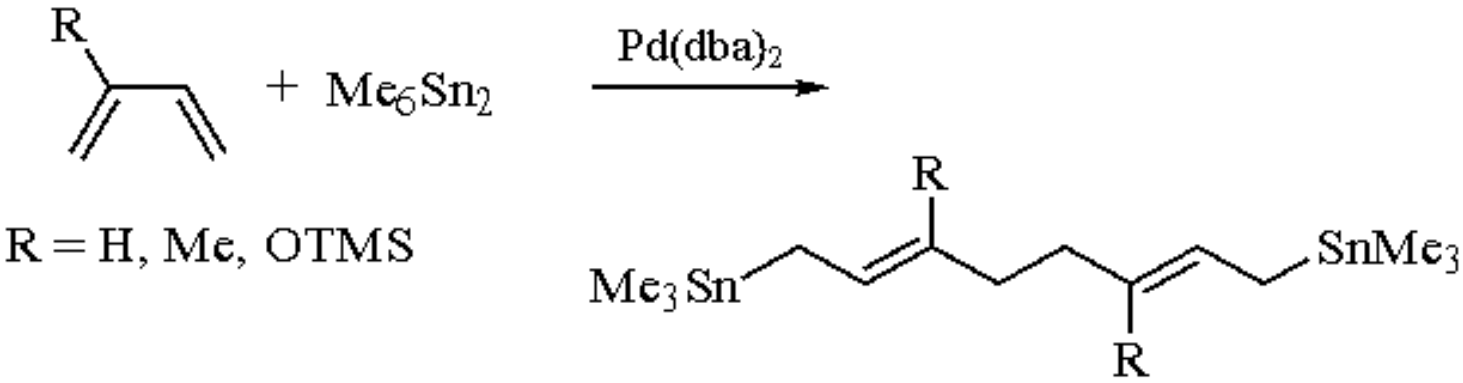

Use as a Source of Trimethylstannyl Radicals.

Thermolysis or photolysis of hexamethyldistannane generates trimethylstannyl radicals, which can in turn be used to generate other synthetically useful radicals. On this basis, Curran has developed the so-called atom transfer method for radical cyclization, in which about 0.1 equiv. of the distannane is used. While in his original work[24] on the cyclization of α-iodo esters, ketones, and malonates Curran used both hexamethyl- and hexabutyldistannane, later papers by his and other groups have reported only the use of Bu_6Sn_2 (for reasons of cost and toxicity). Me_6Sn_2 has been used to effect a selective one-electron radical chain reduction of the 10-methylacridinium ion to 10,10´-dimethyl-9,9´-biacridine.[25] In combination with ***1,1-Di-t-butyl Peroxide*** (as the radical initiator) it can generate sulfonyl radicals from sulfonate esters.[26]

Use as a Source of Other Trimethylstannylmetal Reagents.

Hexamethyldistannane can be cleaved by lithium metal[27] or a lithium alkyl[28] (e.g. MeLi) to give trimethylstannyllithium. These methods cannot be recommended: Me_3SnLi can be better obtained either in a one-step process from Me_3SnCl and Li (via Me_6Sn_2 which is not isolated) or from the reaction between Me_3SnH and LDA (see ***Trimethylstannyllithium*** for details). Hexamethyldistannane can also serve as a source of stannylcuprates ($Me_3SnCu(CN)Li$, $(Me_3Sn)_2Cu(CN)Li_2$,[29] Me_3Sn(2-thienyl)$Cu(CN)Li_2$).[30]

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Hexamethylenetetramine[1]

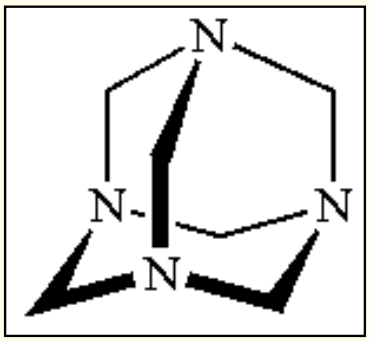

[100-97-0] · $C_6H_{12}N_4$ · Hexamethylenetetramine · (MW 140.22)

(oxidation of benzyl and alkyl halides and amines to aldehydes; ammonolysis of alkyl halides to primary amines; electrophilic formylation of aromatics; useful one-carbon unit in heterocyclic synthesis)

Alternate Name: HMTA.

Physical Data: mp 285-295 °C (subl.); *d* 1.331 g cm^{-3}.

Solubility: sol water, ethanol, ether, chloroform.

Form Supplied in: white solid.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$) sharp singlet at δ 4.70.

Purification: sublimation at aspirator pressure.

Handling, Storage, and Precautions: stable, low toxicity.

Oxidation of Benzylic Halides (Sommelet Reaction).[2]

Treatment of an activated (usually benzylic) halide with HMTA in a protic solvent such as aqueous acetic acid gives the aldehyde, via the Schiff base.[3] The reaction involves an intramolecular hydride transfer, as shown in eq 1. Hydrochloric acid is sometimes added at the end of the reaction to speed the hydrolysis of the Schiff base.

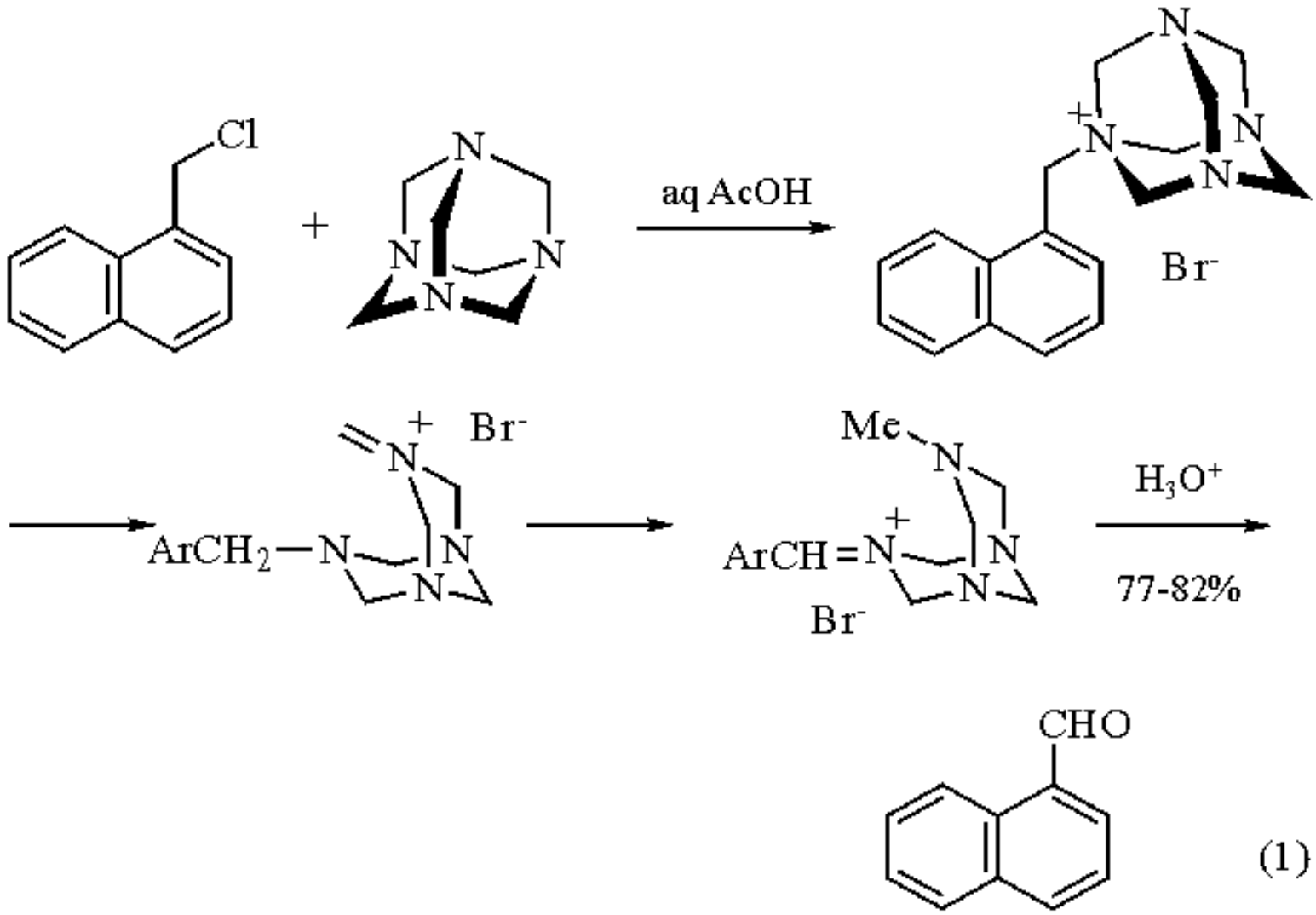

(1)

The method works well with phenolic (eq 2)[4] and heterocyclic (eq 3)[5] substrates, for which other methods would probably be unsuitable.

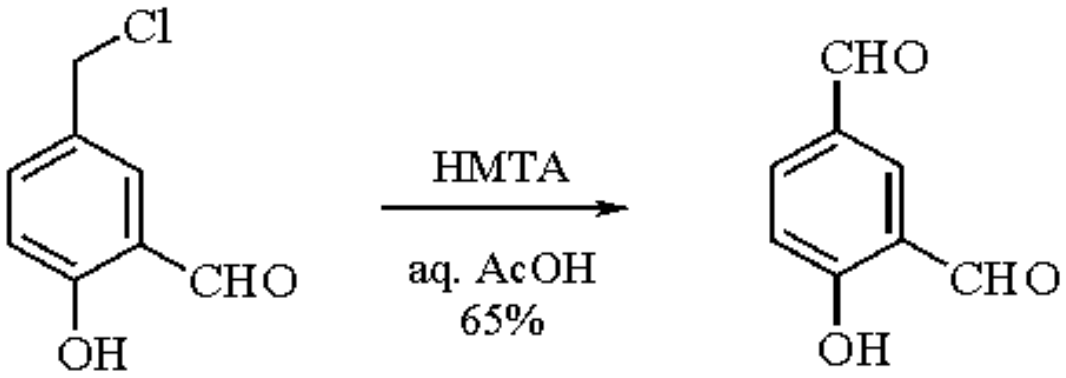

(2)

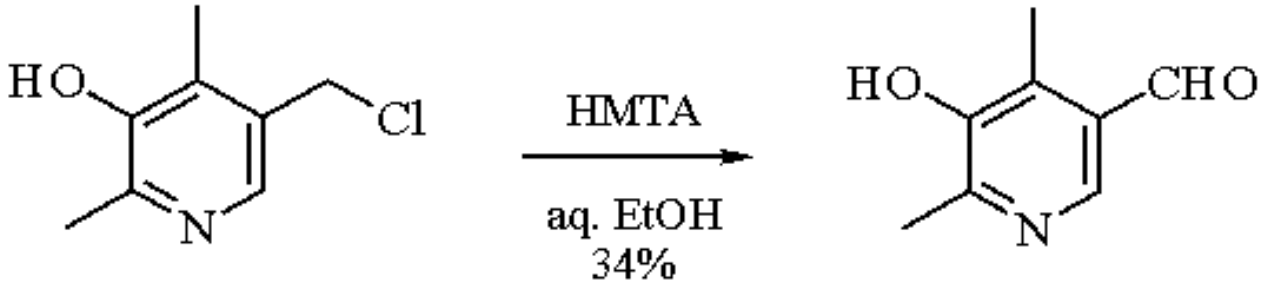

(3)

Secondary halides usually give poor yields, while highly hindered substrates such as 2,6-disubstituted benzyl bromides are unreactive, although mononitrobenzyl bromides are oxidized. With unreactive halides it is often better to form the quaternary salt in chloroform, and decompose it in a protic medium.

In a related reaction, HMTA transforms benzylamines into benzaldehydes (eq 4).[6]

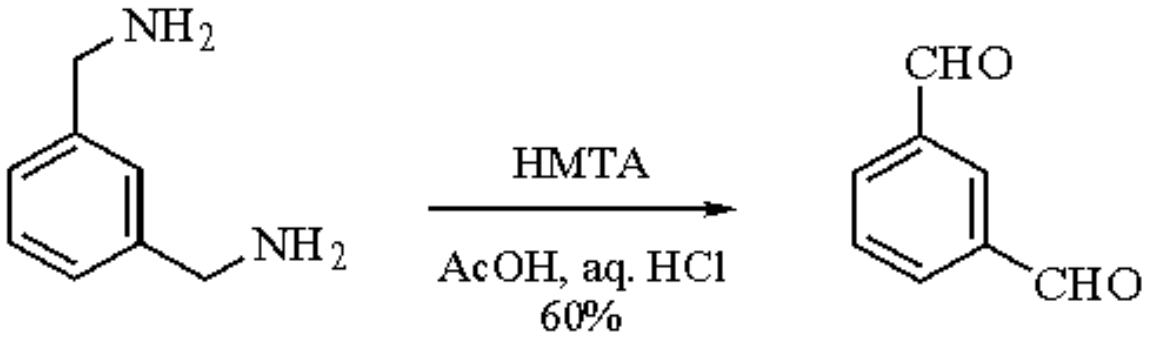

(4)

Ammonolysis of Alkyl Halides (Delépine Reaction).[7,8]

The quaternary salt of HMTA and alkyl halides decomposes under strongly acidic conditions (usually EtOH, concentrated HCl) to give primary amines rather than aldehydes or ketones (eqs 5-7).[9-11]

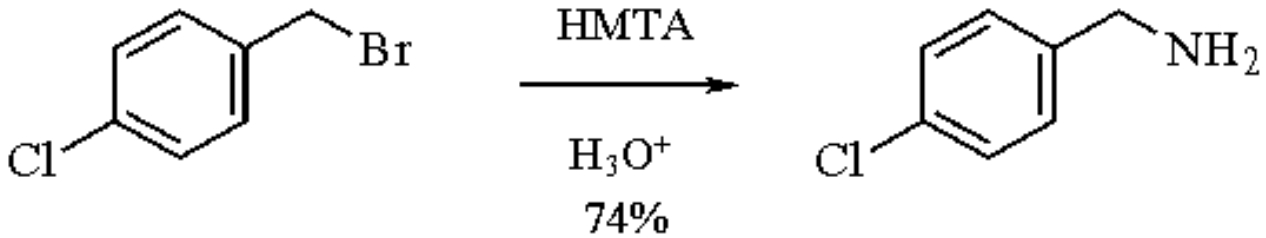

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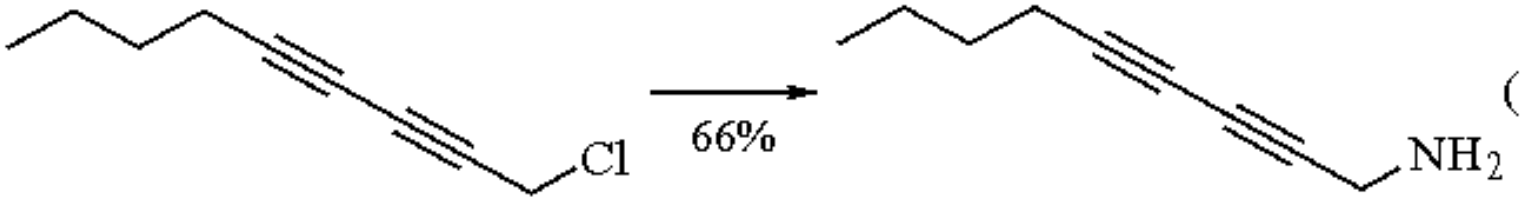

(6)

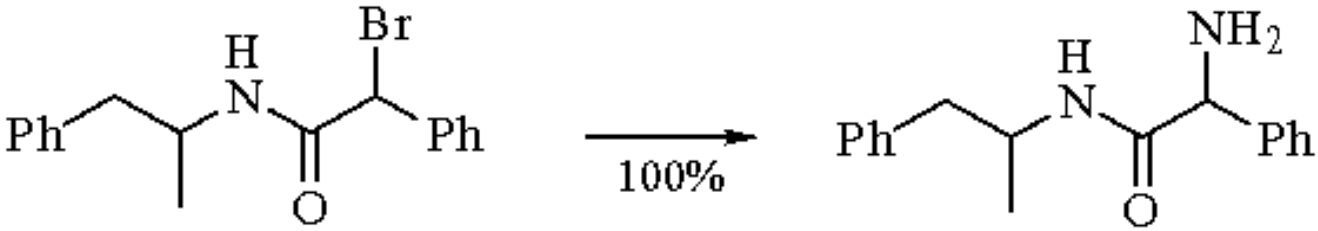

(7)

As in the Sommelet reaction, the bromide or chloride must be activated in order to react with the HMTA. The Delépine reaction provides a ready synthesis of α-amino acids (eq 8). If the decomposition is performed with HCl gas in dry ethanol, the corresponding ethyl ester is obtained instead.[12]

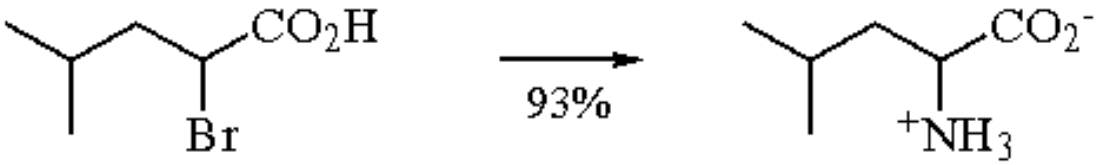

(8)

The reaction may be combined with the Eschweiler-Clark methylation by heating the quaternary salt in formic acid, the formaldehyde deriving from the decomposition of the HMTA (eq 9).[13]

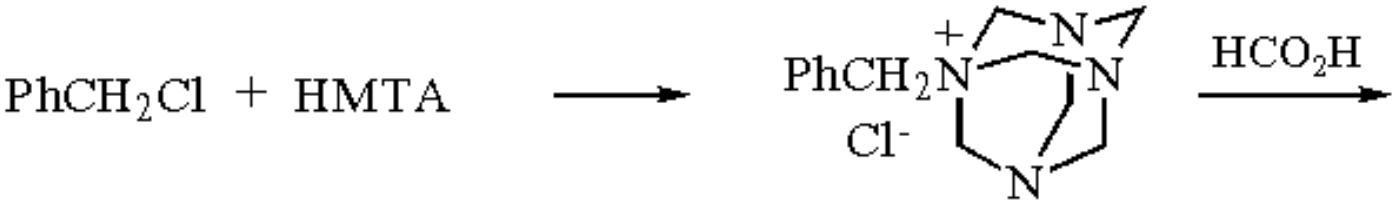

$PhCH_2NMe_2$ (9)

HMTA opens epoxides exclusively at the less substituted site. This is of importance because free amines react unselectively (eq 10).[14]

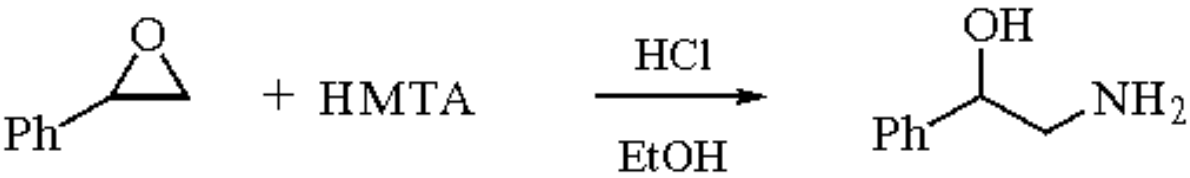

(10)

Overall, HMTA provides a cheap and nonhazardous alternative to ***Sodium Azide*** for the synthesis of certain primary amines from their halides.

Electrophilic Formylation of Aromatics (Duff Reaction).[15]

Electron-rich aromatics (phenols, indoles, etc.) are formylated by HMTA in glacial acetic acid (eqs 11 and 12) or glyceroboric acid (H_3BO_3 in dry glycerol) (eq 13). Yields are sometimes poor.[16-18]

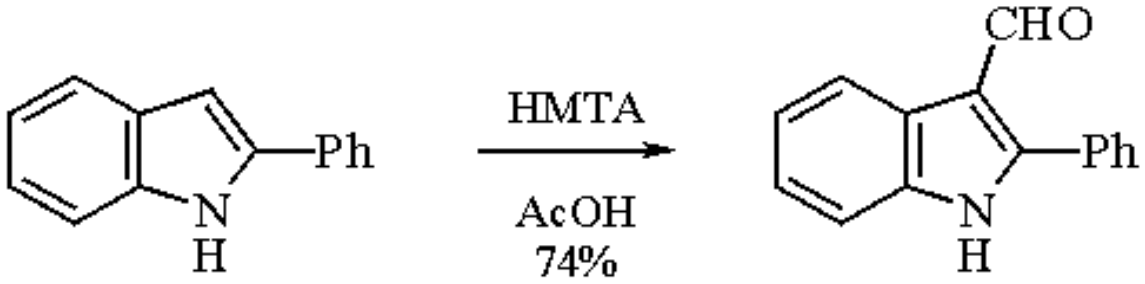

(11)

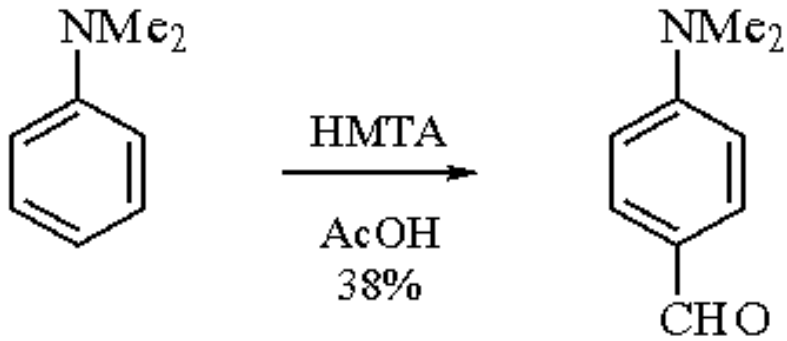

(12)

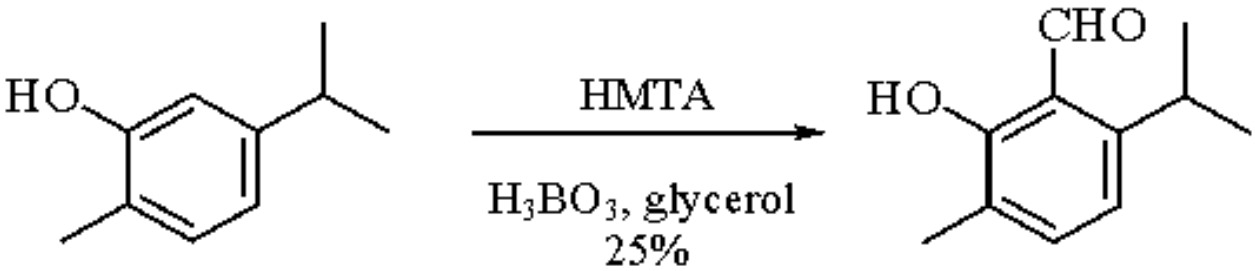

(13)

With phenols there is a strong tendency to give the *ortho* product selectively (eq 13). Yields are higher, and *para* selectivity is observed, when the reaction is conducted in ***Trifluoroacetic Acid*** (eq 14).[19] Even unactivated aromatics react under these conditions.

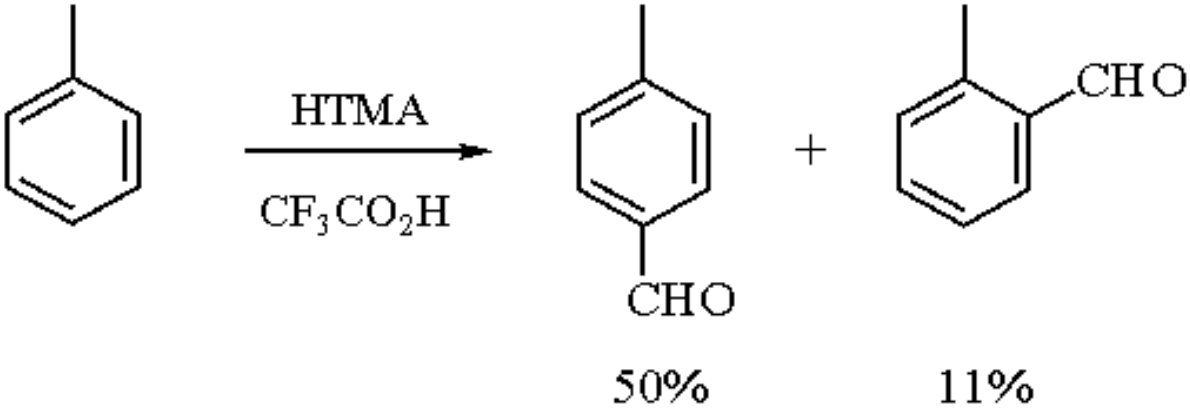

(14)

Use in Heterocyclic Synthesis.

Treatment of phenanthroquinones with HMTA furnishes the fused imidazoles in good yield (eq 15).[20]

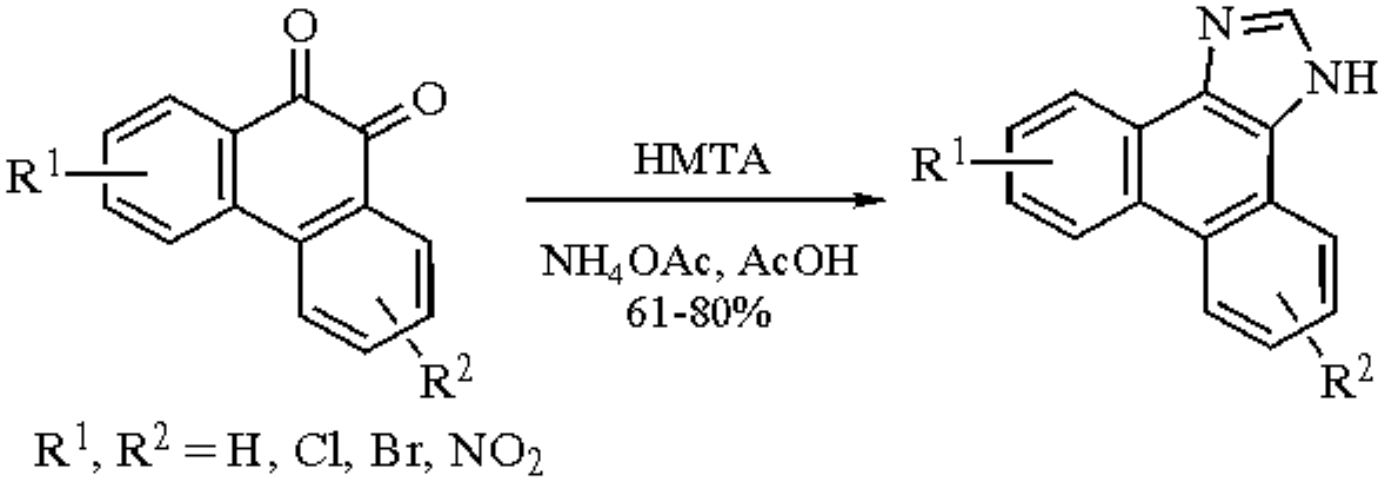

(15)

Benzodiazepines and quinazolines are accessible by treatment of the appropriate chloroacetamides and aminobenzophenones with HMTA (eqs 16 and 17).[21]

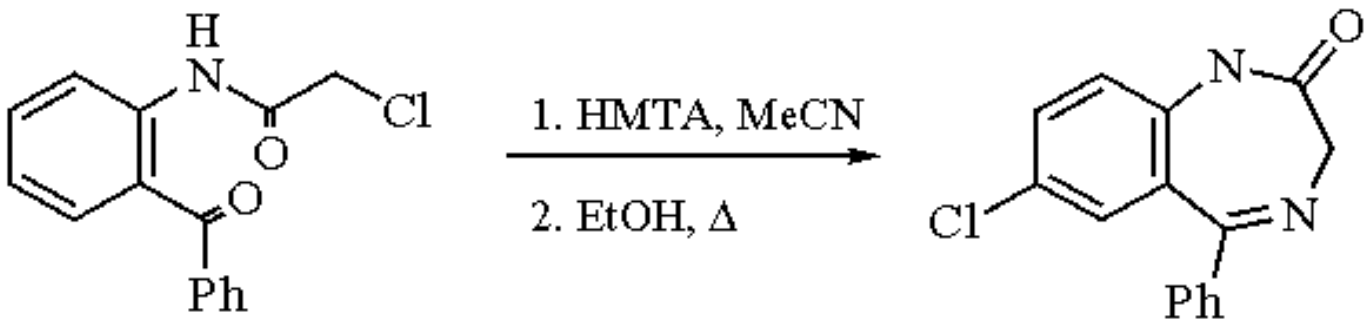

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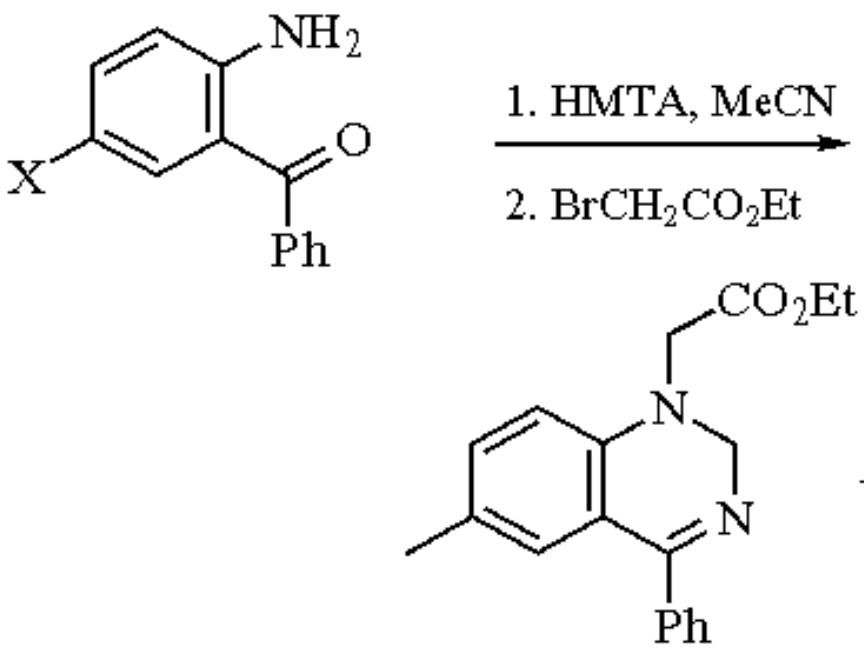

(17)

Isatins undergo ring expansion with HMTA in an alcoholic solvent (eq 18).[22]

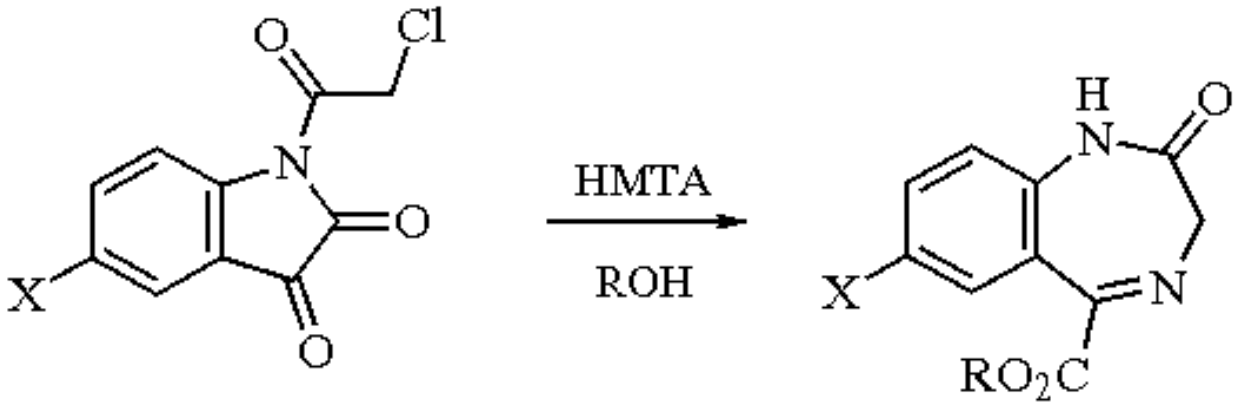

(18)

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Hexamethylphosphoric Triamide

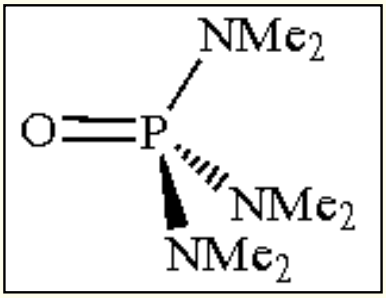

[680-31-9] · $C_6H_{18}N_3OP$ · Hexamethylphosphoric Triamide · (MW 179.24)

(high Lewis acid basicity; dipolar aprotic solvent with superb ability to form cation-ligand complexes; can enhance the rates of a wide variety of main group organometallic reactions and influence regio- or stereochemistry; additive in transition metal chemistry; UV inhibitor in poly(vinyl chloride))

Alternate Names: HMPA; hexamethylphosphoramide; hexametapol; hempa; HMPT.

Physical Data: mp 7.2 °C; bp 230-232 °C/740 mmHg; *d* 1.025 g cm^{-3}; mild amine odor.

Solubility: sol water, polar and nonpolar solvents.

Form Supplied in: water-white liquid. *Drying:* distilled from CaH_2 or BaO[1] at reduced pressure and stored under N_2 over molecular sieves.

Handling, Storage, and Precautions: has low to moderate acute toxicity in mammals.[2a] Inhalation exposure to HMPA has been shown to induce nasal tumors in rats,[2b] and has been classified under Industrial Substances Suspect of Carcinogenic Potential for Man.[2c] Adequate precautions must be taken to avoid all forms of exposure to HMPA.

Introduction.

Hexamethylphosphoric triamide has been used extensively as an additive in organolithium chemistry.[3] It is among the strongest of electron pair donors and is superior to protic solvents in that it solvates the cation much better than the anion.[4] This coordinating ability gives HMPA its unusual chemical properties.[5,6] For instance, HMPA dramatically enhances the rates of a wide variety of organolithium reactions, as well as significantly influencing regio- or stereochemistry. The reactivity or selectivity effects of HMPA are usually rationalized in terms of changes in either aggregation state or ion pair structure.[7] The breaking up of aggregates to form reactive monomers or solvent-separated ion pairs is often invoked.

Organolithium Reagent Solution Structure.

The rate of metalation reactions with ***Lithium Diisopropylamide*** as base are significantly increased through the use of HMPA.[8] Treatment of LDA dimer with HMPA causes sequential solvation of the lithium cation, but no significant deaggregation;[8,9] nor does HMPA promote the break up of tetrameric unhindered phenoxides[10,11] or tetrameric MeLi.[12] A chiral bidentate lithium amide,[13] however, was converted from a dimer to a monomer by HMPA, with an increase in reactivity and enantioselectivity in deprotonation (eq 1). HMPA also converts ***Phenyllithium*** dimer into monomer.[12,14] Other aggregated lithium reagents[12] in THF (MeSLi, LiCl) or ether (Ph_2PLi, PhSeLi) are first deaggregated to monomers, and then solvent-separated ion pair species are formed.[12,15] HMPA may exert its reactivity effects by a combination of one or more of the following:

- 1)lowering the degree of aggregation[16,17] or forming separated ions,[18]
- 2)increasing reactivity through cation coordination,[17]
- 3)activating the aggregate through insertion into the aggregate site normally occupied by the anionic fragment,[5,19]
- 4)promoting triple ion (ate complex) formation.[16a,20]

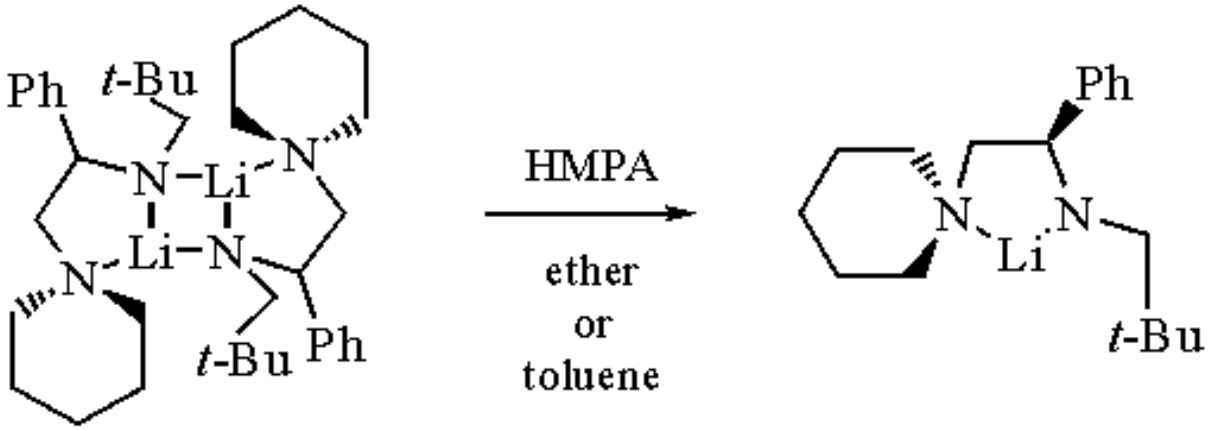

(1)

HMPA can have large effects on equilibria. Phenyllithium reacts with ***Diphenylmercury***, ***Diphenyl Ditelluride***, and iodobenzene in THF to form ate complexes. In THF/HMPA the ate complex formation constants are dramatically higher than in THF.[14,21]

Enolate Formation.

The formation of lithium enolates is one instance where HMPA is sometimes needed.[22] The difficult generation of dimethyl tartrate acetonide enolate[23] and subsequent benzylation (eq 2), as well as the double deprotonation of methyl 3-nitropropanoate,[24] become possible (eq 3) with the addition of HMPA (or ***N,N´-Dimethylpropyleneurea***).[25]

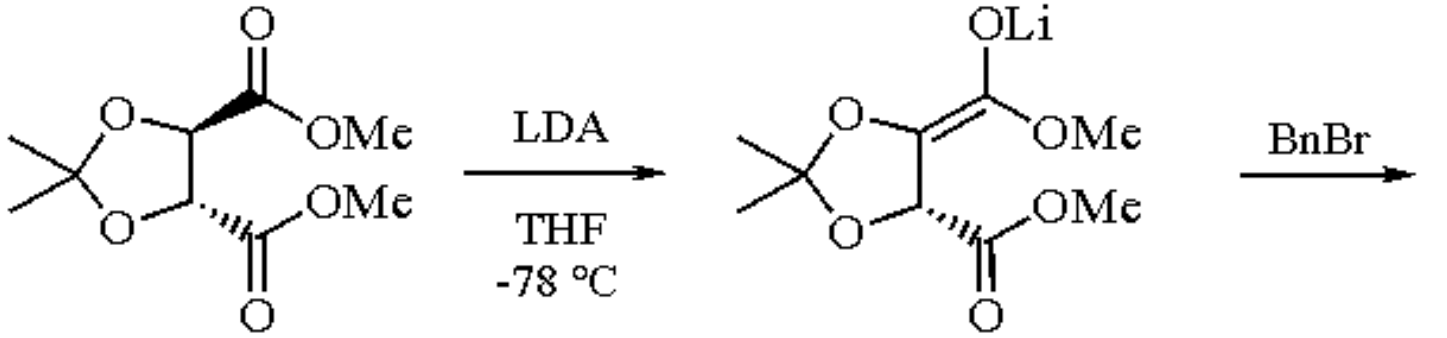

Cosolvent (% vol)	Yield (%)
-	<5
HMPA (17)	54
DMPU (33)	52

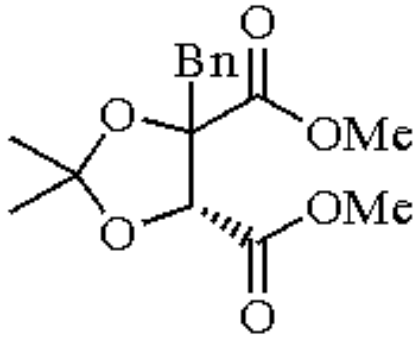

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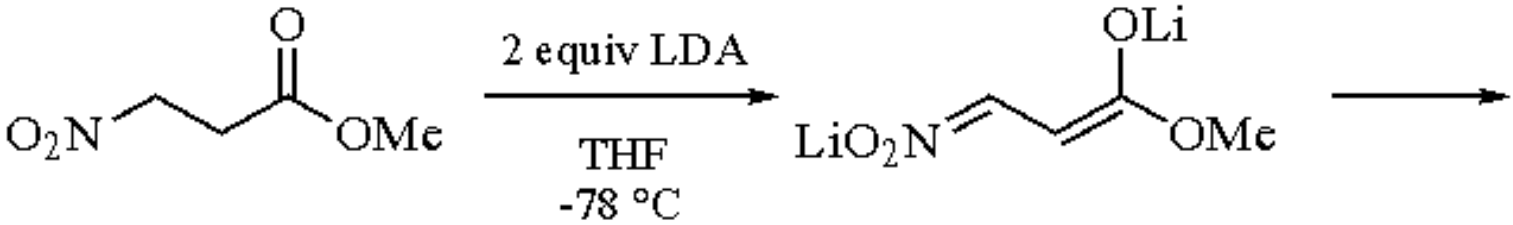

Cosolvent (% vol)	Yield (%)
-	<5
HMPA (17)	50-85
DMPU (33)	50-85

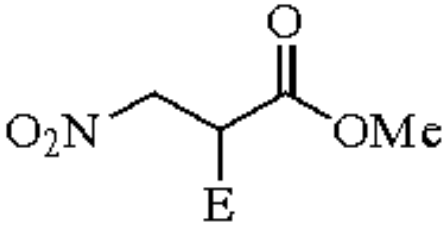

(3)

Enolate Reactivity.

Not only is HMPA necessary to the generation of enolates, it is often needed in the electrophilic trapping of enolates (eqs 4-6).[26,31] Studies of the electrophilic trapping of enolates have demonstrated that substantial increases in reaction rates can be achieved through the use of a polar aprotic solvent like HMPA.[4]

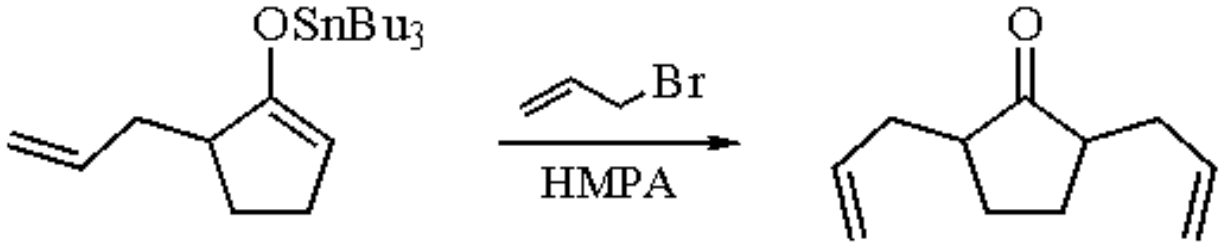

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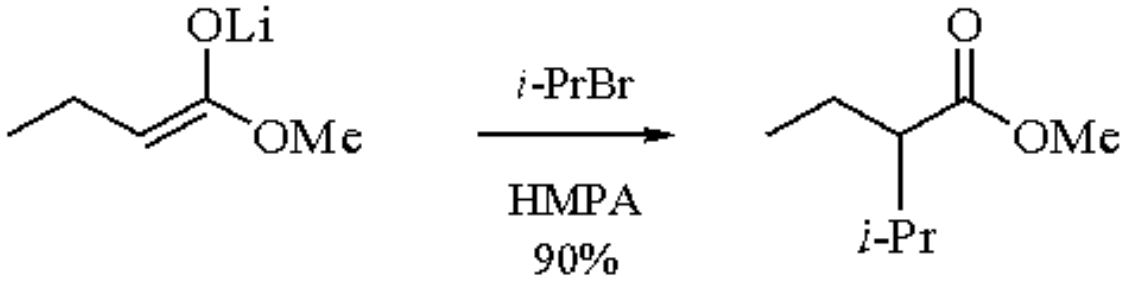

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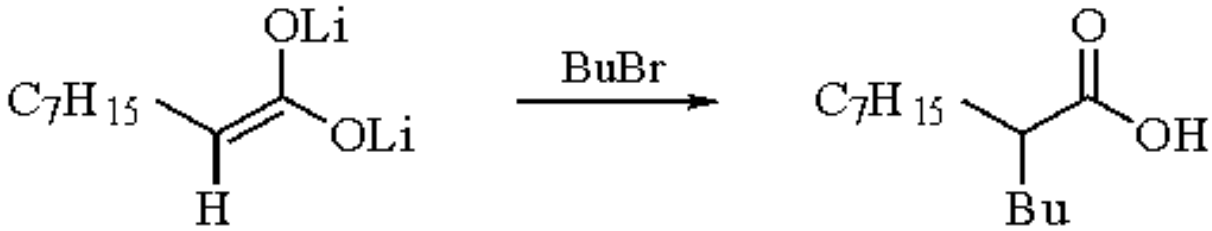

(6)

Solvent	Yield
THF	43%
THF-HMPA	93%

The desired [2,3]-sigmatropic rearrangement of a bis-sulfur cyano-stabilized lithium salt did not proceed (eq 7) without the addition of 25% HMPA.[27] Sometimes higher *O*/*C*-alkylation ratios are obtained in THF-HMPA.[28]

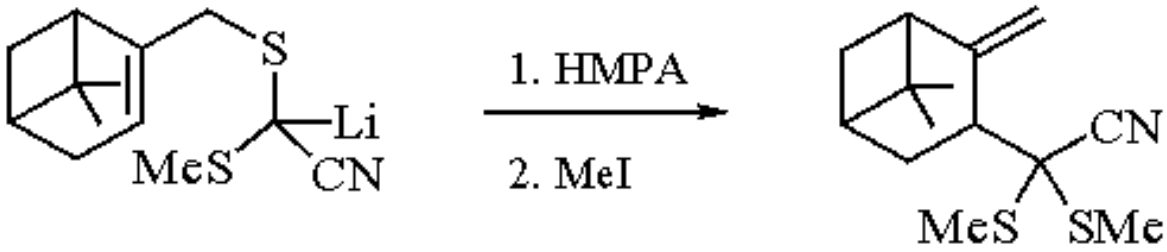

(7)

Enolate Stereochemistry.

Stereochemical control of an ester enolate Claisen rearrangement was accomplished through stereoselective enolate formation.[29] The enolization of 3-pentanone with LDA afforded predominantly the (*E*)-enolate in THF and the (*Z*)-enolate in THF-HMPA, as shown by chlorotrialkylsilane trapping experiments (eq 8). Similar stereoselectivity (*Z*:*E* = 94:6) was obtained with the dipolar aprotic cosolvent DMPU.[30]

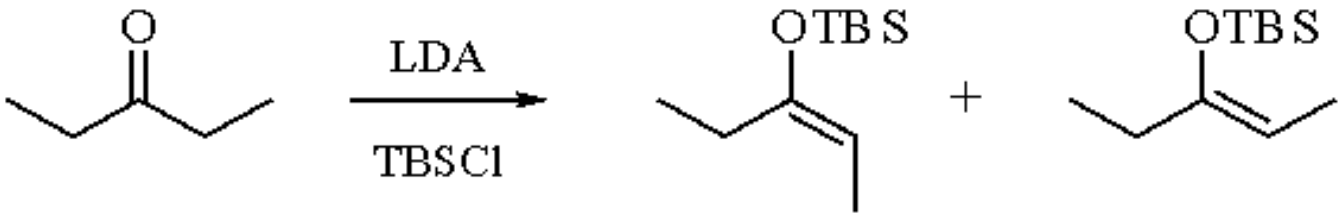

(8)

THF	77	:	23
THF-HMPA	5	:	95

In addition to altering the (*E*/*Z*) isomer ratio of enolates,[17,32] HMPA has a noticeable effect on the metalation of imines and their subsequent alkylation (eq 9).[33] When the metalation (by ***s-Butyllithium***) of an asymmetric imine is performed in THF, a subsequent alkylation gives about a 1:1 mixture of regioisomers. In the presence of HMPA, however, only the regioisomer due to alkylation at the less-substituted site was observed. A synthetically useful solvent effect for HMPA is also observed in the asymmetric synthesis of trimethylsilyl enol ethers by chiral lithium amide bases.[34] The asymmetric induction in THF can be greatly improved by simply adding HMPA as a cosolvent.

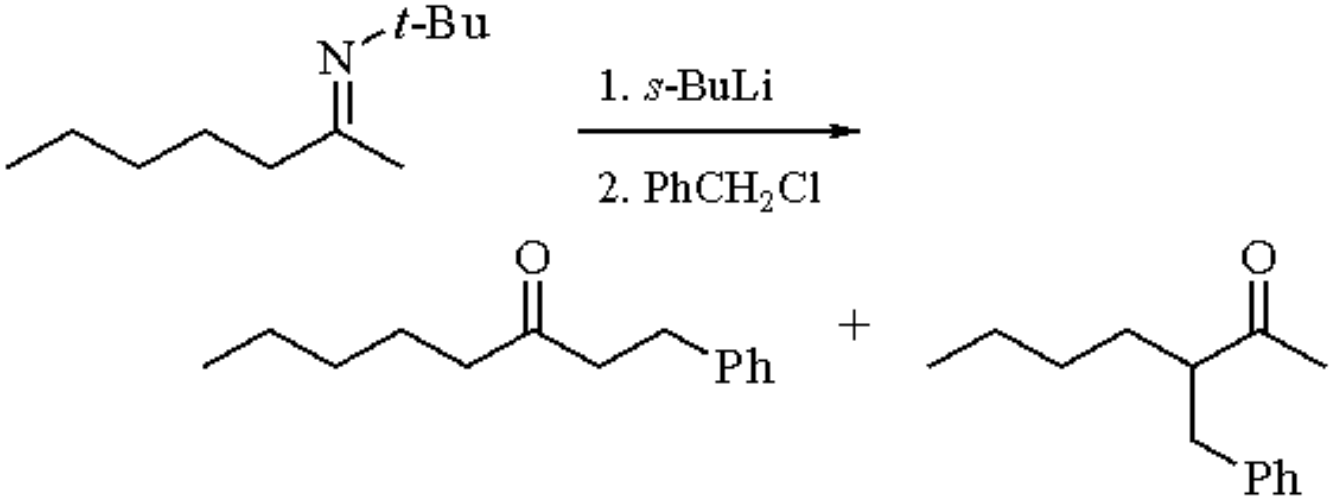

(9)

Carbanion Formation.

Often substrates that cannot be metalated by LDA or ***n-Butyllithium*** in THF can be successfully deprotonated by adding HMPA as a cosolvent. Many other weakly acidic C-H acids, e.g. (**1**)-(**6**), can be successfully metalated in the presence of HMPA.[35] HMPA also aids in the formation of dianions[36] and increases the proton abstraction efficiency of ***Sodium Hydride***.[37,38]

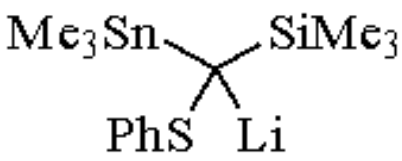

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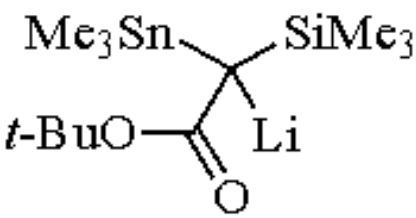

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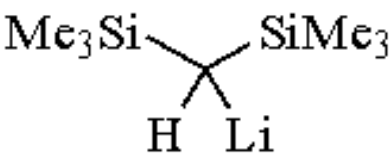

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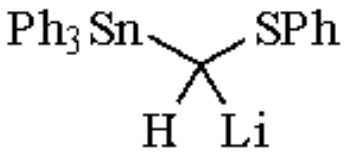

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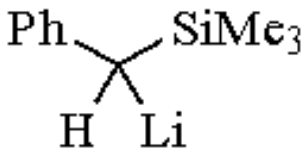

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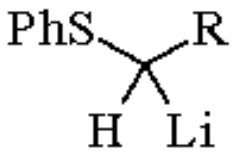

(6)

Carbanion Reactivity.

An increase in reaction rate is observed for the reaction of alkynyllithium reagents with alkyl halides[3] and oxiranes[39] (eq 10). The strongly coordinating HMPA probably complexes the lithium cation, thereby increasing the negative charge density on the carbon and creating a much more nucleophilic alkynyl anion. A similar effect is observed for ***(Trimethylstannylmethyl)lithium***, which does not react with oxiranes in THF but in THF-HMPA the reaction proceeds readily.[40]

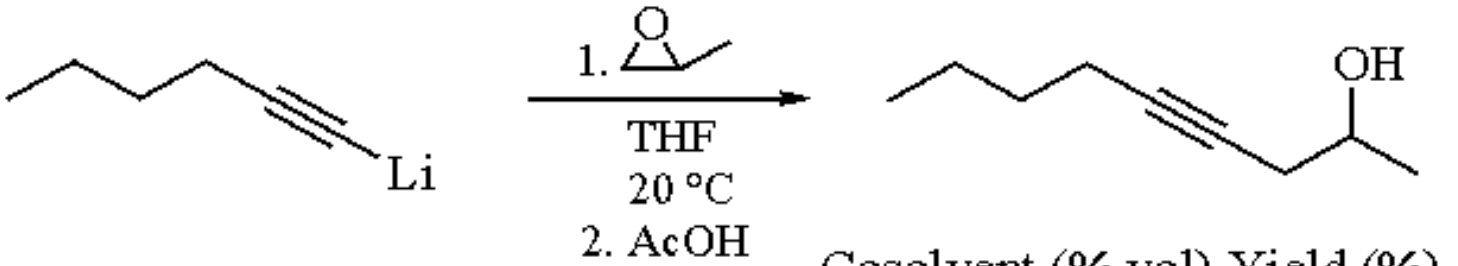

(10)

Cosolvent (% vol)	Yield (%)
-	<5
HMPA (17)	70
DMPU (50)	59

The decarboxylation[41] of 4-*t*-butyl-1-phenyl-1-carboxycyclohexane with ***Methyllithium*** gave a mixture of axial and equatorial products (eq 11), which was highly dependent on the nature of the solvent at the time of aqueous workup. Axial protonation was favored in ether-HMPA.

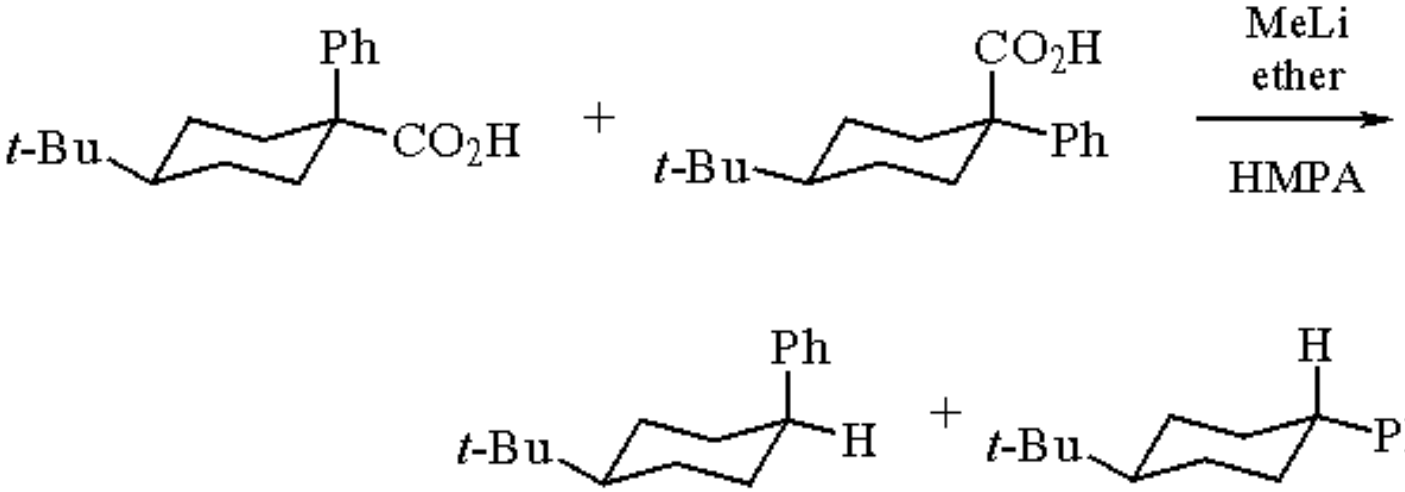

(11)

HMPA is also the only dipolar aprotic solvent to be used extensively with organomagnesium compounds.[42] Large effects are observed when HMPA is used as either a solvent or a cosolvent. As examples, HMPA accelerates addition of an allylic organomagnesium compound to aryl-substituted alkenes,[43] addition of Grignard reagents to ***Carbon Monoxide***,[44] and addition of ***Propargylmagnesium Bromide*** to allylic halides to give allene products.[45]

Carbanion Regioselectivity (1,2- vs. 1,4-Addition).

The regioselectivity of addition of certain organolithium reagents to α,β-unsaturated carbonyl compounds is affected by the addition of HMPA. In the addition of 2-lithio-2-substituted-1,3-dithiane to cyclohexenone, there was a complete reversal of regioselectivity from 1,2-addition in THF to 1,4-addition with 2 equiv of HMPA present (eq 12).[46]

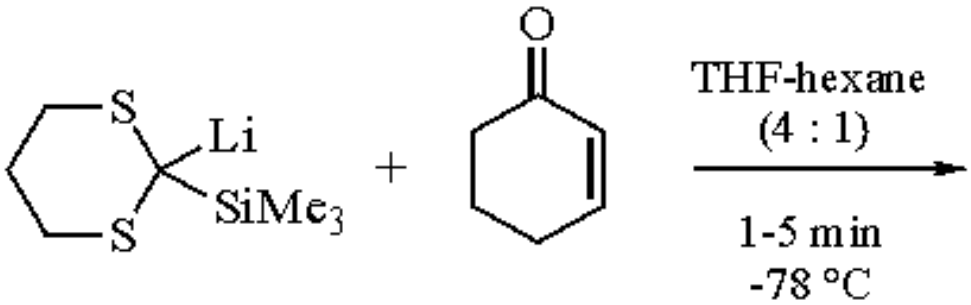

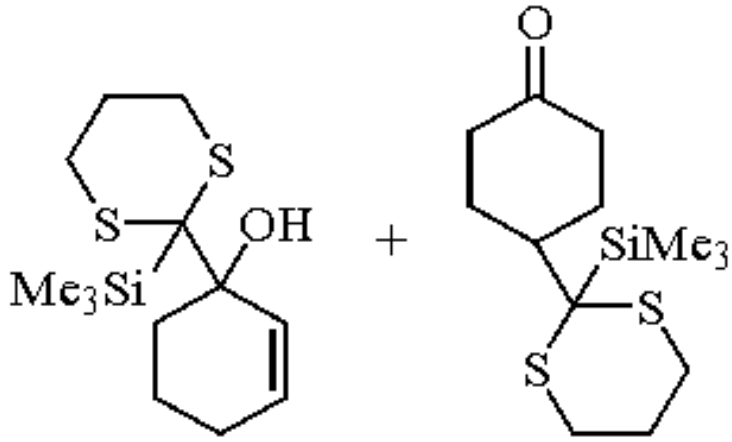

(12)

Additive	1,2-Addition	1,4-Addition
no HMPA	>99	<1
HMPA (2 equiv)	5	95

Lithium reagents that exhibit kinetic 1,4-addition in HMPA are shown as (**7**)-(**14**).[47] These include useful acyl anion equivalents[48] like phenylthio(trimethylsilyl)methyllithium (see ***(Phenylthiomethyl)trimethylsilane***).[49]

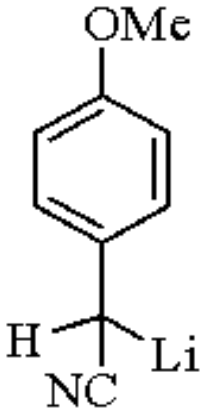

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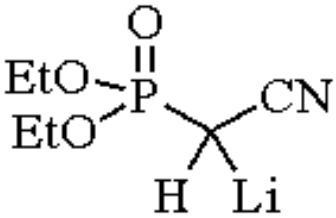

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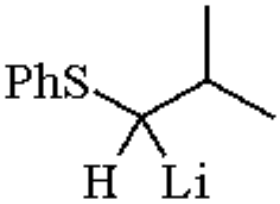

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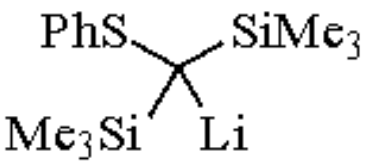

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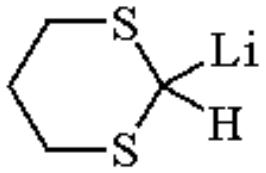

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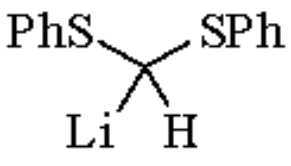

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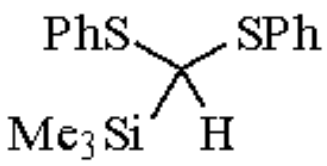

(14)

A carboxy anion equivalent was reported to undergo 1,2-addition in the absence of HMPA;[50] however, with 10 equiv of HMPA present only 1,4-addition was observed (eq 13). The addition of 1 equiv of HMPA promotes conjugate addition of alkyl and phenylthioallyl anions to cyclopentanones (eq 14) through the α-position, whereas in THF alone, irreversible 1,2-addition occurs with both α- and γ-attack.[51] The regioselectivities reported for the addition to cyclic enones of ketene dithioacetal anions[47a,52] or ***t-Butyllithium*** (eq 15)[53] are also influenced by HMPA (and counterion).

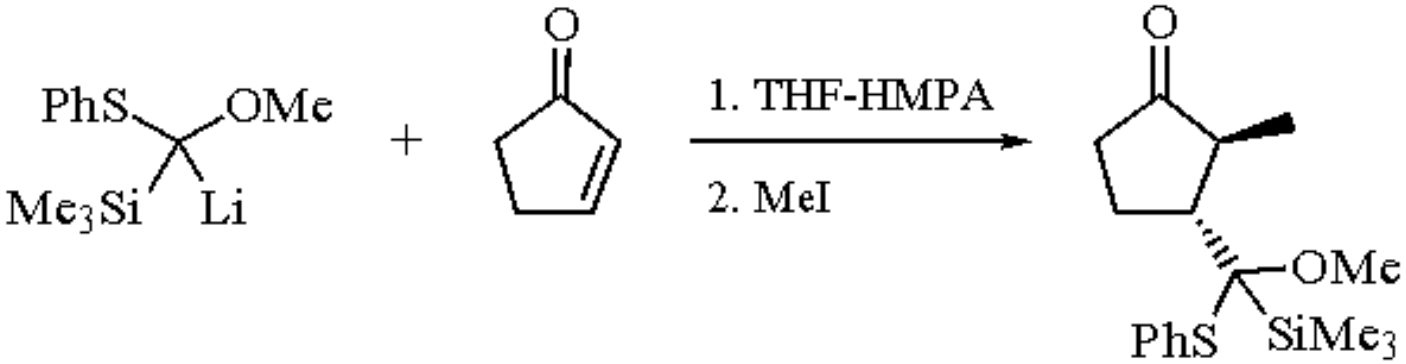

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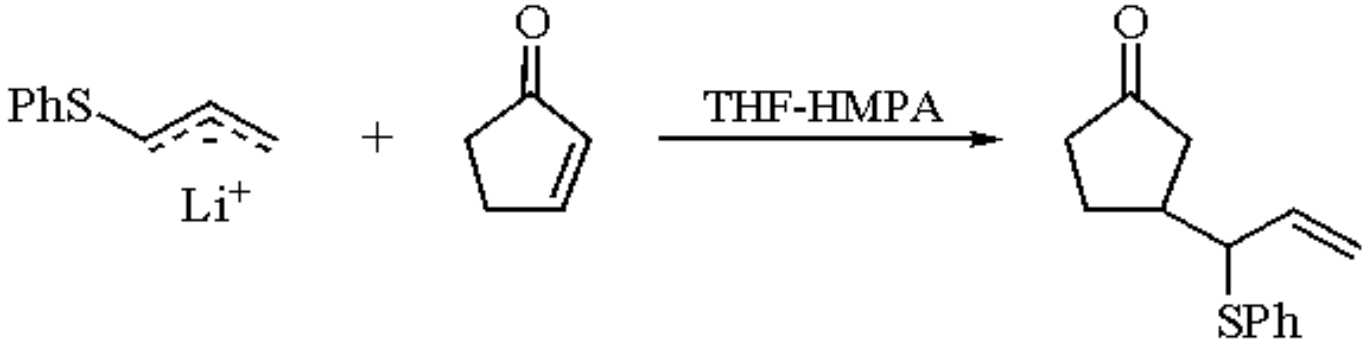

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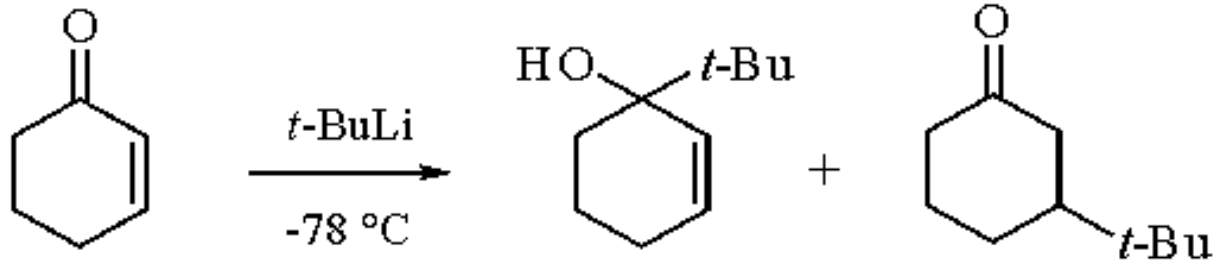

(15)

Solvent		
ether	100	-
THF	95	5
THF-5% HMPA	65	35
THF-20% HMPA	10	90

Ylide Reactivity.

HMPA is used as a cosolvent in the Wittig reaction to increase reaction rate, yield, and stereoselectivity. HMPA functions as a lithium cation-complexing agent and removes LiBr salt from ether solution (LiBr/HMPA complexes form precipitates in ether).[54] Such a salt-free Wittig reaction mixture[55] may be responsible for the high level of *cis*-alkene observed in reactions of nonstabilized ylides with aldehydes in THF or ether with added HMPA[25,56] (eq 16). Similarly, increased (*Z*) selectivity is observed in the Wittig alkenation of 2-oxygenated ketones (eq 17) to generate protected (*Z*)-trisubstituted allylic alcohols.[55,57]

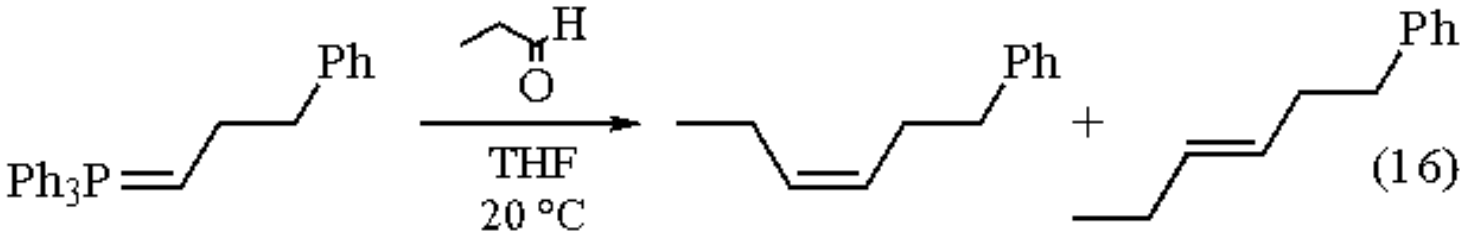

(16)

Cosolvent (% vol)	Yield (%)	(*Z*)		(*E*)
-	46	83	:	17
HMPA (35)	44	92	:	8
DMPU (35)	39	93	:	7

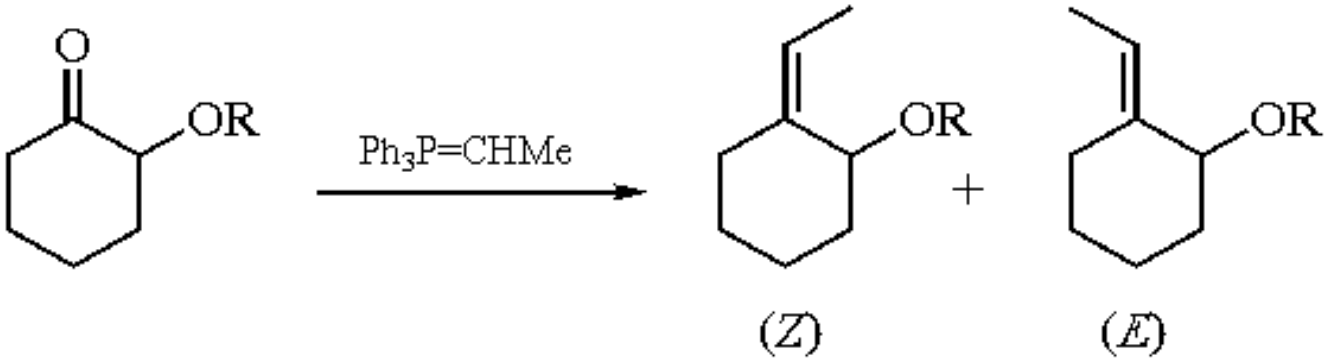

(17)

	THF		THF-HMPA	
R	(*E*):(*Z*)	Yield (%)	(*E*):(*Z*)	Yield (%)
Me	2.6:1	50	8:1	76
Ph	5:1	77	10:1	84
TBS	7.6:1	61	26:1	90
Bz	1.1:1	55	36:1	86

With HMPA, Wittig reactions that give (*E*)-alkenes were also observed (eq 18),[58] as was the directed selectivity of a semistabilized arsonium ylide towards carbonyl compounds. The arsenic ylide was generated from LDA in THF or THF/HMPA solution to give exclusively epoxide (eq 19) or diene (eq 20), respectively.[59]

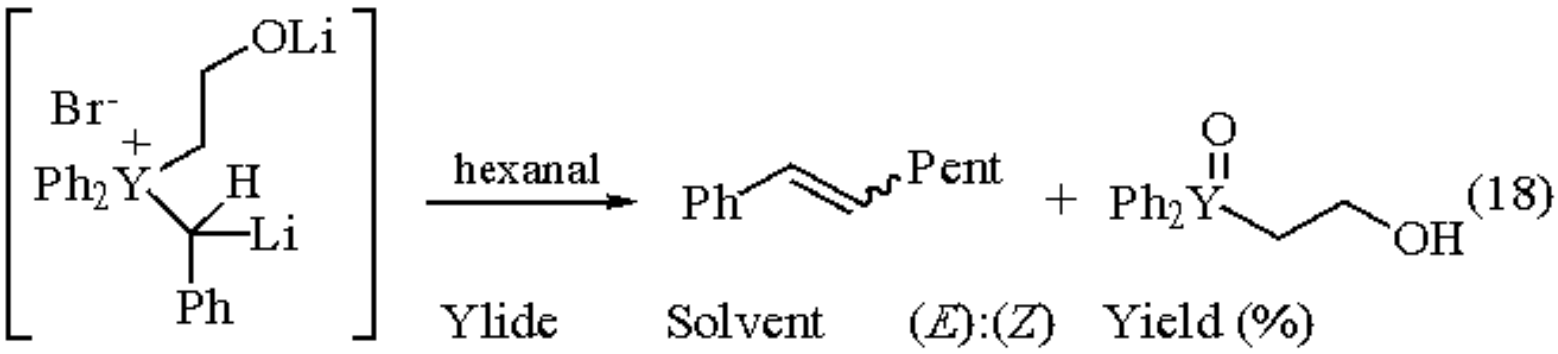

(18)

Ylide	Solvent	(*E*):(*Z*)	Yield (%)
Y = P	THF	65:35	91
Y = P	THF-HMPA	85:15	87
Y = As	THF	-	-
Y = As	THF-HMPA	100:0	65

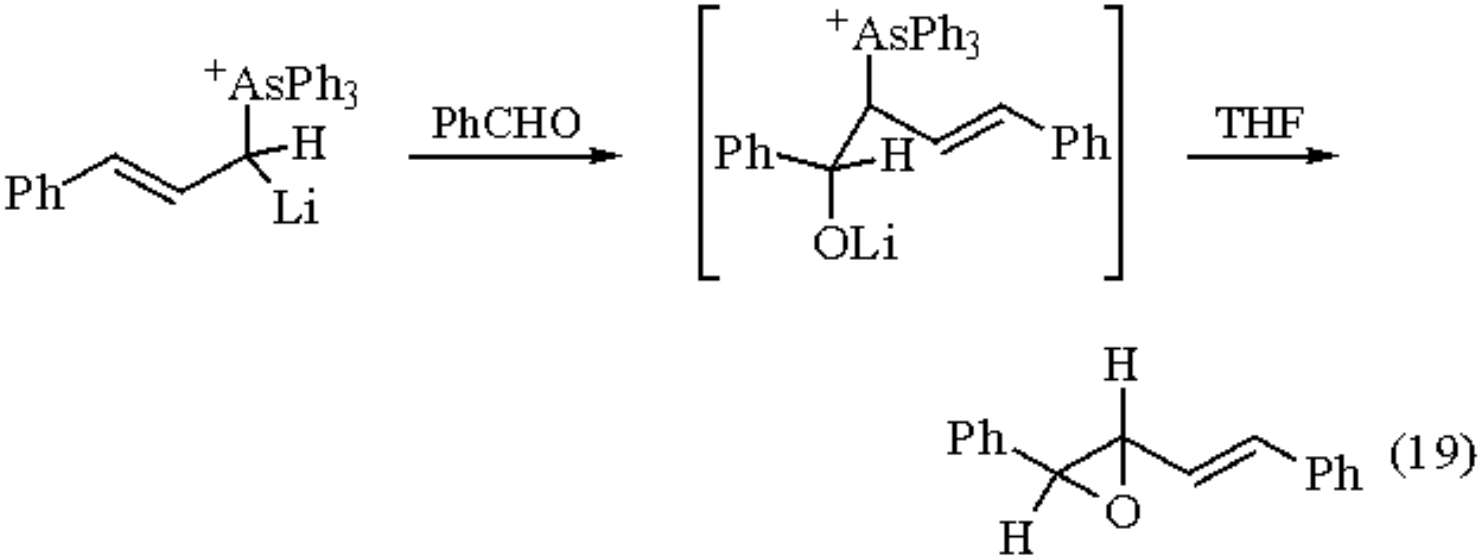

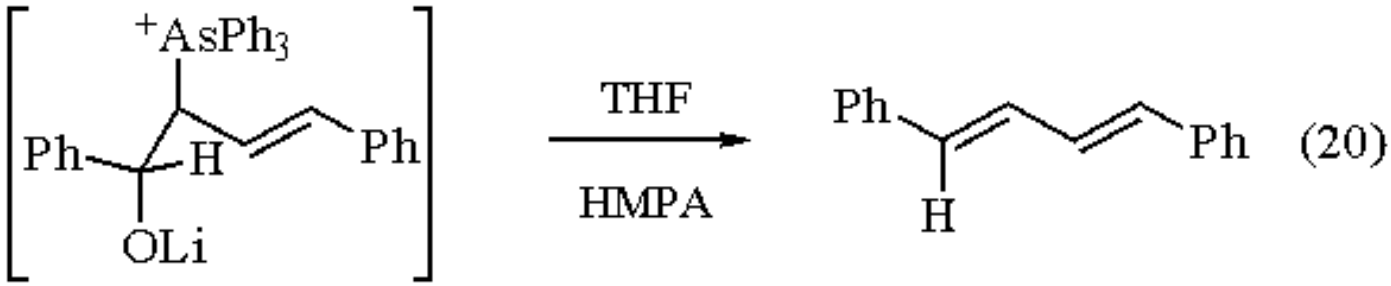

Nucleophilic Cleavage of Esters and Ethers.

The conversion of hindered methyl esters to carboxylic acids, and the demethylation of methyl aryl ethers, can be effectively performed by using HMPA to increase the nucleophilicity of lithium methanethiolate.[60] HMPA (or ***N,N-Dimethylformamide***) will also facilitate the cleavage of methyl aryl ethers and their methylthio analogs by sodium methaneselenolate (see ***Methaneselenol***) to give the phenol or thiophenol, respectively.[60,61] Sodium ethanethiolate (see ***Ethanethiol***) in refluxing DMF or HMPA attacks alkyl aryl selenides to give the corresponding diselenides. The most reactive combination of solvent and halide salt for the decarboxylation of β-keto esters was found to be ***Lithium Chloride***/HMPA, used as part of a stereoselective synthesis of 11-deoxyprostaglandin E_1.[62] In HMPA, the rate of ester cleavage of 2-benzyl-2-methoxycarbonyl-1-cyclopentanone with ***Sodium Cyanide*** is 30 times as fast as the more commonly used DMF.[62a]

Anion Reactivity.

HMPA is one of the most potent electron pair donor solvents available for accelerating S_N2 reactions.[3,43a] The formation, for example, of an α-silyl carbanion for use in a Peterson alkenation reaction[63] can be accomplished by the displacement of silicon using ***Sodium Methoxide***[64] or ***Potassium t-Butoxide***[65] in HMPA (eq 21). The increased nucleophilicity of halide ions in the presence of HMPA is seen by the increased rate of silyl-protecting group removal with fluoride ion (***Tetra-n-butylammonium Fluoride***).[66] The substitution of aryl chlorides can be performed using sodium methoxide in HMPA[67] to give anisole derivatives, or by using sodium methanethiolate (MeSNa) (see ***Methanethiol***) in HMPA[61b,68] to generate either aryl methyl sulfides or aryl thiols, depending on the reaction

conditions. The increased nucleophilicity of a magnesium alkoxide is demonstrated by the cyclization of a chloro alcohol to a 13-membered cyclic ether (eq 22) upon treatment of the compound with ***Ethylmagnesium Bromide*** in refluxing THF/HMPA.[69]

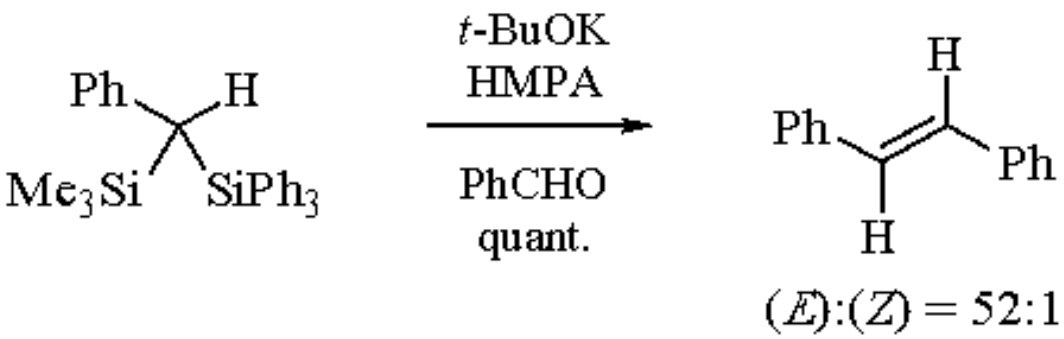

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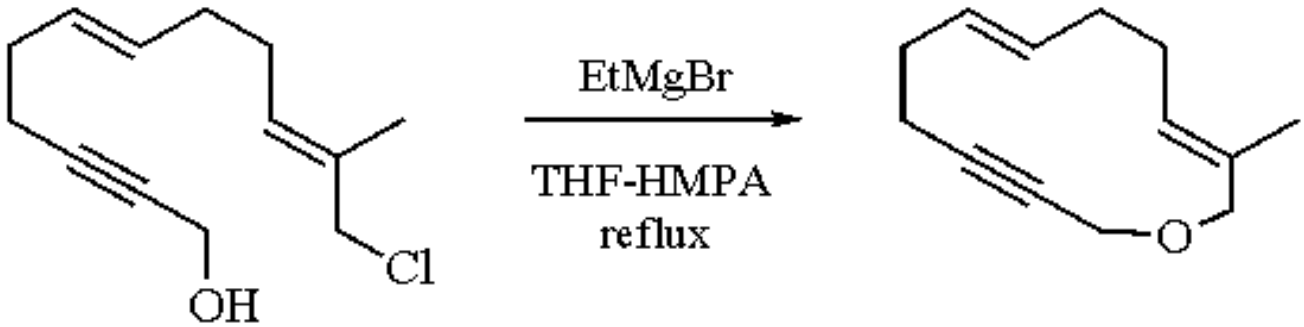

(22)

The conversion of cyclic alkenes to 1,3-cycloalkadienes can be performed through a bromination/dehydrobromination procedure using LiCl/***Lithium Carbonate***/HMPA (eq 23).[70] The dehydrobromination of 2,3-dibromo-3-methyl-1-butanol to generate a vinyl bromide has been accomplished through the use of 2.3 equiv of LDA and 0.5 equiv of HMPA in THF at -78 °C.[71]

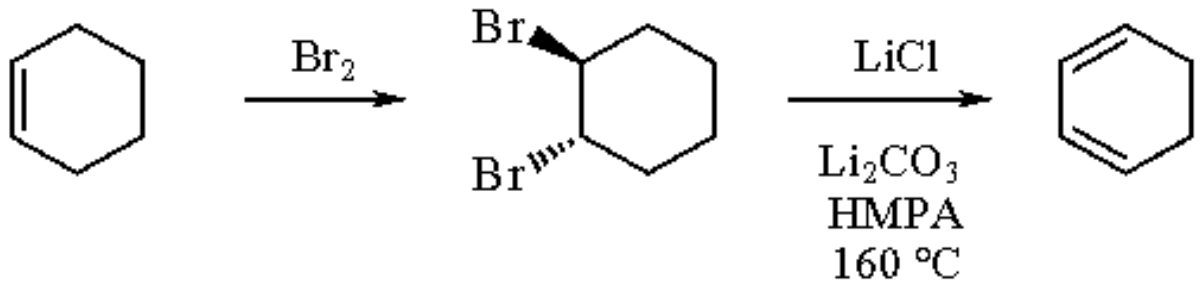

(23)

Low-Valent Metal Coordination (Lanthanoids).

HMPA is used extensively as a solvent for dissolving-metal reductions.[72] Used as a cosolvent (5-10%), it remarkably accelerates the one-electron transfer reduction of organic halides by ***Samarium(II) Iodide***.[73] The reductions work on a variety of primary, secondary, or tertiary halides, including chlorides which could not be reduced in pure THF (eq 24). The samarium Barbier reaction, which requires hours in refluxing THF, can be performed as a titration in THF-HMPA at rt (eq 25).[74] The SmI_2/THF/HMPA system has recently been used in the deoxygenation of organoheteroatom oxides,[75] reductive dimerization of conjugated acid derivatives,[76] and selective reduction of α,β-unsaturated carbonyl compounds.[77] In addition, SmI_2 was used in a tandem radical cyclization,[78] and has been a useful reagent in Barbier-type reactions.[73b,79] The dramatic acceleration of electron transfer is also observed for ***Ytterbium(0)***.[80]

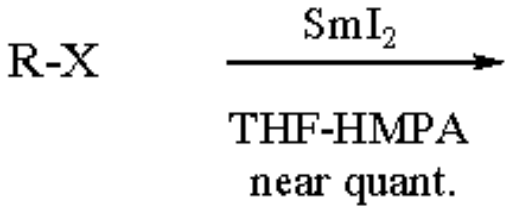

(24)

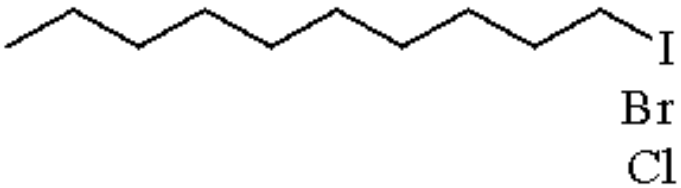

	THF		THF-HMPA	
	Time	Yield	Time	Yield
I	6 h	95%	5 min	>95%
Br	2 days	82%	10 min	>95%
Cl	no reaction		8 h	>95%

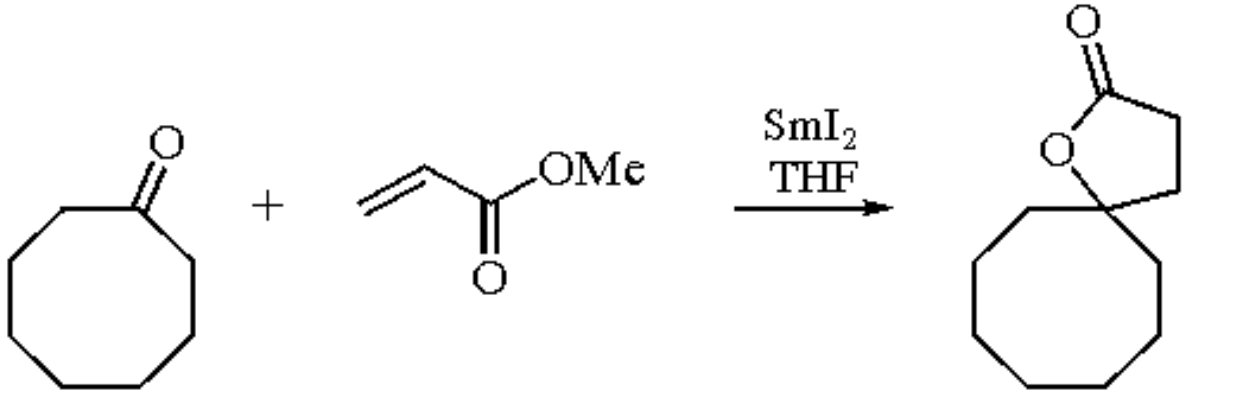

(25)

Additive	Time	Yield
none	4 h	82%
HMPA	1 min	95%

Transition Metal Coordination.

The ability of HMPA to complex to metals and alter reactivity is also expressed in palladium-catalyzed coupling reactions. For example, ethylbenzene can be formed from the Pd^0 catalyzed cross-coupling of ***Benzyl Bromide*** and ***Tetramethylstannane***, with the formation of almost no bibenzyl.[81] The reaction does not proceed in THF, but requires a highly polar solvent like HMPA or ***1-Methyl-2-pyrrolidinone***. Similarly, HMPA is necessary in the Pd^0-catalyzed coupling of acid chlorides with organotin reagents to give ketones. In highly polar solvents like HMPA the transfer of a chiral group from the tin occurs with preferential inversion of configuration (eq 26).[82] The relative rate of transfer of an alkynic or vinyl group to acid chlorides[82a] or aryl iodides[83] is also greatly accelerated by HMPA. It can increase the rate of alkylation of π-allylpalladium chloride by ester enolates,[84] and alter the chemoselectivity by leading to a cyclopropanation reaction instead of an allylic alkylation.[85]

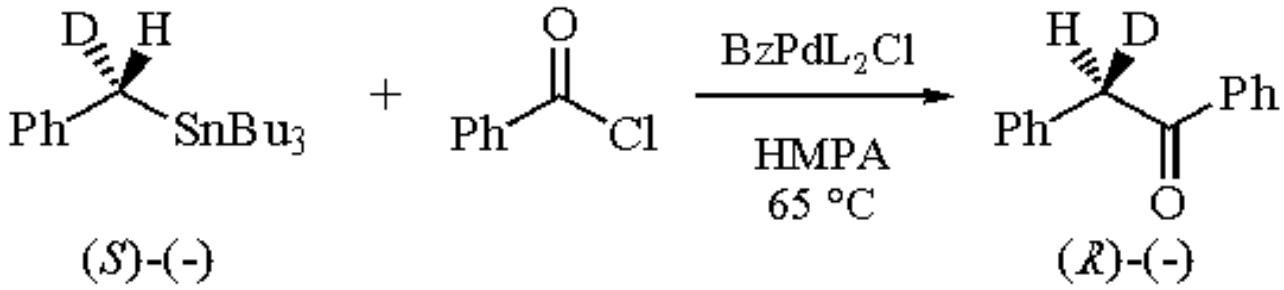

(26)

Hydride Reductions.

The reduction of organic compounds by hydride can be influenced by the choice of cosolvent. Cyanoborohydrides (e.g. ***Sodium Cyanoborohydride***) in HMPA provide a mild, effective, and selective reagent system for the reductive displacement of primary and secondary alkyl halides and sulfonate esters in a wide variety of structural types.[86] A ***Sodium Borohydride***/HMPA reagent system was used in the reduction of *N*,*N*-disulfonamides[87] and in the reduction of dibromides to monobromides.[37a] Similarly, ***Tri-n-butylstannane***/HMPA[88] can be utilized to chemoselectively reduce aldehydes with additional alkene or halide functionality.[89] Finally, the reduction of aldehydes and ketones with hydrosilanes proceeds in the presence of a catalytic amount of Bu_4NF in HMPA.[90] The reaction rate was much lower in DMF than in HMPA, and the reaction yields decreased considerably if less polar solvents like THF or CH_2Cl_2 were used.

Oxidation.

The oxidation of acid sensitive alcohols with ***Chromium(VI) Oxide*** in HMPA is one example of the use of HMPA in oxidation reactions.[91] (CAUTION: Do not crush CrO_3 prior to reaction since violent decomposition can occur. The use of DMPU has been reported to have a similar hazardous effect). Recently, a ***Bromine***/$NaHCO_3$/HMPA system[92] was used for the oxidative esterification of alcohols with aldehydes, where the HMPA considerably accelerated the oxidation by bromine and lowered the rate of unwanted halogenation. Epoxidations of alkenes or allylic alcohols have been accomplished using MoO_5.HMPA.pyridine (***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)***; MoOPH).[93]

Effect of HMPA on Protonation.

The protonation of (9-anthryl)arylmethyllithium with various oxygen and carbon acids in THF or in THF-HMPA had a significant effect on the product ratio of C-α vs. C-10 protonation (eq 27).[94] Another study[95] found that a nitronate protonation led to mainly one diastereomeric product in a THF solution containing HMPA or DMPU (eq 28). Panek and Rodgers[96] observed stereospecific protonation of 10-*t*-butyl-9-methyl-9-lithio-9,10-dihydroanthracene: >99% *cis* protonation was observed in THF or ether with greater than >99% *trans* protonation observed in HMPA.

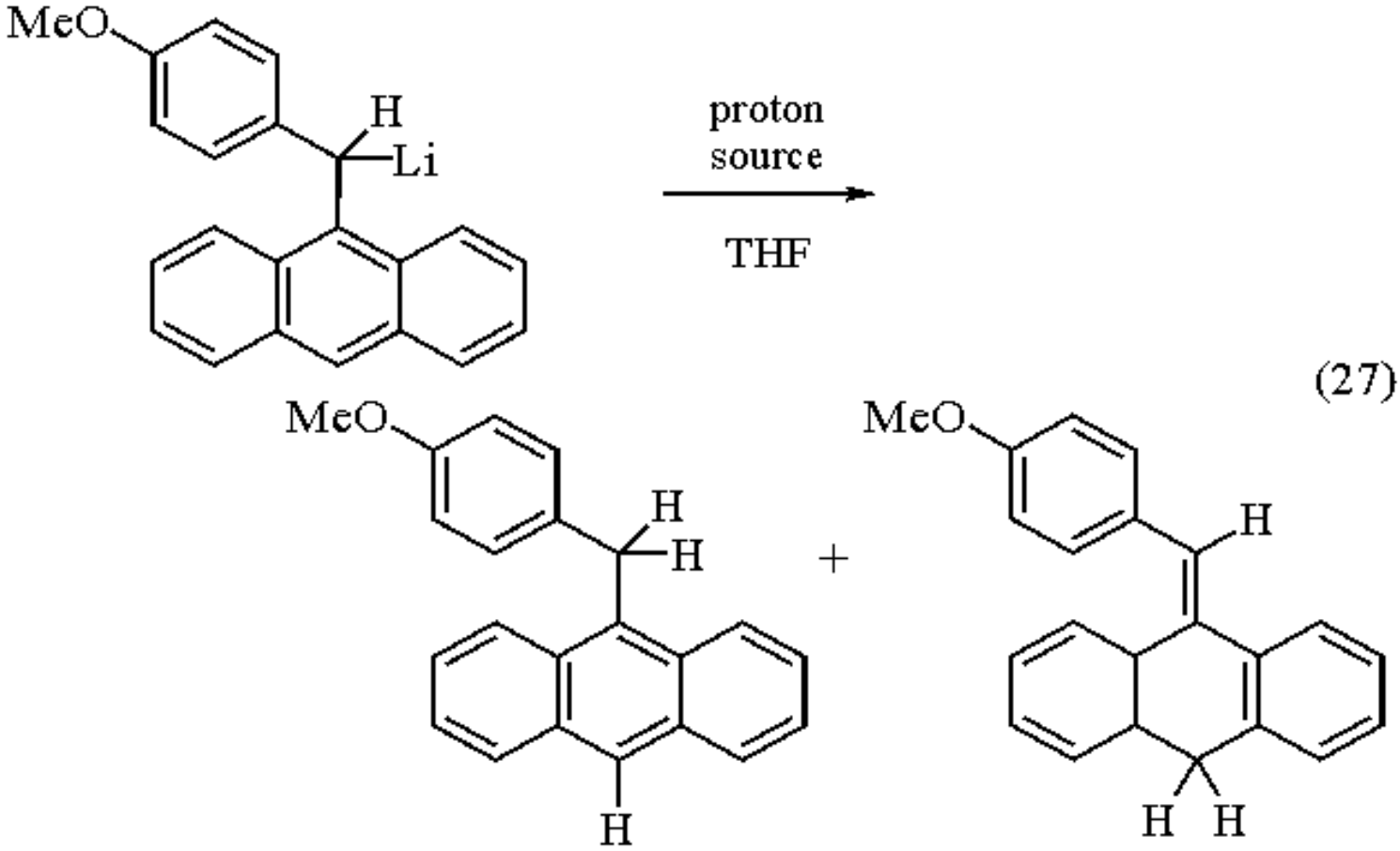

(27)

Additive	Proton. at C-α	Proton. at C-10
none	57	43
HMPA (12 equiv)	>95	<5

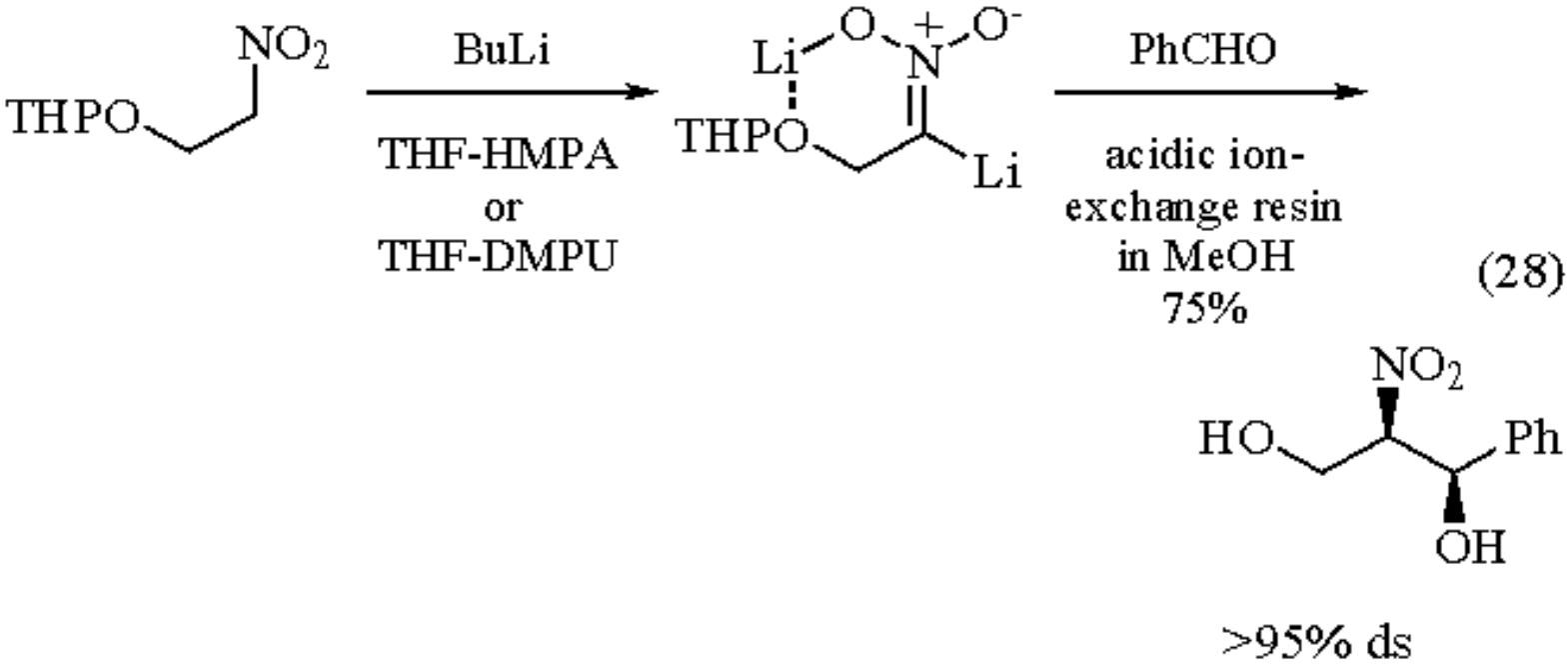

Inhibition by HMPA.

Finally, it should be added that there are a few cases where HMPA slows the rate of a reaction. Such examples typically involved the inhibition of lithium catalysis by strong coordination of HMPA to lithium.[97] For instance, two-bond ^{13}C-^{13}C NMR coupling in organocuprates is poorly observable in ether or THF at very low temperature.[98] Exchange, however, is slowed in THF/HMPA or THF/12-crown-4, so that coupling is easily observed. The effect of HMPA suggests that Li^+ is involved in the exchange process.

HMPA Substitutes and Analogs.

Researchers have searched for an alternative to HMPA. Such a solvent must be stable to polar organometallic compounds and be comparable to HMPA in its many functions. Replacement solvents typically are useful in some applications but have limited value in others. Examples of some useful alternatives are (**15**)-(**19**).[30,42,99]

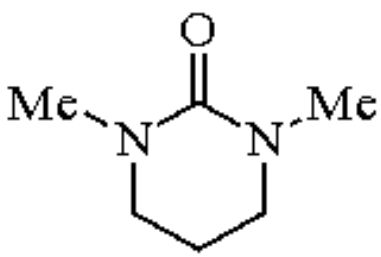

(15) DMPU

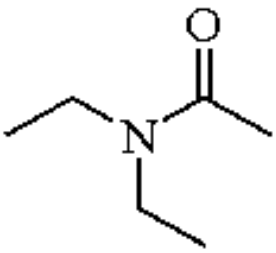

(16) DEA

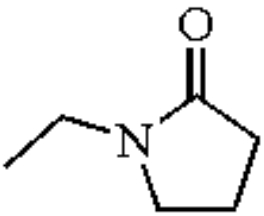

(17) NEP

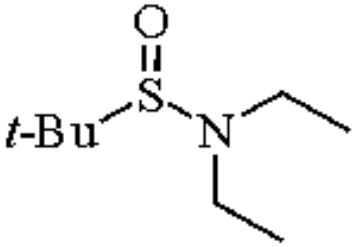

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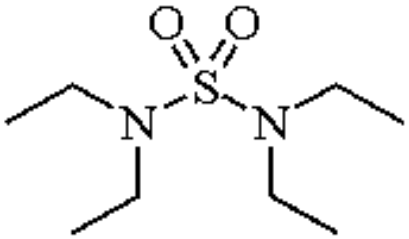

(19) TES

Chiral analogs of HMPA, (**20**)-(**22**), have been used as ligands in transition metal complexes.[93b,100]

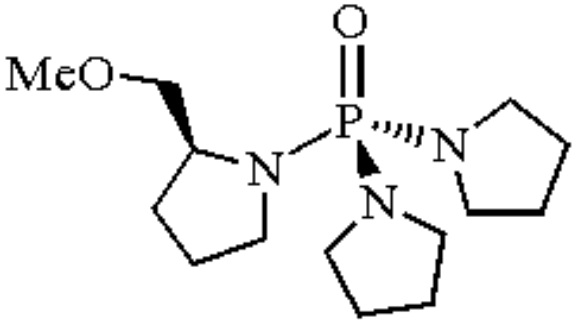

(20)

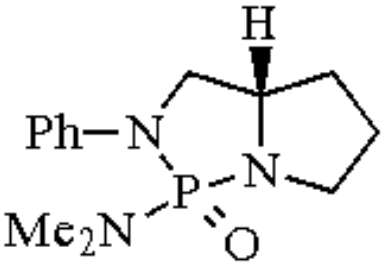

(21)

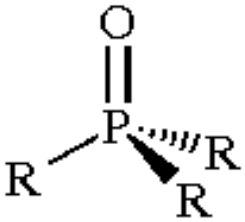

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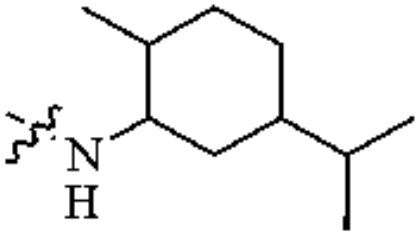

(22)

Related Reagents.

N,N-Dimethylformamide; ***N,N´-Dimethylpropyleneurea***; ***Dimethyl Sulfoxide***; ***Hexamethylphosphoric Triamide-Thionyl Chloride***; ***Lithium Chloride-Hexamethylphosphoric Triamide***; ***1-Methyl-2-pyrrolidinone***; ***Potassium t-Butoxide-Hexamethylphosphoric Triamide***; ***Potassium Hydride-Hexamethylphosphoric Triamide***; ***Potassium Hydroxide-Hexamethylphosphoric Triamide***.

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Hexamethylphosphoric Triamide-Thionyl Chloride[1]

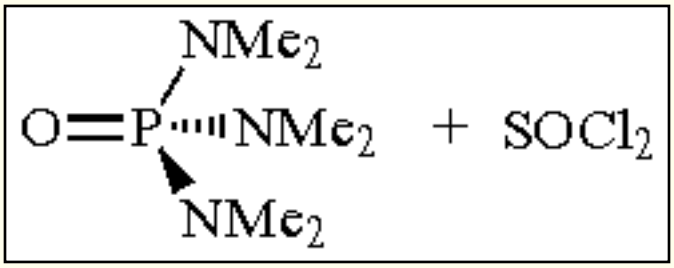

(HMPA)

[680-31-9] · $C_6H_{18}N_3OP$ · Hexamethylphosphoric Triamide-Thionyl Chloride · (MW 179.24) ($SOCl_2$)

[7719-09-7] · Cl_2OS · Hexamethylphosphoric Triamide-Thionyl Chloride · (MW 118.97)

(a chlorinating agent[2] for the preparation of alkyl chlorides, acid chlorides, esters, and amides)

Physical Data: see ***Hexamethylphosphoric Triamide*** and ***Thionyl Chloride***.

Chlorinating Agent.

The use of thionyl chloride with HMPA is a good procedure for the synthesis of alkyl chlorides from primary, secondary, and tertiary alcohols (eq 2).[3] The initial product of the reaction of an alcohol with $SOCl_2$ is thought to be a chlorosulfite (eq 1).[4] The further course of the reaction depends on both the structure of the chlorosulfite and the solvent. Highest yields are obtained with primary alcohols (eq 3).

$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl \qquad (1)$$

$$ROH + SOCl_2 \xrightarrow{HMPA} RCl + SO_2 + HCl \qquad (2)$$

$$BuOH + SOCl_2 \xrightarrow[90\%]{HMPA} BuCl + SO_2 + HCl \qquad (3)$$

Decomposition of the secondary alkyl chlorosulfite is often greatly influenced by the solvent, forming alkenes and alkyl chlorides in dioxane with retention of configuration (S_N1), but forming an alkyl chloride in HMPA with inversion of configuration (S_N2). This method is also advantageous for making allylic chlorides and acid chlorides, in particular for α,β-unsaturated acid chlorides, since $SOCl_2$ does not add to the C=C bond (eq 4).[3] Esters and amides can be made by treating the carboxylic acid with $SOCl_2$-HMPA at -15 °C followed by addition of an alcohol or amine, respectively (eq 5).[2] Esters of tertiary alcohols can be formed in higher yield with HMPA than with pyridine or dimethylaniline.[3]

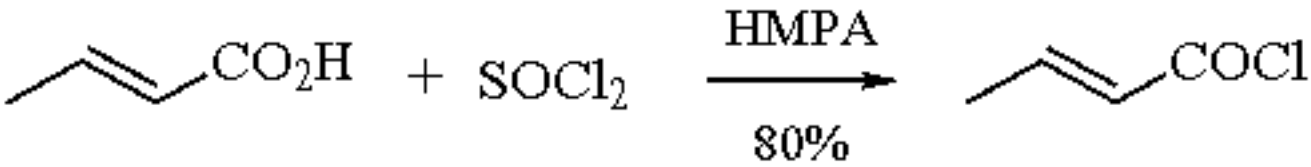

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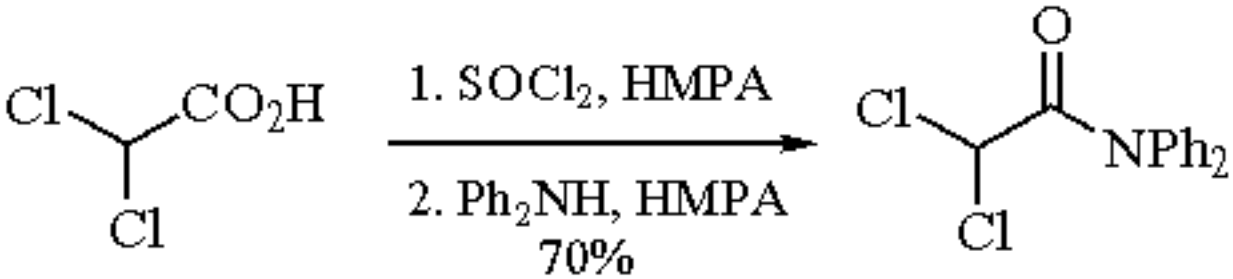

(5)

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Hexamethylphosphorous Triamide[1]

$(Me_2N)_3P$

[1608-26-0] · $C_6H_{18}N_3P$ · Hexamethylphosphorous Triamide · (MW 163.24)

(strong nucleophile;[2] used to synthesize epoxides from aldehydes[2,3] and arene oxides from aryldialdehydes;[4-7] replaces Ph_3P in the Wittig reaction;[8] with CCl_4, converts alcohols to chlorides;[9] with I_2, converts disulfides to sulfides[10] and deoxygenates sulfoxides and azoxyarenes;[11] with dialkyl azodicarboxylate and alcohol, forms mixed carbonates;[12] reduces ozonides[13])

Alternate Name: tris(dimethylamino)phosphine.

Physical Data: mp 26 °C; bp 162-164 °C/760 mmHg, 50 °C/12 mmHg; *n*25D 1.4636; *d* 0.911 g cm^{-3}.

Form Supplied in: commercially available; liquid, pure grade >97% (GC).

Preparative Methods: reaction of ***Phosphorus(III) Chloride*** with anhydrous dimethylamine; the same procedure can be used to obtain higher alkyl homologs.[14]

Purification: distillation at reduced pressure; exposure of hot liquid to air should be avoided.

Handling, Storage, and Precautions: very sensitive to air; best stored in nitrogen atmosphere; reacts with carbon dioxide; inhalation should be avoided. Use in a fume hood.

Synthesis of Epoxides.

Reaction of $(Me_2N)_3P$ with aromatic aldehydes provides convenient direct synthetic access to symmetrical and unsymmetrical epoxides in generally high yields. A typical example is the reaction of *o*-chlorobenzaldehyde, which provides the corresponding stilbene oxide as a mixture of the *trans* and *cis* isomers (eq 1).[2,3]

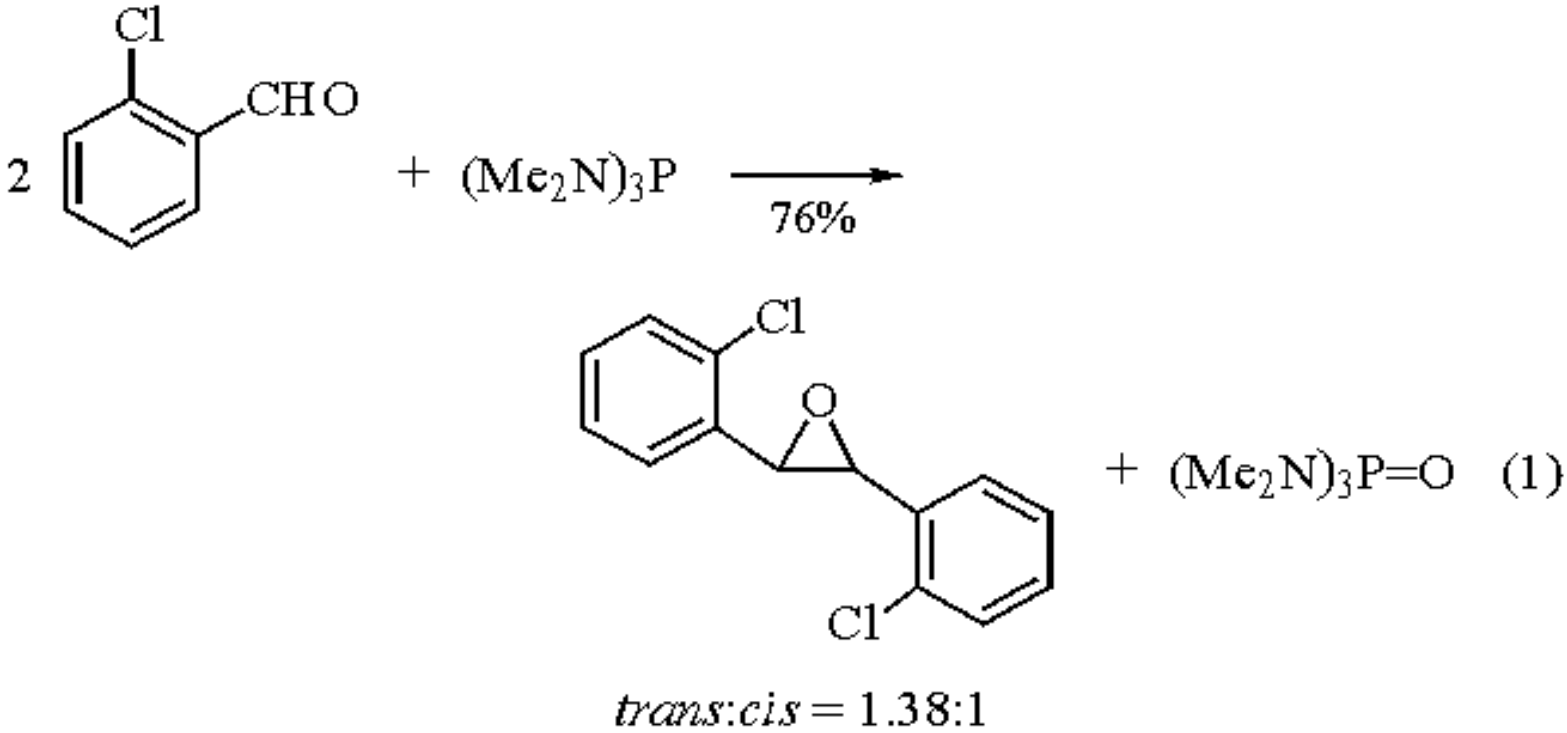

The coproduct, ***Hexamethylphosphoric Triamide***, is readily separated by taking advantage of its water solubility. A competing reaction pathway leads to formation of variable amounts of a 1:1 adduct in addition to the epoxide product (eq 2). Originally the adduct was assigned the betaine structure (**1a**). On the basis of more detailed NMR analysis, this was subsequently revised to the phosphonic diamide structure (**1b**).[15]

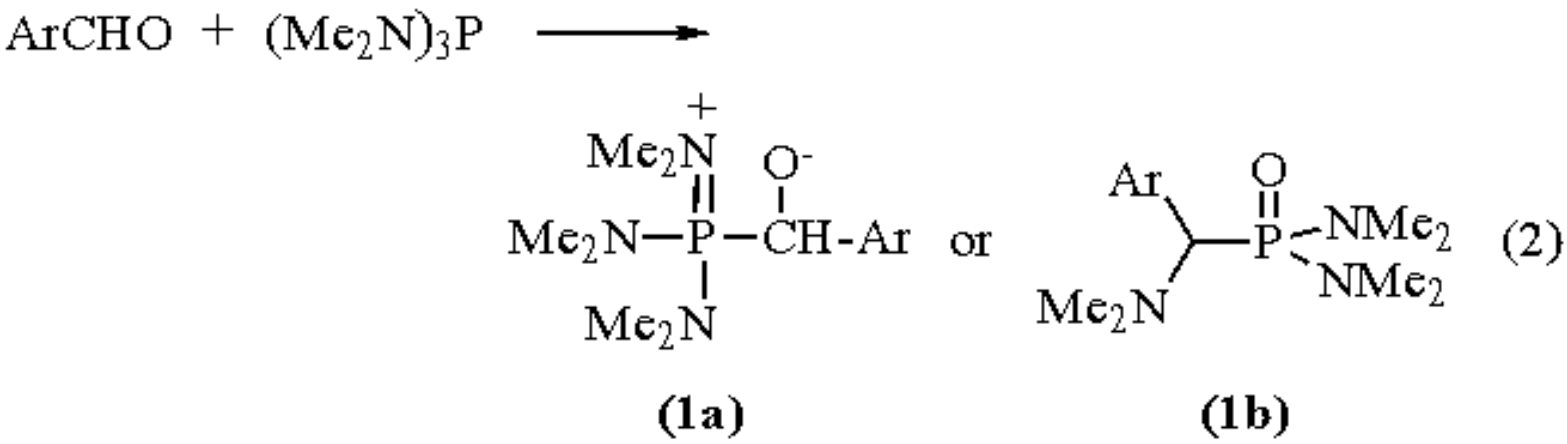

The ratio of products depends upon the electronegativity of the aldehyde and the mode of carrying out the reaction. Aromatic aldehydes with electronegative substituents, especially in the *ortho* position, undergo rapid exothermic reaction to yield epoxides exclusively. Conversely, aldehydes bearing electron-releasing substituents react more slowly to afford mainly 1:1 adducts. Slow addition of $(Me_2N)_3P$ to the aldehyde tends to enhance the ratio of the epoxide product. These observations are compatible with a mechanism in which an initially formed 1:1 adduct reacts with a second aldehyde molecule to form a 2:1 adduct which collapses to yield the observed products (eq 3).

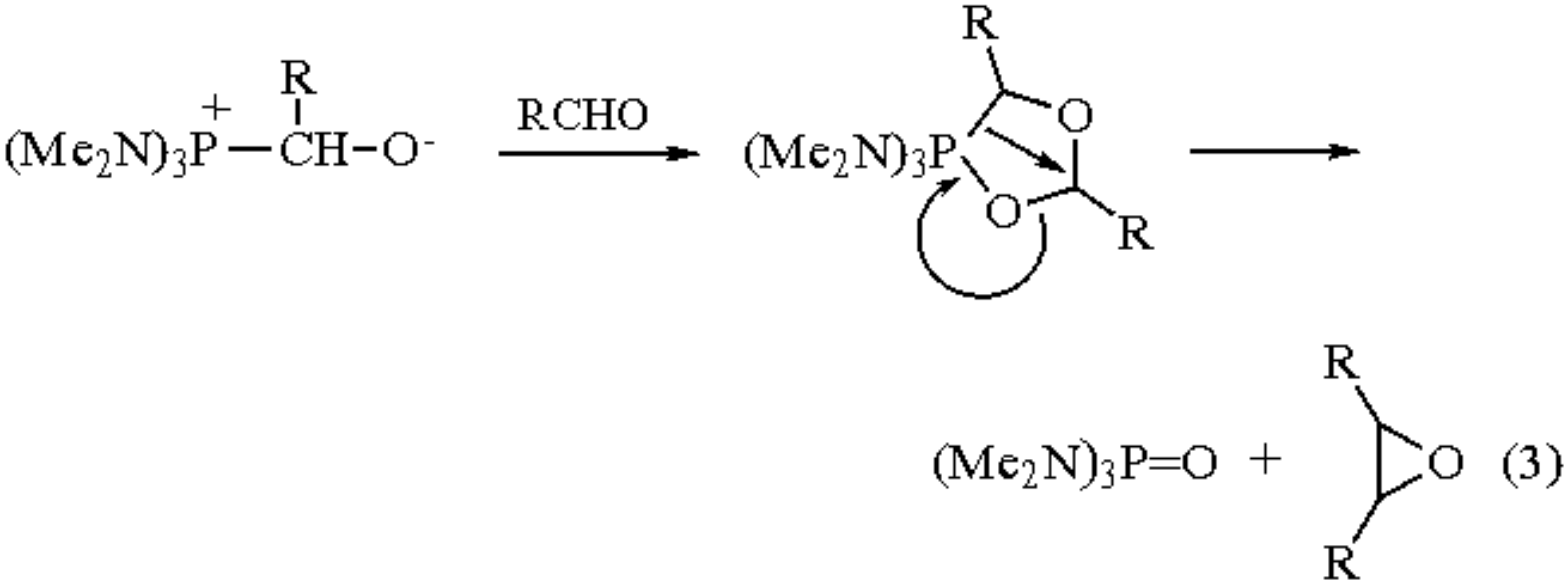

$(Me_2N)_3P$ reacts also with saturated and heterocyclic aldehydes, but 1:1 adducts rather than epoxides are the predominant products. The reaction with ***Chloral*** takes a different course[2] and yields the dichlorovinyloxyphosphonium compound $Cl_2C{=}CH{-}O{-}{+}P(NMe_2)_3\ Cl^-$.

The scope of the reaction is considerably extended by its applicability to the synthesis of mixed epoxides.[2] This is accomplished by addition of $(Me_2N)_3P$ to a mixture of aldehydes in which the less reactive aldehyde predominates. For example, addition of $(Me_2N)_3P$ to a mixture of *o*-chlorobenzaldehyde and 2-furaldehyde yields the corresponding mixed epoxide (eq 4).

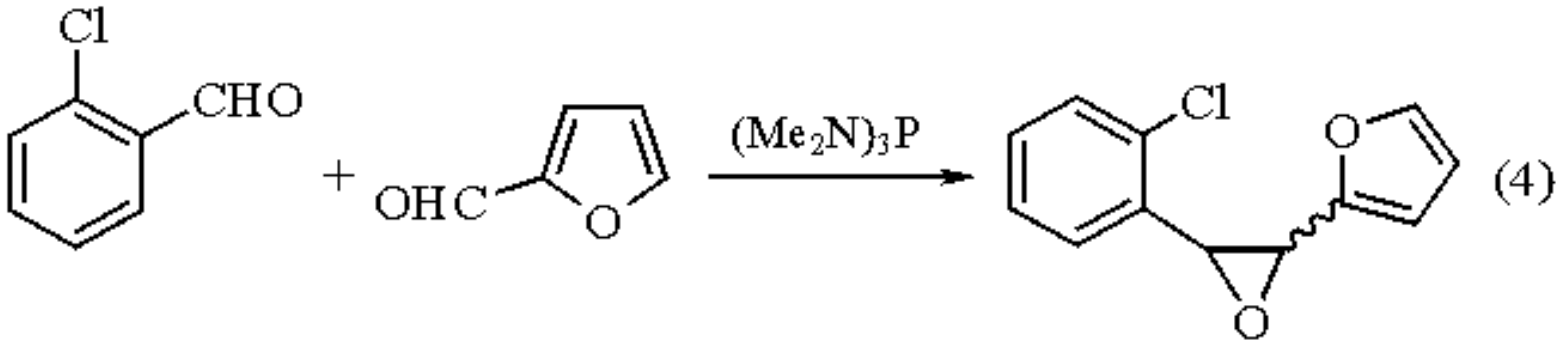

An advantage of the method is that it allows the synthesis of epoxides unobtainable by the oxidation of alkene precursors with peroxides or peracids due to the incompatibility of functional groups with these reagents.

Synthesis of Arene Oxides.

Reaction of $(Me_2N)_3P$ with aromatic dialdehydes provides arene oxides such as benz[*a*]anthracene 5,6-oxide (**2a**) (eq 5).[4-7] These compounds, also known as oxiranes, are relatively reactive, undergoing thermal and acid-catalyzed rearrangement to phenols and facile hydrolysis to dihydrodiols. Consequently, their preparation and purification requires mild reagents and conditions. The importance of this is underlined by successful synthesis of the reactive arene oxide (**2b**) in 75% yield using appropriate care,[7] despite a previous report of failure of the method.[4] While compound (**2b**) is a relatively potent mutagen, it is rapidly detoxified by mammalian cells.[6] The principal limitation

of the method is the unavailability of the dialdehyde precursors, which are obtained through oxidation of the parent hydrocarbons, e.g. by ozonolysis.

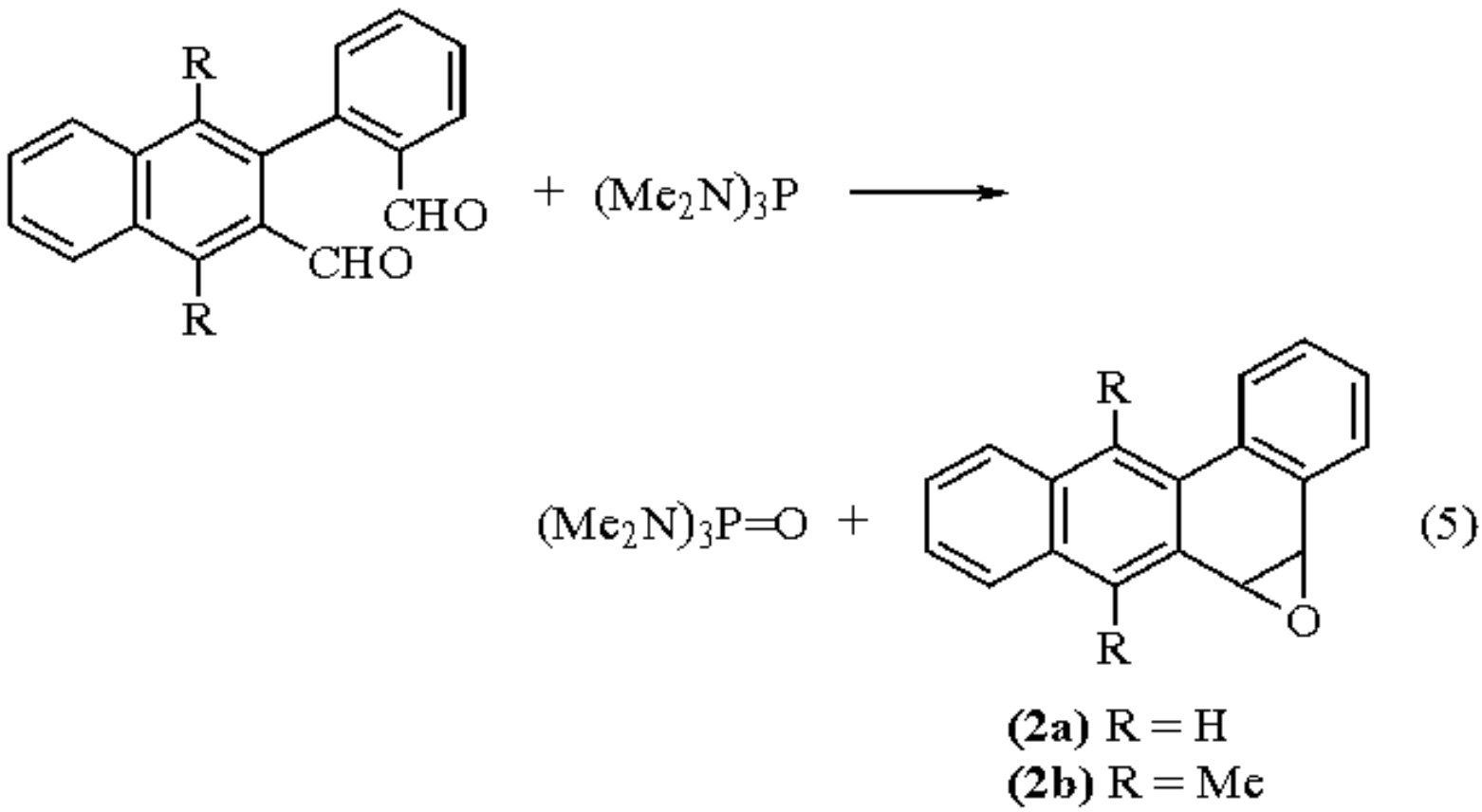

Wittig and Horner-Wittig Reactions.

$(Me_2N)_3P$ may be used in place of ***Triphenylphosphine*** in Wittig reactions with aldehydes and ketones (eq 6).[8] It is advantageous because the water solubility of the byproduct, hexamethylphosphoric triamide, renders it readily removable. This method has been used for the preparation of unsaturated esters as well as alkenes (eq 7).

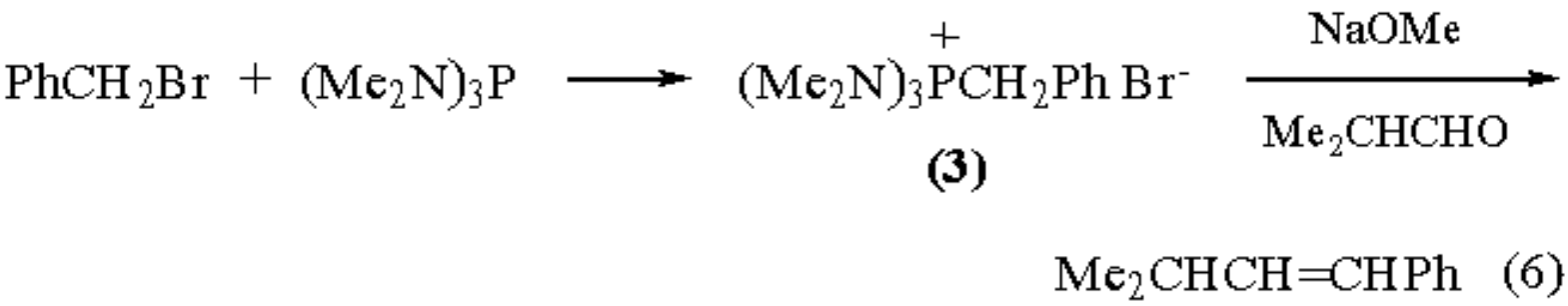

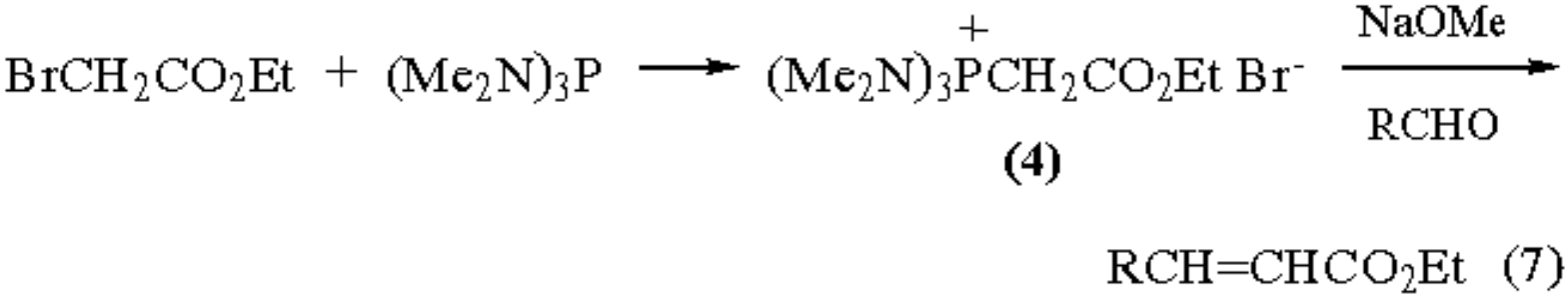

The phosphonic diamide products (**1b**) obtained from the reaction of arylaldehydes having electron-donating groups with $(Me_2N)_3P$ can be deprotonated by ***n-Butyllithium*** in DME at 0 °C.[15] These intermediates participate in Horner-Wittig-type reactions with aromatic aldehydes to give enamines in good yield (eq 8). In the examples studied the enamines have the (*E*) configuration. Mild acid hydrolysis of the reaction mixtures without isolating the intermediate enamines provides the corresponding deoxybenzoins.[15] The overall procedure represents an example of reductive nucleophilic acylation of carbonyl compounds.

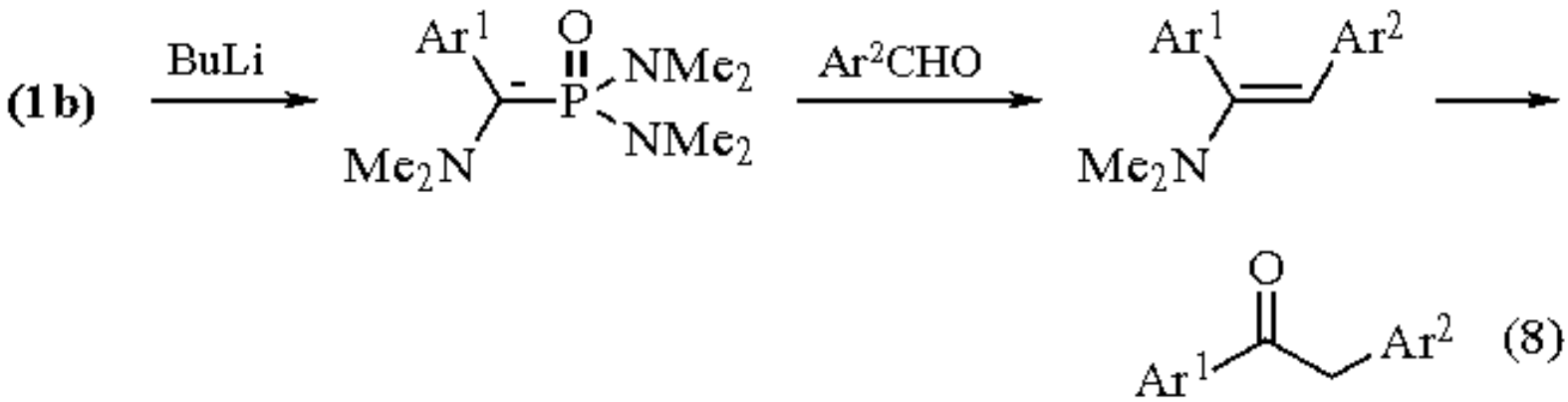

Conversion of Alcohols to Alkyl Chlorides and Other Derivatives.

The reagent combination $(Me_2N)_3P$ and CCl_4 can be used in place of ***Triphenylphosphine-Carbon Tetrachloride*** for the conversion of alcohols to alkyl chlorides (eq 9).[9] An advantage is the ease of removal of the water-soluble coproduct $(Me_2N)_3P{=}O$. The mechanism entails initial rapid formation of a quasiphosphonium ion, followed by reaction with an alcohol with displacement of chloride, and nucleophilic attack by the chloride ion on the carbon atom of the alcohol in a final rate-determining step to yield an alkyl chloride.

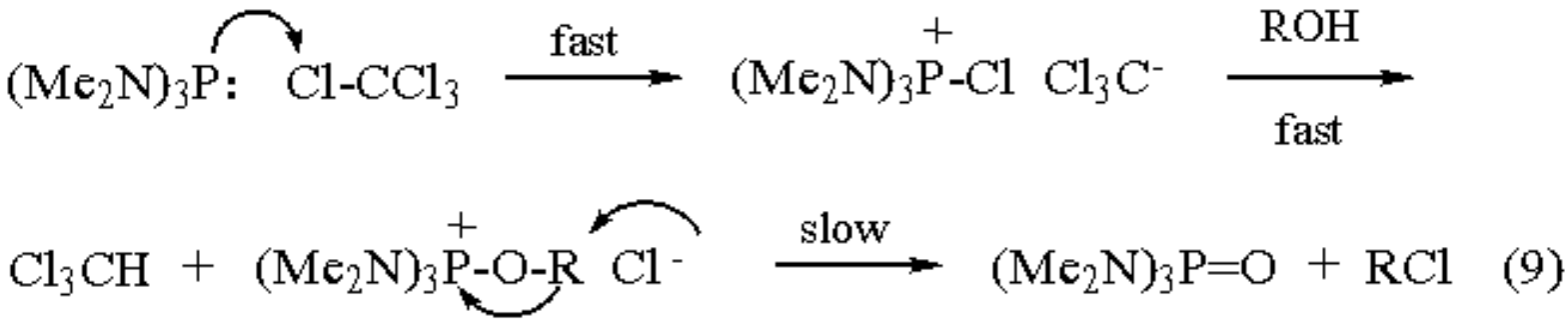

This reagent reacts more rapidly with primary than with secondary alcohols. This property has been made use of to transform the primary hydroxy groups of sugars to salts, which then may be converted to halides (Cl, Br, I), azides, amines, thiols, thiocyanates, etc. by reaction with appropriate nucleophiles (eq 10).[16] Arylalkyl ethers and thioethers may also be prepared by appropriate modification of this method.[17] These reactions generally proceed with high stereoselectivity. Thus reaction of chiral 2-octanol with this reagent afforded 2-chlorooctane with complete inversion of configuration. Also, conversion of the salt prepared from reaction of (*R*)-(-)-2-octanol with $(Me_2N)_3P/CCl_4$ at low temperature to the corresponding hexafluorophosphate salt, followed by reaction of this with potassium phenolate in DMF, gave optically pure (*S*)-(+)-2-phenoxyoctane in 93% yield (eq 11).[17]

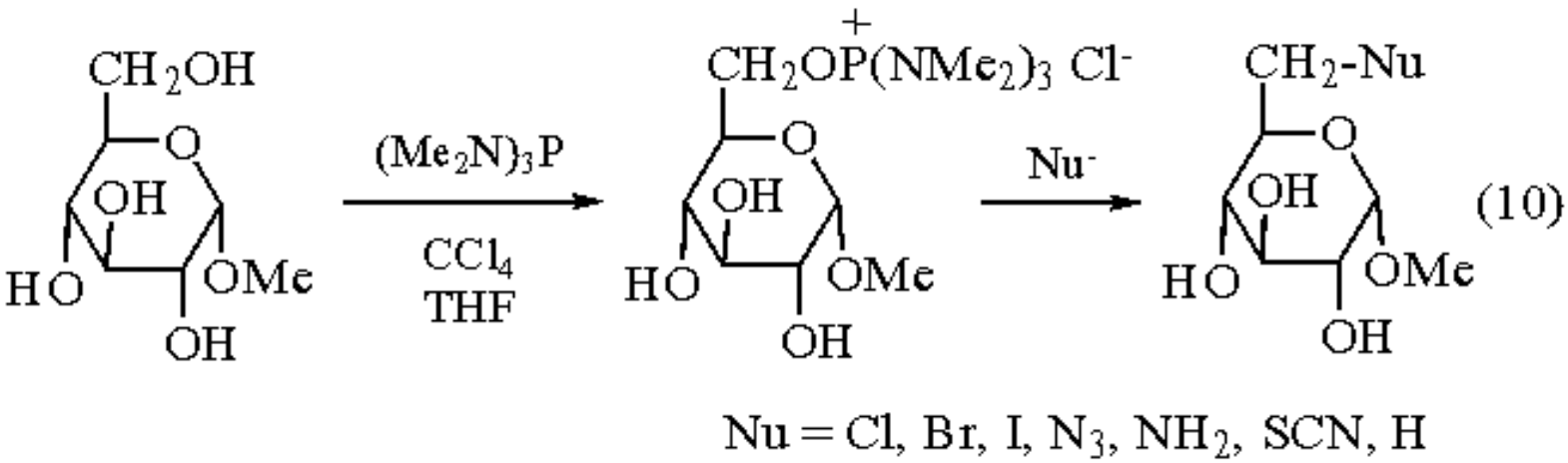

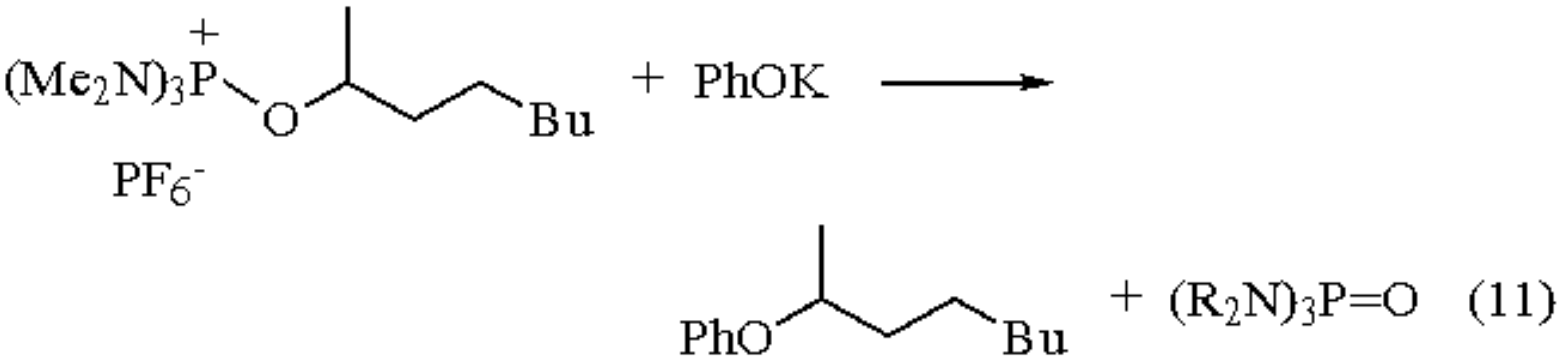

$(Me_2N)_3P/CCl_4$ may also be employed for the selective functionalization of primary long-chain diols.[17] Reactions of diols of this type with $(Me_2N)_3P$ and CCl_4 in THF followed by addition of KPF_5 gives mono salts in high yield (eq 12).[18] THF serves to precipitate the mono salts as they are formed, thereby blocking their conversion to bis salts. Reactions of the mono salts with various nucleophiles provides the corresponding monosubstituted primary alcohols.

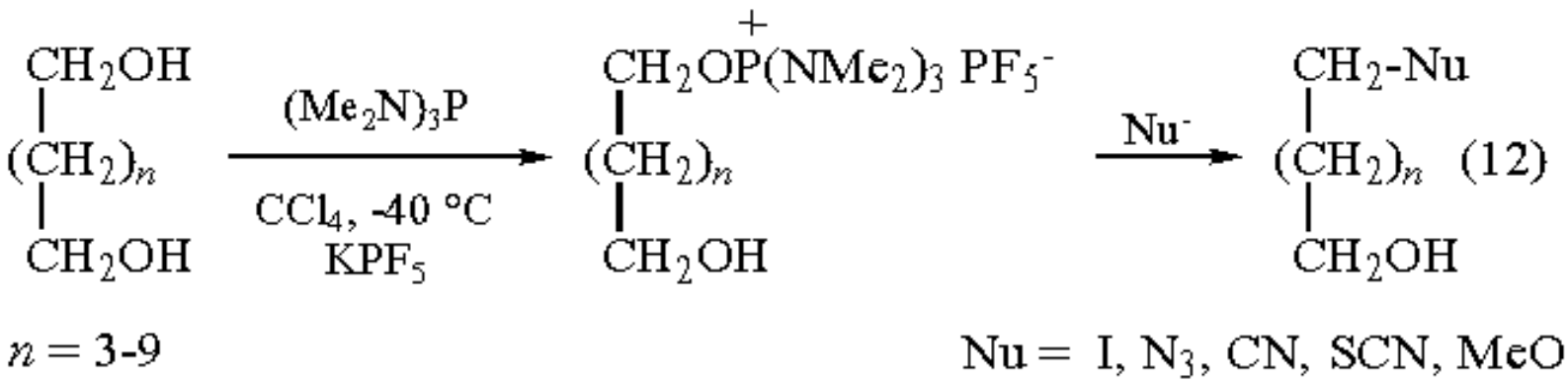

Conversion of Disulfides to Sulfides.

Alkyl, aralkyl, and alicyclic disulfides undergo facile desulfurization to the corresponding sulfides on treatment with $(Me_2N)_3P$ or $(Et_2N)_3P$ (eq 13).[10] For example, reaction of methyl phenyl disulfide with $(Et_2N)_3P$ in benzene at rt for ~1 min furnishes methyl phenyl sulfide in 86% yield. The desulfurization process is stereospecific, in that inversion of configuration occurs at one of the carbon atoms α to the disulfide group. Thus desulfurization of *cis*-3,6-dimethoxycarbonyl-1,2-dithiane affords a quantitative yield of *trans*-2,5-dimethoxycarbonylthiolane (eq 14). It is worthy of note that the rates of these reactions are markedly enhanced by solvents of high polarity.

$$PhSSMe + (R_2N)_3P \longrightarrow PhSMe + (R_2N)_3P{=}S \qquad (13)$$

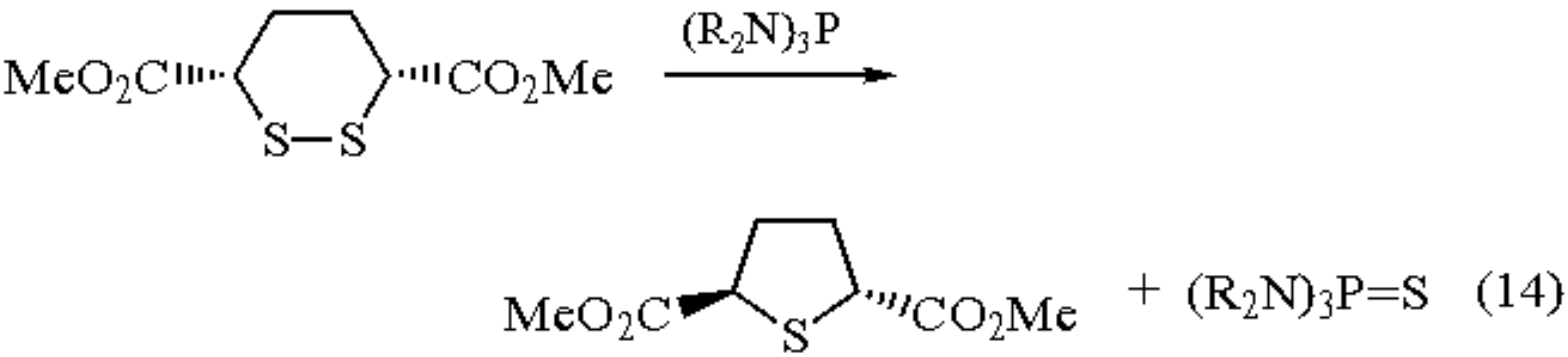

Deoxygenation of Sulfoxides and Azoxyarenes.

Sulfoxides are deoxygenated to sulfides under mild conditions with $(Me_2N)_3P$ activated with ***Iodine*** in acetonitrile (eq 15).[11] Equimolar ratios of the sulfoxide, $(Me_2N)_3P$, and I_2 are generally employed. Yields are superior to those obtained with either $(Me_2N)_3P/CCl_4$ or Ph_3P/I_2. Reaction time is reduced by addition of ***Sodium Iodide***. Azoxyarenes, such as azoxybenzene, are converted to azoarenes with this reagent combination under similar mild conditions (eq 16).[11]

$$Ph_2S{=}O + (Me_2N)_3P \xrightarrow{I_2} Ph_2S + (Me_2N)_3P{=}O \qquad (15)$$

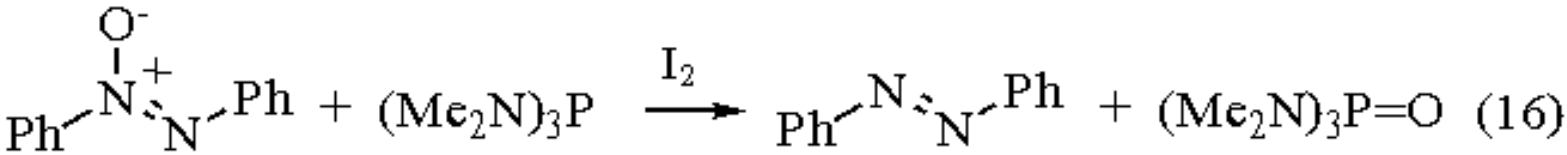

Preparation of Mixed Carbonates.

The reaction of $(Me_2N)_3P$ with alcohols and dialkyl azodicarboxylates proceeds smoothly at rt to provide mixed dialkyl carbonate esters in moderate to good yields (eq 17).[12] An advantage of the method over the chloroformate

method is the neutrality of the conditions employed. It should be noted that the related system ***Triphenylphosphine-Diethyl Azodicarboxylate*** converts alcohols into amines.

$$R^1OH + R^2O_2C\text{-}N{=}N\text{-}CO_2R^2 \xrightarrow{(R^3{}_2N)_3P} R^1O\text{-}CO\text{-}OR^2 + HCO_2R^2 + N_2 \quad (17)$$

Reduction of Ozonides.

In the synthesis of ecdysone from ergosterol, the ozonide product produced from (**5**) was reduced with $(Me_2N)_3P$ under mild conditions to the aldehyde (**6**) without isomerization (eq 18).[13] The scope of this method has not been investigated.

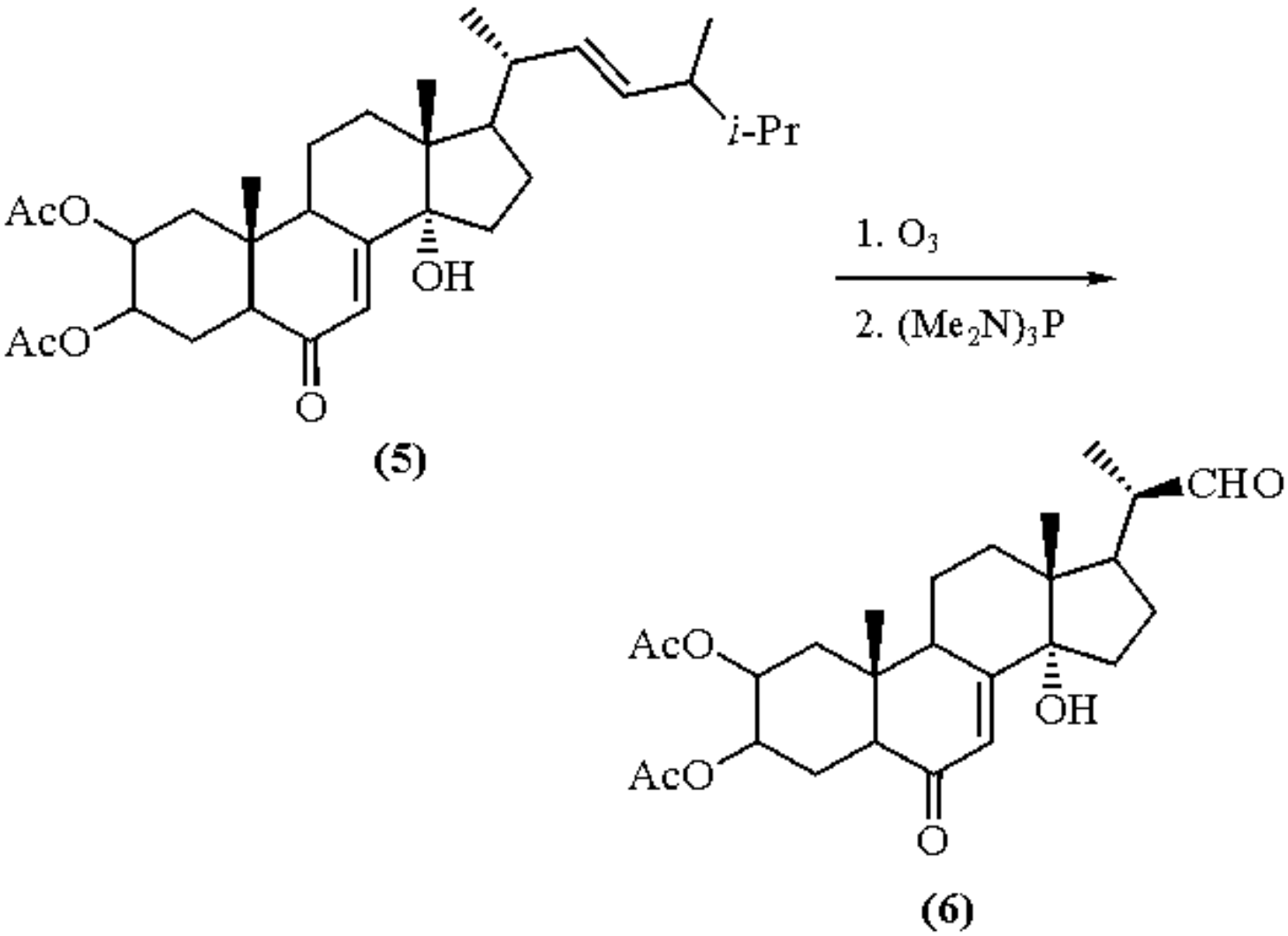

(18)

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n-Hexyllithium

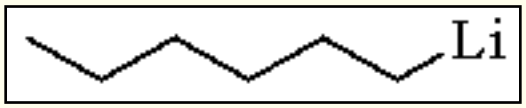

[21369-64-2] · $C_6H_{13}Li$ · *n*-Hexyllithium · (MW 92.13)

(alkylating agent for various functional groups; metalating agent of aryl and heteroaryl ring systems; slightly less reactive than *n*-butyllithium)

Physical Data: viscous liquid in pure state; *d* (2.8 M hexane solution) 0.73 g cm^{-3} (20 °C).

Solubility: sol at all concentrations in aliphatic and aromatic hydrocarbons; reacts exothermically with water and protic solvents.

Form Supplied in: hexane or toluene solutions are available at concentrations from 2 to 3 M and are nonpyrophoric.

Analysis of Reagent Purity: titration of 0.5 N *s*-butanol in toluene (10 mL) with hexyllithium via tared syringe at 20 °C using 2,2´-biquinoline as an indicator.

Handling, Storage, and Precautions: should be handled as ***n-Butyllithium***; store in a cool, dry place in a tightly sealed container under an inert atmosphere.

Alkylation.

Hexyllithium adds to various carbonyl functionalities, which include both acyclic, i.e. acetophenone,[1] and cyclic ketones,[2] leading to dihydrojasmone[3] and steroid derivatives.[4] Carboxylic acid,[5,6] lactone,[7] bicyclic lactam,[8] and ester[9] substrates were also useful. Additions to ***Carbon Dioxide***[10] and ***Carbon Monoxide***[11] were reported. Other functionalities include activated epoxides[12] and alkenes.[13] Stereoselective addition to chiral *N*-metalloimines[14] and oxazolines[15] was achieved.

Unlike *n*-butyllithium, metalations with *n*-hexyllithium have not been cited in the literature, but will eventually appear because of its availability. It is already recognized as an alternative to *n*-butyllithium

which generates hexane instead of butane and thus reduces environmental problems when used on an industrial scale. Compared to *n*-butyllithium, *n*-hexyllithium, as well as *n*-octyllithium and 2-ethylhexyllithium, are less reactive.[16]

---

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1-Hexynylcopper(I)[1]

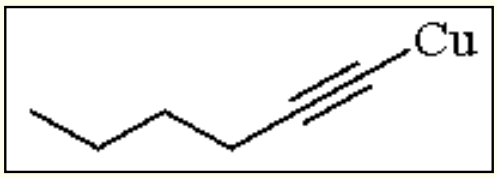

[33589-44-5] · C_6H_9Cu · 1-Hexynylcopper(I) · (MW 144.70)

(coupling agent for the delivery of the 1-hexynyl group to electrophiles,[2] both as such and in the form of higher order lithioorganocuprates;[3] non-transferable dummy ligand used in mixed lithioorganocuprates;[4] dipolarophile used in cycloaddition with nitrile oxides[5])

Physical Data: yellow solid; mp 140-150 °C;[6] IR (KBr) 2962, 2937, 2895, 2870, 1930, 1471, 1455, 1430, 1376, 1357, 1316, 1240, 1210, 1107, 1006, 918, 894, 781, 720, 518 cm^{-1}.[7]

Solubility: sol pyridine, THF, ether; insol water. *Drying:* dried in vacuo at 50 °C.

Preparative Methods: addition of ***Copper(I) Chloride*** to an ammoniacal solution of 1-hexyne;[8] addition of 1-hexyne to a ***Copper(II) Sulfate-Hydroxylamine*** hydrochloride mixture;[2] addition of ***Copper(I) Iodide*** to 1-lithiohexyne.[4]

Handling, Storage, and Precautions: copper(I) salts are potentially explosive when dry; use in a fume hood.

Coupling Agent.

Hexynylcopper combines with acyl halides to yield alkynyl ketones in high yield,[9] the reagent being more efficient than the corresponding organolithium and -magnesium species[10] (see also ***Phenylethynylcopper(I)*** and ***1-Pentynylcopper(I)***). Coupling can also be achieved with aryl,[2,11-13] vinyl,[14] and alkyl halides,[8,15] and with activated amines.[16] The presence of competing functionality usually presents no problem due to the mildly nucleophilic nature of the reagent (eq 1).[13]

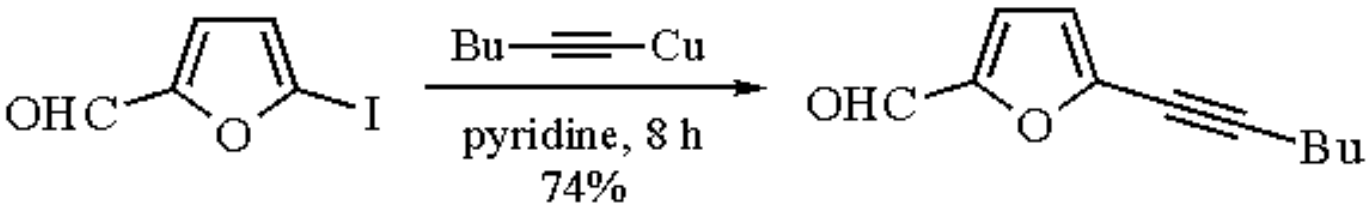

(1)

Lithioorganocuprates.

Hexynylcopper can serve as a nontransferable dummy ligand when incorporated into mixed lithioorganocuprates[4,17-19] (see also ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide*** and ***(3-Methoxy-3-methyl-1-butynyl)copper(I)***). Thus, generation of a mixed vinylic cuprate (eq 2) allows facile vinylation of allyl bromides to proceed.[4]

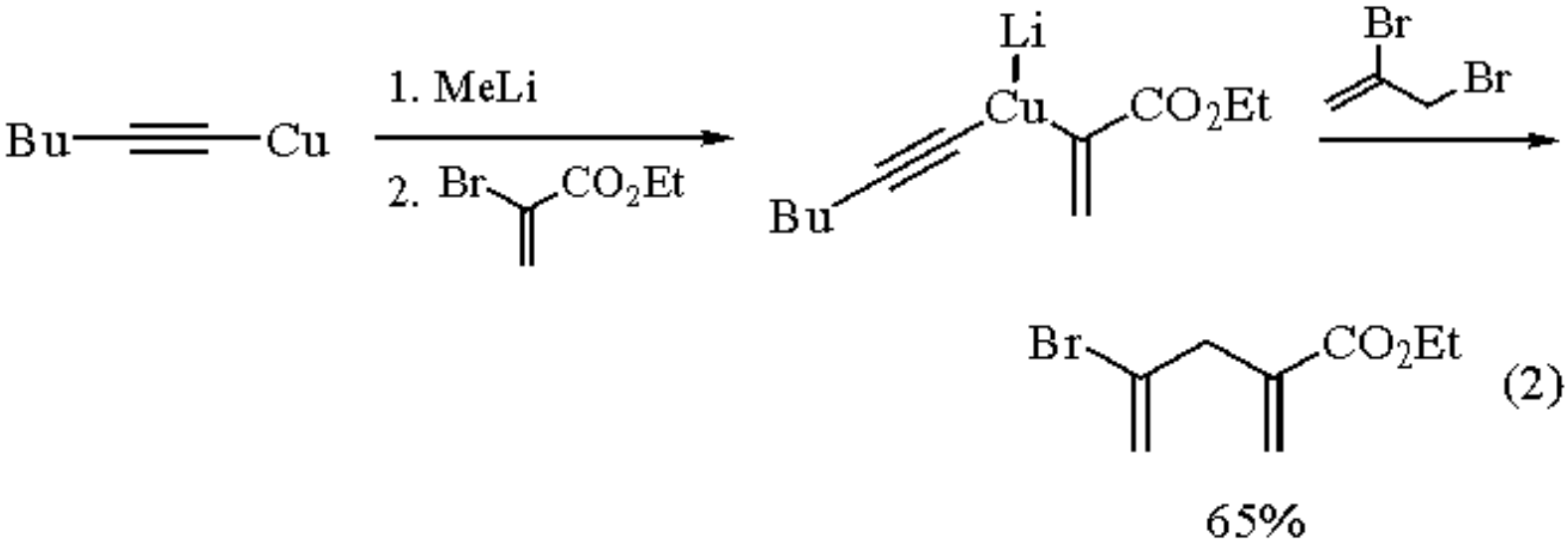

Chemoselectivity is often observed in the delivery of the transferable group.[17] Addition of a *s*-alkoxy transferable group to cinnamaldehyde is reported to proceed with exclusive 1,2-selectivity, and in good yield.[18] Lithium bis(hexynyl)copper effectively delivers one hexynyl group to suitable electrophiles.[20,21] Exclusive 1,2-addition to enals has been reported,[20] and in the addition to iodoalkoxyallenes (eq 3), a good yield of the corresponding S_N2' adduct is obtained.[21]

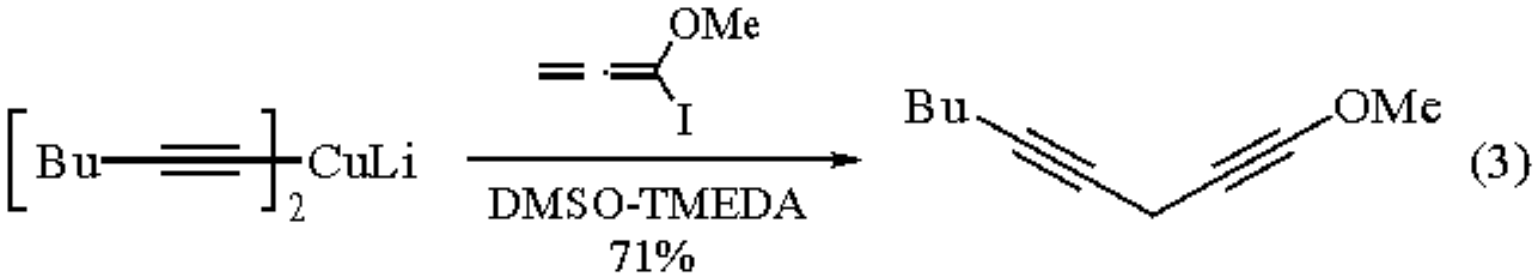

Higher Order Homocuprates.

Treatment of hexynyllithium with ***Copper(I) Iodide*** is reported to generate the higher order homocuprate indicated (eq 4).[3,22] Regardless of composition, this species selectively and efficiently directs 1,2-addition to cyclohexenones in yields ranging from 85 to 95%.[3]

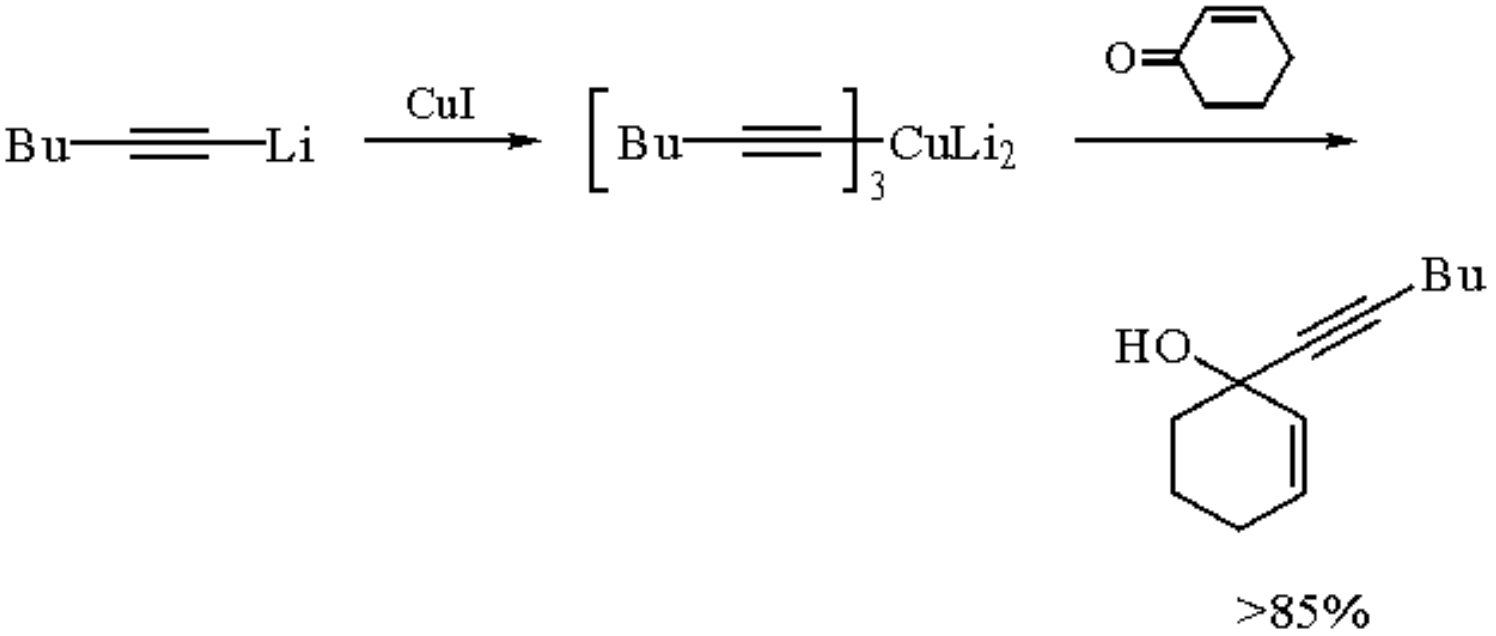

(4)

Cycloaddition Reactions.

Hexynylcopper has also been used as a dipolarophile in the preparation of azetidin-2-ones (eq 5).[5] The cycloaddition is of note in that *cis:trans* adducts are formed in a 12:1 ratio (R = Ph), whereas using ***Phenylethynylcopper(I)*** as the dipolarophile the ratio is close to 1:1.

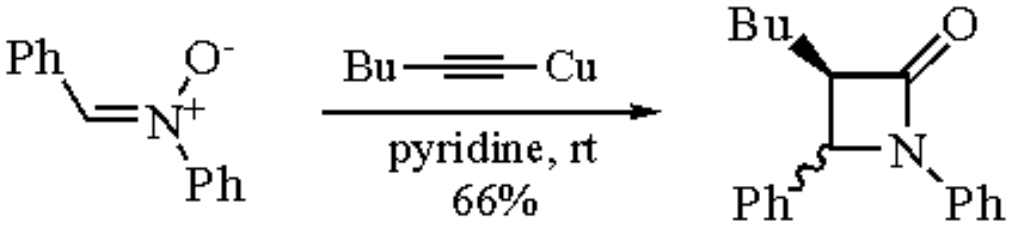

(5)

Related Reagents.

Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate.

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Hydrazine[1]

N_2H_4

(N_2H_4)

[302-01-2] · H_4N_2 · Hydrazine · (MW 32.06) (hydrate)

[10217-52-4] (monohydrate)

[7803-57-8] · H_5N_2O · Hydrazine Monohydrate · (MW 49.07) (monohydrochloride)

[2644-70-4] · ClH_5N_2 · Hydrazine Monohydrochloride · (MW 68.52) (dihydrochloride)

[5341-61-7] · $Cl_2H_6N_2$ · Hydrazine Dihydrochloride · (MW 104.98) (sulfate)

[10034-93-2] · $H_6N_2O_4S$ · Hydrazine Sulfate · (MW 130.15)

(reducing agent used in the conversion of carbonyls to methylene compounds;[1] reduces alkenes,[9] alkynes,[9] and nitro groups;[14] converts α,β-epoxy ketones to allylic alcohols;[32] synthesis of hydrazides;[35] synthesis of dinitrogen containing heterocycles[42-46])

Physical Data: mp 1.4 °C; bp 113.5 °C; *d* 1.021 g cm^{-3}.

Solubility: sol water, ethanol, methanol, propyl and isobutyl alcohols.

Form Supplied in: anhydrate, colorless oil that fumes in air; hydrate and monohydrate, colorless oils; monohydrochloride, dihydrochloride, sulfate, white solids; all widely available.

Analysis of Reagent Purity: titration.[1]

Purification: anhydrous hydrazine can be prepared by treating hydrazine hydrate with BaO, $Ba(OH)_2$, CaO, NaOH, or Na. Treatment with sodamide has been attempted but this yields diimide, NaOH, and ammonia. An excess of sodamide led to an explosion at 70 °C. The hydrate can be treated with boric acid to give the hydrazinium borate, which is dehydrated by heating. Further heating gives diimide.[1]

Handling, Storage, and Precautions: caution must be taken to avoid prolonged exposure to vapors as this can cause serious damage to the eyes and lungs. In cases of skin contact, wash the affected area immediately as burns similar to alkali contact can occur. Standard protective clothing including an ammonia gas mask are recommended. The vapors of hydrazine are flammable (ignition temperature 270 °C

in presence of air). There have been reports of hydrazine, in contact with organic material such as wool or rags, burning spontaneously. Metal oxides can also initiate combustion of hydrazine. Hydrazine and its solutions should be stored in glass containers under nitrogen for extended periods. There are no significant precautions for reaction vessel type with hydrazine; however, there have been reports that stainless steel vessels must be checked for significant oxide formation prior to use. Use in a fume hood.

Reductions.

The use of hydrazine in the reduction of carbonyl compounds to their corresponding methylene groups via the Wolff-Kishner reduction has been covered extensively in the literature.[1] The procedure involves the reaction of a carbonyl-containing compound with hydrazine at high temperatures in the presence of a base (usually ***Sodium Hydroxide*** or ***Potassium Hydroxide***). The intermediate hydrazone is converted directly to the fully reduced species. A modification of the original conditions was used by Paquette in the synthesis of (±)-isocomene (eq 1).[2]

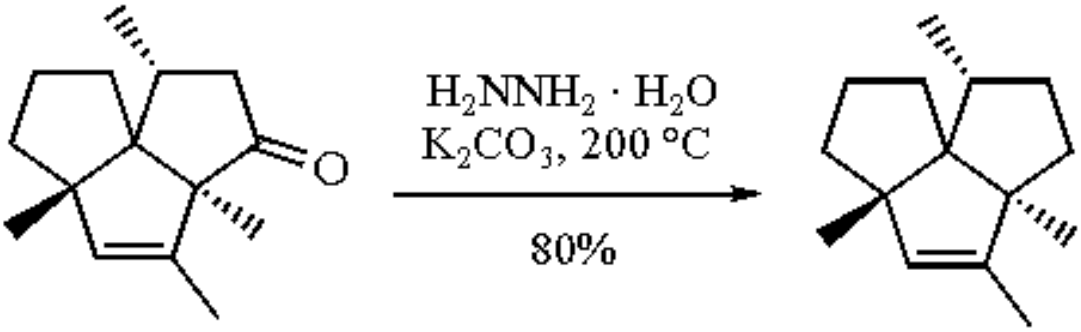

(1)

Unfortunately, the original procedure suffers from the drawback of high temperatures, which makes large-scale runs impractical. The Huang-Minlon modification[3] of this procedure revolutionized the reaction, making it usable on large scales. This procedure involves direct reduction of the carbonyl compound with hydrazine hydrate in the presence of sodium or potassium hydroxide in diethylene glycol. The procedure is widely applicable to a variety of acid-labile substrates but caution must be taken where base-sensitive functionalities are present. This reaction has seen widespread use in the preparation of a variety of compounds. Other modifications[4] have allowed widespread application of this useful transformation. Barton and co-workers further elaborated the Huang-Minlon modifications by using anhydrous hydrazine and ***Sodium*** metal to ensure totally anhydrous conditions. This protocol allowed the reduction of sterically hindered ketones, such as in the deoxygenation of 11-keto steroids (eq 2).[4a] Cram utilized dry DMSO and ***Potassium t-Butoxide*** in the reduction of hydrazones. This procedure is limited in that the hydrazones must be prepared and isolated prior to reduction.[4b] The Henbest modification[4c] involves the utilization of dry toluene and potassium *t*-butoxide. The advantage of this procedure is the low temperatures needed (110 °C) but it suffers from the drawback that, again, preformed hydrazones must be used. Utilizing modified Wolff-Kishner conditions, 2,4-dehydroadamantanone is converted to 8,9-dehydroadamantane (eq 3).[5]

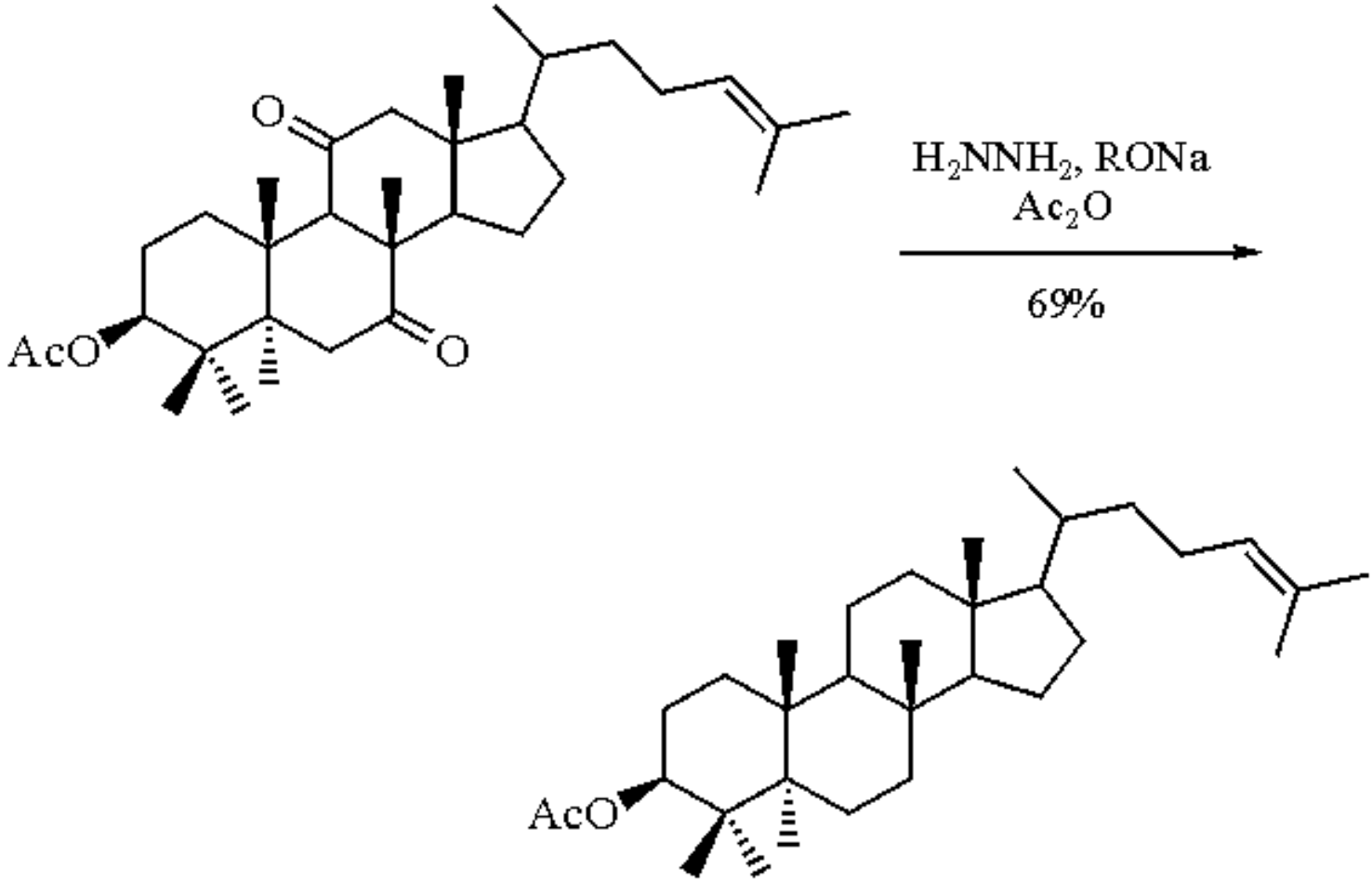

(2)

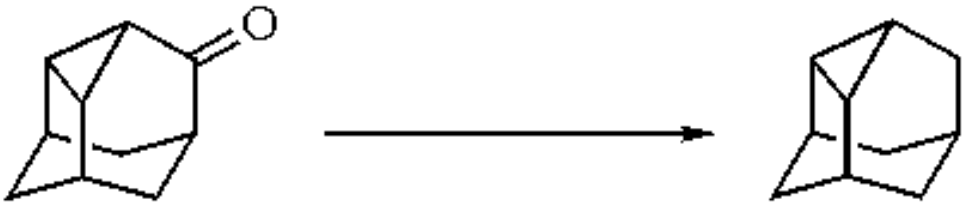

(3)

Hindered aldehydes have been reduced using this procedure.[6] This example is particularly noteworthy in that the aldehyde is sterically hindered and resistant to other methods for conversion to the methyl group.[6a] Note also that the acetal survives the manipulation (eq 4). The reaction is equally useful in the reduction of semicarbazones or azines.

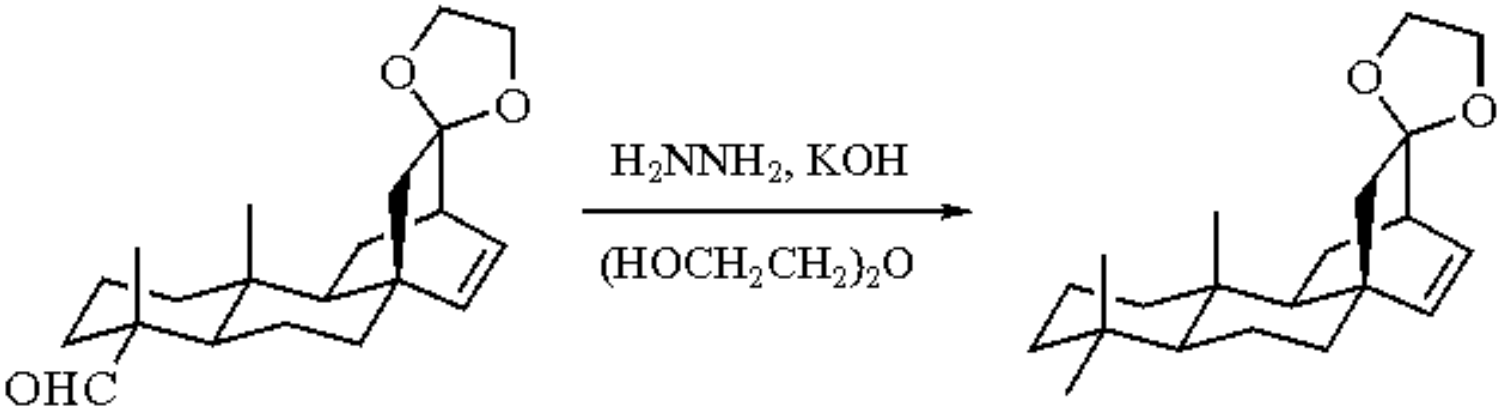

(4)

In a similar reaction, hydrazine has been shown to desulfurize thioacetals, cyclic and acyclic, to methylene groups (eq 5). The reaction is run in diethylene glycol in the presence of potassium hydroxide, conditions similar to the Huang-Minlon protocol. Yields are generally good (60-95%). In situations where base sensitivity is a concern, the potassium hydroxide may be omitted. Higher temperatures are then required.[7]

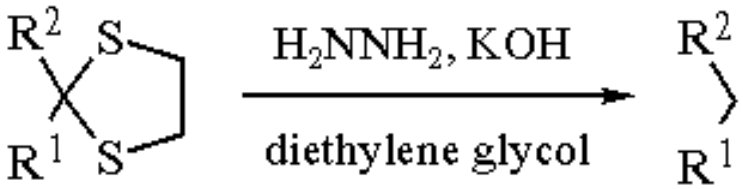

(5)

Hydrazine, via in situ copper(II)-catalyzed conversion to ***Diimide***, is a useful reagent in the reduction of carbon and nitrogen multiple bonds. The reagent is more reactive to symmetrical rather than polar multiple bonds (C=N, C=O, N=O, S=O, etc.)[8] and reviews of diimide reductions are available.[9] The generation of diimide from hydrazine has been well documented and a wide variety of oxidizing agents can be employed: oxygen (air),[10] ***Hydrogen Peroxide***,[10] ***Potassium Ferricyanide***,[11] ***Mercury(II) Oxide***,[11] ***Sodium Periodate***,[12] and hypervalent ***Iodine***[13] have all been reported. The reductions are stereospecific, with addition occurring *cis* on the less sterically hindered face of the substrate.

Other functional groups have been reduced using hydrazine. Nitroarenes are converted to anilines[14] in the presence of a variety of catalysts such as ***Raney Nickel***,[14a,15] platinum,[14a] ruthenium,[14a] ***Palladium on Carbon***,[16] β-iron(III) oxide,[17] and iron(III) chloride with activated carbon.[18] Graphite/hydrazine reduces aliphatic and aromatic nitro compounds in excellent yields.[19] Halonitrobenzenes generally give excellent yields of haloanilines. In experiments where palladium catalysts are used, significant dehalogenation occurs to an extent that this can be considered a general dehalogenation method.[20] Oximes have also been reduced.[21]

Hydrazones.

Reaction of hydrazine with aldehydes and ketones is not generally useful due to competing azine formation or competing Wolff-Kishner reduction. Exceptions have been documented. Recommended conditions for hydrazone preparation are to reflux equimolar amounts of the carbonyl component and hydrazine in *n*-butanol.[22,23] A more useful method for simple hydrazone synthesis involves reaction of the carbonyl compound with dimethylhydrazine followed by an exchange reaction with hydrazine.[24] For substrates where an azine is formed, the hydrazone can be prepared by refluxing the azine with anhydrous hydrazine.[25] *gem*-Dibromo compounds have been converted to hydrazones by reaction with hydrazine (eq 6).[26]

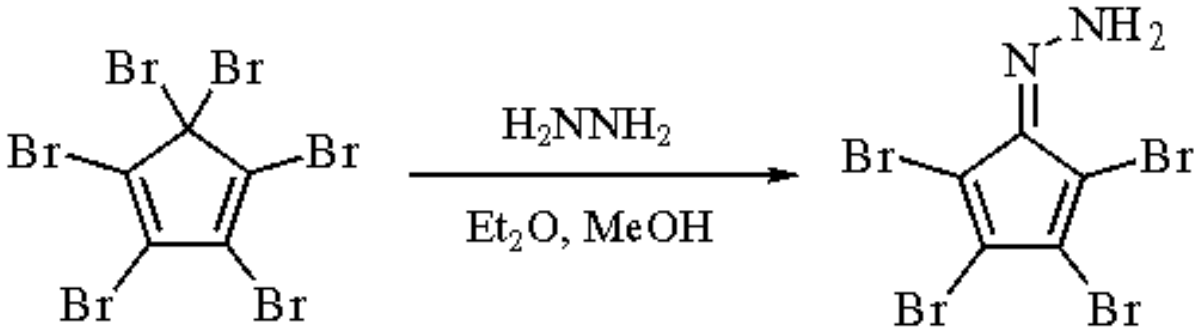

(6)

Hydrazones are useful synthetic intermediates and have been converted to vinyl iodides[27] and vinyl selenides (eq 7) (see also ***p-Toluenesulfonylhydrazide***).[28]

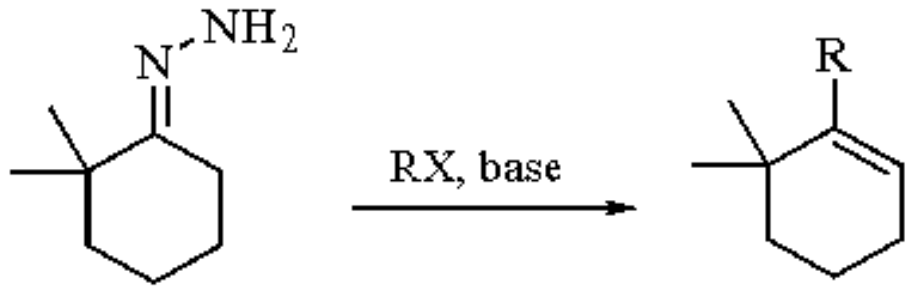

(7)

R = I, PhSe; RX = I_2, PhSeBr
base = pentaalkylguanidine, triethylamine

Diazomalonates have been prepared from dialkyl mesoxylates via the ***Silver(I) Oxide***-catalyzed decomposition of the intermediate hydrazones.[29] Monohydrazones of 1,2-diketones yield ketenes after mercury(II) oxide oxidation followed by heating.[30] Dihydrazones of the same compounds give alkynes under similar conditions.[31]

Wharton Reaction.

α,β-Epoxy ketones and aldehydes rearrange in the presence of hydrazine, via the epoxy hydrazone, to give the corresponding allylic alcohols. This reaction has been successful in the steroid field but, due to low yields, has seen limited use as a general synthetic tool. Some general reaction conditions have been set. If the intermediate epoxy hydrazone is isolable, treatment with a strong base (potassium *t*-butoxide or ***Potassium Diisopropylamide***) gives good yields, whereas ***Triethylamine*** can be used with nonisolable epoxy hydrazones (eq 8).[32]

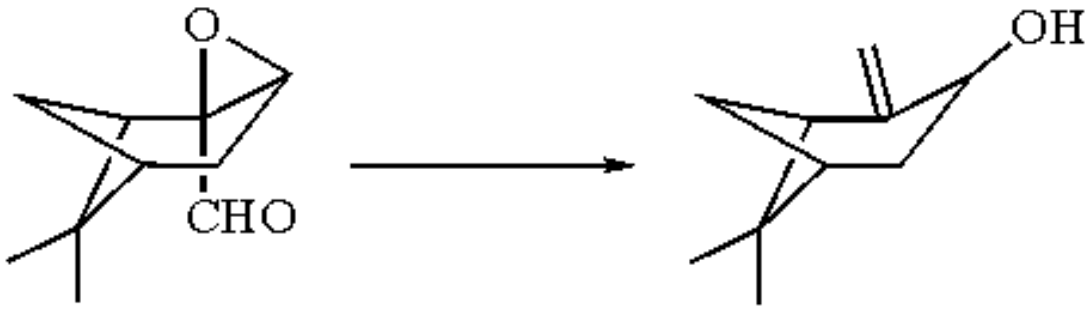

(8)

Some deviations from expected Wharton reaction products have been reported in the literature. Investigators found that in some specific cases, treatment of α,β-epoxy ketones under Wharton conditions gives cyclized allylic alcohols (eq 9). No mechanistic interpretation of these observations has been offered. Related compounds have given the expected products, and it therefore appears this phenomenon is case-specific.[33]

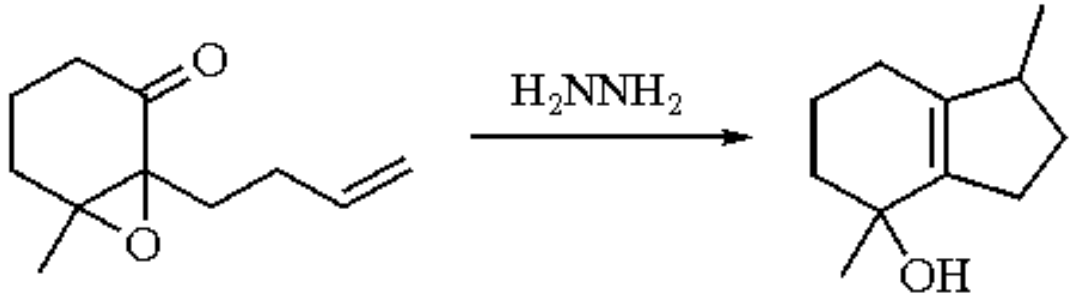

(9)

Cyclic α,β-epoxy ketones have been fragmented upon treatment with hydrazine to give alkynic aldehydes.[34]

Hydrazides.

Acyl halides,[35] esters, and amides react with hydrazine to form hydrazides which are themselves useful synthetic intermediates. Treatment of the hydrazide with nitrous acid yields the acyl azide which, upon heating, gives isocyanates (Curtius rearrangement).[36] Di- or trichlorides are obtained upon reaction with ***Phosphorus(V) Chloride***.[37] Crotonate and other esters have been cleaved with hydrazine to liberate the free alcohol (eq 10).[38]

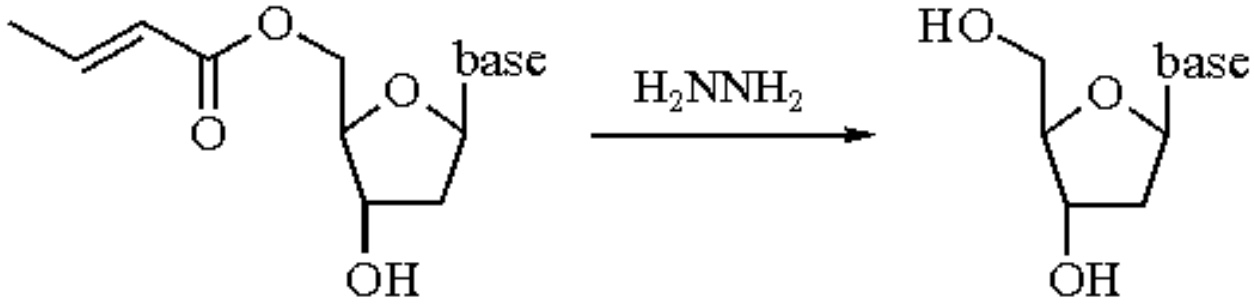

(10)

Hydrazine deacylates amides (Gabriel amine synthesis) via the Ing-Manske protocol.[39] This procedure has its limitations, as shown in the synthesis of penicillins and cephalosporins where it was observed that hydrazine reacts with the azetidinone ring. In this case, ***Sodium Sulfide*** was used.[40]

Heterocycle Synthesis.

The reaction of hydrazine with α,β-unsaturated ketones yields pyrazoles.[41,42] Although the products can be isolated as such, they are useful intermediates in the synthesis of cyclopropanes upon pyrolysis of cyclopropyl acetates after treatment with ***Lead(IV) Acetate*** (eq 11).

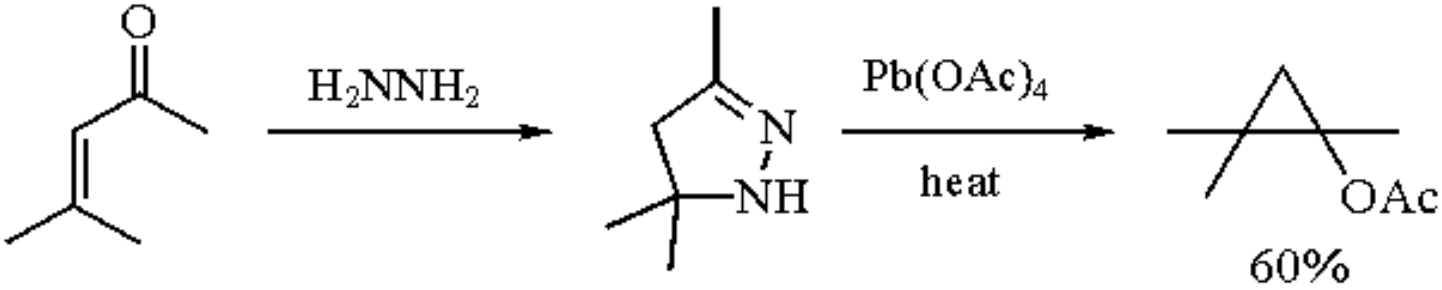

(11)

3,5-Diaminopyrazoles were prepared by the addition of hydrazine (eq 12), in refluxing ethanol, to benzylmalononitriles (42-73%).[43] Likewise, hydrazine reacted with 1,1-diacetylcyclopropyl ketones to give β-ethyl-1,2-azole derivatives. The reaction mixture must have a nucleophilic component (usually the solvent, i.e. methanol) to facilitate the opening of the cyclopropane ring. Without this, no identifiable products are obtained (eq 13).[44]

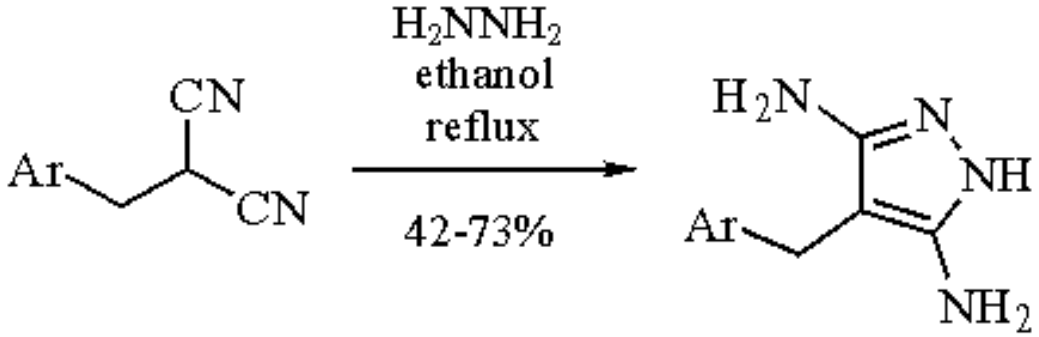

(12)

Ar = Ph, 4-MeC6H4, 3-NO2C6H4

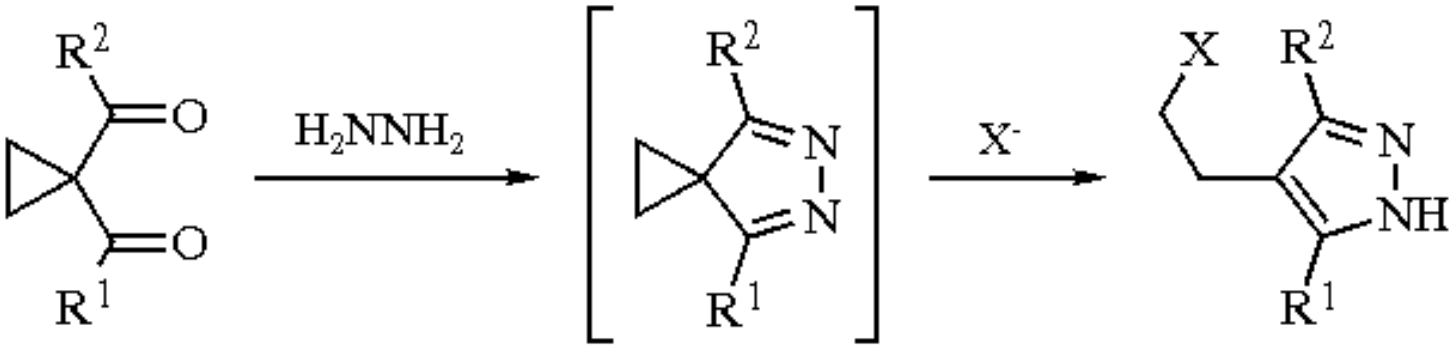

(13)

R1, R2 = Me, Ph
X = Cl, Br, OMe, OEt, OPh, OAc, CN, etc.

In an attempt to reduce the nitro group of nitroimidazoles, an unexpected triazole product was obtained in 66% yield. The suggested mechanism involves addition of the hydrazine to the ring, followed by fragmentation and recombination to give the observed product (eq 14).[45]

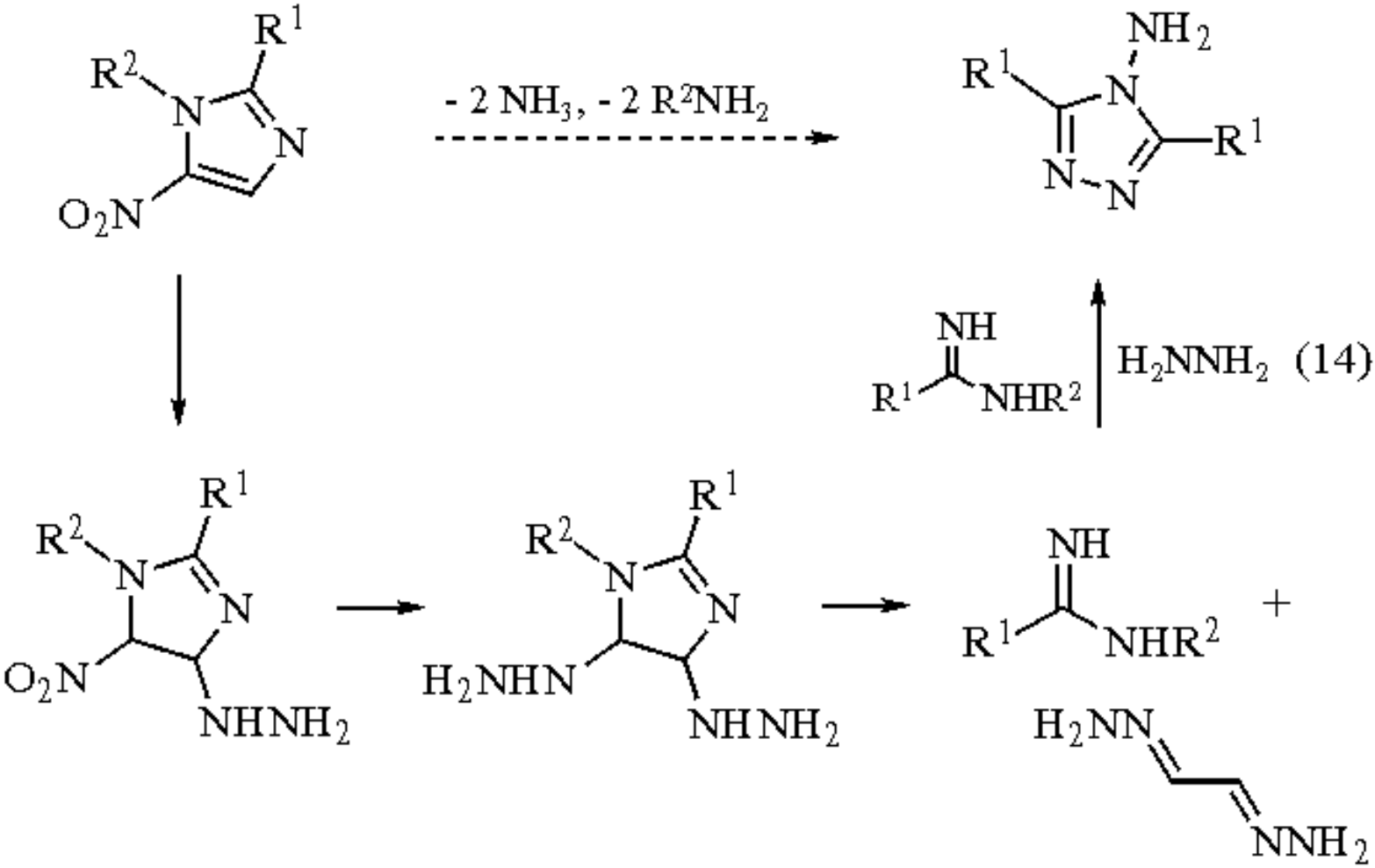

Finally, hydrazine dihydrochloride reacted with 2-alkoxynaphthaldehydes to give a product which resulted from an intramolecular [3+ + 2] criss-cross cycloaddition (42-87%) (eq 15).[46]

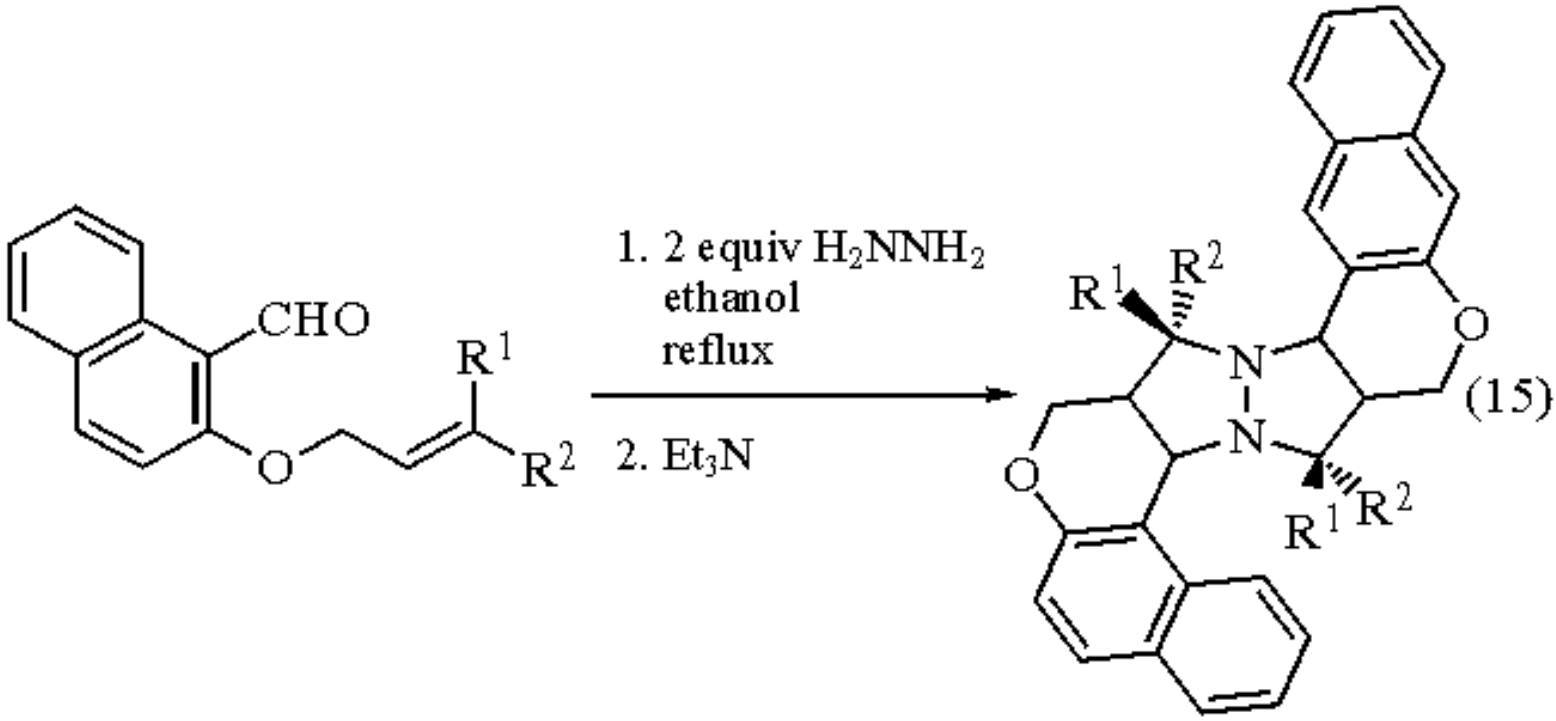

Peptide Synthesis.

Treatment of acyl hydrazides with nitrous acid leads to the formation of acid azides which react with amines to form amides in good yield. This procedure has been used in peptide synthesis, but is largely superseded by coupling reagents such as ***1,3-Dicyclohexylcarbodiimide***.[47]

---

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8-Hydrazinoquinoline

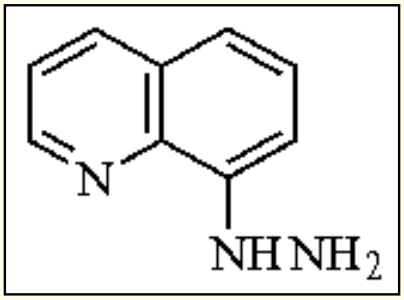

[14148-42-6] · $C_9H_9N_3$ · 8-Hydrazinoquinoline · (MW 159.21)

(Fischer indole synthesis: pyrido[3,2-*g*]indoles)

Alternate Name: 8-HQ.

Physical Data: pale yellow solid; mp 63.5-64 °C.

Solubility: sol ether, dichloromethane, ethanol.

Preparative Methods: the original preparation of the reagent involved the diazotization of commercially available 8-aminoquinoline followed by reduction with tin(II) chloride.[1] An improved one-step method has been developed which starts with the less expensive 8-hydroxyquinoline.[2] Sulfur dioxide (10 g) is dissolved in hydrazine hydrate (80 mL), 8-hydroxyquinoline (10.16 g) is added and the mixture is refluxed for 7 d. Every 48 h, EtOH (10 mL) is added to dissolve any starting material which may have sublimed into the condenser. The mixture is cooled, 2 M NaOH (100 mL) is added, and the resulting emulsion is extracted with $CHCl_3$ (4 × 75 mL). The combined organic layers are washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The residue crystallizes upon standing and may be recrystallized from CH_2Cl_2 and pentane to afford 8.7 g (78%) of 8-HQ as pale yellow needles (eq 1).

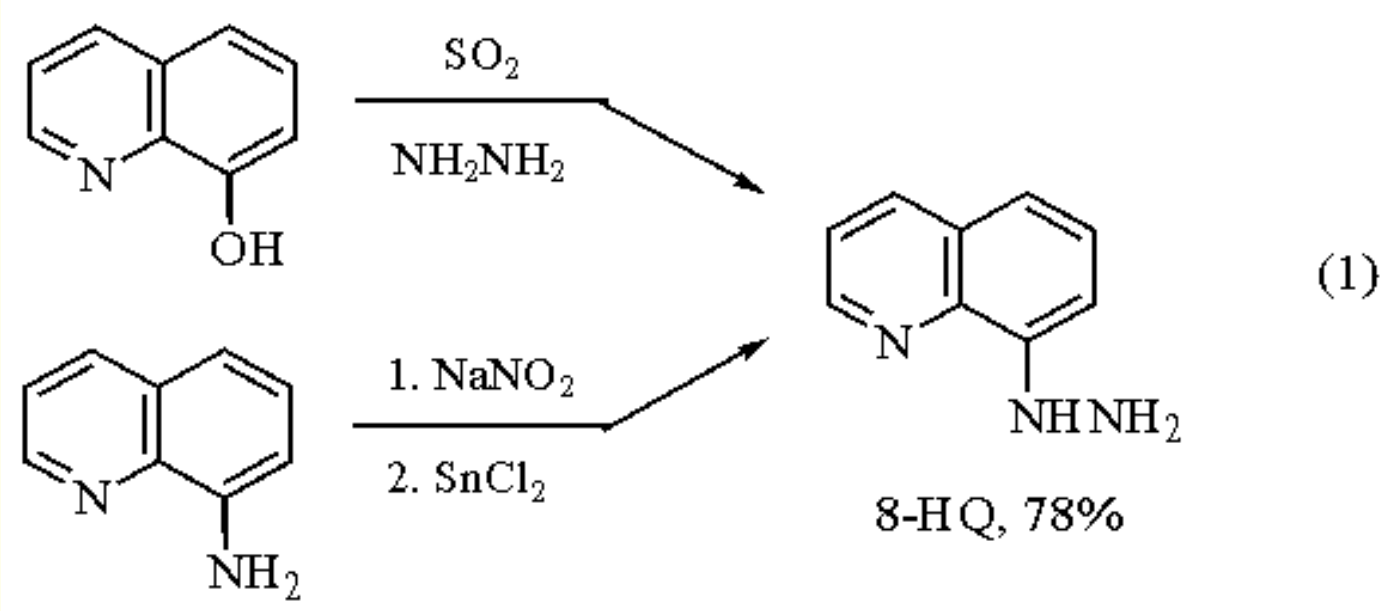

Handling, Storage, and Precautions: the reagent is sensitive to air and light and is best kept under an inert atmosphere at 0 °C in the dark. Slow decomposition occurs with time and the material turns brown. In the early stages it can be repurified by recrystallization. Use in a fume hood.

Pyrido[3,2-*g*]indole Synthesis.

8-Hydrazinoquinoline provides a very useful method for the direct introduction of the pyrido[3,2-*g*]indole subunit. Other isomers of 8-HQ behave in an analogous fashion.[3] Treatment of 5,6,7,8-tetrahydro-8-quinolone with 8-HQ in EtOH results in precipitation of the hydrazone in essentially pure from. This material may then be heated with ***Polyphosphoric Acid*** (PPA), basified, and extracted with CH_2Cl_2 to provide a dihydrodipyridocarbazole (eq 2).[2]

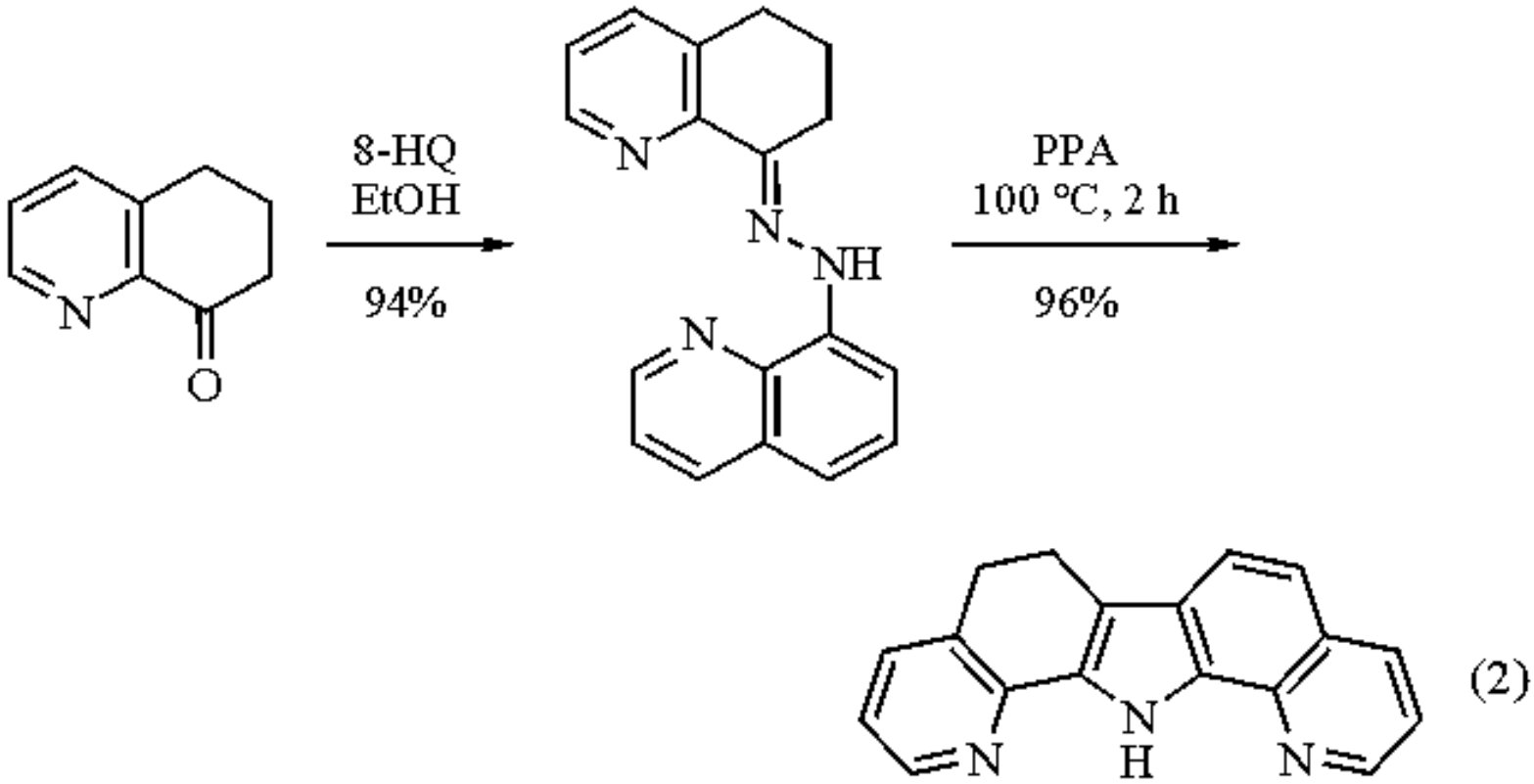

The reaction also works with appropriate diketones to introduce two pyridoindole subunits. If the reactants are only combined in equimolar amounts, an intermediate monoketone derivative may be obtained (eq 3).[2]

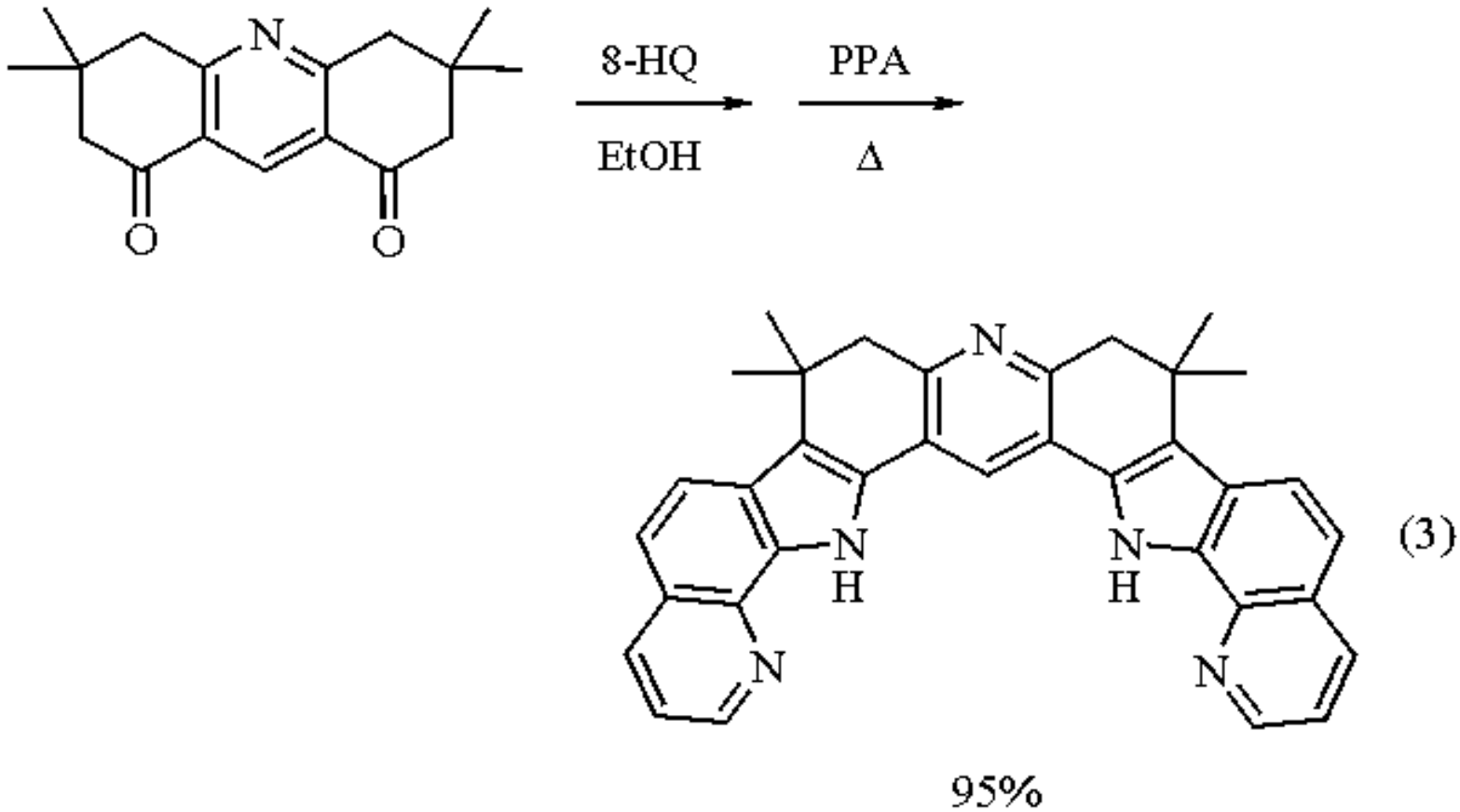

Related Reagents.

Acetone Hydrazone; ***Hydrazine***; ***Phenylhydrazine***; ***Polyphosphoric Acid***.

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Hydrazoic Acid[1]

HN_3

[7782-79-8] · HN_3 · Hydrazoic Acid · (MW 43.04)

(adds electrophilically to alkenes, alkynes, and related conjugated systems;[1c] converts carboxylic acids to amines (Schmidt reaction)[1] and alcohols to azides;[11a] cleaves epoxides;[17] aminates arenes;[19] affords sulfoximines from sulfoxides;[21c] reacts with a variety of other functional groups[1a])

Solubility: sol halogenated hydrocarbons, Et_2O, C_6H_6.

Preparative Methods: treatment of ***Sodium Azide*** with ***Sulfuric Acid*** or ***Polyphosphoric Acid***;[1a,2,3] hydrolysis of ***Azidotrimethylsilane***.[4]

Handling, Storage, and Precautions: highly toxic; extremely explosive; use in a fume hood.

Addition to Unsaturated Systems.

Being a moderately weak acid (pK_a = 4.69 at 25 °C[5]), HN_3 has not been found to undergo electrophilic addition to alkenes except for phenyl-substituted cyclopropenes (eq 1)[6] and electron-rich alkenes, such as vinyl ethers (eqs 2 and 3).[3] With Lewis acid catalysis, it undergoes addition to styrenes and 1,1-dialkylalkenes (eq 4).[3,7]

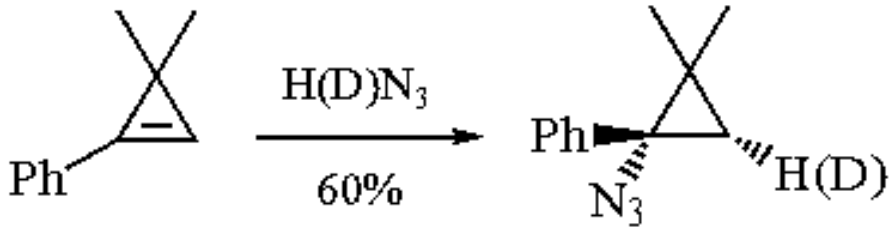

(1)

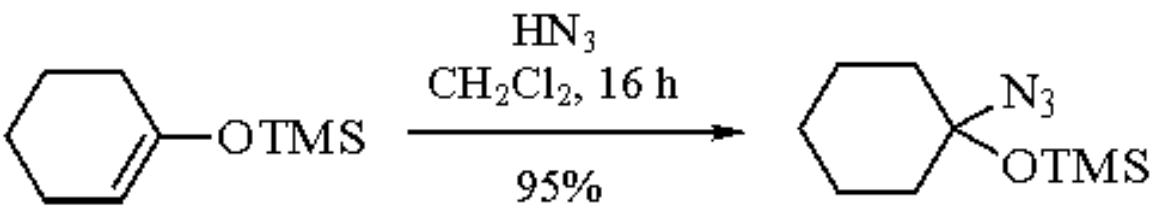

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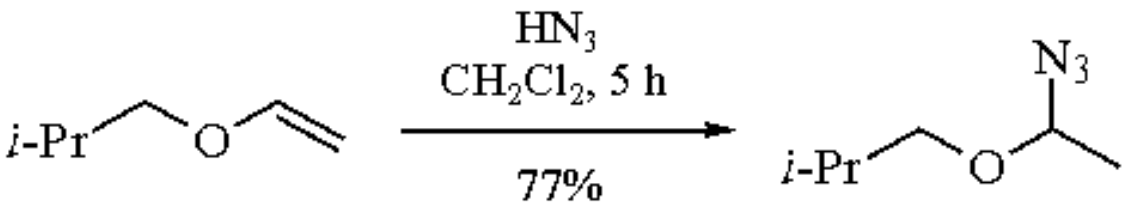

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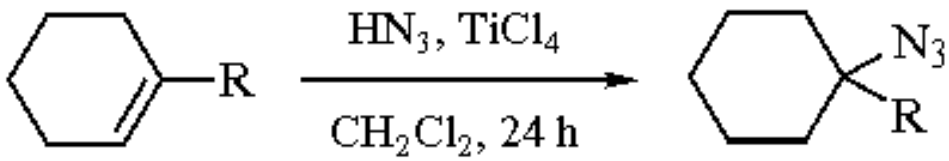

(4)

R = Ph, 73%
R = Me, 39%

Protic acid catalyzed additions of HN_3 to alkenes have also been effected using ***Trifluoroacetic Acid***, ***Trichloroacetic Acid***, or ***Phosphoric Acid***.[8] However, azides readily undergo decomposition in the presence of Lewis acids and strong protic acids.[8b,9] Moreover, the necessity of generating and handling the highly toxic and explosive HN_3 limits the attractiveness of these methods. Recently it has been reported that silica gel and alumina mediate the addition of HN_3 to styrenes, 1,3-dienes (eq 5), and 1,1-dialkylalkenes (eq 6) in the presence of an acid catalyst to give good to excellent yields of alkyl azides.[4] Under these conditions, HN_3 can be conveniently prepared in situ by hydrolysis of ***Azidotrimethylsilane*** over silica gel or alumina.

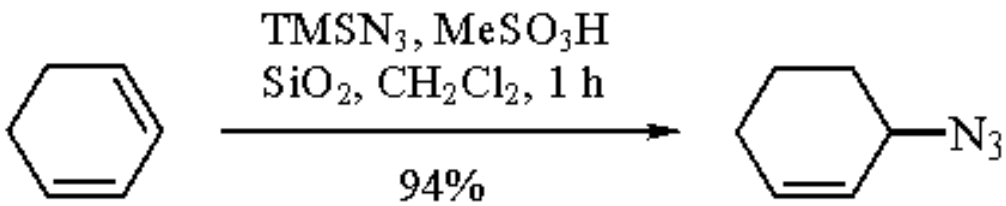

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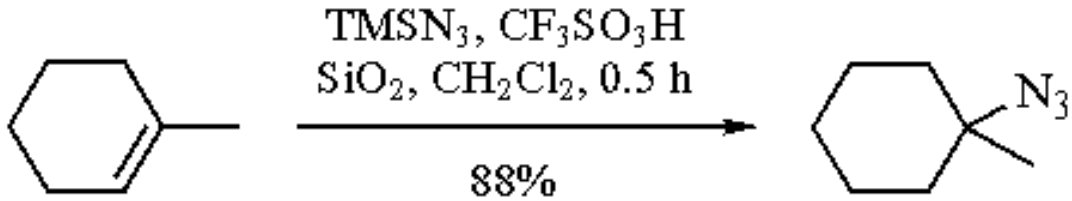

(6)

HN_3 adds to enones and related conjugated systems (eq 7);[1c,10] however, addition does not occur to a number of enones having a phenyl substituent at the β-position.[10]

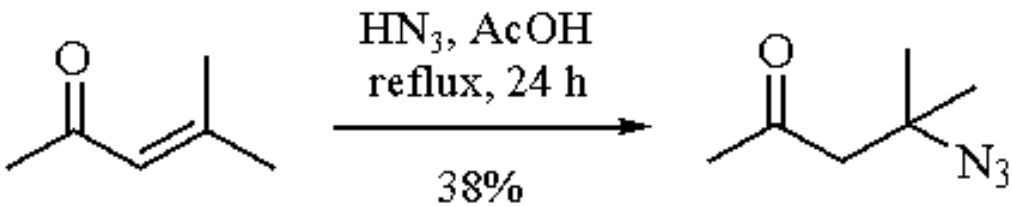

(7)

Alkynes commonly undergo 1,3-dipolar addition of HN_3 to afford triazoles; however, addition leads to azides in

exceptional cases.[1c]

Schmidt Reaction.

Acid-catalyzed reaction of HN_3 with carboxylic acids gives an amine with one less carbon atom.[1] Typically the procedure involves generating HN_3 in situ with NaN_3 and excess H_2SO_4 in the presence of the substrate. Although preformed HN_3 may be used, the presence of an acid catalyst is still required. The reaction is quite general, and the yields are often high for a variety of carboxylic acids, including aliphatic, aromatic, and sterically hindered systems (eq 8). Conditions can be controlled so that dicarboxylic acids yield either mono- or diamines as products.

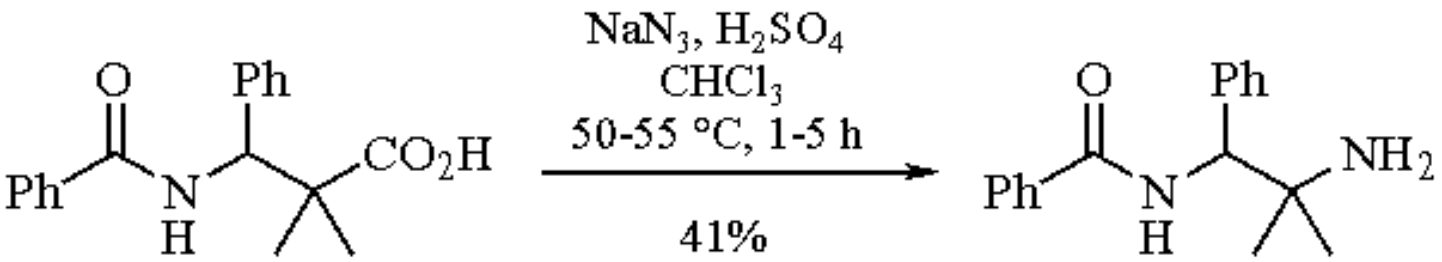

(8)

Ketones and aldehydes similarly react with HN_3 in the presence of H_2SO_4. Whereas reaction with aldehydes typically gives nitriles, ketones afford amides (eq 9). With 2 or more equiv of HN_3, tetrazole products may be formed (eq 10), while imino esters are obtained in the presence of alcohols (eq 11). The different products arise through capture of a common intermediate.

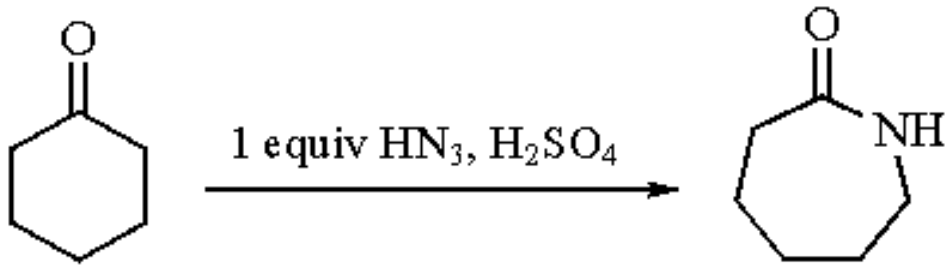

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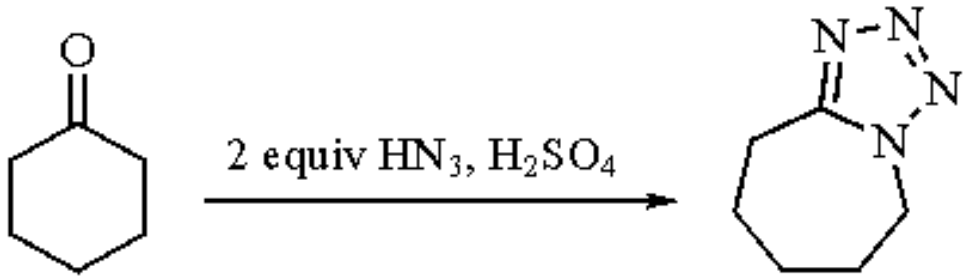

(10)

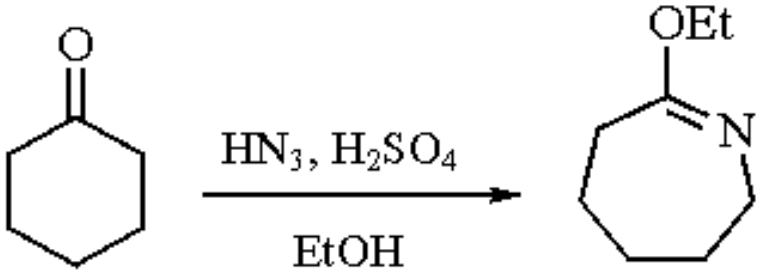

(11)

Reaction with Alcohols.

Benzylic alcohols react with HN_3 in the presence of an acid catalyst to give the corresponding benzylic azides.[11] Typically HN_3 is generated in situ through treatment of NaN_3 with excess H_2SO_4, and the acid further catalyzes the substitution reaction. Moderate to good yields of triarylmethyl azides are formed from the corresponding triarylcarbinols, but diarylcarbinols such as 9-hydroxyfluorene give poorer yields due to further reaction of the azide with the acid catalyst. This problem can be circumvented by using the weaker acid ***Trichloroacetic Acid*** as catalyst (eq 12).[8b,12] Tertiary alcohols are converted to tertiary azides by HN_3 in the presence of H_2SO_4 as catalyst (eq 13).[13]

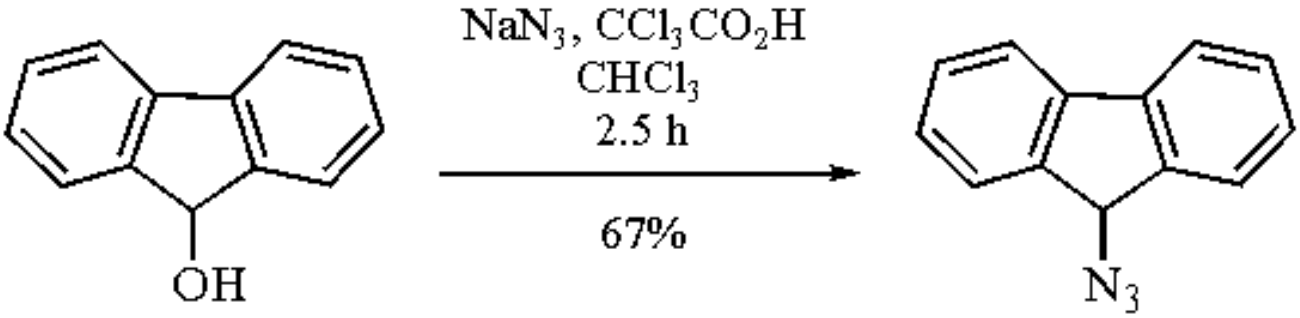

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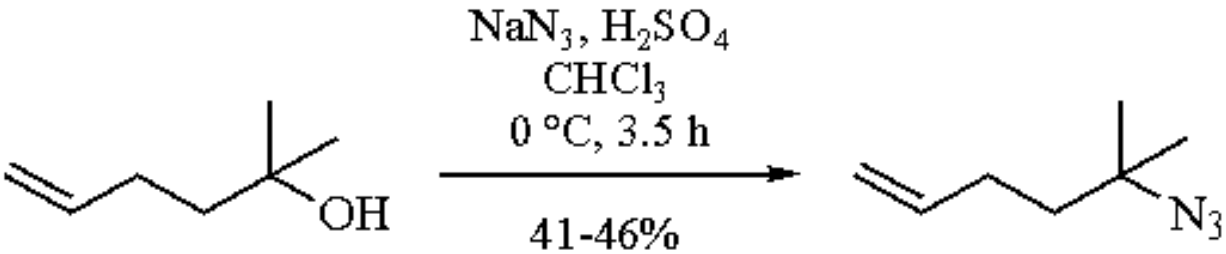

(13)

Acidic conditions in the substitution process can be avoided by subjecting primary and secondary alcohols to Mitsonobu conditions in the presence of HN_3.[14] Azides, with inverted stereochemistry at the carbon center, are formed in high yields (eq 14). A procedure has been developed in which alcohols are converted to azides via the Mitsonobu reaction and are then reduced to amines without prior isolation of the azide.[15] This process allows for a one-pot conversion of alcohols to amines.

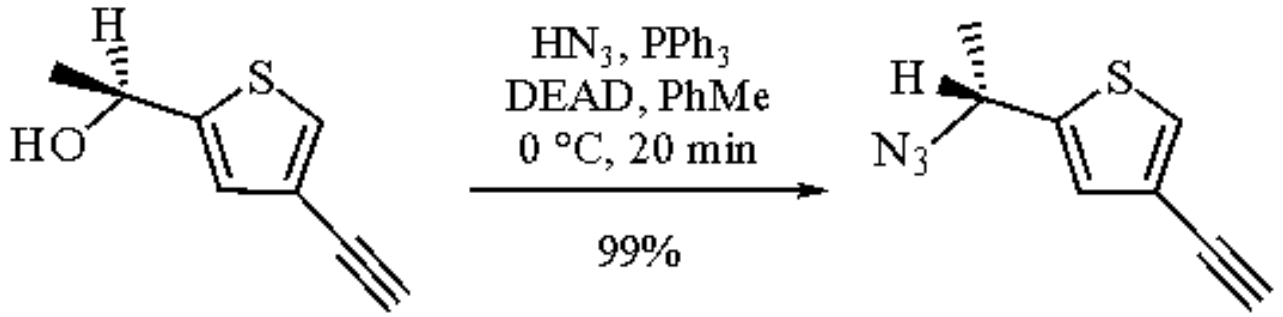

(14)

In a related reaction, tertiary alkyl halides react with HN_3 in the presence of H_2SO_4 to give products derived from the corresponding tertiary azide.[1a]

Cleavage of Epoxides.

HN_3, generated in situ through reaction of Me_3SiN_3 with MeOH, cleaves epoxides in cases in which attempted nucleophilic ring opening with azide ion fails (eq 15).[16]

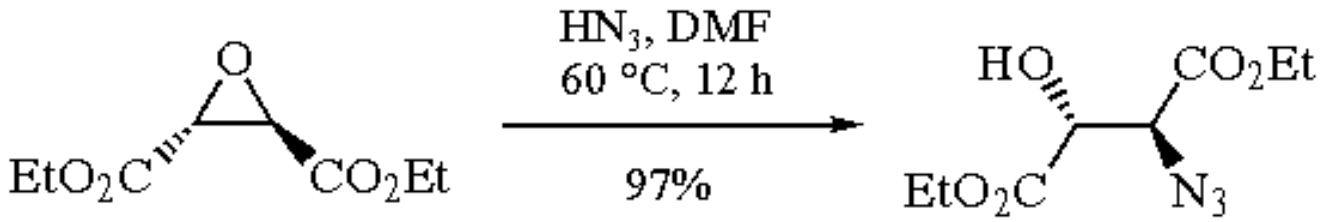

(15)

In the presence of the Lewis acid ***Triethylaluminum***, epoxides are efficiently cleaved under mild conditions in a regio- and stereospecific manner (eq 16).[17] This method is successful for cases in which nucleophilic methods fail or give mixtures of products.

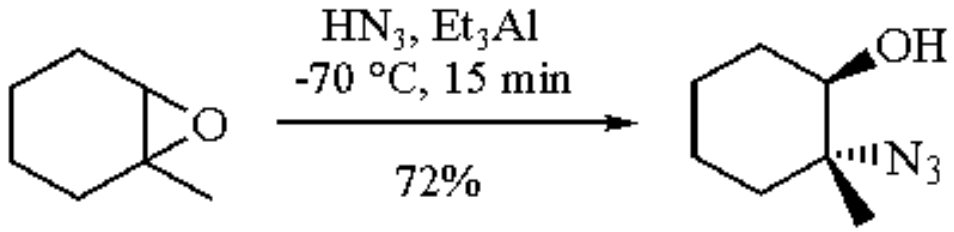

(16)

Reaction with Arenes.

Photolysis of HN_3 in the presence of toluene results in formation of trace amounts of toluidine.[18] Higher yields (65%) of amination products are obtained through reaction of HN_3 with toluene in the presence of ***Aluminum Chloride***.[18,19] Reaction apparently occurs through a conventional electrophilic aromatic substitution mechanism, as revealed by the ratio of *o*-, *m*-, and *p*-substituted products formed. The use of H_2SO_4 as catalyst results in lower yields. Chlorobenzene can be similarly aminated in 19% yield.

Subjection of aryl-substituted alkanes to the oxidant ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** (DDQ) in the

presence of HN_3 results in regioselective oxidative nucleophilic substitution reactions to form benzylic azides (eq 17),[20] which can be readily reduced to benzylic amines.

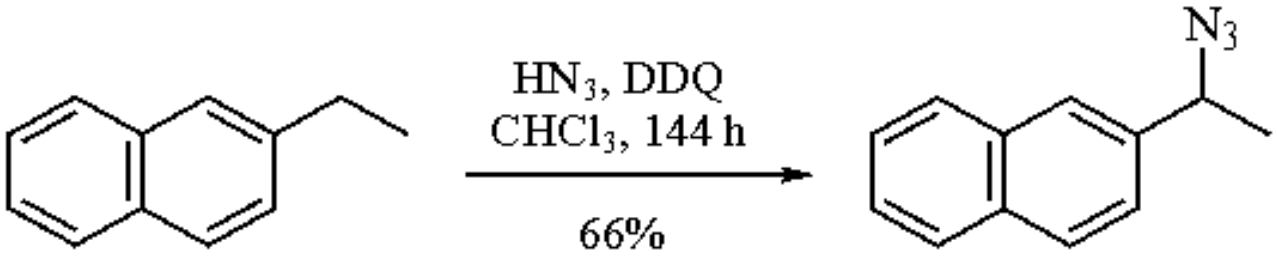

(17)

Aryl nitroso compounds react with HN_3 under mild conditions to give aryl azides in high yields.[1c]

Formation of Sulfoximines.

The reaction of sulfoxides with HN_3 gives sulfoximines in good yields (eq 18).[21] Treatment of a series of appropriately substituted diaryl sulfoxides with HN_3 (generated in situ) gives 1,2,4-benzothiadiazine 1-oxides in moderate to high yields via cyclization of the initially formed sulfoximines (eq 19).[22] Interestingly, reaction of dialkyl sulfides with excess HN_3 in the presence of H_2SO_4 also gives sulfoximines.[21c,23]

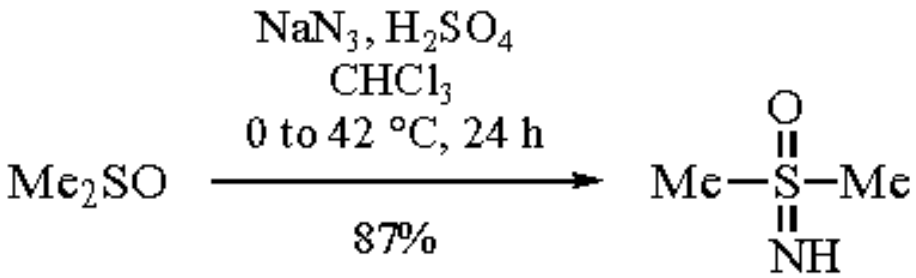

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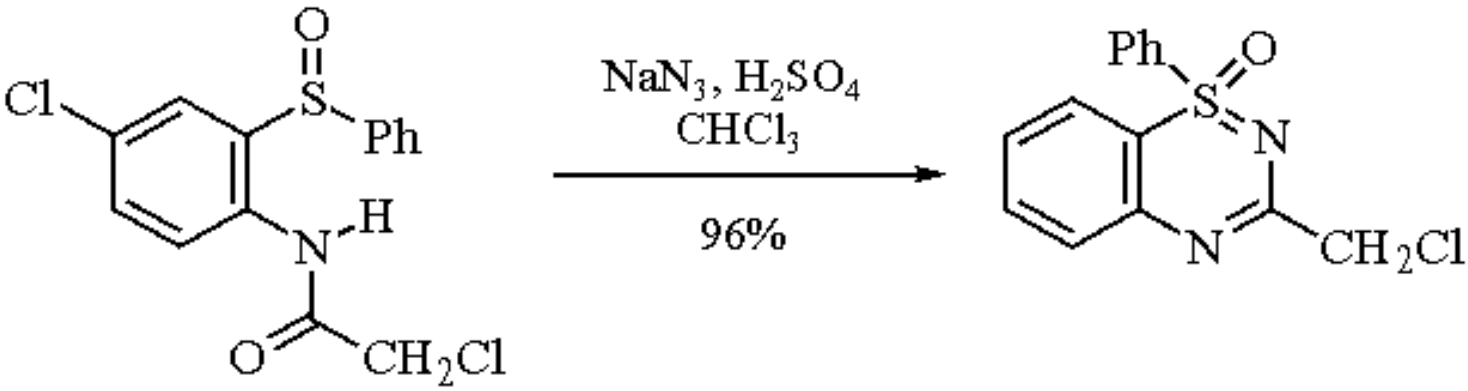

(19)

Reaction with Other Functional Groups.

The reactions of HN_3 with various functional groups have been the subject of several reviews.[1a,24] Several examples are shown in eqs 20-23. The ready reaction of HN_3 with -C&tbond;N bonds affords convenient syntheses of a variety of substituted tetrazoles.

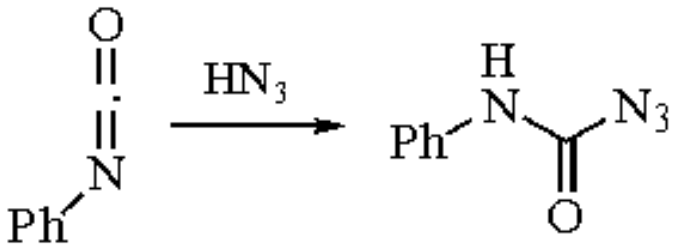

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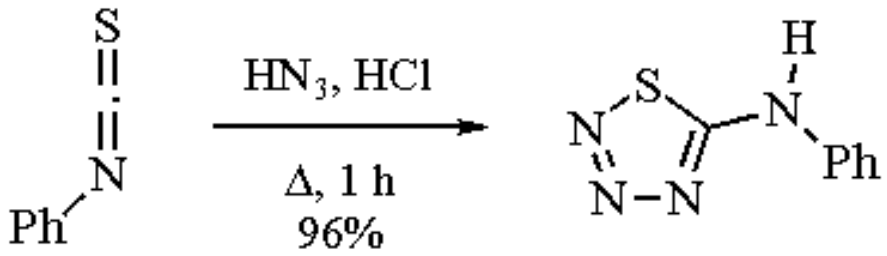

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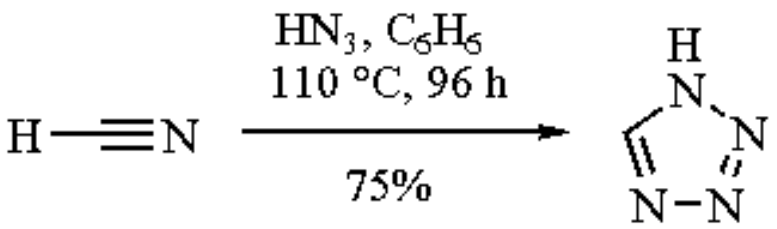

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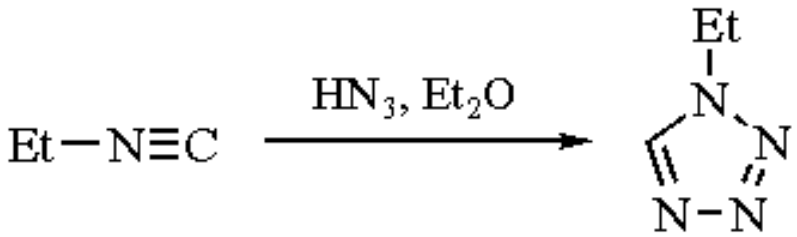

(23)

When subjected to HN_3 in the presence of pyridine, acid chlorides are converted to acyl azides, which can then be converted to isocyanates in good yield.[25]

Cyclic imidates are converted in high yields to azido-substituted amides via reaction with HN_3 generated in situ (eq 24).[26] The method is mild, requiring no acid catalyst, and tolerates the presence of other functional groups.

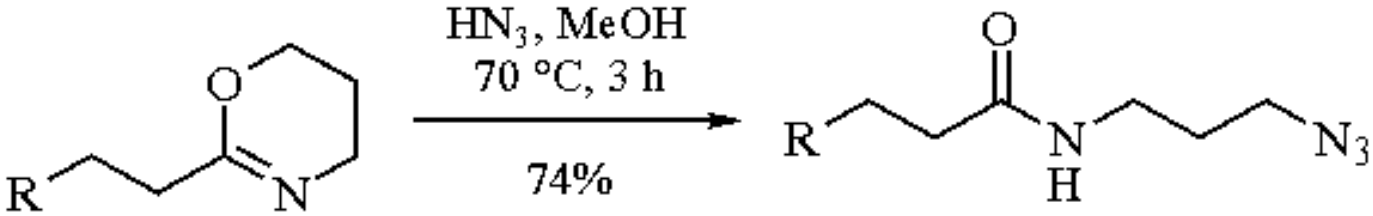

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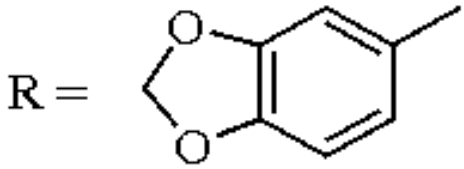

A method for the overall conversion of ketones to amines has been reported.[27] When the acetal or methyl ether derived from a ketone is subjected to HN_3 in the presence of catalytic amounts of ***Trifluoroacetic Acid***, α-alkoxy azides are formed, which are readily reduced to the amines with ***Lithium Aluminum Hydride*** in a one-pot procedure in good overall yields (eq 25).

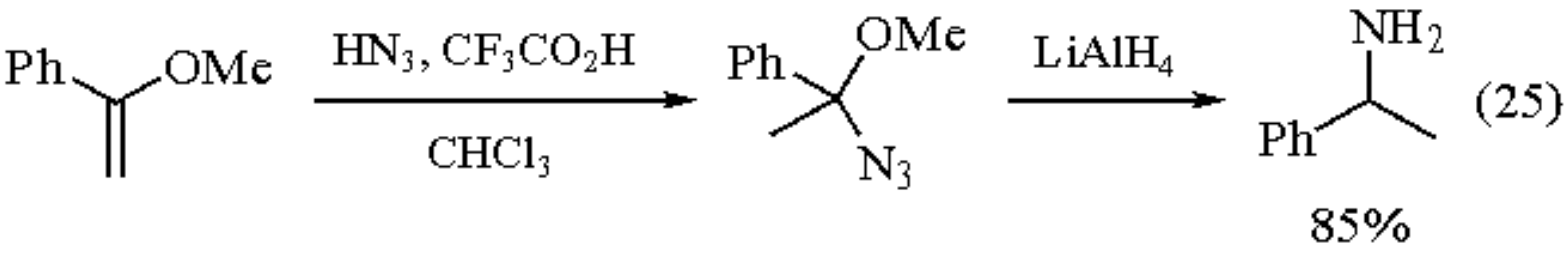

Related Reagents.

Sodium Azide; ***Azidotrimethylsilane***.

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Hydridotetrakis(triphenylphosphine)rhodium[1a,b]

$(PPh_3)_4RhH$

[1828-36-1] · $C_{72}H_{61}P_4Rh$ · Hydridotetrakis(triphenylphosphine)rhodium · (MW 1153.12)

(catalyst for hydrogenation of alkenes[2] and hydrosilylation of alkynes[3])

Physical Data: mp 162-163 °C.

Solubility: slightly sol benzene, toluene, THF, acetone.

Form Supplied in: yellow crystals.

Preparative Methods: from ***Rhodium(III) Chloride*** or rhodium(III) acetylacetonate by reduction with ***Triethylaluminum*** in the presence of ***Triphenylphosphine***.[1a,b]

Purification: by recrystallization from toluene or benzene.

Handling, Storage, and Precautions: solid material is moderately sensitive to oxygen, but in solution it is easily decomposed by air.

Hydrogenation of Activated Alkenes by using a Hydrogen Donor.[2]

A number of different substituted styryl ketones have been reduced by 1-phenylethanol at 50 °C in the presence of catalytic amounts of $(PPh_3)_4RhH$ (eq 1). The initial rate of reduction increases when the aromatic ring contains electron-withdrawing groups and decreases in the presence of electron-releasing substituents.

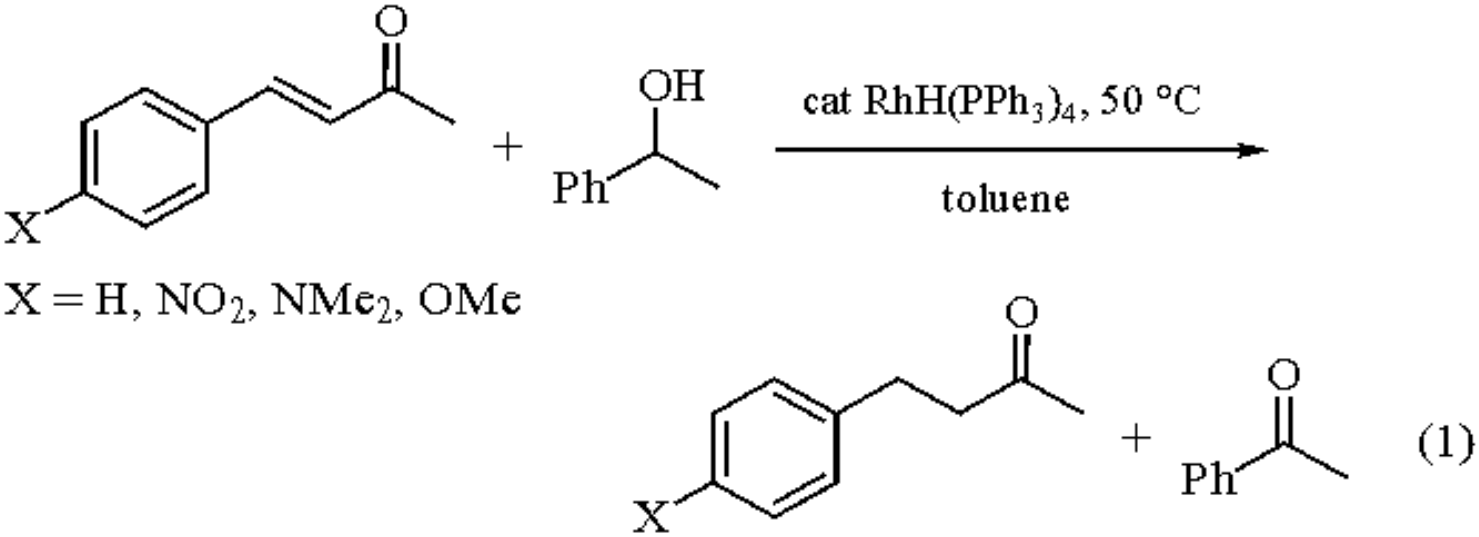

Hydrosilylation of Alkynes.[3]

Hydrosilylation of acetylene with trichlorosilane, triethoxysilane, methyldichlorosilane, methyldiethoxysilane, and *n*-hexyldichlorosilane takes place in either xylene or toluene in the presence of catalytic amounts of $(PPh_3)_4RhH$ (eq 2).

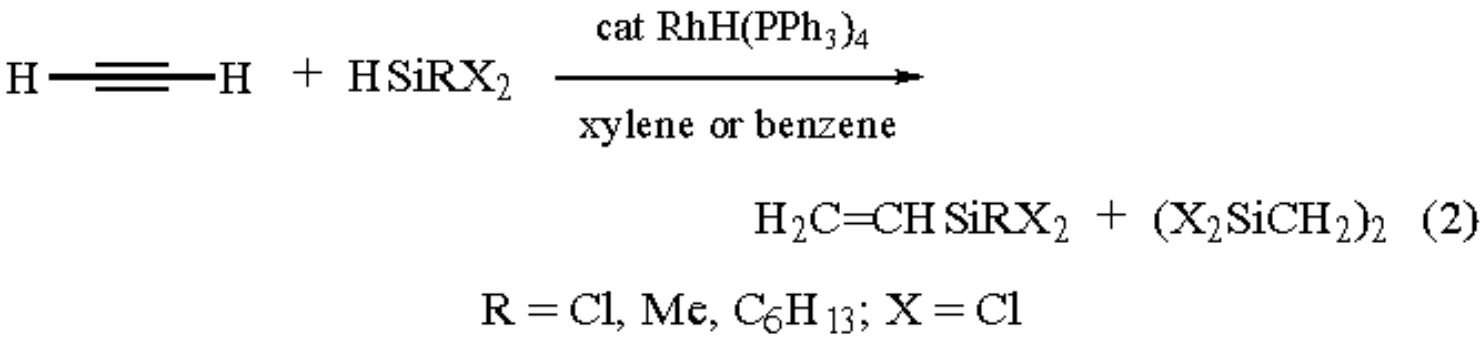

Synthesis of α-Trimethylsilyl Ketones.[4]

α-Trimethylsilyl ketones are useful compounds in the synthesis of di- and trisubstituted alkenes[5] and in aldol reactions.[6] The preparation of such ketones can be carried out by any of the following reactions catalyzed by $(PPh_3)_4RhH$: isomerization of β-trimethylsilyl allyl alcohols, isomerization of β´-trimethylsilyl allyl alcohols, or dehydrogenation of β-trimethylsilyl alcohols via hydrogen transfer to α,β-enones.

Isomerization of 1,3-Diene Monoepoxides to α,β-Unsaturated Carbonyl Compounds.[7]

(*E*)-α,β-Unsaturated carbonyl compounds can be selectively obtained from the Rh-catalyzed isomerization of vinyl epoxides (eq 3). The starting monoepoxides can be prepared according to eq 4.[7]

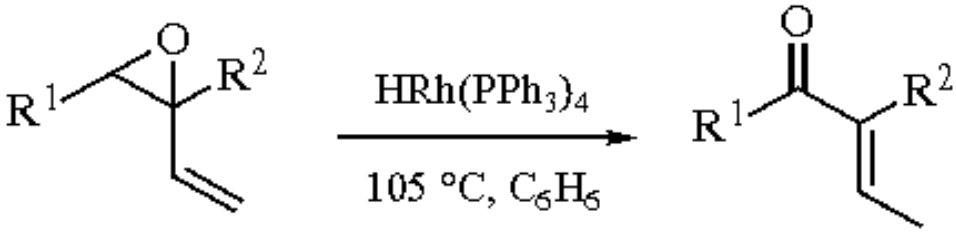

(3)

$R^1 = H, Et, C_5H_{11}, C_7H_{15}; R^2 = H, Et, Pr, i\text{-}Pr$

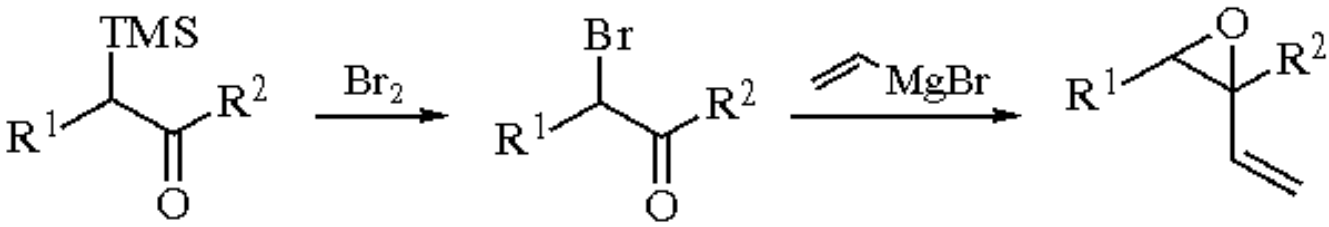

(4)

Other applications include removal of the allyl ether protecting group in the presence of trifluoroacetic acid,[8] and the synthesis of allylsilanes.[9]

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Hydrobromic Acid[1]

BrH

[10035-10-6] · BrH · Hydrobromic Acid · (MW 80.91)

(preparation of alkyl and vinyl bromides; preparation of phenols from alkyl aryl ethers; in combination with hydrogen peroxide is an in situ source of bromine for the preparation of alkyl and aryl bromides)

Physical Data: aqueous solution forms a constant boiling azeotrope containing ca. 48% HBr at 760 mmHg; d = 1.49 g cm^{-3}. Anhydrous gas, d 2.71 g L^{-1}; mp -86.9 °C; bp -66.8 °C.

Solubility: very sol water and protic solvents.

Form Supplied in: as anhydrous gas in cylinders; as aqueous solutions of various concentrations; widely available in all forms.

Analysis of Reagent Purity: titration.

Handling, Storage, and Precautions: hydrogen bromide is a corrosive, colorless, nonflammable gas which forms a white cloud when exposed to air; as concentrated solutions, hydrobromic acid is a colorless to light yellow corrosive liquid which fumes when exposed to air; the acid can cause severe skin burns, damage to the respiratory and digestive tract, and/or visual damage; repeated exposure may cause dermatitis and photosensitization; the gas and solutions of hydrobromic acid should be handled with adequate ventilation and proper skin and eye protection. Use in a fume hood.

Acid Catalysis.

Hydrogen Bromide is completely ionized in all but the most concentrated aqueous solutions, making it a strong Lewis acid. However, the expense of hydrobromic acid relative to ***Hydrochloric Acid*** and other mineral acids, as well as the greater nucleophilicity of bromide, has limited its use as an acid catalyst.

Bromomethylation.

Concentrated hydrobromic acid or anhydrous hydrogen bromide have been used with ***Paraformaldehyde*** or 1,3,5-trioxane for the bromomethylation of aromatic compounds (eq 1). Formation of bis(bromomethyl) ether, a carcinogenic compound, under the reaction conditions is problematic. This side reaction has limited the use of the bromomethylation process. Phenols are so reactive under the reaction conditions that they are frequently deactivated

through preparation of their acyl derivatives prior to bromomethylation. The reaction may be run in the presence of Brønsted acid catalysts.[2] Treatment of dibenzyl diselenide with ***Zinc*** and hydrobromic acid followed by paraformaldehyde and hydrogen bromide produced high yields of bromomethyl benzyl selenide (eq 2).[3] Analogous chemistry is observed with benzyl sulfide (eq 3). Treatment of an aryl alkyl ketone with ***Bis(dimethylamino)methane*** and hydrogen bromide has produced moderate yields of the ketone, which was bromomethylated α to the carbonyl (eq 4).[4]

$$\mathrm{ArH} + \mathrm{CH_2O} + \mathrm{HBr} \longrightarrow \mathrm{ArCH_2Br} \qquad (1)$$

$$\mathrm{RSeSeR} + \mathrm{CH_2O} + \mathrm{HBr} \longrightarrow \mathrm{RSeCH_2Br} \qquad (2)$$

$$\mathrm{RSH} + \mathrm{CH_2O} + \mathrm{HBr} \longrightarrow \mathrm{RSCH_2Br} \qquad (3)$$

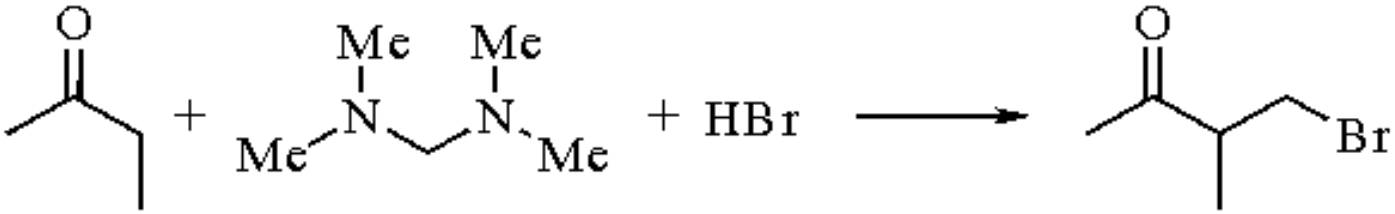

(4)

Addition to Single Bonds in Three-Membered Rings.

Hydrogen bromide is less commonly used for the preparation of derivatives of terpenes containing three-membered rings than hydrochloric acid. Cleavage of cyclopropanes produces addition products which are expected to arise from bromide addition to the most stable carbonium ion (analogous to Markovnikov addition), some rearrangements do occur, and steric factors do play a role in the reaction (eq 5). Simple alkyl derivatives of the parent cyclopropane can give polymeric materials as the main product. As an example, treatment of *cis*-carane with hydrogen bromide results in cleavage of the cyclopropane ring with isolation of the tertiary bromide.[5]

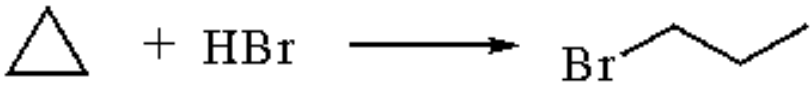

(5)

Cyclopropylcarbinols react with concentrated hydrobromic acid under mild conditions to yield 1-bromo-3-butenes (eq 6).[6] The reaction is regiospecific with secondary and some tertiary alcohols. With alkynic cyclopropylcarbinols, stereospecificity of the product double bond can be controlled through the use of ***Octacarbonyldicobalt***.[7]

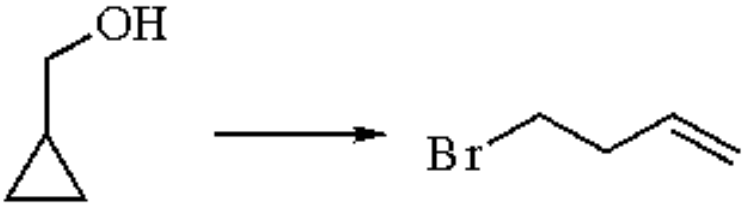

(6)

In acetic acid, acyl cyclopropane derivatives add anhydrous hydrogen bromide to yield 4-bromobutanone derivatives (eq 7). This addition is stereo- as well as regioselective.[8]

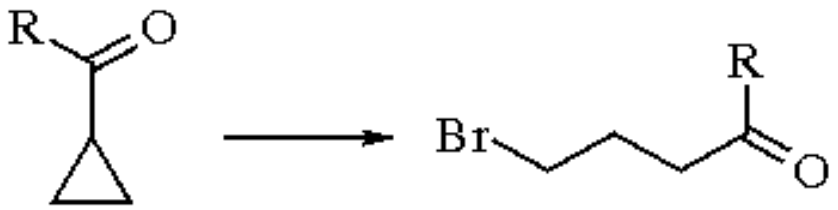

(7)

Oxiranes react readily with hydrobromic acid to yield addition products (eq 8). The reaction proceeds with inversion at carbon. The expected product is that in which the bromide adds to the least-hindered carbon. Addition to epoxycyclohexanes gives products in which attack of bromide is axial.[9] Analogous chemistry is observed with aziridines (eq 9).[10]

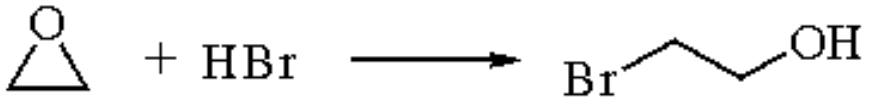

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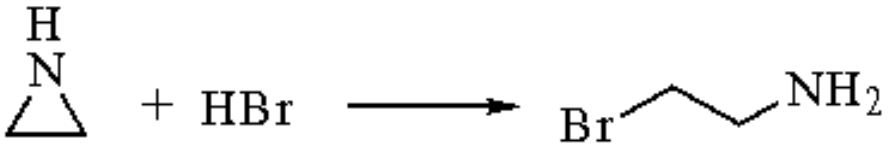

(9)

Addition to Single Bonds in Four-, Five-, and Six-Membered Rings.

Although the parent acylcyclobutanes are stable to hydrogen bromide, [3.2.2]propellanes, [4.2.2]propellanes, and cubanes react to give addition products (eqs 10 and 11) or rearrangement products (eq 12), as shown.[11]

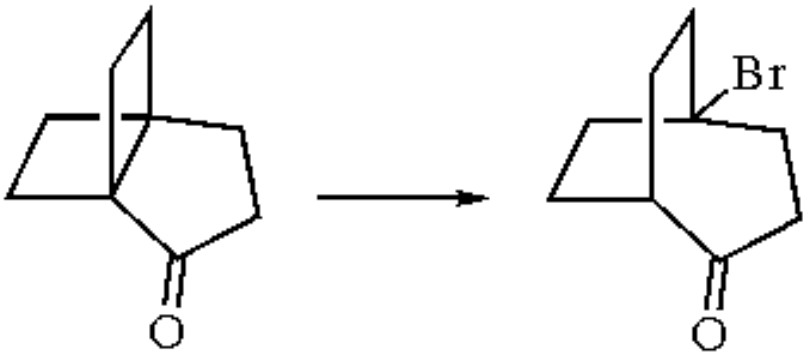

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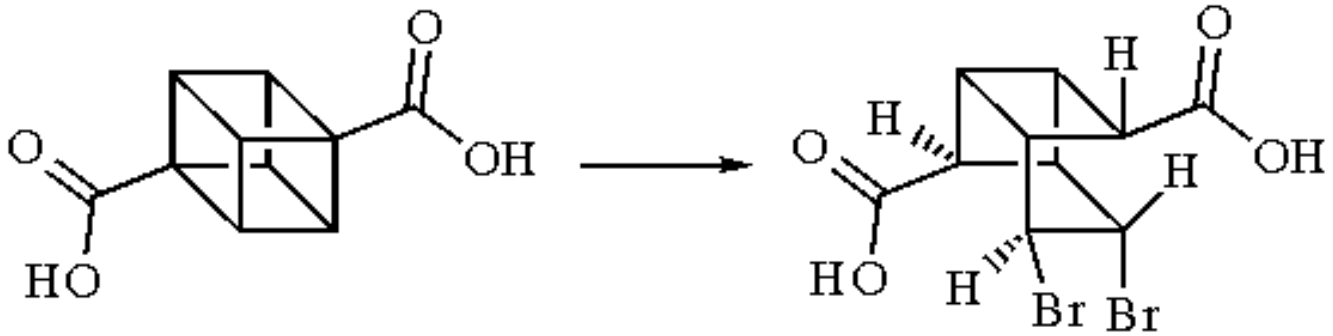

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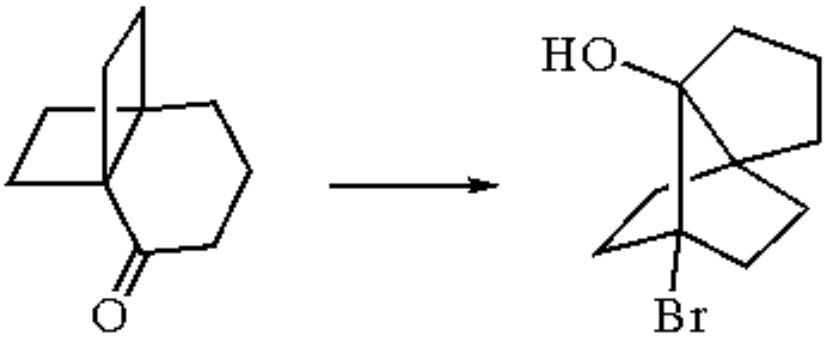

(12)

Oxetanes (eq 13) and tetrahydrofurans (eq 14) can be opened by anhydrous hydrogen bromide under a variety of conditions.[12]

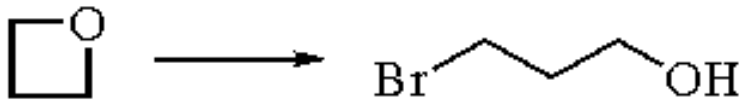

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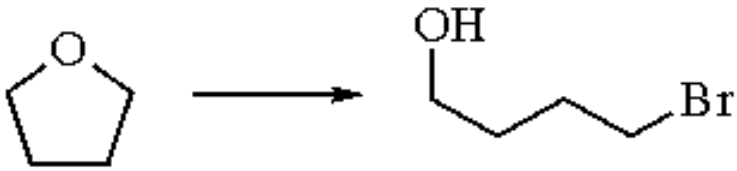

(14)

Four-, five-, and six-membered lactones add anhydrous hydrogen bromide to yield the acyclic bromide (eq 15). When run in glacial acetic acid, the free carboxylic acid is isolated; in alcohols, the ester is produced.[13]

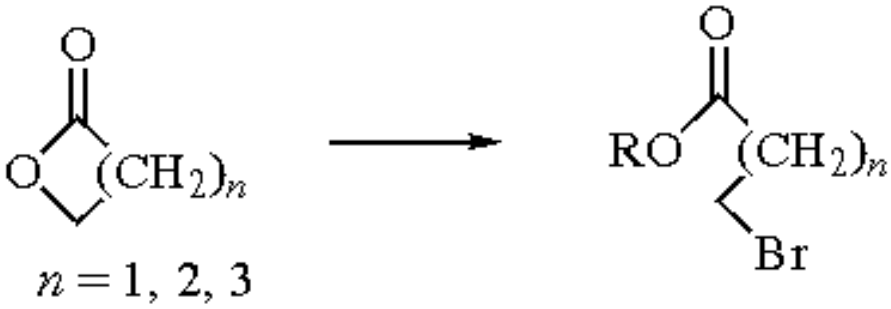

(15)

Reaction with Ethers.

Ethers react with hydrogen bromide under a variety of conditions to yield the corresponding bromide and alcohol (eq 16). Acetic acid is often used as solvent, but other carboxylic acids have also been used. Frequently, under the reaction conditions, the alcohol is also converted to its bromide.[14] Reports of explosive reactions of ethers and hydrogen bromide have been reviewed.[15]

$$R^2OR^1 + HBr \longrightarrow R^2OH + R^2Br + R^1OH + R^1Br \quad (16)$$

Aryl methyl ethers can be cleaved to phenols with hydrogen bromide in glacial acetic acid or by concentrated hydrobromic acid.[16] This transformation is commonly accomplished using boron trihalides, ***Pyridinium Chloride***, or ***Iodotrimethylsilane***.[17]

Addition to Carbon-Carbon Multiple Bonds.

Hydrogen bromide reacts with alkenes more rapidly than hydrogen chloride. When care is taken to avoid radical conditions, the products which are obtained are those expected from Markovnikov addition (eq 17). ***Iron(III) Chloride***, iron(III) bromide, or ***Aluminum Bromide*** are the most commonly used Lewis acids to activate unreactive double bonds. Hydrobromination of double bonds under radical conditions can lead to mixtures of products. When an electron-withdrawing group is attached directly to the double bond, the bromide typically adds β to that group.[18]

$$R^2HC{=}CHR^1 + HBr \longrightarrow R^2H_2C\text{-}CHBrR^1 \quad (17)$$

Treatment of allene with anhydrous hydrogen bromide results in formation of the expected Markovnikov addition product and 1,3-dimethyl-1,3-dibromocyclobutane (eq 18). 1,3-Disubstituted allenes, when treated with anhydrous hydrogen bromide, produce mixtures of HBr addition products resulting from addition of the proton to either the central ketene carbon or to a terminal ketene carbon (eq 19). 1,1-Disubstituted allenes add the proton to the central allene carbon and bromide to the terminal carbon to produce 1,1-dialkyl-3-bromo-1-propenes (eq 20).[19]

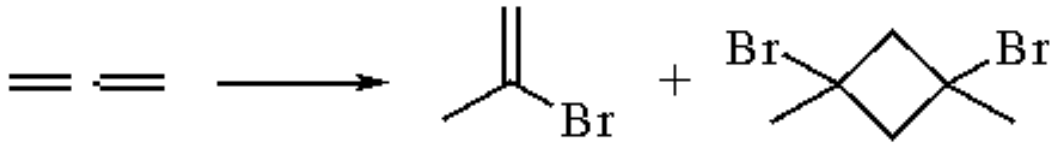

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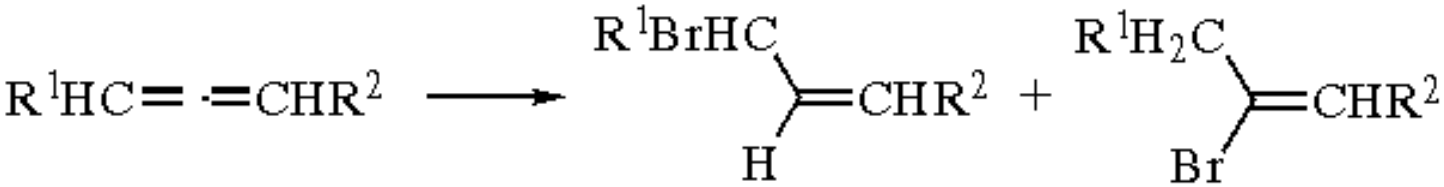

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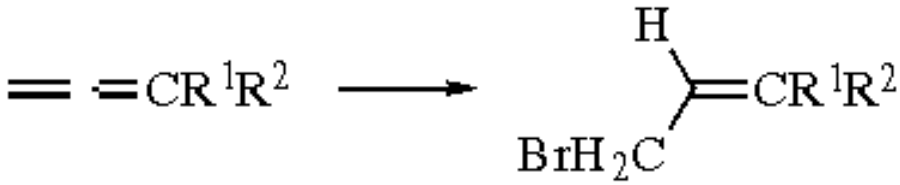

(20)

Addition of hydrogen bromide to alkynes is typically slow. Addition of ammonium bromide salts or ***Copper(I) Bromide*** produces a dramatic acceleration in the rate of the addition (eqs 21 and 22). In the absence of radicals, the isolated products are typically those expected from Markovnikov addition,[20] although mixtures of products have been reported when the carbon α to the triple bond bears an amine.[21] Under radical conditions, hydrogen bromide adds to alkynes to yield anti-Markovnikov products.[22] In the presence of ***Copper(II) Bromide*** and ammonium bromide, aqueous hydrobromic acid adds to vinylacetylene to yield 2-bromobutadiene (eq 23).[23]

$$R^2C{\equiv}CR^1 + HBr \longrightarrow R^2HC{=}CBrR^1 + R^2H_2C\text{-}CBr_2R^1 \quad (21)$$

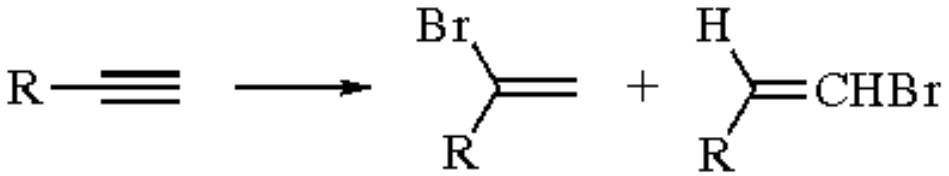

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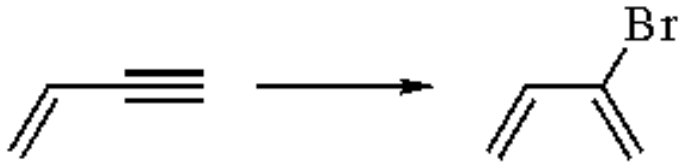

(23)

Hydrobromic acid is superior to hydrochloric acid for the conversion of 3-acylprop-2-ynal diethyl acetals to 3-acylprop-2-enoic acids (eq 24).[24]

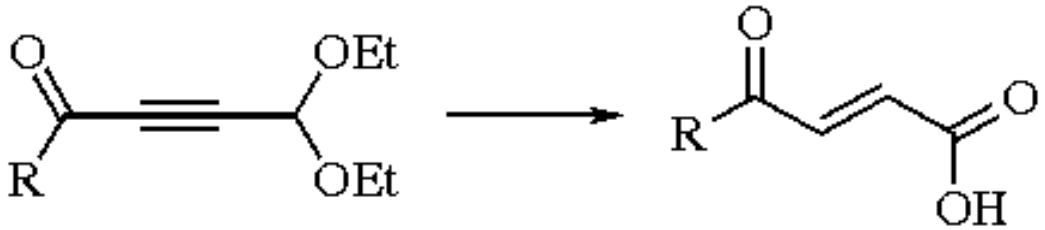

(24)

Reactions with Alcohols.

Hydrobromic acid reacts with primary, secondary, tertiary, allylic, benzylic, and propargylic alcohols to give the corresponding bromides (eq 25). As is the case with the conversion of alcohols to chlorides, a large number of alternative reagents are available. Although hydrobromic acid is readily available, greater selectivity is often achieved using reagents such as ***Zinc Bromide***/***Triphenylphosphine***/***Diethyl Azodicarboxylate***, ***Phosphorus(III) Bromide***, or PPh_3/***Carbon Tetrabromide***. Treatment of alkyl phosphites, phosphonates, and diphenyl phosphinites with hydrogen bromide produces the alkyl bromide in which inversion at carbon has occurred. Yields are higher and conditions milder than the corresponding reaction with hydrogen chloride.[25]

$$ROH \longrightarrow RBr \quad (25)$$

The reactions of carbohydrates and their derivatives with hydrogen bromide at the anomeric hydroxy are especially

facile examples of the conversion of alcohols to bromides.[26]

When treated with hydrogen bromide, cyclobutylcarbinol rearranges to cyclopentyl bromide (eq 26).[27] The analogous [2.1.1]bicyclocarbinol produces the primary bromide with hydrogen bromide (eq 27).[28]

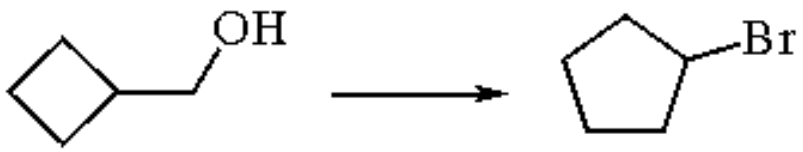

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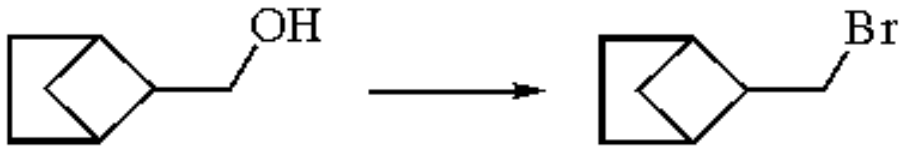

(27)

Concentrated hydrobromic acid reacts with 1,1-dialkylpropargyl alcohols to give products which are dependent upon the reaction conditions. Products isolated when 3-methylbut-1-yn-3-ol was the starting alcohol include 1-bromo-3,3-dimethylallene, 3-bromo-3-methyl-1-butyne, 1-bromo-3-methyl-1,3-butadiene, 1,3-dibromo-3-methylbutene, and 1,2,3-tribromo-3-methylbutane (eq 28). Tertiary propargyl alcohols, in the presence of copper(I) bromide, ammonium bromide, and 45-48% hydrobromic acid, rapidly produce 1-bromoallenes. Secondary propargyl alcohols produce 1-bromoallenes using 60% hydrobromic acid, copper(I) bromide, and ammonium bromide.[29]

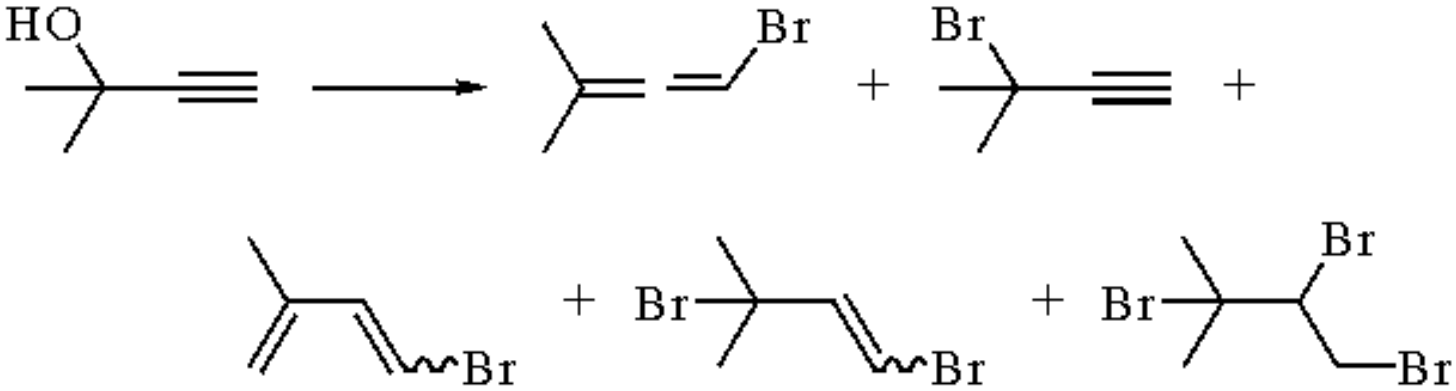

(28)

Reactions with Diazo Compounds.

Arylamines can be converted to aryl bromides by treatment with ***Sodium Nitrite***/hydrobromic acid/***Copper*** or copper(I) bromide (eq 29).[30] Hydrobromic acid converts α-diazo ketones to α-bromo ketones in good yield (eq 30).[31] Pure enantiomers of serine and threonine give good yields and high enantiomeric purity of α-bromo acids when treated with nitrite and hydrobromic acid.[32]

$$ArNH_2 \longrightarrow [ArN_3] \longrightarrow ArBr \qquad (29)$$

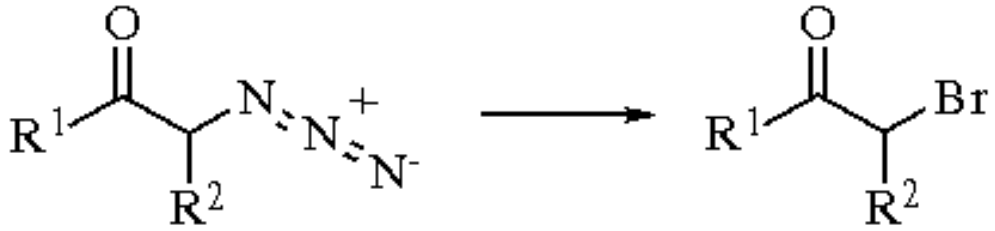

(30)

Reactions with Nitriles.

Addition of anhydrous hydrogen bromide to nitriles produces imidoyl bromides (eq 31).[33] Treatment of *N*-alkylimidoyl bromides with hydrogen bromide results in isolation of the corresponding iminium bromides (eq 32).[34] Methylene bis(thiocyanate) reacts with hydrogen bromide to produce the cyclic imidoyl bromide (eq 33).[35] Methyl and phenyl thiocyanate react with 2 equiv of hydrogen bromide to produce 1-bromothioformimidate salts (eq 34).[36] Cyanogen di-*N*-oxide reacts with hydrobromic acid to produce the hydroxamoyl bromide analog of oxalyl bromide (eq 35).[37]

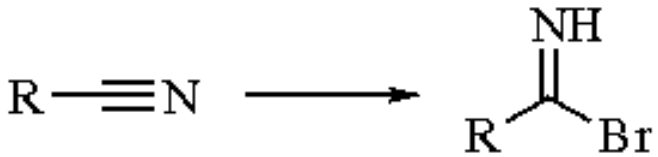

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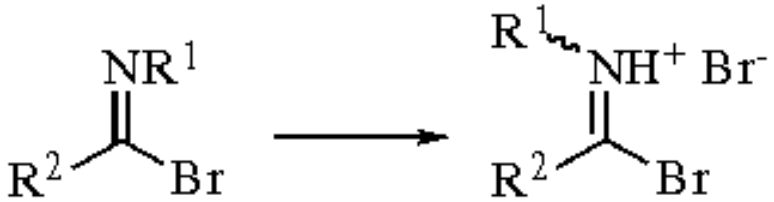

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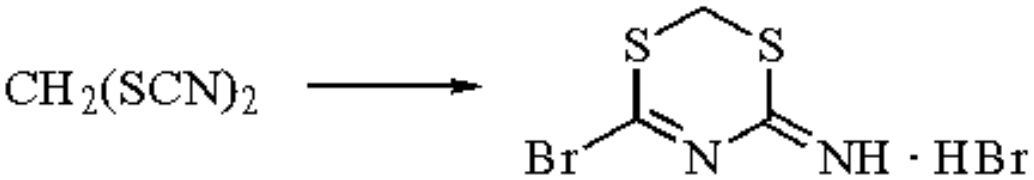

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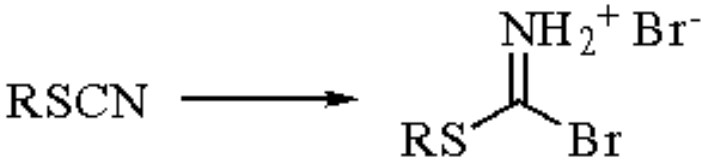

(34)

(35)

Reactions with Sulfur Compounds.

Thiols react with paraformaldehyde and hydrobromic acid to yield bromomethyl thioethers (see bromomethylation above). Benzenesulfonamides, benzenesulfonohydrazides, and benzenesulfinic acids can all react with hydrobromic acid to yield disulfides or sulfenyl bromides, depending upon the reaction conditions (eqs 36-38). Hydrogen bromide appears to be better than hydrogen chloride for the preparation of disulfides from benzenesulfonamides, but less satisfactory than hydrogen chloride for the conversion of benzenesulfonohydrazides to disulfides.[38] Sulfoxides are converted into bromosulfonium bromides or sulfides (eq 39).[39] Chloro(trifluoromethyl)sulfine reacts with anhydrous hydrogen bromide to produce 1-bromo-1-chloro-2,2,2-trifluoroethylsulfenyl bromide in high yield (eq 40).[40] Additional information is included under the section on the in situ generation of ***Bromine*** (see below).

$$ArSO_2NR_2 \longrightarrow ArSBr + ArSSAr \qquad (36)$$

$$ArSO_2NHNR_2 \longrightarrow ArSBr + ArSSAr \qquad (37)$$

$$ArSO_2H \longrightarrow ArSBr + ArSSAr \qquad (38)$$

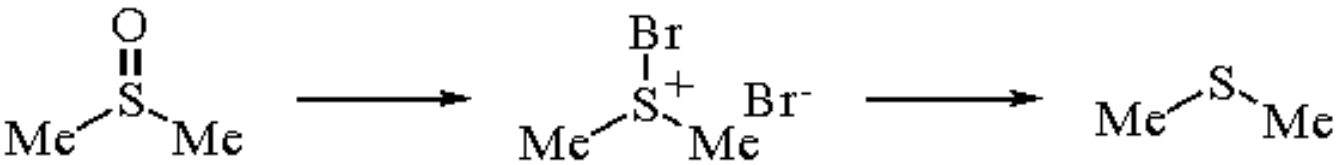

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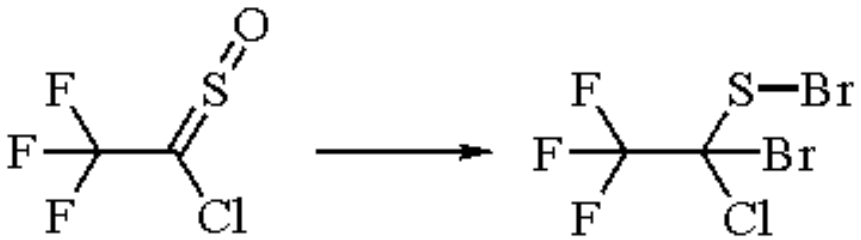

(40)

Reactions with Silicon Compounds.

Phenylsilanes react with hydrogen bromide to yield benzene and the bromosilane (eq 41). The reaction is more facile than the reaction with hydrogen chloride. Increasing the electronegativity of substituents on silicon decreases the ease with which the aryl-silicon bond is broken.[41] *t*-Butyldimethylsilyl ethers of phenols are cleaved to phenols at rt using a mixture of hydrobromic acid and ***Potassium Fluoride*** (eq 42).[42] Triethylaminosilanes are converted to the corresponding bromosilanes in the presence of hydrobromic acid/***Sulfuric Acid*** (eq 43).[43]

(41)

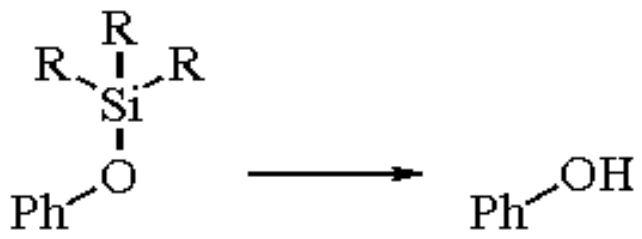

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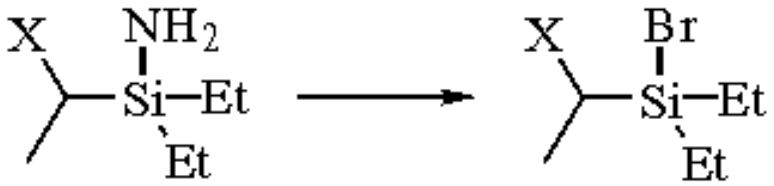

(43)

Transhalogenation Reactions.

Alkyl chlorides can be converted to alkyl bromides using hydrogen bromide in the presence of iron(III) bromide (eq 44).[44] This conversion can also be effected under neutral conditions by heating the chloride with a metal bromide in acetone, an alcohol, or ethyl bromide.[45]

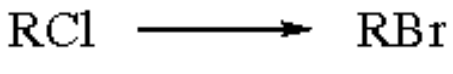

(44)

Acid chlorides react with anhydrous hydrogen bromide to yield the corresponding acid bromides (eq 45).[46] This conversion may also be effected using ***Bromotrimethylsilane***.[47]

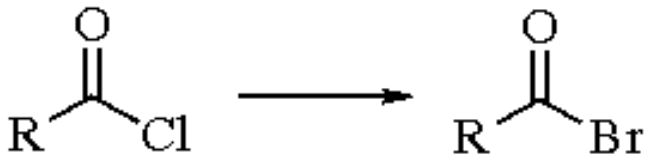

(45)

Trichloromethylsulfenyl chloride reacts with concentrated hydrobromic acid to yield trichloromethylsulfenyl bromide (eq 46).[48] Dichloromethyl methyl sulfide produces dibromomethyl methyl sulfide when treated with anhydrous hydrogen bromide (eq 47).[49]

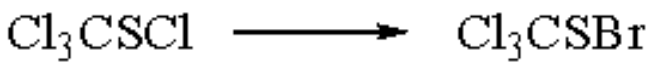

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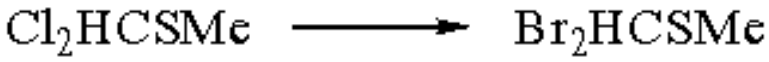

(47)

Bromide Isomerization.

α,α-Dibromo ketones equilibrate to α,α´-dibromo ketones in the presence of dilute hydrobromic acid (eq 48).[50]

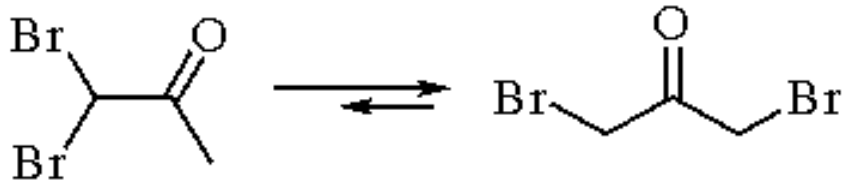

(48)

Organoselenium, Organogermanium, and Organorhenium Chemistry.

Selenols react with paraformaldehyde and hydrogen bromide to produce bromomethyl selenides (see bromomethylation above). Methyl phenyl selenides are cleaved by hydrogen bromide in acetic acid to yield phenyl selenols (eq 49).[51] Alkyl phenyl selenoxides react with hydrogen bromide to yield the alkyl bromides (eq 50).[52] Selenonium nitroylides give bromonitromethane derivatives when reacted with hydrogen bromide in ether (eq 51).[53]

(49)

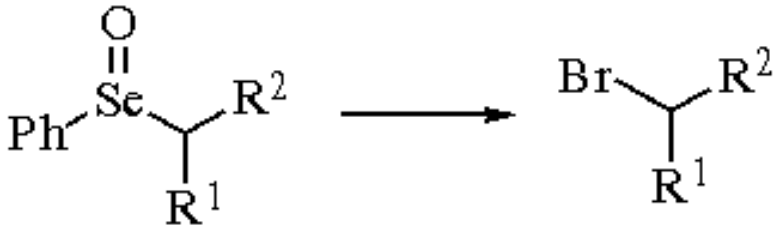

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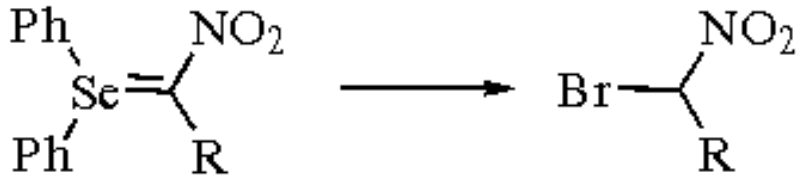

(51)

1,1-Dihydroxy-2,3-diphenylgermirene is converted to the dibromide with anhydrous hydrogen bromide in benzene (eq 52).[54]

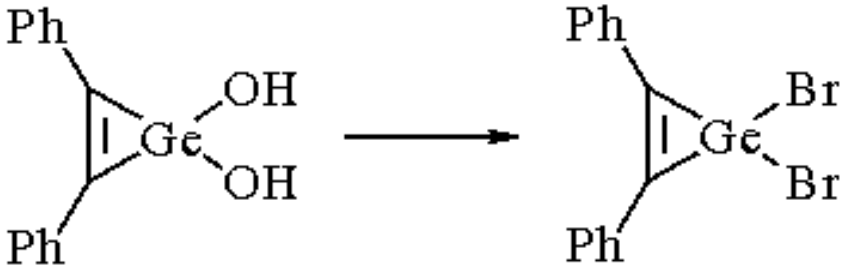

(52)

The pure enantiomer of the pseudotetrahedral rhenium alkyl complex in eq 53 reacts with concentrated hydrobromic acid to produce the pure reduced enantiomer. Cleavage of the rhenium-carbon bond occurs with retention at both carbon and rhenium.[55]

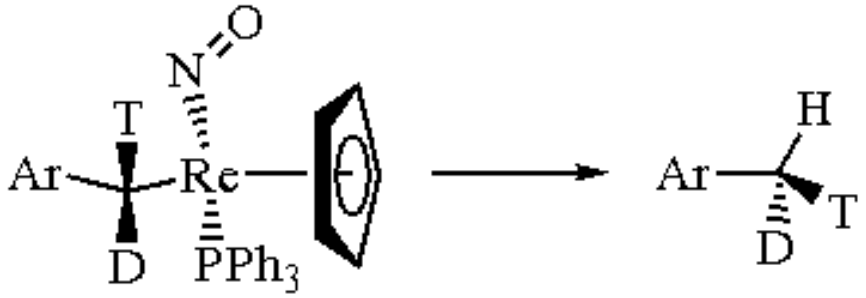

(53)

In Situ Generation of Bromine.

Dimethyl Sulfoxide reacts with hydrobromic acid at about 80 °C to produce dimethyl sulfide, water, and bromine (eq 54). The DMSO/HBr reagent has been used to oxidize 1,3-diketones to 1,2,3-triketones, acetophenones to phenylglyoxals, benzylamines to imines, and 4,5-dihydropyridazin-3(2*H*)-ones to pyridazin-3(2*H*)-ones.[56] The combination is also effective in converting stilbenes, 1,2-dibromo-1,2-diarylethanes, and 2-bromo-1,2-diarylethanols to benzils.[57] It is possible to use a catalytic amount of hydrogen bromide in some of these reactions.

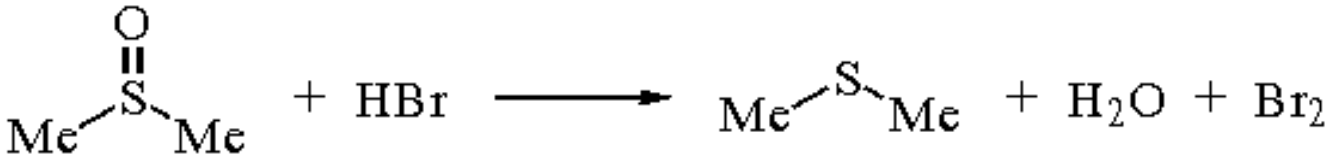

(54)

Hydrobromic acid and ***Hydrogen Peroxide*** are an effective combination for the in situ generation of bromine (eq 55). This combination of reagents can be used for the bromination of alkenes and aromatics, for the preparation of bromohydrins from alkenes, and for the preparation of benzylic bromides.[58]

$$2\ HBr + H_2O_2 \longrightarrow 2\ H_2O + Br_2 \qquad (55)$$

Hydrobromic acid is a source of bromine when irradiated in the presence of air or oxygen (eq 56). Ethylbenzene, when photooxidized, yields a mixture of acetophenone, 1-phenylethanol, and 1-phenylbromoethane.[59]

$$4\ HBr + O_2 \xrightarrow{h\nu} 2\ Br_2 + 2\ H_2O \qquad (56)$$

Related Reagents.

Formaldehyde-Hydrogen Bromide; ***Hydrogen Bromide***.

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Hydrochloric Acid[1]

ClH

[7647-01-0] · ClH · Hydrochloric Acid · (MW 36.46)

(strong Brønsted acid used for general acid catalysis; preparation of salts of amines; preparation of alkyl, allyl, aryl, benzyl, and vinyl chlorides; protodemetalation reagent; in combination with hydrogen peroxide is an in situ source of chlorine for the preparation of alkyl and aryl chlorides)

Physical Data: aqueous solution: freezing point of ca. 31% solution -46 °C; forms constant boiling azeotrope containing 20.22% HCl with water (bp 108.58 °C/760 mmHg; *d* 1.096 g cm^{-3}). Anhydrous gas: *d* 1.639 g L^{-1}; mp -114.22 °C; bp -85.05 °C/760 mmHg.

Solubility: very sol water, protic solvents, ethers.

Form Supplied in: as anhydrous gas in cylinders; as aqueous solutions of various concentrations; widely available in all forms.

Analysis of Reagent Purity: titration.

Handling, Storage, and Precautions: hydrogen chloride is a corrosive, colorless, nonflammable gas which forms a white cloud when exposed to air; as concentrated solutions, hydrochloric acid is a colorless to light-yellow corrosive liquid which fumes when exposed to air; the acid can cause severe skin burns, damage to the respiratory and digestive tract, and/or visual damage; repeated exposure may cause dermatitis and photosensitization; the gas and solutions of hydrochloric acid should be handled with adequate ventilation and proper skin and eye protection. Use in a fume hood.

Acid Catalysis.

Hydrogen Chloride is completely ionized in all but the most concentrated aqueous solutions. In addition, the nucleophilicity[2] of the halide ions follows the general order $I^- > Br^- > Cl^- > F^-$. Consequently, in many of the reactions in which it is employed, it is used as an acid catalyst. Reactions employing hydrochloric acid as a catalyst include the hydrolysis of esters to acids, the hydrolysis of nitriles and imides to amides, acids, and amines,[3] the hydrolysis of amides to acids and amines,[4] the hydrolysis of imines and enamines to ketones and amines, the hydrolysis of nitroso compounds to ketones, the hydrolysis of ketals, aminals, and enol ethers to ketones, the hydrolysis of acetals to aldehydes, and the hydrolysis of ethers to alcohols.[5] Anhydrous hydrogen chloride in an alcohol is frequently used in Fischer esterifications and in acetalization reactions. Hydrochloric acid has been used to effect numerous molecular

rearrangements. Carbon-carbon bond-forming reactions catalyzed by hydrochloric acid include the aldol condensation and the Mannich reaction.[6] The Bergius-Willstatter saccharification process utilizes hydrochloric acid to convert cellulose to fermentable sugar.

Amine Salt Formation.

Many amines form solid hydrochloride salts. The low toxicity of chloride ion and favorable physical properties of many of these salts has resulted in the use of such salts for a large number of pharmaceuticals.[7] Hydrochloride salts are also used for characterization of amines.

Chloroalkylation.

Concentrated hydrochloric acid and anhydrous hydrogen chloride have been used with ***Paraformaldehyde*** for the chloromethylation of aromatic compounds (eq 1). Formation of bis(chloromethyl) ether, a carcinogenic compound, under the reaction conditions is problematic. This side reaction has limited the use of the chloromethylation process.[8] In the presence of thiols, acetaldehyde will react with hydrogen chloride to yield alkyl chloroethyl thioethers (eq 2).[9]

$$\mathrm{ArH} + \mathrm{CH_2O} + \mathrm{HCl} \longrightarrow \mathrm{ArCH_2Cl} \qquad (1)$$

$$\mathrm{RSH} + \mathrm{RCHO} + \mathrm{HCl} \longrightarrow \mathrm{RSCHClR} \qquad (2)$$

Amidomethylation.

N-Acylhemiaminals can react with pyrroles in ethanol saturated with hydrogen chloride to produce the amidomethylated product (eq 3). Such amidomethylations are more commonly performed using ***Sulfuric Acid*** as catalyst.[10]

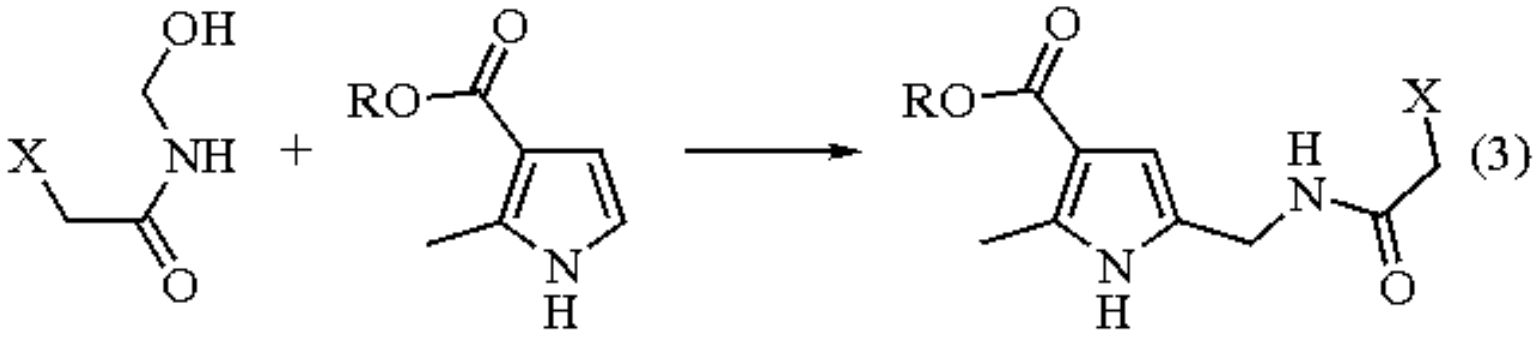

Addition to Single Bonds in Three-Membered Rings.

Hydrogen chloride will react with some cyclopropanes to yield ring-opened products (eq 4). These addition reactions typically yield products expected from Markovnikov addition. Δ^3-Carene (**1**) and Δ^4-carene (**2**) both produce a mixture of sylvestrene dihydrochloride (**3**) and dipentene dihydrochloride (**4**).[11]

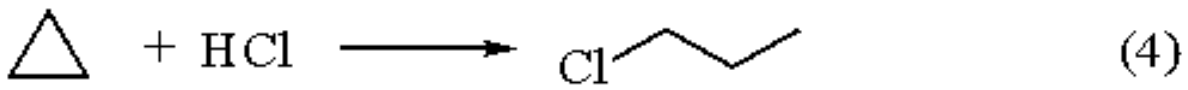

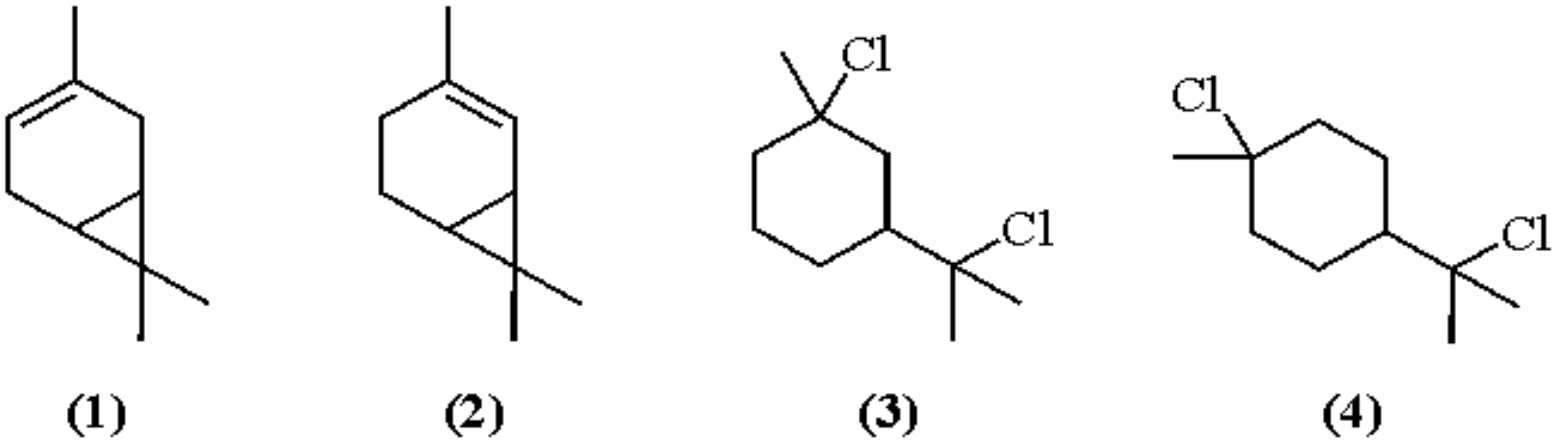

Anhydrous hydrogen chloride can react with oxiranes and aziridines to yield addition products (eqs 5 and 6). Oxiranes and aziridines derived from cyclohexenes open preferentially through axial attack by chloride.[12] Other Lewis acids, including ***Aluminum Chloride***, ***Tin(IV) Chloride***, and ***Iron(III) Chloride***, also produce 2-chloroethanols when reacted with oxiranes. In the presence of sulfur nucleophiles, good yields of the sulfur addition product may be obtained.[13]

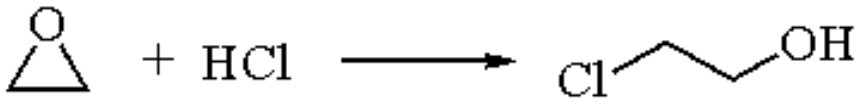

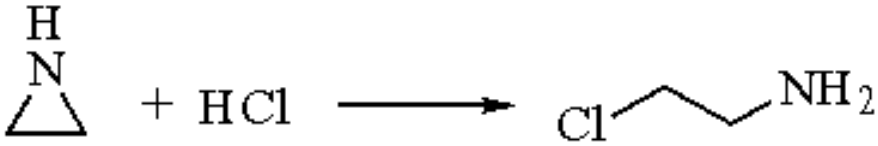

Addition to Single Bonds in Five-Membered Rings.

Treatment of γ-butyrolactone with hydrochloric acid produces 4-chlorobutyric acid in good yield (eq 7).[14] Ring opening of 1,4-dihydro-1,4-epoxybenzene derivatives with hydrochloric acid results in isolation of the corresponding phenols (eq 8). This aromatization may be very regiospecific.[15,5a]

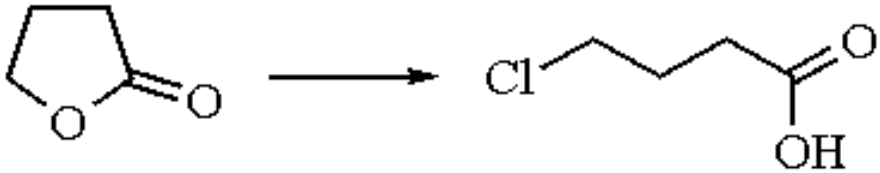

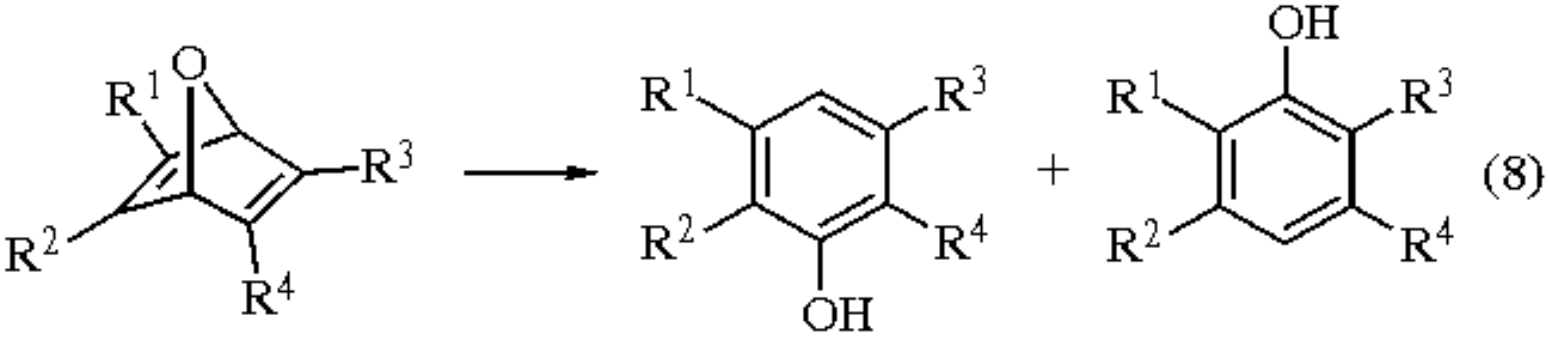

Reaction with Ethers.

In addition to the reactions with cyclic ethers cited above, hydrogen chloride reacts with acyclic ethers to produce the corresponding alcohols and chlorides (eq 9). The rate of the reaction is dependent upon the structure of the ether.[16] In the presence of ***Zinc Chloride***, hydrogen chloride reacts with propargyl ethers to produce propargyl chlorides (eq 10).[17]

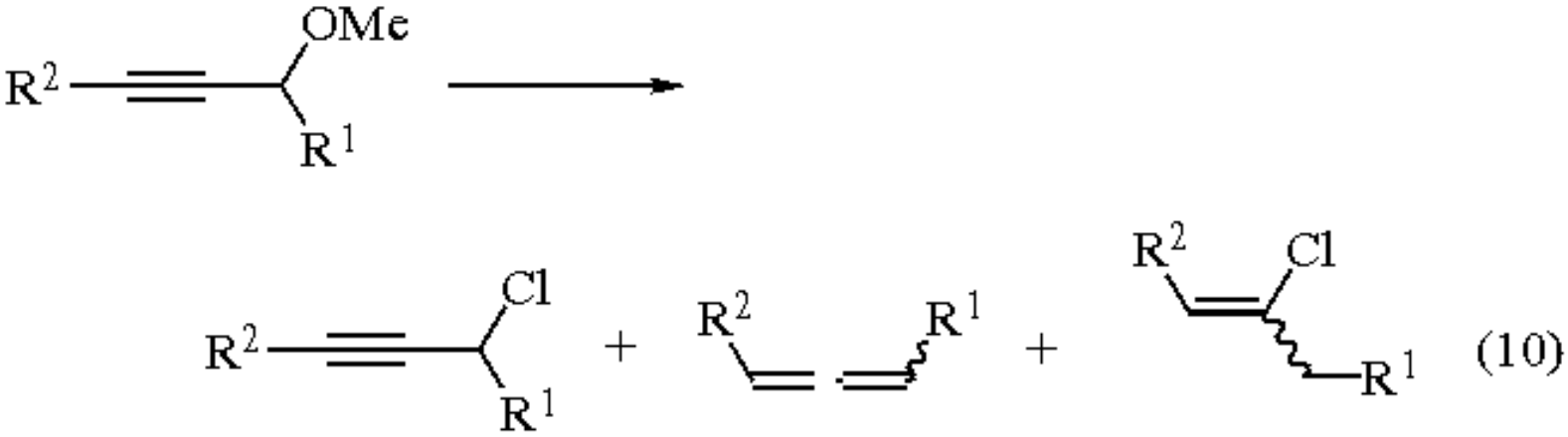

Addition to Carbon-Carbon Multiple Bonds.[1b]

Hydrochloric acid reacts with alkenes to produce either alcohols or alkyl chlorides. Anhydrous hydrogen chloride is typically the reagent used for the preparation of alkyl chlorides (eq 11). The product of the reaction is dependent upon the substrate and reaction conditions; Markovnikov addition is typically observed, but addition may be either *syn* or *anti*. The kinetic product formed from addition of HCl to alkenes may be unstable under the reaction conditions and may rearrange to yield thermodynamically more stable products. Addition of hydrogen chloride to α-pinene (**5**) leads initially to pinene hydrochloride (**6**), which isomerizes mainly to bornyl chloride (**7**) containing some fenchyl chloride (**8**).[18] Analogous rearrangements are observed with camphenes.[19] Addition to some alkenes and alkynes may require elevated temperatures, elevated pressures, or addition of a Lewis acid. The reaction with alkynes produces vinyl chlorides and dichloroalkanes (eq 12).[20] The addition to conjugated double bonds frequently leads to products which are a mixture of 1,2- and 1,4-addition products. When the diene is conjugated to an electron-withdrawing group, anti-Markovnikov addition is common.[21] Selectivity may be observed in the reaction of butadiene derivatives.[22] Allenes

frequently give mixtures of products due to acid-catalyzed migration of double bonds. The major product at low temperature is frequently the product formed from protonation at the central allene carbon.[23]

$$R^2HC{=}CHR^1 + HCl \longrightarrow R^2H_2C\text{-}CHClR^1 \qquad (11)$$

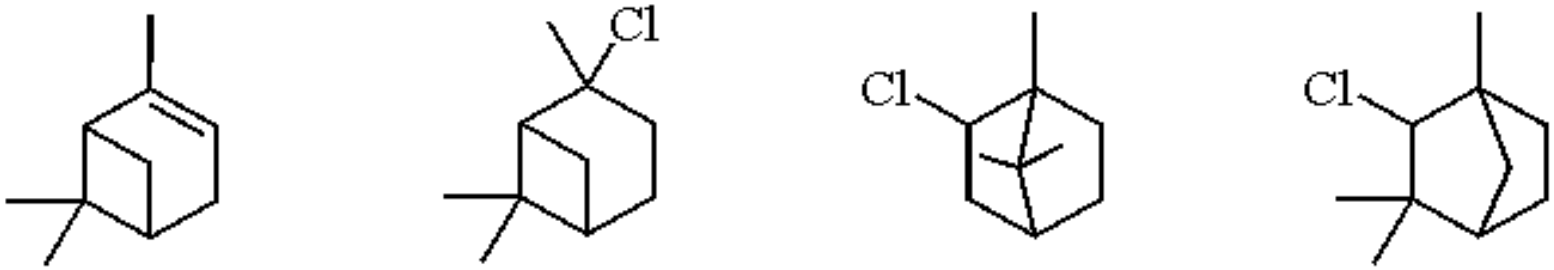

(5) **(6)** **(7)** **(8)**

$$R^2C{\equiv}CR^1 + HCl \longrightarrow R^2HC{=}CClR^1 + R^2H_2C\text{-}CCl_2R^1 \qquad (12)$$

Addition of anhydrous hydrogen chloride to 1-nitro-1-alkenes can produce 1,2-dichloroaldoximes (eq 13).[24]

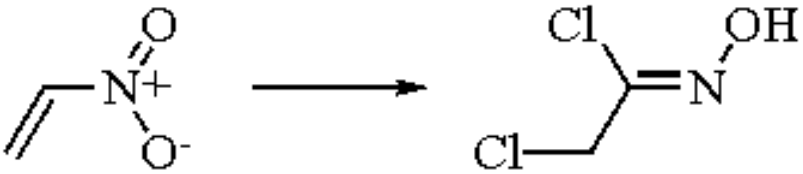

(13)

Reactions with Alcohols.

Concentrated hydrochloric acid and anhydrous hydrogen chloride react with alcohols to produce alkyl chlorides (eq 14).[25] Allylic,[26] benzylic,[27] or tertiary alcohols[28] typically are most useful as substrates for conversion to chlorides. Rearrangement may occur. On a laboratory scale, hydrochloric acid has been largely replaced by the use of phosphorus reagents such as ***Triphenylphosphine***/CCl_4, ***Triphenylphosphine Dichloride***, or Ph_3P/***Diethyl Azodicarboxylate***/Cl^- to achieve the conversion of an alcohol to a chloride.[29] These reagents frequently give less rearrangement and more stereospecificity than hydrochloric acid, ***Phosphorus(V) Chloride***, ***Phosphorus Oxychloride***, ***Thionyl Chloride***, ***Phosphorus(III) Chloride***, or ***Dimethylchloromethyleneammonium Chloride***. Treatment of alkyl phosphites, phosphonates, and diphenyl phosphinites derived from alcohols with hydrogen chloride produces the alkyl chloride in which inversion at carbon has occurred. Yields are lower and conditions are more rigorous than the corresponding reaction with ***Hydrogen Bromide***.[30]

$$ROH \longrightarrow RCl \qquad (14)$$

The reactions of carbohydrates and their derivatives with hydrogen chloride at the anomeric hydroxyl are examples of the facile conversion of alcohols to chlorides.[31] Protected and unprotected sugars react with methanol in the presence of dilute hydrochloric acid to produce the methyl ether at the anomeric center.[32]

Reactions with Diazo Compounds.

The reaction of diazo compounds derived from α-amino acids or α-amino ketones with hydrochloric acid results in isolation of the corresponding racemic α-chloro carbonyl compound (eq 15).[33]

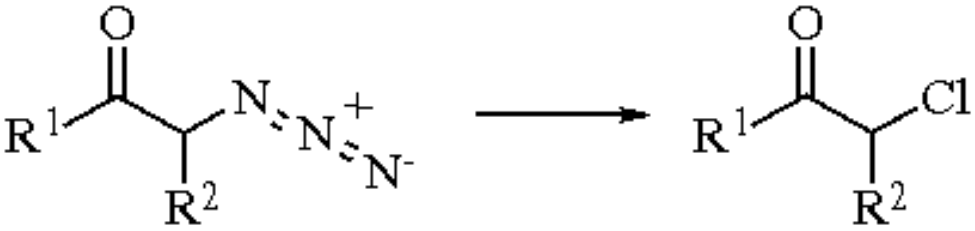

(15)

Reactions with Nitriles and Their Derivatives.

Addition of anhydrous hydrogen chloride to nitriles produces imidoyl chlorides (eq 16).[34] Treatment of *N*-alkylimidoyl chlorides with hydrogen chloride results in isolation of the corresponding iminium halides (eq 17).[35] Aryl cyanates react with hydrogen chloride to produce haloformimidinium halides (eq 18).[36] Molecules containing two nitrile groups frequently give cyclic amidinium products.[37] Hydrogen chloride reacts with nitrile oxides to yield hydroxamoyl chlorides (eq 19). Hydroxamoyl chlorides are also produced in the reaction of phenylnitromethane with hydrogen chloride and in the reaction of acetophenones with isopropyl nitrite and hydrogen chloride.[38]

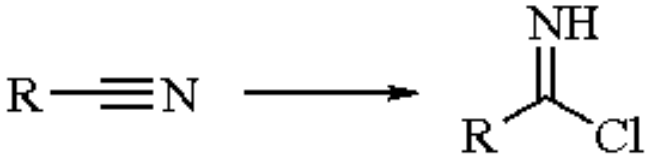

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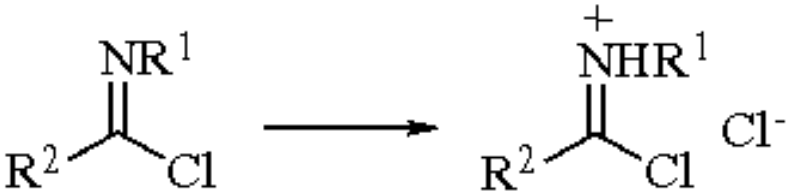

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(18)

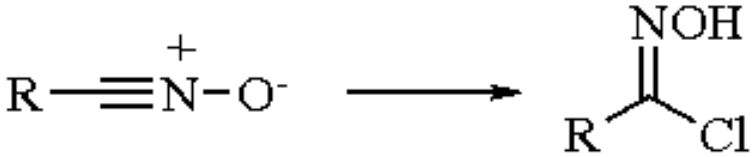

(19)

Reaction with Nitrogen-Sulfur Bonds.

Hydrogen chloride has been used to cleave the nitrogen-sulfur bond of 2,2,2-trifluoro-1,1-diphenylethylsulfenyl-protected amines in high yield (eq 20).[39]

$$R^1NHSR^2 + HCl \longrightarrow R^1NH_2 + R^2SCl \qquad (20)$$

Hydrolysis of 1,1-Dichloroethylenes.

Hydrochloric acid in glacial acetic acid or alcohols has been used to convert 1,1-dichloroethylenes to carboxylic acids (eq 21).[40] This reaction appears to require additional conjugation or the presence of an allylic leaving group to proceed smoothly. The use of sulfuric acid appears to be more general since additional conjugation is not required.[41] ***Potassium Hydroxide*** has also been used to effect this hydrolysis.[42]

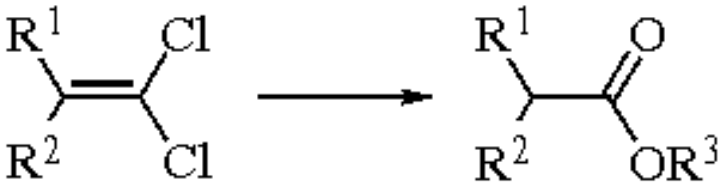

(21)

Silicon and Sulfur Chemistry.

Protodesilylation with hydrochloric acid is most useful for substrates in which the silicon-carbon bond to be cleaved is aryl (eq 22), vinylic (eq 23), benzylic, or allylic (eq 24).[43] Phenylsilanes react with hydrogen chloride to yield benzene and the chlorosilane. The reaction is less facile than the reaction with hydrogen bromide.[44] Increasing the electronegativity of substituents on silicon decreases the ease with which the aryl-silicon bond is broken. Hindered aryl silanes may require fluoride ion.[45] Allylic protodesilylation normally occurs with double bond migration (eq 24).[46] Protodesilylation of a silicon-carbon bond in which the carbon is sp hybridized may require the addition of a fluoride source (eq 25).[47]

$$ArSiR^1R^2R^3 + HCl \longrightarrow ArH \qquad (22)$$

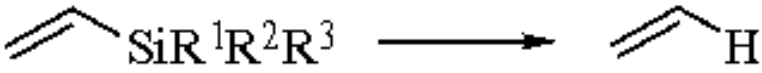

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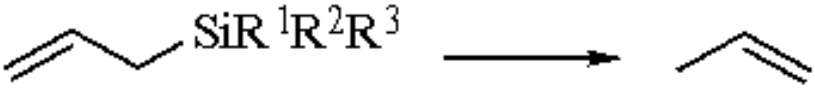

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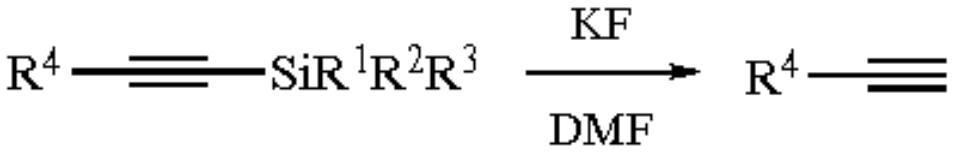

(25)

Triethylaminosilanes are converted to the corresponding chlorosilanes in the presence of hydrochloric acid/sulfuric acid (eq 26).[48]

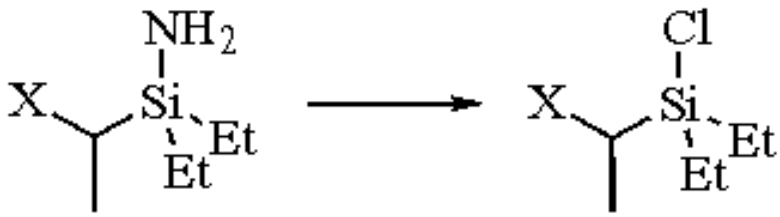

(26)

Silyl ethers may be cleaved using hydrochloric acid (eq 27).[49] Fluoride ion is an alternative which is frequently used when the substrate is acid sensitive.

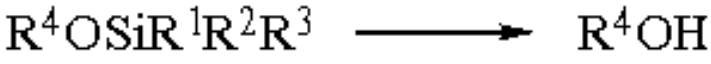

(27)

Acylsilanes have been obtained from 1-silyl-1-enol ethers (eq 28), 1-silyl-1-aminoethylenes (eq 29), and mixed *O*-alkyl-*O*-silyl acetals of acylsilanes (eq 30) upon treatment with dilute hydrochloric acid.[50] Analogous chemistry has been observed with germanium and tin compounds.[51]

(28)

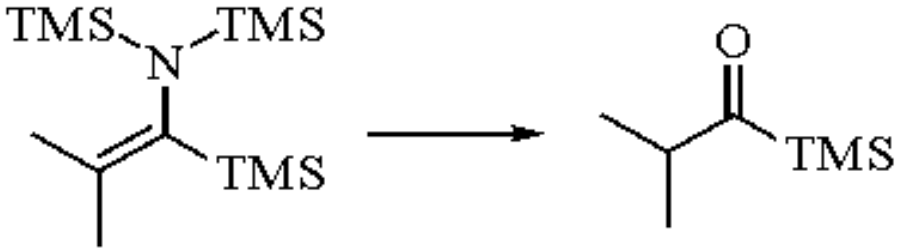

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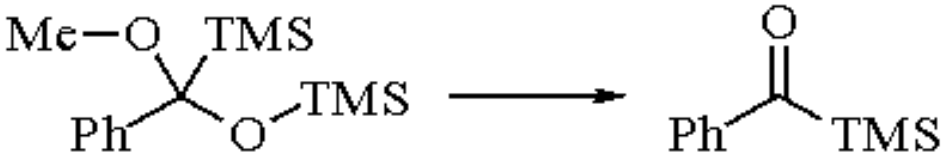

(30)

Phenylsilane reacts with anhydrous hydrogen chloride in ether in the presence of ***Aluminum Chloride*** to yield chlorophenylsilane (eq 31).[52]

$$PhSiH_3 \longrightarrow PhSiH_2Cl \qquad (31)$$

Diphenylsilanediol yields the cyclic siloxane in moderate yield when treated with concentrated hydrochloric acid in ether at reflux (eq 32).[53] This reaction is also effected using amines.

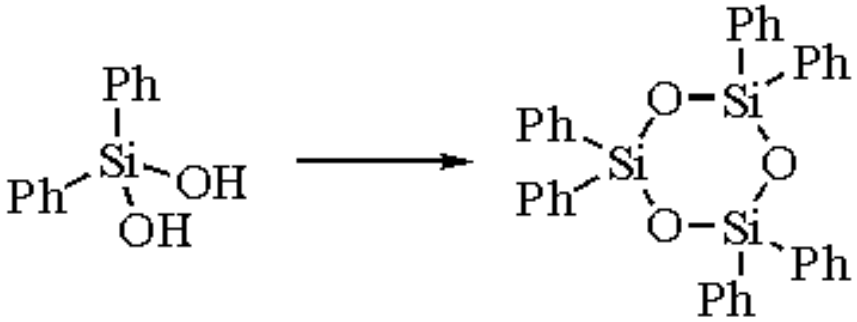

(32)

Thioacyl chlorides have been prepared from thioketenes and anhydrous hydrogen chloride at low temperatures (eq 33).[54]

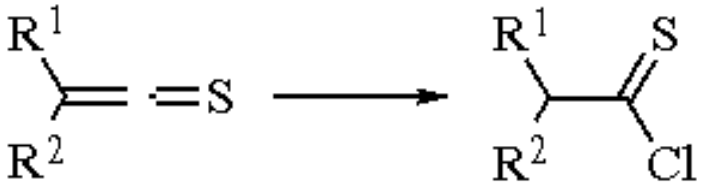

(33)

Transhalogenation Reactions.

3-Bromo-4,5-dihydroisoxazole derivatives can be converted to the corresponding chlorides by treatment with hydrochloric acid and ***Lithium Chloride*** (eq 34).[55]

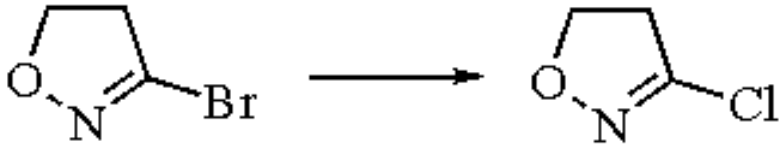

(34)

Organometallic Chemistry.

Carbon-metal bonds are typically cleaved by hydrochloric acid to yield the metal chloride and the hydrocarbon (eq 35).[56] Oxygen-tin bonds are also cleaved by treatment with hydrochloric acid.[57]

$$RM + HCl \longrightarrow RH \qquad (35)$$

Alkyl phenyl selenoxides react with hydrogen chloride to yield the alkyl chlorides (eq 36). Conversion to the bromide with hydrogen bromide proceeds faster and in higher yield.[58]

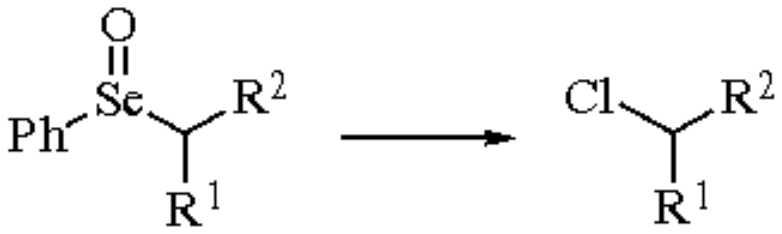

(36)

Treatment of the zirconium metallacycle shown with hydrochloric acid led to formation of the indole in high yield (eq 37).[59]

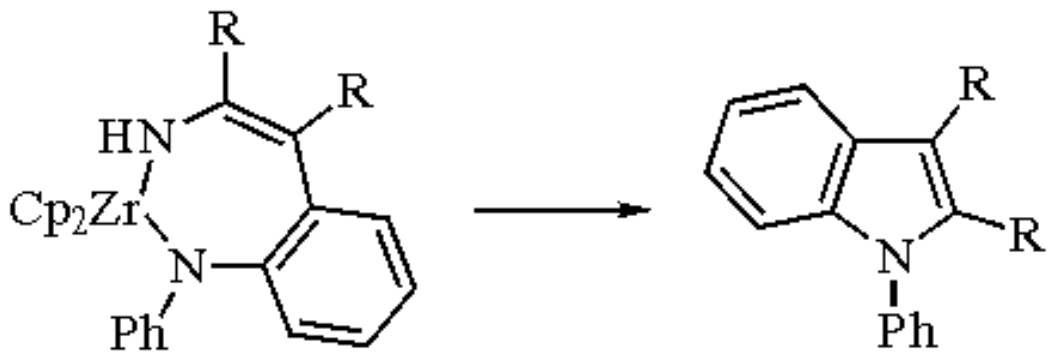

(37)

Treatment of a tungsten complex with 2 equiv of hydrochloric acid in ether led to formation of a new chlorotungsten compound (eq 38).[60]

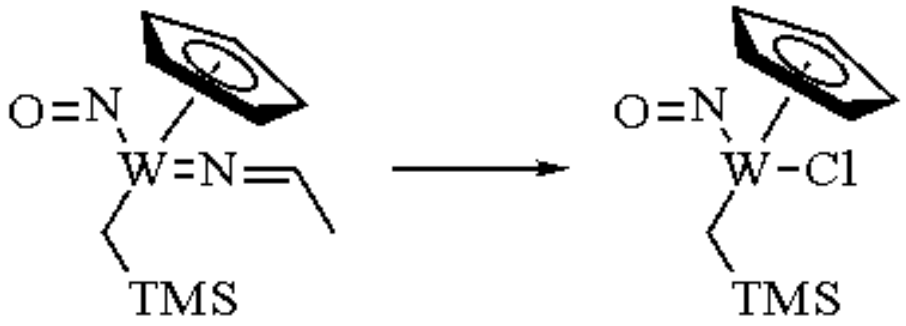

(38)

1,1-Dihydroxy-2,3-diphenylgermirene is converted to the dichloride with anhydrous hydrogen chloride in benzene (eq 39).[61]

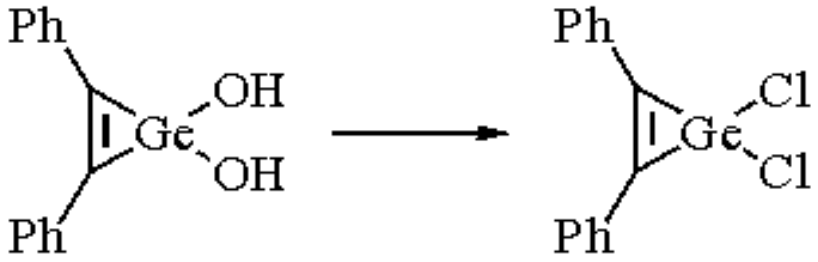

(39)

In Situ Generation of Chlorine and Hypochlorite.

Hydrochloric acid and ***Hydrogen Peroxide*** are an effective combination for the in situ generation of ***Chlorine*** (eq 40). This combination of reagents can be used for the halogenation of alkenes and aromatics.[62]

$$HCl + [O] \longrightarrow Cl_2 \qquad (40)$$

Treatment of 1,2-diphenylacetylene with HCl and ***Iodosylbenzene*** on silica gel appears to proceed through formation of chlorine to yield a mixture of (*E*)- and (*Z*)-1,2-diphenyl-1,2-dichloroethylene. However, under similar conditions, 1,1,2-triphenylethylene produces 2-chloro-1,1,2-triphenylethanol.[63] Chlorides are obtained in higher yields than bromides, which are obtained in higher yields than iodides when HBr or HI are substituted for HCl in the reaction. 1-Phenylpropyne reacts with oxone (***Potassium Monoperoxysulfate***) and hydrochloric acid in DMF to produce 2,2-dichloropropiophenone in high yield.[64] Replacement of oxone with ***m-Chloroperbenzoic Acid*** results in lower yields.

Related Reagents.

Formaldehyde-Hydrogen Chloride; ***Hydrogen Chloride***.

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Hydrofluoric Acid[1]

FH

[7664-39-3] · FH · Hydrofluoric Acid · (MW 20.01)

(strong acid;[1b] fluorinating agent;[1b] forms complexes with organic bases as fluorination agents;[1a] deprotecting reagent[2])

Physical Data: mp -83.5 °C; bp 19.5 °C; *d* 3.0 (air = 1) at 25 °C.

Solubility: 100 wt % in water.

Form Supplied in: gas, colorless mobile liquid, or aq. solution; HF-pyridine, HF-triethylamine and HF-pyridine polymer bound are also available.

Handling, Storage, and Precautions: HF and its containing complexes are severely human tissue corrosive, causing extremely painful and slow-healing burns and ulcers. No glassware should be used for any reaction involving hydrofluoric acid. Wash thoroughly after handling. Since hydrogen fluoride burns may not be noticed for several hours, should you have any suspicion of skin contact, flush skin with water immediately for 5 min and apply calcium gluconate gel (2.5%) on the burned area. The container should be kept in a cool and dark place which should be well ventilated. Avoid storage in glass and some metals since it corrodes most substances except lead, wax polyethylene, and platinum. Use in a fume hood.

Hydrofluorination.

Anhydrous ***Hydrogen Fluoride*** and its base solutions are useful for the fluorination of various compounds and can add to alkenes, alkynes, and some other unsaturated systems (eq 1).[3] Due to the difficulties of handling anhydrous hydrogen fluoride, HF-organic base (amines,[1a] ketones,[4] or ethers[5]) solutions are often used. One of the important reagents is HF in pyridine solution, which contains 9 equiv of HF and 1 equiv of pyridine (Olah's reagent).[6,7] These HF-organic base solutions are very hygroscopic, and the absorption of water has a profound effect on the fluorination activity. HF-melamine (86/14, wt/wt %) complex has been reported to be superior to other HF-amine solutions (eq 2).[8] Aqueous HF solution has been rarely used for this addition because of the competitive incorporation of water.[9] Hydrogen fluoride adds to hydrocarbon alkenes to form the monofluoride, obeying Markovnikov's rule with the complicating effect of polymerization. By using excess HF, polymerization can be reduced. Activated charcoal[10] and ***Boron Trifluoride***[11,12] have been used for catalyzing this reaction. Addition of hydrogen fluoride to halogenated alkenes has less tendency for polymerization, but the ease of this reaction decreases with the increasing number of halogen atoms (eq 3).[12] Chlorine atoms can be exchanged by fluorine under some conditions (eq 4).[5] ***Lead(IV)***

Oxide[13] or ***Lead(IV) Acetate***[14] and anhydrous hydrogen fluoride can generate fluorine in situ to add across the double bond.

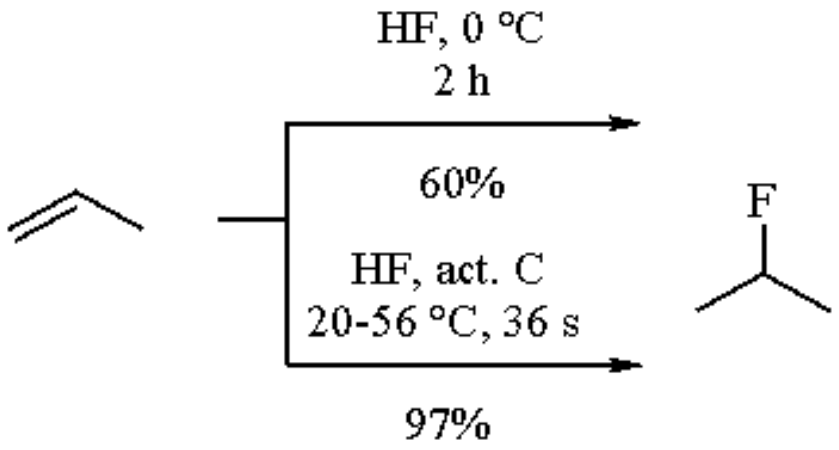

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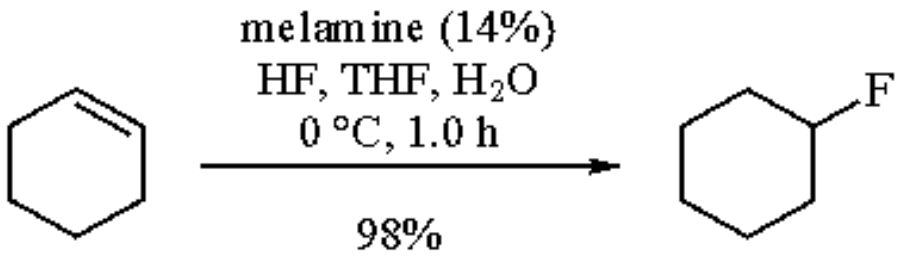

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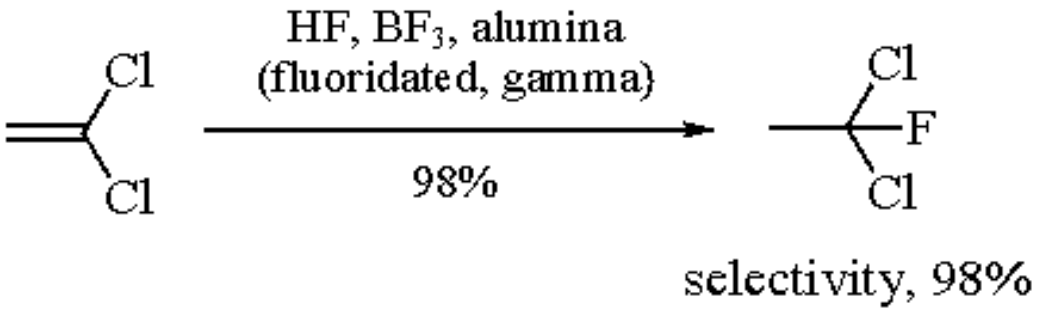

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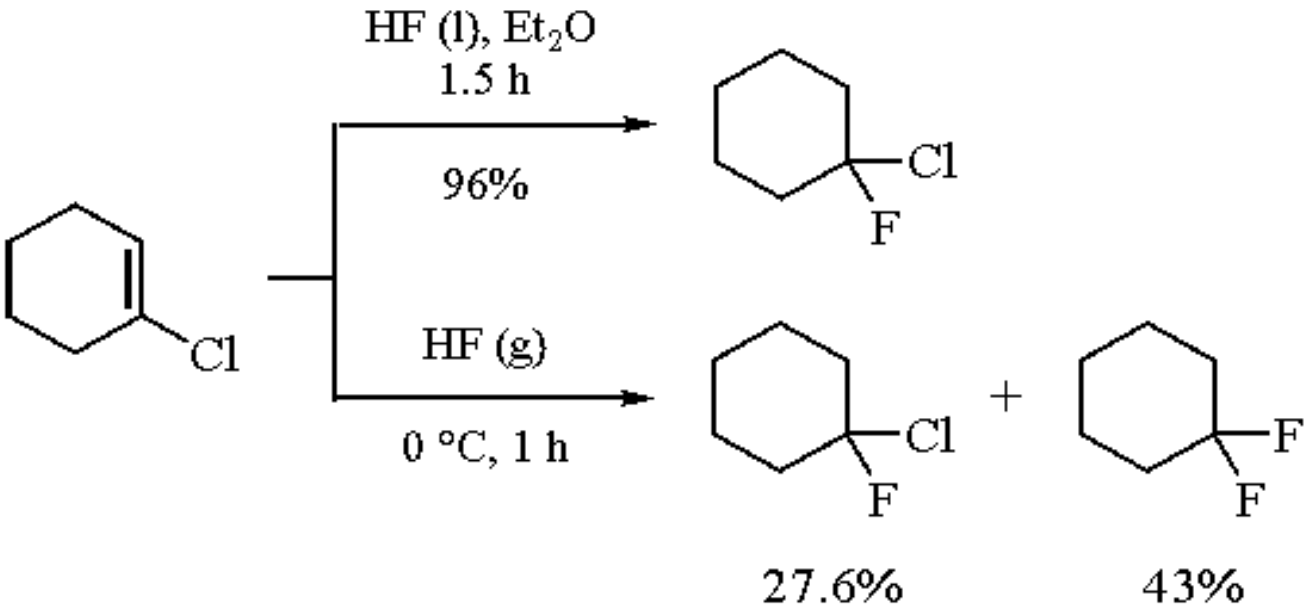

(4)

The addition of hydrogen fluoride across a triple bond can be effected by various reagents (eq 5).[4,9] It is difficult to stop the addition of HF at the intermediate fluoroalkene stage, indicating that the intermediate alkene is more reactive than the parent alkyne. Hydrofluorination of alkynes with solid poly(hydrogen fluoride) is found to be efficient and convenient.[9] HF is also a catalyst for addition of fluorine to alkynes by ***Xenon(II) Fluoride*** to form vicinal tetrafluorides (eq 6).[15] Anhydrous HF has been used in cyclization of 1-bromoalkynes with an *N*-acyliminium ion to form bromofluoro derivatives (eq 7).[16] The electrophilic *anti* addition of the elements of benzeneselenenyl fluoride to an alkyne has been achieved by using *N*-phenylselenophthalimide and Et_3N-3HF (eq 8).[17]

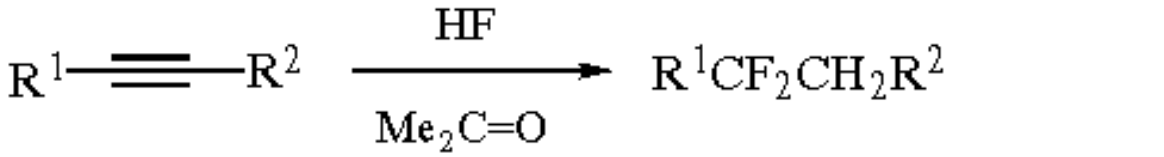

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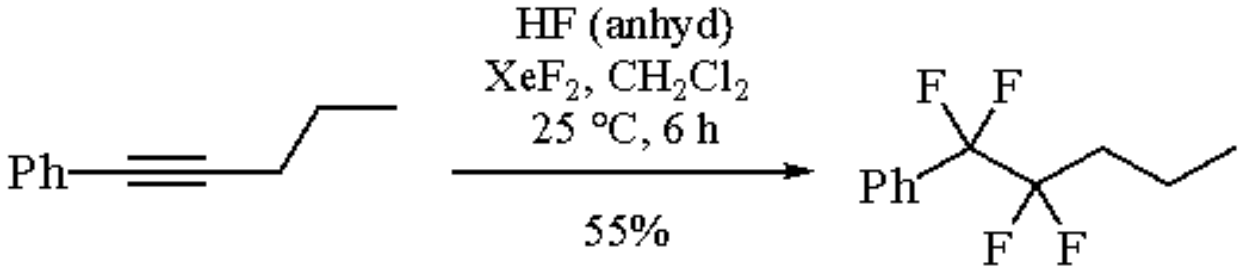

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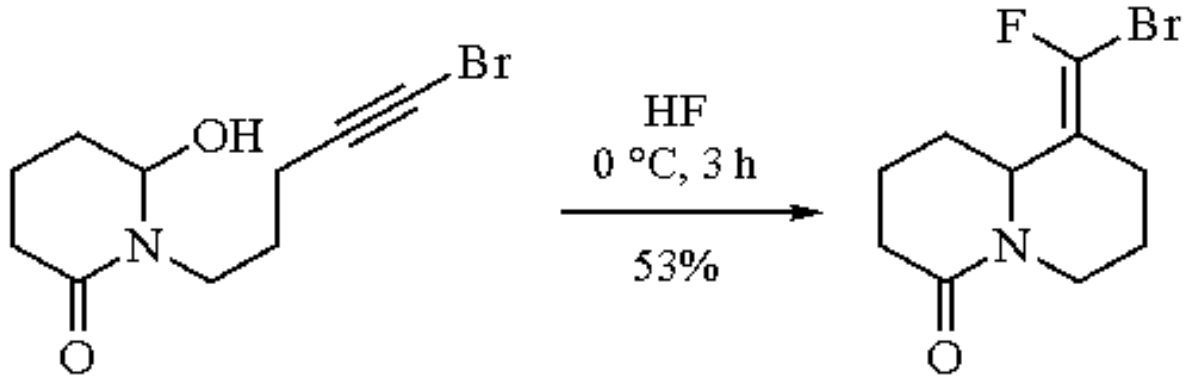

(7)

4:1 isom. mix.

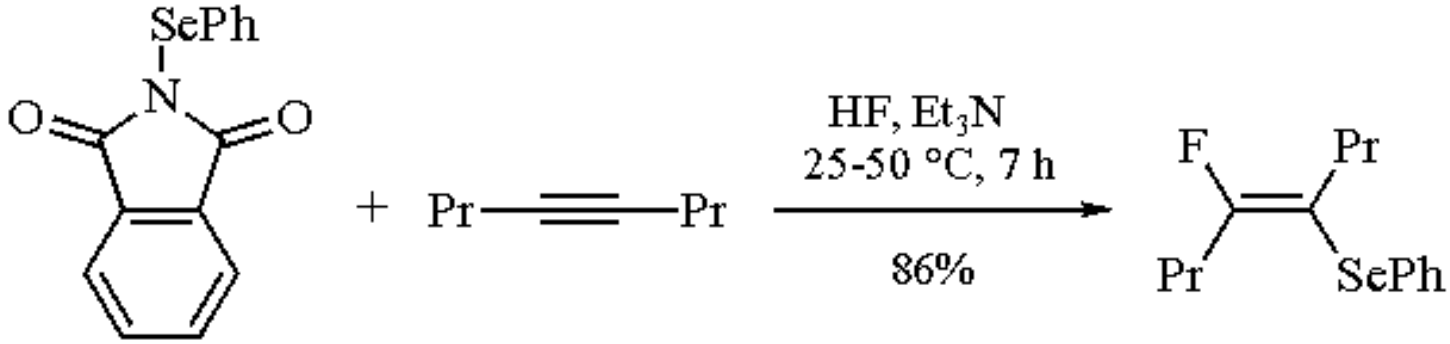

(8)

Hydrogen fluoride can also add directly to other unsaturated compounds. Phenylcarbamoyl fluoride has been prepared by addition of HF to phenyl isocyanate in a quantitative yield (eq 9).[18,19] Hydrogen fluoride can also add across the C=N double bond in moderate to good yields (eq 10).[20]

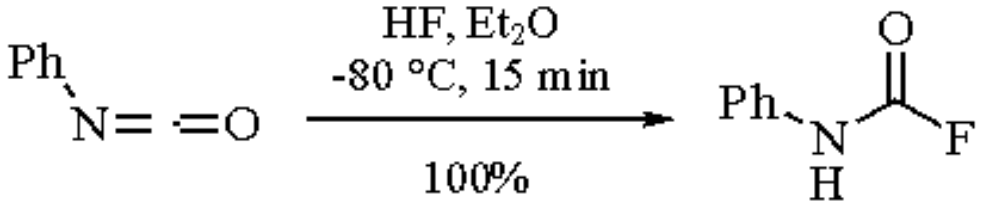

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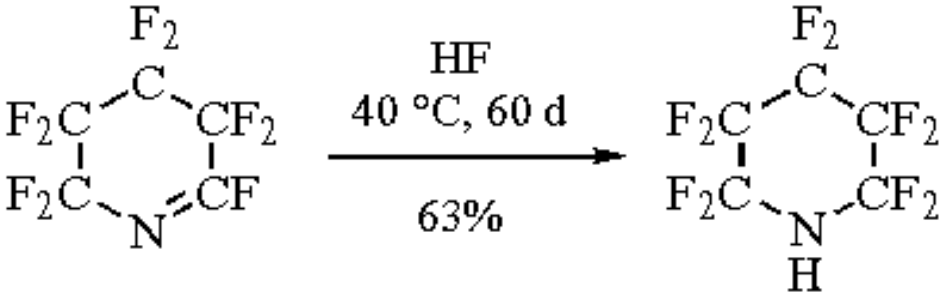

(10)

Hydrogen fluoride and other fluoride sources in combination with electrophilic halogens (such as NCS, NBS, or NIS) can generate halofluorides (ClF, BrF, or IF) in situ, which then add across the alkene to give the halofluorination products.[21] ***N-Bromoacetamide*** or ***N-Bromosuccinimide*** with HF or its base solutions are convenient reagents for bromofluorination (eq 11).[22-25] The addition follows the Markovnikov-type regioselectivity. Bromofluorination of allylic alcohols gives the vicinal fluorobromohydrins, which can form α-fluoro epoxides and/or monofluoro oxetanes (eq 12).[26] Iodofluorinations are often very stereo- and regioselective (eq 13).[27-29] A carbonyl group has been transformed into a CF_2 moiety via its hydrazone by an in situ generated bromine monofluoride (BrF) method.[30]

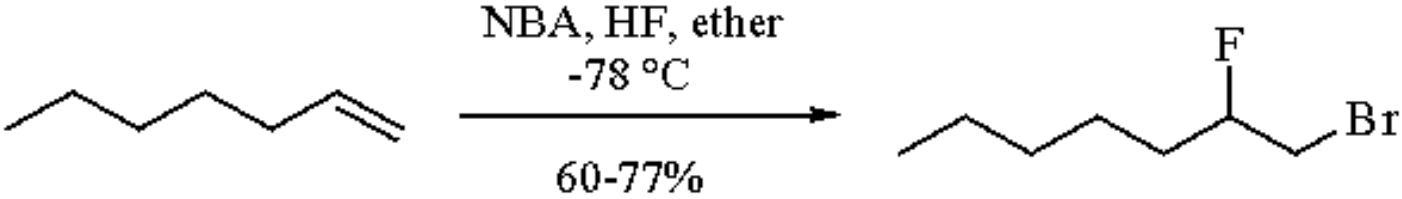

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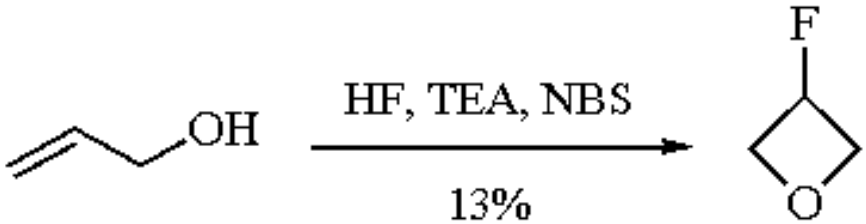

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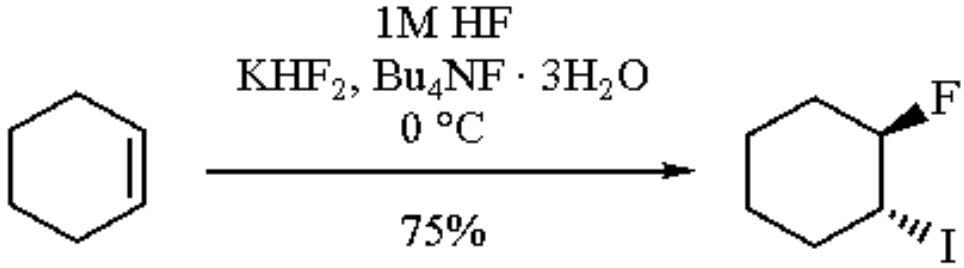

(13)

Friedel-Crafts Reaction and Cyclodehydration.

Liquid anhydrous hydrogen fluoride is an effective dehydrating and condensing agent, comparable to strong acids such as conc. ***Sulfuric Acid***.[31] It catalyzes Friedel-Crafts acylation and alkylation to form a variety of products. Most of the reactions proceed at rt within a very short period of time. Methylcyclopropane reacts with benzene in the presence of HF to give *s*-butylbenzene as the only product (eq 14).[32] SbF_5 and BF_3 have been used as catalysts in some cases (eq 15).[33-35] HF has been used as a catalyst for intramolecular Friedel-Crafts acylation and is sometimes superior to ***Polyphosphoric Acid*** (eq 16).[36] Ring closure of tertiary alcohols and alkenes to an aromatic ring can be achieved by treating substrates with neat HF (eq 17).[37-39] Hydrogen fluoride can also effectively catalyze the Fries rearrangement.[40]

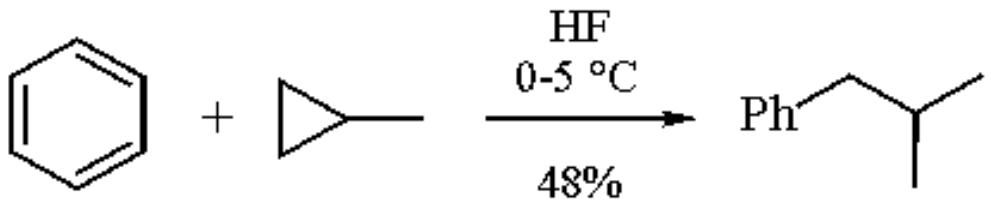

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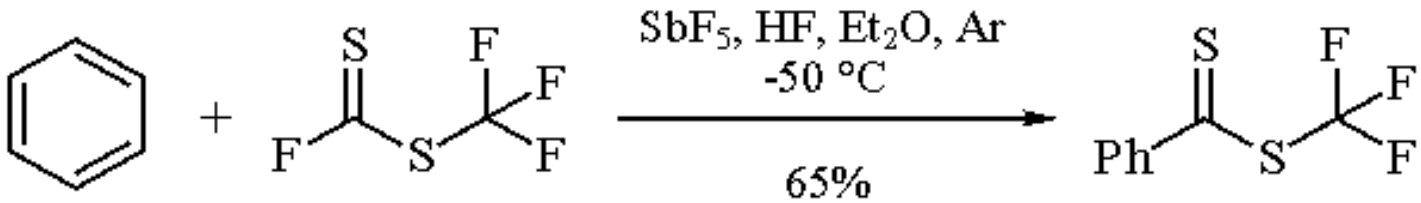

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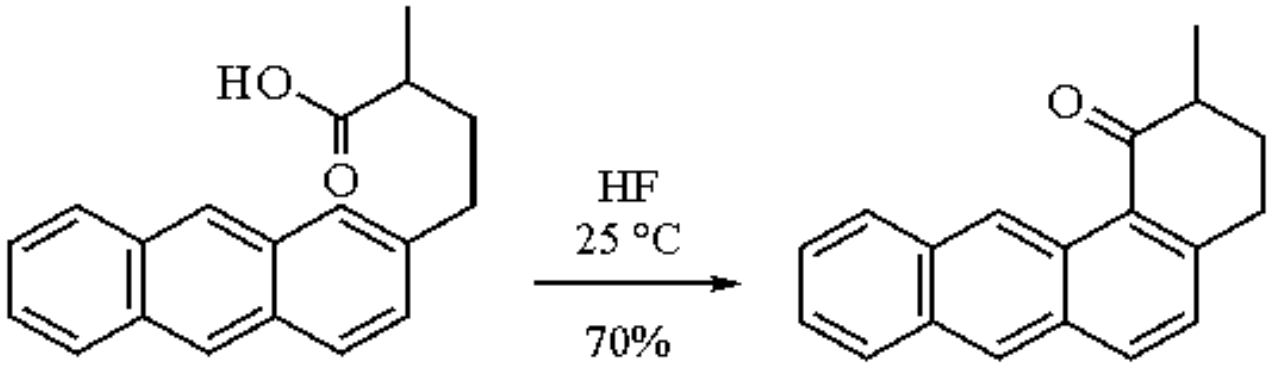

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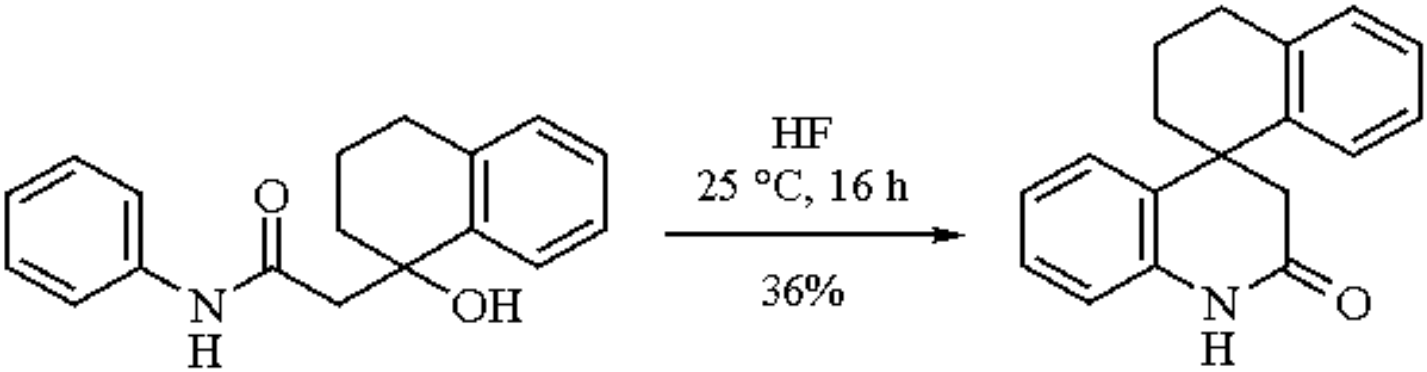

(17)

Hydrogen fluoride cyclodehydration provides a wide range of polycyclic aromatic compounds (eq 18).[41] This is also a very useful method to prepare some heterocyclic compounds (eq 19).[42,43] Trienes can undergo an intramolecular

Diels-Alder reaction with good stereoselectivity, when it is catalyzed by aqueous HF (eq 20).[44]

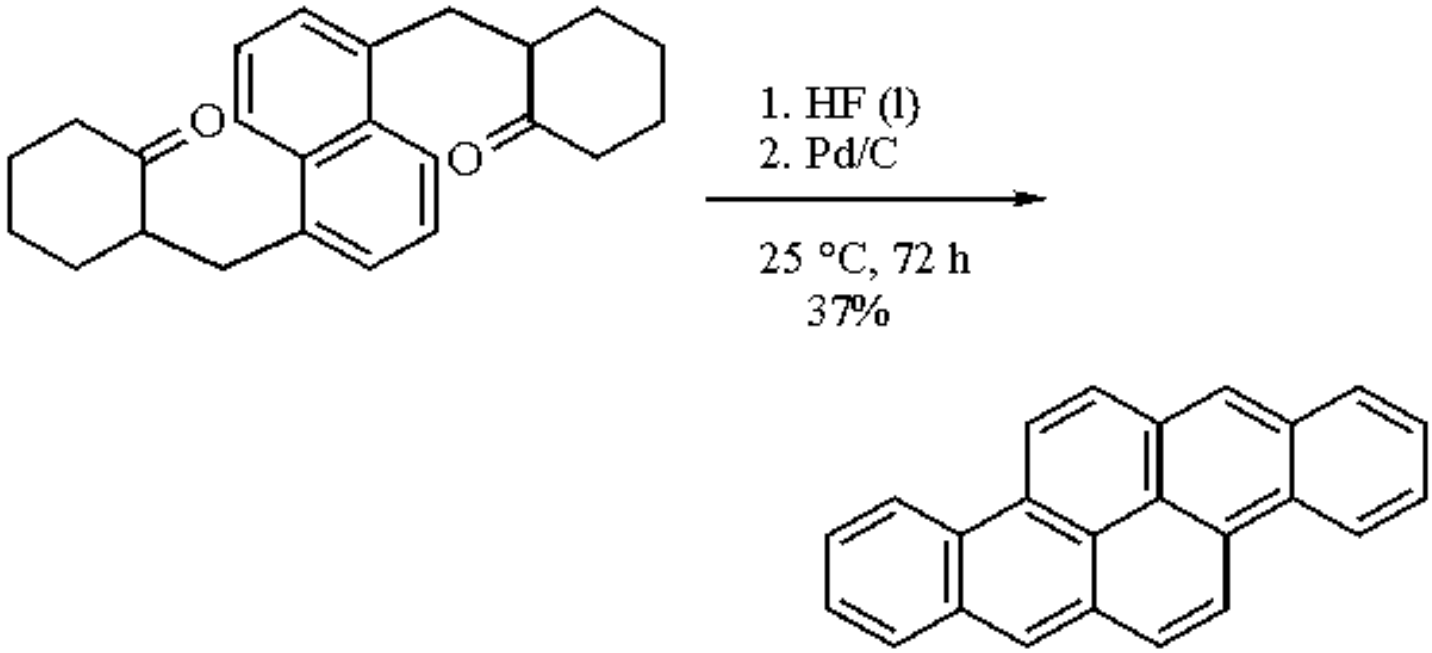

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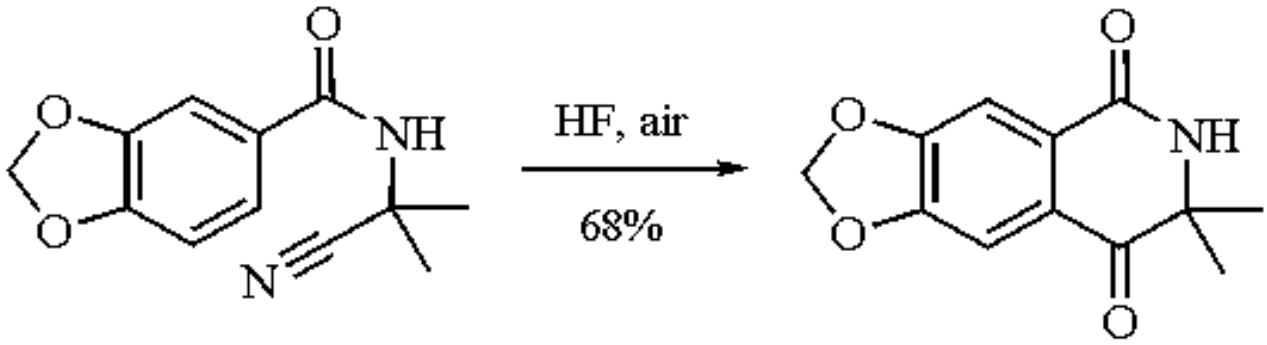

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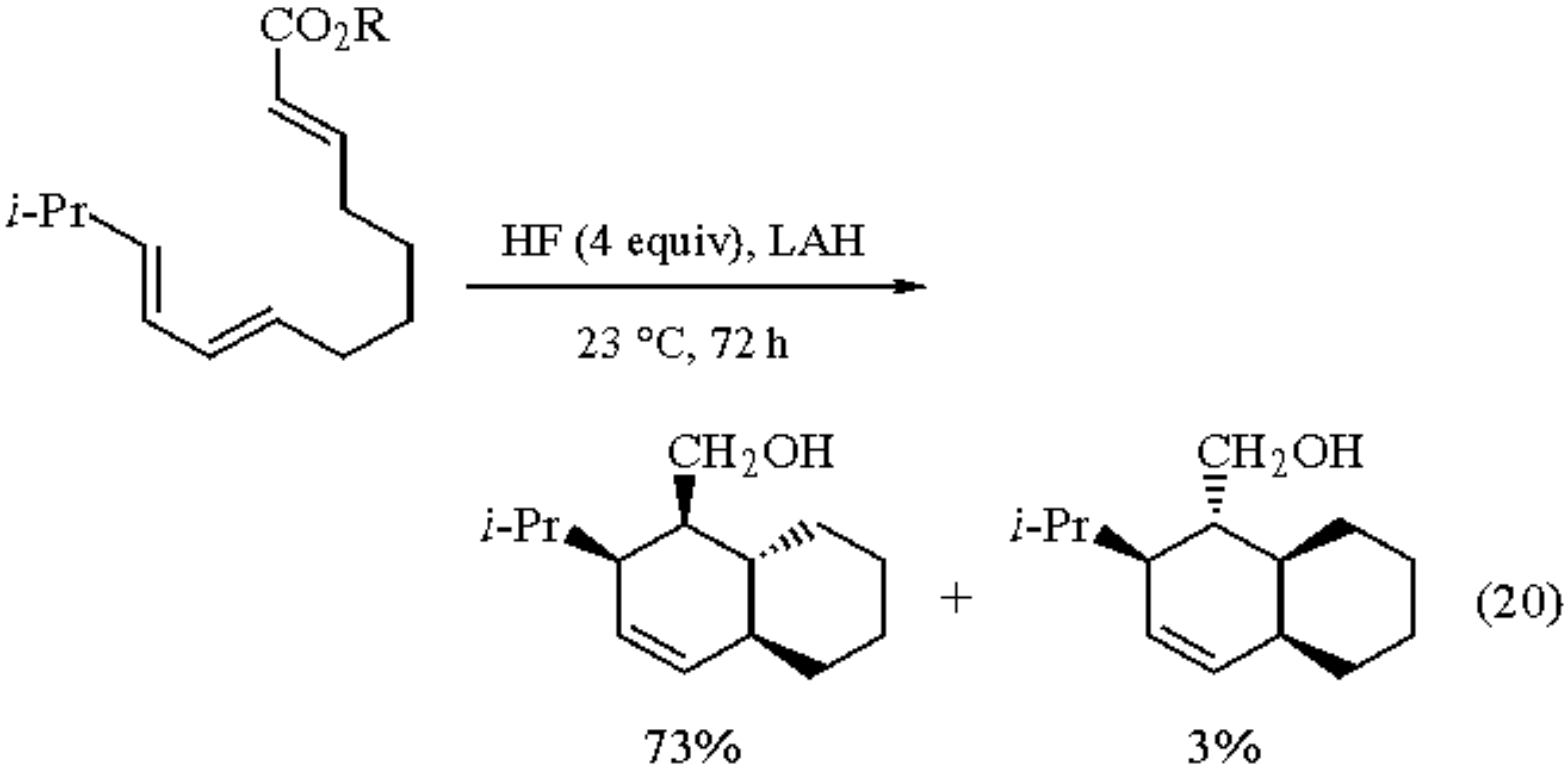

Fluorodehydroxylation and Fluorodeamination.

Secondary and tertiary alcohols and their derivatives, such as acetates and mesylates, are readily fluorinated by HF-amine solutions. Olah's reagent and HF-melamine convert free secondary and tertiary alcohols into the corresponding fluoride in moderate to good yield.[6,45] 1-Adamantanol has been converted to 1-fluoroadamantane by HF-pyridine at rt (eq 21).[46] The mesylates and tosylates of primary alcohols can be converted to the corresponding fluorinated compounds by tetrabutylammonium difluoride; however, secondary mesylates give lower yields due to the formation of alkenes as byproducts (eq 22).[47] Glycosyl fluorides can be made from protected sugars and β-isomers are the major product in most of the cases (eq 23).[48-50]

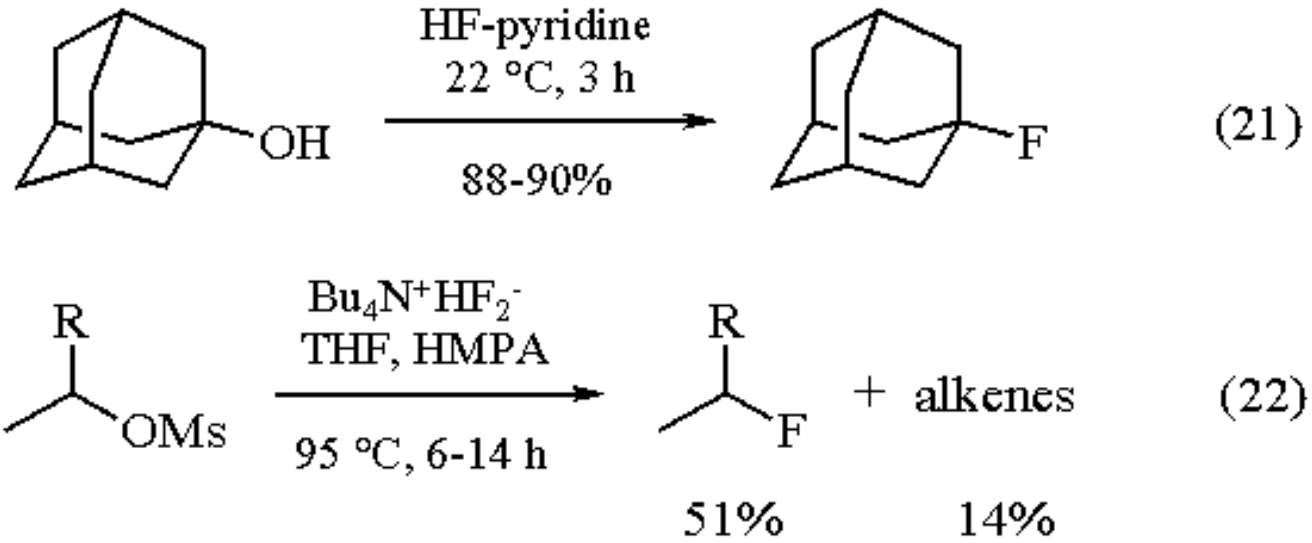

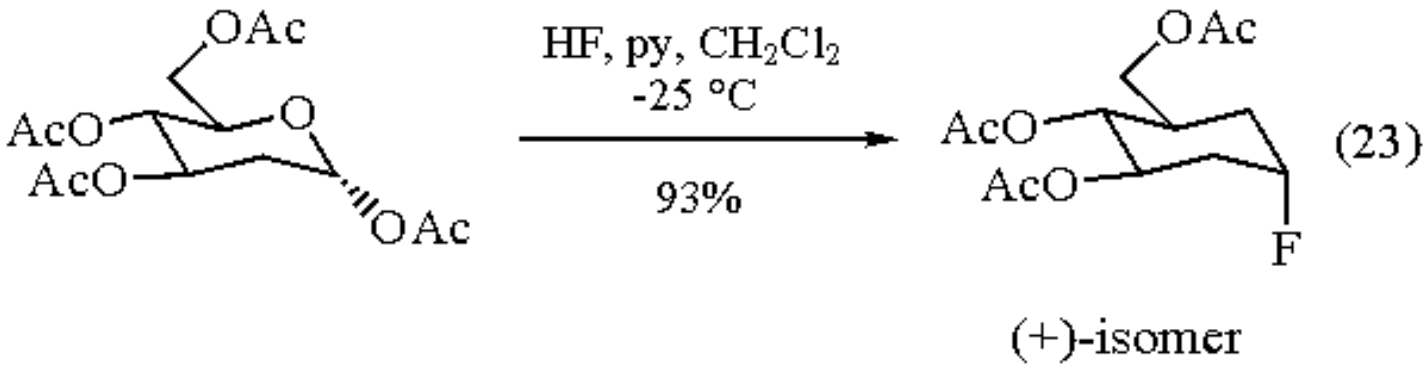

Aromatic amines can be transformed into their corresponding fluorinated compounds by a one-pot diazotization and fluorodediazonization in good yields (eq 24).[51-53] If sodium halide (chloride, bromide or iodide) is added, haloarene isomeric mixtures are formed in good yield with small amounts of fluoroarenes. α-Fluorocarboxylic acids and ketones have been prepared from amino compounds via diazotization in 70% poly(hydrogen fluoride)-pyridine, with some exceptions (eq 25).[54]

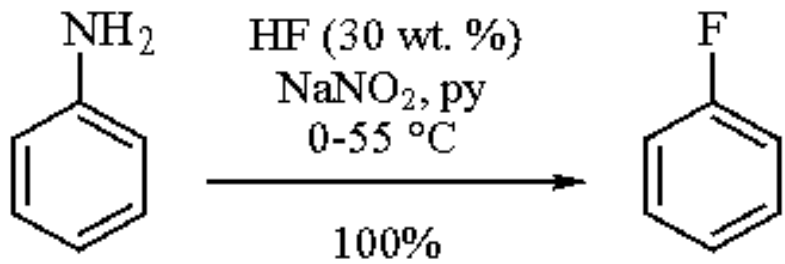

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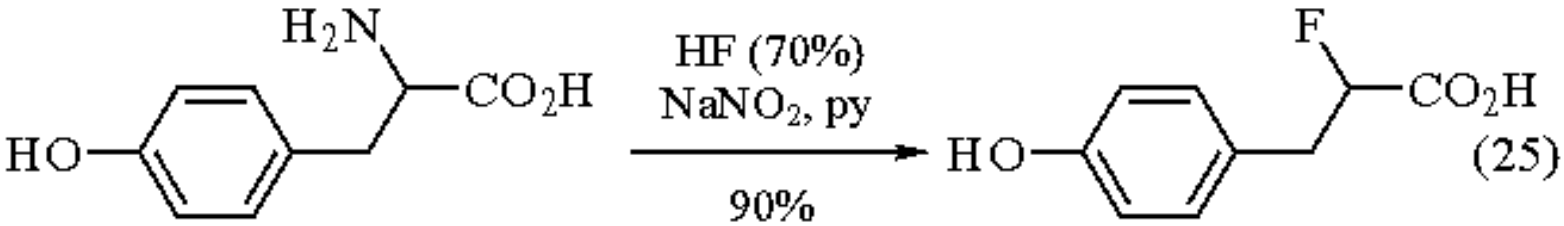

(25)

Halogen-Exchange Fluorination.

For most primary and secondary aliphatic halides, halogen-exchange fluorination can be carried out by using ***Potassium Fluoride*** or other inorganic fluorides. HF reagents are suitable for unreactive cyclic and tertiary alkyl halides where KF or ***Cesium Fluoride*** often fail to give good results. ***Copper(I) Oxide*** and ***Mercury(II) Oxide*** are effective catalysts for this halogen exchange reaction due to the formation of metal fluorides (eq 26).[55,56] The combination of ***Nitronium Tetrafluoroborate*** and HF-pyridine exchanges bridgehead adamantyl halides with fluoride in good yield.[57] Acyl fluorides can be readily made by treating acyl chlorides or anhydrides with hydrogen fluoride (eq 27).[57-59]

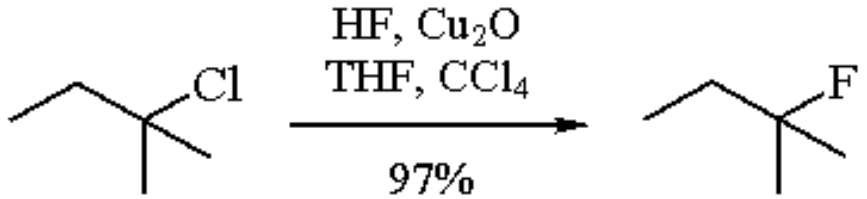

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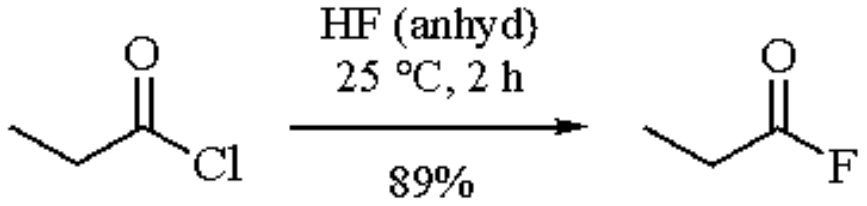

(27)

Trifluoromethylation of phenols can be achieved with carbon tetrachloride and hydrogen fluoride (eq 28).[60] Chlorines on other heteroatoms, such as boron,[61] silicon,[62] phosphorus,[63] and iodine, can be exchanged with fluoride by hydrogen fluoride.

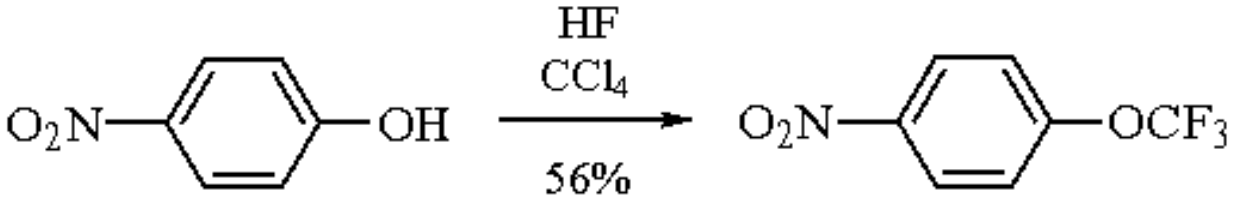

(28)

Ring-Opening Fluorinating Reagent.

Three-membered rings, such as cyclopropanes, epoxides, aziridines, and azirines, can be opened upon treatment with HF reagents. Opening cyclopropanes with HF-pyridine gives fluoropropanes.[29] Treating substituted cyclopropylmethanols with HF-pyridine, in diisopropylamine and chlorobenzene in the presence of KHF_2, affords homoallylic fluorides in good yields (eq 29).[64] Epoxides are much more reactive than cyclopropanes and can be readily opened by a variety of HF reagents.[65-67] These reactions are often regioselective (eq 30).[68] Addition takes place to give the *trans* products when epoxyindane (eq 31), 1,2-epoxytetralin (eq 32), and 2,3-epoxytetralin (eq 33) are treated with HF-diisopropylamine.[69]

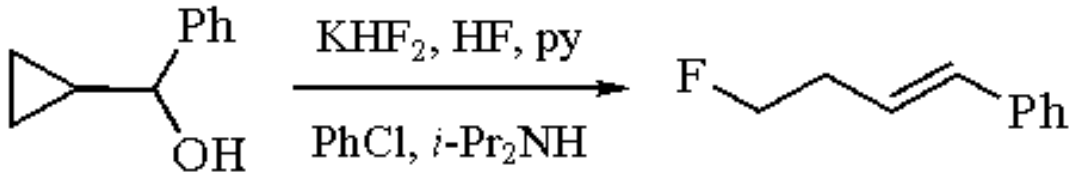

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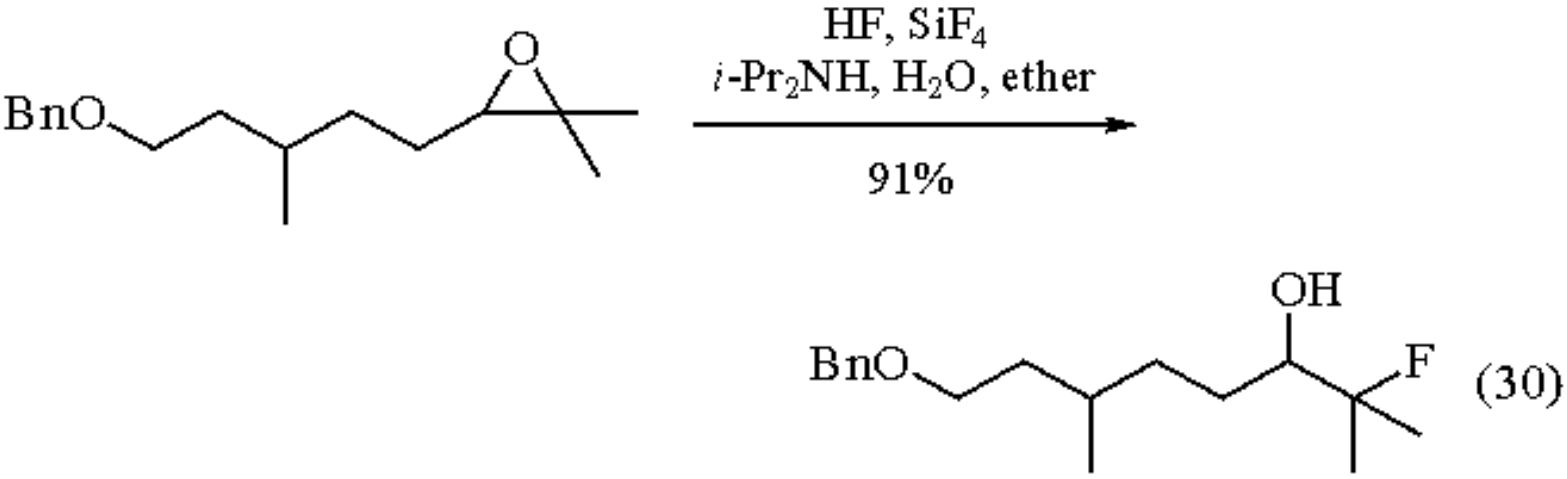

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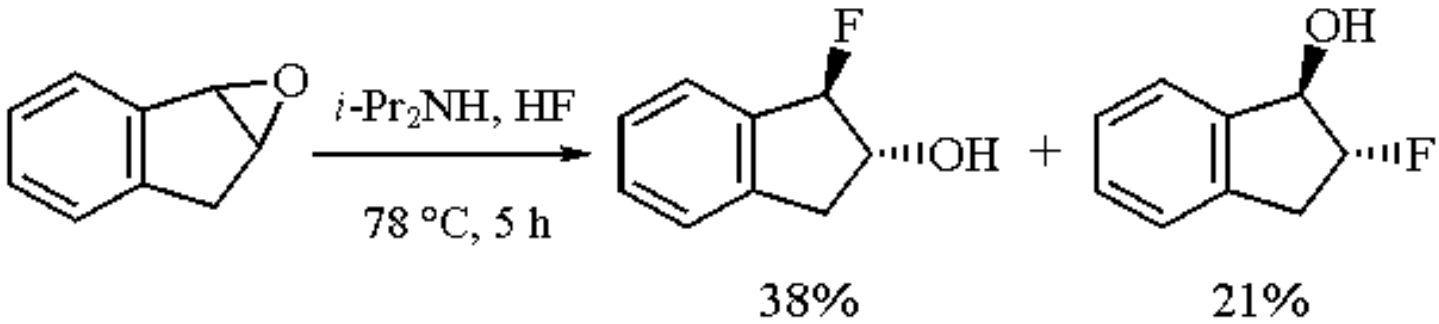

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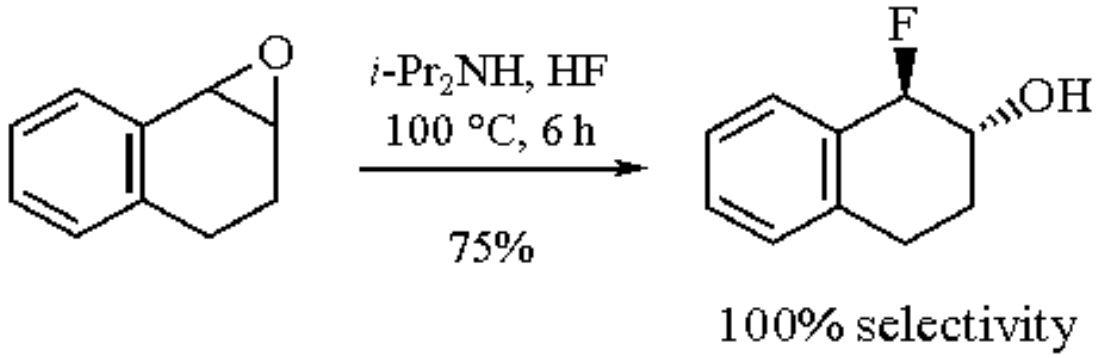

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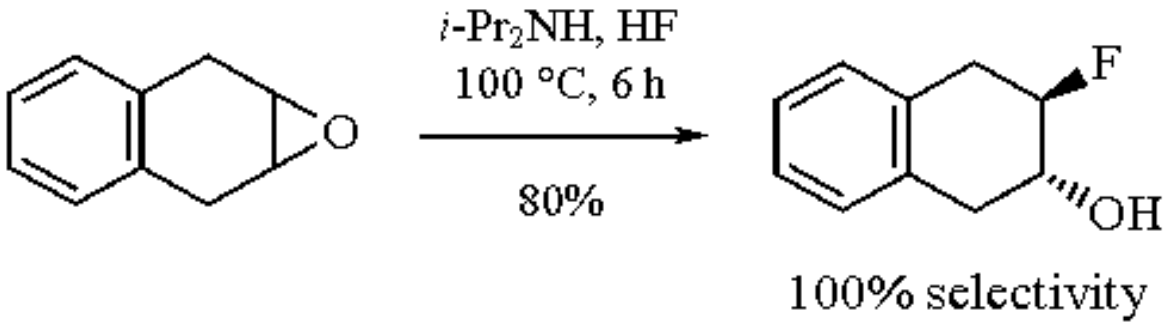

(33)

Addition of HF to aziridines gives β-fluoro amines (eq 34).[70] *N*-Alkylated aziridines are less reactive and often require higher reaction temperatures. On the other hand, *N*-activated aziridines give better regioselectivity but the reactions are often accompanied by the formation of oxazolines (eq 35).[71] Treatment of 1,2-epoxypyrrolidines with HF-pyridine can form different ring-opening products, depending on the stereochemistry of substrates (eqs 36 and 37).[72,73]

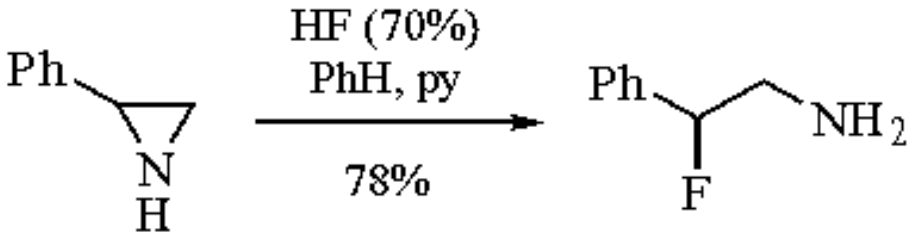

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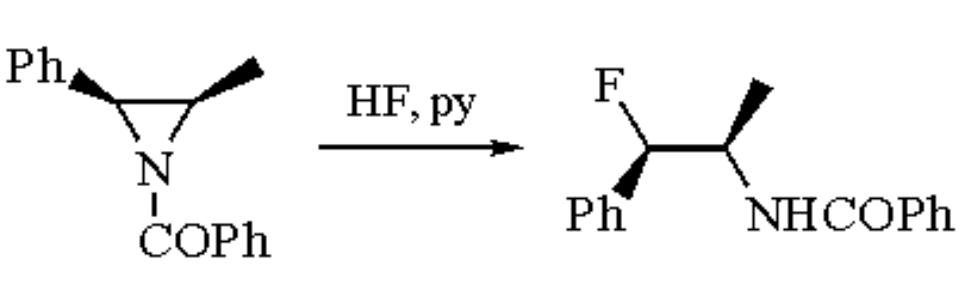

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cis:*trans* = 41:38

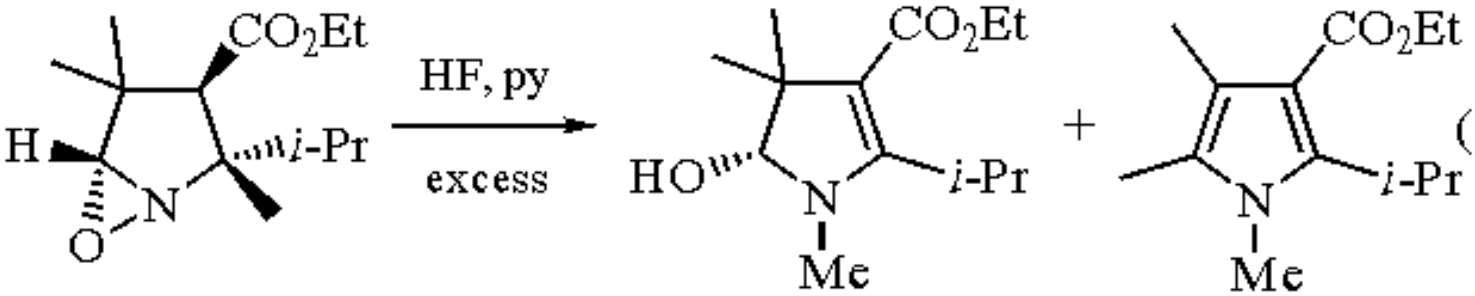

(36)

90% 5%

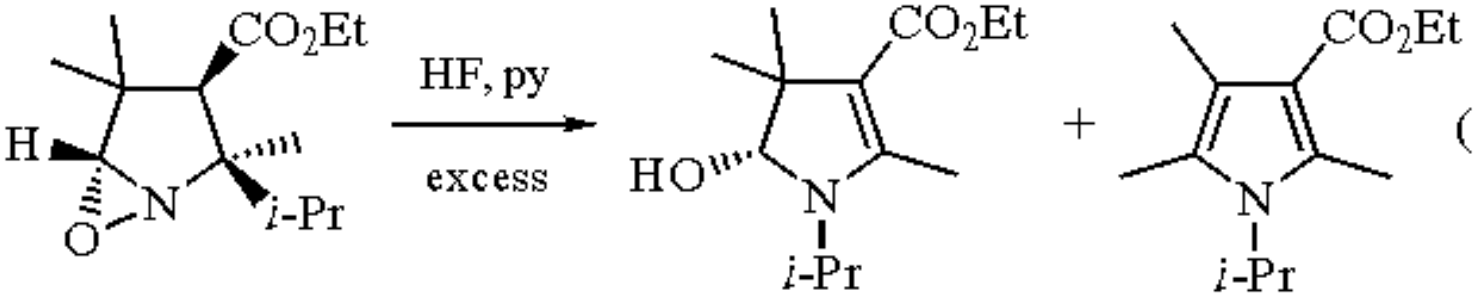

(37)

0% 72%

In the addition of Olah's reagent to azirines, the products are very dependent on the substitution pattern of the azirines. Ethers and larger-ring heterocycles are usually stable to HF, with some exceptions.

Miscellaneous.

Deprotection of peptides with strong acid often causes serious side reactions. By using anhydrous HF in dimethyl

sulfide, most peptide-protecting groups and polymeric support can be cleanly removed.[2,74,75] Other silyl-protecting groups have been removed by aqueous hydrofluoric acid in excellent yields, although this reagent has not been widely used because there are better reagents available.[76] When HF is used with PbO_2, PbF_4, anodic oxidation,[77,78] or other oxidants, it can fluorinate a variety of compounds, and several perfluoroheterocyclic compounds have been made in good yields.[79-82]

Proton Sponge (***1,8-Bis(dimethylamino)naphthalene***)[83] hydrofluoride can be a useful fluoride donor. Adding an anhydrous HF ether solution to the base to form the hydrofluoride salt has been used for fluorination reactions (eq 38).[84]

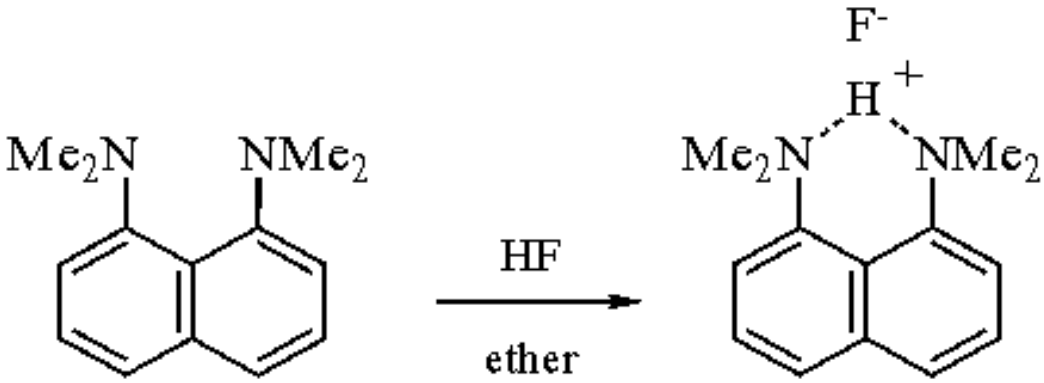

(38)

Related Reagents.

N-Bromosuccinimide-Hydrogen Fluoride; ***Hydrogen Fluoride***; ***Hydrogen Fluoride-Antimony(V) Fluoride***; ***Pyridinium Poly(hydrogen fluoride)***.

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Hydrogen Bromide[1]

HBr

[10035-10-6] · BrH · Hydrogen Bromide · (MW 80.91)

(reagent for electrophilic[5] and radical-mediated[1b] hydrobromination of alkenes and alkynes; cleaves epoxides[1c] and ethers;[20] converts alcohols[13] and chlorides[32] to bromides; converts α-diazo ketones to α-bromomethyl ketones,[28a] and 1,4-cyclohexanediones to phenols[29])

Alternate Name: ***Hydrobromic Acid***

Solubility: sol most organic solvents.[2]

Form Supplied in: widely available as compressed gas; 30% solution in AcOH or $EtCO_2H$; 48% aqueous solution.

Preparative Methods: can be generated in situ by treatment of refluxing tetrahydronaphthalene with Br_2;[3] treatment of Ph_3PHBr with refluxing xylene.[4]

Handling, Storage, and Precautions: highly toxic and corrosive. This reagent should be handled in a fume hood.

Hydrobromination of Alkenes and Alkynes.

HBr undergoes addition readily to most alkenes and alkynes.[1a] However, radical and ionic addition usually compete, affording a mixture of products unless the system is symmetrically substituted (eq 1).[5]

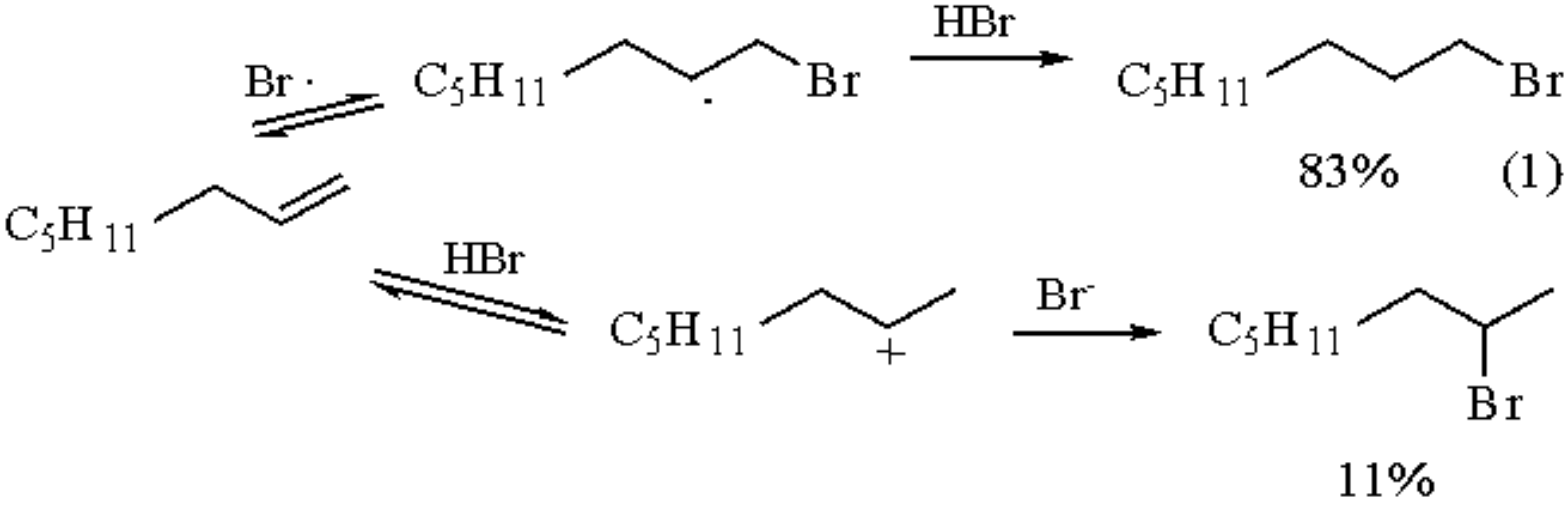

Radical addition can be facilitated by light, peroxides, and other radical-generating systems.[1b] Limiting reaction to ionic addition is more challenging, requiring the rigorous absence of light, oxygen, and peroxide impurities, along with the use of a radical inhibitor.[6] Ionic addition to alkenes without competing radical reaction can also be effected with aqueous HBr at 115 °C and a phase-transfer catalyst (eq 2).[7]

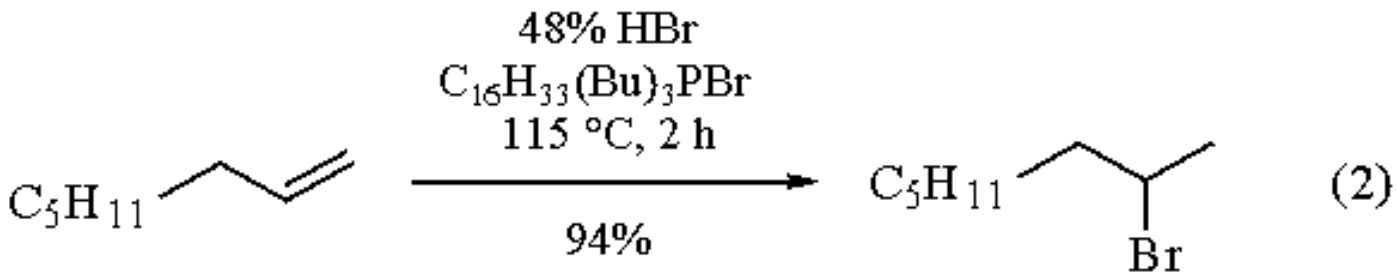

More conveniently, competing radical reaction can be avoided by conducting the addition in the presence of appropriately prepared silica gel or alumina, which also accelerates the rate of ionic addition.[5,8] Addition is rendered even more convenient by the use of various inorganic and organic acid bromides that undergo reaction with silica gel or alumina to afford HBr in situ (eq 3).[5]

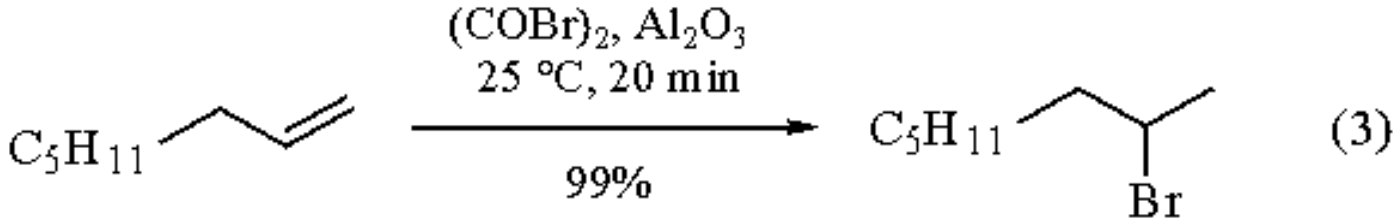

Surface-mediated hydrobromination of phenylalkynes initially affords the *syn* adducts, which undergo subsequent equilibration with the thermodynamically more stable (*Z*) isomers (eq 4).[5] Thus either isomer can be obtained in high yield by the appropriate choice of reaction conditions. Surface-mediated hydrobromination of terminal alkylalkynes affords the corresponding 2-bromo-1-alkenes in good yield (eq 5).[5] Several other methods had previously been developed for this difficult transformation.[9]

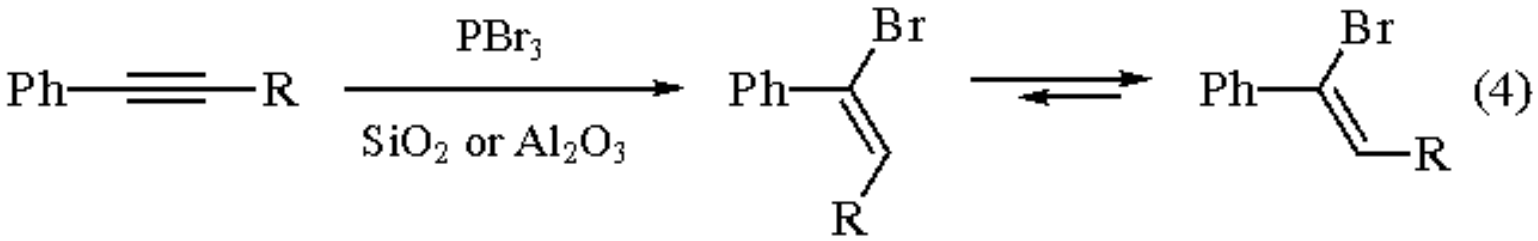

R = Me, Ph or *t*-Bu

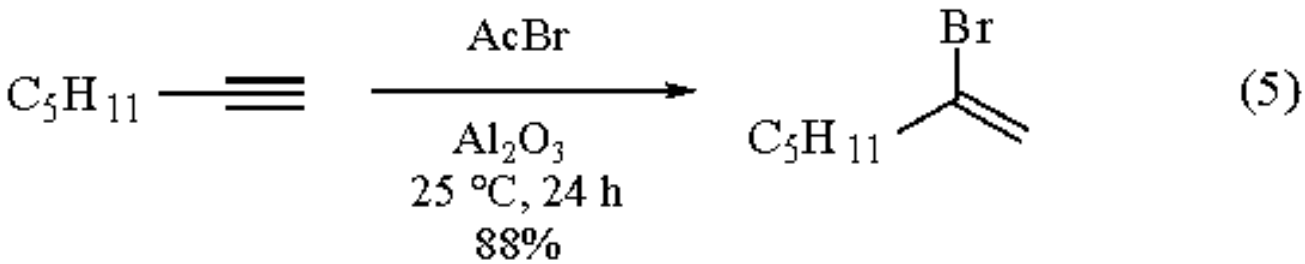

Cleavage of Epoxides to Bromohydrins.

The addition of HBr to epoxides to give bromohydrins proceeds readily with either 48% aqueous HBr or anhydrous HBr in a variety of organic solvents.[1c,10] The stereoselectivity generally parallels that of HCl additions (see ***Hydrogen Chloride***), and is similarly affected by changes in solvent and substitution. Typically, ring opening of unsymmetrical epoxides favors formation of the bromohydrin in which bromine is at the less highly substituted position. This preference is greater for HBr than HCl additions because of the greater size and nucleophilicity of the bromide ion.[1c,11]

Reaction with Alcohols.

The reaction of HBr with alcohols to form alkyl bromides is a general, high-yield reaction that can be effected under a variety of conditions. The conversion of primary and secondary alkyl alcohols to the corresponding bromides with anhydrous HBr requires elevated temperatures (100 °C),[12] but benzylic and allylic alcohols are reactive in $CHCl_3$ solution at 25 °C.[13] Alcohols are also converted to alkyl bromides at elevated temperatures with 48% aqueous HBr.[14] Alcohols resistant to substitution under these conditions are often reactive in the presence of H_2SO_4 as a catalyst.[12,15] The use of phase-transfer catalysts has little effect on the rate of the reaction, but has been found to reduce significantly the extent of skeletal rearrangement that often accompanies substitution (eq 6).[16] Tertiary bromides can be synthesized from the corresponding alcohols under especially mild conditions in the presence of ***Lithium Bromide***.[17]

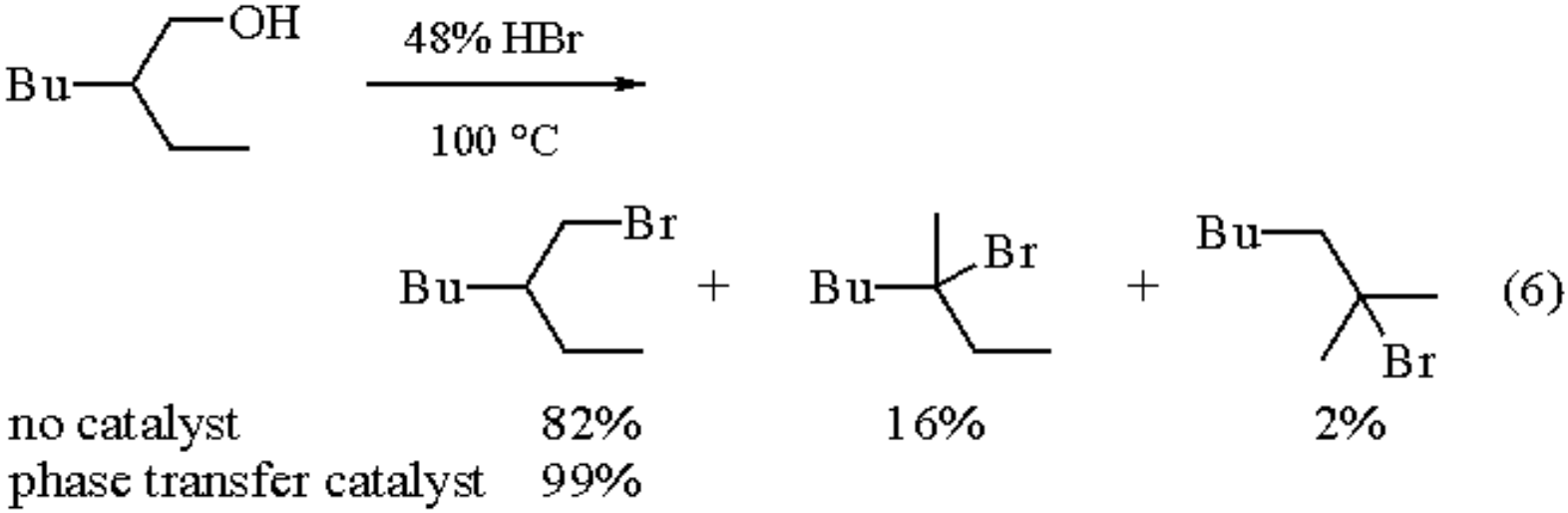

Vicinal diols, when treated with 48% aqueous HBr in AcOH, give 2-bromo acetates with good regio- and stereoselectivity (eq 7).[18] In the absence of AcOH, some diols are dehydrated to give dienes.[19]

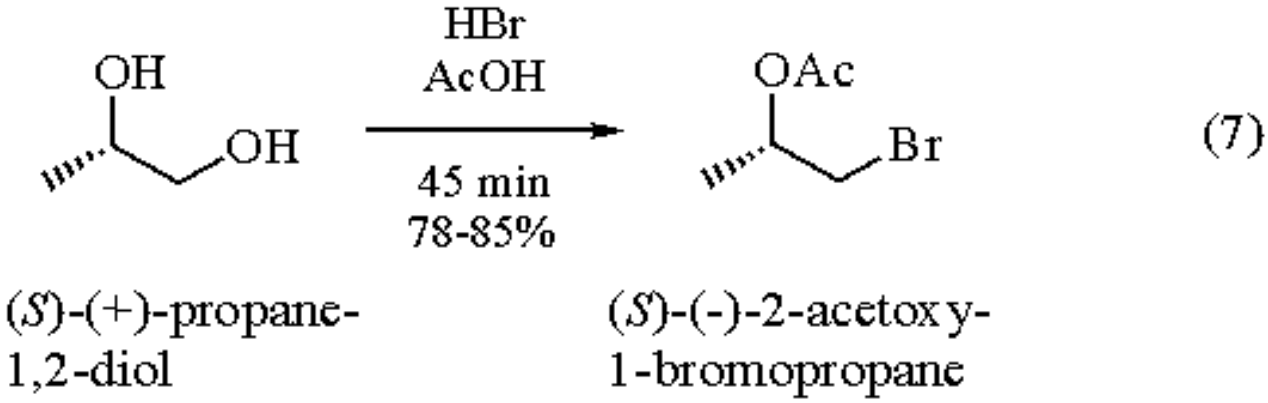

A series of bis(benzylic) diols has been converted to 2,3-disubstituted indenes with HBr in good yields (eq 8), whereas reactions with other hydrogen halides followed a different course.[20] This method failed for the synthesis of monoalkyl indenes but was satisfactory for the synthesis of monoaryl systems.

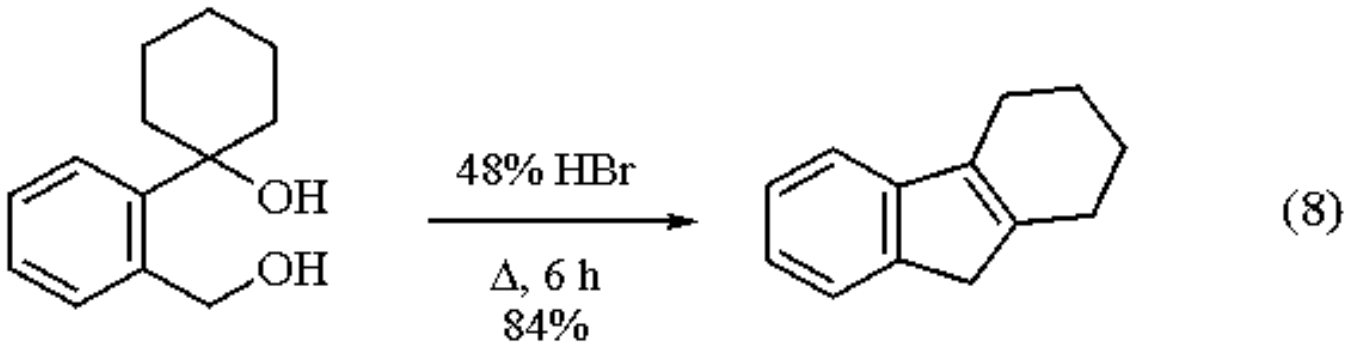

Cleavage Reactions.

The cleavage of ethers by HBr is a synthetically useful method for the synthesis of alkyl bromides and for the deprotection of phenols.[21] Dialkyl ethers are cleaved with 48% aqueous HBr at elevated temperatures in the presence

of H_2SO_4[22] or a phase-transfer catalyst.[23] Under these conditions, most dialkyl ethers give high yields (90-95%) of alkyl bromides, while alkyl aryl ethers give phenols (90%) and alkyl bromides (90%). Aryl methyl ethers are readily cleaved with the use of 48% aqueous HBr to give the phenol and MeBr.[24] The cleavage of cyclic lactones by HBr, in a manner analogous to the cleavage of ethers, has also been reported.[25] When triphenylphosphonium bromide is used as an in situ source of HBr, methyl, ethyl, and benzyl ethers are cleaved at elevated temperatures to give alkene products in good yield along with a tetrasubstituted phosphonium salt (eq 9).[26] Similarly, aryl alkyl ethers are converted to phenols, and benzyl and methyl esters to carboxylic acids.

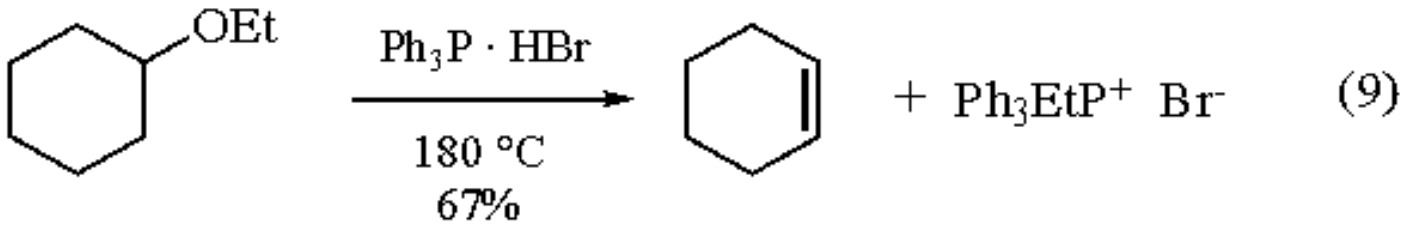

AcOH and CF_3CO_2H solutions of HBr efficiently cleave benzyloxycarbonyl groups from protected peptides.[27] Anhydrous HBr selectively cleaves alkyl groups from aryl amines.[28] Thus dialkyl-substituted anilines were converted to monoalkyl-substituted anilines at 150 °C, and monoalkyl anilines converted to aniline at 195 °C. This method is not useful for cleavage of trialkyl amines.

Synthesis of α-Bromo Ketones.

α-Diazo ketones are converted to α-bromomethyl ketones by either anhydrous HBr in Et_2O or 48% aqueous HBr in various solvents (eq 10).[29] This is a useful, high-yield, method for the regiospecific conversion of a carboxylic acid to the corresponding bromomethyl ketone, since the required α-diazo ketone is readily synthesized from reaction of the corresponding acid chloride with ***Diazomethane***.

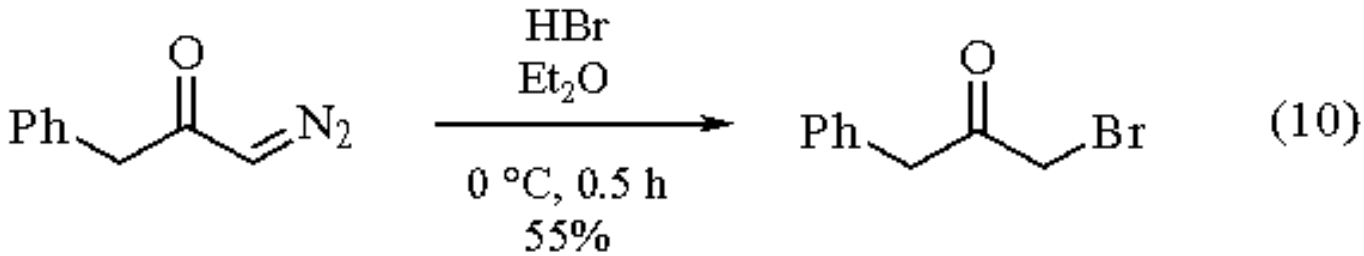

Reductions with HBr.

HBr has been used as a reagent for the reduction of 1,4-cyclohexanediones to phenols,[30] as well as for the cyclization and aromatization of a variety of carbonyl-substituted arenes (eq 11).[31]

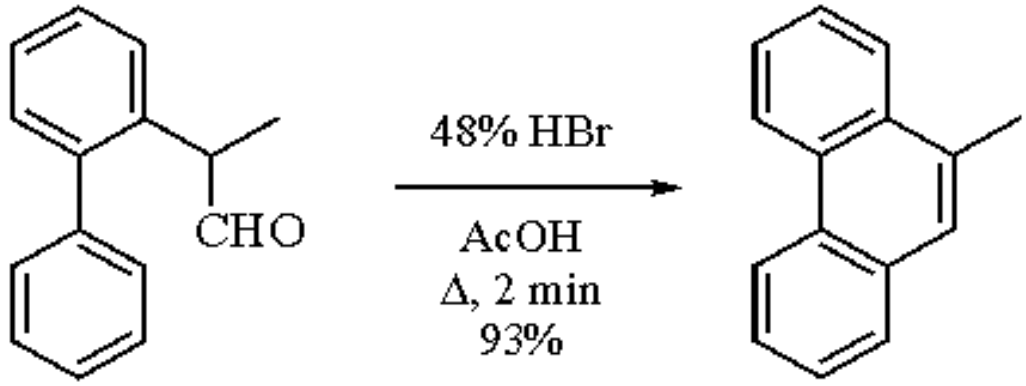

(11)

Although HBr generally reduces aryl sulfoxides, its uses are limited due to ensuing bromination of the aryl ring.[32]

Miscellaneous Reactions.

Alkyl chlorides, which are generally more readily available than alkyl bromides, are converted into the corresponding bromides by anhydrous HBr in the presence of catalytic amounts of $FeBr_3$.[33] Secondary, tertiary, and allylic bromides are formed in high yields from the corresponding chlorides, while primary systems undergo extensive cationic rearrangement. Alkyl iodides have been converted into the corresponding bromides with 42% HBr in the presence of HNO_3.[34]

Several arylamines have been brominated at the *ortho* position by HBr in DMSO.[35] Since removal of the amine functionality is possible in good yield, this provides a regiospecific method of arene bromination.

HBr reacts with aldehydes in the presence of arenes to give bromoalkylated products[36] and in the presence of alcohols to give α-bromomethyl ethers in good yields (eq 12).[37]

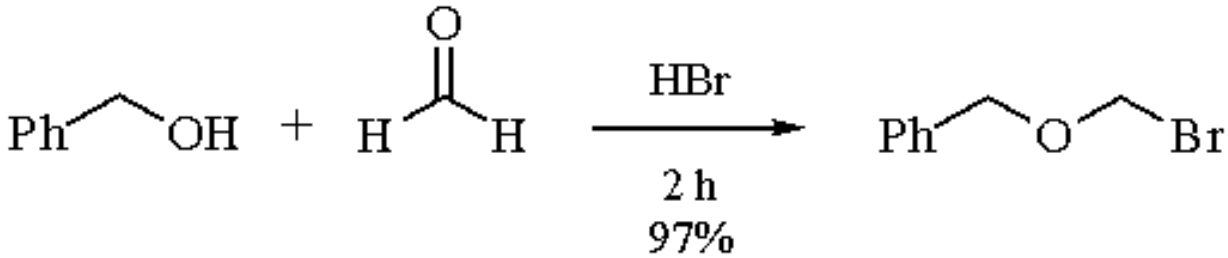

(12)

Addition of anhydrous HBr to α,β-unsaturated aldehydes or ketones, followed by acetalization, readily affords β-bromoacetals (eq 13).[38]

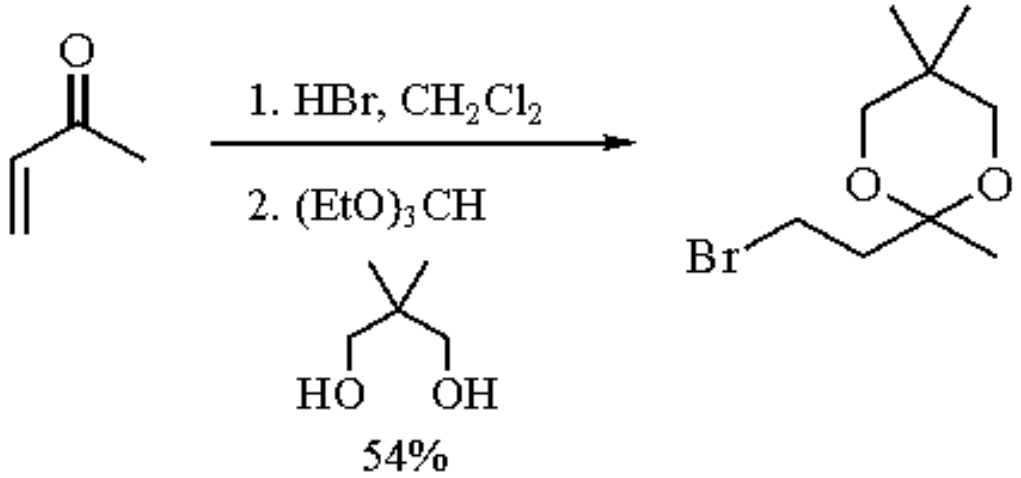

(13)

Related Reagents.

Formaldehyde-Hydrogen Bromide; ***Hydrobromic Acid***.

---

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Hydrogen Chloride[1]

ClH

[7647-01-0] · ClH · Hydrogen Chloride · (MW 36.46)

(reagent for hydrochlorination of alkenes and alkynes;[4] cleaves epoxides[1b] and ethers;[21a] converts alcohols to chlorides[12b] and diols to cyclic ethers;[17] chloroalkylates arenes;[22] converts aldehydes to α-chloro ethers[23b])

Alternate Name: ***Hydrochloric Acid***

Solubility: sol most organic solvents.[2]

Form Supplied in: widely available; compressed gas; 1 M solution in AcOH, Et_2O, or Me_2S; 4 M solution in dioxane; 37% aqueous solution.

Preparative Methods: addition of H_2SO_4 to NaCl or 37% aqueous HCl.[3]

Handling, Storage, and Precautions: highly toxic and corrosive; handle only in a fume hood.

Hydrochlorination of Alkenes and Alkynes.

HCl undergoes solution-phase addition readily to C=C double bonds that are strained or from which the resulting carbocation is benzylic or tertiary.[1a] However, other alkenes do not undergo addition at preparatively useful rates.[4] Although addition can be facilitated by Lewis acid catalysis,[5] mono- and 1,2-disubstituted alkenes undergo polymerization under these conditions.[5a] The rate of addition is inversely proportional to the electron donor strength of the solvent, following the order
heptane &AApprox; $CHCl_3$ > xylene > nitrobenzene >> MeOH > dioxane > Et_2O.[6,7] In the strongly donating solvent Et_2O, even highly reactive alkenes undergo slow addition unless one of the reactants is present in high concentration. Additions conducted in solutions saturated with HCl exhibit an inverse temperature coefficient because of the increased solubility of HCl at lower temperatures.[3b]

Alkynes undergo addition more slowly than alkenes, requiring extended reaction times, elevated temperatures, and, usually, Lewis acid catalysis.[1a] However, dialkylalkynes afford the (*Z*)-vinyl chloride on treatment with refluxing aqueous HCl (eq 1).[8]

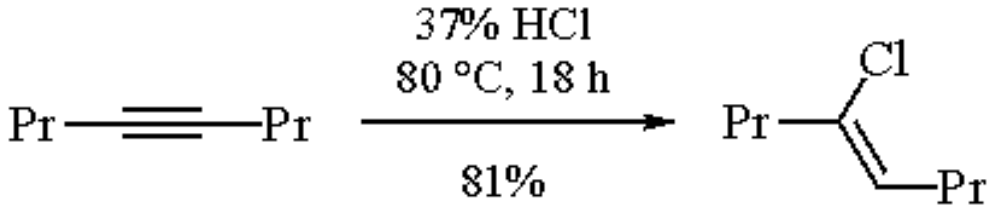

(1)

Addition to alkenes and alkynes is greatly facilitated by the presence of appropriately prepared silica gel or alumina.[4] Alkenes and alkynes that exhibit little or no reaction with HCl in solution readily undergo addition under these conditions. The reaction is rendered even more convenient by the use of various inorganic and organic acid chlorides that afford HCl in situ in the presence of silica gel or alumina. Surface-mediated hydrochlorination of 1,2-dimethylcyclohexene in CH_2Cl_2 gives initially the *syn* adduct, which undergoes equilibration with the thermodynamically more stable *trans* isomer under the reaction conditions (eq 2).[4] Thus either isomer can be obtained in high yield through the proper choice of reaction conditions. Similarly, phenylalkynes initially afford *syn* adducts, which undergo subsequent equilibration with the thermodynamically more stable (*Z*) isomers (eq 3).[4] Again, either isomer can be obtained in high yield.

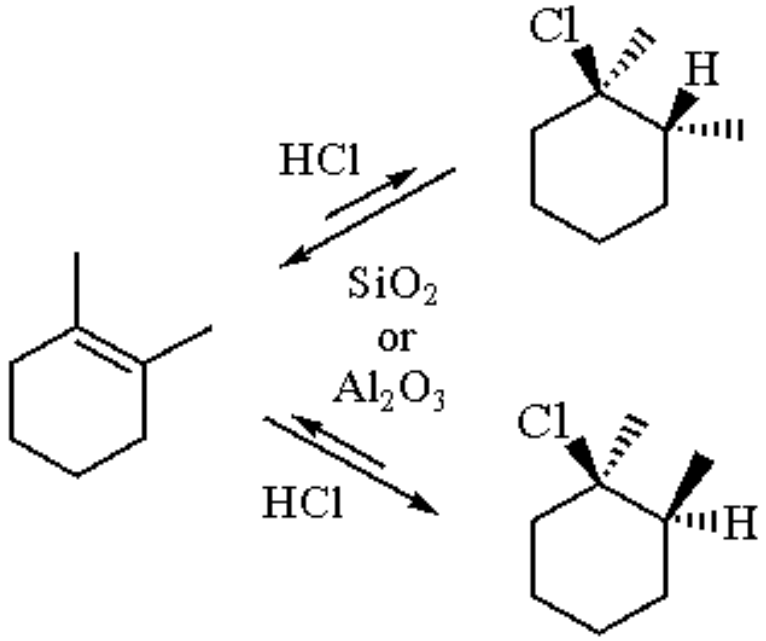

(2)

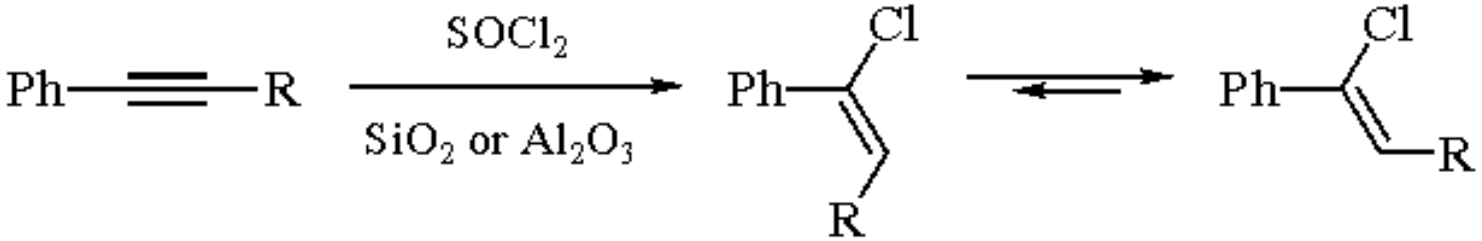

(3)

R = Me or Ph

Cleavage of Epoxides to Chlorohydrins.

The addition of HCl to epoxides to form chlorohydrins proceeds readily with either 37% aqueous HCl or solutions of

anhydrous HCl in a variety of organic solvents.[1b,9] For simple alkyl-substituted oxiranes, addition typically occurs through backside attack of chloride ion on the protonated epoxide, resulting in net inversion of the carbon center (eq 4).[1b,9] For aryl- or vinyl-substituted epoxides (in which more carbocationic character is involved in the transition state during ring opening), the stereochemical outcome may range from complete retention to predominant inversion and is highly solvent dependent.[10] Anhydrous conditions and solvents of low dielectric strength favor *syn* cleavage, while *anti* cleavage is favored in the presence of water or in hydroxylic solvents.[10]

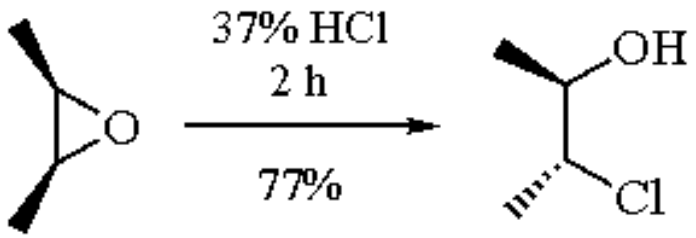

(4)

Cleavage of simple alkyl-substituted epoxides under anhydrous conditions typically favors formation of the chlorohydrin in which chlorine is at the less highly substituted position (eqs 5 and 6).[11] More highly substituted epoxides, particularly aryl-substituted, give increasing amounts of the opposite regioisomer. Regioselectivity is also very sensitive to the solvent system employed for the reaction (eqs 5 and 6).

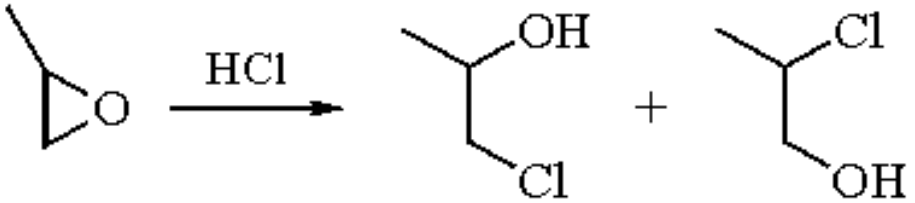

(5)

THF	84%	16%
THF/H_2O	40%	60%

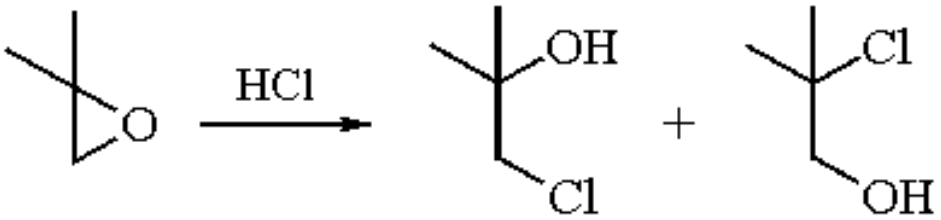

(6)

THF	62%	38%
THF/H_2O	25%	75%

Reaction with Alcohols.

The reaction of HCl with alcohols to form alkyl chlorides is a general reaction, giving good to high yields of products. Primary and secondary aliphatic alcohols are most easily converted to the corresponding chlorides with either 37% aqueous HCl or anhydrous HCl at elevated temperatures in the presence of ***Zinc Chloride***.[12] Phase-

transfer catalysis has also been employed in the synthesis of primary chlorides from alcohols.[13] The need for a catalyst can be avoided by using the highly polar solvent HMPA.[14] Tertiary,[7,15a] benzylic,[15b] and allylic[15c] alcohols are readily converted to chlorides at 25 °C, or lower, without the need for catalysts. Glycerol can be selectively mono- or dichlorinated by controlled addition to HCl to AcOH solutions.[16] Bis(benzylic) diols have been converted in good yields to substituted cyclic ethers with HCl, whereas reaction with HBr or HI followed a completely different course (eq 7).[17]

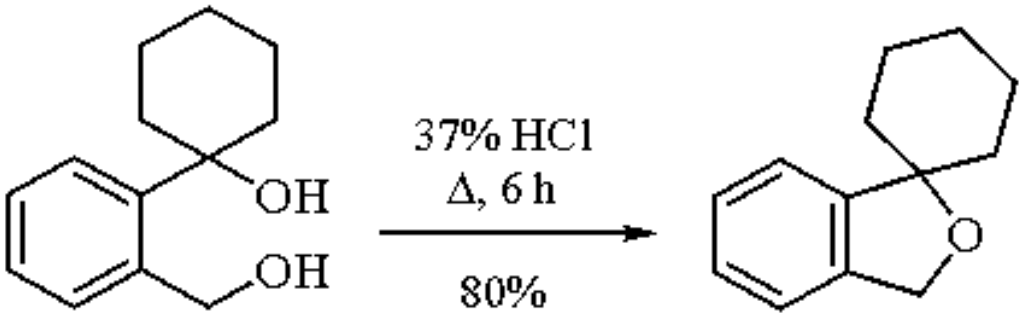

(7)

Reductions with HCl.

HCl has been used to reduce a series of 1,4-cyclohexanediones to the corresponding phenols in good yield (eq 8).[18]

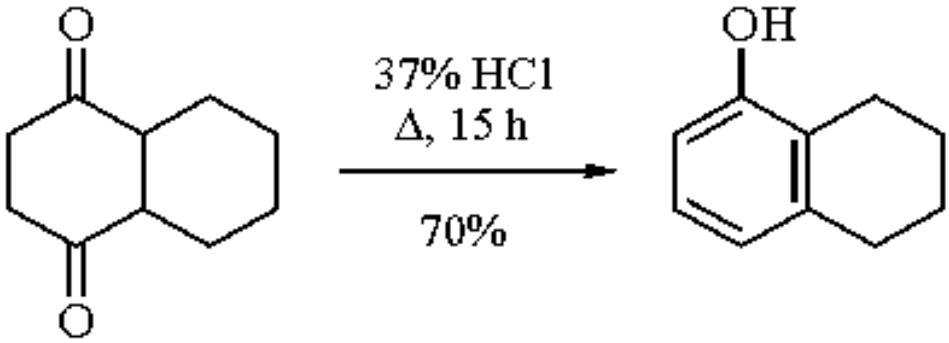

(8)

α-Diazo ketones are reduced to α-chloromethyl ketones by either anhydrous HCl in organic solvents or 37% aqueous HCl in Et_2O.[19] Generally, good to high yields are obtained. Chloroacetone was synthesized in this manner without the complicating formation of dichlorides (eq 9).[19c]

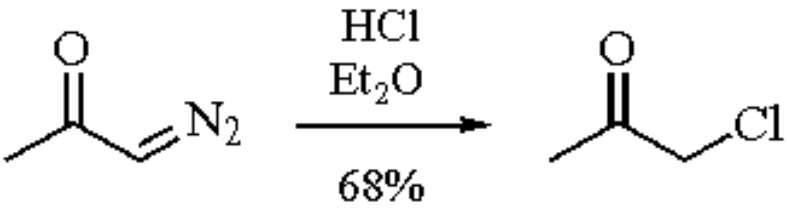

(9)

Although aryl sulfoxides are reduced to sulfides by HCl, accompanying ring chlorination limits the usefulness of the reaction.[20]

Cleavage of Ethers.

Allyl, *t*-butyl, trityl, benzhydryl, and benzyl ethers are cleaved by HCl in AcOH (eq 10).[21a] In some cases, aryl methyl ethers have been successfully cleaved (eq 11).[21b]

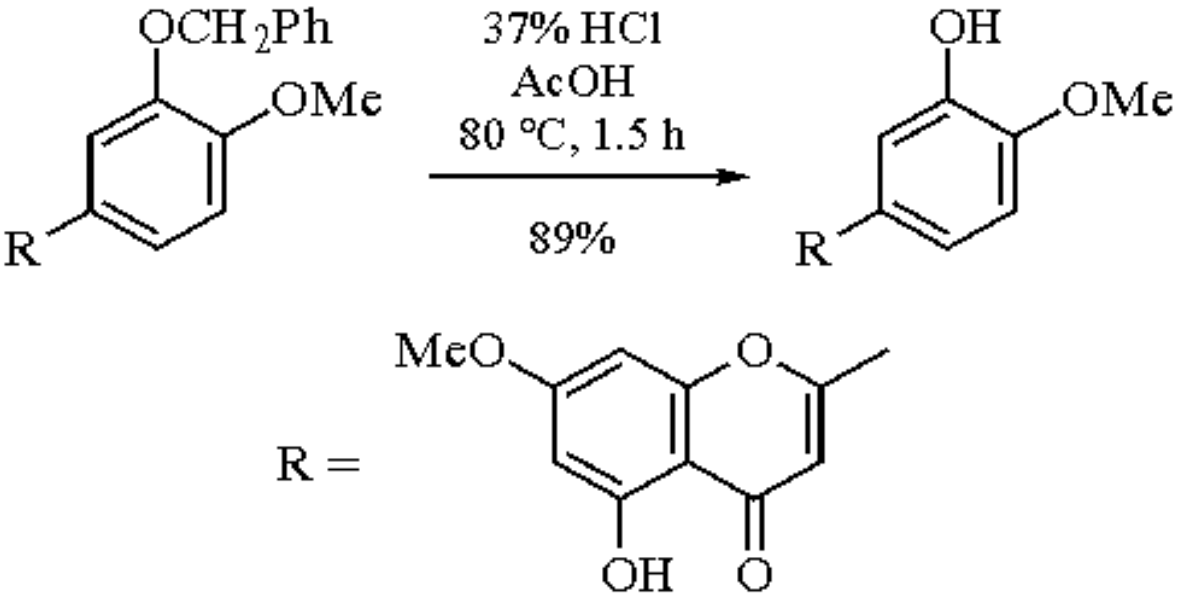

(10)

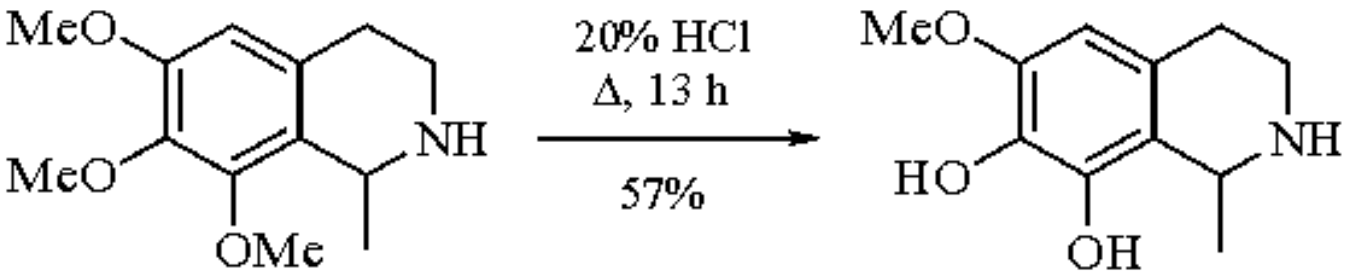

(11)

Reaction with Aldehydes.

Arenes react readily with mixtures of HCl and formaldehyde in the presence of a Lewis acid, usually $ZnCl_2$, to give the chloromethylated derivative.[22] Yields are good and the reaction conditions can be controlled to afford predominantly mono- or disubstituted products. Chloroalkylations can be effected with other aldehydes such as propanal and butanal. In the presence of alcohols, HCl and aldehydes give high conversions to α-chloro ethers (eq 12).[23]

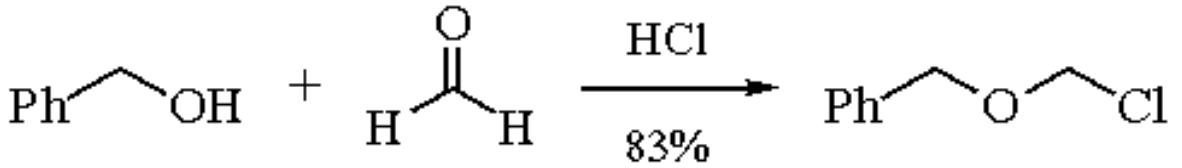

(12)

Related Reagents.

Formaldehyde-Hydrogen Chloride; ***Hydrochloric Acid***.

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Hydrogen Cyanide[1]

HCN

[74-90-8] · CHN · Hydrogen Cyanide · (MW 27.03)

(useful C_1 synthon)

Alternate Names: hydrocyanic acid; prussic acid.

Physical Data: mp -13.4 °C; bp 25.6 °C; *d* (gas) 0.941 g cm^{-3}; *d* (liquid) 0.687 g cm^{-3}.

Solubility: slightly sol ether; miscible with water and alcohol.

Form Supplied in: colorless gas at rt, or bluish-white when liquefied, with a characteristic odor resembling bitter almonds.

Preparative Methods: anhydrous HCN is prepared on a large scale by the catalytic oxidation of ammonia-methane mixtures (Andrussow process).[1c] In the laboratory it can conveniently be prepared by acidifying NaCN or potassium hexacyanoferrate, $K_4[Fe(CN)_6]$.[3]

HCN oligomers:[4] the HCN dimer (HN=CHCN) is too reactive to be isolated. Under acidic conditions the reaction proceeds to the trimer *s*-triazine[5] and under basic conditions to the tetramer ***Diaminomaleonitrile***[6] via the trimer intermediate 2-aminomalononitrile.

Handling, Storage, and Precautions: **Intensely poisonous. Avoid skin contact and inhalation. Must be handled by specially trained experts**. Use in a fume hood. Flash point -17.8 °C (closed cup); explosion limits: upper 40%, lower 5.6% by vol in air; when not pure or stabilized, can polymerize explosively. The principal routes of occupational HCN exposure are inhalation and absorption through the skin. *Inhalation of large amounts of cyanide causes immediate unconsciousness, convulsions, and death from respiratory arrest within 1-15 min*. TLV ceiling of 10 ppm has been recommended since 1980.[2]

Electrophilic Aromatic Substitution.

The preparation of aldehydes from phenols or phenol ethers by treatment of the aromatic substrate with HCN and ***Hydrogen Chloride*** in the presence of Lewis acid catalysts is known as the Gattermann aldehyde synthesis (eq 1).[7] The first stage consists of protonation of the nitrile to give a nitrilium ion or nitrile-Lewis acid complex, regarded as the electrophilic species attacking the substrates.[8]

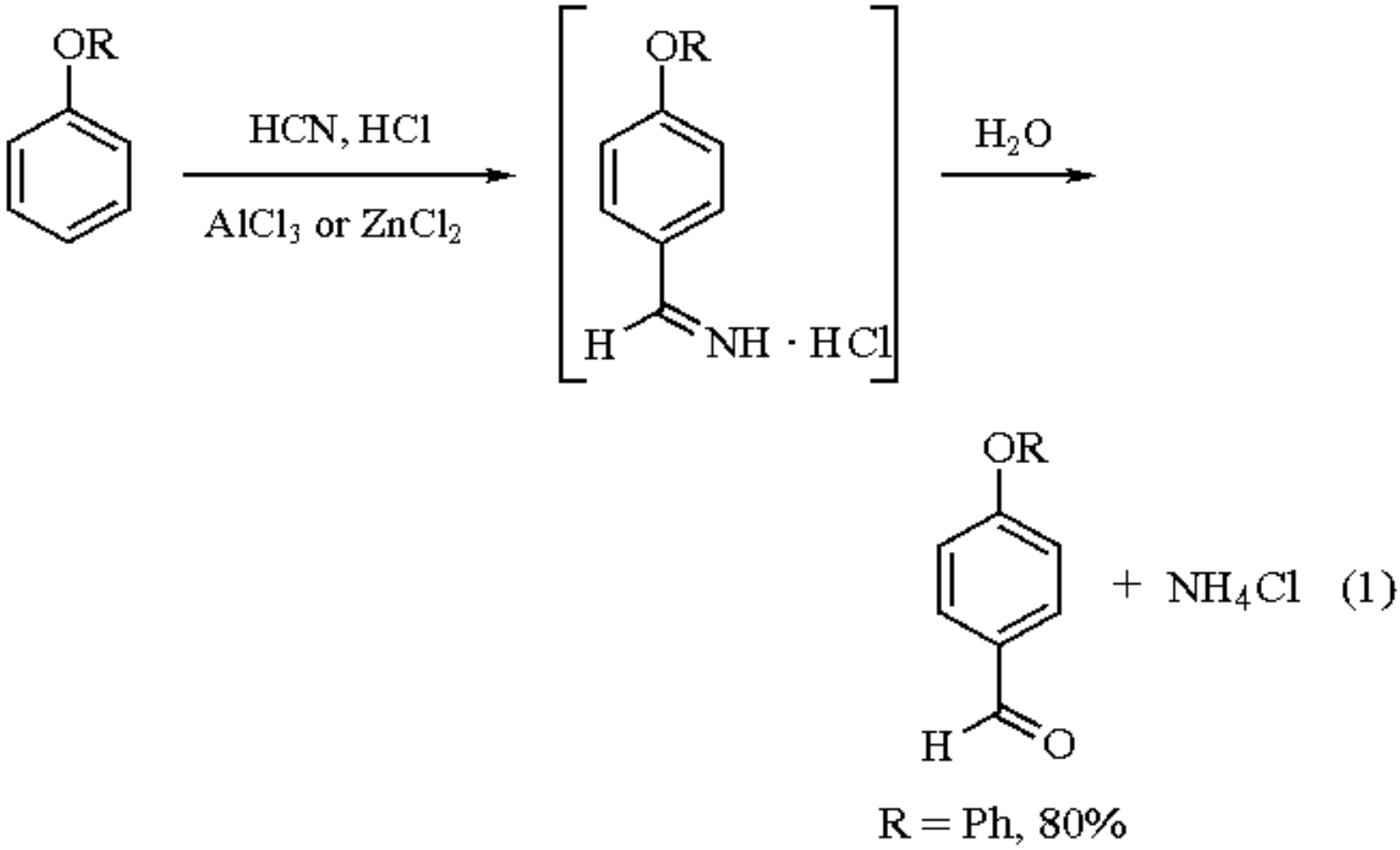

Nucleophilic Substitution.

Chlorotrimethylsilane is converted into ***Cyanotrimethylsilane*** (eq 2),[9] which is also a versatile cyanidation agent,[10] whereas carbonocyanidic acid methyl ester *[17640-15-2]* and ethyl ester *[623-49-4]*, introduced by Mander as selective *C*-acylation agents,[11] are made from the corresponding chloroformates (eq 3).[12]

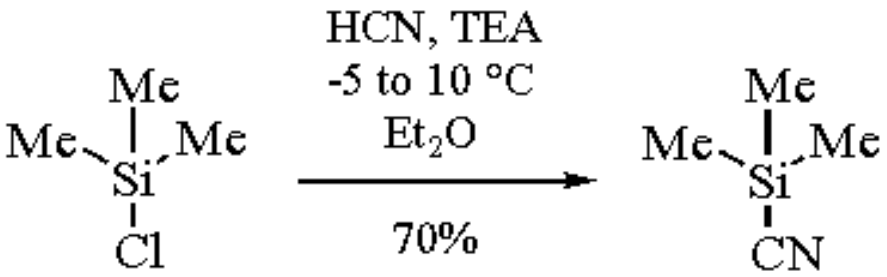

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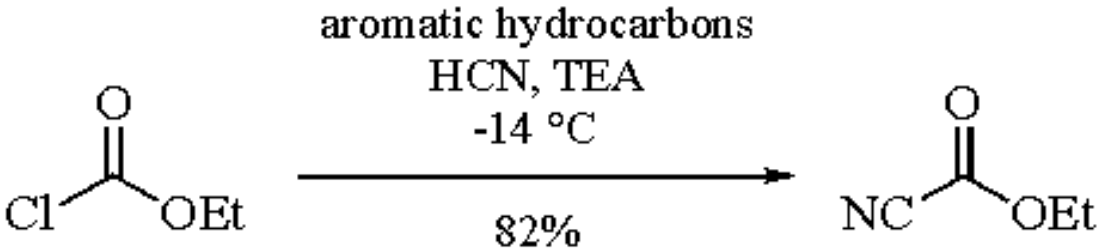

(3)

Epoxide Opening.

Addition of HCN to epichlorohydrin gives an intermediate, which on quaternization with ***Trimethylamine*** and subsequent hydrolysis of the nitrile gives carnitine (eq 4).[13]

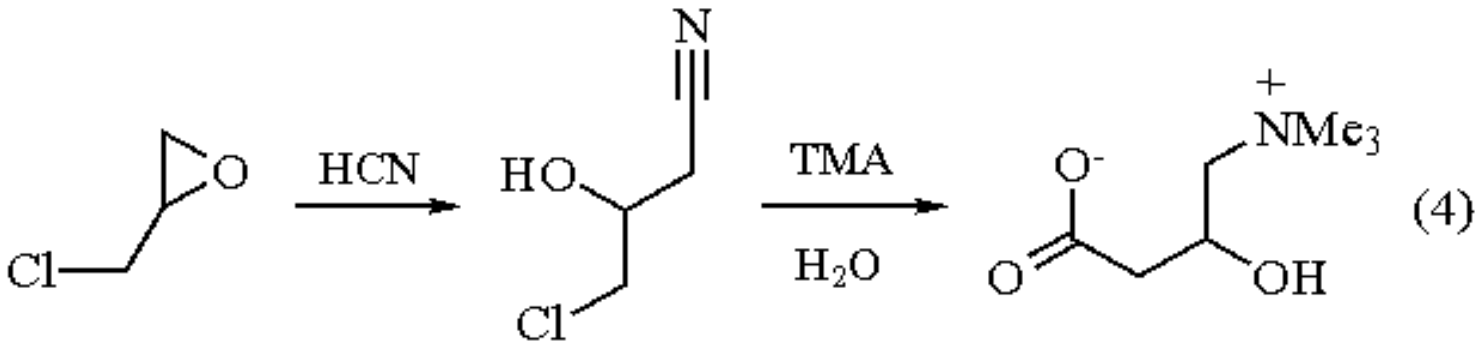

Additions to Alkenes, Dienes, and Alkynes.

These occur in the presence of Ni^0, Pd^0, or cobalt carbonyl complexes.[14,15] The use of Lewis acids as cocatalysts generally improves the activity and lifetime of the catalyst.[16] Ethylene is hydrocyanated to propionitrile in the presence of ***Octacarbonyldicobalt*** or $[M(P(OR)_3)_4]$ (M = Ni, Pd; R = alkyl, aryl); with unsymmetrical higher alkenes, the cobalt catalyst gives exclusively the product from Markovnikov addition (e.g. propene gives 2-cyanopropane in 75% yield),[14] while the nickel and palladium phosphite systems give product mixtures.[17]

In the case of conjugated dienes, nickel catalysts are preferred; the mechanism involves a π-allyl intermediate. Both 1,4- and 1,2-addition occur, although the regiochemistry seems to be controlled by the thermodynamic stability of the intermediate allyl species, e.g. 1,3-pentadiene gives exclusively the branched nitrile (eqs 5 and 6).[18]

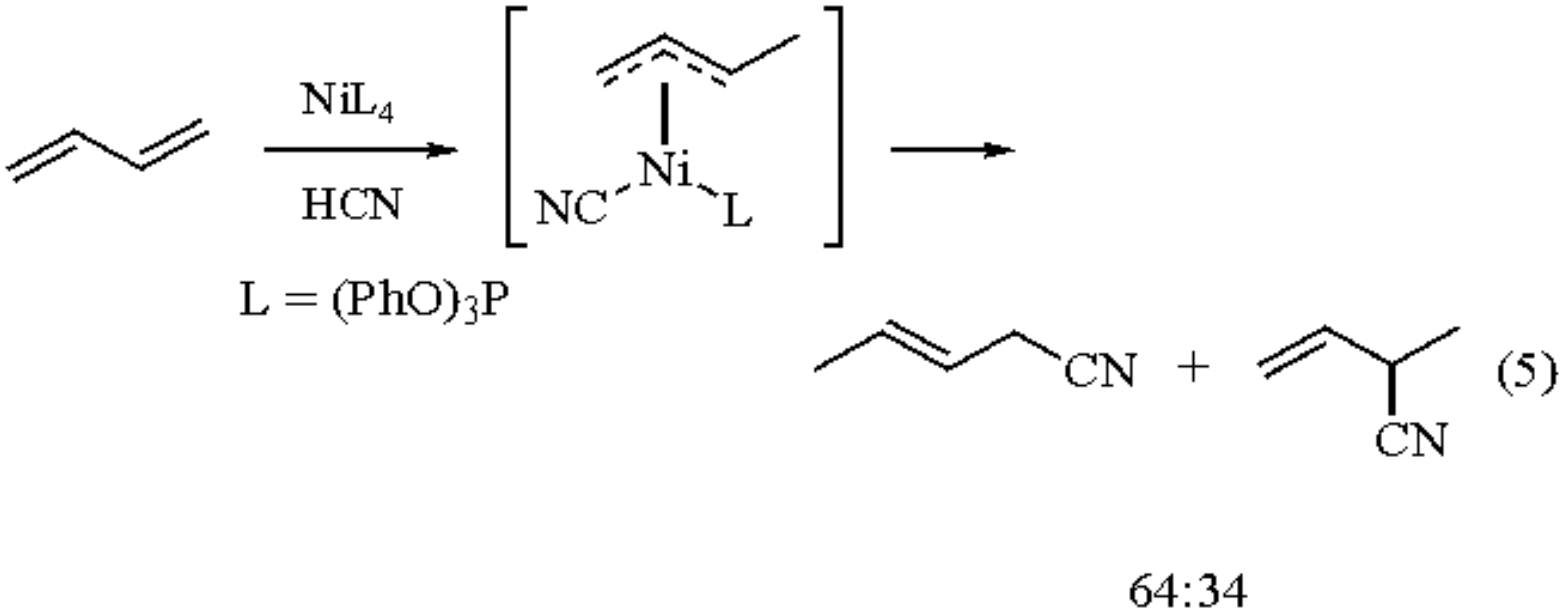

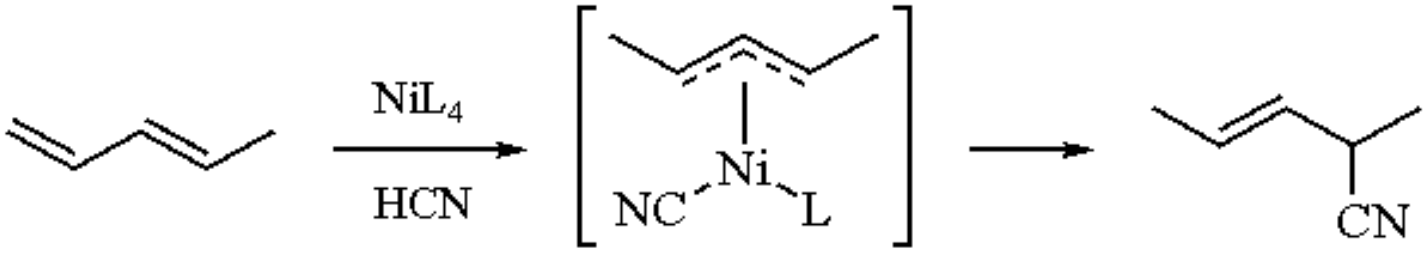

(6)

$L = (PhO)_3P$

In the presence of these catalysts, unconjugated dienes rearrange to conjugated dienes prior to the addition of HCN.

Addition to alkynes is best catalyzed by nickel complexes with *syn* stereochemistry. The regioselectivity is influenced by both steric and electronic effects.[19] The reactions with alkynols show evidence for some chelation between the oxygen and nickel in the transition state (eq 7).[20]

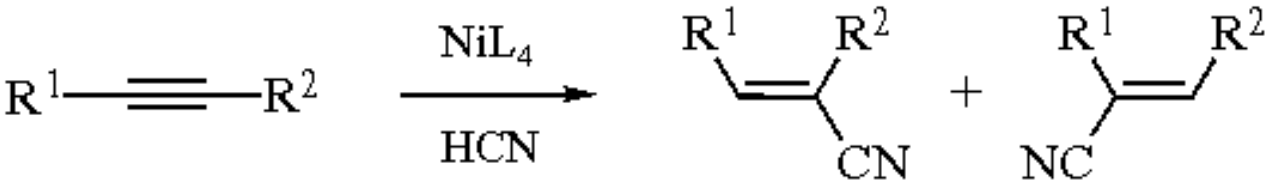

(7)

$L = (PhO)_3P$

$R^1 = Pr$, $R^2 = H$	60%	12:88
$R^1 = t\text{-}Bu$, $R^2 = Me$	78%	90:10
$R^1 = Me_2C(OH)$, $R^2 = H$	30%	20:80

Hydrolysis and cyclization of some cyanoalkenes containing methoxymethyl ethers gives α-alkylidene-γ-lactones (eq 8).[21]

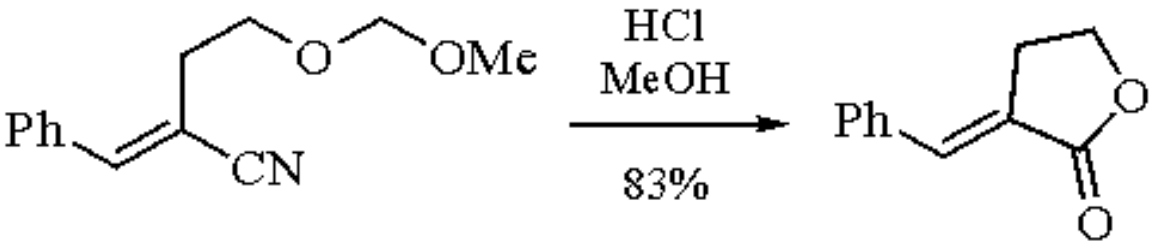

(8)

The asymmetric Markovnikov addition of HCN to vinylarenes in the presence of Ni^0 complexes of 1,2-diolphosphinites derived from sugars gives 2-aryl-2-propionitriles in high yield and enantioselectivity (eq 9).[22]

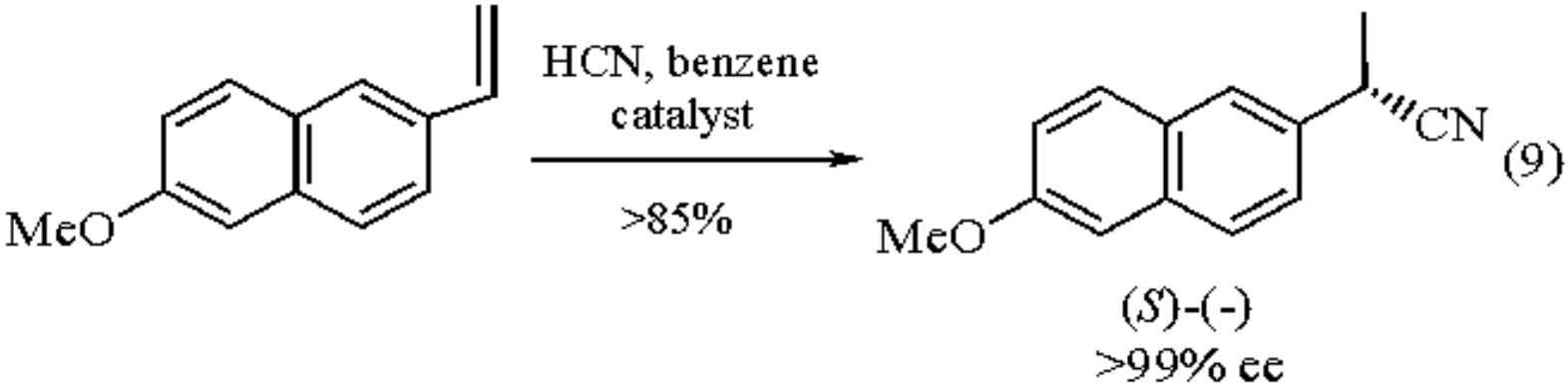

(9)

Asymmetric Hydrocyanation.

Asymmetric hydrocyanation of aldehydes to chiral cyanohydrins is a convenient route to chiral α-hydroxy carboxylic acids and chiral 1-amino-2-alkanols; catalysts are often used, e.g. the cyclic dipeptide cyclo((*S*)-phenylalanyl-(*S*)-histidyl) (eq 10)[23] or the enzyme (*R*)-oxynitrilase (eq 11).[24] This reaction proceeds normally in aqueous solutions with NaCN; however, the noncatalyzed reaction leading to racemic product can be efficiently suppressed by the use of anhydrous HCN in organic solvents.

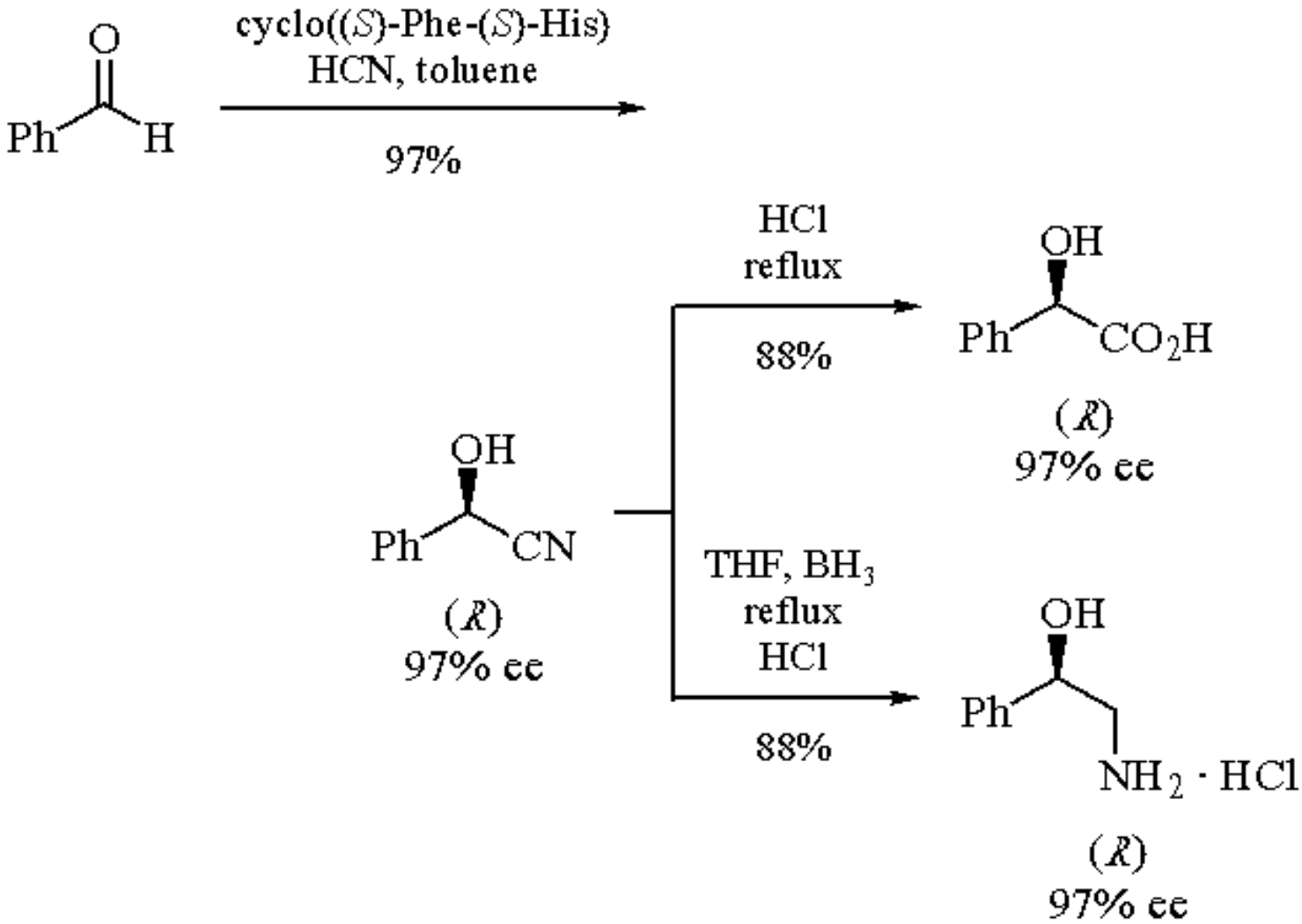

(10)

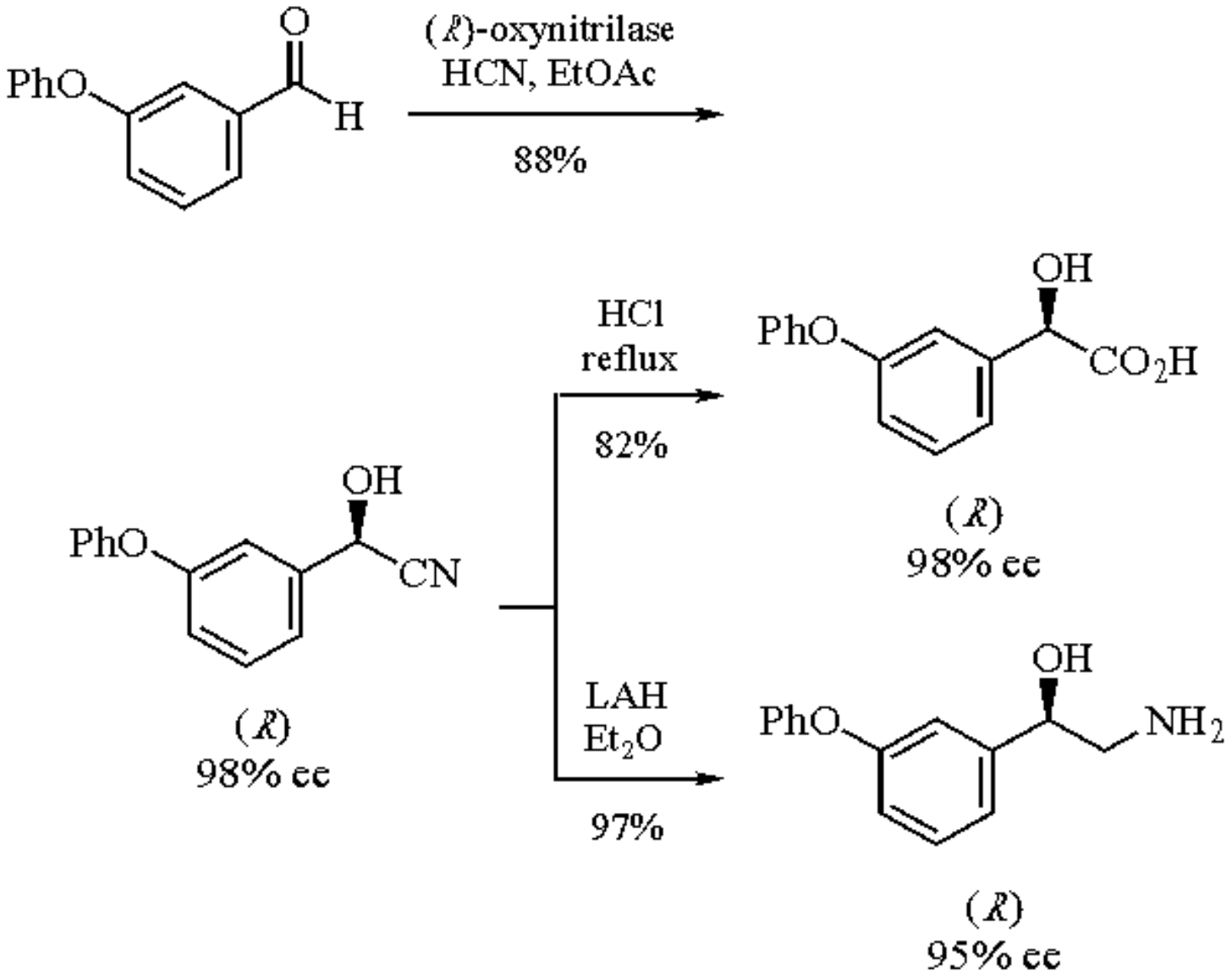

(11)

Enantioselective addition of HCN to ketones in organic solvents catalyzed by (*R*)-oxynitrilase proceeds similarly.[25]

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Hydrogen Fluoride[1]

FH

[7664-39-3] · FH · Hydrogen Fluoride · (MW 20.01)

(strong Brønsted-Lowry acid[2] capable of fluorinating numerous organic substrates;[1] cleaves silyl[3] and peptide[4] protecting groups; effects lignocellulose solvolysis;[5] catalyzes a number of electrophilic aromatic substitution reactions[6])

Alternate Name: ***Hydrofluoric Acid***

Physical Data: mp -83.37 °C; bp 19.54 °C; *d* 1.015 g cm^{-3} (0 °C), 0.958 g cm^{-3} (25 °C).

Solubility: sol water (52.7 wt %, 6 theoretical plates); strong proton donor to alcohols, carboxylic acids, ethers, and ketones (unstable); insol aliphatic hydrocarbons; very slightly sol aromatic hydrocarbons.

Form Supplied in: anhydrous liquid; 48-50% aqueous solution; most common impurity is fluorosilicic acid (<100 ppm).

Purification: for virtually all synthetic purposes, anhydrous hydrogen fluoride (AHF) is supplied in sufficiently high purity from commercial sources. Ultrapure AHF can be obtained by either distillation[7] of commercially available AHF or thermal decomposition[8] of potassium acid fluoride.

Handling, Storage, and Precautions: HF is an extremely toxic material. HF can cause severe damage to the respiratory system and will cause severe burns to tissue, e.g. skin, fingernails, mouth, eyes, etc.; penetration through tissue into bone is possible. If contact with HF occurs, the affected area must be flushed immediately with copious amounts of water for at least 15 min. **Immediate medical attention must be sought**. Recommended personnel protective equipment includes the use of gloves (neoprene/nitrile/rubber composite), goggles, a face-shield, and an apron while working in a well-ventilated hood, preferably equipped with a HF monitor.

AHF is supplied either in lecture bottles or 3 lb metal cylinders; aq HF is supplied in polyethylene bottles. The use of glassware and stainless steel vessels should be avoided when handling either AHF or aq HF.[9] For reactions run at ambient temperature and pressure, polyethylene vessels can be employed; copper and iron vessels are also suitable. However, the use of an autoclave constructed of high metallurgy such as Monel or nickel, employing inert atmosphere techniques, is highly recommended.

Fluorinations.

AHF is an effective reagent for the fluorination of a wide variety of organic substrates.[1] However, AHF in combination with organic bases,[10] for example Olah's reagent (HF-pyridine),[11] and nucleophilic fluoride transfer agents[12] are more frequently employed than AHF, particularly when monofluorination of an organic substrate is desired.

Addition of AHF to unsaturated hydrocarbons occurs by an electrophilic mechanism and, for alkenes, in a Markovnikov fashion. Addition of AHF to alkynes[13] proceeds with poor stereochemical control to give mixtures of (*E*)- and (*Z*)-vinyl halides and is often accompanied by the formation of *gem*-difluoroalkanes and fluoropolymers.

AHF reacts with carboxylic acid halides,[14] esters,[15] and anhydrides[14] to give carboxylic acid fluorides. Acetoacetyl fluoride can be prepared in near quantitative yield by adding AHF to diketene.[16] At temperatures <=0 °C, AHF is known to add to isocyanates[17] to yield the corresponding carbamoyl fluorides.

Epoxides and aziridines undergo ring opening in the presence of AHF. For example, stereospecific ring opening of an epoxide[18] can be accomplished as a means of introducing fluorine into the B ring of a steroid (eq 1).

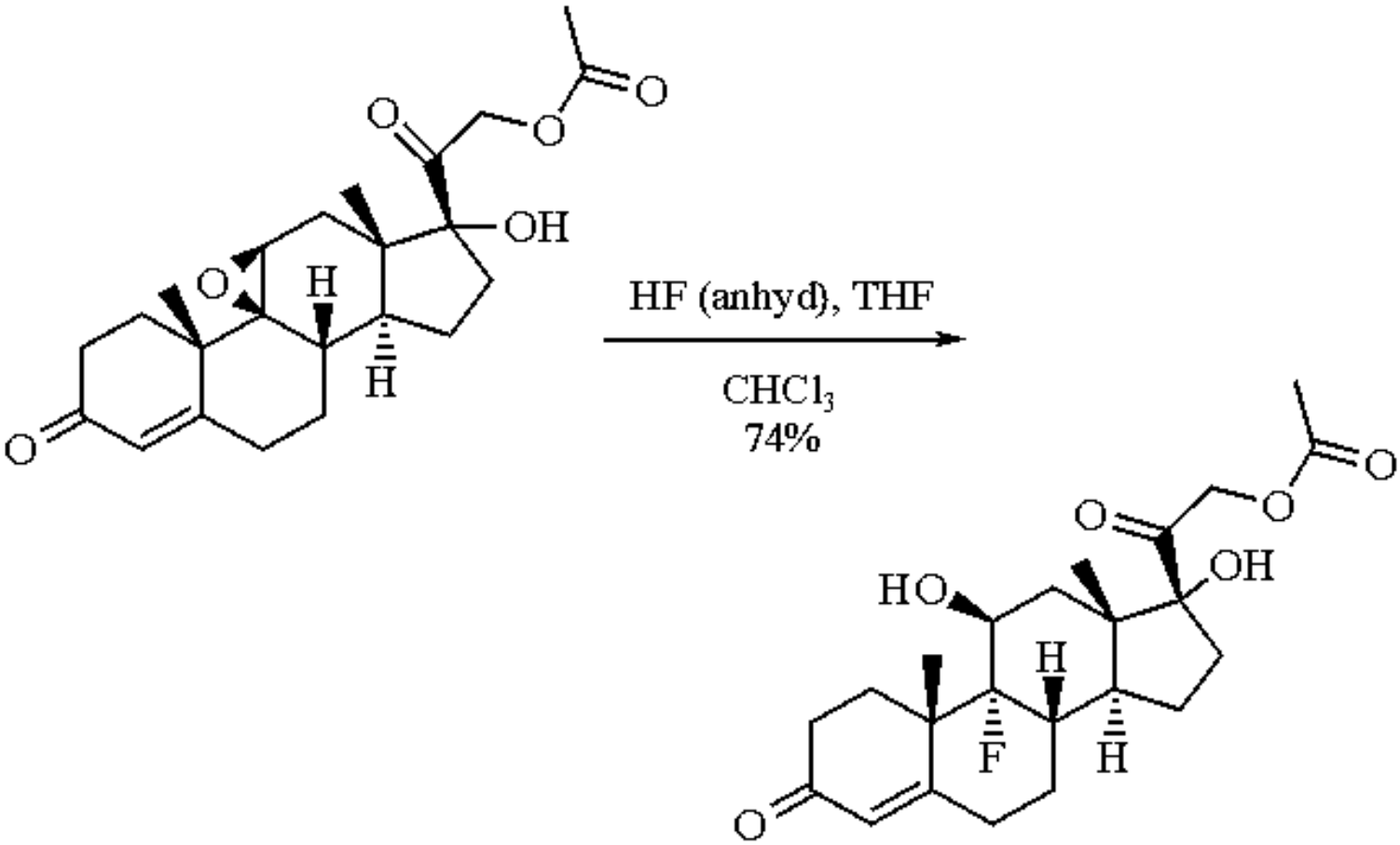

(1)

AHF addition to *trans*-2,3-diphenylaziridine[19] occurs stereospecifically to afford the *erythro* isomer exclusively, whereas the *threo* isomer predominates upon treatment with Olah's reagent (eq 2).

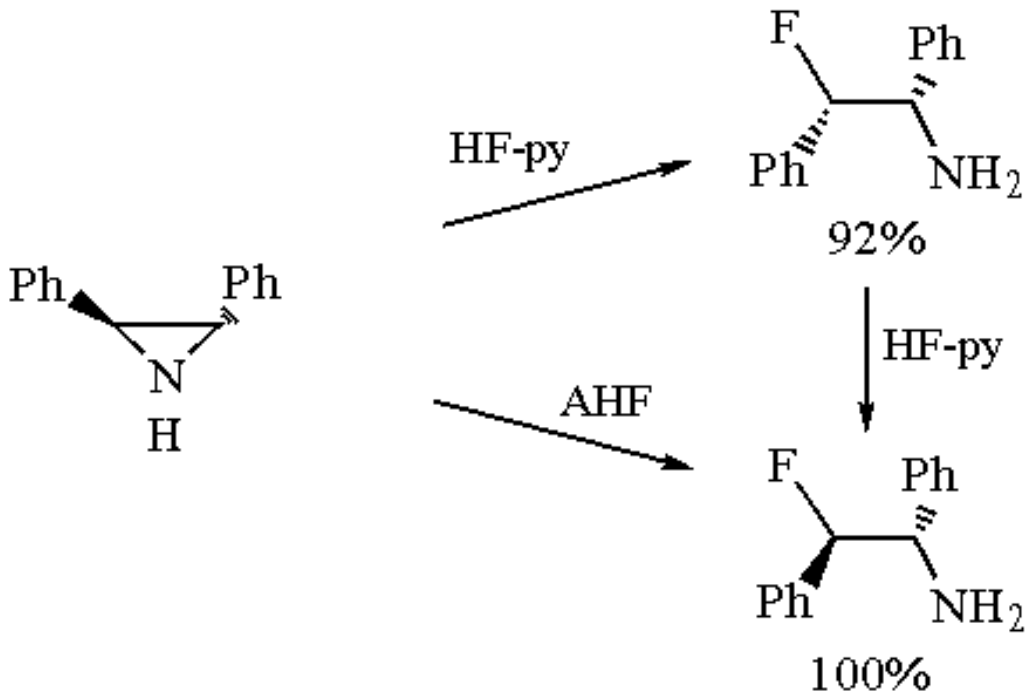

(2)

Halofluorination of alkenes with ***t-Butyl Hypochlorite***, ***N-Bromosuccinimide***, and ***N-Iodosuccinimide*** in the presence of AHF[20] proceeds in good yield, although superior yields again can be obtained with Olah's reagent.[21] In the presence of AHF, addition of ***N-Bromoacetamide*** and *N*-iodosuccinimide to cyclohexene occurs with a high degree of stereoselectivity to produce *trans* isomers in 43% and 72% yield, respectively.[22] Halofluorination occurs in a Markovnikov fashion.[23] Synthesis of *gem*-fluorohalides can be achieved by adding AHF to vinyl halides.[24]

Commercially,[25] the use of AHF for the synthesis of fluoroorganic compounds via either halogen exchange (HALEX) or decomposition of diazonium salts is carried out by this route for economic reasons. For synthetic purposes, inorganic fluorides,[1f] tetraalkylammonium fluorides,[12] and HF.base complexes[10] are preferred fluorinating agents. High yields of α,α,α-trifluoromethoxybenzene[26] via halogen exchange and fluoropyridines via decomposition of the corresponding diazonium salt[27] in the presence of AHF can be obtained.

Bond-Cleaving Reactions.

Desilylation of silyl ethers[28] and silyl enol ethers[29] is most frequently accomplished using HF/MeCN.[3] Compounds containing both alcoholic and phenolic *t*-butyldimethylsilyl ethers can be desilylated with HF/MeCN chemoselectively, leaving the silyl ether of the phenol unscathed (eq 3).[30]

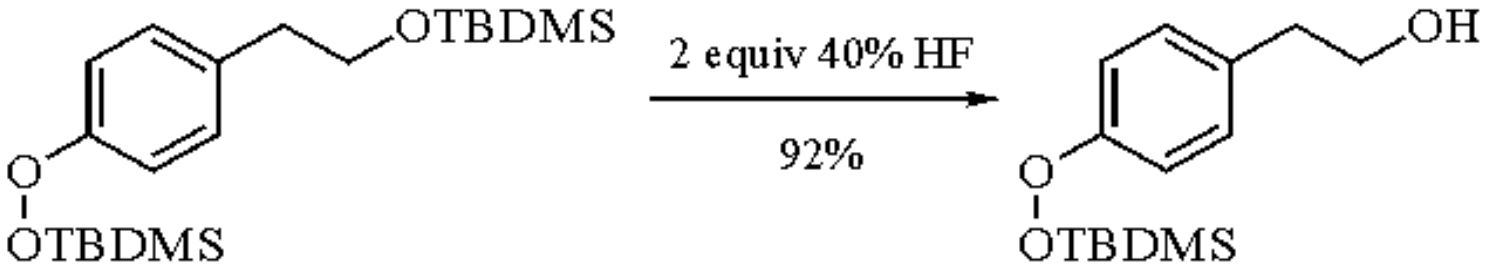

(3)

Cleavage of silyl enol ethers result in the formation of α-alkylidene-β-lactams[31] and migration of C=C bonds, leading to γ-substituted cyclohexenals[32] and β-substituted cyclopentenones.[33]

Concomitant ring formation during desilylation of *t*-butyldimethylsilyl ethers occurs with a high degree of stereoselectivity to give lactones,[34] and is a facile route to butenolides,[35] β-methylene-γ-butyrolactones,[36] bis-β-ketomacrolides,[37] spiroacetals (eq 4),[38] and dispiroacetals.[39]

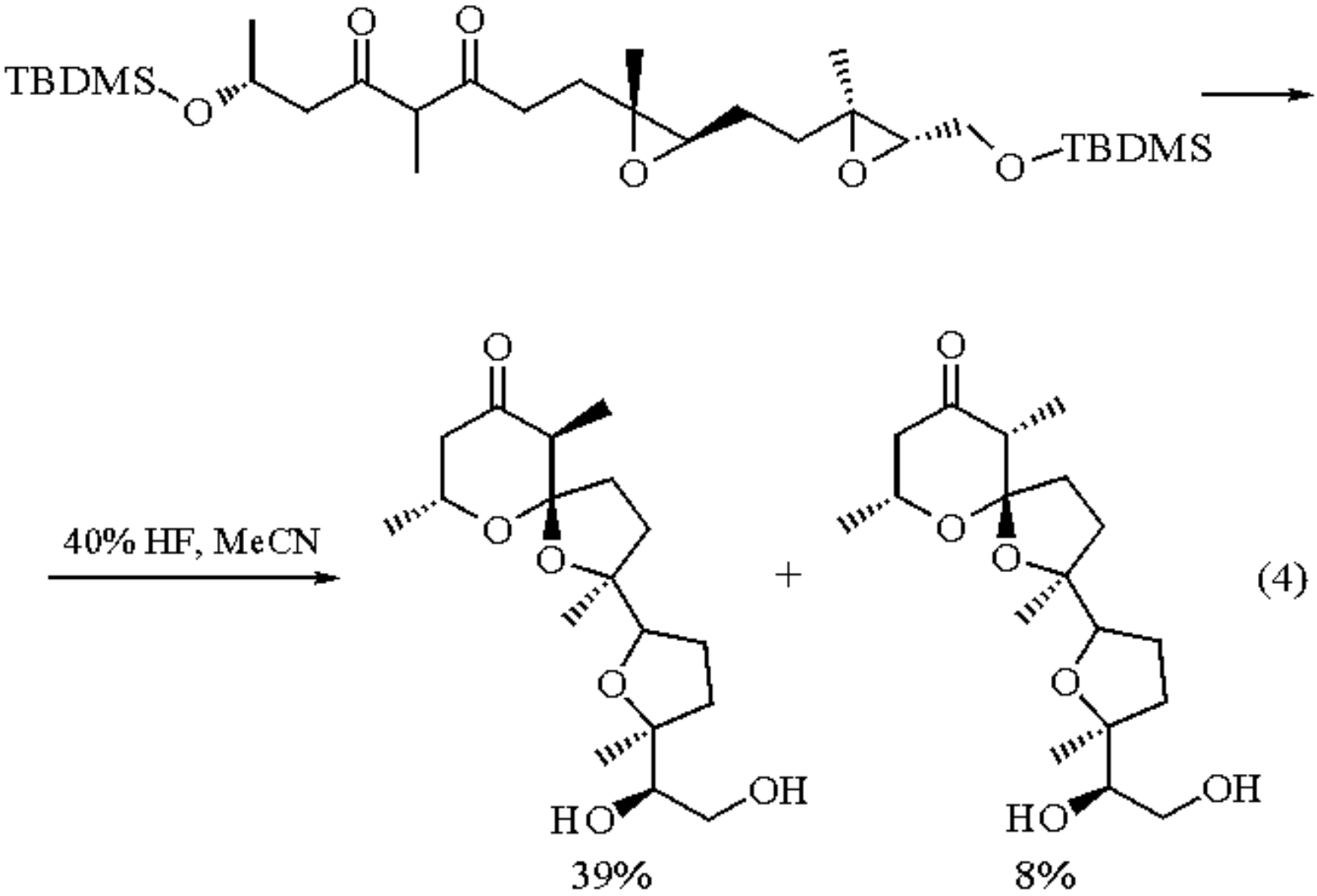

(4)

Similar treatment of *t*-butyldimethylsilyl enol ethers leads to the formation of cyclopentanecarboxylic acid[40] and *cis*/*trans* carbocycles.[41]

Desilylation of *erythro*-α-silyloxyalkylboranes with concomitant protiodeboronation gives alkenes (eq 5) with (*E*:*Z*) ratios as high as 95:5 in 73% isolated yield.[42]

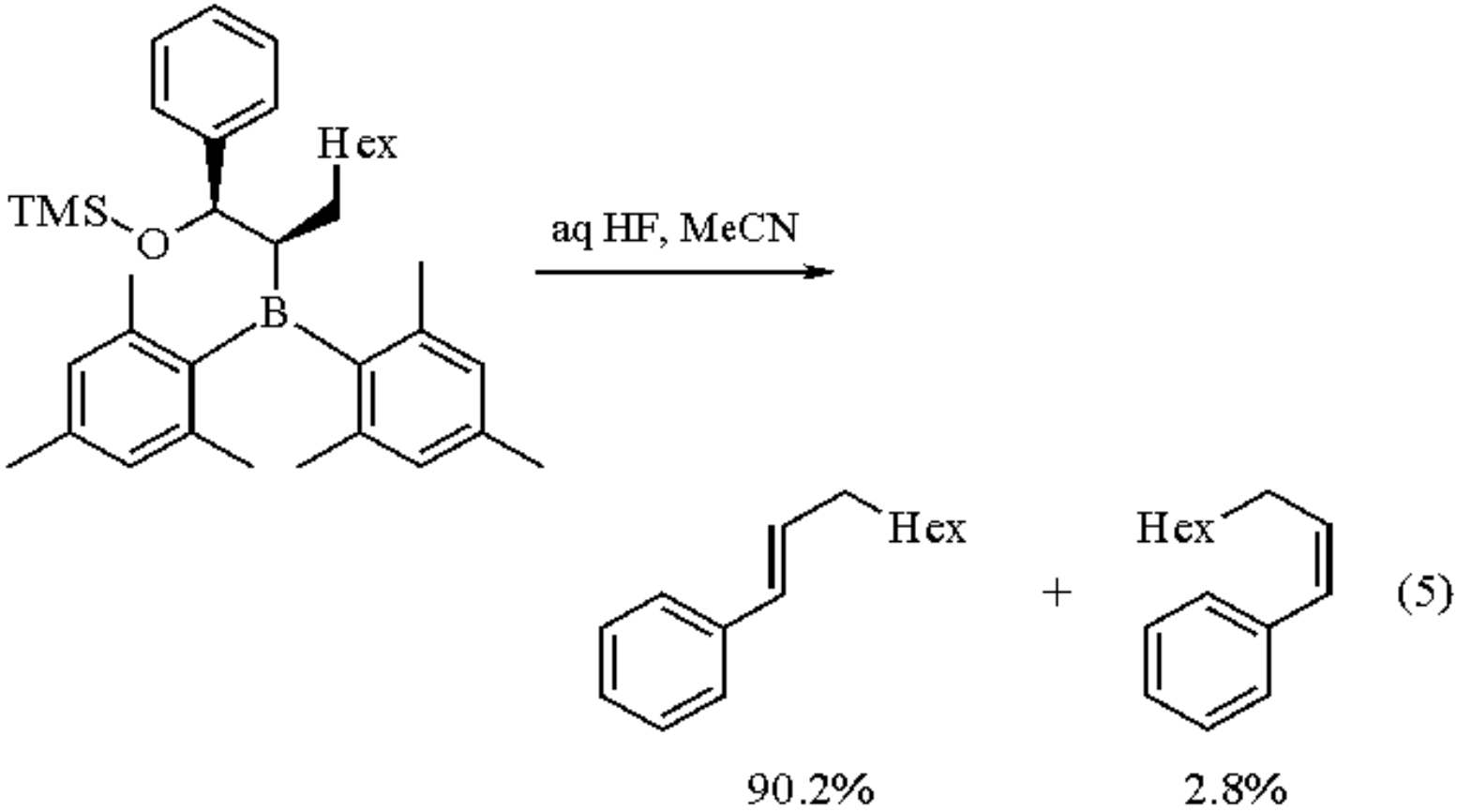

Cleavage of Si-C bonds also is an entry into alkenes,[43] aldehydes,[44] and α,β-unsaturated aldehydes.[45] Cleavage of the Si-N bond gives amines.[46]

Hydrogen fluoride is a versatile reagent in peptide chemistry, cleaving *N*-benzyloxycarbonyl, *S*-benzyl, and *S*-*p*-methoxybenzyl protecting groups of peptides.[5] Removal of protecting groups of aspartine residues (eq 6),[47] *N*-nitroarginine residues,[48] *O*-dimethylphosphinyltyrosine,[49] and the *O*-phosphate ester of tyrosine[50] is accomplished in HF/anisole at 0 °C in <=1 h. However, under similar conditions, side reactions of glutamyl peptides[51] lead to Friedel-Crafts acylation of anisole.

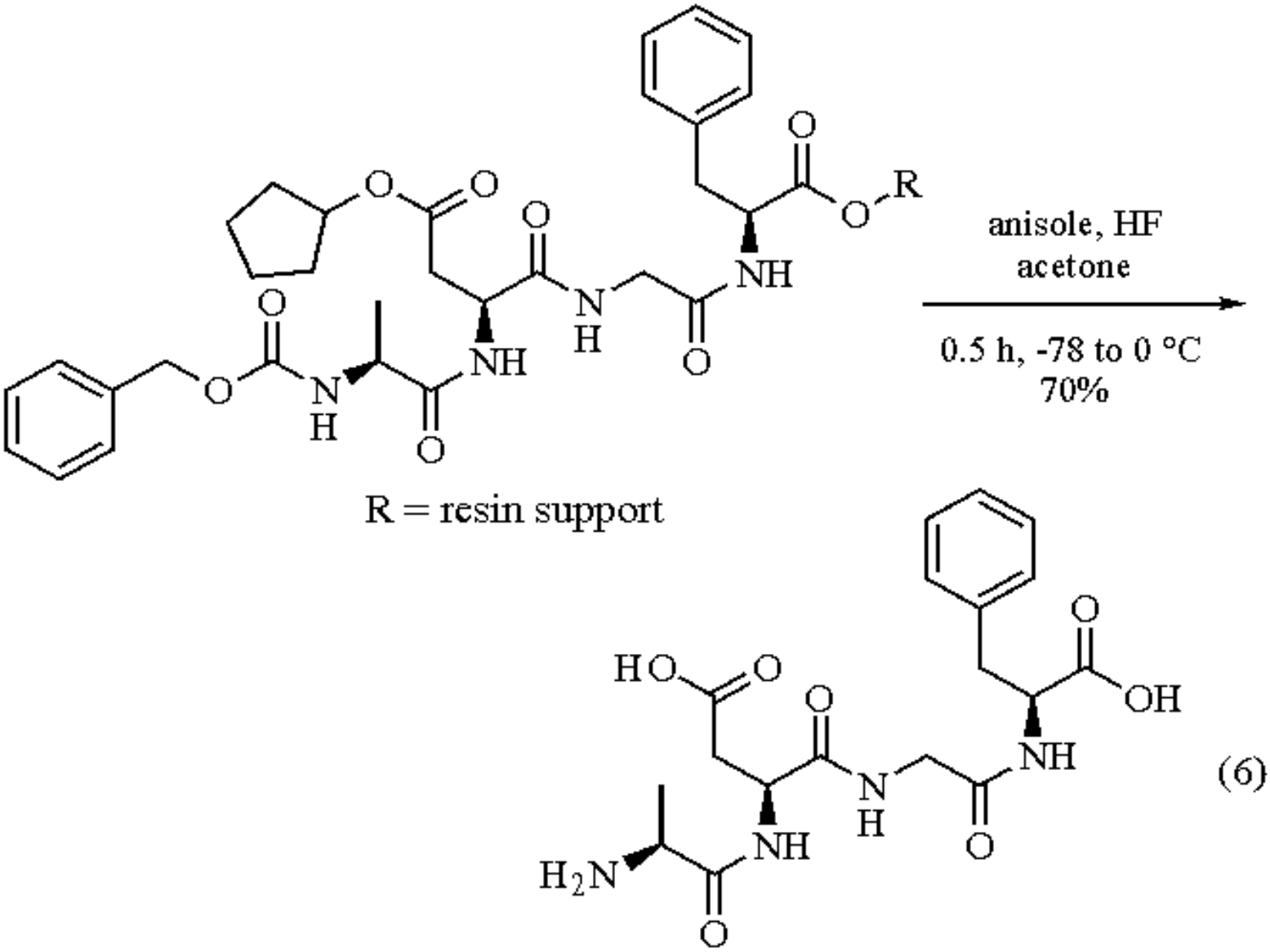

Peptide protecting groups such as phosphonamides[52] and sulfonamides[53] are cleaved in the presence of HF/anisole. In the case of the tripeptide Gly-Lys-Gly, the sulfonyl protecting group of the Lys residue can be chemoselectively removed in the presence of a *t*-Boc protecting group.[54] Polysaccharide solvolysis and glycoprotein deglycosylation is efficiently performed with HF.[55]

Catalyst in Electrophilic Aromatic Substitutions.

In many instances, AHF offers distinct advantages over traditional Lewis acids for the catalysis of electrophilic aromatic substitution reactions. Unlike most Lewis acids, AHF acts as both catalyst and solvent,[56] and can be removed by distillation.[57]

Alkylation of arenes with alkenes,[6a,58] alkyl halides,[6b,59] and methylcyclopropane[60] proceeds in moderate to good yield. Alkylation of arenes with concomitant ring closure leads to cyclic[61] and heterocyclic compounds.[62] Alkylation of benzene with sodium nitronate in the presence of AHF gives benzaldehyde oxime in 78% yield.[63]

The distribution of *o*-, *m*-, and *p*-isomers is known to be a function of temperature. For example, alkylation of phenol

with ***Isobutene*** at -40 °C gives 2-*t*-butylphenol exclusively, while at 0 °C, 3-*t*-butylphenol is obtained in 88% yield; above 30 °C, 4-*t*-butylphenol begins to predominate.[64]

AHF is an excellent catalyst for Friedel-Crafts acylation of substrates as diverse as phenols,[65] thiophenes,[66] and ferrocene.[67] Acylation of phenols is known to proceed with a high degree of regioselectivity to yield *p*-isomers almost exclusively (eq 7).[68]

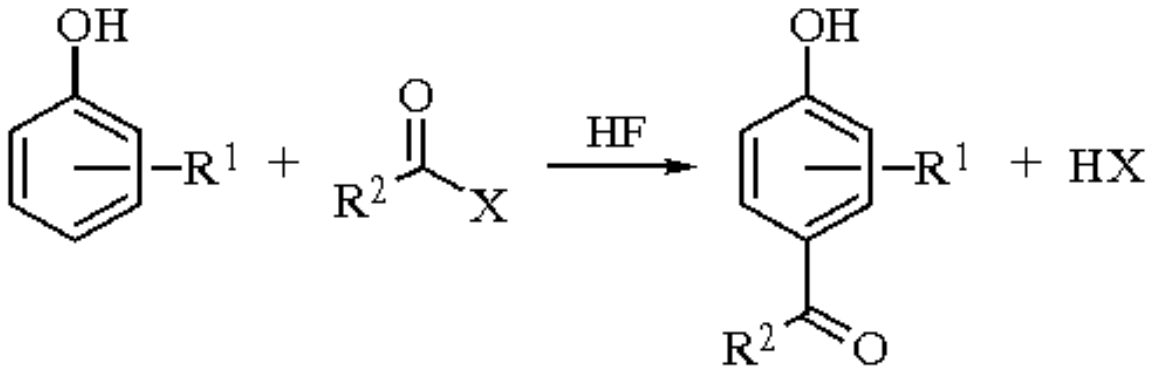

(7)

$R^1 = H, Me, Ph, OMe, SMe$
$R^2 = Me, Et, Ph, CH_2Cl$
$X = F, Cl, Br, OH, OAc$

Similarly, Fries rearrangement of phenyl esters leads to formation of the *p*-isomer[69] unless of course the *para* position is blocked; then *ortho* substitution occurs.[70] Although thiophenol does not undergo acylation in the presence of AHF, thioanisole does, giving the *p*-isomer.[71] As opposed to Lewis acids, AHF-catalyzed acylation of 2-methoxynaphthalene proceeds with high *para* regioselectivity to yield 6-methoxy-2-acetonaphthone.[72]

Intramolecular cyclizations of 3-phenylpropionic acid and 4-phenylbutanoic acid afford α-tetralone and α-hydrindone in 92% and 73% yield, respectively.[73] More sophisticated polycyclic compounds, such as anthracyclinones,[74] can be constructed, as can benzo[*a*]fluoranthene[75] via reductive cyclization.

Other electrophilic aromatic substitutions do not proceed generally as well in AHF, as is the case for the sulfonation of benzene[76] and rearrangement of *p*-cresyl benzenesulfonate[77] to 2-hydroxy-4-methyl diphenyl sulfone. However, nitration,[78] amidomethylation,[79] and thioamidation[80] of aromatic substrates can be achieved in good to excellent yield.

Related Reagents.

N-Bromosuccinimide-Hydrogen Fluoride; ***Hydrofluoric Acid***; ***Hydrogen Fluoride-Antimony(V) Fluoride***.

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Hydrogen Fluoride-Antimony(V) Fluoride[1]

HF/SbF_5

(HF)

[7664-39-3] · FH · Hydrogen Fluoride-Antimony(V) Fluoride · (MW 20.01) (SbF_5)

[7783-70-2] · F_5Sb · Hydrogen Fluoride-Antimony(V) Fluoride · (MW 216.75) ($HSbF_6$)

[16950-06-4] · F_6HSb · Hydrogen Fluoride-Antimony(V) Fluoride · (MW 236.76)

(strong liquid superacid system, used as a catalyst for Friedel-Crafts reactions, isomerization, polymerization, and other acid-related chemistry; efficient for preparation of carbocations and onium ions and their salts[1])

Alternate Name: fluoroantimonic acid; hexafluoroantimonic acid.

Physical Data: HF, bp -19.5 °C; SbF_5, bp 149.5 °C.

Form Supplied in: HF, gas; SbF_5, viscous liquid. Both are commercially available.

Preparative Methods: HF/SbF_5 is prepared by mixing required amounts of freshly distilled ***Hydrogen Fluoride*** and ***Antimony(V) Fluoride*** at low temperature.[2] The reaction is exothermic and must be carried out with careful temperature control. The reagent can also be prepared in situ in the reaction flask.

Handling, Storage, and Precautions: HF/SbF_5 is extremely corrosive, toxic, and moisture sensitive. It fumes when exposed to air; thus it should be stored under anhydrous conditions in a Teflon bottle and handled with gloves in a well-ventilated fume hood.

General Consideration.

Hydrogen fluoride-antimony pentafluoride (fluoroantimonic acid) is probably the strongest liquid superacid system, possessing the widest acidity range.[1] Compared to the widely used Magic Acid system (***Fluorosulfuric Acid-Antimony(V) Fluoride***), the acidity of fluoroantimonic acid is even higher with the same molar concentration of SbF_5. For example, fluoroantimonic acid with 0.5% SbF_5 has a H_0 of -21, while H_0 for HSO_3F/SbF_5 with the same amount of SbF_5 is only -17.[2] Hexafluoroantimonic acid ($HF:SbF_5$ = 1:1) has an estimated H_0 of -30.[1] The X-ray structure of the 1:1 $HF:SbF_5$ complex has recently been established.[3]

Very strong acidity (and low nucleophilicity of its conjugate anion) make fluoroantimonic acid an efficient medium for the preparation of carbocations and onium ions.[1] The same properties have also made the acid an effective catalyst for Friedel-Crafts type reactions, polymerization, isomerization, and other acid-related chemistry.[1]

Friedel-Crafts and Related Chemistry.

Alkylations of deactivated aromatic compounds such as acetophenone are generally difficult to achieve.[4] However, this problem can be overcome with the use of HF/SbF_5. It was demonstrated that acetophenone was readily ethylated with ethyl chloride in the presence of HF/SbF_5 (eq 1).[5] Other primary and secondary alkyl chlorides also react well with the substrate under similar conditions. However, poor results were obtained with tertiary chlorides.

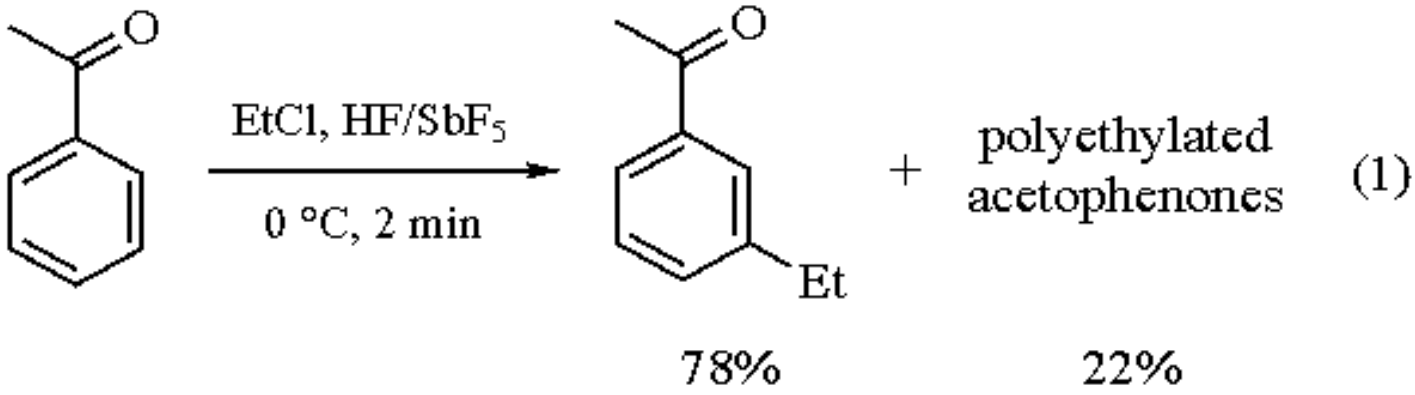

In the presence of HF/SbF_5, even alkanes can alkylate aromatics.[6] This results from protolysis of alkanes to form carbocations and the subsequent trapping of these cations by arenes. The concept of alkane protolysis was also utilized for the preparation of 4,4´-dialkyl-1-tetralones from alkyl phenyl ketones via intramolecular cyclization by using a 5:1 ratio of $HF:SbF_5$ (eq 2).[7] The reaction yields are 68-95%.

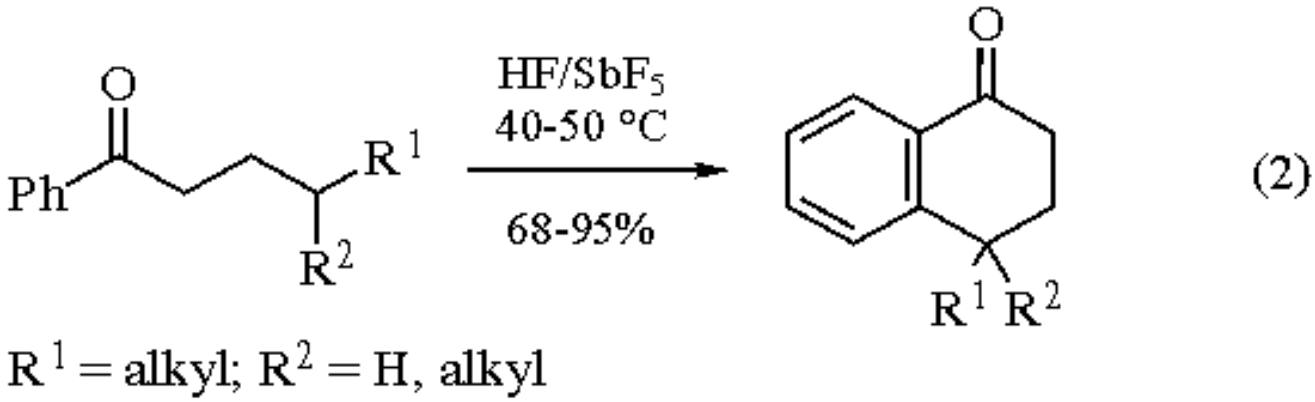

Upon treatment with HF/SbF_5, *para*-substituted phenols (or their methyl ethers) can be diprotonated,[8] first on the oxygen atom and then on the *meta* carbon.[9] The resulting dipositively charged species are exceedingly reactive towards a variety of arenes.[9] 4-Arylcyclohexenones, the primary products of the reactions, can be further transformed to 3-arylcyclohexenones. The ratio between the two isomers depends on conditions such as reaction time, amount of acid, and the nature of substrates. For example, when *p*-cresol is reacted with benzene in the presence of HF/SbF_5, 4-methyl-4-phenylcyclohexenone and 3-phenyl-4-methylcyclohexenone are obtained in 29% and 33% yields,

respectively, after 90 s. With the reaction time increased to 15 min, the yield of 3-phenyl-4-methylcyclohexenone increased to 90% while that of 4-methyl-4-phenylcyclohexenone decreased to 2-3% (eq 3). With the substitution of *p*-cresol with 4-methylanisole, 6,7-benzo-5-methyltricyclo[3.2.1]octan-2-one is obtained as an additional minor product (eq 4).

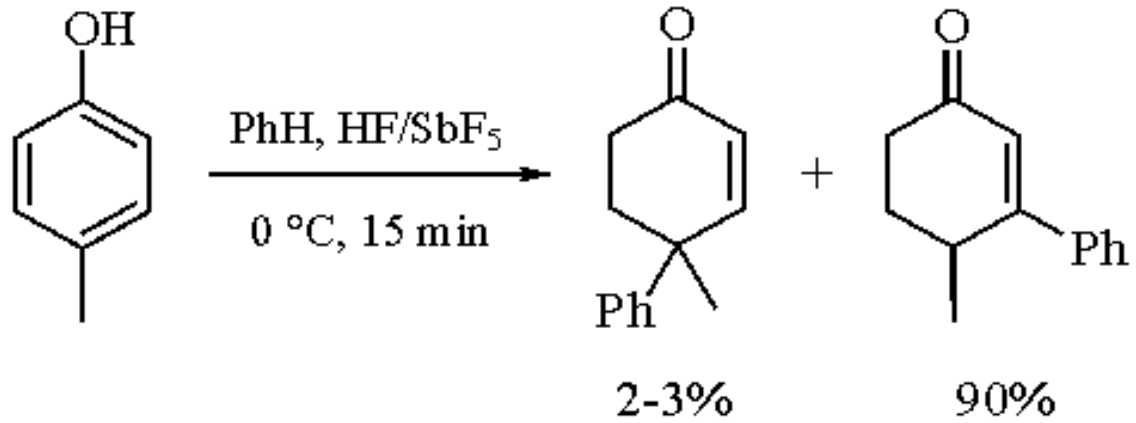

(3)

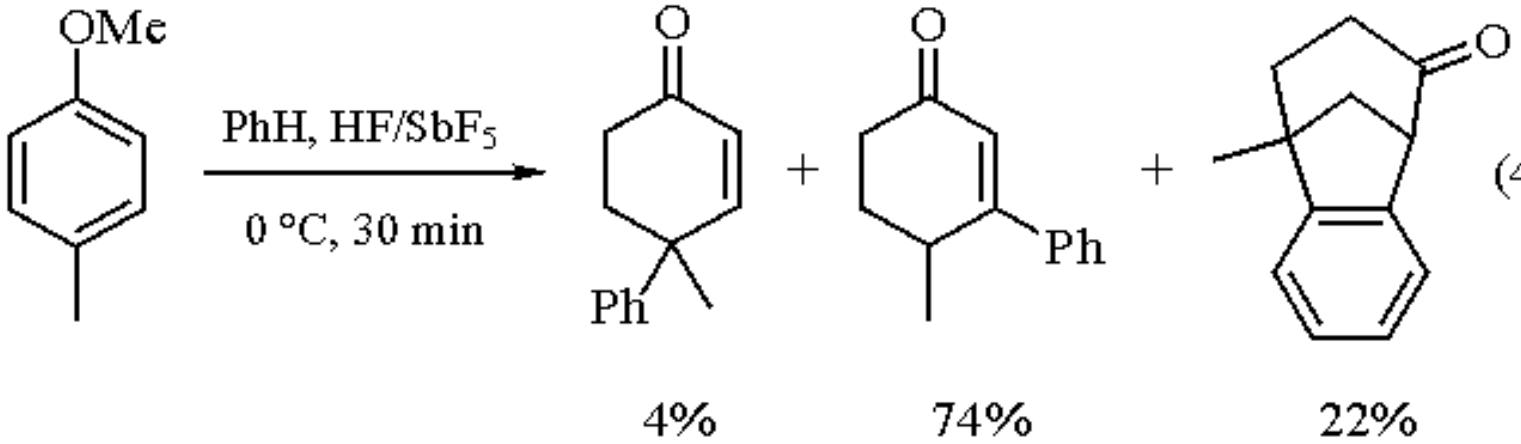

(4)

Condensation of phenols with aromatic compounds has also been successfully applied to the preparation of spiroenones and/or their isomerized ketones via intramolecular cyclization of methoxydiarylethanes or -propanes (eq 5).[10] The starting materials are readily available by Friedel-Crafts acylation of phenols and subsequent reduction of the ketones. In the case of 2´-methoxy-5´-methyl-1,3-diphenylpropane, treatment of the substrate with HF/SbF_5 led to exclusive formation of a tetracyclic ketone (a derivative of benzobicyclo[3.2.1]octane) in 90% yield (eq 6).

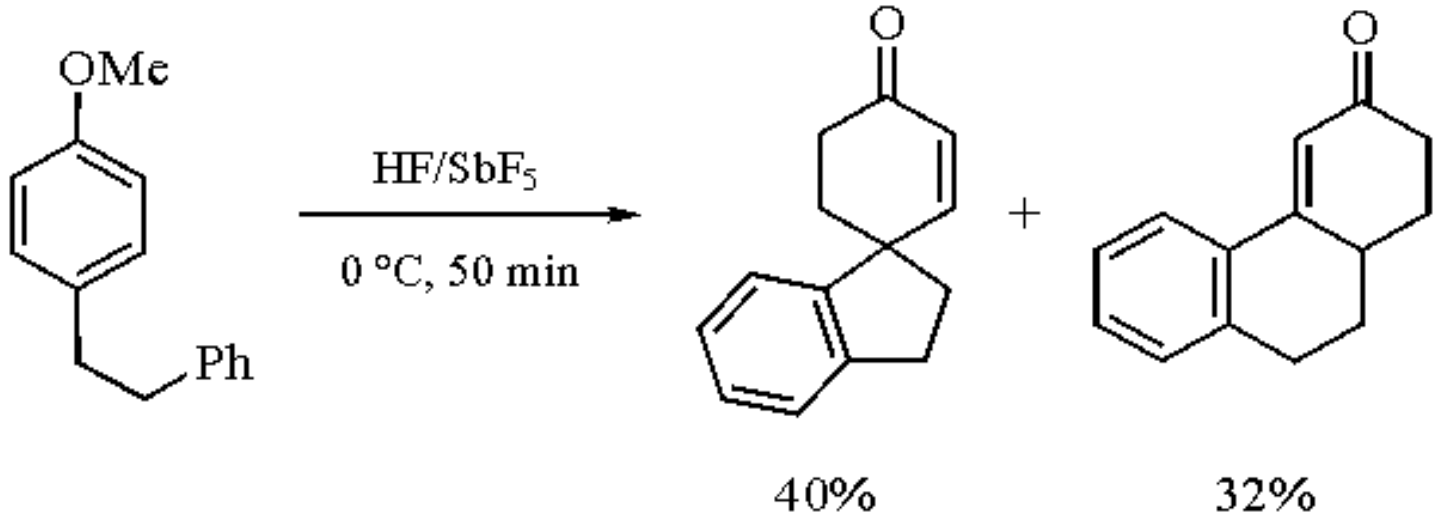

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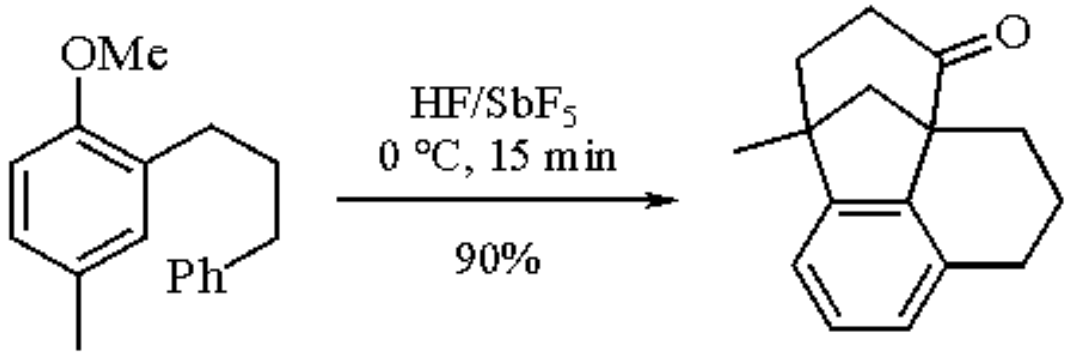

(6)

Electrophilic formylation of arenes with CO in the presence of acids (Gatterman-Koch conditions) is an efficient method for the preparation of aromatic aldehydes. $HF/SbF_5/SO_2ClF$ is the most active system for this reaction.[11] When competitive formylation was performed on benzene and toluene in $HF/SbF_5/SO_2ClF$ at -95 °C, a k_T:k_B ratio of 1.6 was obtained. The observed k_T:k_B ratios for most typical acids range from 155 to 860.[11] It has been demonstrated that even diformylation can be achieved on polynuclear aromatics such as naphthalene and biphenyl with the use of fluoroantimonic acid (eqs 7 and 8).[12] In these cases, dialdehydes are generally formed only when the SbF_5:substrate ratios are larger than 1.

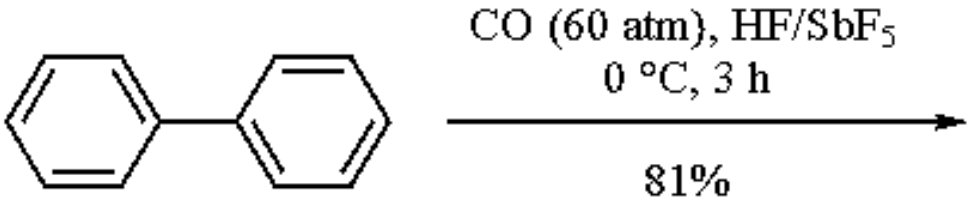

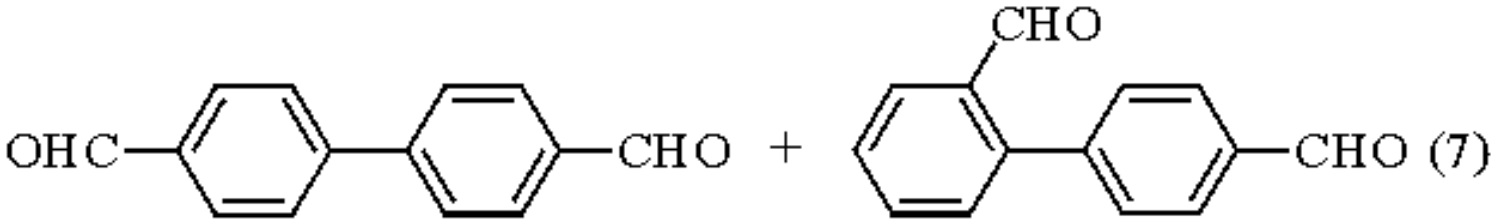

(7)

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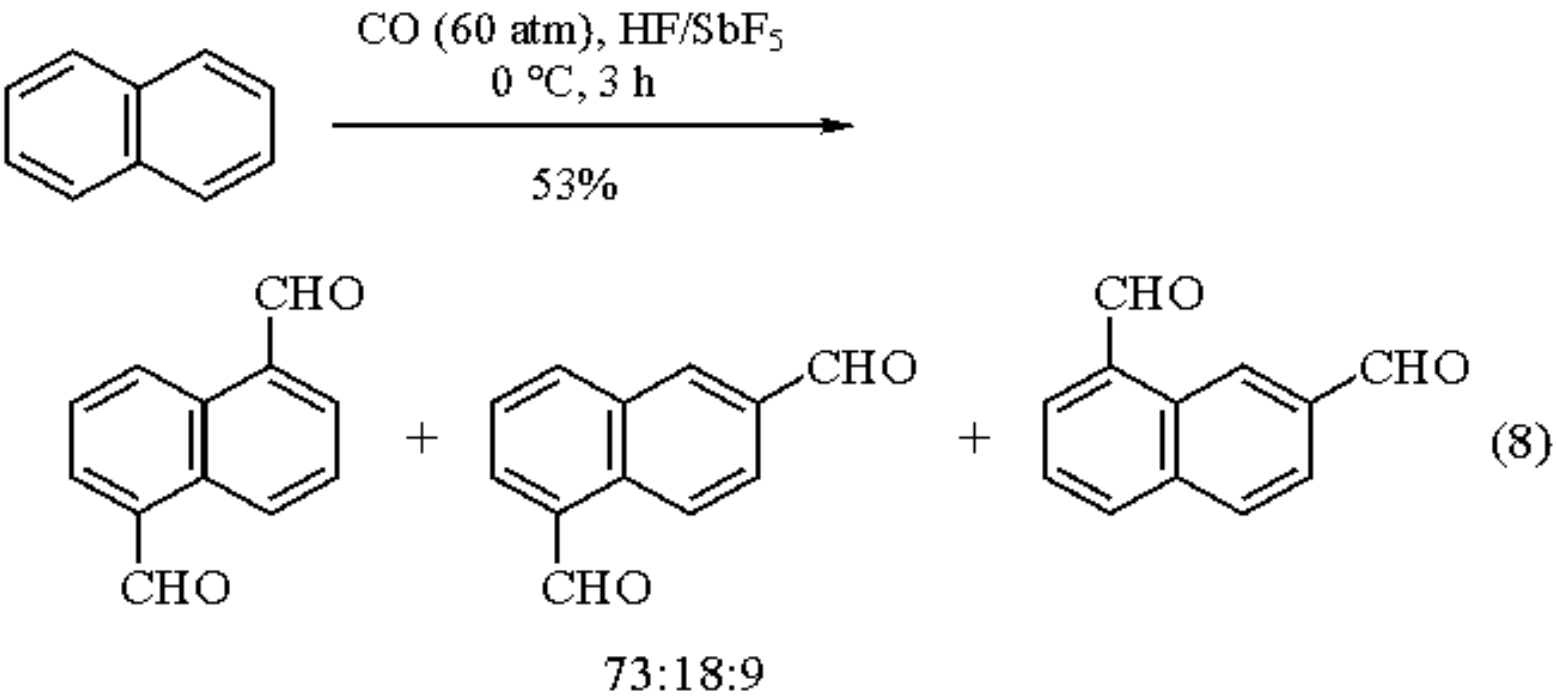

Hydroxylation of aromatics with peroxides and acids generally suffers from secondary oxidation, leading to low selectivity and low reaction yields. With superacids, these secondary reactions can generally be suppressed since *O*-protonation of the newly formed phenols prevents further reaction.[1] The strength of the acids used can play a significant role in the regioselectivity of the reaction. For example, hydroxylation of naphthalene in the weak acid 70% HF-30% pyridine yields 1- and 2-naphthols in a 98.4:1.6 ratio (eq 9); on the other hand, the ratio is changed to 1.8:98.2 when superacidic HF/SbF_5 is used (eq 10).[13] Benzaldehyde and aromatic ketones were reported to be hydroxylated in HF/SbF_5 without formation of products derived from Baeyer-Villiger oxidation.[14] When perfluoro-1-indanone was subjected to similar treatment with the $H_2O_2/HF/SbF_5$ system, 20% perfluorochroman was obtained along with 4% perfluoro-2-(2-carboxyethyl)phenol (eq 11).[15] By increasing the ratio of SbF_5:substrates, phenols can be further hydroxylated in HF/SbF_5. Resorcinols and some other dihydroxyarenes were prepared by this method (eq 12).[16,17] Hydroxylation of anilines by H_2O_2 in HF/SbF_5 yields all three possible isomers, with *meta* derivatives as major products.[18]

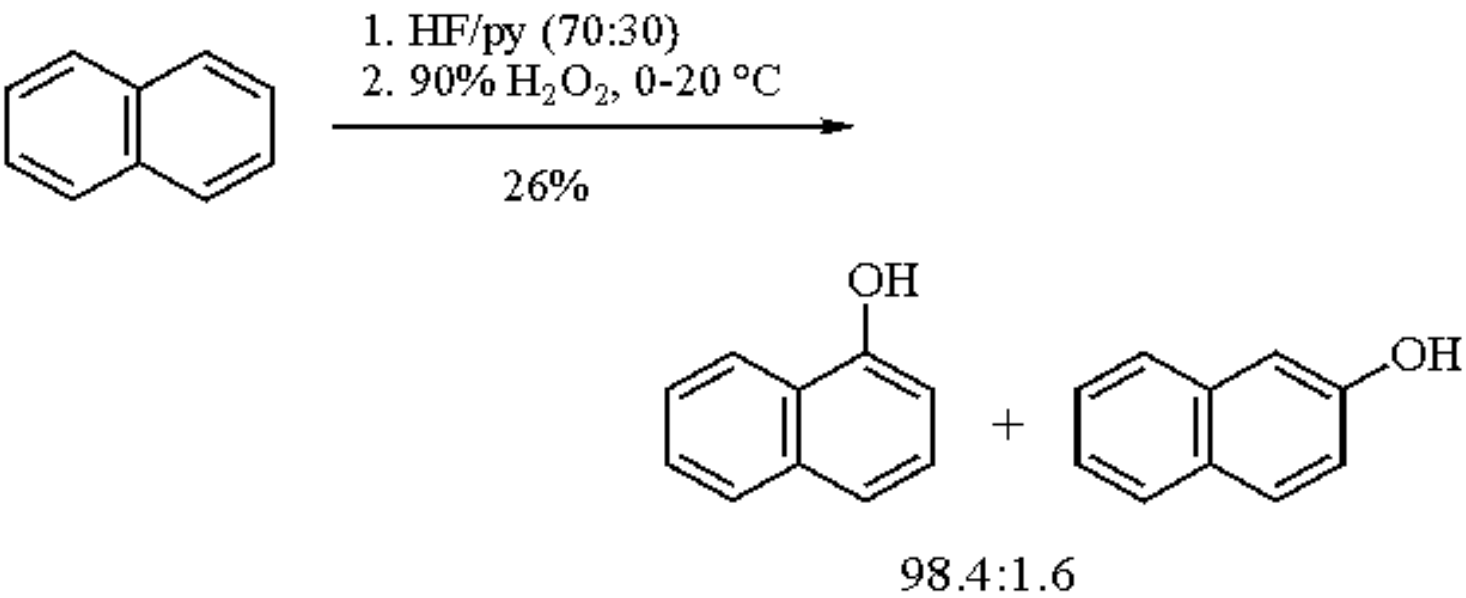
1. HF/py (70:30)
2. 90% H_2O_2, 0-20 °C
26%
OH
OH
+
98.4:1.6

(9)

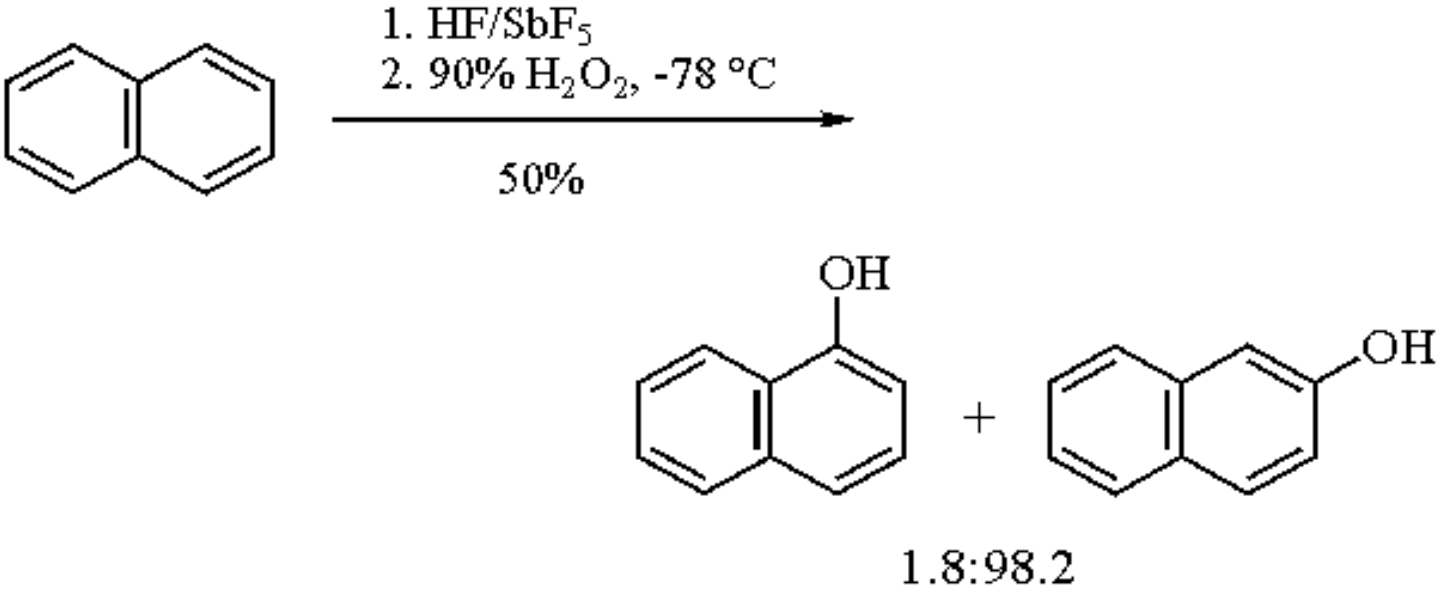
1. HF/SbF_5
2. 90% H_2O_2, -78 °C
50%
OH
OH
+
1.8:98.2

(10)

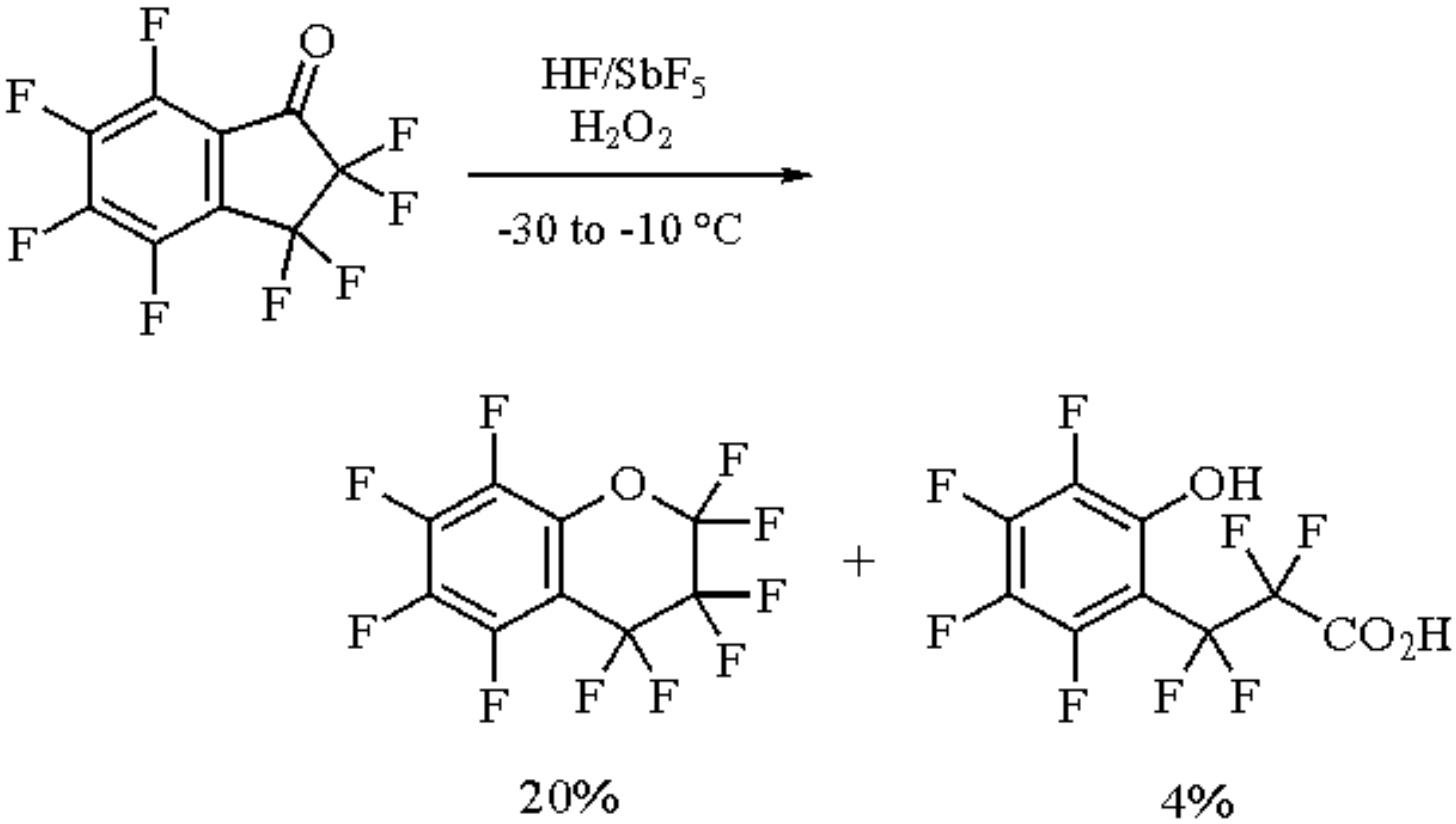

(11)

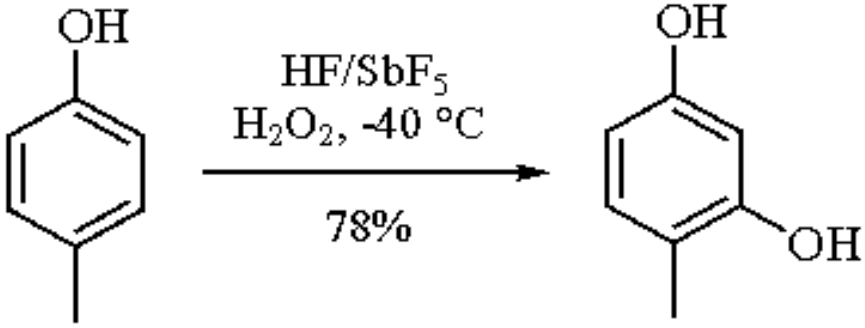

(12)

Bromination of *para*-alkylated or 2,6-dialkylated phenols and their ethers with Br_2 in HF/SbF_5 leads to formation of *meta*-brominated products (eq 13).[19] The results indicate that the bromination occurs on the *O*-protonated substrates, since halogenation of phenols under neutral conditions gives *ortho*- and *para*-substituted products. Sodium or potassium bromide can also be used in place of Br_2 in the reaction.[20]

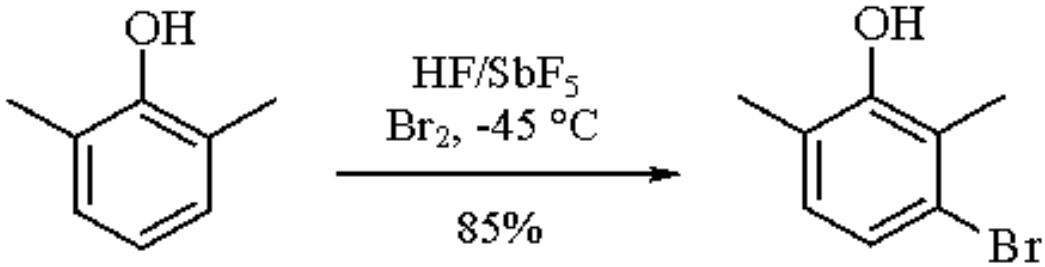

(13)

Generally, nitration of aromatics is considered to be an irreversible reaction. However, the reversibility of the reaction has been demonstrated in some cases in the presence of HF/SbF_5 or superacidic ***Nafion-H***. 9-Nitroanthracene and pentamethylnitrobenzene will transnitrate benzene, toluene, and mesitylene in these acid media.[21]

HF/SbF_5 and other superacids, such as HF/TaF_5 and $HBr/AlBr_3$, are able to promote the hydrogenation of benzene and other aromatics to cyclohexanes and compounds derived from them in the presence of proper hydride donors.[22] The reaction proceeds through an ionic hydrogenation mechanism. The best hydride donors are isoalkanes (cycloalkanes) with tertiary C-H bonds. The use of molecular hydrogen in ionic hydrogenation reactions is also possible in the presence of tertiary C-H bond-containing hydrocarbons.[22a]

Upon treating deuteriated methane with HF/SbF_5, deuterium-protium exchange was observed.[23] Similar exchange was also observed with other alkanes. In the latter cases, protolysis of C-H and C-C bonds to form carbocations accompanies the exchange process.[24] It is interesting to compare the isotope exchange of isobutane using D_2SO_4 and DF/SbF_5.[25] When D_2SO_4 is used, all hydrogens on carbon atoms adjacent to the tertiary carbon atom exchange rapidly, whereas the hydrogen on the tertiary carbon is invariably recovered unexchanged (eq 14).[26] In contrast, with DF/SbF_5 at -78 °C, exchange on the methine proton was observed (eq 15).[25a,b] More recently, it was reported that deuterium-protium exchange occurs even on the *t*-butyl cation through the protio-*t*-butyl dication.[25c]

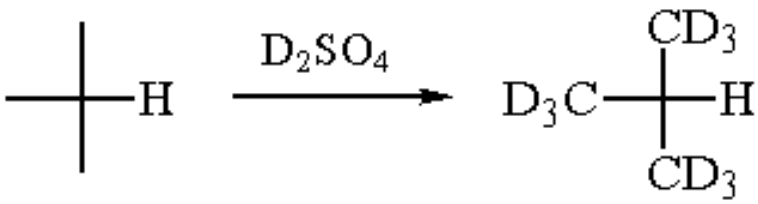

(14)

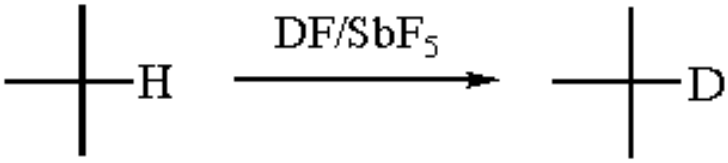

(15)

The carbenium ions formed in the protolysis of alkanes with HF/SbF_5 can be trapped in situ with CO.[27] Hydrolysis of the resulting acyl cations yields the corresponding carboxylic acids (eq 16) (Koch reaction).[28] With excess alkane present, ketones can be obtained (eq 17). It is noteworthy that in the carbonylation of propane, addition of catalytic amounts of bromides or halomethanes enhances the selectivity in favor of secondary C-H bond activation. Most (99%) of the products are derived from the isopropyl cation; only negligible amounts of methane and ethane are formed.[29]

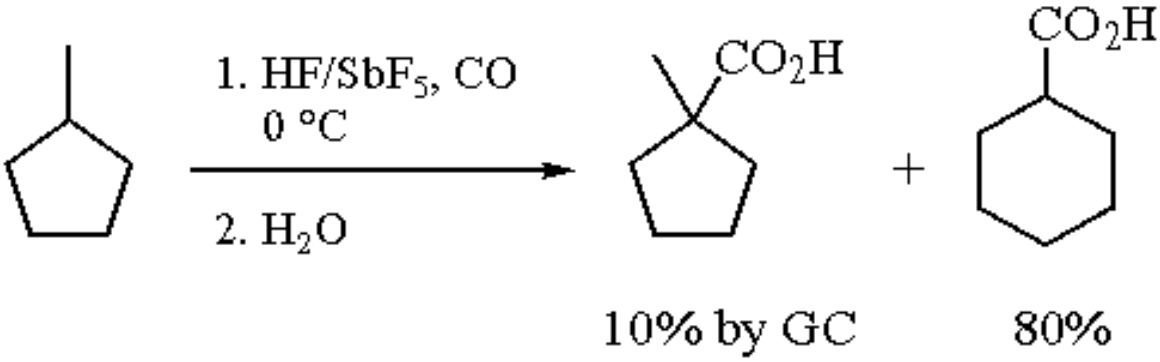

(16)

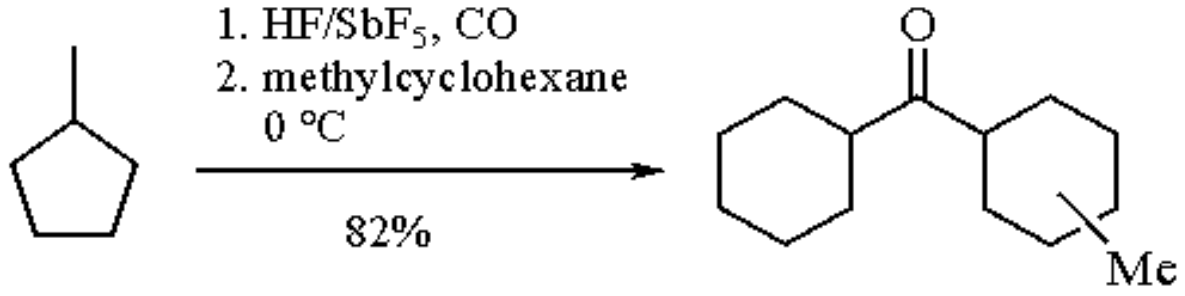

(17)

Superacid-catalyzed oxygenation of alkanes has been well reviewed.[30] Both peroxy compounds and ozone can serve as oxidants. For example, in the oxygenation of neopentane with O_3 in $HF/SbF_5/SO_2ClF$, both methylated and ethylated acetones were obtained.[30]

1,2-Dichloroethane reacts with tetrafluoroethylene in HF/SbF_5 to form 1,1,1,2,2-pentafluoro-3-chlorobutane in 80% yield (eq 18).[31] The product is formed by addition of α-chloroethyl cation, rearranged from the initially formed β-chloroethyl cation, to tetrafluoroethylene and subsequent quenching with fluoride. Small amounts of 1,1,2,2-tetrafluoro-1,3-dichlorobutane and 1,1,2,2-tetrafluoro-1,4-dichlorobutane were also obtained. When 1,2-dibromoethane is used, 1,1,1,2,2-pentafluoro-4-bromobutane was obtained in 50% yield (eq 19).[31] No products arising from rearrangement were observed in this case.

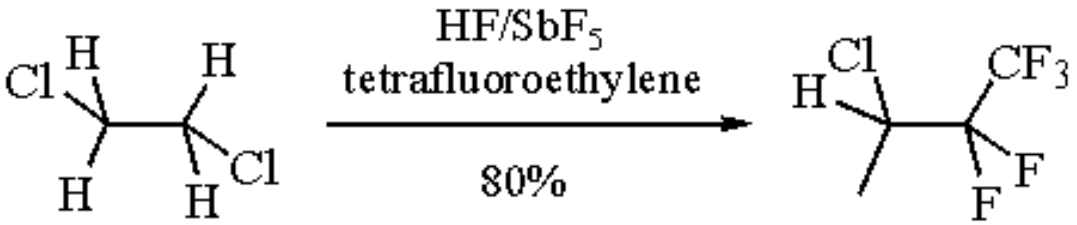

(18)

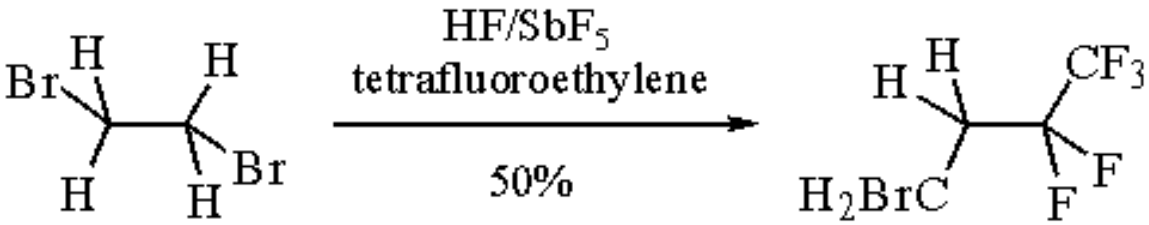

(19)

An interesting synthetic method has been developed for carboxylation of bicyclic enones in HF/SbF_5.[32] It was demonstrated that the diprotonated α,β-unsaturated ketones react with CO to form acylium ions. Quenching of these acylium ions with methanol led to the corresponding carboxylic esters in good yields (eq 20).

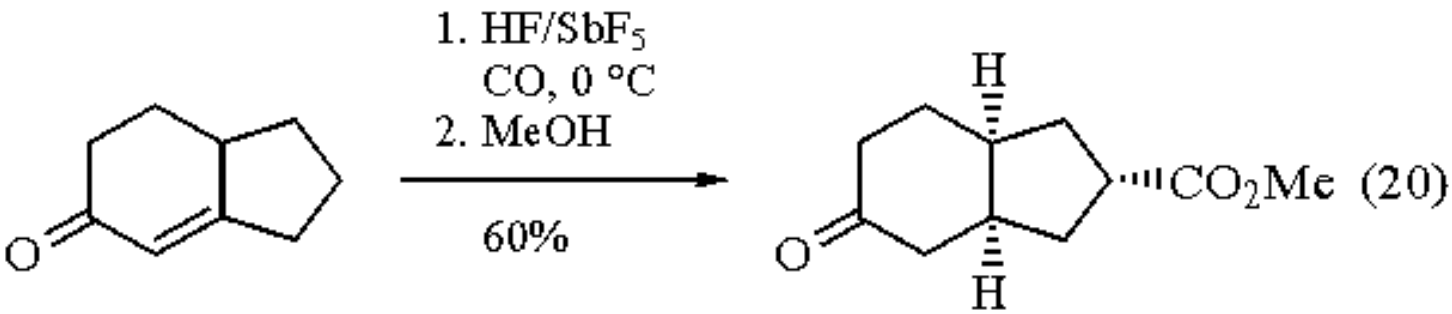

(20)

Generally, alcohols with short carbon chains (C_1-C_4) are not carbonylated under the usual Koch conditions. However, it was found that these alcohols readily react with CO in fluoroantimonic acid to give the corresponding carboxylic acids in high yields.[33a] Even diols reacted under similar conditions to give dicarboxylic acids.[33b] Some cyclization products were also obtained. γ-Butyrolactones react with CO at atmospheric pressure in HF/SbF_5 containing an excess of SbF_5 to give dicarboxylic acids in good yields (eq 21).[33c] Methyl alkyl ketones with alkyl groups having five or more carbons can undergo Koch reaction to form the corresponding oxo carboxylic acids (eq 22).[34]

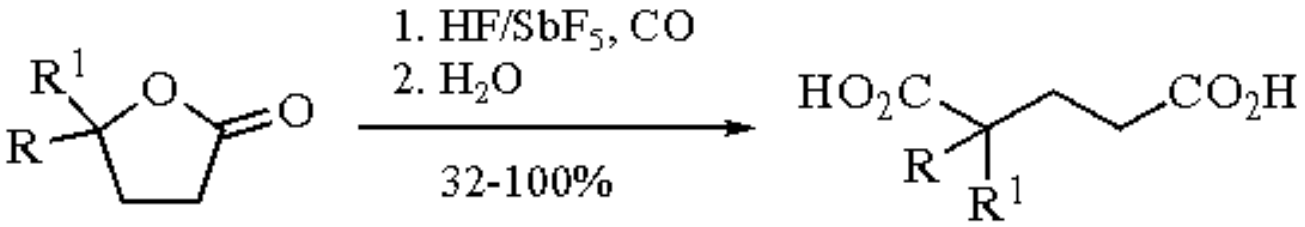

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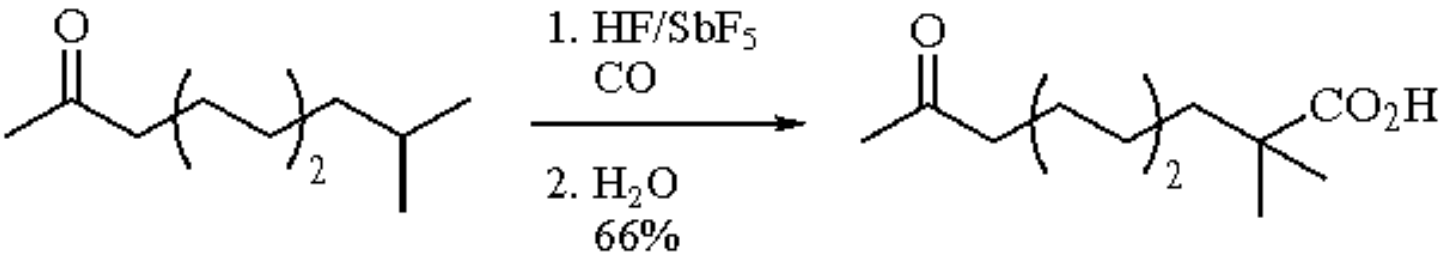

(22)

Oxidation of 3-keto steroids with O_3 has also been carried out in HF/SbF_5 (eq 23).[35] When oxygenations of ethers were performed under similar conditions, oxo alkyl ethers were obtained, with the oxo functionality generally three carbons away from the ether linkage (eq 24).[36]

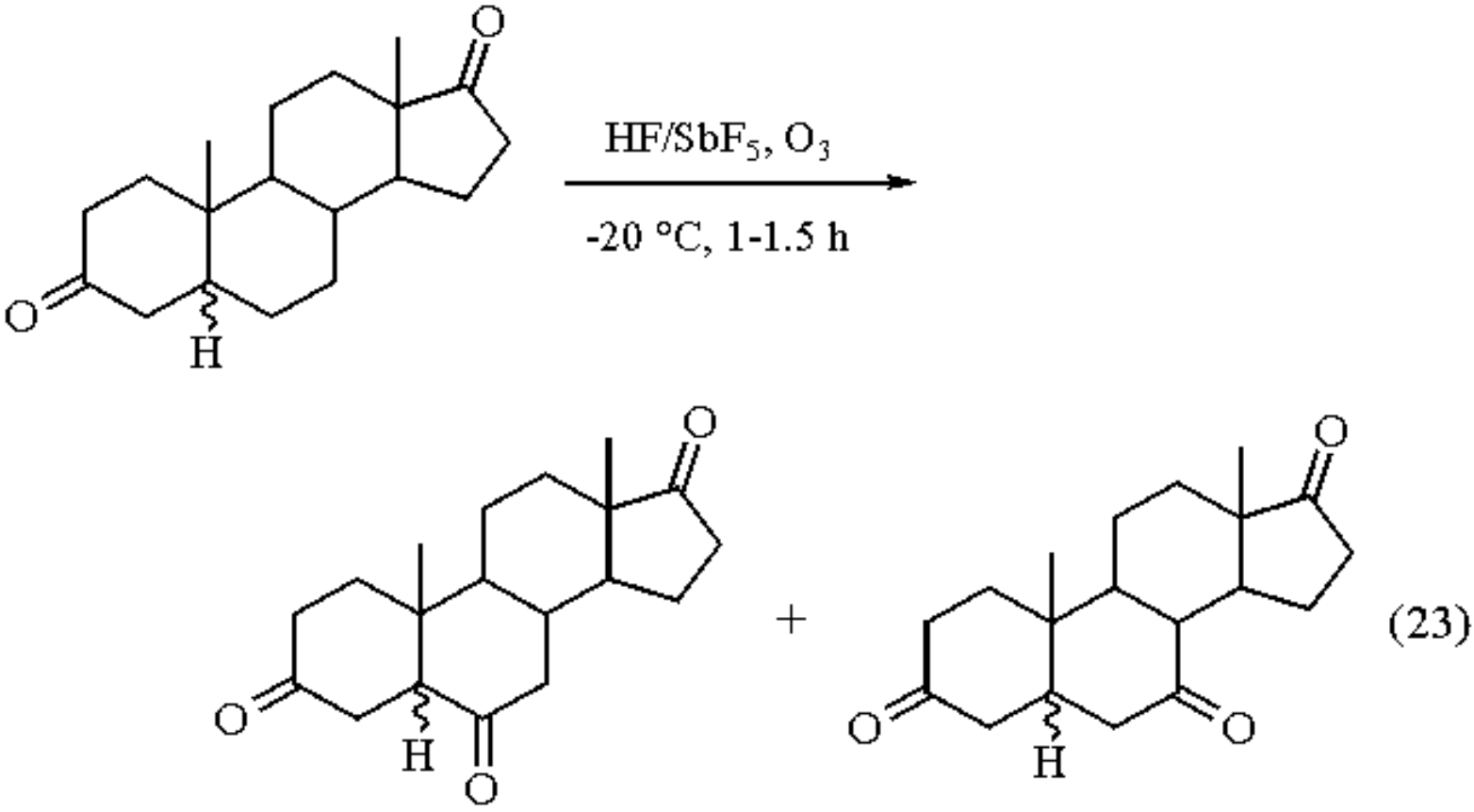

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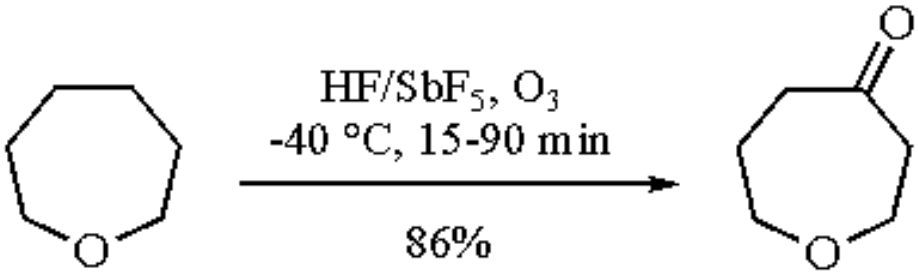

(24)

Superacid-catalyzed ionic hydrogenation is not limited to aromatic compounds; it has been successfully applied in natural product chemistry (eq 25).[37-39] Protonated enones or dienones can be conveniently reduced in the presence of isoalkanes or with molecular hydrogen.

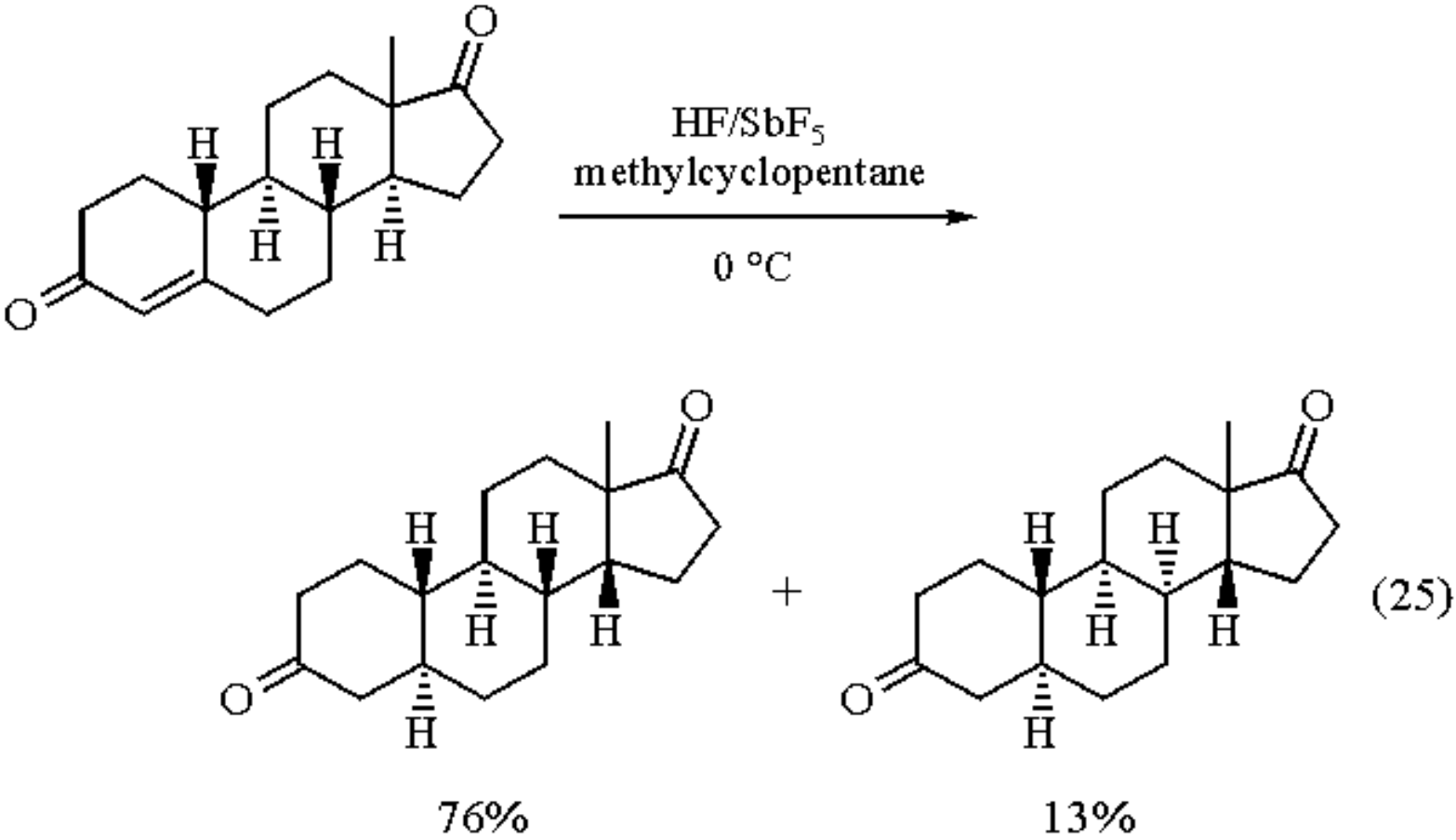

(25)

Isomerization and Rearrangements.

The high acidity of HF/SbF_5 makes fluoroantimonic acid an efficient isomerization catalyst for hydrocarbons. Isomerizations of fluorotoluenes, polyhalobenzenes, and aromatic sulfones have been carried out.[40,41] *Ortho*- or *para*-bromo phenols were reported to isomerize to *meta* isomers in HF/SbF_5 through intramolecular 1,2-Br shifts. In contrast, ***Trifluoromethanesulfonic Acid***-catalyzed isomerizations proceed through an intramolecular mechanism.[42] It was also reported that rearrangements of 4-alkylated and 2,6-dialkylated phenolic ethers can occur in HF/SbF_5. The alkyl groups originally attached to oxygen are rearranged to the *meta* positions of the compounds (eq 26).[43] This dealkylating ability of HF/SbF_5 has been successfully employed in the synthesis of 11-deoxyanthracyclines (eq 27).[44] Rearrangement of *s*-butylbenzene to isobutylbenzene under $AlCl_3$ catalysis necessitates higher temperatures; however, the isomerization proceeds under milder conditions when HF/SbF_5 is used.[45]

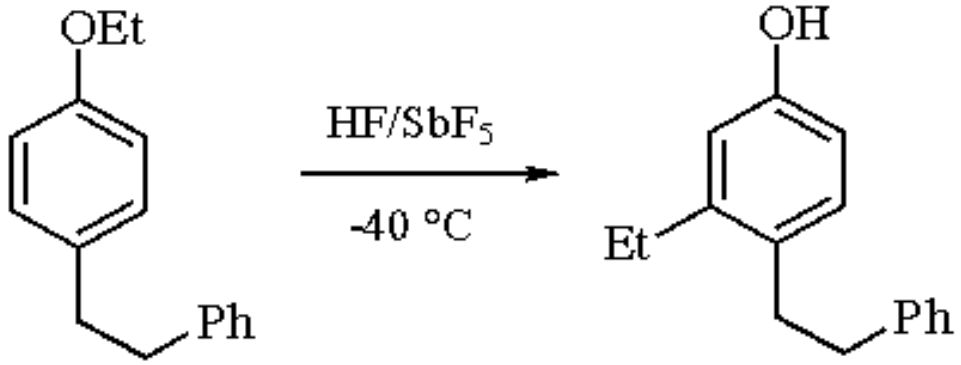

(26)

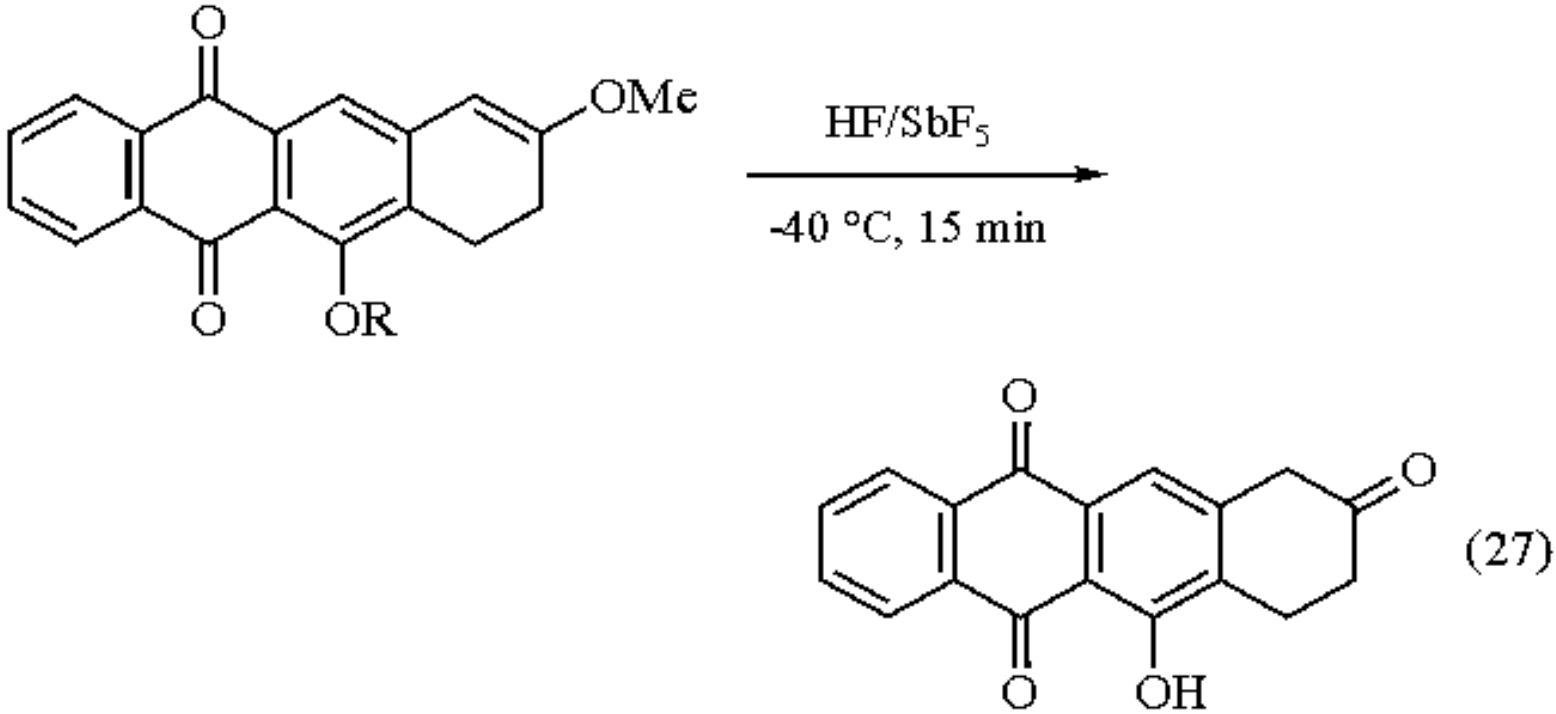

Rearrangement of phenols to dienones occurs readily in superacids. Some simple bicyclic phenols and their ethers were investigated as model compounds using HF/SbF_5.[46] The method is also applicable to natural products.[47] For example, treatment of estrone derivatives in HF/SbF_5 followed by aqueous bicarbonate workup led to estra-4,9-diene-3,17-dione (eq 28). The opposite rearrangement of phenols to dienones, i.e. dienones to phenols, can also be achieved in an HF/SbF_5 medium (eq 29).[48]

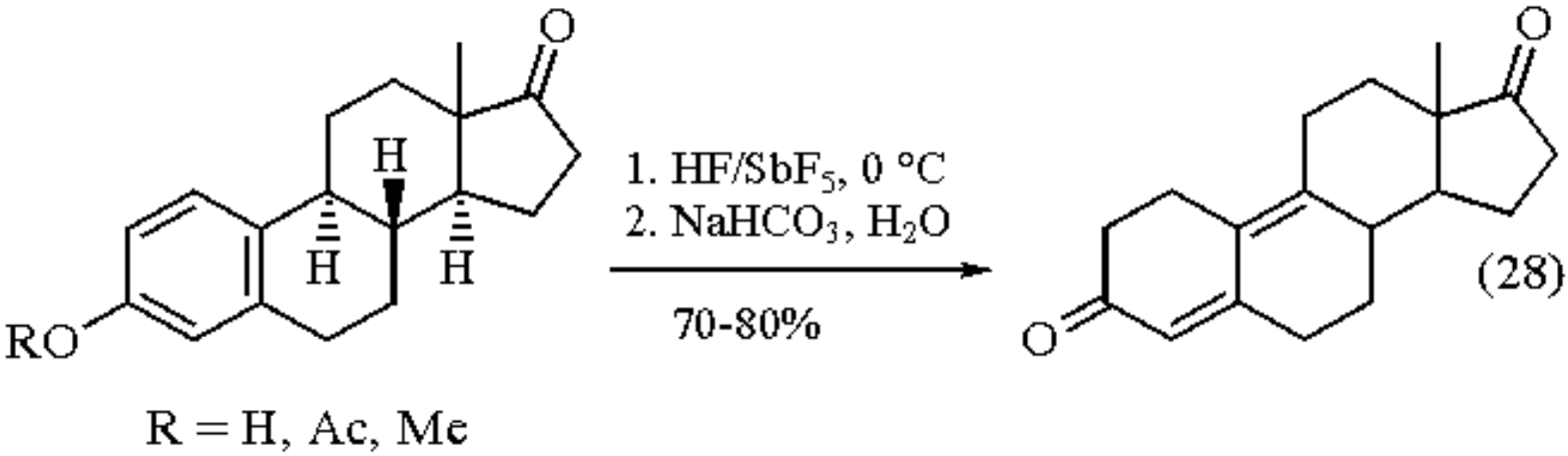

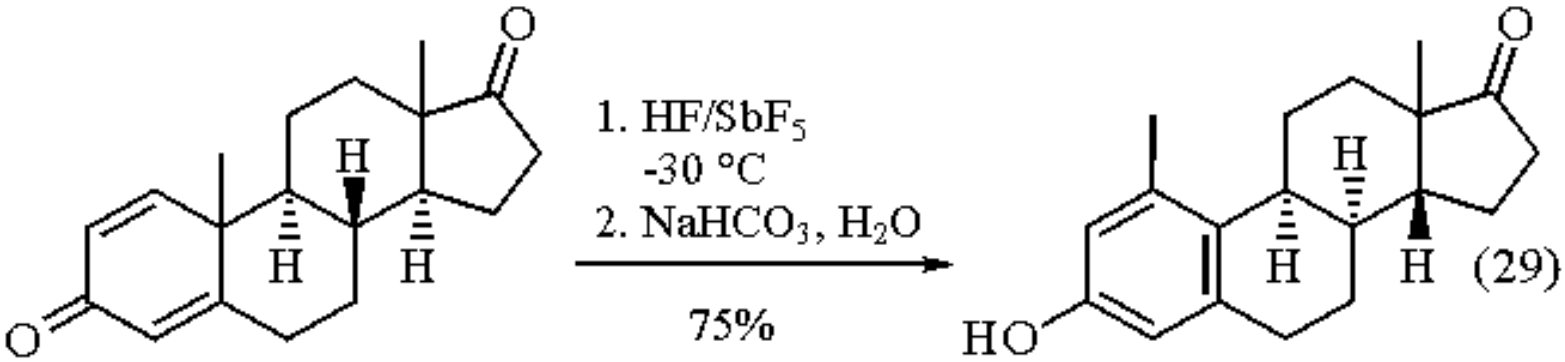

n-Alkanes can be readily isomerized to branched alkanes in superacidic media; HF/SbF_5 has been used for this process.[49] With a catalytic amount of HF/SbF_5, *endo*-trimethylenenorbornane was converted to *exo*-trimethylenenorbornane at rt in 98% yield.[50] With increasing amounts of acid, some adamantane was formed in the reaction mixture. Raising the reaction temperature to 100 °C increases the yield of adamantane to 47% (eq 30).[51]

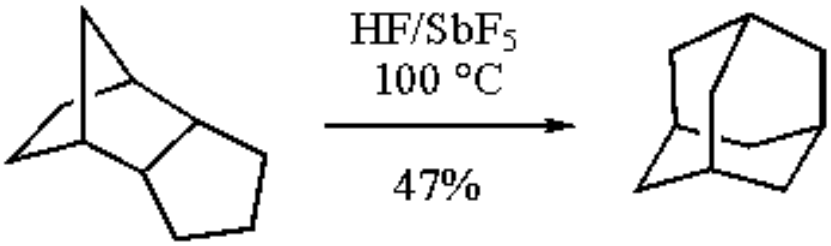

(30)

HF/SbF_5 can induce isomerization of pregnane-3,20-diones to mixtures of isomers containing the 13α-isomer (eq 31).[52] The reaction is proposed to occur through the cleavage of the C(13)-C(17) bond. Many estrane derivatives can be prepared through HF/SbF_5-catalyzed isomerization.[53]

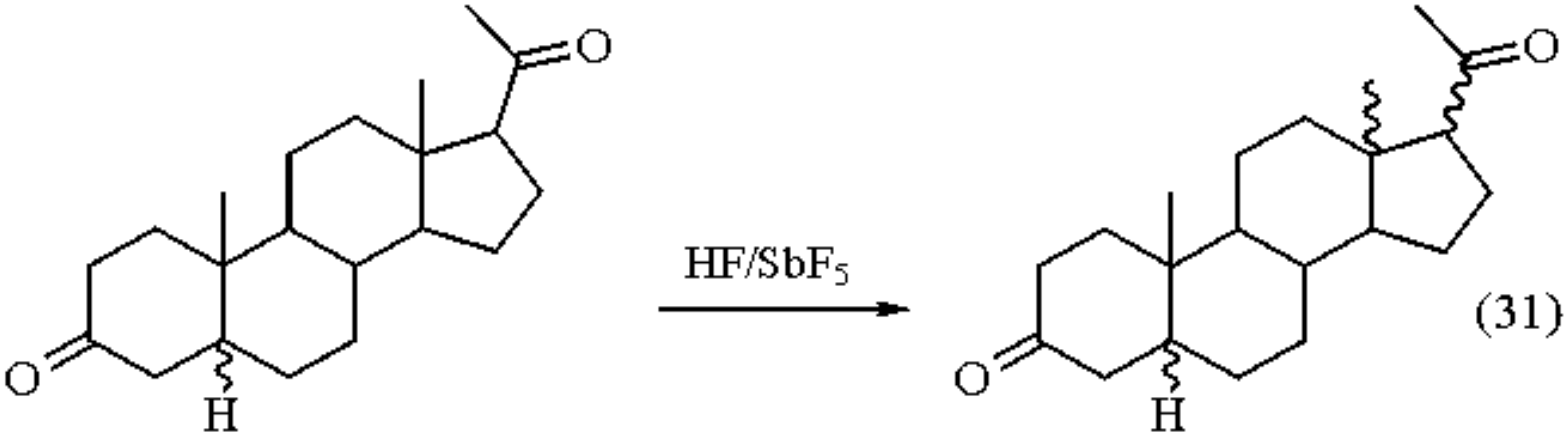

(31)

Isomerization or rearrangement catalyzed by superacids often differs from conventional acid catalysis; the high acidity leads to stabilized reaction intermediates. A pertinent example is the rearrangement of camphor. In concentrated H_2SO_4, it was mainly converted to 3,4-dimethylacetophenone (eq 32);[54] in HF/SbF_5, however, a mixture of three aliphatic ketones was obtained (eq 33).[55]

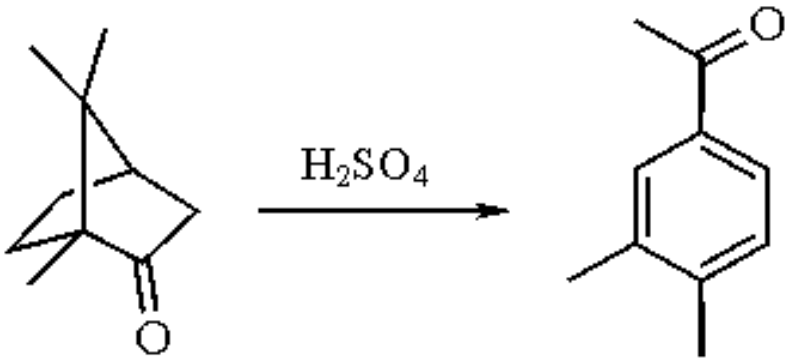

(32)

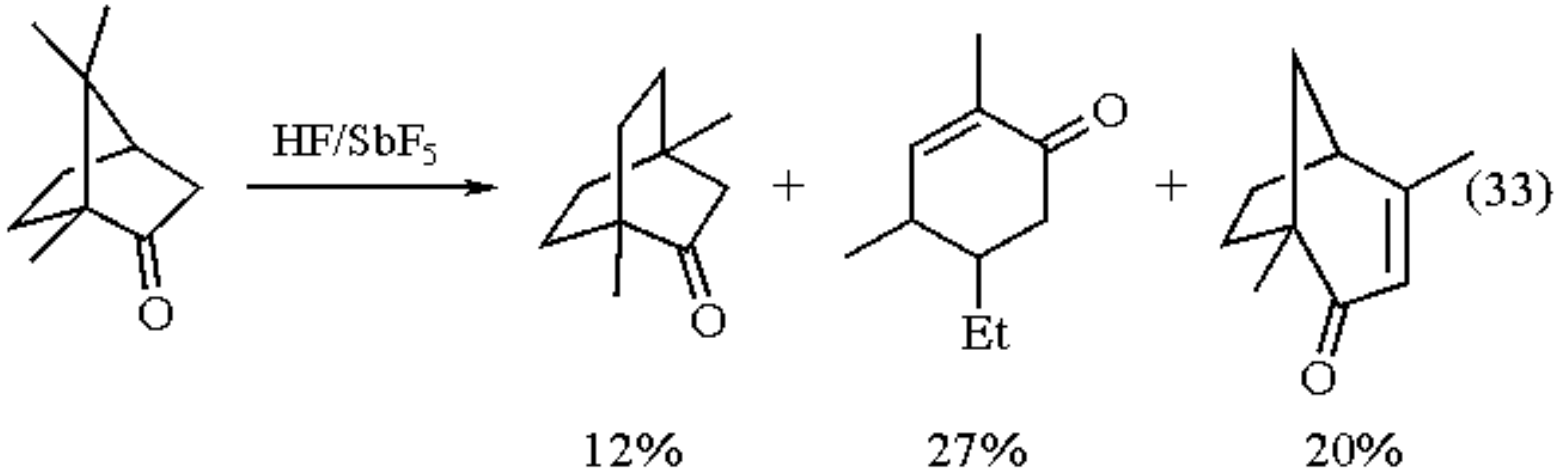

Carbocations and Onium Ions.

The corrosive and toxic nature of HF makes HF/SbF_5 a less frequently used acid system for the preparation of carbocations compared to HSO_3F/SbF_5. It is preferred, however, in the generation of arenium ions, since high acidity is required for their formation (eq 34).[56] Interestingly, upon treatment with HF/SbF_5, azoxybenzene is deoxygenated to form a dication believed to be responsible for the Wallach rearrangement product (eq 35).[57] HF/SbF_5 is able to dehydrate aliphatic ketones to form allyl cations (eq 36).[58] It was found that the rate of dehydration increases with the acidity of the medium.

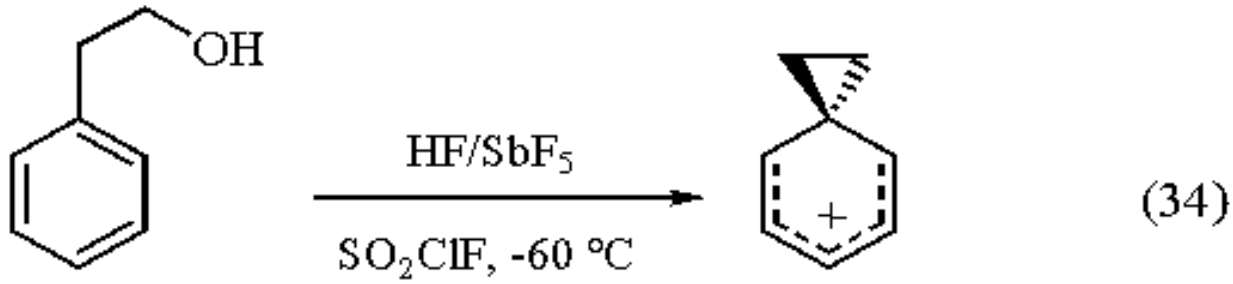

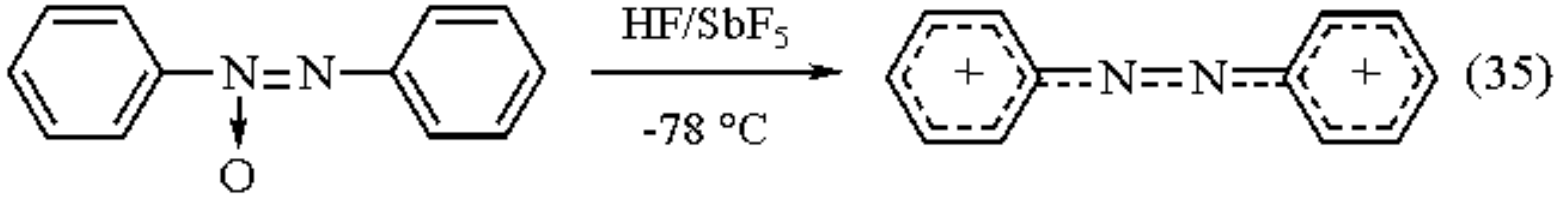

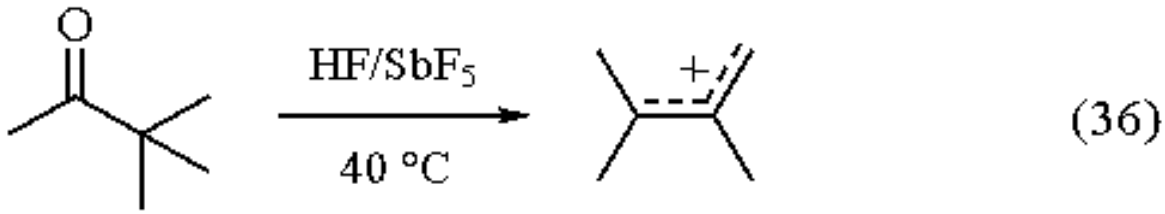

HF/SbF_5 is frequently used for the preparation of onium ions. The early work has been reviewed.[1] More recently, HF/SbF_5 has been employed to protonate $(CN)_2$, XCN (X = halogen), CF_3CN, and $Me_nS(CN)_{2-n}$.[59]

Since SbF_6^- (and $Sb_2F_{11}^-$) is a stable anion, hexafluoroantimonic acid has been widely used in the preparation of carbocations and onium salts.[60] Representative examples include the *t*-butyl cation, and tricyclopropylcarbenium, 1-adamantyl, alkyloxocarbenium, haloacetylium, methoxycarbenium, dimethylbromonium, tetramethylenebromonium, nitronium, and nitrosonium salts (eqs 37 and 38). Many of these salts have found valuable applications in organic synthesis. The X-ray structure of the isolated *t*-butyl hexafluoroantimonate salt has recently been established.[61]

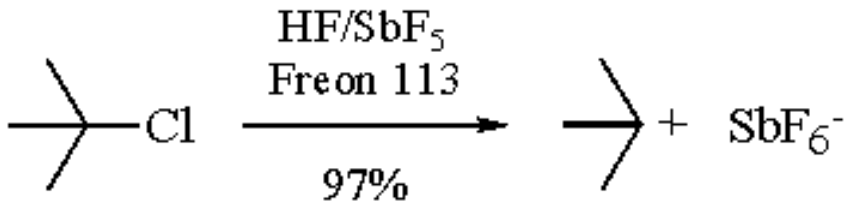

(37)

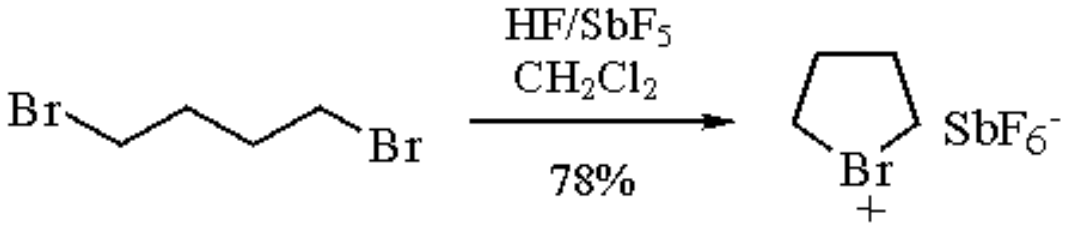

(38)

Polymerization.

HF/SbF_5 is also an efficient cationic polymerization catalyst.[1] Here, only its application in the preparation of macrocyclic ethers is included. The importance of these crown ethers has been well documented; however, their preparation is usually tedious and expensive. It was reported that HF/SbF_5 and other acids such as HF/BF_3 readily oligomerize ethylene oxide to mixtures of cyclic ethers[62] which can be subsequently separated (eq 39). The key to cyclic ether formation is the presence of anhydrous HF in the conjugate acid systems; chain polymers would otherwise be obtained.

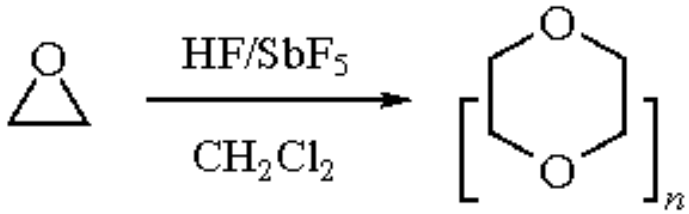

(39)

n	1	2	3	4	5	6	7	8	9	10	>10
Yield (%)	40	1	15	5	4	3	2	2	1	1	25

Related Reagents.

Antimony(V) Fluoride; ***Fluorosulfuric Acid***; ***Fluorosulfuric Acid-Antimony(V) Fluoride***; ***Hydrofluoric Acid***; ***Hydrogen Fluoride***; ***Nafion-H***.

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Hydrogen Hexachloroplatinate(IV)[1]

$H_2PtCl_6.6H_2O$

[16941-12-1] · $Cl_6H_{14}O_6Pt$ · Hydrogen Hexachloroplatinate(IV) · (MW 517.92)

(catalyst for hydrosilylation, hydrogenation, carbonylation, coupling, and oxidation)

Alternate Names: CPA; chloroplatinic acid; hexachloroplatinic acid; Speier's catalyst.

Physical Data: mp 60 °C, *d* 2.431 g cm^{-3}.

Solubility: sol water, alcohol, ether.

Form Supplied in: brownish-yellow crystalline mass; very deliquescent; widely available.
Drying: compound decomposes on heating.

Handling, Storage, and Precautions: harmful if inhaled, swallowed, or absorbed through skin. The compound may be carcinogenic. Use in a fume hood.

Hydrosilylations.

Hydrosilylation is a process in which one or more silicon-hydrogen bonds add to a substrate.[1] The reaction typically involves the addition of silanes to alkenes, carbon-heteroatom double bonds, and alkynes (eq 1).

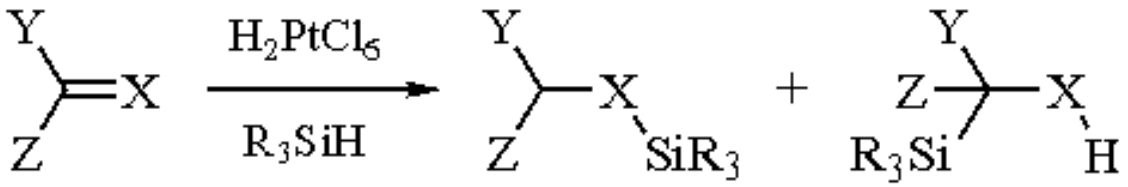

(1)

Y, Z = alkyl, aryl, heterocyclic, etc.
R = alkyl, aryl, Cl, OR, etc.
X = CR_2, O, NR, etc.

This reaction can be catalyzed by a variety of metals and metal complexes. One of the most useful catalysts for hydrosilylation is CPA. A dilute solution of CPA in isopropanol is typically used as the catalyst (Speier's catalyst).[2]

CPA also serves as the starting material for a very active form of homogeneous platinum(0) catalyst known as the Karstedt catalyst.[3] The major features of hydrosilylations are: an induction period; moderate to good yields; facility of the reaction on the nature of the silane, substrate, and the catalytic species; isomerization of the alkene substrate; and applications to a wide variety of substrates. A generally accepted mechanism for hydrosilylation has been proposed by Chalk and Harrod.[4] It involves the coordination of the metal to the alkene followed by oxidative addition of the silane to the metal to give a Pt^{IV} intermediate. Rearrangement gives σ-bonded Pt^{IV} and subsequent reductive elimination gives the hydrosilylated product and Pt^{II} species.

Hydrosilylation reactions of electron-rich alkenes with activated silanes such as halo- or alkoxysilanes are simple. Terminal alkenes react with ***Trichlorosilane*** under CPA catalysis to furnish high yields of the linear trihalosilane (eq 2).[5]

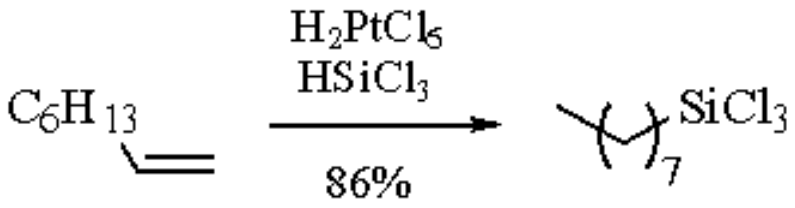

(2)

Hydrosilylations of internal alkenes with trichlorosilane and CPA as the catalyst proceed in a different manner. In these reactions, both bond migration and hydrosilylation occur. For example, reaction of 2-pentene with trichlorosilane for 30 min at 130 °C using CPA as the catalyst furnishes the terminal silane (eq 3).[5]

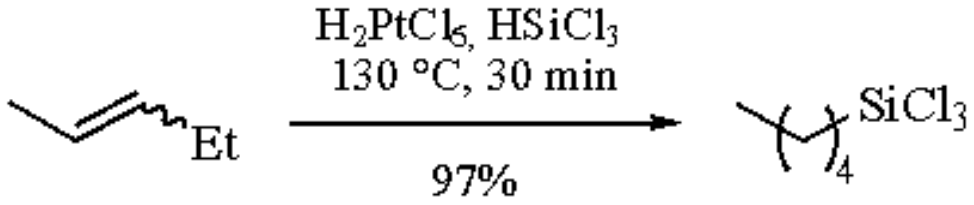

(3)

Styrene undergoes regioselective hydrosilylation with trichlorosilane in the presence of CPA and ***Triphenylphosphine***, providing the β-adduct selectively (eq 4).[6] The regioselectivity depends on the additive as well as the catalyst. For example, reaction of styrene with trichlorosilane and ***Tetracarbonylnickel*** as the catalyst furnished the α-adduct as the sole product. Rhodium catalysts have also been evaluated in hydrosilylations of styrene with various silanes.[7]

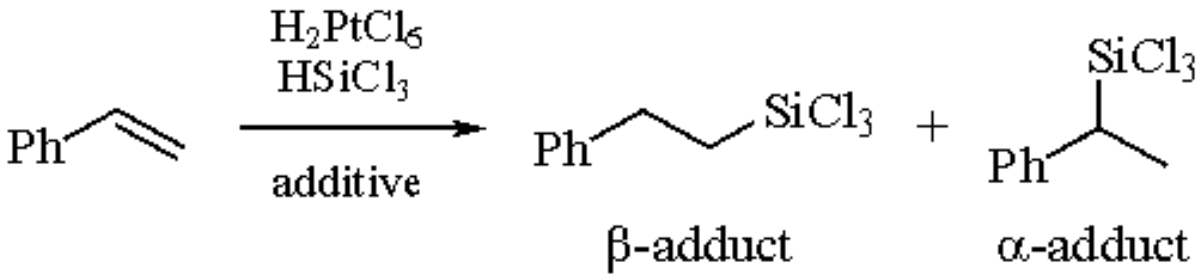

(4)

Additive	β-adduct:α-adduct (GC)
Triphenylphosphine	95:0
Benzyldimethylamine	85:0
Pyridine	92:0
Phenylacetonitrile	64:36

Reactions of terminal alkenes with dichlorosilane provides the monoalkyldichlorosilanes (eq 5).[8] In this reaction, the terminal double bond undergoes hydrosilylation preferentially. Hydrosilylation of terminal alkenes with dichlorosilane using triphenylphosphine complexes of Group 8-10 metals (Ni, Ru, Rh, Pd, Pt) gives the monoalkyldichlorosilanes in excellent yields.[9]

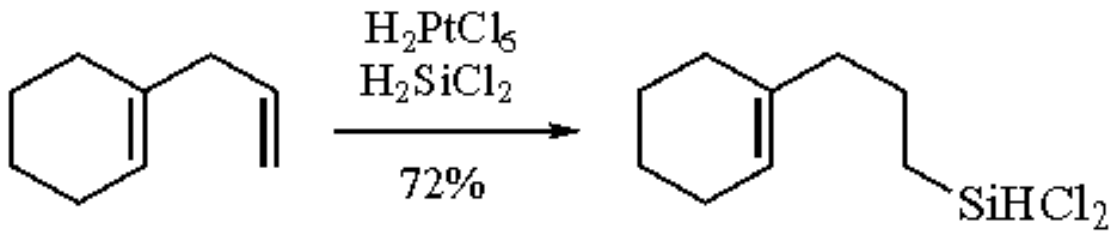

(5)

Internal alkenes produce a mixture of hydrosilylated products upon treatment with dichlorosilane and CPA (eq 6).[5] In this reaction, products from bond migration followed by hydrosilylation were not observed.

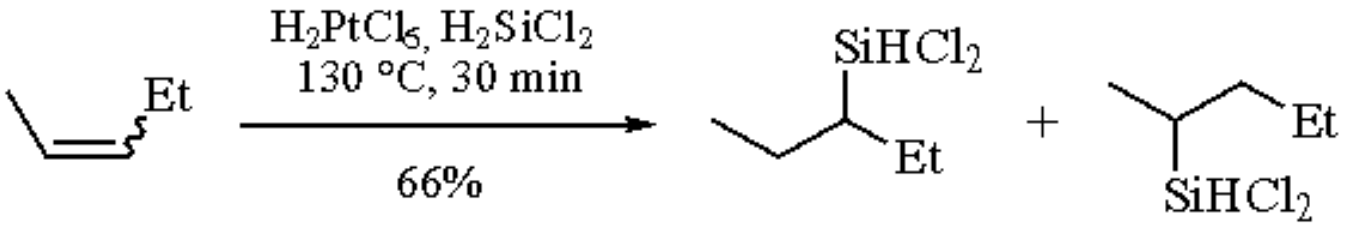

(6)

Hydrosilylation of alkenes with chiral silanes and CPA catalysis proceeds with retention of configuration at the silicon center (eq 7).[10] Similarly, Si-H to Si-D exchanges can also be carried out with retention of configuration using CPA catalysis.

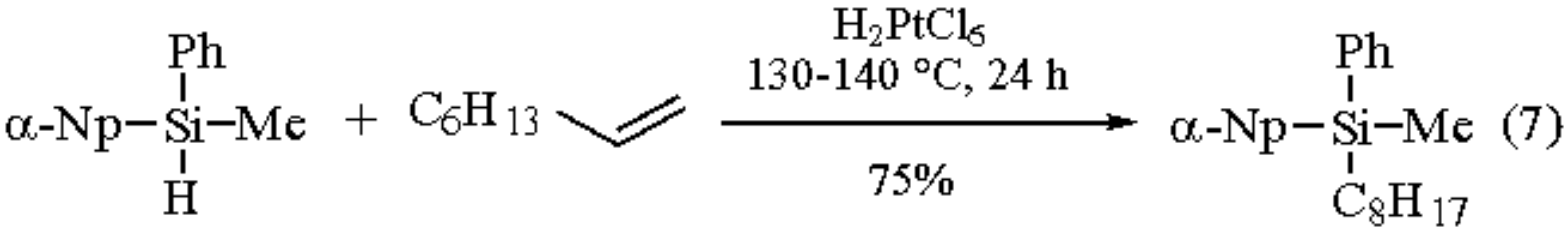

1,1,3,3-Tetramethyldisiloxane, a compound with a preexisting Si-O-Si linkage, undergoes hydrosilylation with terminal alkenes and CPA catalysis to furnish silylated products in moderate yields (eq 8).[11]

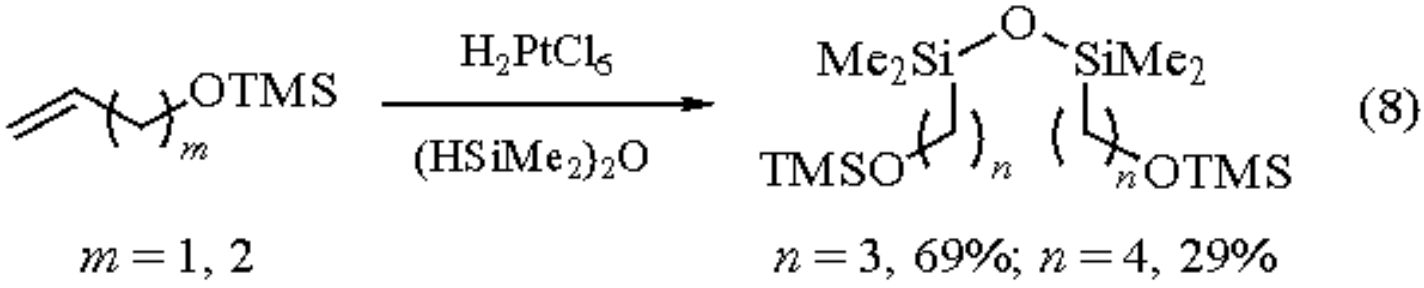

Molecular oxygen and CPA can effectively catalyze the addition of unreactive monoalkyl silanes to terminal alkenes to furnish tetrasubstituted silicon compounds in high yields (eq 9).[12] In the absence of oxygen, these reactions do not go to completion since it is believed that the oxygen reactivates the CPA for hydrosilylation.

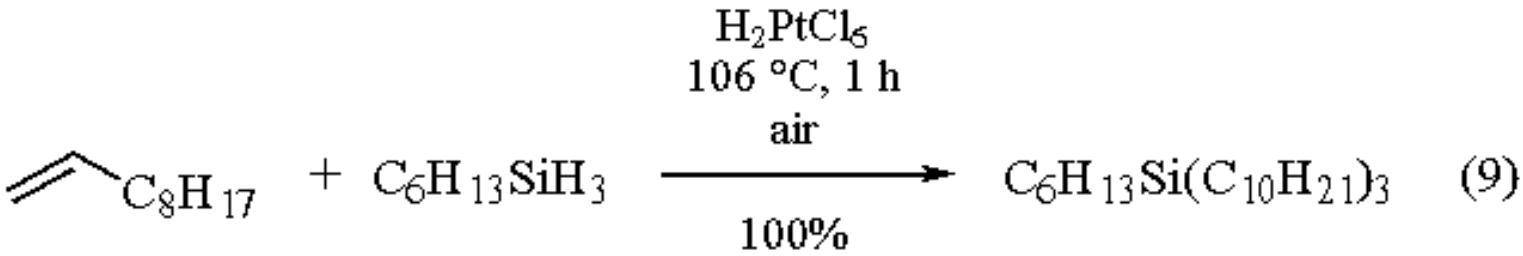

Intramolecular hydrosilylations of alkenylsilanes with CPA catalysis gives a mixture of regioisomeric cyclic silanes (eq 10).[13] The yields and ratio of products depends on the ring size, while the product distribution has been explained using the Chalk and Harrod mechanism for the hydrosilylation reaction. Vinylsilanes and allylsilanes gave no cyclized product.

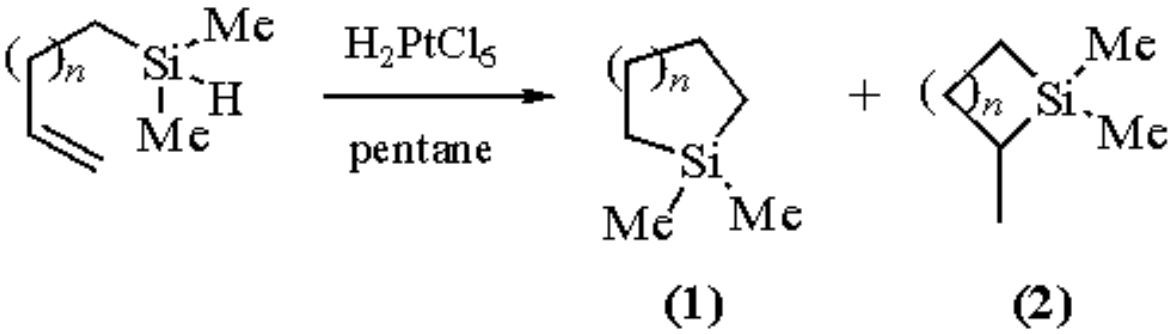

(10)

n	(1):(2)	Yield (%)
0	100:0	46
1	10:90	58
2	1:1	70
3	1:1	16
4	0:100	2

Hydrosilylations using silane have not been extensively investigated. One example involves the hydrosilylation of 1,5-hexadiene with silane and CPA (pretreated with oxygen) catalysis and subsequent intramolecular hydrosilylation of the intermediate to provide a silaheptane as shown in eq 11.[14] $Pt(PPh_3)_4$ was a better catalyst than CPA for this reaction.

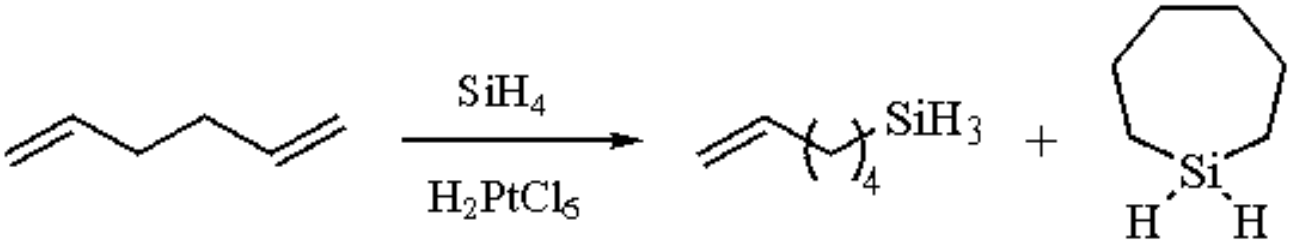

(11)

10:17

Hydrosilylations of alkenes containing a variety of functional groups have also been explored. The success of these reactions depends on the nature of the functional groups. A variety of functional groups survive the hydrosilylation conditions. These include epoxides, nitro groups, esters, carbamates, and acetals.[1d]

Epoxy organosilanes are very useful materials and are extensively used as silane-coupling agents. These compounds can be conveniently synthesized by the hydrosilylation of epoxyalkenes with a variety of alkoxysilanes in the presence of CPA (eq 12).[15]

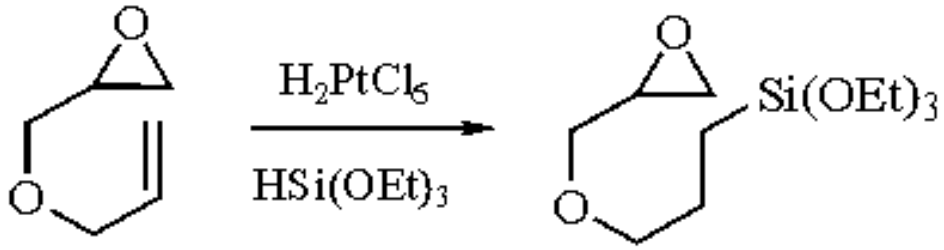

(12)

Unsaturated sulfides undergo hydrosilylation with triethyl- and triethoxysilanes.[16] These reactions are generally nonselective and proceed in only moderate yields (eq 13). The selectivity and yields depend upon the nature of the substrate, hydrosilylating agent, and catalyst. In the case of diallyl sulfide, hydrosilylation using ***Triethylsilane*** and CPA produces the monosilylated product and a byproduct arising from cleavage of the sulfur-carbon bond (eq 14).

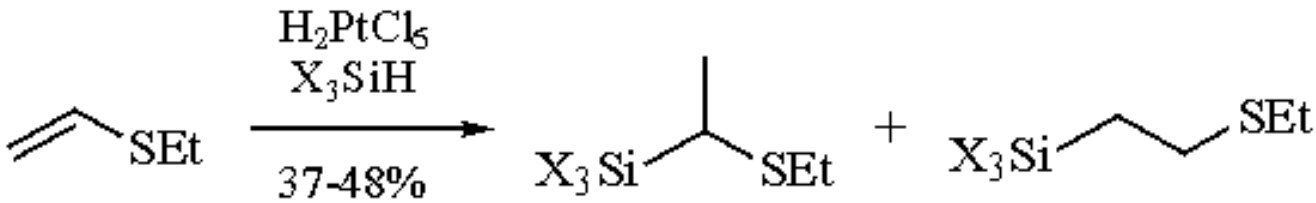

(13)

X = Et or OEt

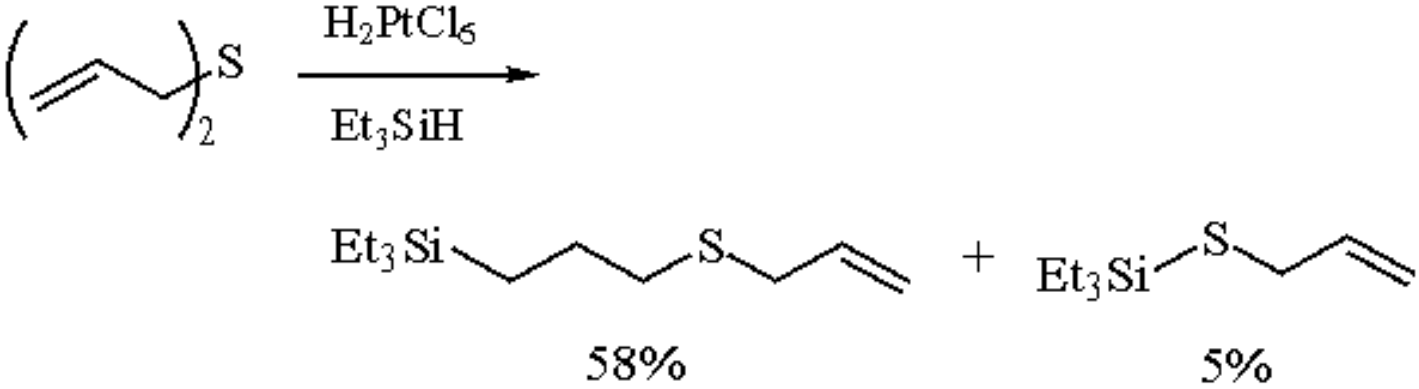

(14)

Allylamine undergoes hydrosilylation with ***Triethoxysilane*** and CPA as the catalyst (eq 15).[17] The effect of additives such as triphenylphosphine and carboxylic acids have been evaluated with respect to regioselectivity. Hydrosilylation of secondary and tertiary allylamines have also been evaluated. With secondary allyl amines, the regioselectivity of the silane addition depends upon the size of the *N*-substituent, and the γ-isomer is formed predominantly. In the case of tertiary allyl amines, the γ-isomer is the sole adduct.[18]

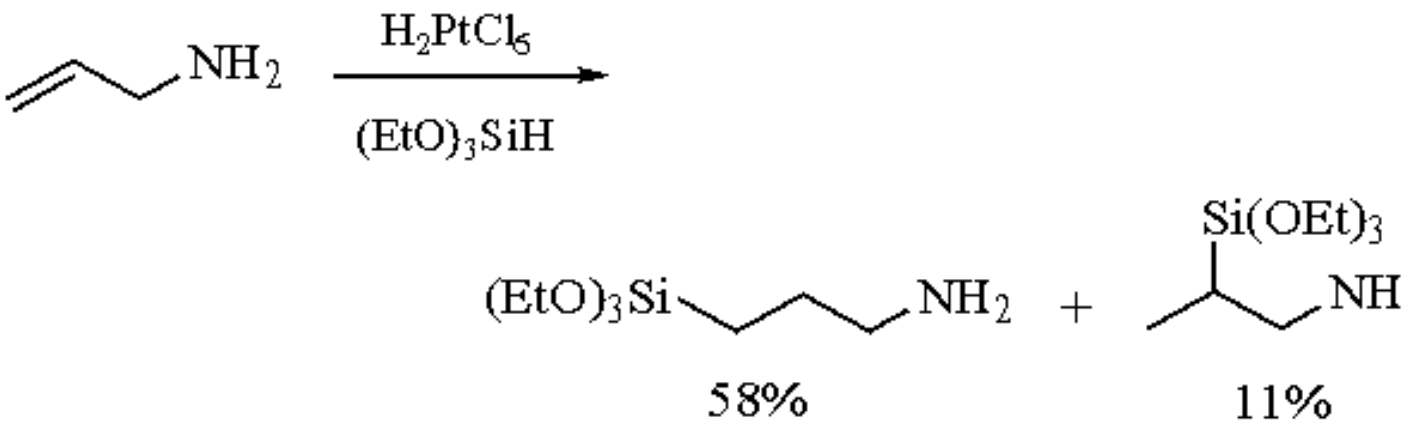

(15)

Acetylene undergoes hydrosilylation with trialkylsilanes in the presence of CPA to provide a mixture of mono- and diadducts (eq 16).[19] A convenient laboratory method for hydrosilylation of acetylene with a variety of silanes to provide synthetically useful vinylsilanes has been reported by Watanabe.[20] Although CPA gives good selectivity and high yields with trichlorosilane, ruthenium, rhodium, and platinum triphenylphosphine complexes were found to be better suited for these reactions.

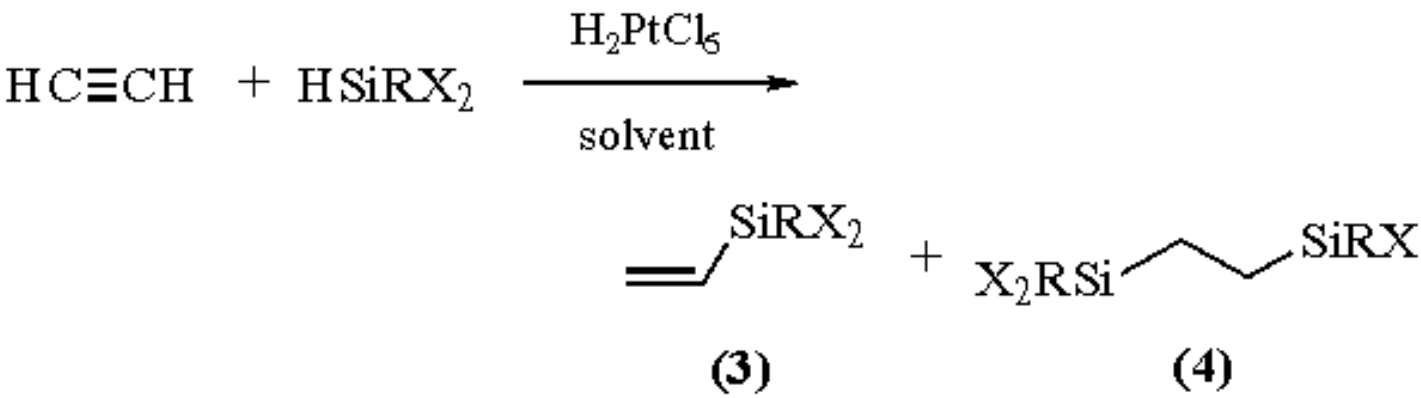

(16)

R	X	Solvent	T (°C)	**(3)** (%)	**(4)** (%)
Cl	Cl	xylene	60	90	0
OEt	OEt	benzene	40	42	37
Me	Cl	xylene	25	8	80
Cl	Cl	xylene	60	90	0

Hydrosilylation of monosubstituted alkynes may also be catalyzed with CPA. Generally the reaction proceeds through *cis* addition of the silane and gives a mixture of α- and *cis* and *trans* β-adducts, with the latter product predominating.[21] A comparison of CPA to Karstedt's catalyst in the hydrosilylation of monosubstituted alkynes has been reported.[22] Maricinec and co-workers have investigated the hydrosilylation of a variety of monosubstituted alkynes with (±)-α-naphthylphenylmethylsilane (eq 17).[23] Several other platinum catalysts were evaluated in this reaction with tetrakis(triphenylphosphine)platinum being as effective as CPA. In a similar fashion, hydrogermylation of monosubstituted alkynes with CPA catalysis gave the *trans*-germyl alkenes as the major product.[24]

Hydrogermylations with chiral germanes and CPA catalysis proceed with retention of configuration.[25]

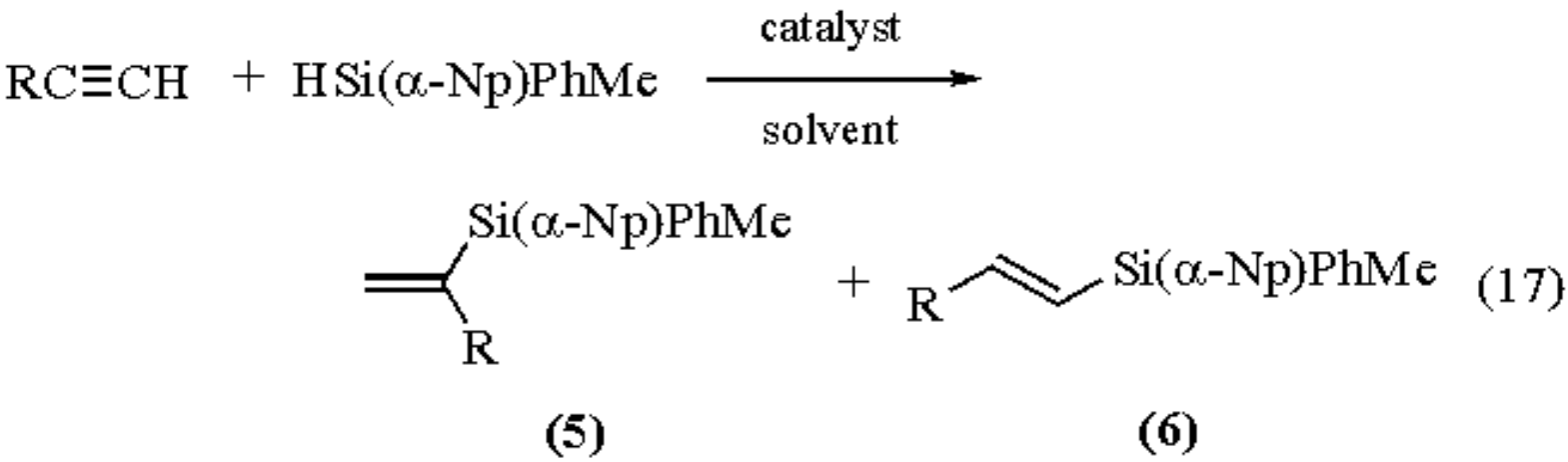

R	Catalyst	Time (h)	T (°C)	Yield (%)	(6):(5)
H	H_2PtCl_6	6	60	99	100:0
Ph	H_2PtCl_6	85	25	99	87:13
CO_2Me	H_2PtCl_6	85	25	10	89:11
CO_2Me	$(PPh_3)_4Pt$	15	60	10	89:11
TMS	H_2PtCl_6	85	25	99	89:11
t-Bu	H_2PtCl_6	85	25	98	100:0

Voronkov and Sushchinskaya[26] have shown that the hydrosilylation of phenylacetylene with triethylsilane and CPA catalysis can be markedly influenced by the addition of aluminum or germanium chlorides. For example, the reaction in the presence of ***Aluminum Chloride*** (CPA:$AlCl_3$ = 1:200) gave 93% of the hydrosilylated products, while in the absence of $AlCl_3$ the yield was only 24% (eq 18).

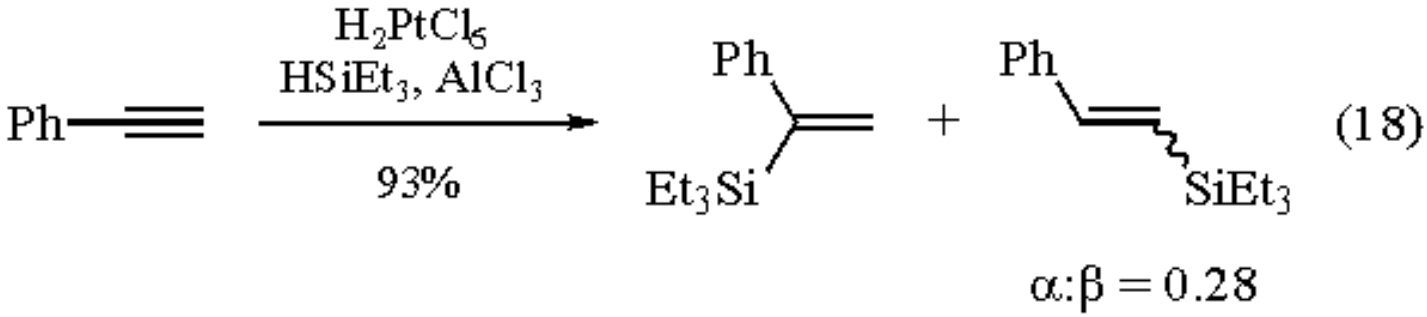

Doyle and co-workers have reported an alternate mode of selectivity of silane addition to monosubstituted alkynes, wherein allylsilanes are formed as the major products, along with minor amounts of the vinylsilanes (eq 19).[27] The reaction involves the slow addition of alkyne to a solution of silane and CPA catalyst. The allylsilanes are formed in good yields. Use of rhodium(II) perfluorobutyrate in place of CPA gave higher yields of the allylsilane. Addition of

silane to a solution of alkyne and CPA gave the normal vinylsilane product.

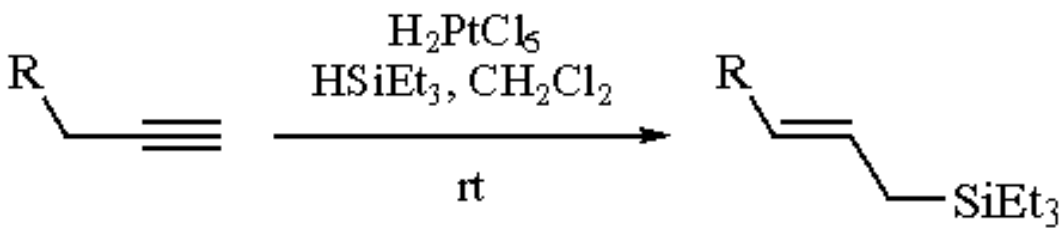

(19)

R	Yield (%)	(*E*)/(*Z*)
C_5H_{11}	60	11
Pr	73	15
MeO	49	2.8
BnO	57	3

Acetylene and monosubstituted alkynes undergo dehydrocondensative hydrosilylation in the presence of catalytic CPA and iodine (eq 20).[28] This method provides a convenient route to silylalkynes. The effect of various halide additives on the product distribution and yields has been examined. Elemental iodine gave good yields of the dehydrocondensation product and these reactions were found to be temperature dependent. Trimethylsilane can be used instead of triethylsilane with similar product distributions. However, the best yields of the dehydrocondensation product were obtained using trialkylsilyl iodides as the reactant. The role of solvents in these reactions has also been reported. Hydrosilylation of phenylacetylene with transition metal complexes containing a Si-H bond proceeds with CPA catalysis giving a *cis-trans* mixture of products in high yields.[29]

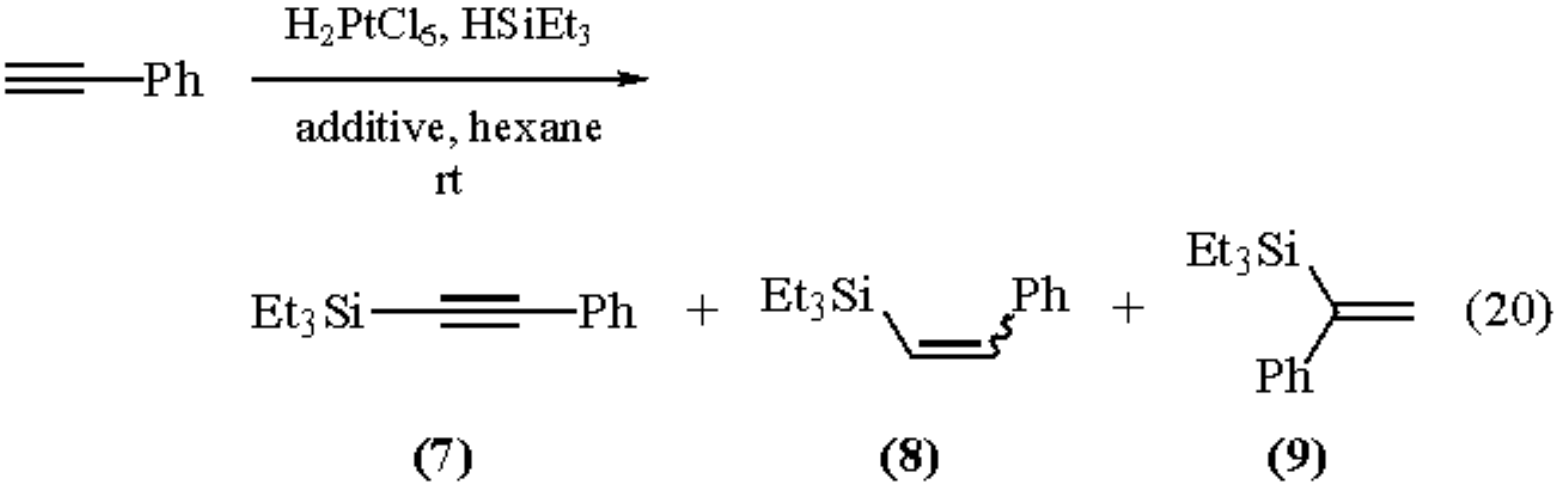

Additive	(7) (%)	(8) (%)	(9) (%)
LiCl	0	84	15
LiI	73	15	12
ZnI_2	0	76	24
I_2	83	9	8
TMSI	92	6	2
Et_3SiI	93	6	trace

Hydrosilylation and hydrogermylation of disubstituted alkynes[30] using CPA as the catalyst have been explored en route to substituted furans (eq 21).[31] Similarly, alkynylsilanes can be hydrosilylated in a highly regioselective manner to give 1,2-disilaalkenes (eq 22).[32]

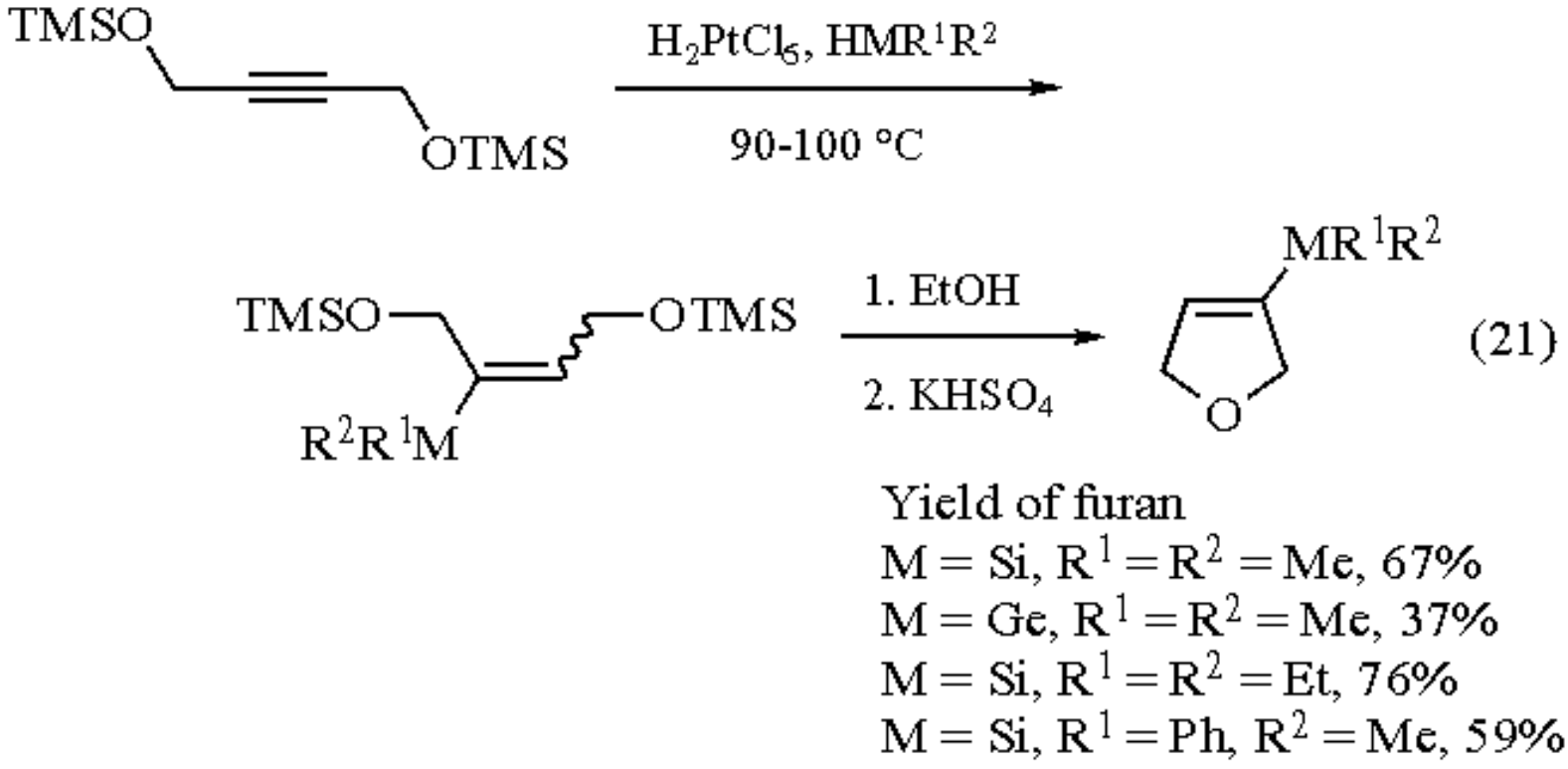

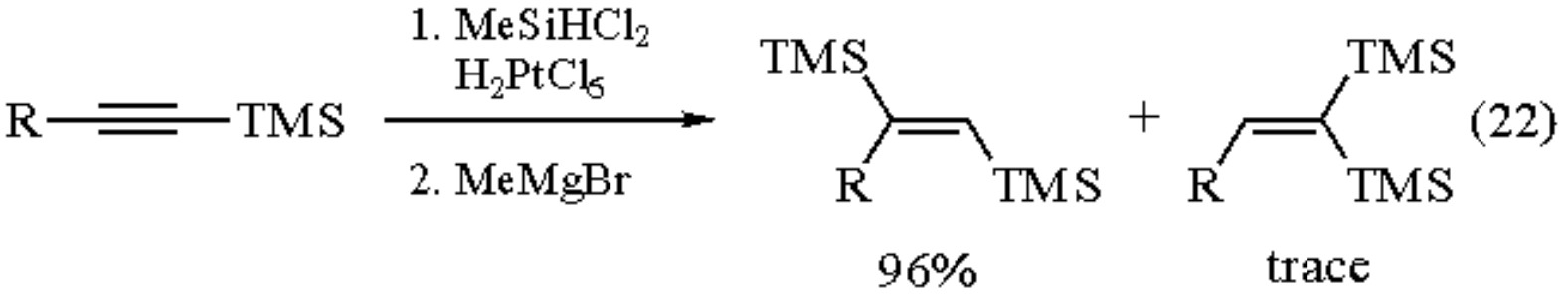

Intramolecular hydrosilylations of silicon-substituted silaalkynes have been achieved using CPA as the catalyst (eq 23).[33] Similar to the results obtained for intramolecular hydrosilylations of alkenes, the product distribution depends on the size of the ring formed.

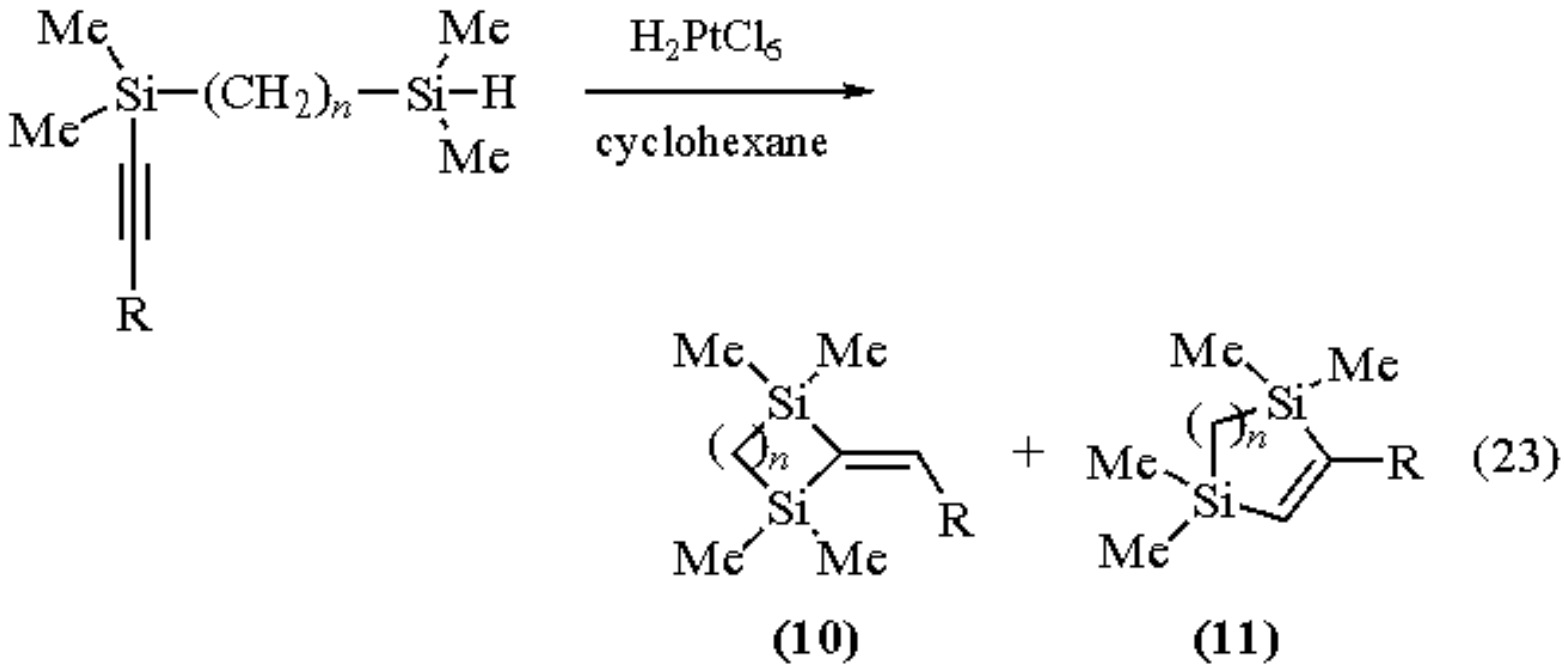

R	n	(10)	(11)	Yield (%)
H	2	100	0	58
H	3	79	21	71
Ph	2	100	0	42

Hydrosilylations of dienes generally provide three 1:1 adducts arising from 1,2- and 1,4-addition. ***Isoprene***, a simple diene, reacts with a variety of silanes in the presence of catalytic CPA to furnish hydrosilylated products. For example, the reaction of isoprene with trichlorosilane and catalytic CPA gave the 1,4-adduct, with addition occurring across the least hindered double bond (eq 24).[34] However, trimethylsilane gave both 1,2- and 1,4-adducts with addition occurring at both ends of the diene.

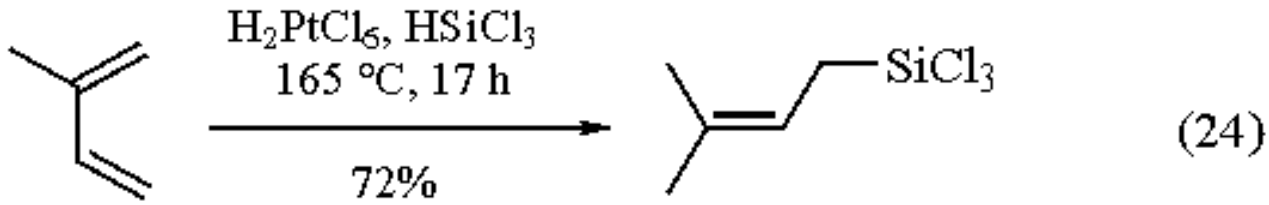

1,4-Bis(trimethylsilyl)-1,3-butadiyne, a stable alternative to the highly reactive 1,3-butadiyne, undergoes hydrosilylation with CPA catalysis and a variety of silanes (eq 25).[35] The product distribution depends on the nature of the silane. The more reactive dimethylchlorosilane gave the 1:2 adduct (**12**) in moderate yields, while reactions with the less reactive and bulkier triisopropylsilane furnished the 1:1 adduct (**14**) in higher yields. Reaction with triethylsilane was unusual in that the product was an allene (**13**) arising from 1,4-addition of a second silane molecule to the intermediate 1:1 adduct (**14**).

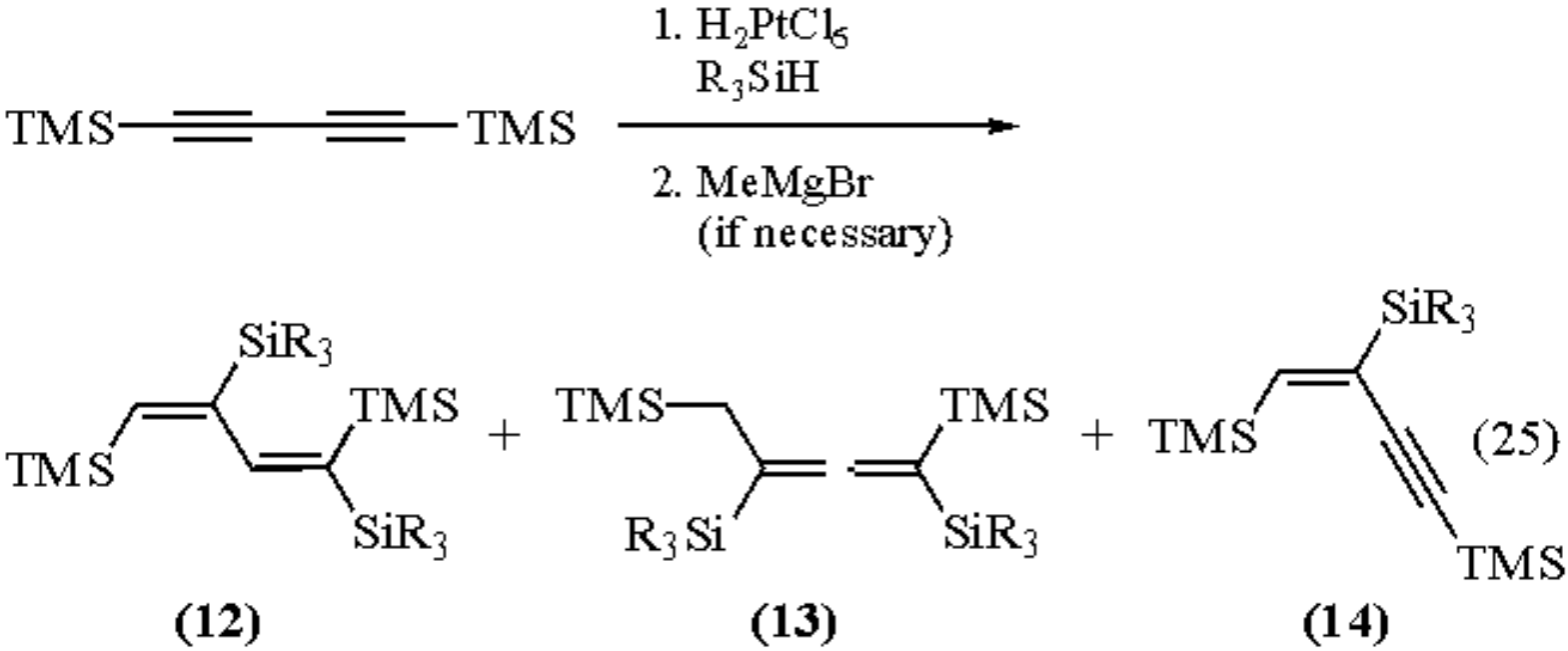

R_3SiH	Conditions	Product (yield)
$HSiClMe_2$	80 °C, 2 h	**(12)** 54%
$HSiEt_3$	80 °C, 0.5 h	**(13)** 100%
$HSiMe_3$	100 °C, 2 h	**(13)** 46%, **(14)** 40%
$HSi(i\text{-}Pr)_3$	90 °C, 8 h	**(14)** 92%

Hydrosilylations of enynes occur at the more reactive alkyne end. An example of enyne hydrosilylation with methyldichlorosilane is shown in eq 26.[36] The reaction requires a small amount of either ***Dibenzoyl Peroxide*** or trichlorosilane as a cocatalyst and is believed to proceed by a radical pathway. An example of a highly chemoselective hydrosilylation has been reported by Voronkov (eq 27).[37] The reactions occur at the alkyne terminus in the presence of an alcohol and alkene.

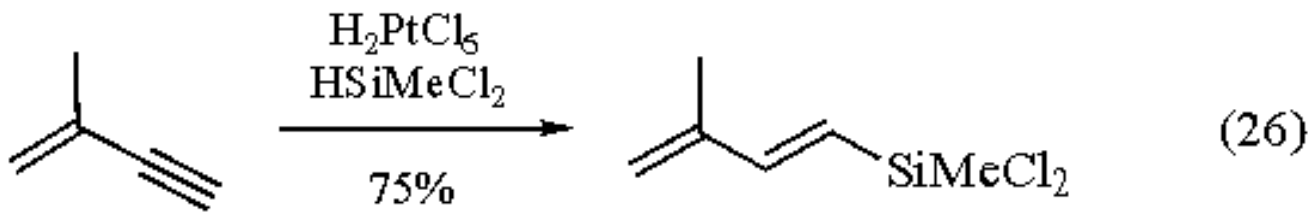

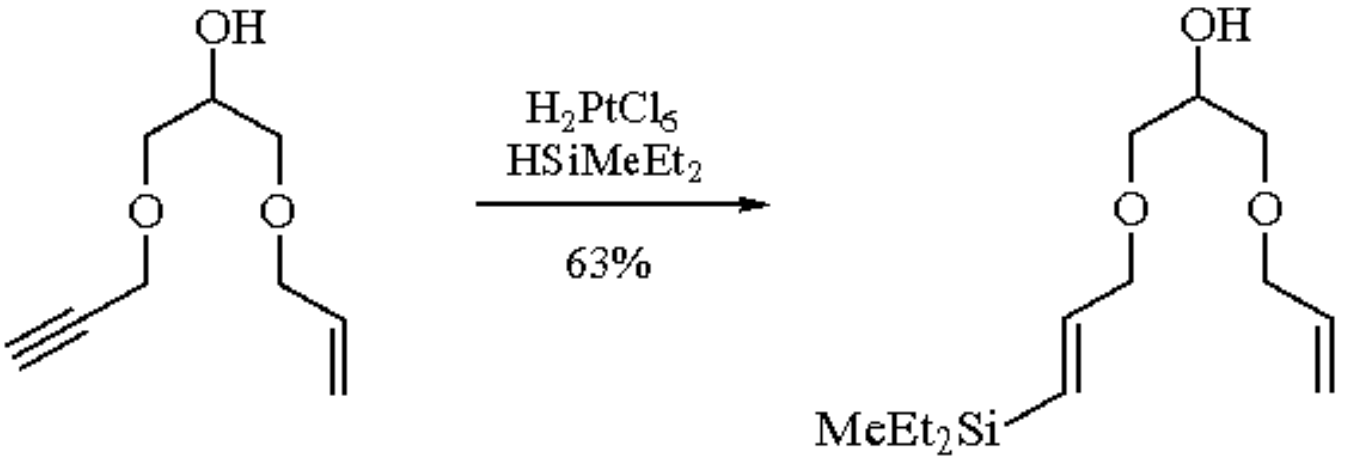

(27)

Hydrosilylations of α,β-unsaturated esters, ketones, and nitriles with CPA catalysis have also been examined. The course of these reactions depends on the nature of the silane and the electron-withdrawing substituent. Hydrosilylation of a series of α,β-unsaturated esters using CPA catalysis was evaluated by Yoshii and co-workers (eq 28).[38] The reactions were generally nonselective and gave all three possible 1,2- and 1,4-addition products. When Wilkinson's catalyst (***Chlorotris(triphenylphosphine)rhodium(I)***) was used in place of CPA, the 1,4-addition products, silylketene acetals, were obtained as the major products.

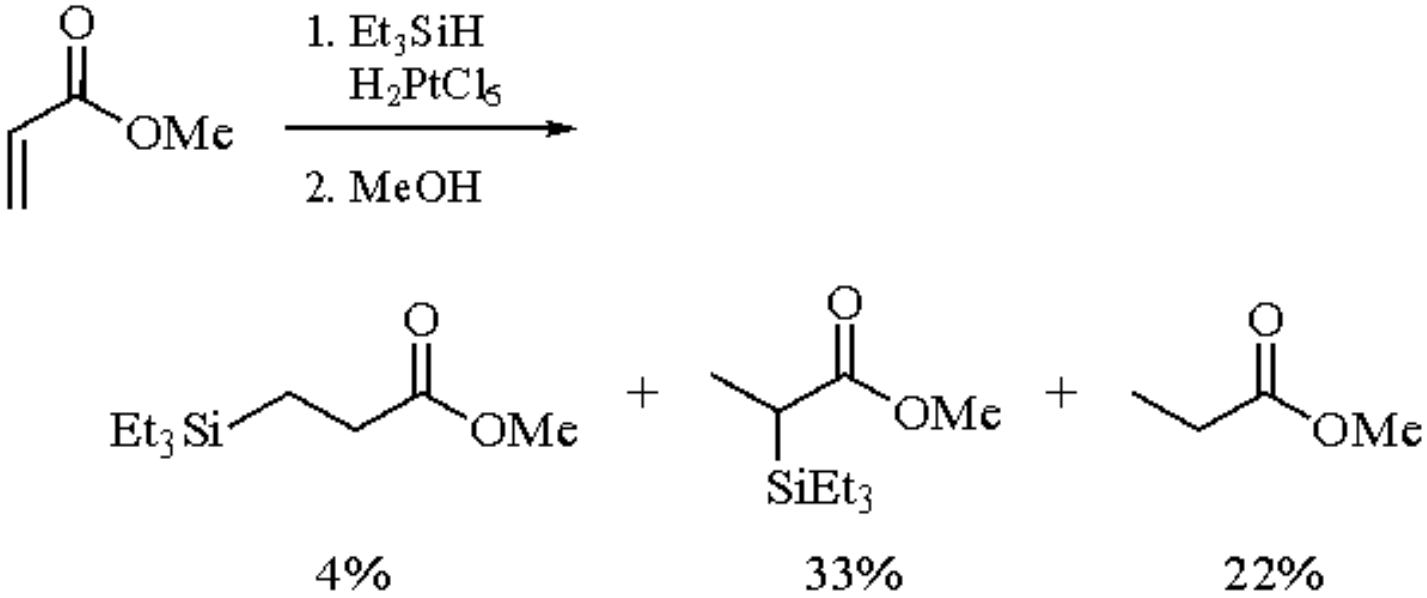

(28)

Hydrosilylation of enones proceeds by a 1,4-addition of the silane to produce the enol silyl ethers, from which the reduced compounds are obtained through hydrolysis.[39] An application of this methodology is illustrated in the synthesis of a precursor to purpnigenin (eq 29).[40] Of the many silanes examined in this reaction, diethylethoxysilane gave the highest yields and least number of side reactions. Hydrosilylations of α,β-unsaturated carbonyl compounds proceeds well with a variety of silanes, generally with good regioselectivity when Wilkinson's catalyst is used.[41]

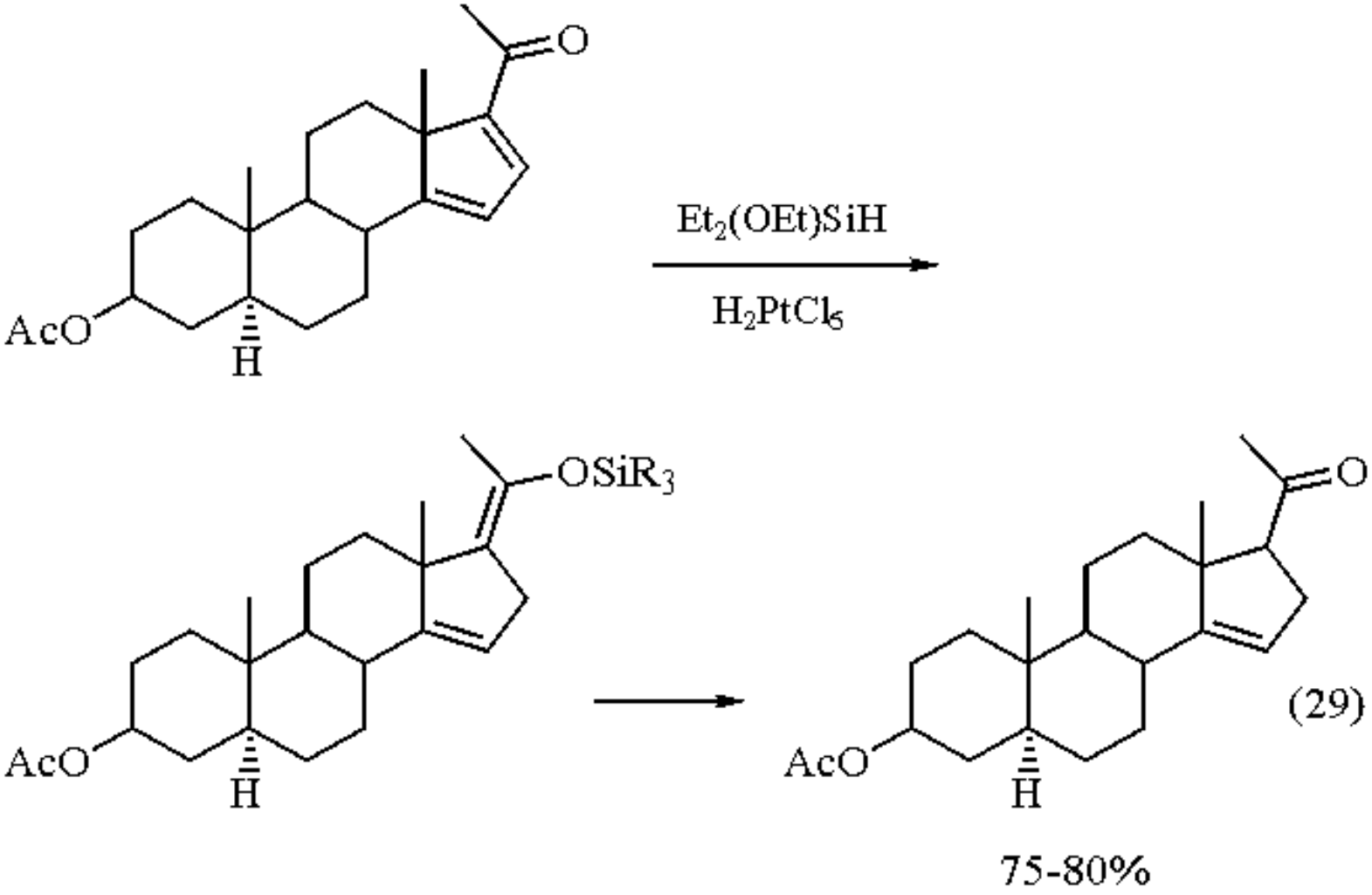

Hydrosilylation of acrylonitrile with trichlorosilane using CPA catalysis does not produce any hydrosilylated products.[42] However, hydrosilylation of α,β-unsaturated nitriles proceeds well when Wilkinson's catalyst is used.[43]

Hydrosilylation Followed by Oxidation.

Tamao and co-workers have developed elegant methodologies for the conversion of the silyl intermediates obtained in hydrosilylation of alkenes and alkynes to a variety of functional groups. The key transformations in these methodologies include the oxidation of a C-Si bond to a hydroxy group with retention of configuration,[44] the conversion of a C-Si bond to a C-Br bond,[45] and conversion of a C-Si bond to a C-C bond.[46]

The hydrosilylation-oxidation sequence can be effectively used for the transformations of terminal alkenes to the corresponding anti-Markovnikov alcohols (eq 30).[44] The silane used in these experiments, methyldiethoxysilane, is commercially available and air stable. Thus the hydrosilylations can be carried out without solvent under air using CPA catalysis. ***Hydrogen Peroxide*** oxidation proceeds smoothly only if there is at least one alkoxy group on the silicon. The reactivity of the carbon attached to silicon can be controlled by the nature of the alkoxy group.

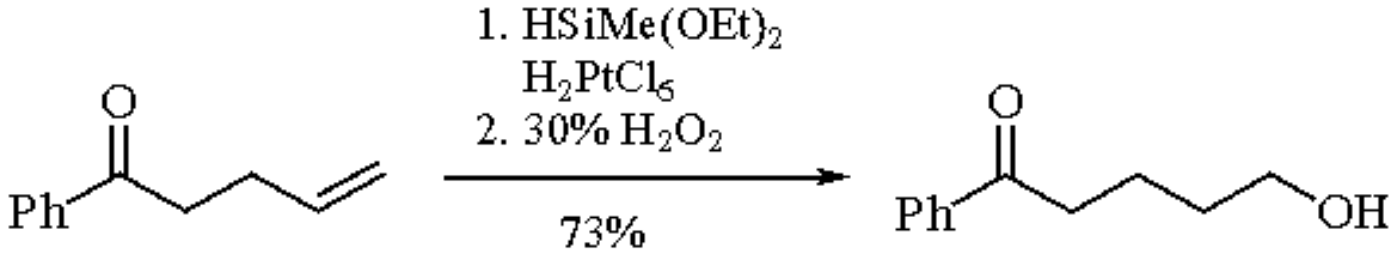

(30)

The hydrosilylation-oxidation sequence can also be effectively used for the conversion of an alkyne to a ketone. An application of this methodology in the synthesis of 5-decanone is shown in eq 31.[44] The reaction involves the hydrosilylation of an alkyne to a vinylsilane using CPA catalysis followed by hydrogen peroxide oxidation to the decanone. The procedure can be carried out without isolating the intermediate vinylsilane.

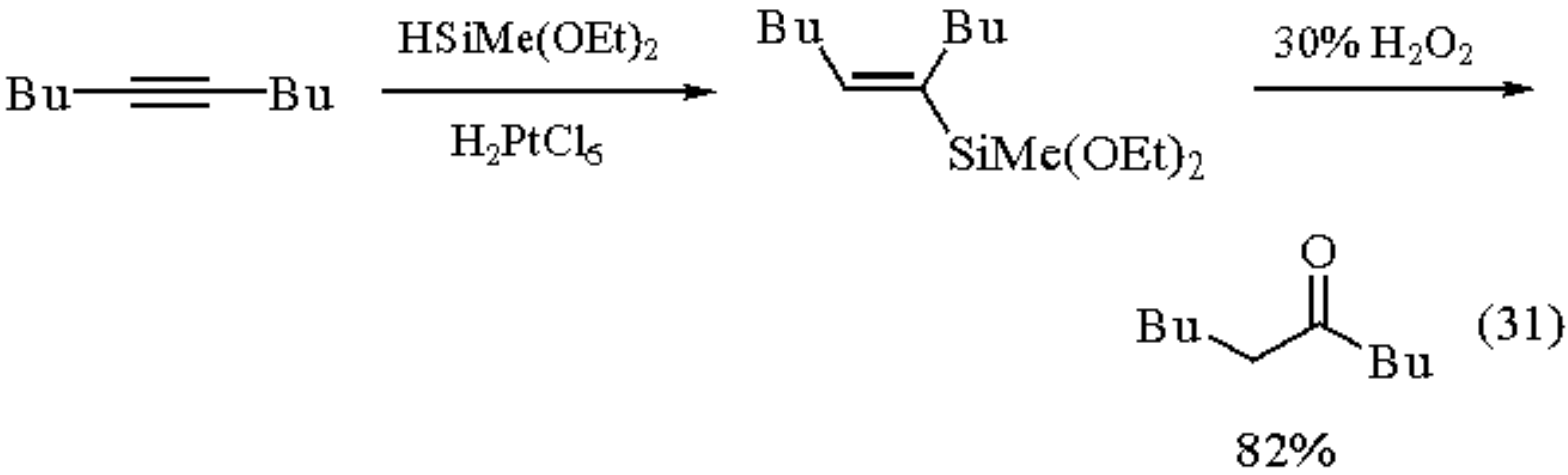

(31)

The hydrosilylation-oxidation sequence is a convenient route for the preparation of α-hydroxy ketones from alkynes (eq 32).[47] The process involves hydrosilylation of an alkyne to a vinylsilane, epoxidation of the vinylsilane using ***m*-Chloroperbenzoic Acid**, and final oxidative cleavage using hydrogen peroxide.

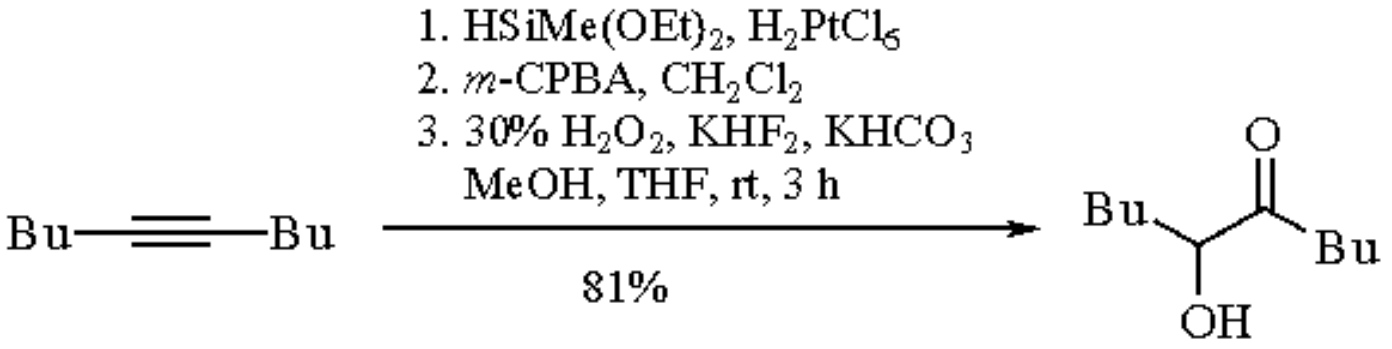

(32)

Regioselective functionalization of unsymmetrical internal alkynes can be effected through the intramolecular hydrosilylation of homopropargyl alcohols (eq 33).[45] The hydrosilylation proceeds selectively through a 5-*exo*-dig ring closure to provide the vinylsilane (**15**). This intermediate can then be oxidized with hydrogen peroxide to give the β-hydroxy ketone in high yields. Alternatively, treatment of (**15**) with bromine provides the vinyl bromide in a highly selective manner. Vinylsilane (**15**) undergoes transition metal-catalyzed cross-coupling reactions with alkenyl and aryl halides to provide a convenient route to homoallyl alcohols (eq 34).[46]

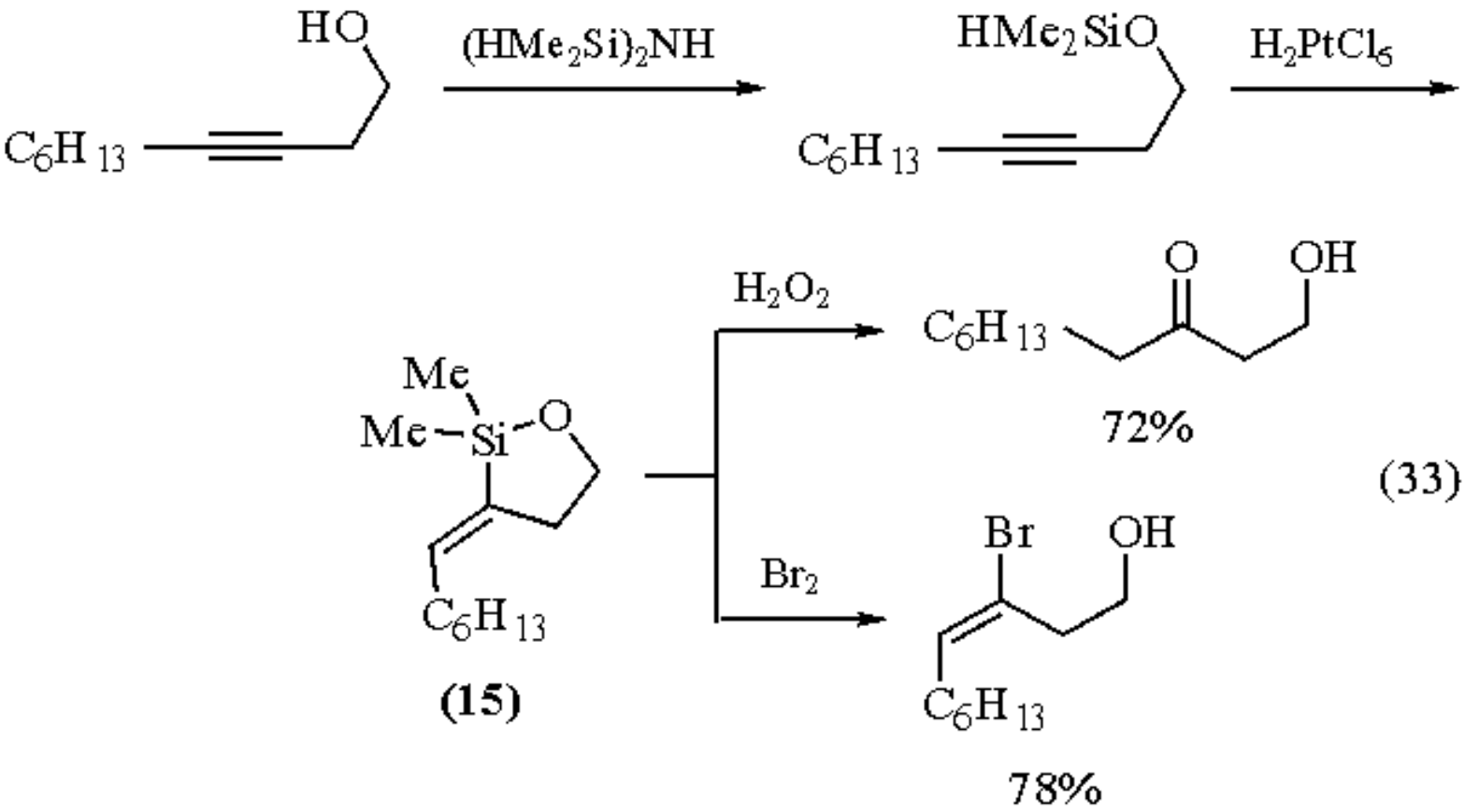

(33)

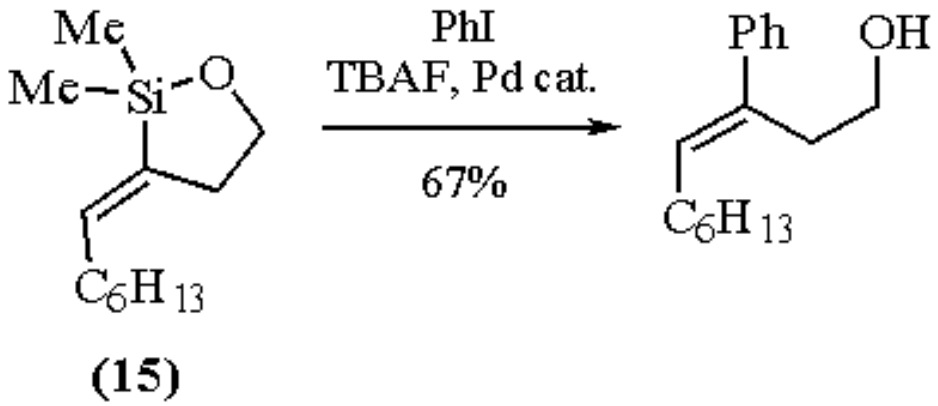

(34)

The hydrosilylation-oxidation sequence is an attractive route to the regio- and stereoselective synthesis of the 1,3-diol skeleton. Intramolecular hydrosilylation of allyl and homoallyl alcohols containing di- or trisubstituted internal alkenes can be achieved through CPA catalysis. The reactions proceed with high regio- and stereoselectivity. The intermediate cyclosiloxane undergoes oxidative C-Si bond cleavage with retention of configuration to furnish the 1,3-diol product (eq 35).[48]

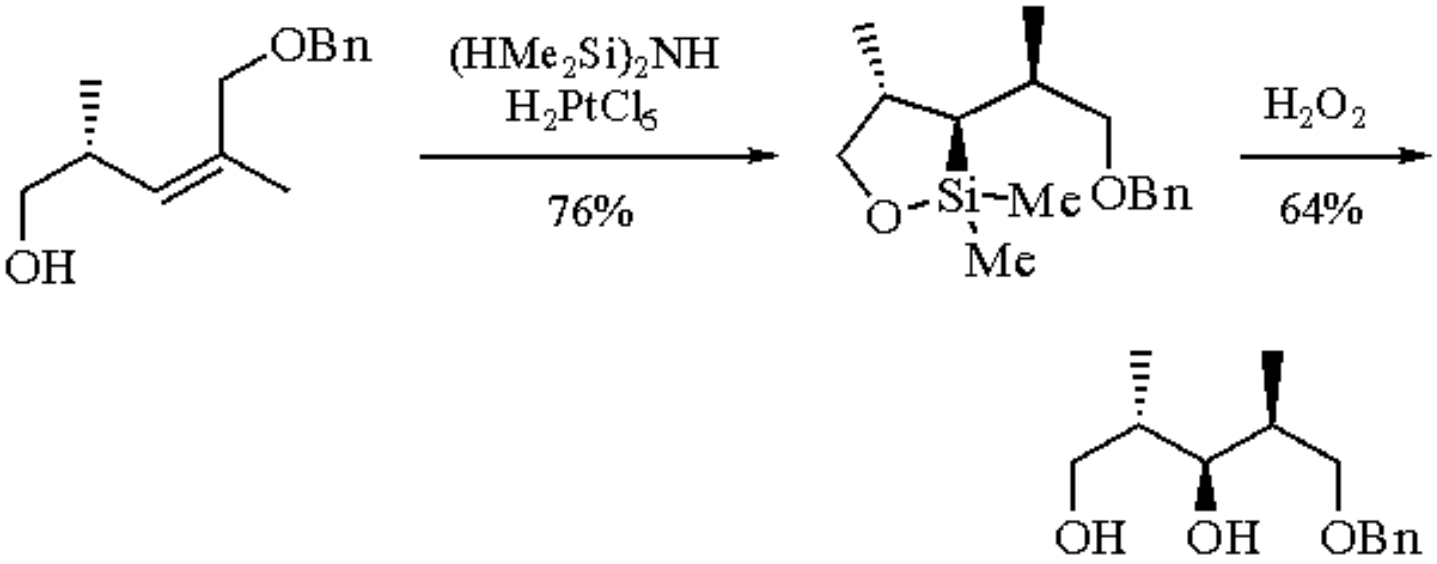

(35)

Hydrogenations and Carbonylations.

A complex prepared from CPA and ***Tin(II) Chloride*** dihydrate functions as a useful homogeneous hydrogenation catalyst. Ethylene can be quantitatively hydrogenated to ethane at 1 atm using this catalyst system (eq 36).[49] Similarly, a 1:1 mixture of acetylene and hydrogen gave ethane and ethylene in a 3:1 ratio. In these reactions, neither CPA nor tin dichloride catalyzed the hydrogenations individually. The homogeneous hydrogenation of polyalkenes using CPA/tin dichloride dihydrate catalyst has been evaluated. The hydrogenation of methyl linolenate using this catalytic system under 500 psi hydrogen gave diene products selectively.[50]

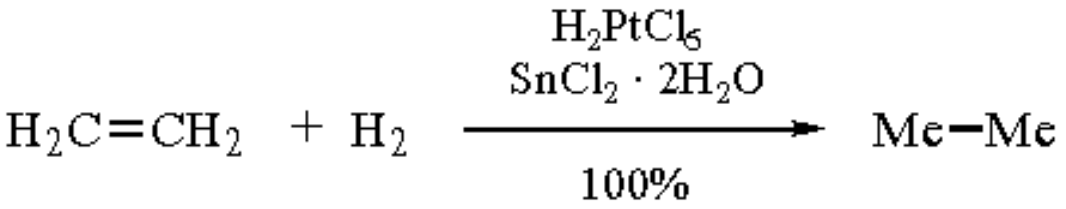

(36)

Terminal alkenes under relatively mild reaction conditions can be converted to a mixture of linear and branched esters by using CO and methanol with a CPA-$SnCl_2$ couple as the catalyst (eq 37).[51] Use of water in place of methanol produced the corresponding carboxylic acids in similar ratios. Internal alkenes gave a mixture of products in very low yields under these carbonylation conditions.

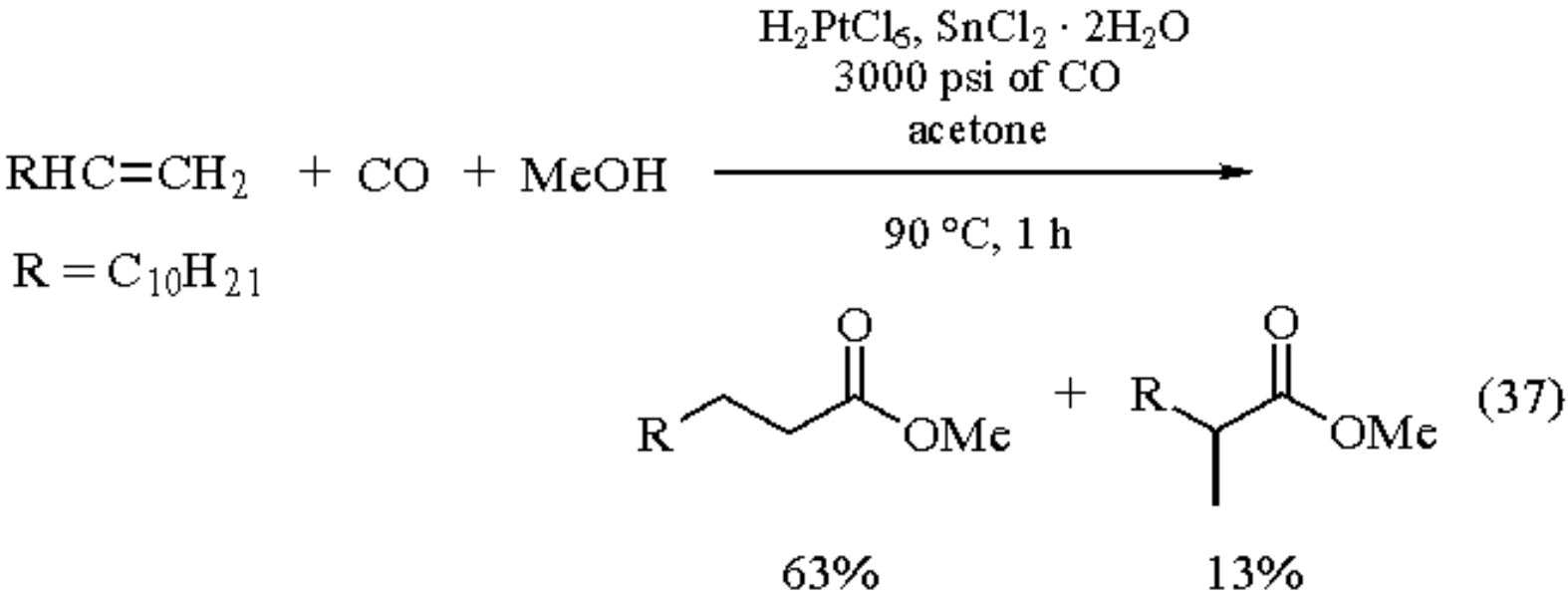

Methyl acetate can be hydrocarbonylated under a carbon monoxide-hydrogen atmosphere using a mixed ***Rhodium(III) Chloride***-CPA catalyst to furnish ethylidene diacetate (eq 38).[52] The reaction gave higher yields with rhodium trichloride-***Palladium(II) Acetate*** as the catalyst.

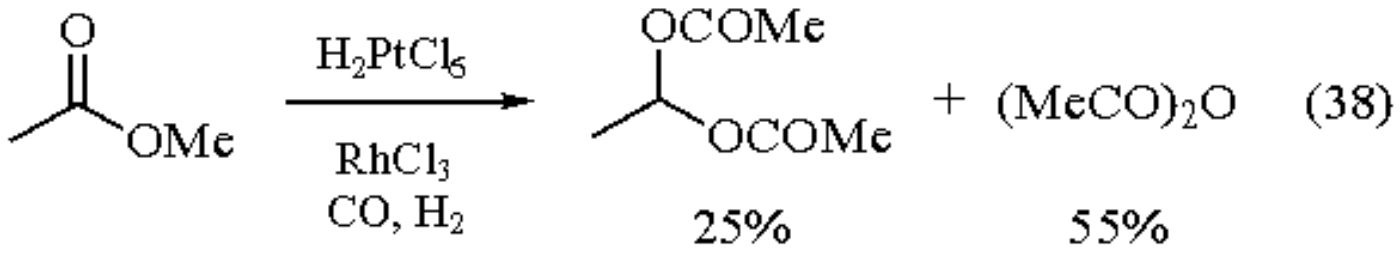

Miscellaneous.

Tetraalkylsilanes undergo redistributions selectively in the presence of trichlorosilane and CPA. Generally, the smallest alkyl group exchanges with the chloro group on the silane (eq 39).[53]

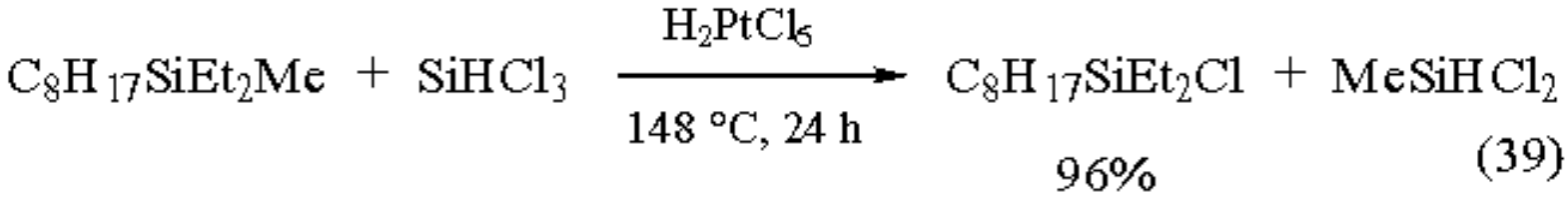

Allyl chloride and allyl bromide react with less hindered silanes under CPA catalysis to provide hydrosilylation products, along with minor amounts of silyl halides. Reactions of bulky silanes with excess allyl bromide in the presence of CPA furnishes the silyl bromide as the major or sole product (eq 40).[54]

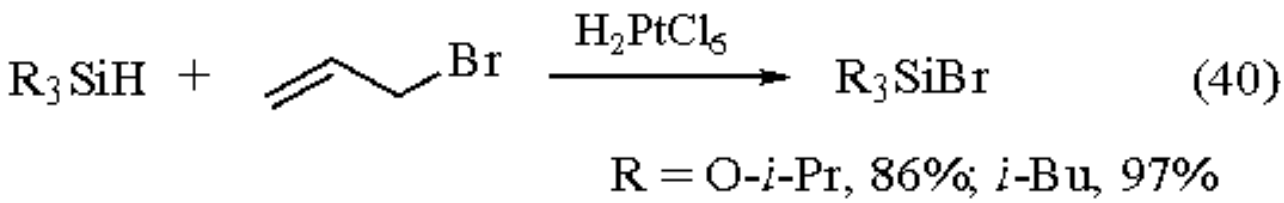

Arenes react with CPA to give the σ-aryl complexes of Pt^{IV}.[55] Regioselectivity of the metallation with monosubstituted benzenes is quite poor, giving both *m*- and *p*-substituted complexes. These complexes then undergo further reaction to produce mixtures of chlorinated arenes and substituted biphenyls (eq 41).

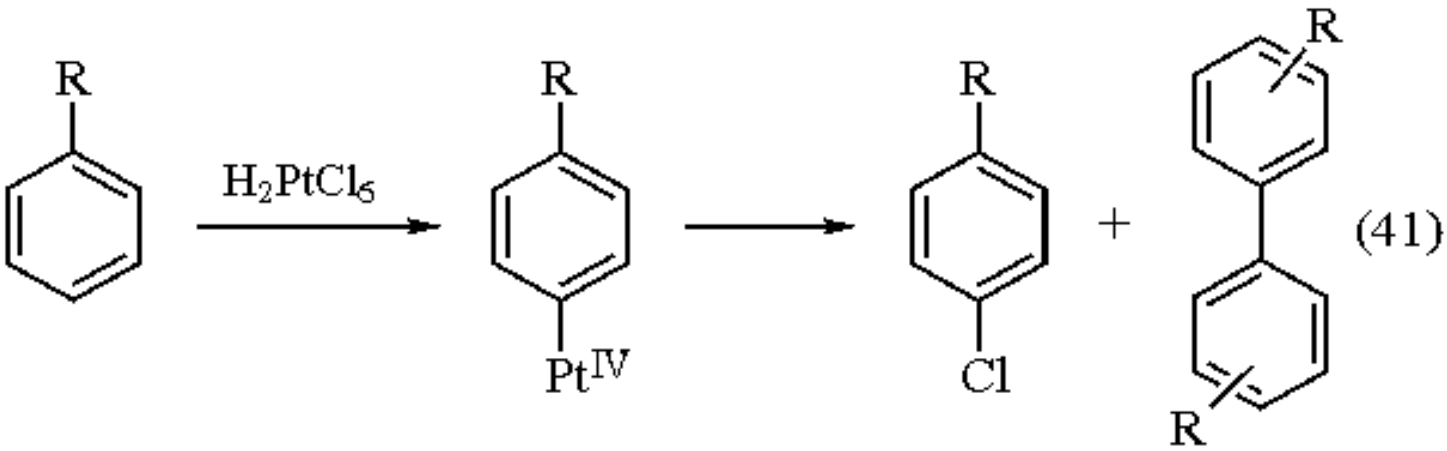

Chlorination of alkanes and arenes in the presence of stoichiometric CPA in refluxing trifluoroacetic acid has been reported (eq 42).[56] These reactions furnish chlorinated arenes or *n*-chloroalkanes and require Pt^{II} as a cocatalyst.

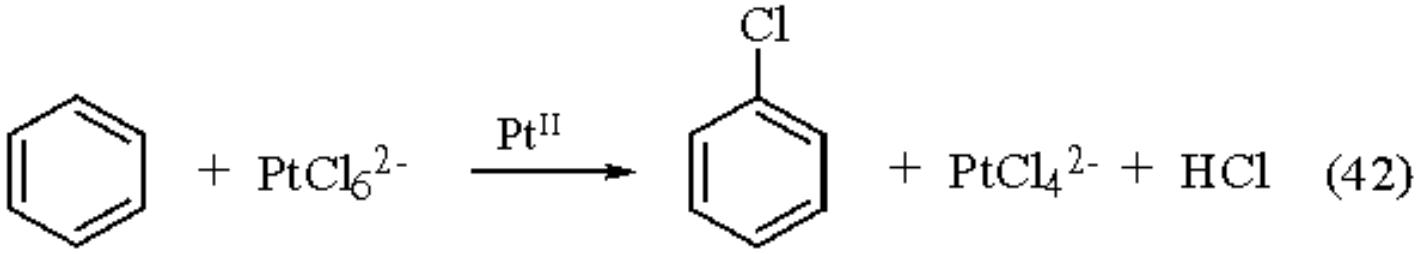

Cyclopropanes react with CPA to form platinacyclobutanes (eq 43).[57] With substituted cyclopropanes, Ziese's dimer provides the best results. Alternatively, cyclopropanes form mixtures of pyrylium ions in very low yields upon treatment with acetic anhydride and catalytic CPA.[58]

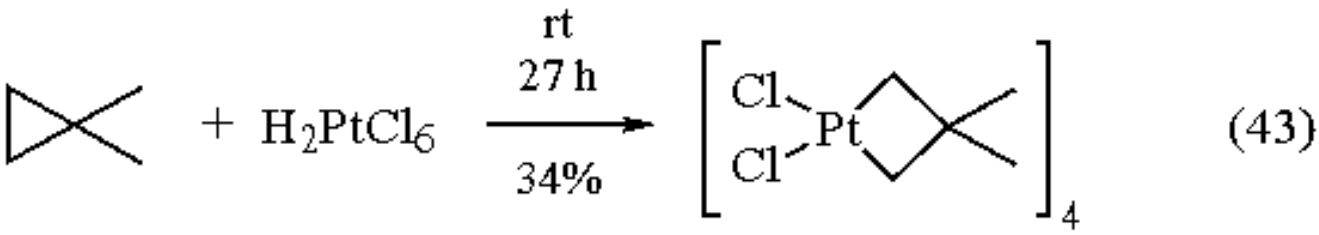

2-Allyloxypyridines may be rearranged to *N*-allylpyridones when using CPA (eq 44).[59] The reaction is carried out by heating the pyridine at 125 °C for 36 h without solvent. The reaction can also be catalyzed by $Pt(PPh_3)_4$.

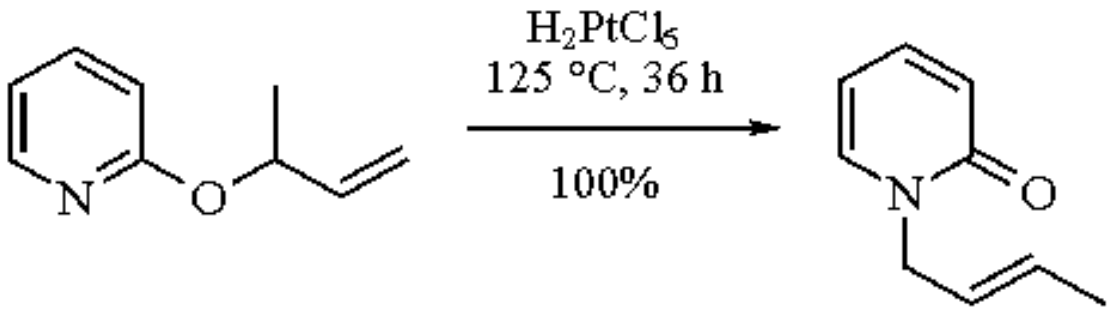

(44)

Alcohols can be converted to carbonyl compounds through a two-electron oxidation process using molecular oxygen, CPA, and visible light.[60] The reaction is catalytic in Pt^{IV} and requires Cu^{II} cocatalysis.

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Hydrogen Iodide[1]

HI

[10034-85-2] · HI · Hydrogen Iodide · (MW 127.91)

(electrophilic hydriodination of alkenes and alkynes;[3-10] cleavage of epoxides,[1b,11,12] ethers, and acetals;[13] conversion of alcohols to iodides;[14-17] reducing agent for many groups including quinones,[24,25] α-diketones,[23] α-ketols,[23] α-halo ketones,[19] α-diazo ketones,[22] and sulfoxides;[30] reductive cyclization of keto acids[27,28])

Alternate Name: hydriodic acid.

Physical Data: 57% aqueous solution: bp 127 °C; *d* 1.70 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: compressed gas; colorless 57% aq solution; widely available.

Preparative Methods: from the reaction of tetrahydronaphthalene with I_2;[2] can be generated in situ (a) from Me_3SiCl and NaI in the presence of water,[3] (b) from I_2 and activated alumina,[4] (c) from KI and H_3PO_4,[5] and (d) from $Et_2PhN.BI_3$ and AcOH.[6]

Purification: distillation of the aqueous azeotrope; concentrated solutions can be regenerated after long storage by treatment with hypophosphorous acid.

Handling, Storage, and Precautions: store protected from air and light at or below rt. Highly corrosive and toxic. This reagent should be handled in a fume hood.

Hydriodination of Alkenes and Alkynes.

Being a stronger acid, HI undergoes addition more readily than ***Hydrogen Chloride*** or ***Hydrogen Bromide*** to most alkenes and alkynes.[1a] Moreover, there is no competing radical addition as with HBr. However, because of the difficulty in generating and transferring anhydrous HI, addition of HI has received less attention than addition of HCl and HBr. As mentioned above, several techniques have been developed for generating HI in situ. These include the use of KI and H_3PO_4 (eq 1);[5] Me_3SiCl and NaI in the presence of water (eq 2);[3] I_2 and activated Al_2O_3 (eq 2);[4] and the $Et_2PhN.BI_3$ complex and AcOH (eq 3).[6] Alternatively, $I(py)_2BF_4$ has been used with the hydride donor Et_3SiH (eq

1).[7]

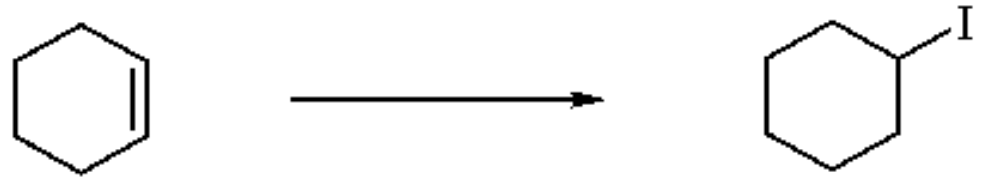

(1)

KI, H_3PO_4, 80 °C, 3 h	88-90%
$I(py)_2BF_4$, HBF_4, Et_3SiH, 20 °C, 1 h	50%

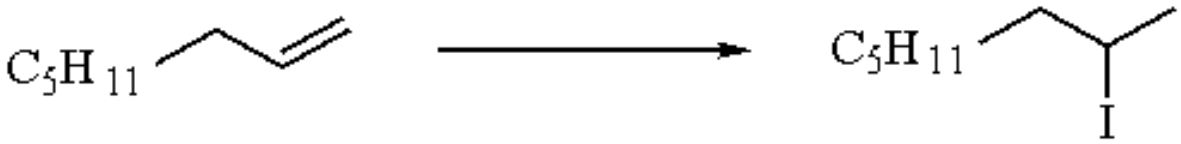

(2)

TMSCl, NaI, H_2O, 25 °C, 1 h	98%
I_2, Al_2O_3, 36 °C, 2 h	83%
57% HI, $C_{16}H_{33}(Bu)_3PBr$, 115 °C, 0.25 h	97%
TMSI, SiO_2, 25 °C, 1 h	98%

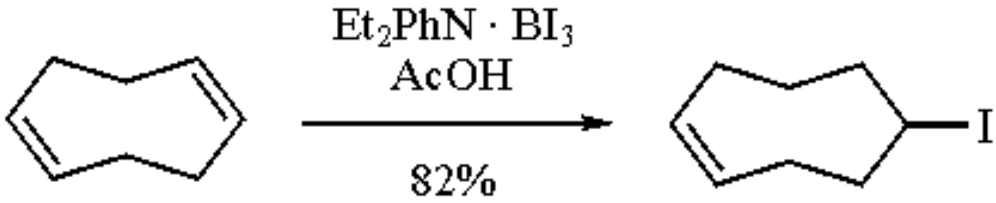

(3)

Aqueous HI has been used with a phase-transfer catalyst to hydriodinate alkenes (eq 2).[8] Similarly, it has been used to convert dialkylalkynes to the corresponding (*Z*)-vinyl iodides (eq 4).[9]

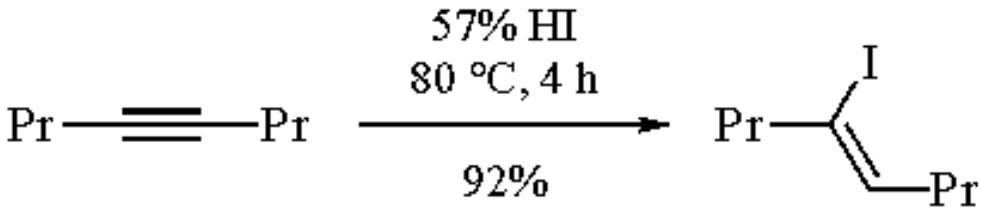

(4)

A particularly convenient method for generating HI in situ involves the use of various inorganic and organic iodides in the presence of appropriately prepared silica gel or alumina (eq 2).[10] These adsorbents also facilitate the addition process. Surface-mediated hydriodination of phenylalkynes affords the (*E*) isomers, resulting from *syn* addition (eq 5).[10] The regiochemical course of these hydroiodinations follows Markovnikov's rule.

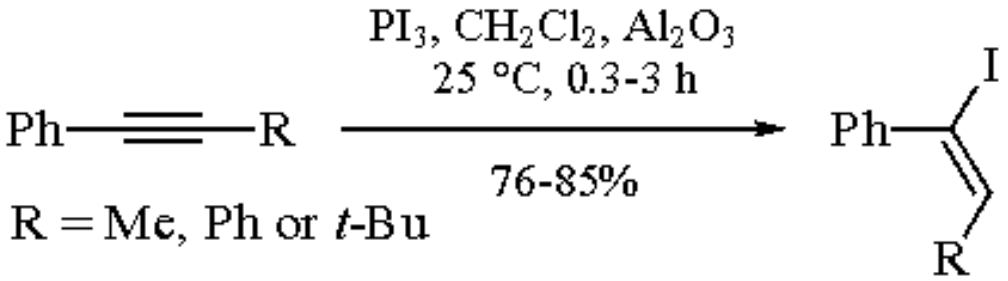

(5)

Cleavage of Epoxides to Iodohydrins.

The addition of HI to epoxides to give iodohydrins proceeds readily using either aqueous HI or anhydrous HI in organic solvents.[1b,11] Because of the difficulty of preparing anhydrous HI, aqueous solutions have most often been used for this transformation. The stereo- and regioselectivity of the addition process is similar to the general trends discussed for the corresponding additions with HCl (see ***Hydrogen Chloride***). Trimethylsilyl-substituted epoxides give the corresponding iodohydrins with particularly high stereo- and regiospecificity (eq 6).[12]

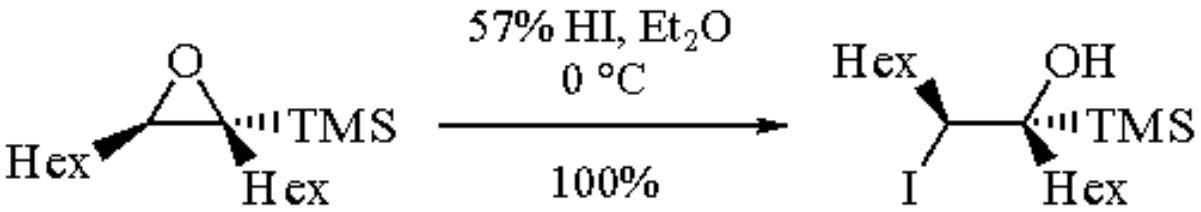

(6)

Cleavage of Ethers and Acetals.

HI readily cleaves ethers to alcohols and/or iodides[13] and is an attractive reagent for this transformation from the standpoint of economy and convenience. Primary and secondary alkyl methyl ethers are cleaved to afford alcohols (or derivatives), while benzyl and tertiary alkyl ethers often yield iodides. Acetals react in a similar fashion to produce ketones, although this deprotection method rarely offers advantages over more common procedures.

Conversion of Alcohols and Chlorides to Iodides.

The reaction of 57% aqueous HI with saturated primary and secondary alcohols at elevated temperatures leads in fair to high yield to the corresponding iodides.[14] Tertiary iodides have been synthesized in good to high yields from the corresponding alcohols under especially mild conditions by 55% aqueous HI in the presence of ***Lithium Iodide***.[15] Allylic alcohols are transformed to allylic iodides by HI generated in situ from Me_3SiCl/NaI.[16] Benzylic alcohols are subject to conversion to the saturated system, presumably via iodine substitution and ensuing reduction (eq 7).[17]

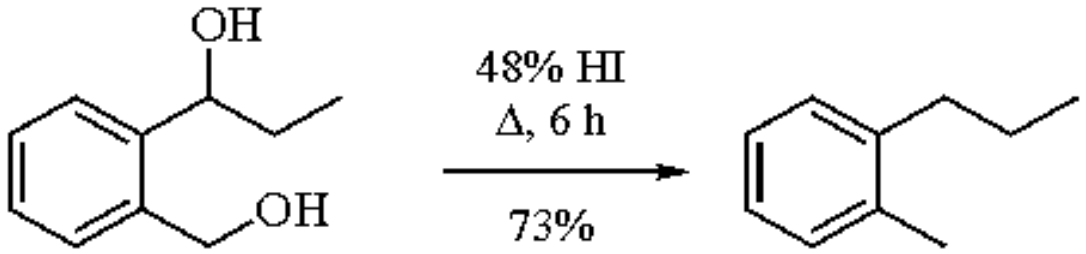

(7)

Alkyl iodides can also be synthesized via treatment of secondary and tertiary alkyl chlorides with anhydrous HI in the presence of catalytic amounts of FeI_3.[18]

Reduction of α-Substituted Ketones.

Treatment of various α-substituted ketones with HI leads to reductive scission of the α-substituent. Reductive dehalogenation of α-halo ketones can thus be accomplished with HI to furnish the corresponding ketones in high yield (eq 8).[19] Reaction occurs readily even with sterically hindered substrates. Related procedures employing cat. NaI or 57% aq HI and phosphorous acid in acetonitrile[20] or NaI in concd H_2SO_4[21] require long reaction times, high temperatures, and/or reactive substrates and are less satisfactory.

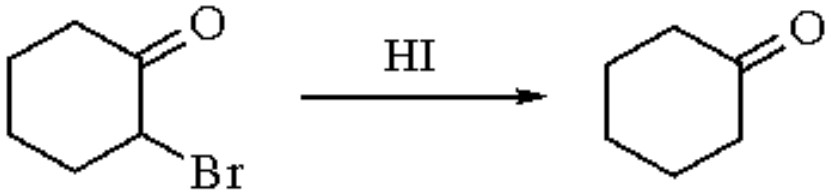

(8)

α-Diazo ketones are reduced to methyl ketones by 47% aqueous HI in $CHCl_3$ (eq 9).[22] The reaction with HI differs from that of HBr and HCl, which give halomethyl ketones as products. Presumably, the initially formed iodomethyl ketone is reduced to the saturated ketone under the reaction conditions.

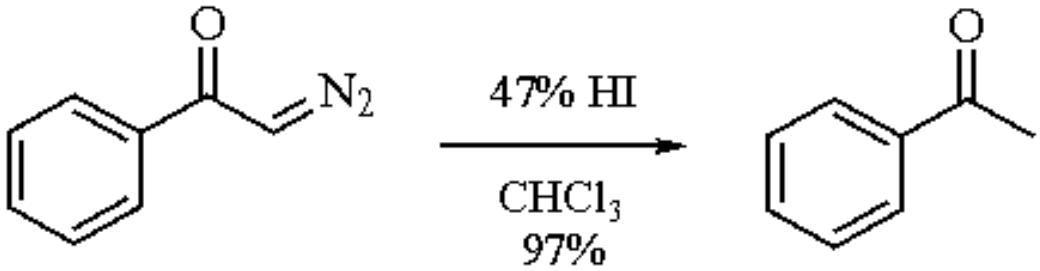

(9)

α-Diketones and α-ketols are reduced to the corresponding saturated ketones in good yields by aqueous HI in acetic acid at reflux (eq 10).[23]

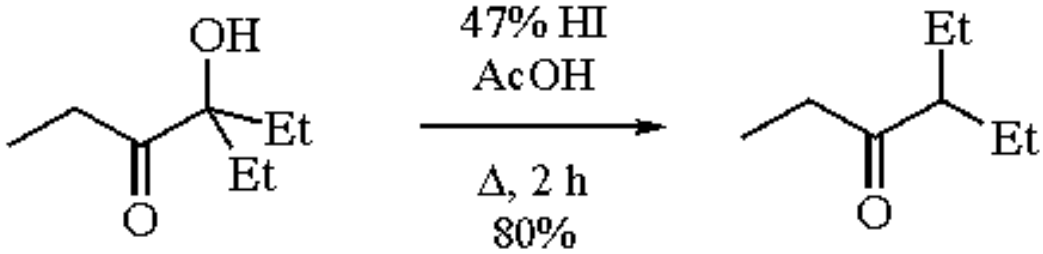

(10)

Reduction of Quinones and Phenols to Arenes.

Polycyclic quinones may be reduced to polyarenes by HI in HOAc at reflux (eq 11).[24,25] In resistant cases, concentrated aqueous HI may be employed; addition of phosphorus often results in cleaner reaction by removing the

I_2 formed. Large excess of HI or prolonged reaction time may lead to overreduction. Since hydroquinones and phenols are intermediates in these reactions, they are also readily reducible with this reagent. Reductive methylation of quinones can be accomplished in high yield by reaction of polycyclic quinones with excess ***Methyllithium*** followed by reduction with HI (eq 12).[26]

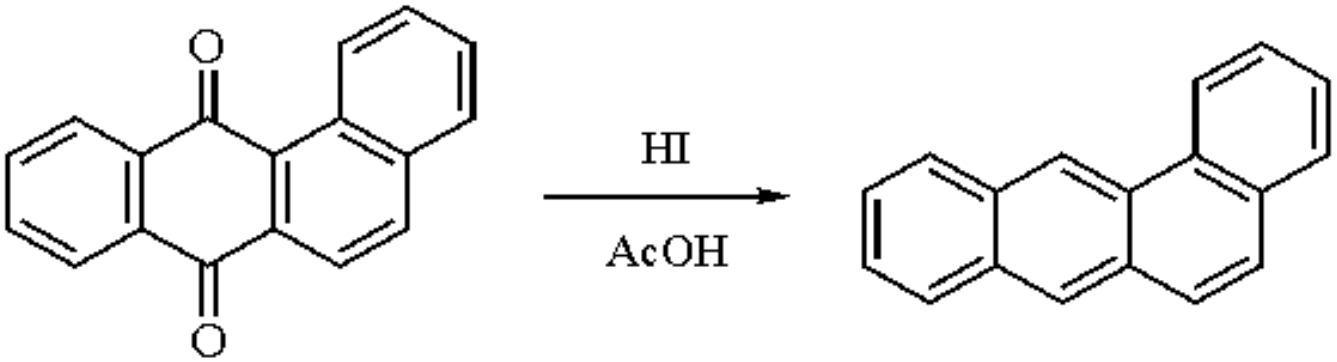

(11)

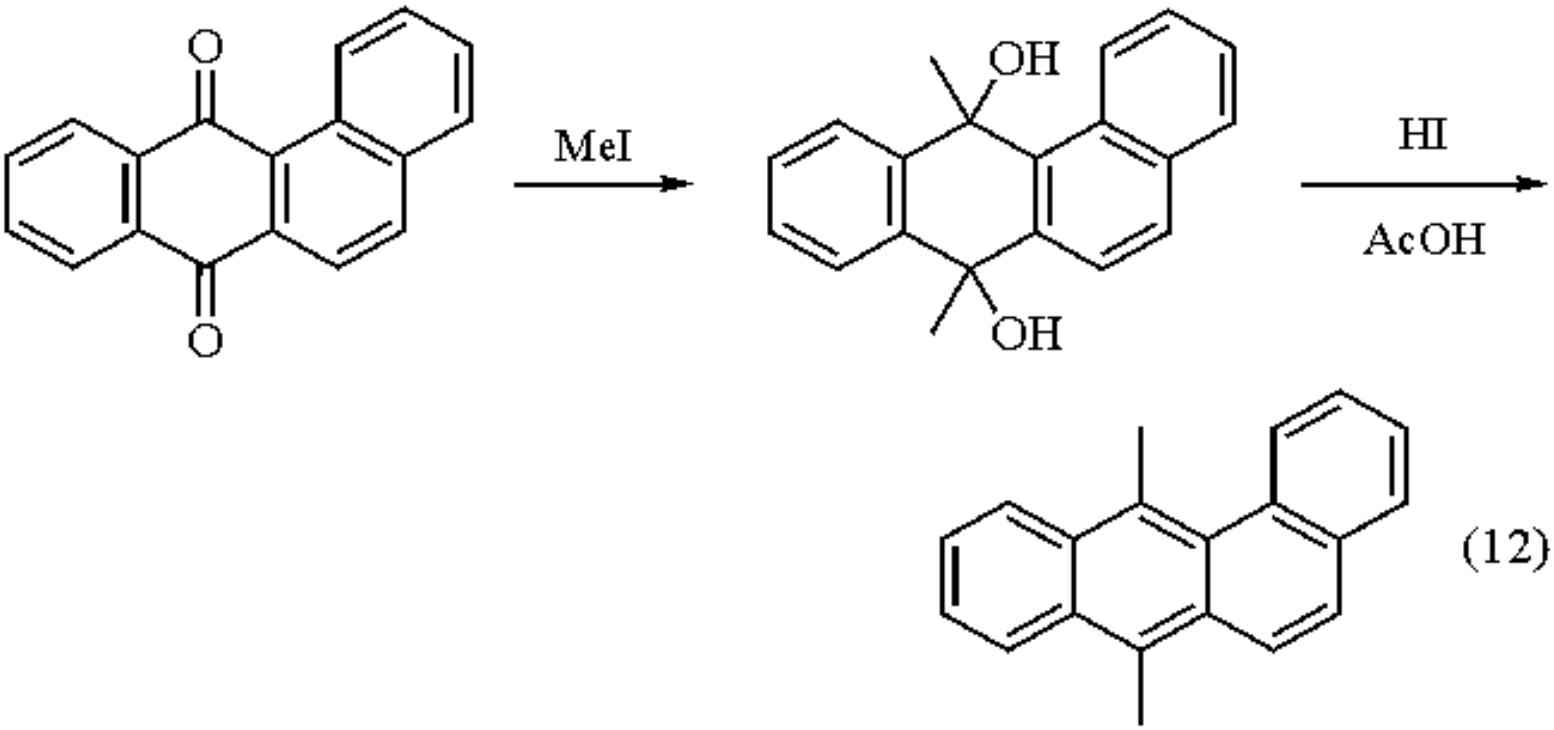

(12)

A method for the construction of fused polyarenes entails reaction of a smaller aromatic ring system with phthalic anhydride followed by reductive cyclization of the keto acid product with HI in acetic acid to form a polyarene with two additional rings (eq 13).[27,28] This method conveniently combines three steps (reduction of the carbonyl group, cyclodehydration, and reduction) into one step.

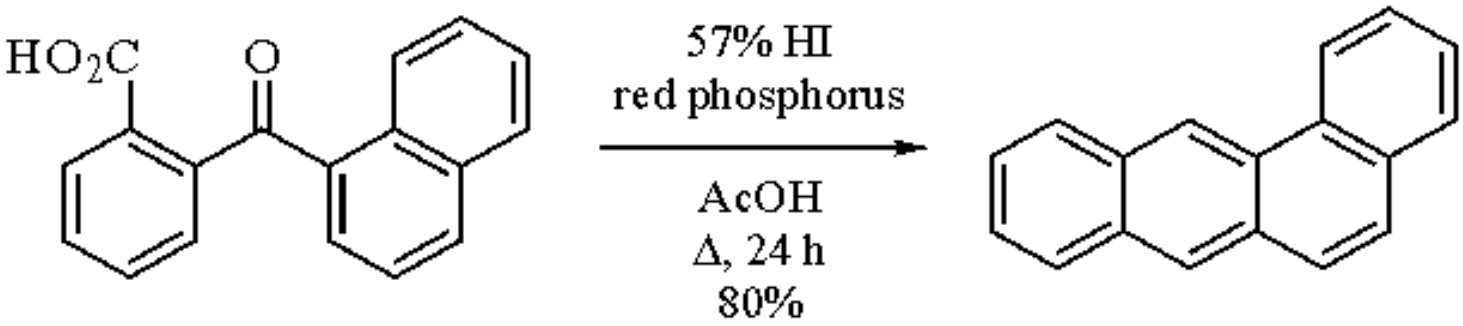

(13)

Reductive Deoxygenation of Aryl Ketones.

The combination HI/P/HOAc effectively deoxygenates aryl ketones (eq 14).[27-29] While this method is utilized infrequently, it represents a useful alternative to the better known Wolff-Kishner and Clemmensen reduction methods.

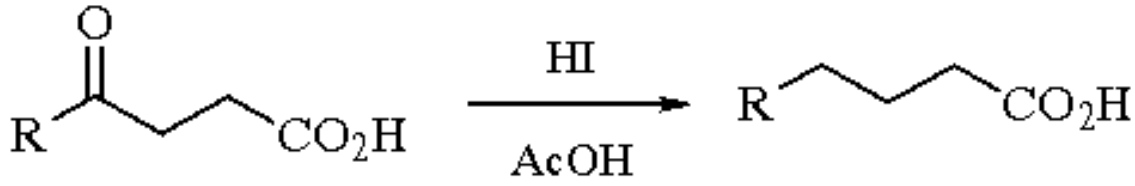

(14)

Reduction of Sulfoxides to Sulfides.

Sulfoxides are readily deoxygenated by HI without the complicating halogenation that often accompanies reduction using HBr or HCl.[30]

Reduction of Alkenylsilanes.

Hydriodic acid reacts with vinylsilanes with replacement of R_3Si by hydrogen (eq 15).[31] A small amount of I_2 and water (or D_2O) is also effective. These reactions usually occur with retention of configuration.

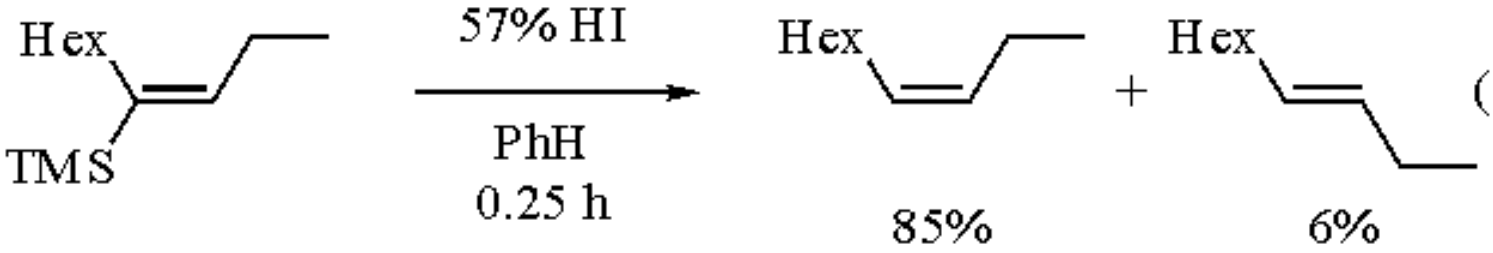

(15)

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Hydrogen Peroxide[1]

HOOH

[7722-84-1] · H_2O_2 · Hydrogen Peroxide · (MW 34.02)

(nucleophilic reagent capable of effecting substitution reactions[2] and epoxidation of electron-deficient alkenes;[3] weak electrophile whose activity is enhanced in combination with transition metal oxides[4] and Lewis acids;[5] strong nonpolluting oxidant which can oxidize hydrogen halides[6])

Physical Data: 95% H_2O_2: mp -0.41 °C; bp 150.2 °C; *d* 1.4425 g cm^{-3} (at 25 °C). 90% H_2O_2: mp -11.5 °C; bp 141.3 °C; *d* 1.3867 g cm^{-3}. 30% H_2O_2: mp -25.7 °C; bp 106.2 °C; *d* 1.108 g cm^{-3}.

Solubility: sol ethanol, methanol, 1,4-dioxane, acetonitrile, THF, acetic acid.

Form Supplied in: clear colorless liquid widely available as a 30% aqueous solution and 50% aqueous solution; 70% and 90% H_2O_2 are not widely available.

Analysis of Reagent Purity: titration with $KMnO_4$ or cerium(IV) sulfate.[7]

Purification: 95% H_2O_2 (caution!) can be prepared from 50% solution by distilling off water in a vacuum at rt.[8]

Handling, Storage, and Precautions: H_2O_2 having a concentration of 50% or more is very hazardous and can explode violently, particularly in the presence of certain inorganic salts and easily oxidizable organic material. A safety shield should be used when handling this reagent.[9] After the reaction is complete, excess H_2O_2 should be destroyed by treatment with MnO_2 or Na_2SO_3 soln. Before solvent evaporation, ensure absence of peroxides. The use of acetone as solvent should be avoided.[10] The reagent should be stored in aluminum drums in a cool place away from oxidizable substances.

Synthesis of Peroxides via Perhydrolysis.

H_2O_2 and the hydroperoxy anion are excellent nucleophiles which react with alkyl halides and other substrates having good leaving groups to furnish hydroperoxides. The hydroperoxide (**2**) has been prepared employing 98% H_2O_2 (eq 1).[11] To a stirred mixture of THF (50 mL), ***Silver(I) Trifluoromethanesulfonate*** (0.04 mol), and pyridine (0.02 mol) kept at 6 °C under argon and protected from light is gradually added 98% H_2O_2 (0.32 mol). The chloride (**1**) (0.02 mol) dissolved in THF (10 mL) is next added dropwise with cooling (6 °C). The reaction mixture is kept at rt for 24

h; the organic layer is separated by gravity filtration, diluted with ether, and washed with saturated aq $NaHCO_3$ at 0 °C. The organic layer is dried. The solvent as well as traces of pyridine and starting material are distilled out at rt under vacuum. The residual material is the hydroperoxide (**2**) which has been distilled in high vacuum using a bath maintained at 40 °C. The hydroperoxide (**3**) has been prepared in a similar fashion employing 30% H_2O_2 (eq 2).[12]

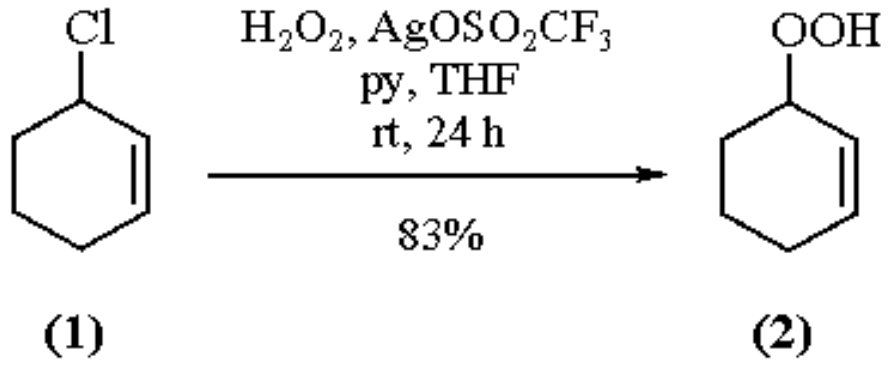

(1)

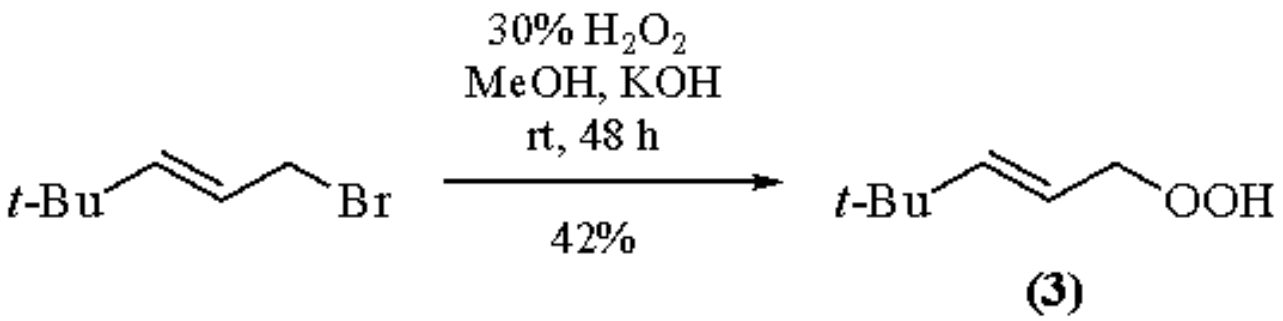

(2)

Tertiary alcohols $R^1R^2R^3COH$ and other alcohols which can readily furnish carbenium ion intermediates are solvolyzed by 90% H_2O_2 in the presence of acid catalysts to yield hydroperoxides $R^1R^2R^3COOH$.[13] Trimeric hydroperoxides having a nine-membered oxa heterocyclic ring have been prepared from ketones and hydrogen peroxide in the presence of acid catalysts.[14]

N-Alkyl-*N*´-tosyl hydrazides are oxidized by H_2O_2 and Na_2O_2 in THF at rt to the corresponding hydroperoxides; by employing this procedure, cyclohexyl hydroperoxide has been obtained in 92% yield.[15]

Several *gem* hydroperoxides have been prepared from acetals (eq 3).[16]

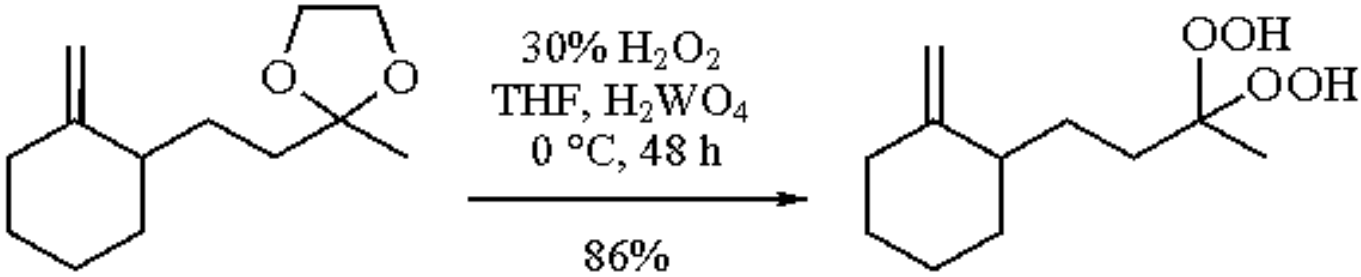

(3)

The prostaglandin PGG_2 (**5**) has been synthesized from the dibromide (**4**) (eq 4).[17]

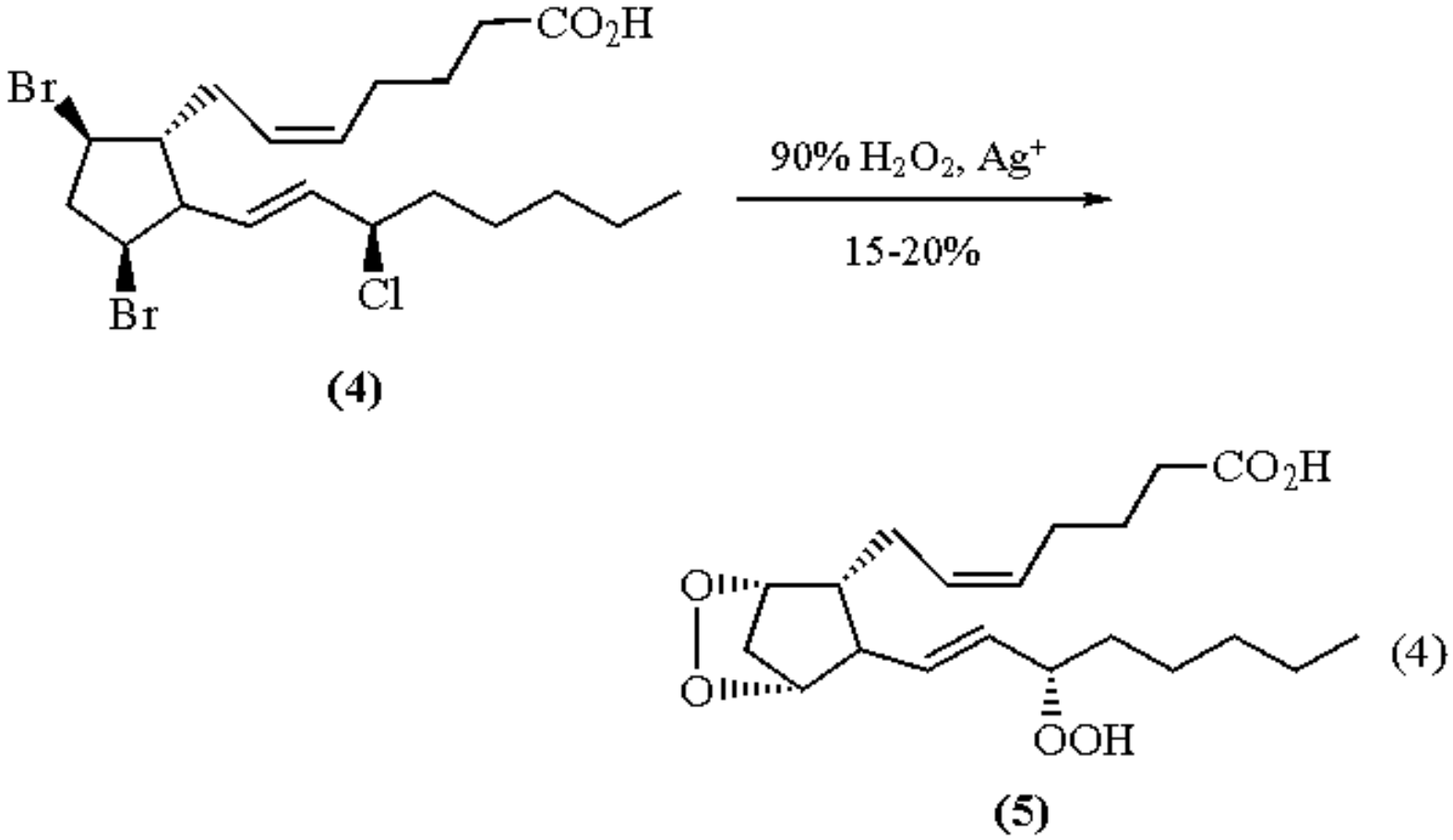

Perhydrolysis of acid anhydrides furnishes the corresponding peroxy acids (for an example, see ***Trifluoroperacetic Acid***). Perhydrolysis of acid chlorides also furnishes peroxy acids.[18] When an organic acid is mixed with H_2O_2 an equilibrium reaction is established, as shown in eq 5.[18] ***Methanesulfonic Acid*** has been used to accelerate the reaction and also to function as solvent (see preparation of ***Perbenzoic Acid***).

$$RCO_2H + H_2O_2 \underset{}{\overset{H^+}{\rightleftharpoons}} RCO_3H + H_2O \qquad (5)$$

A number of diacyl peroxides have been prepared in 90-95% yield by reacting the acid chloride (for example, phenylacetyl chloride) (1 equiv) with 30% H_2O_2 (0.55 equiv) in ether in the presence of pyridine (2 equiv) at 0 °C for 2 h.[19]

Reactions with Amides, Aldehydes, and Ketones.

The oxazolidinone (**6**) is deacylated regioselectively on treatment with ***Lithium Hydroperoxide*** (eq 6).[20] For another example, see Evans.[21]

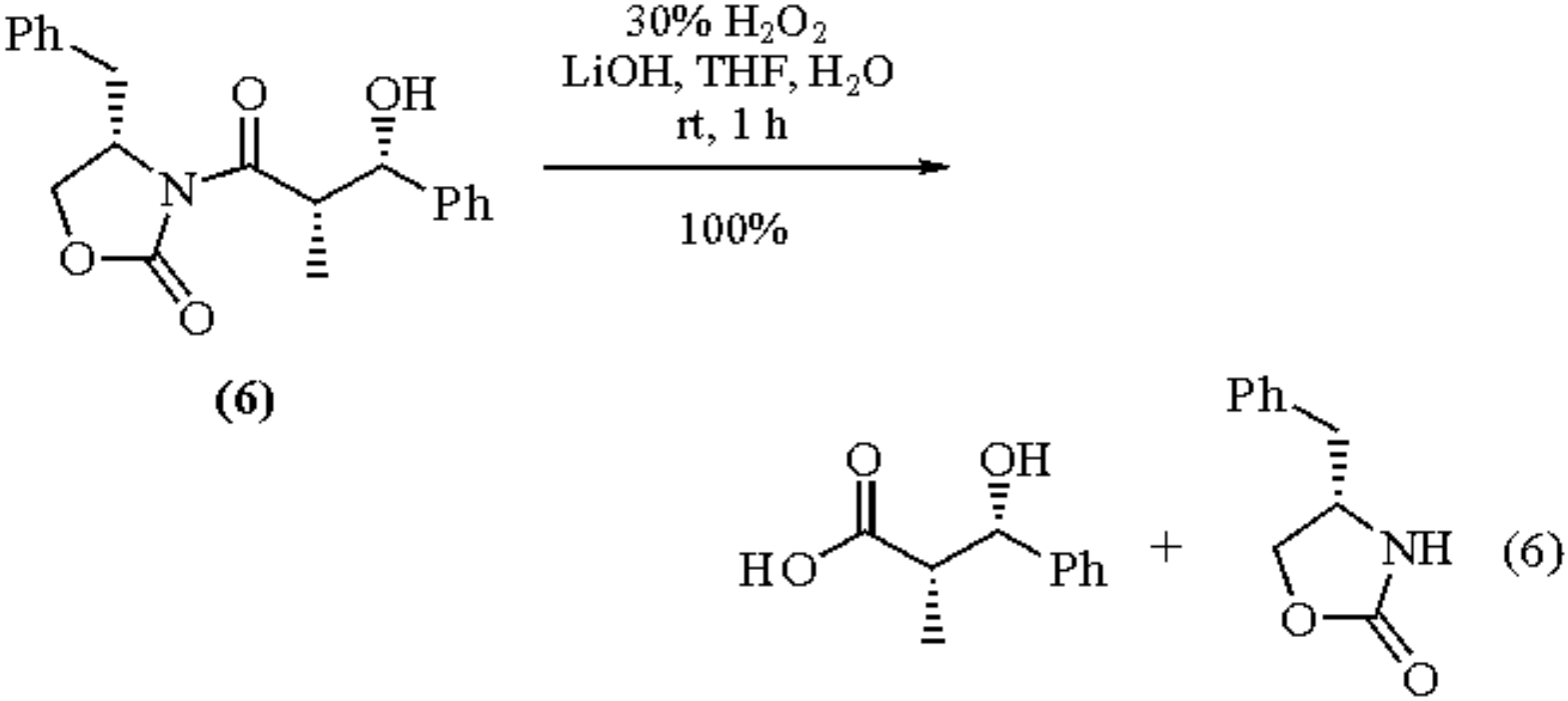

Aromatic aldehydes can be transformed to phenols by oxidizing with H_2O_2 in acidic methanol (eq 7).[22] Dilute alkaline H_2O_2 can convert only aldehydes having an hydroxyl in the *ortho* or *para* position to the corresponding phenols (Dakin reaction).[1b] *m*-CPBA is not useful for the preparation of phenol (**8**) from (**7**).[22]

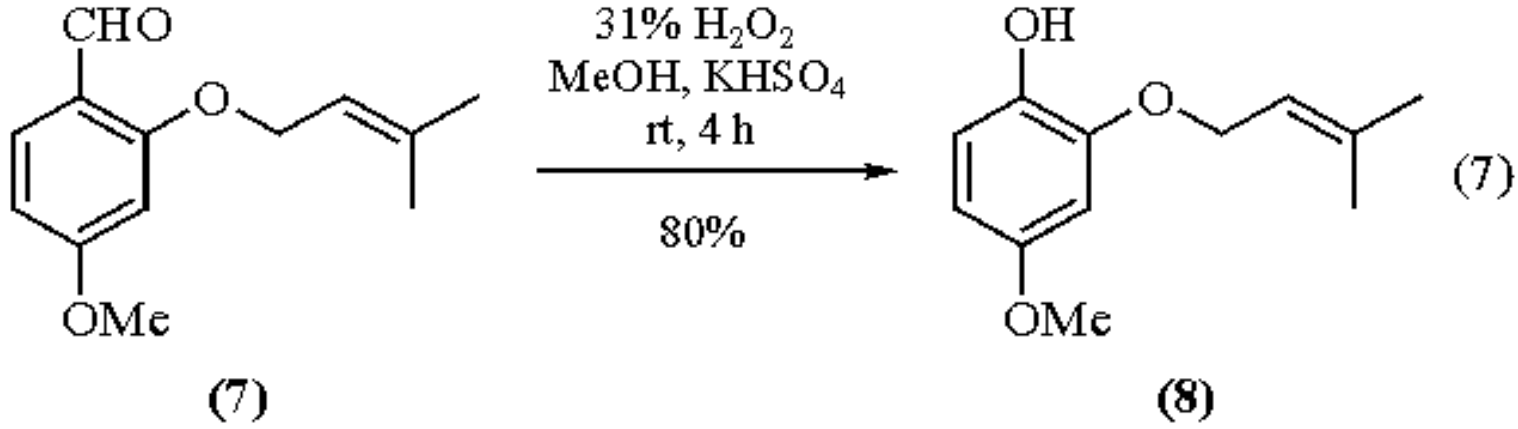

Alkyl and aryl aldehydes are oxidized to the corresponding carboxylic acids in high yields via oxidation with H_2O_2 in the presence of ***Benzeneseleninic Acid*** as catalyst.[23] Cyclobutanones and other strained ketones undergo Baeyer-Villiger oxidation with H_2O_2. The cyclobutanone (**9**) has thus been oxidized to the γ-lactone (**10**) (eq 8).[24] Baeyer-Villiger oxidation of some cyclobutanones proceeds under very mild conditions (-78 °C).[25] Baeyer-Villiger reaction of ketones having isolated double bonds can be carried out with H_2O_2 without reaction at the double bond; however, when organic peroxy acids are used, the alkene often is oxidized.[26]

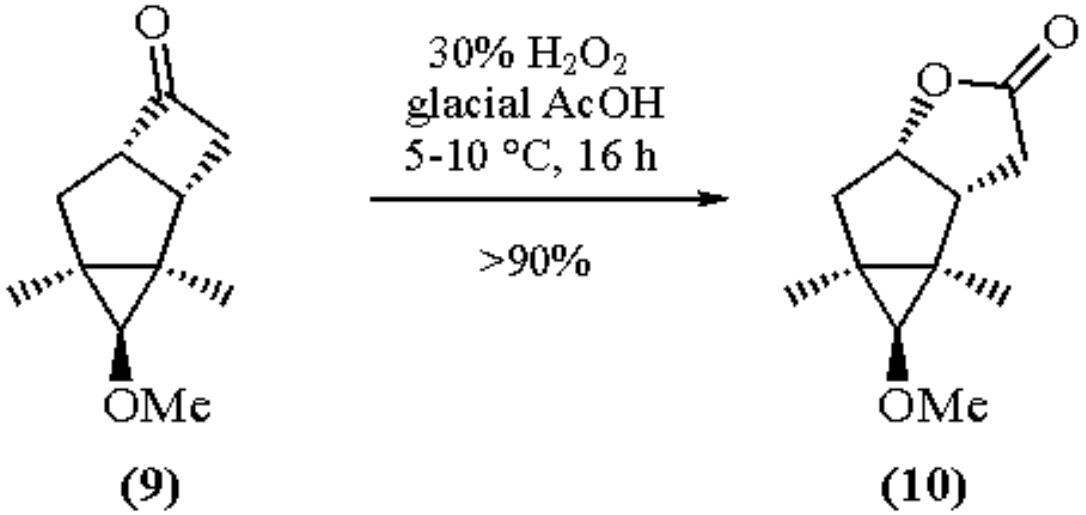

(8)

Epoxidation of α,β-Unsaturated Ketones and Acids.

α,β-Unsaturated ketones furnish the corresponding α,β-epoxy ketones in high yields on treatment with H_2O_2 in the presence of a base.[3] In the cyclopentenone (**11**), approach to the β-face is sterically hindered. Epoxidation of (**11**) at -40 °C furnishes quantitatively a 94:6 mixture of α- and β-epoxides; the selectivity is less when the reaction is carried out at higher temperatures (eq 9).[27] Optically active epoxy ketones (about 99%) have been prepared with high ee by carrying out the epoxidation in the presence of a chiral catalyst such as polymer-supported poly(L-leucine).[28]

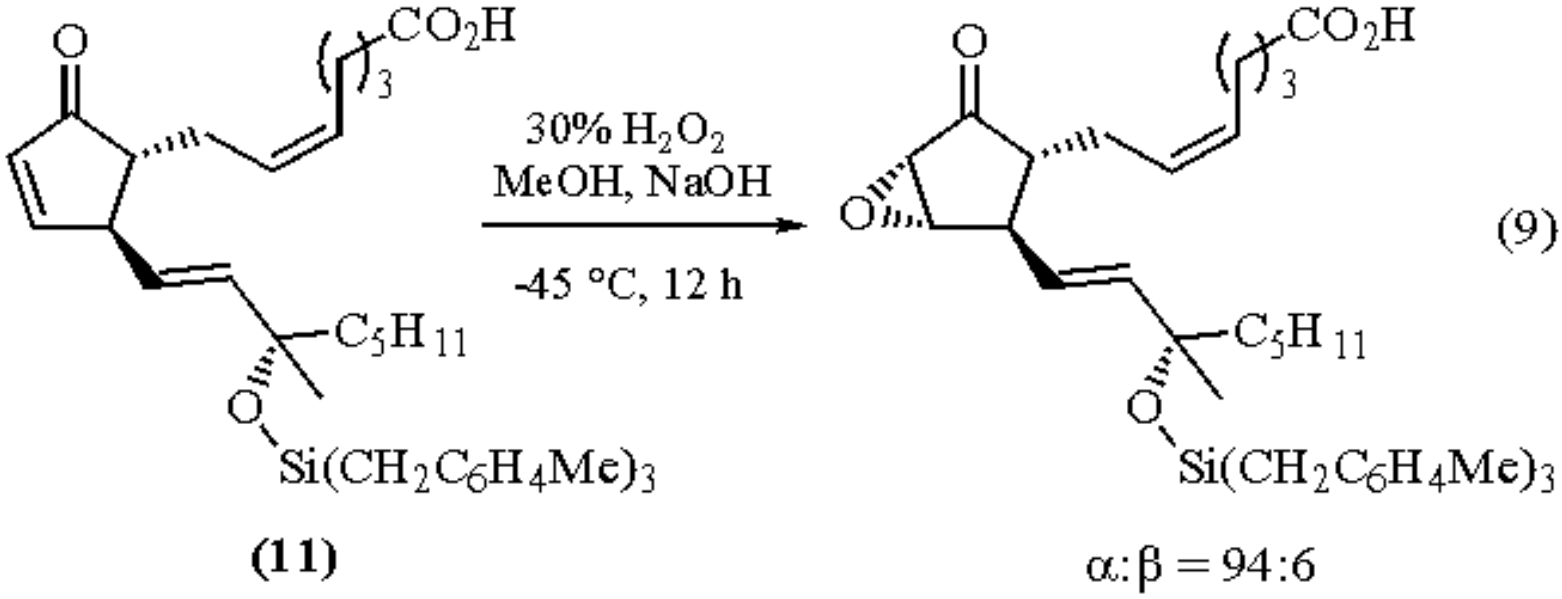

(9)

α,β-Unsaturated acids have been epoxidized with 35% H_2O_2 using a catalyst prepared from 12-tungstophosphoric acid (WPA) and cetylpyridinium chloride (CPC) (pH 6-7, 60-65 °C); by this method, crotonic acid furnishes the α,β-epoxy acid in 90% yield.[29]

Synthesis of Epoxides, Vicinal Diols, Dichlorides, and Ketones from Alkenes.

Terminal alkenes, as well as di- and trisubstituted alkenes, have been epoxidized at 25 °C using a molybdenum blue-***Bis(tri-n-butyltin) Oxide*** catalyst system (eq 10).[30] Epoxides have been prepared with 16% H_2O_2 using a (diperoxotungsto)phosphate catalyst (**12**) in a biphasic system.[31]

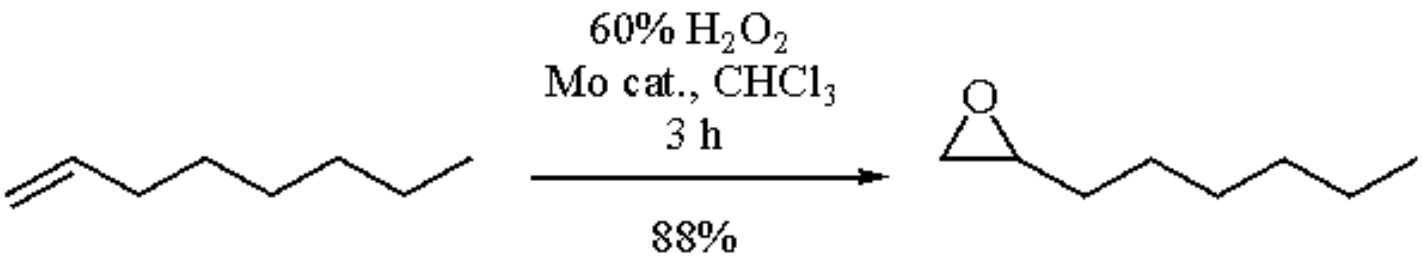

(10)

$$[(C_8H_{17})_3NMe]_3^+[PO_4\{W(O)(O_2)_2\}_4]^{3-}$$

(12)

Asymmetric epoxidation of 1,2-dihydronaphthalene has been achieved employing a chiral manganese(III) salen complex with an axial N-donor; even 1% H_2O_2 can be used as oxidant and the highest ee observed was 64%.[32]

Vicinal diols have been prepared from alkenes by oxidizing with H_2O_2 in the presence of Re_2O_7 catalyst, in dioxane at 90 °C for 16 h; the mole ratio of Re_2O_7:alkene:H_2O_2 is 1:100:120. The reaction proceeds via epoxidation followed by acid-catalyzed ring opening. Cyclohexene furnishes *trans*-cyclohexane-1,2-diol in 74% yield.[33]

Oxidative cleavage of ene-lactams takes place during oxidation with H_2O_2 in the presence of a selenium catalyst (eq 11).[34] The reaction proceeds under neutral and mild conditions. For the preparation of macrocyclic ketoimides, ***Palladium(II) Acetate*** is used as the catalyst.[34]

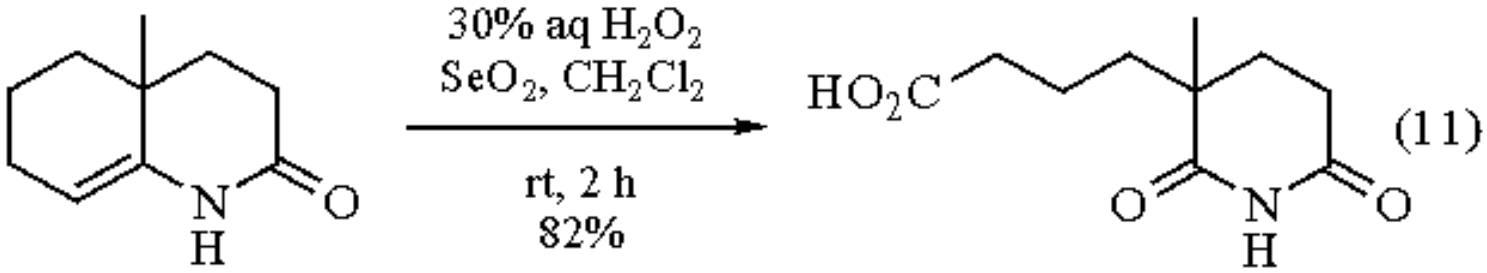

(11)

Alkenes have been chlorinated with concentrated HCl/30% H_2O_2/CCl_4 in the presence of the phase-transfer catalyst ***Benzyltriethylammonium Chloride***. Side reactions take place when gaseous chlorine and sulfuryl chloride react with alkenes; under ionic conditions these side reactions are not favored. The method has also been applied for the bromination of alkenes.[6] 1-Octene furnishes 1,2-dichlorooctane in 56% yield.

Oxidation of Alcohols and Phenols.

The system $H_2O_2/RuCl_3.3H_2O$/phase-transfer catalyst (didecyldimethylammonium bromide) oxidizes a variety of

alcohols selectively; the requirement of ruthenium is very low; ratio of substrate:$RuCl_3$ = 625:1.[35] By this method, *p*-methylbenzyl alcohol was oxidized to *p*-methylbenzaldehyde in 100% yield.

Vicinal diols are oxidized to α-hydroxy ketones by 35% H_2O_2 in the presence of peroxotungstophosphate (PCWP; 1.6 mol %) in a biphasic system using $CHCl_3$ as solvent. 1,2-Hexanediol has been oxidized in 93% yield to 1-hydroxy-2-hexanone.[36]

When 1,4-dihydroxybenzenes are reacted with stoichiometric quantities of iodine, the corresponding *p*-benzoquinones are formed in poor yields; however, they are oxidized in very good yields to *p*-quinones by reaction with 60% H_2O_2 in methanol or aq solution at rt in the presence of catalytic quantities of I_2 or HI. 2-Methyl-1,4-dihydroxynaphthalene has been oxidized to 2-methyl-1,4-naphthoquinone in 98% yield.[37]

Radical Reactions.

Homolytic substitutions of pyrrole, indole, and some pyrrole derivatives have been carried out using electrophilic carbon centered radicals generated in DMSO by Fe^{2+}/H_2O_2 and ethyl iodoacetate or related iodo compounds; the substrate is taken in large excess (eq 12).[38]

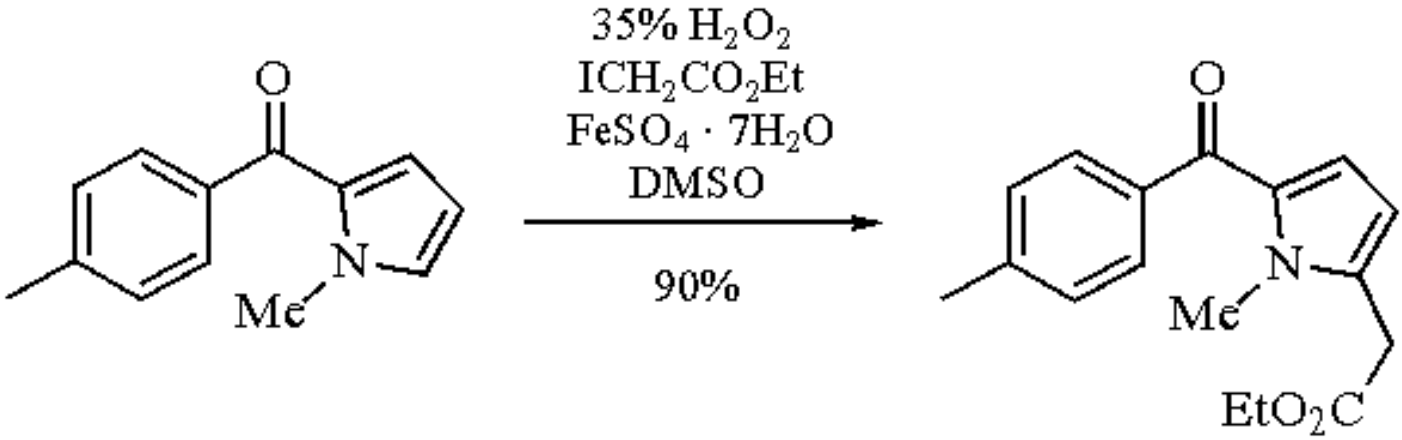

(12)

N-Acylpyrrolidines and -piperidines are oxidized by Fe^{II}/hydrogen peroxide in aqueous 95% acetonitrile to the corresponding pyrrolidin-2-ones and piperidin-2-ones;[39] *N*-phenylcarbamoyl-2-phenylpiperidine was oxidized to the corresponding lactam in 61% yield.

Oxidation of Organoboranes.

Oxidative cleavage of the C-B bond with alkaline H_2O_2 to convert organoboranes to alcohols is a standard step in hydroboration reactions. In some procedures, organoboranes are formed in the presence of 1,4-oxathiane. When a mixture of tri-*n*-octylborane and 1,4-oxathiane in THF was treated initially with NaOH and subsequently with 30% H_2O_2, the organoborane was selectively oxidized to furnish in 98% yield a mixture (93:7) of octan-1-ol and octan-2-ol.[40]

Oxidation of Organosilicon Compounds.

Organosilicon compounds having at least one heteroatom on silicon undergo oxidative cleavage of the Si-C bond when treated with H_2O_2 (eq 13).[41] For additional examples, see Roush[42a] and Andrey.[42b]

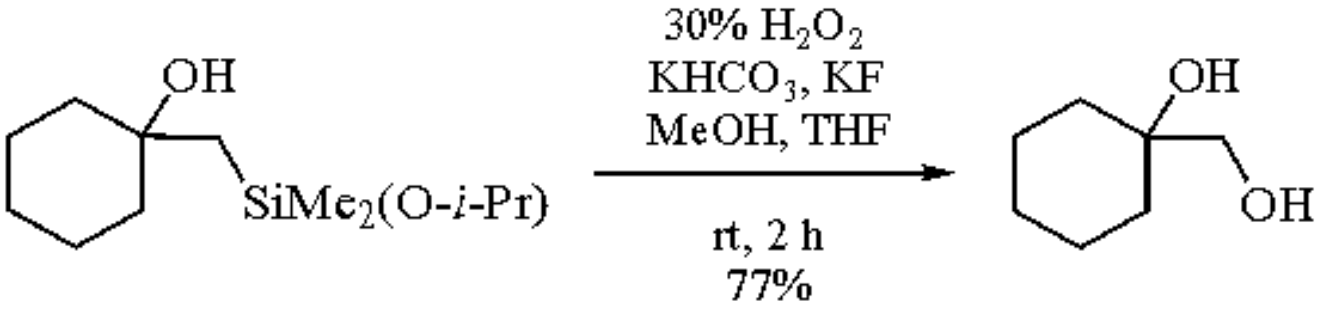

(13)

Oxidation of Amines.

H_2O_2 in the presence of Na_2WO_4 has been used to oxidize (a) 2,4,4-trimethyl-2-pentanamine to the corresponding nitroso compound in 52% yield,[43] and (b) a primary amine (containing β-lactam and phenolic OH) to the corresponding oxime in 72% yield.[44]

The secondary amine 2-methylpiperidine (**13**) has been oxidized to the nitrone (**14**) with H_2O_2/Na_2WO_4 (eq 14);[45] the oxidation product also contains about 6-15% of the isomeric 2-methyl-2,3,4,5-tetrahydropyridine *N*-oxide (***Selenium(IV) Oxide*** is also an effective catalyst for this oxidation).[46] 1,2,3,4-Tetrahydroquinoline is oxidized to the 1-hydroxy-3,4-dihydroquinolin-2(1*H*)-one in 84% yield by H_2O_2/Na_2WO_4.[47] The flavin, $FlEt^+ClO_4^-$ (**15**) is a good catalyst for the H_2O_2 oxidation of secondary amines to nitrones.[48]

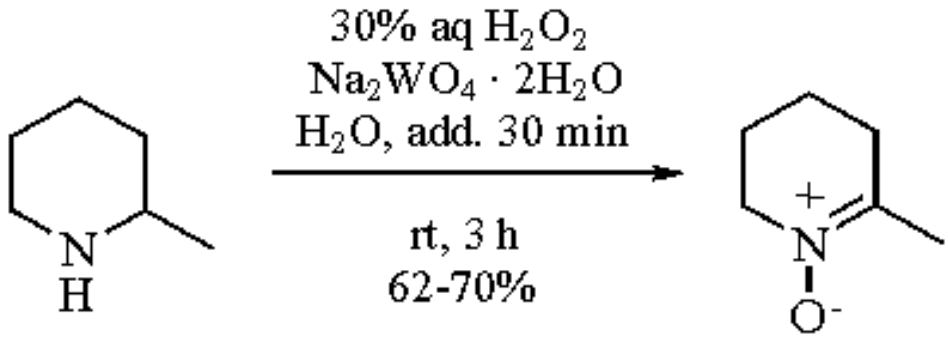

(14)

(13) **(14)**

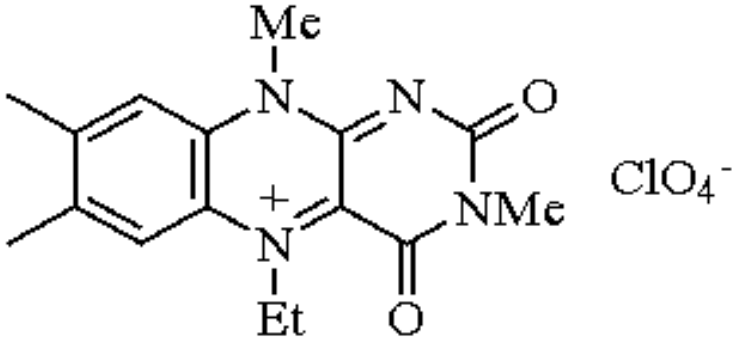

(15)

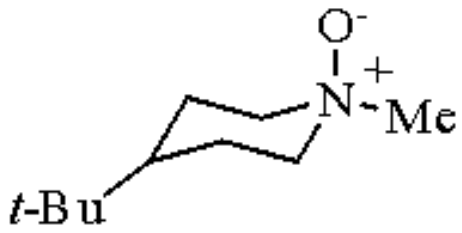

(16)
trans:*cis* = 95:5

The tertiary amine *N*-methylmorpholine has been oxidized to the *N*-oxide in 84-89% yield; the reaction is carried out at 75 °C with 30% H_2O_2 and the reaction time (0.3 mol scale) is about 24 h.[49] The *trans*-*N*-oxide (**16**) has been obtained stereoselectively (*trans*:*cis* = 95:5) by reacting the corresponding *N*-methylpiperidine with 30% H_2O_2 in acetone at 25 °C.[50]

Oxidation of Sulfur-Containing Compounds.

Oxidation of di-*n*-butyl sulfide with H_2O_2 in the presence of the catalyst $FlEt^+ClO_4^-$ (**15**) furnished the corresponding sulfoxide in 99% yield.[48] Sulfides have been oxidized to the corresponding sulfoxides with H_2O_2 in CH_2Cl_2 solution in the presence of the heterocycle (**17**); di-*n*-octyl sulfide yields *n*-octyl sulfoxide in 96% yield, and benzylpenicillin methyl ester is oxidized to the (*S*)-*S*-oxide in 90% yield.[51]

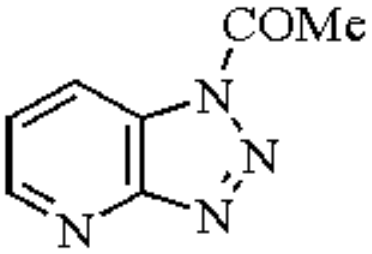

(17)

The oxidation of sulfides to sulfones proceeds in good yields when the reaction is catalyzed by tungstic acid; the cyclic sulfide thietane is oxidized to the sulfone (thietane 1,1-dioxide) in 89-94% yield.[52]

Oxidation of Selenium-Containing Compounds.

Oxidation of the phenyl selenide (**18**) with H_2O_2 in THF furnishes the alkene (**19**) (eq 15);[53] the selenoxide initially formed through oxidation of (**18**) undergoes facile *syn* elimination (see also Grieco[54]).

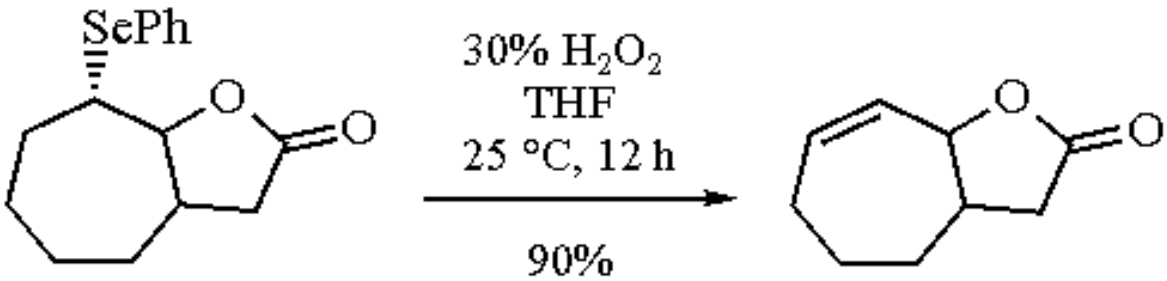

(18) (19) (15)

Hydrogen peroxide has a high (47%) active oxygen content and low molecular weight. It is cheap and is widely available. After delivering oxygen, the byproduct formed in H_2O_2 oxidations is the nonpolluting water. Hence the use of H_2O_2 in industry is highly favored. This reagent is able to oxidize SeO_2, WO_3, MoO_3, and several other inorganic oxides efficiently to the corresponding inorganic peroxy acids which are the actual oxidizing agents in many reactions described above.[4] Use of these oxides in catalytic amounts along with H_2O_2 as the primary oxidant reduces the cost of production, simplifies workup and minimizes the effluent disposal problem. Phase-transfer-catalyzed (PTC) reactions in a two-phase system are well suited for H_2O_2 oxidations and are widely used; epoxides are susceptible to ring opening by water and the PTC procedure allows the preparation of epoxides even with 16% aq H_2O_2 since the epoxide and water are in different phases.[31] Handling chlorine and bromine poses many problems, but HCl/H_2O_2 and HBr/H_2O_2 systems may be used as substitutes for chlorine and bromine, respectively.[6] The solids ***Sodium Perborate***, sodium percarbonate, and ***Hydrogen Peroxide-Urea***, which are prepared from H_2O_2, have wide applications since they release H_2O_2 readily.

Reactions with Nitriles.

Treatment of nitriles (**20**) with $NaOH/H_2O_2$ in aqueous ethanol is a standard synthetic procedure for the preparation of amides (**21**); aromatic nitriles furnish amides in high yields but aliphatic nitriles give amides in moderate yields (50-60%).[55] It has been suggested[56] that addition of the hydroperoxy anion to the nitrile (**20**) furnishes the peroxycarboximidic acid (**22**) which reacts with H_2O_2 to give the amide (**21**) and molecular oxygen.

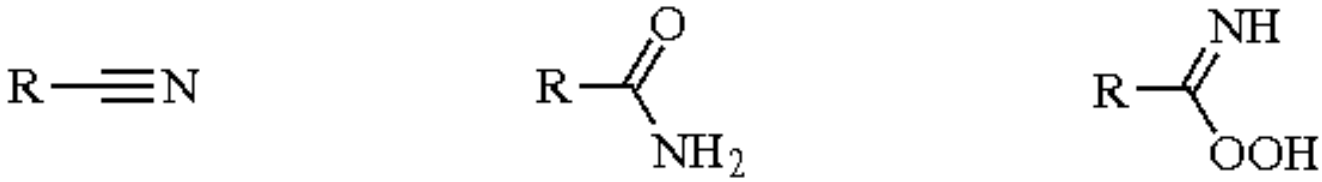

(20) (21) (22)

It has been observed[57] that in the reaction of nitriles with 30% H_2O_2 in the presence of 20% NaOH there is a significant increase in the reaction rate when *n*-tetrabutylammonium hydrogen sulfate (20 mol %) is used as phase-transfer catalyst. The reaction is carried out at 25 °C for 1-2 h employing CH_2Cl_2; aromatic as well as aliphatic amides are obtained in high yields (e.g. eq 16). This method cannot be used if the nitrile has an electron-withdrawing substituent on the carbon atom α to the cyano group.[57]

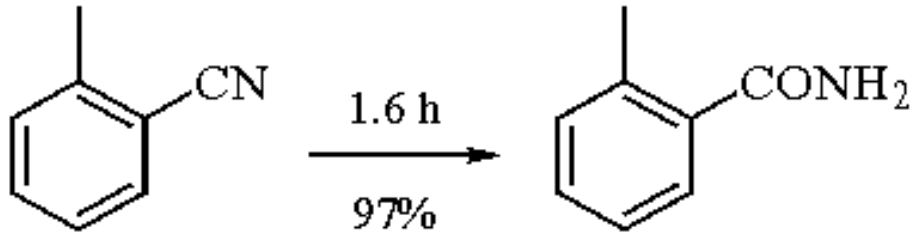

(16)

Treating a DMSO solution of a nitrile with an excess of 30% H_2O_2 in the presence of a catalytic amount of K_2CO_3 for 1-30 min at 25 °C furnishes the corresponding amide in high yields[58] (e.g. eq 17). Under these conditions, esters, amides, and urethanes do not react. α,β-Unsaturated nitriles furnish α,β-epoxy amides.[58] For other routes for the synthesis of amides from nitriles, see Cacchi[57] and Katritzky.[58]

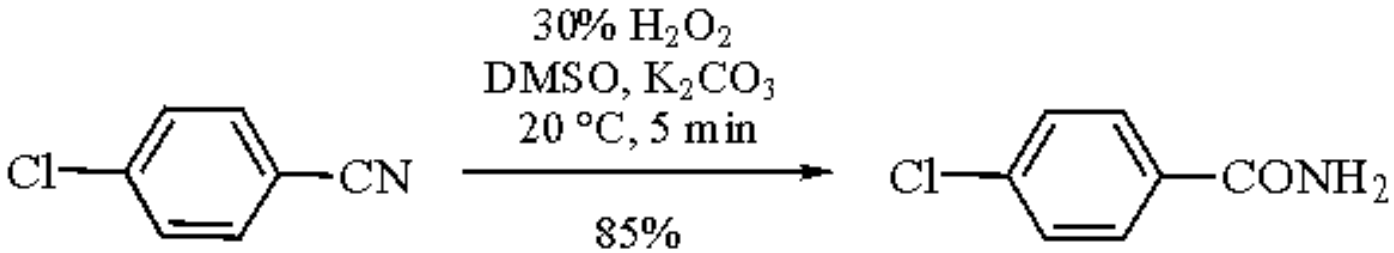

(17)

Related Reagents.

Hydrogen Peroxide-Ammonium Heptamolybdate; ***Hydrogen Peroxide-Boron Trifluoride***; ***Hydrogen Peroxide-Iron(II) Sulfate***; ***Hydrogen Peroxide-Tellurium Dioxide***; ***Hydrogen Peroxide-Tungstic Acid***; ***Hydrogen Peroxide-Urea***; ***Iron(III) Acetylacetonate-Hydrogen Peroxide***; ***Perbenzoic Acid***; ***Peroxyacetimidic Acid***; ***Trifluoroperacetic Acid***.

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A. Somasekar Rao & H. Rama Mohan

Hydrogen Peroxide-Ammonium Heptamolybdate[1]

H_2O_2-$(NH_4)_6Mo_7O_{24}.4H_2O$

(H_2O_2)

[7722-84-1] · H_2O_2 · Hydrogen Peroxide-Ammonium Heptamolybdate · (MW 34.02) ($(NH_4)_6Mo_7O_{24}$)

[12027-67-7] · $H_{24}Mo_7N_6O_{24}$ · Hydrogen Peroxide-Ammonium Heptamolybdate · (MW 1163.88) ($(NH_4)_6Mo_7O_{24}.4H_2O$)

[12054-85-2] · $H_{32}Mo_7N_6O_{28}$ · Hydrogen Peroxide-Ammonium Heptamolybdate · (MW 1235.96)

(epoxidation;[2] oxidation of secondary alcohols to ketones;[2,3] oxidation of aldehydes to acids;[2] chemoselection between epoxidation and alcohol oxidation[2,4])

Physical Data: $(NH_4)_6Mo_7O_{24}.4H_2O$: dec 190 °C; *d* 2.498 g cm^{-3}.

Solubility: $(NH_4)_6Mo_7O_{24}.4H_2O$: sol H_2O (43 g/100 mL); insol alcohol.

Form Supplied in: $(NH_4)_6Mo_7O_{24}.4H_2O$: colorless or slightly greenish or yellowish crystals; widely available.

Handling, Storage, and Precautions: $(NH_4)_6Mo_7O_{24}.4H_2O$: commercially available ammonium heptamolybdate tetrahydrate can be used and stored at rt under air. For H_2O_2, see ***Hydrogen Peroxide***.

Epoxidation.

Molybdenum complexes are among the best catalysts for epoxidations with peroxides.[1] The hydrogen peroxide-molybdate system is superior to others because of its accessibility, low cost, and easy handling. The epoxidation with hydrogen peroxide-molybdate requires tetraalkylammonium salts[2,5] or anion exchange polymers[6] for enhancement of the affinity between substrates and oxidizing agents (peroxomolybdates). Monosubstituted alkenes fail to react and disubstituted alkenes react very slowly. Competition experiments reveal high chemoselectivity for the reaction of tri- vs. disubstituted alkenes (eq 1).[2] Alkene geometry is retained in the product. A primary allylic alcohol activates and directs the epoxidation to the neighboring double bond (eqs 2 and 3).[2]

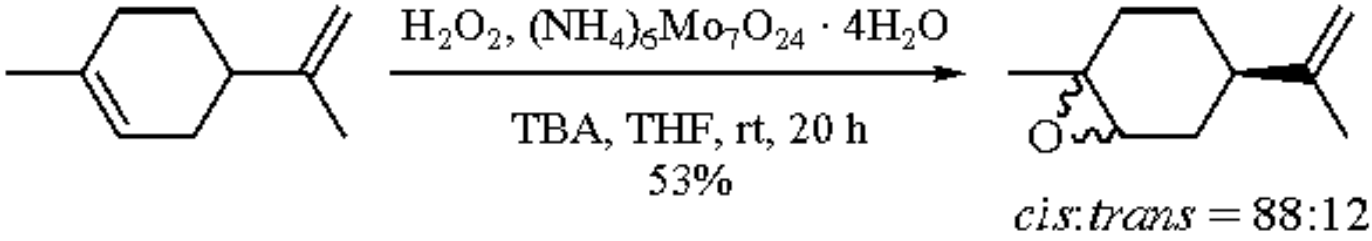

(1)

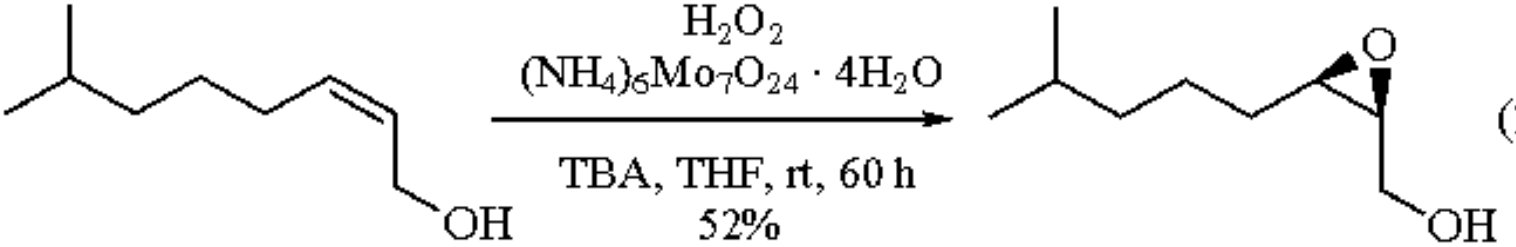

(2)

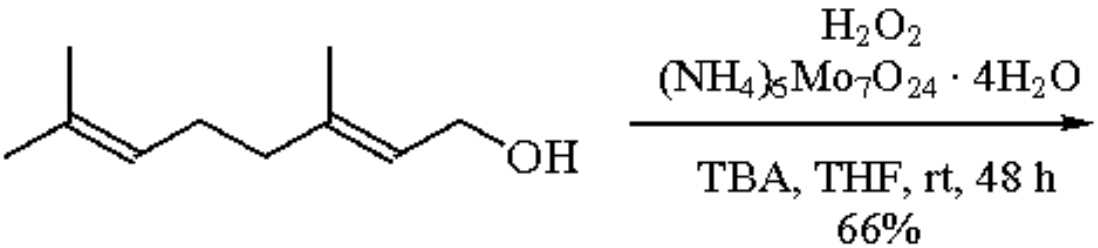

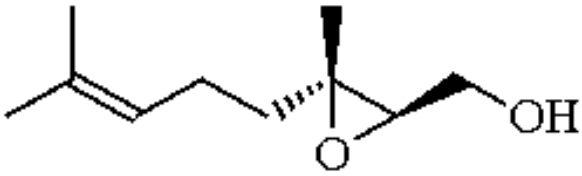

(3)

Oxidation of Alcohols.[7]

Oxidation of secondary alcohols to ketones with hydrogen peroxide-heptamolybdate is accelerated by the addition of ***Potassium Carbonate***.[2,3] The oxidation of a secondary alcohol chemoselectively occurs in the presence of a primary alcohol (eq 4).[2-5]

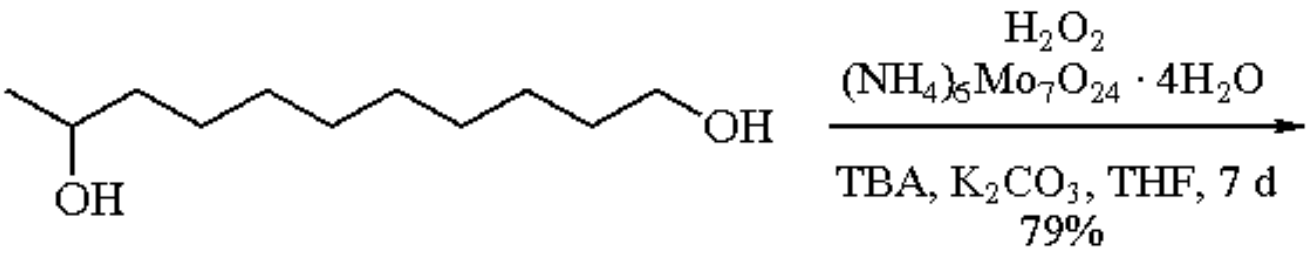

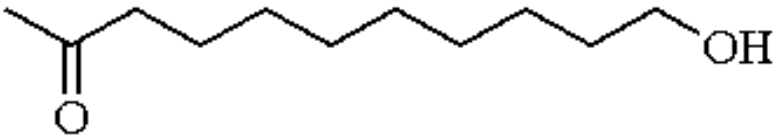

(4)

Steric factors play an important role in these oxidations: the more hindered alcohol is oxidized more rapidly.[2] This steric effect has been exploited for selective oxidations of steroids (eq 5).[2,3] Primary alcohols are oxidized to carboxylic acids at higher temperatures but the major products are the self-condensed esters. Aldehydes are oxidized to carboxylic acids by this reagent (eq 6).[2]

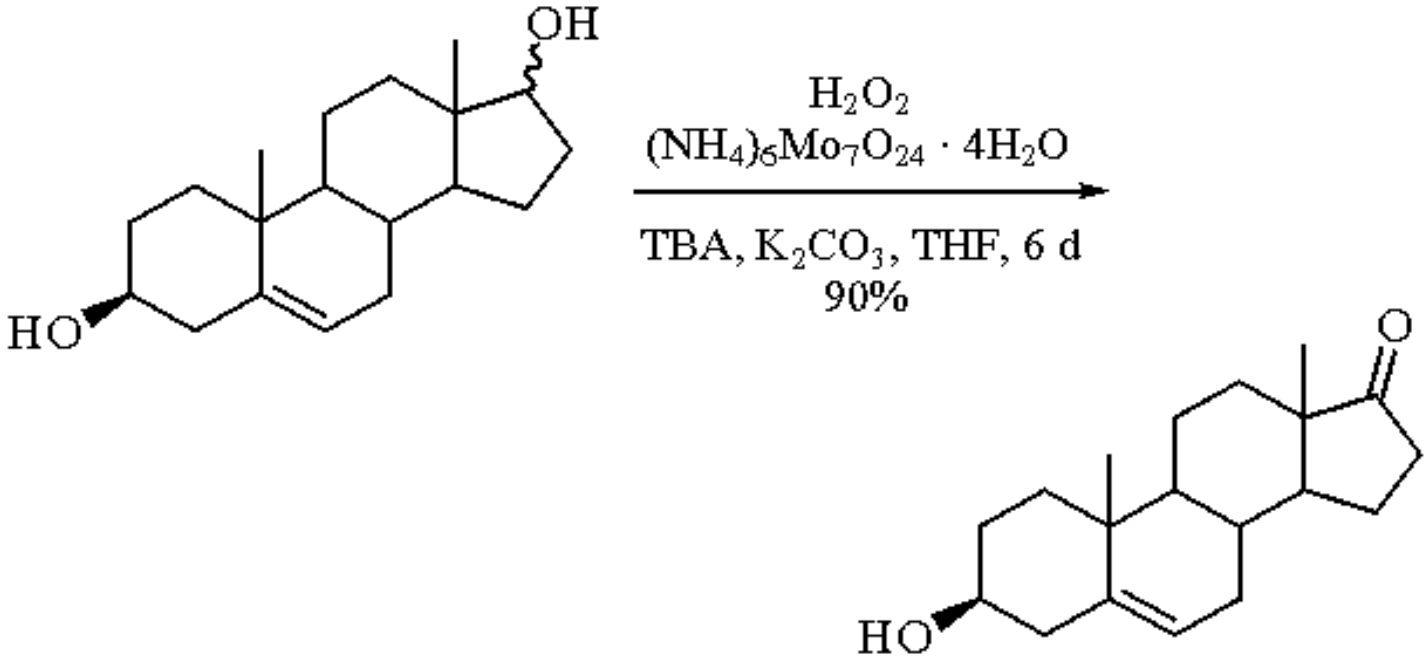

(5)

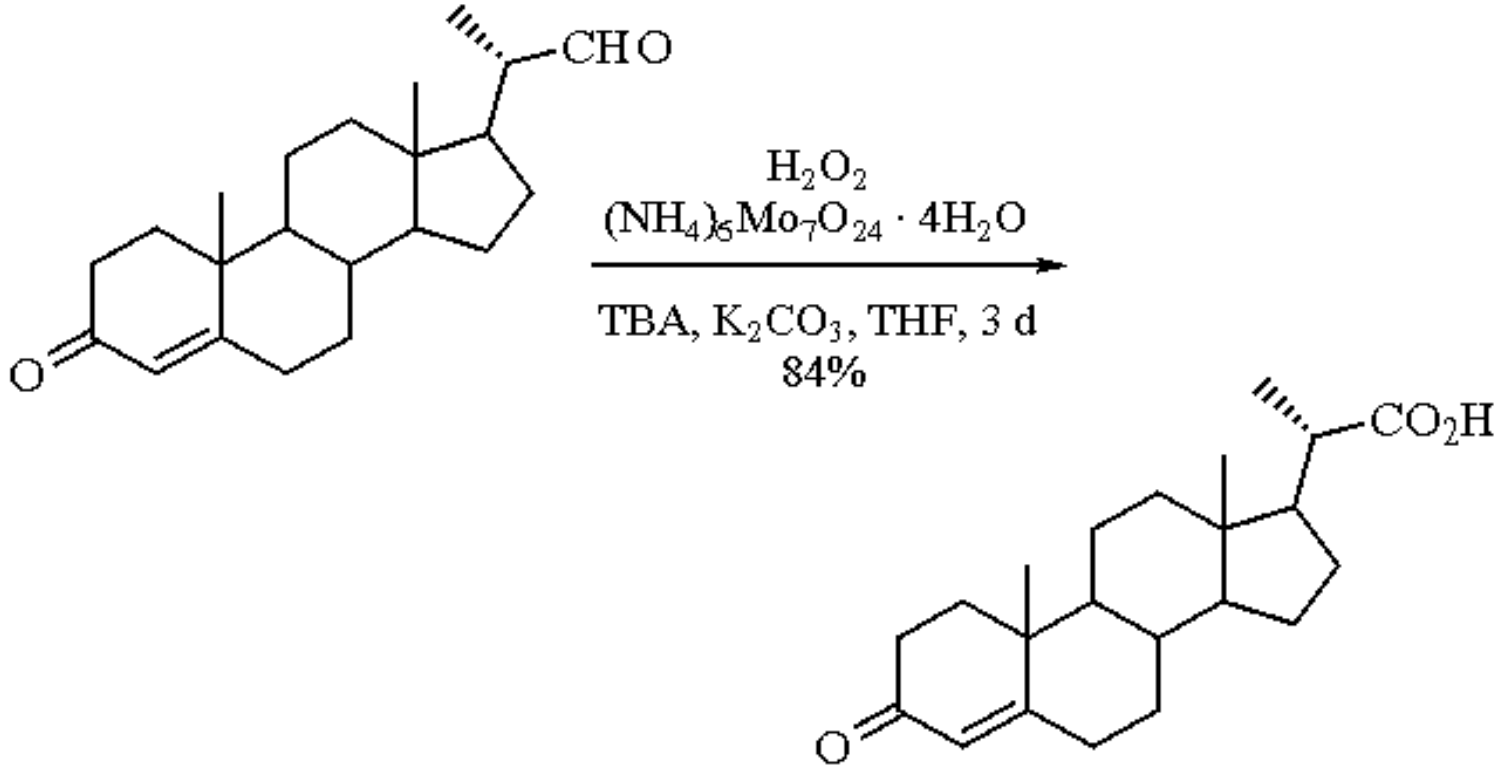

(6)

Chemoselection Between the Epoxidation and the Alcohol Oxidation.

By controlling pH, the chemoselectivity of the oxidation of unsaturated alcohols can be directed to produce either epoxides or ketones.[2] In the absence of potassium carbonate, epoxidation is observed, while in the presence of this base oxidation takes place preferentially (eq 7).[4]

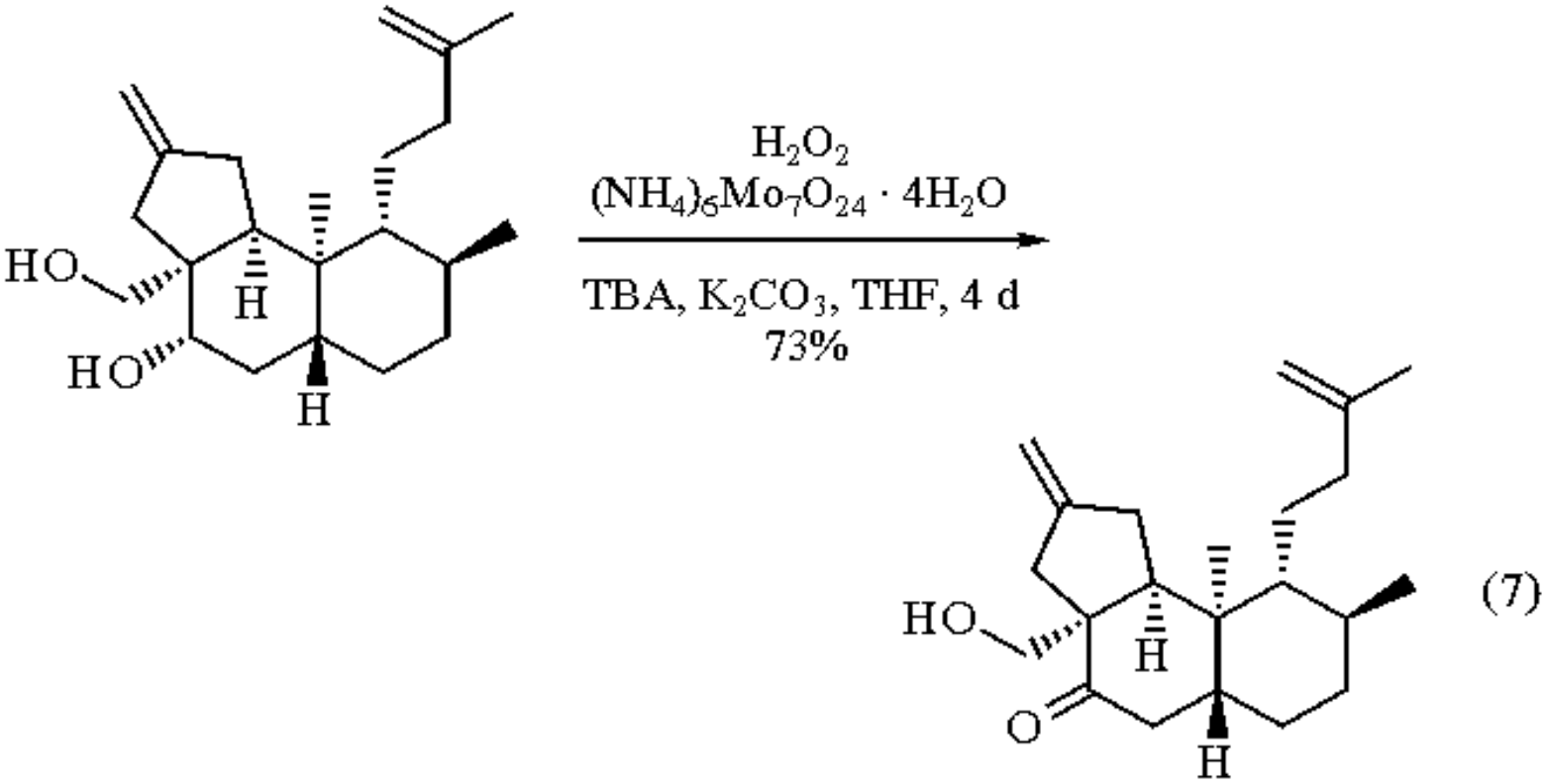

(7)

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Hydrogen Peroxide-Boron Trifluoride[1]

H_2O_2-BF_3.Et_2O

(H_2O_2)

[7722-84-1] · H_2O_2 · Hydrogen Peroxide-Boron Trifluoride · (MW 34.02) (BF_3)

[7637-07-2] · BF_3 · Hydrogen Peroxide-Boron Trifluoride · (MW 67.81) (BF_3.Et_2O)

[109-63-7] · $C_4H_{10}BF_3O$ · Hydrogen Peroxide-Boron Trifluoride · (MW 141.95)

(strong oxidant for the Baeyer-Villiger oxidation of ketones to esters;[2] promotes the benzylic hydroperoxide rearrangement of secondary and tertiary benzylic alcohols;[3] with hydrogen fluoride is a regioselective hydroxylating agent for aromatic rings[4])

Physical Data: BF_3: mp -127 °C; bp -100 °C; *d* 1.57 g cm^{-3}. BF_3.Et_2O: mp -58 °C; bp 126 °C; *d* 1.154 g cm^{-3}.

Form Supplied in: BF_3 is available as a gas packaged in lecture bottles; BF_3.Et_2O is available as a liquid.

Handling, Storage, and Precautions: in all peroxide oxidations of new compounds one must consider the possibility of explosive reactions. BF_3 and its etherate are highly toxic, corrosive to skin, and inhalation should be avoided. Use in a fume hood. See ***Boron Trifluoride Etherate***, ***Boron Trifluoride***, and ***Hydrogen Peroxide***.

Baeyer-Villiger Oxidations.

The difficult Baeyer-Villiger oxidation of straight-chain ketones,[5] which have only primary alkyl groups attached to carbonyl carbon, can be carried out rapidly at rt using a solution of 90% H_2O_2 in BF_3.Et_2O. Primary alkyl migrates in preference to methyl to form esters; some ester hydrolysis to form alcohol may occur.[2] The same oxidation is generally effected in better yield with ***Trifluoroperacetic Acid***, usually prepared using 90% H_2O_2,[5a,6] or with ***Bis(trimethylsilyl) Monoperoxysulfate***, a safer alternative prepared from 30% H_2O_2 (eq 1).[5a,7]

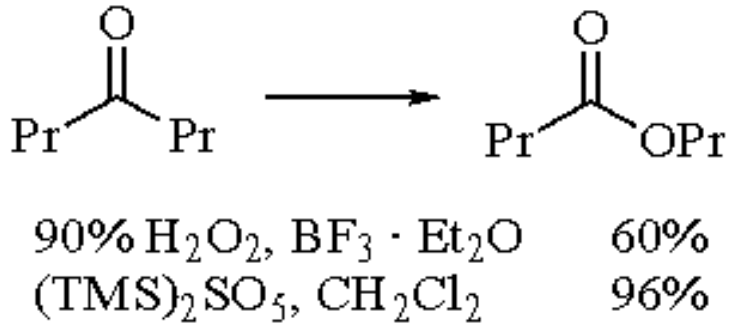

(1)

Benzylic Hydroperoxide Rearrangements.

Phenols can be prepared from benzylic secondary and tertiary alcohols by reaction with an aged preformed reagent from $BF_3.Et_2O$ and 90% H_2O_2. The reagent is especially suited for oxidation of substrates derived from hindered electron-rich acetophenones for which the Baeyer-Villiger oxidation is difficult. The reagent is especially useful for oxidation of molecules which have basic nitrogen in the benzylic alcohol substrate (eq 2).[3] Lewis acid coordination by BF_3 protects the amine function during the oxidation. The protic acid H_2SO_4 is less effective as a catalyst.

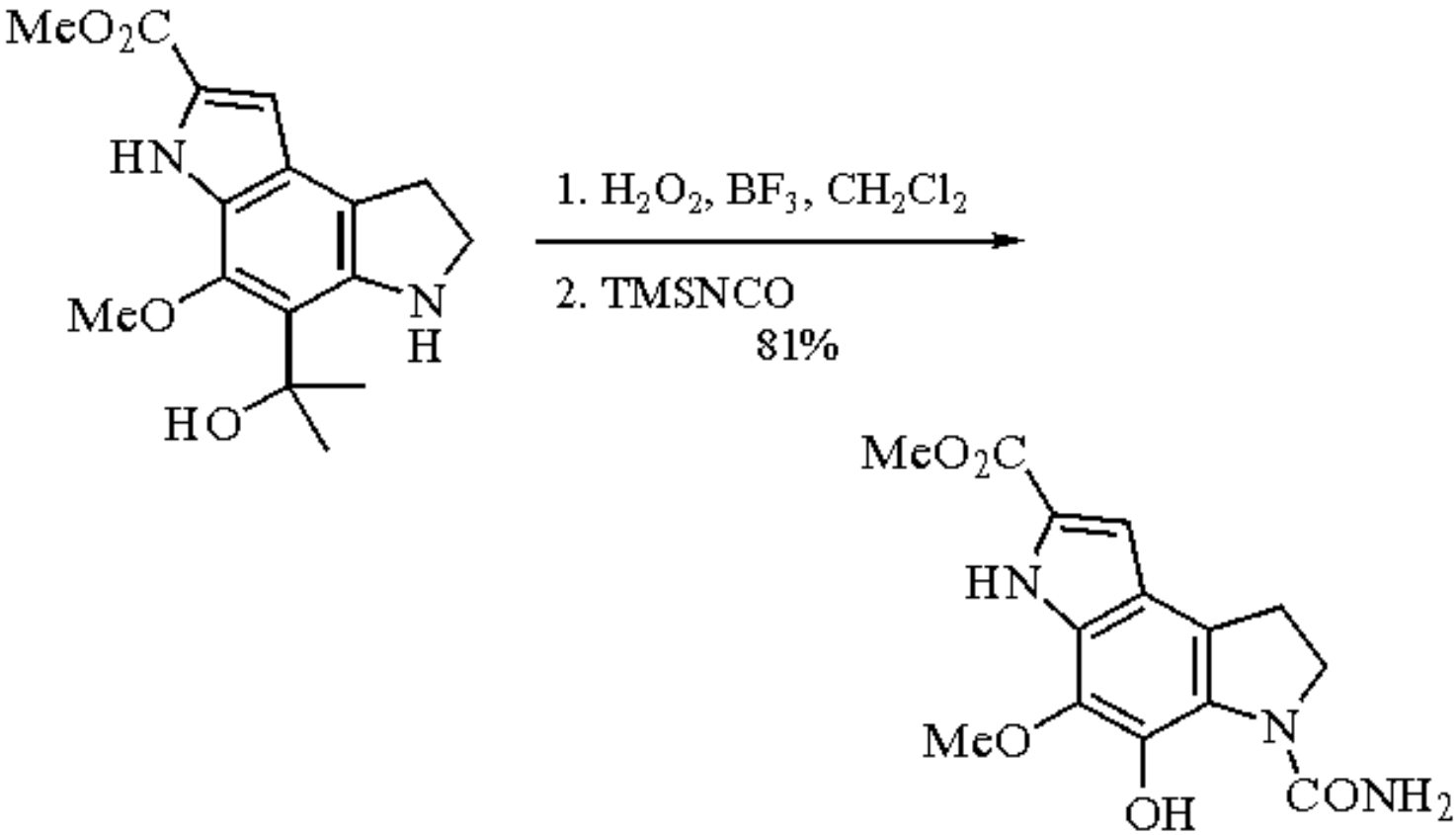

(2)

Selective Hydroxylations.

Regioselective hydroxylation of xylenes can be carried out directly in low yield with the $BF_3.Et_2O$-90% H_2O_2 reagent,[2] and in excellent yield with BF_3 and peroxytrifluoroacetic acid (the preparation of which requires 90% H_2O_2).[8] The safer reagent 30% H_2O_2 with superacidic HF/BF_3 cleanly converts benzene and alkylbenzenes into

monohydroxylated products.[4a] Oxidation of naphthalene with 90% H_2O_2 in HF/BF_3 superacid gives mainly 2-naphthol; in the absence of BF_3, 1-naphthol is formed (eq 3).[4b]

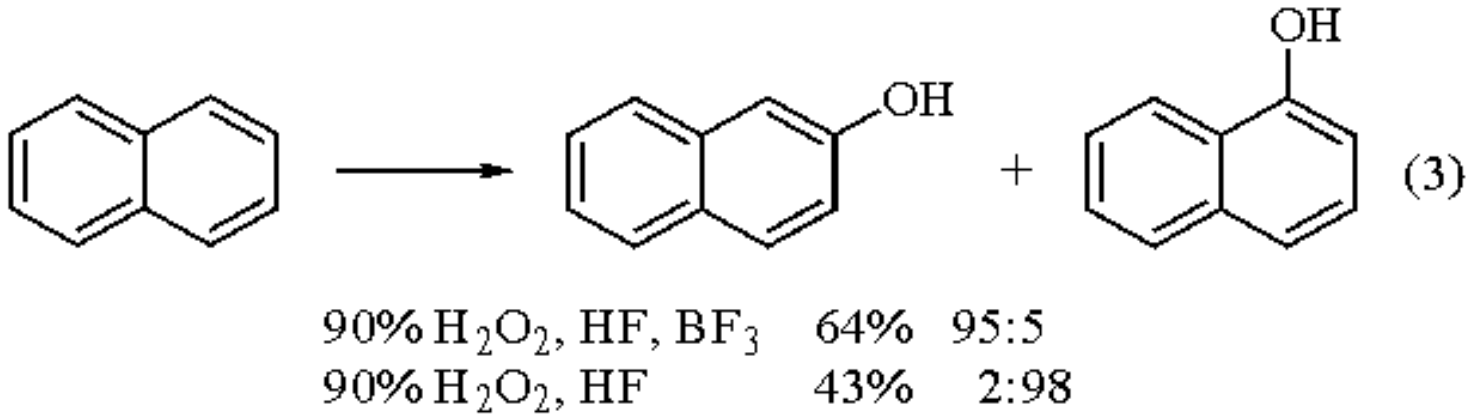

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Hydrogen Peroxide-Iron(II) Sulfate[1]

H_2O_2-$FeSO_4.7H_2O$

(H_2O_2)

[7722-84-1] · H_2O_2 · Hydrogen Peroxide-Iron(II) Sulfate · (MW 34.02) ($FeSO_4.7H_2O$)

[7782-63-0] · FeO_4S · Hydrogen Peroxide-Iron(II) Sulfate · (MW 278.06)

(reagent for generation of organic radicals which undergo dimerization, oxidative insertion, dehydrogenation and hydroxylation; oxo-iron species formed in situ lead to oxo-transfer reactions)

Alternate Name: Fenton reagent.

Physical Data: $FeSO_4.7H_2O$; *d* 1.89 g cm^{-3}; forms tetrahydrate at 56.6 °C and monohydrate at 65.0 °C; loses the last H_2O at about 300 °C.

Solubility: $FeSO_4.7H_2O$: sol H_2O, practically insol in alcohols.

Form Supplied in: $FeSO_4.7H_2O$: blue-green, monoclinic, orderless crystals or granules.

Handling, Storage, and Precautions: $FeSO_4.7H_2O$: oxidizes in moist air to form a basic iron(III) sulfate. Store in closed container. Wear rubber gloves when handling. See ***Hydrogen Peroxide*** and ***Iron(II) Sulfate***.

General.[1,2]

The Fenton reagent, a combination of hydrogen peroxide and iron(II) sulfate, has been known since the 1890s.[2] The mild oxidizing ability of H_2O_2 is considerably enhanced by Fe^{II} ion. The hydroxyl radical generated by the decomposition of H_2O_2 in the presence of Fe^{II} can produce organic radicals (eq 1) which undergo a variety of organic transformations, such as dimerization,[3,4] oxidative insertion,[5] hydroxylation,[6] and dehydrogenation.[7] Since the attack of HO&bdot; on aliphatic compounds is not highly selective, isomeric products are obtained in these reactions except in cases where symmetric reactants containing only equivalent hydrogen atoms are used.

$$Fe^{II} + H_2O_2 \longrightarrow Fe^{III} + OH^- + HO\cdot \qquad (1)$$

Fe^{II} and Fe^{III} ions in solution can be further oxidized by HO&bdot; to form Fe^{IV}=O or Fe^{V}=O species (eq 2).[1c,8] The

high oxidation state of Fe^{IV}=O (or Fe^{V}=O) leads to some interesting oxo-transfer reactions.[9,10]

$$Fe^{III} + HO\cdot \longrightarrow Fe^{IV}{=}O + H^{+} \qquad (2)$$

Synthetic Applications.

2,5-Dimethyl-2,5-hexanediol is produced in 40-46% isolated yield by oxidative dimerization of *t*-butyl alcohol using Fenton reagent with 1 equiv of $FeSO_4.7H_2O$ (eq 3).[3] Analogous oxidative coupling has been accomplished with certain saturated lower, straight- and branched-chain aliphatic carboxylic acids, nitriles, amides, amines, alcohols, and ketones.[4]

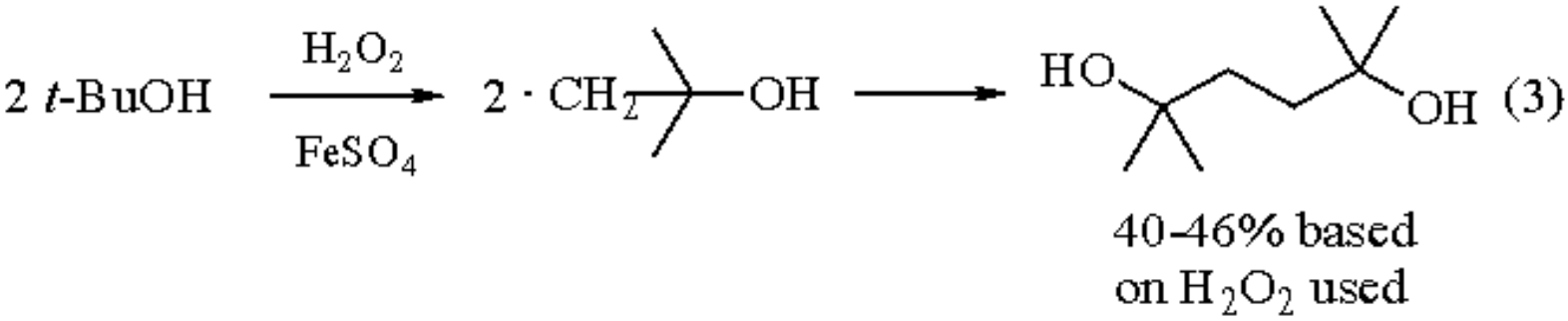

Hydrocarbon derivatives can be converted to the corresponding carboxylic acids in low yields by Fenton reagents and carbon monoxide.[5]

Dehydrogenation of 2-amino-3,4-dihydroquinoxaline to 2-aminoquinoxaline is effected smoothly by H_2O_2 in the presence of trace amounts of Fe^{II} ions (eq 4).[6] The reaction does not proceed without using the iron(II) catalyst. The procedure appears to be general and has been successfully applied to the synthesis of a number of alkyl-, halo-, and hydroxy-substituted 2-aminoquinoxalines.[6]

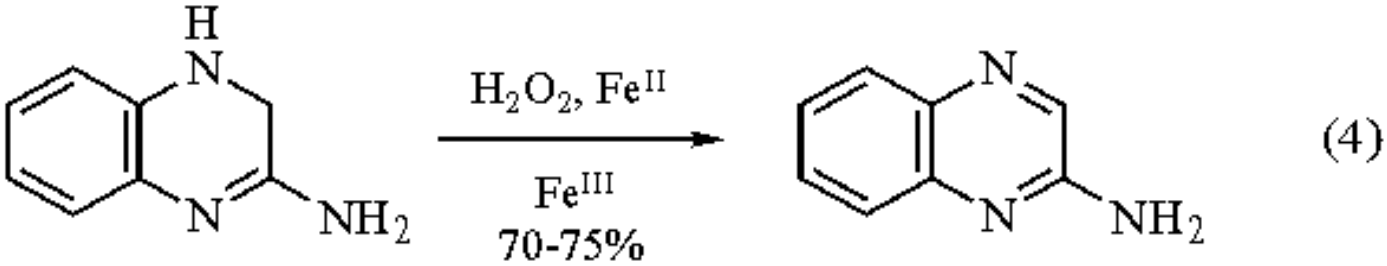

The Fenton reagent has also been employed to hydroxylate aromatic rings (eq 5).[7] However, the yields are usually low, primarily due to the formation of biaryl products. The efficiency of this reaction is highly dependent on the concentrations of Fe^{II} and Fe^{III} ions[7] and can be improved by using phase-transfer catalysts.[11]

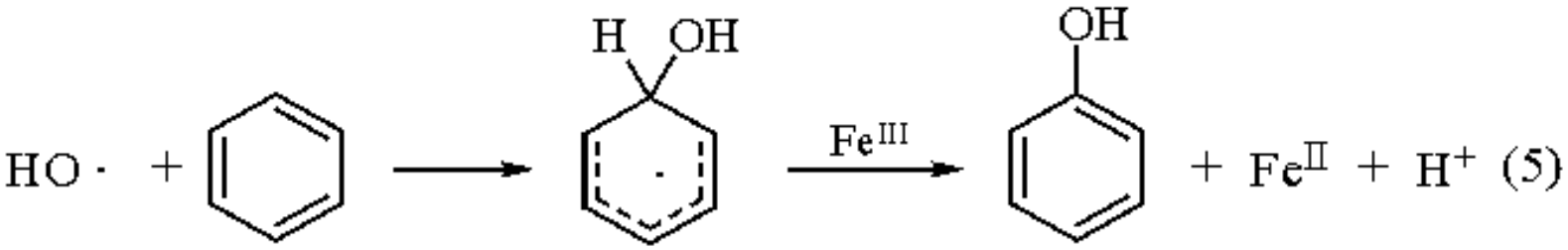

90% Stereoselectivity and 71% yield have been achieved in the synthesis of *cis*-1,3-cyclohexanediol by the reaction of cyclohexanol with Fenton reagent. A Fe^{IV}=O intermediate was proposed to account for the results.[9]

Oxidation of cholesterol with Fenton reagent in acetic acid gave dihydroxylation products as shown in eq 6.[10] Evidently 5α,6α-epoxycholestan-3β-ol was formed via an oxo-transfer process in the early stages, and the subsequent epoxide opening by solvents provided *trans*-diol derivatives.

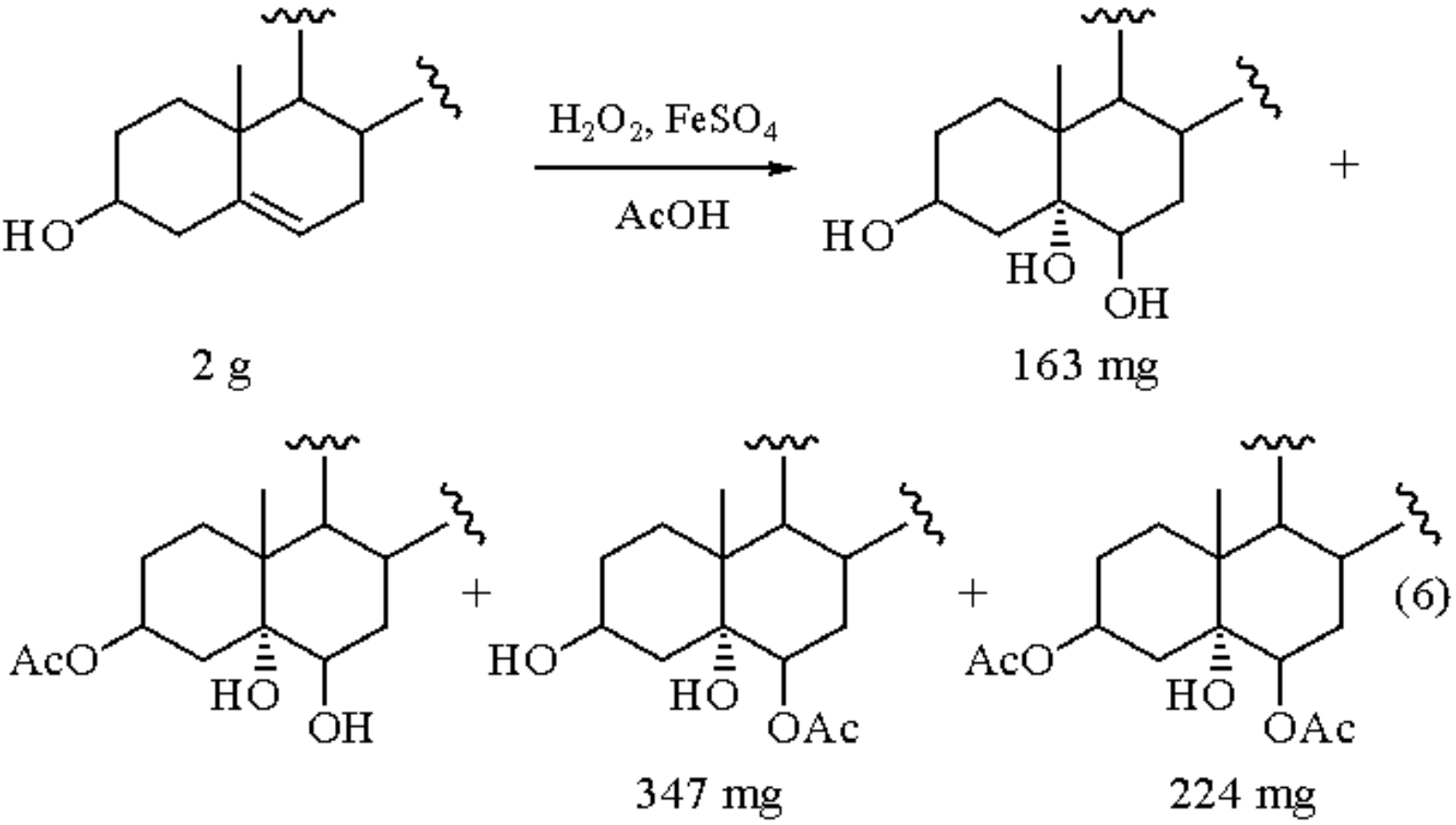

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Hydrogen Peroxide-Tellurium Dioxide[1]

H_2O_2-TeO_2

(H_2O_2)

[7722-84-1] · H_2O_2 · Hydrogen Peroxide-Tellurium Dioxide · (MW 34.02) (TeO_2)

[7446-07-3] · O_2Te · Hydrogen Peroxide-Tellurium Dioxide · (MW 159.60)

(selective oxidizing agent for conversion of sulfides to sulfoxides[1])

Handling, Storage, and Precautions: see ***Hydrogen Peroxide***. A mixture of 30% H_2O_2 (2.4 mL, 24 mmol) and TeO_2 (0.032 g, 2.0 mmol) or TeO_2 (0.32 g, 20 mmol) in methanol (10 mL) can be stored in a refrigerator for a prolonged time without loss of reactivity. For the oxidation of sulfides to sulfoxides, better results are obtained when hydrogen peroxide is added slowly to the mixture of the sulfide and tellurium dioxide in methanol. These operations should be conducted in an efficient fume hood.

Selective Oxidation of Sulfides.

The hydrogen peroxide-tellurium dioxide system is a remarkably selective agent for the oxidation of sulfides to sulfoxides. Sulfides are transformed into sulfoxides in high yields by treatment with hydrogen peroxide in the presence of a catalytic amount of tellurium dioxide at rt. Sometimes a small amount of over-oxidation product, the corresponding sulfone, is produced. This over-oxidation can be suppressed by slow addition of aqueous 30% hydrogen peroxide solution to a mixture of the sulfide substrate and tellurium dioxide in methanol. Even with 1 equiv of TeO_2, the resulting sulfoxide is not oxidized further to sulfone. Aromatic sulfides (eq 1) as well as aliphatic sulfides (eq 2) are transformed to sulfoxides in high yield.

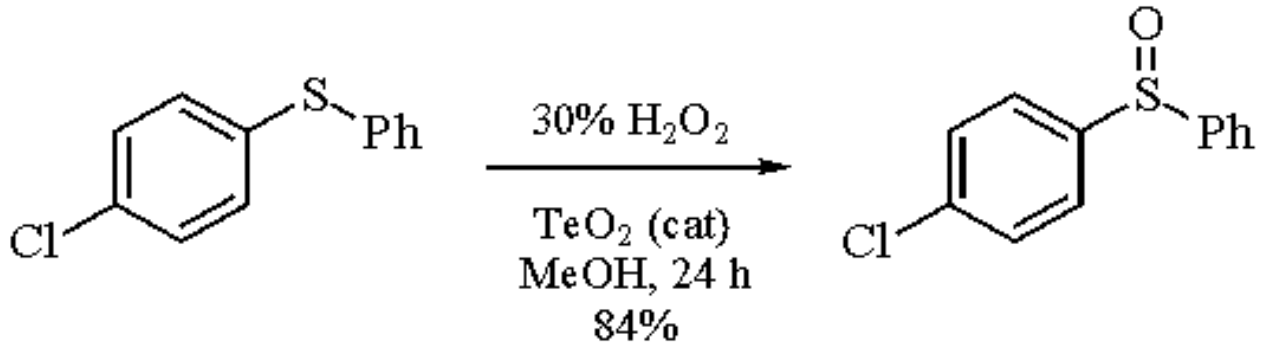

(1)

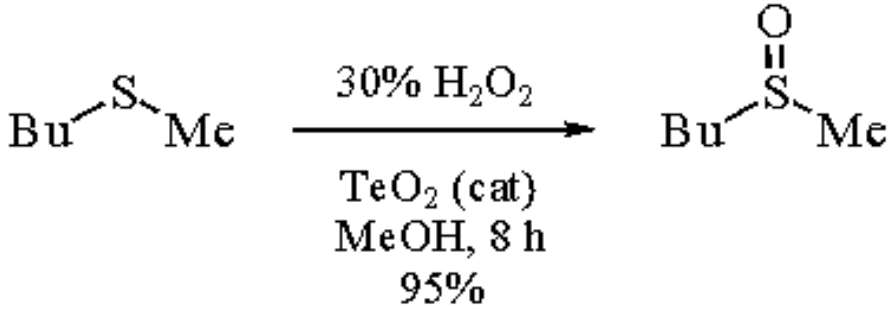

(2)

Usually, the oxidation of aliphatic sulfides proceeds in better yield and requires shorter reaction times than that of aromatic derivatives. Chemoselective oxidation of a sulfide group by the H_2O_2-TeO_2 system in the presence of a double bond can be achieved (eq 3). Thus, to a mixture of crotyl phenyl sulfide (0.165 g, 1.00 mmol) and tellurium dioxide (0.016 g, 0.10 mmol) in methanol (2.0 mL), aqueous 30% hydrogen peroxide solution (0.136 g, 1.20 mmol) is added slowly at rt. After stirring at rt for 24 h, the reaction mixture is partitioned between methylene chloride and water. The product is purified by column chromatography.

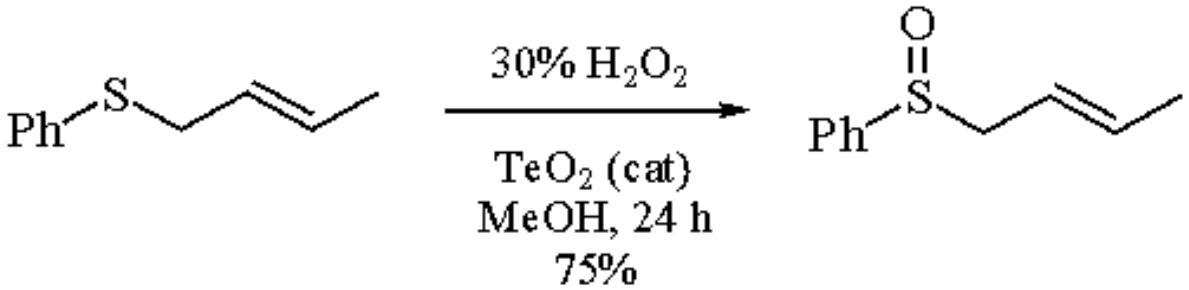

(3)

One problem with the catalytic TeO_2-H_2O_2 system is that the reaction time is relatively long. While the use of a stoichiometric amount of tellurium dioxide considerably shortens the reaction time, the addition of a small amount of concentrated HCl (1/100 molar ratio of sulfide) drastically accelerates the oxidation of sulfide (eq 4).

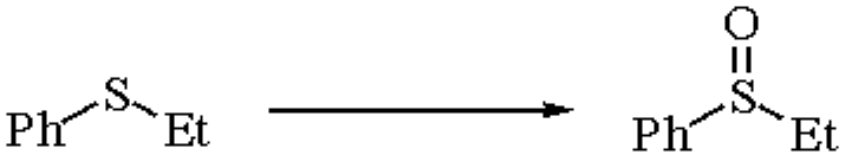

(4)

TeO_2 (cat), H_2O_2, MeOH, 12 h	90%
TeO_2 (1 equiv), H_2O_2, MeOH, 8 h	90%
TeO_2 (cat), H_2O_2, conc HCl (trace), MeOH, 2 h	92%

The effect of concentrated HCl is especially pronounced in the oxidation of a carbohydrate sulfide; this substrate is not oxidized by 1 equiv of the TeO_2-H_2O_2 system after prolonged reaction time, but is oxidized to the sulfoxide in high yield in 2 h by using the catalytic TeO_2-H_2O_2-HCl system (eq 5). It is also noteworthy that the acid-labile isopropylidene group in the carbohydrate sulfide is not affected by the TeO_2-H_2O_2-HCl system. Also the carbonyl group in keto sulfides is not affected by the H_2O_2-TeO_2-HCl system (eqs 5 and 6).

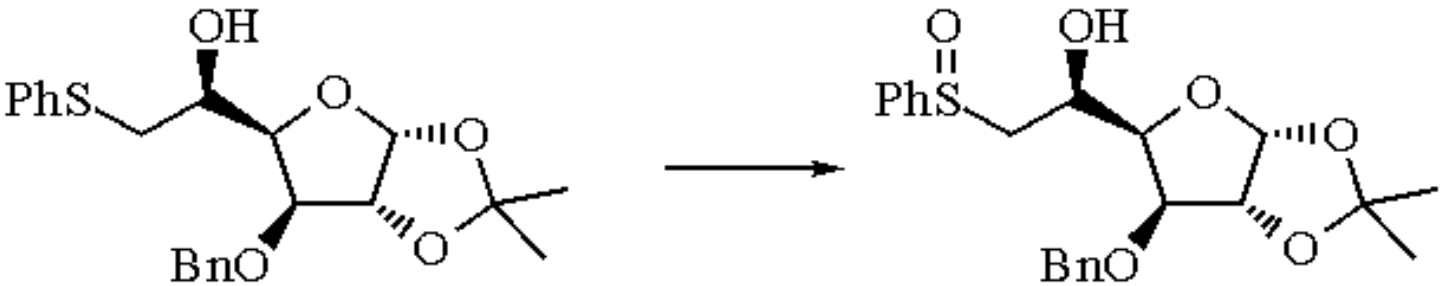

(5)

TeO_2 (1 equiv), H_2O_2, MeOH, 3 days — No reaction

TeO_2 (cat), H_2O_2, conc HCl (trace), MeOH, 2 h — 83%

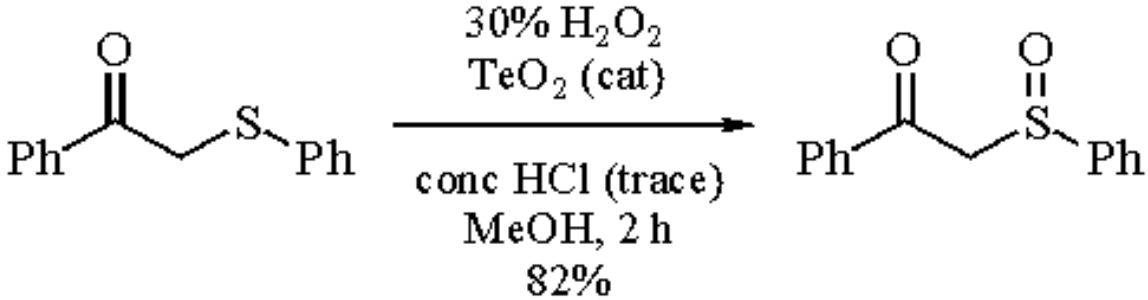

(6)

The reaction of benzaldehyde, geraniol, or ethylene glycol with H_2O_2-TeO_2 leads mainly to recovery of the starting material. In this regard, the TeO_2-H_2O_2 system appears to be superior to widely used reagents such as hydrogen peroxide, peroxy acids, and periodates, which sometimes cause over-oxidation or affect other functional groups.[2] Other recently reported oxidizing agents such as ruthenium porphyrin with heteroaromatic *N*-oxide,[3] $(Ph_4P)[RuO_2(OAc)Cl_2]$ with ***N-Methylmorpholine N-Oxide***,[4] sulfonimidoyl chloride with superoxide,[5] and ***Benzyltrimethylammonium Tribromide***[6] have similar drawbacks.

Oxidizing systems related to the H_2O_2-TeO_2 system include the H_2O_2-SeO_2 system and the H_2O_2-RSO_2H system. Sulfides are selectively oxidized to sulfoxides by treatment with H_2O_2 in methanol containing a catalytic amount of the sulfinic acid,[2a] and the H_2O_2-SeO_2 system is known to be an efficient and chemoselective agent for oxidation of sulfides to sulfones[7] and a selective oxidizing agent for sulfides to sulfoxides in certain cases.[8]

The true oxidizing species in the H_2O_2-TeO_2 system is likely to be peroxytellenious acid (H_2TeO_4), which will be reduced back to H_2TeO_3 and quickly regenerated by H_2O_2 during the reaction in the catalytic cycle shown in eqs 7-9.

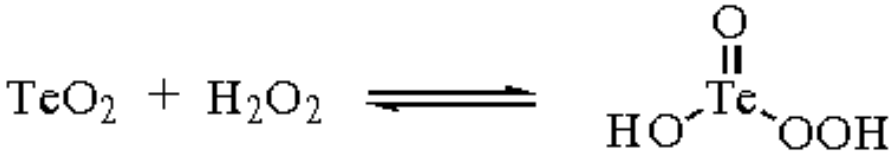

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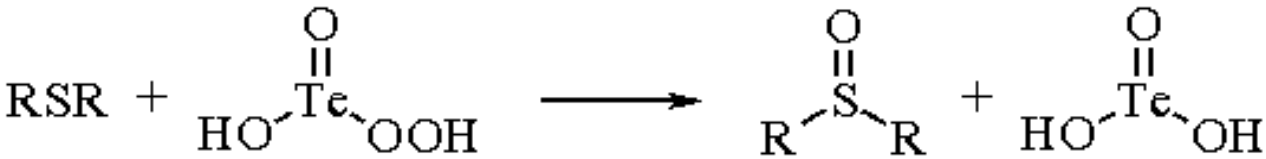

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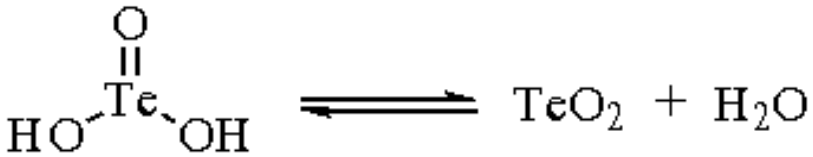

(9)

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Hydrogen Peroxide-Tungstic Acid

H_2O_2-H_2WO_4

(H_2O_2)

[7722-84-1] · H_2O_2 · Hydrogen Peroxide-Tungstic Acid · (MW 34.02) (H_2WO_4)

[7783-03-1] · H_2O_4W · Hydrogen Peroxide-Tungstic Acid · (MW 249.87)

(oxidation of alkenes,[1] alkynes,[15] and other organic substrates[18 -22])

Physical Data: H_2WO_4: *d* 5.500 g cm^{-3}.

Solubility: H_2WO_4: insol cold H_2O; slightly sol hot H_2O.

Form Supplied in: H_2WO_4: yellow powder; widely available.

Handling, Storage, and Precautions: see ***Hydrogen Peroxide***. All operations involving peroxides should be conducted behind a safety shield in a fume cupboard. It is also advisable, prior to work-up, to analyze the reaction mixture for peroxy compounds. These should be destroyed or removed before evaporation of the solvent.

Epoxidation of Alkenes.

Tungstic acid catalyzes the oxidation by hydrogen peroxide of alkenes to the corresponding epoxides.[1] As tungstic acid is a fairly strong acid, the reaction mixture requires buffering to prevent subsequent diol formation. Typical conditions are: tungstic acid 1 mol %, sodium acetate 2-3 mol % (pH 4.5), 35% hydrogen peroxide 1.5 mol % at rt.[2] Under these conditions the epoxidation occurs with complete retention of configuration for both *cis*- and *trans*-alkenes (eq 1). Reactivity increases with nucleophilicity of the double bond. Coordination to the catalyst by hydroxy groups in the substrate also enhances the rate of epoxidation, with allylic alcohols reacting faster than homoallylic alcohols,[3] and isolated alkenes being least reactive (eq 2). Dienols can be selectively epoxidized at the allylic position (eq 3).[4] Conjugated unsaturated acids and even diacids are epoxidized using sodium tungstate and hydrogen peroxide in water at 60-65 °C, with the pH controlled to within 5.8-6.8.[5] The use of pertungstate, $W_2O_{11}^{2-}$, generated from tungstic acid and benzyltriphenylphosphonium chloride, $Ph_3PCH_2Ph^+$ Cl^-, allows unbuffered conditions to be employed (eq 4).[6] The catalyst can be prepared in situ or preformed and stored for a long time. Other epoxidation methods include: sodium tungstate in a two-phase system of phosphate buffer/dichloromethane,[7] and a complex of tungstic acid and tributyltin chloride supported on charcoal.[8] See also ***m-Chloroperbenzoic Acid*** and ***Vanadyl Bis(acetylacetonate)***.

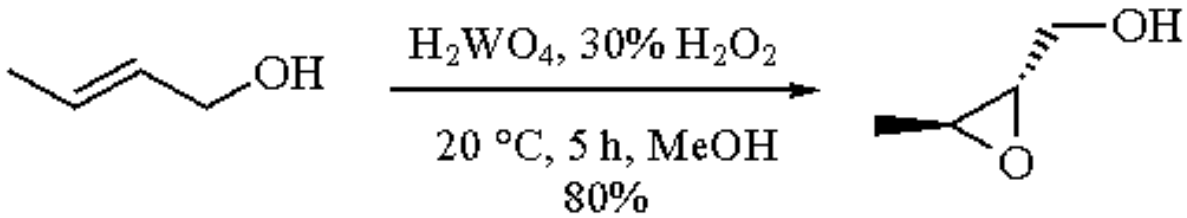

(1)

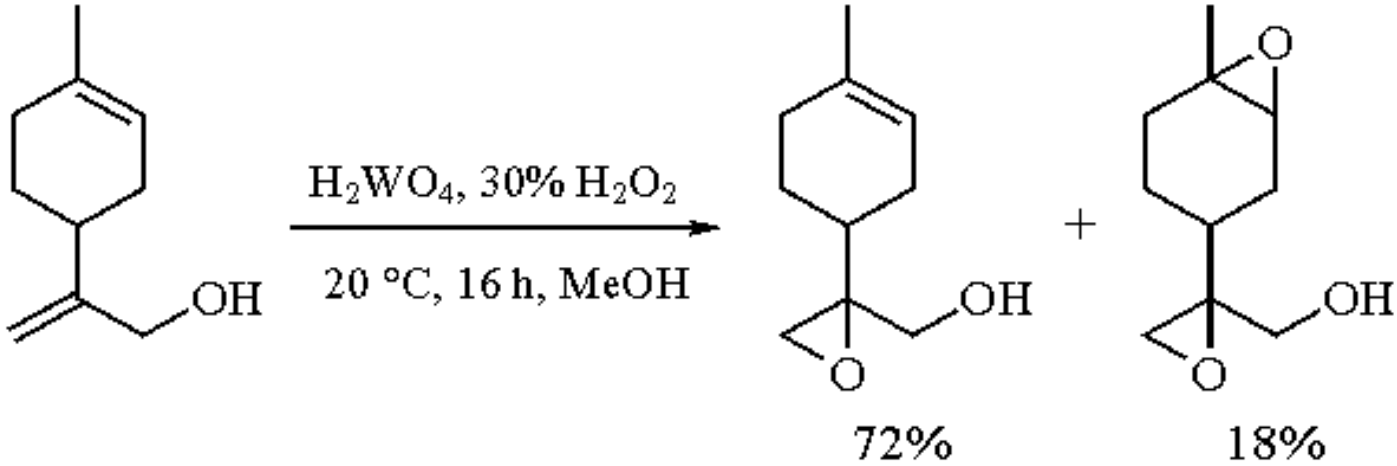

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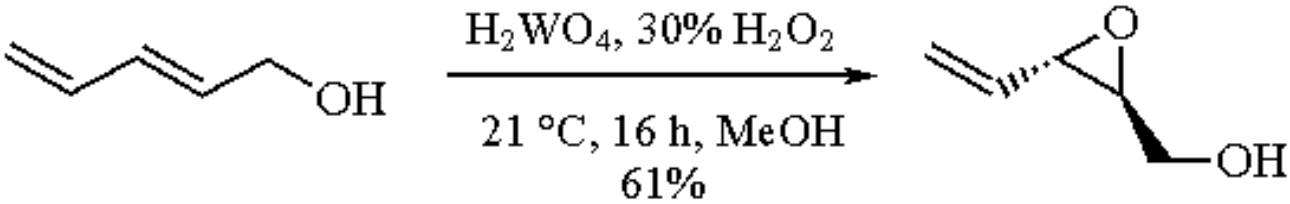

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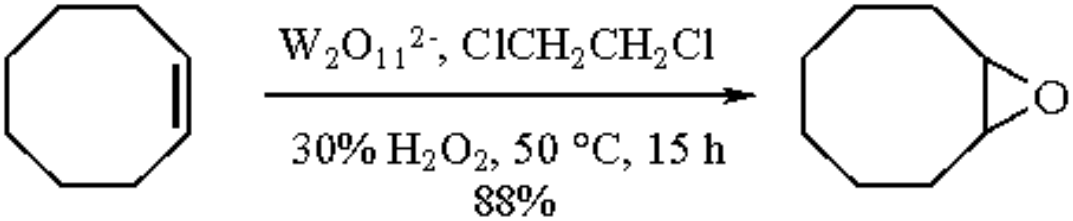

(4)

Diol Formation.

The oxidation of cyclooctadiene to the *trans*-diol has been effected using 30% hydrogen peroxide and a catalytic quantity of tungstic acid in *t*-butanol at 31 °C (eq 5);[9] however, similar conditions have also been used for the cleavage of cyclopentene to glutaraldehyde (eq 6).[10] More concentrated solutions of hydrogen peroxide have also been employed.[11] The use of 90% hydrogen peroxide in 2-propanol has been reported to yield cyclohexane-1,2-diol from cyclohexene. When methanol or ethanol are used as solvents the corresponding glycol monoethers are formed.[12] See also: ***Potassium Permanganate*** and ***Osmium Tetroxide***.

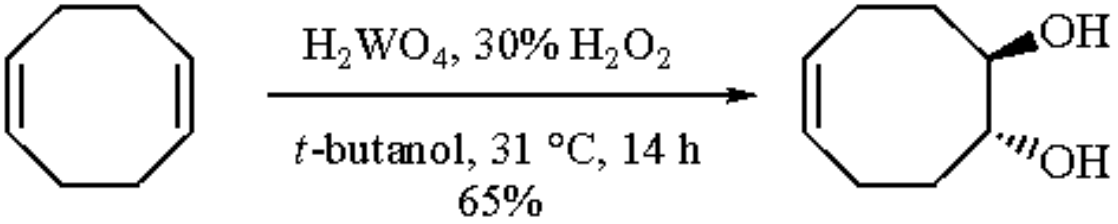

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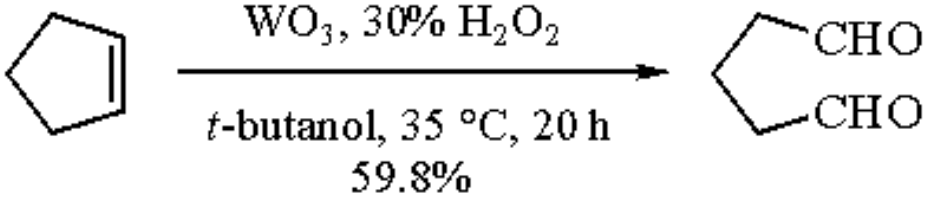

(6)

Carboxylic Acids.

Under the more forcing conditions of refluxing *t*-butanol, epoxidation followed by diol formation and oxidative alkene cleavage occurs. Using these conditions, cyclopentene gives glutaric acid (eq 7)[13] and 1-methyl-1-cyclohexene gives 2-oxoheptanoic acid (eq 8). Cyclohexanone has been oxidized to adipic acid in low yield.[14] See also: ***Sodium Periodate***.

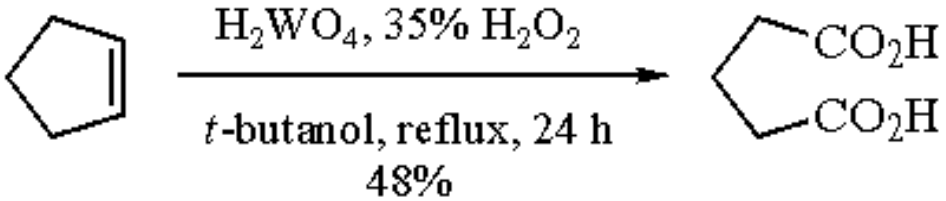

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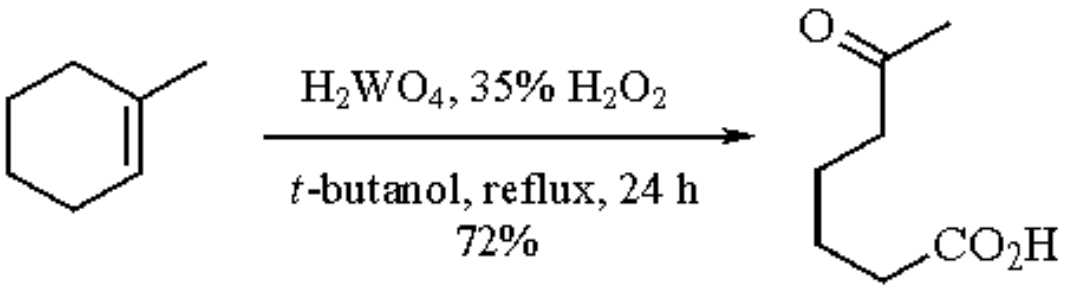

(8)

α-Hydroxy Ketones.

Treatment of 12-tungstophospholic acid with hydrogen peroxide and cetylpyridinium chloride in water gives peroxotungstophosphate, an efficient catalyst for the oxidation of internal alkynes to the corresponding α,β-epoxy ketone (eq 9).[15] The same catalyst will also oxidize *vic*-diols into α-hydroxy ketones (eq 10).[16] See also: ***Iodosylbenzene***.

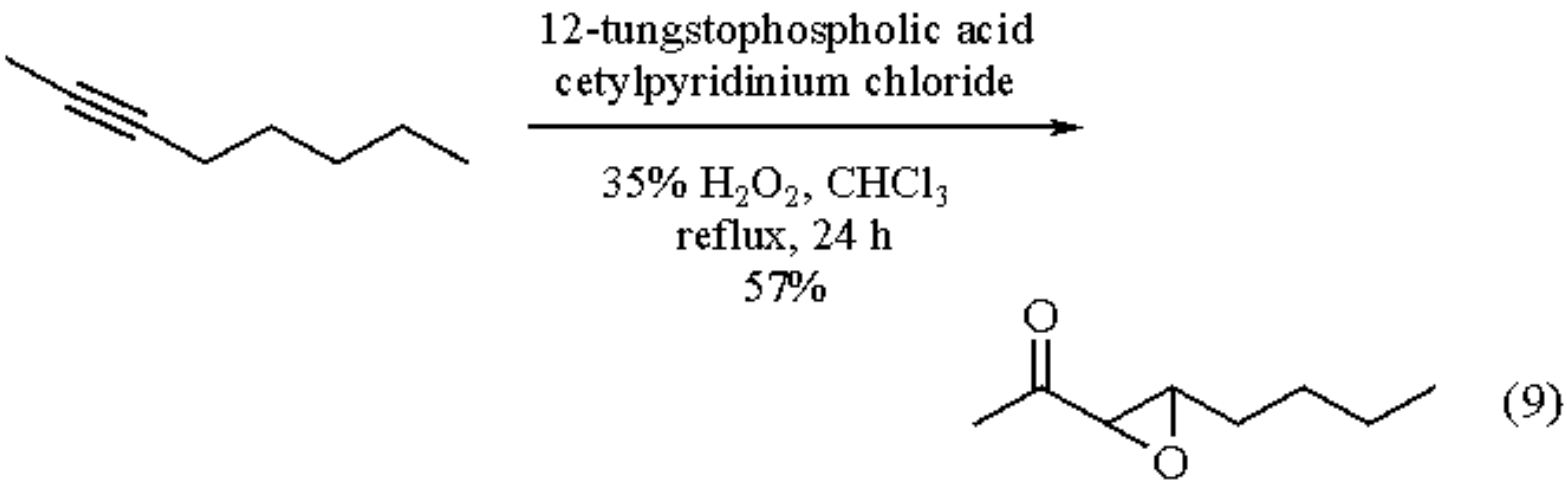

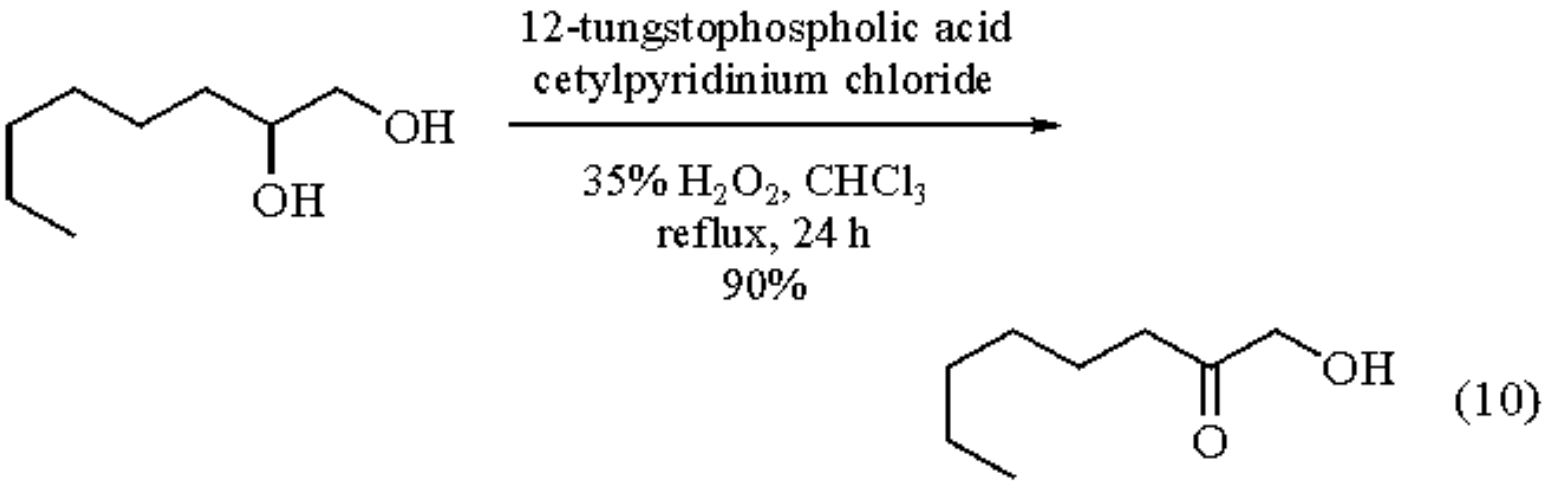

gem-Dihydroperoxides.

Reaction of acetals with hydrogen peroxide and tungstic acid in acetonitrile at low temperature gives the corresponding *gem*-dihydroperoxides (eq 11).[17]

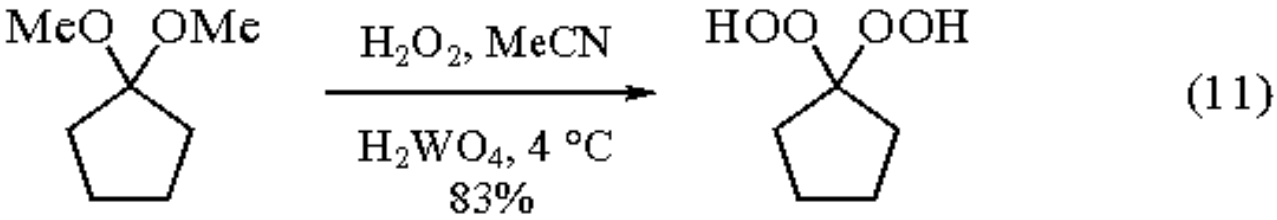

Other Oxidations.

Tungstic acid has been used to catalyze the oxidation by hydrogen peroxide of sulfides to the corresponding sulfones.[18] Various amines have also been oxidized to the corresponding oximes,[19] nitrones,[20] hydroxamic acids,[21] and nitroso compounds.[22]

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Hydrogen Peroxide-Urea[1]

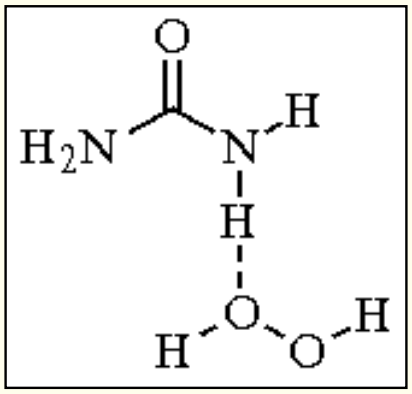

[124-43-6] · $CH_6N_2O_3$ · Hydrogen Peroxide-Urea · (MW 94.09)

(alternative to 90% hydrogen peroxide as a source of anhydrous hydrogen peroxide for use in oxidation reactions)

Alternate Name: UHP.

Physical Data: mp 84-86 °C (dec).[2]

Solubility: sol water and alcohols; low solubility in organic solvents such as dichloromethane.

Form Supplied in: white crystalline powder with urea as impurity; commercially available. *Drying:* over calcium chloride in a desiccator.

Preparative Method: made by the recrystallization of ***Urea*** from aqueous ***Hydrogen Peroxide***

Handling, Storage, and Precautions: the pure material should be stored at low temperature but the commericial material, which has a purity of ca. 90%, may be stored at rt. In a sufficiently forcing test, it can be made to explode; its decomposition is acceleratory above 82 °C. Conduct work with this reagent in an efficient fume hood behind a polycarbonate safety screen.

Epoxidation Reactions.

The hydrogen peroxide-urea complex, which is normally known as urea-hydrogen peroxide (UHP), has been used in anhydrous organic solvents in combination with a number of carboxylic anhydrides together with disodium hydrogen phosphate for the epoxidation of a wide range of alkenes. The carboxylic anhydride of choice depends on the electron density in the double bond.[3] With electron-rich alkenes such as α-methylstyrene and α-pinene (eq 1), good yields of

the expected products can be obtained by using ***Acetic Anhydride***. Other anhydrides have also been used; for example, the epoxide from *trans*-stilbene is obtained in 80% yield using ***Maleic Anhydride***.[4] Monoperoxymaleic acid, prepared by the reaction of maleic anhydride with 90% aqueous hydrogen peroxide, is more reactive than other common peroxy acids with the exception of ***Trifluoroperacetic Acid***.[5] With relatively nonnucleophilic and nonvolatile terminal alkenes such as 1-octene, a good yield of the epoxide can be obtained by substituting ***Trifluoroacetic Anhydride*** for the acetic anhydride (eq 2). The addition of ***Imidazole*** increases the rate at which epoxidation reactions proceed when using UHP and acetic anhydride.[6] Presumably *N*-acetylimidazole is formed and rapidly perhydrolyzed. A comparison of the diastereoselective epoxidations of a steroidal allylic alcohol has been carried out using a range of peroxy acids, including peracetic acid generated by the interaction of acetic anhydride with UHP.[7]

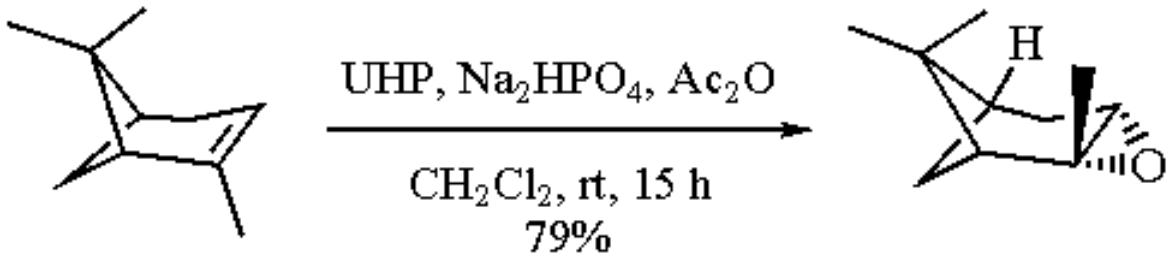

(1)

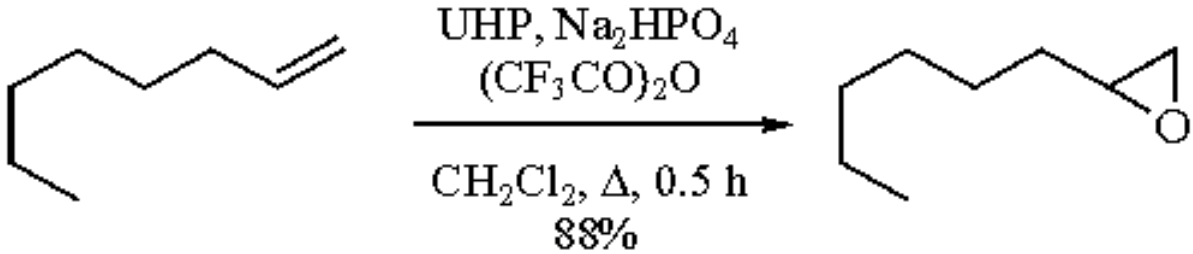

(2)

The epoxidation of electron-deficient alkenes like methyl methacrylate can also be achieved using the trifluoroacetic anhydride method. In the case of α,β-unsaturated ketones such as isophorone (eq 3) and nitro alkenes such as β-methyl-β-nitrostyrene (eq 4), alkaline hydrogen peroxide has been generated from UHP.

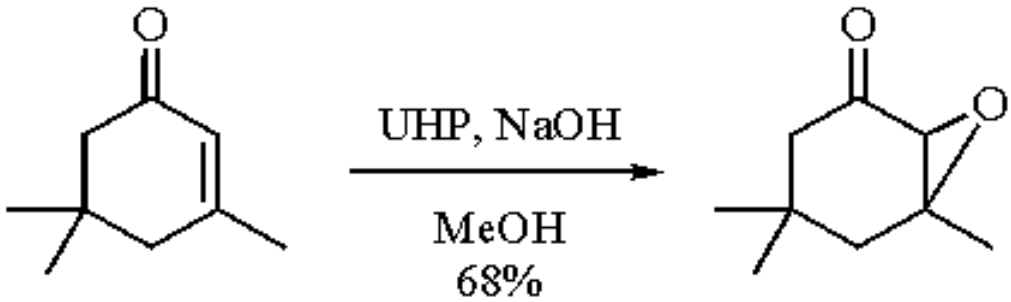

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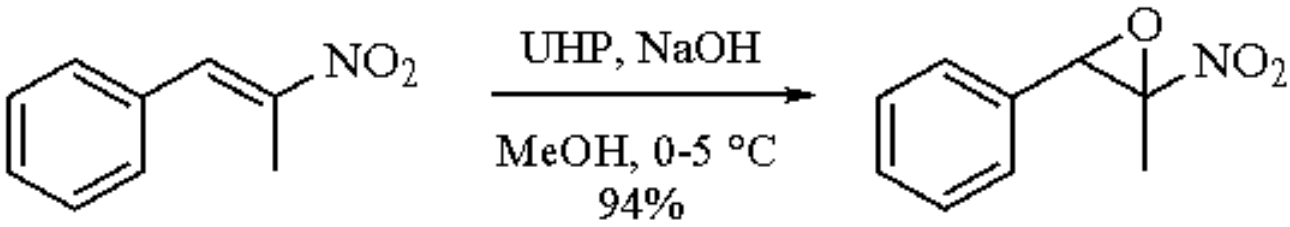

(4)

The selective epoxidation of compounds such as α-ionone can also be achieved. The result of an epoxidation reaction frequently depends on the reagent and precise reaction conditions. This is exemplified in the reactions shown in eq 5. When using peroxytrifluoroacetic acid generated conventionally, water that is always present diverts the reaction exclusively to the hemiacetal (**1**). However, when using the UHP method, the spiroacetal (**2**) predominates over the other product.[8]

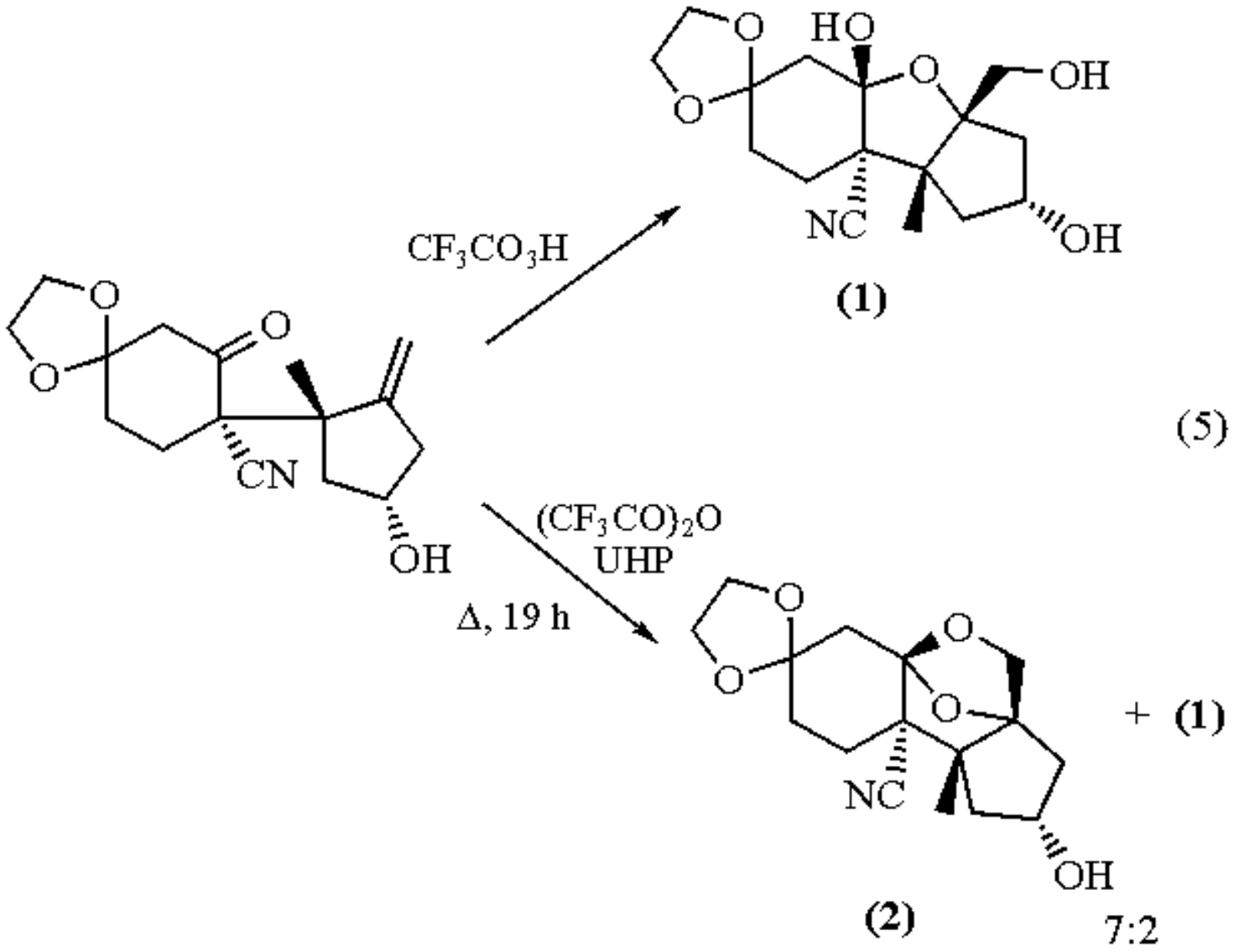

Baeyer-Villiger and Related Reactions.

The oxidation of aldehydes and ketones to afford esters and lactones can be achieved using a variety of peroxycarboxylic acids. The ease with which the reaction occurs is related to the strength of the conjugate acid of the leaving group and so the stronger the carboxylic acid the more powerful is the peroxy acid in its oxidation reactions. Reactions involving ketones are frequently slow when using weakly acidic peroxy acids and so the majority of the reactions using UHP have been carried out with trifluoroacetic anhydride as the coreactant (eqs 6-8).

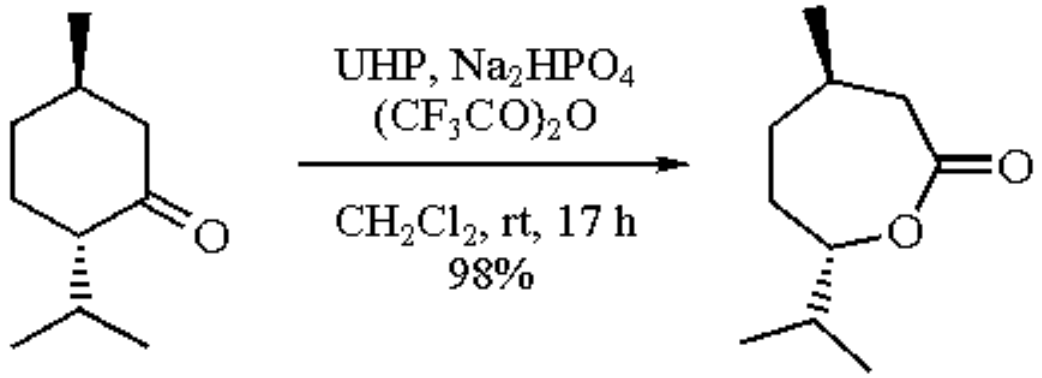

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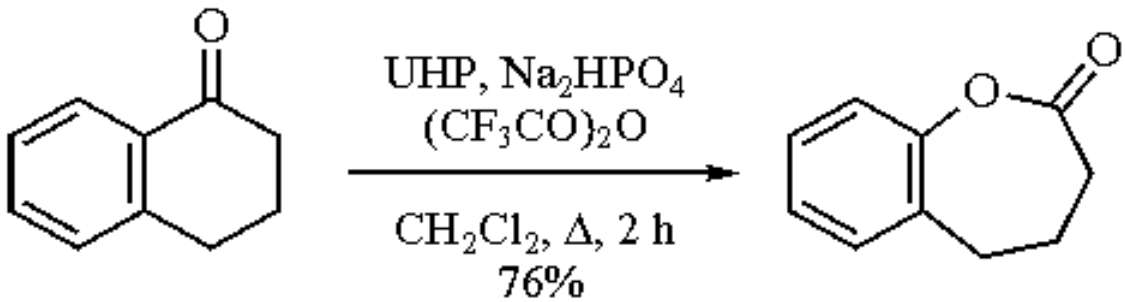

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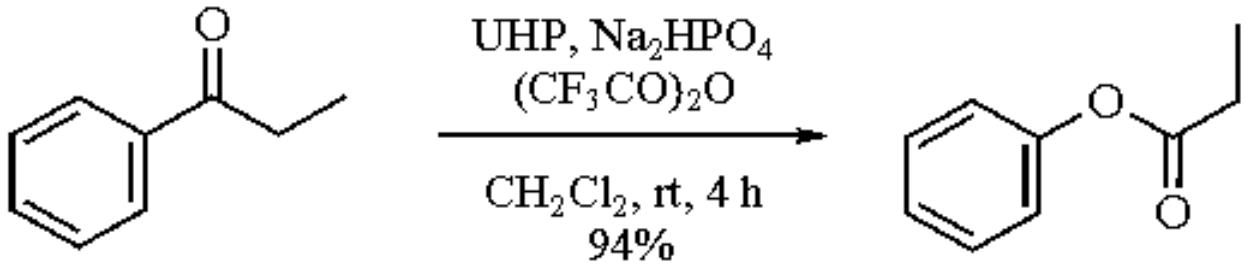

(8)

Dakin reactions, where an aromatic aldehyde has an electron releasing substituent either *ortho* or *para* to the formyl group, can be carried out using UHP-acetic anhydride as shown in eq 9. In the absence of suitable activating substituents, hydrogen migration occurs in place of aryl migration and the product is then a carboxylic acid (eq 10). This is a potentially valuable way of converting a formyl group into a carboxyl group.

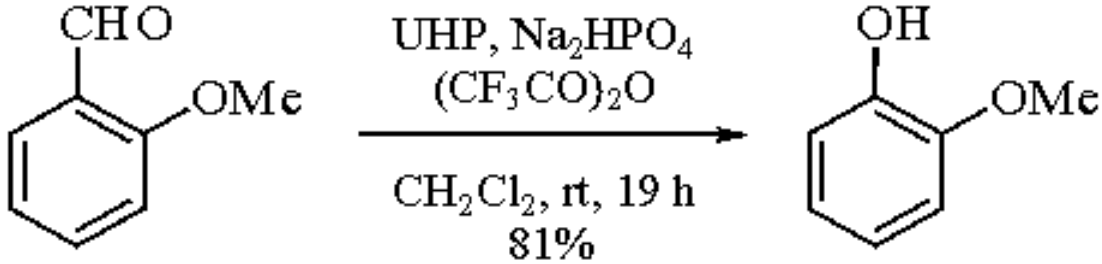

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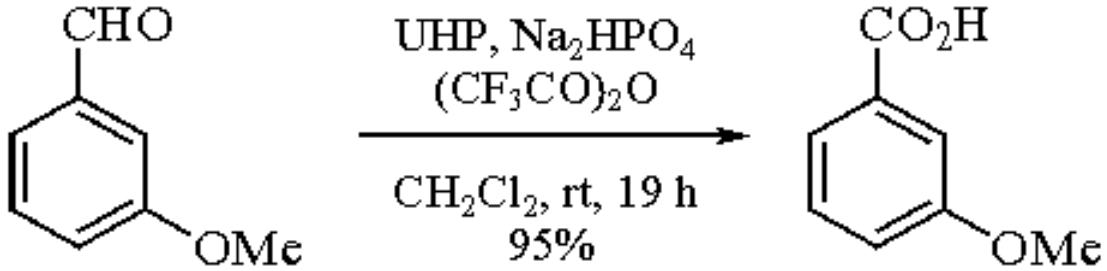

(10)

Heteroatom Oxidation.

The first example of the use of UHP in organic chemistry involved the formation of the *N*-oxide shown in eq 11,[9] and, in a modification of the UHP method, phthalic anhydride has been used to oxidize 4-*t*-butylpyridine to the *N*-oxide in 93% yield.[10] The oxidation of aliphatic aldoximes using UHP-trifluoroacetic anhydride has been achieved in good yields with retention of configuration at neighboring chiral centers (eq 12).[11]

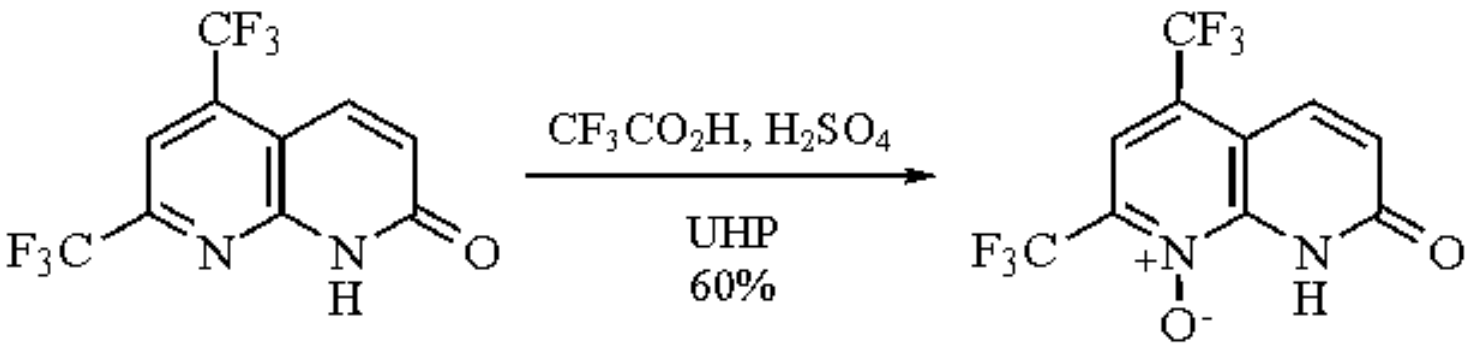

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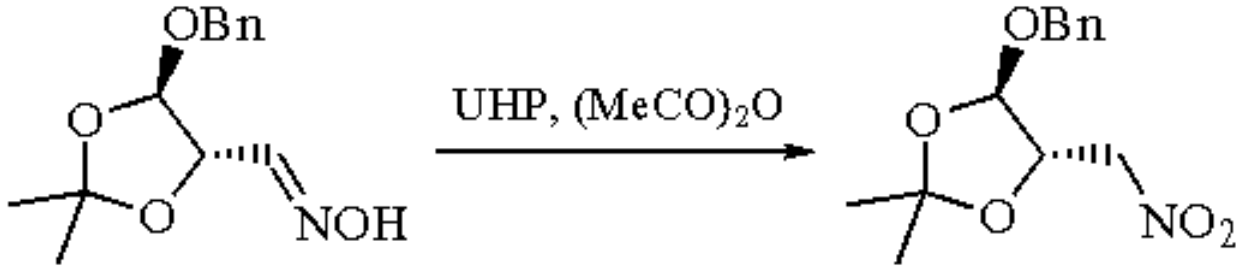

(12)

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Hydrogen Selenide[1]

H_2Se

[7783-07-5] · H_2Se · Hydrogen Selenide · (MW 80.98)

(reduction of carbonyl and nitro groups;[1] addition to activated double and triple bonds;[1] replacement of nitrogen, oxygen, or sulfur atoms by selenium[1,2])

Physical Data: mp -65.7 °C; bp -41.3 °C; *d* 3.66 g L^{-1}; pK_1 3.89; pK_2 11.0.

Solubility: fairly sol water (9.88 mg mL^{-1} at 22.5 °C/760 mmHg).

Form Supplied in: available commercially as gas in bottles or cylinders.

Preparative Methods: H_2Se is made by hydrolysis of Al_2Se_3, by the action of dilute mineral acids on FeSe, by the surface catalyzed reaction of gaseous ***Selenium*** and H_2 above 350 °C, or by heating Se with ***Lithium Hydroxide*** or $Mg(OH)_2$.[3] Se is readily reduced to H_2Se by ***Carbon Monoxide*** and H_2O (water gas) in the presence of ***Triethylamine***.[4]

Handling, Storage, and Precautions: colorless gas with a disagreeable odor; very toxic. It irritates the mucous membranes of the nose, eyes, and upper respiratory tract. It is easily oxidized by atmospheric oxygen and must be handled under inert gas. It burns in air and is decomposed by dust and rubber and in the presence of moisture with separation of Se. Aqueous solutions are oxidized in air with separation of red Se. Use in a fume hood.

Functional Group Reductions.

H_2Se reduces aldehydes and ketones (eq 1) under basic conditions to form diselenides.[5] With photochemical activation, primary and secondary alcohols are obtained[6] from aldehydes and ketones. Arylhydroxylamines, nitrosoarenes, and nitroarenes are reduced to primary aromatic amines with H_2Se formed in situ from Se and water gas.[7] In this reaction, only catalytic amounts of selenium need to be

used since the Se formed during the reaction is reduced by the excess of water gas (eq 2).[7b] ***Acetaldehyde*** treated with H_2Se and HCl gives intermediate bis(1-chloroethyl) selenide, which yields divinyl selenide on dehydrohalogenation (eq 3).[8]

$$\mathrm{PhCHO} \xrightarrow[76\%]{\mathrm{H_2Se.\ py,\ Et_3N}\ \mathrm{rt,\ 10\ d}} \mathrm{PhCH_2SeSeCH_2Ph} \qquad (1)$$

$$\mathrm{PhNO_2} \xrightarrow[86\%]{\mathrm{Se,\ CO,\ H_2O}\ \mathrm{Et_3N,\ THF,\ 80\ ^\circ C}} \mathrm{PhNH_2} \qquad (2)$$

$$\mathrm{MeCHO} \xrightarrow[15\%]{\mathrm{1.\ HCl,\ H_2Se,\ -10\ ^\circ C}\ \mathrm{2.\ PhNEt_2,\ 150\ ^\circ C}} \mathrm{(H_2C{=}CH)_2Se} \qquad (3)$$

Addition to Double and Triple Bonds.

Addition of H_2Se to ***Ethylene*** leads to diethyl selenide as a main product, but severe reaction conditions are required.[9] H_2Se adds to the cyano group in nitriles or to the azomethine group in imidoyl or iminium chlorides to produce selenoamides.[10] The action of H_2Se on formamidines gives *N*-alkylselenoformamidines, while the treatment of *N*-alkylcyanamides or carbodiimides yields *N*-substituted selenoureas (eq 4).[11]

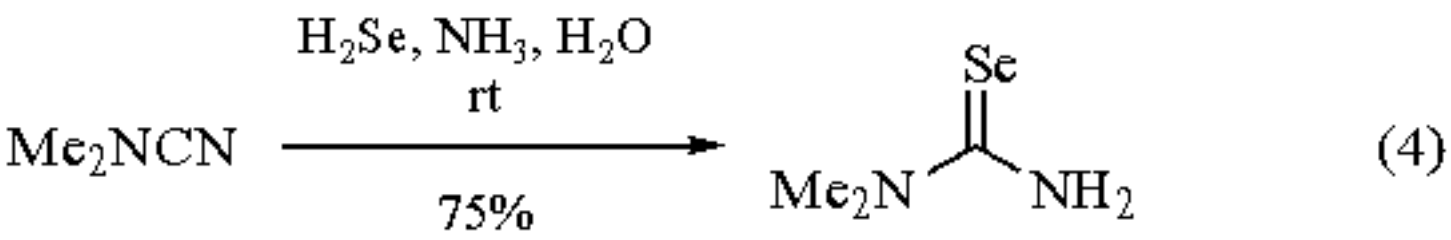

Other Reactions.

Treatment of adenosine, its derivatives, and analogs with H_2Se in aqueous pyridine gives the

corresponding 6-seleno-substituted nucleosides and nucleotides.[12] The reaction of acid chlorides with H_2Se leads to diacyl selenides.[13] Ring opening of ***Ethylene Oxide*** with H_2Se affords a modest yield of a mixture of 2-hydroxyethylselenol and bis(2-hydroxyethyl) diselenide.[14]

Related Reagents.

Hydrogen Sulfide; ***Lithium Selenide***; ***Sodium Hydrogen Selenide***; ***Sodium Selenide***.

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Hydrogen Sulfide[1]

H_2S

[7783-06-4] · H_2S · Hydrogen Sulfide · (MW 34.09)

(nucleophile and precursor of Na_2S, NaSH, K_2S, and KSH for the synthesis of thiols,[2] thioethers,[3] thiocarbonyl compounds,[4] and heterocyclic compounds; reducing agent, particularly for the conversion (via S^{2-}, HS^-, S_2^{2-}) of aromatic nitro compounds to amines[5])

Physical Data: colorless gas; bp -60.75 °C; mp -85.60 °C; *d* (0 °C) 1.539 g L^{-1} (more dense than air); dipole moment (C_6H_6) 0.85-0.97 D. pK_{a1} (aq) 6.88, pK_{a2} (aq) 14.15; E_0(H_2S -> S + $2H^+$ + $2e^-$) -0.14 V.

Solubility: sol H_2O (0.12 mol L^{-1} at 20.1 °C); sol polar and nonpolar organic solvents.

Form Supplied in: liquefied gas in steel cylinders.

Handling, Storage, and Precautions: extremely toxic, malodorous gas; use of a well-ventilated hood is a necessity; a scrubber flask containing 20% aqueous NaOH prevents loss of H_2S to the atmosphere. The sense of smell is paralyzed at concentrations of 150-250 ppm and death may ensue at concentrations above 300 ppm. An irritant to the eyes and mucous membranes; highly flammable; ignites spontaneously in air at around 250 °C; mixtures of H_2S (4.5-45%) and air are explosive; corrosive (especially in aqueous solutions) to many metals; anhydrous H_2S is unreactive to stainless steel at ambient temperatures.

Formation of Na_2S, NaSH, K_2S, and KSH.

Passage of H_2S into excess aq NaOH or KOH yields ***Sodium Sulfide***, and K_2S, which can be used in situ.[6] ***Sodium Hydrogen Sulfide*** and ***Potassium Hydrogen Sulfide*** are produced in ethanolic base saturated with H_2S;[7] addition of, for example, excess KOEt yields K_2S.[7a] In the formation of KSH, H_2S is passed into an ethanolic KOH solution until the mixture does not test alkaline with phenolphthalein.[7c] Solutions of hydrogen sulfide salts are in equilibrium with the sulfide and H_2S: 2NaSH &ibond; Na_2S + H_2S.

Thiols.

Thiols or their salts are obtained by displacement reactions[2] by SH^- or S^{2-} (derived from H_2S) on primary or secondary halides or sulfonate esters, on oxiranes and aziridines, on quaternary ammonium salts, and on activated aromatic

halides (eq 1).[8] The displacement of chloride ion shown in eq 1 takes precedence over the addition reaction of H_2S to the nitrile group (see below). Halonitrobenzenes may undergo both substitution of halogen and reduction of the nitro group.[2a,6,9] High temperatures are required for unactivated aryl halides (eq 2).[10] Elimination and thioether formation are side reactions with aliphatic substrates. To minimize thioether formation, an excess of H_2S is employed (see the above equilibrium).

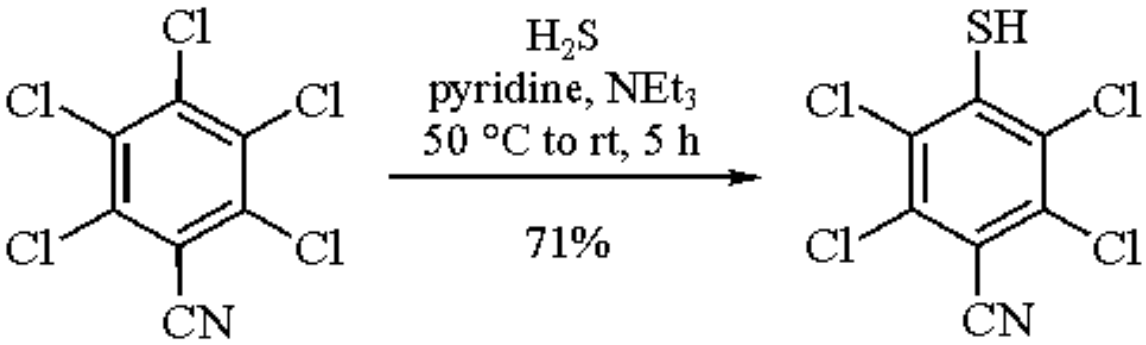

(1)

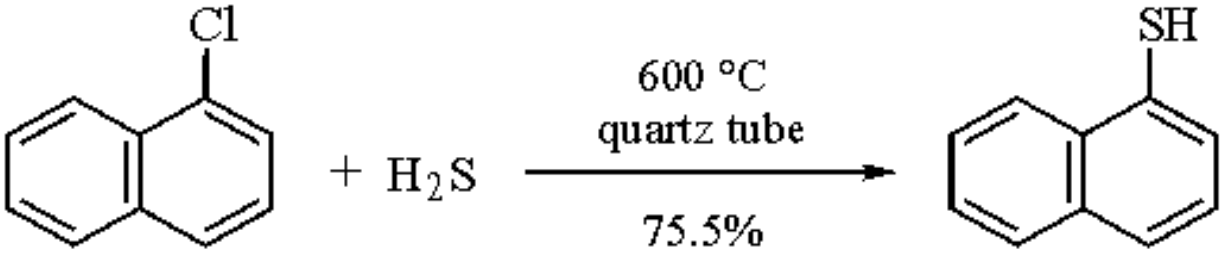

(2)

Benzyl thiols can be obtained directly from the alcohol by the action of H_2S in the presence of ***Octacarbonyldicobalt*** (eq 3).[11a] Direct reaction between H_2S and alcohols normally requires high temperatures, high pressures, and special catalysts; this method is not generally suited for a laboratory preparation.[2b] The reaction of α-aryl-α-amino nitriles with H_2S under mild conditions gives high yields of thiols uncontaminated with α-amino thioamides (eq 4).[11b]

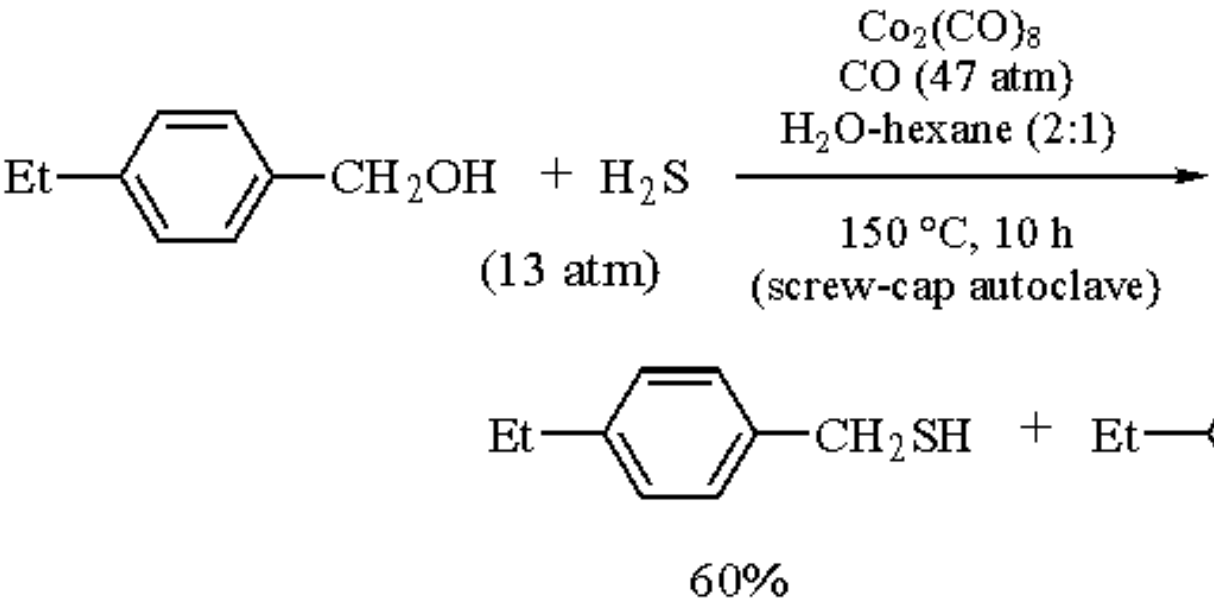

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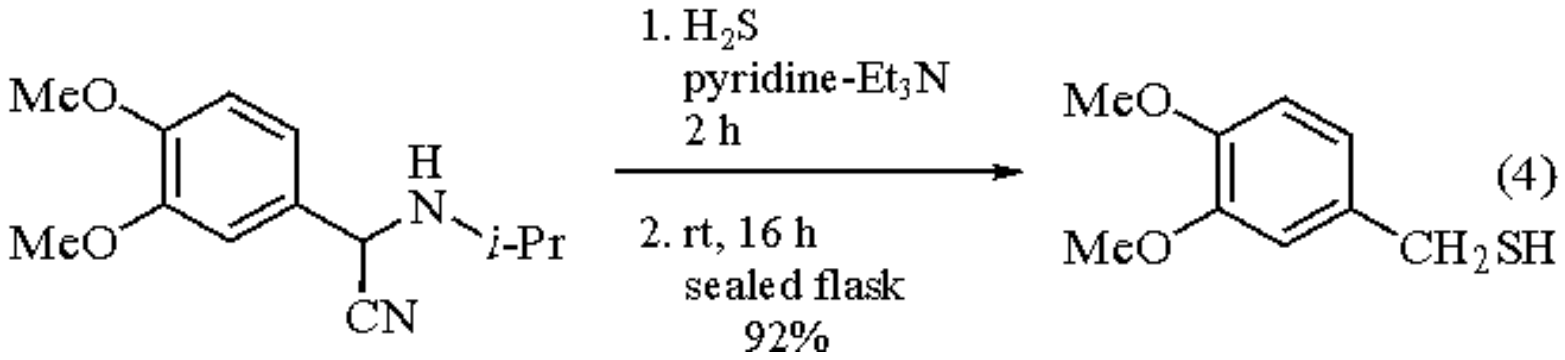

(4)

Thiolacids and their derivatives are obtained from the acid chloride or anhydride (eqs 5 and 6).[7c,12] Potassium thiotosylate, useful in the synthesis of thiotosylates, is obtained in a similar way from tosyl chloride (eq 7).[13] The solution must be saturated with H_2S. *gem*-Dithiols are obtained by treatment of ketones with H_2S and an organic base (or the preformed enamine may be used) (eq 8),[14] and best yields are obtained with cyclic ketones. Use of the ketimine or enamine gives satisfactory yields (53-83%) of *gem*-dithiols of acyclic ketones.[14b] Addition of H_2S to propionaldehyde in the presence of ***Chlorotrimethylsilane*** results in the silyloxythiol (eq 9).[15] A Michael-type of addition of H_2S to α,β-unsaturated systems provides β-mercapto derivatives that are readily desulfurized, thus providing a method for the selective reduction of the carbon-carbon double bond (eq 10).[16] Attempted reduction of this double bond (eq 10) by borohydride, hydride, and silane reagents was unsuccessful.

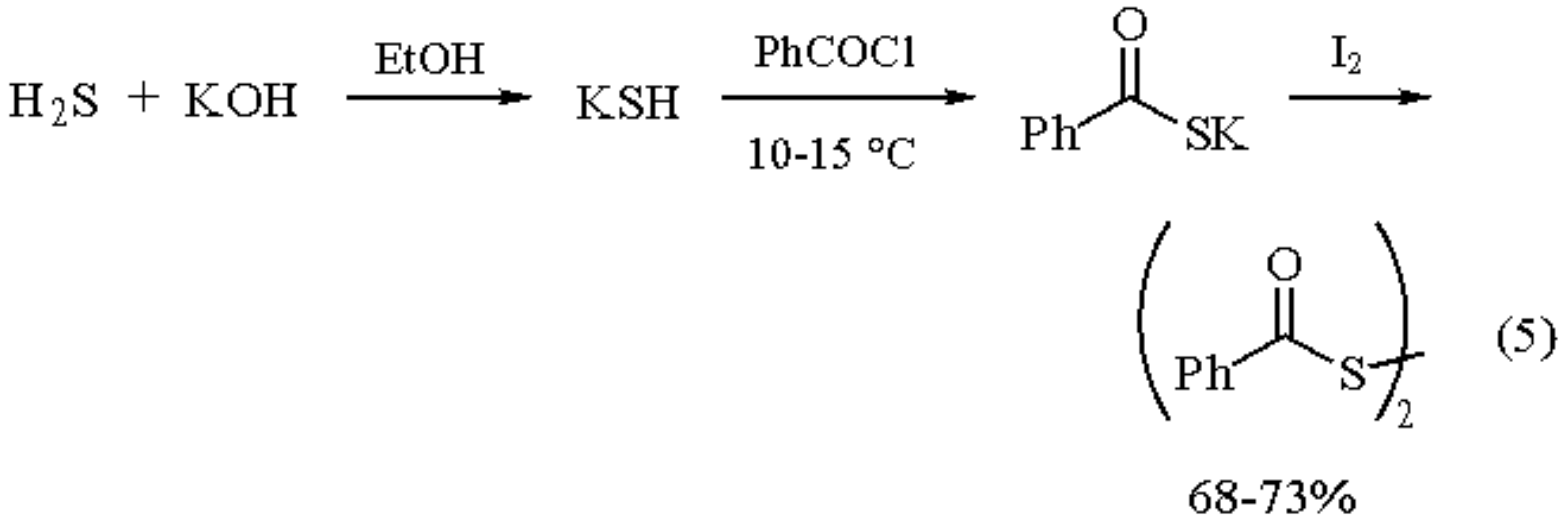

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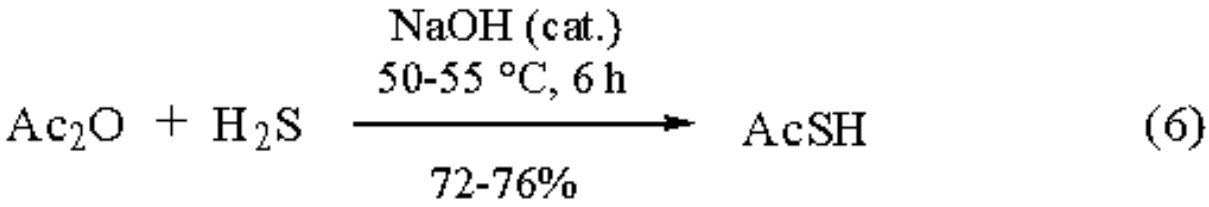

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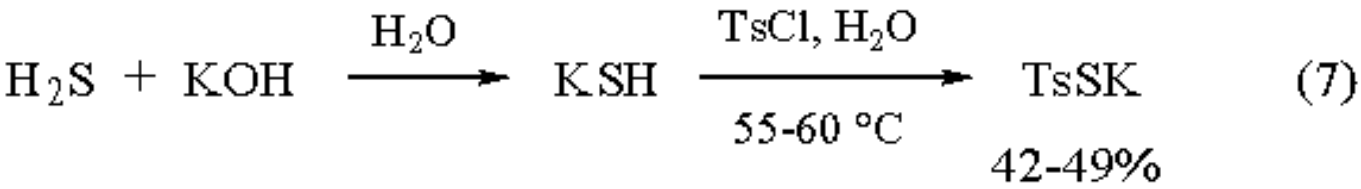

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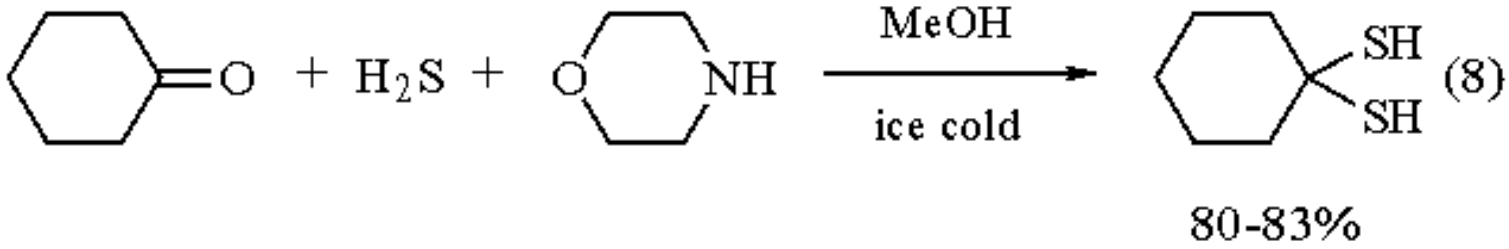

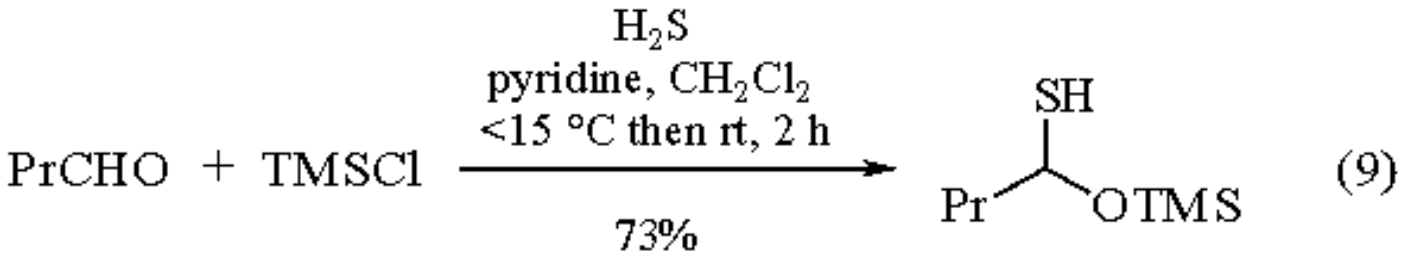

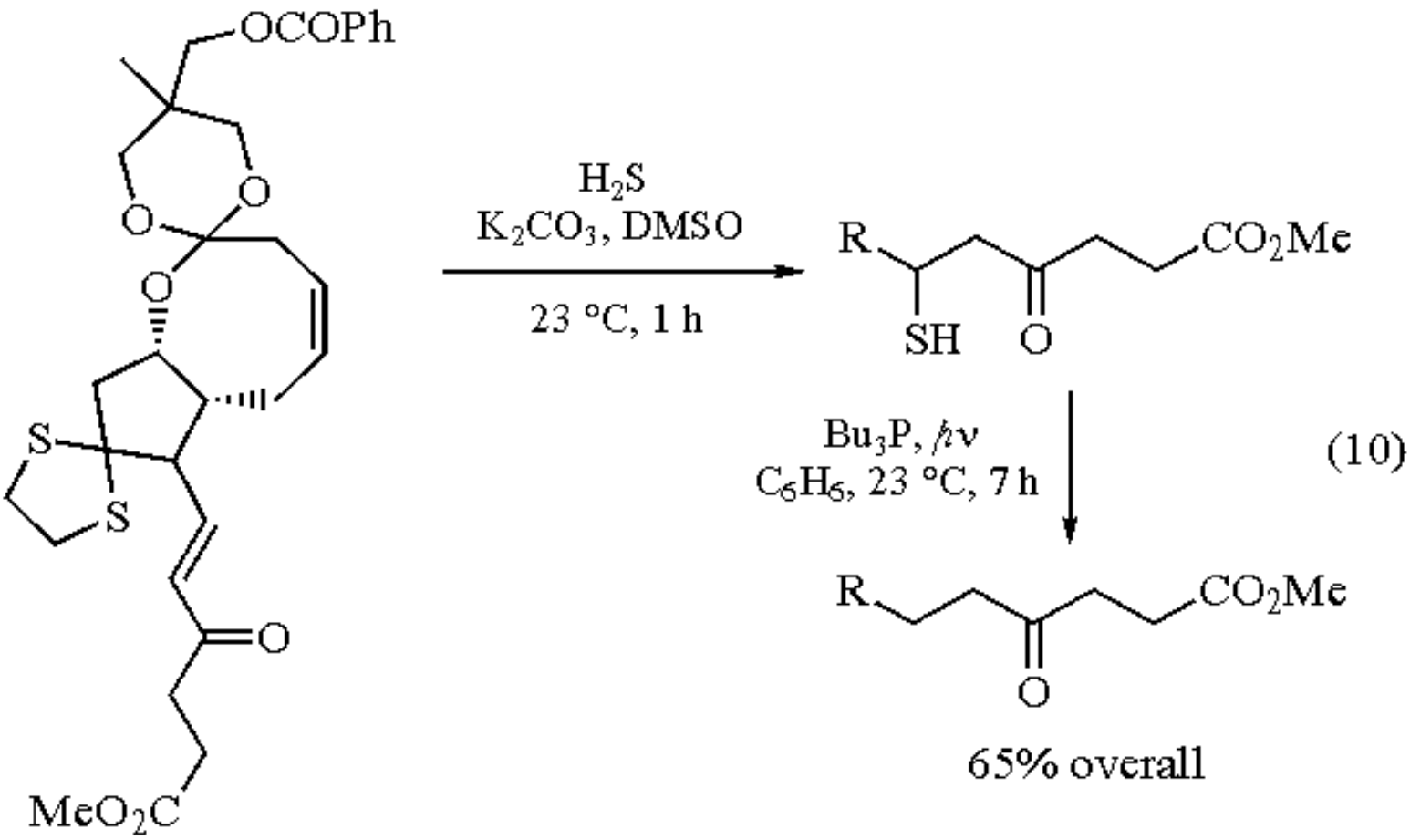

Thioethers and Disulfides.

Conversion of H_2S to sulfide ion, followed by treatment with a primary or secondary halide, sulfonate ester, quaternary ammonium salt, or an oxirane, aziridine, or activated aryl halide gives a good yield of symmetrical thioether via a thiolate intermediate.[3] Base-catalyzed addition of H_2S to electrophilic alkenes yields first the thiol which couples with excess alkene to give the thioether (eq 11).[17a] Disulfides are obtained via dithiol intermediates from addition of H_2S to aldehydes, ketones, and imines.[17b]

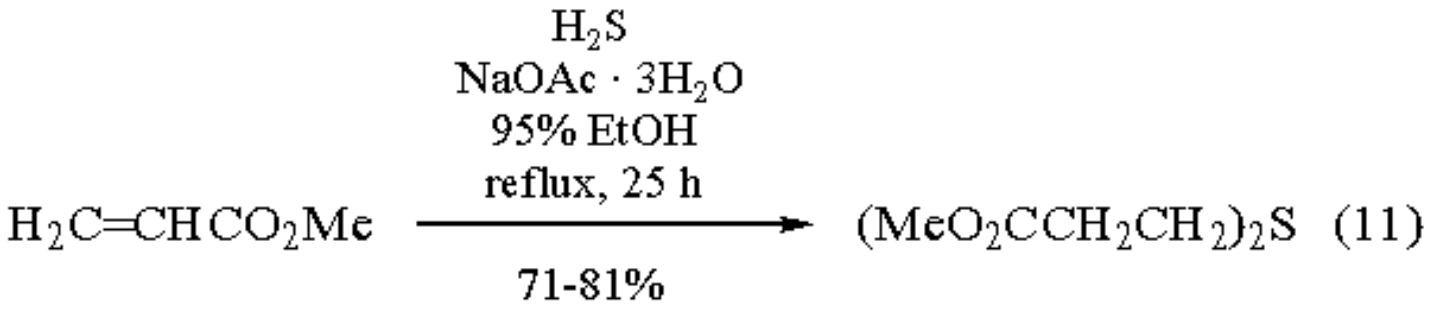

(11)

Thiocarbonyl Compounds.

Thioaldehydes, thioketones, thioesters, thioamides, and related compounds may be prepared by addition of H_2S (or SH^-, S^{2-}) to a C=X or a C=C-X bond where X is a group that is replaceable by sulfur.[4] In the total synthesis of chlorophyll, an important thioaldehyde intermediate was obtained by addition of H_2S to an imine salt (eq 12).[18] Related syntheses of thioaldehydes involve additions to Vilsmeier intermediates (iminium salts, etc).[19] The more common thioketones are prepared by addition of H_2S to ketones typically in the presence of HCl;[7b,14f,20] *gem*-dithiols[14] may be intermediates and they can be thermolyzed to thioketones. While aromatic thioketones are readily available (eq 13),[20a,b] their enethiolizable aliphatic analogs are often contaminated by the enethiol. Trimerization to 1,3,5-trithianes is a common side reaction. Methods for preparation of aliphatic thioketones (stable for 1 month at -15 °C) free from enethiols, and their conversion to pure enethiols free of the thioketone tautomer, have been reported (eq 14).[21] Aliphatic thioketones also are obtained in good yields (52-75%) by treatment of ketone anils with H_2S followed by removal of aniline from the initial adduct with ***Benzoic Anhydride***.[22] Thioketones are obtained by addition of H_2S to imines and iminium salts.[23]

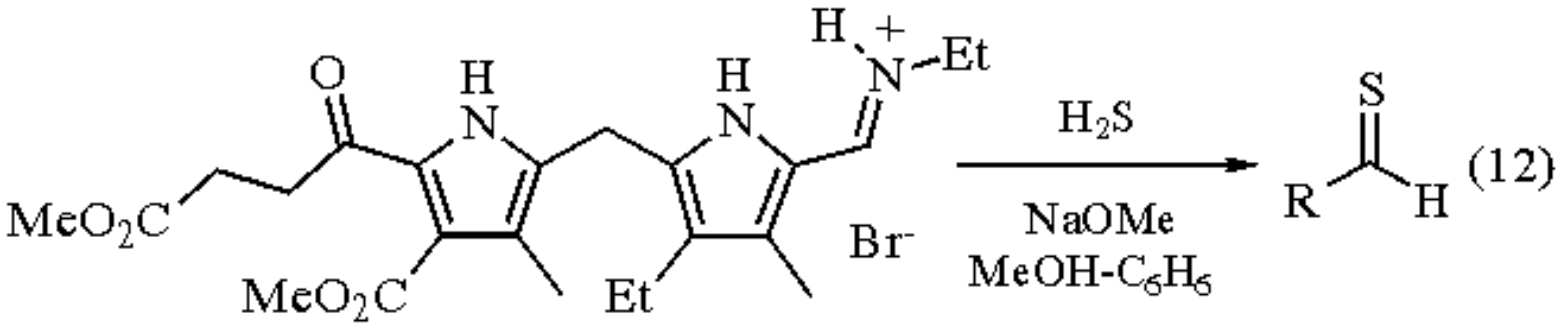

(12)

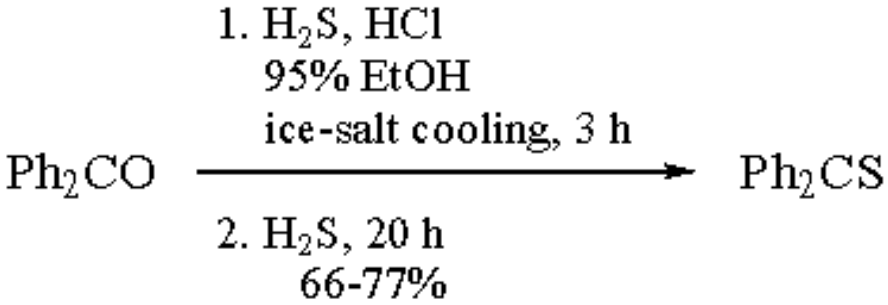

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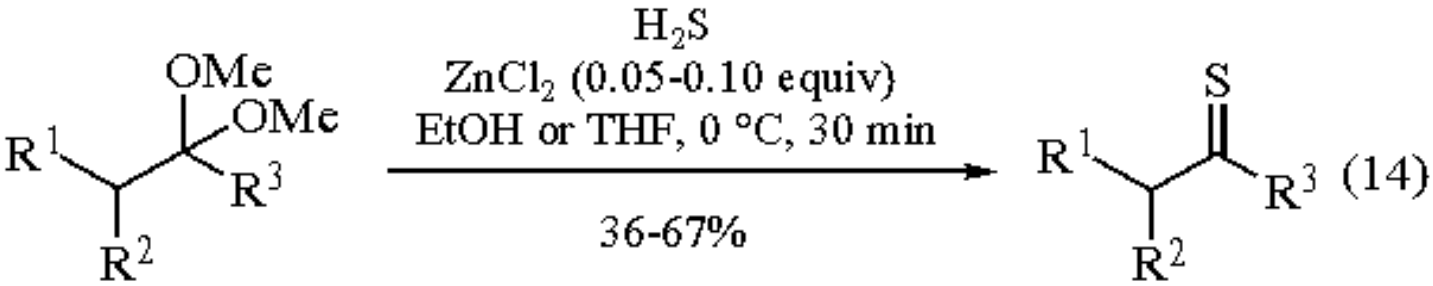

Derivatives of thiocarboxylic acids[4c,24] are obtained from H_2S and orthoesters (eq 15),[25] carboxylic acid ester enolates (eq 16),[26] and imino esters.[27] A method for reduction of a tertiary alcohol to an alkane involves its conversion to a thioformate ester followed by treatment with ***Tri-n-butylstannane*** (eq 17).[27b] Addition of H_2S to thioimino esters provides derivatives of dithiocarboxylic acids (eq 18).[4d,28] The thioamide function[4e,29] is obtained by addition of gaseous or liquid H_2S to nitriles (eq 19),[17b,30] ynamines,[31] various imines (eq 20),[32] and to orthoesters or chloroform in the presence of an amine (eq 21).[32f,33] Thioureas, thiobiurets, and thio heterocycles,[32d,34] thioimides (eq 22),[32b,35] and thioacylhydrazines[36] are obtained by similar reactions.

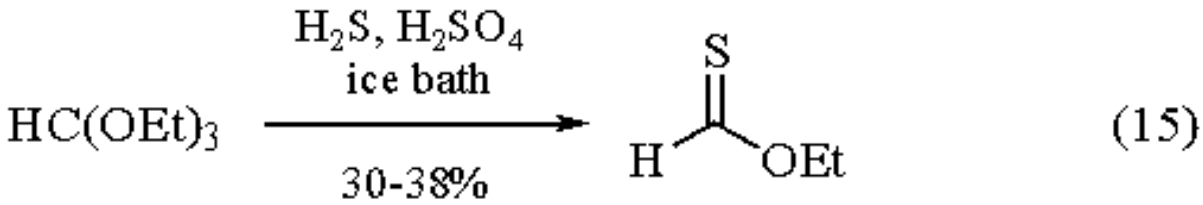

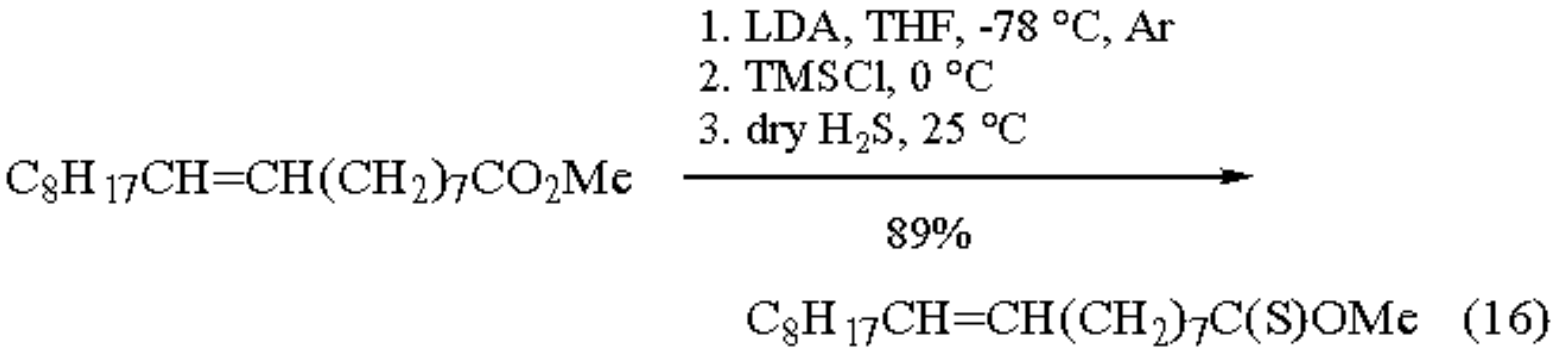

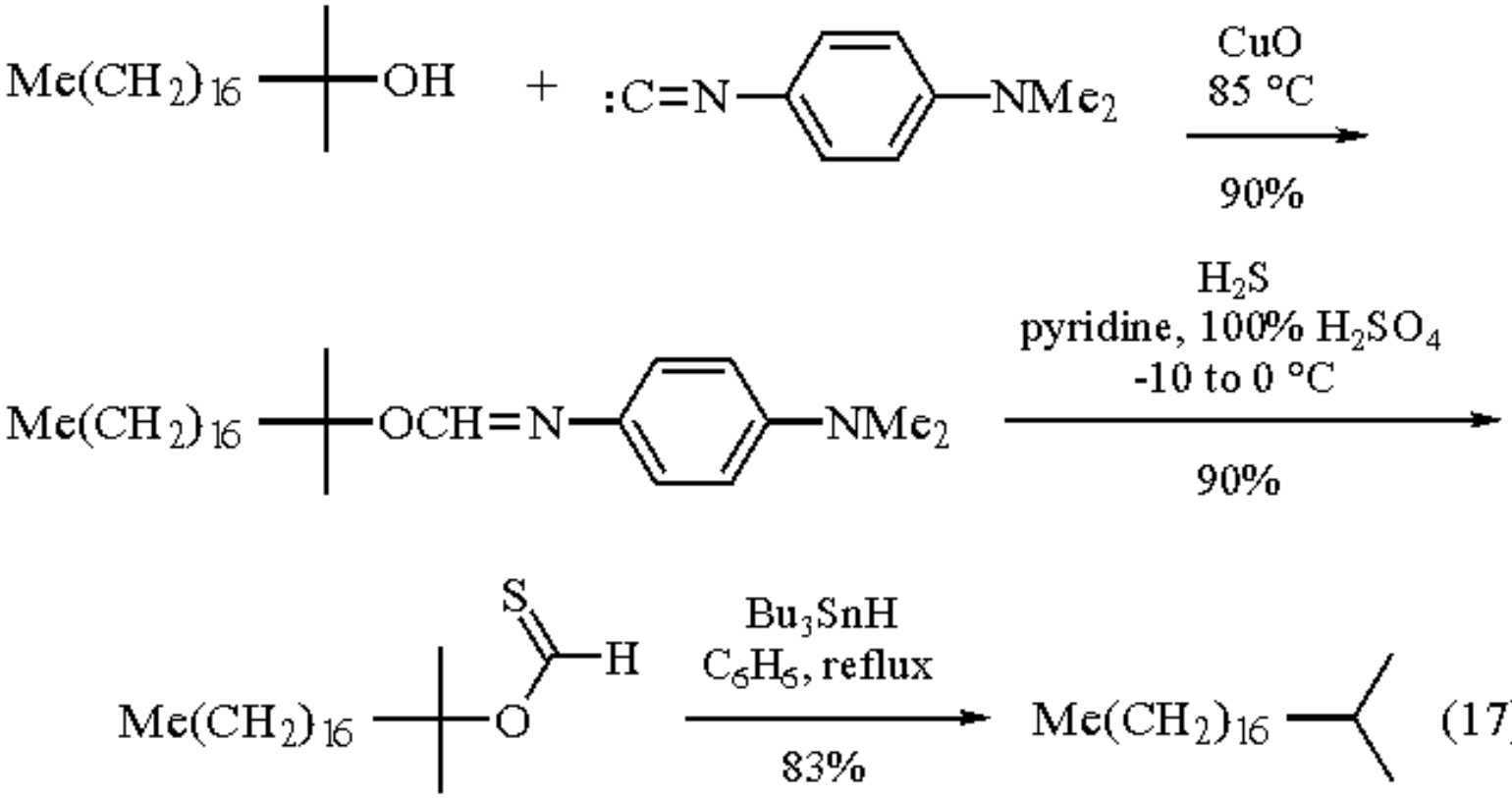
Me(CH2)16
OH
+
:C=N
NMe2
CuO
85 °C
90%
Me(CH2)16
OCH=N
NMe2
H2S
pyridine, 100% H2SO4
-10 to 0 °C
90%
S
H
Me(CH2)16
O
Bu3SnH
C6H6, reflux
83%
Me(CH2)16

(17)

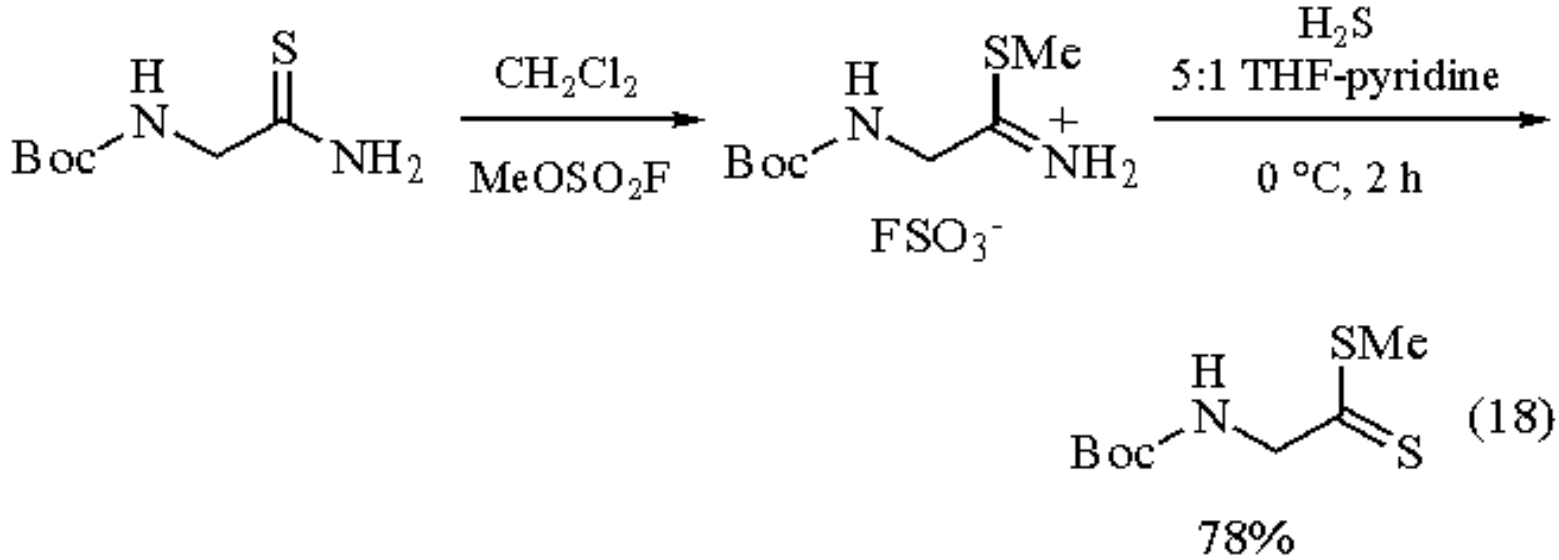
H
S
Boc
N
NH2
CH2Cl2
MeOSO2F
SMe
H
N
+
Boc
NH2
FSO3-
H2S
5:1 THF-pyridine
0 °C, 2 h
SMe
H
N
Boc
S
78%

(18)

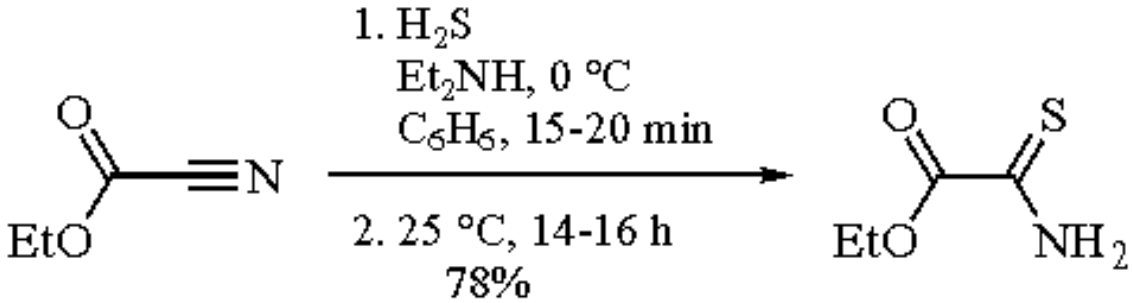
O
N
EtO
1. H2S
Et2NH, 0 °C
C6H6, 15-20 min
2. 25 °C, 14-16 h
78%
O
S
EtO
NH2

(19)

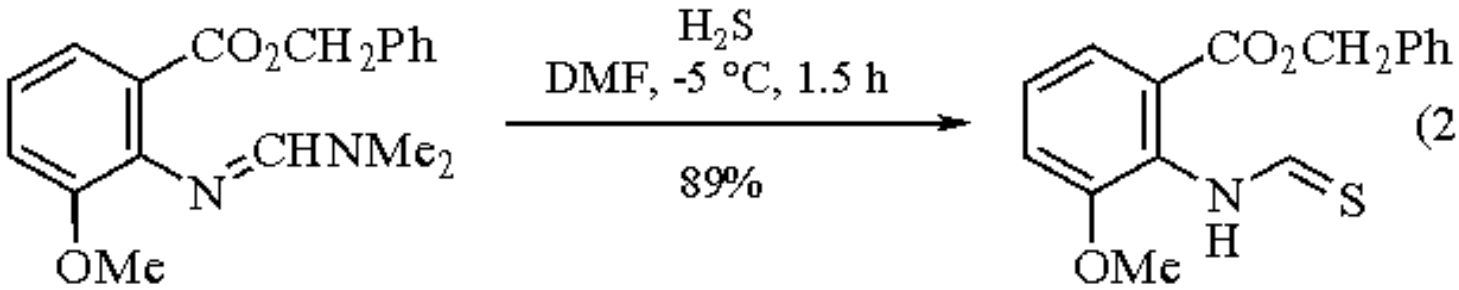

(20)

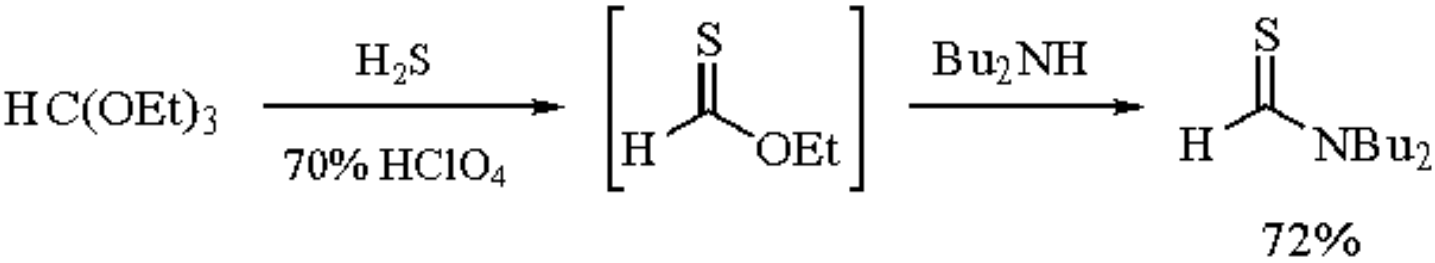

(21)

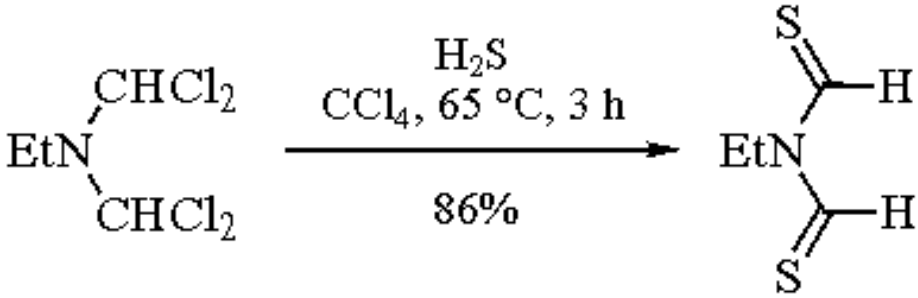

(22)

Heterocyclic Compounds.

The following types of sulfur-containing heterocyclic compounds obtained from hydrogen sulfide are listed according to ring size and the number of sulfur and other heteroatoms: 3 (1 S),[37] 4 (1 S),[38a,b] 4 (2 S),[39] 5 (1 S),[40a-d] 5 (2 S),[41] 5 (1 S, 1 N),[42] 5 (1 S, 2 N),[43] 6 (1 S),[44] 6 (3 S),[45] 8 (2 S).[46] The first synthesis of a cyclopenta[*b*]thiophene by a keto alkyne cyclization is shown in eq 23.[40c] Hydrogen sulfide plays a key role (possibly by reducing elemental chlorine) in the suppression of chlorinated byproducts in the synthesis of α-methylthioindoles (eq 24).[47]

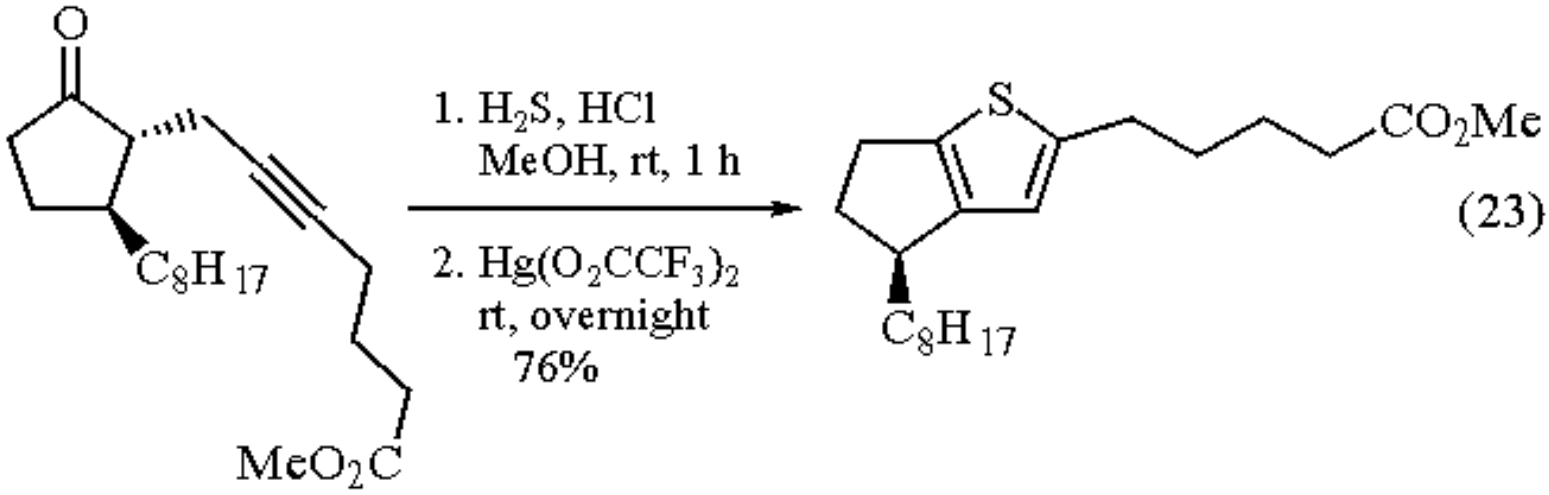

(23)

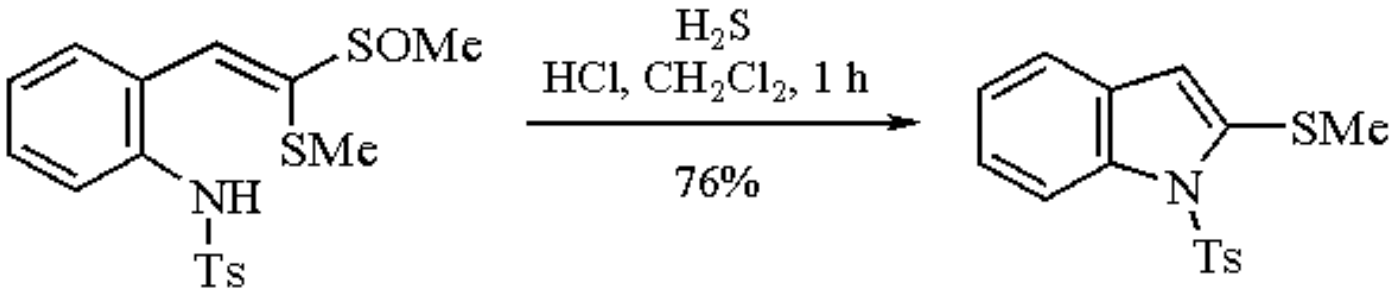

(24)

Reductions.

Hydrogen sulfide reduces nitro groups (eq 25),[5,9,48] nitroso groups,[49] azido groups,[50] the S=O group (eq 26),[51] the chlorosulfonyl group,[52] sulfur-sulfur,[53] sulfur-nitrogen,[54] nitrogen-nitrogen,[55] carbon-nitrogen,[11b,56] and carbon-mercury[57] bonds, the C-I and C-O bonds of some α-iodo and α-alkoxy ketones,[58] osmate esters,[59] and 1,2,3-tricarbonyl compounds[60a] and their hydrates[60b-d] (the 2-carbonyl functionality is reduced to the alcohol and dimers (eq 27)[60d] may be formed). Benzil is reduced quantitatively either to deoxybenzoin or benzoin, depending on conditions.[14c] The carbonyl group of aldehydes and ketones undergoes nucleophilic reduction with H_2S and a reducing thiol to give good yields of thiols via thiocarbonyl derivatives (eq 28).[61] The reduction of the azido group in 4-azidobutyryl derivatives of alcohols provides a mild method for deprotection of the hydroxy function (eq 29).[50a] Reduction of the azido group by elemental hydrogen instead of H_2S in the deprotection scheme may be accompanied by the reduction of other functional groups (eg alkene).

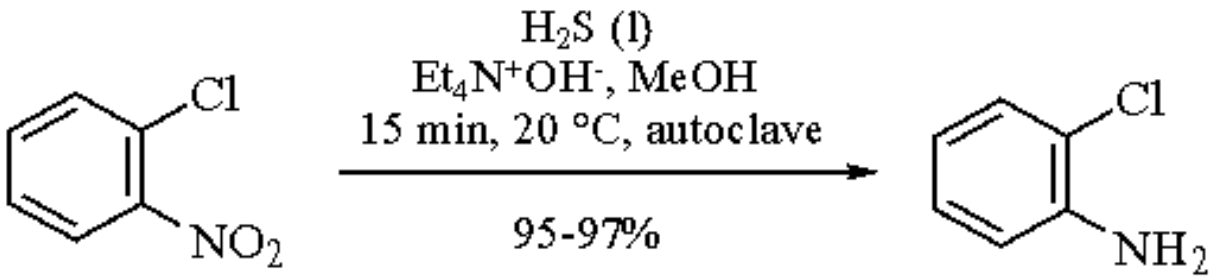

(25)

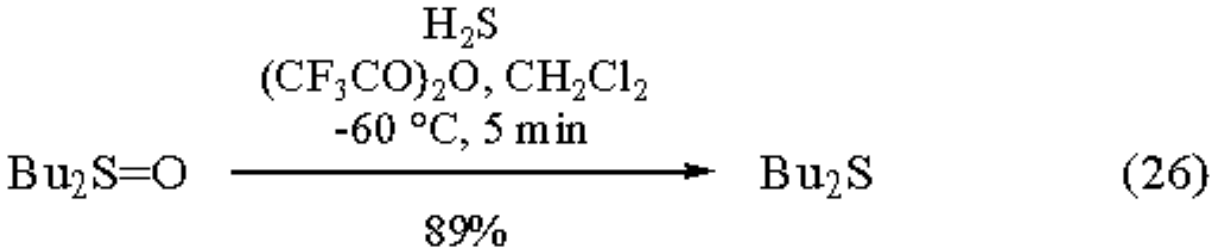

(26)

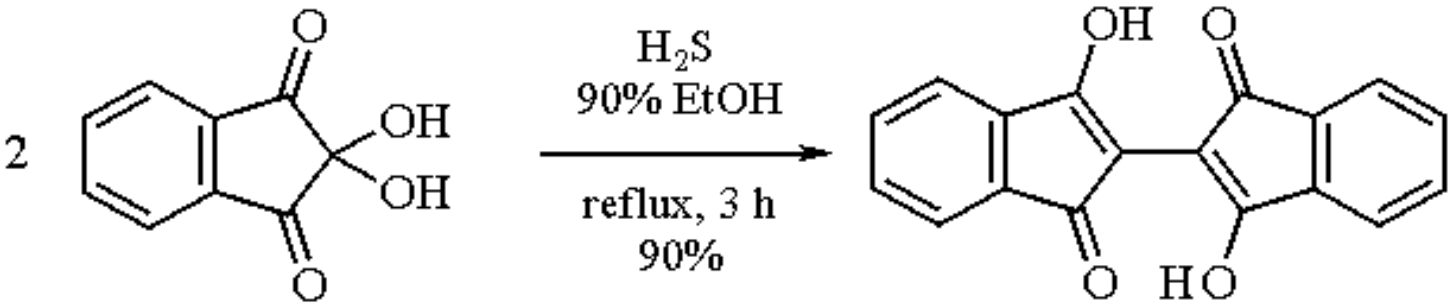

(27)

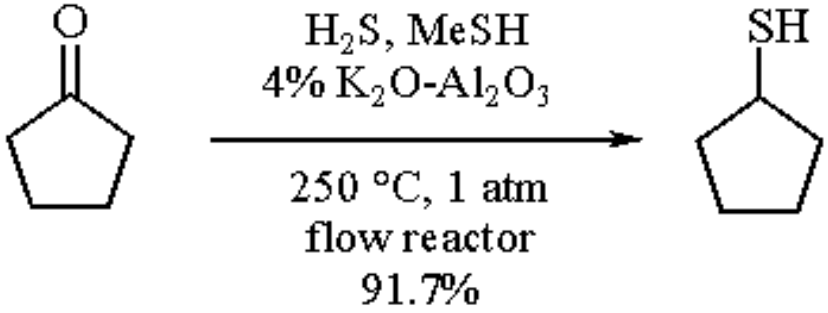

(28)

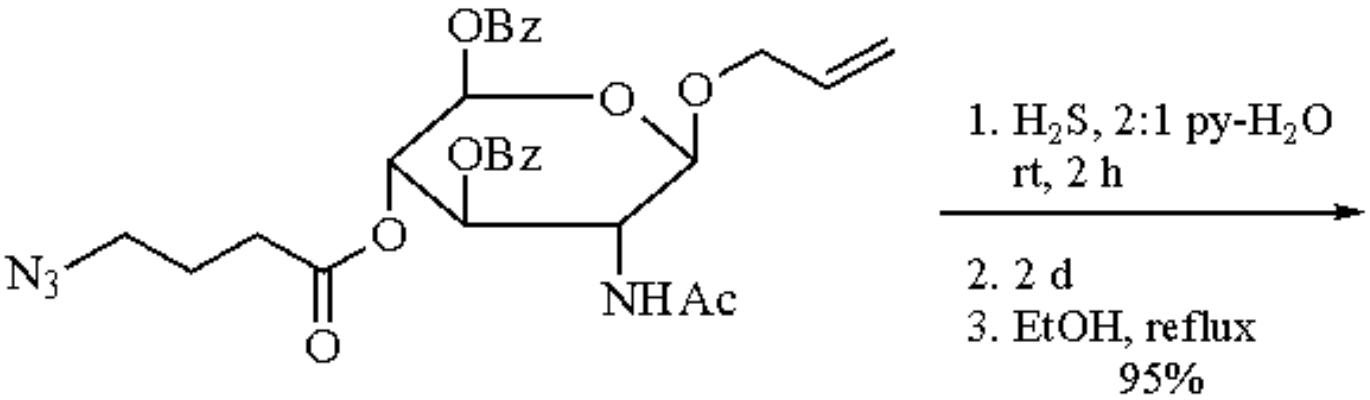

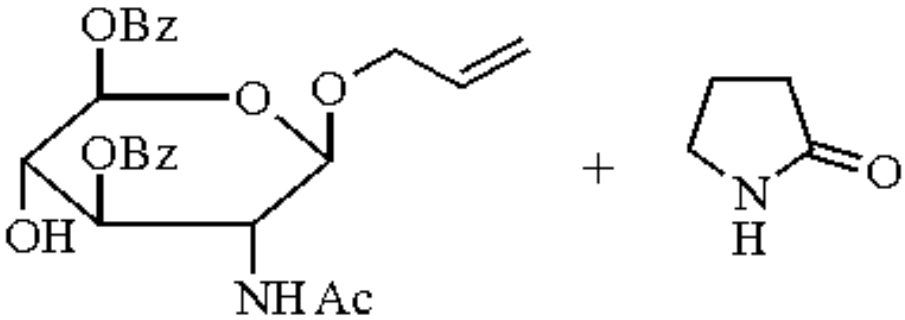

(29)

Miscellaneous.

Workup procedures of reactions that use salts of heavy metals (Hg, Pb, Ag, Cu) involve precipitation of the metal as its sulfide by H_2S.[62]

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Hydrogen Telluride[1]

H_2Te

[7783-09-7] · H_2Te · Hydrogen Telluride · (MW 129.62)

(mild reducing agent for aromatic nitro, azoxy, azo, nitroso, hydroxylamino, imino, and aldehyde groups, and the carbon-carbon double bonds of enamines and electron-deficient alkenes; useful in reductive alkylation of amines with aldehydes and ketones)

Physical Data: bp -2.2 °C; mp -51.2 °C; *d* 5.81 g L^{-1}; pK_{a1} 2.64; pK_{a2} 10.8, 11.80; E_0(H_2Te -> $Te + 2H^+ + 2e^-$) +0.51 V.

Solubility: sol alkali, water (dec), ether, benzene.

Preparative Method: hydrolysis of Al_2Te_3 in an atmosphere of CO_2.[1] Can be generated in situ.

Handling, Storage, and Precautions: a malodorous, colorless gas. Use in a well-ventilated fume hood. Decomposes completely to elemental ***Tellurium*** and hydrogen above 0 °C. Unstable to heat and light. Oxidizes very rapidly in air to Te^0. Flammable. Corrosive (H_2Te is a stronger acid than HF). Irritant. Highly toxic, but the ready decomposition of H_2Te to relatively nontoxic elemental Te suggests it is unlikely to be a serious hazard if precautions are taken. (Ingestion or inhalation of small amounts of elemental tellurium produces transient, garlic-like breath that is said to be eliminated by oral dosage with vitamin C.) Hydrogen telluride is a strong reducing agent and may react explosively with strong oxidants. Forms insoluble heavy metal tellurides. Possible contaminants are H_2S, H_2Se, and HCl.

Reductions.

Aromatic nitro compounds are reduced to amines (47-94%) by addition of powdered Al_2Te_3 to a THF solution of the nitro derivative under N_2. Water is added gradually to the warmed solution to generate H_2Te in situ, and the mixture is refluxed (eq 1).[2] Likewise, phenylhydroxylamine gives aniline (98%); nitrosobenzene, azobenzene, and azoxybenzene give hydrazobenzene (63%, 96%, and 86%, respectively). Imines and enamines (eq 2) may be reduced at lower temperatures by the in situ procedure.[3] Addition of ***Triethylamine*** improves yields in reduction of imines. A convenient reductive alkylation of amines with carbonyl compounds involves in situ generation of both imine and H_2Te (eq 3).[3] Yields varied from a low of 12% for $PhNH_2$ and *n*-$C_7H_{15}CHO$ to a high of 96% for *n*-$BuNH_2$ and *n*-$C_7H_{15}CHO$. Hydrogen telluride cleaves bis(methylgermyl)carbodiimides to bis(methylgermyl) tellurides and dicyanodiamide.[4] The in situ reduction of aldehydes and ketones to alcohols proceeds in yields of 50-100%, and reduction of the carbon-carbon double bond occurs with several α,β-unsaturated carbonyl compounds (yields 54-

89%).[5] With the latter, reduction of the carbonyl group also may occur. Use of D_2O in the procedure for reduction to alcohols generates D_2Te, which introduces deuterium into the alcohol, thus avoiding the use of the more costly $NaBD_4$ (eq 4).[5] Hydrogen telluride reduces ***Tetracyanoethylene*** to tetracyanoethane (90%) but offers no advantage over ***Hydrogen Sulfide***.[6] Similar reductions of nitrogen-containing functional groups and aldehydes have been accomplished with benzenetellurol.[7] Treatment of aliphatic aldehydes with H_2Te generated in situ under acidic conditions affords moderate yields (34-56%) of dialkyl ditellurides (eq 5).[8] Under basic conditions (Et_3N), alcohols are produced.

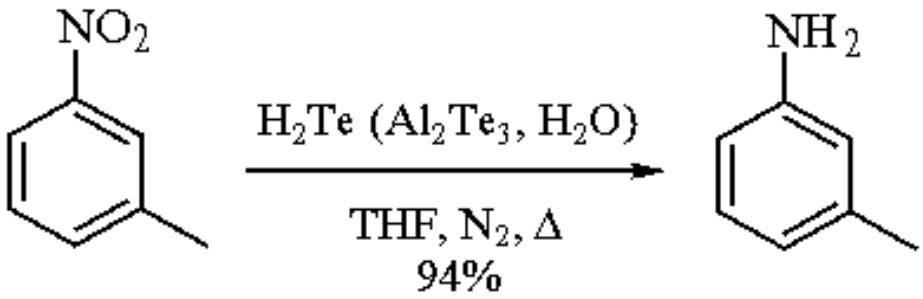

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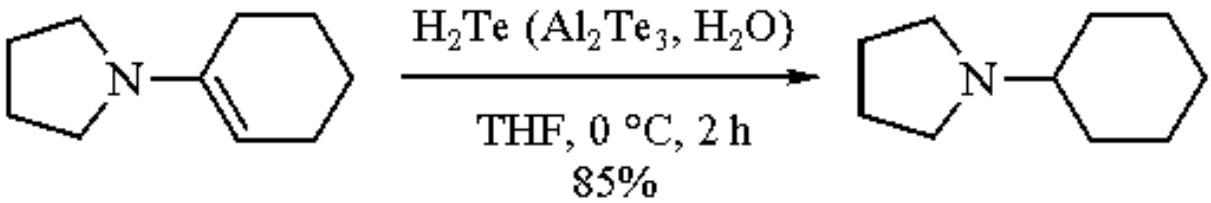

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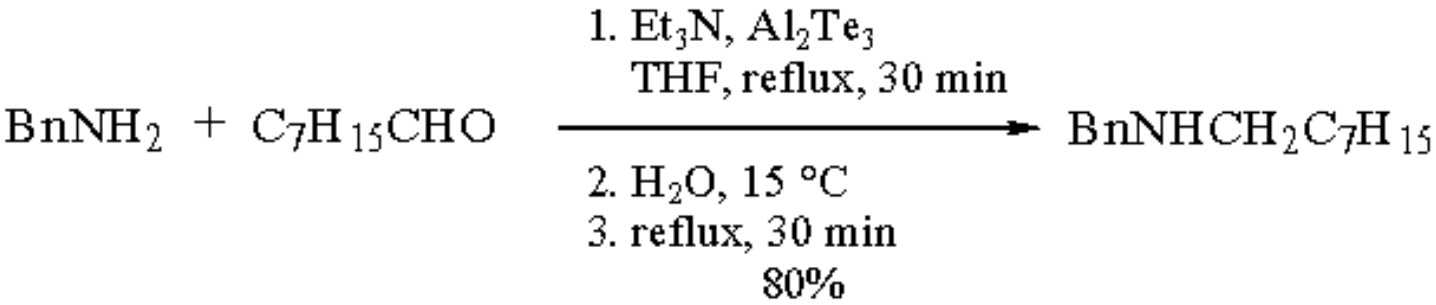

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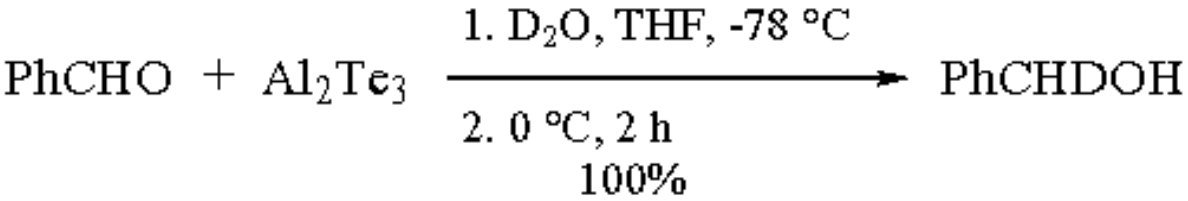

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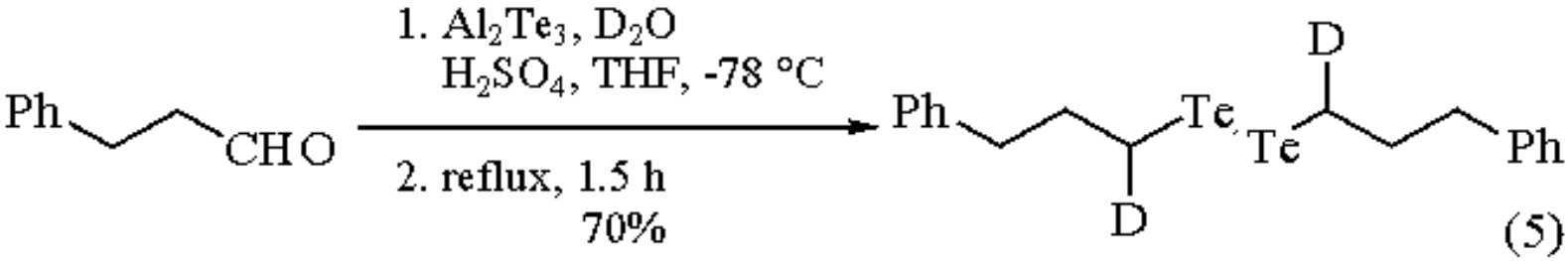

(5)

Related Reagents.

Hydrogen Selenide; ***Hydrogen Sulfide***; ***Sodium Sulfide***; ***Sodium Telluride***.

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2-Hydroperoxyhexafluoro-2-propanol[1]

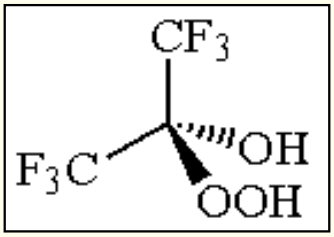

[32751-01-2] · $C_3H_2F_6O_3$ · 2-Hydroperoxyhexafluoro-2-propanol · (MW 200.05)

(oxidizing agent capable of Baeyer-Villiger oxidation;[1] selective alkene epoxidation;[2] conversion of aldehydes to carboxylic acids;[3] *N*-, *S*-, *Se*-oxidation;[4] strong parallels in structure and function to biologically active flavin oxidants[5-7])

Alternate Name: HPHP.

Physical Data: liquid at rt.

Solubility: sol CH_2Cl_2.

Preparative Method: prepared by the reaction of hexafluoroacetone (HFA)[8] with either 30% or 90% ***Hydrogen Peroxide*** by the following representative procedure. A 250 mL roundbottomed flask is fitted with Claisen adapter, pressure-equalizing, graduated addition funnel, dry ice condenser, and $CaCl_2$ drying tube. Anhydrous HFA (14 mL, 0.12 mol) is collected in the addition funnel and the roundbottom is charged with CH_2Cl_2 (100 mL) and 90% H_2O_2 (3.0 mL, 0.11 mol), and then cooled to -60 °C. After dropwise addition of HFA, the mixture is allowed to warm to rt and a clear, homogeneous solution results which can be titrated (NaI, $Na_2S_2O_3$, ca. 0.7 M) and stored conveniently at -5 °C. Under these conditions, the reagent is stable for at least 2 months.

Handling, Storage, and Precautions: slowly decomposes at rt to form CO_2, O_2, CF_3OOH and other products. Hexafluoroacetone is a highly toxic, nonflammable gas and should only be handled in a fume hood. Concentrated solutions of hydrogen peroxide must be handled with care.

Baeyer-Villiger Oxidation.

The oxidation of ketones to esters or lactones, usually performed with peroxycarboxylic acids, can be readily accomplished using HPHP in CH_2Cl_2 at reflux (4-5 h).[1] Nonaromatic ketones are cleanly oxidized to the corresponding esters (Table 1) while the oxidation of aromatic ketones is accompanied by tar formation, probably due to electrophilic aromatic substitution. Notably, mesitylene affords mesitol. Aniline is converted to nitrobenzene, but pentafluoroaniline gives only decafluoroazobenzene in low yield.

Table 1 Baeyer Villiger Oxidations Using HPHP

Compound	Product	Yield (%)
Methyl isobutyl ketone	Isobutyl acetate	73
Methyl *n*-pentyl ketone	*n*-Pentyl acetate	81
Cyclohexanone	Caprolactone	50
Acetophenone	Phenyl acetate	34
Aniline	Nitrobenzene	65
Pentafluoroaniline	Decafluoroazobenzene	10
Mesitylene	Mesitol	40

Selective Epoxidations.

With its close similarity to peroxyimidic, -carbamic, and -carboxylic acids, solutions of HPHP in methylene chloride or 1,2-dichloroethane transform unhindered alkenes to epoxides at rt or reflux.[2] Oxidations can be carried out either using stoichiometric quantities of oxidant, or in a two-phase mixture of substrate, solvent, catalytic hexafluoroacetone, and excess H_2O_2. Epoxidation of allylic alcohols or acetates occurs with high *syn* stereoselectivity. The alkenes shown in Table 2 gave the corresponding epoxides (yield and stereochemistry indicated parenthetically). A similar process was subsequently reported to occur with hexachloroacetone.[9]

Table 2 Epoxidation of Alkenes Using HPHP

Compound	Product	Yield (%)
1-Dodecene	1,2-Epoxydodecane	
Cyclododecene	Epoxycyclododecene	96
Cholesterol	Epoxycholesterol	α, 70; β, 35
Tetramethylene	Tetramethylene oxide	60
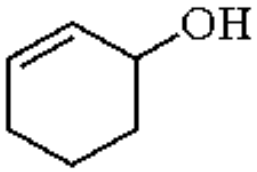	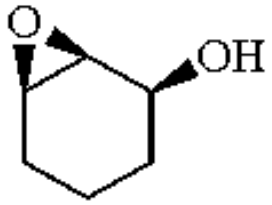	90
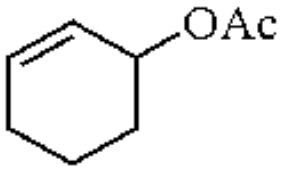	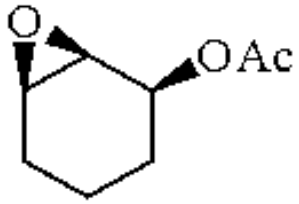	75; *syn*:*anti* = 4:1
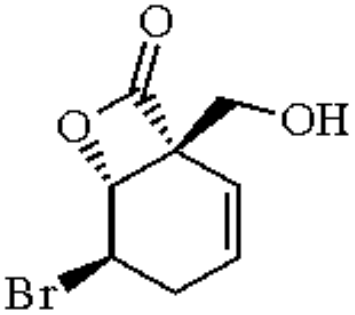	no reaction	
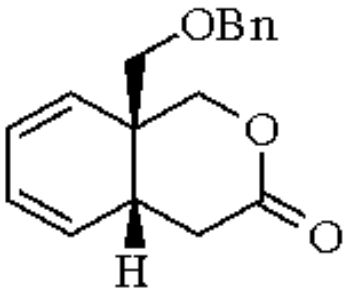	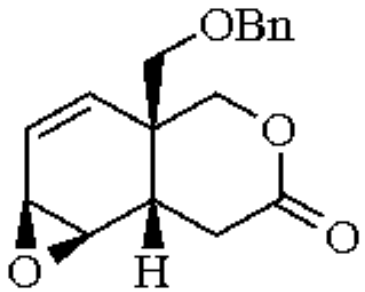	90

Oxidation of Aldehydes to Carboxylic Acids.

HPHP is also synthetically useful as a nucleophilic reagent for the conversion of aldehydes to carboxylic acids in the

presence of other functional groups (Table 3).[3] Unlike most chromium and manganese reagents, HPHP does not oxidize alcohols, and it provides a useful, nonmetal-based alternative to ***Silver(II) Oxide***. Like epoxidations, aldehyde oxidations can be performed with H_2O_2 and a catalytic quantity of HPHP in a two-phase CH_2Cl_2-Na_2CO_3 system. The aldehydes shown in Table 3 can be converted to the corresponding carboxylic acids.

Table 3 Oxidation of Aldehydes to Carboxylic Acids Using HPHP

Compound	Product	Yield (%)
n-Heptanal	*n*-Heptanoic acid	92
n-Dodecanal	*n*-Dodecanoic acid	72
$CH_2{=}CH(CH_2)_8CHO$	$CH_2{=}CH(CH_2)_8CO_2H$	75
PhCH=CHCHO	$PhCH{=}CHCO_2H$	40

Oxidation of Amines to Amine Oxides and Sulfides to Sulfoxides and Sulfones.

As shown in Table 4, HPHP oxidizes tertiary amines to *N*-oxides in 60-95% yield, and can also transform sulfides to sulfoxides (1 equiv HPHP) or to sulfones (2 equiv).[4] Competitive amine-versus-sulfide experiments indicate that sulfur oxidation is faster. Conversion of diallyl sulfide to diallyl sulfoxide illustrates the additional selectivity which can be expected. Rates are fastest in CH_2Cl_2 and diminish considerably in hydrogen-bonding solvents.

Table 4 Heteroatom Oxidations Using HPHP

Compound	Product	Yield (%)
$PhCH_2NMe_2$	$PhCH_2N(O)Me_2$	95
N-Methylmorpholine	*N*-Methylmorpholine oxide	90
$PhNEt_2$	$PhN(O)Et_2$	60
N,N-Diallyl-*O*-methyl-tyrosine methyl ester	*N,N*-Diallyl-*O*-methyl-tyrosine methyl ester *N*-oxide	90
Bu_2S	$Bu_2S{=}O$	99
Ph_2S	$Ph_2S{=}O$	99
Diallyl sulfide	Diallyl sulfoxide	98
Deacetoxycephalosporin V *p*-nitrobenzyl ester	Sulfoxide	75
(±)-Methionine	(±)-Methionine sulfoxide	89

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3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one

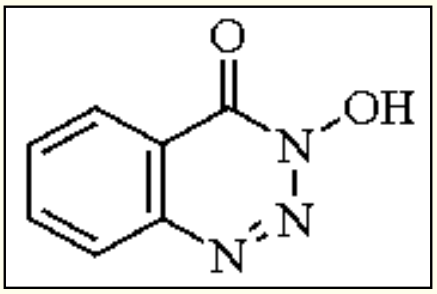

[28230-32-2] · $C_7H_5N_3O_2$ · 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one · (MW 163.15)

(additive to improve yields and decrease racemization in DCC-promoted peptide synthesis[1])

Alternate Names: Dhbt-OH; 3-hydroxy-4-keto-3,4-dihydro-1,2,3-benzotriazine.

Physical Data: mp 180-181 °C (dec).

Preparative Method: reaction of ***Sodium Nitrite*** with *o*-aminobenzhydroxamic acid.[2]

Solubility: sol most organic solvents.

Handling, Storage, and Precautions: regarded as an irritant rather than toxic. Possible explosive hazard.

Peptide Synthesis.

An appreciable amount of racemization (up to 70%) is often found to accompany the DCC-promoted synthesis of peptides (see ***1,3-Dicyclohexylcarbodiimide***). The use of Dhbt-OH as an additive improves yields (by up to 15%) and decreases racemization to almost undetectable levels in all the solvents tried (DMF, THF, CH_2Cl_2, DMSO).[1] Undesirable side-products resulting from attack on the triazine-ring carbonyl have meant that this reagent has been little used, ***1-Hydroxybenzotriazole*** being preferred. Recently, Dhbt-amino esters have shown promise in solid-phase peptide synthesis.[3,4] By premixing the *N*-protected amino acid and DCC before addition of Dhdt-OH, side-reactions are eliminated. Dhbt-amino esters have a useful self indication property in peptide synthesis, the liberated Dhbt-O^- anion giving a transient yellow color to the reaction until all the reacting amino groups have been consumed.

Miscellaneous.

Oligodeoxynucleoside phosphorodithiolates have been been efficiently synthesized using a Dhbt-OH-based phosphorus reagent.[5] Reductive decarboxylation of cinnamic acid with ***Tri-n-butylstannane*** was accomplished in

excellent yield via the Dhbt-ester (eq 1).[6]

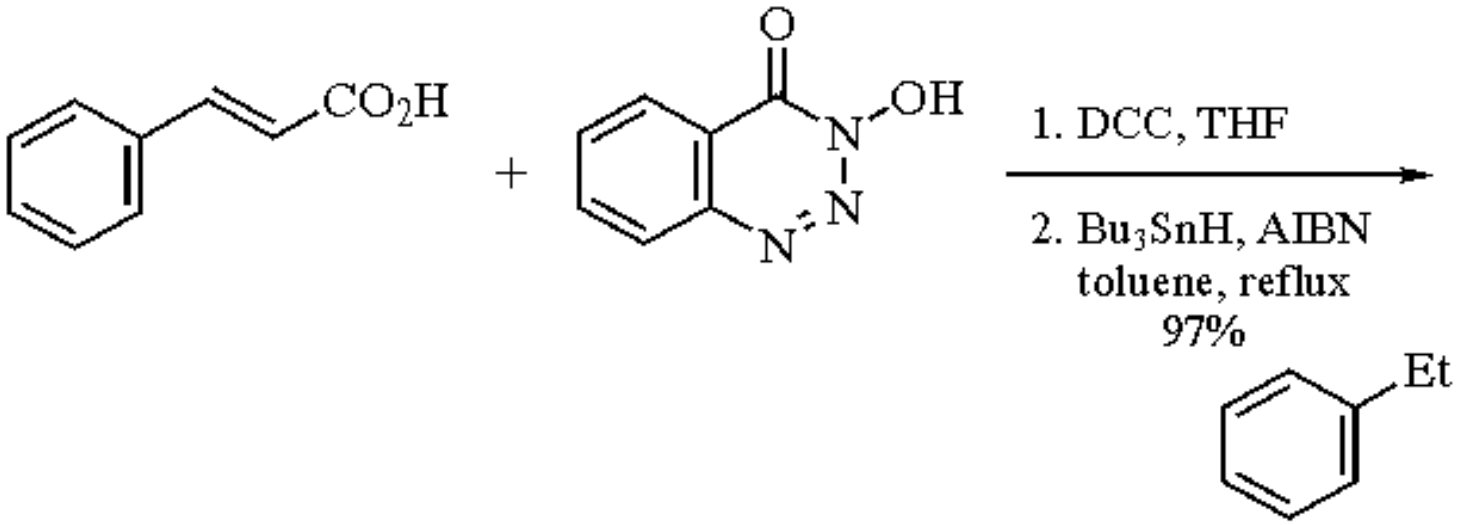

(1)

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1-Hydroxybenzotriazole[1]

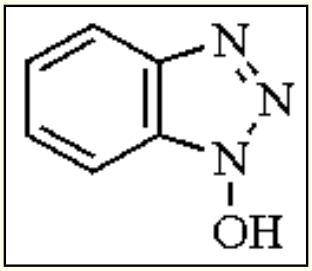

[2592-95-2] · $C_6H_5N_3O$ · 1-Hydroxybenzotriazole · (MW 135.14) (hydrate)

[123333-53-9]

(peptide synthesis; nucleotide synthesis)

Alternate Names: HOBT; HOBt.

Physical Data: mp 155-160 °C; exact melting point depends on the amount of water of hydration present.

Form Supplied in: white solid usually containing 12-17% water of hydration; widely available commercially.

Analysis of Reagent Purity: should be a white solid; if it becomes discolored, it is advisable to purify.

Purification: recrystallize from either water or aqueous ethanol.

Handling, Storage, and Precautions: should be stored in the dark; avoid contact with strong acids, oxidizing agents, and reducing agents; heating above 180 °C causes rapid exothermic decomposition; toxicity not fully investigated so should be treated with caution.

Peptide Coupling.

1-Hydroxybenzotriazole is most widely used in reactions involving the coupling of amino acid units to give peptides.[1] In this context it has been used mainly as an additive to a coupling reaction, although there are also examples of HOBT being incorporated into the coupling reagent itself. The most common use of 1-hydroxybenzotriazole in peptide synthesis is in conjunction with a carbodiimide such as ***1,3-Dicyclohexylcarbodiimide*** (DCC). Although it is quite possible to couple amino acids using DCC alone, it is found that the addition of 1-hydroxybenzotriazole to the reaction system results in improved reaction rates and suppressed epimerization of the chiral centres present in the peptide (eq 1).[2] This reaction appears to proceed via DCC-mediated formation of a hydroxybenzotriazole ester intermediate which then reacts with the amino function of a second amino acid to give the coupled product.

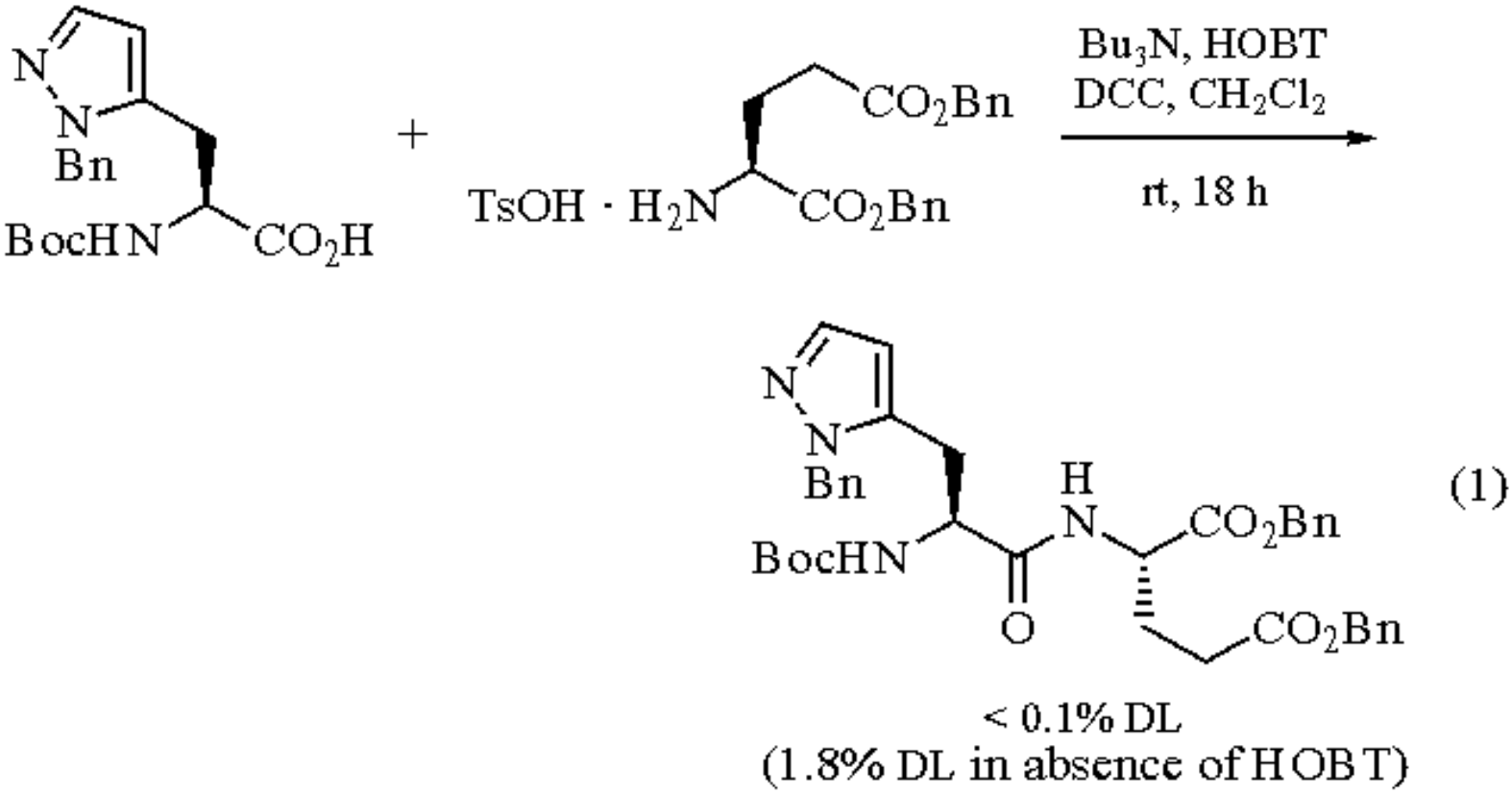

This coupling protocol is not limited to the synthesis of small peptides in solution, but can also be used in the solid-phase preparation of larger peptides, and for the coupling of larger peptide fragments. It should be noted, however, that there are some drawbacks to this method; most notably, it is sometimes difficult to purify the peptide due to contamination with dicyclohexylurea and the method is unsatisfactory for the coupling of *N*-methylated amino acids.[3] The problem of purification can often be overcome by using an alternative carbodiimide, e.g. ones that give water-soluble byproducts can be used, such as EDC.MeI (see ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride***).[4] Polymer-bound variants of HOBT have also been used to overcome purification problems,[5] since the urea byproduct can be removed from the polymer-bound active ester intermediate (**1**) by washing with chloroform-isopropyl alcohol mixtures. Once the urea has been removed, the active ester can be reacted with the second peptide fragment to give the product (eq 2), regenerating the polymer-bound HOBT. While this method appears quite successful for the preparation of small peptide fragments, it is clearly unsuitable for the preparation of larger peptides by solid-phase synthesis.

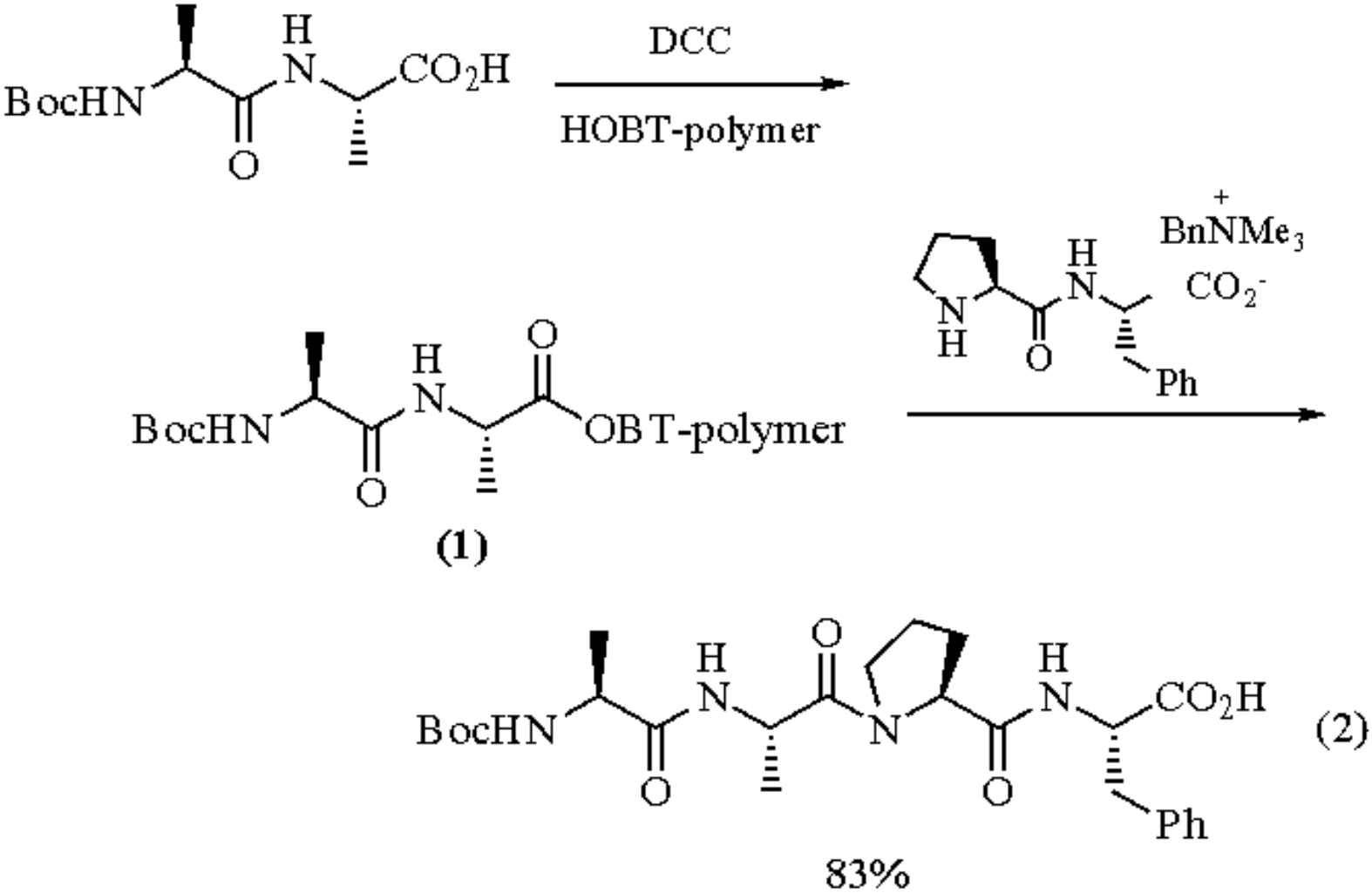

Although the addition of HOBT to the carbodiimide-mediated coupling of amino acids has been shown to suppress epimerization of the chiral centres present, there are still a number of cases where the level of epimerization is unsatisfactory. One method for further suppressing epimerization is to add ***Copper(II) Chloride*** to the reaction system.[6] In this case it is important that the correct stochiometry is determined, since the copper(II) chloride not only suppresses epimerization, but it also slows down the reaction rate and reduces the overall yield (eq 3).

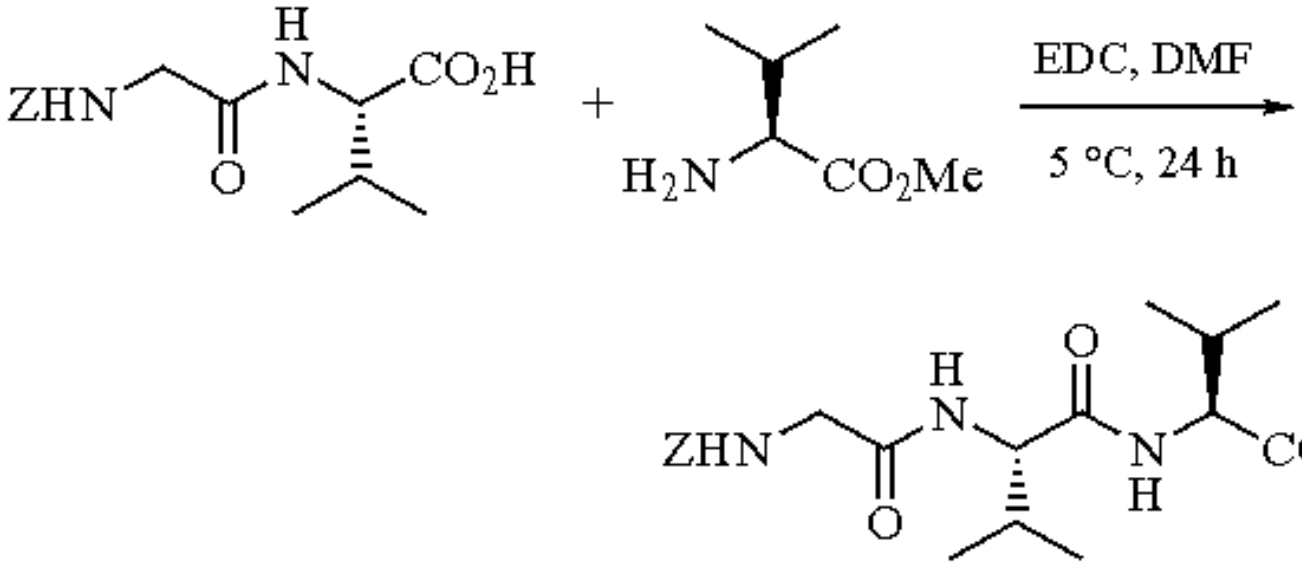

(3)

HOBT	$CuCl_2$	% DL	% Yield
0 equiv	0 equiv	38	22
1 equiv	0 equiv	1.3	96
1 equiv	0.25 equiv	<0.1	79

The problem of epimerization during carbodiimide-mediated coupling of amino acids can also be overcome by the use of an alternative coupling agent. Once such system that still employs HOBT as an additive involves the use of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) and *N*-methylmorpholine (NMM) (eq 4).[7] See also ***Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride***.

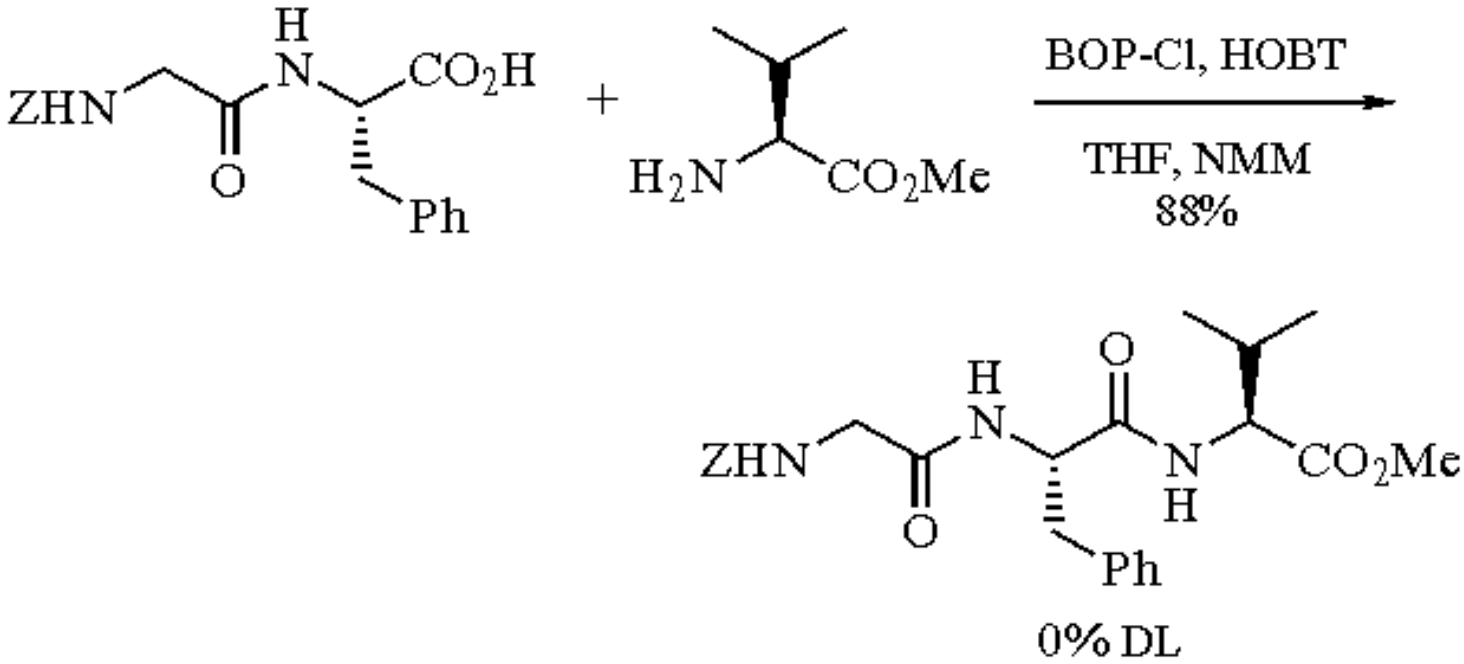

(4)

HOBT has also been used as an additive in other reactions involving amino acid derivatives.[8] It would appear that most reaction systems that are capable of generating a hydroxybenzotriazole ester intermediate will give successful coupling. One such system involves the use of amino acid derived trichlorophenyl esters.[9] These can be readily reacted with a

second amino acid unit in the presence of HOBT to give the coupled product with little or no racemization (eq 5). *p*-Nitrophenyl and pentachlorophenyl esters can also be employed with similar success. This reaction again is thought to proceed via the hydroxybenzotriazole ester intermediate and it has been shown that use of the potassium salt of HOBT in conjunction with a crown ether can lead to substantial rate increase,[10] presumably by enhancing the rate of formation of the active ester intermediate.

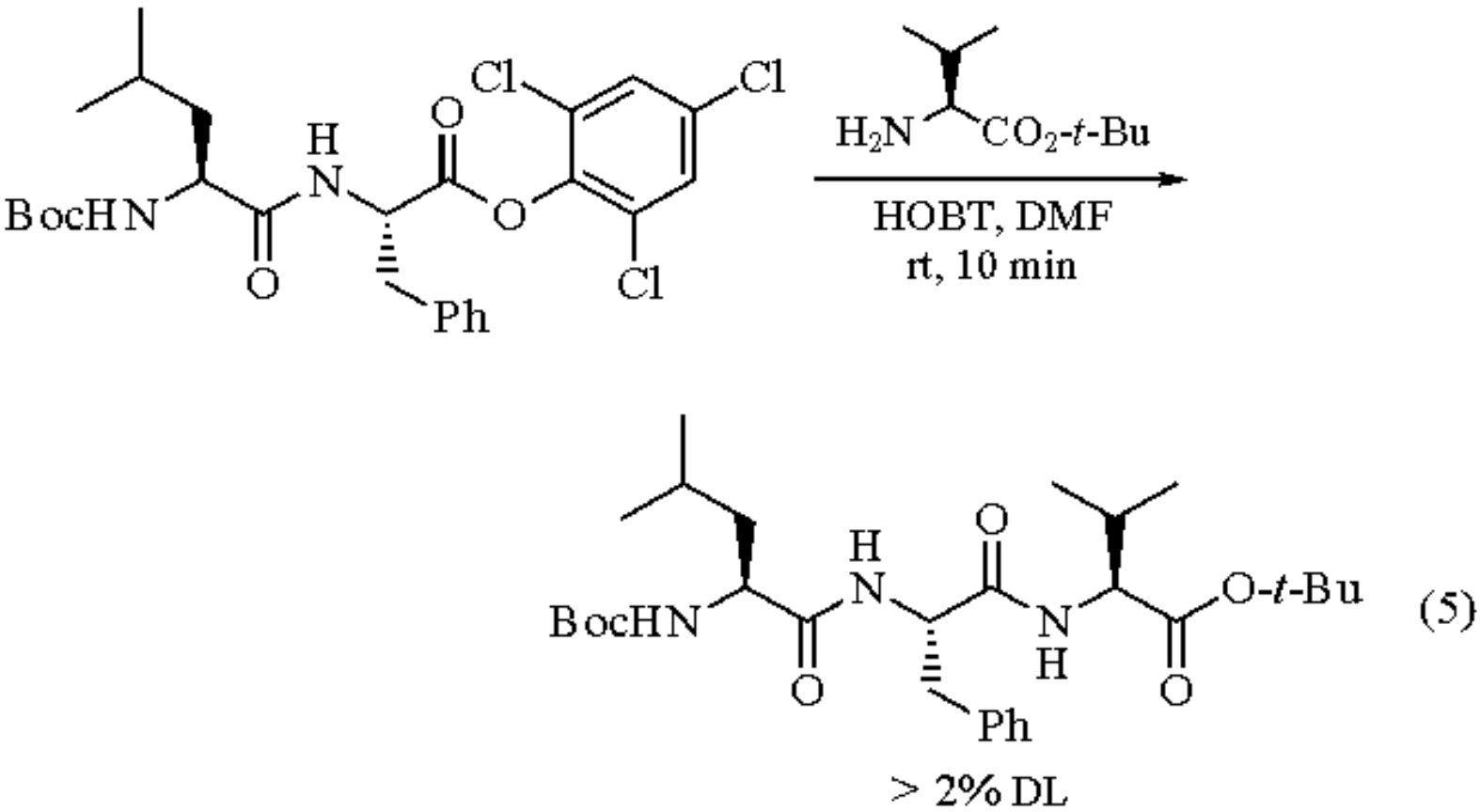

(5)

HOBT has also been used in conjunction with amino acid chlorides to facilitate peptide bond formation. This has proved of particular use in the case of FMOC-protected amino acid chlorides in solid-phase peptide synthesis where direct coupling is rather slow and suffers from competing oxazolone formation.[11]

As mentioned earlier, HOBT has also been incorporated into the peptide coupling reagent itself and one example of such a reagent is benzotriazol-1-yloxytris(dimethylamino)phosphonium chloride (BOP).[12] BOP is prepared by the reaction of HOBT with ***Hexamethylphosphorous Triamide*** in the presence of carbon tetrachloride, and is very effective in the coupling of amino acids (eq 6). See also ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (also known as BOP).

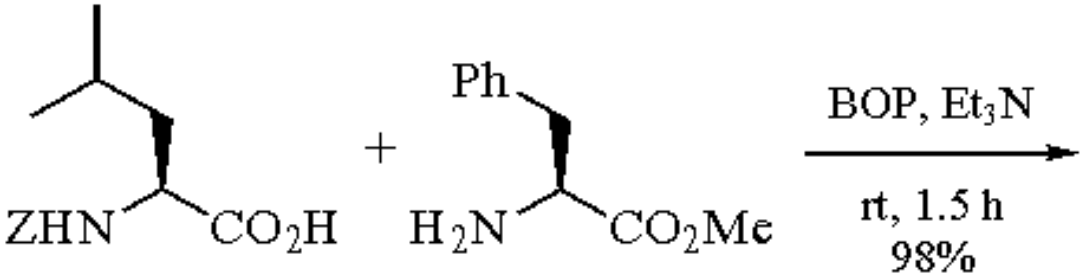

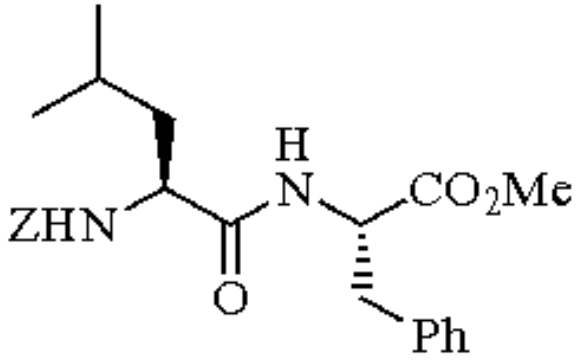

(6)

A second peptide coupling reagent that incorporates the HOBT unit is ***O-Benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium Hexafluorophosphate*** (HBTU),[13] which can be prepared by the reaction of tetramethylurea with oxalyl chloride followed by treatment with HOBT and ***Potassium Hexafluorophosphate***. HBTU can then be used as a direct coupling agent as outlined in eq 7.

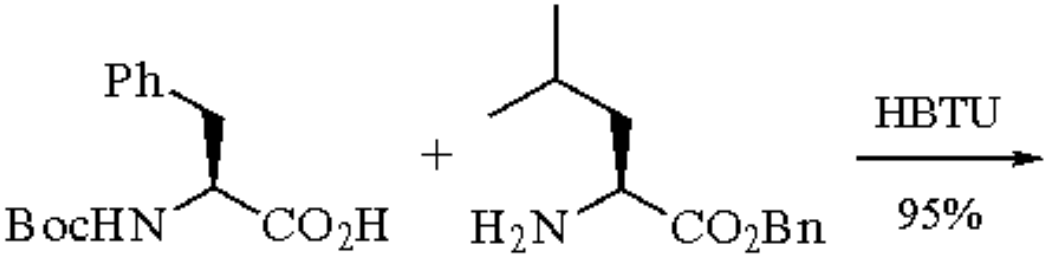

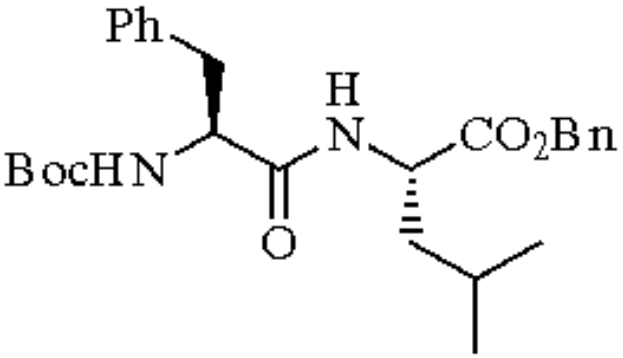

(7)

Nucleotide Synthesis.

Phosphotriester derivatives of HOBT have been employed in the synthesis of nucleotides.[14] The phosphotriesters are readily formed by reaction of HOBT with the corresponding aryl phosphorodichloridates in the presence of pyridine

and can then be used to couple nucleosides as outlined in eq 8. This reaction takes advantage of the fact that a differentially protected nucleoside will react rapidly with the reagent, displacing one molecule of HOBT to form an intermediate phosphotriester (**2**), but at this stage reaction with a second nucleoside molecule is extremely slow due to steric hindrance. Consequently the intermediate can then be reacted with a second nucleoside, the more reactive primary hydroxy displacing the second molecule of HOBT and giving the coupled product. This method for coupling nucleosides has been applied to both solution and solid-phase synthesis of a variety of RNA fragments.

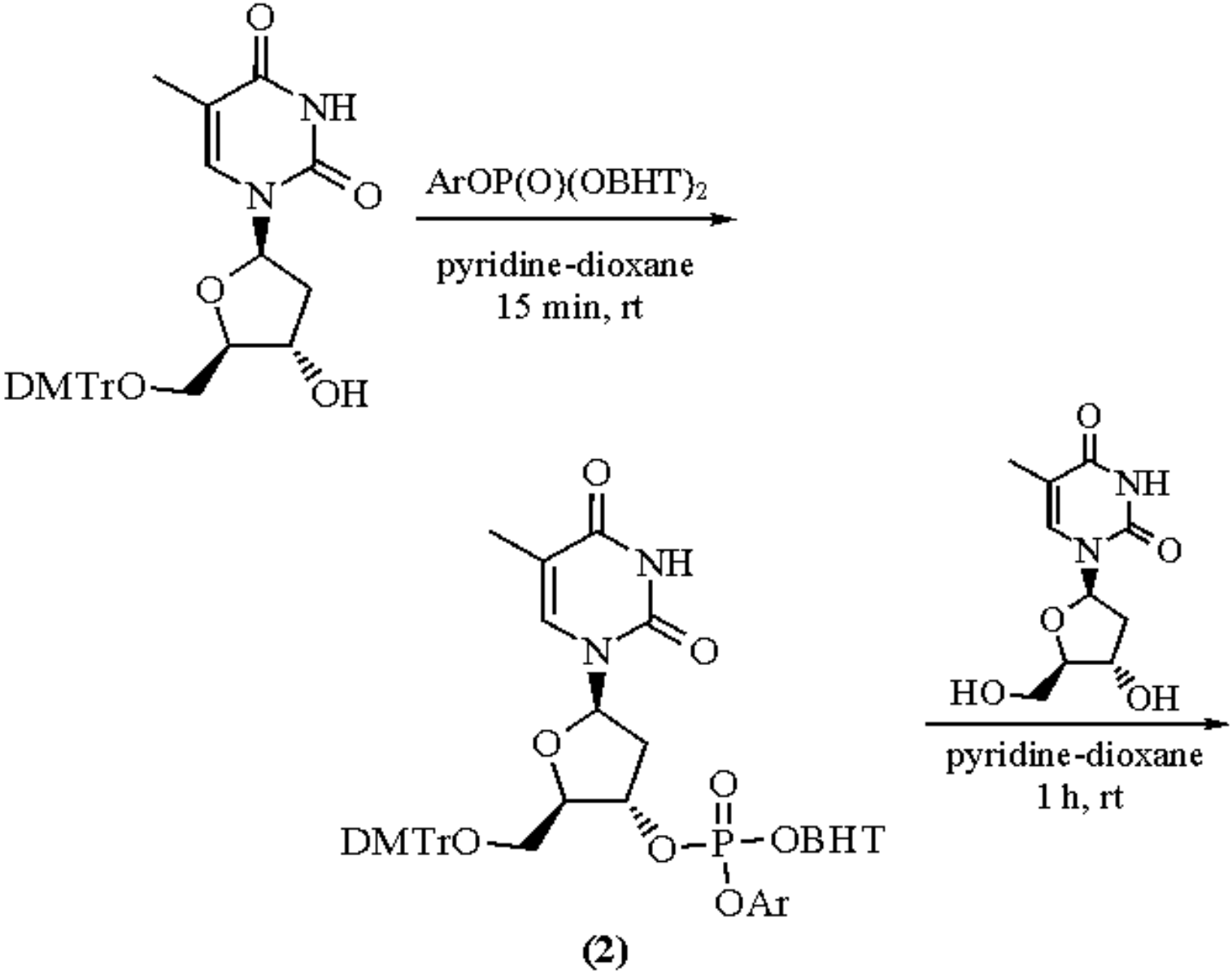

Ar = 2-chlorophenyl

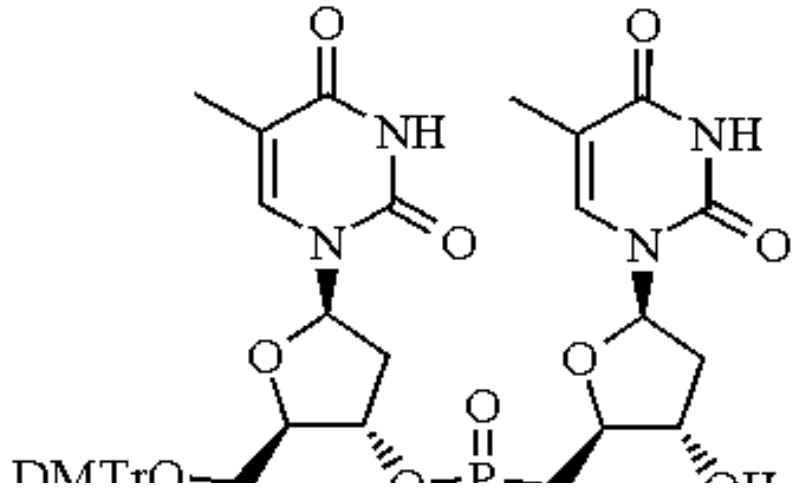

(8)

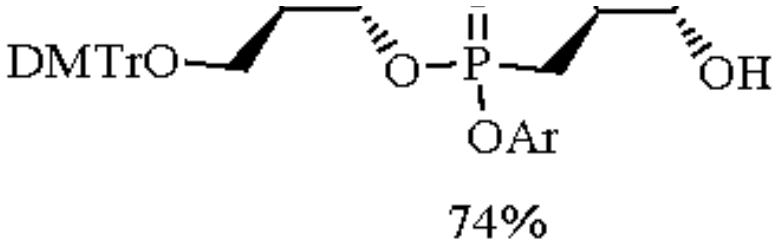

Other Applications.

HOBT has also been employed as a catalyst for the conversion of isoamides into maleimides (eq 9).

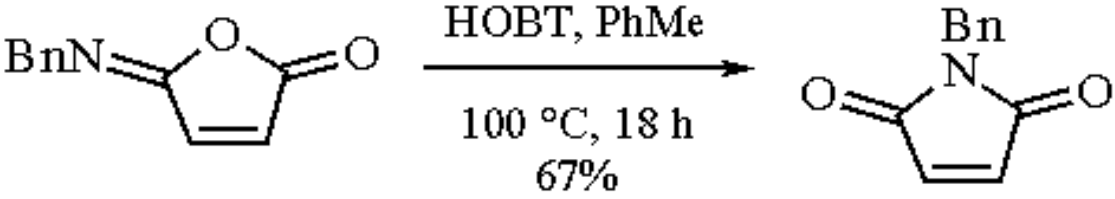

(9)

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1. For recent general reviews on peptide synthesis involving the use of HOBT, see: Bodanszki, M. *Int. J. Pept. Protein Res.* **1985**, *25*, 449; Kent, S. B. H.; *Annu. Rev. Biochem.* **1988**, *57*, 957; Bodanszky, M. *J. Protein Chem.* **1989**, *8*, 461; Fields, G. B.; Nobel, R. L. *Int. J. Pept. Protein Res.* **1990**, *35*, 161.
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(*S*)-(2-Hydroxy-*N,N*-dimethylpropanamide-*O,O´*)oxodiperoxymolybdenum(VI)

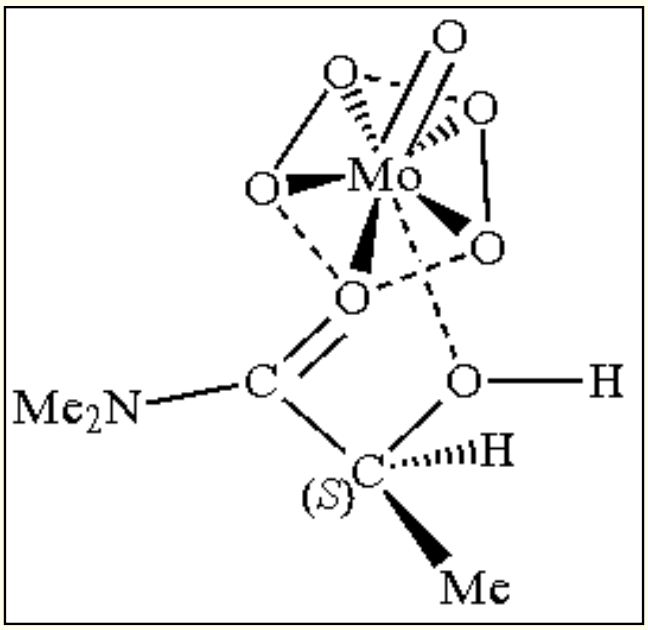

[70355-53-2] · $C_5H_{11}MoNO_7$ · (*S*)-(2-Hydroxy-*N,N*-dimethylpropanamide-*O,O´*)oxodiperoxymolybdenum(VI) · (MW 293.11)

(enantioselective epoxidation of unfunctionalized simple alkenes[1])

Physical Data: mp 149 °C (dec). According to X-ray structural analysis, the molecule has the pentagonal bipyramidal geometry with sevenfold coordinated molybdenum.

Solubility: sol ethanol; insol ether.

Form Supplied in: yellow microcrystalline powder. *Drying:* dried under vacuum.[1]

Preparative Method: to 5mL aqueous hydrogen peroxide solution (30%) is added, in portions, 1 g molybdenum(VI) oxide at 20 °C. The mixture is stirred at 20 °C for 20 min and at 40 °C for 4 h. After most of the molybdenum oxide has dissolved the mixture is filtered. The yellow solution is treated at 10 °C with 1 equiv of ligand dissolved in approx. 4 mL methanol. The mixture is stirred for 30 min at 20 °C, concentrated and kept 12 h at 0 °C. When the complex does not crystallize after addition of dichloromethane or benzene, the mixture is diluted with ethanol and carefully (shield protection) concentrated on a rotary evaporator. The procedure is repeated five times. The mixture is then further concentrated. The complex is usually obtained as a yellow microcrystalline powder, but if it is obtained as an oil the addition of diethyl ether with stirring at 5 °C yields a yellow powder.

Handling, Storage, and Precautions: necessary care should be taken when preparing and handling

peroxometal compounds. Fast and complete concentration of the mixture containing the compound may lead to deflagration of the complex. The complex decomposes at temperatures above 100 °C, changing color from yellow to blue and black. The complex is stored at 5 °C in <0.5 g portions.

Asymmetric Epoxidation.[2]

Methods[3] are known for asymmetric epoxidation of prochiral alkenes having activated C=C double bonds (styrene, allyl alcohol, conjugated ketones, quinone). The title optically active metal-peroxo complex (**1**) is capable of asymmetric epoxidation of simple unfunctionalized alkenes. Simple prochiral alkenes such as propene or *trans*-2-butene are epoxidized stoichiometrically to optically active oxiranes by (**1**) in nitrobenzene at 20 °C/1 bar. The chemical yield is about 70%. The enantiomeric excess is around 30% and the configuration of the dominant oxirane enantiomer is (*R*). A marked increase in enantiomeric yield for trimethyloxirane from 2-methyl-2-butene is observed on reducing the reaction rate by lowering the temperature. The increasing steric hindrance of the alkyl group in 3-methyl-1-butene surprisingly leads to a decrease in the asymmetric induction. The continuously monitored enantiomeric composition of the oxiranes during the reaction remained constant within experimental accuracy. This shows that the alkene epoxidation is asymmetrically induced and that no enrichment of the enantiomers of the epoxide that is formed takes place by kinetic resolution. The asymmetric induction decreases in the order of propene > 1-butene > 3-methyl-1-butene with the preferential formation of (*R*)-alkyloxiranes.[1] The ee increases with inversion of prochiral recognition for 3,3-dimethyl-1-butene, resulting in the preferential formation of (*S*)-*t*-butyloxirane. *trans*-2-Butene undergoes higher asymmetric induction than does *trans*-2-pentene, whereby (2*S*,3*S*)-*trans*-2-methyl/ethyl-3-methyloxiranes are preferentially formed. The asymmetric epoxidation of *cis*-2-pentene leads to the preferential formation of (2*S*,3*R*)-2-ethyl-3-methyloxirane. Geminal ethyl/methyl disubstitution at the double bond in 2-methyl-1-butene shows no enantiofacial discrimination and, consequently, only racemic 2-ethyl-2-methyloxirane is formed. In connection with the synthesis of aranciamycinone,[4] complex (**1**) has been used for the asymmetric epoxidation of the nonfunctionalized alkene (**2**).[5] The alkene (**2**) (eq 1) is treated with diluted solutions (1 mmol in 300 mL of dichloromethane) of the molybdenum(VI)-oxodiperoxo complex. Decreasing the temperature to 0 °C raises the enantiomeric yield to 53% ee. The absolute configuration of the predominantly formed enantiomer (**3**) was determined by an unequivocal sequence of reactions to a known glycoside.

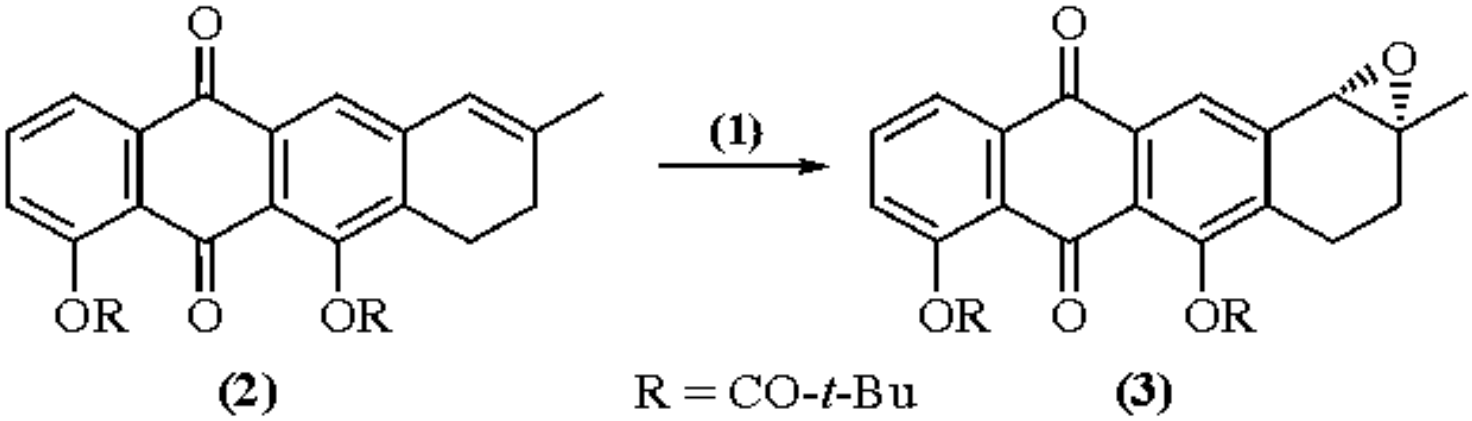

(1)

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β-Hydroxyethyltriphenylarsonium Bromide

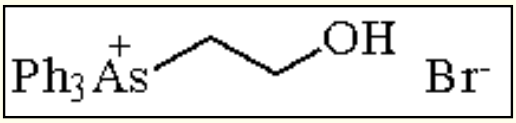

[57813-28-2] · $C_{20}H_{20}AsBrO$ · β-Hydroxyethyltriphenylarsonium Bromide · (MW 431.22)

(epoxidation reagent for aromatic aldehydes with solid KOH under phase-transfer conditions)

Physical Data: mp 199 °C.

Preparative Methods: prepared from triphenylarsine and bromoethanol without solvent at 110 °C for 4 h in 69% yield;[1] mp and ^{1}H NMR spectrum coincide with those reported by another method[2] in which the reaction was carried out in an autoclave.

Handling, Storage, and Precautions: the toxicity of this reagent is unknown at present. Use in a fume hood.

2,3-Epoxy alcohols can be directly synthesized from aromatic aldehydes at ambient temperature in good yields by treatment with β-hydroxyethyltriphenylarsonium bromide using solid ***Potassium Hydroxide*** as a base (eq 1).

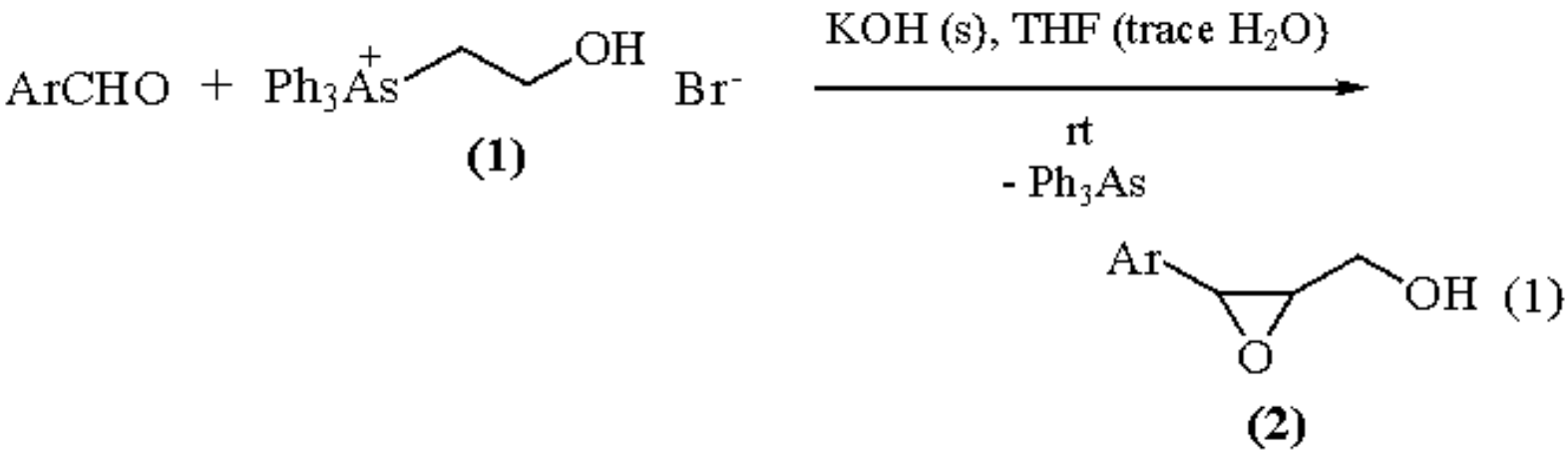

Weak bases such as triethylamine, piperidine, and K_2CO_3 do not promote this reaction; strong bases such as $KN(SiMe_3)_2$ and BuLi, usually employed to generate nonstabilized arsonium ylides,[3] are not suitable for this reaction. Using solid-liquid phase-transfer process (KOH (s)/THF (trace H_2O) system), the 2,3-epoxy alcohol products are obtained in good yields. The (*E*):(*Z*) ratio in each case is around 9:1 with the (*E*)-isomer predominating.

The general procedure is as follows. Arsonium salt (**1**) (1.2 mmol), aldehyde (1 mmol), and KOH (s) (1.2 mmol) are mixed in 4 mL of THF (trace H_2O) under N_2 and stirred at 25 °C. After the reaction is complete, the reaction mixture is

filtered. The products (**2**) (eq 1) are obtained after flash chromatography.

The related compound, (*E*)-4-hydroxy-2-butenyltriphenylarsonium halide (**3**), is a precursor of a good ylide epoxidation reagent for aromatic aldehydes. This reagent is prepared (75% yield) by treatment of Ph_3As with (*E*)-4-chloro-2-buten-1-ol and a catalytic amount of ***Potassium Iodide*** in MeCN. (*E*)-4-Chloro-2-buten-1-ol, in turn, is prepared via ***Lithium Aluminum Hydride*** reduction of butyne-1,4-diol with subsequent treatment with ***Thionyl Chloride*** (eq 2).[4]

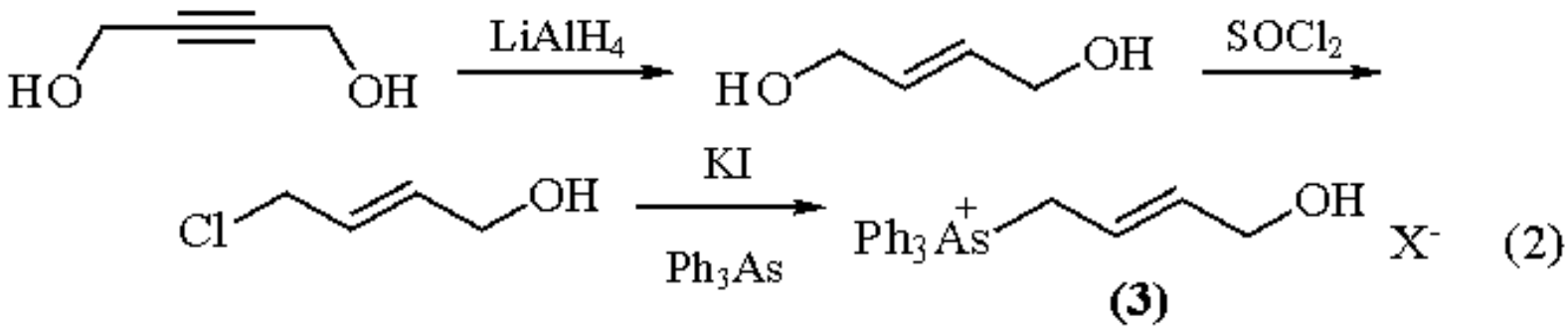

Aromatic aldehydes react with arsonium salt (**3**) in MeCN (trace H_2O) at ambient temperature in the presence of $KF.Al_2O_3$[5] for 12-35 h to give exclusively (*E*)-5-aryl-4,5-*trans*-epoxy-2-penten-1-ols in moderate to good yields (53-78%) (eq 3). When cinnamaldehyde is used as substrate, (*E*)-5-(2-styrenyl)-4,5-*trans*-epoxy-2-penten-1-ol is obtained in 70% yield.[4] The formation of highly stereoselective *trans*-epoxide may be explained by the mechanism shown in eq 4.

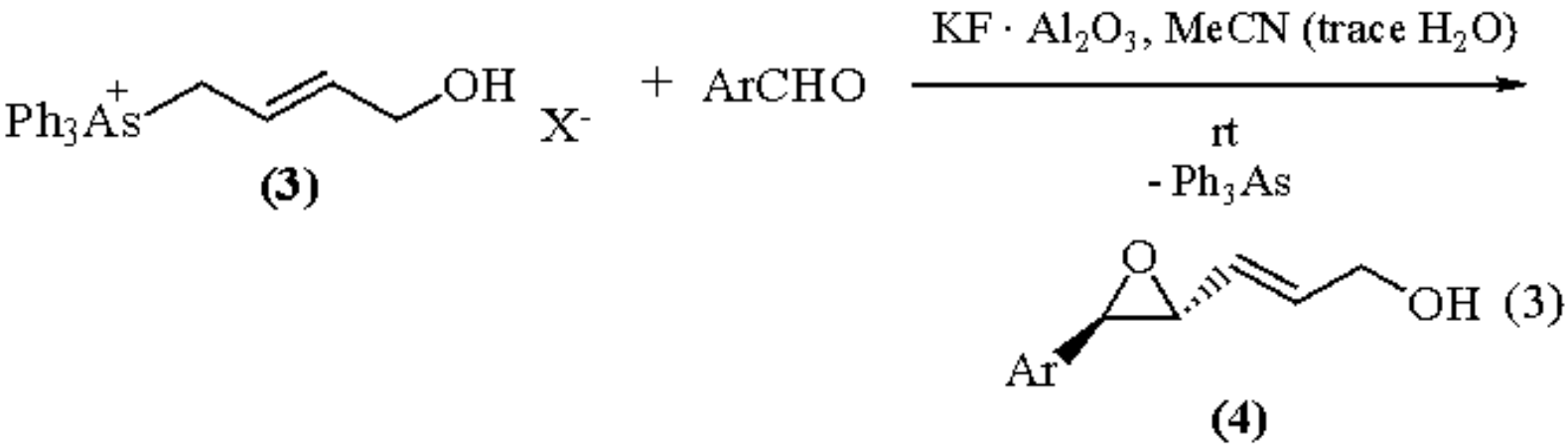

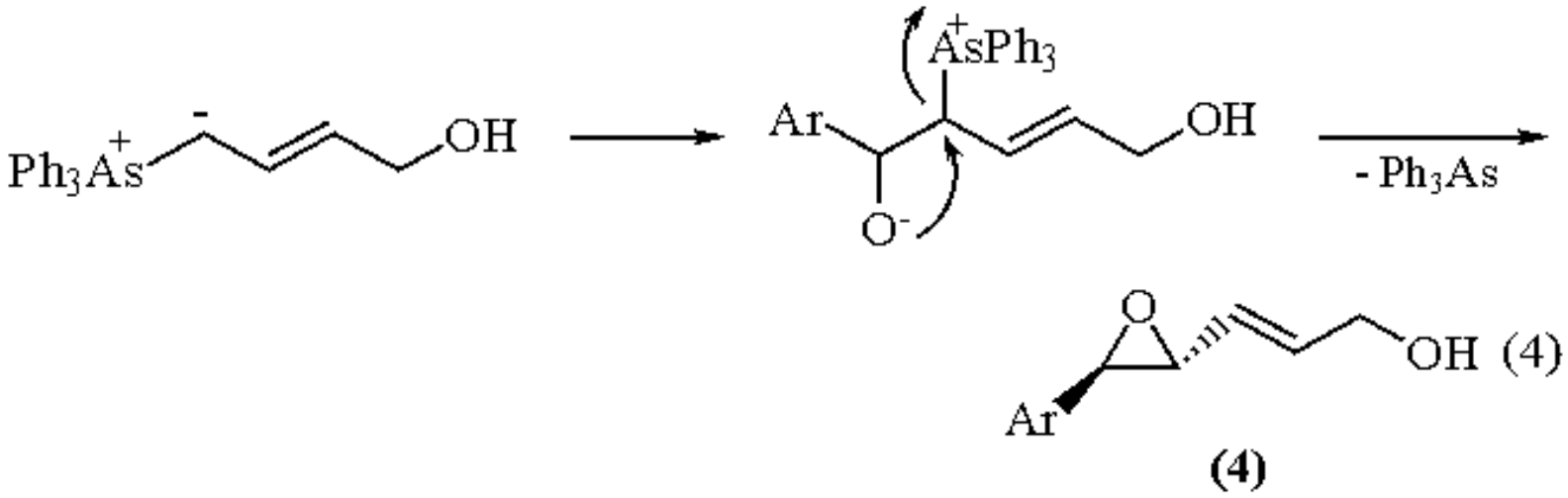

The following is a typical procedure. A mixture of arsonium salt (**3**) (310mg), PhCHO (0.5 mmol), and $KF.Al_2O_3$ (120 mg) in MeCN (2 mL, trace H_2O) is stirred at ambient temperature under N_2 for 28 h (monitored by TLC). The reaction mixture is filtered and washed with acetone. The filtrate is evaporated under reduced pressure and the product is purified by flash chromatography.

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3-Hydroxyisoborneol[1]

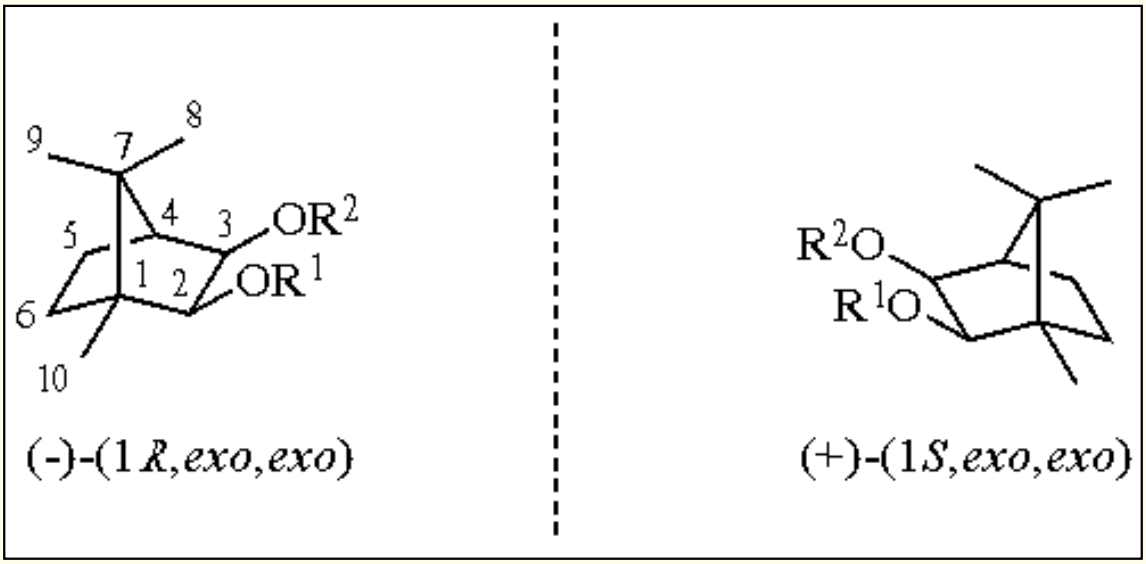

(**1**; R^1 = neopentyl, R^2 = H) (1*R*,*exo*,*exo*)

[85695-96-1] · $C_{15}H_{28}O_2$ · 3-Hydroxyisoborneol 2-Neopentyl Ether · (MW 240.43) (**2**; R^1 = neopentyl, R^2 = H) (1*S*,*exo*,*exo*)

[85718-76-9] · $C_{15}H_{28}O_2$ · 3-Hydroxyisoborneol · (MW 240.43) (**3**; R^1 = H, R^2 = neopentyl) (1*R*,*exo*,*exo*)

[85695-92-7] · $C_{15}H_{28}O_2$ · 3-Hydroxyisoborneol · (MW 240.43) (**4**; R^1 = benzyl, R^2 = H) (1*R*,*exo*,*exo*)

[104154-98-5] · $C_{17}H_{24}O_2$ · 3-Hydroxyisoborneol 2-Benzyl Ether · (MW 260.41) (**5**; R^1 = H, R^2 = benzyl) (1*R*,*exo*,*exo*)

[73440-88-7] · $C_{17}H_{24}O_2$ · 3-Hydroxyisoborneol · (MW 260.41) (**6**; R^1 = Ph_2CH, R^2 = H) (1*R*,*exo*,*exo*)

[85695-93-8] · $C_{23}H_{28}O_2$ · 3-Hydroxyisoborneol 2-Benzhydryl Ether · (MW 336.51) (**7**; R^1 = 1-naphthylmethyl, R^2 = H) (1*R*,*exo*,*exo*)

[85695-95-0] · $C_{21}H_{26}O_2$ · 3-Hydroxyisoborneol 1-Naphthylmethyl Ether · (MW 310.47) (**8**; R^1 = 2-naphthylmethyl, R^2 = H) (1*R*,*exo*,*exo*)

[85695-94-9] · $C_{21}H_{26}O_2$ · 3-Hydroxyisoborneol 2-Naphthylmethyl Ether · (MW 310.47)

(chiral auxiliary; acrylate[2] and acyl nitroso[3] derivatives undergo stereoselective [4 + 2] cycloadditions; enoate derivatives undergo stereoselective 1,4-conjugate additions of organocopper reagents;[4] enol ether derivatives undergo stereoselective Pauson-Khand cyclizations,[5] [4 + 2][6] and [2 + 2][7] cycloadditions; alkynyl ether derivatives undergo stereoselective Pauson-Khand cyclizations[5])

Alternate Name: 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-diol.

Physical Data: (**1**) mp 4-5 °C; [α]25D (EtOH) -42.4° (*c* = 1.40). (**2**) mp 4-5 °C; [α]25D (EtOH) +42.6° (*c* = 2.52). (**3**) oil; [α]25D (EtOH) -18.8° (*c* = 1.08). (**4**) oil; bp 130 °C/0.05 mmHg; [α]25D ($CHCl_3$) -36.1° (*c* = 1.44). (**5**) mp 43 °C; [α]25D (EtOH) +0.4° (*c* = 4.99). (**6**) mp 57 °C; [α]25D (EtOH) -107.6° (*c* = 1.70). (**7**) mp 69-70 °C; [α]25D (EtOH) -79.2° (*c* = 0.90). (**8**) mp 70-71 °C; [α]25D (EtOH) -61.5° (*c* = 0.57).

Preparative Methods: the 3-hydroxyisoborneol derivatives are readily prepared from (+)- or (-)-camphor. The preparation of the 2-neopentyl ether derivative (**1**) is representative (eq 1).[2b] Analogous alkylation with different electrophiles allows for easy variation of the shielding moiety.[2c,8] The corresponding 3-substituted derivatives have been prepared from either 3-hydroxyisoborneol after separation of the regioisomeric mixture or from 3-*exo*-hydroxycamphor regioselectively after reduction with ***Lithium Tri-s-butylborohydride*** (L-Selectride).[2c,9]

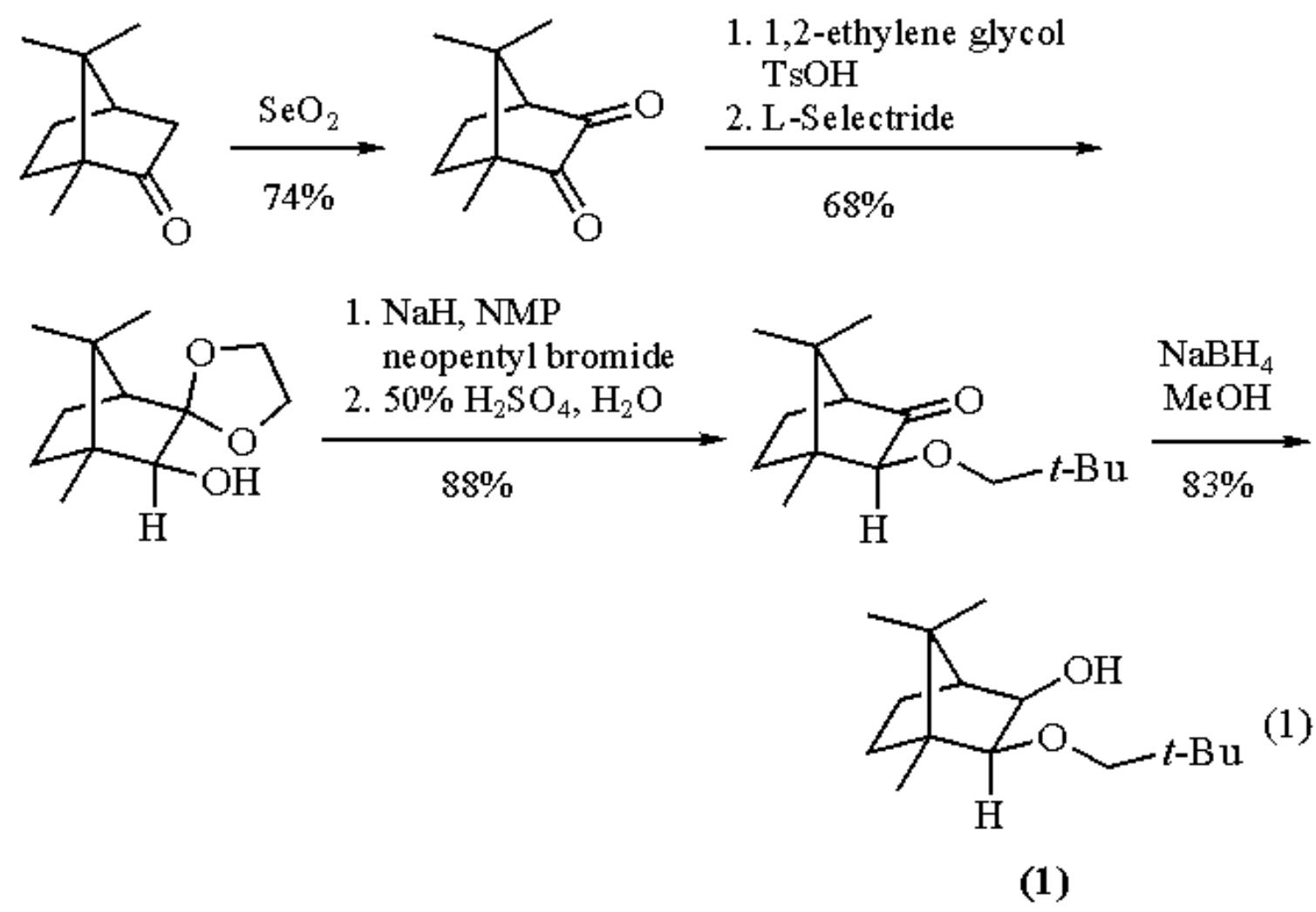

Handling, Storage, and Precautions: these auxiliaries vary from oils to white crystalline solids depending on the ether substituent and are stable indefinitely at ambient temperatures in sealed containers.

Introduction.

The abundance of (+)-camphor in the chiral pool provided Oppolzer with an excellent framework to develop a chiral auxiliary which provides high levels of stereoselectivity in a wide range of reaction classes. The 3-hydroxyisoborneol skeleton provides two derivatizable positions at C-2 and C-3 of the molecule which are in close proximity to each other. By appending a reactive functionality to one and a sterically shielding appendage to the other, high stereodirecting ability can be envisioned. Likewise by reversing the roles of C-2 and C-3 it is possible to tune the auxiliary to fit the reaction parameters and desired product configuration. These characteristics have provided a means for π-facial differentiation to acrylates, enol ethers, and alkynyl ethers.

Preparation of Derivatives.

Enoate derivatives are prepared from the corresponding chiral alcohol by treatment with acryloyl chloride in the presence of ***Triethylamine*** and catalytic ***4-Dimethylaminopyridine*** or the appropriate carboxylic acid chloride and ***Silver(I) Cyanide***.[2b] Alkynyl ethers are readily available from the potassium alkoxide by treating with ***Trichloroethylene***, in situ dechlorination with ***n-Butyllithium***, and electrophilic trapping.[10] Trapping the intermediate anion with a proton source or ***Iodomethane*** followed by Lindlar reduction of the alkynyl ether affords the corresponding vinyl and 1-(*Z*)-propenyl ether, respectively, while reduction of the alkynyl ether with ***Lithium Aluminum Hydride*** affords the 1-(*E*)-propenyl ether.

[4 + 2] Cycloadditions of Acrylate Derivatives.[2]

Acrylate derivatives undergo highly stereoselective Diels-Alder cycloadditions with 1,3-dienes when promoted by a Lewis acid, ***Dichlorotitanium Diisopropoxide*** or ***Titanium(IV) Chloride*** (eq 2). With the latter, care must be taken to avoid acid mediated cleavage of the auxiliary ether linkage. Generally, 2-substituted auxiliaries (**10**) show higher facial and *endo* selectivity than the corresponding 3-substituted analogs. This has been rationalized by a buttressing effect caused by the C-10 methyl forcing the ether side chain into close proximity to the acrylate. Of the range of shielding moieties examined, the neopentyl ether was shown to provide the highest selectivity. The stereochemical outcome can be explained by assuming that the acrylate adopts an *s-trans* conformation on coordination of the Lewis acid[11] and that the diene approaches from the face opposite the neopentyl ether. It should be noted that the analogous cycloadditions with crotonate derivatives give ve ry poor yields (<7%).[2b] Similar highly stereoselective Diels-Alder cycloadditions have also been reported for fumarate and allenic ester derivatives.[12]

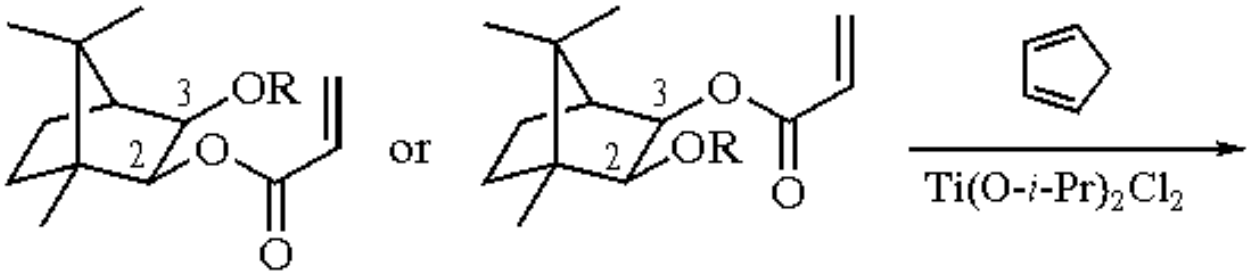

(9) (10)

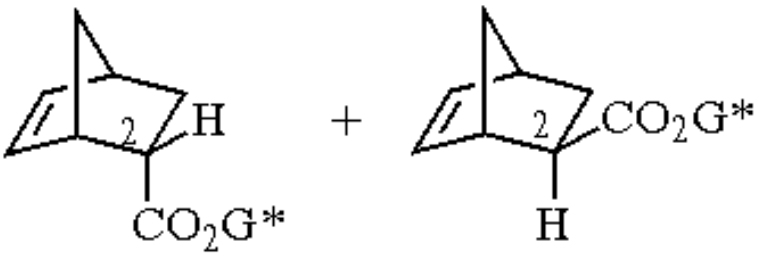

(2)

Acrylate	R	Temp (°C)	Yield (%)	*endo*:*exo*	*endo* adduct % de	*endo* adduct config.
(9)	Benzyl	0	91	86:14	46	(2*S*)
(9)	Diphenylmethyl	-20	94	86:14	64	(2*S*)
(9)	1-Naphthylmethyl	0	97	85:15	54	(2*S*)
(9)	2-Naphthylmethyl	-20	98	90:10	69	(2*S*)
(9)	Neopentyl	-20	95	96: 4	97	(2*S*)
(10)	Diphenylmethyl	-20	74	95: 5	91	(2*R*)
(10)	1-Naphthylmethyl	0	97	93: 7	88	(2*R*)
(10)	2-Naphthylmethyl	-20	98	95: 5	92	(2*R*)
(10)	Neopentyl	-20	96	96: 4	99	(2*R*)

[4 + 2] Cycloadditions of Enol Ether Derivatives.[6]

Asymmetric, inverse electron demand Diels-Alder reactions between nitroalkenes and alcohol (**1**)-derived vinyl and 1-(*E*)- and 1-(*Z*)-propenyl ethers have been reported to proceed with high stereoselectivity (eq 3). The resulting cycloadducts undergo an intramolecular [3 + 2] cycloaddition at rt to afford nitroso acetals which, after hydrogenolytic cleavage, provide tricyclic α-hydroxy lactams in high enantiomeric excess. The auxiliary alcohol can be recovered in 86-92% yield. The overall sense of asymmetric induction is dependent on the Lewis acid promoter employed, either Ti(O-*i*-Pr)$_2$Cl$_2$ or ***Methylaluminum Bis(2,6-diphenylphenoxide)*** (MAPh).[6b] This has been rationalized by a switch from a highly *endo* selective cycloaddition with Ti(O-*i*-Pr)$_2$Cl$_2$ to a highly *exo* selective cyclization with MAPh. When promoted by Ti(O-*i*-Pr)$_2$Cl$_2$ the corresponding 1-(*E*)-propenyl ether shows exclusive *endo* selectivity and 99% facial selectivity; however, facial

selectivity for the 1-(*Z*)-propenyl ether is only 50%.

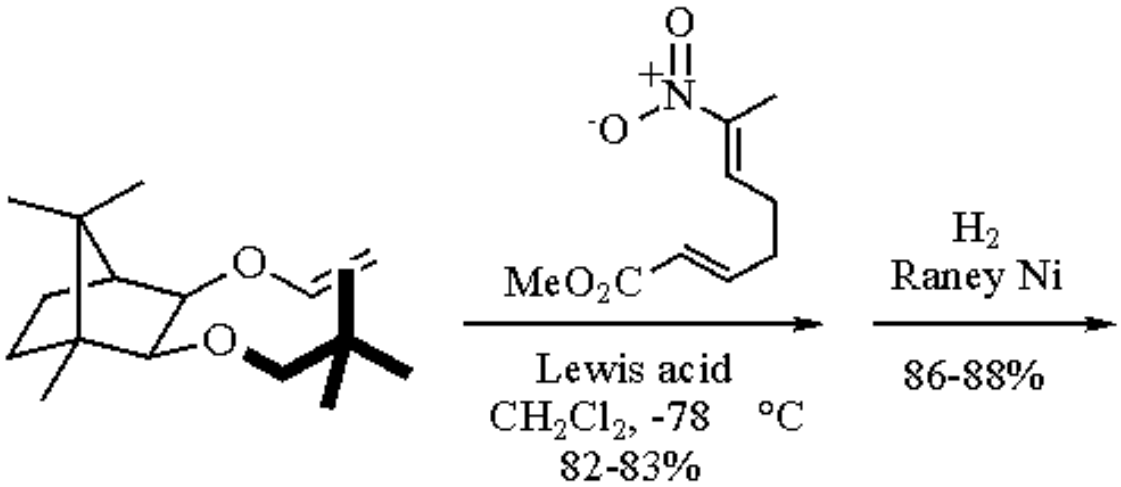

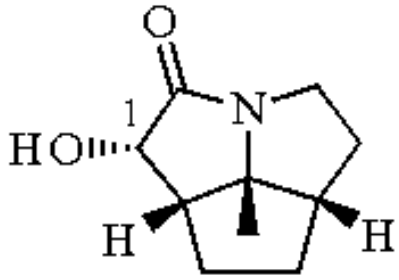

(3)

98% ee (1*S*) $Ti(O\text{-}i\text{-}Pr)_2Cl_2$
99% ee (1*R*) MAPh

[4 + 2] Cycloadditions of Acyl Nitroso Derivatives.[3]

In situ formation of the acyl nitroso derivative by oxidation of the hydroxy carbamic acid under Swern-Moffat conditions in the presence of a functionalized diene affords the corresponding cycloadduct in 94% yield and 96% diastereomeric excess (eq 4). The resulting cycloadduct can be further elaborated to prepare optically active functionalized amino alcohols.

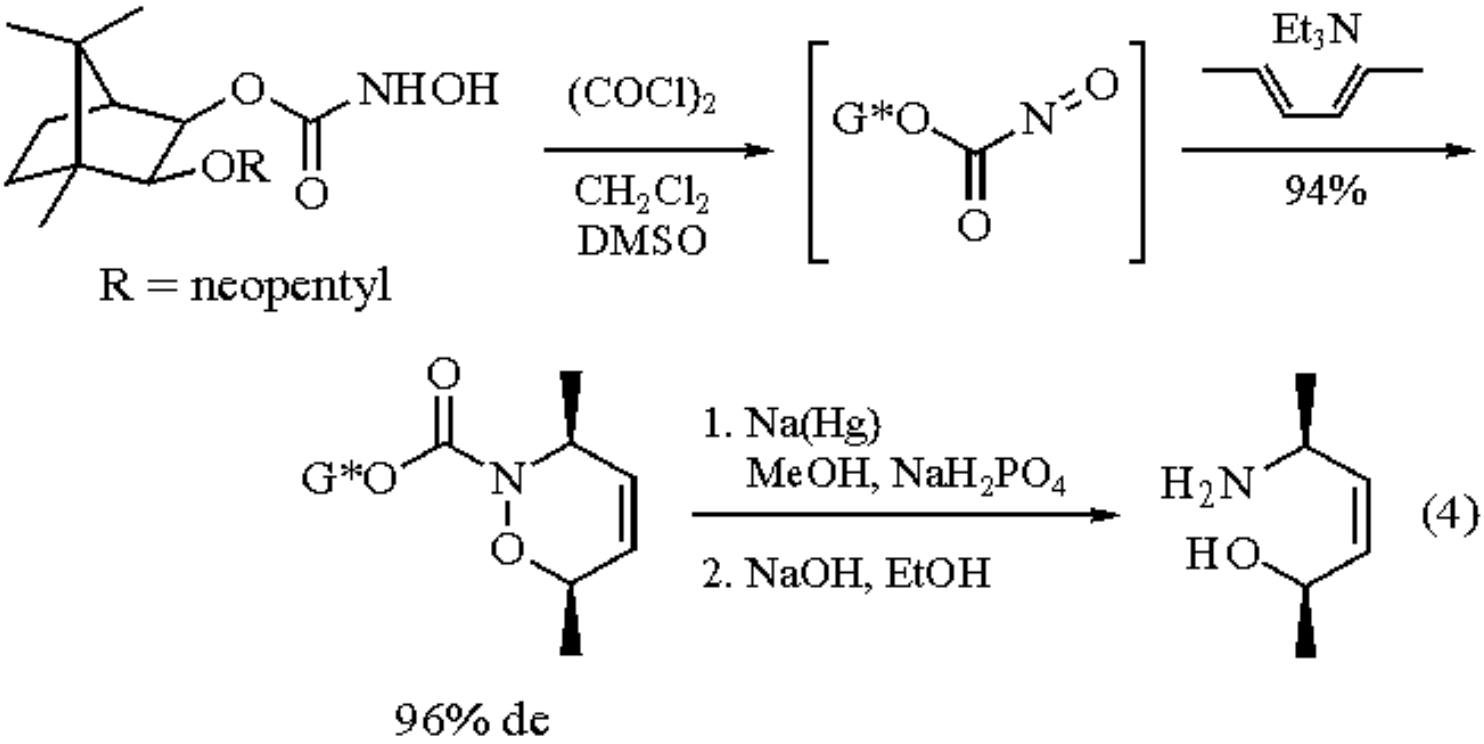

1,4-Conjugate Additions of Enoate Derivatives.[4]

Boron trifluoride-mediated conjugate additions of organocopper reagents to (*E*)-enoates derived from auxiliary (**1**) proceed with high stereoselectivity, affording optically active carboxylic acids after saponification (eq 5). The organocopper reagent is formed by addition of an alkyllithium reagent to ***Copper(I) Iodide***, ***Tri-n-butylphosphine***, and ***Boron Trifluoride Etherate*** in equimolar amounts, where Bu_3P is believed to stabilize the reagent. The overall sense of asymmetric induction can be controlled by changing either the order of substituent introduction (R^1 and R^2) or the configuration of the auxiliary. The stereochemical course of the reaction has been rationalized by assuming that the enoate exists in an *s-trans* conformation and the organocopper reagent approaches from the face opposite to the neopentyl ether. Conjugate additions of this type have been applied to the total synthesis of several natural products.

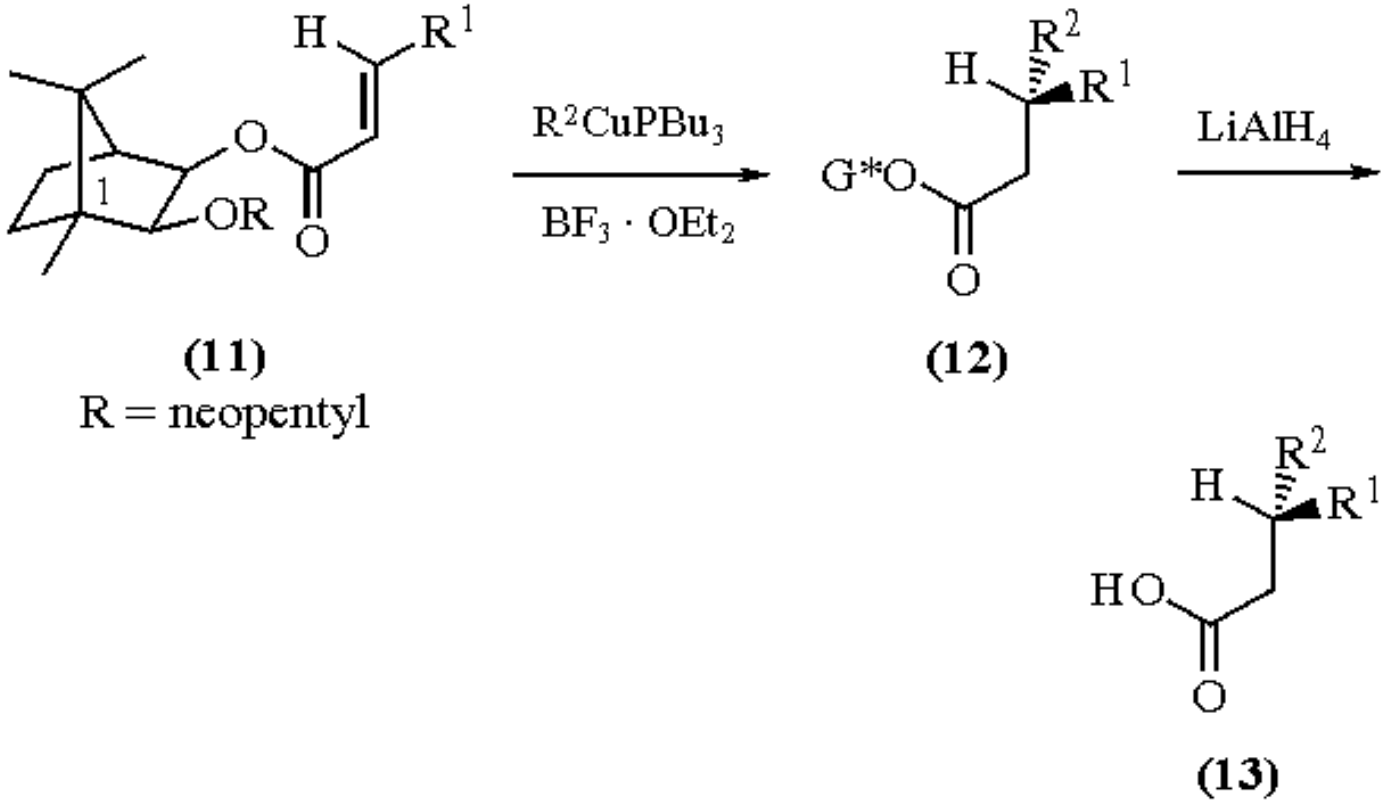

(11)
R = neopentyl

(12)

(13)

(5)

(11) config.	R^1	R^2	(12) yield (%)	(13) % ee	config.
(1*R*)	Bu	Me	82	94	(*R*)
(1*R*)	Et	Me	85	92	(*R*)
(1*R*)	$Me_2C{=}CH(CH_2)_2$	Me	90	92	(*S*)
(1*S*)	Me	$Me_2C{=}CH(CH_2)_2$	81	98	(*S*)
(1*R*)	Me	$H_2C{=}CH$	85	94	(*R*)

Pauson-Khand Bicyclization.[5]

Alkynyl and enol ether derivatives have been studied in the cobalt mediated intramolecular Pauson-Khand reaction and found to provide high diastereoselectivity, superior to previous work with the auxiliary 2-phenylcyclohexanol.[13] The 3-substituted auxiliary alcohol (**3**) provides higher selectivity than the 2-substituted analog. Also, the alkynyl ether derivatives exhibit higher reactivity and selectivity than the corresponding enol ether derivatives (eq 6).

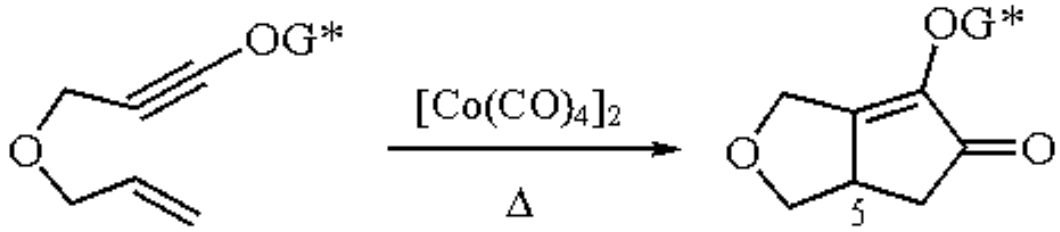

(14)

(6)

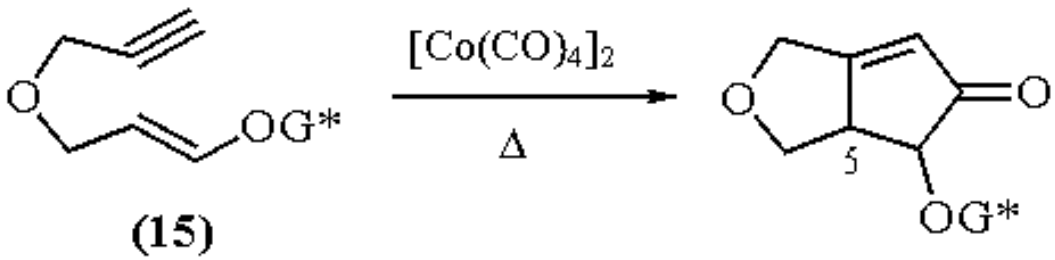

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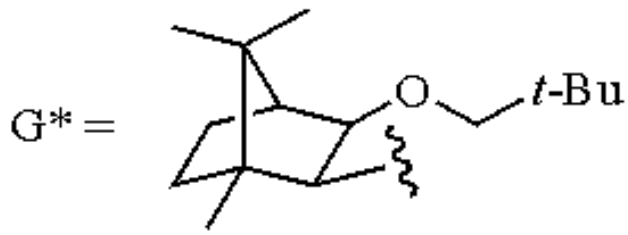

(3)

Enyne	Conditions	Yield (%)	Diastereomer ratio	Config.
(14)	18 °C, 2 h; 25 °C, 2 h; N_2	54	94: 6	(5*R*)
(15)	20 °C, 2 h; 50 °C, 12 h; CO	53	90:10	(5*S*)

Photochemical [2 + 2] Cycloadditions.[7]

Photochemical [2 + 2] cycloadditions between alkenes and chiral phenylglyoxylate derivatives of 3-hydroxyisoborneol show minimal diastereoselectivity (16% de).[14] Better results are obtained in [2 + 2] cycloadditions between chiral enol ethers and ***Dichloroketene*** (eq 7). After ring expansion and expulsion of the auxiliary (***Diazomethane***, ***Chromium(II) Perchlorate***), chiral α-chlorocyclopentenones are obtained in 60% yield. The observed diastereoselectivity is believed to arise from the enol ether *s-trans* conformation and approach of the ketene to the face opposite to the neopentyl ether.

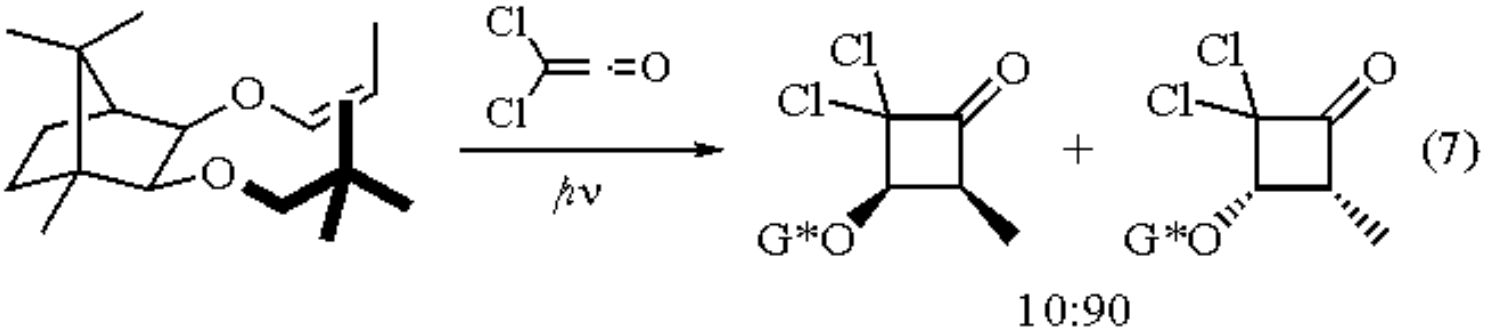

Nondestructive Auxiliary Cleavage.

The high stability of the ether linkage to the shielding moiety generally allows for a very high recovery of the auxiliary alcohol. For acyl derivatives, primary alcohols can be obtained by $LiAlH_4$[2b] or AlH_3[15] reduction. Hydrolysis of the auxiliary under basic conditions providing the carboxylic acid has been accomplished with NaOH in aq. ethanol,[3] NaOH in methanol,[4b] or KOH in ethanol.[16] Intramolecular transesterification has been applied using KO-*t*-Bu in THF.[17] Enol ethers derived from Pauson-Khand cyclizations of alkynyl ether derivatives can be readily cleaved to the corresponding ketone and recovered auxiliary by catalytic HCl in methanol.[5]

Related Reagents.

10,2-Camphorsultam; ***10-Dicyclohexylsulfonamidoisoborneol***; ***(S)-Ethyl Lactate***; α-***Methyltoluene-2,α-sultam***; ***(R)-Pantolactone***.

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Hydroxylamine[1]

$HONH_2$

($HONH_2$)

[7803-49-8] · H_3NO · Hydroxylamine · (MW 33.04) ($HONH_2.HCl$)

[5470-11-1] · ClH_4NO · Hydroxylamine Hydrochloride · (MW 69.50) ($(HONH_2)_3.H_3PO_4$)

[20845-01-6] · $H_{12}N_3O_7P$ · Hydroxylamine phosphate · (MW 197.12) ($(HONH_2)_2.H_2SO_4$)

[10039-54-0] · $H_8N_2O_6S$ · Hydroxylamine Sulfate · (MW 164.17)

(nucleophile in aromatic substitution,[63] oxime-,[36] hydroxamic acid-,[30] pyridine-[61] and isoxazole-forming[56] reactions; reducing agent;[66] in combination with dehydrating agents, used for the conversion of aldehydes to nitriles[43])

Physical Data: $HONH_2$: hydroscopic white needles or flakes; decomposes rapidly at rt; mp 32.05 °C; bp 56.5 °C/22 mmHg, 70 °C/60 mmHg, 110 °C/760 mmHg. $HONH_2.HCl$: white crystals; mp 151 °C; *d* 1.67 g cm^{-3}; pK_{a1} 5.97; pK_{a2} 13.7.[10] $(HONH_2)_3.H_3PO_4$: mp 169-171 °C. $(HONH_2)_2.H_2SO_4$: mp 170 °C (dec).

Solubility: $HONH_2$: decomposes in hot water; sol cold water, methanol; sparingly sol ether, benzene, chloroform, carbon disulfide.[2] $HONH_2.HCl$: 83 g/100 mL in cold water; very sol hot water; 4.43 g/100 mL in EtOH; 16.4 g/100 mL in MeOH; insol ether.

Form Supplied in: hydroxylamine hydrochloride is widely available and is the most commonly used hydroxylamine salt. Each of the other salts listed above is also commercially available, as are $HONH_2.HCl$-d_4 and $HONH_2.HCl$-^{15}N.[6]

Preparative Methods: hydroxylamine base has been prepared by the action of sodium butoxide on the hydrochloride in butanol.[3] The free base can be isolated as a white solid at -30 °C and is stable to storage for several days at -20 °C.[4] It can be prepared just prior to use or, more typically, in situ from one of the salts by treatment with hydroxide, alkoxide, carbonate, or amine base (see below). The preparation of hydroxylamine via the electrochemical reduction of nitric acid has been reported.[5]

Handling, Storage, and Precautions: all of the salts of hydroxylamine are corrosive and hygroscopic. Specific precautions in the literature indicate that the free base is a much more hazardous substance to work with than are the salts.[7] $HONH_2$: a moderately toxic, corrosive irritant to the eye, skin, and mucous membranes. *Explodes at 130 °C. Explodes in air when heated above 70 °C.* May ignite spontaneously in

air, or in contact with PCl_3 or PCl_5. Calcium reacts to give the heat-sensitive explosive bis(hydroxylamide). In the event of a spill, cover with sodium bisulfite and sprinkle with water. $HONH_2$.HCl: harmful if inhaled or swallowed (oral LD_{50} 400-420 mg kg^{-1}; mouse). Not compatible with oxidizing agents. May explode if heated above 115 °C; do not store above 65 °C. A comprehensive review of the biological activity of hydroxylamine and its salts has appeared.[2]

Introduction.

Hydroxylamine, usually as one of its more stable salts, has been used as a nucleophile in a wide variety of reactions and only the most common uses of this versatile reagent are described here. The name hydroxylamine is used throughout this review as a interchangable designator for either the free base or one of its salts. Where appropriate, the specific derivative will be named.

General Reactivity with Simple Electrophiles.

Hydroxylamine and its derivatives undergo reaction with many simple electrophiles such as alkylating, acylating, phosphinylating, and silylating agents, aldehydes and ketones, and Michael acceptors. The potent nucleophilic reactivity of hydroxylamine evident in these transformations is thought to arise as a consequence of what has been labeled the α-effect, an effect observed in a variety of nucleophiles which possess a heteroatom in the position α to the attacking nucleophilic atom.[8] Hydroxylamine reacts with simple electrophiles typically at both nitrogen and oxygen, with multiple reactions often giving rise to undesired side-products. Many derivatives of hydroxylamine have been prepared in an effort to circumvent this potential problem of ambident reactivity (see below).[9]

Reactions with Alkylating Agents: *N* vs. *O* Selectivity.

The products obtained in the reaction of simple alkylating agents with hydroxylamine are exemplary of the ambident reactivity discussed above. In a study directed toward the preparation of *O*-alkylated hydroxylamines, it was found that several benzylic and one alkyl halide react preferentially at oxygen in *t*-butoxide/*t*-butanol solution (eq 1).[10] Results similar to those obtained with benzyl bromide were found for five other benzylic halides.

$$\text{R-X} + \text{NH}_2\text{O}^- \longrightarrow \text{R-ONH}_2 + \text{R-NHOH} + \text{R}_2\text{NOH} \quad (1)$$

RX	Yield (%)	Product distribution
$PhCH_2Br$	52	66:22:12
1-Bromo-2-ethylhexane	30	79:21: -

Selective *N*-alkylation has been accomplished in a wide variety of cases using the hydroxylamine derivative *t*-butyl *N*-benzyloxycarbamate.[11] The preparation of *N*-octylhydroxylamine.HCl is illustrative of this process (eq 2). Ethyl 3-methylhydroxy-4-isoxazolecarboxylate[12] is another versatile reagent which has been developed for this purpose. *O*-

Trimethylsilyl- and *O*-(*t*-butyldiphenylsilyl)hydroxylamine[13] have also seen use in the preparation of *N*-alkylhydroxylamine derivatives, although these reagents have not been shown to be as generally useful in this regard as the previously mentioned two. *N*-Allylation has recently been accomplished via the Pd^0-mediated reaction of *N*,*O*-bis(Boc)hydroxylamine with allylic carbonates, chlorides, and acetates.[14] A similar study showed that the use of $HONH_2$.HCl in the same reaction leads to *N*,*N*-diallylated products.[15] ***N,O-Dimethylhydroxylamine***.HCl has been prepared on a large scale by dimethylation (***Dimethyl Sulfate***) of ethyl hydroxycarbamate at pH 11-12 followed by acidolysis.[16]

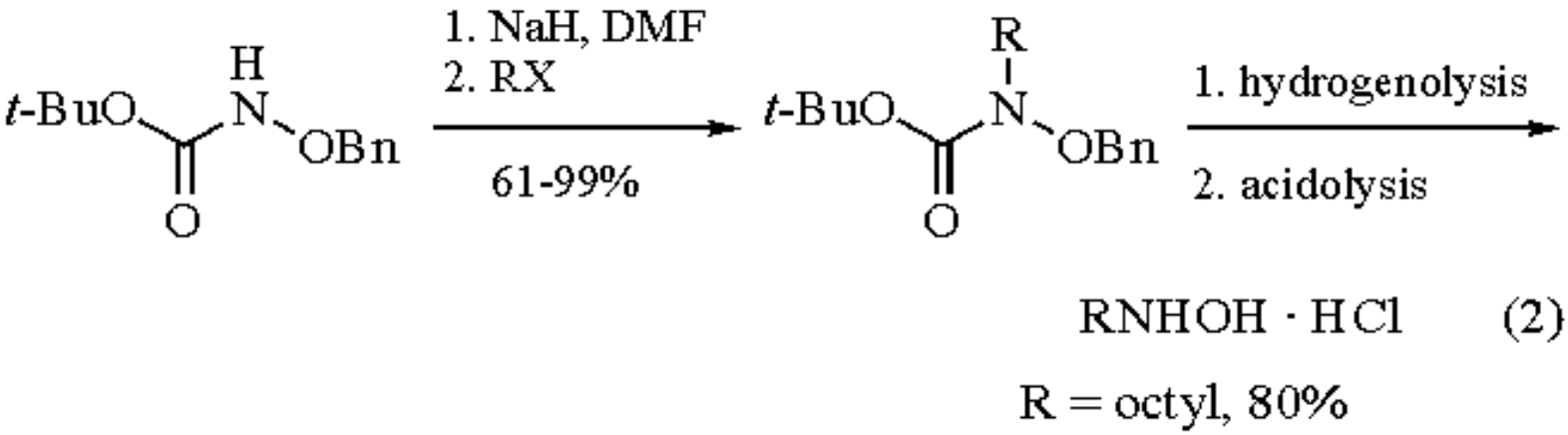

Reactions with Silylating Agents.

O-Mono-, *N*,*O*-bis-,[17] and *N*,*N*,*O*-tris(trimethylsilylated)[18] derivatives of hydroxylamine have been prepared. One distinct advantage of these silylated hydroxylamine reagents is their solubility in nonpolar solvents in which hydroxylamine and its salts show poor solubility. ***N,O-Bis(trimethylsilyl)hydroxylamine*** undergoes facile *O*,*N*-silyl transfer upon treatment with ***n-Butyllithium*** in ether, allowing the generation the lithium salt of *N*,*N*-bis(trimethylsilyl)hydroxylamine in situ.[19] This species plays an important role in the preparation of *O*-arenesulfonyl- and *O*-arenecarbonylhydroxylamines.[20]

Reactions with α-Halo or α-Hydroxy Esters: Preparation of *N*-Hydroxy-α-amino Acids.

Hydroxylamine and its derivatives have been reacted with both α-halo and α-hydroxy esters as a method to prepare *N*-hydroxy-α-amino acid derivatives.[21] While hydroxylamine has seen some utility along these lines with *t*-butyl esters (eqs 3 and 4),[22,23] the use of derivatives such as *N*-[(trichloroethoxy)carbonyl]-*O*-benzylhydroxylamine[24] and ***O-Benzylhydroxylamine Hydrochloride***[25] appear to offer some advantages. The latter reagent has been used in the displacement of the triflates of (*R*)- or (*S*)-α-hydroxy esters, leading to *N*-hydroxy-α-amino methyl esters with both excellent chemical yield and optical purity.[26]

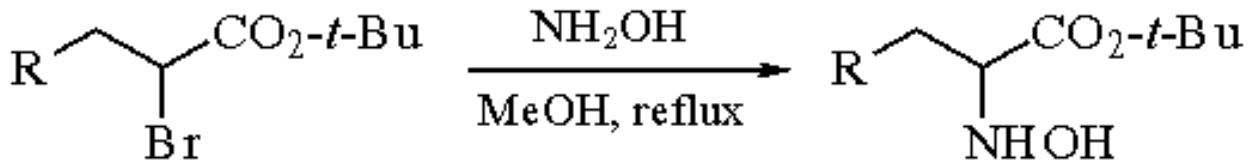

(3)

R = H, 98%; Me, 97%; Et, 97%

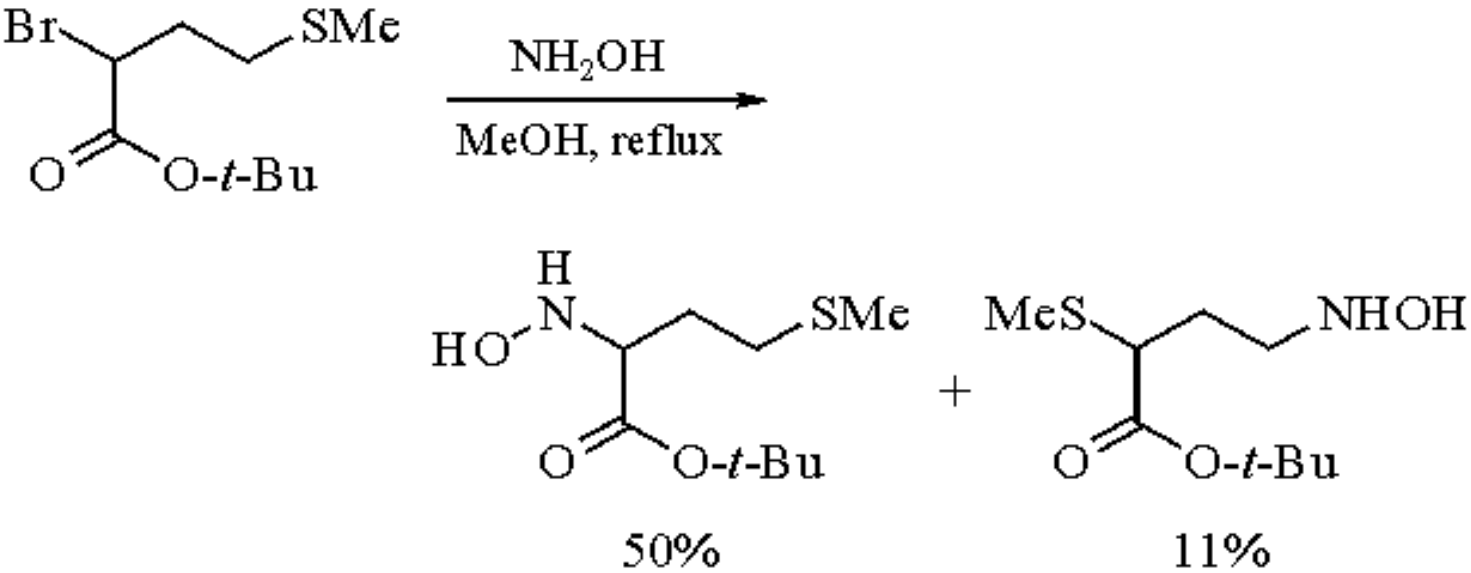

(4)

Reactions with Michael Acceptors.

The reaction of hydroxylamine hydrochloride with Michael acceptors offers a convenient synthesis of β-amino acids and esters. The preparation of (±)-β-aminophenylpropionic acid has been reported wherein the reduction of the hydroxyamine is effected with a second equiv of $HONH_2$.HCl (eq 5).[27] In a more comprehensive investigation of this reaction, it was found that catalytic reduction of the intermediate hydroxylamine leads to better yields (70% in the case shown in eq 5) of the amino acid.[28]

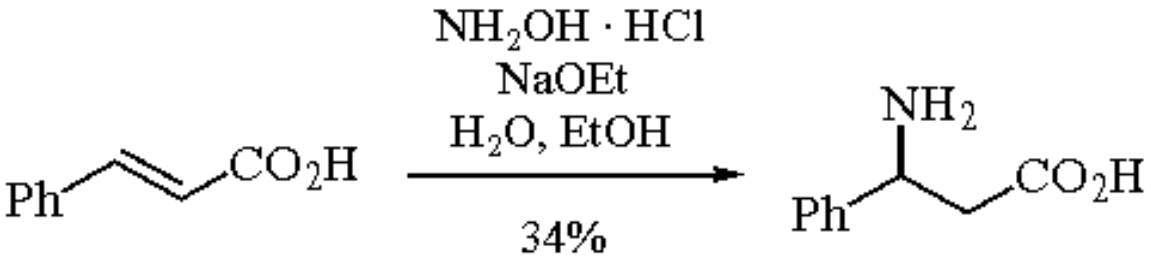

(5)

Tandem Michael additions are also known, the reaction of phorone with hydroxylamine giving a highly congested, cyclic hydroxylamine derivative (eq 6).[29]

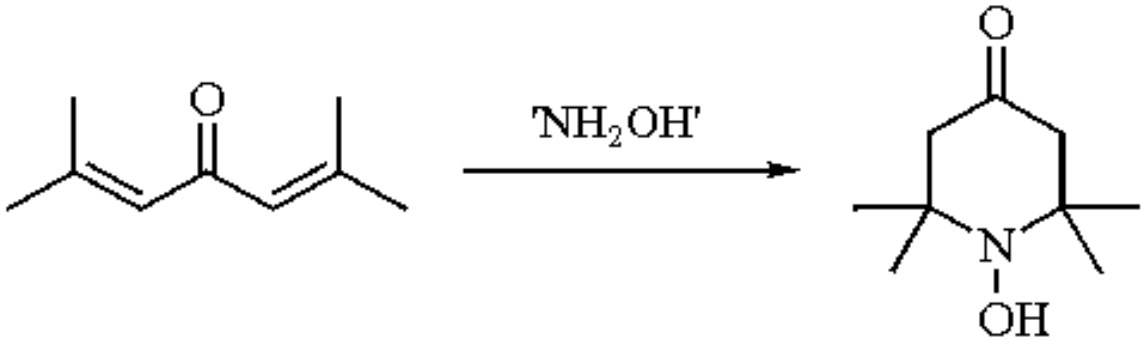

(6)

Reaction with Acid Derivatives: Preparation of Hydroxamic Acids.

Hydroxylamine and its derivatives have been reacted with esters and acid halides to prepare hydroxamic acids. The reaction of $HONH_2$.HCl with esters is particularly useful along these lines because overacylation is not a problem (eq 7).[30,31]

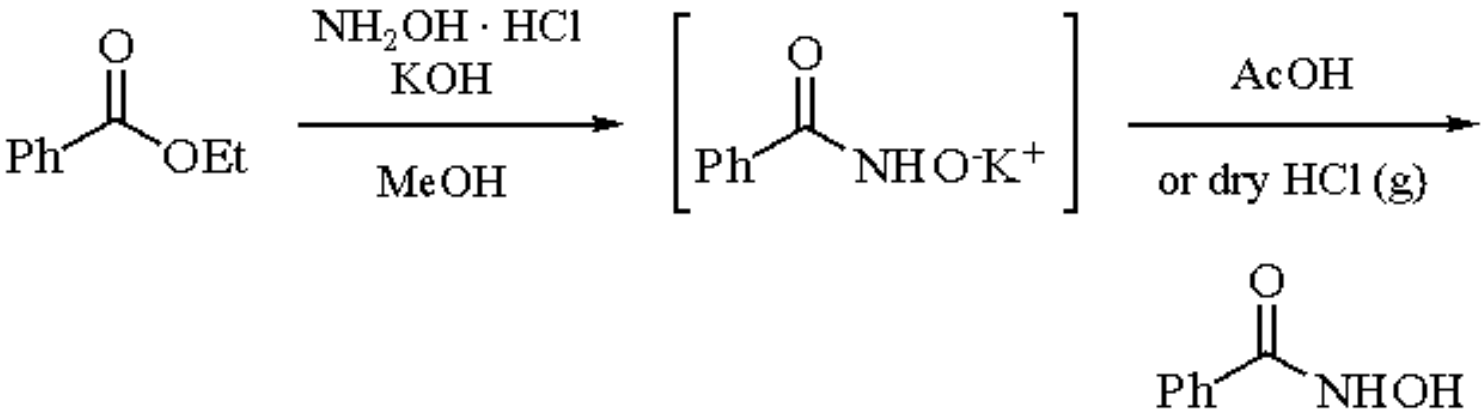

(7)

Reaction of hydroxylamine with acid halides can result in the formation of di- and triacylated products in addition to the desired hydroxamic acid. As is the case with alkylation, several hydroxylamine derivatives have been developed to address this problem. *O*-benzyl-,[32] *N*,*N*,*O*-tris(trimethylsilyl)- (eq 8),[33] *N*-Boc-*O*-TBDMS-, and *N*-Boc-*O*-THP-hydroxylamine (eq 9)[34] have all proven to be useful for the synthesis of protected hydroxamic acids.

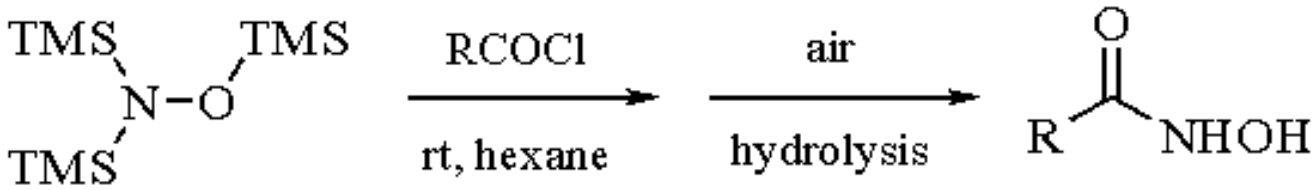

(8)

R = Me, 85%; Et, 92%; Ph, 95%

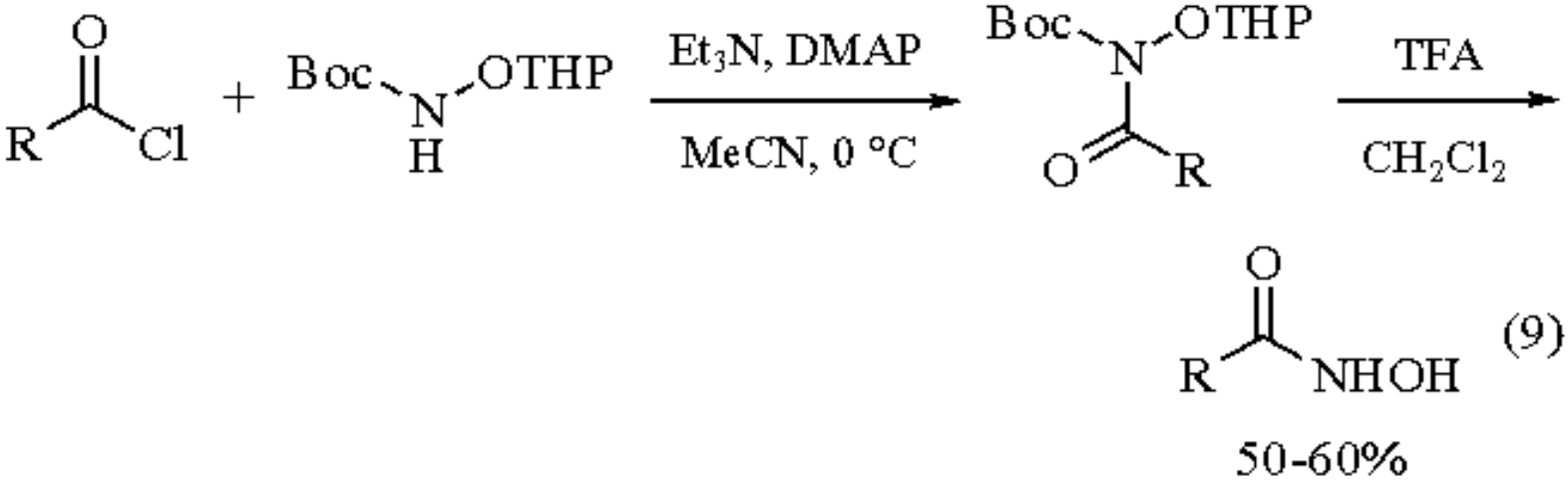

(9)

The reaction of succinic anhydride with hydroxylamine (prepared from NaOMe and $H_2NOH.HCl$ in MeOH) leads to *N*-hydroxysuccinimide.[35]

Reaction with Aldehydes and Ketones: Oxime Formation.

Reaction of hydroxylamine with an aldehyde or ketone under basic or acidic conditions leads to the formation of the corresponding oxime. For example, the (*E*) and (*Z*) isomers of 4-acetylpyridine oxime have been prepared via the reaction of 4-acetylpyridine with $HONH_2.HCl$ (eq 10).[36]

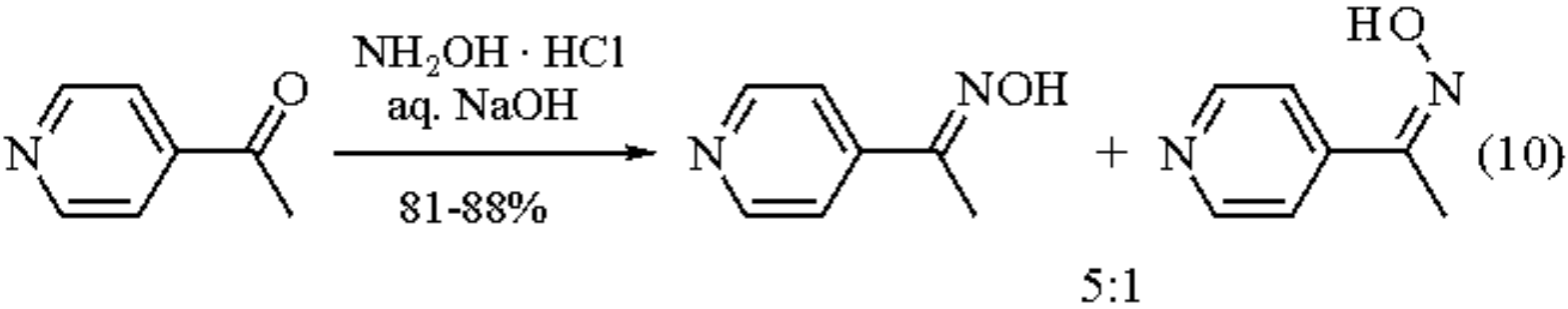

(10)

Other examples of this reaction include the preparation of the oxime of methyl glyoxylate (eq 11)[23] and the oximes of some difluoromethylene-containing chiral aldehydes (eq 12).[37]

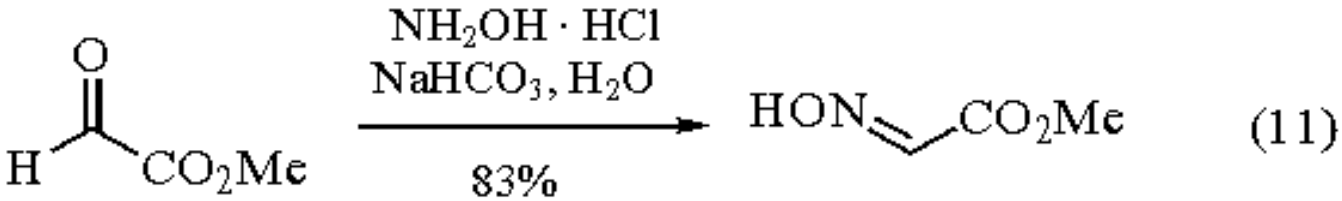

(11)

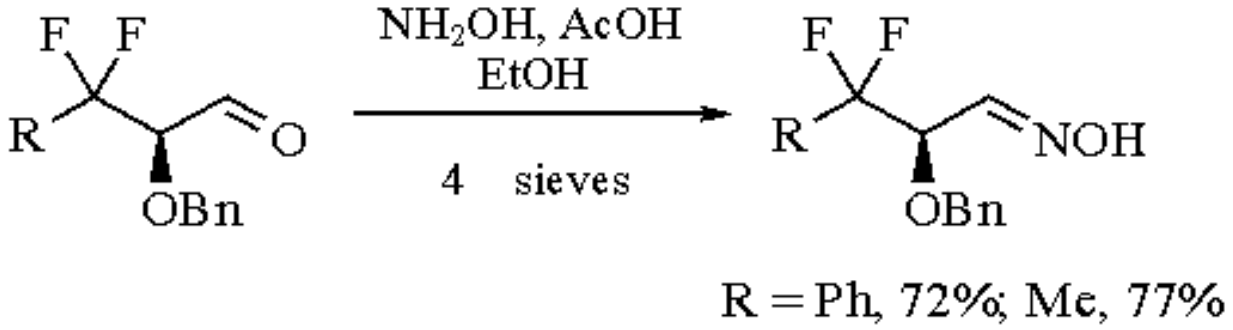

(12)

Both hydrazones (eq 13)[38] and enol esters (eq 14)[39] are efficient carbonyl surrogates in this transformation.

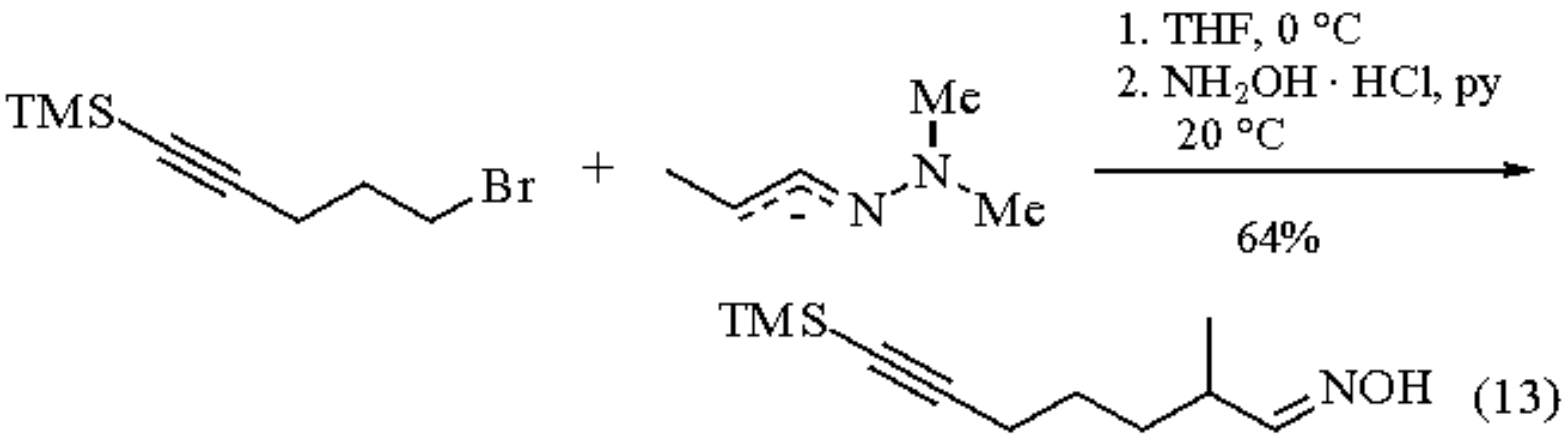

(13)

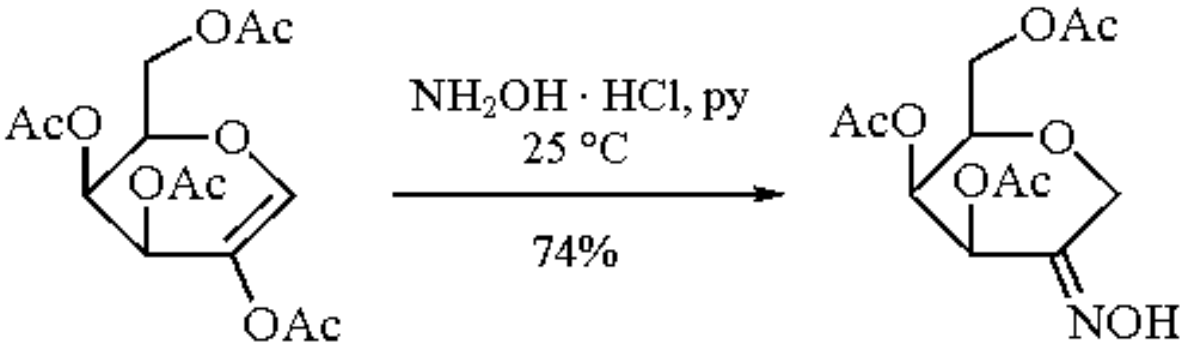

(14)

A solid-phase reagent which binds carbonyl compounds as their corresponding oximes has been developed and employed in the isolation of steroidal ketones.[40] α-Halo ketones produce α-hydroxylamino oximes on treatment with hydroxylamine.[41] The mechanism of this nucleophilic addition-dehydration process has been studied by a number of groups.[42]

Reaction with Aldehydes: Nitrile Formation.

Nitriles can be effectively prepared directly from aldehydes by a wide variety of methods involving hydroxylamine. Two convenient methods employ $HONH_2$.HCl and either refluxing formic acid[43] or pyridine with azeotropic removal of water with refluxing toluene (eq 15).[44] The former reaction has been used to convert a 4-formyl β-lactam into its corresponding nitrile derivative.[45]

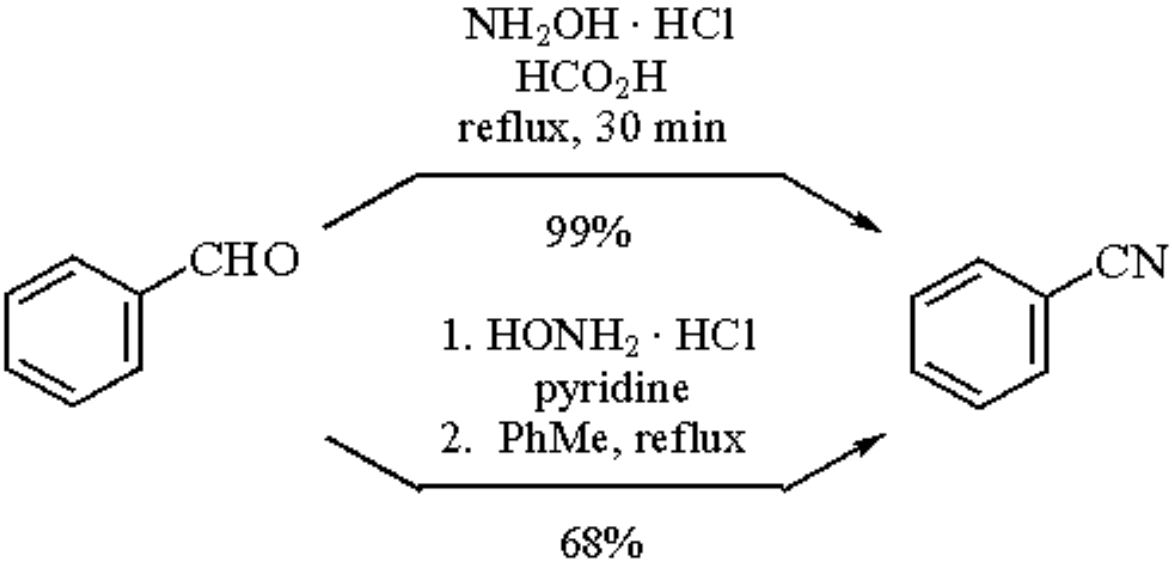

(15)

Two hydroxylamine-derived reagents, *O*-(2-aminobenzoyl)hydroxylamine[46] and ***Hydroxylamine-O-sulfonic Acid***,[47] have also been used to effect this transformation, although in a more limited number of cases. Several methods exist which do not rely on hydroxylamine, including $NH_4Cl/Cu^0/py/O_2$,[48] $EtNO_2$/NaOAc/AcOH,[49] and *N*,*N*-dimethylhydrazine/MeOH/MMPP.$6H_2O$[50] (MMPP = magnesium monoperoxyphthalate).

Reaction with Phosphinylating Agents.

Both *N*- and *O*-phosphinylated hydroxylamine are available via reaction of the appropriate hydroxylamine derivative with diphenylphosphinyl chloride. Use of hydroxylamine base results in the formation of ***O-(Diphenylphosphinyl)hydroxylamine***,[4] while employment of $TMSONH_2$ followed by hydrolysis gives *N*-diphenylphosphinylhydroxylamine (eq 16).[51]

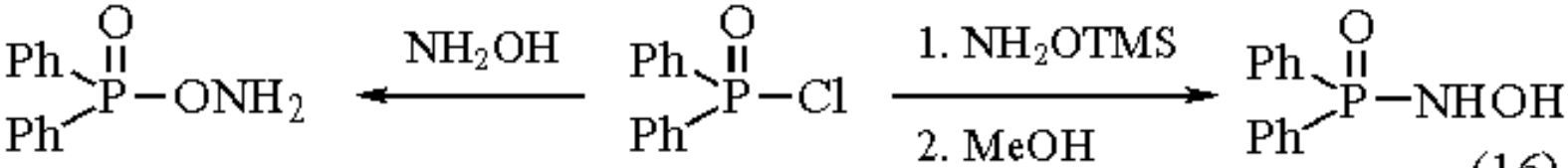

(16)

Reaction with Miscellaneous Electrophiles.

Hydroxylamine reacts with nitriles to yield amide oximes (eq 17).[52,53] The reaction of hydroxylamine with uracil and cytosine has been applied in the Chemical Cleavage of Mismatch (CCM) technique for identifying DNA mutants.[54]

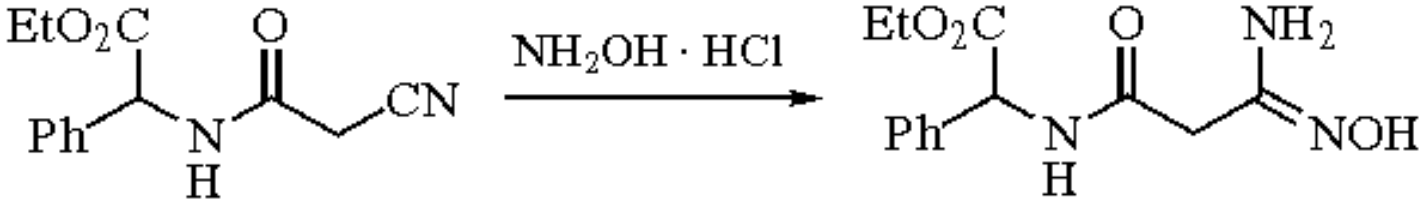

(17)

Preparation of Isoxazoles and Isoxazolines.

Isoxazoles are conveniently prepared via the reaction of $HONH_2.HCl$ with 1,3-dicarbonyl compounds or their equivalents.[55] In some cases, the regiochemistry of the reaction can be controlled. For example, the regiochemistry of the reaction of hydroxylamine with acylketene dithioacetals depends on reaction conditions (eqs 18 and 19).[56]

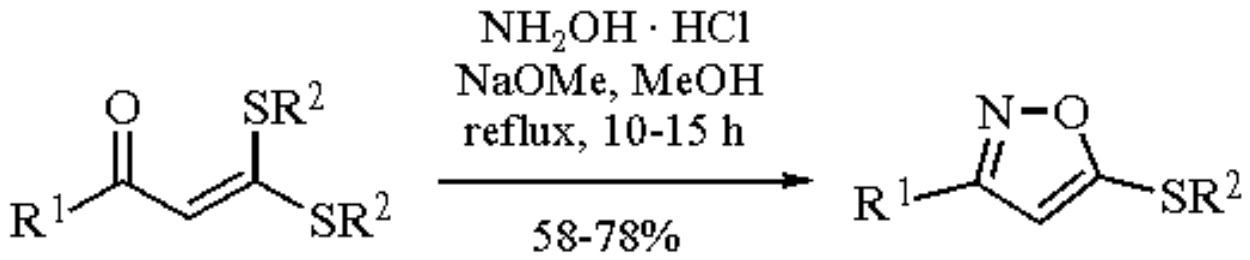

(18)

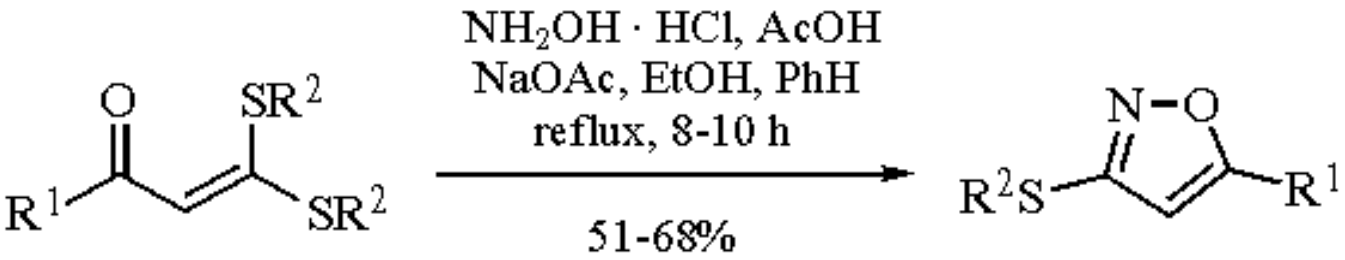

(19)

In like fashion, reaction conditions are important in the preparation of 3-amino-5-*t*-butylisoxazole from 4,4-dimethyl-3-oxopentanenitrile (eqs 20 and 21).[57]

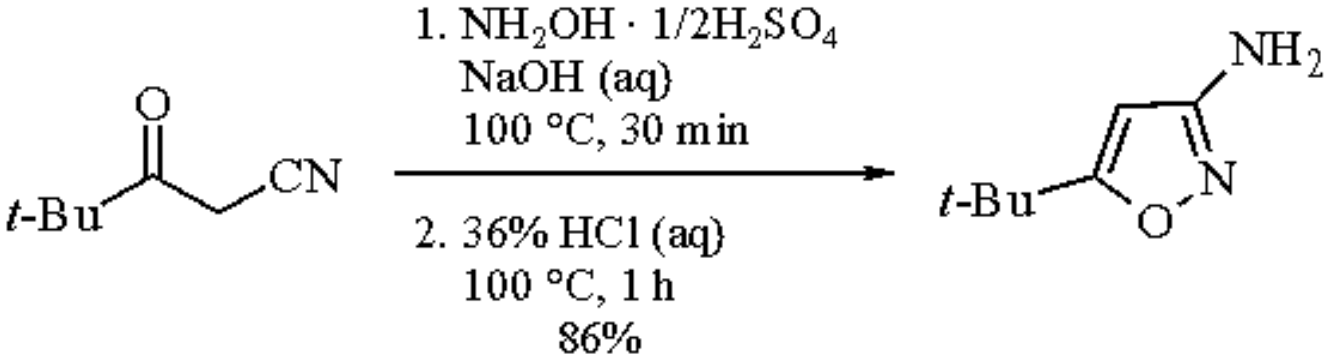

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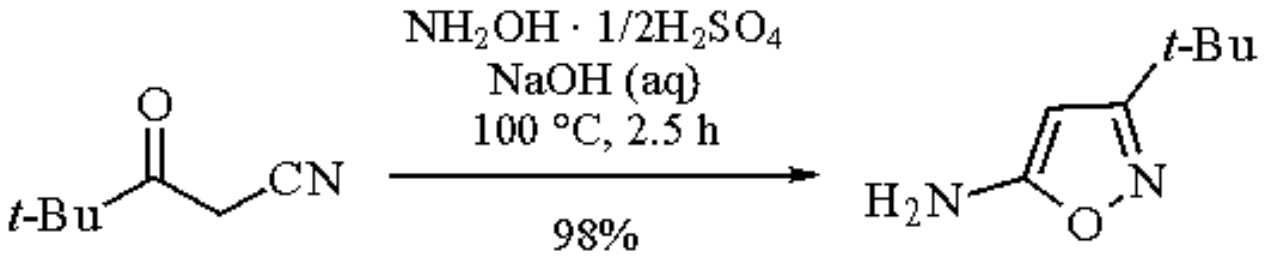

(21)

Functionalized 4,5-dihydroisoxazoles[58] have been prepared by the reaction of α,β-epoxy ketones with $HONH_2.HCl$ (eq 22)[59] and also by the cycloaddition reaction between styrene and aryl nitrile oxides prepared in situ from trichloromethylarenes and hydroxylamine.[60]

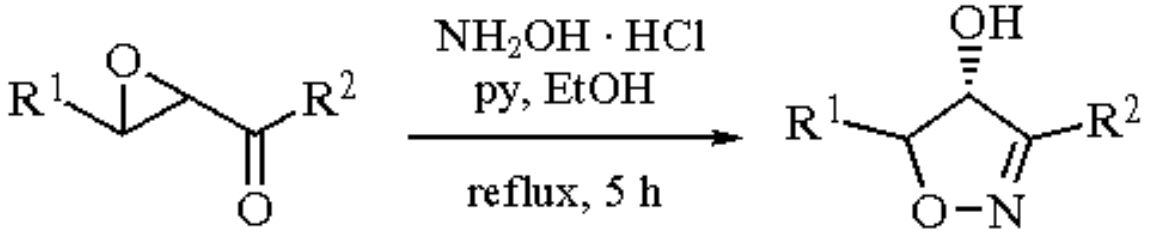

(22)

R^1 = Ph, cyclopropane derivs.; R^2 = Ph; 55-84%

Preparation of Substituted Pyridines.

Two novel approaches to the synthesis of substituted pyridines have appeared. Treatment of dihydropyran acetals[61] with $HONH_2$.HCl (eq 23) or bicyclic acetals[62] with $HONH_2$.HCl and ***Aluminum Chloride*** (eq 24) leads to good yields of pyridines. The first process appears to be the more general of the two, though it is limited somewhat by the availability of starting materials.

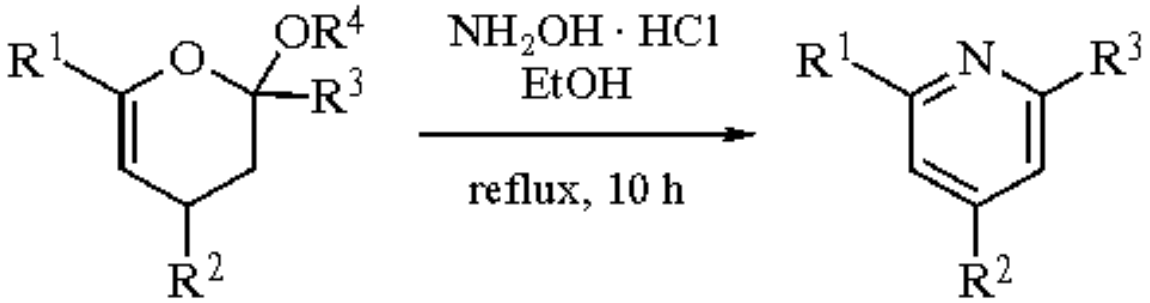

(23)

R^4 = Me, Et

R^1	R^2	R^3	Yield
Ph	Ph	H	81%
Ph	Cy	H	40%
2-furyl	Ph	H	95%

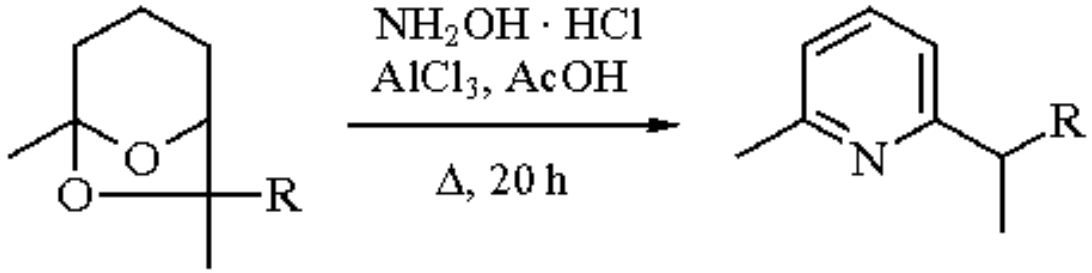

(24)

R =Me, 83%; Et, 99%; Pr, 84%

Aromatic Substitution Reactions.

In certain cases, hydroxylamine can act as a nucleophile in aromatic substitution reactions. This has shown to be the case in the reactions with 6-nitroquinoxalines (eq 25)[63] and *N*,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine (eq 26).[64] Other examples are known.[65]

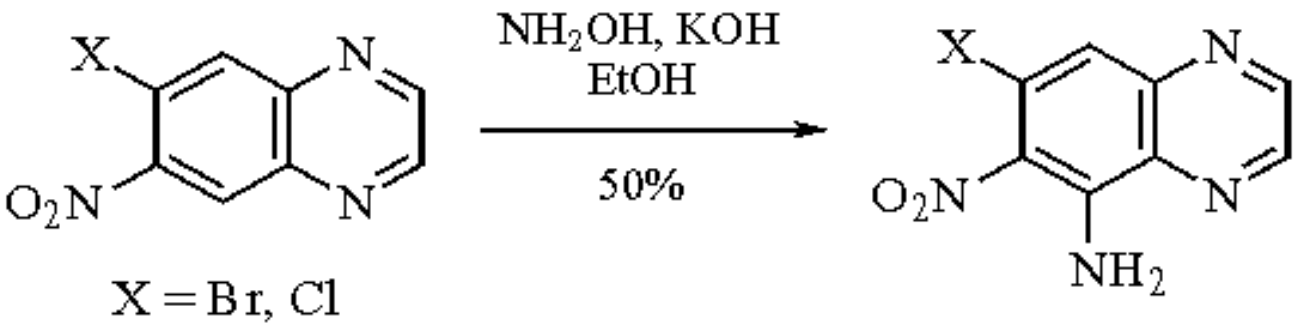

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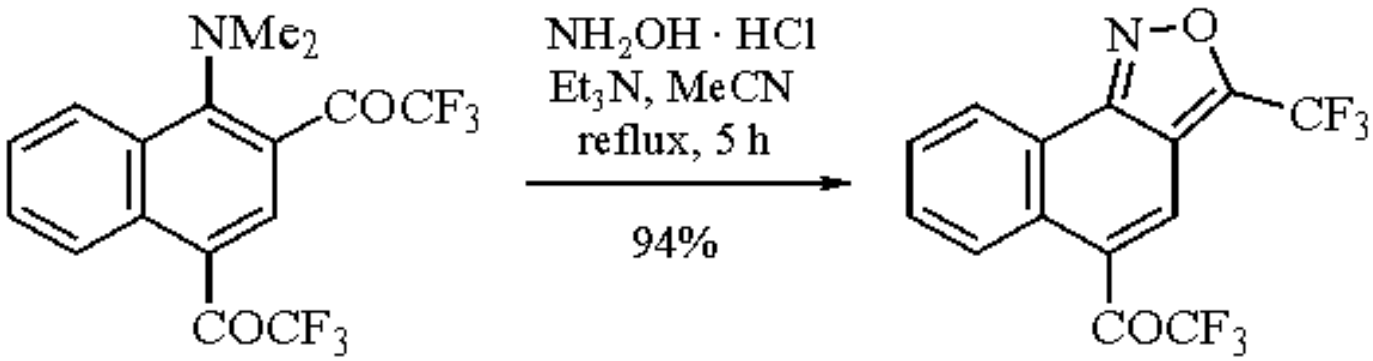

(26)

Use as a Reducing Agent.

The combination of hydroxylamine and ethyl acetate in DMF represents a useful in situ preparation of ***Diimide*** and this procedure has been reported to reduce a variety of unsaturated compounds (eq 27).[66,67] Diimide formation from hydroxylamine has been used to explain the reductive cyclization of some *o*-nitroazobenzenes.[68]

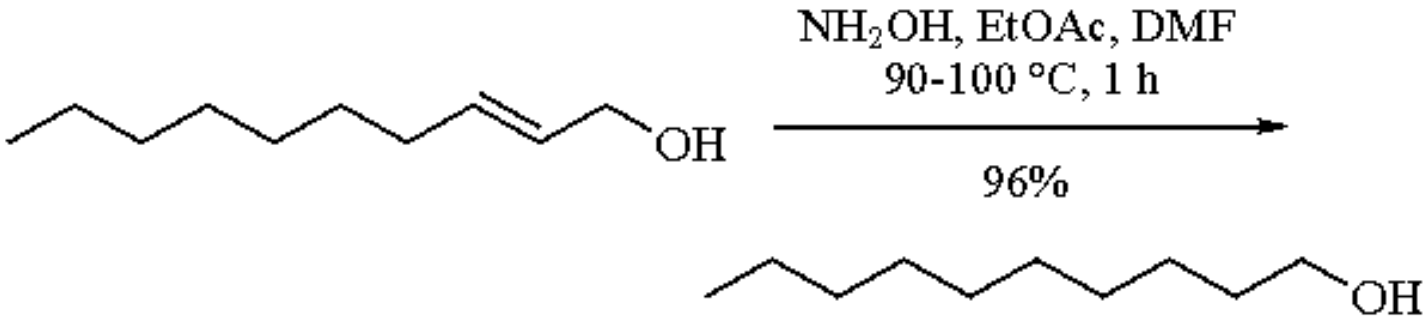

(27)

Use in Peptide Chemistry.

Hydroxylamine has been used as a reagent to cleave the acetoacetyl amino acid protecting group[69] and has also been employed to cleave the asparaginyl-glycyl peptide bond.[70]

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Hydroxylamine-*O*-sulfonic Acid

H_2NOSO_2OH

[2950-43-8] · H_3NO_4S · Hydroxylamine-*O*-sulfonic Acid · (MW 113.11)

(amination; hydroxymethylation; reduction; conversion of alkenes to primary amines[1-3])

Alternate Name: HOSA.

Physical Data: mp 210 °C (dec).

Solubility: sol cold water, methanol; slightly sol ethanol; insol ether, $CHCl_3$.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: quantitative analysis of HOSA can be made by iodometric titration.[4,5]

Preparative Methods: by reacting hydroxylamine sulfate with 30% fuming H_2SO_4[4] or 60% oleum[6] at rt, or by heating a mixture of hydroxylamine sulfate and chlorosulfonic acid at 100 °C for several hours.[5]

Handling, Storage, and Precautions: hygroscopic; should be stored in tightly sealed bottles in a refrigerator. Aqueous solutions are unstable, decomposing rapidly above 25 °C. It is thus important to use freshly prepared solutions in reactions. Use in a fume hood.

Introduction.

The use of HOSA in organic synthesis results from its ability to act both as a nucleophile and as an electrophile (eq 1), as well as being able to provide an in situ route to other chemical entities, such as diimide.

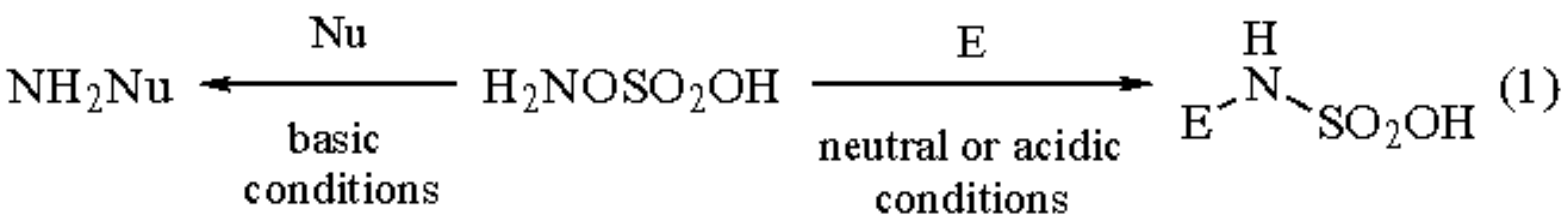

Amination at Nitrogen.

Monosubstituted and 1,1-disubstituted hydrazines can be prepared in fair to good yields by reacting HOSA with primary or secondary amines, respectively, in basic aqueous solution (eq 2).[7,8] Tertiary amines give 1,1,1-hydrazinium salts when they are treated with HOSA under basic conditions in aqueous or alcoholic solution (eq 3).[7-9]

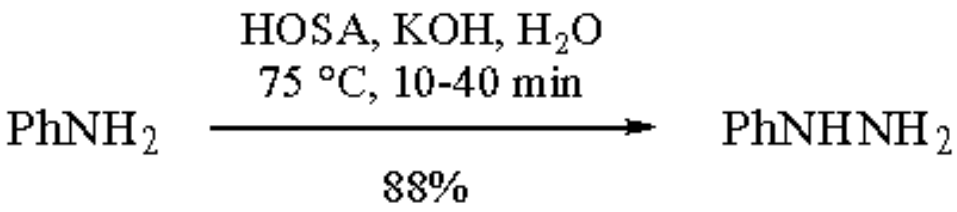

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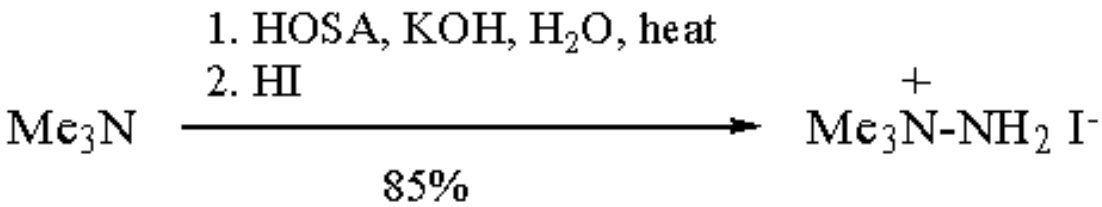

(3)

Many nitrogen heterocycles, including pyridine,[7,8] quinoline,[7,8] pyrimidine,[9] azetidine,[10] pyridazine,[11] tetrazole,[12] indole (eq 4),[13,14] benzimidazole,[14,15] triazine,[16] benzoxazole,[17] and purine[14,18] ring systems, can also be aminated on nitrogen using HOSA.

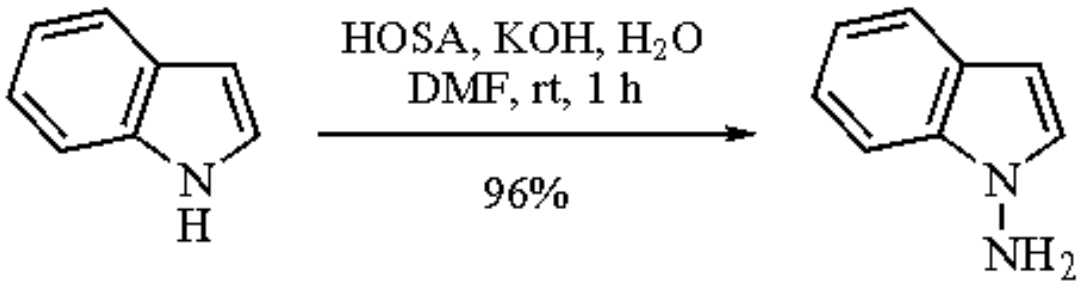

(4)

Amination at Carbon.

One of the two published reports on carbanion aminations with HOSA[19] concerns its reaction with some β-diketo compounds to furnish symmetrically substituted pyrroles (eq 5).

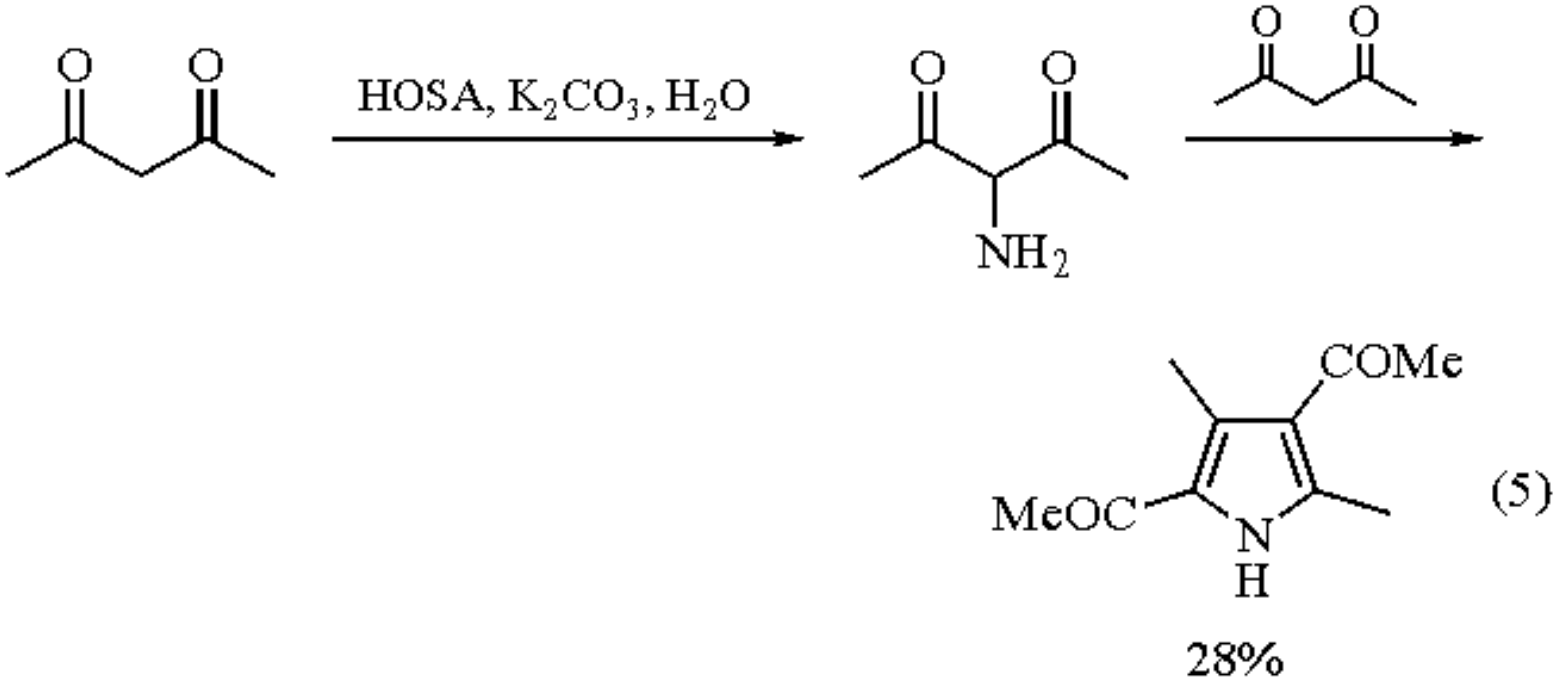

The other attempted amination with HOSA[20] yielded a trace amount of an amino acid from an α-lithiated carboxylic acid. Triphenylborane, prepared from phenylmagnesium bromide and boron trifluoride, reacts with HOSA to give aniline in 35% yield.[21]

Two different methods have been reported for the direct amination of an aromatic ring in low yields using HOSA. The first employs ***Aluminum Chloride*** as a catalyst (eq 6);[22,23] the second is an homolytic amination procedure in which a protonated amino radical is generated using iron(II) ion together with HOSA (eq 7).[24]

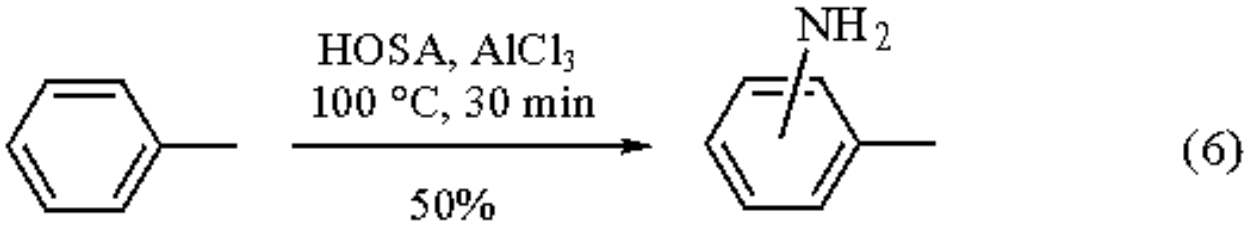

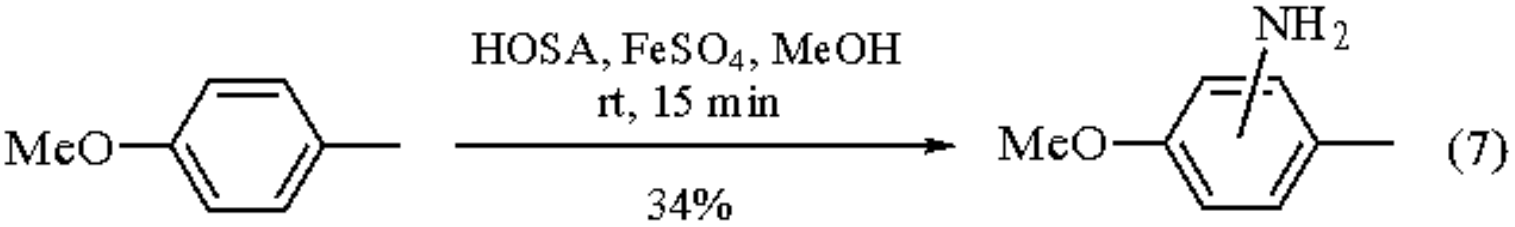

Certain heterocycles react with HOSA to give *C*-substituted amino derivatives (eq 8).[25]

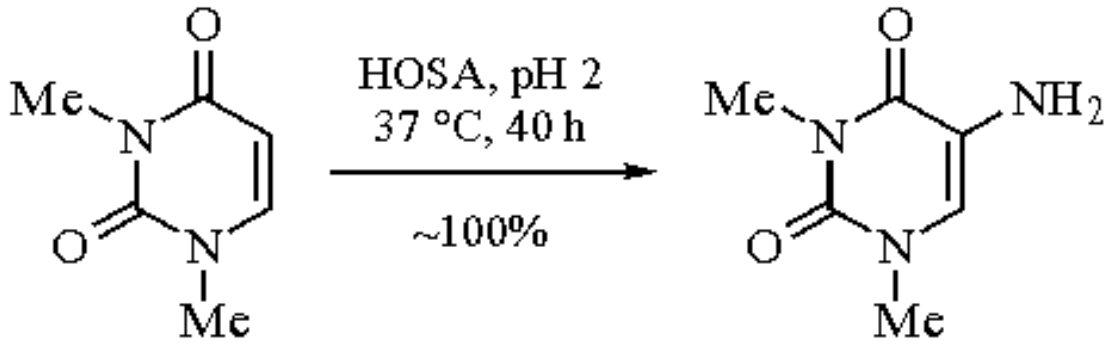

(8)

Amination at Sulfur.

Organosulfur compounds, including thiols,[26] thioacids (eq 9),[27] thioamides,[27,28] dithioacids,[27] and thioethers (eq 10),[29] undergo amination with HOSA in good yields.

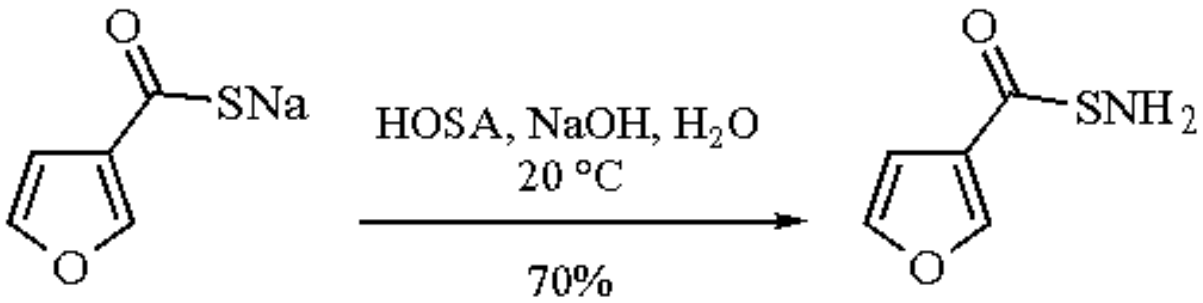

(9)

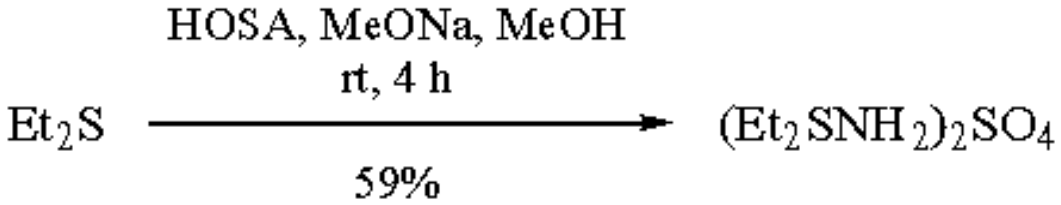

(10)

Hydroxymethylation.

Quinolines can be hydroxymethylated in the 2-and/or 4-position using HOSA in methanol (eq 11).[30]

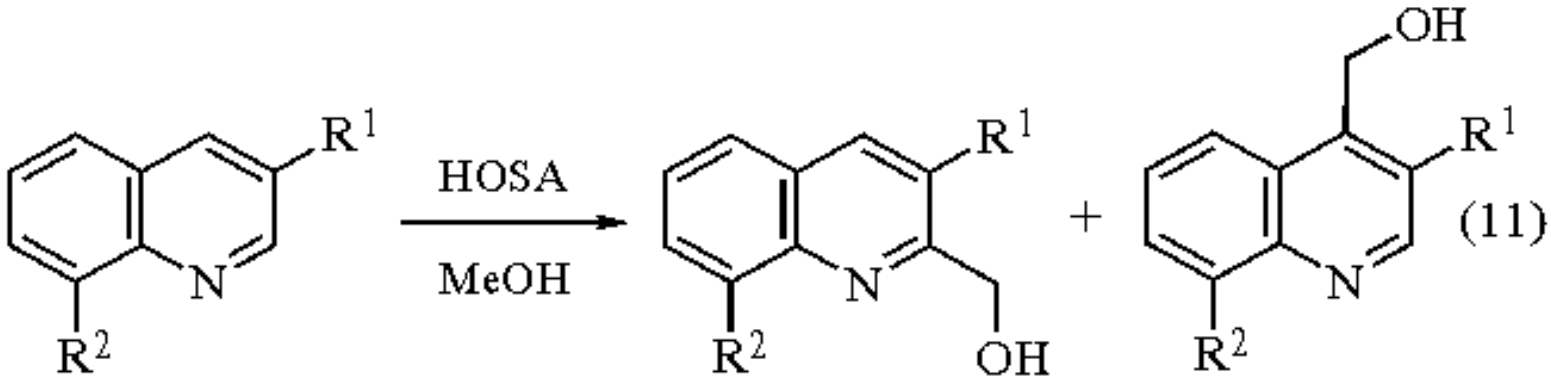

$R^1 = R^2 = H$	55%	25%
$R^1 = Me, R^2 = Cl$	-	95%

Reduction.

HOSA, alone[31] or together with hydroxylamine sulfate,[32] provides under basic conditions a source of ***Diimide***, HN=NH, which will reduce multiple bonds (eqs 12 and 13). Yields obtained by using HOSA alone seem to be lower compared with those obtained with HOSA-hydroxylamine sulfate.

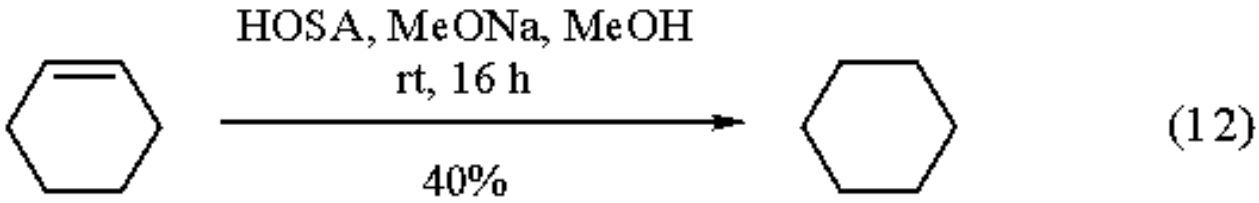

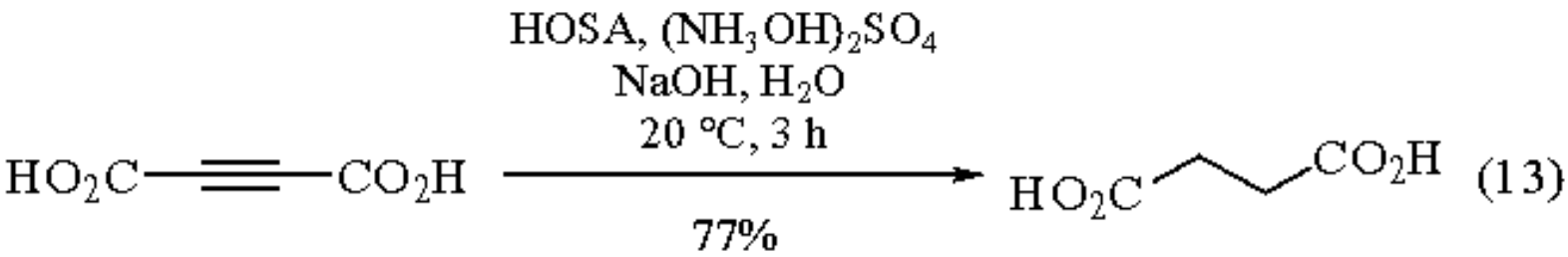

Conversion of Alkenes into Primary Amines.

Methods for the conversion of alkenes into primary amines via the corresponding organoboranes using HOSA have been developed.[33 -36] Organoboranes are prepared in situ by the addition of ***Diborane*** to the alkene in THF (eq 14)[33] or by the addition of ***Boron Trifluoride Etherate*** to the alkene and ***Sodium Borohydride*** in diglyme, in which HOSA is soluble (eq 15).[35]

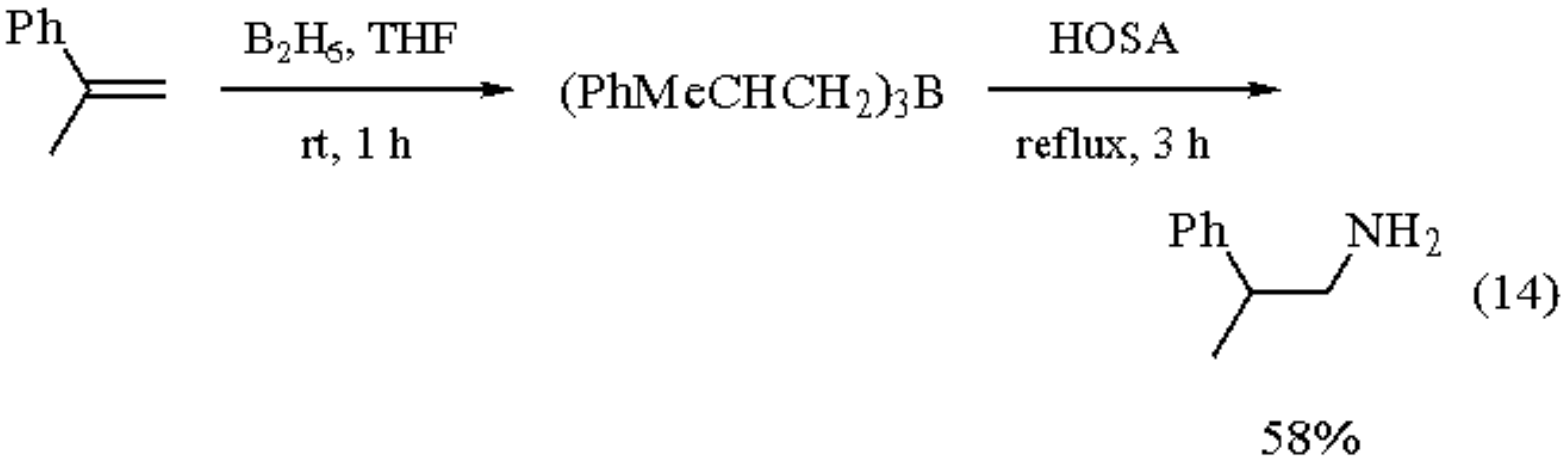

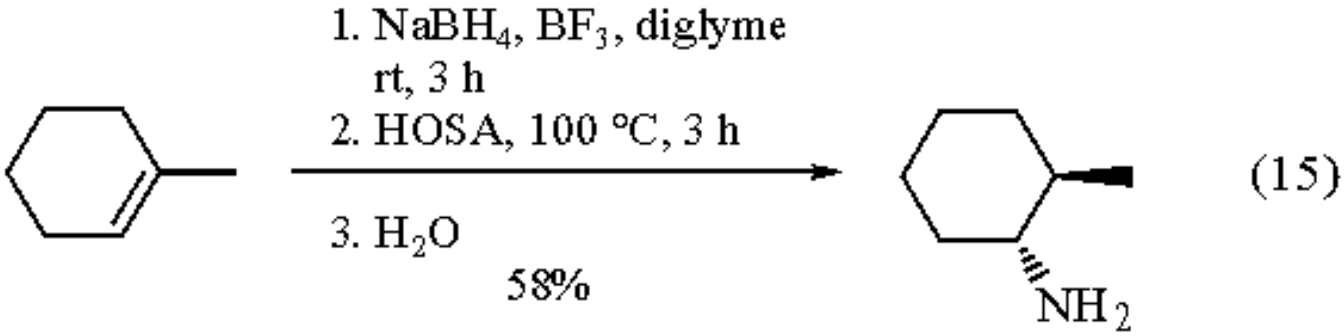

The limitation to quantitative utilization of the alkyl groups has been overcome by preparing a mixed organoborane, $R^1R^2{}_2B$, in which R^1 shows a significantly greater migratory aptitude than R^2. For this purpose, organodimethylboranes, prepared by hydroboration of alkenes with dimethylborane, were treated with HOSA to afford the corresponding primary amines stereospecifically in almost quantitative yields (eq 16).[37]

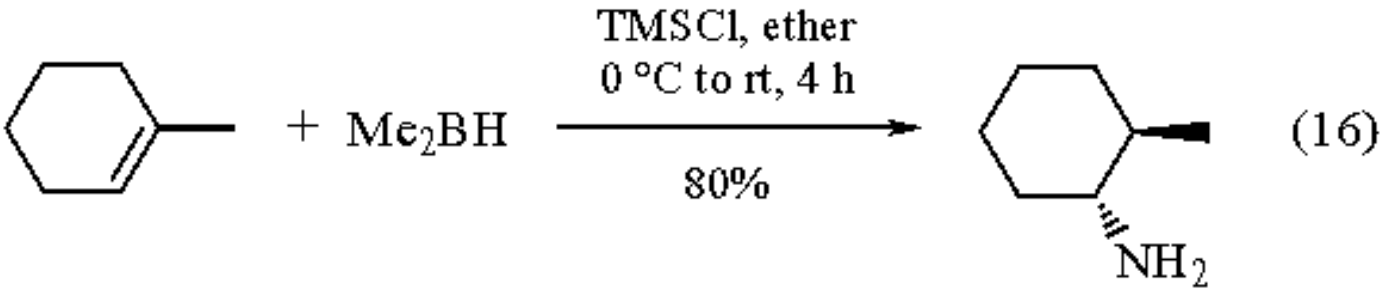

α-Chiral primary amines of high optical purity can be obtained from the chiral boronic esters through the intermediate formation of alkyl methyl borinic esters and their stereospecific reaction with HOSA in very good yields (eq 17).[38,39] Synthesis of chiral α-methylorganyl primary amines, which are difficult to prepare via direct asymmetric hydroboration, can be accomplished by treating borinate esters with HOSA (eq 18).[40]

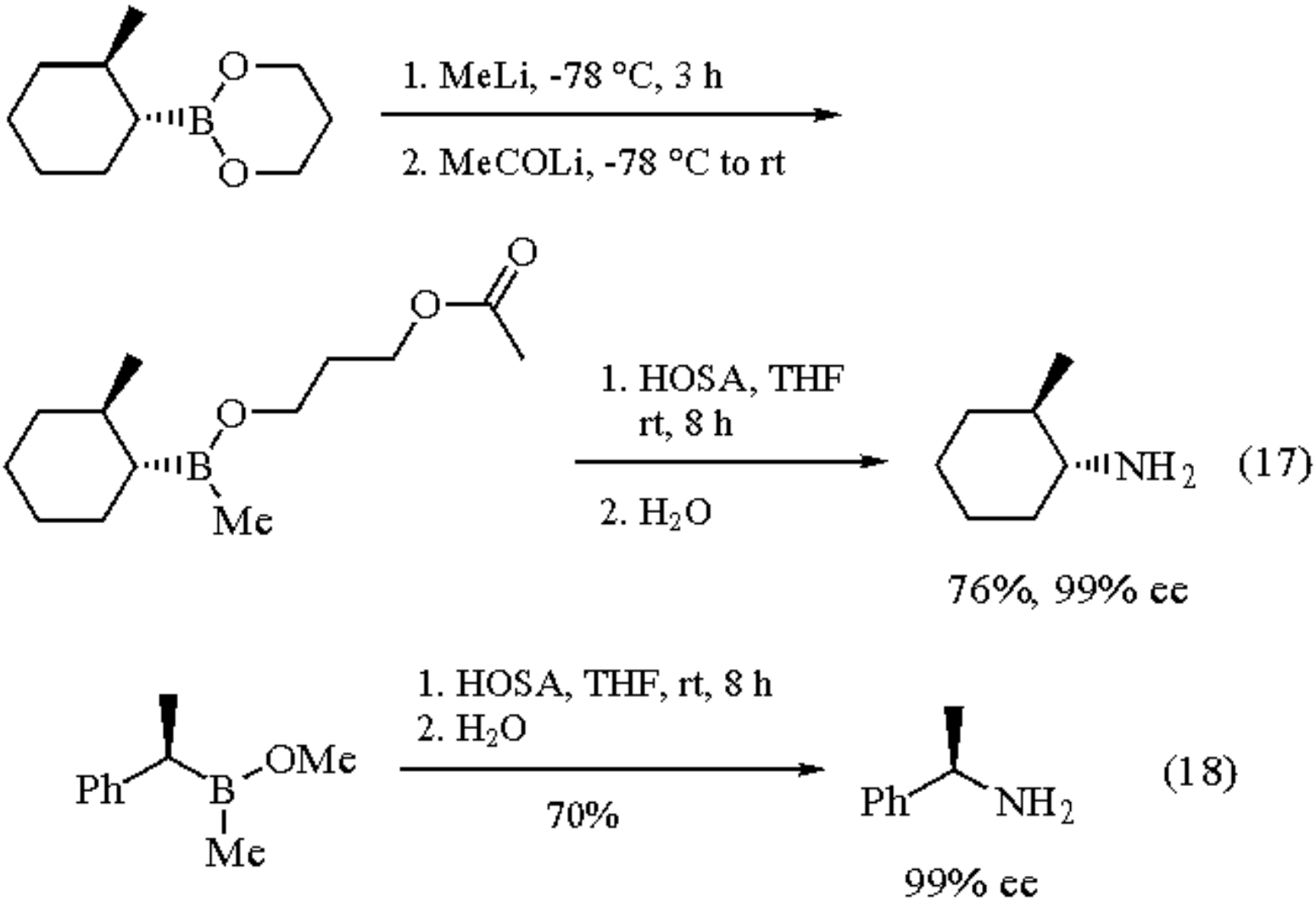

Conversion of Carboxylic Acids to Primary Amines.

Heating a carboxylic acid or its anhydride with HOSA in mineral oil at 160-180 °C[41] or in polyphosphoric acid at 115-125 °C[42] gives a primary amine in a low yield (eq 19).

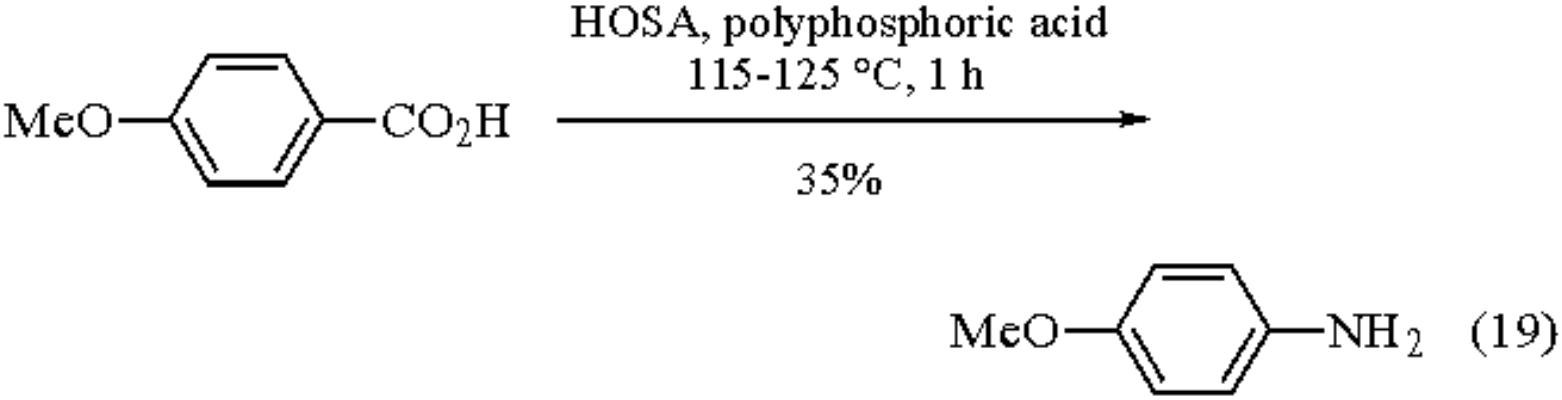

Conversion of Primary Amines to Hydrocarbons

(Reductive Deamination).

In an indirect route, a primary amine is converted into its sulfonamide which is isolated, dissolved in aqueous base, and then treated with HOSA to give the hydrocarbon in a high yield (eq 20).[43] In a direct route, a primary amine is allowed to react with 2-3 equiv of base to give the hydrocarbon in a moderate yield (eq 21).[44]

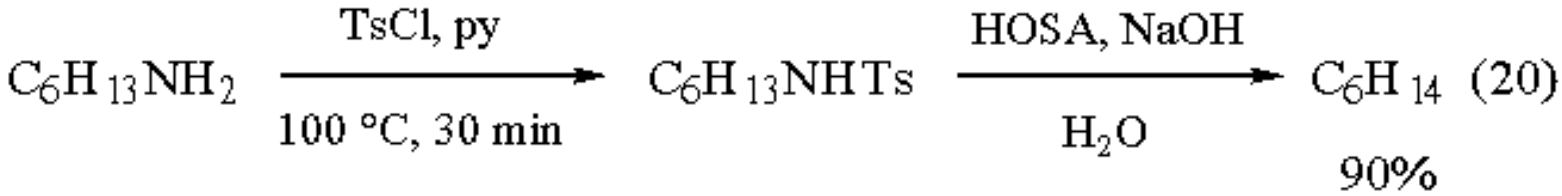

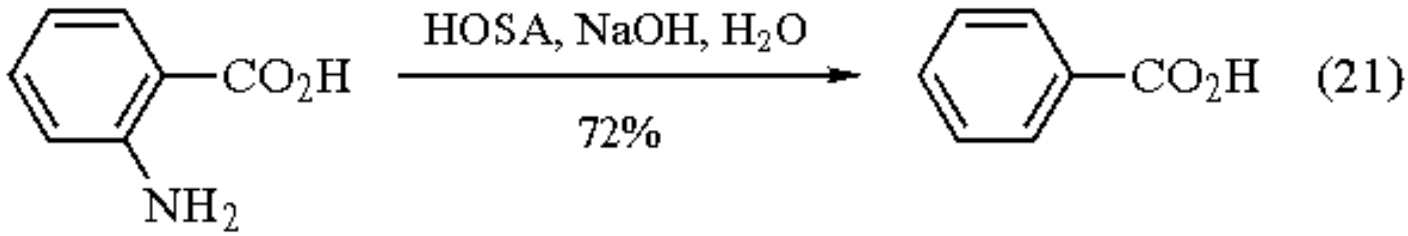

Conversion of Carbonyl Compounds to Oxime Sulfonates.

Aldehydes and ketones react with HOSA in aqueous solution to give oxime-*O*-sulfonic acids and salts in good yields (eq 22).[45,46]

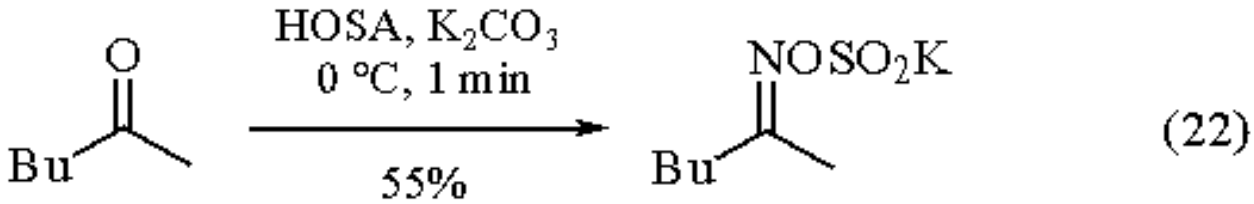

Conversion of Aldehydes to Nitriles.

With aldehydes, prolonged treatment with HOSA, at rt or above, generates nitriles (eq 23).[46,47]

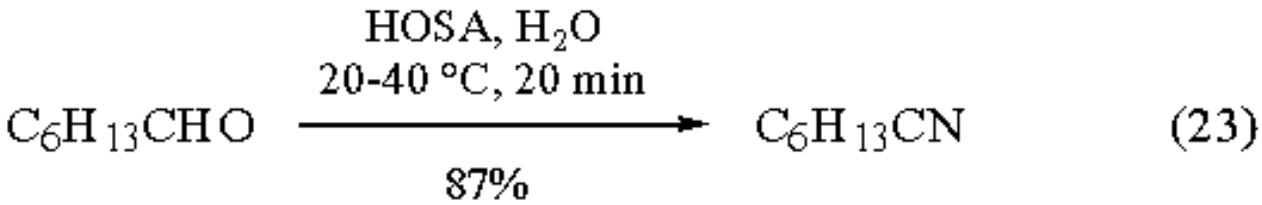

Conversion of Ketones to Oximes.

Reaction of aliphatic ketones with HOSA at 100 °C gives oximes in high yields (eq 24).[48] The method has the

advantage over the standard oxime preparation procedure employing hydroxylamine hydrochloride in that no adjustment in pH of the reaction medium is required to facilitate reaction and a solvent is not necessary, the ketone and HOSA simply being mixed together.

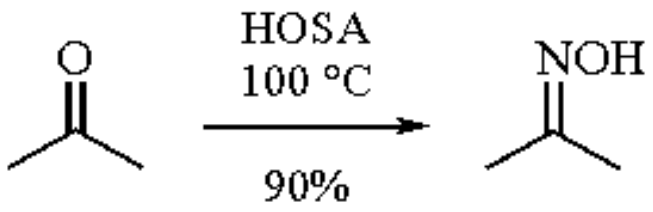

(24)

Conversion of Ketones to Amides.

Under the conditions described above, alkyl aryl ketones yield *N*-aryl aliphatic amides, again in high yields (eq 25).[48] Alicyclic ketones have been converted to lactams using HOSA (eq 26).[49]

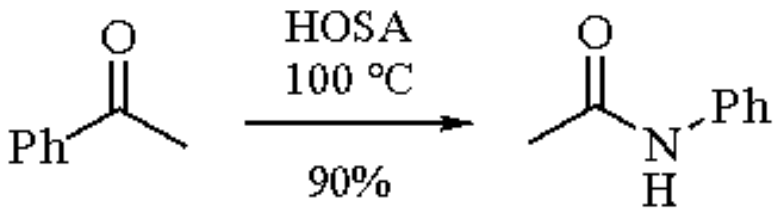

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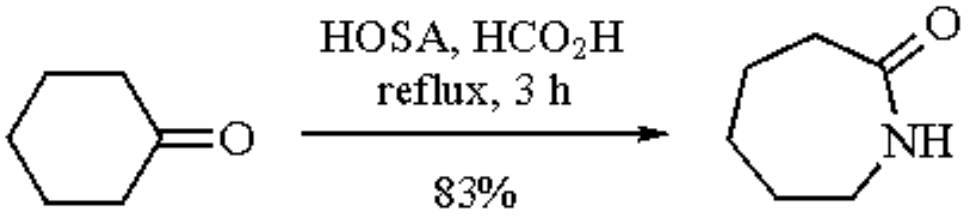

(26)

Conversion of Oximes to Diazo Compounds.

Oximes react with HOSA in aqueous base to give diazo compounds (eq 27).[50]

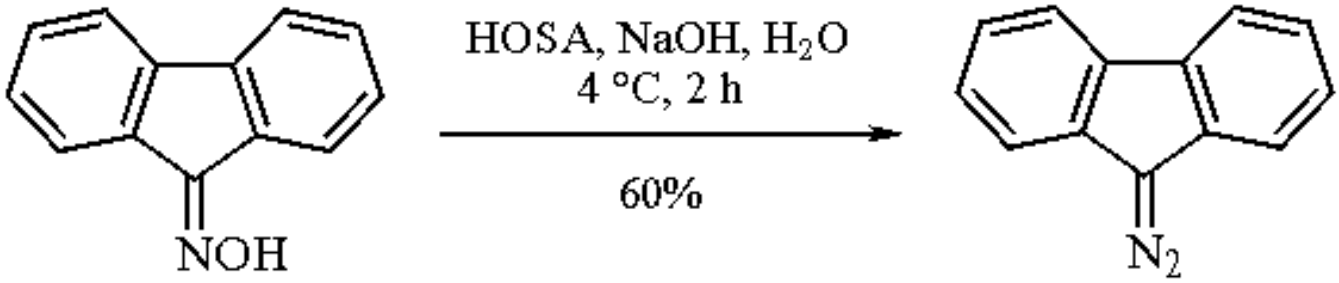

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(*S*)-3-Hydroxy-5-methyl-2,4-imidazolidinedione

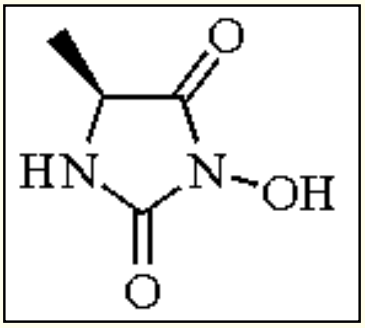

[30293-99-3] · $C_4H_6N_2O_3$ · (*S*)-3-Hydroxy-5-methyl-2,4-imidazolidinedione · (MW 130.12)

(acyl activating agent for asymmetrically selective peptide synthesis[1])

Alternate Name: (-)-3-hydroxy-5-methylhydantoin.

Physical Data: mp 163-164 °C; $[\alpha]_D$ -36.0°.

Preparative Method: prepared from alanine (eq 1).[1]

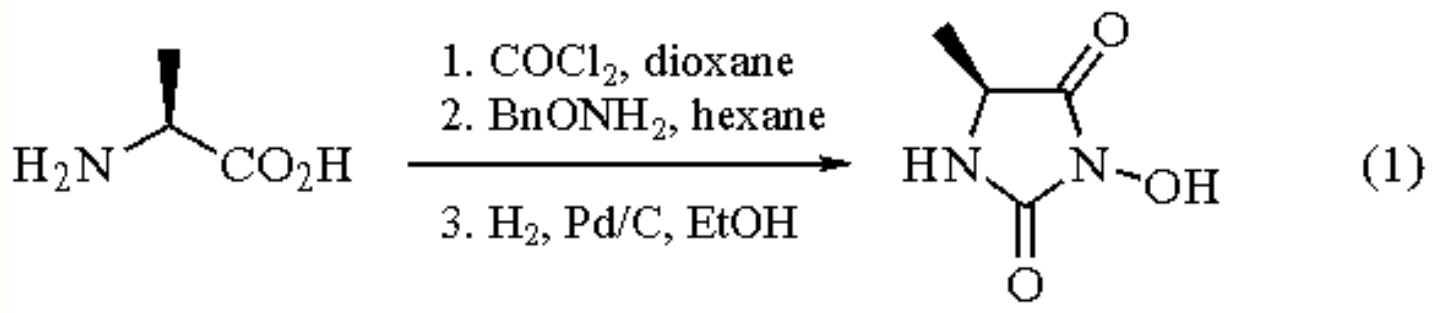

Asymmetric Peptide Synthesis.[1]

The reagent activates amino acids through ***1,3-Dicyclohexylcarbodiimide*** (DCC) coupling to the *N*-hydroximide for subsequent coupling with chiral amino acids. The asymmetric center induces preferential reaction with L-amino acids and high optical purities of L-L-dipeptides can be achieved (eq 2). Enantioselectivity is improved if the 5-methyl group is replaced by isobutyl.[1]

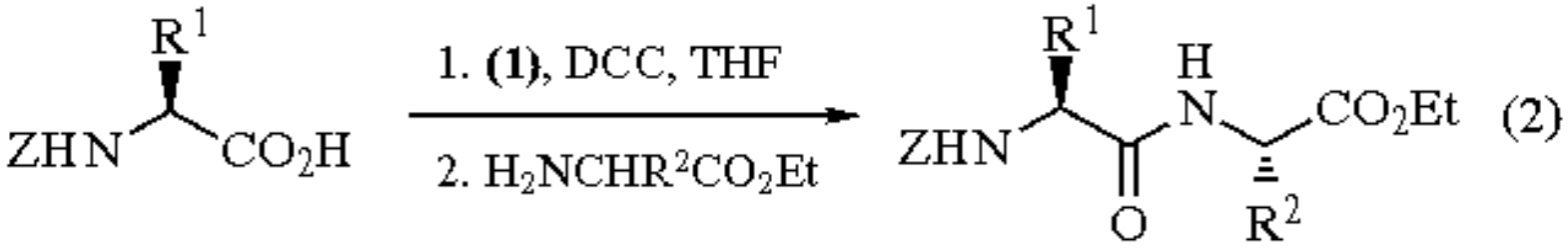

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Kenneth A. Murray

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(2*S*,2´*S*)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine[1]

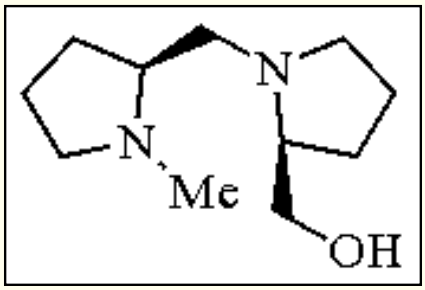

[66283-23-6] · $C_{11}H_{22}N_2O$ · (2*S*,2´*S*)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine · (MW 198.35)

(chiral ligand for alkyllithium,[2] dialkylmagnesium,[3] alkynyllithium,[4] and functionalized organolithiums[5] in the enantioselective addition to aldehydes; accelerates the basicity of alkyllithiums;[5] catalyzes the addition of dialkylzinc to aldehyde[2])

Physical Data: bp 112 °C/4.5 mmHg; [α]28D -130° (*c* 0.36, EtOH).

Solubility: sol hexane, toluene, Me_2O, Et_2O, *n*-Pr_2O, THF, dimethoxymethane.

Preparative Method: reduction of *N*-[*N*(-benzyloxycarbonyl)prolyl]proline methyl ester with ***Lithium Aluminum Hydride*** affords the title reagent in 81% yield.

Enantioselective Addition of Alkyllithium Reagents to Aldehydes.

(2*S*,2´*S*)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine (**1**) is a chiral amino alcohol which binds well to alkyllithium reagents.[2] Enantioselective addition of ***n-Butyllithium*** to benzaldehyde in the presence of (**1**) in a mixed solvent of Me_2O and dimethoxymethane (DMM) (1:1) at -123 °C affords (*S*)-1-phenylpentan-1-ol with 95% ee in 77% yield.[2] In the addition to 3-methylbutanal, the corresponding (*S*)-alcohol is obtained in 80% ee (eq 1).

(2S,2´S)-2-Hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]pyrrolidine

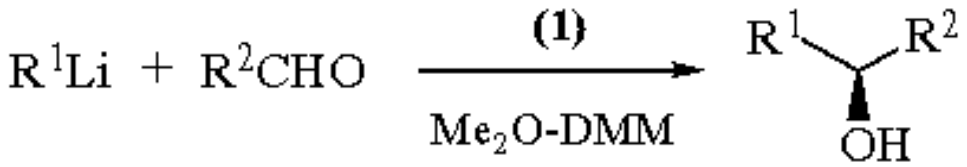

(1)

$R^1 = Bu$, $R^2 = Ph$, 77%, 95% ee; $R^1 = Bu$, $R^2 = i\text{-}Bu$, 57%, 80% ee

These ee's are higher than those of the preceding reports[1a] and are comparable with those of the reports appearing afterwards.[1b,c] It should be noted that the absolute configuration of the alcohol obtained in the addition of EtLi to PhCHO depends on the solvent employed [(*R*): EtOH; (*S*): DMM]. The sense of the enantioselectivity of the addition of ***Methyllithium*** is opposite to that of BuLi. When the derivative of (**1**) possessing a neopentyl group (**2**) is used in the addition of MeLi to PhCHO, (*R*)-1-phenylethanol with 86% ee is obtained in 82% yield.[2b]

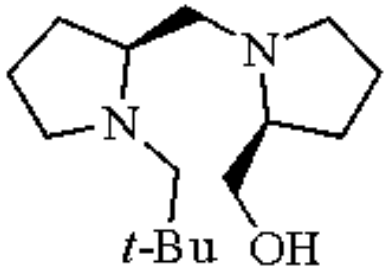

(2)

Enantioselective Addition of Dialkylmagnesium to Aldehydes.

Amino alcohol (**1**) is a chiral ligand for dialkylmagnesium reagents in the enantioselective addition to aldehydes.[3] Reaction of Et_2Mg with PhCHO in the presence of (**1**) in toluene at -110 °C affords (*R*)-1-phenylpropan-1-ol with 92% ee in 74% yield. When *n*-Bu_2Mg is employed, (*R*)-1-phenylpentan-1-ol with 88% ee is obtained in 94% yield. It should be noted that the sense of the enantioselectivity of *n*-Bu_2Mg-(**1**) is opposite to that of *n*-BuLi-(**1**) (eq 2).

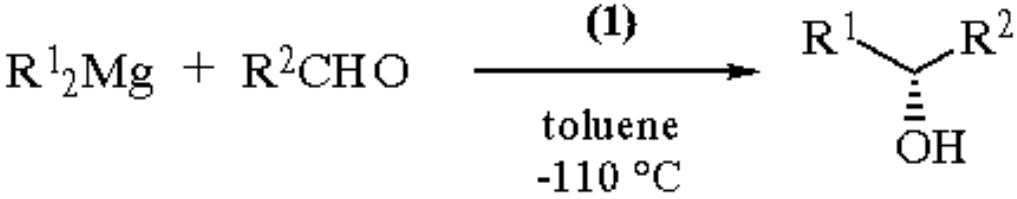

(2)

$R^1 = Et$, $R^2 = Ph$, 74%, 92% ee; $R^1 = Bu$, $R^2 = Ph$, 94%, 88% ee

Enantioselective Addition of Alkynyllithium to Aldehydes.

The enantioselective addition of alkynyllithium to aldehydes in the presence of (**1**) provides optically active propargylic alcohols. (*S*)-1-Phenyl-2-propyn-1-ol with 92% ee is obtained in 87% yield from the enantioselective

addition of ***Lithium (Trimethylsilyl)acetylide*** to PhCHO in the presence of (**1**) and the subsequent removal of the Me_3Si group (eq 3).[4a]

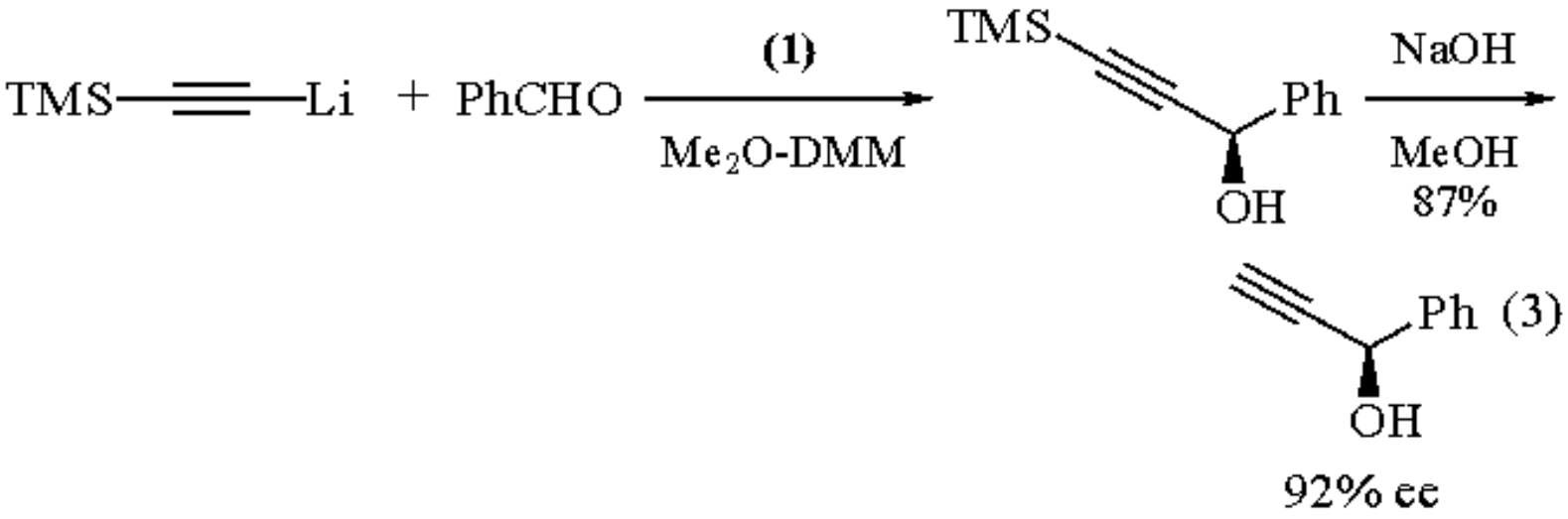

Optically active aliphatic propargylic alcohols are converted to corticoids (90% ee) via biomimetic polyene cyclization,[4b] and to 5-octyl-2(5*H*)-furanone.[4c] The ee's of propargylic alcohols obtained by this method are comparable with those of the enantioselective reduction of alkynyl ketones with metal hydrides,[6] catalytic enantioselective alkylation of alkynyl aldehydes with dialkylzincs using a chiral catalyst (***(S)-Diphenyl(1-methylpyrrolidin-2-yl)methanol***) (DPMPM),[7a] and the enantioselective alkynylation of aldehydes with alkynylzinc reagents using *N*,*N*-dialkylnorephedrines.[7b,c]

Enantioselective Addition of Functionalized Organolithiums to Aldehydes.

Amino alcohol (**1**) is a chiral ligand for various functionalized organolithiums derived from acetonitrile and *N*-nitrosodimethylamine (eq 4).

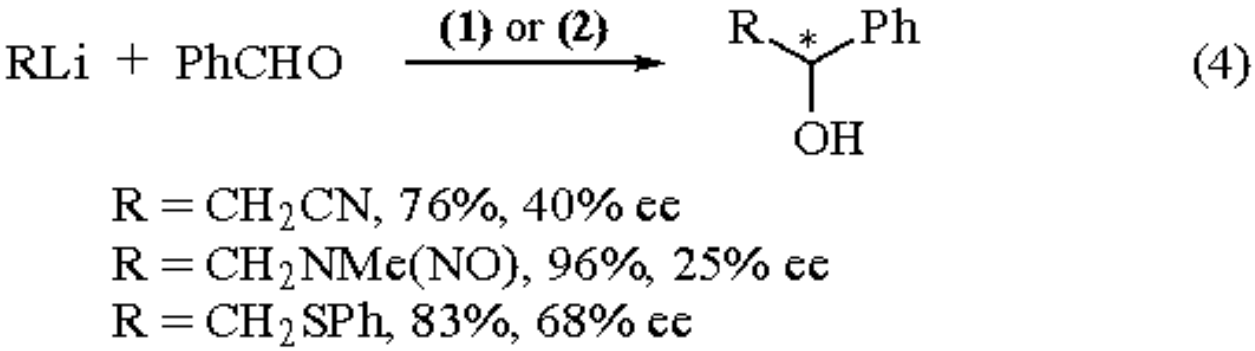

An optically active β-hydroxy nitrile with 40% ee is obtained from the reaction of $LiCH_2CN$ with PhCHO in the presence of (**1**).[5] The same compound with higher ee (93% ee) is obtained using cyanomethylzinc bromide and the chiral ligand DPMPM.[8]

Amino alcohol (**1**) accelerates the basicity of BuLi. Thus methyl phenyl sulfide is deprotonated by BuLi in the presence

of (**1**) to afford $PhSCH_2Li$. Deprotonation does not occur without (**1**). Enantioselective addition of $PhSCH_2Li$ to PhCHO using (**1**) affords an optically active β-hydroxy sulfide, which is converted to (*R*)-2-phenyloxirane with 68% ee.[5]

Addition of Diethylzinc to Benzaldehyde.

The addition of ***Diethylzinc*** to PhCHO without added catalysts is very sluggish. Amino alcohol (**1**) acts as a catalyst precursor for the addition of Et_2Zn to PhCHO under mild conditions to afford 1-phenylpropan-1-ol in 76% yield (eq 5).[2b,3] Although the obtained alcohol is racemic, the result of the addition of Et_2Zn to PhCHO in the presence of amino alcohol (**1**) led to the recently developed highly enantioselective addition of Et_2Zn to PhCHO using chiral amino alcohols.[1b,c]

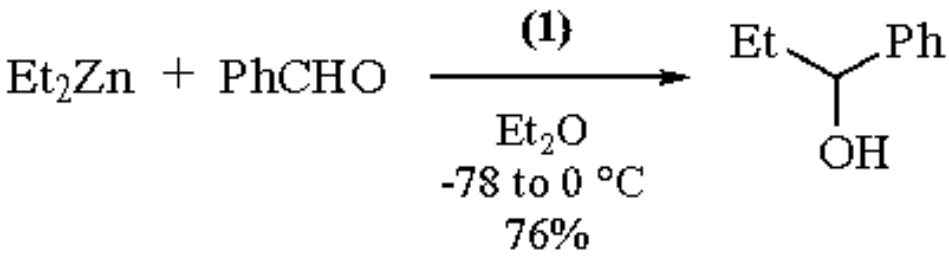

(5)

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Kenso Soai

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6-Hydroxynicotinic Acid

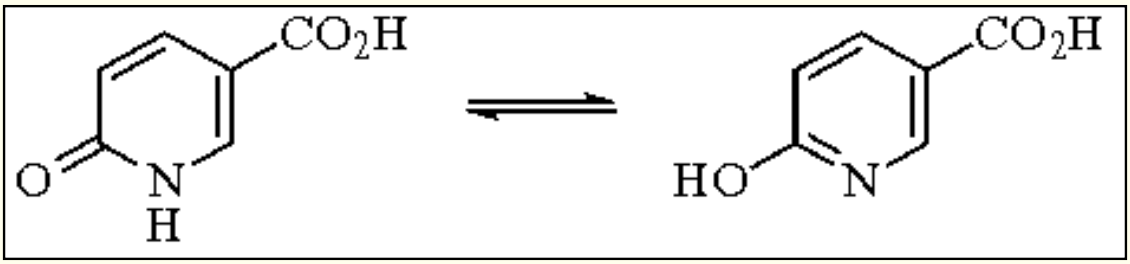

[5006-66-6] · $C_6H_5NO_3$ · 6-Hydroxynicotinic Acid · (MW 139.12)

(building block for the synthesis of pyridine derivatives useful as agrochemicals, pharmaceuticals, liquid crystals; metal complexing agent)

Physical Data: mp 314-316 °C (dec); pK_{a1} 3.8, pK_{a2} 10.8.

Solubility: sol DMSO, DMF, aq. NaOH; sol 0.6 g L^{-1} at 20 °C in water, 4 g L^{-1} in methanol; insol nonpolar organic solvents.

Form Supplied in: off-white solid, &egt;98% purity; impurities: max. 0.5% nicotinic acid, 0.3% water.

Analysis of Reagent Purity: HPLC, Karl Fischer (H_2O).

Preparative Methods: industrially, through bacterial oxidation of nicotinic acid[1] or 3-cyanopyridine;[2] from coumalic acid and NH_3.[3]

Handling, Storage, and Precautions: LD_{50} (oral, rat) >5000 mg kg^{-1}; no special precautions are necessary.

Reactivity.

6-Hydroxynicotinic acid displays reactivity patterns typical for both pyridones[4a] and pyridinecarboxylic acids.[4b] The carboxyl function can be transformed without affecting the pyridone moiety. Esters can be prepared either by the normal Fischer esterification procedure or through various known activation methods[5a] (e.g. ***N,N´-Carbonyldiimidazole***),[5b] including selective chlorination with ***Thionyl Chloride***.[5c] The same methods can be used to prepare amides or hydrazides of 6-hydroxynicotinic acid (eq 1).

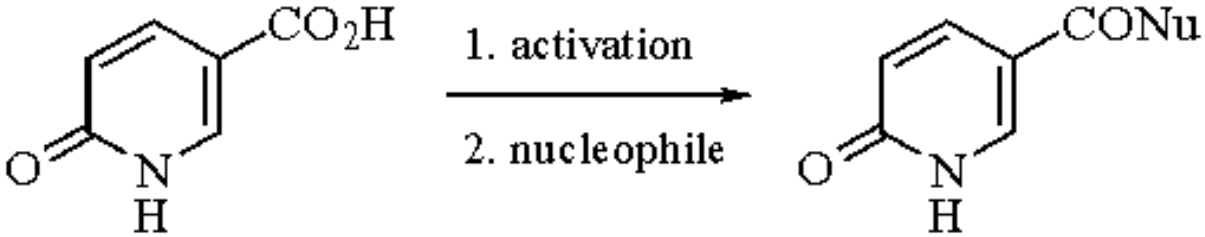

(1)

nucleophile = alcohol, amine, thiol, etc.

6-Hydroxynicotinic acid chloride can also be hydrogenated to the corresponding aldehyde or alcohol under Rosenmund conditions.[6a,b] Moreover, the carboxyl group can be converted into a trifluoromethyl group using ***Sulfur Tetrafluoride***.[7]

As a pyridone, 6-hydroxynicotinic acid undergoes *N*-alkylation (eq 2) in good yields (typically, 70 and 84% for R^1 = Me and Bn, respectively)[8a,b] and *O*-acylation (eq 2), as well as substitution by strong electrophiles in the *ortho* position (eq 3) under mild conditions (0 °C). In this case, the carboxyl group can be easily substituted by a second electrophile, particularly under basic conditions.

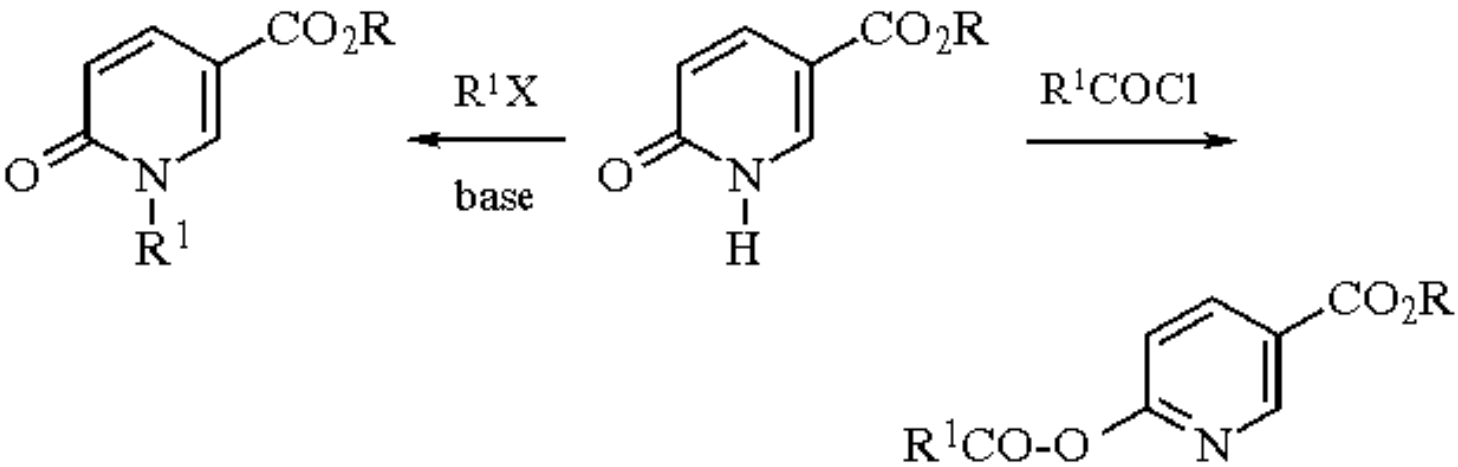

(2)

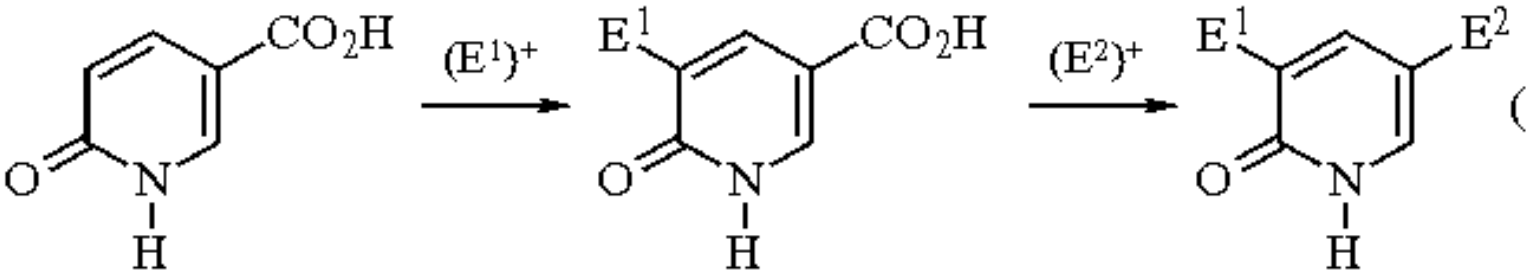

(3)

E^1 = Cl, Br, I, NO_2 E^2 = Cl, Br, I, NO_2

Halogens (Cl_2, Br_2, I_2) or hypohalites, as well as nitric acid, have been used as electrophiles to produce a variety of disubstituted pyridones, e.g. E^1 = Cl,[9a] Br,[9b] NO_2,[9c] E^1 = E^2 = Cl,[9d] I,[9e] NO_2[9f] (eq 3). Such pyridones, like 6-hydroxynicotinic acid itself, can be converted into chloro-[10a,b,c] or bromopyridines[10d] through halodehydroxylation. Subsequently, the halopyridines can be engaged in nucleophilic substitutions with alcohols, amines, phenols, thiols, fluoride, and silicon[11] or carbon nucleophiles, to produce diversely substituted pyridines (eq 4). Finally, 6-

hydroxynicotinic acid can take part as the diene in Diels-Alder cycloadditions with electron-deficient dienophiles.[12]

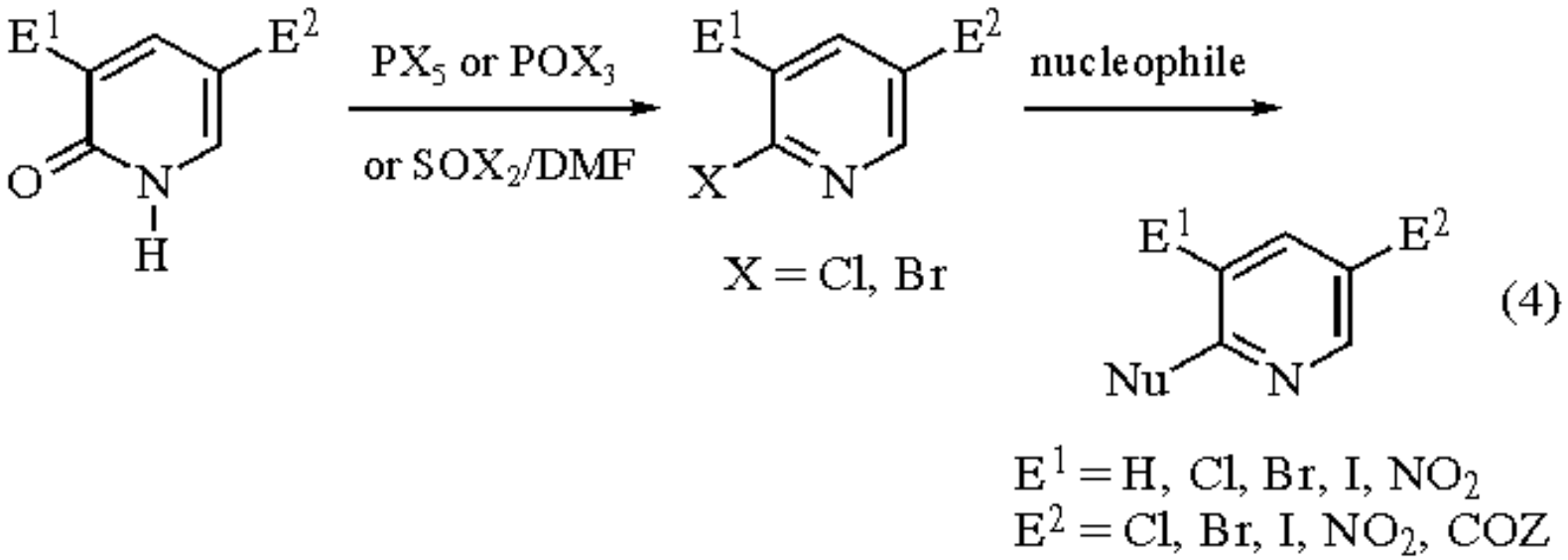

Applications.

6-Hydroxynicotinic acid has been used as a complexing agent to elute metal-bound proteins in affinity chromatography of enzymes.[13] A few important synthetic derivatives of 6-hydroxynicotinic acid are illustrated below. Optically active esters of type (**1**) (eqs 1 and 2) (R^1 = aryl, R^2 = chiral alkyl) are used as components of liquid crystals and optical switching devices.[14] A large number of patents describe the preparation and use of chloropyridines of general structure (**2**) (X = primary or secondary amine) as insecticides.[15] Compounds (**2**) have been prepared on an industrial scale from the corresponding alcohol (**2**) (X = OH) derived from 6-chloronicotinic acid chloride[16] (eq 4). The compound (**3**), also derived from 6-chloronicotinic acid, represents a class of nicotinamide analogs useful for the treatment of psoriasis in humans.[17]

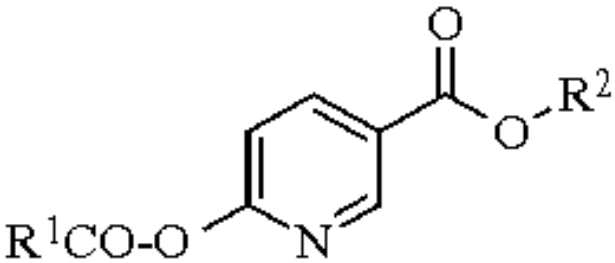

(1)

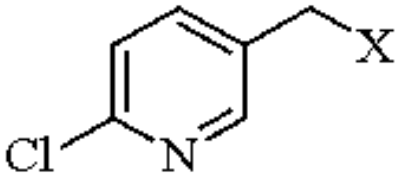

(2)

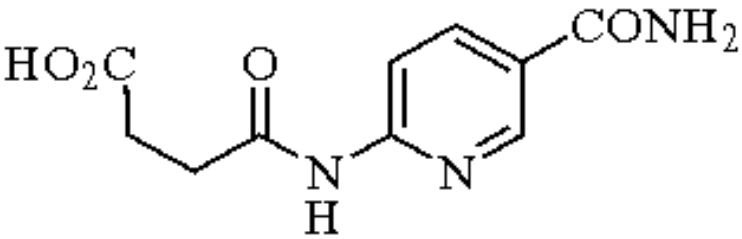

(3)

A great variety of 6-hydroxy- or 6-aminonicotinic amides have shown potentially useful biological activities.[18] 2,3,5-Trichloropyridine has been prepared on a large scale from 6-hydroxynicotinic acid (eqs 3 and 4) as an intermediate for the production of herbicides[19] of structure (**4**). A further application of the ring chlorination (eq 3) is illustrated by the synthesis of growth-stimulating agents (**5**) via 5,6-dichloronicotinic acid.[20a,b] The *N*-alkylation of 6-hydroxynicotinic acid or derivatives (eq 2) has served notably to prepare nucleoside analogs (e.g. **6**).[21]

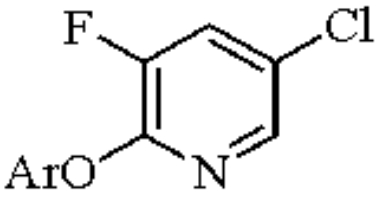

(4)

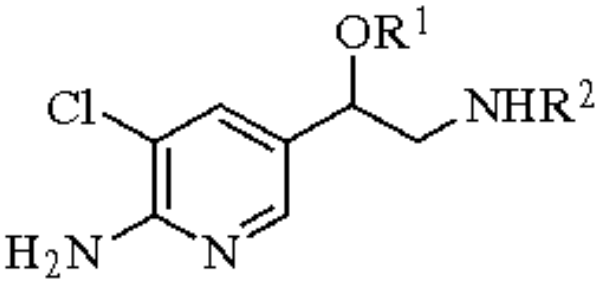

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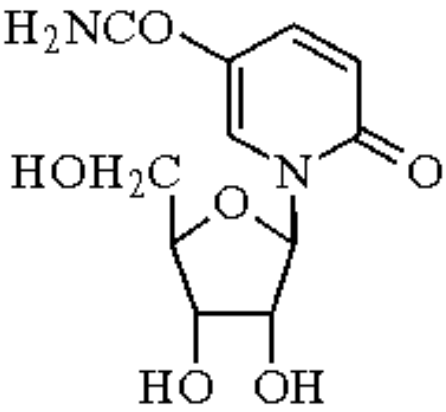

(6)

Related Reagents.

2-Ethoxypyridine 1-Oxide; ***N-Hydroxypiperidine***; ***3-Hydroxypyridine***; ***2-Hydroxypyridine***; ***Pyridine***; ***Pyridine N-Oxide***; ***2-Pyridinethiol***.

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Jean-Paul Roduit

Lonza, Visp, Switzerland

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(1*S*,2*S*,5*S*)-2-Hydroxypinan-3-one

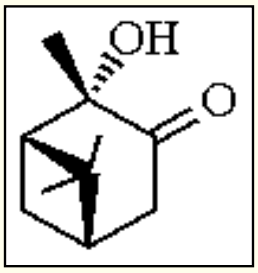

(1*S*,2*S*,5*S*)

[1845-25-6] · $C_{10}H_{16}O_2$ · (1*S*,2*S*,5*S*)-2-Hydroxypinan-3-one · (MW 168.26) (1*R*,2*R*,5*R*)

[24047-72-1]

(chiral auxiliary for the asymmetric synthesis of α-substituted α-amino carboxylic acids,[1,2] phosphonic acids,[3] and phosphinic acids,[4] and of α-substituted benzylamines[5] and (2-pyridyl)methylamines;[6] resolution of racemic α-amino acids[7])

Alternate Name: (1*S*,2*S*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one.

Physical Data: mp 36-38 °C; bp 245 °C; *d* 1.059 g cm^{-3};[α]20D -37° (*c* = 0.5, $CHCl_3$).

Solubility: sol $CHCl_3$, CCl_4, ether, methanol, hot pentane.

Form Supplied in: available as the neat compound.

Analysis of Reagent Purity: NMR.

Preparative Method: prepared by oxidation of α-pinene.[8]

Purification: distillation, or recrystallization from pentane.

Handling, Storage, and Precautions: no reported instability or toxicity.

Asymmetric Synthesis of α-Amino Acids.

Chiral ketimines prepared from the title ketone and glycinates can be deprotonated and treated with electrophiles, such as alkyl halides (eq 1),[1] or Michael acceptors,[2] to give α-substituted α-amino acids with moderate to excellent levels of

diastereoselectivity.

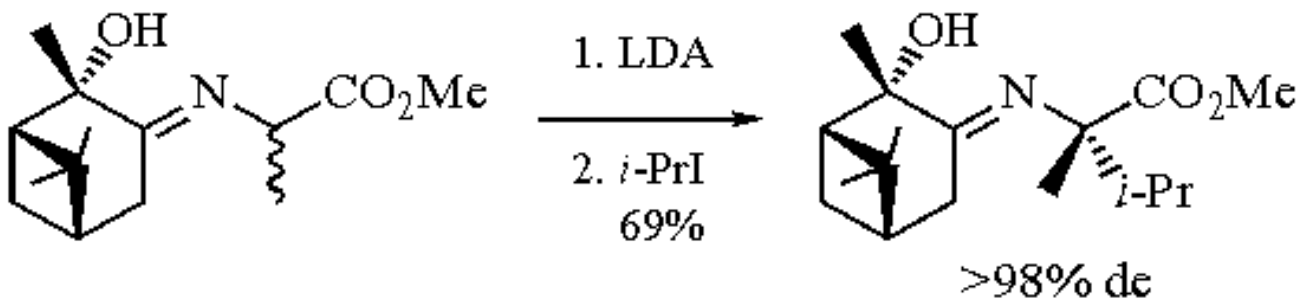

(1)

The product imine diastereomers can usually be separated by chromatography, which enables synthesis of enantiomerically pure α-amino acids even if the reaction is not completely diastereoselective, and provides an alternative to the resolution of racemic α-amino acids.[7] The imine is cleaved by mild hydrolysis with aqueous citric acid or by reaction with hydroxylammonium acetate.

This method is of special value for the synthesis of α,α-disubstituted α-amino acids.[1b,d] Analogous chiral ketimine glycinates prepared from camphor[1e,9a] or a protected D-galactodialdehyde[9b] are also synthetically useful, and in some cases give higher diastereoselectivities; with these reagents, however, separation of the imine diastereomers by chromatography does not seem to be possible. Several other chiral glycinate enolate equivalents have been reported, many of which give excellent levels of selectivity.[10] If the synthetic objective is to prepare β-hydroxy-α-amino acids by reaction of a chiral glycinate with a carbonyl compound, one of these alternative reagents should be chosen.

Asymmetric Synthesis of α-Substituted α-Amino Phosphonic and Phosphinic Acids.

The title reagent can also be used to prepare chiral Schiff bases from α-amino phosphonic[3] and phosphinic[4] acid esters. Deprotonation and alkylation then gives α-substituted products with good to excellent diastereoselectivity (eq 2). Chromatographic separation of the imine diastereomers is often possible, giving access to enantiomerically pure products after hydrolysis. The corresponding Schiff bases prepared from camphor sometimes give higher diastereoselectivities in reactions with activated alkyl halides.[11] A useful alternative reagent based on a chiral phosphonamide has also been reported recently.[12]

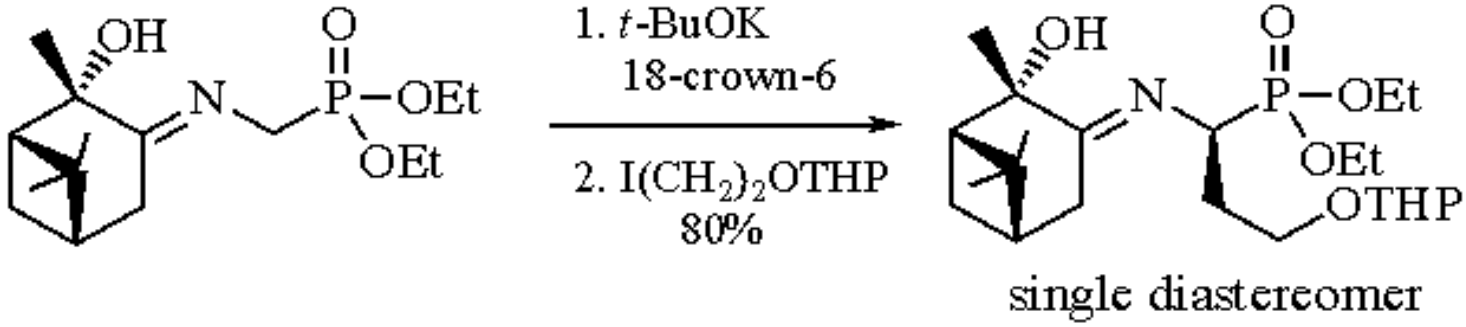

(2)

Asymmetric Synthesis of α-Substituted Benzylamines and (2-Pyridyl)methylamines.

A strategy for the synthesis of chiral α-substituted benzylamines (eq 3)[5] and (2-pyridyl)methylamines[6] by alkylation of chiral ketimines has also been developed.

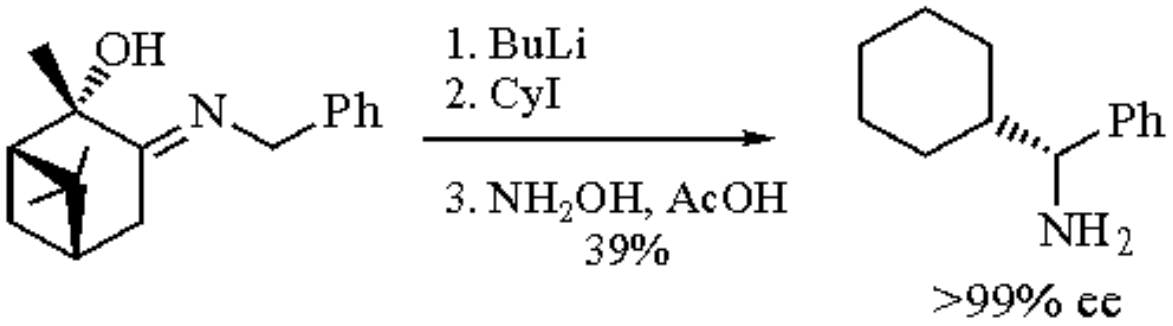

(3)

Ketimines derived from benzylamine and camphor can also be alkylated, but these reactions generally give lower diastereoselectivities.[13] Alternative approaches based on a chiral oxazoline or chiral oxazolidinones have been reported;[14] however, these reagents often give lower diastereoselectivities or problems with partial racemization during the reaction sequence required for cleaving off the chiral auxiliary.

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Tobias Rein

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N-Hydroxypiperidine[1]

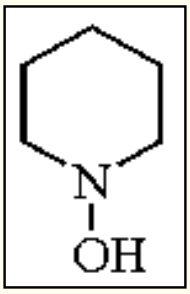

[5801-58-5] · $C_5H_{11}NO$ · *N*-Hydroxypiperidine · (MW 101.17)

(acylation reactions; peptide synthesis)

Alternate Name: HOPip.

Physical Data: mp 39 °C; bp 110 °C/55 mmHg.

Form Supplied in: white solid; limited commercial availability.

Analysis of Reagent Purity: mp; should be a white solid; if it becomes discolored, it should be purified before use.

Preparative Method: prepared, in approximately 62% yield, by the oxidation of *N*-ethylpiperidine with ***Hydrogen Peroxide*** followed by Cope elimination in refluxing toluene.[2]

Purification: recrystallize from *n*-hexane or petroleum ether (40-60 °C fraction) at -60 °C.

Handling, Storage, and Precautions: best stored in a stoppered vessel at 0 °C or below; avoid contact with reducing agents; toxicity not fully investigated so should be treated with caution.

Acylation Reactions.

N-Hydroxypiperidine has been coupled with carboxylic acids using ***1,3-Dicyclohexylcarbodiimide*** (DCC) to give an activated ester which is capable of reacting directly with amines under acid catalysis (eqs 1-3).[3] This has proved of particular interest in the preparation of peptides because the activated ester intermediates are usually stable crystalline materials, and their coupling reactions have been demonstrated to proceed without racemization.[4] Unfortunately this procedure has not found widespread application because, as can be seen from eq 3, the reaction rate is rather sensitive to steric hindrance.[5]

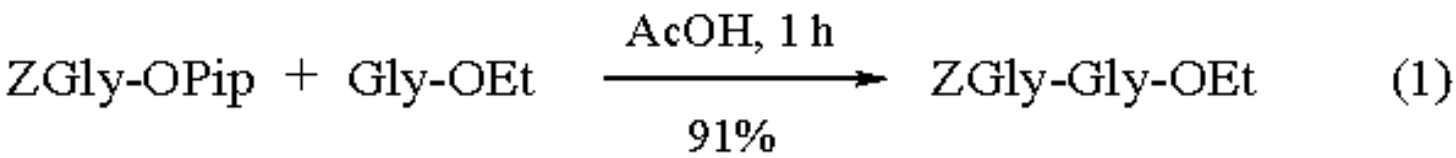

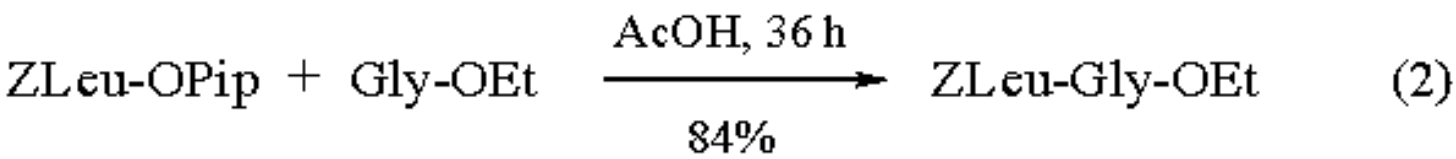

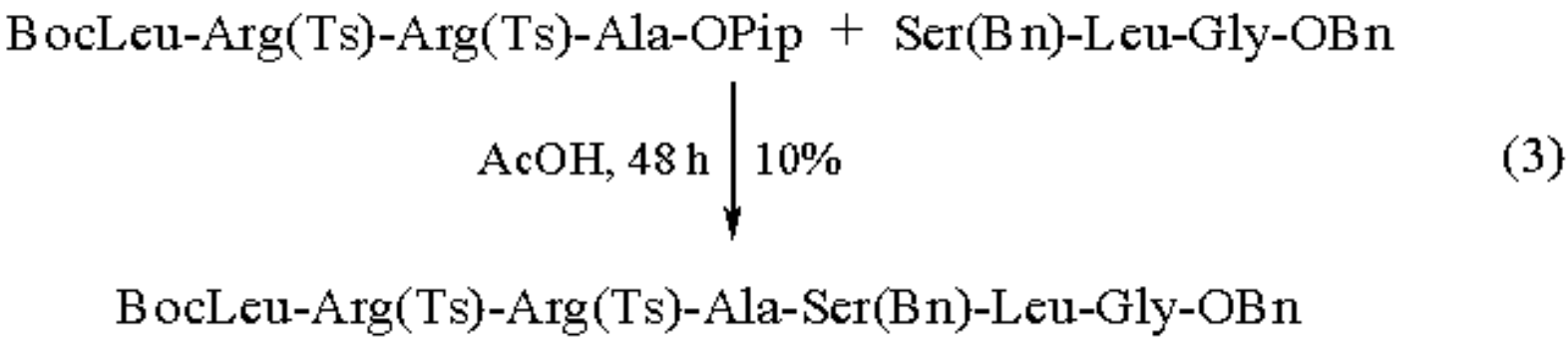

The lack of reactivity of the activated ester systems towards sterically hindered amines can be useful if selective acylation of an amine is required.[3a] For example, the activated ester (**1**) will benzoylate primary amines such as *n*-butylamine at rt over 48 h, whereas more hindered amines such as *t*-butylamine are untouched (eq 4). There is also no reaction with less nucleophilic amines such as aniline or with hydroxy groups under these conditions.

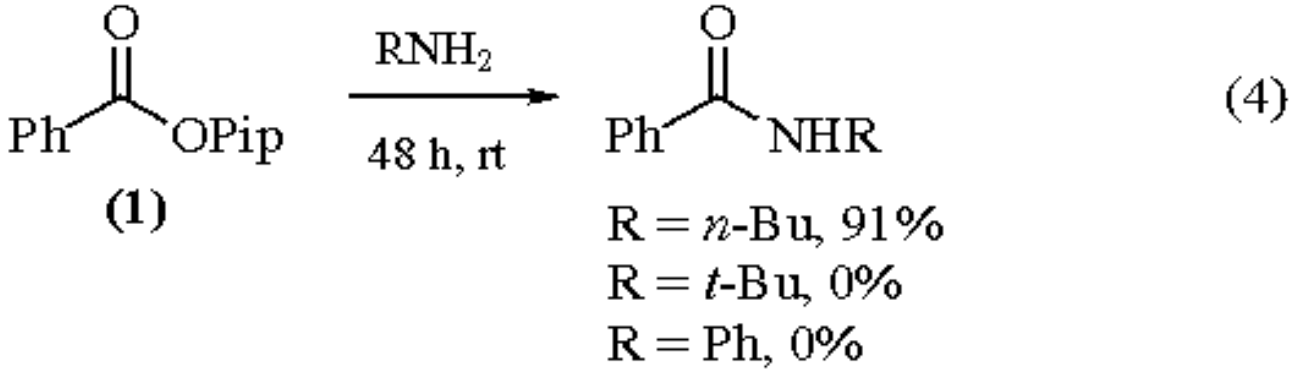

Peptide Synthesis using the Kaiser Resin.

Perhaps the most common use of *N*-hydroxypiperidine today is in conjunction with solid-phase peptide synthesis using the Kaiser resin.[1,4,6] This involves the use of a polystyrene or polyamide (PA) based resin support on which peptides (up to about 40 residues) can be synthesized, the peptide being attached to the support by means of a hydroxylamine ester linkage. Once the desired peptide has been constructed on the support, it can be released under mild conditions by reaction with *N*-hydroxypiperidine (eq 5). The resulting *N*-hydroxypiperidine ester can then be cleaved by the action of ***Zinc-Acetic Acid***, to give the peptide free at the carboxyl terminus. This two-step operation proceeds in good overall yields and without racemization of the peptide unit. It is also compatible with a

wide range of common amino acid protecting groups,[6] making this a useful method for peptide synthesis.

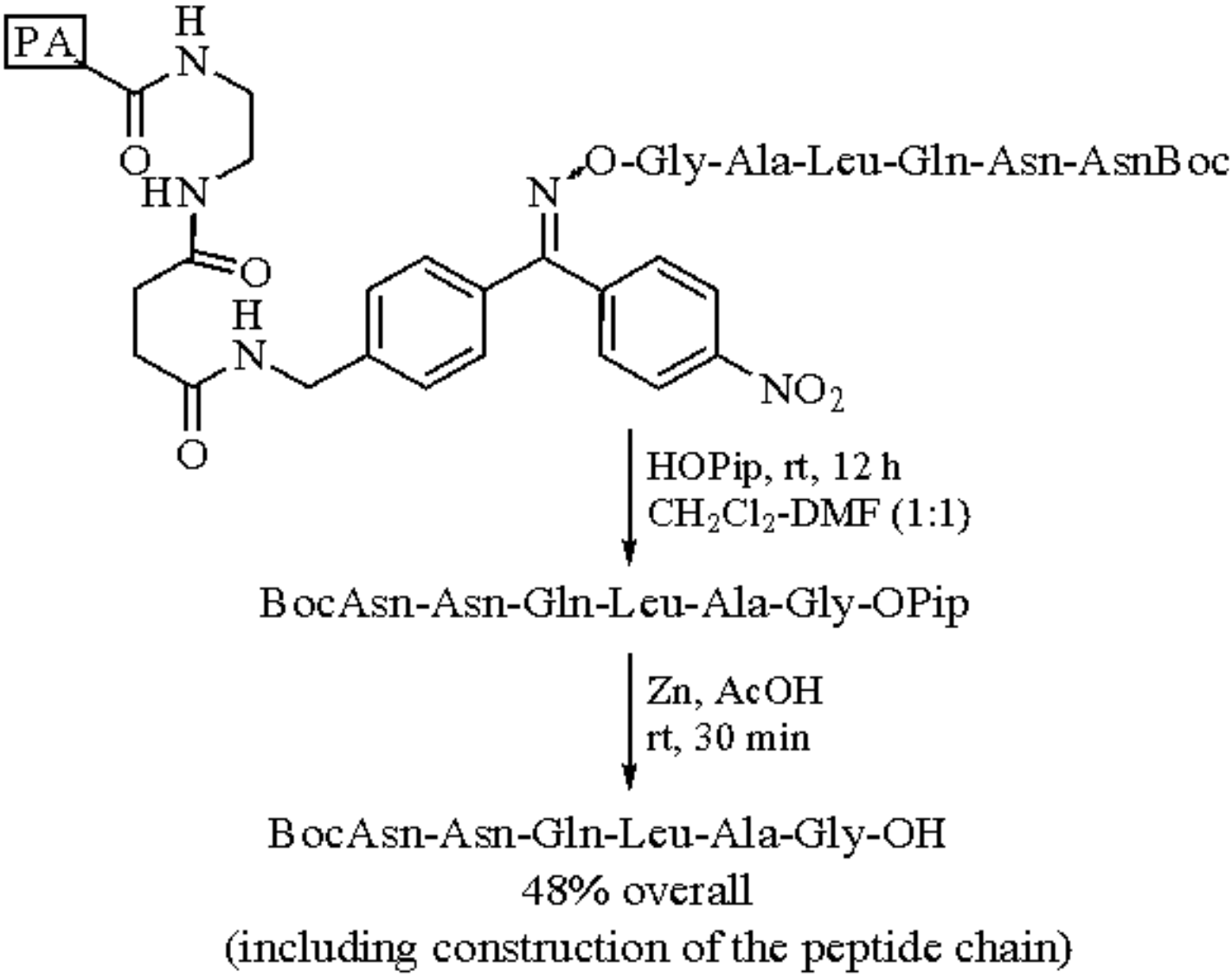

(5)

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Barry Lygo

Salford University, UK

3-Hydroxypyridine

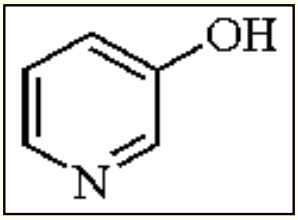

[109-00-2] · C_5H_5NO · 3-Hydroxypyridine · (MW 95.11)

(acylation reactions; peptide synthesis)

Alternate Name: 3-pyridinol.

Physical Data: mp 126-129 °C; bp 151-153 °C/3 mmHg.

Form Supplied in: off-white solid; widely available commercially.

Analysis of Reagent Purity: mp; should be an off-white solid; if it becomes discolored it should be purified before use.

Purification: recrystallize from water or ethanol.

Handling, Storage, and Precautions: best stored in a stoppered vessel at 0 °C or below; avoid contact with strong acids and oxidizing agents; it is toxic and an irritant and so appropriate precautions should be taken.

Peptide Synthesis.

3-Hydroxypyridine has been coupled with amino acids using ***1,3-Dicyclohexylcarbodiimide*** (DCC) to give an activated ester (**1**) which can be used in the formation of peptides[1] as illustrated in eq 1. This can be useful if the purification of the peptide product proves to be a problem using other methods, since the intermediate (**1**) is soluble in dilute acid and hence easily removed from the reaction medium. In addition, the byproducts of the coupling reaction can easily be removed with aqueous acid.

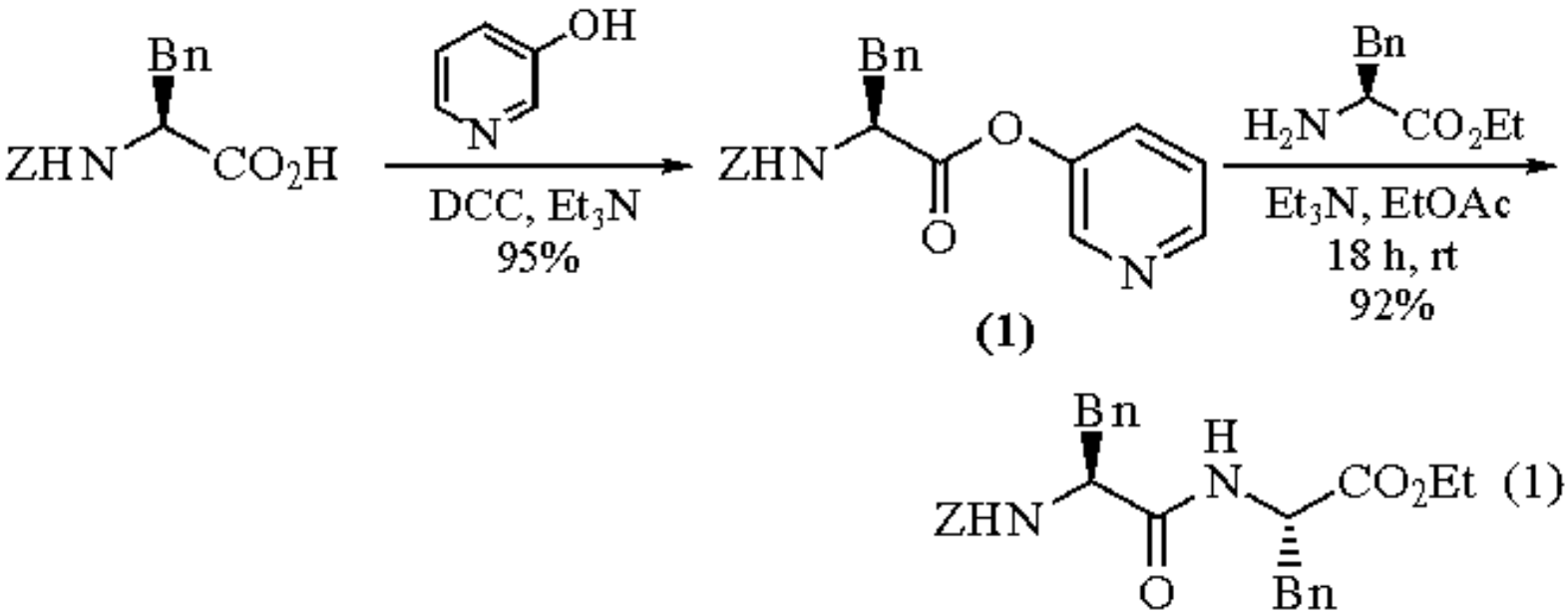

Acylation Reactions.

3-Hydroxypyridine can be readily *O*-acylated using ***Acetyl Chloride*** and the product is of use as a selective acylating agent for alcohols and amines.[2] For example, it will react with primary amines at rt to give good yields of the corresponding amides, whereas secondary amines react more slowly and diarylamines do not react at all (eq 2).

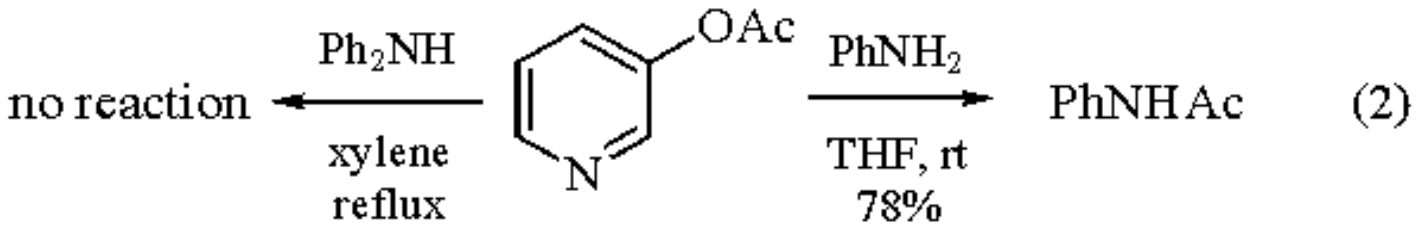

It is possible to increase the reactivity of 3-acetoxypyridine towards amines by the addition of Lewis acids such as ***Boron Trifluoride*** (eq 3), and this does allow some fine-tuning of the reactivity.

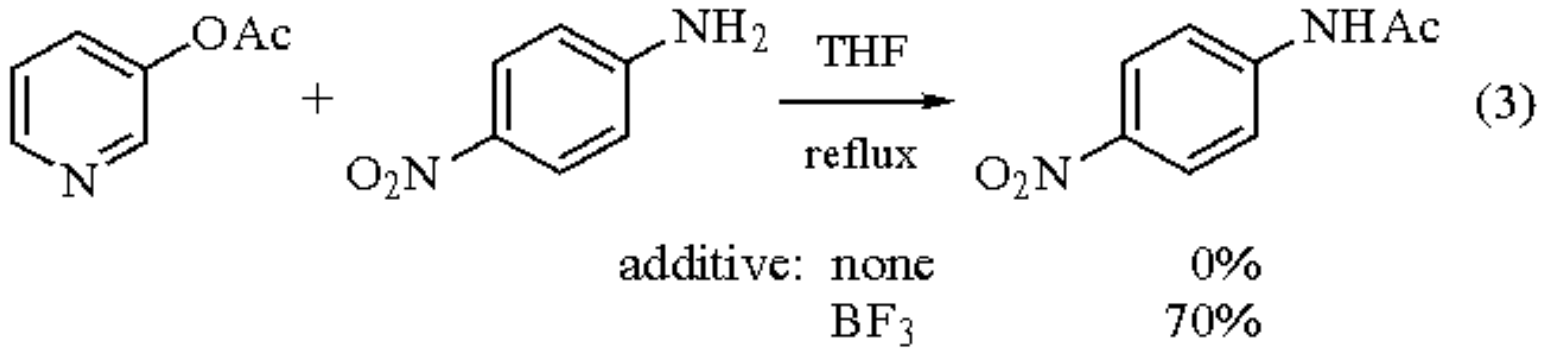

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1. Taschner, E.; Rzeszotarska, B.; Lubiewska, L. *AG(E)* **1965**, *4*, 594.
2. Ueno, Y.; Takaya, T.; Imoto, E. *BCJ* **1964**, *37*, 864.

2-Hydroxypyridine[1]

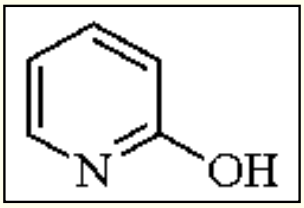

(-ol form)

[72762-00-6] · C_5H_5NO · 2-Hydroxypyridine · (MW 95.11) (-one form)

[142-08-5]

(acylating agent; nitrile formation; peptide coupling)

Alternate Names: 2-pyridinol; 2(1*H*)-pyridone.

Physical Data: mp 105-107 °C; bp 181-185 °C/24 mmHg.

Form Supplied in: off-white solid; widely available commercially.

Analysis of Reagent Purity: mp; should be an off-white solid; if it becomes discolored it should be purified before use.

Purification: distill under vacuum then recrystallize from ethanol.

Handling, Storage, and Precautions: best stored in a stoppered vessel at 0 °C or below; avoid contact with strong acids and oxidizing agents; it is toxic and an irritant and so appropriate precautions should be taken.

Introduction.

The pyridone tautomer is treated separately (see ***2-Pyridone***), where cycloaddition chemistry is discussed. This entry deals with uses of the reagent as an acylating and activating agent.

Bifunctional Catalysis.

2-Hydroxypyridine has been used as a bifunctional catalyst[2] in a number of reactions,[3] most notably in the formation of amides. In this context the addition of 2-hydroxypyridine to the reaction between methyl ester (**1**) and amine (**2**)

significantly enhances the yield of the amide product (eq 1).

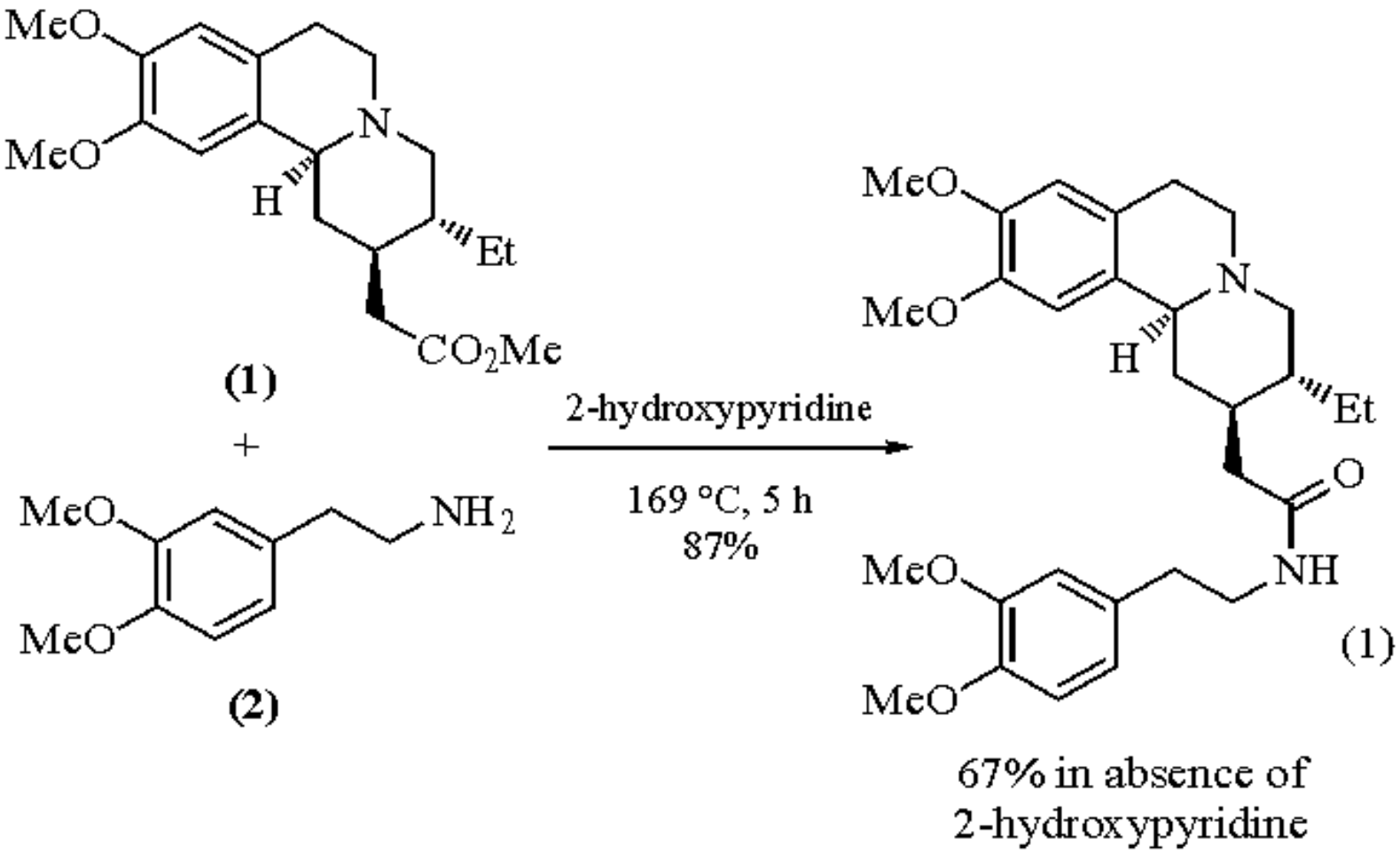

Acyl Derivatives of 2-Hydroxypyridine.

The coupling of 2-hydroxypyridine with amino acids has been used as a means of activating the carboxyl function for peptide synthesis. The active esters can then be readily reacted with the amino function of another amino acid with minimal epimerization of any chiral centers (eq 2).[4]

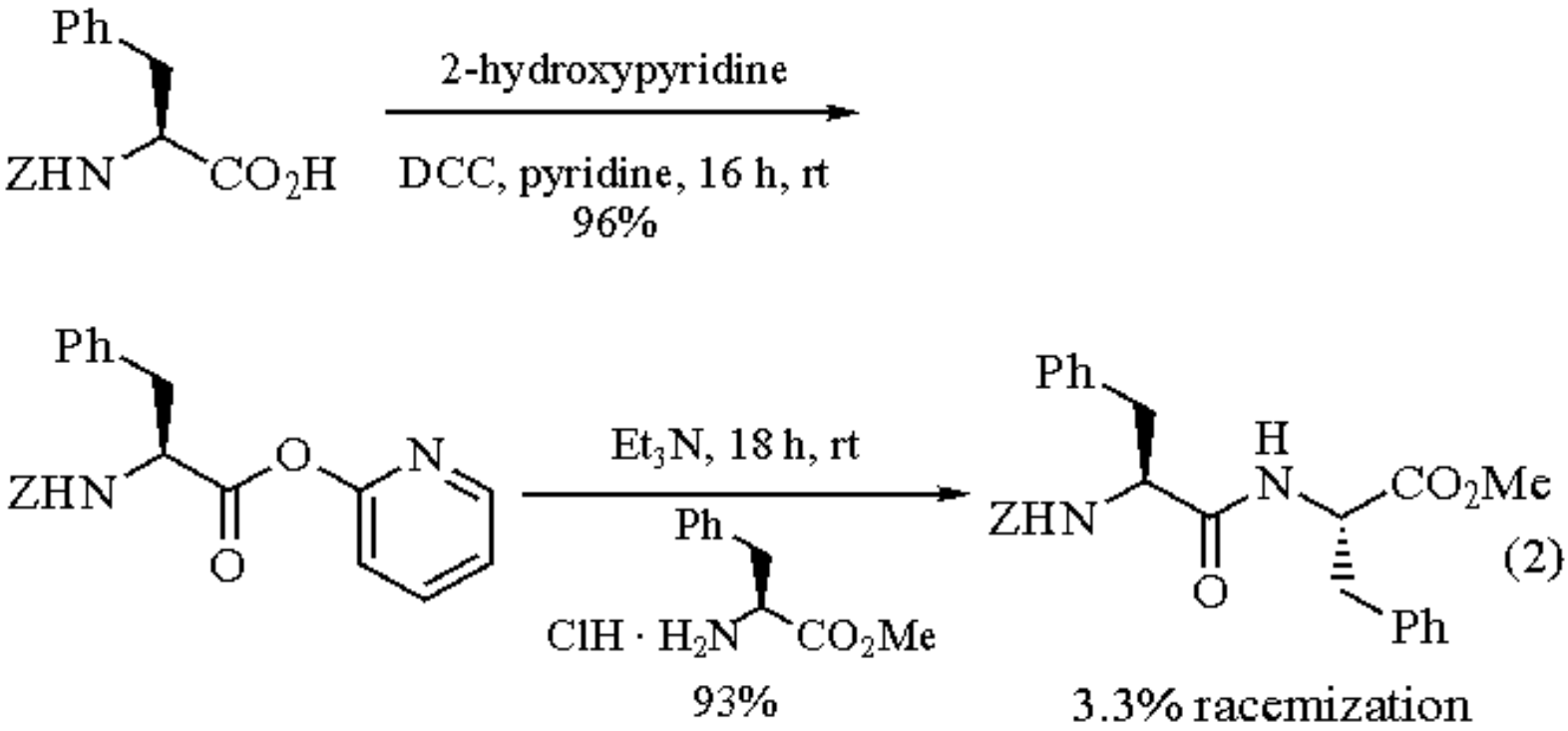

The reaction rates for these coupling reactions decrease considerably in polar solvents such as DMF, which means that this method is only really useful for small peptide units which are soluble in less polar solvent systems such as dichloromethane. For larger peptides, it has been shown that good reaction rates can be achieved if this coupling reaction is used in conjunction with a Merrifield resin.

These active esters will also acylate a range of carbon nucleophiles including Grignard reagents,[5] organocopper reagents,[6] and ester enolates.[7] This chemistry has been used to prepare keto derivatives of amino acids as illustrated in eq 3.

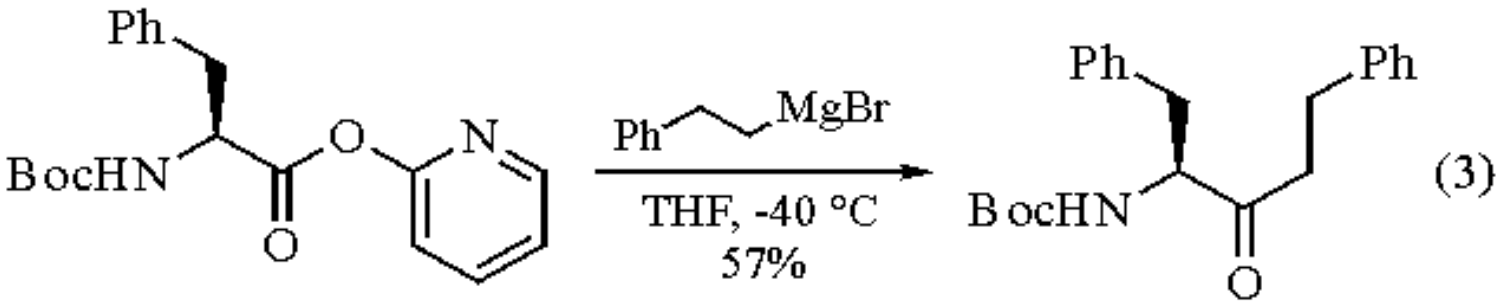

O-Acyl derivatives of 2-hydroxypyridine have also been employed as general acylating agents;[3b,8] for example, the benzyloxycarbonate derivative will readily react with amino acids to give the corresponding benzyloxycarbamate. In the case of free amino acids such as serine, this reagent shows high chemoselectivity for the amino function (eq 4).

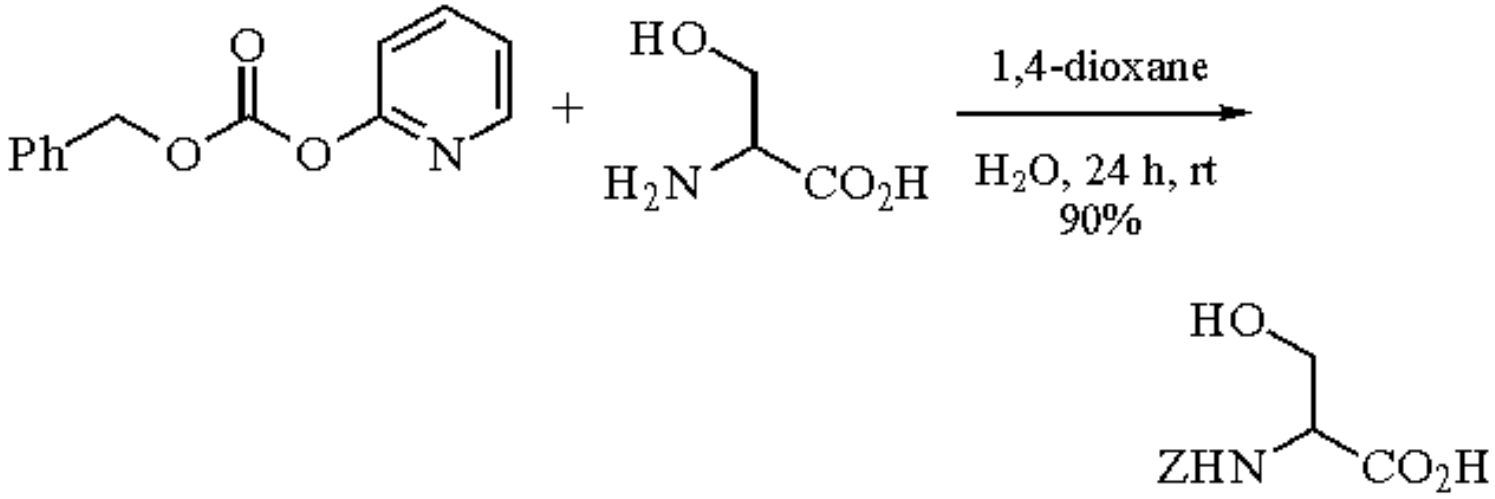

(4)

2-Trifluoroacetoxypyridine (TFAP), which is readily prepared from 2-hydroxypyridine, will trifluoroacetylate both amines and alcohols, as illustrated in eq 5.

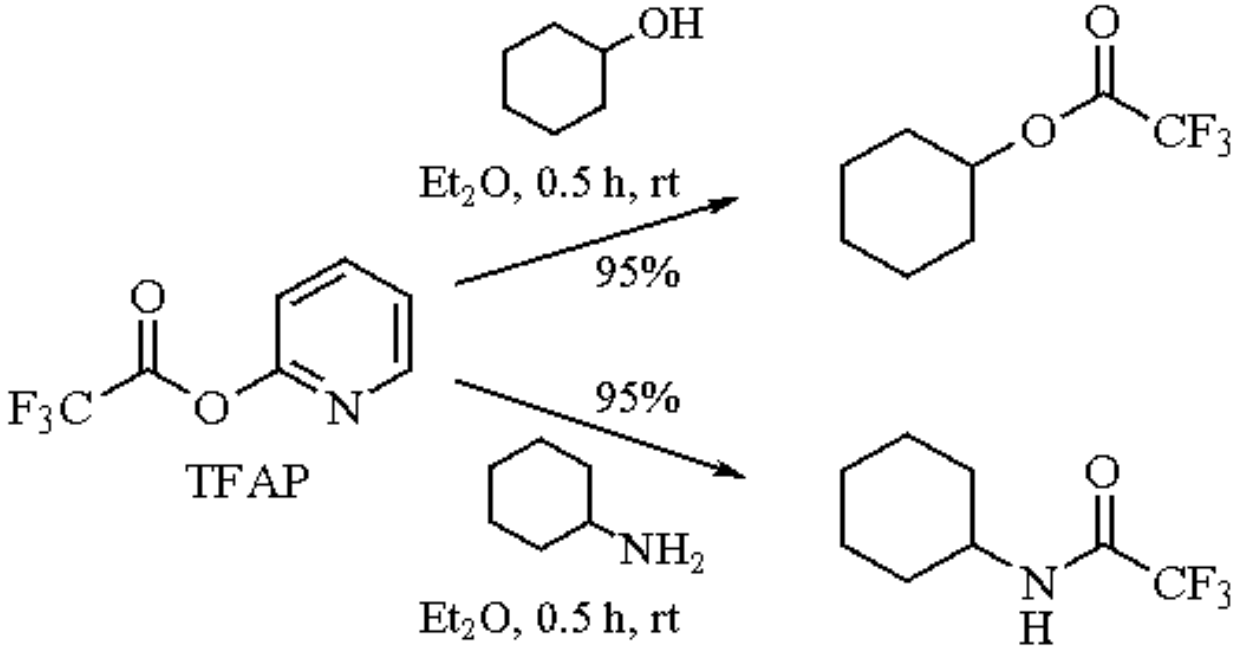

(5)

As well as being a simple trifluoroacetylation agent, TFAP is also capable of effecting the dehydration of oximes and amides to give nitriles, as exemplified in eq 6.

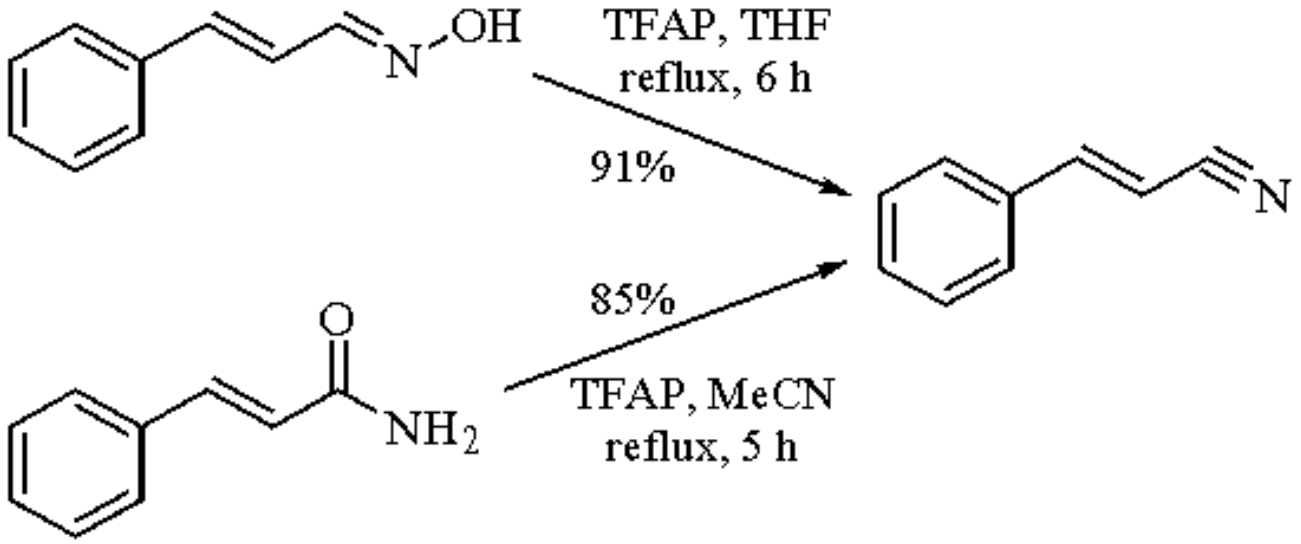

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N-Hydroxypyridine-2-thione

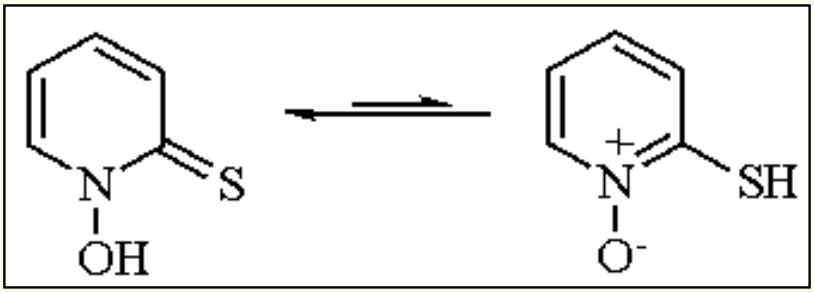

[1121-30-8] · C_5H_5NOS · *N*-Hydroxypyridine-2-thione · (MW 127.18)

(reaction with a carboxylic acid or acid chloride leads to the corresponding *O*-acyl thiohydroxamate; treatment of these intermediates with a radical source leads to alkyl or aryl radicals [R&bdot;], the fate of which depends on the precise reactions conditions[1])

Alternate Name: 1-hydroxy-2-(1*H*)-pyridinethione; the tautomeric *N*-oxide form *[1121-31-9]*, although the minor component, is often the source of alternate names for this compound, which include 2-pyridinethiol 1-oxide, 2-mercaptopyridine *N*-oxide, 2-mercaptopyridine 1-oxide, and the abbreviated form pyrithione.

Physical Data: mp 70-72 °C.

Form Supplied in: both the pyridinethione and the corresponding sodium salt (sometimes as the hydrate) are commercially available. A 40% aqueous solution of the sodium salt is also available and cheaper (also referred to as sodium omadine). The free thione can be obtained from this by acidification to neutrality using concentrated aq HCl, filtration of the crude product, and crystallization from EtOH. Alternatively, evaporation of the aqueous solution (<50 °C) and crystallization of the residue from ethanol provides the sodium salt, mp 285-290 °C, after slow crystallization from ethanol and drying at 50 °C under vacuum.[3]

Preparative Methods: prepared from 2-bromopyridine by oxidation to the *N*-oxide using either ***Perbenzoic Acid*** or ***Peracetic Acid***, followed by displacement of bromide using either ***Sodium Dithionite*** or ***Sodium Sulfide*** and ***Sodium Hydroxide***.[2] An alternative is to treat the *N*-oxide with ***Thiourea*** and then hydrolyze the resulting thiouronium salt.

Handling, Storage, and Precautions: all operations in this area should be carried out with due regard to both the thermal and photochemical sensitivity of the reagents and intermediate *O*-acyl thiohydroxamates.

Preparation of *O*-Acyl Thiohydroxamates.

There are three commonly used options available for the preparation of *O*-acyl thiohydroxamates, outlined in eqs 1-

3.[1,4] Firstly, the carboxylic acid can be activated by conversion into a mixed anhydride from ***Isobutyl Chloroformate*** and then coupled directly with the pyridinethione (**1**). Alternatively, *O*-acyl thiohydroxamates (**2**) can be obtained using the DCC (***1,3-Dicyclohexylcarbodiimide***) coupling method (eq 1). If acid chlorides are used, these are best converted into the hydroxamates (**2**) by reaction with the sodium salt (**3**) in the presence of ***4-Dimethylaminopyridine*** (eq 2). A further option is to activate the pyridinethione component by formation of the bicyclic system (**4**) from the parent and ***Phosgene*** and then react this with the triethylammonium salt of the carboxylic acid (eq 3). Compound (**4**) is commercially available as 1-oxa-2-oxo-3-thiaindolizinium chloride (2-oxo-[1.4.2]oxathiazolo[2,3-*a*]pyridinium chloride).[1,4b] The latter two methods appear to be the most favored; the sensitive esters are used promptly with little purification, often just filtration through a short silica column.[3]

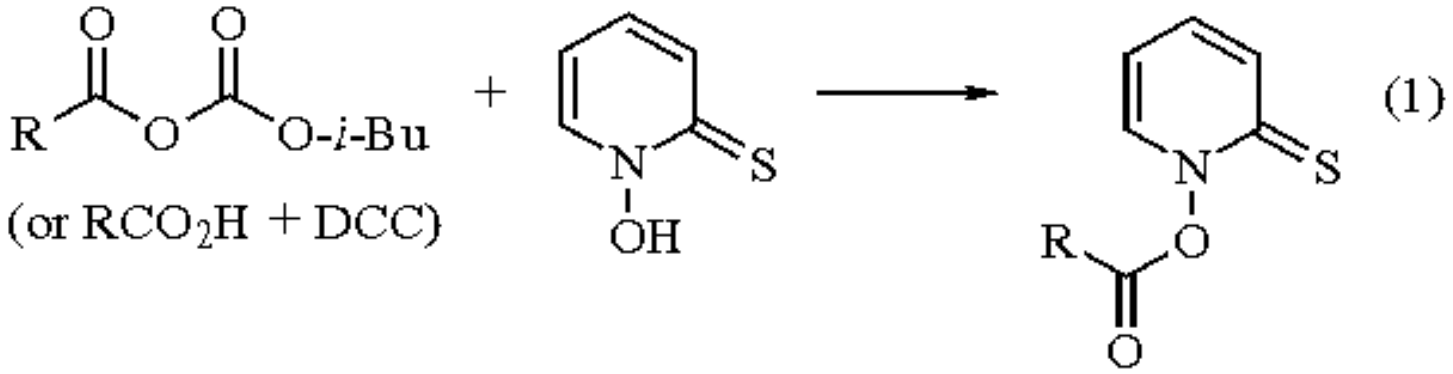

(1) **(2)**

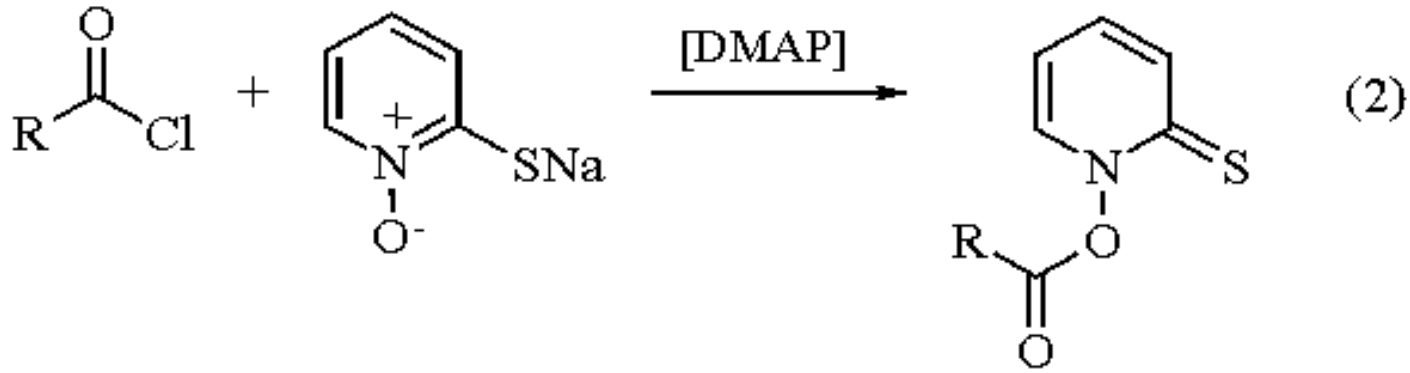

(3) **(2)**

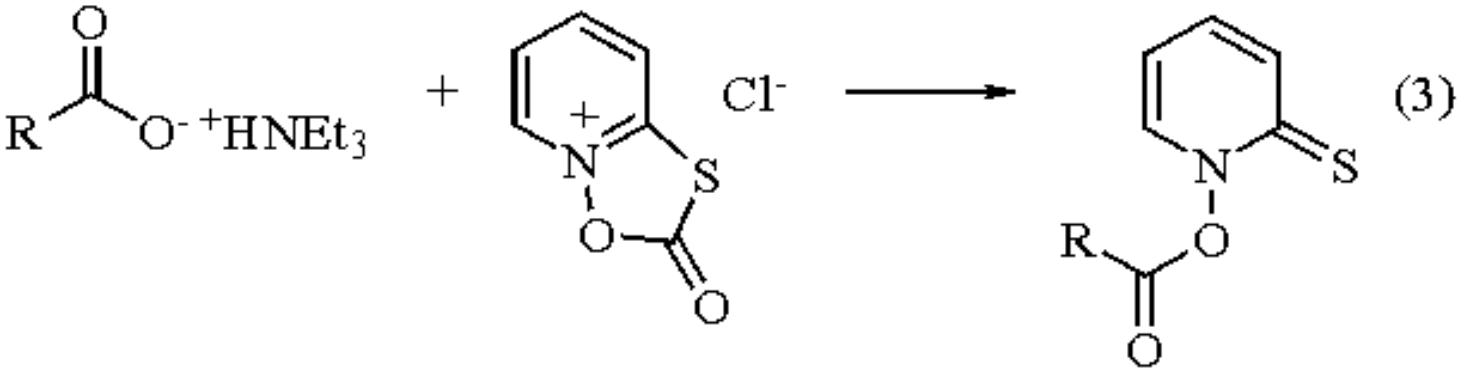

(4) **(2)**

Decarboxylation.

Perhaps the best-known application of this type of pyridinethione derivative in synthesis is in the overall, radical-mediated decarboxylation of carboxylic acids, i.e. RCO_2H -> RH (eq 4).[1,4b] The transformation is of a wide generality and usually proceeds in good to excellent yields. The chain carrier and hydrogen radical source is either ***Tri-n-butylstannane*** or a tertiary thiol, most often *t*-butanethiol (but see Barton and Crich[6]), and the reactions are generally triggered thermally when tin hydride is employed, or photolytically (tungsten lamp suffices) when a thiol is used.[5] The latter method offers considerable advantages in terms of product purification; for details of this aspect as well as sound advice on how to conduct these and related radical reactions in general, consult Motherwell and Crich.[1]

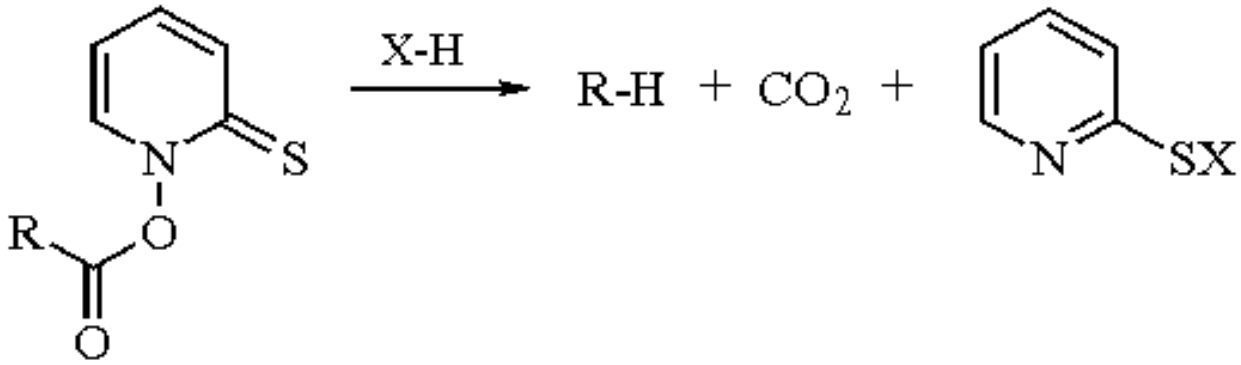

(4)

$X = Bu_3Sn$, *t*-BuS, $C_{11}H_{23}Me_2CS$

A wide variety of functionality can be incorporated into the substrate acids, such as in the decarboxylation of α-amino acid derivatives which leads to amines (eq 5).[4d] Application of this methodology to the appropriate aspartate and glutamate derivatives provides access to the useful radicals (**5**) which can be trapped in many ways, such as by halides (overall, a Hunsdiecker reaction),[4d] as can many other radical species obtained using this chemistry (see below).

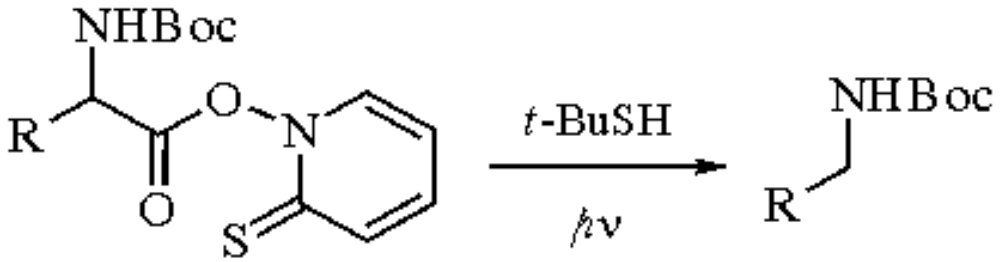

(5)

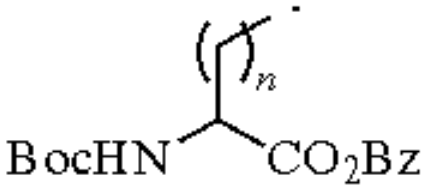

(5)

Alcohol Deoxygenation.

A limitation of the useful Barton-McCombie procedure for the deoxygenation of alcohols is its application to tertiary alcohols because of difficulties in preparing the required xanthate or other derivatives. A solution to this is to first form a monoester with ***Oxalyl Chloride*** and then react the remaining acyl chloride function with the sodium salt (**3**) (eq 6).[6] In these reactions, although *t*-butanethiol is suitable as the chain carrier, in some cases 3-ethyl-3-pentanethiol gives superior yields (50-90%). The intermediate tertiary radicals can be trapped by powerful Michael acceptors such as 1,2-dicyanoethylene.

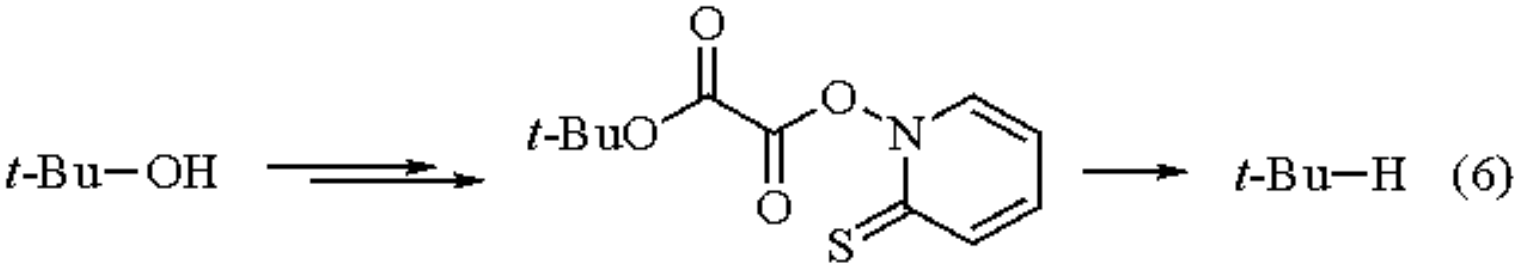

(6)

Decarboxylative Rearrangement.

When *O*-acyl thiohydroxamates are simply heated or photolyzed alone, a decarboxylative rearrangement occurs to give 71-92% yields of 2-thiopyridines (eq 7).[4b,7] While the thermal process involves some contribution from a cage recombination mechanism, the photolytic reaction is a purely radical chain process.

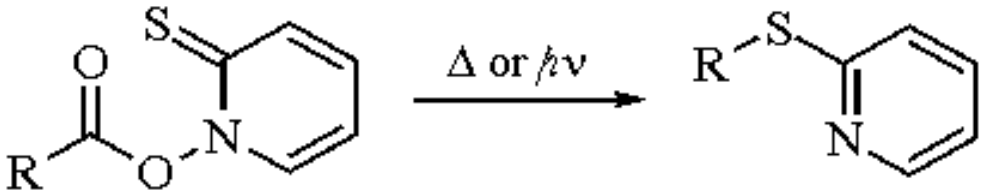

(7)

Formation of Sulfides, Selenides, Tellurides, and Selenocyanates.

When *O*-acyl thiohydroxamates are decomposed in the presence of disulfides, diselenides, or ditellurides, mixed sulfides, selenides, or tellurides are formed, respectively (eq 8).[8] If the reactions are triggered thermally, a large excess of the disulfide etc. has to be used to avoid competition from decarboxylative rearrangement (see above); however, light-induced reactions proceed at lower temperatures and, in such cases, only a slight excess of the trap is required. When the trapping agent is dicyanogen triselenide then selenocyanates, RSeCN, are produced.

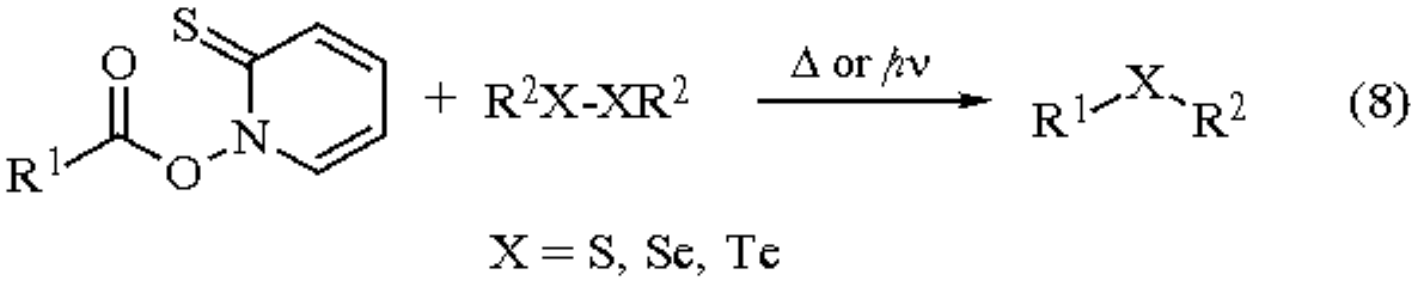

Decarboxylative Sulfonation.

When a solution of an *O*-acyl thiohydroxamate in CH_2Cl_2 containing excess SO_2 is photolyzed at -10 °C, the initially formed radicals are intercepted by the latter before decarboxylative rearrangement can take place. The resulting radicals (RSO_2&bdot;) then react with a second molecule of the *O*-acyl thiohydroxamate to give an *S*-pyridyl alkylthiosulfonate (38-91%) and the radical R&bdot; (eq 9).[9] The products are useful as precursors to unsymmetrical sulfones and sulfonamides, significantly by a nonoxidative procedure.

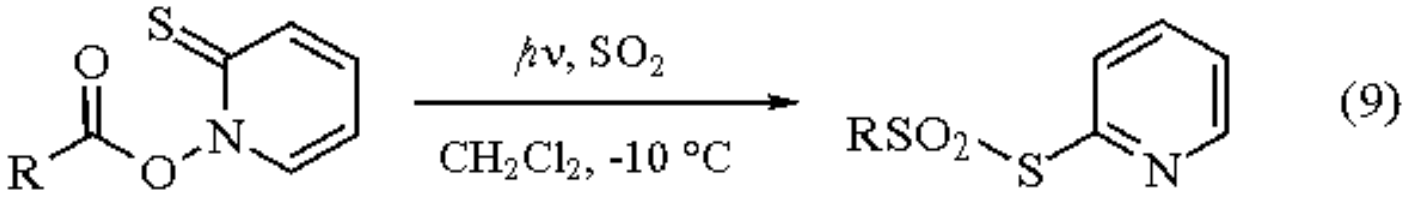

The Hunsdiecker Reaction.

The classical Hunsdiecker reaction is somewhat restricted due to the relatively harsh conditions required. In the Barton version, alkyl radicals generated from *O*-acyl thiohydroxamates, under either thermal or photolytic conditions, are efficiently trapped either by Cl_3C-X (X = Cl or Br; Cl_3C&bdot; is the chain carrier) or by ***Iodoform***.[1,4b,10] The method is applicable to sensitive substrates for which the classical methods are unsuitable,[4d,11] thus allowing the preparation of a wide range of alkyl chlorides, bromides, and iodides by the one-carbon degradation of a carboxylic acid. Similar reactions of aromatic acid derivatives tend to require an additional radical initiator (e.g. ***Azobisisobutyronitrile***), if high yields (55-85%) are to be obtained.[12]

Decarboxylative Hydroxylation.

A close relative of the foregoing degradation, the transformation RCO_2H -> ROH can be carried out in two ways. Perhaps the most practical version consists of thermolysis or photolysis of an *O*-acyl thiohydroxamate, typically in oxygen-saturated toluene, followed by reduction of the initial hydroperoxide (eq 10).[4b,13] In similar fashion to decarboxylative sulfonation (see above), the intermediate radicals are trapped much faster (~10^4) by oxygen than by H-abstraction from the thiol chain carrier. As an alternative, the initial hydroperoxides can be *O*-tosylated in pyridine to give the corresponding nor-aldehyde or ketone (53-62%). The alternative, mechanistically more convoluted but still efficient and simple procedure (82-93%), has tris(phenylthio)antimony, $(PhS)_3Sb$, as the radical trap in the presence of both oxygen and water (in practice, wet air).[14]

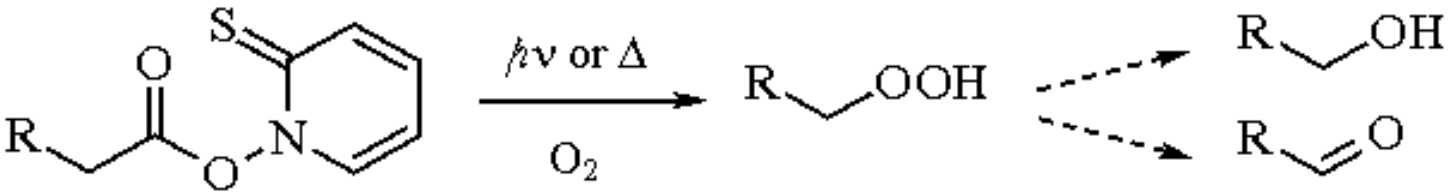

(10)

Decarboxylative Phosphorylation.

In similar fashion to the foregoing, radicals generated by decomposition of an *O*-acyl thiohydroxamate can be trapped by tris(phenylthio)phosphine (eq 11).[15] In some cases, the use of alternative thiohydroxamates may be advantageous.

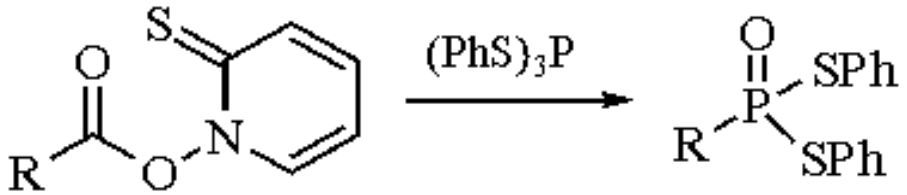

(11)

Michael Additions and Other Radical Reactions.

As decomposition of *O*-acyl thiohydroxamates provides radicals, these can subsequently participate in a variety of other reactions, the most common of which are Michael additions to electron-deficient alkenes. The most commonly successful pathway (eq 12) involves reaction of the intermediate carbon-centered radical adjacent to the electron-withdrawing group with a second molecule of the thiohydroxamate, rather than hydrogen abstraction, to give an α-*S*-pyridyl derivative,[1,6,7b] which can subsequently be manipulated in a variety of ways.[16] Other thiohydroxamates can lead to higher yields; the mildness and potential of this methodology is illustrated in eq 13.[17]

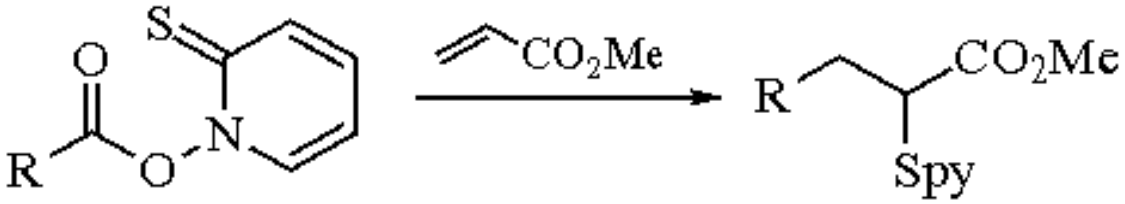

(12)

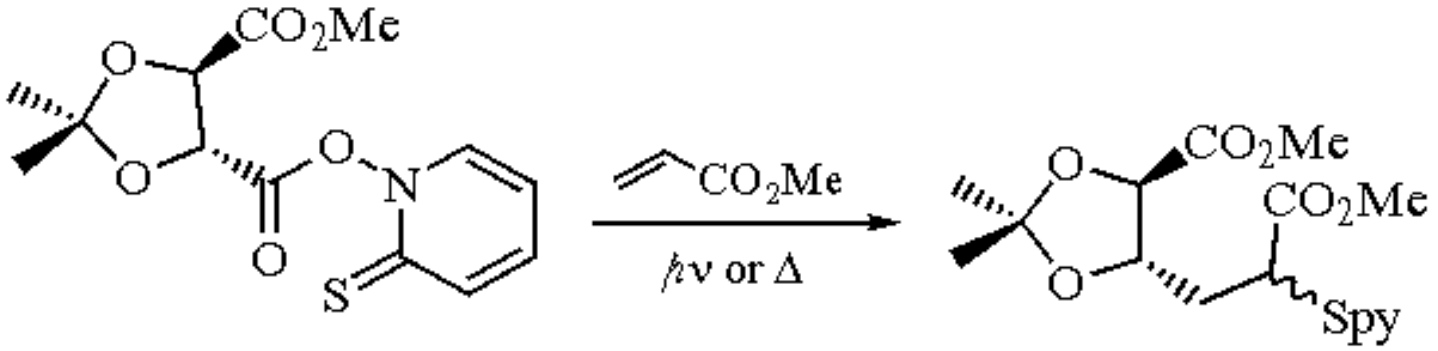

(13)

Similar reactions, but using nitroalkenes as traps, lead to the corresponding α-pyridylthio nitroalkanes, which are useful as precursors to the one-carbon homologated carboxylic acids, aldehydes, or the related ketones, by starting

with an α-substituted nitroalkene (eq 14).[7b,18]

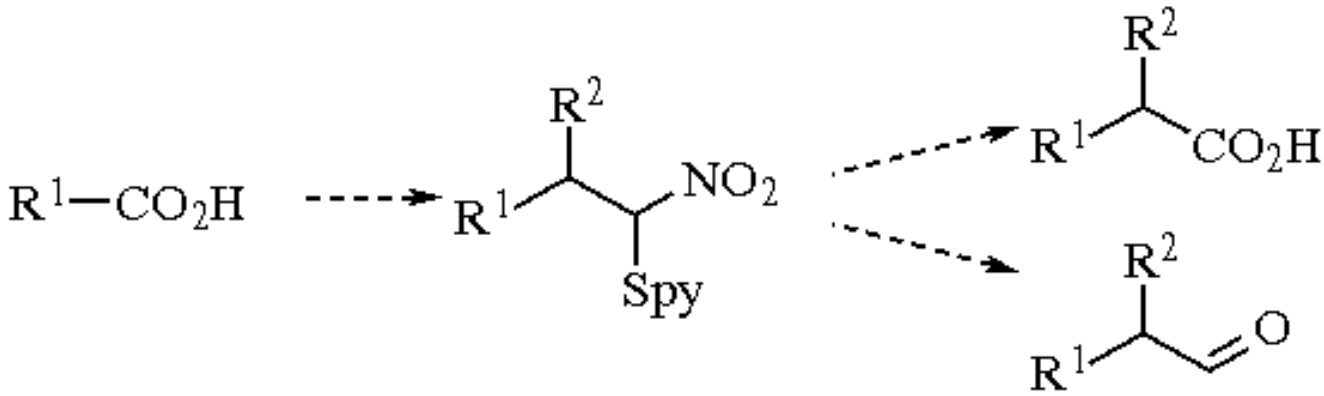

(14)

Radicals derived from decarboxylation of perfluorocarboxylic acids will undergo addition to ethyl vinyl ether to provide the expected homologs in ~60% yields (eq 15).[19]

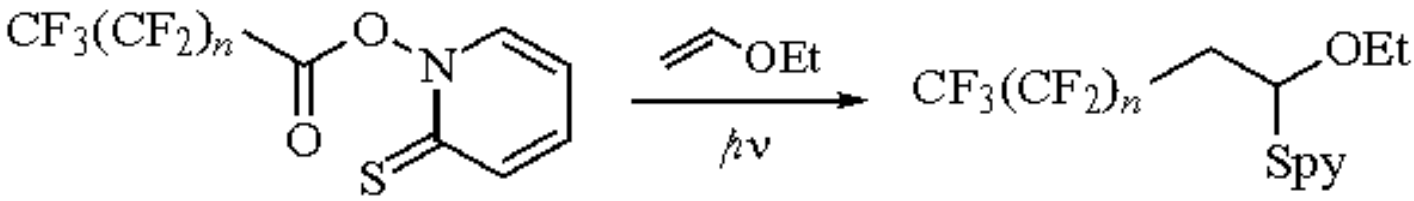

(15)

Protonated pyridines can also be used as acceptors of carbon radicals generated from thiohydroxamates in general.[20] A useful extension of the Michael addition reactions is to incorporate an additional *t*-butylthio substituent into the acceptor component (eq 16).[18b,21] Tandem reactions are also possible, as exemplified by the conversion of a cyclopentenecarboxylic acid into a bicyclo[2.2.1]heptane (eq 17).[22]

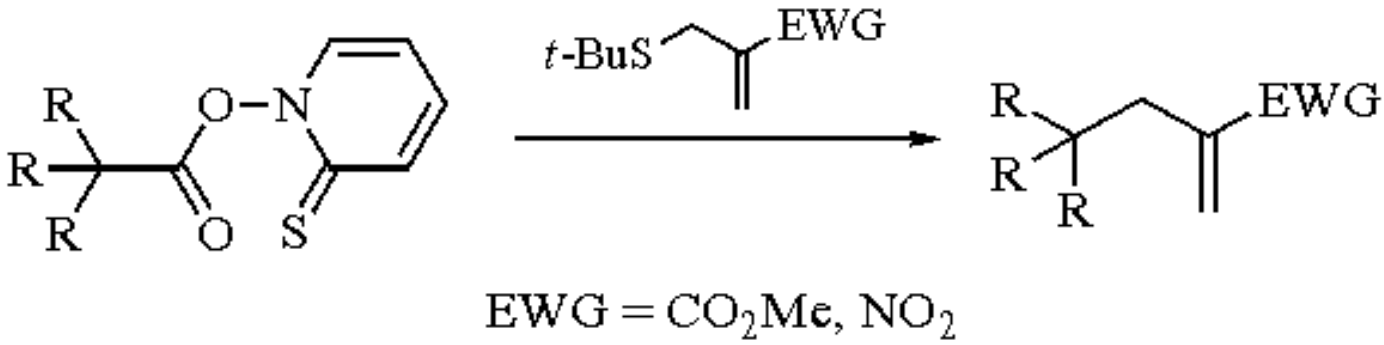

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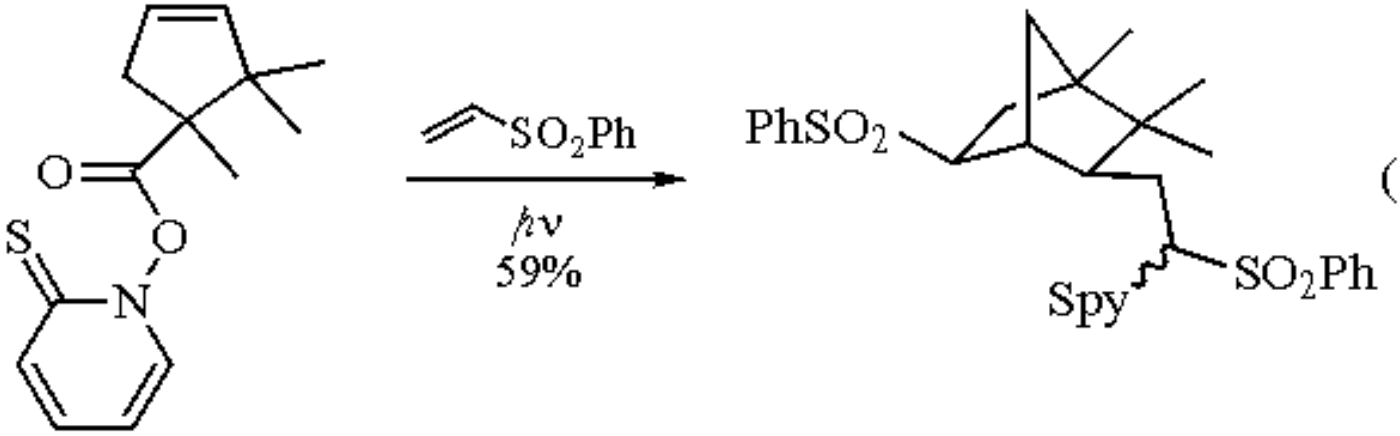

Carbon radicals obtained from thiohydroxamates can also be trapped intramolecularly by unactivated alkene functions especially in the 5-*exo*-trig mode,[7b,23] as can aminyl radicals generated in the same way; better yields of cyclic products are obtained in the presence of a weak acid which presumably protonates the *N*-centered radical prior to cyclization (eq 18).[24]

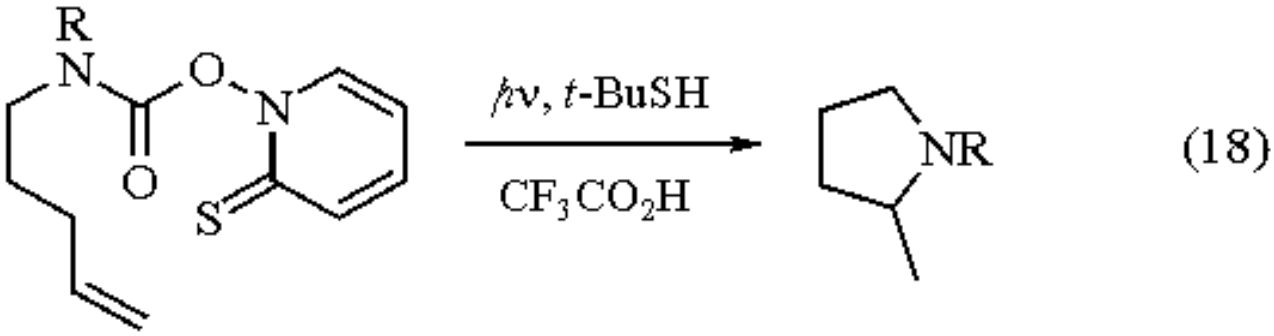

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1. For an excellent overview of this area, including practical examples, see Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, Academic: London, 1992.
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10. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *TL* **1983**, *24*, 4979.
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3-Hydroxy-2-pyrone[1]

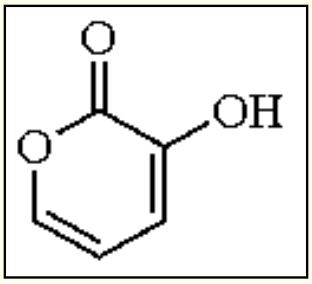

[496-64-0] · $C_5H_4O_3$ · 3-Hydroxy-2-pyrone · (MW 112.09)

([4 + 2] cycloaddition vinylketene diene equivalent[2,3])

Physical Data: white, crystalline solid; mp 92 °C; mp (dihydrate) 80-85 °C; bp 112 °C/20 mmHg; sublimes at 50 °C/4 mmHg; λ_{max} 294 nm (H_2O).

Solubility: 4-5 g/100 mL H_2O; sol EtOH, Et_2O, $CHCl_3$, hot C_6H_6; slightly sol CS_2, petroleum ether.

Preparative Methods: acid-catalyzed decarboxylation-dehydration of mucic acid provides 3-hydroxy-2-pyrone in 20-40% yield: a three-neck round-bottom flask equipped with an overhead stirrer, thermometer, and distillation head is charged with a 1:1 mixture of mucic acid and powdered $KHSO_4$. The mixture is heated at 160-165 °C while ca. 1 mL of a light brown distillate per 2 g of mucic acid used is collected. The distillate is filtered and the pH adjusted to 7 using 6 N HCl. Continuous extraction with ether for ca. 12 h is followed by drying of the ether extract; concentration by rotary evaporation provides the crude product as a yellow solid. Recrystallization from petroleum ether or sublimation provides pure white crystalline material.[3,4] 3-Hydroxy-2-pyrone also has been prepared by oxidation of ***2-Pyrone***.[5]

A degradation product commonly formed in nonenzymic browning of fruits, 3-hydroxy-2-pyrone and its analogs are useful synthetic reagents. When used in Diels-Alder reactions, bicyclic lactone adducts result and these can be elucidated into a variety of highly functionalized, stereochemically defined cyclohexenes, cyclohexadienes, and benzenes.

Although unreactive towards simple alkenes, 3-hydroxy-2-pyrone undergoes slow [4 + 2] cycloadditions with reactive dienophiles, including maleates, maleic anhydride, acrylates, acrylonitriles, methacrylates, crotonates, benzoquinone, and acetylenedicarboxylates.[3,6-8] Reaction temperatures and times required for cycloaddition are in the range 80-200 °C for 2-72 h, so that pyrolytic decarboxylation of the adduct is common. Typical is the regio- and stereospecific synthesis of tricyclic ketones using the hydroxypyrone and indene (eq 1);[9] isolated chemical yields usually are good. Similarly, chloronaphthazarin (**1**) (eq 2) undergoes cycloaddition with 3-hydroxy-2-pyrone with in situ extrusion of CO_2 and dehydrochlorination to provide digitopurpone diacetate (**3**), a model compound for anthracyclinone construction.[10]

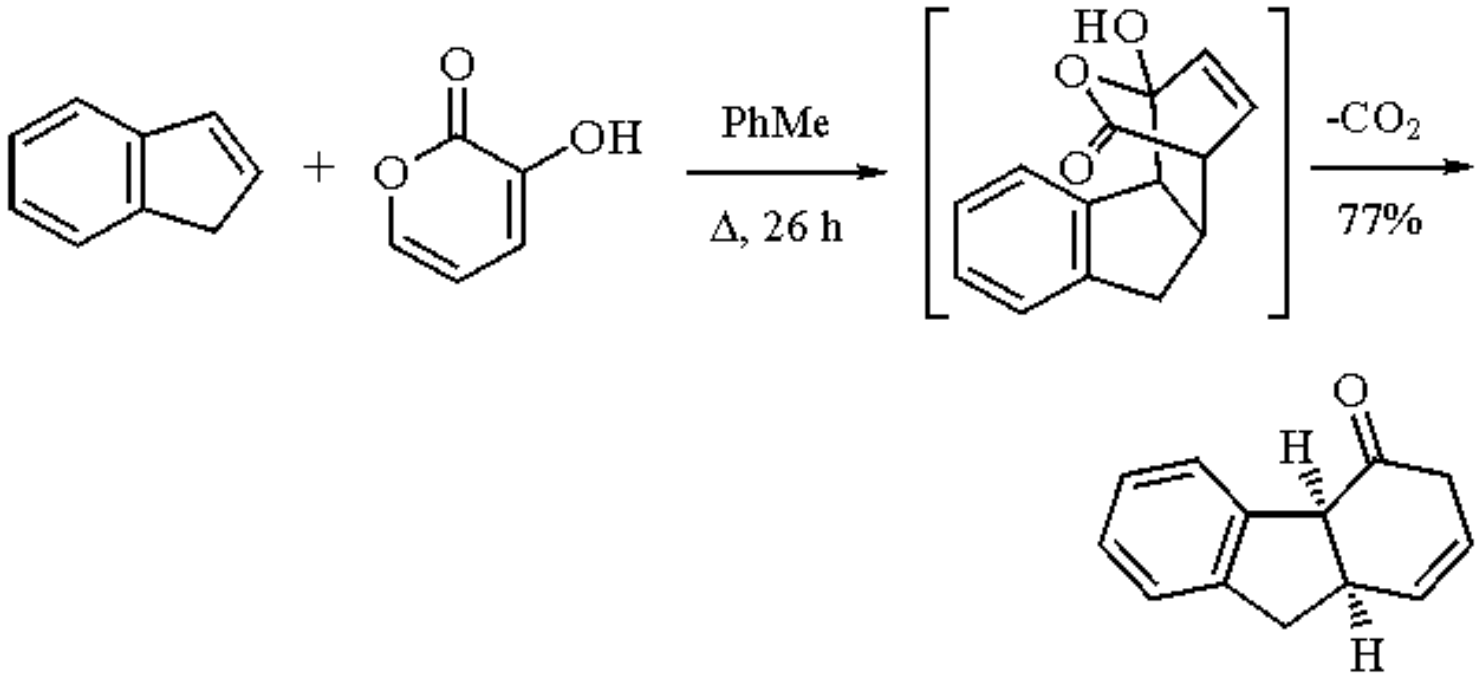

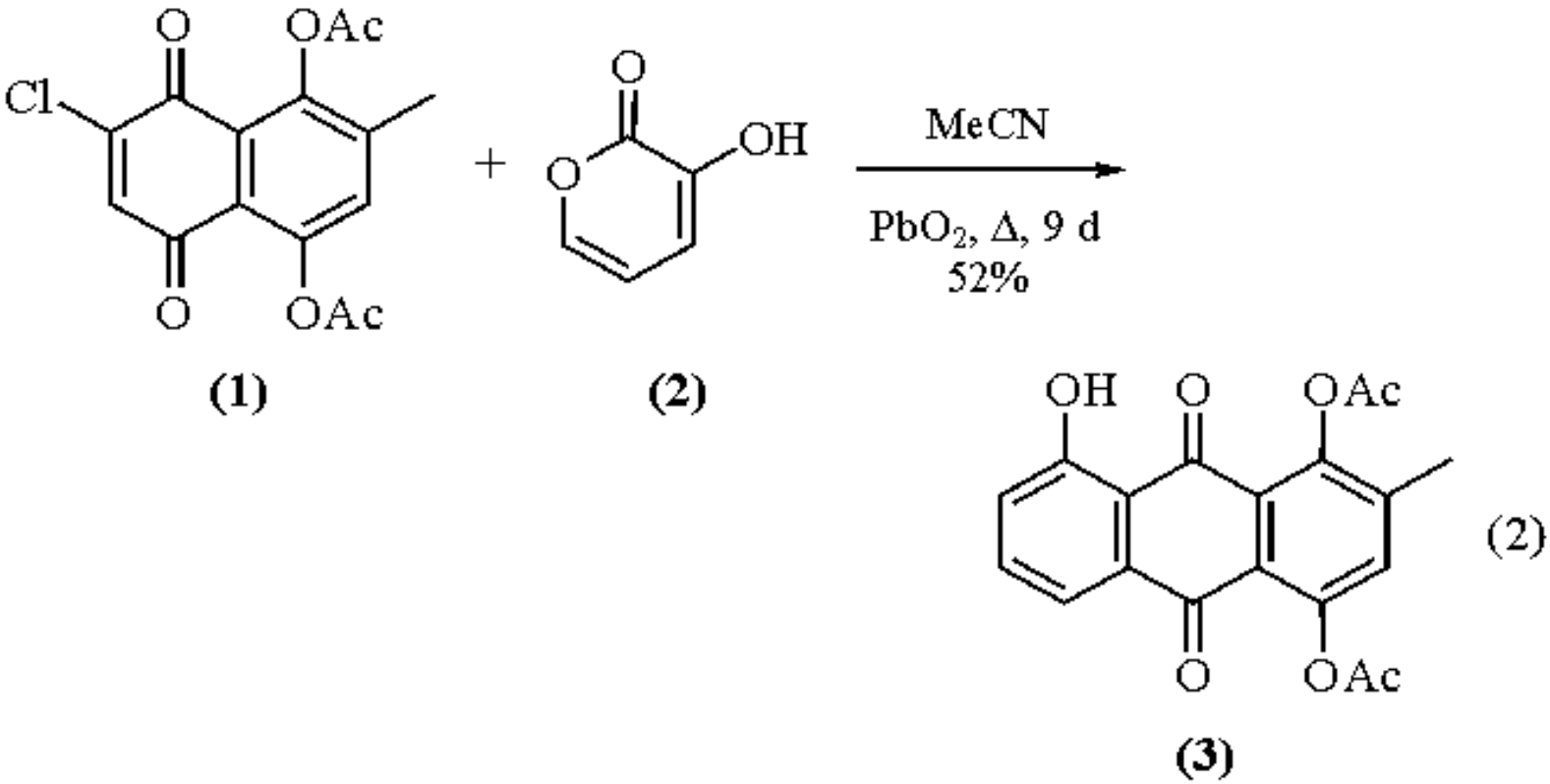

Inhibition of adduct decarboxylation can be achieved using high-pressure cycloaddition conditions, which proceed at temperatures 50-180 °C lower than the corresponding thermal conditions.[11] Eq 3 compares the results of thermal[3] and high-pressure[11] addition of methyl crotonate to 3-hydroxy-2-pyrone. Esterification of the 3-hydroxy group allows for asymmetric inverse electron demand, high-pressure Diels-Alder reactions, providing a stereoselective route to highly oxygenated cyclohexanes when vinyl ethers are used as dienophiles (eq 4).[12]

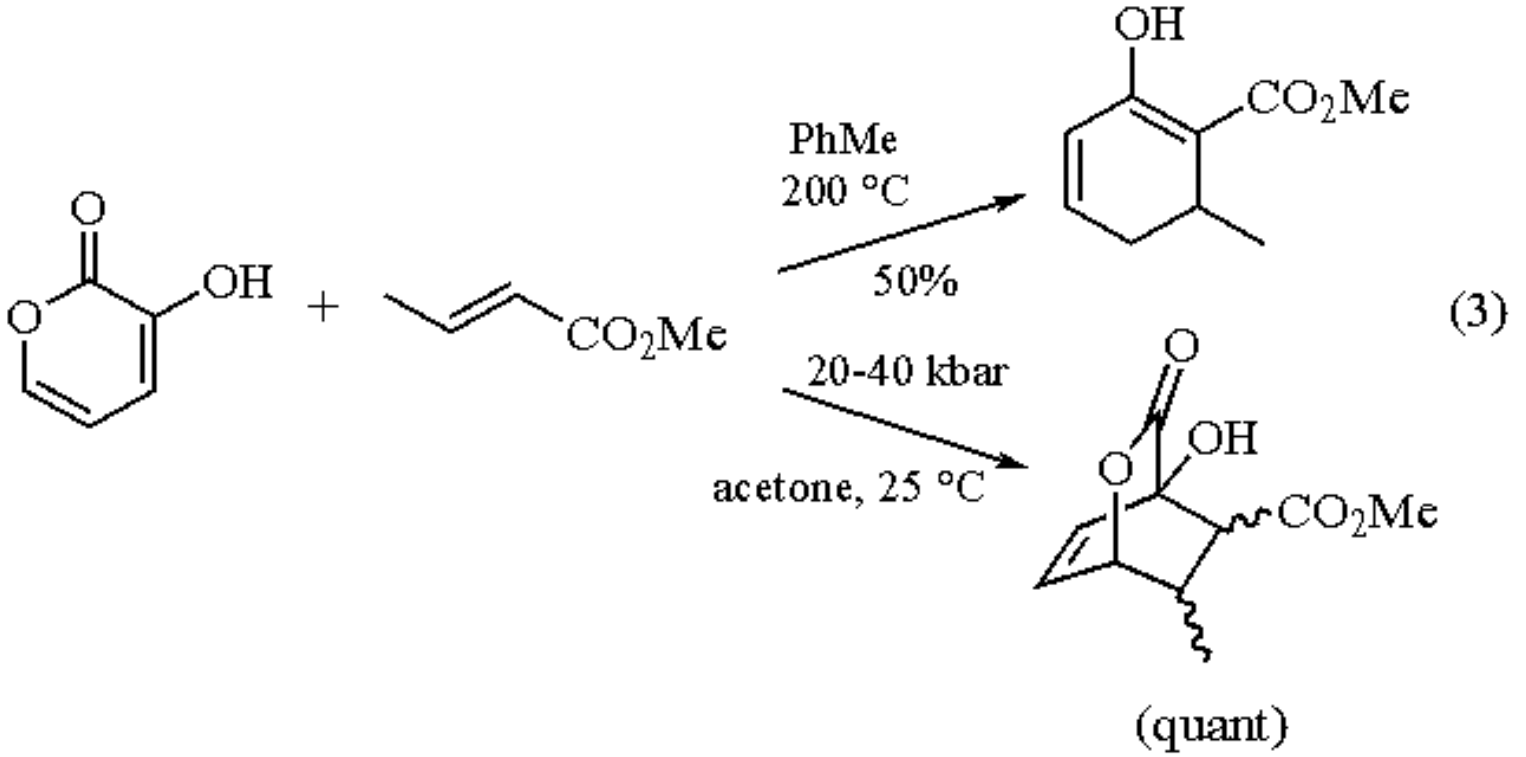

(3)

(quant)
3:2 mixture of diastereomers

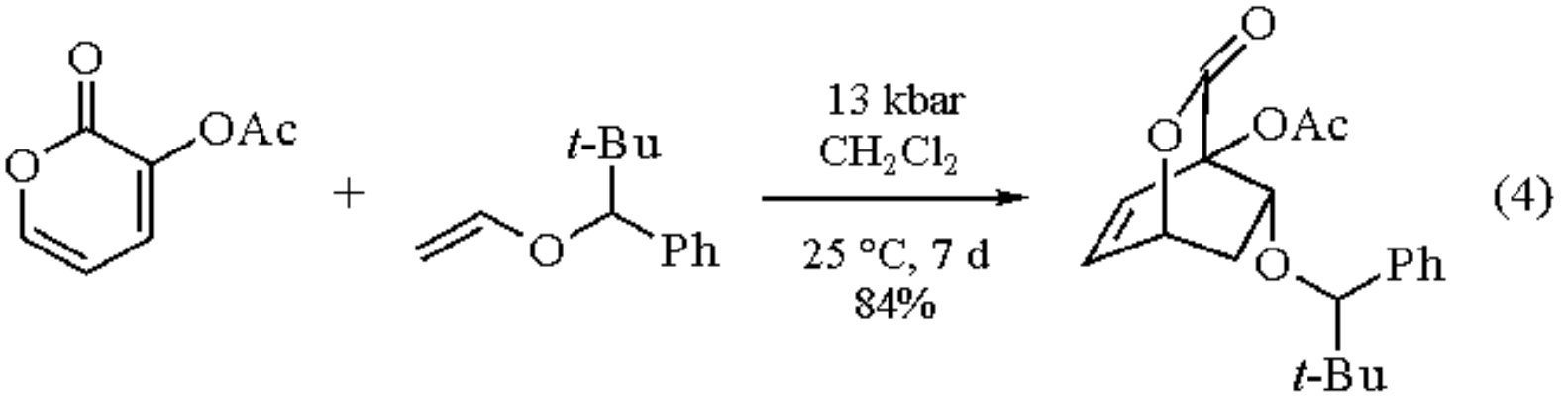

(4)

73:27 mixture of diasteromers

Both thermal and high-pressure Diels-Alder dimerizations of 3-acetoxy-2-pyrone lead to a normal *endo* dimer (**4a**), which reverts to the monomer upon heating at the melting point. Photodimerization, on the other hand, leads to regioisomeric *exo* dimers, (**5**) and (**6**). The parent hydroxypyrone appears to polymerize under thermal or high-pressure conditions, but does yield a single photodimer (**4b**).[13] At very high temperatures, substituted 2-pyrones are known to undergo rearrangements through reversible ring opening to vinylketene aldehydes, which undergo a [1,5]-sigmatropic hydrogen shift before reclosing to the isomeric pyrone form.[14] These rearrangements normally are observed at temperatures exceeding 350 °C, and so should not lead to rearrangement adducts under typical thermal Diels-Alder reaction conditions.

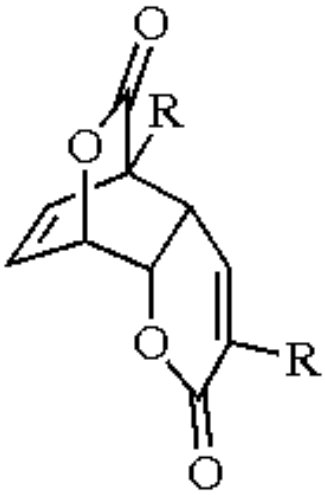

(4a) R = OAc
(4b) R = OH

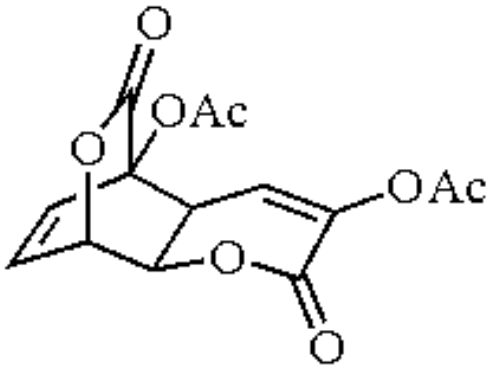

(5)

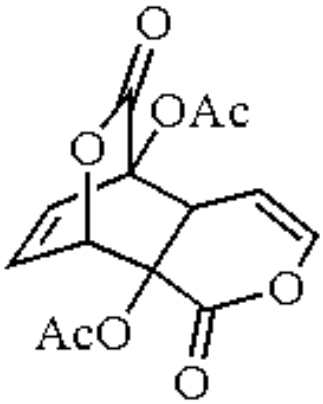

(6)

A series of reagents based upon the sulfur analog 3-mercapto-2-pyrone have been introduced[2] and are excellent alternatives to 3-hydroxy-2-pyrone. 3-*p*-Tolylthio-2-pyrone acts as a classical Diels-Alder diene; lactone adducts from reaction with acrylates, acrylonitrile, and methacrylates form in 42-70% yields at temperatures <=90 °C.[2] Inverse electron demand thermal Diels-Alder reactions of 3-*p*-tolylsulfinyl-[15] and 3-*p*-tolylsulfonyl-2-pyrone[16] with vinyl ethers or vinyl thioethers are highly efficient; cycloaddition proceeds at sufficiently mild temperatures so that decarboxylation of the lactone does not compete. These pyrones have been used in formal total syntheses of chorismic acid,[15,16] vitamin D_3 analogs,[17] and shikimates.[18] For example, 3-*p*-tolylsulfonyl-2-pyrone[19] undergoes highly diastereoselective, Lewis acid promoted,[20,21] inverse electron demand [4 + 2] cycloaddition with (*S*)-2-methyl-1-phenylpropyl vinyl ether to provide a sulfonyl lactone (eq 5),[22] which can be used to prepare (-)-methyl triacetyl-4-epishikimate.[18] Diastereoselectivity is considerably enhanced compared to cycloadditions using 3-acetoxy-2-pyrone[12] (e.g. eq 4).

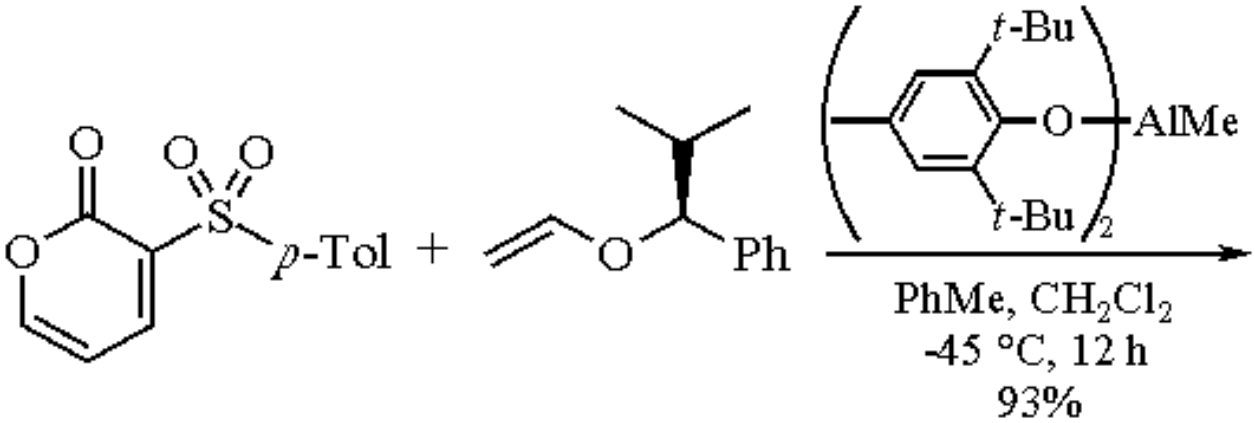

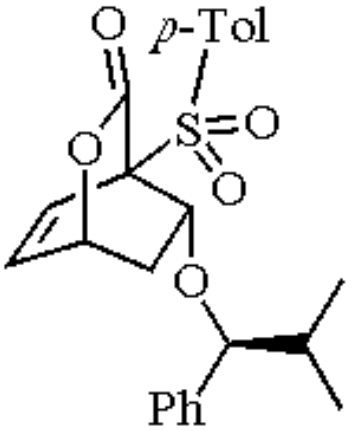

(5)

49:1 mixture of diastereomers

Related Reagents.

2-Pyridone; ***2-Pyrone***.

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N-Hydroxysuccinimide

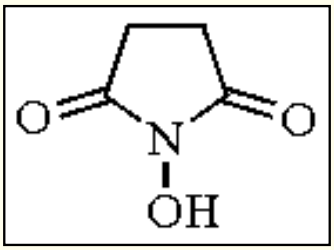

[6066-32-6] · $C_4H_5NO_3$ · *N*-Hydroxysuccinimide · (MW 115.10)

(activating agent for carboxylic acids in amide synthesis and related coupling reactions; acyl transfer reagent)

Alternate Name: HOSu.

Physical Data: mp 96-98 °C (99-100 °C).

Solubility: sol H_2O, DMF, alcohols, EtOAc; insol cold ether.

Form Supplied in: colorless crystalline solid, widely available.

Preparative Methods: by heating ***Succinic Anhydride*** with ***Hydroxylamine*** or, better, hydroxylamine hydrochloride followed by crystallizations from ether, 1-butanol, and finally EtOAc.[1]

Purification: can be crystallized from 1-butanol, EtOAc, or EtOH-EtOAc.

Peptide Bond Formation.

The most important use of *N*-hydroxysuccinimide is in the formation of (isolable) activated derivatives of N^{α}-protected α-amino acids, which subsequently undergo generally smooth coupling reactions with amino esters. Typically, ***1,3-Dicyclohexylcarbodiimide*** (DCC) is used as the initial coupling agent (the HOSu-DCC method) (eq 1).[1-3] *N*-Hydroxyphthalimide can be employed in much the same way, but a distinct advantage in the case of HOSu is its high water solubility, which facilitates product purification.

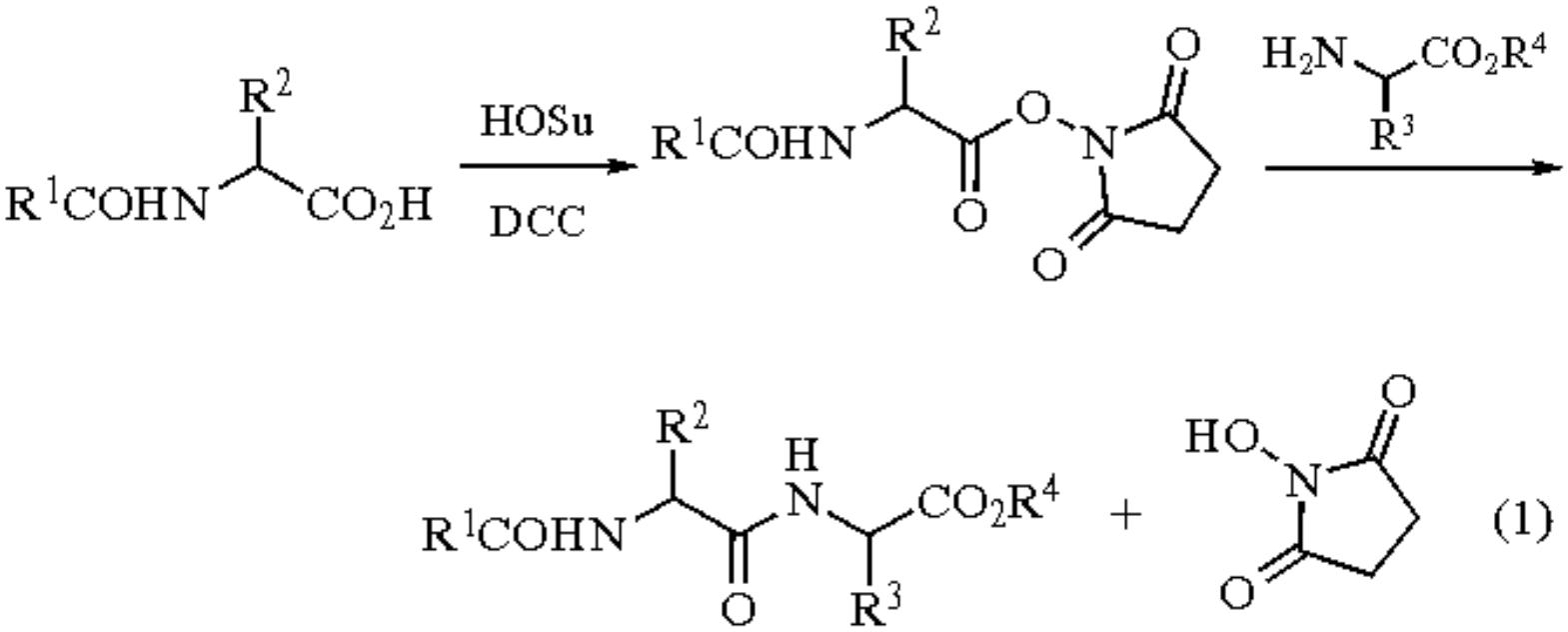

In some cases, up to 3% racemization has been observed when using the HOSu-DCC method, which renders it unsuitable for some types of peptide synthesis.[4,5] Esters derived from HOSu are relatively reactive, as shown by a kinetic study of their rates of hydrolysis in aqueous buffers[6] although, in some examples, *endo-N*-hydroxy-5-norbornene-2,3-dicarboximide has proven superior to HOSu in peptide bond formation.[7] Of course, the HOSu-DCC method is not limited to peptide synthesis and is well suited to the preparation of amides in general, both from ammonia and primary amines (e.g. eq 2).[8]

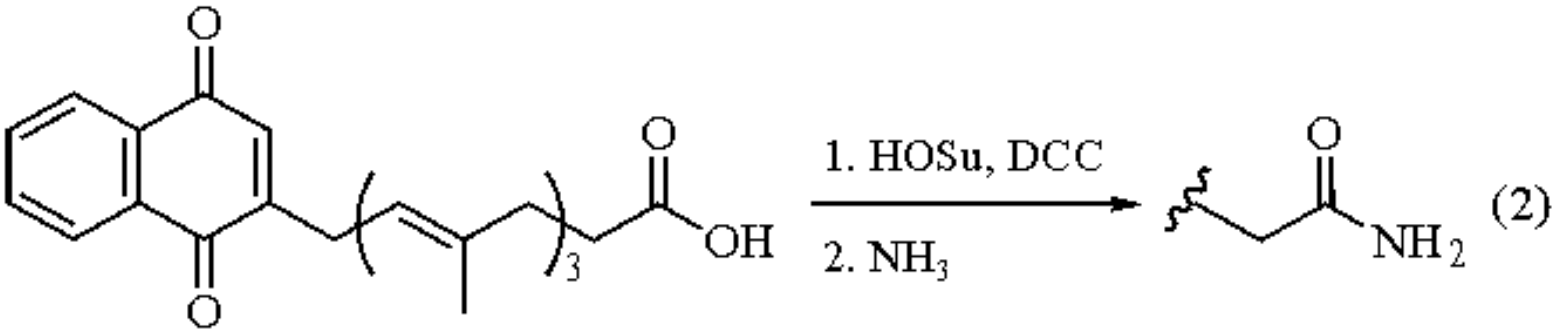

In order to avoid the need for DCC, a number of activated derivatives of *N*-hydroxysuccinimide itself have been developed which react directly with, for example, an α-amino acid to provide the required activated α-amino acid esters. These include the commercially available carbonate (**1**), a stable crystalline solid obtained from HOSu and ***Trichloromethyl Chloroformate*** or from *O*-trimethylsilyloxysuccinimide and ***Phosgene***,[9] and the related phosphate (**2**) derived from HOSu and ***Diphenyl Phosphorochloridate*** under Schotten-Baumann conditions.[10] Another alternative (also commercially available) is the oxalate (**3**), formed from HOSu and ***Oxalyl Chloride***.[11] In general, these intermediates react rapidly with an N^{α}-protected α-amino acid, usually in the presence of a mild base such as pyridine, to provide excellent yields of the required hydroxysuccinimide esters, generally with less racemization than is sometimes associated with the HOSu-DCC method. It is also possible to carry out the entire process of peptide synthesis in one pot using these reagents.

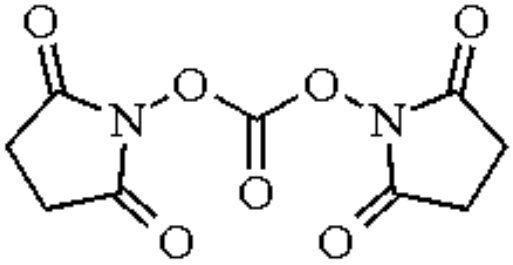

(1)

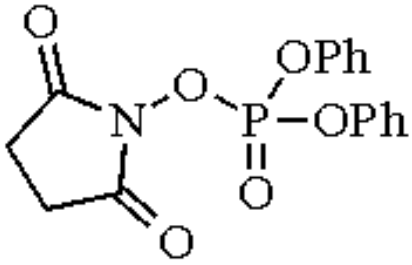

(2)

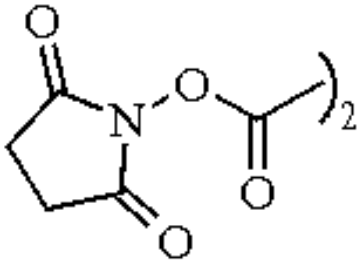

(3)

A rather different approach to peptide bond formation and amide synthesis in general is to treat a mixture of a carboxylic acid and an amine with an isocyanide (***2-Morpholinoethyl Isocyanide*** is especially suitable), which effectively acts as a dehydrating agent (eq 3). The procedure can result in extensive racemization of both reactants and products which may be supressed by the addition of HOSu; presumably an HOSu ester is the penultimate intermediate.[12] The addition of HOSu also decreases racemization in polypeptide synthesis when Bates reagent $\{[(Me_2N)_3P^+]_2O\ (BF_4^-)_2\}$ is used as the coupling agent.[13]

$$R^1CO_2H + H_2NR^2 + R^3NC \longrightarrow R^1CONHR^2 + R^3NHCHO \qquad (3)$$

A rather unusual coupling reaction between HOSu and glyoxylic acid tosylhydrazone leads to succinimidyl diazoacetate (eq 4); again, the leaving ability of the HOSu residue renders this a useful compound for effecting the direct transfer of a diazoacetyl function to amines, phenols, and peptides.[14]

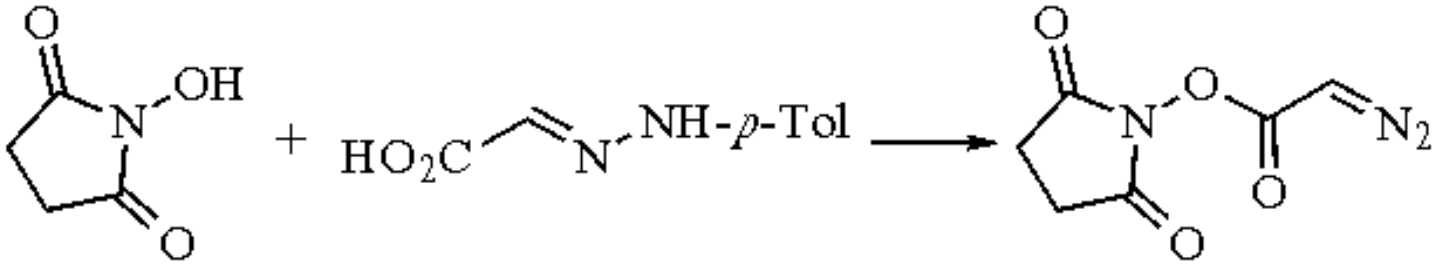

(4)

Modified Barton-McCombie intermediates are best prepared from pentafluorophenyl chlorothionoformate and a catalytic quantity (15-20%) of HOSu in refluxing benzene rather than by using ***4-Dimethylaminopyridine***, the rather more conventional catalyst of acyl group transfer (eq 5).[15]

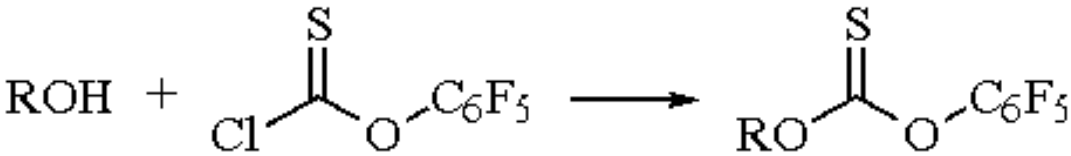

(5)

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[Hydroxy(tosyloxy)iodo]benzene[1]

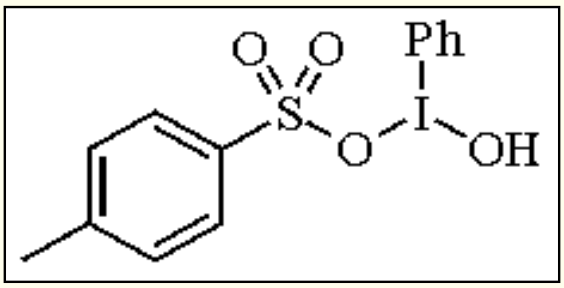

[27126-76-7] · $C_{13}H_{13}IO_4S$ · [Hydroxy(tosyloxy)iodo]benzene · (MW 392.22)

(reagent for the phenyliodination and oxytosylation of various functional groups;[4] excellent Hofmann reagent;[16] useful for bis-lactonizations,[7] oxidations and oxidative transformations[20])

Alternate Names: HTIB; Koser's reagent; phenyliodine(III) (hydroxyl)tosylate.

Physical Data: nearly colorless crystalline solid (pale `yellow' cast); mp 140-142 °C,[2] 136-138.5 °C.[3]

Solubility: insol Et_2O; largely insol CH_2Cl_2, $CHCl_3$, MeCN (rt); moderately sol H_2O; sol MeCN (reflux), MeOH, DMSO.

Form Supplied in: white solid; commercially available in 96% purity.

Preparative Methods: conveniently prepared by the treatment of ***(Diacetoxyiodo)benzene***/MeCN mixtures with warm solutions of ***p-Toluenesulfonic Acid*** in MeCN. When the acid is introduced, $PhI(OAc)_2$ dissolves to give deep yellow solutions from which HTIB readily separates. If the reaction mixtures are kept near the reflux temperature, the crystallization of HTIB from the solvent can be controlled. At lower temperatures, HTIB separates more rapidly but can, if necessary, be recrystallized by heating the final mixtures of dissolution or from fresh MeCN. Preparations of HTIB can be readily conducted on a 50-100 g scale.

Handling, Storage, and Precautions: a fairly stable compound which may be stored at rt; for extended storage, keep refrigerated in a dark bottle.

General Considerations.

Although hydroxy(tosyloxy)iodobenzene is largely insoluble in CH_2Cl_2, $CHCl_3$, and MeCN at rt, all are excellent solvents for the mediation of HTIB reactions. When HTIB is employed in CH_2Cl_2, the completion of a reaction is

signaled by the disappearance of the crystalline phase as the iodane is consumed. Since HTIB/MeCN mixtures afford deep yellow solutions at the reflux temperature, reactions conducted under these conditions can sometimes be followed by the fading of the color. HTIB is soluble in MeOH and in this solvent may lead to products containing one or more methoxy groups. DMSO should probably be avoided since HTIB may be reduced by this solvent under some conditions. Acetone reacts with HTIB.

HTIB is mildly electrophilic at iodine and may conveniently be regarded as the chemical equivalent of hydroxy(phenyl)iodonium tosylate[Ph+IOH $^-$OTs]. Thus HTIB reacts with a variety of organic substrates to give either phenyliodonium tosylates or tosylate esters. Phenyliodination occurs first and whether such reactions proceed to the oxytosylation stage depends on the stability of the iodonium compounds toward nucleophilic collapse. HTIB is also a mild oxidizing agent.

Selected Transformations of Organic Functional Groups.

Alkenes, Dienes.

The treatment of alkenes with HTIB (CH_2Cl_2) affords *vic*-ditosyloxyalkanes.[4] Dioxytosylation is thought to be initiated by the *trans* addition of HTIB to the carbon-carbon double bond, and, with alkyl-substituted alkenes, ultimately proceeds with *cis* stereospecificity (eq 1). In some cases (i.e. norbornene, neat styrene), dioxytosylation is accompanied by skeletal rearrangements. Several dienes have been observed to undergo conjugate dioxytosylation with HTIB but the 1,4-ditosyloxyalkenes are not very stable, and the yields are low.[4,5]

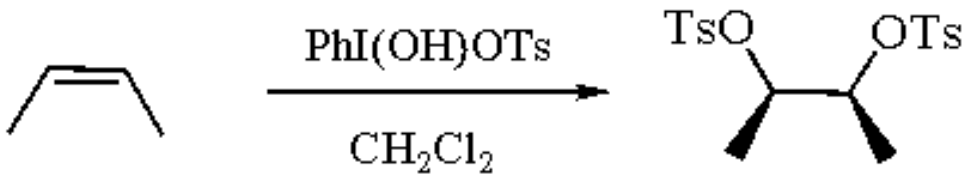

(1)

Alkenoic and Alkenedioic Acids.

Participation of the carboxyl group occurs when unconjugated alkenoic acids are mixed with HTIB.[6] Of seven alkenoic acids studied, five gave tosyloxylactones (eq 2). In two cases, TsOH was eliminated, and unsaturated lactones[6] were obtained, elimination apparently being favored by alkyl substitution at the carbon-carbon double bond. The oxytosyllactonization of 5-norbornene-*endo*-2-carboxylic acid proceeds with skeletal rearrangement. Alkenic dicarboxylic acids react with HTIB (CH_2Cl_2, rt) to give bis-lactones (eq 3).[7] More significantly, bis-lactonization proceeds with *cis* stereospecificity. The mildness and operational convenience of the HTIB procedure recommend this approach as an excellent alternative to methods requiring the treatment of alkenedioic acids or their tetrabutylammonium salts with an excess of ***Lead(IV) Acetate***[8] or the treatment of silver alkenedioates with ***Iodine/Silver(I) Acetate*** .[9]

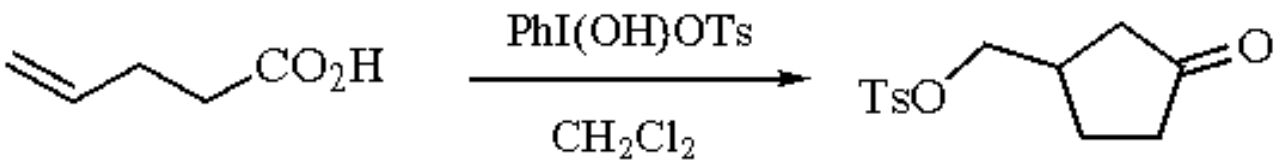

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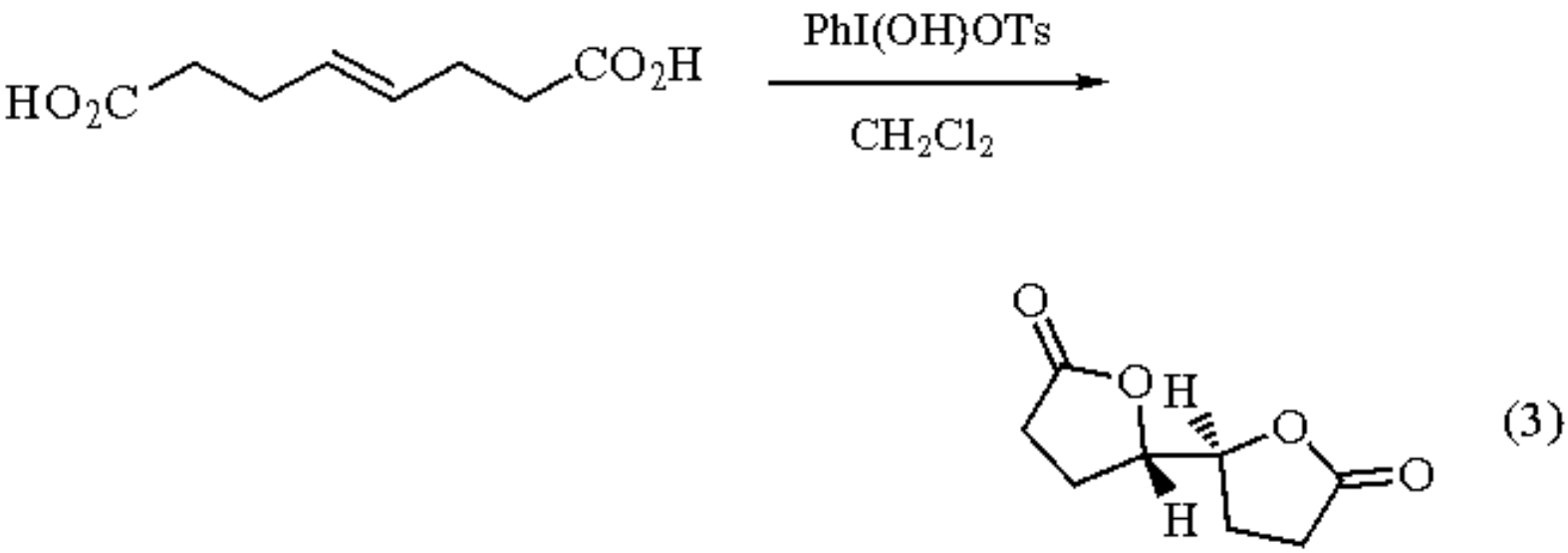

Alkynes.

Terminal alkynes react with HTIB in $CHCl_3$ under reflux to give either alkynyl(phenyl)iodonium tosylates, β-tosyloxyvinyl(phenyl)iodonium tosylates, or mixtures of both.[10] The production of alkynyliodonium salts is favored by the presence of either aryl or bulky alkyl (e.g. *t*-Bu, *s*-Bu) groups in the alkyne (eq 4), while terminal alkynes with linear alkyl groups lead exclusively to the vinyliodonium compounds (eq 5). A desiccant (silica bead) has been employed with HTIB in CH_2Cl_2 (rt) to facilitate the alkynyliodonium pathway with propyne and 1-hexyne, but the product yields were low.[11] Internal alkynes afford β-tosyloxyvinyliodonium tosylates with HTIB.[10] When HTIB is employed in methanol, both terminal and internal alkynes undergo oxidative rearrangement to give carboxylate esters, $R^1R^2CHCO_2Me$.[12]

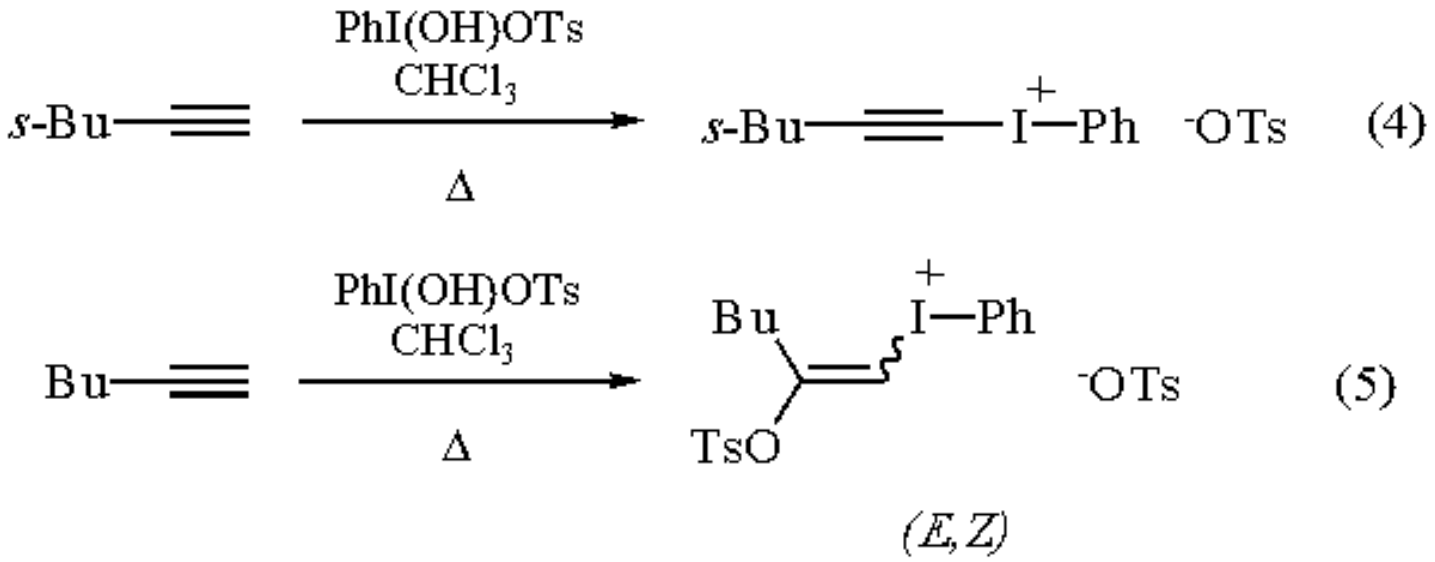

Ketones, β-Dicarbonyl Compounds, Silyl Enol Ethers, Silyl Ketene Acetals.

The treatment of ketones with HTIB (MeCN or CH_2Cl_2) affords α-toxyloxy ketones (eq 6),[13] presumably via α-phenyliodonio ketone tosylates [RCOC+IPh,$^-$OTs]. Silyl enol ethers (CH_2Cl_2, rt) also afford α-tosyloxy ketones with HTIB and can be employed to direct the regiochemistry of oxytosylation, while esters can be functionalized at α-carbon via their silyl ketene acetals (eq 7).[14] The conversion of β-dicarbonyl compounds to their α-toxyloxy derivatives with HTIB has also been demonstrated.[13] The reactions of 5-oxo- and 4,6-dioxocarboxylic acids with HTIB (CH_2Cl_2) eventuate in the production of keto and diketo lactones (eq 8).[15]

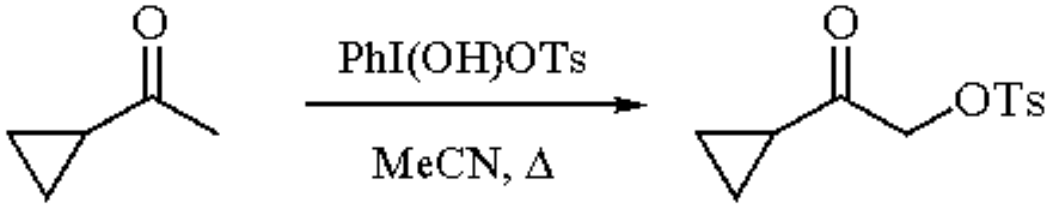

(6)

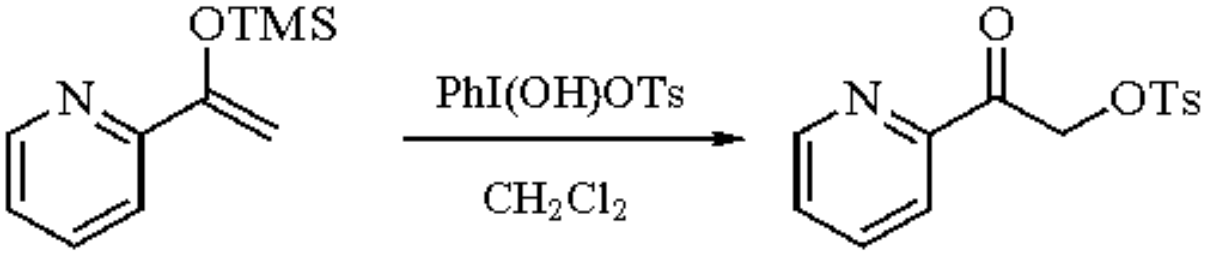

(7)

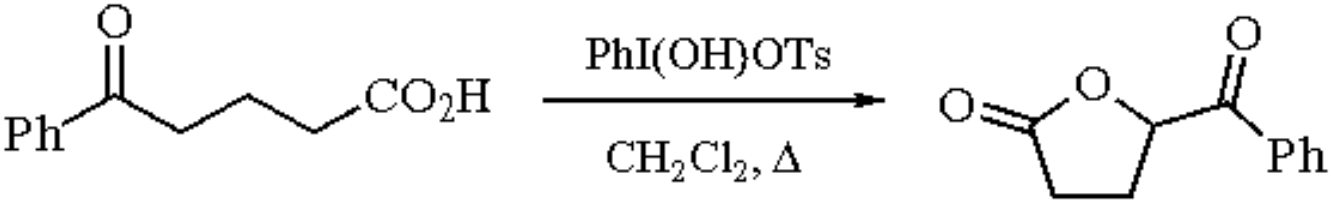

(8)

Carboxamides.

One of the most useful applications of HTIB is for the conversion of aliphatic primary carboxamides to amines (MeCN, reflux); the amines separate from the solvent (on cooling) as their hydrogen tosylate salts (eq 9).[16] This is a particularly advantageous method for the production of amines from long-chain amides,[17] which afford low yields (or none) of amines under the standard conditions (e.g. NaOH/Br_2, Δ) for the Hofmann reaction. The synthesis of bridgehead amines from carboxamides in the adamantane, cubane, and homocubane series of compounds has also been described.[18] Such reactions proceed via intermediate *N*-phenyliodoniocarboxamide tosylates [RCONH+IPh$^-$OTs] and their rearrangement with loss of TsOH and iodobenzene to alkyl isocyanates.[19] This is not a good method for the preparation of aromatic amines since they can be oxidized by HTIB as they are produced.

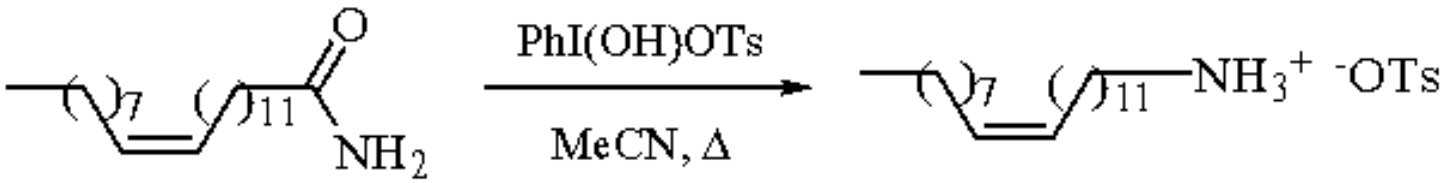

(9)

Further Applications of HTIB.

The synthetic utility of HTIB is further underlined by its use for the oxidation of allenes and allenyl ethers (CH_2Cl_2) to aldehydes or ketones,[20] the ligand-transfer oxidation of iodoarenes to give [hydroxy(tosyloxy)iodo]arenes (CH_2Cl_2),[21] the oxidative deiodination of alkyl iodides to alkyl tosylates ($CHCl_3$ or CH_2Cl_2),[22] including cubyl and homocubyl examples,[23] and as an iodination `catalyst' for the conversion of alkynols to α- and/or β-iodoenones.[24] Various [hydroxy(toxyloxy)iodo]arenes, ArI(OH)OTs, have been employed for the synthesis of diaryliodonium, aryl(2-furyl)iodonium, and aryl(2-thienyl)iodonium tosylates.[25] HTIB has also been used for the conversions of flavanones to flavones (MeOH)[26] and isoflavones (MeCN),[27] aromatic ketones to methyl arylalkanoates (MeOH or $(MeO)_3CH$),[28] chalcones to deoxybenzoins containing the $(MeO)_2CH$ group at the α-carbon (MeOH),[29] and flavonols to their *vic*-dimethoxy adducts (MeOH).[30]

Analogs of HTIB.

Various derivatives of HTIB with substituents in the iodoarene nucleus, ArI(OH)OTs,[21,25,31,32] and three arenesulfonyloxy analogs[33] have been reported. [Hydroxy(mesyloxy)iodo]benzene, $PhI(OH)O_3SMe$,[11,14,23,34,35] and [hydroxy((+)-10-camphorsulfonyloxy)iodo]benzene[36] are also known. [Hydroxy((bis(phenyloxy)phosphoryl)oxy)iodobenzene], $PhI(OH)OP(O)(OPh)_2$, shows considerable potential for phosphate ester synthesis. Thus far, the α-oxyphosphorylation of ketones and β-dicarbonyl compounds,[37] the oxyphosphoryllactonization of alkenoic acids,[37] and the conversion of terminal alkynes[38] to monoketol phosphates with HPIB have been reported.

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3-Hydroxy-3*H*-1,2,3-triazolo[4,5-*b*]pyridine

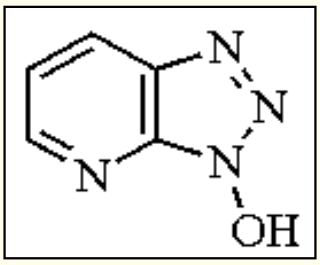

[39968-33-7] · $C_5H_4N_4O$ · 3-Hydroxy-3*H*-1,2,3-triazolo[4,5-*b*]pyridine · (MW 136.13)

(coupling additive for peptide synthesis[1-4])

Alternate Names: HOAt; 7-aza-1-hydroxybenzotriazole.

Physical Data: mp: sample decomposes at temperatures above 205 °C.

Solubility: sol DMF.

Form Supplied in: white solid; commercially available.

Purification: by crystallization from ethanol or water.

Handling, Storage, and Precautions: is very stable, not hygroscopic, and can be stored indefinitely. HOAt solutions in DMF (0.3 M) can be stored in an inert atmosphere for weeks. Syntheses of peptides carried out with freshly prepared and 4-week old solutions show similar quality for the crude product.[5] Violent decomposition may occur when dried at elevated temperatures.

General Considerations.

HOAt is the 7-aza derivative of ***1-Hydroxybenzotriazole*** (HOBt), the most common peptide coupling additive.[6,7] These reagents are employed to decrease racemization, inhibit side reactions such as formation of *N*-acylurea, and increase yield and purity during peptide assembly. These compounds are used in conjunction with carbodiimides or active esters such as the pentafluorophenyl ester or built into stand-alone reagents such as ***N-[(Dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium Hexafluorophosphate N-Oxide*** (HATU) and 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP). Although known for many years, HOAt[8-12] has only recently been applied as an additive in peptide synthesis. The greater effectiveness of HOAt relative to HOBt is shown by its use in the coupling of 2-phenylpropionic acid with the highly hindered secondary amine (**1**) (eq 1), a reaction difficult to achieve in the presence of HOBt.[1]

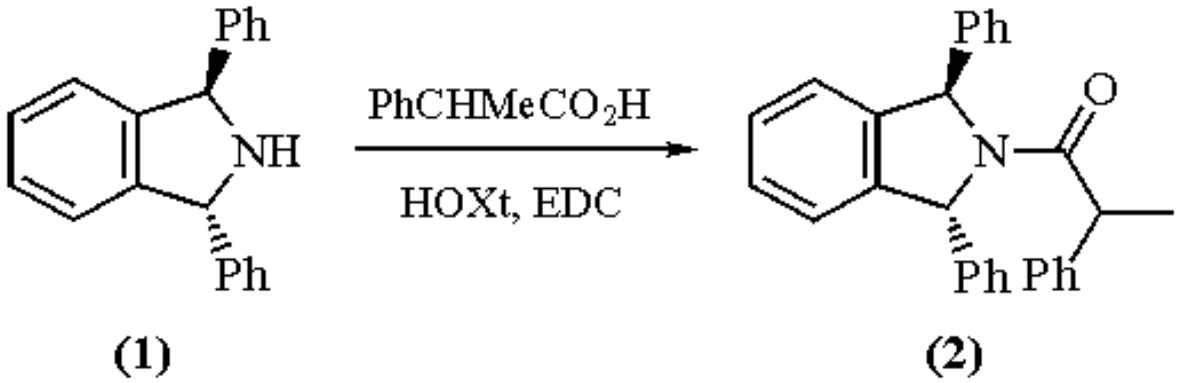

(1)

The extent of racemization during stepwise and segment condensation methods for the assembly of peptides in solution via ***1,3-Dicyclohexylcarbodiimide*** (DCC) or ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride*** (EDC) in the presence of HOAt and HOBt has been examined. When the amino acid ester is used as a salt, various bases such as ***Diisopropylethylamine*** (DIPEA), *N*-methylmorpholine (NMM), and ***1,8-Bis(dimethylamino)naphthalene*** (Proton Sponge, PS) were also needed (eq 2) (Table 1). In all examples, racemization was lowered when HOBt was replaced with HOAt (run 1 vs. 2, 3 vs. 4, 5 vs. 6, 8 vs. 9). The level of epimerization was further lowered when methylene chloride (DCM) was substituted for DMF as the solvent (runs 8 vs. 10).[1]

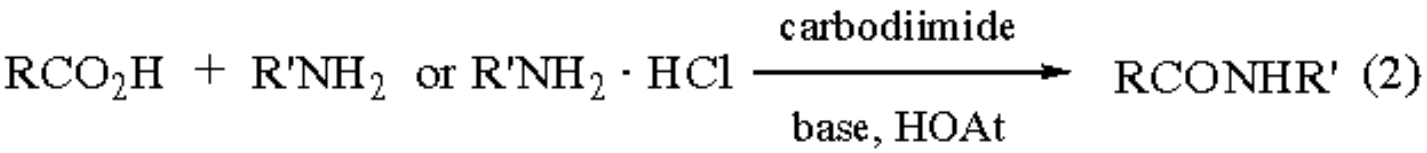

(2)

Table 1 Racemization during HOAt/HOBt-Mediated Carbodiimide Couplings in DMF Solution

Entry	RCOOH	R¢NH$_2$ or R¢NH$_2$·HCl	Conditions	DL-isomer (%)
1	Z Phg OH	H Val OMe·HCl	HOAt, EDC, PS (1 equiv) 9 h	<1 2
2	Z Phg OH	H Val OMe·HCl	HOBt, EDC, PS (1 equiv) 9 h	3.7
3	Z Phe Val OH	H Ala OMe·HCl	HOAt, EDC, NMM (1 equiv) 1.25 h	<1 2
4	Z Phe Val OH	H Ala OMe·HCl	HOBt, EDC, NMM (1 equiv) 2.25 h	4.1
5	Bn Val OH	H Val OMe·HCl	HOAt, EDC, NMM (1 equiv) 20 h	28.1
6	Bn Val OH	H Val OMe·HCl	HOBt, EDC, NMM (1 equiv) 20 h	45.4
7	Bn Val OH	H Val OMe	DCC, 24 h	61.5
8	Bn Val OH	H Val OMe	HOAt, DCC, 24 h	14.4
9	Bn Val OH	H Val OMe	HOBt, DCC, 24 h	41.9
10	Bn Val OH	H Val OMe	HOAt, DCC, DCM, 24 h	<1 2

HOAt has also been applied to automated stepwise solid-phase synthesis via the Fmoc/*t*-Bu strategy.[2,3,5] The effectiveness of HOAt-based reagents was demonstrated in the assembly of the acyl carrier protein fragment 65-74 (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Gln-Gly-NH$_2$). Coupling times and excesses of reagents (amino acid and activator) were reduced in order to exaggerate poor couplings. In *N*,*N*′-diisopropylcarbodiimide and pentafluorophenyl-mediated couplings, the superiority of HOAt over HOBt was clearly shown in terms of greatly enhanced purity. The extent of amino acid deletions depended on the exact conditions. Addition of HOXt in the case of guanidinium or phosphonium salt-based couplings did not significantly improve the coupling yield.

Solid-phase segment couplings were also aided by the use of HOAt. In a model study, Fmoc-Phe-Ser(*t*-Bu)-OH was coupled to H-Pro-PAL-PEG-PS-resin.[3,13] With HOAt in the presence of DCC, the extent of racemization was lowered

dramatically relative to HOBt. A more complex example involved synthesis of the *N*-terminal domain of γ-zein protein by eight repetitive couplings of the appropriate protected hexapeptide.[14]

N-Methyl amino acids are often very difficult to couple cleanly and in good yield, especially by solid-phase techniques. Excellent results were obtained for DIPCDI/HOAt-mediated couplings, leading to various cyclosporin (CsA) segments, including H-MeLeu-MeLeu-Ala-NH_2, H-Val-MeLeu-Ala-NH_2, and H-MeLeu-MeVal-Ala-NH_2, all of which were obtained in >99% yield.[15]

The HOAt-based uronium salt 1-(1-pyrrolidinyl-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate *N*-oxide (HAPyU) was employed in solution for the efficient cyclization of a linear hexapeptide constructed exclusively from L-amino acids. Such systems are difficult to cyclize without *C*-terminal racemization.[16]

Significant improvements in the synthesis of phosphonamidate peptides were achieved via the HOAt esters of the phosphonochloridates (eq 3).[17]

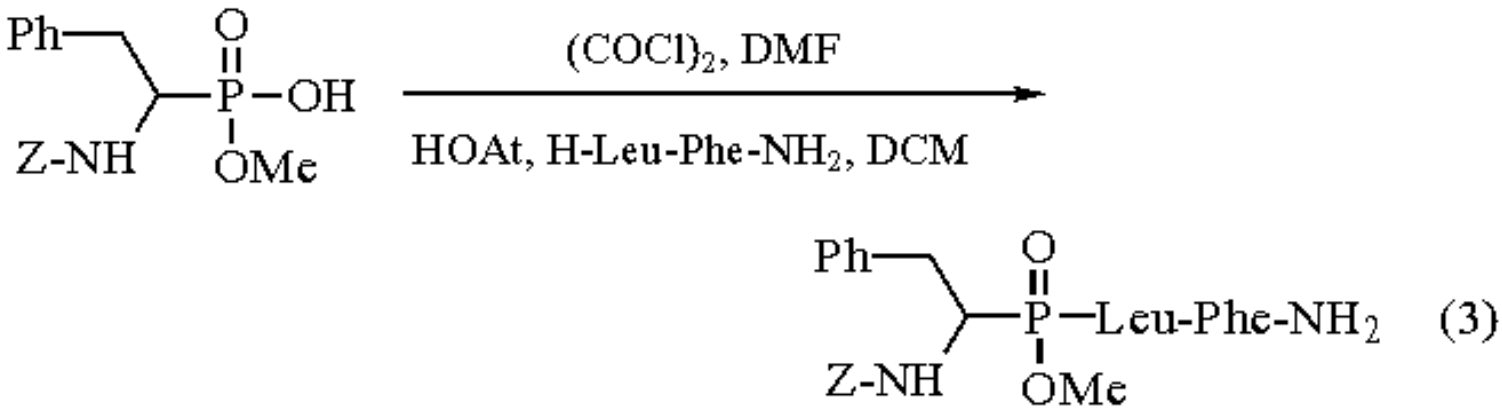

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2-Hydroxy-1,2,2-triphenylethyl Acetate[1]

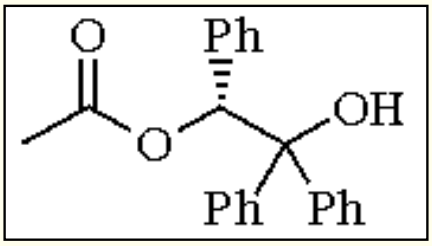

(*R*)

[95061-47-5] · $C_{22}H_{20}O_3$ · 2-Hydroxy-1,2,2-triphenylethyl Acetate · (MW 332.42) (*S*)

[95061-51-1]

(enantiopure acetate for stereoselective aldol addition of the dilithioenolate to aldehydes to give chiral nonracemic β-hydroxy acids)

Alternate Name: HYTRA.

Physical Data: mp 239 °C (toluene); (*R*) [α]20D (*c* = 1, pyridine) +215° to +217°; (*S*) [α]20D (*c* = 1, pyridine) -214° to -216°.

Solubility: sol pyridine, boiling toluene; slightly sol THF, chloroform, cold toluene.

Form Supplied in: white solid; both isomers are commercially available.

Stereoselective Aldol Reactions.

The (*R*)- and (*S*)-2-hydroxy-1,2,2-triphenylethyl acetates (HYTRA) offer a simple solution for a stereoselective aldol addition of α-unsubstituted enolates. When a suspension of HYTRA is treated in THF with 2 equiv of ***Lithium Diisopropylamide***, a clear solution of the enolate forms (eq 1). Subsequent dilution with 2-methylbutane followed by the addition of 2-methylpropanal affords predominantly the (*R*,*R*)-diastereomeric adduct. Alkaline hydrolysis not only delivers (*R*)-3-hydroxy-4-methylpentanoic acid in 86-94% ee but also liberates the optically pure auxiliary reagent (*R*)-1,2,2-triphenylethane-1,2-diol, which can be removed and reused (eq 1).[2,3]

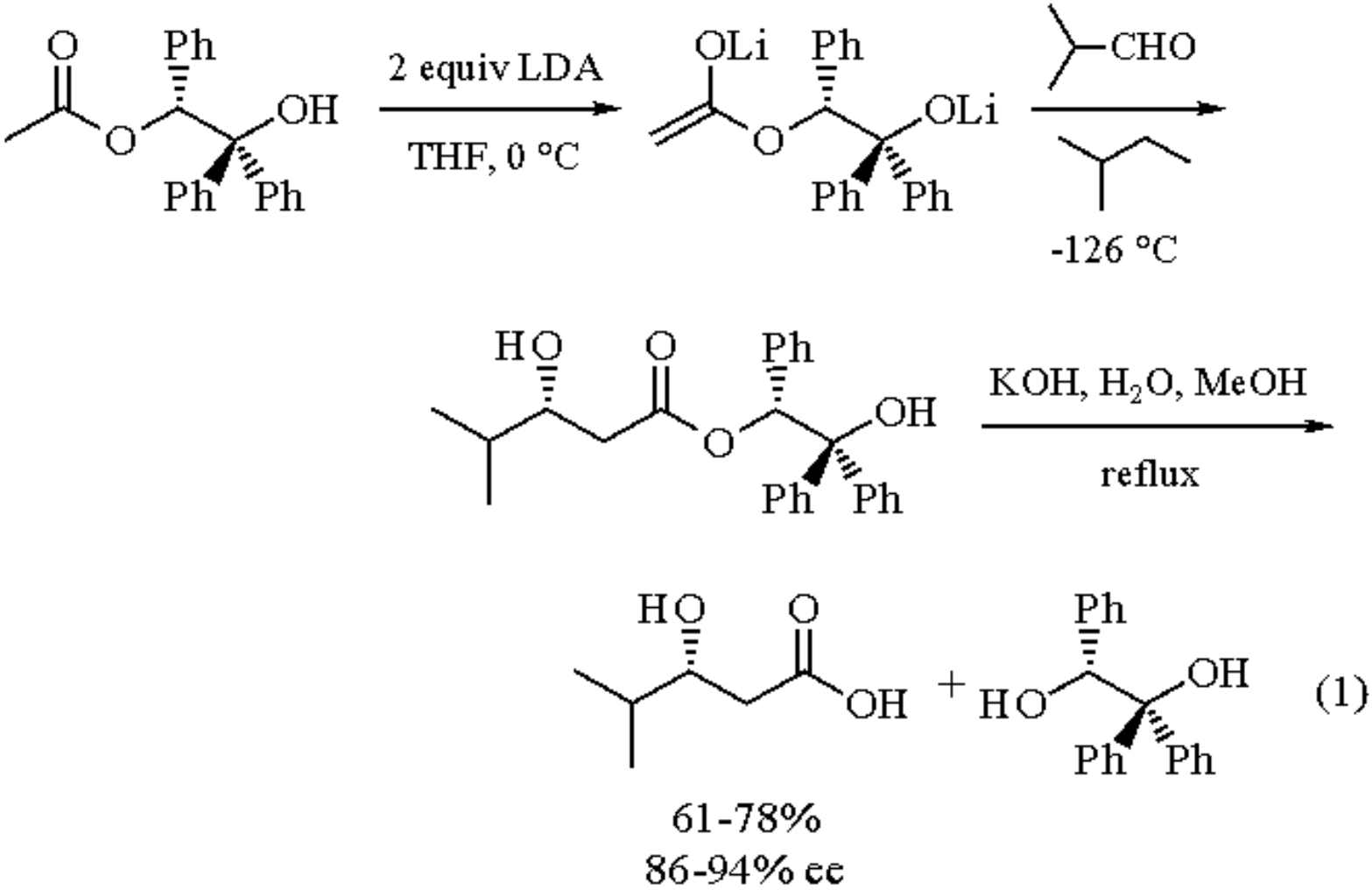

The diastereoselectivity has been enhanced by a transmetalation of the lithium enolate with ***Magnesium Bromide*** or ***Magnesium Iodide*** prior to the addition of benzaldehyde (eq 2).[3-5]

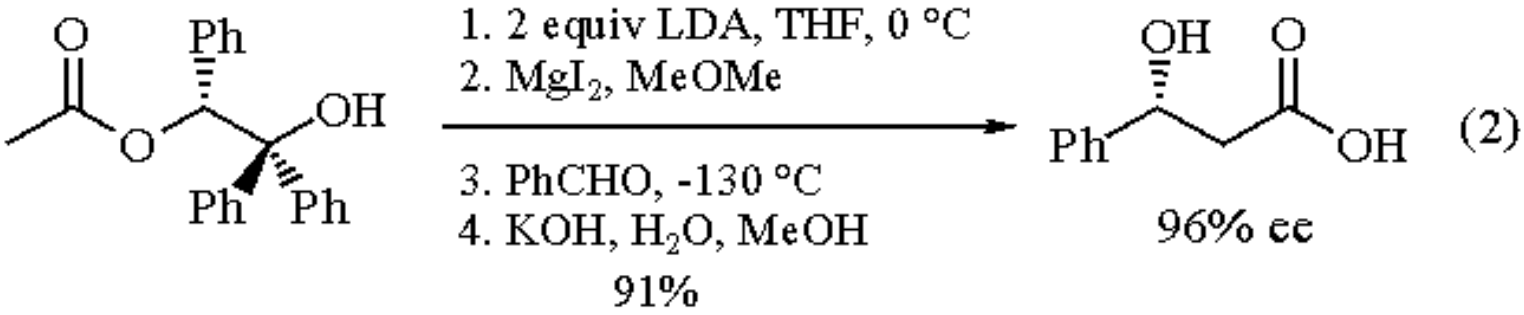

On the other hand, enantiomeric excesses up to 94% are reached even at -78 °C, provided that ***Lithium Hexamethyldisilazide*** (LHMDS) (3 equiv) is used for deprotonation instead of LDA (2 equiv) (eq 3).[6]

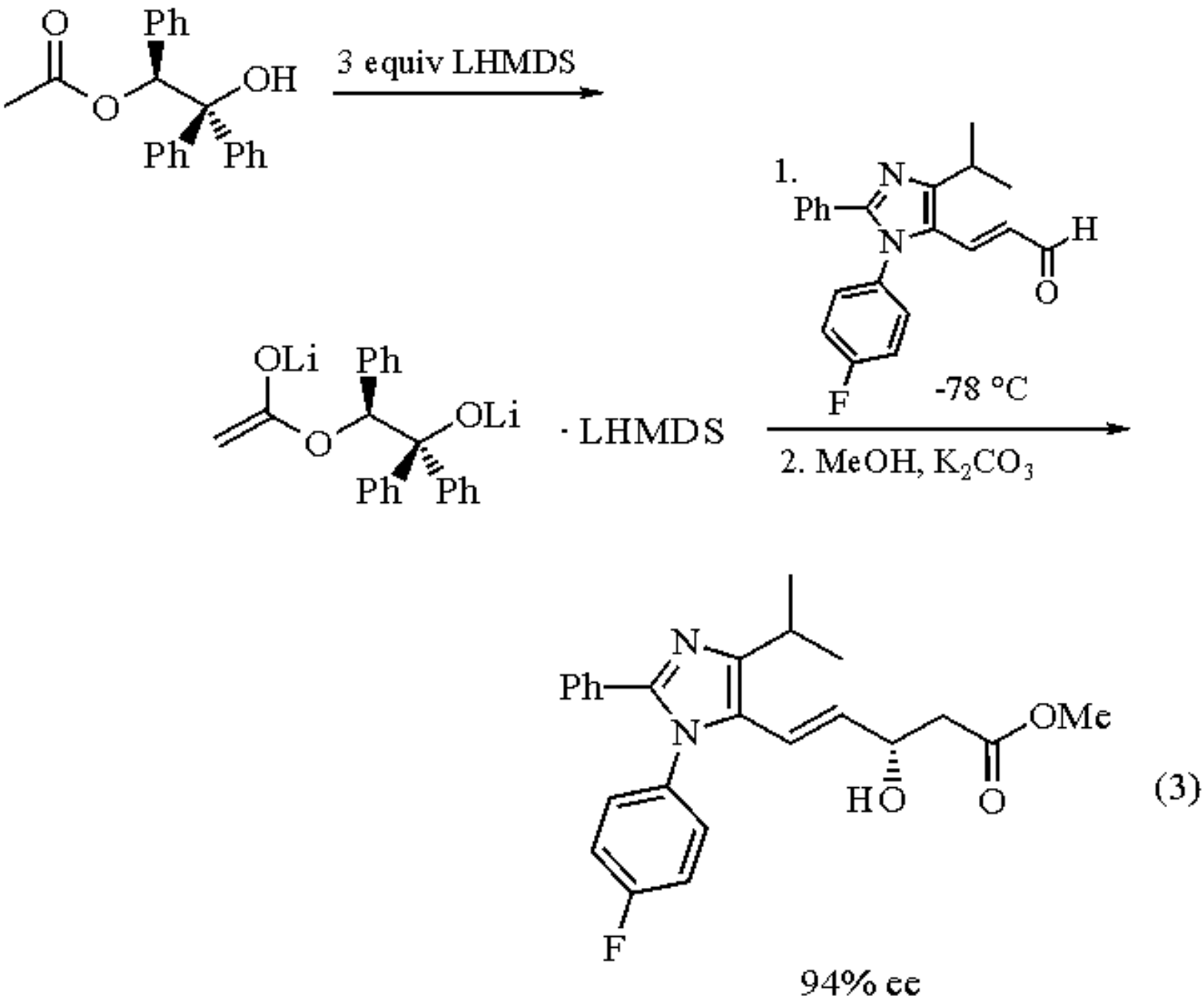

(3)

Predictable *lk*-topicity [i.e. (*R*)-enolate attacks predominantly the *re*-face of the carbonyl group whereas the (*S*)-reagent approaches predominantly from the *si*-face] has been observed in all additions of doubly deprotonated HYTRA to achiral as well as to enantiomerically pure aldehydes.[7,8] The aldol reaction of HYTRA has been used for the syntheses of natural products such as shikonin and alkannin,[9] D- and L-digitoxose (**1**),[10] FK506,[11] statin (**2**)[8] and analogs,[12] detoxinine (**3**)[13] and tetrahydrolipstatin (**4**).[14] Besides compactin and mevinolin (**5**),[15] a series of nonnatural HMG-CoA reductase inhibitors which serve as hypocholesterolemic agents have been synthesized by this method.[6,16] Peptide isosters,[17] deoxy- and aminodeoxyfuranosides,[18] 3-amino-2-hydroxybutanoic acid (GABOB) (**6**)[19] and intermediates for the preparation of antidepressants[20] are available as well.

(1) L-Digitoxose

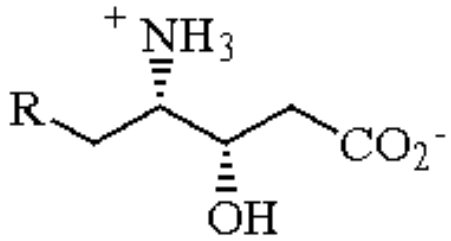

(2) R = $CHMe_2$: Statin
R = Ph, cyclohexyl: Statin analogs

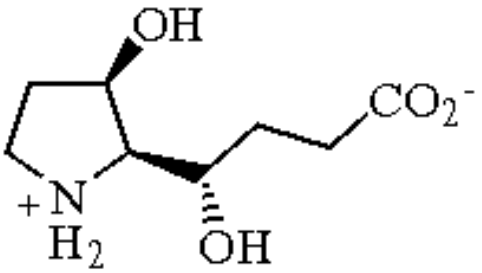

(3) Detoxinine

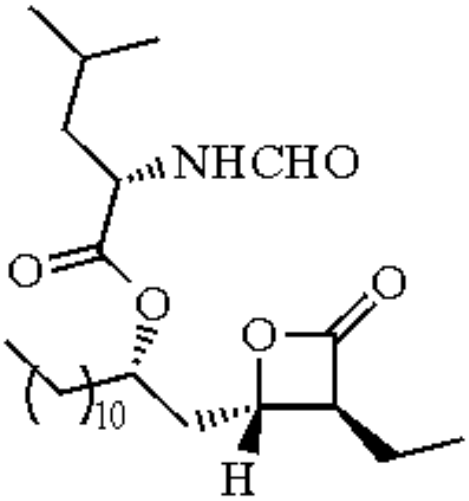

(4) Tetrahydrolipstatin

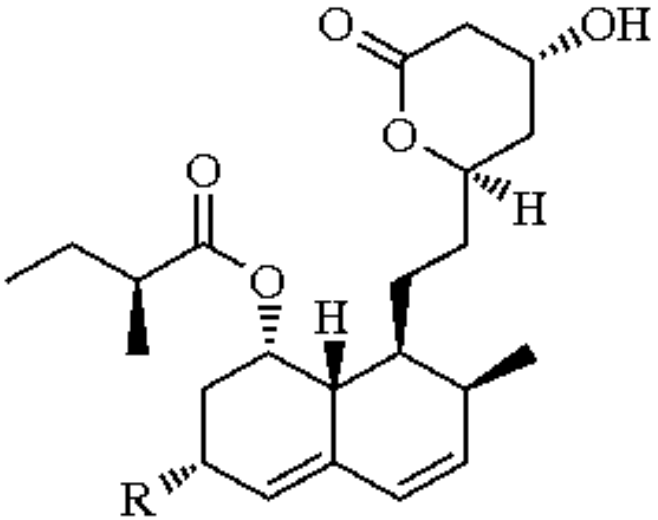

(5) R = H: Compactin
R = Me: Mevinolin

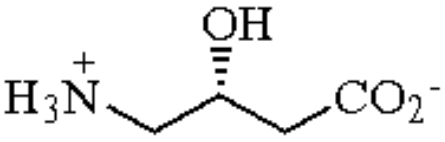

(6) *(R)*-GABOB

Related Reagents.

Boron Triiodide; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***(S)-4-Benzyl-2-oxazolidinone***; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***; ***trans-2,5-Bis(methoxymethyl)pyrrolidine***; ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***α-Methyltoluene-2,α-sultam***; ***1,1,2-Triphenyl-1,2-ethanediol***.

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Hypobromous Acid

HOBr

[13517-11-8] · BrHO · Hypobromous Acid · (MW 96.91)

(preparation of bromohydrins[5,8,12] by addition to alkenes; brominating reagent[3] and oxidant[4])

Solubility: sol H_2O, H_2O-DMSO, H_2O-acetone, H_2O-dioxane, H_2O-DME.

Form Supplied in: stable only in solution;[1,2] usually prepared in situ immediately before use.

Preparative Methods: traditional preparative methods[2-4] are the addition of ***Bromine*** to aqueous mixtures of mercury or silver salts to precipitate the bromide ion formed as a byproduct. Newer methods employ a source of positive bromine such as ***N-Bromosuccinimide***,[5-7] ***N-Bromoacetamide***,[8,9] or ***1,3-Dibromo-5,5-dimethylhydantoin*** (dibromantin)[10] to generate the equivalent to HOBr in aqueous solution.

Handling, Storage, and Precautions: strong oxidant; use in a fume hood.

Bromohydrin Synthesis.

The title reagent (**1**) usually adds to unhindered alkenes following Markovnikov's rule, in which the initial electrophilic adduct is a bromonium ion (eqs 1 and 2).[5,11] The resulting carbocation or bridged bromonium ion then reacts with hydroxide or water to yield the product bromohydrin.[8] Reactions are generally run in water or solutions of water and DMSO, acetone, or dioxane at 0-25 °C, although aqueous DME at -20 °C has also been employed (eqs 1 and 2).[7] Reactions run in moist DMSO generate bromohydrins in a regiospecific and stereospecific fashion with a minimum of rearrangement.[12] The role of the solvent in the reaction has been demonstrated by radiolabeling.[5]

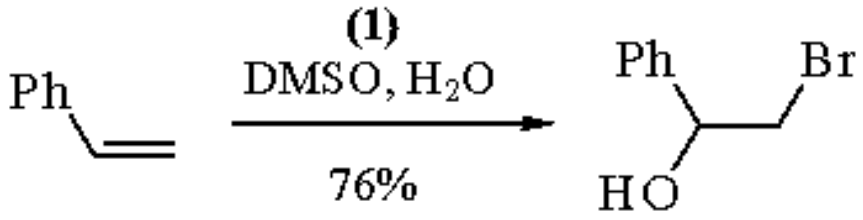

(1)

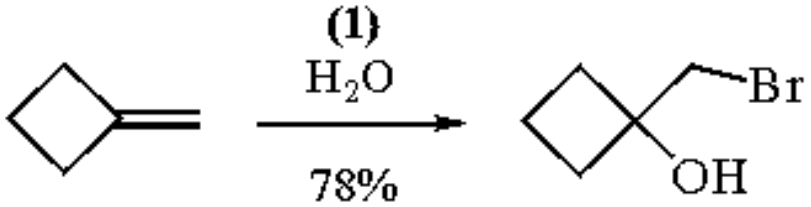

(2)

Participation by a neighboring functional group may influence the regioselectivity of HOBr addition.[6,7,9] Oxime-assisted bromonium ion reaction has been invoked in the formation of a bromohydrin intermediate to the neurotoxin (±)-perhydrohistrionicotoxin (eq 3).[7] Similarly, participation by the 7-acetoxy group results in a single bromohydrin product in the addition of HOBr to a cholestane derivative (eq 4).[9]

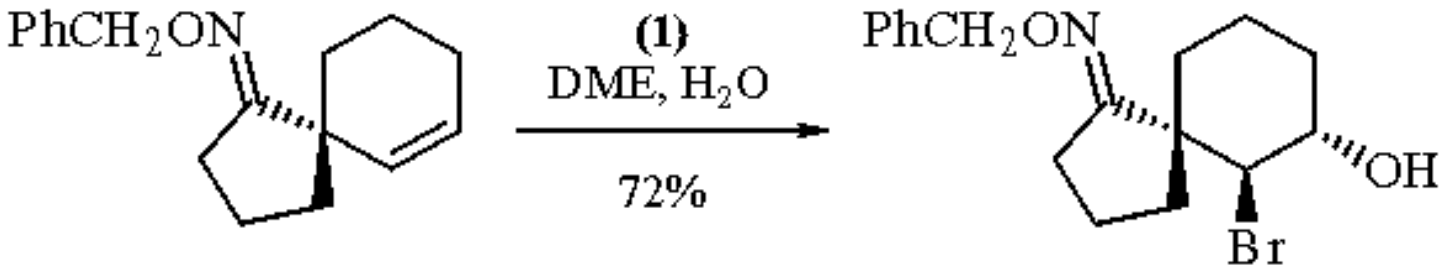

(3)

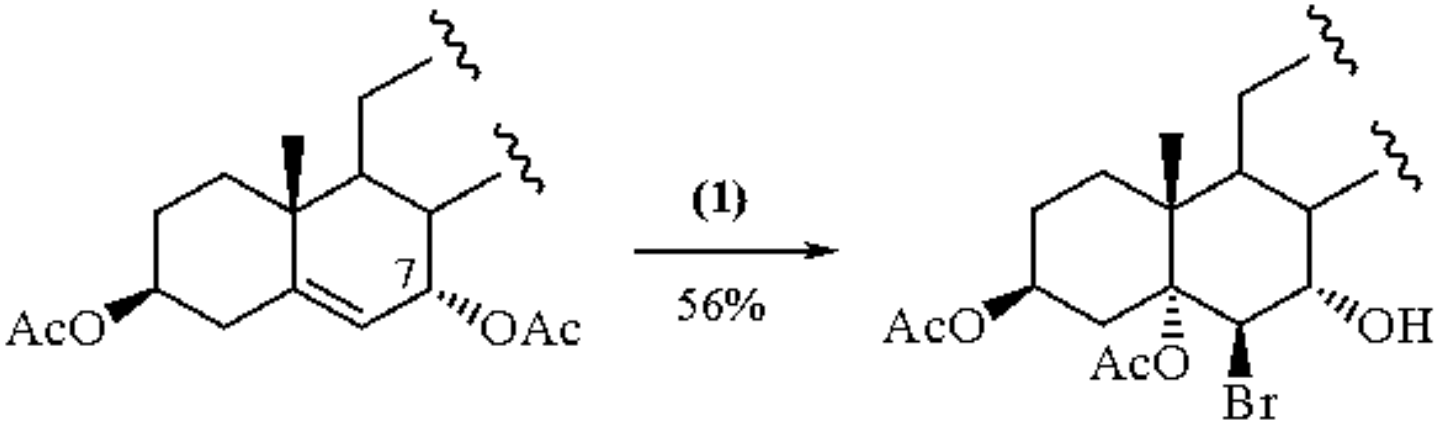

(4)

Oxidation and Bromination.

The title reagent has been employed in the oxidation of a thiazole thiourea to a thiazolo[3,2-*b*]thiadiazoline (eq 5).[4] Reaction of HOBr with a variety of aryl methyl ketones yields ring-brominated products in a rapid reaction at rt.[3]

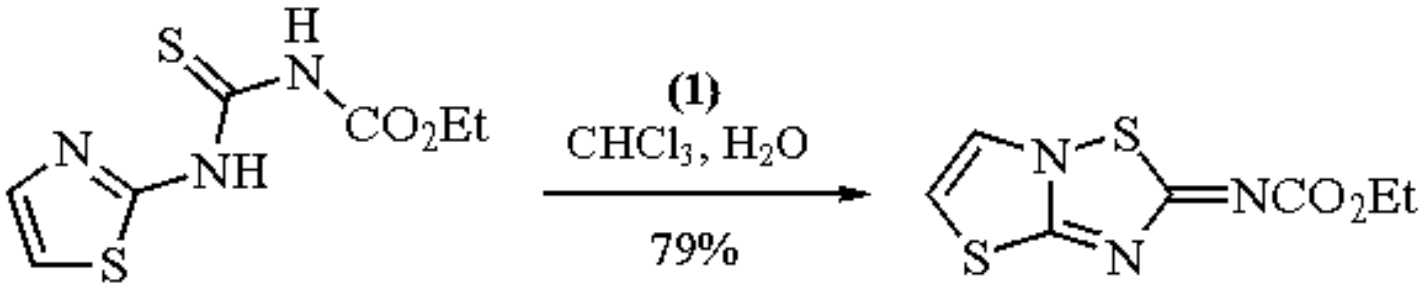

(5)

Related Reagents.

Hypochlorous Acid is utilized as an oxidant and for the preparation of chlorohydrins in a manner analogous to that of (**1**).

---

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Hypochlorous Acid

HOCl

[7790-9-3] · ClHO · Hypochlorous Acid · (MW 52.46)

(preparation of chlorohydrins[6-9] and allylic chlorides[5,11] by addition to alkenes; chlorinating reagent[4] and oxidant[12])

Solubility: sol H_2O, Et_2O, CH_2Cl_2.

Form Supplied in: stable only in solution;[1,2] usually prepared in situ immediately before use. Most preparations are in water, water-acetone, or water-dioxane solutions under acidic conditions at 0-25 °C. The reagent can also be extracted into ether or other organic solvents for use under nonaqueous reaction conditions.

Analysis of Reagent Purity: standardized by iodometric titration.

Preparative Methods: traditionally prepared[3] by addition of ***Chlorine*** to a cold aqueous solution of ***Sodium Hydroxide*** and ***Mercury(II) Chloride*** to generate NaOCl. Careful acidification then liberates HOCl. A more convenient procedure is the use of commercial bleach (stabilized 5.25% ***Sodium Hypochlorite*** solution)[4] or 70% ***Calcium Hypochlorite***.[5] Reagents such as ***Chloramine-T***,[6] ***N-Chlorosuccinimide***,[7] and chlorourea[8] serve as equivalents to HOCl by the production of a positive Cl species in aqueous solution.

Handling, Storage, and Precautions: strong oxidizing agent; use in a fume hood.

Chlorohydrin Synthesis.

The title reagent (**1**) usually adds to unhindered alkenes following Markovnikov's rule, in which the initial electrophilic adduct is a chloronium ion (eqs 1 and 2).[7,8] The resulting carbocation or bridged chloronium ion then reacts with hydroxide or water to yield the product chlorohydrin. In some instances, anti-Markovnikov and dichloride side products are also observed.[9] α,β-Unsaturated acids, esters, nitriles, aldehydes, and ketones with an unsubstituted α-hydrogen predominantly add Cl to the α-position and OH to the β-position.

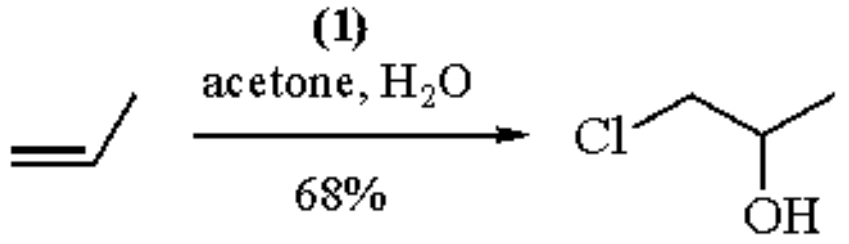

(1)

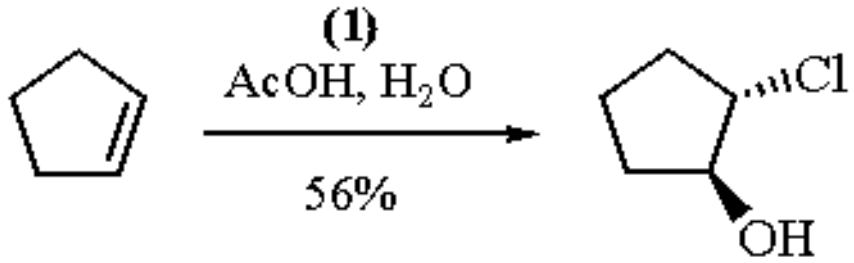

(2)

Allylic Chloride Synthesis.

Reaction of (**1**) with highly substituted alkenes[5] or conjugated ketones[10] in a two-phase reaction mixture yields allylic chlorides rather than chlorohydrins (eq 3). Other functional groups, such as alcohols, aldehydes, epoxides, ethers, esters, ketones, and nitriles, are generally unaffected. In some cases, a mixture of allylic chloride and vinyl chloride products is obtained. This reaction has been applied to (+)-carvone and (+)-limonene in a synthetic route to various monocyclic sesquiterpenes.[11]

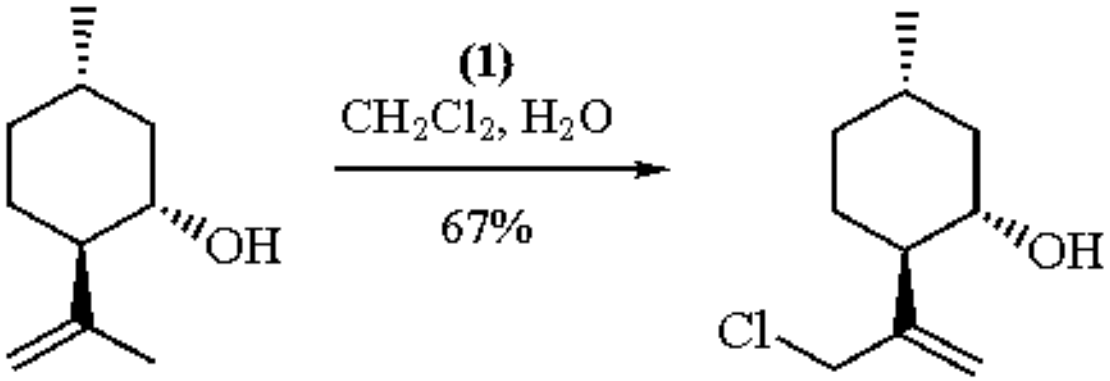

(3)

Oxidation and Chlorination.

The title reagent has been used to oxidize a cyclic acetal in the preparation of optically active α-amino acids (eq 4).[12]

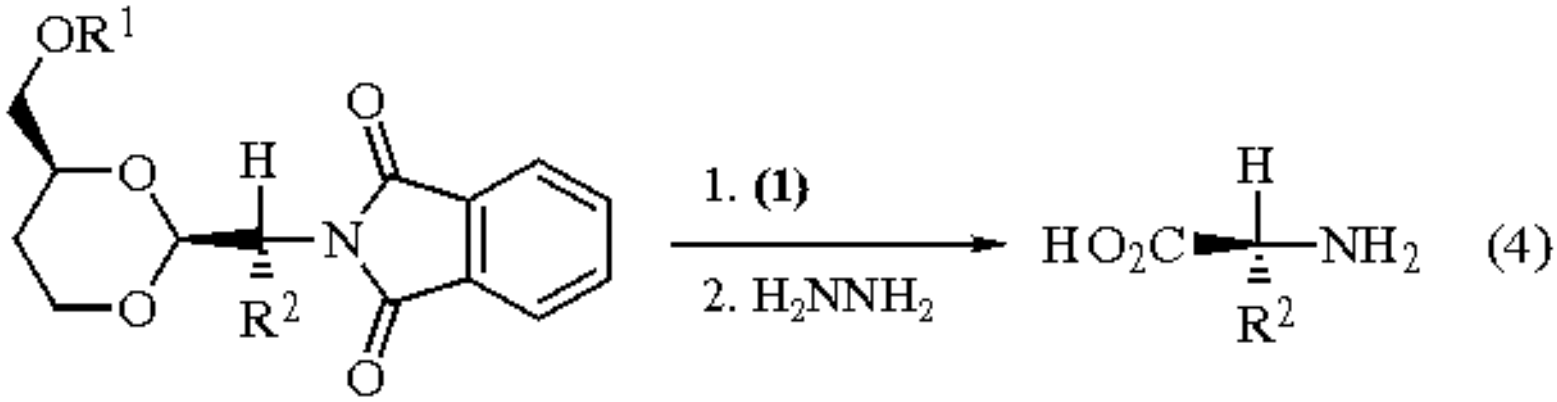

Oxidation by hypochlorite solutions is used industrially on a large scale for bleaching and sterilization applications.

Aqueous (**1**) at 25 °C rapidly transforms cyclic oximes into α-chloronitroso derivatives, which are intermediates in the preparation of secondary nitro compounds (eq 5).[4] Maintaining a pH of 5.5 in the chlorination medium was found to be critical in this reaction.

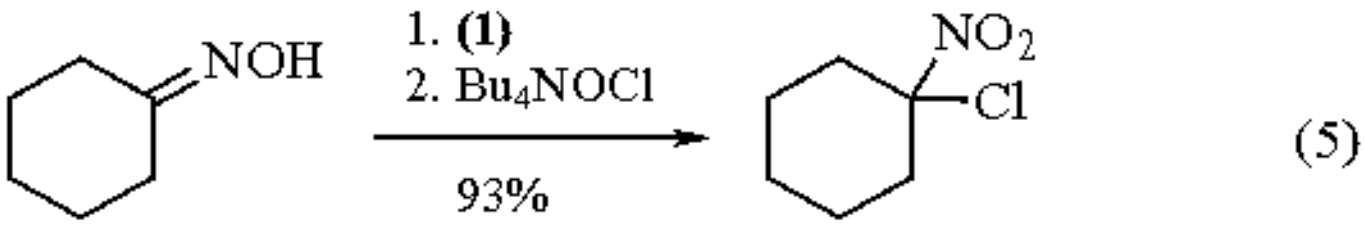

Related Reagents.

Hypobromous Acid is utilized as an oxidant for the preparation of bromohydrins in a manner analagous to that of (**1**). Direct chlorohydroxylation of alkenes can be achieved with ***t-Butyl Hydroperoxide*** or ***1,1-Di-t-butyl Peroxide*** and ***Titanium(IV) Chloride***,[13] as well as with ***Chlorotrimethylsilane*** and 30% ***Hydrogen Peroxide***.[14] Since these peroxide reactions probably proceed through an epoxide intermediate, the resulting chlorohydrin is the opposite regioisomer from that obtained by addition of (**1**).

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Hypofluorous Acid[1]

HOF

(HOF)

[14034-79-8] · FHO · Hypofluorous Acid · (MW 36.01) (HOF.MeCN)

[147583-45-7] · C_2H_4FNO · Hypofluorous Acid-Acetonitrile · (MW 77.07)

(the HOF.MeCN complex is used for tertiary hydroxylations,[2] epoxidations,[3] and oxidation of amines,[4] alcohols and ketones,[5] aromatics,[6] and sulfides[7])

Physical Data: mp -117 °C; bp -79 °C/1 mmHg; ^{19}F NMR δ +27.5 ppm (of the MeCN complex, -8.5 ppm).

Handling, Storage, and Precautions: HOF is a very unstable substance and of little use in synthetic chemistry. Neat liquid HOF can be unpredictably explosive at temperatures above -40 °C. Its acetonitrile complex is much more stable but nevertheless has to be prepared in situ and, for all practical purposes, has to be reacted soon after its formation. The concentration of the reagent is determined iodometrically (HOF + 2KI -> I_2 + KF + KOH). Both forms of the hypofluorous acid may be toxic and should be treated accordingly. Use in a fume hood.

Epoxidation.

HOF was synthesized originally by Appelman,[8] but it was hardly a useful synthetic reagent since it was difficult to make and could be generated only in very minute amounts. Still, it was demonstrated that it can react with a few unsaturated compounds.[9] Recently, it was discovered that HOF can be prepared simply by passing ***Fluorine*** through aqueous ***Acetonitrile***, thus forming a stabilized complex HOF.MeCN.[3,10] Possessing a strong electrophilic oxygen, it is an excellent oxygen transfer agent which epoxidizes a wide variety of alkenes (eq 1),[3a,c] including very deactivated ones which cannot be directly epoxidized by any other method (eq 2).[3b]

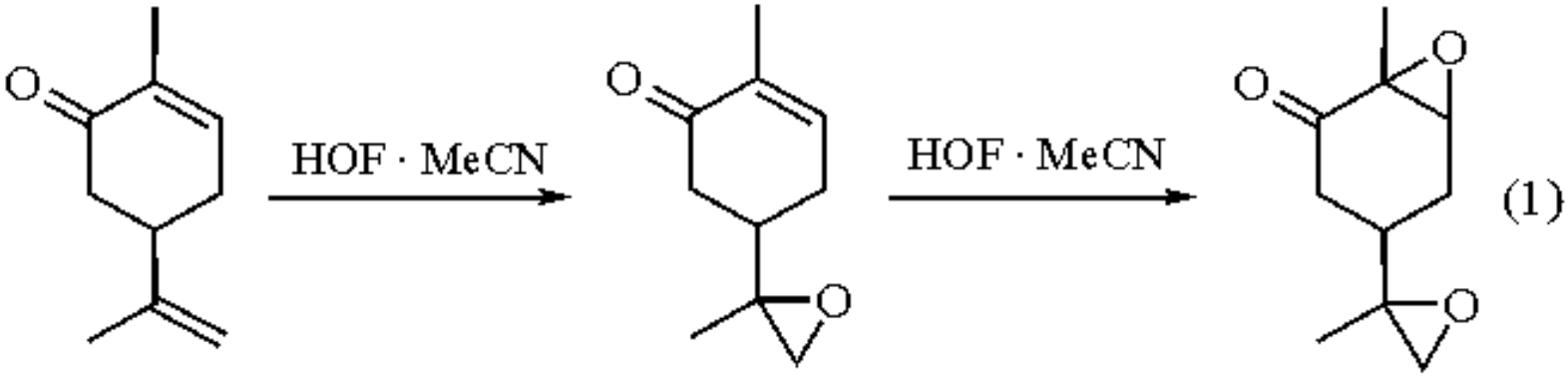

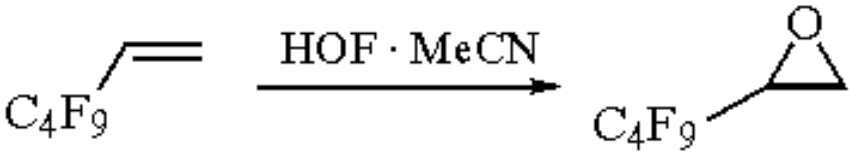

Other Oxidations.

The electrophilic properties of the oxygen have been put to use for attacking the deactivated, relatively electron-rich, tertiary C-H bond, resulting in tertiary hydroxylation as demonstrated, for example, by 4-*t*-butylcyclohexanol acetate (eq 3).[2] Being a strong oxidizer, HOF.MeCN can oxidize amines to the corresponding nitro derivatives (eq 4),[4] alcohols to ketones (eq 5),[5] and sulfides to sulfones.[7] The reactions proceed at 0 °C, in a few minutes and usually in very good yields. On prolonging the reaction time and using an excess of reagent, ketones are also oxidized to the corresponding esters much faster than with the peroxy acids used in the conventional Baeyer-Villiger oxidation (eq 5).[5] The reagent can also hydroxylate and otherwise oxidize many aromatic compounds (eq 6), although yields are moderate.[6] It should be mentioned that ***Xenon(II) Fluoride***/H_2O form in situ HOXeF, which adds the elements of H and OF across some alkenes (eq 7).[11]

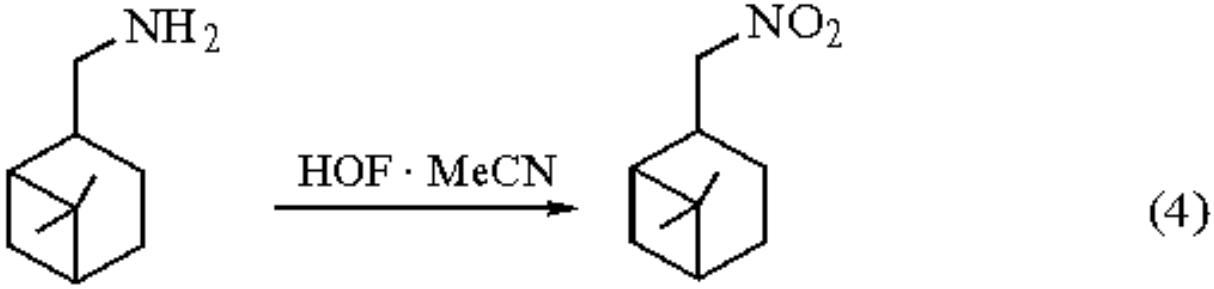

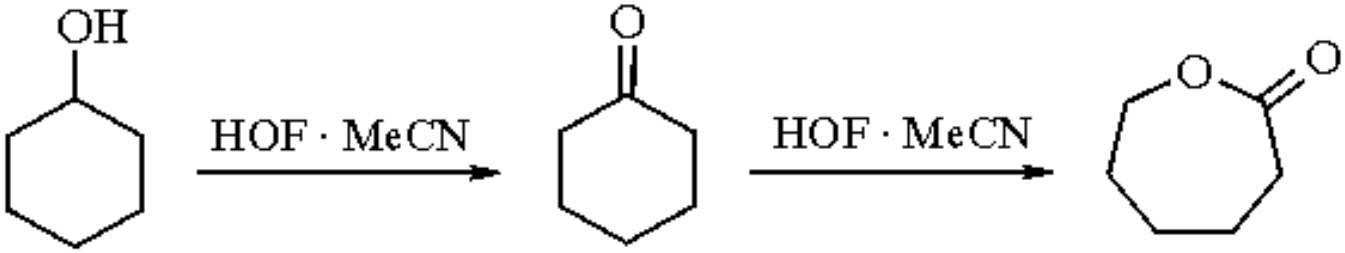

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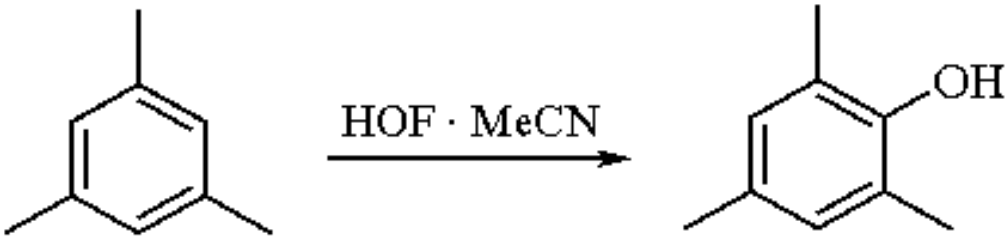

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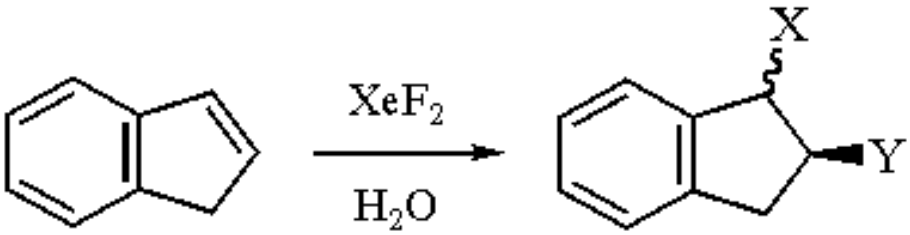

(7)

X = OH, Y = F (*cis* and *trans*)
X = F, Y = OH (*cis* and *trans*)

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Hypophosphorous Acid[1]

H_3PO_2

[6303-21-5] · H_3O_2P · Hypophosphorous Acid · (MW 66.00) (tautomer)

[14332-09-3]

(reduction of aromatic diazonium salts,[1,2] nitro compounds,[3] and pyrrole derivatives;[4] synthesis of organic derivatives of hypophosphorous acid;[1,5,6] generation of selenols[7])

Alternate Name: HPA.

Physical Data: mp 26.5 °C; decomposes at 140 °C; *d* 1.493 g cm^{-3} (19 °C); pK_a 1.1.

Solubility: sol water, alcohol, ether, dioxane.

Form Supplied in: widely available as 50% aqueous solutions (*d* 1.274 g mL^{-1}).

Preparative Methods: the anhydrous acid is prepared from the commercial solution or from inorganic salts.[1,8]

Handling, Storage, and Precautions: decomposes upon heating above 140 °C into H_3PO_4 and poisonous, spontaneously flammable PH_3. Slowly decomposes at rt. Air sensitive. Use in a fume hood.

Reduction of Arenediazonium Compounds.

Hypophosphorous acid is widely accepted as the preferred reagent for the reduction of diazonium salts.[1,2,9] ***Copper(I) Oxide*** is a very effective catalyst of this reaction[9] (eq 1). Dediazonation with HPA can also be used in Pschorr-type cyclizations.[10]

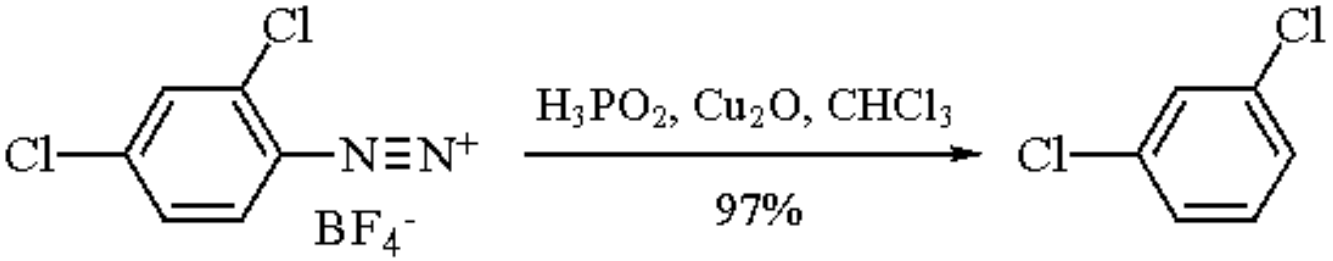

(1)

Alkylphosphinic Acids.

Radical addition of HPA or its alkali salt to alkenes is initiated by organic peroxides and gives phosphinic acid derivatives in good yields (eq 2).[1,6,11,12] The alkene to HPA ratio controls the formation of alkyl- or dialkylphosphinic acid.[1,11] Alkyl phosphinates also add to alkenes in the presence of peroxides.[1] Alkylphosphinic acids can be prepared from HPA and alcohols,[13] and alkenylphosphinic acids have been obtained from enol esters.[14]

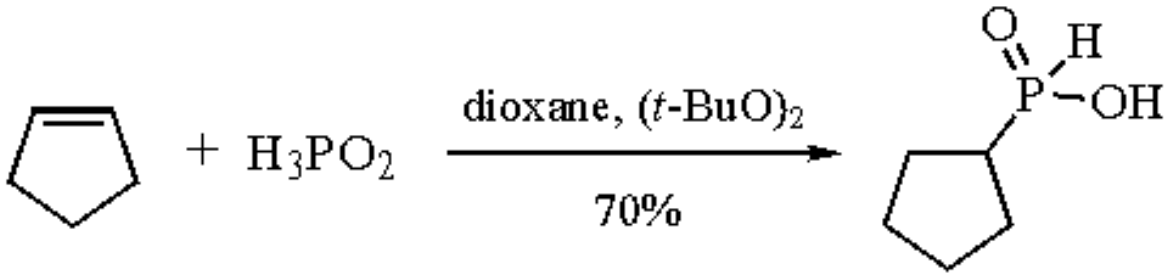

(2)

Hydroxyalkylphosphinic Acids.

HPA reacts with aldehydes, ketones, and 1,2-ketones to provide 1-hydroxyalkylphosphinic acids (eq 3).[1] When carbonyl compounds are used in excess, bis(1-hydroxyalkyl)phosphinic acids are formed.

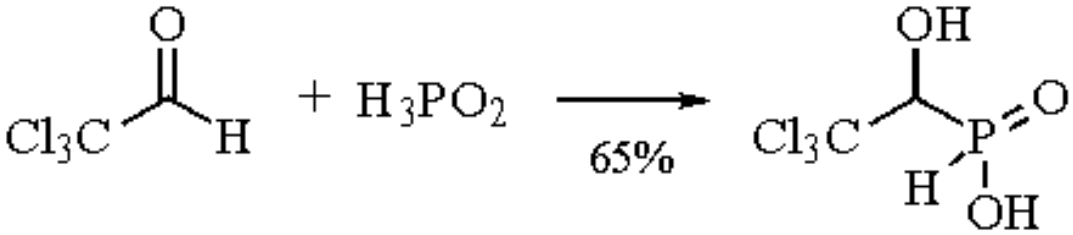

(3)

1,2-Alkadienylphosphinic Acids.

Reactions of HPA with alkynic alcohols are accompanied by alkyne-allene rearrangement and lead to 1,2-alkadienylphosphinic acids (eq 4).[15]

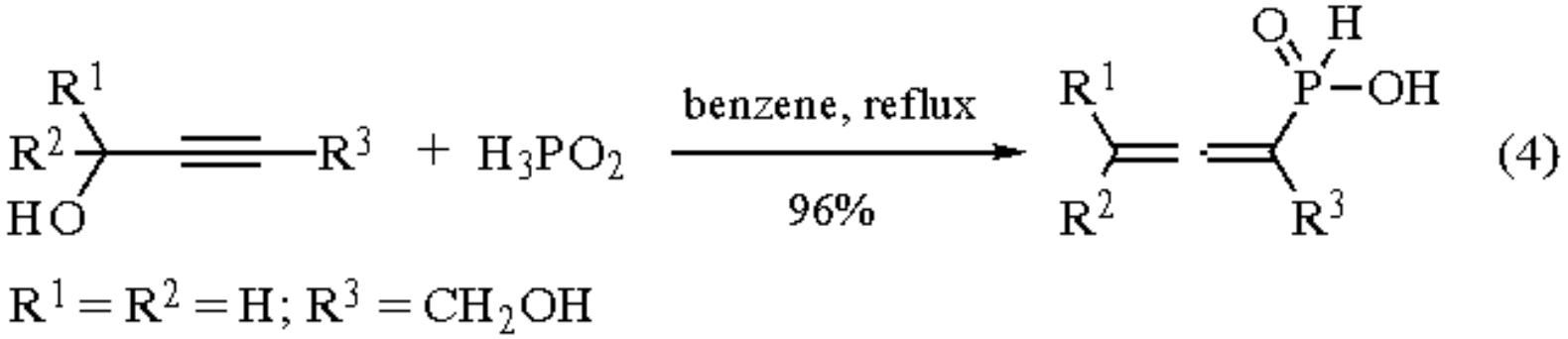

Aminoalkylphosphinic Acids.

HPA reacts with azomethines under mild conditions, providing good yields of 1-(alkylamino)alkylphosphinic acids.[1] Synthetic possibilities of this reaction have been extended by replacing the azomethines with a mixture of aldehyde or ketone and amine or hydrazine.[6,16] Thus reaction of HPA with equimolar amounts of formaldehyde and secondary amines at rt in aqueous solution gives the corresponding dialkylaminophosphinic acids (eq 5). With an excess of amine and formaldehyde, bis(dialkylaminoalkyl)phosphinic acids are formed.[1,16]

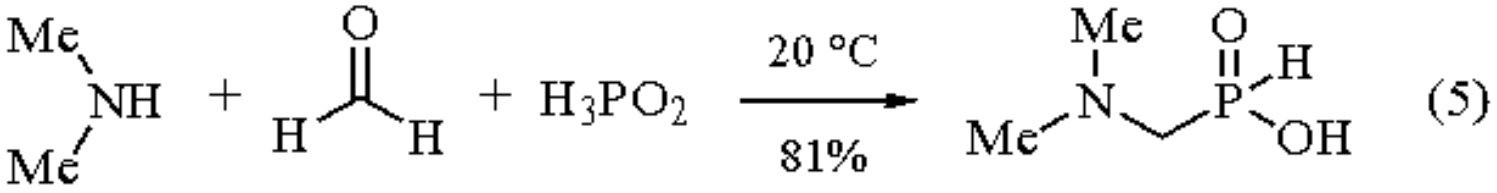

Alkyl Hypophosphites.

A particularly easy preparation of alkyl hypophosphites involves the reaction of crystalline HPA with orthocarbonyl compounds (eq 6).[5] Treatment of HPA with diazoalkanes also gives good yields of the desired esters.[17] Reaction of HPA with orthoformates in the presence of ***p-Toluenesulfonic Acid*** leads to the formation of alkyl dialkoxymethylphosphinates.[18]

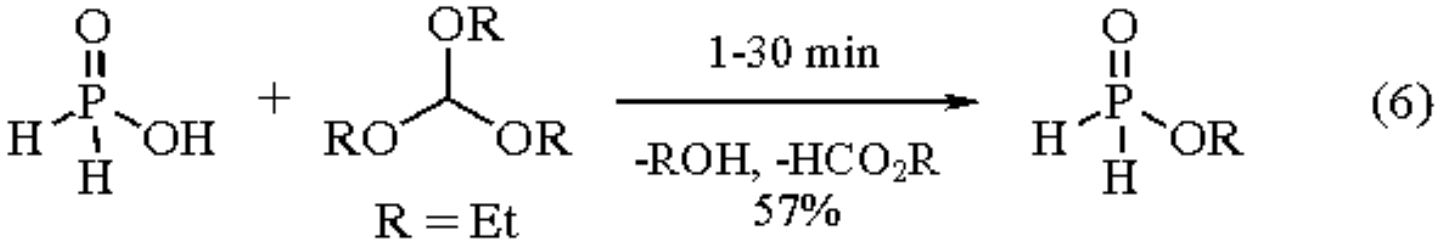

Reduction with Hypophosphorous Acid.

Palladium on Carbon catalyzed reduction with HPA converts the nitro group of arenes into an amino group,[3] and quinones into hydroquinones.[19] HPA in combination with ***Hydrogen Iodide*** is used for reduction and reductive alkylation of pyrrole derivatives.[4]

Selenols.

A commercial 50% solution of HPA is a convenient reagent for generation of selenols from diselenides or selenic acids.[7]

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Imidazole

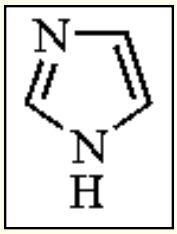

[288-32-4] · $C_3H_4N_2$ · Imidazole · (MW 68.09)

(nucleophilic catalyst for silylations and acylations; buffer; weak base; iodination methods)

Alternate Names: Im; iminazole; 1,3-diazole; glyoxaline.

Physical Data: mp 90-91 °C; bp 255 °C, 138 °C/12 mmHg.

Solubility: sol water, alcohols, ether, acetone, chloroform.

Form Supplied in: colorless crystalline solid; widely available. *Drying:* 40 °C in vacuo over P_2O_5.

Purification: can be crystallized from C_6H_6, CCl_4, CH_2Cl_2, EtOH, petroleum ether, acetone-petroleum ether, or water; can also be purified by vacuum distillation, sublimation, or by zone refining.

Introduction.

Imidazole has a pK_a of 7.1 and is thus a stronger base than thiazole (pK_a 2.5), oxazole (pK_a 0.8), and pyridine (pK_a 5.2). It is both a good acceptor and donor of hydrogen bonds. The pK_a for loss of the N-H is ~14.2, i.e. imidazole is a very weak acid.

Silylations.

Imidazole is a standard component in silylations of alcohols as well as carboxylic acids, amines, and a variety of other functions, typically in combination with a silyl chloride in DMF (eq 1).[1] A very widely used procedure for alcohol protection is by conversion into the corresponding *t*-butyldimethylsilyl (TBDMS or TBS) ether using the method;[2] in other solvents such as pyridine or THF the reactions are much slower, probably because the primary silylating reagent is *t*-$BuMe_2Si$-Im. In this and many other aspects, imidazole resembles another very useful transfer catalyst, ***4-Dimethylaminopyridine*** (DMAP). Similarly, bulkier and hence more stable silyl groups, such as *t*-butyldiphenylsilyl (TBDPS)[3] and triisopropylsilyl (TIPS),[4] can be introduced. Times for completion of reaction at 20 °C vary (0.5-20 h);

these silylating agents, originally developed for nucleoside protection,[5] usually react faster with primary alcohols and with certain secondary alcohols, thus allowing selective protection of polyols to be achieved efficiently. (A faster alternative involves the use of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) in place of imidazole, in a variety of solvents such as CH_2Cl_2, C_6H_6, or MeCN, in combination with R_3SiCl).[6] 1,3-Diones can be efficiently *O*-silylated using TBDMSCl-Im[7] or ***Hexamethyldisilazane*** (HMDS) and imidazole;[8] other reagents are not as suitable, even in cases where the enol content is high. The products are useful as *trans*-silylating agents.[7] The HMDS-Im combination is also useful for the silylation of thiols.[9]

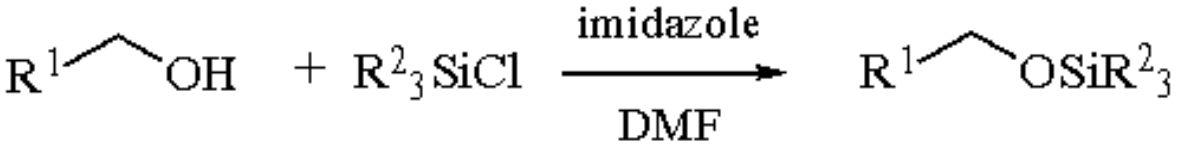

(1)

Ester Hydrolysis.

Inspired by evidence that the imidazole ring of histidine residues present in various hydrolytic enzymes is responsible for their proteolytic activities, imidazole itself has been shown to be an excellent catalyst of ester hydrolysis (e.g. eq 2).[10] In intramolecular transesterifications and hydrolyses of 2-hydroxymethylbenzoic acid derivatives, the accelerating role of imidazole is due to its ability to act as a proton transfer catalyst rather than as a nucleophile.[11]

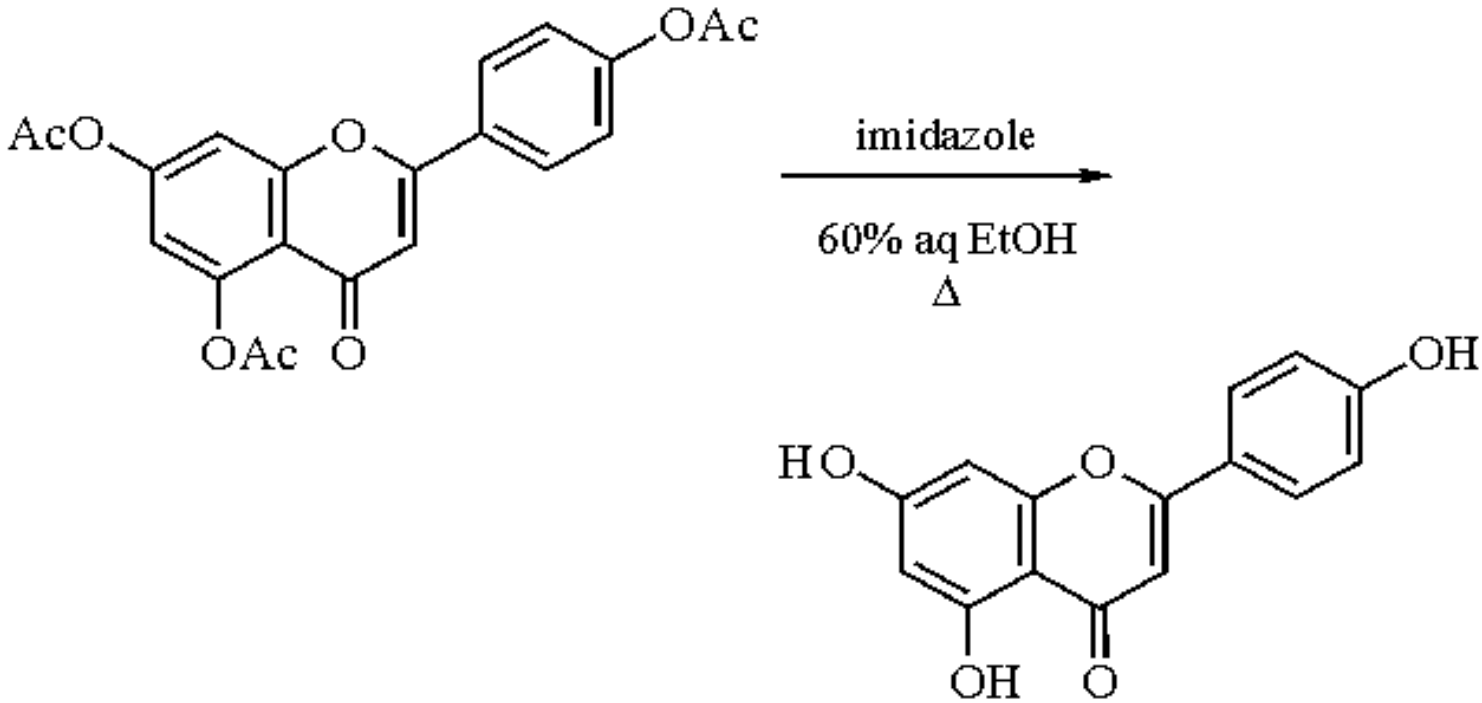

(2)

Peptide Coupling.

Peptide couplings involving *p*-nitrophenyl and related esters (see ***p-Nitrophenol***) are dramatically accelerated by the addition of imidazole.[12] However, such reactions, which probably proceed by way of an acylimidazole, can be prone to racemization, in which case ***1,2,4-Triazole*** can be a superior activator.[13] Imidazole also catalyzes peptide coupling using the ***Triphenyl Phosphite*** method, with negligible racemization when the reactions are carried out in dioxane or DMF,[14] and is useful for the activation of phosphomonoester groups in nucleotide coupling, in combination with an

arylsulfonyl chloride.[15]

Acylimidazoles and Nucleophiles.

Acylimidazoles are readily prepared from the parent carboxylic acids by reaction of the derived acid chloride with imidazole or directly using ***N,N´-Carbonyldiimidazole***. These intermediates react smoothly with a variety of nucleophiles including Grignard reagents (eq 3),[16] ***Lithium Aluminum Hydride*** (eq 4),[16] and nitronates (eq 5).[17] At -20 °C, aroylimidazoles can be reduced to the corresponding aldehydes in the presence of an ester function.[16]

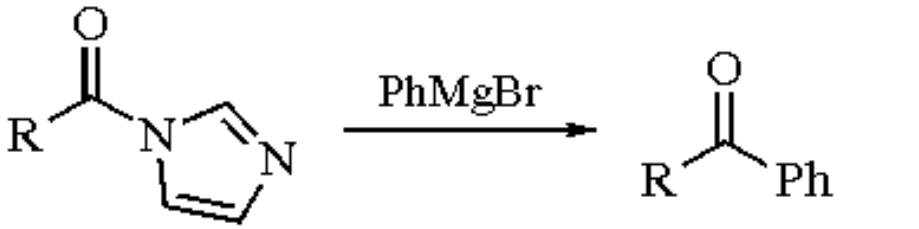

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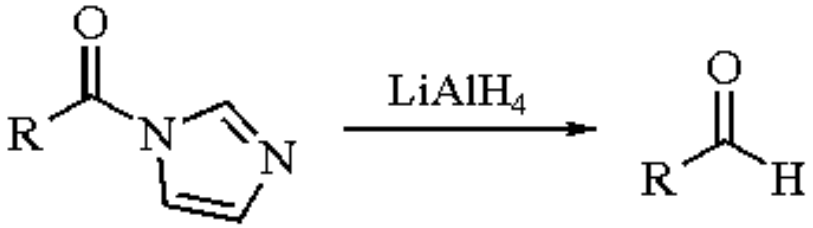

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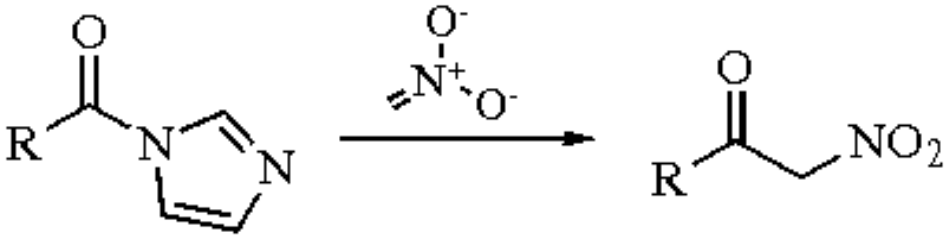

(5)

The activation provided by an imidazole substituent is further illustrated in a route to 1,3-oxathiole-2-thiones from sodium 1-imidazolecarbodithioate, derived from the sodium salt of imidazole and CS_2 (eq 6).[18]

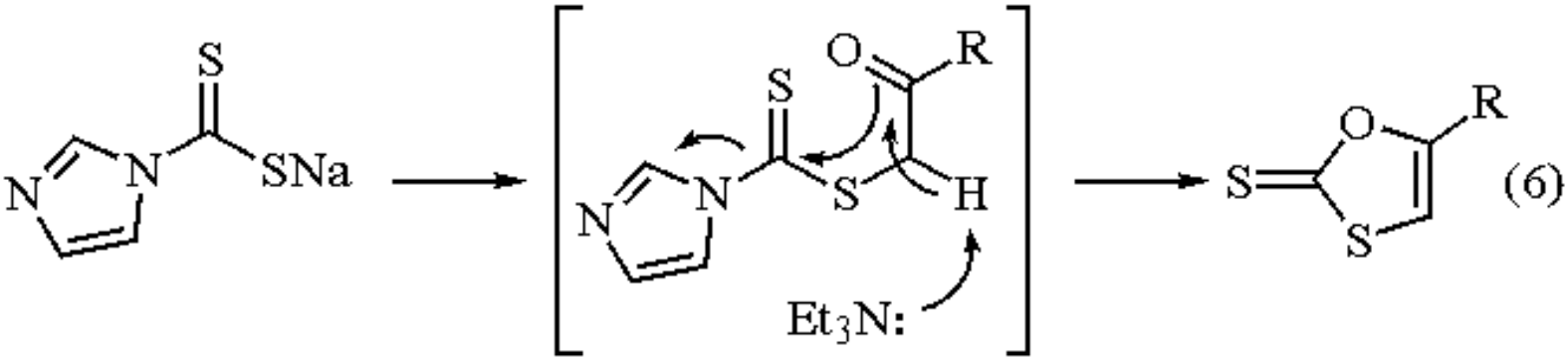

(6)

Other Uses.

Imidazole is one of the best catalysts for the preparation of acid chlorides from the corresponding carboxylic acids and phosgene.[19] Aryl triflates can be obtained from phenols, or better phenolates, using ***Trifluoromethanesulfonic Anhydride*** in combination with imidazole; *N*-triflylimidazole is the reactive species.[20] Photochemical deconjugations of enones can be erratic but are promoted by the presence of a weak base such as imidazole or pyridine in polar solvents.[21]

Iodination of Alcohols.

Imidazole, ***Triphenylphosphine***, and ***Iodine*** in hot toluene,[22] or preferably toluene-acetonitrile mixtures,[23] is an excellent combination for the conversion of alcohols into iodides, ROH -> RI. Secondary alcohols react with inversion (but see below), although the method can be used for the selective iodination of primary hydroxyls. Applications in the area of natural product synthesis[24] emphasize the mildness and generality of the method as well as providing alternative recipes; sometimes, 2,4,5-triiodoimidazole can be a superior reagent.[22] Similarly, Ph_3P-Cl_2-Im can be used for the preparation of alkyl chlorides, ROH -> RCl, and the addition of imidazole in the ***Triphenylphosphine-Carbon Tetrachloride*** method for alcohol chlorination has a beneficial effect.[25]

Diol Deoxygenation.

The Ph_3P-Im-I_2 combination can also be used to convert *vic*-diols into the corresponding alkenes, although 2,4,5-triiodoimidazole is more effective than imidazole itself.[26] Alternative combinations are ***Triphenylphosphine-Iodoform-Imidazole***, which can deoxygenate *cis*-diols but which is better suited to *trans*-isomers,[27] and ***Chlorodiphenylphosphine***-I_2-Im, which can be used to deoxygenate *vic*-diols when both are secondary or when one is secondary and one is primary.[28]

Epoxidation.

t-Butyl Hydroperoxide in combination with $MoO_2(acac)_2$ can be used to oxidatively cleave alkenes, but will epoxidize such functions in the presence of a metalloporphyrin or a simple amine, the choice of which depends upon the substrate structure. Imidazole is the most suitable for 1-phenylpropene, ***Pyridine*** for stilbene, and *N*,*N*-dimethylethylenediamine for 1-alkenes.[29]

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Imidazolium Dichromate

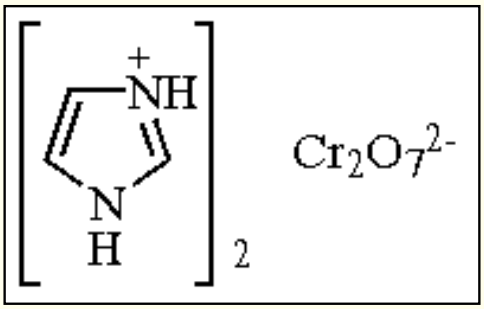

[109201-26-5] · $C_6H_{10}Cr_2N_4O_7$ · Imidazolium Dichromate · (MW 354.20)

(mild selective reagent for the oxidation of allylic and benzylic alcohols to the corresponding carbonyl compounds)

Alternate Name: IDC.

Physical Data: mp 130-131 °C; nonhygroscopic; air stable yellow crystals.

Solubility: readily sol DMF, DMSO; very slightly sol acetone, dichloromethane, trichloromethane.

Preparative Method: easily prepared by the addition of ***Imidazole*** to a solution of an equimolar amount of ***Chromium(VI) Oxide*** in a minimum amount of water.[1] The yellow crystals are collected, washed with acetone, and dried in vacuo at rt.

Handling, Storage, and Precautions: all chromium(VI) reagents must be handled with care. The mutagenicity of chromium(VI) compounds is well documented.[2] This reagent should be handled in a fume hood.

Oxidation of Allylic and Benzylic Alcohols to Carbonyl Compounds.

Imidazolium dichromate oxidizes cinnamyl alcohol and benzhydrol to cinnamaldehyde (91%) and benzophenone (93%), respectively, at rt.[1] Allylic alcohols are oxidized faster than benzylic alcohols and saturated aliphatic alcohols react slowest. Geraniol is oxidized to geranial (82% yield) with 6% (*E*) to (*Z*) isomerization at the double bond. 4-(3-Hydroxypropyl)benzyl alcohol is selectively oxidized to 4-(3-hydroxypropyl)benzaldehyde (eq 1). The selectivity achieved with IDC is comparable to that of ***4-(Dimethylamino)pyridinium Chlorochromate*** (DMAP.$HCrO_3Cl$).[3,4]

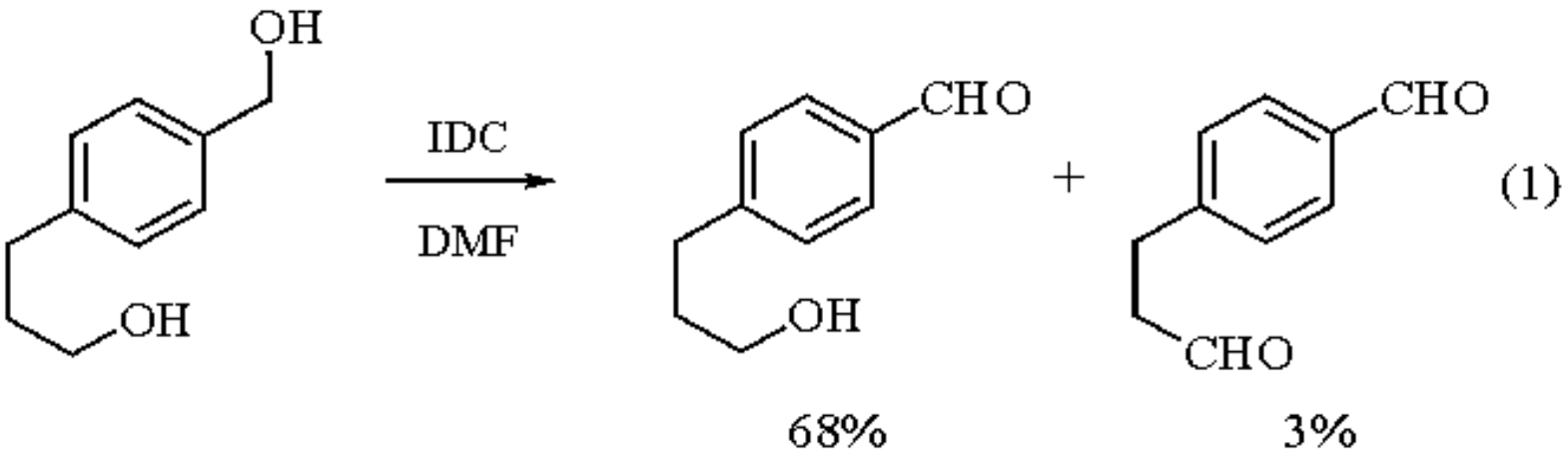

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Indium

In

[7440-74-6] · In · Indium · (MW 114.82)

(effective mediator for the allylation of carbonyl compounds)

Physical Data: mp 156 °C; *d* 7.300 g cm^{-3}.

Form Supplied in: available in the form of bars, foils, wire, granules, shot, and powders of various sizes. For synthetic purposes, indium powder of about 60 mesh is the most convenient form.

Handling, Storage, and Precautions: no special precautions are required.

Allylation of Carbonyl Compounds.[1]

Indium is a very effective mediator for the addition of allyl groups to carbonyl compounds under very mild reaction conditions. Typically, the organoindium reagent is prepared in situ by the addition of an allyl iodide to a suspension of indium powder in a suitable solvent. The preparation of highly activated indium powder (Rieke indium) via reduction of indium(III) chloride has been reported,[2] but in the vast majority of cases commercial indium powder is sufficient. Allyl bromides are equally well suited for this reaction, but allyl chlorides are not sufficiently reactive, resulting in diminished yields. Studies by Butsugan and co-workers[1] suggest that the active organoindium species is the allylic indium sesquihalide (eq 1), which is in accord with results of Gynane and Worrall.[3]

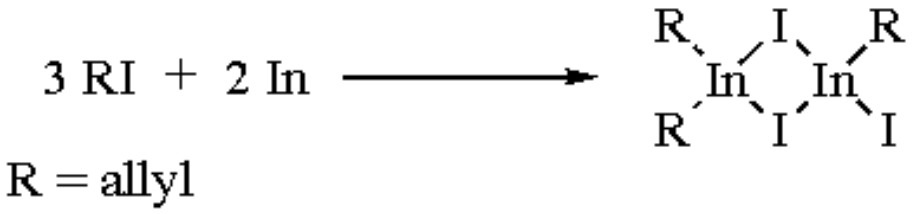

(1)

Studies of the variation of the yields of allylation as a function of the ratio of indium:allyl iodide:ketone have shown that two-thirds of the allyl groups are transferred to carbonyl compounds, and thus the stoichiometry of the reaction is 2:3:2 (indium:allyl halide:ketone).[1] In cases where quantitative utilization of the allyl halide is important, this can be achieved by substituting indium(I) iodide for metallic indium.[4]

Allylindium sesquihalides react readily with a variety of carbonyl compounds, including ketones (eqs 2 and 3),[1] aldehydes (eqs 4 and 5),[1] acid anhydrides,[5] quinones,[6] and aldimines.[7] In general, the stereoselectivity obtained in

these reactions is low to moderate. For example, indium-mediated allylation of 4-*t*-butylcyclohexanone (eq 3) gives an 83:17 mixture of axial:equatorial products. In the case of substituted allyl halides (eqs 4 and 5), regioselectivity is extremely high as only the products of γ-coupling are observed. α,β-Unsaturated carbonyl compounds give exclusively 1,2-addition products (eq 6).[1]

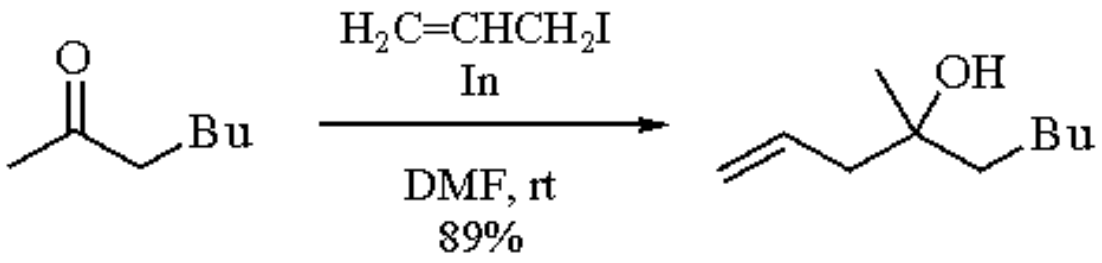

(2)

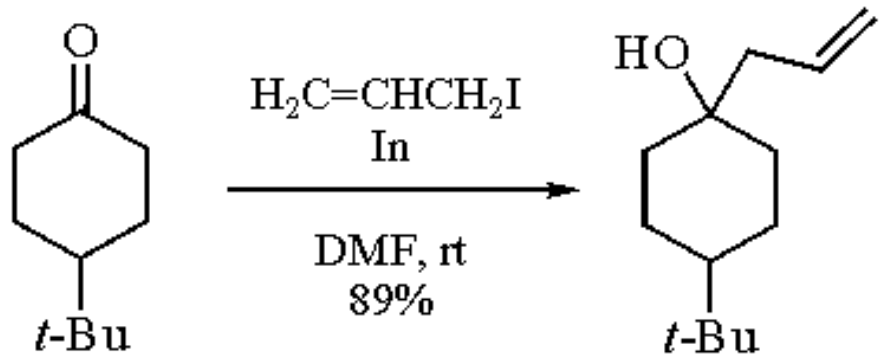

(3)

ax:eq = 83:17

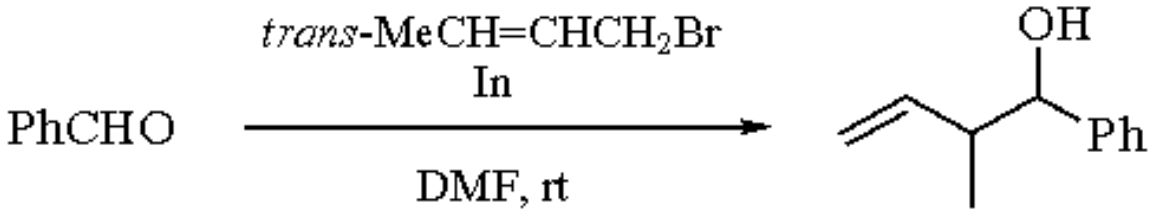

(4)

erthyro:*threo* = 66:34

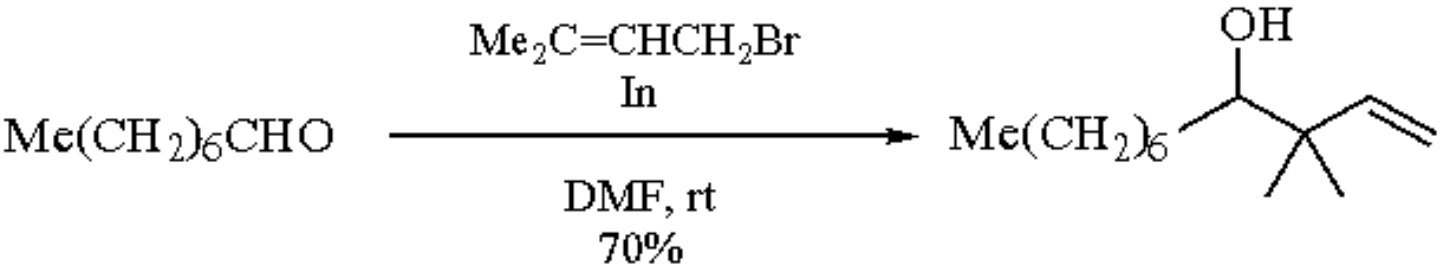

(5)

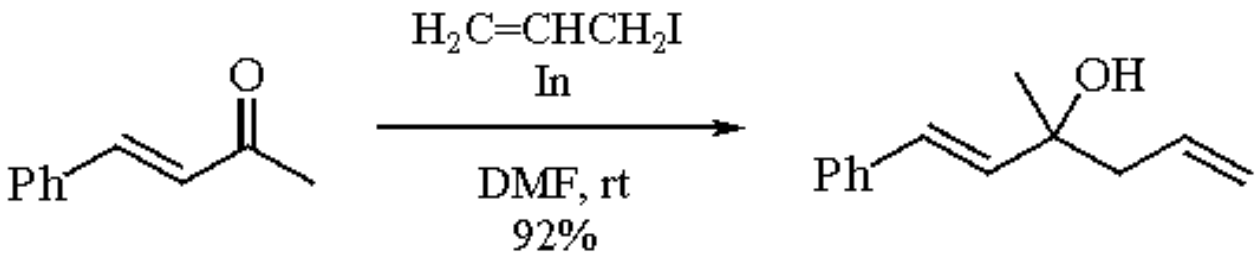

(6)

One significant advantage of allylindium sesquihalides over alternative organometallic allylating reagents (allylmagnesium halides, allyllithium compounds) is their low basicity. Yields remain high even in the presence of an active hydrogen, such as in the case of salicylaldehyde (eq 7).[1] This property has been exploited by Chan and Li, who have reported indium-mediated allylations of carbonyl compounds carried out in water.[8] These workers report that in contrast to similar reactions with zinc and tin, where acid catalysts, heat, or sonication are often required, the indium-mediated reaction proceeds readily without the need of a promoter.

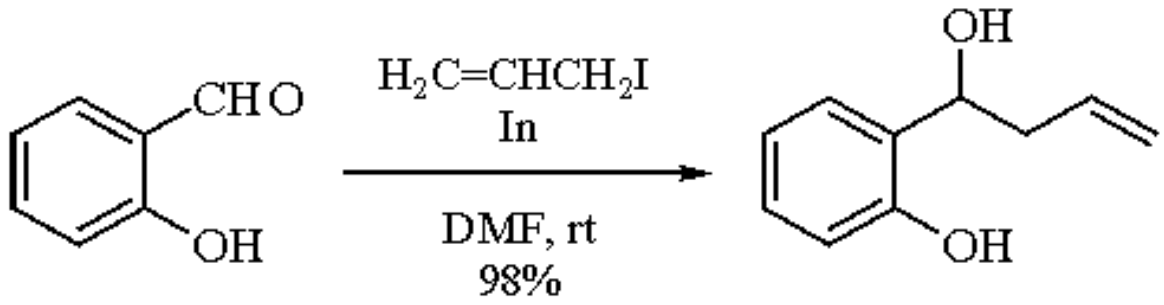

(7)

The mildness of the reaction conditions employed for indium-mediated allylation can also be advantageous when allylating labile carbonyl compounds. For example, attempts to allylate the tricarbonyliron butadiene complex (**1**) with allylmagnesium bromide fail completely, yielding only unidentifiable decomposition products. In contrast, the indium-mediated allylation of (**1**) (eq 8) proceeds smoothly to give the corresponding homoallyl alcohols in 91% yield.[9]

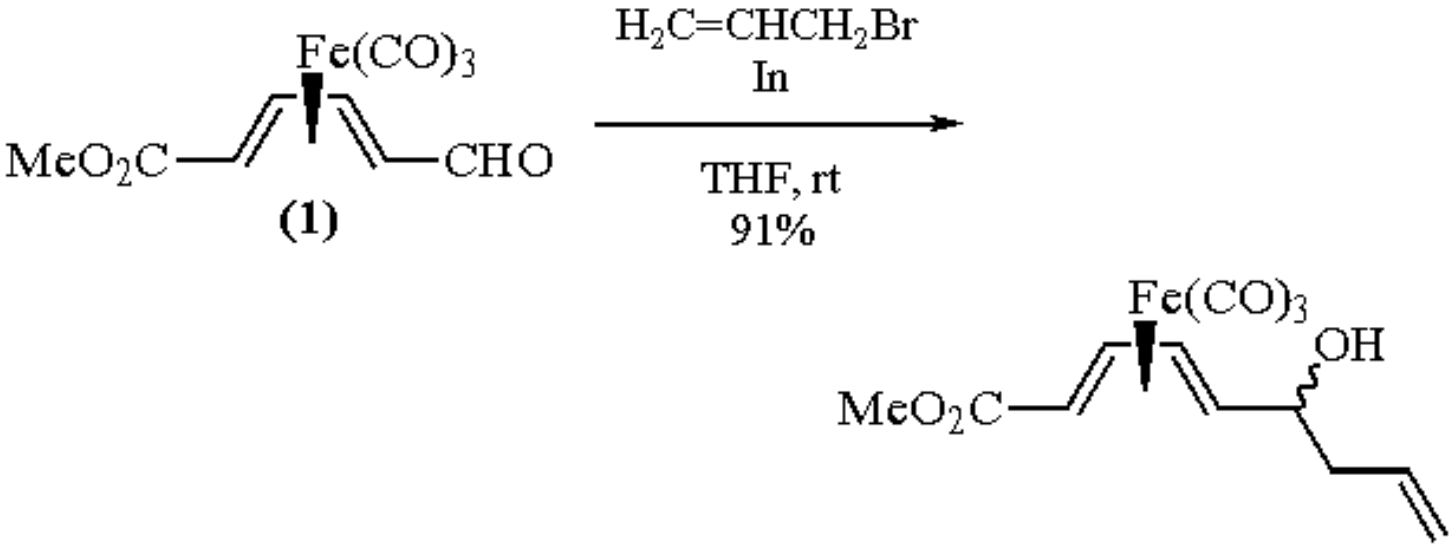

(8)

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Iodine

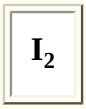

[7553-56-2] · I_2 · Iodine · (MW 253.80)

(electrophilic reagent that adds to alkenes[1] and alkynes[2] to give diiodides; alkenyl carboxylic acids react to give iodolactones[3] and alkenyl amides lead to iodolactams;[4] dehydrogenates amines[5] and reacts with ketones, in the presence of base, to give α-iodo ketones;[6] carboxylic acids are converted to α-iodo acid derivatives[7] and carbanions react to give the substituted iodides;[8] organoboranes can give alkyl iodides[9] and vinylboranes lead to substituted alkenes;[10] important spotting reagent for TLC analysis[11])

Physical Data: mp 113.6 °C; bp 185.24 °C; *d* 4.930 g cm^{-3}; vapor pressure 0.31 mmHg at 25 °C.

Solubility: the solubility of iodine, expressed in g/kg of solvent at 25 °C is: H_2O, 0.34; benzene, 164.0; CCl_4, 19.2; $CHCl_3$, 49.7; ethyl acetate, 157; ethanol, 271.7; diethyl ether, 337.3; *n*-hexane, 13.2; toluene, 1875.[12] Soluble glacial acetic acid; relatively insol dichloromethane.

Form Supplied in: the natural abundance isotope is ^{127}I. It is a massive bluish-black solid. When sublimed it forms near opaque, doubly refractory orthorhombic crystals that have a metallic luster. Heating iodine generates a violet-colored vapor. Commercially available in >99.5% purity, with bromine and chlorine the primary contaminants. Natural abundance iodine is diatomic, I-I.

Preparative Methods: commercially available but can be prepared by the reaction of potassium iodide and copper(II) sulfate.[13] It is also prepared by chlorination of natural brines or by treatment of brine with silver nitrate and then iron(II) iodide, followed by addition of chloride to liberate iodine.[14]

Purification: vacuum sublimation.

Handling, Storage, and Precautions: somewhat corrosive.[15] It is stored in a dark bottle or jar, at ambient temperatures. Iodine vapors have a sharp characteristic odor and they are irritating to eyes, skin, and mucous membranes (lachrymatory). Prolonged exposure should be avoided. Ingestion of large quantities can cause abdominal pain, nausea, vomiting, and diarrhea. If 2-3 g of iodine are ingested, death may occur.

Introduction.

Diatomic iodine (I_2) is a member of the halogen family that is widely used in organic chemistry. Iodine is less electronegative than the other halogens, and iodides are generally less stable than other halides.[16] Oxides of iodine and

compounds where iodine is in a positive valence state are much more stable than the other halogens. Iodine forms binary compounds with all elements except sulfur, selenium, and the noble gases, although it does not react directly with carbon, nitrogen, or oxygen.[15] Its applications in organic chemistry range from detection of organic molecules in TLC, to addition reactions with unsaturated molecules, to reactions as an electrophilic agent with nucleophilic species. Iodine is used not only as an agent for incorporating an iodine atom but also as an oxidizing agent, a dehydrogenation agent, and as a radiolabel in many biologically important systems.

One of the most common uses of iodine is as a spotting agent for the detection of organic molecules in TLC.[11] Many organic molecules either adsorb iodine vapors or react with iodine vapor to produce a visible spot on the TLC plate. In general, basic compounds and reducing compounds pick up iodine vapors very well, but acidic compounds and oxidizing compounds do not.[11] Many natural products can be detected via TLC, including steroids,[17] phenolic compounds,[18] and alkaloids.[19]

Addition to Alkenes.

Iodine is a highly polarizable molecule that behaves as electrophilic iodine (I^+) in the presence of a suitable Lewis base, such as an alkene or an alkyne. When an alkene reacts with molecular iodine, a characteristic iodonium ion is formed, and subsequent reaction with the nucleophilic gegenion (I^-) leads to the vicinal diiodide. There are many examples of this type of reaction. Addition of iodine to cyclohexene to give *trans*-1,2-diiodocyclohexane is a simple example (eq 1).[1] The reaction is believed to involve a radical intermediate, evidenced by formation of dimeric coupling products in many alkene iodination reactions. Reaction of styrene with iodine (neat), for example, gives not only 1,2-diiodo-2-phenylethane but also 1,4-diiodo-2,3-diphenylbutane as a minor product (eq 2).[20]

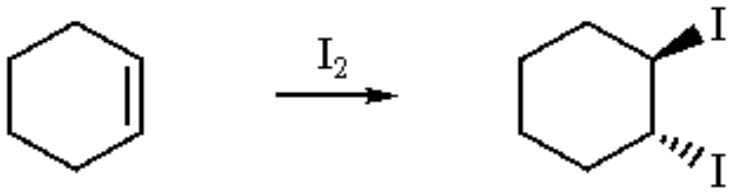

(1)

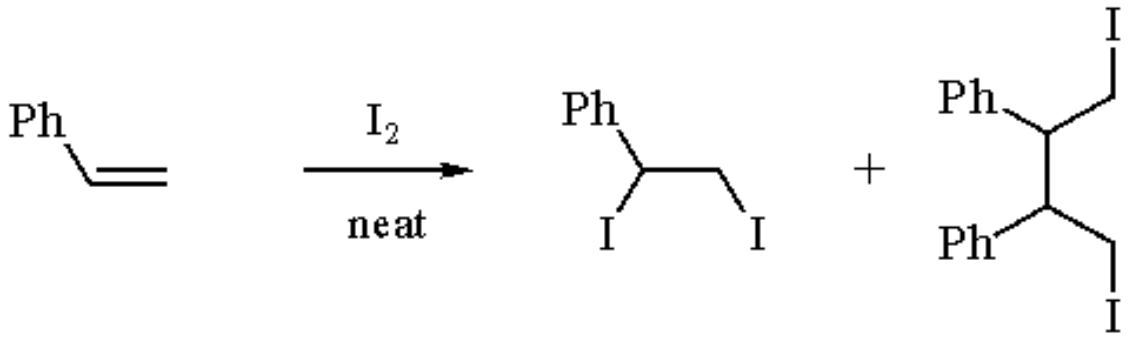

(2)

The iodine reaction can be modified by addition of other reagents, such as methanol, to produce iodo ethers. When iodine in methanol is reacted with cyclohexene, in the presence of ***Cerium(IV) Ammonium Nitrate*** (CAN), a 92% yield of 2-methoxy-1-iodocyclohexane is obtained (eq 3).[21a] Similar results are obtained when iodine and ***Copper(II) Acetate*** are used.[21b]

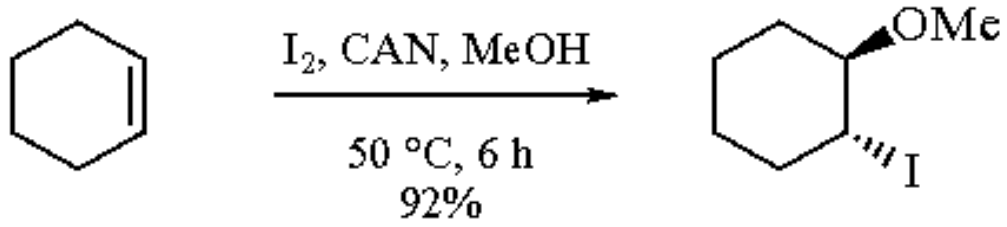

(3)

Iodine reacts with dienes to form a mixture of 1,2-diiodoalkenes and 1,4-diiodoalkenes. When done in the presence of ***Copper(I) Cyanide***, the 1,4-addition product predominates and 1,3-butadiene thus reacts to give an 84% yield of 1,4-dicyano-2-butene (eq 4).[22] Allenes react with iodine to give diiodides. When 2,3-pentadiene reacts with iodine in carbon tetrachloride, 2,3-diiodo-3-pentene is formed (eq 5).[23] When the reaction is done in methanol, however, 3-methoxy-2-iodo-3-pentene is the product.

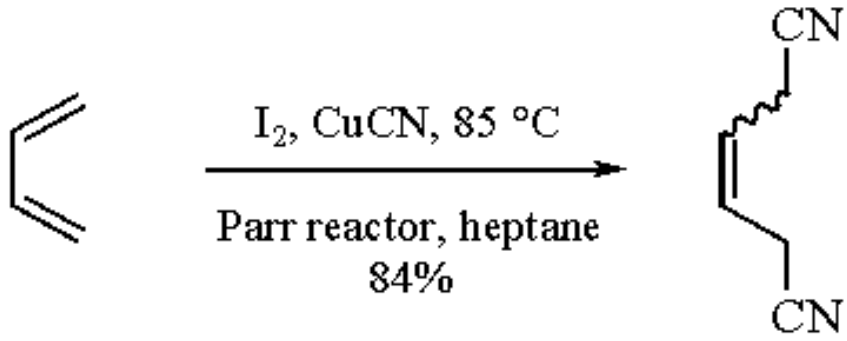

(4)

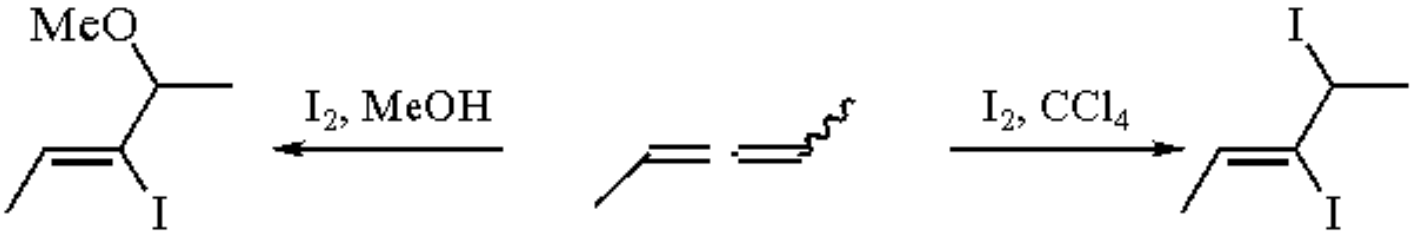

(5)

There are two very interesting and useful variations of the fundamental addition reactions to alkenes: iodolactonization[3] (to form iodolactones) and iodolactamization (to produce iodolactams). When an alkenyl acid reacts with iodine in the presence of a base (such as sodium bicarbonate), the initially formed iodonium ion reacts with the carboxylate anion (generated in situ) to form the iodolactone (eq 6).

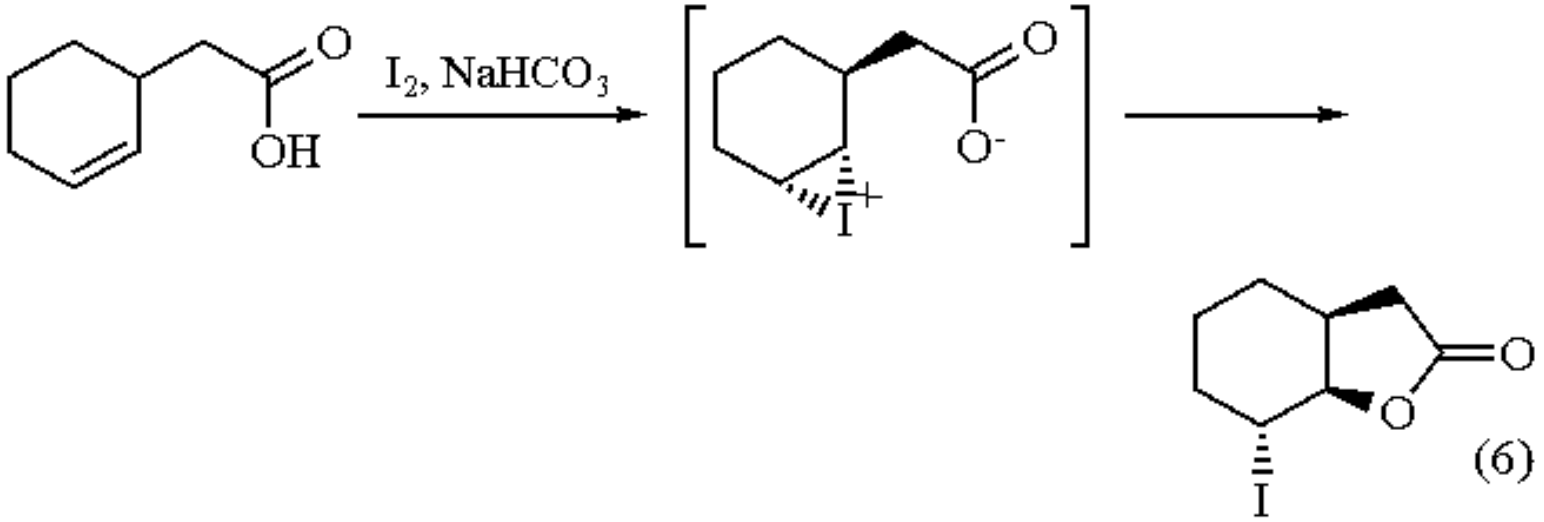

Lactones are also formed when iodine reacts with alkenyl amides or alkenyl carbamates. In initial studies, amides led to the formation of lactones whereas carbamates gave oxazolidinones. When *N*-(*S*)-phenethyl-2-allyl-4-pentenamide reacts with 3 equiv of iodine in aqueous THF, a 77% yield of 2-allyl-5-iodomethyl-δ-butyrolactone is obtained (16% optical purity) (eq 7).[24] Similarly, reaction of *N*-Cbz-*N*-methyl-2-propenamine with iodine in dichloromethane leads to a 95% yield of *N*-methyl-4-iodomethyl-2-oxazolidinone (eq 8).[25]

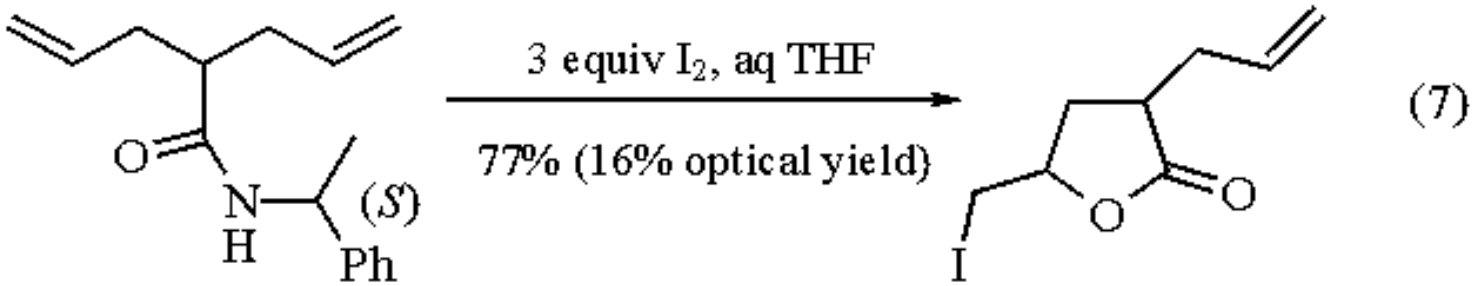

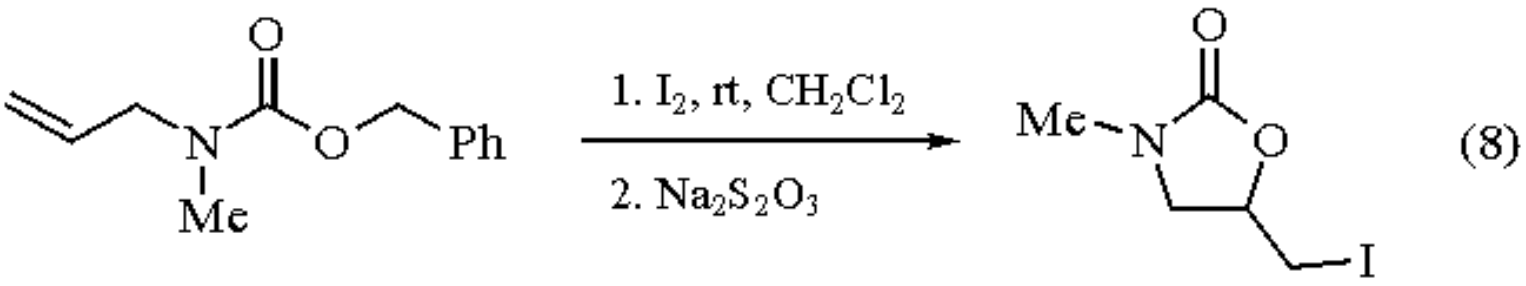

The more difficult lactam forming reaction (iodolactamization) can be accomplished by treatment of primary alkenyl amides with ***Trimethylsilyl Trifluoromethanesulfonate***, followed by iodination, as in the conversion of 4-pentenamide to 5-iodomethyl-2-pyrrolidinone in 68% yield (eq 9).[4] There are several other cyclization reactions that are initiated by the reaction of iodine with an alkene, in the presence of a nucleophilic atom elsewhere in the molecule.[26]

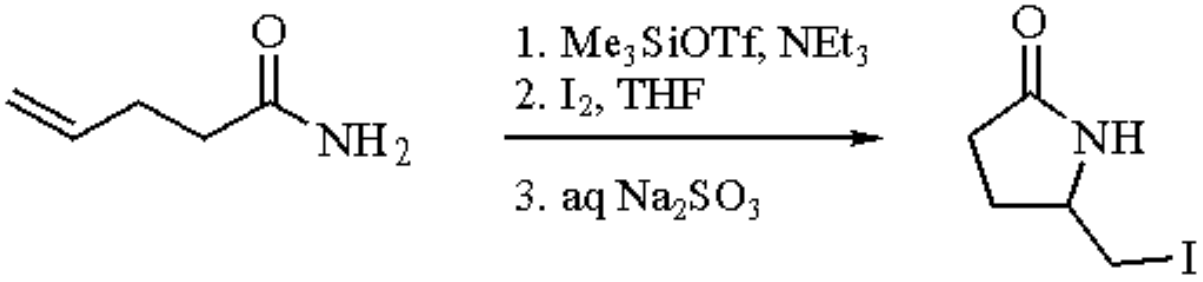

(9)

Addition to Alkynes.

Iodine undergoes addition reactions with alkynes as well as alkenes, although the reaction is generally more sluggish. Reaction of 1,4-dichloro-2-butyne with iodine, for example, requires 1,2-dichloroethane as a solvent and heating to 83 °C for 120 h to give (*E*)-1,4-dichloro-2,3-diiodo-2-butene (eq 10).[27] Treatment of this alkene with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** leads to formation of iododienes. Another example is 1-hexyne, which reacts with iodine in methanol to produce (*E*)-1,2-diiodo-1-hexene (eq 11).[2] When ***Silver(I) Nitrate*** is added to this mixture, however, a mixture of 1,1-diiodo-2-hexanone, 1-iodo-1-hexyne, and (*E*)-1,2-diiodo-1-hexene is formed (31%, 46%, 23% yields).[15]

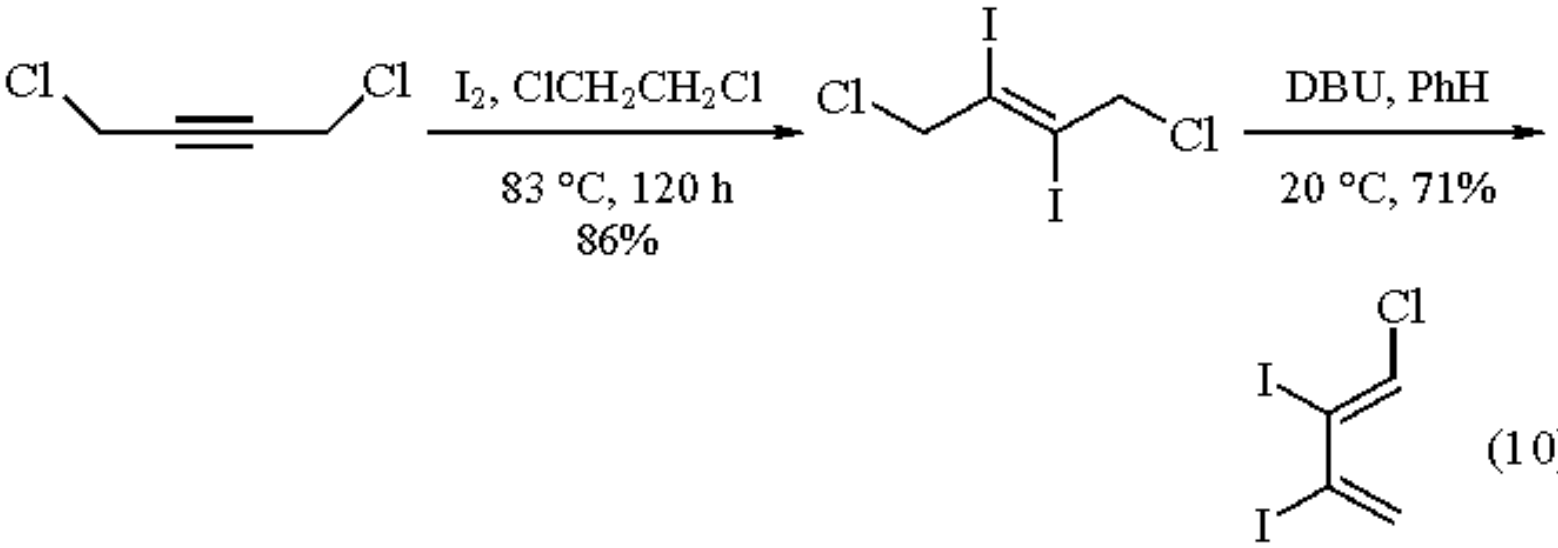

(10)

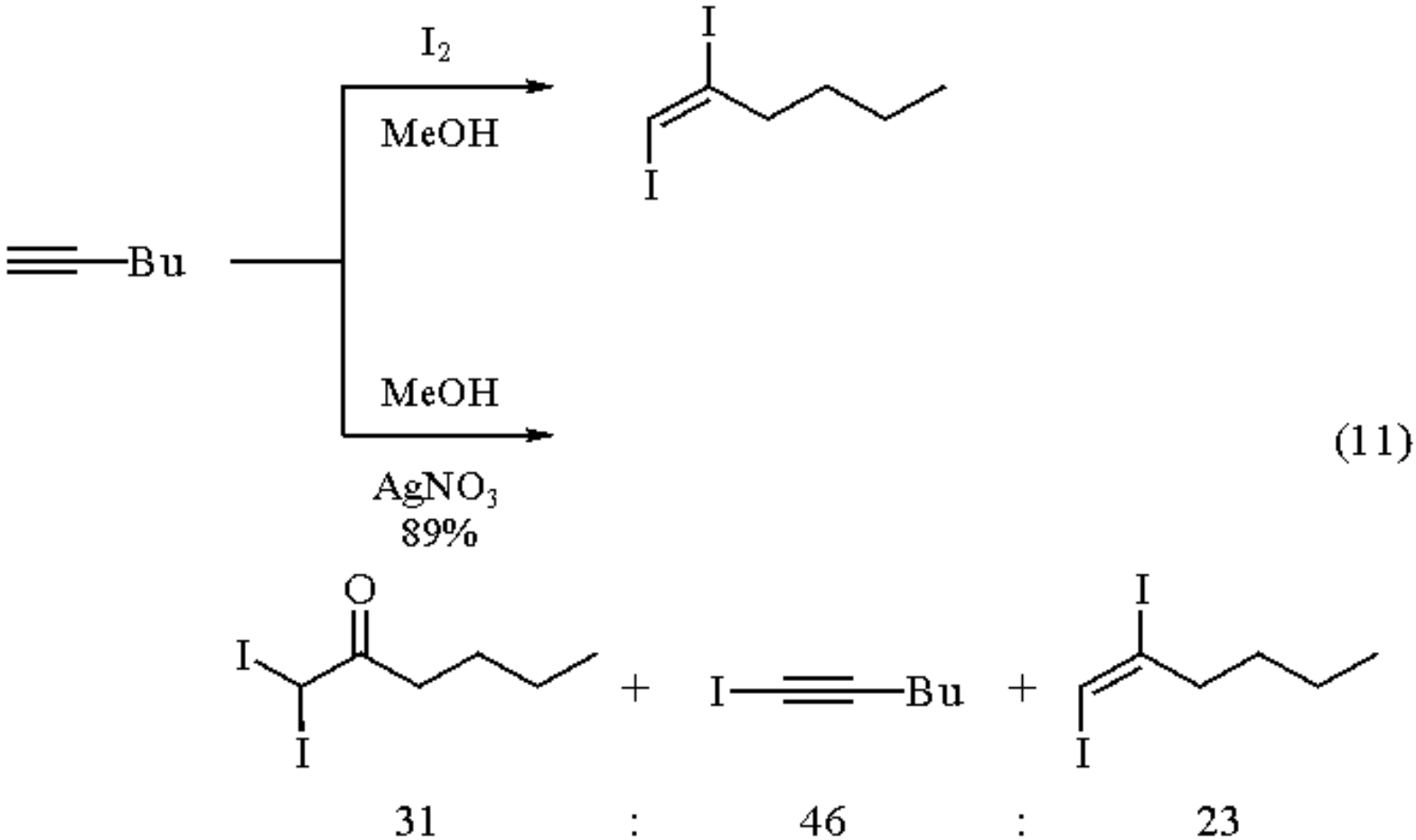

(11)

Cleavage of Cyclopropanes.

Iodine also reacts with cyclopropanes, leading to ring opening and formation of a diiodide.[28] The cyclopropane ring in benzocyclopropanes, for example, reacts with iodine to produce the diiodide (eq 12). Cyclopropylcarbinyl systems are opened by iodine, and when a leaving group is available, such as trimethyltin, an alkenyl iodide is formed (eq 13).

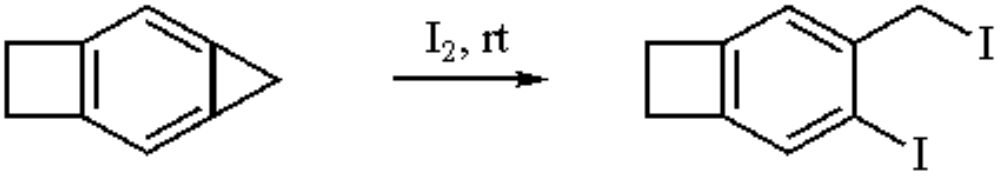

(12)

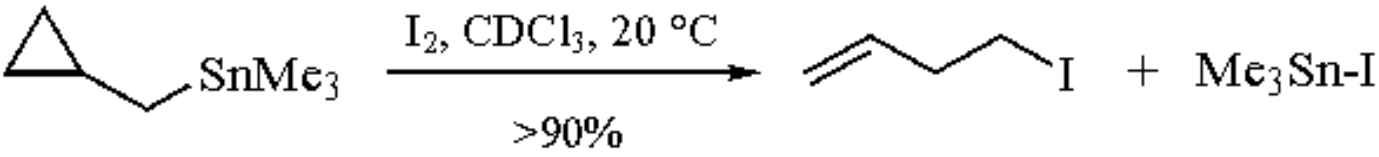

(13)

Conversion of Alcohols to Iodides.

Alcohols react with iodine and red phosphorus to produce a phosphorus iodide, in situ. Phosphorus iodides have poor shelf lives (they are unstable and decompose under mild conditions) and are prepared immediately prior to use. An

example is the conversion of cetyl alcohol to cetyl iodide in 85% yield (eq 14).[29] This is the most common method for the conversion of aliphatic alcohols to aliphatic iodides.

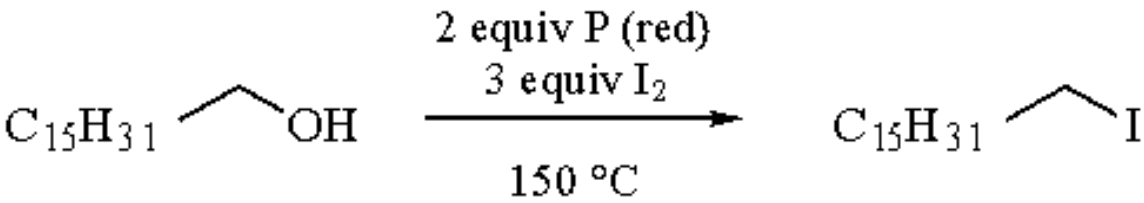

(14)

Reaction with Amines.

Dehydrogenation is another important reaction of iodine, and it is particularly useful for generation of enamines. Reaction of nuciferine with iodine, in dioxane containing sodium acetate, leads to an 87% yield of the enamine dehydronuciferine (eq 15).[30] Amines in general lead to enamines, as in the conversion of triethylamine to *N,N*-diethylvinylamine (eq 16).[5] This reaction can be applied to many systems.[31] For systems that do not contain an amino moiety, e.g. arenes such as ethylbenzene, a flow reactor and high temperatures (650 °C) are required for dehydrogenation. This particular example uses a molten ***Lithium Iodide*** reactor to convert ethylbenzene to the alkene product, styrene, in 96% yield (eq 17).[32]

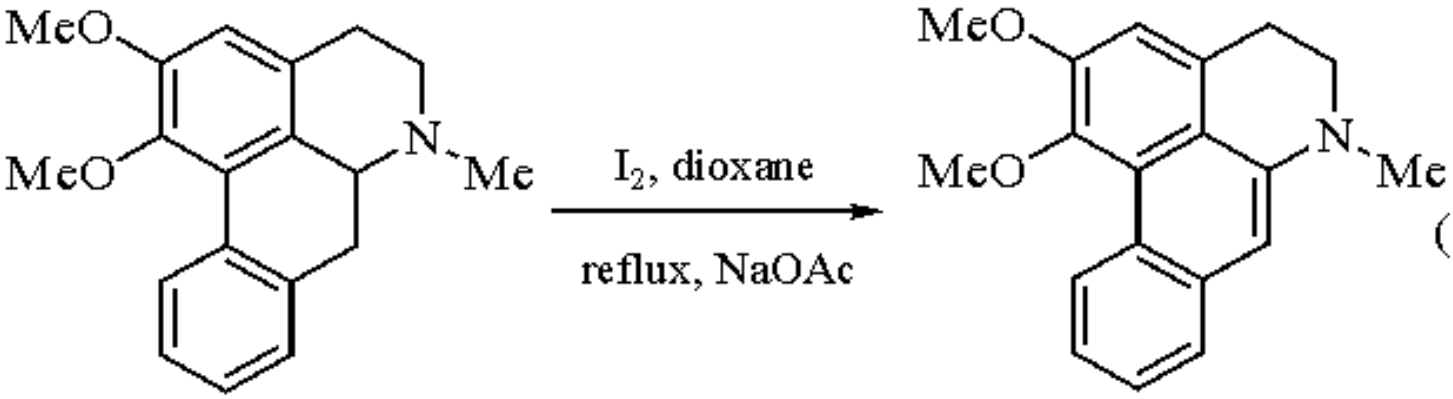

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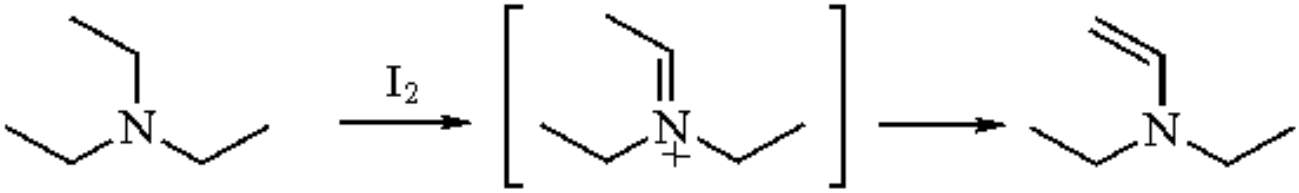

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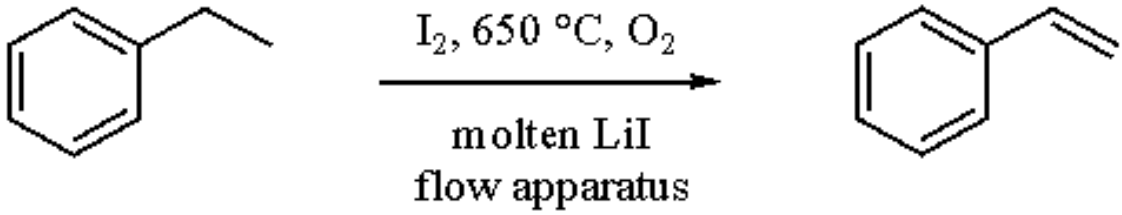

(17)

Reactions with Ketones, Aldehydes, and Carboxylic Acid Derivatives.

Iodine reacts with ketones as well as with alkenes. The reaction is usually done in the presence of base and proceeds via the enolate anion. This is the fundamental process that occurs in the Lieben iodoform reaction,[33] in which a methyl ketone reacts with iodine and sodium hydroxide to give iodoform (CHI_3) with oxidative cleavage of the methyl group to produce a carboxylic acid. The H_3C-C bond of methyl carbinols [RCH(OH)Me] is also cleaved with this reagent to give the corresponding acid and iodoform. The iodoform reaction constitutes a classical test for the presence of a methyl ketone moiety or a methyl carbinol moiety in an unknown molecule.

Oxidative cleavage is not always the case in this reaction, especially when sodium methoxide is substituted for sodium hydroxide. Steroidal ketones react with iodine and sodium methoxide to give a 58% yield of the α-iodo ketone, when air is excluded from the reaction (eq 18).[6] When oxygen is introduced, an 85% yield of the α,α-diiodo ketone is produced.[6] Reaction of aryl ketones can lead to a different result. 1,2-Diphenyl-1-ethanone reacts with iodine and sodium methoxide at low concentrations to give a 99% yield of 1,2-diphenyl-2-hydroxy-2-ethanone (eq 19).[34] When the concentration of the ketone substrate is increased, the yield of the hydroxy ketone is diminished and a dimer is formed, 1,2,3,4-tetraphenyl-1,4-butanedione (47% yield at 0.2 M).[34]

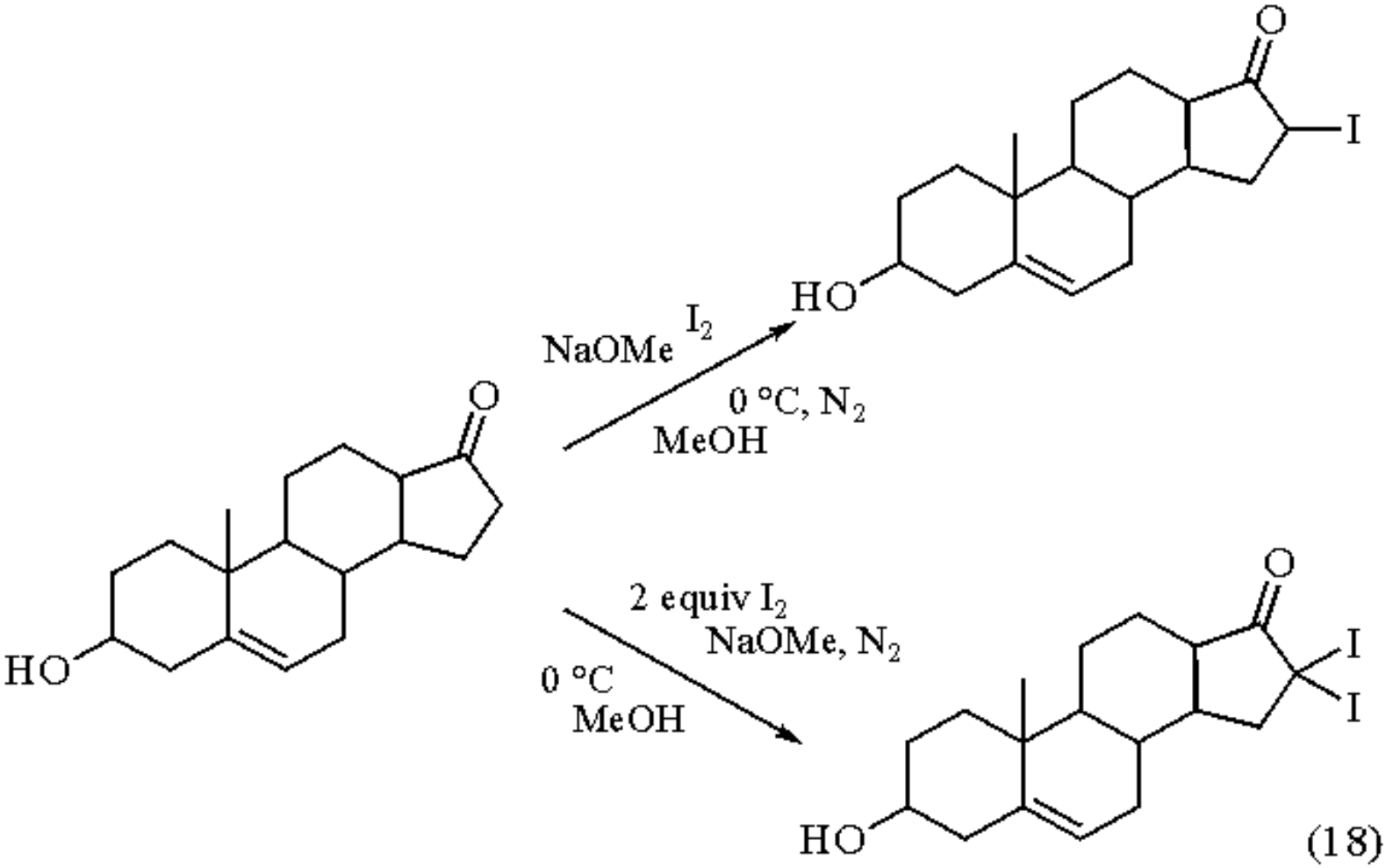

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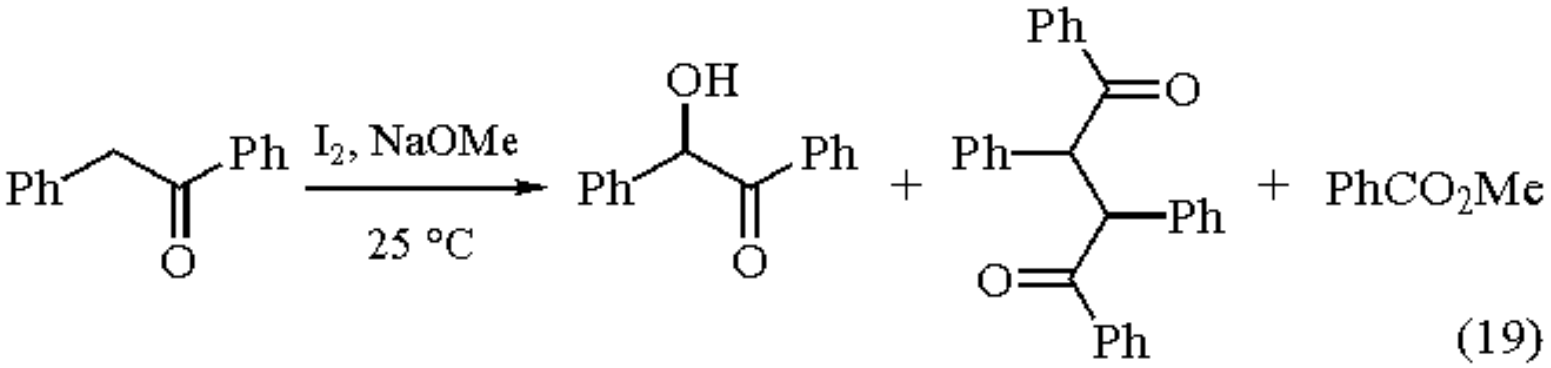

0.0071 M	99%	trace	trace
0.2 M	46%	47%	3%

The iodoform reaction clearly shows that iodine behaves as an electrophile in the presence of enolate anions, particularly enolate anions of carboxylic acid derivatives. When 6-heptenoic acid is treated with 2 equiv of ***Lithium Diisopropylamide***, and then quenched with iodine, a 70% yield of 2-iodo-6-heptenoic acid is obtained (eq 20).[7] In this particular reaction, 12% of the dicarboxylic acid 2,3-di-4-pentenyl-1,4-butanedioic acid is also obtained, leading to the belief that radical anions are produced in this reaction.[7] Such coupling reactions are also observed with esters which form succinic acid ester derivatives, as in the reaction of ethyl 2-methylpropanoate with 2 equiv of LDA and subsequent reaction with iodine to give an 85% yield of diethyl 2,2,3,3-tetramethyl-1,4-butanedioate (eq 21).[35]

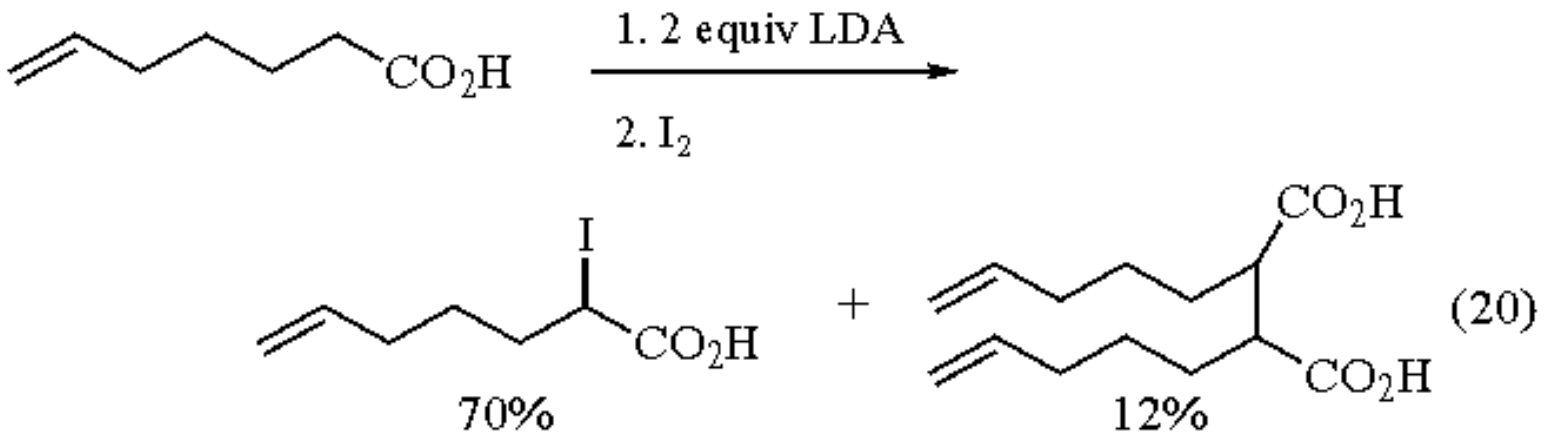

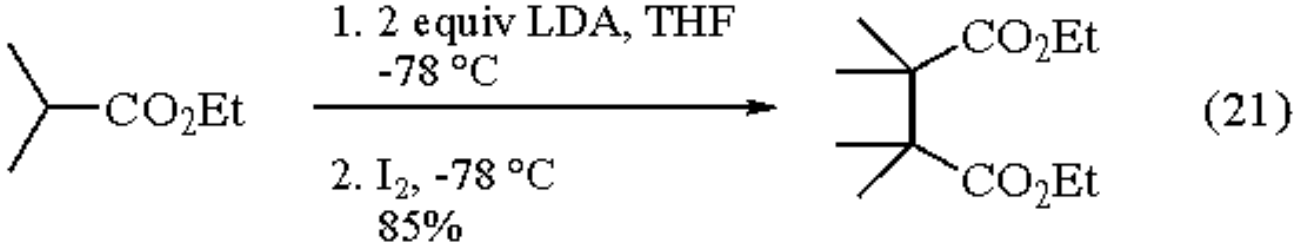

Carboxylic acid derivatives can react with iodine without an intermediary enolate anion to produce α-iodocarboxylic acids. α-Iodocarboxylic acid chlorides can also be produced, as when hexanoic acid reacts with iodine and ***Thionyl Chloride***, at 85 °C, to give an 80% yield of 2-iodohexanoyl chloride (eq 22).[36] Similarly, butanoic acid reacts with ***Chlorosulfonic Acid*** and iodine to give a 94% yield of 2-iodobutanoic acid (eq 23).[37] These examples are nothing more than the iodine analog of the Hell-Volhard-Zelinsky reaction.[38] The silver salt of pentanoic acid reacts with iodine to produce 1-iodobutane in 67% yield, where decarboxylation occurs under the reaction conditions (eq 24).[39] In general,

alkyl iodides are formed from silver carboxylates. This is the iodine version of the Hunsdiecker reaction.[40] Similar reaction occurs when mercury(II) oxide is added, although the yield is lower.

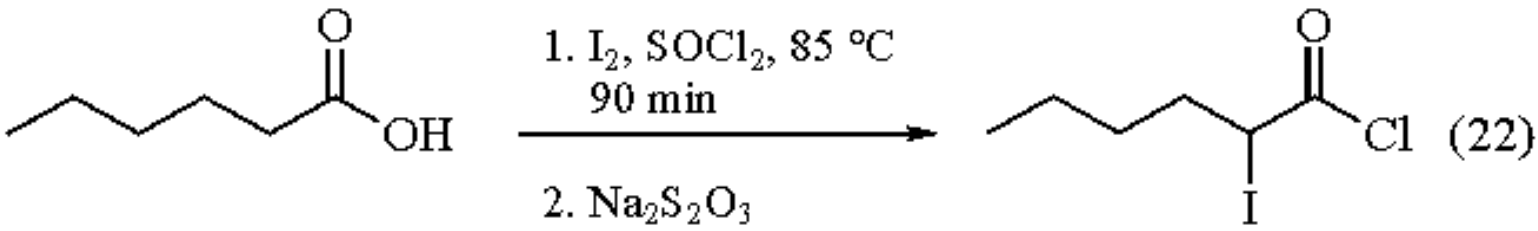

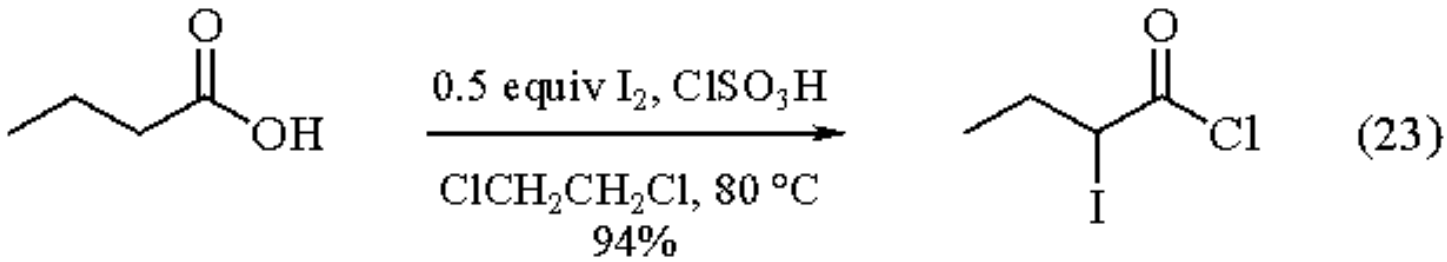

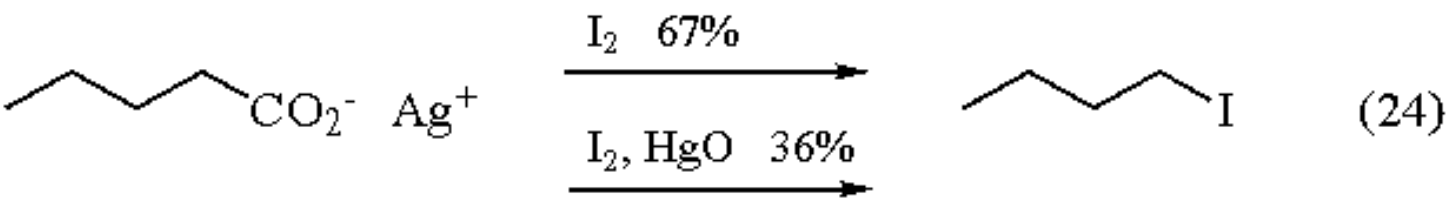

Iodination of Aromatic and Heteroaromatic Compounds.

Just as enolate anions react with the electrophilic iodine, so also other carbanions react. Iodoimidazoles can be formed, as when *N*-tritylimidazole reacts with ***n-Butyllithium*** and then with iodine, to give a 41% yield of 2-iodo-*N*-tritylimidazole (eq 25).[8]

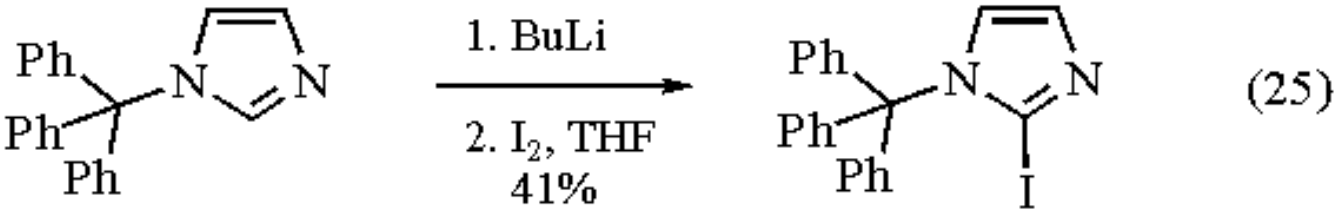

Iodoindoles can also be produced by this approach. Reaction of indole with *n*-butyllithium and quenching with iodine first produces an *N*-iodoindole, but this is unstable and rearranges under the reaction conditions to 3-iodoindole, in near quantitative yield (eq 26).[41] When this iodo derivative is converted to the *N*-phenylsulfonyl derivative, reaction with LDA and then iodine gives a 98% yield of 2,3-diiodo-*N*-phenylsulfonylindole.[41]

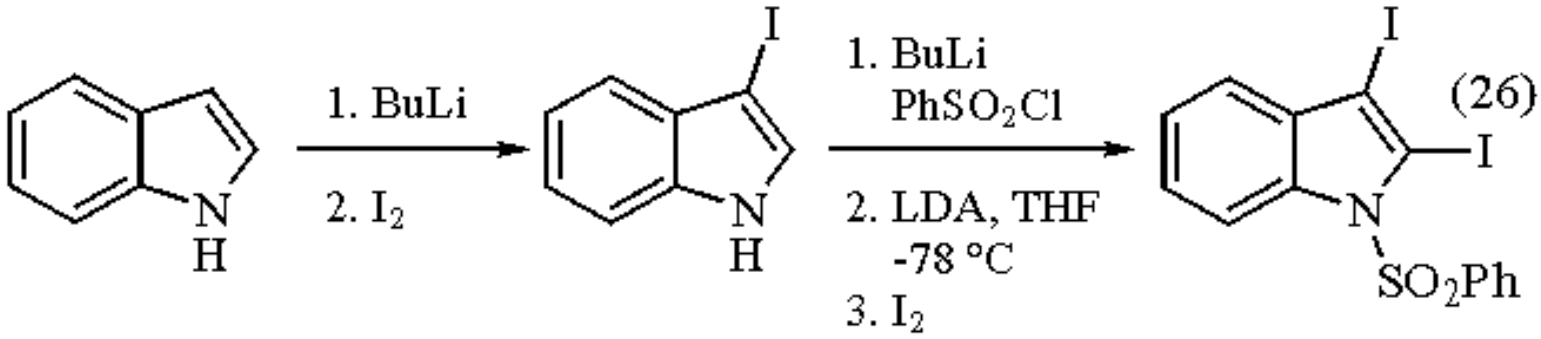

Iodopyridine derivatives can also be generated with this technique. 3-Fluoropyridine reacts with LDA and iodine to give a 50% yield of 4-iodo-3-fluoropyridine (eq 27),[42] and 2-chloropyridine reacts with *n*-butyllithium and then iodine to give a 60% yield of 2-chloro-3-iodopyridine (eq 28).[43]

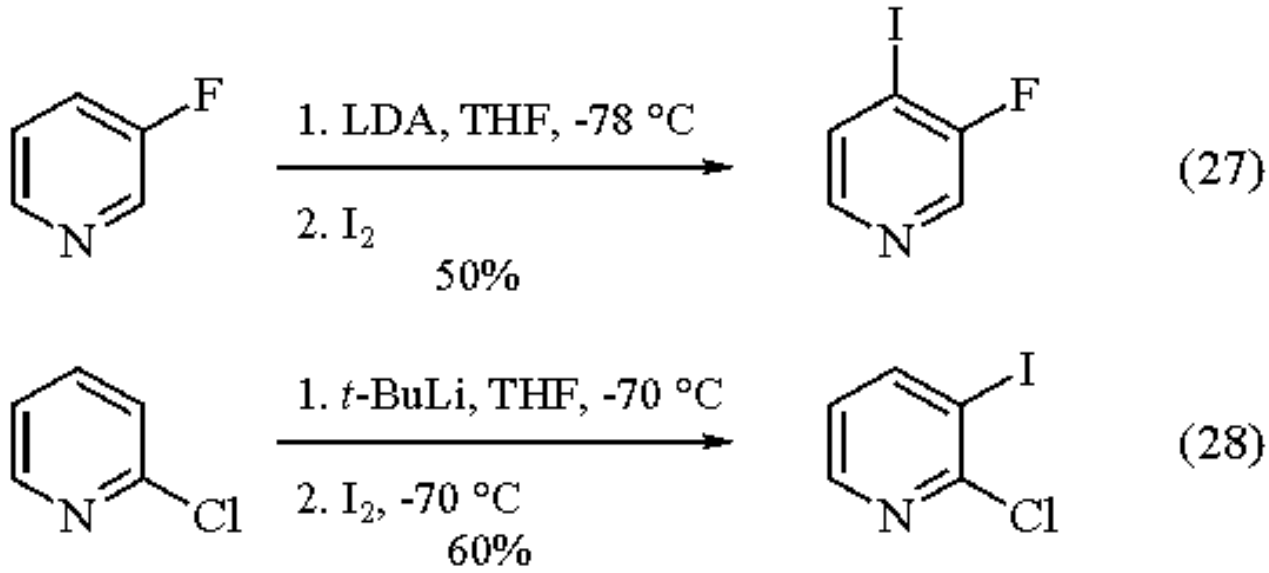

Iodofuran derivatives can be formed, as in the reaction of 2-(dimethyl-*t*-butylsilyl)furan-3-carboxylic acid with *n*-butyllithium and iodine, to give a 71% yield of the 4-iodofuran-3-carboxylic acid (eq 29).[44]

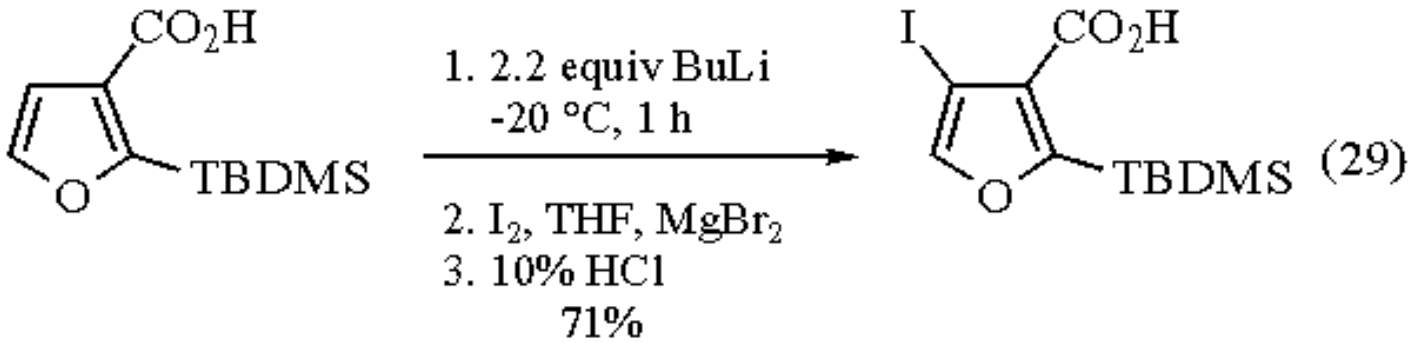

Simple aromatic derivatives can be iodinated to generate iodo-substituted aromatic compounds, if activating substituents are present on the aromatic ring. 1,3-Dicyanobenzene, for example, reacts with LDA and iodine to give a 79% yield of 2-iodo-1,3-dicyanobenzene (eq 30).[45] In general, unactivated aromatics are less useful since formation of the requisite carbanion is somewhat more difficult.

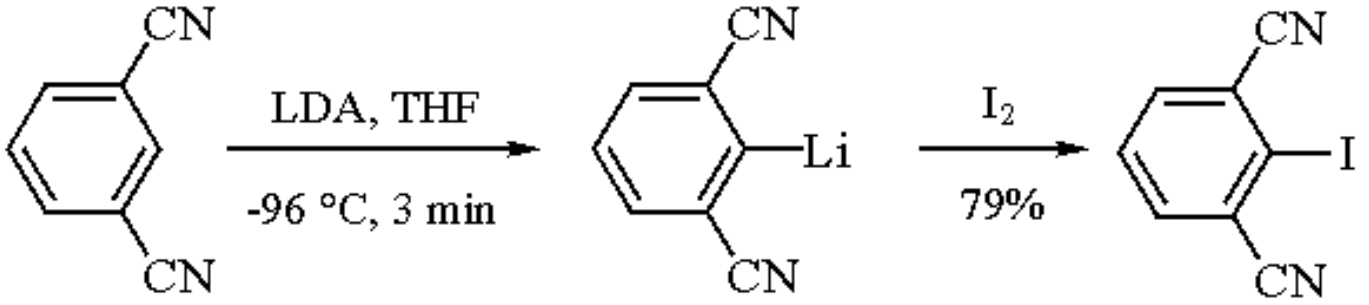

(30)

Conversion of Organoboranes to Iodides.

Another important area of chemistry where iodine reactions are important involves organoboranes. When an alkene is reacted with a borane to produce a trialkylborane, subsequent reaction with iodine and sodium hydroxide leads to an iodoalkane. 1-Decene reacts with tri-*n*-butylborane and then basic iodine to give a 65% yield of 1-iododecane (eq 31).[9]

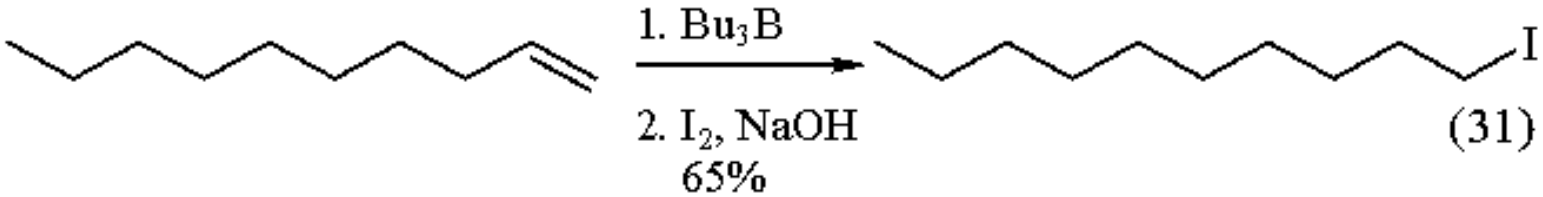

(31)

Substituted alkenes can also be prepared from vinylboranes by reaction with iodine and sodium hydroxide. Reaction of dicyclohexylborane with 1-hexyne gives the vinylborane, and subsequent reaction with basic iodine, in THF, gives a 93:7 *cis*:*trans* mixture of 1-cyclohexyl-1-hexene in 85% yield (eq 32).[10] When the reaction is done in dichloromethane, a 77:23 *cis*:*trans* mixture is produced, but in only 13% yield.[10a] The poor yield is probably due to the poor solubility of iodine in dichloromethane.

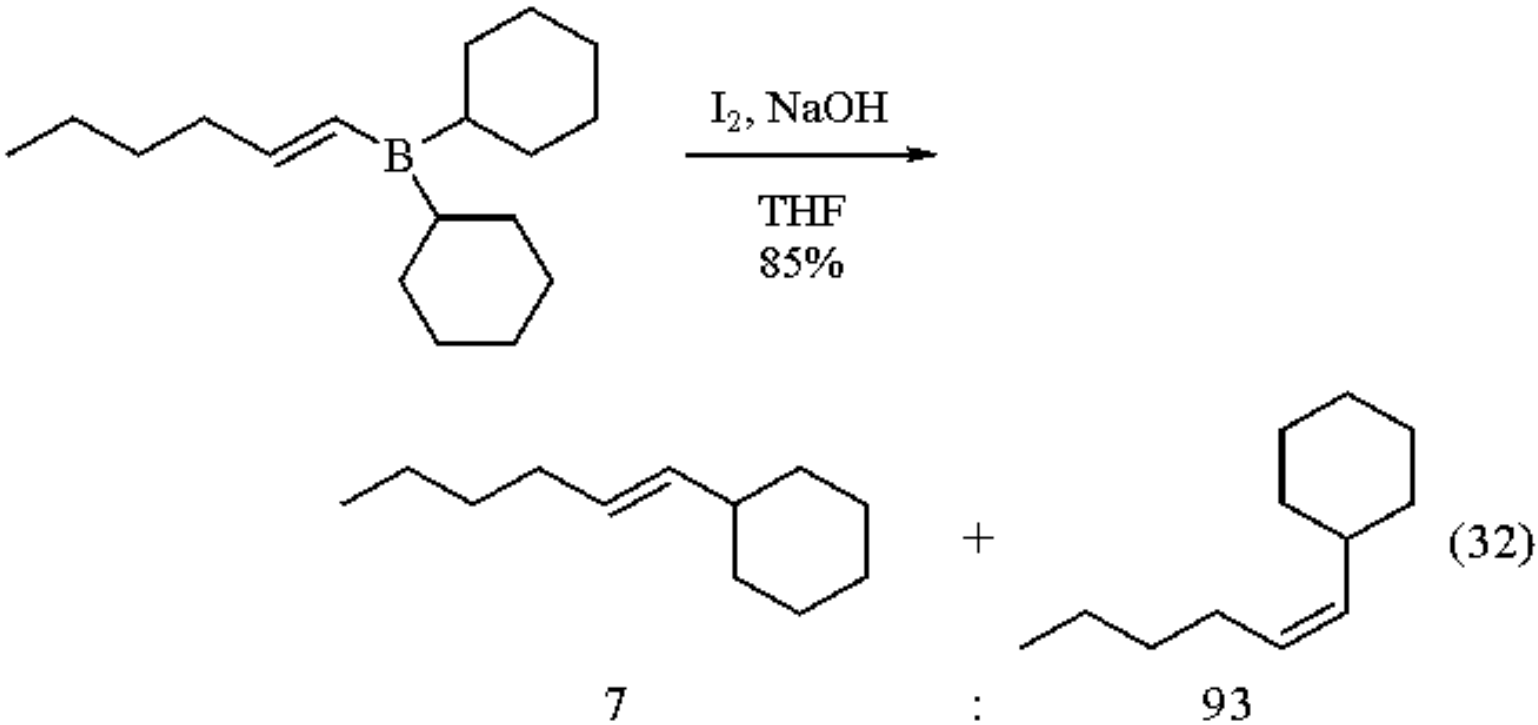

(32)

Miscellaneous Reactions.

There are several specialized reactions of iodine that are useful in certain applications. Iodine induces coupling of sodium cyclopentadienide to form 9,10-dihydrofulvalene.[46] Iodine has also been used to cleave iron-carbon bonds in organoiron species.[47] Iodine reacts with hydrazone derivatives to give vinyl iodides.[48]

Reaction with Organic Halides.

An important reaction of iodine is exchange with an alkyl iodide. The most common method for exchanging an iodide is the Finkelstein reaction,[49] which involves treatment of alkyl halides with ***Sodium Iodide*** to produce alkyl iodides via an S_N2 reaction. Reaction of 1-bromobutane and sodium iodide in dry acetone, for example, gives 1-iodobutane. This exchange also occurs with alkyl iodides. The metal iodides used in this reaction are commercially available, but can be prepared from iodine.

Iodine itself is capable of exchanging the halide atom in alkyl halides, including alkyl iodides, to produce alkyl iodides. The reaction temperatures required are usually greater than 150 °C.[50] Aryl iodides undergo this exchange reaction at even higher temperatures (150-190 °C).[51] α-Iodo ketones also react with iodine, but this occurs at ambient temperatures.[52] The product of these reactions is, of course, another iodide but this is very important in radiolabeling using radioactive iodine isotopes. All of the reactions of iodine involve the use of the natural abundance stable isotope of iodine, ^{127}I. Radiolabeled molecules can be incorporated in a wide range of biological and mechanistic studies. There are at least 10 available isotopes of iodine, but only three are commonly used for labeling: ^{123}I, ^{125}I, and ^{131}I. If these isotopic iodines are used in the preceding reactions, radiolabeled iodides are produced. In the case of the Finkelstein reaction, sodium iodide or ***Potassium Iodide*** can be produced by synthesizing those salts with radiolabeled iodine. A variety of organic molecules have been radiolabeled for use in biological studies. These include fatty acids,[53] aniline derivatives,[54] quinolines,[55] nucleic acids,[56] steroids,[57] alkyl iodides,[58] aryl iodides,[59] carboxylic acids,[60] and carbohydrates.[61]

Related Reagents.

Dimethyl Sulfoxide-Iodine; ***Iodine-Aluminum(III) Chloride-Copper(II) Chloride***; ***Iodine-Cerium(IV) Ammonium Nitrate***; ***Iodine-Copper(II) Acetate***; ***Iodine-Copper(I) Chloride-Copper(II) Chloride***; ***Iodine-Copper(II) Chloride***; ***Iodine-Nitrogen Tetroxide***; ***Iodine-Potassium Iodate***; ***Iodine-Silver Acetate***; ***Iodine-Silver Benzoate***; ***Iodine-Silver(I) Fluoride***; ***Iodine-Silver Trifluoroacetate***; ***Lead(IV) Acetate-Iodine***; ***Mercury(II) Oxide-Iodine***; ***Thallium(I) Acetate-Iodine***; ***Triphenylphosphine-Iodine***.

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Iodine-Aluminum(III) Chloride-Copper(II) Chloride

I_2-$AlCl_3$-$CuCl_2$

(I_2)

[7553-56-2] · I_2 · Iodine-Aluminum(III) Chloride-Copper(II) Chloride · (MW 253.80)
($AlCl_3$)

[7446-70-0] · $AlCl_3$ · Iodine-Aluminum(III) Chloride-Copper(II) Chloride · (MW 133.33)
($CuCl_2$)

[7447-39-4] · Cl_2Cu · Iodine-Aluminum(III) Chloride-Copper(II) Chloride · (MW 134.45)

(iodinating reagent for arenes)

Physical Data: $AlCl_3$: mp 192 °C (2.5 atm); subl. 180 °C. $CuCl_2$: mp 498 °C; *d* 3.054 g cm^{-3}.

Solubility: $AlCl_3$: sol benzene, CCl_4, chloroform; reacts violently with H_2O. $CuCl_2$: sol H_2O, ethanol, acetone.

Form Supplied in: $AlCl_3$: commercially available; colorless hexagonal plates. $CuCl_2$: yellow to brown, deliquescent microcrystalline powder.

Handling, Storage, and Precautions: $AlCl_3$: moisture sensitive. $CuCl_2$: irritating to skin, mucous membranes; forms dihydrate in moist air. Iodination reactions using this combination of reagents should be performed in a fume hood.

Iodinating Reagents.

Aryl iodides can be prepared by reaction of arene derivatives with ***Iodine*** and ***Antimony(V) Chloride***[1]

and copper salts.[2,3] These procedures can be applicable to more reactive substrates such as anisole and xylenes, but not to less reactive substrates such as benzene and halogenated benzene. The reaction of arenes containing halogen with I_2 and a mixture of ***Aluminum Chloride*** and ***Copper(II) Chloride*** gives the corresponding aryl iodides in good yield (eq 1).[4] The reaction fails with ethyl benzoate, acetophenone, and *o*-nitroanisole. The reagents are used in the ratio I_2:$AlCl_3$:$CuCl_2$ = 0.5:1:1.

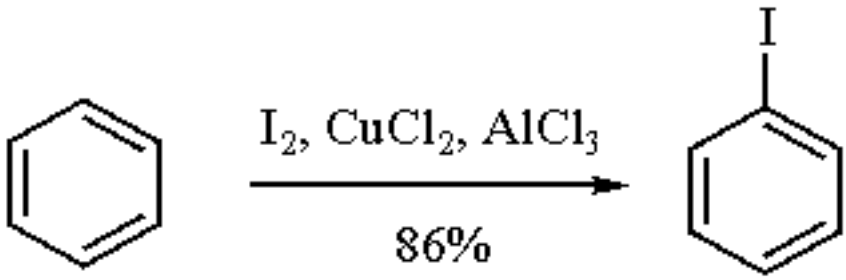

(1)

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Iodine Azide[1]

[14696-82-3] · IN_3 · Iodine Azide · (MW 168.93)

(additions to multiple bonds;[1-4] regioselective and stereoselective introduction of the azide function[1-3] and other nitrogen functions including amines; synthesis of aziridines[5] and azirines[6])

Physical Data: dark crystals;[7] explosive when neat.

Solubility: sol most organic solvents.

Form Supplied in: not available commercially; prepared in situ in solution.

Preparative Methods: the first reported preparation[7] from AgN_3 and I_2 is not recommended. IN_3 can be prepared in situ from ***Sodium Azide*** and ***Iodine Monochloride*** preferably in MeCN,[2] DMF, ether, or CH_2Cl_2.[2,3] It can also be prepared from TlN_3 and ICl[3c] in MeCN or CH_2Cl_2,[3] or from ***N-Iodosuccinimide*** and ***Hydrazoic Acid*** in CH_2Cl_2.[3] The following is a typical procedure for addition to alkenes:[2] to a slurry of 15.0 g (0.25 mol) of NaN_3 in 100 mL of MeCN at -10 to 0 °C is added, over 10-20 min, 18.3 g (0.113 mol) of ICl neat or in MeCN. After 10-20 min of further stirring, 0.1 mol of alkene is added neat or in MeCN and the mixture is warmed to 20 °C and stirred for 8-24 h. The red-brown slurry is poured into 250 mL of water and extracted three times with 85 mL portions of ether. The combined ether fractions are washed with 5% aq sodium thiosulfate until colorless (see precautions), then with water, and dried. Removal of the solvent in vacuo is followed by chromatography (neutral alumina) to afford the iodo azide adduct in 80-90% yield.

Handling, Storage, and Precautions: solutions of IN_3 in MeCN can be stored in the refrigerator for 1 d. Explosions have been reported on evaporation of solutions of IN_3 to dryness. Therefore, after reaction with multiple bonds, the mixture should be washed with sodium bisulfite until colorless to destroy excess IN_3 reagent. Violent reaction can also occur on addition of IN_3 to alkenes containing low-valent S-functions. An explosion shield should be used when handling this reagent. Operations should be conducted in a fume hood.

Additions to Alkenes.

Addition of IN_3 to alkenes (see also ***Bromine Azide***) usually proceeds via a three-membered ring iodonium species,

resulting from attack of I^+ on the double bond. The reaction is highly stereoselective (*anti*) and regioselective. Thus *cis*- and *trans*-2-butene give stereospecifically the *threo* and *erythro* adducts, respectively. The azide-carbon bond usually forms at the more substituted carbon or the one better able to support a positive charge in the transition state. *trans*-1-Phenylpropene gives, stereo- and regiospecifically, *erythro*-1-azido-2-iodo-1-phenylpropane (eq 1). *Anti* elimination of HI from the adduct leads to a vinyl azide.[4a] However, steric hindrance can influence the position of attack by azide ion. Thus *t*-butylethylene affords the terminal azide (eq 2).[2b]

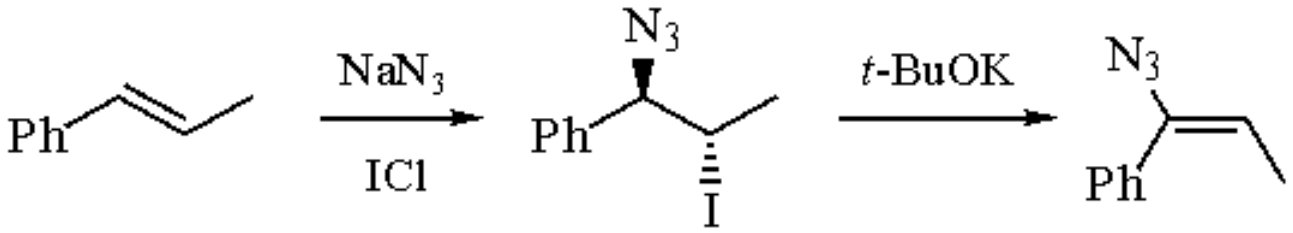

(1)

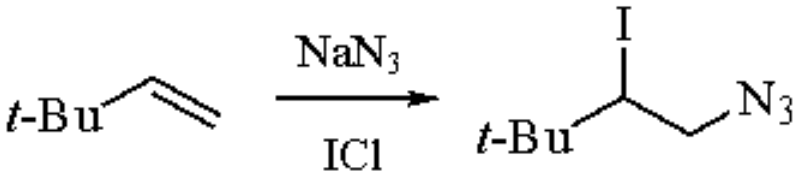

(2)

The structure of the adduct with phenylcyclohexene has been questioned[8a] but it has been proven to be the one expected (eq 3).[8b,c] With 2-cholestene the *trans* diaxial adduct, 2β-azido-3α-iodocholestane, results from the α-iodonium species,[1,2] but products from β-attack on other steroid alkenes are also known.[9a] In rare cases, *syn* addition has been reported,[9] for instance to strained cyclobutenes.[9b,c]

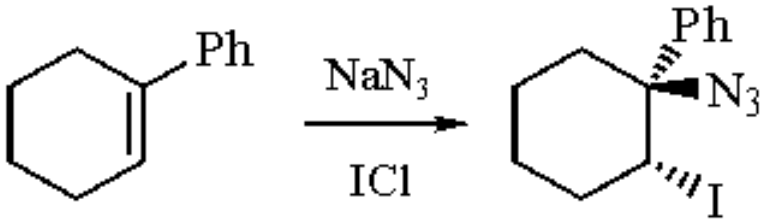

(3)

Addition of IN_3 to conjugated ketones can lead to a mixture of regiosomers, sometimes depending on the presence of oxygen or on the method of generation of the reagent.[3,4] In such cases the addition can proceed via a radical mechanism,[3,11] in which the azide radical rather than I^+ is the attacking species and different regioisomers can result.[3] For instance, cyclopentenone affords 2-iodo-2-cyclopentenone, while cyclohexenone gives a mixture of products.[3e]

Enantioselective addition of IN_3 to conjugated amides derived from sultams or oxazolidones as chiral auxiliaries has been reported.[10] Although diastereoselection only averages 34% (eq 4), crystallization raises this to 94%.

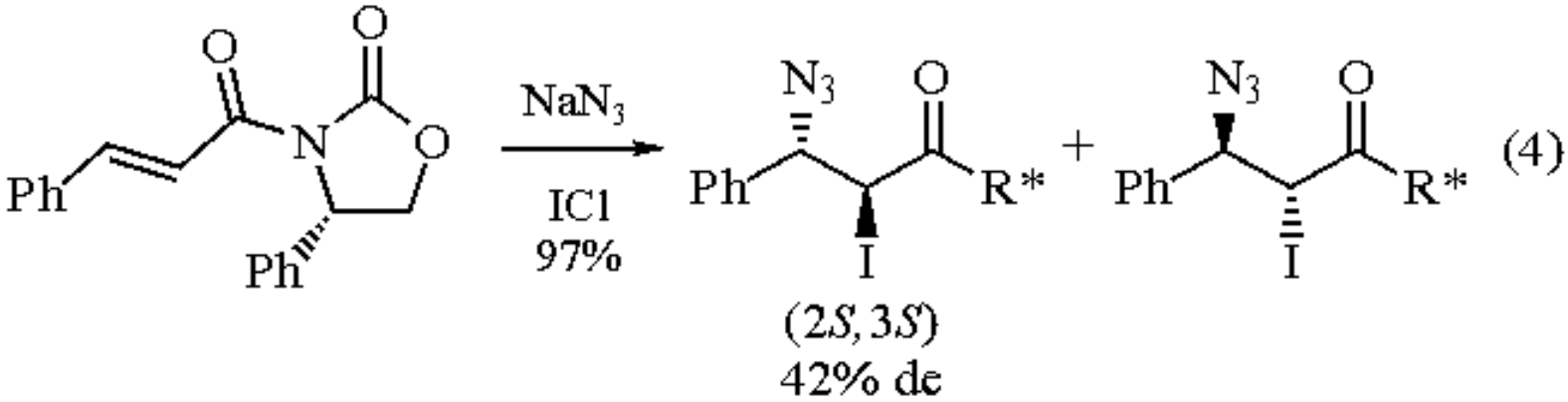

Enol ethers, as expected, give α-azido-β-iodo ethers,[12a] but benzofuran and some indoles give a mixture of *cis*- and *trans*-2,3-diazido products.[12b] Allenes can give mono- or bis-adducts.[13] When the monoadduct is an allyl azide, then [3,3] rearrangements are observed (eq 5). When the monoadduct is a vinyl azide, addition of a second molecule of IN_3 is faster than the first addition and a bis-adduct results. The cyclopropane group in norcarane is opened by IN_3 to give a mixture of products.[14]

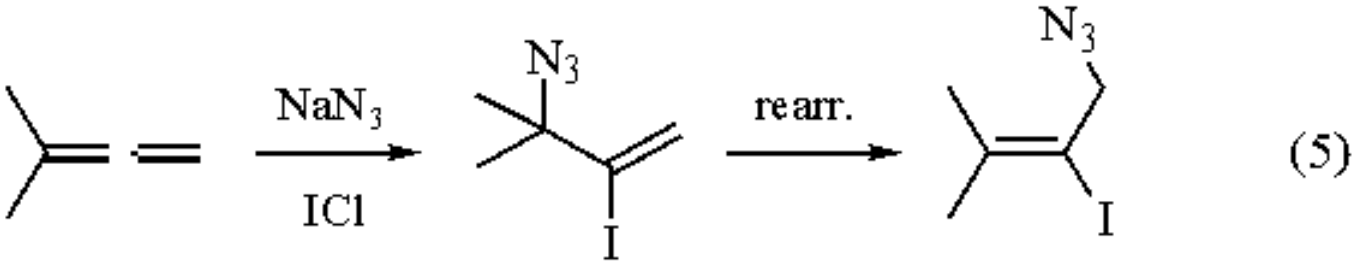

Synthesis of Aziridines.

IN_3 addition to alkenes followed by ***Lithium Aluminum Hydride*** (or ***Diborane***) reduction is a convenient method (Hassner aziridine synthesis) for the preparation of aziridines.[6] This method has been applied to the synthesis of monoaziridine derivatives of terpenes such as squalene, farnesol, and geraniol (eq 6).[15]

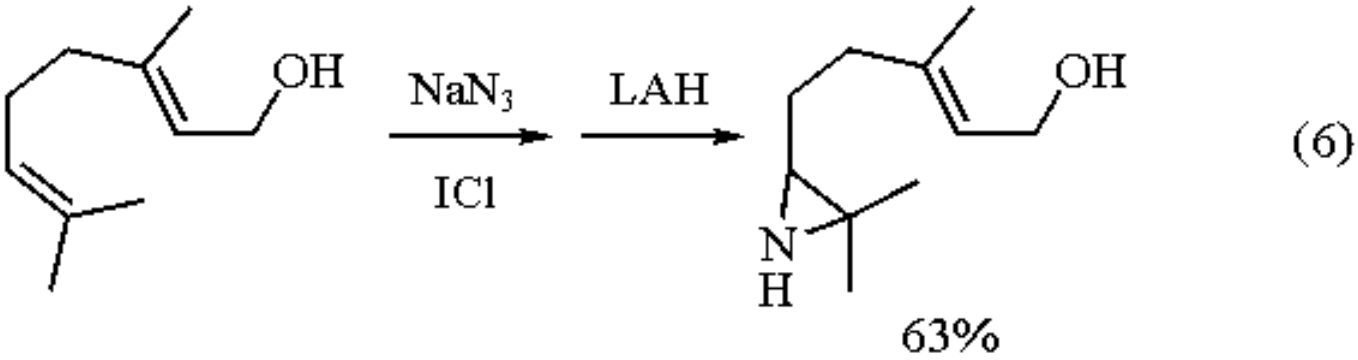

With *anti*-oriented iodo and azide functions, LAH leads to a large amount of IN_3 elimination.[6] Many other reagents can be used for the reduction of IN_3 adducts to aziridines,[6,16] including ***Hydrazine-Raney Nickel***, $Me_2NH.BH_3$, and phosphines or phosphites; the last reagents lead to *N*-phosphorylated aziridines.[16a] When alkyl- or aryldichloroborane is used, it provides stereospecific entry into *N*-substituted aziridines (eq 7).[16d]

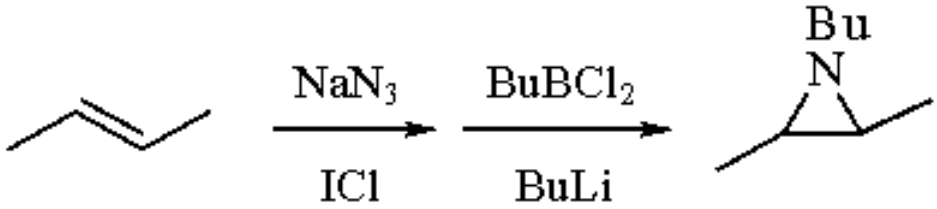

(7)

Selective reduction of the adducts has also been achieved, as in the formation of β-amino acids from acrylic esters.[17] Rearrangements during IN_3 additions have been observed in rearrangement-prone systems such as methylenenorbornene, benzonorbornadiene, the pinenes, and tritylethylene.[18] In α- and β-pinene, rearrangement is accompanied by trapping with MeCN followed by N_3^- to afford tetrazoles.[19]

Synthesis of Vinyl Azides and Azirines.

Various bases, especially ***Potassium t-Butoxide***, cause stereospecific elimination of HI from the adducts and the resulting vinyl azides serve as useful intermediates for the synthesis of azirines (eq 8),[6,20] ketones,[21] and cyanoketenes,[22] and for the amination of aromatic compounds.[23]

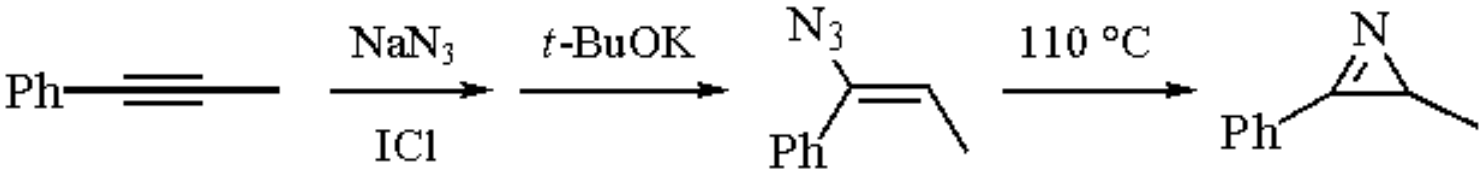

(8)

Miscellaneous Reactions.

Addition of IN_3 to methylphenylacetylene leads to 2-azido-1-iodo-1-phenylpropene.[24] IN_3 also adds to isocyanides to produce iodotetrazoles.[2] Dimethyl thioacetals react with IN_3 to afford an α-azido thioether which can undergo Schmidt rearrangement in the presence of ***Trifluoroacetic Acid***.[25]

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Iodine-Cerium(IV) Ammonium Nitrate

I_2-$(NH_4)_2Ce(NO_3)_6$

(I_2)

[7553-56-2] · I_2 · Iodine-Cerium(IV) Ammonium Nitrate · (MW 253.80) ($(NH_4)_2Ce(NO_3)_6$)

[15078-94-1] · $CeH_8N_8O_{18}$ · Iodine-Cerium(IV) Ammonium Nitrate · (MW 548.28)

(iodination of ketones, alkenes, and α,β-unsaturated ketones; oxidative aromatization of cyclohexenones; *cis*-hydroxylation of alkenes)

Physical Data: $(NH_4)_2Ce(NO_3)_6$: dec 225 °C.

Solubility: $(NH_4)_2Ce(NO_3)_6$: sol H_2O (136 g/100 mL at 12 °C), MeOH, EtOH, MeCN.

Form Supplied in: $(NH_4)_2Ce(NO_3)_6$: orange-red monoclinic crystals. *Drying:* $(NH_4)_2Ce(NO_3)_6$ can be dried by heating at 90 °C for 8 h.

Handling, Storage, and Precautions: bottles of $(NH_4)_2Ce(NO_3)_6$ should be kept tightly sealed to preclude contact with moisture and air. This reagent should be handled in a fume hood.

Iodination.

Oxidative iodination of ketones can be accomplished by utilizing ***Cerium(IV) Ammonium Nitrate*** (CAN) (0.5 molar equiv) and ***Iodine*** (0.5 molar equiv) at 25-50 °C in AcOH or MeOH (eq 1). The reaction is regioselective, providing the more highly substituted α-iodo ketones in very good yields (eq 2). This method is superior to an earlier alternative using I_2-$Cu(OAc)_2$ in AcOH.[1] Direct iodination of some ketones using I_2-CAN in MeCN or AcOH at 80 °C-reflux gives the corresponding α,α´-diiodo ketones in good yield (eq 3).[2] Asakura and Robins have reported a mild procedure for selective preparation of 5-iodouracil nucleosides with I_2-CAN (eq 4).[3] The method provides advantages over procedures reported heretofore. Cycloalkenes and steroidal alkenes react with I_2 in ROH (R = Me, Et, *n*-Pr, and *i*-Pr) in the presence of CAN to give the corresponding vicinal alkoxyiodocycloalkanes in good yield (eq 5). In the case of *t*-BuOH, *trans*-iodo nitrates are obtained (eq 6).[4] Moreover, it is interesting that cycloalka-1,3-dienes react with I_2 in the presence of CAN to give the *trans*-2-alkoxy-1-iodo compounds, not the 1,4-addition products (eq 7).[5] In the case of α,β-unsaturated ketones and

esters, *trans*-β-alkoxy-α-iodo derivatives are also obtained in 70-92% yield (eq 8).[6] Similar reagents have been used for the synthesis of aryl iodides (eq 9).[7]

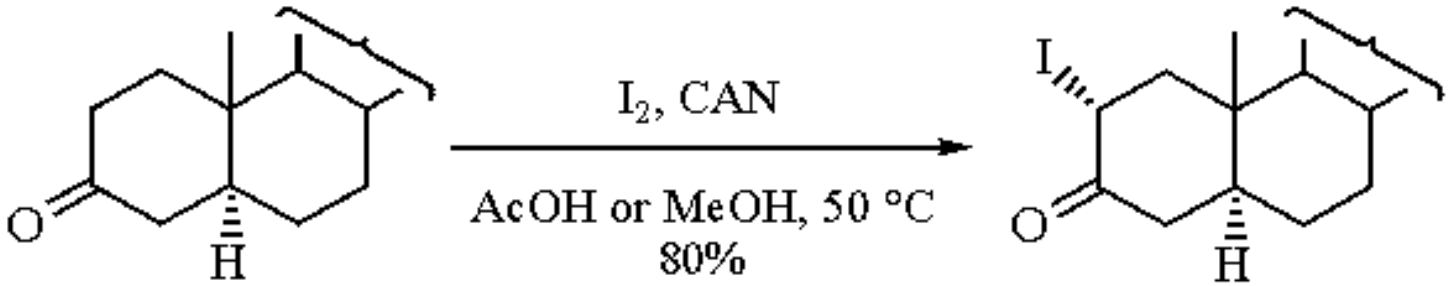

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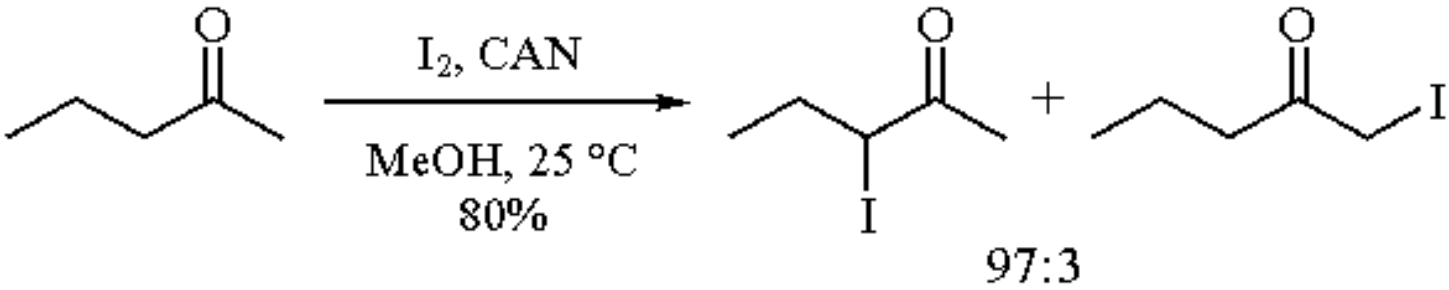

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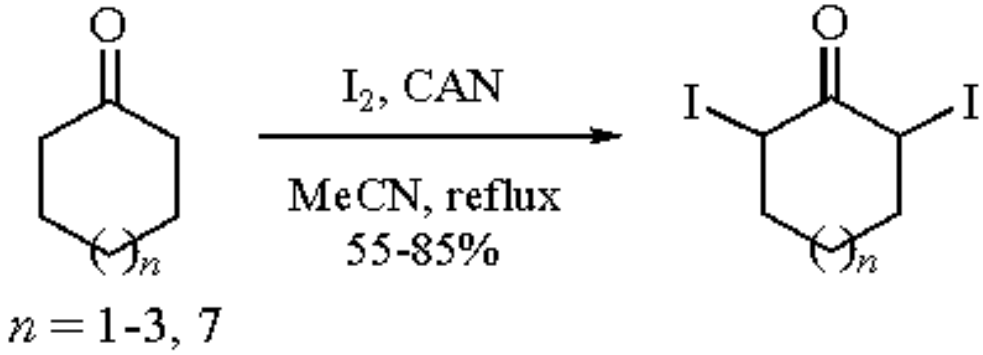

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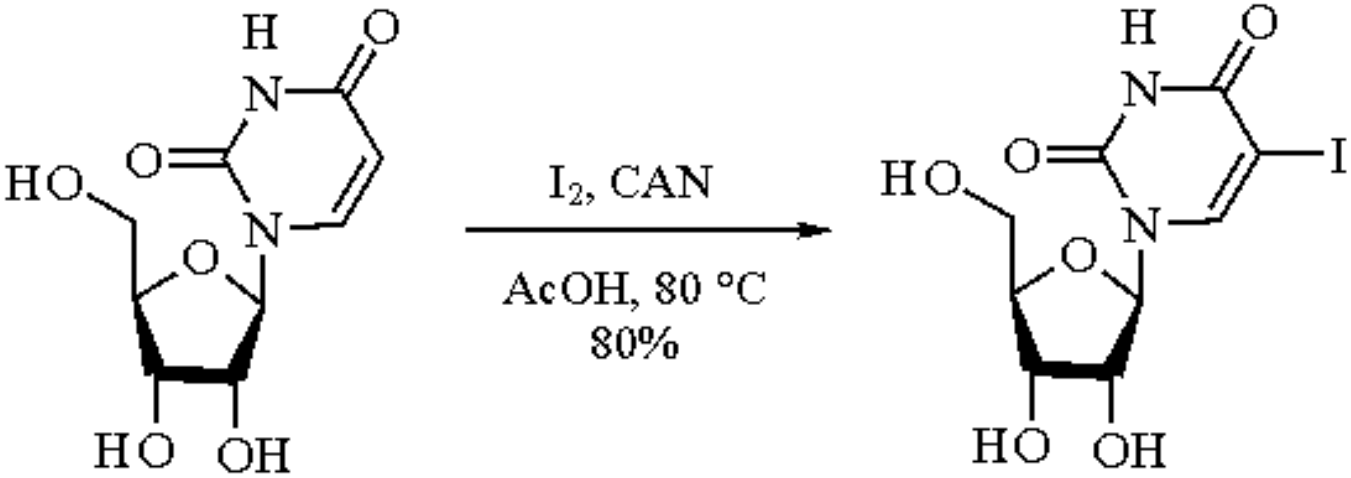

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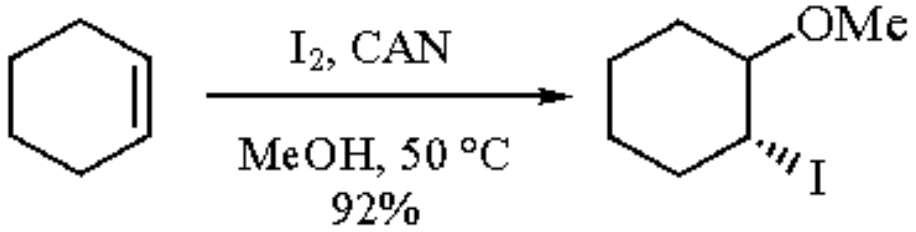

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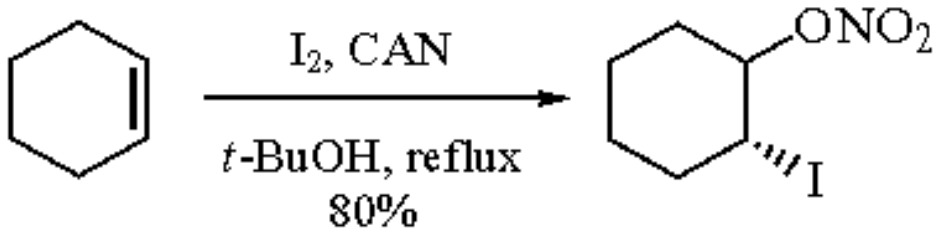

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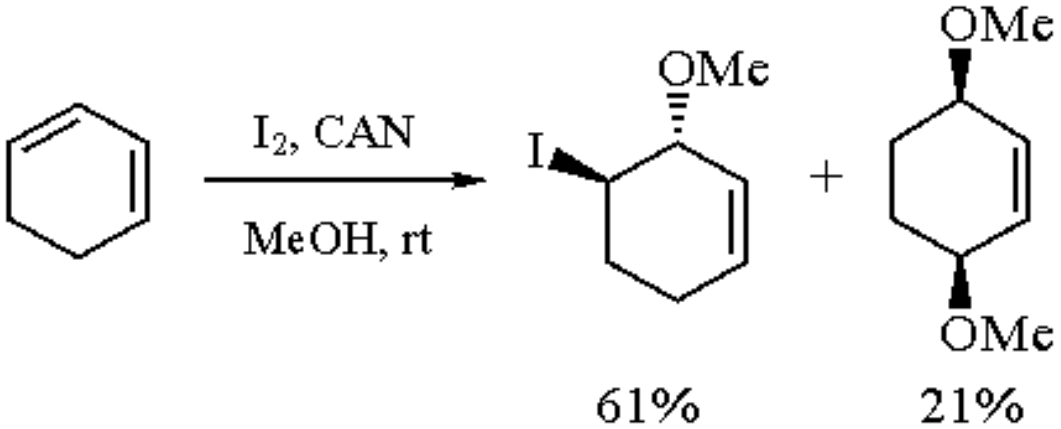

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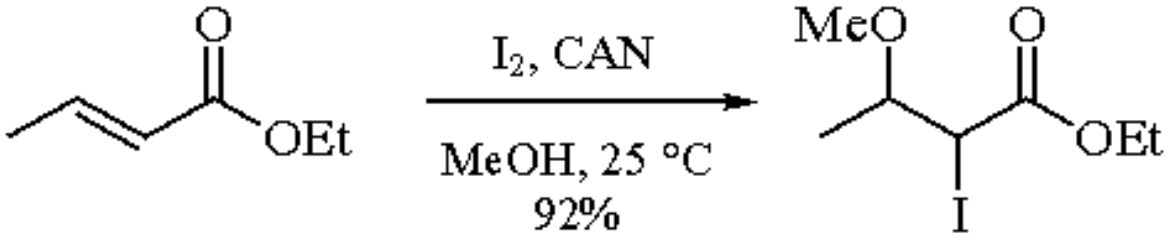

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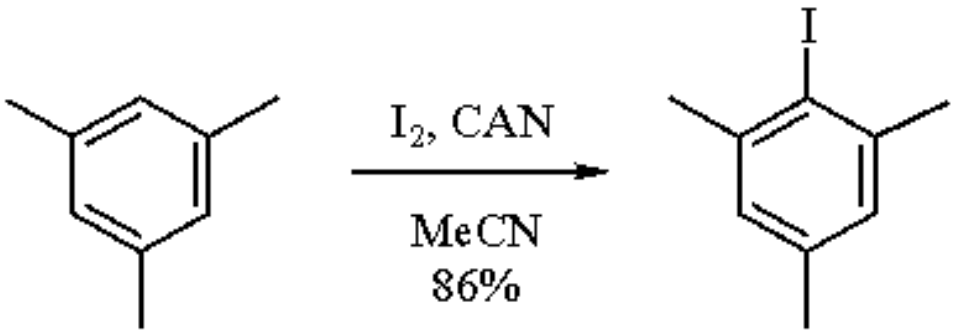

(9)

Oxidations.

Much work has been reported on the *cis*-hydroxylation of alkenes using the Prévost reaction and Woodward

modification. The reaction of alkenes with I_2 and CAN in AcOH gives a mixture of products which can be hydrolyzed by KOH in MeOH-H_2O to *cis*-diols in high yields (eq 10).[8] The oxidative aromatization of α,β-unsaturated cyclohexenones to ethers has been investigated.[9-14] The reaction of cyclohexenone derivatives with I_2-CAN in ROH (R = Me, Et, *n*-Pr, *i*-Pr, Bu) under reflux gives the corresponding alkyl phenyl ethers in good yields (eq 11). This reaction is also applicable to diols (ethylene glycol, 1,3-propanediol, 1,4-butanediol).[15]

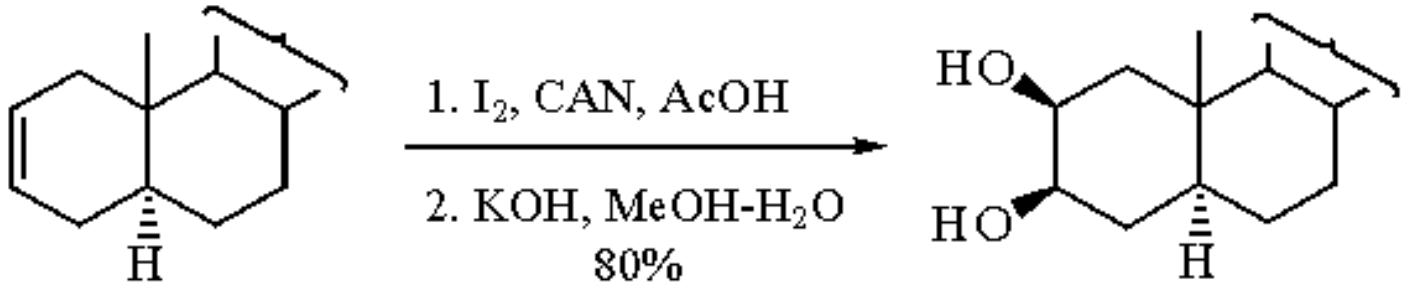

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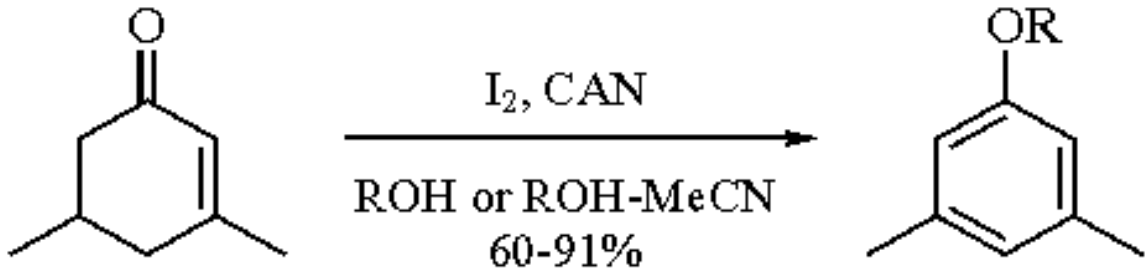

(11)

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15. Horiuchi, C. A.; Fukunishi, H.; Kajita, M.; Yamaguchi, A; Kiyomiya, H.; Kiji, S. *CL* **1991**, 1921.

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Iodine-Copper(II) Acetate

I_2-$Cu(OAc)_2.H_2O$

(I_2)

[7553-56-2] · I_2 · Iodine-Copper(II) Acetate · (MW 253.80) ($Cu(OAc)_2$)

[142-71-2] · $C_4H_6CuO_4$ · Iodine-Copper(II) Acetate · (MW 181.65) ($Cu(OAc)_2.H_2O$)

[6046-93-1] · $C_4H_8CuO_5$ · Iodine-Copper(II) Acetate · (MW 199.67)

(iodination of ketones, alkenes, and aromatic compounds; oxidation of cycloalkenes and alkyl-substituted ketones)

Physical Data: $Cu(OAc)_2.H_2O$: mp 115 °C; *d* 1.882 g cm^{-3}.

Solubility: $Cu(OAc)_2.H_2O$: sol H_2O, ethanol; slightly sol ether, glycerol.

Form Supplied in: $Cu(OAc)_2.H_2O$: dark blue-green solid.

Handling, Storage, and Precautions: both reagents are toxic and should be handled in a fume hood.

Iodination.

The I_2-$Cu(OAc)_2$ reagent can be used for the directed iodination of ketones in acetic acid at 60 °C, leading to the corresponding α-iodo ketones (eqs 1 and 2).[1] Cyclohexene and steroidal alkenes react with ***Iodine*** in MeOH or AcOH in the presence of ***Copper(II) Acetate*** to give *trans*-1-iodo-2-methoxycyclohexane (eq 3)[2] and steroidal *trans*-iodo acetates (eq 4) in good yields.[2] Activated arenes such as mesitylene, aniline, and anisole can be iodinated in high yield by this reagent (eq 5).[3] Although phenol is iodinated mainly at the *ortho*-position, aniline and anisole are iodinated at the *para*-position. Iodination of estrogen derivatives having a hydroxy group at C-3 regioselectively affords 2-iodoestradiol derivatives (eq 6).[4]

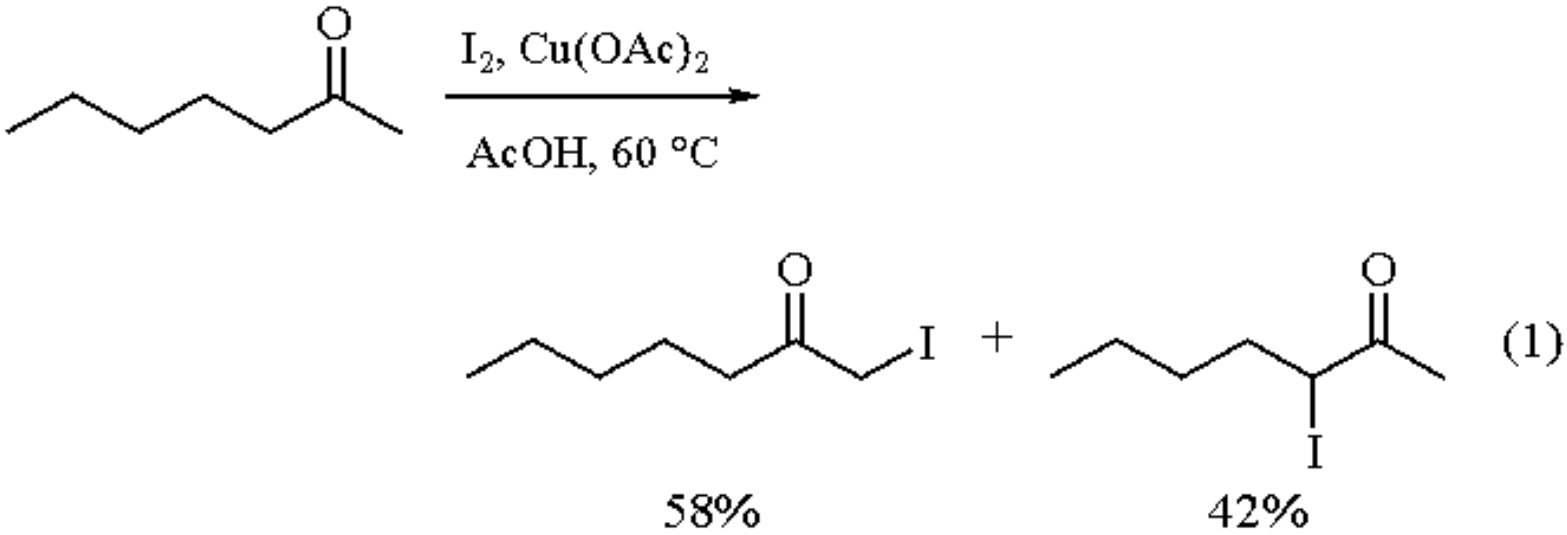
O
I2, Cu(OAc)2
AcOH, 60 °C
O
I
+
O
I
(1)
58%
42%

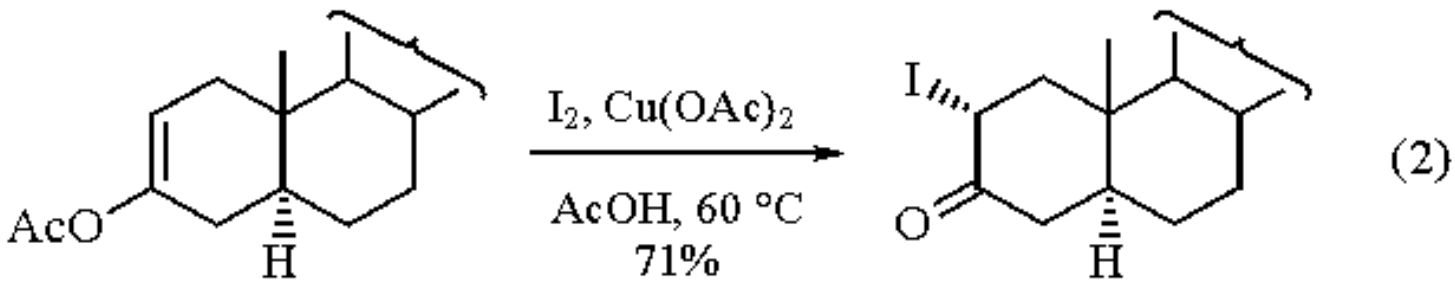
AcO
H
I2, Cu(OAc)2
AcOH, 60 °C
71%
I
O
H
(2)

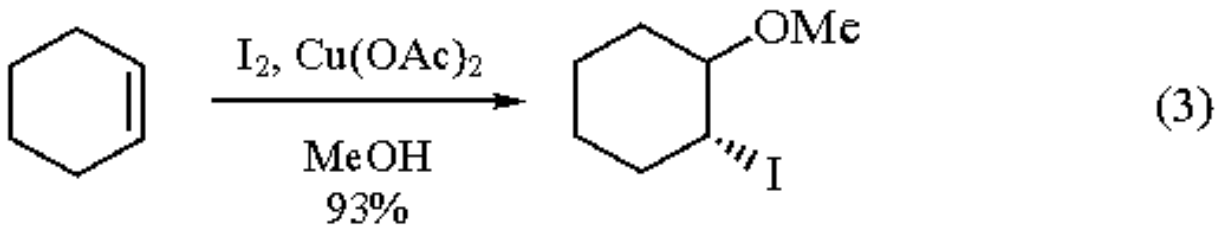
I2, Cu(OAc)2
MeOH
93%
OMe
I
(3)

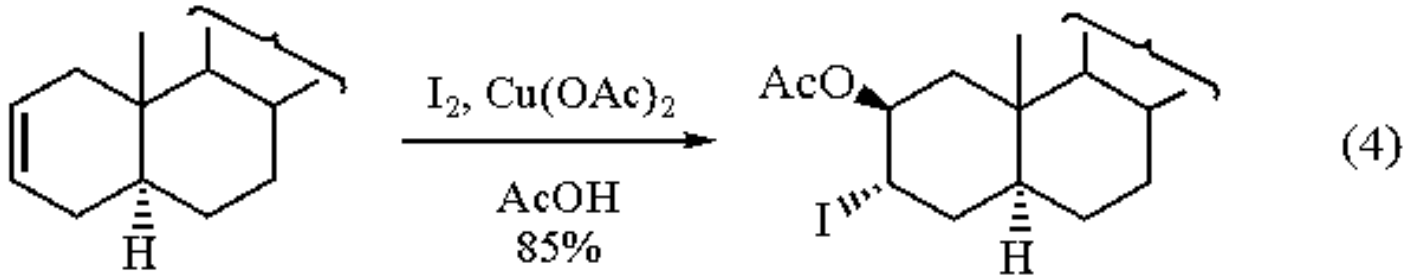
H
I2, Cu(OAc)2
AcOH
85%
AcO
I
H
(4)

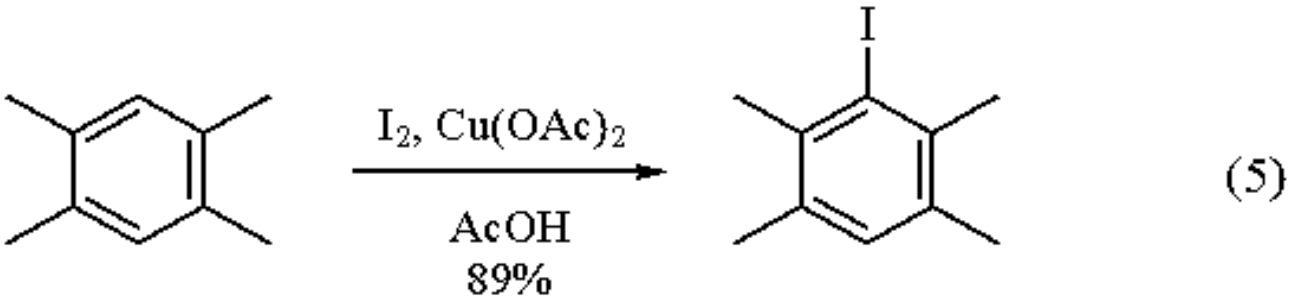
I2, Cu(OAc)2
AcOH
89%
I
(5)

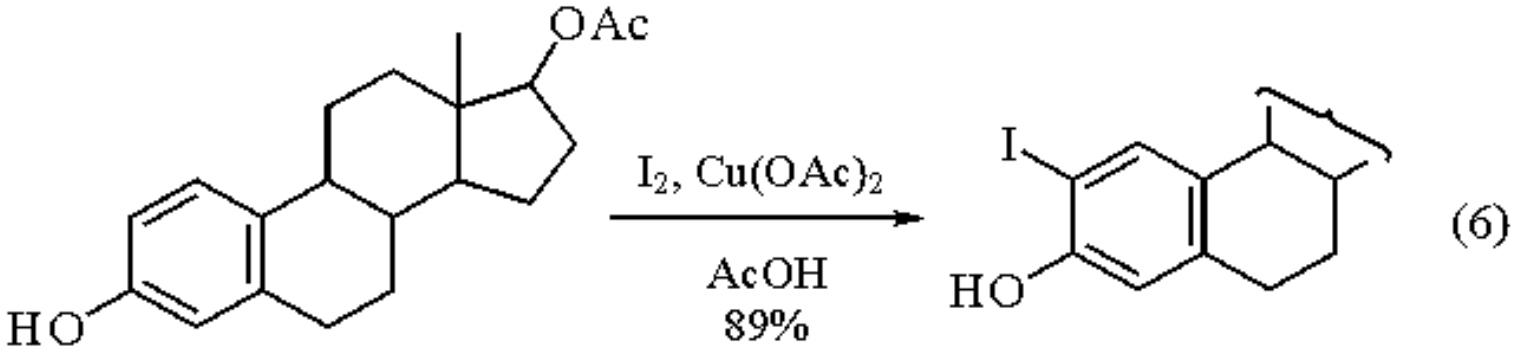

Oxidation.

Much work has been reported on the *cis*-hydroxylation of alkenes using the Prévost reaction and its Woodward modification. The reaction of alkenes with I_2 and $Cu(OAc)_2$ in AcOH yields a mixture of products which is hydrolyzed by KOH in MeOH-H_2O to provide *cis*-diols. In the case of 5α-cholest-2-ene, the more hindered 2β,3β-diol is produced in high yield (eq 7). Cyclohexene and cycloheptene similarly give the *cis*-diol in good yield. This synthetic method affords several advantages over the Prévost reaction and other methods used heretofore.[5]

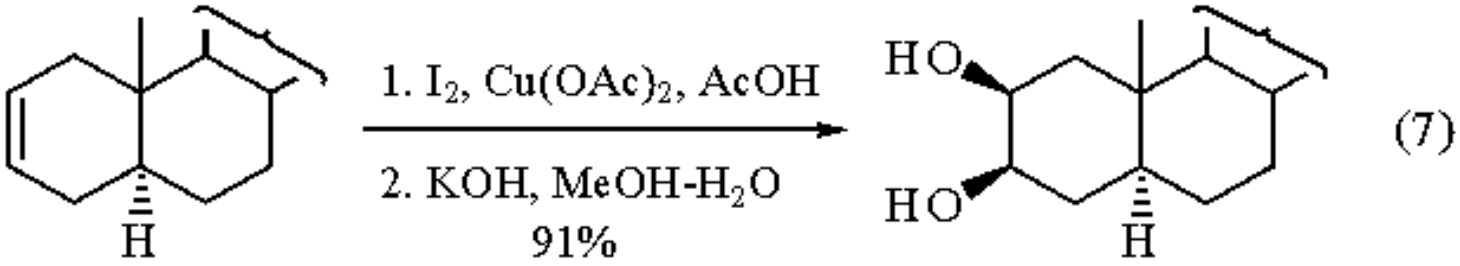

The reaction of diosphenol with I_2 and $Cu(OAc)_2$ in AcOH-H_2O (5:1) at 80 °C gives 3-hydroxythymo-1,4-quinone (79%).[6] Moreover, treatment of 3-iodo-3,6-dialkyl-1,2-cyclohexanediones with I_2-$Cu(OAc)_2$ gives 3-hydroxy-2,5-dialkyl-1,4-benzoquinones in 38-88% yield.[9] On the other hand, reaction with $Cu(OAc)_2$ under reflux affords 3,3´-dihydroxy-2,2´,5,5´-tetraalkyl-4,4´-diphenoquinones (eq 8).[7] A similar oxidation has been used for the synthesis of 3-alkyl-1,2-cyclohexanediones from 2-alkylcyclohexanones (40-70%) (eq 9).[8]

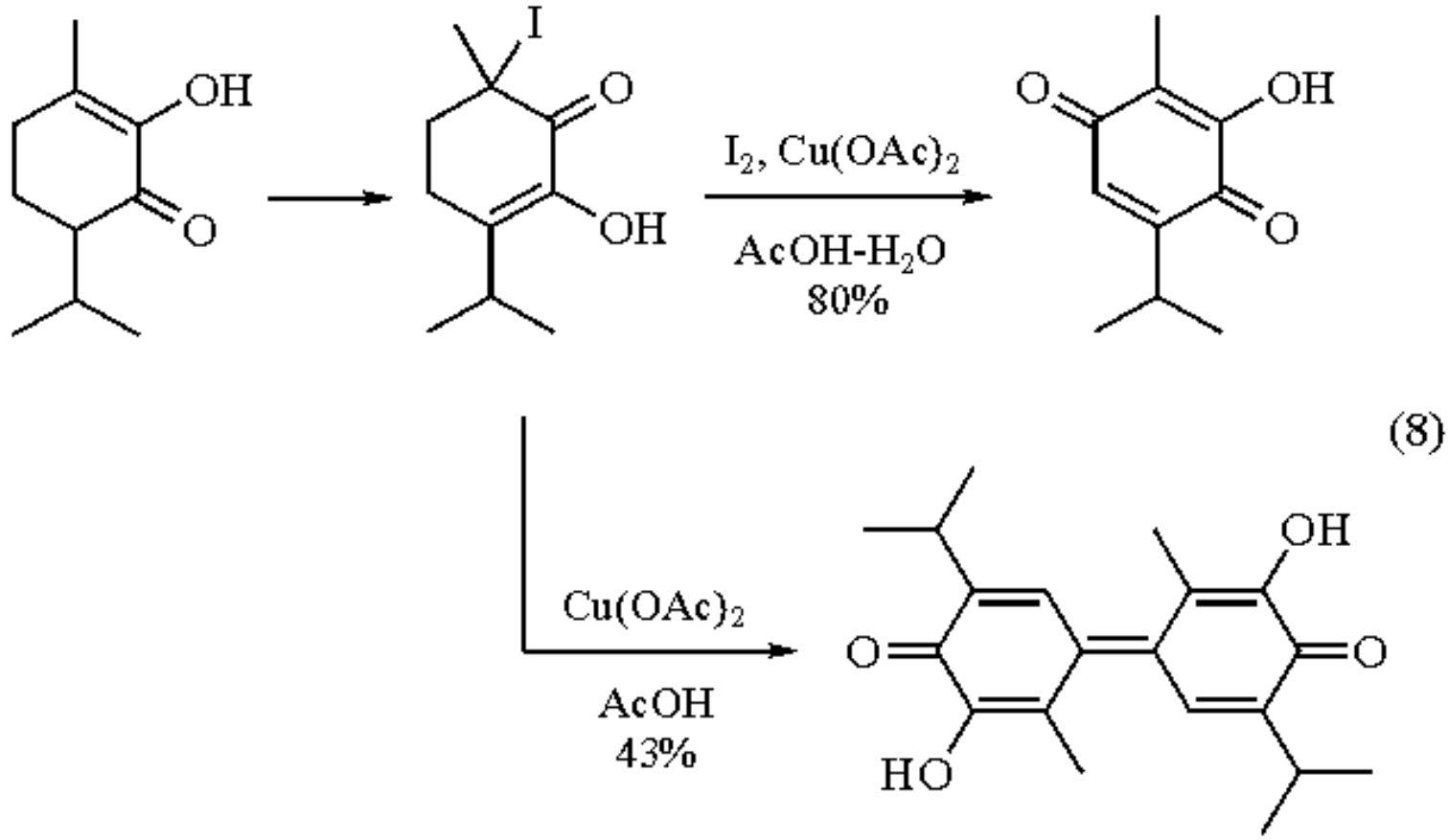

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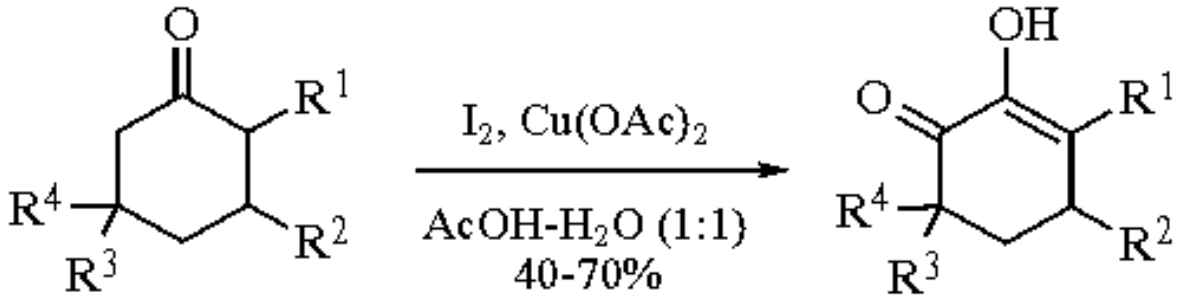

(9)

R^1 = H, Me, Et, Ph, Cy

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1. Horiuchi, C. A; Satoh, J. Y. *S* **1981**, 312.
2. (a) Georgoulis, C.; Valery, J. M. *BSF(2)* **1975**, 1431. (b) Horiuchi, C. A.; Satoh, J. Y. *BCJ* **1987**, *60*, 426.
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Iodine-Copper(I) Chloride-Copper(II) Chloride

I_2-CuCl-$CuCl_2$

(I_2)

[7553-56-2] · I_2 · Iodine-Copper(I) Chloride-Copper(II) Chloride · (MW 253.80) (CuCl)

[7758-89-6] · ClCu · Iodine-Copper(I) Chloride-Copper(II) Chloride · (MW 99.00) ($CuCl_2$)

[7447-39-4] · Cl_2Cu · Iodine-Copper(I) Chloride-Copper(II) Chloride · (MW 134.45)

(iodination of carboxylic acids)

Physical Data: CuCl: mp 430 °C; bp 1490 °C; *d* 4.14 g cm^{-3}. $CuCl_2$: mp 498 °C; *d* 3.054 g cm^{-3}.

Solubility: CuCl: sparingly sol H_2O; practically insol ether, acetone. $CuCl_2$: sol H_2O, ethanol, acetone.

Form Supplied in: CuCl: white crystals. $CuCl_2$: yellow to brown, deliquescent, microcrystalline powder.

Handling, Storage, and Precautions: CuCl: stable in dry air; becomes green on exposure to air and brown on exposure to light. $CuCl_2$: irritating to skin and mucous membranes; forms dihydrate in moist air. Iodination reactions using this combination of reagents should be performed in a fume hood.

Iodination.

Direct α-iodination of acetic acid, propionic acid, butyric acid, or valeric acid using a slight excess of

Iodine and 0.5 equiv each of ***Copper(I) Chloride*** and ***Copper(II) Chloride*** gives the corresponding α-iodo carboxylic acid in high yield (eq 1).[1] This synthetic method affords several advantages over classical α-iodo carboxylic acid procedures.

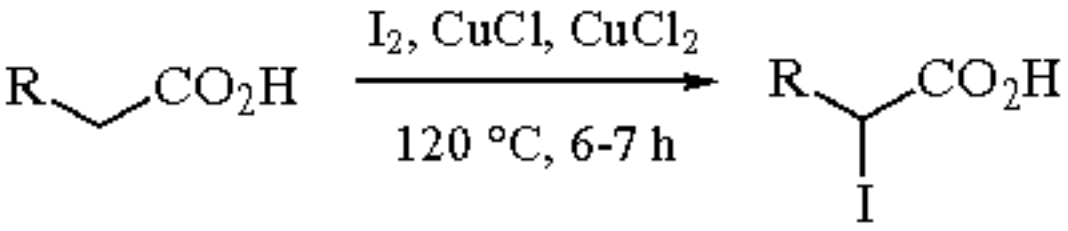

(1)

R = H, 95%; R = Me, 90%; R = Et, 85%; R = Pr, 85%

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1. Horiuchi, C. A.; Satoh, J. Y. *CL* **1984**, 1509.

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Iodine-Copper(II) Chloride

I_2-$CuCl_2$

(I_2)

[7553-56-2] · I_2 · Iodine-Copper(II) Chloride · (MW 253.80) ($CuCl_2$)

[7447-39-4] · Cl_2Cu · Iodine-Copper(II) Chloride · (MW 134.45) ($CuCl_2.2H_2O$)

[10125-13-0] · $H_4Cl_2CuO_2$ · Iodine-Copper(II) Chloride · (MW 170.49)

(iodinating agent)

Physical Data: see ***Iodine*** and ***Copper(II) Chloride***.

Handling, Storage, and Precautions: see ***Iodine*** and ***Copper(II) Chloride***.

Aromatic Iodination.

Iodine-copper(II) chloride is a useful reagent combination for the preparation of aryl iodides from aromatic hydrocarbons.[1] Thus, heating mesitylene with I_2-$CuCl_2$ at 150 °C gives iodomesitylene in 86% yield (eq 1). The reaction proceeds in moderate to good yields with unsubstituted aromatics and compounds with alkyl, halogen, hydroxy, alkoxy, and dimethylamino substituents. Iodination fails, however, with strongly deactivated ring systems such as methyl benzoate, aniline, thiophene, and pyridine.[1] Because of the limitations of the simple I_2-$CuCl_2$ iodinating system, alternative procedures have been studied. For example, a mixture of I_2-$AlCl_3$-$CuCl_2$ is effective for the preparation of aryl iodides, one advantage being that lower reaction temperatures are required.[2] Recently, a very efficient iodinating system has been developed using alumina-supported iodine-copper(II) chloride;[3] in the absence of solvent at 40-120 °C, monoiodination of polymethylbenzenes, alkoxy aromatics, and polynuclear aromatic hydrocarbons occurs in high yield. The I_2-Al_2O_3-$CuCl_2$ system exhibits very good selectivity, i.e. alkoxy aromatic substrates are almost exclusively *para*-iodinated (eq 2).

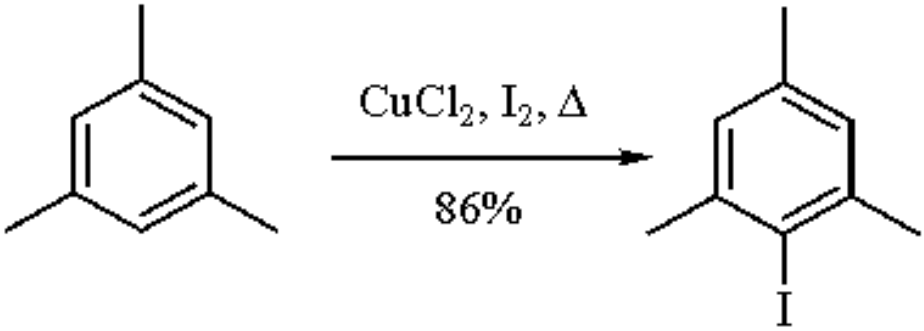

(1)

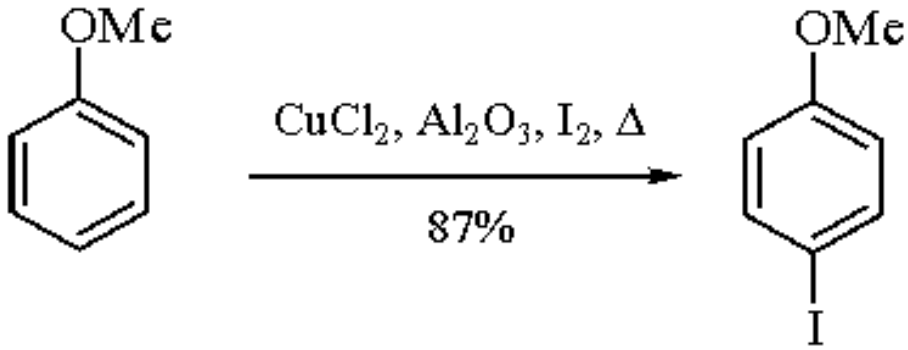

(2)

Iodination of Alkynes.

The liquid-phase halogenation of alkenes with copper(II) chloride is well known and has been studied in some detail.[4] The halogenation of alkylphenylalkynes with $CuCl_2$-LiCl and $CuCl_2$-I_2 in acetonitrile has also been examined.[5] Chloroiodination with $CuCl_2$-I_2 proceeds more smoothly than chlorination and affords completely regiospecific and highly stereospecific (*E*)-chloroiodoalkenes in high yields (eq 3).

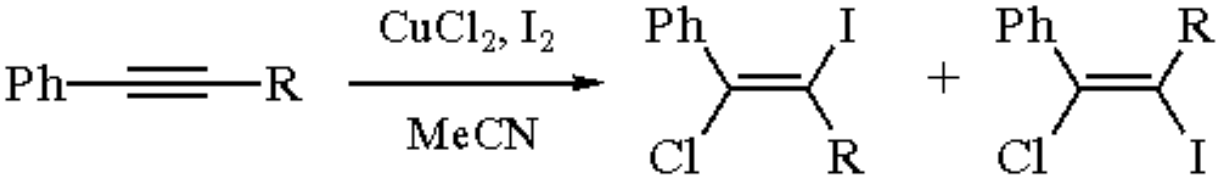

(3)

R = H, 93%, (*E*):(*Z*) = 100:0; R = Me, 93%, (*E*):(*Z*) = 100:0; R = *t*-Bu, 95%, (*E*):(*Z*) = 90:10

α-Iodination of Carboxylic Acids.

Combinations of iodine and copper(II) salts have been used for the introduction of iodine at the α-position of aliphatic straight-chain carboxylic acids.[6] While ***Iodine-Copper(II) Acetate*** gives a slightly higher yield of iodinated acid than $CuCl_2$-I_2, the reaction time with the latter reagent combination is considerably shorter. An ***Iodine-Copper(I) Chloride-Copper(II) Chloride*** mixture is also effective for this transformation.

Oxidant in Photochemical Reactions.

Photocyclization of 4,4´-dimethoxy-α,α´-dimethylstilbene in the presence of air with added $CuCl_2$-I_2 gives a significantly higher yield (54%) of the desired phenanthrene derivative than the same reaction performed with iodine alone (0.6%).[7]

Related Reagents.

Copper(II) Chloride; ***Iodine***; ***Iodine-Aluminum(III) Chloride-Copper(II) Chloride***; ***Iodine-Copper(II) Acetate***; ***Iodine-Copper(I) Chloride-Copper(II) Chloride***; ***Sodium Iodide-Copper***.

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Iodine Isocyanate[1]

INCO

[3607-48-5] · CINO · Iodine Isocyanate · (MW 168.92)

(additions to multiple bonds;[1-11] regioselective and stereoselective introduction of the isocyanate, amine, or carbamate function;[1-8] formation of aziridines,[1-7] 2-oxazolidones,[1,2] 2-amino alcohols,[1,2] 1,2-diamines,[5] and azepines;[6] interconversion of alkene stereoisomers[9])

Physical Data: usually prepared in situ in solution.[1-4]

Solubility: sol most organic solvents.

Form Supplied in: not available commercially; prepared in solution.

Preparative Methods: INCO can be prepared in situ from silver cyanate and I_2 in anhydrous ether,[2,4] MeCN (faster),[2] THF,[2] or CH_2Cl_2 (faster).[4d] The preformed solution can be stored in the dark at -20 to -30 °C for 48 h,[2] and sometimes reacts faster with alkenes.[10] The purity of AgNCO is critical; it should be white or pale-gray, prepared fresh or kept in the dark in a desiccator.[2] A typical procedure for addition to alkenes is as follows:[2] to a stirred slurry of 20 g (0.13 mol) of fresh AgCNO in 200 mL anhydrous ether at 0 °C is added 0.1 mol of alkene followed by 25.4 g (0.1 mol) of I_2. The mixture is stirred at rt for 1-5 h (brown color lightens). Filtration of the salts through a filter aid (Celite) and washing with aqueous sodium bisulfite gives a solution of the iodo isocyanate which is converted to the methyl β-iodo carbamate by treatment with 100 mL of MeOH and 2-3 drops of dil LiOMe. Alternatively, the iodo isocyanate can be converted into a stable sodium bisulfite adduct, which can regenerate the isocyanate or lead to an aziridine.

Additions to Alkenes.

Addition of INCO to alkenes (see also ***Iodine Azide***) proceeds via a three-membered cyclic iodonium species resulting from attack of I^+ on the double bond. The reaction is highly stereoselective (*anti*) and regioselective. Thus *cis*- and *trans*-2-butene give, stereospecifically, the *threo*- and *erythro*-adducts, respectively.[8] The new N-C bond usually forms at the more substituted carbon or the one better able to support a positive charge in the transition state (eq 1),[1] although 1-hexene and methylenecyclohexene give a mixture of regioisomers.[8]

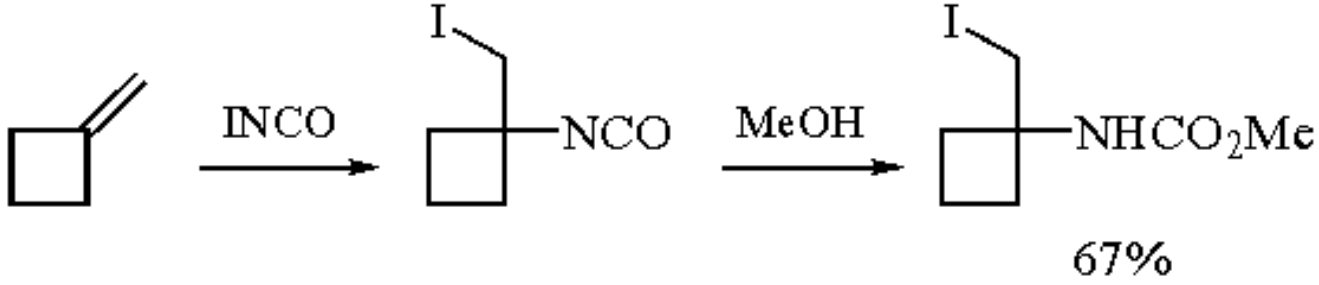

(1)

Steric effects play an important role in the attack by cyanate ion; thus *t*-butylethylene affords the terminal isocyanate. 2-Cholestene gives the diaxial adduct, 2β-isocyanato-3α-iodocholestane (eq 2),[2b] whereas 5-cholestene does not react.[1]

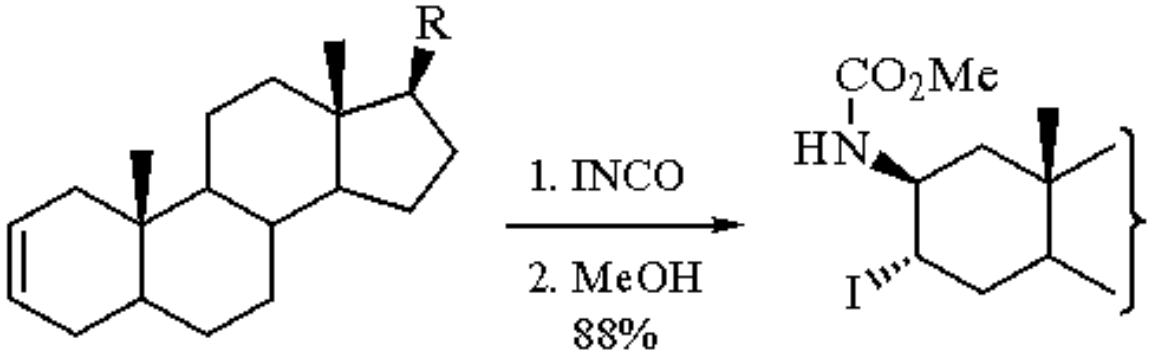

(2)

Mono addition of INCO to dienes or trienes can be achieved with the less-substituted double bond reacting first (eq 3).[8] Electron-poor double bonds, as in conjugated ketones or esters, do not react well with INCO.

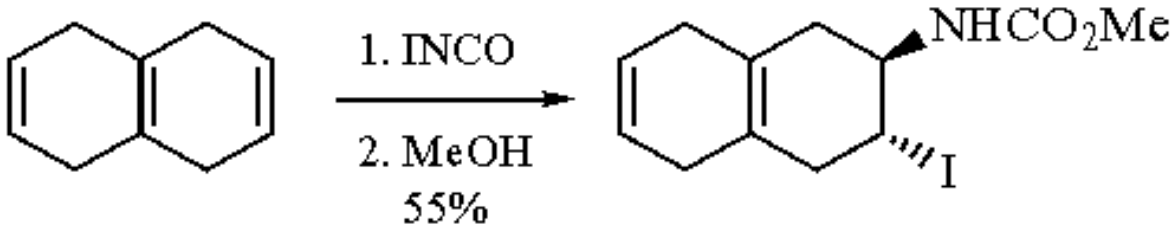

(3)

Rearrangements have occasionally been observed, as in the case of 3,3-diphenylpropene which gives, in low yield, an iodo carbamate resulting from phenyl migration,[11] and also in the case of rearrangement-prone alkenes such as 5-methylene-2-norbornene (eq 4).[8] Enol acetates react fast but give an unstable adduct.[10]

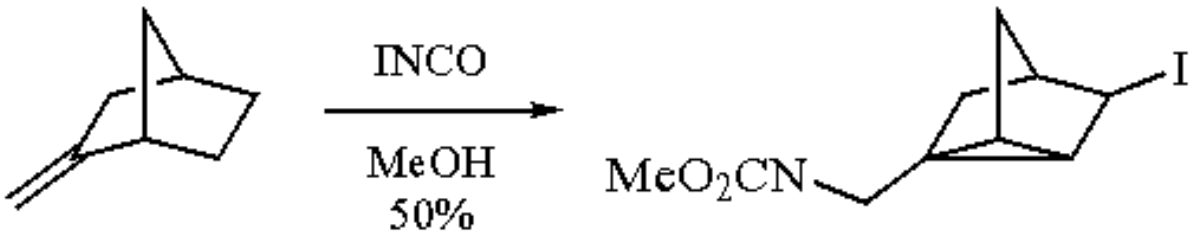

(4)

Formation of Amines or Carbamates.

After the INCO adducts are converted with alcohol into the corresponding carbamates, the iodo function can be reduced by ***Zinc-Acetic Acid***-ether (eq 5), except in diaxial adducts which tend to undergo elimination.[8] Alternatively,

the carbamates can be hydrolyzed to amines and the iodo amine salt can be reduced by ***Lithium Aluminum Hydride*** to an amine.[4b]

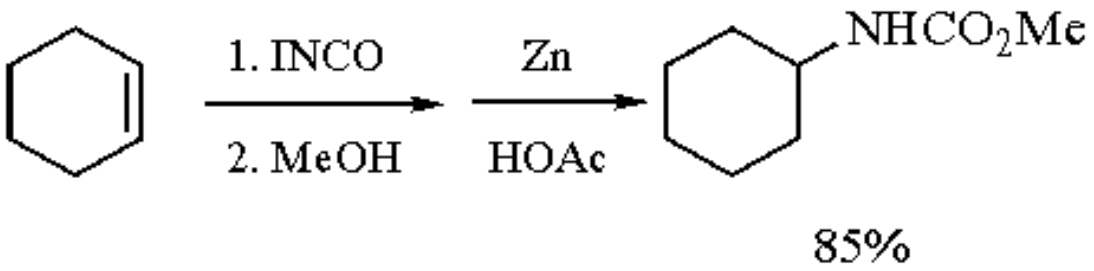

(5)

Synthesis of Aziridines.

The iodo carbamates resulting from INCO addition to alkenes followed by reaction with alcohol are readily converted into aziridines with base (refluxing ***Potassium Hydroxide*** in MeOH) (eq 6).[1,2] Alternatively, the INCO adducts can be hydrolyzed by aq HI or HCl to *trans*-2-iodoalkylamines, which when heated with base afford aziridines.[2b,4b]

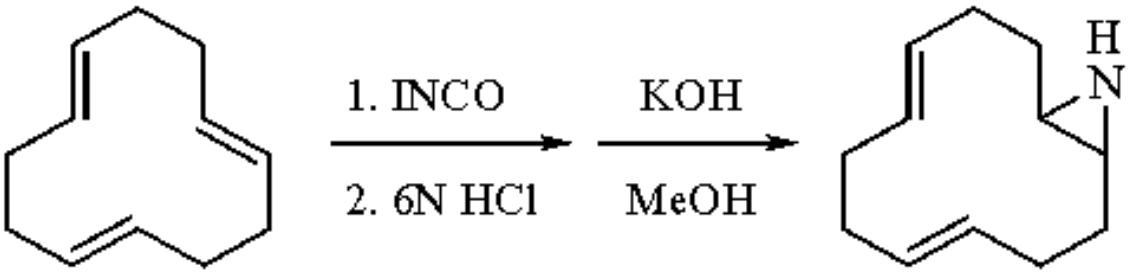

(6)

Aziridines can be converted into *trans*-2-amino alcohol derivatives (by heating with ***Acetic Acid***),[2b] or into *trans*-1,2-diamines (by treatment with ***Sodium Azide*** followed by hydrogenation).[5]

Synthesis of 2-Oxazolidones and *cis*-2-Amino Alcohols.

Pyrolysis of β-iodo carbamates neat at 140-190 °C or in solvents (*i*-PrOH, TCE, diglyme) leads to the formation of 2-oxazolidones (eq 7).[1]

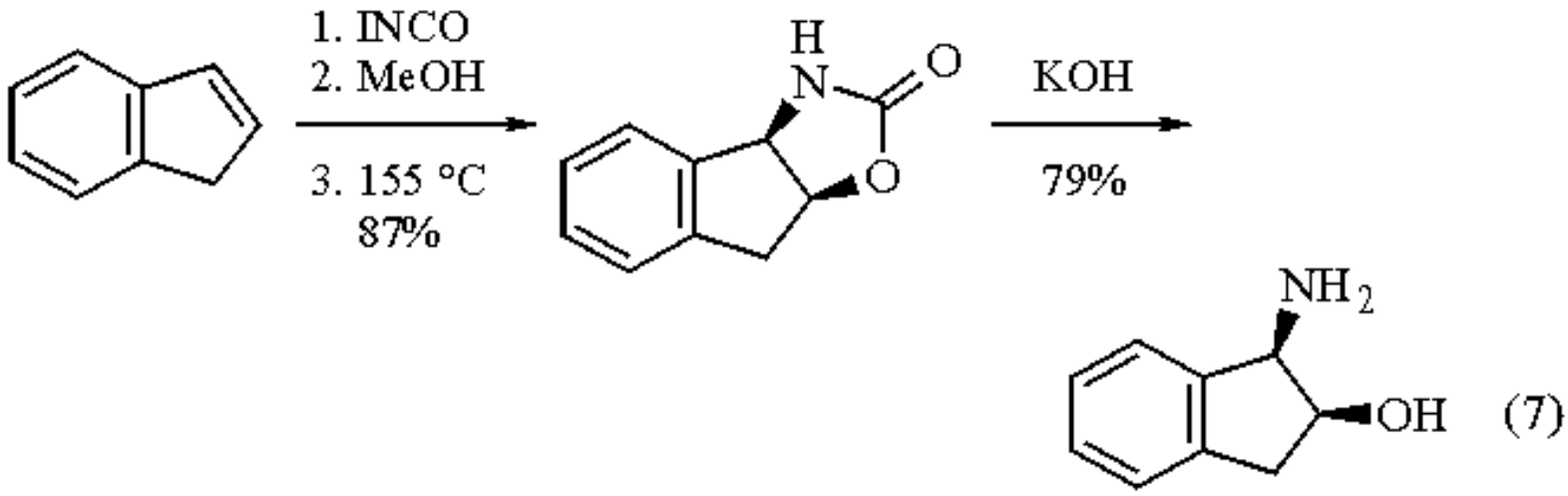

Since addition of INCO to cycloalkenes affords *trans*-2-iodo carbamates and formation of 2-oxazolidones proceeds with inversion of configuration, hydrolysis (KOH in aq MeOH) of the oxazolidones provides a stereospecific entry to *cis*-2-amino alcohols (eq 7).[1]

Miscellaneous Reactions.

Addition of a preformed solution of INCO in THF to phenylacetylene yields a monoadduct which provides acetophenone on workup with dil HCl. A general route to 1*H*-azepines involves INCO addition to 1,4-dihydrobenzenes and conversion of the resulting fused aziridines into azanorcaradienes which rearrange to azepines (eq 8).[6]

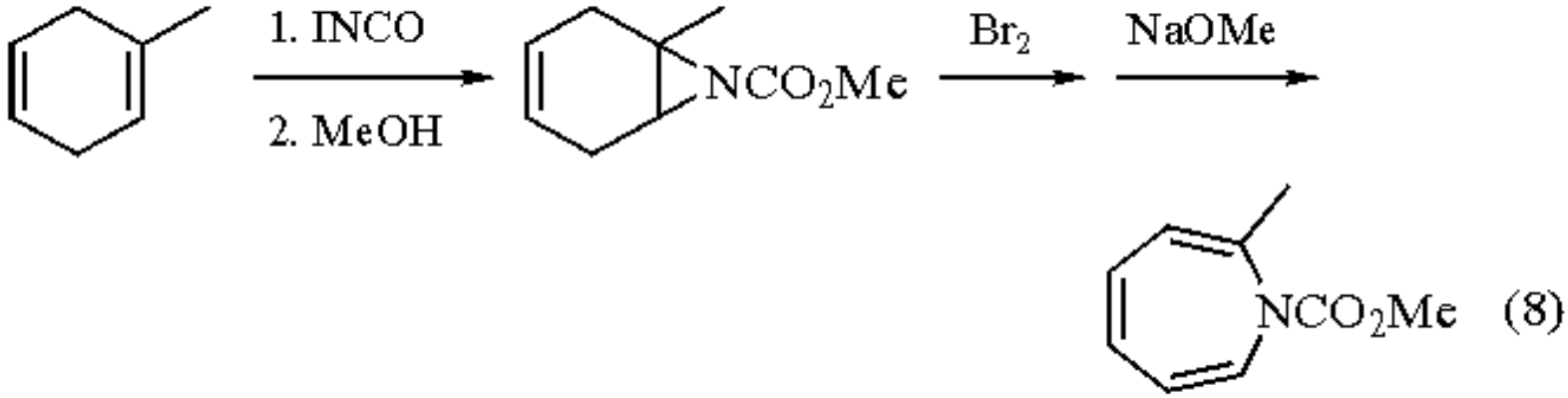

Interconversion of *cis*- and *trans*-alkenes can be achieved using this reagent; for example, from a *cis*-alkene via the 2-oxazolidone and the derived (inverted) 2-amino alcohol. The latter is ring-closed with acid to a *trans*-aziridine, which on deamination with *n*-BuONO yields a *trans*-alkene (eq 9).[9]

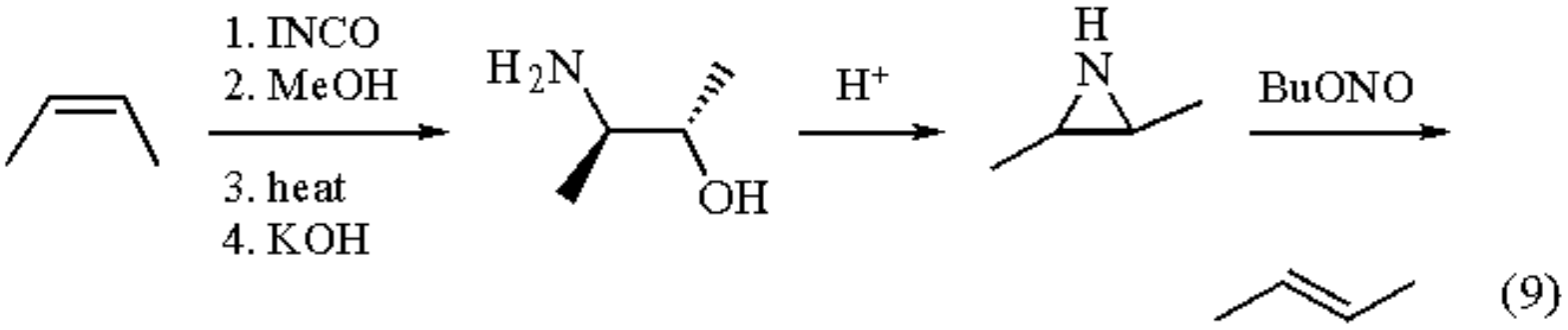

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Iodine Monobromide

IBr

[7789-33-5] · BrI · Iodine Monobromide · (MW 206.80)

(diastereoselective cyclizations of homoallylic carbonates;[1] electrophilic addition to alkenes;[2] α-bromination of steroidal aldehydes and ketones;[3,4] cleavage of carbon-metal bonds[5])

Physical Data: mp 40 °C; bp 116 °C (dec); *d* 4.416 g cm^{-3}.

Solubility: sol alcohol, ether, CS_2, acetic acid, acetone, CH_2Cl_2, MeCN, DME, toluene (but with limited solubility below -80 °C); sol H_2O, but hydrolyzes to HBr and IOH.

Form Supplied in: brownish-black crystals or very hard, black solid; widely available (usually 97-98% purity).

Handling, Storage, and Precautions: corrosive solid and vapor; readily absorbed through skin and mucous membranes; use in a fume hood and wear gloves and appropriate protective clothing; air-, moisture-, and light-sensitive; should be stored refrigerated (under N_2) in a tightly sealed amber bottle. Forms explosive mixtures with potassium and sodium, and reacts extremely exothermically with phosphorus and tin.

Electrophilic Cyclization of Homoallylic Carbonates.[1]

Iodine monobromide provides very good diastereoselectivity in electrophilic cyclizations of homoallylic carbonates (eq 1). Isolated yields of α-iodo cyclic carbonates are excellent, and these products can be easily and efficiently converted into the corresponding epoxides (eq 2). Optimal diastereoselectivity is obtained from reactions performed in toluene at -80 to -85 °C. Use of ***Iodine***/MeCN[6] or ***Iodine Monochloride***/CH_2Cl_2 yields much lower diastereoselectivity than iodine monobromide under similar conditions. Results of an equilibration experiment strongly indicate that the diastereoselectivity in iodine monobromide-induced cyclization stems from kinetic control.

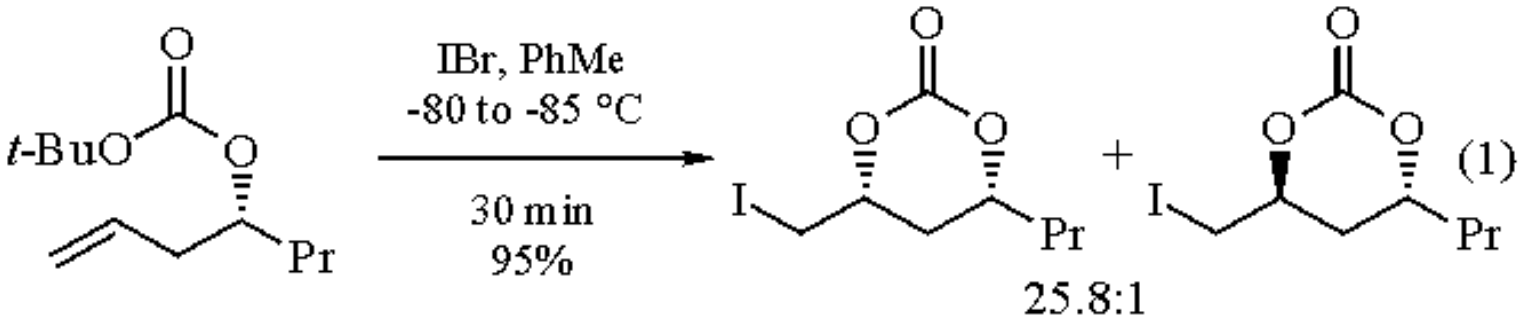

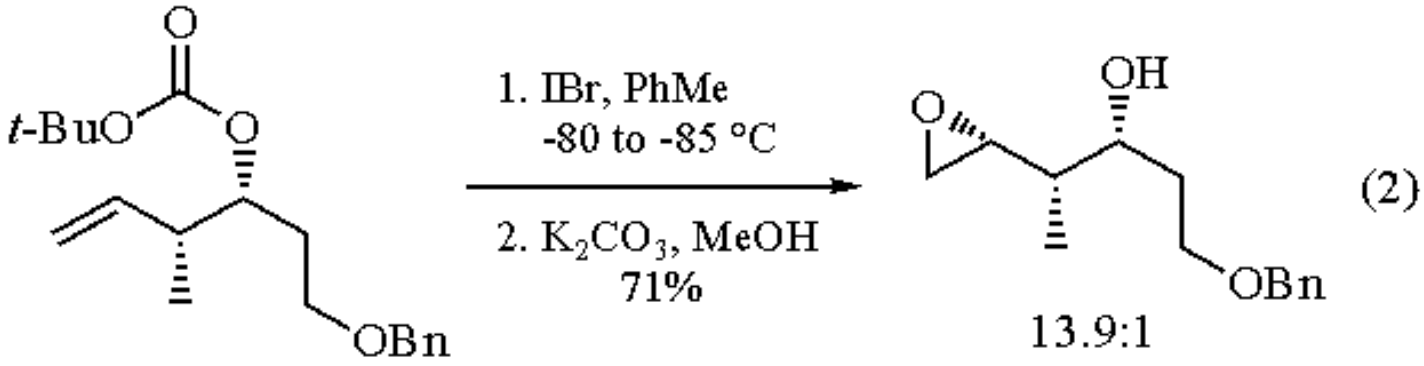

Electrophilic Addition to Alkenes.[2]

Iodine monobromide addition across alkenes is very facile, yielding vicinal bromoiodoalkanes. In general, addition occurs with high *anti* stereospecificity, and mechanistic studies have implicated an iodonium ion intermediate in the overall reaction sequence. The regiochemistry of iodine monobromide addition is very sensitive to the initial alkene structure, such that anti-Markovnikov products are possible (Table 1).

Table 1 Regiochemistry of IBr Addition to Alkenes

Alkene	% Markovnikov	% anti-Markovnikov
$MeCH{=}CH_2$	65	35
$EtCH{=}CH_2$	45	55
i-$PrCH{=}CH_2$	15	85
t-$BuCH{=}CH_2$	0	100
$PhCH{=}CH_2$	100	0

α-Bromination of Steroidal Aldehydes and Ketones.

Iodine monobromide is an effective monobrominating reagent for steroidal aldehydes (eq 3).[3] The ratio of diastereomeric products is in part a function of the reaction site's proximity to an asymmetric center, with β-orientation favored for the entering bromine. In an analogous application, methyl 3-oxo-5β-cholanate has been monobrominated (IBr/$MeCO_2H$; 50% yield) to produce the 2β-bromo ketone.[4]

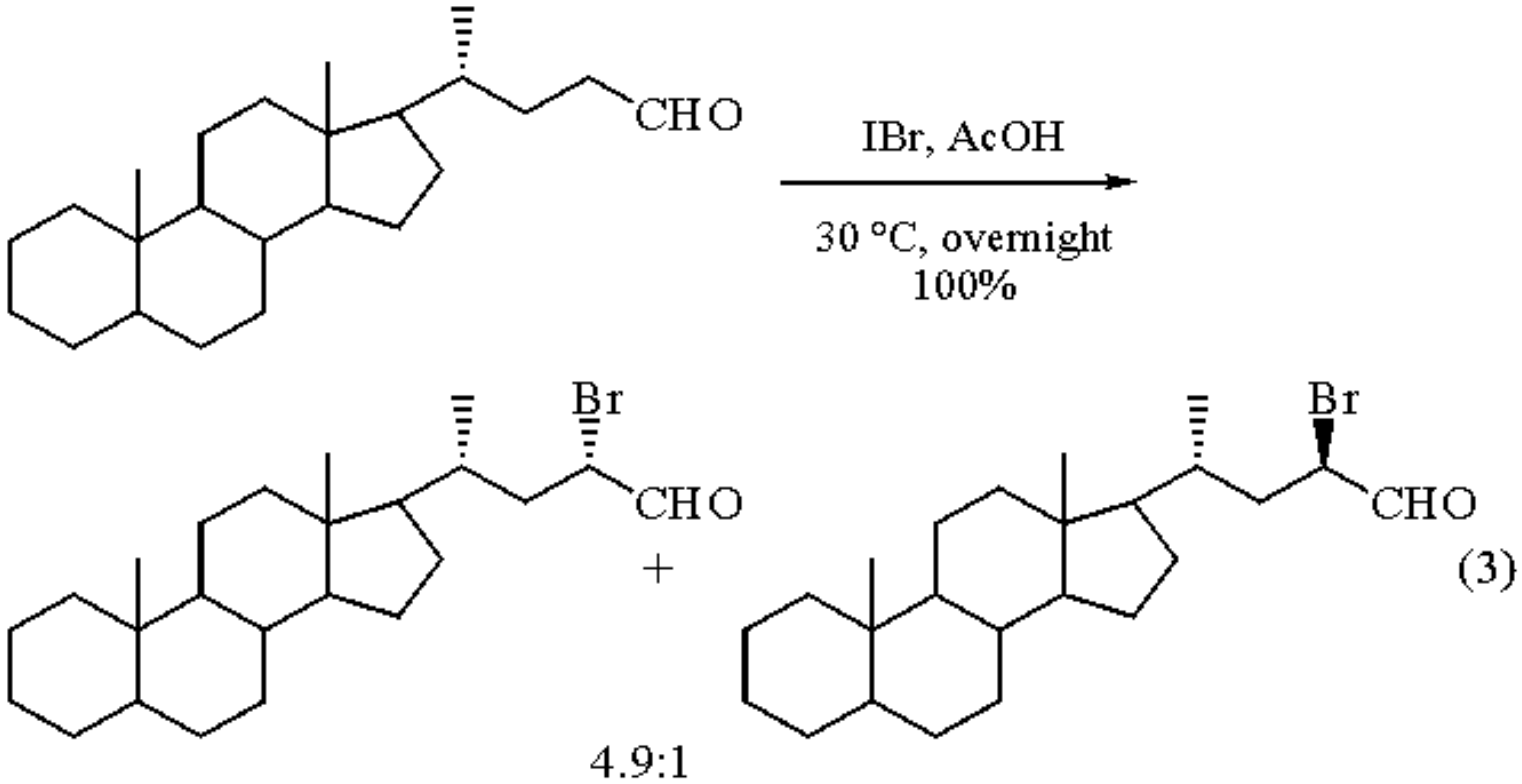

Bond Cleavage Reactions.[5]

Cleavage of carbon-metal bonds by iodine monobromide typically produces the organic iodide and the metal bromide. Cleavage of organotin,[5a-c] organoarsenic,[5d] organoantimony,[5d] organogermanium,[5e] and organolead[5e] bonds has been investigated (see also ***Iodine Monochloride*** for use in cleaving carbon-metal bonds).

Other Applications.

Iodine monobromide has been used for brominating phenol and aryl ether derivatives.[7] Ethers and esters have been cleaved by catalytic iodine monobromide in the presence of ***Bromotrimethylsilane***.[8] Aryl acetals can be directly oxidized to the corresponding esters in moderate yield.[9]

---

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Iodine Monochloride[1]

ICl

[7790-99-0] · ClI · Iodine Monochloride · (MW 162.35)

(iodinating reagent for aromatic compounds;[2] chloroiodinating reagent for unsaturated compounds;[3] cleaves carbon-metal bonds[4])

Physical Data: mp 27.2 °C (α-form; black needles, ruby-red by transmitted light); mp 13.9 °C (β-form; black platelets, brownish-red by transmitted light); bp 97 °C (β-form, partial decomposition); *d* 3.10 g cm^{-3}.

Solubility: sol alcohol, ether, CS_2, acetic acid, acetone, pyridine; sol H_2O, but hydrolyzes to HCl and IOH.

Form Supplied in: low melting black or brownish-red solid; widely available (usually 97-98% purity).

Handling, Storage, and Precautions: corrosive solid and vapor; readily absorbed through skin and mucous membranes; use in a fume hood and wear gloves and appropriate protective clothing; air-, moisture-, and light-sensitive; should be stored refrigerated (under N_2) in a tightly sealed amber bottle. Explodes on contact with potassium metal; mixtures with sodium metal can explode if impacted. Reaction with PCl_3 is extremely exothermic.

Iodination of Aromatic Compounds.

As a source of electrophilic iodine, iodine monochloride is an effective reagent for iodination of a wide variety of aromatic compounds,[2] including heterocyclic aromatic compounds (eq 1).[5] In a related mode of reactivity, uracil bases and protected nucleosides can be iodinated in excellent yield (eq 2).[6] See also ***Iodine-Silver(I) Fluoride*** and ***Trifluoroacetyl Hypoiodite*** for iodination of aromatic compounds.

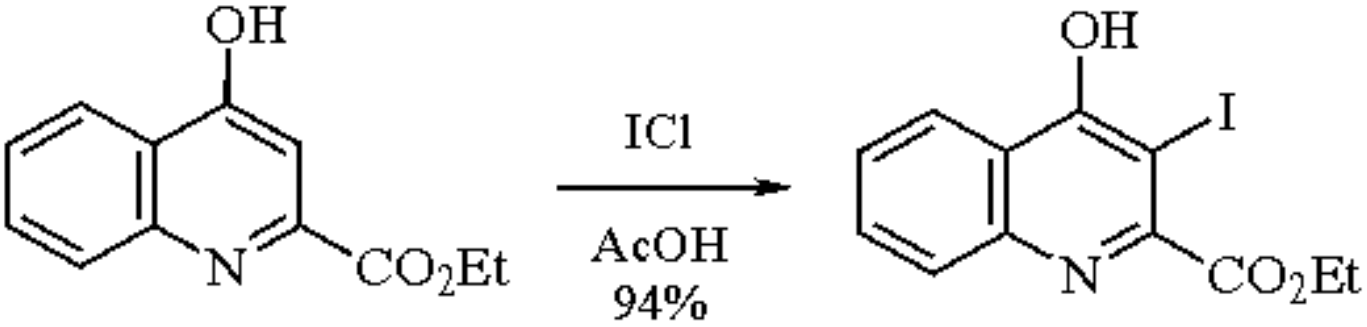

(1)

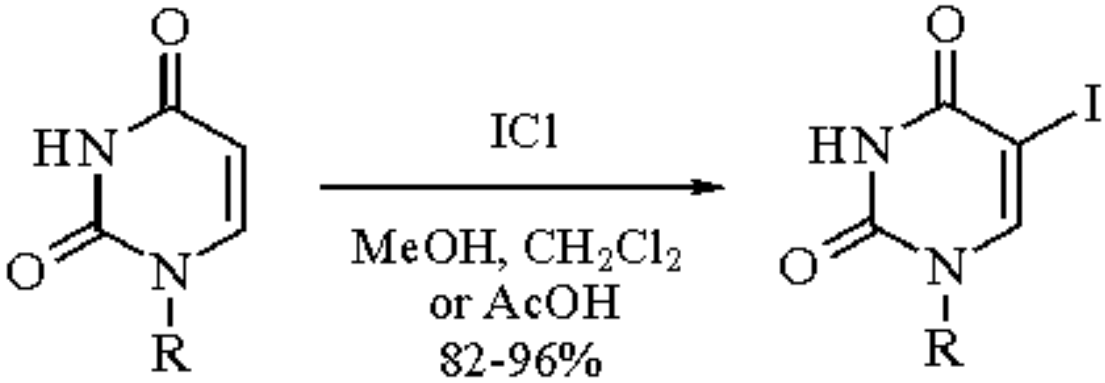

(2)

Chloroiodination of Unsaturated Compounds.[3]

Formation of vicinal chloroiodoalkanes via iodine monochloride addition to alkenes generally occurs with high *anti* stereospecificity, implicating the intermediacy of an iodonium ion in the reaction sequence. Unsymmetrical alkenes typically undergo predominantly Markovnikov addition (e.g. reaction of 1-hexene produces a 66:34 mixture of 2-chloro-1-iodohexane and 1-chloro-2-iodohexane in 75% overall yield[7]). Regioselectivity and stereoselectivity in additions to alkynes are very dependent on the alkyne structure.

Bond Cleavage Reactions.[4]

Except in the case of C-Fe and C-Co bonds, cleavage of carbon-metal bonds by iodine monochloride specifically produces the organic iodide and the metal chloride. Organosilicon[8] (eq 3), organoboron[9] (eq 4), and organoaluminum[10] (eq 5) bond cleavage reactions are probably of greatest utility to synthetic organic chemists.

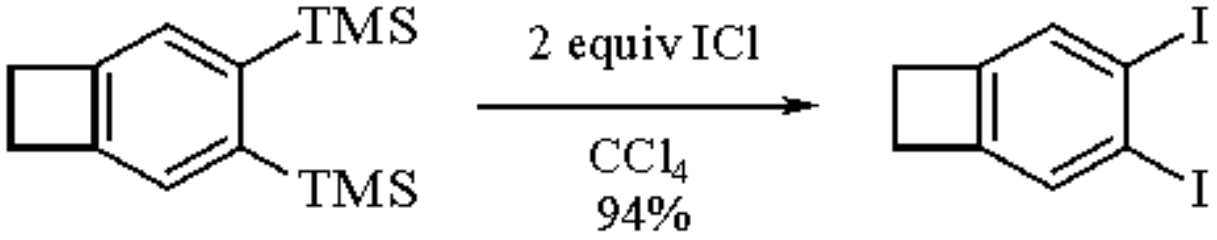

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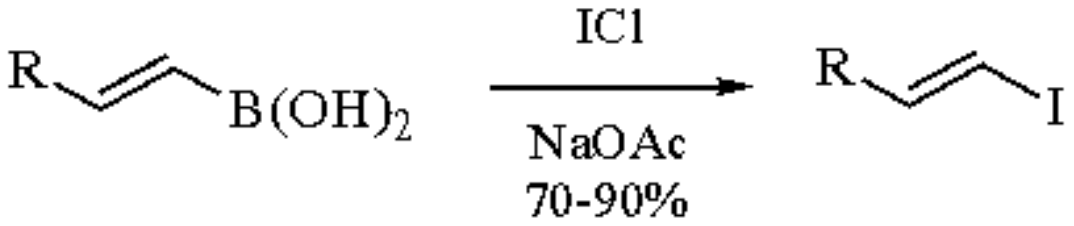

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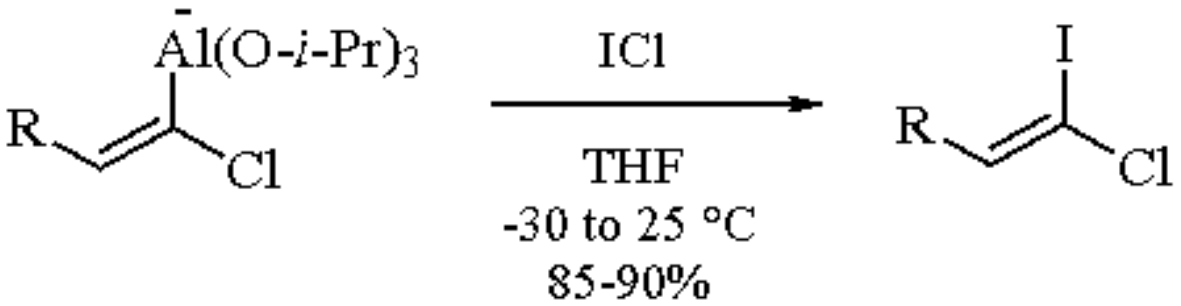

(5)

Other Applications.

Iodine monochloride can function as a chlorinating agent because of its tendency to disproportionate to molecular iodine and molecular chlorine in nonpolar solvents.[11] Oxidation of dioxolanes to esters has been reported to proceed in good to excellent yield.[12] Also, a variety of conditions have been reported for the in situ generation of iodine monochloride, including ***t-Butyl Hypochlorite*/*Iodine***,[13] ***Antimony(V) Chloride***/I_2,[14] and ***Iodine-Copper(II) Chloride***.[15]

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Iodine Monofluoride[1]

[13873-84-2] · FI · Iodine Monofluoride · (MW 145.90)

(adds iodine and fluorine atoms across double and triple bonds;[2] iodinates aromatic rings;[3] converts carbonyls, through their hydrazones, to the CF_2 group[4])

Physical Data: bp +1 °C (dec to I_2 and IF_3); has not been isolated in pure form; chocolate-colored polymeric solid at low temperatures;[8] relatively stable in the gas phase.[9]

Preparative Methods: unlike most organic reagents, the notation of [IF] has been used to designate a two-step reaction taking place when a mixture of two different agents, one a source of electrophilic iodine and the other of nucleophilic fluorine, is reacted with a substrate. The true molecule of IF can be prepared in situ by a reaction between the corresponding elements[5] or by reacting ***Iodine*** with IF_5[6] or iodine with ***Silver(I) Fluoride***.[7] Many reactions, but not all, of [IF] and IF are quite similar.

Handling, Storage, and Precautions: use in a fume hood.

Iodofluorination of Alkenes.

Adding the elements of iodine and fluorine across double bonds by using ***N-Iodosuccinimide*** (NIS) and anhydrous ***Hydrogen Fluoride*** is an old procedure employed extensively in steroid chemistry (eq 1).[10] The addition proceeds via a cyclic iodonium ion with good regio- and stereospecificity (*anti* addition). Since anhydrous HF is inconvenient for lab use, Olah suggested replacing it with the easier-to-handle HF.pyridine (eq 2).[2a] Many variations on this procedure have since appeared. These include the following combinations: NIS-Et_3N/3HF,[11] NIS-AgF/CaF_2,[12] NIS-Bu_4NHF_2,[13] NIS-NH_4HF_2/ultrasound,[14] and I(py) +2 or I(collidine) +2BF_4^-.[15]

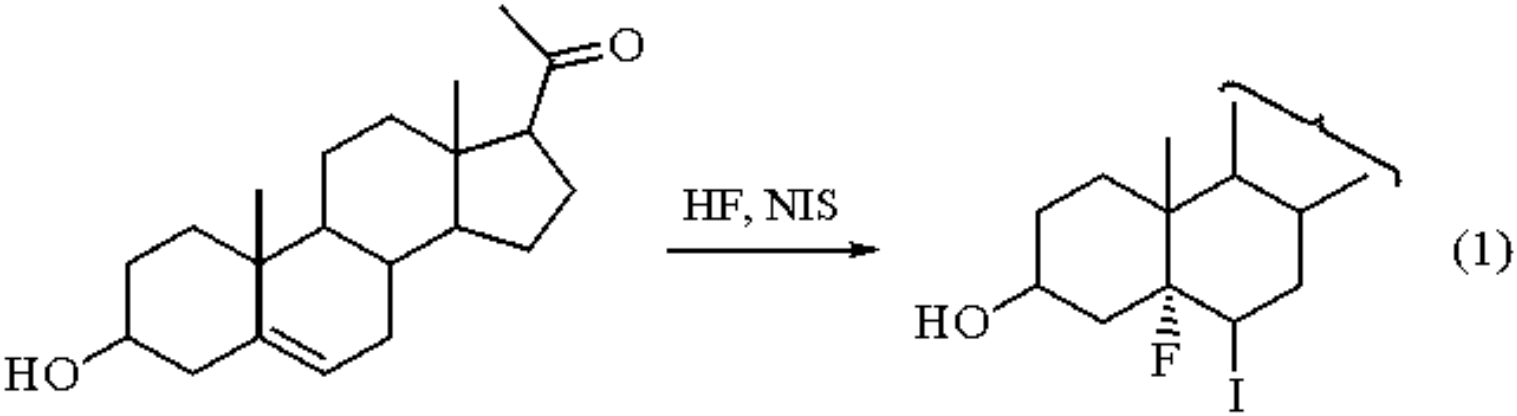

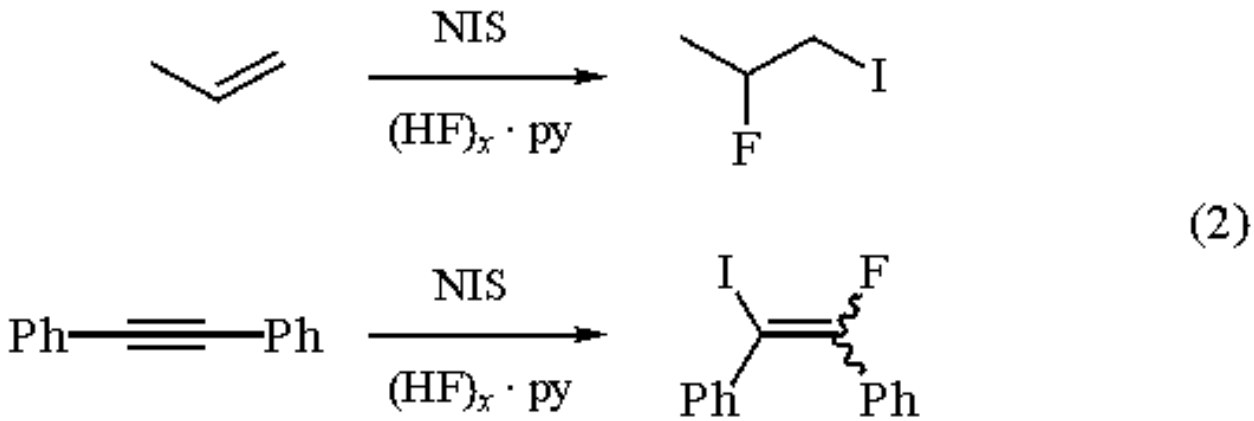

Molecular IF, prepared in situ from the elements, adds across double bonds with similar results to [IF], but it also adds quite efficiently to much less reactive enones, usually with subsequent elimination of HF and resulting in the difficult-to-obtain α-iodo enones (eq 3).[2b] Various alkynes react as well to form α,α-difluoro-β,β-diiodo derivatives (eq 4).[2c]

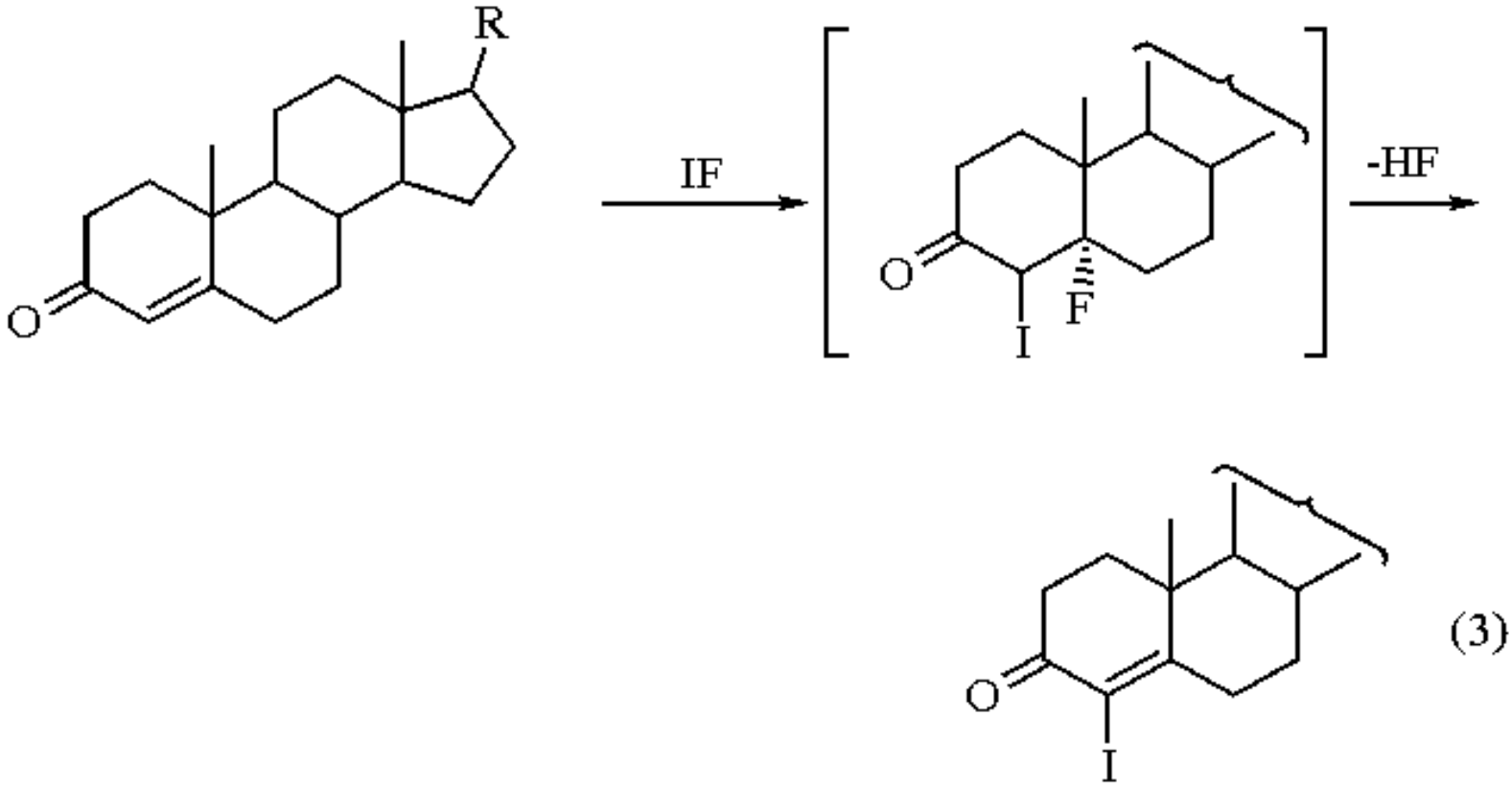

(3)

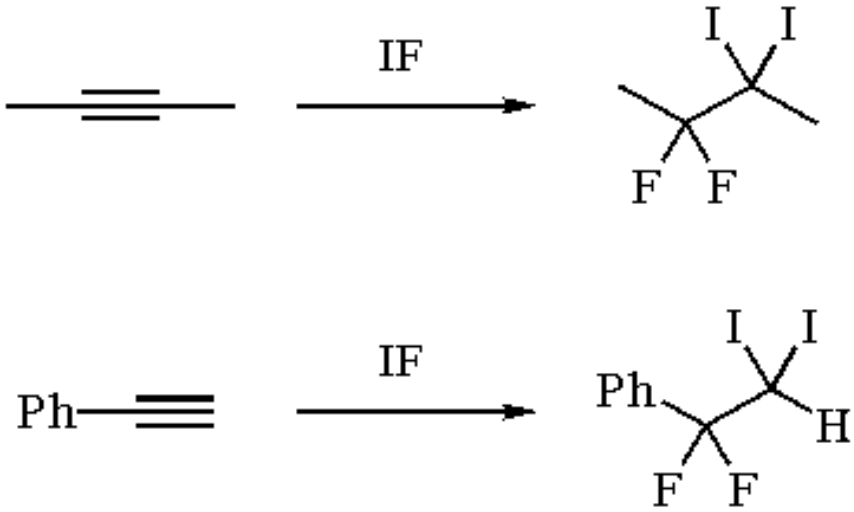

(4)

The strong electrophilicity of the iodine in molecular IF is the driving force behind the successful iodination of various aromatic compounds. In the case of aromatic rings such as toluene, mono-, di-, or triiodo derivatives can be made at will by varying the temperature and amount of the reagent (eq 5), while with deactivated rings such as benzonitrile only the *meta* monoiodo derivative is obtained in high yields (eq 6).[3]

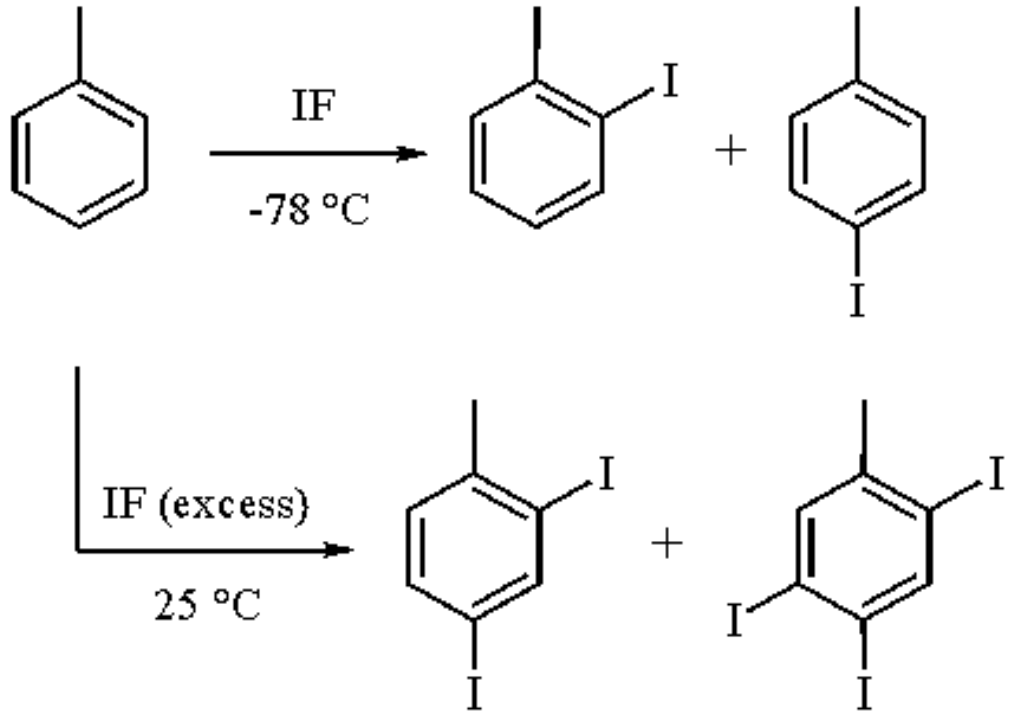

(5)

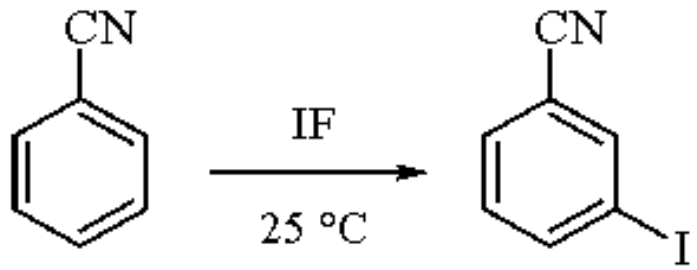

(6)

Iodine monofluoride has found yet another use in converting ketones, via their hydrazones, into the corresponding CF_2 derivatives (eq 7).[4] The reaction is general; aliphatic, alicyclic, benzylic, and steroidal carbonyls react successfully. Mono- and disubstituted hydrazones, semicarbazones, and DNPs can react as well. It should be noted that with [IF], this reaction does not give satisfactory results.[16]

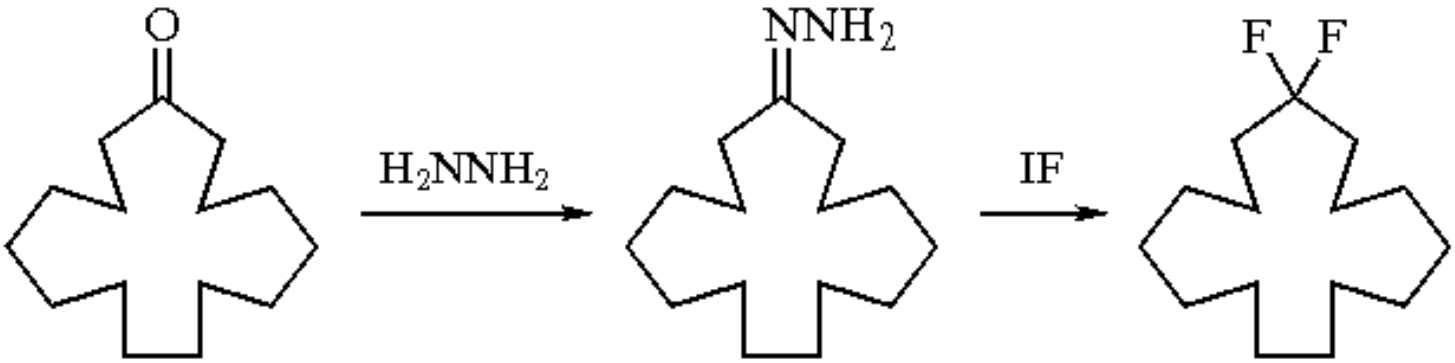

(7)

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Iodine Nitrate[1]

INO_3

[14696-81-5] · INO_3 · Iodine Nitrate · (MW 188.91)

(additions to alkenes;[1-7] regioselective and stereoselective introduction of the iodine and oxygen (nitrate) function;[1-6,8] in the case of INO_2, introduction of iodine and nitro groups;[6c,7] iodination of alkylbenzenes[9])

Physical Data: prepared in situ in solution.[1,2]

Solubility: sol most organic solvents.

Form Supplied in: not available commercially; prepared in situ.

Preparative Methods: iodine nitrate (INO_3) and iodine nitrite (INO_2, more appropriately called nitryl iodide) often show similar chemical properties and can be prepared in situ from iodine and silver nitrate or silver nitrite, respectively. The first reported[4] preparation of INO_3 was from ***Mercury(II) Nitrate*** and ***Iodine*** in ether. ***Silver(I) Nitrate*** and I_2 in ether, acetonitrile, or MeOH, as well as $AgNO_3$ and ***Iodine Monochloride*** in $CHCl_3$-pyridine, have been used successfully for additions to alkenes,[1,4] although the latter reagent also leads to iodopyridinium adducts.[1] ***Nitrogen Dioxide*** and I_2 have also been used to generate INO_3.[2] The first reports[7] of INO_2 addition to alkenes employed ***Silver(I) Nitrite*** and I_2 in ether to produce iodo nitro adducts, but this reagent also can lead to INO_3 adducts.[6c,7]

A typical procedure for addition of INO_3 to alkenes is as follows:[1] to $AgNO_3$ (6.8 g, 0.04 mol) in 50 mL dry $CHCl_3$ and 15 mL anhyd. pyridine is added dropwise 6.5 g (0.04 mol) ICl in 20 mL $CHCl_3$. AgCl is filtered and washed with $CHCl_3$-pyridine and 0.04 mol of (*E*)-4,4-dimethyl-2-pentene is added. After 3 h of stirring, the mixture is poured into ether, filtered, and concentrated to yield 8.7 g (76%) of *erythro*-3-iodo-4,4-dimethyl-2-pentyl nitrate and 5% of an iodopyridinium salt.

A typical procedure for INO_2 addition is as follows:[7] $AgNO_2$ (7.55 mmol) and I_2 (15.1 mmol) in 75 mL ether is stirred for 30 min and 2-cholestene (7.55 mmol) is added under N_2. Workup after 4 h gives 2.033 g (51%) of 2β-iodo-3α-nitrocholestane and 5% (by IR) of 3α-iodo-2β-cholestanyl nitrate.

Handling, Storage, and Precautions: solutions of INO_3 or INO_2 are not stable on standing. These reagents should be handled in a fume hood.

Additions to Alkenes.

Addition of INO_3 to alkenes usually proceeds by ionic attack of I^+, leading to a three-membered ring iodonium species. The reaction is stereoselective (*anti*) and regioselective and steric hindrance plays a role[1,2] (see ***Iodine Azide***). With 2-cholestene, the *trans*-diaxial 3α-iodo-2β-nitrate adduct results either with $AgNO_3$-I_2 (79%) or with N_2O_4 and I_2 (60%) (eq 1).[2] In contrast, when N_2O_4 is added to 2-cholestene and I_2, the product is 2β-iodo-3α-nitrocholestane (60%) from radical attack by $.NO_2$ (eq 1).[7] The same product results from INO_2 addition to the alkene.[7]

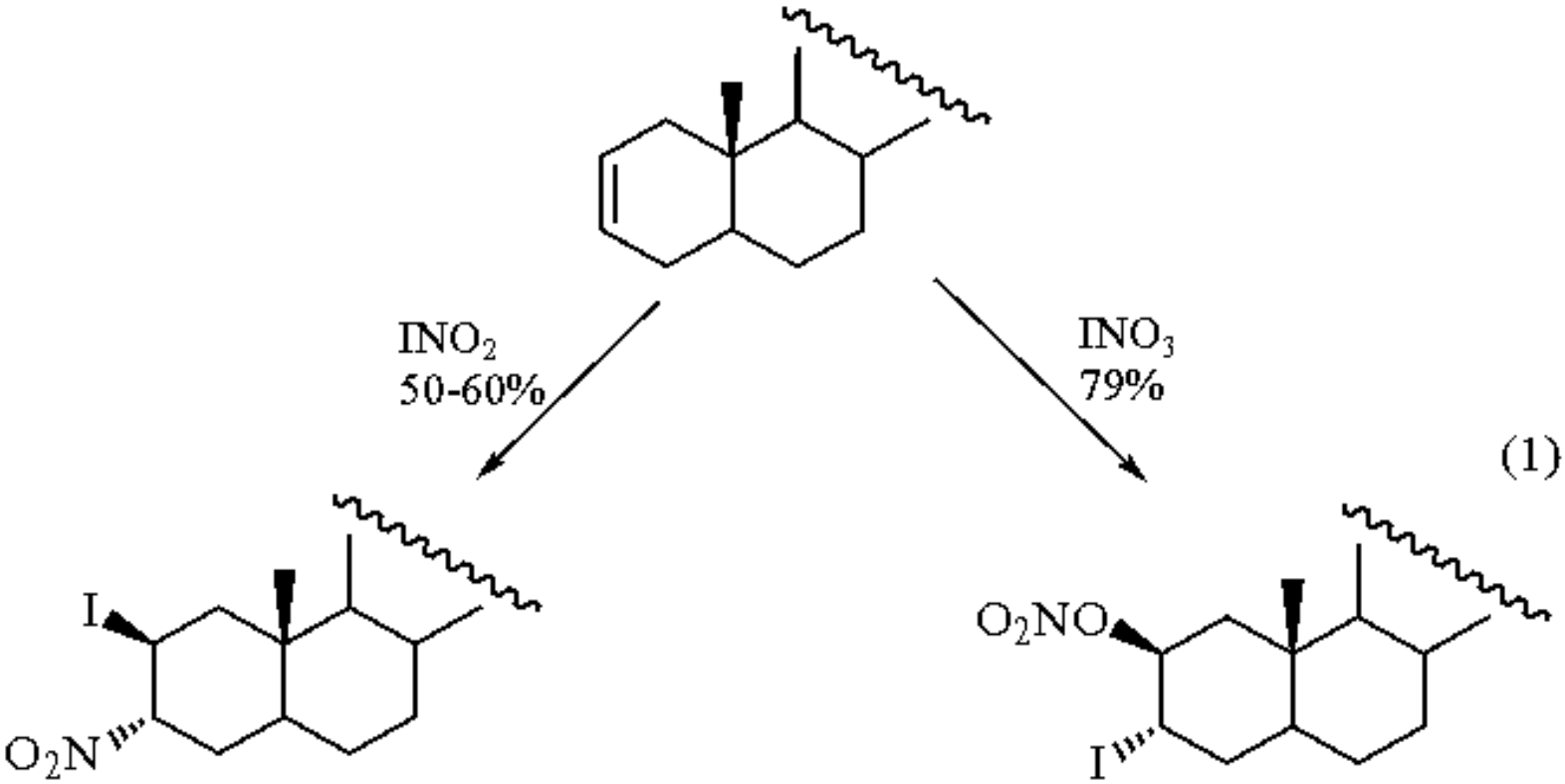

(1)

In the presence of pyridine, some alkenes give large amounts of an iodopyridinium adduct, e.g. styrene gives 40% and dihydropyran gives 72% (*trans*) (eq 2).[1,5] The INO_3 adducts can be converted with Zn-Cu in HOAc into unstable iodohydrins which can be reduced to alcohols (eq 3).[1]

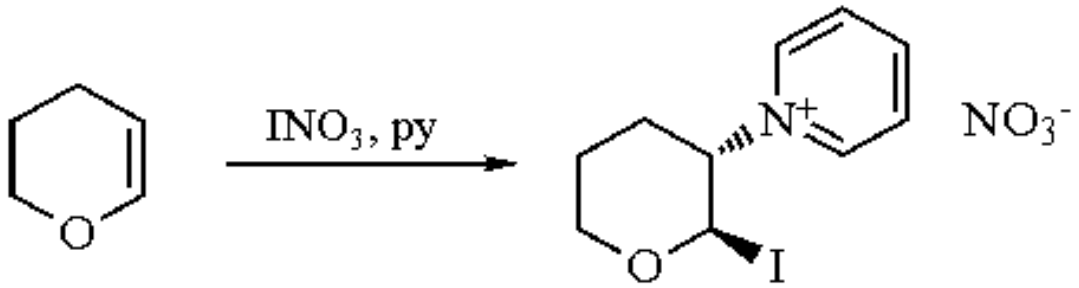

(2)

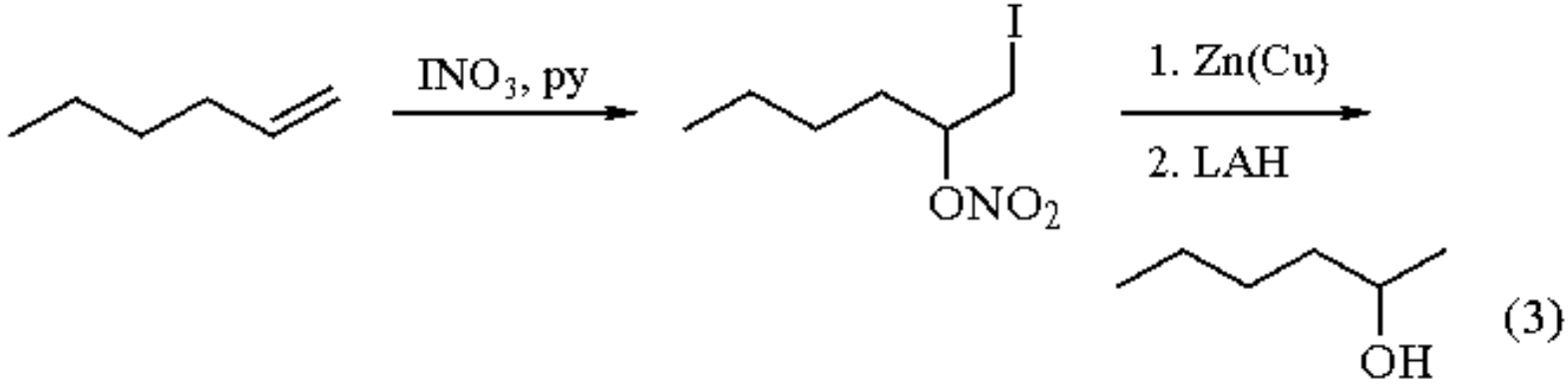

Addition of INO_3 to unsaturated fatty acids gives mixtures of INO_3 adducts and iodo ketones.[8] The reagent oxidizes secondary alcohols to ketones in fair yields.

Reaction of INO_2 with alkenes affords iodo nitro adducts which eliminate HI readily to give unsaturated nitro compounds (eq 4),[6a,7] but, in some sugar adducts, elimination of INO_2 has been reported.[6c] $AgNO_2$-I_2 has been used to iodinate alkylbenzenes at 20 °C, e.g. toluene gives a 5:2 mixture of *p*- and of *o*-iodotoluene.[9]

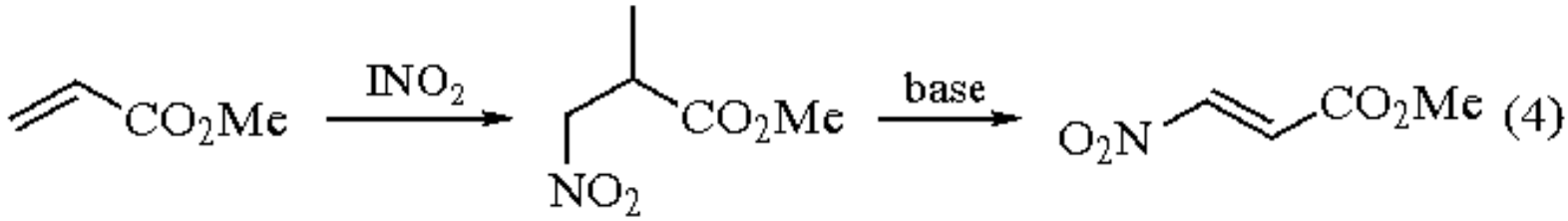

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Iodine-Nitrogen Tetroxide

I_2-N_2O_4

(I_2)

[7553-56-2] · I_2 · Iodine-Nitrogen Tetroxide · (MW 253.80) (N_2O_4)

[10544-72-6] · N_2O_4 · Iodine-Nitrogen Tetroxide · (MW 92.02)

(adds to carbon-carbon multiple bonds to form the corresponding β-iodo-α-nitro compounds;[2] useful precursors for various nitro derivatives;[3,4] experimental variation with $I_2/AgNO_2$;[5,6] radical intermediates;[7] provides good chemo- and regioselectivity)

Alternate Names: iodine-nitrogen dioxide; iodine-dinitrogen tetroxide.

Physical Data: N_2O_4: mp -11.2 °C; bp 21.2 °C; *d* 1.449 g cm^{-3}; colorless substance; brown color due to NO_2 (nitrogen dioxide) in equilibrium: 0.1% (bp), 20% (27 °C), 40% (50 °C).[8] I_2: see ***Iodine***.

Solubility: N_2O_4: decomposes in H_2O; sol alcohol, chloroform, CS_2.

Form Supplied in: N_2O_4: brown liquid/gas supplied in pressure cylinders.

Purification: if necessary, N_2O_4 can be separated from lower nitrogen oxides and nitric acid by fractional distillation under dry oxygen. Gaseous N_2O_4 can be purified by passing through silica and P_4O_{10}; purified N_2O_4 can be resublimed at -70 °C and stored at rt in pressure vessels made of glass or V2A steel.[1,8]

Handling, Storage, and Precautions: N_2O_4 is highly corrosive and very toxic when inhaled;[8b] it is sensitive to moisture and decomposes with water or above 150 °C. This reagent must be handled in a well-ventilated fume hood.

General Discussion.

Nitrogen Dioxide derived from N_2O_4 adds to carbon-carbon multiple bonds to yield, in the presence of ***Iodine***, β-iodo-α-nitroalkanes and -alkenes, both versatile precursors of various nitrogen-containing products. The reaction of I_2/N_2O_4 with isolated double bonds gives the corresponding base-sensitive β-iodo-α-nitroalkanes, usually in good yield. The transformation is conveniently carried out at 0 °C or rt in an organic solvent like ether or

dichloromethane.[9] Reactions with unsymmetrically substituted alkenes lead to the iodonitroalkane with the nitro group at the less-substituted position (eq 1).[2] Both *trans*- and *cis*-stilbene are stated to furnish the same 1-iodo-2-nitro-1,2-diphenylethane (eq 2), proposedly of *erythro* configuration.[2]

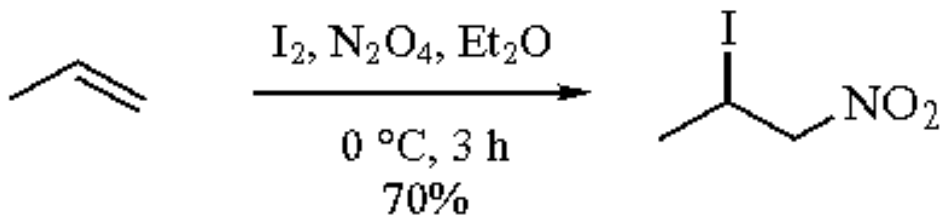

(1)

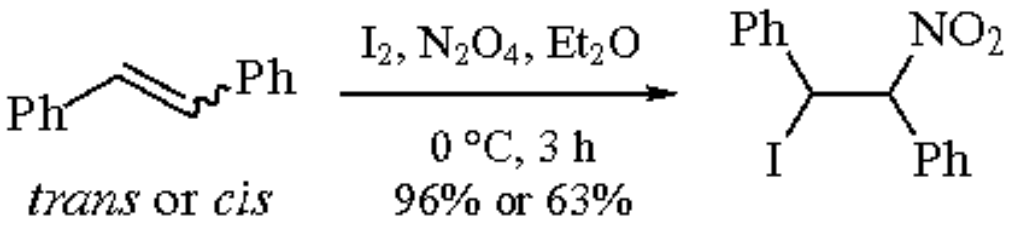

(2)

Analogous results are obtained using $I_2/AgNO_2$[5,6,9] or $I_2/NaNO_2$;[10] these reagent combinations generate the same active species. Thermodynamic data on the equilibrium 2 O_2N&bdot; + Hal_2 &ibond; 2 O_2N-Hal confirm that nitryl halides NO_2X with X = F, Cl, Br do exist, with decreasing content in the equilibrium, but rule out the presence of detectable amounts of O_2N-I (nitryl iodide).[11,12]

In the addition of NO_2/I to C=C moieties, many other functional groups such as carboxy, acetal, ester (eq 3), or trialkylsilyl[13-15] are tolerated, as is some steric hindrance, cf. the cases of camphene[2] or 2-cholestene.[9] In general, best results are obtained with alkyl- or aryl-substituted alkenes, but carboxy- or halo-substituted[12] alkenes (including difluoroethylene[16]) also add I/NO_2 well.

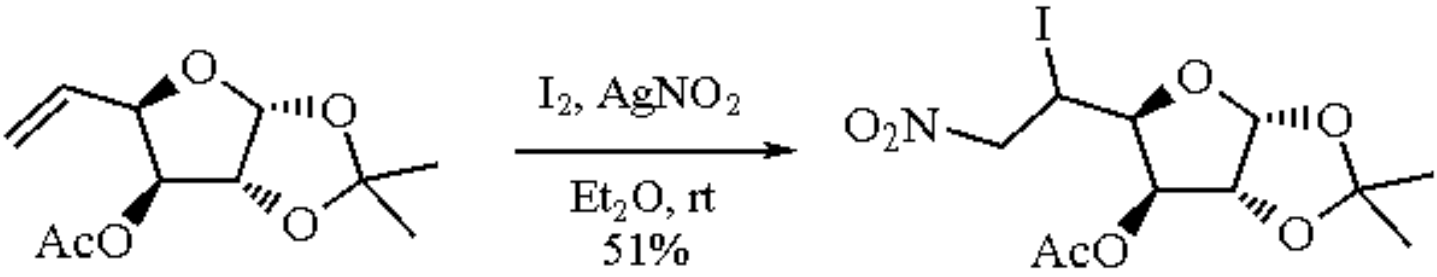

(3)

Mechanistic considerations based on product analyses lead to the conclusion that the overall addition starts with the (probably reversible) attack of NO_2&bdot; on the double bond, forming the more stable radical intermediate.[2,9] In the presence of iodine (or bromine or chlorine, if these do not react faster alone),[12,17] the nitroalkyl radical is trapped to form the β-halo-α-nitroalkane. This mechanism accounts for both the reactivities and regioselectivities observed; in the case of electron-rich double bonds an ionic mechanism may compete, as shown by the formation of a some β-iodoalkyl nitrate.[9,17] Usually, however, side reactions like dihalogenation or formation of β-iodoalkyl nitrates are not important and become significant only if the reaction is carried out inversely or without solvent (eq 4).[1a,17,18]

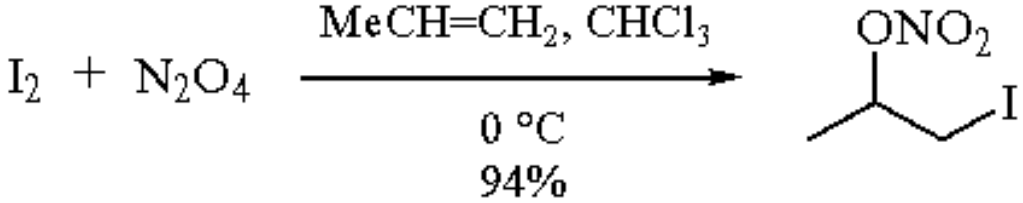

(4)

Additions of NO_2/I to conjugated enynes and dienes have also been reported, but without experimental details.[19] While the reaction of 1,3-enynes with I_2/N_2O_4 proceeds selectively at the double bond (in a 3,4-mode), 1-iodo-4-nitro-2-alkenes are produced from 1,3-dienes.[19] With nonconjugated dienes, selective monoaddition has been observed.[4]

Further transformations of iodonitro addition products (often prone to decompose on standing) are sometimes effected without isolation, and include the elimination of HI to yield the respective nitroalkene[6] and reduction by ***Sodium Borohydride*** to give the corresponding nitroalkane.[4] While additions with nitryl chloride- or bromide-generating reagents give similar or sometimes even better yields of adducts,[1,12] the further elaboration of the adducts proceeds best with the iodo derivatives.

The reaction of I_2/N_2O_4 with alkynes similarly leads to monoadducts in high yield,[2,3] with analogous reactivity and regioselectivity. Due to steric requirements in the vinyl radical intermediates, iodonitroalkene products of varying (*E*/*Z*) ratios are obtained (eq 5).[1c,2,3,15,20] Subsequent base-induced HI elimination from these β-iodonitroalkenes provides a convenient way to obtain nitroalkynes.[3]

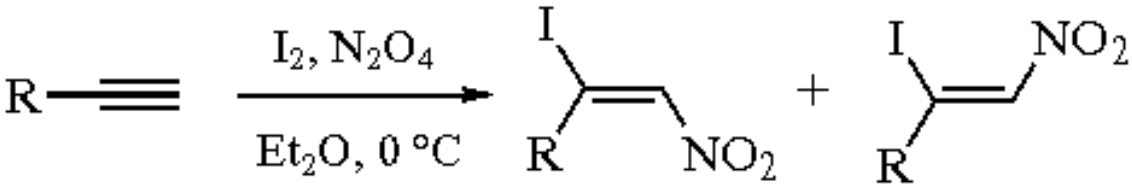

(5)

R = Bu, 90%, (*E*):(*Z*) = 75:25; *t*-Bu, 85%, (*E*):(*Z*) = 18:82

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20. Most earlier results on product distribution and configurational assignments should be taken with caution, if crude product and NMR analyses are lacking; cf. Ref. 3 and Verbruggen, R. Dissertation, University of Louvain, 1974.

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Iodine-Potassium Iodate

I_2-KIO_3

(I_2)

[7553-56-2] · I_2 · Iodine-Potassium Iodate · (MW 253.80) (KIO_3)

[7758-05-6] · IKO_3 · Iodine-Potassium Iodate · (MW 214.00)

(conversion of alkenes to iodohydrins;[1] iodination of some aromatic molecules;[2] the iodohydrins (or iodoacetates) formed are readily converted to *cis*-diols[3])

Physical Data: KIO_3: mp 560 °C; *d* 3.930 g cm^{-3}. I_2: see ***Iodine***.

Solubility: KIO_3: sol water: 9.16 g/100 g water at 25 °C and 32.2 g/100 g water at 100 °C.[4] In other work, the solubility in water was measured to be: 8.40 g KIO_3/100 g water at 25 °C; 13.7 g/100 g at 50 °C; and 24.4 g/100 g at 100 °C.[5] It shows some solubility in aqueous dioxane mixtures: 8.472 g/100 g (0% dioxane:100% water); 5.30 g/100 g (10% dioxane); 3.172 g/100 g (20% dioxane); 1.811 g/100 g (30% dioxane); 0.886 g/100 g (40% dioxane); and 0.471 g/100 g (50% dioxane). KIO_3 insol pure dioxane and most common organic solvents.

Form Supplied in: the active reagent is generated in situ, as needed. KIO_3: colorless monoclinic crystals; commercially available in at least 99.5% purity.

Preparative Method: in reactions with alkenes, the following ratio of reactants is typical: alkene:KIO_3:I_2, 4:1:2 in acetic acid.[3] The iodine and potassium iodate are premixed in acetic acid at ambient temperatures and then treated with the organic substrate and allowed to react at a suitable temperature.

Handling, Storage, and Precautions: the reagent should be prepared in solution, as needed, and used in situ. Potassium iodate is an irritant, particularly of the upper respiratory tract. Ingestion causes headache, nausea and vomiting, dizziness, and gastrointestinal irritation. Avoid ingestion, skin contact, and eye contact. Potassium iodate is a powerful oxidant and should not be stored near combustible materials, near flammable materials, or near powdered metals. Mixing with powdered metals can cause an explosion. It should be stored in a separate and tightly closed container. This combination reagent should be handled in a fume hood.

Addition to Alkenes.

Potassium iodate is a powerful oxidant and ***Iodine*** is an electrophilic reagent. When mixed together in acid media, the combined reagent converts alkenes to iodohydrins, which can be converted to *cis*-diols. Cornforth reacted propene with a mixture of iodine and potassium iodate, in aqueous sulfuric acid, and obtained a 92% yield of 1-iodo-2-propanol, along with 8% of 2-iodo-1-propanol (eq 1).[1] When the same reaction is done in acetic acid and aqueous dioxane, a 78% yield of the iodohydrin is obtained.

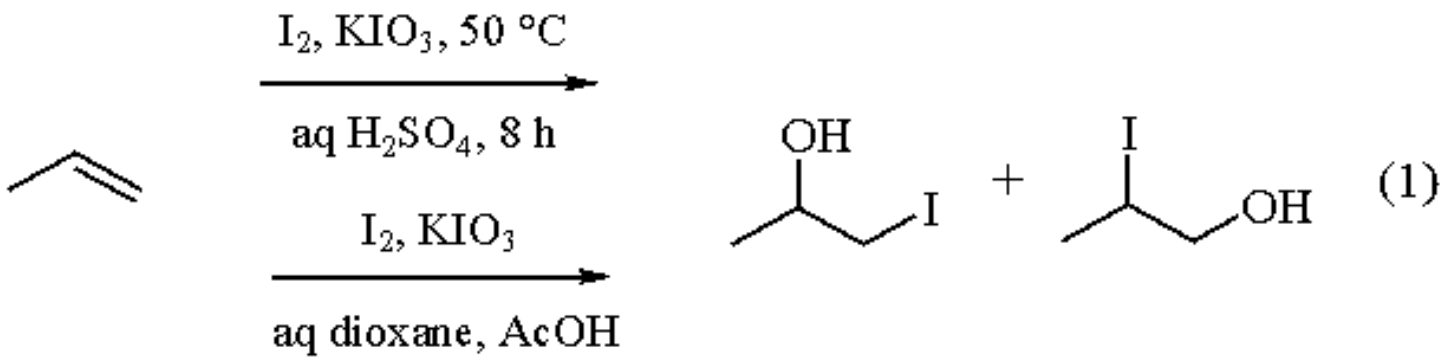

This fundamental iodohydrin procedure has been modified to produced *syn*-diols from alkenes. When cyclohexene is treated with I_2/KIO_3 in acetic acid, the *trans*-iodohydrin is formed. Subsequent reflux of this product with aqueous acetic acid or with aqueous DMSO produces *syn*-1,2-cyclohexanediol in 70% yield.[1] This same procedure has been applied to 5α-cholest-2-ene to give 2β-acetoxy-3α-iodo-5α-cholestene (eq 2). Refluxing in aqueous acetic acid leads to an 84% yield of 5α-cholestene-2β,3β-diol.[1,6] This two-step procedure is a useful alternative to the Woodward-Prévost reaction (see ***Iodine-Silver Acetate***) that produces *syn*-diols from alkenes. This I_2/KIO_3 procedure is attractive for this purpose since it does not rely on expensive silver reagents.

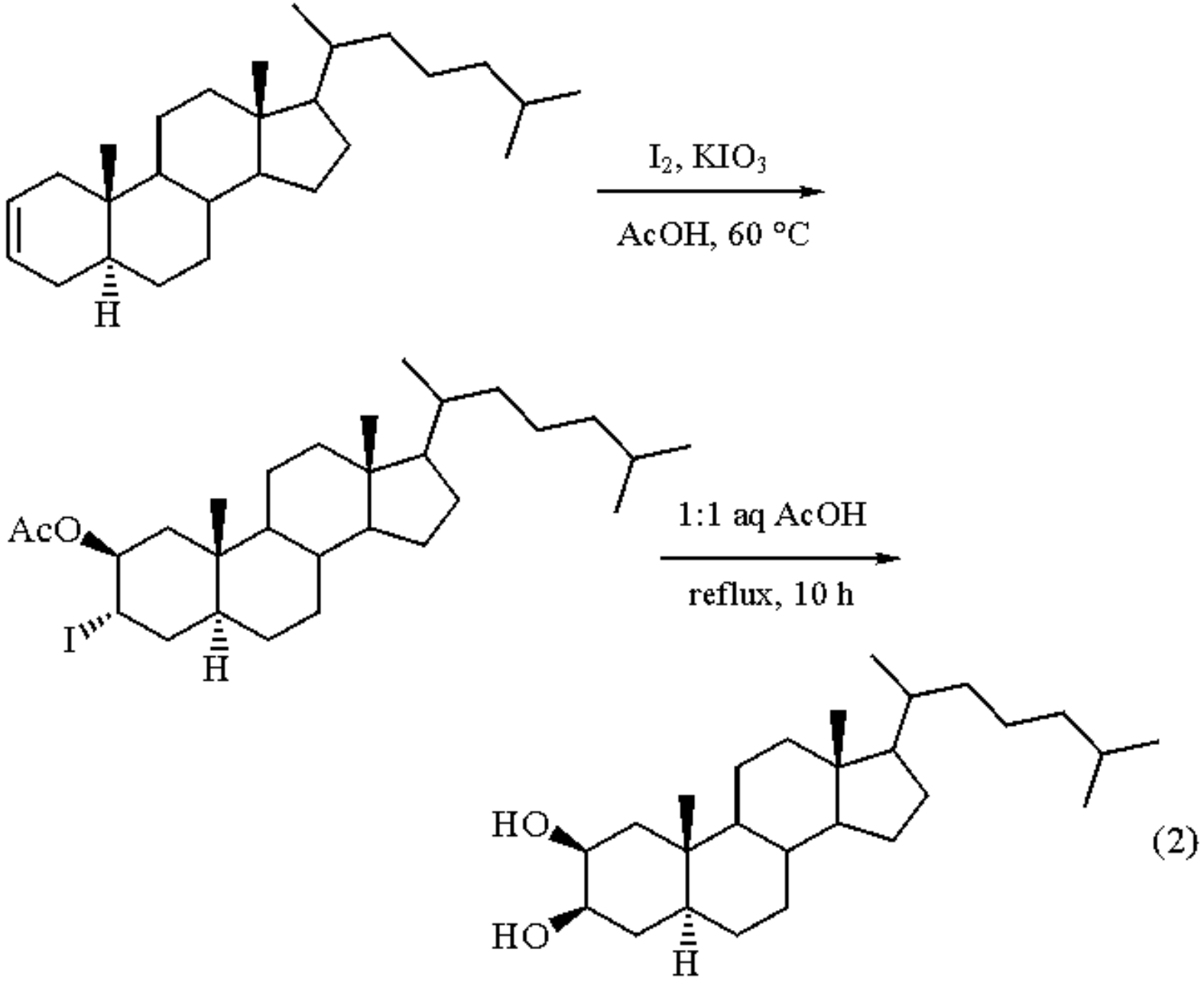

Quinones can be converted to iodoquinones with this mixed reagent. When 2-dimethylamino-1,4-benzoquinone is treated with iodine/potassium iodate in a solvent of ether and aqueous sulfuric acid, 2-dimethylamino-3-iodo-1,4-benzoquinone is formed, but in only 22% yield (eq 3).[3]

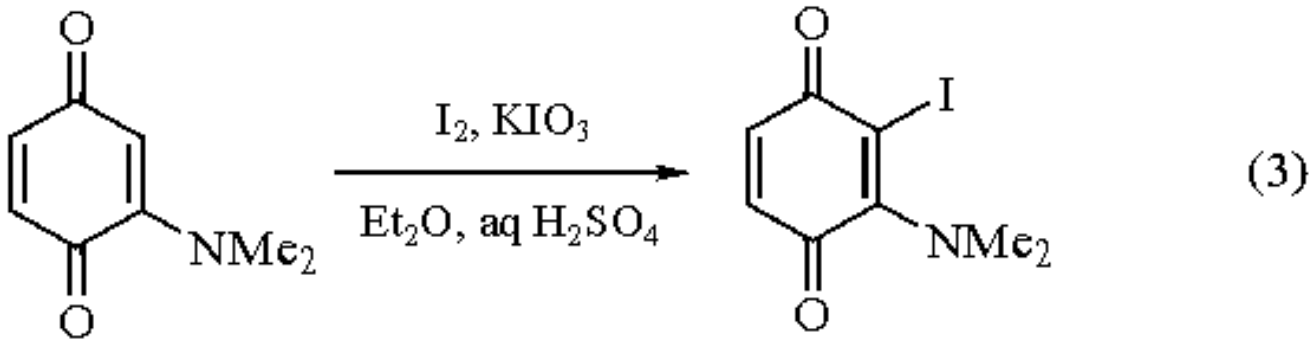

1. Cornforth, J. W.; Green, D. T. *JCS(C)* **1970**, 846.
2. Wunderer, H. *CB* **1972**, *105*, 3479.
3. Mangoni, L.; Adinolfi, M.; Barone, G.; Parrili, M. *TL* **1973**, 4485.
4. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Wiley: New York, 1978; Vol. 13, p 666.
5. Linke, W. F. *Solubilities of Inorganic and Metal-Organic Compounds*; Van Nostrand: New Jersey 1965; Vol. 2, p 235.
6. Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. *G* **1975**, *105*, 377.

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Iodine-Silver Acetate[1]

I_2-AgOAc

(I_2)

[7553-56-2] · I_2 · Iodine-Silver Acetate · (MW 253.80) (AgOAc)

[563-63-3] · $C_2H_3AgO_2$ · Iodine-Silver Acetate · (MW 166.92)

(source of positive iodine for stereoselective 1,2-functionalization of alkenes)

Physical Data: AgOAc: mp 210 °C (dec). I_2: see ***Iodine***.

Solubility: AgOAc: slightly sol acetic acid (0.54 g L^{-1}), methanol (0.17 g L^{-1}).

Form Supplied in: AgOAc: white solid; widely available.

Analysis of Reagent Purity: Ag can be assayed conveniently by volumetric titration of Ag^I.

Purification: usually used as supplied, but ***Silver(I) Acetate*** can be purified by treatment with acetic acid for a prolonged period, filtering, and drying of the solid in a vacuum oven at 40 °C for 48 h.

Handling, Storage, and Precautions: protect from light.

1,2-Dihydroxylation of Alkenes.

In acetic acid, which is the solvent of choice for these reactions, electron-rich alkenes can be converted into 1,2-dihydroxylated derivatives. The stereochemical outcome is dependent upon the conditions; if the reaction is performed in dry solvent, *trans*-1,2-diacetates are formed (the Prévost reaction) (eq 2).[2] On the other hand, if moist acetic acid is used as the solvent, monoacetylated *cis*-1,2-diols are formed (the Woodward-Prévost reaction) (eq 3).[3] A mechanism involving the intermediate formation of an acetoxonium ion has been suggested (eq 1).

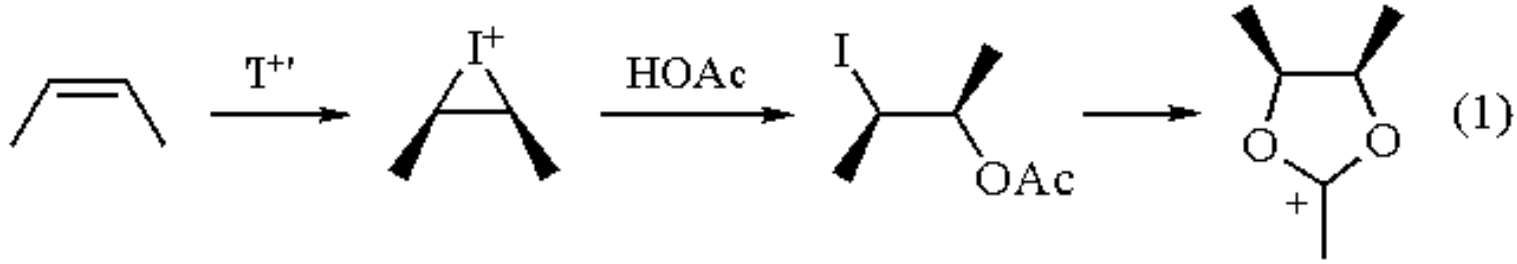

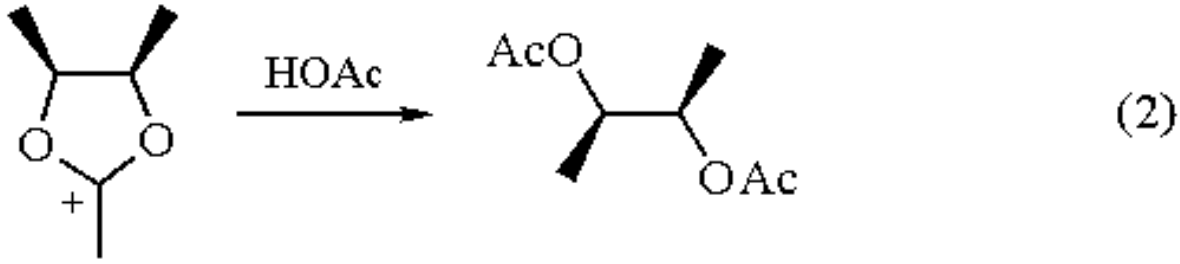

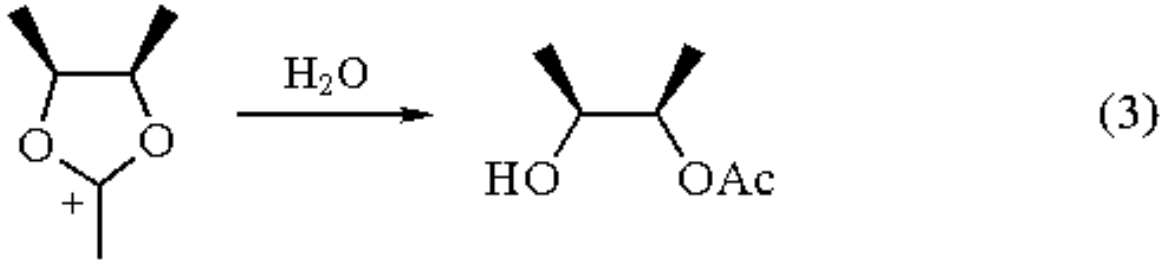

One interesting aspect of the *cis*-hydroxylation method is that it is complementary to oxidation with ***Osmium Tetroxide***, which also gives *cis*-1,2-diols, but these are formed by attack on the least hindered face of the molecule (eq 4). Using the Woodward-Prévost conditions, the *cis*-1,2-diol resulting from attack on the most hindered face predominates (eq 5).

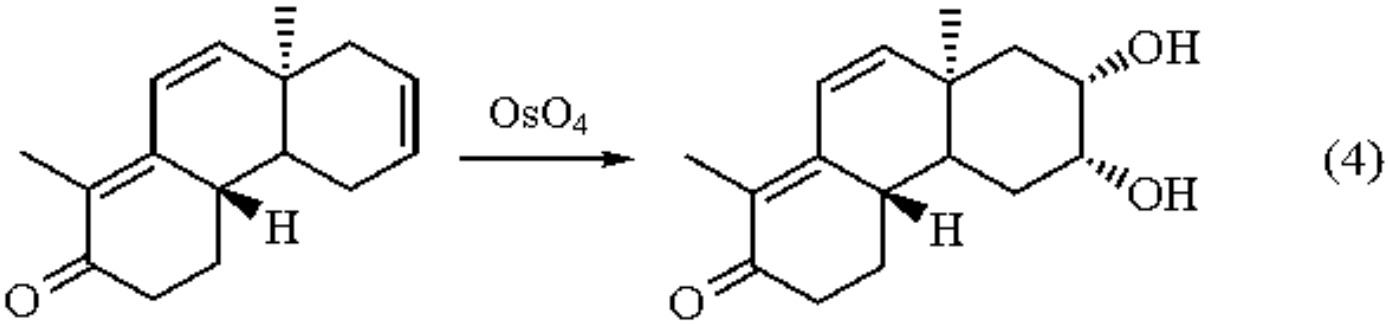

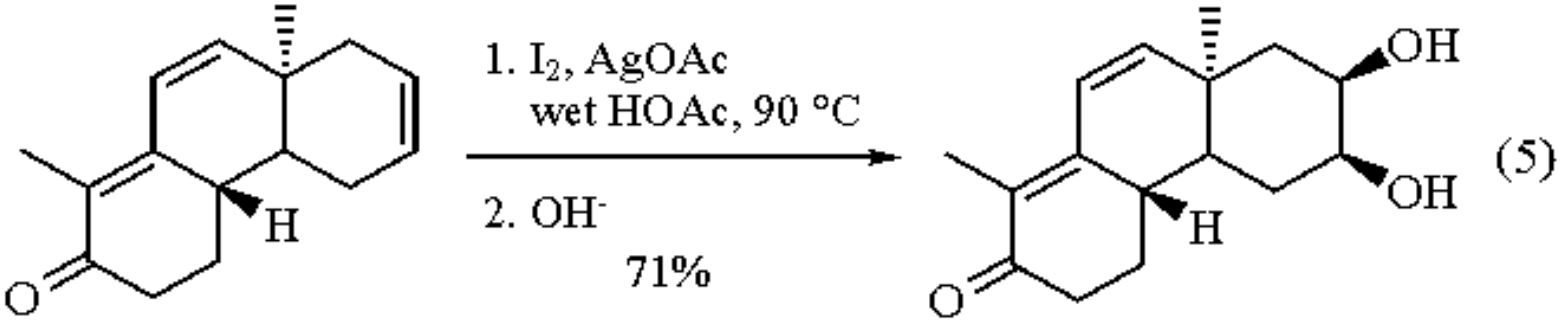

In the oxidation of 1-alkylindenes under both wet and dry conditions, identical facial selectivities were observed, supporting the proposed common acetoxonium ion intermediate (eqs 6 and 7). For example, the identical ratios (**1**)/(**2**) and (**3**)/(**4**), respectively, changed from 0.45 to >100 when going from R = Me to R = *t*-Bu, an effect of the increasing substituent size.[4]

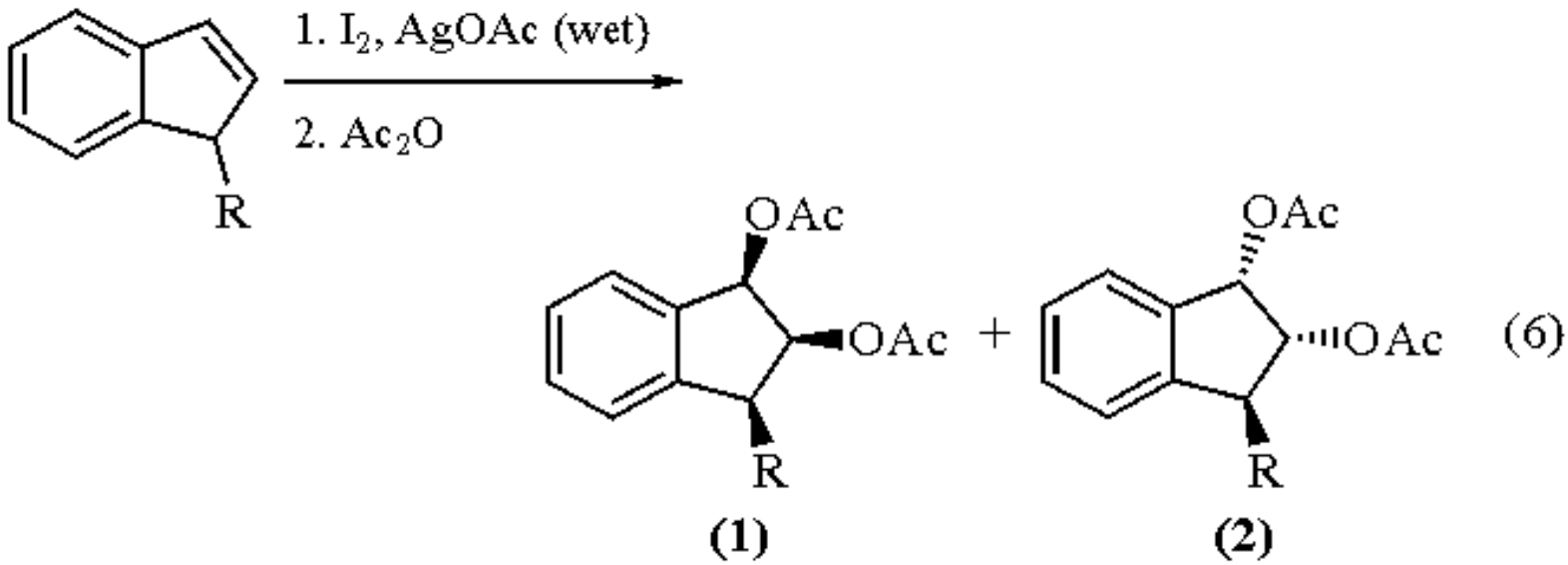

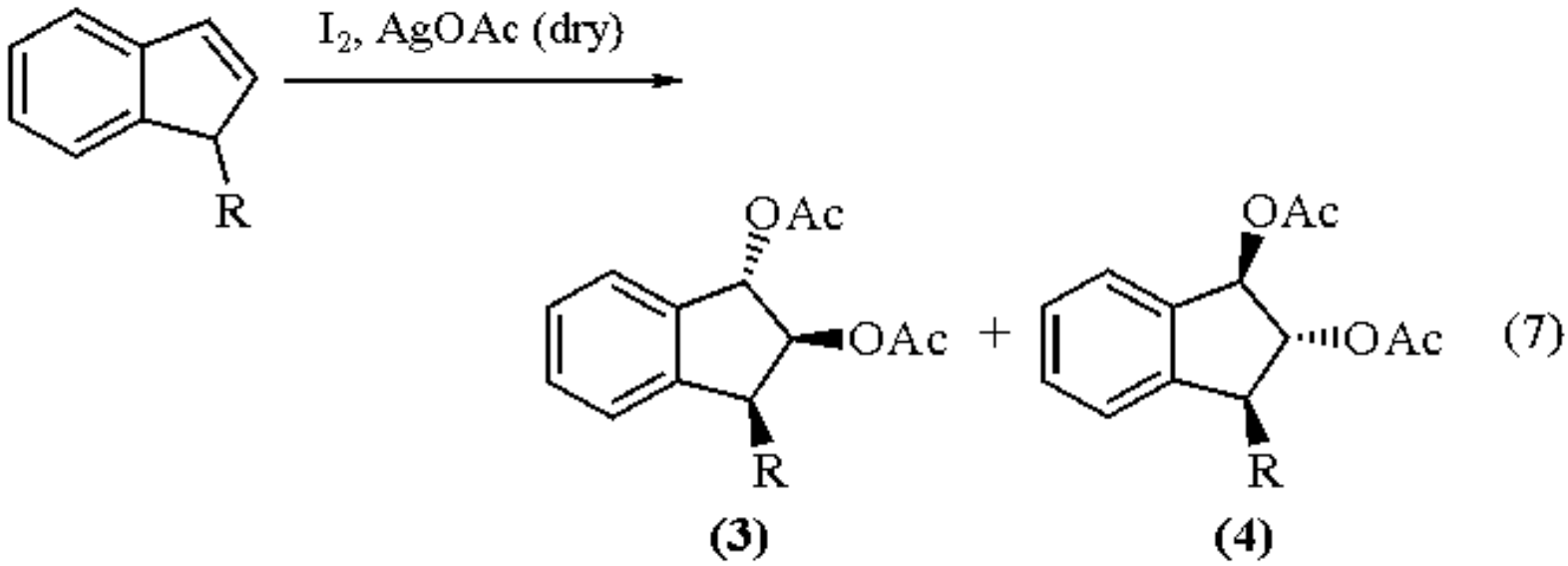

Under certain conditions, 1,2-dihydroxylation does not occur; instead, intramolecular opening of the intermediate iodonium ion is observed, e.g. the lactam oxygen in (**5**) acts as a nucleophile to give (**6**) (eq 8).[5]

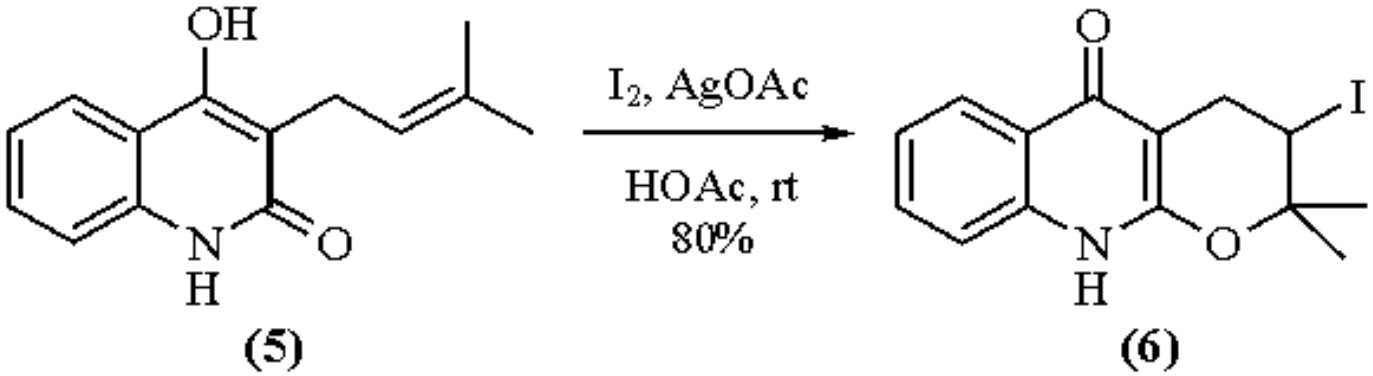

(8)

Oxidation of Enol Silyl Ethers.

Enol ethers, and in particular enol silyl ethers, can be transformed into the corresponding α-iodinated ketones by oxidation with I_2/AgOAc in CH_2Cl_2 followed by cleavage of the silyl ether (eq 9).[6]

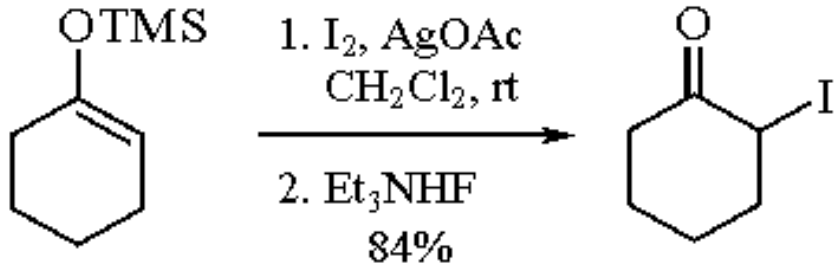

(9)

Related Reagents.

Iodine-Silver Benzoate; ***Iodine-Silver Trifluoroacetate***.

---

1. (a) Wilson, C. V. *OR* **1957**, *9*, 332. (b) Gunstone, F. D. *Adv. Org. Chem.* **1960**, *1*, 122.
2. Prévost, M. C. *CR(C)* **1933**, *197*, 1661.
3. Woodward, R. B.; Brutcher, F. V., Jr. *JACS* **1958**, *80*, 209.
4. Cedheim, L.; Eberson, L. *ACS* **1975**, *B29*, 904.
5. Subramanian, M.; Mohan, P. S.; Shanmugam, P.; Rajendra Prasa, K. J. *ZN(B)* **1992**, *47*, 1016.
6. Rubottom, G. M.; Mott, R. C. *JOC* **1979**, *44*, 1731.

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Iodine-Silver Benzoate

I_2-$PhCO_2Ag$

(I_2)

[7553-56-2] · I_2 · Iodine-Silver Benzoate · (MW 253.80) ($PhCO_2Ag$)

[532-31-0] · $C_7H_5AgO_2$ · Iodine-Silver Benzoate · (MW 228.99)

(the mixture gives silver iododibenzoate as an active reagent which converts alkenes to *cis*-dibenzoates under mild conditions[1])

Alternate Names: Prévost's reagent; silver iododibenzoate.

Physical Data: cream-colored solid.

Solubility: the most common solvent for this reagent is benzene. No data are available for the solubility of the dibenzoate reagent. $PhCO_2Ag$: sol water to the extent of 2.66 g L^{-1} at 25 °C;[2] slightly sol ethanol, 0.169 g L^{-1} (cold) and 0.465 g L^{-1} (reflux).[2]

Form Supplied in: prepared as needed.

Preparative Method: prepared by reaction of ***Iodine*** with 2 equiv of ***Silver(I) Benzoate***.[1] In general, 2 equiv of silver benzoate are refluxed in benzene with 1 equiv of iodine per mole of alkene to be reacted.[3] If the reagent is to be isolated prior to reaction with the alkene, it is first washed with saturated aqueous ammonia to remove silver benzoate and then with saturated aqueous sodium bicarbonate to remove benzoic acid.

Purification: the crystalline complex can be purified by extraction with benzene in a Soxhlet apparatus.[3]

Handling, Storage, and Precautions: no special precautions have been reported for the dibenzoate.

Prévost Reaction.

The reaction of 2 equiv of silver benzoate and iodine initially forms $PhCO_2I$, but this reacts further to form silver iododibenzoate, $(PhCO_2)_2AgI$, containing two benzoate groups.[3] This intermediate can react further under the proper conditions to give the tribenzoate silver derivative, but the dibenzoate is taken to be the reactive species in reactions with alkenes, which is the most important reaction of this reagent. Prévost found that silver benzoate and iodine converts alkenes such as styrene to the 1,2-dibenzoate (eq 1), which can be saponified to the 1,2-diol.[4a] This

transformation (formally a hydroxylation) is now called the Prévost reaction.[4] Reaction with cyclic alkenes generates *trans*-diols, in contrast to permanganate and osmium hydroxylations which give *cis*-diols (see ***Potassium Permanganate*** and ***Osmium Tetroxide***). This reaction is generally related to the Hunsdiecker reaction (the coupling reaction of silver carboxylate; see ***Iodine***). When an alkene reacts with the silver iododibenzoate, an iodonium salt is generated and this is reacts with silver benzoate to form a cationic dioxolane species. Attack by a second molecule of benzoate gives the ester, a *trans*-dibenzoate. Saponification generates the *trans*-diol. A similar hydroxylation reaction, also called the Prévost reaction, uses silver acetate and iodine[5] (see ***Iodine-Silver Acetate***), although the acetate reaction (often called the Woodward-Prévost reaction) gives the *cis*-diol.

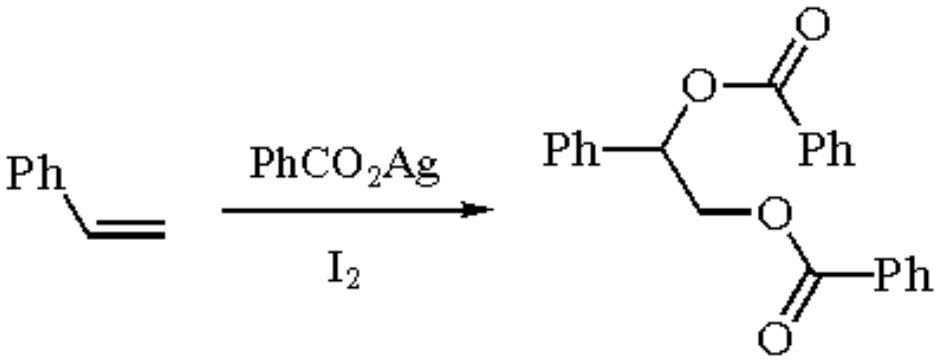

(1)

A synthetically useful example of the reaction with silver benzoate is the conversion of a dibenz[*a*,*j*]acridine derivative to the *trans*-dibenzoate in 35% yield (eq 2).[6] With relatively simple systems (such as styrene), the yields are usually quite good (80-90%).

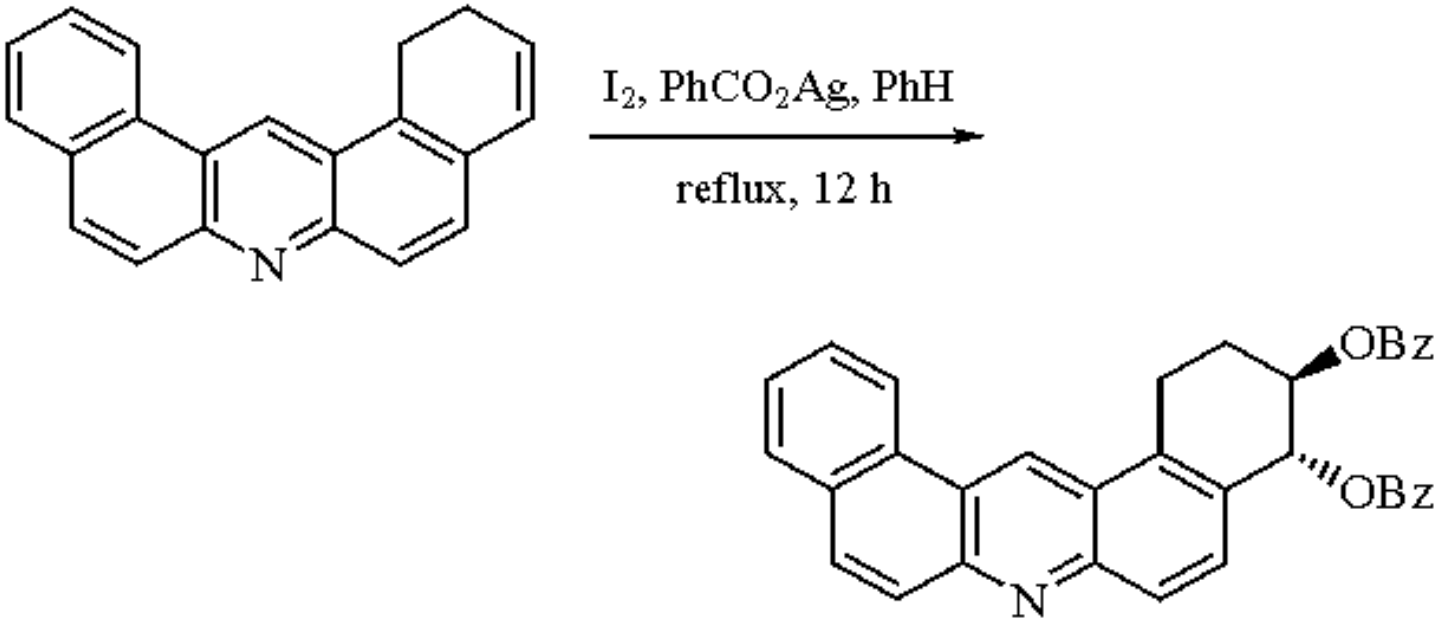

(2)

There are interesting variations in the reaction when other functional groups are present. When 5-isopropyl-5-allylbarbituric acid is treated with silver benzoate and iodine, for example, a 28% yield of a furopyrimidine is obtained (eq 3).[7] The initially formed benzoate intermediate reacts with the proximate imide moiety to produce the final product.

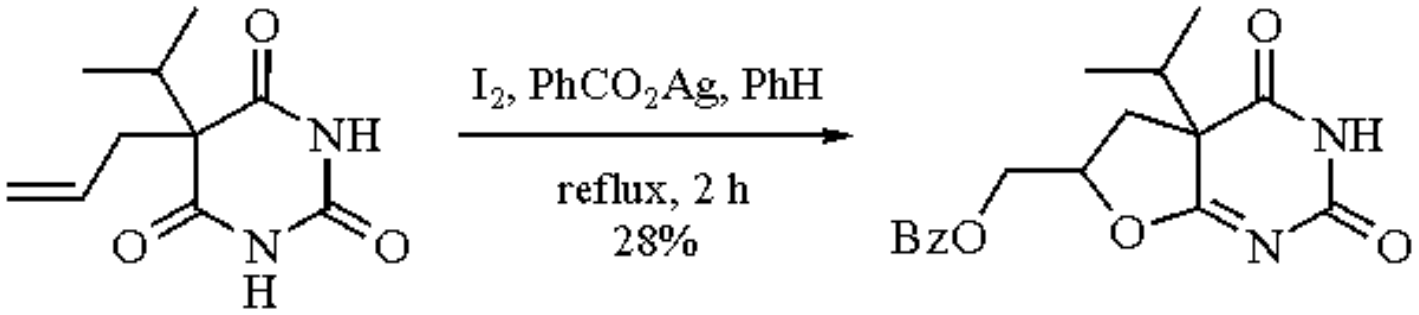

(3)

In addition to quinone derivatives, silver iododibenzoate reacts with aromatic hydrocarbons to give different products.[8] Electron-deficient benzene derivatives such as nitrobenzene give biphenyl derivatives, electron-rich benzene derivatives such as anisole give iodoanisole derivatives, and alkylbenzenes give essentially no reaction.[8,9]

Oxidative Cleavage of 1,2-Diols.

Using an excess of this reagent, 1,2-diols can be cleaved oxidatively.[10] For example, the fatty chain diol in eq 4 is cleaved selectively using $I_2/PhCO_2Ag$.[11]

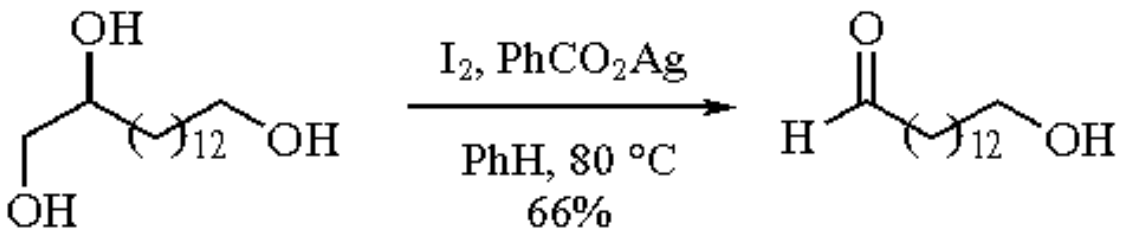

(4)

Allylic Oxidations.

In certain cases, oxidation of alkenes with $I_2/PhCO_2Ag$ in benzene causes allylic oxidation (eq 5).[12]

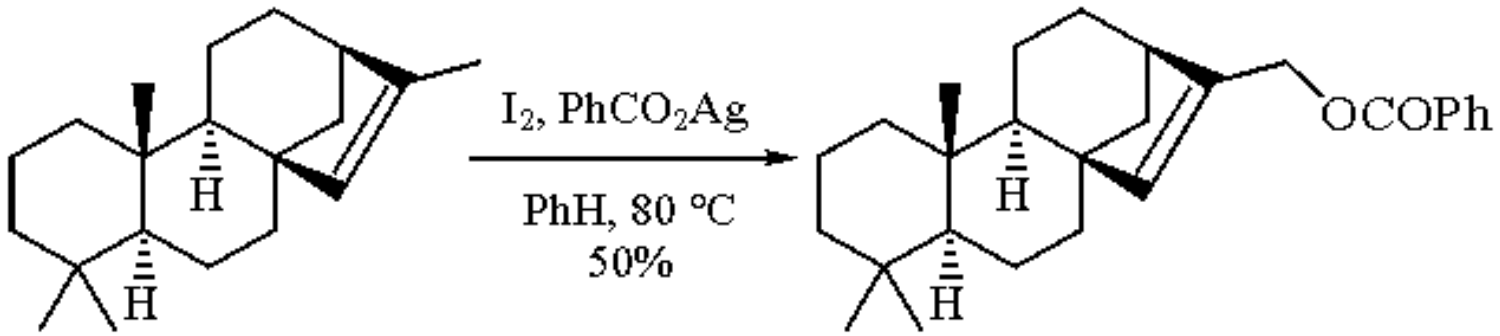

(5)

Related Reagents.

Iodine-Silver Trifluoroacetate.

1. Hershberg, E. B. *HCA* **1934**, *17*, 351.
2. Linke, W. F. *Solubilities of Inorganic and Metal-Organic Compounds*; Van Nostrand: New Jersey, 1958, Vol 1, pp 46-47.
3. Ferretti, A.; Tessi, G. *JCS* **1965**, 5203.
4. (a) Prévost, C. *CR(C)* **1933**, *196*, 1129. (b) Prévost, C. *CR(C)* **1935**, *200*, 942. (c) Prévost, C.; Lutz, R. *CR(C)* **1934**, *198*, 2264. (d) Wilson, C. V. *OR* **1957**, *9*, 332.
5. Birkenbach, L.; Goubeau, J.; Berninger, E. *CB* **1932**, *65*, 1339.
6. Rosario, C. A.; Holder, G. M.; Duke, C. C. *JOC* **1987**, *52*, 1064.
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9. Sletzinger, M.; Dawson, C. R. *JOC* **1949**, *14*, 670.
10. Raman, P. *PIA(A)* **1956**, *44*, 321.
11. Lüning, B.; Paulsson, L. *ACS* **1967**, *21*, 830.
12. Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R.; Rutledge, P. S. *JCS* **1962**, 1850.

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Iodine-Silver(I) Fluoride

I_2-AgF

(I_2)

[7553-56-2] · I_2 · Iodine-Silver(I) Fluoride · (MW 253.80) (AgF)

[7775-41-9] · AgF · Iodine-Silver(I) Fluoride · (MW 126.87)

(source of electrophilic iodine, I^+, in electrophilic aromatic substitution reactions;[1] IF addition reagent across double bonds;[2] mild oxidant which fluoridates selected polycyclic aromatic hydrocarbons via radical cationic intermediates[3])

Physical Data: AgF: mp 435 °C; bp 1150 °C; *d* 5.85 g cm^{-3}.

Solubility: AgF: sol acetonitrile; sparingly sol aromatic and halogenated solvents.

Form Supplied in: AgF: orange and brown chunks.

Handling, Storage, and Precautions: AgF: corrosive, harmful dust, hygroscopic, light sensitive. This reagent should be handled in a fume hood.

Electrophilic Reactions.

Up to 50% yield of an aryl iodide is obtained when ***Iodine*** and ***Silver(I) Fluoride*** are added to neat, activated aromatic compounds; much poorer yields result if the aromatic compound is weakly activated or deactivated toward electrophilic aromatic substitution (eq 1)[1] (see ***Trifluoroacetyl Hypoiodite*** for a superior iodinating reagent in electrophilic aromatic substitution reactions). Quantitative *trans* addition to double bonds is observed when a dilute solution of iodine (or bromine) in benzene is slowly added to a suspension of AgF in a solution of the target alkene in benzene (eq 2).[2]

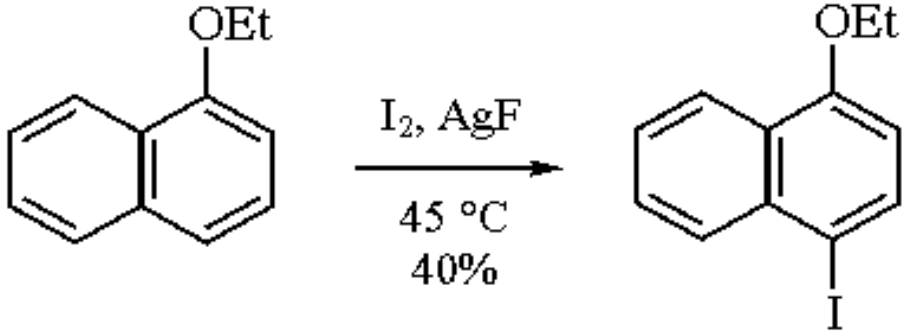

(1)

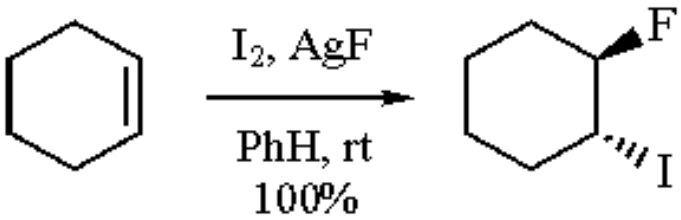

(2)

Fluorination.

Polycyclic aromatic hydrocarbons with low oxidation potentials are oxidized by the Ag^+/Ag redox couple to radical cations which are attacked by a fluoride nucleophile to give low yields (10-50%) of fluorinated products.[3]

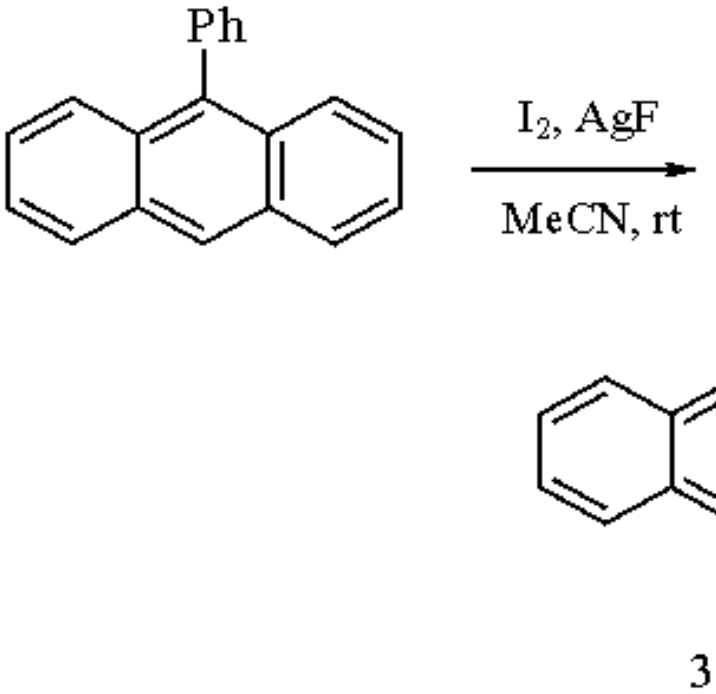

(3)

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1. Bergmann, E. D.; Shahak, I. *JCS* **1959**, 1418.
2. Hall, L. D.; Jones, D. L. *CJC* **1973**, *51*, 2902.
3. O'Malley, R. F.; King, R. F. *JOC* **1984**, *49*, 2803.

Iodine-Silver Trifluoroacetate

I_2-CF_3CO_2Ag

(I_2)

[7553-56-2] · I_2 · Iodine-Silver Trifluoroacetate · (MW 253.80) (CF_3CO_2Ag)

[2966-50-9] · $C_2AgF_3O_2$ · Iodine-Silver Trifluoroacetate · (MW 220.89)

(a source of positive iodine for iodination of aromatic compounds and for oxidation of alkenes)

Physical Data: CF_3CO_2Ag: mp 257-269 °C (dec).

Solubility: CF_3CO_2Ag: sol benzene, diethyl ether, water.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: contents of Ag can be assayed conveniently by volumetric titration of Ag^I.

Preparative Method: extraction of an aqueous solution of $AgNO_3$ and CF_3CO_2Na with ether.[1]

Handling, Storage, and Precautions: should be protected from light.

Introduction.

The combination of ***Iodine*** and ***Silver(I) Trifluoroacetate***, usually in a chlorinated solvent, is believed to involve the formation of a complex between silver trifluoroacetate and electrophilic iodine trifluoroacetate.[1]

Aromatic Iodination.

The reagent can iodinate various aromatic compounds, the conditions being dependent upon the reactivity of the substrate. For example, benzoic acid was iodinated in nitrobenzene at 150 °C to give 3-iodobenzoic acid in 84% yield.[2] On the other hand, iodination of veratrole is performed in refluxing chloroform (eq 1).[3]

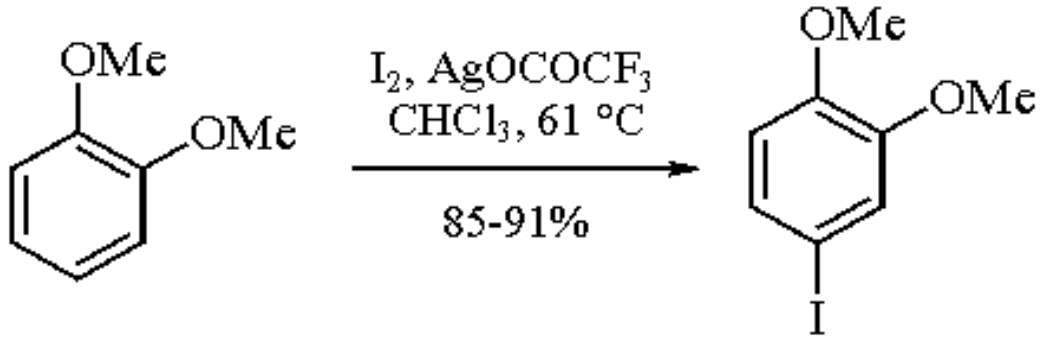

(1)

An elegant application of this mild aromatic iodination procedure was reported by Carruthers and co-workers (eq 2).[4]

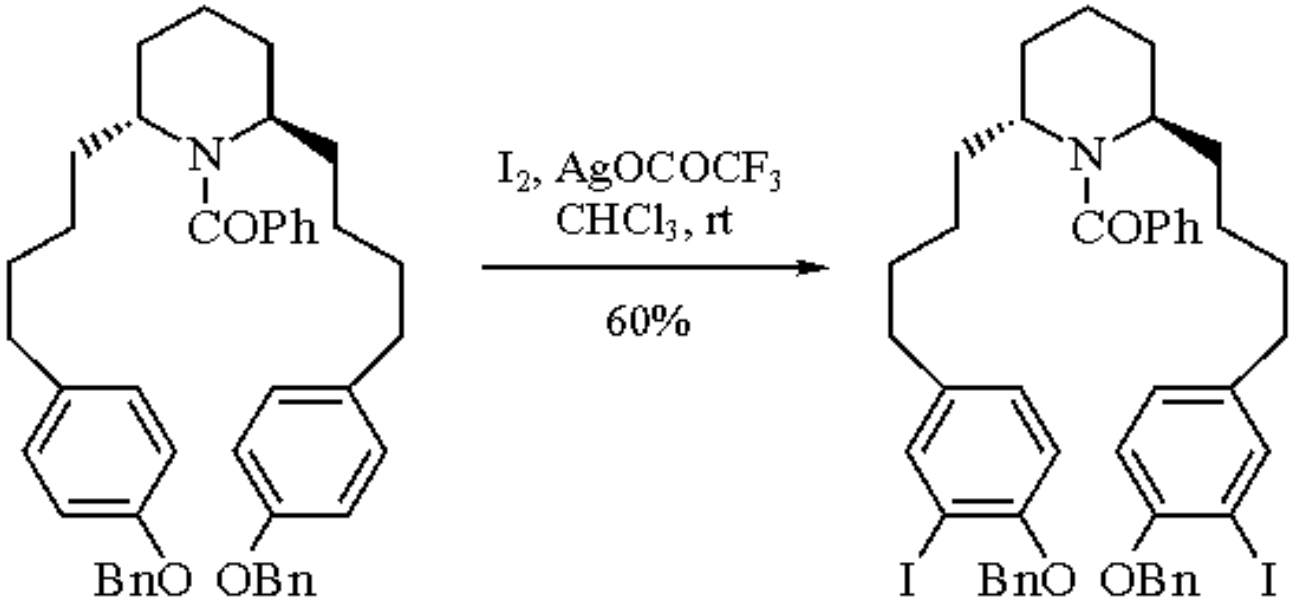

(2)

Oxidation of Alcohols and Ketones.

Primary alcohols can be oxidized to the corresponding aldehydes in low yields. Secondary alcohols are oxidized to the corresponding ketones, but the reaction is complicated by further oxidation to the 1,2-dicarbonyl compounds. Ketones are transformed into the corresponding 1,2-dicarbonyl compounds, e.g. biacetyl can be isolated in 50% yield from 2-butanone. These reactions are usually not of synthetic value but, in cases where such functional groups are present, care should be taken to prevent their oxidation.[5]

Oxidation of Alkenes.

The positively charged iodine reacts with electron-rich alkenes by analogy with the combination ***Iodine-Silver Acetate***. Depending on the structure of the substrate, the intermediate iodonium ion can undergo intra- or intermolecular consecutive reactions. The simplest case is represented by the treatment of 5α-cholest-2-ene with I_2-CF_3CO_2Ag, where an intermolecular iodotrifluoracetoxylation was observed (eq 3).[6]

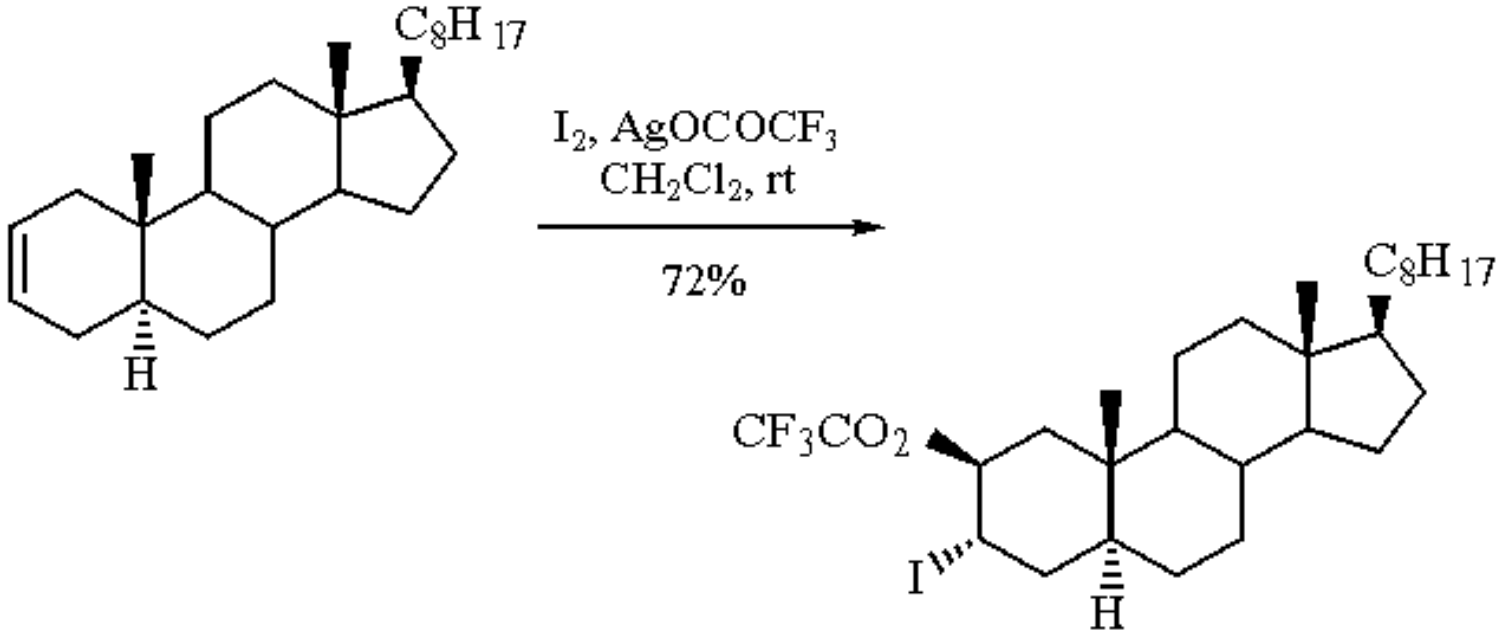

(3)

cis-Vinylsilanes behave similarly, i.e. on reaction with I_2-CF_3CO_2Ag, the corresponding 1,2-adduct can be isolated. On elimination with ***Potassium Fluoride***, *trans*-vinyl iodides are formed (eq 4). However, addition of only iodine to the same *cis*-vinylsilane gave the corresponding *cis*-vinyl iodide. Other halogens (Cl_2, Br_2) gave the 1,2-adduct, which can be converted into the corresponding *trans*-vinyl halide by treatment with ***Sodium Methoxide***.[7]

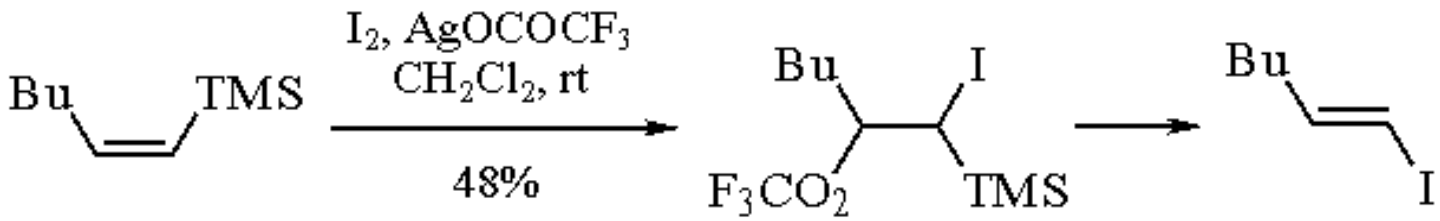

(4)

In a more elaborate approach, tetrahydrofurans were prepared in a stereoselective manner from the corresponding homoallylic alcohols by treatment with I_2-CF_3CO_2Ag (eqs 5-8).[8] From a stereochemical point of view it is interesting to note that the products observed are the results of *syn* addition across the double bond, which is contrary to the expected direction of addition. On the other hand, ***Benzeneselenenyl Chloride*** adds to form the corresponding 2,5-*trans*-tetrahydrofurans, i.e. the result of an *anti* addition. Both (*E*)- and (*Z*)-alkenes behave similarly, i.e. *syn* addition with I_2-CF_3CO_2Ag and *anti* addition with PhSeCl. Another unexplained observation is that the direction of the nucleophilic attack is dependent upon the stereochemistry of the alkene, i.e. (*E*)-alkenes are attacked by iodine on the most hindered side (eqs 5 and 7), whereas (*Z*)-alkenes are attacked on the least hindered side (eqs 6 and 8).

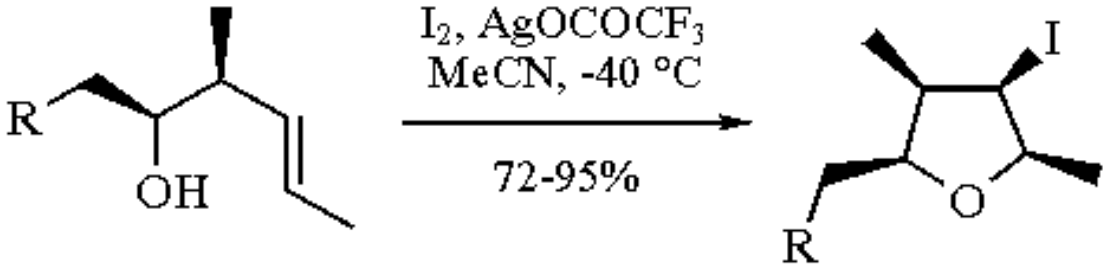

(5)

R = H, OBn, OTBDMS

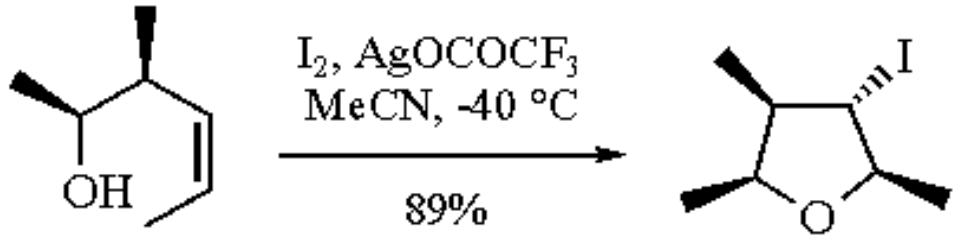

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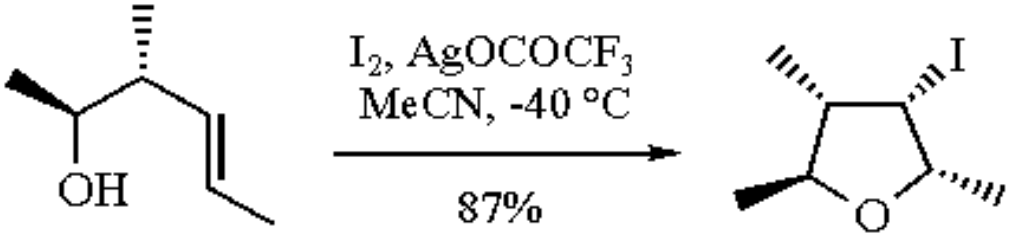

(7)

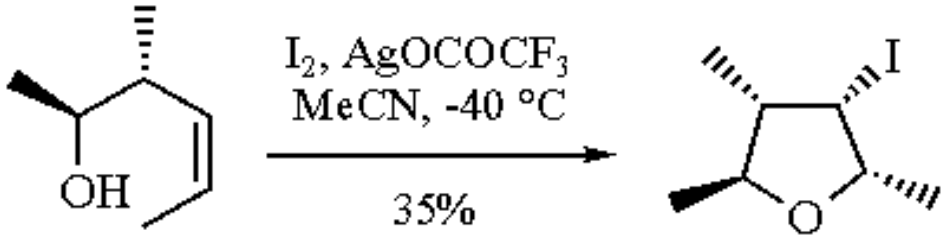

(8)

The use of acetonitrile as the solvent is critical for the success of these reactions.

Related Reagents.

Iodine-Silver Benzoate.

---

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Lars-G. Wistrand

Nycomed Innovation, Malmö, Sweden

Iodine Tris(trifluoroacetate)[1]

$(CF_3CO_2)_3I$

[14353-86-7] · $C_6F_9IO_6$ · Iodine Tris(trifluoroacetate) · (MW 465.96)

(formation of trifluoroacetoxy-substituted alkanes,[5,6] reacts with alkenes to form bis(trifluoroacetates);[10] iodinates arenes;[7,8] preparation of iodonium salts via [bis(trifluoroacetoxy)iodo]arenes;[9] induces 1,2-migration in arylalkenes;[11] formation of α,β-trifluoroacetoxy diesters from cyclic ethers[5,12,13])

Alternate Names: ITT; tris(trifluoroacetoxy)iodane.

Physical Data: mp 120 °C (dec).

Solubility: sol CH_2Cl_2, $CHCl_3$.

Form Supplied in: yellow crystals; not commercially available.

Analysis of Reagent Purity: elemental analysis.[4]

Preparative Methods: ***Trifluoroacetic Acid*** oxidation of ***Iodine***;[2] reaction of ***Silver(I) Trifluoroacetate*** with ICl_3;[3] reduction of $IO_2(CO_2CF_3)$ with I_2;[2] or action of ***Nitric Acid/Trifluoroacetic Anhydride*** on I_2.[4]

Purification: sublimation (90 °C/10^{-3} mmHg).[4]

Handling, Storage, and Precautions: stable compound; store in the absence of moisture in a sealed container under nitrogen, protected from light. Handle in a fume hood.

Oxidation of Alkanes.

Alkanes react rapidly with iodine tris(trifluoroacetate). In the case of cyclohexane, $(AcO)_3I$ does not react at rt, but ITT reacts in 3 d (eq 1).[5]

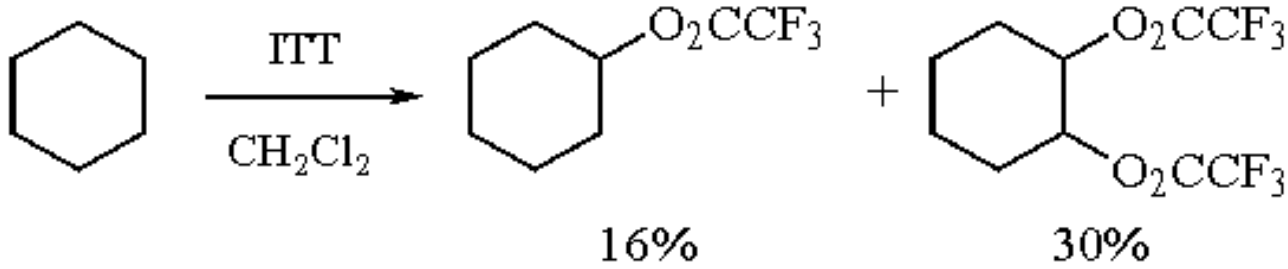

(1)

16% 30%

cis:*trans* = 9:1

Alkanes possessing tertiary C-H groups are oxidized within minutes to form trifluoroacetate esters (eqs 2-4).[5]

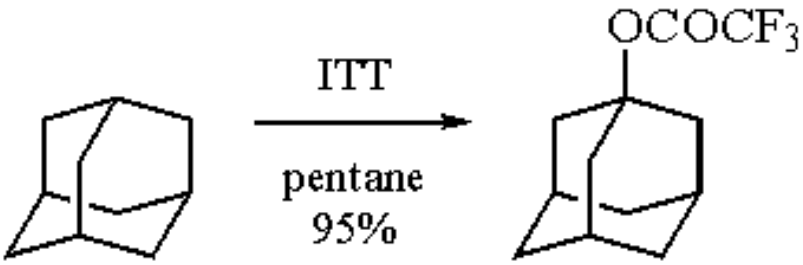

(2)

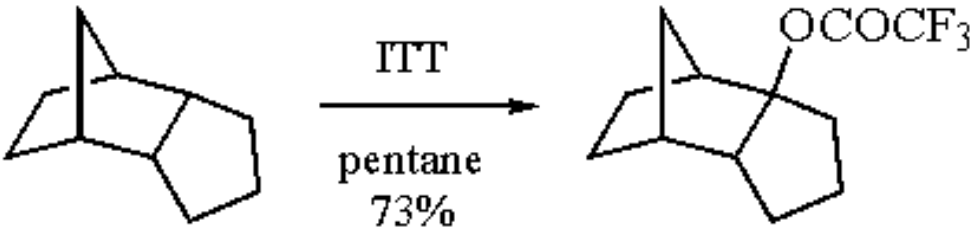

(3)

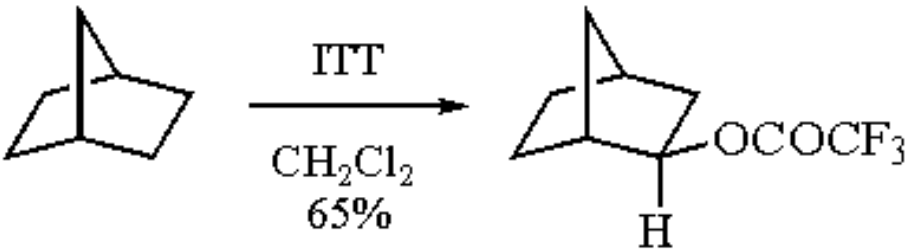

(4)

99.9% *exo*

8α*H*-Cedrane reacts rapidly at rt to yield the ring contracted ketone (eq 5).[6]

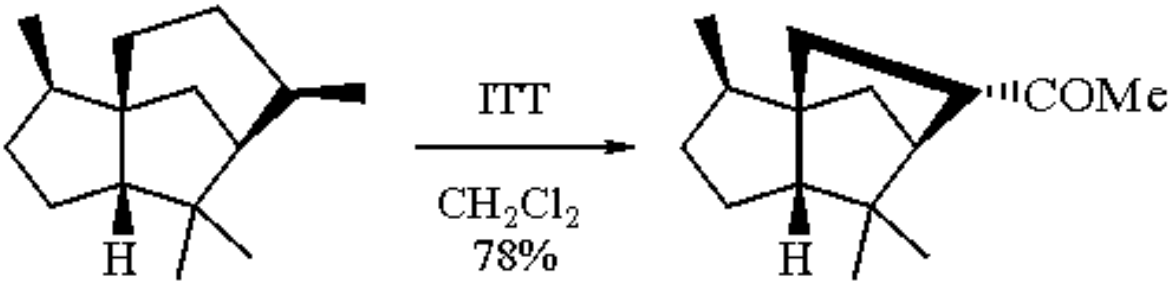

(5)

Reaction with Arenes.

The reaction of arenes with ITT leads to introduction of the $(CF_3CO_2)_2I$ group onto the aromatic ring to yield the corresponding [bis(trifluoroacetoxy)iodo]arenes (eqs 6 and 7).[7] The reaction of ITT with a variety of aromatic compounds, including those substituted with electron-withdrawing groups, can be employed in a general method for the synthesis of iodoarenes.[8] For example, treatment of *p*-methoxyacetophenone with ITT at rt followed by reduction of the intermediate I^{III} species with aqueous ***Sodium Iodide*** provides the aryl iodide in excellent yield (eq 8).[8]

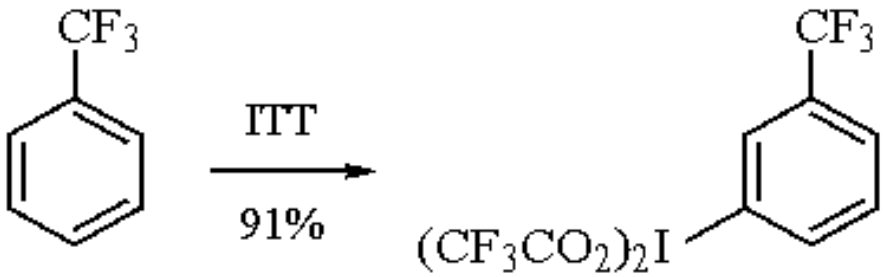

(6)

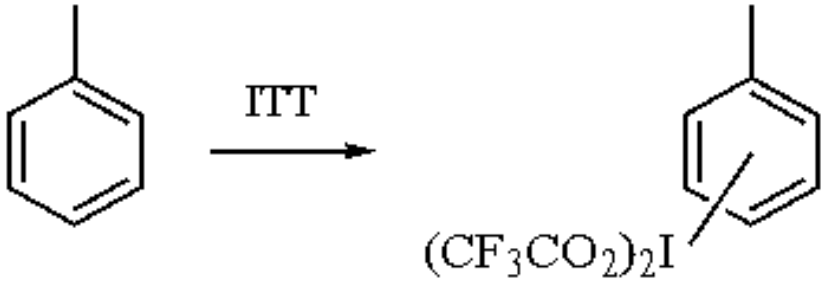

(7)

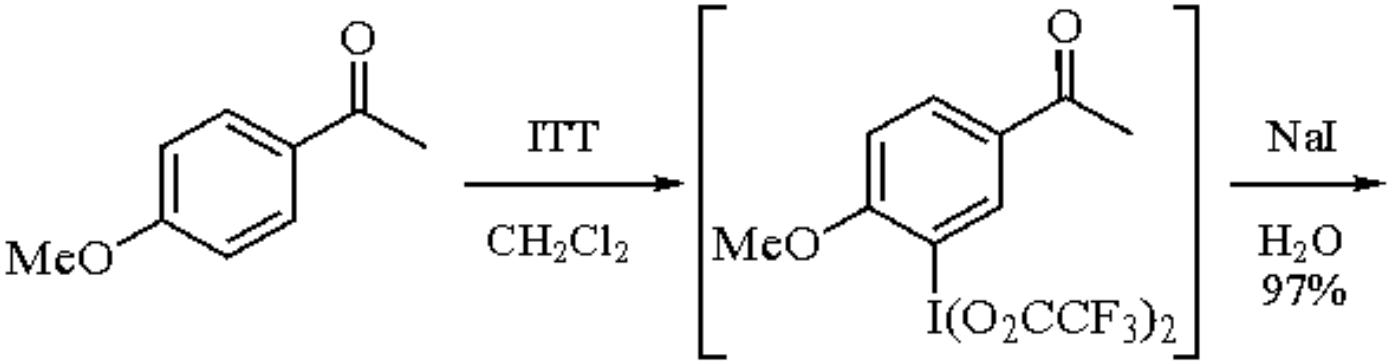

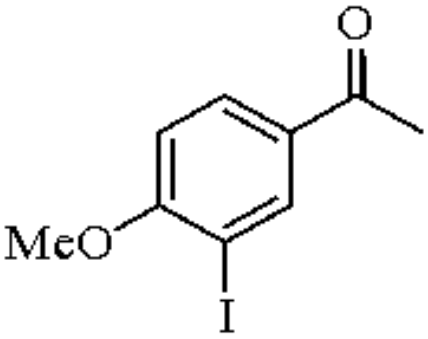

(8)

Similarly, toluene yields a 2:3 *o*:*p* ratio and chlorobenzene yields a 6:94 *o*:*p* ratio of products.

[Bis(trifluoroacetoxy)iodo]arenes can be used for the preparation of iodonium salts (eq 9).[9]

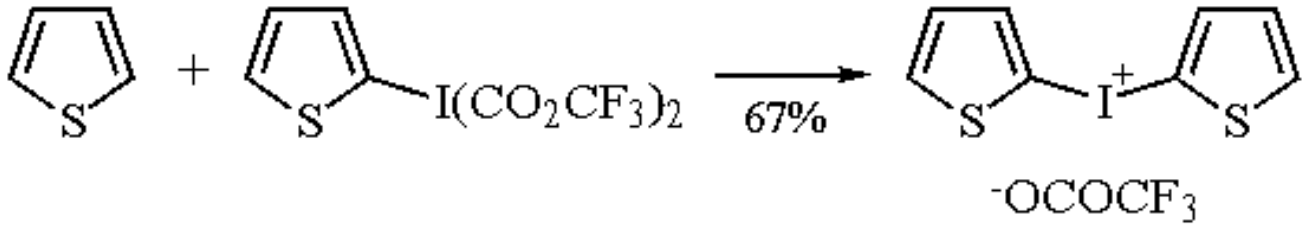

(9)

Miscellaneous Reactions.

Alkenes yield *vic*-*cis*-bis(trifluoroacetoxy) diesters upon addition of ITT (eq 10).[10]

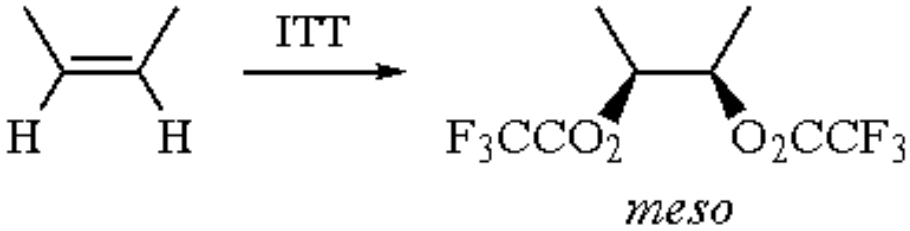

(10)

1,2-Migration occurs in the reaction of $Ar_2C{=}CH_2$ with ITT following addition of water (eq 11).[11]

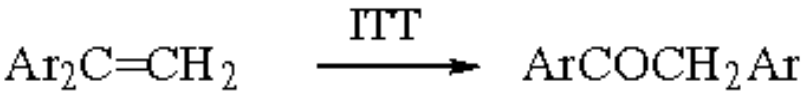

(11)

Ethers react with ITT to yield α,β-(trifluoroacetoxy) diesters (eqs 12 and 13).[5,12,13]

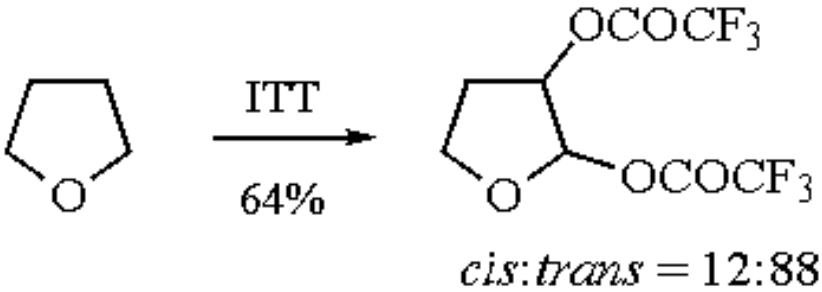

(12)

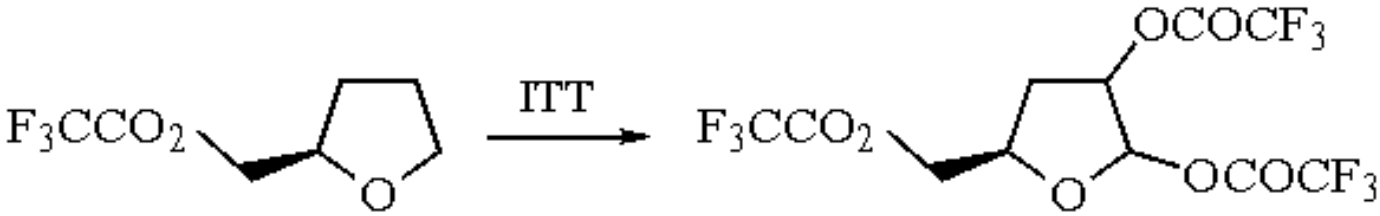

(13)

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Iodoacetonitrile

ICH_2CN

[624-75-9] · C_2H_2IN · Iodoacetonitrile · (MW 166.95)

(used for alkylation of nucleophiles;[1-14] undergoes Reformatsky[15] and Wittig-type[16] reactions with aldehydes)

Alternate Name: iodomethyl cyanide.

Physical Data: bp 182-184 °C/720 mmHg, 75 °C/10 mmHg; *d* 2.307 g cm^{-3}.

Solubility: insol hexane; slightly sol H_2O; sol benzene, alcohol, acetone, ether, CH_2Cl_2.

Form Supplied in: yellow to amber liquid; commercially available.

Handling, Storage, and Precautions: lachrymator; avoid inhalation of vapors; flammable (toxic fumes); possible mutagen; refrigerate. Handle in a fume hood.

Iodoacetonitrile is commonly used for the alkylation (cyanomethylation) of a wide variety of nucleophiles (eq 1), including ketone enolates,[1] ester enolates,[2] amines,[3,4] thiols,[5] phosphines,[6] enolic hydroxyls,[7] enol-TMS intermediates,[8] borates,[9] thioamides,[10] arene π-complexes,[11] and miscellaneous nitrogen heterocycles.[12,13] The value of the resulting alkylation products often lies in their versatility with respect to further synthetic transformations, either straightforward reactions such as conversion to amides, amines, or acids, or more substrate-specific reactions including rearrangements,[14] ring expansion,[12] conversion to formaldehyde iminium intermediates,[3] or conversion to novel heterocycles.[13]

$$\text{Nu-H} \xrightarrow[\text{B}^-]{\text{ICH}_2\text{CN}} \text{Nu-CH}_2\text{CN} + \text{BH} + \text{I}^- \qquad (1)$$

In a Reformatsky-type reaction, aldehydes (not ketones) react with ICH_2CN in the presence of freshly prepared metallic ***Nickel*** (eq 2)[15] to give β-hydroxy nitriles. Yields are good due to the low basicity of the cyanomethylnickel halides, and the selectivity for aldehydes in the presence of ketones may prove useful in complex substrates.

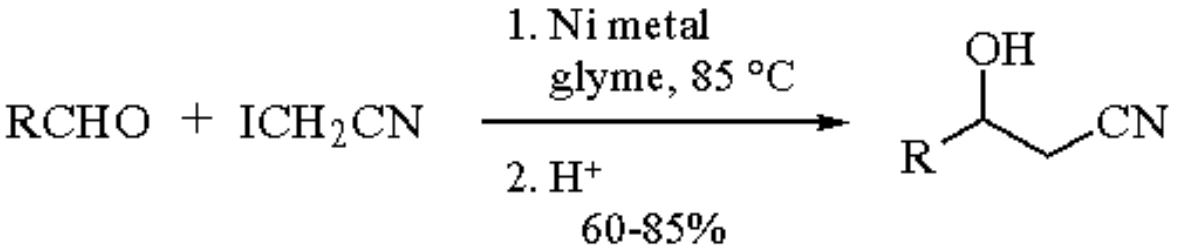

(2)

α,β-Unsaturated nitriles are available in good yield by the reaction of ICH_2CN with carbonyl compounds mediated by tri-*n*-butylstibine, under mild and essentially neutral conditions (eq 3).[16]

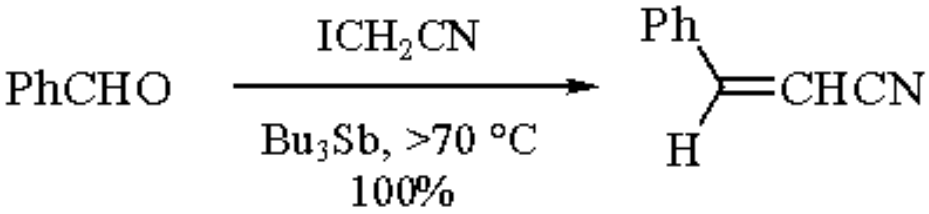

(3)

The reaction of ICH_2CN with thioamides provides a racemization-free route to β-keto nitriles through the intermediacy of an α-cyanoenamine (eq 4).[17] When primary thioamides are alkylated with ICH_2CN, a substituted thiazole is the predominant product (eq 5).[18]

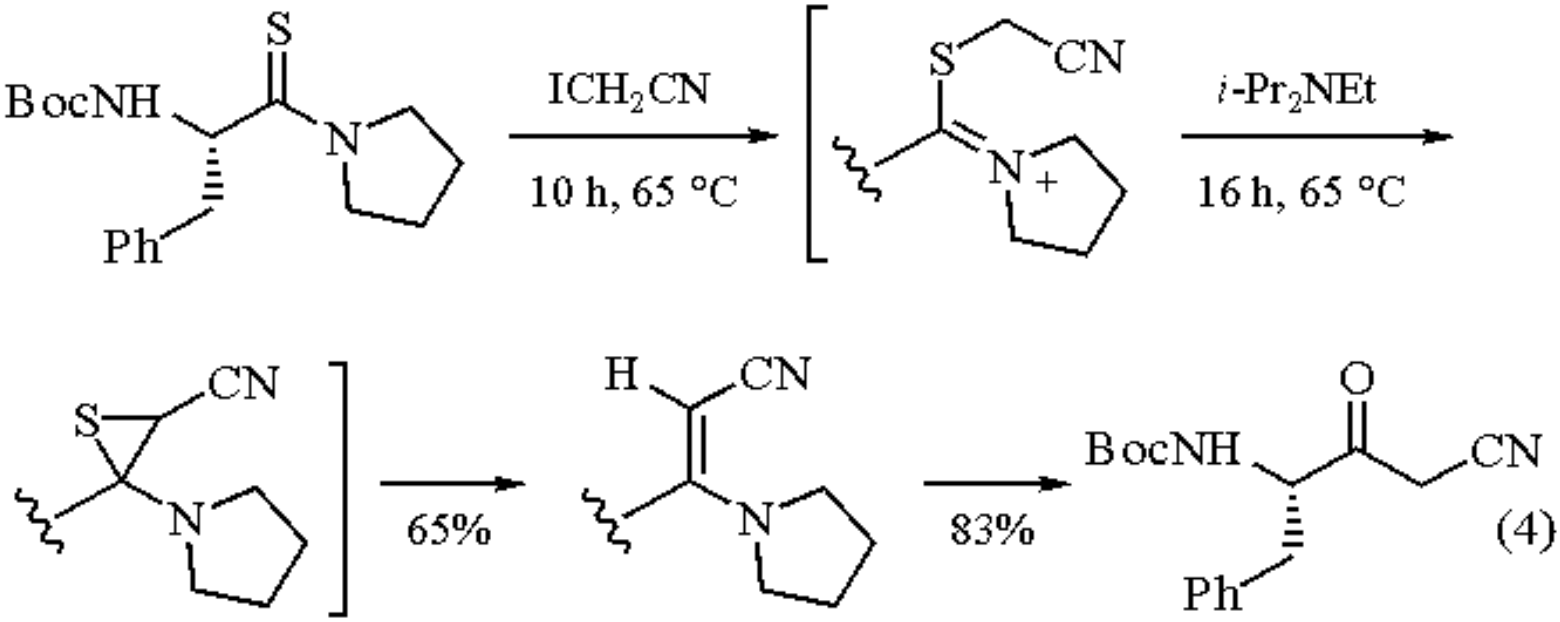

(4)

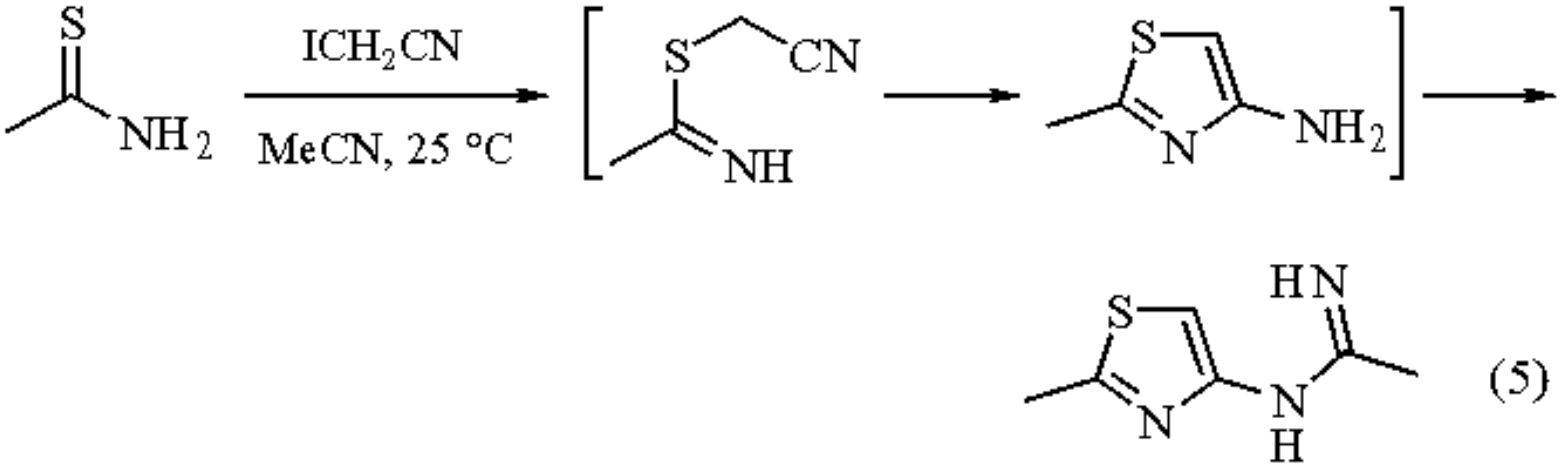

(5)

Radical addition of ICH_2CN to alkyl-substituted alkynes leads to γ-iodo-β,γ-unsaturated nitriles, which are good precursors for radical translocation reactions (eq 6).[19]

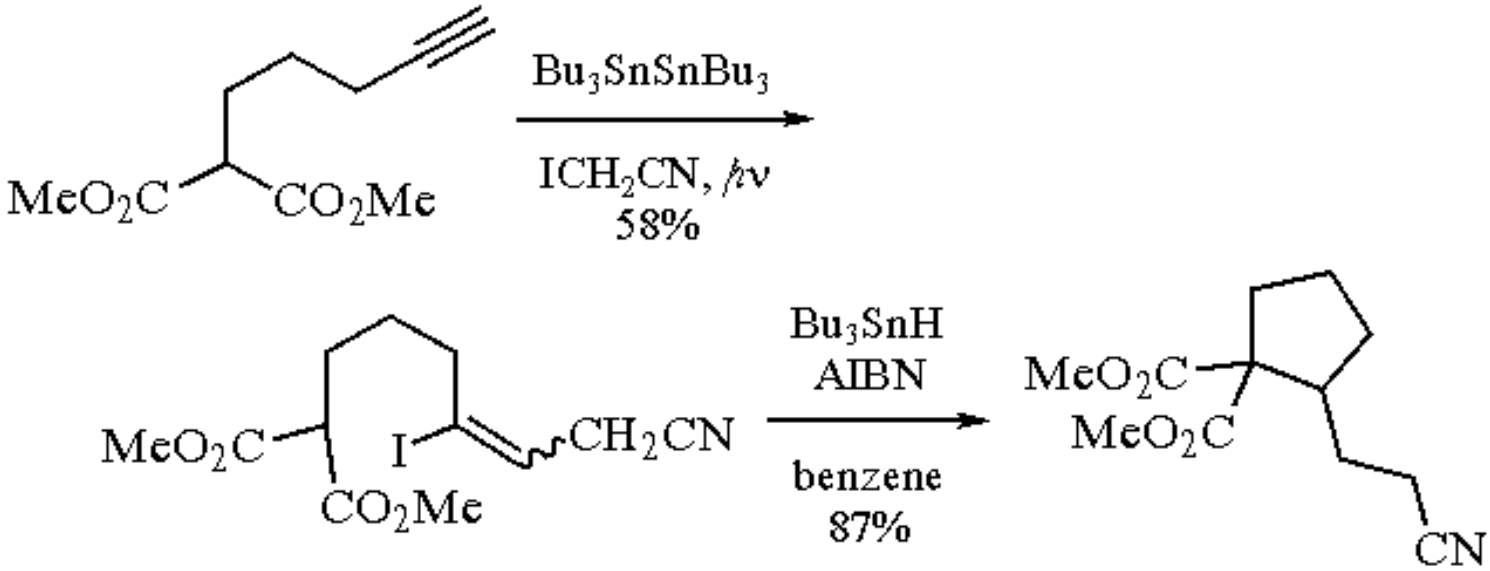

(6)

γ-Keto-nitriles (useful in the synthesis of heterocycles) and β,γ-unsaturated nitriles with controlled geometry and substitution pattern are synthesized by treating alkynyltrialkylborates with ICH_2CN followed by oxidation or protonolysis (eq 7).[20]

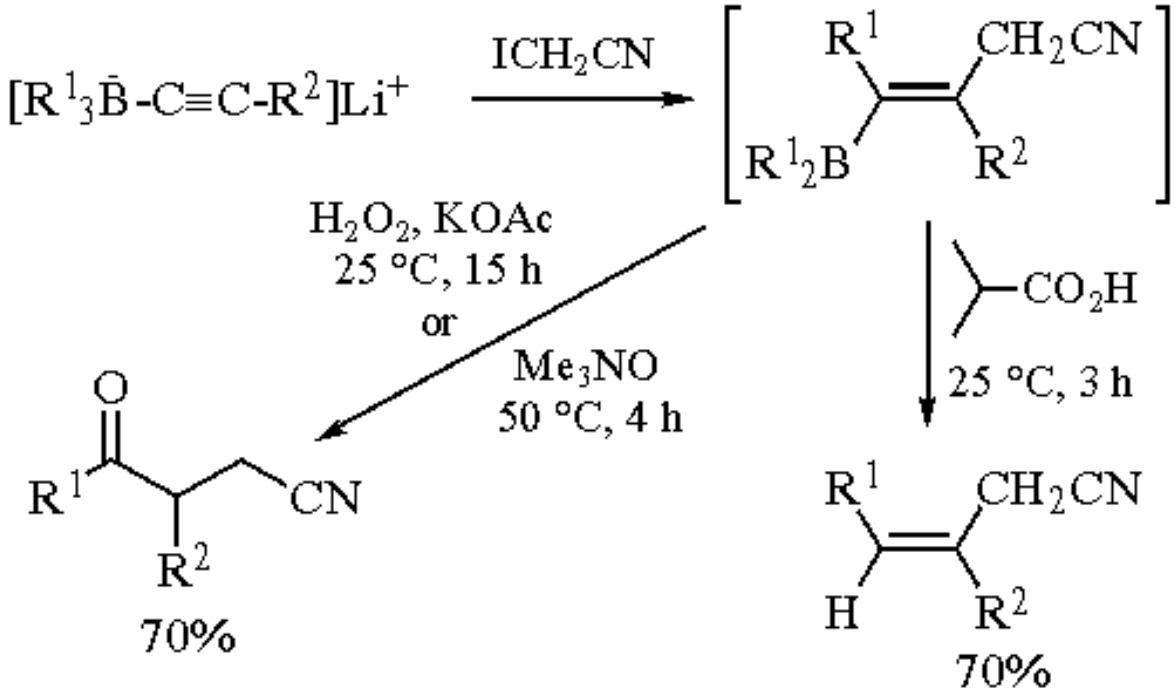

(7)

Related Reagents.

Chloroacetonitrile.

---

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Gordon L. Bundy

(Iodoethynyl)trimethylsilane

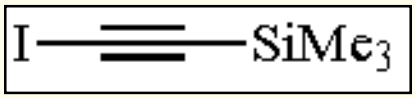

[18163-47-8] · C_5H_9ISi · (Iodoethynyl)trimethylsilane · (MW 224.13)

(alkyne coupling reagent predominantly used in conjunction with organocopper species or palladium catalysis)

Physical Data: bp 96 °C, 55 °C/20 mmHg; *n*20D 1.5110.

Form Supplied in: not commercially available.

Preparative Methods: all involve iodination of trimethylsilylacetylenes. Direct iodination of metalated (lithium or magnesium) trimethylsilylacetylene has been largely supplanted due to the modest yields obtained.[1] Utilizing ***Trimethylsilylacetylene*** and ***Bis(trimethylsilyl) Peroxide*** in the presence of ***Copper(I) Iodide*** gives good yields.[2] Substituting ***Zinc Iodide*** requires using the lithium acetylide.[3] Copper(I) iodide (0.05 equiv.) in the presence of iodine, sodium carbonate, and a phase-transfer catalyst gives good yields without having to use *n*-butyllithium or a Grignard reagent to first deprotonate the trimethylsilylacetylene.[4] The most popular procedure uses ***Bis(trimethylsilyl)acetylene***, treating it with ***Iodine Monochloride*** in dichloromethane at 25 °C to obtain excellent yields of (iodoethynyl)trimethylsilane.[5,6]

Handling, Storage, and Precautions: use in a fume hood.

Introduction.

(Iodoethynyl)trimethylsilane has been largely confined to aryl- and vinylcopper coupling, where it serves well since the reverse procedure, i.e. coupling with alkynylcopper reagents, is not straightforward due to the lack of reactivity of alkynyl moieties bound to copper.

Cross Coupling with Organocopper Reagents.

Vinylcopper species, prepared by the copper-catalyzed addition of ***Ethylmagnesium Bromide*** to monosubstituted alkynes, react with (iodoethynyl)trimethylsilane (eq 1) in the presence of 1.2-2 equiv of

TMEDA to afford the enyne in good yield.[7] In the absence of TMEDA, iodine exchange to the vinyl group occurs instead of alkynyl-vinyl coupling. In a similar fashion,[8] addition of lithium tributylstannyl(cyano)cuprate across the alkyne gave a vinylcuprate which required the addition of ***Lead(IV) Acetate-Copper(II) Acetate*** to couple successfully with (iodoethynyl)trimethylsilane. In the absence of zinc(II) chloride, very low yields of the desired product are obtained.

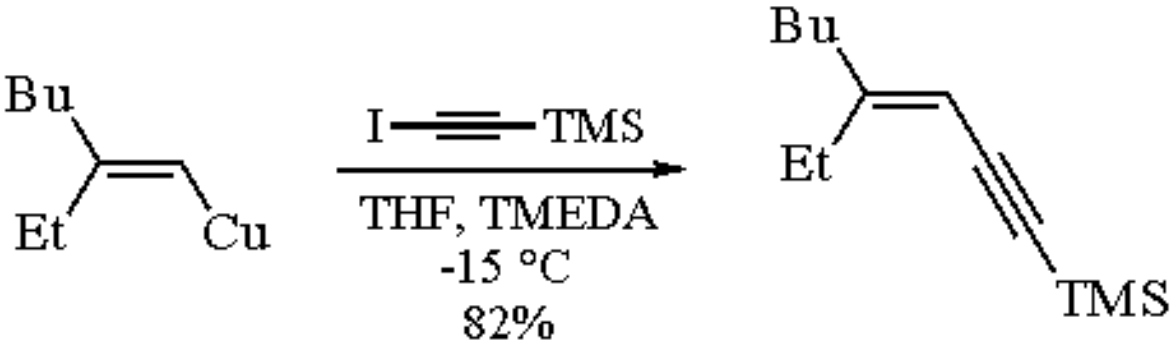

(1)

Allenylcopper species, prepared by ***n-Butyllithium*** deprotonation of substituted allenes followed by addition to ***Copper(I) Bromide***, have been coupled with (iodoethynyl)trimethylsilane to give allenyne products (eq 2).[9]

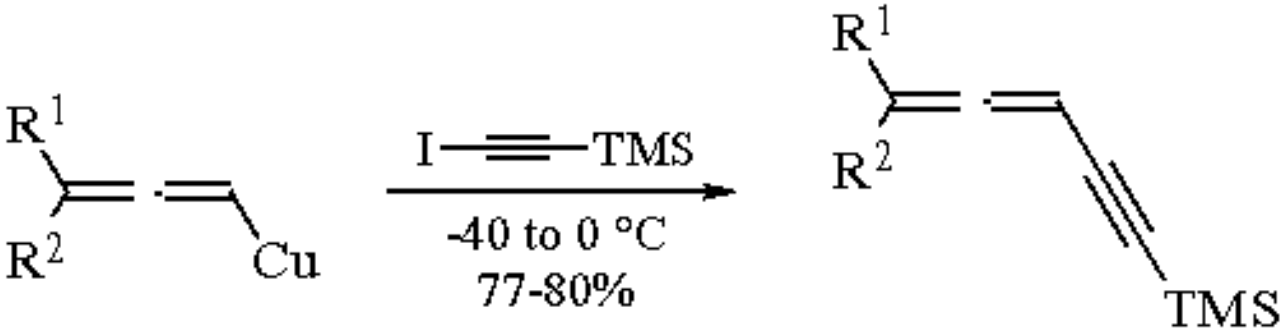

(2)

$R^1 = t\text{-Bu}, R^2 = H; R^1 = R^2 = Me$

Arylcopper(I) adducts, prepared by adding an aryllithium or Grignard reagent to a slight excess of copper(I) bromide in ethereal solvent, give rise to arylalkynes when treated with (iodoethynyl)trimethylsilane (eq 3).[10] Yields are modest to good, with ***Phenylcopper*** giving 64%. It was noted that substitution of a catalytic amount of copper(I) bromide, with either ***Phenyllithium*** or ***Phenylmagnesium Bromide***, or using ***Lithium Diphenylcuprate***, gives iodine transfer to the phenyl group, resulting in the copper acetylide which undergoes coupling with the reactive (iodoethynyl)trimethylsilane to give bis(trimethylsilyl)butadiyne. Although yields are modest, the above sequence is complementary to the Stephens-Castro coupling where aryl iodides are heated in the presence of relatively unreactive copper acetylides to obtain arylalkynes.

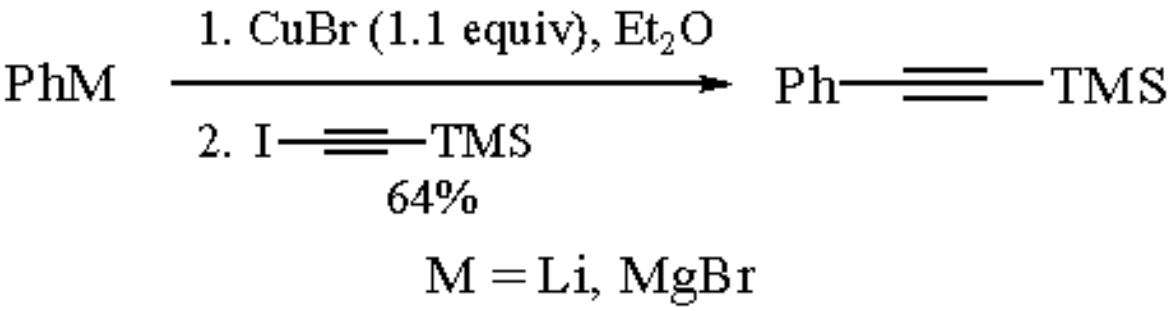

(3)

Both (bromo- and (iodoethynyl)trimethylsilane undergo base-induced desilylation, followed by decomposition, when subjected to Cadiot-Chodkiewicz coupling conditions. Switching to the more stable (bromoethynyl)triethylsilane affords good yields of the terminal diynes after protodesilylation (eq 4).[11]

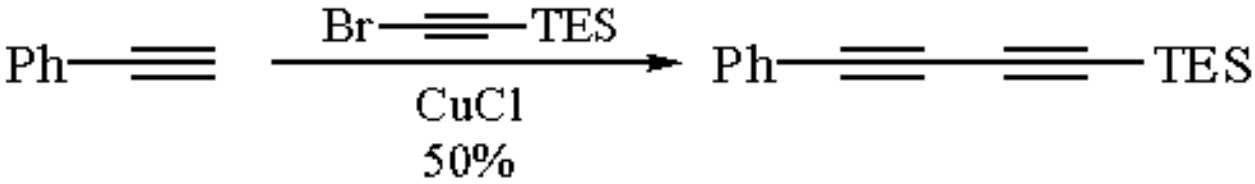

(4)

Palladium-Catalyzed Coupling.

Palladium catalysis (eq 5) has been successfully applied to the coupling of (iodoethynyl)trimethylsilane and acrylate esters. ***Palladium(II) Acetate*** (0.004 equiv.), reduced in situ to palladium(0), in the presence of the alkyne, methyl acrylate, carbonate base, and a phase-transfer salt at 25 °C, gave a 40% yield of the coupled product.[12]

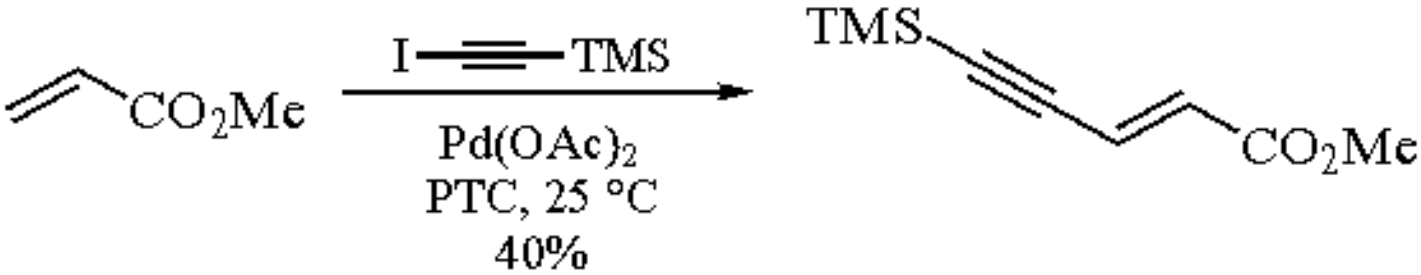

(5)

At some point, cleavage of the alkynyl-silane bond is generally desired, which can be accomplished quickly and almost quantitatively by treatment with alkali in methanol at 25 °C.[13]

---

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Iodoform

CHI_3

[75-47-8] · CHI_3 · Iodoform · (MW 393.72)

(precursor to both mono- and diiodocarbene for addition to alkenes and arenes; adds to alkenes by a radical chain mechanism when correctly initiated; iodine atom donor for quenching carbon radicals; used in conjunction with chromium(II) chloride for the homologation of aldehydes to (*E*)-iodoalkenes)

Alternate Name: triiodomethane.

Physical Data: mp 120-123 °C; *d* 4.008 g cm^{-3}.

Solubility: sol ethanol, acetone, ether, benzene, carbon disulfide, dichloromethane, THF; slightly sol petroleum ether.

Purification: crystallization from ethanol.

Handling, Storage, and Precautions: yellow crystalline solid with a disagreeable odor. Decomposes at high temp with evolution of iodine.

Diiodocarbenoid Precursor.

Diiodocarbene, formed by base-induced decomposition of iodoform, with or without phase-transfer catalysis, adds to alkenes giving diiodocyclopropanes which may be rearranged with Ag^I to iodoalkenes (eq 1).[1] Under phase-transfer conditions, reaction with adamantane gives 1-(diiodomethyl)adamantane.[2]

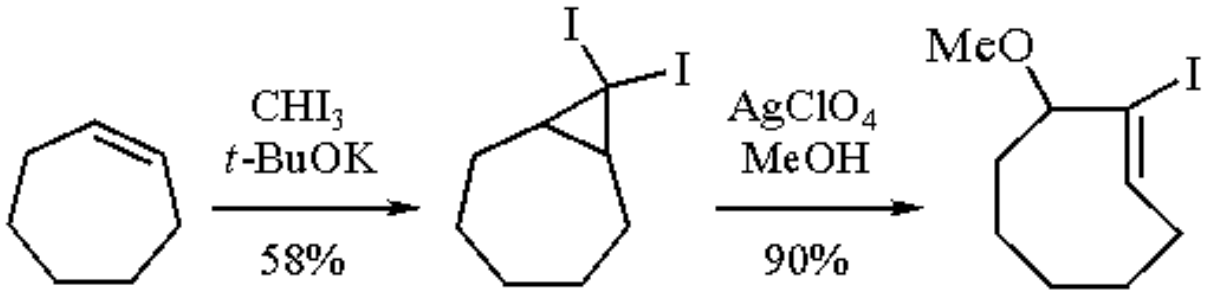

(1)

The triiodomethyl anion, formed from iodoform and 50% ***Potassium Hydroxide***, can be trapped by addition to pyridinium and isoquinolinium salts (eq 2).[3]

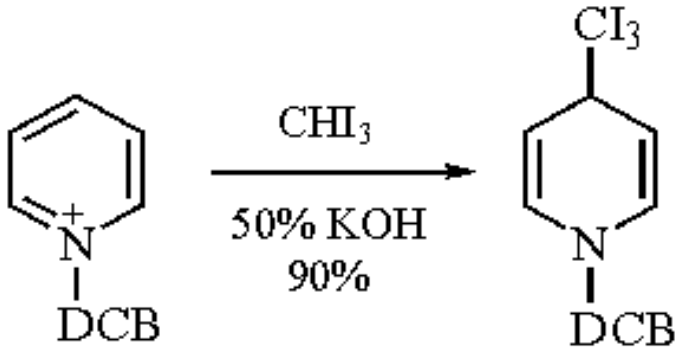

(2)

DCB = 2,6-dichlorobenzyl

Monoiodocyclopropanes may be prepared by reaction of alkenes with iodoform in the presence of copper, albeit in only low yield.[4] The iodocarbenoid formed from iodoform and ***Diethylzinc*** adds to alkenes in moderate yield with clean retention of configuration and with high preference for the *syn*-isomer (eq 3).[5]

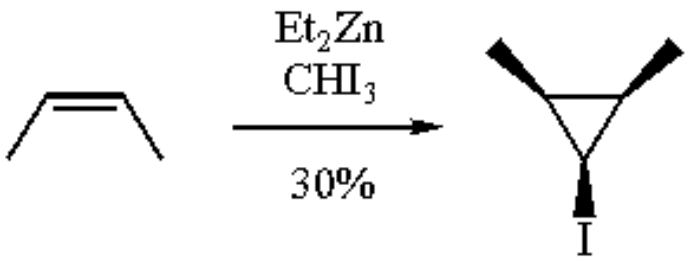

(3)

syn only

Photolysis of iodoform in the presence of alkenes also leads to the formation of monoiodocyclopropanes, also with retention of configuration (eq 4). With *cis*-2-butene the *syn*:*anti* ratio was 1.6:1 (eq 5).[5c,6] Interestingly, with cyclic *cis*-alkenes such as cyclooctene only the *endo*-iodocyclopropane was formed both under photolytic conditions and with diethylzinc.[5c] Flash photolysis experiments indicated that the photochemical reaction proceeds via homolysis of iodoform to iodine atoms and diiodomethyl radicals.[7] Accordingly, photolysis in the presence of a more reactive alkene, norbornene, gave a mixture of radical and carbene addition products.[8]

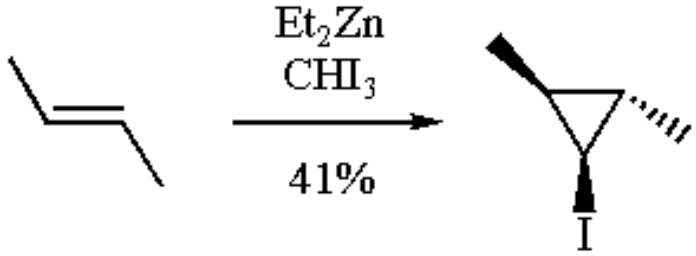

(4)

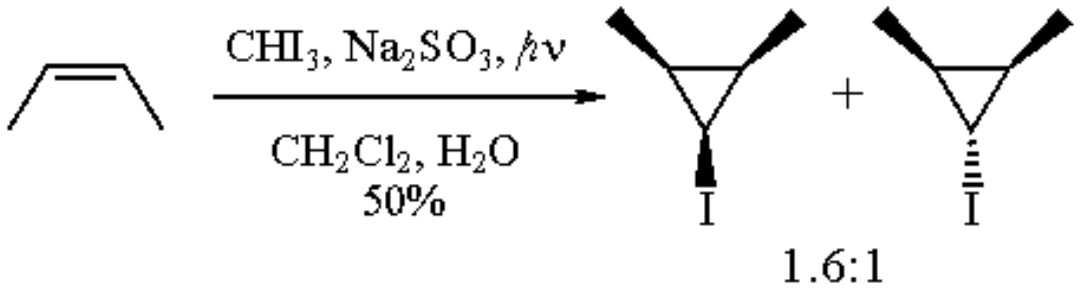

(5)

Arenes also react with the diethylzinc/iodoform couple to give a cyclopropane adduct that suffers further reaction with diethylzinc and rearrangement to cycloheptatrienes (eq 6).[9]

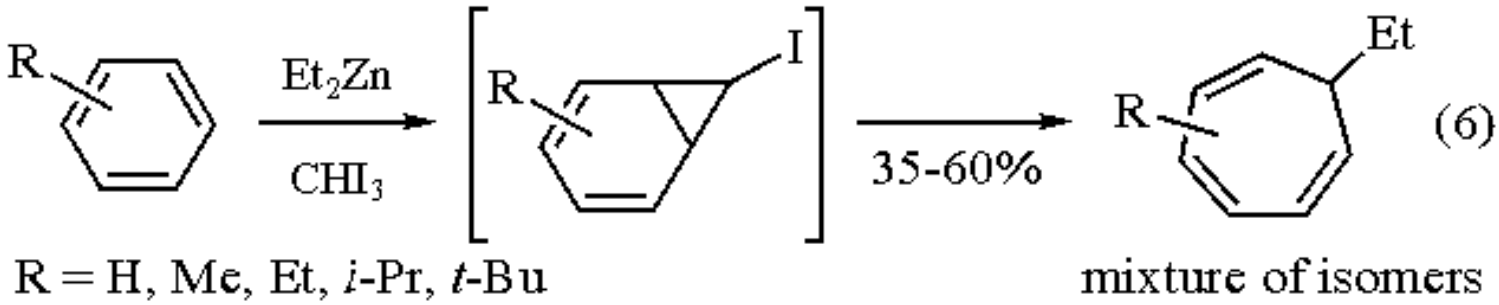

(6)

Radical Reactions.

Triethylborane initiates the radical addition of iodoform to ketene silyl acetals, resulting in the isolation of β-iodo-α,β-unsaturated esters (eq 7).[10] With tetraiodomethane the corresponding β,β-diiodide was obtained. Radical addition of iodoform to methyl acrylate is also reported to be initiated with ***Pentacarbonyliron*** (eq 8).[11]

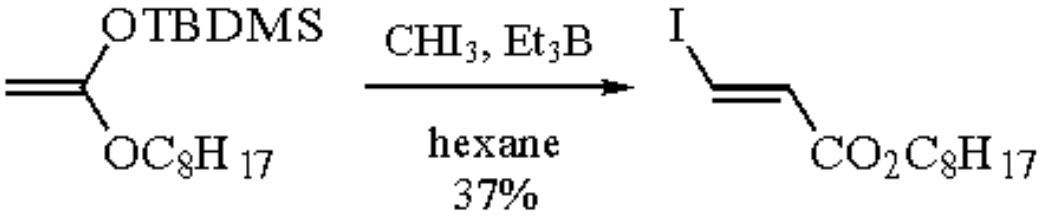

(7)

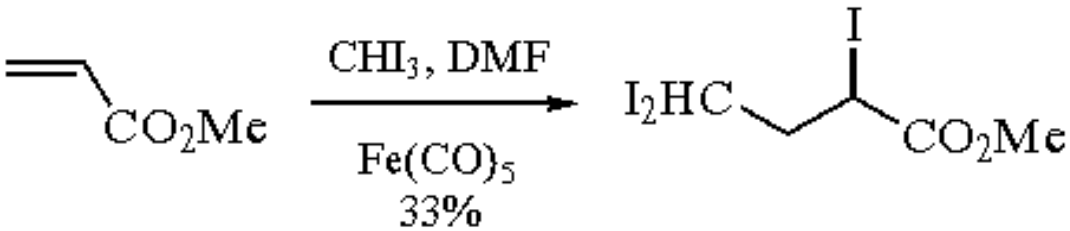

(8)

Addition to limonene (eq 9) serves to illustrate that terminal alkenes are more readily attacked than internal alkenes and that the reaction is not limited to electron-deficient substrates.[12]

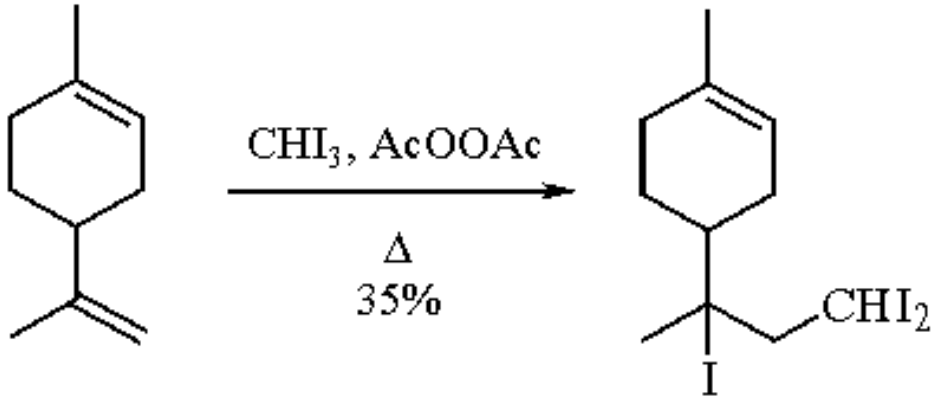

(9)

Iodoform acts as an iodine atom donor in the Barton version of the Hunsdiecker reaction. Aliphatic, and to some extent aromatic, carboxylic acids undergo this oxidative decarboxylation and optimum yields were obtained when cyclohexene was used as solvent in place of benzene.[13] The reaction, which may be initiated thermally,[13,16] photolytically,[14] or with ultrasound,[15] tolerates many functional groups and has been applied to cyclopropanecarboxylic acids (eq 10)[16] and notably to electron-rich aromatic acids (eq 11).[13]

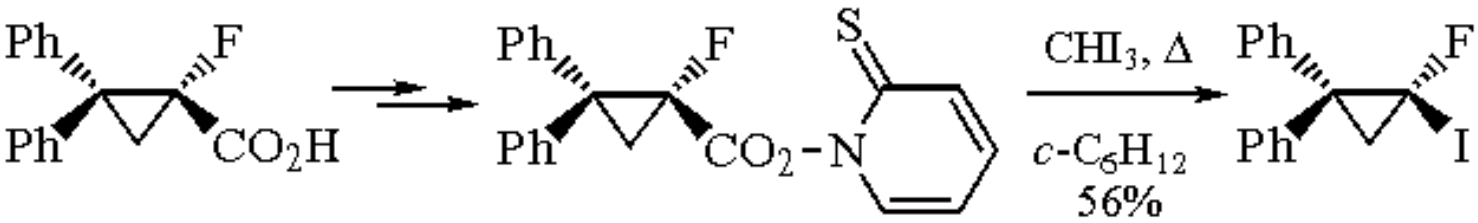

(10)

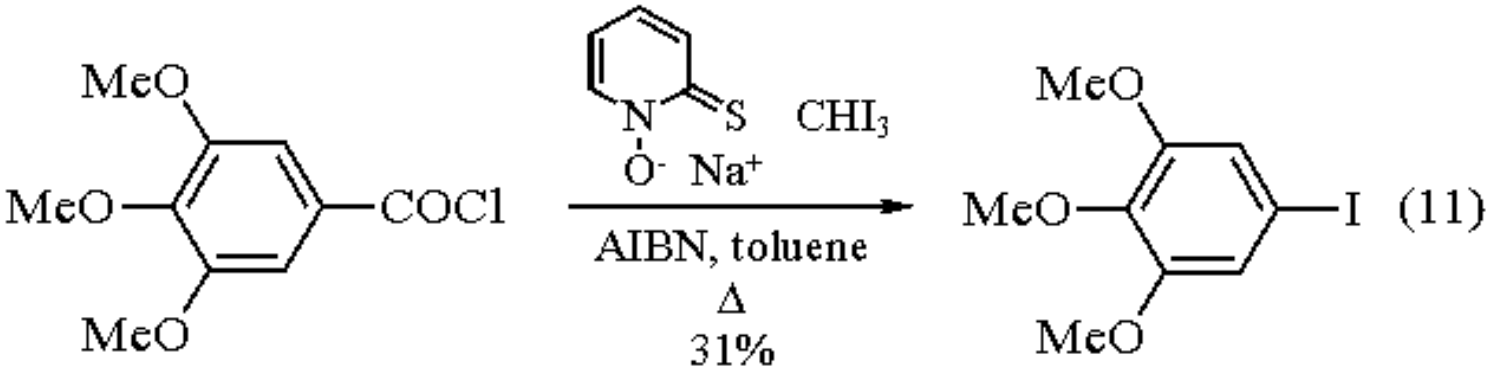

(11)

Alkenation Reactions.

Takai has described a very simple procedure for the homologation of aldehydes to iodoalkenes which involves treatment with iodoform and ***Chromium(II) Chloride*** and which proceeds with high selectivity for the (*E*)-product (eqs 12 and 13).[17]

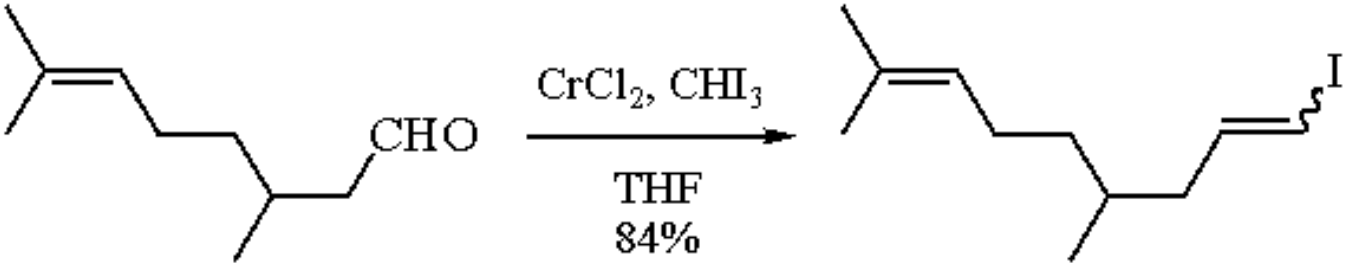

(12)

(E):(Z) = 82:18

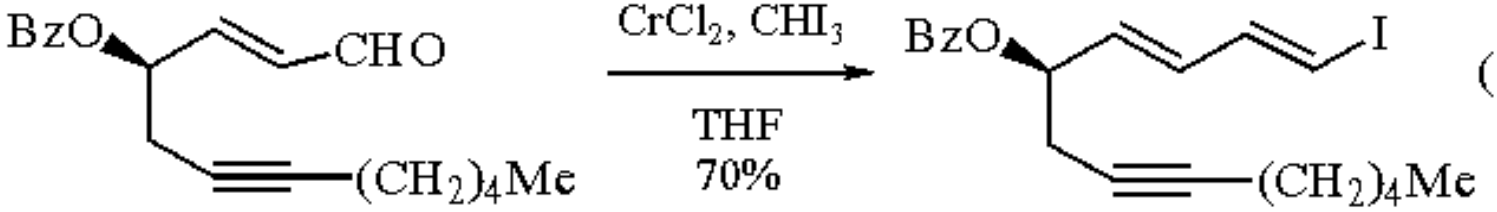

(13)

Although ketones are less reactive, as demonstrated by competition reactions, good yields of iodoalkenes are nonetheless obtained (eq 14).[17]

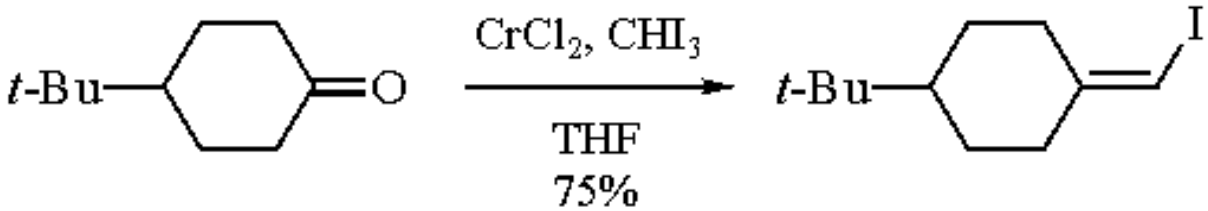

(14)

In the course of a synthesis of Macbecin I, Baker and Castro devised a synthesis of β-iodomethacrylic acid that involved alkylation of diethyl methylmalonate with iodoform followed by saponification and decarboxylation (eq 15).[18]

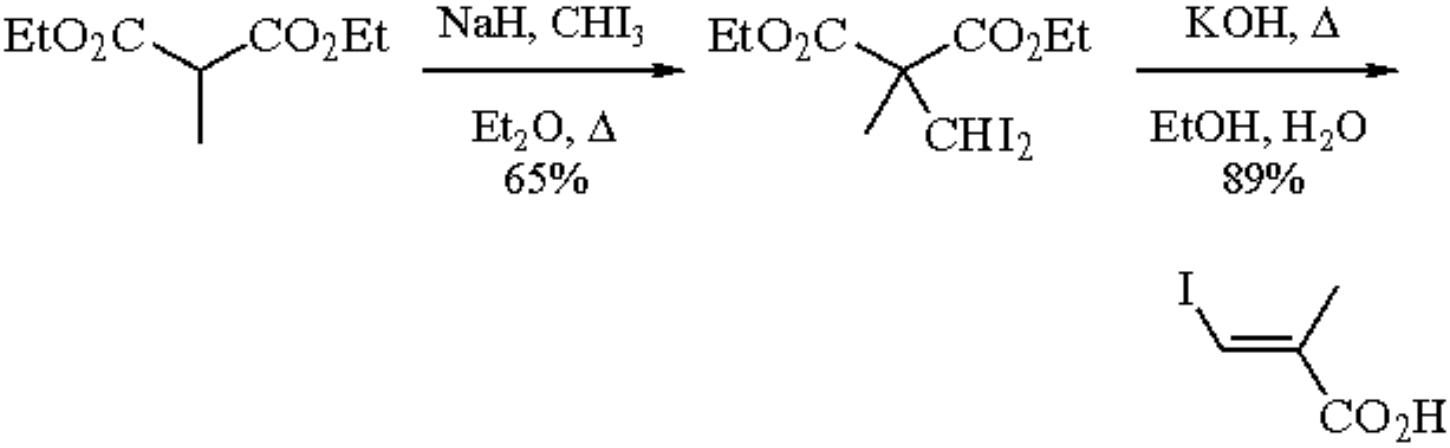

(15)

Other Applications.

Deuterated or tritiated methylene diiodide may be prepared from iodoform as reported by Saljoughian (eq 16), providing a convenient method for the incorporation of deuterium or tritium into cyclopropane rings via the Simmons-

Smith reaction.[19]

$$CHI_3 + Na_3AsO_3 + NaOT \xrightarrow[\text{HTO}]{60\ ^\circ C} TCHI_2 + NaI + Na_3AsSO_4 \quad (16)$$

74%

The Finkelstein reaction of iodoform with ***Silver(I) Fluoride*** or ***Mercury(II) Fluoride*** provides mixtures of diiodofluoromethane and difluoroiodomethane (eq 17).[20]

$$CHI_3 \xrightarrow[\text{or } HgF_2]{AgF} \underset{35\%}{CHFI_2} + \underset{15\%}{CHF_2I} \quad (17)$$

Related Reagents.

Bromoform; ***Diethylzinc-Iodoform***; ***Diiodomethane***; ***Triphenylphosphine-Iodoform-Imidazole***.

---

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Iodo(iodomethyl)mercury

ICH_2HgI

[141-51-5] · CH_2HgI_2 · Iodo(iodomethyl)mercury · (MW 468.42)

(reagent for the methylenation of alkenes[1])

Physical Data: pale yellow crystals; mp 113-116 °C.

Solubility: sol THF, hot benzene.

Preparative Method: treatment of ***Mercury(0)*** with 5 equiv of ***Diiodomethane*** with mechanical stirring and irradiation with a sunlamp resulted in the disappearance of the liquid mercury. Upon cooling and addition of benzene, a precipitate was obtained, which after recrystallization from hot (93 °C) diiodomethane gave pale yellow crystals of product in 48% yield.[2]

Handling, Storage, and Precautions: little information is available about iodo(iodomethyl)mercury, but as with all mercury reagents, care should be taken when handling these toxic reagents. Use in a fume hood.

Iodo(iodomethyl)mercury was first prepared in 1880.[3] However, it was not until 1964 that its use as a methylene transfer reagent was reported.[1] The reaction of iodo(iodomethyl)mercury with cyclohexene affords the corresponding cyclopropane, norcarnene, in 24% yield after 8 d (eq 1). The reaction benefits from the addition of an equimolar quantity of ***Diphenylmercury*** (eq 2). The reaction is stereospecific, and the alkene geometry is retained during the cyclopropanation reaction (eqs 3 and 4). There is also sensitivity to the electronic nature of the alkene, since tetrachloroethylene was found to be inert to cyclopropanation (eq 5).

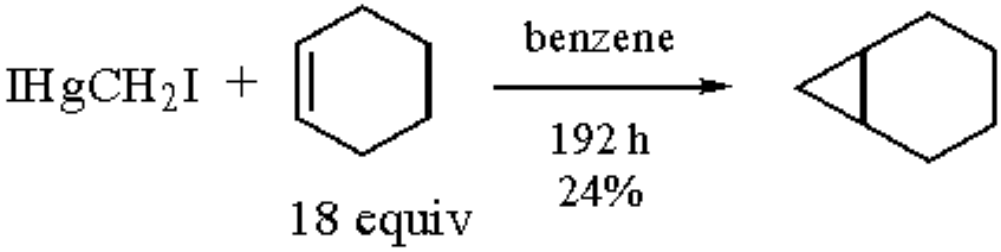

(1)

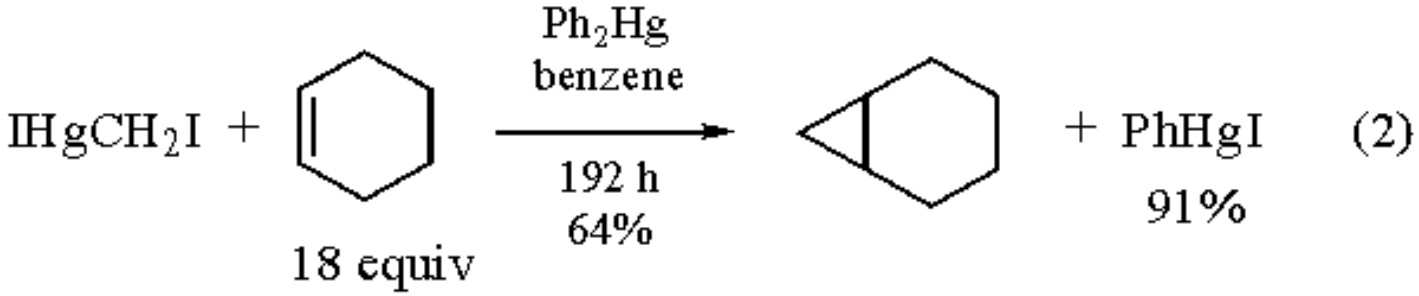

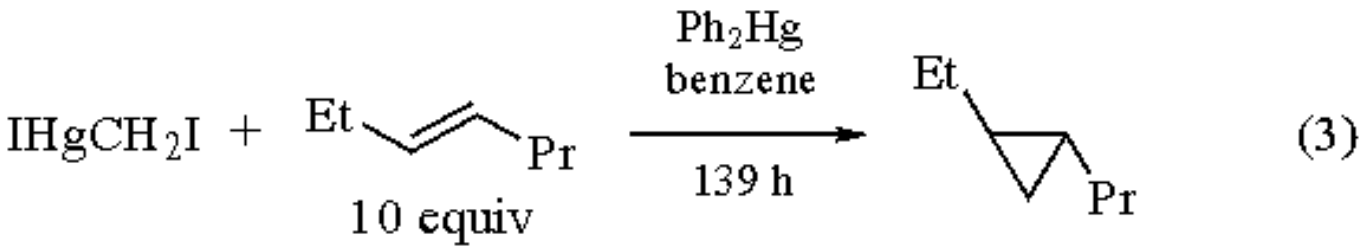

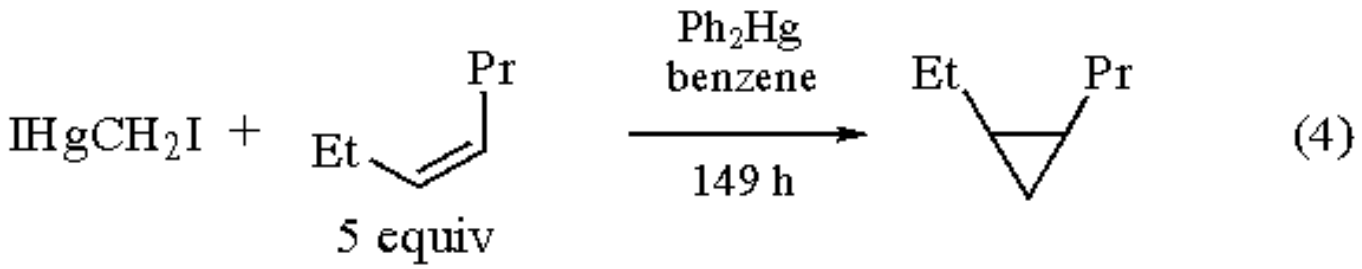

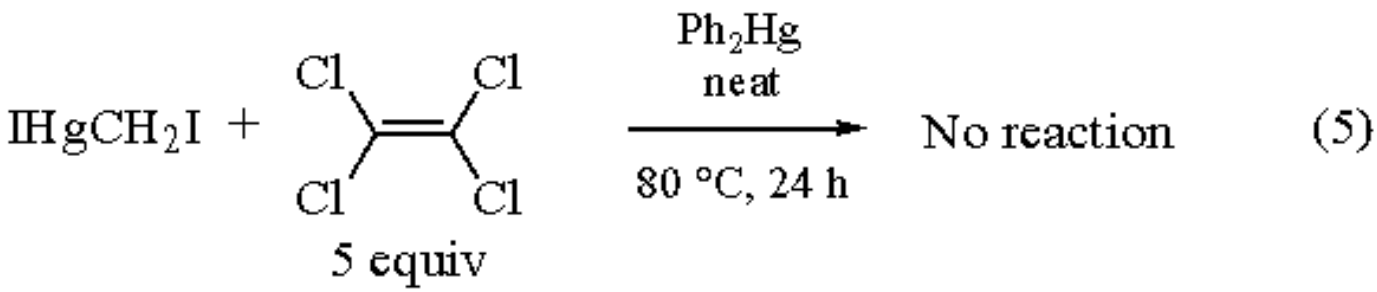

More recently, the use of iodo(iodomethyl)mercury for the methylenation of bis(trimethylsilyl)acetylene has been reported.[4] The unstable cyclopropene could be isolated in 10% yield, but by repeating the reaction in the presence of 1,3-diphenylisobenzofuran the Diels-Alder adduct could be isolated in 35% yield (eq 6).

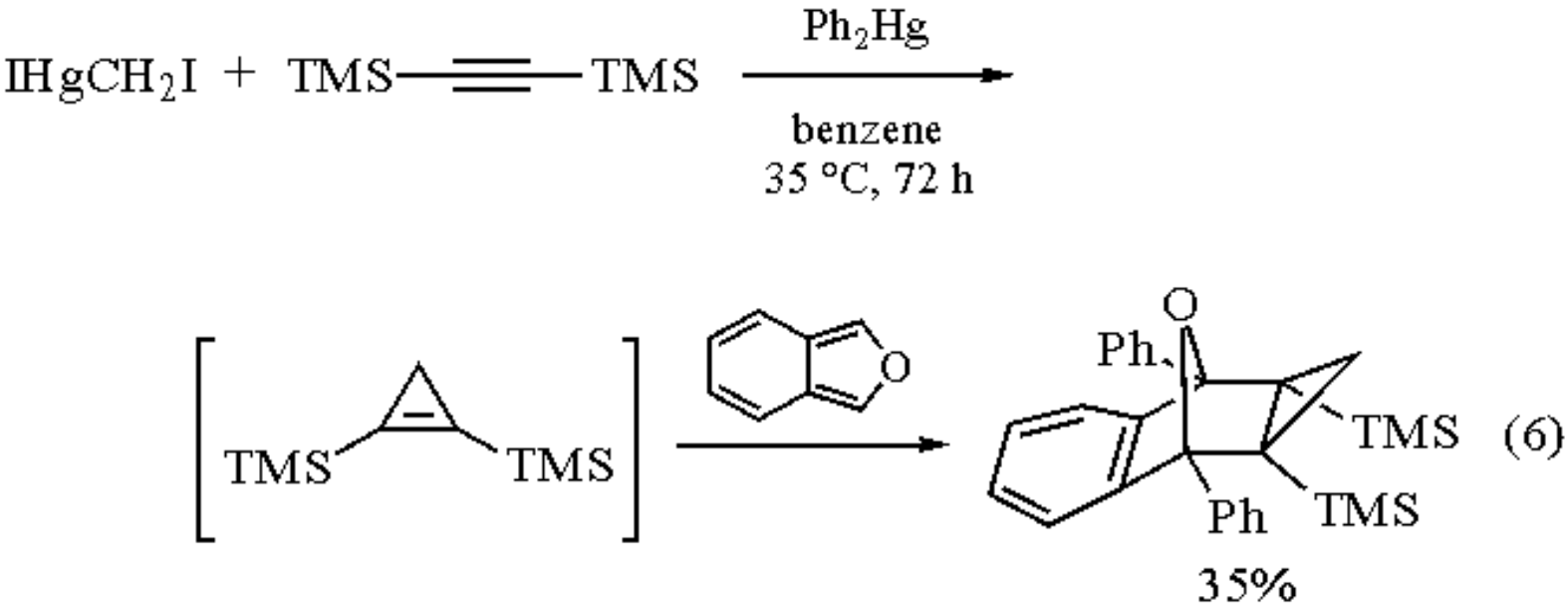

It is believed that there is an exchange process between iodo(iodomethyl)mercury and diphenylmercury which affords the more reactive methylenating reagent bis(iodomethyl)mercury (eq 7).[5] Other mercury-containing reagents, including bis(bromomethyl)mercury and ***Phenyl(trichloromethyl)mercury***, have been reported to cyclopropanate alkenes.[6]

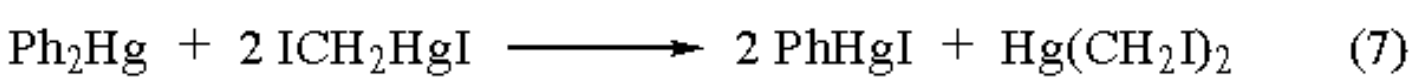

For many applications it would seem that the related Simmons-Smith cyclopropanation[7] using ***Diiodomethane*** and a ***Zinc/Copper Couple*** is more effective than the use of mercury-containing reagents. However, to date, stereoselective reactions have not been exploited with the mercury reagents.

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1. (a) Seyferth, D.; Eisert, M. A.; Todd, L. J. *JACS* **1964**, *86*, 121. (b) Seyferth, D.; Turkel, R. M.; Eisert, M. A.; Todd, L. J. *JACS* **1969**, *91*, 5027.
2. Blanchard, Jr., E. P.; Blomstrom, D. C.; Simmons, H. E. *JOM* **1965**, *3*, 97.
3. Sakurai, J. *JCS* **1880**, *37*, 658.
4. Garratt, P. J.; Tsotinis, A. *JOC* **1990**, *55*, 84.
5. Seyferth, D.; Haas, C. K.; Dagani, D. *JIC* **1982**, *59*, 111.
6. Seyferth, D.; Burlitch, J. M.; Minasz, R. J.; Mui, J. Y-P.; Simmons, Jr., H. D.; Treiber, A. J. H.; Dowd, S. R. *JACS* **1965**, *87*, 4259.
7. (a) Simmons, H. E.; Smith, R. D. *JACS* **1959**, *81*, 4256. (b) Simmons, H. E.; Blanchard, E. P.; Smith, R. D. *JACS* **1964**, *86*, 1347.

I. Craig Baldwin & Jonathan M. J. Williams

Loughborough University of Technology, UK

Iodomethane

MeI

[74-88-4] · CH_3I · Iodomethane · (MW 141.94)

(methylating agent for carbon, oxygen, nitrogen, sulfur, and trivalent phosphorus)

Alternate Name: methyl iodide.

Physical Data: bp 41-43 °C; *d* 2.28 g cm^{-3}.

Solubility: sol ether, alcohol, benzene, acetone; moderately sol H_2O.

Form Supplied in: colorless liquid; stabilized by addition of silver wire or copper beads; widely available.

Purification: percolate through silica gel or activated alumina then distill; wash with dilute aqueous $Na_2S_2O_3$, then wash with water, dilute aqueous Na_2CO_3, and water, dry with $CaCl_2$ then distill.

Handling, Storage, and Precautions: toxic, corrosive and a possible carcinogen. Liquid should be stored in brown bottles to prevent liberation of I_2 upon exposure to light. Keep in a cool, dark place. Use only in well ventilated areas.

C-Methylation.

Methyl iodide is an active alkylating agent employed in the *C*-methylation of carbanions derived from ketones, esters, carboxylic acids, amides, nitriles, nitroalkanes, sulfones, sulfoxides, imines, and hydrazones.[1] The quantity of methyl iodide utilized in methylations varies from a slight (1.1 equiv) to a large excess (used as solvent).

The monomethylation of carbanions derived from 1,3-cyclohexanedione and acetylacetone has been described (eqs 1 and 2).[2] Selective monomethylation of β-diketones is dependent upon the base employed; variable amounts of *O*-methylation, dimethylation, and carbon-carbon bond cleavage may occur. The tetraethylammonium enolate of β-diketones reportedly provides higher yields of *C*-methylation without competing side reactions (eq 3).[3] Dimethylation is sometimes a desired reaction pathway. In this case, a large excess of both methyl iodide and base favors the dimethylated product (eq 4).[4] Recently, the combination of a potassium base and a catalytic amount of ***18-Crown-6*** (eq 5) has been described to provide a higher yield of dimethylation.[5,6]

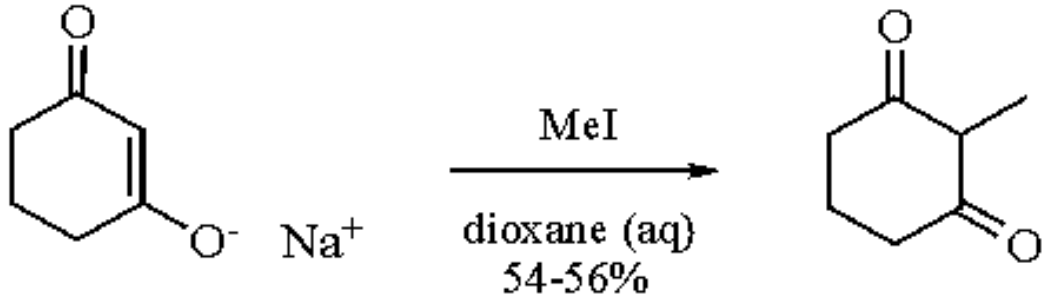
O
O⁻ Na⁺
MeI
dioxane (aq)
54-56%
O
O

(1)

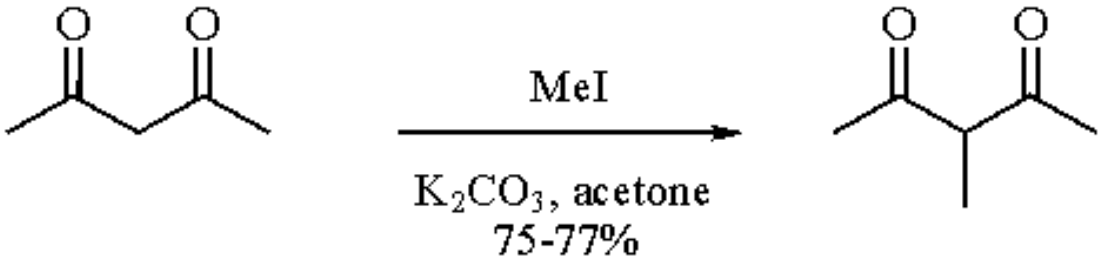
O O
MeI
K2CO3, acetone
75-77%
O O

(2)

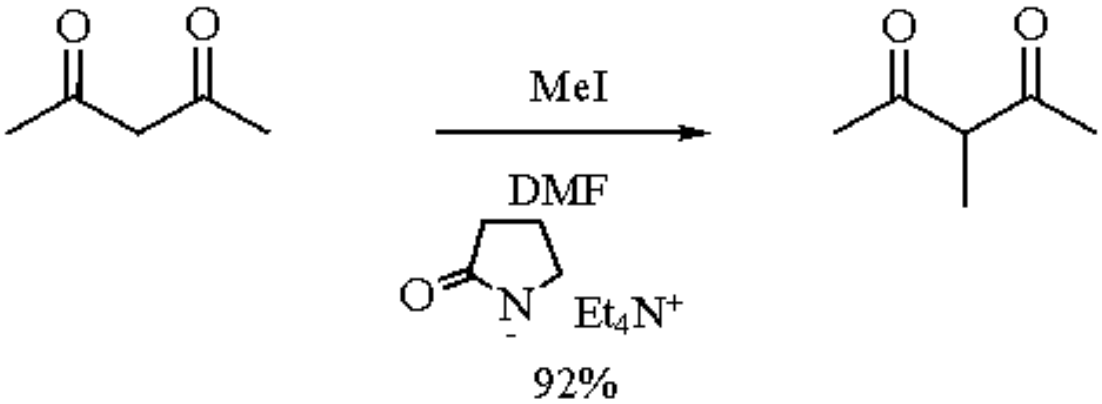
O O
MeI
DMF
O N⁻ Et4N⁺
92%
O O

(3)

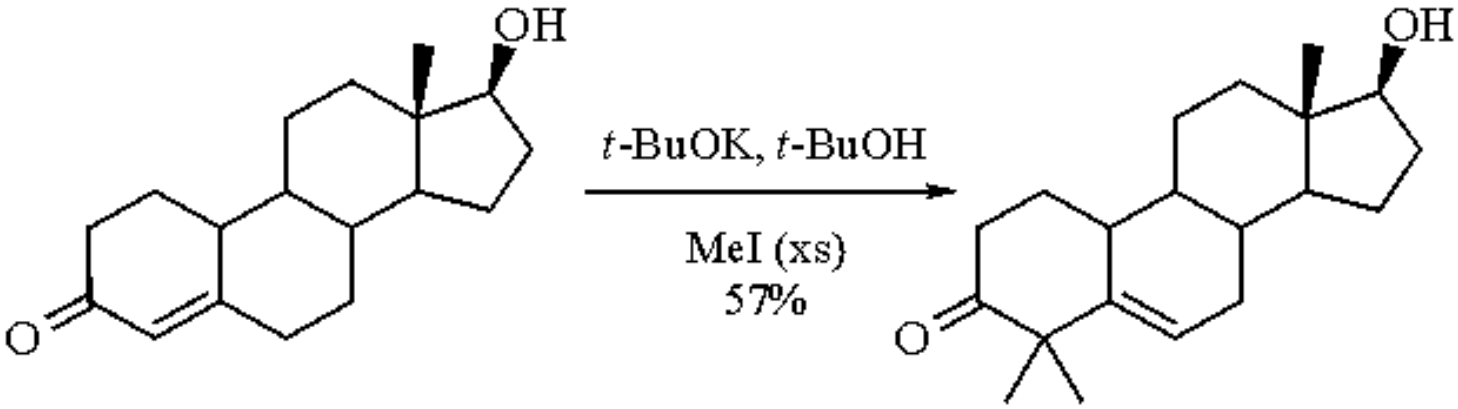
OH
O
t-BuOK, t-BuOH
MeI (xs)
57%
OH
O

(4)

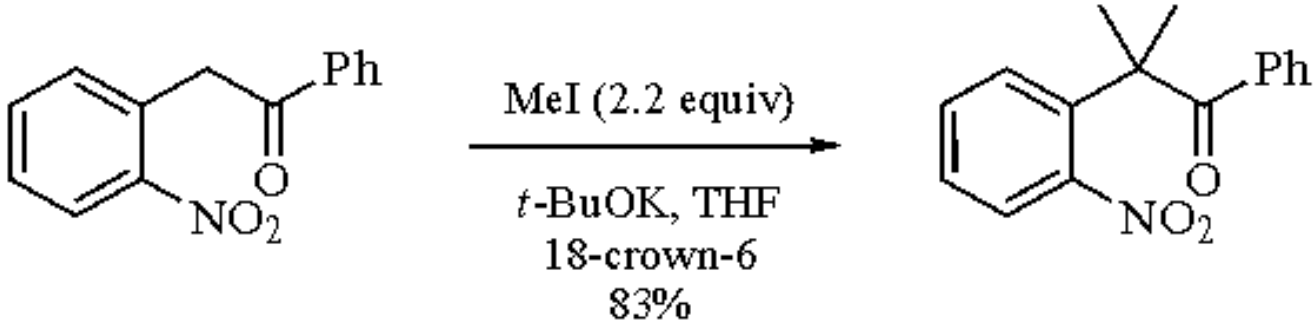
Ph
O
NO2
MeI (2.2 equiv)
t-BuOK, THF
18-crown-6
83%
Ph
O
NO2

(5)

Methylation of kinetically derived enolates is most readily accomplished via the corresponding silyl enol ether.[7] Lithium enolates, generated by treatment of the silyl enol ether with ***Methyllithium***, may then be alkylated with methyl iodide (eq 6).[8] Alternatively, quarternary ammonium enolates are produced by treatment of the silyl enol ether with the corresponding fluoride salt. For example, monomethylation of a ketone is cleanly effected by treatment of an anhydrous mixture of the trimethylsilyl enol ether of the ketone in methyl iodide with benzyltrimethylammonium fluoride (eq 7).[9] Kinetic enolates produced from the conjugate addition of an organocuprate to an unsaturated ketone or a dissolving metal reduction of an enone may be methylated directly.[7c] However, the choice of solvent is crucial for the success of these reactions. Ether, the solvent typically used in organocopper conjugate additions, is a poor solvent for alkylation reactions.[10] ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA), ***Hexamethylphosphoric Triamide*** (HMPA) and liquid ***Ammonia*** have been used as additives to increase the efficiency of alkylation. Alternatively, the solvent used in the conjugate addition can be removed in vacuo and replaced with a more effective medium for alkylation. For example the rate of methylation of the enolate produced in the conjugate addition of ***Lithium Dimethylcuprate*** to an enone is approximately 10^5 times faster in DME than in ether (eq 8).[11]

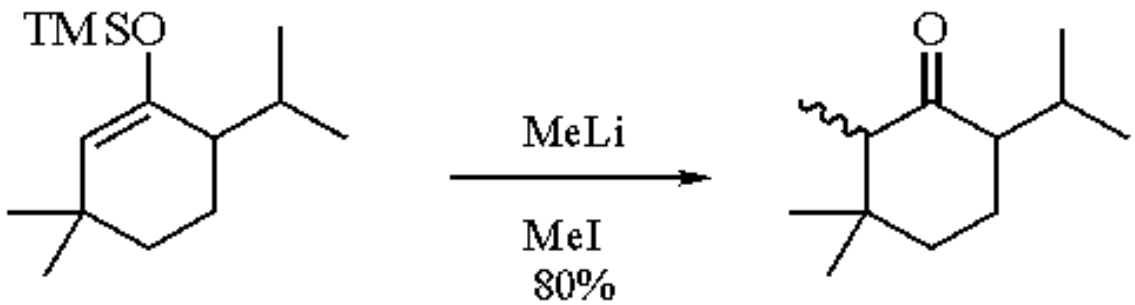

(6)

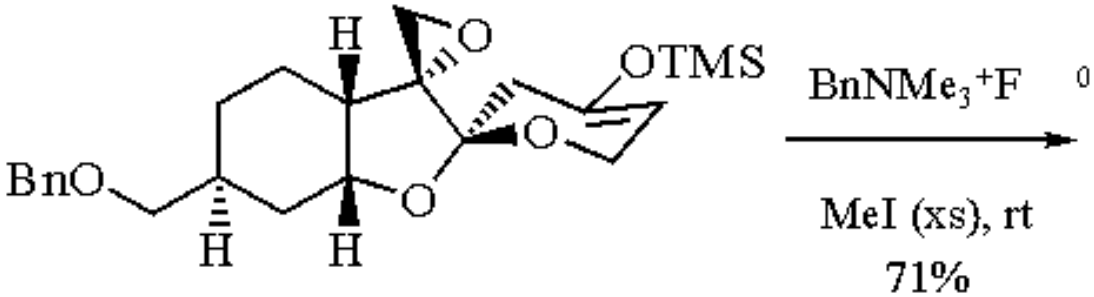

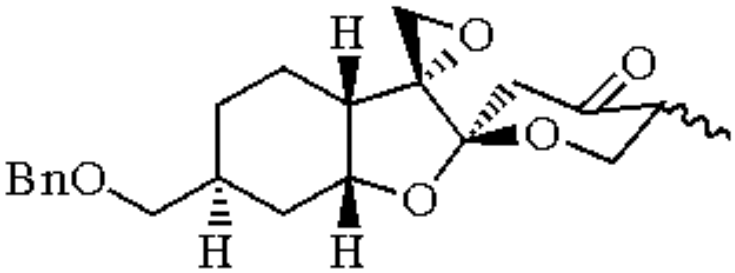

(7)

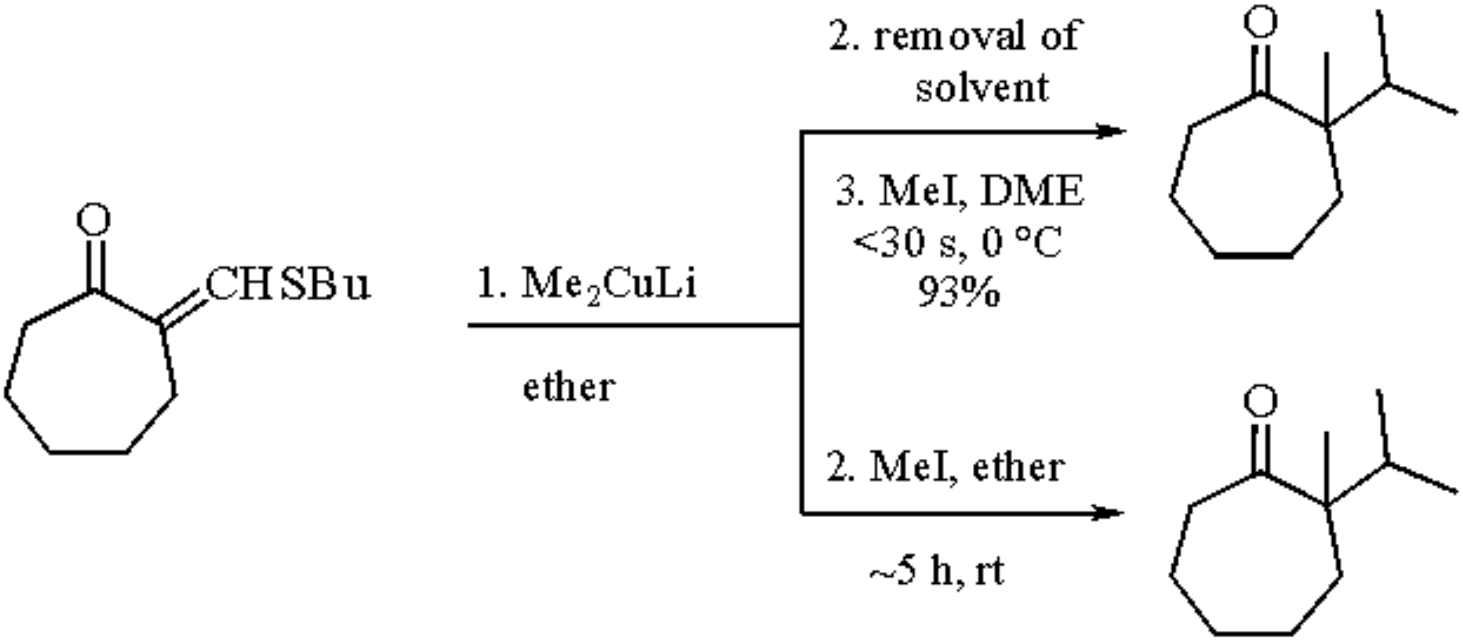

(8)

The stereoselectivity of the methylation of ketone enolates is determined by the structure of the substrate.[12] Stereoselective methylation of cyclic ketone enolates has been examined in detail and current models reliably predict the stereochemical outcome (eqs 9-11).[13-15] Diastereoselective methylation of acyclic ketone and ester enolates has been accomplished employing a variety of chiral auxiliaries (eq 12).[12,16] Efficient catalytic enantioselective methylation of 6,7-dichloro-5-methoxy-1-indanone has been accomplished via a chiral phase-transfer catalyst (eq 13).[17] An enantiomeric excess of 92% was observed when employing ***Chloromethane*** as the methylating agent, whereas methyl iodide provided a product of only 36% enantiomeric excess.

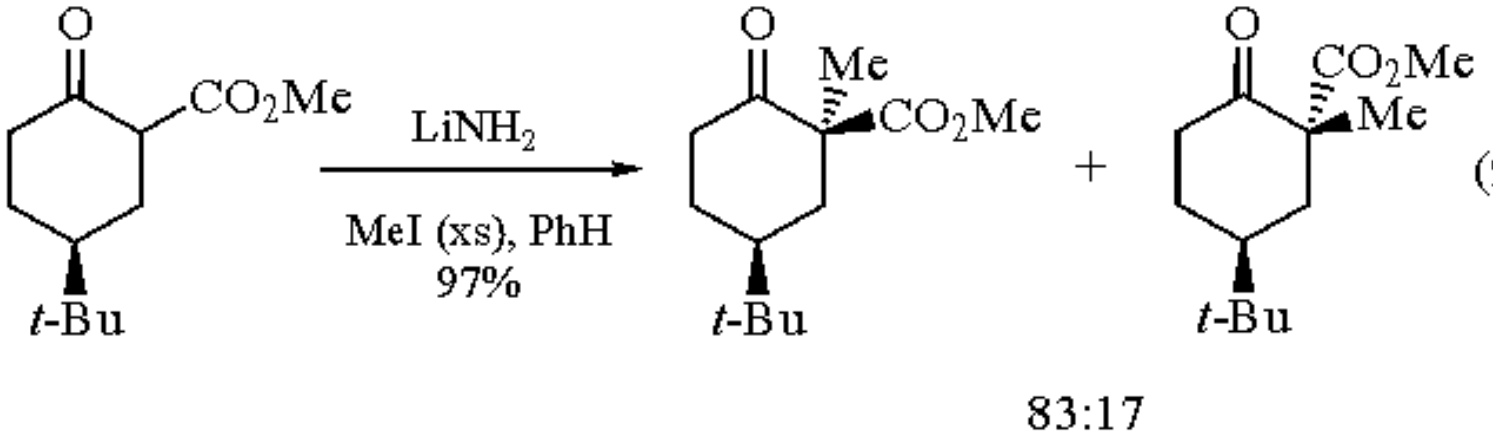

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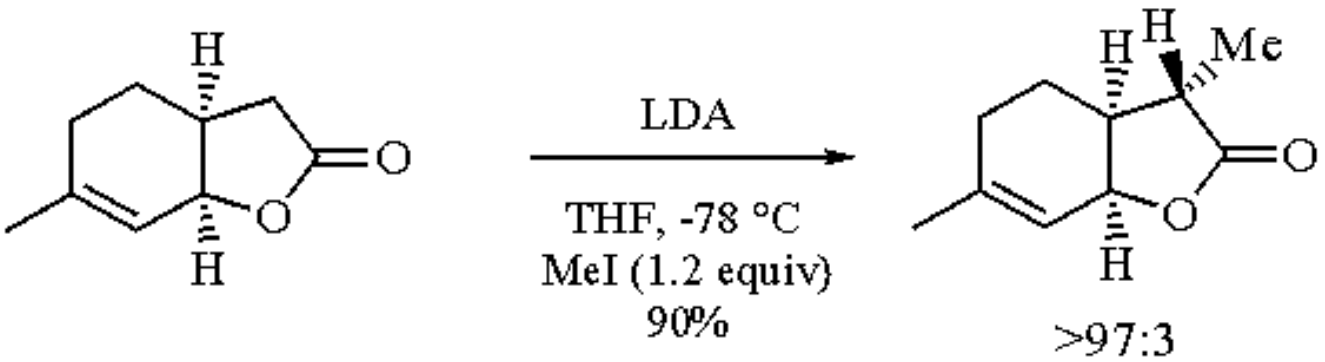

(10)

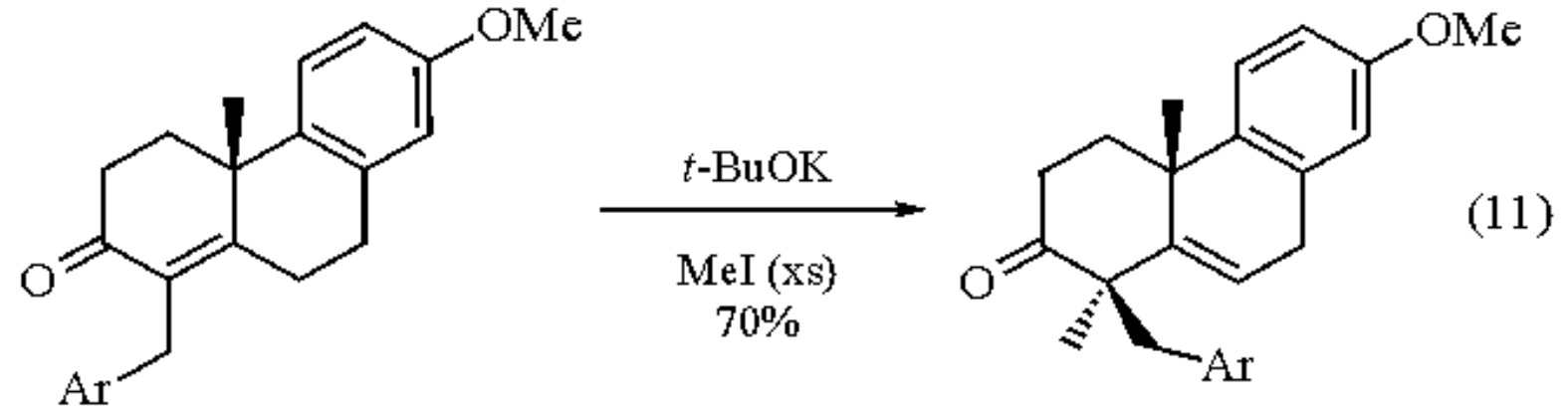

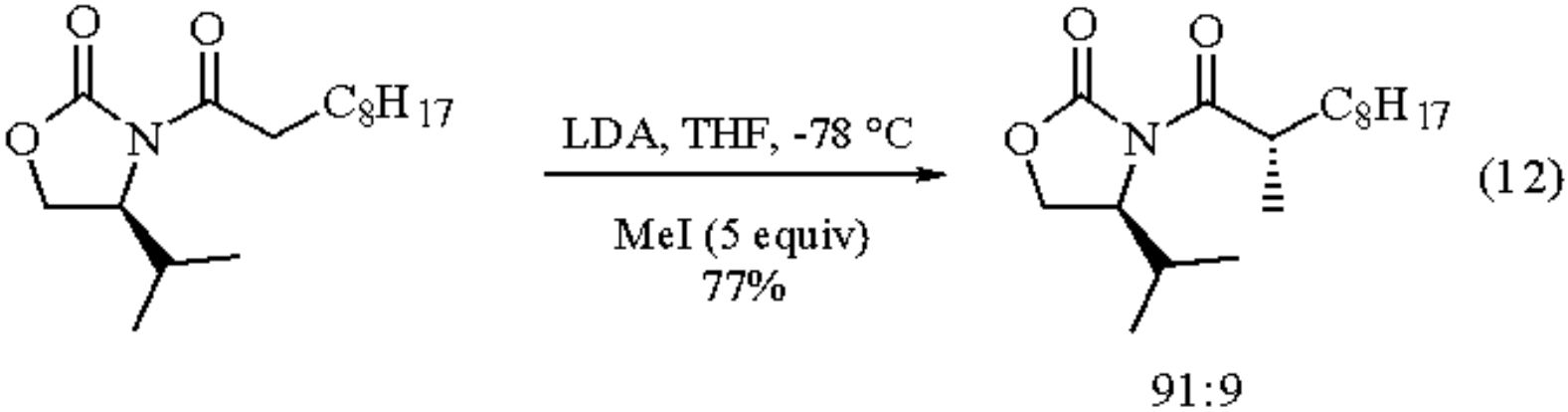

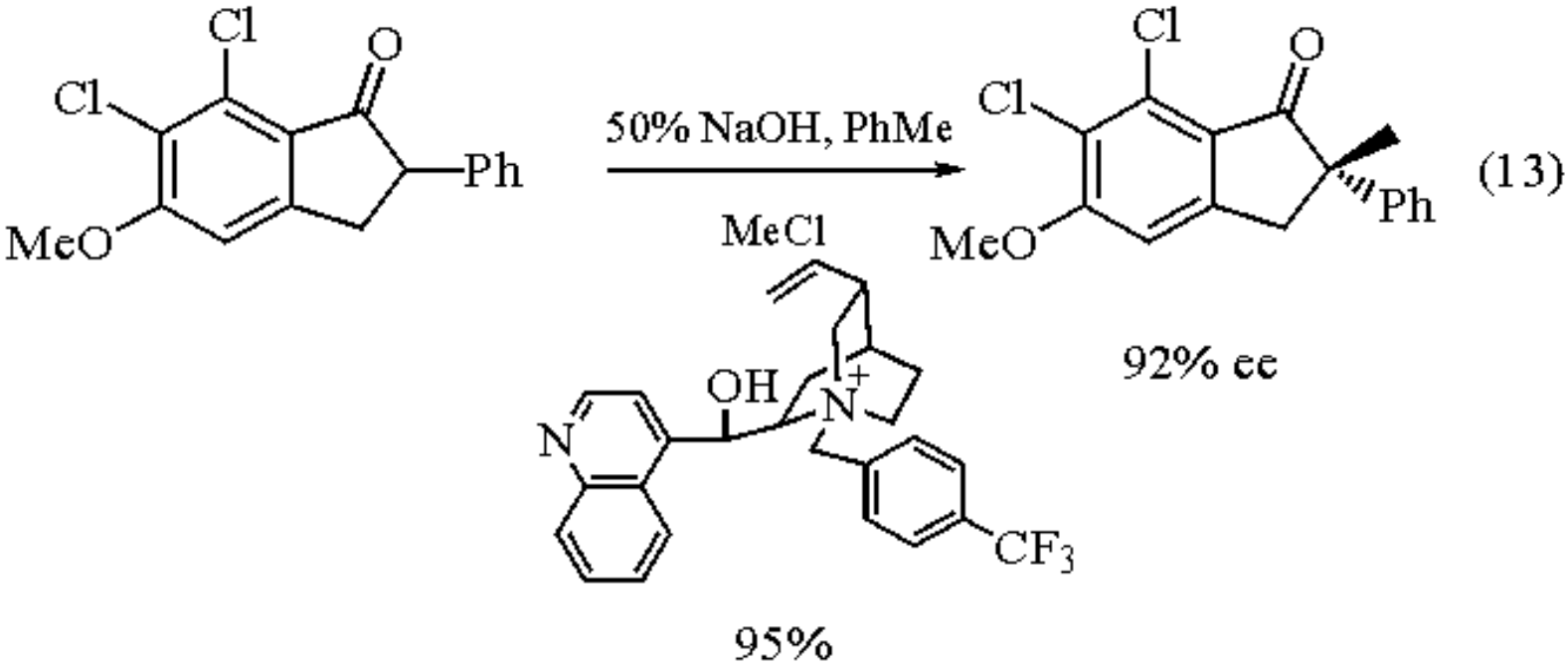

O-Methylation.

Carboxylic acids can be converted to the corresponding methyl ester by stirring a mixture of the carboxylic acid in methanol with an excess of methyl iodide and ***Potassium Carbonate***.[18] A recent report describes the esterification of carboxylic acids using ***Cesium Fluoride*** and methyl iodide in DMF (eq 14).[19] ***Dimethyl Sulfate*** has also been advantageously utilized to effect *O*-methylation of carboxylic acids as well as alcohols (eq 15).[18c,20] These methods

often serve as useful alternatives to ***Diazomethane*** for preparative scale esterification of carboxylic acids.

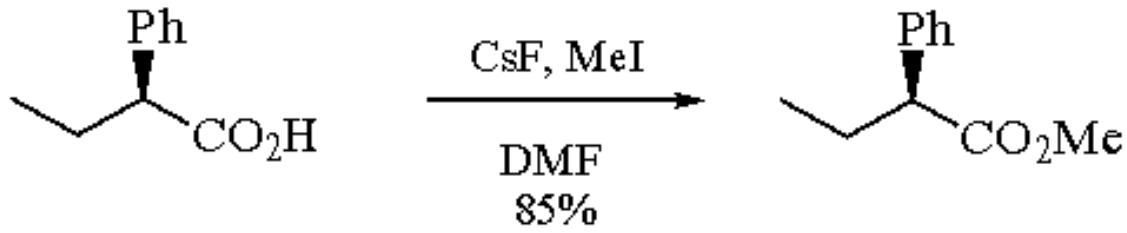

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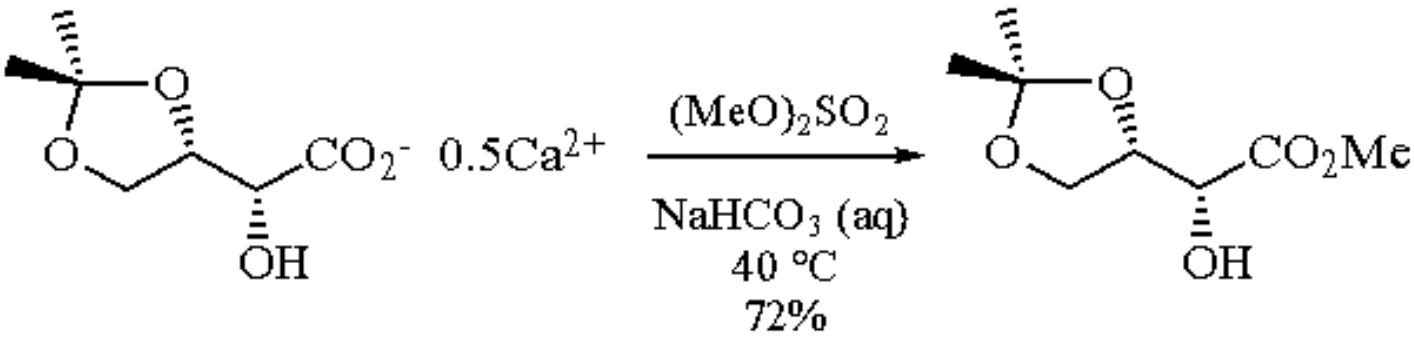

(15)

Phenolic hydroxyls are readily methylated by methyl iodide under basic conditions. The most common conditions are methyl iodide and potassium carbonate in acetone (eq 16).[18a,21] The use of ***Lithium Carbonate*** as the base allows for the selective protection of phenols with a pK_a < 8 (eq 17).[18c] The *peri*-hydroxy group of an anthraquinone is methylated using methyl iodide and ***Silver(I) Oxide*** in chloroform (eq 18).[18a,22]

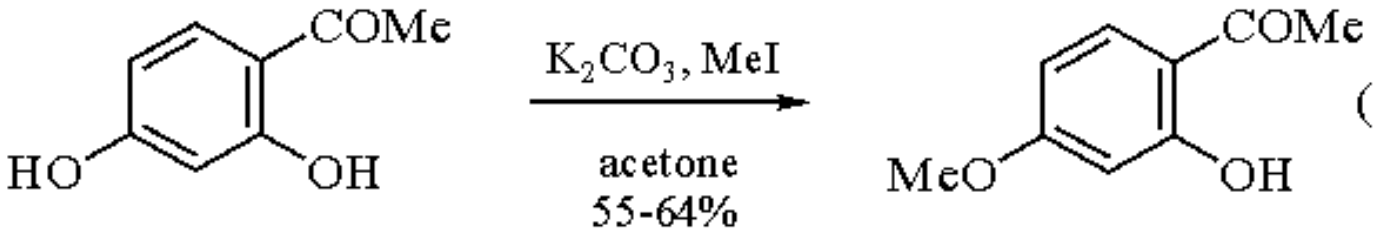

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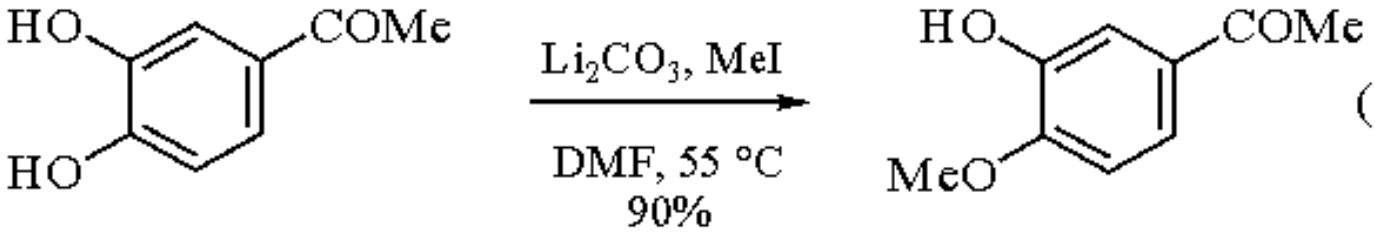

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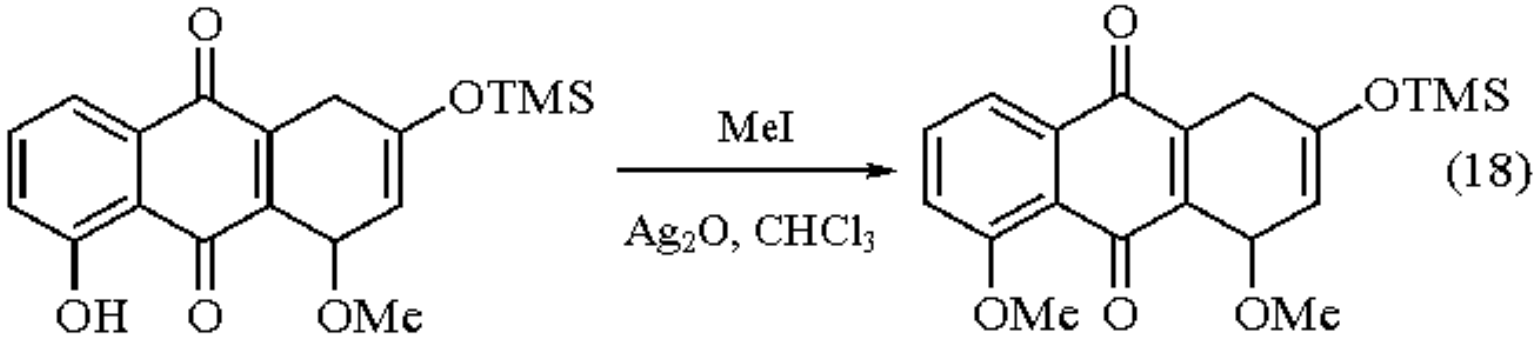

(18)

Aliphatic alcohols are also methylated by methyl iodide under basic conditions in dipolar aprotic solvents (eqs 19 and 20).[23] Typical conditions employ ***Sodium Hydride*** as a base, DMF as the solvent and an excess of methyl iodide.[24] Alternatively, dimethyl sulfate or ***Methyl Trifluoromethanesulfonate*** may be used as the methylating agent. Under acidic conditions, diazomethane will also methylate aliphatic hydroxy groups. Finally, methylation of a hydroxy group may be achieved under essentially neutral conditions using silver(1) oxide (eq 21).[23,25]

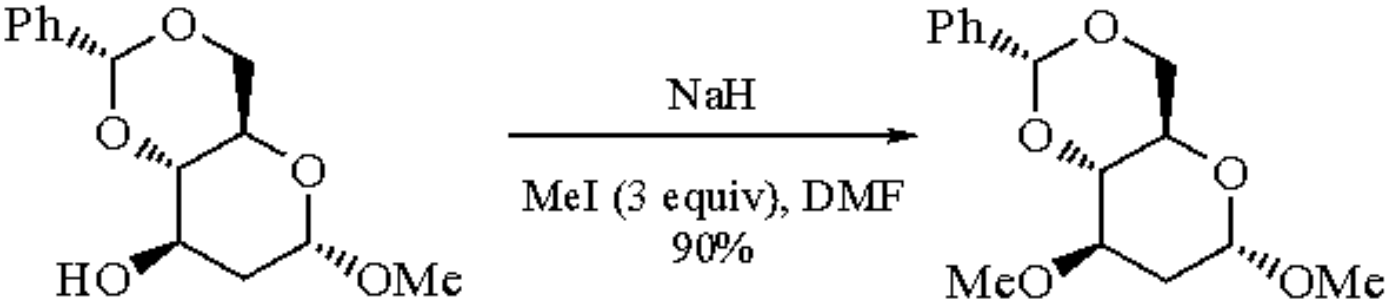

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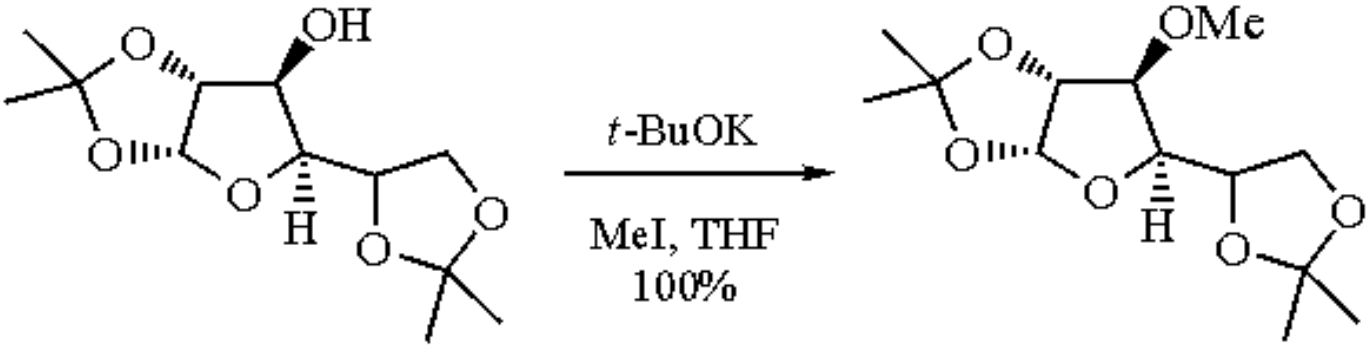

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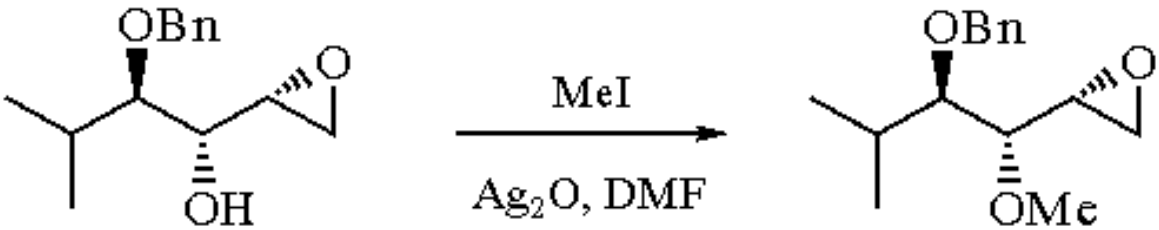

(21)

S-Alkylation.

Methyl iodide alkylates thioalkoxides and sulfides to produce sulfides and sulfonium ions, respectively. For example, thioalkoxides produced from thiocarbonyl compounds are methylated with methyl iodide to generate the corresponding methyl thioether (eq 22).[26] Sulfonium halides, derived from the reaction of methyl iodide with an alkyl sulfide, are sometimes labile in solution and may undergo further reaction (eq 23).[27,28] ***Dimethyl Sulfoxide*** when refluxed with an excess of methyl iodide produces trimethyloxosulfonium iodide, which is collected as a white solid and recrystallized from water. Similarly, methylation of ***Dimethyl Sulfide*** produces trimethylsulfonium iodide.[29] Treatment of trimethyloxosulfonium and trimethylsulfonium salts with a base yields the corresponding ylides, which serve as useful methylene transfer reagents. ***Silver(I) Perchlorate*** promotes the methylation of less reactive sulfides (eq 24).[30]

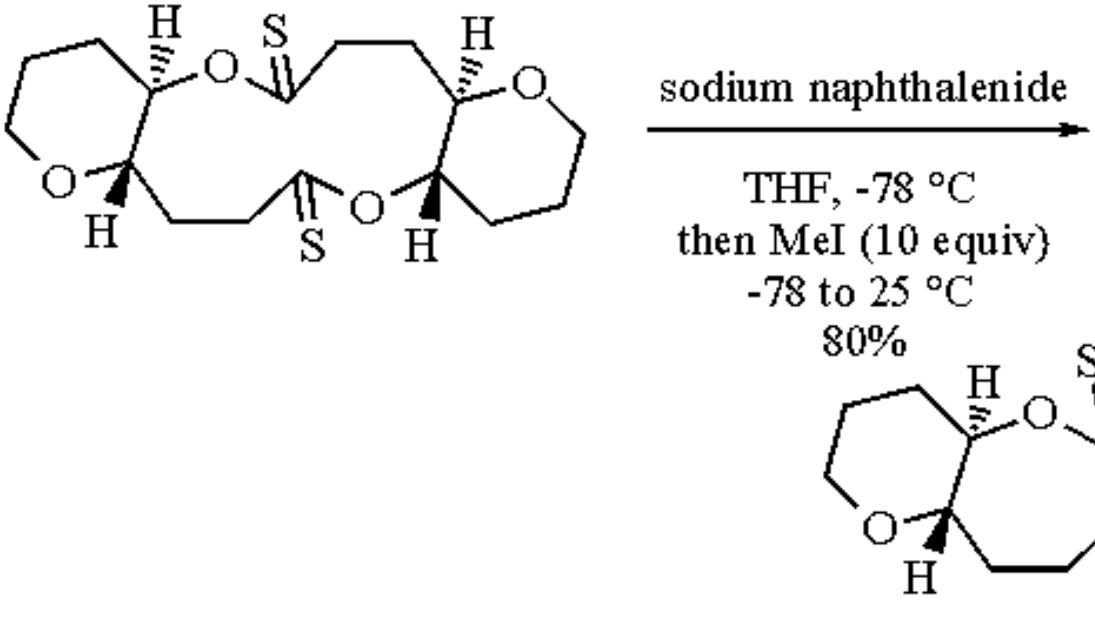

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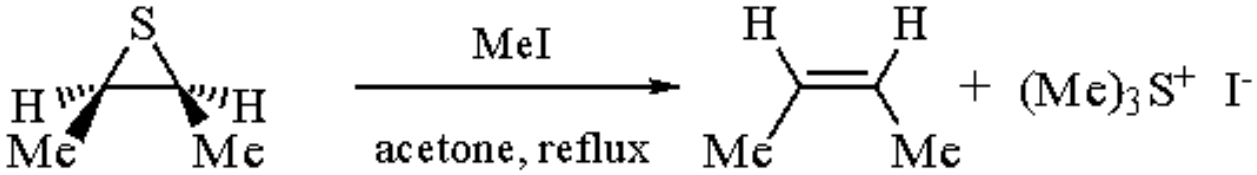

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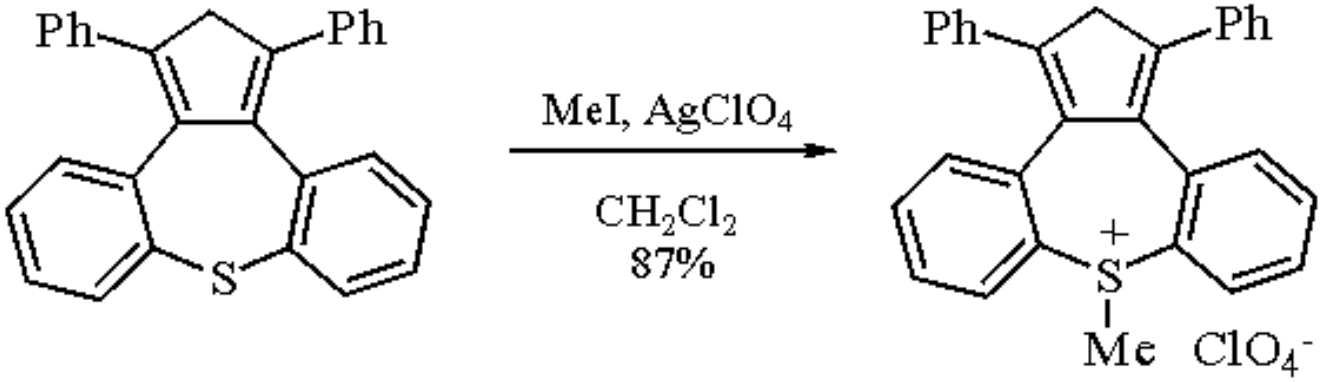

(24)

Hydrolysis of sulfonium salts serves as a useful protocol for removal of a protecting group or hydrolysis of a carboxylic acid derivative. For example, thioamides are converted into the corresponding methyl esters by methylation with methanolic methyl iodide followed by treatment with aqueous potassium carbonate (eq 25).[31] Methyl thiomethyl ethers are readily hydrolyzed using an excess of methyl iodide in aqueous acetone (eq 26).[32] Under similar reaction conditions, thioacetals are hydrolyzed to the corresponding carbonyl compounds (eq 27).[33]

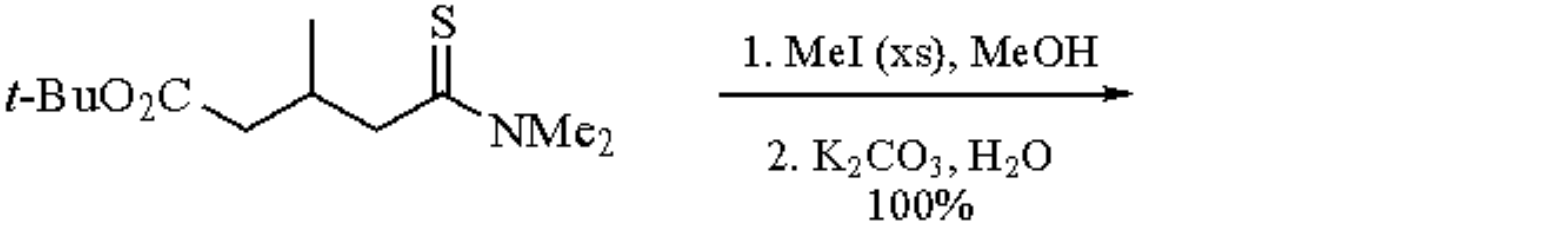

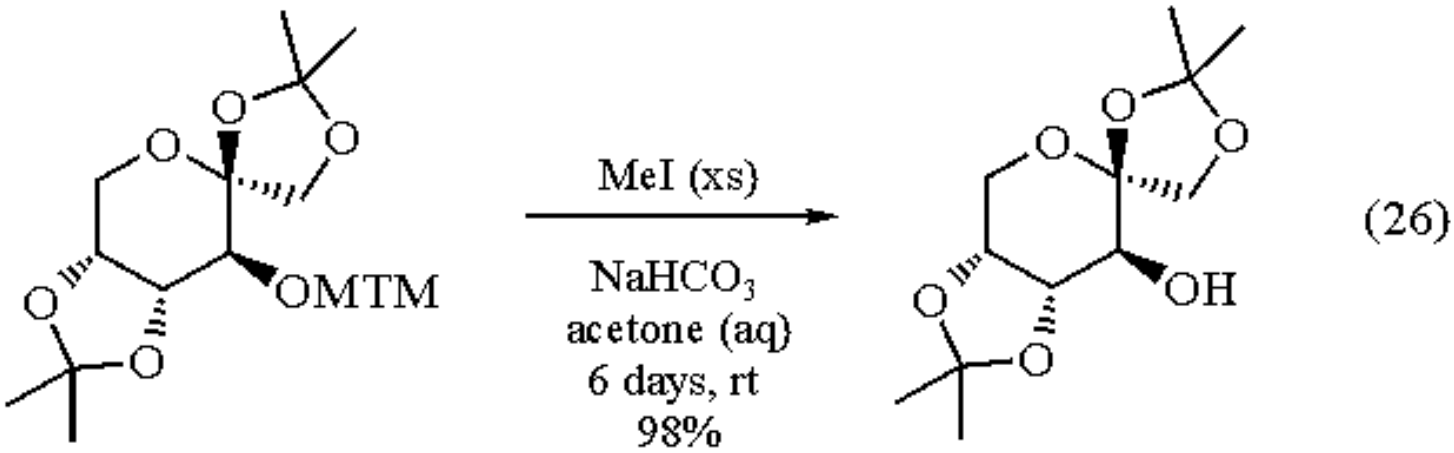

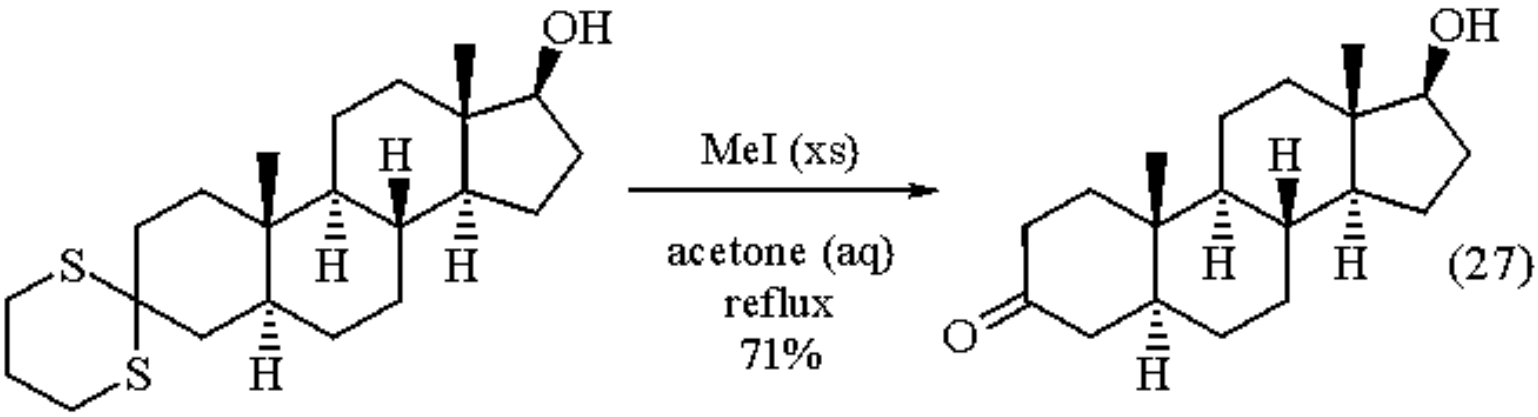

N-Methylation.

The direct monomethylation of ammonia or a primary amine with methyl iodide is usually not a feasible method for the preparation of primary or secondary amines since further methylation occurs. However, methylation of secondary and tertiary amines leading to the production of tertiary amines and quaternary ammonium salts, respectively, is a useful method. Secondary *N*-methylalkylamines can be prepared from primary amines by a multi-step sequence involving first methylation of the benzylidene of the primary amine followed by hydrolytic removal of the benzylidene group (eq 28).[34] An alternative to the methylation procedure using methyl iodide is the employment of Eschweiler-Clarke conditions.[35] Exhaustive *N*-methylation of amines results in the production of a quaternized amine. The use of ***2,6-Lutidine*** as base is beneficial to carry out quaternization of amines due to the slow rate of methylation of 2,6-lutidine (eq 29).[36] Quaternized ammonium salts are employed in the Hofmann elimination (eqs 30 and 31).[37,38] As in the case

of alcohol methylation, silver(I) salts may be used to facilitate the methylation process (eq 32).[39] Finally, conditions for the methylation of indole have been reported (eq 33).[40]

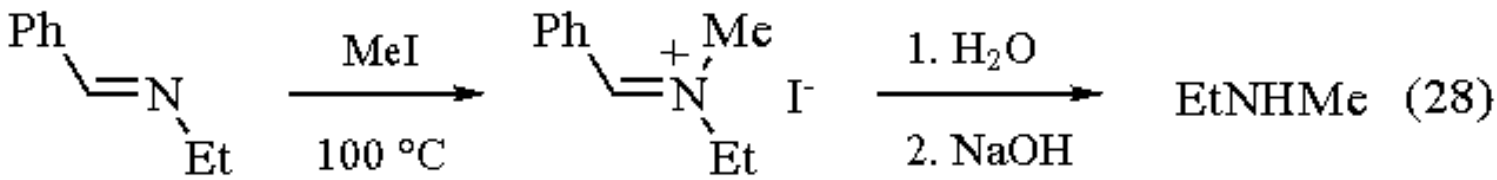

(28)

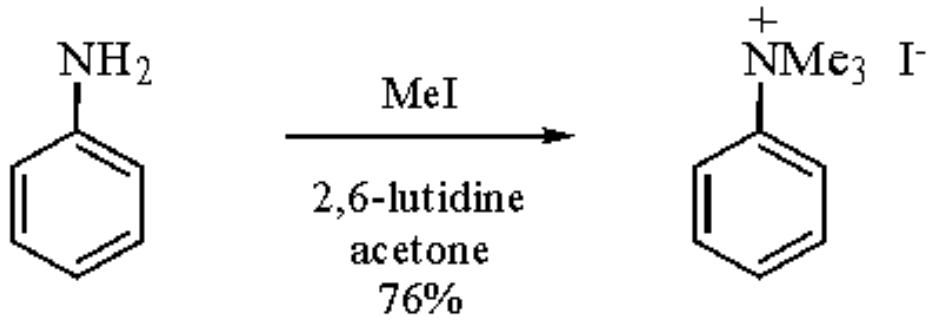

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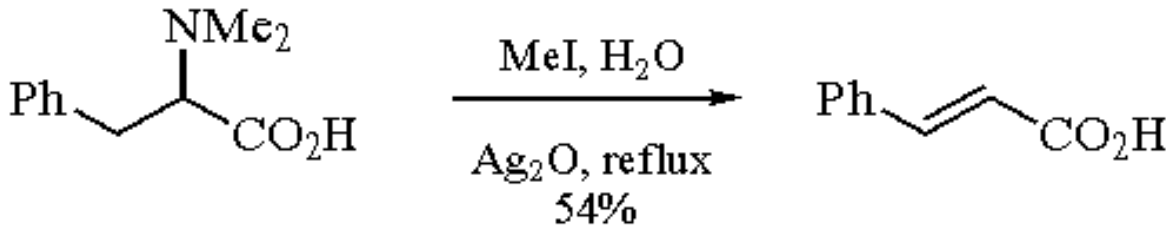

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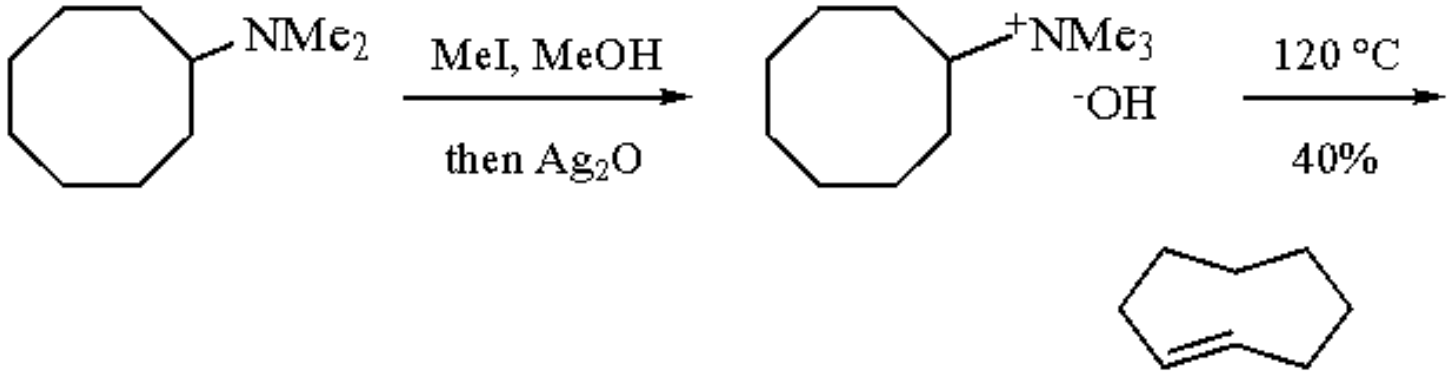

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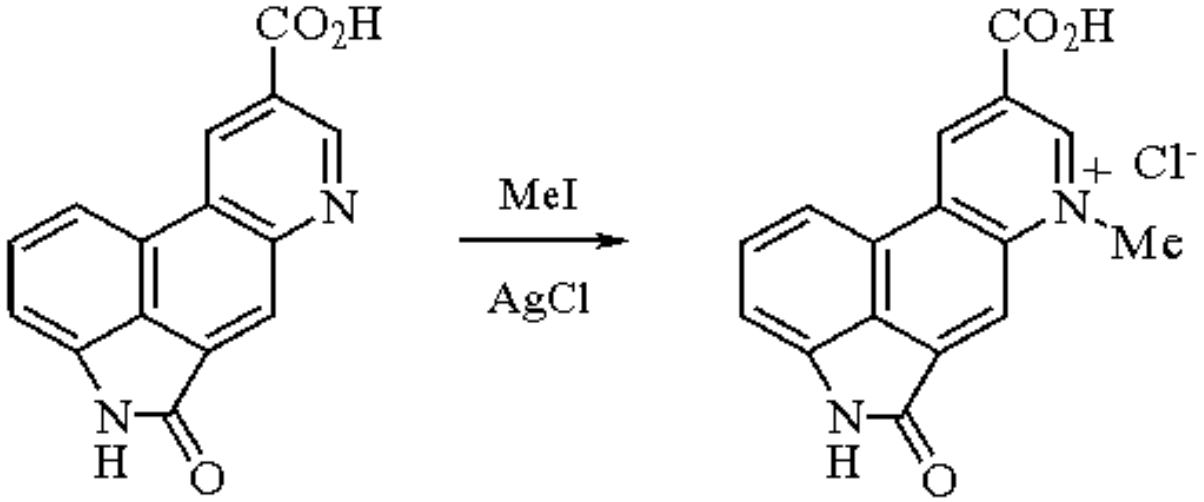

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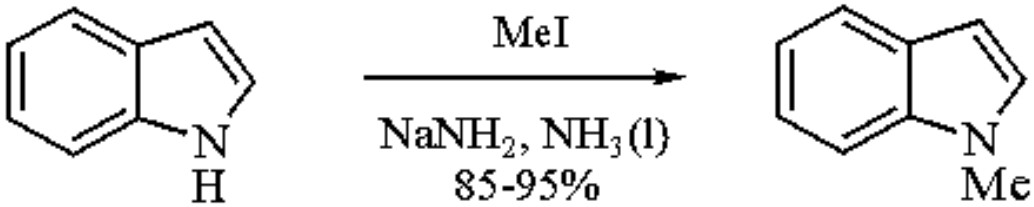

(33)

P-Methylation.

Phosphonium salts are prepared by the quaternization of phosphines with methyl iodide.[41] The displacement reaction is usually conducted in polar solvents such as acetonitrile or DMF. Dialkyl phosphonates are prepared from the reaction of trialkyl phosphites with alkyl halides, commonly known as the Arbuzov reaction.[42] For example, diisopropyl methylphosphonate is prepared by heating a mixture of methyl iodide and ***Triisopropyl Phosphite*** (eq 34).[43]

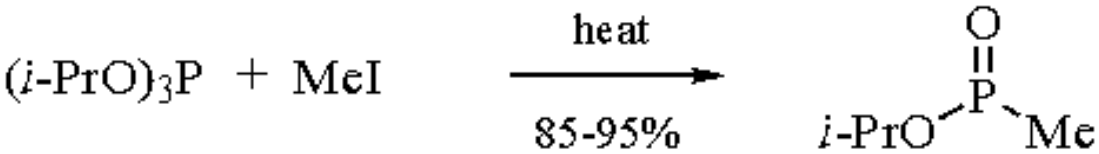

(34)

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Gary A. Sulikowski & Michelle M. Sulikowski

Iodomethyl Methyl Ether

ICH_2OMe

[13057-19-7] · C_2H_5IO · Iodomethyl Methyl Ether · (MW 171.97)

(reactive methoxymethylating agent for phosphorus,[1] carbon,[2] oxygen,[3] and nitrogen[4] nucleophiles; iodomethylating agent for aromatic systems[5])

Alternate Name: iodomethoxymethane.

Physical Data: bp 122 °C (dec), 39 °C/20 mmHg; *d* 2.030 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: liquid, commercially available (stabilized with copper).

Preparative Methods: displacement of chloride from ***Chloromethyl Methyl Ether*** by iodide ion, followed by distillation of the product (eq 1);[2a,2b,5b] reaction of ***Formaldehyde*** or trioxane with methanol and ***Hydrogen Iodide*** (eq 2);[6] reaction of methylal (***Dimethoxymethane***) with ***Iodotrimethylsilane*** (eq 3).[1a] This last route has the advantage of not using or producing highly carcinogenic materials such as chloromethyl methyl ether or ***Bis(chloromethyl) Ether***.

$$ClCH_2OMe \xrightarrow{KI} \underset{\textbf{(1)}}{ICH_2OMe} \qquad (1)$$

$$CH_2O \xrightarrow[HI]{MeOH} \textbf{(1)} \qquad (2)$$

$$MeOCH_2OMe \xrightarrow{Me_3SiI} \textbf{(1)} \qquad (3)$$

Handling, Storage, and Precautions: corrosive and a lachrymator; a strong alkylating agent and as such is likely to be harmful if swallowed or absorbed through the skin. It should be handled accordingly. Use in a fume hood.

Methoxymethylations.

The addition of a methoxymethyl group to a reactive functionality is a useful process in organic chemistry. Quite often this can be carried out by using the reagents ***Chloromethyl Methyl Ether*** and ***Bromomethyl Methyl Ether***. However, occasionally the more reactive iodomethyl methyl ether (**1**) has been used instead.

Reaction of (**1**) with Grignard reagents produces methoxymethylated compounds, e.g. (**3**) from (**2**) (eq 4), in high yield.[2b]

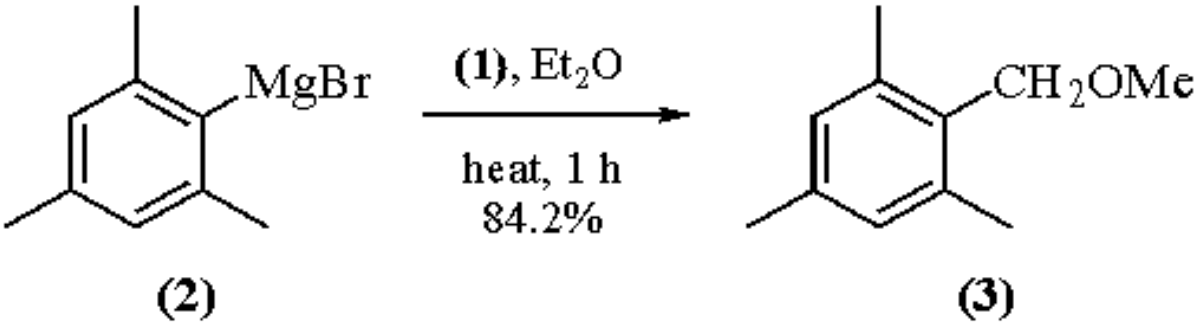

(4)

The lithium salts of vinyl carbanions can also be methoxymethylated with (**1**).[2a] Reaction with alkoxides affords the methoxymethylated ethers (MOM ethers) in good yield, e.g. (**5**) from (**4**) (eq 5).[3a]

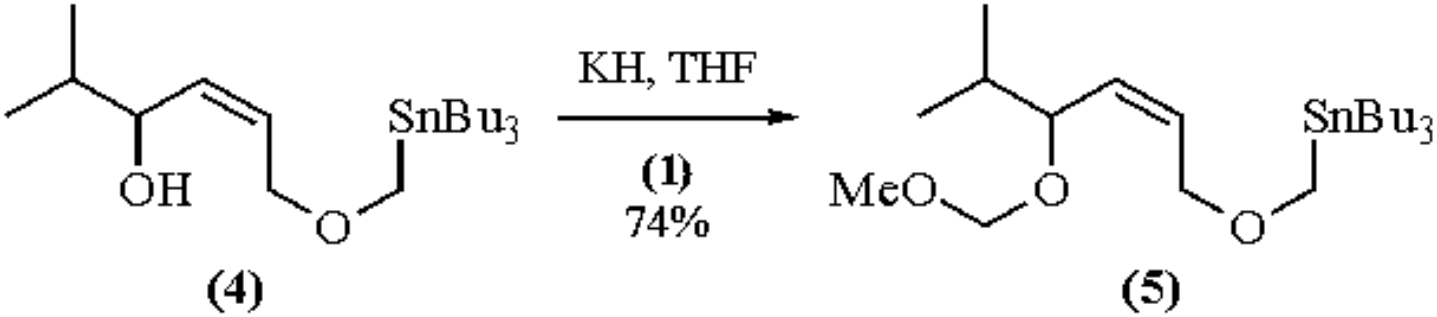

(5)

The commonly used methoxymethyltriphenylphosphonium halide (**6**) can also be easily prepared from (**1**) and ***Triphenylphosphine*** in good yield (eq 6) under milder conditions than with chloromethyl methyl ether.[1a]

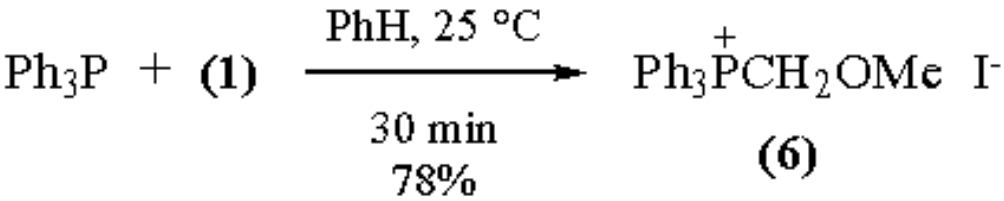

(6)

Reaction with various amines, e.g. ***Triethylamine*** or ***Hexamethylenetetramine***, leads to the salts in good yield as expected.[4] A nice use of the reagent was in the trapping of the cyclopentanone enolate (**8**) generated by addition of the organolithium (**7**) to cyclopentenone to furnish the bis-alkylated cyclopentanone (**9**) in fine yield. This compound was then taken on to sarkomycin (**10**) (eq 7).[7]

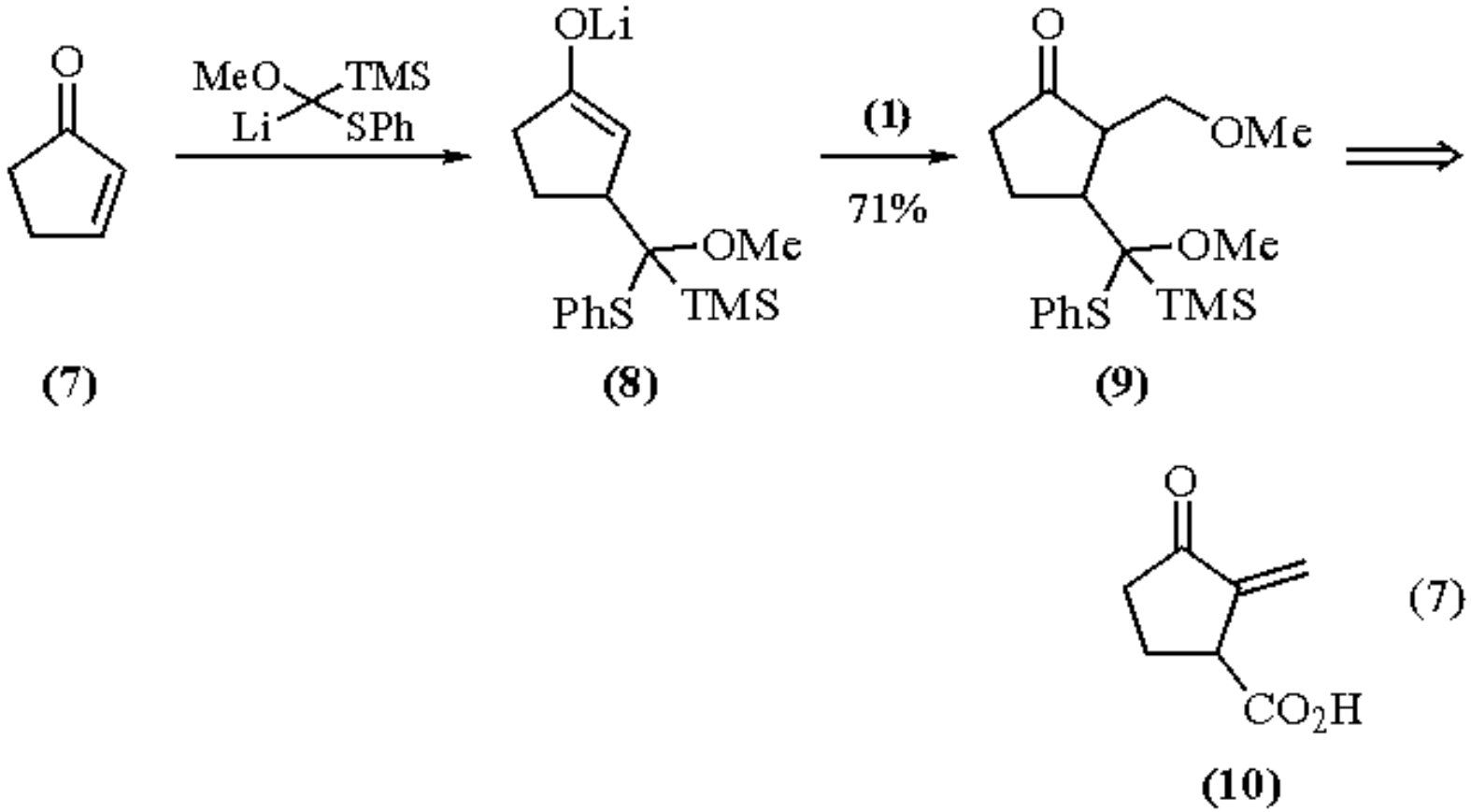

Iodomethylations.

Treatment of various aromatic compounds such as styrene and their derived polymers, e.g. polystyrene, with iodomethyl methyl ether (**1**) in the presence of a Lewis acidic metal iodide, e.g. SnI_4 or ***Zinc Iodide***, affords the iodomethyl aromatic derivatives (eq 8).[5]

$$\mathrm{ArH} + \mathbf{(1)} \xrightarrow[\text{or } ZnI_2]{SnI_4} \mathrm{ArCH_2I} \qquad (8)$$

Related Reagents.

Bromomethyl Methyl Ether; ***Chloromethyl Methyl Ether***.

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(Iodomethyl)trimethylsilane[1]

Me_3SiCH_2I

[4206-67-1] · $C_4H_{11}ISi$ · (Iodomethyl)trimethylsilane · (MW 214.14)

(electrophile for the preparation of allylsilanes[2] and propargylsilanes;[3] forms carbon alkylation adducts useful for alkene synthesis;[4] alkylation adducts are frequently a source of fluoride-induced reactive intermediates, forming nitrogen[5] and sulfur[6] alkylation adducts that function as ylide precursors; readily undergoes metal-halogen exchange to generate a reagent for Peterson methylenation[7])

Alternate Name: trimethylsilylmethyl iodide.

Physical Data: bp 140-142 °C; *d* 1.442 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: highly flammable liquid; corrosive; irritant; should be stored cold, protected from light, and stabilized with copper metal. Handle in a fume hood.

Allylsilane and Propargylsilane Synthesis.

(Iodomethyl)trimethylsilane has been used to prepare allylsilanes, which are typically utilized in Lewis acid or fluoride ion-promoted reactions with carbonyl compounds to provide homoallylic alcohols. Treatment of Me_3SiCH_2I with ***Methyltriphenylphosphonium Bromide*** and base produces an intermediate phosphonium salt which can be further utilized to prepare allylsilanes from carbonyl compounds.[2a,b] This procedure has been modified so that this series of transformations can be done as a one-pot procedure (eq 1).[2c]

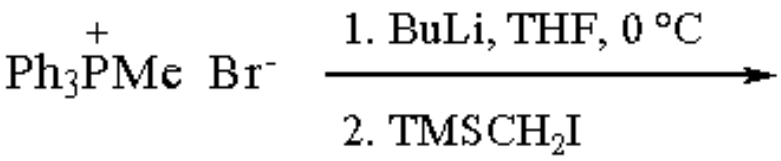

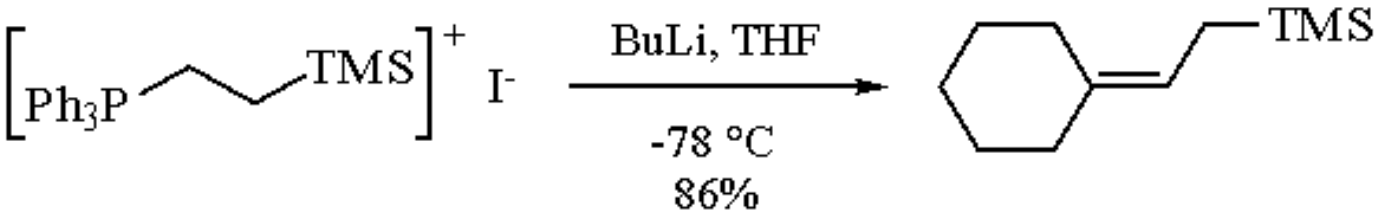

(1)

More recently, it has been demonstrated that activated vinylcuprates can be directly added to Me_3SiCH_2I to give functionalized allylsilanes in moderate yields (eqs 2-4).[8]

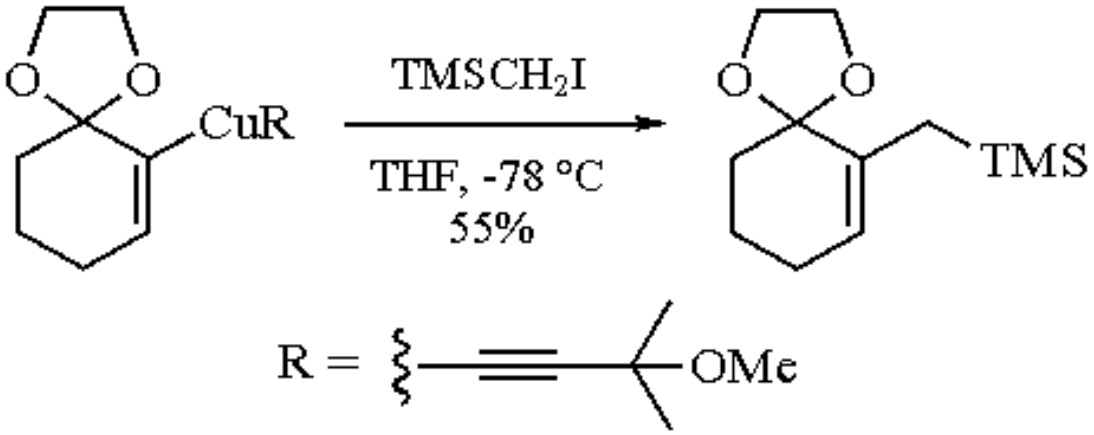

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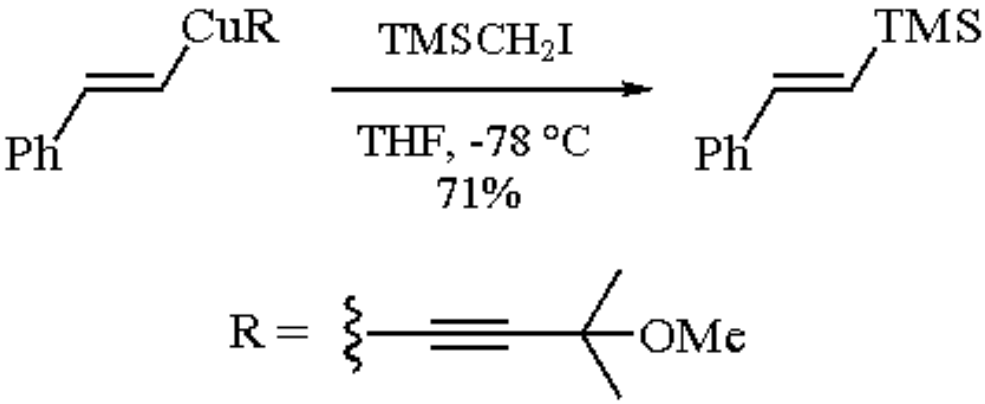

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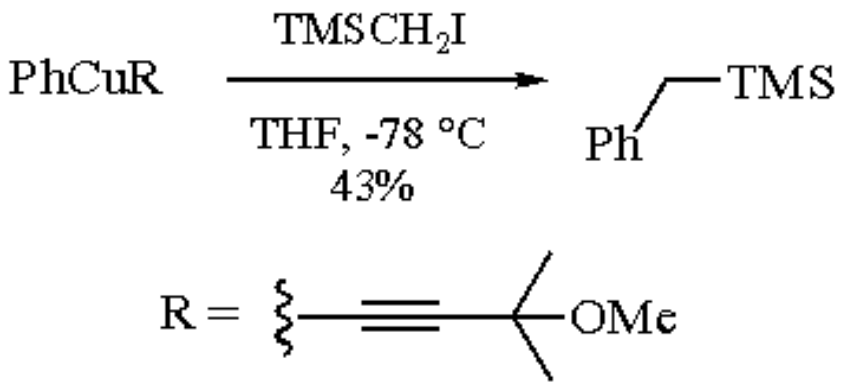

(4)

The synthesis of propargylsilanes has also been thoroughly explored, and these useful reagents are readily prepared by the addition of substituted lithioacetylides to Me_3SiCH_2I.[3] Propargylsilanes have subsequently been used in ***Titanium(IV) Chloride***-promoted reactions with acetals to yield functionalized α-allenylsilanes or functionalized alkenes.

Alkene Synthesis.

α-Alkylation of ketones with Me_3SiCH_2I, followed by a bromination/elimination sequence, gives rise to α-methylene ketones (eq 5).[4a]

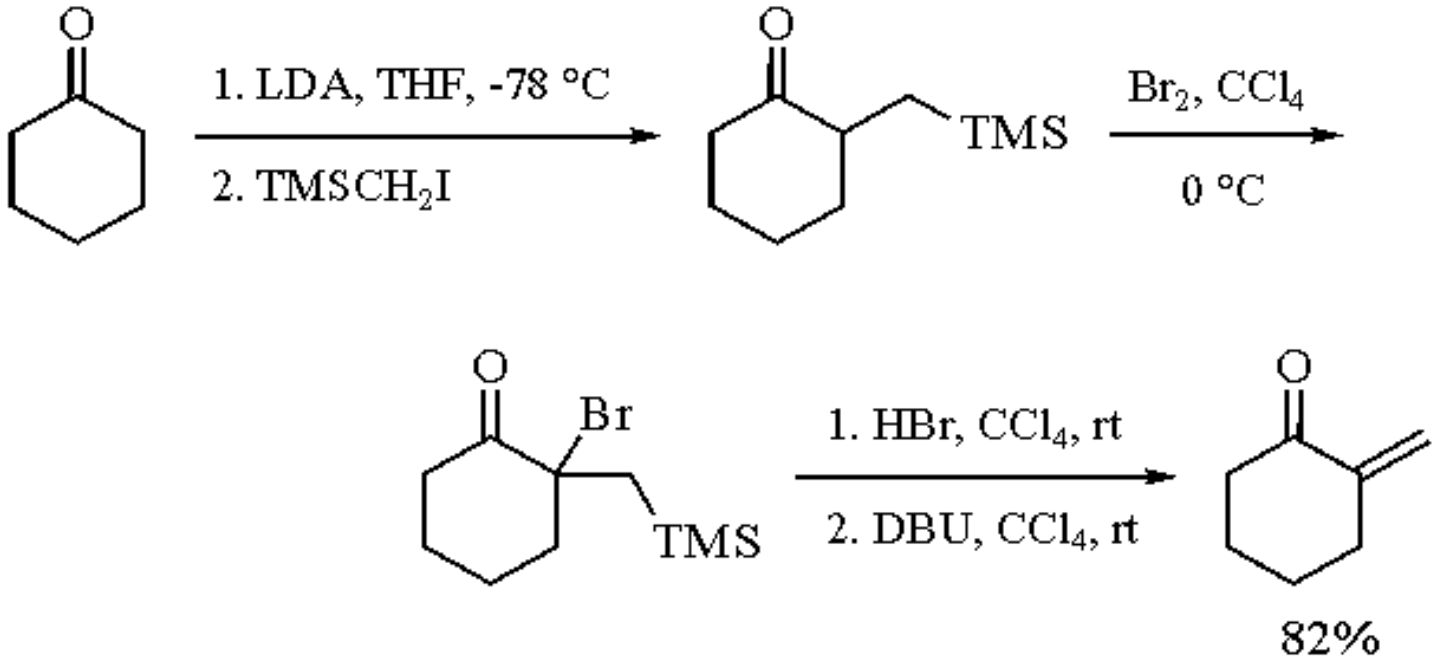

(5)

α-Alkylation of sulfones with Me_3SiCH_2I, followed by fluoride-induced elimination of the resultant β-silyl sulfones, cleanly produces alkenes, and this method has been applied to the synthesis of terminal alkenes, 1,4-dienes (by sequential dialkylation with ***Allyl Bromide*** and Me_3SiCH_2I), 1,3-dienes (eq 6), and *exo*-methylene compounds (eq 7).[4b] The intermediate β-silyl sulfones function as a synthon for $CH_2{=}CH^-$.

(Iodomethyl)trimethylsilane

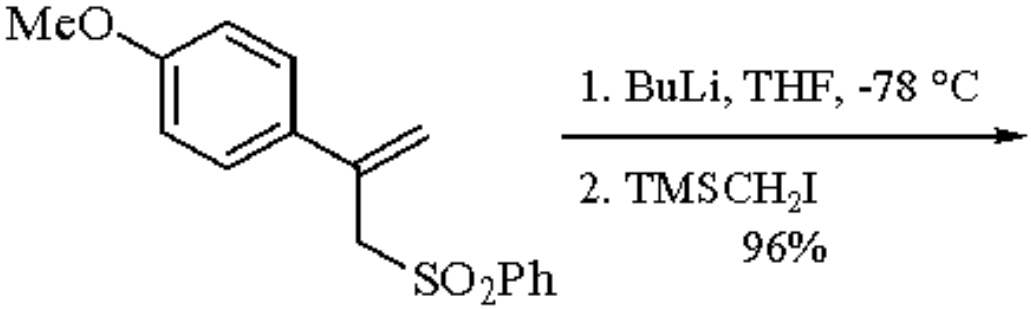

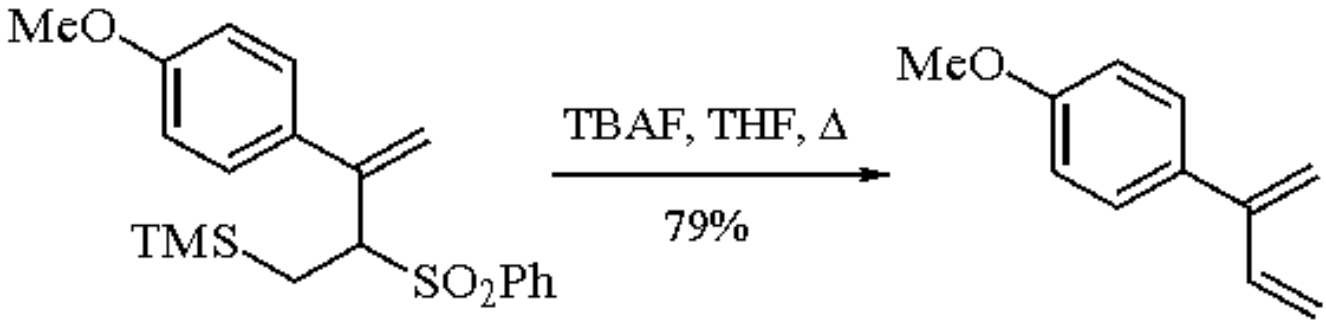

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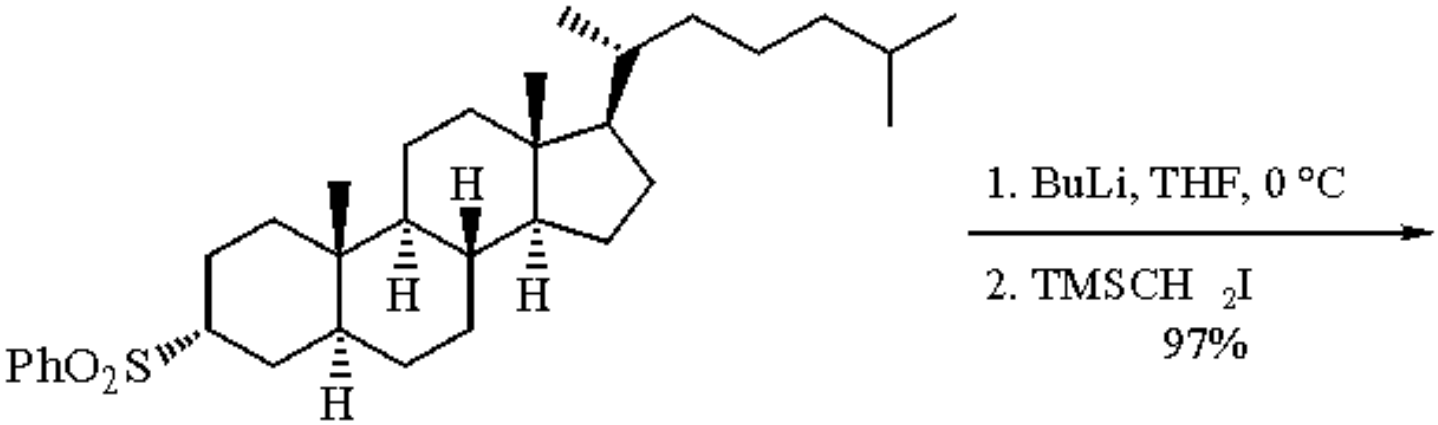

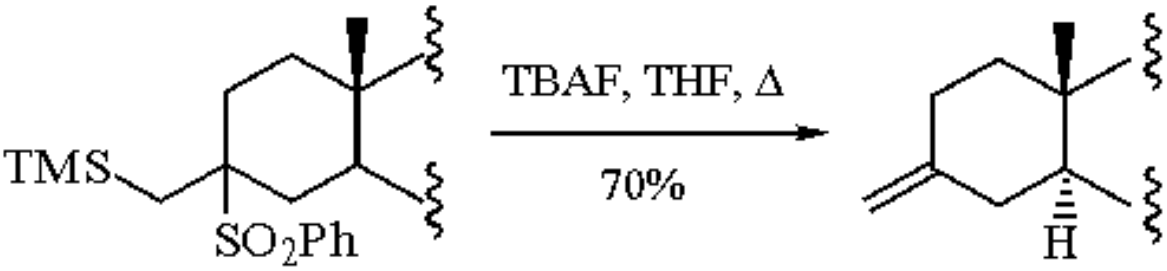

(7)

Generation of Nitrogen and Sulfur Ylides.

N-Trimethylsilylmethyl amides, prepared by the alkylation of the deprotonated amide with Me_3SiCH_2I, provide convenient access to nonstabilized azomethine ylide precursors. This method involving fluoride-promoted generation of a nonstabilized imidate ylide for 1,3-dipolar cycloaddition has been applied to the efficient construction of a key intermediate for the synthesis of the pyrrolizidine alkaloids retronecine and indicine by in situ trapping of the ylide

intermediate with ***Methyl Acrylate*** (eq 8).[5] This more versatile desilylation method of ylide generation and trapping with dipolarophiles demonstrates applicability to a wider range of synthetic targets than those derived from α-deprotonation of iminium salts, where an often unwanted anion-stabilizing substituent is required.

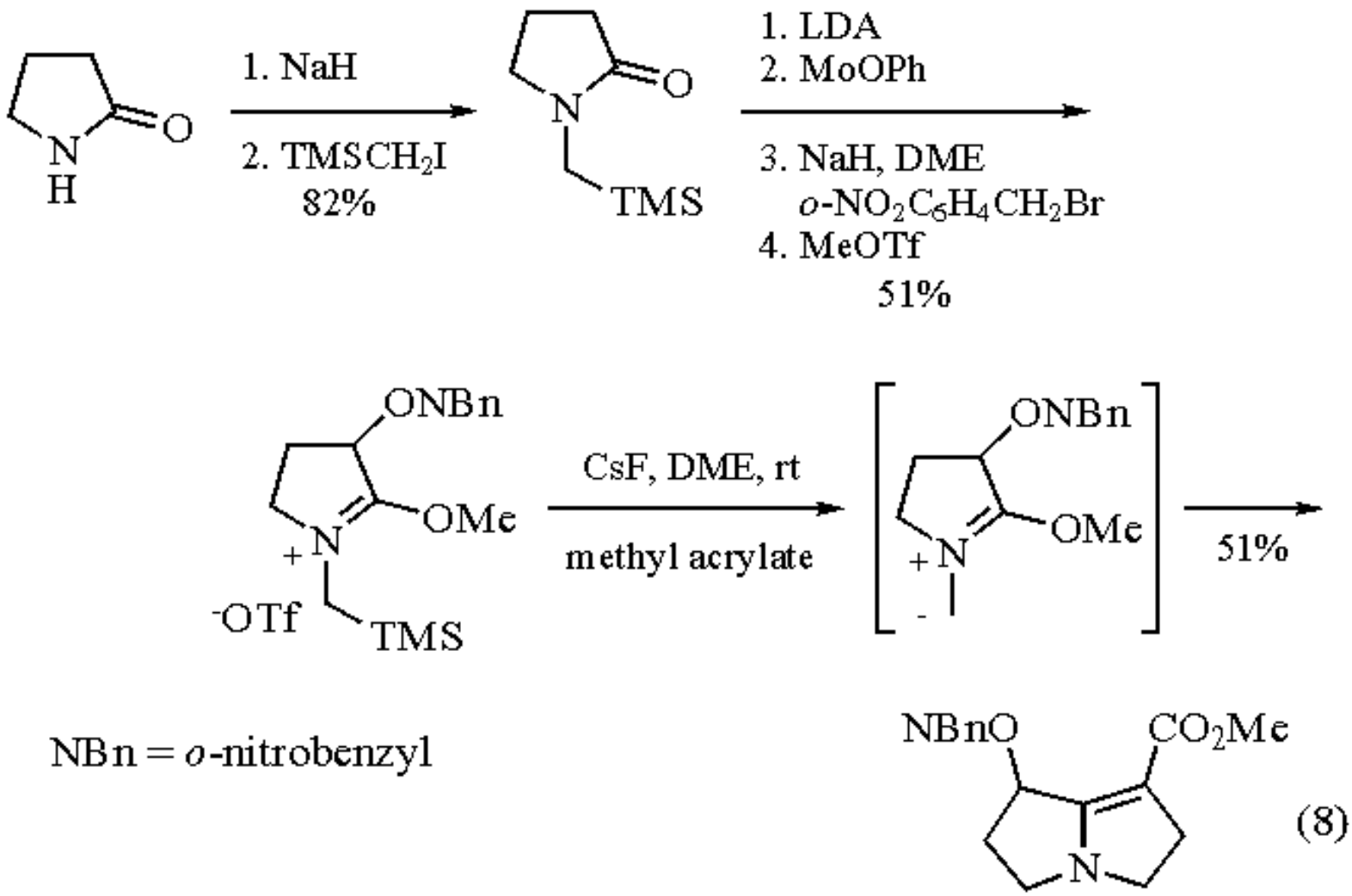

Similarly, the ***Cesium Fluoride***-induced desilylation of α-trimethylsilylbenzylsulfonium alkyl triflate salts produces sulfur ylides, which rapidly equilibrate in DME solution to the thermodynamically more stable ylide prior to reaction with aromatic aldehydes to produce predominantly *trans*-diaryl epoxides in high yields.[6a] In the absence of an aldehyde trapping agent, Sommelet-Hauser rearrangements occur.

Related Reagents.

(Chloromethyl)trimethylsilane; ***Trimethylsilylmethyllithium***; ***Trimethylsilylmethylmagnesium Chloride***; ***Trimethylsilyl Trifluoromethanesulfonate***.

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1. There are currently no published reviews on the use of this reagent. For a review of (chloromethyl)trimethylsilane, see Anderson, R. *S* **1985**, 717.
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Iodomethylzinc Iodide[1]

ICH_2ZnI

(**1**; ICH_2ZnI)

[4109-94-8] · CH_2I_2Zn · Iodomethylzinc Iodide · (MW 333.22) (**2**; $BrCH_2ZnBr$)

[4109-95-9] · CH_2Br_2Zn · Bromomethylzinc Bromide · (MW 239.22) (**3**; $(ICH_2)_2Zn$)

[14399-53-2] · $C_2H_4I_2Zn$ · Bis(iodomethyl)zinc · (MW 347.25) (**4**; $(ICH_2)_2Zn.DME$)

[131457-21-1] · $C_6H_{14}I_2O_2Zn$ · Bis(iodomethyl)zinc-Dimethoxyethane · (MW 437.39) (**5**; $(BrCH_2)_2Zn$)

[92601-82-6] · $C_2H_4Br_2Zn$ · Bis(bromomethyl)zinc · (MW 253.25) (**6**; $(ClCH_2)_2Zn.DME$)

[131457-22-2] · $C_6H_{14}Cl_2O_2Zn$ · Bis(chloromethyl)zinc-Dimethoxyethane · (MW 254.49)

(methylene transfer reagent: cyclopropanates alkenes,[1] a^1/d^1 multicoupling reagent,[2] transmetalation with various metal halides affords other iodomethylmetal compounds[3])

Alternate Name: Simmons-Smith reagent.

Physical Data: an X-ray crystal structure of $(ICH_2)_2Zn$ complexed to a glycol bis-ether is known;[4] DME complexes of $(ICH_2)_2Zn$ and $(ClCH_2)_2Zn$ and an acetone complex of $(ICH_2)_2Zn/ZnI_2$ have been characterized by NMR spectroscopy;[4] ^1H NMR spectra attributed to THF complexes of $BrCH_2ZnBr$ and $(BrCH_2)_2Zn$ have been reported.[5]

Solubility: ICH_2ZnI generated from either CH_2I_2/Zn-Cu couple or $EtZnI/CH_2I_2$ is generally prepared in ethereal solvents (Et_2O, DME). The Et_2Zn/CH_2I_2 method of reagent generation can utilize noncoordinating solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, etc.).

Preparative Methods: the two most widely used methods of preparing halomethylzinc reagents are the Simmons-Smith and Furukawa procedures, utilizing ***Diiodomethane/Zinc/Copper Couple*** and CH_2I_2/***Diethylzinc*** (or ***Chloroiodomethane***/Et_2Zn),[6] respectively. The reagent is often prepared in the presence of the substrate (usually an alkene). Various methods of reagent preparation are discussed below. The precursors are widely available.

Reagent Preparation.

There are a number of protocols for generating iodomethylzinc reagents, which can be categorized into three general classes: type 1, the oxidative addition of a dihalomethane to zinc metal, as typified by the original Simmons-Smith procedure;[7,8] type 2, the reaction of a zinc(II) salt with a diazoalkane, first reported by Wittig and co-workers;[9] and type 3, an alkyl exchange reaction between an alkyl zinc and a 1,1-dihaloalkane, often referred to as the Furukawa procedure.[10]

Type 1 reagent generation has been used most often in synthetic contexts due to the ease with which the reagent precursors can be handled. Although the initial method of preparation of the Zn-Cu couple was difficult and not easily reproducible,[7] several simpler and highly reproducible methods soon followed.[11] Treatment of the Zn-Cu couple with CH_2I_2 and a crystal of ***Iodine*** in Et_2O followed by heating to reflux generates the active reagent. Other modifications include the use of CH_2I_2/Zn/CuCl,[12a] CH_2I_2/Zn-Ag couple,[12b] CH_2Br_2/Zn/$TiCl_4$,[12c] and CH_2Br_2/Zn/AcCl/CuCl.[12d]

Type 2 reagent generation has been utilized much less frequently. The method consists of the treatment of an ethereal suspension of a zinc(II) salt ($ZnCl_2$, $ZnBr_2$, ZnI_2, or $Zn(OBz)_2$) with CH_2N_2 or an aryldiazomethane.[9a]

Type 3 halomethylzinc generation (originally reported in 1966)[10a] involves treatment of a solution (Et_2O, hexane, toluene, etc.) of Et_2Zn with CH_2I_2 to generate the reagent. The use of a 2:1 ratio of CH_2I_2 to Et_2Zn generates $(ICH_2)_2Zn$,[4] while a 1:1 ratio presumably generates $EtZnCH_2I$.[10] The reaction is accelerated by the presence of trace amounts of oxygen.[6b] Treatment of Et_2Zn with substituted diiodides, such as benzylidene and ethylidene iodide, also gives rise to active cyclopropanating reagents.[13] Recently, the substitution of $ClCH_2I$ for CH_2I_2 and the use of $ClCH_2CH_2Cl$ (DCE) as the reaction solvent has been demonstrated to provide a more reactive reagent for certain applications.[6a] In addition, the combination of EtZnI and CH_2I_2 has also been shown to provide ICH_2ZnI, thus avoiding the need for the highly pyrophoric Et_2Zn.[14]

Cyclopropanations.

The cyclopropanation of alkenes utilizing halomethylzinc reagents (ICH_2ZnI being the prototypical reagent), known as the Simmons-Smith reaction,[7] has proven to be an extremely versatile and general reaction. Typical examples of alkenes that have been successfully cyclopropanated are provided in eqs 1-5. A variety of isolated alkenes have been cyclopropanated with the Simmons-Smith reagent (e.g. eq 1),[1a,12b] and ICH_2ZnI provides for a unique preparation of numerous spiro derivatives (eq 2).[15] Electron-rich alkenes such as enol ethers (eq 3)[16a-c] and enamines (eq 4)[16d,e] also have been found to be good substrates under the proper conditions, as have certain steroidal enones (eq 5).[16f,g] Simmons-Smith reagents thus have been demonstrated to cyclopropanate alkenes ranging from electron rich to electron deficient. This contrasts with the analogous reagents generated from CH_2I_2/R_3Al[17] and $ClCH_2I$/Sm(Hg):[18] the former reacts preferentially with isolated alkenes, while the latter cyclopropanates allylic alcohols almost exclusively. Certain vinyl metal species (Al, Si, Ge, Sn, B) can also be cyclopropanated with some success with the Simmons-Smith reagent.[19] For example, vinylalanes produced in situ from alkynes and ***Diisobutylaluminum Hydride*** react readily with CH_2Br_2/Zn-Cu couple; the intermediate cyclopropylalanes react with bromine to produce cyclopropyl bromides (eq 6).[19b] Generally, the reaction is most successful with electron-rich alkenes, indicative of the electrophilic nature of halomethylzinc reagents.[1a]

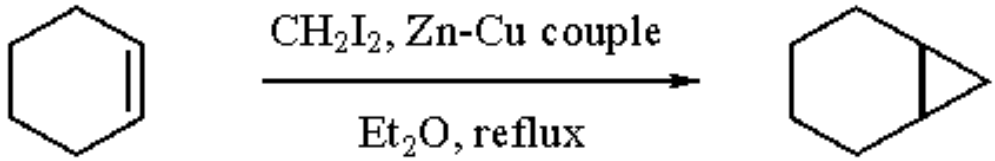

(1)

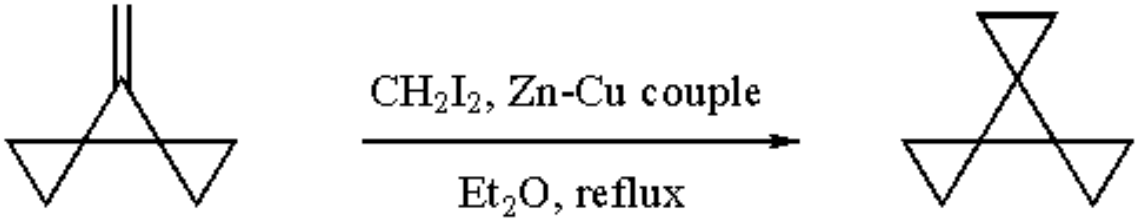

(2)

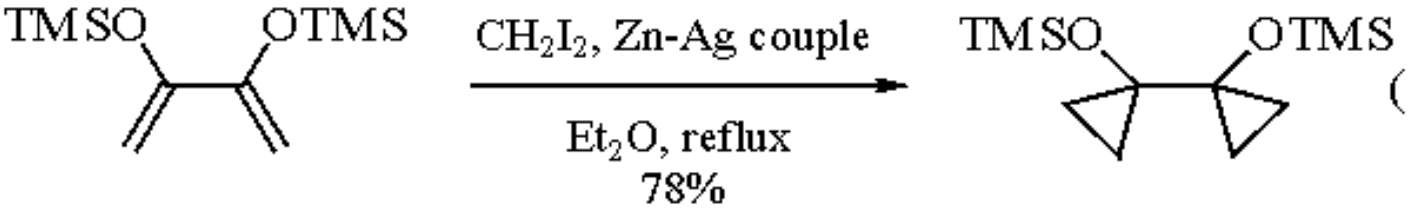

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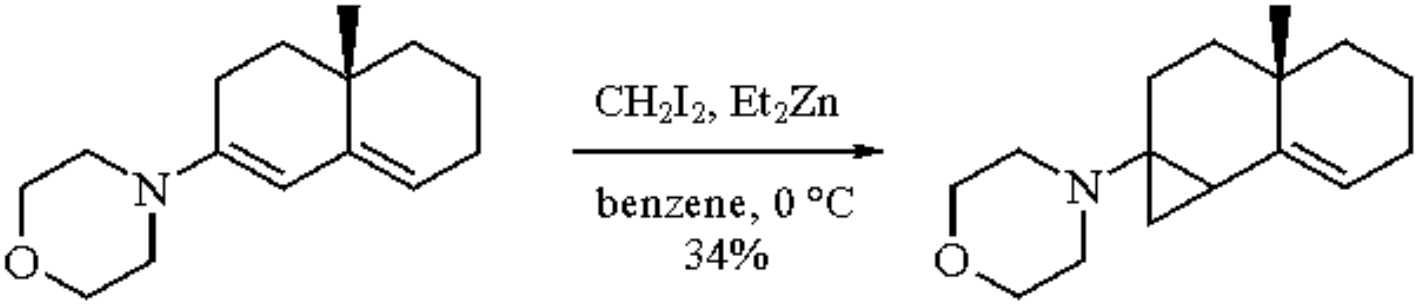

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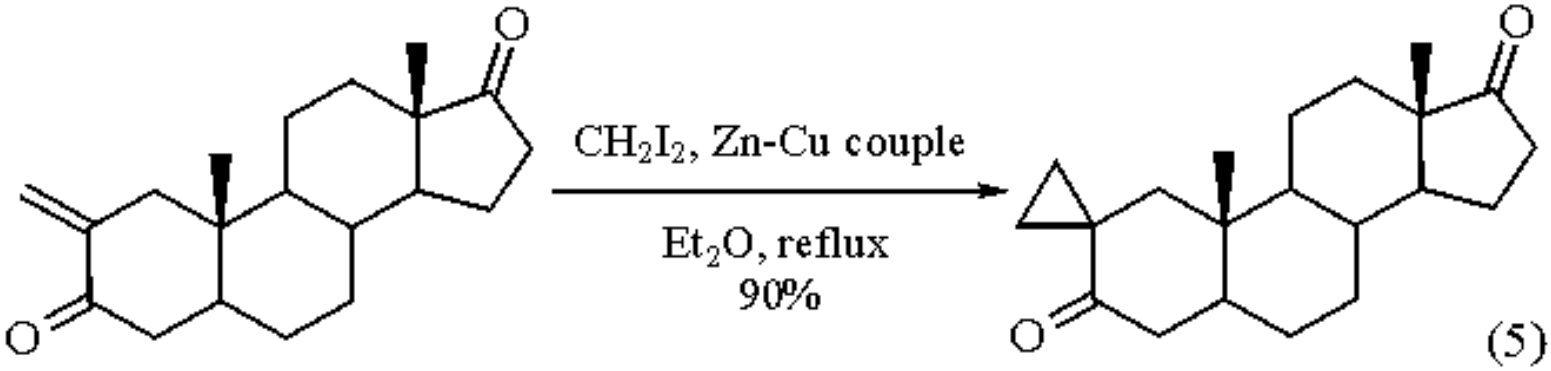

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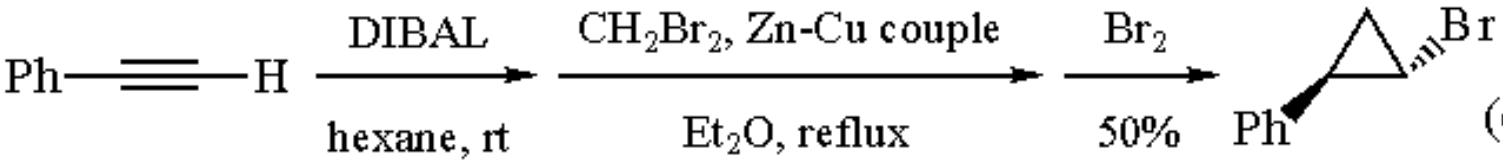

(6)

The reaction is not limited to unsubstituted methylene transfers.[13] The combination of $MeCHI_2$[13a-c] or $PhCHI_2$[13a,d] with

Et_2Zn also provides active cyclopropanation reagents. The diastereoselectivity is highly substrate dependent, but good diastereoselectivity can be achieved in certain cases (eq 7), particularly with cyclic alkenes. The stereoselectivity is solvent dependent, with ethereal solvents affording the higher levels of selectivity.[13d] Halogen-substituted carbenoids can also be prepared from various $XCHI_2$ (X = I, Br, F) or X_2CHI (X = Br, Cl) and Et_2Zn (eq 8).[13e-g]

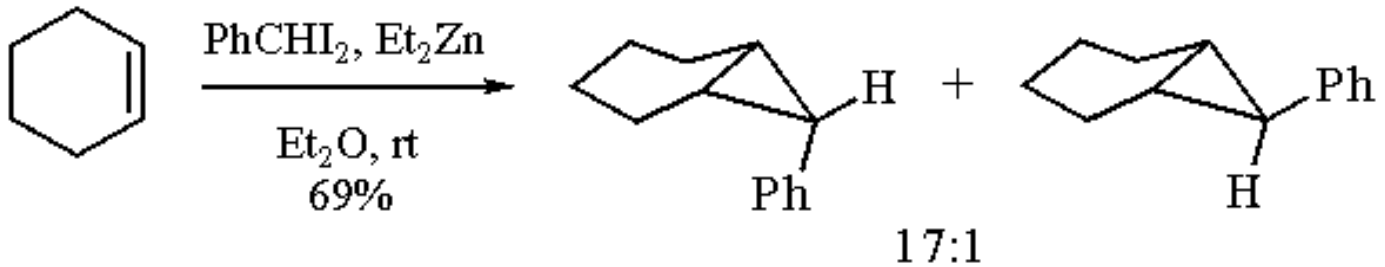

(7)

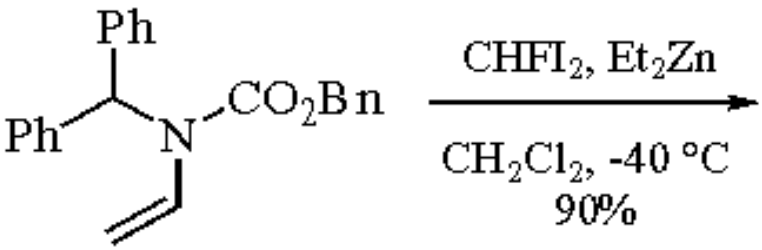

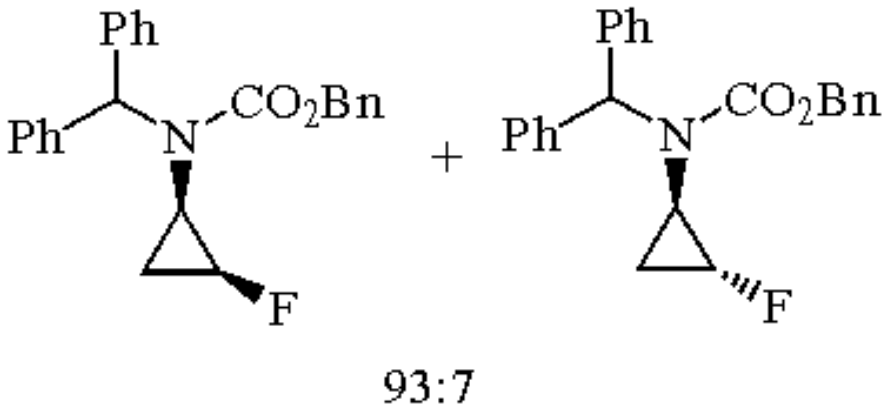

(8)

Perhaps the most intriguing aspect of the Simmons-Smith reaction is the strong accelerating and stereodirecting effect of oxygen functions proximal to the alkene. First discovered in 1959,[20] this reaction has been often utilized in synthetic efforts[21] and the reaction itself has been the subject of several investigations.[22] For example, cyclopropanation of 2-cyclohexen-1-ol provides the *syn*-cyclopropane almost exclusively.[22a] A study of various cyclic allylic alcohols demonstrates the generality of the effect (eq 9):[22c] the larger rings afford *trans* adducts due to conformational effects. The diastereoselectivity of the cyclopropanation of acyclic secondary allylic alcohols depends upon the configuration of the alkene. *cis*-Alkenes react with diastereoselectivities of >99:1 (eq 10), while *trans*-alkenes react with much less selectivity (<2:1).[22f] Homoallylic alcohols also show a similar directing effect in certain cases (eq 11).[20,21e]

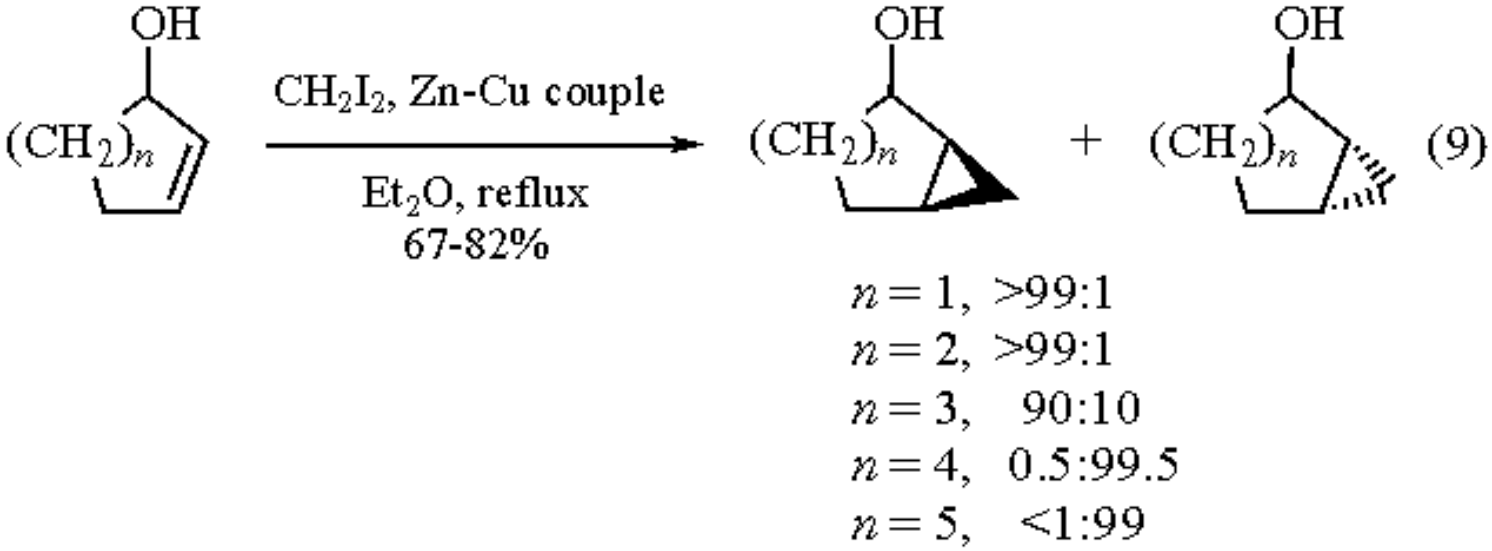

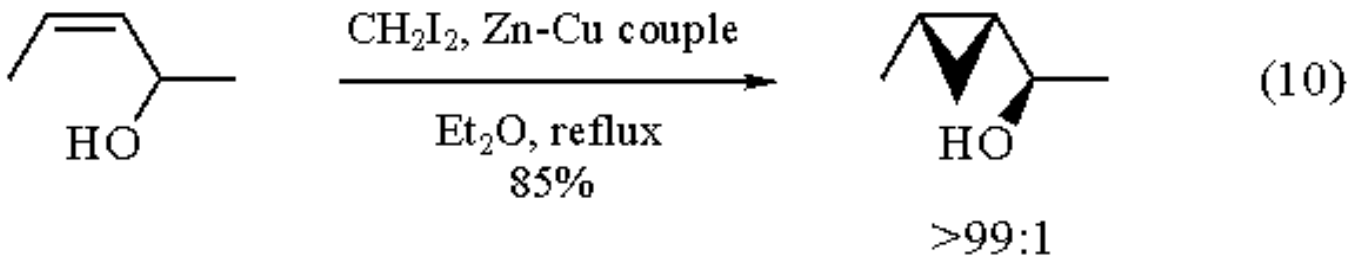

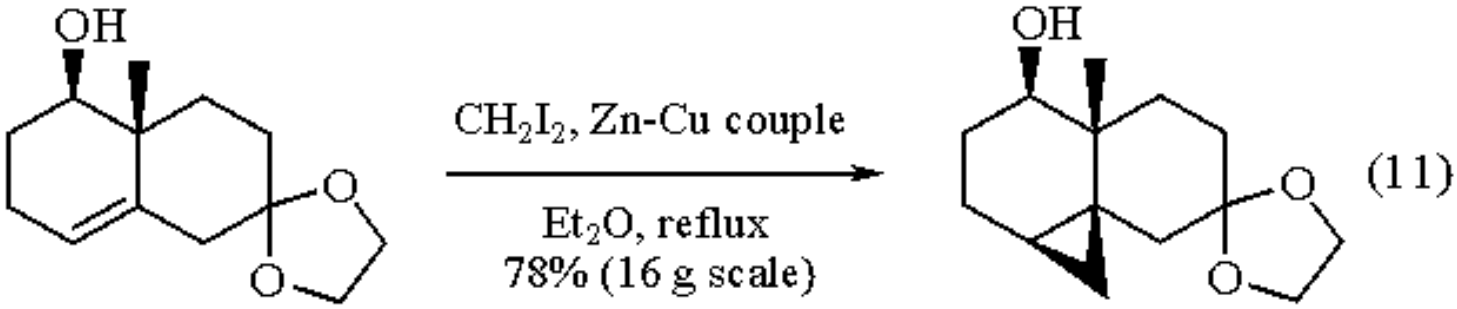

Chiral auxiliary mediated cyclopropanations which exploit this oxygen-directing effect have recently been developed. The first Simmons-Smith reactions exhibiting effective diastereofacial control by chiral auxiliaries were reported simultaneously by two groups in 1985.[23,24] Chiral acetals derived from cyclic enones undergo highly diastereoselective cyclopropanations upon treatment with CH_2I_2/Zn-Cu couple (eq 12). Acyclic enones are cyclopropanated with greatly attenuated diastereoselectivity.

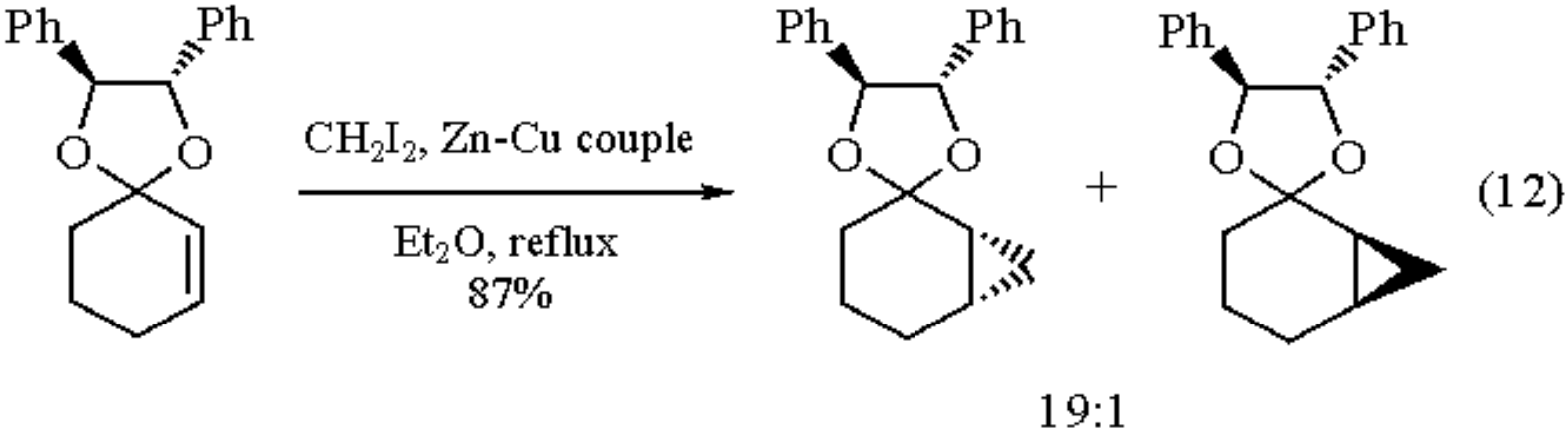

Similarly, chiral acetals[24] derived from α,β-unsaturated aldehydes and diisopropyl tartrate are cyclopropanated in a highly diastereoselective manner by CH_2I_2/Et_2Zn (eq 13). Diastereoselectivities are uniformly high for dioxolane acetals derived from *trans*-disubstituted α,β-unsaturated aldehydes, but acetals derived from α,β-unsaturated ketones react less selectively, as do 2-alkenyl-1,3-dioxane acetals.

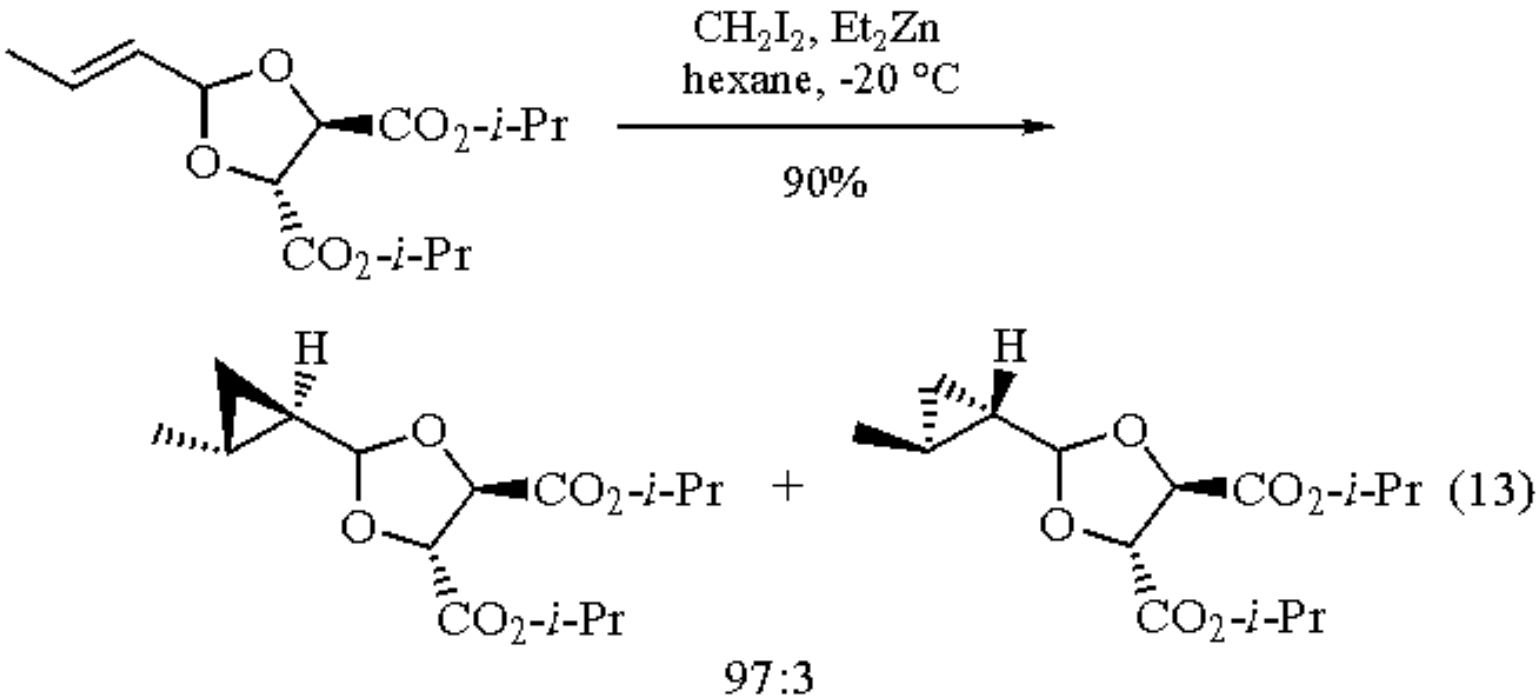

A related oxygen-directed cyclopropanation has also been reported.[25] Vinyl boronates derived from tartaric esters or amides were shown to undergo highly diastereoselective cyclopropanations upon treatment with CH_2I_2/Zn-Cu couple. These adducts were conveniently converted to enantiomerically enriched cyclopropanols. The carbohydrate 2-hydroxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose appended to an allylic alcohol also functions as an effective chiral auxiliary, affording cyclopropanes with extremely high levels of diastereoselectivity (eq 14).[26] Other chiral auxiliaries have also been shown to direct halomethylzinc cyclopropanations with good to excellent stereocontrol.[13g,27]

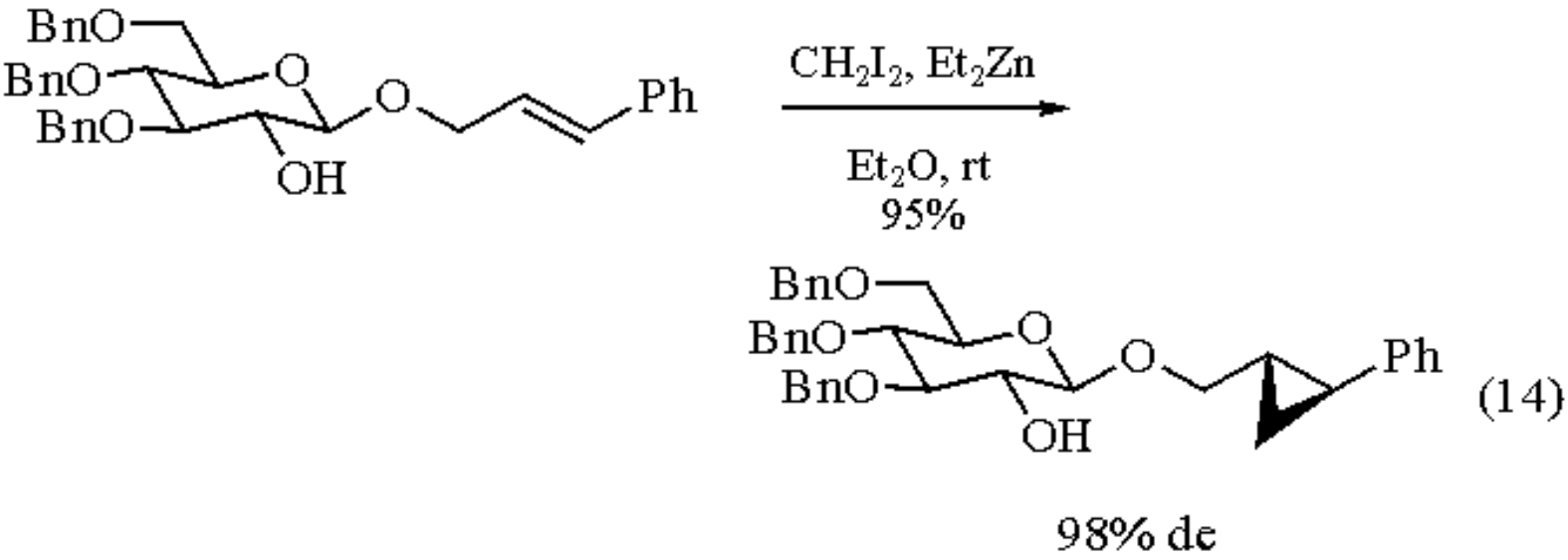

Although the potential for preparing enantioselective halomethylzinc reagents was recognized early on,[28] only since 1992 have encouraging levels of enantioselectivity been observed.[29] The best results reported to date utilize chiral C_2-symmetric sulfonamides in substoichiometric amounts as the source of chirality (eq 15).[29a] A zinc complex of this ligand is proposed to act as a chiral Lewis acid catalyst in this reaction. All of the enantioselective halomethylzinc cyclopropanations reported to date utilize allylic alcohols as substrates, and the free hydroxy group appears to play an essential role.[29]

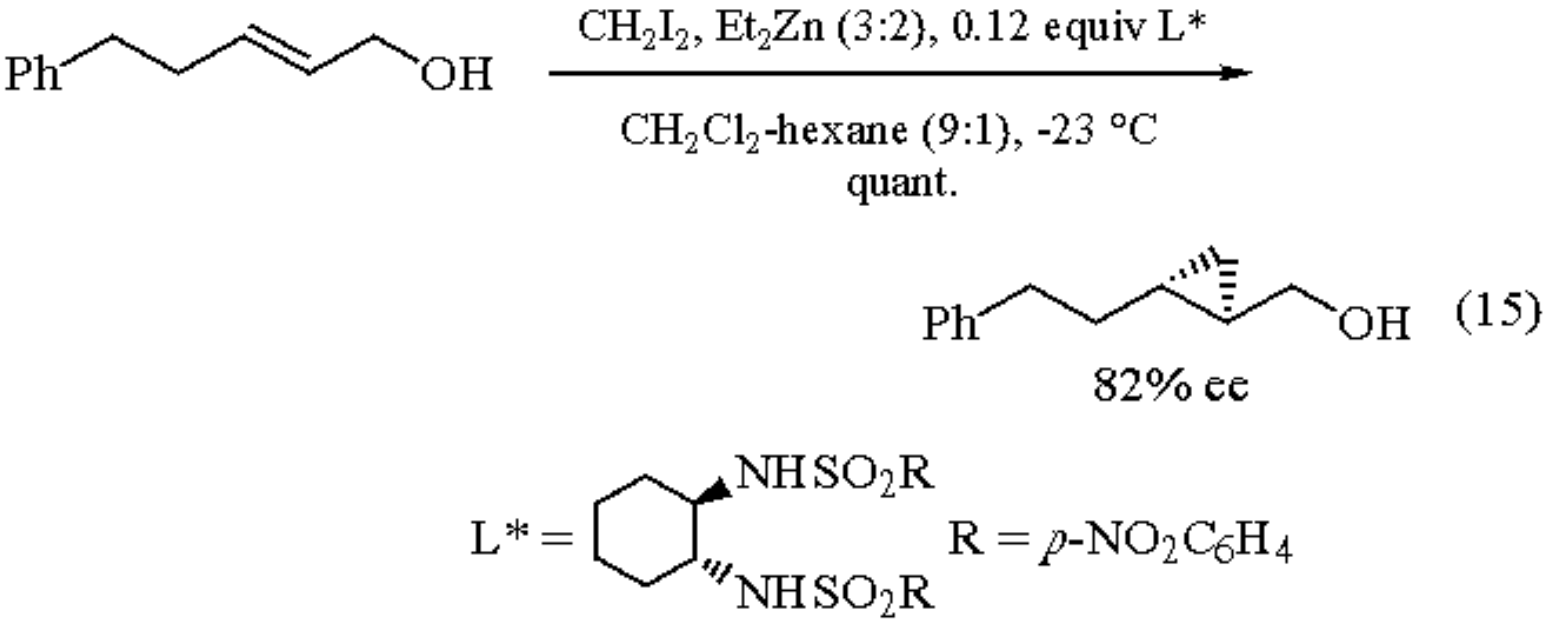

Methylene Homologation Reactions.

The carbon bound iodine atom of ICH_2ZnI can be easily displaced by nucleophiles to generate new organozinc reagents.[9b] For example, various copper nucleophiles displace the carbon bound iodine from ICH_2ZnI or $(ICH_2)_2Zn$, generating new organometallic reagents that react with allyl halides.[2,30] Copper nucleophiles such as CuCN/LiCl, $NCCH_2Cu$, copper amides, vinylcoppers, and heteroarylcopper compounds all participate in this reaction (eq 16). This reaction has proven to be especially useful for the conversion of alkenylcoppers into allylic copper-zinc reagents which react with aldehydes affording homoallylic alcohols (eq 17). An expedient route to α-methylene-γ-butyrolactones that

exploits this behavior has also been developed (eq 18).[30e]

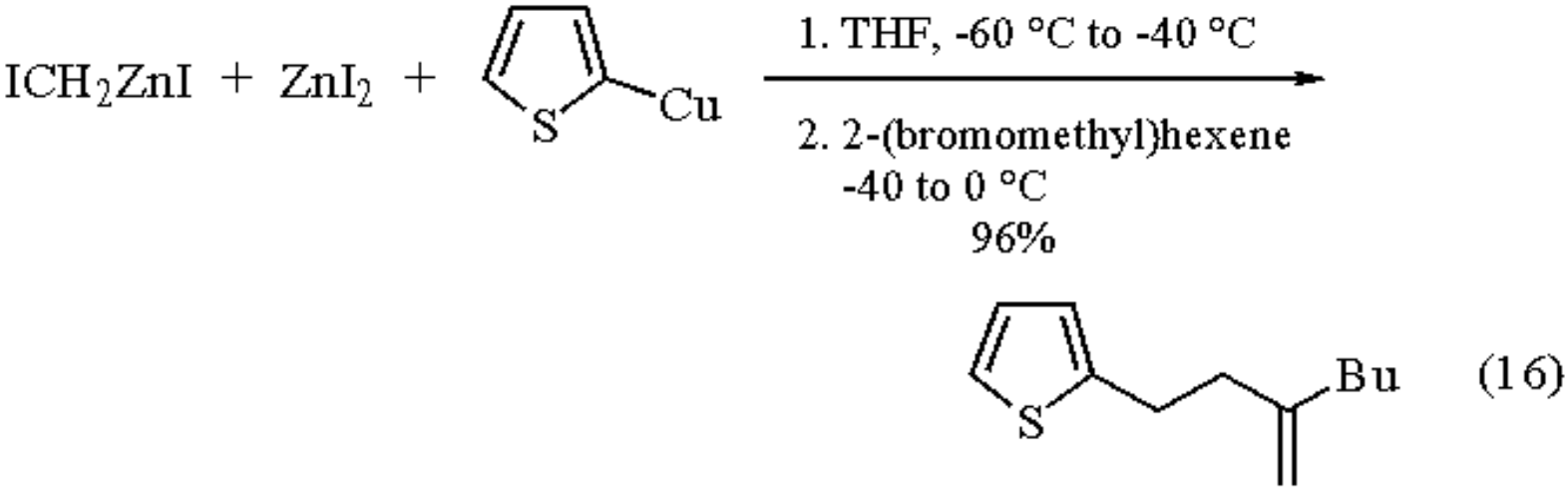

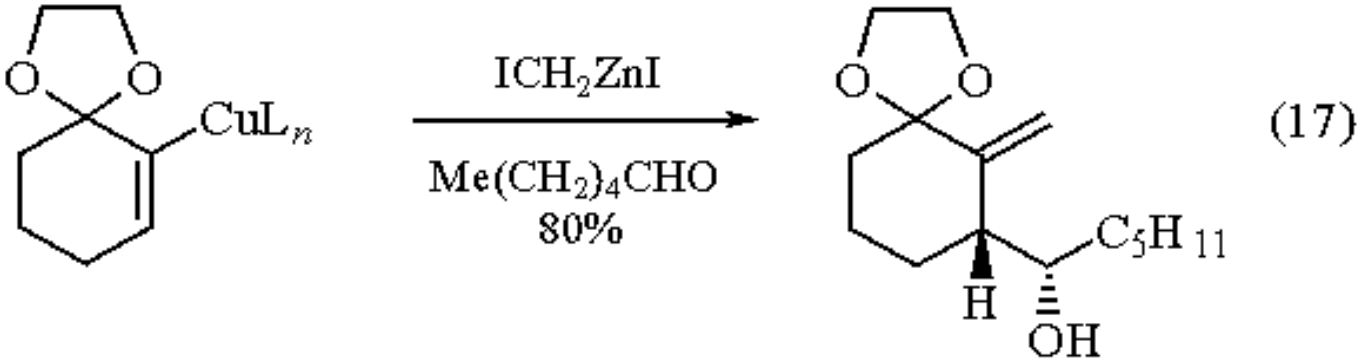

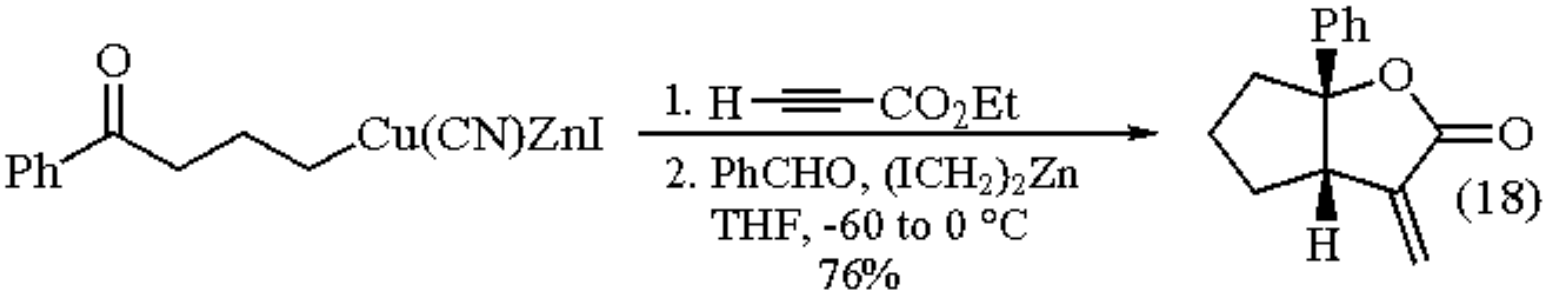

Transmetalation Reactions.

Like other alkylzinc reagents,[31] halomethylzinc reagents have also been shown to participate in transmetalation reactions.[3,14a] This methodology provides an expedient route to iodomethylmercury and iodomethyltin compounds. For example, treatment of Me_3SnCl with ICH_2ZnI derived from EtZnI and CH_2I_2 provides Me_3SnCH_2I in 78% yield.[14a] Bu_3SnCH_2I may be prepared similarly in 96% yield.[32] Substituted diiodides also provide zinc reagents that participate well in this reaction.[14a]

[2,3]-Rearrangements.

A method for the generation of sulfur ylides from allylic phenyl sulfides and CH_2I_2/Et_2Zn has been described.[33] The intermediate sulfur ylides undergo a sigmatropic [2,3]-rearrangement affording homoallylic sulfides (eq 19). The reaction gives (*E*)-alkenes selectively.

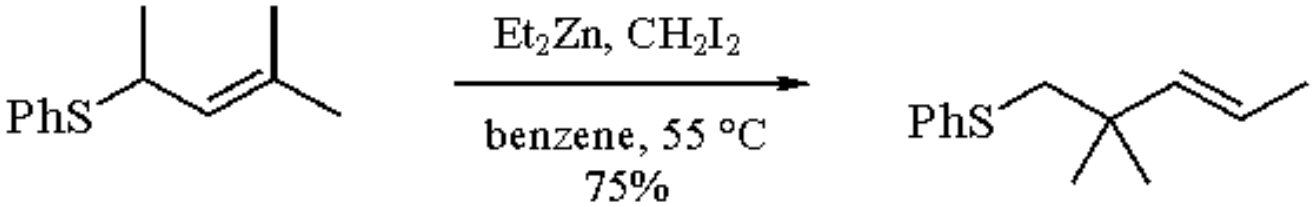

(19)

Related Reagents.

1,1-Diiodoethane; ***Diiodomethane***.

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Iodonium Di-*sym*-collidine Perchlorate

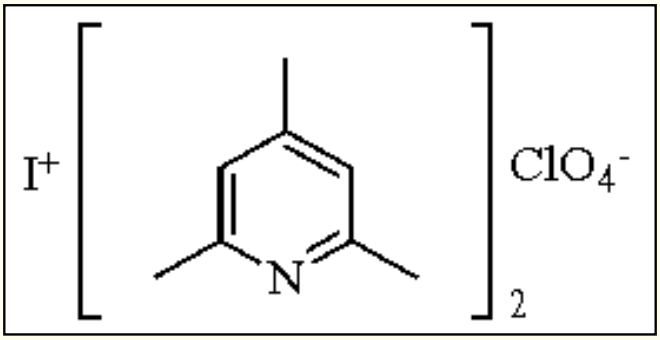

[69417-67-0] · $C_{16}H_{22}ClIN_2O_4$ · Iodonium Di-*sym*-collidine Perchlorate · (MW 468.75)

(very reactive electrophile, superior source of I^+,[1] useful in the synthesis of *cis*-β-hydroxy amines,[2] activates glycosides for glycosylation;[5,6] can be used for iodolactonization[12,13] and vicinal *cis*-diol[14] preparation)

Alternate Name: IDCP.

Solubility: sol chloroform; insol ether.

Form Supplied in: fine colorless crystalline powder. *Drying:* see ***Bromonium Di-sym-collidine Perchlorate***.

Handling, Storage, and Precautions: see ***Bromonium Di-sym-collidine Perchlorate***.

cis-Oxyamination.[2]

IDCP (**1**) is useful in the synthesis of *cis*-hydroxyamino sugars, e.g. methyl *N*-acetylristosaminide has been obtained from an oxazoline which can be made by the reaction of a trichloromethyl imidate with IDCP. The imidate can be prepared by reaction of the corresponding allylic alcohol with ***Trichloroacetonitrile*** in presence of ***Sodium Hydride*** (eq 1).

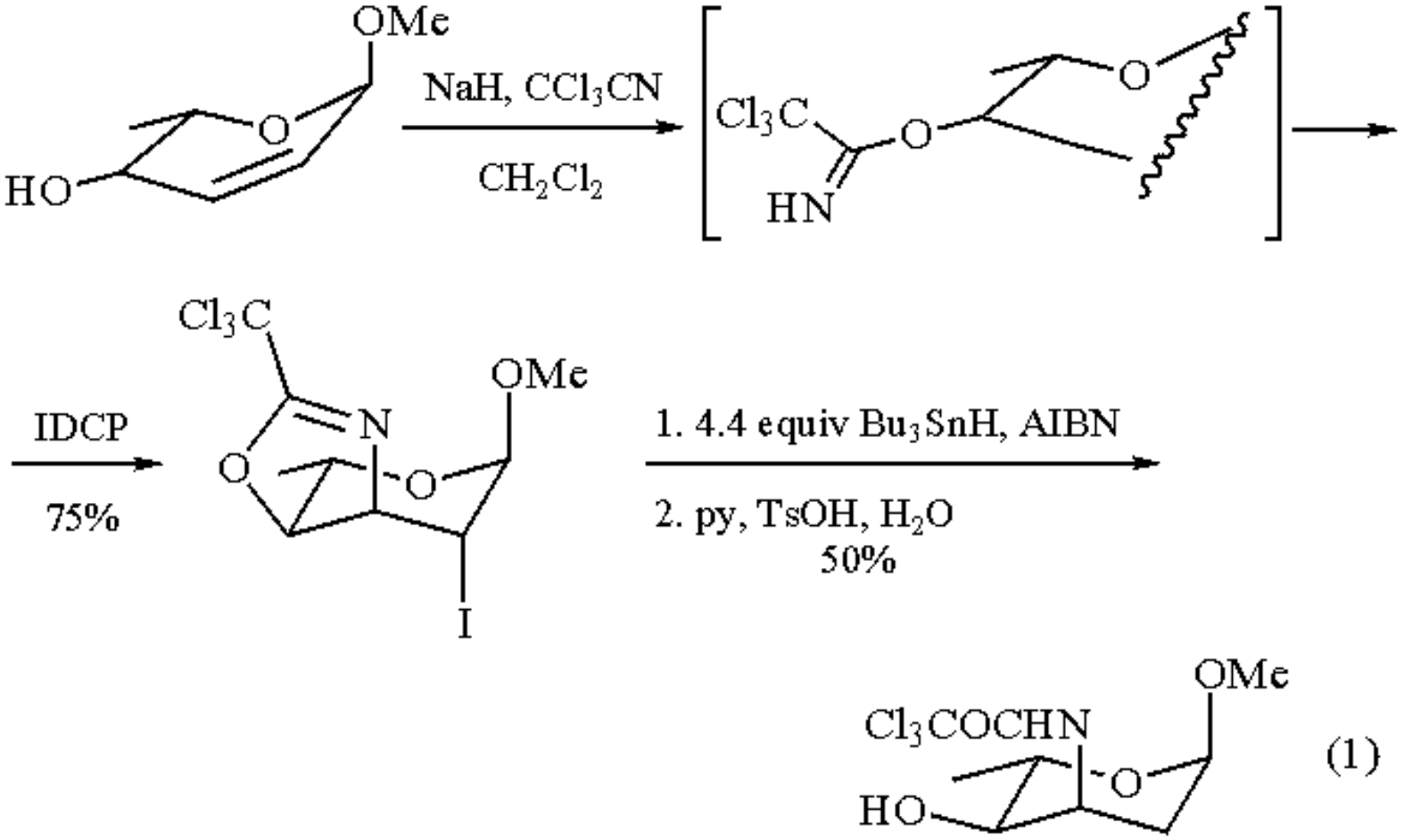

(1)

The synthesis of methyl α,L-garosaminide,[3] a key component of aminocyclitol antibiotics, is complicated by the presence of a *cis*-hydroxyamino group and by the tertiary character of the hydroxy group. The problems have been resolved by use of the allylic epoxide as starting material. This epoxide was converted in three steps into an allylic amine. Treatment of iodonium salt gave the iodooxazolidinone in 82% yield. The product was reduced and the ethoxy ethyl group was removed and finally converted to the desired product by hydrolysis (eq 2).

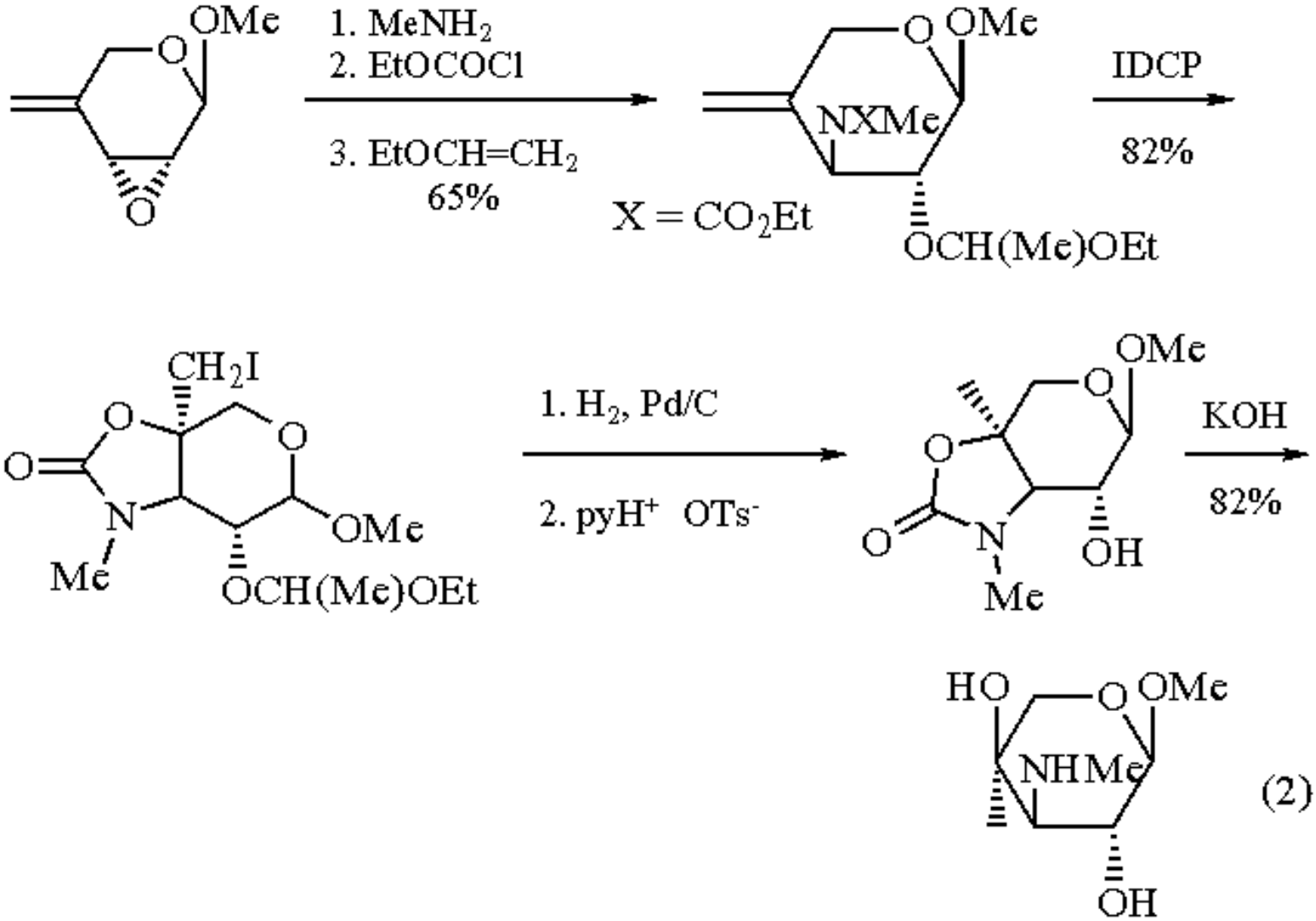

(2)

Similar methodology can convert an internal allylic amine into a *cis*-β-hydroxyamine, as illustrated in a synthesis of holacosamin, a component of some glycosteroids (eq 3).[4]

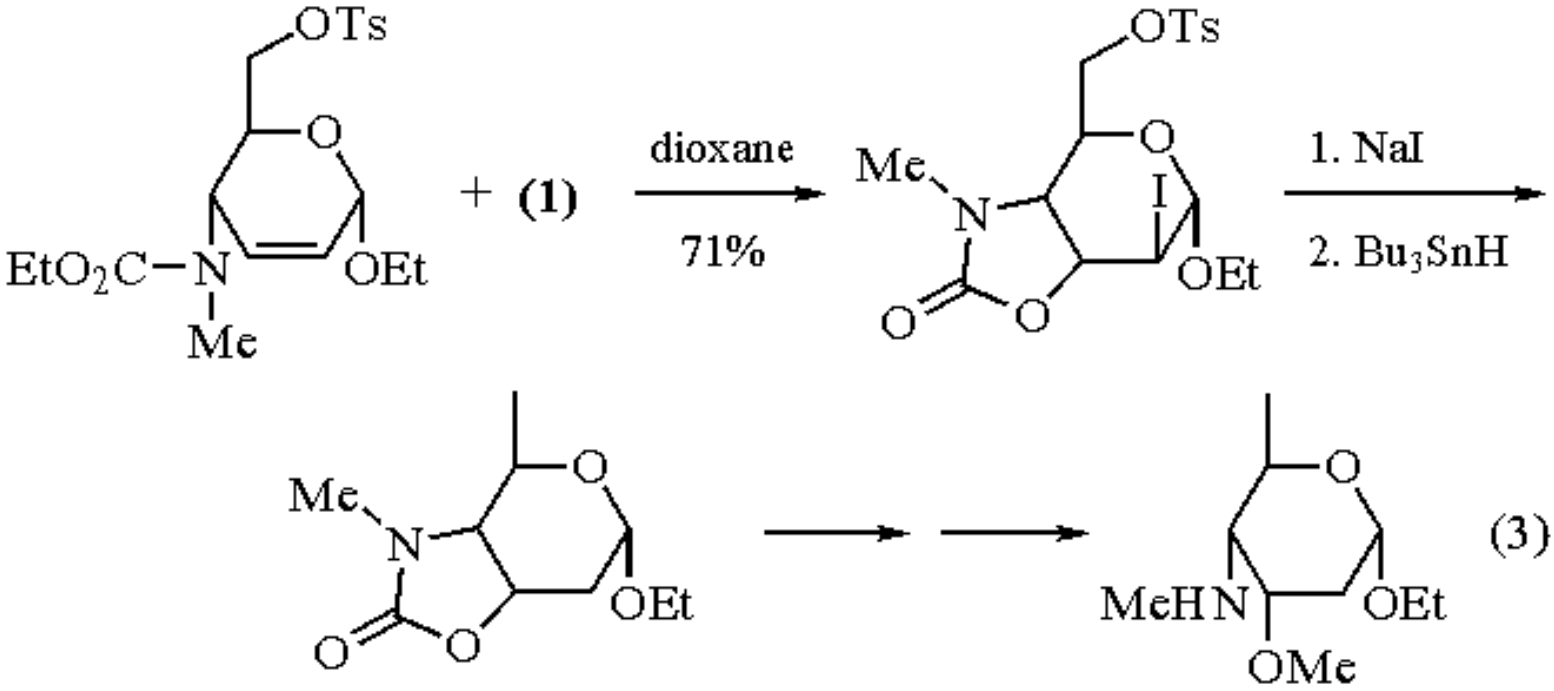

α-Linked Disaccharides.[5]

The reagent functions as a superior source of I^+, probably because of the nonnucleophilic counterion. Thus a pyranoid diene reacts with IDCP to give a planar ion to which an alcohol adds in a 1,4-sense to give an α-glycoside. Thus tetraacetylfructose reacts to give an α-disaccharide in 45% yield (eq 4). The β-isomer is not detected.

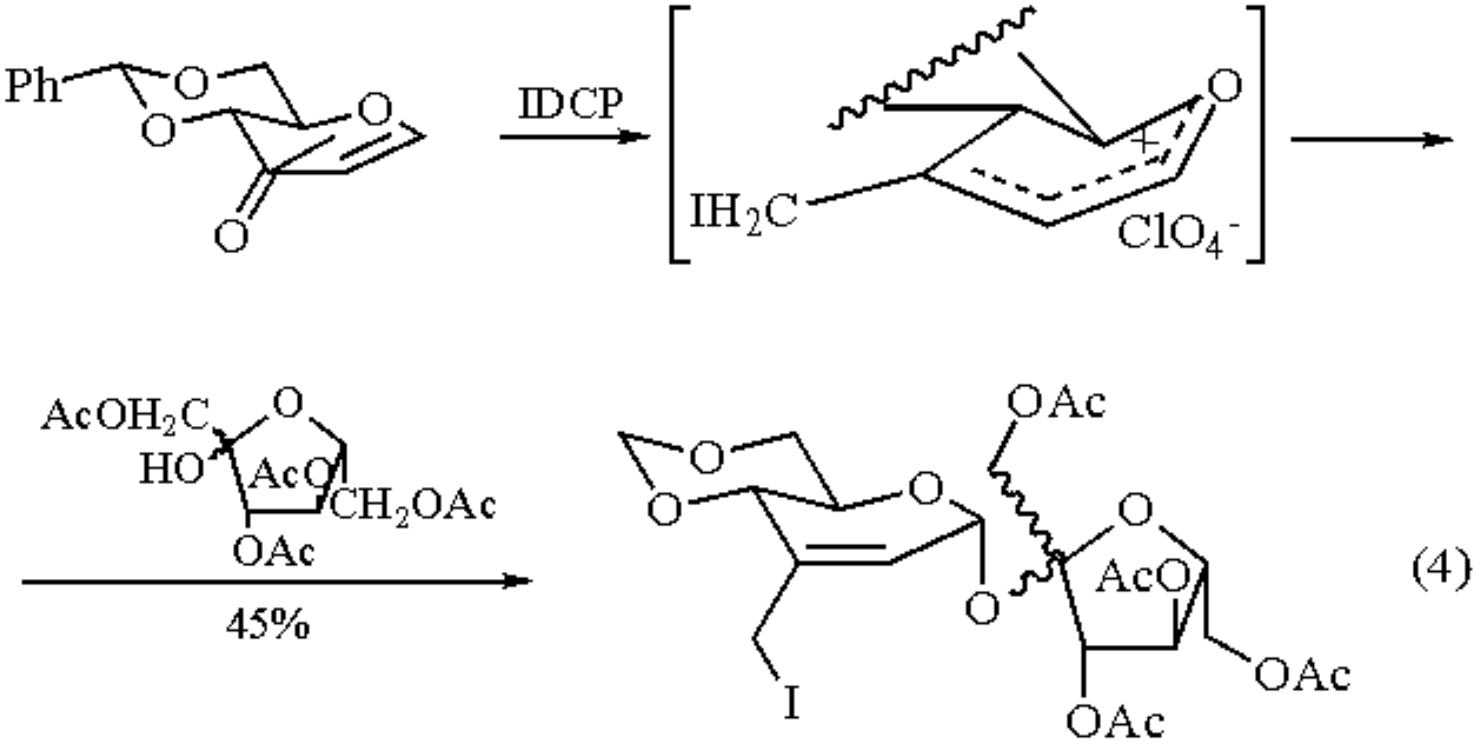

Examples are known where this reagent has activated pent-4-enyl glycosides for glycosylation,[6] but α- and β-glycosides were obtained in various proportions regardless of the nature of donors or acceptors (primary or secondary

hydroxyl groups). Glycosylations of 1,2:5,6-di-*O*-isopropylidene-α-D-galactopyranose and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside were investigated with pent-4-enyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside derivatives in which 6-OH was protected by a benzyl, a trityl, or a TBDMS group in order to assess the effect of the bulk of the 6-substituents. The presence of a bulky 6-substituent (a) increases significantly the proportion of the α-product; (b) decreases the yield when a secondary hydroxy group is glycosylated, but the effect is less or opposite when a primary hydroxy group is involved; (c) lowers the increase in yield of the α-product when a primary hydroxy group is glycosylated; (d) gives a much better yield of the α-anomer when there is a higher proportion of ether in the solvent.

Chemospecific glycosidation of partially benzoylated thioglycosides (disarmed acceptors) with perbenzylated thioglycosides (armed donors) can be realized in the presence of the promotor IDCP (eq 5).[7]

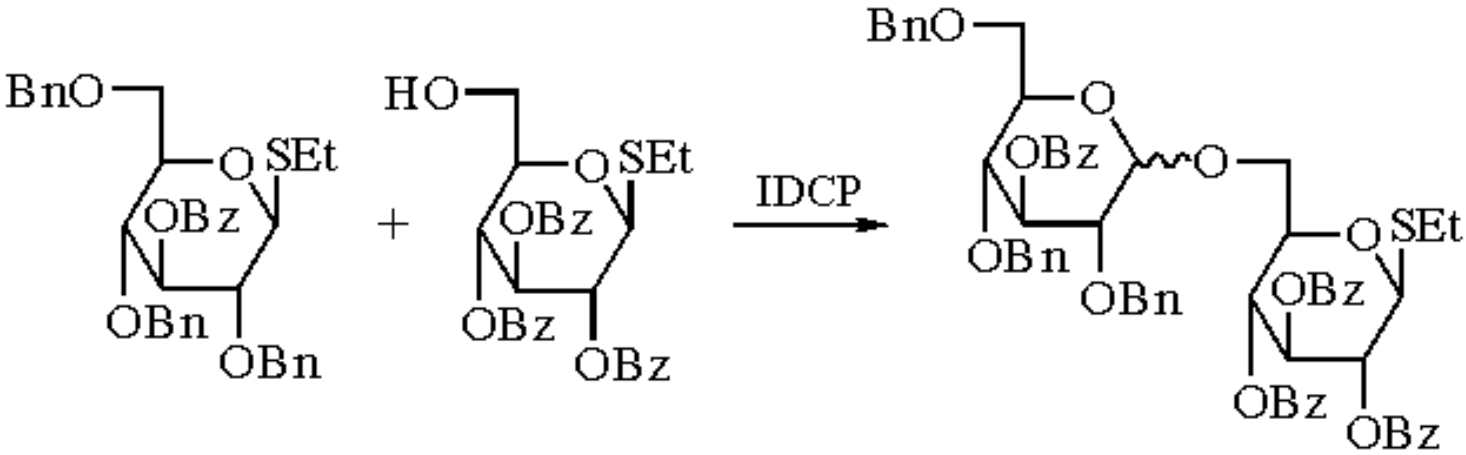

(5)

Reaction of IDCP with unsaturated alcohols and carboxylic acids in dichloromethane at ambient temperature has afforded three- to seven-membered ring iodoethers and four- to seven-membered ring iodolactones, respectively, in moderate yields and generally with high regioselectivity. The reaction has particular utility for synthesis of 2-(1-iodoalkyl)oxiranes and -oxetanes.[11] Glycosylation has also been achieved by electrophile-induced activation of anomeric *O*-glycosyl *N*-allyl carbamates (eq 6).[8]

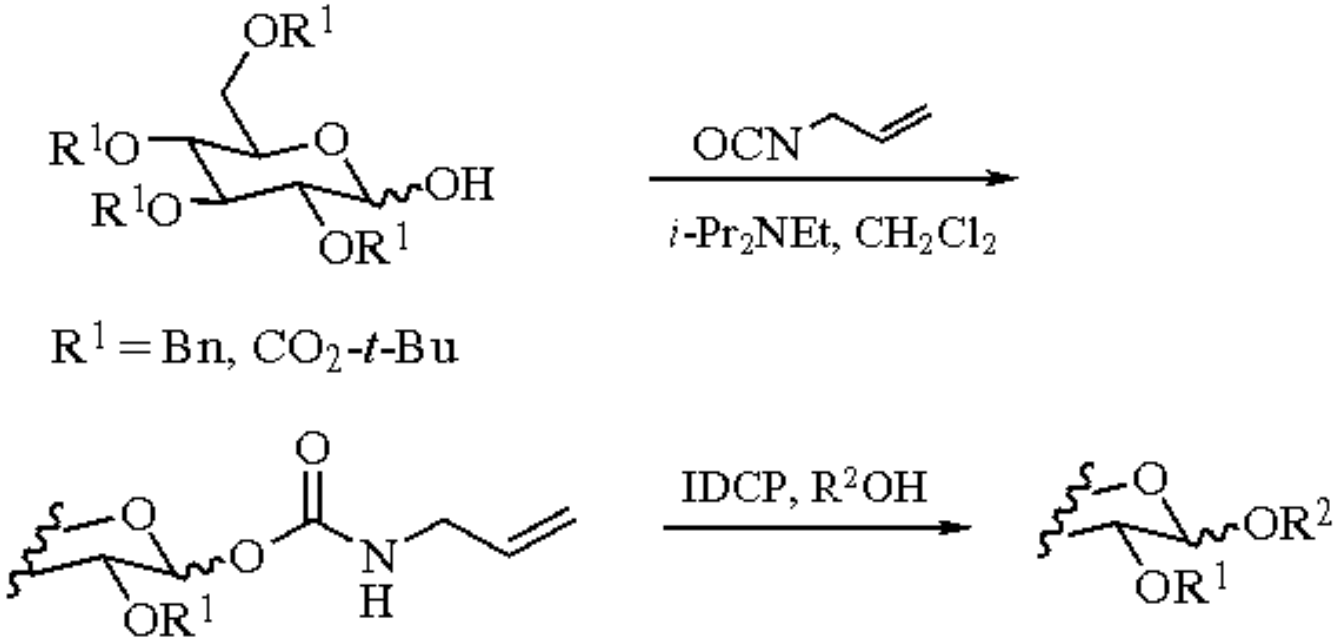

(6)

Treatment of fully benzylated 1-methylene-D-glucose with IDCP gives easy access to 1-iodoheptuloses or a 1-iodomethylene derivative.[9] The latter compound is, in turn, further amenable to similar IDCP-mediated addition reaction. In the synthesis of ciclamycin O the required trisaccharide glycol was assembled by substituent-directed iodinative coupling of glycals as shown in (eq 7).[10]

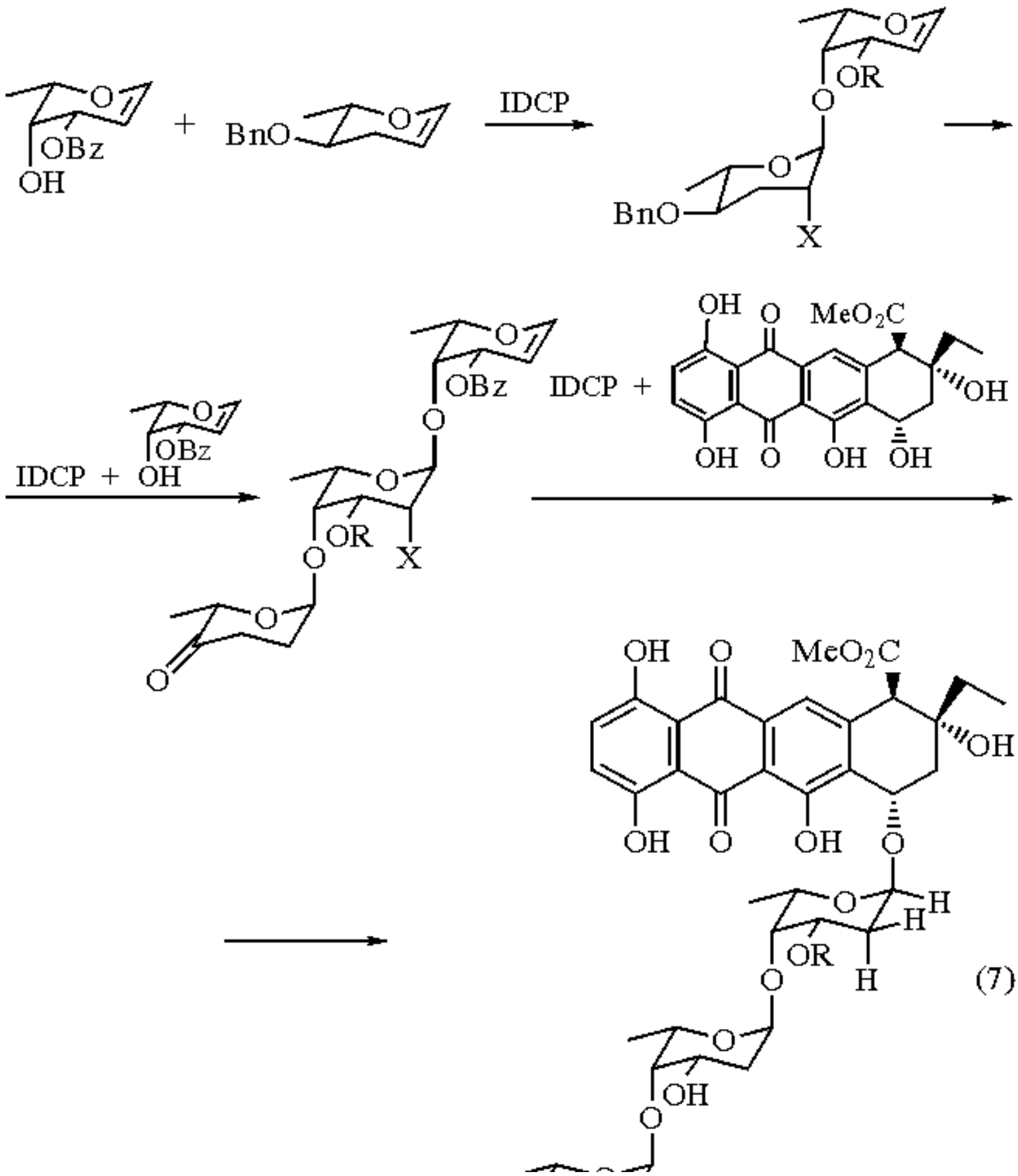

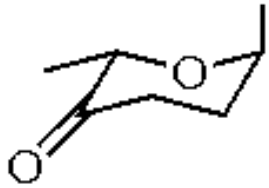

Iodolactonization of heptadienoic acid derivatives having oxazolidin-2-ones or a sultam[12] as chiral auxiliary gave the chiral iodolactone with moderate to excellent enantioselectivity.[13]

Vicinal *cis*-Diols.[14]

An allylic alcohol is converted into its primary urethane derivative, which is then subjected to iodonium ion induced cyclization to give a single iodocarbonate. The carbonate is then deiodinated reductively and hydrolyzed to afford the vicinal diol.

---

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Iodo(phenyl)bis(triphenylphosphine)palladium(II)[1]

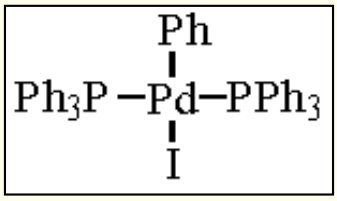

[55123-60-0] · $C_{42}H_{35}IP_2Pd$ · Iodo(phenyl)bis(triphenylphosphine)palladium(II) · (MW 835.03)

(used for the cross coupling of organic halides with other groups[3-9] and also the carbonylation of organic halides with subsequent coupling[10-13])

Form Supplied in: prepared and used in situ.

Preparative Methods: formed from $Pd(PPh_3)_n$ and PhI. The $Pd(PPh_3)_n$ can be generated from ***Palladium(II) Acetate*** and ***Triphenylphosphine***.[2]

Handling, Storage, and Precautions: very reactive and unstable, therefore formed in situ. Decomposition results in palladium metal, which should be retained for recycling.

Cross Coupling.

The title reagent is used to couple organic halides with carbanions stabilized by various metals. The organic halide initially oxidatively adds to the palladium catalyst, and so must be stable to β-elimination. This means that aryl and alkenyl halides are generally used. The general coupling reaction is shown in eq 1.

$$R^1M + R^2X \xrightarrow{(Ph_3P)_2PdPhI} R^1R^2 + MX \qquad (1)$$

Organomercury reagents have been used with various groups including R^1 = aryl, Me and R^2 = aryl, acyl.[3,4] The organometallic may also be a Reformatsky reagent[5] or a Grignard reagent.[6] Alkylstannanes[7] have also been used.

Terminal alkynes are so acidic that they may be used directly without the need to form an organometallic (eq 2).[8,9]

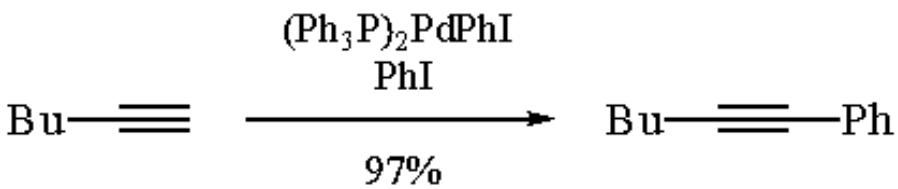

(2)

Other palladium reagents can be used to effect the aforementioned coupling reactions and the transformation may be either stoichiometric or catalytic in palladium. Generally, the choice of a particular palladium reagent is a matter of experimentation. This

Iodo(phenyl)bis(triphenylphosphine)palladium(II)

is also the case for the carbonylation reactions below.

Carbonylation.

$IPhPd(PPh_3)_2$ catalyzes carbonylation of organometallics with ***Carbon Monoxide***. This process is often accomplished in sequence with the aforementioned cross coupling. For example, ketones can be synthesized from organomercurials as shown in eq 3.[10]

$$R_2Hg \text{ or } RHgX \xrightarrow[\text{70-90\%}]{(Ph_3P)_2PdPhI,\ CO} R_2CO \qquad (3)$$

R = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-$Me_2NC_6H_4$, *p*-$NH_2C_6H_4$, *o*-hydroxybiphenyl, 2-thienyl; X = Cl, Br, OAc

Aryl halides can be carbonylated and the intermediate acyl organometallics coupled with other groups. For example, treatment of active methylene compounds with aryl halides and CO.[11] When the reaction is carried out in the presence of alcohols or amines, esters or amides are formed.[12] Cyanocarbonylation has also been reported (eq 4).[13]

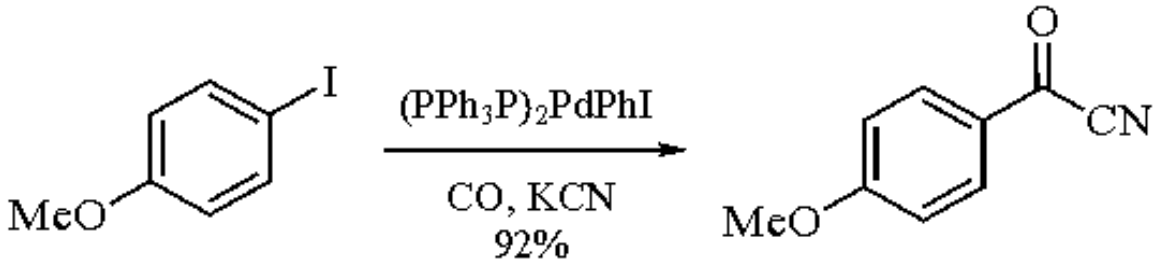

(4)

Other Reactions.

$IPhPd(PPh_3)_2$ has also been used for the reduction of iminoyl chlorides to the corresponding Schiff bases.[14] The germylation of organic halides has also been reported (eq 5).[15]

$$PhI \xrightarrow[(ClGeMe_2)_2,\ \text{92\%}]{(PPh_3P)_2PdPhI} PhGeMe_2Cl \qquad (5)$$

---

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2-Iodopropane

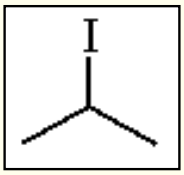

[75-30-9] · C_3H_7I · 2-Iodopropane · (MW 170.00)

(heterolytic and homolytic alkylating agent; mediator of thiocarbonate conversion to alkenes; can add across carbon-carbon triple and double bonds; used in the preparation of the α-isopropoxymethylene blocking group)

Alternate Name: isopropyl iodide.

Physical Data: mp -90 °C; bp 88-90 °C; *d* 1.073 g cm^{-3}.

Form Supplied in: colorless liquid; stabilized with copper.

Purification: the reagent can be washed with aqueous $Na_2S_2O_3$ or $NaHSO_3$, then water, dried over magnesium sulfate and distilled at slightly reduced pressure. Alternately, the reagent can be simply filtered through a plug of activated alumina.[1]

Handling, Storage, and Precautions: the reagent is a cancer suspect agent and should be handled in a fume hood with protective gloves. Storage in the dark over a small quantity of mercury is recommended.

Alkylation.

2-Iodopropane is commonly employed as an alkylating agent toward, for example, the anions of esters,[2] nitriles,[3] sulfones,[4] phenols,[5] and pyrroles.[6] α,β-Unsaturated esters[7] and amides[8] undergo α-alkylation. Monoalkylation of the dianions of β-keto esters,[9] β-ketophosphonates,[10] and the trianion of Boc-protected glycine[11] has been achieved. The asymmetric alkylation of the sultam-derived glycinate equivalent (**1**) has been reported (eq 1).[12] An enantioselective synthesis of 3-substituted 2-keto esters has been achieved by the SAMP hydrazone method (eq 2).[13] A method for replacement of the *N*-methyl group of codeine (**2**) with an isopropyl group has been reported (eq 3).[14]

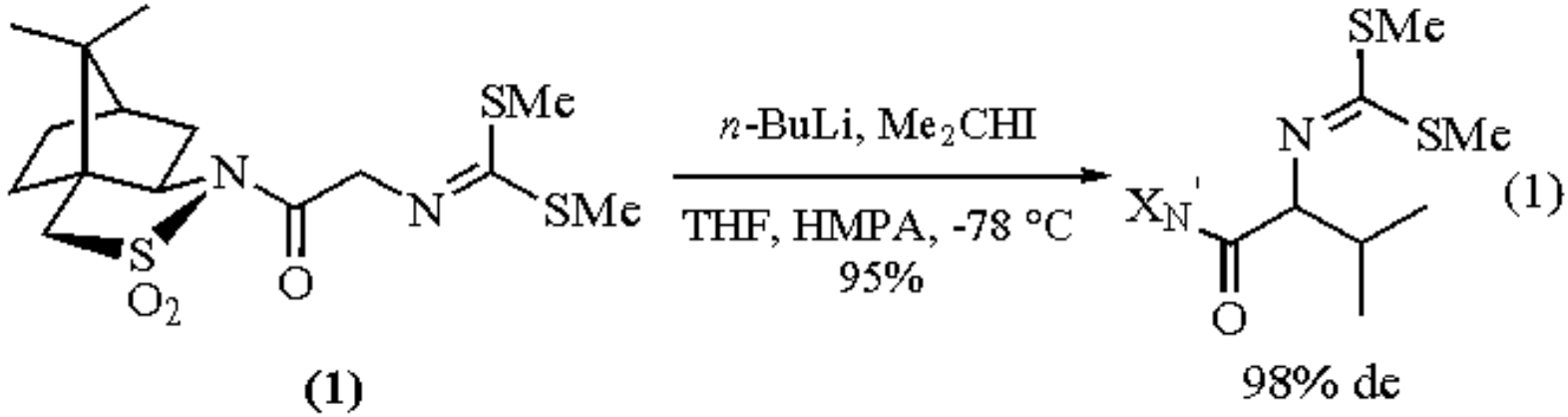

(1)

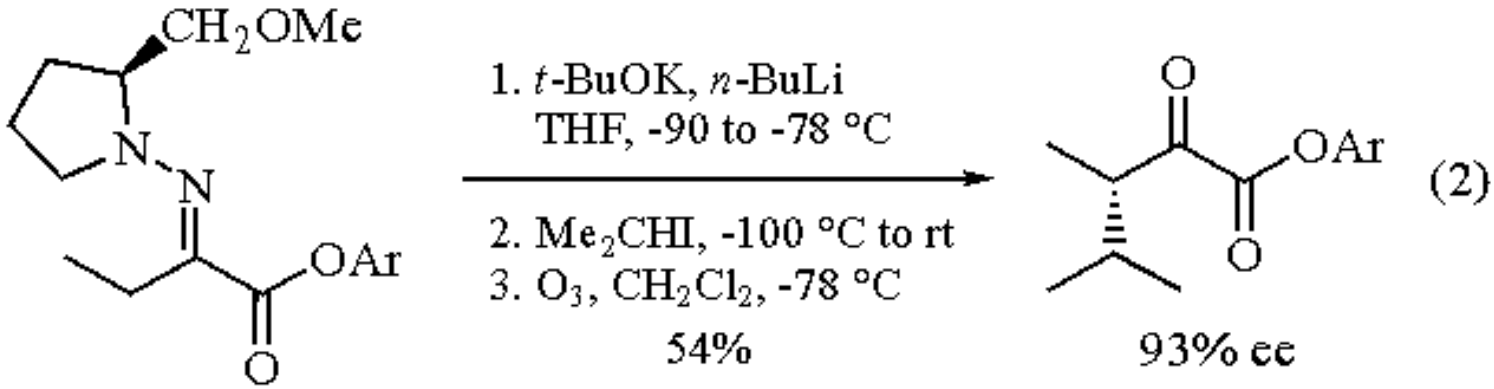

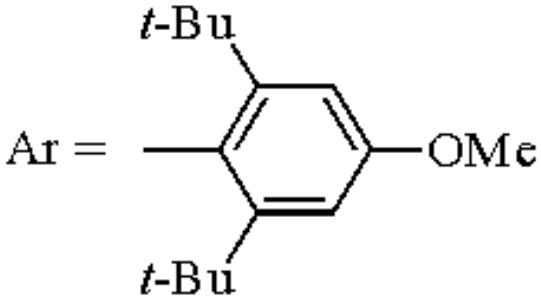

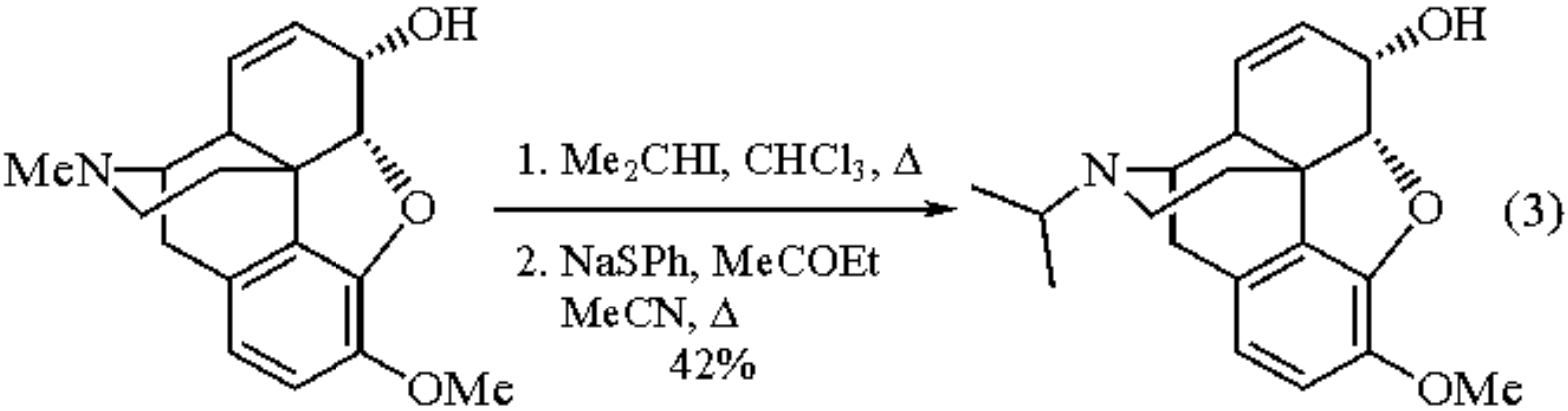

(2)

Homolytic Alkylation.

4-Methylpyridine (**3**) on protonation undergoes regioselective alkylation with 2-iodopropane in the presence of

Hydrogen Peroxide and an Fe^{2+} salt (eq 4).[15]

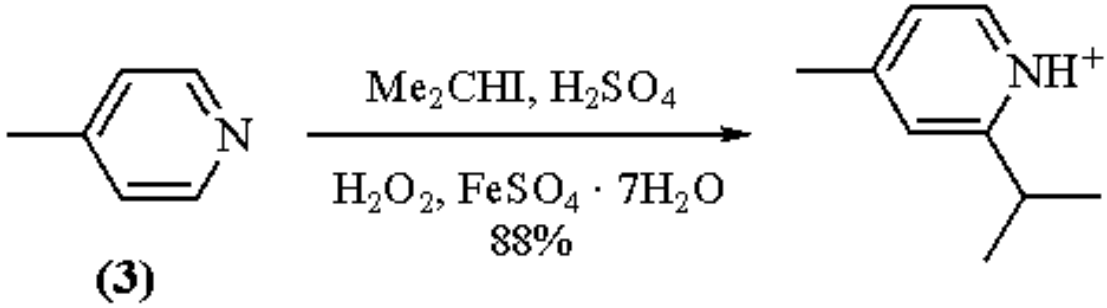

Alkene Synthesis.

Heating the thiocarbonate (**4**) in neat 2-iodopropane at reflux afforded the corresponding iodo thiocarbonate. Subsequent reduction with ***Zinc*** dust provided the alkene (**5**) in good overall yield (eq 5).[16]

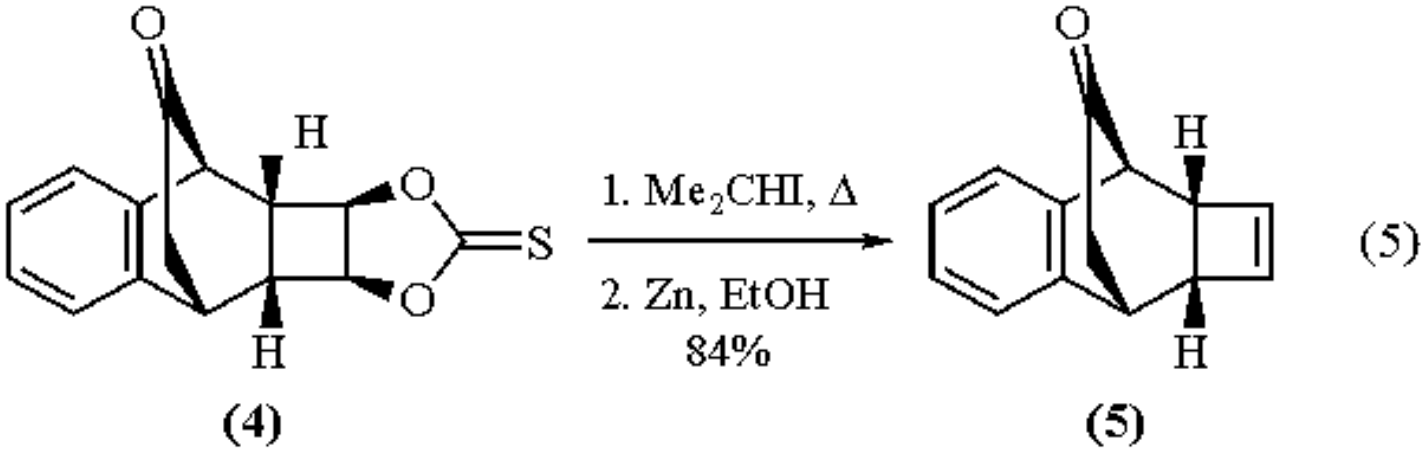

Addition Across Carbon-Carbon Triple and Double Bonds.

Triethylborane induced addition of 2-iodopropane to alkynes[17] and vinylsilanes[18] has been reported (eqs 6 and 7). Similarly, the former process can also be induced with ***Triphenylstannane***.[19]

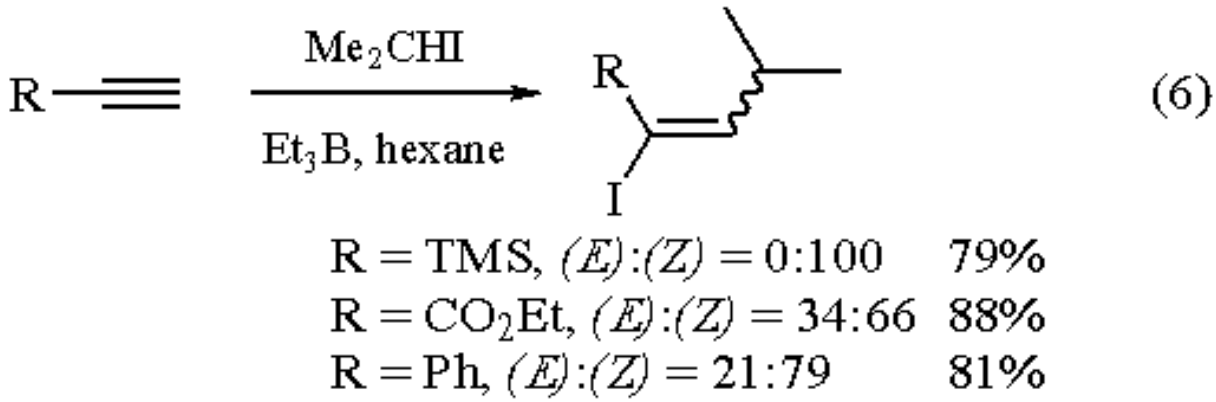

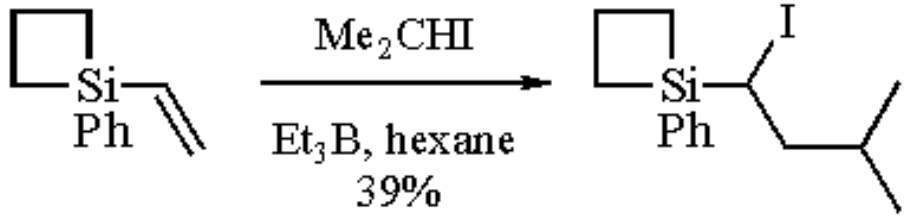

(7)

Isopropoxymethylene Blocking Group.

The ketone (**6**) has been methylated at the more sterically congested site by the use of the isopropoxymethylene blocking group (eq 8).[20]

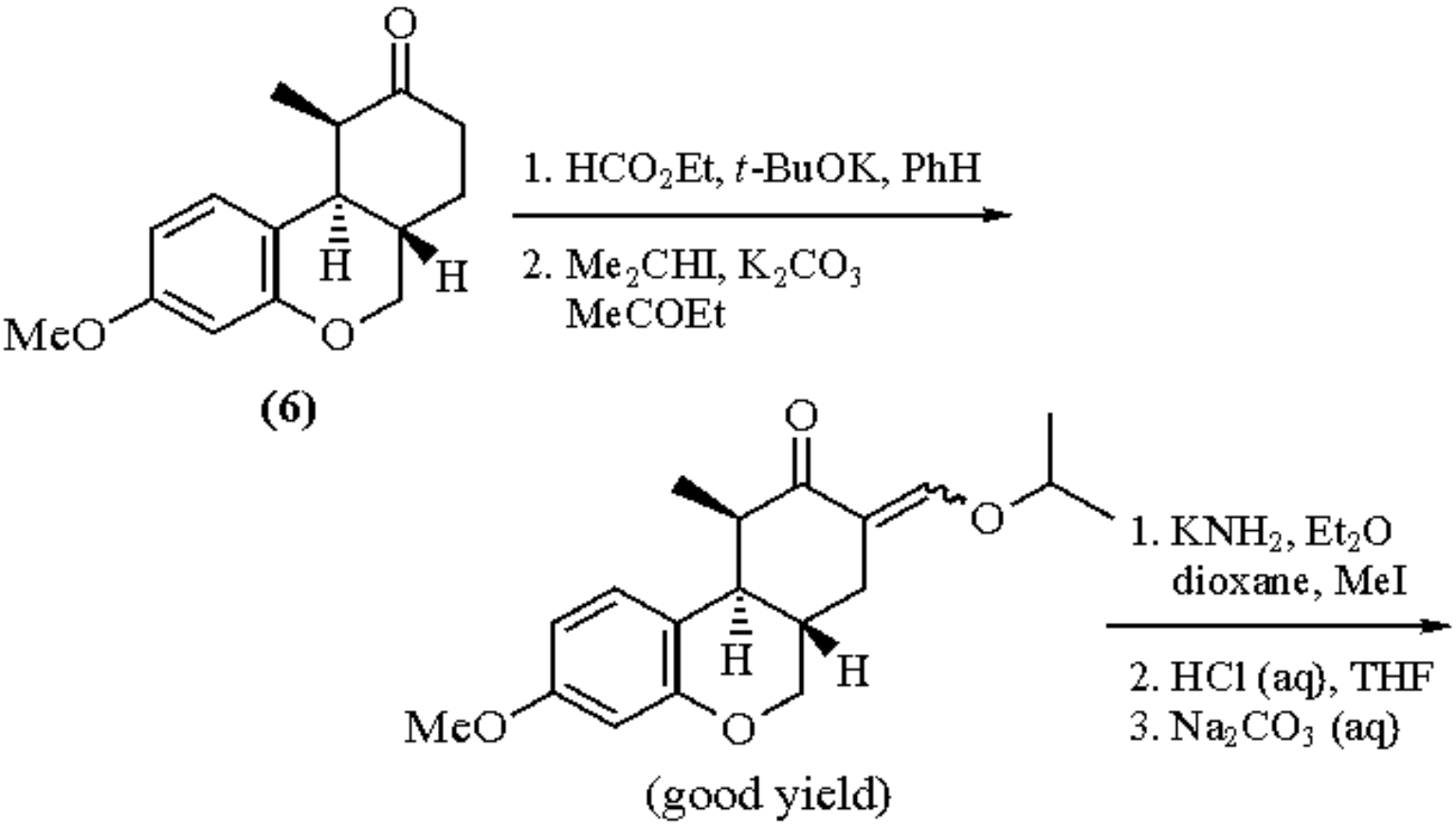

(8)

52%

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(3-Iodopropyl)trimethylsilane

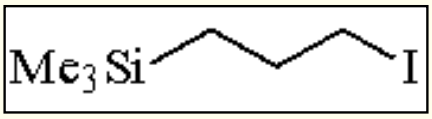

[18135-48-3] · $C_6H_{15}ISi$ · (3-Iodopropyl)trimethylsilane · (MW 242.20)

(reagent equivalent to $^{-}CH_2CH_2CH_2^{+}$[1])

Physical Data: clear liquid; bp 84-86 °C/25 mmHg.

Solubility: sol hexane, THF

Preparative Methods: from commerical (3-chloropropyl)trimethylsilane and NaI[2] or, alternatively, from the *p*-toluenesulfonate of commerically available 3-(trimethylsilyl)-1-propanol and NaI.[1]

Handling, Storage, and Precautions: no detail has been reported. However, the usual handling for common alkyl iodides (e.g. iodohexane) may be followed.

Introduction of 3-(Trimethylsilyl)propyl Group.

Phosphines and amines are alkylated by the title iodide (**1**) to give silylpropylated compounds (eq 1).[3,4]

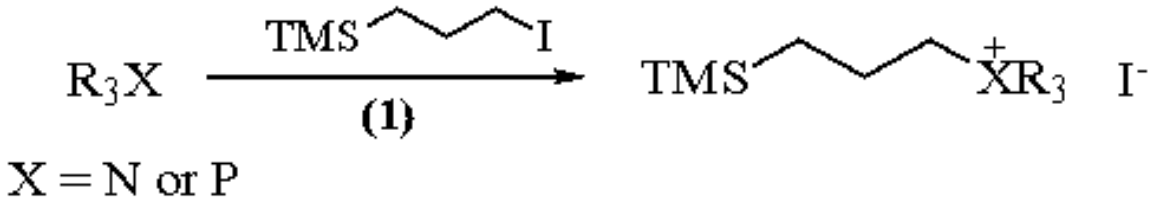

(1)

Preparation of 2-Alkylcyclopentanones.

Reagent (**1**) serves as a $^{-}CH_2CH_2CH_2^{+}$ equivalent, which is illustrated in a preparation of cyclopentanones from carboxylic acids (eq 2).[1,2]

(3-Iodopropyl)trimethylsilane

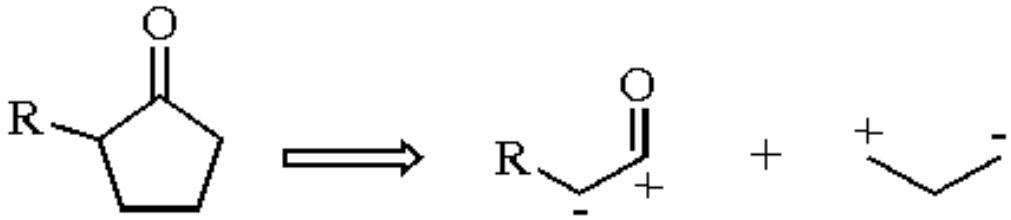

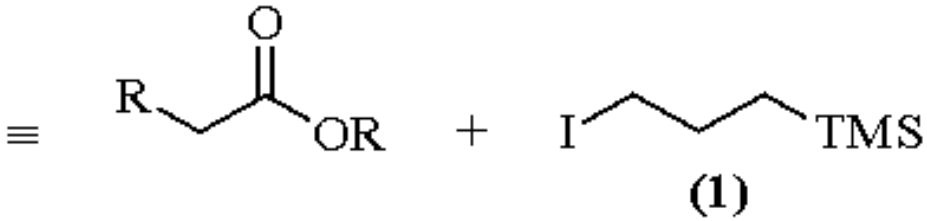

(2)

Thus alkylation of carboxylic acid dianions with (**1**) affords the 2-[3-(trimethylsilyl)propyl]alkanoic acids in good yields. After the conversion of these acids to the corresponding acyl chlorides with ***Oxalyl Chloride***, intramolecular acylation of the alkylsilane with ***Aluminum Chloride*** affords cyclopentanones in good yields. Examples are shown in eqs 3 and 4.

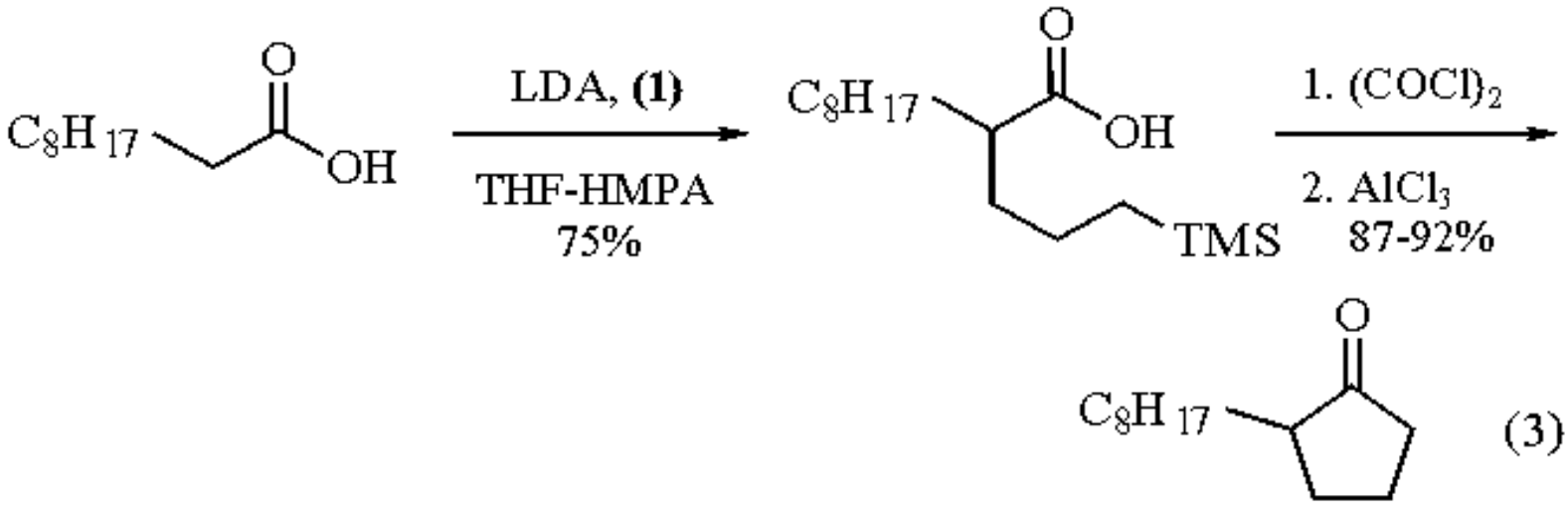

(3)

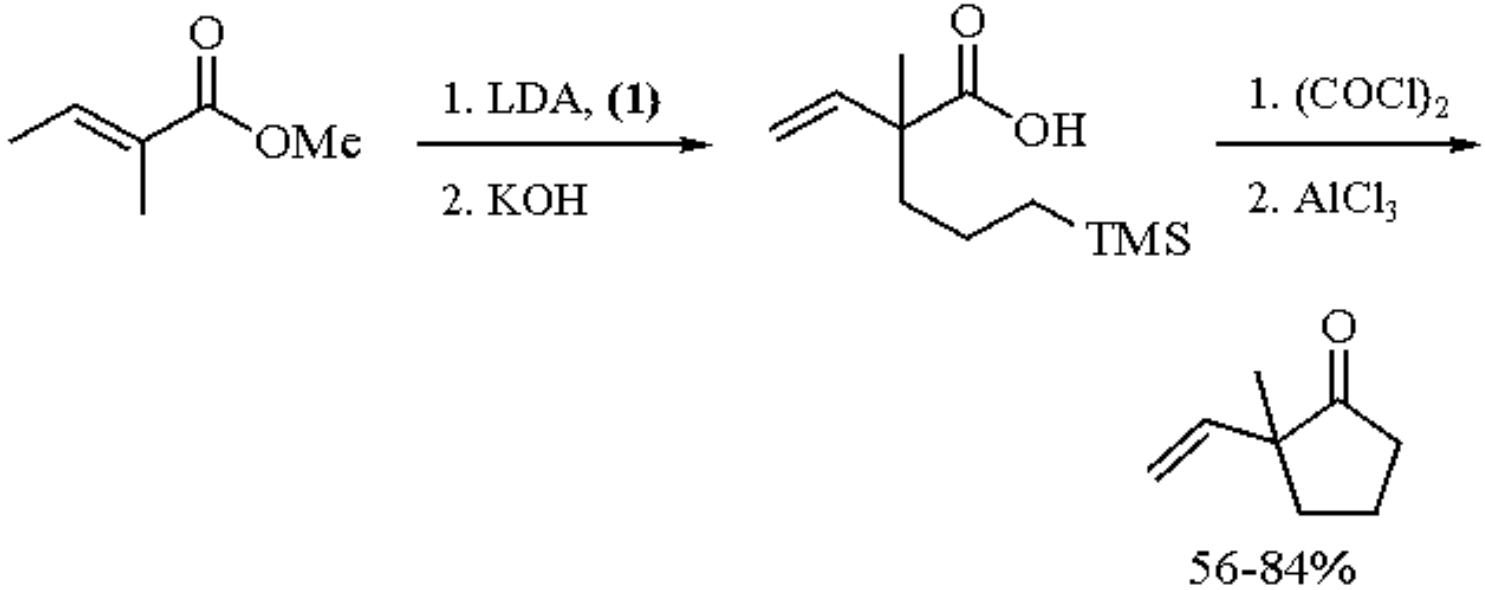

(4)

A related bromide, $Me_3Si(CH_2)_3Br$, is also known and may be used in a similar way.[1]

---

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Iodorhodium(III) Tetraphenylporphyrin

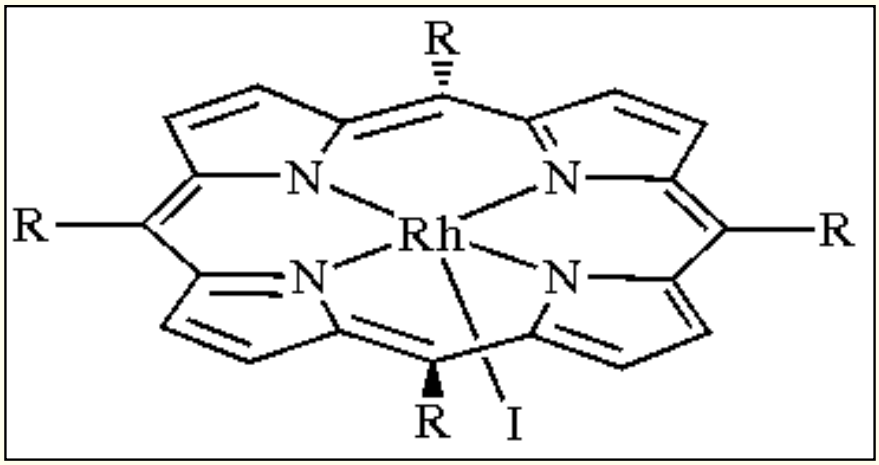

(R = Ph)

[69509-35-9] · $C_{44}H_{28}IN_4Rh$ · Iodorhodium(III) Tetraphenylporphyrin · (MW 842.57) (R = mesityl)

[85990-32-5] · $C_{56}H_{52}IN_4Rh$ · Iodorhodium(III) Tetramesitylporphyrin · (MW 1010.93)

(catalyst for cyclopropanation of alkenes by diazoesters[1])

Alternate Name: Rh(TPP)I.

Physical Data: NMR (δ in $CDCl_3$) 7.7 and 8.2 (multiplets, 20H, phenyl), 8.8 (singlet, 8H, pyrrole); visible (CH_2Cl_2) λ_{max} = 575 nm (ε = 4000), 535 nm (15 700), 422 nm (151 000).[2]

Solubility: sol dichloromethane, chloroform, acetone, ethyl acetate; insol pentane.

Preparative Method: readily prepared from the commerically available tetraphenylporphyrin and ***Tetracarbonyl(di-μ-chloro)dirhodium*** using a modification of Callot's method.[2] The initially formed Rh^{I} species is oxidized to Rh^{III} using ***Iodine*** or ***N-Iodosuccinimide***.

Handling, Storage, and Precautions: not air or moisture sensitive. For prolonged storage, the reagent should be protected from light. Toxicity has not been thoroughly investigated.

Numerous transition metal compounds are known to catalyze the cyclopropanation of alkenes by diazoesters.[3] Among these, compounds based on copper, palladium, and rhodium have been the leading choices for catalysts. Callot and co-workers reported that iodorhodium(III) tetraphenylporphyrin [Rh(TPP)I] (**1**) is also an efficient catalyst for this transformation.[1]

Porphyrin catalysts offer two distinct advantages over other transition metal species. The most important of these is their propensity to provide more of the *syn* cyclopropyl ester than most commonly used catalysts, which produce predominantly the *anti* diastereomer (eq 1).[1,4,5] The *syn* preference can be enhanced considerably by using bulkier macrocycles such as iodorhodium(III) tetramesitylporphyrin [Rh(TMP)I] (**2**) (eq 1).[5] *Syn*/*anti* ratios of up to 7.8:1 have been reported when *cis* disubstituted alkenes are used as substrates.[6]

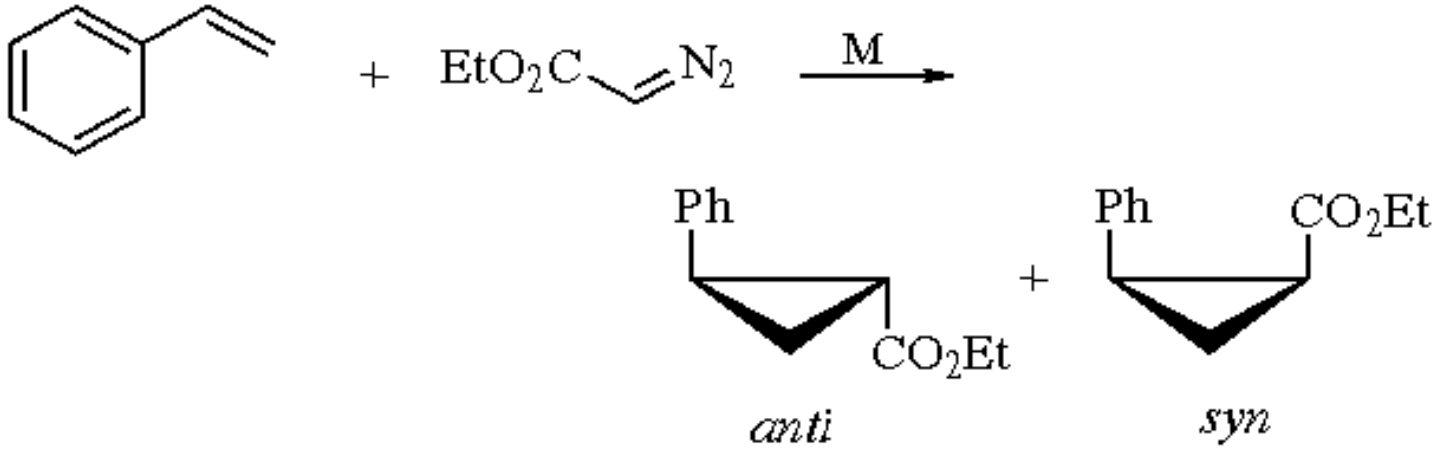

(1)

M	*syn*:*anti*	Total yield (%)
Rh(TPP)I	88:12	71
Rh(TMP)I	98:2	78
$CuCl(OPh)_3$	40:60	84
$Rh_2(OAc)_4$	63:37	93

The second advantage is the higher number of turnovers porphyrin catalysts afford: several thousand compared to several hundred for other catalysts. Therefore, considerably less catalyst is needed to promote the reaction. In addition, the reactivity of the porphyrin catalysts approaches that of rhodium carboxylates, which have been reported to be the most efficient catalysts for this process.[7] Yields typically vary from 50-80% with (**1**) depending on the nature of the alkene substrate. Dimerization products (maleates and fumarates) resulting from diazoester attack on the putative metallocarbene intermediate are minimized by using large excesses of alkene or by slow addition of the diazoester.

Competitive cyclopropanation reactions have revealed steric interactions to be the dominant factor in determining relative reactivity for unfunctionalized alkenes.[6] In general, aromatic alkenes are slightly more reactive than aliphatic alkenes, and tetrasubstituted alkenes are poor substrates for the porphyrin catalysts. Differences between other substituted alkenes are modest but follow the trend reported by Doyle for rhodium acetate-catalyzed reactions.[8] The difference in reactivities can be enhanced by use of (**2**).

At present, rhodium porphyrins are the most useful catalysts for obtaining *syn* cyclopropyl esters from alkenes and diazoesters. Enantioselectivities reported using chiral porphyrin ligands are not synthetically useful.[6,9] When the chiral systems are fully developed, they should be particularly useful since optically pure *syn* cyclopropyl esters are not readily accessible with current methodology.[10]

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10. For some substrates, very high enantiomeric excesses can be realized for the *anti* diastereomer. See: (a) Aratani, T. *PAC* **1985**, *57*, 1839. (b) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *HCA* **1988**, *71*, 1553. (c) Lowenthal, R. E.; Abiko, A.; Masamune, S. *TL* **1990**, *31*, 6005. (d) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *JACS* **1991**, *113*, 726. (e) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *JACS* **1991**, *113*, 1423.

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N-Iodosuccinimide

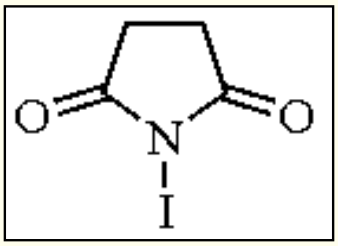

[516-12-1] · $C_4H_4INO_2$ · *N*-Iodosuccinimide · (MW 224.99)

(electrophilic iodination of arenes, alkenes, and alkynes; activation of glycosyl donors)

Alternate Names: NIS; 1-iodo-2,5-pyrrolidinedione.

Physical Data: mp 193-199 °C (dec).

Solubility: sol dioxane, THF, MeCN; insol ether, CCl_4.

Form Supplied in: white powder; widely available, but quite expensive.

Preparative Method: reaction of *N*-silversuccinimide with I_2 in anhydrous dioxane, removal of AgI by fitration, and addition of CCl_4 to promote crystallization.[1]

Purification: recrystallization from dioxane-CCl_4 at -20 °C.

Handling, Storage, and Precautions: stored at 0 °C under nitrogen, and protected from light and moisture to avoid decomposition; an irritating solid and precautions should be taken to avoid inhalation of the powder.

Introduction.

N-Iodosuccinimide is an efficient reagent for the electrophilic iodination of organic compounds for which the reactivity of I_2 is often insufficient. A variety of functional groups are electrophilically iodinated using NIS with similar effectiveness to the corresponding brominations using ***N-Bromosuccinimide*** (NBS).[2] Electrophilic attack on soft nucleophiles (e.g. as in dithiane deprotection) is achieved in the presence of other sensitive groups with optimum selectivity by iodination using NIS under mild conditions (see also ***1,3-Diiodo-5,5-dimethylhydantoin***).[3] For other iodinations a more powerful source of iodonium ion can be generated by the combination of NIS with protic acids including AcOH, TsOH, and TfOH.[4]

Reaction with Organometallic Derivatives.

Similarly, the lesser reactivity of NIS compared with NBS allows it to be used for the synthesis of vinyl iodides by iodination of vinylaluminum intermediates in the presence of reactive alkenic groups.[5] NIS has also been found to be an excellent reagent for the oxidative cyclization of dipeptide dianions to β-lactams (eq 1).[6]

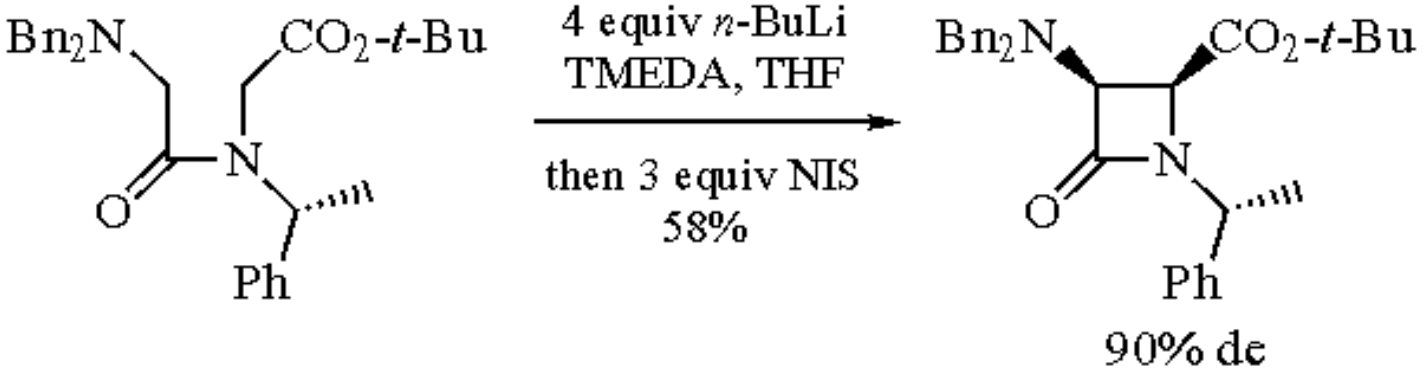

(1)

Iodination of Alkenic Compounds.

Iodolactonization and related reactions with alkenes can be achieved using NIS in aprotic solvents. In addition, iodoesters may also be prepared by the reaction of alkenes with NIS in the presence of carboxylic acids (eq 2),[7] and allylic trichloroacetimidates may be cyclized to 5-iododihydro-1,3-oxazines (eq 3).[8]

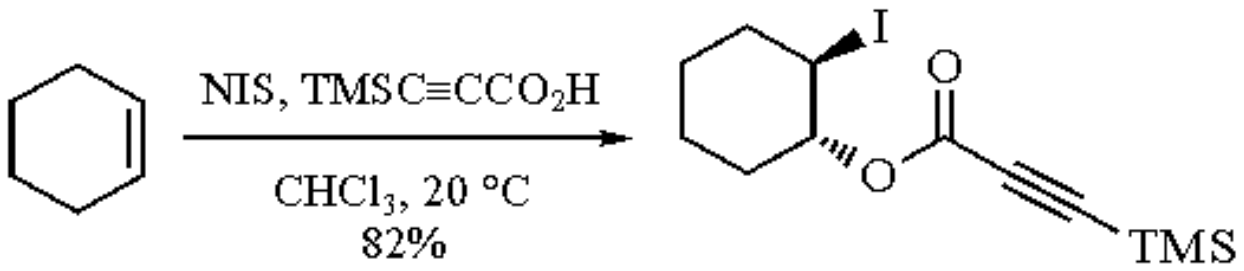

(2)

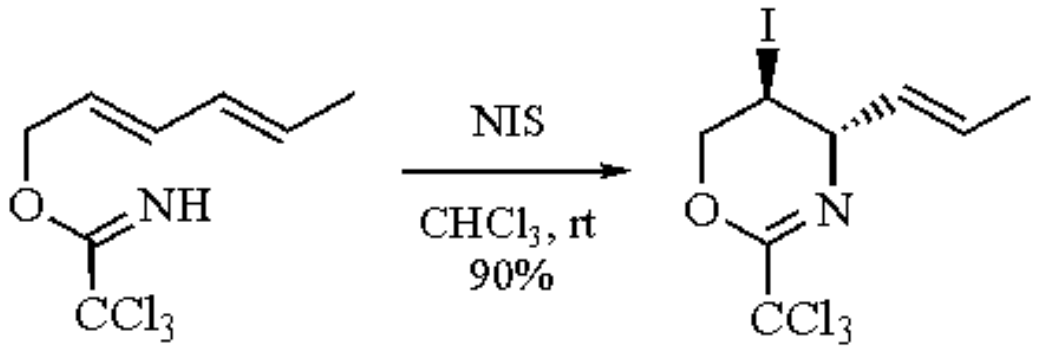

(3)

In combination with protic acid, NIS has been used for the preparation of α-iodo enones and β,β-dihalo enones (eqs 4 and 5; HTIB = ***[Hydroxy(tosyloxy)iodo]benzene***).[9] More reactive alkenes such as enol acetates react with NIS to afford α-iodo ketones.[10] The reaction of enol ethers with NIS in the presence of an alcohol, affording iodoacetals, allows the synthesis of acetals by dehalogenation or mixed ketene acetals by elimination.[11]

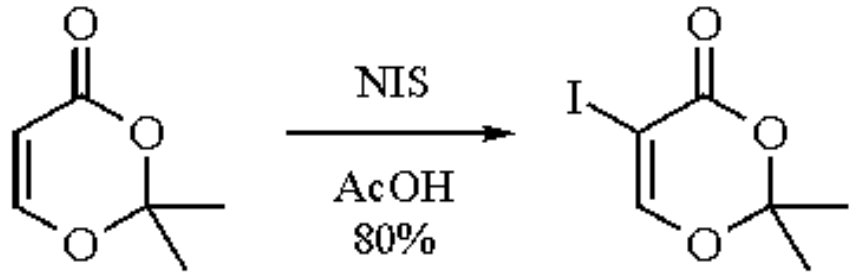

(4)

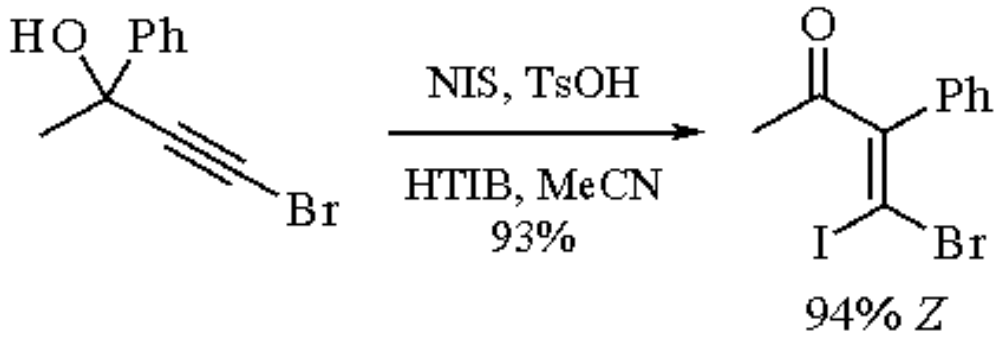

(5)

Activation of Glycosyl Donors.[12]

NIS is a useful reagent for the coupling of glycals to alcohols (eq 6)[13] or other carbohydrates,[14] affording 2-iodoglycosides which are readily dehalogenated to 2-deoxysugars, or can serve as precursors to 2-aminosugars via the epoxide intermediate.[15] Selective activation of glycosyl thioethers for coupling with carboxylic acids and heterocyclic compounds is achieved under mild conditions by reaction with NIS and ***Trifluoromethanesulfonic Acid*** (eq 7).[16] In addition, the combination of NIS and TfOH is also the reagent of choice for the activation of 4-pentenylglycosides.[17]

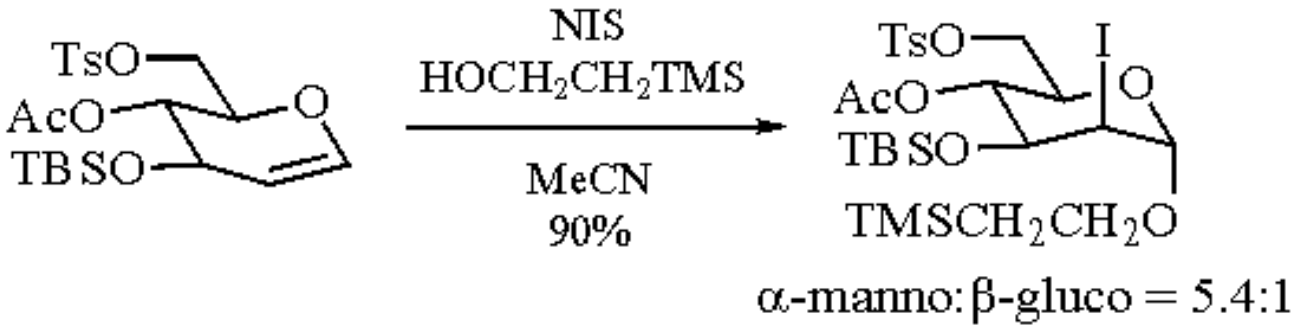

(6)

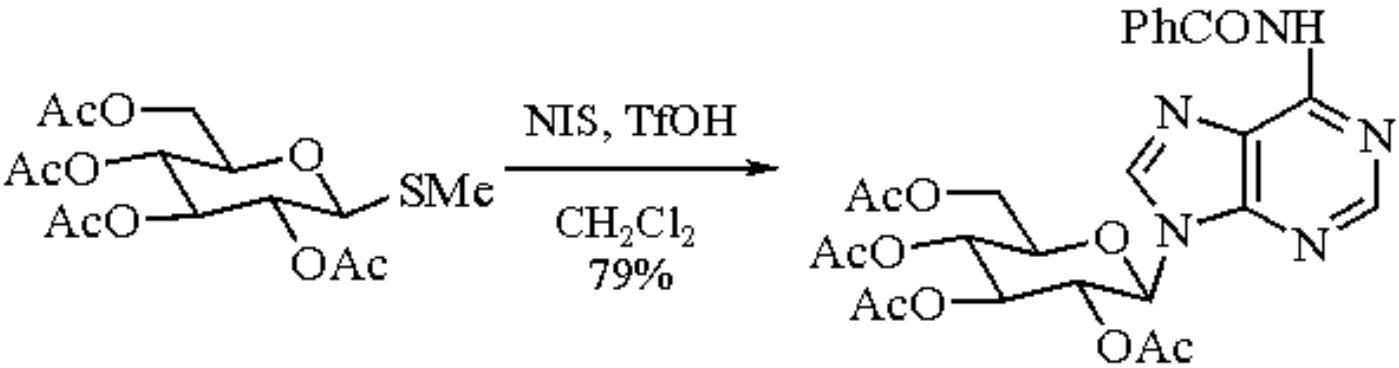

(7)

Oxidation Reactions.

Hypoiodite intermediates may be generated from the reaction of simple alcohols with NIS. When conducted under photochemical irradiation, the products of Barton-type or fragmentation reactions of alkoxyl radical intermediates may be obtained.[18] Aldehydes are oxidized to methyl esters via hemiacetal intermediates by reaction with NIS in methanol at rt.[19] However, such conditions are not effective for the oxidation of simple alcohols. The combination of NIS and ***Tetra-n-butylammonium Iodide*** in dichloromethane has been developed for the oxidation of a variety of alcohols to the corresponding carbonyl compounds (eq 8).[20] This reagent system is most widely used for the oxidation of lactols to lactones, in which near-quantitative yields are generally obtained under mild conditions (eq 9).[21]

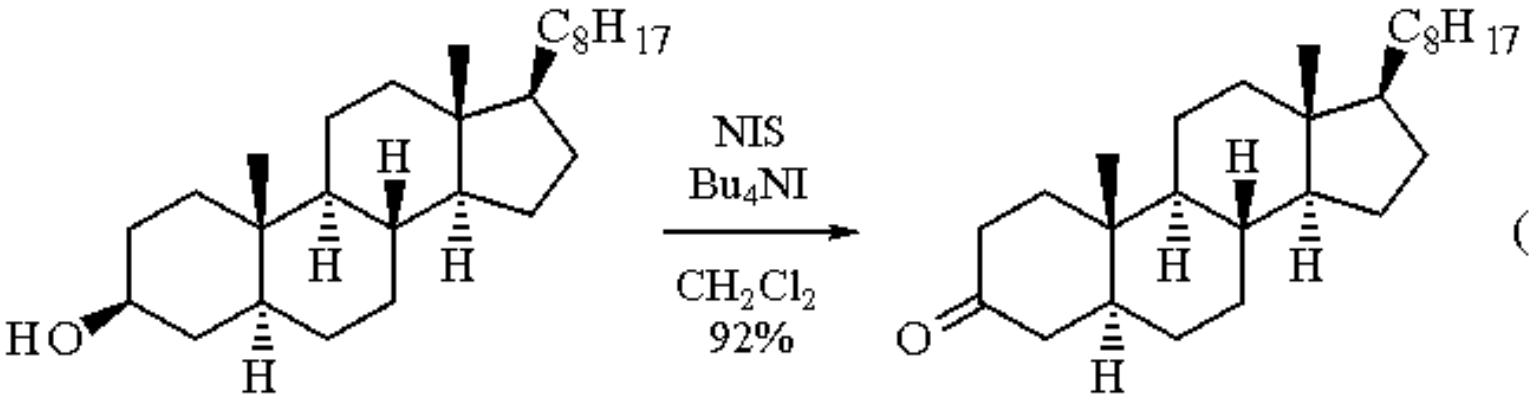

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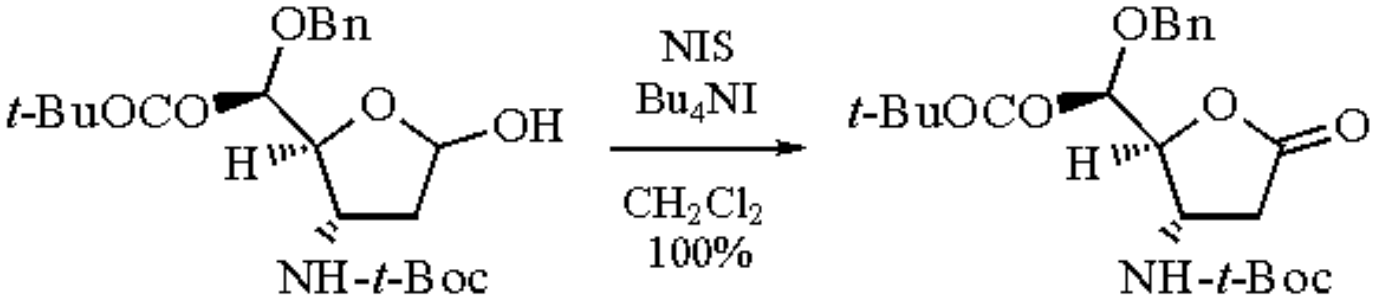

(9)

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Iodosylbenzene[1]

$(PhIO)_n$

[536-80-1] · C_6H_5IO · Iodosylbenzene · (MW 220.01)

(oxygen atom transfer to ketones,[4] metal-catalyzed oxygen atom transfer to alkenes,[7-13] formation of α-diketones,[14] bridgehead triflates,[16] α,β-unsaturated lactones and ketones,[19] α-hydroxymethyl acetals,[20] α-keto triflates,[17] α-hydroxy ketones,[18] C-C coupling,[22-24] oxidation of amines,[25,26] azidation[22-30])

Alternate Name: iodosobenzene.

Physical Data: mp 210 °C with decomposition (explodes); polymeric.

Solubility: slightly sol H_2O, MeOH. In MeOH the reagent is $PhI(OMe)_2$. Both solvents, as well as CH_2Cl_2 and MeCN, are used for reactions.

Form Supplied in: white to slightly yellow solid from synthesis.[2,3]

Preparative Method: prepared as a white solid by base hydrolysis of commercially available ***(Diacetoxyiodo)benzene*** in 75% yield.[2]

Purification: washing the solid with $CHCl_3$ to remove traces of PhI. The material is obtained in about 99% purity as determined iodometrically.[3]

Handling, Storage, and Precautions: indefinitely stable; refrigeration should be used for long-term storage.

Oxygen Atom Transfer from PhIO: α-Lactones from Ketenes (Uncatalyzed Epoxidation).

Ketenes react with PhIO to yield an intermediary α-lactone which undergoes polymerization to a polyester in yields ranging from 63 to 90% (eq 1).[4] Likewise, tetracyanoethylene forms tetracyanoethylene oxide in 74% yield upon reaction with PhIO.[4] α-Lactones have also been prepared by the ozonation of ketenes[5] and via the addition of triplet dioxygen to ketenes.[6]

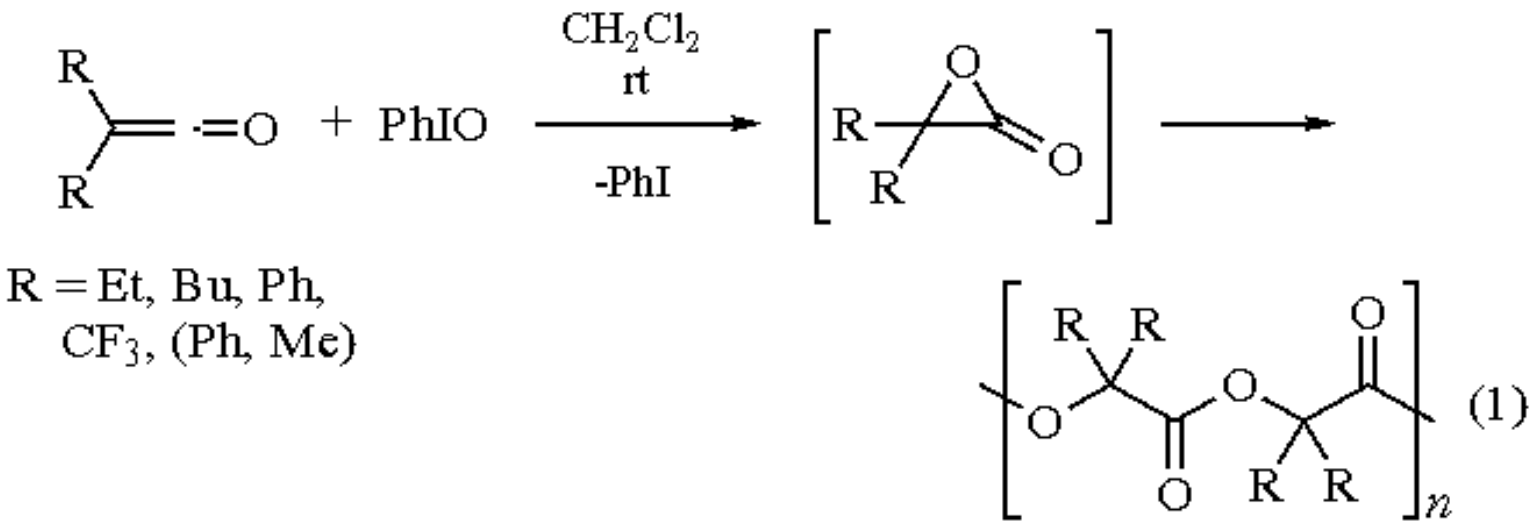

Metal-Catalyzed Oxygen Transfer: Epoxide Formation.

Iron(III) and manganese(III) porphyrins catalyze oxygen transfer from PhIO to aromatic substrates to yield phenolic products, probably via arene oxides.[7] Alkene epoxidation can also be achieved using this system. Simpler ligands such as Schiff's bases,[8] amides,[9] phosphines,[10] and salts of heteropolyaromatics[11] have been used. Bleomycin complexes of iron, copper, and zinc also cause oxidation of alkenes.[12] Noteworthy is the epoxidation of cyclohexene (eq 2).[13] These systems are of theoretical interest as models for cytochrome P-450 and have not as yet achieved general preparative significance.

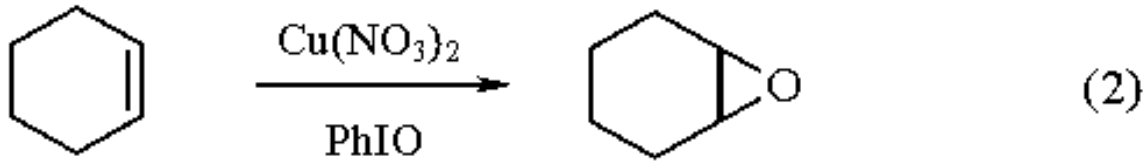

Oxidation of Alkynes to α-Diketones.

Ruthenium catalysis is effective in the oxidation of internal (eq 3) and terminal alkynes (eq 4).[14] Secondary alcohols are oxidized to ketones in good yield using *m*-iodosylbenzoic acid and the base-extractable *m*-iodobenzoic acid can be recycled.[15]

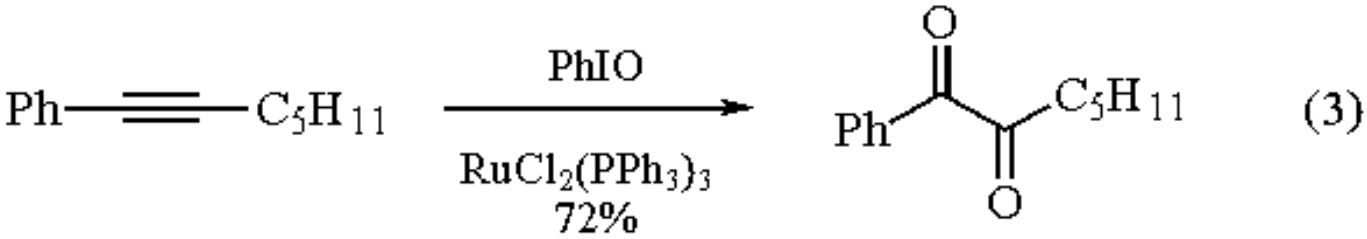

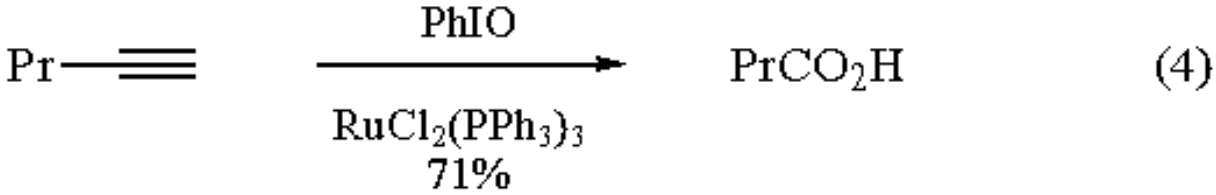

Activated PhIO using TMSOTf: Oxidative Displacement of Bridgehead Iodine to Yield Bridgehead Triflates.

A series of cubyl triflates was synthesized using PhIO and ***Trimethylsilyl Trifluoromethanesulfonate*** (forms the reactive intermediate $[PhIOTMS]^+$ TfO^-) (eq 5).[16] Cubyl alcohol is unstable and this direct functionalization was critically useful.

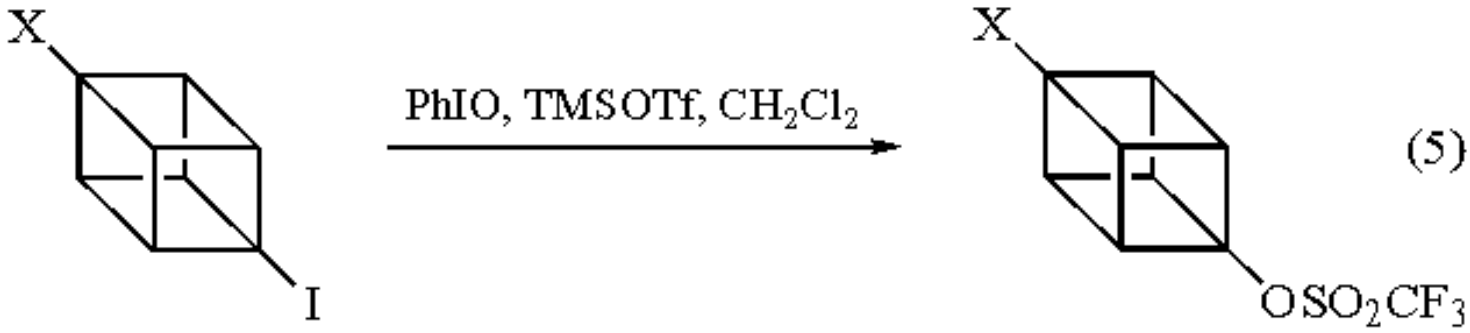

X = H, Me, CO_2Me, I, Br, Cl

Oxidation of Silyl Enol Ethers to α-Keto Triflates with PhIO-TMSOTf.

The oxidation of silyl enol ethers to α-keto triflates is a generally useful reaction (eqs 6 and 7).[17]

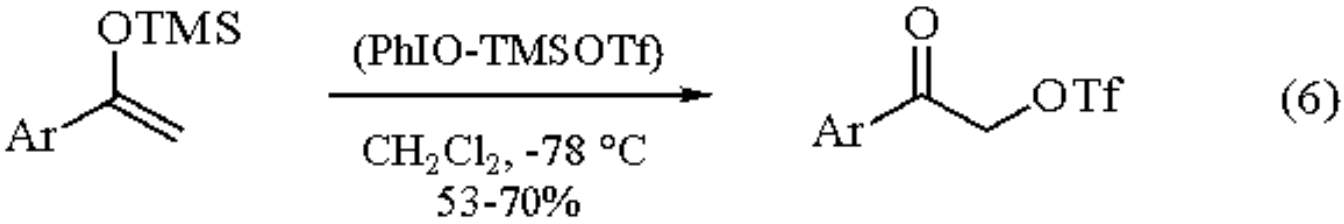

Ar = phenyl, furan, thiophene

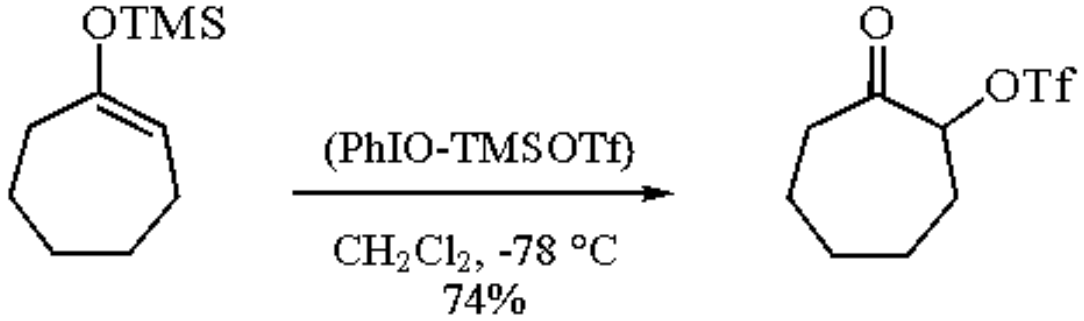

(7)

Oxidation of Silyl Enol Ethers with PhIO in H_2O-$BF_3.Et_2O$ to α-Hydroxy Ketones.

A direct route to α-hydroxy ketones is achieved via oxidation of aromatic, heteroaromatic, and aliphatic silyl enol ethers with PhIO in ***Boron Trifluoride Etherate***-H_2O (eq 8).[18] This is a simple and broadly useful reaction for the α-hydroxylation of ketones.

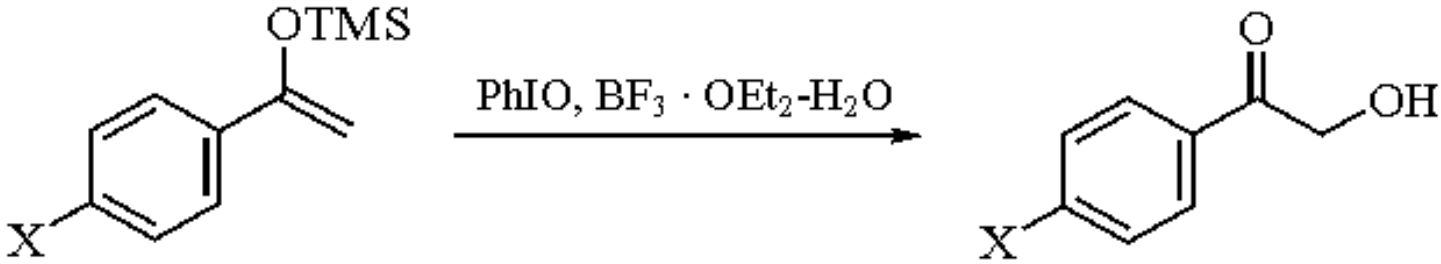

(8)

X = H, 65%; Cl, 70%; NO_2, 78%; 2-pyridyl, 62%; 3-pyridyl, 64%; cyclohexyl, 80%; 2-benzofuran, 59%

Oxidation of Lactones to Higher Homologous α,β-Unsaturated Lactones.

Ring expansion of lactones occurs via oxidation of the derived trimethylsilyloxycyclopropanols to give the higher homologous α,β-unsaturated lactones (eq 9).[19] Silyl enol ethers behave analogously (eqs 10 and 11).[19]

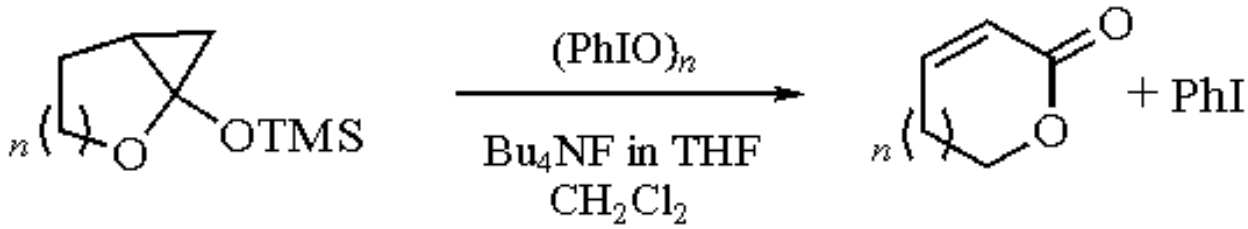

(9)

n = 1, 72%; 2, 75%; 3, 62%; 9, 78%

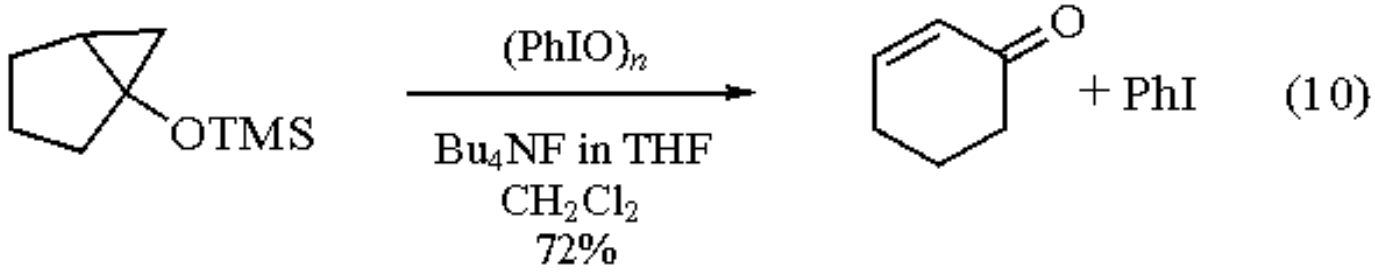

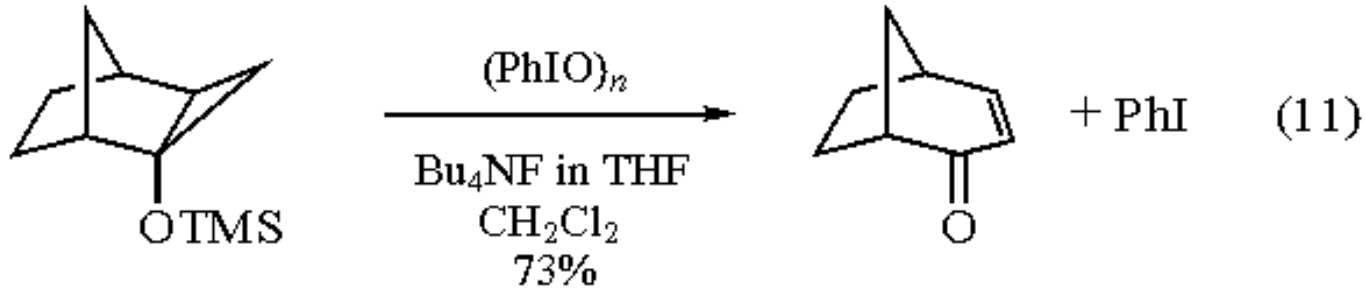

Oxidation of Ketones to Form α-Hydroxydimethyl Acetals.

The reagent $PhI(OAc)_2$-KOH-MeOH is equivalent to PhIO-KOH-MeOH; however, $PhI(OAc)_2$ is commercially available whilst PhIO is not. Consequently, the reagent ***(Diacetoxyiodo)benzene***, [$PhI(OAc)_2$], is now used even though the original process was discovered using PhIO/MeOH.[20a] This reagent has been employed in the synthesis of the steroidal dihydroxyacetone side chain (eq 12).[20b]

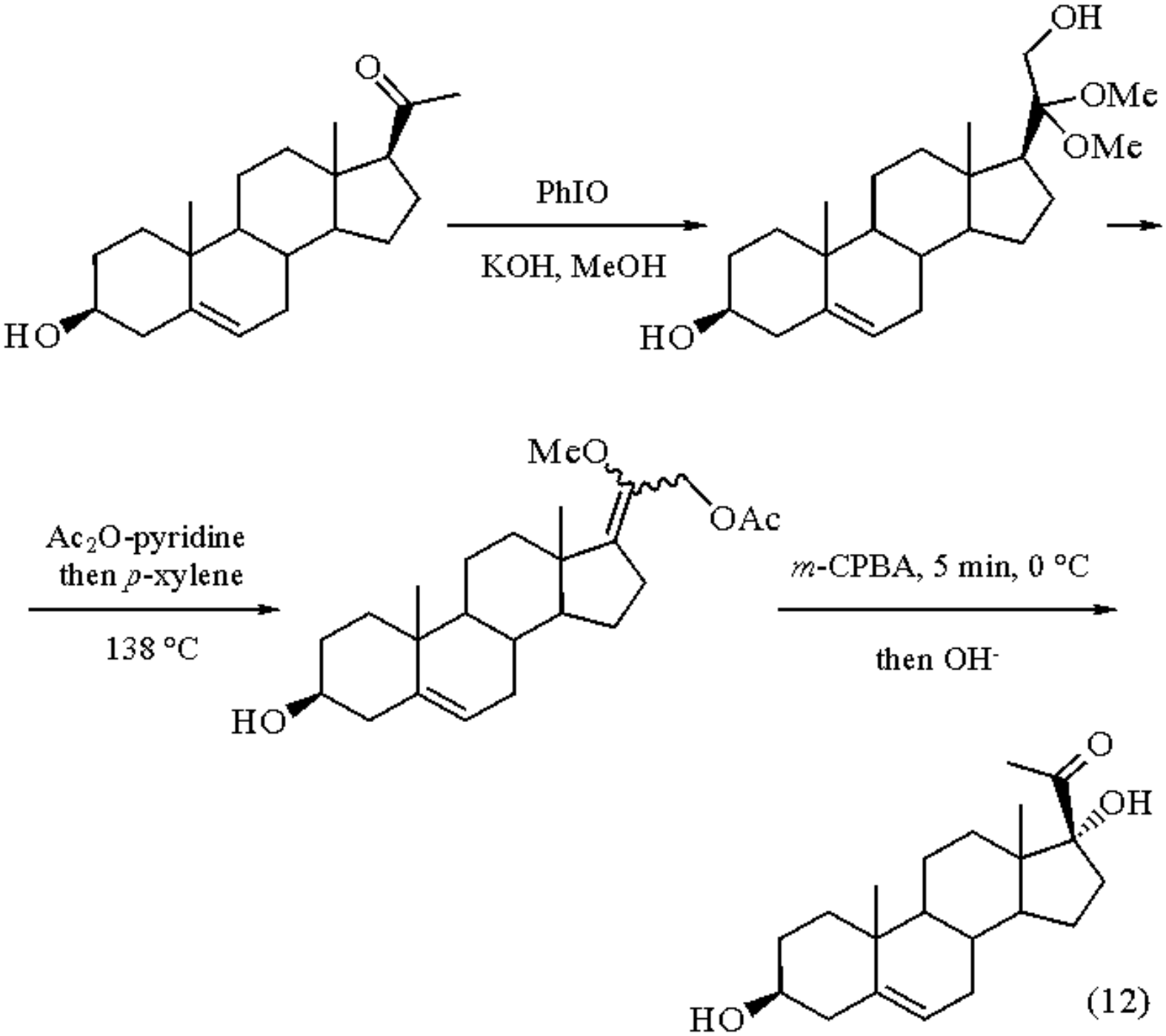

Formation of Carbon-Carbon Bonds: 1,4-Diketones via Coupling Reaction with PhIO/BF_3.Et_2O.

The addition of BF_3.Et_2O to PhIO yields an intermediary reagent, [$PhI^+OBF_3^-$], which is reactive with silyl enol ethers derived from ketones. In the presence of water or an alcohol, α-hydroxylation or α-alkoxylation occurs (eq 13),[18] while in the absence of a protic nucleophile self-coupling occurs to yield a 1,4-diketone (eq 14).[21]

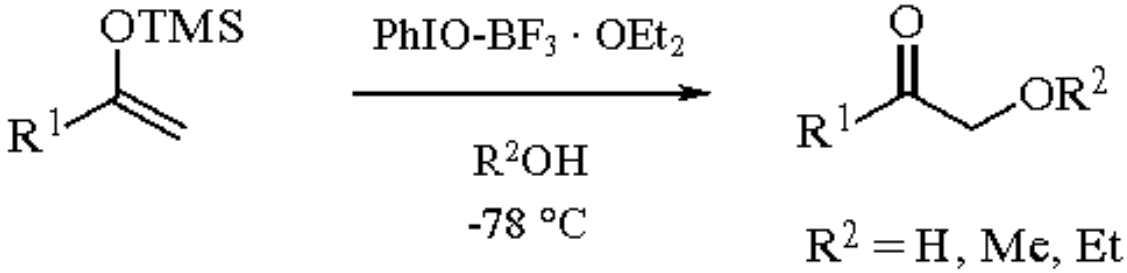

(13)

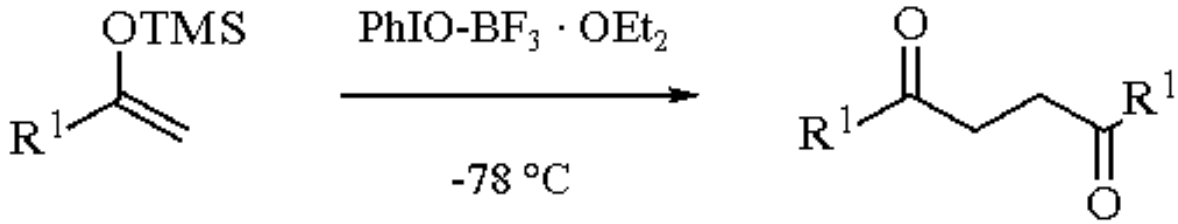

(14)

Unsymmetrical coupling occurs via in situ generation of a phenyliodonium intermediate at -78 °C and subsequent introduction of a silyl enol ether as a coupling partner (eq 15).[22]

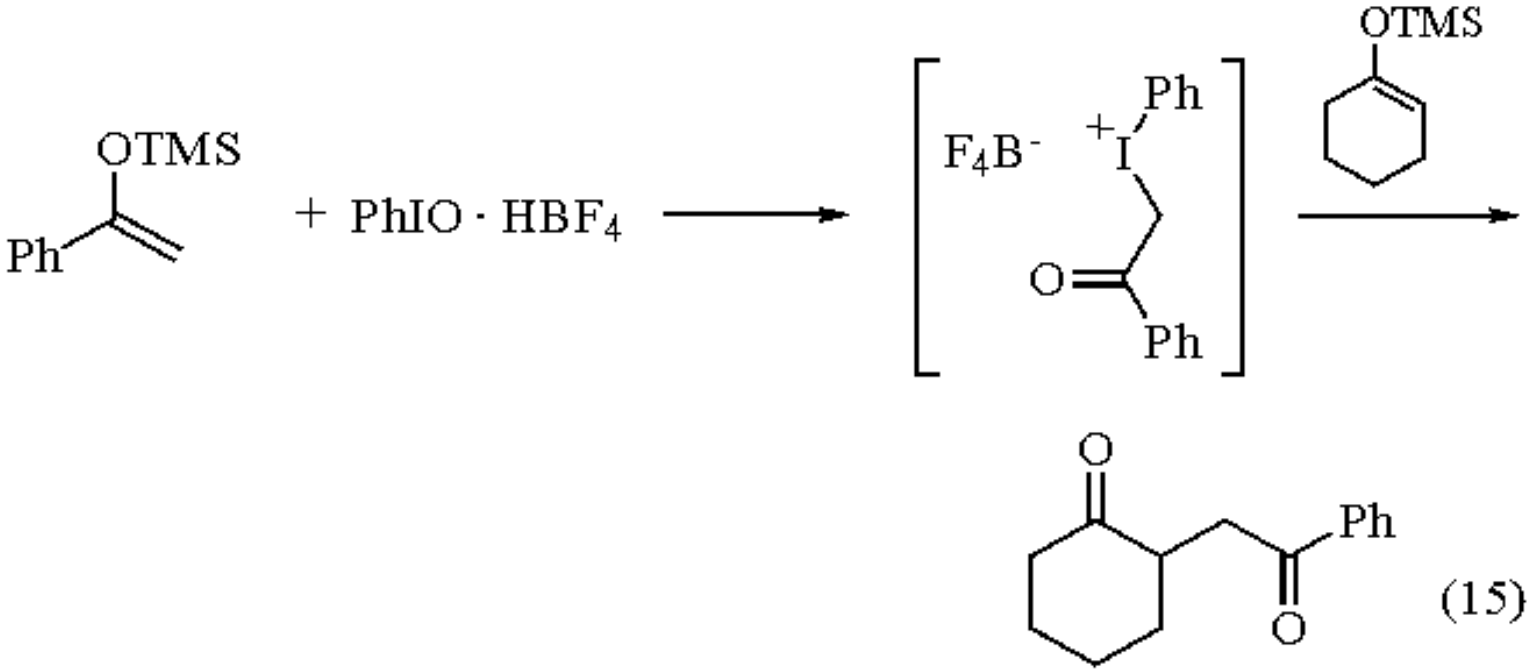

(15)

Allylation of aromatic compounds takes place when allylmetal (Group 14) compounds react with aromatic compounds and iodosylbenzene in the presence of boron trifluoride etherate (eq 16).[23,24]

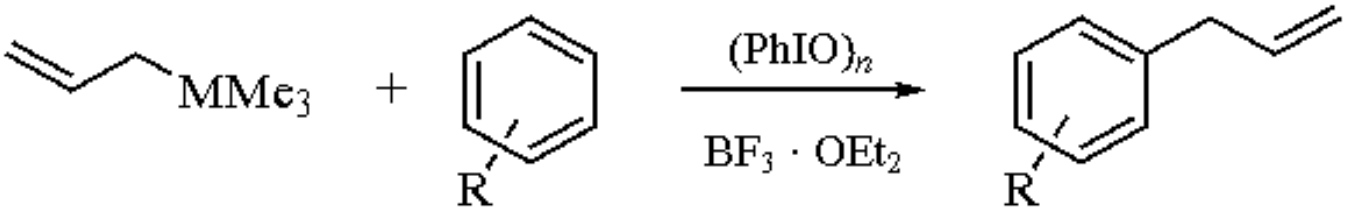

(16)

M = Si, Ge, Sn

Oxidation of Amines.

Primary amines yield nitriles (eq 17) or ketones (eq 18).[25]

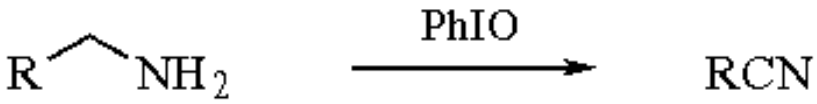

(17)

R = Ph, 48%; C_5H_{11}, 56%

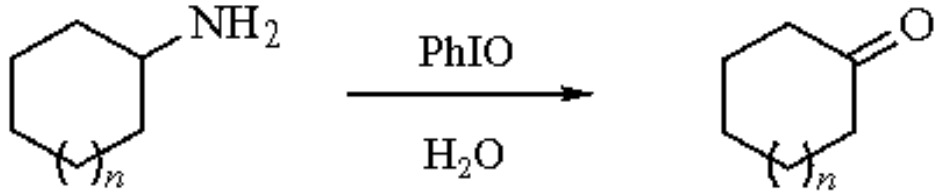

(18)

$n = 1, 2$

Cyclic secondary amines yield lactams (eq 19).[25] *N*-Methyl cyclic amines as well as nicotine behave analogously (eq 20).[25]

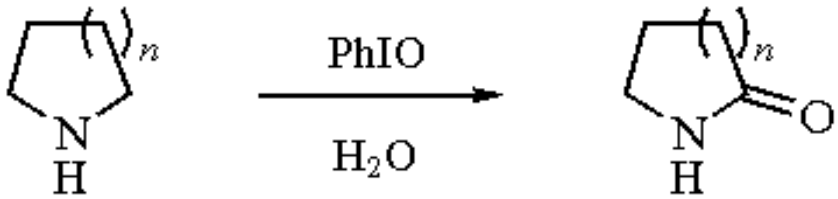

(19)

$n = 1$, 49%
$n = 2$, 58%

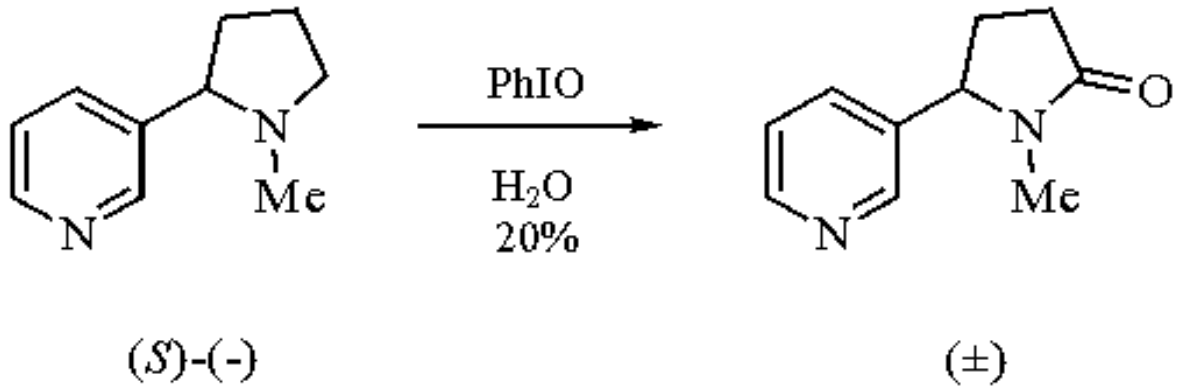

Cyclic amino acids such as L-proline, pipecolinic acid, and L-2-pyrrolidinone-5-carboxylic acid undergo oxidative decarboxylation with iodosobenzene in various solvents (including water) to yield the corresponding lactam (eq 21).[26]

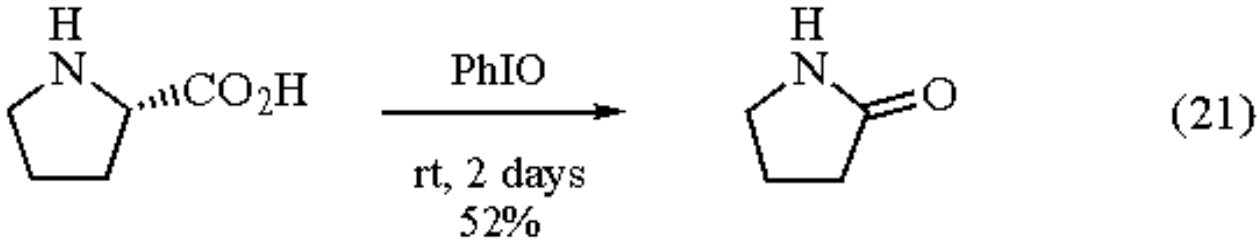

Formation of Azides Using PhIO-NaN_3 or PhIO-$TMSN_3$.

Cholesterol is converted to the allylic azide with PhIO-NaN_3-$MeCO_2H$, namely 7α-azidocholest-5-en-3β-ol.[27] A similar reaction occurs with $Pb(OAc)_4$-TMSCl.[28]

Formation of β-Azido Ketones using PhIO-$TMSN_3$.

The reaction between ***Azidotrimethylsilane*** and PhIO must be carried out at low temperatures. At rt they react violently. Eq 22 shows the β-azido functionalization of triisopropylsilylenol ethers.[29]

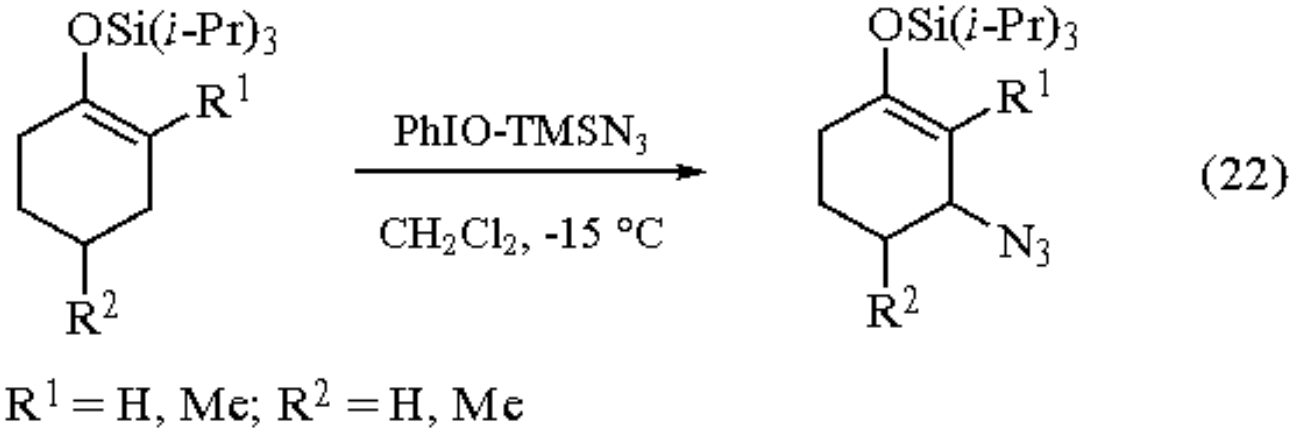

N,*N*-Dimethylarylamines under these conditions yield *N*-methyl-*N*-azidomethyl arylamines (eq 23).[30]

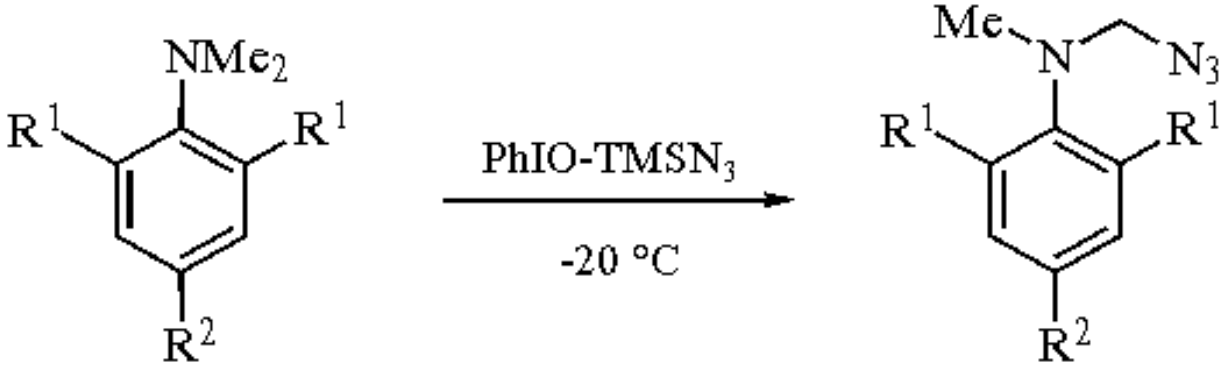

(23)

$R^1 = Me$; $R^2 = Me, NMe_2$

The thiocarbonyl group of 2-thiouracil is converted to the carbonyl group with PhIO (eq 24).[31]

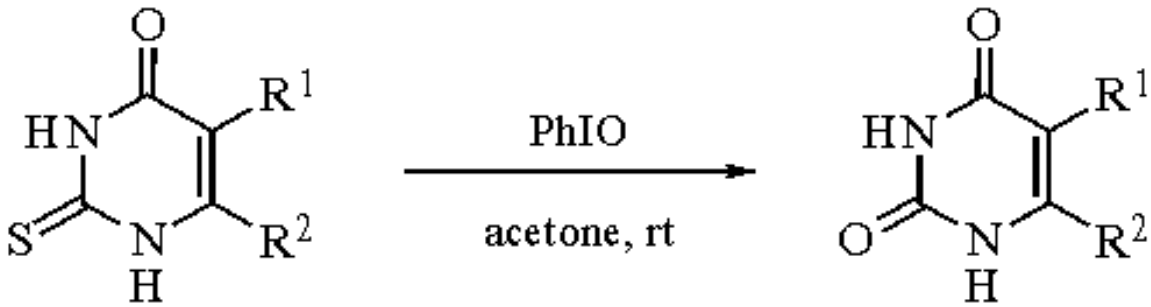

(24)

$R^1 = R^2 = H$; $R^1 = Me, R^2 = H$; $R^1 = H, R^2 = Me$

Related Reagents.

Iodosylbenzene-Boron Trifluoride; ***Iodosylbenzene-Dichlorotris(triphenylphosphine)ruthenium***.

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Iodosylbenzene-Boron Trifluoride[1]

$PhIO.BF_3$

(PhIO)

[536-80-1] · C_6H_5IO · Iodosylbenzene-Boron Trifluoride · (MW 220.01) ($PhIO.BF_3$)

[108208-48-6] · $C_6H_5BF_3IO$ · Iodosylbenzene-Boron Trifluoride · (MW 287.82)

(iodonium-transfer reagent to alkenyl-[2a] and alkynylsilanes;[2b] oxidizing agent for silyl enol ethers[3])

Physical Data: PhIO: mp 210 °C (dec).

Solubility: PhIO is a polymer, linked by I-O-I bonds. Therefore it is insoluble in most organic solvents. Upon dissolution in acetic acid and methanol, it is known to react to form (diacetoxyiodo)benzene and (dimethoxyiodo)benzene, respectively.[10]

Form Supplied in: PhIO is a pale yellow solid. Some commercial compounds are contaminated with iodyl benzene ($PhIO_2$: colorless solid).

Analysis of Reagent Purity: iodometric titration.

Preparative Method: see Salzman and Sharefkin.[11]

Handling, Storage, and Precautions: PhIO decomposes explosively if heated to 210 °C. The solid gradually disproportionates to iodobenzene and iodyl benzene at rt and must be stored at -20 °C.

Iodosylbenzene is activated by coordination of ***Boron Trifluoride Etherate*** to the oxygen atom, presumably via the formation of the highly electrophilic species $C_6H_5I^{\delta+}$-$OBF_3^{\delta-}$.[2] This species undergoes an iodonium-transfer reaction, which makes possible the synthesis of alkenyl- and alkynyl(phenyl)iodonium salts. Because of the superleaving ability of the phenyliodonium group, alkenyliodonium salts serve as the progenitors for generating alkylidenecarbenes via base-induced α-elimination under mild conditions (eq 1)[4] and as the highly activated species of alkenyl halides in nucleophilic vinylic substitutions (eq 2).[2a] Nucleophilic vinyl substitutions of (*E*)-alkenyliodonium salts with *n*-Bu_4NX proceed with exclusive inversion of configuration.[5] Tandem Michael-carbene insertion reactions of alkynyl(phenyl)iodonium salts provide a useful tool for the synthesis of cyclopentenes (eq 3) and furans.[6]

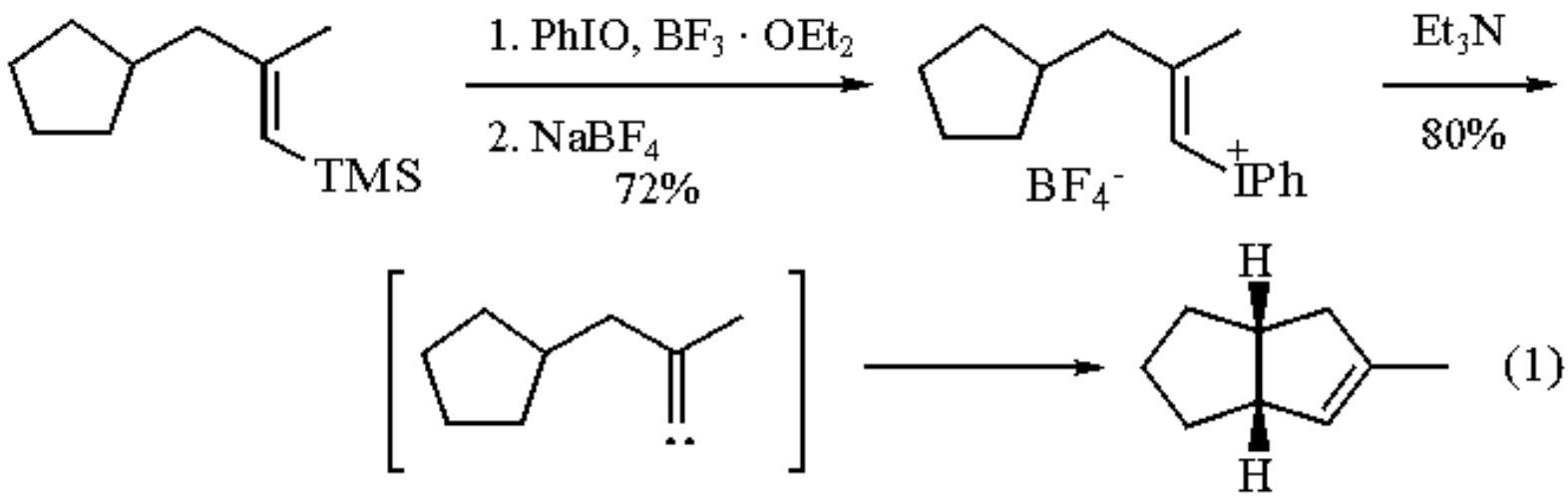

(1)

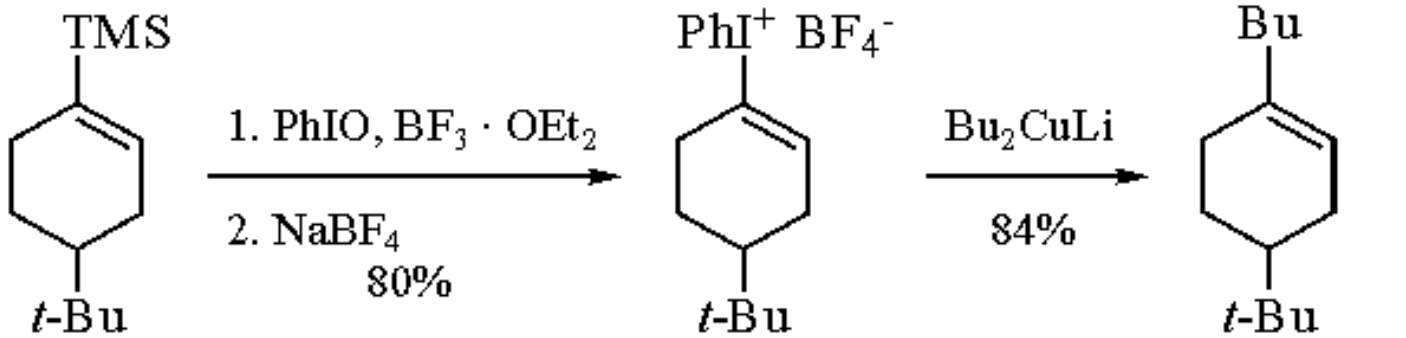

(2)

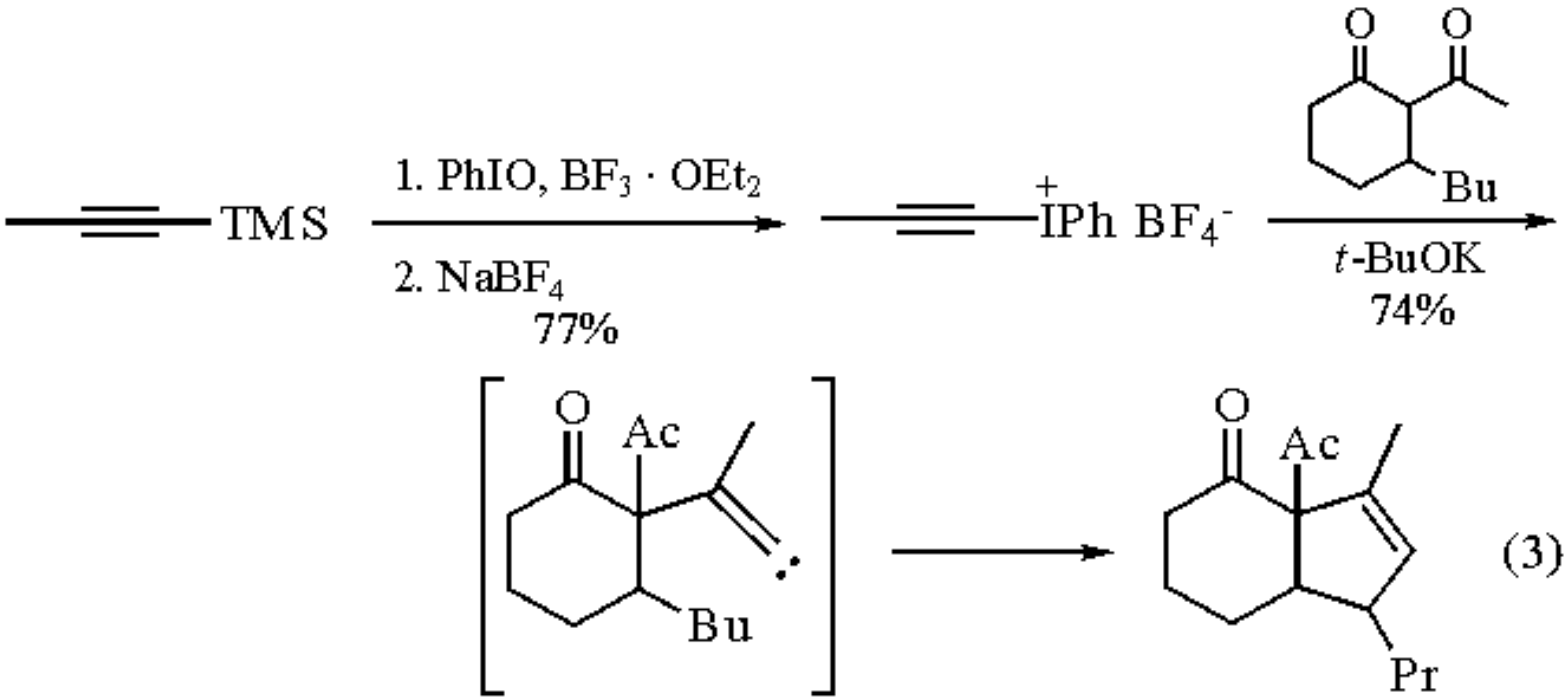

(3)

Treatment of propargylsilanes, -germanes, and -stannanes with iodosylbenzene-BF_3 promotes a reductive iodonio-Claisen rearrangement under mild conditions, yielding *o*-propargyliodoarenes (eq 4).[7] Intermediate allenyl(phenyl)iodinanes are involved in this reaction.

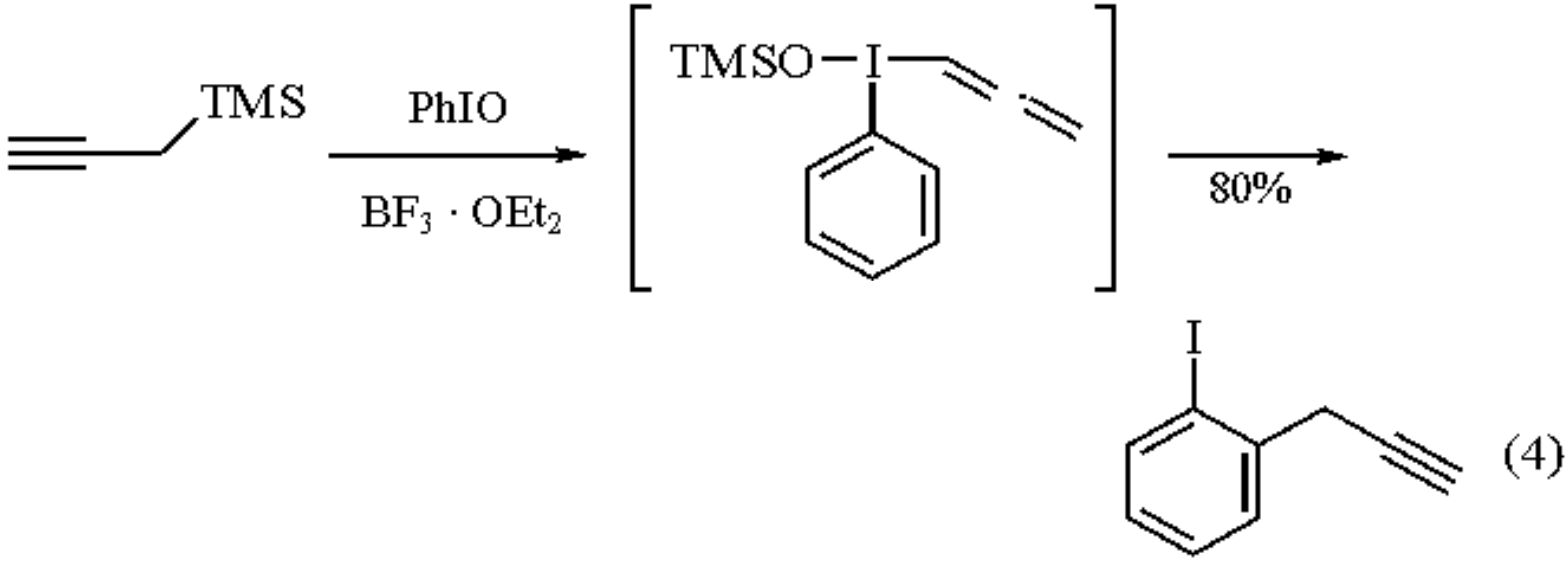

Carbon-tin bond cleavage by iodosylbenzene-BF_3 makes possible the conversion of trimethylstannyl groups into hydroxy groups with retention of stereochemistry and the stereoselective osmylation of alkenes utilizing an intramolecular hypervalent tin-oxygen interaction.[8] Oxidative Grob fragmentation of γ-stannyl alcohols gives unsaturated carbonyl compounds and lactones (eq 5).[9]

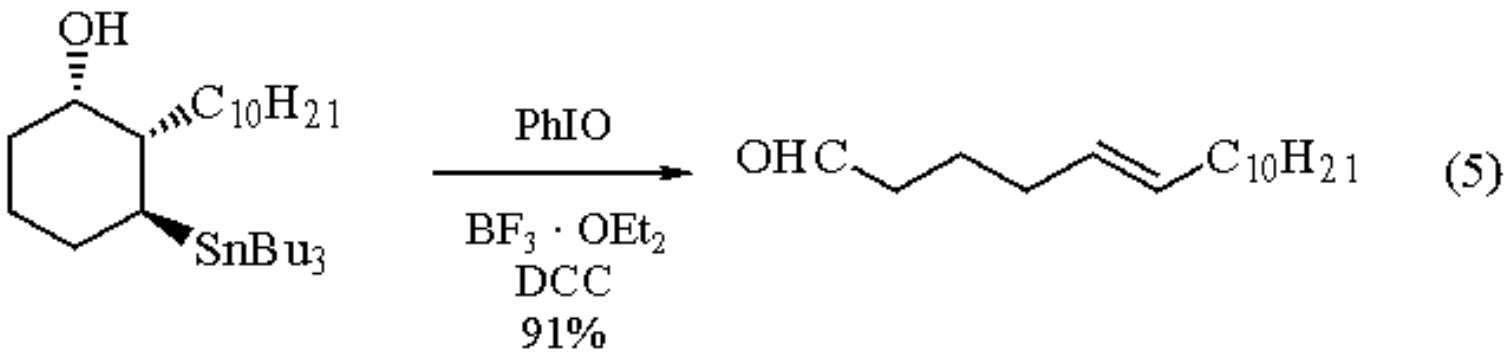

Oxidation of silyl enol ethers gives α-hydroxy and α-methoxy ketones (eq 6).[3]

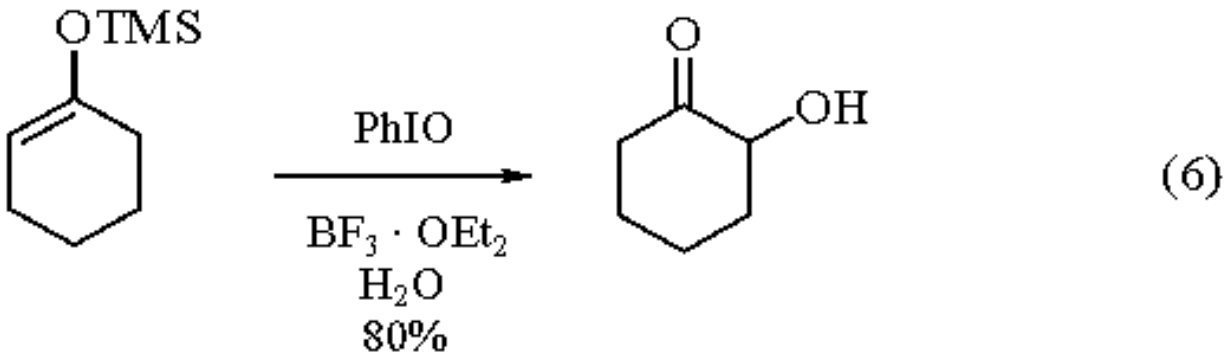

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Iodosylbenzene-Dichlorotris(triphenylphosphine)ruthenium

$PhIO\text{-}RuCl_2(Ph_3P)_3$

(PhIO)

[536-80-1] · C_6H_5IO · Iodosylbenzene-Dichlorotris(triphenylphosphine)ruthenium · (MW 220.01) ($RuCl_2(Ph_3P)_3$

[15529-49-4] · $C_{54}H_{45}Cl_2P_3Ru$ · Iodosylbenzene-Dichlorotris(triphenylphosphine)ruthenium · (MW 958.87)

(mild oxidant for selective catalytic transformation of alkynes and several functional groups)

Physical Data: see ***Iodosylbenzene*** and ***Dichlorotris(triphenylphosphine)ruthenium(II)***.

Oxidation of Alkynes.

This reagent combination oxidizes disubstituted alkynes to α-diketones.[1] The reactions are carried out at rt by stirring the substrate in a CH_2Cl_2 suspension of PhIO (2-3 equiv) in the presence of the catalyst (1%) until the oxidant totally dissolves. The best results are obtained with aryl-substituted alkynes (eq 1), while alkynes with aliphatic substituents tend to undergo cleavage to carboxylic acids. Terminal alkynes react exclusively via cleavage (eq 2). Alkynyl ethers and amines afford α-keto esters and α-keto amides, respectively.[2]

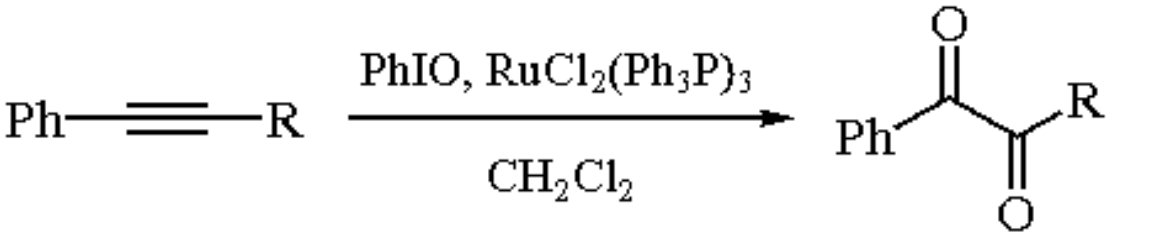

(1)

R = Ph	86%
R = OEt	70%
R = NMe_2	84%

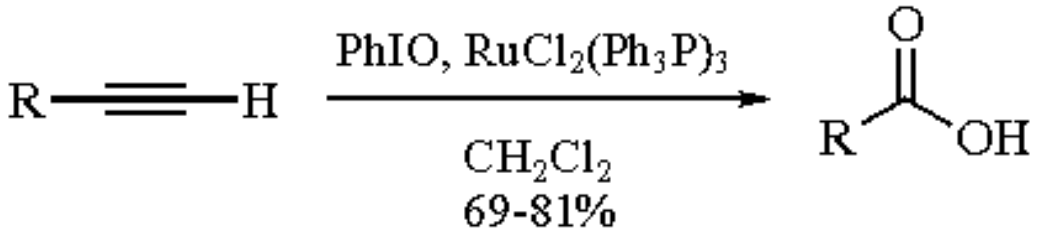

(2)

Oxidation of Alcohols and Phenols.

Primary alcohols are oxidized by PhIO-$RuCl_2(Ph_3P)_3$ to aldehydes which react further to form carboxylic acids (eq 3), while secondary alcohols afford ketones (eq 4).[3] The scope and limitations of this system in alcohol oxidations are similar to the combination of ***N-Methylmorpholine N-Oxide*** and ruthenium catalysts described by Sharpless.[4] The oxidation of primary alcohols may be stopped at the aldehyde stage when iodosyl diacetate[5] or *m*-iodosylbenzoic acid[6] is used instead of PhIO (eqs 5 and 6).

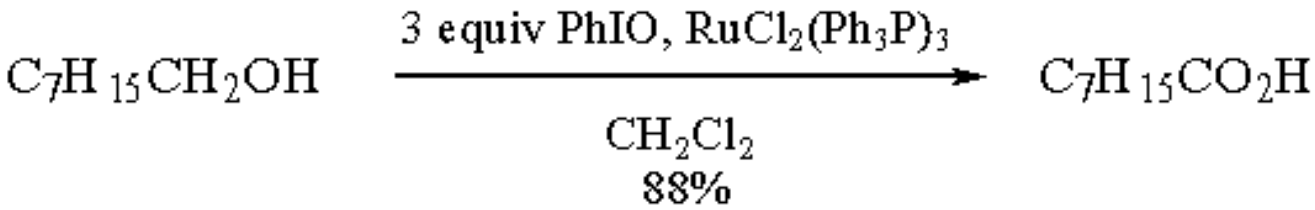

(3)

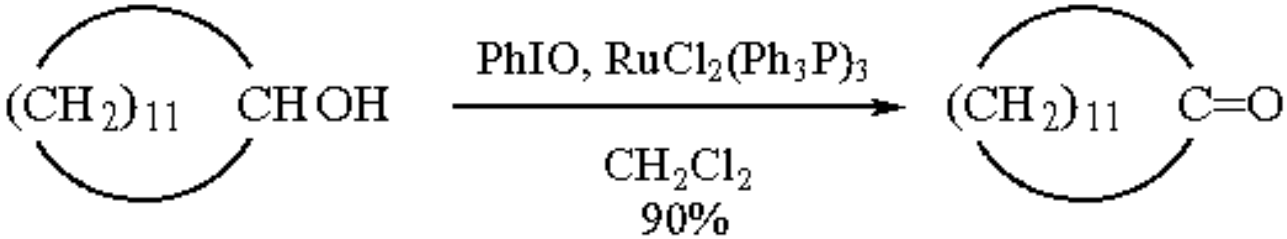

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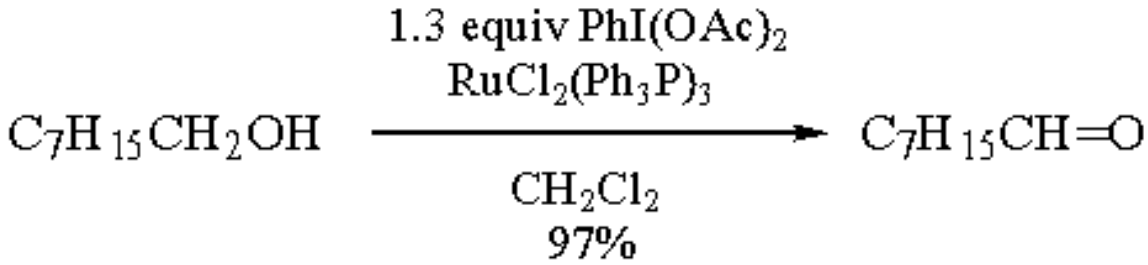

(5)

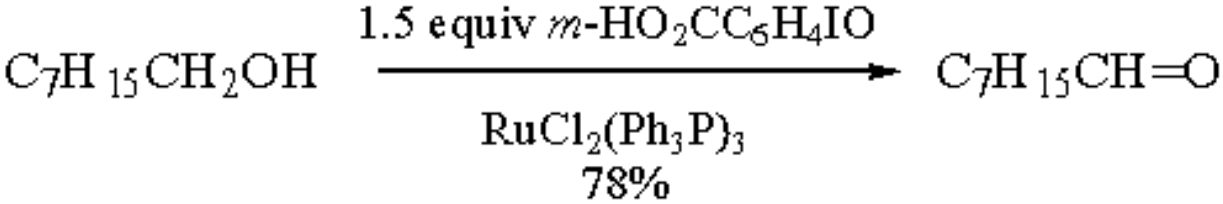

(6)

Hydroquinones are oxidized to quinones by PhIO (eq 7). In these transformations the reaction proceeds with similar yields in the presence or absence of catalyst. Catalysis, however, is required for oxidation of sterically

hindered phenols to quinones (eq 8). ***Boron Trifluoride Etherate*** as catalyst affords higher yields than $RuCl_2(Ph_3P)_3$,[7] and *m*-iodosylbenzoic acid-$RuCl_2(Ph_3P)_3$ or PhIO in AcOH lead to comparable results.

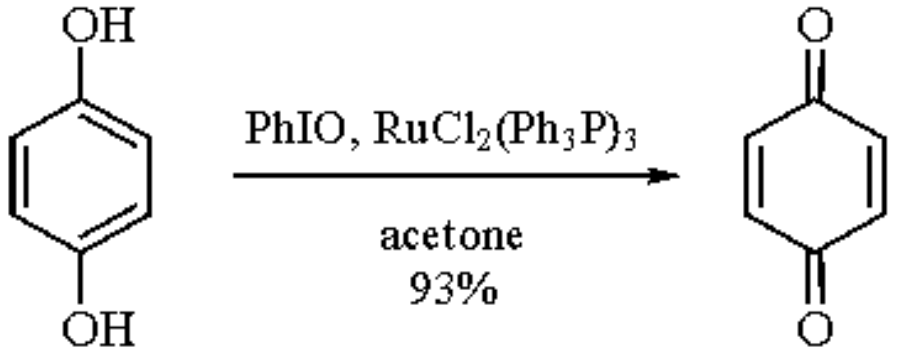

(7)

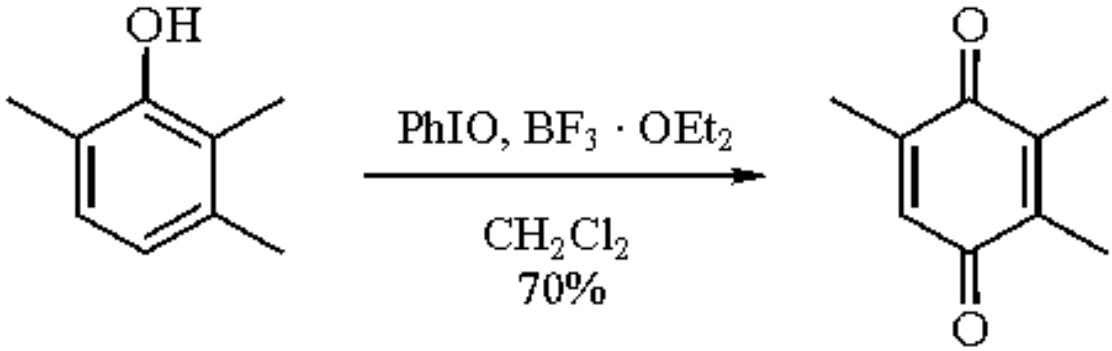

(8)

Oxidation of Sulfides and Selenides.

While the Ru-catalyzed oxidation of sulfides and selenides with PhIO proceeds to sulfones and selenones (eq 9), respectively, sulfoxides may be obtained selectively with *m*-iodosylbenzoic acid (eq 10).[6]

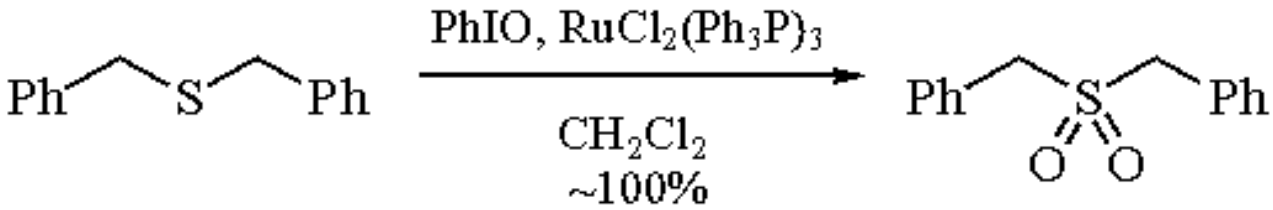

(9)

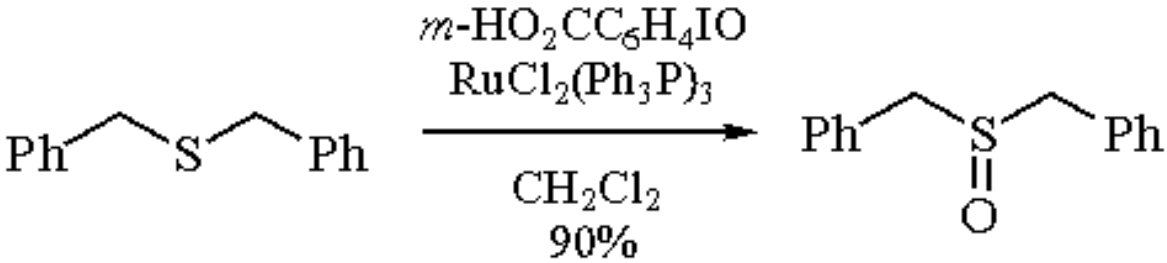

(10)

Oxidation of Amines.

Activated secondary amines are dehydrogenated to imines by PhIO alone or with Ru catalysis (eq 11).[8]

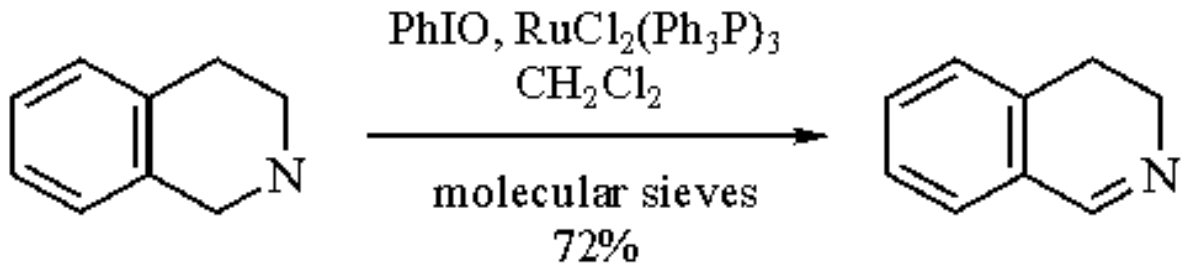

(11)

Other Variations of the System.

$RuCl_2(Ph_3P)_3$ may be replaced by other Rh salts, such as ***Ruthenium(III) Chloride*** with practically no effect on the results. Other oxidants which have been used in combination with rhodium salts include *N*-methylmorpholine *N*-oxide (oxidation of alcohols),[5] *N*-methylmorpholine/H_2O_2 (alcohols),[9] ***t-Butyl Hydroperoxide*** (amines,[10,11] hydroquinones,[12] nitriles[13]), ***Hydrogen Peroxide*** (hydroquinones and phenols),[14] ***Oxygen*** (alcohols,[15] catechols,[16] sulfides,[17]), ***Bis(trimethylsilyl) Peroxide*** (alcohols),[18] ***Acetone*** (alcohols),[19] and CCl_4 (alcohols).[20]

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4-Iodo-2-trimethylgermyl-1-butene

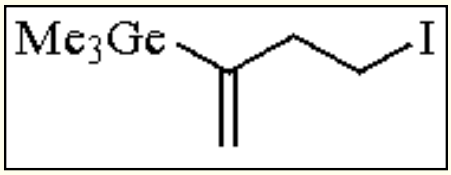

[124897-71-8] · $C_7H_{15}GeI$ · 4-Iodo-2-trimethylgermyl-1-butene · (MW 298.71)

(precursor of lithium (3-trimethylgermyl-3-butenyl)cyanocuprate, a synthetically useful reagent for effecting annulation reactions[1-3])

Alternate Name: 3-iodo-1-methylenepropyltrimethylgermane.

Physical Data: colorless liquid; distillation temperature (bulb-to-bulb) 85-92 °C/15 mmHg.

Solubility: sol THF, $CHCl_3$.

Preparative Methods: from 4-chloro-2-lithio-1-butene (**1**) (see ***4-Chloro-2-trimethylstannyl-1-butene***) and from 1-trimethylsilyl-4-trimethylsilyloxy-1-butyne (**3**), as shown in eqs 1 and 2, respectively.[1,5] Of these two methods, the latter is experimentally more convenient and is also less expensive.

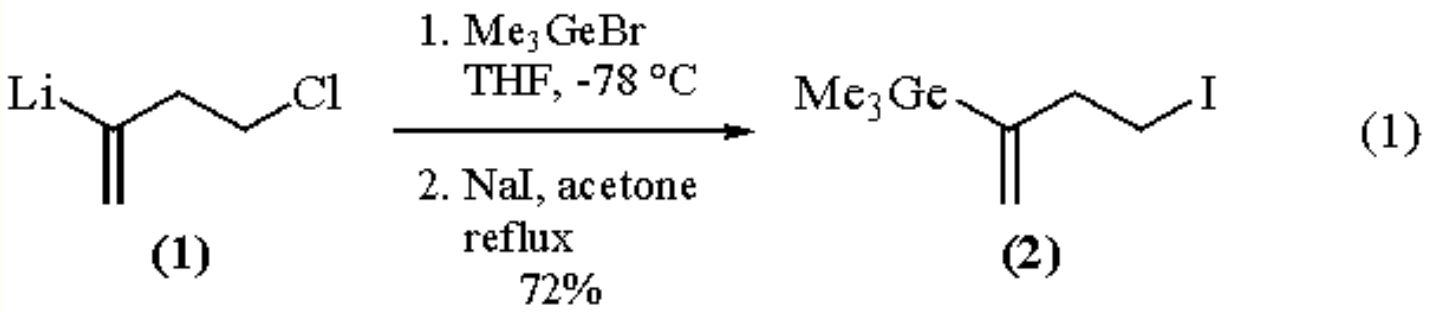

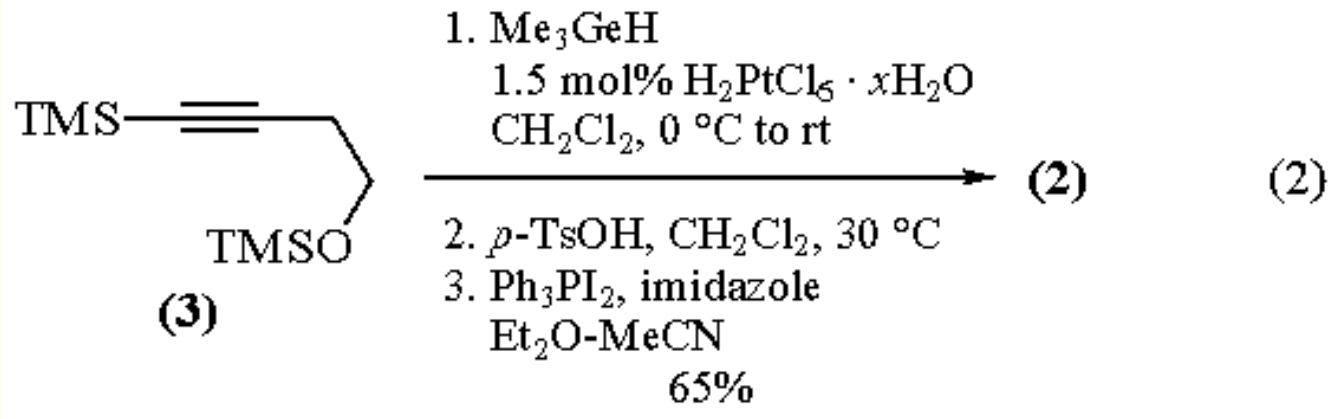

Handling, Storage, and Precautions: organogermanium compounds[4] and alkyl iodides are toxic and, therefore, the reagent should be prepared, distilled, and used in a fume hood. When stored in a freezer over copper wire under an inert atmosphere, the reagent is stable indefinitely. Should be distilled just prior to use; reactions should be carried out using dry THF and an inert atmosphere.

Annulation Methods.

The title reagent (**2**), upon sequential treatment with ***t-Butyllithium*** and ***Copper(I) Cyanide***, is readily converted into the structurally novel lower order heterocuprate (**4**) (eq 3).[1,2] The latter species has been employed in the development of the new, synthetically valuable annulation sequences outlined below.

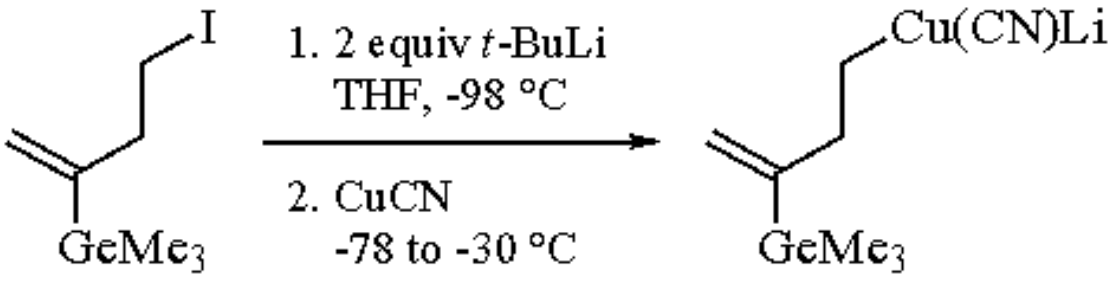

(2) (4) (3)

Conjugate addition of (**4**) to the enone (**5**) affords the keto vinylgermane (**6**), which upon treatment with ***Iodine*** is transformed into the corresponding vinyl iodide (**7**) (eq 4).[1] Reaction of (**7**) with ***n-Butyllithium*** in THF provides, highly stereoselectively, the alkene alcohol (**8**), which serves as a suitable intermediate for the total synthesis of the isolabdane diterpenoid ambliol B (**9**).[1]

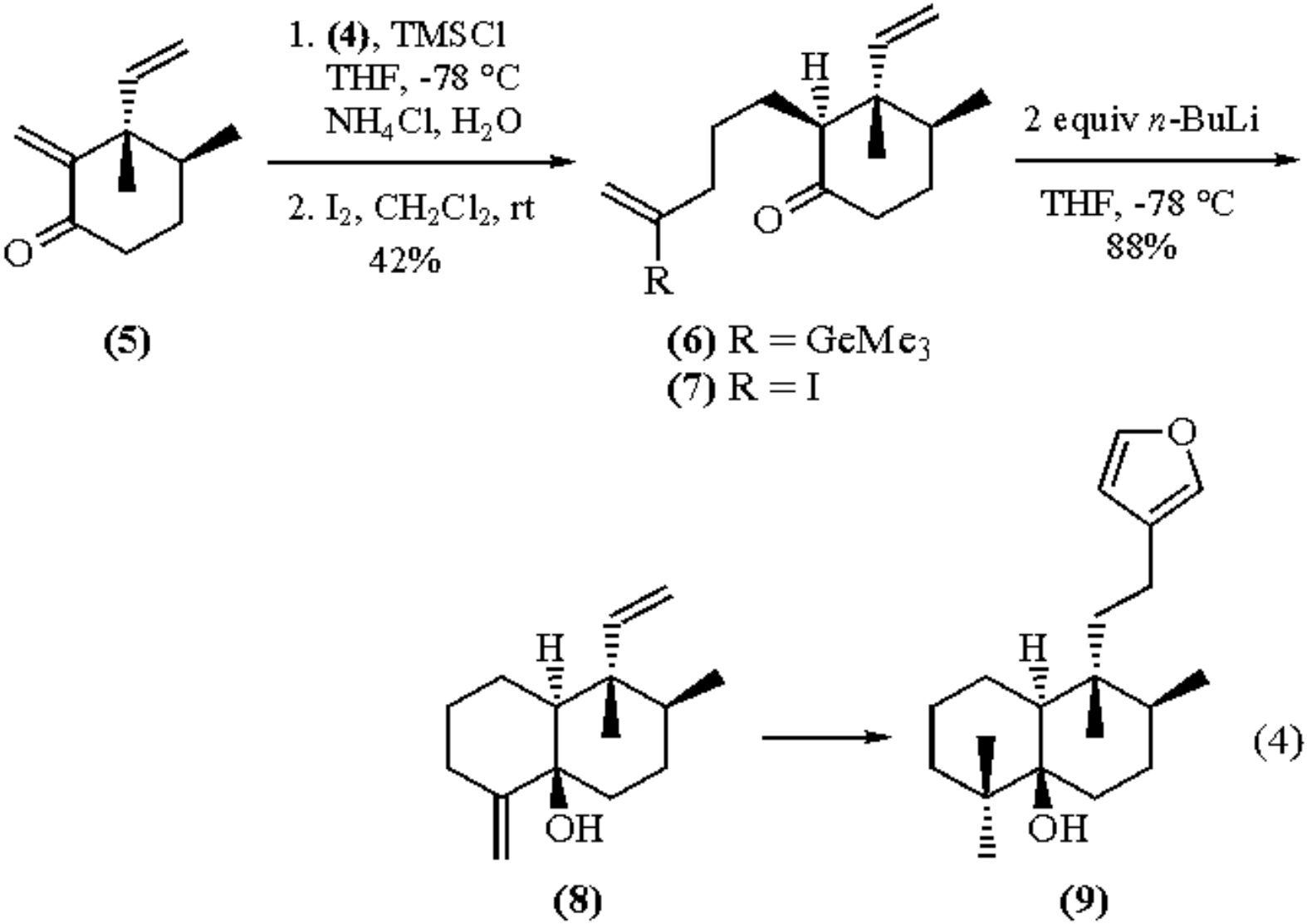

Reagent (**4**) has also found effective use in the development of a methylenecyclopentane annulation method shown in general terms by the conversion of (**10**) into (**11**).[2] This annulation process is regioisomeric with respect to the transformation of (**10**) into (**12**) (eq 5)[6] (see also ***4-Chloro-2-trimethylstannyl-1-butene***).

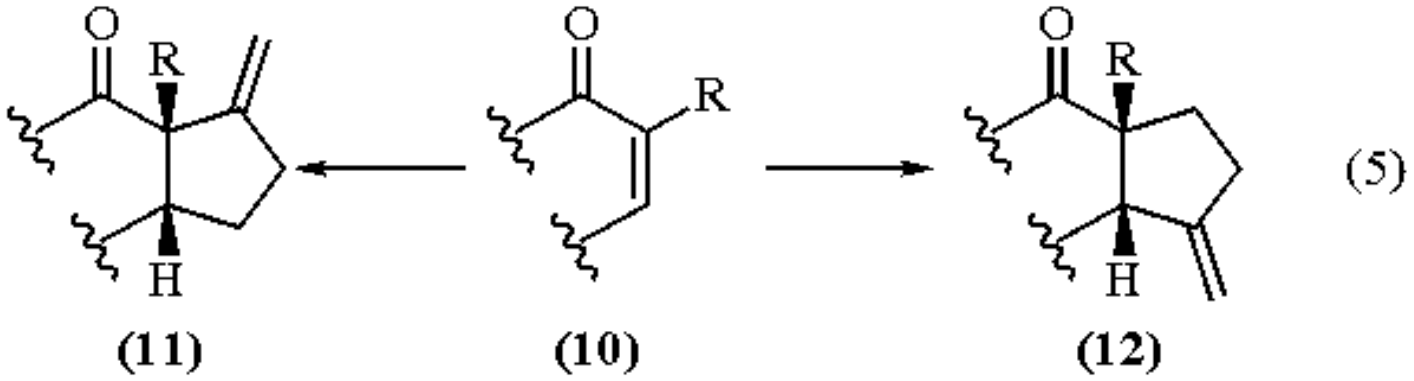

A specific example of the new method is shown in eq (6).[2] Conjugate addition of reagent (**4**) to (*R*)-(-)-carvone (**13**) provides (**14**), which is readily converted into (**15**). In the key step, the keto iodide (**15**) is treated with base in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** to afford the annulation product (**16**). Structures (**17**) and (**18**) represent likely intermediates in the reaction pathway of this novel cyclization process.[2]

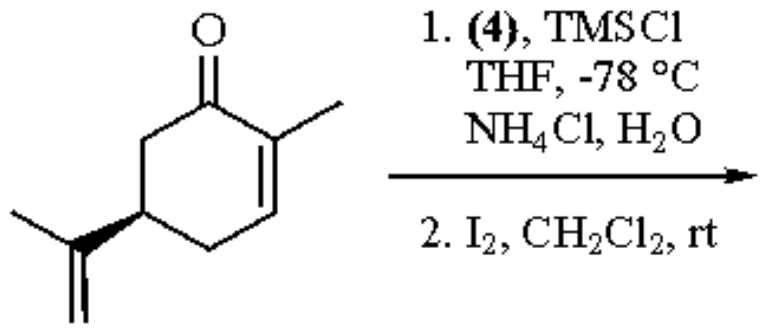

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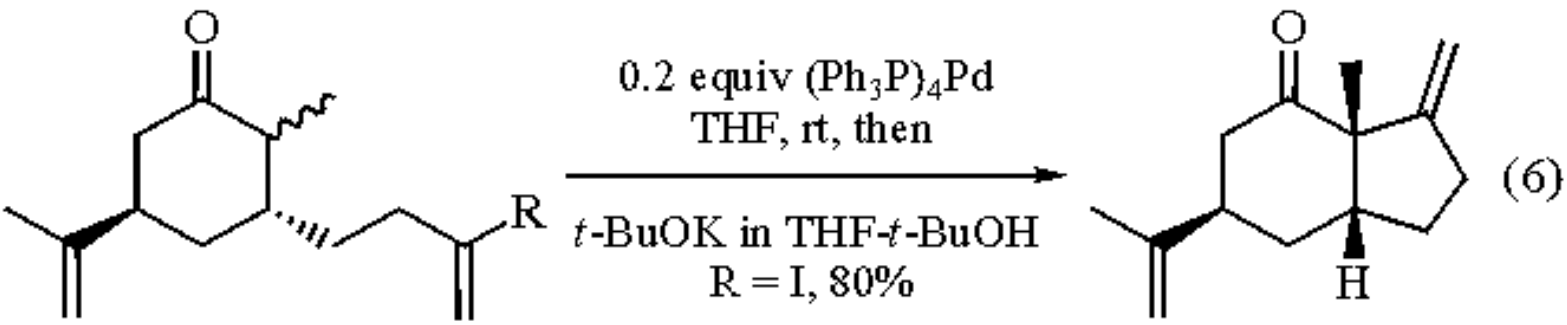

(14) R = $GeMe_3$ (88%)
(15) R = I (94%)

(16)

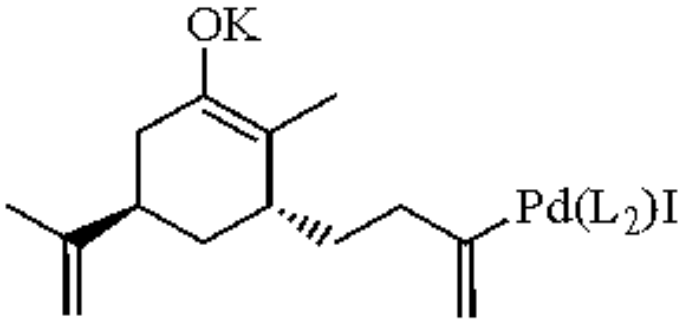

(17) L = Ph_3P

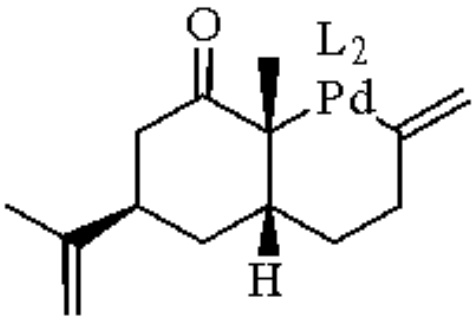

(18) L = Ph_3P

When the α,β-unsaturated ketone substrate contains an α-proton in place of an α-alkyl group, the initially formed annulation product (β,γ-unsaturated ketone) isomerizes under the basic reaction conditions to the corresponding α,β-unsaturated ketone (eq 7).[2]

4-Iodo-2-trimethylgermyl-1-butene

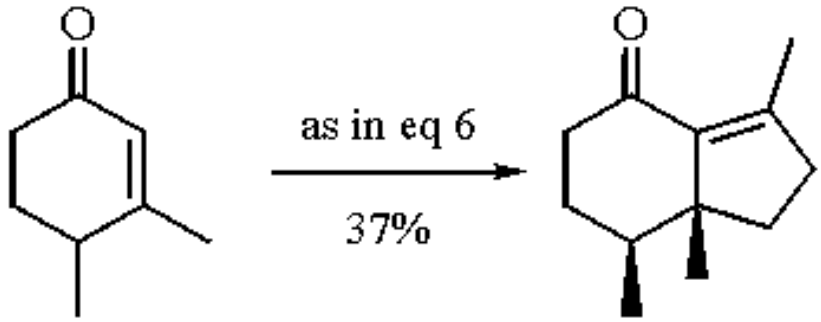

(7)

This new annulation method played an important role in a total synthesis of the tetraquinane diterpenoid crinipellin B (**19**) (eq 8).[3]

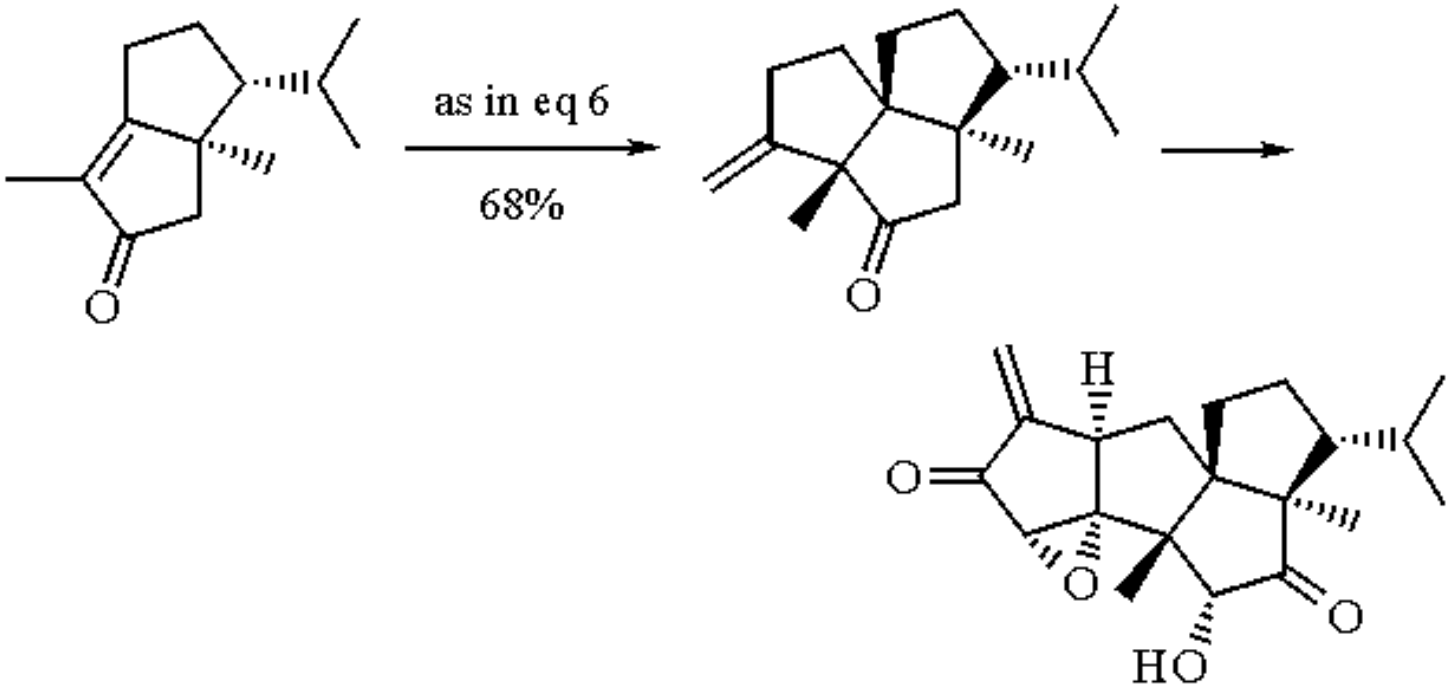

(8)

(19)

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1. Piers, E.; Marais, P. C. *CC* **1989**, 1222.
2. Piers, E.; Marais, P. C. *JOC* **1990**, *55*, 3454.
3. Piers, E.; Renaud, J. *JOC* **1993**, *58*, 11.
4. Schauss, A. G. *Biol. Trace Elem. Res.* **1991**, *29*, 267.
5. Piers, E.; Lemieux, R. *JCS(P1)* **1995**, 3.
6. (a) Piers, E.; Karunaratne, V. *T* **1989**, *45*, 1089. (b) Piers, E.; Renaud, J. *S* **1992**, 74.

Edward Piers & Christine Rogers

University of British Columbia, Vancouver, BC, Canada

Iodotrimethylsilane[1]

Me_3SiI

[16029-98-4] · C_3H_9ISi · Iodotrimethylsilane · (MW 200.11)

(a versatile reagent for the mild dealkylation of ethers, carboxylic esters, lactones, carbamates, acetals, phosphonate and phosphate esters; cleavage of epoxides, cyclopropyl ketones; conversion of vinyl phosphates to vinyl iodides; neutral nucleophilic reagent for halogen exchange reactions, carbonyl and conjugate addition reactions; use as a trimethylsilylating agent for formation of enol ethers, silyl imino esters, and *N*-silylenamines, alkyl, alkenyl and alkynyl silanes; Lewis acid catalyst for acetal formation, α-alkoxymethylation of ketones, for reactions of acetals with silyl enol ethers and allylsilanes; reducing agent for epoxides, enediones, α-ketols, sulfoxides, and sulfonyl halides; dehydrating agent for oximes)

Alternate Names: TMS-I; TMSI; trimethylsilyl iodide.

Physical Data: bp 106-109 °C; *d* 1.406 g cm^{-3}; *n*20D 1.4710; fp -31 °C.

Solubility: sol CCl_4, $CHCl_3$, CH_2Cl_2, $ClCH_2CH_2Cl$, MeCN, PhMe, hexanes; reactive with THF (ethers), alcohols, and EtOAc (esters).

Form Supplied in: clear colorless liquid, packaged in ampules, stabilized with copper; widely available.

Analysis of Reagent Purity: easily characterized by ^1H, ^{13}C, or ^{29}Si NMR spectroscopy.

Preparative Methods: although more than 20 methods have been reported[1] for the preparation of TMS-I, only a few are summarized here. ***Chlorotrimethylsilane*** undergoes halogen exchange with either ***Lithium Iodide***[2] in $CHCl_3$ or ***Sodium Iodide***[3] in MeCN, which allows in situ reagent formation (eq 1). Alternatively, ***Hexamethyldisilane*** reacts with ***Iodine*** at 25-61 °C to afford TMS-I with no byproducts (eq 2).[4]

$$\text{TMSCl} \xrightarrow[\text{or NaI, MeCN}]{\text{LiI, CHCl}_3} \text{TMSI} + \text{LiCl or NaCl} \qquad (1)$$

$$\text{TMS-TMS} + \text{I}_2 \xrightarrow{25\text{-}61\ ^\circ\text{C}} \text{TMSI} \qquad (2)$$

Several other methods for in situ generation of the reagent have been described.[5,6] It should be noted, however, that the reactivity of in situ generated reagent appears to depend upon the method of preparation.

Purification: by distillation from copper powder

Handling, Storage, and Precautions: extremely sensitive to light, air, and moisture, it fumes in air due to hydrolysis (HI), and becomes discolored upon prolonged storage due to generation of I_2. It is flammable and should be stored under N_2 with a small piece of copper wire. It should be handled in a well ventilated fume hood and contact with eyes and skin should be avoided.

Use as a Nucleophilic Reagent in Bond Cleavage Reactions.

Ether Cleavage.[5,7]

The first broad use of TMS-I was for dealkylation reactions of a wide variety of compounds containing oxygen-carbon bonds, as developed independently by the groups of Jung and Olah. Simple ethers initially afford the trimethylsilyl ether and the alkyl iodide, with further reaction giving the two iodides (eq 3).[7,8] This process occurs under neutral conditions, and is generally very efficient as long as precautions to avoid hydrolysis by adventitious water are taken. Since the silyl ether can be quantitatively hydrolyzed to the alcohol, this reagent permits the use of simple ethers, e.g. methyl ethers, as protective groups in synthesis. The rate of cleavage of alkyl groups is: tertiary &AApprox; benzylic &AApprox; allylic >> methyl > secondary > primary. Benzyl and *t*-butyl ethers are cleaved nearly instantaneously at low temperature with TMS-I. Cyclic ethers afford the iodo silyl ethers and then the diiodide, e.g. THF gives 4-iodobutyl silyl ether and then 1,4-diiodobutane in excellent yield.[7,8] Alcohols and silyl ethers are rapidly converted into the iodides as well.[8a,9] Alkynic ethers produce the trimethylsilylketene via dealkylative rearrangement.[4b] Phenolic ethers afford the phenols after workup.[5,7,10] In general, ethers are cleaved faster than esters. Selective cleavage of methyl aryl ethers in the presence of other oxygenated functionality has also been accomplished in quinoline.[11] γ-Alkoxyl enones undergo deoxygenation with excess TMS-I (2 equiv), with the first step being conjugate addition of TMS-I.[12]

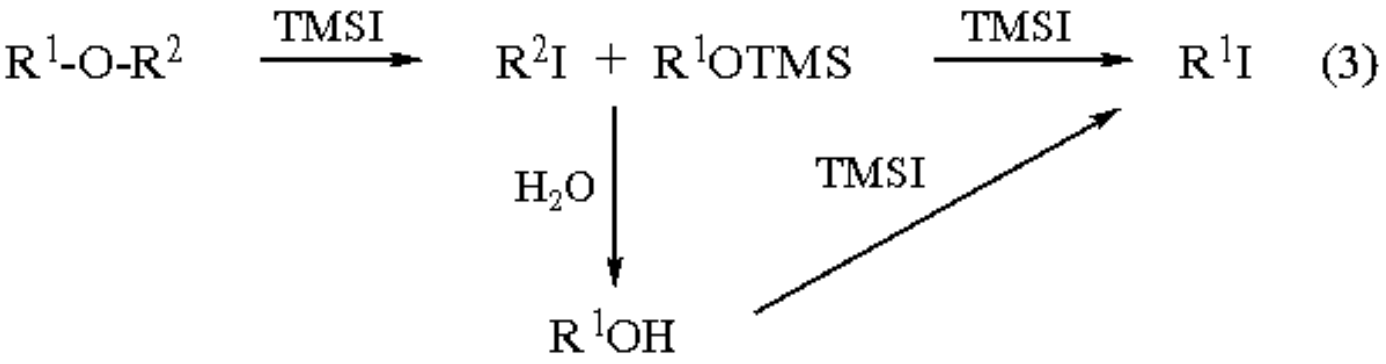

Cleavage of Epoxides.

Reaction of epoxides with 1 equiv of TMS-I gives the vicinal silyloxy iodide.[8e] With 2 equiv of TMS-I, however, epoxides are deoxygenated to afford the corresponding alkene (eq 4).[13a,b] However, allylic alcohols are efficiently prepared by reaction of the intermediate iodosilane with base.[13c,d] Furthermore, acyclic 2-ene-1,4-diols react with TMS-I

to undergo dehydration, affording the corresponding diene.[13e]

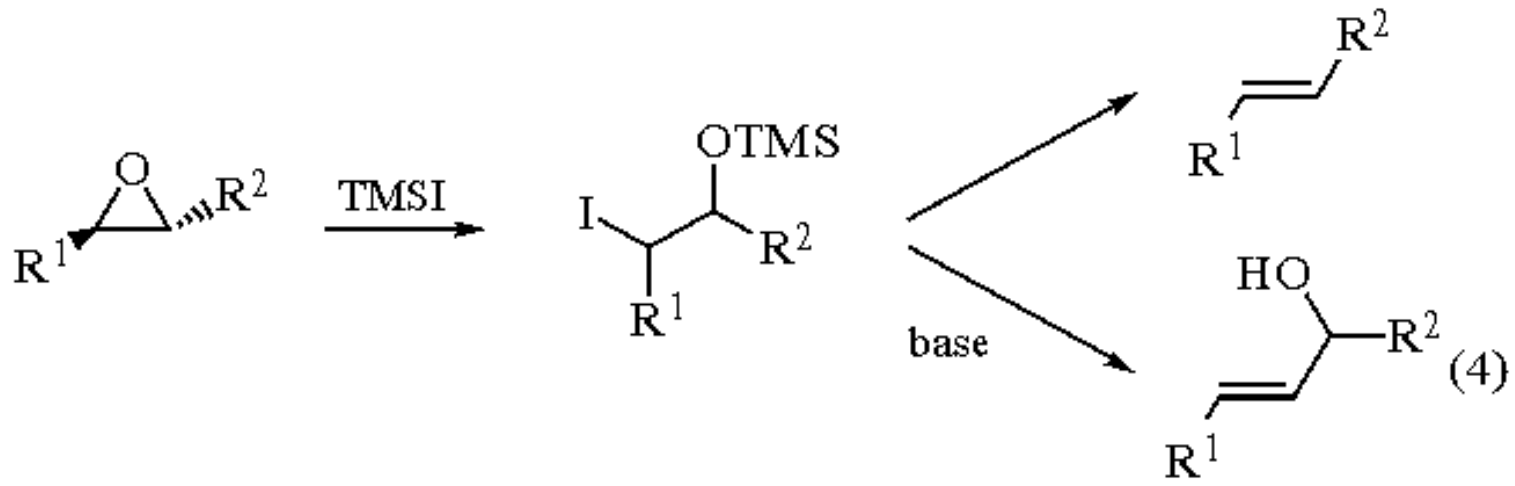

Ester Dealkylation.[14]

Among the widest uses for TMS-I involves the mild cleavage of carboxylic esters under neutral conditions. The ester is treated with TMS-I to form an initial oxonium intermediate which suffers attack by iodide (eq 5). The trimethylsilyl ester is cleaved with H_2O during workup. Although the reaction is general and efficient, it is possible to accomplish selective cleavage according to the reactivity trend: benzyl, *t*-butyl > methyl, ethyl, *i*-propyl. Neutral transesterification is also possible via the silyl ester intermediate.[15] Aryl esters are not cleaved by TMS-I, however, since the mechanism involves displacement of R^2 by I^-. Upon prolonged exposure (75 °C, 3 d) of simple esters to excess TMS-I (2.5 equiv), the corresponding acid iodides are formed.[14b,16] β-Keto esters undergo decarboalkoxylation when treated with TMS-I.[17] An interesting rearrangement reaction provides α-methylene lactones from 1-(dimethylaminomethyl)cyclopropanecarboxylates (eq 6).[18]

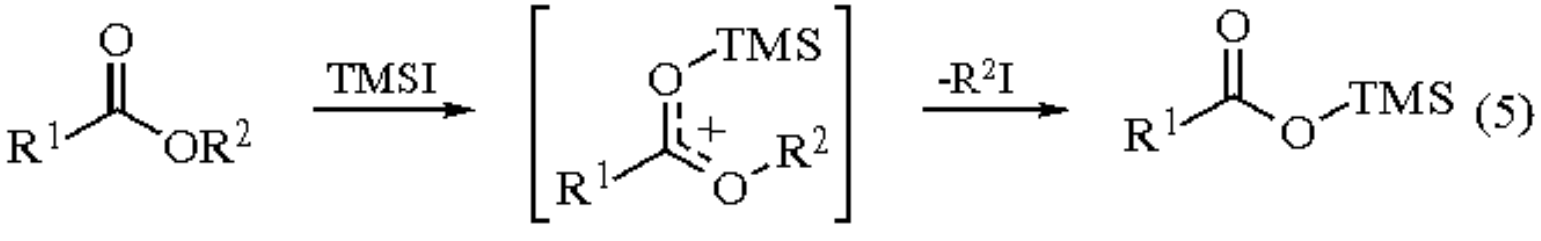

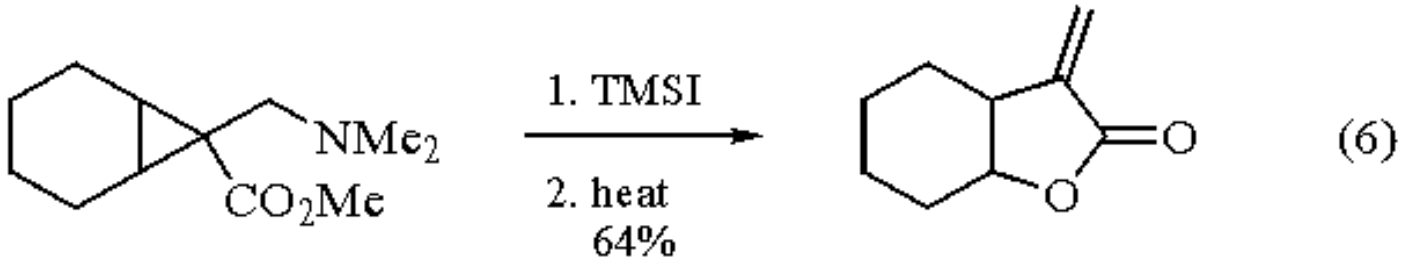

Lactone Cleavage.[14,19]

Analogous to esters, lactones are also efficiently cleaved with TMS-I to provide o-iodocarboxylic acids, which may be

further functionalized to afford bifunctional building blocks for organic synthesis (eq 7). Diketene reacts with TMS-I to provide a new reagent for acetoacylation.[20]

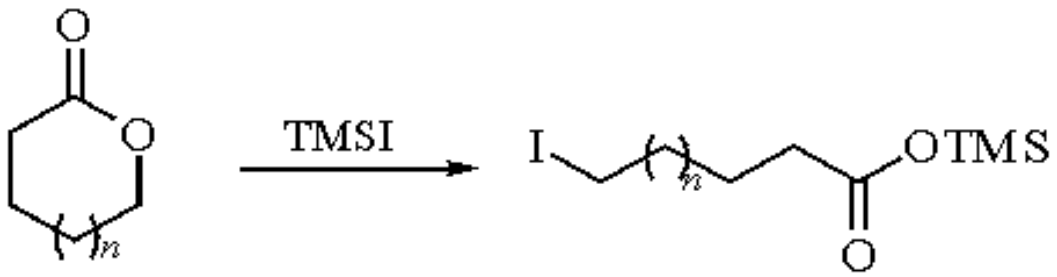

(7)

Cleavage of Carbamates.[21]

Since strongly acidic conditions are typically required for the deprotection of carbamates, use of TMS-I provides a very mild alternative. Benzyl and *t*-butyl carbamates are readily cleaved at rt,[22] whereas complete cleavage of methyl or ethyl carbamates may require higher temperatures (reflux). The intermediate silyl carbamate is decomposed by the addition of methanol or water (eq 8). Since amides are stable to TMS-I-promoted hydrolysis,[7a] this procedure can be used to deprotect carbamates of amino acids and peptides.[21d]

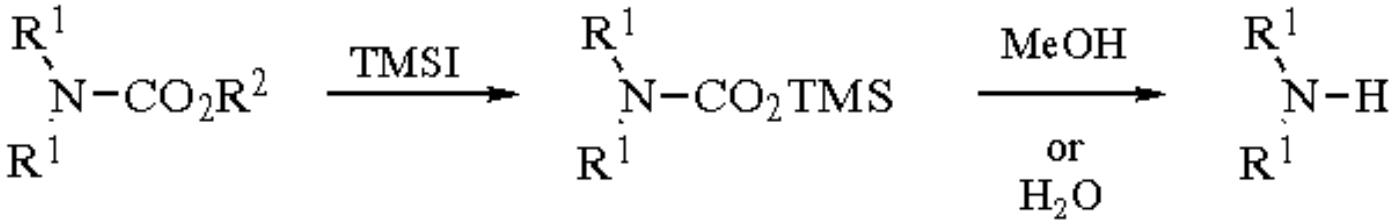

(8)

A recent example used TMS-I to deprotect three different protecting groups (carbamate, ester, and orthoester) in the same molecule in excellent yield (eq 9).[23]

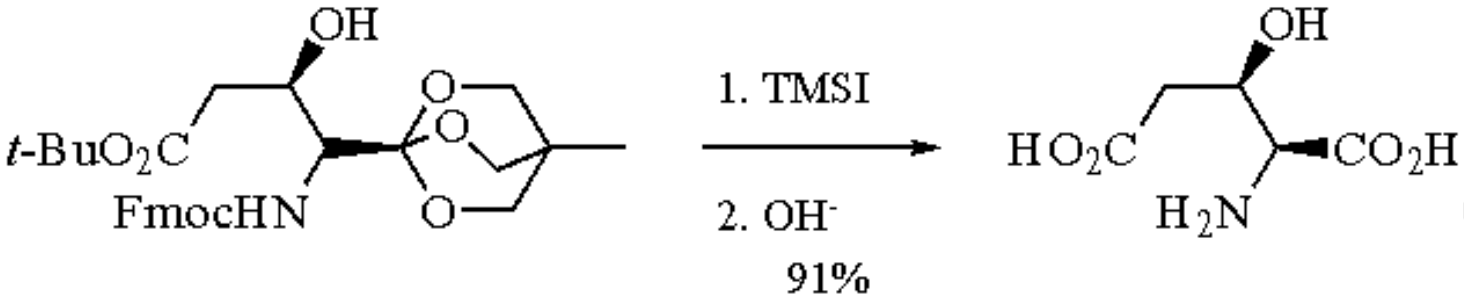

(9)

Cleavage of Acetals.[24]

Acetals can be cleaved in analogy to ethers, providing a newly functionalized product (eq 10), or simply the parent ketone (eq 11). Glycals have also been converted to the iodopyrans with TMS-I,[25] and glycosidation reactions have been conducted with this reagent.[26]

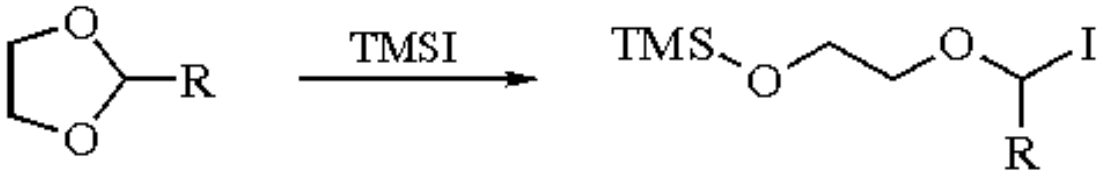

(10)

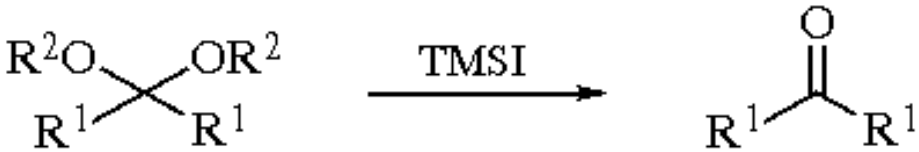

(11)

Orthoesters are converted into esters with TMS-I. The dimethyl acetal of formaldehyde, methylal, affords iodomethyl methyl ether in good yield (eq 12)[27a] (in the presence of alcohols, MOM ethers are formed).[27b] α-Acyloxy ethers also furnish the iodo ethers,[28] e.g. the protected β-acetyl ribofuranoside gave the α-iodide which was used in the synthesis of various nucleosides in good yield (eq 13).[28b] Aminals are similarly converted into immonium salts, e.g. Eschenmoser's reagent, ***Dimethyl(methylene)ammonium Iodide***, in good yield.[29]

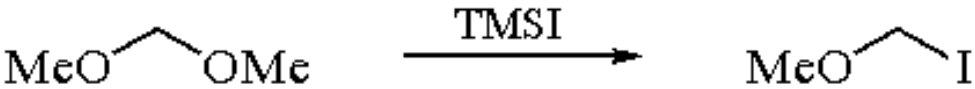

(12)

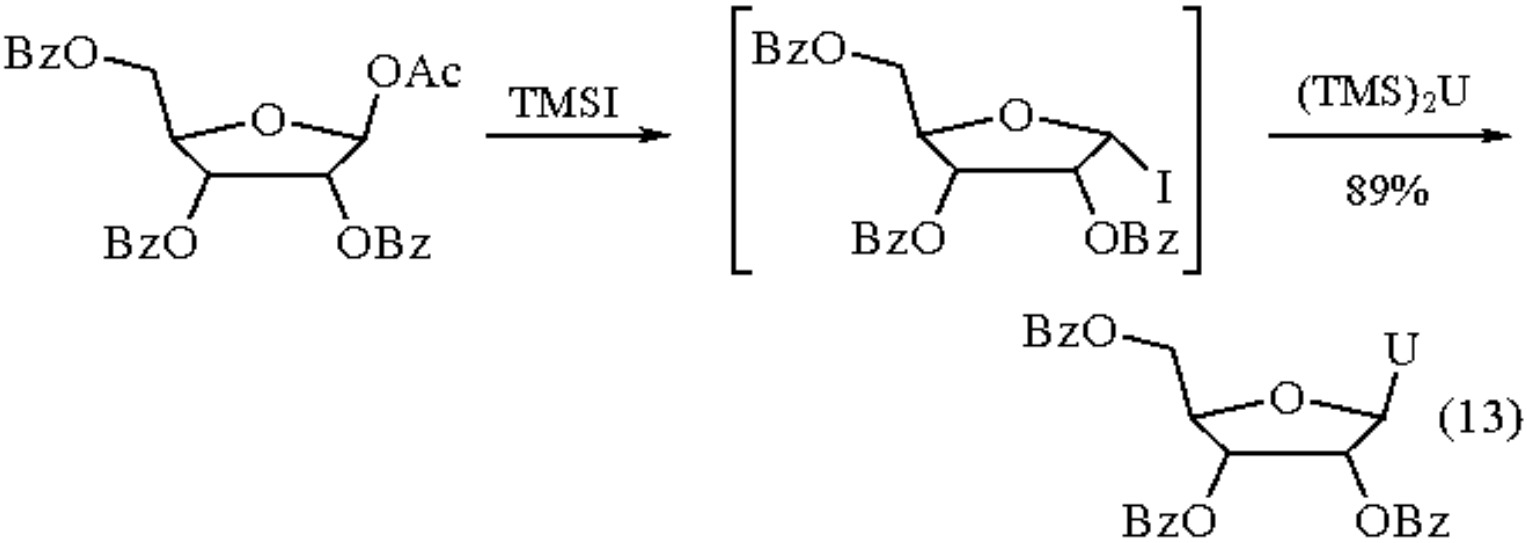

(13)

Cleavage of Phosphonate and Phosphate Esters.[30]

Phosphonate and phosphate esters are cleaved even more readily with TMS-I than carboxylic esters. The reaction of phosphonate esters proceeds via the silyl ester, which is subsequently hydrolyzed with MeOH or H_2O (eq 14).

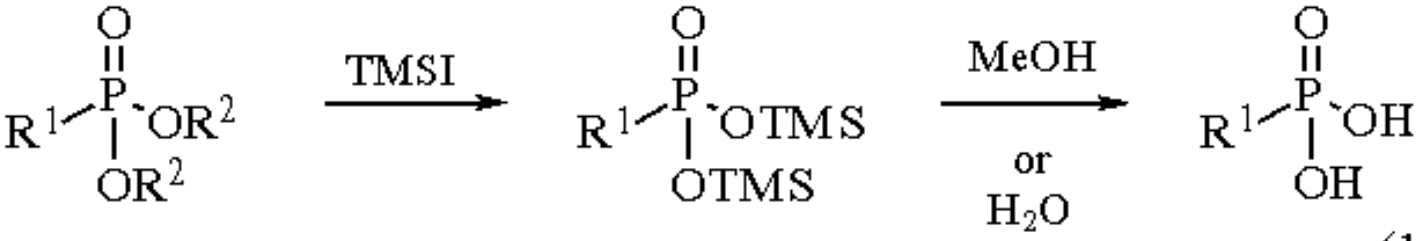

(14)

Conversion of Vinyl Phosphates to Vinyl Iodides.[31]

Ketones can be converted to the corresponding vinyl phosphates which react with TMS-I (3 equiv) at rt to afford vinyl iodides (eq 15).

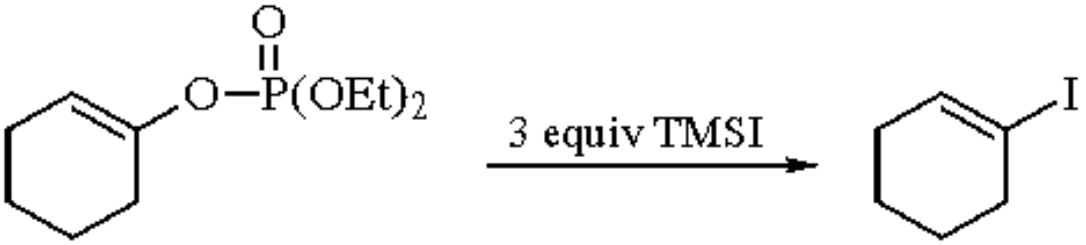

(15)

Cleavage of Cyclopropyl Ketones.[32]

Cyclopropyl ketones undergo ring opening with TMS-I, via the silyl enol ether (eq 16). Cyclobutanones react analogously under these conditions.[33]

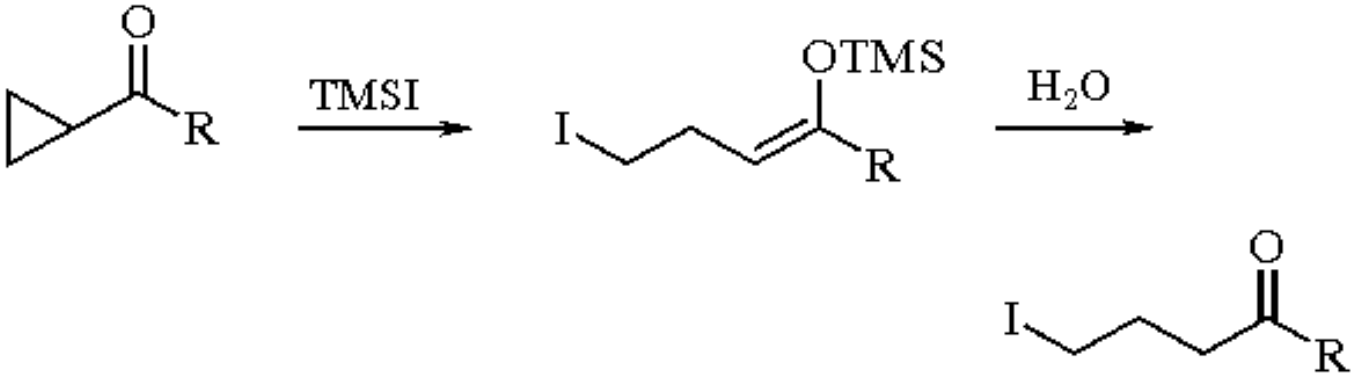

(16)

Halogen Exchange Reactions.[34]

Halogen exchange can be accomplished with reactive alkyl halides, such as ***Benzyl Chloride*** or ***Benzyl Bromide***, and even with certain alkyl fluorides, by using TMS-I in the presence of $(n\text{-Bu})_4NCl$ as catalyst (eq 17).

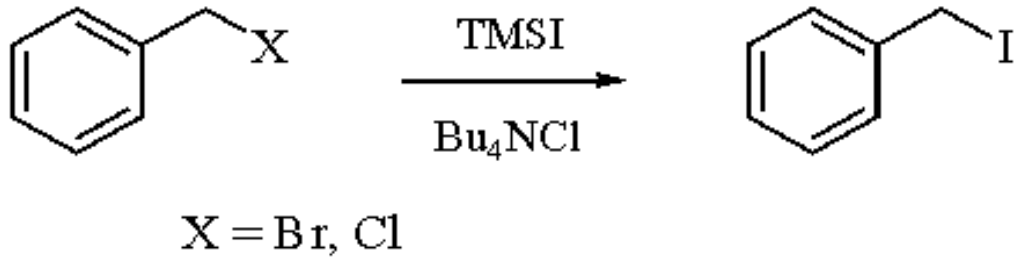

(17)

Use of TMS-I in Nucleophilic Addition Reactions.

Carbonyl Addition Reactions.[35]

α-Iodo trimethylsilyl ethers are produced in the reaction of aldehydes and TMS-I (eq 18). These compounds may react further to provide the diiodo derivative or may be used in subsequent synthesis.

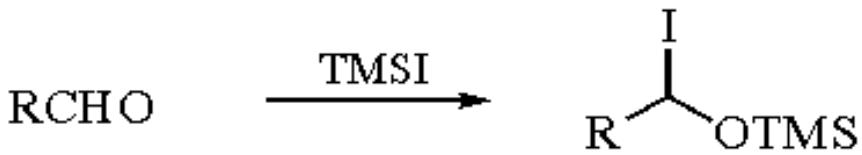

(18)

An example of a reaction of an iodohydrin silyl ether with a cuprate reagent is summarized in eq 19.[36] An interesting reaction of TMS-I with phenylacetaldehydes gives a quantitative yield of the oxygen-bridged dibenzocyclooctadiene, which was then converted in a few steps to the natural product isopavine (eq 20).[35,37]

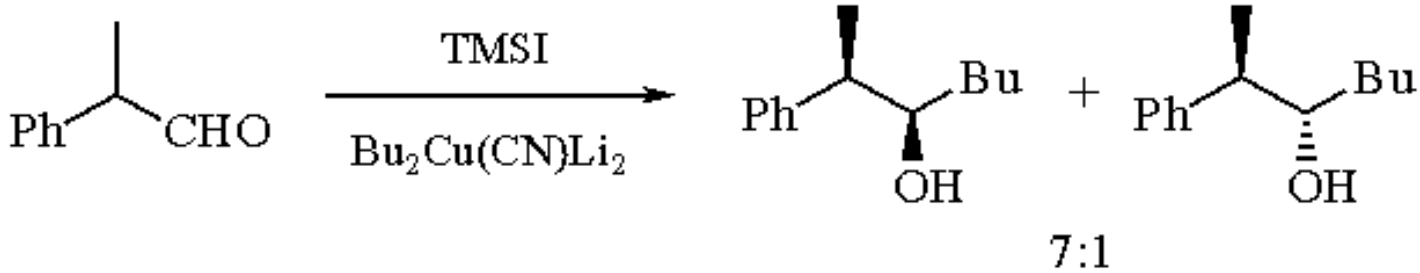

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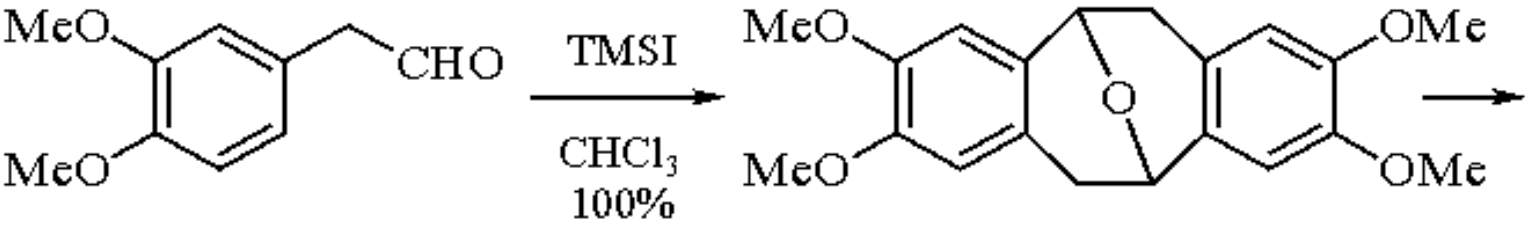

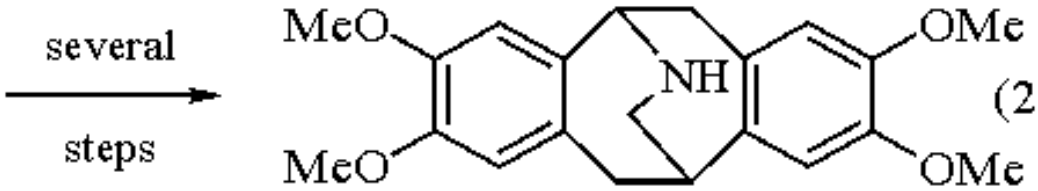

(20)

β-Iodo ketones have been produced from reactions of TMS-I and ketones with α-hydrogens.[38] This reaction presumably involves a TMS-I catalyzed aldol reaction followed by 1,4-addition of iodide.

Conjugate Addition Reactions.[39]

α,β-Unsaturated ketones undergo conjugate addition with TMS-I to afford the β-iodo adducts in high yield (eq 21). The reaction also works well with the corresponding alkynic substrate.[40]

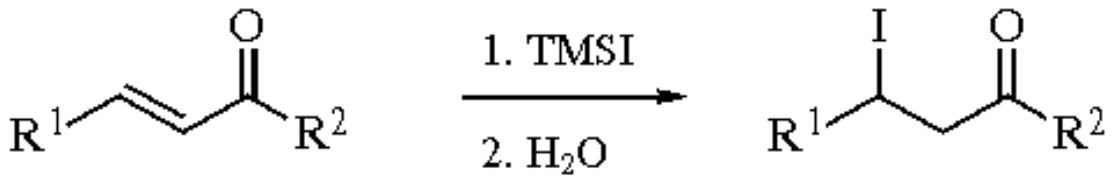

(21)

TMS-I has also been extensively utilized in conjunction with organocopper reagents to effect highly stereoselective conjugate additions of alkyl nucleophiles.[41]

Use of TMS-I as a Silylating Agent.

Formation of Silyl Enol Ethers.[42]

TMS-I in combination with ***Triethylamine*** is a reactive silylating reagent for the formation of silyl enol ethers from ketones (eq 22). TMS-I with ***Hexamethyldisilazane*** has also been used as an effective silylation agent, affording the thermodynamic silyl enol ethers. For example, 2-methylcyclohexanone gives a 90:10 mixture in favor of the tetrasubstituted enol ether product.[42a] The reaction of TMS-I with 1,3-diketones is a convenient route to 1,3-bis(trimethylsiloxy)-1,3-dienes.[42c]

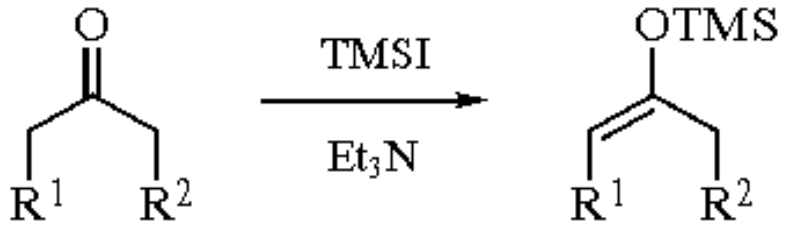

(22)

In an analogous process, TMS-I reacts with lactams in the presence of Et_3N to yield silyl imino ethers (eq 23).[43a]

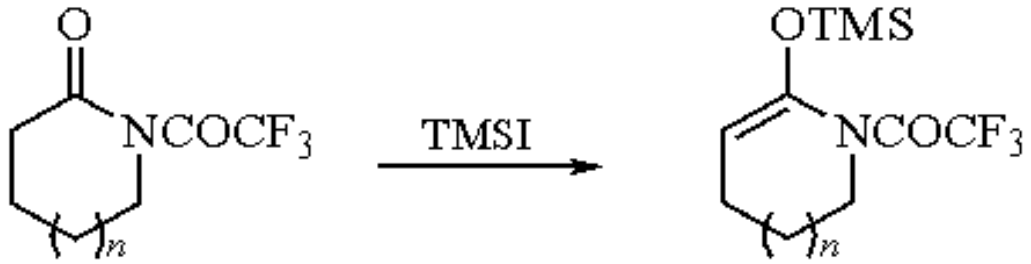

(23)

Halogenation of Lactams.[43b]

Selective and high yielding iodination and bromination of lactams occurs with ***Iodine*** or ***Bromine***, respectively, in the presence of TMS-I and a tertiary amine base (eq 24). The proposed reaction mechanism involves intermediacy of the silyl imino ether.

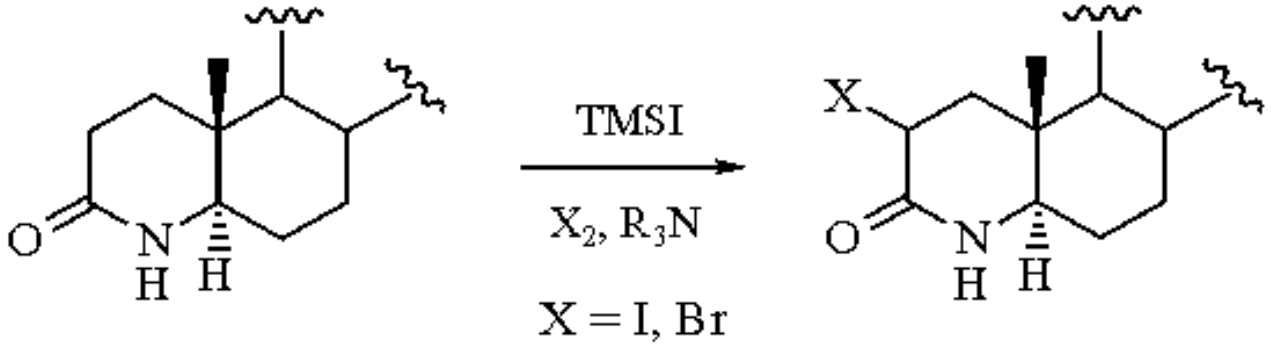

(24)

Reaction with Carbanions.[44]

TMS-I has seen limited use in the silylation of carbanions, with different regioselectivity compared to other silylating reagents in the example provided in eq 25.

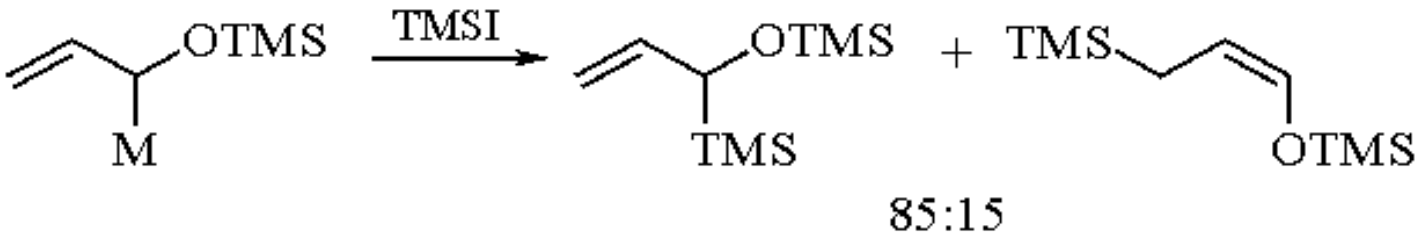

(25)

Silylation of Alkynes and Alkenes.[45]

A Heck-type reaction of TMS-I with alkenes in the presence of Pd^0 and Et_3N affords alkenyltrimethylsilanes (eq 26).

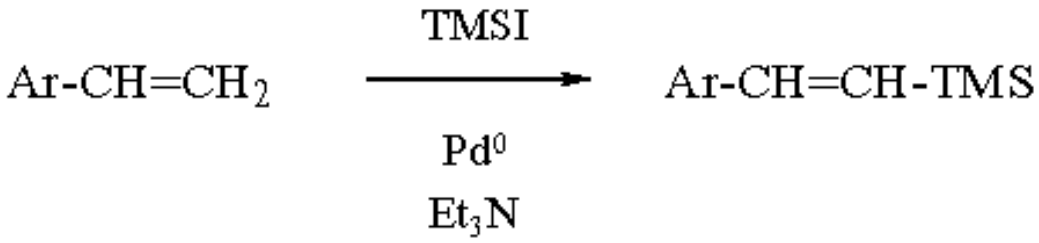

(26)

Oxidative addition of TMS-I to alkynes can also be accomplished with a three-component coupling reaction to provide the enyne product (eq 27).

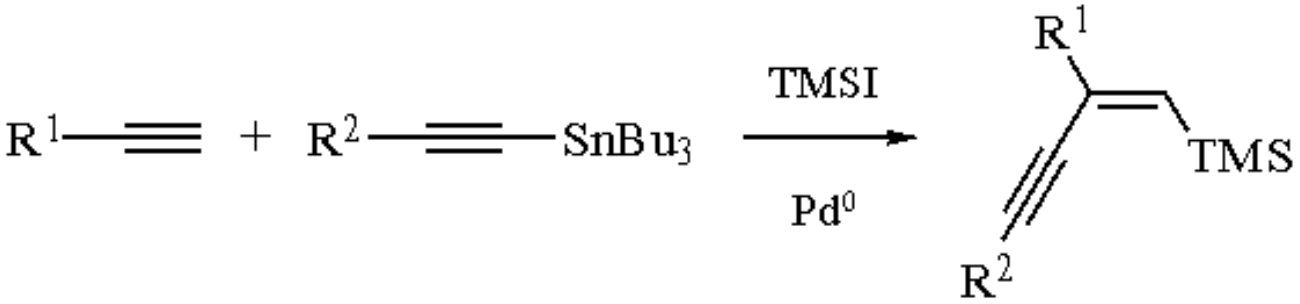

(27)

Use of TMS-I as a Lewis Acid.

Acetalization Catalyst.[46]

TMS-I used in conjunction with $(MeO)_4Si$ is an effective catalyst for acetal formation (eq 28).

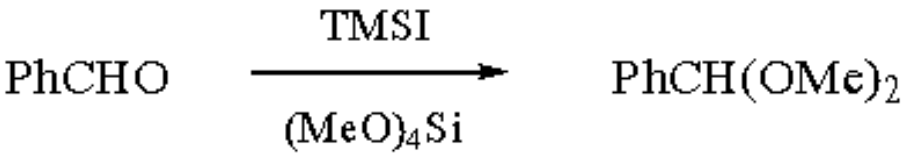

(28)

Catalyst for α-Alkoxymethylation of Ketones.

Silyl enol ethers react with α-chloro ethers in the presence of TMS-I to afford α-alkoxymethyl ketones (eq 29).[47]

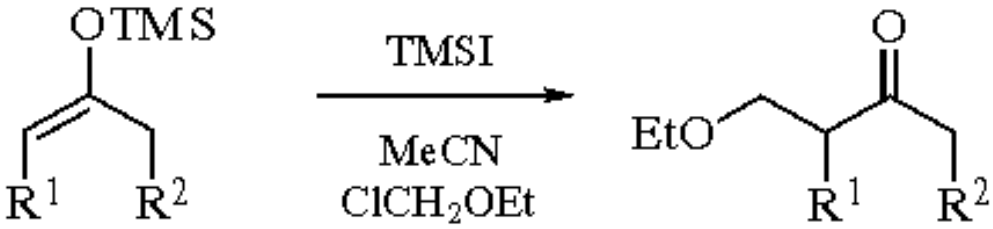

(29)

Catalyst for Reactions of Acetals with Silyl Enol Ethers and Allylsilanes.

TMS-I catalyzes the condensation of silyl enol ethers with various acetals (eq 30)[48] and imines,[49] and of allylsilanes with acetals.[50]

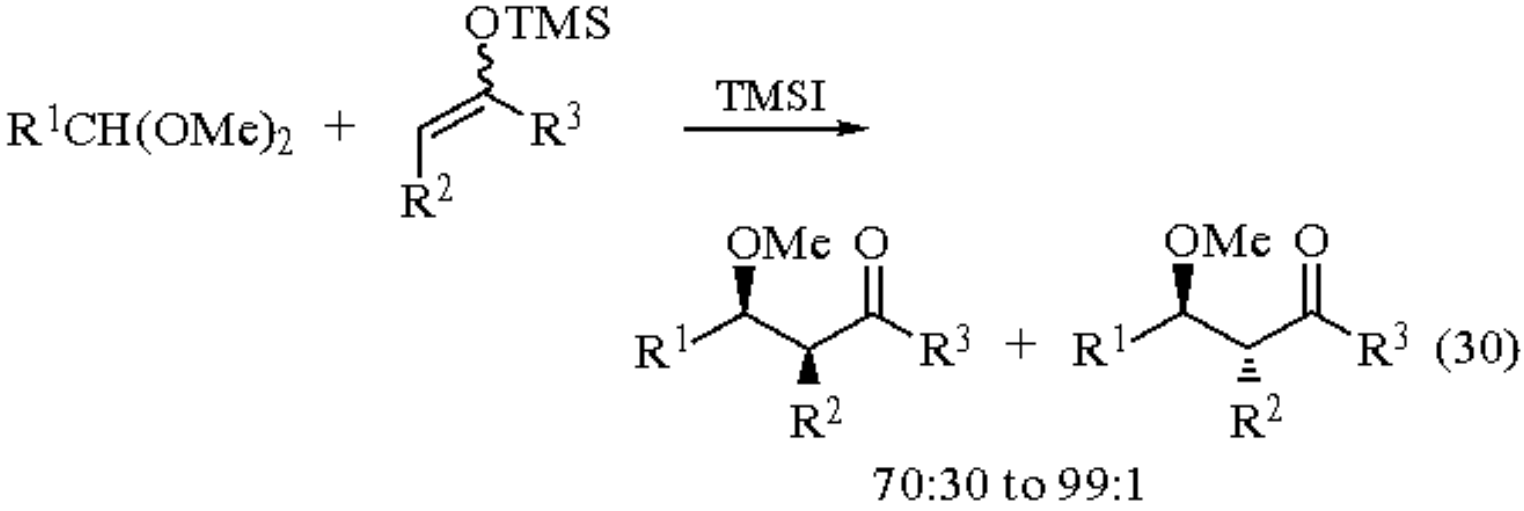

Use of TMS-I as a Reducing Agent.

TMS-I reduces enediones to 1,4-diketones,[51] while both epoxides and 1,2-diols are reduced to the alkenes.[13a,b,52] The Diels-Alder products of benzynes and furans are converted in high yield to the corresponding naphthalene (or higher aromatic derivative) with TMS-I (eq 31).[53]

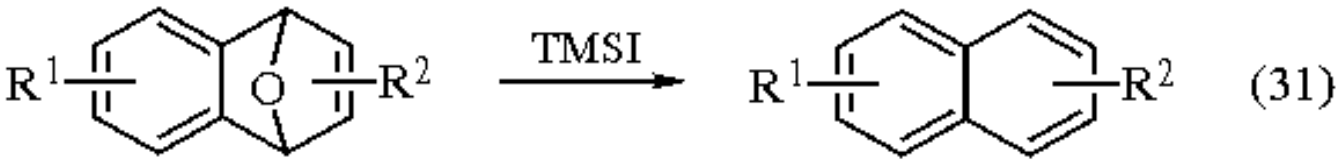

Styrenes and benzylic alcohols are reduced to the alkanes with TMS-I (presumably via formation of HI).[54] Ketones produce the symmetrical ethers when treated with trimethylsilane as a reducing agent in the presence of catalytic TMS-I.[55]

Reduction of α-Ketols.[56,57]

Carbonyl compounds containing α-hydroxy, α-acetoxy, or α-halo groups react with excess TMS-I to give the parent ketone. α-Hydroxy ketone reductions proceed via the iodide, which is then reduced with iodide ion to form the parent ketone (eq 32).

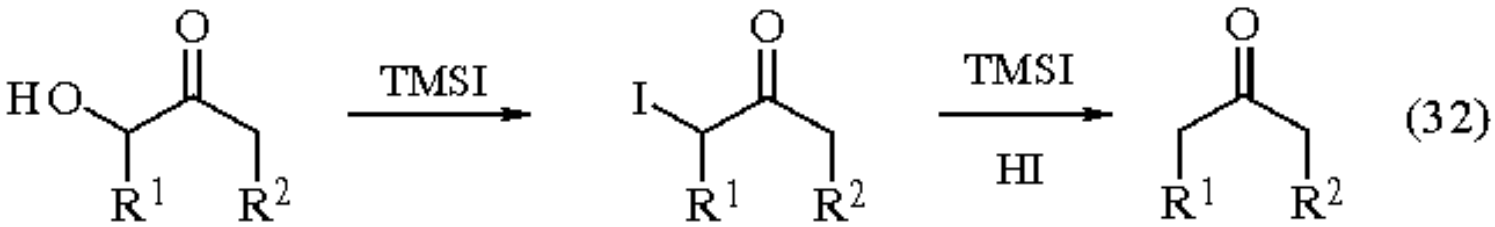

Sulfoxide Deoxygenation.[58]

The reduction of sulfoxides occurs under very mild conditions with TMS-I to afford the corresponding sulfide and iodine (eq 33). Addition of I_2 to the reaction mixture accelerates the second step. The deoxygenation occurs faster in pyridine solution than the reactions with a methyl ester or alcohol.[59]

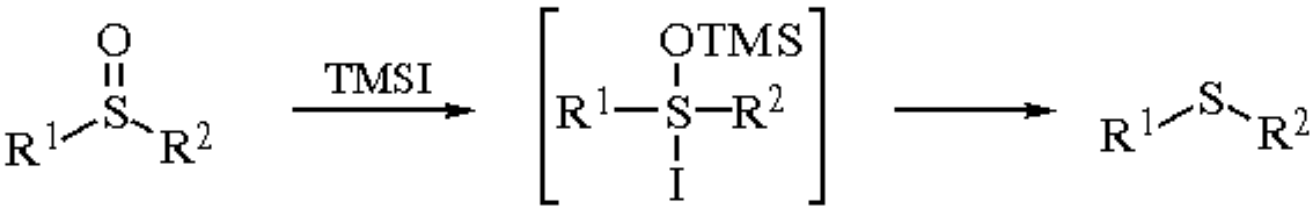

(33)

Pummerer reactions of sulfoxides can be accomplished in the presence of TMS-I and an amine base, leading to vinyl sulfides.[60] An efficient synthesis of dithioles was accomplished with TMS-I and Hünig's base (***Diisopropylethylamine***) (eq 34).[61]

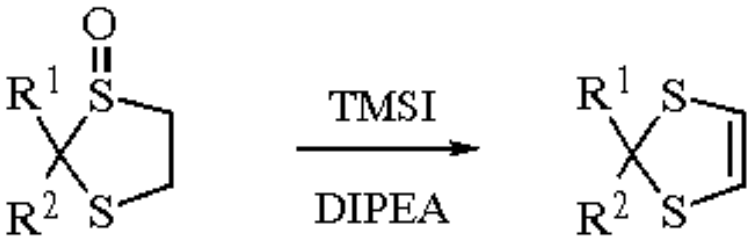

(34)

Reaction with Sulfonyl Halides.[62]

Arylsulfonyl halides undergo reductive dimerization to form the corresponding disulfides (eq 35). Alkylsulfonyl halides, however, undergo this process under somewhat more vigorous conditions. Although sulfones generally do not react with TMS-I, certain cyclic sulfones are cleaved in a manner analogous to lactones.[63]

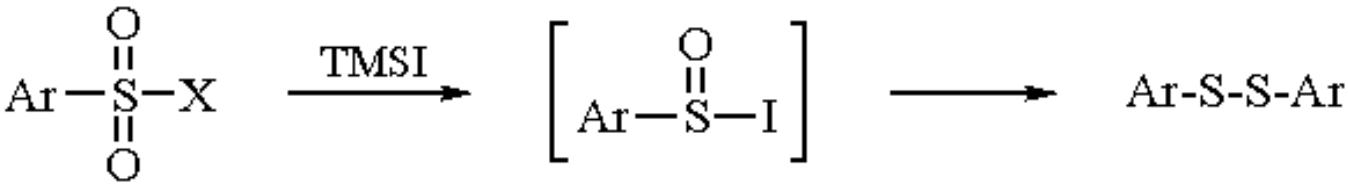

(35)

Other Reactions of TMS-I.

Reaction with Phosphine Oxides.[64]

Phosphine oxides react with TMS-I to form stable adducts (eq 36). These *O*-silylated products can undergo further thermolytic reactions such as alkyl group cleavage.

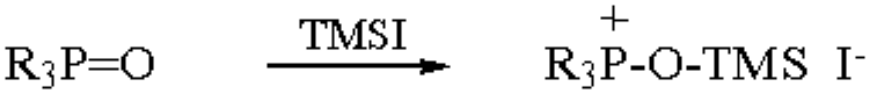

(36)

Chlorophosphines undergo halogen exchange reactions with TMS-I.[65]

Reaction with Imines.

Imines react with TMS-I to form *N*-silylenamines, in a process analogous to the formation of silyl enol ethers from ketones.[66]

Reaction with Oximes.[67]

Oximes are activated for dehydration (aldoximes, with hexamethylsilazane) or Beckmann rearrangement (ketoximes) with TMS-I (eq 37).

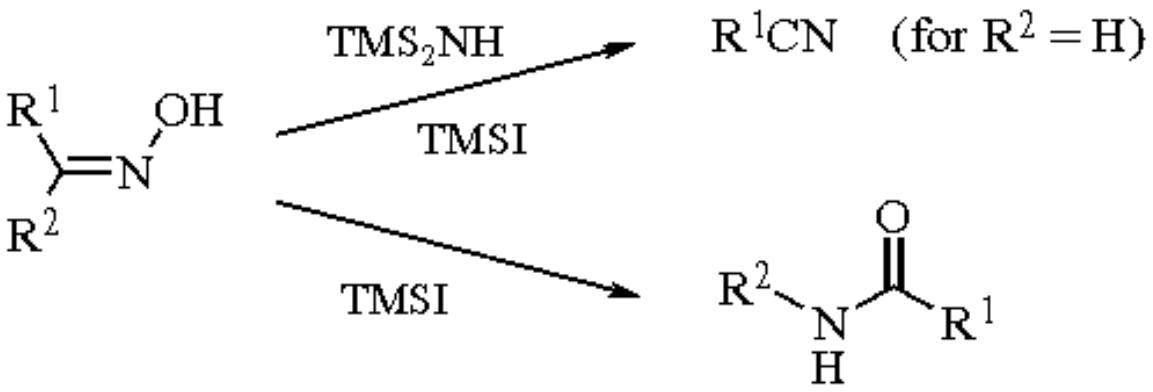

Reactions with Nitro and Nitroso Compounds.[68]

Primary nitro derivatives react with TMS-I to form the oximino intermediate via deoxygenation, which then undergoes dehydration as discussed for the oximes (eq 38). Secondary nitro compounds afford the silyl oxime ethers, and tertiary nitro compounds afford the corresponding iodide. Nitroalkenes, however, react with TMS-I at 0 °C to afford the ketone as the major product (eq 39).[69]

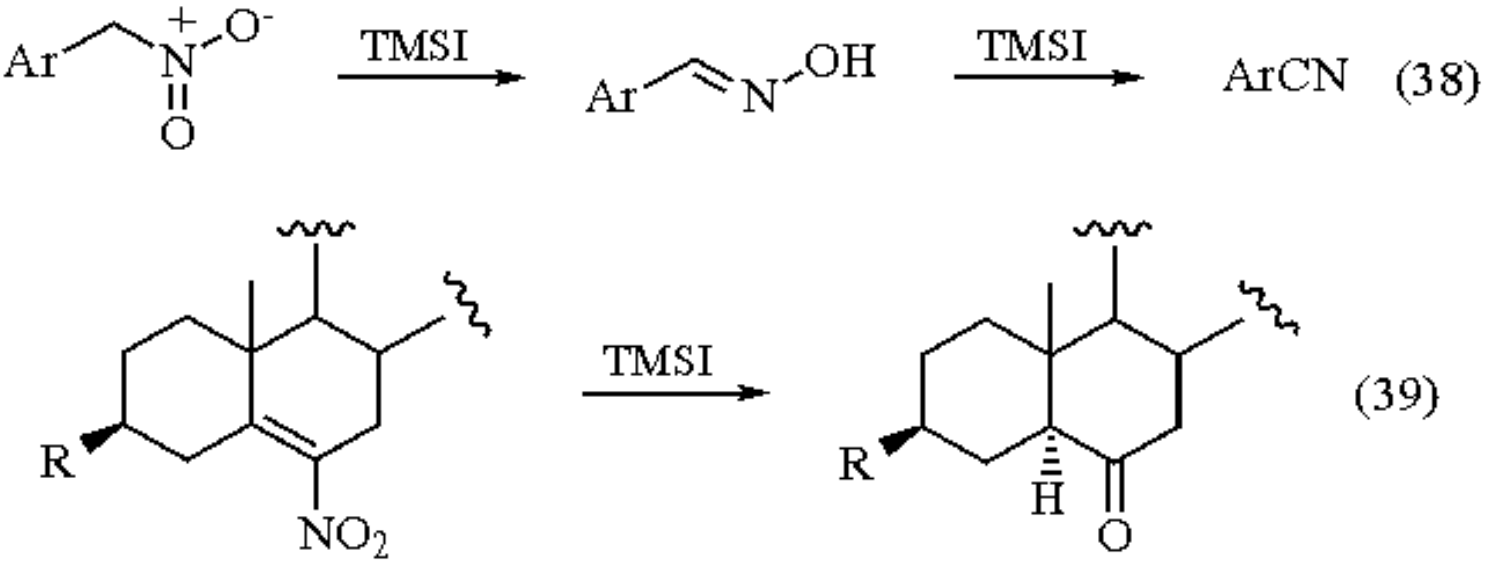

An interesting analogy to this dehydration process is found in the reductive fragmentation of a bromoisoxazoline with

TMS-I, which yields the nitrile (eq 40).[70]

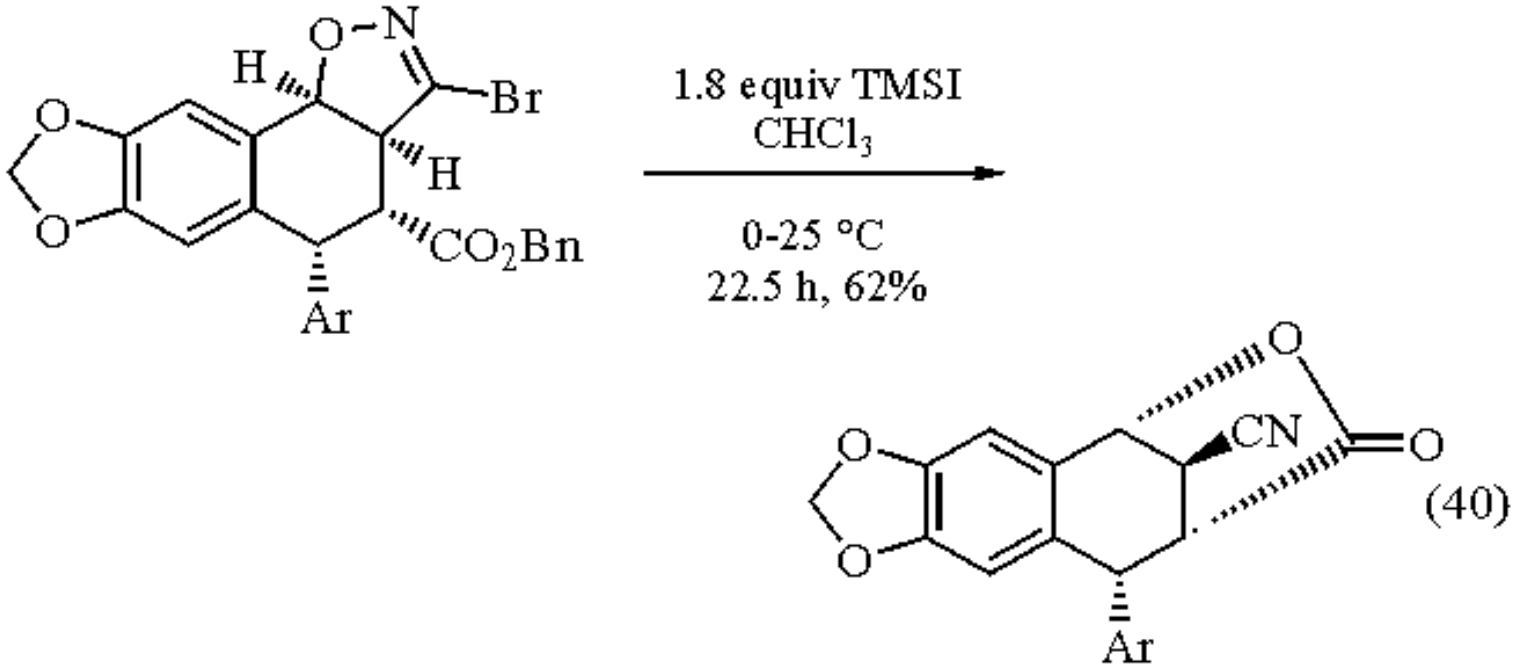

Rearrangement Reactions.

An interesting rearrangement occurs on treatment of a β-alkoxy ketone with TMS-I which effects dealkylation and retro-aldol reaction to give the eight-membered diketone after reductive dehalogenation (eq 41).[71] Tertiary allylic silyl ethers α to epoxides undergo a stereocontrolled rearrangement to give the β-hydroxy ketones on treatment with catalytic TMS-I (eq 42).[72]

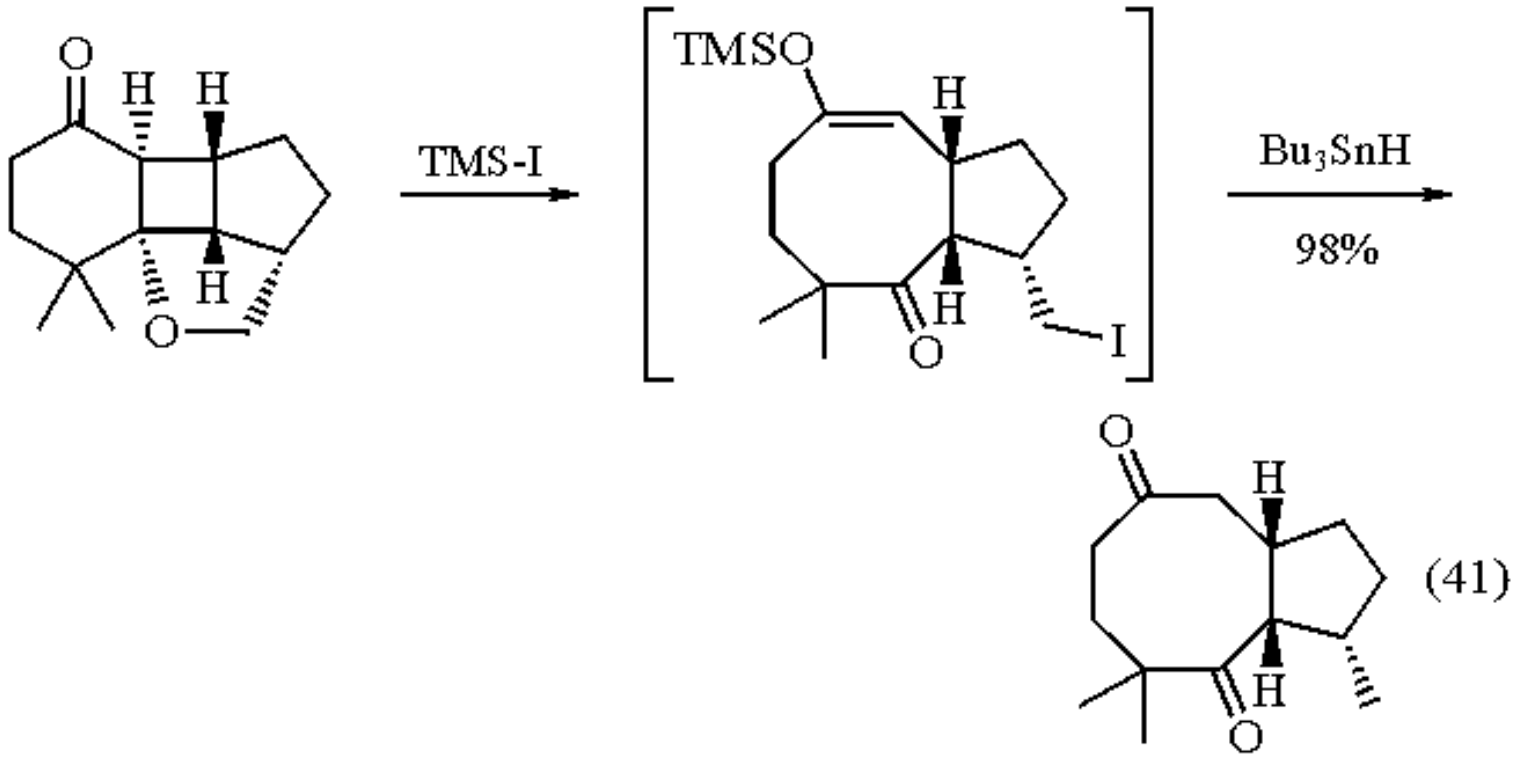

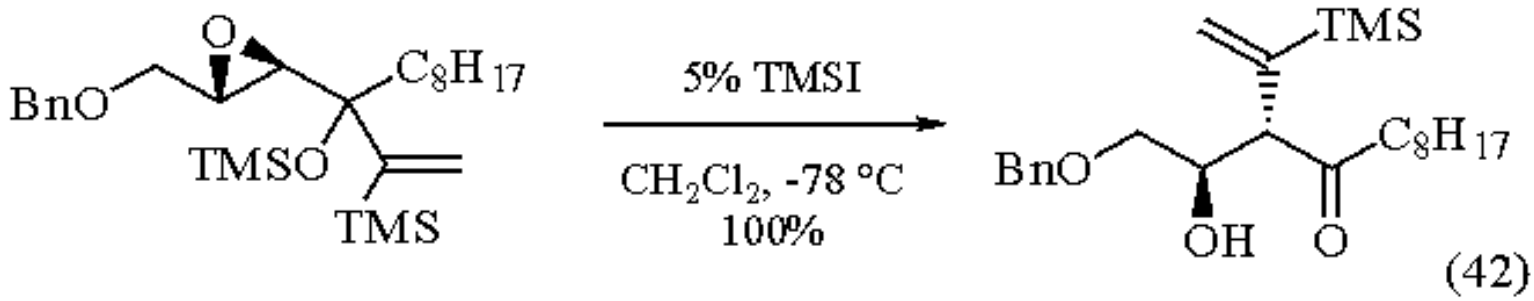

Related Reagents.

Bromotrimethylsilane; ***Chlorotrimethylsilane***; ***Trimethylsilyl Trifluoromethanesulfonate***.

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(*E*)-1-Iodo-3-trimethylsilyl-2-butene[1]

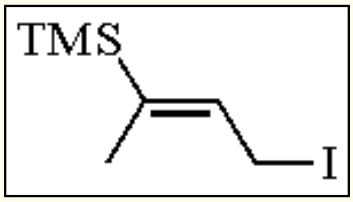

[52815-00-6] · $C_7H_{15}ISi$ · 1-Iodo-3-trimethylsilyl-2-butene · (MW 254.21) (*E*)

[52685-51-5]

(annulation reagent; alkylative equivalent of 3-buten-2-one; 3-ketobutyl synthon)

Alternate Name: (3-iodo-1-methyl-1-propenyl)trimethylsilane.

Physical Data: bp 60 °C/20 mmHg.

Solubility: freely sol organic solvents.

Form Supplied in: not commercially available.

Preparative Methods: the first reported preparation[2] of this reagent lacked full experimental details. The preparation given (eq 1) is a compilation of the work of several groups; the various steps have been selected to give optimum yields. 2-Propyn-1-ol is converted[3] into its 3-(trimethylsilyl) derivative (**1**), which is then reduced[4] using ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al). The intermediate vinylaluminum is reacted with ***Iodine*** to produce the (*Z*)-iodoalkene (**2**). Treatment of this with ***Lithium Dimethylcuprate*** gives the allylic alcohol (**3**);[5] transformation into ***(E)-(3-Chloro-1-methyl-1-propenyl)trimethylsilane*** (**4**) followed by halogen exchange[6] with ***Sodium Iodide*** then gives reagent (**5**).

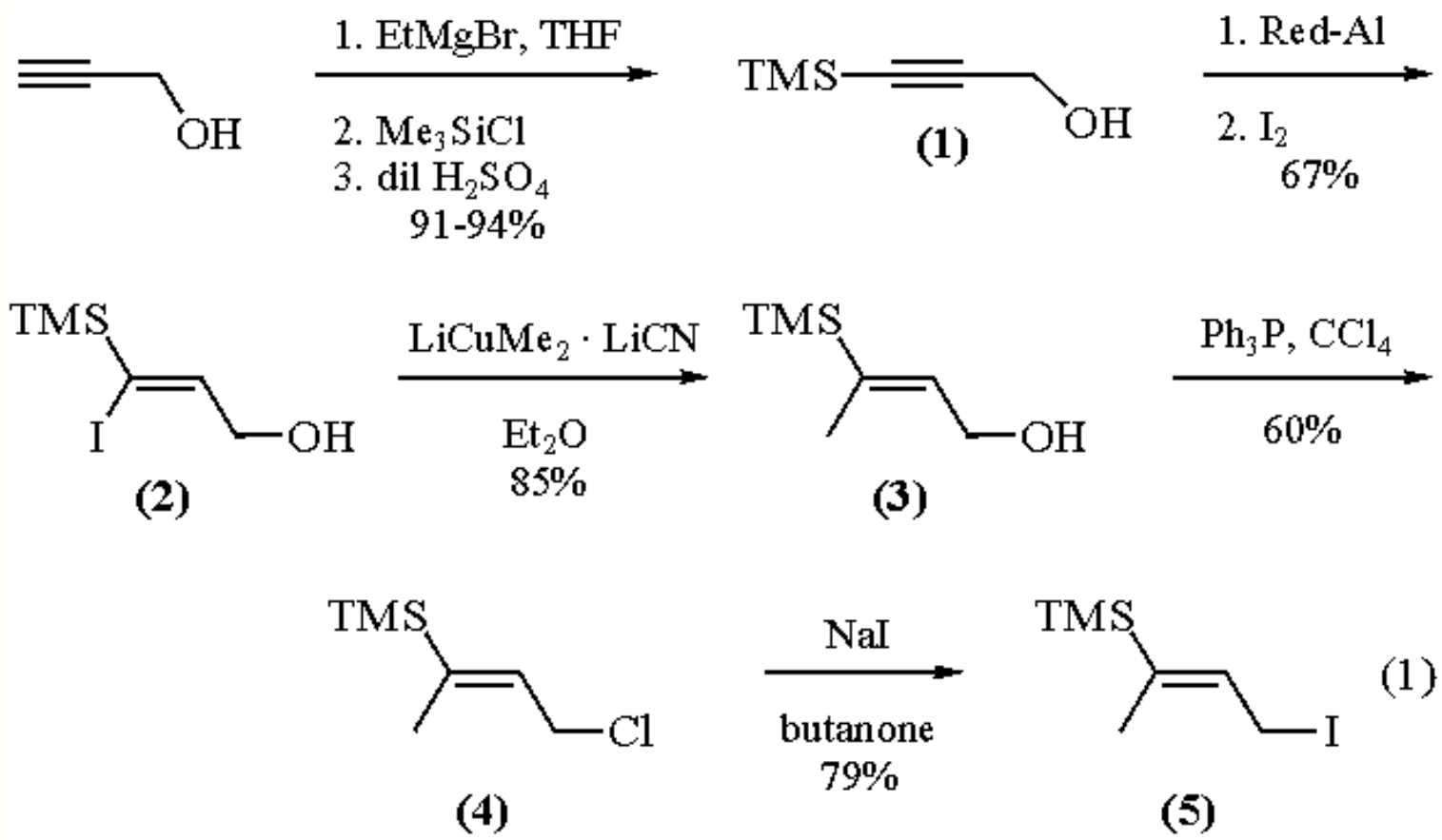

An alternative, high-yielding synthesis of (**3**) (eq 2) involves the use of HMPA, but is otherwise straightforward.[7]

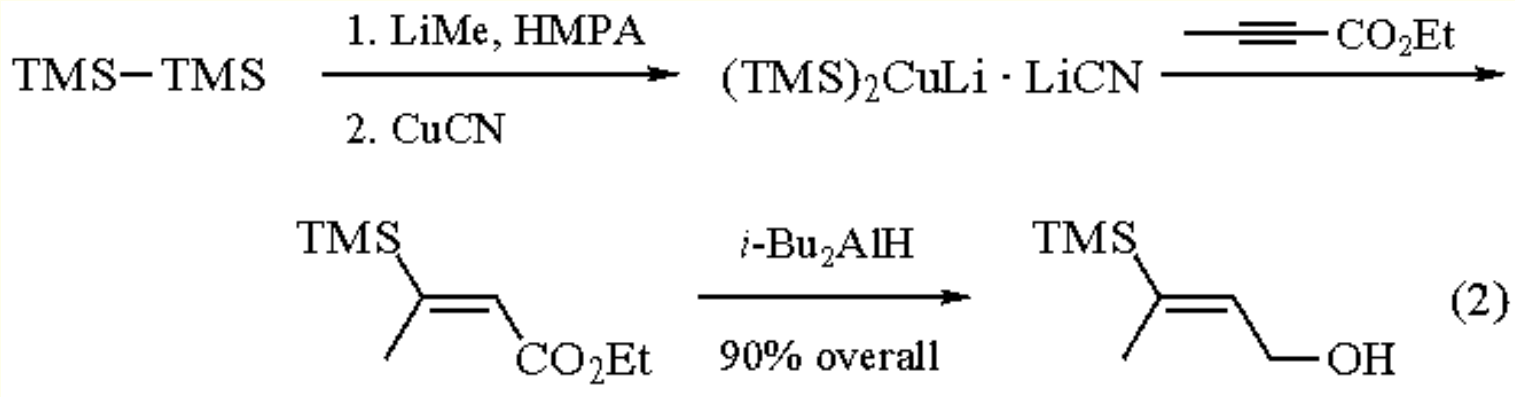

Enolate Alkylation.

One of the most useful applications of the Michael reaction[8] is Robinson annulation, using 3-buten-2-one as electrophilic acceptor. However, the Michael reaction, being reversible, is prone to side reactions, and Robinson annulation itself is of only significant utility in relatively simple cases. Hence there has been considerable effort[9] devoted to devising alkylative equivalents of 3-buten-2-one, with the goal of achieving regiospecific enolate alkylation under nonequilibrating conditions. Allylic halides possess sufficiently high reactivity for such alkylation. Useful reagents which have been devised include ***1,3-Dichloro-2-butene*** (Wichterle's reagent),[10] Stork's halomethylisoxazoles,[11] and Stotter's γ-iodotiglate.[12] However, these alternatives can all present problems either before or during further transformation to liberate the 3-ketoalkyl chain prior to

final cyclization. For example, the Wichterle sequence requires the use of concentrated sulfuric acid to hydrolyze the vinyl chloride moiety.

The use of halomethyl vinylsilanes would appear to offer significant promise. As allylic halides, they should be sufficiently reactive to permit regiospecific alkylation; as vinylsilanes, they can be converted, via α,β-epoxysilanes, into carbonyl compounds.[13] The conditions for this last transformation, with simple α,β-epoxysilanes, are rather vigorous, requiring hot methanol/sulfuric acid.

Examples of Use.

Iodide (**5**) reacts with lithium enolates,[9,14] generated in a variety of ways, including kinetic generation from enol acetates (eq 3), regiospecific production by lithium-ammonia reduction of enones, and similar regiospecific production by lithium dimethylcuprate addition to enones (eq 4). Enamines can also be used in a sequence which demonstrates the possibility of reducing enones without affecting the vinylsilane (eq 5); the reagent used in this case was chloride (**4**) in the presence of ***Potassium Iodide***, i.e. via the in situ generated iodide (**5**).

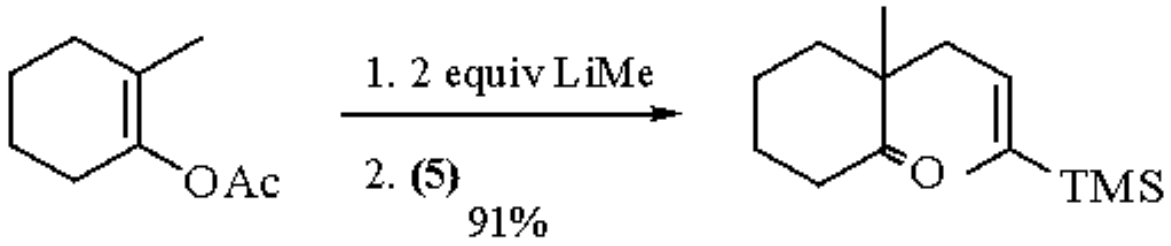

(3)

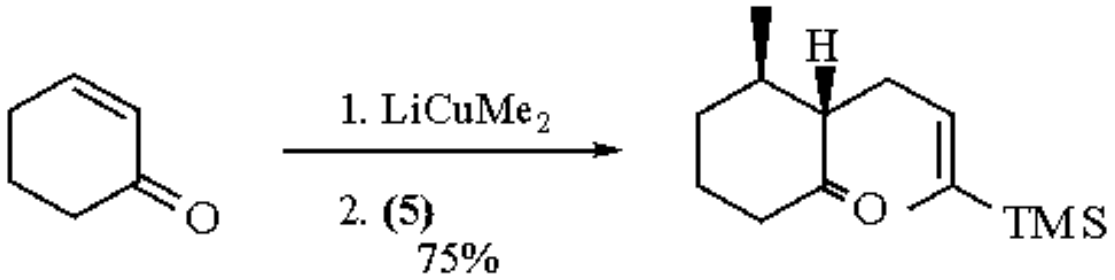

(4)

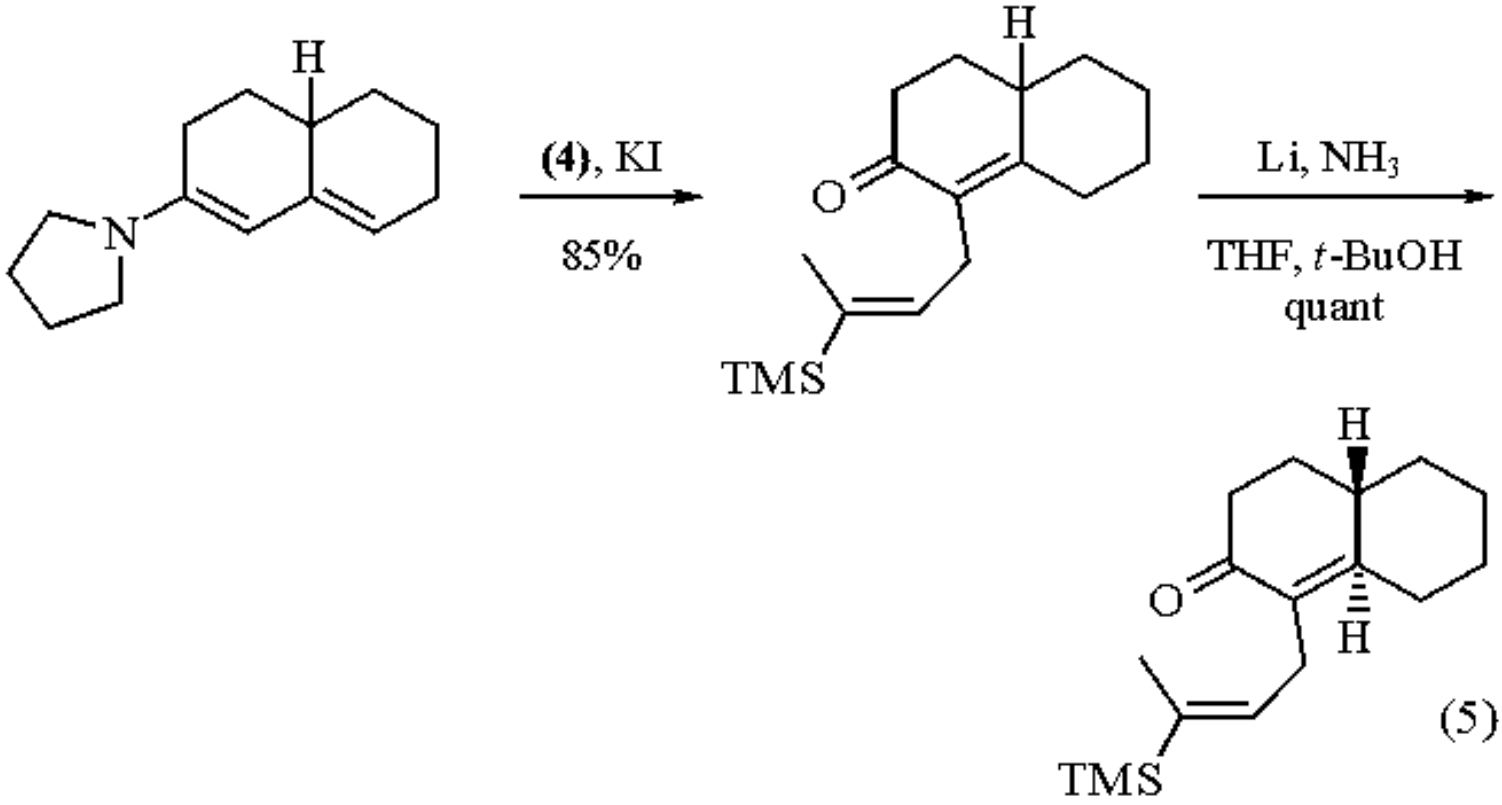

Release of the latent carbonyl function in these vinylsilanes can be achieved[9,14] under much milder conditions than for simple epoxysilanes, which require hot methanol/sulfuric acid. Here, treatment of the epoxide, formed using ***m-Chloroperbenzoic Acid***, with formic acid for 30 s led cleanly to the dione (eq 6); alternatively, use of a slight excess of *m*-CPBA and a reaction time of 4 h achieved the same conversion. The extreme and contrasting ease of this transformation has been ascribed to nucleophilic participation of the carbonyl group in epoxide opening (eq 7).

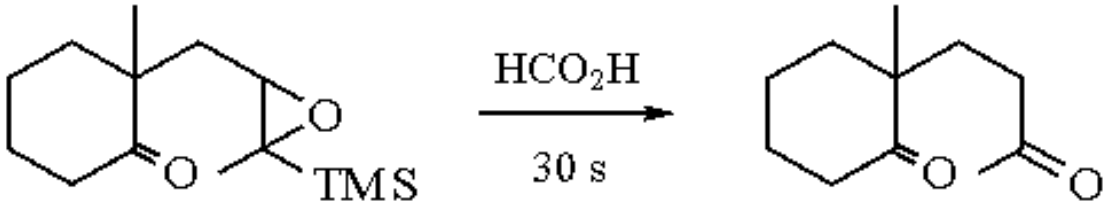

(6)

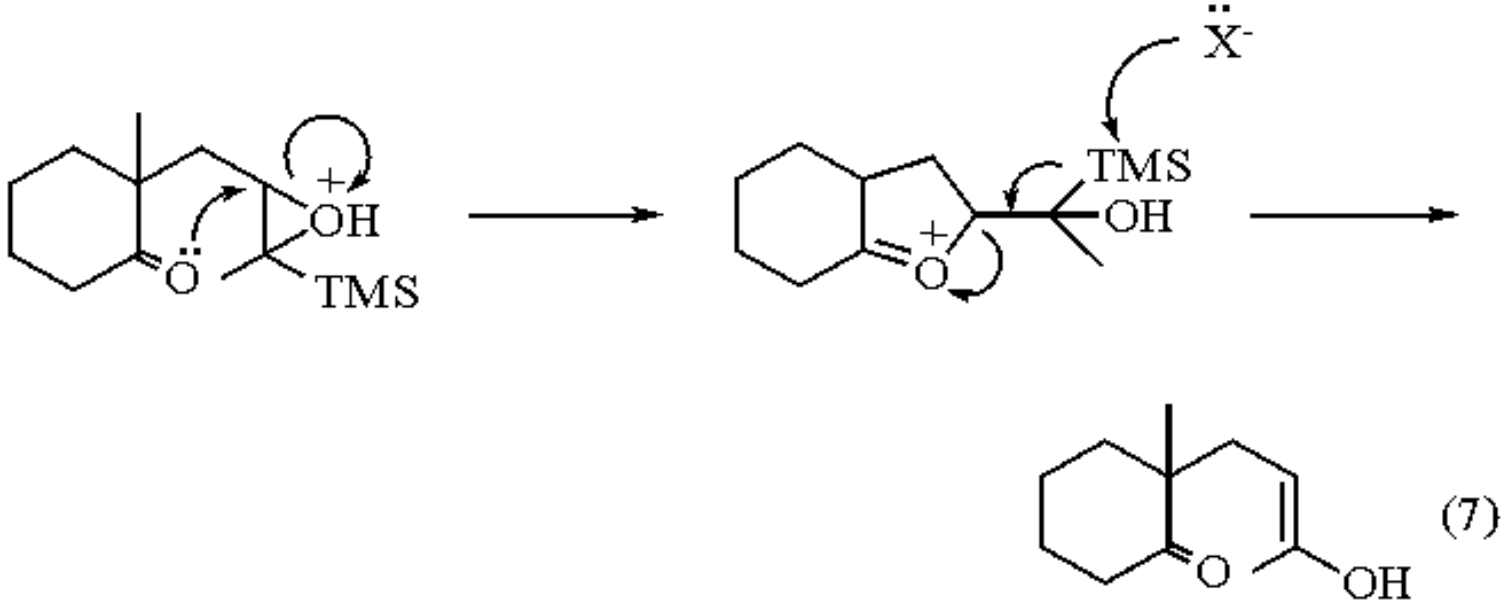

(7)

The diones so formed can be cyclized under basic conditions to the corresponding enones (eqs 8 and 9).

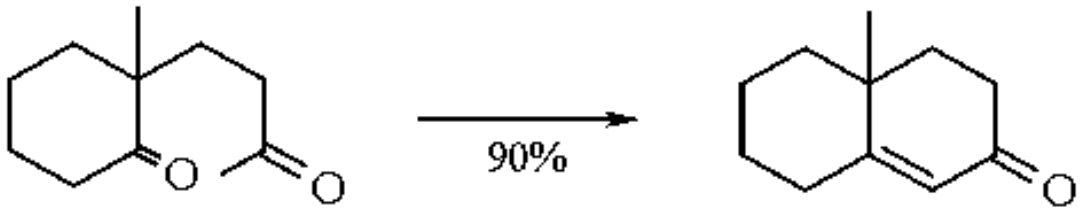

(8)

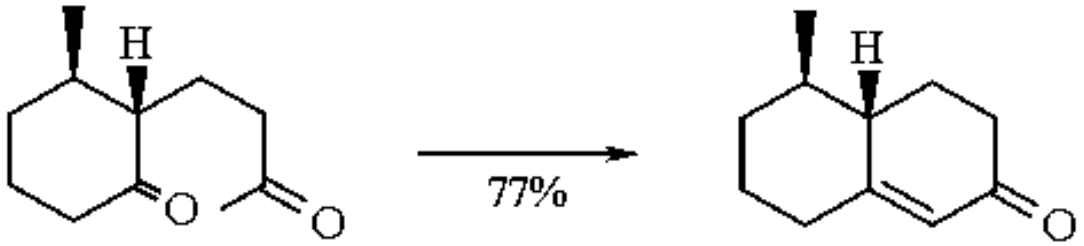

(9)

Iodide (**5**) has also been used[15] in a regiocontrolled route (eq 10) to 4,5-disubstituted 2-(and 3-)cyclohexenones. Alkylation of the anion of sulfone (**6**) with (**5**) gave (**7**), subsequent transformations leading sequentially to enones (**8**) and (**9**). No further manipulation of these enones has been reported.

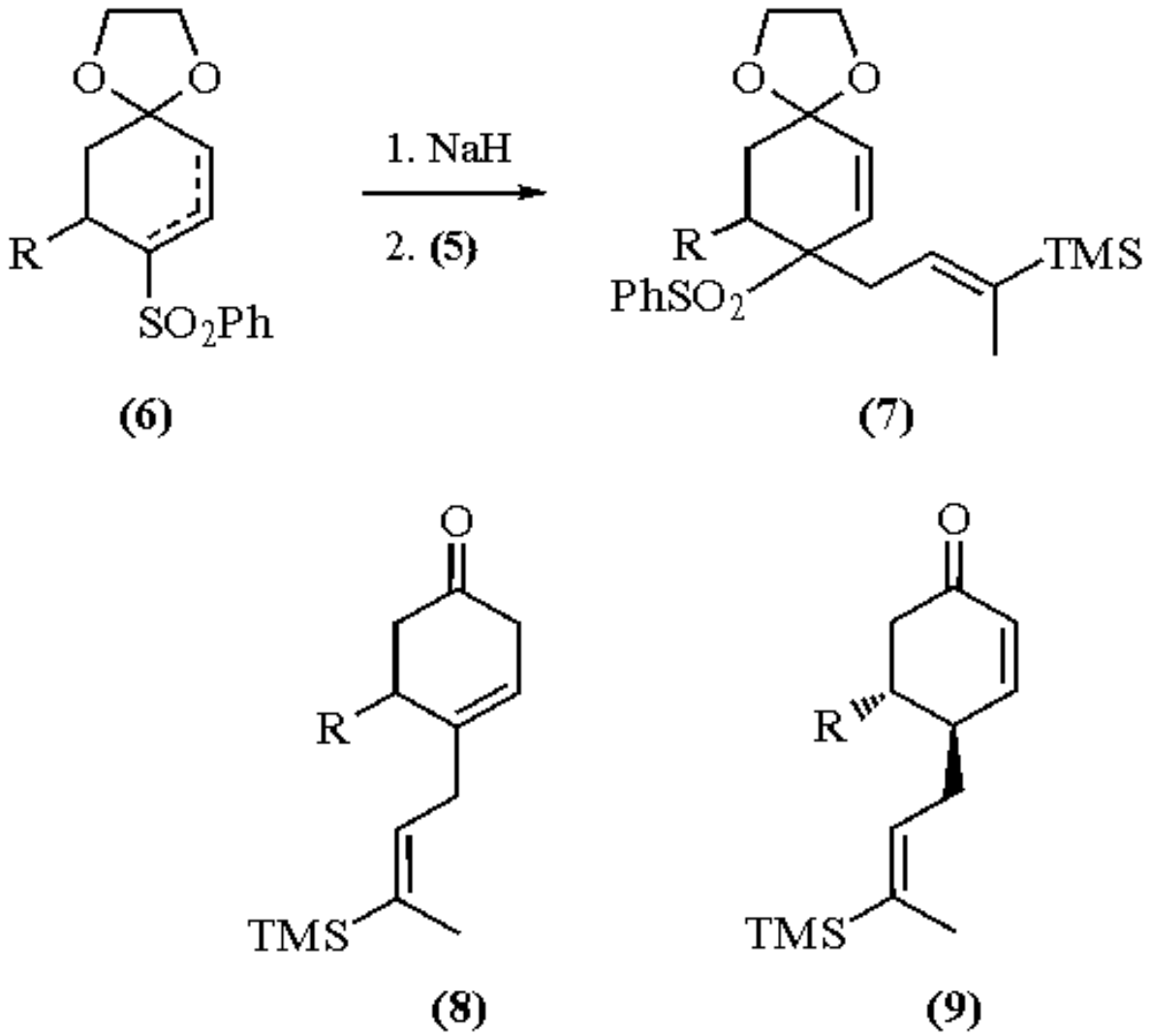

A different application[16] of reagent (**5**) can be seen in the total synthesis of artemisinin (**10**). Alkylation of the kinetic enolate of (**11**), derived from (-)-isopulegol, with (**5**) gave an 6:1 mixture of epimeric products from which the major isomer (**12**) was isolated in 62% yield. Further transformations led to vinylsilane (**13**). Liberation of the latent carbonyl group to provide ketone (**14**) was again achieved under very mild conditions, although here the possibility of carbonyl participation would seem less likely. Further steps then led to artemisinin (**10**).

(E)-1-Iodo-3-trimethylsilyl-2-butene

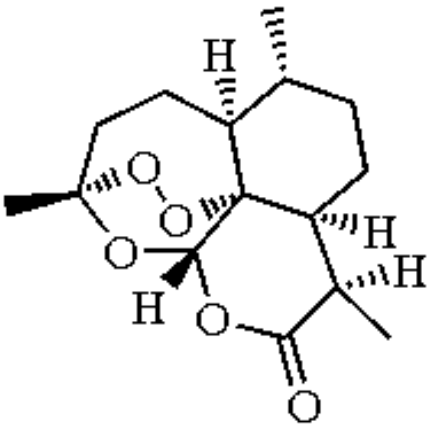

(10)

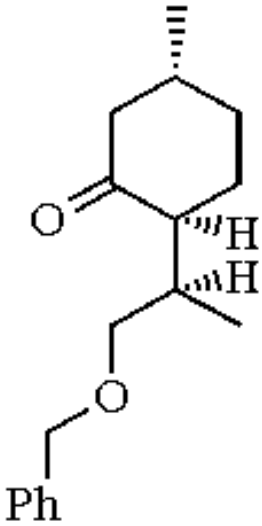

(11)

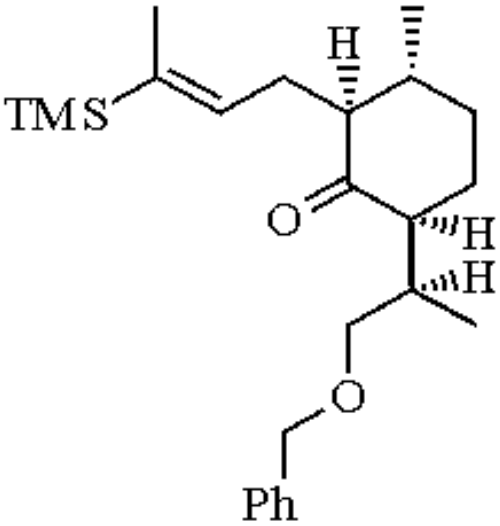

(12)

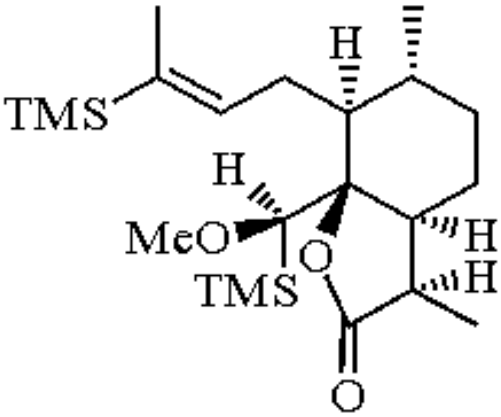

(13)

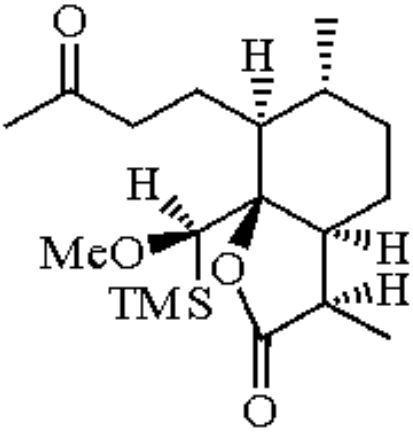

(14)

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3-Iodo-2-trimethylsilylmethyl-1-propene

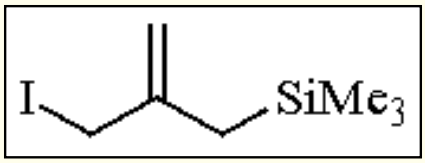

[80121-73-9] · $C_7H_{15}ISi$ · 3-Iodo-2-trimethylsilylmethyl-1-propene · (MW 254.21)

(a bifunctional conjunctive reagent that serves as a dipolar trimethylenemethane synthon;[1,6] treatment with SnF_2 affords a dianionic trimethylenemethane synthon[9])

Physical Data: bp 25 °C/0.5 mmHg.[2]

Solubility: wide range of organic solvents.

Preparative Method: from the corresponding mesylate upon treatment with ***Sodium Iodide*** in acetone.[2] The mesylate can be prepared from the commercially available alcohol.[3]

Purification: distillation in the dark (25 °C/0.5 mmHg, trap at -78 °C).[2]

Handling, Storage, and Precautions: can be stored in the dark at -20 °C for up to 3 months without significant deterioration.[2]

Dipolar Synthon for Trimethylenemethane.

The most common use of this reagent is as a 1,3-dipolar synthon for trimethylenemethane (TMM) (eq 1).[1]

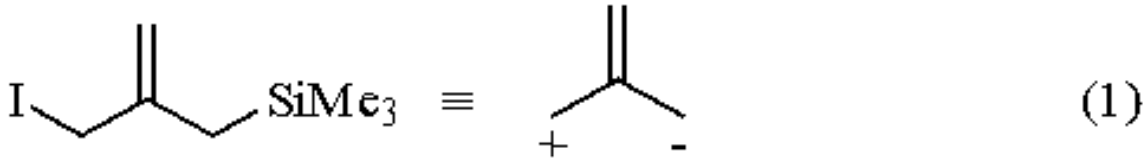

(1)

The dipolar character is unmasked in two separate synthetic steps. In the first, the synthon reacts at the positive end upon treatment with a nucleophile such as an enolate or metalloenamine.[2] In the second step, the nucleophilic end is unveiled, usually by treatment with fluoride ion. This nucleophile attacks the carbonyl or imine, completing the sequence. A similar reagent to the iodide, also a 1,3-dipolar synthon for TMM, is derived by treatment of the corresponding acetate with Pd^0.[1] The resulting 1,3-dipolar synthon differs from the iodide in several ways:

- 1)one synthetic step is required to complete addition of the activated reagent;
- 2)the reaction simulates a cycloaddition, with an electron deficient alkene as a reaction partner, rather than a carbonyl or imine;
- 3)the nucleophilic end of the synthon reacts first, in contrast to the iodide.

Reagent (**1**) has been used successfully with several classes of substrates.[1,4,5] For example, ketone (**2**) was used in a synthesis employing the dipolar synthon as a means of annulating the third ring of the coriolin skeleton (eq 2).[4]

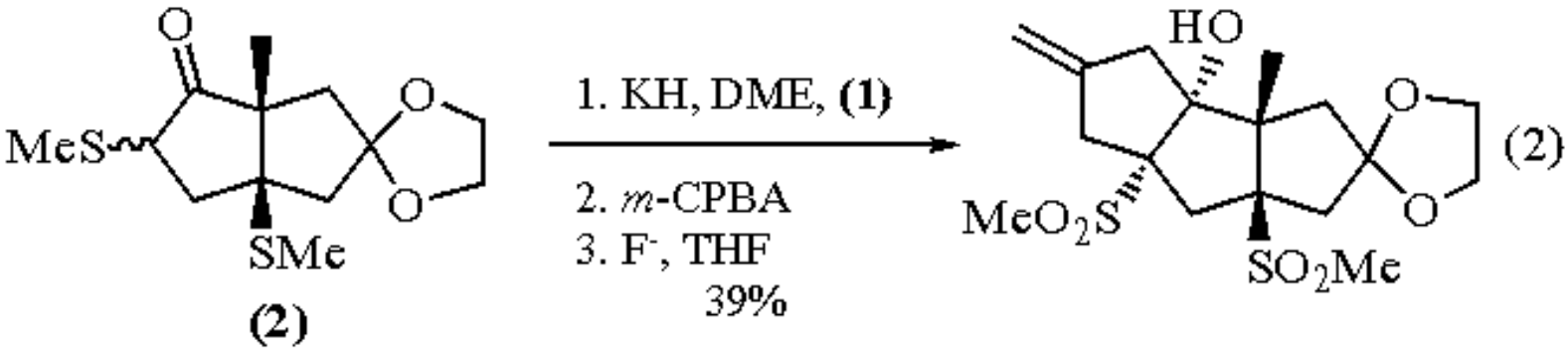

Enone alkylation using (**1**), followed by Michael addition of the activated silane constitutes a second class of reactions employing this synthon.[6] As shown in eq 3, the mode of addition in systems containing a second conjugated double bond can be controlled by changing the method used to activate the silane toward nucleophilic attack. Use of a Lewis acid favors 1,6-addition leading to seven-membered rings,[6b,7] while treatment with fluoride ion favors 1,4-addition and formation of five-membered rings.[6b]

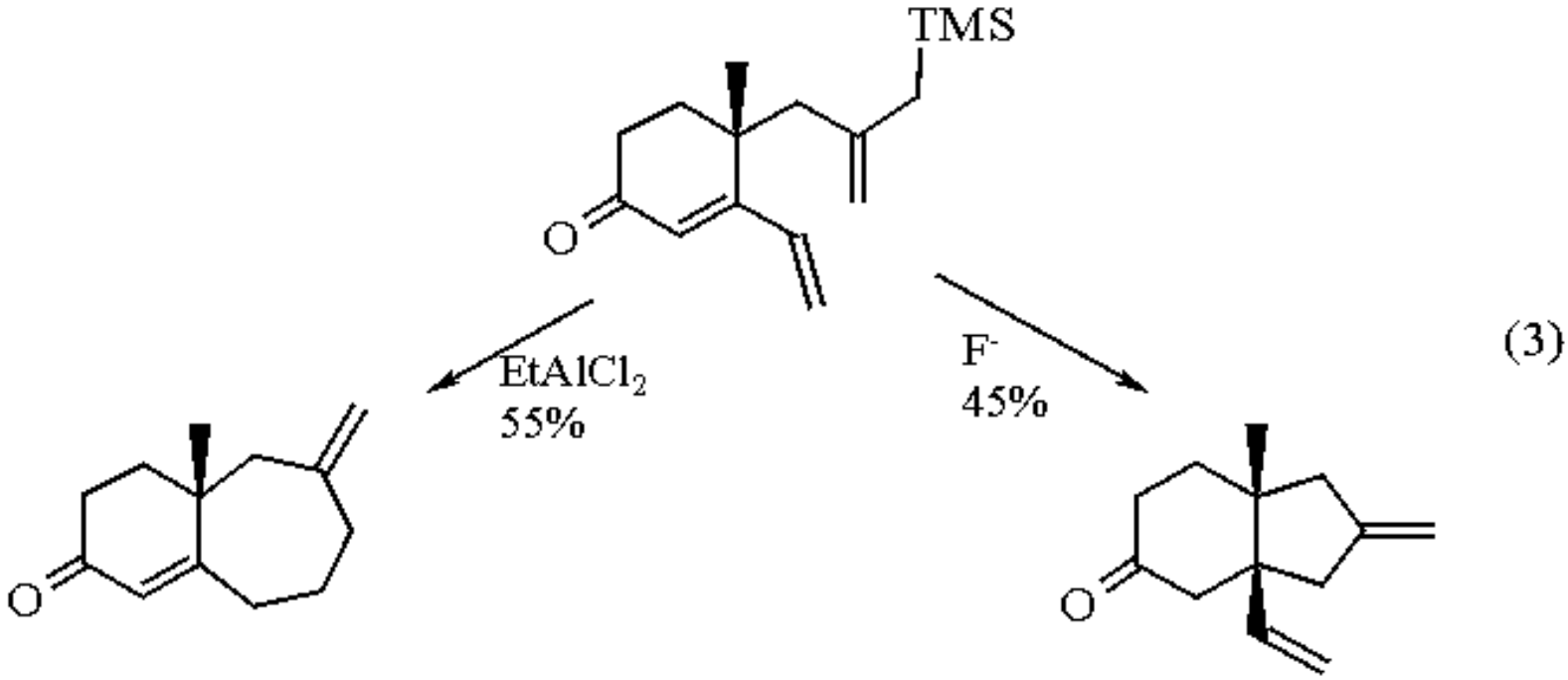

Finally, imines can be used in the synthesis of nitrogen-containing heterocycles.[8] One particularly interesting method involves a sequential photoexcitation-electron-transfer desilylation method for generating a diradical species capable of forming a spirocyclic product (eq 4).[8c] Notably, the ionic cyclization method involving fluoride ion leads, in this case,

to mixtures of products including only small amounts (ca. 7%) of the desired spirocycle.[8c]

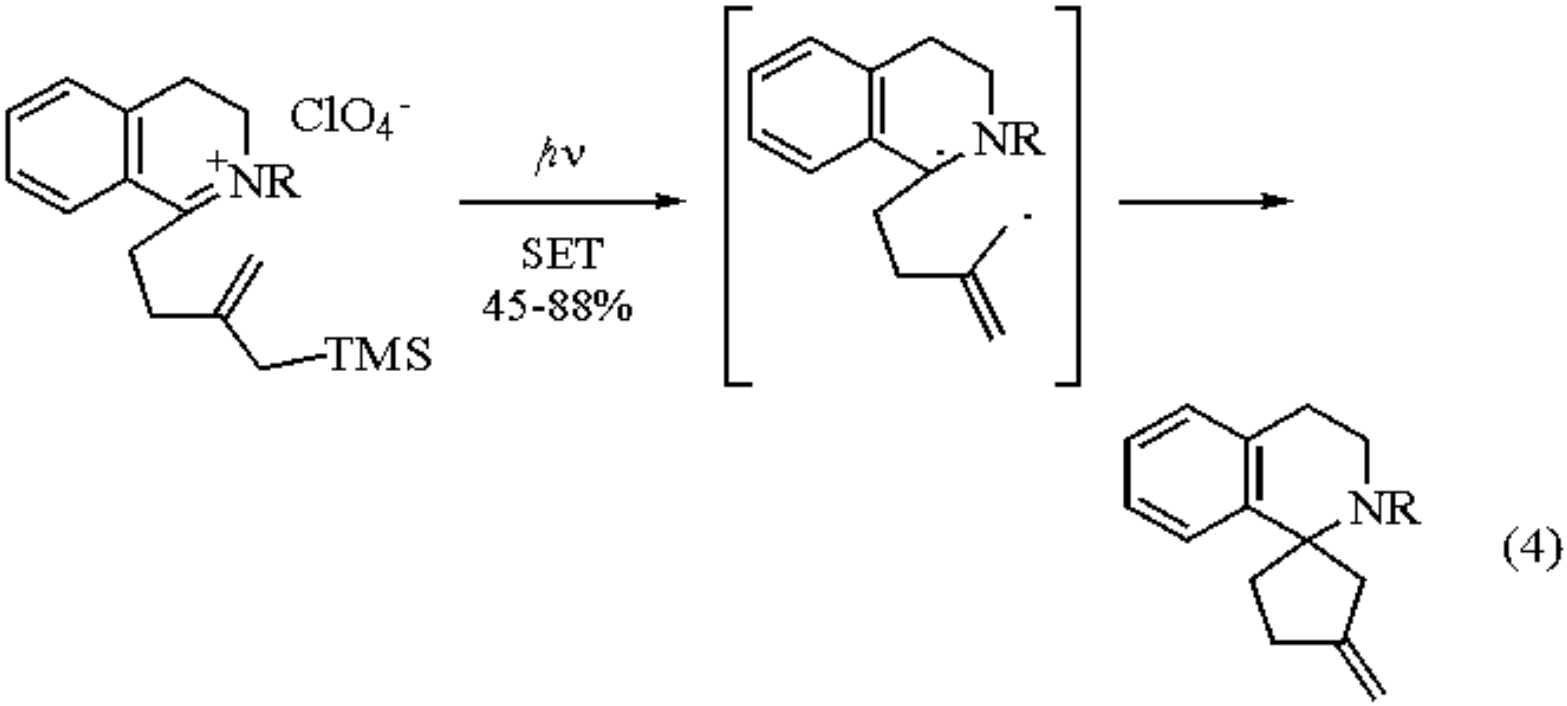

(4)

Dianionic Synthon for Trimethylenemethane.[9]

Reagent (**1**), upon metalation with ***Tin(II) Fluoride*** can be used as a dianionic synthon for trimethylenemethane (eq 5).[10] This versatile synthon, in conjunction with bis-electrophiles such as (**4**), has been used to synthesize rings that range in size from five to eight members. An intramolecular hemiacetalization reaction followed by cyclization of the allylsilane makes possible the formation of seven- and eight-membered rings (eq 6).[9b]

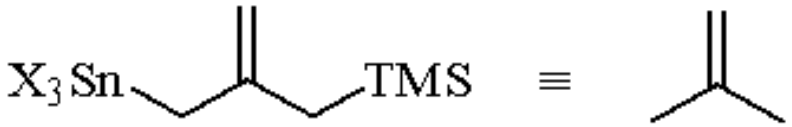

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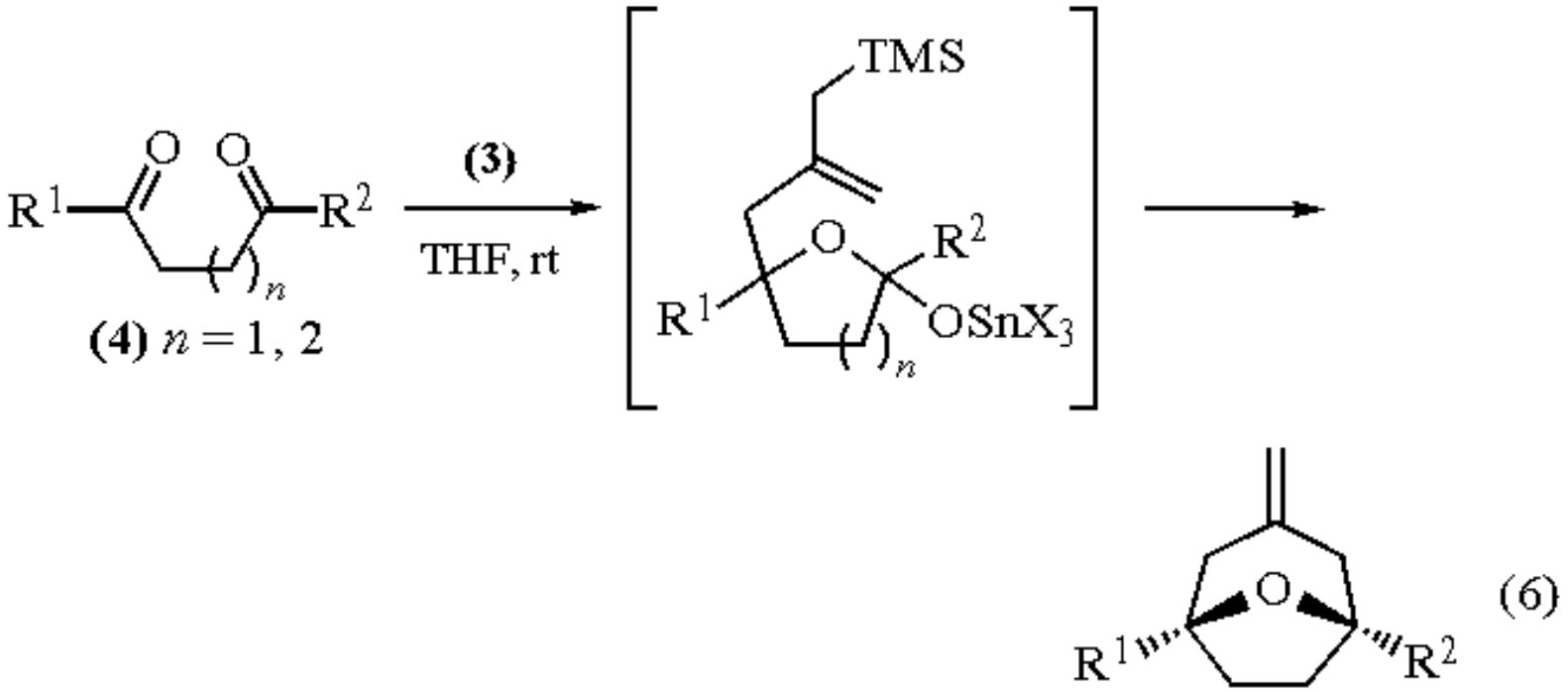

Related Reagents.

3-Acetoxy-2-trimethylsilylmethyl-1-propene.

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3-Iodo-1-trimethylsilylpropyne

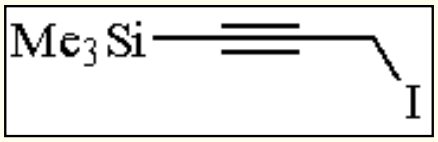

[78199-88-9] · $C_6H_{11}ISi$ · 3-Iodo-1-trimethylsilylpropyne · (MW 238.16)

(addition to aldehydes in the presence of tin(II) chloride or metallic tin and aluminum to provide α-hydroxyallenes and β-alkynic alcohols; propargylic alkylating agent)

Alternate Name: (3-iodo-1-propynyl)trimethylsilane; trimethylsilylpropargyl iodide.

Physical Data: bp 42 °C/2 mmHg.

Solubility: typical reaction solvents are DMF, dichloromethane, THF.

Analysis of Reagent Purity: ^{1}H NMR.[1]

Preparative Methods: from ***Iodine*** and [3-(trimethylsilyl)-2-propynyl]-*o*-phenylene phosphite in dichloromethane (52%), or iodine and 3-(trimethylsilyl)-2-propyn-1-ol and ***Tri-n-butylphosphine*** (47%);[1] from trimethylsilylpropargyl bromide and ***Sodium Iodide***;[2] by treatment of trimethyl(2-propynyl)stannane with ***Ethylmagnesium Bromide***, ***Bromotrimethylsilane*** in THF followed by I_2 in CCl_4 (65-70%).[3]

Handling, Storage, and Precautions: the distilled trimethylsilylpropargyl iodide was found by ^{1}H NMR to have decomposed to the extent of 20% after 5 d at -10 °C in the dark.[1] Care should be taken when working with the tin derivative. Organostannane reagents are highly toxic and readily absorbed through the skin. Proper safety equipment (i.e. fume hood, gloves, protective eyewear) should be utilized when handling the organostannane derivative.[4]

Addition to Aldehydes.

Considerable attention has been focused on the control of regioselectivity in the addition of allenic and propargylic organometallic reagents to carbonyl compounds. Mukaiyama and Harada have found that the addition of trimethylsilylpropargyl iodide to aldehydes in a DMF/***1,3-Dimethyl-2-imidazolidinone*** (DMI) mixture in the presence of ***Tin(II) Chloride*** results in the formation predominantly of the α-hydroxy allenes (α-allenic alcohols) (eq 1).[2]

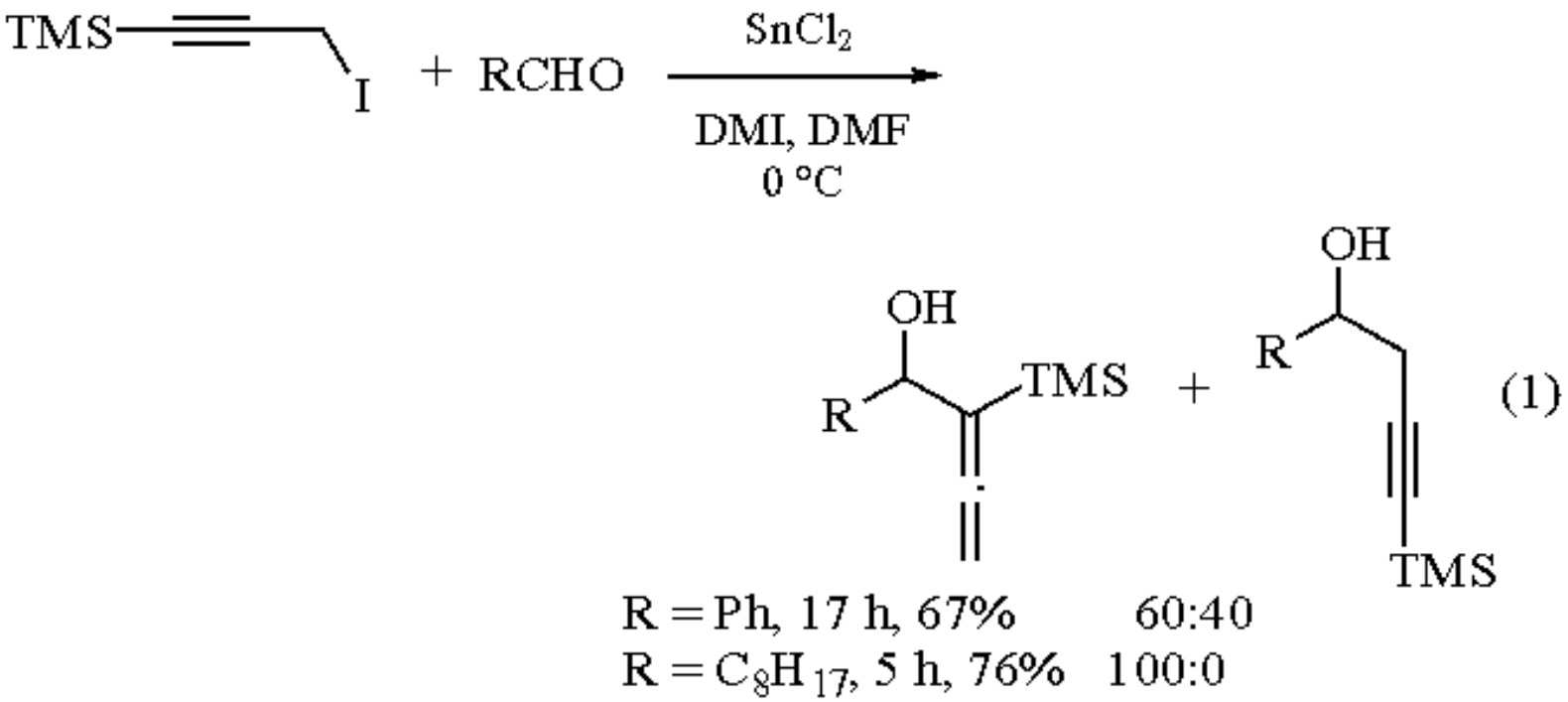

In a complimentary study, Nokami et al. found that trimethylsilylpropargyl iodide reacts with metallic ***Tin*** in the presence of metallic ***Aluminum*** to give bis(trimethylsilylpropargyl)tin diiodide. This then reacts with aldehydes to give either α-allenic or β-alkynic alcohols (homopropargyl alcohols) selectively, depending on the choice of solvent (eq 2).[5]

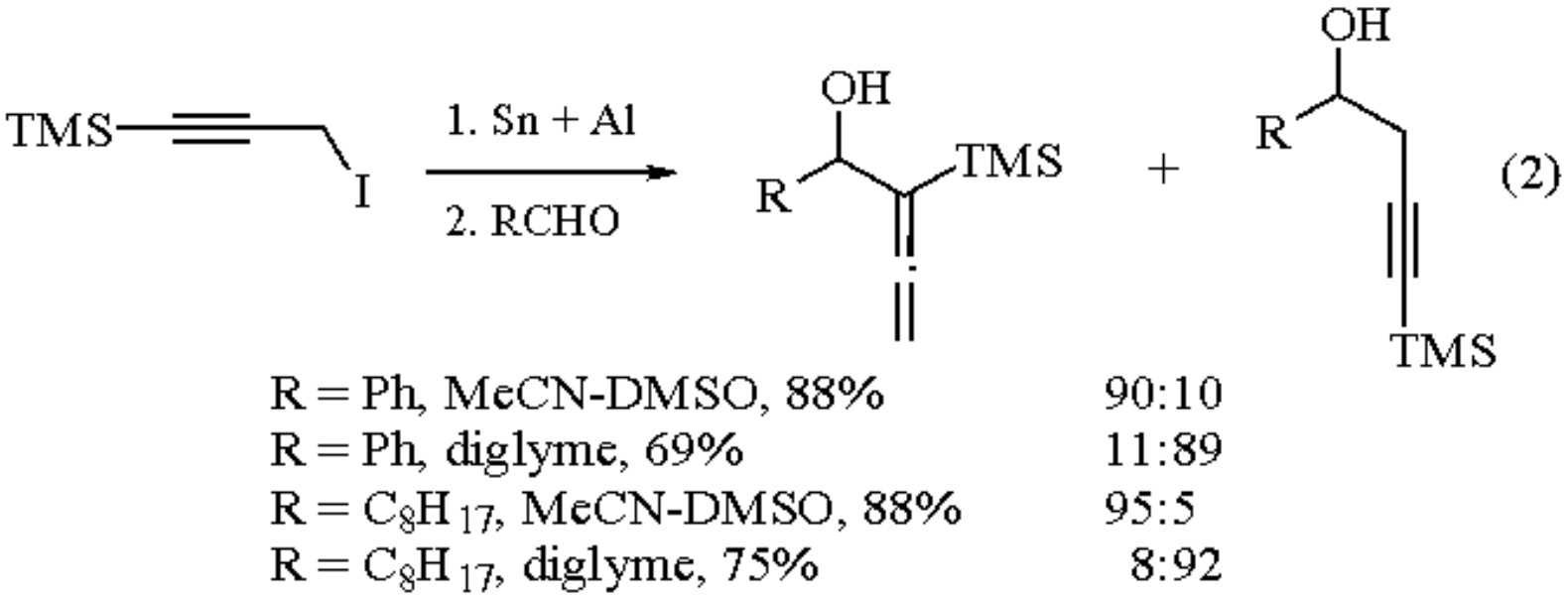

Analogous additions to aldehydes and ketones with metallated derivatives of 3-bromo-1-trimethylsilylpropyne (which is commercially available) are also known. Either α-allenic[6] or β-alkynic alcohols[7] may be obtained selectively by using the appropriate metal derivative. The organolithium species prepared from 1-trimethylsilylpropyne has also been utilized.[8]

Alkylation Reactions.

3-Iodo-1-trimethylsilylpropyne has been used in the trapping of enolates generated in 1,4-additions of organometallic

reagents to 2-cyclopentenone derivatives.[1] Noyori et al. used this reaction in the three-component coupling synthesis of prostaglandins (eq 3).[9] Reaction of trimethylsilylpropargyl iodide with an alkynic Grignard reagent in the presence of ***Copper(I) Cyanide*** has also been demonstrated in the synthesis of a preclavulone A model (eq 4).[10]

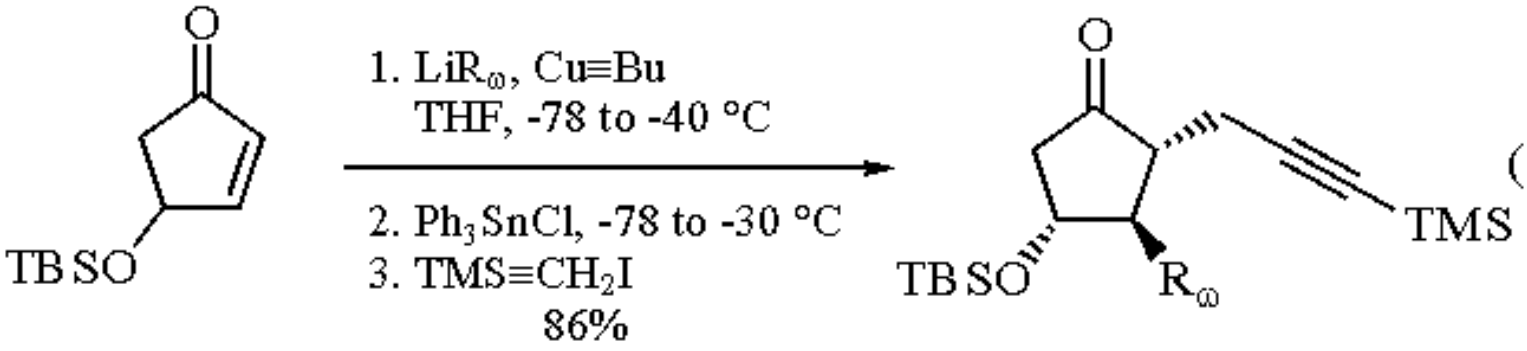

(3)

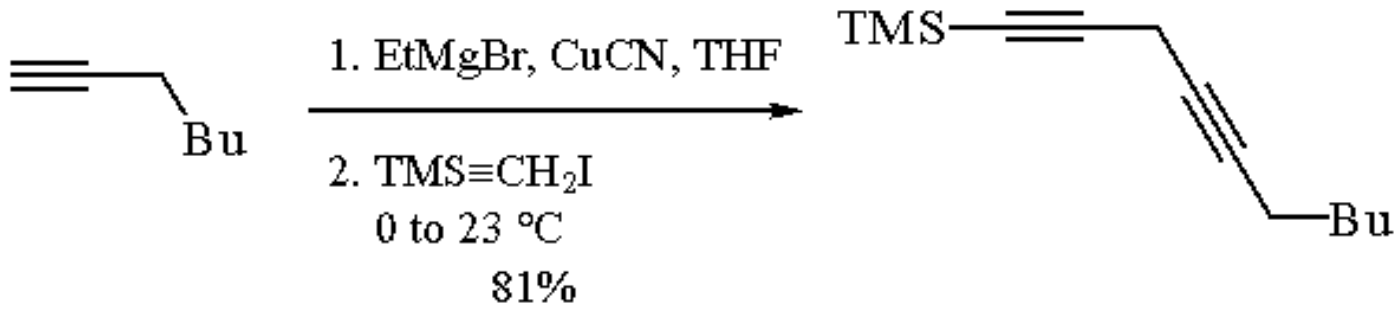

(4)

3-Bromo-1-trimethylsilylpropyne has also been used as an alkylating agent for trapping enolates and other carbanions.[11] It has also been used in the preparation of alkynic ylides.[12]

Related Reagents.

1,3-Bis(triisopropylsilyl)propyne; ***3-Triphenylstannyl-1-propyne***.

---

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6. (a) (Al/HgCl$_2$) Daniels, R. G.; Paquette, L. A. *TL* **1981**, *22*, 1579. (b) (Al/HgCl$_2$) Mesnard, D.; Miginiac, L. *JOM* **1991**, *403*, 299 (*CA* **1991**, *114*, 164 340j).
7. (a) (Mg) Karaev, S. F.; Guseinov, S. O.; Akhundov, E. A. *ZOB* **1981**, *51*, 1373 (*CA* **1981**, *95*, 204 036n). (b) (Zn/HgCl$_2$) see Ref. 6a. (c) (Zn/HgCl$_2$) Mesnard, D.; Miginiac, L. *JOM* **1990**, *397*, 127 (*CA* **1991**, *114*, 143 511a). (d) (*i*-Bu$_2$Te) Zhou, Z.-L.; Huang, Y.-Z.; Shi, L.-L.; Hu, J. *JOC* **1992**, *57*, 6598. (e) (SbBu$_3$) Zhang, L.-J.; Mo, X.-S.; Huang, J.-L.; Huang, Y.-Z. *TL* **1993**, *34*, 1621.
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Y.; Kurozumi, S.; Noyori, R. *T* **1990**, *46*, 6689.
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11. (a) Miller, R. B. *SC* **1972**, *2*, 267. (b) Sum, P.-E.; Weiler, L. *CJC* **1978**, *56*, 2301. (c) Orsini, F.; Pelizzoni, F. *SC* **1984**, *14*, 805.
12. (a) Belyaev, N. N.; Stadnichuk, M. D.; Petrov, A. A.; Belyaev, A. N. *ZOB* **1972**, *42*, 715 (*CA* **1972**, 77, 75 252g). (b) Corey, E. J.; Fleet, G. W. J.; Kato, M. *TL* **1973**, 3963. (c) (Ph_3As) Shen, Y.; Liao, Q. *JOM* **1988**, *346*, 181. (d) Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *S* **1991**, *5*, 414. (e) (*i*-Bu_2Te) Ref. 7d.

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4-Iodo-2-trimethylstannyl-1-butene[1]

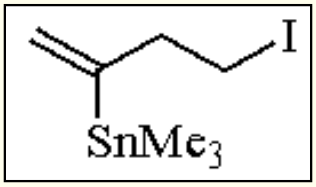

[99474-77-8] · $C_7H_{15}ISn$ · 4-Iodo-2-trimethylstannyl-1-butene · (MW 344.83)

(cyclopentane annulation;[2,3] intramolecular Stille coupling;[4] bifunctional reagent[5-7])

Alternate Name: (3-iodo-1-methylenepropyl)trimethylstannane.

Physical Data: bp 50-55 °C/0.1 mmHg.[8]

Analysis of Reagent Purity: ^{1}H NMR.[8]

Preparative Methods: by addition of trimethylstannylcuprate to 1-butyn-4-ol[9,10] followed by a Mitsunobu reaction,[11] or via the tosylate of 2-trimethylstannyl-1-buten-4-ol (NaI, DMF).[8]

Purification: by distillation.[8]

Handling, Storage, and Precautions: organostannanes should be considered as toxic compounds.[12] This reagent should be handled in a well ventilated fume hood and gloves should be worn.

Methylene Cyclopentane Annulations.

Alkylation-Intramolecular Stille Coupling.

Bicyclic dienes have been prepared by alkylation of the *N*,*N*-dimethylhydrazone of a cyclohexanone with 4-iodo-2-trimethylstannyl-1-butene, followed by the cleavage of the hydrazone, formation of the enol triflate and palladium-catalyzed Stille coupling (eq 1) (see also ***5-Chloro-2-trimethylstannyl-1-pentene***).[8,13]

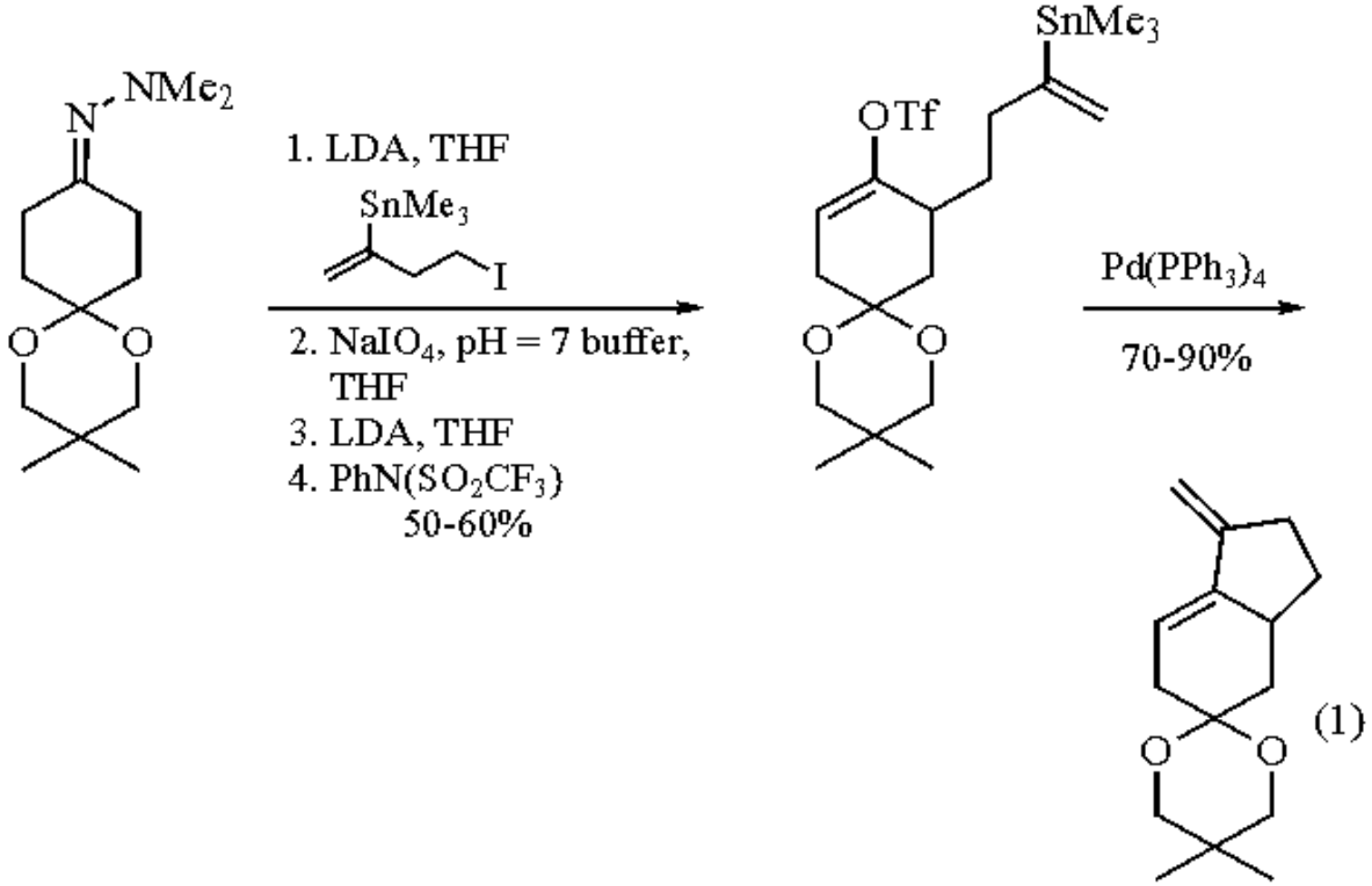

Alkylation-Vinyllithium Addition.

Treatment of the stannane derived from the alkylation of cyclohexanone with 4-iodo-2-trimethylstannyl-1-butene (see above) with ***Iodine*** affords the vinyl iodide. Treatment of this intermediate with ***n-Butyllithium*** affords an allylic, angular hydroxy annulation product (eq 2).[14]

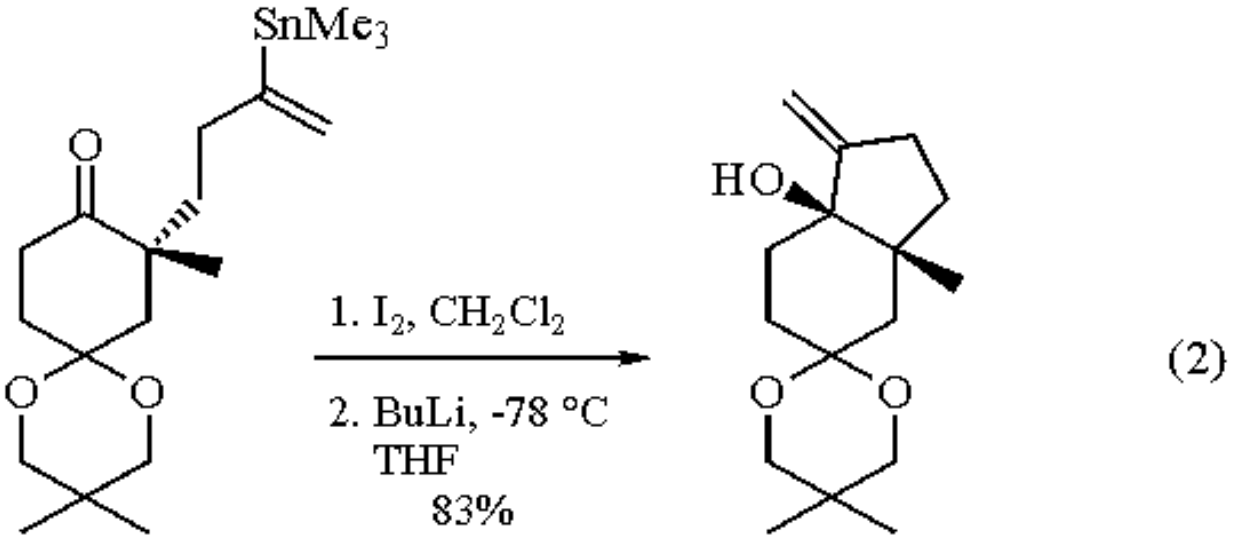

This annulation sequence provides the complimentary regioisomer to that obtained by a vinylcuprate-intramolecular

alkylation sequence.

Radical Annulation.

Addition of ***Tri-n-butylstannane*** to 4-iodo-2-trimethylstannyl-1-butene in the presence of ***N-Phenylmaleimide*** affords the bicyclic imide in 59% yield (eq 3). This reaction failed with methyl acrylate and phenyl vinyl sulfone.[12]

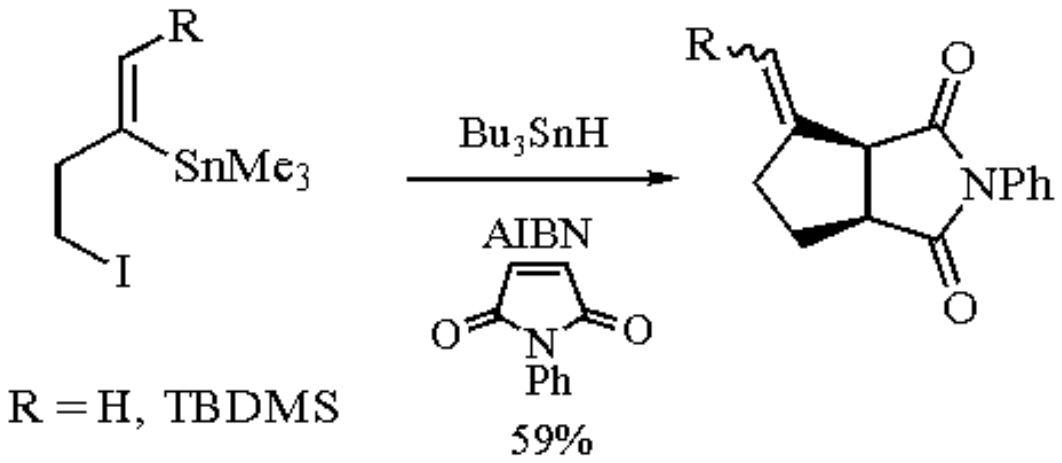

(3)

However, 1-*t*-butyldimethylsilyl-4-iodo-2-trimethylstannyl-1-butene undergoes an analogous reaction with acrylonitrile, methyl acrylate, and methyl vinyl ketone.[11]

Miscellaneous Related Reagents.

See also ***4-Chloro-2-trimethylstannyl-1-butene***, ***4-Iodo-2-trimethylgermyl-1-butene***, ***5-Chloro-2-trimethylstannyl-1-pentene***, and ***(Z)-5-Chloro-3-trimethylstannyl-2-pentene***.

A number of homologs of the title reagent have been prepared, differing in chain length and o-substitution (eq 4).[9] These have been used as methylenecyclopentane annulation reagents via the alkylation-intramolecular Stille coupling methodology (see above).[8]

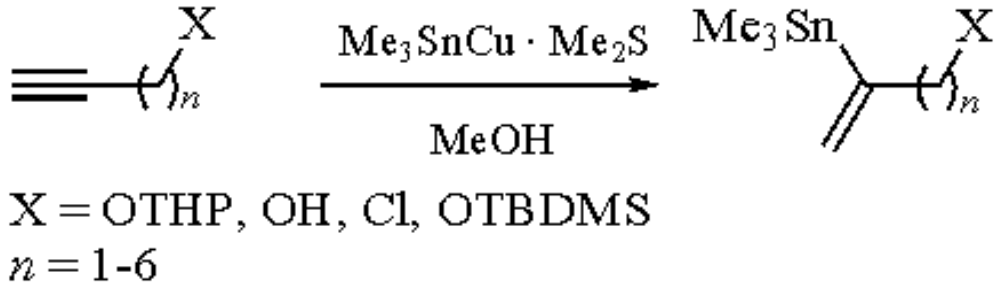

(4)

A number of (*E*)- and (*Z*)-6-iodo-3-trimethylstannyl-2-hexenoates and related bifunctional reagents (**1,2**) have been prepared and used as cyclohexane annulation reagents through alkylation and intramolecular Stille coupling (eq 5).[15,16]

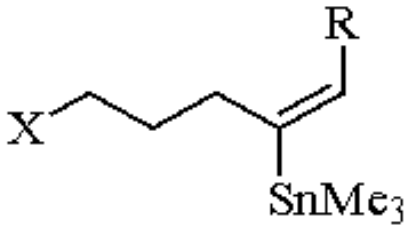

(1)

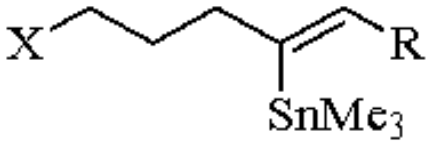

(2)

X = I, Cl; R = CO_2Me, CH_2OH, CH_2OMOM, $CH_2OTBDMS$

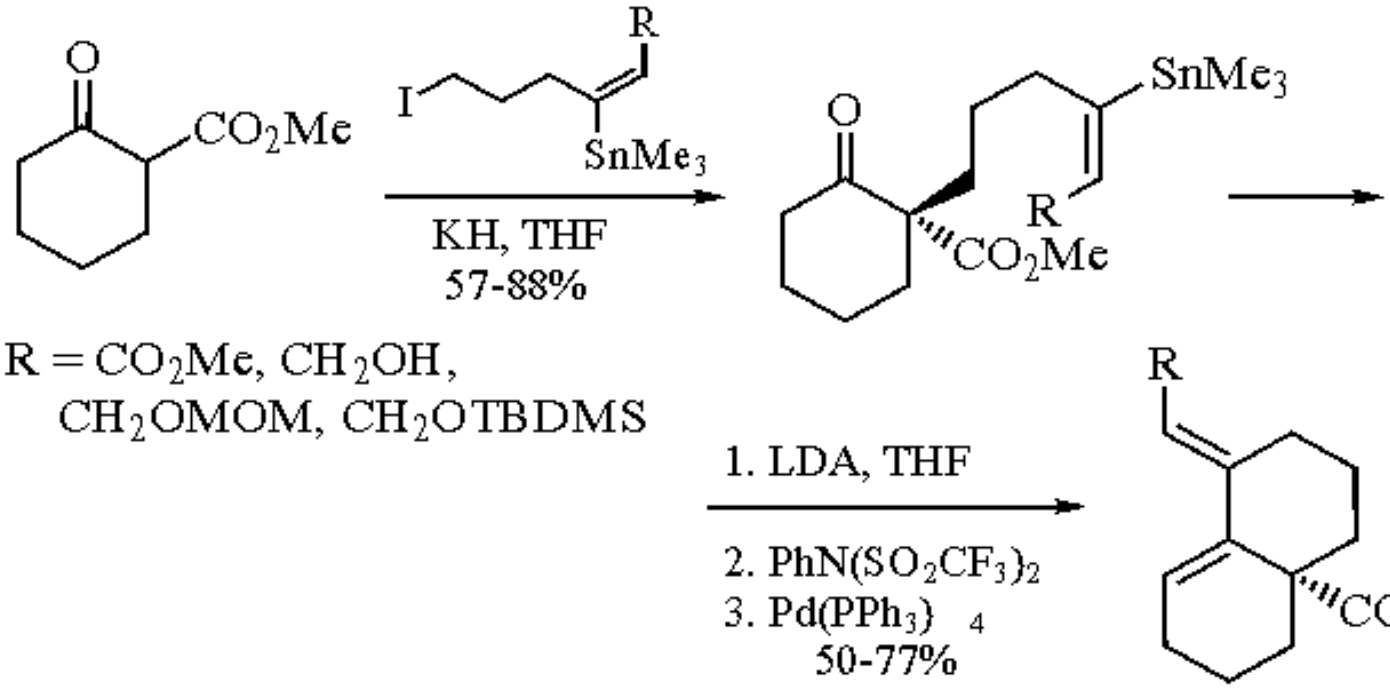

(5)

One of these reagents [(*E*)-1-(*t*-butyldimethylsiloxy)-6-iodo-3-trimethylstannyl-2-hexene] has been used in the synthesis of (±)-8,15-diisocyano-11(20)-amphilectene (eq 6).[17]

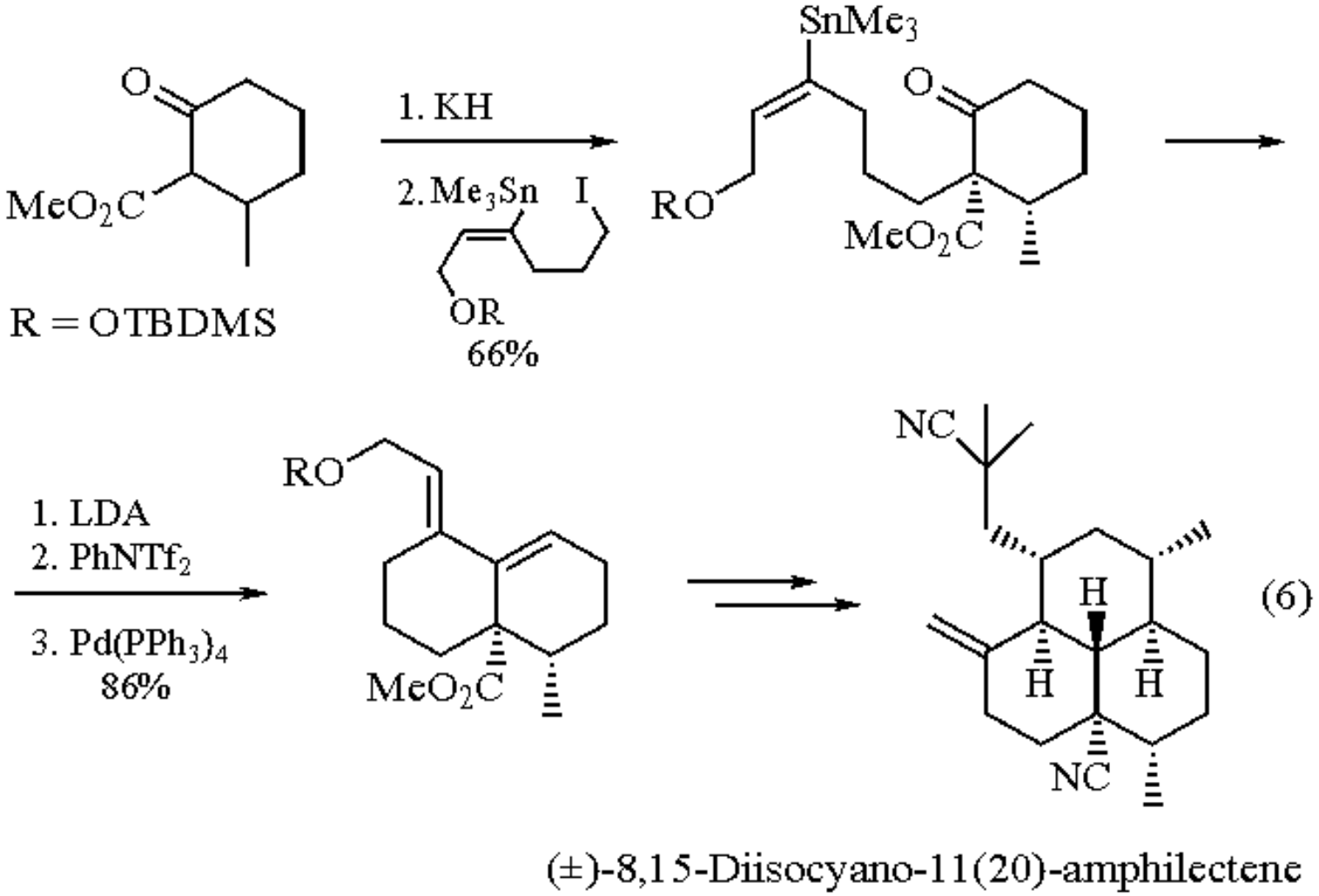

An annulation sequence using (*Z*)-1-bromo-4-methyl-3-trimethylstannyl-2-pentene has led to the synthesis of (±)-(14*S*)-dolasta-1(15),7,9-trien-14-ol and (±)-amijitrienol (eq 7).[18-20]

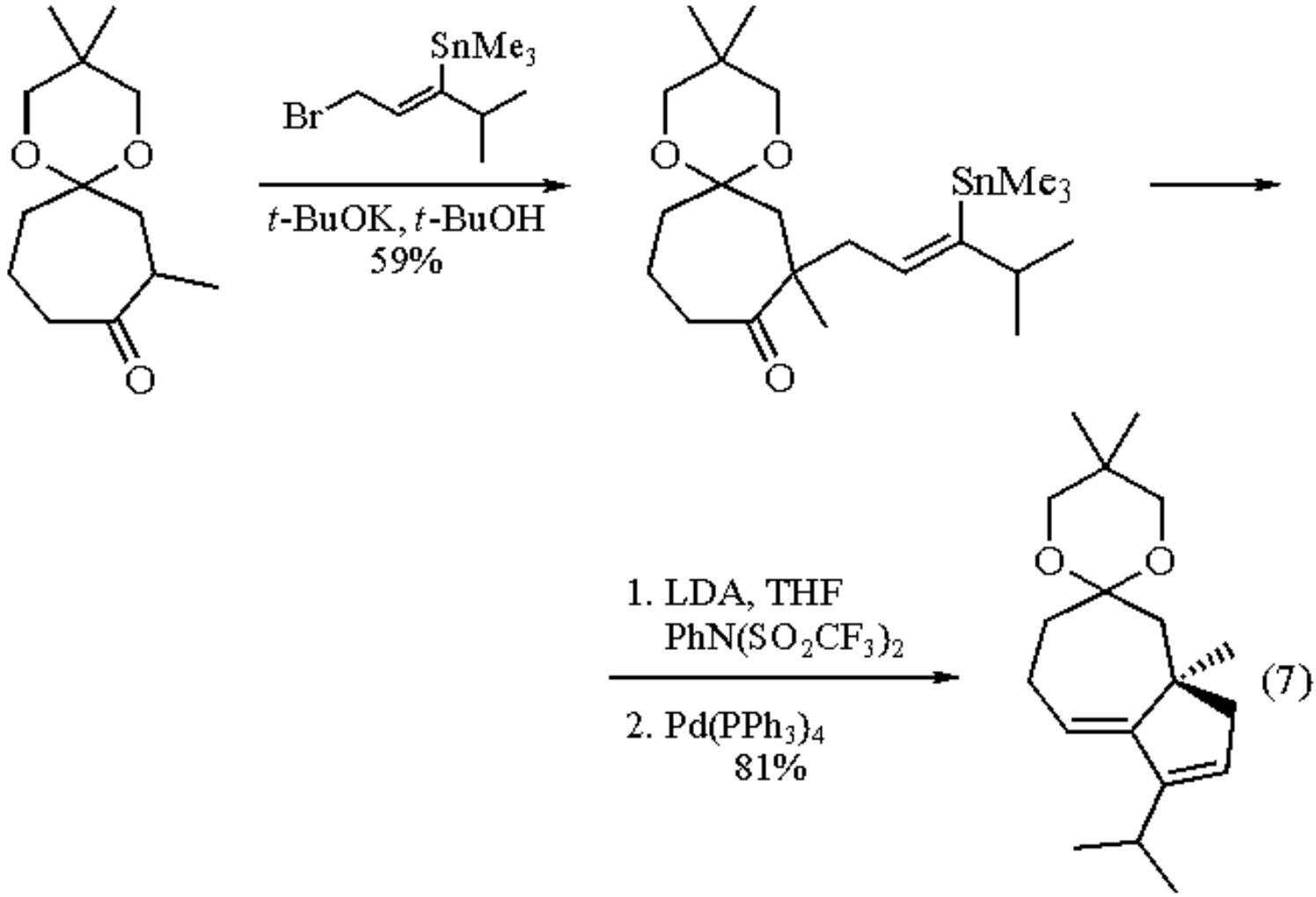

Another route to the synthesis of conjugated dienes has been accomplished using a ***Copper(I) Chloride***-mediated intramolecular coupling strategy.[21] This has been used to couple vinylstannanes and vinyl iodides in the absence of Pd^0 catalysts (eq 8 and Table 1). In only one case (entry 4), the reaction was not stereospecific. At 60 °C, a 13:1 mixture of (2*E*,3*E*) and (2*Z*,3*E*) isomers was obtained (See footnote to Table 1). Running the reaction at 25 °C afforded a 30:1 mixture of products. It was noted that the Pd^0 mediated coupling of this substrate was not stereospecific and in fact the copper-catalyzed reaction was superior.[21]

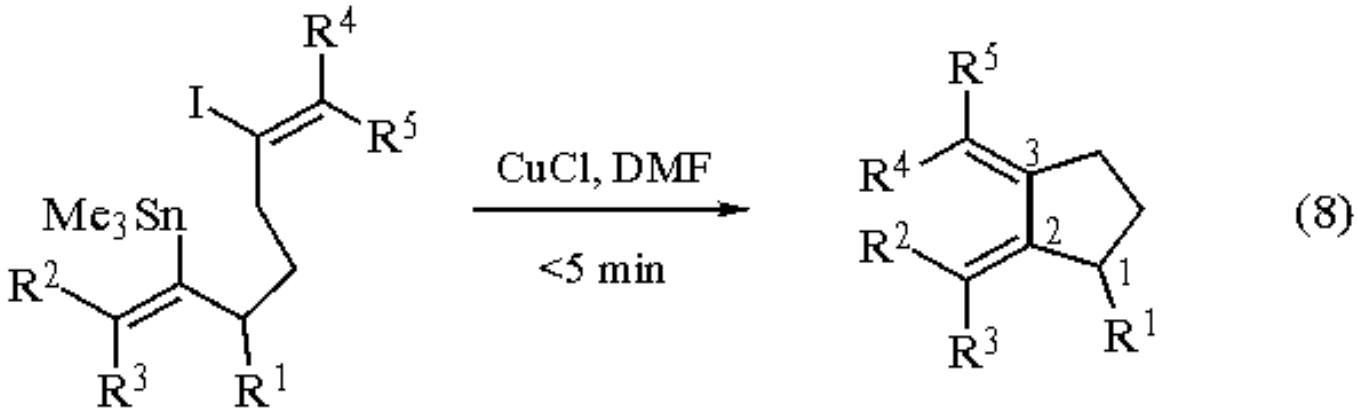

Table 1 Copper-Mediated Coupling Reactions

Entry	R^1	R^2	R^3	R^4	R^5	Yield (%)
1	CO_2Et	H	Me	H	Me	80
2	CH_2OH	H	Me	H	Me	86
3	CO_2Et	H	Me	Me	H	83
4	CO_2Et	Me	H	H	Me	94[a]
5	CO_2Et	Me	H	Me	H	89

[a] Obtained as a 30:1 mixture of (2*E*, 3*E*) and (2*Z*, 3*E*) isomers.

A general cyclopentane annulation sequence was developed using a vinylstannane that is embedded in a preexisting cycloalkene (eq 9). Initial attempts to extend this methodology to cyclohexane and cyclohexane annulations were accomplished only in low yield (12% and 35%, respectively).[22]

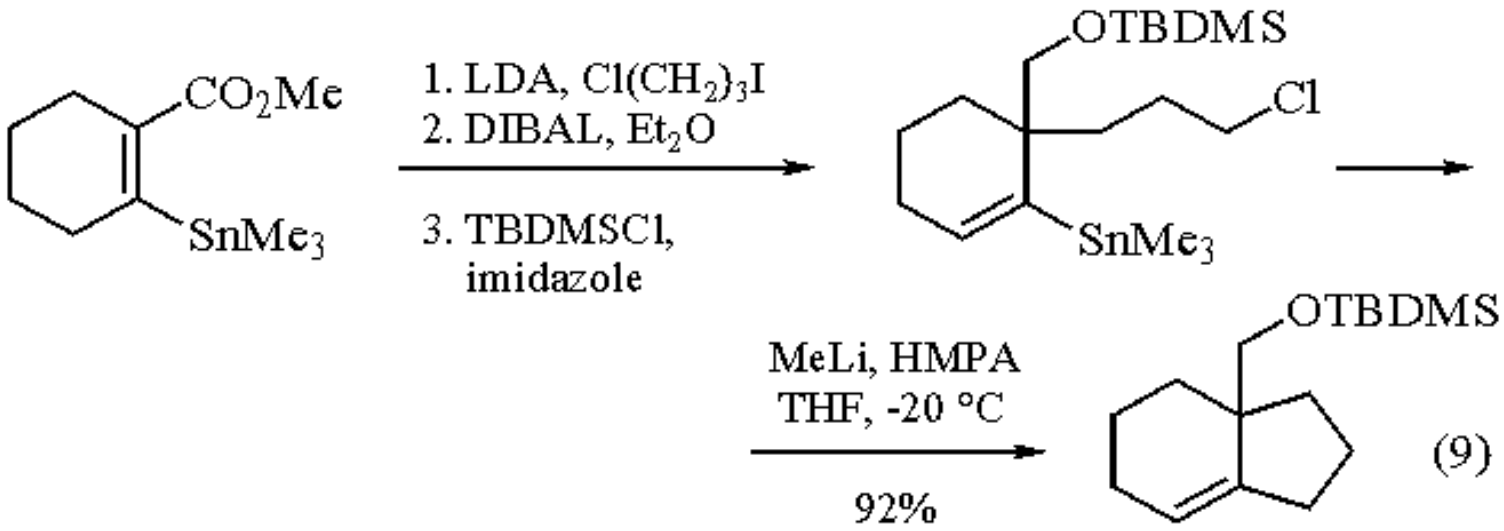

(9)

It was found subsequently that substitution of a pendent o-bromo functionality allows cyclization to both five- and seven-membered rings (eqs 10 and 11).[23]

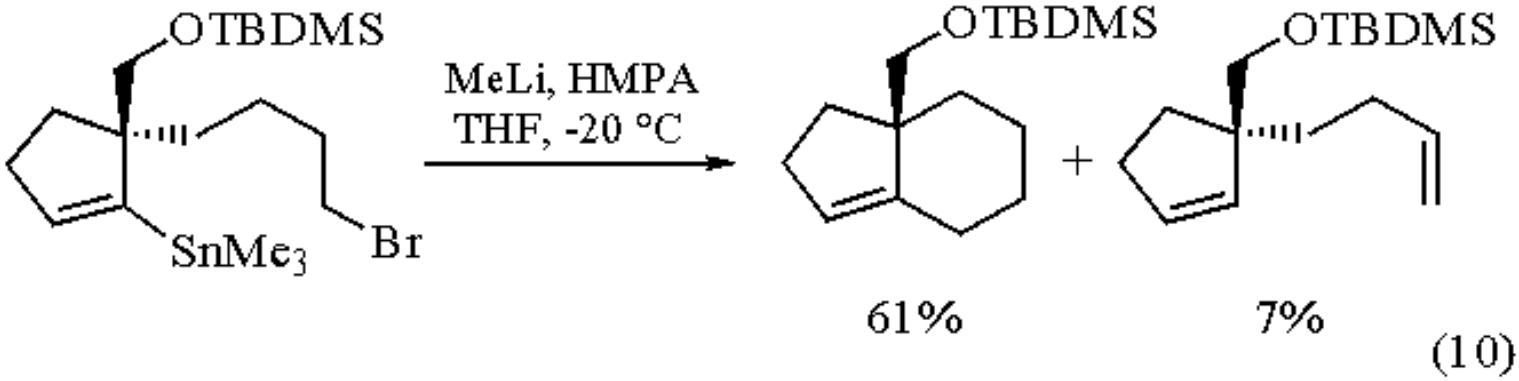

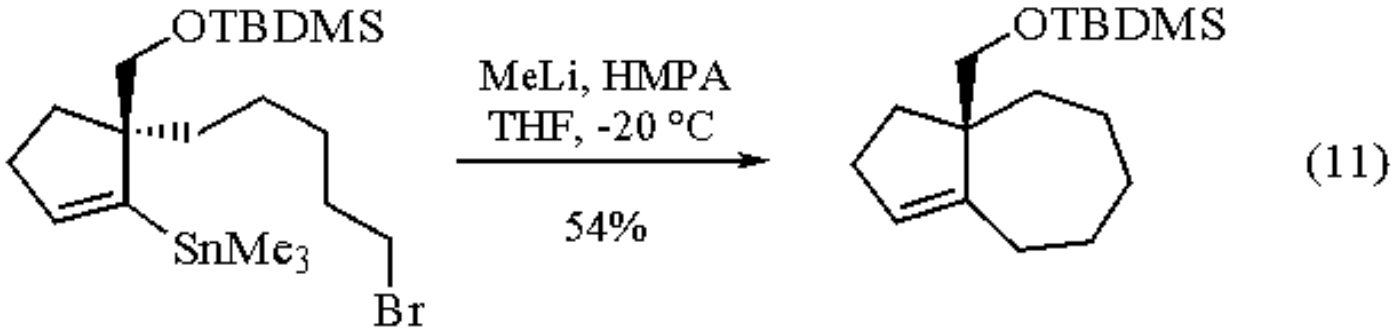

This methodology was used in the synthesis of (±)-chiloscyphone and (±)-6-*epi*-chiloscyphone (eq 12).[23]

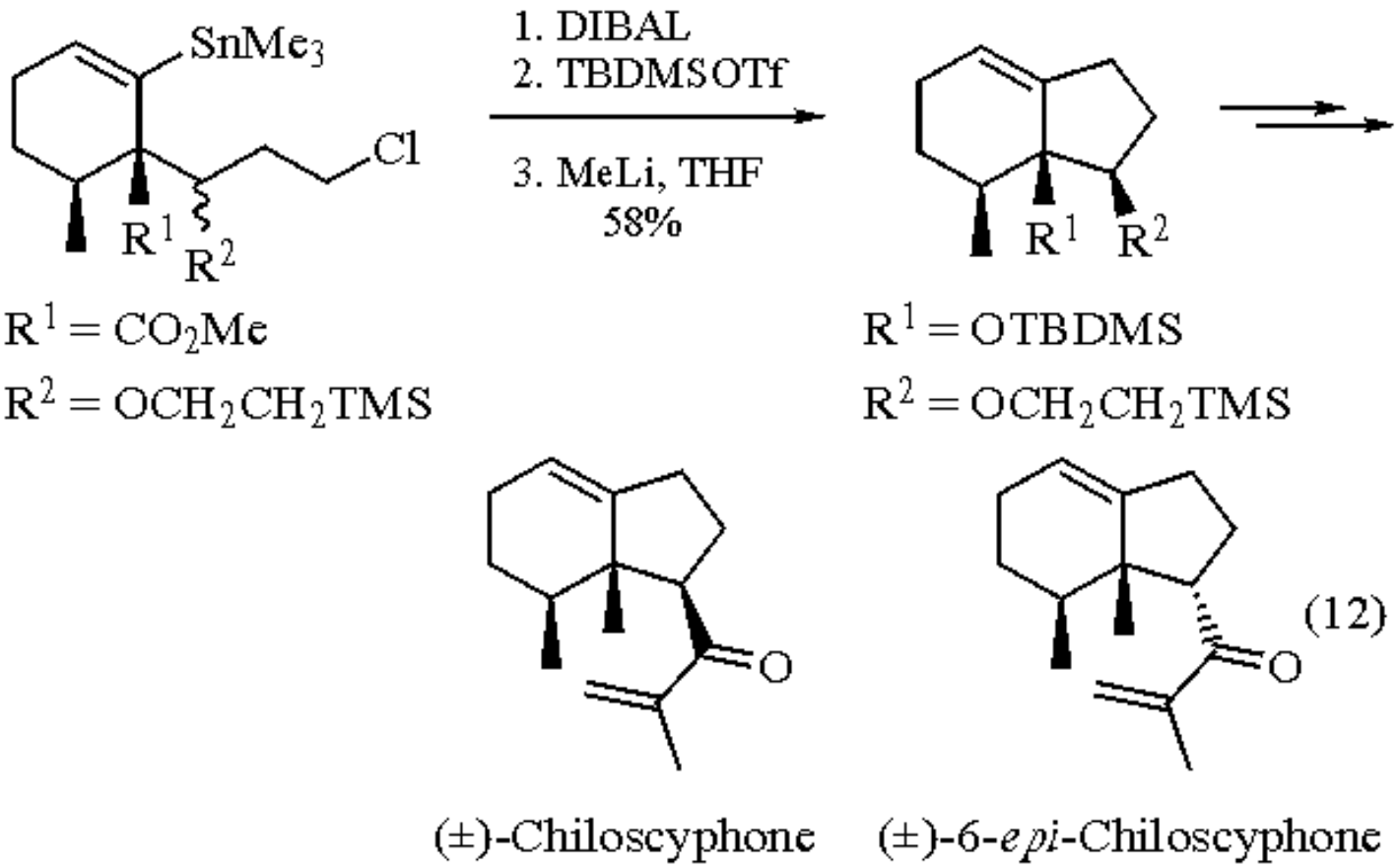

An entry into the preparation of [3.2.1]cycloheptenols utilizes vinylstannane-o-oxo compounds. Treatment of vinylstannanes (eq 13) with *n*-butyllithium affords the cyclopentenols in good yield.[24] The starting stannanes were

prepared by stannylcupration of ***Acetylene*** and cyclohexenone.[25]

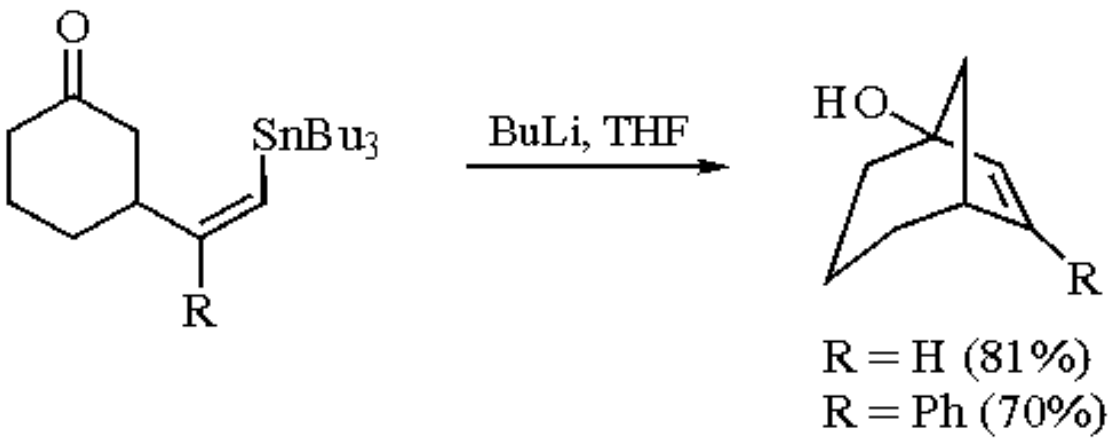

(13)

Cyclobutenes can be synthesized using a variation of this methodology. Treatment of the o-*p*-toluenesulfonate-vinylstannanne with BuLi effects a tin-lithium exchange and ring closure (eqs 14 and 15).[24] Preparation of the substrate is accomplished by stannylcupration of ***Allene***,[26,27] acetylene, or phenylacetylene[25] followed by treatment with ***Ethylene Oxide***, and conversion to the tosylate.[24]

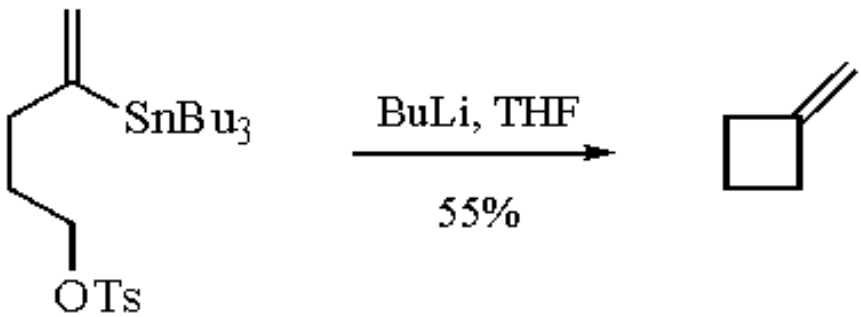

(14)

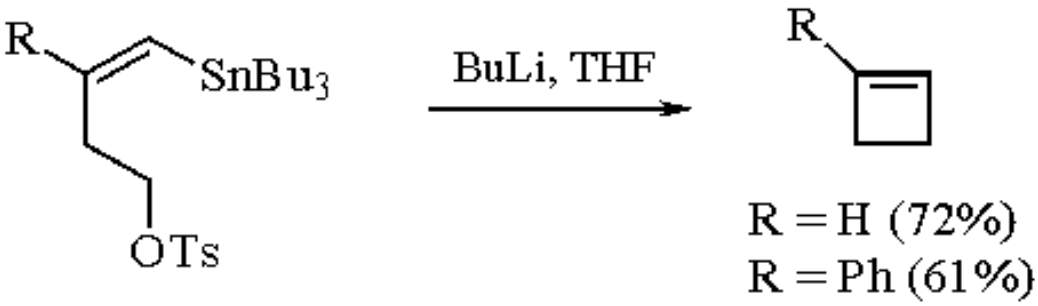

(15)

A disubstituted stannane, (*E*)-1,4-di(*t*-butyldimethylsiloxy)-2-trimethylstannyl-2-butene, has been used as an isocoumarin annulation reagent. This was accomplished by palladium-catalyzed coupling of this reagent with methyl 2-iodo-4-methylbenzoate followed by acid-catalyzed deprotection/cyclization (eq 16). This was a key sequence in the synthesis of lacramin A.[28]

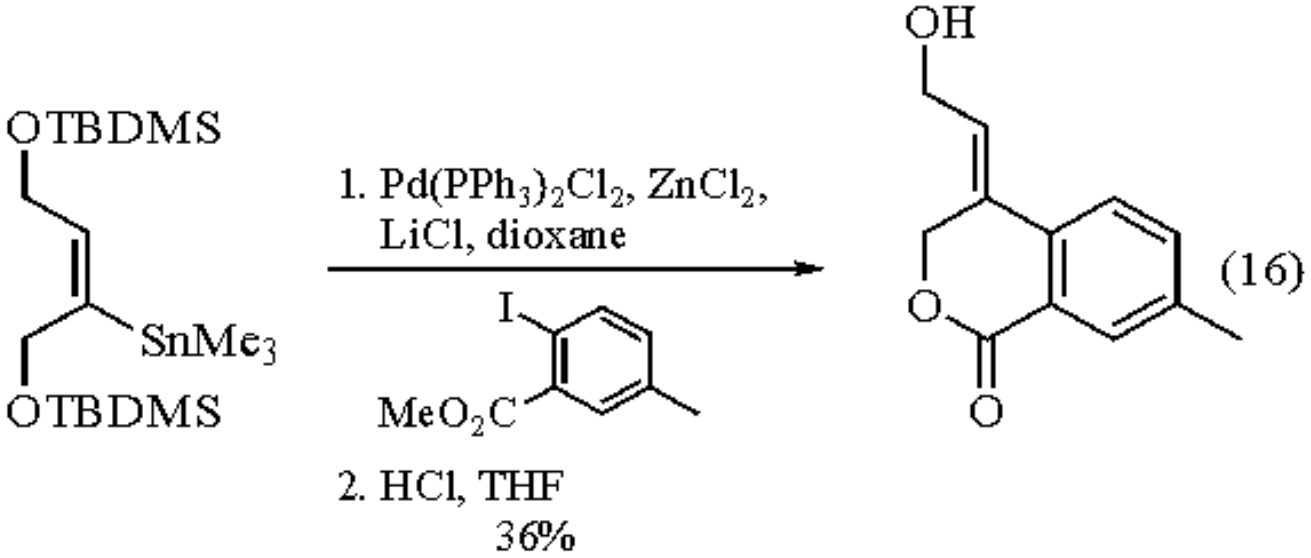

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16. Piers, E.; Friesen, R. W. *CJC* **1987**, *65*, 1681.
17. Piers, E.; Llinas-Brunet, M. *JOC* **1989**, *54*, 1483. See also: Piers, E.; Llinas-Brunet, M.; Oballa, R. M. *CJC* **1993**, *71*, 1484.
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Joseph S. Warmus

Iodylbenzene[1]

$PhIO_2$

[696-33-3] · $C_6H_5IO_2$ · Iodylbenzene · (MW 236.01)

(ring cleavage of indole and imidazole derivatives;[2] quinone formation;[3] dehydrogenation of 3-keto steroids to dienones;[4] other enone dehydrogenations;[5] allylic oxidations;[6] the Nef reaction[7])

Alternate Name: iodoxybenzene.

Physical Data: mp 230 °C, *explosive decomposition* 250-253 °C.

Solubility: sol H_2O (2.8 g L^{-1} at 12 °C, 12 g L^{-1} at 100 °C). $PhIO_2$ is polymeric in the solid state and dissolution in solvent is due to a chemical reaction.

Analysis of Reagent Purity: by iodiometric titration.[12]

Preparative Methods: by disproportionation of ***Iodosylbenzene***,[8] by treatment of ***Phenyliodine(III) Dichloride*** with ***Sodium Hypochlorite***,[9] by ***Peracetic Acid*** (40%) oxidation of iodobenzene,[10] or oxidation with ***Potassium Bromate*** in ***Sulfuric Acid***[11] (which is the best method).

Purification: by crystallization from hot water[8] or by washing with chloroform followed by drying.[9,10]

Handling, Storage, and Precautions: should be freshly prepared and should not be heated in the absence of solvent because of the danger of explosion. This reagent should be handled in a fume hood.

Iodylbenzene is a weaker oxidant compared with iodosylbenzene. The systems $PhIO_2/(PhSeO)_2O$ and $PhIO_2/(PhSe)_2$ are synthetically useful and the oxidative capabilities of $PhIO_2$ are improved by Lewis acids or ***p-Toluenesulfonic Acid***.

Ring cleavage of amino acids using *p-t*-$BuC_6H_4IO_2$ in chlorobenzene is a useful reaction. For example, tryptophan *N*-benzoyl methyl ester gives the kynurenine derivative (eq 1),[2] and histidine-*N*-Cbz-methyl ester undergoes a similar process (eq 2).[2]

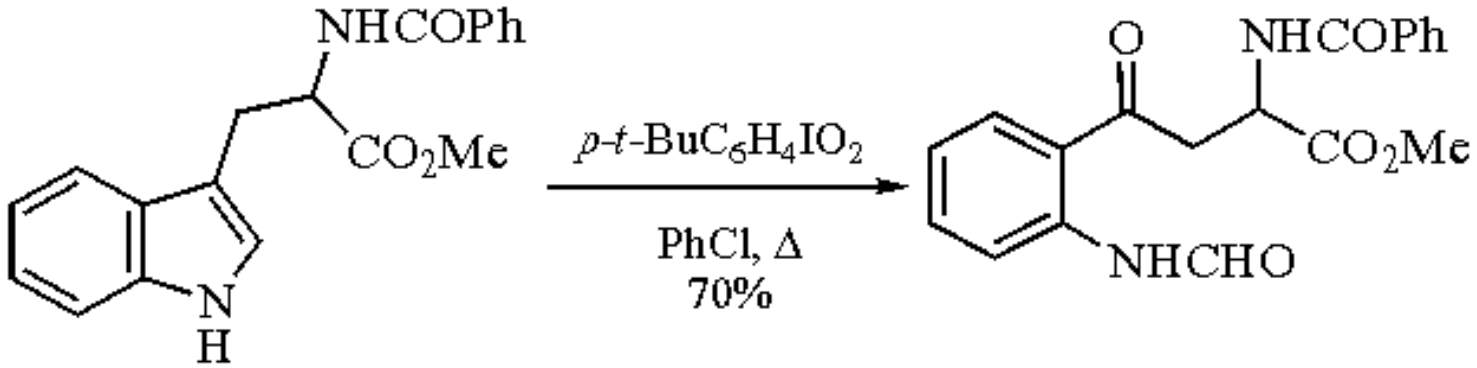

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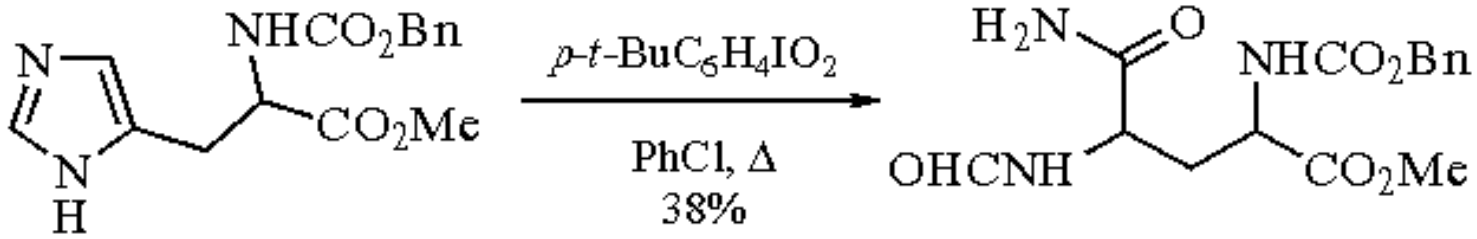

(2)

$PhIO_2$ itself or *m*-iodylbenzoic acid as the *N,N,N,´N´*-tetramethyl-*N´´*-*t*-butylguanidinium salts in CH_2Cl_2 are useful reagents for the oxidation of phenols to benzoquinones. β-Naphthol is oxidized to 1,2-naphthoquinone in 65% yield.[3] Use of *m*-iodylbenzoic acid has the advantage that it is recoverable as its reduction product, *m*-iodobenzoic acid. *m*-Iodylbenzoic acid is made by commercial hypochlorite solution oxidation of *m*-iodobenzoic acid.[4]

The dehydrogenation of steroidal 3-ketones either to the enone or dienone is an important process. The catalytic system of $PhIO_2$ and ***Diphenyl Diselenide*** offers an excellent method for this transformation (eq 3).[4]

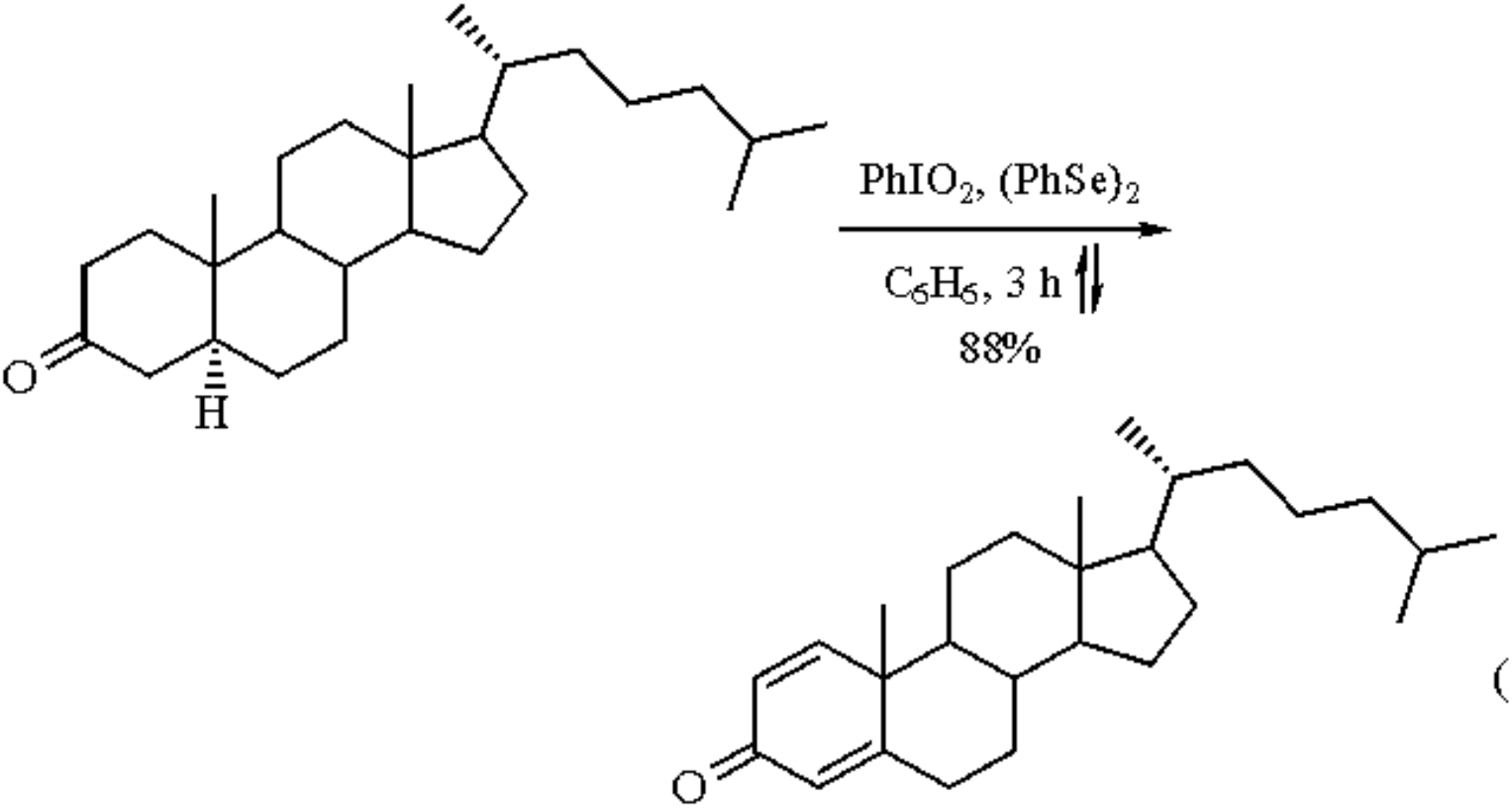

(3)

$PhIO_2/(PhSeO)_2O$ was singularly useful in the synthesis of a 4a-methyl-4a*H*-fluorenone (eq 4).[5]

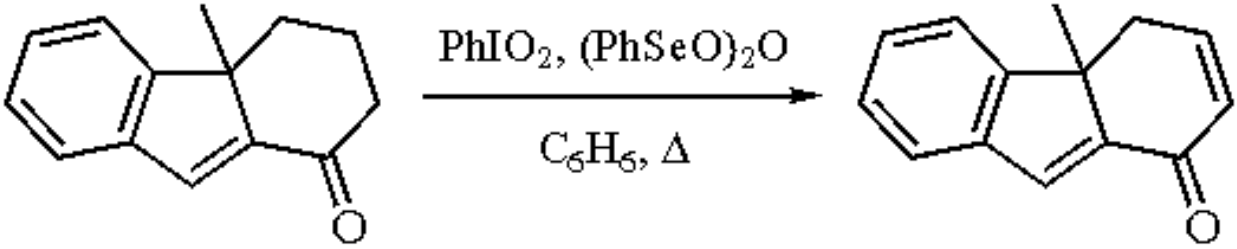

(4)

A valuable application of the $PhIO_2$/***2,2´-Dipyridyl Diselenide*** system is illustrated in the allylic oxidation of alkenes such as (1*S*)-(-)β-pinene to pinocarvone (eq 5),[6] cholesteryl benzoate to 4-ketocholesteryl benzoate (eq 6),[6] and α-terpineol to 6-keto-α-terpineol (eq 7).[6]

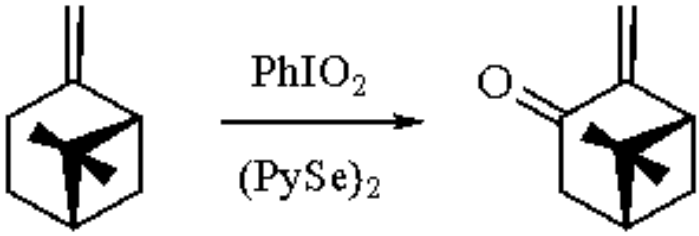

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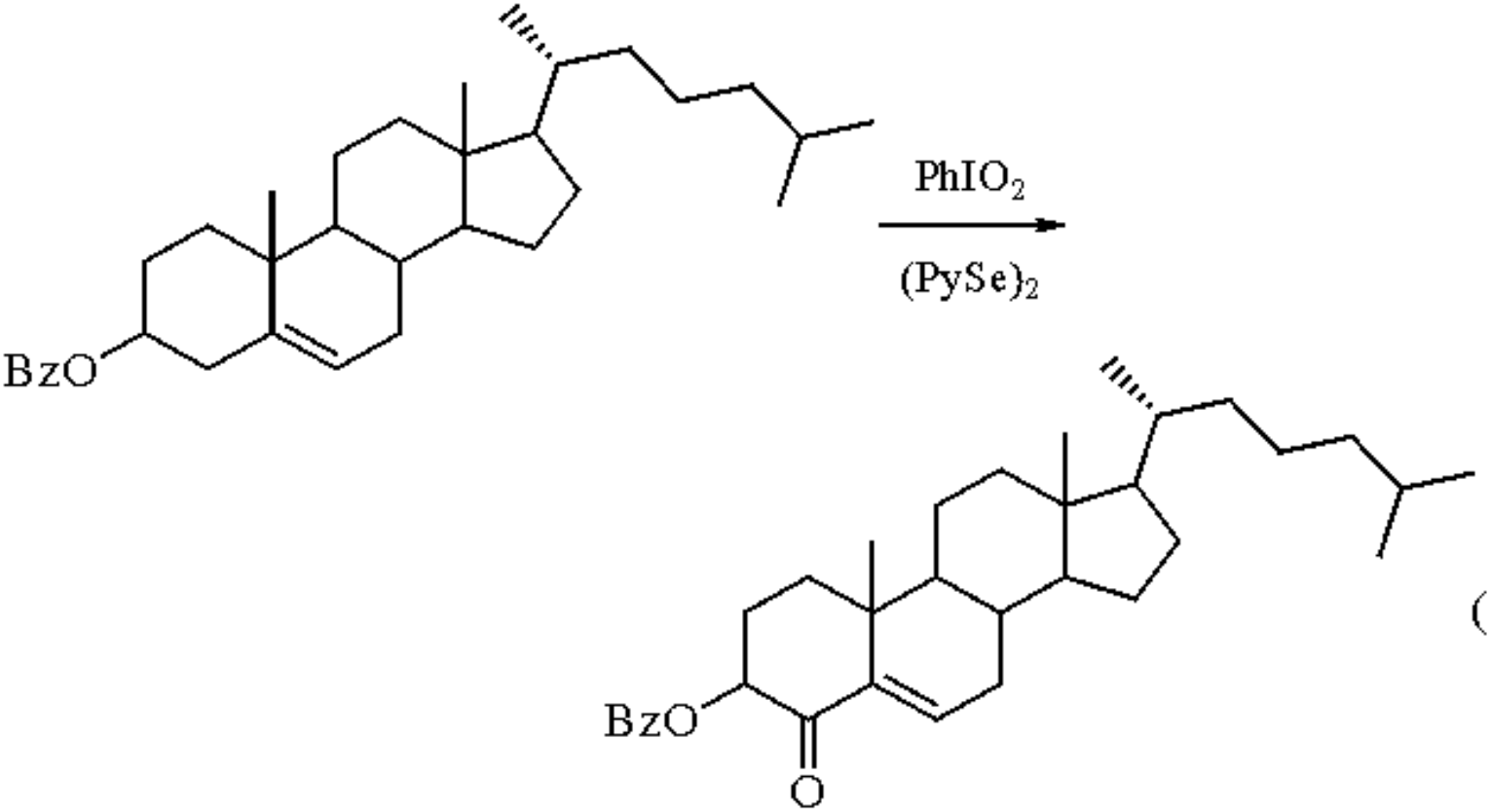

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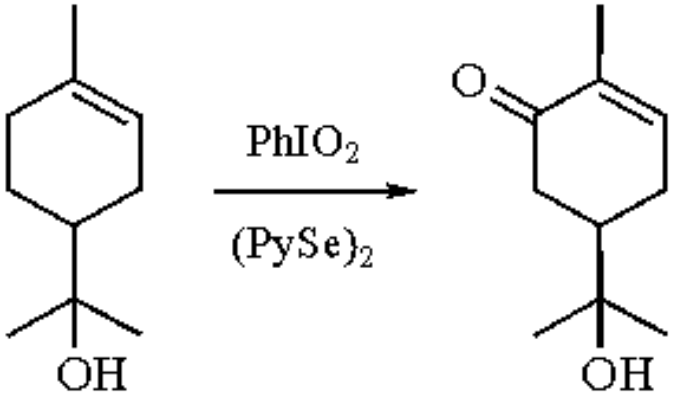

(7)

m-Iodylbenzoic acid in the presence of excess *N,N,N,´,N´*-tetramethyl-*N´´*-*t*-butylguanidine is a mild and efficient reagent for the Nef reaction for conversion of secondary nitro compounds to ketones, even in the presence of other oxidizable groups (eq 8).[7]

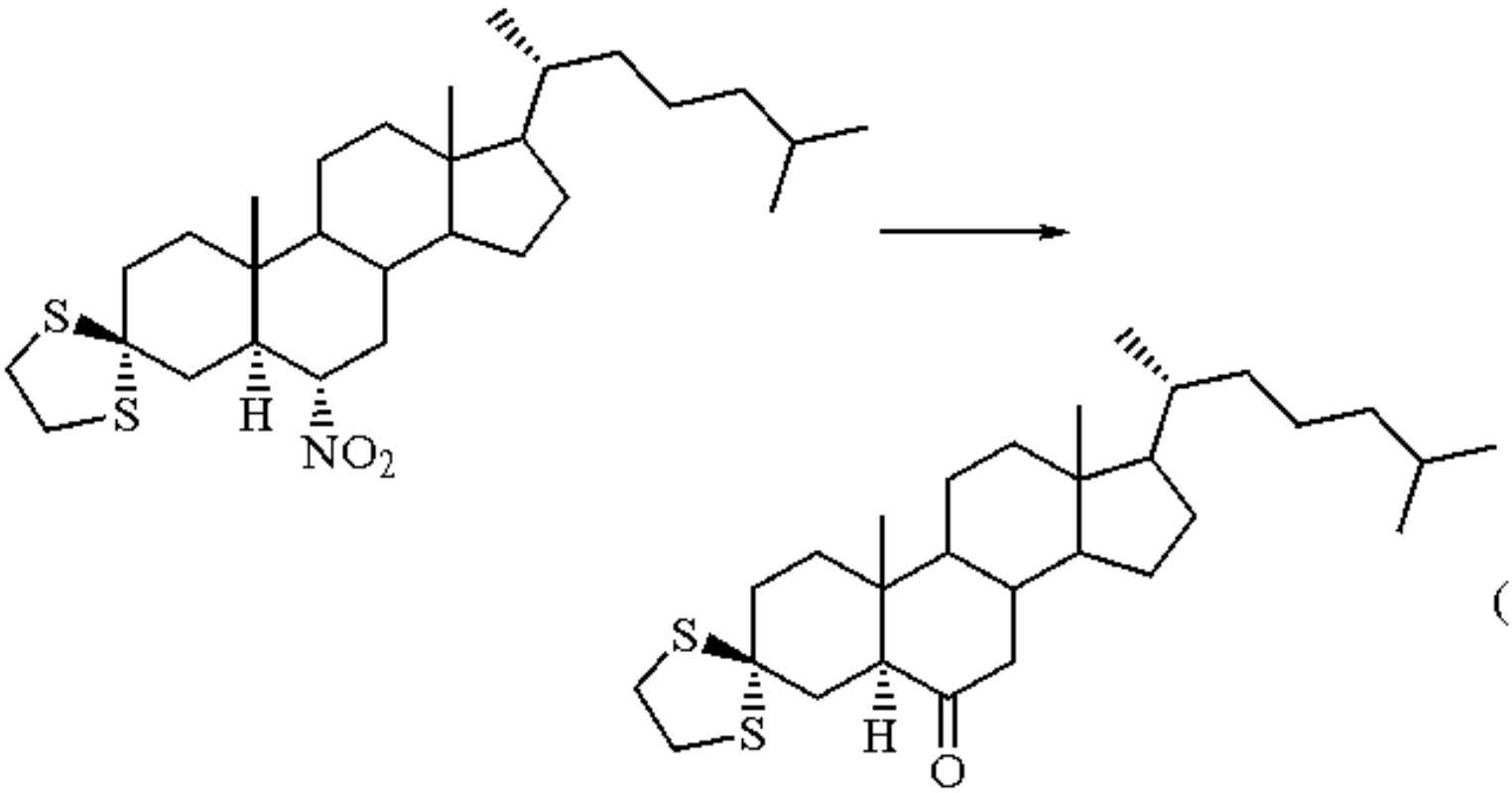

(8)

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Iridium Catalysts[1]

Ir

[7439-88-5] · Ir · Iridium · (MW 192.22)

(moderately active hydrogenation catalysts useful for selective hydrogenation of α,β-unsaturated aldehydes to allylic alcohols;[2] for stereoselective hydrogenation of C-C double bonds;[3] for selective hydrogenation of aromatic nitro compounds[4,5] and quinolines[6])

Physical Data: mp 2454 °C; bp ca. 4800 °C; *d* (20 °C) 22.65 g cm^{-3}.

Solubility: sol aqua regia after fusion with Na_2O_2 or a mixture of KOH and KNO_3.

Form Supplied in: Ir/C (usually 5% Ir), Ir black, and IrO_2 (a precursor of Ir black) are commercially available.

Preparative Methods: $IrCl_3.3H_2O$, $IrCl_4.xH_2O$, Na_2IrCl_6, $(NH_4)_2IrCl_6$ are usual starting reagents for the preparation of supported and unsupported Ir catalysts. Unsupported Ir catalysts have been prepared by reducing IrO_2 (an Adams' type) at 165 °C under a stream of hydrogen[4] or by reducing $Ir(OH)_3$ or $Ir_2O_3.3H_2O$ (precipitated by adding aq NaOH or LiOH to an aq solution of $IrCl_3.3H_2O$) in H_2O at 80-90 °C under 8 MPa H_2.[7] Unsupported and supported Ir catalysts have also been prepared by the reaction of $IrCl_4.xH_2O$ with $NaBH_4$ in EtOH.[8]

Handling, Storage, and Precautions: Ir catalysts are rather stable and can be stored in the air without losing activity. Not attacked by any of the acids nor by aqua regia; only superficially oxidized on heating in air; oxidized at red heat to form IrO_2; direct contact with explosive gas mixtures containing H_2 or with alcoholic solvents, especially such as MeOH or EtOH, should be avoided.

Selective Hydrogenation of α,β-Unsaturated Aldehydes to Allylic Alcohols.

Allylic alcohols have been obtained in high yields from the hydrogenation of α,β-unsaturated aldehydes in EtOH with 5% Ir/C catalyst (eqs 1 and 2).[2] With 2-propenal (acrolein), however, the yield of allyl alcohol was lower (60%).

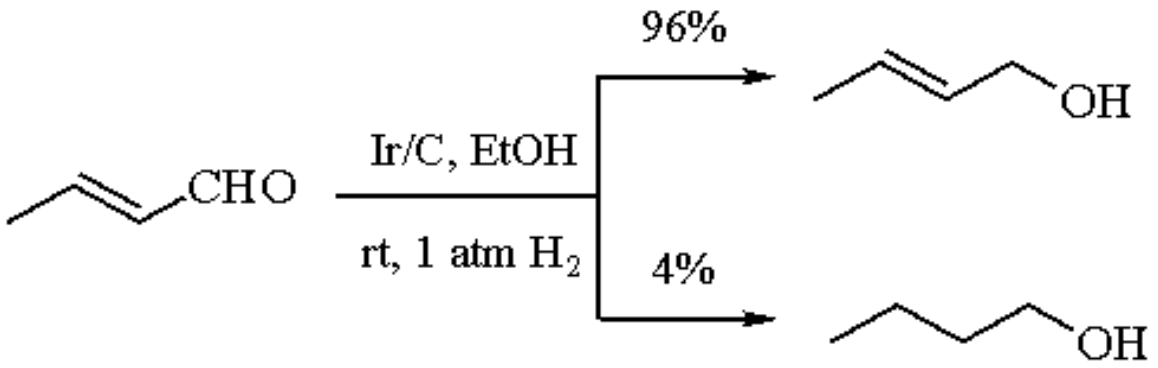

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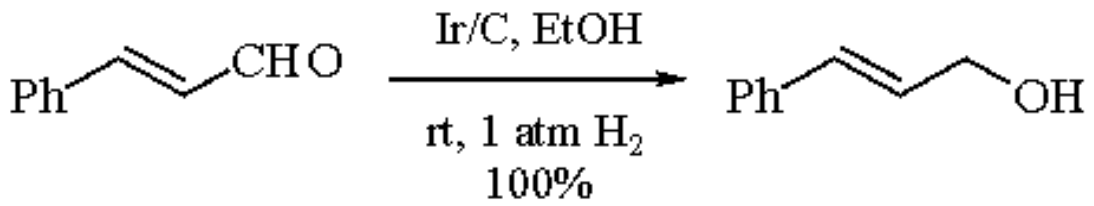

(2)

A number of alternative methods for the enal reductions using heterogeneous catalysts have also been reported.[9] Some of the effective catalyst systems are: Pt,[10] Pt/C or Pt/$CaCO_3$,[9] modified by $FeSO_4$-$Zn(OAc)_2$; Pt-Ge-Nylon (3% Ge);[11] prereduced Re_2O_7/pyridine;[12] and Raney type Ag-Zn.[13]

Stereoselective Hydrogenation of C-C Double Bonds.

Ir catalysts are highly stereoselective in the hydrogenation of alkenic and aromatic compounds. Thus hydrogenation of 1,2-dimethylcyclohexene and *o*-xylene with Ir black in *i*-PrOH at 25 °C and atmospheric pressure of H_2 gave *cis*-1,2-dimethylcyclohexane in 98.7 and 98.6% yields, respectively.[14] Eq 3 compares the stereoselectivity of the six platinum metals in the hydrogenation of 1,2-dimethylcyclohexene and *o*-xylene (data in parentheses) in *t*-BuOH.[3] Similarly, deuteration of $\Delta^{9,10}$-octalin with 5% Ir/C (25 °C, 2.5-2.7 MPa D_2) gave *cis*-decalin in 97.8% selectivity.[15] However, as has been observed with 1,2- and 1,6-dimethylcyclohexenes,[16] the deuteration products obtained with Ir catalyst are extensively exchanged in spite of high stereoselectivity in the formation of the *cis* isomer. The high stereoselectivity of Ir catalysts is associated with their low alkene isomerization activity during hydrogenation.[3] Excellent examples of stereoselective synthesis using Ir catalysts have been reported in the hydrogenation of the 16-methylene steroid (**1**) to the 16β-methyl derivative (**2**) (eq 4)[17] and in the hydrogenation of the unsaturated ketone (**3**) to the saturated ketone (**4**) (eq 5),[18] which was an important step in the total synthesis of (±)-9-isocyanopupukeanane. Both the hydrogenations gave mixtures of stereoisomers with other metal catalysts.

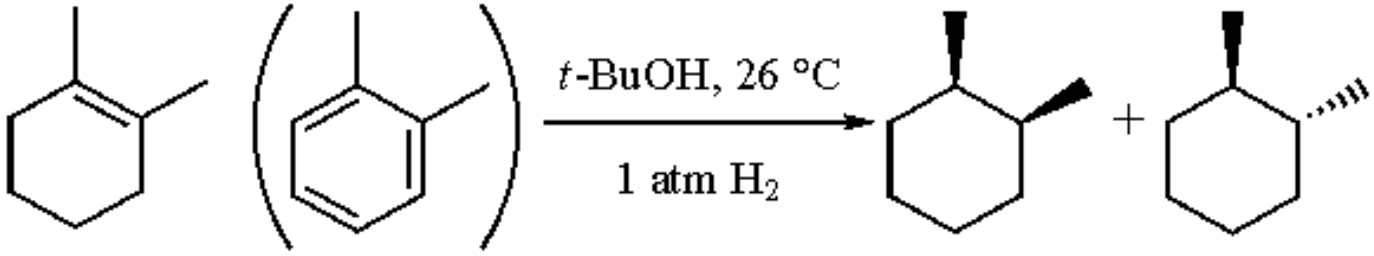

(3)

Catalyst	
Ru	93.5 (94.6):6.5 (5.4)
Rh	87.6 (95.8):12.4 (4.2)
Pd	26.4 (57.7*):73.6 (42.3*)
Os	98.7 (97.9):1.3 (2.1)
Ir	99.2 (99.2):0.8 (0.8)
Pt	79.1 (89.6):20.9 (10.4)

* 50 °C

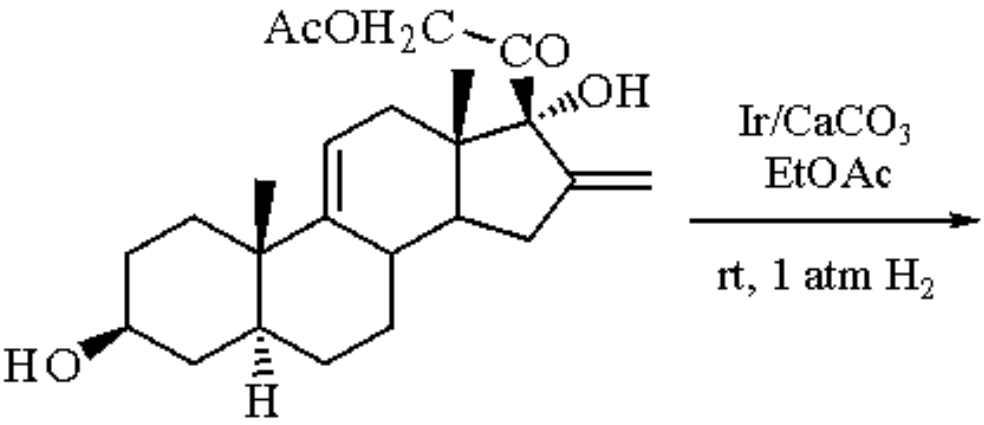

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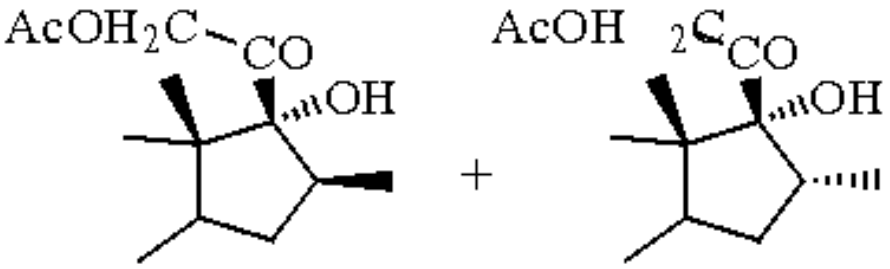

(4)

(2) <2%

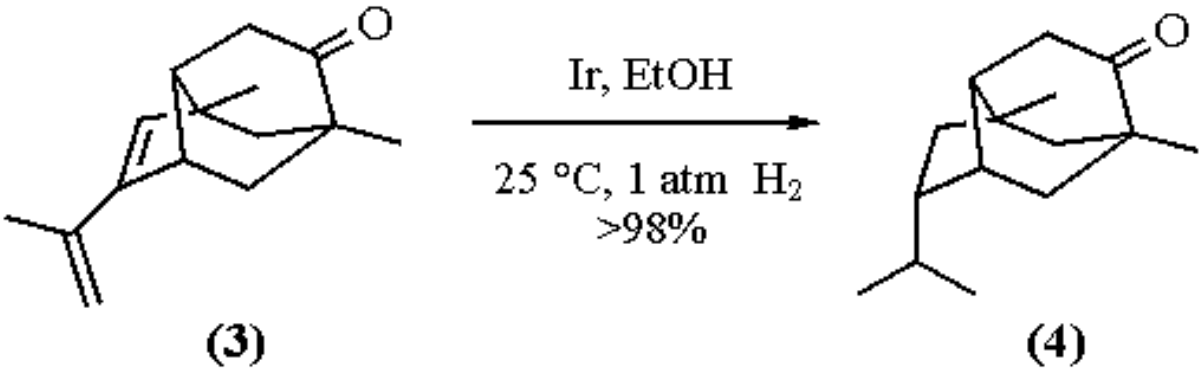

(5)

Selective Hydrogenation of Aromatic Nitro Compounds.

Hydrogenation of aromatic nitro compounds with Ir catalysts often slows down after the uptake of 2 mol of H_2 and the corresponding hydroxylamines are obtained in good yields (eqs 6-8).[4,5] Usually higher yields are obtained at neutral pH, at low temperatures, and with substrates having electron-withdrawing substituents.[4,19]

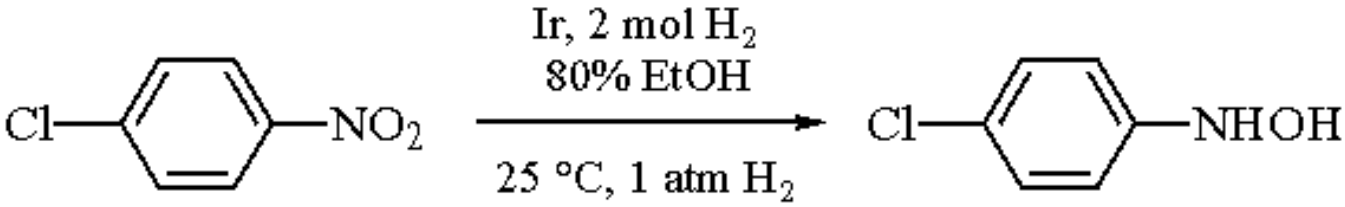

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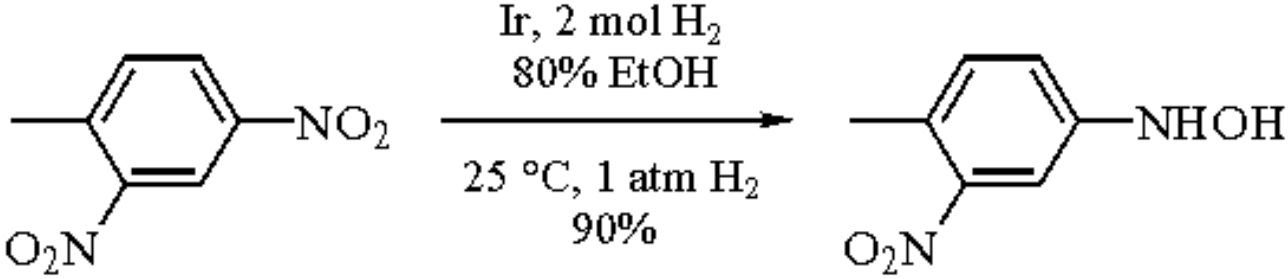

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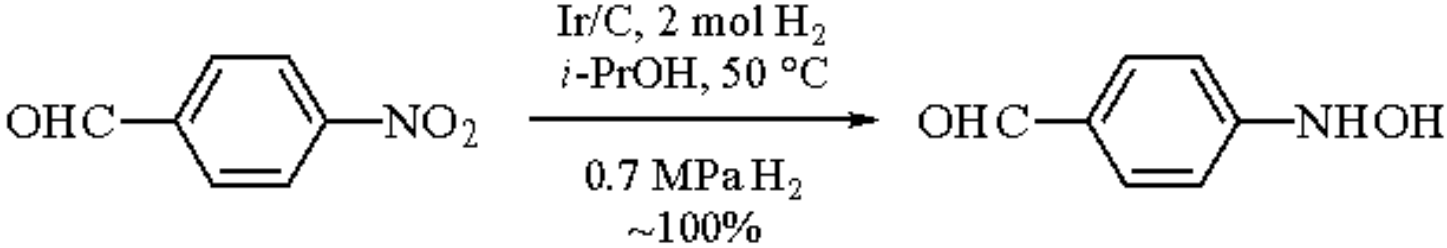

(8)

Hydrogenation of halonitrobenzenes with Ir catalysts is accompanied by only slight dehalogenation. For example, hydrogenation of 3,4-dichloronitrobenzene with 5% Ir/C in *i*-PrOH gave the corresponding dichloroaniline almost quantitatively.[5] The rate of the dechlorination was only 1/250th of the rate of the hydrogenation. Other effective methods for suppressing dehalogenation have also been described using Pt/C and Ni catalysts in the presence of some inhibitors or a sulfided Pt/C catalyst.[20]

Selective Hydrogenation of Quinolines in the Heterocyclic Ring.

Both 2- and 4-methylquinolines are hydrogenated with iridium catalysts exclusively to the corresponding 1,2,3,4-tetrahydroquinolines without any additives (eqs 9 and 10).[6] With Pd, Pt, Ru, Rh, and Ni catalysts the same selective hydrogenation can be achieved only in the presence of sulfur compounds or carbon monoxide.

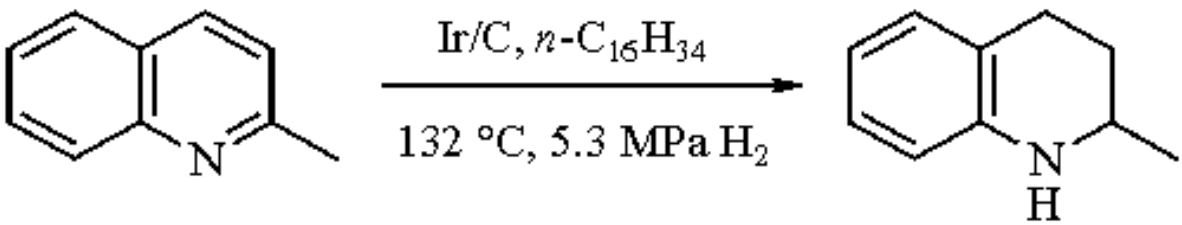

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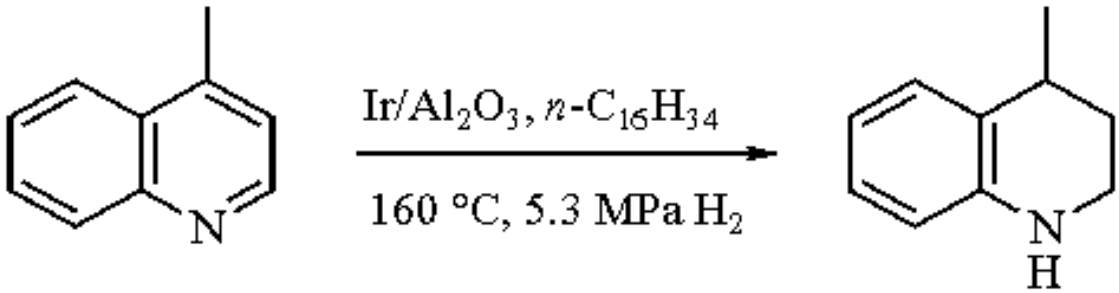

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Iridium(IV) Chloride

$IrCl_4$

[10025-97-5] · Cl_4Ir · Iridium(IV) Chloride · (MW 334.02)

(catalyst precursor for the stereoselective reduction of cyclohexanones[1-3])

Physical Data: decomposes on heating.

Solubility: sol cold H_2O, alcohol.

Form Supplied in: dark brown, hygroscopic, amorphous mass. Pure iridium tetrachloride does not seem to have been made. Products sold as such contain water (about 10%) and may also contain some chloroiridic acid [H_2IrCl_6]. The manufacturer should state the iridium content. The ammonium salt [$(NH_4)_2IrCl_6$], which can be obtained in a pure state, can be used instead.

Stereoselective Reductions.

Iridium tetrachloride is a catalyst precursor for the reduction of unhindered (conformationally biased or rigid) cyclohexanones to cyclohexanols with the hydroxy group largely axial (often >95%). The reactions are carried out in 90% aqueous 2-propanol and require the presence of phosphorous acid, H_3PO_3, or its dimethyl or trimethyl ester. The phosphorus-containing compound acts as the main reducing agent in the system and 2-propanol as a very minor one. Dimethyl phosphite, $(MeO)_2P(O)H$, is the most convenient to use as phosphorous acid is hygroscopic and trimethyl phosphite is both very toxic and has an unpleasant odor.

Experimentally the reaction is very simple. There is no need to exclude atmospheric oxygen or moisture. The reactants are merely heated at reflux until reaction is complete. The phosphorus compound should be present in at least 100% excess with respect to the ketone. Some examples of the reduction of simple cyclohexanones are given in eqs 1-4.[2]

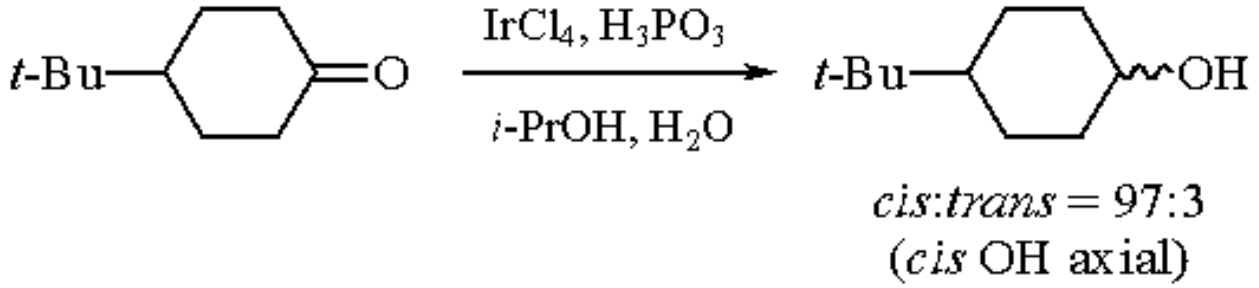

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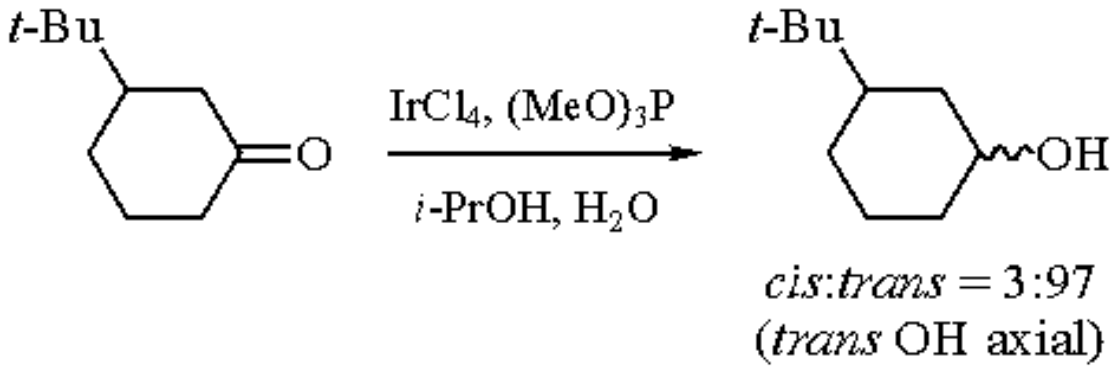

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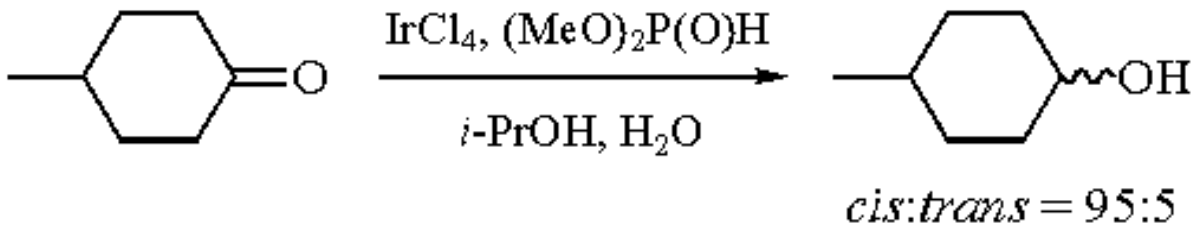

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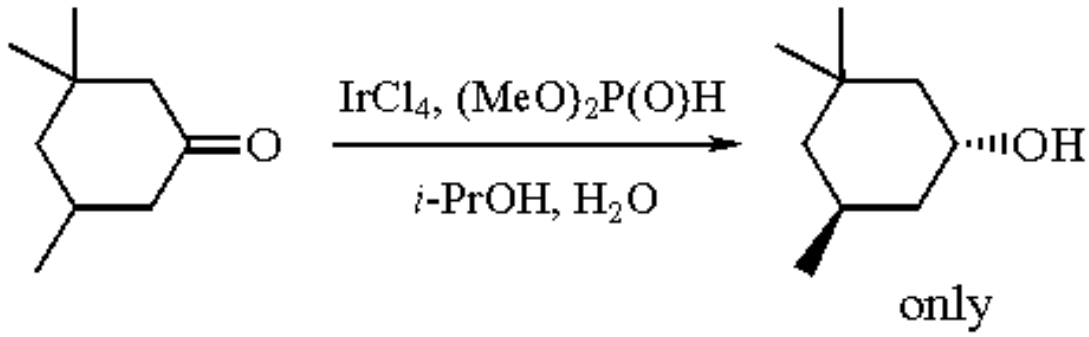

(4)

The Selectride reagents, developed by Brown,[4,5] give equal or even greater selectivity in the reduction of cyclohexanones to axial alcohols, but require anhydrous reaction conditions, an inert atmosphere, and often low temperatures.

Regioselective and Stereoselective Reductions.

Hindered ketones such as 2,2,6-trimethylcyclohexanone are not reduced. This property has been used for the regio- and stereoselective reduction of some steroidal di- and triketones in which the hindered carbonyl group(s) are not reduced (eqs 5 and 6).[6]

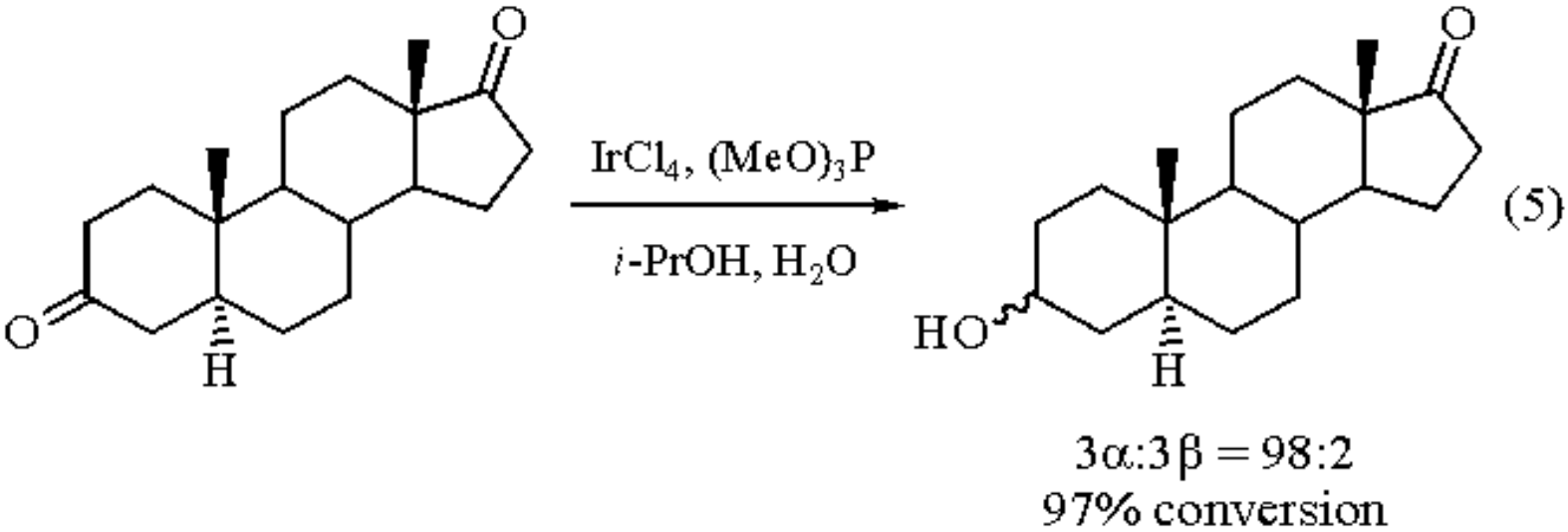

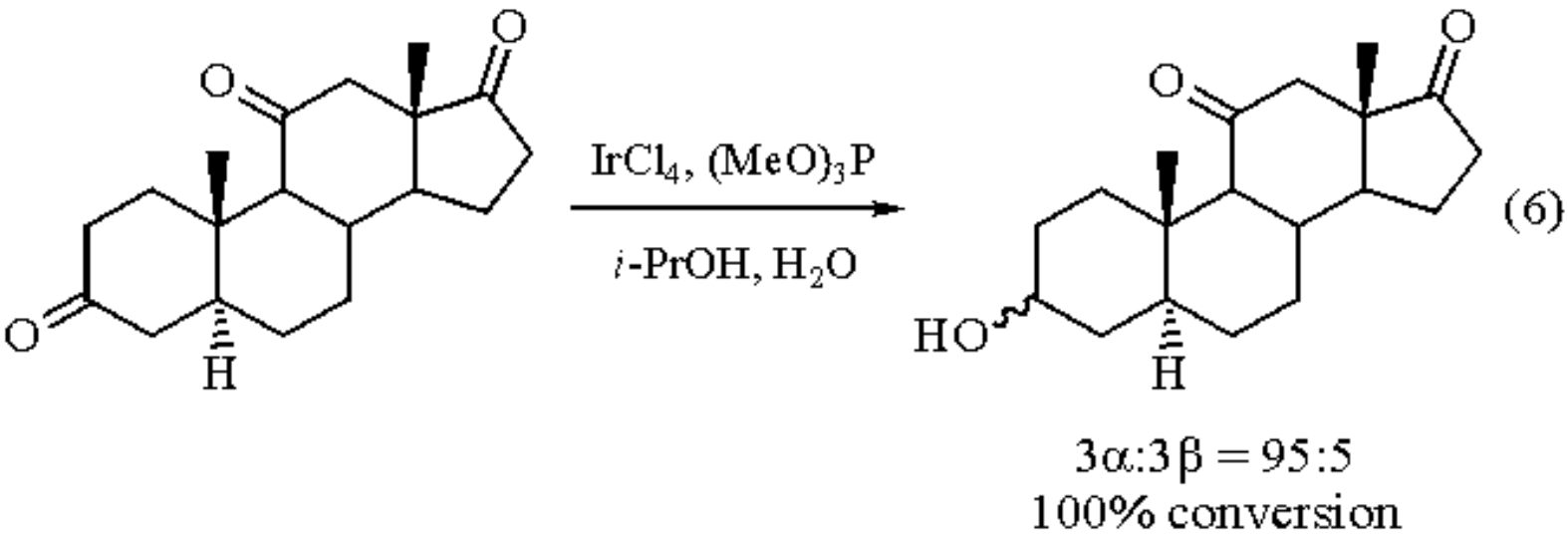

Similar transformations can be carried out with K-Selectride (***Potassium Tri-s-butylborohydride***), but seem difficult to take to completion.[7]

Catalyst.

The identity of the catalyst in these reductions is not known, but is presumably an iridium-phosphite complex. Some such complexes have been made in an attempt to shed light on the nature of the catalyst.[8,9]

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Iron

Fe

[7439-89-6] · Fe · Iron · (MW 55.85)

(efficient catalyst for a wide variety of organic transformations)

Physical Data: mp 1535 °C; *d* 7.860 g cm^{-3}.

Solubility: insol water, alkalis, alcohols, ethers; sol acid (attacked or dissolved).

Form Supplied in: chip, foil, filings, powder, wire.

Analysis of Reagent Purity: atomic absorption methods can be used.

Handling, Storage, and Precautions: moisture sensitive.

General.

Iron is used to catalyze a wide variety of organic transformations. The nature of the iron catalyst depends on the reaction conditions (solvent, cocatalysts, etc.) employed for a specific transformation. The reaction descriptions included in this entry will be limited to those utilizing iron powder and to some reactions in which iron(0) is generated in situ, serving as the active catalyst during the reaction.

Iron Powder.

Formation of Lactones.

The lactonization of γ-bromo-α,β-unsaturated carboxylic methyl esters and acids is promoted by heating the substrate in the presence of iron powder (eq 1). Iron apparently facilitates the elimination of methyl bromide and rotation about the double bond.[1]

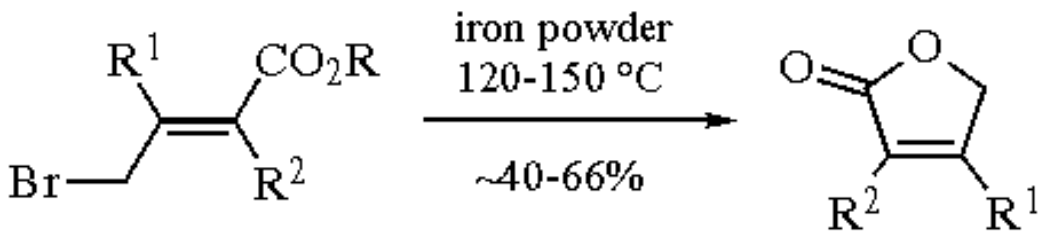

(1)

Preparation of Nonconjugated Dienes.

Nonconjugated dienes are conveniently prepared from allylic halides via an iron-promoted coupling reaction in DMF (Table 1).[2] Excellent yields are obtained in many cases and some catalytic effect of added halide salts is also observed. The iron salts in the DMF residue were analyzed as 70% Fe^{2+} and 30% Fe^{3+} (via oxidation of Fe^{2+}). Similar types of reaction are observed with a variety of transition metal catalysts, including Pd- and Ni-based catalysts.

Table 1 Coupling of Allyl Chlorides with Iron in DMF (150 °C, 1 h)

Allyl chloride	Conversion (%)	Product	Crude yield (%)
Allyl chloride	65	1,5-Hexadiene	61.5
b-Methallyl chloride	77	2,5-Dimethyl-1,5-hexadiene	60
Allyl chloride + b-methallyl chloride (1:1)	98	1,5-Hexadiene	21
		2-Methyl-1,5-hexadiene	44.8
		2,5-Dimethyl-1,5-hexadiene	24.1

Preparation of Ketones from Carboxylic Acids.

Carboxylic acids react with hydrogen-reduced iron powder to give an iron dicarboxylate intermediate which, upon thermolysis, decomposes to give the condensed ketone, CO_2, and FeO (eq 2).[3]

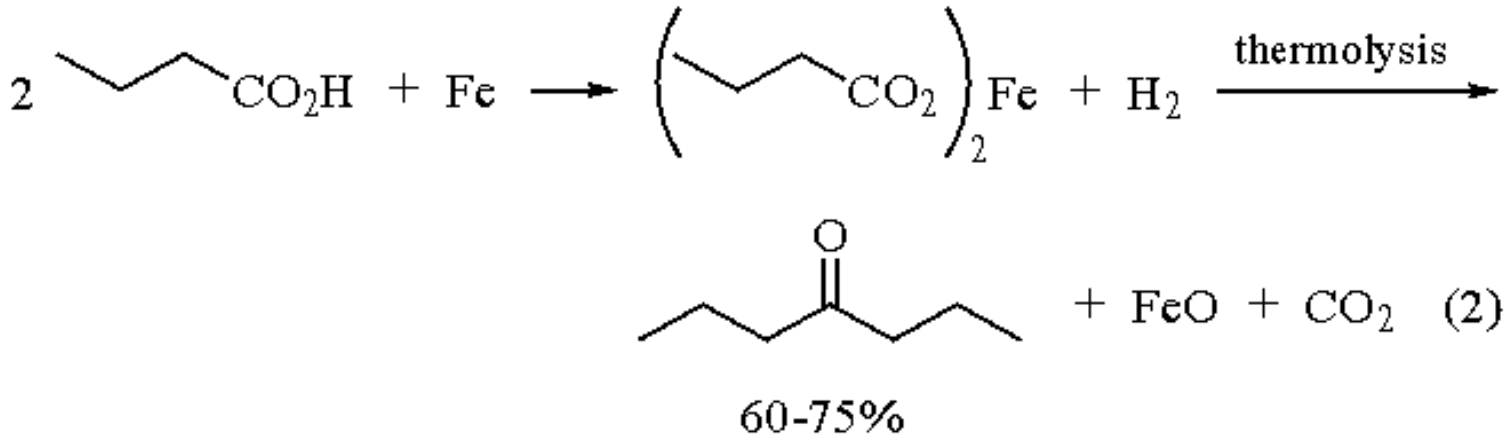

Reduction.

The reduction of nitroaromatics to anilines with iron powder is carried out in a mixture of methanol and concentrated ***Hydrochloric Acid*** (eq 3). In the absence of methanol, only partial reduction is observed.[4]

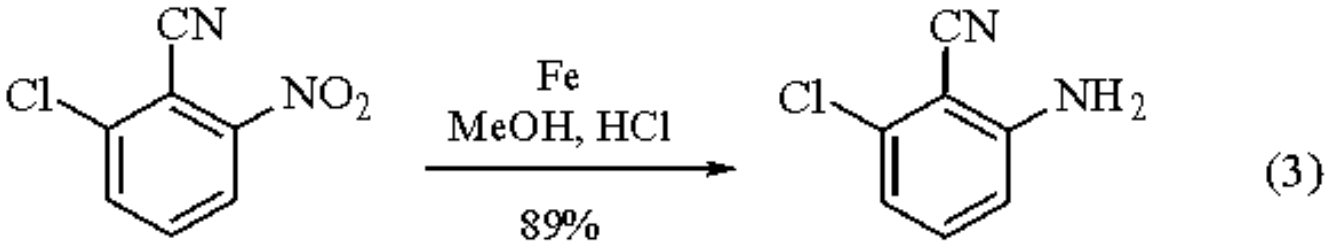

The reduction of optically active nitroalkanes to active amines is accomplished with iron in ***Acetic Acid***. The reaction proceeds with &egt;82% optical purity. Other reducing agents, such as ***Lithium Aluminum Hydride***, gave a completely racemic mixture of amines.[5]

Iron Cluster Compounds.

Gif Catalyst-Air Oxidation of Saturated Hydrocarbons.

The Gif catalyst, $Fe_2FeO(OAc)_6py_{3.5}$, is a triiron cluster compound that is generated from the reaction of iron dust, acetic acid, and pyridine. The use of this and a reducing agent in acetic acid and pyridine promotes the air oxidation of saturated hydrocarbons. It is a selective reagent in that least hindered, secondary positions are preferentially attacked, leading to the formation of ketones. It does not epoxidize simple alkenes.

The Gif catalyst is but one of a number of (μ_3-oxo) triiron complexes, some of which have been used as a catalyst for the epoxidation of alkenic alcohol acetates with molecular oxygen (see ***μ_3-Oxohexakis(μ-trimethylacetato)tris(methanol)triiron(III) Chloride***).[6]

Iron(0) Catalysts: Reduction of Fe^{III} Compounds.

Deprotonation of Aldehydes and Ketones: Preparation of Silyl Dienol Ethers.

Grignard reagents have been shown[7] to reduce Fe^{III} compounds to air sensitive Fe^0 and it is this reduced species that is responsible for catalyzing a number of useful organic reactions.[8] For example, aldehydes and ketones are smoothly converted to the corresponding, thermodynamically favored, trimethylsilyl enol ethers upon treatment with Fe^0, ***Chlorotrimethylsilane***, and ***Triethylamine*** (eq 4). When a stoichiometric amount of Fe^0 catalyst is reacted (no additional Grignard reagent) with cycloalkenones, the exocyclic through-conjugated dienol ether is predominantly formed.[9] When a stoichiometric amount of Grignard reagent is reacted with the cyclohexenone in the presence of a catalytic amount of ***Iron(III) Chloride*** (Kharasch reagent),[10] the endocyclic through-conjugated dienol ether is formed. Likewise, when 0.5-1 equiv of Fe^0 catalyst and 1 equiv of Grignard reagent is reacted with the same cyclohexenone (oxygen excluded), the endocyclic through-conjugated dienol ether is again the predominant dienol ether formed.

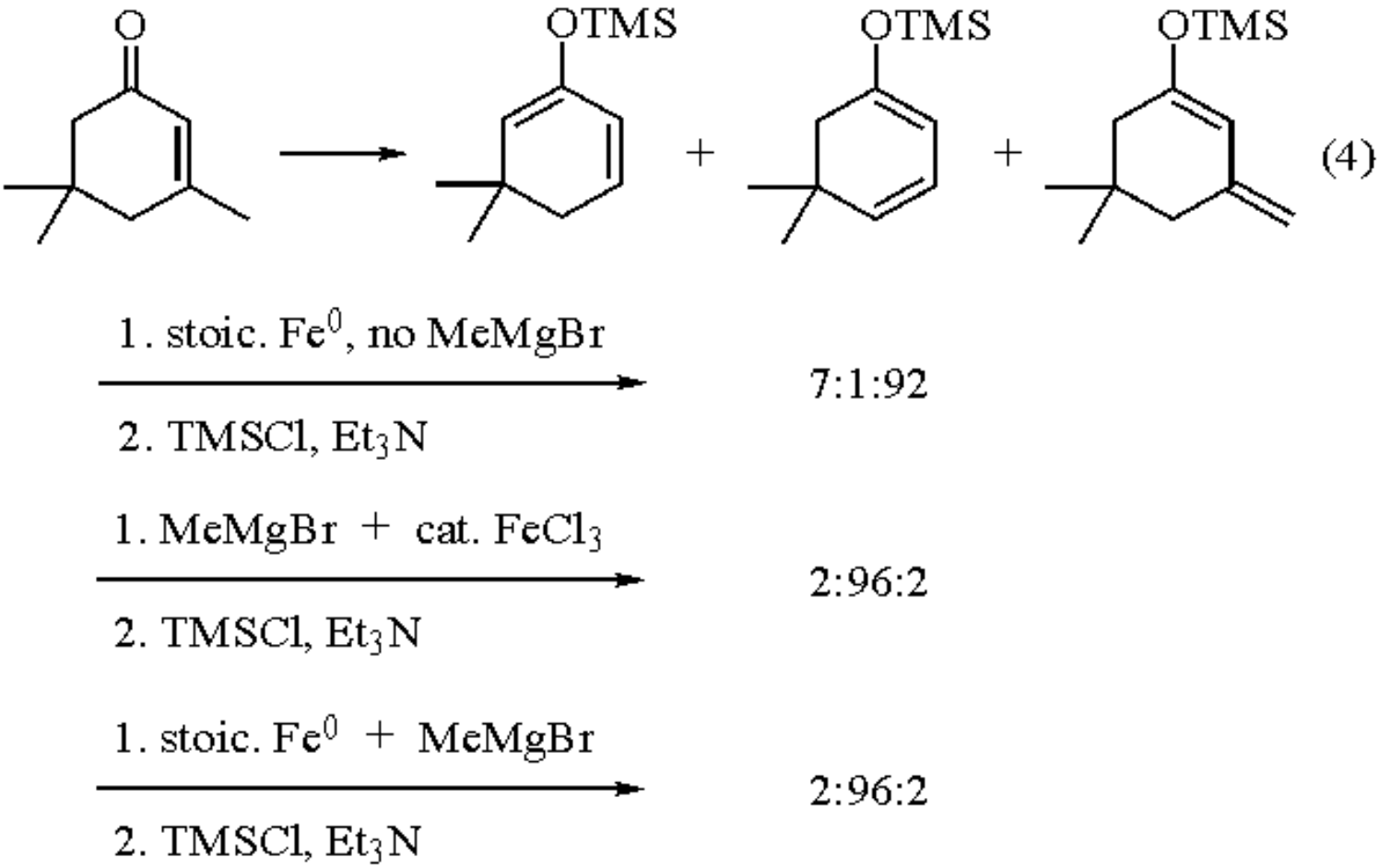

Iron(0) compounds have been proposed to be the active catalyst in a number of other organic reactions. For example, cross coupling reactions between Grignard reagents and alkyl, vinyl, allyl, and phenyl halides are catalyzed by various iron(III) complexes, such as ***Tris(dibenzoylmethide)iron(III)***.[11] It is proposed that the reaction between the Grignard reagent and the iron(III) compound produces the active iron(0) catalyst.

---

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Iron(III) Acetylacetonate-Hydrogen Peroxide[1]

$Fe(MeCOCHCOMe)_3$-H_2O_2

($Fe(acac)_3$)

[14024-18-1] · $C_{15}H_{21}FeO_6$ · Iron(III) Acetylacetonate-Hydrogen Peroxide · (MW 353.21) (H_2O_2)

[7722-84-1] · H_2O_2 · Iron(III) Acetylacetonate-Hydrogen Peroxide · (MW 34.02)

(β-epoxidation of cholesterol derivatives;[2] *trans*-epoxidation of alkenes[3])

Alternate Name: tris(acetylacetonate)iron(III)-hydrogen peroxide.

Physical Data: $Fe(acac)_3$: mp 184 °C, *d* 1.33 g cm^{-3}.

Solubility: slightly sol cold and hot water; sol alcohol, acetone, benzene, chloroform.

Form Supplied in: dark red powder; widely available.

Preparative Method: reagent combination is generated in situ, via dropwise addition of 30% ***Hydrogen Peroxide*** (49 mmol) to a stirred solution of ***Tris(acetylacetonato)iron(III)*** (2.7 mmol), and substrate (0.26 mmol) in acetonitrile.[2,3]

Handling, Storage, and Precautions: use in a fume hood. $Fe(acac)_3$ causes severe eye irritation and may cause skin irritation. Toxic fumes of carbon monoxide and carbon dioxide are generated on decomposition. It is incompatible with strong oxidizing agents; thus the H_2O_2 has to be used in excess because it is decomposed by Fe^{III} ion.[4] Reactions should be worked up by decomposition of excess H_2O_2 with saturated aqueous sodium sulfite and then extraction of product with ether. See also ***Hydrogen Peroxide***.

β-Epoxidation of Cholesterol Derivatives.[2]

Steroidal alkenes are stereoselectively epoxidized from the β-face with $Fe(acac)_3$-H_2O_2 (eq 1), via a radical process.[5] In contrast, organic peracids (***m-Chloroperbenzoic Acid***) yield the α-epoxide via attack from the least hindered face.[6] Cholest-4-en-3β-ol yields β-epoxidation with $Fe(acac)_3$ and organic peracids, but this is due to hydroxyl coordination. Other cholest-4-ene derivatives yield β-epoxidation with $Fe(acac)_3$ and α-epoxidation with organic peracids (eq 2).[2]

Low yields of epoxide with some substrates are usually caused by formation of the allylic oxidation product, and indeed use of $Fe(acac)_3$-***t-Butyl Hydroperoxide*** or other transition metal acac salts yield predominantly allylic oxidation.[5a]

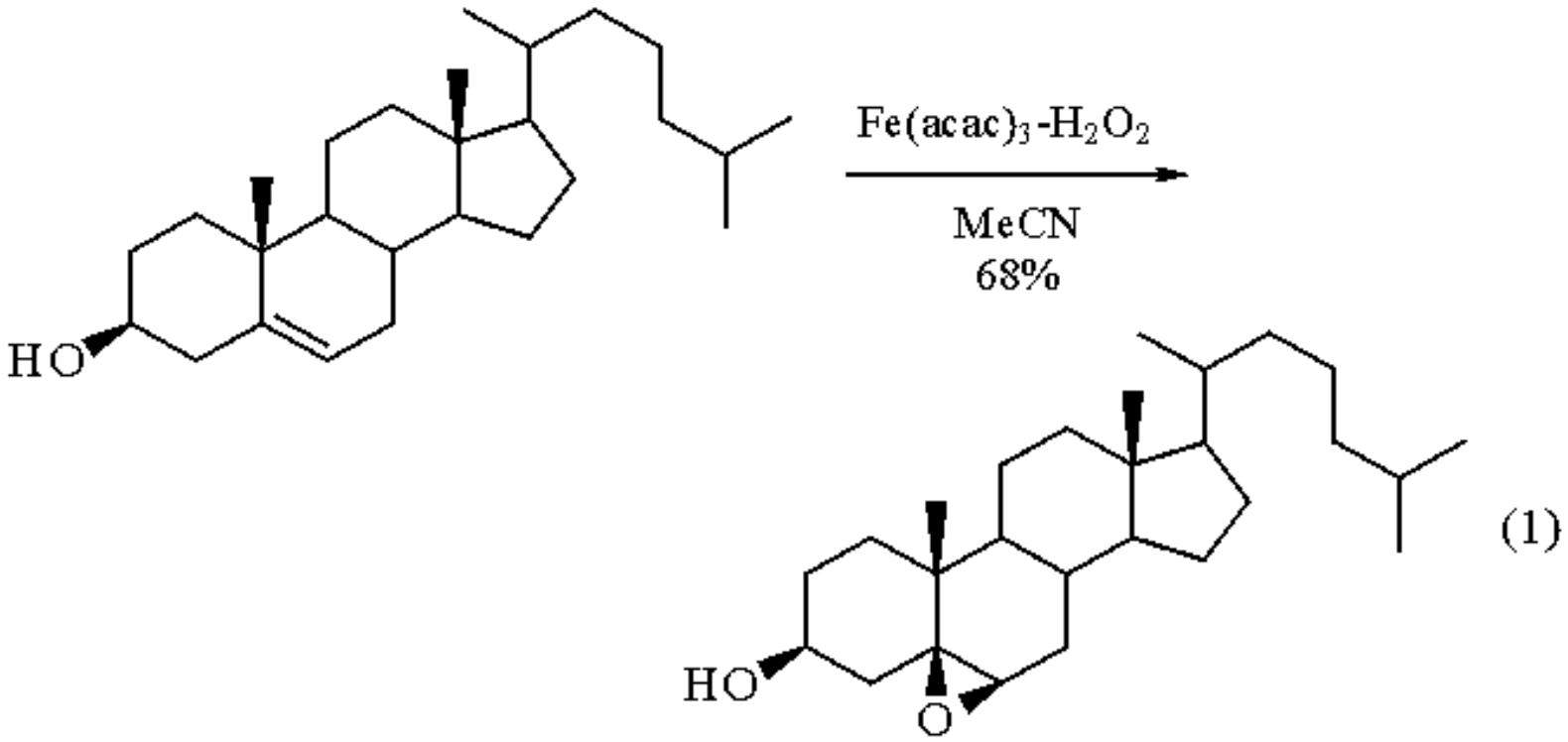

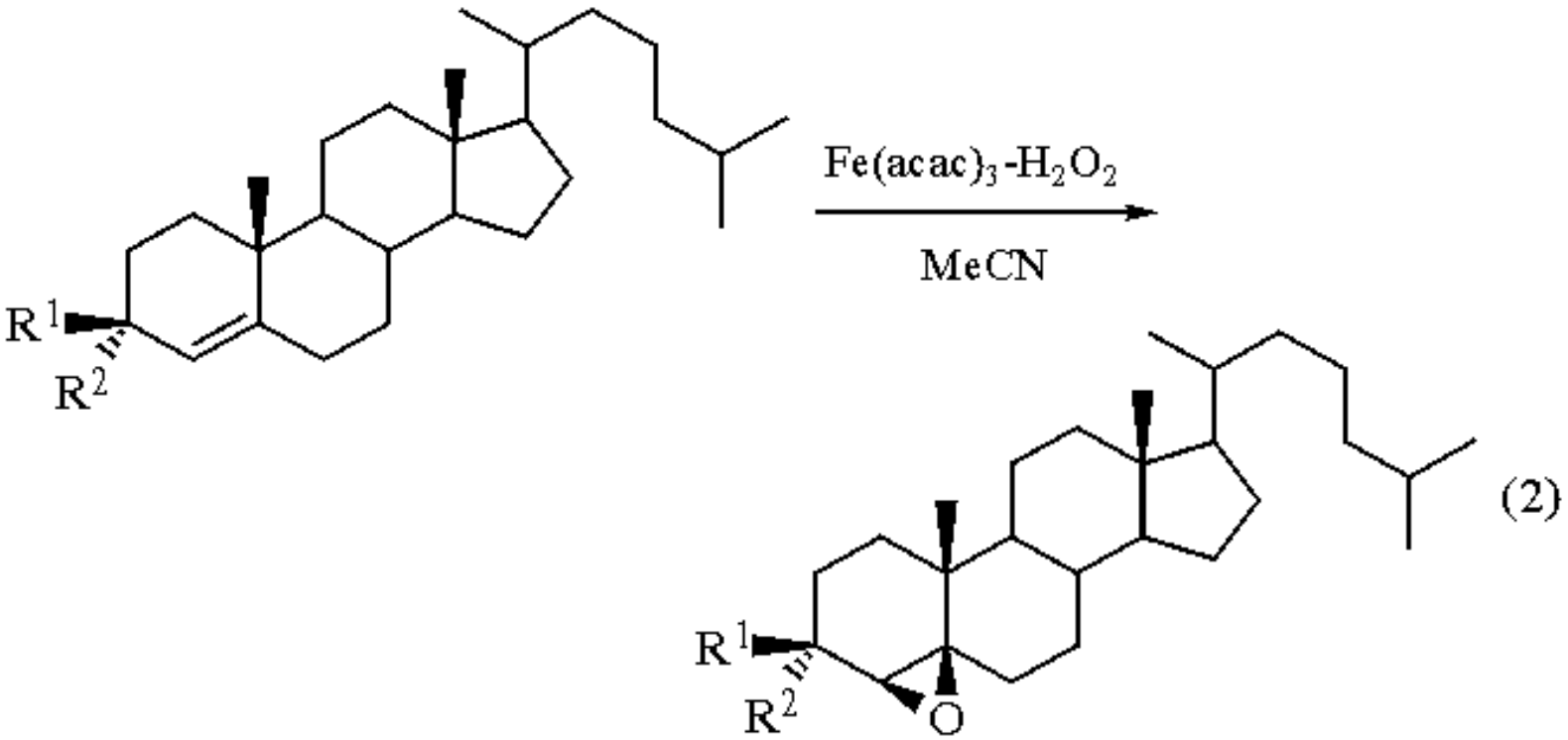

$R^1 = OH, R^2 = H$, 38%; $R^1 = H, R^2 = OH$, 46%; $R^1 = R^2 = H$, 74%

trans-Epoxidation of Alkenes.[3]

trans-Epoxide is obtained selectively in the $Fe(acac)_3.H_2O_2$ mediated oxidation of both *cis* and *trans* alkenes (eq 3).[3] This contrasts with *m*-CPBA oxidation in which alkene geometry is conserved.[7]

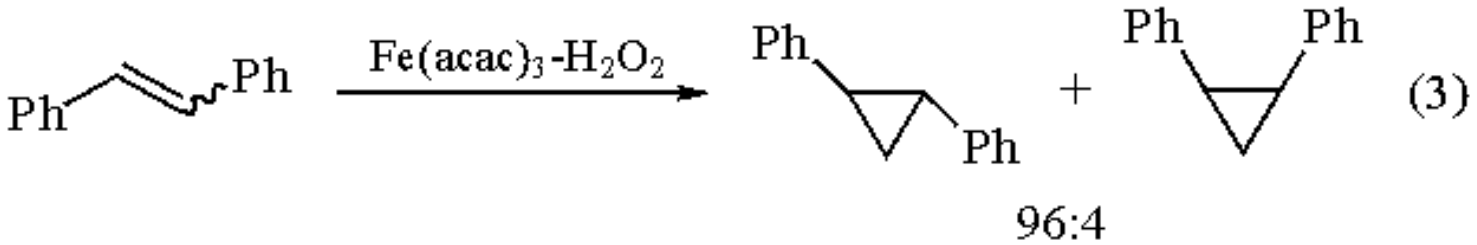

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Iron(III) Azide[1]

$Fe(N_3)_3$

[14215-32-8] · FeN_9 · Iron(III) Azide · (MW 181.94)

(preparation of azidoalkanes[1])

Alternate Name: ferric azide.

Form Supplied in: made in situ.

Preparative Methods: the reagent is prepared and used in situ[1] by addition of ***Sodium Azide*** (15 mmol) and ***Iron(III) Sulfate*** (7.5 mmol) in methanol (20 mL) to the organoborane (5 mmol) stirred at rt for 30 min under nitrogen. The mixture is then cooled to 0 °C and 30% ***Hydrogen Peroxide*** added via a syringe pump (0.1 mL min^{-1}). Slow addition of hydrogen peroxide increases yields.

Handling, Storage, and Precautions: is poisonous by ingestion or skin contact. It is an unstable explosive, sensitive to impact. Decomposition yields toxic fumes of NO_x and Na_2O. Organic azides are sensitized by metal salts or traces of strong acid.[8] $Fe_2(SO_4)_3$ is harmful if swallowed or inhaled. It causes eye and skin irritation. Use in a fume hood.

Azidoalkanes.[1]

Azidoalkanes are useful intermediates in the synthesis of a variety of nitrogen derivatives, especially amines via reduction with ***Lithium Aluminum Hydride***. Trialkylboranes react with iron azide in the presence of hydrogen peroxide to generate alkyl azides (eq 1) at rt.[1] This procedure provides a good overall transformation of alkenes to azides in an anti-Markovnikov fashion, via conversion to the organoborane followed by the one-pot azidation with $Fe(N_3)_3$ (eqs 2-4). Secondary amines can be made stereospecifically via thermal conversion of an alkyl azide to a nitrene and reaction with an alkyl dichloroborane.[2]

$$BR_3 + Fe(N_3)_3 + H_2O_2 \longrightarrow RN_3 \qquad (1)$$

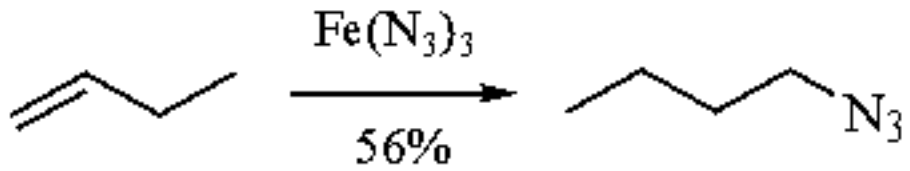

(2)

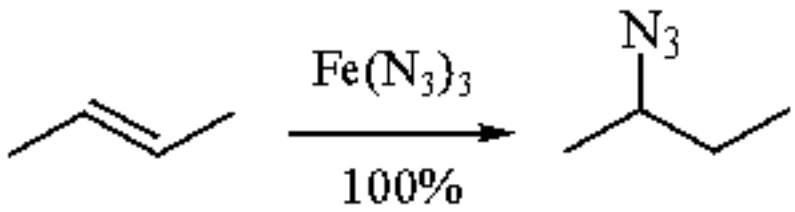

(3)

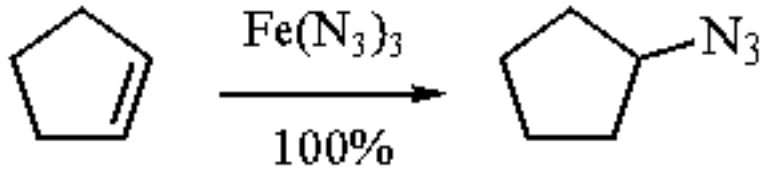

(4)

Reaction mixtures (5 mmol scale) are worked up with 3 N NaOH (20 mL) and 30% H_2O_2 to decompose residual organoborane. The products are extracted into ether.[1] Alternate procedures for generation of alkyl azides are available: nucleophilic displacement with azide ion[3] (high temperatures) and use of lead azide generated in situ from lead(IV) acetate azide[4] (toxicity and formation of regioisomers) offer no advantages over the iron azide method. The azidation reaction is related to the use of ***Iron(III) Chloride***, ***Iron(III) Thiocyanate***, and $Fe(SeCN)_3$ to generate alkyl halides,[5] thiocyanates,[5] and selenocyanates,[6] respectively. The $Fe(N_3)_3$ reaction mechanism is postulated to be different from the latter salts, being a radical process[1] thought to be initiated by H_2O_2 and trace Fe^{II} always present in $Fe_2(SO_4)_3$.[7]

---

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Iron(III) Chloride[1]

$FeCl_3$

[7705-08-0] · Cl_3Fe · Iron(III) Chloride · (MW 162.20)

(mild oxidant capable of phenolic coupling,[1] dimerizing aryllithiums[6] and ketone enolates;[7,8] mild Lewis acid: catalyzes ene reactions,[21] Nazarov cyclizations,[18-20] Michael additions,[24] and acetonations[29])

Alternate Name: ferric chloride.

Physical Data: mp 306 °C; *d* 2.898 g cm^{-3}.[25]

Solubility: 74.4 g/100 mL cold water, 535.7 g mL^{-1} boiling water; v sol alcohol, MeOH, ether, 63 g mL^{-1} in acetone (18 °C).

Form Supplied in: black crystalline powder; widely available.

Preparative Methods: anhydrous $FeCl_3$ available commercially is adequate for most purposes. However, the anhydrous material can be obtained from the hydrate by drying with thionyl chloride[7] or azeotropic distillation with benzene.[12]

Handling, Storage, and Precautions: is hygroscopic and corrosive; inhalation or ingestion may be fatal. It causes eye and skin irritation. It should be stored and handled under an inert dry atmosphere.[36] Use in a fume hood.

Oxidative Properties.[1]

$FeCl_3$ oxidizes a wide array of functionalities, such as certain phenols to quinones (eq 1), dithiols to disulfides (eq 2), and 2-hydroxycyclohexanone to 1,2-cyclohexanedione.[1] Inter- and intramolecular oxidative dimerization of aromatics gives rise to such products as magnolol, metacyclophanes,[1] and crinine alkaloids (eq 3).[2] Phenolic ethylamines and *N*-acetyloxyamides can be cyclized to indoles (eq 4)[3] and oxindoles (eq 5),[4] respectively. Dimerization of aryllithium or Grignard reagents yields intermediates for cyclophane[5] and perylenequinone[6] synthesis (eq 6). Inter-[7] and intramolecular[8] ketone enolates can be converted to 1,4-diketones (eq 7), and lithium salts of allylic sulfones afford 1,6-disulfones.[9]

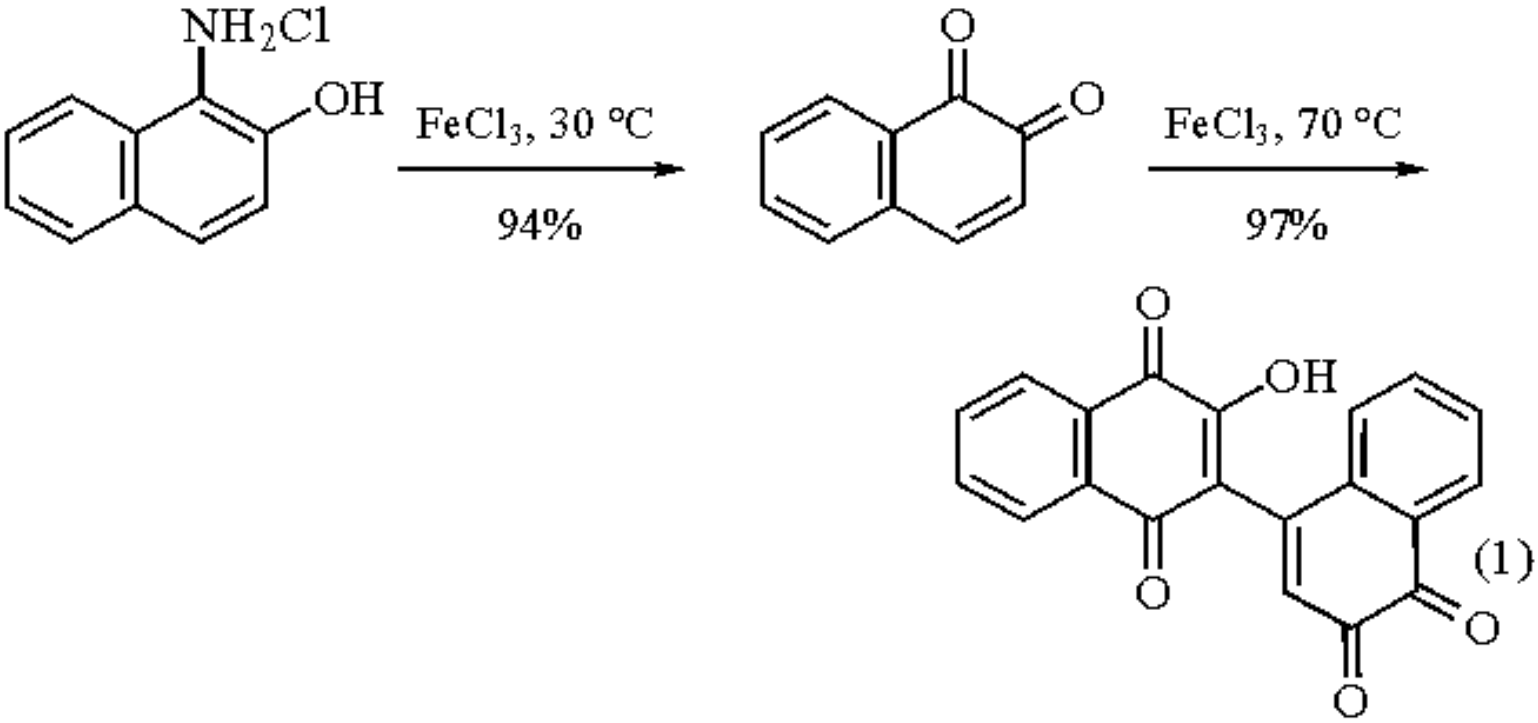
NH2Cl
OH
FeCl3, 30 °C
94%
O
O
FeCl3, 70 °C
97%
O
OH
O
O
O
(1)

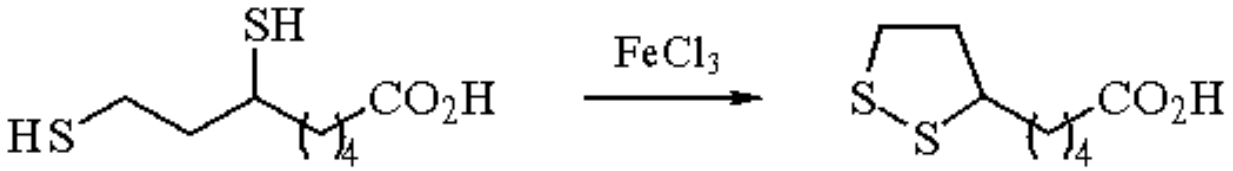
SH
HS
CO2H
4
FeCl3
S
S
CO2H
4
(2)

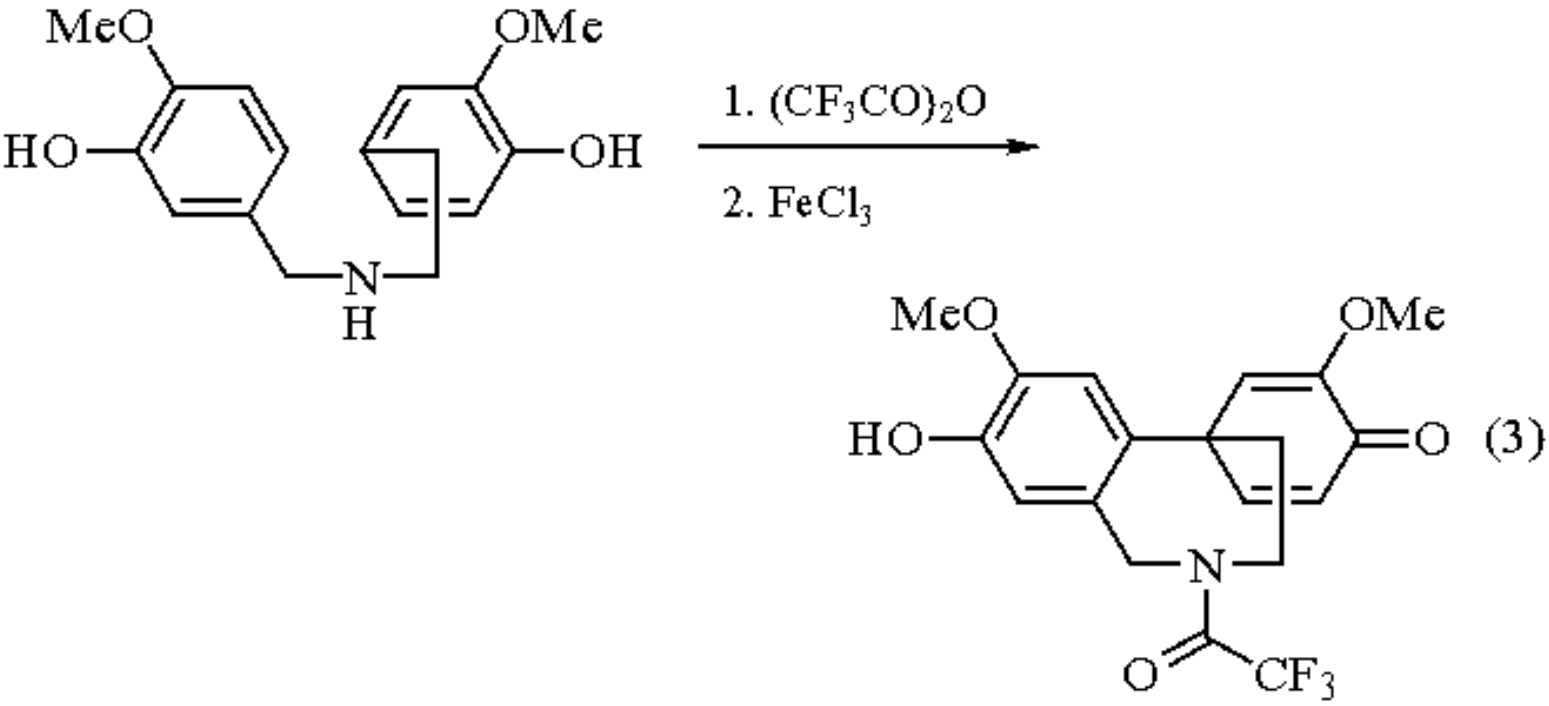
MeO
OMe
HO
OH
N
H
1. (CF3CO)2O
2. FeCl3
MeO
OMe
HO
O
(3)
N
O
CF3

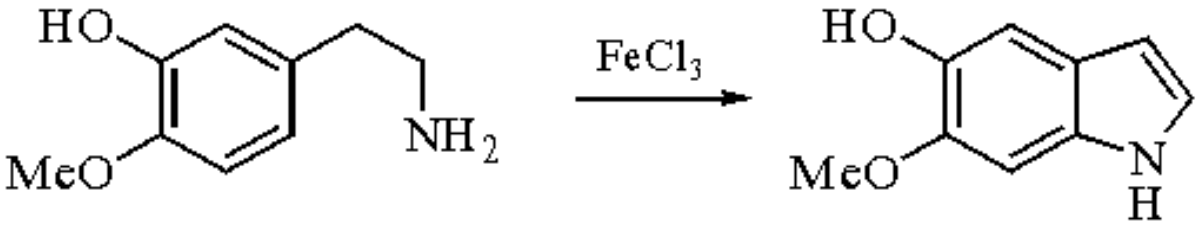

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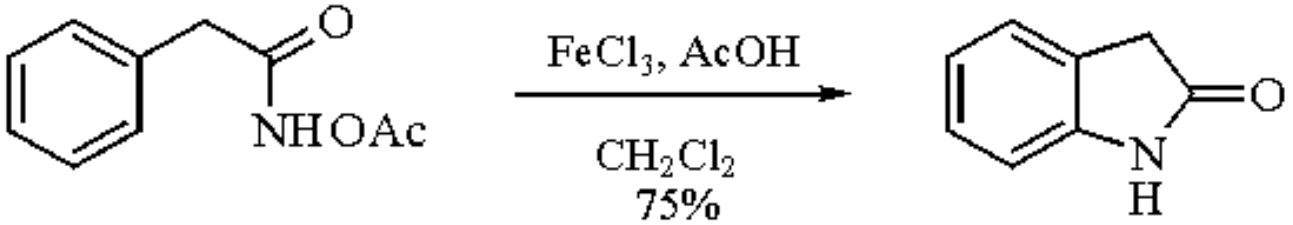

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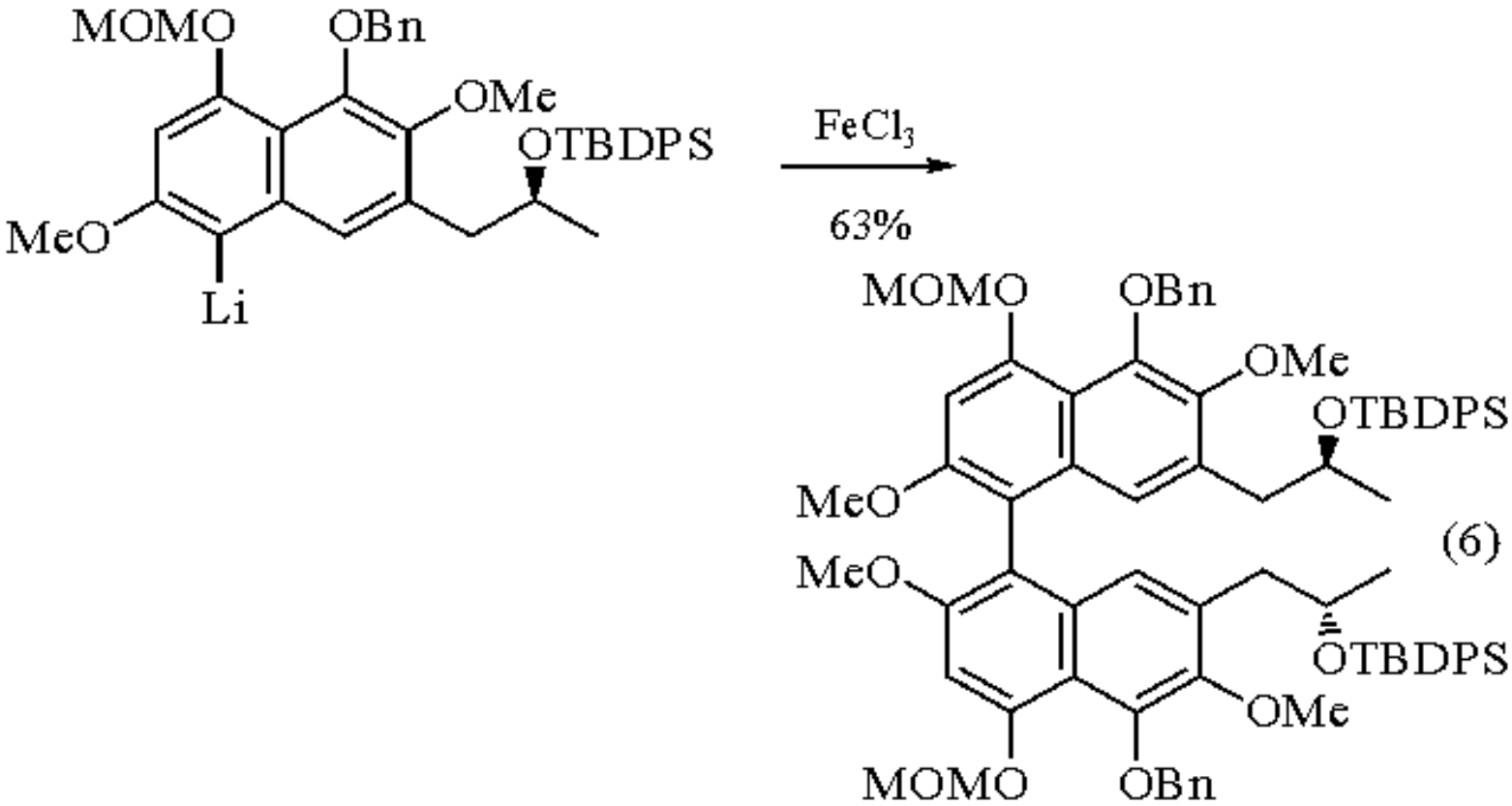

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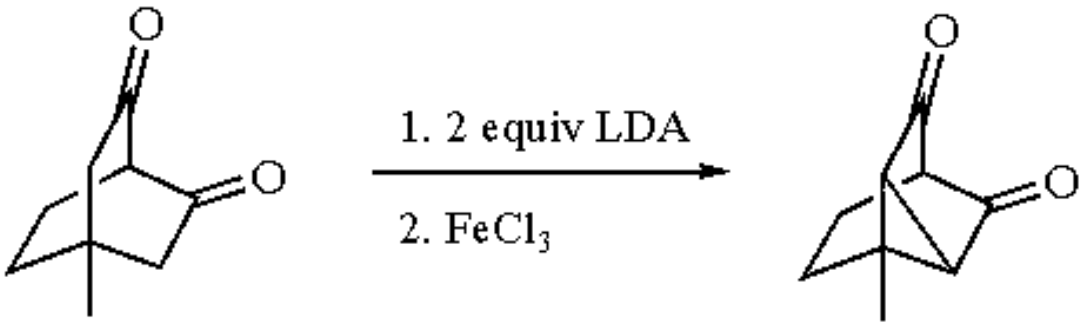

(7)

Stereoselective cross-coupling of alkenyl halides with Grignard reagents is catalyzed by $FeCl_3$ (45-83%) (eqs 8 and 9).[10] Propargyl halides also react to afford allenes.[11] A study of Fe^{III} catalysts revealed that

Tris(dibenzoylmethide)iron(III) was the most useful.[12]

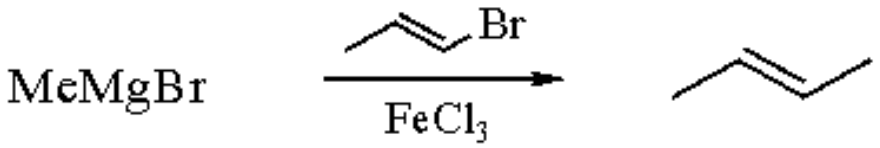

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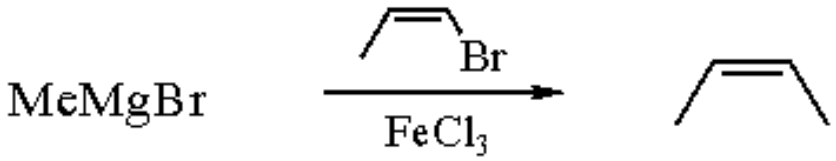

(9)

Alkylcyclopentanones can be dehydrogenated to cyclopentenones, but ***Copper(I) Chloride*** is a better catalyst.[13] Trimethylsilyloxybicyclo[*n*.1.0]alkanes can be oxidatively cleaved, providing a three-step method of ring expansion (eq 10).[14] Cycloalkanones are cleaved with $FeCl_3$/MeOH under O_2 to o-oxo esters; this reaction works best with flanking methyl groups (eq 11).[15] Photooxidation of alkenes with $FeCl_3$ can yield a variety of useful chloroketones depending on the starting material,[16] and photoreaction of carbohydrates in pyridine induces a selective C(1)-C(2) bond cleavage, in contrast to ***Titanium(IV) Chloride*** (C(5)-C(6) cleavage) (eq 12).[17] $FeCl_3$/EtOH can also be used to disengage tricarbonyliron complex ligands.

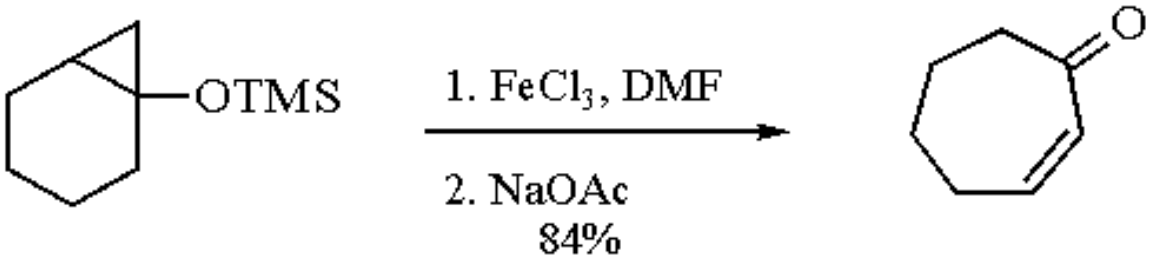

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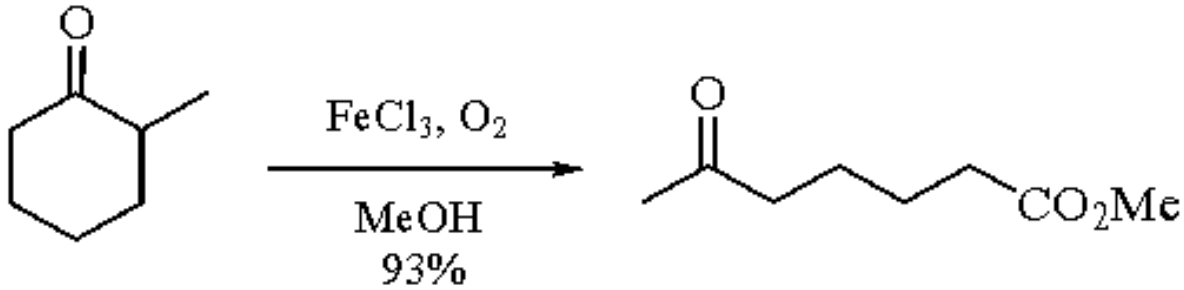

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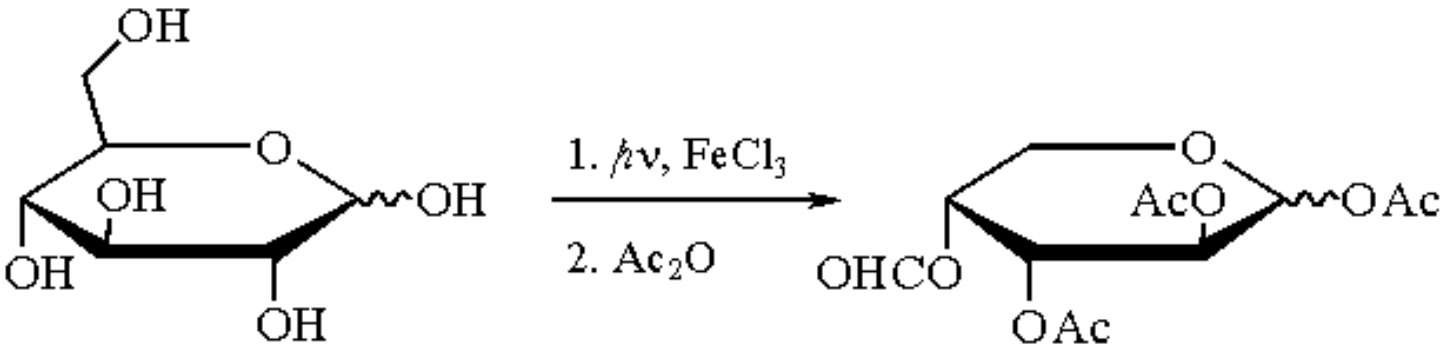

(12)

Lewis Acid Mediated Reactions.

Silicon-directed Nazarov cyclizations occur readily in dichloromethane catalyzed by $FeCl_3$, utilizing the cation-stabilizing effect of silicon.[18] Cyclohexenyl systems afford only *cis*-fused ring products. The reaction has been elaborated to the preparation of linear tricycles with β-silyldivinyl ketones at low temperature (eq 13).[19] Optically active β´-silyl divinyl ketones have been used to demonstrate that cyclization occurs with essentially complete control by silicon in the *anti* S'_E sense.[20] $FeCl_3$ is the best Lewis acid catalyst for the intramolecular ene reaction of the Knoevenagel adduct from citronellal and dimethyl malonate at low temperature (eq 14).[21] However, the basic alumina supported catalyst can give more reliable results. The ene reaction of an unsaturated ester of an allylic alcohol yields a chlorolactone cleanly at 25 °C.[22] This reaction produces only one of four possible diastereomers, with clean *trans* addition to the double bond occurring (eq 15). 1-Silyloxycycloalkanecarbaldehydes undergo ring expansion to 2-silyloxycycloalkanones (82-89%) (eq 16). $FeCl_3$ catalysis provides the best selectivity derived from rearrangement of the more substituted α-carbon atom.[23] $FeCl_3$-catalyzed addition of primary and secondary amines to acrylates occurs exclusively 1,4 with no polymerization (79-97%) (eq 17).[24]

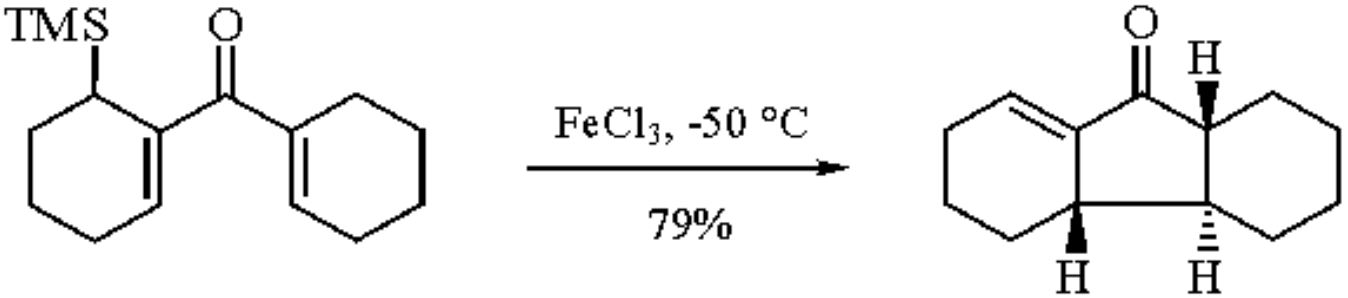

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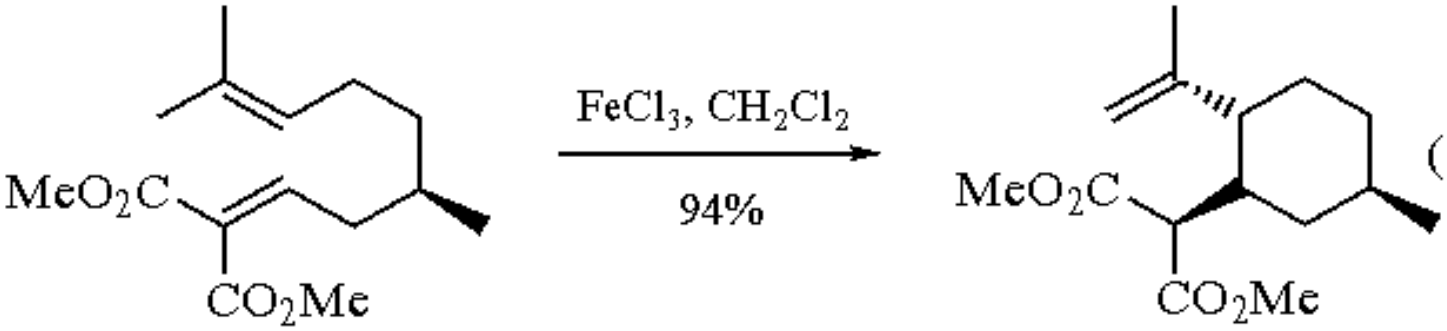

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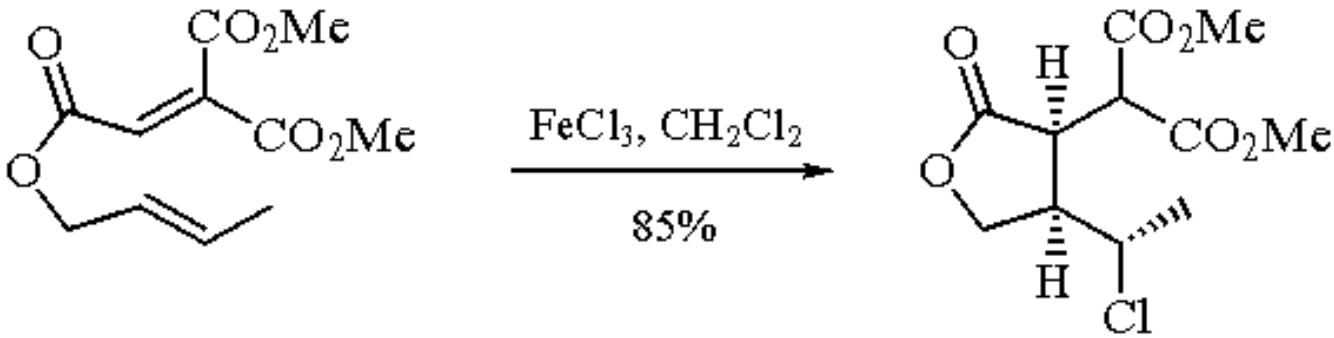

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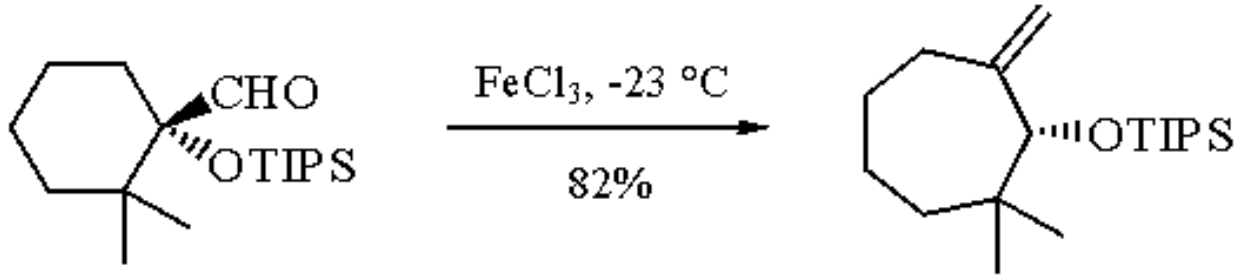

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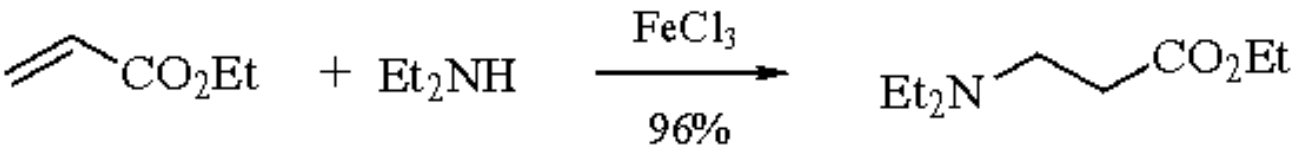

(17)

In the field of protecting group chemistry $FeCl_3$ will cleave benzyl[25] and silyl ethers,[26] convert MEM ethers to carboxylic esters,[27] and when dispersed on 3Å molecular sieves catalyzes the formation of MOM ethers.[28] In the area of carbohydrate chemistry, $FeCl_3$ is proving a versatile reagent for acetylation, acetonation, acetolysis, transesterification, *O*-glycosidation of β-per-*O*-acetates, formation of oxazolines, direct conversion of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-acylamido-β-D-glucopyranoses into their *O*-glycosides, preparation of 1-thioalkyl(aryl)-β-D-hexopyranosides from the peracetylated hexopyranoses having a 1,2-*trans* configuration,[29] and as an anomerization catalyst for the preparation of alkyl-α-glycopyranosides (eq 18).[30]

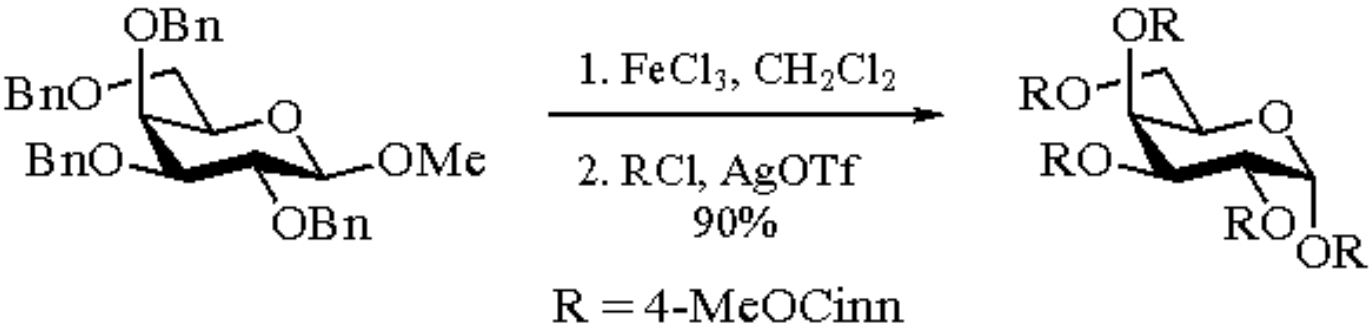

(18)

Substituted amidines have been prepared from a nitrile compound, an alkyl halide, an amine, and $FeCl_3$ in a one-pot synthesis (40-80%) (eq 19).[31] $FeCl_3$ in ether converts epoxides into chlorohydrins. Fused bicyclic epoxides yield *trans*-chlorohydrins (eq 20).[32] Friedel-Crafts acylation of activated (Me, OMe substituents) aromatics occurs readily with optically active *N*-phthaloyl-α-amino acid chlorides catalyzed by $FeCl_3$ (1-5 mol%).[33] Trialkylboranes react with $FeCl_3$ in THF/H_2O to afford alkyl chlorides in excellent yield.[34] *t*-Alkyl and benzylic chlorides can be converted to the iodides on reaction with ***Sodium Iodide*** in benzene catalyzed by $FeCl_3$.[35]

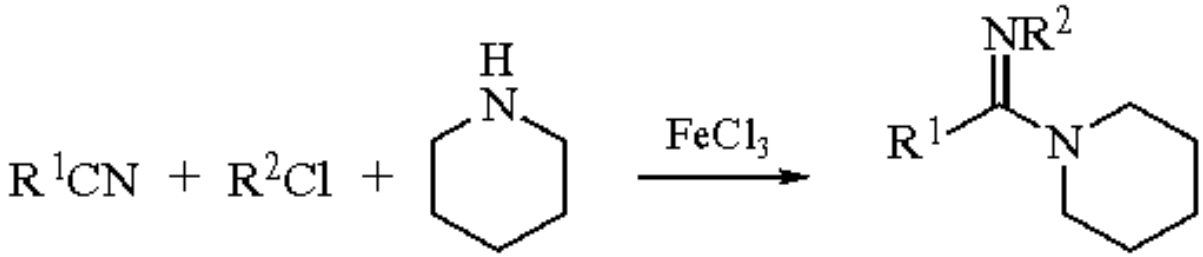

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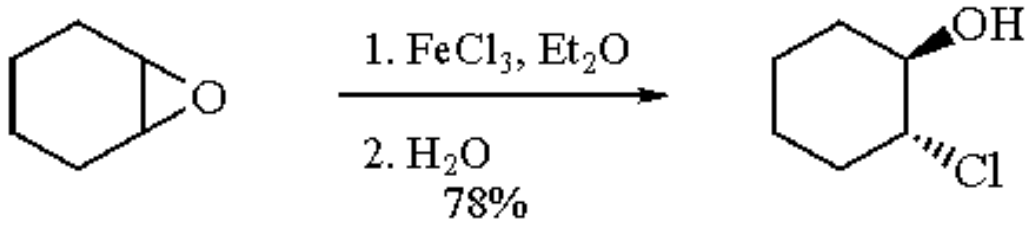

(20)

Related Reagents.

Iron(III) Chloride-Acetic Anhydride; ***Iron(III) Chloride-Alumina***; ***Iron(III) Chloride-Dimethylformamide***; ***Iron(III) Chloride-Silica Gel***; ***Iron(III) Chloride-Sodium Hydride***.

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Iron(II) Chloride[1]

$FeCl_2$

[7758-94-3] · Cl_2Fe · Iron(II) Chloride · (MW 126.75)

(synthesis of ferrocene[2] and derivatives;[3] Sandmeyer reaction;[4] alkane C-H functionalizations;[6,7] alkyne reductions;[5] catalytic additive[8])

Alternate Name: ferrous chloride.

Physical Data: mp 670-674 °C; sublimes; *d* 3.16 g cm^{-3}.

Solubility: 64.4 g/100 mL cold water (10 °C), 105.7 g/100 mL hot water (100 °C); 100 g/100 mL alcohol; sol acetone; insol ether.

Form Supplied in: green to yellow solid; widely available, can be obtained as 99.999% ultra dry material.

Preparative Methods: chlorobenzene (1 kg) and sublimed (anhydrous) ***Iron(III) Chloride*** is refluxed for 3.5 h. The iron(II) chloride is filtered and washed with anhydrous benzene (97% yield).[1]

Handling, Storage, and Precautions: incompatible with strong oxidizing agents; hygroscopic; may decompose on exposure to air, HCl being produced. It is an irritant. Use in a fume hood.

Ferrocene Synthesis.

Iron(II) chloride reacts with sodium cyclopentadienide in THF to give ferrocene (eq 1). This method has been described in detail[2] and is applicable to many ferrocene derivatives.[3]

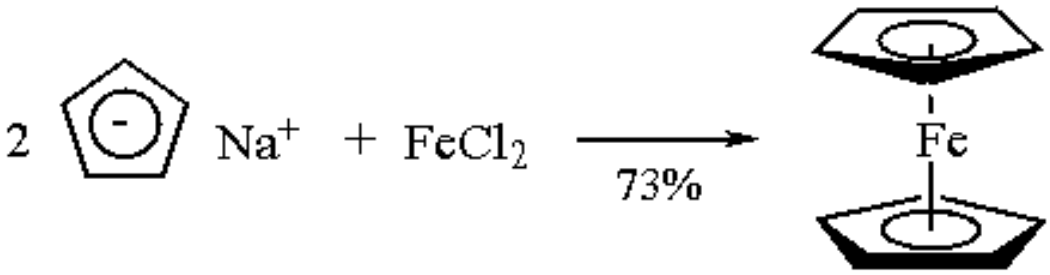

(1)

Sandmeyer Reaction.

The Sandmeyer reaction has been performed with iron(II) chloride, in place of ***Copper(II) Chloride***. The reactions proceed in good yield, except with methyl substituents, where phenols are obtained (eq 2).[4]

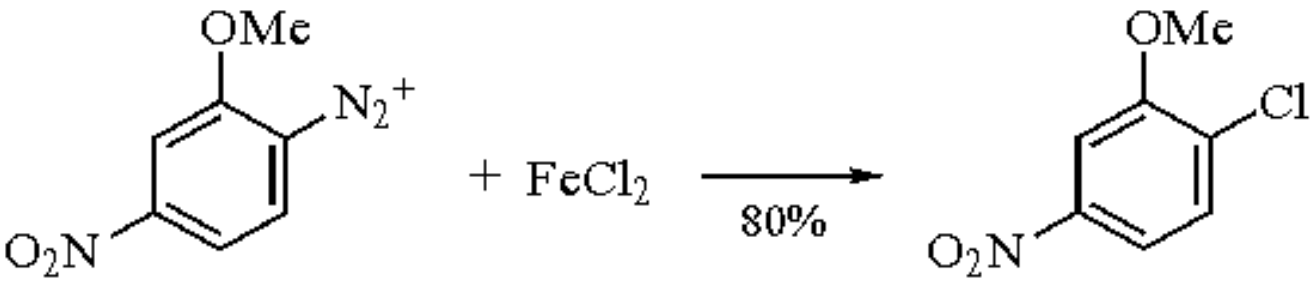

(2)

$FeCl_2$-Lipoamide-NaH Reductions.

Iron(II) chloride in combination with simple dithiols are effective catalysts for the reduction of alkynes to alkenes with ***Sodium Borohydride*** (22-93% yields) (eq 3).[5] The best reaction conditions employ 5 equiv $NaBH_4$, 7.5 mol% lipoamide, and 10 mol% $FeCl_2$ stirred at rt for 8 h.

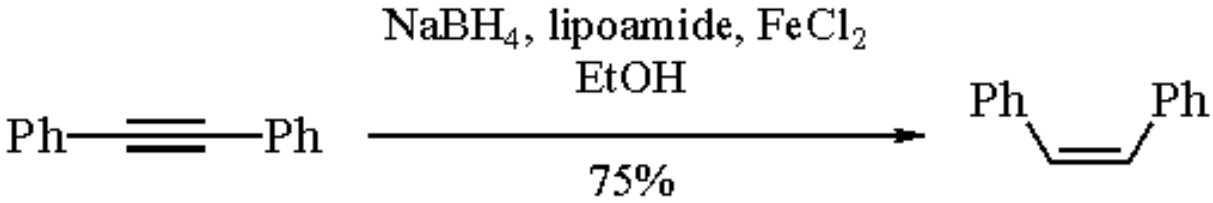

(3)

Amination of the C-H Bond.

Reaction of ***Chloramine-T*** with rigorously dry $FeCl_2$ and adamantane in dichloromethane under nitrogen, and column chromatography of the crude reaction mixture after 2 h, gives a 63% yield of the tertiary sulfonamide (eq 4).[6]

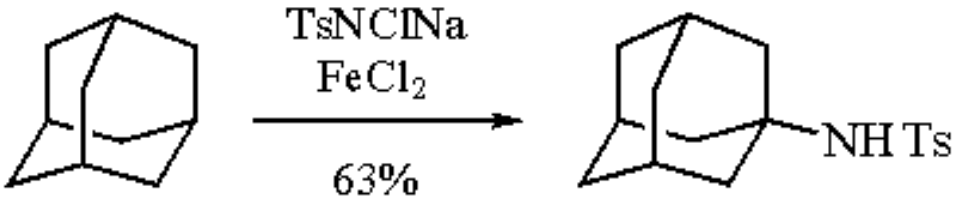

(4)

Gif^{IV} Oxidation Catalyst.

$FeCl_2.4H_2O$ is one of the catalysts used in the Gif^{IV} oxidation of saturated hydrocarbons using molecular oxygen. However, many iron catalysts have been used with varying results. $FeCl_2$ provides a good ratio of secondary to tertiary hydroxylation with a reasonable turnover (30). A combination of adamantane (2 mmol), ***Zinc*** (20 mmol), and $FeCl_2$ (7 μmol) in pyridine-acetic acid is stirred for 18 h, open to the atmosphere, to yield oxidation products (eq 5).[7]

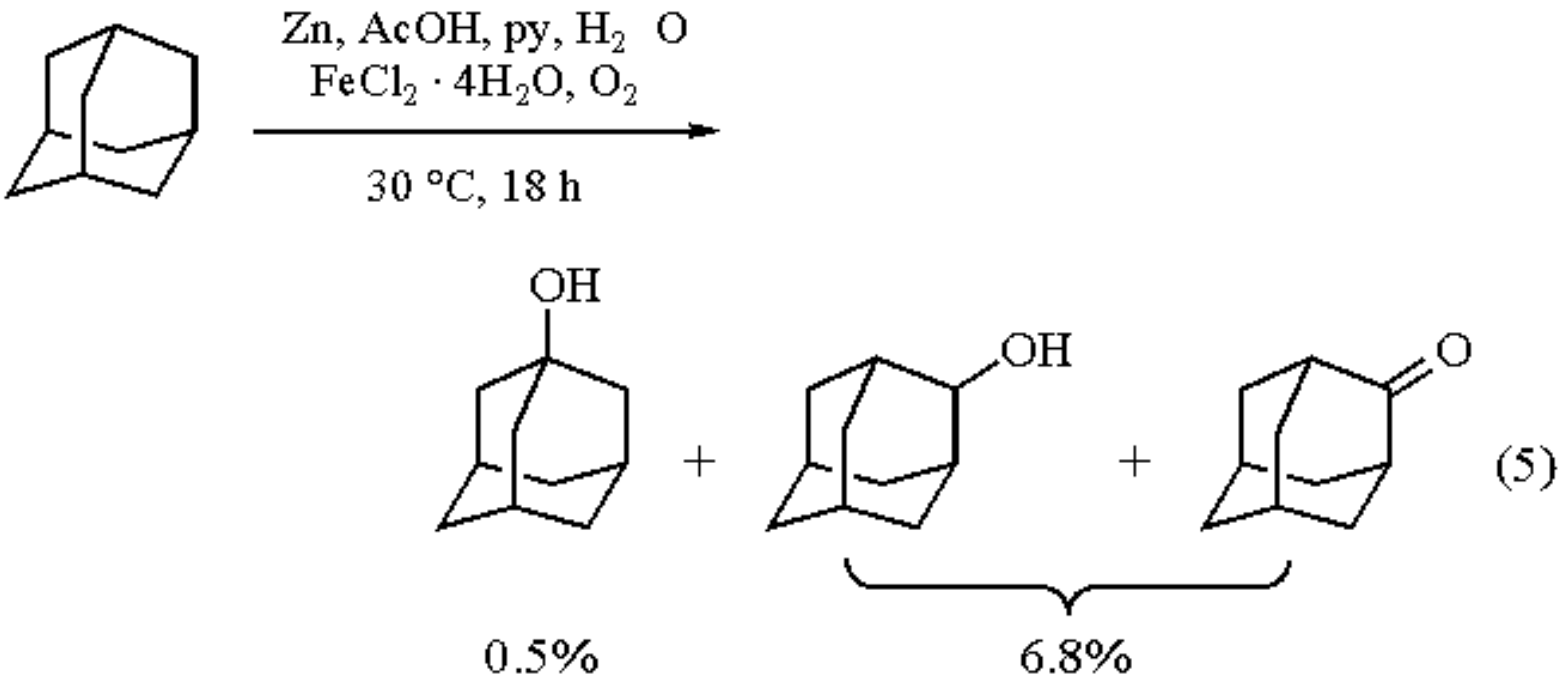

Raney Cobalt Catalyst Additive.

Unsaturated alcohols can be obtained from α,β-unsaturated aldehydes via hydrogenation with Raney cobalt catalyst. $FeCl_2$ addition to the catalyst increases yields.[8]

Related Reagents.

Sodium Triethylborohydride-Iron(II) Chloride.

---

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Iron(III) Chloride-Acetic Anhydride[1]

$FeCl_3$-Ac_2O

($FeCl_3$)

[7705-08-0] · Cl_3Fe · Iron(III) Chloride-Acetic Anhydride · (MW 162.20) (Ac_2O)

[108-27-7] · $C_4H_6O_3$ · Iron(III) Chloride-Acetic Anhydride · (MW 102.10)

(Lewis acid cleaving ethers,[2] *gem*-diacetates,[8] imides[11])

Alternate Name: ferric chloride-acetic anhydride.

Preparative Method: this reagent combination is used in situ via addition of anhydrous ***Iron(III) Chloride*** (6.2 mmol), to the substrate (35.5 mmol) and ***Acetic Anhydride*** (15 mL).[2]

Handling, Storage, and Precautions: reactions can be mildly exothermic. $FeCl_3$ is hygroscopic and corrosive, inhalation or ingestion may be fatal. Acetic anhydride is moderately toxic by inhalation, ingestion, and skin contact. It is a skin and severe eye irritant. It can react vigorously with oxidizing agents, and will react vigorously with water.[12] Use in a fume hood.

Cleavage of Ethers.[2]

Iron(III) chloride in acetic anhydride was first reported to cleave diethyl ether to ethyl acetate,[3] and has been developed into a very useful ether-cleavage reagent.[2a] Iron(III) chloride is added to the substrate and acetic anhydride. For simple substrates the reaction may be heated on a steam bath, while for sensitive functionality it is best conducted at 0 °C and monitored by TLC. The acetate ester is obtained as the product (44-92%). The reaction can be performed using ethyl acetate[2a] or ether[2b] as cosolvent and detailed procedures are available.[2] Reactions are usually worked up via extraction into hexane, and washing with water and sodium bicarbonate. Alternatively, saturated Na_2HPO_4 can be used to form $FePO_4$, which can be filtered off prior to extraction. This system will cleave a wide range of ethers: *n*-alkyl, isopropyl, *t*-butyl, benzyl, and TBDMS. The reaction conditions are compatible with easily isomerized alkenes (eq 1). Optically active ethers usually afford racemic acetates; however, the synthesis of (*R*)-(+)-4-acetoxycyclopent-2-enone[4] provides a notable exception (eq 2). The $FeCl_3$-Ac_2O procedure is the one of choice when an alcohol deprotection is to be

followed by acylation with a hindered acid chloride.[5] It also provides an excellent route to cyanohydrin esters from ketones (eq 3).[6] Deprotection of ethers is covered extensively in the literature.[1,7]

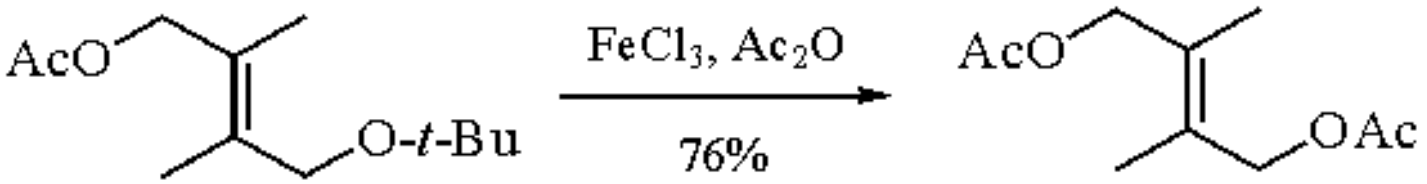

(1)

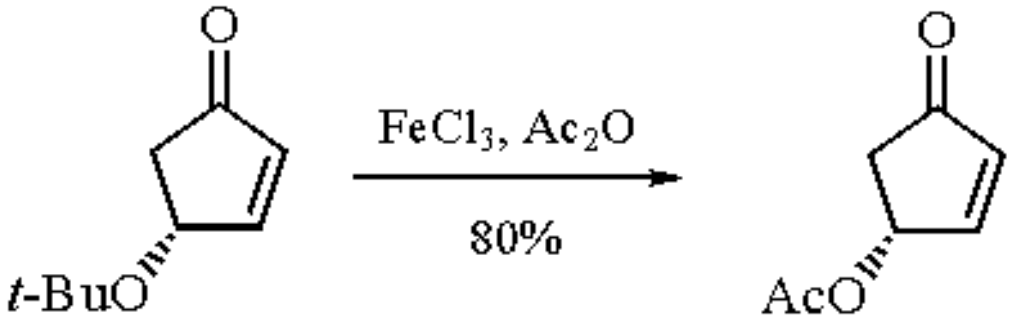

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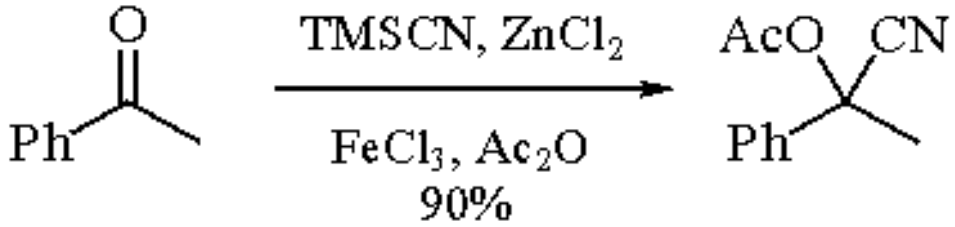

(3)

gem-Diacetates from Aldehydes.[8]

Aldehydes are converted to geminal diacetates (63-93%) via addition of iron(III) chloride to a solution of aldehyde in acetic anhydride (eq 4). A wide range aldehydes react: aliphatic, aromatic, heteroaryl, and α,β-unsaturated aldehydes. Alternative reaction conditions include acid catalysis[9] and ***Phosphorus(III) Chloride***.[10]

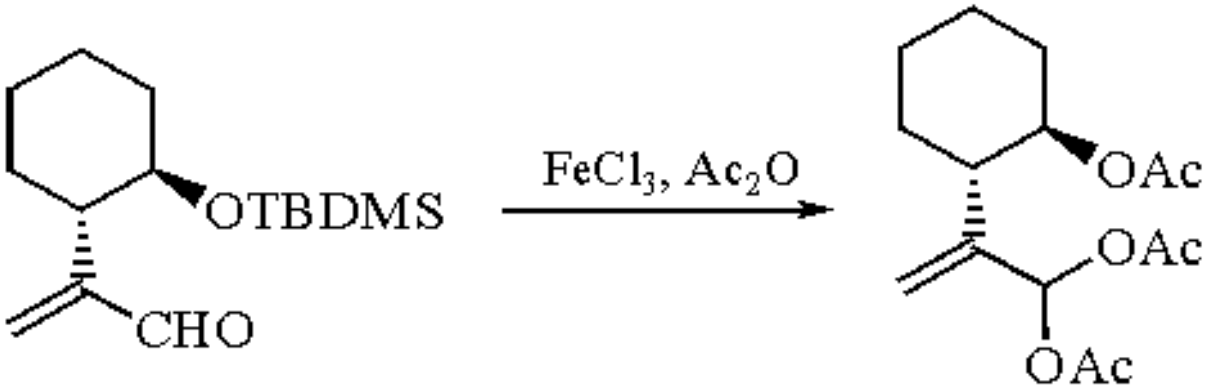

(4)

Imides.[11]

α-*t*-Butoxy- or α-acetoxyacrylonitriles can be converted into imides with $FeCl_3$-Ac_2O (eq 5) via cleavage of the *t*-butyl ether and addition to the nitrile. However this reaction is limited to *t*-butoxy- and acetoxyacrylonitriles.

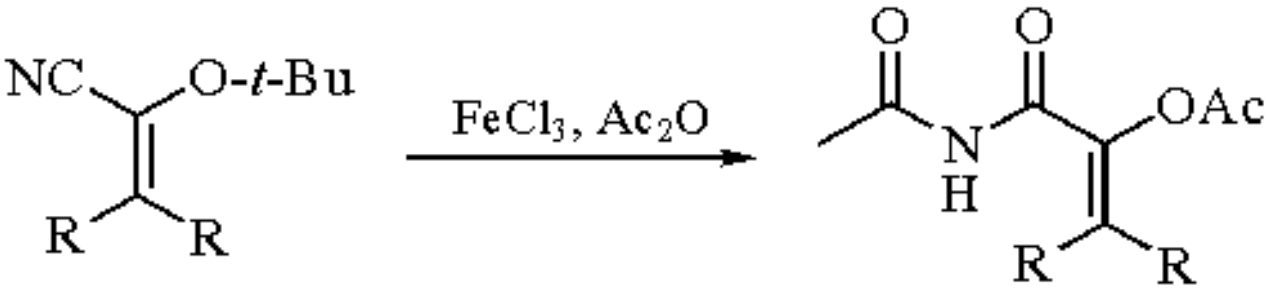

(5)

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Iron(III) Chloride-Alumina[1]

$FeCl_3$-Al_2O_3

($FeCl_3$)

[7705-08-0] · Cl_3Fe · Iron(III) Chloride-Alumina · (MW 162.20) (Al_2O_3)

[1344-28-1] · Al_2O_3 · Iron(III) Chloride-Alumina · (MW 101.96)

(proton scavenger; mild Lewis acid catalyst for ene reactions[1,2])

Alternate Name: ferric chloride-alumina.

Form Supplied in: the individual reagents are commercially available.

Preparative Method: anhydrous ***Iron(III) Chloride*** (62 mmol) is added to anhydrous CH_2Cl_2 (160 mL) under argon. The mixture is stirred vigorously while 50 g chromatography grade basic ***Alumina*** is added in small portions under argon. Stirring is continued for 1 h to obtain homogeneous adsorbtion and the solvent is then removed under reduced pressure. The basic alumina supported $FeCl_3$ obtained can be stored under argon for several months without loss of catalytic activity.

Handling, Storage, and Precautions: should be stored and manipulated in an inert, dry atmosphere; $FeCl_3$ is hygroscopic and corrosive, inhalation or ingestion may be fatal; basic alumina is an irritant. Use in a fume hood.

Lewis Acid Catalyzed Intramolecular Ene Reactions.[1]

Anhydrous iron(III) chloride on basic alumina proved to be the best Lewis acid catalyst for the intramolecular ene reaction of the Knoevenagel adduct from citronellal and dimethyl malonate. The *trans*-1,2-disubstituted cyclohexane was obtained as the major product in a 98.8:1.2 ratio in 92% yield in dichloromethane at -78 °C (eq 1).[1,2] The thermal ene reaction[3] yields a 9:1 ratio in 75% yield.[1]

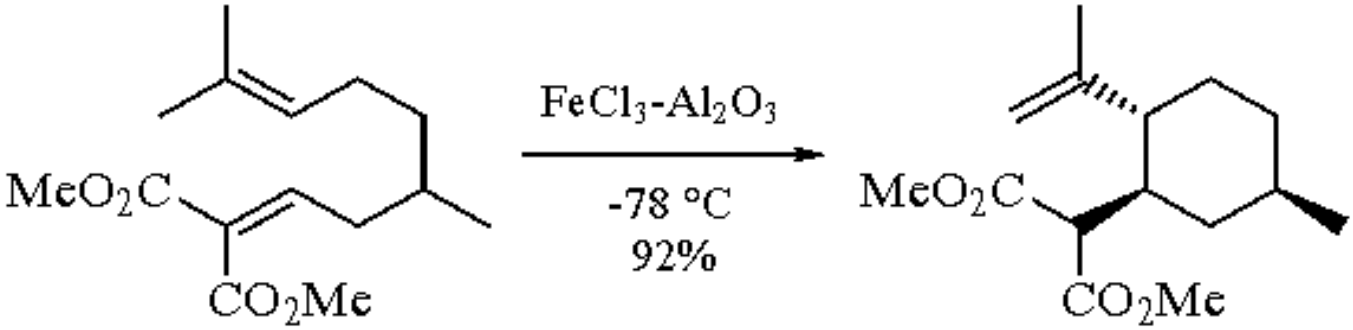

(1)

Strong Lewis acid catalysts, (e.g. ***Aluminum Chloride*** and ***Titanium(IV) Chloride***) yield complex mixtures.[1] Anhydrous ***Zinc Chloride***[4] and alkyl aluminum halides[5] yield product but the overall yields and ratios are not quite as good.[1] $FeCl_3$ also works well; however, competing reactions attributable to traces of water were sometimes observed. The supported catalyst avoids this problem presumably because the catalyst acts as a proton scavenger similar to alkylaluminum halides.[2,6] The $FeCl_3$-Al_2O_3 mediated cyclization can be utilized for 1,6-dienes additionally to yield *trans*-1,2-substituted cyclopentanes. The allylsilane moiety on the ene component is necessary otherwise the reaction is limited to trisubstituted alkenes (eq 2).[7] Silica gel at high pressure (15 kbar) (see ***Iron(III) Chloride-Silica Gel***) may provide an alternative[8] as a mild acid catalyst for highly sensitive functionality, although the yield (73%) and selectivity (9.4:1) for eq 1 does not compare with $FeCl_3$-Al_2O_3 and is only equivalent to the best thermal ene reaction conditions.[1]

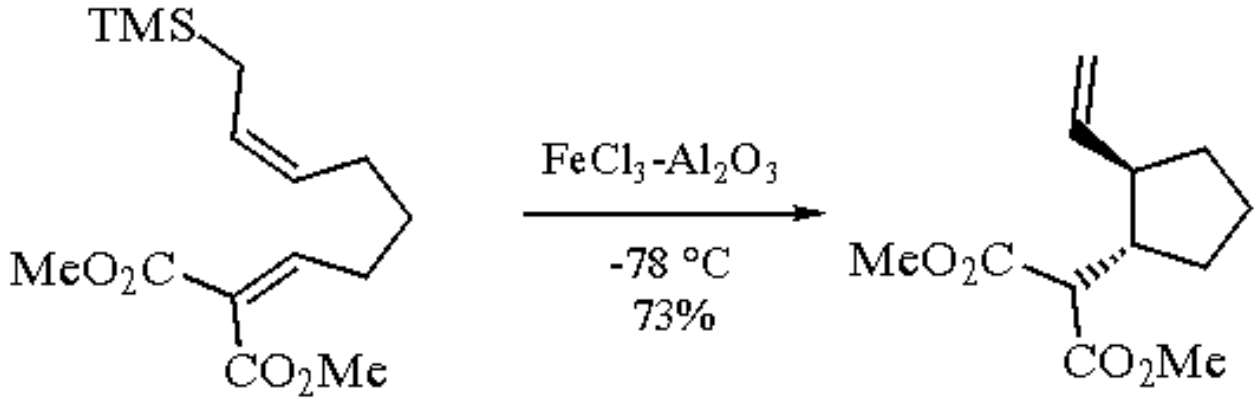

(2)

Electrophilic Cyclizations.

Intramolecular electrophilic cyclization of doubly activated imines using $FeCl_3$-Al_2O_3 yields an annulated piperidine lactone (eq 3). However, better chemoselectivities but lower yields are obtained with gallium trichloride or ***Trifluoroacetic Acid***.[9] Trialkylsilyl triflates yield the substituted piperidine predominantly. In the corresponding cyclizations to pyrrolidines, $FeCl_3$-Al_2O_3 was inferior to $GaCl_3$.[10]

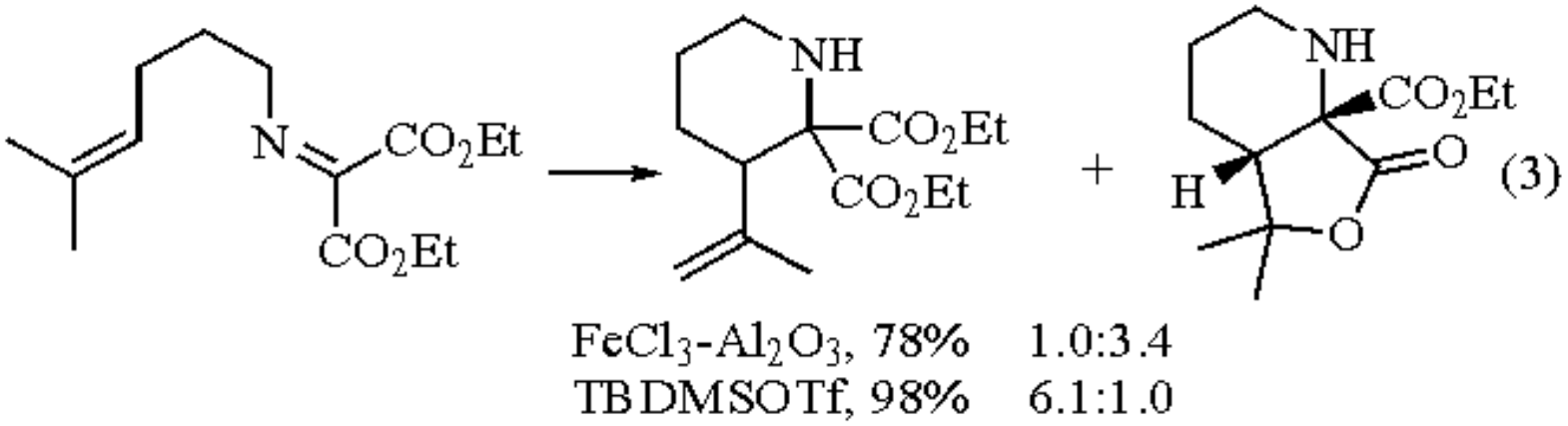

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Iron(III) Chloride-Dimethylformamide[1]

$[Fe(DMF)_3Cl_2][FeCl_4]$

[36654-49-6] · $C_9H_{21}Cl_6Fe_2N_3O_3$ · Iron(III) Chloride-Dimethylformamide · (MW 543.73)

(mild oxidant; oxidative coupling[2] of phenols, ketone enolates,[3] and allylic sulfones;[4] ring expansion of silyloxybicyclo[*n*.1.0]alkanes;[5] oxidative decomplexation of chromium carbonyl complexes[6])

Alternate Name: ferric chloride-DMF.

Physical Data: mp 220 °C.

Preparative Method: ***N,N-Dimethylformamide*** (1.5 mol) is added with stirring to a solution of ***Iron(III) Chloride*** (1 mol) in dry ether (1.6 L) to yield a precipitate which is filtered and dried in vacuo to yield a yellowish green powder (95%) which is sufficiently pure to use for oxidation reactions.[2]

Purification: recrystallize from dichloromethane and ethanol to give needles.

Handling, Storage, and Precautions: stable to air and moisture; $FeCl_3$ is hygroscopic and corrosive; inhalation or ingestion may be fatal; DMF is mildly toxic by skin contact and inhalation; it is a skin and eye irritant. Use in a fume hood.

Oxidative Coupling of Phenols.[2]

Oxidative aryl-aryl coupling represents a challenging synthetic transformation. Iron(III) chloride in DMF or $[Fe(DMF)_3Cl_2][FeCl_4]$ is a good reagent for intramolecular (eq 1) and intermolecular (eq 2) phenol coupling reactions.[1,2] As the redox potential of substrates differ, many alternate reagents exist for this transformation (intiated by one-electron abstraction from the substrate by the oxidant). Alternative reagents used are ***Vanadyl Trichloride***,[7] ***Thallium(III) Trifluoroacetate***,[8] manganese(II) acetylacetonate,[9] ***Potassium Ferricyanide***,[10] copper(II) amine complexes,[11] photolysis,[12] ***(Diacetoxyiodo)benzene***,[13] electrochemical anodic oxidation,[1a] and $FeCl_3$ in the solid state.[14]

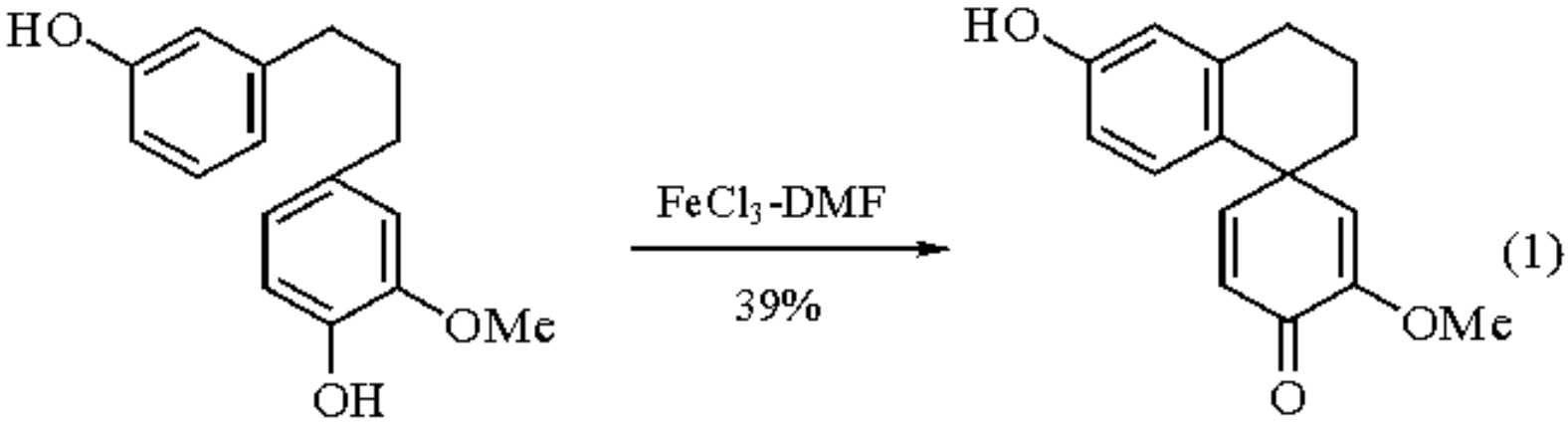

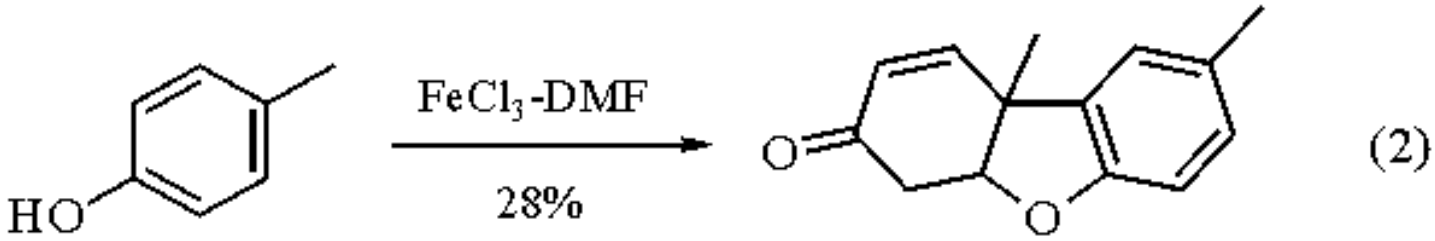

Oxidative Coupling of Ketone Enolates.

Addition of anhydrous $FeCl_3$ in DMF to an enolate in THF yields the 1,4-ketone (eq 3).[3] This reaction has also been applied in an intramolecular fashion (eq 4).[15]

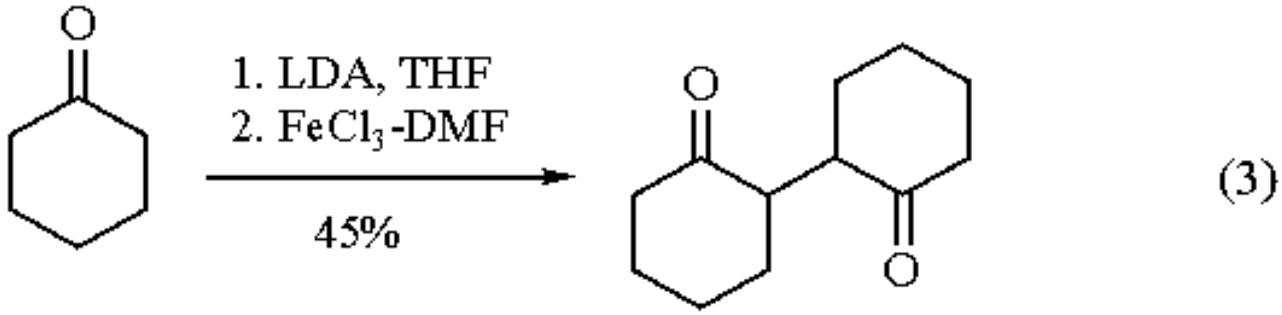

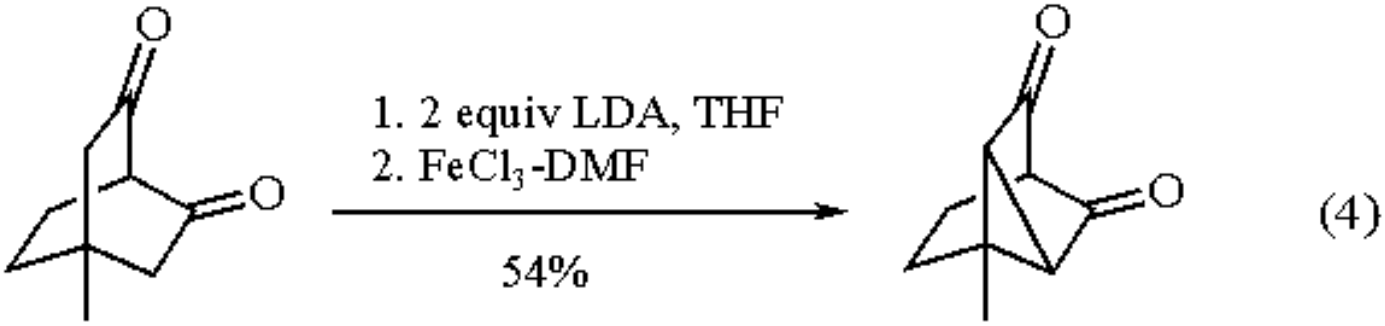

Oxidative Dimerization of Allylic Sulfones.

Lithium salts of allylic sulfones are oxidized by addition of $[Fe(DMF)_3Cl_2][FeCl_4]$ at 0 °C (eq 5) to give 1,6-disulfones by 3-3´ coupling.[4] These products can undergo Cope rearrangement to 1,2-disulfones.

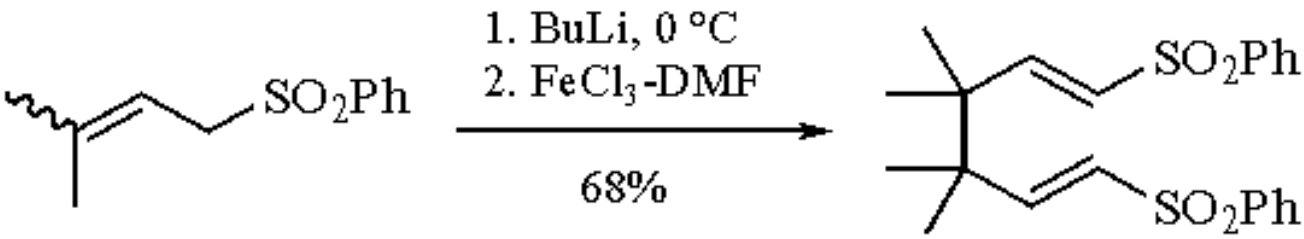

(5)

Ring Expansion of Cyclic Ketones.

Trimethylsilyloxybicyclo[*n*.1.0]alkanes (available by Simmons-Smith reaction of enolates of cycloalkanones) can be oxidized by $FeCl_3$ in DMF at 0 °C to afford the one-carbon ring homologation product (eq 6).[5] This method has been utilized to synthesize 3-methoxycycloheptatrienones (eq 7).[16]

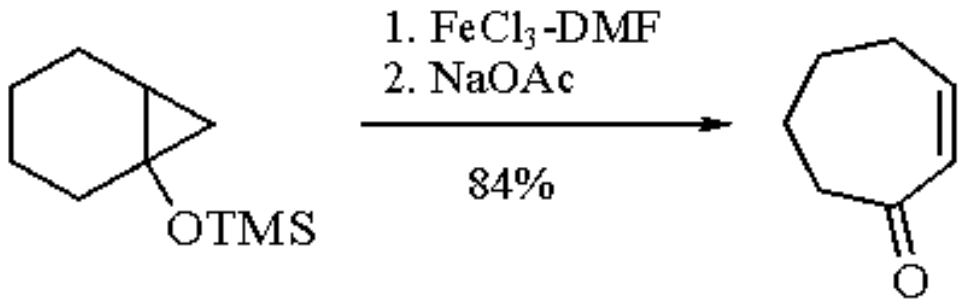

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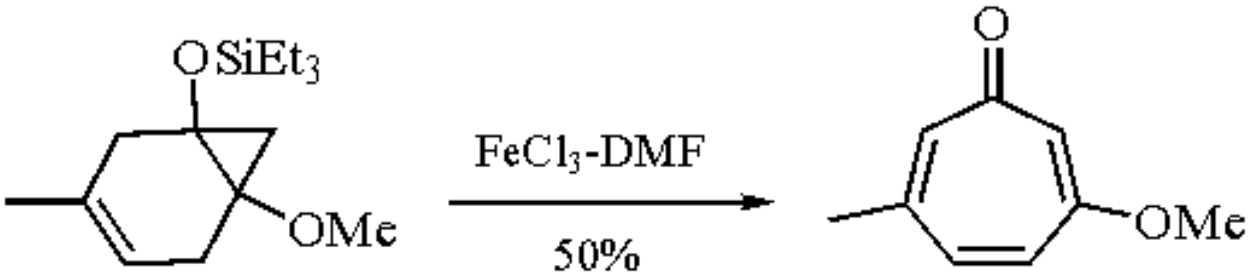

(7)

Oxidative Demetallation of Chromium Carbonyl Complexes.

$[Fe(DMF)_3Cl_2][FeCl_4]$ is an excellent reagent for oxidative workup of chromium tricarbonyl complexes to obtain the arene ligand or aryl product.[6] ***Cerium(IV) Ammonium Nitrate*** represents a viable alternative.[17]

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Iron(III) Chloride-Silica Gel[1]

$FeCl_3$-SiO_2

($FeCl_3$)

[7705-08-0] · Cl_3Fe · Iron(III) Chloride-Silica Gel · (MW 162.20) (SiO_2)

[112926-00-8] · O_2Si · Iron(III) Chloride-Silica Gel · (MW 60.09)

(Lewis acid; dehydration;[2] acetal cleavage;[3,4] rearrangements;[2,6,7] thioacetalization;[9] mild oxidant; oxidative cyclizations[10-13])

Alternate Name: ferric chloride-silica gel.

Form Supplied in: pale yellow powder, 5% wt on silica gel; commercially available.

Preparative Methods: several procedures have been reported for preparation of this reagent depending on the synthetic transformation required. The two procedures described below have been used for cleavage of acetals.[1,2]

Silica gel (10 g, 70-230 mesh) is added to a solution of $FeCl_3.6H_2O$ (1.2 g) in acetone at rt. The solvent is removed on a rotary evaporator and the mixture then heated in vacuo at 60 °C for 30 min/0.1 mmHg to yield a yellow powder.[1]

Anhydrous $FeCl_3$ (4 g) and chromatography grade silica gel (50 g 70-230 mesh) are stirred together in the absence of solvent at rt for 24 h to achieve homogeneous adsorption. A pale yellowish green powder is obtained.[2]

Handling, Storage, and Precautions: the material obtained by procedure 1 is moisture- and light-sensitive, but can be stored for extended periods under dry nitrogen at rt in a brown bottle. The material obtained in procedure 2 is used immediately. $FeCl_3$ is hygroscopic and corrosive; inhalation or ingestion may be fatal. Silica gel is an irritant. Use in a fume hood.

Lewis Acid.

Iron(III) chloride-silica gel will dehydrate alcohols,[1] cleave acetals, open epoxides, rearrange carbonium or oxonium intermediates, catalyze ene reactions, and effect thioacetalization.

Alcohol Dehydration.

$FeCl_3$-SiO_2 is an effective reagent for the dehydration of allylic, tertiary, and sterically strained alcohols (eqs 1 and 2). The reaction is carried out by mixing the alcohol with 100× its weight of $FeCl_3$-SiO_2 in a volatile solvent, followed by evaporation under a high vacuum; this is usually sufficient to complete the reaction.[1] Dehydration of tertiary alcohols has been reported with the reagent prepared by procedure 2.[2]

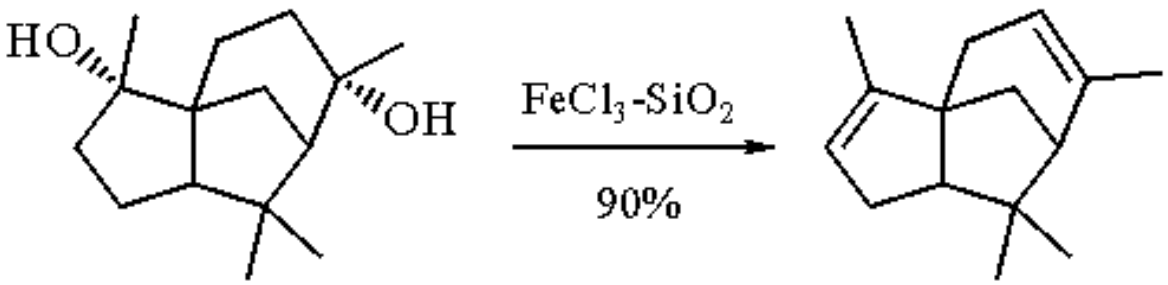

(1)

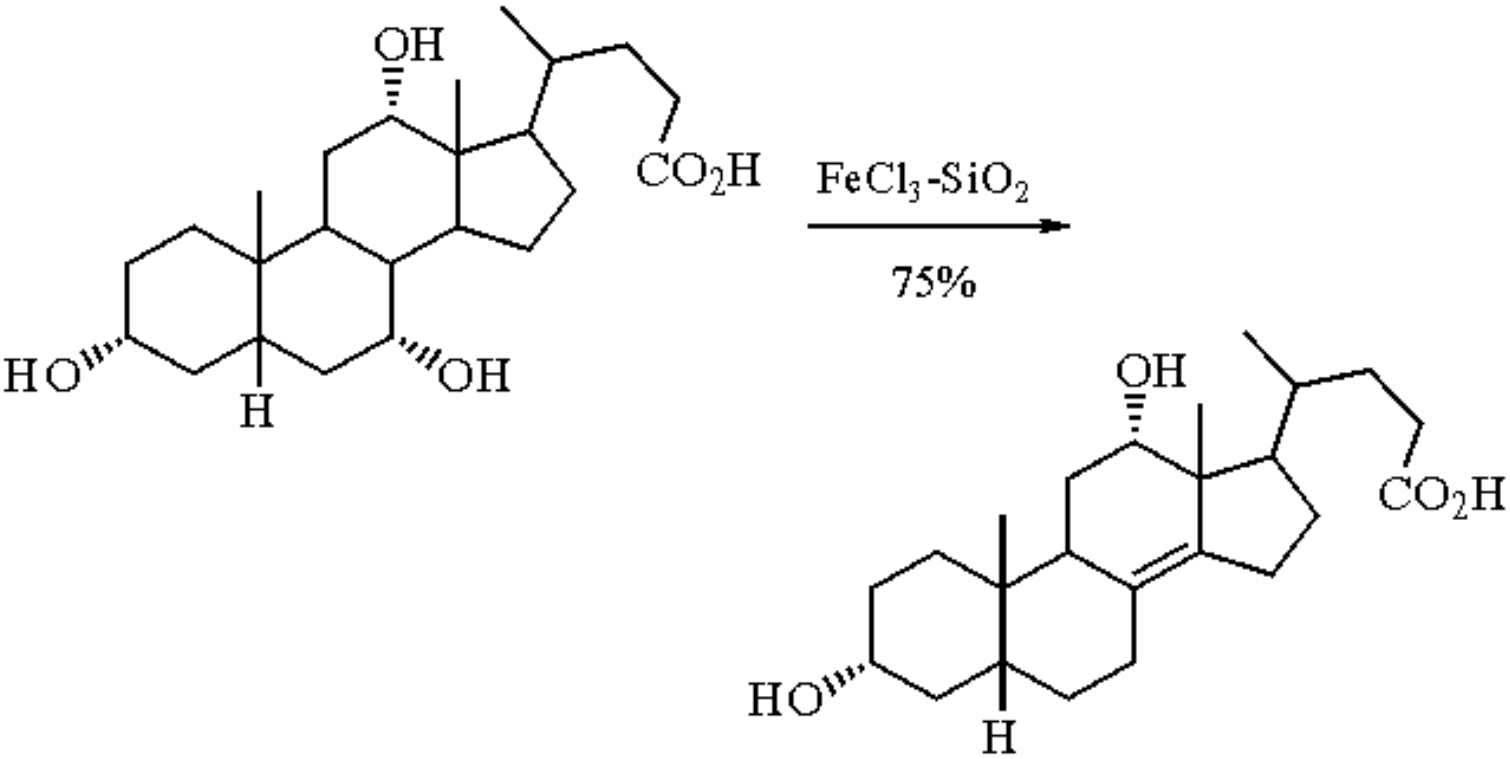

(2)

Cleavage of Acetals.

The $FeCl_3$-SiO_2 reagent cleaves acetals in 2-8 h in chloroform at rt, and is now a well established procedure. Cleavage of TBDMS and trityl ethers is sluggish with typically 30% deprotection after 20 h, which provides for a very mild method for selective deprotections (eq 3). Interestingly, a TBDMS ether can be cleaved without affecting an isopropylidene group in acetone, as the solvent maintains the equilibrium in favor of the isopropylidene group (eq 4).[3,4] Benzyl ether cleavage was not observed in the presence of an acetal; chelation of iron to the latter ensures selectivity.[3] However, rapid benzyl ether deprotection has been reported in the absence of solvent, essentially using the same procedure as for dehydration.[5]

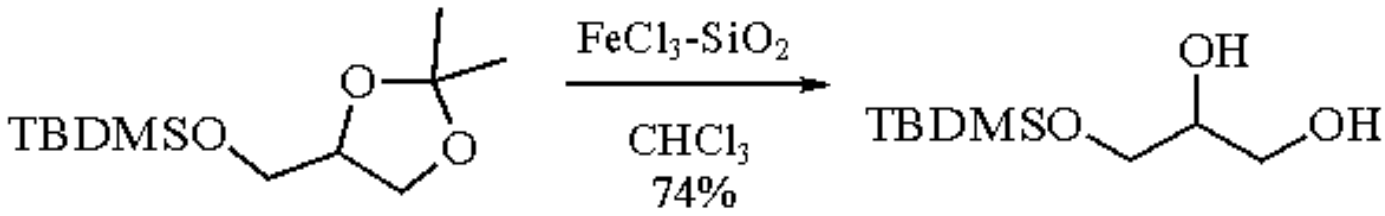

(3)

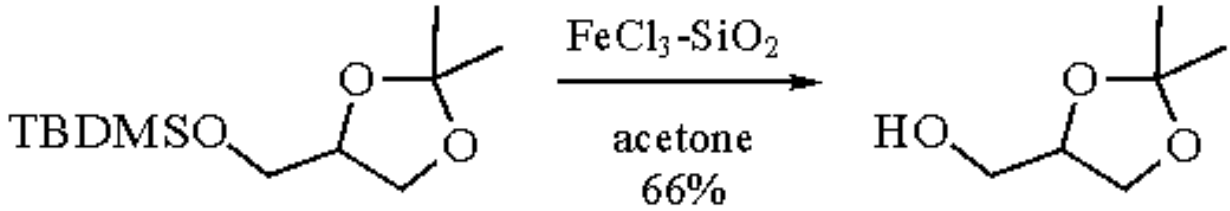

(4)

Rearrangements.

Tertiary cyclobutanols are converted to cyclopentene derivatives with $FeCl_3$-SiO_2 prepared by procedure 2 (eq 5).[2,6] Acyloin (eq 6) and pinacol rearrangements[1] (eq 7) are also observed with $FeCl_3$-SiO_2 from procedure 1. $FeCl_3$-SiO_2 has been reported to catalyze intramolecular ene reactions, although ***Iron(III) Chloride-Alumina*** is superior.[7]

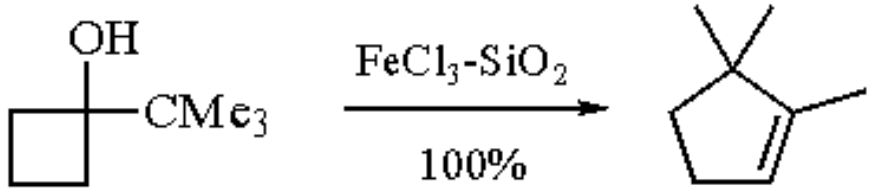

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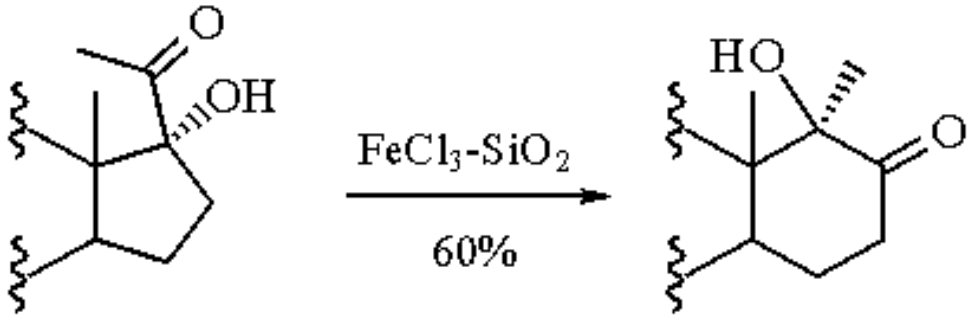

(6)

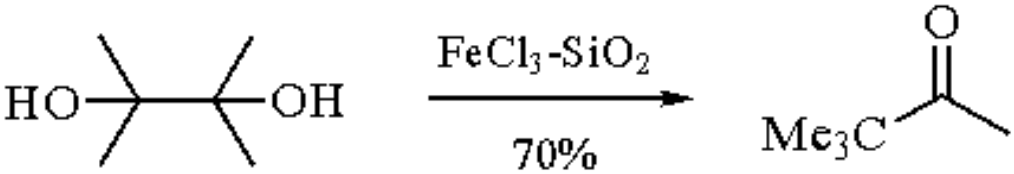

(7)

Epoxides.

$FeCl_3$-SiO_2 containing 2% water facilitates the conversion of epoxides to diols in good yield (eq 8). Anhydrous $FeCl_3$-SiO_2 converts epoxides to mixtures of chlorohydrins.[1]

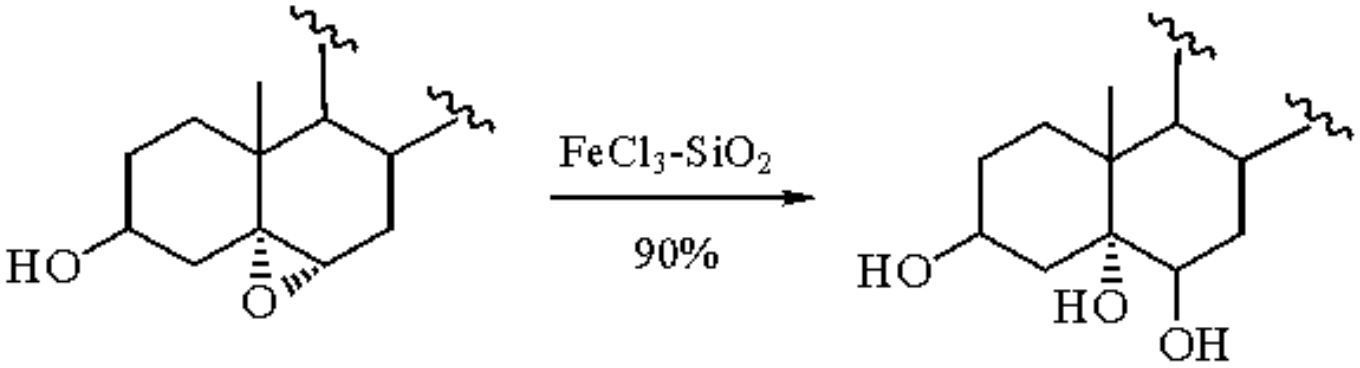

(8)

Thioacetalization.

Carbonyl compounds are thiacetalized with $FeCl_3$-SiO_2 (procedure 2) in excellent yields at rt.[8] Reaction occurs very rapidly in dichloromethane with 1,2-ethanedithiol, with the color turning from gray to pale yellow indicating completion of the reaction (eq 9); this method works well for hindered and aromatic ketones, unlike many of the alternate procedures.[9]

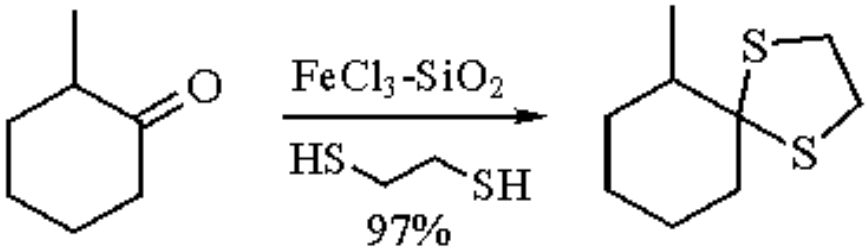

(9)

Oxidations with $FeCl_3$-SiO_2.[10]

Simple di- and trimethoxybenzenes can be coupled in good yield in dichloromethane with 1.1 equiv of $FeCl_3$-SiO_2. Solvent is removed on a rotary evaporator and the mixture is left spinning for 1 h at 30 °C (eq 10).[5,11] Precocene II has been dimerized in light petroleum with $FeCl_3$-SiO_2 to a mixture of two products (eq 11).[12] Intramolecular couplings are observed with appropriately substituted 1,2-diphenylethanes and [2.2]metacyclophanes.[5] Tricarbonylcyclohexadieneiron complexes are oxidatively cyclized with $FeCl_3$-SiO_2 (eq 12) via concentration from THF on a rotary evaporator (40 min).[13] This reaction highlights the moderation in reactivity of this supported reagent as ethanolic $FeCl_3$ can be used to oxidatively disengage an $Fe(CO)_3$-complex ligand.[14]

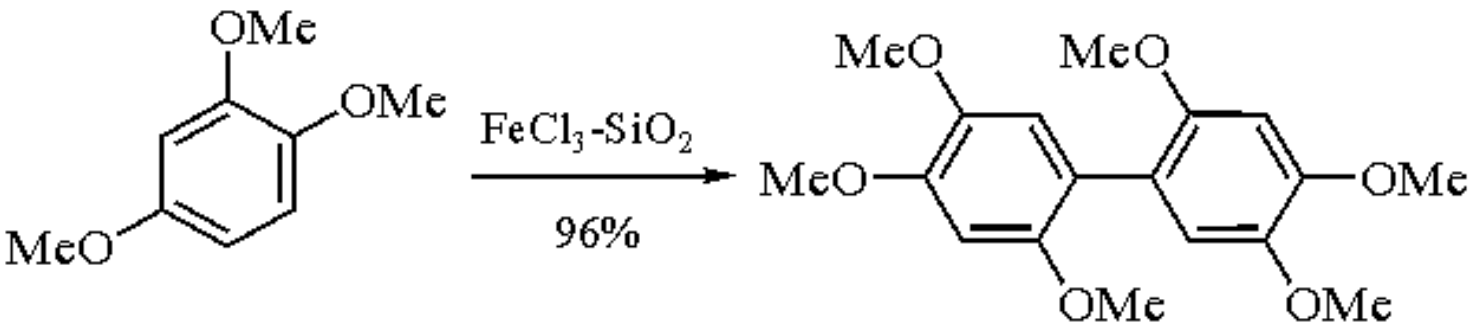

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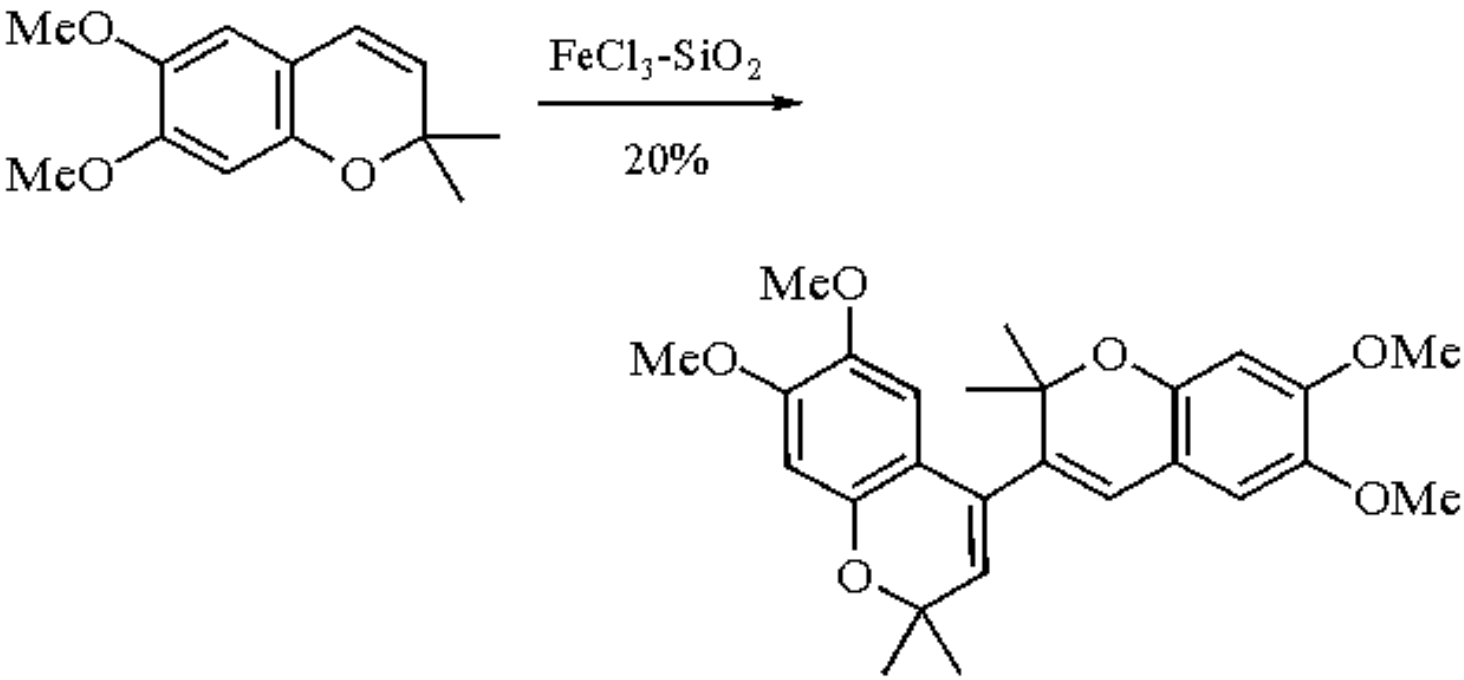

(11)

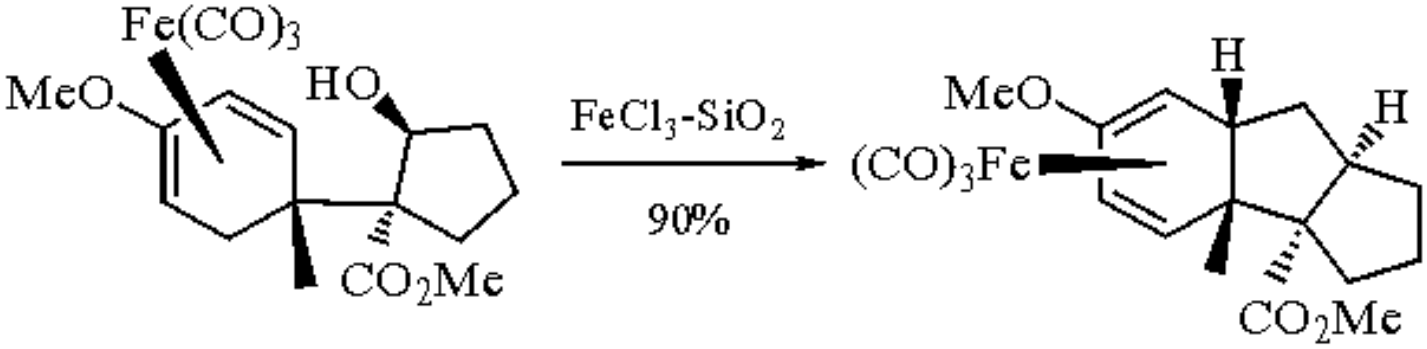

(12)

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Andrew D. White

Iron(III) Chloride-Sodium Hydride[1]

$FeCl_3$-NaH

($FeCl_3$)

[7705-08-0] · Cl_3Fe · Iron(III) Chloride-Sodium Hydride · (MW 162.20) (NaH)

[7646-69-7] · HNa · Iron(III) Chloride-Sodium Hydride · (MW 24.00)

(mild reduction of aldehydes and ketones to alcohols;[2] reduction of alkenes and alkynes[3])

Alternate Name: ferric chloride-sodium hydride.

Preparative Method: generated in situ via addition of a solution of ***Iron(III) Chloride*** (14 mg equiv) in THF (20 mL) to a suspension of ***Sodium Hydride*** (42 mg equiv) in THF (5 mL). The yellow suspension is stirred at rt for 4 h under argon. A solution of the carbonyl compound (2 mmol) in THF (2 mL) is added and stirring continued at rt.

Handling, Storage, and Precautions: $FeCl_3$ is hygroscopic and corrosive; inhalation or ingestion may be fatal. NaH is a flammable solid which reacts violently with water. The powder ignites spontaneously in air. It should be handled in an inert dry atmosphere. Use in a fume hood.

Reduction of Carbonyl Compounds.[2]

$FeCl_3$-NaH is one of a class of reagents called complex reducing agents (CRA), which essentially lower the basicity of NaH. An iron hydride species is assumed to be the active component. A mixture of $FeCl_3$ and NaH in a 1:3 ratio produces the best results for reductions of aldehydes and ketones to alcohols in good yields (75-85%) (eqs 1 and 2). A related reagent, NaH-***Zinc Chloride-Chlorotrimethylsilane***, reduces a variety of aldehydes and ketones in good yield (81-100%).[4] $FeCl_2$-NaH also reduces carbonyl compounds to alcohols, but in lower yields.[2]

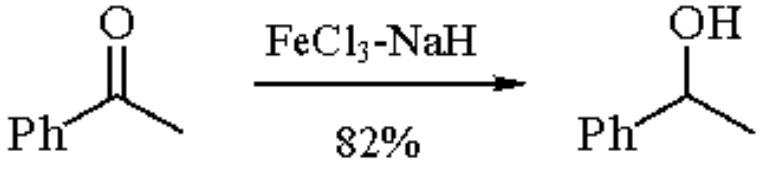

(1)

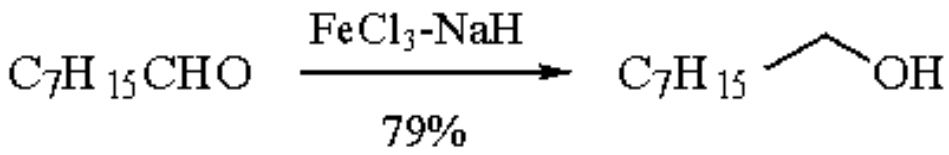

(2)

Reduction of Alkenes and Alkynes.[3]

Double and triple bonds of aliphatic and aromatic alkenes and alkynes, are reduced to alkanes with $FeCl_3$ or ***Iron(II) Chloride*** in THF (eq 3). Enones can be reduced to the corresponding saturated alcohol (eq 4). An alternate reagent NaH-*t*-BuONa-$FeCl_3$ represents a viable alternative for this reduction as it requires fewer equivalents of CRA and is selective. Also it does not reduce aldehydes or ketones.[5] Many combinations of these reagents containing different metal salts and sodium alkoxides have been developed for reduction of organohalides and alkenes/alkynes to alkanes.[1,5,6] The metal hydrides NaH, ***Potassium Hydride***, and LiH in combination with ***n-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine*** or *t*-BuONa-TMEDA have been used as metallating and reducing agents.[7]

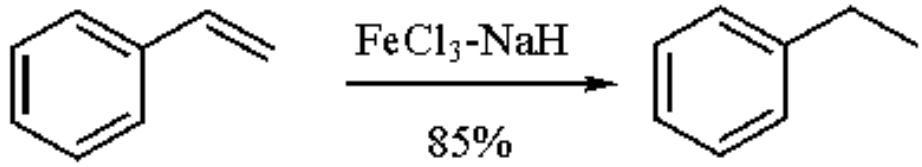

(3)

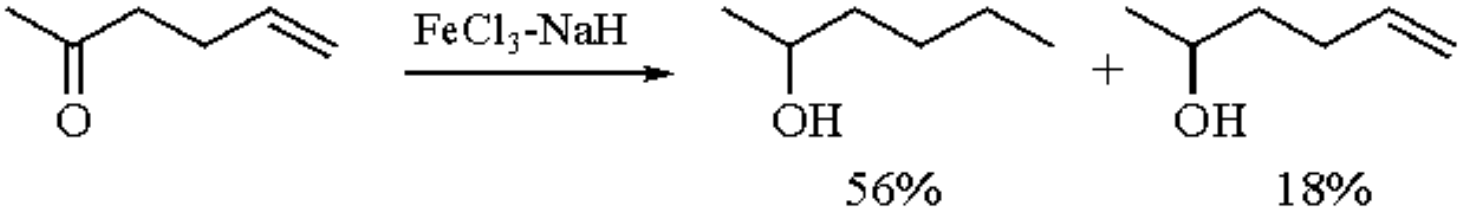

(4)

The combinations of $FeCl_3$-***Lithium Aluminum Hydride***[8] to reduce alkenes to alkanes and $FeCl_3$-BuLi to deoxygenate epoxides to alkenes[9] are of related interest.

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Andrew D. White

Iron-Graphite

$C_{24}Fe$

[65522-66-9] · $C_{24}Fe$ · Iron-Graphite · (MW 344.09)

(reducing agent for organic bromides;[1] debrominates *vic* dihalides to alkenes;[1] debrominates α-bromo ketones[1])

Analysis of Reagent Purity: the determination of iron and potassium content by means of atomic absorption spectroscopy has been described.[1]

Preparative Method: ***Potassium-Graphite*** (C_8K), prepared from 1.17 g of potassium (30 mmol) and graphite (3 g), was covered with THF (15 mL) and a solution of ***Iron(III) Chloride*** (1.62 g, 10 mmol) in THF (20 mL) added dropwise with stirring. After 30 min, the solution was heated to 70 °C for 10 min.

Handling, Storage, and Precautions: freshly prepared $C_{24}Fe$ is used in situ under argon. Air exposure results in complete loss of reactivity. Potassium-graphite reacts violently with water, and care should be taken to avoid such exposure.

Debrominations.

Vicinal dibromides undergo highly stereospecific debromination to give alkenes when treated with a slurry of iron-graphite ($C_{24}Fe$) in wet THF at reflux (1 mmol in 10 mmol $C_{24}Fe$, THF 35 mL, H_2O 1 mL). Elimination is *anti*, such that *anti*-dibromides give (*E*)-alkenes and *syn*-dibromides give (*Z*)-alkenes (eq 1). Based on a limited number of examples, diastereomerically pure dibromides give product alkenes of &egt;97.5% geometric purity. 1,2-Dibromoalkanes give terminal alkenes without detectable amounts of 2-alkenes.

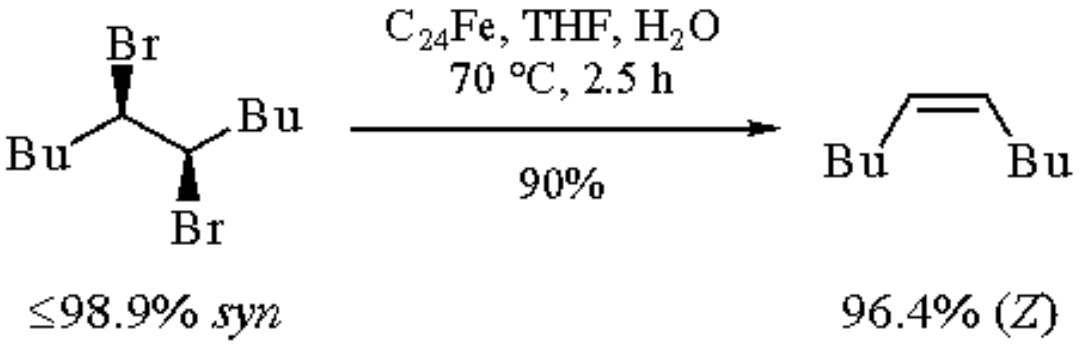

(1)

$C_{24}Fe$ debrominates α-bromo ketones to the parent ketones in high yields under conditions nearly identical to those for dibromoalkanes. Replacement of water by D_2O allows high levels of deuterium incorporation, while attempts to react other electrophiles with the presumed iron enolate intermediate gives only modest yields of condensation products (eq 2).

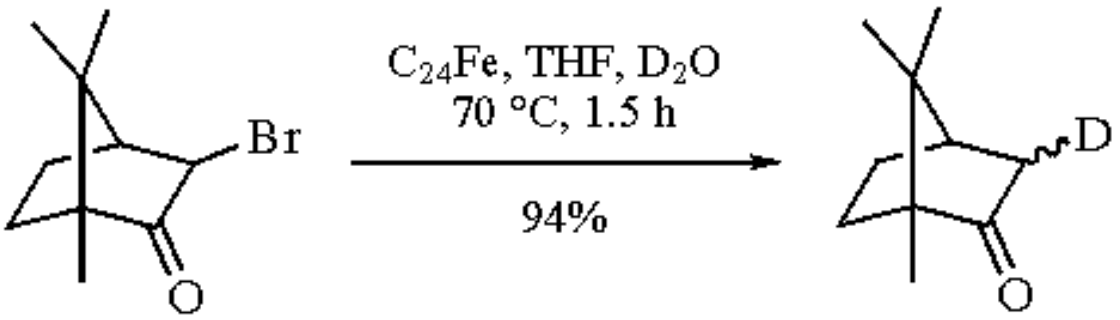

(2)

exo:*endo* = 85:15

Oxyallyl Cations.

α,α´-Dibromo ketones give oxyallyl cations under exposure to iron-graphite in benzene, which have been reacted with enamines or furan to give the products of [3 + 2] (eq 3) or [3 + 4] (eq 4) cycloaddition, respectively.

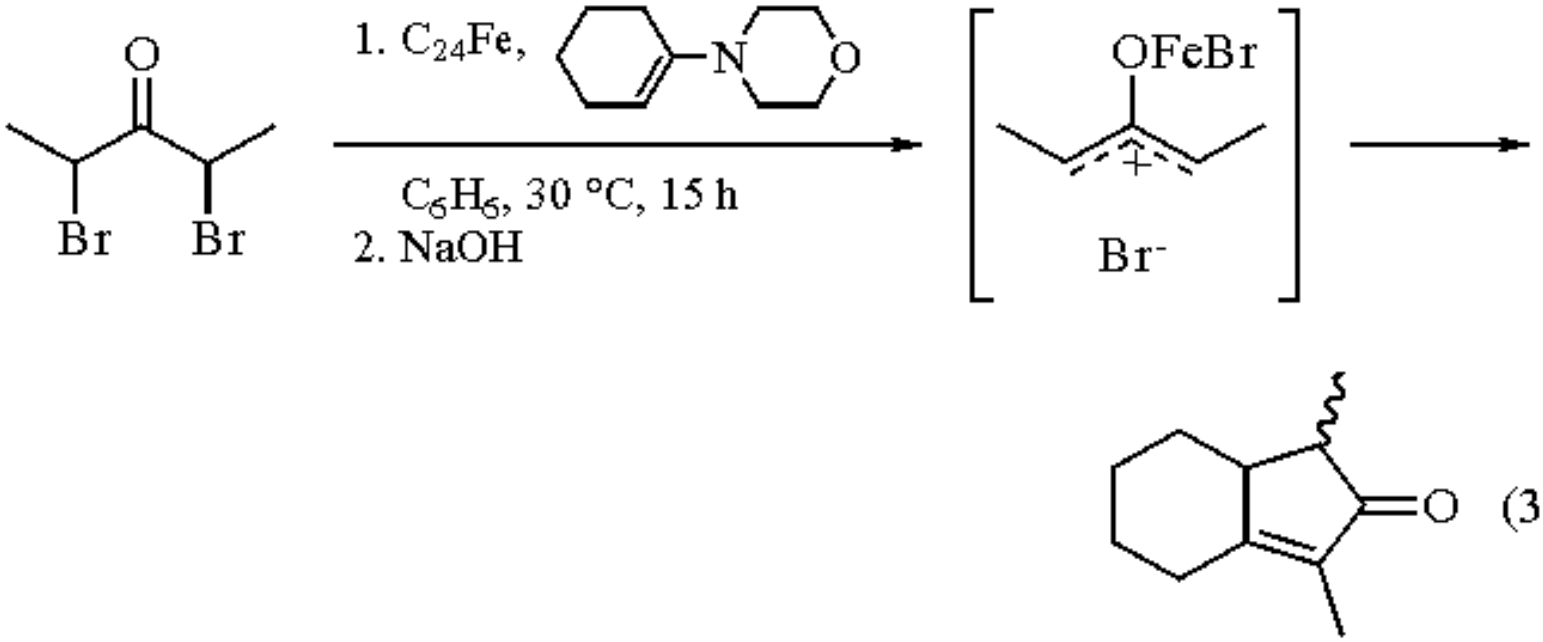

(3)

84%

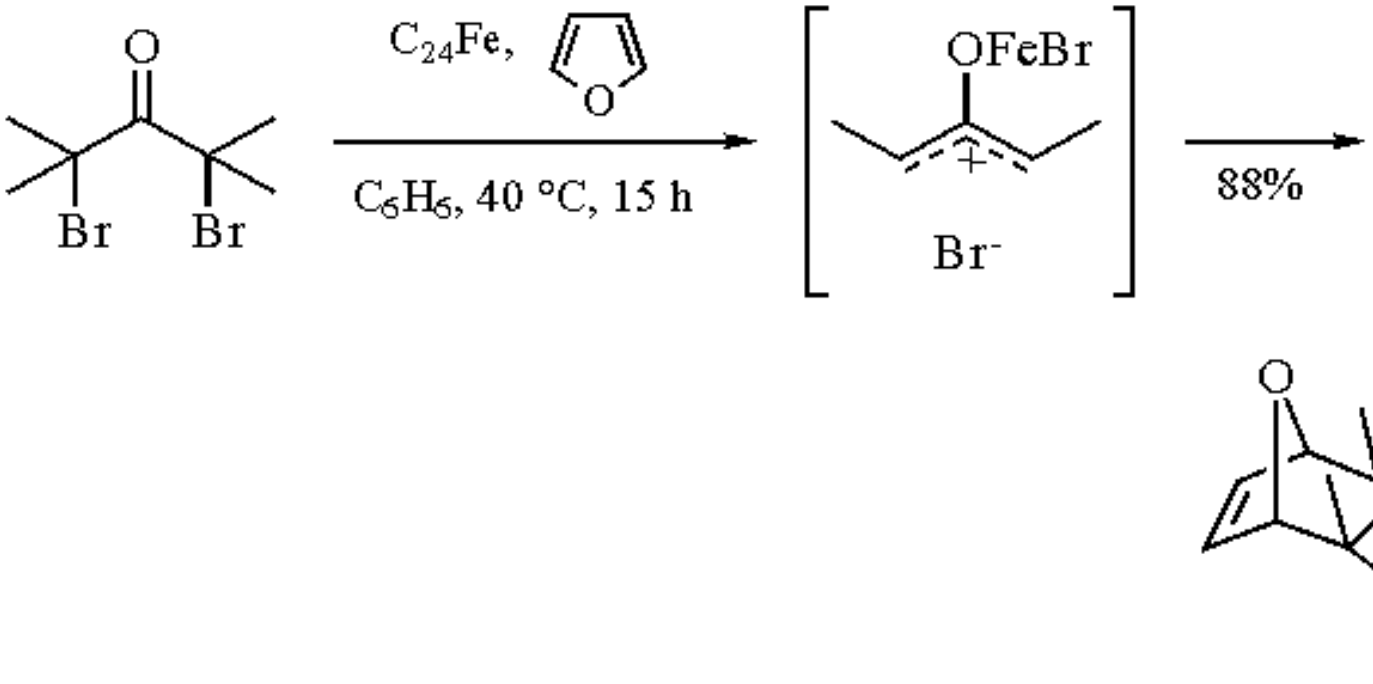

(4)

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Iron(III) Nitrate-K10 Montmorillonite Clay[1]

$Fe(NO_3)_3$-K10

· FeN_3O_9 · Iron(III) Nitrate-K10 Montmorillonite Clay

(mild, inexpensive NO^+ source;[2] oxidizes aromatic rings to radical cations[3])

Alternate Name: clayfen.

Solubility: clay support: insol water, organic solvents. $Fe(NO_3)_3$: sol water, acetone, ethanol.

Form Supplied in: rusty yellow, free-flowing floury powder.

Preparative Method: controlled solvent elimination from K10 clay (30 g) suspended in a solution of $Fe(NO_3)_3.9H_2O$ (22.5 g) in acetone (375 mL).[1]

Handling, Storage, and Precautions: most applications require freshly prepared (1-2 h) reagent. Clayfen is *unstable*, prone to vigorous or slow exothermic decomposition, together with evolution of NO_2 gas. Careful observance of the preparation procedure[1] is critical (in particular, T <50 °C and a crust on the glassware at the flaking-off stage). Never store in gas-tight containers, nor in contact with strongly reducing material such as aluminum. Nitrates are dangerous, and are to be used only with the appropriate precautions and protections. In particular, scaling-up should be attempted only after appropriate safety tests. This reagent should be handled in a fume hood.

Oxidation of Alcohols into Carbonyls.

Clayfen is an efficient and selective oxidation reagent[4,5] for the synthesis of ketones from secondary alcohols, aromatic aldehydes from benzylic alcohols (eq 1), and benzils from benzoins (eq 2). The reaction with primary aliphatic alcohols leads to complex product mixtures.

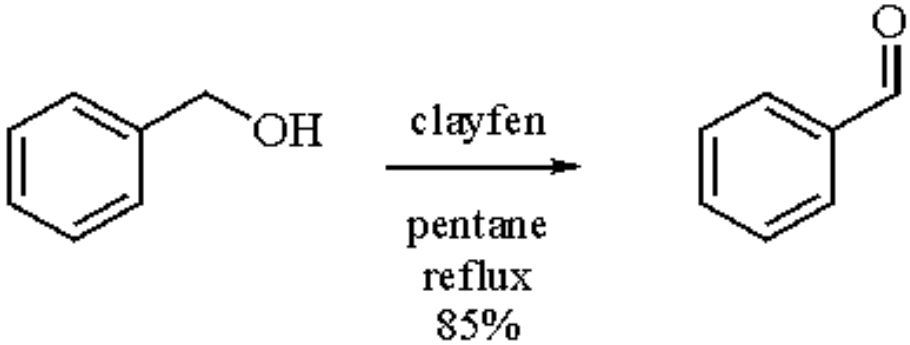

(1)

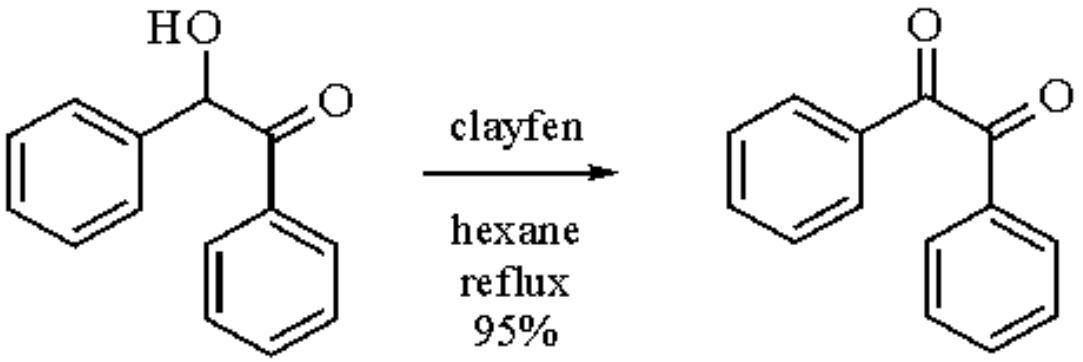

(2)

Nitrites formed with retention of configuration[2] are intermediates, indicating that in these reactions clayfen acts as an NO^+ source.

Oxidative Coupling of Thiols.

As a source of nitrosonium ions, clayfen couples thiols to disulfides[6] through transient thionitrites. In a manner similar to claycop (***Copper(II) Nitrate-K10 Bentonite Clay***), its reaction with ***Thiophenol*** (eq 3) is a good reactivity test.[1]

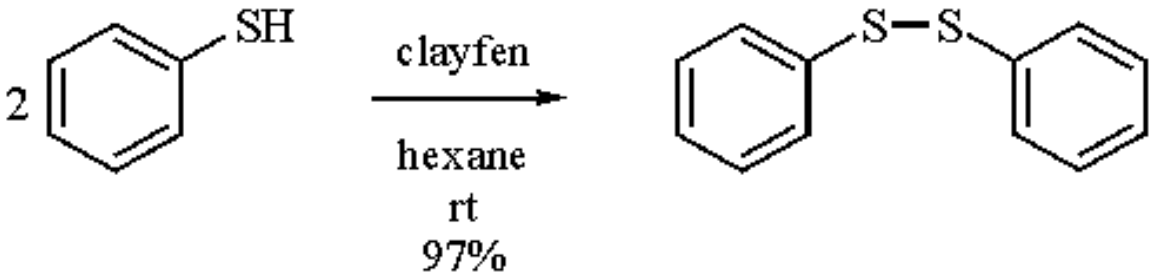

(3)

Carbonyl Group Deprotection.

Clayfen regenerates carbonyl groups from a variety of masking functionalities. For such applications, advantages of this reagent include its low cost, its efficiency under mild conditions, and the easy workup. The following are examples of this use of clayfen.

- 1)Generation of ketones and aldehydes from thioacetals[7] (*S*,*S*-diethyl acetals; 1,3-dithianes; 1,3-dithiolanes). This reaction (eq 4) does not require an additional source of water. Claycop is more suitable than clayfen for this particular purpose on account of its greater stability.

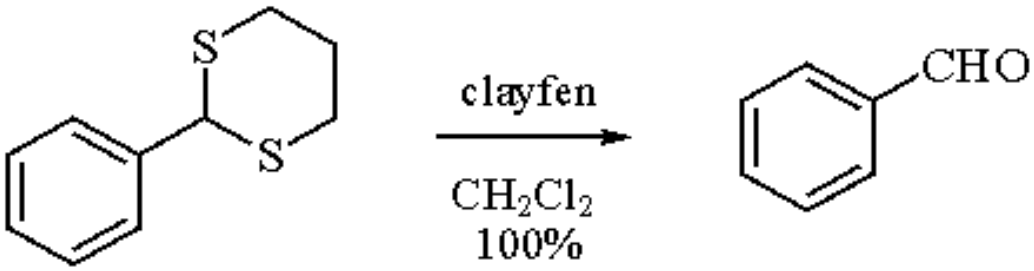

(4)

- 2)Generation of carbonyl groups from selenol acetals.[8] Clayfen complements and improves earlier procedures for the cleavage of bis(phenylseleno)acetals (eq 5), with better yields than with bis(methylseleno) derivatives.

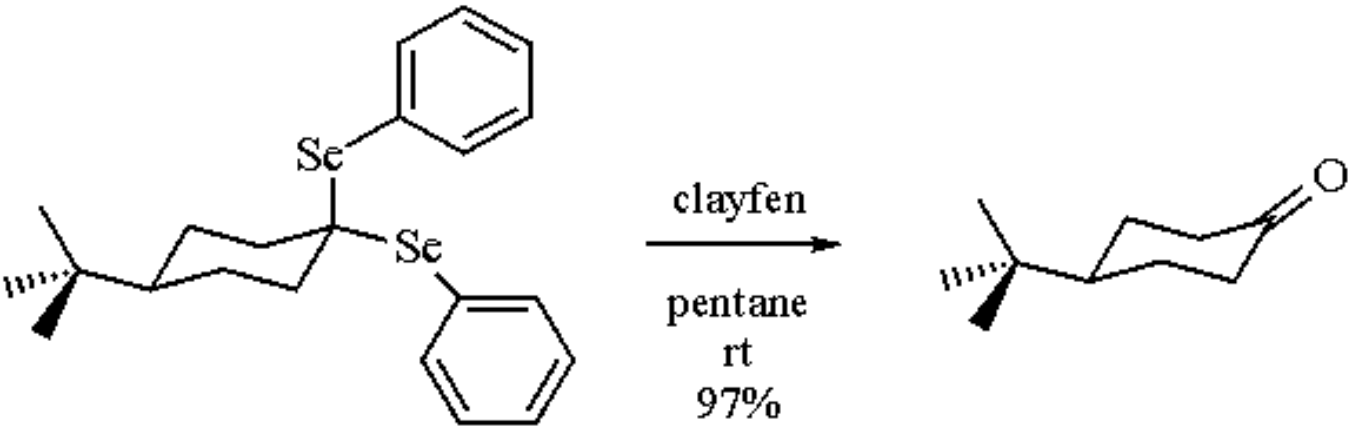

(5)

- 3)Preparation of carbonyl compounds from imine derivatives (*N*,*N*-dimethylhydrazones;[9] tosylhydrazones;[10] phenylhydrazones;[10] 2,4-dinitrophenylhydrazones;[10] semicarbazones[10]). For the cleavage of $R^1R^2C{=}NR^3$ to $R^1R^2C{=}O$ (eq 6), clayfen offers an inexpensive alternative to previous methods, which sometimes require tedious and harsh conditions. However, the results of reactions involving imine derivatives of α,β-unsaturated carbonyl compounds are unsatisfactory, as is sometimes also the case with alternative methods[11,12]

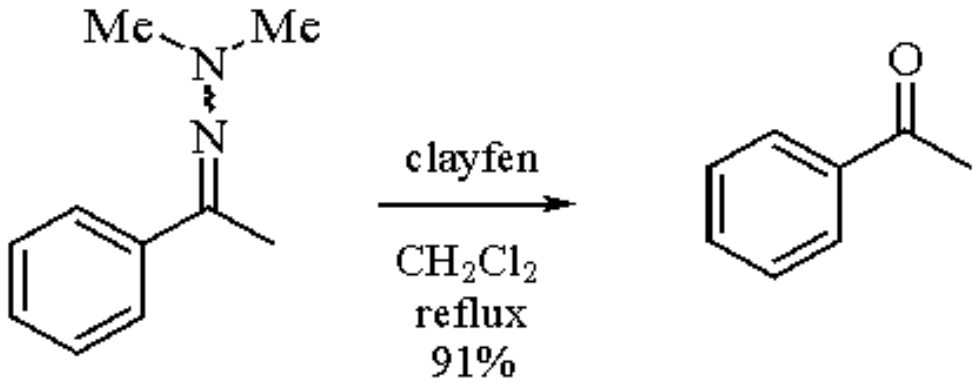

(6)

Conversion of Hydrazines to Azides.

Treatment of various hydrazines with clayfen gives the corresponding azides in fair yield, by the nitrosation route (eq 7).[13] This provides a convenient access to intermediates essential for the preparation of iminophosphoranes.[14]

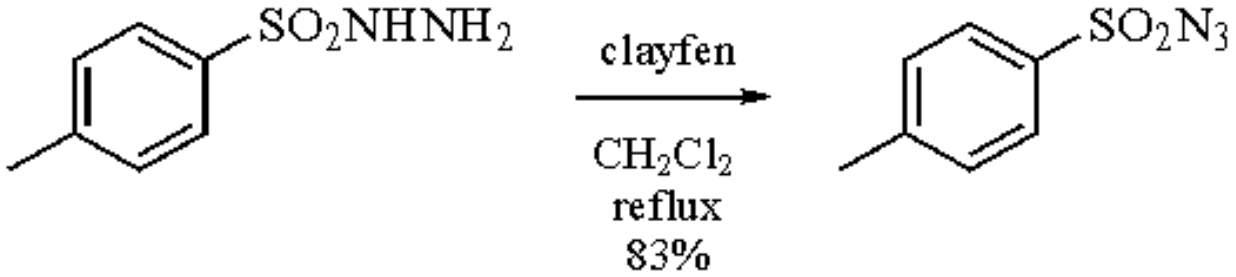

(7)

Aromatization of 1,4-Dihydropyridines.

1,4-Dihydropyridinedicarboxylates aromatize smoothly when treated by clayfen at rt (eq 8).[15] Use of claycop rather than clayfen leads to slightly higher yields and is devoid of the risks accruing from the instability of the latter.

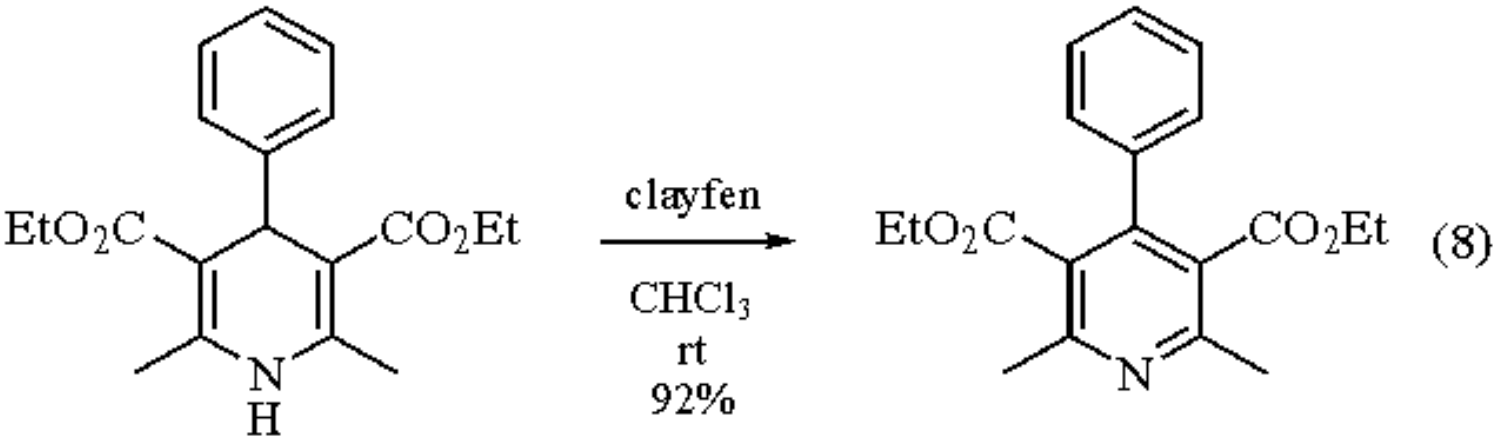

Thiocarbonyl-to-Carbonyl Transformation.

In this transformation promoted by NO^+ ions, clayfen gives excellent results (77-100%) with aromatic substrates (eq 9)[16] and offers a cheap alternative to ***Nitrosonium Tetrafluoroborate***.[17] 1,2-Dioxa-4,5-dithiane six-membered rings are transient intermediates in these transformations.[18]

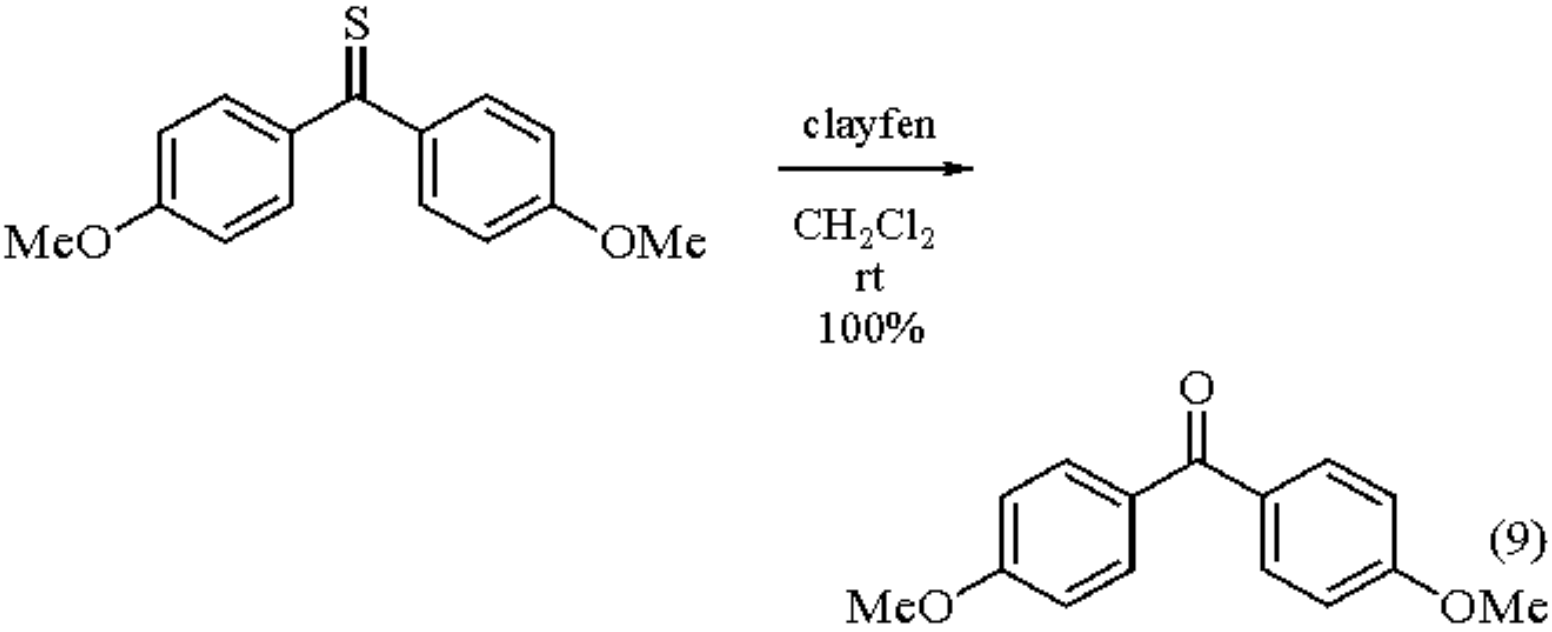

Regioselective Nitration of Phenols.

Clayfen nitrates phenols under extremely mild reaction conditions to produce exclusively *ortho* or *para* mononitration products (eq 10).[3,19]

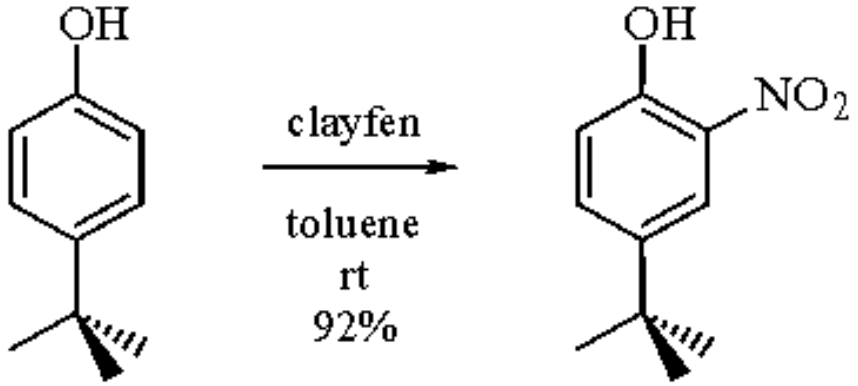

(10)

The reaction is performed at rt in ether, in THF, or in toluene. The solvent is chosen so that it dissolves the nitro derivative formed. Aldehyde and nitrile groups are unaffected under these mild conditions. With *meta*-substituted phenols the reaction is nicely regioselective at the *ortho* position. For instance, the sole nitration product of estrone is 2-nitroestrone (eq 11).[19]

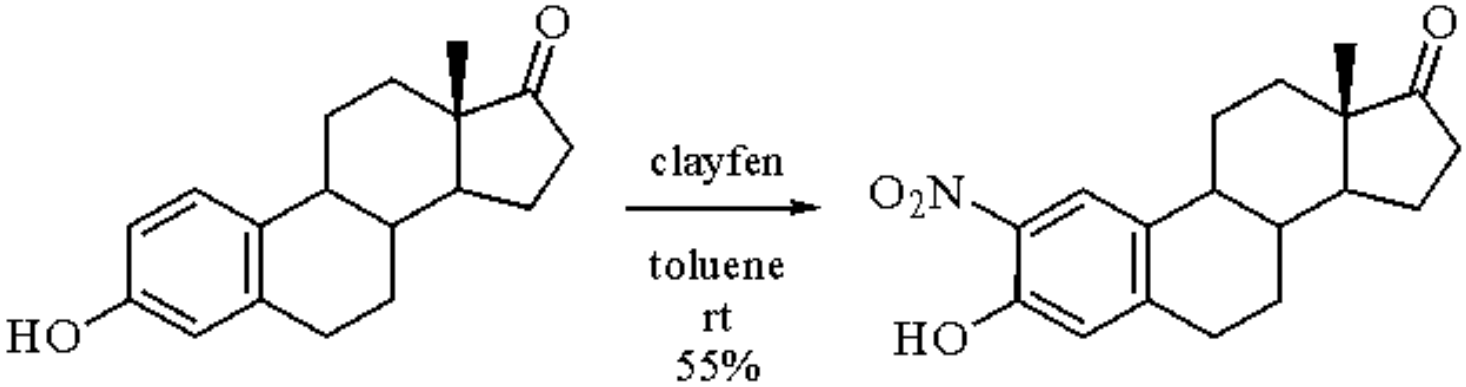

(11)

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Dow Chemical Company, Midland, MI, USA

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Iron(II) Perchlorate

$Fe(ClO_4)_2$

($Fe(ClO_4)_2.6H_2O$)

[13520-69-9] · Cl_2FeO_8 · Iron(II) Perchlorate · (MW 362.87)

(aromatic and aliphatic hydroxylation; reductive decarboxylation of peracids; dehydration and monooxygenation of organic compounds)

Alternate Name: ferrous perchlorate.

Physical Data: dec >100 °C.

Solubility: ~98 g/100 mL H_2O at 0 °C; sol alcohol, $HClO_4$.

Form Supplied in: light green crystalline powder.

Handling, Storage, and Precautions: eye irritant; hygroscopic; contact with combustible material may cause fire. **Warning**: conversion to lower hydrates by unintentional dehydration may cause explosion. Use due caution in handling, as for all perchlorates. Use in a fume hood.

Aromatic Hydroxylation (Fenton Oxidation).[1]

Aromatic substrates are hydroxylated under mild conditions when treated with iron(II) salts, such as iron(II) perchlorate or ***Iron(II) Sulfate***, ***Hydrogen Peroxide***, and an appropriate oxidant (eg Fe^{3+}, Cu^{2+}, O_2) in aqueous acetonitrile (eq 1). Yields are generally less than 50%. The rate-determining step in the reaction was shown to be the production of a hydroxyl radical which reacts directly with the aromatic substrate, generating a phenolic radical intermediate. This is ultimately converted to the corresponding phenol. An interesting rearrangement of a hydrogen atom during the oxidation (NIH shift),[2] as observed during enzymatic hydroxylation, also takes place during the reaction.

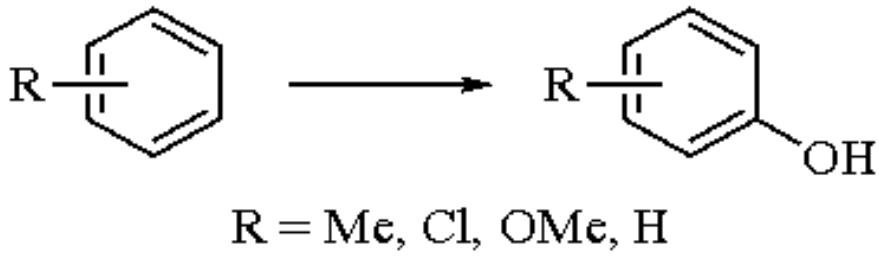

(1)

Aliphatic Hydroxylation.

C-H bond activation by metal complexes is of fundamental importance in hydrocarbon functionalization.[3] The regio- and stereospecific conversion of *O*-cholestan-3α-yl *S*-methyl dithiocarbonate to cholestane-1α,3α-diyl diacetate demonstrates the coordination of iron-dioxygen complexes, formed by the reaction of iron(II) perchlorate and oxygen, with electron-rich *S*-alkyl xanthates to lead to the oxidation of neighboring C-H bonds (eq 2).[4] In the absence of Fe^{II}, no reaction takes place.

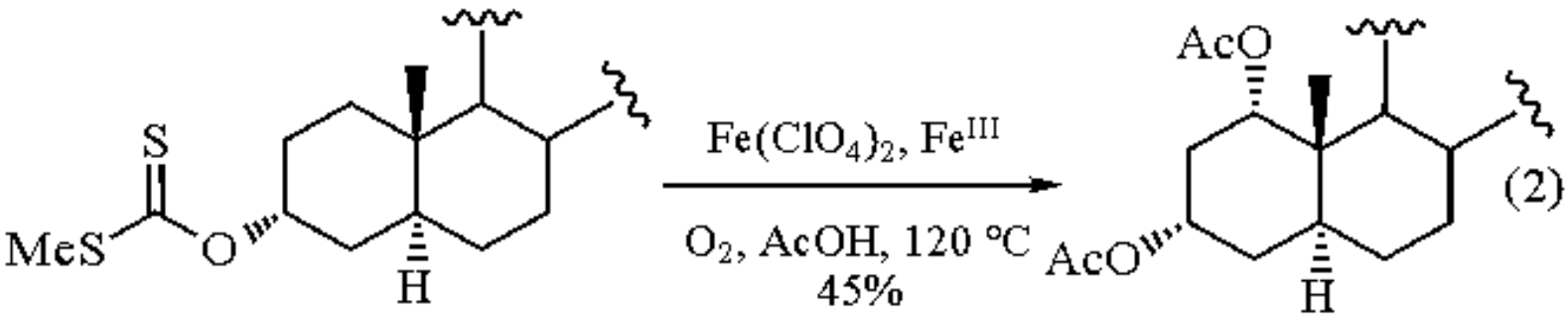

Reductive Decarboxylation of Peracids.

Peroxycyclohexanecarboxylic acid is converted to cyclohexanol (25%) and cyclohexanecarboxylic acid (75%) when treated with iron(II) perchlorate at 0 °C in acetonitrile (eq 3).[5] Treating *cis*- or *trans*-3-hydroxyperoxycyclohexanecarboxylic acid in a similar manner leads to nearly pure *cis*-1,3-cyclohexanediol (85:15 *cis*:*trans*), indicating participation by hydroxy.

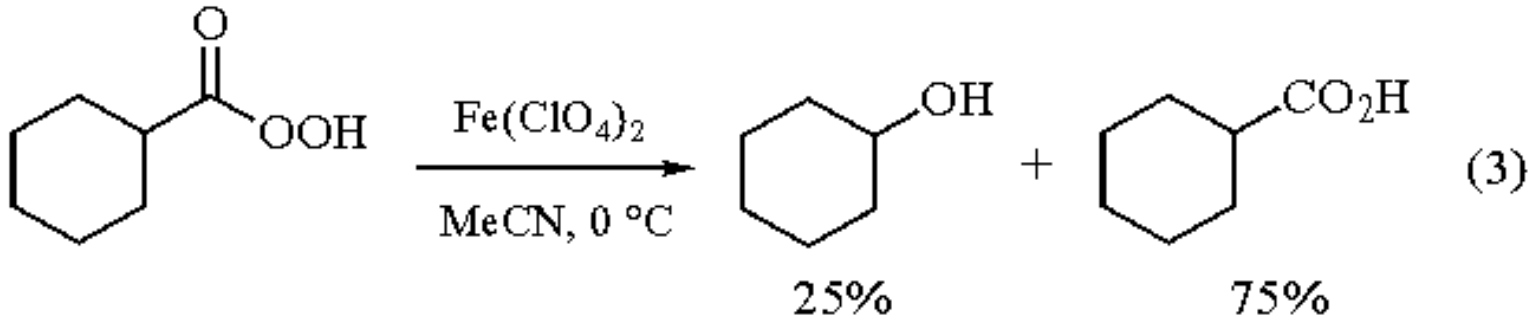

Dehydration and Monooxygenation of Organic Compounds.

Iron(II) perchlorate hexahydrate is used to prepare $Fe(MeCN)_4(ClO_4)_2$, a catalyst used in combination with H_2O_2 to dehydrogenate and monooxygenate organic substrates in dry acetonitrile.[6] No products resulting from &bdot;OH radical chemistry are observed, which suggests that classical Fenton-type chemistry[1,7] does not occur under these conditions. With alcohols, aldehydes, methylstyrene, thioethers, sulfoxides, and phosphines, the active catalyst, $Fe(H_2O_2)^{2+}$, promotes the monooxygenation to aldehydes, carboxylic acids, epoxide, sulfoxides, sulfones, and phosphine oxides, respectively.

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Iron(II) Phthalocyanine

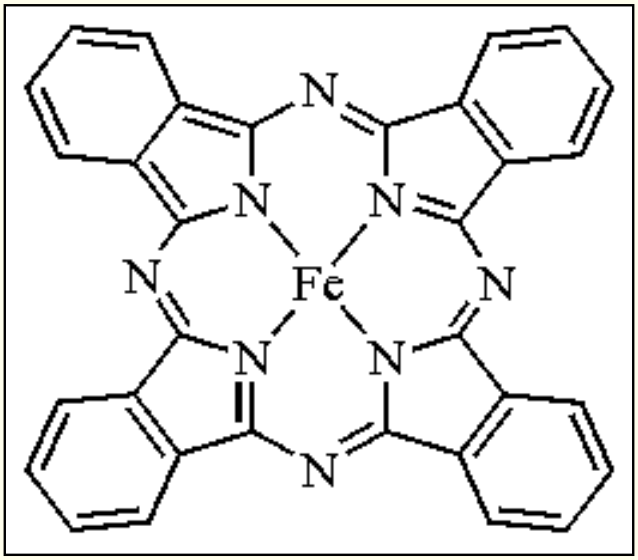

[132-16-1] · $C_{32}H_{16}FeN_8$ · Iron(II) Phthalocyanine · (MW 568.41)

(oxidation of terminal alkenes to methyl ketones; 1,4-oxidation of 1,3-dienes; allylic oxidation of cyclic alkenes; siloxane elimination from silylamides to form nitriles)

Physical Data: mp >300 °C.

Form Supplied in: black powder.

Handling, Storage, and Precautions: store tightly sealed in a cool, dry place.

Preparation of Methyl Ketones from Alkenes (Wacker Oxidation).

Methyl ketones are conveniently prepared from terminal alkenes by Wacker oxygenation using a catalytic amount of ***Palladium(II) Chloride*** and ***Copper(II) Chloride***.[1] The reaction can be slow and chlorinated byproducts are usually observed. Iron phthalocyanine (Fe(Pc)) serves as the oxygen-activating complex in a multicatalyst system used to perform Wacker-type[2] oxidation reactions (eq 1).[2b] This catalyst system offers a chloride-free environment in which alkenes are smoothly converted to methyl ketones with molecular oxygen, under mild conditions, in moderate to high yield. Unlike typical Wacker oxidations using $CuCl_2$, no chlorinated byproducts are formed.[1a,3] In addition, the removal of chloride from the system increases the rate of reaction.[4] In the catalyst system, Fe(Pc) reoxidizes hydroquinone to benzoquinone, which serves to reoxidize Pd^0 to Pd^{II} after Pd^{II} catalyzes the oxidation of the alkene to the ketone (eq 1). In the present catalyst system, acid ($HClO_4$) is added to prevent the rapid precipitation of Pd

from the aqueous DMF reaction mixture. The reoxidation of hydroquinone by other means,[5] including electrochemical reoxidation,[6] has been reported.

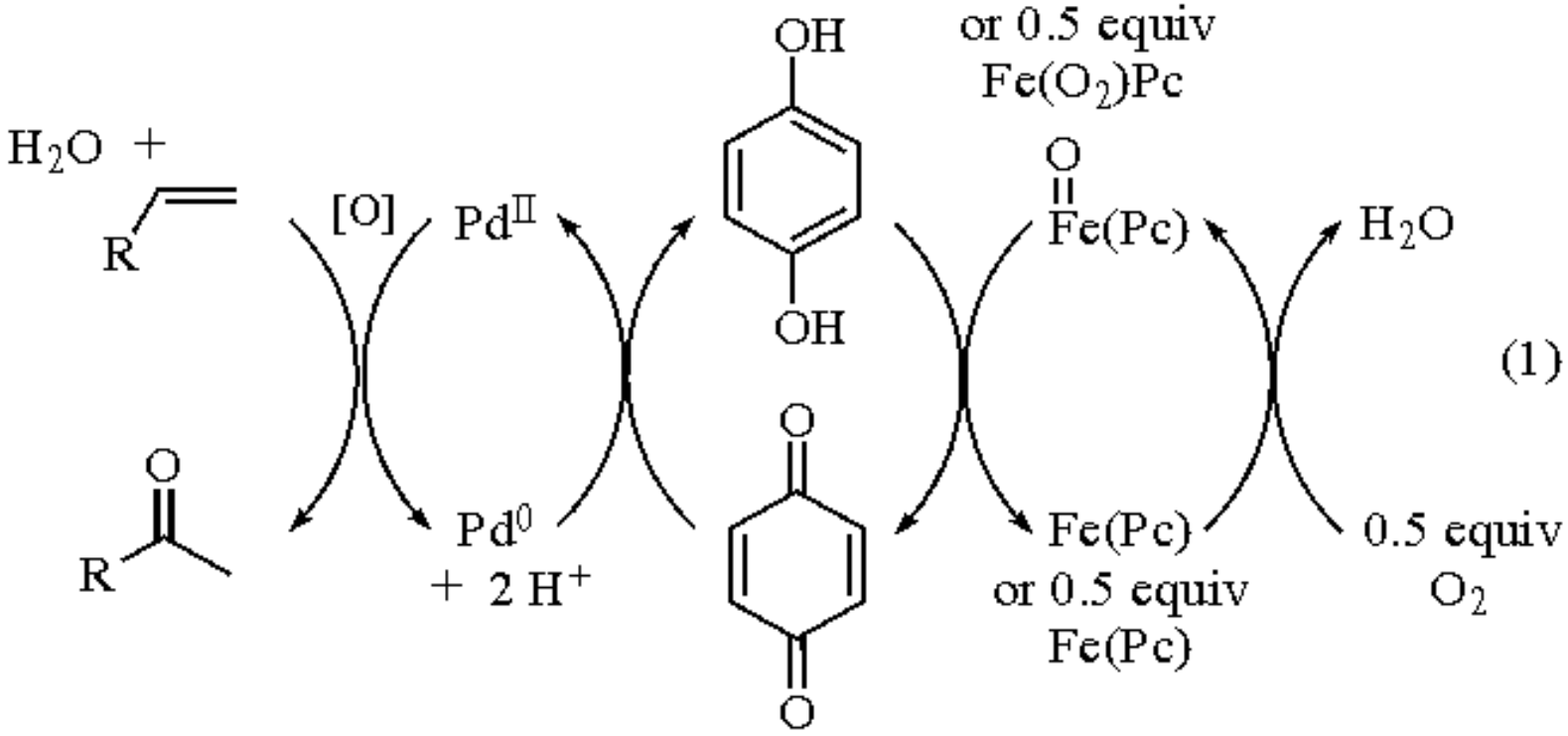

1,4-Oxidation of Conjugated Dienes.[7]

Conjugated dienes can be oxidized to *cis*-1,4-diols and 1,4-diacetates when treated with the above catalyst system in acetic acid or alcohol (eqs 2 and 3).

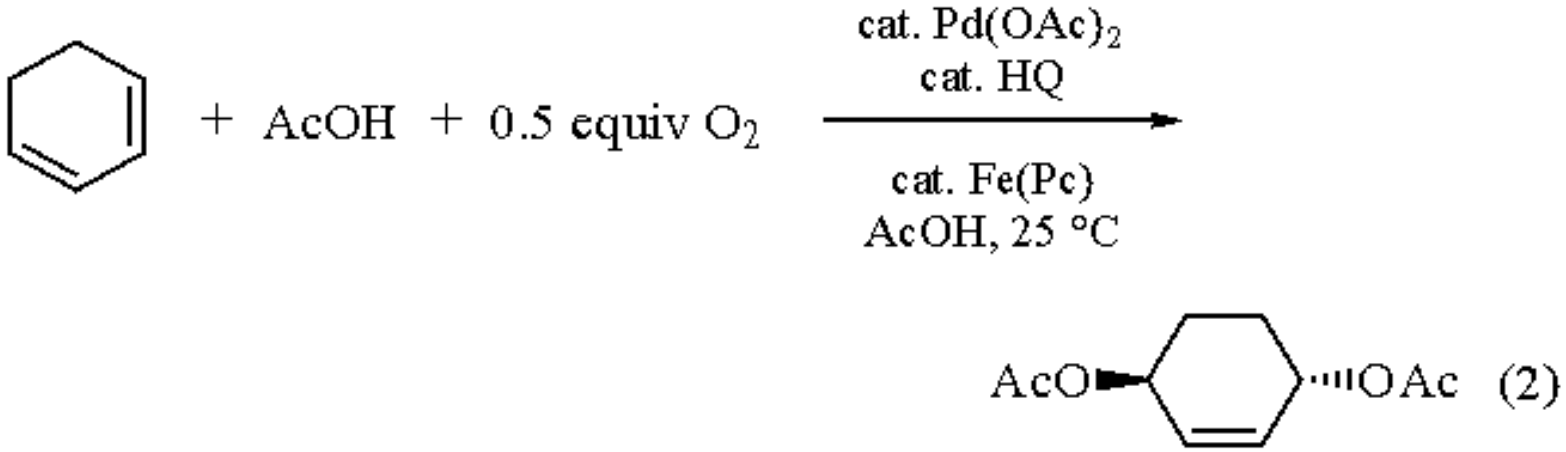

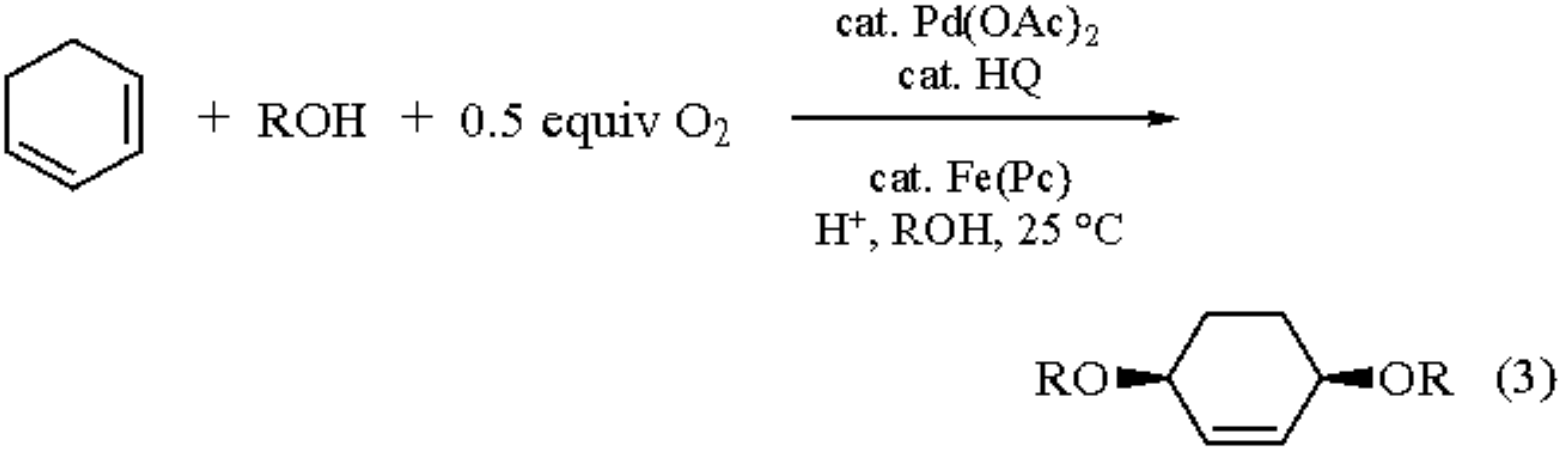

Aerobic Allylic Oxidation of Alkenes.[6c]

Exposure of cyclohexene to the above described catalyst system in acetic acid gives the desired allylic oxidation product (eq 4). Again, Fe(Pc) and molecular oxygen take the place of less convenient oxygen sources such as MnO_2.[8]

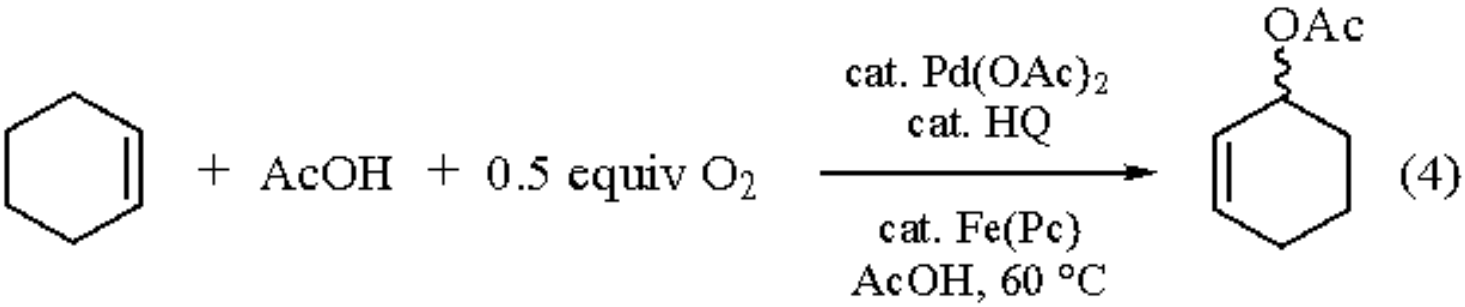

Epoxidation of Alkenes.

In a comparison of transition metal phthalocyanines, iron(II) phthalocyanine most effectively catalyzes the epoxidation of alkenes when ***Iodosylbenzene*** is the oxygen donor.[9] It is less effective than other metal-phthalocyanine catalysts when NaOCl is used as the oxygen donor. A mixture of *cis*- and *trans*-epoxides are produced from *cis*-alkenes. In the presence of 2,6-di-*t*-butyl-*p*-cresol, highly stereoselective epoxidation of the *cis*-alkene is observed.

Preparation of Nitriles from Amides.[10]

Iron phthalocyanine readily catalyzes the decomposition of bis(trimethylsilyl)amides to give nitriles under relatively mild conditions (75 °C, 6 h, 100%, eq 5). This serves as a useful alternative to the less general thermal decomposition of bis(silylamides)[11] or the thermal decomposition of monosilylamides in the presence of stoichiometric amounts of an acidic reagent.[12] Catalytic amounts of fluoride ion or simple Lewis acids such as $FeCl_3$, $ZnCl_2$, or $AlCl_3$, are also effective reagents for this transformation.

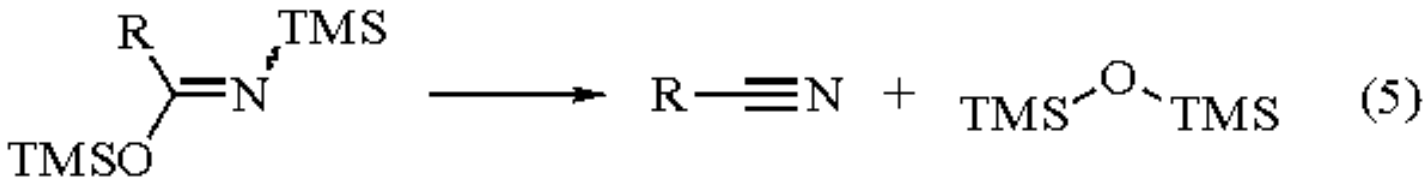

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Iron(III) Sulfate

$\mathbf{Fe_2(SO_4)_3}$

($Fe_2(SO_4)_3$)

[10028-22-5] · $Fe_2O_{12}S_3$ · Iron(III) Sulfate · (MW 399.91) ($Fe_2(SO_4)_3.5H_2O$)

[-] · $Fe_2O_{12}S_3$ · Iron(III) Sulfate · (MW 490.01)

(catalyst for the dehydration of alcohols to give alkenes; serves as a useful oxidant during the alkoxylation of quinones; catalyzes the ring opening of 2-oxazolines with amines)

Alternate Names: ferric sulfate; ferric sesquisulfate; ferric tersulfate; diiron trisulfate.

Physical Data: hygroscopic.

Solubility: slowly sol H_2O; sparingly sol alcohol.

Form Supplied in: grayish white powder.

Handling, Storage, and Precautions: moisture sensitive; harmful dust; irritant.

Preparation of Alkenes: Dehydration of Alcohols.[1]

Silica gel supported iron(III) sulfate efficiently catalyzes the dehydration of secondary and tertiary alcohols under moderate conditions to give the corresponding alkenes. Iron(III) sulfate-SiO_2 was found to be more active than all other silica gel supported sulfates tested ($CuSO_4$, $NaHSO_4$, $Al_2(SO_4)_3$, $SnSO_4$, $ZnSO_4$, etc.), but promoted undesirable side reactions in some cases (Table 1).

Table 1 Dehydration Catalyzed by $Fe_2(SO_4)_3$ SiO_2

Substrate	Solvent	Time	Product	Yield (%)
Cyclododecanol	Hexane	60	Cyclo-dodecene	99
Cyclododecanol	CH_2Cl_2	60	Cyclo-dodecene	17
Cyclooctanol	CH_2Cl_2	30	Cyclo-octene	87
1-Phenylethanol	CH_2Cl_2	5	Styrene	0
Cholesterol	CH_2Cl_2	30	3,4-Didehydro-cholesterol	20

Primary alcohols generally give complex mixtures of products. The order of reactivity, tertiary > secondary > primary, implies that the generation of a cationic intermediate is a key step in the reaction. Conventional methods for dehydration utilize simple reagents such as HBr, H_2SO_4, and $NaHSO_4$, as well as non-silica gel complexed $NaHSO_4$ and $CuSO_4$.

Preparation of Alkoxyquinones: Addition of Alcohols to 1,4-Benzoquinones.[2]

Iron(III) sulfate oxidizes the initial adduct formed by the reaction of an alcohol with a dimethoxynaphthoquinone derivative under acidic conditions to give the desired alkoxyquinone in good to excellent yield (eq 1) (Table 2). In the absence of an added oxidant the starting material oxidizes the initial adduct, alkoxyhydroquinone, which greatly reduces the potential yield of the reaction. Other oxidants, such as DDQ and air/light, were found to be less effective than iron(III) sulfate.

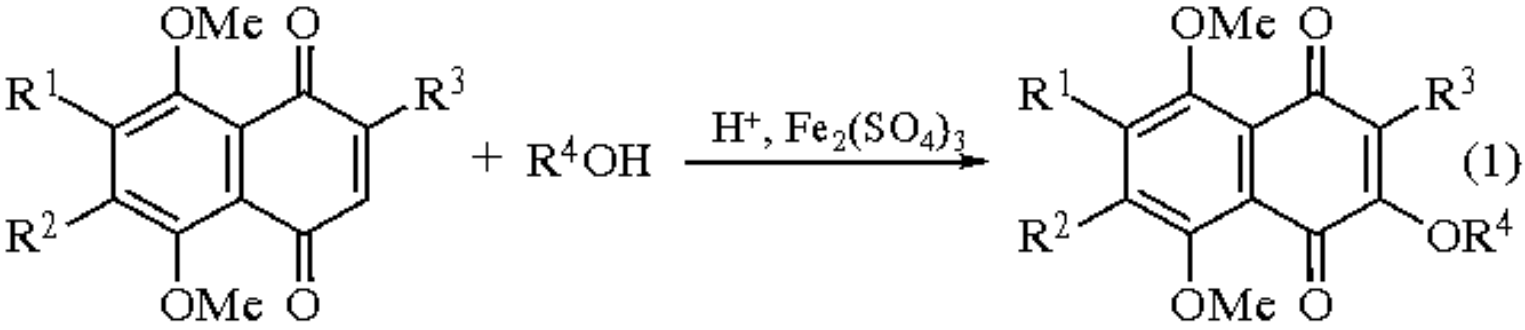

$R^1 = H$, COMe; $R^2 = H$; $R^3 = H$, COMe; $R^4 = H$, Me, Et

Table 2 Alkoxylation of Quinones in the Presence of Iron(III) Sulfate

R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	95
COMe	H	H	H	35
H	COMe	H	H	45
H	H	COMe	H	95
H	H	H	Me	90
COMe	H	H	Me	36
H	COMe	H	Me	54
H	H	H	Et	80

Preparation of Substituted Ethylenediamines.

The catalyzed, nucleophilic ring opening of 2-oxazolines with amines provides a convenient method for preparing unsymmetrically substituted ethylenediamines (eq 2).[3] Coordination of the oxazoline with $Fe_2(SO_4)_3$ and other Lewis acids increases the electrophilic character of the oxazoline and increases its susceptibility for nucleophilic attack at the 2 (reversible) and 5 (irreversible) positions. Better yields were obtained with alternative catalysts, including $Zn(OAc)_2$, ***p-Toluenesulfonic Acid***, and ***Boron Trifluoride Etherate***. This method serves as an alternative to the reported synthesis of ethylenediamines from aziridines, phthalimides, nitriles, and 2-aminopropionamides.

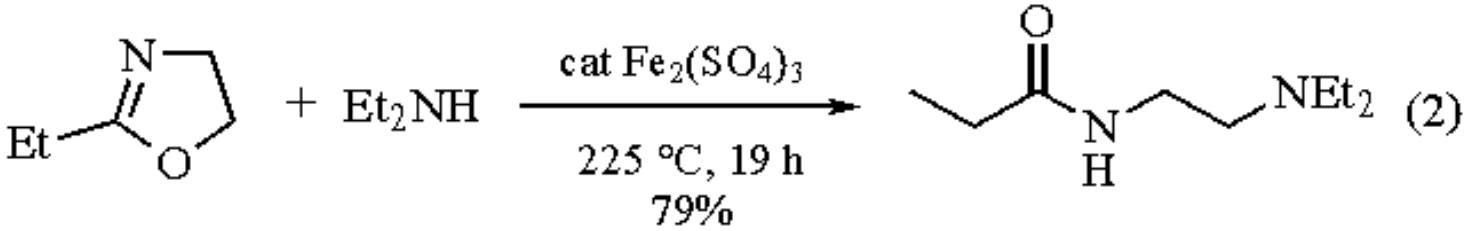

Stereoselective 1,4-Addition of Alcohols to Phenylazostilbene to give Alkoxyphenylhydrazones.

The addition of alcohols to phenylazostilbenes in the presence of 2 equiv of iron(III) sulfate gives predominantly, or exclusively, the *anti* isomer of the resulting alkoxyphenylhydrazone.[4] No reaction took place in the absence of the iron ion (or copper ion) (eq 3).

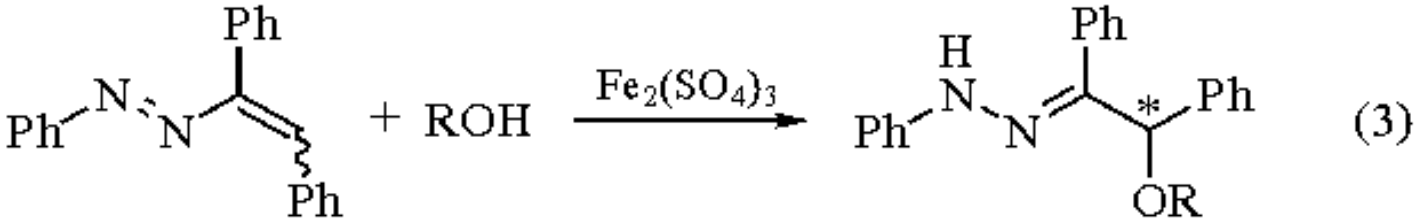

R = Me, Et, Pr, *i*-Pr, Bu

Miscellaneous Reactions.

Alcohols react with 3-aroylpropionic acids in the presence of hydrated iron(III) sulfate to produce 3-aroylpropionic esters.[5] The condensation of cyclohexanone under the catalysis of hydrated iron(III) sulfate in the presence of cyclohexane, benzene, or toluene produces the desired aldol products in 49-52% yield.[6] The alkylation of *p*-cresol with mixed 2,3-dimethyl-1- and 2-butene in 1.5:1 cresol:alkene ratio in the presence of iron(III) sulfate gives 4,2-$Me(Me_2CHCMe_2)C_6H_3OH$ in ~75% yield.[7]

---

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Iron(II) Sulfate[1]

$FeSO_4$

($FeSO_4.7H_2O$)

[7720-78-7] · FeO_4S · Iron(II) Sulfate · (MW 278.06)

(reductive cleavage of N-O bonds;[2-14] Skraup synthesis;[15] carboxylation of aromatic bases[17])

Alternate Name: ferrous sulfate.

Physical Data: mp 300 °C (-$7H_2O$); bp dec 671 °C; *d* 1.89 g cm^{-3}; refractive index 1.471.

Solubility: sol water (48 g/100 mL); slightly sol ethanol; sol methanol.

Form Supplied in: light blue or light green crystals; many commercial sources.

Handling, Storage, and Precautions: air and moisture sensitive; keep in a tightly closed container. Incompatible with strong oxidizing agents; irritant; ingestion may be lethal.[18]

Reductive Cleavage of N-O Bonds.[2-14]

Basic iron(II) sulfate is the reducing agent of choice for the conversion of *o*-nitrobenzaldehydes to *o*-aminobenzaldehydes.[2] $FeSO_4.7H_2O$ has been used in combination with ammonia;[3] however, ammonium hydroxide is the most synthetically useful base.[2] Detailed syntheses of *o*-aminobenzaldehyde have been reported using $FeSO_4/NH_4OH$ (eq 1).[2,4] The *o*-aminobenzaldehydes should be prepared immediately prior to use as they are prone to polymerize extensively on standing and when treated with acid. *o*-Aminobenzaldehyde is stable for up to 2 months at 5 °C.[5] Several alternate strategies are available for synthesis of *o*-amino aldehydes;[1] more recently, dihydrolipoamide-iron(II) under weakly alkaline conditions has been reported as a general nitrobenzene reducing agent.[6]

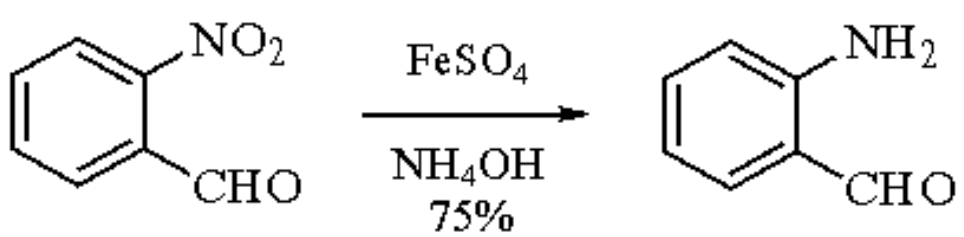

(1)

Reductive cyclization utilizing $FeSO_4.7H_2O$ has been used to synthesize thieno[*c*]-fused 1,5-naphthyridine 5-oxides (eq

2) (30-86%).[7] Reduction of the N-O bond in 1,2,4-oxadiazolines and amidoximes and hydrolysis of the intermediate iron complexes to amidines (eq 3)[8] provides an alternative to the reducing agents P/***Hydrogen Iodide***[9] or ***Pentacarbonyliron***.[10] Iron(II) sulfate has been used to cleave various *C*-substituted oxiridines.[11] Bicyclic oxaziridines have been cleaved to amides,[12] and tricyclic oxaziridines yield seven-,[13] eight- and nine-membered oxolactams (eqs 4 and 5).[14]

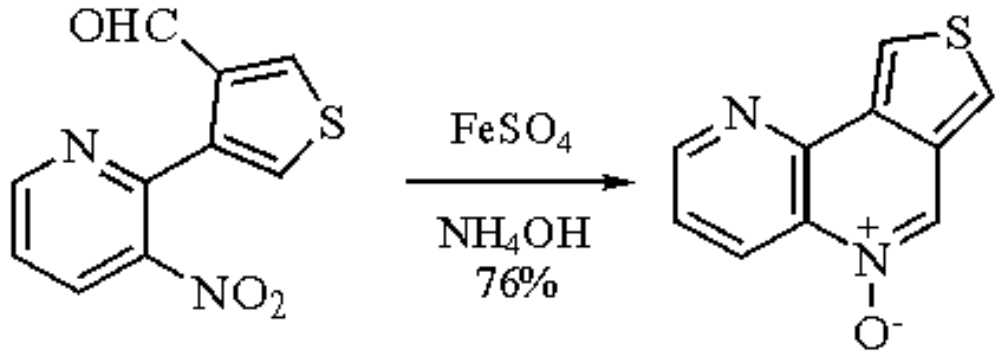

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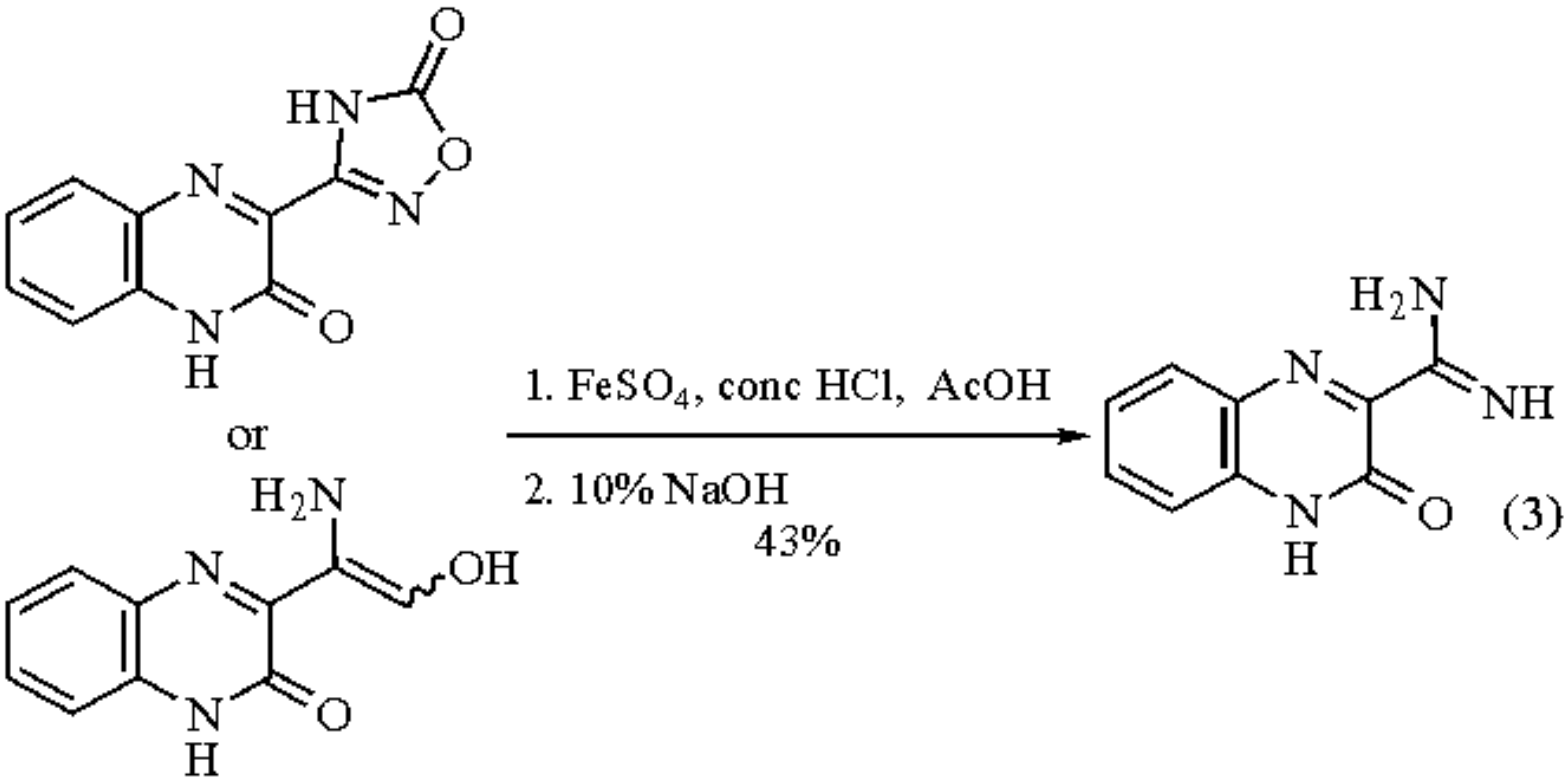

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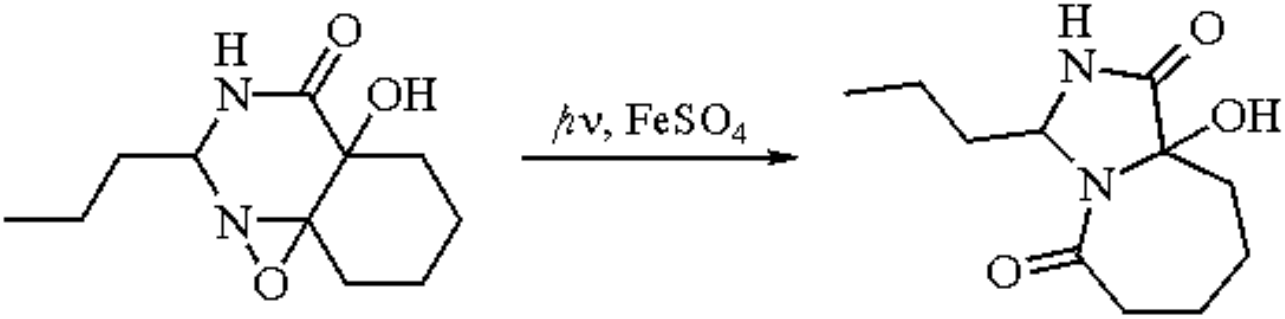

(4)

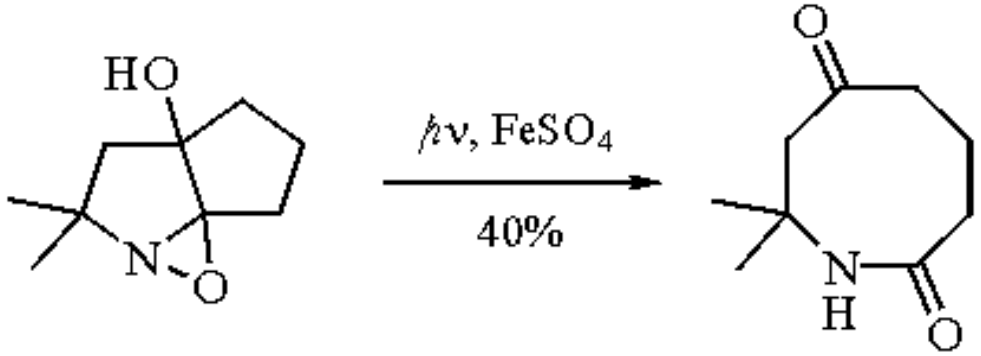

(5)

Skraup Synthesis.

The Skraup synthesis of quinolines from a nitrobenzene, glycerol, and H_2SO_4 proceeds with extreme violence unless $FeSO_4.7H_2O$ is included. A detailed synthetic procedure for quinoline has been reported,[15] which is amenable to synthesis of derivatives (eq 6).[16]

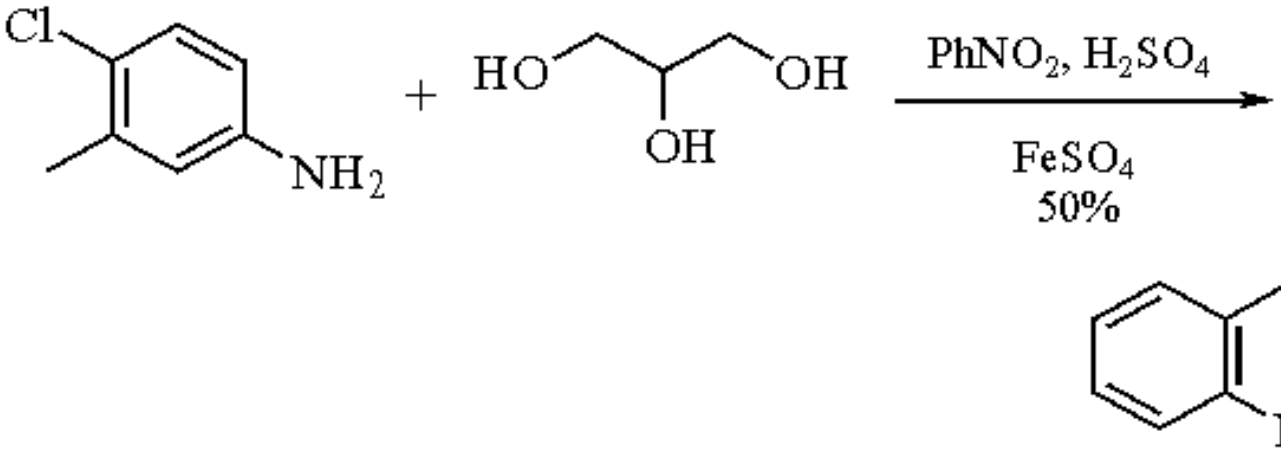

(6)

Carboxylation of Aromatic Bases.

Heteroaromatic bases can be carboxylated via reaction with the carboxyl radical generated with H_2O_2, keto ester, and $FeSO_4.7H_2O$ (eq 7).[17]

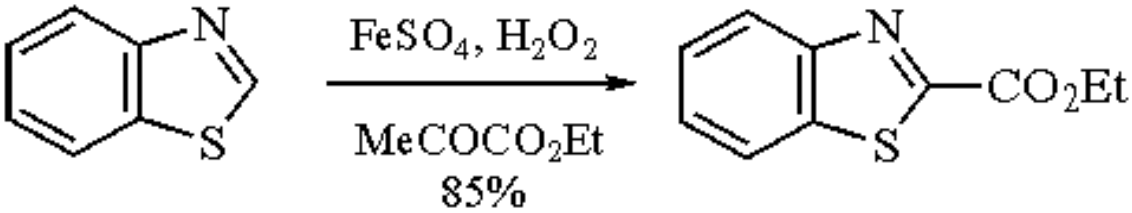

(7)

Related Reagents.

Copper(II) Acetate-Iron(II) Sulfate; ***Hydrogen Peroxide-Iron(II) Sulfate***; ***Iron(II) Sulfate-Oxygen***.

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Iron(II) Sulfate-Oxygen[1]

$FeSO_4.7H_2O$-O_2

($FeSO_4.7H_2O$)

[7720-78-7] · FeO_4S · Iron(II) Sulfate-Oxygen · (MW 278.06) (O_2)

[7782-44-7] · O_2 · Iron(II) Sulfate-Oxygen · (MW 32.00)

(selective oxidant for 15-hydroxylation of steroids,[1] direct hydroxylation of aromatic and aliphatic substrates[7,8])

Alternate Name: ferrous sulfate-oxygen.

Preparative Methods: the reagent combination is generated in situ via dropwise addition of an aqueous solution (500 mL) of ***Iron(II) Sulfate*** (15 g, 54 mmol) to a stirred buffer (0.1 M Na_2HPO_4, pH 6.8, 2.5 L) solution of substrate (2.25 mmol) under bubbling oxygen at 70 °C. Room temperature may be adequate for some substrates.

Handling, Storage, and Precautions: is air and moisture sensitive; keep in a tightly closed container; incompatible with strong oxidizing agents; irritant; ingestion may be lethal.

Hydroxylation of Steroids.[1]

The bile acids deoxycholic (eq 1),[1] nordeoxycholic, and taurodeoxycholic acids[2] are 15-hydroxylated in aqueous buffer by dropwise addition of iron sulfate under a stream of oxygen at 70 °C. Acetone can be used as a cosolvent to improve solubility of some steroids.[3] It has been postulated that a positively charged species [Fe^{2+}-O_2] interacting with the carboxyl sidechain is responsible for the regiochemistry observed.[4] These transformations are in contrast to that observed with a hydroxylating system developed earlier by Udenfriend[5] which mimics the biological transformation of deoxycholic acid to cholic acid (eq 2)[6] via 7-hydroxylation with $FeSO_4$-O_2-ascorbic acid-EDTA.

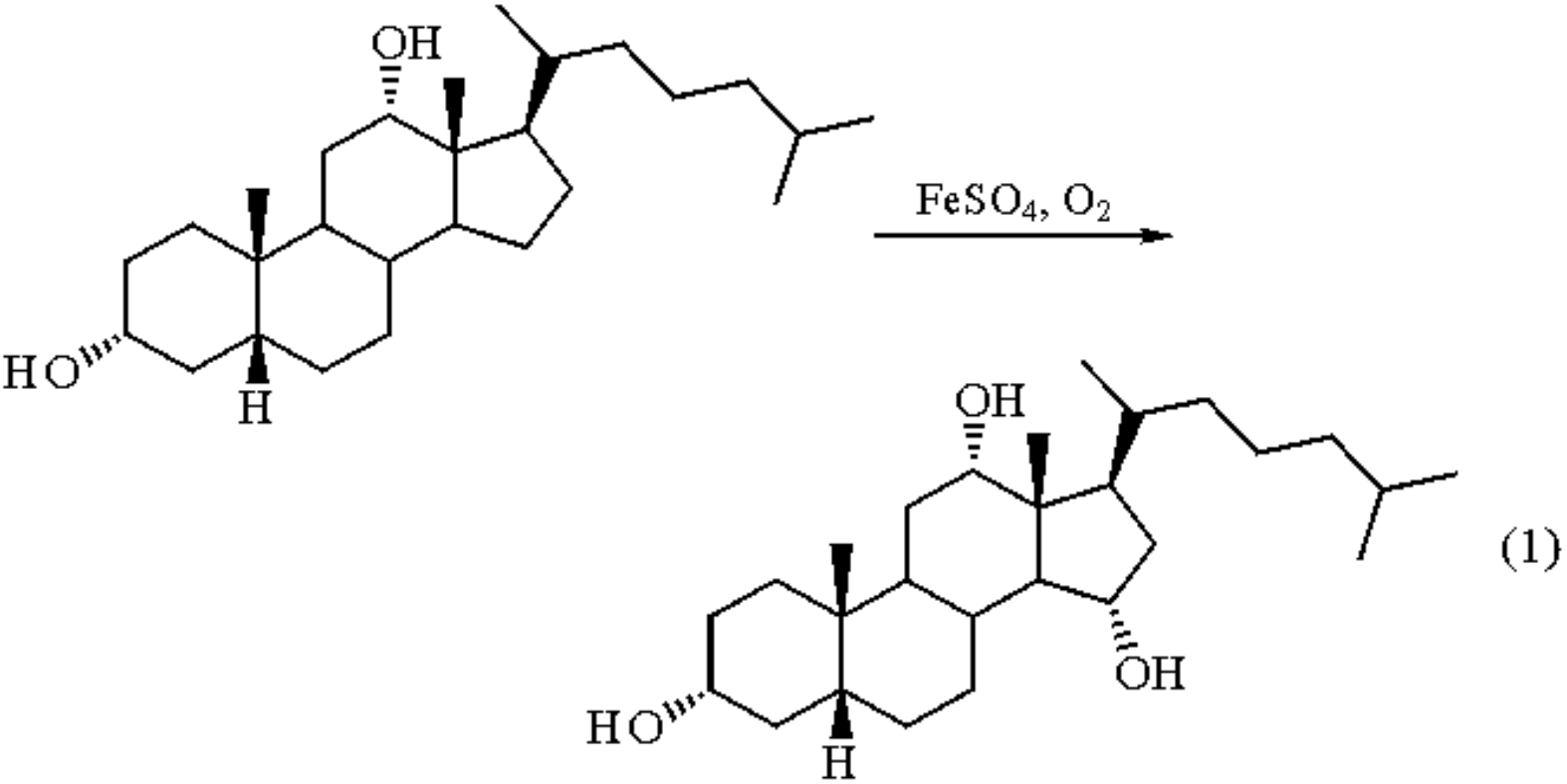

(1)

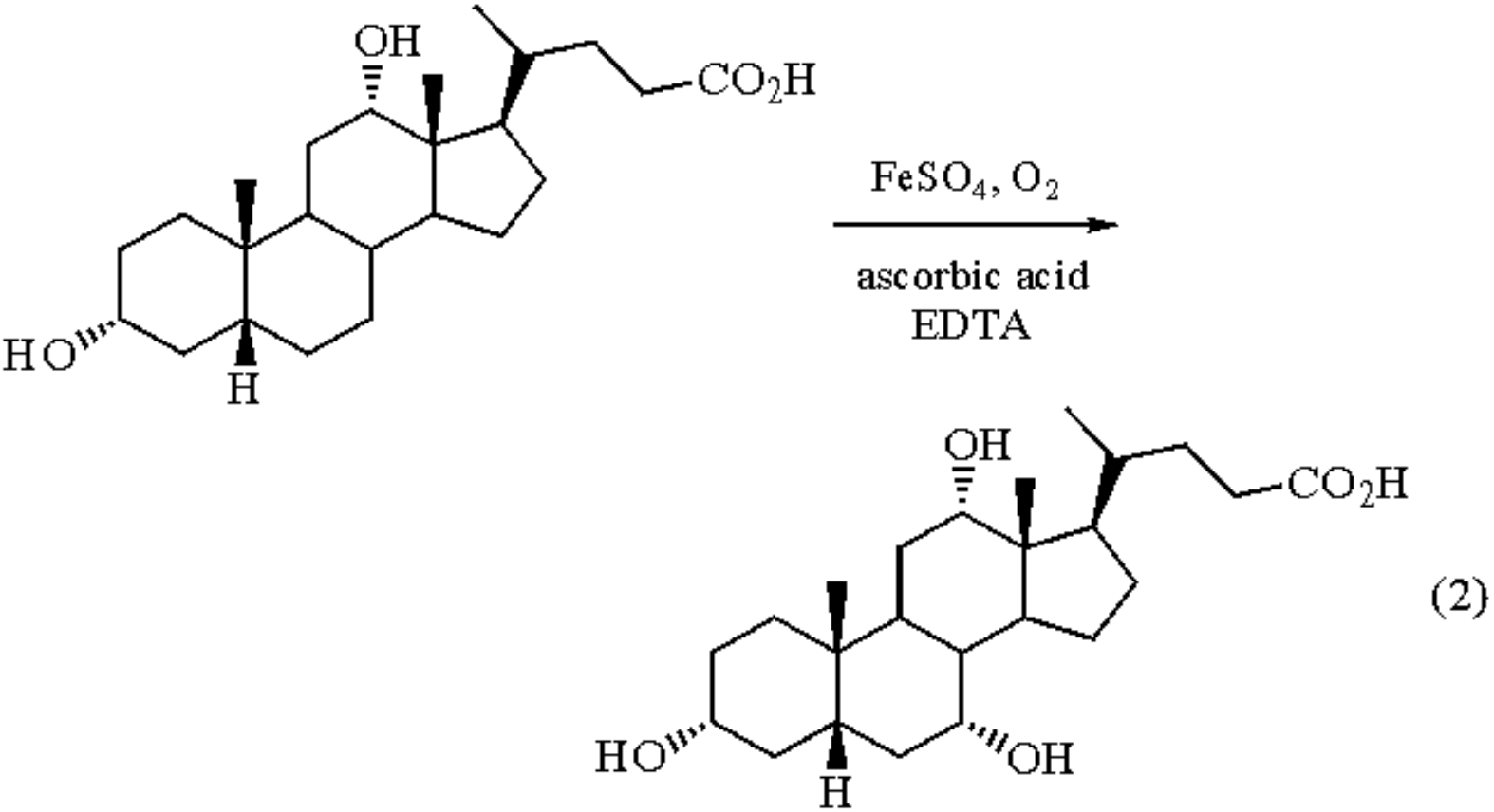

(2)

Direct Hydroxylation of Aromatic and Aliphatic Substrates.

It should be pointed out that direct hydroxylation of organic substrates, so efficiently accomplished in nature (via

metalloenzymes), is very difficult to achieve synthetically. Adamantane carboxylic acids can be oxygenated with $FeSO_4$-O_2 in buffer solution at 40 °C (eq 3).[7] Aromatic compounds can also be hydroxylated: benzoic acid yields 41% of five products and phenol two products (eq 4).[8] Many alternate reagents have been reported for direct aryl hydroxylations, mostly as modifications of either Fenton's reagent ($FeSO_4$-H_2O_2) or Udenfriend's reagent ($FeSO_4$-O_2-ascorbic acid-EDTA).[9] Recently, attention has focused on alkane hydroxylations using metalloporphyrins,[10] cluster catalysts,[11] and the Gif oxidation.[12]

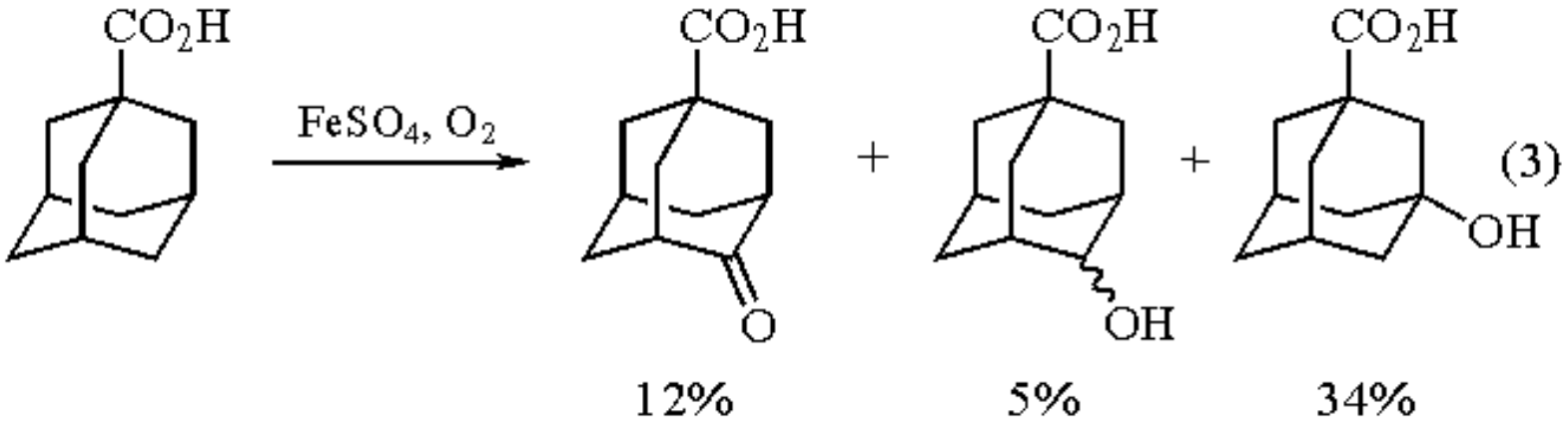

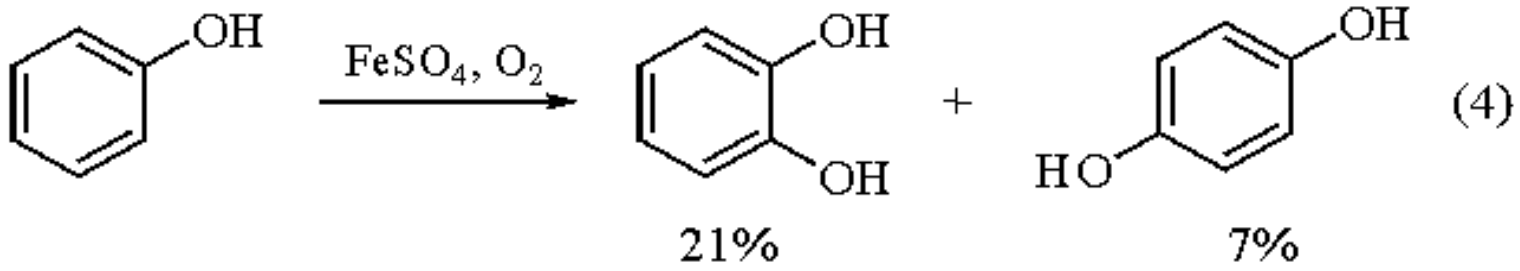

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Andrew D. White

Iron(III) Thiocyanate[1]

$Fe(SCN)_3$

[4119-52-2] · $C_3FeN_3S_3$ · Iron(III) Thiocyanate · (MW 230.12)

(reacts with trialkylboranes to give alkyl thiocyanates;[2] thiocyanation of unsaturated acids and esters[7])

Alternate Name: ferric thiocyanate.

Solubility: very sol water; dec in hot water; sol alcohol, ether, acetone.

Preparative Method: the reagent is prepared and used in situ, via dropwise addition of a mixture of iron(III) ammonium sulfate (6 equiv) and potassium thiocyanate (18 equiv) in water to a solution of organoborane in THF. The mixture is refluxed for 24 h. The products are obtained via extraction with petroleum ether several times and distillation.[2]

Handling, Storage, and Precautions: metal thiocyanates on heating to decomposition, or on contact with acid or acid fumes, emit highly toxic fumes. Organic thiocyanates have low acute toxicity, but prolonged absorption may produce skin eruptions, running nose, nausea, and vomiting. Violent reactions have occurred with strong oxidizers.[8] Use in a fume hood.

Alkyl Thiocyanates.[2]

Trialkylboranes react with iron(III) thiocyanate to yield alkyl thiocyanates in good yield, with two alkyl groups per borane being utilized (eq 1). A small amount of the isothiocyanate is observed, easily separable on distillation of the alkyl thiocyanate. This reaction has been extended to mixed trialkylboranes which contain a useful secondary alkyl group, which is transferred preferentially to a primary alkyl group (eq 2).[3] This method presents a mild alternative to the usual displacement reaction between an alkyl halide and ***Sodium Thiocyanate***.[4]

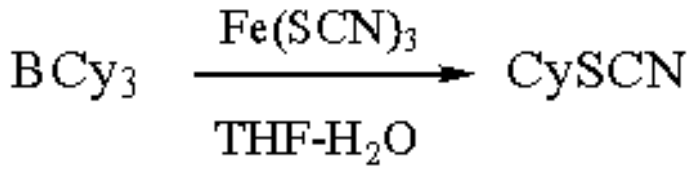

(1)

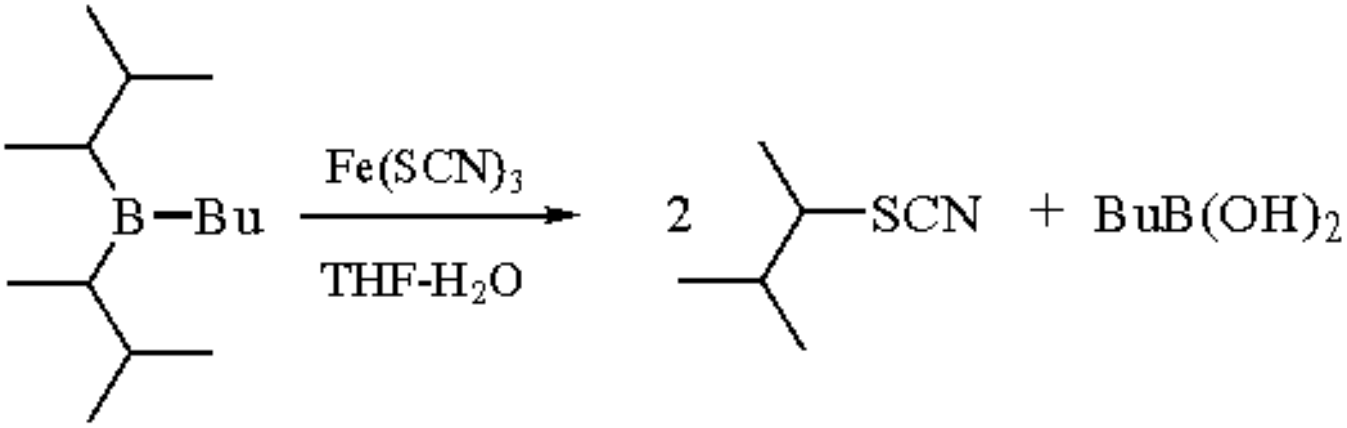

(2)

Alkyl selenocyanates can be synthesized via reaction of iron(III) selenocyanate with an organoborane. Iron(III) selenocyanate is generated in situ via addition of a solution of iron(III) ammonium sulfate and potassium selenocyanate in water to the trialkylborane in THF. Alkyl selenocyanates are obtained in 40-47% yields.[5] Better yields are obtained for primary alkyl groups via reaction of an alkyl halide with potassium selenocyanate.[6] However, the $Fe(SeCN)_3$ method is applicable to secondary and tertiary alkyl selenocyanates (eq 3).[3]

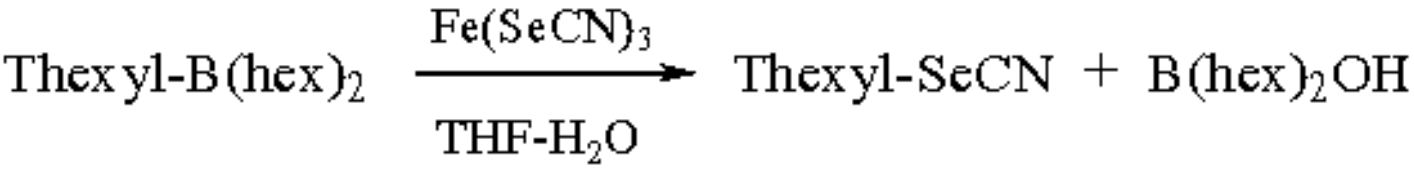

(3)

Thiocyanation of Acids and Esters.

Ethylenic carboxylic acids react with $(SCN)_2$ to give mixtures of thiocyanate and isothiocyanates. Addition of $Fe(SCN)_3$ affords cleanly the vicinal dithiocyanate carboxylic acids in excellent yields (84-100%).[7]

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Isatoic Anhydride[1]

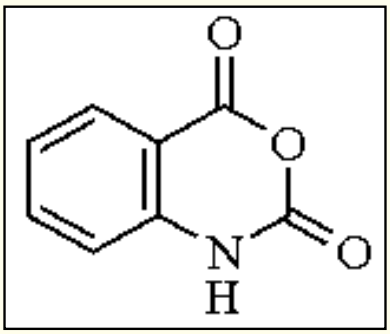

[118-48-9] · $C_8H_5NO_3$ · Isatoic Anhydride · (MW 163.14)

(reacts with either electrophiles or nucleophiles; derivatives have been widely used in pesticides, dyes, pigments, flavors, fragrances, pharmaceuticals, and miscellaneous industrial chemicals)

Alternate Name: 2*H*-3,1-benzoxazine-2,4(1*H*)-dione.

Physical Data: mp 233 °C; bp 350 °C.

Solubility: sol most organic solvents.

Form Supplied in: gray-brown powder; commercially available.

Handling, Storage, and Precautions: store in a dry, cold area. Use in a fume hood; gradually decomposes at high temperature upon exposure to air and water, and generates toxic gases (CO, NO, CO_2).

Reactions with Electrophiles.

N-Substituted isatoic anhydrides can be obtained by reacting isatoic anhydride with various electrophiles (CH_2N_2, Me_2SO_4, MeI, RSCl) as shown in eq 1.[1-3] Aromatic substitution of isatoic anhydride usually occurs at the 6-position, as shown in eq 2.[4] However, the 8-substituted isatoic anhydride is obtained when the 6-position is already occupied (eq 3).[5]

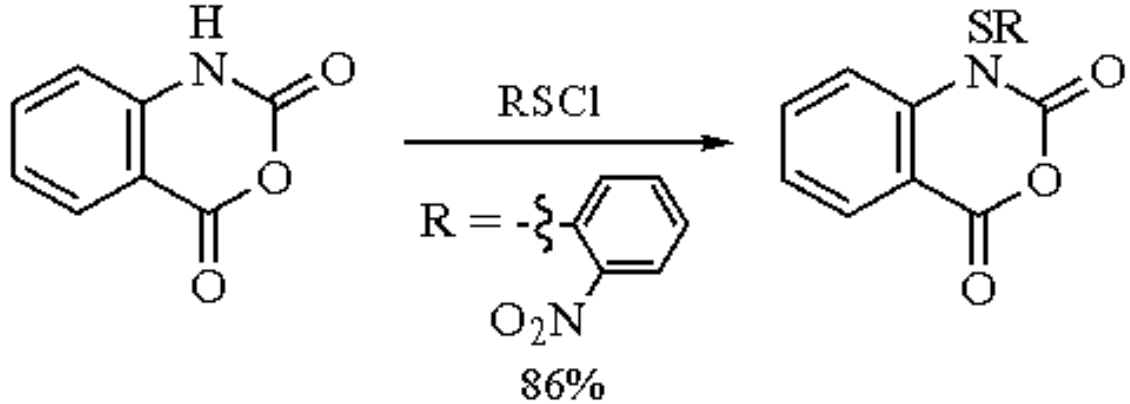

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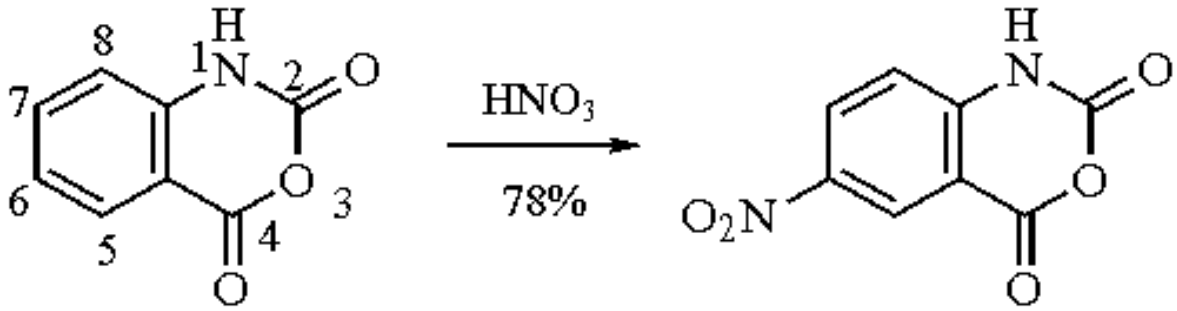

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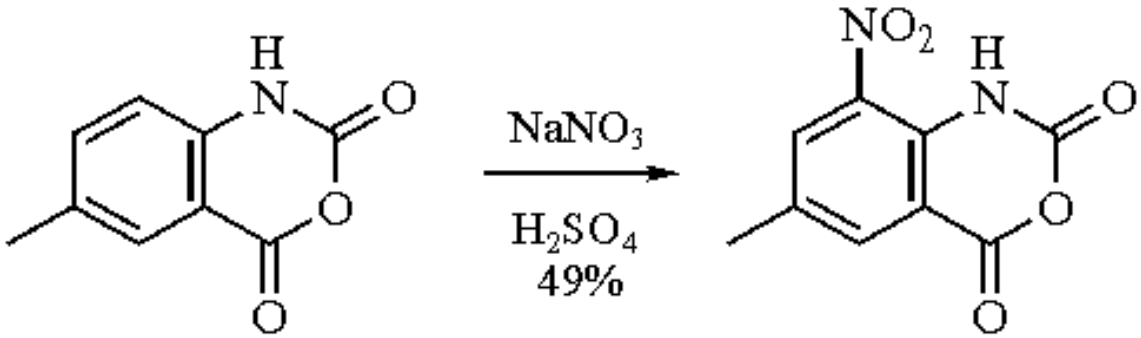

(3)

Reactions with Nucleophiles.

Due to the different reactivity of the carbonyl groups, various nucleophiles react with isatoic anhydride at either the C-2 or C-4 position under controlled conditions.[1] In principle, C-4 acts like an anhydride and is more reactive than C-2, which is closer to a carbamate in reactivity. In contrast, ionization can transform isatoic anhydride into 2-carboxyphenyl isocyanate, which reacts with nucleophiles only at C-2.[1,6] Under the influence of acid or base catalysts, isatoic anhydride reacts with H_2O, ROH, and RSH at C-4 to give the corresponding anthranilic acid, anthranilate ester, and anthranilate thioester, respectively.[6,7] A less hindered primary amine (*n*-butylamine) also attacks C-4 to produce the corresponding anthranilamide (path a, eq 4). A bulky amine (*t*-butylamine) reacts through path b to give *o*-ureidobenzoic acid because C-2 is relatively unhindered relative to C-4.[8] However, *N*-substitution (*N*-methylisatoic anhydride) blocks C-2, and all nucleophiles attack at the 4-position.[9] In addition, highly nucleophilic species, such as carbanions, attack the C-4 carbonyl group and release a CO_2 molecule.[1]

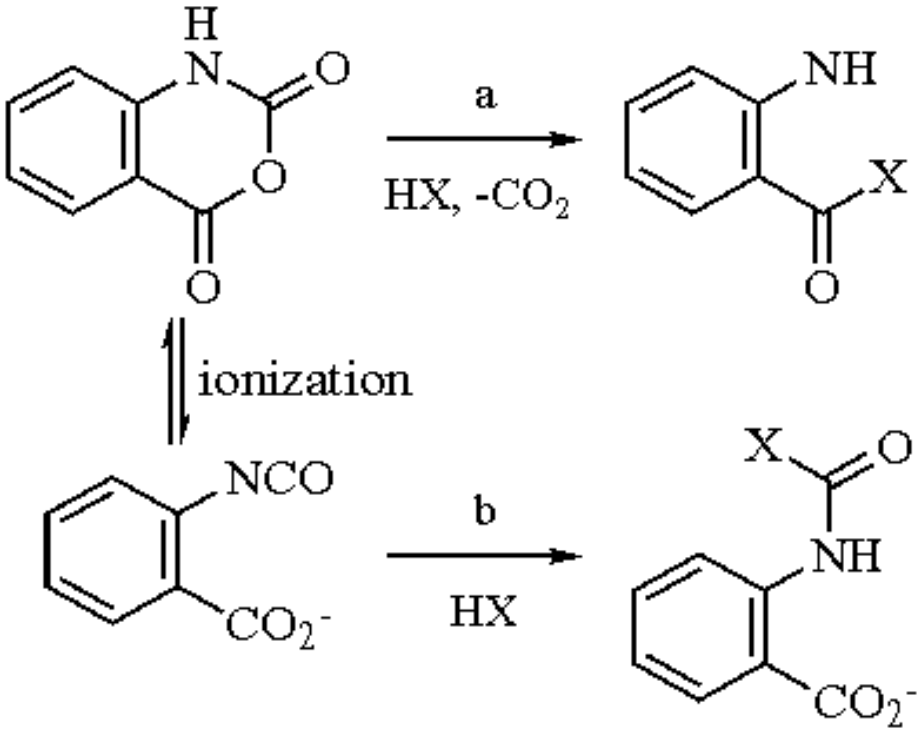

(4)

Solvent effects are also important in reactions of isatoic anhydride with nucleophiles. In general, polar aprotic solvents increase the yield of anthranilamide significantly.[10] For example, the yield of the reaction of *t*-butylamine with isatoic anhydride is raised to 74% in DMF from 9% in water. In addition, the concentration as well as the ratio of the reactants is important.[11] For example, the highest yield of anthranilamide was obtained by reacting 5 equiv of ammonia with a 2 M solution of isatoic anhydride (eq 5). Increasing the concentration of the substrate or changing the ammonia:substrate ratio decreased the yield of anthranilamide. Polymeric side products were formed when only 0.5 equiv of ammonia were used.

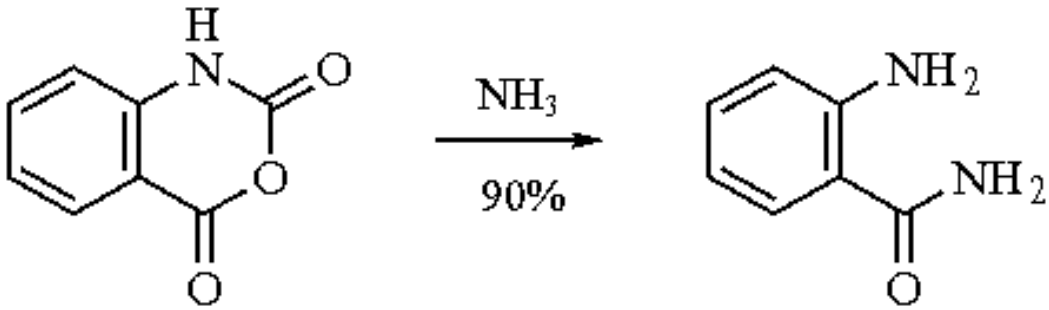

(5)

Formation of Heterocycles.

The preparation of nitrogenous heterocycles from isatoic anhydride has been reported.[1] For example, the reaction of a derivative of isatoic anhydride with a lithium enolate gave a quinoline-type alkaloid (eq 6).[12] The reactions of isatoic anhydride with amides, ureas, thioureas, isocyanates, and thiocyanates produce quinazolinones in one step (eq 7).[1,13] The synthesis can also be carried out in a stepwise fashion. The displacement of the 3-oxygen of isatoic anhydride by an amine or hydrazine results in evolution of CO_2 gas. The reaction of the product *o*-aminobenzoylhydrazine with an orthoester, chloroformate, or phosgene also gives a quinazolinone (eq 8).[1,14] Treatment of the intermediate *N*-(2-aminobenzoyl)-α-amino ester with nitrous acid generates a benzotriazine (eq 9).[15] On the other hand, ethyl glycinate reacts with isatoic anhydride to give a moderate yield of benzodiazepinone in the presence of pyridine (eq 10).[16] A

benzotriazepinone was produced directly from the reaction of benzoylhydrazine with isatoic anhydride (eq 11).[17]

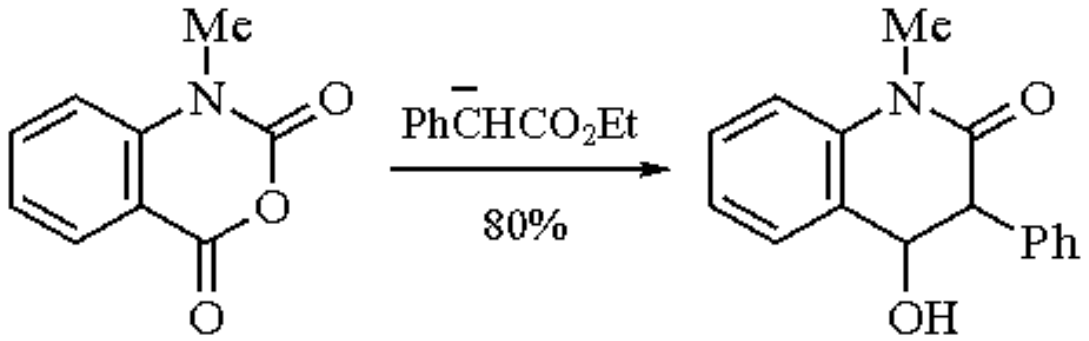

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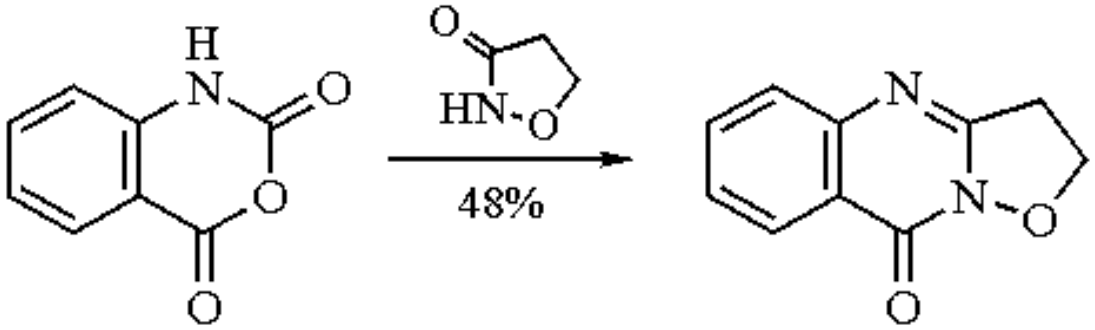

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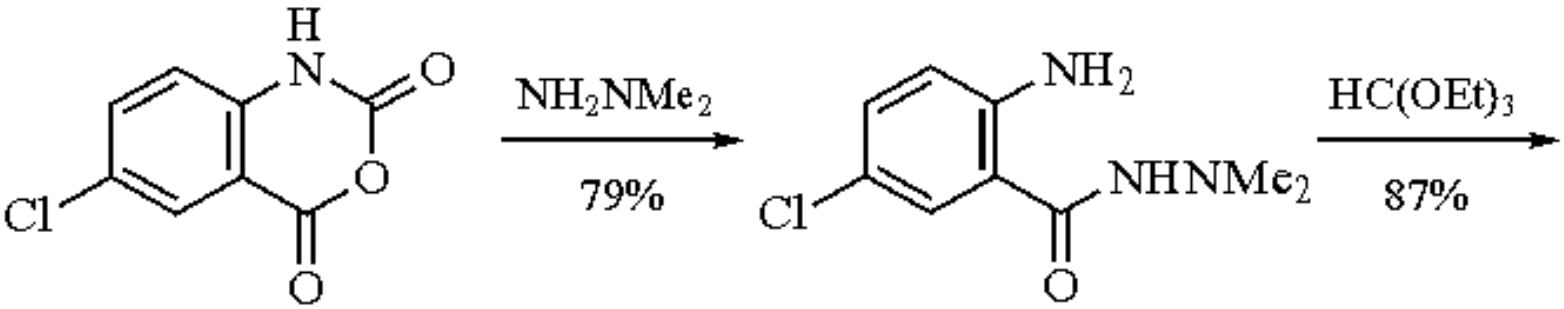

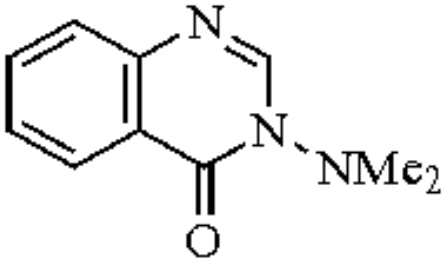

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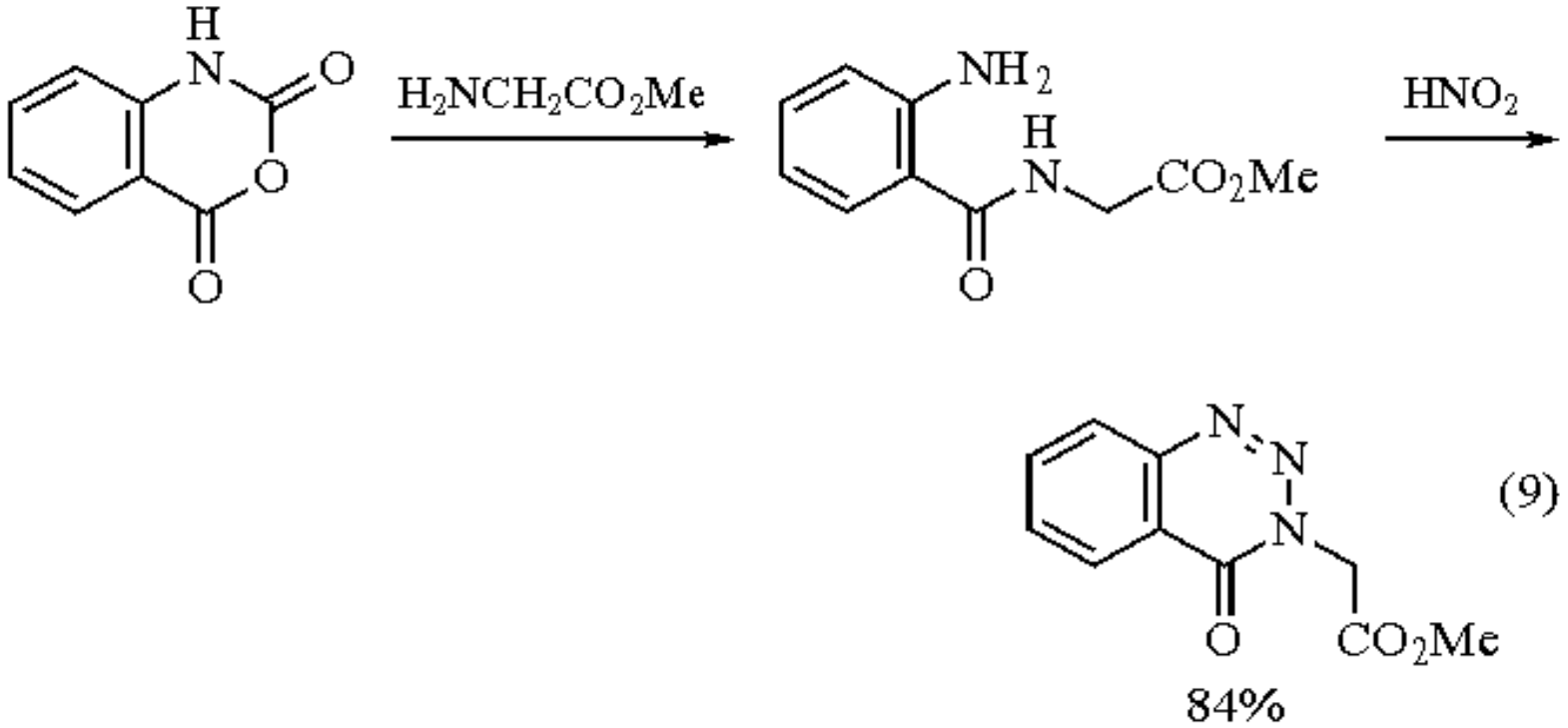

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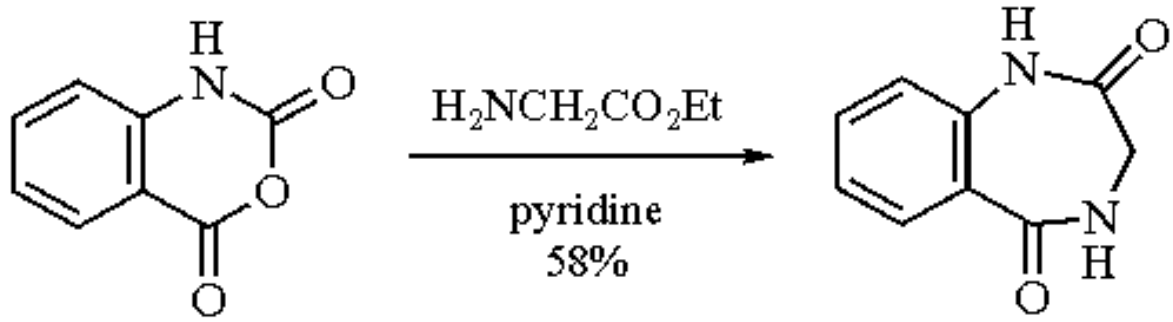

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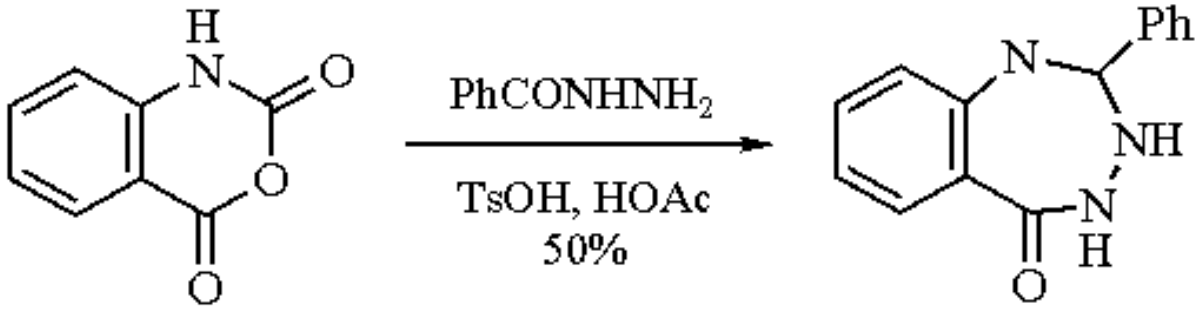

(11)

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Isobutene

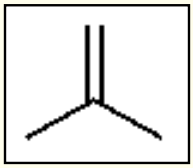

[115-11-7] · C_4H_8 · Isobutene · (MW 56.12)

(carboxy and hydroxy protection; photochemical cycloaddition with enones; ene reaction with enophiles; Friedel-Crafts and other alkylations; reacts with carbenes; acid-catalyzed cycloadditions)

Alternate Name: isobutylene.

Physical Data: mp -140.4 °C; bp -6.9 °C; vapor density 1.947.

Solubility: insol H_2O; sol THF, pet ether, benzene.

Form Supplied in: gas (lecture bottle); widely available.

Handling, Storage, and Precautions: flammable gas; store and use with adequate ventilation. Do not store with oxidizing materials and compounds that add across double bonds.

Protection for the Carboxy Group.

Isobutene has been widely used in synthesis to convert carboxylic acids into corresponding *t*-butyl esters.[1,2] *t*-Butyl esters of aliphatic acids (eq 1),[3] aromatic carboxylic acids (eq 2),[4] and *N*-protected amino acids (eq 3)[5] have been prepared. The hindered *t*-butyl esters are stable to saponification but can be cleaved by acid-catalyzed hydrolysis, with liberation of isobutene.

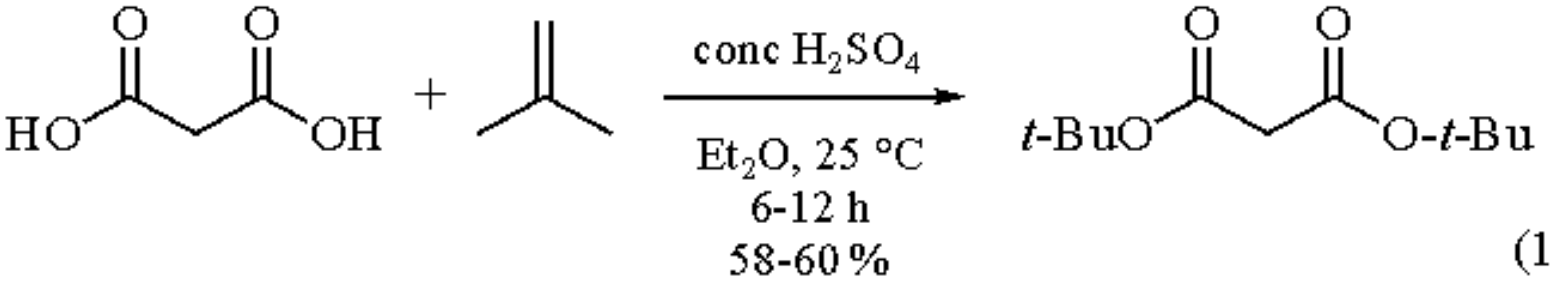

(1)

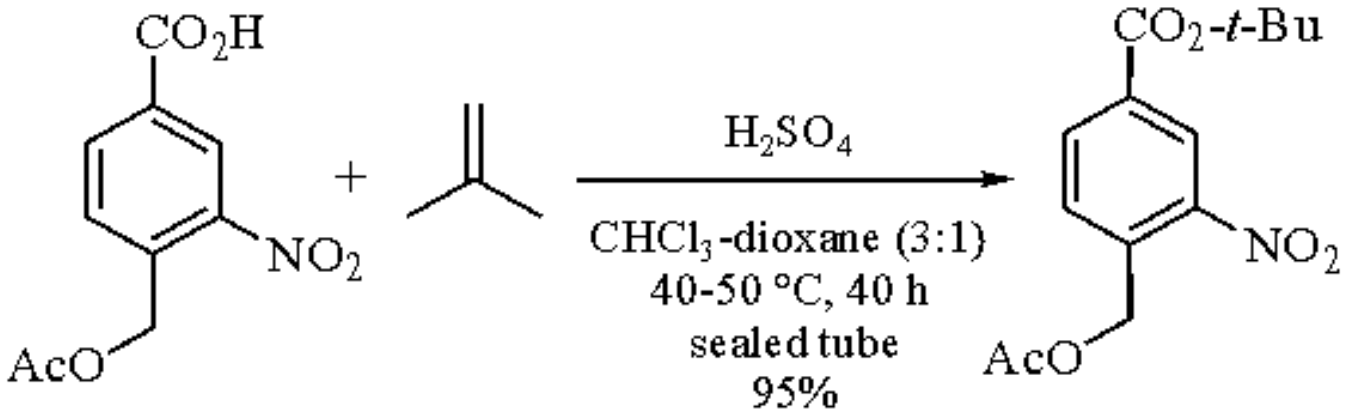

(2)

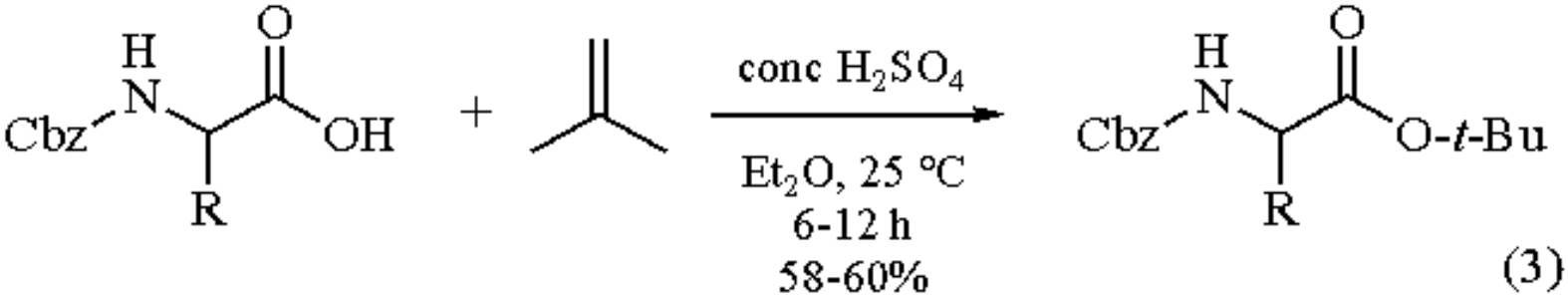

(3)

Protection for the Hydroxy Group.

In the presence of acid catalysts, isobutene reacts to convert a variety of alcohols and phenols to their corresponding *t*-butyl ethers. *t*-Butyl ethers are stable to most reagents but are readily cleaved by strong acids. Propargyl alcohols (eq 4),[6] steroidal alcohols (eq 5),[7] and phenols (eq 6)[8] have been protected. The *t*-butyl group has also been used to protect the hydroxy group of valinol (eq 7),[9] serine derivatives (eq 8),[10] and tyrosine.[11]

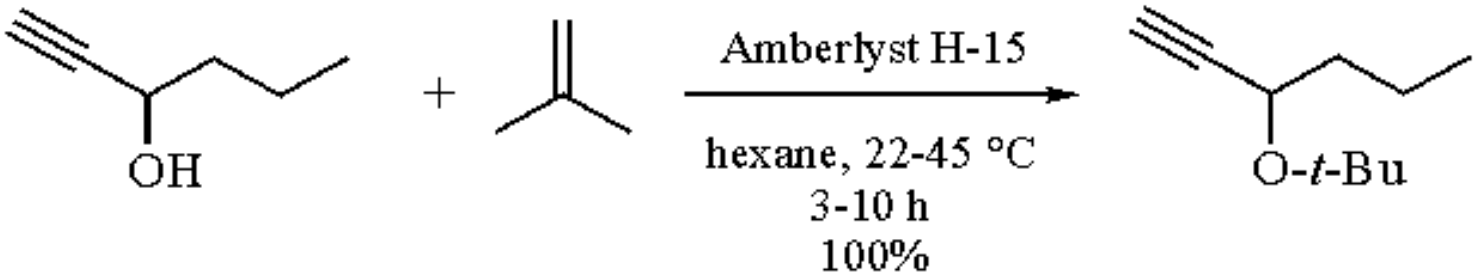

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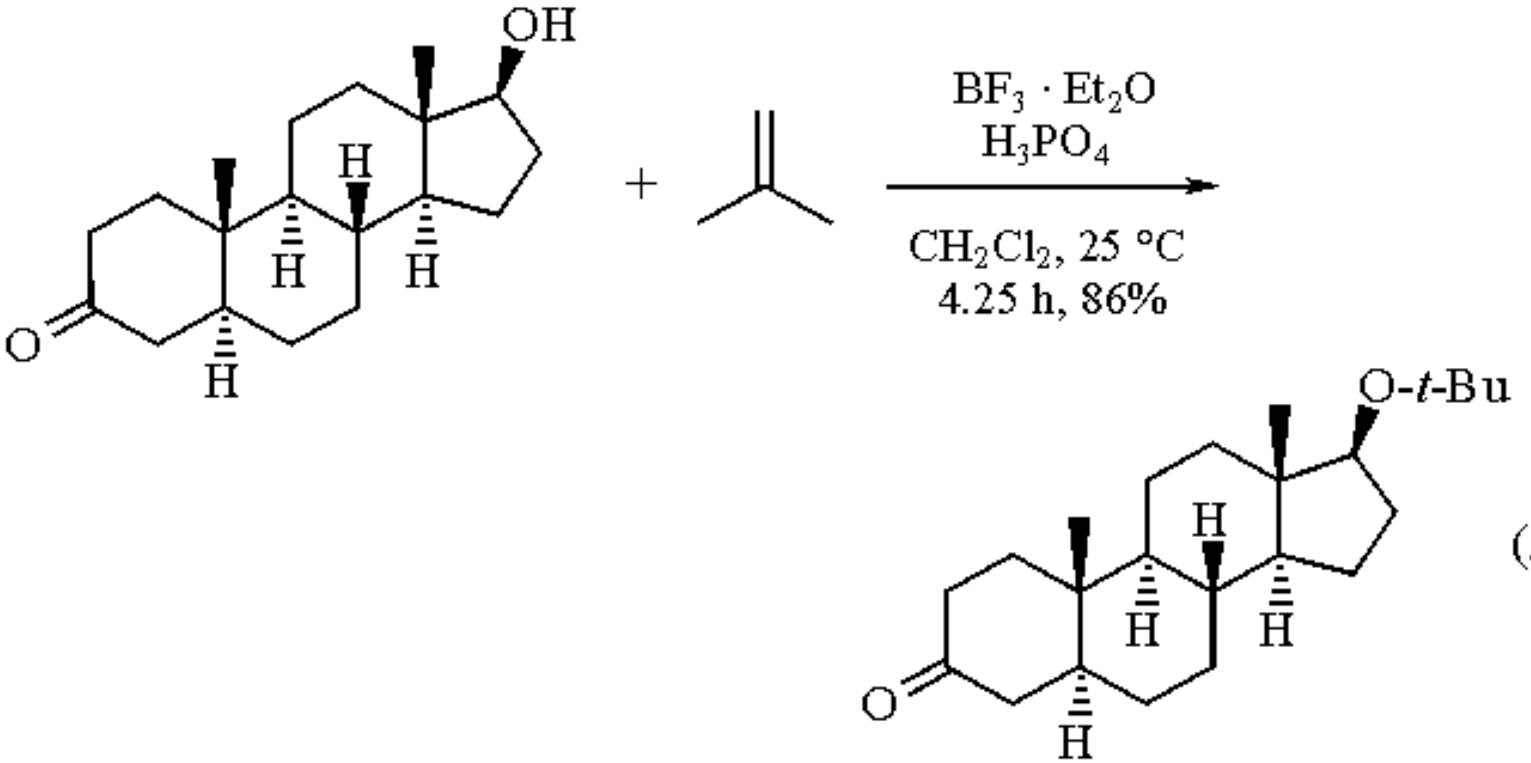
OH
H
H
H
O
H
+
BF3 · Et2O
H3PO4
CH2Cl2, 25 °C
4.25 h, 86%
O-t-Bu
H
H
H
O
H

(5)

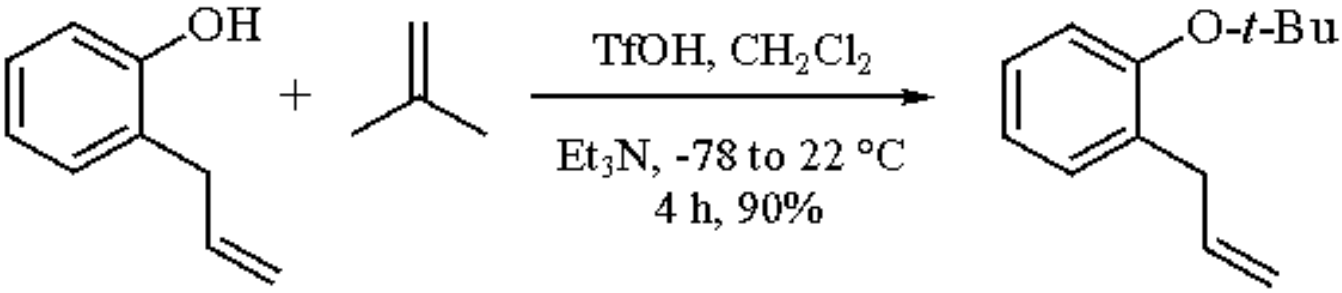
OH
+
TfOH, CH2Cl2
Et3N, -78 to 22 °C
4 h, 90%
O-t-Bu

(6)

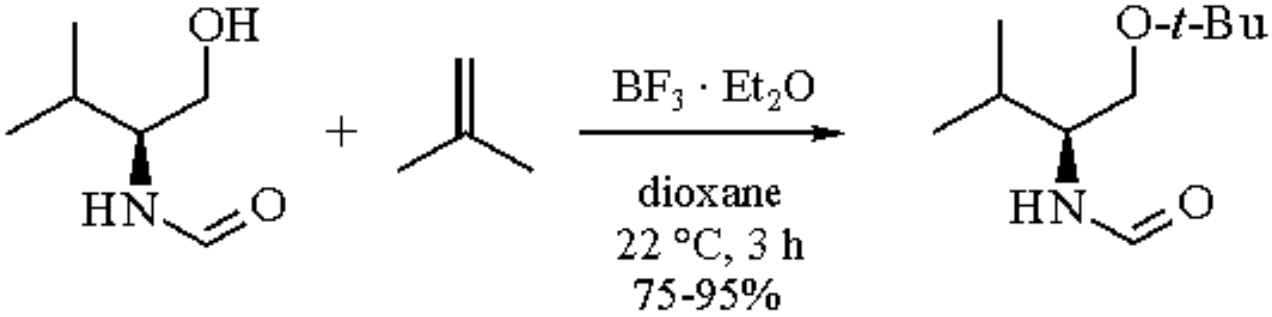
OH
HN
O
+
BF3 · Et2O
dioxane
22 °C, 3 h
75-95%
O-t-Bu
HN
O

(7)

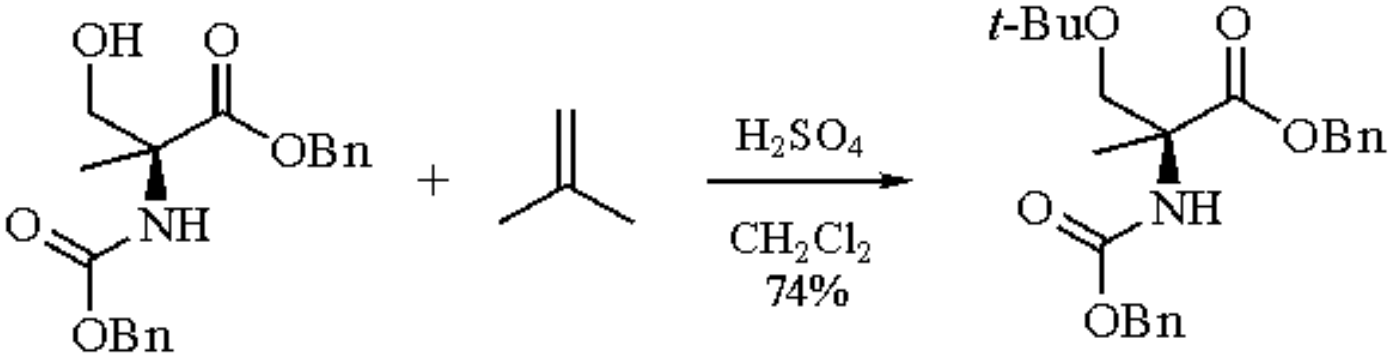
OH
O
OBn
O
NH
OBn
+
H2SO4
CH2Cl2
74%
t-BuO
O
OBn
O
NH
OBn

(8)

Photochemical Cycloadditions.

Isobutene has been widely used in intermolecular [2 + 2] photocycloaddition reactions with enones.[11] The weakly polarized isobutene is often used to study the regioselectivity of the photocycloaddition. Cyclohexenones (eq 9),[12] cyclopentenones (eq 10),[13] and functionalized enones (eq 11)[14] undergo cycloaddition with isobutene. Paterno-Büchi photoadditions with isobutene have produced various oxetanes (eq 12).[15]

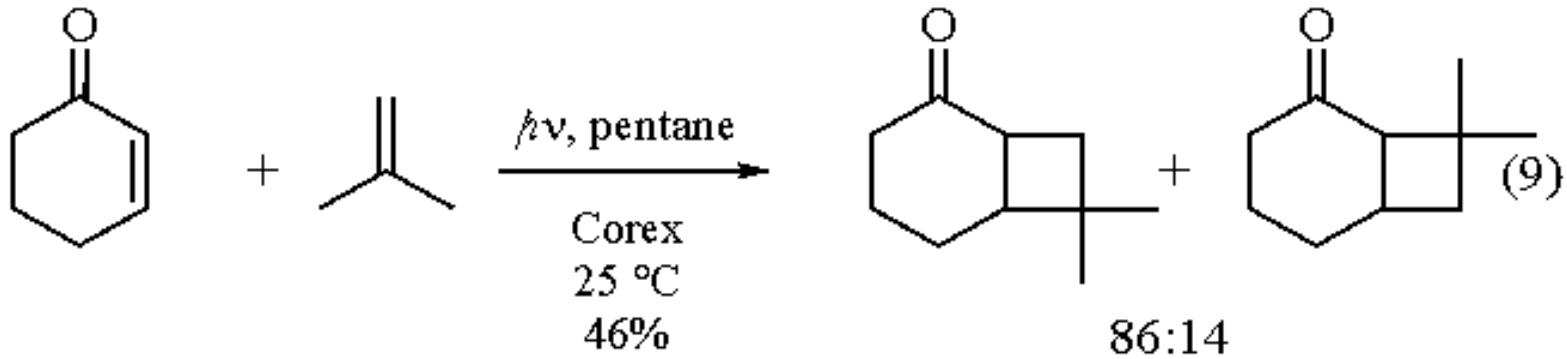

(9)

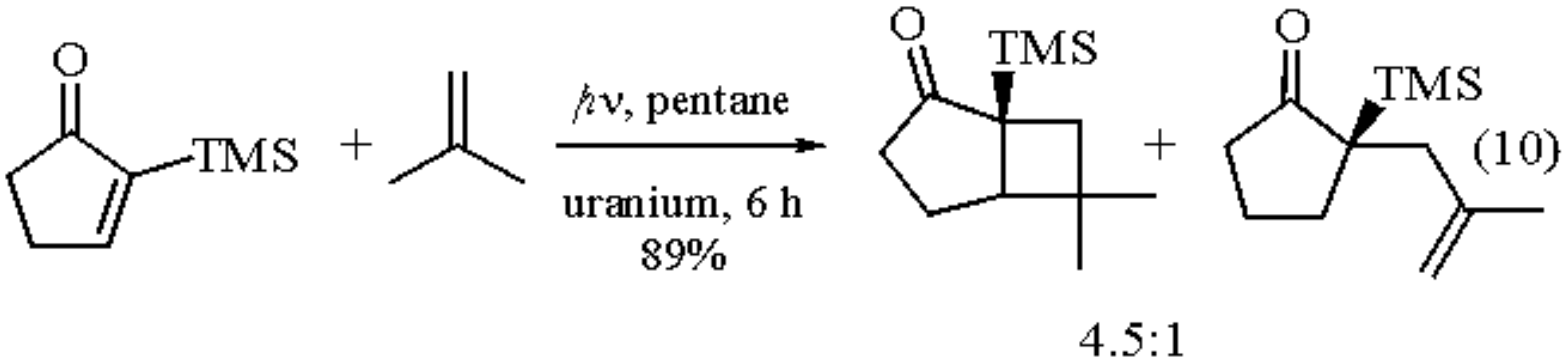

(10)

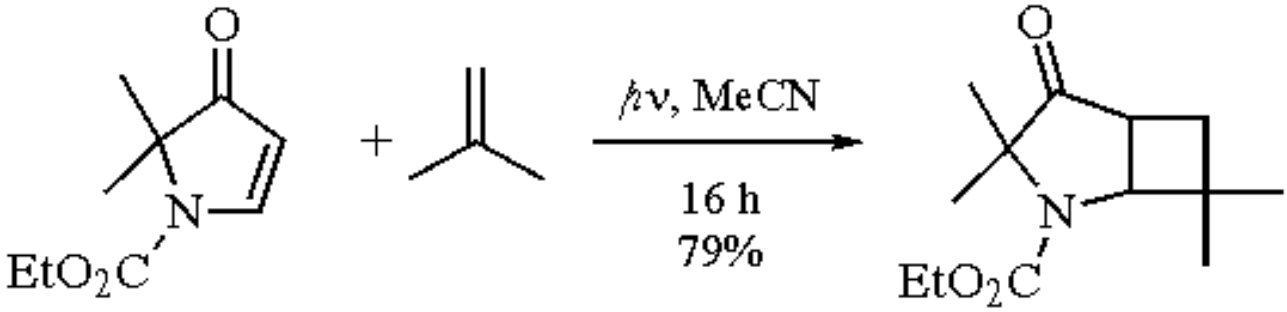

(11)

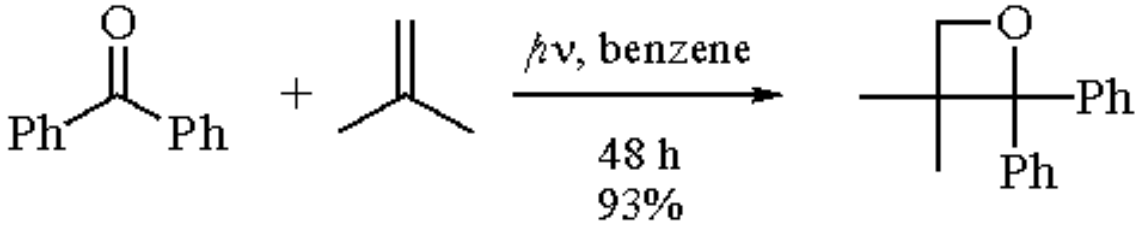

(12)

Ene Reactions.

In the presence of Lewis acids, isobutene adds to various enophiles to yield ene adducts.[16] Enophiles such as alkoxyaldehyde (eq 13),[17] dialkyl aminoaldehyde (eq 14),[18] haloaldehyde (eq 15),[19] and vinyl sulfoxides (eq 16)[20] have been utilized. Chiral organoaluminum (eq 17)[21] and organotitanium reagents (eq 18)[22] have been reported to give high levels of asymmetric induction in the ene reaction of isobutene with activated aldehydes.

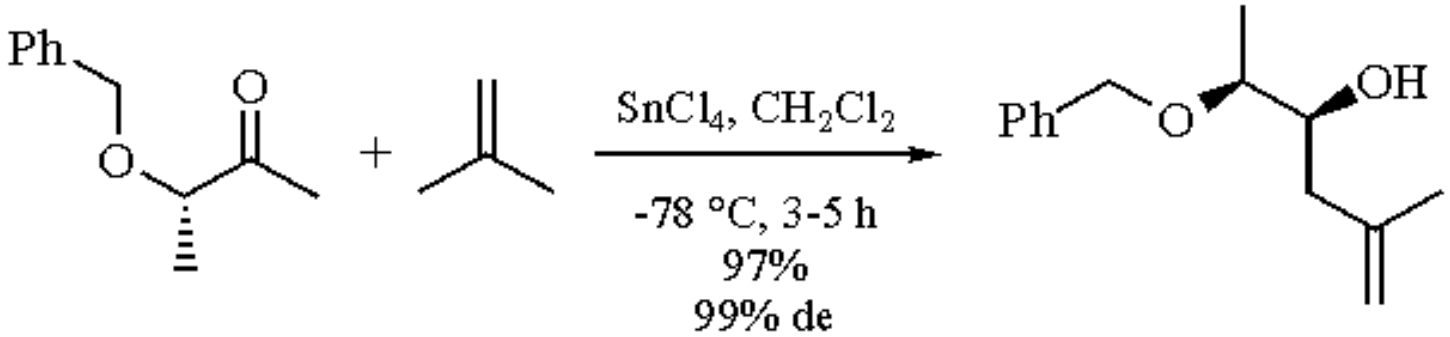

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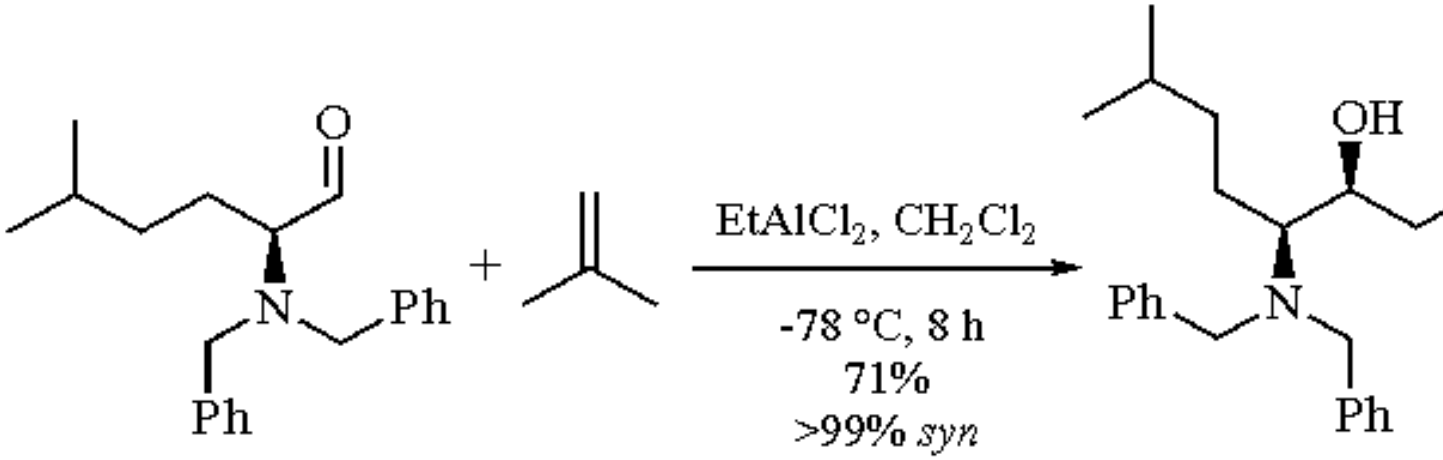

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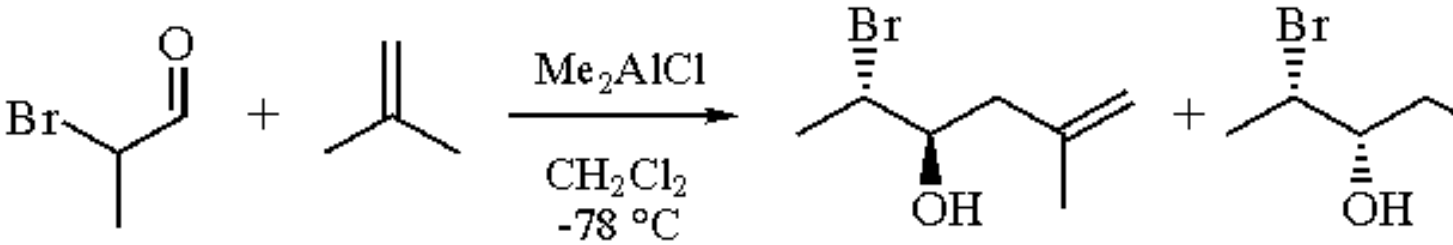

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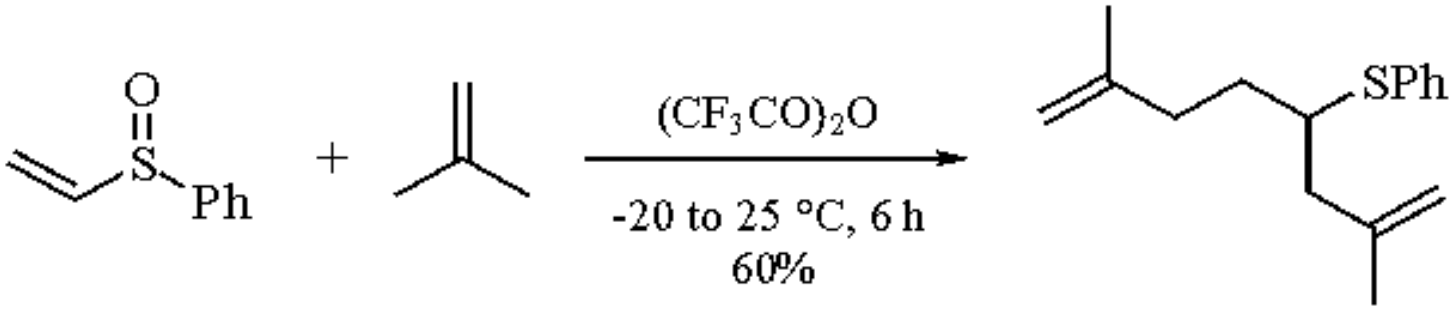

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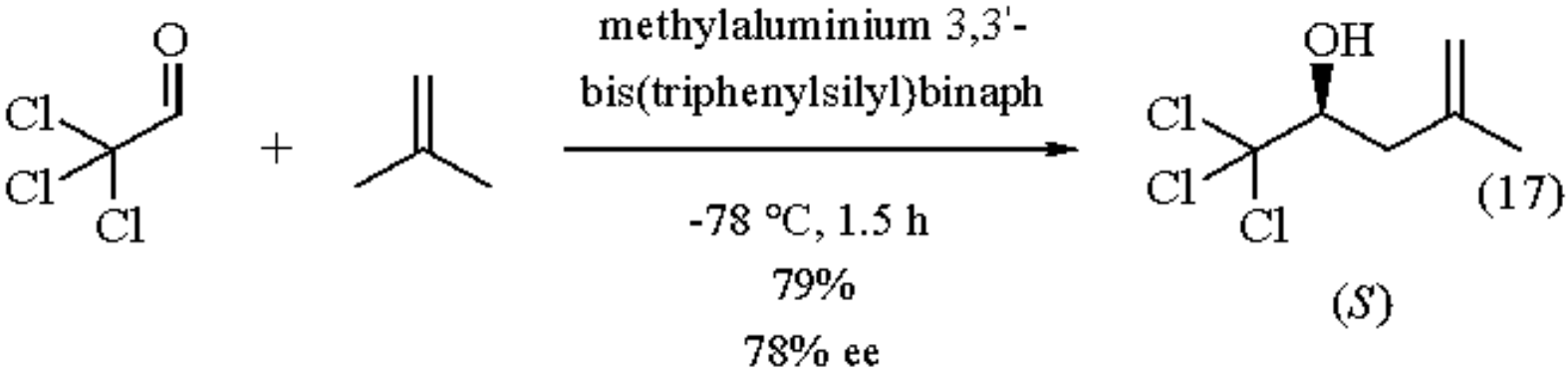

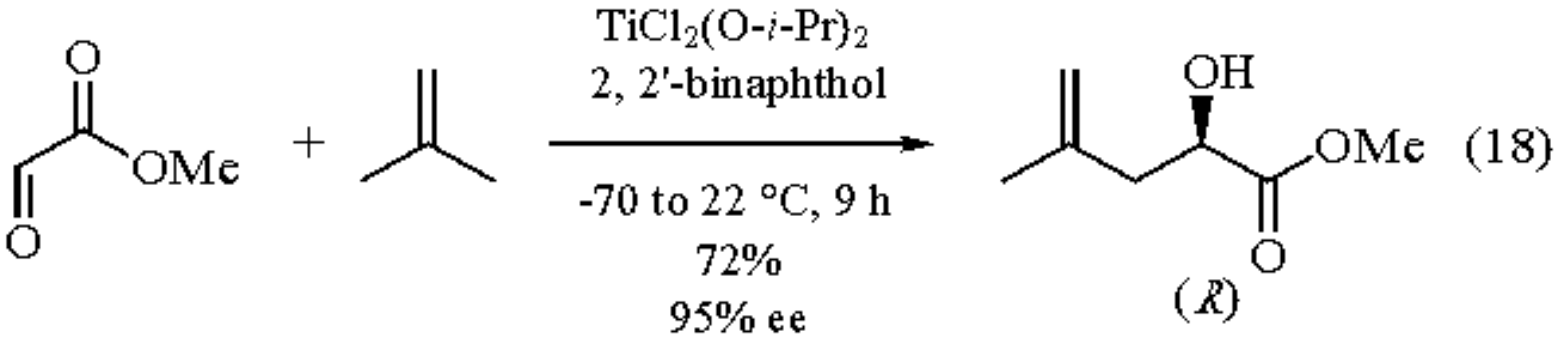

Friedel-Crafts and Other Alkylation Reactions.

A variety of *t*-butyl-substituted aromatics have been prepared with isobutene in the presence of acids (eqs 19-21).[23-25] Due to steric factors, the regiochemistry is enhanced. Isobutene can be alkylated by benzylic and allylic halides in the presence of ***Zinc Chloride*** (eqs 22-24).[26,27]

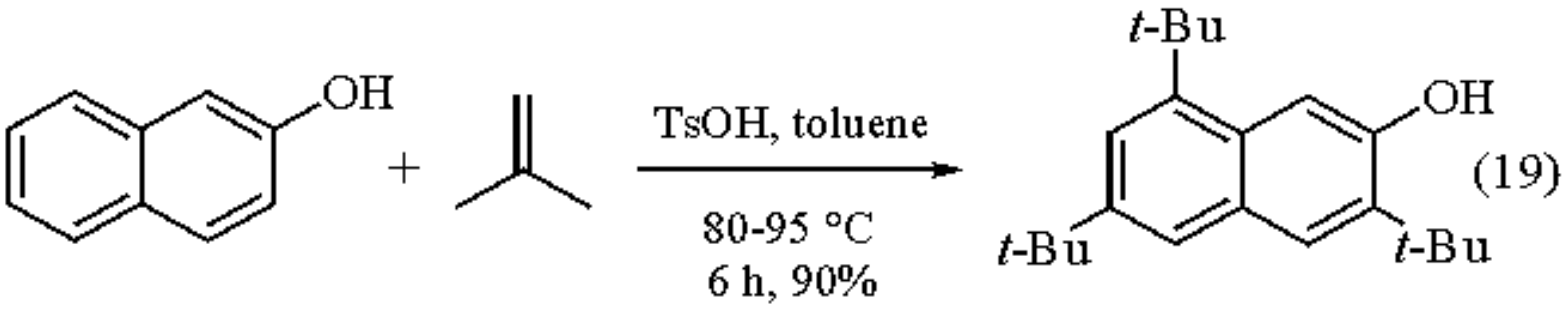

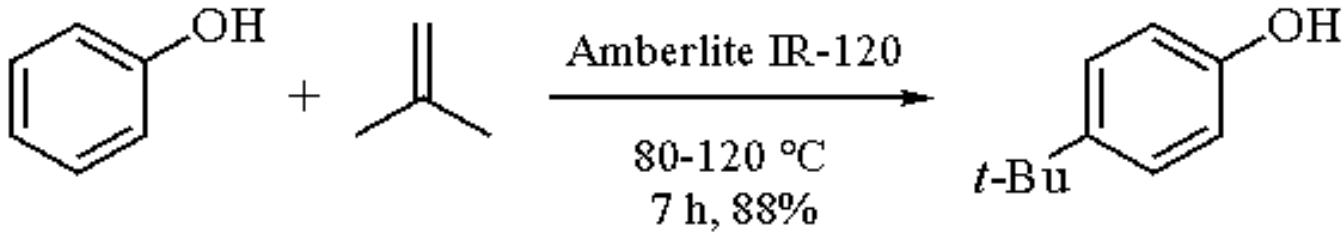

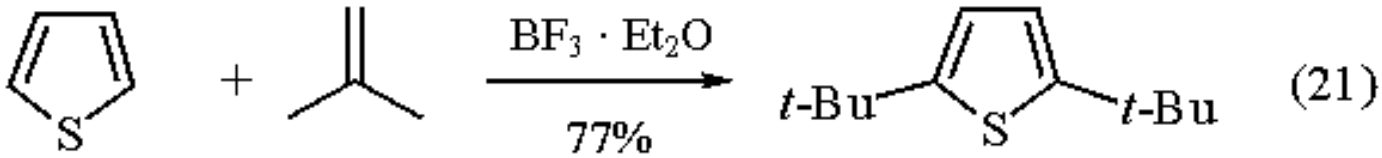

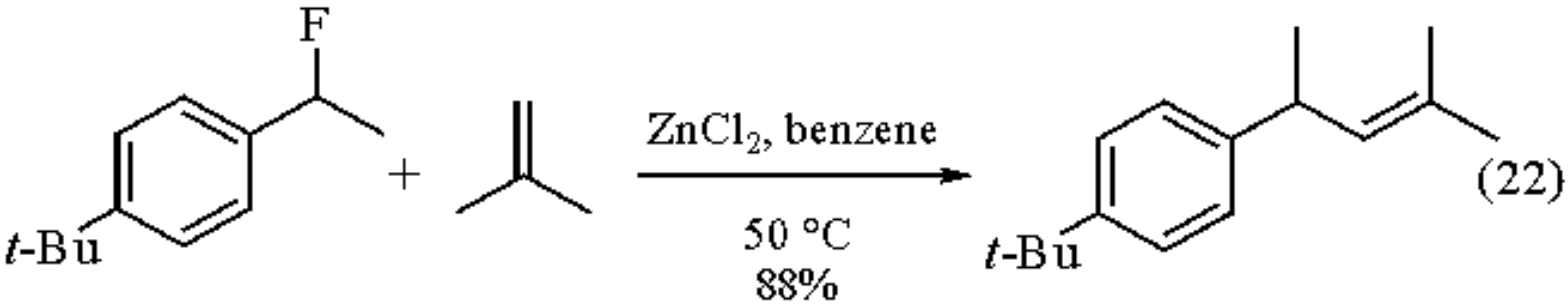

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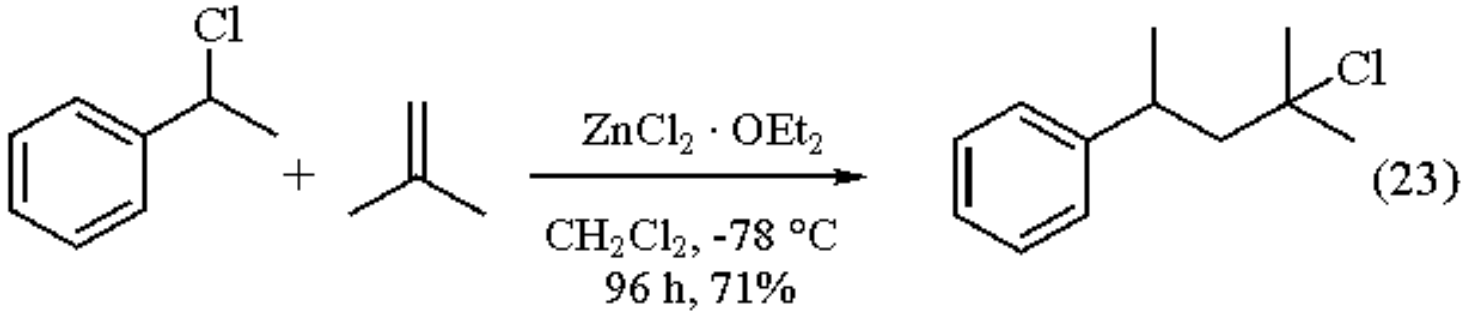

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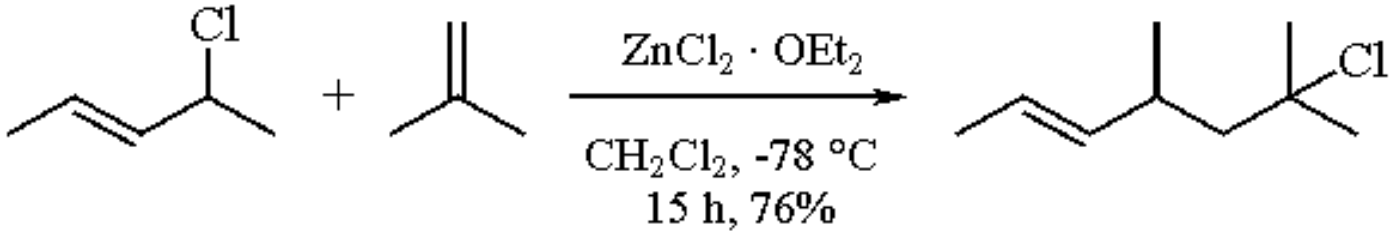

(24)

Carbene Chemistry.

Isobutene reacts readily with carbenes and metallocarbenes to form substituted cyclopropanes (eqs 25-27).[28] Reaction of ***Ethyl Diazoacetate*** with isobutene in the presence of a chiral copper catalyst affords the cyclopropane in high optical purity (eq 28).[29] Isobutene has also been used to form titanocyclobutanes that are more stable forms of the Tebbe reagent (see μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***) (eq 29).[30]

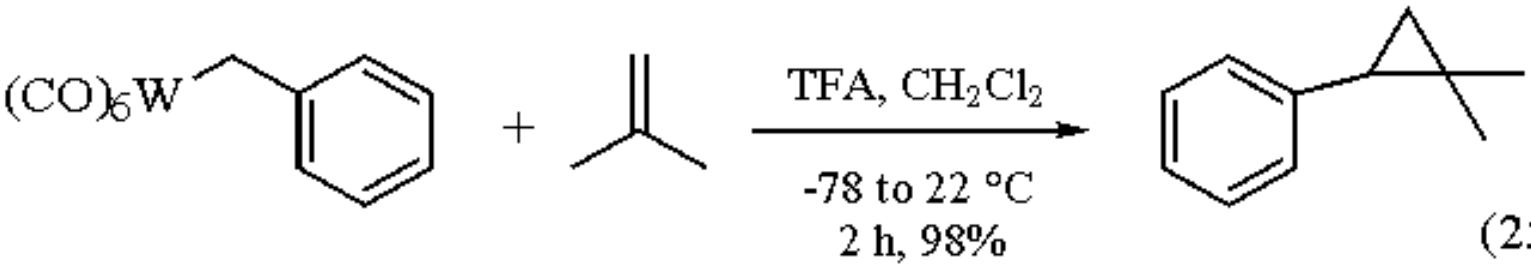

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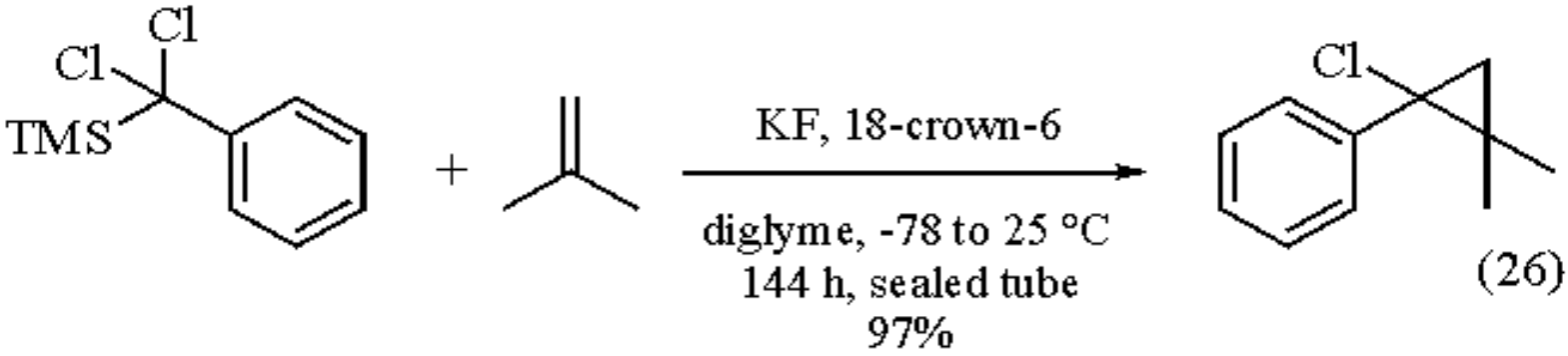

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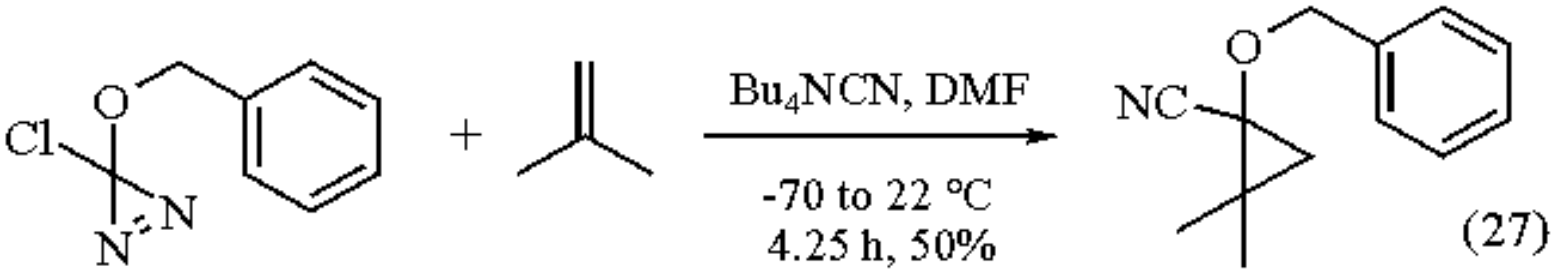

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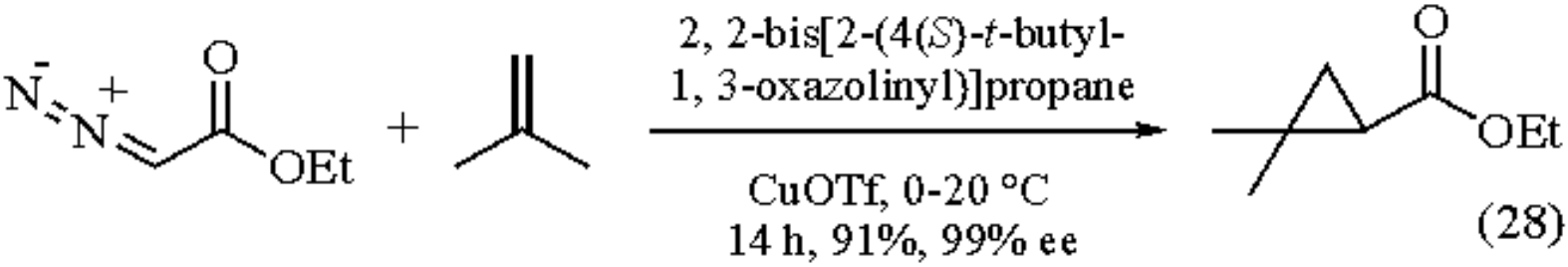

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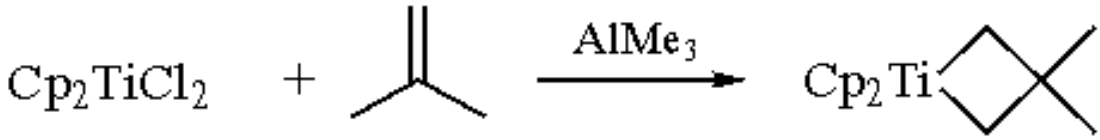

(29)

Other Acid-catalyzed Cycloadditions.

Isobutene has been used to form pyrylium salts (eqs 30 and 31),[31] oxetanes by ***Boron Trifluoride***-catalyzed [2 + 2] cycloaddition (eq 32),[32] and 3,4-dihydropyrans by Diels-Alder reactions (eq 33).[33]

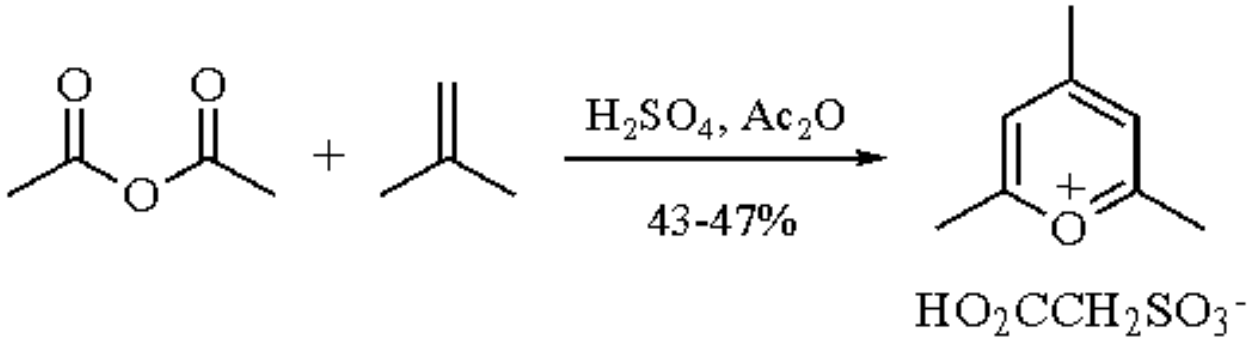

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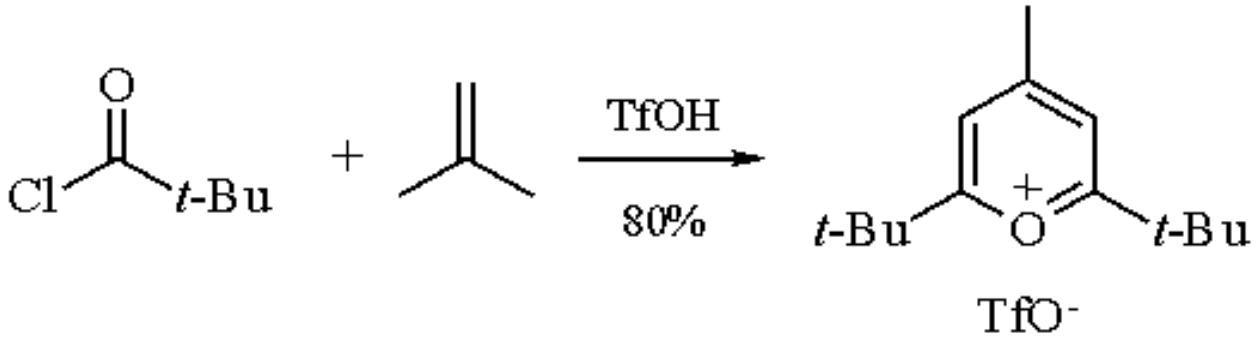

(31)

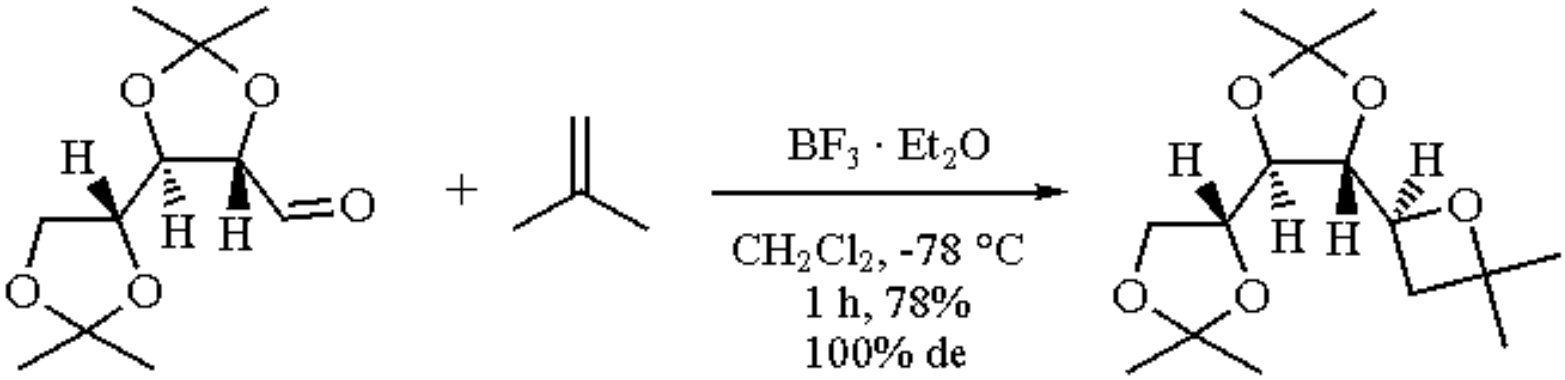

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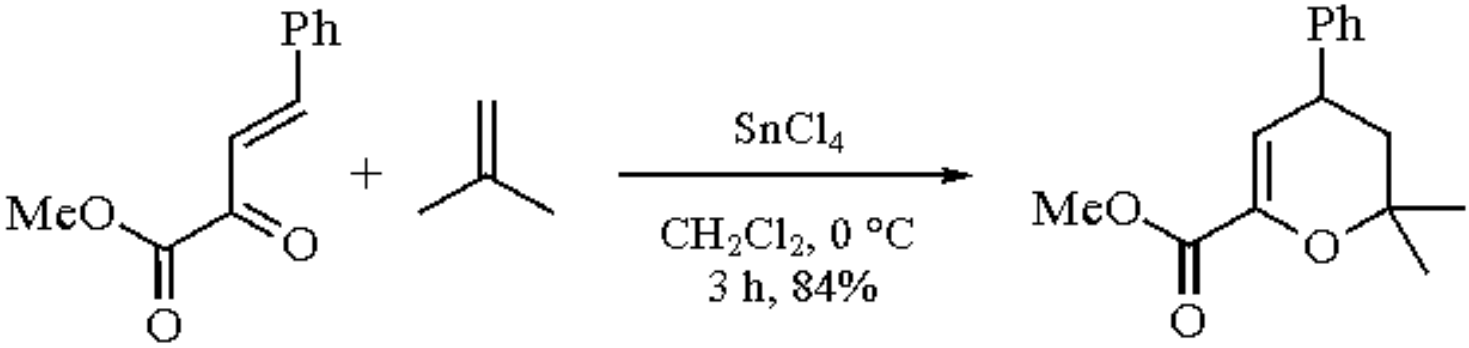

(33)

Miscellaneous Reactions.

Isobutene, as the carbenium ion source for Ritter reactions, produces *N*-*t*-butyl amides (eq 34).[34] Isobutene undergoes highly regioselective cycloaddition with isocyanate to form azetidinones and with nitrones to yield isoxazolidines (eqs 35 and 36).[35,36] Allyl thioethers are formed by the electrophilic addition of ***Benzenesulfenyl Chloride*** to isobutene (eq 37).[37] Alkenylphosphonous dichlorides and alkenylthionophosphonic dichlorides are also formed by addition of PCl_5 and P_2S_5 (eqs 38 and 39).[38]

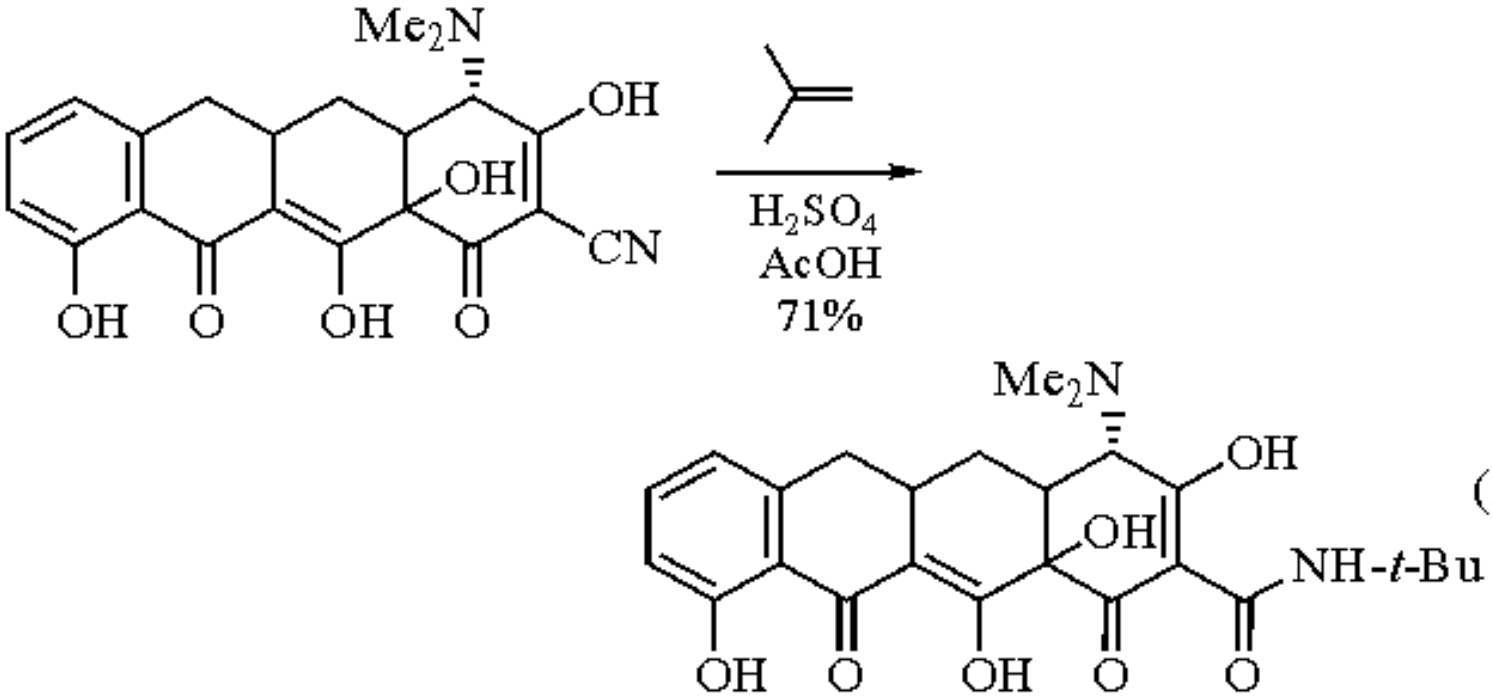
Me2N
OH
OH
CN
OH
O
OH
O
H2SO4
AcOH
71%
Me2N
OH
OH
NH-t-Bu
OH
O
OH
O
O

(34)

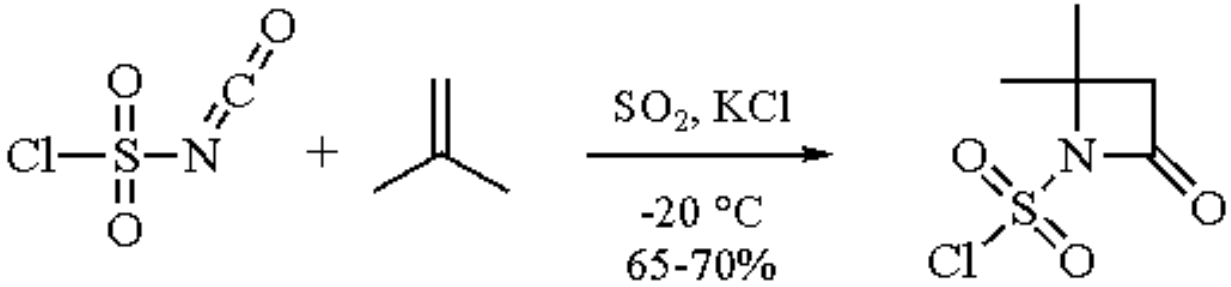
Cl
S
N
C
O
O
O
O
SO2, KCl
-20 °C
65-70%
N
O
S
O
Cl
O

(35)

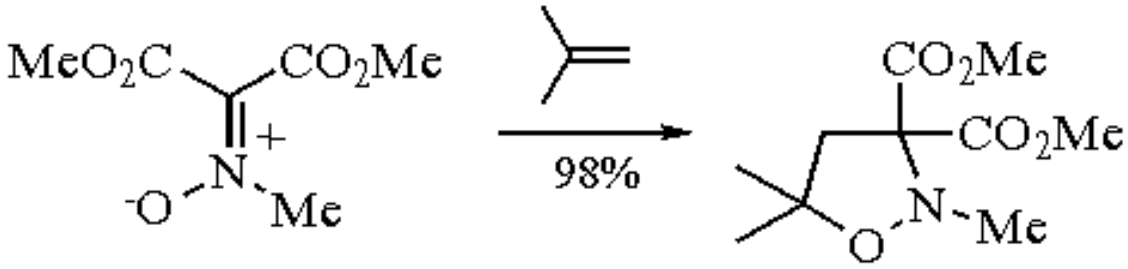
MeO2C
CO2Me
N
Me
98%
CO2Me
CO2Me
N
Me
O

(36)

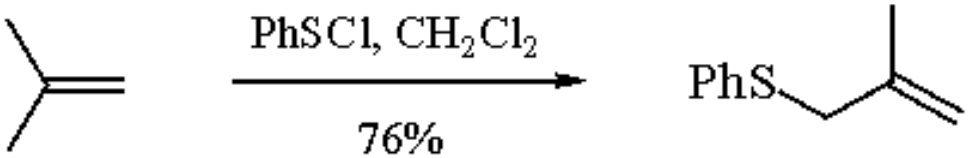
PhSCl, CH2Cl2
76%
PhS

(37)

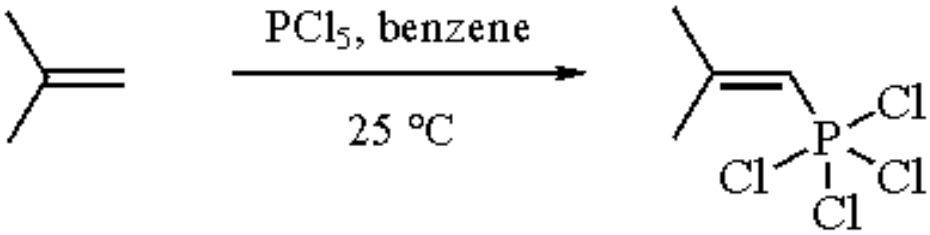
PCl5, benzene
25 °C
Cl
P
Cl
Cl
Cl

(38)

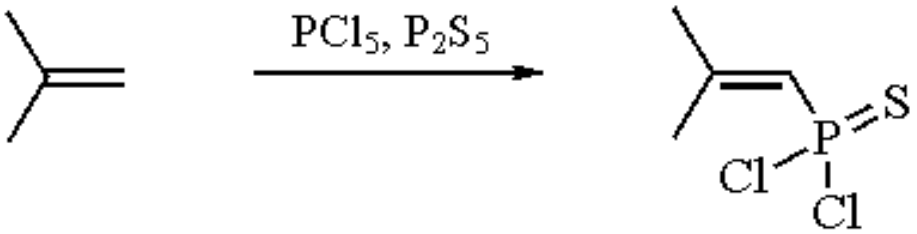

(39)

Related Reagents.

t-Butyl 2,2,2-Trichloroacetimidate.

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Isobutyl Chloroformate

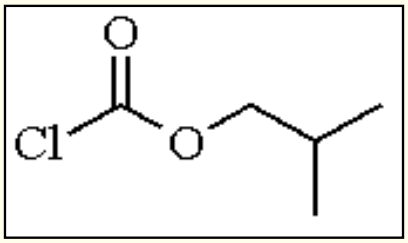

[543-27-1] · $C_5H_9ClO_2$ · Isobutyl Chloroformate · (MW 136.59)

(used for making mixed anhydrides which serve as active intermediates for peptide synthesis;[1-3] used to block the 5´-hydroxy function of deoxyribosides in oligonucleotide synthesis;[4] condensing reagent[5])

Physical Data: bp 128.8 °C; *d* 1.04 g cm^{-3}.

Solubility: miscible with benzene, chloroform, ether.

Form Supplied in: clear colorless liquid.

Handling, Storage, and Precautions: gradually decomposed by water and alcohol; highly toxic; vapor irritates eyes and mucous membranes; stable on storage.[6,7] Use in a fume hood.

Peptide Reagent.[1,3]

Protected amino acids, such as the *N*-benzyloxycarbonyl (Cbz) derivatives, are brought into solution in toluene or THF by addition of enough ***Triethylamine*** to form the salt, and isobutyl chloroformate is added at 0 °C to produce the mixed anhydride. A solution of an amino acid ester (or peptide ester) to be *N*-acylated is added in an inert solvent and the mixture is allowed to come to rt. Evolution of carbon dioxide begins immediately (eq 1). The isobutyl chloroformate is preferred to lower esters for preparation of peptides of moderate or high molecular weight;[6,7] ethyl chloroformate is preferred for synthesis of dipeptides.

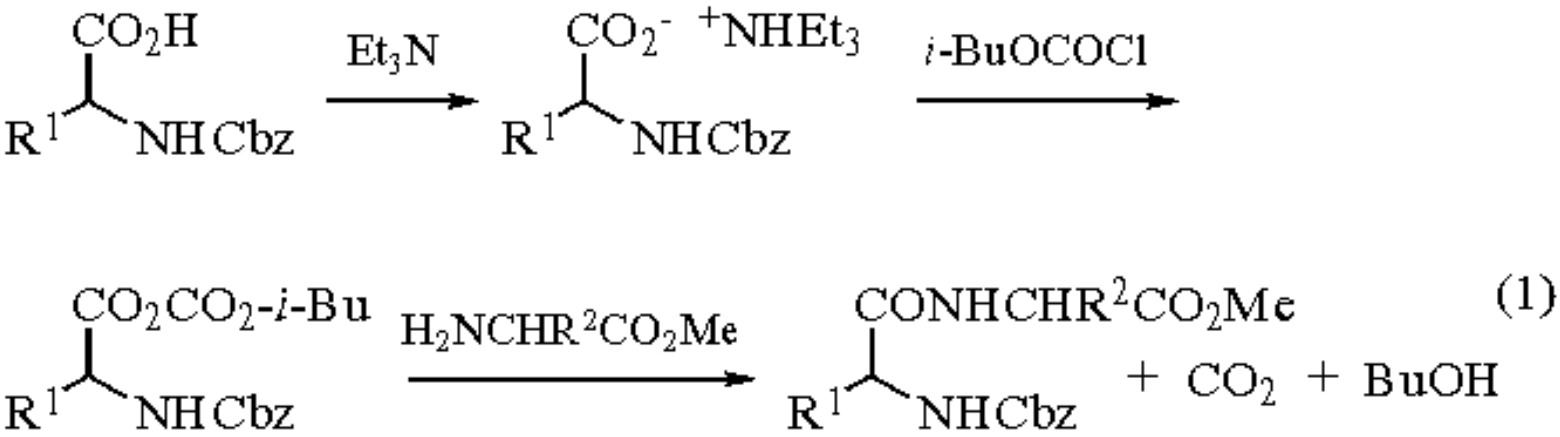

Boc-Gly-Gly-OEt and Boc-Gly-Gly-Gly-OEt have been successfully synthesized in reasonable yields (77% and 88%, respectively) via mixed anhydride derivatives from isobutyl chloroformate.[8] Previously it was reported[9] that considerable quantities of diacylated side products are formed in mixed anhydride syntheses with glycine when ethyl chloroformate is used.

5´-Hydroxy Function Blocking Agent for Deoxyribosides.

The reagent has been used to block the 5´-hydroxy function of deoxyribosides in oligonucleotide synthesis (eq 2).[4] The reagent shows good selectivity for the 5´-hydroxy group, as is evident in the high yield of (**2**). The blocking group is removed smoothly by alkaline hydrolysis to give (**4**).

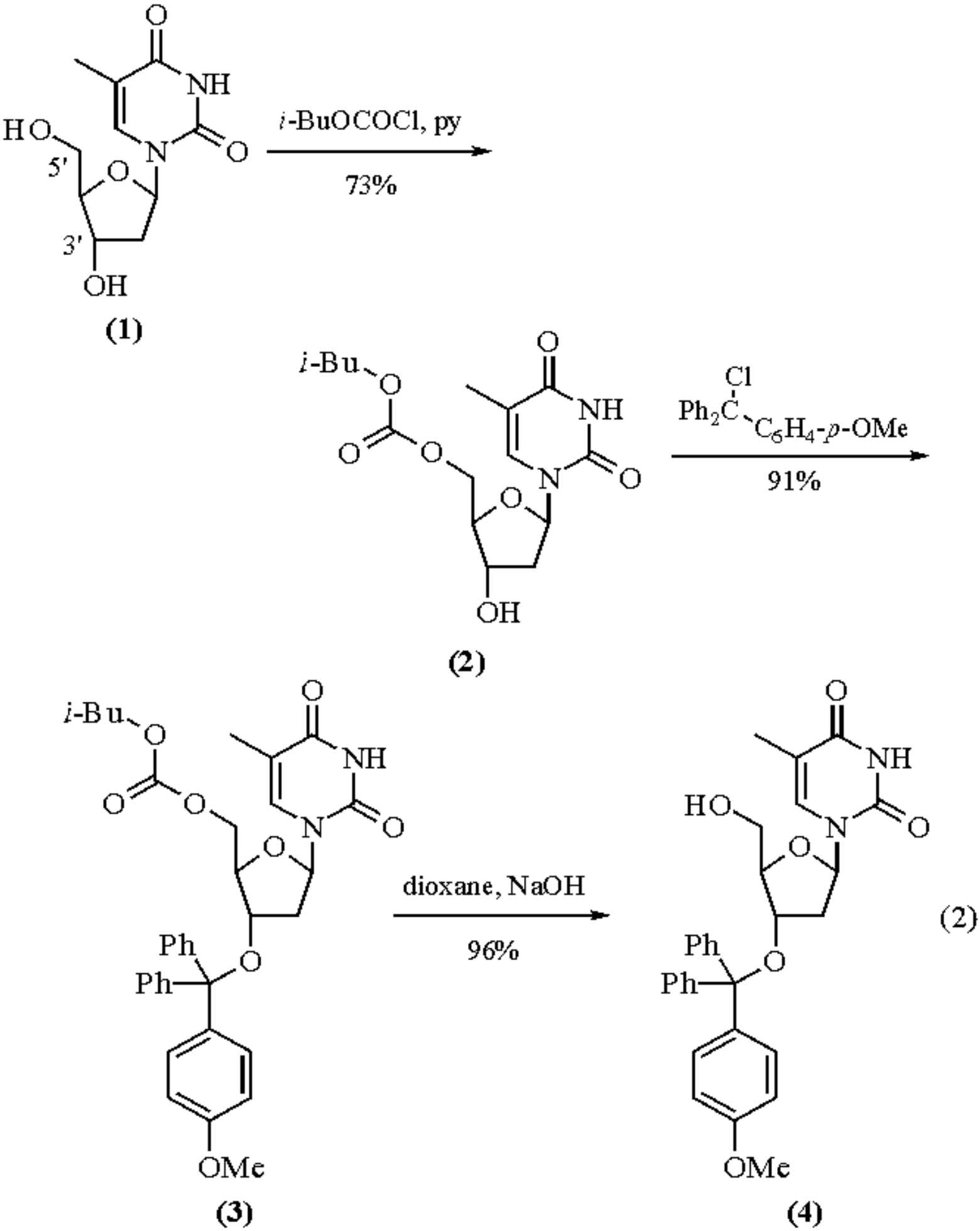
i-BuOCOCl, py
73%
(1)
(2)
Cl
Ph2C
C6H4-p-OMe
91%
dioxane, NaOH
96%
(3)
(4)
(2)

N-Protection.[10]

In the synthesis of enantiomerically pure symmetric vicinal diamines involving chirality transfer from a single chiral source, 1,2-diphenylethane-1,2-diamine, hydrolysis of the bisacetamides to the corresponding vicinal diamines was attempted using a number of amide hydrolysis procedures. However, the various base- and acid-catalyzed procedures did not result in a clean hydrolysis of the acetamide groups. This was achieved by converting amines into biscarbamate derivatives, followed by treatment with 30% HBr in acetic acid (eq 3).

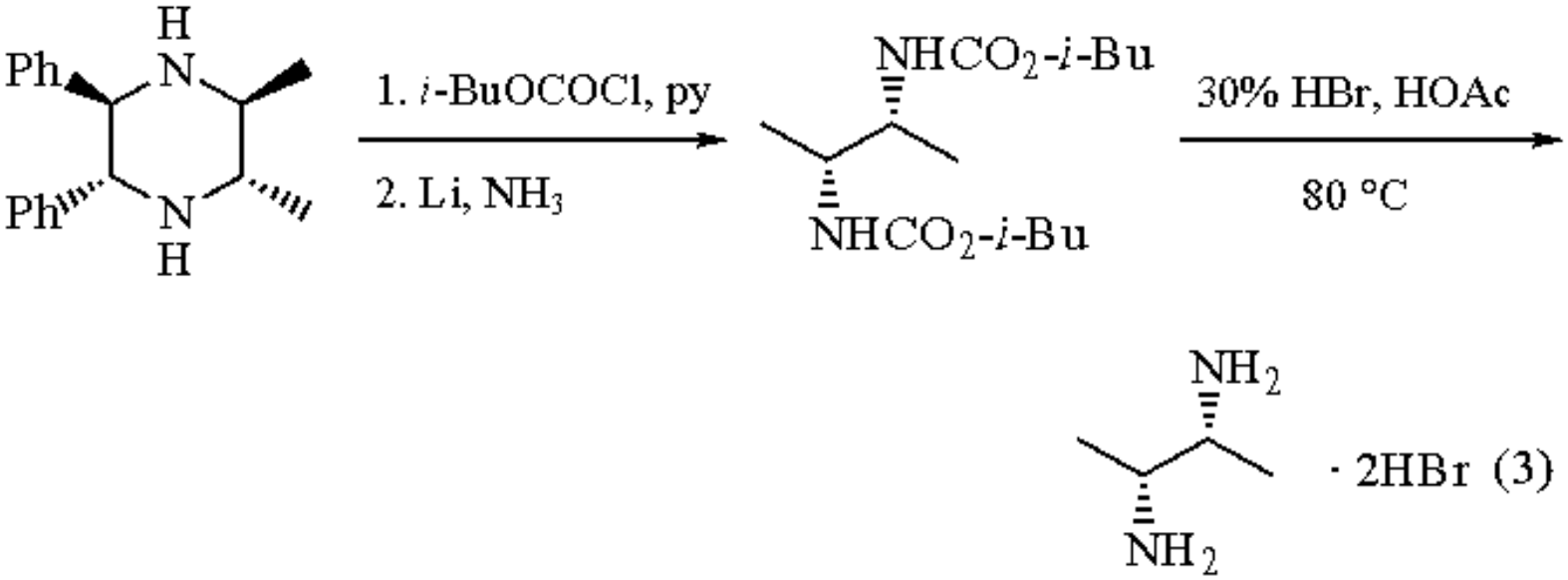

Cyclodehydration.[5]

In the synthesis of 1,4-dihydropyran[3,4-*b*]indolones, the reagent was used along with triethylamine for cyclodehydration of hydroxymethylindoleacetic acid to produce the lactone (eq 4).

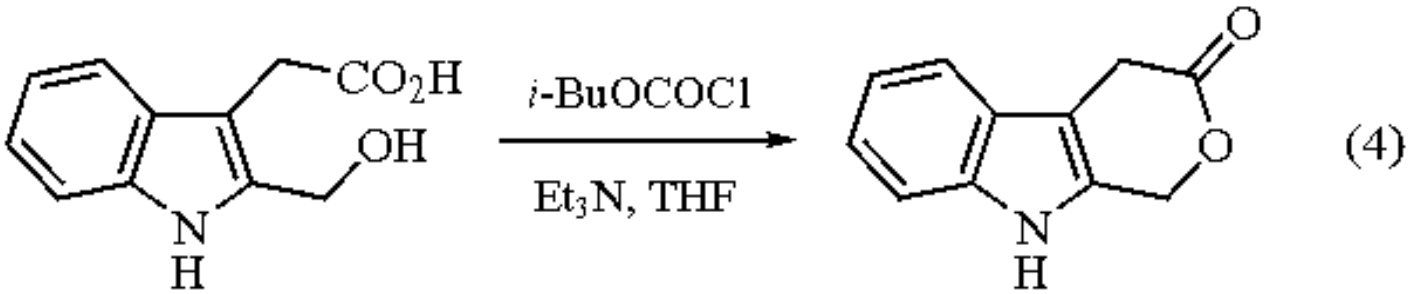

Regioselective Arylation.[11]

Arylation in the 4-position in pyridines results from 1:1 adduct formation between an aryltriisopropoxytitanium reagent and an *N*-isobutyloxycarbonylpyridinium salt, and after successive ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** dehydrogenation and cleavage of the 1-substituent (eq 5).

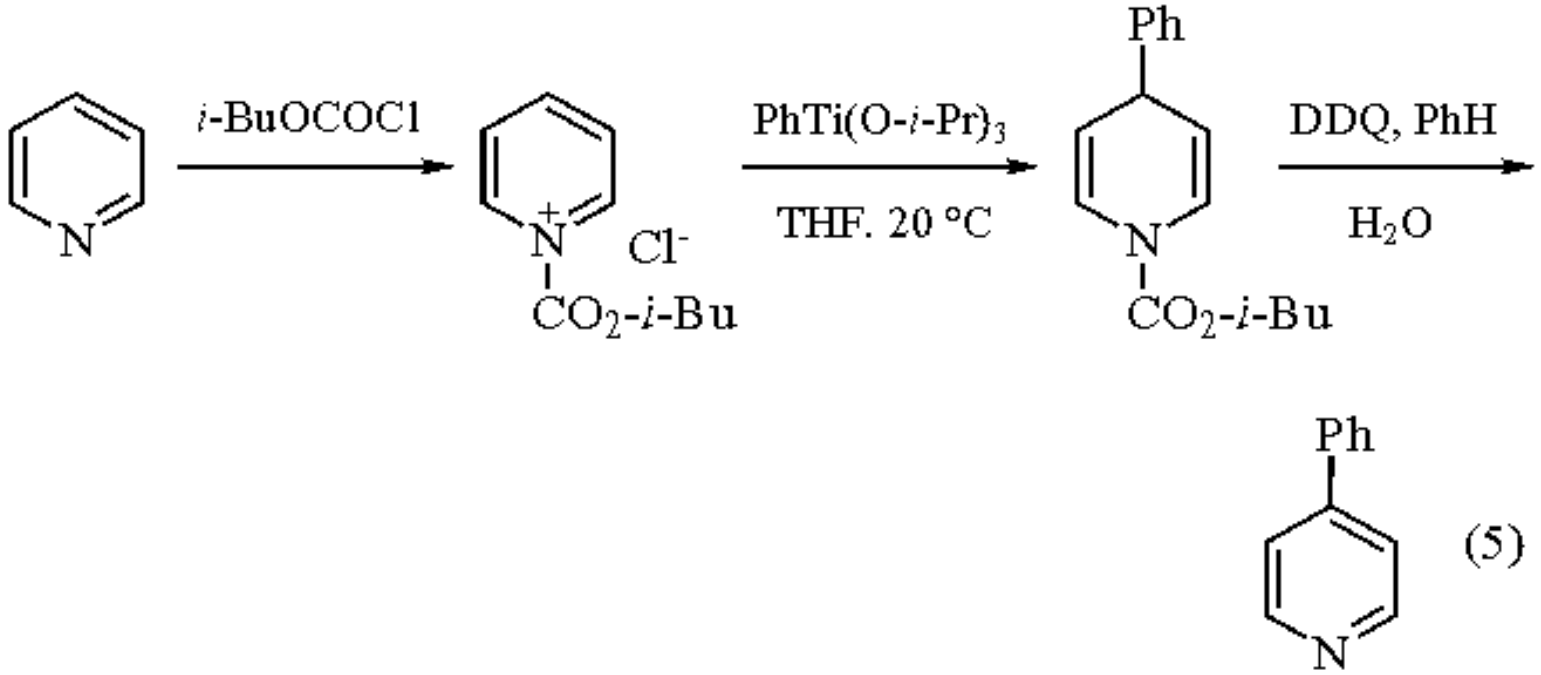

Isobutyl Sulfonate.[12]

With ***Silver(I) p-Toluenesulfonate***, alkyl chloroformate forms sulfonic carbonic anhydride which when heated liberates carbon dioxide, producing alkyl sulfonate. In order to find out the mechanism of the decomposition of the mixed anhydride, reaction of isobutyl chloroformate and silver *p*-toluenesulfonate was investigated. If the free alkyl cation, i.e. isobutyl carbonium ion, is formed, the rearrangement to *s*-butyl and *t*-butyl carbonium ion would be expected, finally resulting in the formation of *s*-butyl *p*-toluenesulfonate. *t-B*utyl *p*-toluenesulfonate is unstable and is not expected to survive under the reaction conditions. In fact, decomposition gave a mixture of isobutyl *p*-toluenesulfonate and *s*-butyl *p*-toluenesulfonate in a 0.8:1 mol ratio, with a quantity of isobutene and free *p*-toluenesulfonic acid. Isobutene was considered to be derived from the *t*-butyl cation.

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Isocyanic Acid[1]

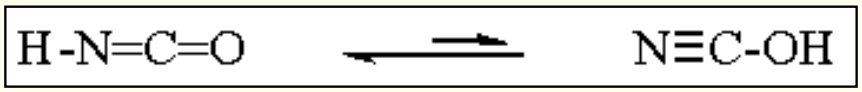

(HNCO)

[75-13-8] · CHNO · Cyanic Acid · (MW 43.03) (HOCN)

[420-05-3] · CHNO · Isocyanic Acid · (MW 43.03) (KOCN)

[590-28-3] · CKNO · Potassium Cyanate · (MW 81.12) (NaOCN)

[917-61-3] · CNNaO · Sodium Cyanate · (MW 65.01) (AgOCN)

[3315-16-0] · CAgNO · Silver Cyanate · (MW 149.89)

(synthesis of isocyanates, allophanates, and some heterocyclic compounds)

Physical Data: mp -86 °C; bp 23.5 °C (by extrapolation); *d* 1.14 g cm^{-3}; pK_a 3.66.

Solubility: poorly sol aliphatic hydrocarbons; sol benzene, toluene, CCl_4, ether, THF, etc. *Drying:* over P_2O_5.

Analysis of Reagent Purity: see Belson and Strachan.[1c]

Preparative Methods: by the depolymerization of cyanuric acid,[1a,b] or by heating urea.[1c] The gas can be absorbed in ether, THF, $CHCl_3$, or CCl_4. Aqueous solutions of HNCO can be prepared in situ by reacting NaOCN or KOCN with 1 equiv of dil HCl or AcOH at temperatures of approx 0-15 °C.

Handling, Storage, and Precautions: isocyanic acid (gas, liquid, or as concentrated solution in anhyd organic solvents) readily polymerizes from -20 °C to rt to give an easily separable mixture of cyanuric acid and cyamelide (a polymer whose structure is as yet unknown), but dilute solutions in ether or CCl_4 can be kept at rt without serious decomposition.[1c] In contact with moisture, even at 0 °C, it hydrolyzes to NH_3 and CO_2.[1c] Stored at dry ice or liquid nitrogen temperature, it is quite stable.[1c] Besides being a strong acid, lacrymator, and vesicant, it possesses an acrid odor. The highly toxic character of isocyanic acid requires that it should be used only in a well-ventilated fume hood.

Introduction.

Of the two acids, cyanic acid (H-O-C&tbond;N) and isocyanic acid (H-N=C=O) (**1**), that arise from the ambident nucleophile cyanate, (**1**) is the more stable of the two. Since cyanic acid is kinetically unstable,[1a,b] it is vital to recognize at the outset that much of the preparative work mentioned in the scientific literature for cyanic acid has, in fact, utilized isocyanic acid. Isocyanic acid, for all practical purposes, whether in the gaseous, liquid, or solid state, has the carbimide structure H-N=C=O, and, although in principle it can tautomerize to give cyanic acid, the observed proportion of cyanic acid in organic solvents is essentially negligible.[1c] Even in aqueous media, it is the isocyanic acid tautomer that predominates.[1c]

Addition of Polar Compounds to Isocyanic Acid.

Because of the presence of electrophilic functionality (-N=C=O) in isocyanic acid (**1**), a wide range of polar reagents[2] adds across its HN=C bond, such that their nucleophilic end attacks at carbon, and the positive part at nitrogen. In this way, cyclohexylamine forms *N*-cyclohexylurea in 75% yield,[3a] alcohols (primary, secondary, and tertiary ROH) give moderate yields[3b-d] of crystalline allophanates (**2**), often contaminated with carbamates, and ***Diphenylphosphine*** reacts efficiently with (**1**) in degassed benzene at rt to form carbamoyldiphenylphosphine (**3**) in 75% yield.[4a] With an excess of ***Trifluoroacetic Anhydride*** at rt, (**1**) gives perfluorodiacetamide (**4**) in 90% yield.[4b]

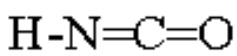

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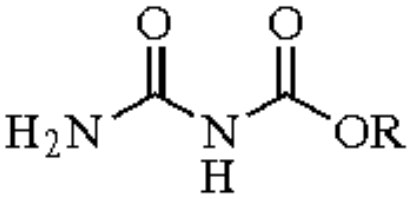

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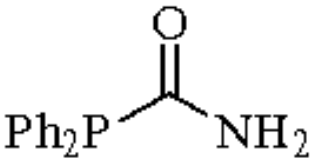

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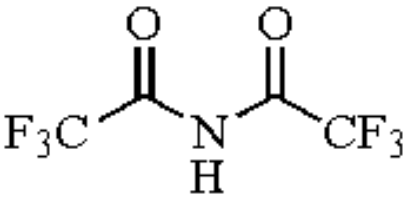

(4)

Formation of Isocyanates.

Because of the ionizable H-N bond, isocyanic acid behaves like a pseudo hydrogen halide. In the presence of a suitable catalyst and appropriate conditions, it adds to reactive unsaturated compounds, and undergoes substitution reactions at Si, Sn, and P. Thus several novel isocyanates have been prepared,[5a] by reaction of (**1**) with electron-rich alkenes,[5b] vinyl ethers,[5c] reactive carbonyl compounds,[5d-g] chlorosilanes,[5f] phosphorus halides,[5f] organometal oxides,[5h] and pentafluoroguanidine,[5i] etc. Some selected examples of isocyanates thus obtained (including yields) are:

- 1)α,α-Dimethylbenzyl isocyanate ($PhCMe_2NCO$, 41%)[5b] from α-methylstyrene.
- 2)1-Butoxy-1-methylethyl isocyanate ($BuOCMe_2NCO$, 71%)[5c] from *n*-butyl isopropenyl ether.
- 3)1-(2-Methacryloyloxyethoxy)ethyl isocyanate (**5**) (83%)[5c] from vinyloxyethyl methacrylate.
- 4)Hydroxymethyl isocyanate ($HOCH_2NCO$, 90-95%)[5d] from formaldehyde at -78 °C. Most carbonyl compounds

capable of forming hydrates, e.g. chloral, trifluoroacetaldehyde, hexafluoroacetone, perfluorobutanone, *s*-dichlorotetrafluoroacetone, give α-hydroxy isocyanates which display their normal reactivity pattern. For example, $HOCH_2NCO$ polymerizes explosively above 0 °C, but it reacts with dihydropyran under catalysis with ***p-Toluenesulfonic Acid*** at -5 °C to give 2-tetrahydropyranyloxymethyl isocyanate ($THPOCH_2NCO$, 67%) and it has been converted into chloromethyl isocyanate ($ClCH_2NCO$) at -78 °C.[5e]

- 5)Acetyl isocyanate (AcNCO, 15%)[5f] from acetyl chloride.
- 6)Trimethylsilyl isocyanate (Me_3SiNCO, 57%)[5f] from Me_3SiCl.
- 7)Diphenyl phosphor(isocyanatidite) [$(PhO)_2PNCO$, 70%][5f] from diphenyl phosphorochloridite [$(PhO)_2PCl$], and [$PhOP(NCO)_2$, 61%][5f] from $PhOPCl_2$.
- 8)Trifluoroacetyl isocyanate (CF_3CONCO 37%)[5g] from trifluoroacetic anhydride.
- 9)Tri-*n*-butyltin isocyanate (Bu_3SnNCO, 90%)[5h] from dibutyltin oxide.
- 10)Bis(difluoramino)fluoraminomethyl isocyanate (**6**) (30-50%)[5i] from pentafluoroguanidine. Compound (**6**) on fluorination in the absence of NaF gives tris(difluoramino)methyl isocyanate [$(F_2N)_3CNCO$] in 80% yield.[5j]

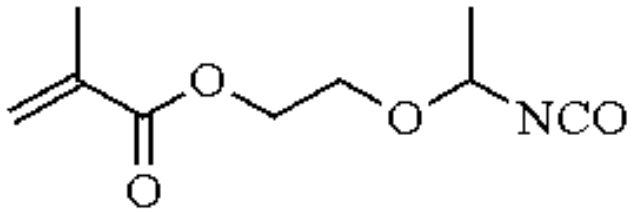

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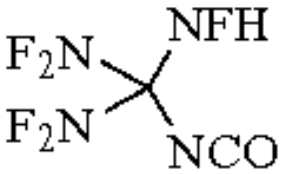

(6)

Formation of Heterocycles.

Because of the ambident reactivity of isocyanic acid, when β-propiolactone and (**1**) are combined (1:1) with a catalytic amount of ***Boron Trifluoride Etherate*** at -22 to 0 °C, 3,4,5,6-tetrahydro-2*H*-1,3-oxazine-2,4-dione is obtained in 95% yield (eq 1).[6] Likewise, the vinylogous carbamate (**7**) upon condensation with (**1**) and acetaldehyde in ether at rt gives, in 72% yield, dihydropyrimidin-2-one (**8**) (eq 2), useful in the synthesis of the marine toxin saxitoxin.[7] Treatment of (**6**) with 1 equiv of (**1**) and 0.1 equiv of urea at -35 °C for 3 h gives the 5-fluorodihydro-*s*-triazine-2,4(1*H*,3*H*)-dione (**9**) in 90-100% yield (eq 3).[5i] Finally, the facile addition of the H-N bond of (**1**) across the HN=C bond of another molecule explains why (**1**) readily trimerizes to give cyanuric acid and the polymer cyamelide

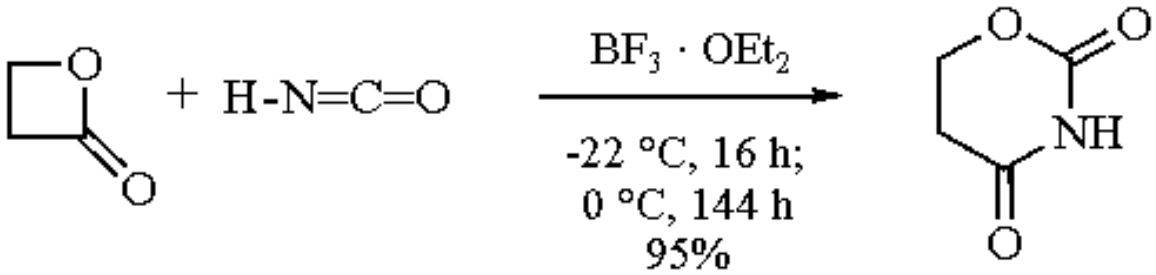

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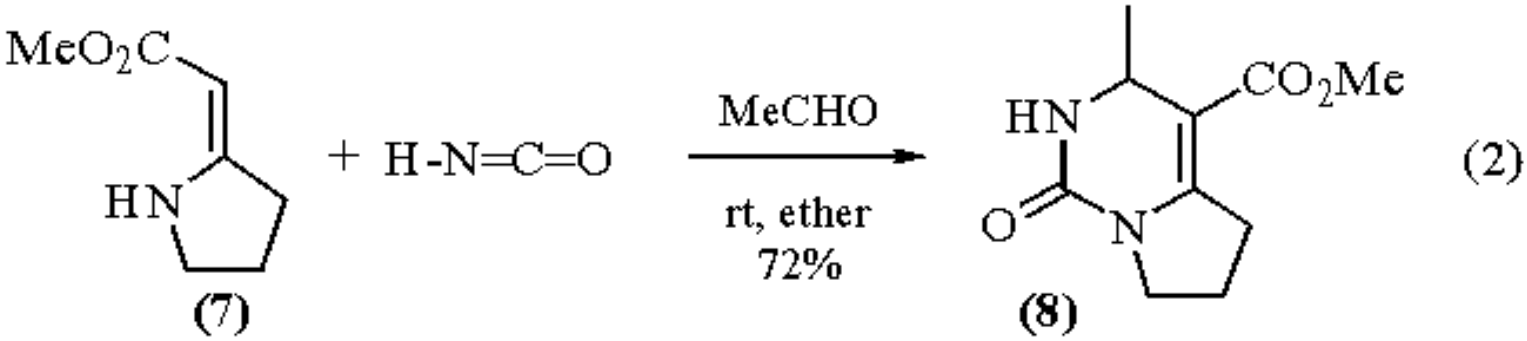

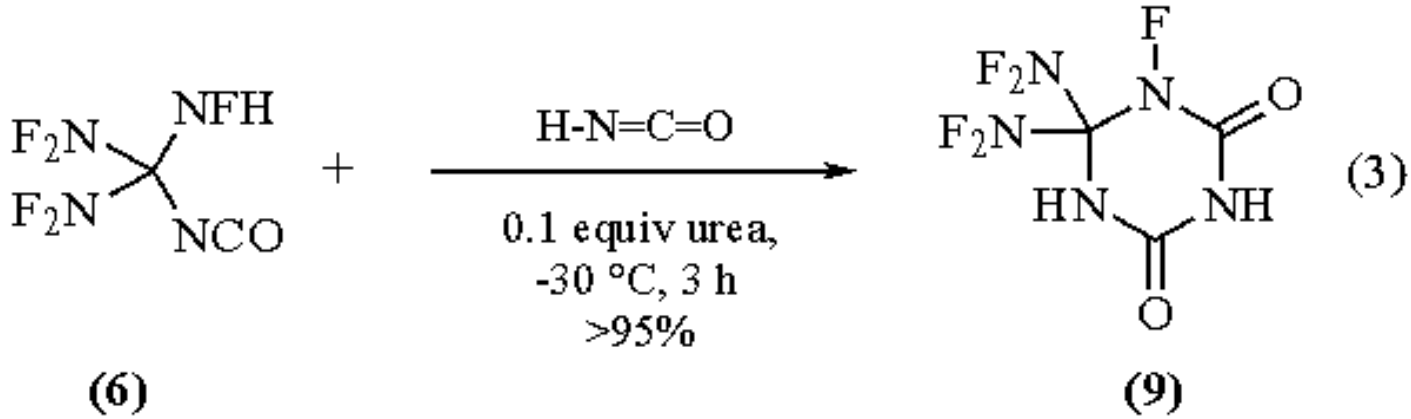

Cyanic Acid Salts (Potassium, Sodium, and Silver).

In contrast to cyanic acid, its alkali metal salts (potassium cyanate, sodium cyanate, and silver cyanate) are stable,[1d] economical, and convenient starting materials for the synthesis of inorganic and organic isocyanates as well as for the in situ preparation of aqueous (**1**). In assessing their reactivity pattern, it is important to note that, whereas both Na^+ and K^+ are hard electrophiles, Ag^+ is a soft electrophile.

Inorganic Isocyanates.

Inorganic isocyanates are prepared by the displacement of halogen attached to the element of interest (B, Si, Ge, Sn, Pb, N, P, As, Sb, O, S, Cl, Br, and I) with a salt of cyanic acid. However, not all elements (N and O) give stable isocyanates, and some (e.g. I-NCO) can only be prepared in situ and utilized accordingly.[8] Thus reaction of AgOCN with ***Bromodimethylborane*** gives Me_2B-NCO in 90% yield.[9] Similarly, isocyanates have been prepared by the displacement of a halogen at Si, Ge, Sn, S, and P with AgOCN.[8] Isocyanates of Si (TMS-NCO), S (e.g. $PhSO_2$-NCO, *p*-$MeC_6H_4SO_2$-NCO, and $ClSO_2$-NCO), and I (I-NCO) are covered separately in this encyclopedia. More recently, methyl phenylsulfenylcarbamate (PhS-$NHCO_2Me$) and *N*-phenyl-*N*´-(phenylsulfenyl)urea (PhS-NH-CO-NHPh) have been obtained, in 47% and 36% yield, by trapping the in situ formed phenylsulfenyl isocyanate (PhSCl + AgOCN -> PhSNCO) in benzene, with MeOH or $PhNH_2$, respectively.[10] With NaOCN, displacement of a chloro group at P in MeP(O)ClF, MeP(O)ClN_3, and $PhPCl_2$, takes place to give the expected isocyanates.[8,11]

Organic Isocyanates.

Although conversion of a simple alkyl halide, sulfate, tosylate, or phosphate into its respective isocyanate using cyanic acid salts can be satisfactorily achieved in the laboratory, this topic is a subject of numerous patents. Thus while Et-NCO can be obtained in good yields by simply heating Et_2SO_4, ethyl *p*-toluenesulfonate, or triethyl phosphate[12] with KOCN, the reaction of EtBr with KOCN is best performed[8] in dimethyl sulfone as a solvent. In some cases, the choice of the solvent employed is very critical to the success of the reaction. Use of an aprotic solvent such as DMF alone should be avoided, since organic isocyanates readily trimerize in DMF to give isocyanurates.[13] Diluting DMF with xylene essentially overcomes this problem, and in this way $MeOCH_2$-NCO has been obtained from NaOCN and $MeOCH_2Cl$.[14] AgOCN in ether and 2,3-dichloro-1,4-dioxane (**10**) give the diisocyanate (**11**) in 40-50% yield (eq 4).[15]

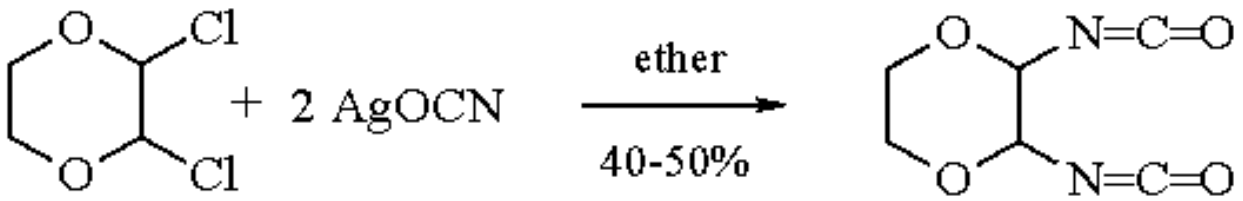

(4)

(10) **(11)**

When crotyl bromide is treated with AgOCN in ether for 3 h at rt, 2-butenyl isocyanate (67%) and 1-methylallyl isocyanate (28%) are obtained in 84% yield.[16] The reaction of AgOCN with 3-bromopropanoyl bromide in benzene under sonication in an ice-water bath gives 3-bromopropanoyl isocyanate ($BrCH_2CH_2CO$-NCO) in 55% yield.[17] This procedure, when extended to 4-bromobutanoyl chloride, gives 4-bromobutanoyl isocyanate ($BrCH_2CH_2CH_2CO$-NCO) in only 10% yield.[17] The displacement of a halogen at carbon with metal cyanates has also been accomplished in the presence of a phase transfer catalyst.[18] Thus when bromoalkyl (meth)acrylate (**12**) (15 mmol) in 5 mL of anhyd MeCN is added to a slurry of NaOCN (22.5 mmol) and Bu_4NBr (3 mmol) in 15 mL of dry MeCN at rt and the mixture is heated at 55 °C for 21 h, the isocyanate (**13**) (59%) and the isocyanurate (**14**) (32%) are readily obtained. When the above mixture is heated at 65 °C for 62 h, the isocyanurate (**14**) is obtained in 75% yield. However, when the above reaction is performed in the presence of water (1.2 equiv), and the mixture is heated at 60 °C for 24 h, the symmetrical urea (**15**) is obtained in 81% yield. Substituting the water with 6 equiv of MeOH gives the carbamate (**16**) in 90% yield.[18] Finally, it should be noted that treatment of alkyl halides with alkali metal or silver cyanate is of no preparative value in the synthesis of cyanates.[19]

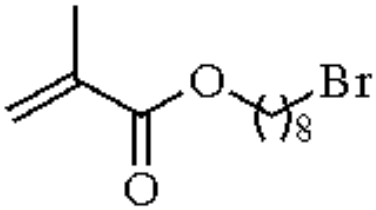

(12)

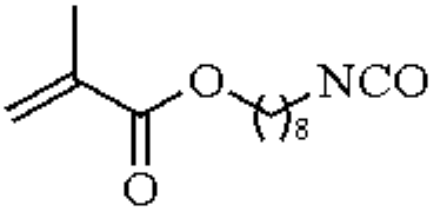

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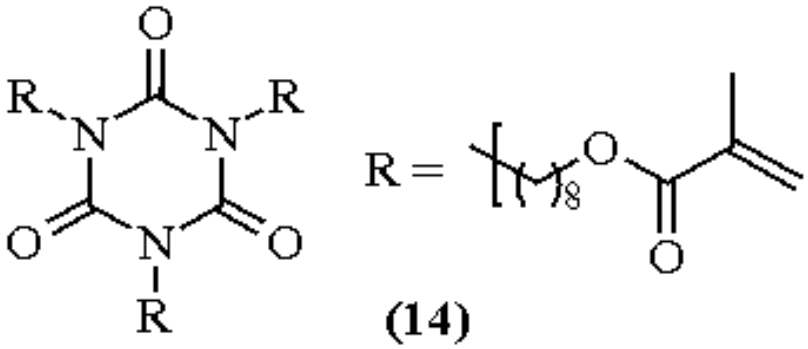

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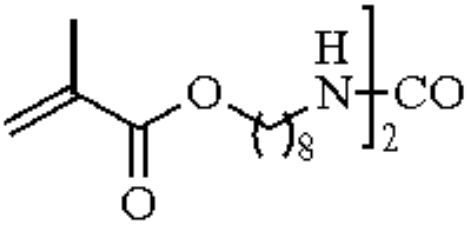

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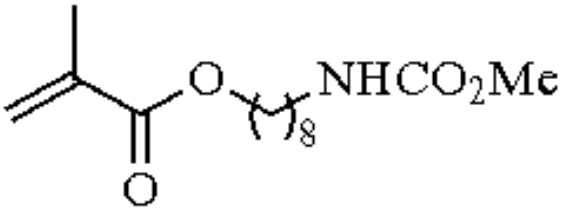

(16)

N-Carbamates and Polyurethanes.

The reaction of alkali metal cyanates with simple alkyl halides in DMF, in the presence of a suitable alcohol, provides a direct synthesis of *N*-substituted carbamates.[20] The initial reaction is an S_N2 process, which exhibits the expected reactivity, i.e. allylic, benzylic, and primary halides react faster than secondary halides, and the reaction fails with tertiary halides. In a typical experiment, an appropriate alkyl halide (50 mmol) in 5 mL of DMF is added to a well stirred slurry of KOCN (75 mmol) and EtOH (85 mmol) in DMF (40 mL) at 100-120 °C. After heating for an additional 4.5-45 h (depending upon the substrate), the *N*-carbamate can be isolated readily. In this way, 2-chlorobutane gives *s*-$BuNHCO_2Et$ (55%); the yields of *n*-$BuNHCO_2Et$ and $BnNHCO_2Et$) from *n*-BuCl and $PhCH_2Cl$ are 77% and 88%, respectively. By appropriately increasing the molar ratio of KOCN and EtOH, both the chlorine atoms in α,α´-dichloro-*p*-xylene or (*E*)-1,4-dichloro-2-butene can be displaced to obtain the expected *N*-biscarbamates in 70% and 77% yield.[20] Substituting EtOH with a diol $[HO(CH_2)_nOH]$ in the above reaction is the key to the synthesis of the poly(polymethylene tetramethylenedicarbamate) type of polyurethanes (eq 5).[21]

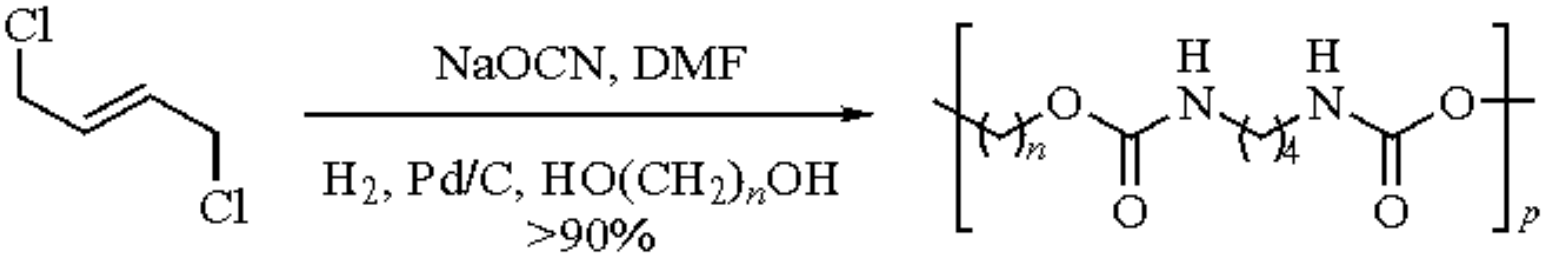

(5)

A simple synthesis of methyl *N*-(1-adamantyl)carbamate [1-(methoxycarbonylamino)adamantane] has been achieved in 54% yield by reaction of 1-adamantanol or its nitrate with KOCN, MeOH, and concd H_2SO_4 in $CHCl_3$.[22] The reaction probably proceeds by the alkylation of the 1-adamantyl cation with in situ formed carbamic acid (H_2NCO_2H) or methyl carbamate.

O-Carbamates.

Addition of alcohols to isocyanic acid in ether gives mixtures of *O*-alkyl carbamates and allophanates (**2**). However, when ***Trifluoroacetic Acid*** (2 equiv) is added to a suspension of 1 equiv of alcohol and 2 equiv of NaOCN (curiously enough, KOCN cannot be substituted for NaOCN) in benzene or methylene chloride and slowly stirred at rt, excellent yields of *O*-alkyl carbamates are obtained.[23] This method is applicable to the synthesis of carbamates from primary, secondary, or tertiary alcohols[24] (2 h reaction time affords 60-90% yield), including propargyl alcohol (eq 6), cyclic and acyclic 1,3-diols, phenols, aldoximes, ketoximes, *n*-BuSH, and *t*-BuSH.[23]

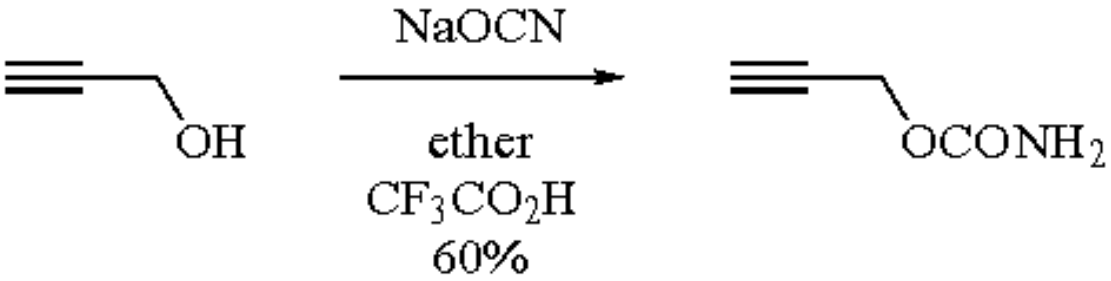

(6)

Reaction with Allenyl Cations.

Potassium cyanate in 70:30 acetone-water (v/v) reacts at rt, under solvolytic conditions,[25] with 1,3,3-triphenylchloroallene (**17**) to form an unstable propargylcarbamic acid which, upon treatment with base, gives the propargylamine (**18**) in 45% yield (eq 7).

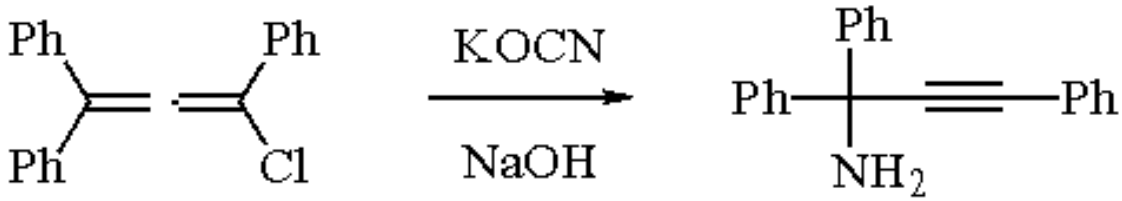

(7)

(17) **(18)**

Reaction with Photogenerated Arylvinyl Cations.

When a two-phase mixture of 1-bromo-1,2,2-tris(*p*-methoxyphenyl)ethylene (**19**) (1 mmol), KOCN (10 mmol), and *n*-Bu_4NCl (2 mmol) in CH_2Cl_2 (90 mL) and H_2O (10 mL) is irradiated through a Pyrex filter under N_2 at 10-15 °C, the photogenerated arylvinyl cation (**20**) is captured by the cyanate ion via *N*-attack to form the β-aryl isocyanate (**21**) (eq 8). This readily cyclizes to give 7-methoxy-3,4-bis(*p*-methoxyphenyl)-1-isoquinolone (**22**) in 93% (at 70% conversion) yield.[26] The presence of the *p*-MeO group in the aromatic ring helps stabilize the vinyl cation and thus is responsible, in part, for the excellent yields obtained in this reaction.

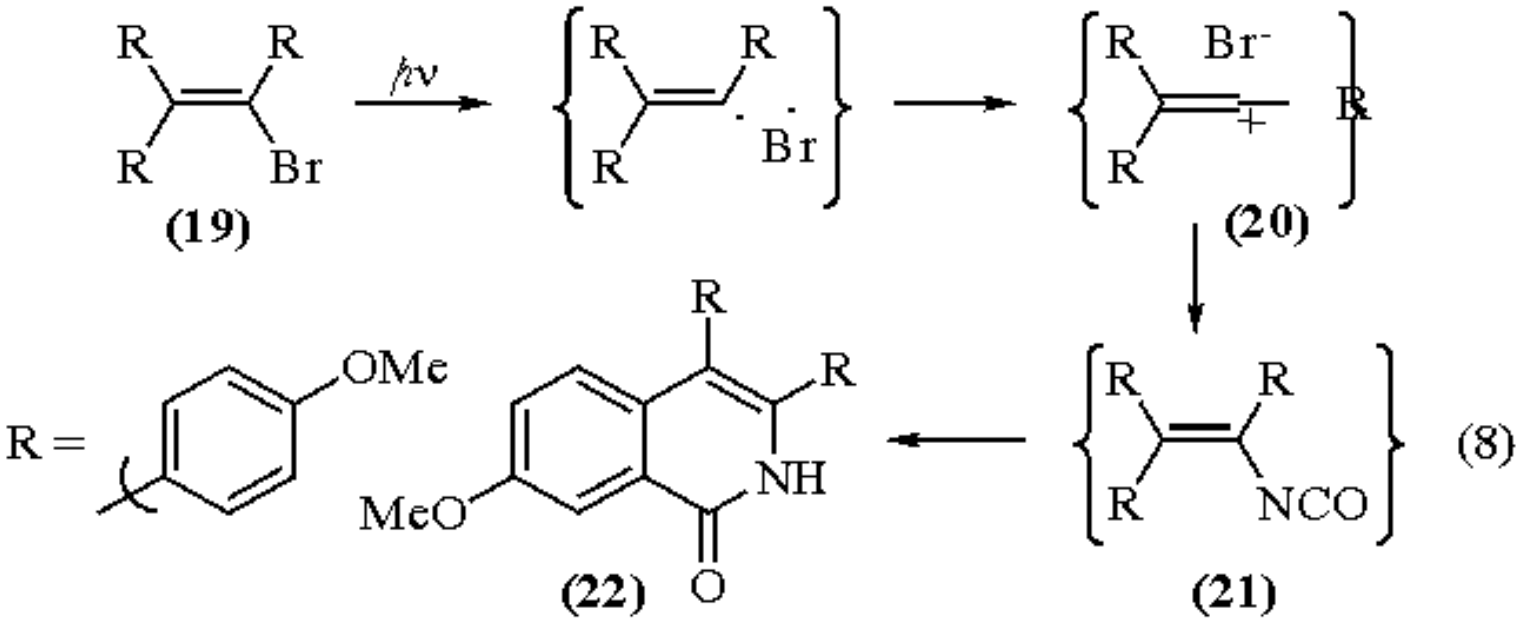

Reaction with a α-Chlorocarbenium Ion.

Potassium cyanate in DMF reacts with the Vilsmeier-Arnold reagent (**23**) to form initially a highly reactive intermediate, 4-(dimethylamino)-1-oxa-3-azabutatrienium chloride (**24**), which reacts with DMF to give the Gold salt (**25**) in 86% yield (eq 9).[27] Similarly, when bis(4-chlorophenyl)chlorocarbenium hexachloroantimonate (**26**) is refluxed with KOCN in 1,2-dichloroethane, and the intermediate 1-oxa-3-azabutatrienium salt (**27**) is treated with 4,4´-dichlorobenzophenone, tetrakis(4-chlorophenyl)-2-azaallenium hexachloroantimonate (**28**) is obtained in 67% yield (eq 10).[28]

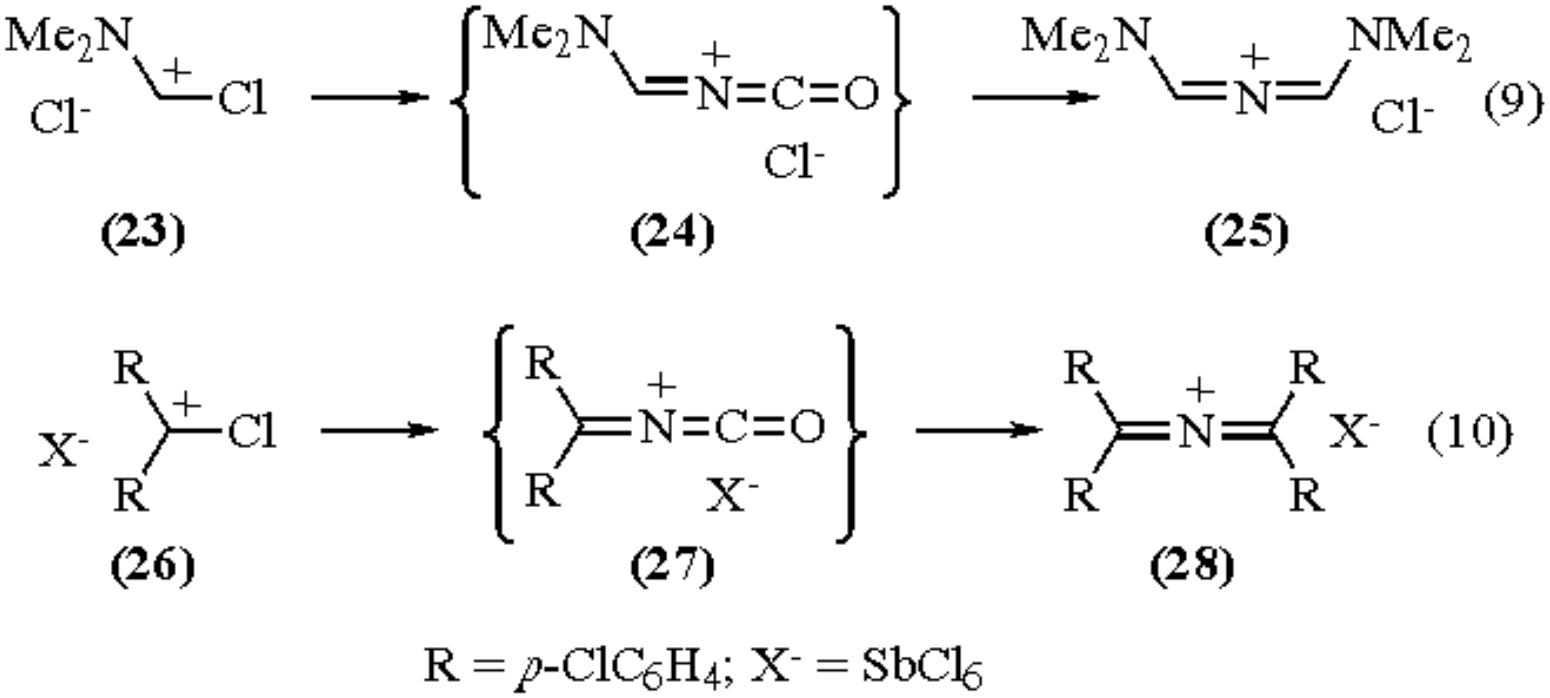

Reaction with Amines.

When 1 equiv of NaOCN or KOCN is added to an ice-cold solution of dilute HCl or AcOH, the in situ generated (**1**) reacts with aromatic and aliphatic amines to give ureas (RNH_2 -> $RHNCONH_2$ and R_2NH -> R_2NCONH_2). With excess isocyanic acid, biuret (R_2NCONH_2 -> $R_2NCONHCONH_2$) can also be formed.[1b] Hence, the temperature, pH, and the stoichiometry of the reagents employed should be carefully chosen.[29] More recently, 2-ureido-3,4,5-trimethoxybenzoic acid has been prepared from 2-amino-3,4,5-trimethoxybenzoic acid on >100 kg scale, with yields approaching nearly 100%.[30] Also, *N*-(2-sulfoethyl)urea ($H_2NCONHCH_2CH_2SO_3H$) has been obtained from taurine ($H_2NCH_2CH_2SO_3H$), KOCN, and HCl in 88% yield.[31a] Ureido derivatives of amines have been utilized in an efficient entry to the synthesis of cinodine antibiotics,[31b] and in a model study aimed at the synthesis of the marine hepatotoxin cylindrospermopsin.[31c]

Heterocyclic Synthesis.

The cyclization reactions of various bifunctional compounds with isocyanic acid or cyanate salts provide a general method for heterocyclic ring formation. Representative examples of these reactions are illustrated in eqs 11-18 by syntheses of 5,6-dimethoxy-4-methyl-2(1*H*)-quinazolinone from an *o*-aminoacetophenone (eq 11),[32] 4-methyl-5-pentyl-4-imidazolin-2-one from 3-bromo-2-octanone (eq 12);[33] N^3-substituted hydantoins (**30**) from chloroacetanilides (**29**) (eq 13);[34] 3-aryl-1,2,4-oxadiazol-5(4*H*)-ones (**33**) from aryl hydroxamoyl chlorides (**31**), presumably via the intermediate nitrile oxide (**32**) (eq 14);[35] 1-phenyl-3-trifluoromethyl-Δ^2-1,2,4-triazolin-5-one (**36**) from *N*-phenyltrifluorohydrazonoyl bromide (**34**), probably by [3 + 2] dipolar cycloaddition with the nitrilimine (**35**) (eq 15);[36] 7-methyl-2-phenyl-1,2,4,7-tetraazaspiro[4.5]decan-3-one (**38**) from the phenylhydrazone (**37**) (eq 16);[37] 2-morpholinothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**40**) from the carboximidoyl chloride (**39**) (eq 17);[38] and 3,3´-bis(1,2,4-oxadiazol-5(4*H*)-one) potassium salt from dichloroglyoxime (eq 18).[39] Similar reactions of (**1**) occur with azines to form bitriazoles[40] and with Schiff bases to form four- or six-membered heterocyclic structures.[41]

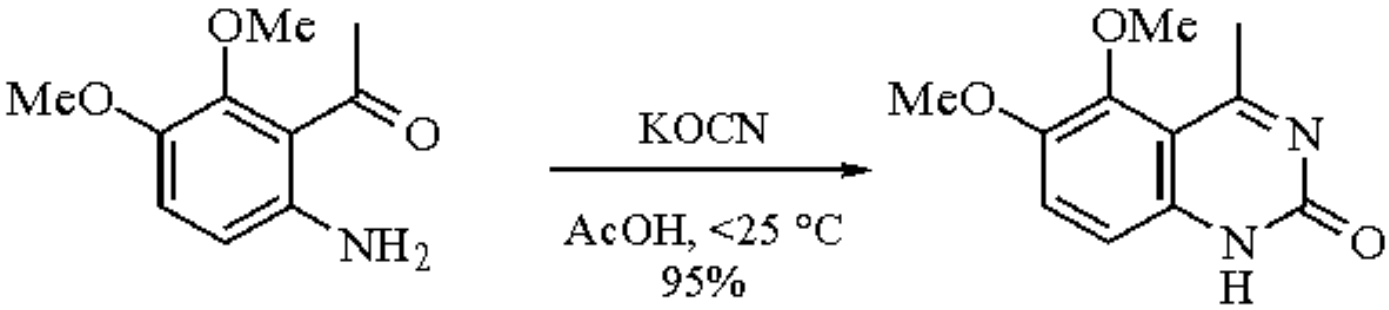

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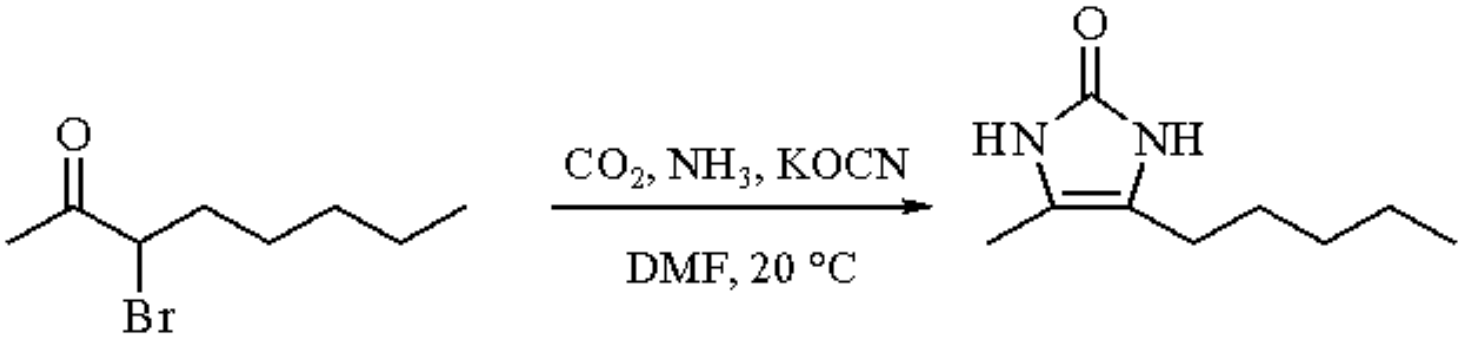

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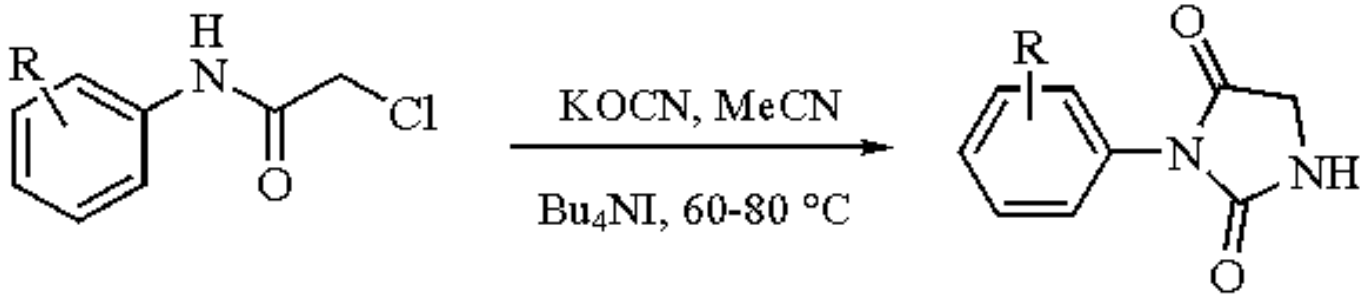

(13)

(29) (30)

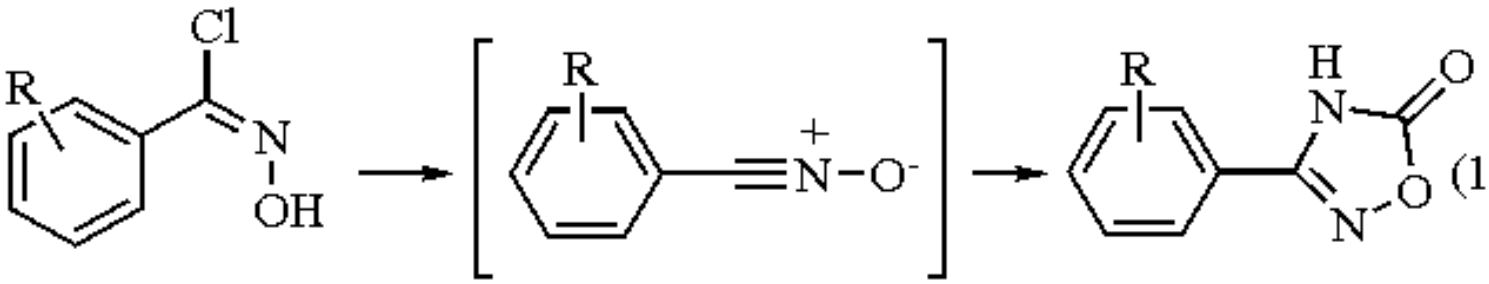

(14)

(31) (32) (33)

R = H, *o*-Me, *p*-Me, *p*-Br, *m*-NO_2, *p*-NO_2

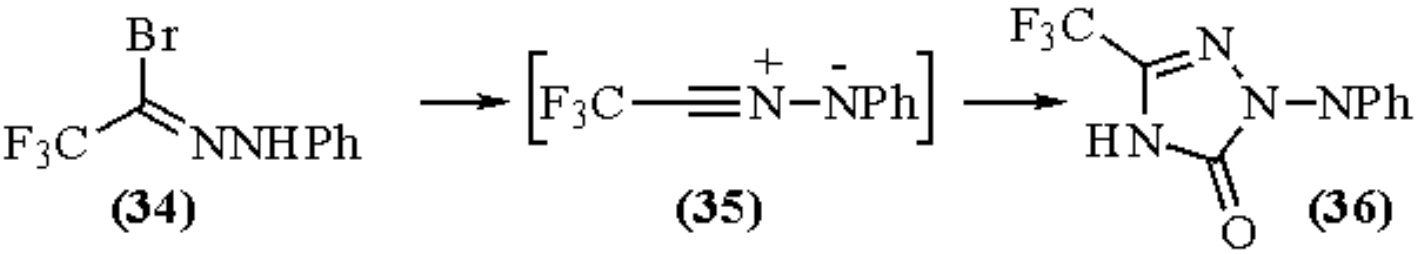

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(34) (35) (36)

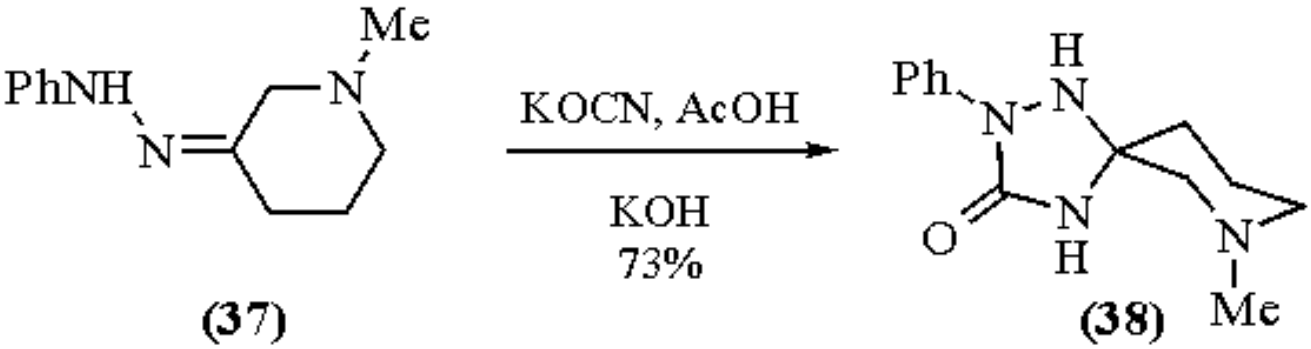

(16)

(37) (38)

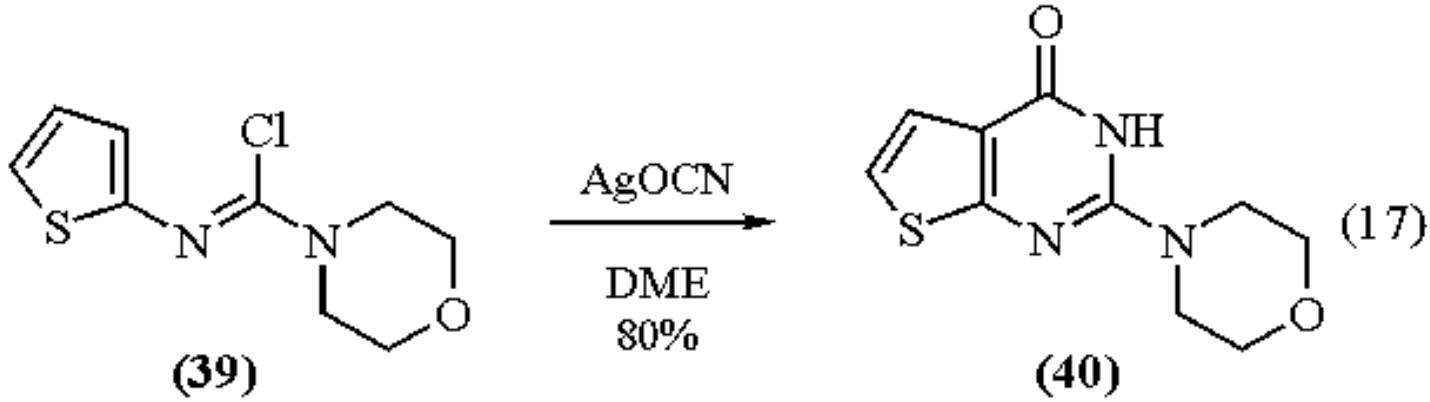

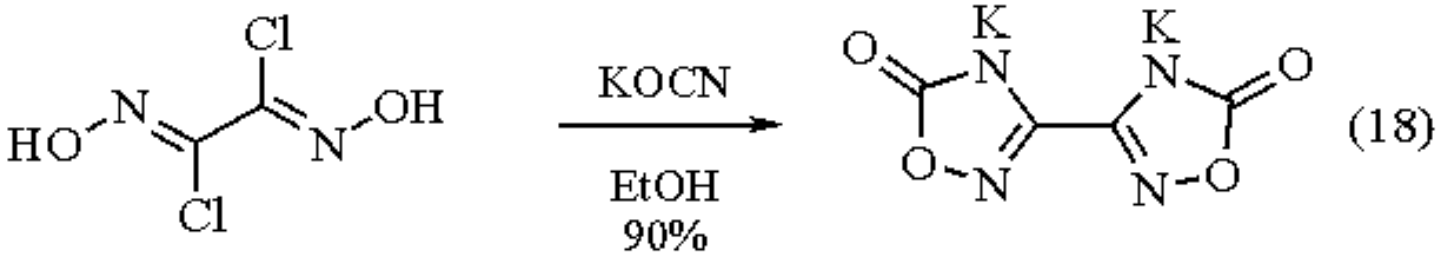

Silver(I) Catalyzed Cyclization of *O*-Propargyl and *O*-(2,3-Butadienyl) Carbamates.

Silver cyanate, while serving as a source of Ag^+, can be efficiently utilized as a catalyst for the amino cyclization of *O*-propargyl[42] and *O*-(2,3-butadienyl)[43] carbamates according to eqs 19 and 20. Success of the cyclization according to eq 19 depends upon the presence of *t*-BuOK, while in eq 20, Et_3N is necessary. When R^1 = *t*-Bu (eq 20), the *trans* isomer is the predominant product, but with R^1 = Me or Et, mixtures of *trans* and *cis* isomers are produced. The reaction works best with R^2 = Ts, and poorly with R^2 = Ac.

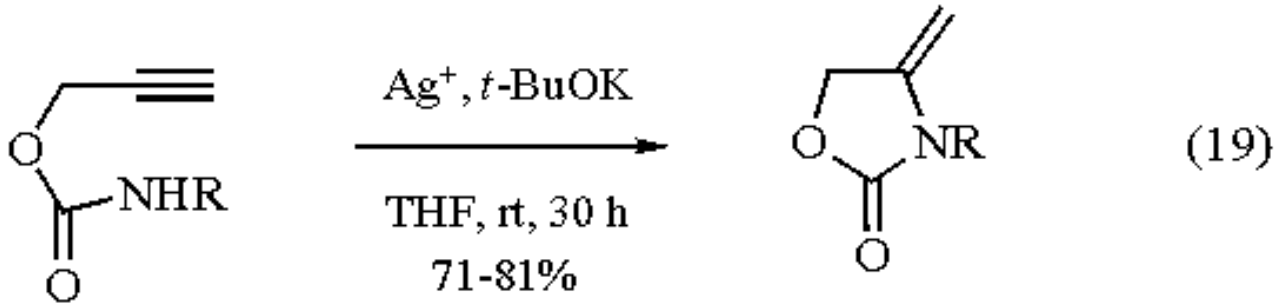

R = PhCO, Ac, (*E*)-MeCH=CH-CO-

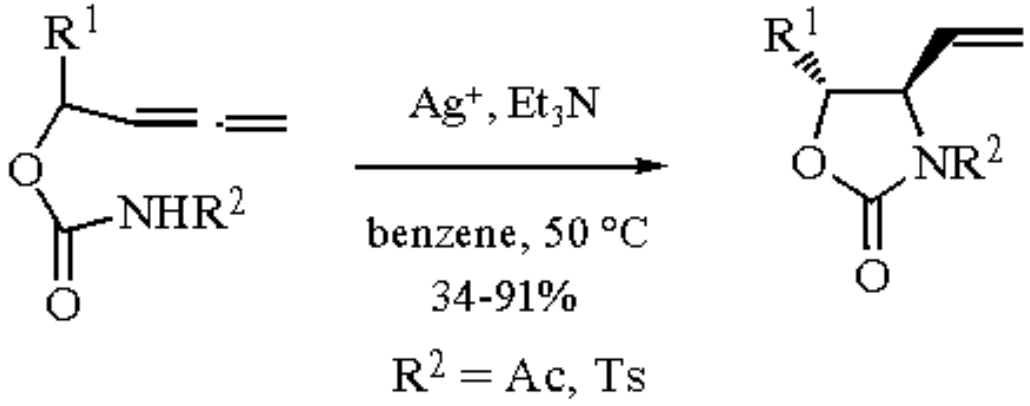

(20)

Related Reagents.

Benzenesulfonyl Isocyanate; ***Chloroacetyl Isocyanate***; ***Chlorosulfonyl Isocyanate***; ***Iodine Isocyanate***; ***Methyl Isocyanate***; ***Phenyl Isocyanate***; ***p-Toluenesulfonyl Isocyanate***; ***Trichloroacetyl Isocyanate***; ***Isocyanatotrimethylsilane***.

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Isocyanomethyllithium[1]

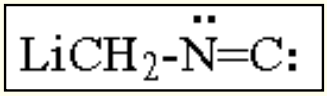

[33742-77-7] · C_2H_2LiN · Isocyanomethyllithium · (MW 46.99)

(useful for the nucleophilic introduction of the α-aminomethyl group;[1] heterocyclic synthesis[1])

Alternate Name: lithiomethyl isocyanide.

Preparative Method: can be prepared by adding 25 mL of a solution of methyl isocyanide (0.1 mol, 4 M in anhyd THF) dropwise, to a stirred solution of *n*-BuLi (0.105 mol, i.e. 66 mL of a 1.6 M in hexane) in anhyd THF (100 mL) at -70 °C under nitrogen and stirring for additional 10 min.[2]

Handling, Storage, and Precautions: unstable above -60 °C, and is best utilized immediately after its preparation. Due to its extreme toxicity, all operations involving methyl isocyanide should to be performed in a well-ventilated hood. In order to eradicate its unpleasant odor, it is essential to clean glassware with acid.

Introduction.

Isocyanomethyllithium (**1**) is generated by lithiation of an α-C-H bond of ***Methyl Isocyanide*** with ***n-Butyllithium*** in THF at temperatures below -60 °C. In contrast to the cyano group (pK_a for MeCN = 25), which can help delocalize the adjacent negative charge through resonance, the isocyano moiety behaves as an electron-withdrawing group, and activates the α-C-H bond largely through an inductive effect. Like other isocyanides, the lithiated species is probably stabilized to some extent by resonance between the iminylidene contribution (**2a**) and the zwitterionic nitrilium form (**2b**). Perhaps isocyanomethyllithium (**1**) is best regarded as a dipole-stabilized carbanion which may be represented by either form (**2a**) or (**2b**).

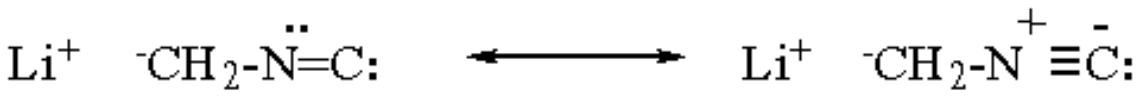

(2a) **(2b)**

The synthetic utility of (**1**) arises from to its ambivalent reactivity. As an α-metalated isocyanide, its anionic carbon can act as a nucleophile, in both addition (e.g. carbonyl compounds) and displacement reactions (e.g. alkyl halides, tosylates, epoxides, etc.), and at the same time it can display the chemistry associated with the isocyanide moiety. An outcome of this reactivity combination is the use of (**1**) as a synthon for the nucleophilic introduction of the α-

aminomethyl group as well as for heterocyclic synthesis.

Reaction with Aldehydes and Ketones.

The reagent (**1**) reacts with aldehydes and ketones (e.g. **3**) in 1:1 ratio at -70 °C initially to give a tetrahedral intermediate, 2-isocyano lithioalkoxide (**4**), which owing to its reactive O-Li bond and the electron-deficient isocyanide carbon, attains an equilibrium with 2-lithiooxazoline (**5**) (eq 1). Some synthetically useful manipulations of intermediates (**4**) and (**5**) are given below.

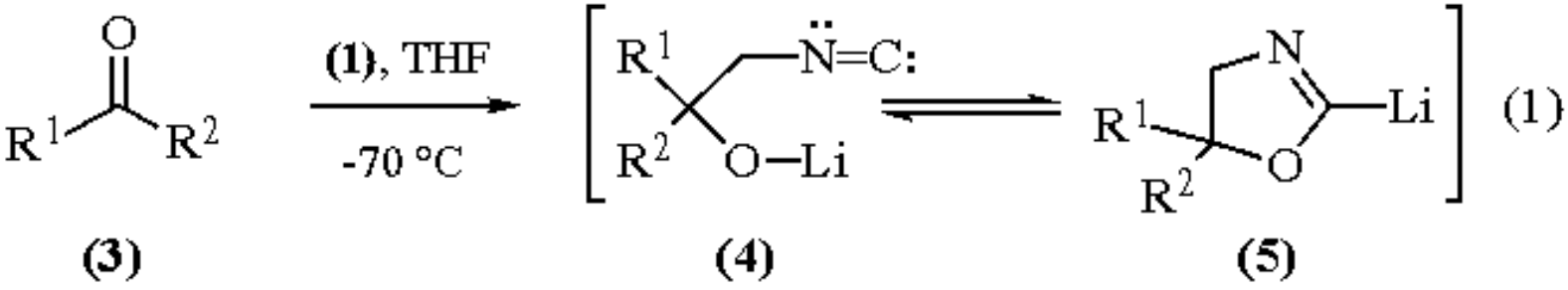

At -70 °C the equilibrium lies entirely towards (**4**), since addition of AcOH immediately after the carbonyl compound (e.g. benzaldehyde and acetophenone) gave 2-isocyano alcohols (**6**) in 75% and 80% yield respectively.[2] In the case of benzaldehyde[2] the intermediate (**4**) can also be trapped with Ac_2O or PhCOCl to give the acetate or benzoate of (**4**). In the presence of proton donors such as water at rt or, better, methanol at -70 °C, 2-oxazolines (**7**) are obtained in 60-90% yield.[3] This novel synthesis of 2-oxazolines (**7**) has been applied to a variety of aldehydes (e.g. benzaldehyde, cinnamaldehyde, 2-furaldehyde) and ketones (e.g. acetone, acetophenone, benzophenone, and cyclohexanone, etc.).[3] In some instances, 2-(hydroxyalkyl)-2-oxazolines (**8**; $R^1 = R^2 = Ph$) have been observed as byproducts in this reaction. Indeed, such a reaction has been utilized preparatively in the synthesis of a benzylisoquinoline alkaloid precursor. Oxazoline (**10**) is obtained in 61% yield, by reaction of (**1**) with 2 equiv of piperonal (**9**), followed[4] by acetylation with ***Acetic Anhydride*** and ***Pyridine*** (eq 2).

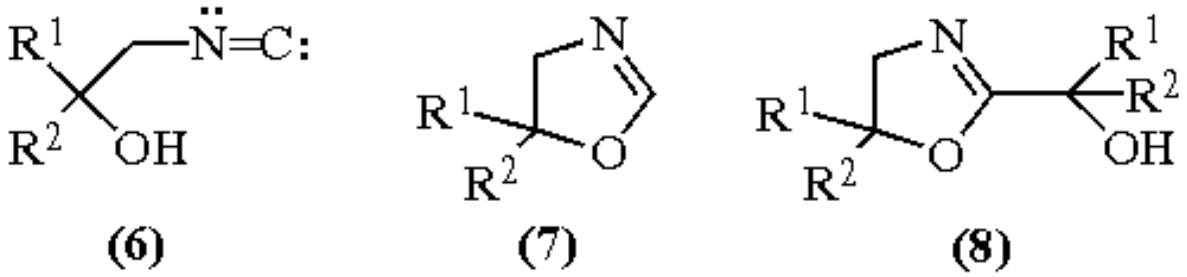

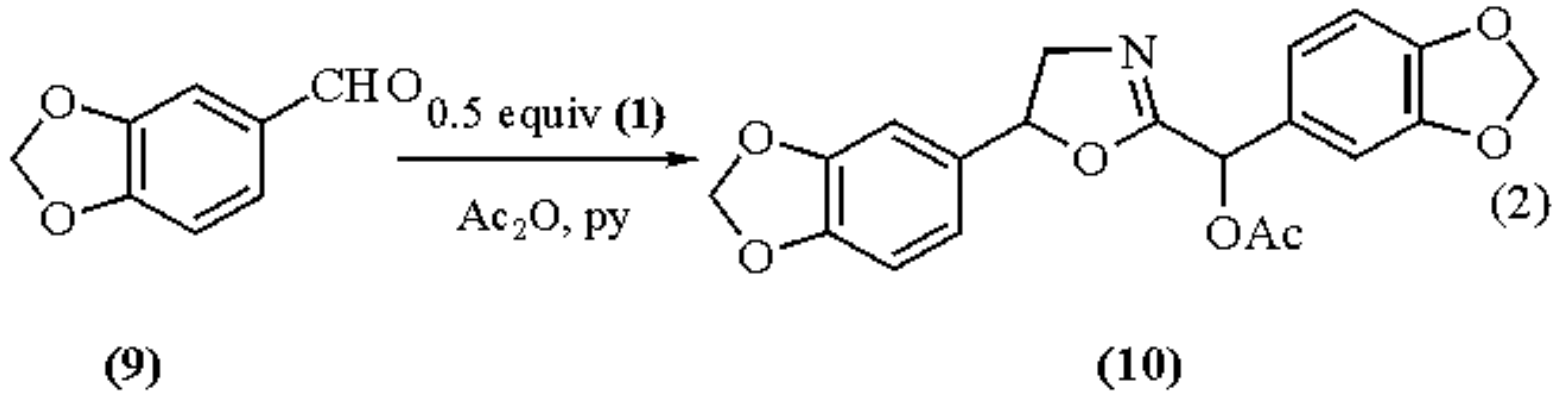

When the addition product (i.e. **4**) derived from the reaction of (**1**) with aryl or vinyl carbonyl compounds, e.g. acetophenone, benzophenone or cinnamaldehyde, was refluxed for 40 h, α-methylstyrene (65%), 1,1-diphenylethylene (40%), and 1-phenyl-1,3-butadiene (28%), were formed by LiOCN elimination.[5] This outcome is presumably a case of a rarely observed 1,3-dipolar cycloreversion, initiated by the thermal fragmentation of the 2-lithiooxazoline (**5**).

2-Oxazoline (**7**; R^1 = Me, R^2 = Ph) was obtained in 87% yield[6] when 2-isocyano alcohol (**6**; R^1 = Me, R^2 = Ph) was treated with anhydrous acid or base, thus demonstrating the greater thermodynamic stability of the 2-oxazoline.

Treatment of 2-isocyano alcohol (**6**; R^1 = H, R^2 = Ph) with ***p-Toluenesulfonyl Chloride*** followed by KOH provides a useful synthesis of β-isocyanostyrene in 65% yield.[6]

2-Isocyano alcohol (**6**) or the 2-oxazoline (**7**) derived from cyclohexanone (eq 3) was converted with methanolic HCl to β-amino alcohol hydrochloride (**11**) in 63% yield; further treatment with aqueous ***Sodium Nitrite*** for 24 h at rt gave cycloheptanone in 71% yield (eq 3). This reaction sequence demonstrates the utility of (**1**) for the addition of an aminomethyl group to a carbonyl compound,[7] and as an application of the Tiffeneau-Demjanov ring expansion reaction. Likewise, bicyclo[3.3.3]undeca-2,6-dione (**14**), a precursor for the synthesis of the bridgehead alkene tricyclo[3.3.3.$0^{2,6}$]undec-2(6)-ene (**15**), was obtained[8] from bicyclo[3.2.2]nona-6,8-dione (**12**) via β-amino alcohol (**13**). For such β-amino alcohols which are sensitive to methanolic HCl, hydrolysis of (**6**) or (**7**) can be accomplished[9] under neutral (heating with aqueous MeOH) or mildly basic (MeOH in basic alumina) conditions, to give the *N*-(β-hydroxyalkyl)formamide, which is then deformylated with *p*-TsOH in dichloromethane or by warming with 2N NaOH.

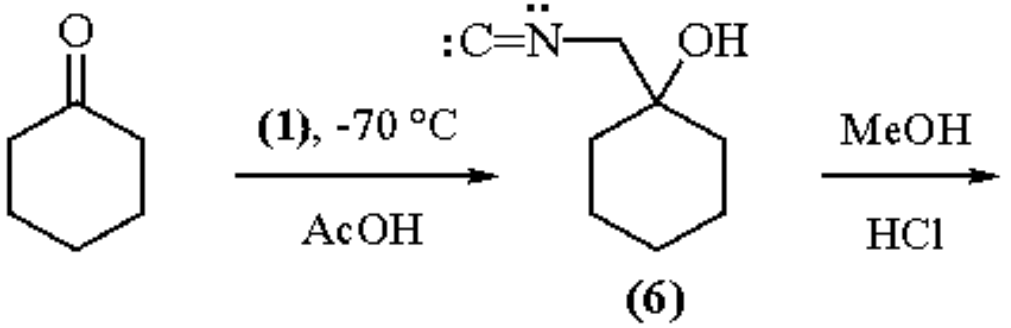

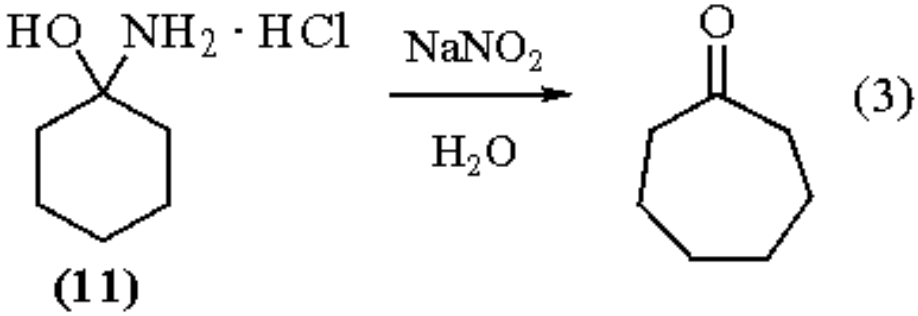

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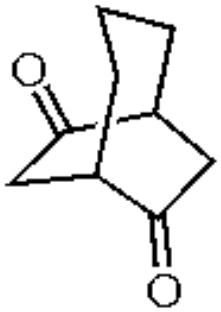

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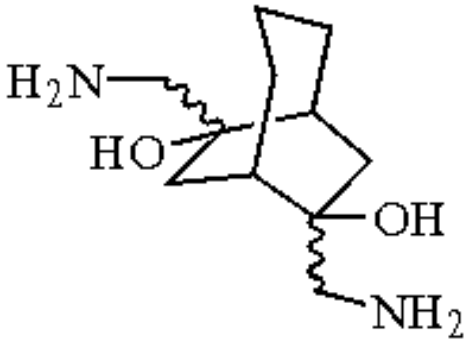

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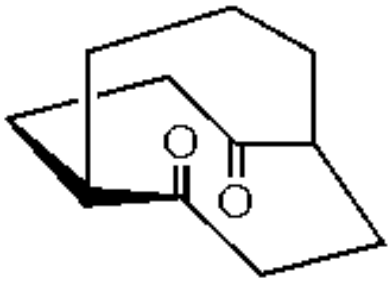

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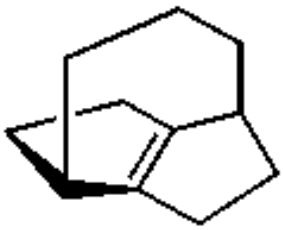

(15)

Reaction with Acylating Agents.

Addition of (**1**) to acylating agents (RCOX; X = Cl, OMe, NMe_2, etc.) gives readily enolizable α-isocyano ketones which via lithium enolate (**16**) attain equilibrium with 2-lithiooxazole (**17**) (eq 4). Protonation of (**17**) or enolate (**16**)

(via enol **18**) with glacial acetic acid gives oxazole (**19**). In contrast to esters and *N*,*N*-dialkylamides (RCOX; X = OMe, NMe_2) where one mole of (**1**) is consumed, for acid chlorides (RCOX; X = Cl), two moles of (**1**) are required, since one mole is utilized in the conversion of initially formed α-isocyano ketone to its lithium enolate (**16**). In this way, *N*,*N*-dialkylamides ($RCONMe_2$; R = $PhCH_2$, *i*-Pr, Et, Ph, *p*-MeC_6H_4) were converted to 5-substituted oxazoles (**19**) (R = $PhCH_2$, *i*-Pr, Et, Ph, *p*-MeC_6H_4) in 41, 55, 48, 67, and 85% yields, respectively.[10] With ***Benzoyl Chloride*** or ethyl benzoate, 5-phenyloxazole (**19**) (R = Ph) was obtained in 72% yield. With ***Diethyl Carbonate*** and (**1**), $CNCH_2COOEt$ was obtained in 35% yield.[11]

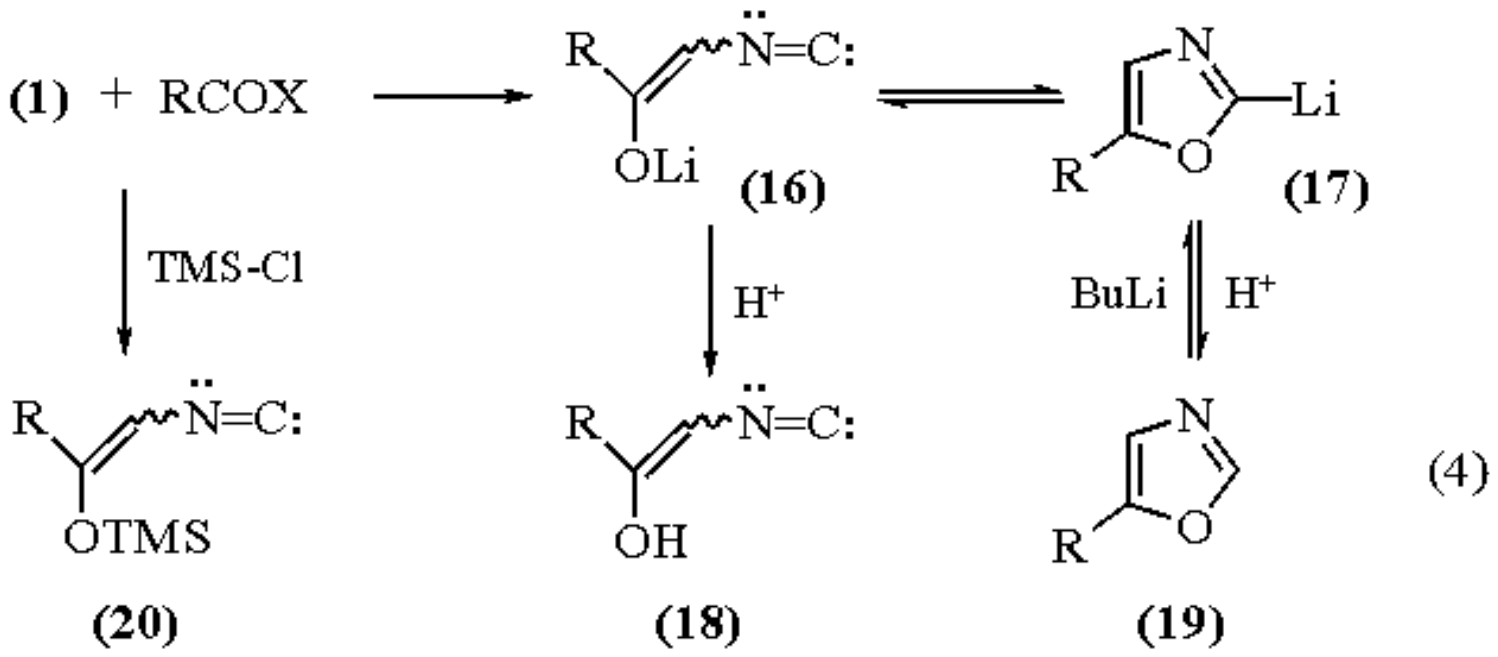

This oxazole synthesis, when applied to a δ-lactone (eq 5), initially gave complex mixtures. However, when 1.1 equiv of (**1**) was allowed to react with 0.12 M solution of a lactone (**21**) in 33% DMF-THF, oxazole adduct (**22**) was produced in ~70% yield.

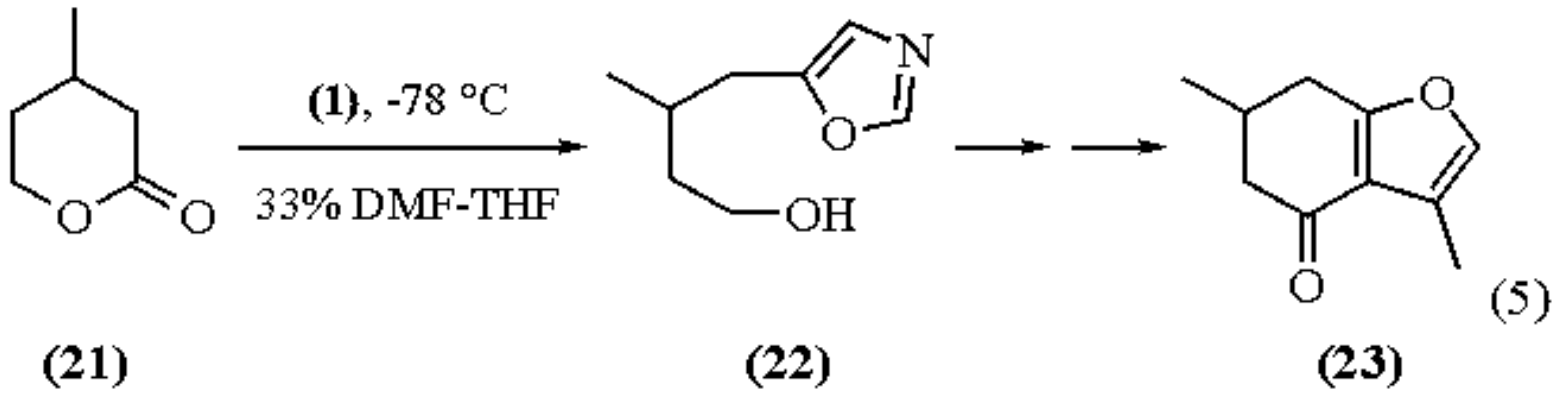

The solvent DMF seems to be critical for the successful outcome of this reaction. This strategy has been applied to the racemic synthesis of furanoterpene evodone (**23**)[12] and furanoeremophilane ligularone (**26**) (eq 6).[13] Reaction of diester (**27**) with 2 equiv of (**1**) at -78 °C gave, on protonation of intermediate (**28**), β-oxazolyl β-keto ester (**29**), an intermediate in the racemic synthesis of sesquiterpene gnididione and isognididione, in 75% yield (eq 7).[14] Likewise, oxazole (**31**), an intermediate in the synthesis of ellipticine, was obtained in 80% yield when the addition product of (**1**) and methyl 2-(3-indolyl)propionate (**30**) was quenched with glacial acetic acid (eq 8).[15]

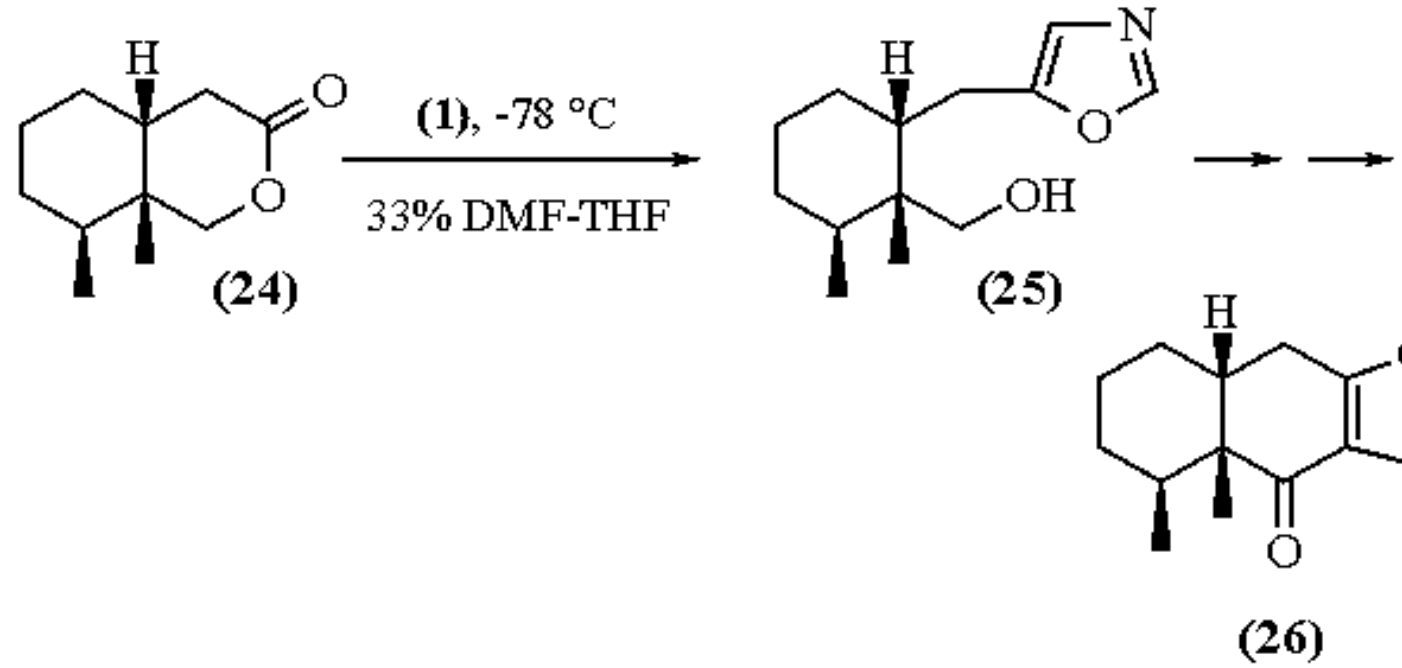
H
O
O
(24)
(1), -78 °C
33% DMF-THF
H
N
O
OH
(25)
H
O
O
(26)

(6)

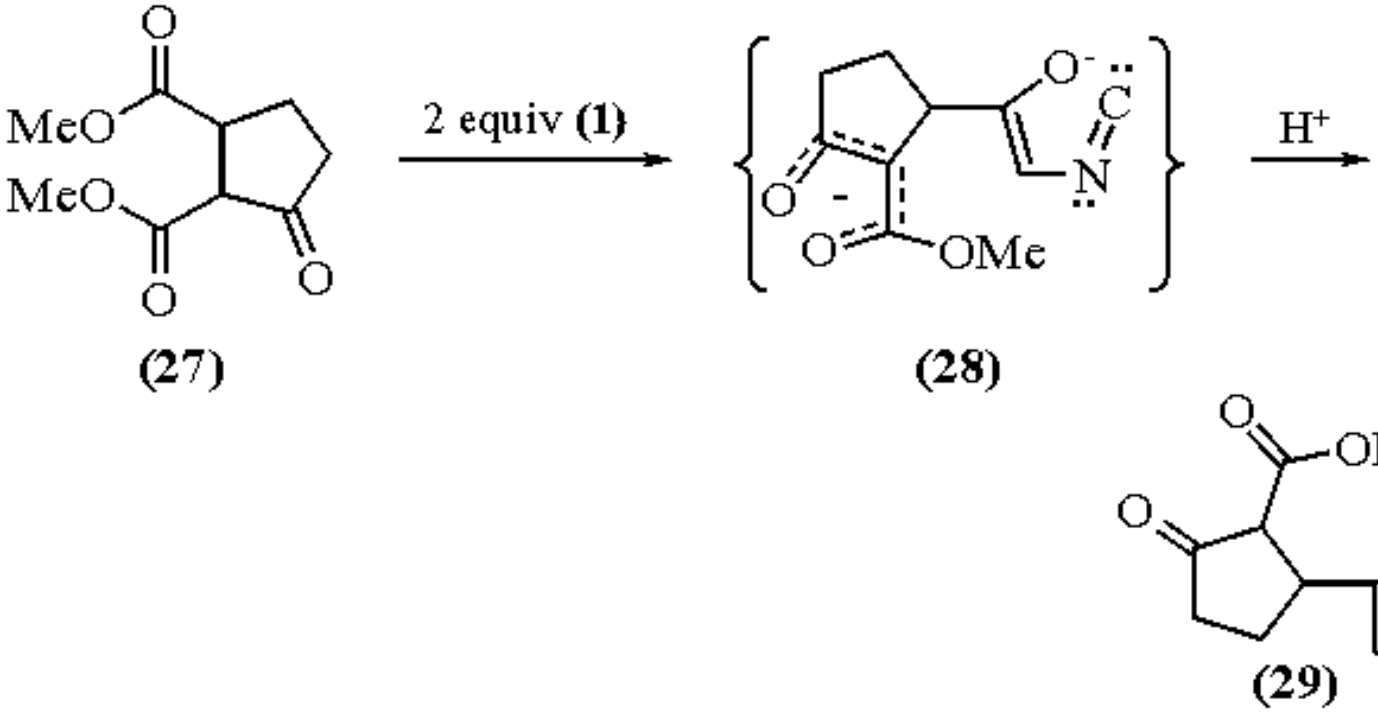
O
MeO
MeO
O
O
(27)
2 equiv (1)
O⁻
C
N
O
-
O
OMe
(28)
H⁺
O
OMe
O
O
N
(29)

(7)

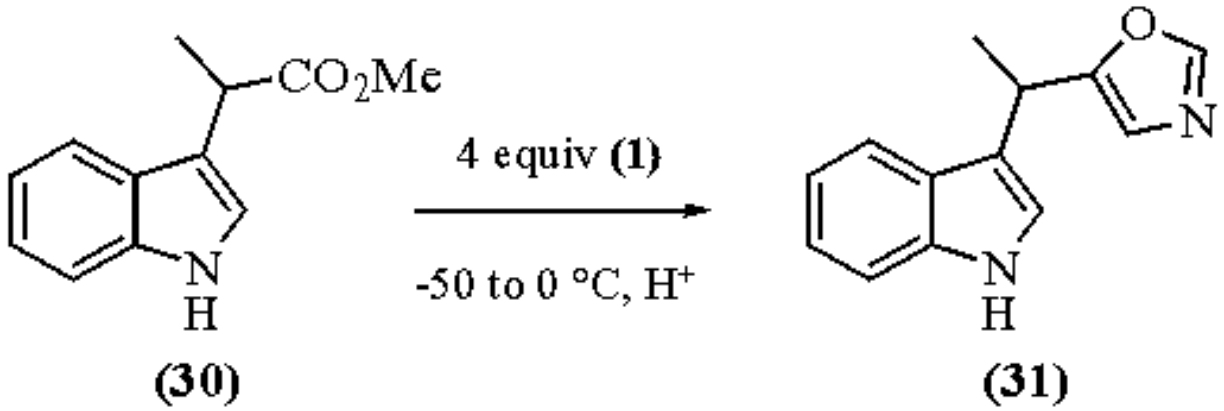

(8)

When (**1**) reacts with benzonitrile, 5-phenylimidazole (**32**) is obtained in 40% yield.[16] Likewise, reaction of (**1**) with ***Phenyl Isocyanate***, ***Phenyl Isothiocyanate***, or ***Carbon Disulfide***/***Iodomethane*** gave heterocycles (**33**), (**34**), and (**35**), respectively, in moderate yields.[6,16,17] Also, addition of (**1**) to diethyl carbonate or ***Ethyl Chloroformate***, followed by mild hydrolysis, gives glycine ethyl ester.[11]

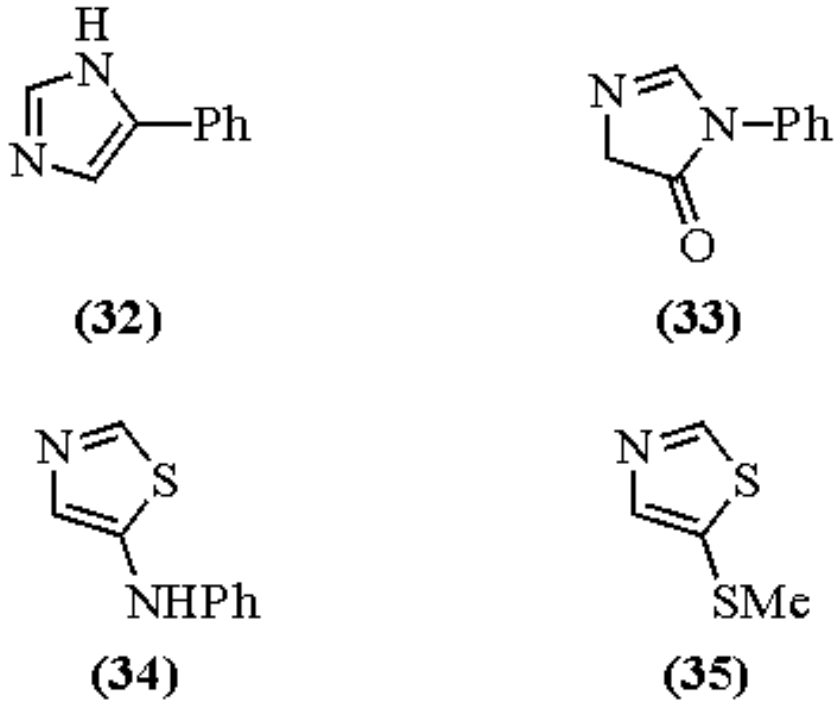

Alkylation with Alkyl Halides.

Substitution of alkyl bromides with (**1**) has been shown to proceed at -70 °C to give monoalkylated products. Thus, butyl isocyanide, 4-isocyano-1-butene, 1-isocyano-3-pentene, and 4-isocyano-1-phenyl-1-butene were obtained[18] from propyl bromide, ***Allyl Bromide***, 1-bromo-2-butene, and 3-bromo-1-phenyl-1-propene in 39, 27, 70, and 41% yields, respectively.

Alkylation of Epoxides.

Cleavage of epoxides (**36**) with (**1**) takes place from -70 to 0 °C at the less-substituted carbon atom in 42-85%

yields.[19] The intermediate 3-isocyano lithioalkoxide (**37**) on protonation gives γ-isocyano alcohols (**38**), which can be either hydrolyzed[9] to γ-amino alcohols (**39**) or cyclized by warming in MeOH or, better, with ***Copper(I) Oxide***, to 5,6-dihydro-4*H*-1,3-oxazine (**40**). In this way, a range of γ-isocyano alcohols (**38**) are readily obtained from epoxides (**36**) (yields in parenthesis) [i.e. ethylene oxide (42%), propylene oxide (78%), styrene oxide (74%), *cis*-2,3-epoxybutane (48%), 1-chloro-2,3-epoxypropane (48%), 1,1-diethoxy-2,3-epoxypropane (49%), and cyclohexene oxide (85%)].

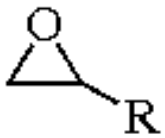

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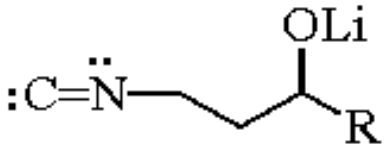

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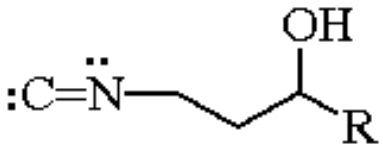

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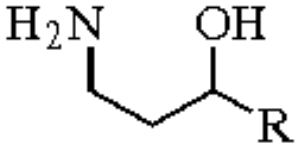

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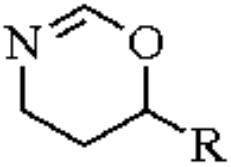

(40)

Substituted Methyl Isocyanides.

Reagent (**1**) is useful as a precursor for the synthesis of isocyanomethyl *p*-tolyl sulfone[20] and (trimethylsilyl)methyl isocyanide.[6]

Related Reagents.

N-(Diphenylmethylene)methanamine; ***N-t-Butoxycarbonyl-N-methylaminomethyllithium***; ***N´-t-Butyl-N,N-dimethylformamidine***; ***Dimethylaminomethyllithium***; ***Methyl Isocyanide***; ***Nitromethane***; ***N-Nitrosodimethylamine***; ***p-Tolylsulfonylmethyl Isocyanide***.

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19. Schöllkopf, U.; Jentsch, R.; Madawinata, K.; Harms, R. *LA* **1976**, 2105. Schöllkopf, U.; Jentsch, R. *AG(E)* **1973**, *12*, 323.
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Isocyanatotrimethylsilane

$Me_3SiN{=}C{=}O$

[1118-01-1] · C_4H_9NOSi · Isocyanatotrimethylsilane · (MW 115.23)

(preparation of primary amides from Grignard reagents;[1-3] synthesis of trifluoroacetyl isocyanate;[4] synthesis of cyclic imides[5])

Alternate Name: trimethylsilyl isocyanate.

Physical Data: colorless oil; bp 90-92 °C; fp -2 °C; *d* 0.851 g cm^{-3}.

Solubility: sol ethers, *o*-dichlorobenzene, etc.

Form Supplied in: commercially available.

Preparative Method: from ***Chlorotrimethylsilane*** and silver isocyanate.[6]

Handling, Storage, and Precautions: harmful vapor; irritant; flammable liquid; moisture sensitive; use in a fume hood.

Amidation.

Grignard reagents are carboxamidated by isocyanatotrimethylsilane to afford primary amides, presumably by way of the *N*-silyl amides (eqs 1 and 2).[1-3] The use of dioxane as an additive to the ether or THF solvent eliminates the formation of silylated Grignard products.[1] Isocyanatotriphenylsilane reacts similarly with phenyllithium and phenylmagnesium bromide to give benzamide (77-80%).[7] Reaction of heterocyclic benzyllithium reagents with isothiocyanatotrimethylsilane affords primary thioamides in moderate yield (eq 2).[2] *N*-Hydroxyurea has been prepared from *O*-silylhydroxylamine and isocyanatotrimethylsilane.[4]

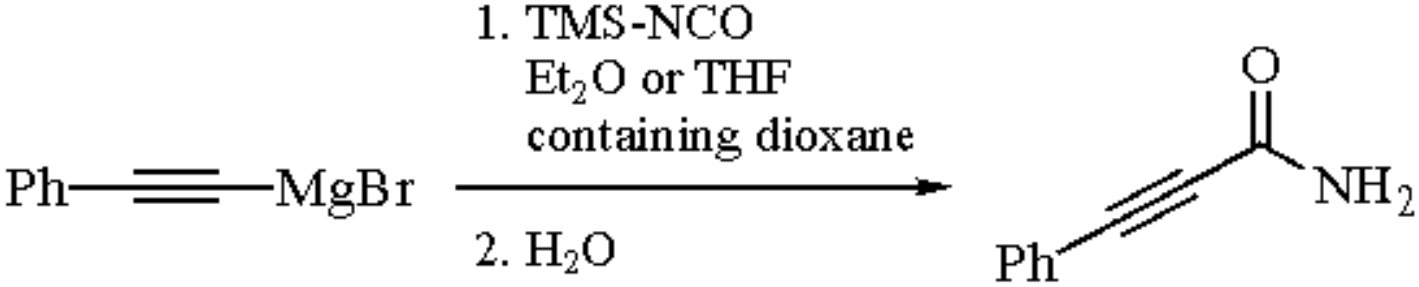

(1)

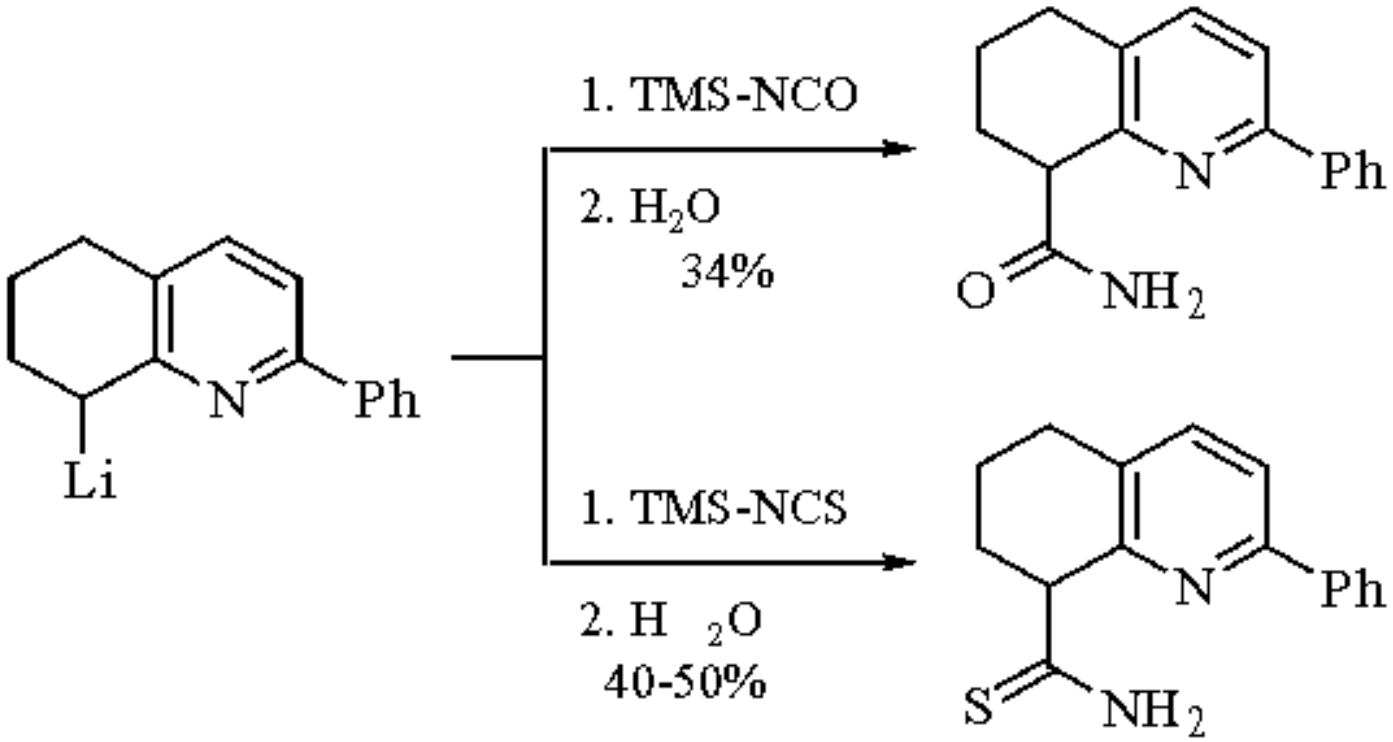

(2)

Preparation of Acyl Isocyanates.

Isocyanatotrimethylsilane has been used to convert trifluoroacetyl chloride to trifluoroacetyl isocyanate.[5] In the reaction with 1-naphthalenecarbonyl chloride, cyclization of the intermediate acyl isocyanate provides the imide through an intramolecular Friedel-Crafts reaction (eq 3).[8]

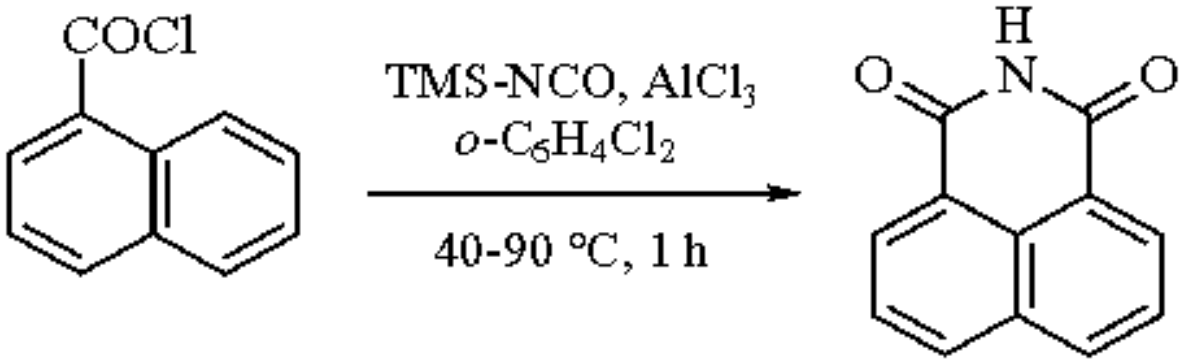

(3)

Related Reagents.

Benzenesulfonyl Isocyanate; ***3-(2-Benzyloxyacetyl)thiazolidine-2-thione***; ***Chlorosulfonyl Isocyanate***; ***Isocyanic Acid***; ***p-Toluenesulfonyl Isocyanate***; ***Trichloroacetyl Isocyanate***.

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Isopentyl Nitrite[1]

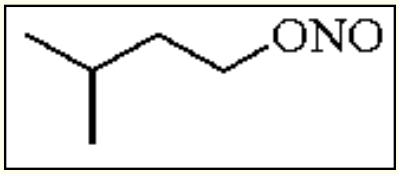

[110-46-3] · $C_5H_{11}NO_2$ · Isopentyl Nitrite · (MW 117.17)

(oxidant and nitrosating agent;[2] converts activated methylenes to oximes,[3] alkyl[4] and aryl[5] primary amines to diazo compounds and diazonium salts, hydrazines to azides,[6] 2,6-disubstituted phenols to diphenoquinones,[7] anthranilic acids to benzynes,[8] aminophenols to quinone diazides,[9] and phosphoramidates to phosphates[10])

Alternate Name: amyl nitrite.

Physical Data: bp 99 °C; *d* 0.872 g cm^{-3}.

Solubility: sol most nonhydrocarbon, organic solvents.

Form Supplied in: liquid; commercially available.

Handling, Storage, and Precautions: may be distilled prior to use. The material is a flammable, toxic liquid, which should be stored under nitrogen in a cool place. Use in a fume hood.

Nitrosation Reactions.

Isopentyl nitrite is a mild reagent for the introduction of the nitroso group. The nitrosations of aryl groups[11] and π-excessive heterocyclic systems (eq 1)[2,12] have been described. The nitrosation of alkenic carbons (eq 2)[13] is known, as is the conversion of silyl ketene acetals to α-nitroso esters (eq 3).[14] Isopentyl nitrite reacts with ureas, secondary amines, and amides to generate *N*-nitroso compounds.[15] Tertiary amines having an α-silyloxy substituent have been converted by isopentyl nitrite to *N*-nitroso compounds in which the silyloxy methyl group has been cleaved (eq 4).[16]

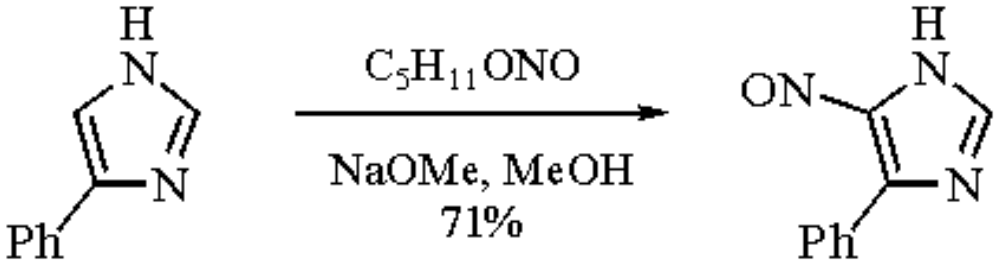

(1)

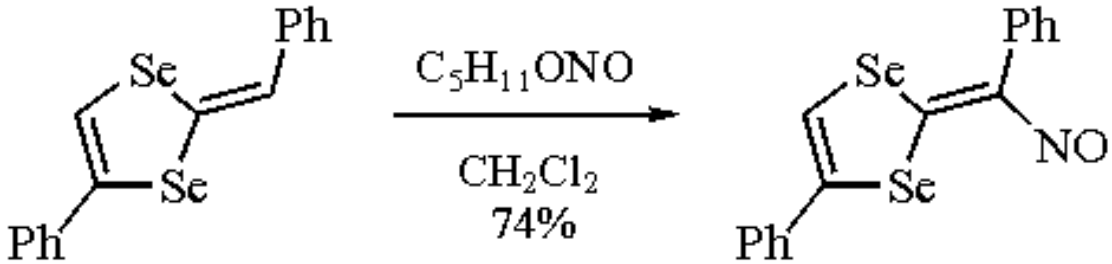

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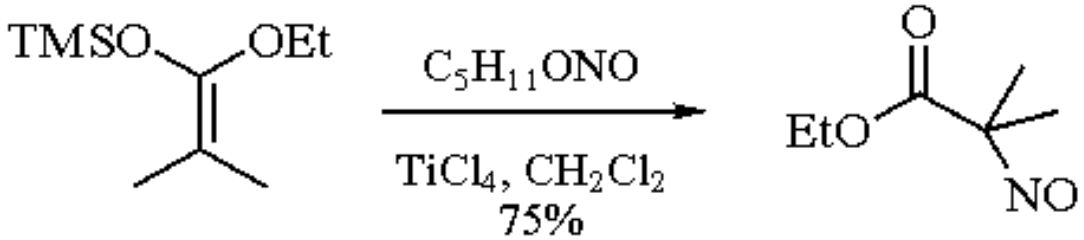

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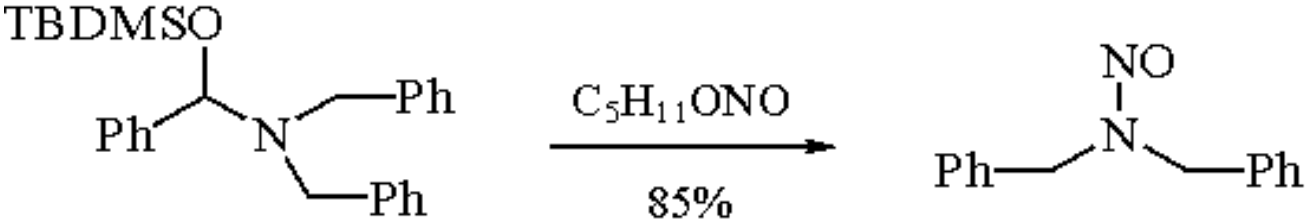

(4)

Oxime Formation.

Nitroso groups on carbons bearing α-hydrogens normally tautomerize to the oxime. The conversion of a methylene group adjacent to a carbonyl-containing functionality to an oxime group is a general reaction of isopentyl nitrite.[3,17-21] The reaction works well on acyclic[17] and cyclic systems, with ring sizes of four (eq 5),[18] five (eq 6),[19] six,[20] seven,[3] and eight atoms[21] having been described. As shown in eq 5, the *anti*-oxime is preferred to the *syn*-oxime in α-keto oximes of four-membered rings[18] and this preference has been assumed in other ring sizes.[19d,e] In situ hydrolysis of α-keto oxime compounds has given α-diketones.[20b,22] Other groups can also activate methylene and methyl groups toward oxidation with isopentyl nitrite. Methylene groups α to a nitrile functionality can form oximes with isopentyl nitrite (eq 7),[23] as can methylene or methyl groups adjacent to aromatic or heteroaromatic rings (eq 8).[24]

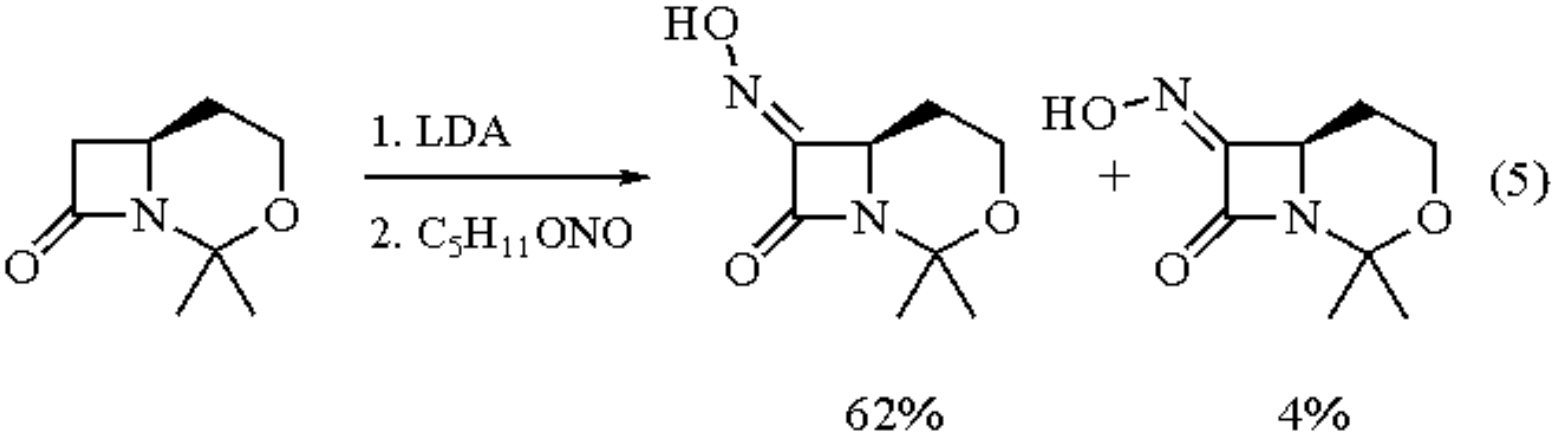

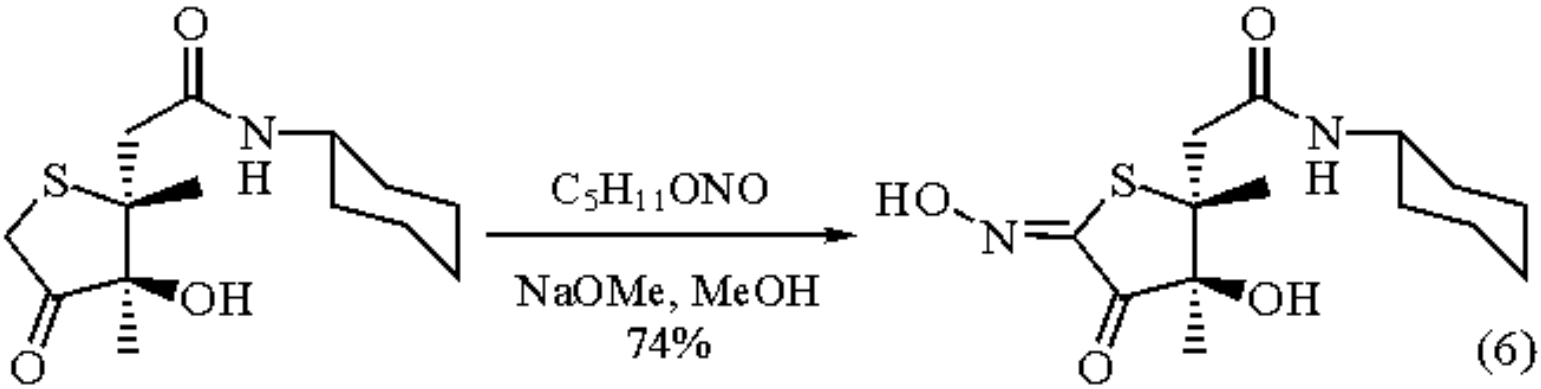

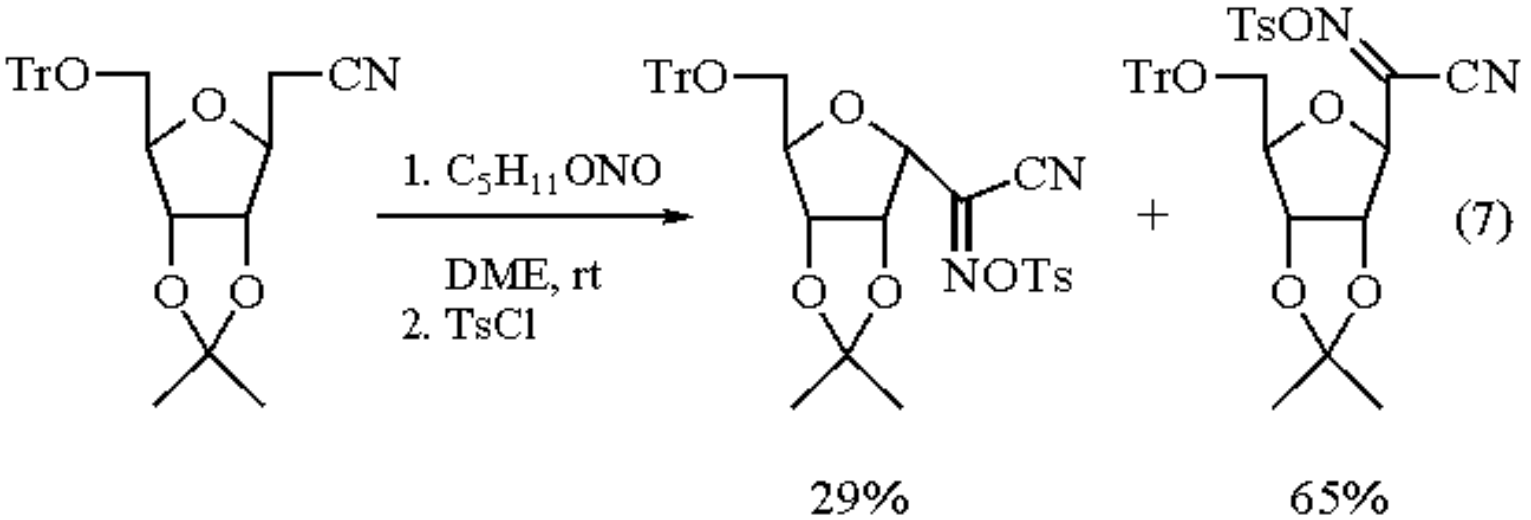

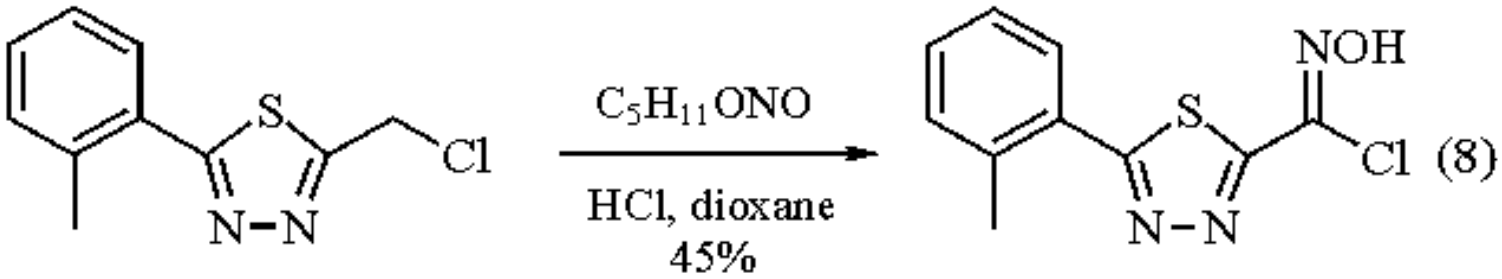

Diazo and Diazonium Compounds.

Isopentyl nitrite is a preferred reagent for the conversion of aromatic or heteroaromatic amines to diazonium salts in polar organic solvents such as ethanol,[25] isopropanol,[26] acetic acid,[27] acetonitrile,[28] DMF,[29] and acetone (eq 9).[5] In other organic solvents, isopentyl nitrite and solvent react with the aromatic or heteroaromatic amine to give substitution products. Isopentyl nitrite in THF[30] or dichloromethane[31] converts the amino group to a hydrogen while isopentyl nitrite in benzene (or other aromatic solvents) gives phenyl substitution for the amine.[32] Halogenated solvents such as diiodomethane[33] or carbon tetrachloride[34] react with isopentyl nitrite and the amine-containing substrate to give halogen substitution for the amine (eq 10). The use of dimethyl disulfide as a solvent with isopentyl nitrite gives methylthio substitution for the amine.[35]

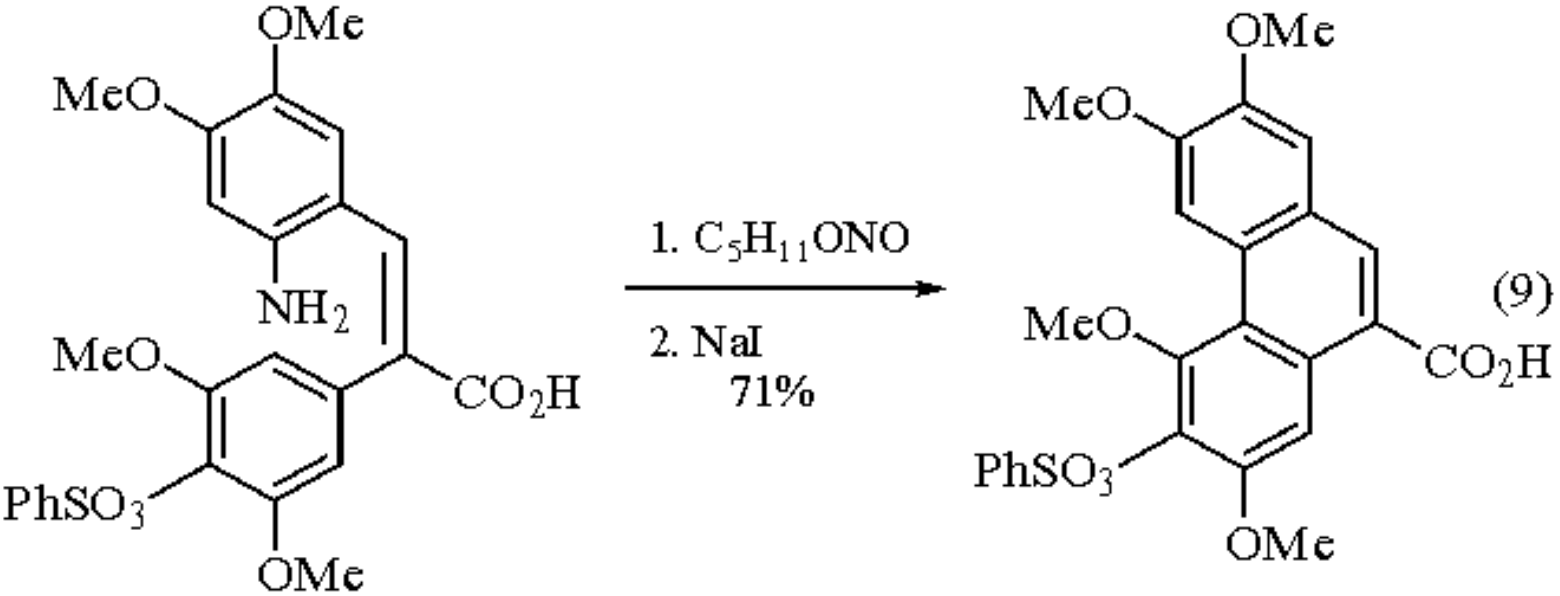

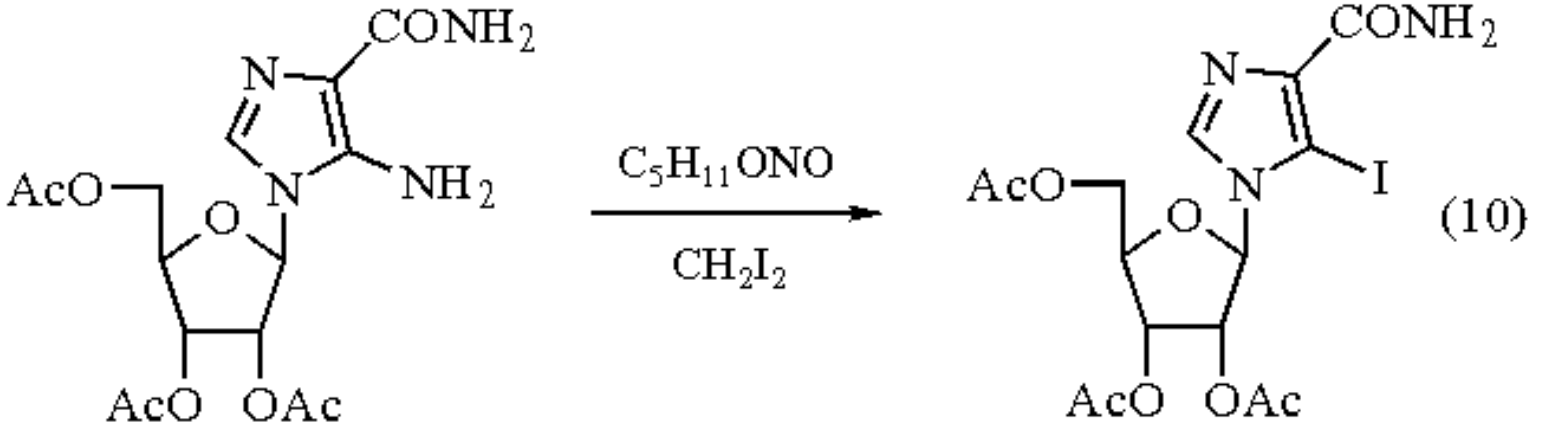

Anthranilic acid[8,36] and derivatives[37] are converted to benzyne intermediates by isopentyl nitrite in organic solvents. Solvents such as glyme,[8] dimethoxyethane,[36a] THF,[36b,37a,b] acetone,[36c,37c] and dioxane[36d,e,37d] have been employed in these reactions with good yields of benzyne cycloadducts with both 2π- and 4π-electron partners.

Aliphatic amines are also converted to alkane diazonium compounds with isopentyl nitrite in organic solvents.[38] In THF,[38a] the overall reaction observed is substitution of hydrogen for the amine as was observed with aromatic and heteroaromatic amines. In acetic acid,[38b,c] acetate substitution for the amine is observed. In chloroform, intramolecular cyclization by attack of a secondary alcohol at the amine-bearing carbon has been observed.[38d] Isopentyl nitrite reacts with amines derived from acetylsilane *O*-silyl cyanohydrins to generate α-silyl ketones (eq 11).[39]

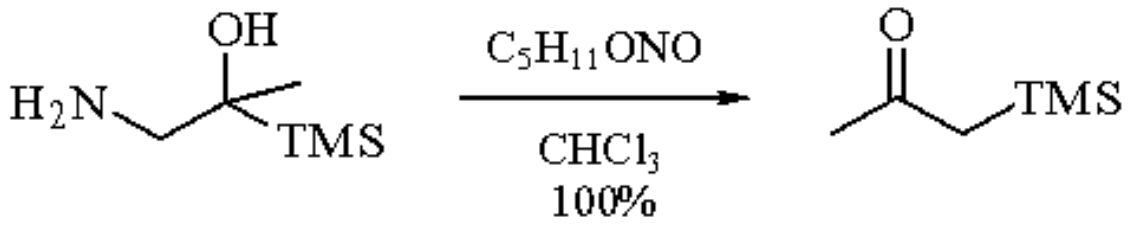

(11)

Diazo compounds are also generated from amines with isopentyl nitrite. α-Amino esters are converted to α-diazo esters with isopentyl nitrite and traces of an organic acid or water (eq 12).[4,40] Both 1,2- and 1,4-aminophenols are converted to quinone diazides with isopentyl nitrite in the presence of trace amounts of acid (eq 13).[9,41]

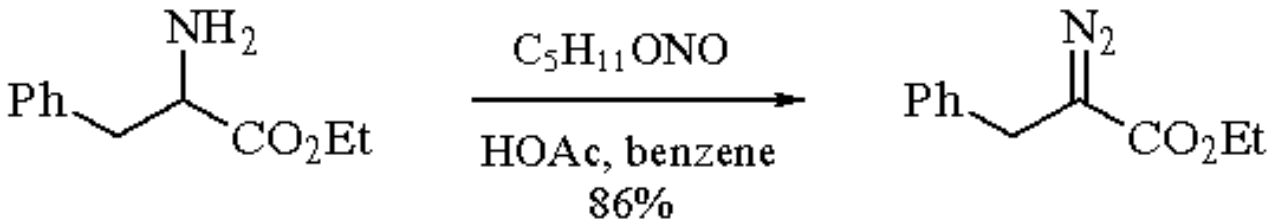

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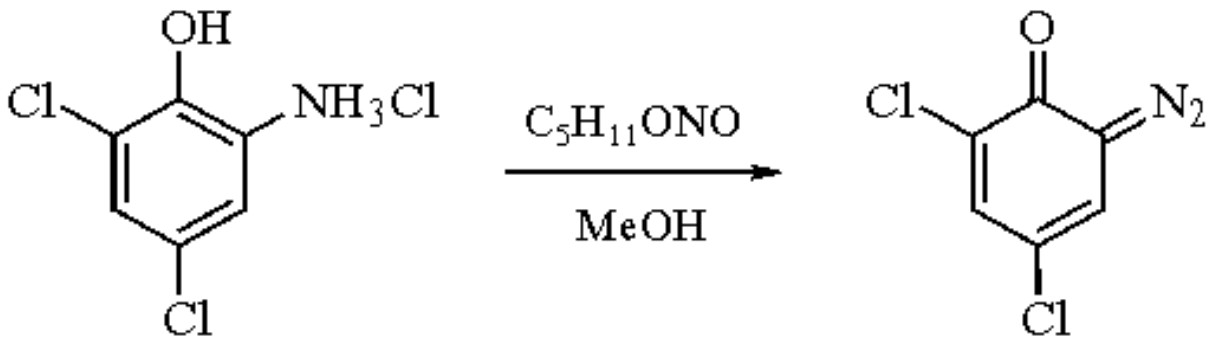

(13)

Azide Formation.

Acyl azides (eq 14),[6,42,43] which are important intermediates for the generation of peptide bonds and for the Curtius rearrangement,[6,42] are formed from acyl hydrazines with isopentyl nitrite. This transformation is rapid in the presence of a variety of different functional groups. The acetylhydrazine derived from D-glucosamine has been converted to the corresponding azido sugar with isopentyl nitrite in aqueous THF.[44]

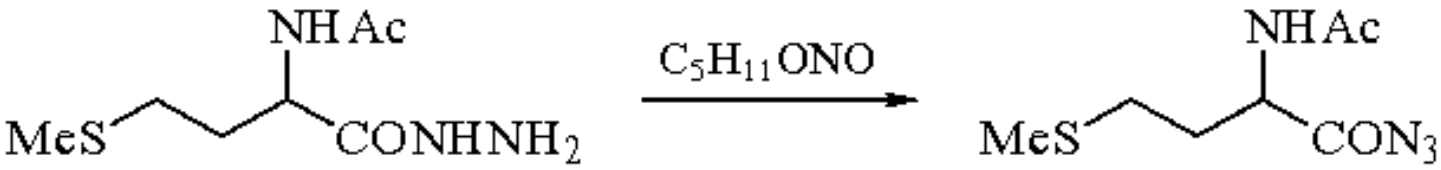

(14)

Phosphoramidate Cleavage.

The phosphoramidate group has been utilized to protect phospho monoesters.[10,45] Part of the versatility of this particular protecting group is the facile cleavage of the P-N bond with isopentyl nitrite followed by treatment with pyridine to give an isolable monophosphate pyridinium salt.[4,45]

Other Reactions.

Isopentyl nitrite is one of several reagents that has been utilized for the coupling of 2,6-disubstituted phenols to give diphenoquinones (eq 15).[7] In this particular procedure the coupling may occur via the dimerization of radical intermediates. Isopentyl nitrite has also been utilized in the hydrolysis of primary amides to carboxylic acids[46] and in the hydrolysis to aldehydes and ketones of dithioacetals, which are resistant to both basic and acidic hydrolysis (eq 16).[47]

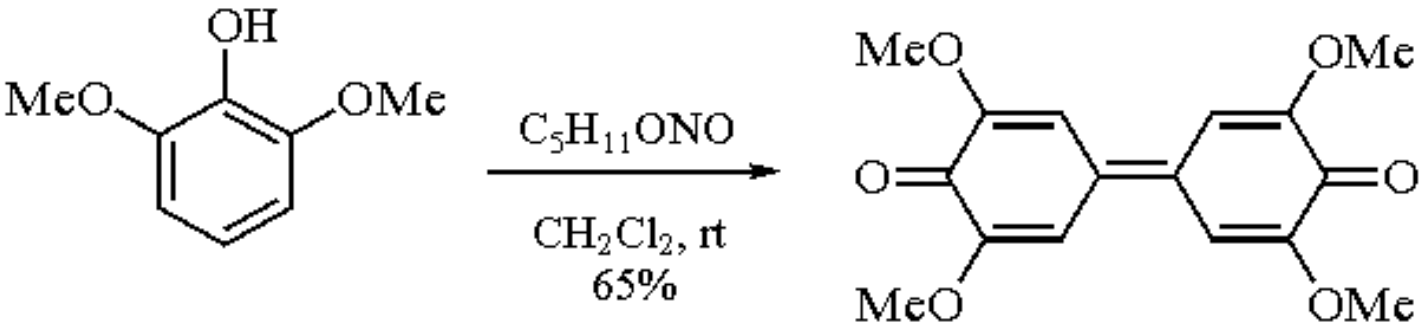

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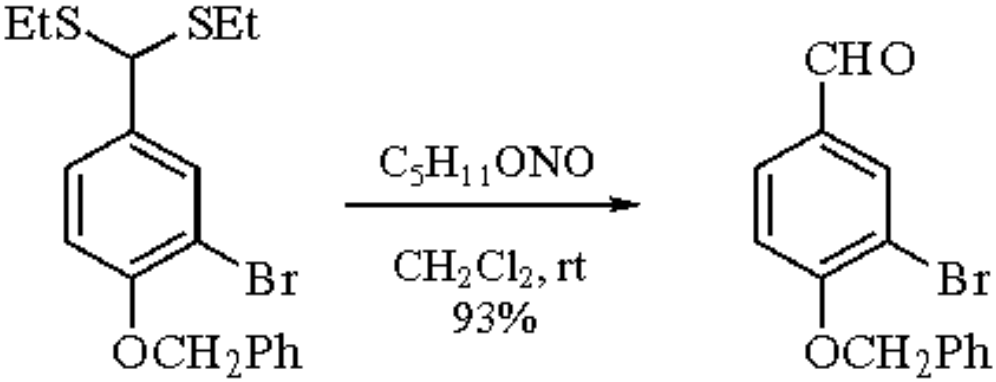

(16)

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Isoprene

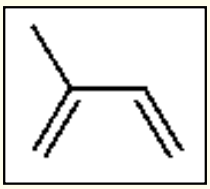

[78-79-5] · C_5H_8 · Isoprene · (MW 68.13)

(Diels-Alder diene and dienophile; natural product subunit)

Physical Data: mp -145.9 °C; bp 34.1 °C; *d* 0.6809 g cm^{-3} (20 °C).[1]

Solubility: sol most common hydrocarbons; practically insol water; forms binary and ternary azeotropes.[1]

Form Supplied in: liquid; widely available.

Preparative Methods: because of its industrial importance, many sequences have been developed suitable for the large scale synthesis of isoprene.[1] Eq 1 shows a typical example.[3]

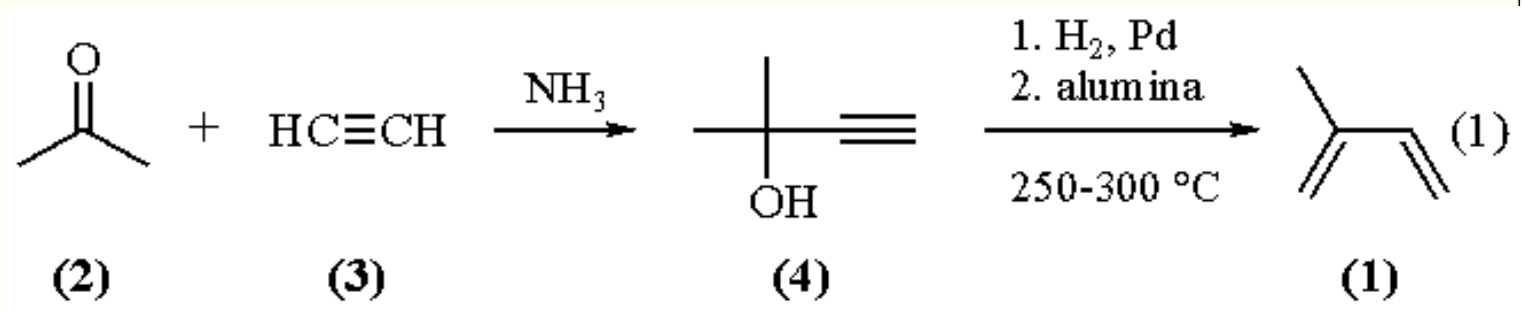

Handling, Storage, and Precautions: highly flammable; forms explosive peroxides; forms dangerous ozonide; low narcotic effect but does cause bronchial irritation at high concentrations.[2]

Diels-Alder Chemistry.

Isoprene (**1**) has been employed as a substrate in numerous Diels-Alder reactions. Several publications have considered the equilibrium (eq 2) between the cisoid isomer (*s-cis*-**1**) and the transoid isomer (*s-trans*-**1**).[4] While the difference in energy between the two isomers is insufficient to affect the Diels-Alder reactions, this equilibrium may play a role in certain polymerizations.[5] The facile Diels-Alder reaction between ***Maleic Anhydride*** and isoprene has received considerable mechanistic scrutiny.[6] Similarly, combination of (**1**) and ***Cyclopentadiene*** yields the expected 2-isopropenylbicyclo[2.2.1]hept-5-ene.[7] Reaction of isoprene (**1**) and ***Acrylic Acid*** (**5**) affords the carboxylic acid (**6**) (eq 3), a useful synthetic intermediate as is shown by its conversion into terpinolene (**7**) (eq 4).[8] Reaction of isoprene and 2-

bromoacrylic acid gives a reasonable yield (eq 5) of the α-bromo acid (**8**).[9]

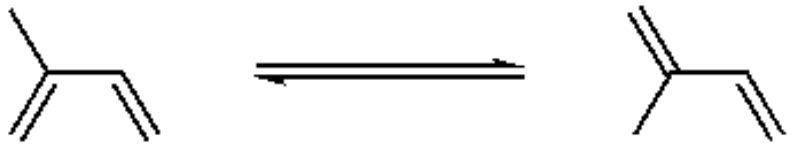

(2)

s-cis *s-trans*

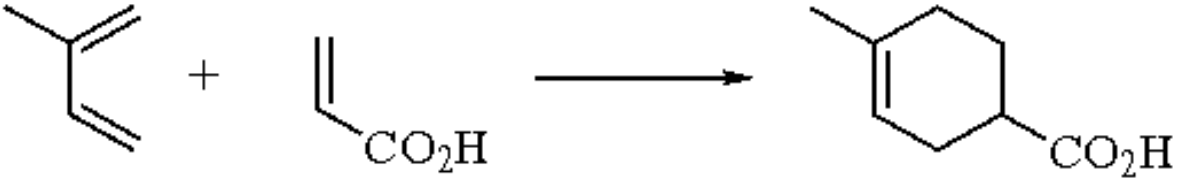

(3)

(1) **(5)** **(6)**

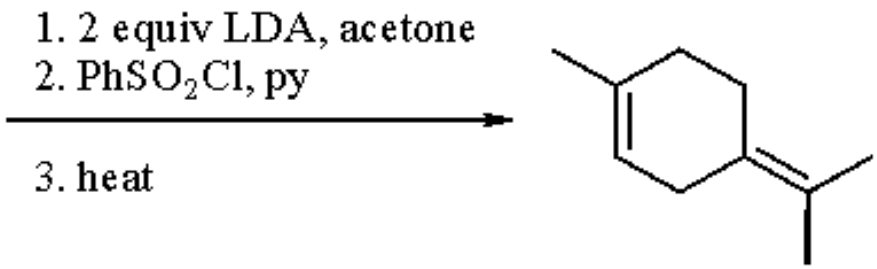

(4)

(6) **(7)**

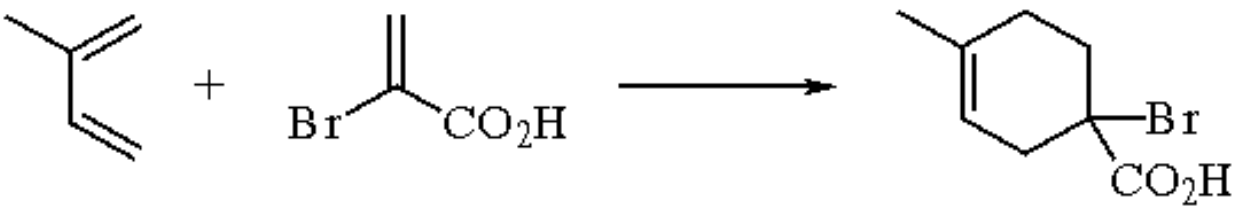

(5)

(8)

Lewis acid catalyzed reaction of (**1**) and ***Methyl Vinyl Ketone*** (**9**) exhibits a significant variation in isomer distribution of (**10**) and (**11**) (eq 6) versus the same reaction run without catalysis.[10] This effect also extends to the reaction of (**1**) and ***Acrolein***.[10] ***Tin(IV) Chloride*** mediated reaction of isoprene with isopropenyl methyl ketone (**12**) gives 1,4-dimethylcyclohex-3-enyl ketone (**13**) in good yield (eq 7).[11] This methodology can be extended to the synthesis of unusual spirocycles. Tin(IV) chloride mediated reaction of isoprene with 2-methylenecyclopentanone (eq 8) provides (**14**) and (**15**) in a ratio of 24:1. In the absence of the catalyst, the ratio of (**14**) to (**15**) fell to 2:1.[12] Applied to sesquiterpene synthesis, this approach has led to successful production of α-alaskene (**16**) and δ-acoradiene (**17**) using 3-methyl-2-methylenecyclopentanone as the common precursor.[13]

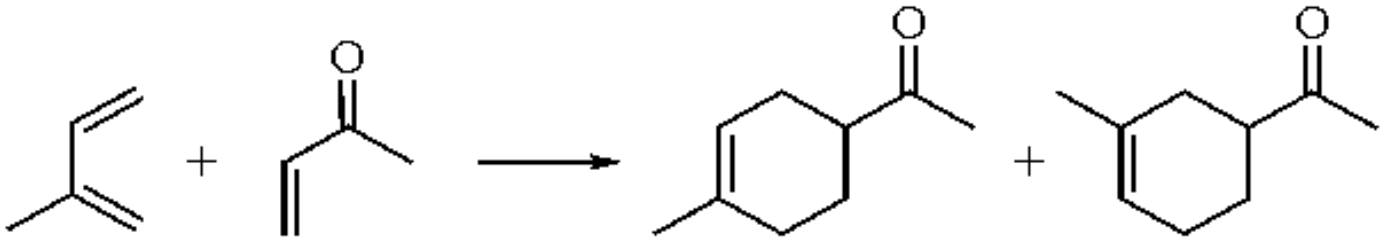

(6)

(9) **(10)** **(11)**

120 °C, no cat	71:29
25 °C, $SnCl_4 \cdot 5H_2O$	93:7

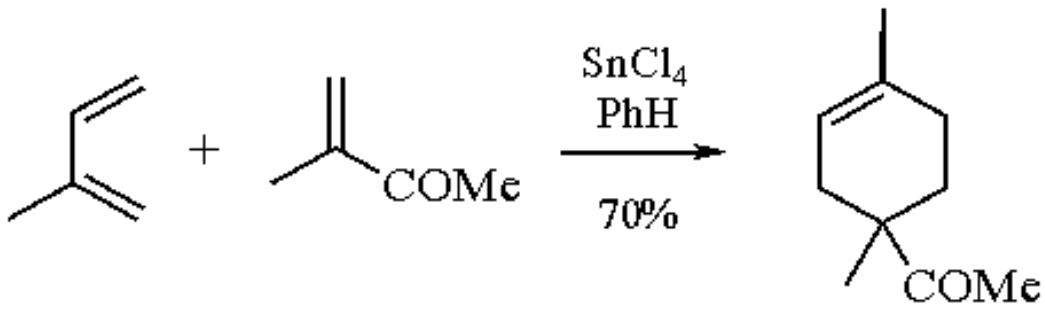

(7)

(12) **(13)**

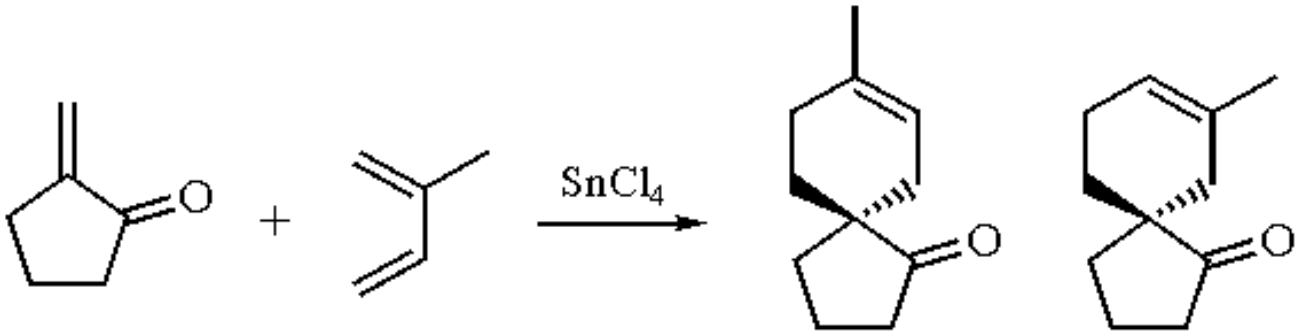

(8)

(14) **(15)**

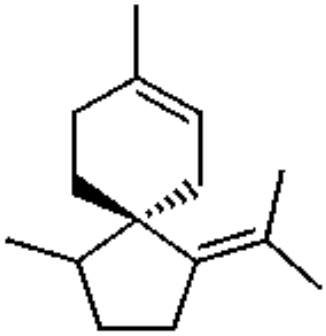

(16)

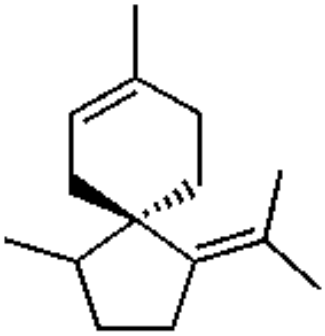

(17)

For Diels-Alder reactions that combine isoprene with a simple dienophile (**18**) in a reaction that is able to produce two regioisomers (**19**) and (**20**), the so-called 1,4-isomer (**19**) will generally predominate (eq 9).[14]

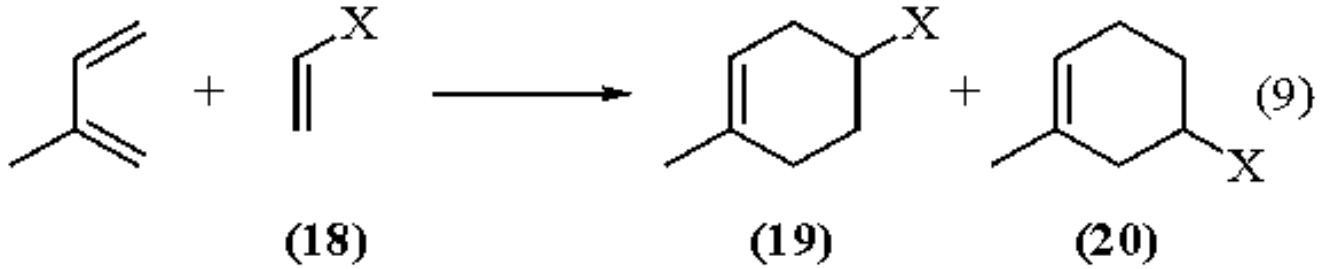

Like cyclopentadiene, isoprene may function as both a diene and a dienophile. With careful exclusion of peroxides and air, dimerization of isoprene affords four substituted cyclohexene Diels-Alder adducts (**21**), (**22**), (**23**), and (**24**) as well as two dimethylcyclooctadienes (**25**) and (**26**).[15]

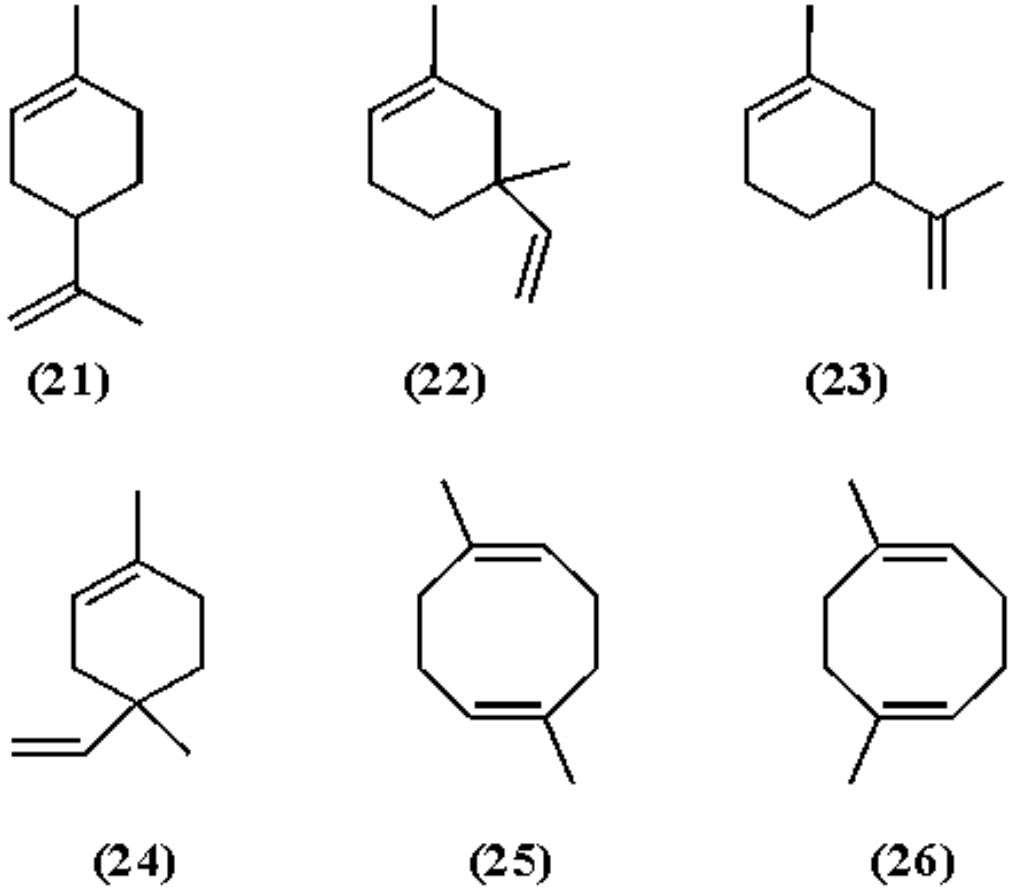

An interesting Diels-Alder variant consists of the reaction of isoprene with the vinylchromium complex (**27**) to give (**28**) and (**29**) with 92:8 regioselectivity (eq 10). Adduct (**28**) is easily transformed into (**30**).[16]

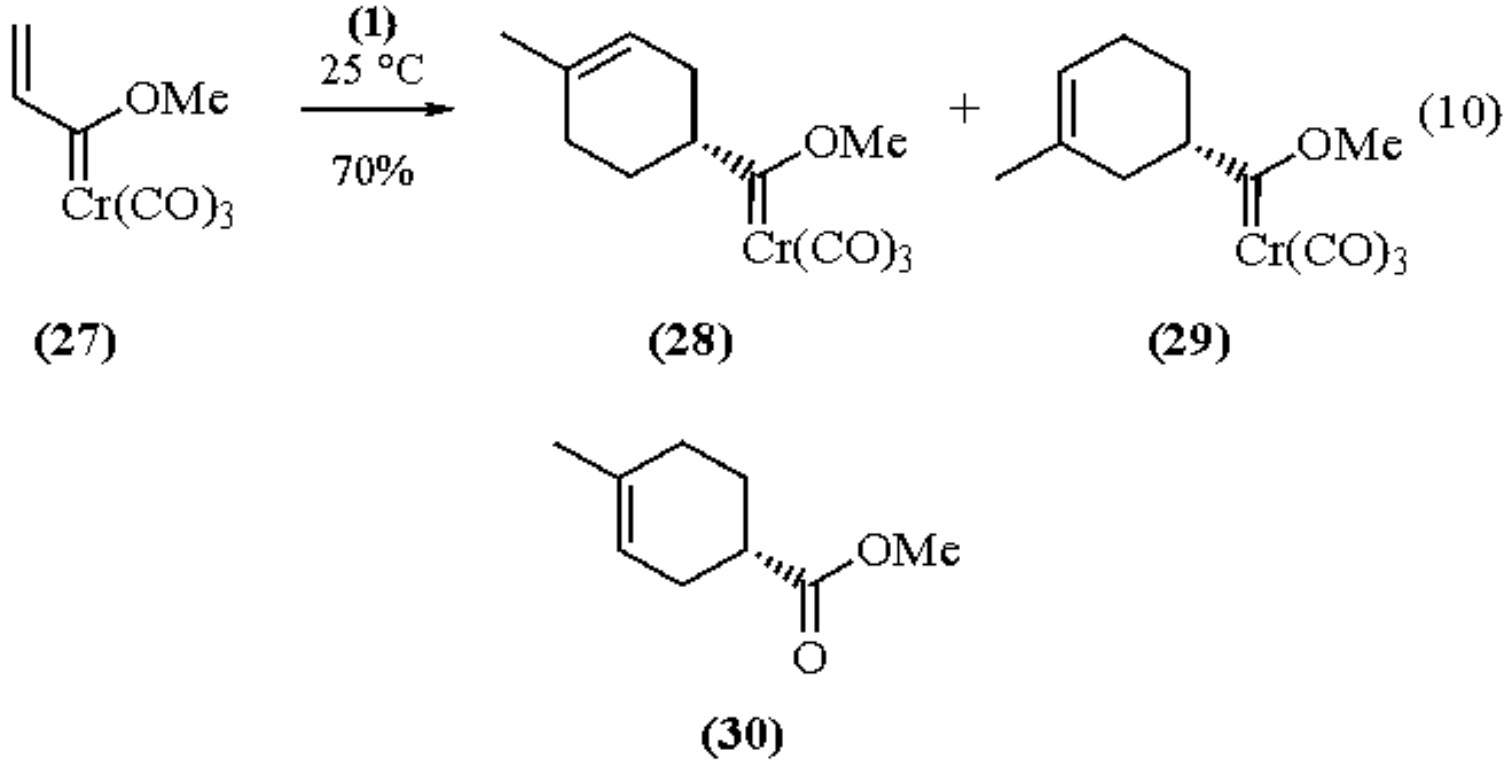

Reaction of isoprene with 2-(morpholino)acrylonitrile (**31**) gives the adducts (**32**) and (**33**) (eq 11).[17] Each of these adducts can be hydrolyzed with water in ether/THF in the presence of ***Silver(I) Nitrate*** to yield the corresponding unconjugated cyclohexenone. Combination of isoprene, the anthracene analog (**34**) of juglone, and boron triacetate provides (**35**) (eq 12) exclusively in 60% yield.[18]

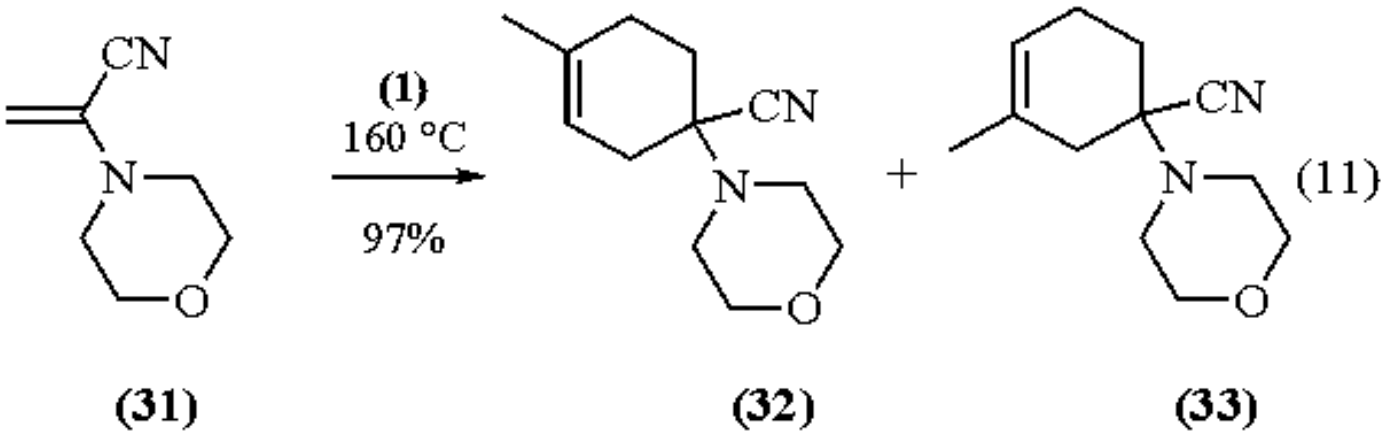

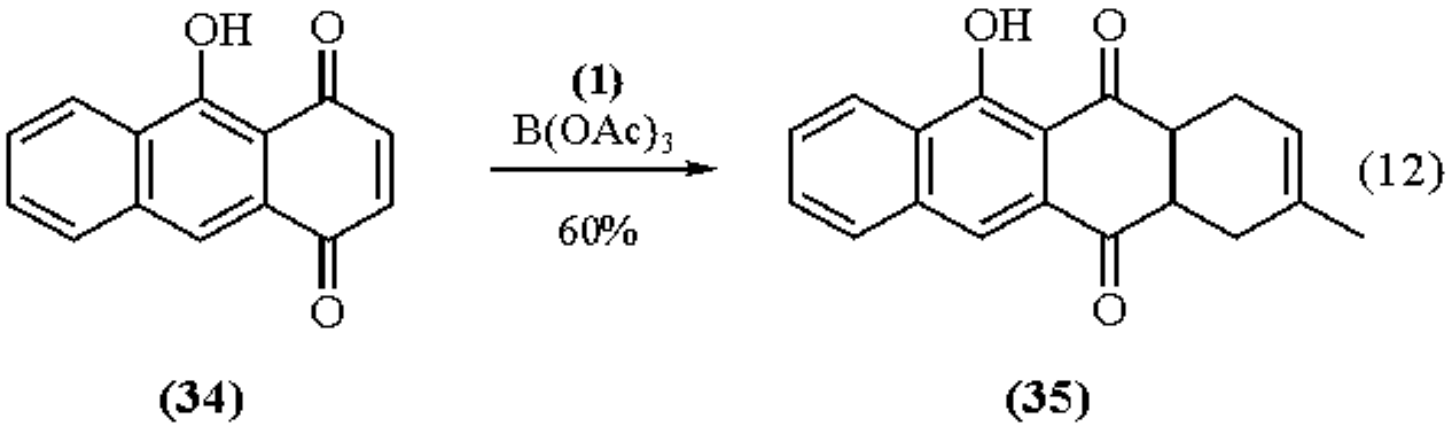

Dimerization, Oligomerization, and Polymerization.

Even in the typical Diels-Alder reaction, two byproduct cyclooctadienes, (**25**) and (**26**), are produced.[15] A variety of conditions and reagents (e.g. UV radiation,[19] sulfuric acid,[20] and Ziegler-Natta catalysts[21]) have been explored for dimerization of isoprene. The ratio of products, especially with regards to the presence of higher homologs, often varies greatly from one system to another. An efficient head-to-tail dimerization of isoprene can be achieved with certain organophosphine-ligated palladium catalysts.[22] One known reaction (eq 13) affords a reasonable yield of the *trans,trans,cis*-cyclododecatriene (**36**) as well as the linear dimer (**37**).[23] Numerous radical-mediated dimerizations of isoprene have been examined.[24] Polymerization of isoprene is also a vast topic, but the fundamental references have been reviewed.[1] Isoprene undergoes reaction with alkali metals, tritylsodium, and other organometallic reagents to produce a variety of products.[25] Thus reaction of isoprene, ***Sodium Naphthalenide***, and diethylamine gives (**38**) and (**39**) (eq 14).[26]

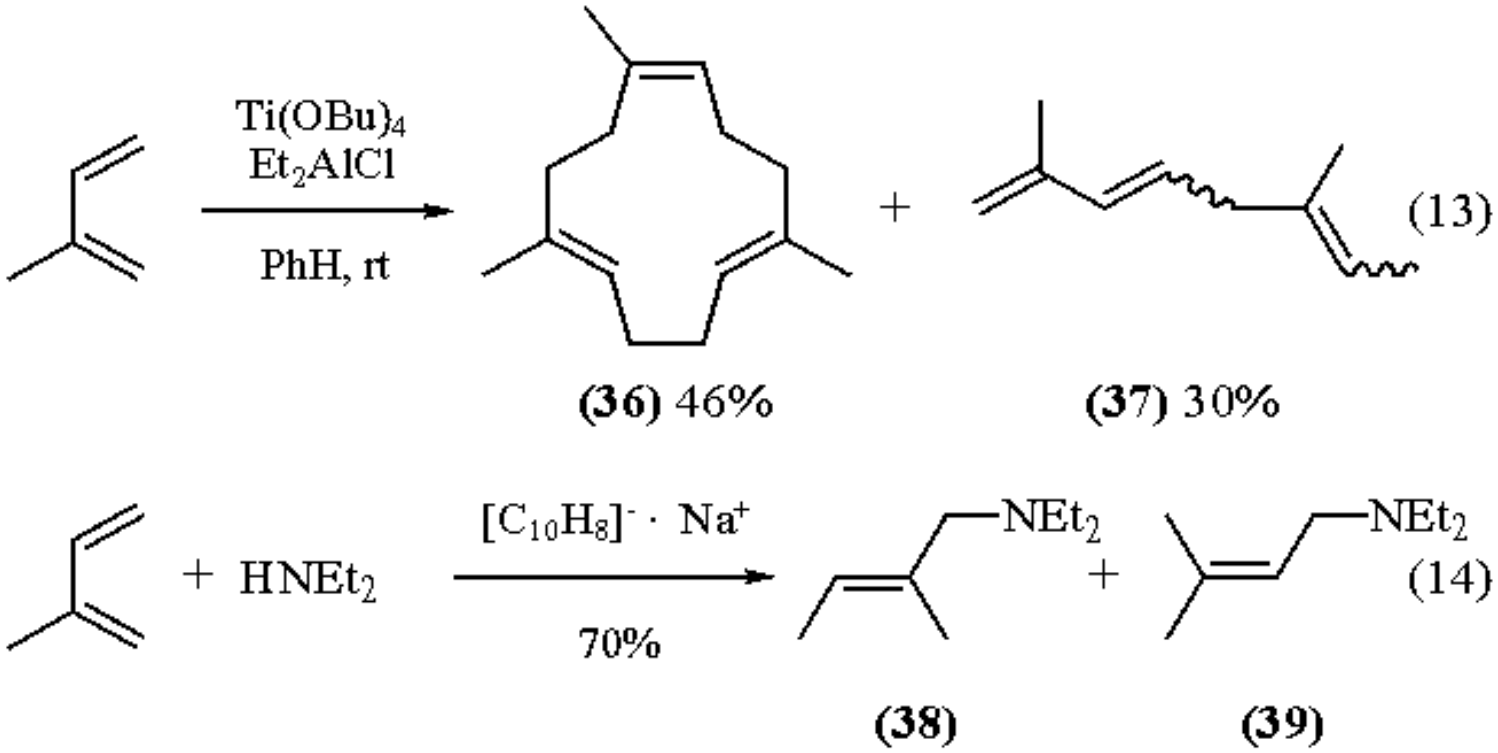

Building Block Chemistry.

Novel means exist whereby isoprene units (or their equivalents) can be attached to preexisting substrates in order to create the skeletal backbone of complex natural products. That these isoprenylation reactions[27] are often quite efficient is illustrated (eq 15) by the reaction of (**1**) with substituted phenols (**40**) to afford 2,2-dimethylchromans (**41**).[28] Epoxidation of isoprene produces a monoepoxide that has proven a useful synthetic intermediate.[29]

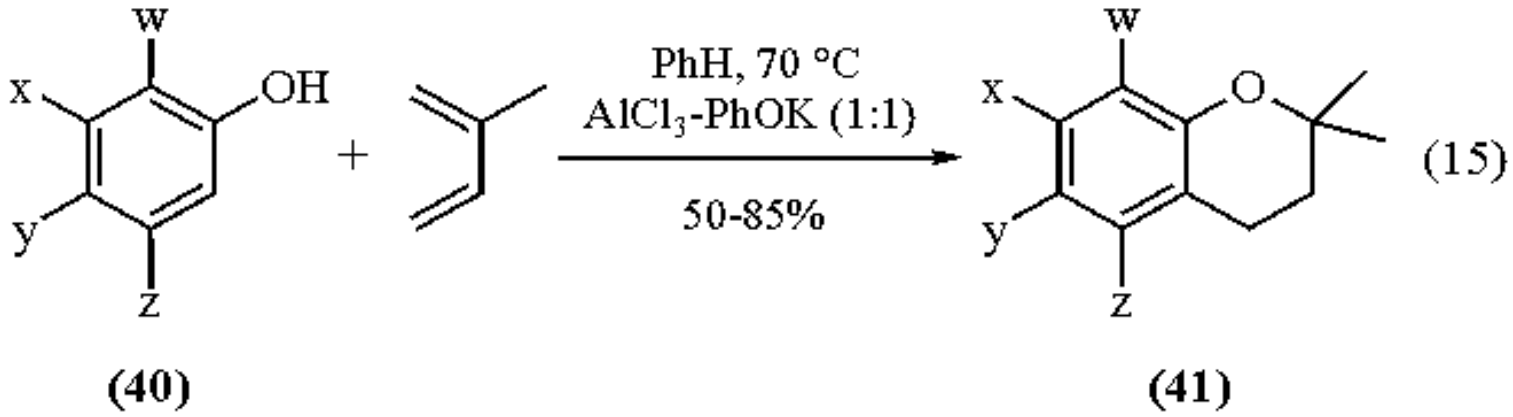

Miscellaneous Chemistry.

Isoprene reacts with dichlorophenylphosphine to afford, after hydrolysis, 3-methyl-1-phenyl-2-phospholene 1-oxide.[30] Isoprene undergoes an interesting cycloaddition with α,α´-dihalo ketones in the presence of ***Zinc/Copper Couple*** on alumina to yield cycloheptenones.[31] Halogenation of (**1**) and carbene addition to (**1**) have been reviewed.[1]

Related Reagents.

1,3-Butadiene; ***Cyclopentadiene***; ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***; ***1-Trimethylsilyloxy-1,3-butadiene***; ***2-Trimethylsilyloxy-1,3-butadiene***.

---

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Isoprene Epoxide

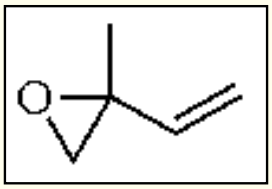

[1838-94-4] · C_5H_8O · Isoprene Epoxide · (MW 84.13)

(ambident electrophile)

Alternate Names: 2-methyl-2-vinyloxirane; 3,4-epoxy-3-methyl-1-butene.

Physical Data: bp 80 °C; *d* 0.8563 g cm^{-3} (22 °C).

Solubility: sol most organic solvents.

Form Supplied in: clear liquid.

Preparative Methods: often made by reacting ***Isoprene*** with ***N-Bromosuccinimide*** and converting the bromohydrin to the epoxide under basic conditions.[1] Few attempts to epoxidize conjugated dienes have been reported. Recently, a manganese catalyst has been employed in a method developed to epoxidize isoprene selectively in one step (eq 1).[2]

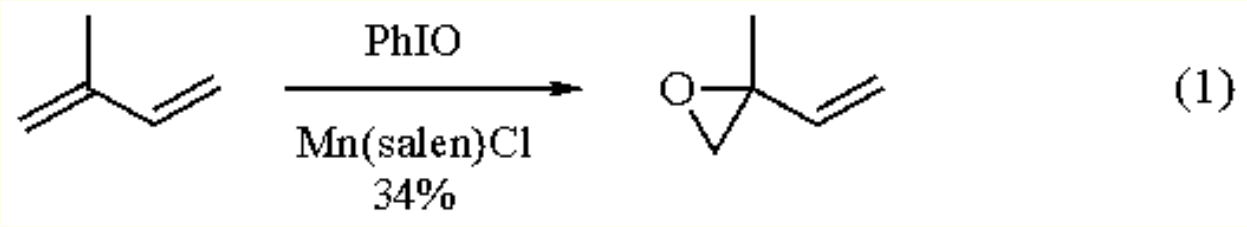

Handling, Storage, and Precautions: flammable liquid, flash point -7 °C; irritant; use in a fume hood.

Nucleophilic Opening at C-4.

Isoprene epoxide is often used as a model substrate for S_N2' reactions.[3] Organocuprates deliver carbon nucleophiles to the vinyl terminus in this reaction.[4] One drawback to this method of introducing a five-carbon synthon is usually the lack of control over the geometry of the resulting trisubstituted alkene. However, in a synthesis of vitamin K_1, the Cu^I-catalyzed reaction of a Grignard reagent afforded the (*E*)-alkene with high selectivity; a &egt;99:1 (*E*):(*Z*) mixture could be isolated after recrystallization (eq 2).[5]

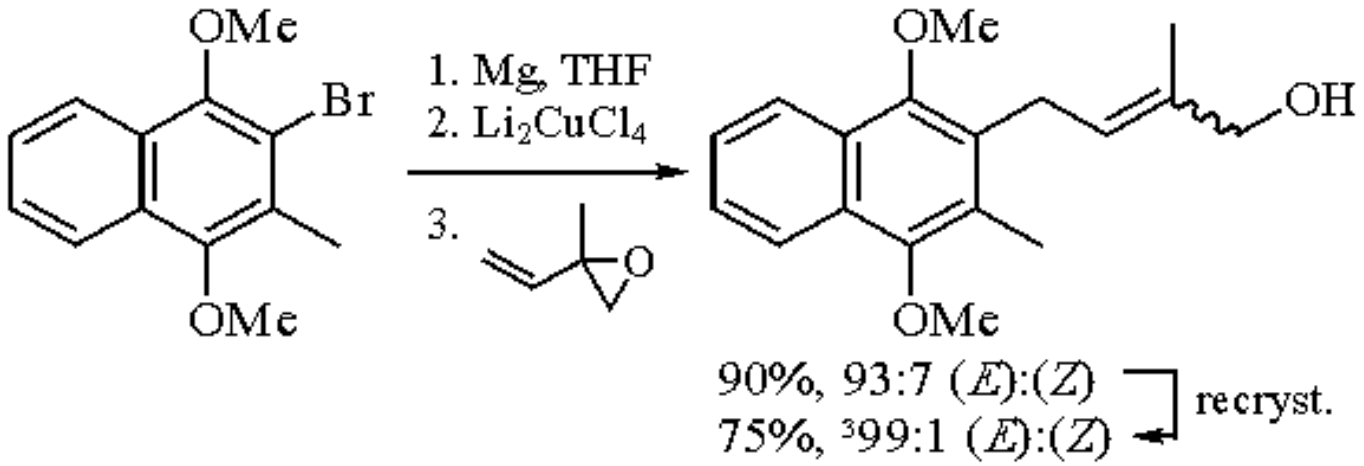

(2)

Palladium catalysts also have been used to facilitate the S_N2' addition of nucleophiles to isoprene epoxide.[6] The coupling reactions occur at mild temperatures in polar solvents. This method has been used for the large scale synthesis of an amino alcohol (eq 3).[7] While control of the geometry of the resulting alkene is problematic, distillation of the (*E*):(*Z*) mixture through a Vigreux column affords the higher boiling (*E*) isomer in 35-55% yield.

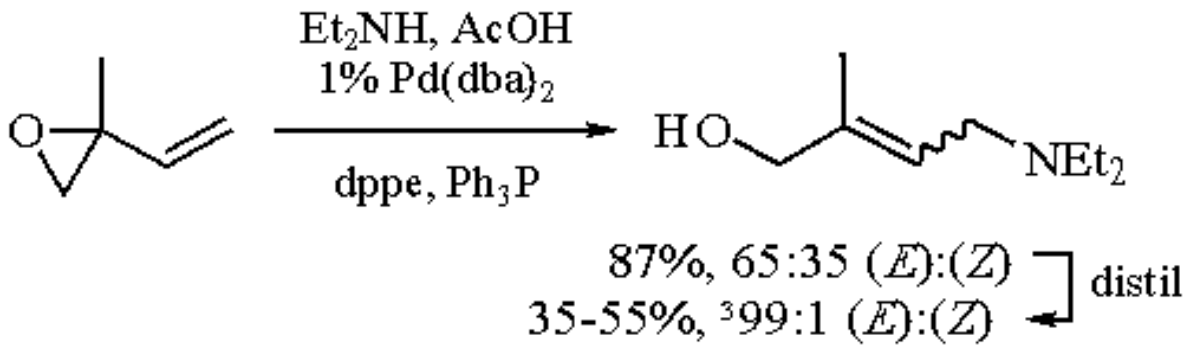

(3)

Carbonylation with carbon monoxide (30 atm) at the alkene terminus of isoprene epoxide has been accomplished with a palladium catalyst to yield the homologated ethyl ester (eq 4).[8] Other alkenyloxiranes afford β-lactones and dienes.

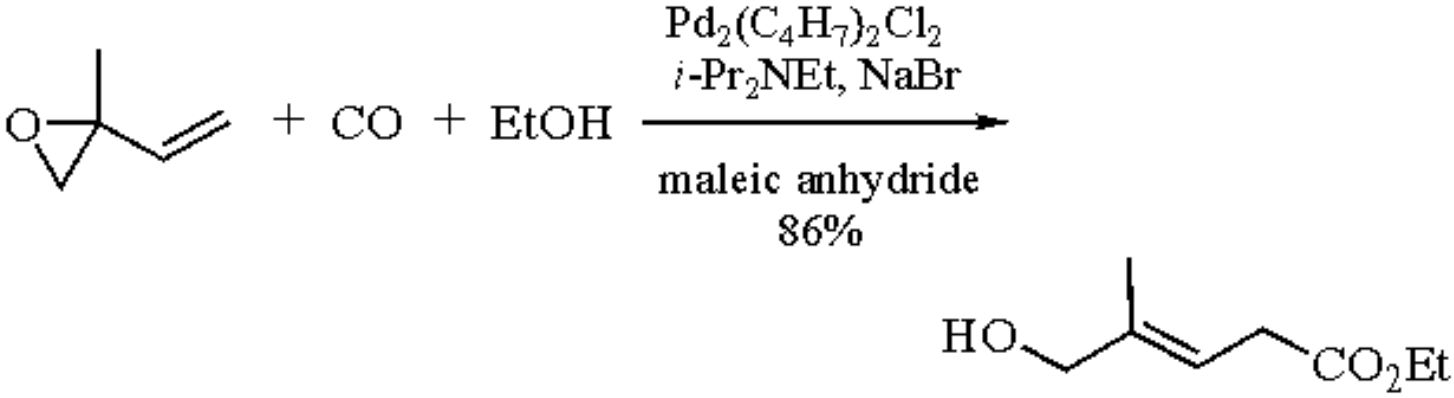

(4)

Nucleophilic Opening at C-1.

Cyanide has been used to open epoxides to provide β-hydroxy nitriles under phase-transfer conditions. These

conditions are not very successful for isoprene epoxide because the product is water soluble. This problem has been overcome by the use of ***Acetone Cyanohydrin*** to selectively open isoprene epoxide at the C-1 terminus. The product is isolated without an aqueous workup (eq 5).[9]

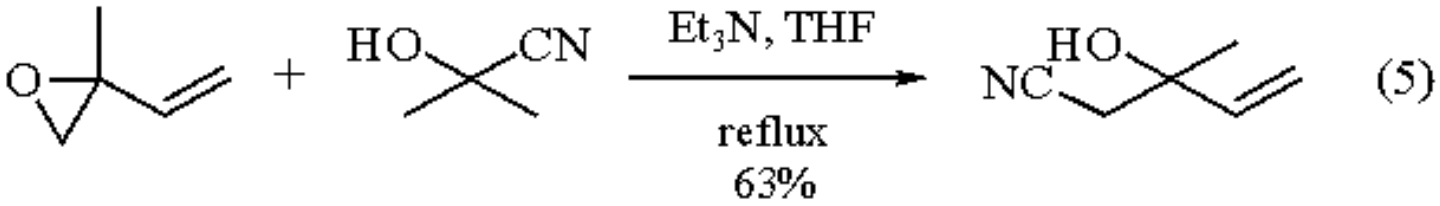

Functionalization at C-2.

In synthesis, one goal that remains elusive is the stereoselective construction of quaternary centers in acyclic systems. Employing ***Chromium(II) Chloride***, it is possible to functionalize the tertiary position of isoprene epoxide with reasonable diastereoselectivity (eq 6).[10] The reaction rate is slower and the yield is lower when the same reaction is run with butadiene monoxide.

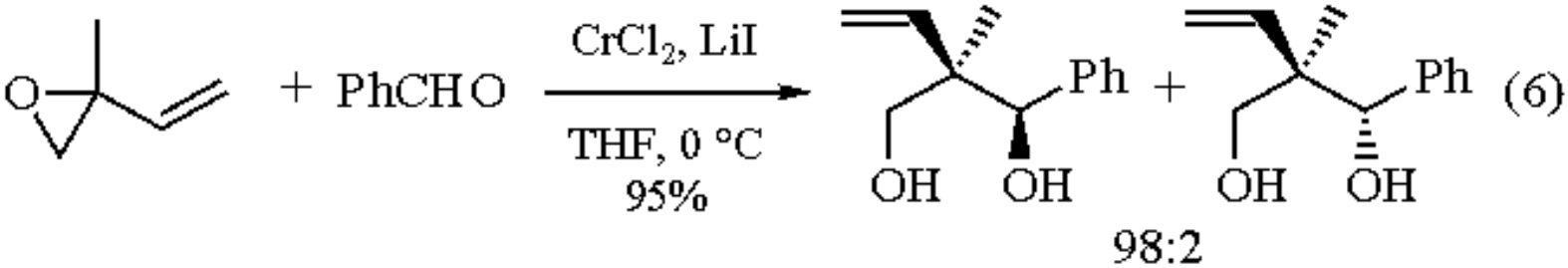

Related Reagents.

1,3-Butadiene Monoxide; ***Ethylene Oxide***; ***Propylene Oxide***.

---

1. Reist, E. J.; Junga, I. G.; Baker, B. R. *JOC* **1960**, *25*, 1673.
2. Thomsen, D. S.; Schiott, B.; Jorgensen, K. A. *CC* **1992**, 1072.
3. Marshall, J. A. *CRV* **1989**, *89*, 1503.
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6. (a) Larock, R. C.; Ding, S. *JOC* **1993**, *58*, 804. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *T* **1989**, *45*, 979.
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8. Shimizu, I; Maruyama, T.; Makuta, T.; Yamamoto, A. *TL* **1993**, *34*, 2135.
9. Mitchell, D.; Koenig, T. M. *TL* **1992**, *33*, 3281.
10. Fujimura, O.; Takai, K.; Utimoto, K. *JOC* **1990**, *55*, 1705.

Isopropenyl Acetate[1]

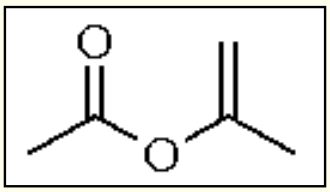

[108-22-5] · $C_5H_8O_2$ · Isopropenyl Acetate · (MW 100.13)

(conversion of carbonyl compounds to their enol acetates;[5] acetylation of oxygen,[12] nitrogen,[14] and carbon;[12a] acetone equivalent in Lewis acid catalyzed aldol reactions;[15] conversion of malonic acids to their isopropylidene derivatives[17])

Physical Data: bp 97 °C;[2] *d* 0.909 g cm^{-3}; fp 18 °C.

Solubility: sol benzene, acetic acid.

Form Supplied in: 99 and 99+% pure liquid widely available.

Analysis of Reagent Purity: the acetone content may be determined by addition of an excess of ***Hydroxylamine*** hydrochloride to an ethanolic solution, followed by back titration against sodium hydroxide.[3]

Handling, Storage, and Precautions: flammable liquid; mild irritant; narcotic in high concentrations. LD_{50} orally in rats: 3.0 g kg^{-1}.[4]

Enol Acetylation.

In the presence of catalytic acid, isopropenyl acetate reacts with enolizable ketones to give the enol acetate plus acetone. This reactivity has been exploited to accomplish selective enolization of ketones, and to provide dienol acetates for Diels-Alder reactions. Each of these reactions is described in more detail in the following sections.

Selective Generation of Kinetic and Thermodynamic Enol Acetates.

While the use of isopropenyl acetate with catalytic acid is considered to provide conditions for the generation of kinetic enols, the ratio of kinetic to thermodynamic isomers obtained for a given enolizable ketone appears to be

highly dependent on the individual system being studied. For example, in steroid chemistry, isopropenyl acetate has been used to provide significant yields of the kinetic Δ^2-enol (**2**) over the thermodynamically favored Δ^3-enol (**3**) (eq 1).[5] For comparison, the results of the corresponding thermodynamically controlled enol acetylation reaction using perchloric acid catalyst and ***Acetic Anhydride*** are also given.

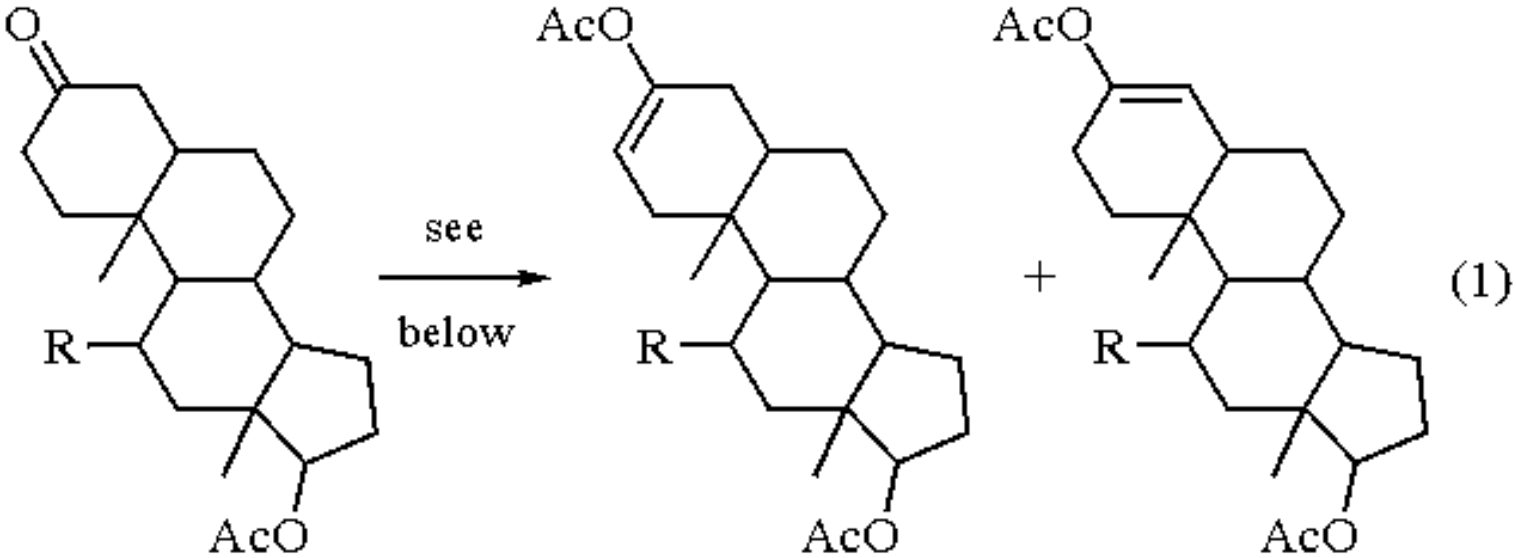

(1a) R = OH		**(2a)** R = OAc	**(3a)** R = OAc
	isopropenyl acetate, H_2SO_4, reflux 1 h	47%	53%
	acetic anhydride, $HClO_4$, PhH, CCl_4	25%	75%
(1b) R = H		**(2b)** R = H	**(3b)** R = H
	isopropenyl acetate, H_2SO_4, reflux 1 h	29%	71%
	acetic anhydride, $HClO_4$, PhH, CCl_4	6%	94%

As shown in eq 1, introduction of an 11β-hydroxy group causes a 16-18% increase in the amount of the kinetic Δ^2-enol acetate (**2**) regardless of the reaction conditions. Additionally, enol acetylation proceeds with concomitant acetylation of the 11β-hydroxy group under these same reaction conditions. While these conditions provide only a moderate predilection for formation of the kinetic enol acetate in the cases presented above, other related systems have shown excellent selectivity utilizing this method.[6,7]

Selective Generation of (*E*)- or (*Z*)-Enol Acetates.

The (*E*)- and (*Z*)-enol acetates of β-keto esters can be selectively generated by careful choice of acetylation conditions.[8] Under acidic conditions isopropenyl acetate gives, almost exclusively, the (*Z*) isomer (**6a**) (eq 2). This selectivity is believed to arise because the reactive form of methyl acetoacetate under acidic conditions is the internally hydrogen bound (*Z*)-enol (**5**) (eq 2). Alternatively, the corresponding (*E*)-enol acetate (**6b**) may be selectively generated under basic conditions utilizing ***Acetyl Chloride*** as the acetylating agent (eq 3). The selectivity in this reaction is believed to be due to the solvent-separated ion (**7**) generated in ***Hexamethylphosphoric Triamide*** and ***Triethylamine***. For the anion (**7**), the (*E*) conformation places the negatively charged oxygen atoms at a maximum separation.

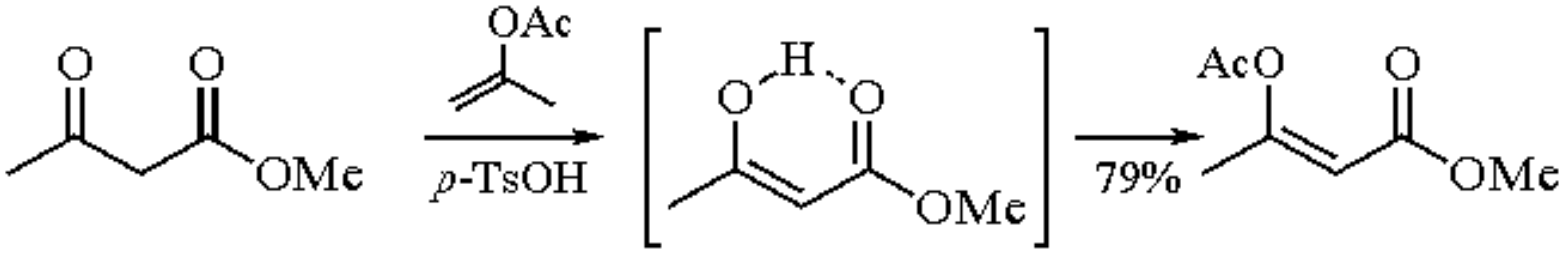

(4) **(5)** (*Z*)-**(6a)** (2)

(*Z*):(*E*) = 18:1

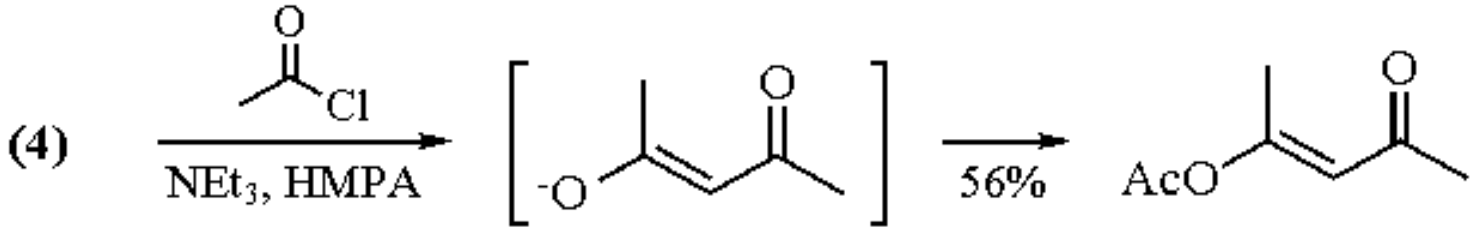

(4) **(7)** (*E*)-**(6b)** (3)

(*Z*):(*E*) = 1:15

The use of isopropenyl acetate and catalytic acid for the formation of dienol acetates from α,β-unsaturated aldehydes and ketones is known to favor the formation of the (*E*) isomer (**10a**) (eq 4).[9] For the enolization of ***Crotonaldehyde*** (**8**) the reaction gives 1-acetoxy-1-propene (**10**) as an 83:17 (*E*:*Z*) mixture. This selectivity is credited to the intermediacy of cation (**9**) in this process. Cation (**9b**), which would lead to the (*Z*) isomer (**10b**), is disfavored due to an unfavorable steric interaction between the vinyl and acetoxy groups (eq 5).

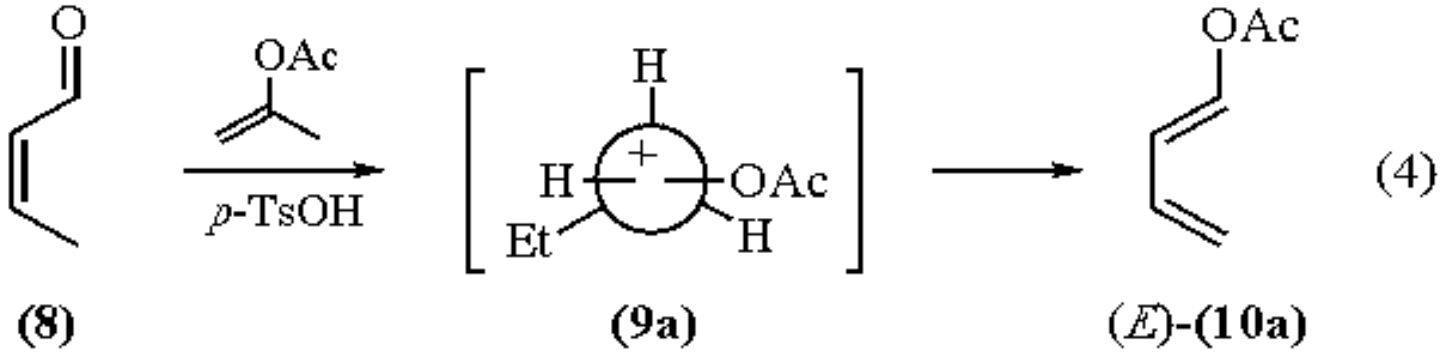

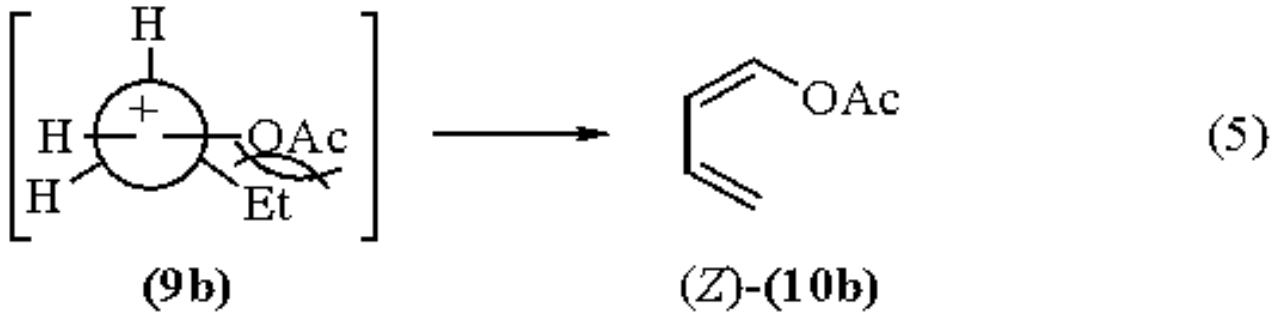

Dienol Acetates for the Diels-Alder Reaction.

Wolinsky and Login[10] found that the methodology described above allows for the in situ generation of reactive dienes for use in Diels-Alder reactions (eqs 6 and 7). The enol acetate of 2-methyl-2-butenone (**11**) is generated by reaction with isopropenyl acetate and ***p-Toluenesulfonic Acid***. In the presence of ***Dimethyl Acetylenedicarboxylate*** (DMAD), the resulting diene undergoes a cycloaddition reaction, giving, after loss of acetic acid, the phthalic acid derivative (**12**) in 80% yield (eq 6). Similarly, crotonaldehyde (**8**) is converted to 1-acetoxy-1-propene (**10**), as shown in eq 4. Diene (**10**) is then trapped with chloromaleic anhydride (**13**). Loss of acetic acid and HCl gives phthalic anhydride (**14**) in 70% yield (eq 7).

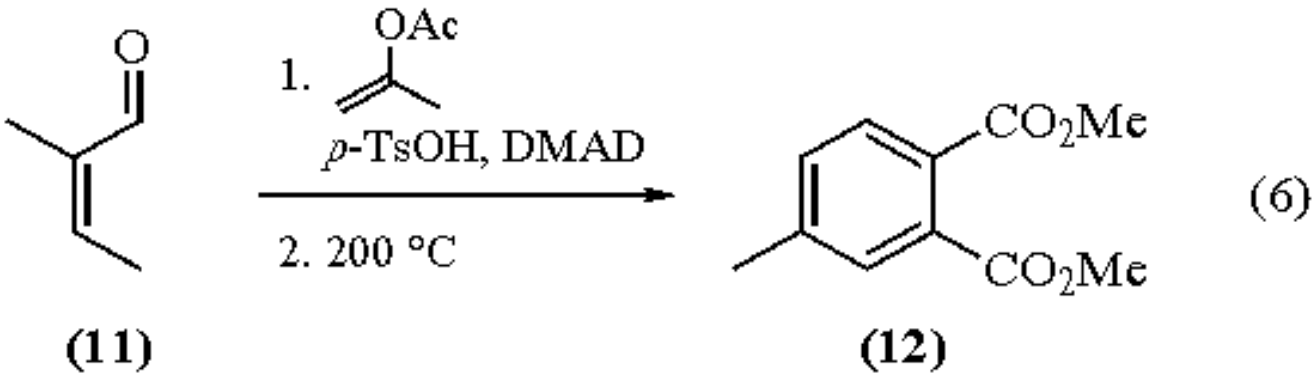

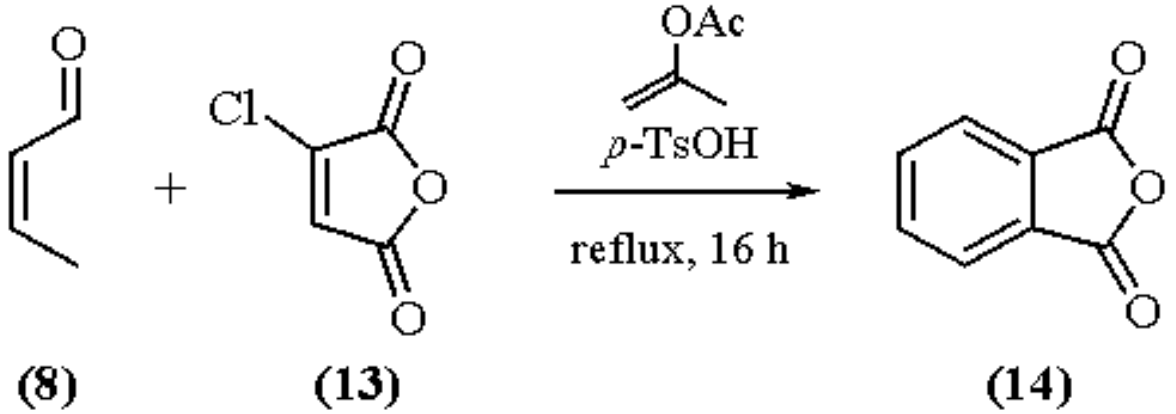

(7)

Acetylation of Other O, N, and C Centers.

In addition to the preparation of enol acetates from ketones, isopropenyl acetate has also seen use in the acetylation of other O, N, and C centers. Hydroxy acetylation was first noted[11] as a simultaneous reaction occurring during the enol acetylation of steroids bearing unprotected hydroxy groups (eq 1). The reagent has since been used more deliberately for the protection of alcohols.[12] More recently the reagent has been used in conjunction with enzymes to afford chiral acylated material.[13] Kaupp and Matthies[14] were surprised to observe *N*-acetylation of the benzothiazepine derivative (**15**) with no formation of the isomer (**17**) (eq 8). Attempts by the authors to generate the expected isomer (**17**) were unsuccessful.

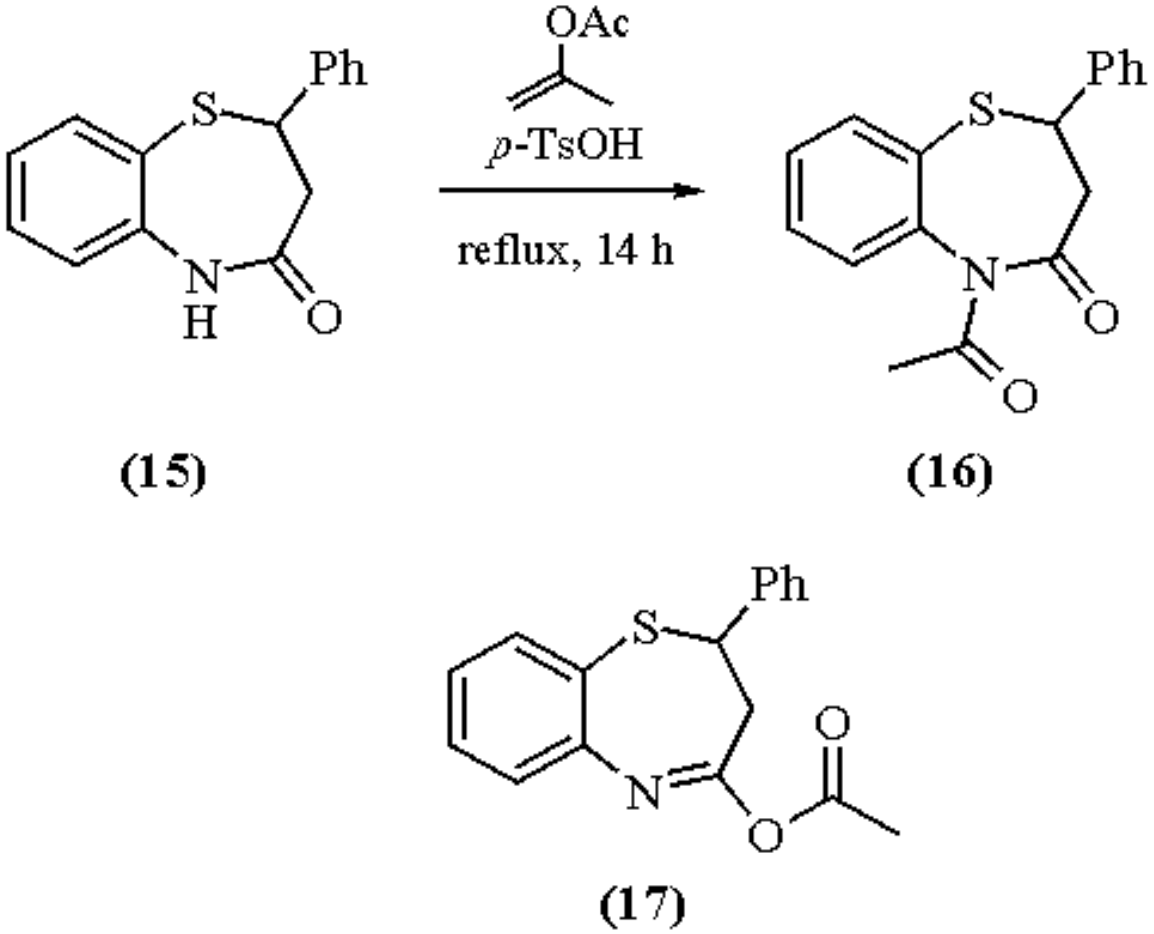

(8)

The 5-position of some *N*-methylpyrrole derivatives (**18**) were successfully acetylated using isopropenyl acetate in the presence of catalytic acid under refluxing conditions (eq 9).[12a]

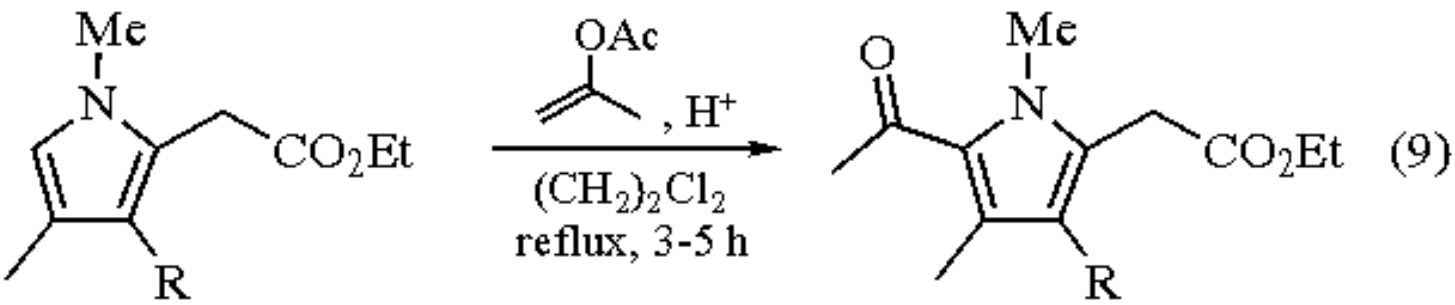

(18a) R = CO_2Et
(18b) R = H

(19a) 81%
(19b) 55%

Aldol Reactions.

Isopropenyl acetate participates in some aldol-type reactions. This enol ester, like enol ethers, can react with various acetals (**20**) in the presence of a Lewis acid to afford the aldol-type addition products (**21** and **22**) (eq 10).[15] This same reactivity is observed in the condensation of ***Succinic Anhydride*** with isopropenyl acetate.[16]

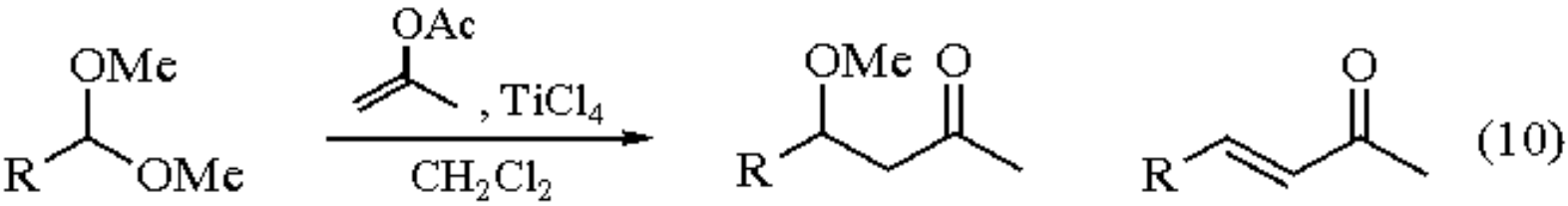

(20a)	R = Ph	**(21a)**	81%	**(22a)**	5%
(20b)	R = *i*-Pr	**(21b)**	92%	**(22b)**	0%
(20c)	R = CH=CHPh	**(21c)**	0%	**(22c)**	65%

Isopropenyl Acetate as a Source of Acetone.

Under certain reaction conditions, isopropenyl acetate reacts to deliver an equivalent of acetone for acetonide formation or for oxidative addition to an enol. Under acidic conditions, isopropenyl acetate has been used to generate isopropylidene derivatives of malonic acids.[17] Isopropenyl acetate also undergoes an oxidative addition reaction with ketones in the presence of ***Manganese(III) Acetate***.[18] An acetone subunit is added to the α-position of a ketone to give a 1,4-diketone.

Related Reagents.

Acetic Anhydride.

---

1. Hagemeyer, H. J., Jr.; Hull, D. C. *Ind. Eng. Chem.* **1949**, *41*, 2920.
2. *The Merck Index*, 11th ed.; Budavari, S., Ed.; Merck: Rahway, NJ, 1989; p 5092.
3. Jeffery, E. A.; Satchell, D. P. N. *JCS* **1962**, 1876.
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6. Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *JOC* **1986**, *51*, 5311.
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9. Fukuda, W.; Sato, H.; Kakiuchi, H. *BCJ* **1986**, *59*, 751.
10. Wolinsky, J; Login, R. B. *JOC* **1970**, *35*, 3205.
11. Villotti, R.; Ringold, H. J.; Djerassi, C. *JACS* **1960**, *82*, 5693. The experimental data are cited by Djerassi, C. *Steroid Reactions*; Holden-Day: San Francisco, CA, 1963; p 41.
12. (a) Gizur, T.; Harsanyi, K. *SC* **1990**, *20*, 2365. (b) Shiao, M.-J.; Lin, J. L.; Kuo, Y.-H.; Shih, K.-S. *TL* **1986**, *27*, 4059. (c) Alarcon, P.; Pardo, M.; Soto, J. L. *JHC* **1985**, 273. (d) Pauluth, D.; Hoffmann, H. M. R. *LA* **1985**, 403.
13. Asensio, G.; Andreu, C.; Marco, J. A. *CB* **1992**, 2233.
14. Kaupp, G.; Matthies, D. *CB* **1987**, 1741.
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16. (a) Merenyi, F.; Nilsson, M. *ACS* **1963**, *17*, 1801; **1964**, *18*, 1368; Nilsson, M. *ACS* **1964**, *18*, 441. (b) Merenyi, F.; Nilsson, M. *OS* **1972**, *52*, 1.
17. (a) Davidson, D.; Bernhard, S. A. *JACS* **1948**, *70*, 3426. (b) Singh, R. K.; Danishefsky, S. *OS* **1981**, *60*, 66. (c) Maier, G.; Wolf, B. *S* **1985**, 871.
18. Dessau, R. M.; Heiba, E. I. *JOC* **1974**, *39*, 3457.

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Isopropenyllithium[1]

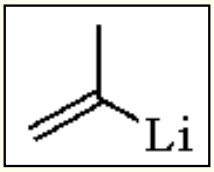

[3052-45-7] · C_3H_5Li · Isopropenyllithium · (MW 48.02)

(terpenoid synthesis; precursor of isopropenyl metals[2])

Alternate Name: 2-lithiopropene.

Physical Data: ^{1}H NMR data have been reported.[5a]

Preparative Methods: can be prepared in ethereal solution by reaction of ***Lithium*** powder (containing 2% of Na) with isopropenyl chloride or bromide (eq 1)[4] or by transmetalation between an organolithium and isopropenyltrialkyltin (eq 2).[5]

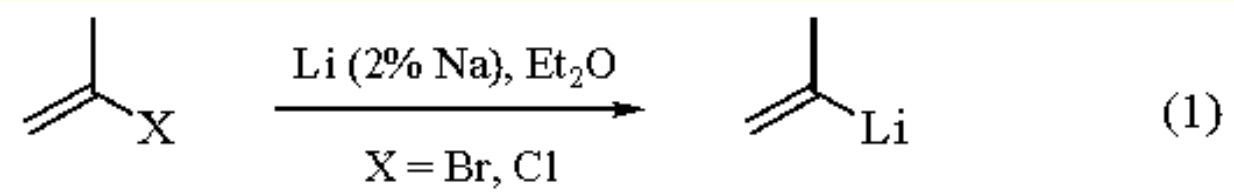

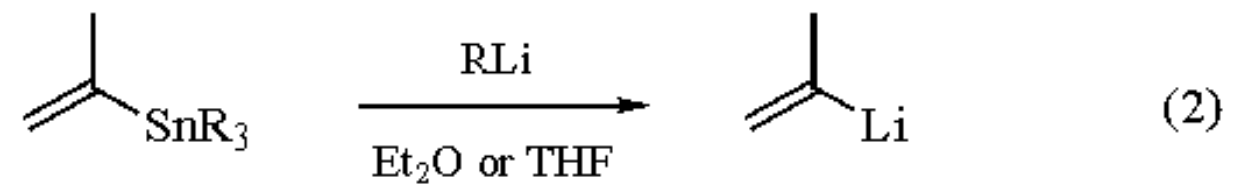

Related reagents can be prepared by reaction of ***n-Butyllithium*** with an arenesulfonyl hydrazone (eq 3)[6] and by the metal-halogen exchange reaction[7] between vinyl bromides or iodides and ***t-Butyllithium*** (eq 4).

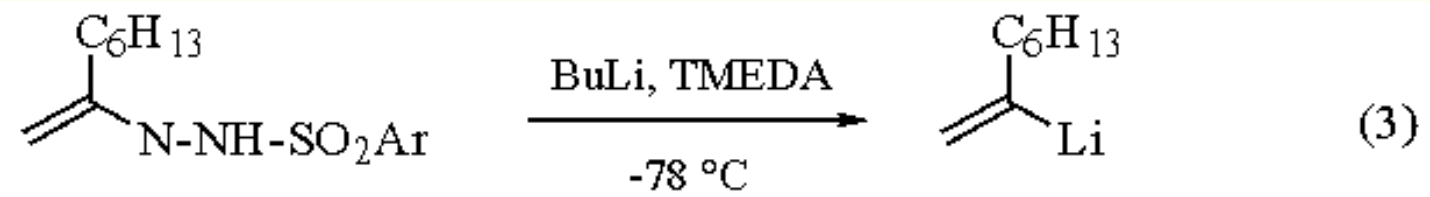

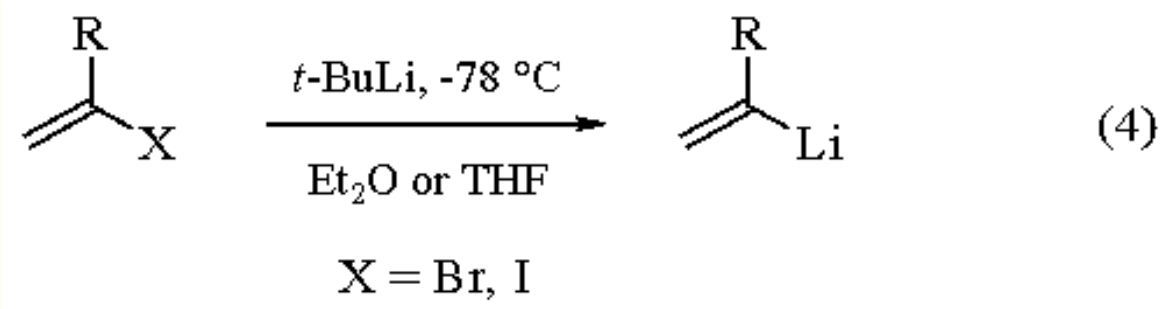

Handling, Storage, and Precautions: the solution of isopropenyllithium in diethyl ether must be handled with care since it is flammable and may ignite on contact with moisture and air. It should be stored and handled in an inert atmosphere (argon) and measured or transferred by means of a hypodermic syringe or cannula. The solution may deteriorate with time and the concentration of the reagent should be measured by titration[3] before use.

Reactions.

Isopropenyllithium reacts with various electrophiles,[1-7] for example, aldehydes (eq 5),[7] ketones,[8] alkyl halides (eq 6),[4] amides (eq 7),[9] and epoxides (eq 8).[10]

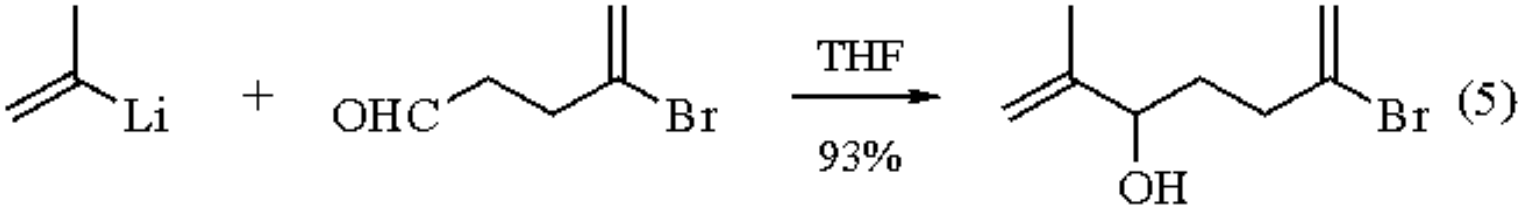

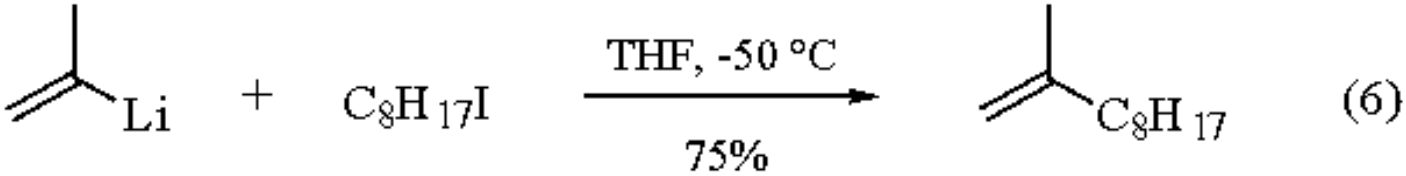

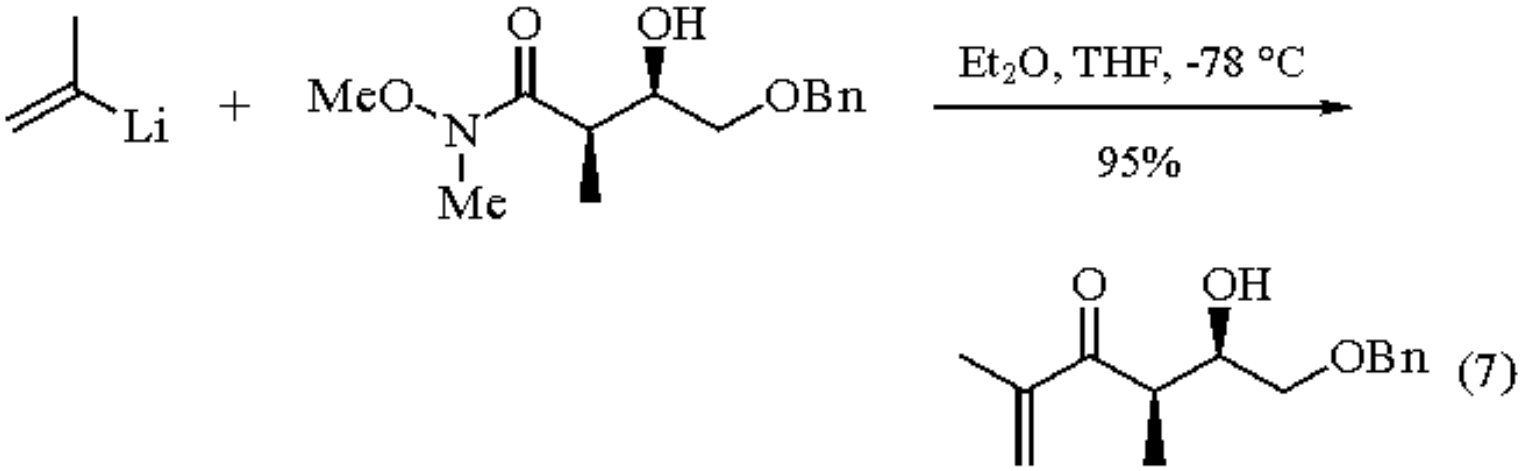

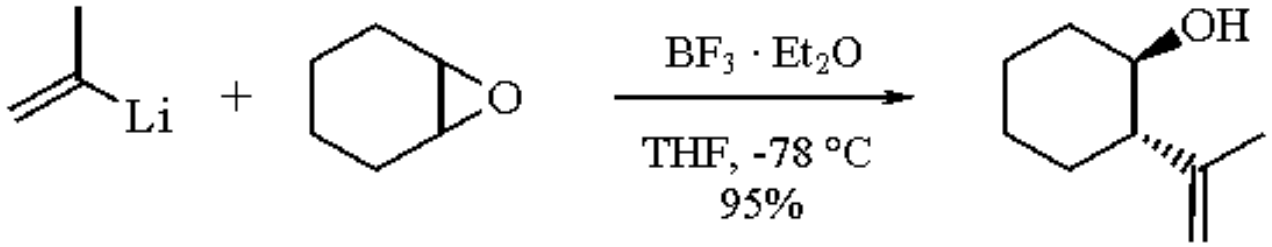

(8)

The conjugate addition of isopropenyllithium to α,β-enones can be accomplished by using 2 equiv of MAD (***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)***) (eq 9).[11]

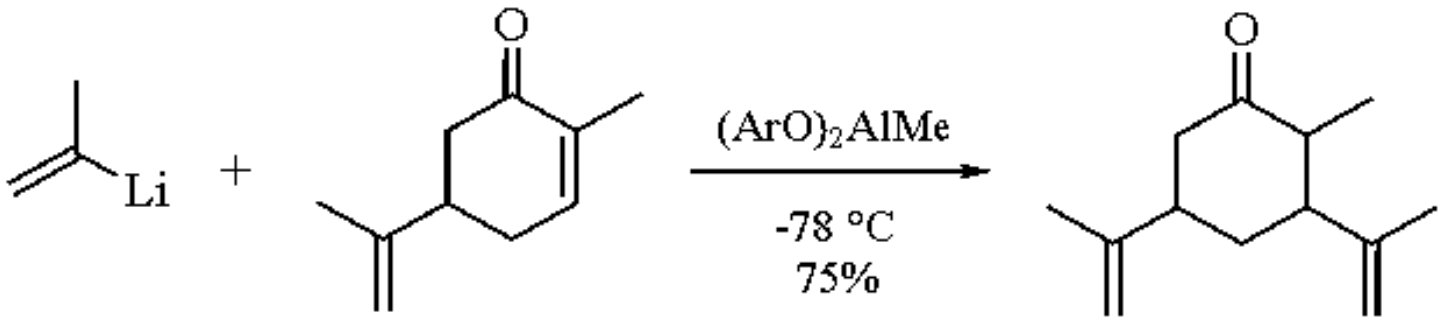

(9)

Isopropenyllithium reacts with trialkylboranes and tetraphenylphosphonium bromide (eqs 10 and 11).[12,13]

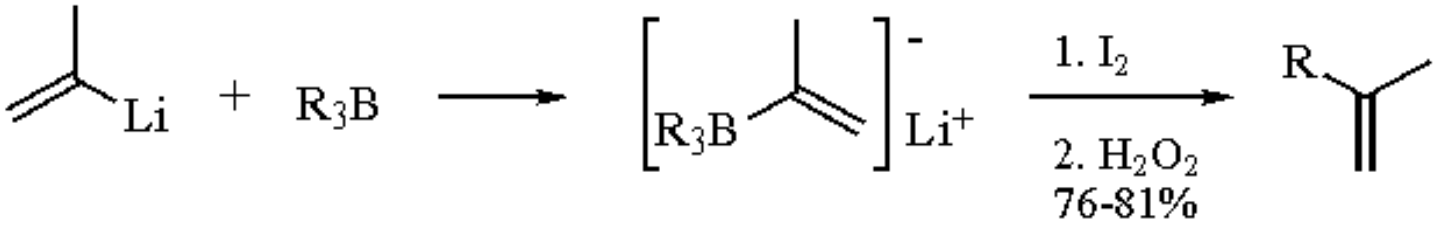

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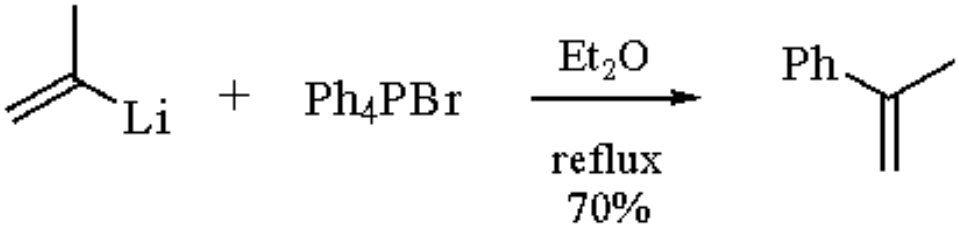

(11)

The corresponding cuprates,[2] obtained by transmetalation between copper salts and isopropenyllithium (see ***Lithium Diisopropenylcuprate***), react with alkyl halides (eq 12)[14] and α,β-enones in a 1,4-fashion (eq 13).[15]

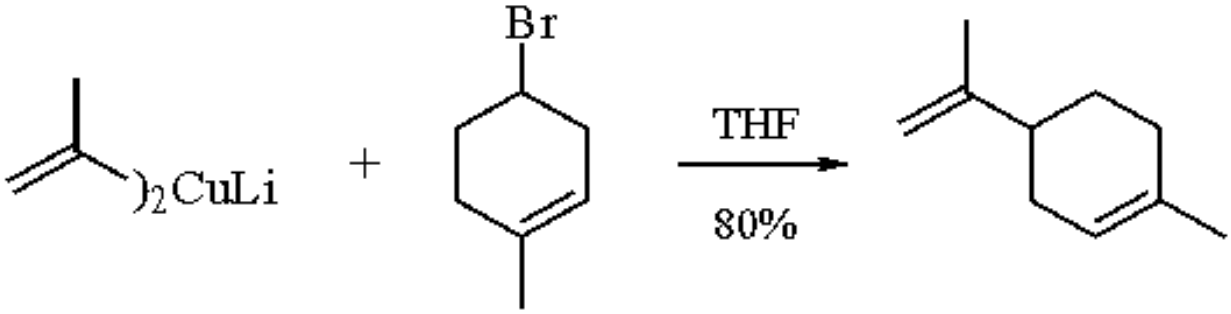

(12)

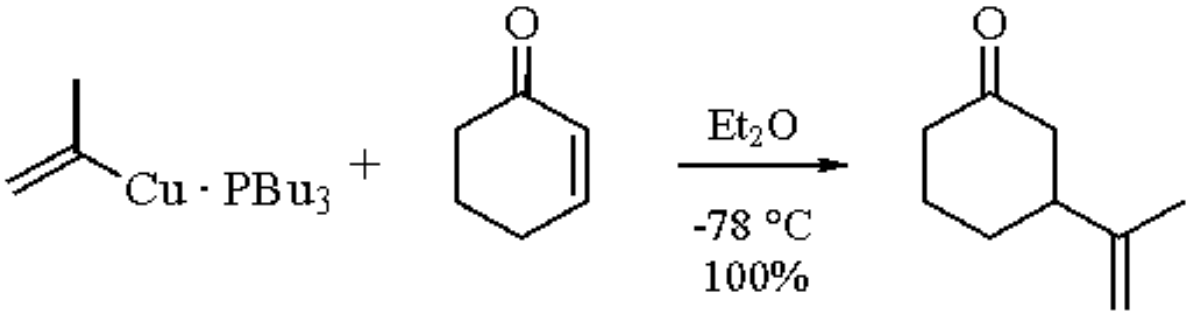

(13)

The organocerium reagent, prepared from isopropenyllithium and anhydrous ***Cerium(III) Chloride***, reacts cleanly with easily enolizable ketones to afford the addition products in good yield (eq 14).[16]

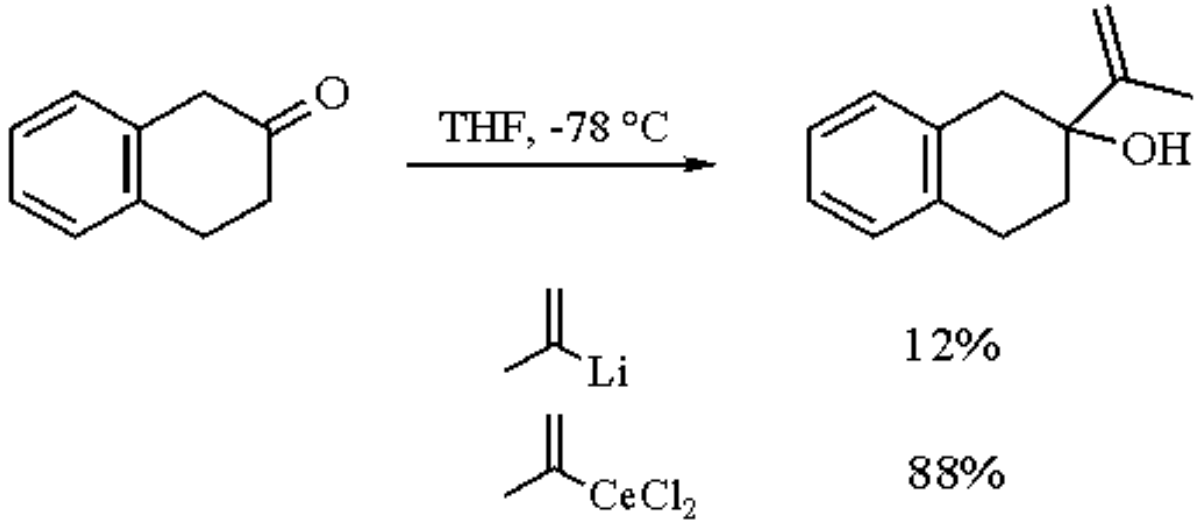

(14)

Related Reactions.

α-Substituted vinyllithium reagents[7a,17] have been described. 4-Chloro-2-lithio-1-butene, readily prepared by transmetalation from the tin derivative, reacts smoothly with aldehydes or ketones (eq 15).[5b]

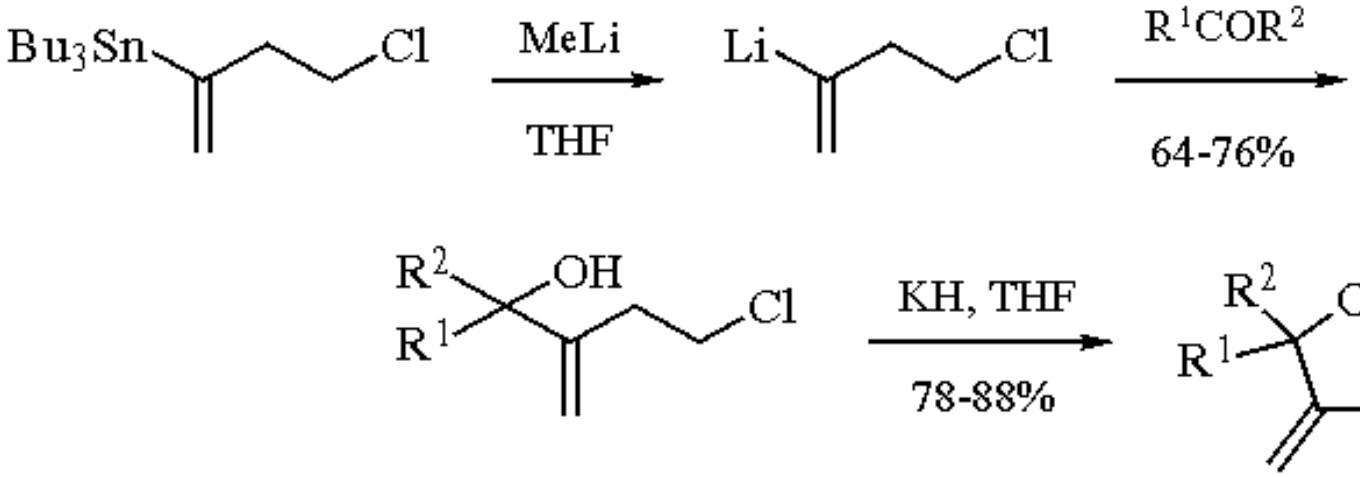

(15)

The reaction of an α-substituted vinyllithium with copper salts leads to an α-substituted vinylcuprate which reacts easily with an allyl bromide (eq 16).[18]

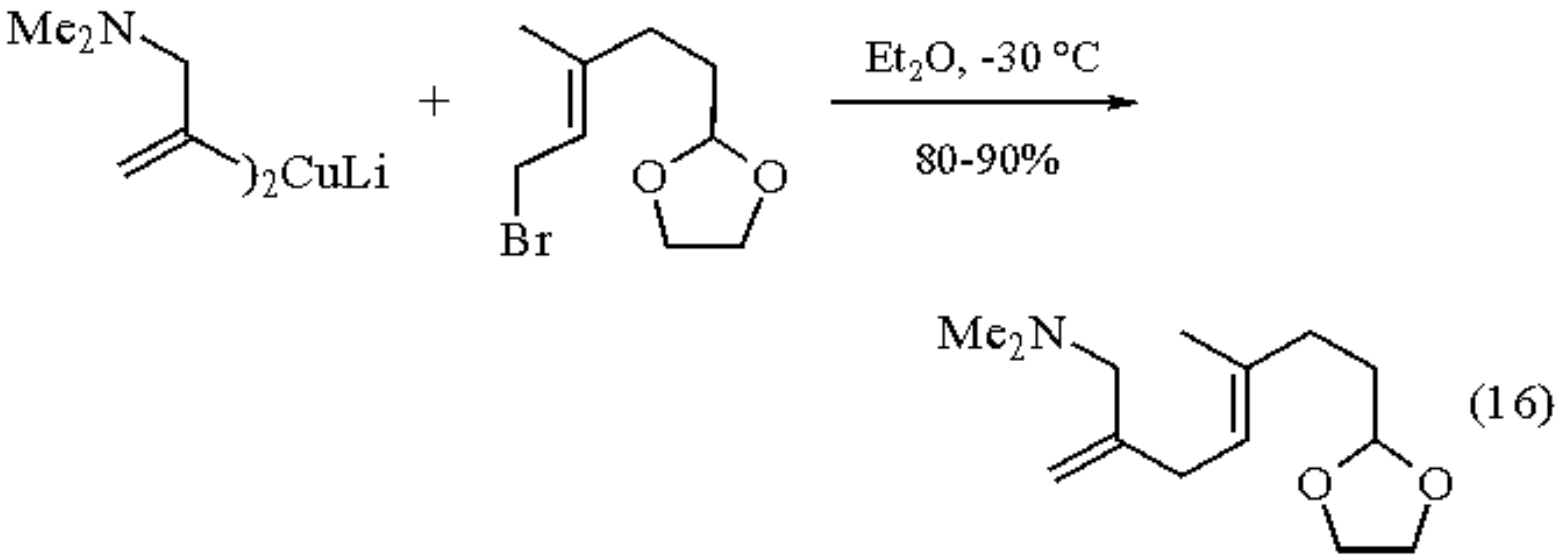

Related Reagents.

1,3-Butadienyl-1-lithium; ***1,3-Butadienyl-2-lithium***; ***Isopropenylmagnesium Bromide***; ***1-Propenyllithium***; ***Vinyllithium***.

---

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Isopropenylmagnesium Bromide[1]

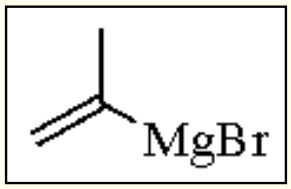

[1730-25-2] · C_3H_5BrMg · Isopropenylmagnesium Bromide · (MW 145.29)

(terpenoid synthesis; precursor of isopropenyl metals[2])

Alternate Name: 2-(bromomagnesio)propene.

Preparative Method: reaction of 2-bromopropene with magnesium in THF.[4]

Handling, Storage, and Precautions: the solution of isopropenylmagnesium bromide in THF must be handled with care since it is flammable and may ignite on contact with moisture and air. It should be stored and handled in an inert atmosphere (argon or nitrogen) and measured or transferred by means of a hypodermic syringe or cannula. The solution may deteriorate with time and the reagent should be titrated[3] before use.

Reactions.

Isopropenylmagnesium bromide reacts with various electrophiles, for example, aldehydes, ketones, esters, carboxylic acids, lactones, dialkyl oxalates, anhydrides, acid chlorides, nitriles, amides, and epoxides (eq 1).[1,4,5]

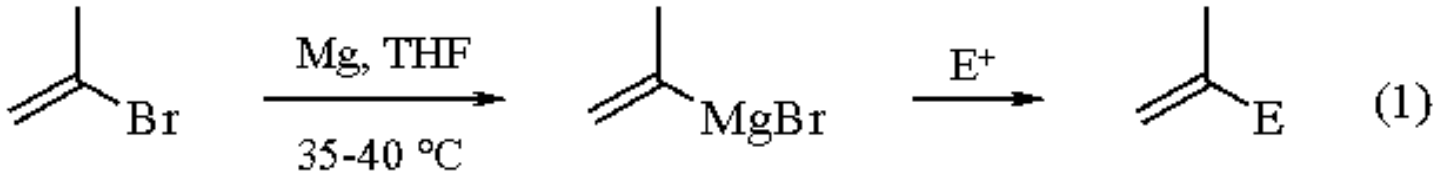

In the presence of copper(I) salts (1-5%) in THF, it undergoes a very efficient conjugate addition to α,β-unsaturated ketones (eq 2).[6] Under the same conditions, it reacts with alkyl halides (eq 3),[7] epoxides (eq 4),[8] and oxetane.[8]

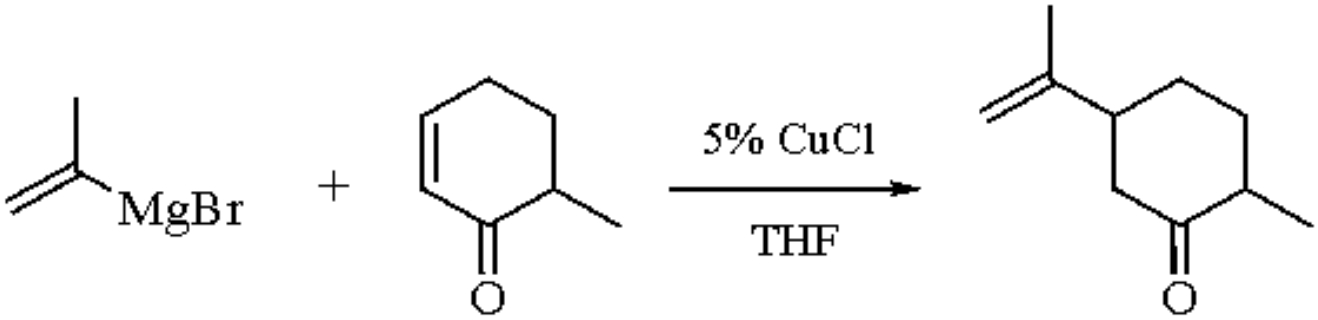

(2)

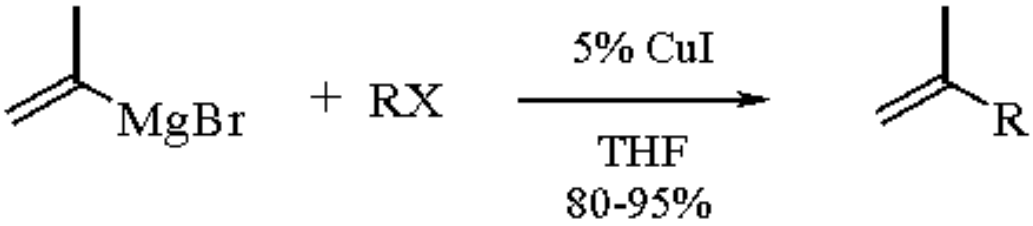

(3)

X = I, OTs R = C_8H_{17}

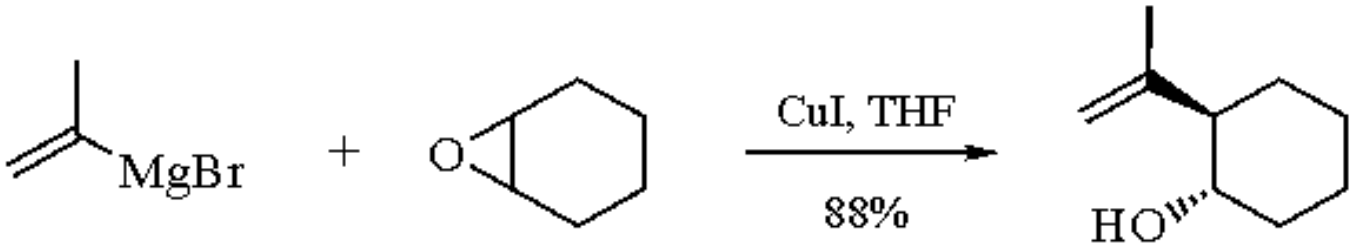

(4)

Under palladium or nickel catalysis, isopropenylmagnesium bromide reacts with vinyl (eqs 5 and 6)[9,10] and aryl halides or sulfides (eqs 7 and 8)[10,11] to give dienes or aryl alkenes in good yields.

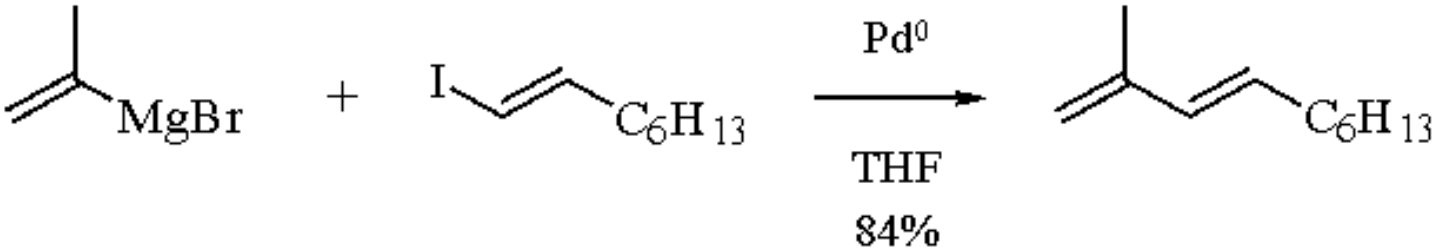

(5)

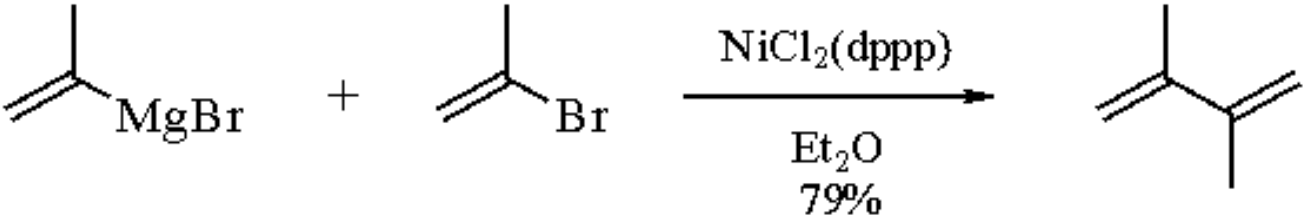

(6)

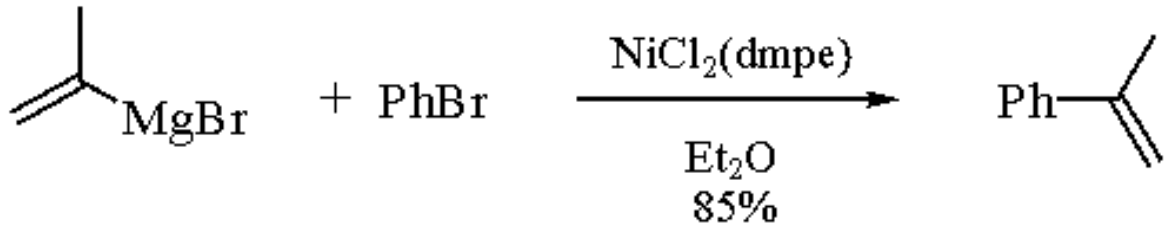

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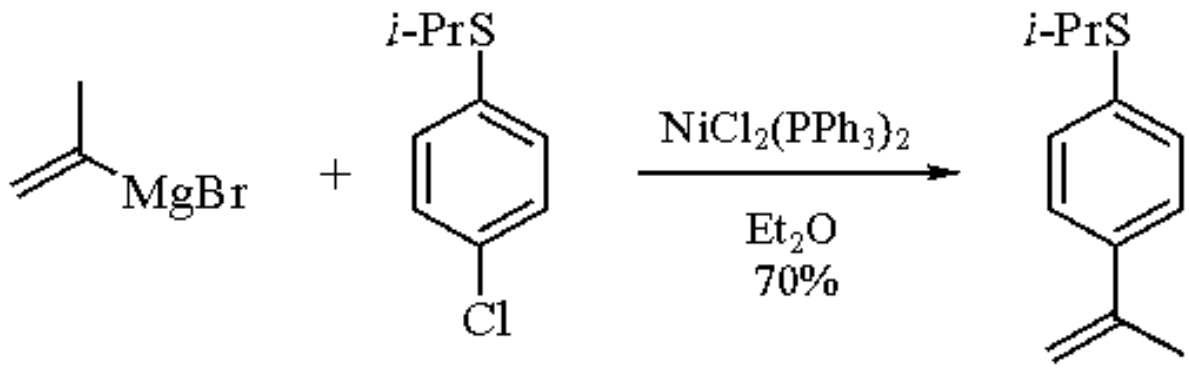

(8)

Related Reactions.

2-(3-Trimethylsilyl-1-propenyl)magnesium Bromide-Copper(I) Iodide reacts with epoxides and the allylsilanes obtained can be converted to α-methylene-γ-lactones (eq 9).[12]

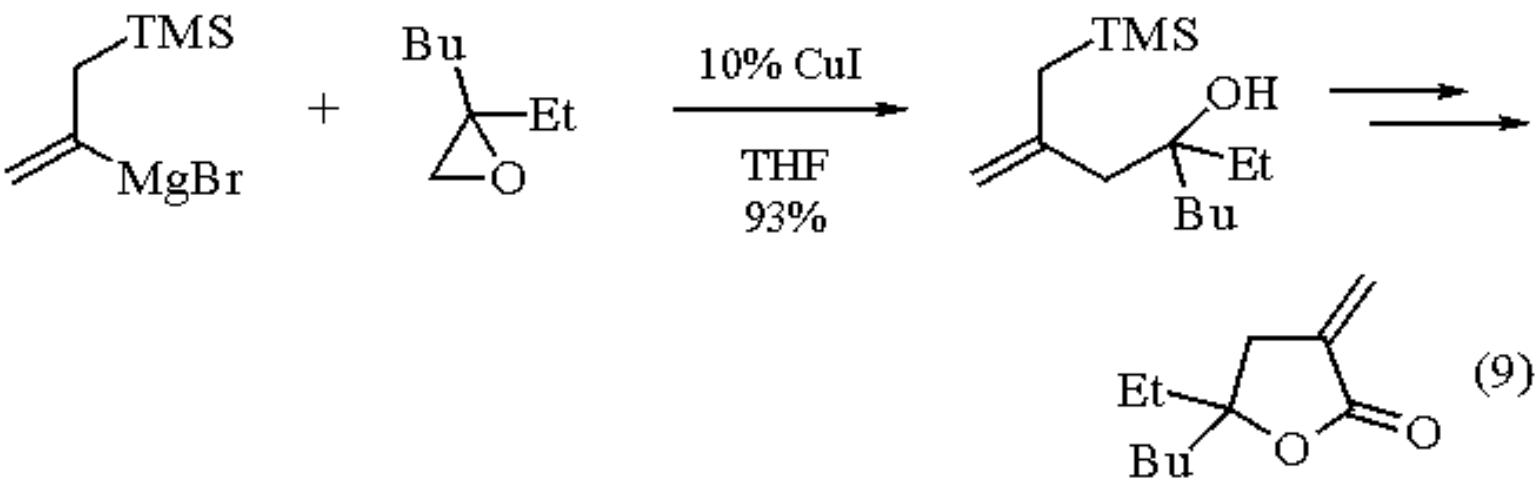

(9)

In the presence of ***Copper(I) Iodide***, the same α-substituted vinylmagnesium bromide reacts with α,β-unsaturated ketones in an annulation sequence to give methylenecyclopentanes (eq 10).[13]

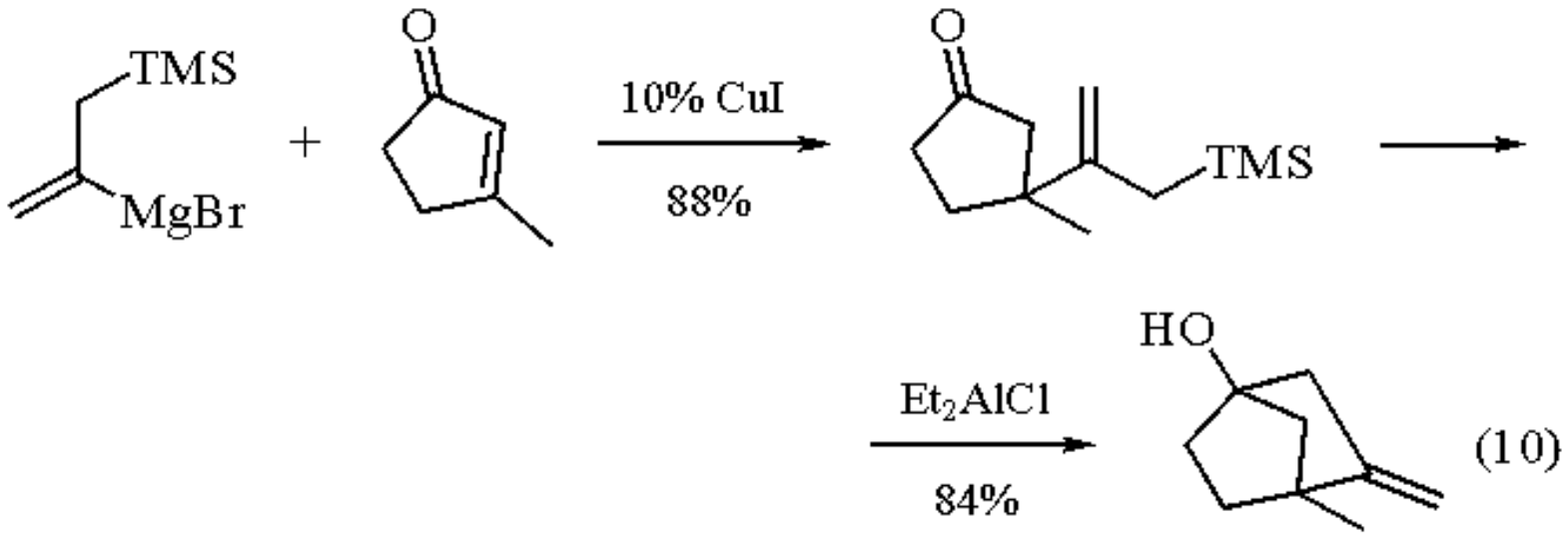

(10)

The nickel-catalyzed cross-coupling reaction of α-substituted vinylmagnesium bromides with vinyl bromides leads to terminal 1,3-dienes (eq 11).[14]

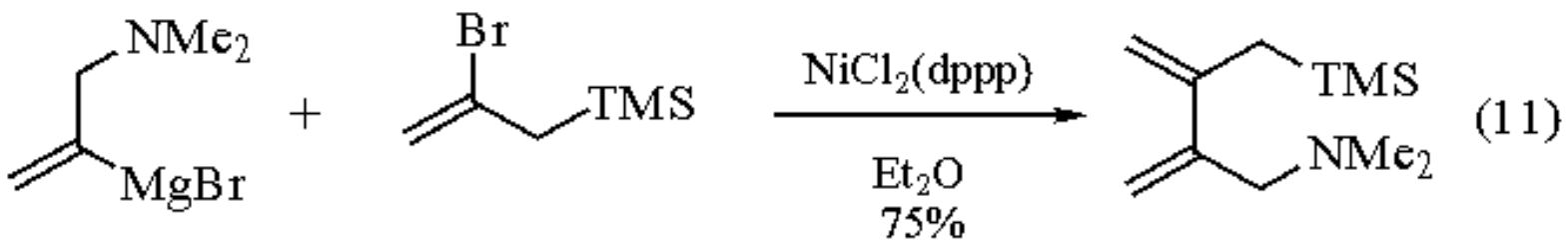

(11)

Related Reagents.

Isopropenyllithium; ***Vinylmagnesium Bromide***.

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Ecole Normale Supérieure, Paris, France

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Isopropenyltriphenylphosphonium Bromide

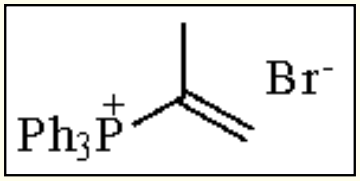

[7301-95-3] · $C_{21}H_{20}BrP$ · Isopropenyltriphenylphosphonium Bromide · (MW 383.28)

(Michael-Wittig combinatorial reagent for preparation of 2-methyl allylic ethers,[1] 3-methyl-2*H*-1-benzopyrans,[1] 3-methyl-2-cyclopentenones,[2] 3-methyl-2,5-dihydrothiophenes,[3] and 1-methyltricyclo[3.2.1.$0^{2,7}$]octan-6-ones[4])

Alternate Name: ITB.

Physical Data: mp 195-197 °C.

Solubility: sol alcohol, CH_2Cl_2, DMF, DMSO.

Preparative Method: prepared by fusion of ***Triphenylphosphine*** with anhydrous ***Nickel(II) Bromide*** followed by addition of dry benzonitrile and azeotropic removal of the residual water, addition of 2-bromopropene, and heating of the resultant mixture from 50-80 °C to 200 °C over a period of 2 d.[1] Workup includes steam distillation to remove benzonitrile, filtration of a black insoluble material, and extraction of the filtrate with CH_2Cl_2. After drying and concentration at reduced pressure, the crude solid thus obtained is purified by recrystallization from CH_2Cl_2-EtOAc.

Michael-Wittig Chain Extension.

Although Michael addition of organolithiums to ITB had been known earlier,[5] the synthetic utility of ITB was only realized when Schweizer[1] reported his results on comparison studies of ITB with ***Vinyltriphenylphosphonium Bromide*** (VTB). As in the case of VTB, the treatment of ITB with sodium ethoxide and benzaldehyde in DMF gave the corresponding chain-extended product in 71% yield via the Michael-Wittig reaction sequence (eq 1).

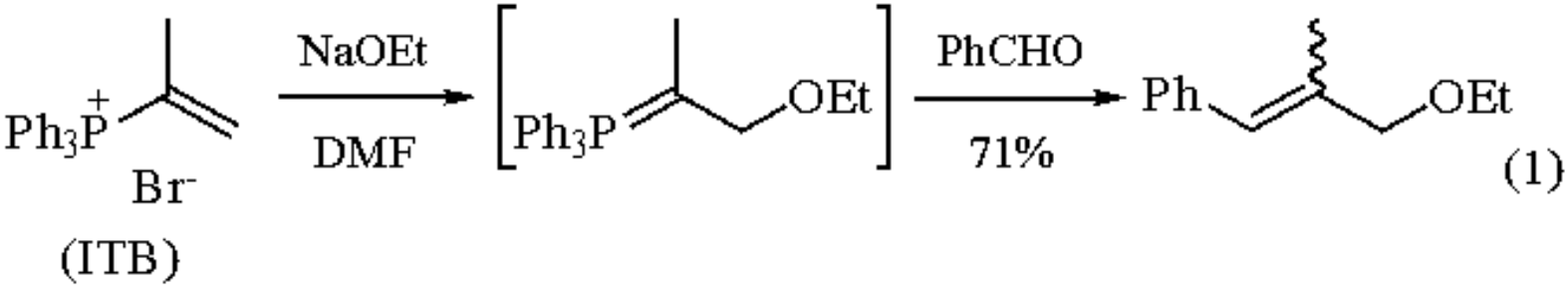

Michael-Wittig Cyclization.

When the nucleophile used in the Michael-Wittig reaction sequence with ITB contains a carbonyl moiety, cyclization of the phosphorane intermediate occurs to give rise to a variety of methyl-substituted cyclic compounds. Thus 3-methyl-2*H*-1-benzopyran[1] (eq 2), 3-methyl-2,5-dihydrofuran[1] (eq 3), 2-methyl-3*H*-pyrrolizines[1] (eq 4), 3-methyl-2-cyclopentenones[2] (eq 5), and 3-methyl-2,5-dihydrothiophenes[3] (eq 6) can all be prepared.

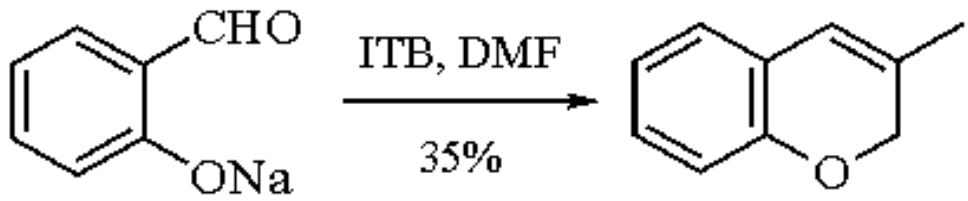

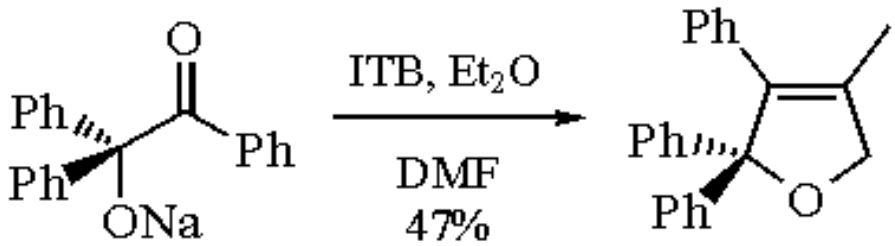

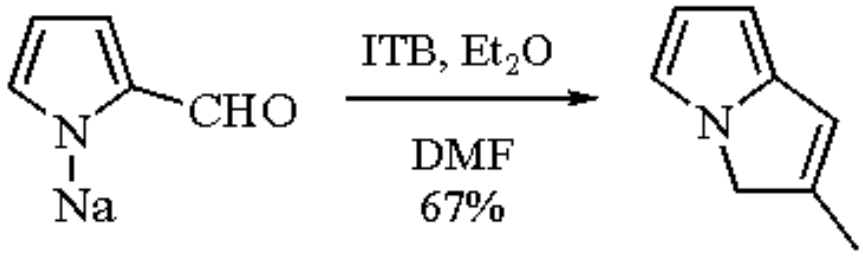

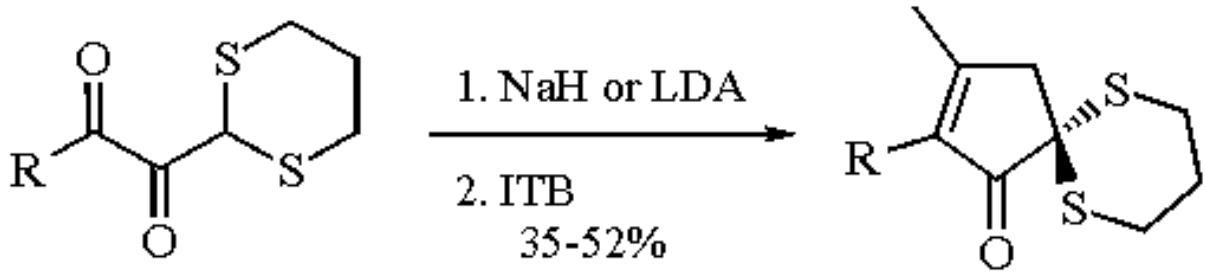

R = Me, Et, C_5H_{11}

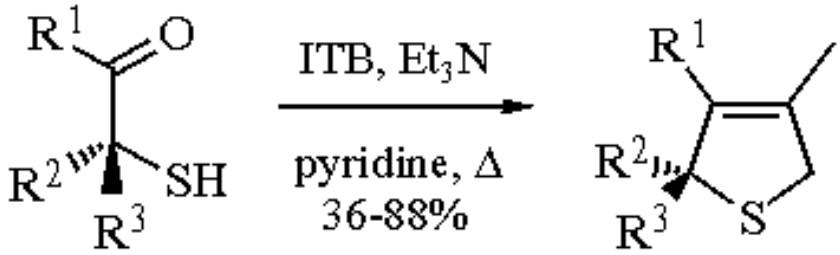

(6)

$R^1 = H$; $R^2, R^3 = -(CH_2)_5-$
$R^1, R^2 = -(CH_2)_4$; $R^3 = H$

Bicycloannulation of 2-cyclohexenones with ITB provides 1-methyltricyclo[3.2.1.0^{2,7}]octan-6-ones via Michael addition followed by intramolecular cyclopropanation (eq 7).[4] In addition, 3-methylpyrazole hydrobromide has been obtained via 1,3-dipolar cycloaddition of ITB with ***Diazomethane*** followed by thermal decomposition of the 1-pyrazoline cycloadduct (eq 8).[6]

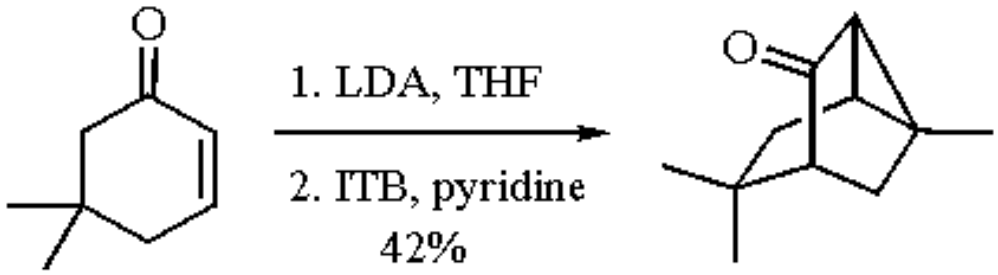

(7)

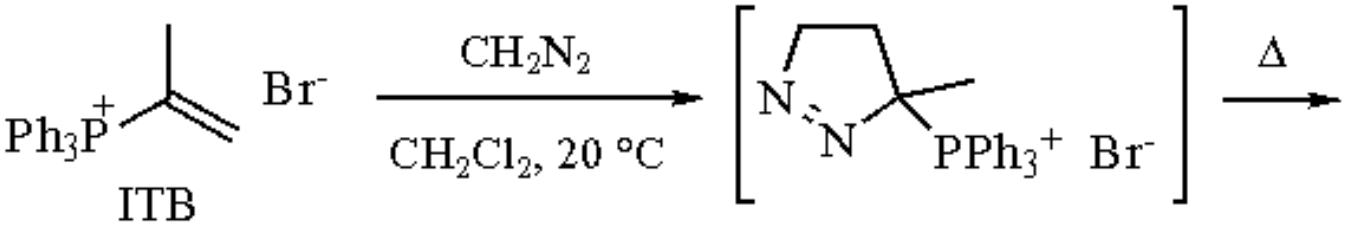

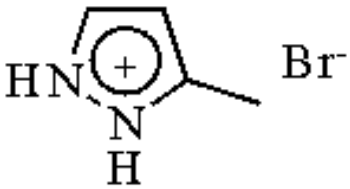

(8)

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2. Kawamoto, I.; Muramatsu, S.; Yura, Y. *TL* **1974**, 4223.
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Isopropyldiphenylsulfonium Tetrafluoroborate[1]

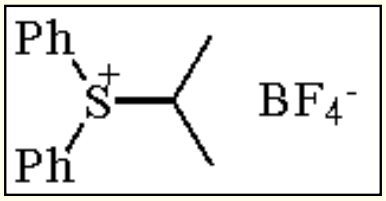

[1660-43-7] · $C_{15}H_{17}BF_4S$ · Isopropyldiphenylsulfonium Tetrafluoroborate · (MW 316.20)

(transformation of carbonyls to *gem*-dimethyloxiranes;[2] conversion of α,β-unsaturated systems[3] and diene esters[4] to geminal substituted cyclopropanes)

Preparative Methods: this reagent is not commercially available and must be made prior to use. The ylide isopropylidenediphenylsulfurane, obtained by deprotonation with an appropriate base, is usually formed in situ and used immediately because of its extremely low stability.[2] Two methods have been reported for the preparation of the sulfurane. Ethyldiphenylsulfonium tetrafluoroborate (formed by the reaction of diphenyl sulfide with triethyloxonium tetrafluoroborate, eq 1) is suspended in a solution of DME. The ylide is formed by addition of $LiCHCl_2$ at -70 °C and reacted with MeI (1.1 equiv). The desired sulfonium salt precipitates from solution. The isopropylidenediphenylsulfurane is formed by addition of LDA to this suspension at -78 °C (eq 2).[2]

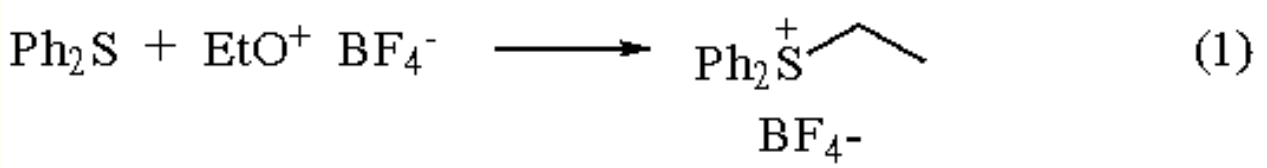

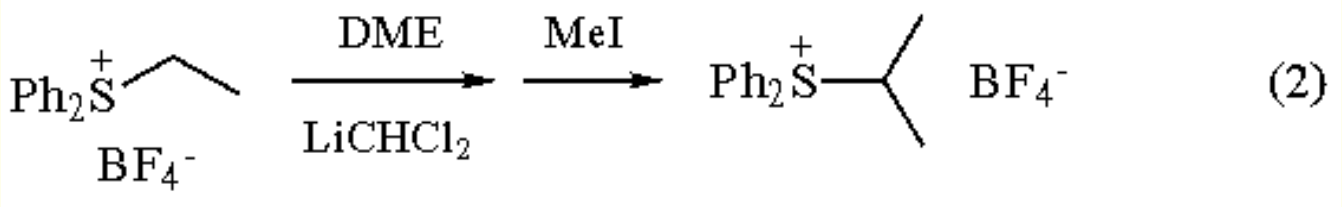

A second, but less efficient, method of preparation involves the reaction of diphenyl sulfide, $AgBF_4$, and neat isopropyl iodide (eq 3).[2]

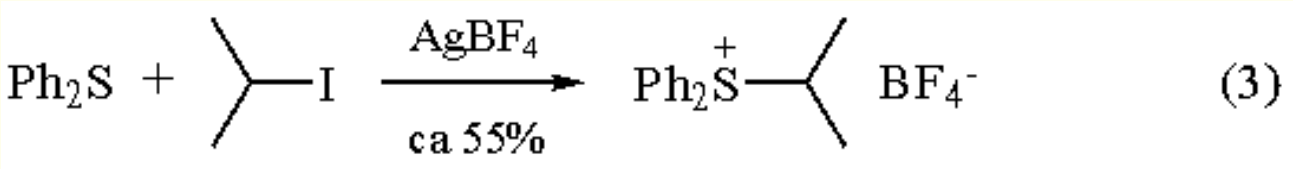

Three different base/solvent systems have been used to generate the isopropylidenediphenylsulfurane ylide: DME/$LiCHCl_2$, *t*-BuOK/THF,[5] and PhLi/THF.[6] All methods have proven equally efficient. Different diastereomer ratios have been obtained with the *t*-BuOK/THF method compared to the other systems.[7]

Reaction with Carbonyls to Form Oxiranes.

Addition of 1 equiv of benzaldehyde to a solution of the ylide, formed as described above, in DME at -60 °C results in the formation of the oxirane (eq 4) in 75-80% isolated yield.[2] Ketones may also react in good yields, but reaction times are somewhat longer.

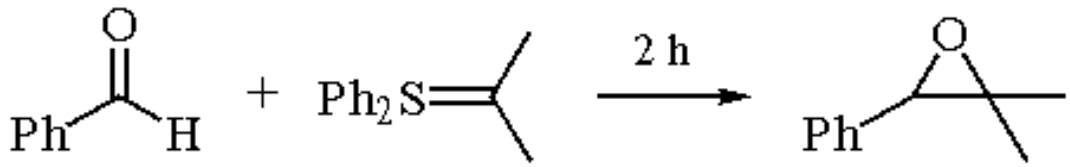

(4)

Van Tamelen et al.[8] used isopropylidenediphenylsulfurane to synthesize radiolabeled 4-norsqualene 2,3-oxide (eq 5) and homosqualene oxide.

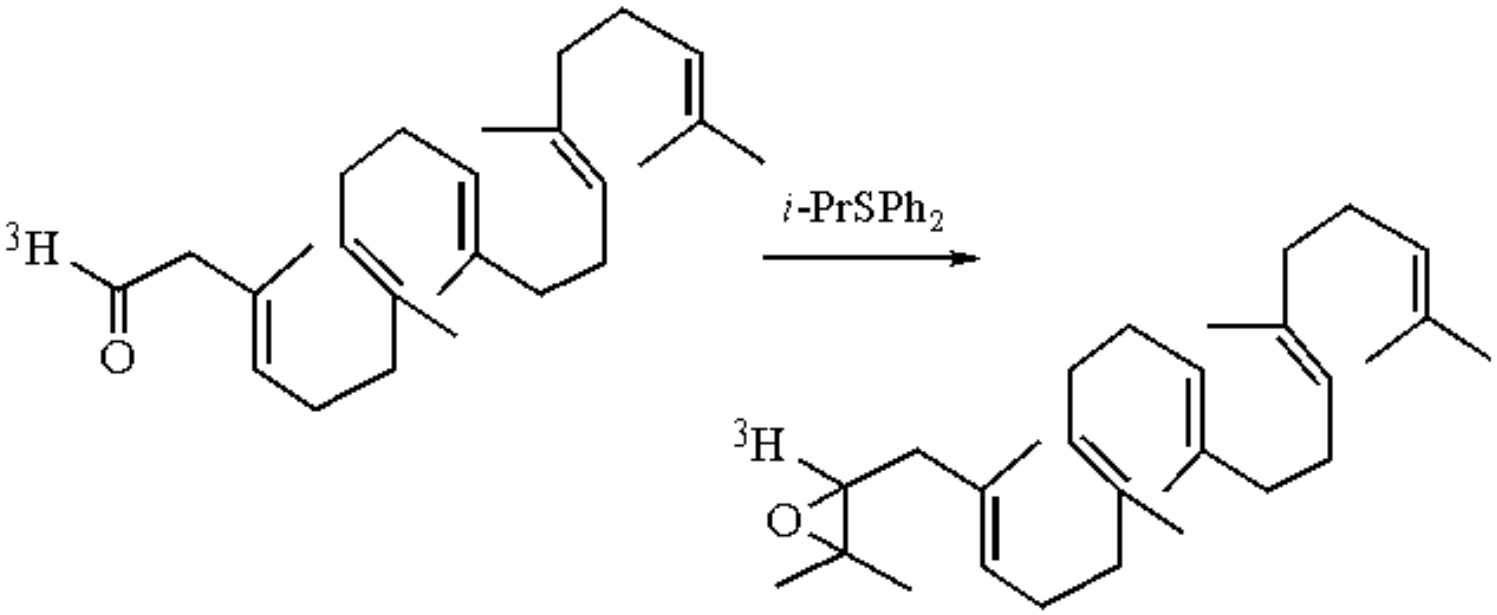

(5)

Reactions with α,β-Unsaturated Compounds.

If the carbonyl is α,β-unsaturated, reaction takes place at the alkene via addition/substitution to form *gem*-dimethyl-substituted cyclopropanes. For example, the *gem*-disubstituted cyclopropane was prepared from cyclohexenone in 74% yield (eq 6).[9]

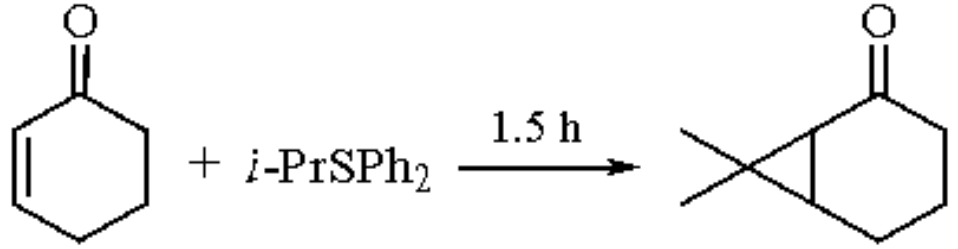

(6)

Meyers et al. have reacted the ylide with a chiral bicyclic lactam to yield a tricyclic *gem*-disubstituted cyclopropane intermediate which, after four steps, gave deltamethric acid whose esters act as very potent insecticides (eq 7).[10]

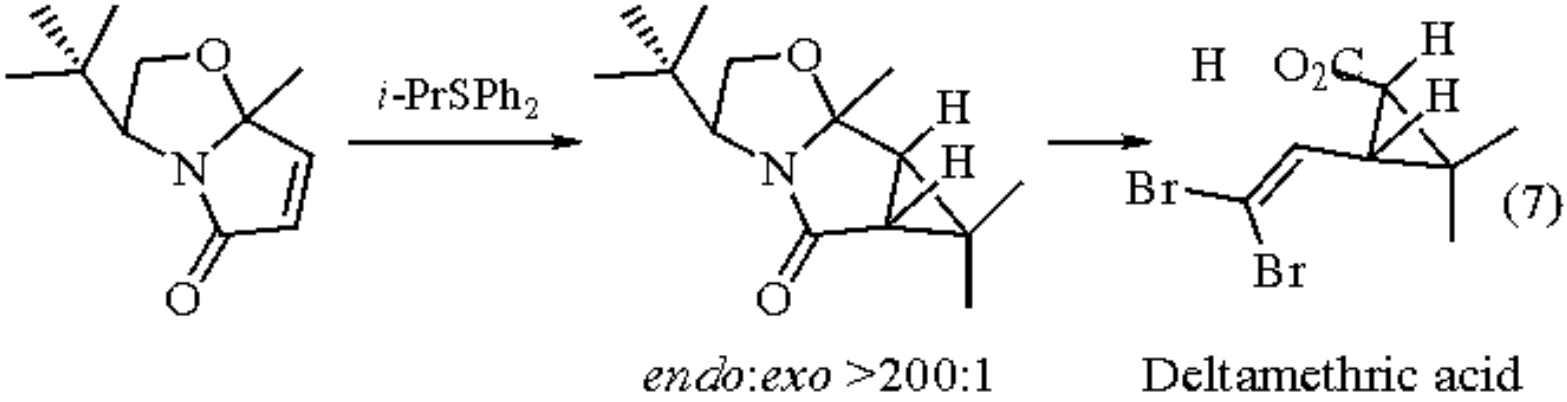

(7)

In 1988, Krief et al. used isopropylidenediphenylsulfurane to synthesize (1*R*,3*S*),*cis*-hemicaronic aldehyde, a precursor to the (1*R*,3*S*),*cis*-dibromovinylchrysanthemic acid constituent of deltamethrin (eq 8).[6,11]

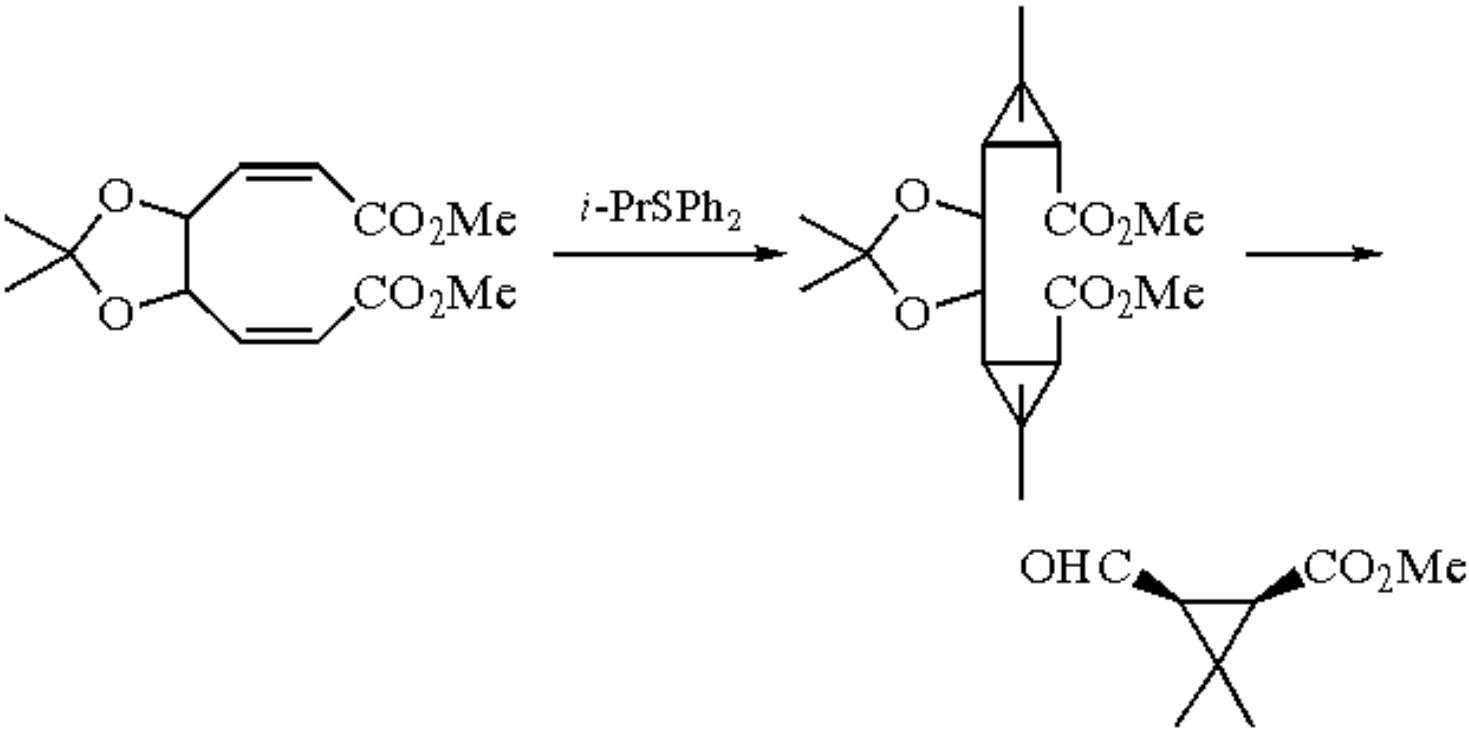

(8)

Wender et al. in 1989 used the ylide to synthesize an essential intermediate in the synthesis of phorbol (eq 9), a tumor promoter.[12]

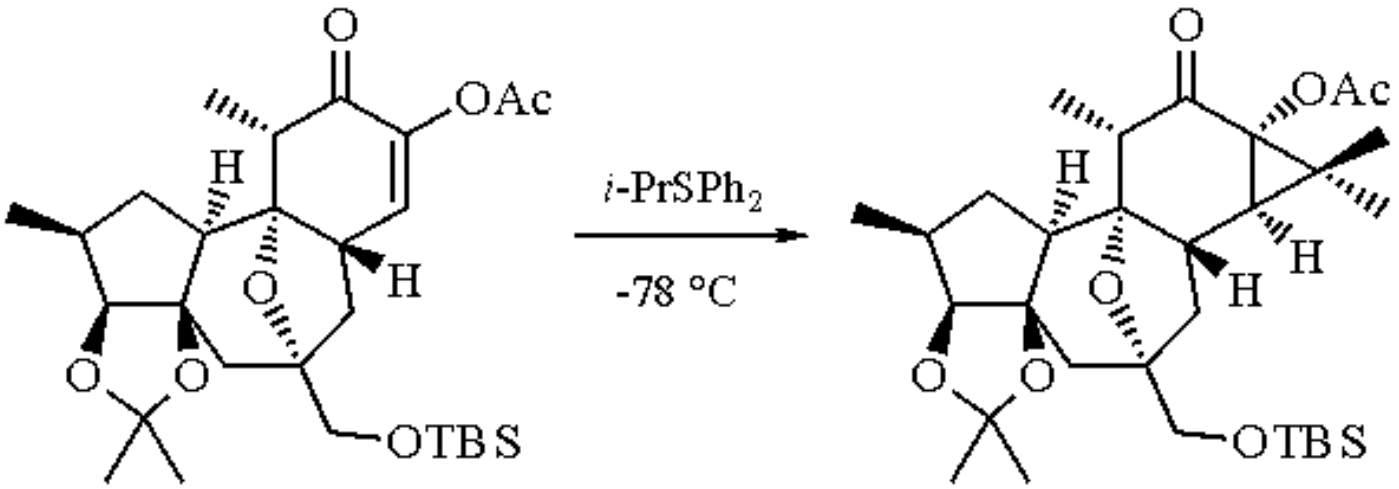

(9)

Reaction with Diene Esters.

Rapoport et al. developed an elegant synthesis of the carene ring system via reaction of 1-ethoxycarbonyl-1,3-cyclohexadiene with isopropylidenediphenylsulfurane (eq 10).[4] The regiochemistry of the cyclopropane formation depends upon the solvent used in the reaction. This dependency of the regioisomer distribution provides a convenient route to either of the two carene ring systems.

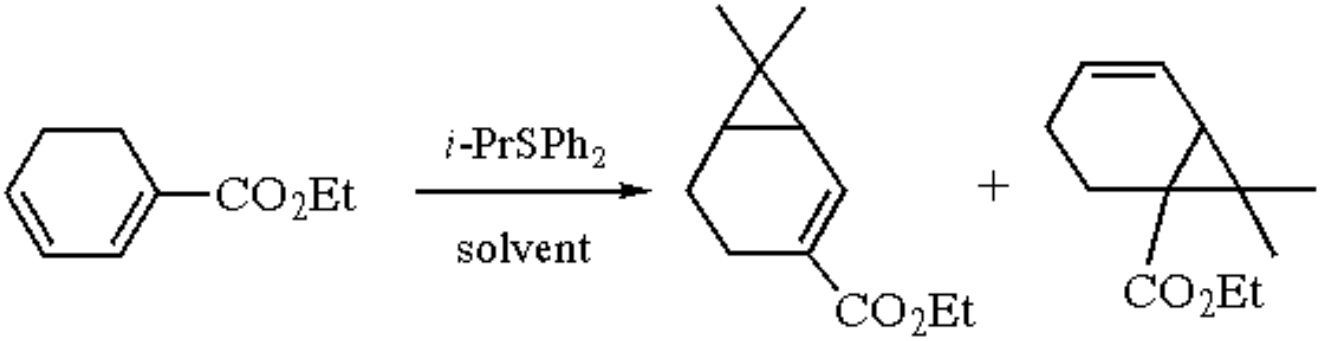

(10)

Solvent	Ratio
DME	4:1
THF	1:2

---

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(2,3-*O*-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[1]

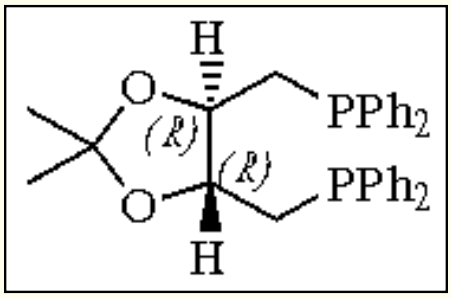

(*R*,*R*)

[32305-98-9] · $C_{31}H_{32}O_2P_2$ · (2,3-*O*-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane · (MW 498.57) (*S*,*S*)

[37002-48-5]

(chiral bidentate phosphine, useful in asymmetric catalysis[1])

Alternate Name: DIOP.

Physical Data: mp 88-89 °C; [α]20D -12.5° (*c* 4.6, C_6H_6).

Solubility: sol most usual organic solvents.

Form Supplied in: white solid; both enantiomers available.

Preparative Methods: can be prepared in four steps from diethyl tartrate.[2] The two phosphorus groups are introduced in the last step of the reaction sequence using $LiPPh_2$,[2] $KPPh_2$,[3] or $LiP(BH_3)PPh_2$.[4] DIOP has also been prepared from 1,2:3,4-diepoxybutane.[5]

Handling, Storage, and Precautions: air stable.

Introduction.

DIOP was the first example of a C_2 chelating diphosphine for transition metal complexes to be used in asymmetric catalysis. It was also one of the first examples of a useful C_2 chiral auxiliary.[6] DIOP can be considered as an example

of the first generation of chelating diphosphine ligands with a chiral carbon skeleton, which were followed over the next 20 years by many examples of chelating diphosphines, one of the most efficient of which is BINAP (***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl***).[1d] The ready availability of DIOP has stimulated research in asymmetric catalysis beyond the area of asymmetric hydrogenation.

Asymmetric Hydrogenation.

Conjugated acids (eq 1)[2,7] or various α-*N*-acyldehydroamino acids (eq 2)[2,8,9] are structural units which sometimes give quite high ee's in the presence of rhodium complexes formed in situ (such as Rh(Cl)(cod)(DIOP)) or isolated as cationic complexes, for example $[Rh(cod)(DIOP)]^+ PF_6^-$. Hydrogenation of *N*-acetamidocinnamic acid using $[Rh(DIOP)_2]^+ BF_4^-$ instead of $[Rh(cod)(DIOP)]^+ BF_4^-$ as catalyst (80 °C, 1 bar H_2) gives a slower reaction but with a significant increase in the ee (94% ee instead of 82% ee).[10]

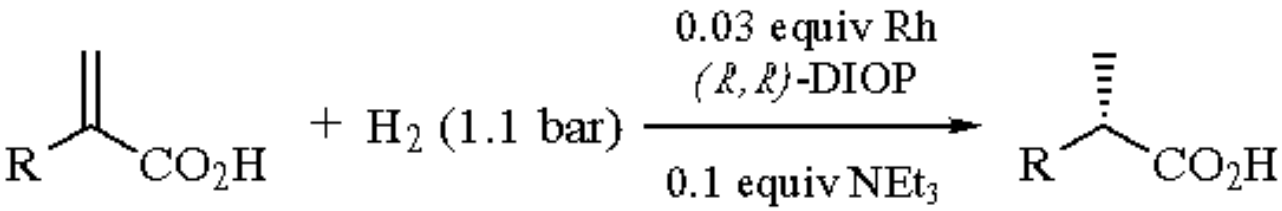

(1)

R = Ph	benzene-EtOH	95%	63% ee
R = 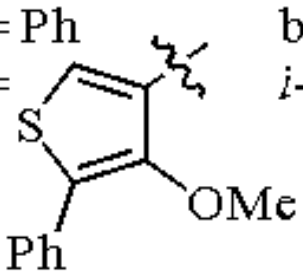	*i*-PrOH	97%	88% ee

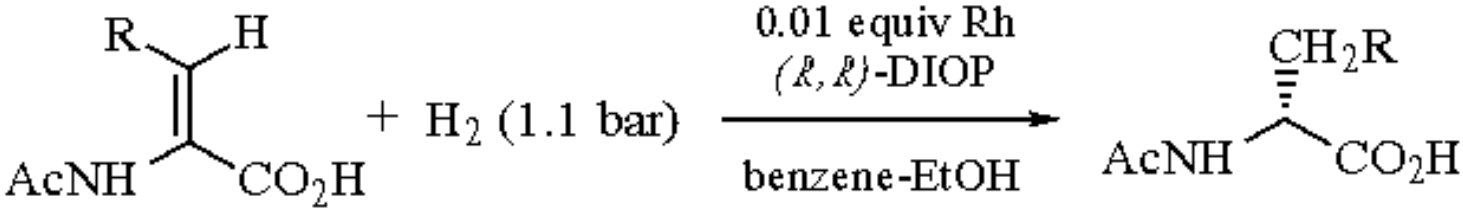

(2)

R = H	95%	73% ee
R = Ph	90%	82% ee

Enamides lacking a carboxy group on the double bond also act as excellent substrates in asymmetric hydrogenations, as exemplified in eq 3.[11]

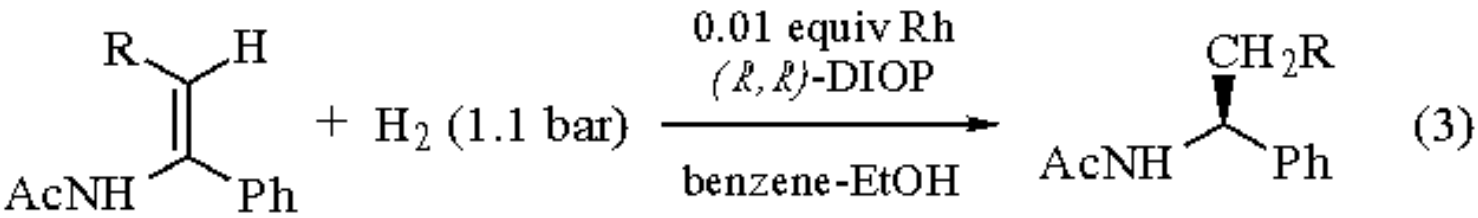

R = Et	90%	90% ee
R = Me	90%	92% ee

Ketones are known to be quite unreactive in homogeneous hydrogenations catalyzed by rhodium complexes. However, catalytic amounts of a base enhance the reactivity. In this way, acetophenone is hydrogenated to 2-phenylethanol in 80% ee in the presence of [Rh(Cl)(cod)(DIOP)]/NEt_3[12] or $N(CH_2OH)_3$.[13] Aromatic α-amino ketones are reduced to the alcohols with high ee's. For example, 2-naphthyl-*N*,*N*-diethylaminoethanol is produced in 95% ee by hydrogenation of the corresponding ketone.[13] Imines are very difficult to hydrogenate in the presence of rhodium catalysts, including [Rh(Cl)(cod)(DIOP)].[1] However, it was recently discovered that iridium complexes with a chiral chelating diphosphine are selective catalysts for the hydrogenation of imines. DIOP gives the best result (63% ee) for the reduction of $RN{=}C(Me)CH_2OMe$ (R = 2,5-$Me_2C_6H_3$).[14]

Asymmetric Hydrosilylation.

Hydrosilylation of ketones catalyzed by chiral metal complexes, followed by hydrolysis, produces enantiomerically enriched alcohols. Rhodium complexes with chiral chelating diphosphines have been used successfully. In this context, DIOP was one of the ligands investigated. Aryl alkyl ketones provide the corresponding alcohols in low ee with Ph_2SiH_2, but α-$NpPhSiH_2$ gives ee's in the range of 50-60%.[12] This silane is also excellent for hydrosilylation of *i*-butyl levulinate (84% ee) and *n*-propyl pyruvate (85% ee).[15] Imines are transformed into amines (ee <= 65%) by Ph_2SiH_2 with a rhodium-DIOP catalyst.[16]

Asymmetric Hydroformylation.

DIOP was very useful in the early stages of investigation of asymmetric hydroformylation of alkenes in the presence of rhodium or palladium catalysts. The combination of $PtCl_2$(diphosphine) and $SnCl_2$, where the diphosphine is a DIOP derivative (DIPHOL, eq 4), is an excellent system, although requiring high pressures.[17] In the case of the hydroformylation of styrene, the branched aldehyde is the major product. The various hydroformylations or hydroesterifications have been reviewed.[1e] Asymmetric hydroformylation of *N*-acylaminoacrylic acid esters is efficiently catalyzed by $[Rh(CO)(PPh_3)_3]$ + DIOP, giving the branched aldehyde in 60% ee.[18]

(2,3-O-Isopropylidene)-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

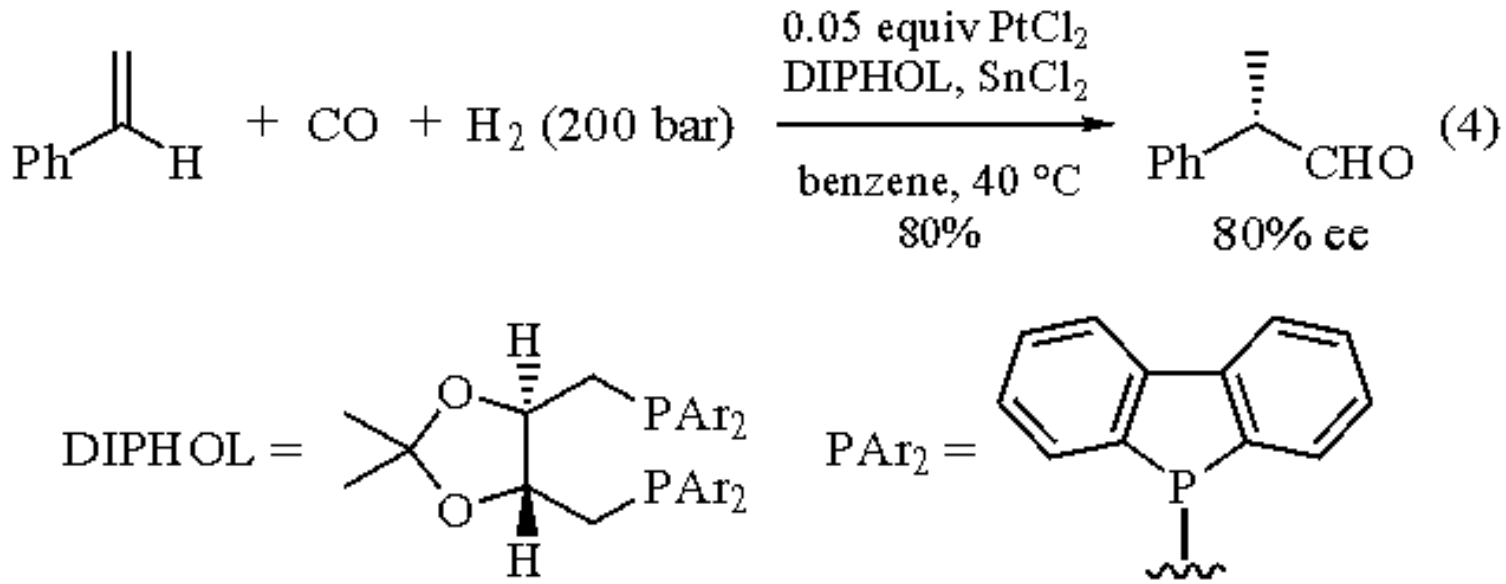

Asymmetric Hydroboration.

Hydroborations of alkenes by catecholborane have been catalyzed by [Rh(Cl)(cod)(diphosphine)].[19] For example, norbornene gives, after oxidation, *exo*-norborneol (82% ee) when a DIOP derivative (2-MeO-DIOP) was used (eq 5). Lower ee's were observed with DIOP, DIPAMP, and BINAP. The effectiveness of DIOP was also noticed in another report.[20]

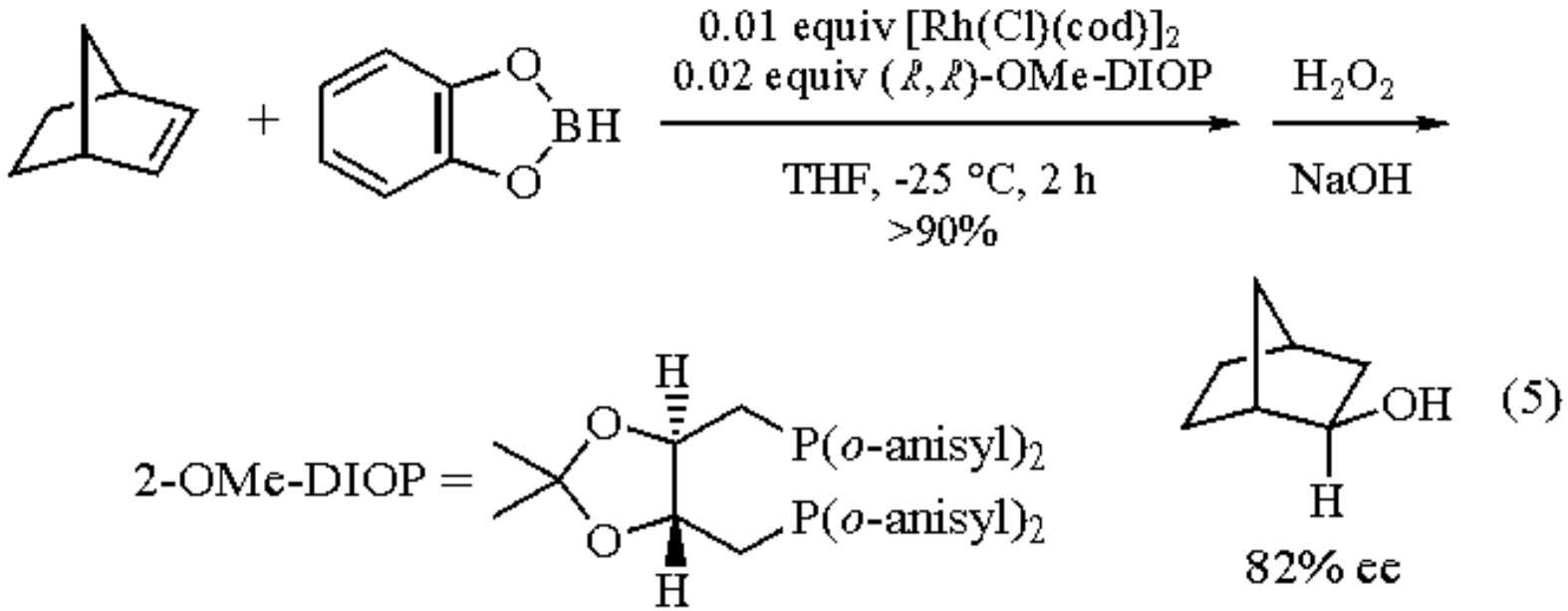

Miscellaneous Reactions.

Hydrocyanation of norbornene is catalyzed by [Pd(DIOP)$_2$], leading to *exo*-2-cyanonorbornane (16% ee), while [Pd(BINAP)$_2$] gives 40% ee.[21] An asymmetric rearrangement was catalyzed by a nickel(0) complex bearing a diphosphine ligand (eq 6).[22] A DIOP derivative (MOD-DIOP) was more efficient than DIOP or BINAP. MOD-DIOP has previously been found to improve the enantioselectivity, with respect to DIOP, in rhodium-catalyzed

hydrogenation of conjugated acids (ee's 90-95%).[23] Structural modifications of DIOP are very easy to perform by changing the nature of the aromatic rings or the acetal group, allowing tuning of the enantioselectivity. Many publications describe modified DIOP derivatives. DIOP has been utilized in several stoichiometric reactions, for example in an intramolecular Wittig reaction for the synthesis of the bis-nor-Wieland-Miescher ketone (52% ee).[24]

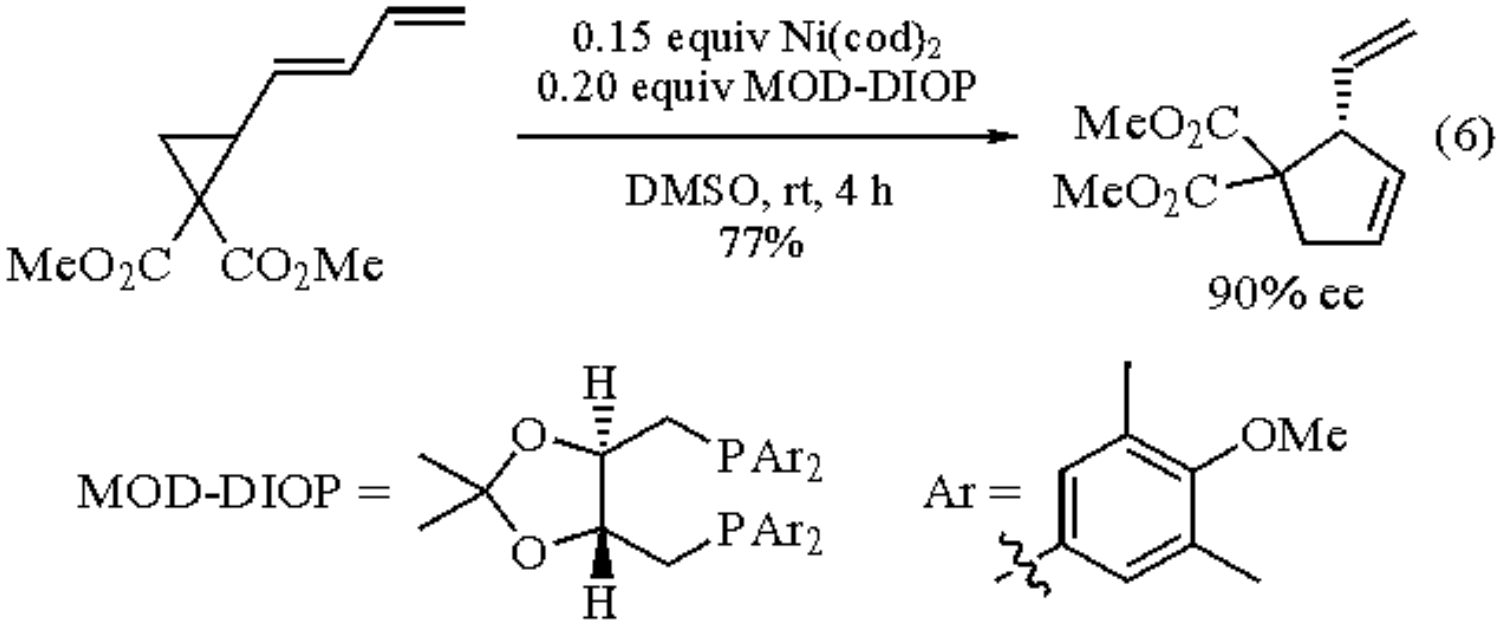

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21. (a) Hodgson, M.; Parker, D.; Taylor, R. J.; Ferguson, G. *OM* **1988**, *7*, 1761. (b) Elmes, P. S.; Jackson, W. R. *AJC* **1982**, *35*, 2041.
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23. Morimoto, T.; Chiba, M.; Achiwa, K. *TL* **1989**, *30*, 735.
24. Trost, B. M.; Curran, D. P. *TL* **1981**, *22*, 4929.

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Isopropylidenetriphenylphosphorane

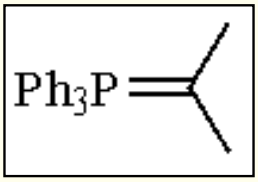

[16666-80-1] · $C_{21}H_{21}P$ · Isopropylidenetriphenylphosphorane · (MW 304.39)

(highly reactive phosphorus ylide used in natural product alkene formation[1-3] and *gem*-dimethylcyclopropane formation[4])

Physical Data: red-colored ylide in solution.

Solubility: sol THF, DMSO, toluene, diethyl ether. *Drying:* the precursor phosphonium salt should be vacuum dried before use to drive off any residual water.

Preparative Methods: prepared in situ from commercially available isopropyltriphenylphosphonium iodide or bromide and an appropriate base. An isopropyltriphenylphosphonium bromide-sodium amide instant ylide[5] pre-mix is also available.

Handling, Storage, and Precautions: should be used immediately after formation. Most ylide solutions slowly decompose with time.

Wittig Reaction.

Many natural products have an alkene terminus substituted with two methyl groups, and isopropylidenetriphenylphosphorane (**1**) has proven ideal for its construction. Terpenoids,[1] pheromones,[2] and other natural products[3] with this substitution pattern have successfully been synthesized using this reagent (eq 1).

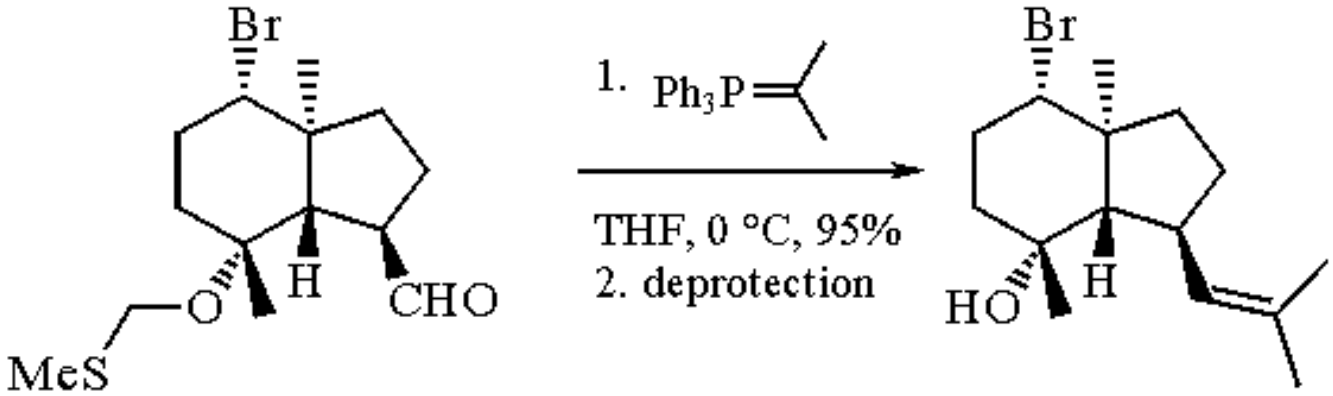

(1)

(±)-Oppositol

Tetrasubstituted alkene natural products have been obtained when isopropylidenetriphenylphosphorane reacts with cyclic ketones[6] (eq 2) and benzophenone.[7] Very few Wittig reagents are sufficiently reactive to allow formation of tetrasubstituted alkenes, and even the highly reactive (**1**) will fail to couple with hindered ketones.[8] Oxaphosphetanes are the only observable intermediates in the reactions of (**1**) with aldehydes[9] and ketones.[10] A single-electron transfer (SET) mechanism has been offered for oxaphosphetane formation in the reaction of both aldehydes[11] and ketones[7,8b] with (**1**).

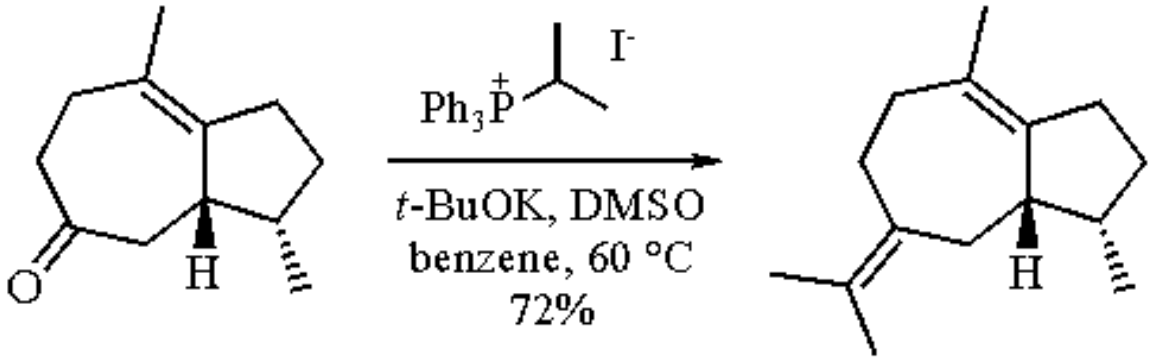

(2)

α-Bulnesene

Wittig reaction with (**1**) also occurs with lactols[12] to give alkenes, with acyl chlorides to give allenes,[13] with isocyanates to give ketenimines,[14] and with imidates to give azadienes.[15] With this phosphorane, 1,2,3-tricarbonyl compounds give alkenes at the reactive central carbon,[16] and (cyclobutadienecarbaldehyde)irontricarbonyl gives a (vinylcyclobutadiene)iron tricarbonyl complex.[17] Isopropylidenetriphenylphosphorane reacts with ***Borane-Dimethyl Sulfide*** to give a triphenylphosphine-monoalkylborane adduct, which can undergo hydroboration reactions.[18] The reagent can react sequentially with an anhydride and an alkyllithium to generate alkenes (eq 3).[19]

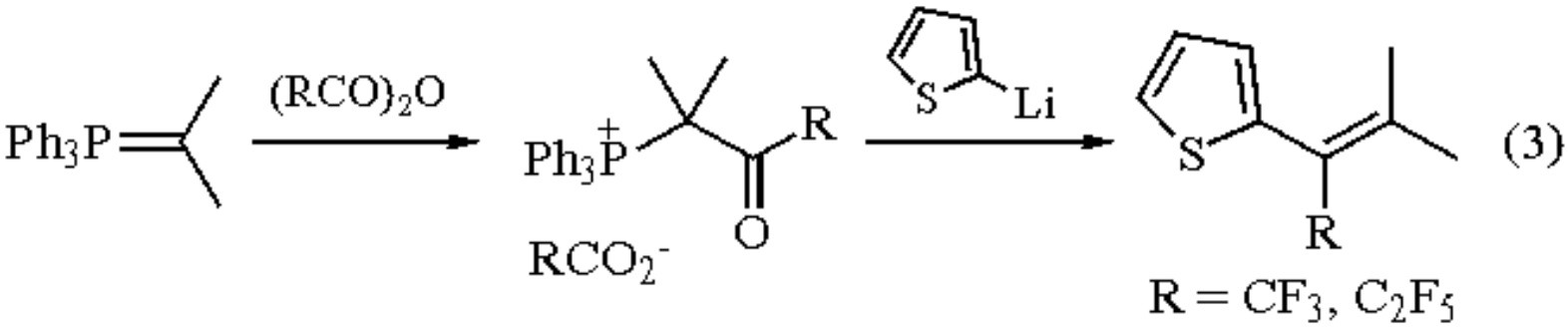

Cyclopropane Formation.

Isopropylidenetriphenylphosphorane can add to activated double bonds, such as α,β-unsaturated esters, to give *gem*-dimethylcyclopropanes after elimination of triphenylphosphine.[20] If an aldehyde is also present in the conjugated π-system, the Wittig reaction can compete with the cyclopropanation reaction (eq 4).[4] The initial lithium halide-betaine complex can decompose directly to the dienoic ester, which undergoes no further reaction. Addition of a second equivalent of (**1**) to the lithium halide-betaine complex allows cyclopropane formation to occur. Ratios of the dienoic ester and the cyclopropane are solvent and base dependent.

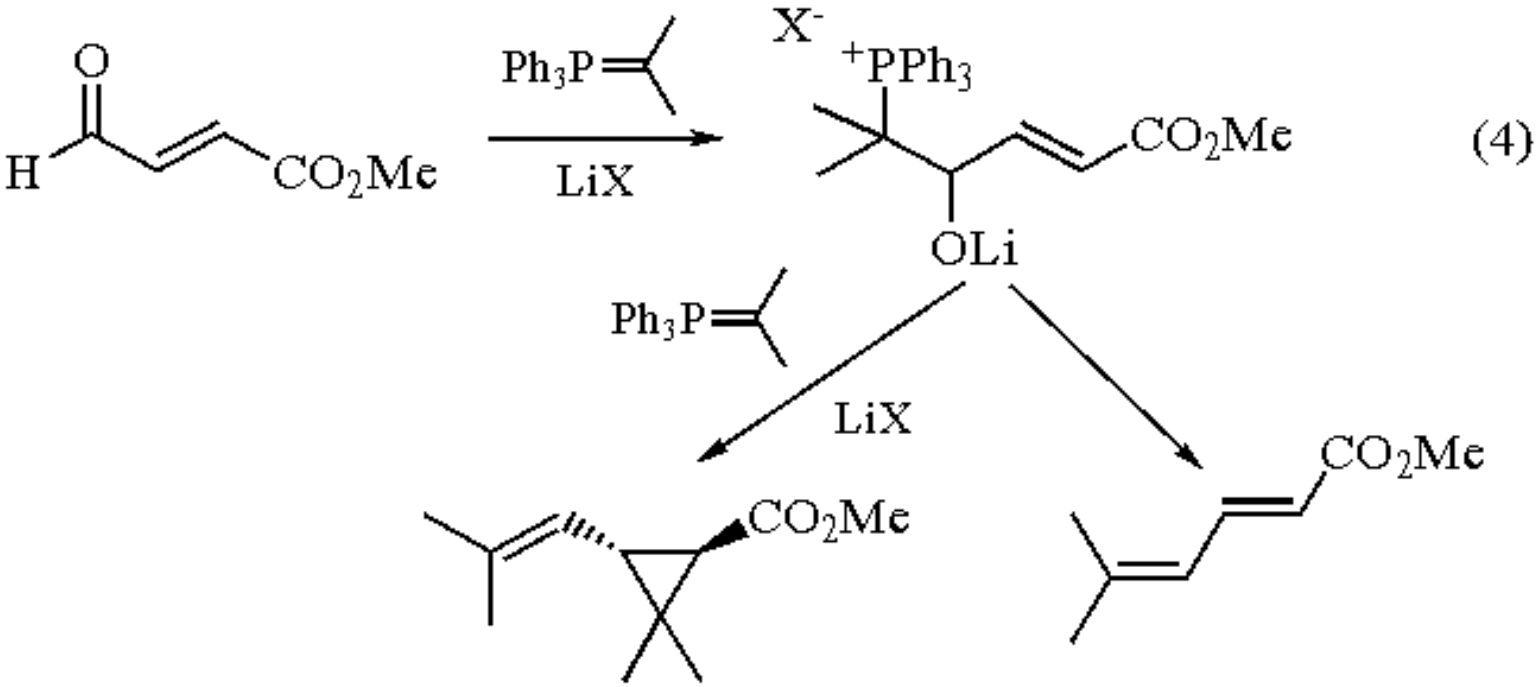

Tandem cyclopropanations can occur with dienoic esters.[21] Racemic,[22] chiral,[23] and deuterated[24] chrysanthemic acid esters are readily prepared with isopropylidenetriphenylphosphorane. 2-Metallo-2-nitropropanes afford *gem*-dimethylcyclopropanes in comparable yields.[25] Other methods to introduce a *gem*-dimethylcyclopropane structure include replacement of bromine in *gem*-dibromocyclopropanes[26] and the reaction of chromium(II) salts and 2,2-dibromopropane with alkenes;[27] however, disposal of heavy metal salts is necessary with these alternative methods. The highly reactive isopropylidenetriphenylphosphorane has been shown to react with a triene to give a cyclopropane in 75% yield.[28]

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Isopropylmagnesium Bromide[1]

***i*-PrMgX**

(X = Br)

[920-39-8] · C_3H_7BrMg · Isopropylmagnesium Bromide · (MW 147.31) (X = Cl)

[1068-55-9] · C_3H_7ClMg · Isopropylmagnesium Chloride · (MW 102.86)

(adds to many unsaturated functional groups; isopropyl can displace halide and like groups; functions as a strong base and a Lewis acid[1b-f])

Physical Data: *i*-PrMgCl is mainly dimeric in Et_2O.[2]

Solubility: *i*-PrMgBr and *i*-PrMgCl are sol Et_2O, THF; insol hydrocarbons.

Form Supplied in: solutions of *i*-PrMgCl in Et_2O and THF are commercially available.

Analysis of Reagent Purity: see ***Methylmagnesium Bromide***.

Preparative Methods: in spite of the commercial availability of *i*-PrMgCl solutions, *i*-PrMgBr[4] and *i*-PrMgCl are often prepared from reaction of an isopropyl halide and Mg, usually in Et_2O or THF.[1c,e,3]

Handling, Storage, and Precautions: see ***Methylmagnesium Bromide***. Isopropyl Grignard reagents do not significantly attack Et_2O or THF at normal reaction temperatures.

Representative Applications.[1b-f]

See also ***Methylmagnesium Bromide***. An isopropyl Grignard reagent is used most frequently in reactions that result in attachment of its organic group to an electrophilic carbon atom of the substrate, most often of a carbonyl group, nitrile, or other unsaturated function. The reaction with a chiral ketone (eq 1) serves as a reminder that, particularly with hindered substrates, isopropyl and other secondary Grignard reagents (see also ***t-Butylmagnesium Chloride***) can act significantly by transfer of an H atom rather than an alkyl group.[5]

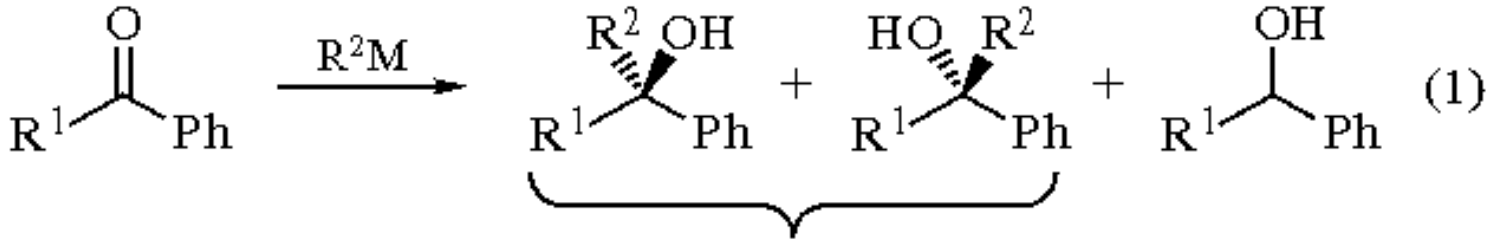

i-PrMgBr, THF, -78 °C	29%	69:31	51%
MeMgBr, THF, -78 °C	99%	100:0	0%
MeLi, Et_2O, toluene, -83 °C	97%	57:43	0%

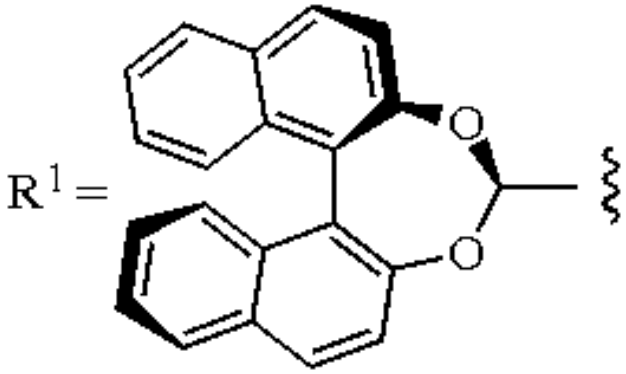

Related Reagents.

s-Butyllithium; ***t-Butylmagnesium Chloride***; ***Methylmagnesium Bromide***.

---

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Isoselenocyanatotrimethylsilane[1]

$Me_3SiN{=}C{=}Se$

[16966-40-8] · C_4H_9NSeSi · Isoselenocyanatotrimethylsilane · (MW 178.19)

(chemoselective cyanosilylation of aldehydes;[2] selenocyanosilylation of oxiranes and oxetane[3])

Alternate Name: trimethylsilyl isoselenocyanate.

Physical Data: mp 5 °C; bp 175-177 °C, 65 °C/20 mmHg, 75-76 °C/30 mmHg; *n*20D 1.5153; *d*204 1.228 g cm^{-3}.

Solubility: sol most aprotic solvents: hexane, benzene, CH_2Cl_2, THF, MeCN, etc.

Preparative Methods: by reactions of Me_3SiCl or Me_3SiI with KSeCN or AgSeCN. The following simple method is recommended: a mixture of ***Chlorotrimethylsilane*** (10 mmol), ***Potassium Selenocyanate*** (18 mmol; dried at 90 °C under vacuum (0.05 mmHg) for 4 h), and hexane or CH_2Cl_2 (20 mL) is stirred for 5 h at rt. After filtration and removal of the solvent, the residue is distilled under vacuum.

Handling, Storage, and Precautions: strongly sensitive to moisture and air; its preparation should be carried out under a nitrogen atmosphere; a one-pot procedure is recommended in which $Me_3SiNCSe$ is not isolated and the substrate is added to the isoselenocyanate reaction mixture.

Chemoselective Cyanosilylation of Aldehydes.[2]

There is virtually no reaction between the title reagent and aldehydes in the absence of catalyst. ***Zinc Chloride*** and KSeCN increase the reaction rate, whereas KSeCN/18-crown-6 has a slight rate-diminishing effect. The reaction proceeds smoothly only in nonpolar solvents such as hexane and CH_2Cl_2, giving the corresponding *O*-silylated cyanohydrins (eq 1).

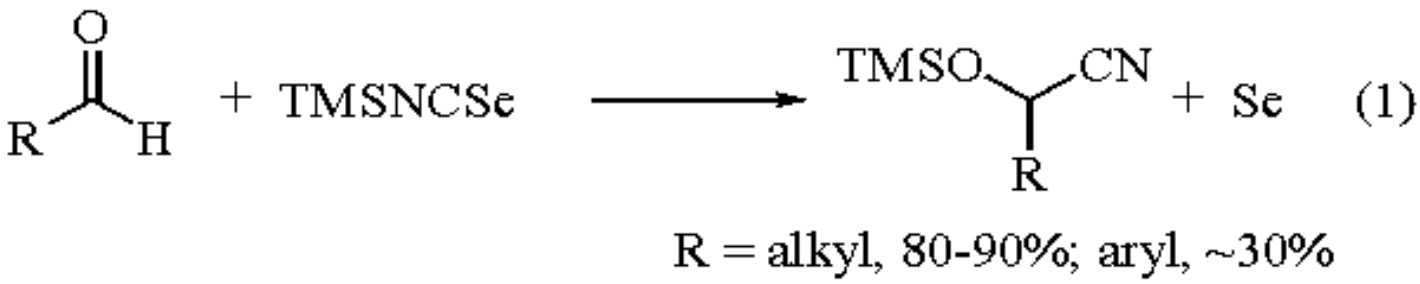

No reaction takes place with ketones and the reaction is very slow with aromatic aldehydes and α,β-unsaturated aldehydes. Consequently, highly chemoselective cyanosilylation of aldehydes is achieved: the results of competition experiments between hexanal and 2-heptanone (1:1 mixture, eq 2), between hexanal and benzaldehyde (1:1 mixture, eq 3), and between propionaldehyde and crotonaldehyde (1:1 mixture, eq 4) are summarized. The use of ***Cyanotrimethylsilane*** in place of the title reagent leads to lower chemoselectivities. Unfortunately, only slight chemoselectivity is achieved between hexanal and isobutyraldehyde (eq 5).

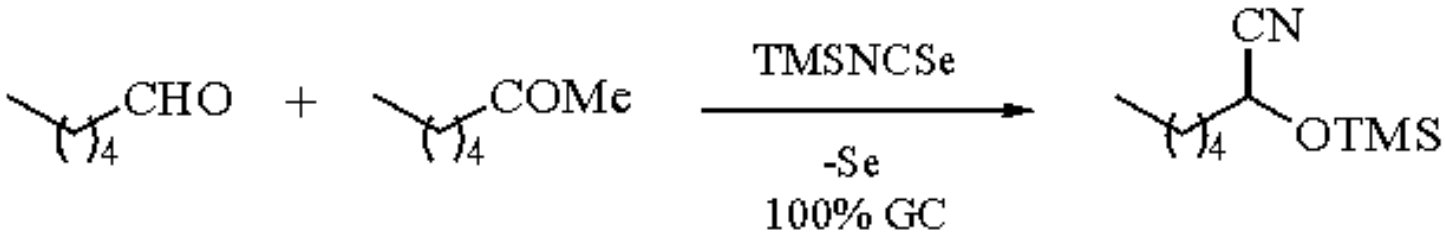

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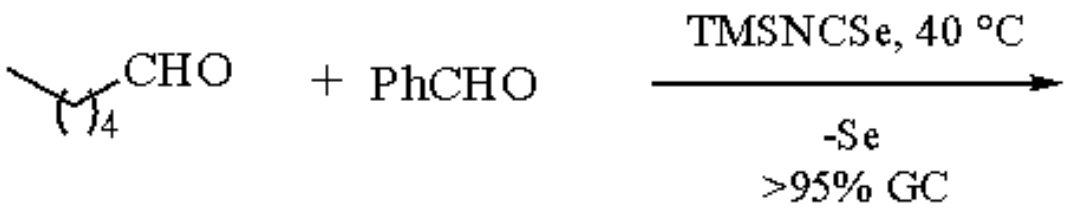

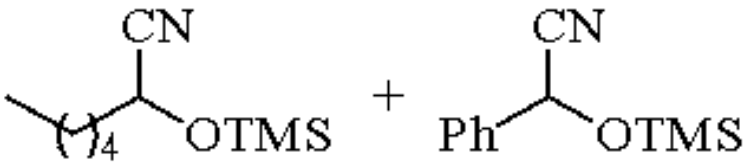

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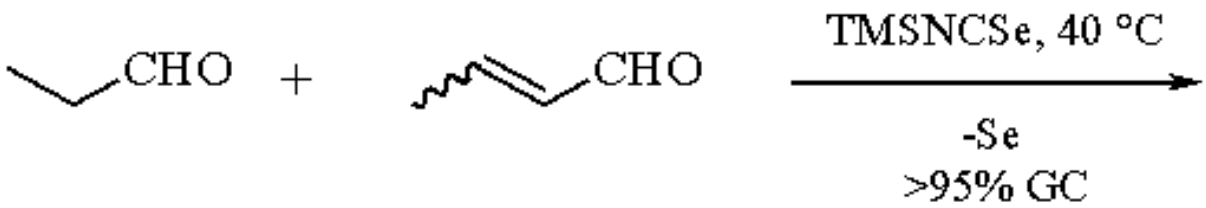

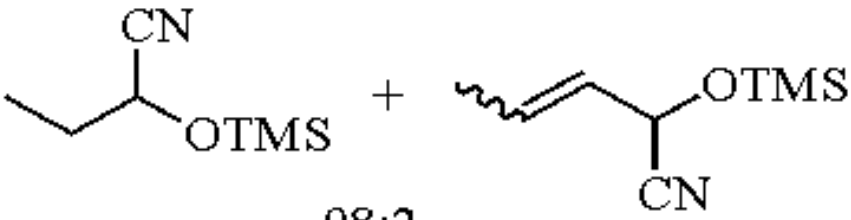

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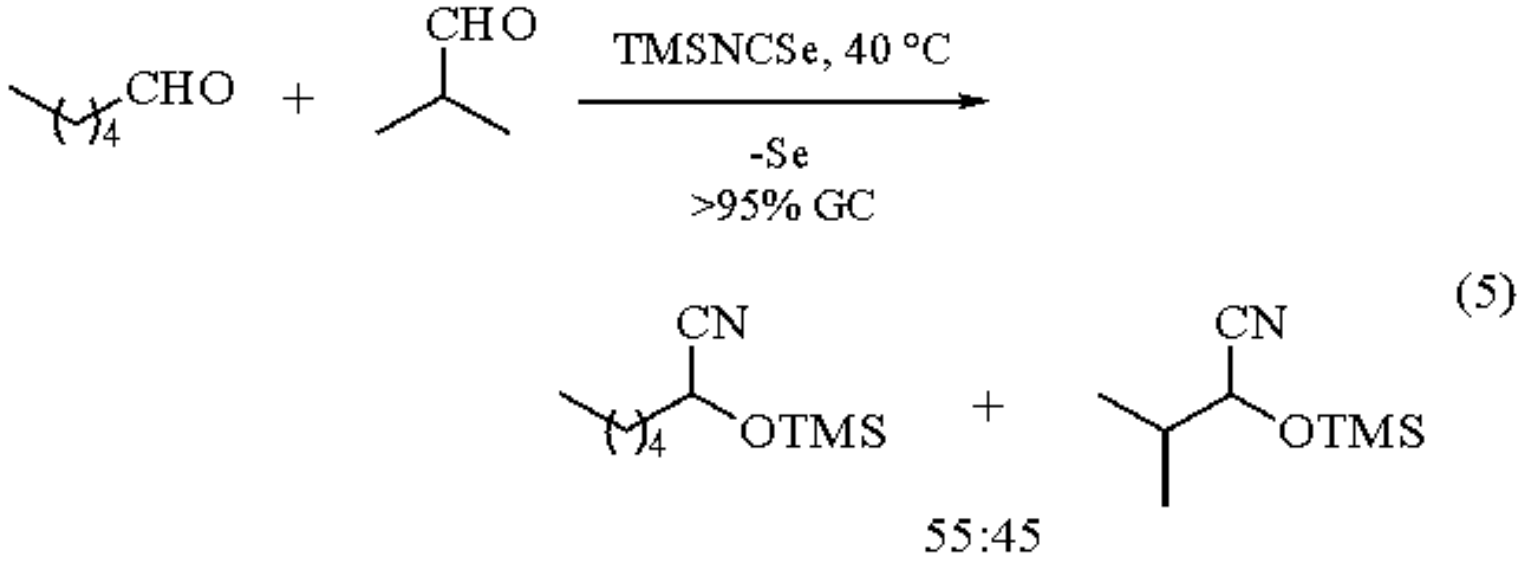

(5)

Ring Opening of Oxiranes and Oxetane.[3]

The reaction with oxiranes gives trimethylsiloxyalkyl selenocyanates (eq 6) in good to excellent yields. KSeCN, KSeCN/18-crown-6, KSeCN/XAD-4 (KSeCN impregnated on Amberlite XAD-4 resin), $ZnCl_2$, and Ti(O-*i*-Pr)$_4$ promote the reaction.

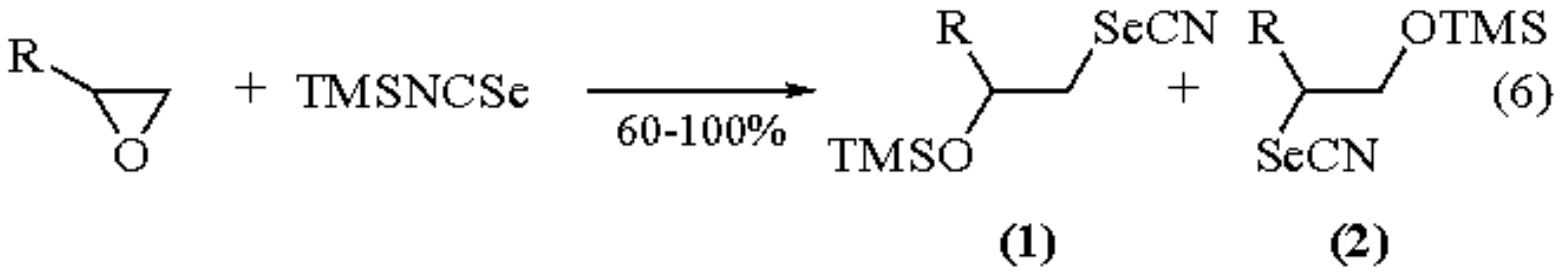

(6)

In general, the reaction proceeds smoothly in polar solvents such as MeCN. The reaction of 1,2-epoxyalkanes having a substituent at the C-3 position gives products in which the epoxide is opened selectively at the less-hindered carbon (product **1** in eq 6). On the other hand, the reaction of 2-phenyloxirane or 2,2-dimethyloxirane gives a mixture of regioisomers, the ratio of which depends on the catalyst and the solvent (eqs 7 and 8). The reaction of oxetane produces 3-trimethylsiloxypropyl selenocyanate in excellent yield.

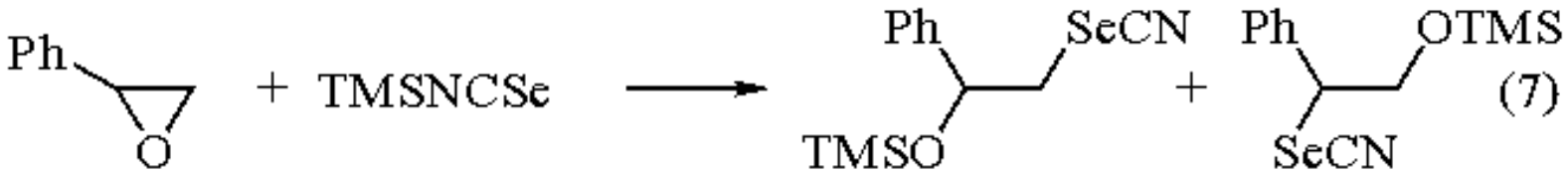

(7)

KSeCN, hexane, 60 °C, 7 h	75:25	93%
Ti(O-*i*-Pr)$_4$, hexane, 40 °C, 0.5 h	3:97	72%

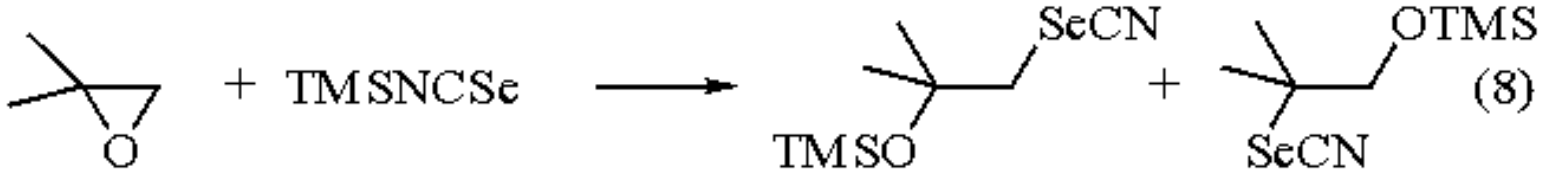

KSeCN/XAD-4, hexane, 60 °C, 7 h	82:18	84%
Ti(O-*i*-Pr)$_4$, hexane, 40 °C, 3 h	34:66	71%
KSeCN, MeCN, 60 °C, 2 h	37:63	66%

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Itaconic Anhydride

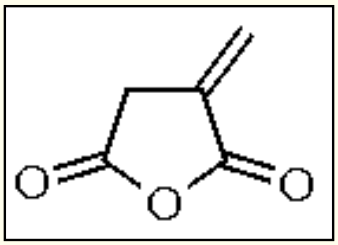

[2170-03-8] · $C_5H_4O_3$ · Itaconic Anhydride · (MW 112.09)

(asymmetrical unsaturated anhydride; used as a dienophile[5] and in reactions with various nucleophiles[9,10])

Physical Data: mp 70-72 °C; bp 114-115 °C/12 mmHg.

Form Supplied in: white solid; widely available.

Preparative Methods: besides its synthesis from citric acid,[1] itaconic anhydride (**1**)[2] can also be prepared by chemical dehydration of itaconic acid.[3] The thermal isomerization of itaconic anhydride to citraconic anhydride (**2**) is facile.[4]

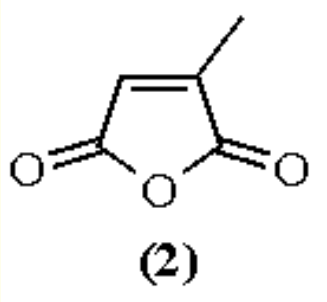

Handling, Storage, and Precautions: moisture sensitive; irritant.

Pericyclic Chemistry.

Diels-Alder chemistry employing (**1**) as a dienophile is well developed. ***Cyclopentadiene*** has been used to protect the exocyclic methylene of (**1**) with regeneration of the alkene moiety via a retro-Diels-Alder thermolysis.[5] By operating at 6.5 kbar for 8-10 d, excellent regioselectivity and face selectivity has been obtained in the reaction of (**1**) with the chiral diene (**3**).[6] Itaconic anhydride, with its conjugated carbonyl group participating in secondary orbital overlap, undergoes 1,3-dipolar cycloaddition (eq 1) with the nitrone (**4**) to afford (**5**).[7]

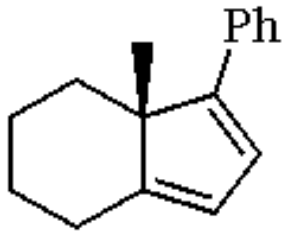

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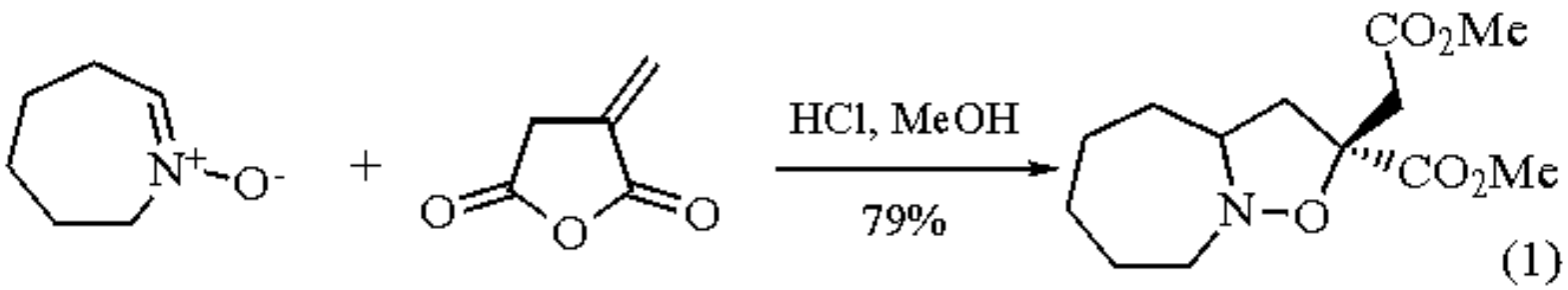

(1)

(4) (1) (5)

Reaction with Nucleophiles.

Because a variety of 2-methylenebutanedioic acids and acid derivatives display useful[8] pesticidal, herbicidal, and growth-regulatory activities, much effort has gone into exploring the reaction of the anhydride moiety with nucleophiles. Ring opening of (**1**) is highly regioselective. Thus (**1**) reacts with alcohols[9] to afford (**6a**) (with preferred addition at the unconjugated carbonyl). With amines,[10] similar regioselectivity affords the corresponding amides (**6b**). Reaction with hydroxylamine derivatives gives acids (**6c**), imides, or isoimides depending on conditions.[10b] Friedel-Crafts acylation of (**1**)[11] yields the ring-opened product (**7**) involving acylation at the less-substituted carbonyl.

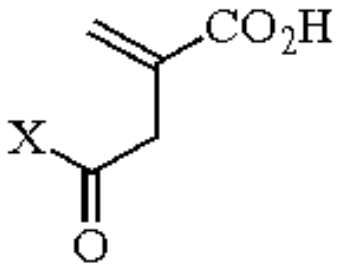

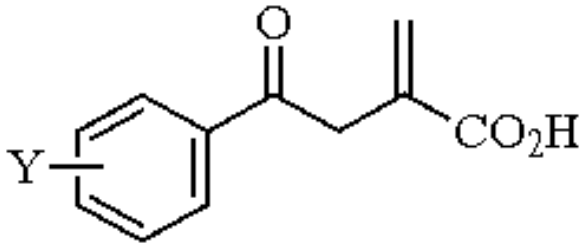

(6a) X = OR
(6b) X = NH_2, NHR, NR_2
(6c) X = NHOR

(7)

Miscellaneous Chemistry.

Halogenation of (**1**) yields halomethylmaleic anhydrides (**8**).[12] Asymmetric hydrogenation of (**1**) has been explored.[13] Hydrocobaltation of (**1**) gives (**9**).[14] Reaction of (**1**) with thiourea in water or in acetic acid produces a variety of

heterocycle products,[15] as does the reaction of (**1**) with enamino esters.[16]

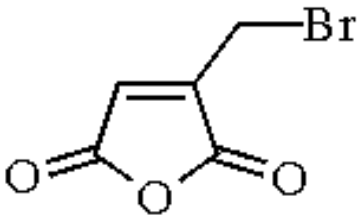

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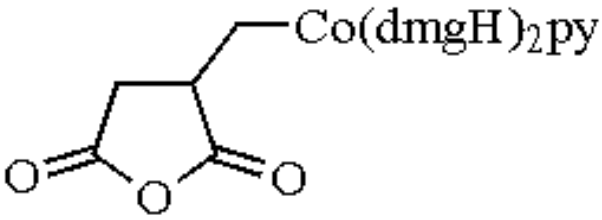

(9)

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Ketene[1]

$H_2C=C=O$

[463-51-4] · C_2H_2O · Ketene · (MW 42.04)

(mild acetylating reagent;[1] performs [2 + 2] cycloadditions with alkenes and alkynes;[1c] performs nucleophilic addition to acetyl chlorides;[2] capable of certain organometallic transformations[3])

Physical Data: mp -150 °C; bp -56 °C.

Solubility: generally introduced as a gas but is soluble in a wide variety of solvents.

Preparative Methods: by the thermal decomposition of acetone,[4] diketene,[5] acetic anhydride,[6] alkoxy[7] or siloxy acetylenes,[8,9] and carboxylic acid over zeolites.[10] Acetic anhydride gives the purest stream of this gas. The use of acetone, diketene, or acetic acid may leave impurities such as acetone and carbon monoxide.

Handling, Storage, and Precautions: poisonous gas with a toxicity approximately eight times greater than phosgene.[11] All operations utilizing ketene should be carried out in an appropriate isolated apparatus in a well-ventilated fume hood.[5,11]

Acetylating Reagent.

The electrophilic nature of the sp carbon in ketene makes it a powerful yet mild acetylating reagent.[1,12,13] Unlike other reagents such as ***Acetic Anhydride***, ketene has no leaving group; the opening of the double bond being its equivalent.[14] This feature ensures fewer byproducts in the reaction mixture, allowing for easier purification of the product. Ketene will acetylate a wide variety of functional groups, including carboxylic acids, alcohols, amines, amides, thiols and 1,3-dione systems.[1a,14-16] One of the more recent uses of ketene in this area is the acetylation of β-diketone Cu^{II} intermediates (eq 1).[12] This reaction proceeds quickly at room temperature, without the need of a catalyst, the sole product being that arising from *C*-acetylation. Other attempts to introduce substitution into this system using alternative reagents not only required higher temperatures and the use of catalysts, but have resulted in the formation of both *C*- and *O*-acetylated products.[17,18] These reactions also resulted in the loss of the Cu-O bond, which the ketene reaction does not affect.

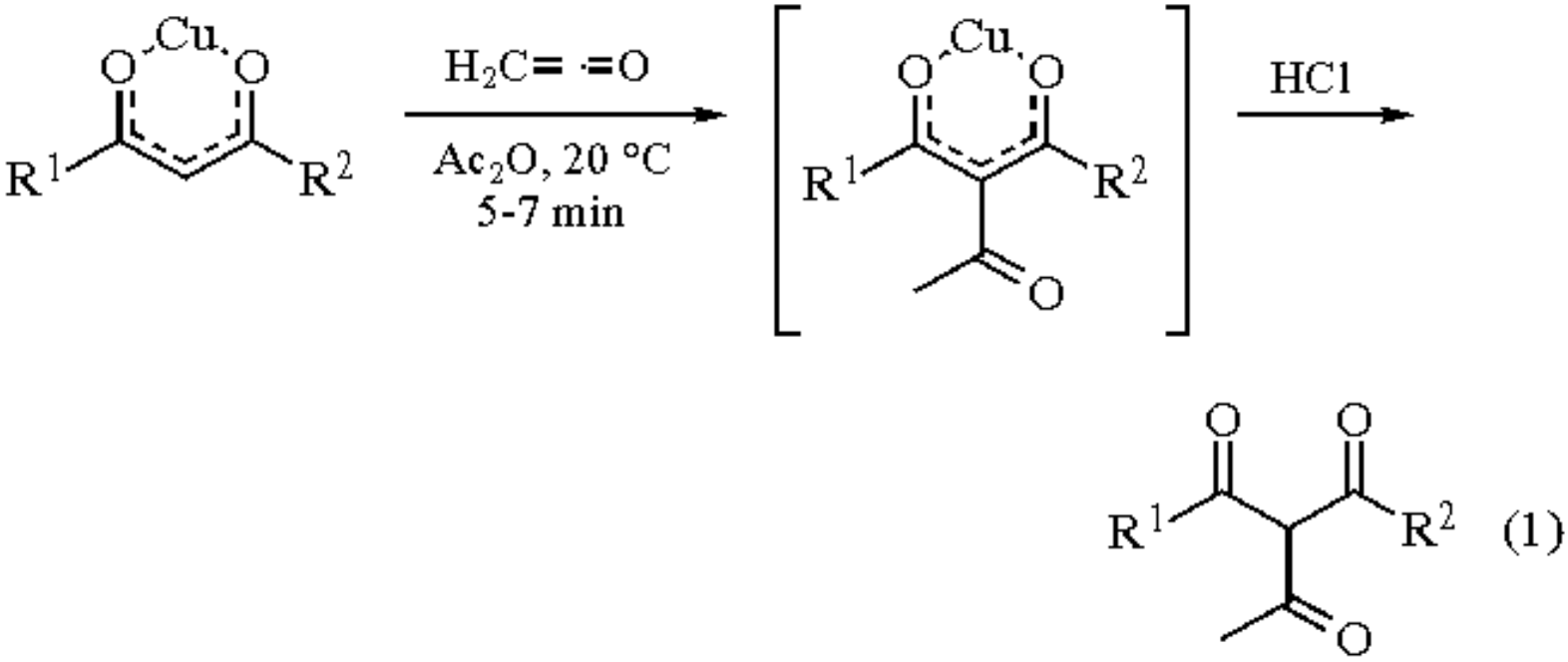

Ketene has also been used in acetylating cyclic diones to form the corresponding 1,3-cycloalkadienes (eq 2).[15,16] The formation of the 1,3-cycloalkadienes was previously accomplished by a Birch reduction of the corresponding aromatic derivatives.[15] For rings larger than six atoms in size, the use of ketene will result in *C*-acetylation as well as *O*-acetylation, and ***Isopropenyl Acetate*** has been shown to be more effective in this case.

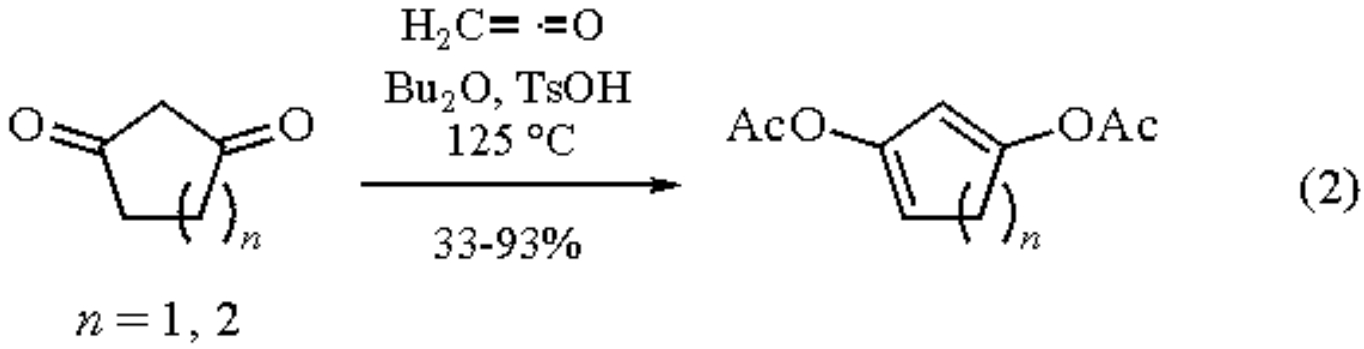

Ketene is also a good acetylating reagent in reactions where the starting material has been absorbed onto a solid medium. The acetylation of phenol usually requires the use of high temperatures and a catalyst.[19] Even under these conditions, the reaction proves to be inconsistent. If phenol is first absorbed onto silica, however, acetylation may take place in good yield by passing a stream of ketene through the medium as a gas at room temperature. Phenol derivatives absorbed on alumina have also been shown to acetylate quantitatively at 0 °C when exposed to ketene gas.[19] This reaction has been shown to be quite versatile and may accommodate a wide variety of alcohols on many absorbants including celite, magnesium oxide, and zinc oxide.[20] The ease of acetylation using ketene may also be shown by the following example (eq 3). The thermal fragmentation of 1-alkoxyalkynes in chloroform allows for the easy formation of ketene in situ. When this process is carried out in the presence of an amine, the ketene is trapped upon formation, giving the resulting amide.[7] As shown in eq 3, this reaction offers a mild process for acetylation which should be suitable for a wide variety of nucleophiles.[7]

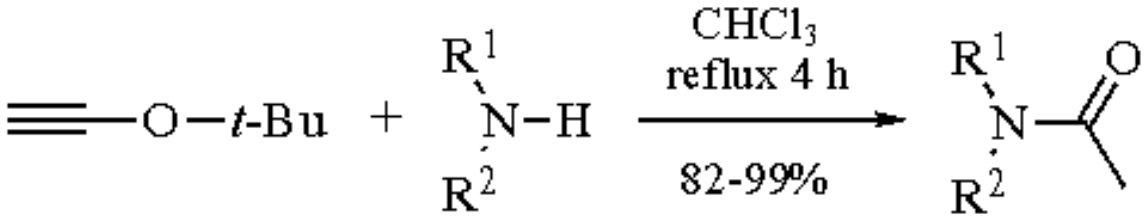

(3)

$R^1 = H, i\text{-Pr}$
$R^2 = C_6H_{13}, t\text{-Bu}, HOCH_2CH_2, Bn, Ph, i\text{-Pr}, Cy$

Cycloadditions.

Cycloaddition involving ketene and its derivatives is probably the most characteristic reaction involving this reagent. Examples of 1,2-cycloaddition to form four-membered rings are known to occur between ketene and C&tbond;C, C=C, C=O, C=N, C=S, N=N, N=O, N=S, and P=N groups.[1c,1a] These reactions are generally considered to proceed via a $_{\pi}2_s + {}_{\pi}2_a$ thermally allowed cycloaddition following the Woodward-Hoffmann rules.[1c] The cycloaddition proves to be highly selective,[13] the most nucleophilic alkenic carbon becoming bonded to the sp carbon of ketene in the product. Addition occurs with retention of configuration of the alkene.[1a] In many cases, ketene proves to be too unreactive for the task at hand and ***Dichloroketene*** has become the reagent of choice in recent years. The relative reactivities of some ketenes in reference to cycloadditions are shown in Scheme 1.[1a]

$$Cl_2C{=}{=}O \;>\; Ph_2C{=}{=}O \;>\; Me_2C{=}{=}O \;>\; H_2C{=}{=}O$$

Scheme 1

Alkene Addition.

There are few examples of alkene addition to ketene itself. The alkene generally has to be activated either through the use of an EDG or strain in the system, such as the case with cyclopentadiene (eq 4)[21,22] and 1,3-cyclohexadiene (eq 5).[22] Linear conjugated dienes will sometimes react with ketene but yields are generally quite low and the reaction is not synthetically useful. Again, dichloroketene is generally used in this case due to its greater reactivity (eq 6).[1c,23]

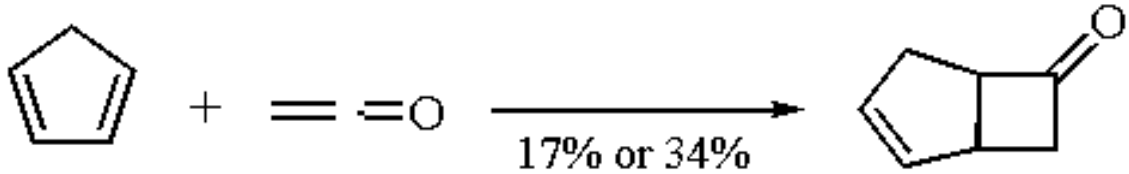

(4)

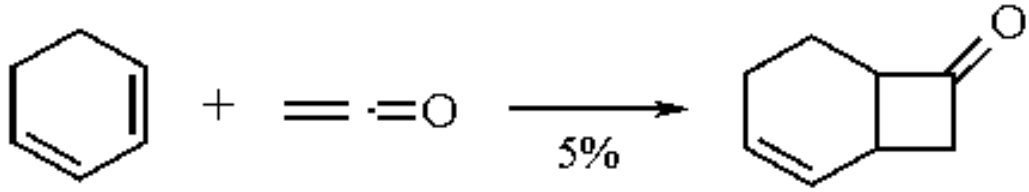

(5)

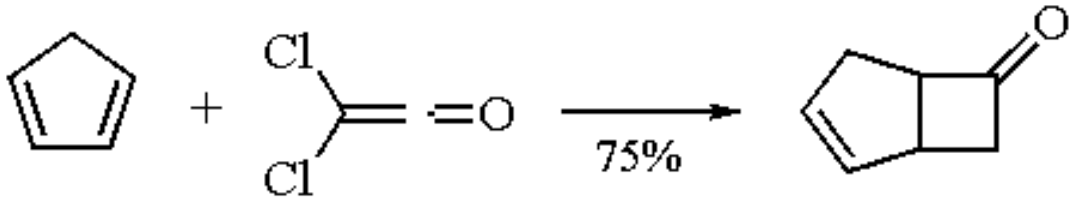

(6)

One example of the use of ketene with an activated alkene is in the case of vinyl ethers.[24,25] Staudinger had shown in 1920 that ***Diphenylketene*** would add to ethyl vinyl ether to form the 1,2-cycloaddition product.[1c] This reaction was repeated by others,[26,27] and in 1960 Hurd was able to show that ketene itself would also add to a vinyl ether.[24] Seija built upon this methodology later when he used a variety of vinyl ethers along with ketene to gain access to the synthetically interesting bicyclo[1.1.0]butane systems, as shown in eq 7.[25] The reaction is regiospecific in that the methylene group in the product is bonded to the carbon attached to the ether oxygen.[24,25]

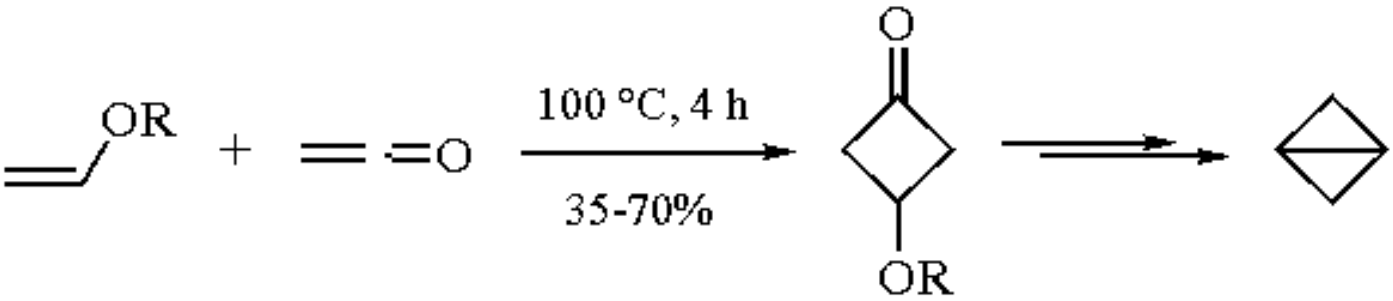

(7)

Alkyne Addition.

The alkyne bond is sufficiently high in energy to perform 1,2-cycloadditions with ketene in the formation of cyclobutenones.[28] Wasserman[29] and Pericás[30] utilized this reaction in the formation of 1,3-cyclobutanedione. The latter synthesis used the alkyne as a source of ketene as well as the cycloaddition partner (eq 8). More recently, siloxyalkynes have been shown to undergo the same type of reaction utilizing a wide variety of R groups (eq 9); a multitude of cyclobutenone systems can thereby be constructed.[31]

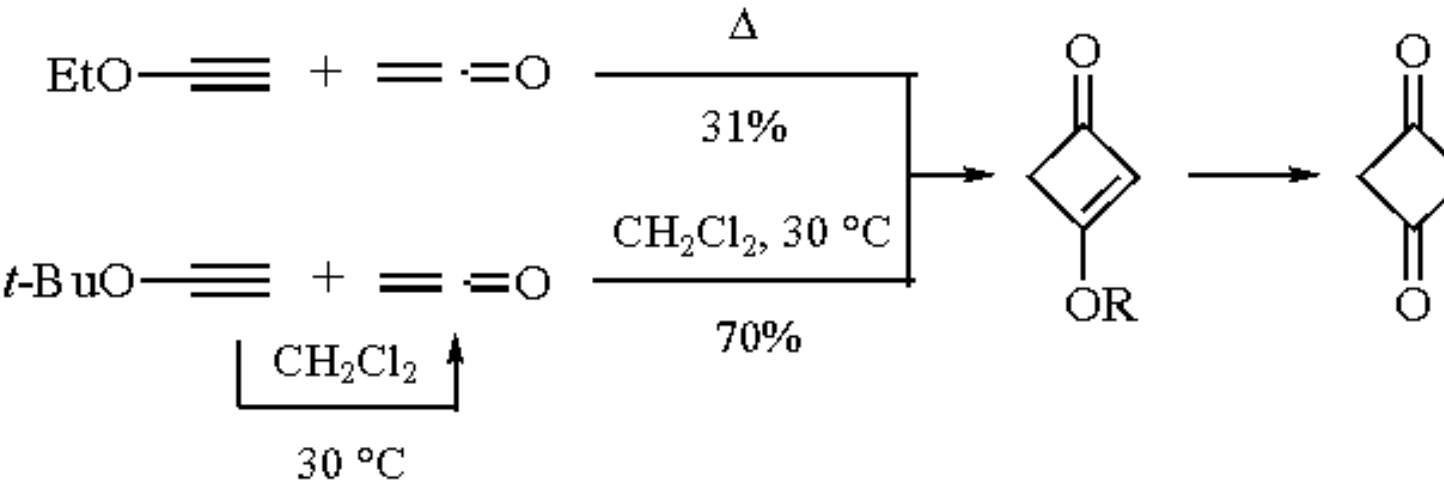

(8)

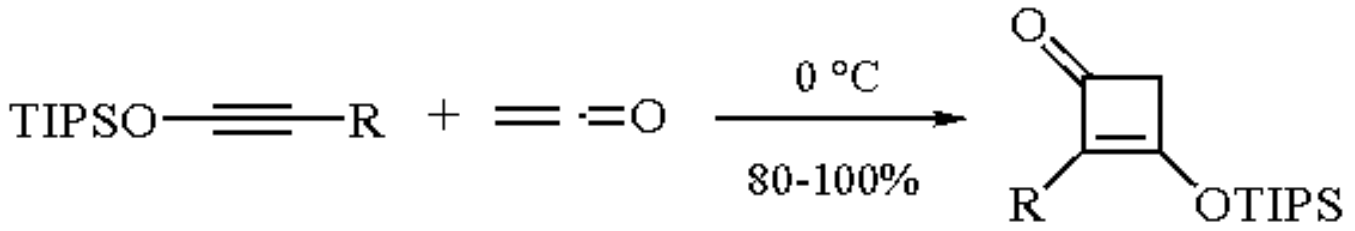

(9)

C=X Cycloaddition.

The cycloaddition reaction of ketene to a C=O bond is a very synthetically useful reaction which allows formation of the 2-oxetanone system (β-lactone).[1] The rate of reaction is controlled somewhat by the polarization of the carbonyl bond. The greater the positive charge of the carbonyl carbon, the greater the rate of reaction.[32] The cycloaddition of ketene with the carbonyl bond requires a catalyst for reaction to occur.[1a] Ketene will readily couple with chloral in the presence of a catalyst to form β-(trichloromethyl)-β-propiolactone.[33] Using chiral cinchona alkaloid catalysts, it is possible to form the chiral 4-(trichloromethyl)-2-oxetanone beginning with ketene and chloral. Acid hydrolysis of the cyclic product allows the formation of optically pure (*S*)- or (*R*)-malic acid in 79% yield (eq 10).[32,34]

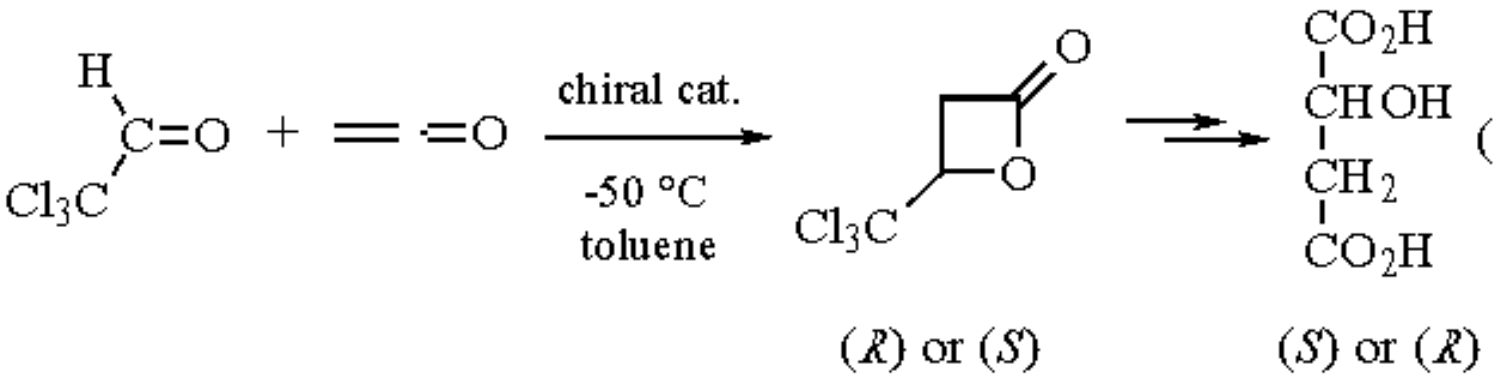

(10)

This compares quite well with more involved routes which begin with chiral tartaric acids[35] or the use of enzymatic catalysts, which allow for synthesis of the (*S*)-isomer but not the unnatural (*R*)-isomer.[36] Chiral polymeric cinchona alkaloids have also been employed in the reaction.[37] The use of polymeric catalysts allows greater ease of recycling and in some cases, such as poly(cinchona alkaloidacrylate), the enantioselectivity and yields were comparable to their monomeric counterparts.[37]

The cycloaddition of ketene to a C=N bond was first discovered by Staudinger in 1907 and is often referred to by that name.[38] The reaction proceeds regioselectively via a nonconcerted mechanism to give the β-lactam (eq 11).[39-41] Ketene itself is quite unreactive towards the imine group;[1c,42] however, reactions with the disubstituted ketenes proceed well.[42] Among the more popular ketenes utilized for this reaction are diphenyl-, chlorophenyl-, and dibromoketene.[42]

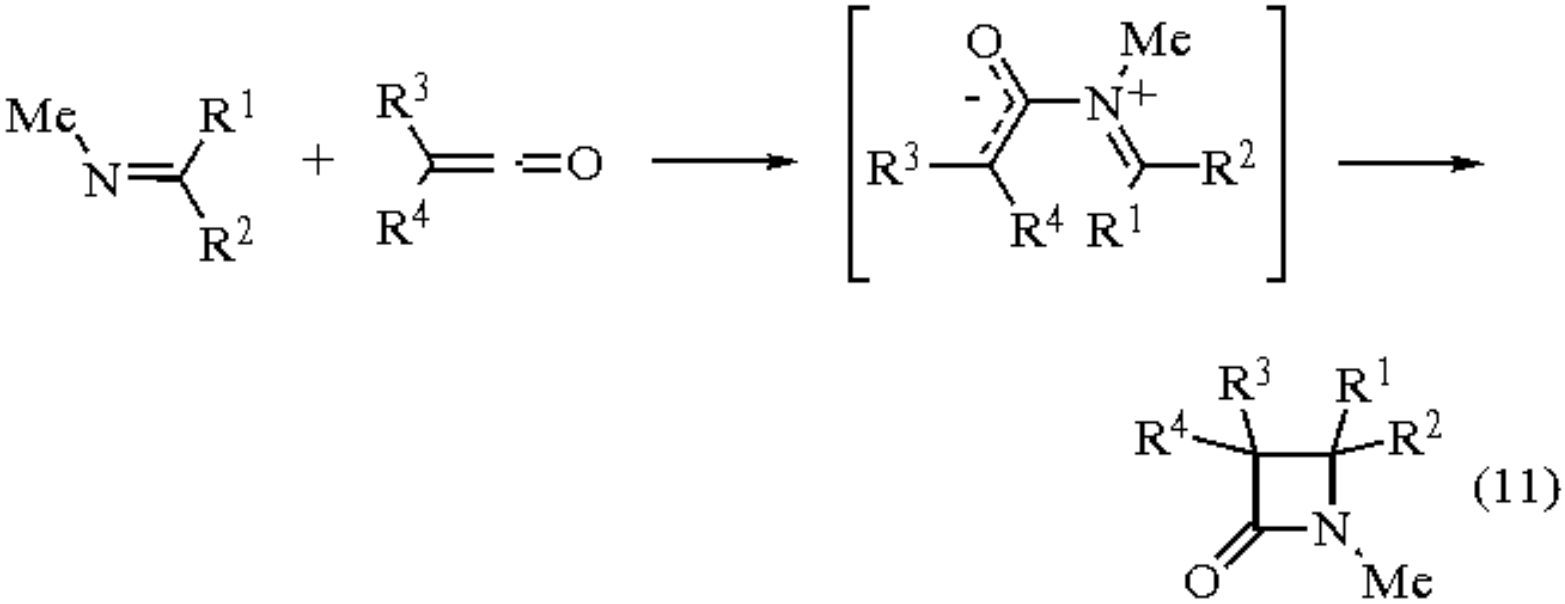

(11)

Diazomethane Cycloaddition.

The reaction of ketene with ***Diazomethane*** offers a simple, high yielding synthesis of cyclopropanone, a molecule of both theoretical and synthetic interest.[43] In the presence of methanol and excess ketene, cyclopropanone may be further acetylated, as shown in eq 12. Reaction with excess diazomethane results in the formation of cyclobutanone.[43,44] Earlier methods to prepare cyclopropanone from cyclobutanediones met with little success.[45]

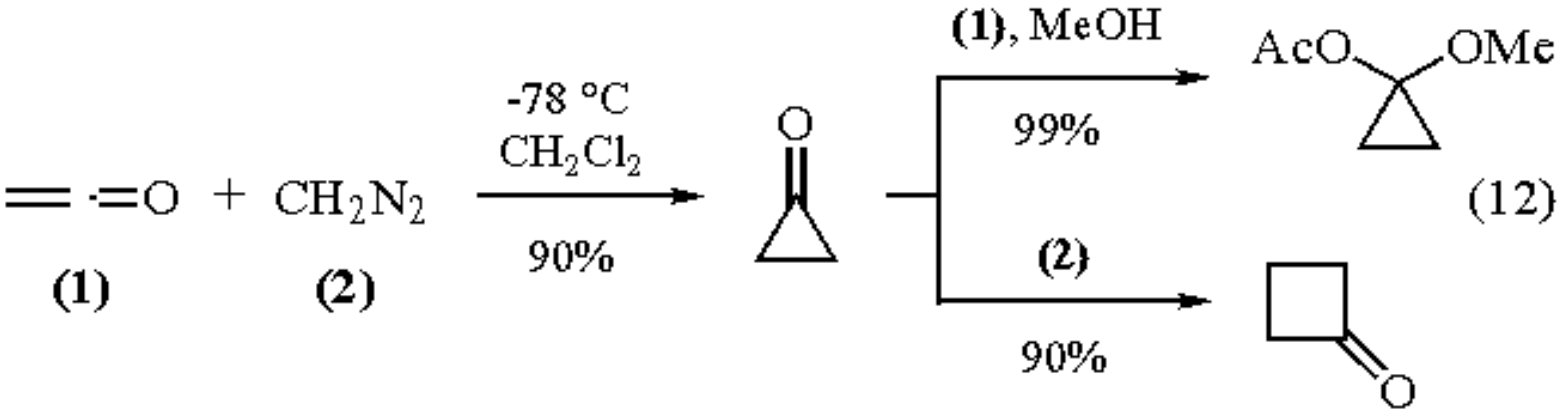

(12)

1,3- and 1,4-Cycloaddition.

Cyclizations of this type are quite rare using ketene itself, although ketene derivatives have been known to undergo 1,3- and 1,4-cyclizations.[1]

Allene Formation.

The reaction of ketene with an ylide proves to be a convenient method for the formation of allenes. In the reaction with the ylide shown in eq 13, the α-vinylidene-γ-butyrolactone, which holds biological interest, may be formed in high yield.[46]

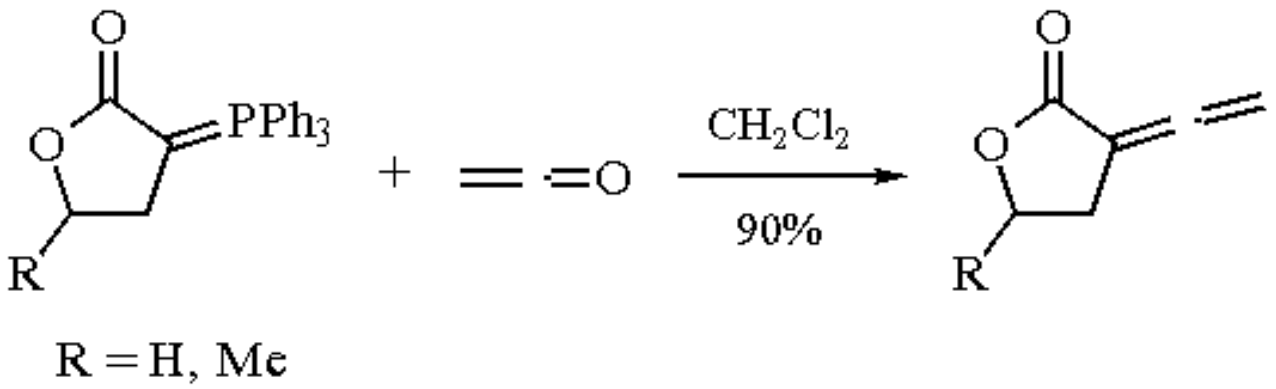

(13)

The same methodology has been employed in more complex systems, such as the formation of 4,5-dihydropyrazolo[1,5-*a*]pyridine beginning with azine phosphoranes (eq 14).[47]

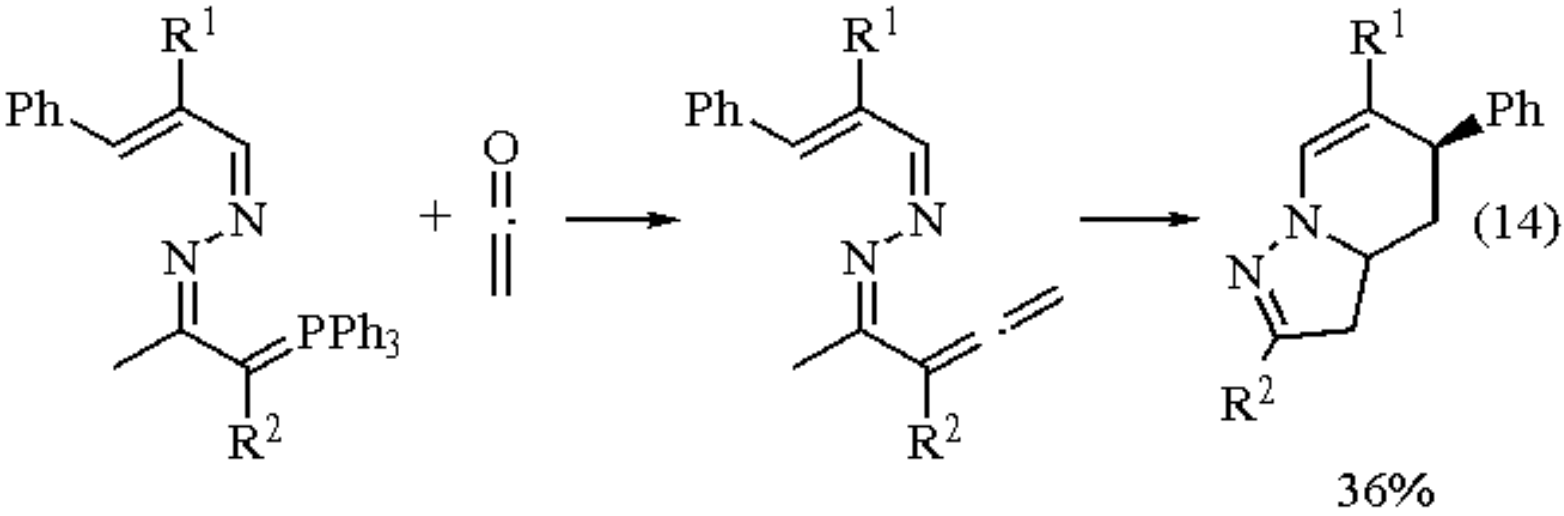

(14)

If a ketene derivative is utilized (phenylacetoxyketene or monophenyoxyketene), the product will spontaneously eliminate acetic acid or phenol to aromatize, giving the pyridine ring.[47] The ability to use either ketene or its derivatives offers good flexibility in the synthesis of these molecules.

Organometallic Compounds.

Although not as well known as the organic chemistry of ketene, the organometallic chemistry of ketene does occur in a wide variety of systems.[3] An example is the insertion of ketene into metal hydrides, as shown in eq 15.[3,48]

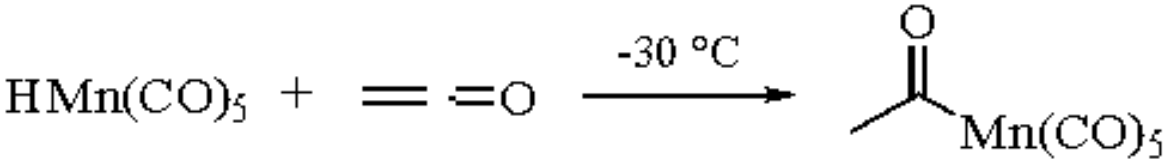

(15)

Ketene will also insert into metal-alkyl bonds.[3] The mechanism of these reactions is unknown, but it should be noted that the products follow the same type of pattern as the acetylation reactions. Some more recent work in the organometallic area is the formation of disilver ketenide (eq 16).[49] This complex was formed via reaction of silver

acetate with ketene gas formed from pyrolysis of acetone or via in situ formation of ketene using acetic anhydride. The latter method could be run at temperatures as low as -28 °C in the presence of an amine base for a catalyst. The reaction was also run using enol acetates as the ketene source.[49] The formation of this complex shows the potential carbon acidity of the hydrogen atoms attached to ketene. The silver ketenide complex is quite stable but undergoes the transformations shown in eqs 17-19.

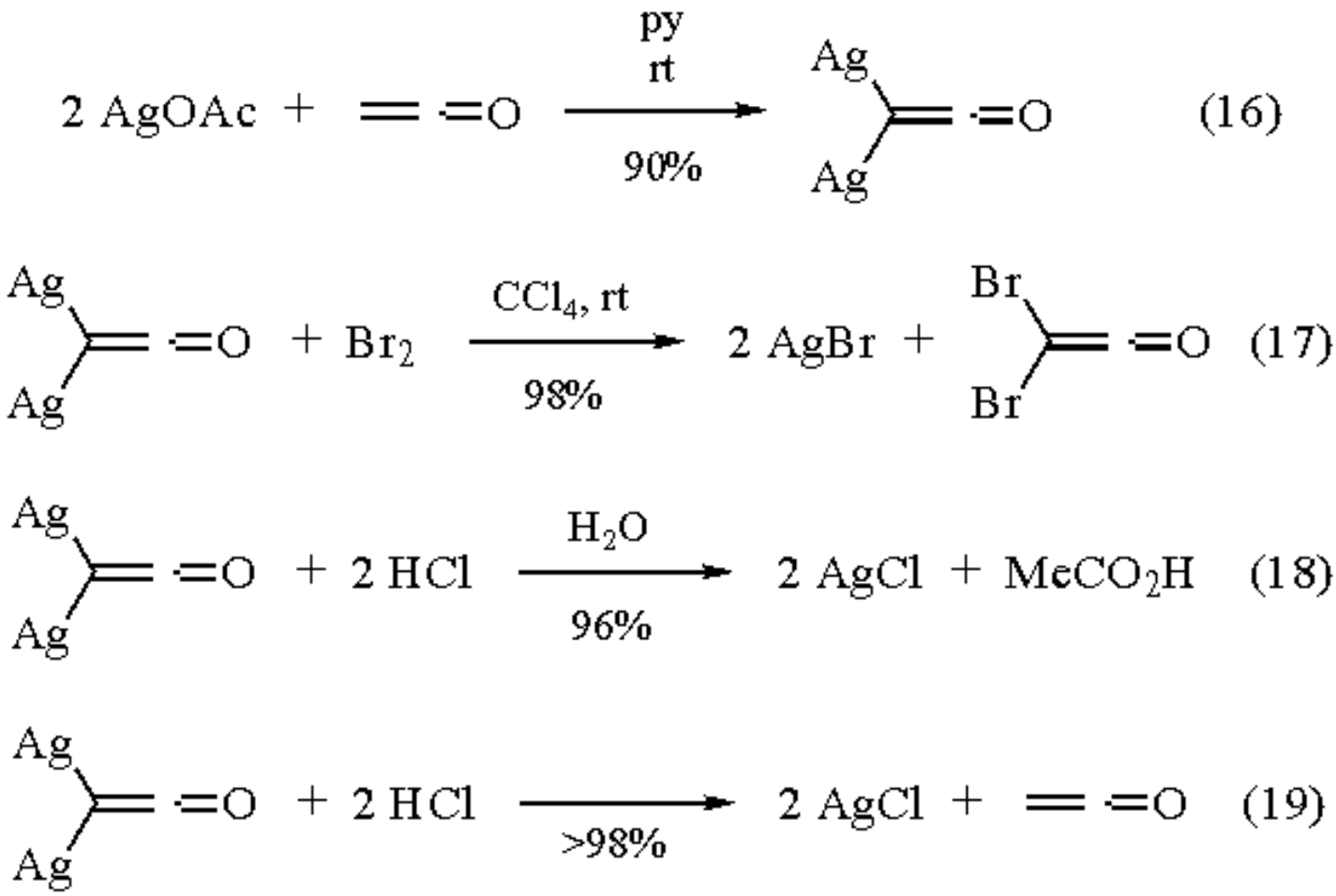

Although silver ketenide is more inert than expected, it has the potential of being a useful synthetic reagent for the introduction of disubstituted ketenes or regeneration of ketene itself.[49]

Ketene as a Nucleophile.

In acetylation reactions, ketene behaves as an electrophilic agent, but in the presence of hemiacetal chlorides,[2] acid chlorides, acetals,[2] etc., ketene behaves as a nucleophile. In a study by Hurd and Kimbrough, ketene was mixed with the hemiacetal chloride in the presence of ***Zinc Chloride*** to give, after workup, the corresponding acid.[50] Hurd went on to extend the study to acetals as well as the chloro derivatives.[2] More recently, Goure reacted ***Trifluoroacetyl Chloride*** with ketene followed by addition of ethyl 3-amino-4,4,4-trifluoro-2-butenoate. Subsequent rearrangement of this intermediate led to the pyridinecarboxylate in 86% yield.[51] The use of ketene in this reaction allows a two-step, one-pot synthesis of the previously unknown 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate (eq 20). Other methods utilized to form this compound lack the ability to incorporate a functional group in the 5 position of the pyridine ring.[51,52]

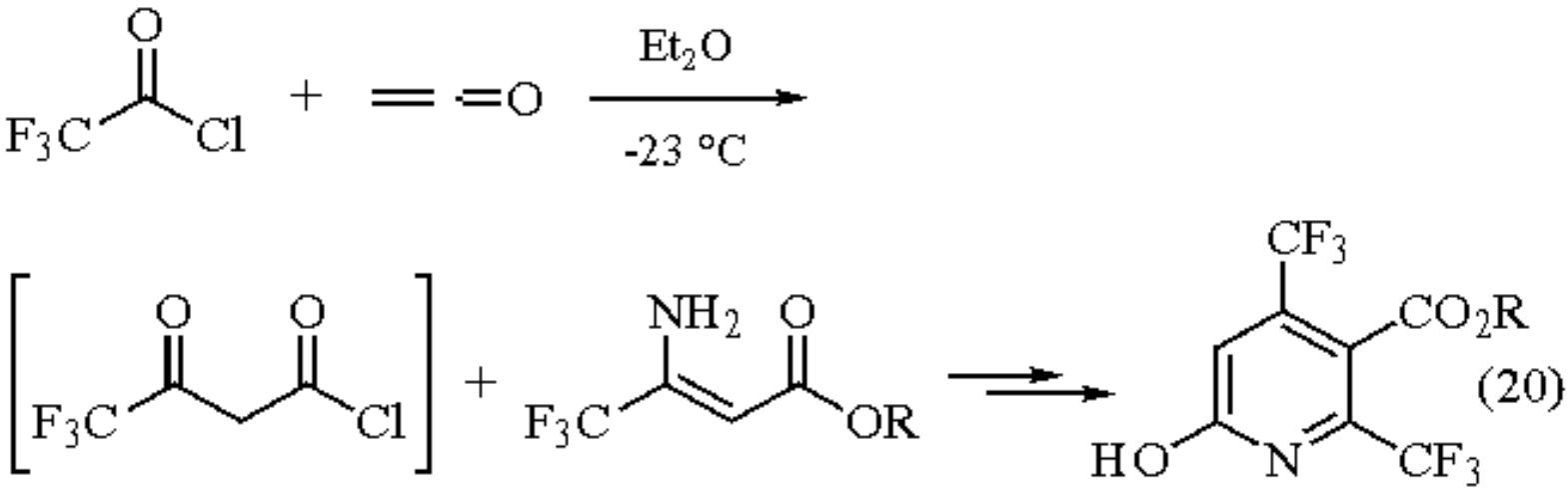

Miscellaneous.

Recently, ketene has become a tool for mechanistic probes and the formation of high energy molecules. It is known that the transformation of methanol to hydrocarbons goes through a ketene intermediate at some point. With this in mind, the thermal decomposition of ketene is being studied on metal surfaces in an effort to further elucidate this, as yet, unknown mechanism.[53,54]

Ketene is also used to form singlet methylene ($^1CH_2$) in an effort to study the insertion reactions of this short-lived intermediate.[55] Its use is also noted in the formation of distonic ions: ions that have a separated charge and radical site. The use of ketene in this instance offers an advantage over the known methods in that it allows greater ease of formation of the distonic ions and greater flexibility over the type of ion formed.[56]

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Ketene Bis(trimethylsilyl) Acetal[1,2]

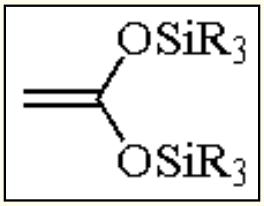

(R = Me)

[24697-35-6] · $C_8H_{20}O_2Si_2$ · Ketene Bis(trimethylsilyl) Acetal · (MW 204.46) (R = Et)

[24697-36-7] · $C_{14}H_{32}O_2Si_2$ · Ketene Bis(triethylsilyl) Acetal · (MW 288.64)

(stable equivalent of acetic acid dianion; enolate surrogate useful for aldol reactions[6] and similar Mukaiyama reactions; inverse-electron-demand dienophile for Diels-Alder reactions[8])

Alternate Name: 1,1-bis(trimethylsiloxy)ethylene.

Physical Data: R = Me, bp 50 °C/10 mmHg; R = Et, bp 77 °C/1 mmHg.

Solubility: freely sol organic solvents.

Form Supplied in: clear colorless liquid.

Analysis of Reagent Purity: NMR in dry (molecular sieves) solvent (data in Ainsworth and Kuo[3]). Likely impurities are trimethylsilyl (trimethylsilyl)acetate (bp 61 °C/10 mmHg) and α-trimethylsilylacetic acid.

Preparative Methods: disilylation of acetic acid dianion and silylation of the enolate of trimethylsilyl acetate are problematic because a mixture of *O*- and *C*-silyl compounds is generated in roughly equal proportions (eq 1)[3] and these isomers are nearly inseparable.

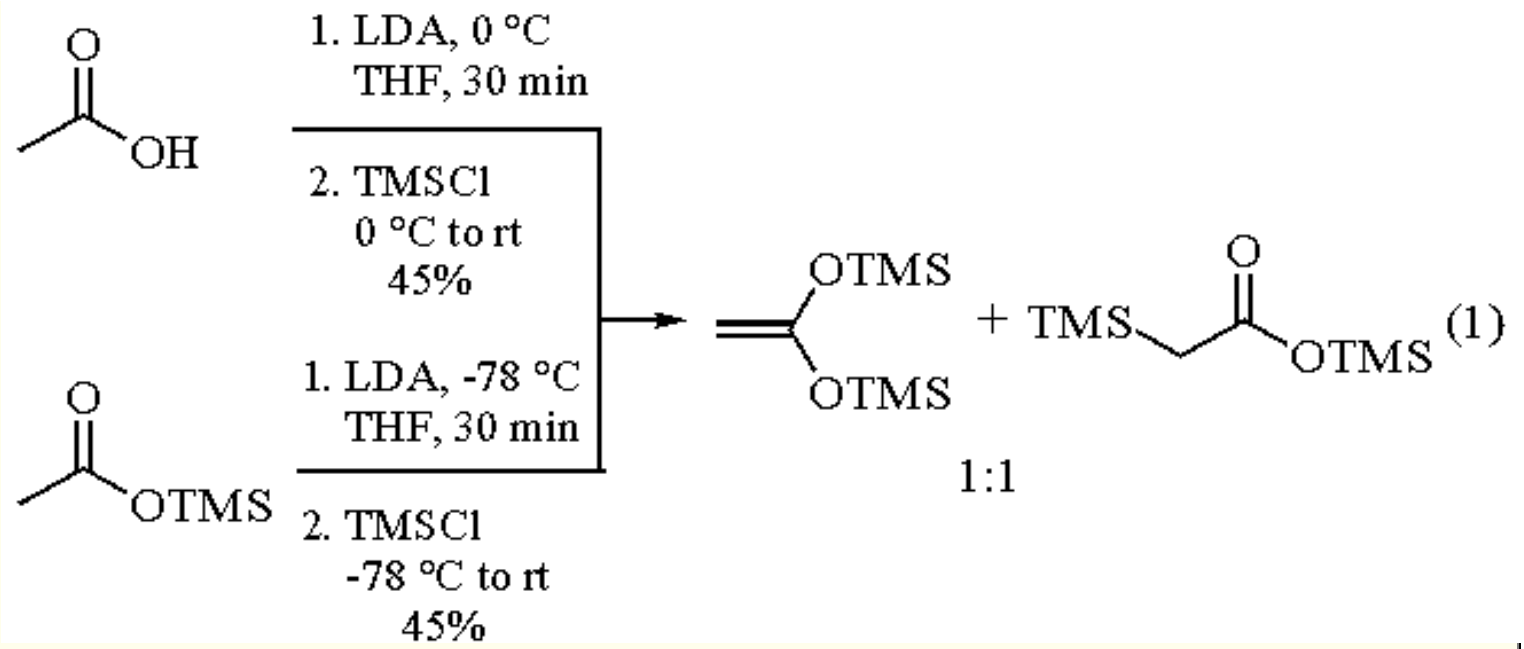

The reaction conditions can be modified to produce either of these compounds in good yields (eqs 2 and 3).[2] Rapid generation, and the subsequent quenching of the highly dissociated sodium enolate, at low temperature, is important for the preponderant formation of the *O*-silyl product.[4] In a related reaction, trimethylsilyl acetate upon reaction with excess of ***Triethylamine*** and ***Trimethylsilyl Trifluoromethanesulfonate*** gives a mixture of two bis-silylated isomers (eq 4).[5]

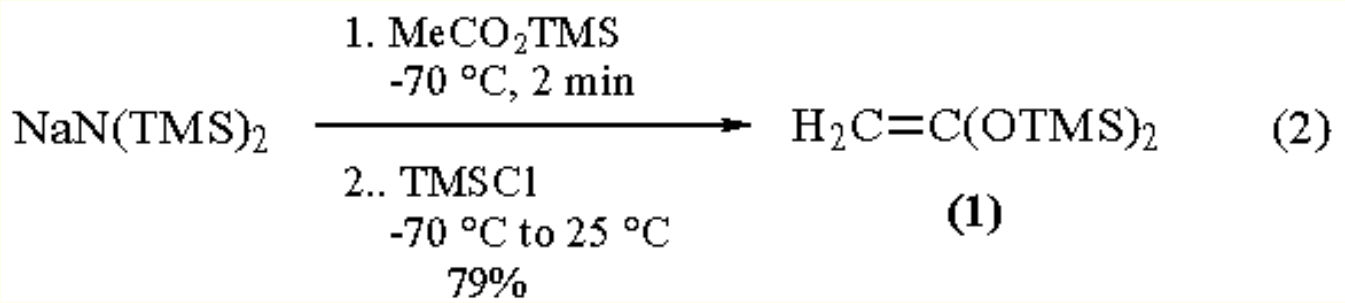

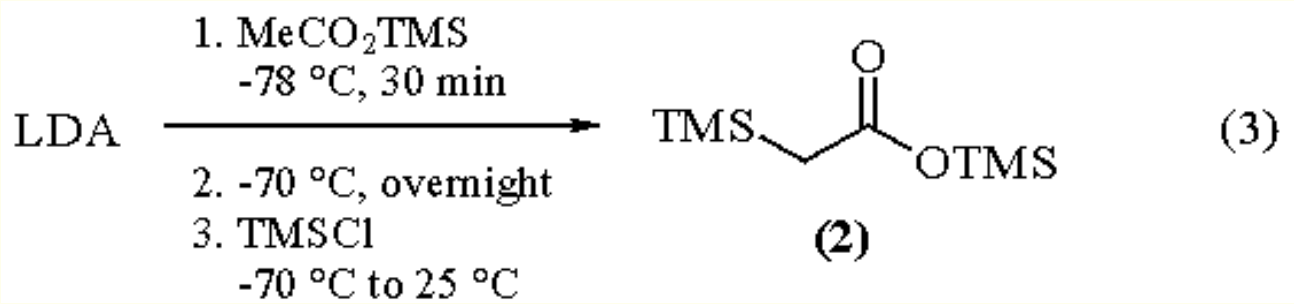

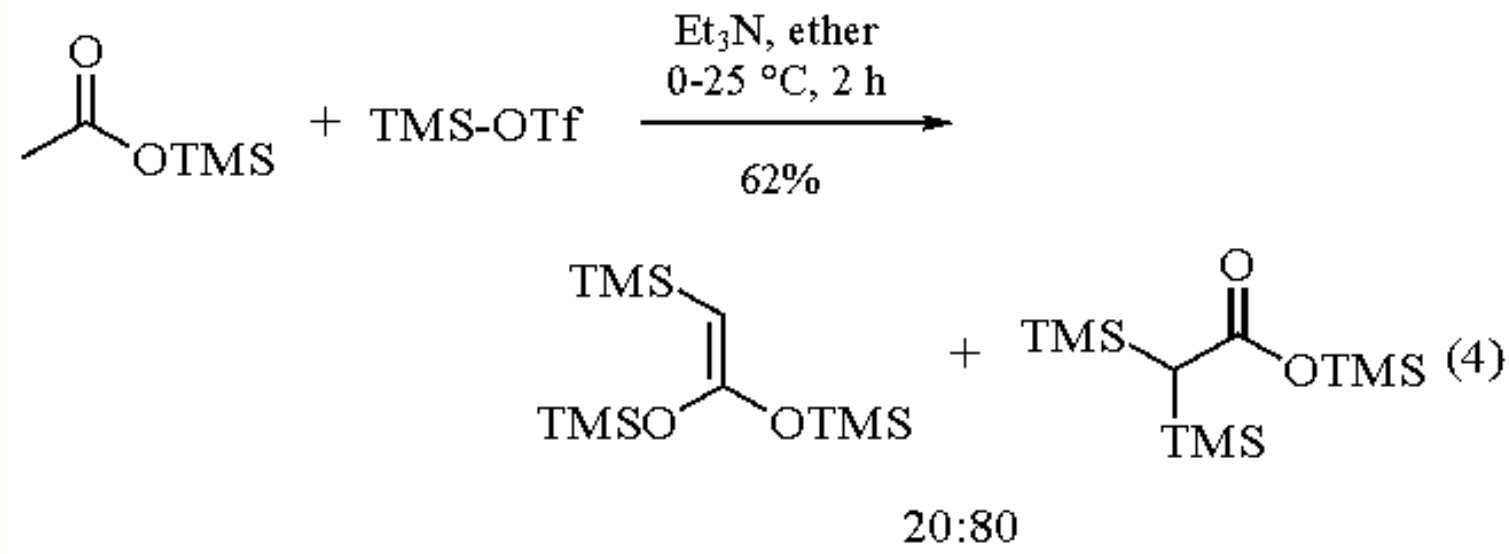

The first synthesis of the ketene bis(triethylsilyl) acetal involved the treatment of triethylsilyl α-(triethylstannyl)acetate (**3** in eq 6) with triethylsilyl iodide.[1] The intermediate (**3**) in turn was prepared from ketene and triethylsilyloxytriethylstannane (eq 5).

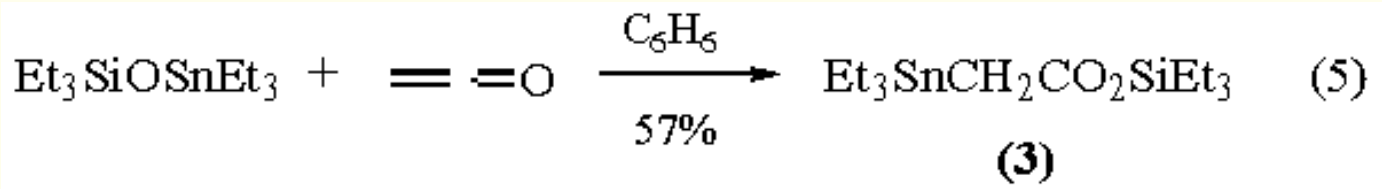

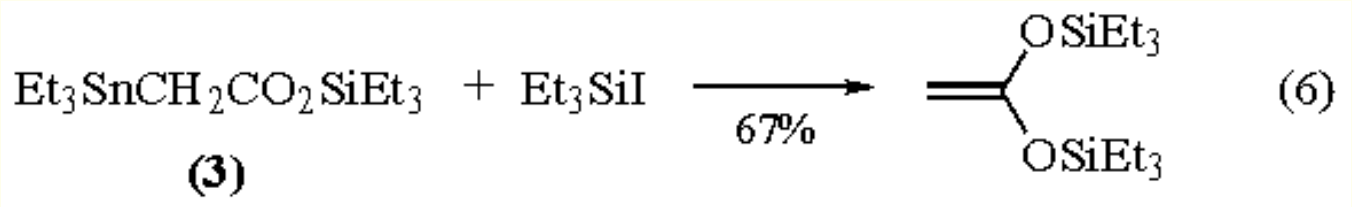

Handling, Storage, and Precautions: flammable; extremely moisture-sensitive. Use in a fume hood.

O to *C* Migration.

In contrast to the alkyl trialkylsilyl ketene acetals, the thermal *O* to *C* migration is sluggish in the case of ketene bis(trialkylsilyl) acetals. Yet the migration can be effected by heating the compound to temperatures above 170 °C. The reaction can be facilitated by addition of catalytic amounts of HgI_2, ***Chlorotrimethylsilane***, or ***Iodotrimethylsilane*** (eq 7).[1]

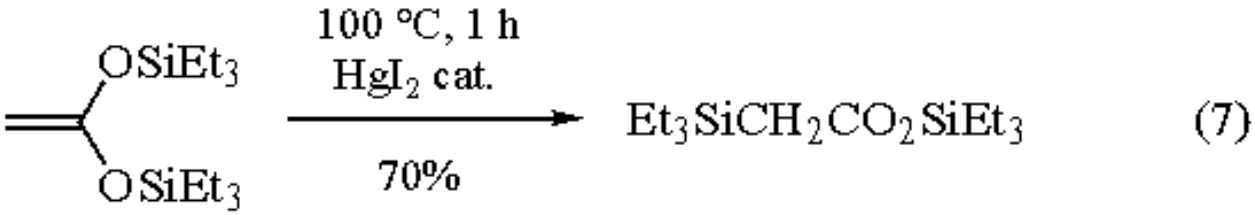

Electrophilic Reactions.

Bis(trimethylsilyl) acetal (**1**) adds to cinnamaldehyde to give exclusive 1,2-addition upon treatment with ***Titanium(IV) Chloride*** (eq 8). The same product can be prepared by reaction of the *C*-silyl compound (**2**) with the aldehyde in the presence of ***Tetra-n-butylammonium Fluoride*** (eq 8).[6]

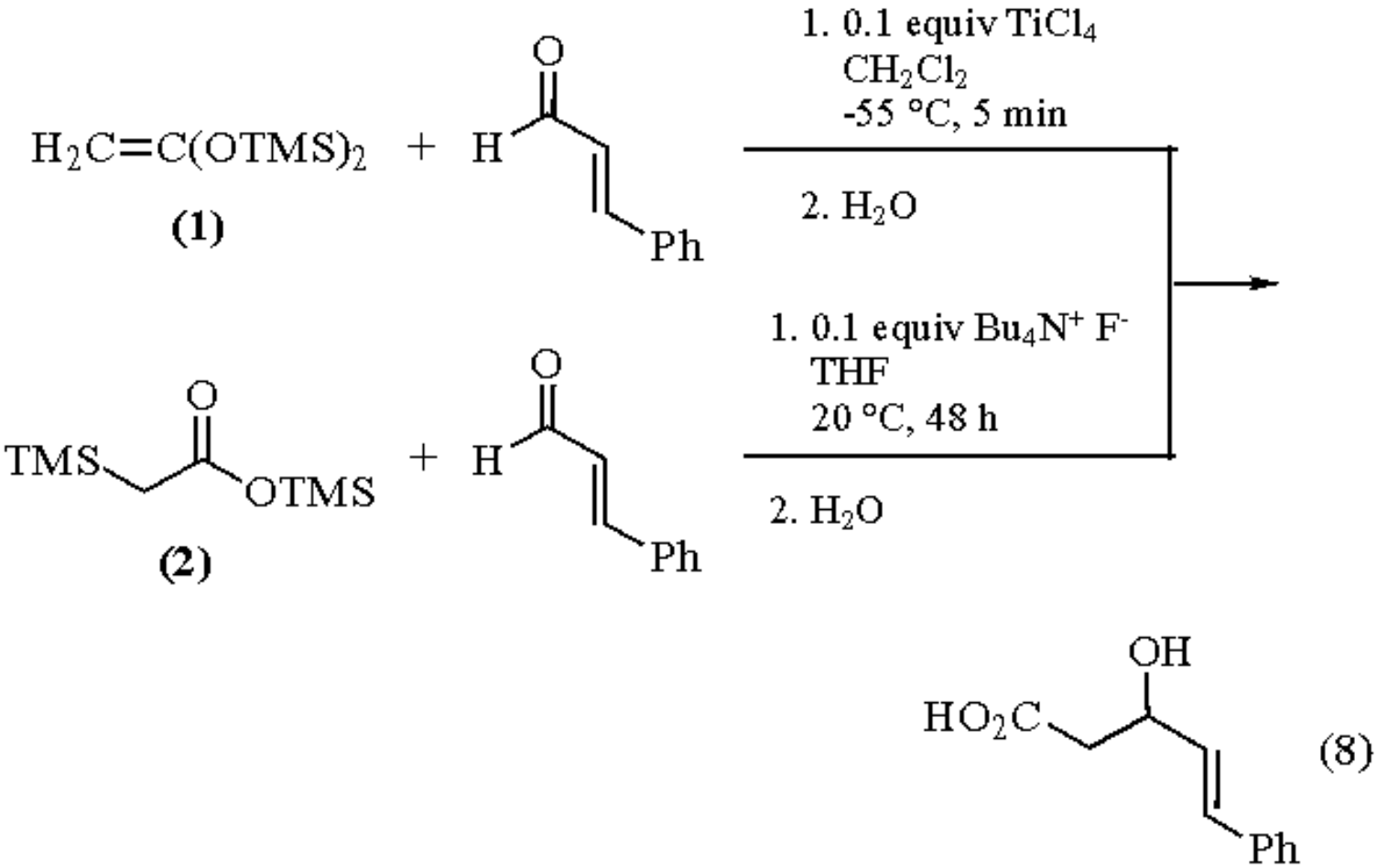

Ketene acetal (**1**) reacts with dry ***Sulfur Dioxide*** to give trimethylsilyl [(trimethylsilyloxy)carbonyl]methanesulfinate (eq 9).[7] Reaction with $SiCl_4$ produces 1,1-bis(trimethylsilyloxy)-2-trichlorosilylethylene (eq 10).[1]

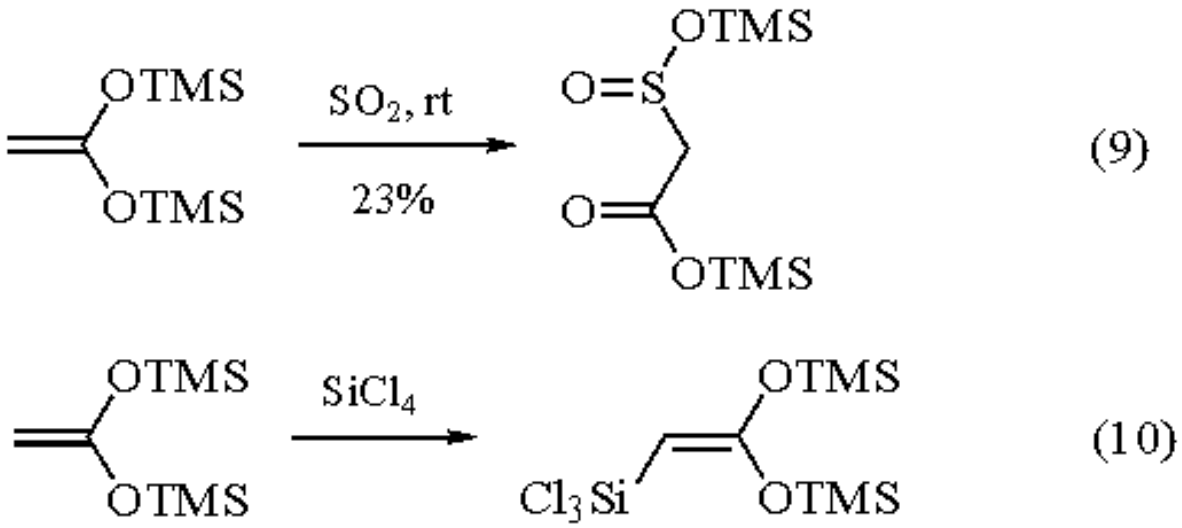

Cycloaddition Reaction.

Bis(trialkylsilyl) acetal (**1**) is an excellent inverse-electron-demand dienophile, as illustrated by the [4 + 2] cycloaddition reaction (eq 11).[8] Note that the initial adduct readily loses N_2 and subsequently, the elements of TMS-OH. With 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine, compound (**1**) reacts 6 times faster than ethylene and about 30 times faster than styrene or 1-trimethylsilyloxyethylene at 20 °C in dioxane.

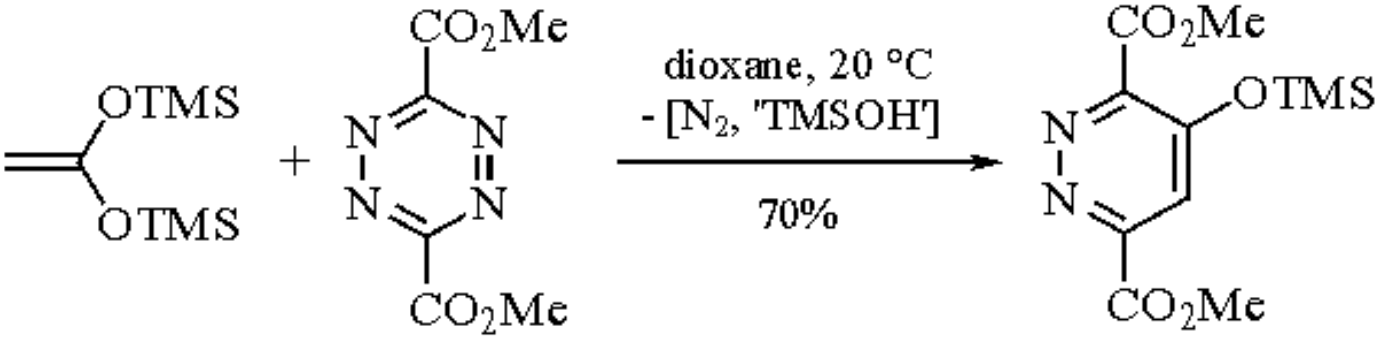

(11)

Related Reagents.

Dilithioacetate; ***Ethyl Lithioacetate***; ***Ethyl Trimethylsilylacetate***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Trimethylsilylacetic Acid***; ***Tris(trimethylsilyloxy)ethylene***.

---

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Ketene *t*-Butyldimethylsilyl Methyl Acetal[1]

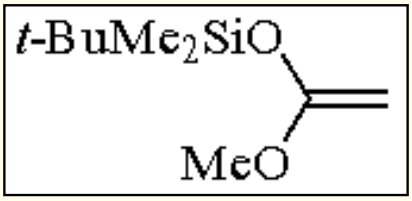

[91390-62-4] · $C_9H_{20}O_2Si$ · Ketene *t*-Butyldimethylsilyl Methyl Acetal · (MW 188.34)

(silylation of a variety of substrates;[3] promotion of Pummerer reaction of sulfoxides;[4-8] Lewis acid mediated aldol-type[8-22] and Michael additions,[31-38] under either stoichiometric or catalytic conditions)

Physical Data: colorless liquid; bp 76-76.5 °C/24 mmHg.

Solubility: sol *n*-pentane, diethyl ether, dichloromethane, etc.

Analysis of Reagent Purity: (NMR) ^{1}H 0.14 (s, 6H), 0.93 (s, 9H), 2.95 (d, 1H, J = 3.0 Hz), 3.10 (d, 1H, J = 3.0 Hz), 3.49 (s, 3H) ppm.

Preparative Method: obtained by reaction of methyl acetate with ***Lithium Diisopropylamide*** in THF/HMPA and subsequent trapping with ***t-Butyldimethylchlorosilane*** (72% yield).[2]

Handling, Storage, and Precautions: should be stored in the absence of moisture at -15 °C.

Silylation.

The reagent silylates a variety of substrates (alcohols, acids, thiols, phenols, imides) under mild conditions (a catalytic amount of ***p-Toluenesulfonic Acid*** is occasionally added) with excellent yields (91-100%).[3]

Pummerer Reaction.

The reagent transforms sulfoxides in the presence of catalytic amounts of ***Zinc Iodide*** into the corresponding α-silyloxy sulfides (eq 1).[4] Vinyl sulfoxides undergo a Michael-Pummerer type reaction to give γ-silyloxy-γ-phenylthio esters (eq 2).[5]

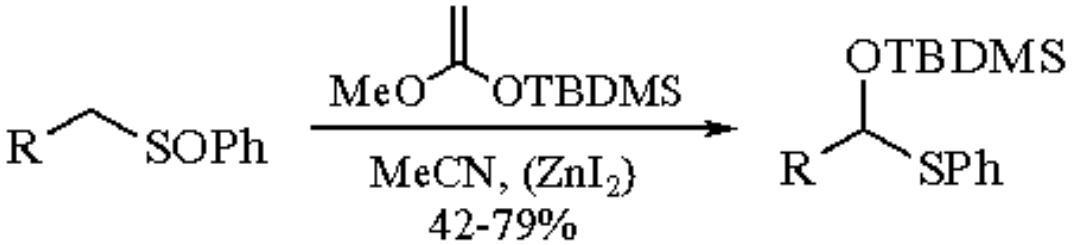

(1)

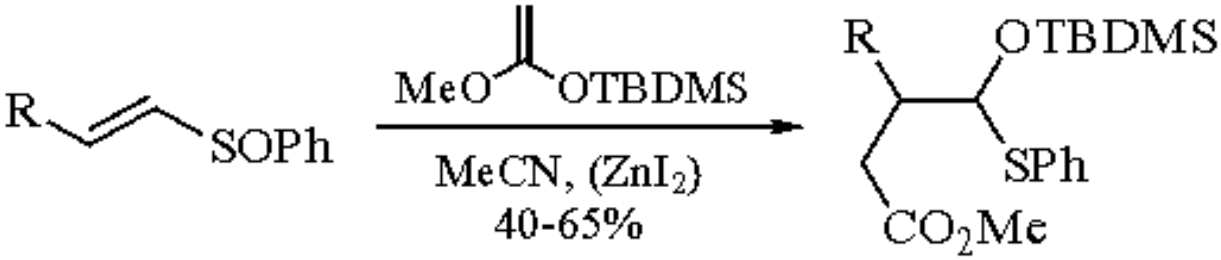

(2)

As an extention of this reaction, the reagent promotes the intramolecular Pummerer-type rearrangement of o-carbamoyl sulfoxides to give α-thio lactams.[6] The reaction proves particularly useful in the field of β-lactam synthesis (eq 3).[7,8a]

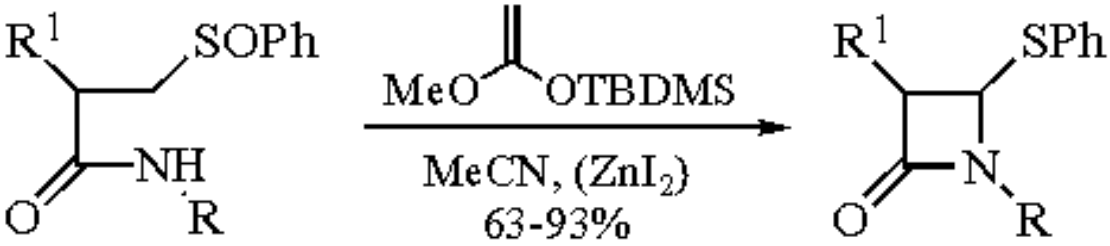

(3)

Addition to C=X Double Bonds (X = N, O).[1b]

The reagent undergoes Lewis acid catalyzed Mukaiyama-type additions[1b] to azetinones, or their corresponding iminium ions, to give *trans*-azetidin-2-one esters with good yields and excellent stereoselectivity (eq 4).[7b,8,9]

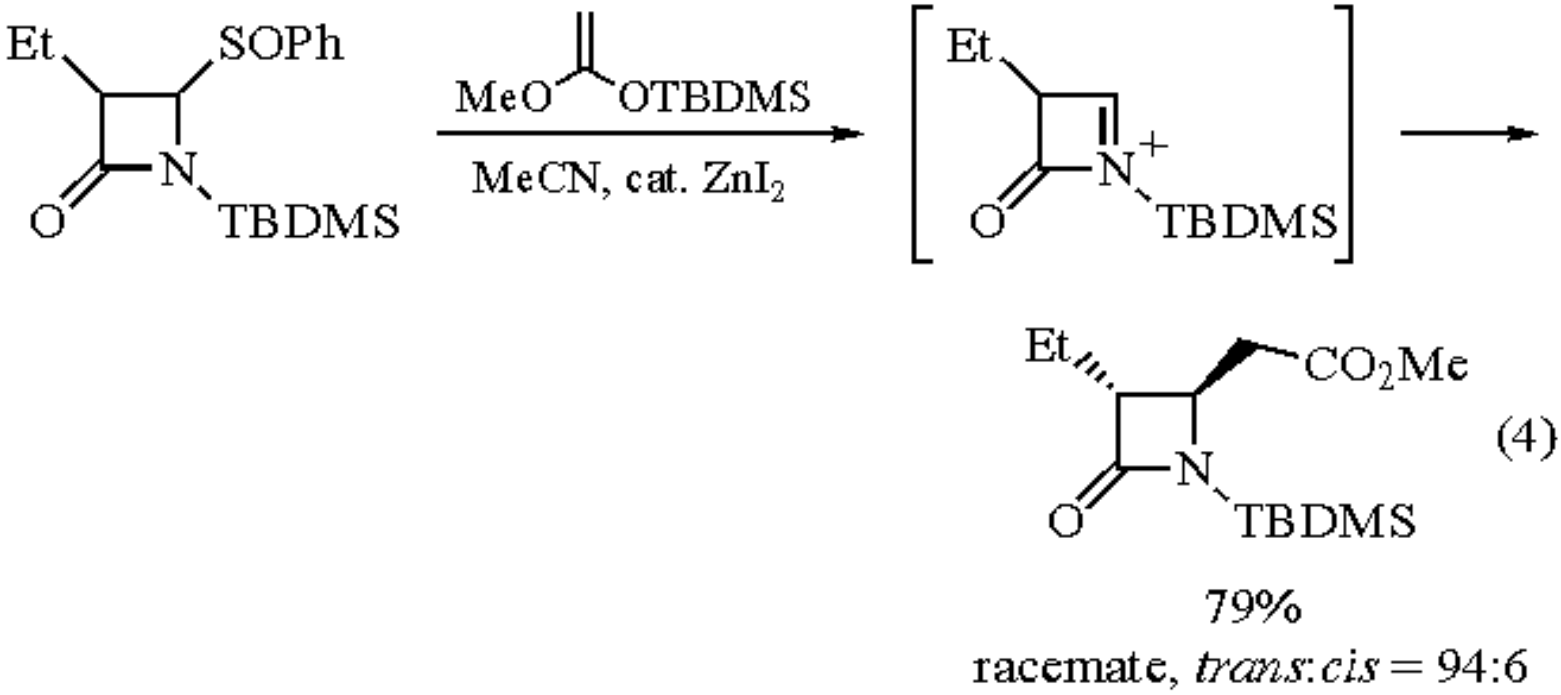

In the presence of a diphosphonium salt (7 mol %),[10a] ***Trimethylsilyl Trifluoromethanesulfonate*** (10 mol %),[10b] or ***Iron(III) Nitrate-K10 Montmorillonite Clay***,[10c] the reagent adds to imines or *N*-tosyliminium ions to give the corresponding β-amino esters in good yield.

ZnI_2-catalyzed additions of the reagent to chiral α,β-dialkoxy nitrones (eq 5; R^1 = H) proceed with good yield (86-100%) and high diastereoselectivity (ca. 90:10) in favor of the *syn* isomer (R^1 = H, R^2 = CH_2Ph, R^3 = Me). The *anti* isomer is obtained (ca. 90:10) by increasing the steric hindrance of R^2 and R^3 (R^2 = $CHPh_2$, R^3 = *t*-Bu).[11a,b] Addition to a different nitrone (eq 5; R^1 = Me) gives the *anti* isomer (R^1 = Me, R^2 = CHMePh, R^3 = Me) in quantitative yield and 100% diastereofacial selectivity. This material has been further elaborated to *N*-benzoyl-L-daunosamine.[11c,d]

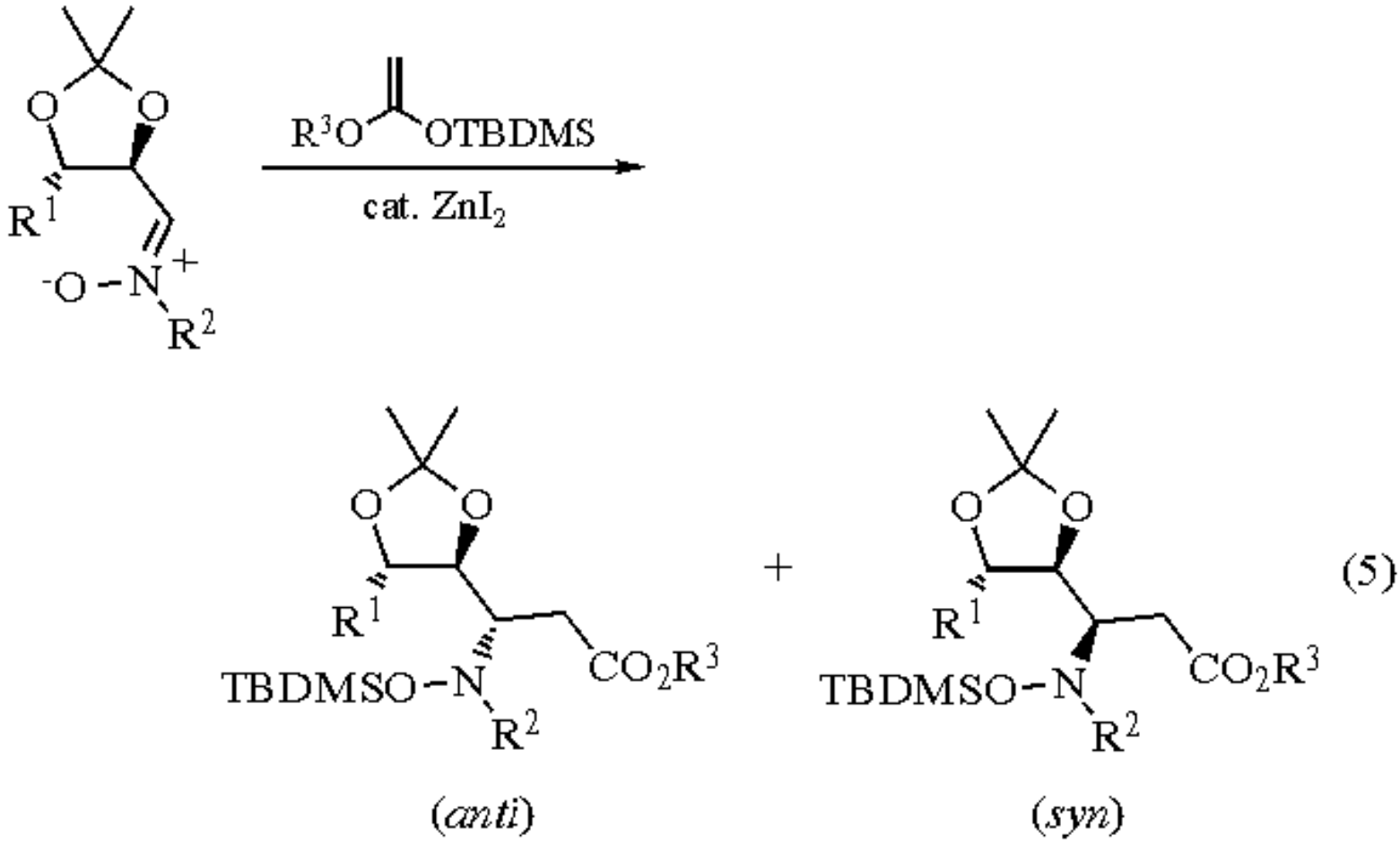

New catalysts have been recently developed for promoting the aldol-type addition of acetate-derived silyl ketene acetals with high efficiency: 10-methylacridinium perchlorate (5 mol %),[12a] cationic mono- and dinuclear iron complexes (5 mol %),[12b] *t*-butyldimethylsilyl chloride-indium(III) chloride (10 mol %),[12c] [1,2-benzenediolato(2-)-*O*,*O*´]oxotitanium (20 mol %),[12d] phosphonium salts (7 mol %),[12e] and trityl salts (5-20 mol %).[12f-i] The reagent undergoes Lewis acid promoted Mukaiyama-type additions[1b] to chiral aldehydes with moderate to good stereocontrol (eq 6).[13] It is remarkable that high chelation control can be obtained by using a catalytic amount (3 mol %) of ***Lithium Perchlorate***.[13e,f]

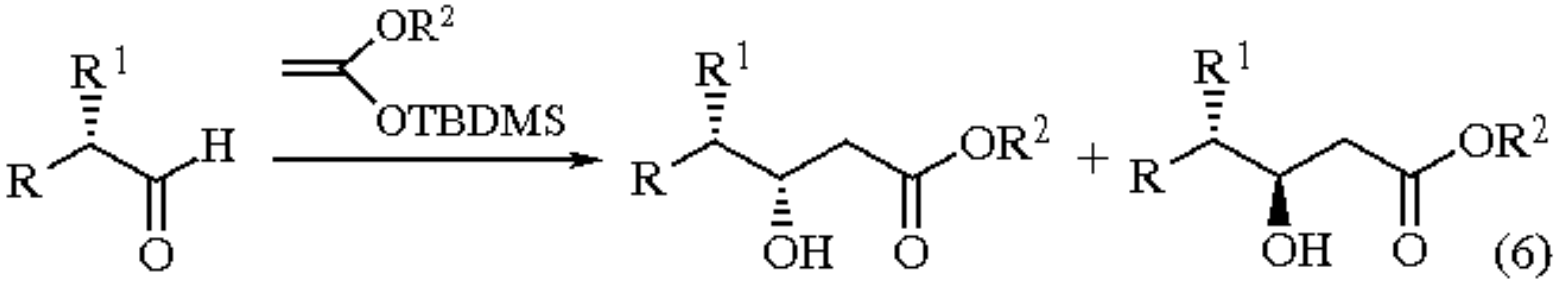

R	R^1	Promoter	R^2	Ratio	Yield (%)
Ph	Me	$BF_3 \cdot OEt_2$	*t*-Bu	97: 3	81[13a]
Ph	Me	10 kbar, 50 °C	Me	71:29	73[13b]
Me	OBn	$SnCl_4$	*t*-Bu	65:35	65[13c,d]
Me	OBn	cat. $LiClO_4$	Me	92: 8	84[13e,f]
$TBDMSOCH_2$	OBn	$SnCl_4$	Me	>98:<2	90[13g,h]
$CyCH_2$	$NHCO_2$-*i*-Pr	$TiCl_4$	Me	96: 4	95[13k,l]

With other substrates and under different conditions (eqs 7 and 8), non-chelated products are obtained with excellent selectivity.[13f,14]

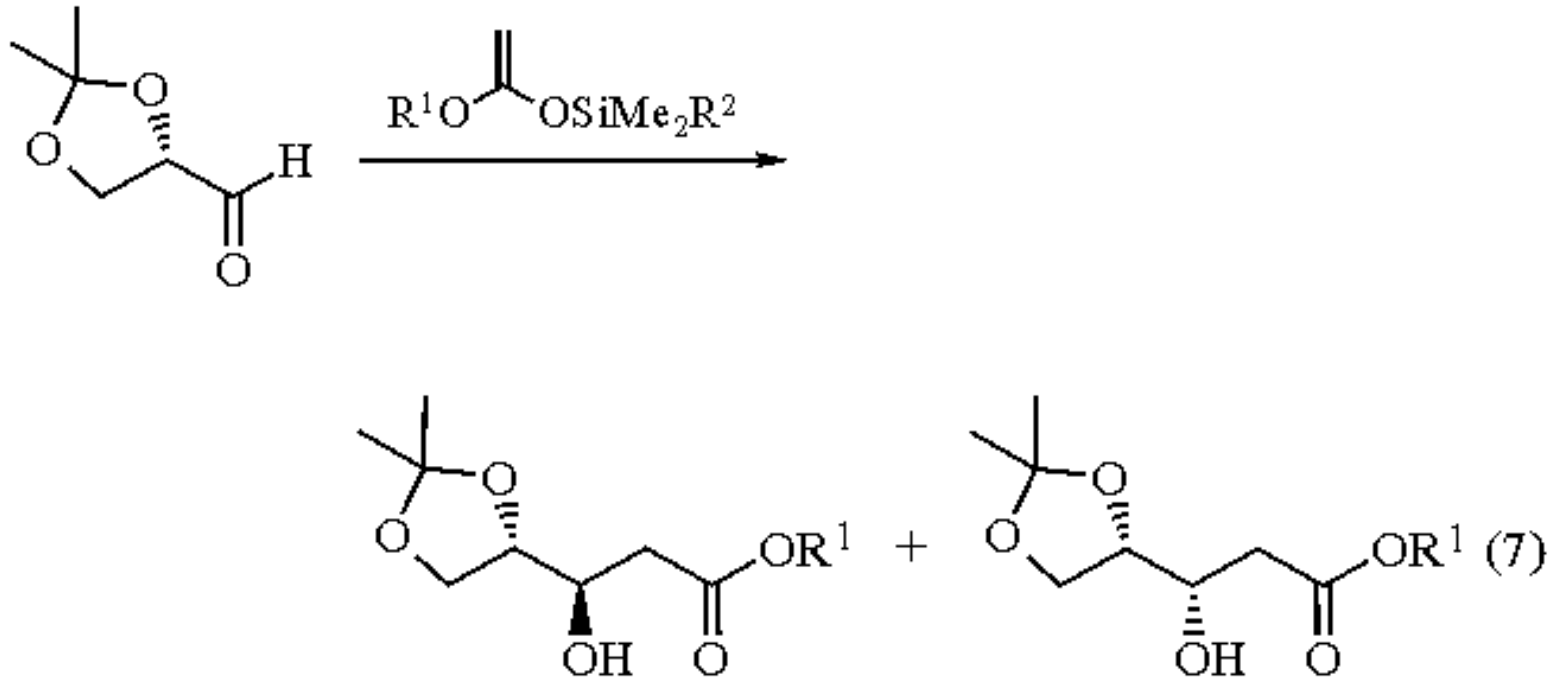

$R^1 = Me$, $R^2 = t$-Bu	cat. ZnI_2	96:4	67%[14a,b]
$R^1 = Et$, $R^2 = Me$	cat. $Eu(dppm)_3$	95:5	100%[14c]

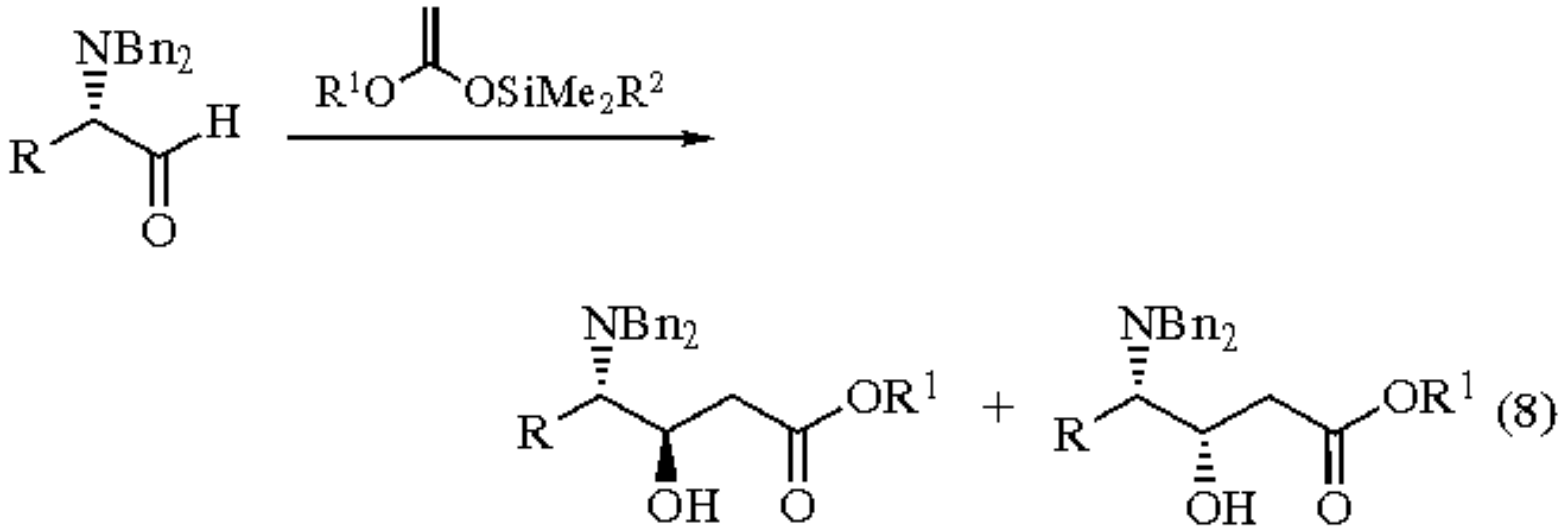

$R^1 = Bn, R^2 = Me$	$EtAlCl_2$	>99:<1	94%[14d]
$R^1 = Me, R^2 = t\text{-}Bu$	cat. $LiClO_4$ in CH_2Cl_2	>98:<2	58%[13f]

In the field of *C*-glycoside synthesis, selective β-glycosylation is realized via neighboring group participation of a 2α-acyl group.[15a] In the case of 2-deoxy sugars the neighboring participation of a group at the 3α-position is exploited for selective formation of the β-anomer (β:α = 91:9) (eq 9).[15b]

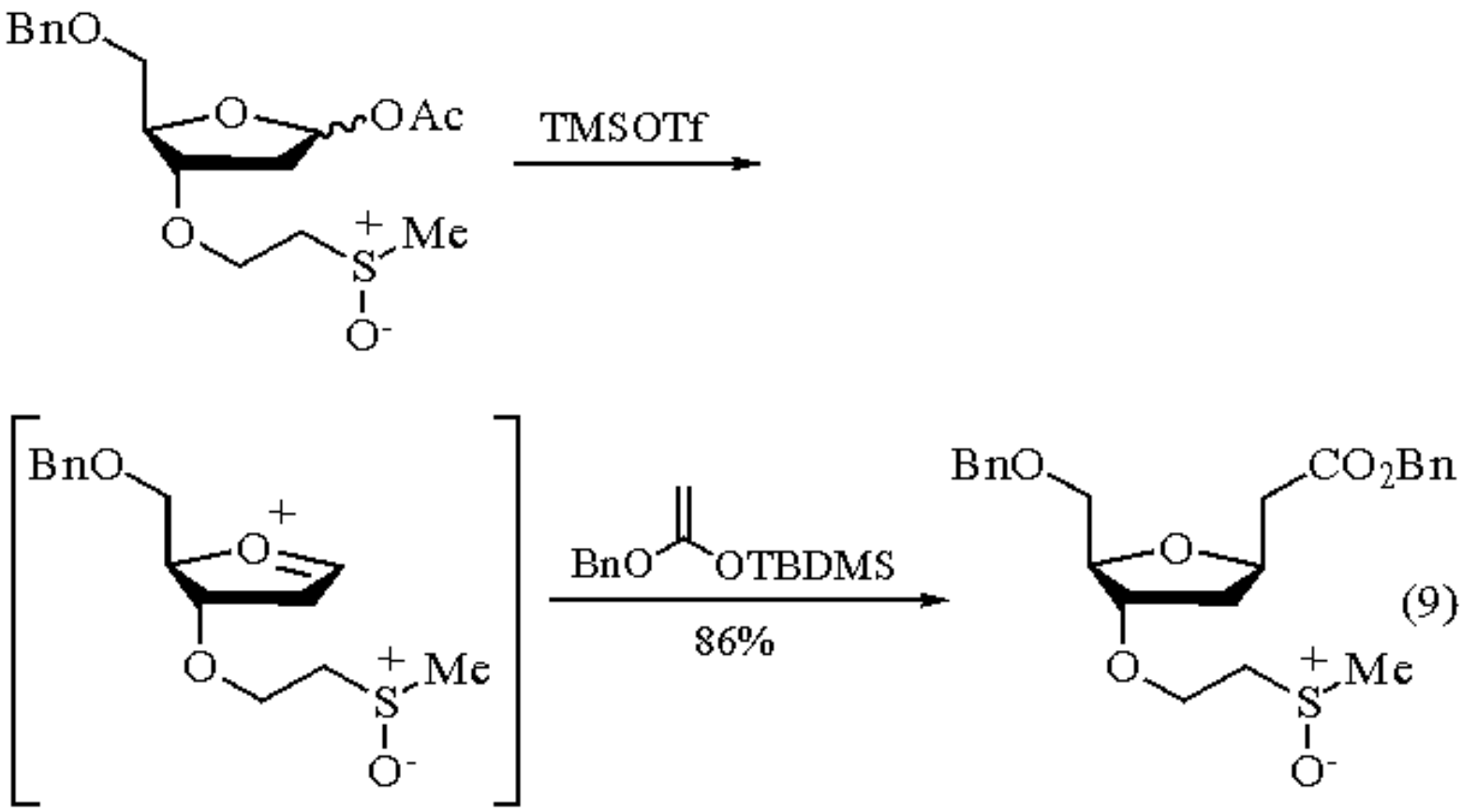

Enantioselective Aldol-Type Additions.

Highly enantioselective aldol-type reactions are successfully carried out by the combined use of a chiral diamine-coordinated tin(II) triflate and tributyltin fluoride (eq 10).[16,17] A catalytic amount of chiral bis(sulfonamido)zinc(II), easily prepared from diethylzinc and chiral sulfonamides, promotes the aldol addition in high yield and good enantiomeric excess (72-93%) only with chloral and bromal (CX_3CHO).[18]

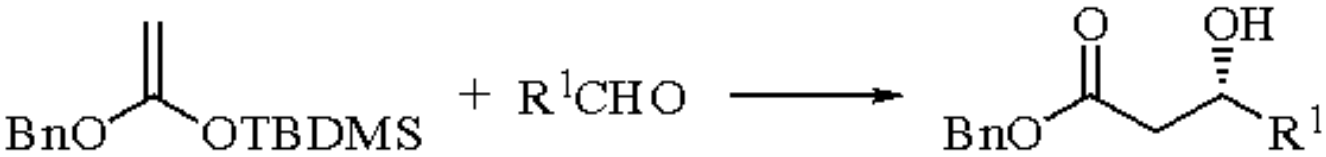

(10)

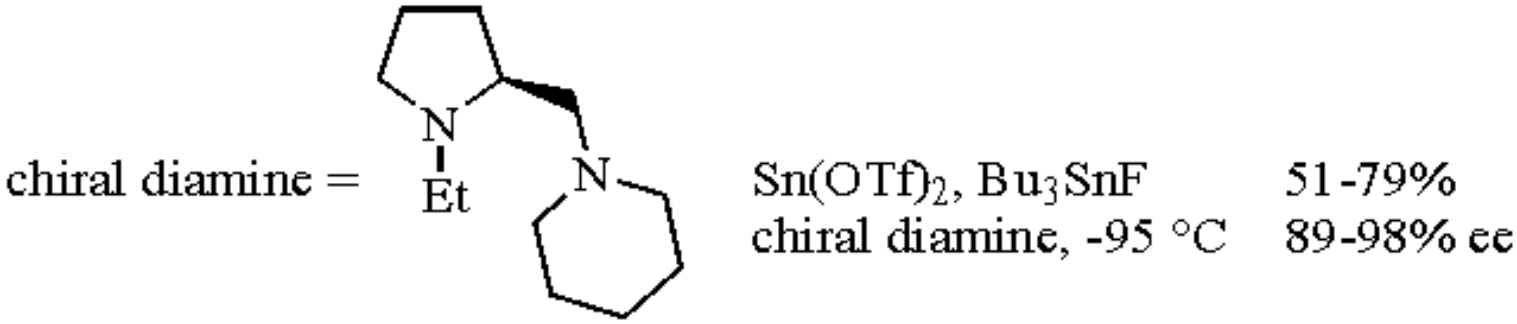

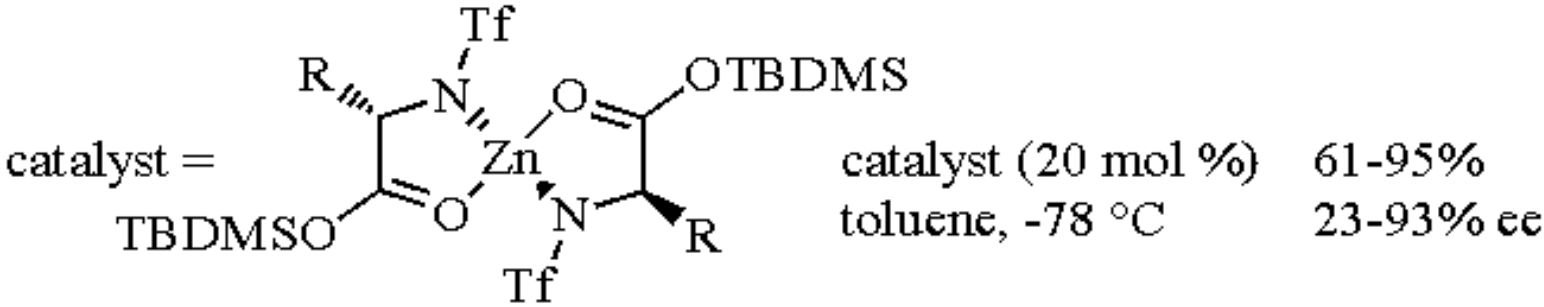

Chiral borane complexes (20 mol %) catalyze the aldol-type addition to achiral aldehydes in good to excellent yield and enantiomeric excess (eq 11).[19-21]

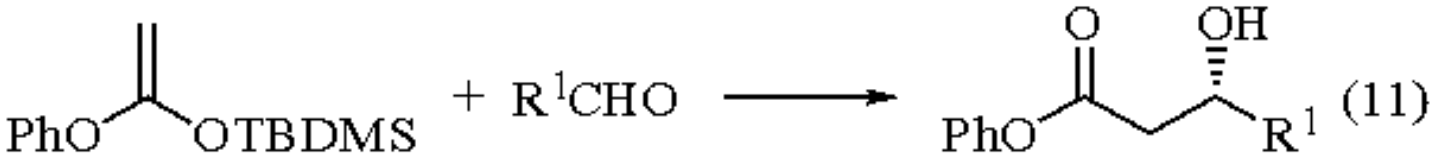

catalyst (20 mol %)
EtCN, -78 °C

catalyst =

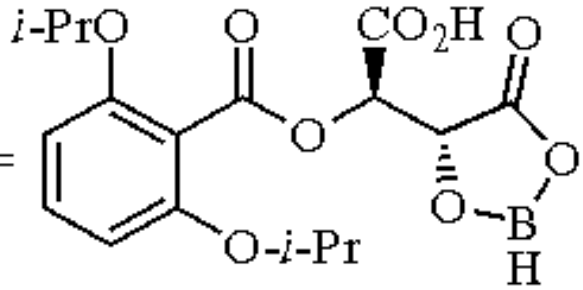

49-63%[19]
76-84% ee

catalyst (20 mol %)
$EtNO_2$, -78 °C

catalyst =

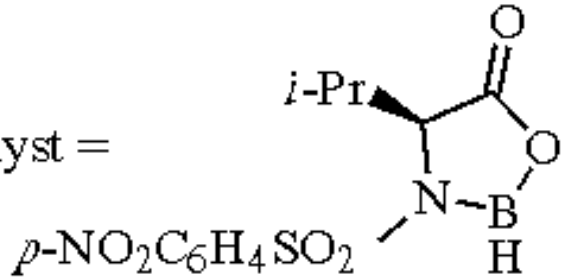

60-66%[20]
79-80% ee

catalyst (20 mol %)
EtCN, -78 °C

catalyst =

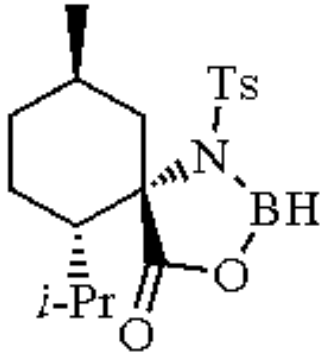

77-87%[21]
84-93% ee

A chiral boron reagent, derived from equimolar amounts of (*R*)- or (*S*)-binaphthol and triphenyl borate, promotes the condensation of chiral imines with *t*-butyl acetate silyl ketene acetal in high diastereomeric excess (eq 12).[22]

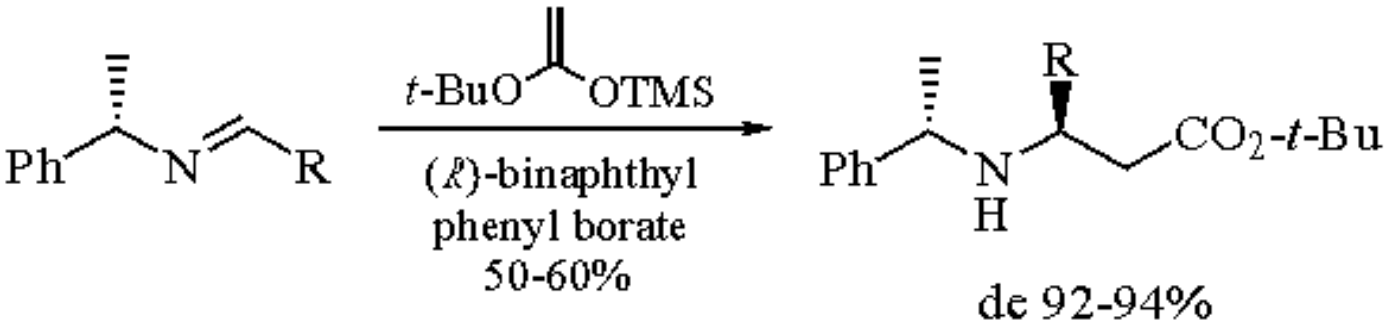

Addition to Various Electrophiles.

Various Lewis acids promote the addition of the reagent to an allylic acetate, following a carbon-Ferrier rearrangement pathway.[23] ***Titanium(IV) Chloride*** promotes the addition of the reagent to 2,2-dialkoxycyclopropanecarboxylic esters to give 3-alkoxy-2-cyclopentenones (eq 13).[24]

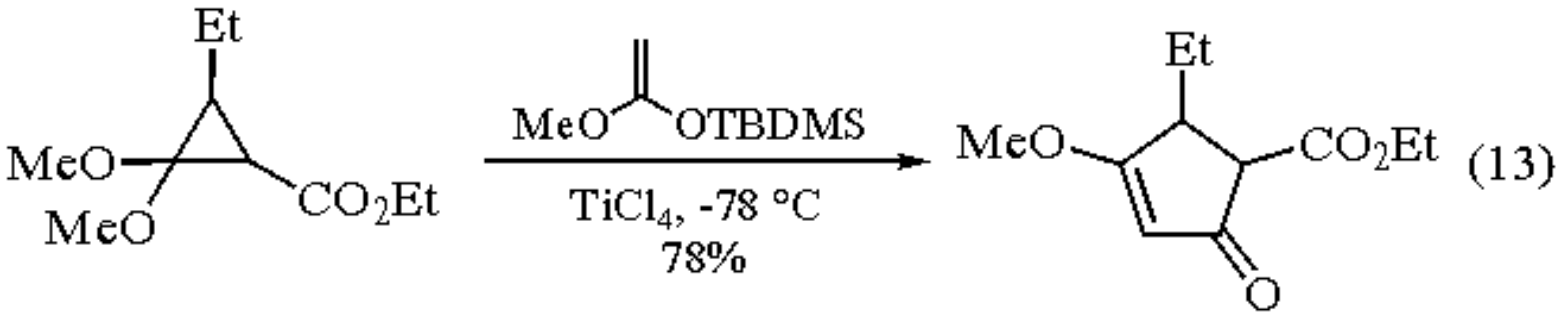

1,3-Dioxolan-2-ylium cations, derived from aldehyde ethylene acetals and trityl cation, react with the reagent to give the corresponding β-keto esters.[25] ***Montmorillonite K10*** catalyzes the addition of the reagent to pyridine derivatives with electron withdrawing groups to give *N*-silyldihydropyridines.[26] The ketene silyl acetal of ethyl acetate reacts with a chiral bromide to give the corresponding *syn*-lactone in 64% yield via a direct S_N2-type displacement and inversion of stereochemistry (eq 14).[27]

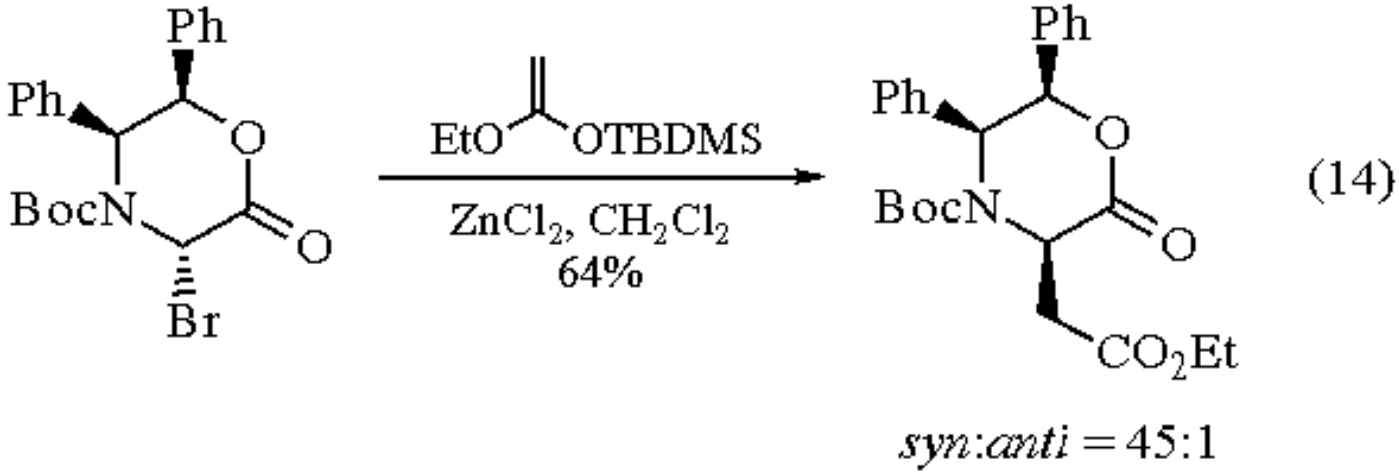

Six-membered chiral acetals, derived from aliphatic aldehydes, undergo aldol-type coupling reactions with silyl ketene acetals in the presence of $TiCl_4$ with high diastereoselectivity (eq 15).[28] This procedure, in combination with oxidative destructive elimination of the chiral auxiliary, has been applied to the preparation of (*R*)-(+)-α-lipoic acid[28a] and mevinolin analogs.[28b]

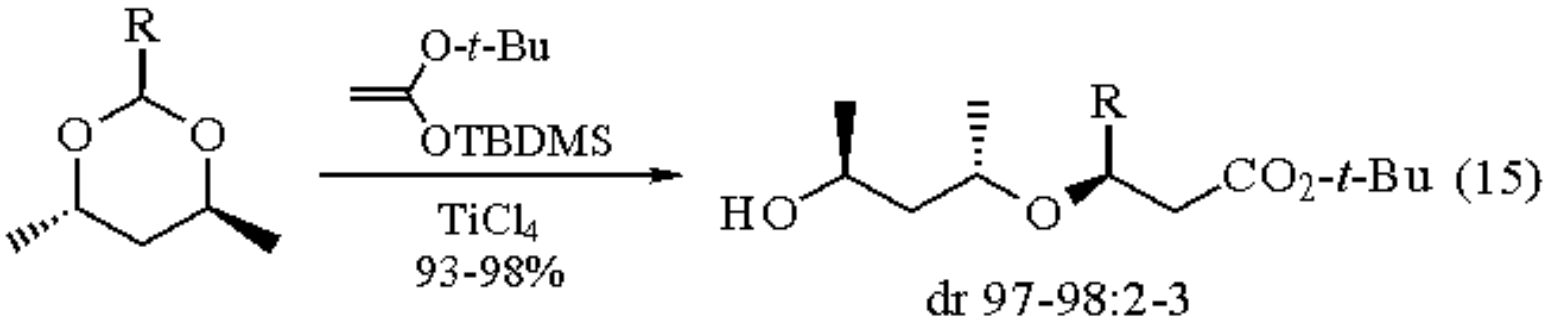

Addition to chiral, bicyclic acetals has been exploited in an approach to the synthesis of the tetrahydropyran subunit of the polyether nigerin.[29] The particular acetal generated by the ***Diisobutylaluminum Hydride*** reduction of aliphatic esters undergoes aldol addition in good yields (eq 16).[30]

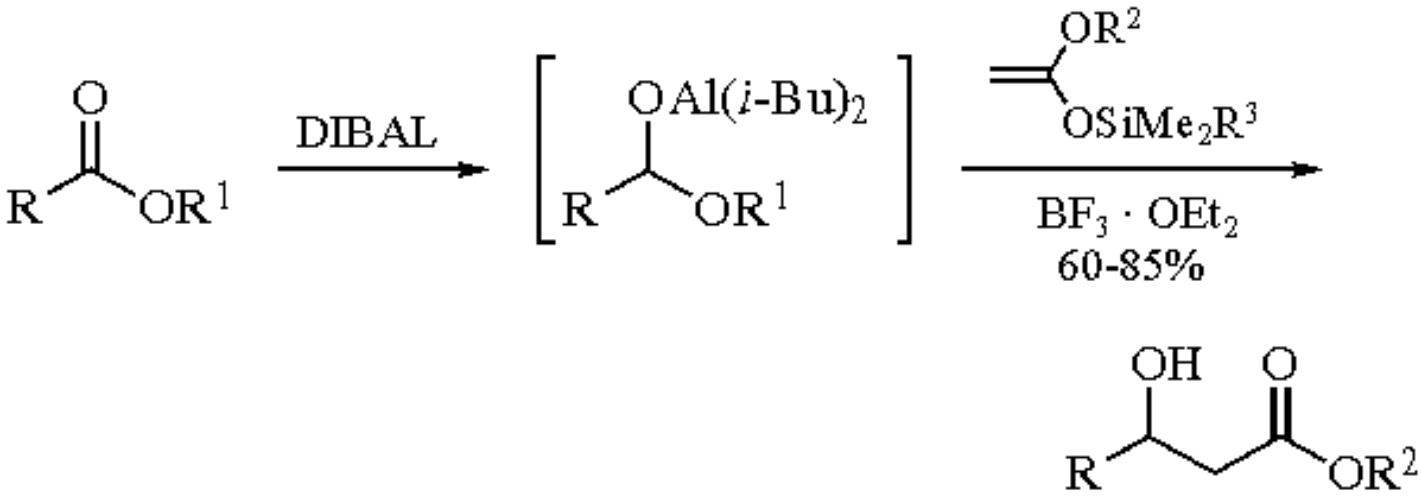

(16)

Michael Addition.

The reagent undergoes Michael addition to α,β-enones in acetonitrile in the absence of a Lewis acid to afford the corresponding *O*-silylated Michael adducts in high yield. These silyl enol ethers undergo site-specific reaction with a variety of electrophiles (eq 17).[31a,b] Inability to repeat this procedure led to the discovery that the `noncatalyzed' Michael reaction is due to traces of phosphorus compounds introduced by drying acetonitrile with P_4O_{10}. The new catalyst system, formed from P_4O_{10} in acetonitrile, was found to be highly effective with a variety of substrates.[31c]

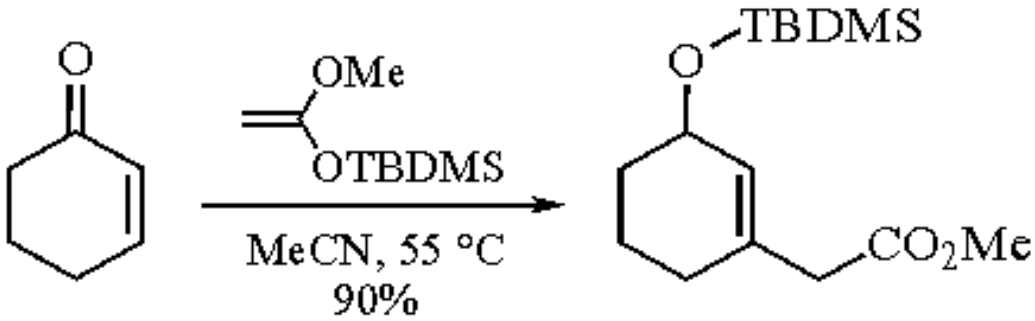

(17)

In those instances where the thermal Michael reaction is sluggish due to sterically hindered substrates, the use of high pressure (15 kbar, 20 °C),[32a] or of $LiClO_4$ (3 mol % in CH_2Cl_2[13f] or 1.0-2.5 M in Et_2O[32b]) prove extremely advantageous (eq 18). The lithium perchlorate-catalyzed Michael reaction can be carried out on α,β-unsaturated δ-lactones and on sterically demanding β,β-disubstituted unsaturated carbonyl systems in high yield and under mild conditions.[32b]

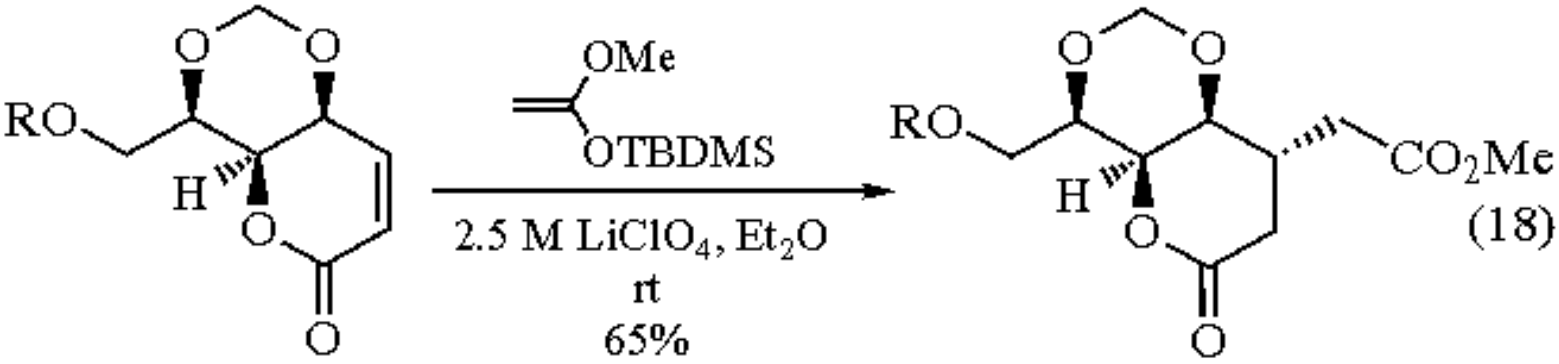

Michael addition of the reagent to enoates and enones occurs at low temperature (-50 to -78 °C) in the presence of catalytic amounts of various Lewis acids.[33] A catalytic amount of ***Triphenylmethyl Perchlorate*** (5 mol %) effectively catalyzes the tandem Michael reaction of ethyl acetate-derived silyl ketene acetal to α,β-unsaturated ketones and the sequential aldol addition to aldehydes with high stereoselectivity.[34] HgI_2 mediates the Michael addition to chiral enones, followed by Lewis acid-mediated addition to aldehydes. The Michael-aldol protocol has been used for the stereoselective synthesis of key intermediates on the way to prostaglandins, compactin, and ML-236A (eq 19).[35]

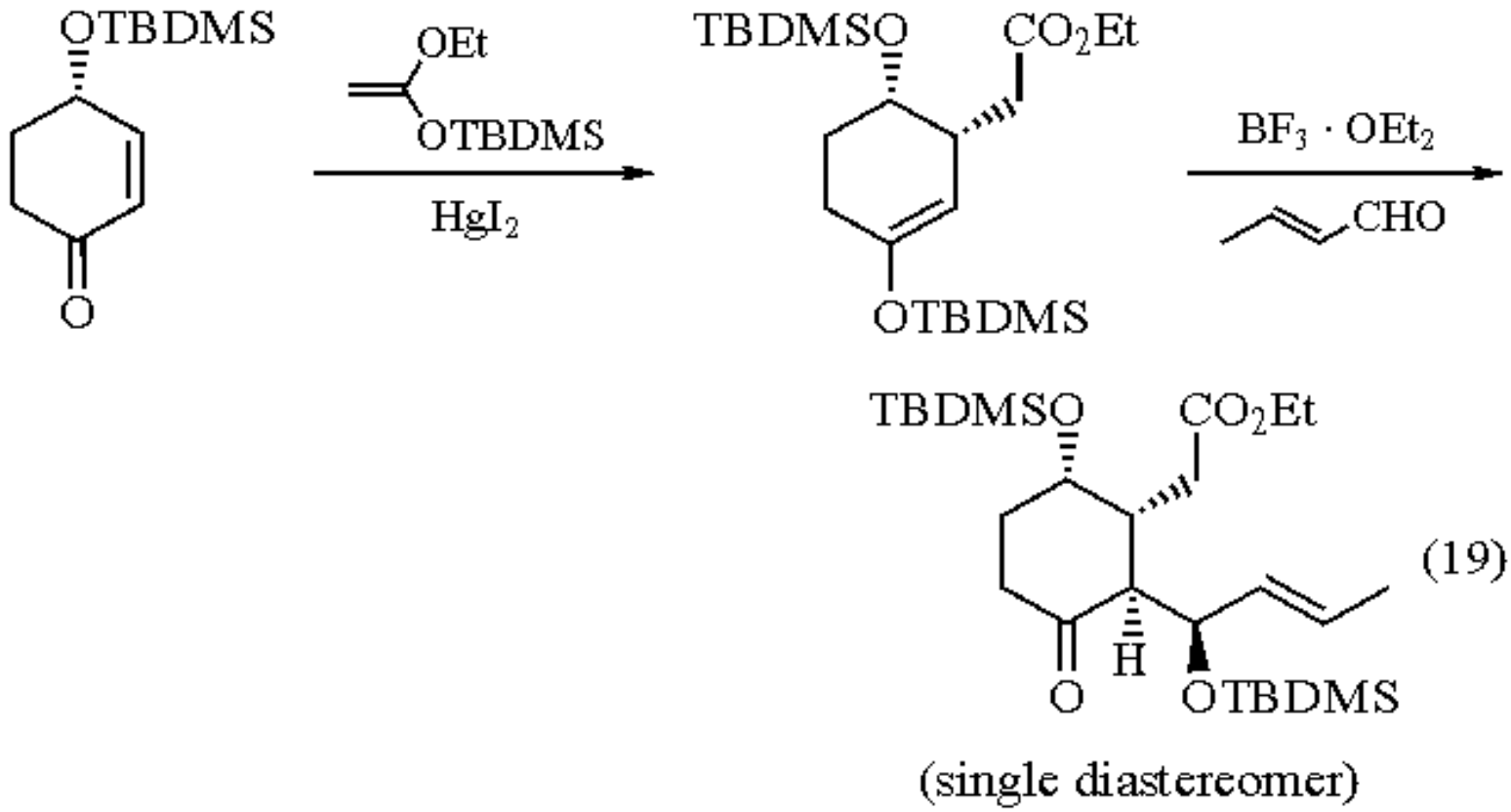

The mechanism of the $TiCl_4$-mediated Michael addition of silyl ketene acetals has been investigated, and criteria for suppressing the electron transfer process have been devised.[36] Chiral enones show good to excellent diastereofacial preference in $TiCl_4$-mediated reactions with silyl ketene acetals (eq 20).[37]

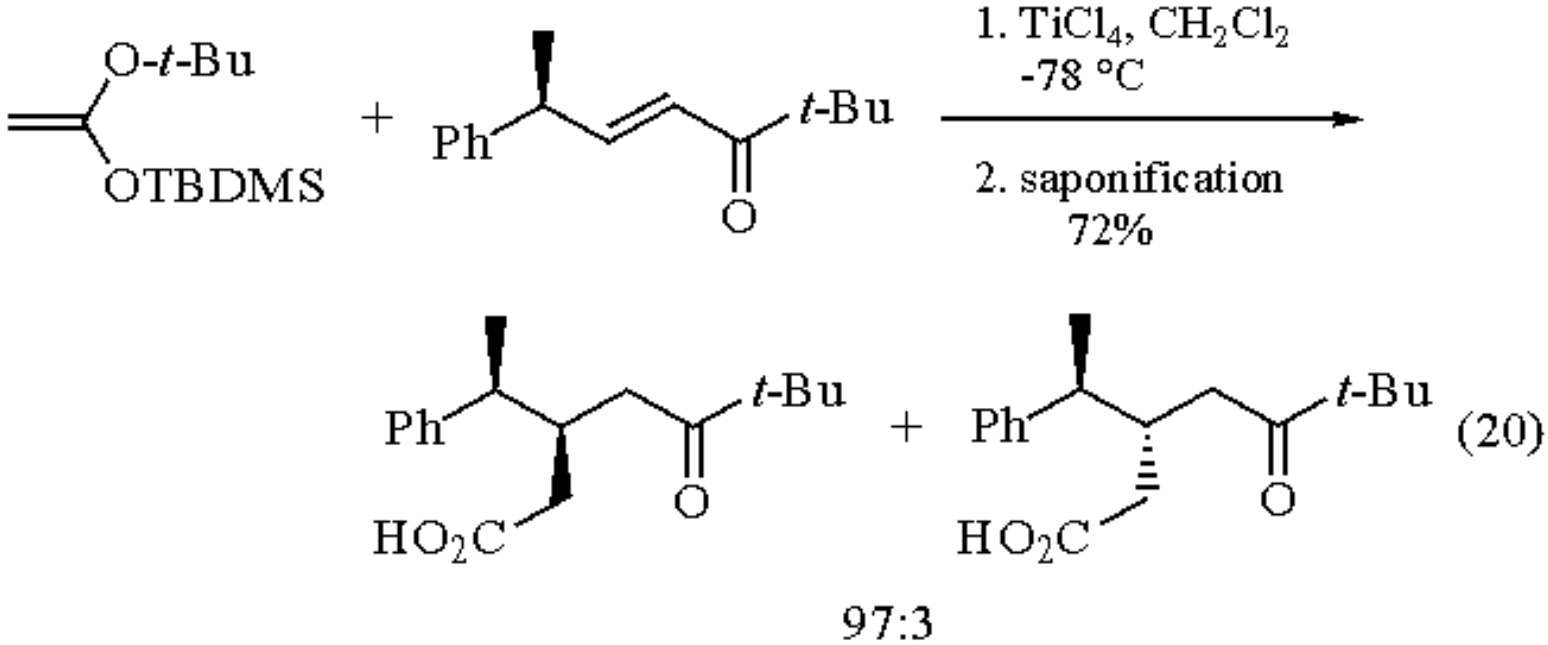

ZnI_2-mediated multiple Michael additions to bis-enoates proceed in good yield and with modest stereocontrol (eq 21).[38]

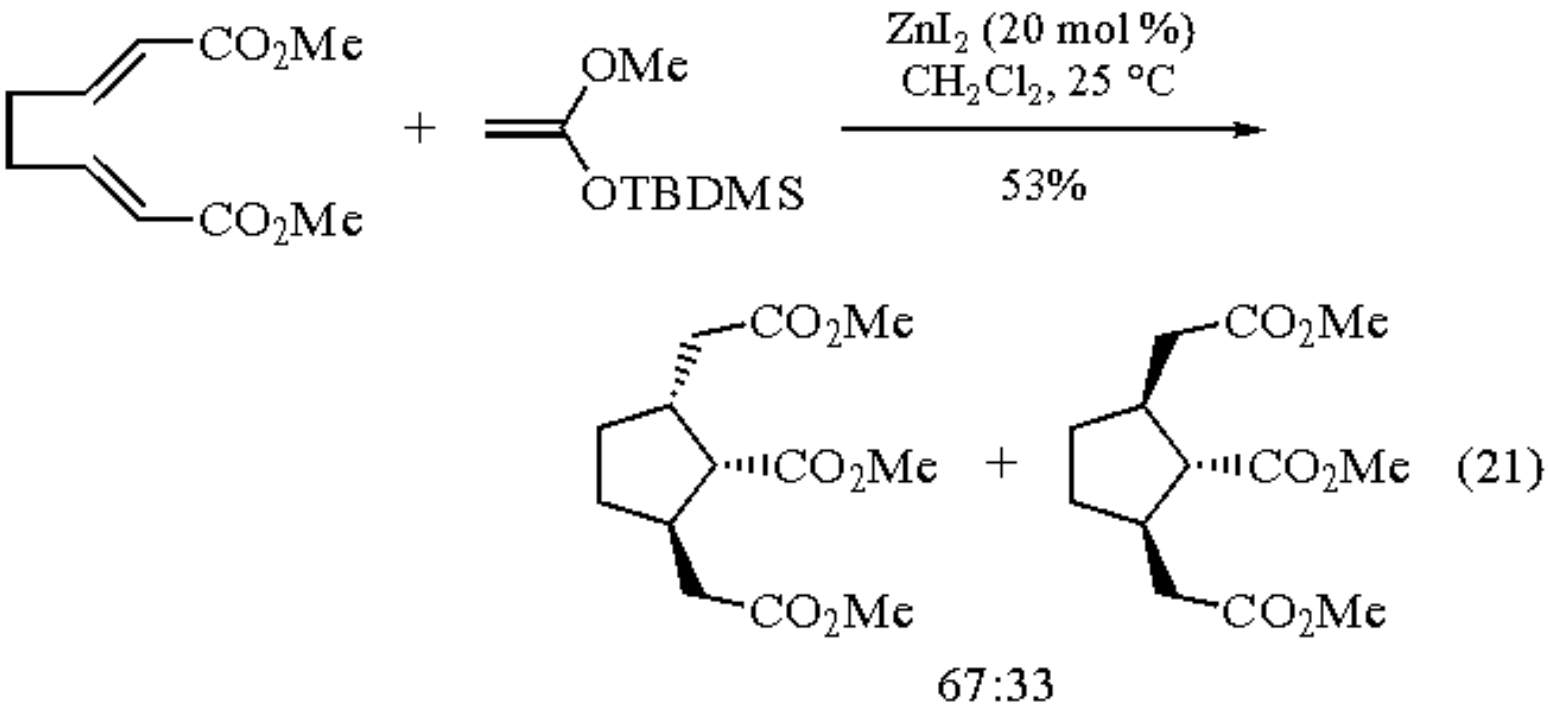

Related Reagents.

1-t-Butylthio-1-t-butyldimethylsilyloxypropene; ***1-t-Butylthio-1-t-butyldimethylsilyloxyethylene***.

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Ketene Diethyl Acetal

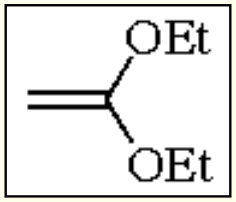

[2678-54-8] · $C_6H_{12}O_2$ · Ketene Diethyl Acetal · (MW 116.18)

(inverse electron demand Diels-Alder reactions; thermal and photochemical [2 + 2] cycloadditions; naphthoquinone and anthraquinone synthesis; Paterno-Büchi photocycloadditions)

Physical Data: bp 68 °C/100 mmHg, 84-86 °C/200 mmHg.

Solubility: sol THF, ether, benzene; decomposes in water, ethanol.

Form Supplied in: liquid, not commercially available.

Preparative Method: reaction of 2-bromo-1,1-diethoxyethane with potassium *t*-butoxide in *t*-butanol.[1]

Handling, Storage, and Precautions: storage in an alkaline glass bottle dusted with potassium *t*-butoxide is recommended.

Inverse Electron Demand Diels-Alder Reactions.

Ketene diethyl acetal undergoes Diels-Alder reactions with various electron deficient dienes especially heterodienes such as α,β-unsaturated aldehydes and ketones (eq 1),[2] acylketenes (eq 2),[3] triazines,[4] acyliminium ions (eq 3),[5] and azodicarboxylates.[6] The Diels-Alder adducts often undergo further reaction, as in the case of cycloaddition of ketene diethyl acetal to 2-pyrones which undergo Diels-Alder reaction followed by retro-Diels-Alder reaction and elimination to allow rearomatization to produce good yields of substituted aromatics (eq 4).[7]

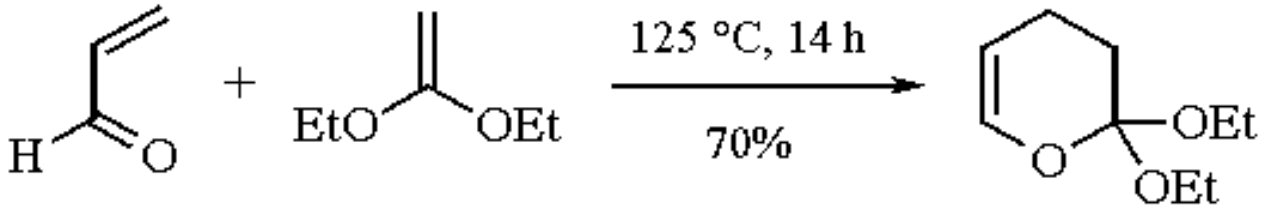

(1)

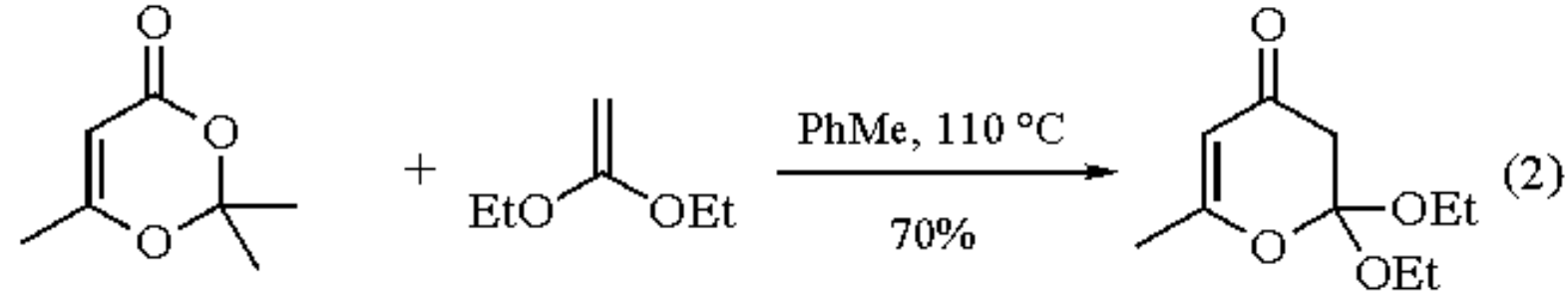

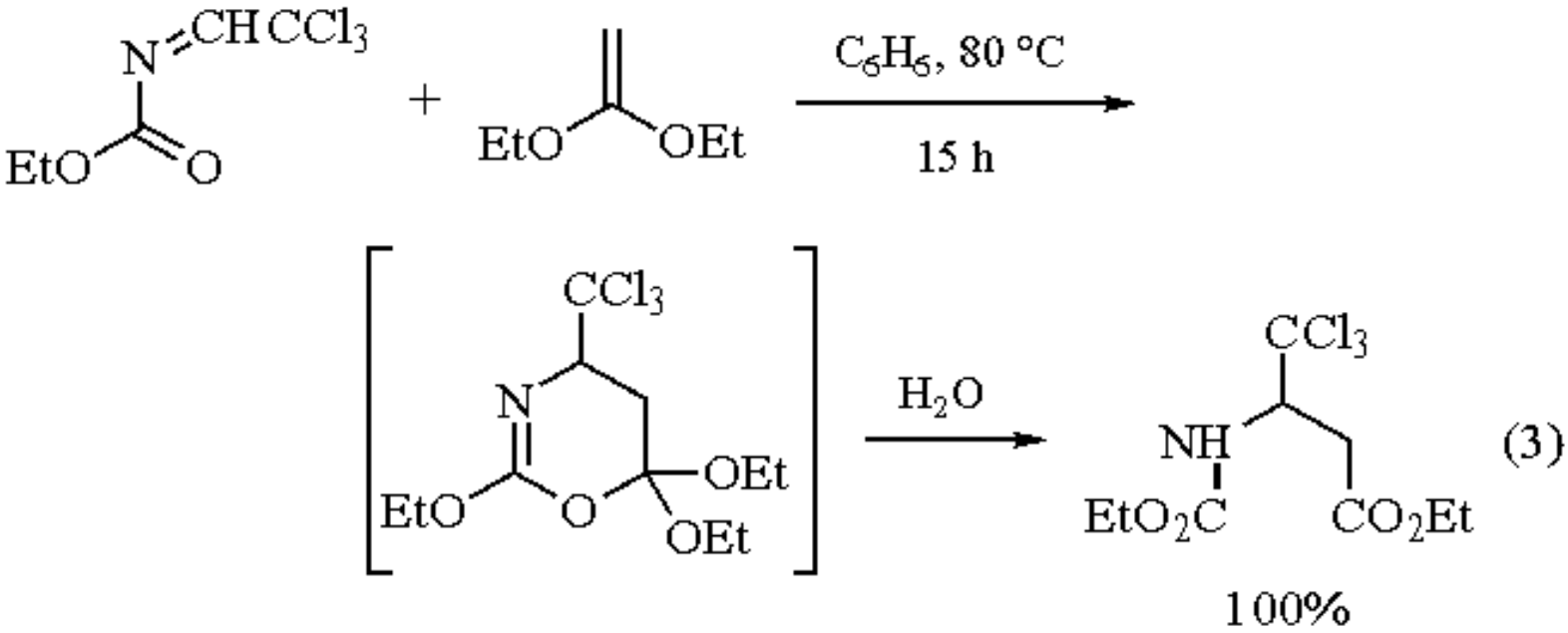

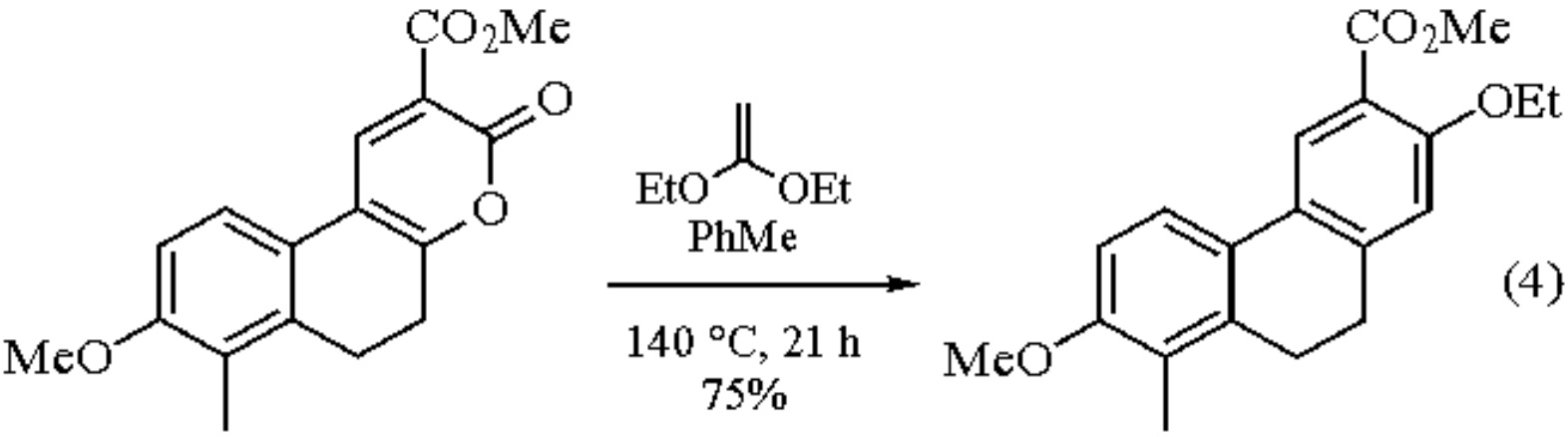

Thermal [2 + 2] Cycloadditions.

Diethyl ketene acetal readily reacts with fumarate[8] and acrylate esters (eq 5)[9] in highly regioselective thermal [2 + 2] cycloadditions to give cyclobutanone acetals, and with propiolate esters[10] to provide cyclobutenone acetals (eq 6), in good yield. Reaction with aryl isocyanates can provide substituted β-lactams (eq 7),[11] but isocyanates with stabilizing groups on the nitrogen generally give ring opened products.[12] Dichloroketene undergoes thermal [2 + 2] cycloaddition with the ketene acetal followed by ring opening (eq 8).[13]

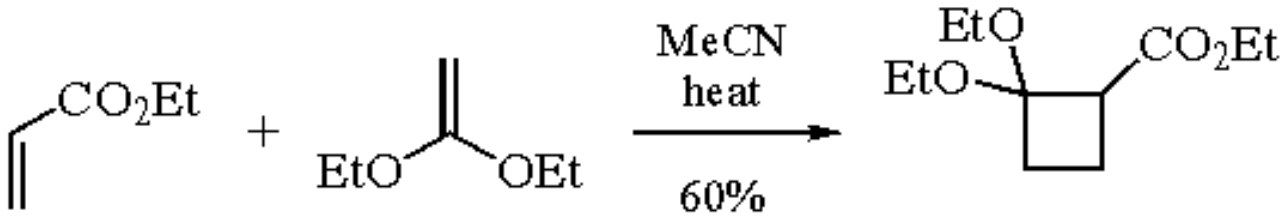

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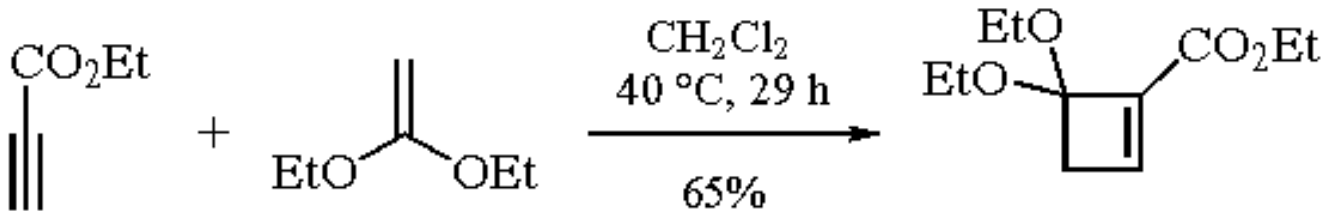

(6)

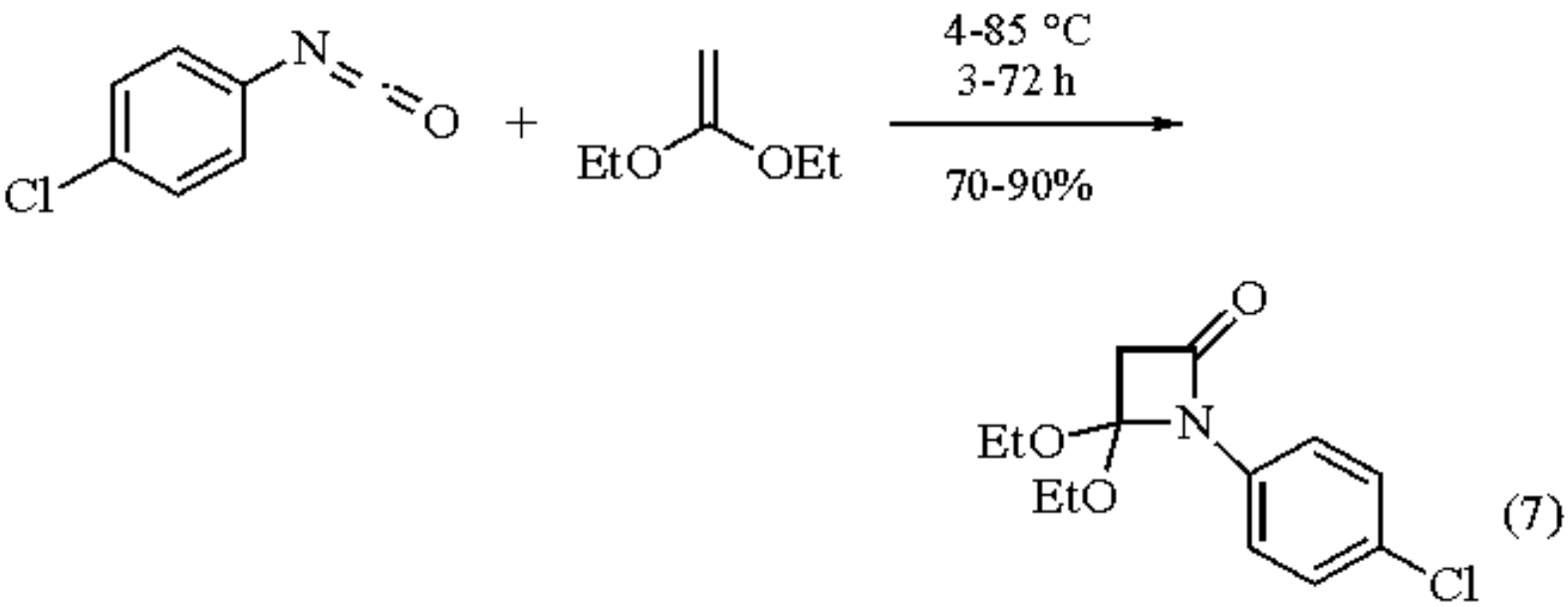

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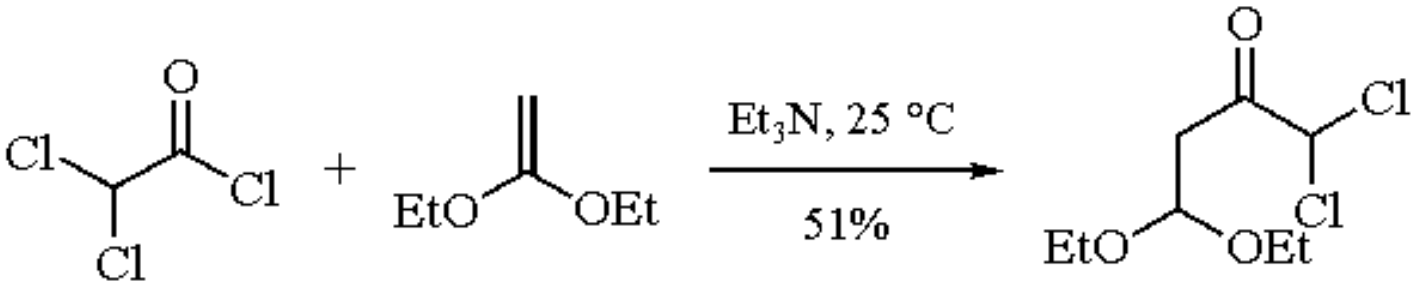

(8)

Photochemical [2 + 2] Cycloadditions with Enones.

One of the most common uses of ketene diethyl acetal has been in [2 + 2] photocycloadditions with enones.[14] This is a highly regioselective process which provides access to cyclobutanone acetals in high yields (eqs 9-11).[15-17] These intermediates can serve as important synthetic building blocks. One example which displays some asymmetric induction has been reported (eq 12).[18]

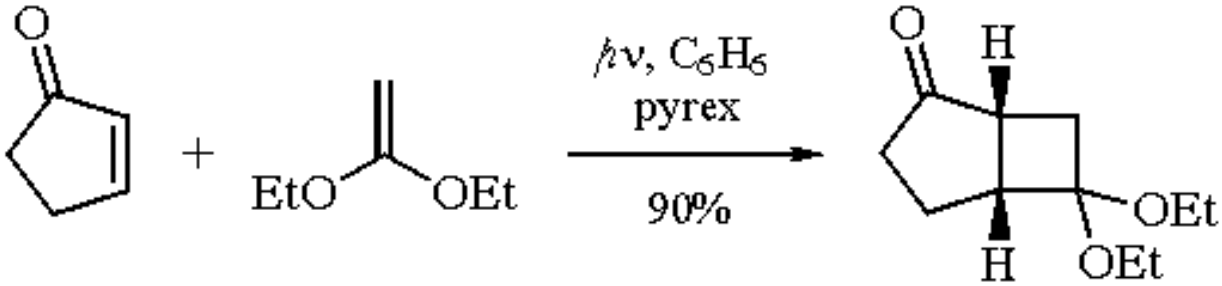
O
+
EtO
OEt
hν, C6H6
pyrex
90%
O
H
OEt
H
OEt

(9)

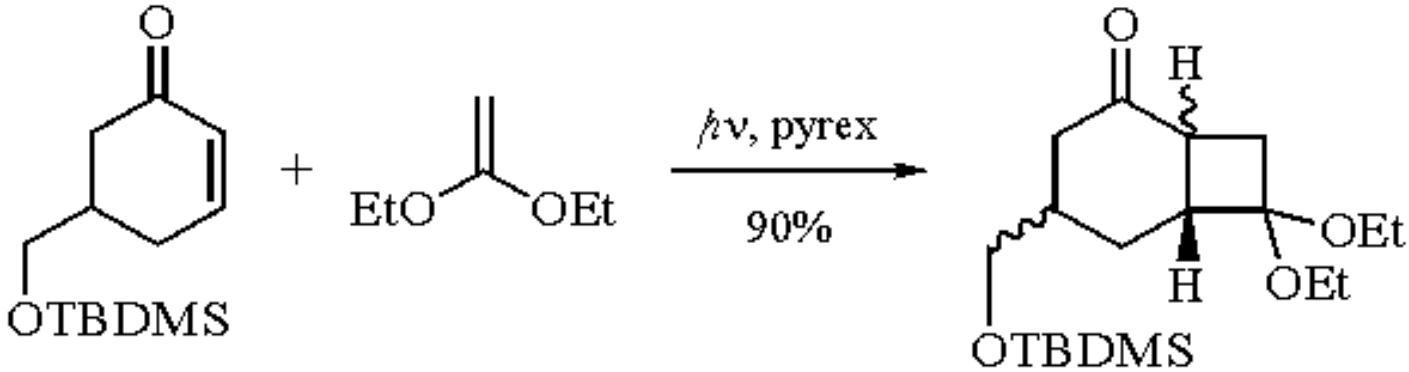
O
OTBDMS
+
EtO
OEt
hν, pyrex
90%
O
H
OEt
H
OEt
OTBDMS

(10)

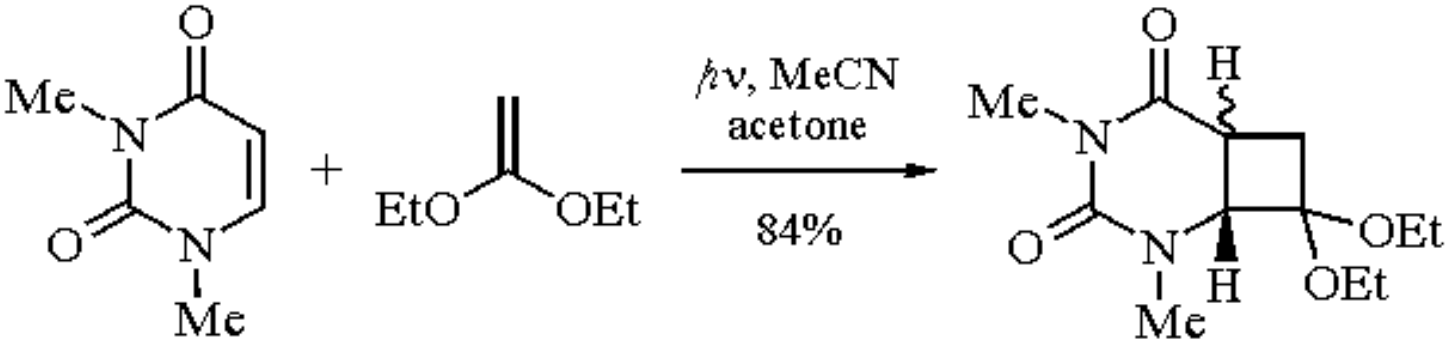
O
Me
N
O
N
Me
+
EtO
OEt
hν, MeCN
acetone
84%
O
H
Me
N
O
N
Me
H
OEt
OEt

(11)

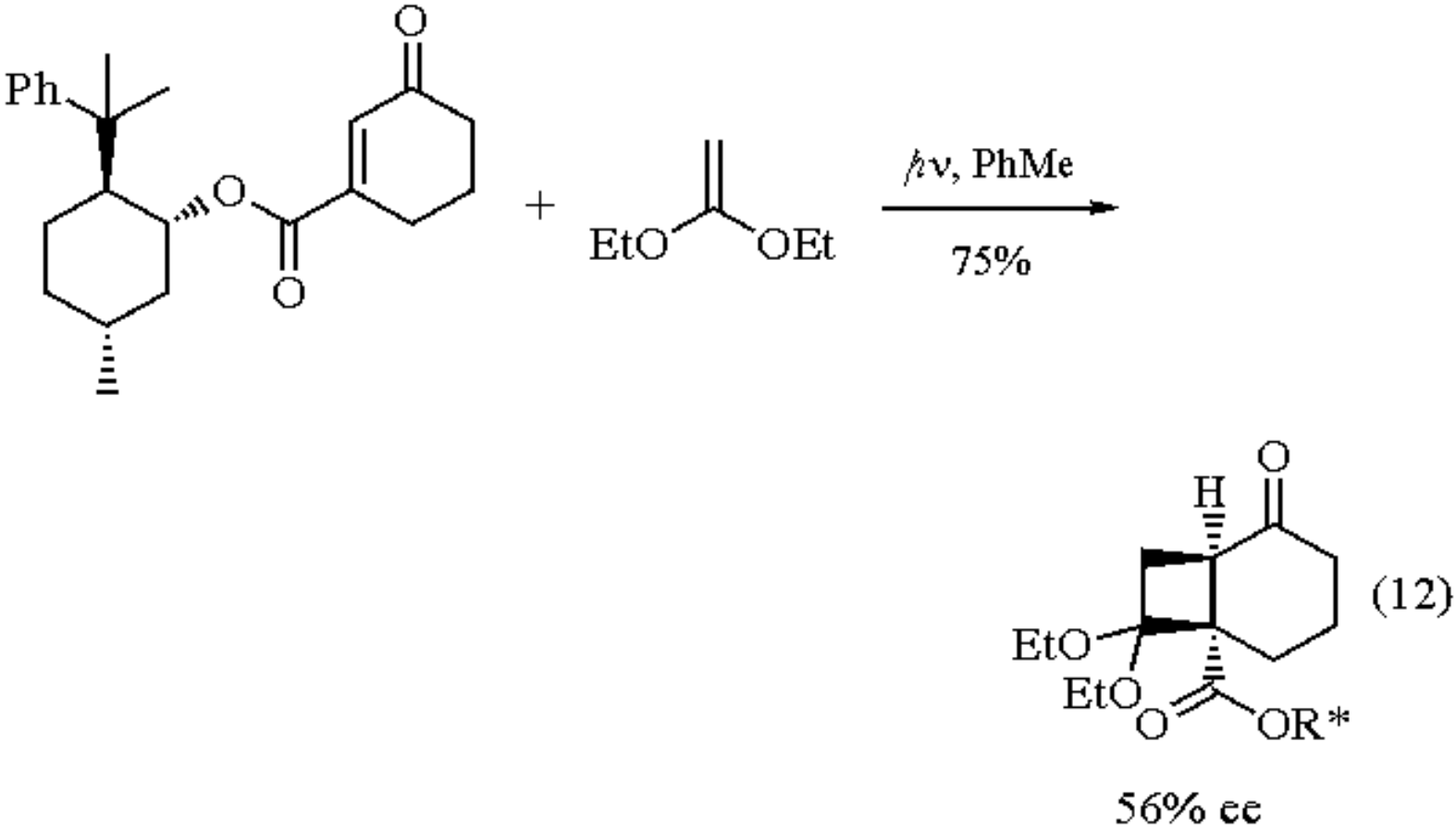

Naphthoquinone and Anthraquinone Synthesis.

The reaction of diethyl ketene acetal with benzo- and naphthoquinones to prepare naphtho- and anthraquinones respectively has been widely studied (eqs 13 and 14).[19-21] The yields vary depending on the substitution of the quinone, and benzofurans are sometimes byproducts.[22] A similar reaction has been carried out on pyridinium salts.[23]

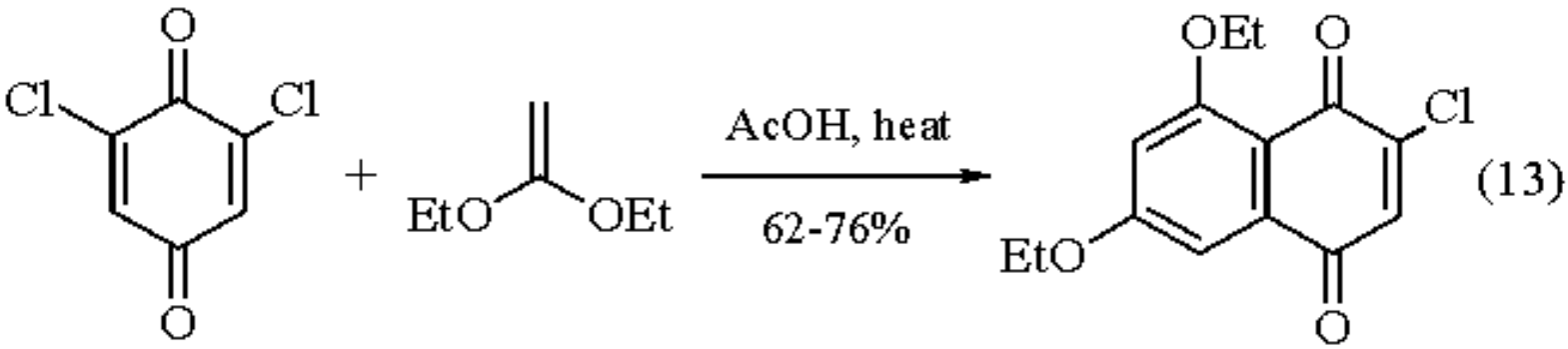

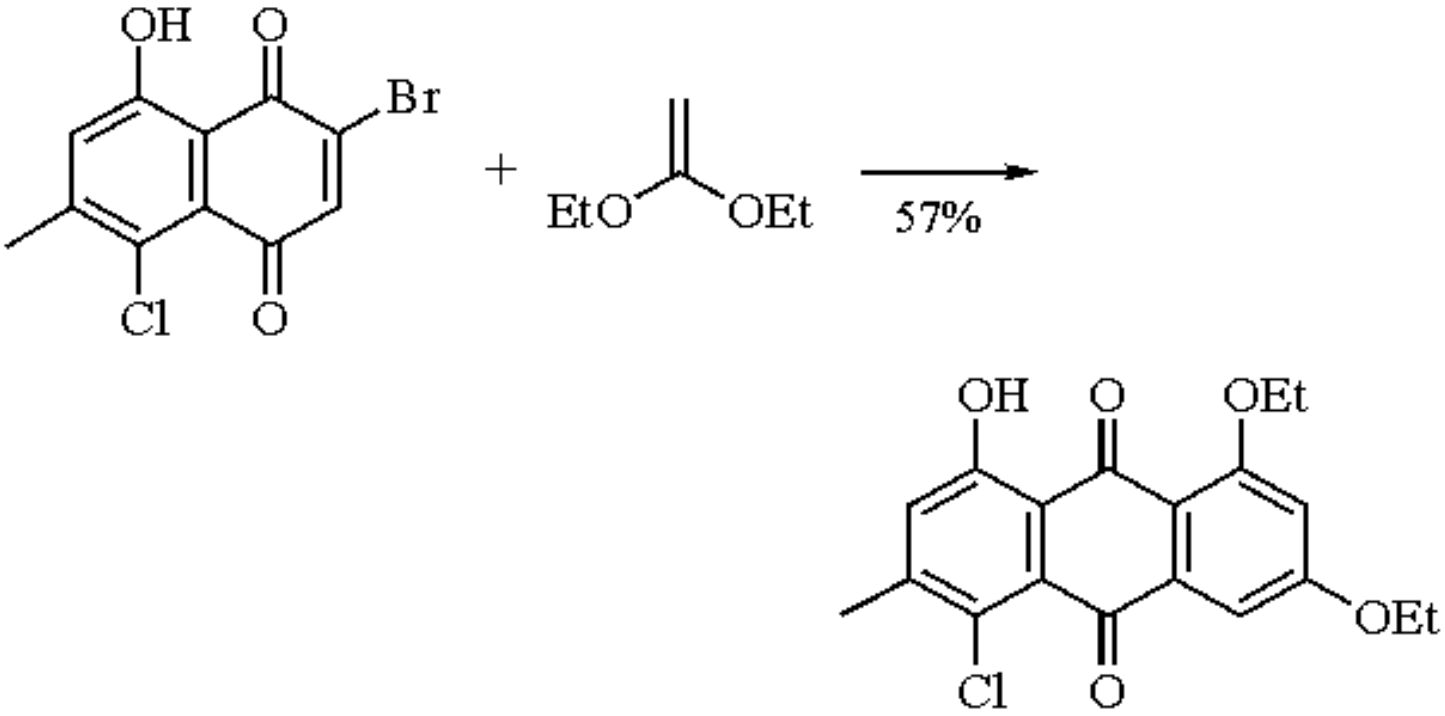

(14)

Paterno-Büchi [2 + 2] Photocycloadditions.

Ketene diethyl acetal reacts with various ketones in the Paterno-Büchi reaction to produce substituted oxetanes in modest yields (eqs 15 and 16).[24-26] More electrophilic carbonyls tend to give higher yields.

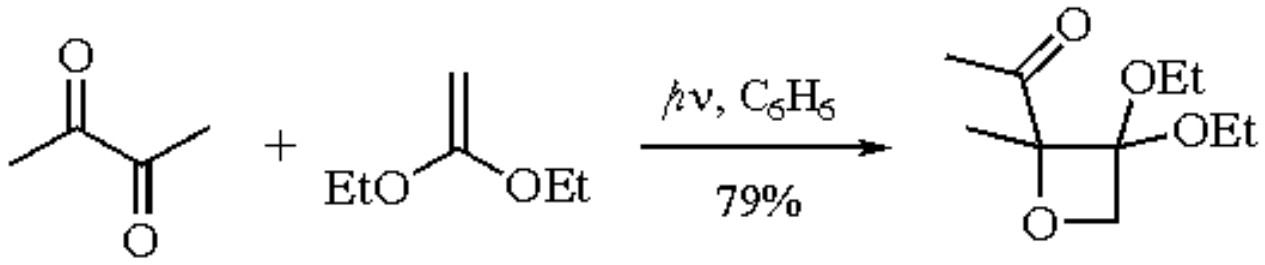

(15)

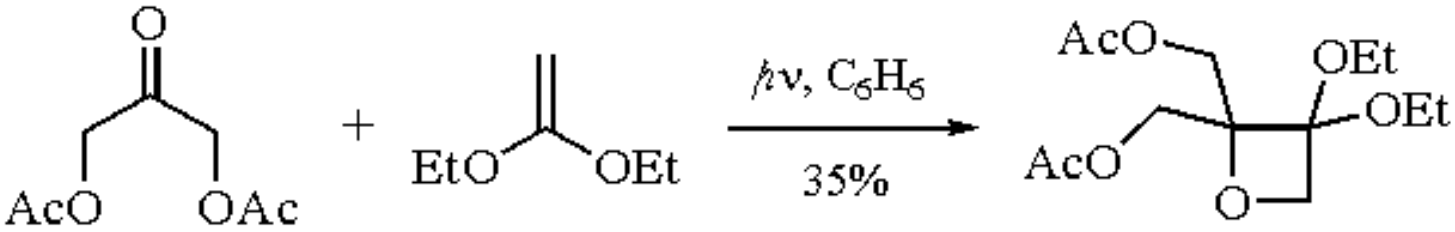

(16)

Miscellaneous Reactions.

Ketene diethyl acetal has been used in the palladium-catalyzed orthoester Claisen rearrangement of allylic alcohols (eq 17)[27] and in reaction with phenyl selenocyanate (eq 18).[28]

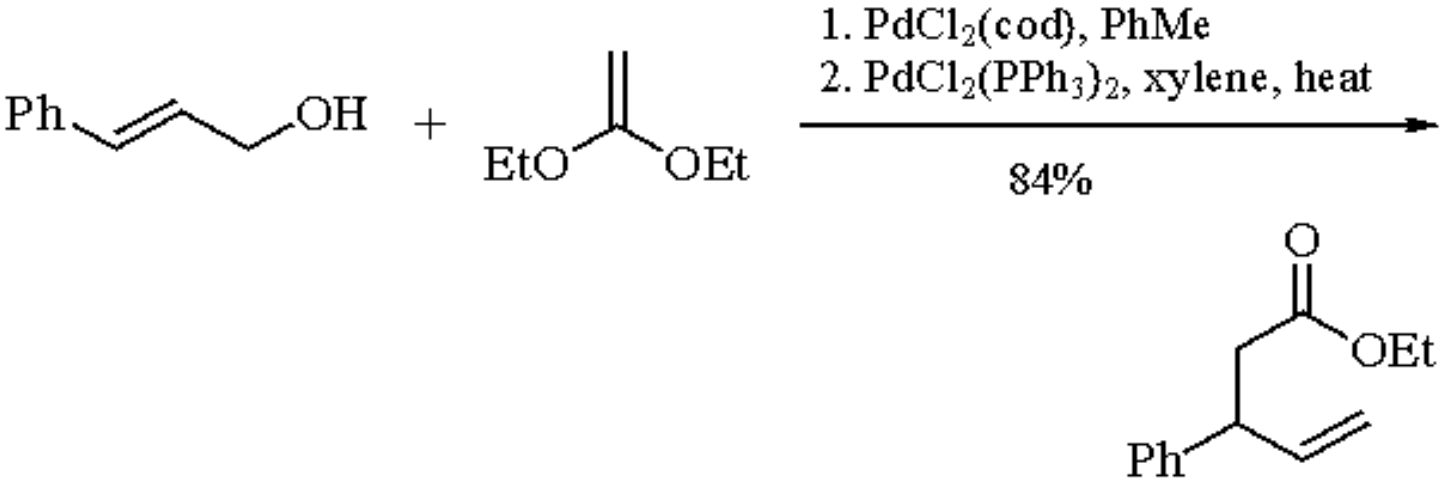

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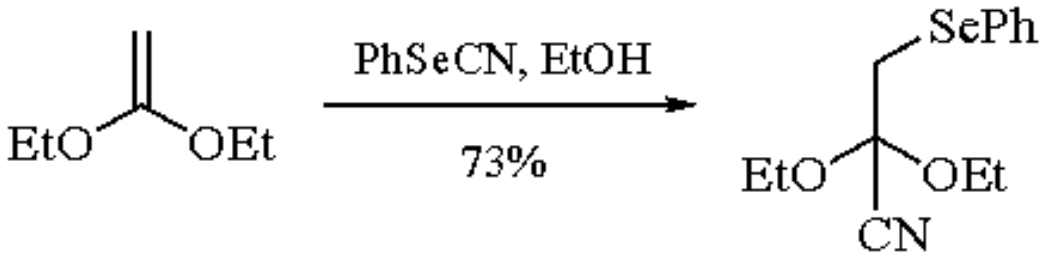

(18)

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Ketene Dimethyl Thioacetal Monoxide[1]

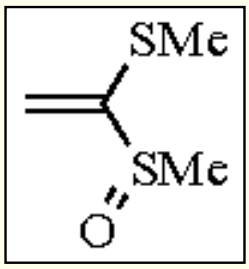

[111674-84-1] · $C_4H_8OS_2$ · Ketene Dimethyl Thioacetal Monoxide · (MW 136.26)

(formylmethyl synthon used as an acceptor in conjugate addition reactions[1])

Alternate Names: ketene bis(methylthio)acetal monoxide; 1-(methylsulfinyl)-1-methylthioethylene.

Physical Data: yellow liquid; bp 145-150 °C/27 mmHg; ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 2.64 (3H, s), 5.51 (1H, d, *J* = 2 Hz), 6.01 (1H, d, *J* = 2 Hz); IR (neat) 3490, 1593, 1429, 1330, 1070, 970, 893 cm^{-1}; MS (70 eV), *m*/*e* (rel. intensity) 136 (5.9, M^+), 126 (0.8), 120 (1.6), 108 (3.2), 90 (8.4), 73 (100.0), 58 (15.1).[2]

Solubility: sol most common organic solvents (i.e. THF, Et_2O, DME, CH_2Cl_2, MeCN, *t*-BuOH, CS_2, benzene).

Preparative Methods: prepared from glyoxylic acid in six steps.[1a] A shorter synthesis involving a two-pot reaction sequence has been developed.[2]

Conjugate Addition Reactions.

The reagent functions as a two-carbon acceptor in Michael reactions with a variety of sodium enolates of β-dicarbonyl compounds (i.e. β-keto esters (eq 1),[1] malonates,[1] and β-diketones[1]), and in conjugate addition reactions with lithium enolates of simple carbonyl compounds (i.e. ketones,[3a] esters (eq 2),[1] α,β-enoates (eq 3),[1] and α-methylthio esters[1]), and enamines.[1] The reagent provides for umpolung reactivity since hydrolysis of the dithioacetal monoxide affords a 1,4-disposition of carbonyl functionality rather than the 1,5-disposition obtained in the Michael reaction.

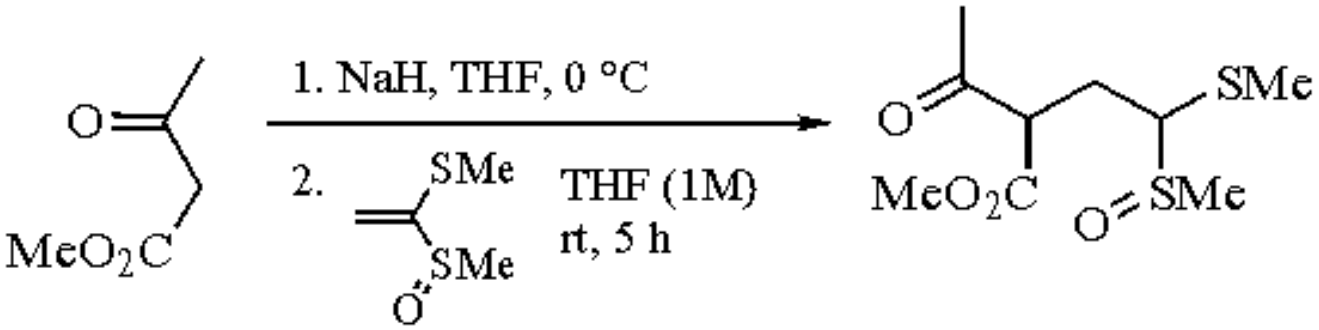

92% (1)

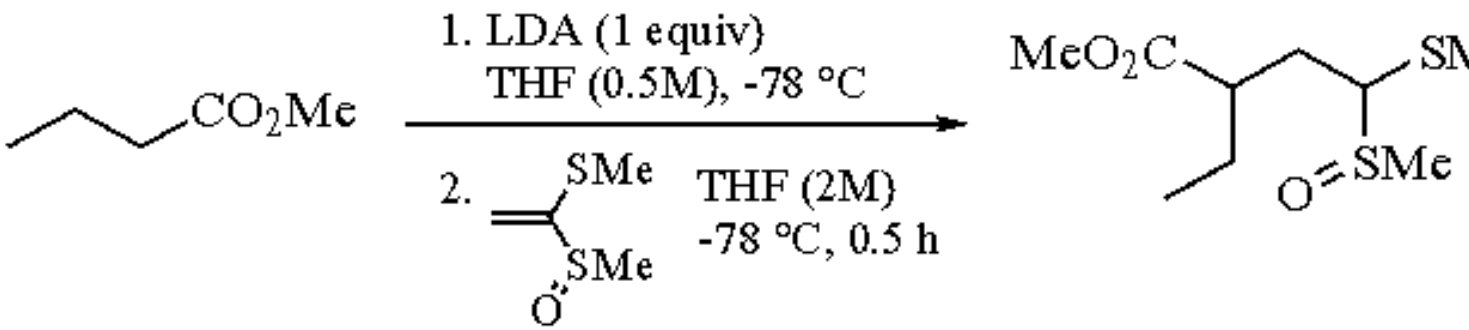

93% (2)

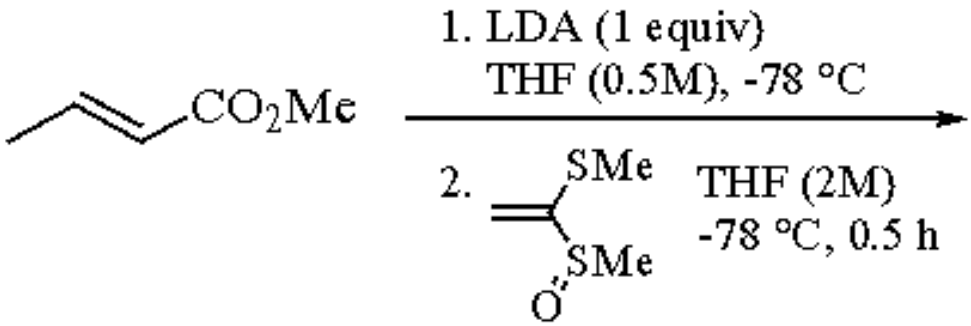

88%

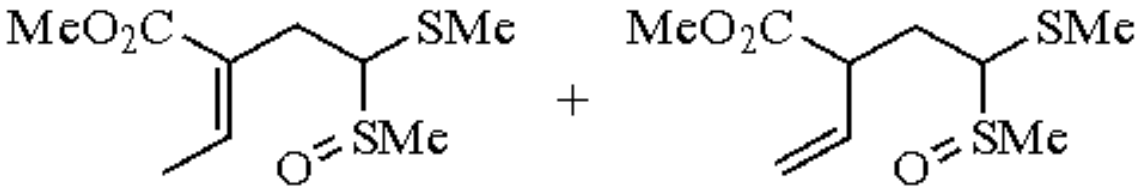

(3)

The synthesis of oxygenated Aspidosperma alkaloids involves addition of a tetracyclic nine-membered ring lactam enolate to CH_2=C(SOMe)SMe (eq 4).[3b] Conjugate additions of nitroalkanes proceed quantitatively when ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** is used as the base.[4] Syntheses of the natural products (±)-prostaglandin $F_{2\alpha}$[5,6] and (±)-1-acetylaspidoalbidine[3a] employ this particular methodology as a key step.

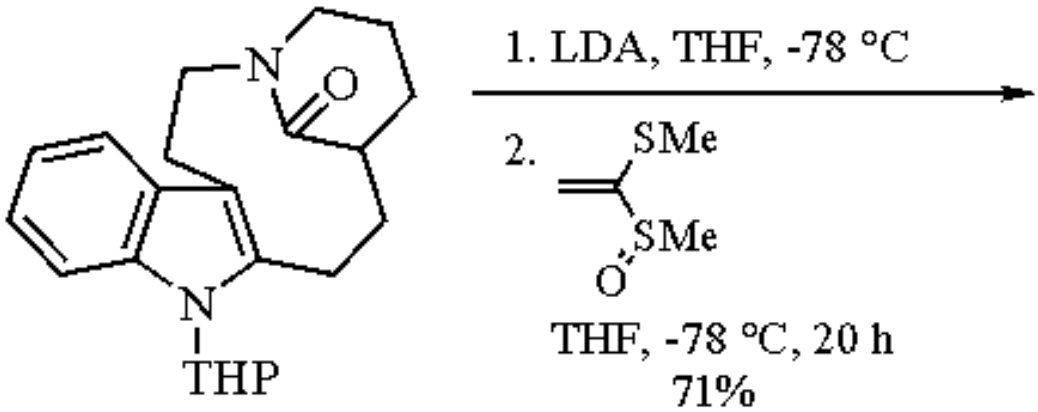

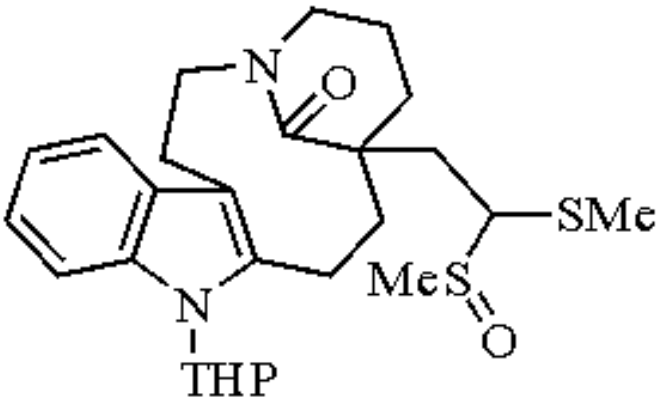

(4)

mixture of four stereoisomers

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1. (a) Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Wepplo, P. J.; Schlessinger, R. H. *TL* **1973**, 4711. (b) Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Schlessinger, R. H. *TL* **1973**, 4715.
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Ketenylidenetriphenylphosphorane

$Ph_3P{=}C{=}C{=}O$

[15596-07-3] · $C_{20}H_{15}OP$ · Ketenylidenetriphenylphosphorane · (MW 302.3)

(cumulated phosphonium ylide)

Physical Data: mp 171-172 °C;[1] IR;[1] ^{31}P NMR;[1] crystal structure.[2]

Preparative Methods: prepared most conveniently by a β-elimination from ***(Methoxycarbonylmethylene)triphenylphosphorane*** using ***Sodium Hexamethyldisilazide*** or ***Sodium Amide*** as a base (eq 1).[1,3] Other preparations have been reported.[4,5]

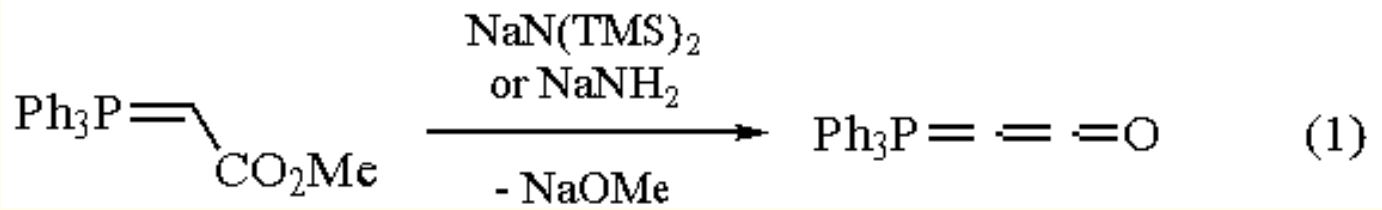

Handling, Storage, and Precautions: absence of moisture and air is necessary.

Reactivity.

In spite of its structural similarity with ketenes, the cumulated ylide displays no tendency to dimerize.[6] However, addition of an electrophile X^+ from a compound X-Y affords a phosphonium salt which reacts in a manner that is typical for ketenes (eq 2).

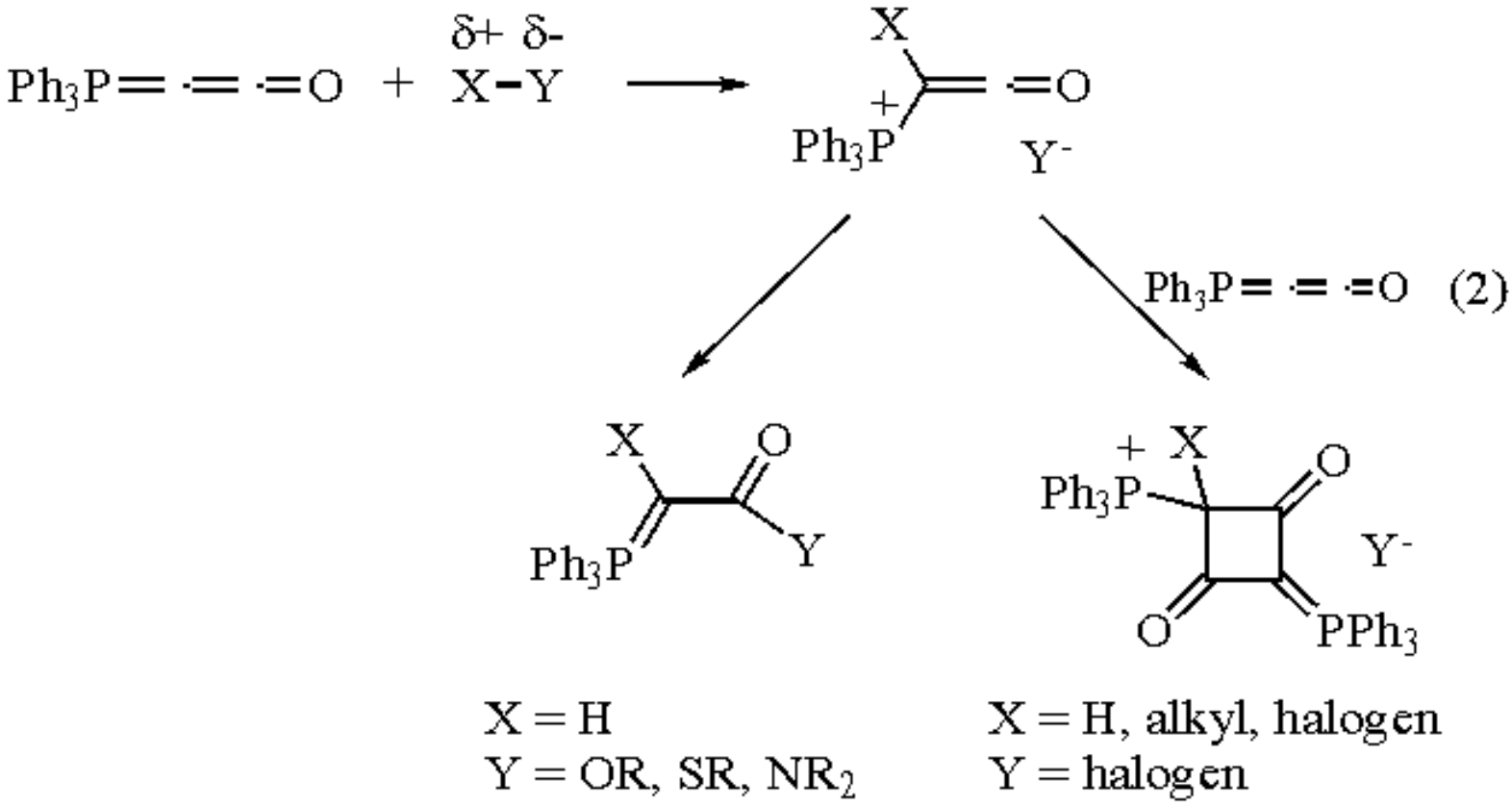

Whenever the starting ylide is a stronger nucleophile than Y^-, the phosphonium salt undergoes [2 + 2] cycloaddition with a second molecule of unreacted ylide to give 1,3-cyclobutanedione derivatives. If the anion Y^- is a stronger nucleophile than the cumulated ylide, then a new carbonyl substituted ylide is formed in which the compound X-Y has been added to the C=C bond of the starting ylide. The cyclic ylide salts formed in the reactions with hydrochloride or halogeno compounds serve as substrates for a series of subsequent reactions (e.g. conversion to the corresponding bis-ylide, Wittig reaction, isomerization, ring opening).[4,7] The stabilized phosphoranes resulting from the cumulated ylide and alcohols, thiols, or acidic NH compounds are very useful for the synthesis of a great variety of α,β-unsaturated carboxylic acid derivatives via the Wittig reaction.[8] α,β-Unsaturated esters can be synthesized (*E*) stereoselectively in this way by means of a three-component synthesis, without isolating the intermediate phosphorane.[9] Synthesis of heterocycles is possible if the acidic compound contains an additional group capable of cyclization (e.g. in the Wittig reaction) with the initially formed ylide function (eq 3). This synthetic principle has proved to be most useful for the synthesis of five- and six-membered heterocycles,[10,11] as well as for the preparation of macrocyclic lactones.[12,13]

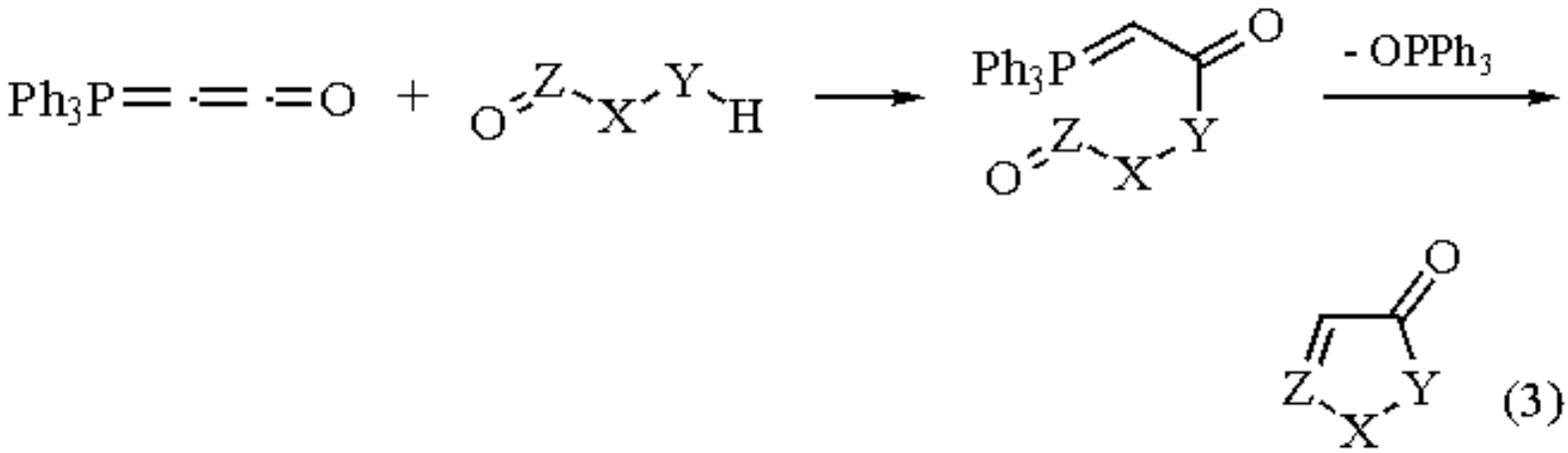

(3)

Grignard reagents react with ketenylidenetriphenylphosphorane to give addition compounds which are hydrolyzed to acyl ylides.[3] This chain-lengthening difunctionalization of a Grignard reagent together with subsequent carbonyl alkenation allows the synthesis of a wide range of (*E*)-α,β-unsaturated ketones (eq 4).

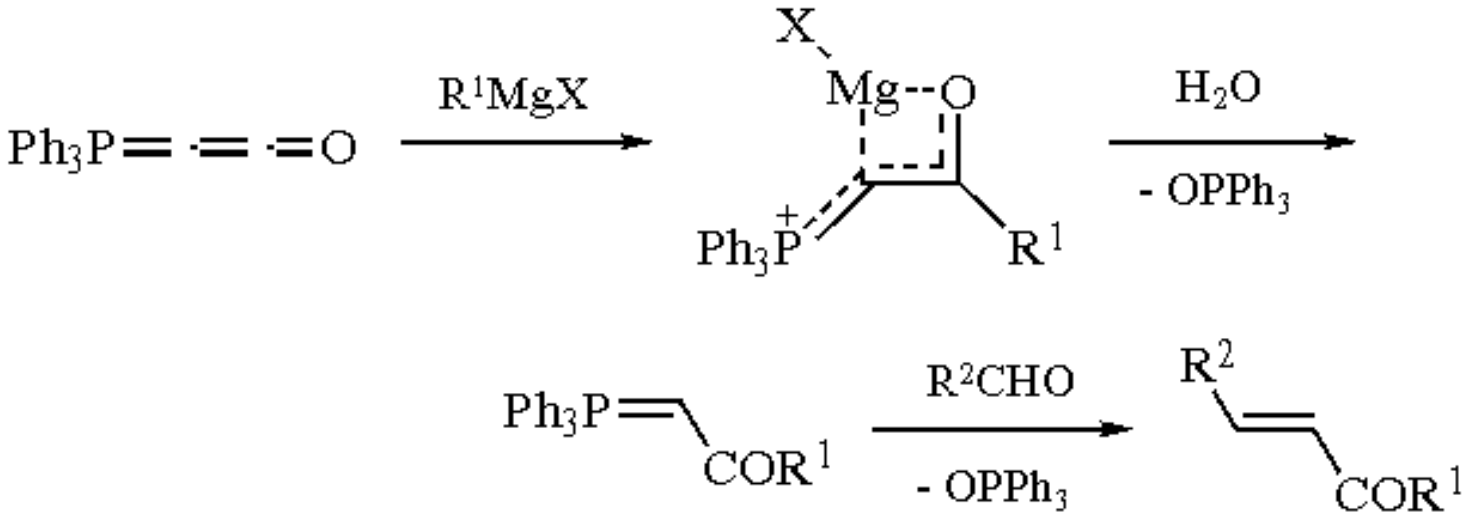

(4)

Reaction of ketenylidenetriphenylphosphorane with aldehydes and ketones yields 1,3-cyclobutanediones, presumably via [2 + 2] cycloaddition of a second molecule of cumulated ylide to the C=C bond of an intermediate Wittig product or its precursor (eq 5).[4]

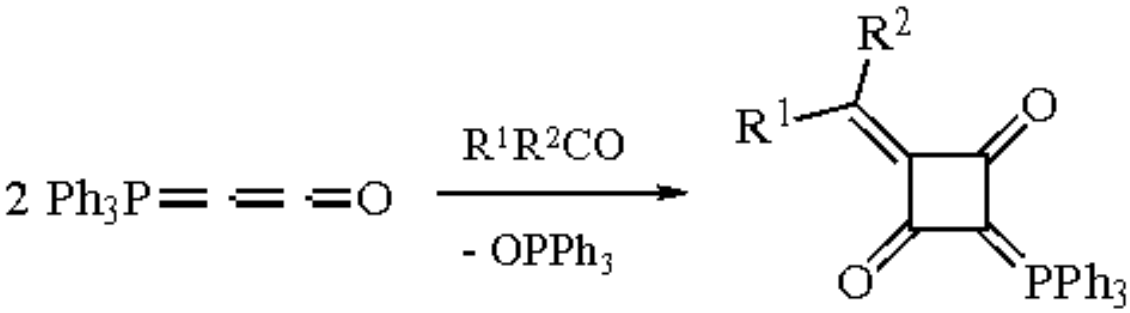

(5)

Cycloaddition at the C=C bond of the cumulated ylide also occurs in the reaction with various other compounds. Thus acyl, thioacyl, and imidoyl heterocumulenes as well as α,β-unsaturated carbonyl compounds react to give six-membered heterocycles in formal [4 + 2] cycloadditions (eqs 6 and 7).[14,15] Heteroallenes yield four-membered rings

in a [2 + 2] cycloaddition or six-membered rings resulting via a [4 + 2] cycloaddition of a second molecule of heteroallene to a dipolar 1:1 intermediate (eq 8).[4] The phosphonium ylides which can be synthesized in this way can usually be converted to the parent phosphorus-free derivatives, thus providing a synthetic approach to a series of heterocyclic systems.

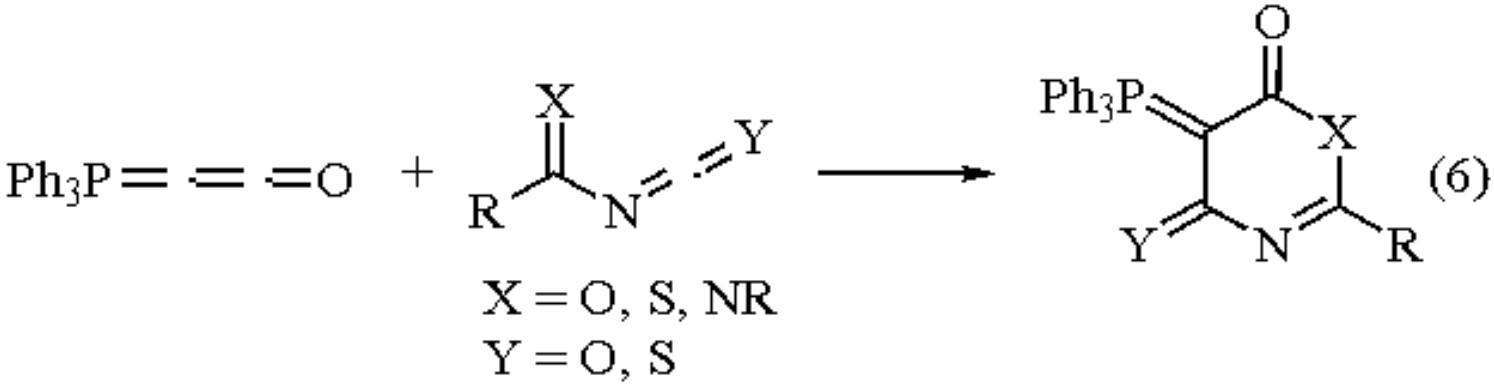

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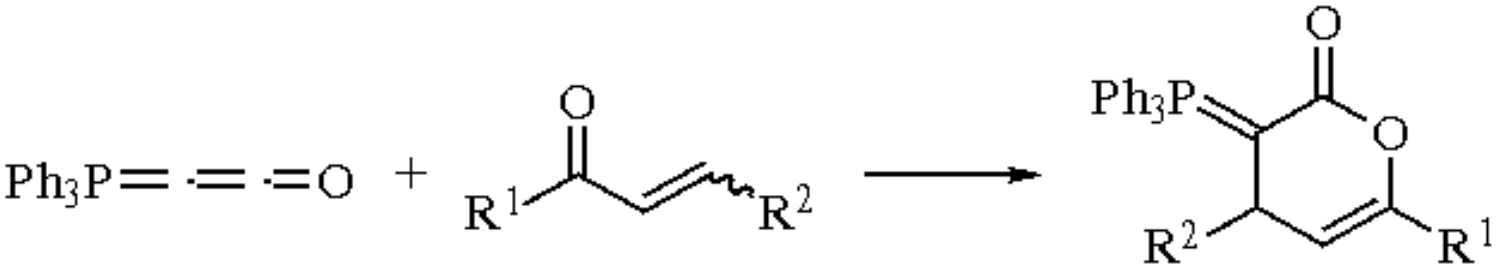

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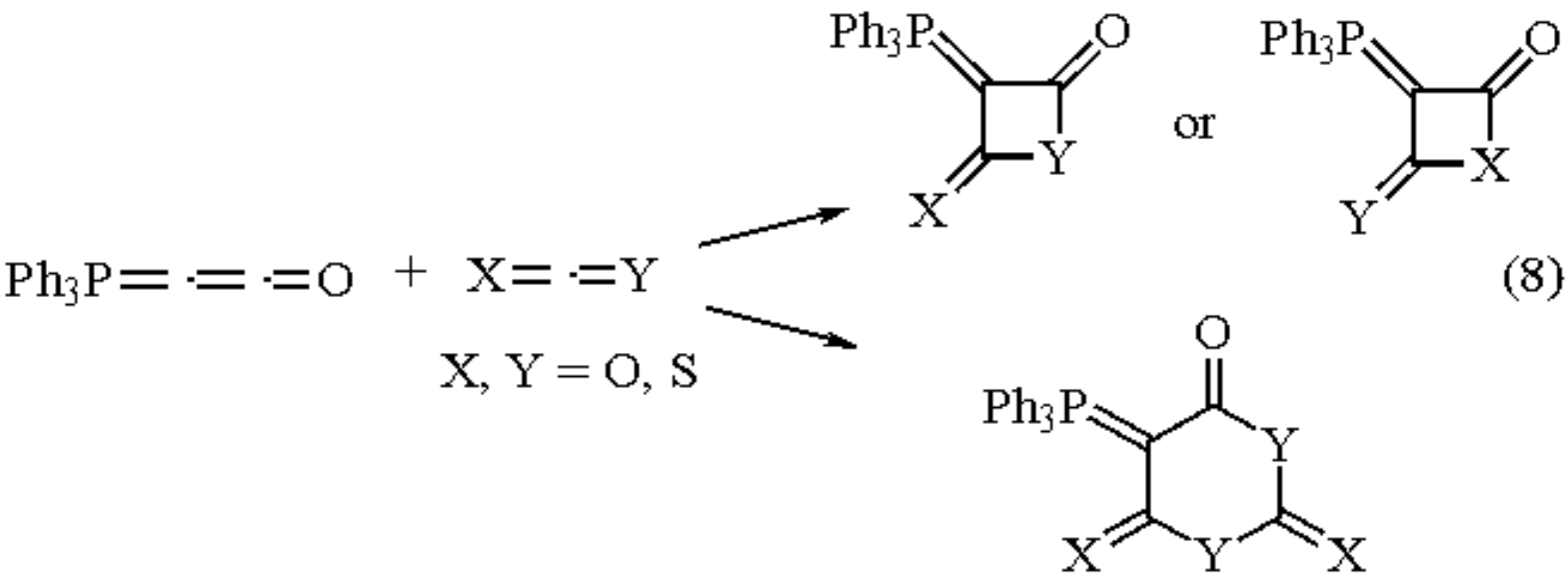

(8)

The cumulated ylide has also been used as a metal complex ligand.[16]

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1. Bestmann, H. J.; Sandmeier, D. *CB* **1980**, *113*, 274.
2. Daly, J. J. *JCS(A)* **1967**, 1913.
3. Bestmann, H. J.; Schmidt, M.; Schobert, R. *S* **1988**, 49.
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5. Review: Bestmann, H. J.; Zimmermann, R. *MOC* **1982**, *E1*, 759.
6. For a detailed discussion concerning the electronic structure of the cumulated ylide and its reactivity, see Ref. 4.
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Lanthanide Shift Reagents

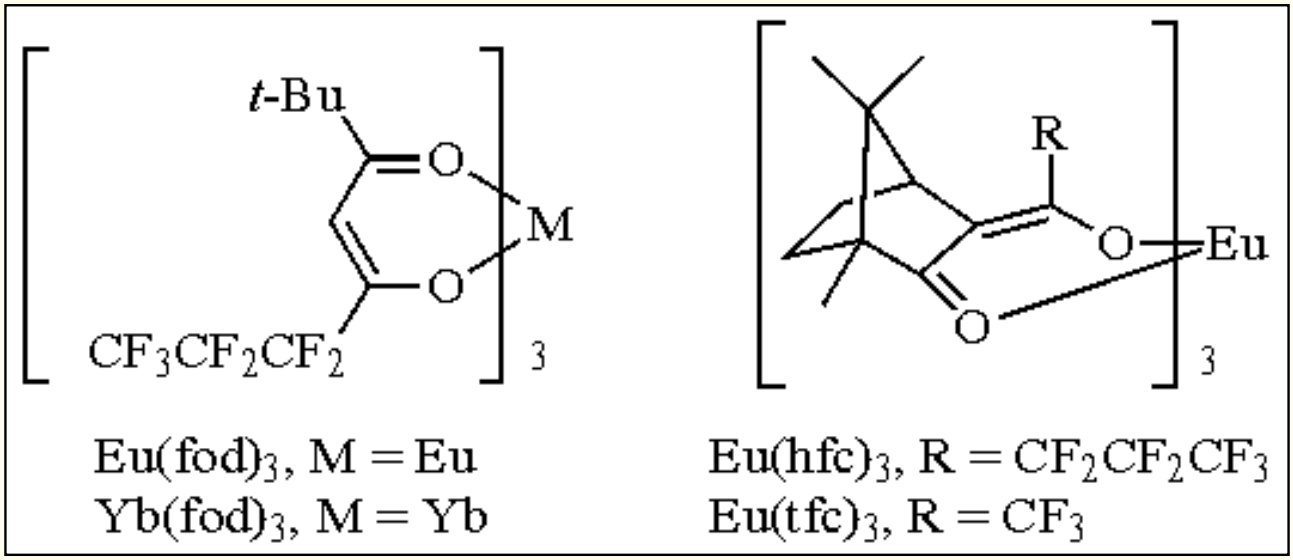

($Eu(fod)_3$)

[17631-68-4] · $C_{30}H_{30}EuF_{21}O_6$ · $Eu(fod)_3$ · (MW 1037.50) ($Yb(fod)_3$)

[18323-96-1] · $C_{30}H_{30}F_{21}O_6Yb$ · $Yb(fod)_3$ · (MW 1058.58) ($Eu(hfc)_3$)

[34788-82-4] · $C_{42}H_{42}EuF_{21}O_6$ · $Eu(hfc)_3$ · (MW 1193.73) ($Eu(tfc)_3$)

[34830-11-1] · $C_{36}H_{42}EuF_9O_6$ · $Eu(tfc)_3$ · (MW 893.72)

(mild Lewis acids capable of catalyzing a variety of synthetic transformations)

Alternate Names: $Eu(fod)_3$ = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium; $Yb(fod)_3$ = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)ytterbium; $Eu(hfc)_3$ = tris[3-(heptafluoropropylhydroxymethylene)-(+ or -)-camphorato]europium; $Eu(tfc)_3$ = tris[3-(trifluoromethylhydroxymethylene)-(+ or -)-camphorato]europium.

Physical Data: $Eu(fod)_3$: mp 203-207 °C; $Yb(fod)_3$: mp 108-111 °C; $Eu(hfc)_2$: mp 156-158 °C; $Eu(tfc)_3$: mp 195-198 °C.

Solubility: generally sol in a wide variety of organic solvents; commonly used in chlorinated solvents such as CH_2Cl_2 and $CHCl_3$.

Form Supplied in: hygroscopic solids; commercially available. *Drying:* if necessary, they can be dried and stored over P_2O_5.

Purification: can generally be used directly without purification. Occasionally contain insoluble material which can be removed by filtration of a solution of the reagent through a millipore filter or a plug of cotton or glass wool. Insoluble material can also be separated and removed by centrifugation.

Handling, Storage, and Precautions: though hygroscopic, they can be handled for short periods of time in the presence of air without deleterious effect. In general, the use of glove bags or dry boxes is not required.

Fluorinated lanthanide dionato complexes are commonly employed as NMR shift reagents.[1] The Lewis acidity of these reagents has allowed them to be exploited as catalysts for a variety of synthetic transformations. In general, they are easy to use and handle and are mild enough to tolerate a variety of acid labile functionality. A wide array of these complexes is commercially available. They have an octahedral geometry with the general structure (**1**) but are capable of expanding their coordination environment in order to accommodate additional Lewis bases. Generally they are believed to function by coordination at a single site, though chelation to two sites has also been suggested to occur.[2-4] Achiral versions generally employ the heptafluorooctanedionato (fod) ligand while complexes of optically active camphor derived ligands, 3-(trifluoromethylhydroxymethylene)camphorato (tfc) or 3-(heptafluoropropylhydroxymethylene)camphorato (hfc), have been investigated in connection with enantioselective synthesis. Both the (+)- and (-)-isomers of $Eu(hfc)_3$ and $Eu(tfc)_3$ are commercially available. Most commonly employed is the europium derivative, $Eu(fod)_3$. In several cases, $Yb(fod)_3$ has been reported to be a stronger Lewis acid than $Eu(fod)_3$ and a more effective catalyst for certain transformations.

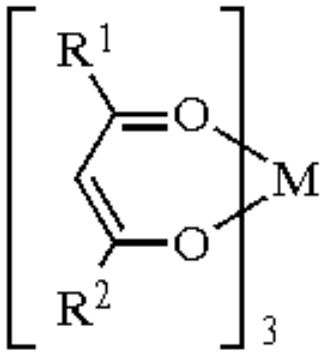

(1)

The first report of their use as catalysts involved the $Eu(fod)_3$ induced rearrangement of oxaspiropentanes to cyclobutanones (eq 1).[5] The lanthanide complex is more effective at catalyzing this reaction than other more conventional Lewis acid catalysts.

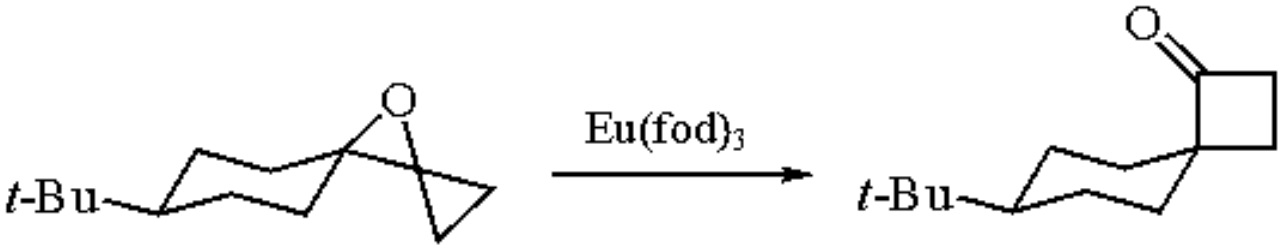

(1)

During a study of its shift reagent properties, $Eu(tfn)_3$ (tris(1,1,1,2,2,3,3,7,7,8,8,9,9,9-tetradecafluoro-4,6-nonanedionato)europium) was found to smoothly catalyze the Diels-Alder dimerization of (**2**) (eq 2).[6] More recently, it has been demonstrated that $Yb(fod)_3$ will catalyze the cycloaddition of a variety of dienes with acrolein (eqs 3-5).[7] Several of these reactions cannot be readily accomplished with other catalysts or reaction conditions because of problems associated with the polymerization of acrolein.

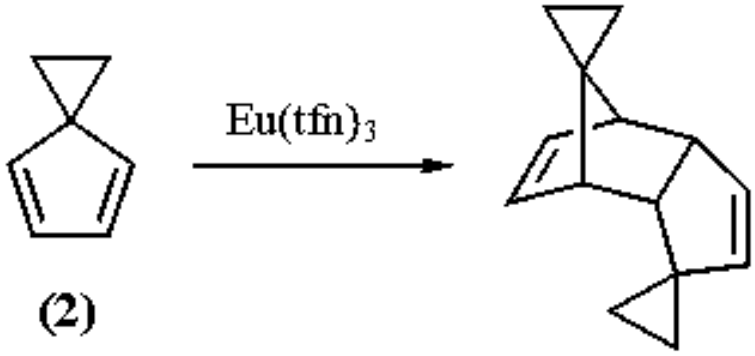

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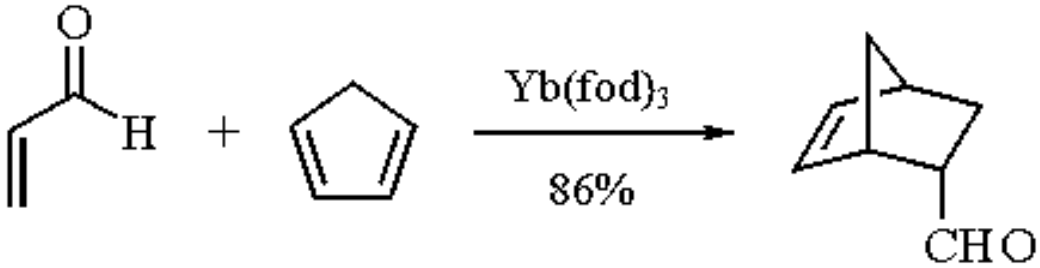

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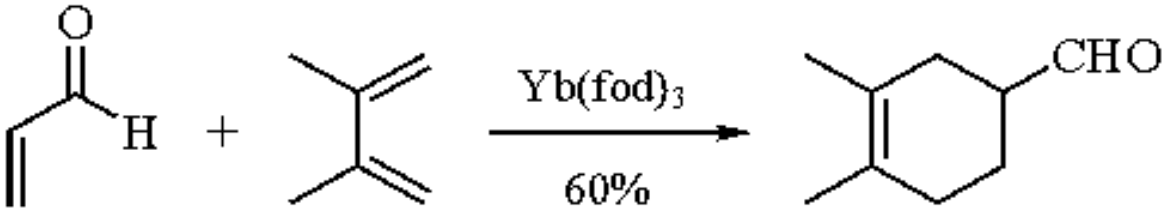

(4)

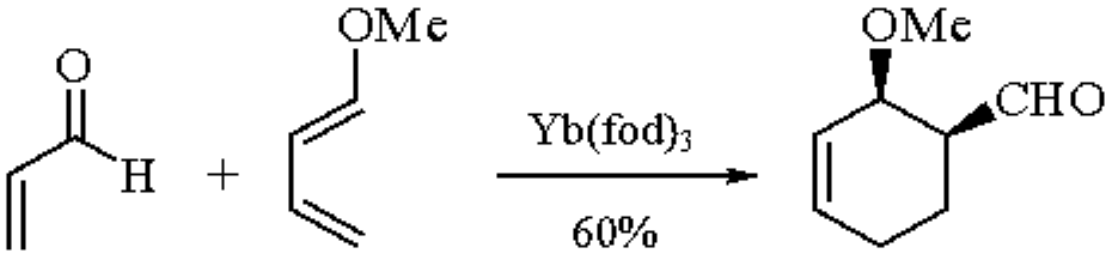

(5)

The lanthanide shift reagent catalyzed Diels-Alder cycloaddition reaction of oxygenated dienes with aldehydes has been extensively investigated. $Eu(fod)_3$ effectively catalyzes this reaction at room temperature and, in many cases, allows the relatively unstable silyl enol ether intermediates to be isolated (eqs 6-11).[3,8-10]

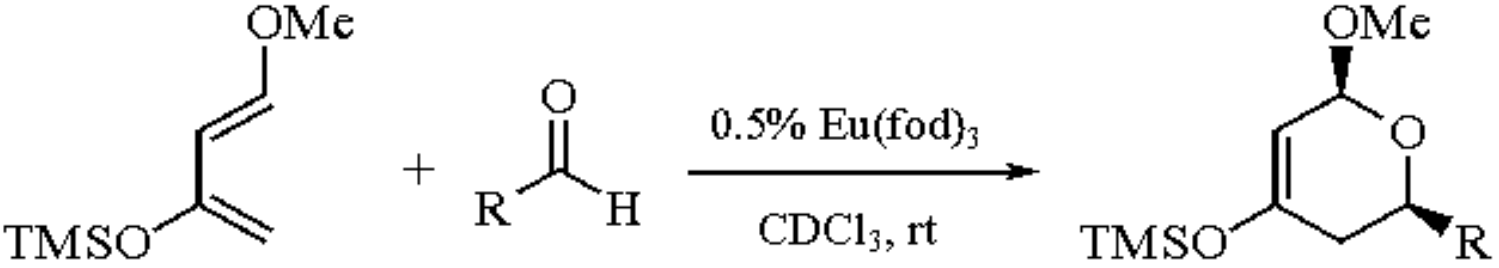

(6)

R = Ph, 82%
R = 2-furyl, 86%
R = CH=CHPh, 94%

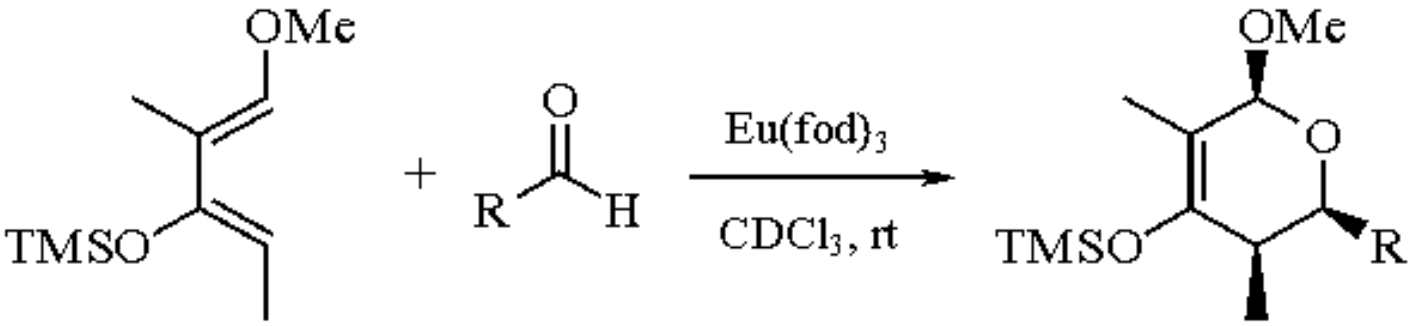

(7)

R = Ph, 66%
R = Me, 66%
R = C_6H_{13}, 49%

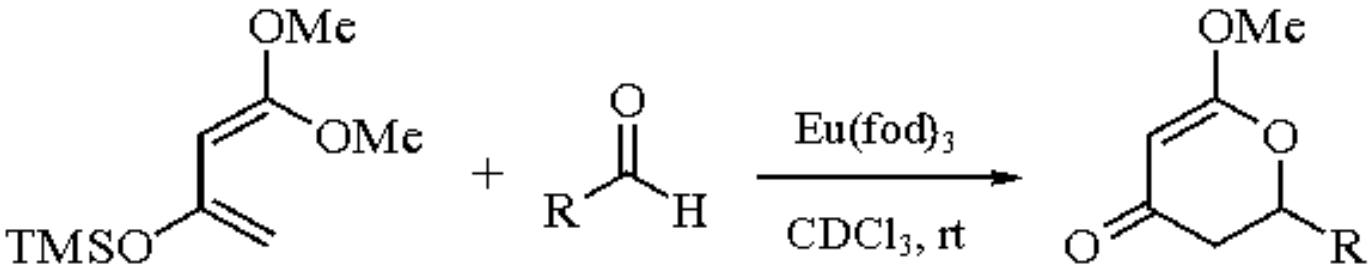

(8)

R = Ph, 85%
R = C_6H_{13}, 73%

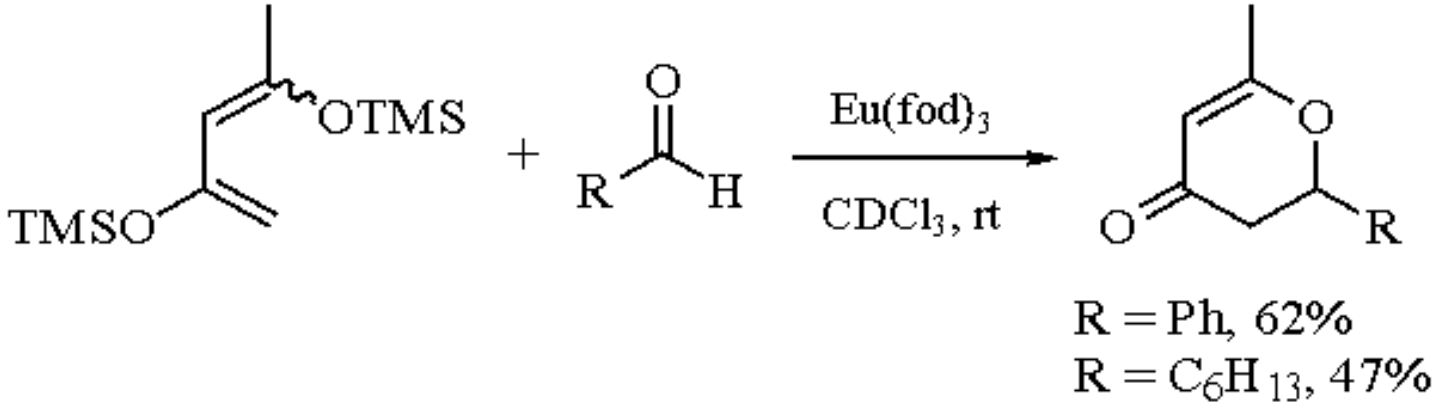

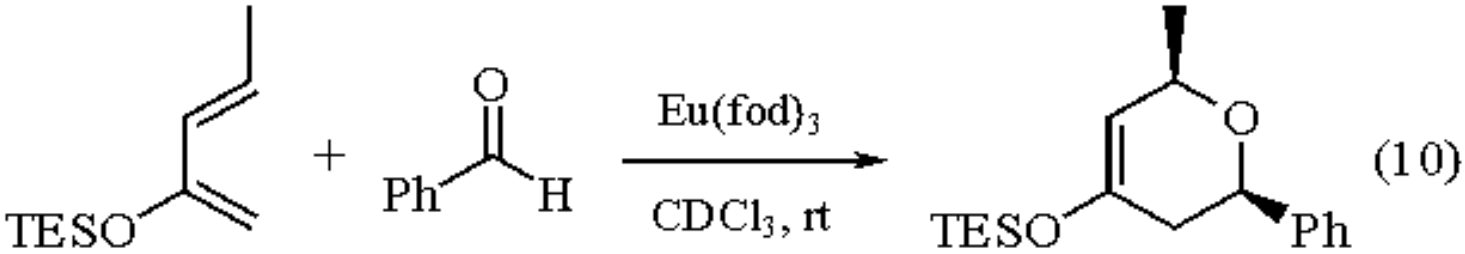

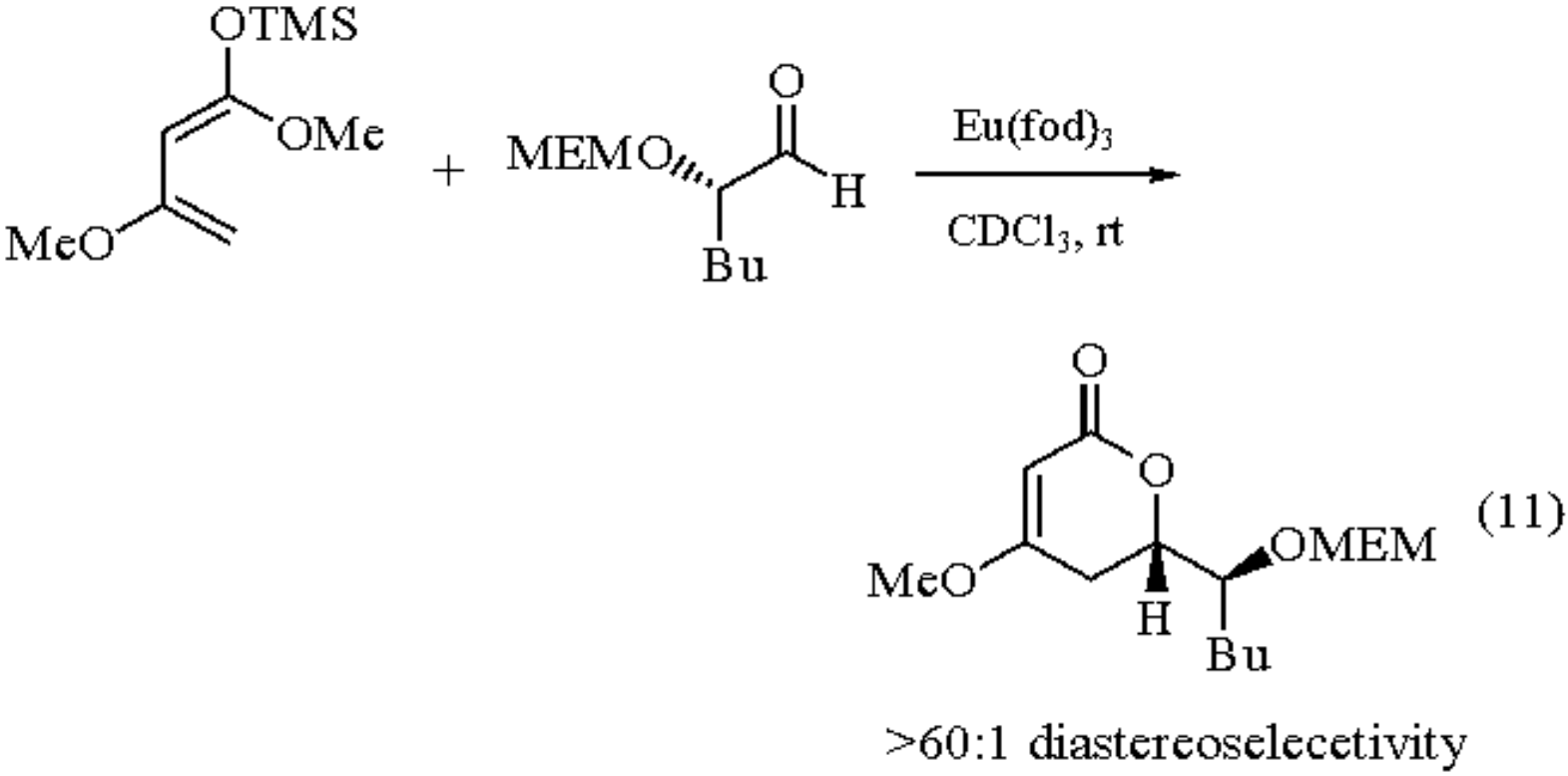

Enol ethers undergo [4 + 2] cycloaddition with α,β-unsaturated aldehydes in the presence of catalytic amounts of lanthanide shift reagents to give dihydropyran derivatives (eqs 12 and 13).[11]

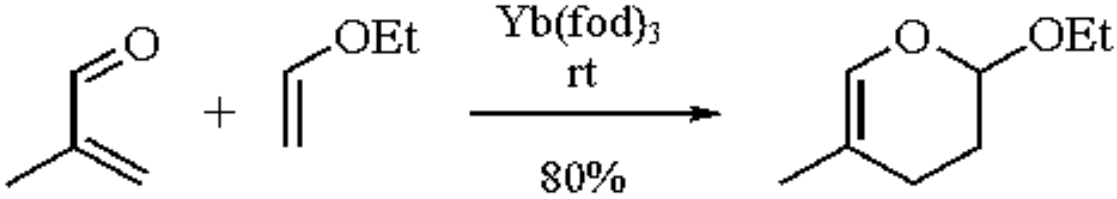

(12)

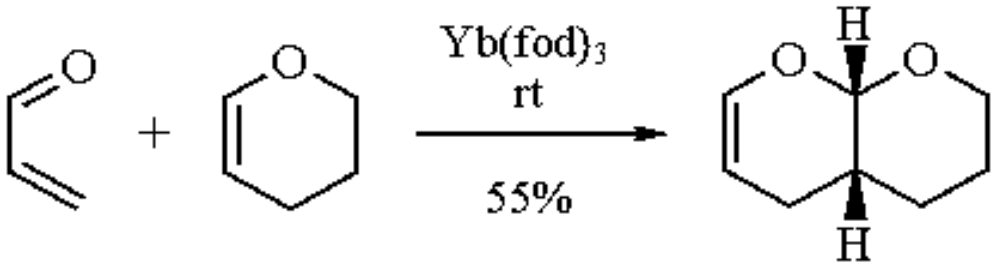

(13)

Lanthanide shift reagents catalyze the addition of silyl enol ethers to aldehydes.[4,12] The yield and diastereoselectivity obtained with lanthanide shift reagents are often better than those observed with more conventional catalysts (eq 14).

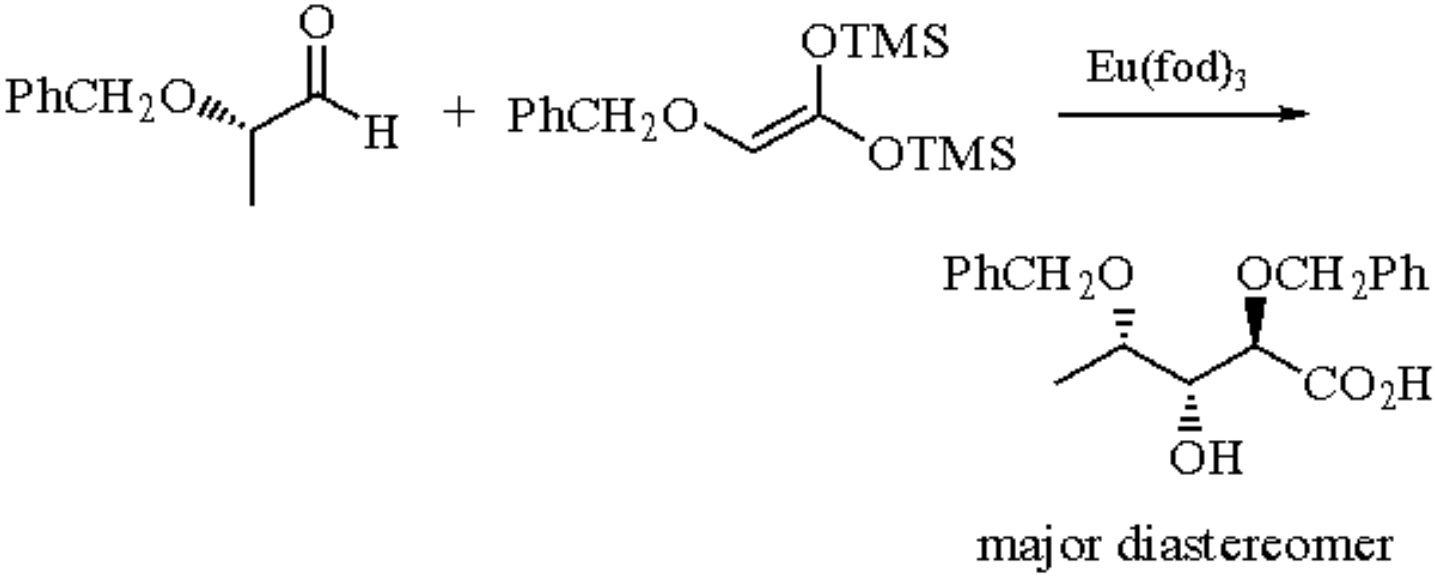

(14)

Shift reagents also catalyze the [2 + 2] cycloaddition of ketenimines with aldehydes to produce 2-iminooxetanes (eq 15).[13] Again, the acid labile product is not stable to other catalysts.

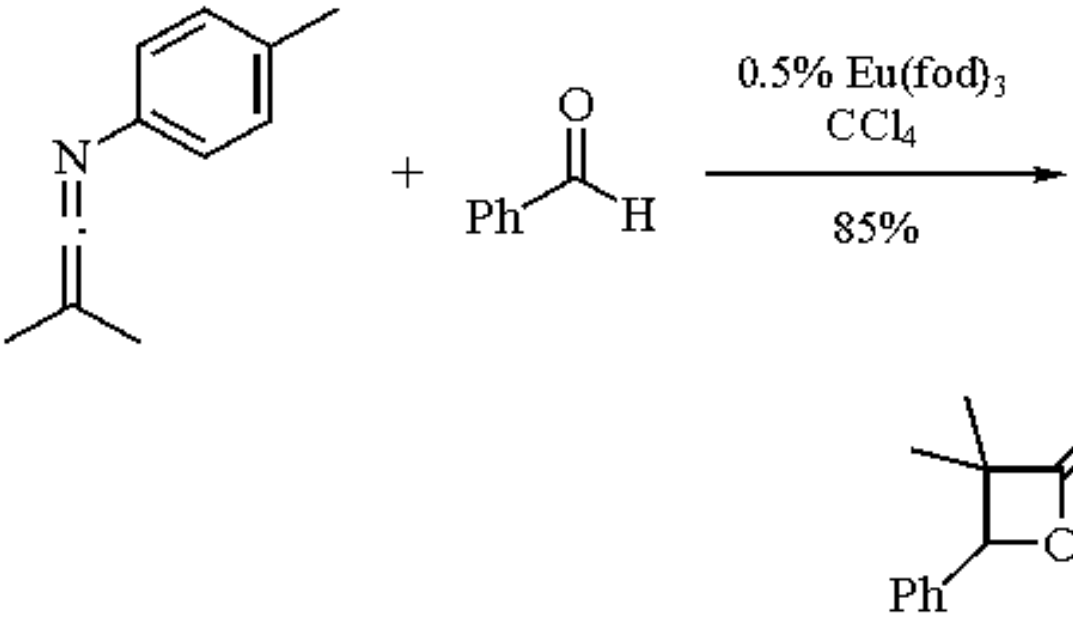

(15)

The ene reaction of aldehydes with alkyl enol ethers is effectively catalyzed by $Yb(fod)_3$ (eq 16).[14]

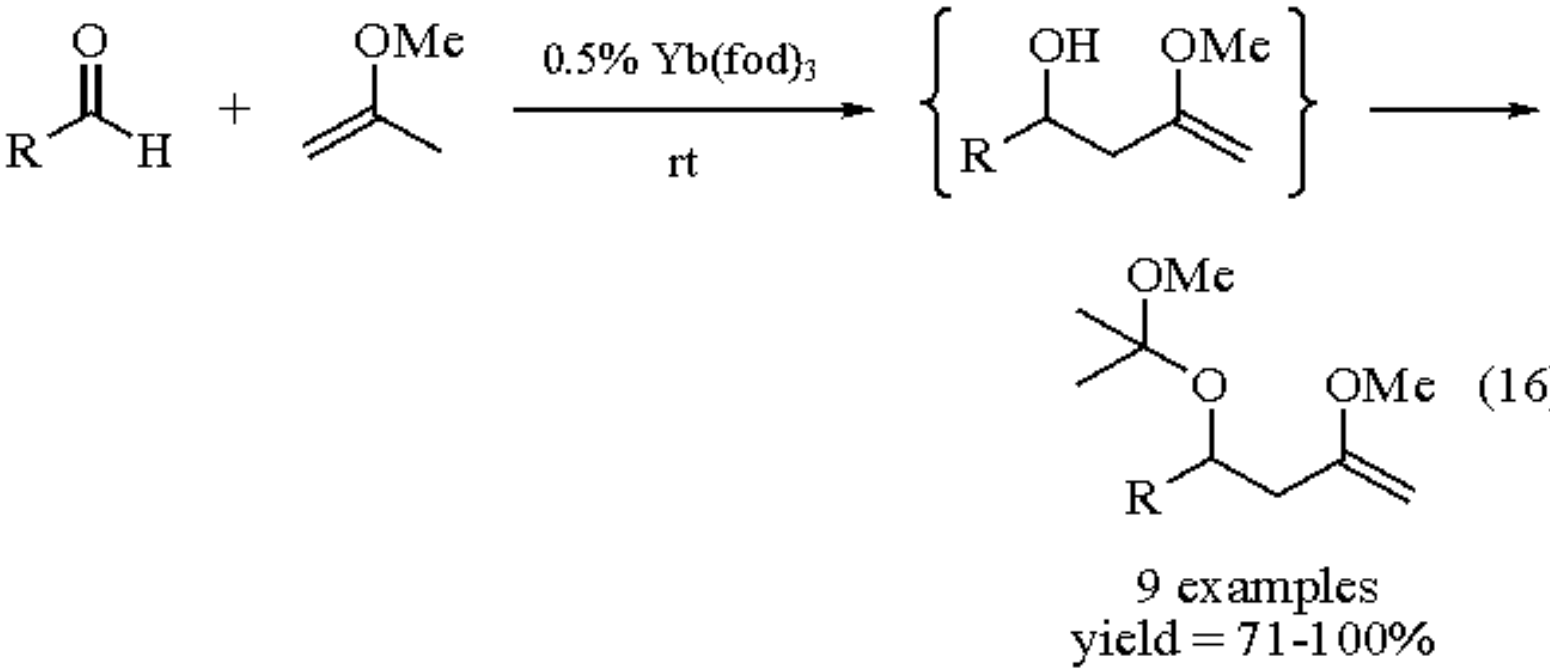

(16)

The optically active camphor derivative $Eu(hfc)_3$ has been used as an enantioselective catalyst. Though the enantioselectivity with this catalyst alone is often modest (eq 17),[8,15] when used in concert with additional chiral auxiliaries, high levels of enantioselectivity have been obtained in the hetero-Diels-Alder cycloaddition reaction (eq 18).[15] The reduction of methyl phenylglyoxylate by the NADH mimic *N*-benzyldihydronicotinamide is catalyzed by lanthanide shift reagents with a modest level of asymmetric induction (eq 19).[16]

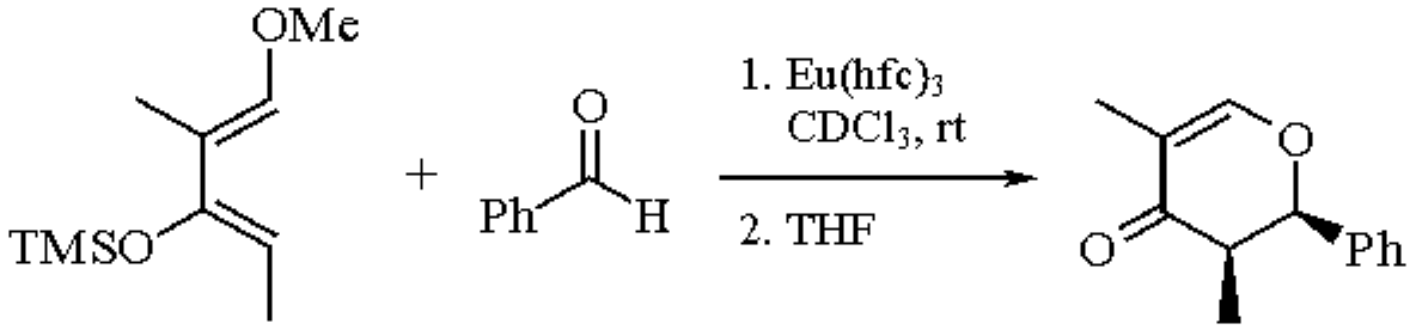

(17)

50% ee

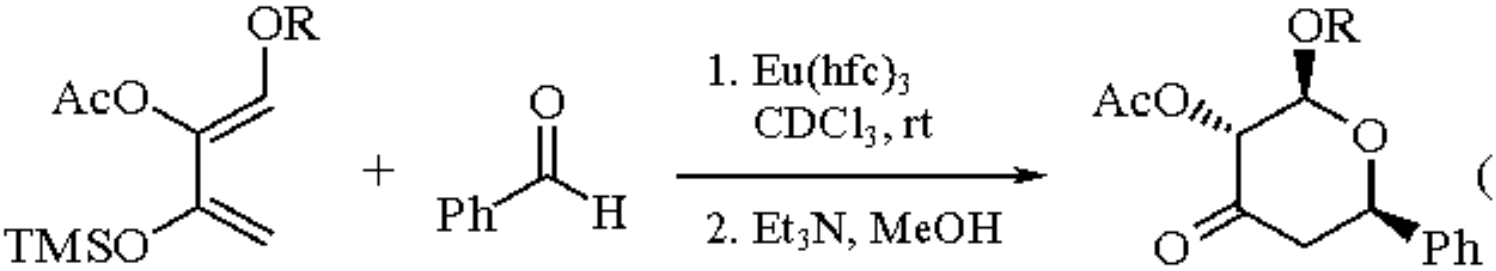

(18)

R = 1-menthyl, 86% de

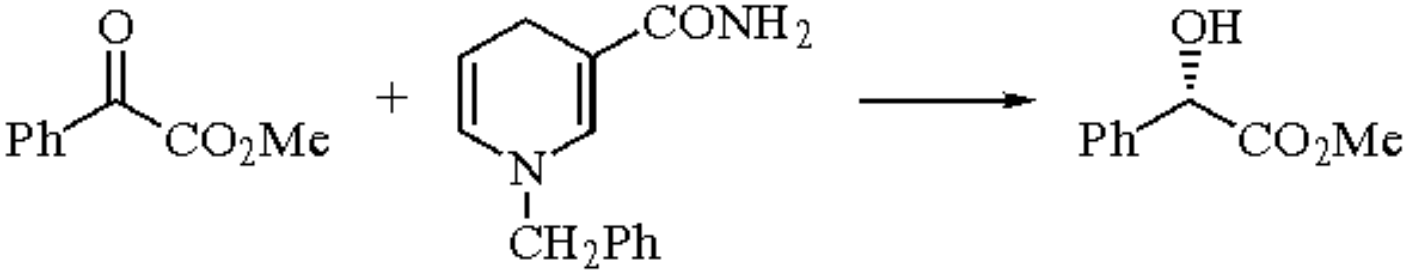

(19)

$Eu(tfc)_3$, CH_2Cl_2, rt	28%, 55% ee
$Eu(tfc)_3$, MeCN, 70 °C	98%, 25% ee

---

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Lanthanum(III) Chloride[1]

$LaCl_3.7H_2O$

(anhydrous)

[10099-58-8] · Cl_3La · Lanthanum(III) Chloride · (MW 245.26) (heptahydrate)

[17272-45-6] · $Cl_3H_{14}LaO_7$ · Lanthanum(III) Chloride · (MW 371.40)

(mild Lewis acid for acetalization;[2] selective reducing agent in association with $NaBH_4$[3] or $LiAlH_4$;[4] preparation of organolanthanum reagents;[5] catalyst for various acid mediated reactions[6-8])

Physical Data: triclinic crystals; mp (hydrate) 91 °C (dec); mp (anhyd) 852 °C; bp 1750 °C; density (anhyd) 3.8 g cm^{-3}.

Solubility: 3.89 g L^{-1} in H_2O; sol methanol, ethanol; anhydrous form sol pyridine.

Form Supplied in: white crystals, deliquescent.

Preparative Methods: anhydrous lanthanum chloride is obtained from the hydrate by refluxing in thionyl chloride, or by heating to 400 °C in a HCl stream (see also ***Cerium(III) Chloride***). The reagent can also be prepared by treatment of a lanthanum benzoate suspension with dry ethereal HCl solution.[9]

Handling, Storage, and Precautions: anhydrous $LaCl_3$ should be freshly prepared and used without delay. Oral toxicity: LD_{50} 4.2 g kg^{-1} in rats.

Acetalization and Thioacetalization.

$LaCl_3$ has been used in the preparation of acetals (eqs 1 and 2), though it is less efficient than ***Erbium(III) Chloride*** or ytterbium(III) chloride.[2,10]

$$C_5H_{11}CHO \xrightarrow[\text{90\%}]{\substack{LaCl_3 \cdot 7H_2O \\ HC(OMe)_3 \\ \text{rt, 10 min}}} C_5H_{11}CH(OMe)_2 \qquad (1)$$

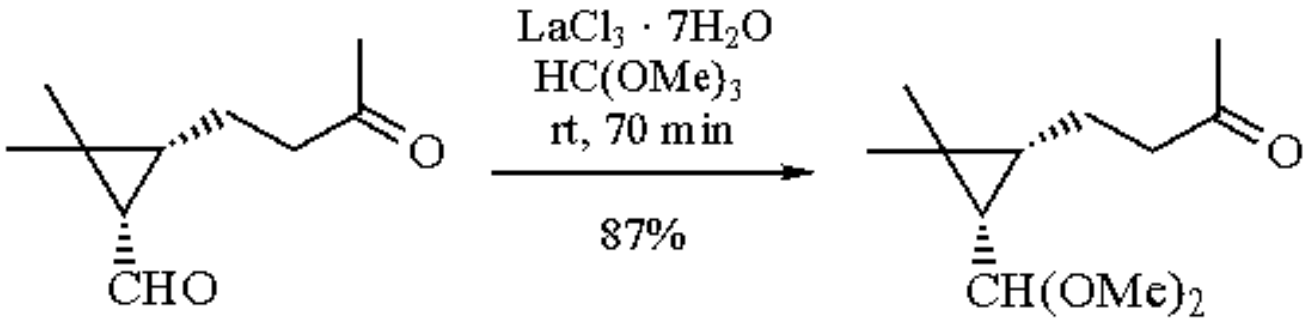

(2)

The anhydrous form of $LaCl_3$ permits the convenient production of thioacetals (eqs 3 and 4).[11] Hindered (camphor) and aromatic (benzophenone) ketones react in low yield. Lanthanum trichloride is much less efficient than ***Samarium(III) Chloride*** for acetal cleavage.[12]

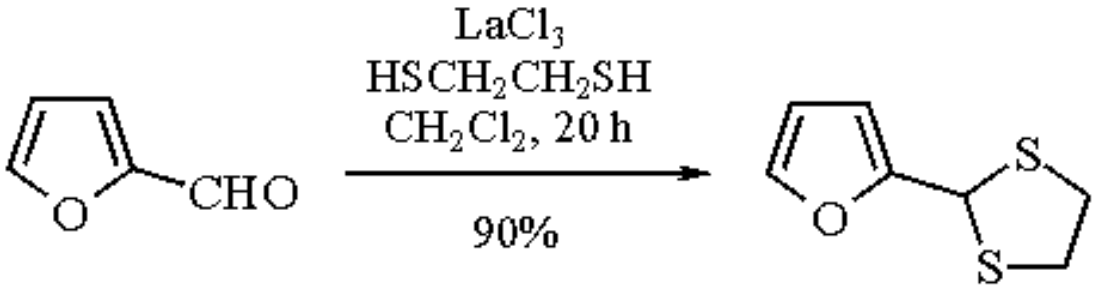

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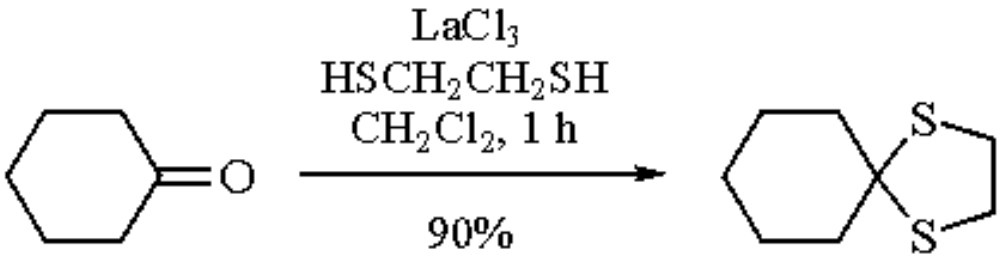

(4)

Regioselective Reduction of α,β-Unsaturated Carbonyl Compounds.

In the presence of ***Sodium Borohydride***, α,β-unsaturated ketones are reduced to allylic alcohols in high yield (eq 5).[3] In THF, ***Lithium Aluminum Hydride*** shows the same selectivity with both ketones and aldehydes (eq 6).[4]

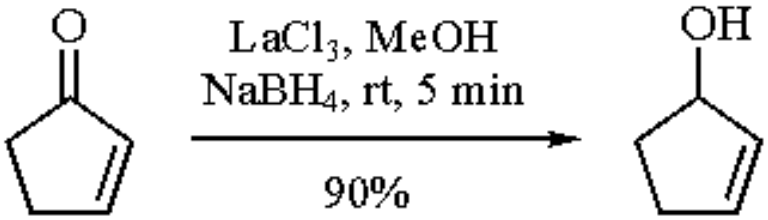

(5)

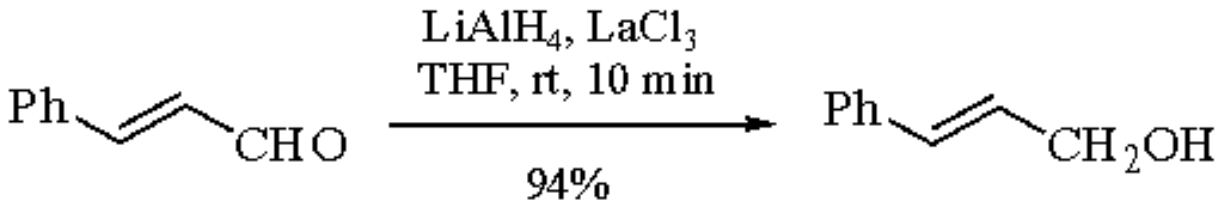

(6)

Organolanthanum Reagents.

Upon treatment with 1 equiv of ***n-Butyllithium***, anhydrous $LaCl_3$ yields a reagent of reduced basicity and good nucleophilicity, similar to the analogous cerium reagent (eq 7).[5] With ***Methyllithium***, the reagent exhibits a good selectivity for additions to aldehydes in the presence of a ketone (eq 8). Lanthanum gives the highest selectivity of all the lanthanides tested.[13]

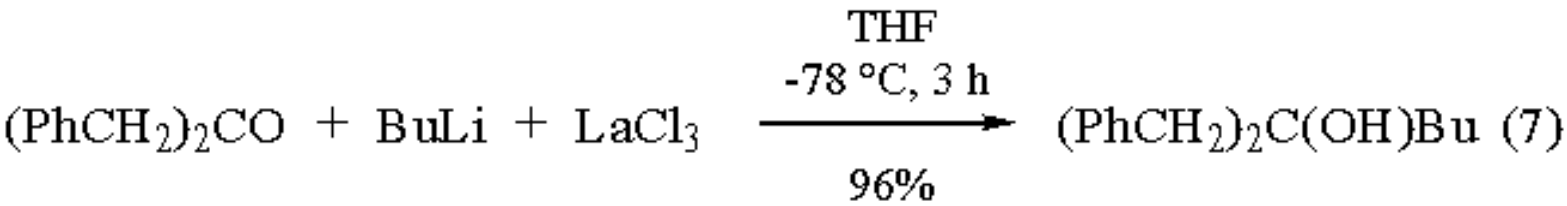

(7)

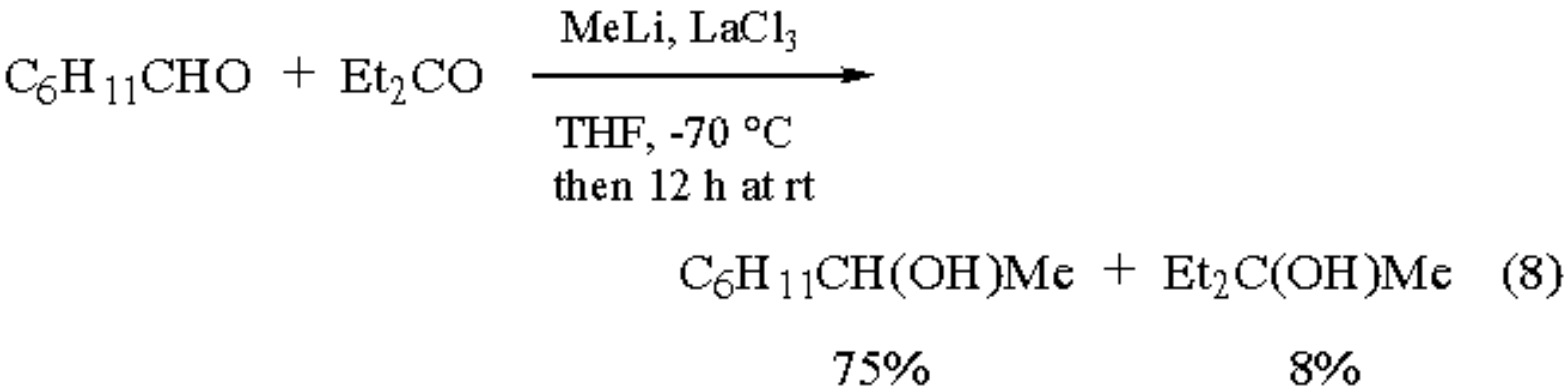

(8)

Catalytic Properties in Various Reactions.

The Diels-Alder cycloaddition of acrolein with *n*-butyl vinyl ether is catalyzed by lanthanum chloride.[6] Cross-aldol reactions can be effected with ketene trimethylsilyl acetals and aldehydes. For instance, the trimethylsilyl ether of methyl 2-methylpropionate couples with benzaldehyde in the presence of catalytic amounts of $LaCl_3$; a mixture of the protected and unprotected hydroxy esters is obtained (eq 9).[7]

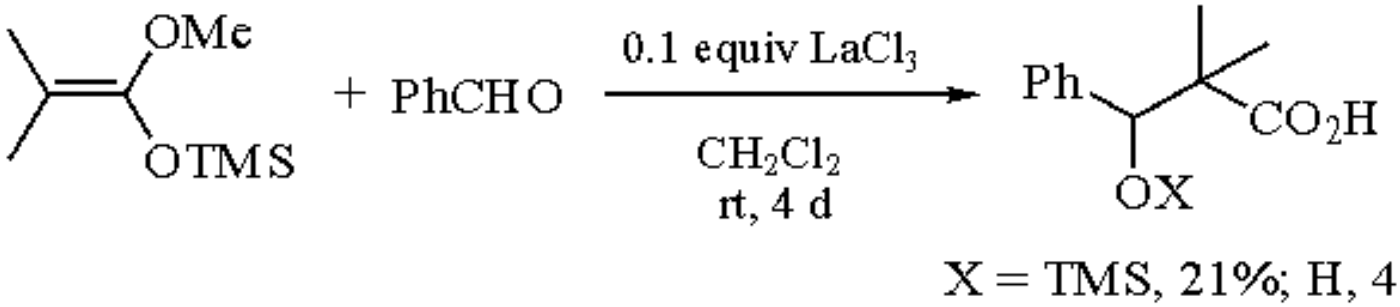

(9)

A mixture of $LaCl_3$ and ***Tin(II) Chloride*** condenses α-bromo ketones with aldehydes to form aldol products (eq 10). Although cerium chloride is preferred for most cases, lanthanum chloride offers a combination of the highest yield and satisfactory selectivity.[8] With α,α´-dibromo ketones, the same reagent mixture leads to oxyallyl cations which add to furan under mild conditions (see ***Cerium(III) Chloride***).[14]

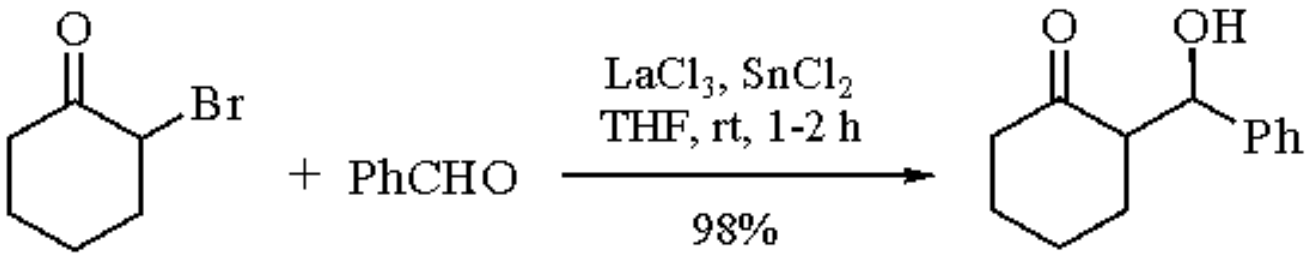

(10)

threo:*erythro* = 83:17

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Lanthanum(III) Triflate[1]

$La(CF_3SO_3)_3$

[52093-26-2] · $C_3F_9LaO_9S_3$ · Lanthanum(III) Triflate · (MW 586.10)

(Lewis acid catalyst useful for aldol, Michael, Diels-Alder, and other C-C bond forming reactions; also useful for preparing organolanthanum reagents, which react with hindered tertiary amides to afford ketones)

Alternate Name: lanthanum trifluoromethanesulfonate.

Physical Data: mp >360 °C.

Solubility: sol H_2O; partially sol THF, CH_2Cl_2; sparingly sol Et_2O; insol hexane.

Preparative Methods: to an aqueous solution of triflic acid (50% v/v), a slight excess of lanthanum oxide (La_2O_3) is added; the resulting mixture is stirred for 15 min at rt and then filtered to remove the unreacted oxide; the filtrate is concentrated in vacuo at about 60 °C; residual water is removed by azeotropic distillation with toluene in vacuo to dryness; the resulting hydrate is placed in a flask equipped with a stirring bar, a stopcock filled with a glass wool plug, and a NaOH trap, and is then dehydrated by heating under vacuum (140 °C/0.1 mmHg or 180 °C/1.0 mmHg) for 16 h. The anhydrous $La(OTf)_3$ is a white to gray-white solid.[2-4]

Handling, Storage, and Precautions: anhydrous $La(OTf)_3$ is hygroscopic and should be stored and weighed in a glove-box. Use in a fume hood.

Preparation of Organolanthanum Reagents.[1,4]

Organolanthanum triflates $RLa(OTf)_2$ (R = alkyl, aryl), readily available by reaction of organolithium compounds with equimolar anhydrous $La(OTf)_3$ in ethereal solvents, are very effective nucleophiles in reactions with carbonyl derivatives but exhibit relatively low basicity. Generally these reagents behave in a parallel manner to their organocerium chloride counterparts,[5] but are soluble in ethereal solvents and thus are more reactive. In particular, the addition reaction of $RLa(OTf)_2$ to the highly enolizable compound 1,3-diphenylacetone is complete within a few minutes at -78 °C, affording the carbinol product in essentially quantitative yield (eq 1). The analogous reaction utilizing $RCeCl_2$ requires a higher reaction temperature (0 °C) and a longer reaction time (1.5 h).[5] One application of $MeLa(OTf)_2$ in organic synthesis is depicted in eq 2 in which efficient 1,2-addition is achieved.[6] In this case, the use

of MeLi or MeMgBr reagents gives a mixture of the starting material and mono- and di-1,2- and 1,4-addition products.

$$\mathrm{MeLi} + \mathrm{La(OTf)_3} \xrightarrow[\text{-78 to 0 °C}]{\text{THF}} \mathrm{MeLa(OTf)_2} \xrightarrow[\text{-78 °C, 30 min}]{(\mathrm{PhCH_2})_2\mathrm{CO}} (\mathrm{PhCH_2})_2\mathrm{C(OH)Me} \quad (1)$$

98%

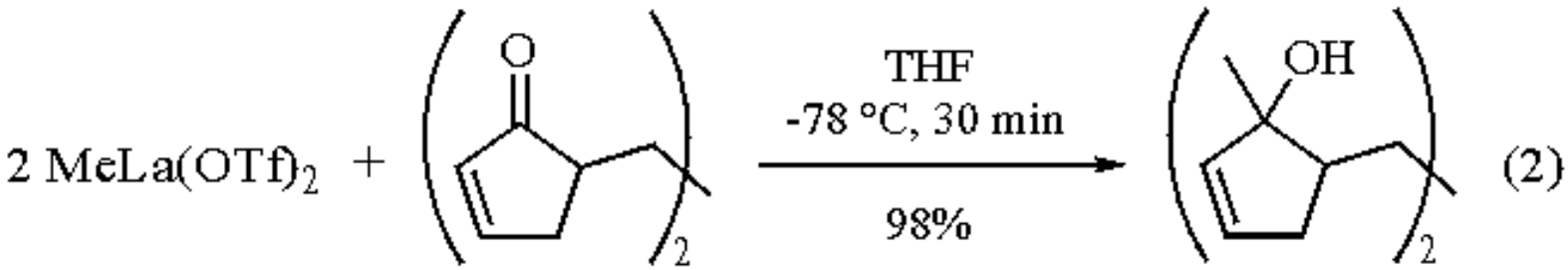

A unique characteristic of organolanthanum triflate reagents is that they smoothly react with sterically hindered aliphatic, aromatic, and heterocyclic tertiary amides to provide the corresponding ketones in excellent yields (eq 3); unsatisfactory results are obtained when employing organocerium or conventional RLi or RMgX reagents.[4] If amides possess additional donor functionality (i.e. MeO), an excess of the $RLa(OTf)_2$ reagent is needed to ensure complete conversion. Even so, further addition to the ketone product is not usually observed due to the formation of stable tetrahedral adducts prior to aqueous workup.

$$\mathrm{MeLa(OTf)_2} + \mathrm{PhCONEt_2} \xrightarrow[\text{95\%}]{\text{THF, -78 °C, 30 min}} \mathrm{PhCOMe} \quad (3)$$

Lewis Acid Catalyst for Aldol, Michael, and Diels-Alder Reactions.

$La(OTf)_3$ has been used as a Lewis acid catalyst to promote aldol condensations between silyl enol ethers and formaldehyde under aqueous conditions (eq 4).[7] $La(OTf)_3$ can catalyze the Michael addition of silyl enol ethers to α,β-unsaturated ketones at rt in CH_2Cl_2 to afford the expected products in high yields (eq 5). In some of the cases studied, as little as 1 mol % of $La(OTf)_3$ is sufficient, and other lanthanide triflates are also effective. Enol silanes derived from ketones, thioesters, and esters are suitable, and no 1,2-addition products are obtained.[8] $La(OTf)_3$ is also an effective catalyst for the Diels-Alder cycloaddition of carbonyl-containing dienophiles with cyclopentadiene.[8] For all three catalytic processes mentioned here, $La(OTf)_3$ can be almost quantitatively recovered upon aqueous workup and can be reused.[7,8]

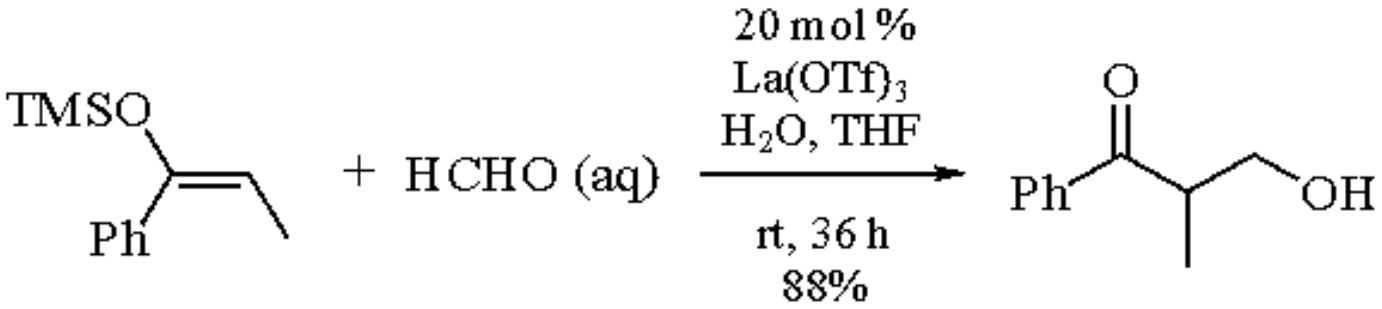

(4)

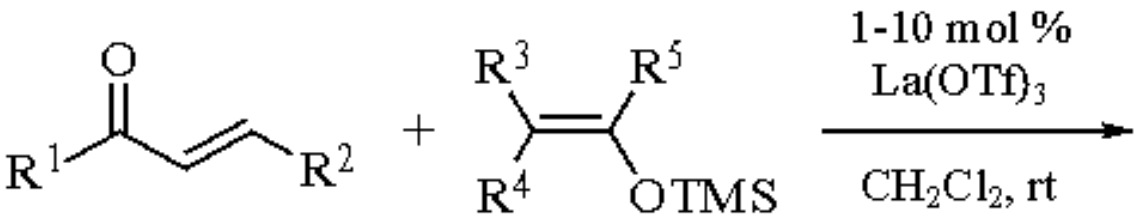

R^3, R^4 = Me or H
R^5 = OR, SR, R

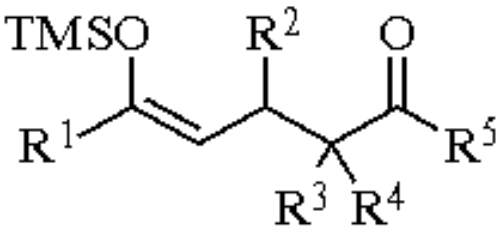

(5)

Synthesis of Amidines.

In the presence of 1 mol % of $La(OTf)_3$, reaction of primary amines (2 equiv) with nitriles results in the formation of *N,N´*-disubstituted amidines in good yields (eq 6);[3] when primary diamines (1 equiv) are employed, cyclic amidines are obtained in good to excellent yields (eq 7).[3]

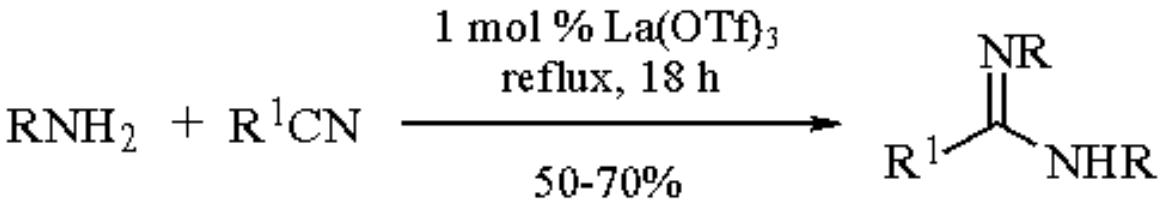

(6)

R = primary, secondary, Ar; R^1 = Me

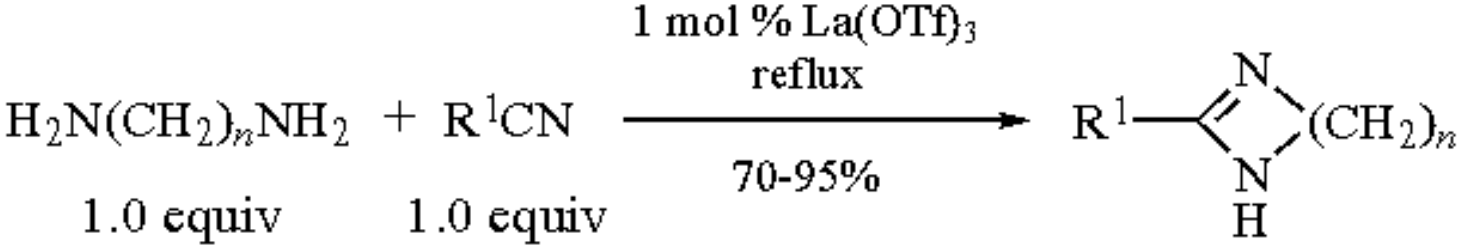

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Lead(II) Acetate

$Pb(OAc)_2.3H_2O$

[301-04-2] · $C_4H_{12}O_7Pb$ · Lead(II) Acetate · (MW 379.33)

(desulfurization reagent[2,3])

Physical Data: mp 75 °C when rapidly heated; above 100 °C it begins to lose acetic acid and decomposes completely above 200 °C; *d* 2.55 g cm^{-3}.

Solubility: 0.456 g mL^{-1} in H_2O at 15 °C; 2.0 g mL^{-1} in H_2O at 100 °C; 0.033 g mL^{-1} in ethanol; slightly sol diethyl ether; freely sol glycerol.

Form Supplied in: colorless crystals or white granules or powder; slowly effloresces; widely available; may contain insoluble lead carbonate resulting from exposure to air. *Drying:* dry at rt because of facile dehydration. Drying over H_2SO_4 at rt leads to formation of the anhydride.

Purification: recrystallize from water containing 2-3% acetic acid.

Handling, Storage, and Precautions: poisonous; carcinogen; LD_{50} 200 mg kg^{-1} (intraperitoneal in rats); avoid breathing dust and handle only in a fume hood. Keep tightly closed for storage; readily converts to complex salts. Incompatible with acids, alkalies, sulfates, sulfites, citrates, tartrates, chlorides, carbonates, tannin, phosphates, resorcinol, salicylic acid, and phenol.

Neutralization of HCl.[1]

In the synthesis of α-aminodiethylacetic acid via acid hydrolysis of the cyanohydrin of diethyl ketone, the crude amino acid hydrochloride is neutralized by lead hydroxide (prepared by hydrolysis of this reagent with sodium hydroxide) to yield the amino acid in liberated form (eq 1). This procedure appears to be superior to that using ***Lead(IV) Oxide*** for this neutralization.

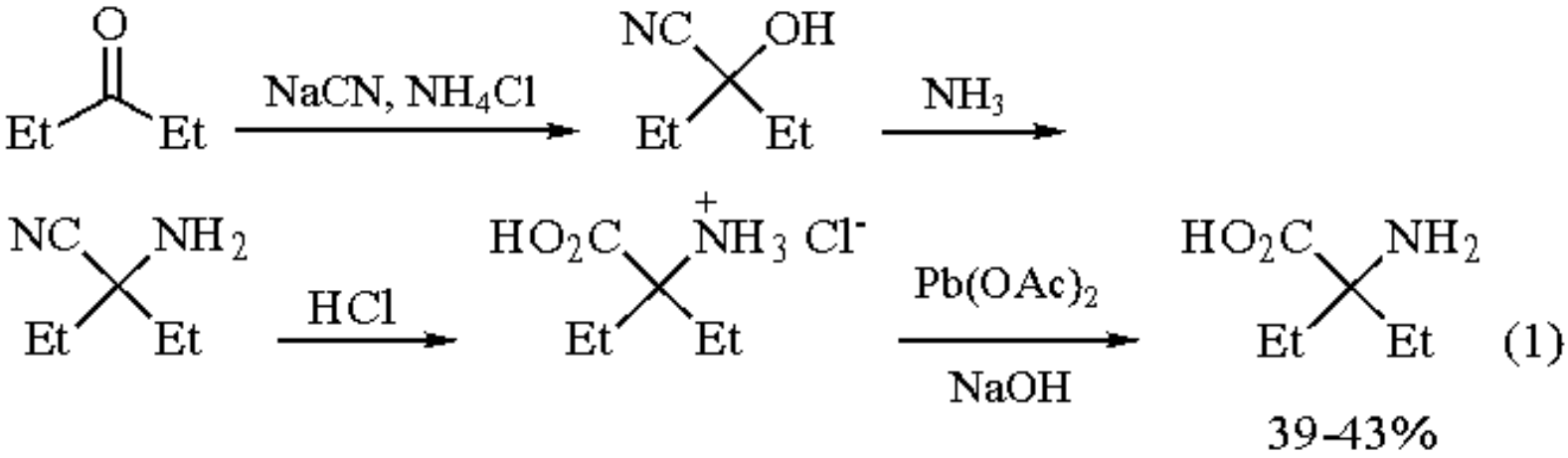

Removal of Selenium and Selenious Acid.[2]

Selenium(IV) Oxide and selenious acid are good reagents for the oxidation of the α-methylene carbon of carbonyl compounds to give 1,2-dicarbonyl compounds. However, it is difficult to remove the resulting colloidal selenium and excess of the oxidant from the desired product in this method. A procedure for the oxidation of paraldehyde to glyoxal and the isolation of the product as the bis-bisulfite addition compound specifies the use of lead(II) acetate. Thus the addition of aqueous solution of this reagent to the reaction mixture gives insoluble lead selenite as a precipitate which is removed readily by filtration.

Conversion of Isocyanides into Isothiocyanates.[3]

Reactions of isocyanides with dibenzoyl disulfide occur smoothly in the presence of this reagent to give isothiocyanates in high yield (eq 2). The activity of this reagent is almost identical with that of ***Thallium(I) Acetate***. In this reaction, a complex of the reagent with dibenzoyl disulfide is believed to be the key intermediate in the sulfurization of the isocyanide (eq 3).

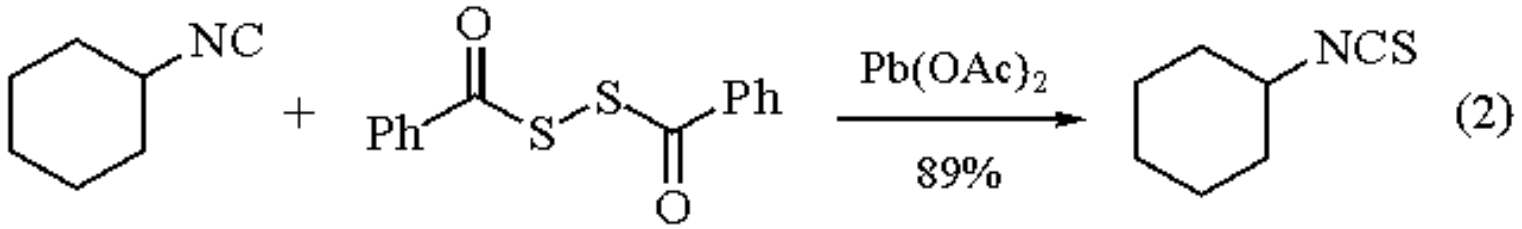

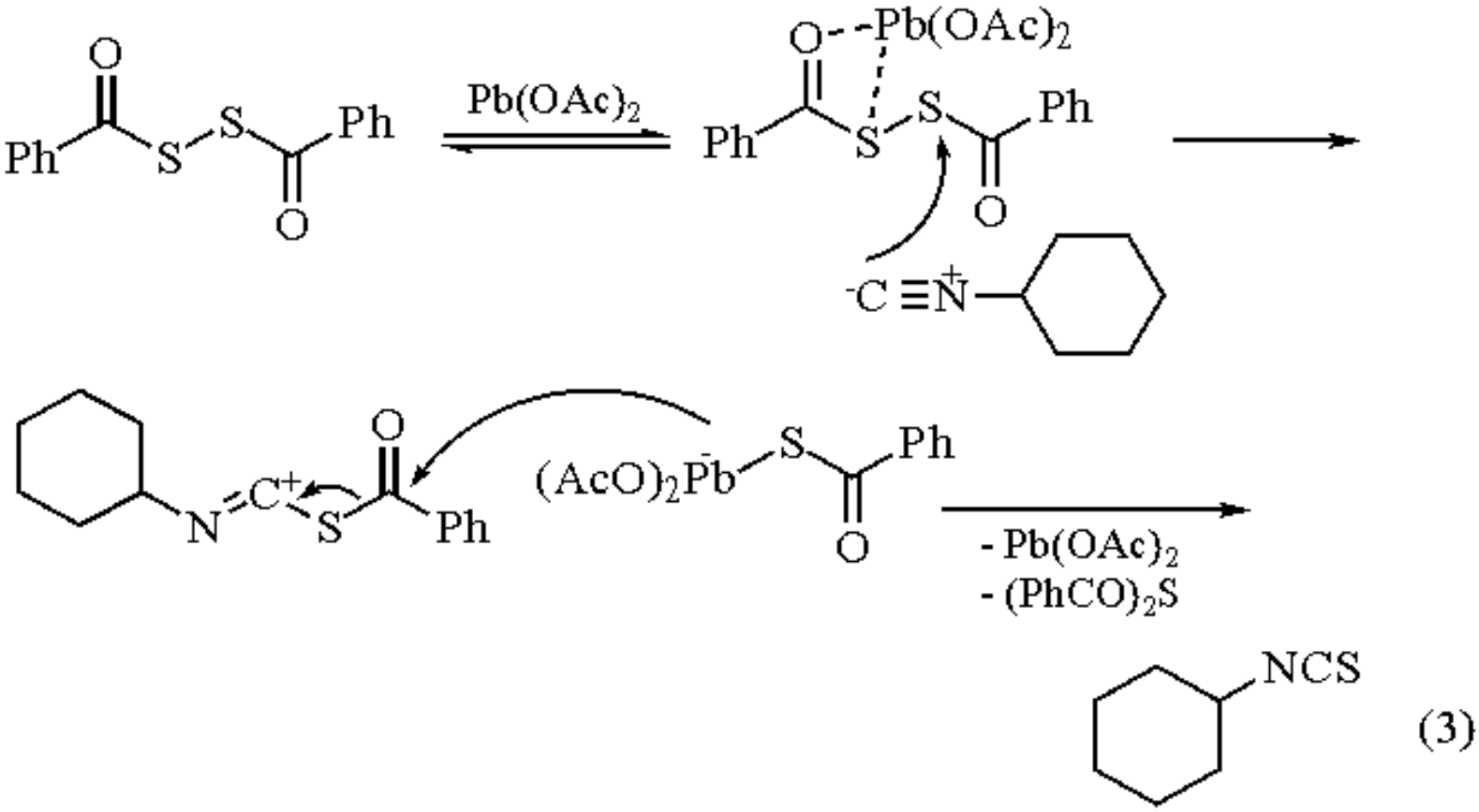

Elimination of H_2S.[4]

This reagent is used for the conversion of thioureas to cyanamides by elimination of H_2S under mild conditions, as illustrated in eq 4.

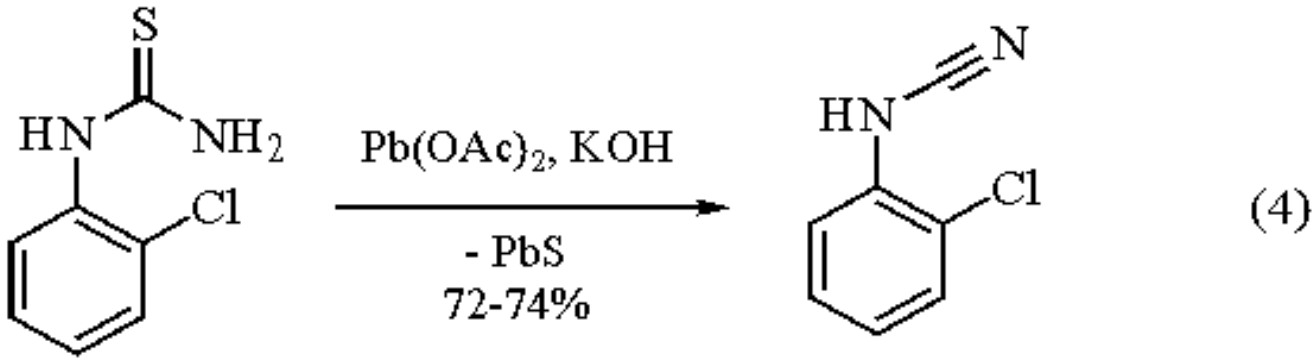

Acetoxylation of Allylic Bromide.[5]

This reagent is used for the preferential replacement of a bromine atom by an acetoxy group in 1-chloro-3-bromocycloalkenes (eq 5). Lead(II) acetate is superior to ***Silver(I) Acetate*** for this transformation.

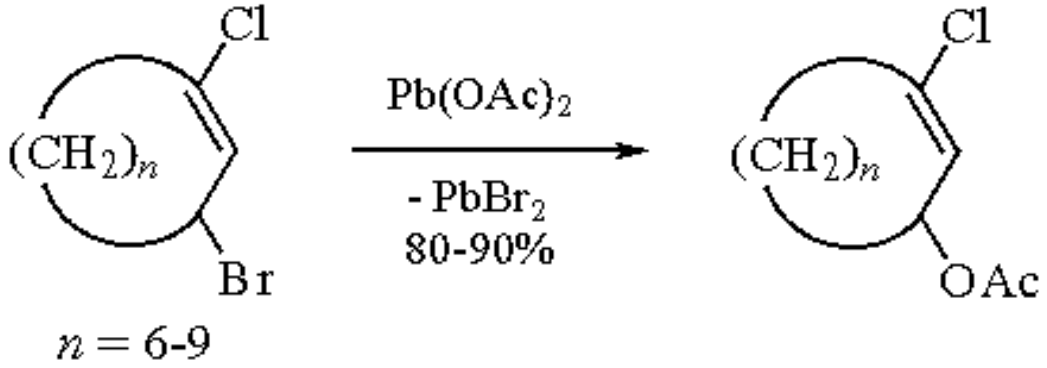

(5)

Preparation of Cyclic Disulfides.[6]

Reactions of dithiols with an aqueous solution of this reagent give lead dithiolates in nearly quantitative yield. The dithiolates react with sulfur in benzene at rt to give the cyclic disulfides in high yields without the formation of polymeric disulfides (eq 6).

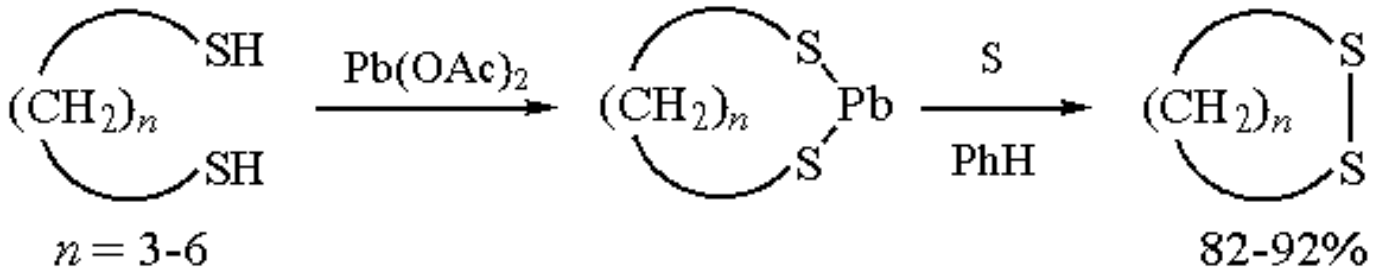

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Lead(IV) Oxide

PbO_2

[1309-60-0] · O_2Pb · Lead(IV) Oxide · (MW 239.19)

(oxidation of phenols[1] and hydroquinones[2] to quinones; oxidation of methyl groups in methylated phenols to carboxyl groups;[3] oxidative cyclization[4] and oxidative decarboxylation;[5] formation of hydrazyl radical[6])

Alternate Name: lead dioxide.

Physical Data: evolves oxygen when heated, first forming Pb_3O_4, and then PbO at high temperatures; *d* 9.38 g cm^{-3}.

Solubility: insol water; sol HCl with evolution of Cl_2; sol dil HNO_3 in the presence of H_2O_2; sol oxalic acid; sol alkaline iodide solutions with liberation of iodine; sol hot caustic alkaline solutions.

Form Supplied in: black powder; widely available.

Purification: commercial PbO_2 is not always satisfactory; it is necessary to prepare the fresh active reagent by one of the methods described by Kuhn[7] and Wilmarth.[8]

Handling, Storage, and Precautions: harmful by inhalation, in contact with skin, and if swallowed; irritating to eyes and respiratory system; danger of cumulative effects; reproductive hazard; contact with combustible material may cause fire; should be handled in a fume hood.

Historically, PbO_2 was used to effect a variety of oxidative transformations. However, because of its general toxicity and because of the inconvenience and expense of disposing of lead byproducts, PbO_2 has largely been replaced by other oxidizing agents, such as ***Cerium(IV) Ammonium Nitrate***, ***Silver(I) Oxide***, and ***Salcomine***.

Oxidation of Phenols.

This reagent oxidizes phenols to the corresponding *p*-benzoquinones and/or diphenoquinones in polar solvents, e.g. acetic acid or formic acid (eq 1).[1a] The product distribution depends on the mole ratio of phenol/PbO_2 and reaction conditions. A mechanism in which the initial step is the formation of the metal phenoxide has been proposed. In nonpolar solvents the oxidation yields mainly polymeric ethers.[1b]

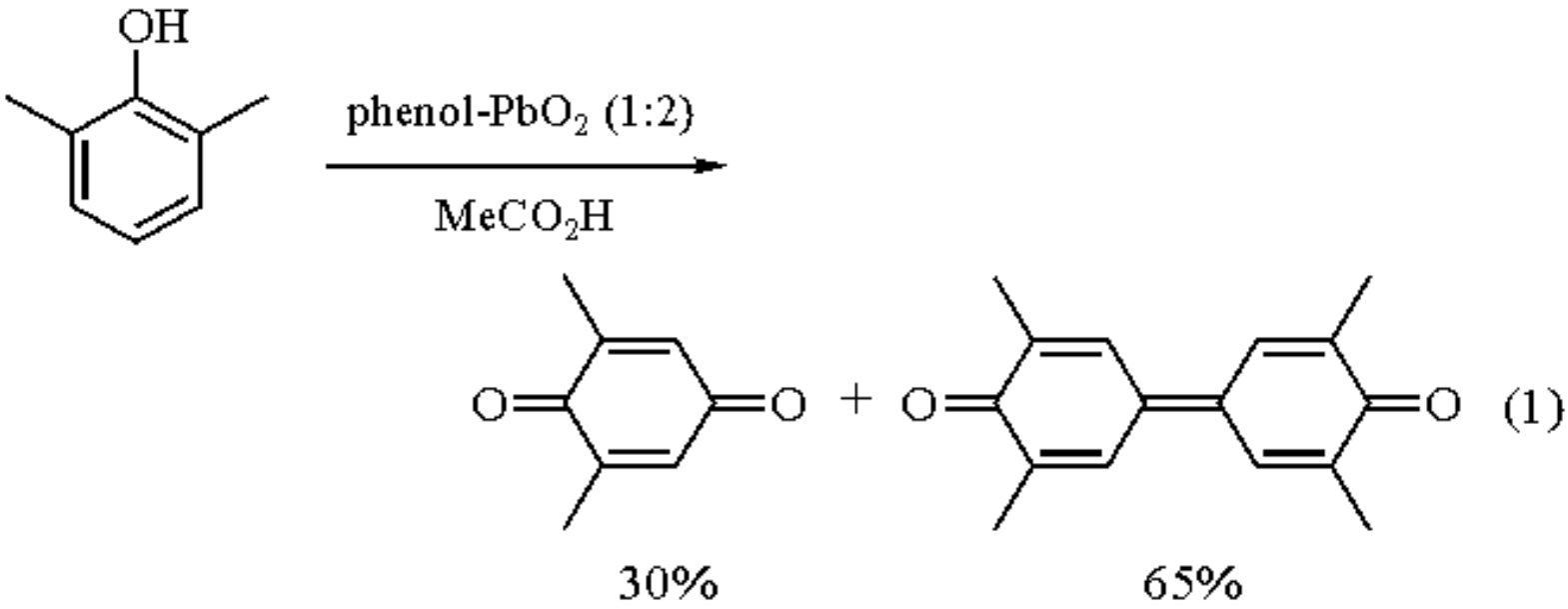

Oxidation of Hydroquinones to Quinones.

PbO_2 can oxidize catechol and its derivatives to the corresponding quinones. In nucleophilic solvents, addition and a subsequent oxidation lead to substituted *o*-quinones. For example, when catechol is treated with PbO_2 in methanol which contains sodium methoxide, 4,5-dimethoxy-*o*-benzoquinone is obtained (eq 2).[3]

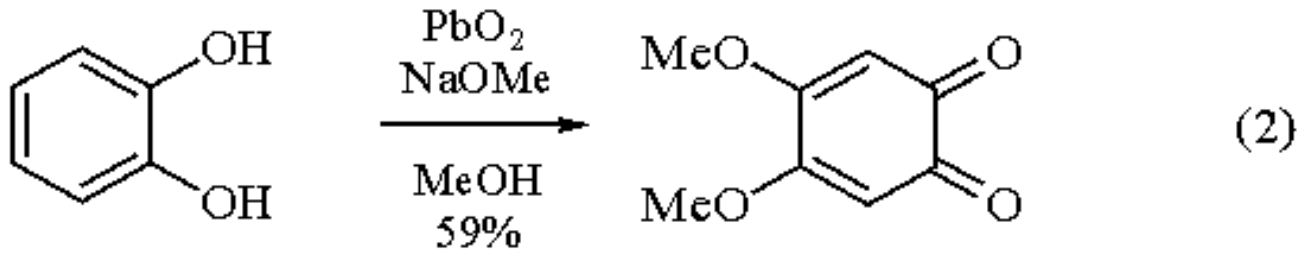

The intermediate *o*-quinone can also be trapped by annulation with *o*-phenylenediamine in acetic acid-benzene to form α-methoxyphenazine after a second oxidation.[9] PbO_2 also oxidizes 2,6-dihydroxynaphthalene to 2,6-naphthoquinone (eq 3),[10] and 2,6-naphthylenedibenzenesulfonamide to 2,6-naphthoquinone dibenzosulfonimide.[11]

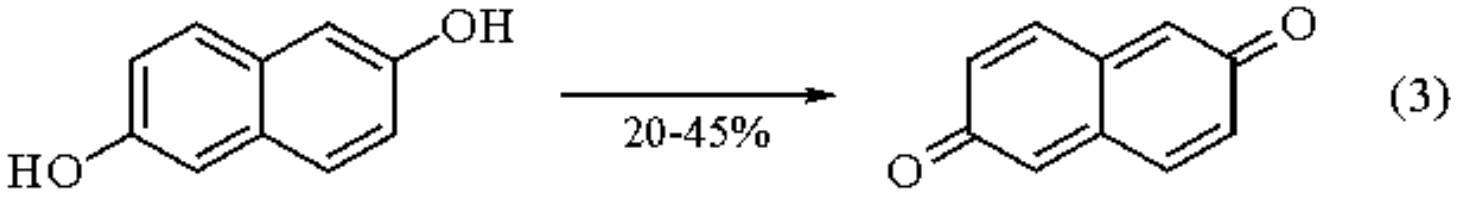

Oxidative Cyclization.

Oxidation of a substituted *p*-hydroxybenzophenone with PbO_2 afforded dehydrogriseofulvin (eq 4), and oxidation of a related *o*-carboxydiphenyl ether gave a spiranic lactone.[4]

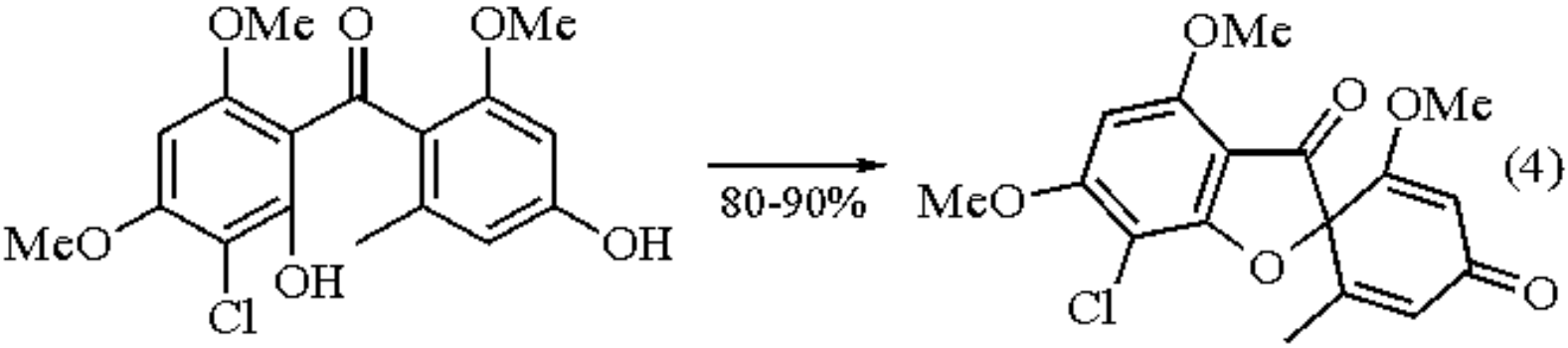

Oxidative Decarboxylation.

PbO_2 oxidizes 1,2-dicarboxylic acids and their anhydrides to the doubly decarboxylated alkenes (eq 5).[5]

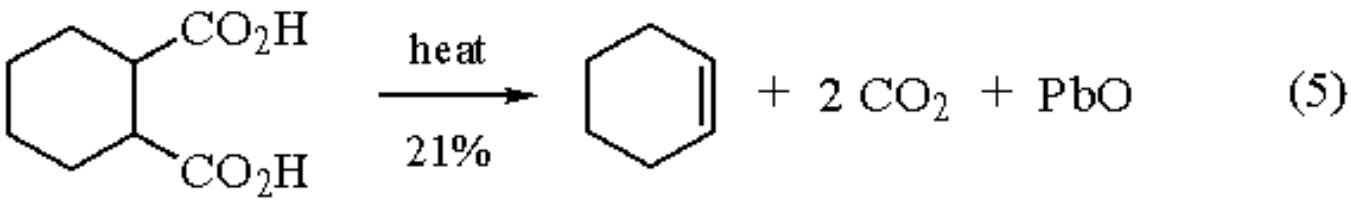

In the presence of PbO_2, nepetonic acid (a β-carboxy ketone) is oxidized with decarboxylation to (-)-3-methylcyclopenten-1-yl methyl ketone (eq 6).[12] *Caution*: The reactants should be well mixed and air should be excluded from the hot residue of the decarboxylation reaction.

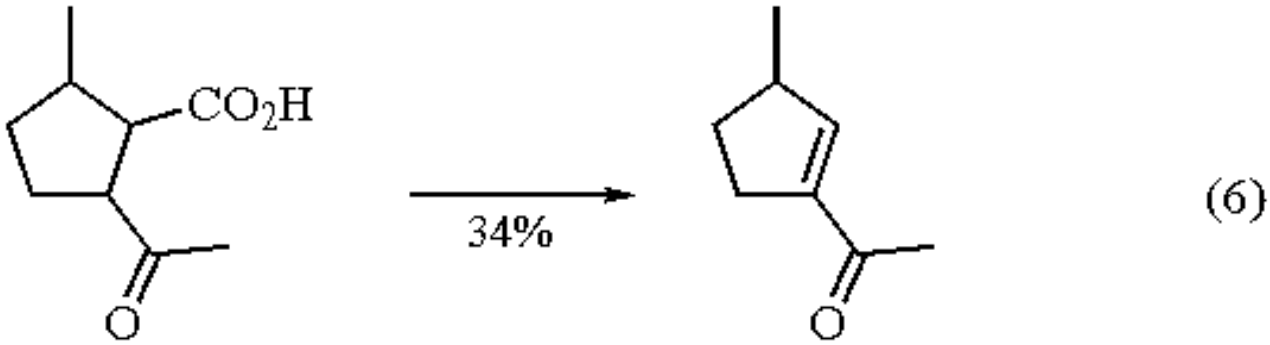

Other Oxidation Reactions.

The methyl groups of methylated phenols can be oxidized to carboxyl groups by PbO_2 (eq 7).[3] The oxidation of 1,1,4,4-tetraphenyl-2,3-dibenzoyltetrazane with PbO_2 affords the hydrazyl radical.[6]

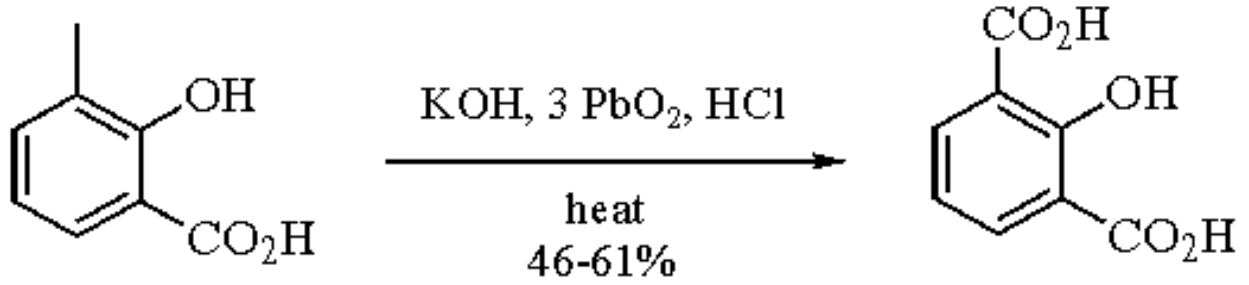

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11. (a) Ziegler, J. B.; Shabica, A. C. *JACS* **1954**, *76*, 594. (b) Adams, R.; Wankel, R. A. *JACS* **1951**, *73*, 2219.
12. McElvain, S. M.; Eisenbraun, E. J. *JACS* **1955**, *77*, 1599.

Kathlyn A. Parker & Dai-Shi Su

Brown University, Providence, RI, USA

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Lead(IV) Acetate[1]

$Pb(OAc)_4$

[546-67-8] · $C_8H_{12}O_8Pb$ · Lead(IV) Acetate · (MW 443.37)

(oxidizing agent for different functional groups;[1] oxidation of unsaturated and aromatic hydrocarbons;[2] oxidation of monohydroxylic alcohols to cyclic ethers;[3] 1,2-glycol cleavage;[4] acetoxylation of ketones;[1] decarboxylation of acids;[5] oxidative transformations of nitrogen-containing compounds[6])

Alternate Name: lead tetraacetate; LTA.

Physical Data: mp 175-180 °C; *d* 2.228 g cm^{-3}.

Solubility: sol hot acetic acid, benzene, cyclohexane, chloroform, carbon tetrachloride, methylene chloride; reacts rapidly with water.

Form Supplied in: colorless crystals (moistened with acetic acid and acetic anhydride); widely available, 95-97%.

Analysis of Reagent Purity: iodometrical titration. *Drying:* in some cases, acetic acid must be completely removed by drying the reagent in a vacuum desiccator over potassium hydroxide and phosphorus pentoxide for several days.

Handling, Storage, and Precautions: the solid reagent is very hygroscopic and must be stored in the absence of moisture. Bottles of lead tetraacetate should be kept tightly sealed and stored under 10 °C in the dark and in the presence of about 5% of glacial acetic acid.

Oxidations of Alkenic and Aromatic Hydrocarbons.

Lead tetraacetate reacts with alkenes in two ways: addition of an oxygen functional group on the double bond and substitution for hydrogen at the allylic position.[2] In addition to these two general reactions, depending on the structure of the alkene, other reactions such as skeletal rearrangement, double bond migration, and C-C bond cleavage can occur, leading to complex mixtures of products, and these reactions therefore have little synthetic value (eq 1).[1a,b,2,7] Styrenes afford 1,1-diacetoxy derivatives when the LTA reaction is performed in acetic acid (eq 2), while in benzene solution products resulting from the addition of both the methyl and an acetoxy group to the alkenic double bond are formed.[7,8] Other nucleophiles, such as azide ion, carbanions, etc. can be introduced onto the alkenic bond in a similar fashion.[9] In the LTA oxidation of cyclic alkenes, depending on ring size, structure, solvent, and reaction conditions,

several types of products are formed. Thus 1,2-diacetates and 3-acetoxycycloalkenes are obtained from cyclohexene (cyclopentanecarbaldehyde is also formed),[10] cycloheptene, and cyclooctene.[11] Norbornene reacts with LTA to give rearrangement products in which 2,7-diacetoxynorbornane predominates (eq 3).[12] Conjugated dienes undergo 1,2- and 1,4-diacetoxylation,[13] while cyclopentadiene in wet acetic acid gives monoacetates of *cis*-cyclopentene-1,2-diol (eq 4).[14]

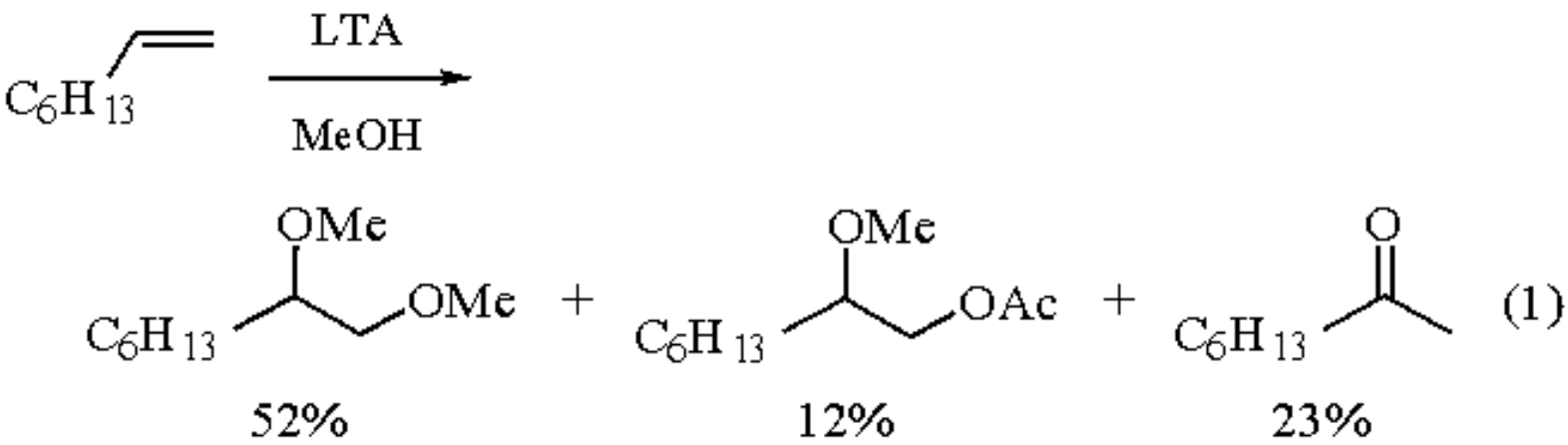

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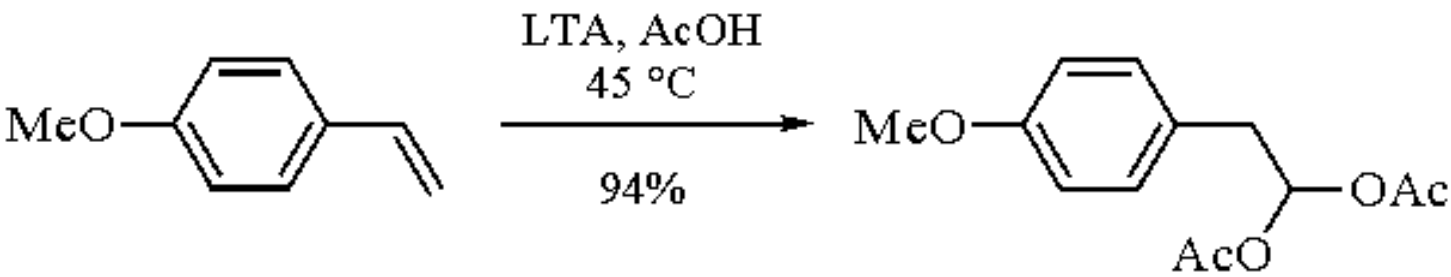

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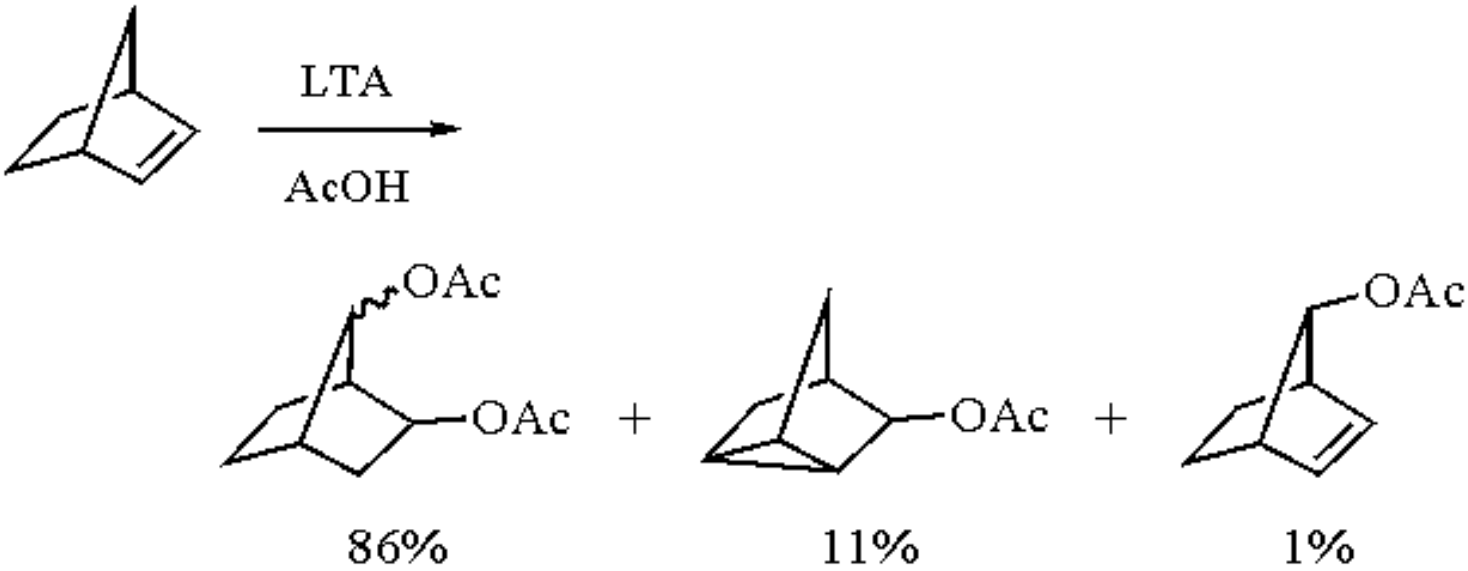

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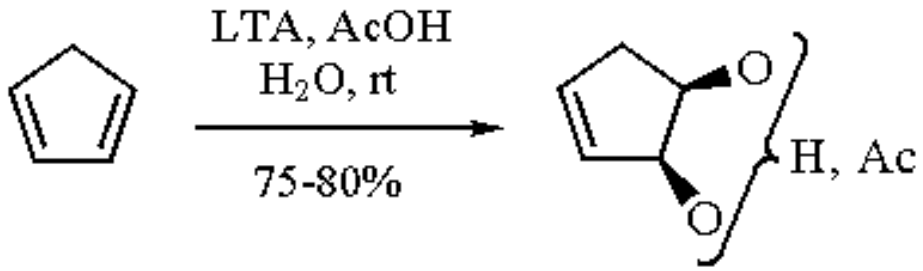

(4)

Aromatic hydrocarbons react with LTA in two ways: on the aromatic ring and at the benzylic position of the side chain. Oxidation of the aromatic ring results in substitution of aromatic hydrogens by acetoxy or methyl groups.[1c] Benzene itself is stable towards LTA at reflux and is frequently used as solvent in LTA reactions. However, mono- and polymethoxybenzene derivatives are oxidized by LTA in acetic acid to give acetoxylation products (eq 5).[15] Oxidation of anthracene in benzene gives 9,10-diacetoxy-9,10-dihydroanthracene, whereas in AcOH a mixture of 10-acetoxy-9-oxo-9,10-dihydroanthracene and anthraquinone is obtained.[16] The LTA oxidation of furan affords 2,5-diacetoxy-2,5-dihydrofuran (eq 6).[17]

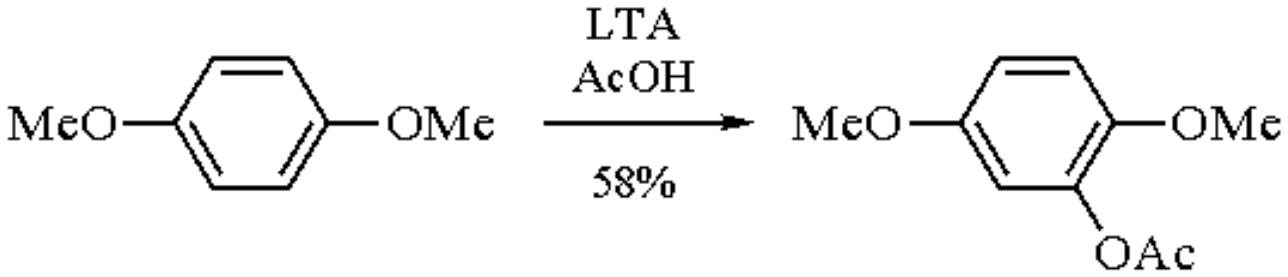

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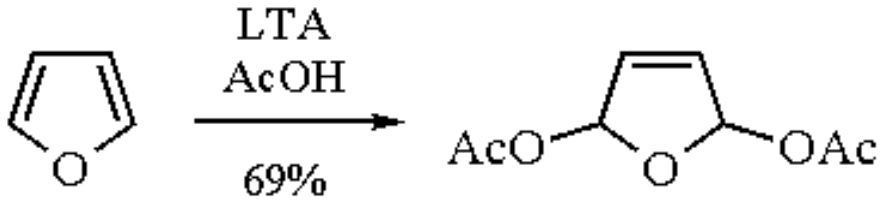

(6)

Aromatic compounds possessing a C-H group at the benzylic position are readily oxidized by LTA to the corresponding benzyl acetates. Benzylic acetoxylation is preferably performed in refluxing acetic acid (eq 7).[18] Acetoxylation at the benzylic position can be accompanied by methylation of the aromatic ring, followed sometimes by acetoxylation of the newly introduced methyl group.[18]

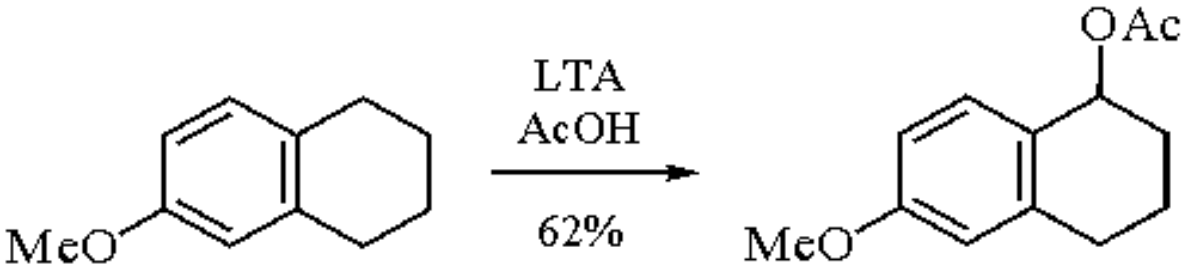

(7)

Oxidative Cyclization of Alcohols to Cyclic Ethers.

The LTA oxidation of saturated alcohols, containing at least four carbon atoms in an alkyl chain or an appropriate carbon skeleton, to five-membered cyclic ethers represents a convenient synthetic method for intramolecular introduction of an ether oxygen function at the nonactivated δ-carbon atom of a methyl, methylene, or methine group (eq 8).[3,19,20] The reactions are carried out in nonpolar solvents, such as benzene, cyclohexane, heptane, and carbon tetrachloride, either at reflux temperature[1a,d,3,20,21] or by UV irradiation at rt.[22]

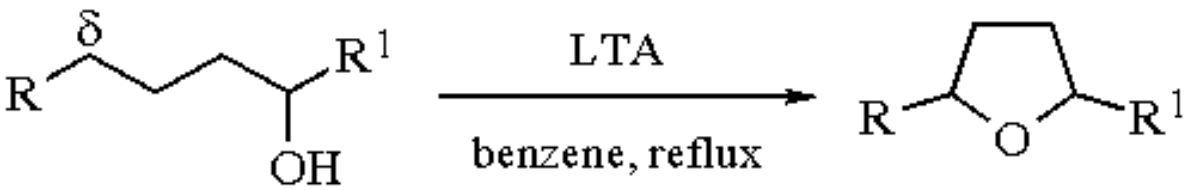

(8)

The conversion of alcohols to cyclic ethers is a complex reaction involving several steps: (i) reversible alkoxylation of LTA by the substrate; (ii) homolytic cleavage of the RO-Pb bond in the resulting alkoxy-lead(IV) acetate with formation of an alkoxy radical; (iii) intramolecular 1,5-hydrogen abstraction in this oxy radical whereby a δ-alkyl radical is generated; (iv) oxidative ring closure to a cyclic ether via the corresponding δ-alkyl cation (eq 9).[3,20] The crucial step is the formation of the δ-alkyl radical by way of 1,5-hydrogen migration. This type of rearrangement is a general reaction of alkoxy radicals, and, independently of the radical precursor, involves a transition state in which the δ-CH group must be conformationally suitably oriented with respect to the attacking oxygen radical.[1,3,23,24] Regioselective hydrogen abstraction proceeds preferentially from the δ-carbon atom, since in that case an energetically favorable quasi-six-membered transition state is involved.[3,23,24]

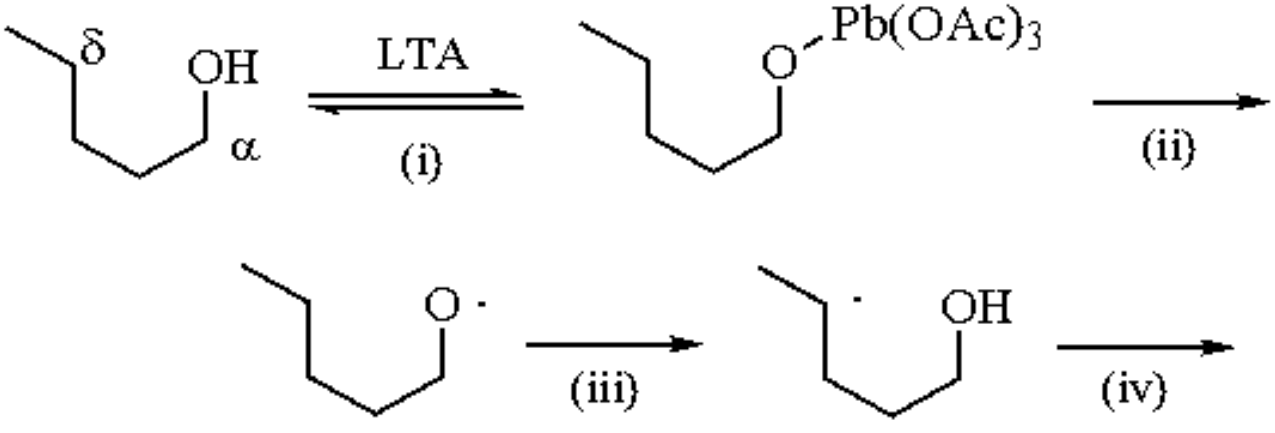

(9)

The LTA oxidation of primary aliphatic alcohols affords 2-alkyltetrahydrofurans in 45-75% yield. A small amount of tetrahydropyran-type ether is also formed (eq 10).[3a,20] The oxidation rate depends on the structural environment of the pro-activated carbon atom, with the rate decreasing in the order: methine > methylene > methyl δ-carbon atom.[3] When the δ-carbon atom is adjacent to an ether oxygen function, the reaction rate and the yield of cyclic ethers increases.[25] An ether oxygen attached to the δ-carbon atom increases considerably the yield of six-membered cyclic ethers (eq 11). An aromatic ring adjacent to a δ-methylene group does not noticeably affect the yield of tetrahydrofuran ethers, but when the phenyl group is attached to an ε-methylene group, the yield of six-membered cyclic ethers are enhanced.[26]

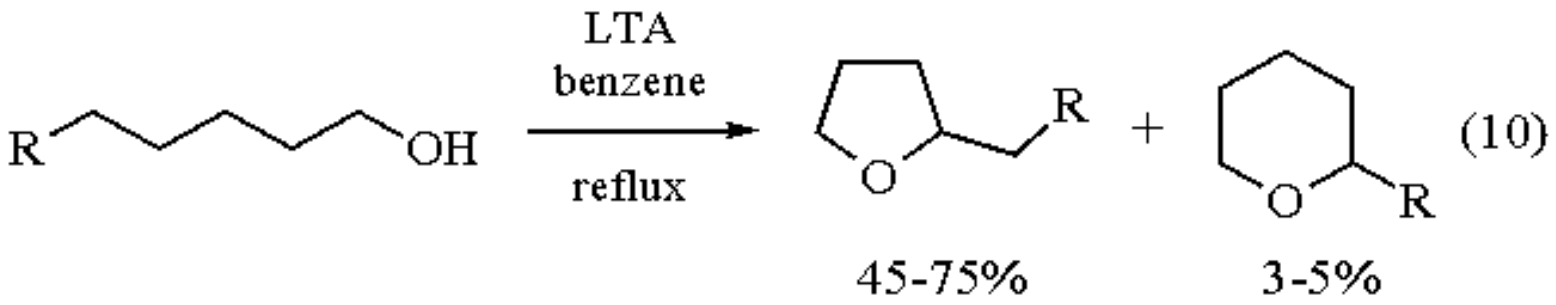

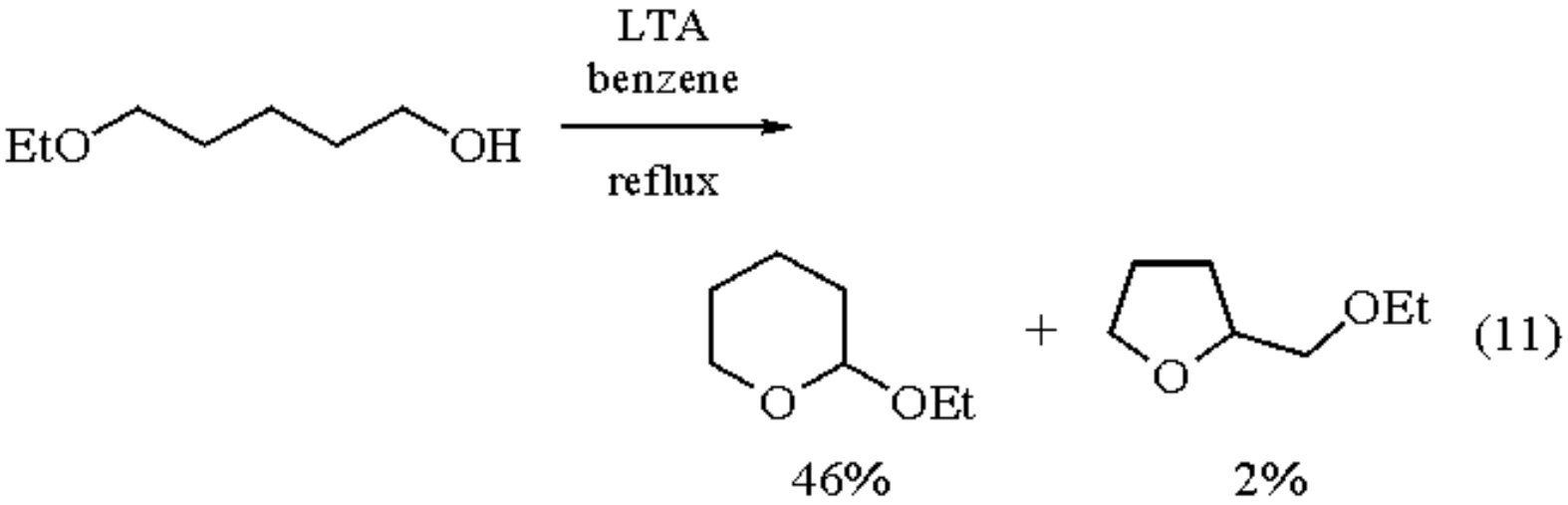

Secondary aliphatic alcohols containing a δ-methylene group afford a *cis*/*trans* mixture of 2,5-dialkyltetrahydrofurans in about 33-70% yield (eq 12).[20,22] The LTA oxidation of secondary alcohols is much slower than that of primary alcohols and isomeric six-membered cyclic ethers are not formed.[20,21] Tertiary aliphatic alcohols, because of unfavorable steric and electronic factors, are less suitable for the preparation of tetrahydrofurans by LTA oxidation.[22,27]

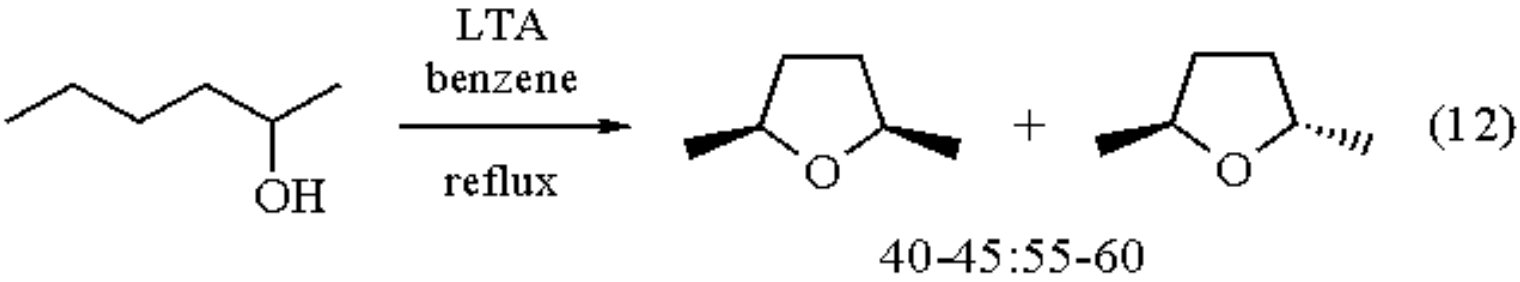

In the cycloalkanol series, the ease of intramolecular formation of cyclic ether products strongly depends on ring size. Cyclohexanol, upon treatment with LTA, affords only 1% of 1,4-cyclic ether, whereas cycloalkanols with a larger ring, such as cycloheptanol and cyclooctanol, can adopt appropriate conformations necessary for transannular reaction, affording bicyclic ethers in moderate yields (eq 13).[28] Large-ring cycloalkanols, such as cyclododecanol, cyclopentadecanol, and cyclohexadecanol, also give the corresponding 1,4-epoxy compounds as major cyclization products.[3a,28] However, the special geometry of cyclodecanol is not favorable for the normal reaction and the 1,4-cyclic ether is formed in only 2.5% yield, whereas 1,2-epoxycyclodecane (13%) and the rearranged 8-ethyl-7-oxabicyclo[4.3.0]nonane (13%) are the predominant cyclization products.[29]

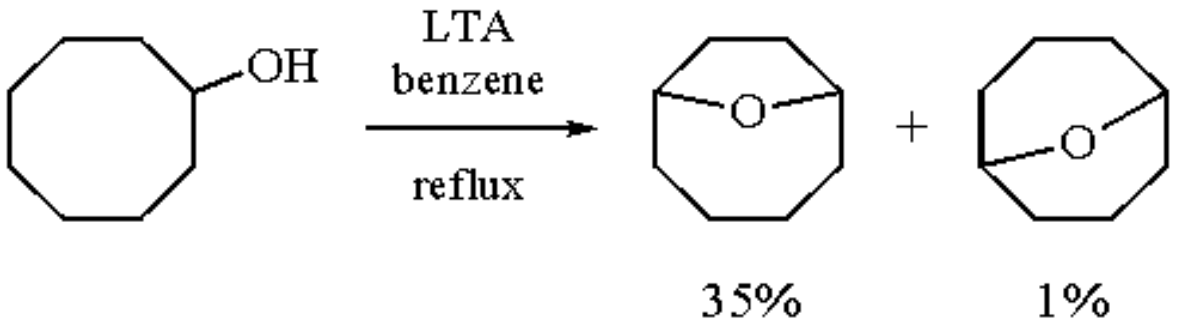

(13)

The LTA oxidation of alcohols to cyclic ethers has been successfully applied as a synthetic method for activation of the angular 18- and 19-methyl groups in steroidal alcohols containing a β-oriented hydroxy group at C-2, C-4, C-6, and C-11 (eq 14).[3c,30,31] Hydroxy terpenoids with suitable stereochemistry can also undergo transannular cyclic ether formation (eq 15).[32]

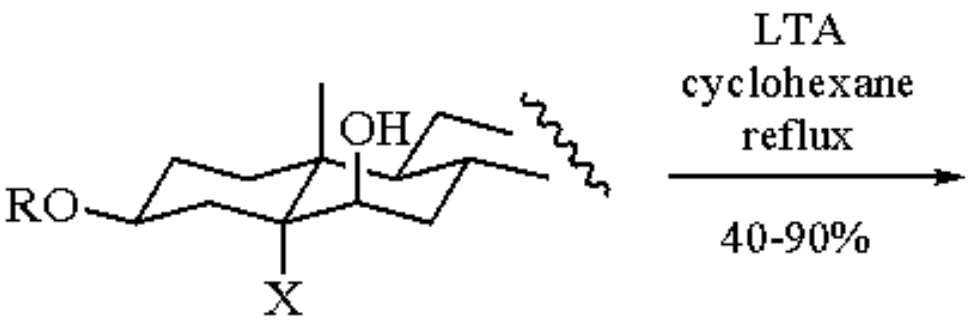

X = H, Cl, Br, OH

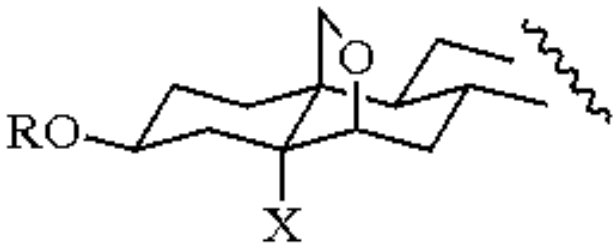

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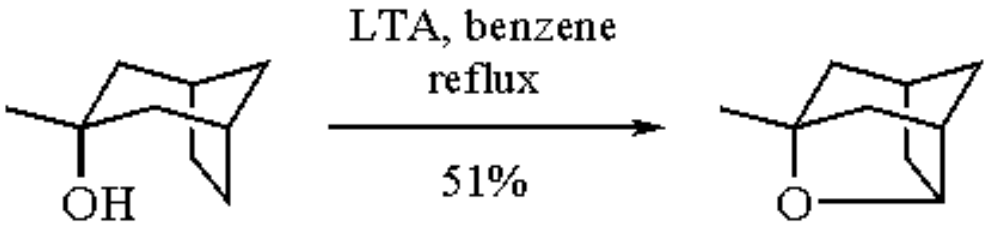

(15)

Another possible reaction of alkoxy radical intermediates, formed in the LTA oxidation of alcohols in nonpolar solvents, is the β-fragmentation reaction.[3] This process, which competes with intramolecular 1,5-hydrogen abstraction, consists of cleavage of a bond between the carbinol (α) and β-carbon atoms, thus affording a carbonyl-containing fragment and products derived from an alkyl radical fragment (usually acetates and/or alkenes).[1a,3,22] Interesting synthetic applications of the LTA β-fragmentation reaction are the formation of 19-norsteroids from their 19-hydroxy precursors and the preparation of 5,10-secosteroids (containing a ten-membered ring) from 5-hydroxy steroids (eq 16).[32]

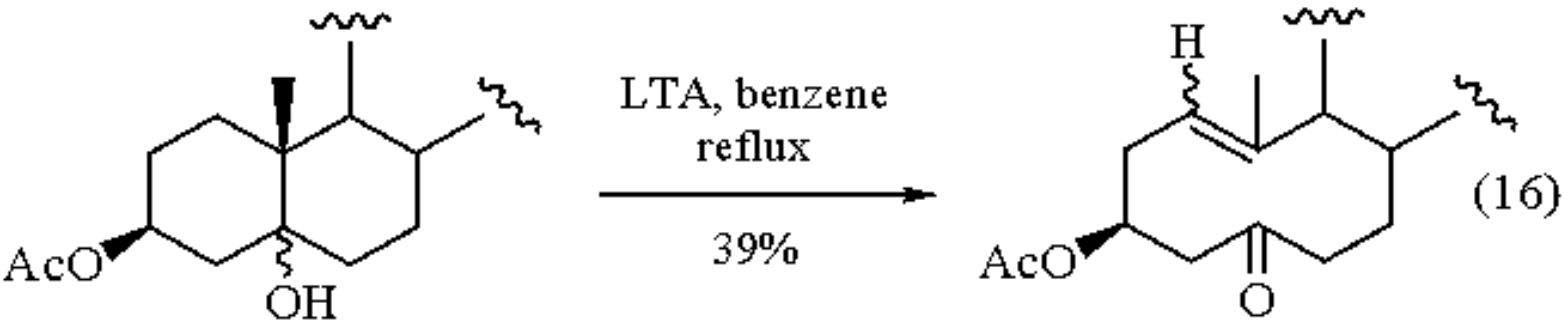

In the LTA oxidations of primary and secondary alcohols in nonpolar solvents, the corresponding aldehydes or ketones are usually obtained as minor byproducts (up to 10%).[3,20,21] However, in the presence of excess pyridine or in pyridine alone, either with heating or at rt, the cyclization and β-fragmentation processes are suppressed and good preparative yields of aldehydes or ketones are obtained (eq 17).[20,21,33] Carbonyl compounds are also obtained when the LTA oxidation of alcohols is carried out in benzene solution in the presence of manganese(II) acetate.[33]

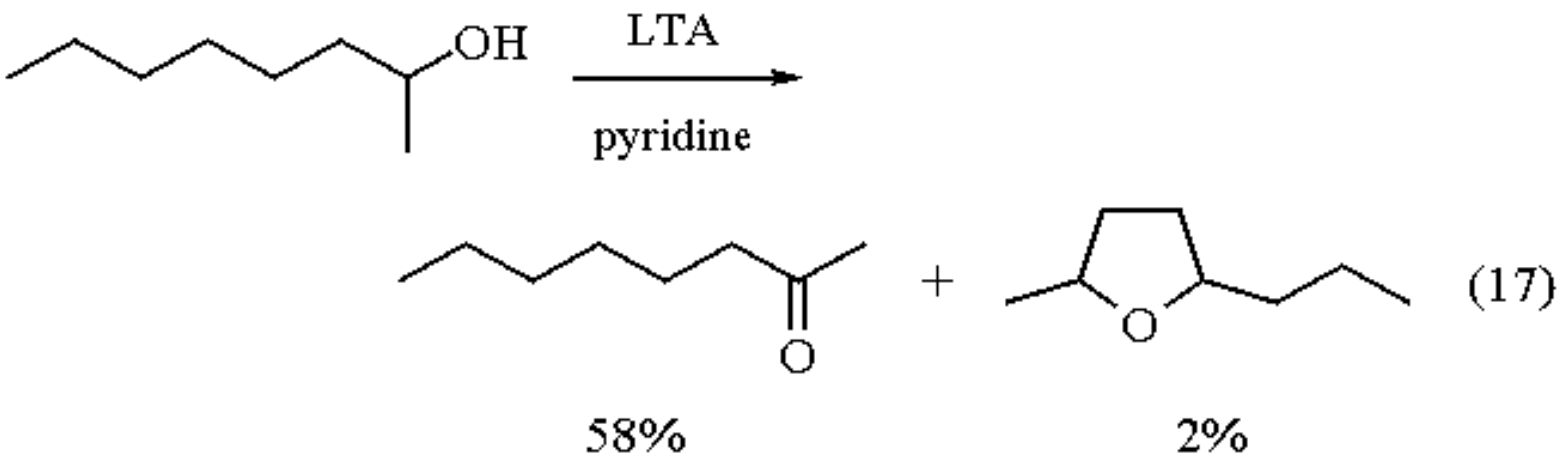

In addition to cyclic ethers, β-fragmentation products, and carbonyl compounds, acetates of starting alcohols are also usually formed in the LTA oxidation, in yields up to 20%.[20]

Unsaturated alcohols, possessing an alkenic double bond at the δ or more remote positions, react with LTA in nonpolar solvents to give acetoxylated cyclic ethers in good yield (eq 18),[34,35] while 5-, 6- and 7-alkenols undergo in great predominance an *exo*-type cyclization, affording six-, seven- and eight-membered acetoxymethyl cyclic ethers, respectively.[35]

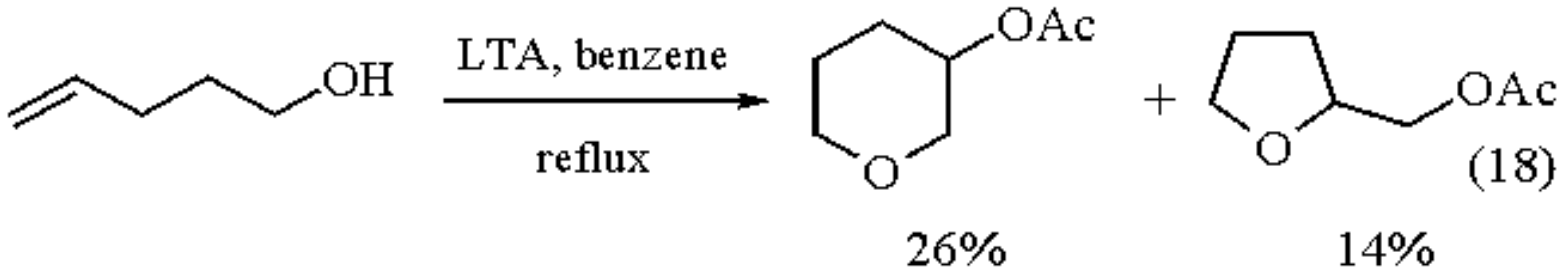

1,2-Glycol Cleavage.

LTA is one of the most frequently used reagents for the cleavage of 1,2-glycols and the preparation of the resulting carbonyl compounds (eq 19).[1,4] The reactions are performed either in aprotic solvents (benzene, nitrobenzene, 1,2-dichloroethane) or in protic solvents such as acetic acid.[36,37] The rate of LTA glycol cleavage is highly dependent on the structure and stereochemistry of the substrate. In general, there is correlation between the oxidation rate and the spatial proximity of the hydroxy groups.[36] 1,2-Diols having a geometry favoring the formation of cyclic intermediates are much more reactive than 1,2-diols whose structure does not permit such intermediates to be formed (eq 20).[38,39] The oxidation rates often provide a reliable means for the determination of the stereochemical relationship of the hydroxy groups.[39,40]

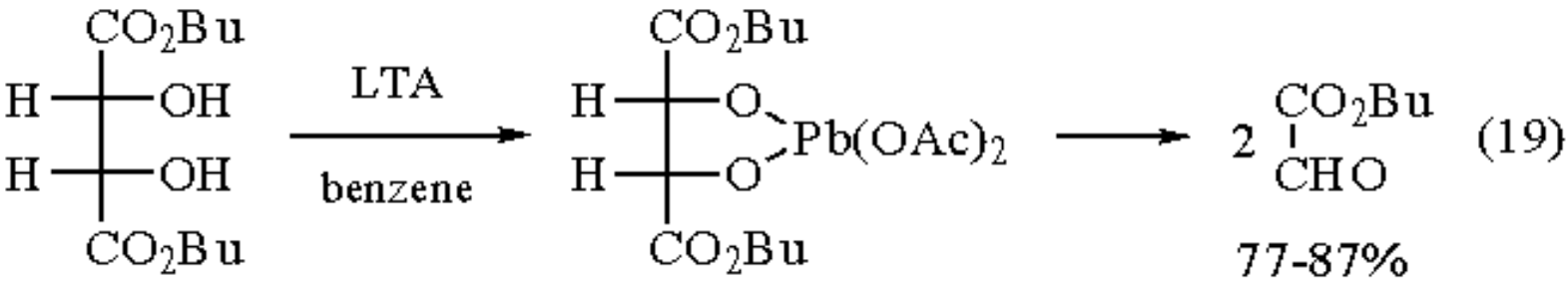

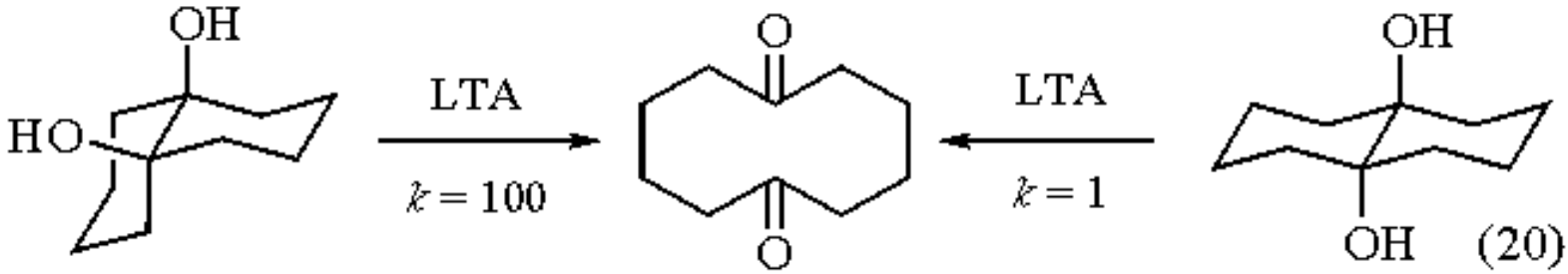

1,2-Glycol cleavage by LTA has been widely applied for the oxidation of carbohydrates and sugars (eq 21).[4,37] Because of structural and stereochemical differences, the reactivity of individual glycol units in sugar molecules is often different, thus rendering the LTA reaction a valuable tool for structural determination and for degradation studies in carbohydrate chemistry.[41]

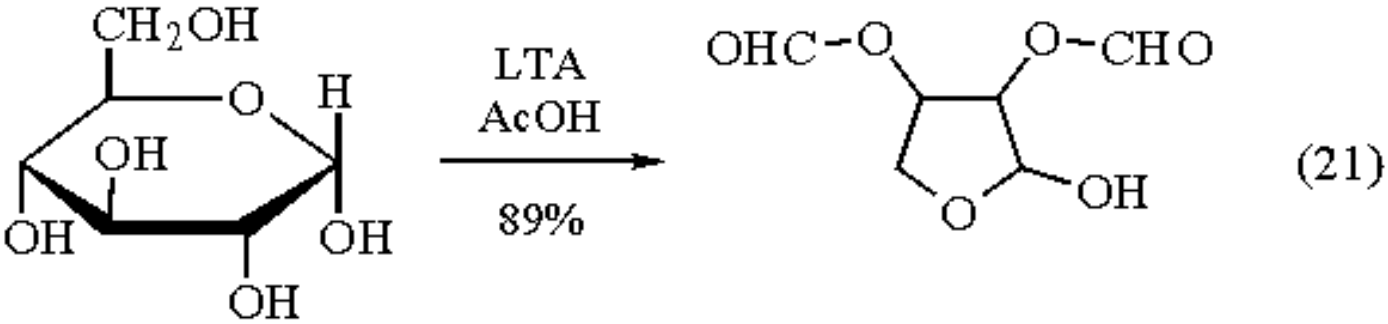

α-Acetoxylation of Ketones.

The reaction of enolizable ketones with LTA is a standard method for α-acetoxylation (eq 22).[1,3,42] The reactions are usually carried out in hot acetic acid or in benzene solution at reflux. The reaction proceeds via an enol-lead(IV) acetate intermediate, which undergoes rearrangement to give the α-acetoxylated ketone. Acetoxylation of ketones is catalyzed by ***Boron Trifluoride***.[43] Enol ethers, enol esters, enamines,[1] β-dicarbonyl compounds, β-keto esters, and

malonic esters are also acetoxylated by LTA.[42]

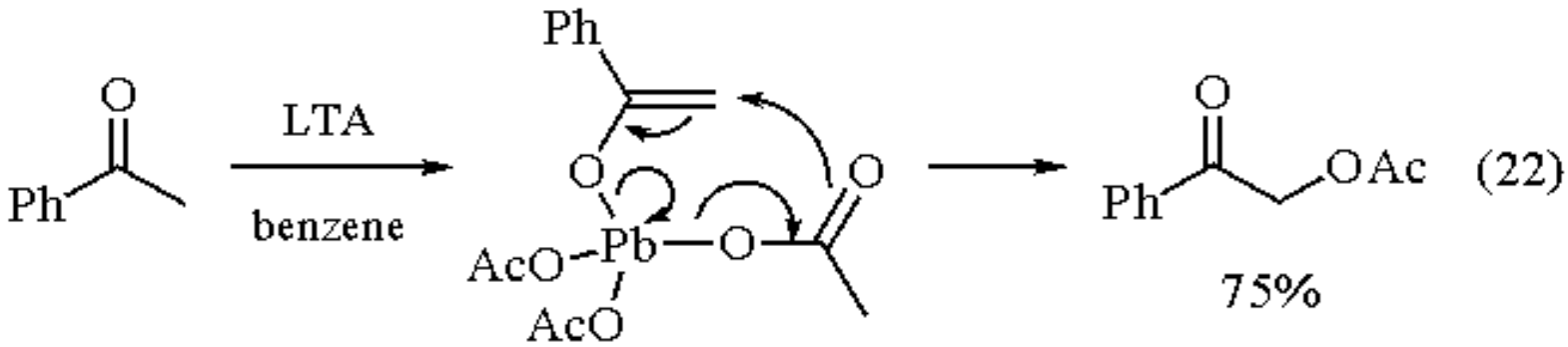

Decarboxylation of Acids.

Oxidative decarboxylation of carboxylic acids by LTA depends on the reaction conditions, coreagents, and structure of acids, and hence a variety of products such as acetate esters, alkanes, alkenes, and alkyl halides can be obtained.[1,5] The reactions are performed in nonpolar solvents (benzene, carbon tetrachloride) or polar solvents (acetic acid, pyridine, HMPA).[5] Mixed lead(IV) carboxylates are involved as intermediates, and by their thermal or photolytic decomposition decarboxylation occurs and alkyl radicals are formed (eq 23).[5,44,45]

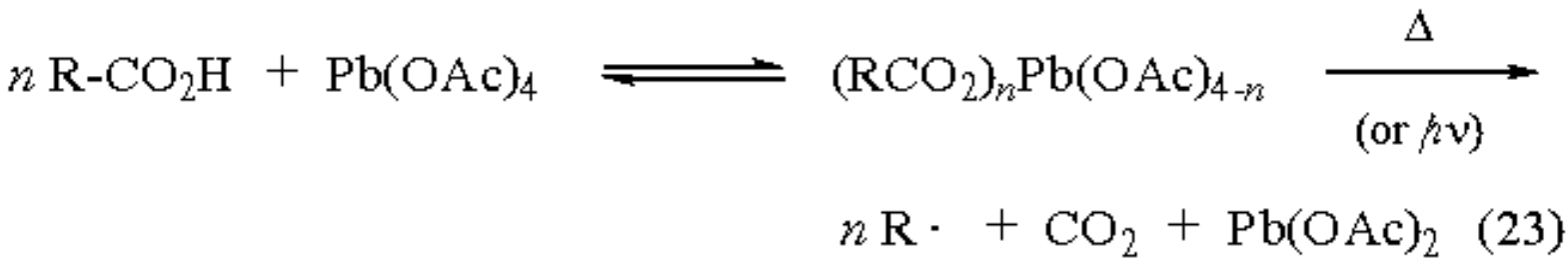

Oxidation of alkyl radicals by lead(IV) species give carbocations and, depending on the reaction conditions and structure of the substrate acids, various products derived from the intermediate alkyl radicals and corresponding carbocations (dimerization, hydrogen transfer, elimination, substitution, rearrangement, etc.) are obtained.[5] Decarboxylation of primary and secondary acids usually affords acetate esters as major products (eq 24).[44] When a mixture of acetates and alkenes is formed, it is recommended (in order to improve the yields of acetate esters) to run the reaction in the presence of potassium acetate (eq 25).[5] The LTA decarboxylation of tertiary carboxylic acids gives a mixture of alkenes and acetate esters.[46] For the preparative oxidative decarboxylation of acids to alkenes, see ***Lead(IV) Acetate-Copper(II) Acetate***.

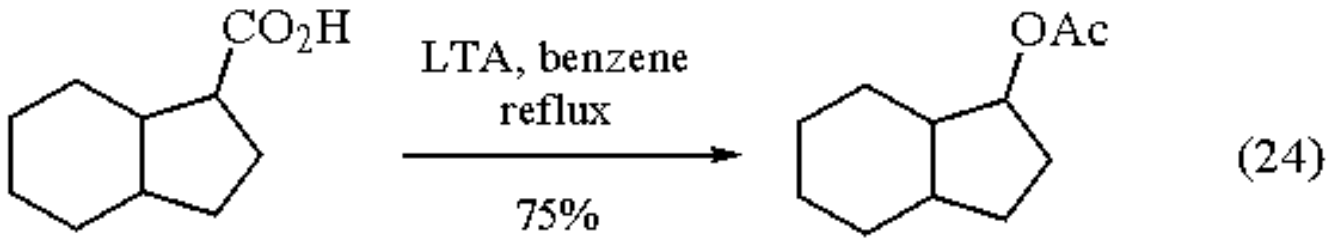

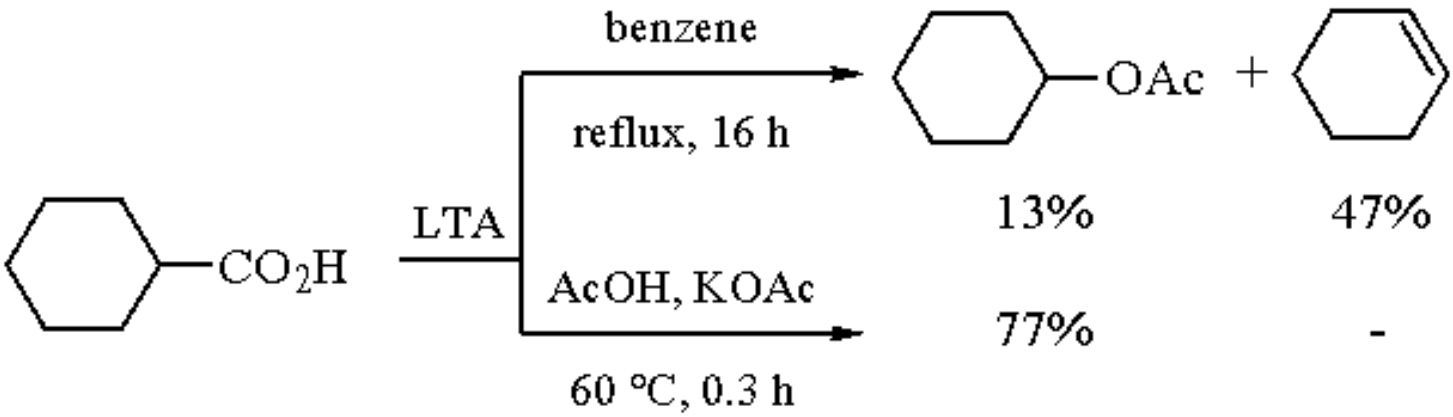

(25)

A useful modification of the LTA reaction with carboxylic acids is the oxidation in the presence of halide ions, whereby the corresponding alkyl halides are obtained (eqs 26 and 27).[47] Halodecarboxylations of acids are performed by addition of a molar equivalent of the metal halide (lithium, sodium, potassium chloride) to a carboxylic acid and LTA, the reactions being performed in boiling benzene solution.[5,47] For the iododecarboxylation of acids, see ***Lead(IV) Acetate-Iodine***.

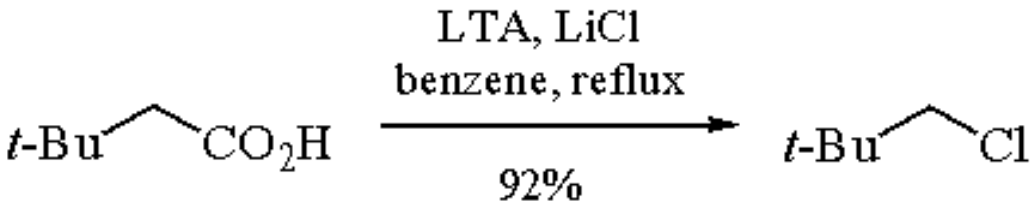

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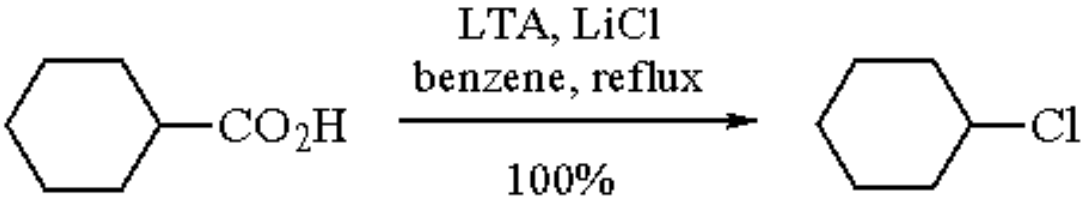

(27)

Bis-decarboxylation of 1,2-dicarboxylic acids by LTA is a useful method for the introduction of alkenic bonds (eq 28).[48] The reactions are performed in boiling benzene in the presence of pyridine or in DMSO. In some cases, LTA bis-decarboxylation can be effected by using acid anhydrides (eq 29).[49] Bis-decarboxylation of 1,1-dicarboxylic acids yields the corresponding ketones (eq 30).[50]

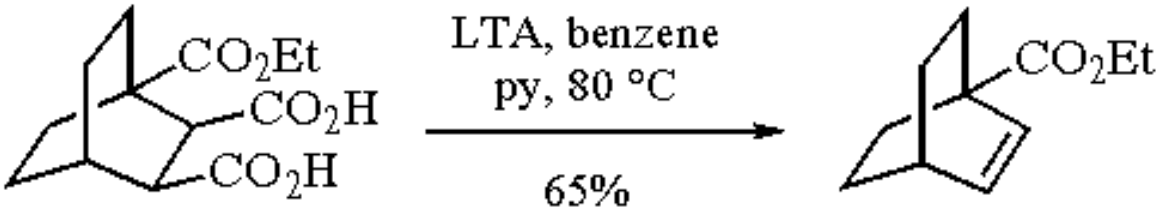

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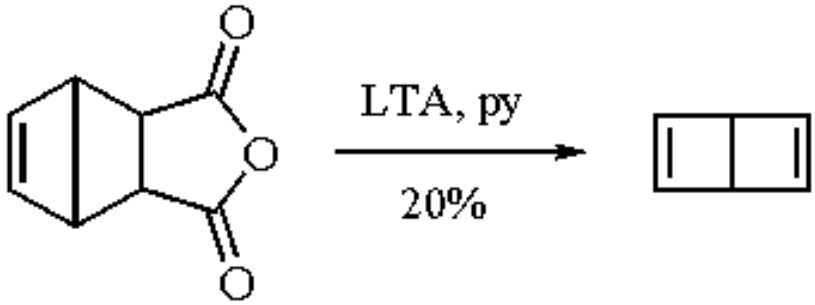

(29)

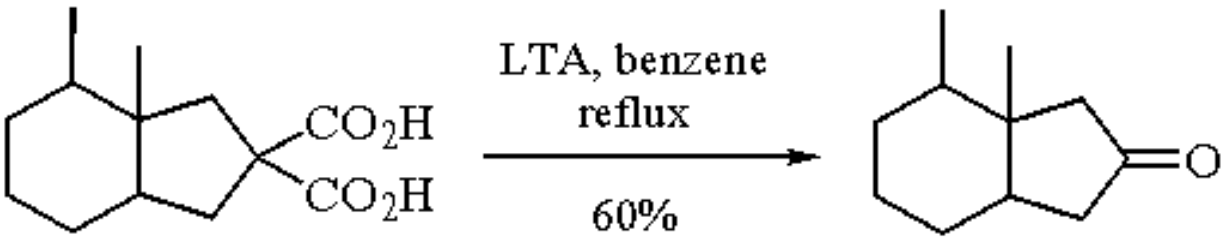

(30)

Oxidative Transformations of Nitrogen-Containing Compounds.

The LTA oxidation of aliphatic primary amines containing an α-methylene group results in dehydrogenation to alkyl cyanides (eq 31).[51] However, aromatic primary amines give symmetrical azo compounds in varying yield (eq 32).[52]

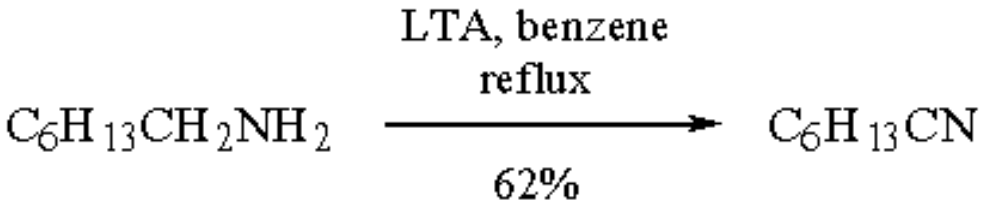

(31)

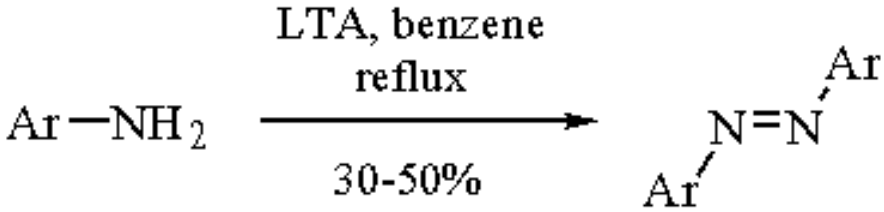

(32)

Primary amides react with LTA in the presence of alcohols to give the corresponding carbamates (eq 33), but in the absence of alcohol, isocyanates are formed.[53]

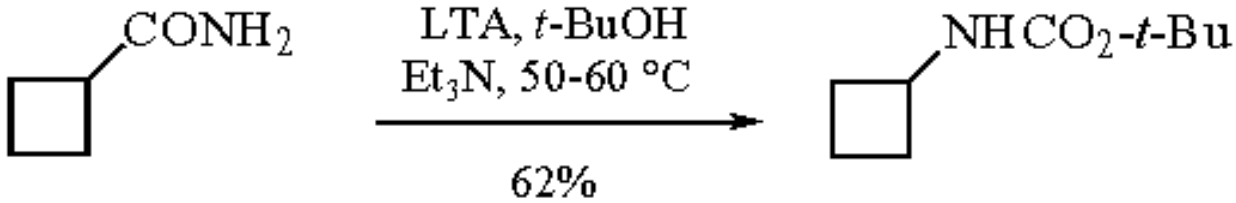

(33)

Aliphatic ketoximes, upon treatment with LTA in an inert solvent, undergo acetoxylation at the α-carbon producing 1-

nitroso-1-acetoxyalkanes (eq 34),[54] whereas hydrazones afford azoacetates (eq 35) or, when the reactions are performed in alcohol solvent, azo ethers.[55] Arylhydrazines, *N*,*N*´-disubstituted hydrazines,[56] and *N*-amino compounds[57] are oxidized by LTA to different products.

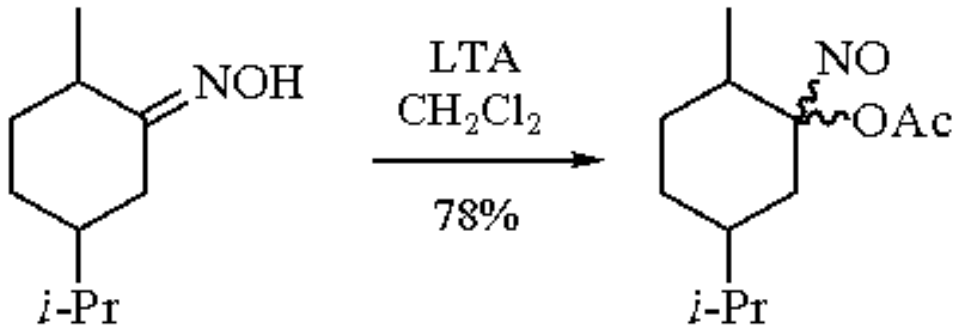

(34)

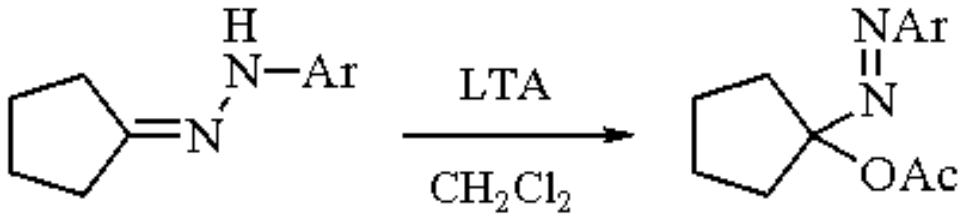

(35)

Other Applications.

By LTA oxidation of phenols, acetoxycyclohexadienones, quinones, and dimerization products can be formed.[58] Alkyl sulfides,[59] alkyl hydroperoxides,[60] and organometallic compounds[61] are also oxidized by LTA.

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Lead(IV) Acetate-Copper(II) Acetate[1]

$Pb(OAc)_4$-$Cu(OAc)_2.H_2O$

($Pb(OAc)_4$)

[546-67-8] · $C_8H_{12}O_8Pb$ · Lead(IV) Acetate-Copper(II) Acetate · (MW 443.40) ($Cu(OAc)_2.H_2O$)

[142-71-2] · $C_4H_8CuO_5$ · Lead(IV) Acetate-Copper(II) Acetate · (MW 199.67)

(oxidative decarboxylation of acids to alkenes[1a])

Physical Data: see ***Lead(IV) Acetate*** and ***Copper(II) Acetate***.

Oxidative decarboxylation of aliphatic and alicyclic carboxylic acids by lead tetraacetate (LTA) usually affords a mixture of saturated hydrocarbons, alkenes, acetate esters, and other products, whose distribution depends upon the structure of the starting acid.[1a,b] However, when LTA is used in the presence of catalytic amounts of copper(II) acetate, the rates of decarboxylation are greatly enhanced and the yields of alkenes are increased so that the reactions become of synthetic value (eq 1).[2] This effect of copper(II) acetate is attributed to the rapid scavenging of the intermediately formed alkyl radicals by copper(II) ions (eq 2).[1a,3,5-7] A catalytic amount of $Cu(OAc)_2$ is sufficient, since it is regenerated in the course of the reaction (eq 3).[3,6] The reactions are usually carried out in an inert atmosphere in benzene solution, under thermal or photolytic conditions, using a minimal concentration of $Cu(OAc)_2$ (about 0.005 M).[1a,3]

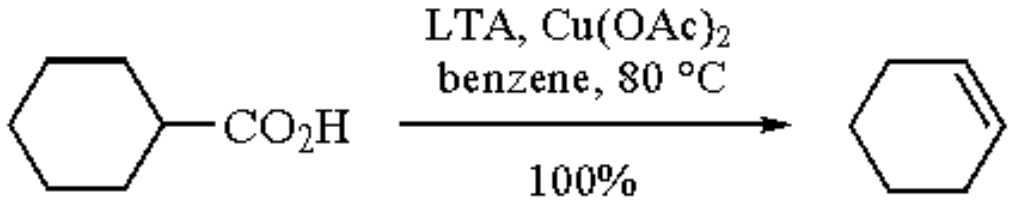

(1)

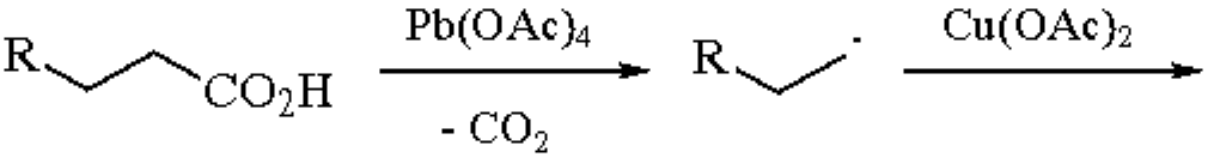

+ CuOAc (2)

$$CuOAc + Pb^{IV} \longrightarrow Cu(OAc)_2 + Pb^{III}, \text{ etc.} \qquad (3)$$

The LTA-$Cu(OAc)_2$ reagent is particularly applicable for the oxidative decarboxylation of primary and secondary acids, whereby primary carboxylic acids afford terminal alkenes in high yields (eqs 4 and 5).[2-4,8-10] In the case of secondary acids, if unsymmetrical, oxidative elimination can take place in two directions, and frequently both possible alkenes are obtained (eqs 6 and 7).[2,11-14] Oxidative decarboxylation of secondary acids by the LTA-$Cu(OAc)_2$ reagent is approximately 20 times faster than that of primary acids.[1a,15]

$$Me(CH_2)_7CO_2H \xrightarrow[\text{87\%}]{\text{LTA, } Cu(OAc)_2,\ \text{PhCl, } h\nu\text{, 30 °C}} Me(CH_2)_5CH{=}CH \qquad (4)$$

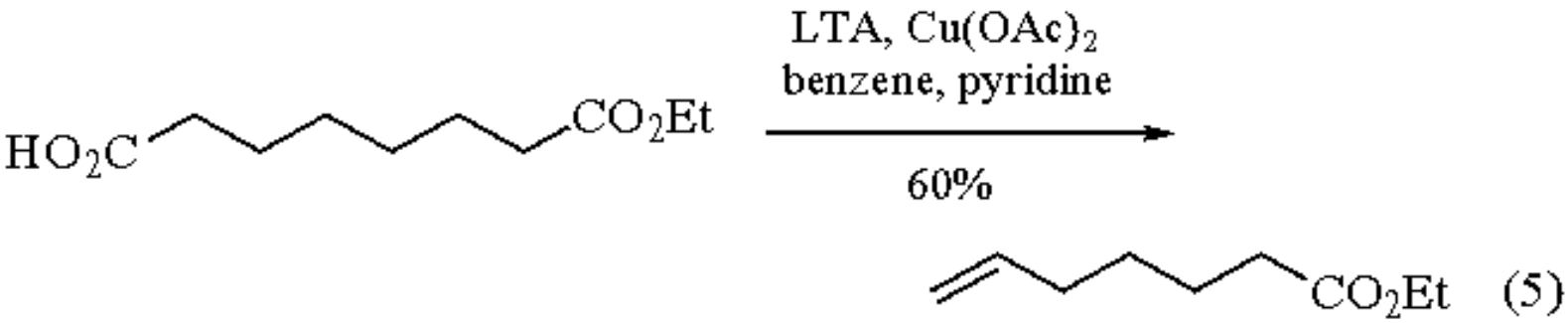

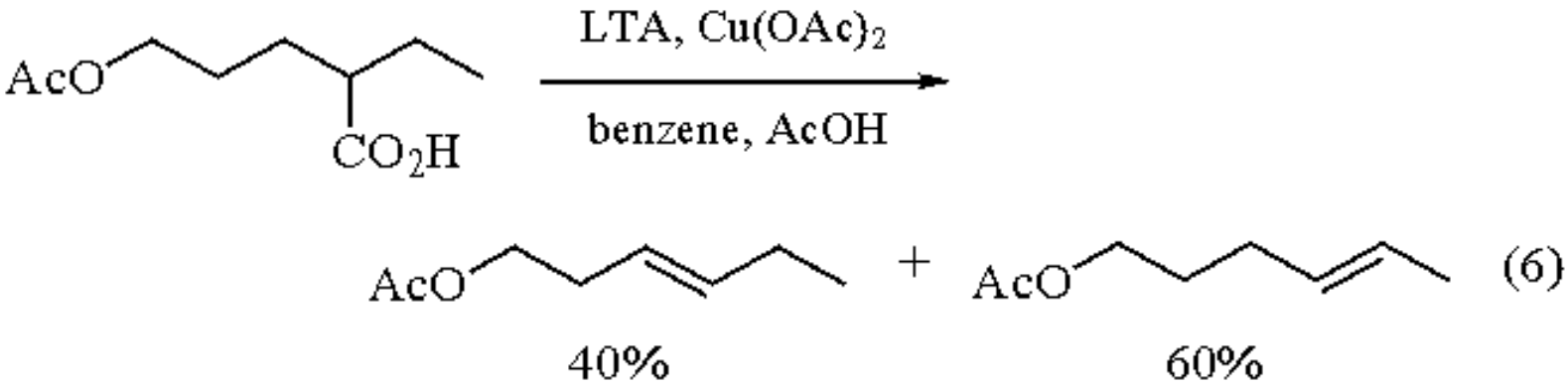

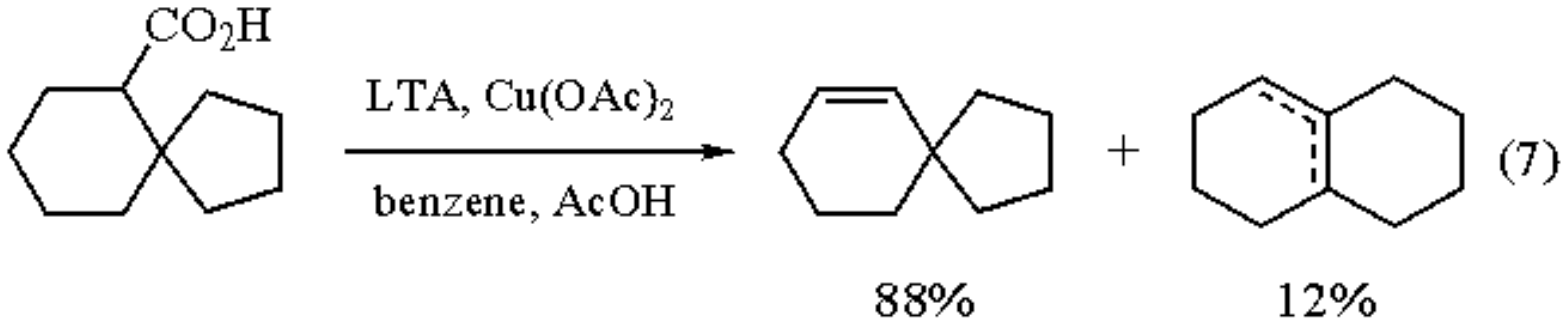

Decarboxylation of tertiary carboxylic acids by LTA-$Cu(OAc)_2$ proceeds about 100 times faster than that of primary acids, and usually affords alkenes as main products (eqs 8 and 9).[6,16-19] However, with tertiary carboxylic acids, in

contrast to the behavior of primary and secondary acids, LTA alone reacts in the same way, so that addition of the Cu^{II} catalyst is not necessary.[1a]

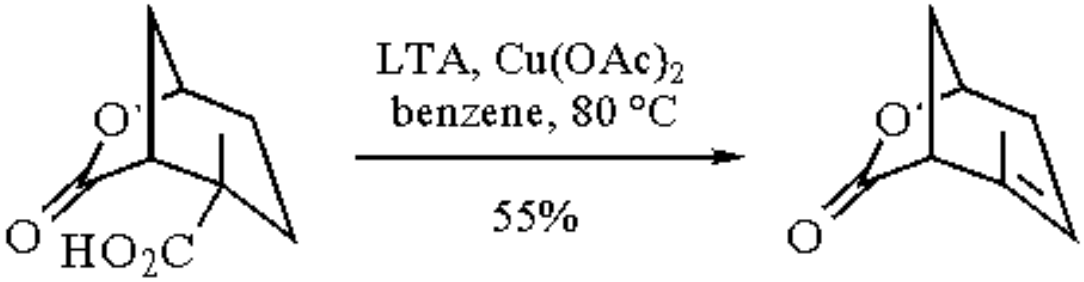

(8)

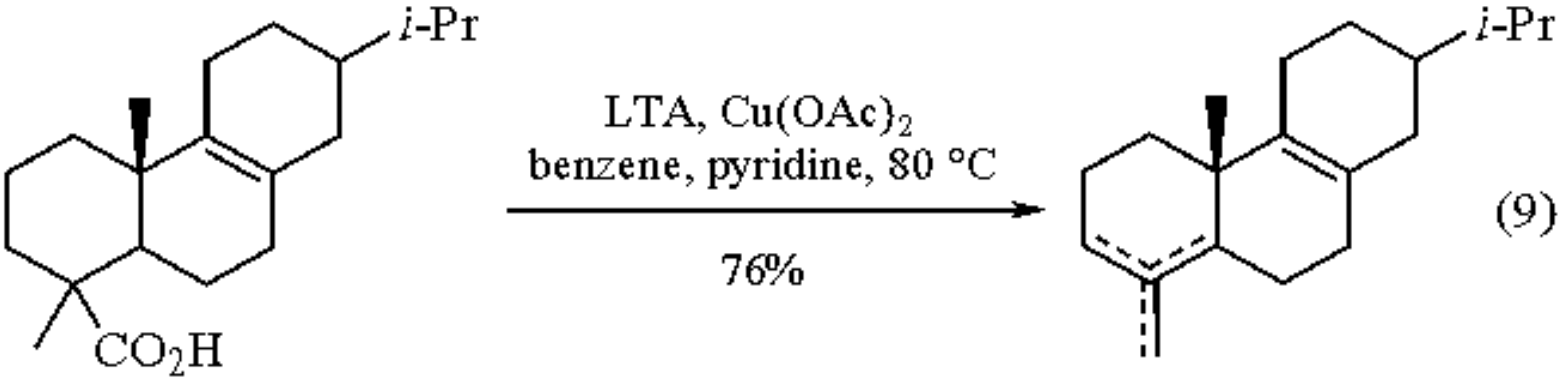

(9)

In the oxidative decarboxylation of acids by LTA-$Cu(OAc)_2$ the solvent can play an important role, because the relative rates of oxidative elimination with alkene formation and competitive oxidative substitution leading to acetate ester formation may be considerably influenced by the solvent. Thus decarboxylation of cyclobutanecarboxylic acid by LTA-$Cu(OAc)_2$ in benzene affords cyclobutene as the main reaction product; in acetonitrile-acetic acid, cyclobutene is formed in low yield, the major products being a mixture of isomeric acetates (eq 10).[1a,2,7] A portionwise addition of LTA to a refluxing solution of carboxylic acid in benzene in the presence of pyridine and $Cu(OAc)_2$, in the absence of air, has been suggested as an improved procedure for oxidative decarboxylation to alkenes.[11]

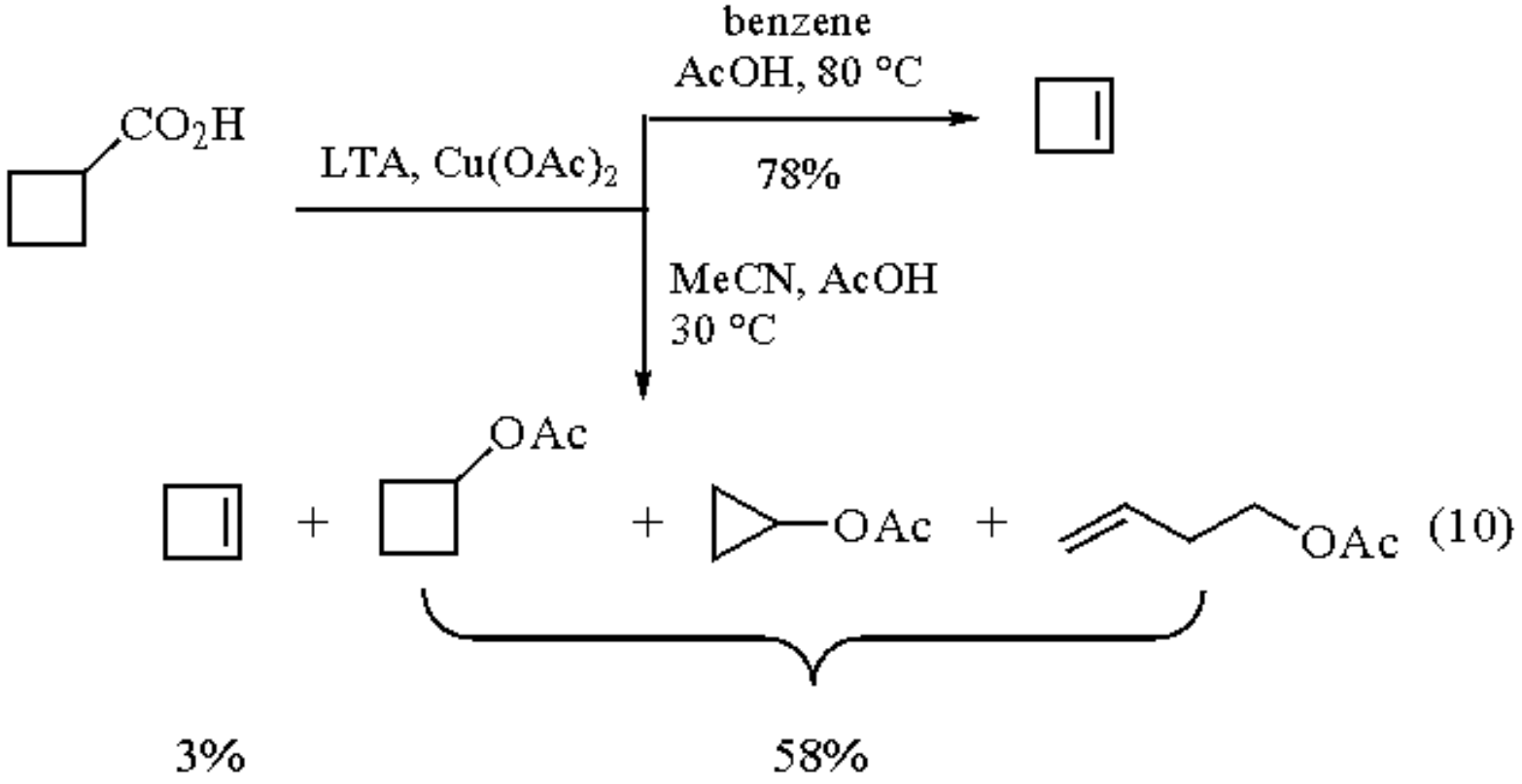

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&ZZbreve;ivorad &CCbreve;eković & Mihailo Lj. Mihailović

Lead(IV) Acetate-Iodine[1]

$Pb(OAc)_4$-I_2

($Pb(OAc)_4$)

[546-67-8] · $C_8H_{12}O_8Pb$ · Lead(IV) Acetate-Iodine · (MW 443.37) (I_2)

[7553-56-2] · I_2 · Lead(IV) Acetate-Iodine · (MW 253.80)

(functionalization of nonactivated δ-carbon atoms;[2] mono- and disubstitution on methyl and methylene groups;[3,4] cyanohydrin-cyano ketone rearrangement;[5] β-fragmentation reactions;[6] iododecarboxylation[7])

Physical Data: see ***Lead(IV) Acetate*** and ***Iodine***.

Functionalization of Nonactivated δ-Carbon Atoms.

The original method for oxidative functionalization of δ-carbon atoms by lead tetraacetate (LTA), involving conversion of alcohols to cyclic ethers, is modified by using LTA-I_2 as reagent.[1] This modification is known as the LTA-hypoiodite reaction.[1] The reactions are performed under irradiation conditions (500 W lamp) in nonpolar solvents such as cyclohexane and CCl_4.[2] The selective introduction of a functional group on the δ-carbon atom by oxidative transformation of alcohols is based on the specific reactivity of LTA-I_2 for the conversion of alcohols to hypoiodites, and on the facile homopolar decomposition of alkyl hypoiodites, under irradiation, with formation of alkoxy radical intermediates (eq 1).[1,2]

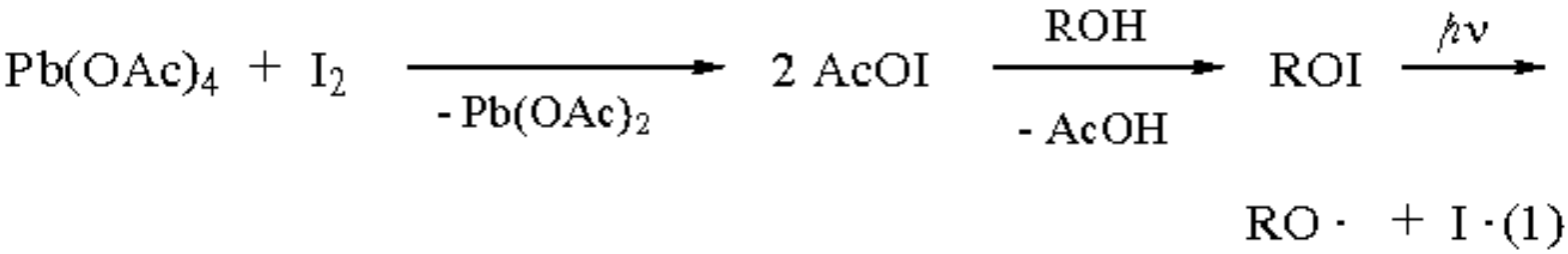

Alkoxy radicals generated by this method from primary and secondary alcohols undergo intramolecular hydrogen transfer from the δ-carbon atom, thus forming intermediary δ-carbon radicals (eq 2), which under these experimental conditions are then intercepted by iodine with formation of 1,4-iodohydrins.[1,2] Depending on the conformational relationship of the hydroxy group, iodine, and δ-carbon atom in the iodohydrin, different products can be obtained (eq 2). In the case of a linear arrangement, the hydroxy group approaches the δ-carbon atom from the back side of iodine,

whereby oxidative monosubstitution takes place with elimination of HI, resulting in closure of a tetrahydrofuran ring (eq 2, path i).[1,8] This reaction has often been applied for the functionalization (with cyclic ether formation) of steroidal 18- and 19-methyl groups, and methyl groups in other rigid molecules (eqs 3 and 4).[3,9,10]

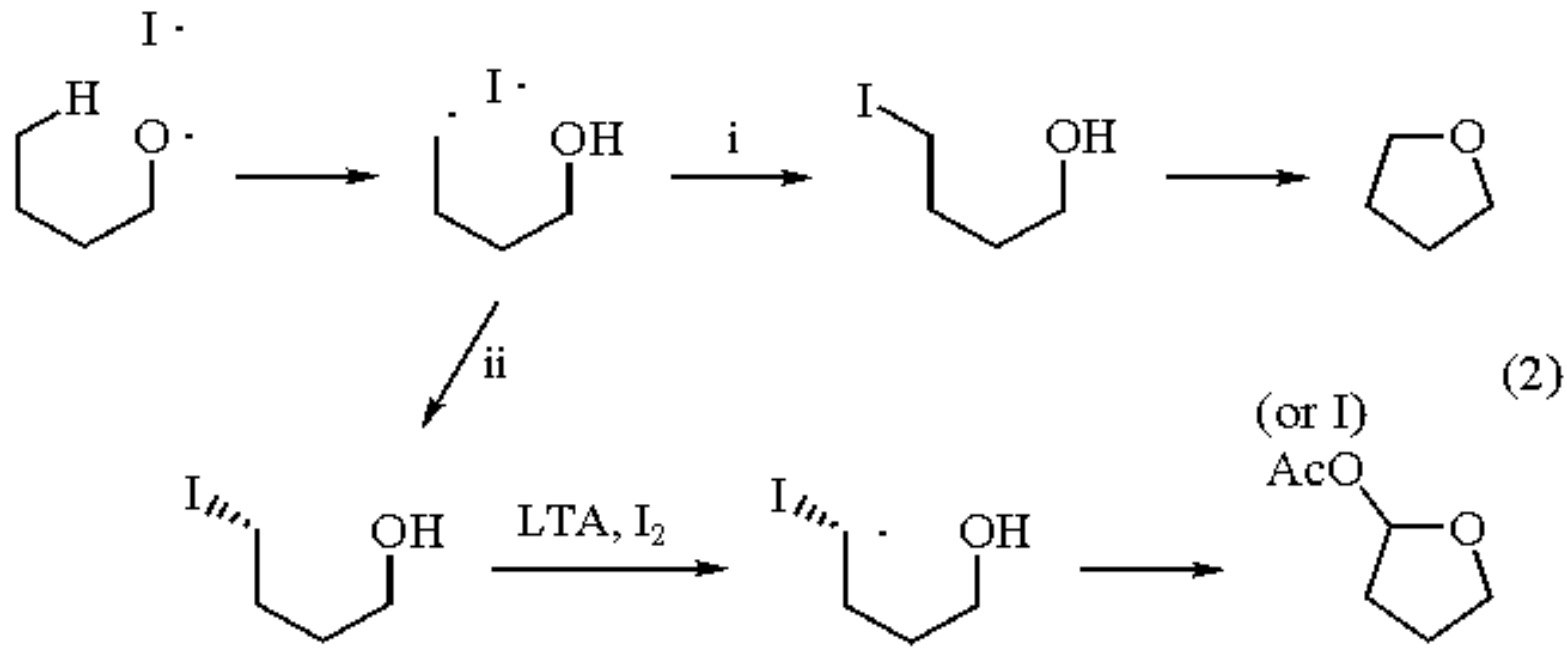

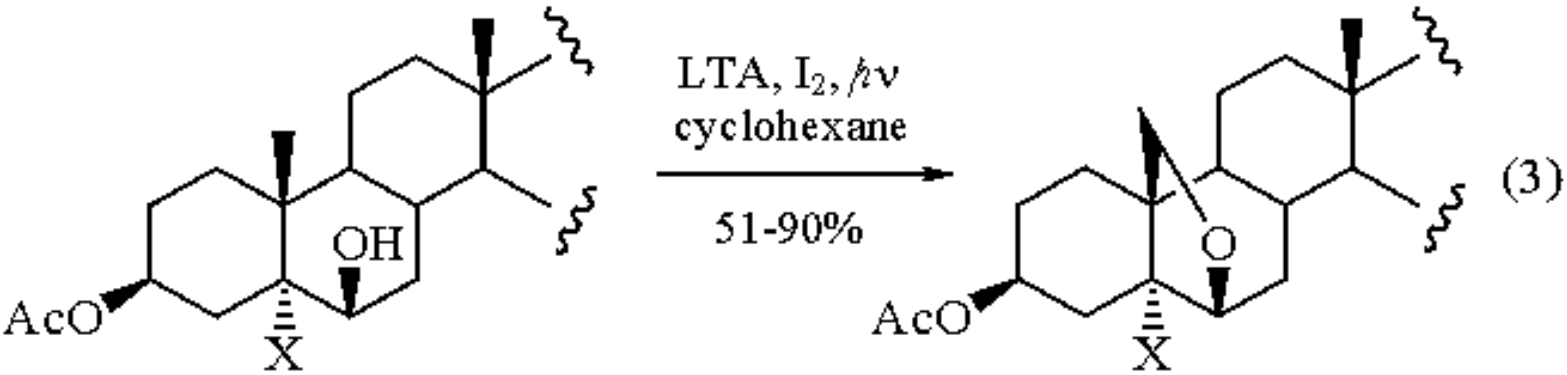

X = H, Cl, Br, OAc, OMe, OH

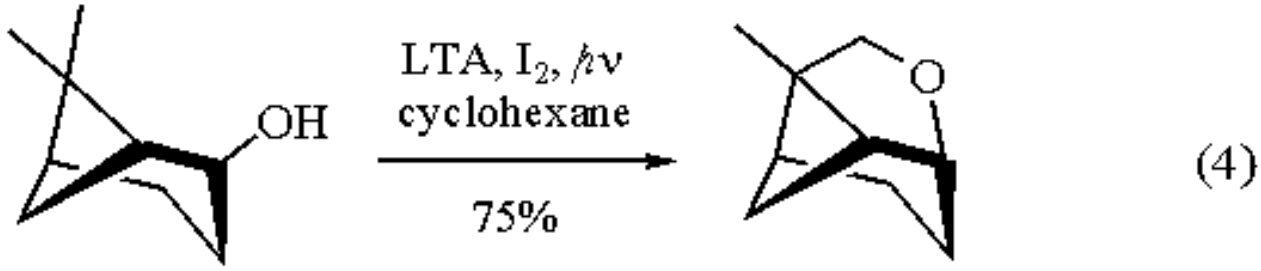

However, when a linear relationship of iodine, δ-carbon atom, and hydroxy group is not possible in the iodohydrin, a second oxidative sequence with double substitution on the δ-methyl group takes place (eq 2, path ii),[1,8] and acetoxy or iodo cyclic ethers are formed. Such a reaction at the angular 19-methyl group of 4β-hydroxy steroids affords 19-acetoxy- (or iodo-) 4β,19-cyclic ethers (eq 5).[8,11]

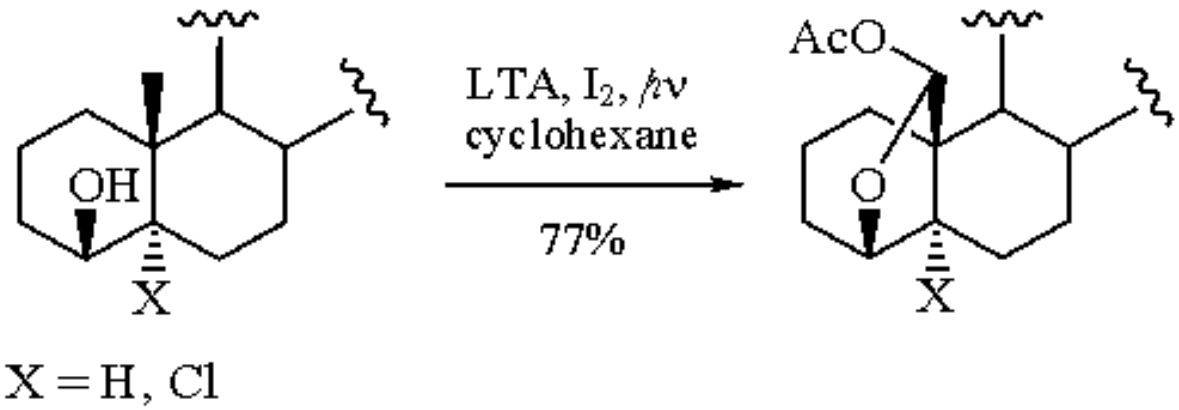

(5)

The LTA-I_2 oxidation of primary and secondary alcohols possessing a nonactivated δ-methylene group proceeds either with monosubstitution, i.e. cyclic ether formation, or double substitution to give unsaturated cyclic ethers (eq 6).[4,12]

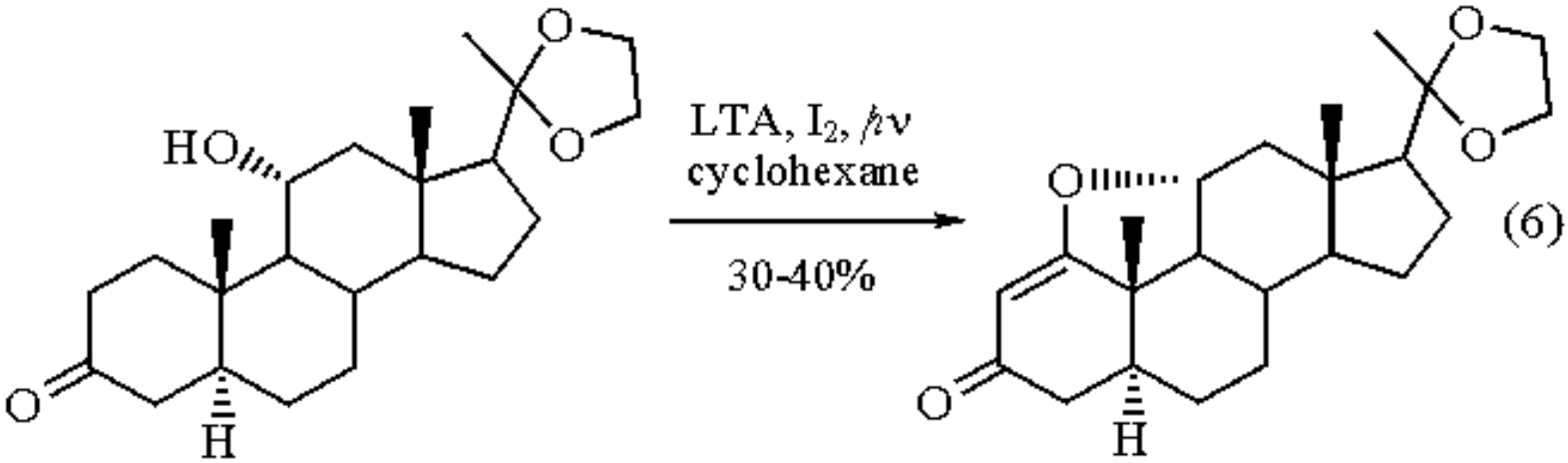

(6)

By the LTA-I_2 oxidation of steroidal alcohols having a methine group at the δ-position, unsaturated cyclic ethers are obtained via alkenic alcohols as intermediates (eq 7).[4,13]

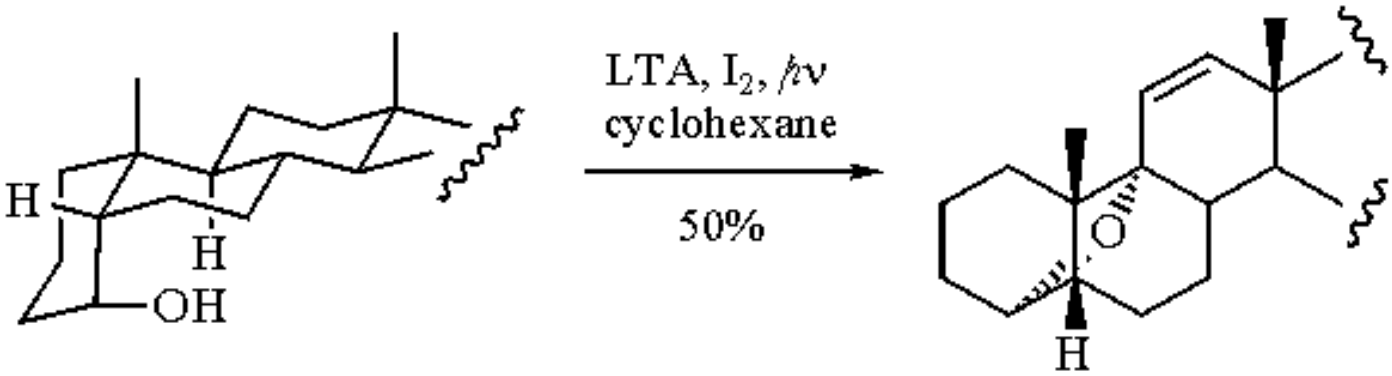

(7)

Cyanohydrin-Cyano Ketone Rearrangement.

A particularly interesting and specific reaction of the LTA-iodine reagent is the oxidative rearrangement of

cyanohydrins to δ-cyano ketones (eq 8).[1,5,14] Other hypoiodite forming reagents do not effect this rearrangement.

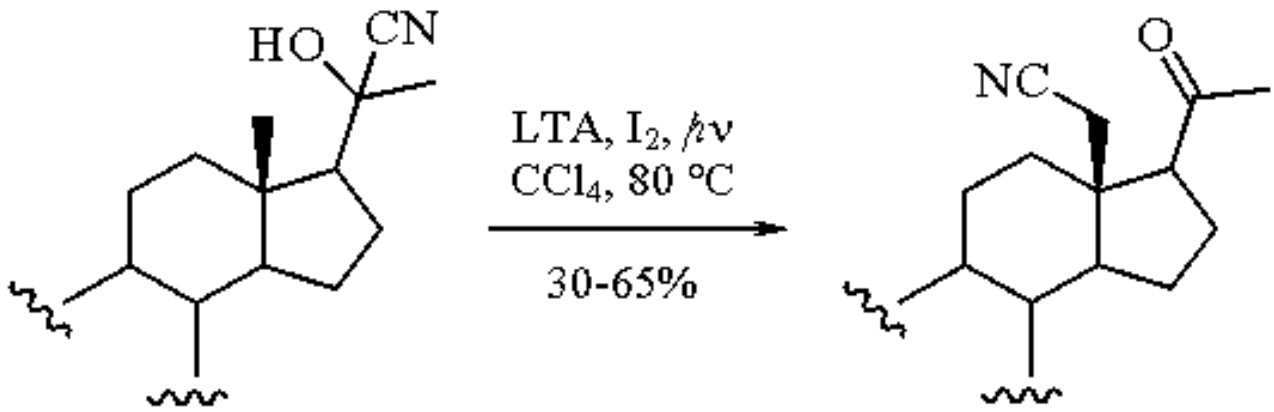

(8)

The cyanohydrin-cyano ketone rearrangement is successfully realized by the LTA-I_2 oxidation of 20-cyano-20-hydroxy steroids, and this reaction offers a good method for the introduction of a functional group, with C-C bond formation, at the nonactivated 18-methyl group in a one-pot reaction.[1,5] 1,4-Migration of the cyano group involves intramolecular addition of a δ-alkyl radical to the cyano group, followed by β-cleavage of the resulting imino radical, to give an α-hydroxy-δ-cyano radical and, as final product, the corresponding δ-cyano ketone (eq 9).[1]

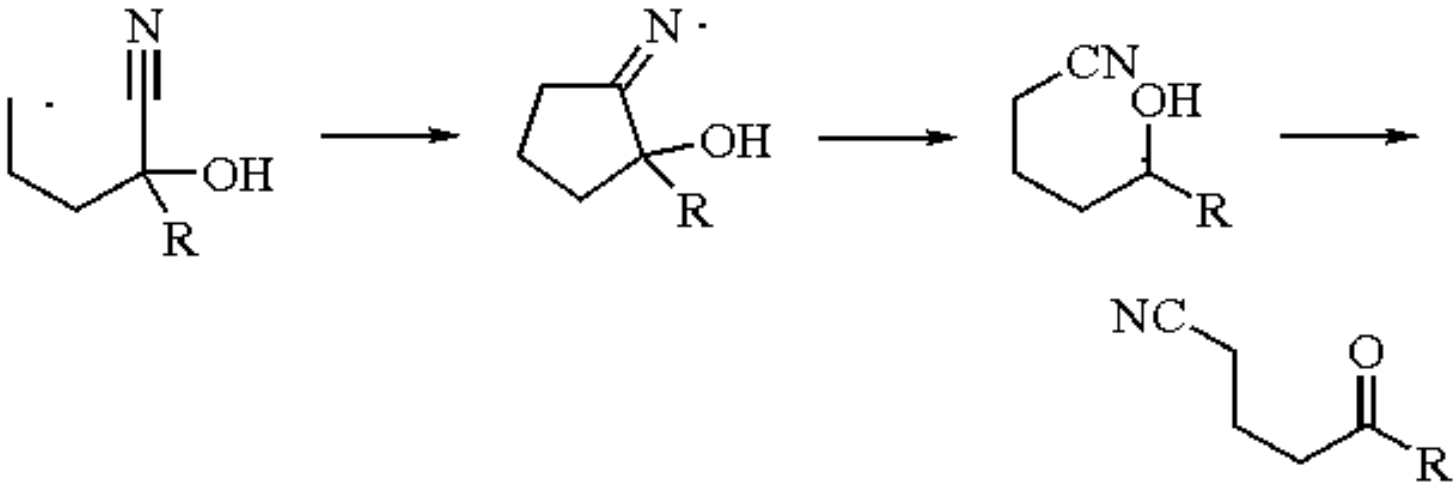

(9)

It is important to note that all of the described reactions of hydroxy compounds with LTA-I_2 can take place only when at least one of the reactive centers, the hydroxy group or the δ-carbon atom, are part of a fixed system.[1]

β-Fragmentation Reaction.

In addition to cyclization, alkoxy radicals generated by means of LTA-I_2 can also undergo β-cleavage, this process being favored when stable alkyl radical and oxo-containing fragments are formed.[6] In this case, homolytic C_α-C_β bond breaking can be more important than functionalization at C_δ (eq 10).[6,15,16]

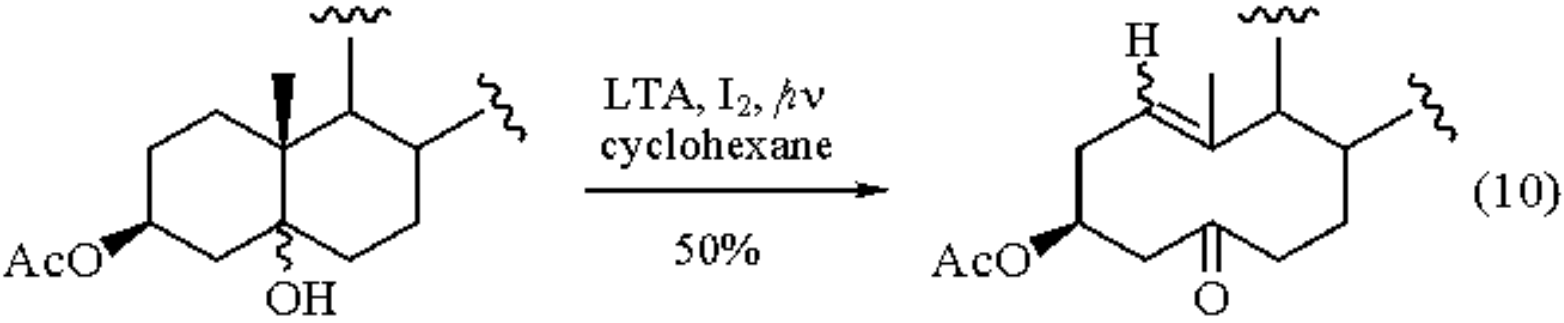

The relatively stable tertiary radicals generated by β-fragmentation in the LTA-I_2 reaction can be either quenched by iodine to give iodides or oxidized to the corresponding carbocations, which usually undergo proton elimination affording unsaturated products (eqs 10 and 11).[1] When cleavage of a bridged C_α-C_β bond is involved, the LTA-I_2 β-fragmentation can be usefully applied for the preparation of medium or large carbocyclic and heterocyclic rings (eqs 10 and 12).

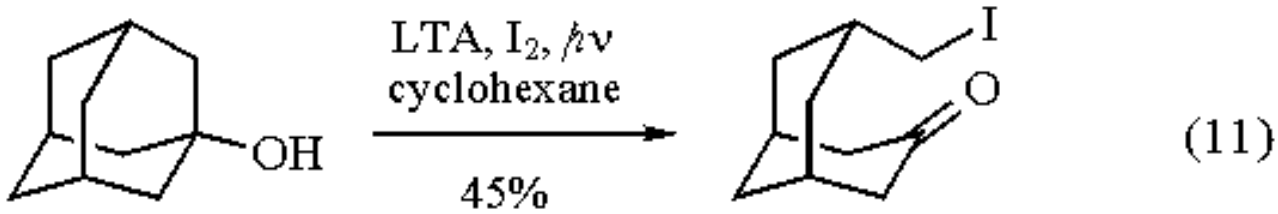

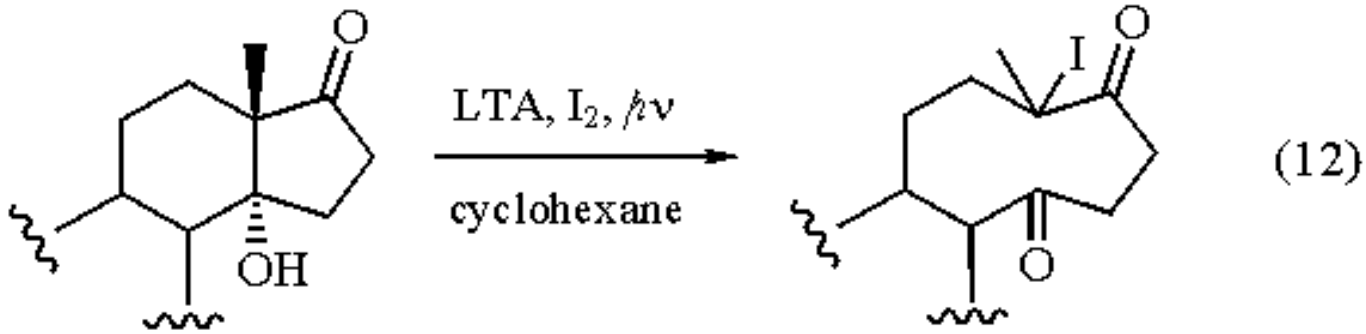

Iododecarboxylation.

When treated with I_2 and LTA in refluxing CCl_4 under irradiation with a tungsten lamp, carboxylic acids undergo iododecarboxylation.[17] Good yields of alkyl iodides are obtained from primary and secondary acids (eqs 13 and 14).[17,18-20]

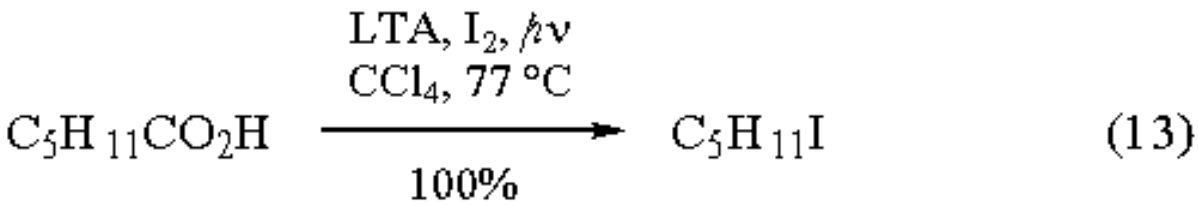

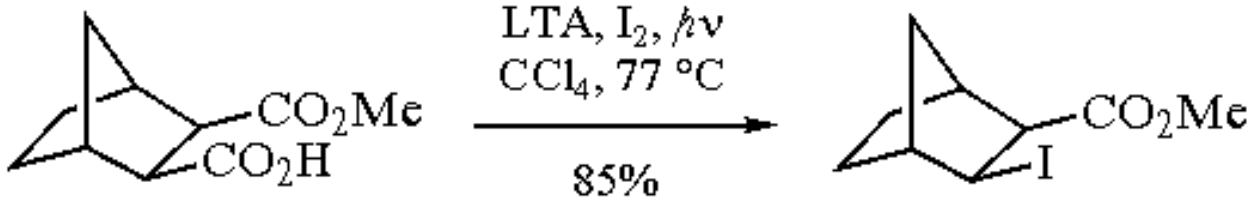

(14)

In the dark, the reaction proceeds more slowly and in lower yield. Decarboxylation of carboxylic acids by LTA-I_2 under thermal conditions, i.e. by heating at 150-180 °C in a suitable solvent, gives (particularly with primary acids) esters of these acids in fairly good yield (up to 54%) (eq 15).[21]

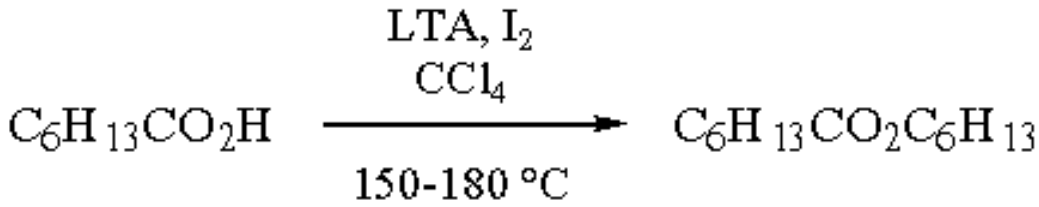

(15)

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&ZZbreve;ivorad &CCbreve;eković & Mihailo Lj. Mihailović

University of Belgrade, Yugoslavia

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Lead(IV) Trifluoroacetate[1]

$Pb(OCOCF_3)_4$

[16656-82-9] · $C_8F_{12}O_8Pb$ · Lead(IV) Trifluoroacetate · (MW 659.13)

(functionalization of saturated hydrocarbons;[2] trifluoroacetoxylation, plumbation, and dimerization of substituted benzene derivatives;[3,4] oxidation of alkenic compounds[5])

Alternate Name: lead tetrakis(trifluoroacetate); LTTFA.

Physical Data: too hygroscopic for mp determination.

Solubility: reacts with aliphatic and aromatic hydrocarbons (such as heptane, benzene, toluene, etc.), but is stable and sol in trifluoroacetic acid (TFA), C_6F_6, CH_2Cl_2, and $MeNO_2$.

Form Supplied in: commercially available in the form of white crystals moistened with TFA. *Drying:* for some reactions, TFA must be completely removed; this is achieved by drying the reagent in vacuo (over KOH and P_2O_5) for several days.

Analysis of Reagent Purity: the oxidizing capability and purity of the reagent can be determined iodometrically.

Preparative Method: can be prepared in situ from ***Lead(IV) Acetate*** and ***Trifluoroacetic Acid***.

Handling, Storage, and Precautions: the solid reagent is very reactive and hygroscopic, and must be stored in the dark, in the absence of moisture, and below 10 °C.

Functionalization of Saturated Hydrocarbons.

The powerful oxidizing properties of lead tetrakis(trifluoroacetate) have been used for the introduction of functional groups on nonactivated carbon atoms,[1a] particularly of bridged hydrocarbons.[2,6] In these reactions, generally performed at rt, LTTFA is generated in situ from lead tetraacetate (LTA) and an excess of TFA in CH_2Cl_2 as solvent (eq 1).[2,6] The reactivity of the labile trifluoroacetoxy ester group permits alternative functionality to be introduced.[7] Thus by running the LTTFA oxidation of adamantane in the presence of acetonitrile, *N*-(1-adamantyl)acetamide is obtained in 85% yield.[6,7] Other nucleophiles such as CN^-, RS^-, Ar^-, and C^- can also be introduced on bridged carbon atoms in this way.[7] Only monosubstituted derivatives are obtained.[2]

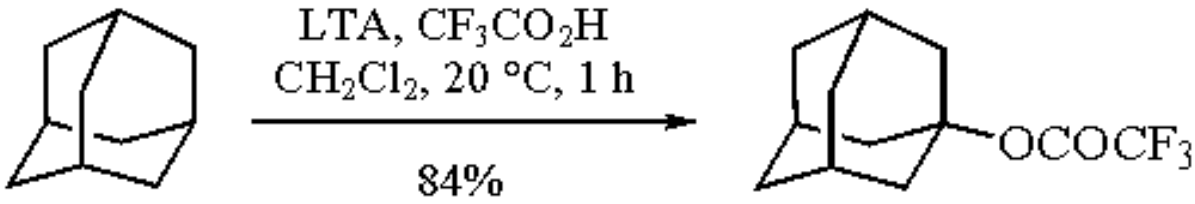

(1)

Trifluoroacetoxylation of Benzenoid Compounds.

The synthesis of *p*-substituted aryl trifluoroacetates can be conveniently achieved in yields up to 76% by reaction of substituted benzenes with LTTFA in TFA (eq 2).[4,8] Nitrobenzene fails to react after two weeks at rt, while anisole reacts very violently.[8] Aryllead tris(trifluoroacetates) as intermediates are also formed from the corresponding arylmercury(II) or arylthallium(III) trifluoroacetates and from aryltrimethylsilanes, upon reaction with LTTFA.[4,9,10] The aryltrifluoroacetate esters are usually hydrolyzed and isolated as the corresponding phenols.[3,4]

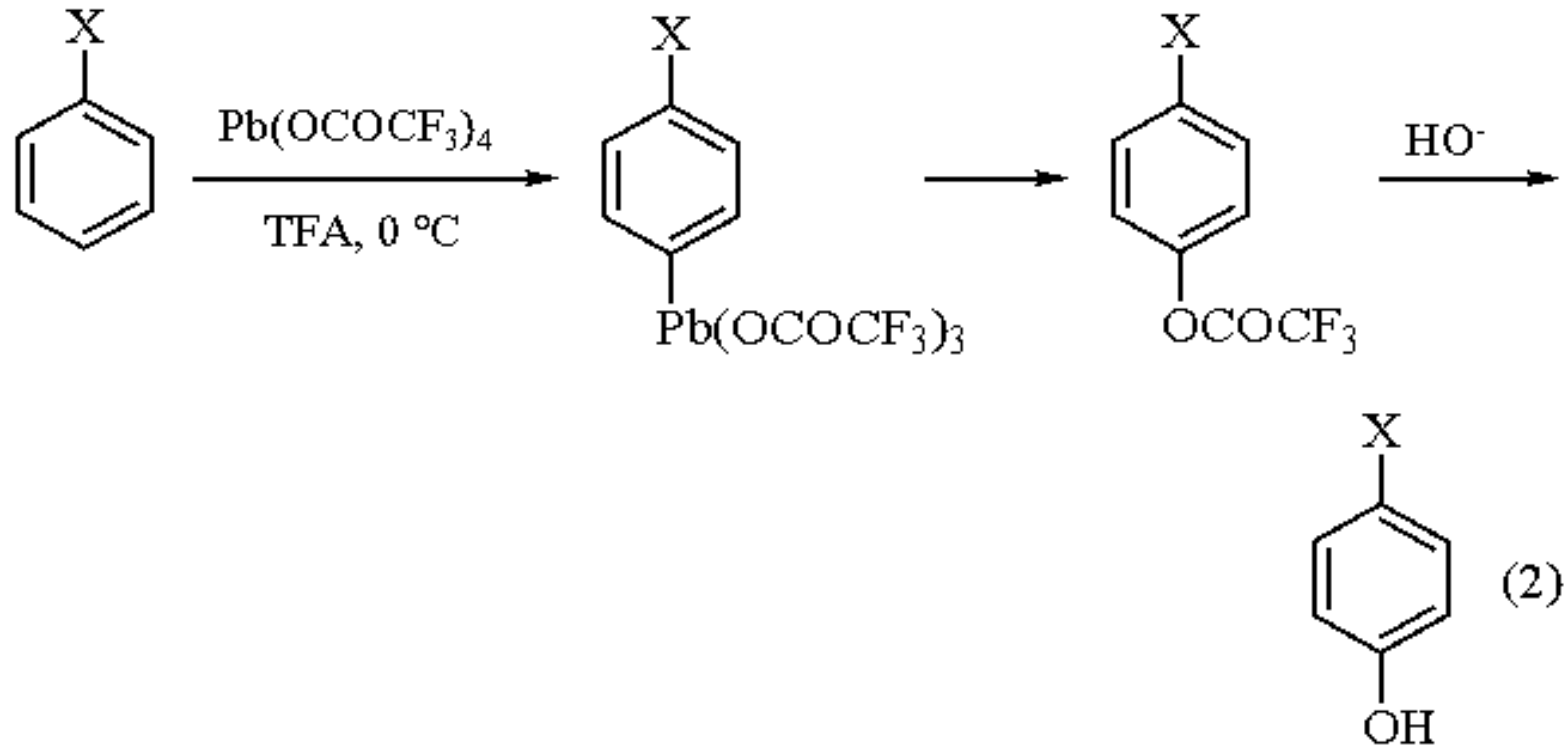

(2)

X = H, Me, Et, *i*-Pr, *t*-Bu, F, Cl, Br

41-76%

By oxidation of methyl substituted benzenes with LTTFA (LTA + TFA) in TFA and CH_2Cl_2 at low temperature (0 °C or below), coupling occurs producing biaryl and diarylmethane compounds (7-65%) (eq 3).[11]

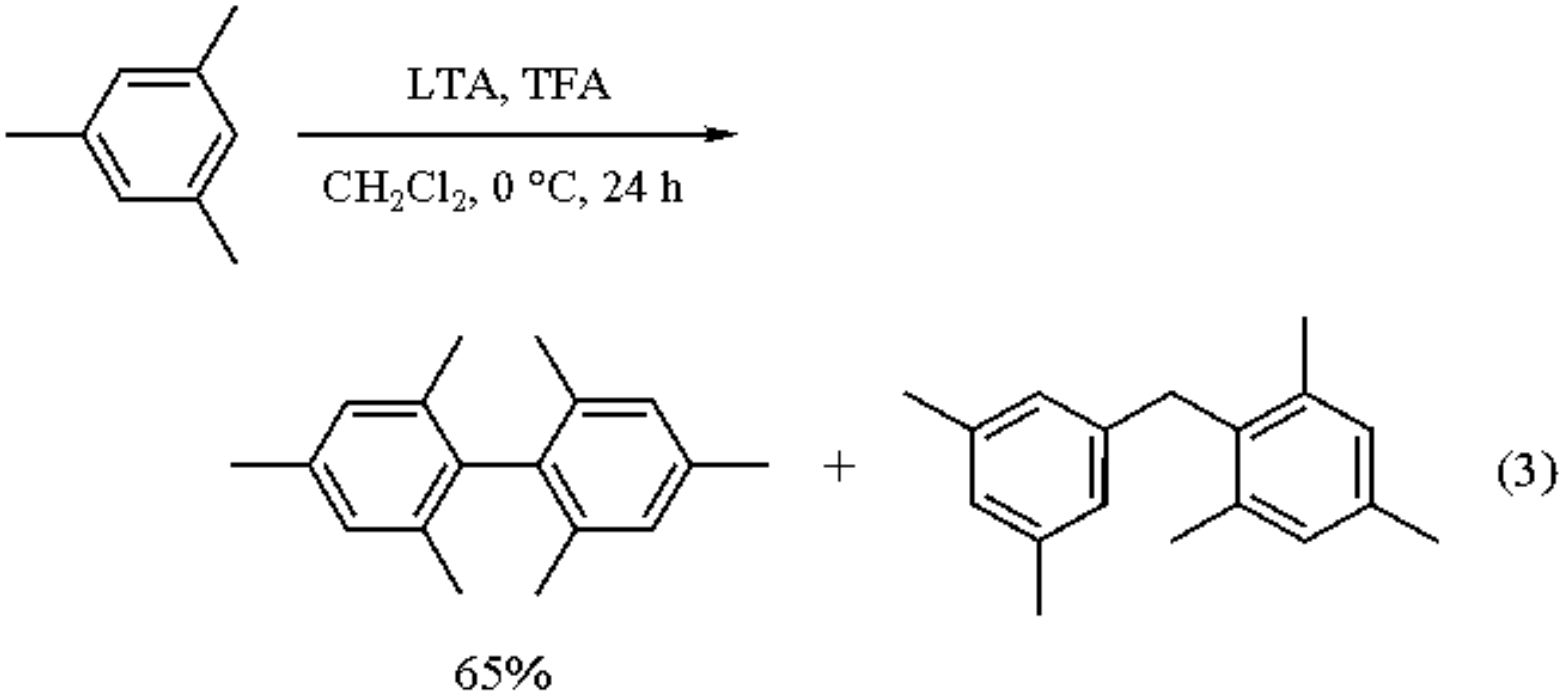

Oxidation of Alkenic Compounds.

LTTFA, as an electrophilic oxidizing agent, reacts readily with alkenic bonds. Thus styrene and substituted styrenes undergo oxidative rearrangement to give 1,1-bis(trifluoroacetoxy) derivatives, which are easily hydrolyzed to the corresponding carbonyl products (eq 4).[12,13]

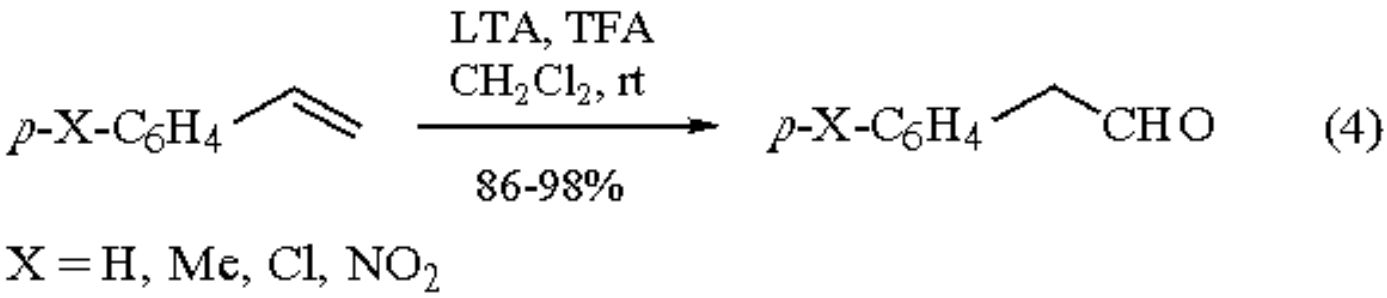

Conjugated dienes also react with LTTFA and undergo 1,4-addition, affording 1,4-bis(trifluoroacetate) esters (eq 5).[12]

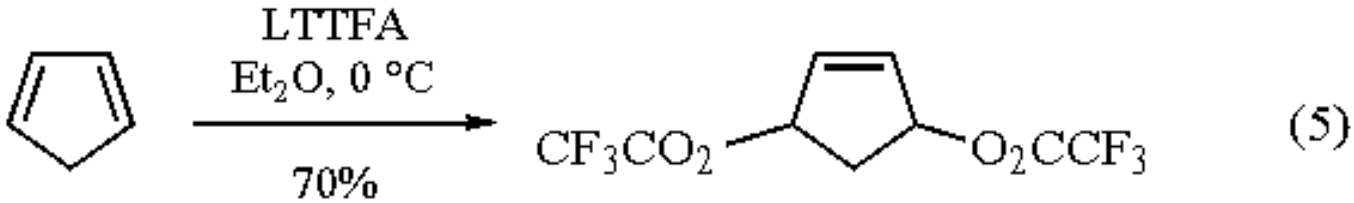

When treated with LTTFA, allylic hydroxy steroids are converted to epoxy trifluoroacetates (eq 6), whereas homoallylic steroid alcohols undergo C-C bond cleavage to give secosteroid compounds.[5]

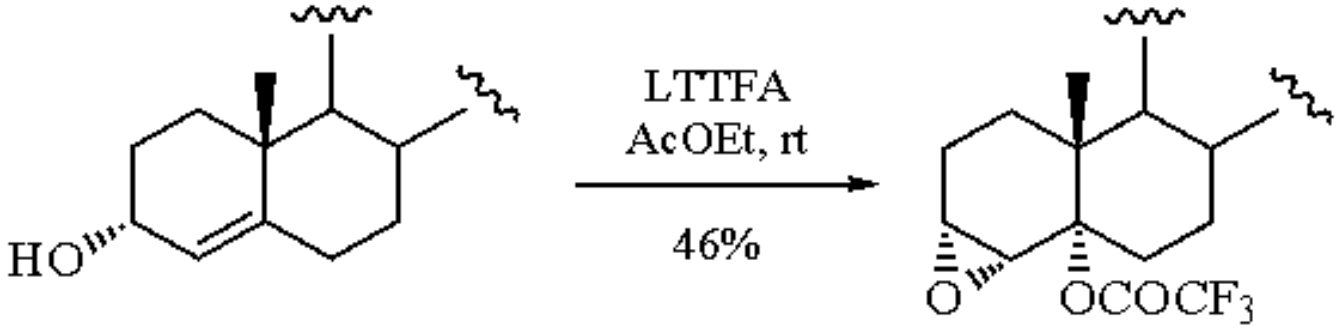

(6)

Hydroxysulfenylation of alkenes to 1,2-hydroxythio ethers, via the corresponding trifluoroacetoxy addition intermediates, is readily achieved by means of LTTFA (LTA + TFA) and diaryl disulfides in TFA/CH_2Cl_2, at low temperature (from 0 °C to -40 °C) (eq 7).[14]

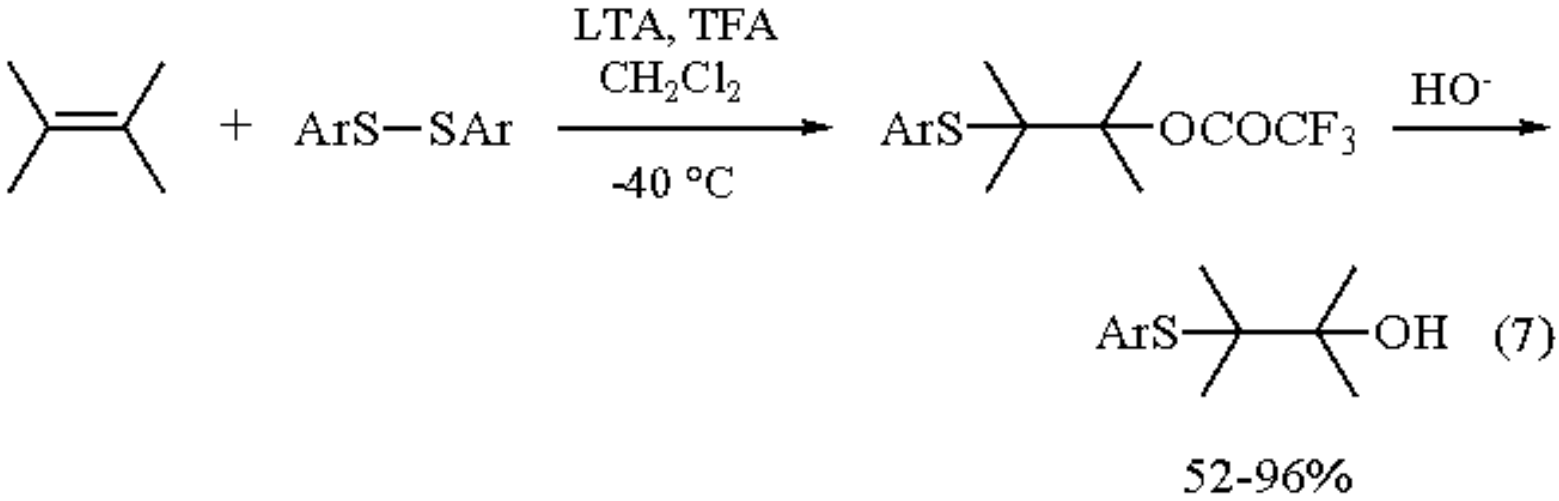

(7)

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t-Leucine *t*-Butyl Ester[1]

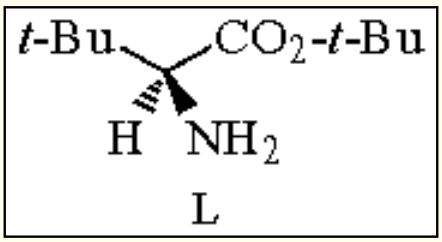

(D)

[61169-85-5] · $C_{10}H_{21}NO_2$ · *t*-Leucine *t*-Butyl Ester · (MW 187.32) (L)

[31556-74-8] (DL)

[99285-38-8]

(chiral auxiliary used in asymmetric alkylations,[1] 1,2-additions,[2] and 1,4-additions[3] of aldehyde and ketone derived Schiff bases)

Physical Data: D,[4a] [α]20D -56°; bp 90-91 °C/21 mmHg. L,[4a] [α]20D +51.7° (92.3% ee); bp 87-89 °C/18 mmHg.

Solubility: sol hexanes, benzene.

Preparative Methods: prepared by esterification of *t*-leucine with ***Isobutene*** and conc ***Sulfuric Acid*** (under pressure).[4] Typical yields are 62-64% and 12-14% of recovered amino acid. *t*-Leucine itself is commercially available in racemic and optically pure forms. It can also be prepared by oxidation of pinacolone to trimethylpyruvic acid, followed by oxime formation and zinc reduction. Resolution of the *N*-formyl derivative of *t*-leucine has been carried out using brucine.[4a]

Handling, Storage, and Precautions: none.

Asymmetric Alkylations.

The use of nitrogen derivatives of carbonyl compounds (imines, imides, amides, sultams, oxazolines) is often the most efficient procedure for achieving α-alkylations.[1] Chiral auxiliaries bearing heteroatoms in a 1,2-relationship appear to work best, as they have chelation sites for the metal cation. High levels of asymmetric induction can thus be achieved due to the system rigidity. Cyclic ketones have been alkylated via the lithiated enamine formed from L-*t*-leucine *t*-butyl ester (eq 1).[5] High enantiomeric excesses and predictability of absolute configuration make this

method attractive.

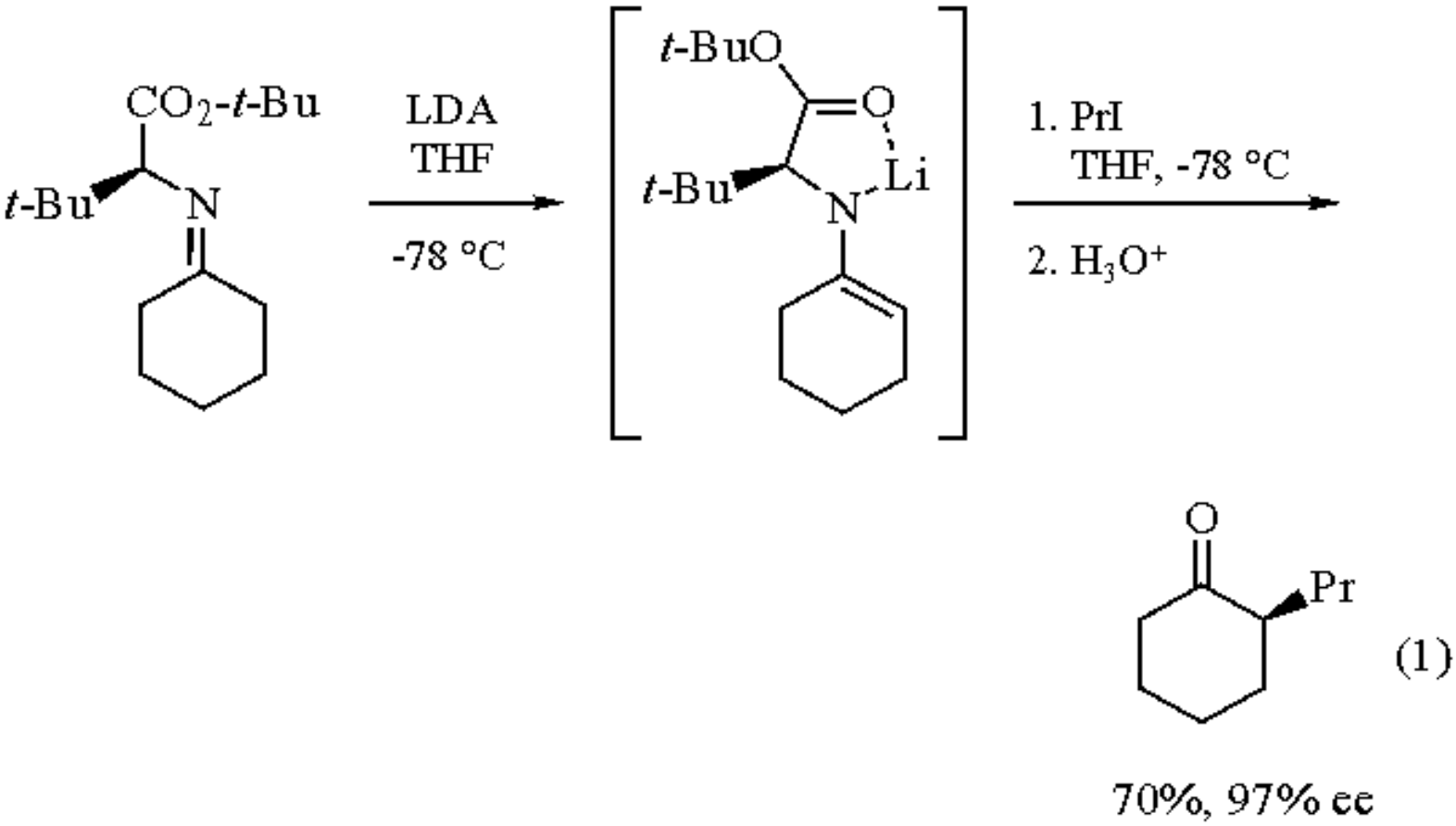

1,2-Additions.

The imine prepared from L-*t*-leucine *t*-butyl ester and benzaldehyde has been used to prepare D-phenylglycine in 96.5% ee via a diastereoselective hydrocyanation.[2] A rigid five-membered ring transition state involving hydrogen bonding between nitrogen and carbonyl oxygen has been proposed. Attack of cyanide ion from the opposite side of the bulky *t*-butyl group accounts for the stereochemical outcome (eq 2).

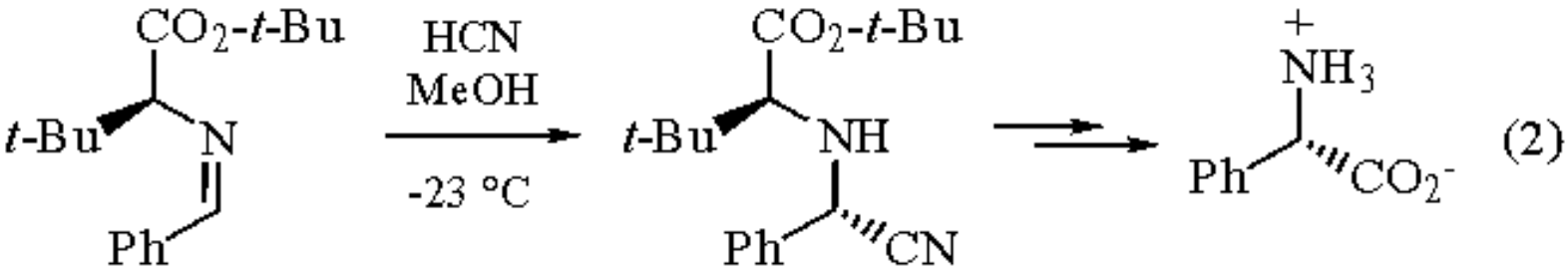

1,4-Additions.

Asymmetric Michael additions[1] of Grignard reagents can be performed on α,β-unsaturated aldimines[3a] derived from either enantiomer of *t*-leucine *t*-butyl ester (eq 3).

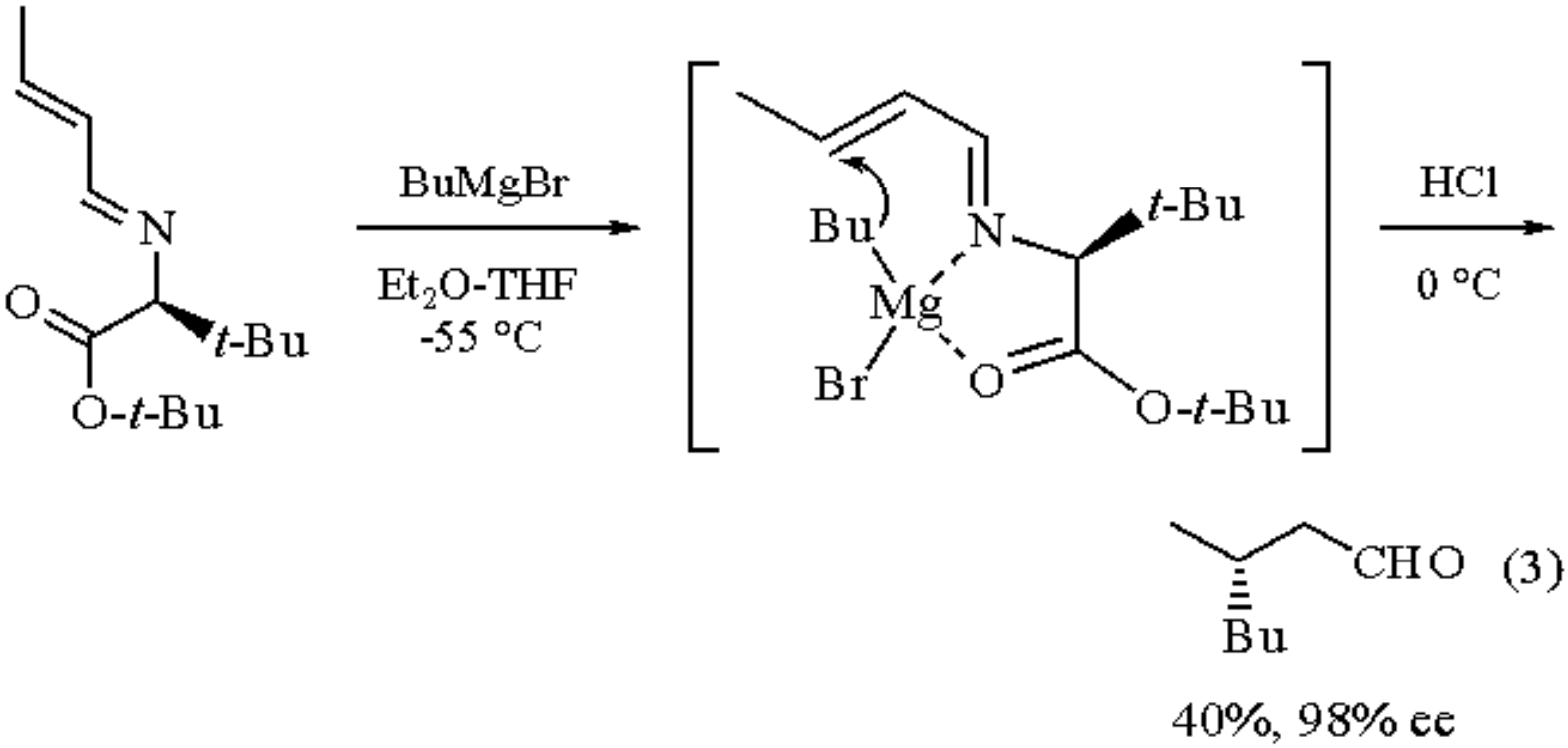

Similarly, malonate anions[3b,c] add to aldimines with reasonably high enantioselectivity. The new asymmetric center, however, has the opposite absolute configuration to that shown in eq 3. A chelated aldimine of (*E*) geometry is the proposed intermediate for this reversal of stereoselection (eq 4).

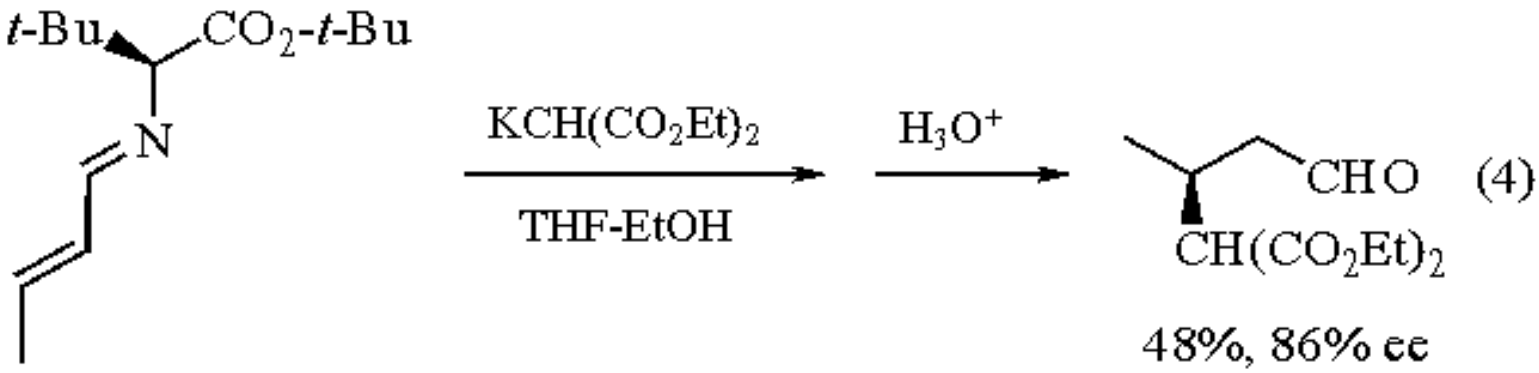

Cyclic aldimines can also be used, and subsequent alkylation of the magnesioenamine intermediate achieved with good to excellent diastereoselectivity.[3d,e,f] *Cis* or *trans* products can be obtained, depending on the procedure chosen (eq 5).

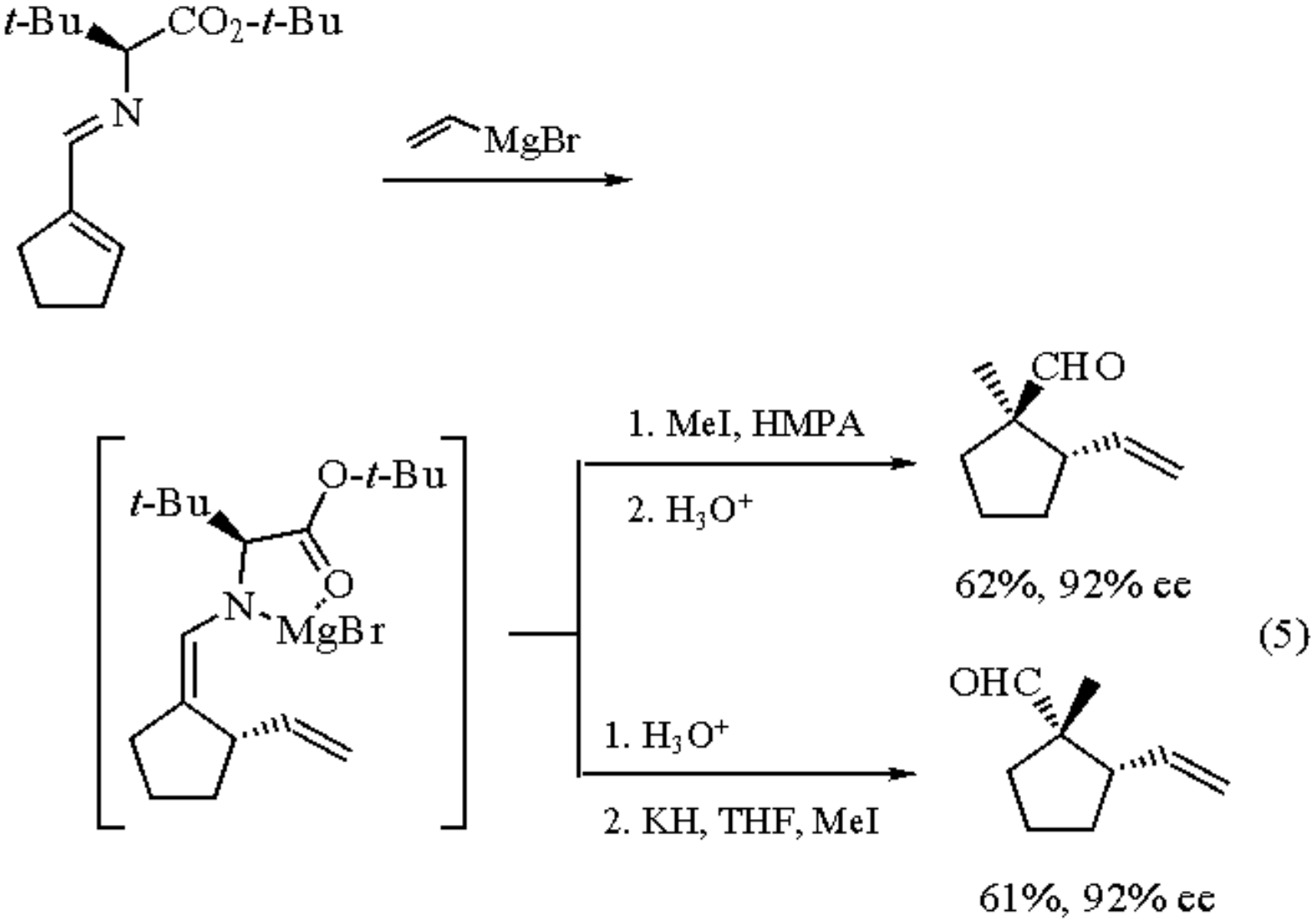

A few natural product syntheses feature the use of both acyclic[6] and cyclic[7,8] aldimines of either enantiomer of *t*-leucine *t*-butyl ester. Kinetic resolution of racemic aldehydes has also been achieved using L-*t*-leucine *t*-butyl ester.[8]

For the three types of reactions presented above, *t*-leucine *t*-butyl ester has been shown to be the most efficient amino acid derivative. It is often mentioned that valine *t*-butyl ester affords lower enantioselectivities. Work-up procedures allow recovery of reusable optically pure auxiliary.

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Lipases[1]

[9001-62-1] · (MW 30000-100000)

(catalyst for asymmetric transformations of chiral or prochiral alcohols or acids by hydrolysis or esterification reactions[1])

Solubility: powder sol aqueous solutions; suspension in organic media.

Form Supplied in: usually a white or brownish powder, but also immobilized on an appropriate support. Lipases from microbial sources are virtually homogeneous in terms of hydrolytic activity, while mammalian and plant lipase preparations contain several interfering enzymes including proteases and esterases.

Analysis of Reagent Purity: assay by titrimetry.[2]

Handling, Storage, and Precautions: must be stored in a refrigerator at 0-5 °C. Avoid breathing or inhaling dust. Avoid too vigorous stirring.

Lipase General Aspects.

Enzymes are now widely recognized as practical catalysts for asymmetric synthesis.[1b,c] Lipases are among the most widely applied and versatile biocatalysts in organic synthesis as can be witnessed by a number of recent reviews.[1] There are several reasons for this. They are readily available, do not require cofactors, are inexpensive and highly stable, exhibit broad substrate specificity, do not require water-soluble substrates, mechanistically are relatively well understood and, finally, are splendidly suited to retain a high degree of activity in organic media.

More than 20 lipases are now commercially available, either free or immobilized, from animal, plant, and microbial sources.[2] Amongst the lipases, the pig pancreatic lipase (PPL), the yeast lipase from *Candida cylindracea* (*rugosa*) (CCL), and the bacteria lipases from *Pseudomonas fluorescens* (*cepecia*) (PFL) and other unclassified *Pseudomonas* species (PSL) have been most widely used. The experimental methods are very straightforward and little different in their execution from conventional chemical reactions. Hydrolysis reactions are conducted on the soluble lipase in buffered aqueous solutions, commonly in the presence of an organic cosolvent. In organic media the enzyme is added as a powder or in an immobilized form and the resulting suspension stirred or (better) shaken at approximately 40 °C. The enzyme is removed by filtration.

Since their action toward substrates in terms of chemo-, regio-, and enantioselectivity varies considerably, it is important to have a large selection of lipases to find the right enzyme for a specific reaction by traditional biocatalyst screening. Alternative strategies for improving enantioselectivity of the already existing commercial lipases have been developed,[1a,3] including product recycling,[4] solvent screening,[5] water content control,[6] and immobilization. In addition to this, several active site models have been proposed to predict the enantiopreference of certain lipases.[1a,7]

Lipases have been used in three main types of asymmetric transformations: kinetic resolution of racemic carboxylic acids or alcohols, enantioselective group differentiations of *meso* dicarboxylic acids or diols, and enantiotopic group differentiation of prochiral dicarboxylic acid and diol derivatives. Hydrolysis has been the most widely used technique, but complementary esterification or transesterification procedures are increasingly coming into use. Lipases are used most frequently in transformations involving chiral alcohols rather than acids, unlike the pig liver esterase (PLE),[1a,b,c] which is most frequently employed on esters of chiral carboxylic acids. Lipases are also gaining increasing importance in solving problems of regioselectivity of various polyol and carbohydrate compounds.[1c,e,f,8] They have found application in stereoselective transformations involving lactonization and oligomerization of hydroxy acids and esters.[1e,f] Finally, a minor but useful advantage of the lipases is their mildness, which is particularly important in transformations involving labile compounds.[1a]

The range of nucleophiles that lipases accept is not confined to water or alcohols. There are numerous examples of amines,[9] hydrazine,[10] phenols,[11] and hydrogen peroxide.[12] Proteases have frequently been used in biocatalytic transformations involving ester hydrolysis and esterification reactions and their different stereoselection often provides a useful complement to the lipases.[1a,c,f]

Kinetic resolution of racemic compounds is by far the most common transformation catalyzed by lipases, in which the enzyme discriminates between the two enantiomeric constituents of a racemic mixture. It is important to note that the maximum yield of a kinetic resolution is restricted to 50% for each enantiomer based on the starting material. The prochiral route and transformations involving *meso* compounds, the *meso*-trick, have the advantage of potentially obtaining a 100% yield of pure enantiomer. A theoretical quantitative analysis of the kinetics involved in the biocatalytic processes described above has been developed.[1a,d,e] The enantiomeric ratio (E), an index of enantioselectivity, can be calculated from the extent of conversion and the corresponding enantiomeric excess (ee) values of either the product or the remaining substrate. The results reveal that for an irreversible process, such as hydrolysis, the optimum in both chemical and optical yield for the faster hydrolyzed enantiomer is to be expected near 40% conversion, and for the remaining slower hydrolyzed enantiomer around 60% conversion. For a high enantiomeric ratio (>100), high enantioselectivity is expected for both enantiomers at 50% conversion.

Under almost anhydrous conditions in organic medium,[1e,f] lipases can be used in the reverse mode for direct ester synthesis from carboxylic acids and alcohols, as well as transesterifications (acyl transfer reactions) which can be divided into alcoholysis (ester and alcohol), acidolysis (ester and acid), and interesterification (ester-ester interchange). The direct esterification and alcoholysis in particular have been most frequently used in asymmetric transformations involving lipases. The parameters that influence enzymatic catalysis in organic solvents have been intensively studied and discussed.[1a,e,f]

Besides ester synthesis being favored over hydrolysis, there are several major advantages of undertaking biocatalytic reactions in anhydrous media: increased solubility of nonpolar substrates, ease of product and enzyme recovery, enhanced thermal stability of enzymes and substrate specificity, and enantioselectivity regulation by the solvent. The main disadvantages include lower catalytic activity in organic media and reversibility, which limits the yield and works against the kinetic resolution, lowering the enantioselectivity of such processes. There are several strategies available to overcome these problems.[1a,e,f] Enol esters, such as vinyl or isopropenyl esters, are by far the most commonly used acyl transfer agents to ensure irreversibility by tautomerization of the enol leaving group.[13,14] Anhydrides,[15] *S*-phenyl thioacetate,[16] acyloxypyridines,[17] and oximes[18] have also been applied in a similar manner as acyl donors. Active trifluoro-[19] and trichloroethyl[20] esters have similarly been used to suppress the reversibility by speeding the acyl-enzyme formation and generating the weakly nucleophilic trifluoro- or trichloroethanol. Primary alcohols have also been used as acyl acceptors in transesterifications (deacylations) involving esters of more bulky and less nucleophilic secondary alcohols.[21]

Kinetic Resolution by Hydrolysis.

Until very recently, kinetic resolution of racemic alcohols as ester derivatives was by far the most common type of asymmetric transformations involving lipases.[1a] There are number of examples involving acyclic secondary alcohols, such as the glyceraldehyde derivative in eq 1[22] and various related alkyl- and aryloxy substituted chloride and tosylate glycerol derivatives.[22,23]

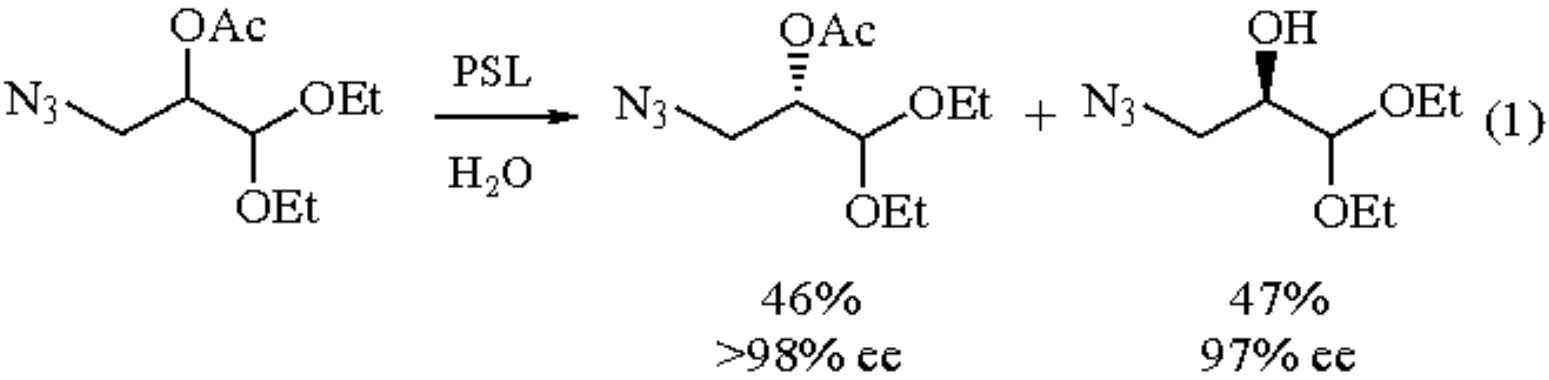

A wide variety of other alcohol substrates has been resolved,[1a] including aryl substituted secondary alcohols,[20,24] α-alkyl-β-hydroxy esters,[25] β-hydroxy nitriles,[26] and fluoroorganic compounds.[27] Active chloroacetate esters are commonly used to speed up the hydrolysis reactions, as exemplified in eq 2.[28] Primary acyclic alcohols possessing a stereogenic center that have been resolved include 2,3-epoxy alcohols,[29,30] 2-amino alcohols,[31] and crown ethers.[32]

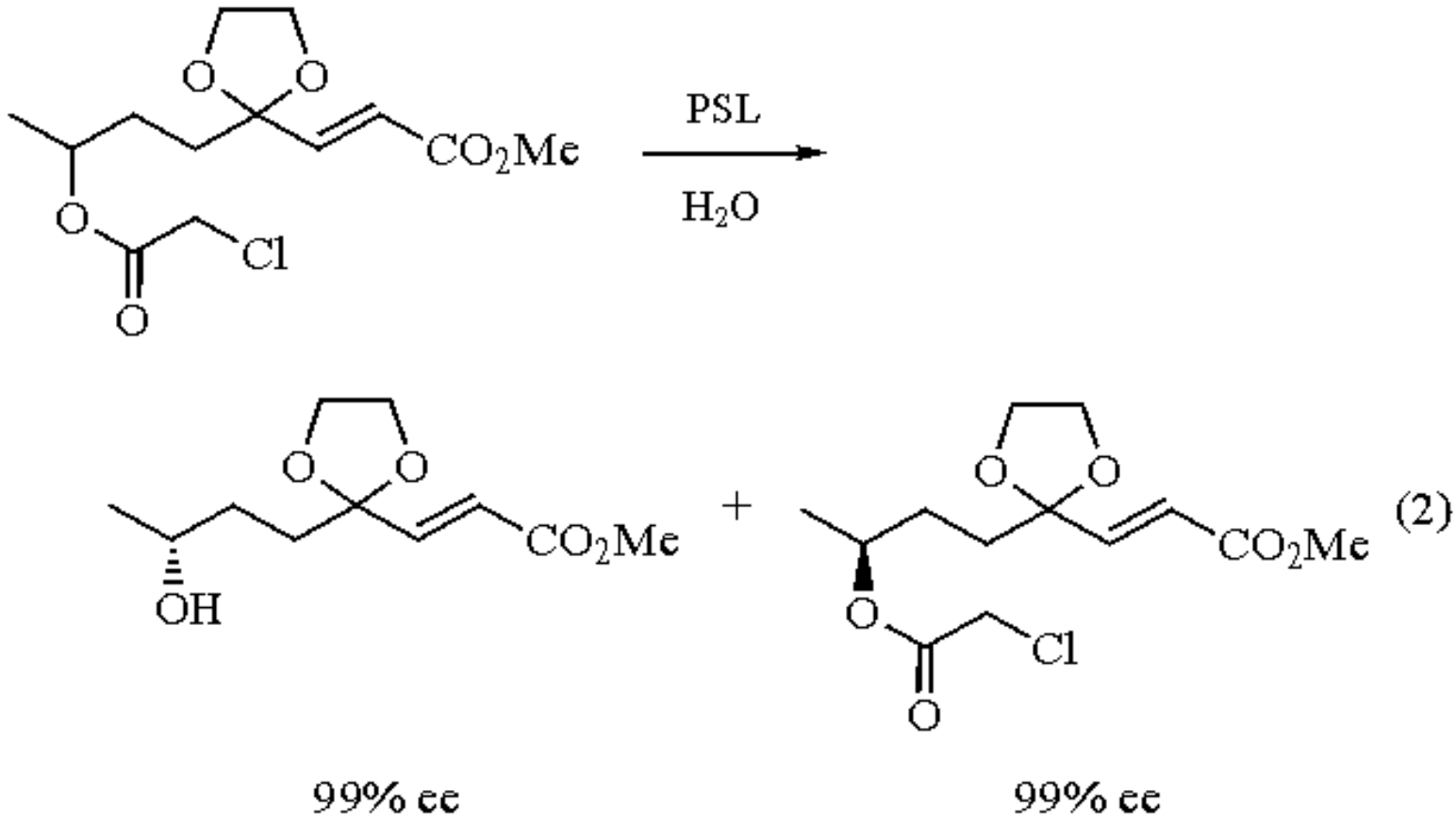

Lipase-catalyzed asymmetric hydrolysis has also been conducted on numerous monocyclic, variously substituted five-, six-, and seven-membered cycloalkane and cycloalkene secondary alcohols and diols.[1a] More recent reports include *cis*-4-acetoxyflavan,[33] substituted cyclopentenones,[34] and the 1,2-bis(hydroxymethyl)cyclobutanol derivative exemplified in eq 3.[35]

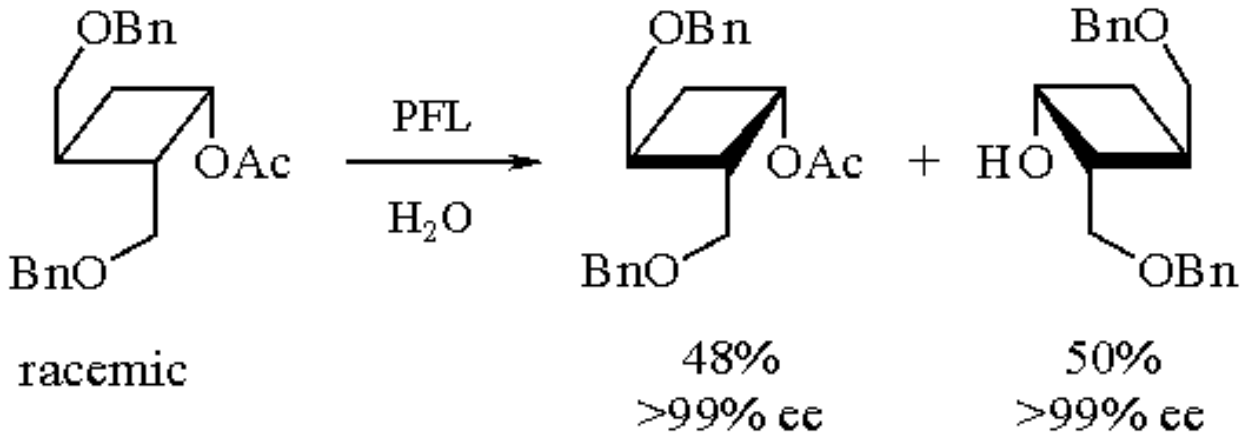

(3)

Various bicyclic racemic alcohols have been resolved by asymmetric hydrolysis of their corresponding esters. Generally, the *exo* isomers appear to be far inferior substrates compared with the *endo* substrates.[1a] Eq 4 illustrates the resolution of a bicyclic derivative of the Corey lactone type.[36]

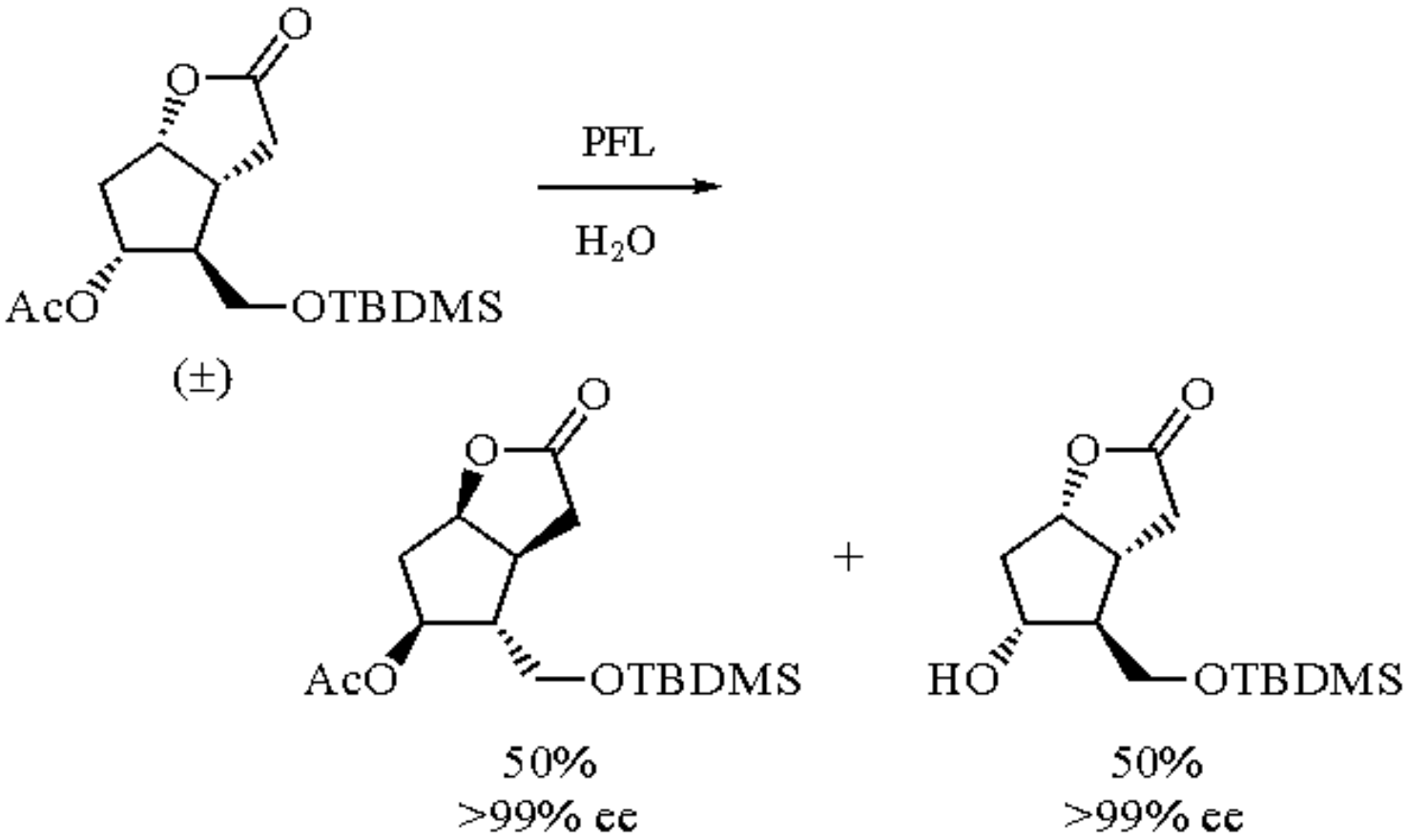

(4)

There are also several reports on the enantioselective hydrolysis of bicyclic secondary alcohols possessing the bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane framework.[37] Again, with this type of substrate the lipases appear to exhibit strong preference for the *endo* isomers with the (*R*)-configured esters preferentially hydrolyzed.

Various chiral acids have also been resolved by lipase-catalyzed asymmetric hydrolysis.[1a] The reports include variously α-substituted acids[3,38] as well as the tertiary α-benzyloxy ester exemplified in eq 5.[39] Remethylation and repeated hydrolysis afforded the (*S*)-enantiomer in eq 5 optically pure. More recent examples include esters of glycidic acid,[40] β-aryl-β-hydroxy acid,[41] and sulfinyl alkanoates.[42]

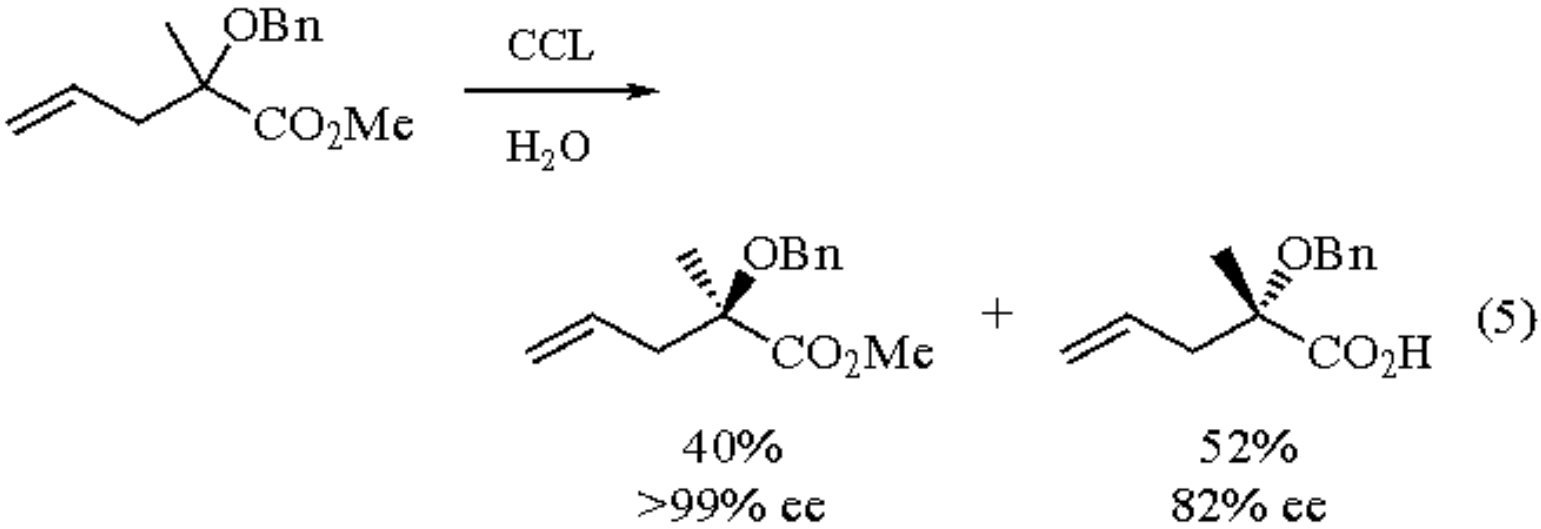

Kinetic Resolution by Transesterification.

Asymmetric transformation involving acylation of chiral alcohols is by far the most common example of kinetic resolution by lipase-catalyzed transesterification, most commonly with irreversible vinyl esters.[1a,15] This field is now becoming the most widely applied technique involving lipases. Recent reports of the numerous secondary alcohol substrates include various monocyclic (eq 6)[43] and acyclic[44] compounds, cyanohydrins,[45] sulfones,[46] and glycals,[47] to name a few.

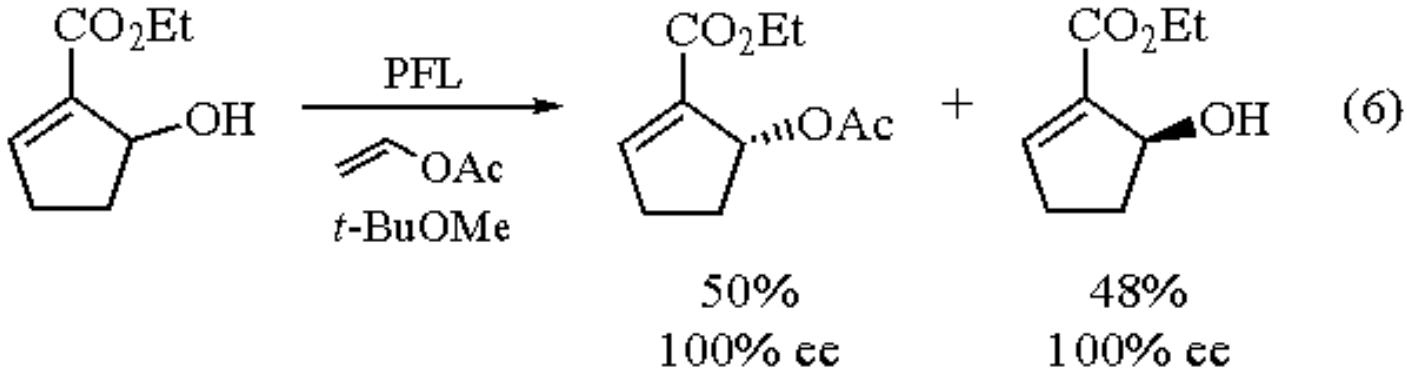

There are also several reports of enantioselective transesterification involving primary alcohols possessing stereogenic centers by similar acylation procedures, such as 2,3-epoxy alcohols (eq 7),[48] norbornene-derived iodolactones,[49] and 1,3-propanediols.[50]

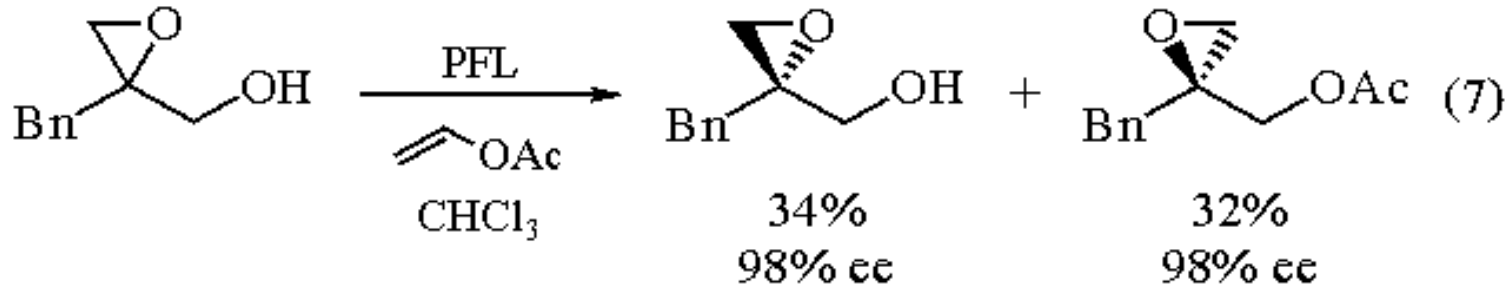

Enantioselective lipase-catalyzed transesterification involving deacylation of esters of racemic primary or secondary alcohols with primary alcohols, most frequently *n*-butanol, serving as an acyl acceptor, is fairly common.[1a] Recent examples include esters of amino alcohols,[51] isoserine,[52] chlorohydrins,[53] and various tosyloxybutanoate esters (eq 8).[54]

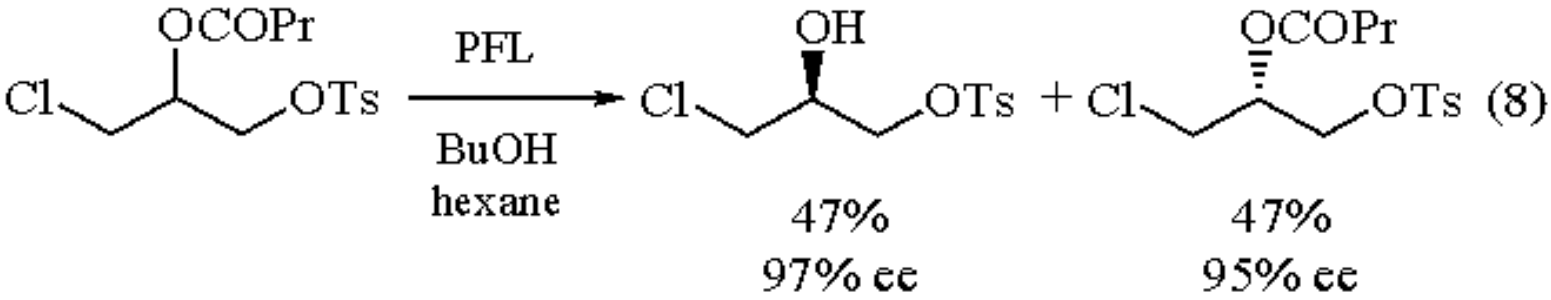

Kinetic resolution involving acidolysis of esters of racemic secondary alcohols and acids or transesterification of chiral acids does not have many examples in the literature.[1a]

Kinetic Resolution by Direct Esterification.

This is the least common strategy for kinetic resolution and is most commonly executed on racemic alcohols with carboxylic acids in organic solvents.[1a] Reports include several alicyclic secondary alcohols such as menthol[55] and various aliphatic secondary alcohols.[56] Kinetic resolution of a variety of racemic saturated, unsaturated, and α-substituted carboxylic acids has also been effected by direct esterification with various alcohols.[20,57]

In addition to this, there are several reports of asymmetric esterification of racemic alcohols with anhydrides as acyl donors. Examples include various primary and secondary alcohols,[15] bicyclic secondary alcohols of the norbornane type,[58] amino alcohols,[59] and ferrocenes.[60] This is exemplified in eq 9 for 1-phenylethanol.[15]

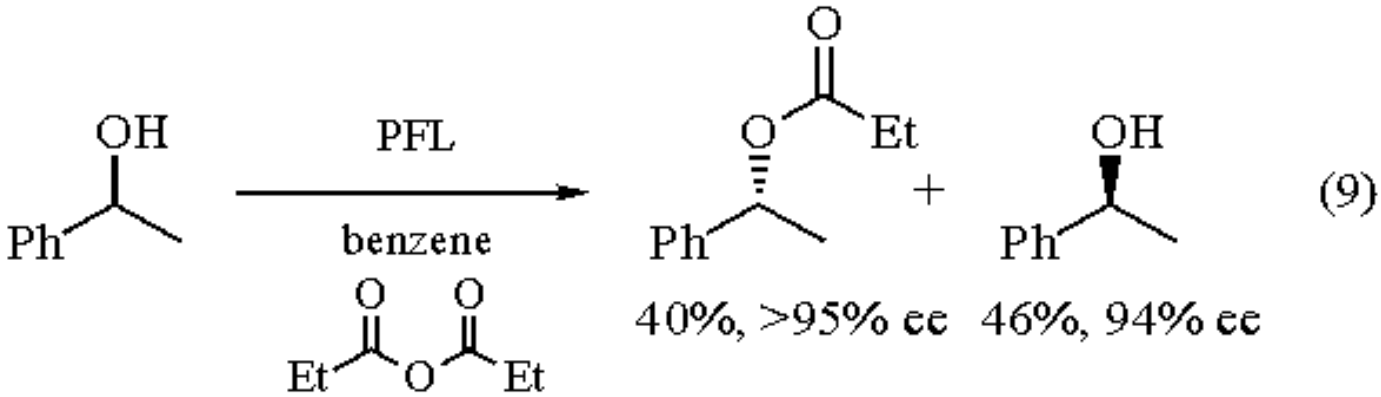

Prochiral Compounds.

The enantiodifferentiation of prochiral compounds by lipase-catalyzed hydrolysis and transesterification reactions is fairly common, with prochiral 1,3-diols most frequently employed as substrates.[1a] Recent reports of asymmetric hydrolysis include diesters of 2-substituted 1,3-propanediols[61] and 2-*O*-protected glycerol derivatives.[8] The asymmetric transesterification of prochiral diols such as 2-*O*-benzylglycerol[8,13a] and various other 2-substituted 1,3-propanediol derivatives[13b,62] is also fairly common, most frequently with ***Vinyl Acetate*** as an irreversible acyl transfer agent.

There are also recent reports of the lipase-catalyzed enantioselective hydrolysis of prochiral diacid derivatives such as 2-substituted malonates,[63] barbiturates,[64] and highly substituted, sterically hindered 1,4-dihydropyridine derivatives using acyloxymethyl groups to enhance the reaction rate.[65] An example of a prochiral diester hydrolysis is illustrated in eq 10.[66]

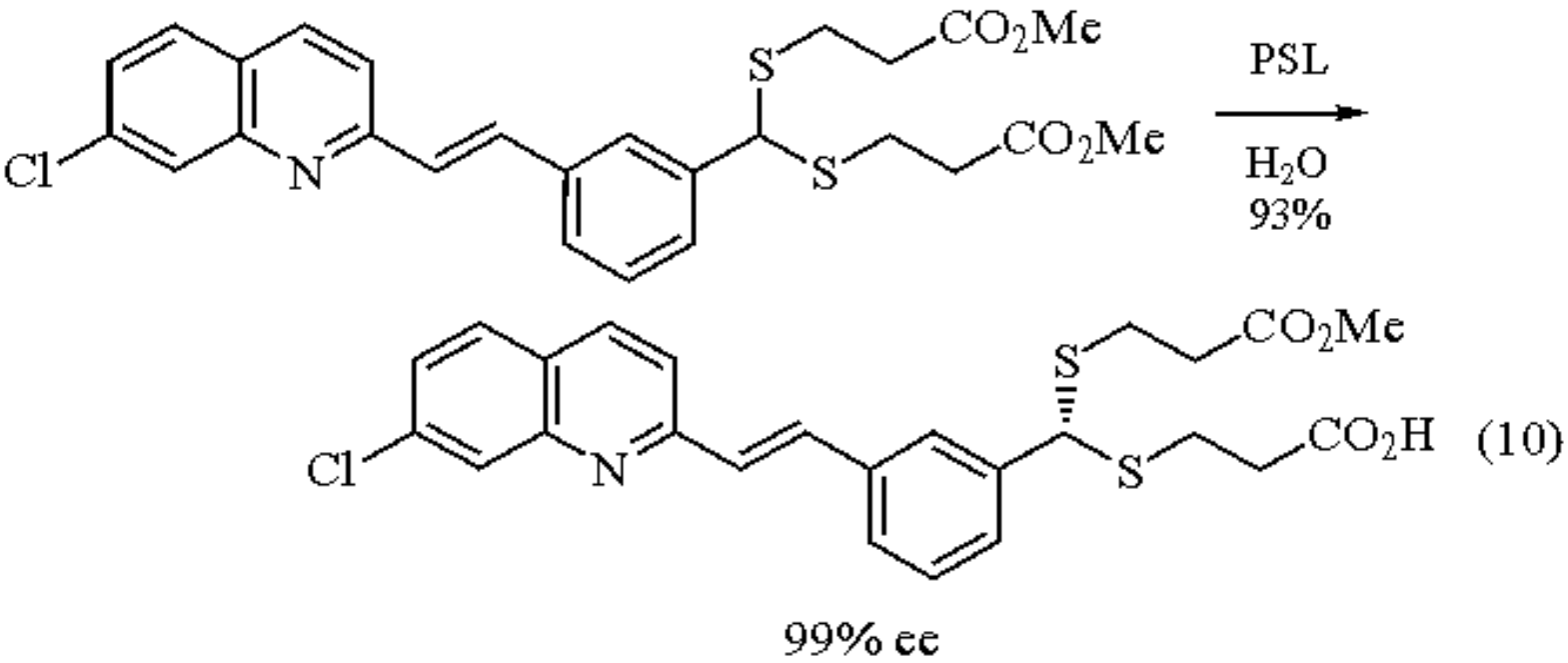

(10)

Meso Compounds.

Although pig liver esterase is by far the most suitable enzyme for asymmetric transformations involving *meso* compounds, especially diacids, there are several reports on the lipase-catalyzed hydrolysis and transesterification reactions of cyclic diol derivatives.[1a] The former includes variously substituted cycloalkene diacetates, cyclohexylidene protected erythritol diacetate,[67] piperidine derivatives,[68] and the *exo*-acetonide in eq 11.[69] Complementary results are clearly demonstrated in eqs 11 and 12 for the hydrolysis and esterification processes.

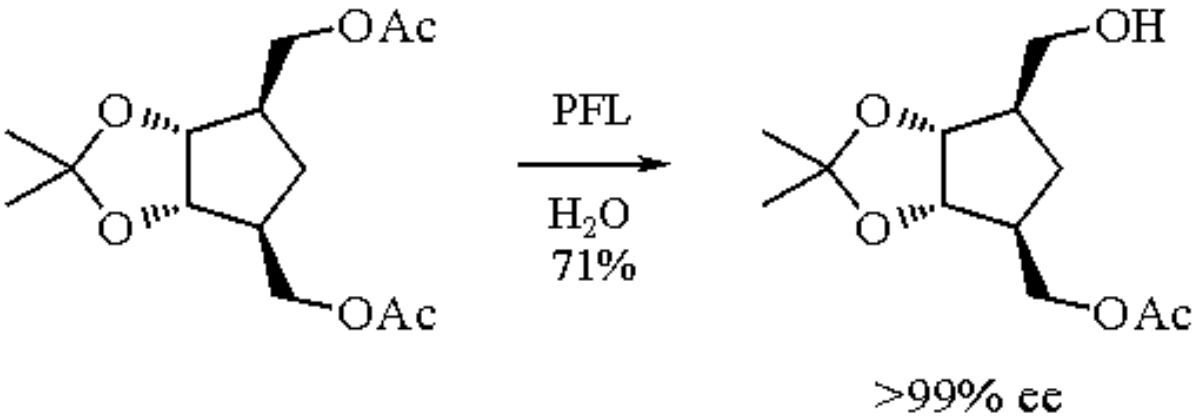

(11)

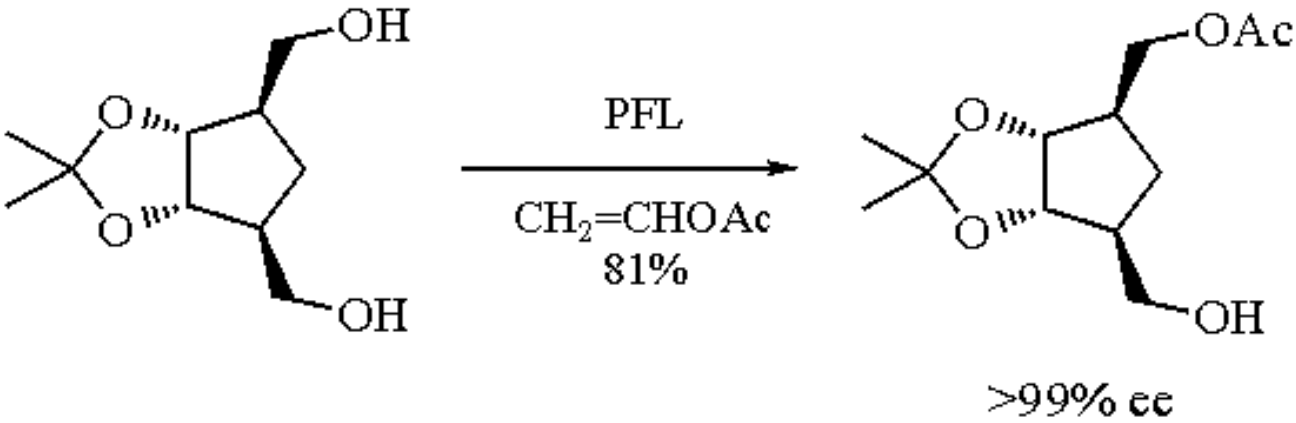

(12)

The asymmetric transesterification of cyclic *meso*-diols, usually with vinyl acetate as an irreversible acyl transfer agent, includes monocyclic cycloalkene diol derivatives,[70] bicyclic diols,[71] such as the *exo*-acetonide in eq 12,[69] bicyclic diols of the norbornyl type,[72] and organometallic 1,2-bis(hydroxymethyl)ferrocene possessing planar chirality.[73]

Regioselective Biotransformations with Lipases.

Lipases are gaining increasing importance in solving problems of regioselectivity of various polyol and carbohydrate compounds.[1a,c,e,f,8] A variety of diols or the corresponding acetates as well as polyhydric phenol acetates[74] have been acylated or deacylated in a highly regioselective manner in high yields by lipase-catalyzed transesterification reactions. Regioselective direct esterification of aliphatic 1,2-diols[75] and inositol derivatives[76] using anhydrides as acylating agents has recently been reported. Primary hydroxyl groups are exclusively transformed, as would be anticipated on steric grounds. One example of a highly regioselective and at the same time highly enantioselective hydrolysis of a racemic diester is demonstrated in eq 13.[77]

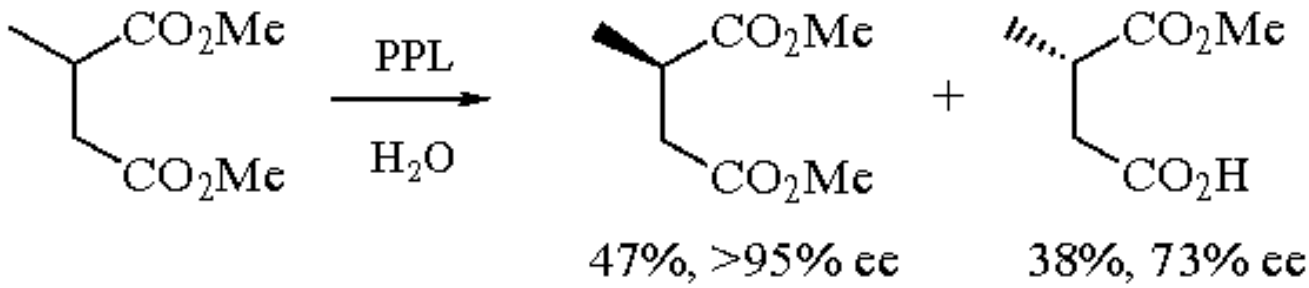

(13)

There are also several reports on highly regioselective transesterification of various steroid derivatives, one example

being displayed in eq 14 in which butyration occurred exclusively at the 3β-hydroxyl group by *Chromobacterium viscosum* lipase (CVL).[78] Opposite regioselectivity toward the 17β-hydroxyl group was observed with subtilisin protease.[78]

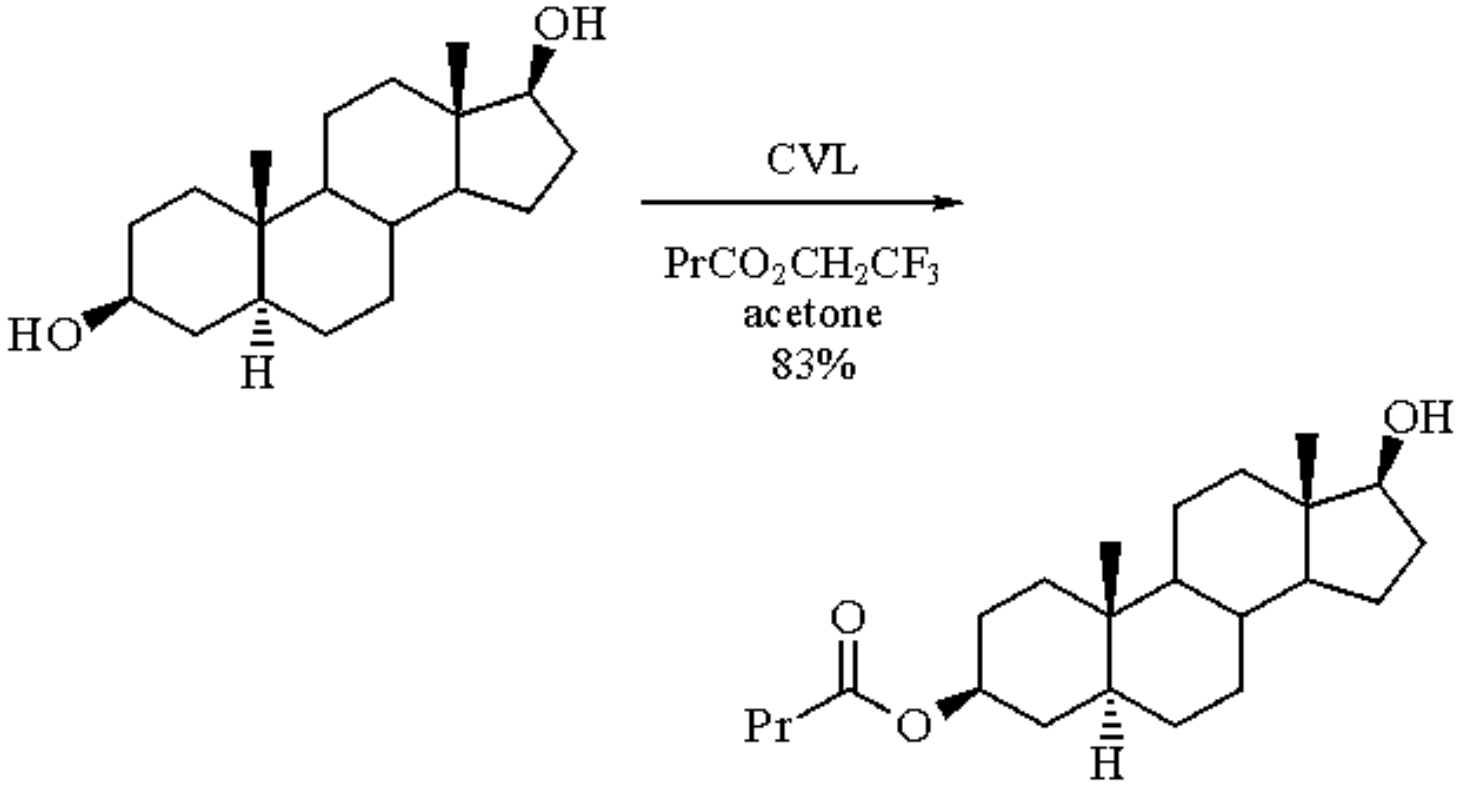

(14)

There are numerous examples of highly regioselective lipase-catalyzed hydrolysis and acylation/deacylation processes involving monosaccharide and carbohydrate derivatives.[1a,f,8] Usually, the biotransformation processes occur preferentially and in many cases exclusively on the primary hydroxyl group (eq 15),[79] but highly regioselective transformations have also been described on secondary alcoholic groups for various carbohydrate derivatives possessing an acyl or alkyl protection on the primary hydroxyl moiety. Recent reports include highly regioselective acetylation of pyranosidic and furanosidic monosaccharide derivatives[80] and alkoxycarbonylation of nucleosides with oxime carbonates.[18]

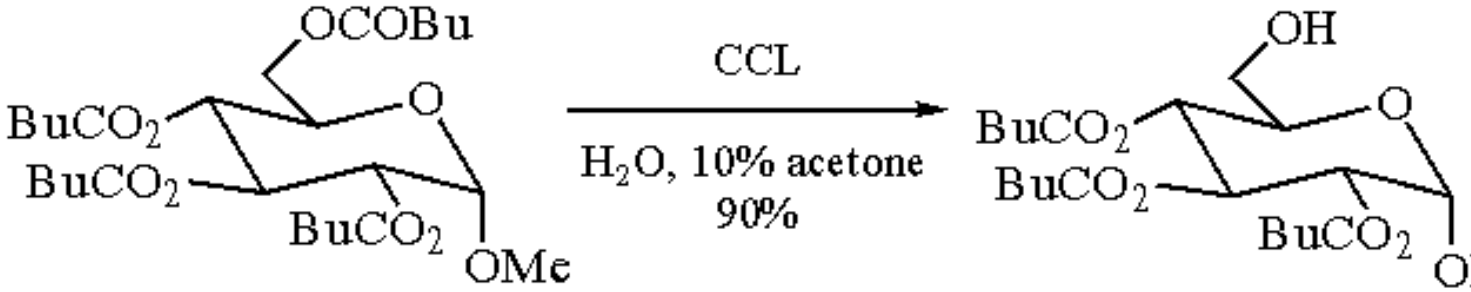

(15)

Lactonization and Polycondensation.

The lipase-catalyzed intramolecular transesterification of a range of o-hydroxy esters has been investigated extensively[1a,e,f] and was observed to be very dependent on the chain length of the substrate (eq 16).

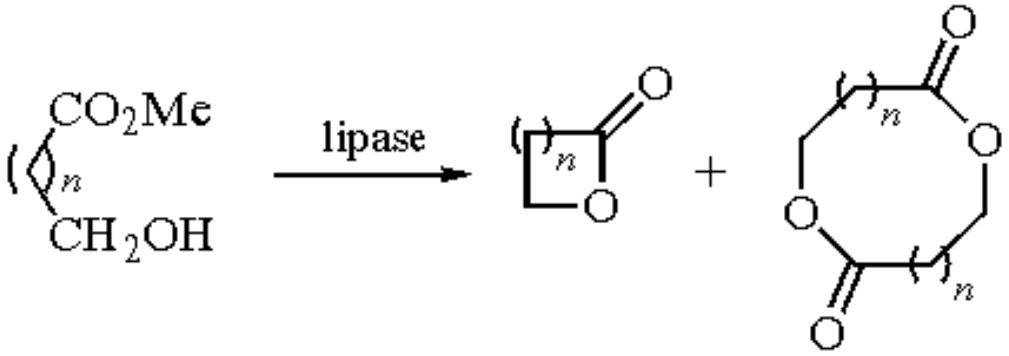

(16)

For longer-chain hydroxy esters (n = 13, 14) the corresponding macrolide was accomplished in high yield with very little diolide formed (diolide increased considerably with lower n). With medium-sized hydroxy esters the product profile became considerably more complex, consisting of a complex mixture of di-, tri-, tetra-, and pentalactones.[28,81] Shorter-chain unsubstituted β-, δ-, and ε-hydroxy esters almost exclusively underwent intermolecular transesterification to afford the corresponding oligomers. δ-Substituted δ-hydroxy esters[82] and γ-hydroxy esters[83] underwent lactonization with a high degree of enantioselectivity.

Prochiral γ-hydroxy diesters underwent enantioselective lactonization with PPL to afford the (S)-lactone in a highly enantioselective fashion (eq 17).[83a] Formation of macrocyclic lactones by the condensation of diacids or diesters with diols, leading to mono- and dilactones,[84] linear oligomeric esters, or high molecular weight optically active polymers,[85] depending upon type of substrates as well as reaction conditions, has also been described.

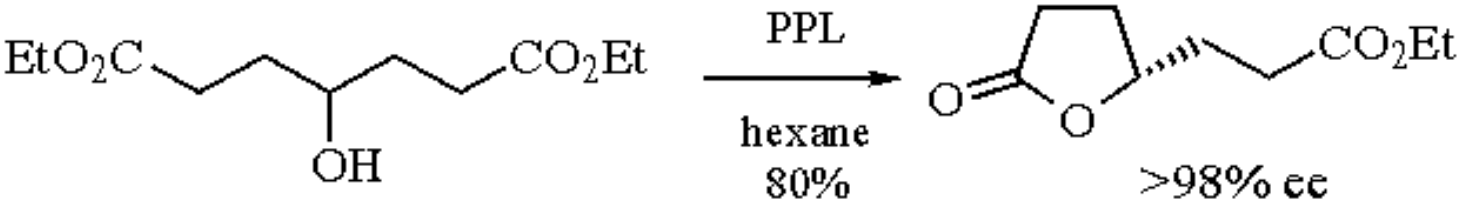

(17)

Mildness and Miscellaneous Reactions.

The mildness of the lipases has been particularly well suited in transformations involving labile compounds that are likely to undergo decomposition when conventional chemical methods are applied,[1a] such as the long-chain polyunsaturated o-3-type fatty acids[86] and highly labile prostaglandin precursor derivatives.[87] Under mild conditions, lipase was exploited to hydrolyze the peracetal protected hydroperoxy derivative in eq 18 to afford the corresponding acid without affecting the peracetal protection moiety.[88]

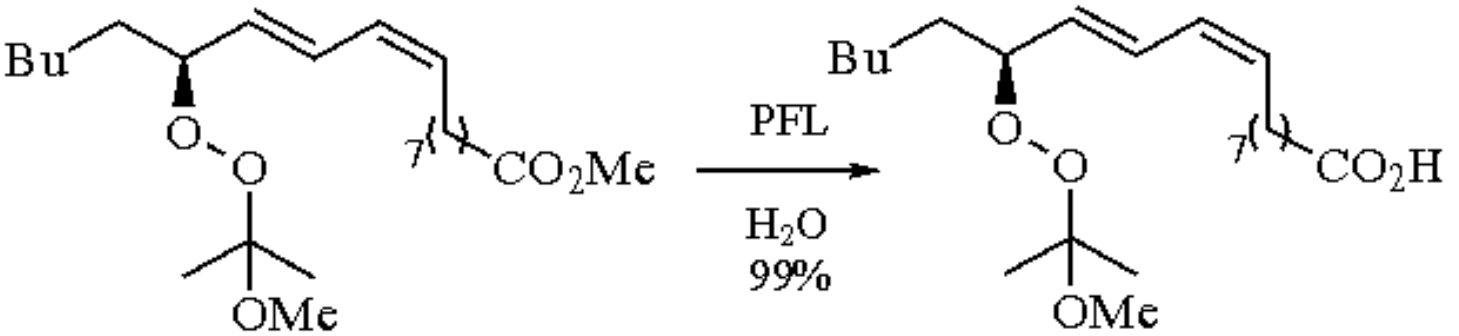

(18)

Various miscellaneous lipase-catalyzed reactions have been reported,[1a] including lipase-mediated epoxidation of alkenes,[12] transamidation,[89] thiotransesterification of thioesters for the preparation of optically active thiols,[90] regio- and chemoselective peptide acylation,[91] lactamization,[92] and highly enantioselective hydrolysis of racemic oxazolin-5-ones which undergo a rapid keto-enol tautomerism to afford optically pure amino acids, thus exceeding the 50% yield limit.[93]

Finally, lipases are able to differentiate enantiotopic faces of appropriately substituted enol esters to afford optically active ketones,[94] indicating that simultaneously upon hydrolysis of the acyl group, protonation occurs from one specified side of the double bond of the enol ester without formation of an enol intermediate (eq 19).[94a]

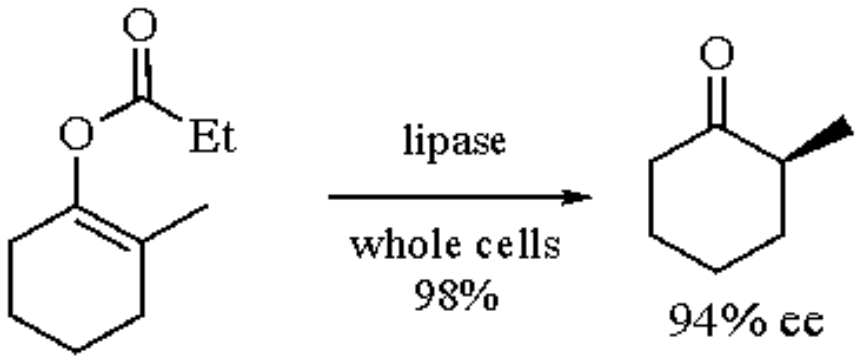

(19)

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Lithioacetonitrile

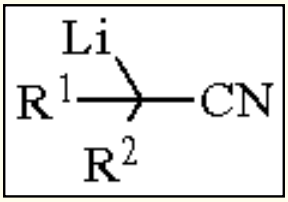

($R^1 = R^2 = H$)

[20428-58-4, 55440-71-6] · C_2H_2LiN · Lithioacetonitrile · (MW 46.99) (R^1 = Me, R^2 = H)

[59263-57-9] · C_3H_4LiN · 2-Lithiopropionitrile · (MW 61.01) ($R^1 = R^2$ = Me)

[55440-70-5, 50654-53-0] · C_4H_6LiN · 2-Lithioisobutyronitrile · (MW 75.04)

(C_2 carbanion for nucleophilic cyanomethylation of alkyl halides, epoxides, carbonyl electrophiles, α,β-enals (1,2-addition), α,β-enones (1,2- or 1,4-addition), heteroelectrophiles, C=N double bonds, and diene and arene transition metal complexes; cyanomethylenation of aldehydes and ketones[1])

Preparative Methods: addition of ***Acetonitrile*** to ***n-Butyllithium*** in Et_2O and warming to 25 °C provides lithioacetonitrile as a white solid in 81% yield; this material is insol hexane, octane, Et_2O, THF, and DME but is sol DMSO.[2a] Lithioacetonitrile can also be prepared from lithium dialkylamides in THF; this material is sol THF even at low temperatures.

Handling, Storage, and Precautions: should be handled in a fume hood.

Alkylation.

The alkylation of lithioacetonitrile and related metalated derivatives with alkyl halides or sulfonates[2b-5] and with epoxides[6-8] proceeds in good yield (eq 1).[2b] An interesting example involves the alkylation with spiro[4.2]hepta-1,3-diene in which cyclopentadienyl anion functions as the leaving group.[9] The regioselective ring opening of epoxides with lithioacetonitrile finds application in the synthesis of γ-hydroxy nitriles.[6-8] The addition of ***Copper(I) Iodide*** to lithioacetonitrile gives a (cyanomethyl)cuprate that reacts efficiently with primary allylic bromides (eq 2).[10]

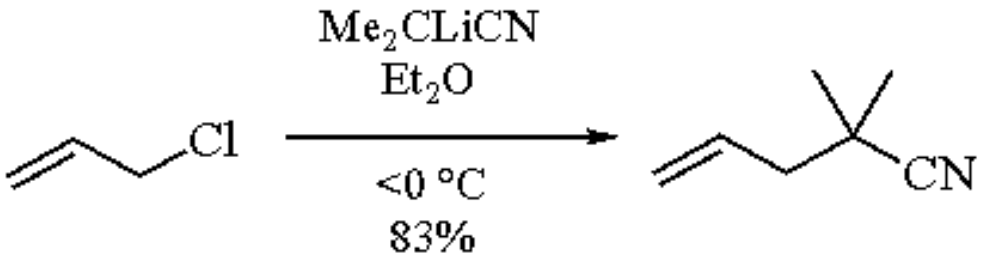

(1)

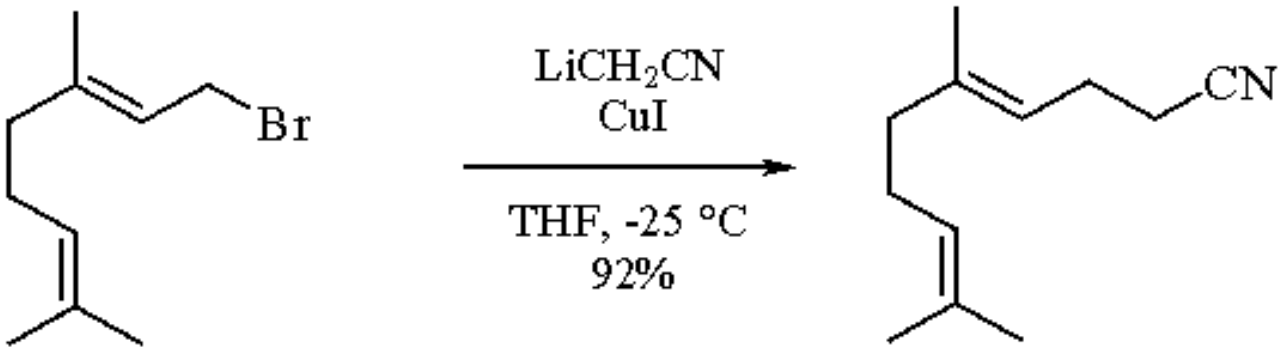

(2)

Addition to C=O Bonds.

The addition of lithioacetonitrile to diaryl, alkyl aryl, and alkyl ketones[11] as well as aryl[11-13] and aliphatic aldehydes[13b] provides the expected β-hydroxy nitriles (eq 3). The dehydration of these intermediates, typically using 85% ***Phosphoric Acid***,[11] provides substituted acrylonitriles. Bis(addition) products are observed under some conditions.[14] The addition of lithioacetonitrile[15a] or 2-lithiopropionitrile[15b] to cyclohexanones gives β-hydroxy nitriles principally with axial selectivity for the cyanomethyl or 1-cyanoethyl groups, respectively (eq 3). Organomanganese or organocerium reagents derived from lithioacetonitrile using $Mn(OCO\text{-}t\text{-}Bu)_2$ and ***Cerium(III) Chloride***, respectively, undergo selective carbonyl addition reactions.[16]

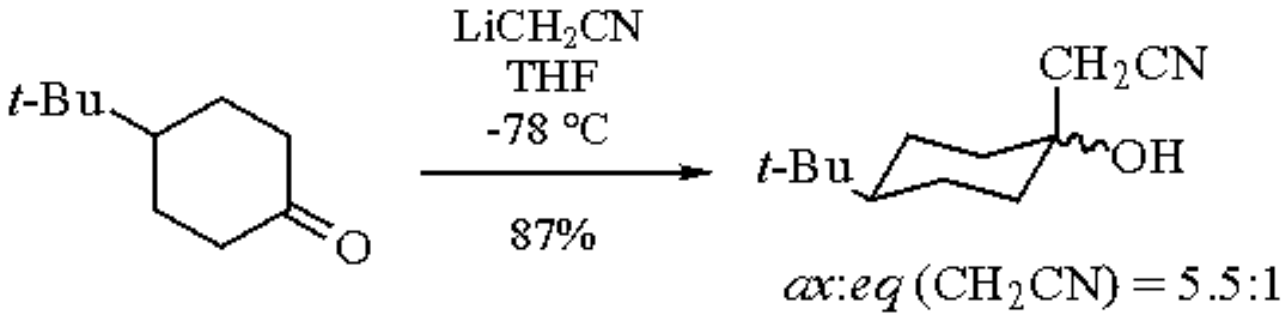

(3)

The addition of nitrile-stabilized anions to carbonyl electrophiles other than aldehydes and ketones affords several potentially useful products. The addition of 2-lithiopropionitrile to a trimethylsilyl ketone proceeds with migration of a silyl group from carbon to oxygen and cyanide elimination to give a trimethylsilyl enol ether (eq 4).[17] Lithioacetonitrile adds to *N*-methoxycarbonyl-protected succinimides to give γ-hydroxy lactams in modest yield.[18] The reaction of nitrile-stabilized anions with *N*,*N*′-di-*t*-butyldiaziridone leads to an acyclic hydrazide derivative with lithioacetonitrile and a pyrazolinone with 2-lithiopropionitrile.[19] The addition of 2-lithiopropionitrile to a γ-lactone gives an intermediate α-cyano ketone that cascades to a substituted tetrahydrofuran.[20]

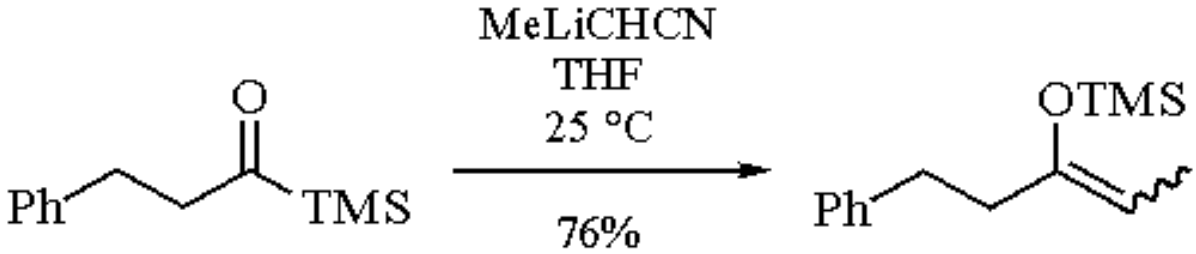

(4)

Michael Addition.

The addition of nitrile-stabilized carbanions to α,β-unsaturated aldehydes favors 1,2-addition.[21,22] In an interesting variant of this process, the reaction of tricarbonyl(sorbaldehyde)iron with lithioacetonitrile initially gives a *cis*/*trans* mixture of acrylonitriles (eq 5). Migration of the $Fe(CO)_3$ group, reduction of the nitrile, and reiteration of the addition process furnishes the next higher homolog in the series (eq 5).[23]

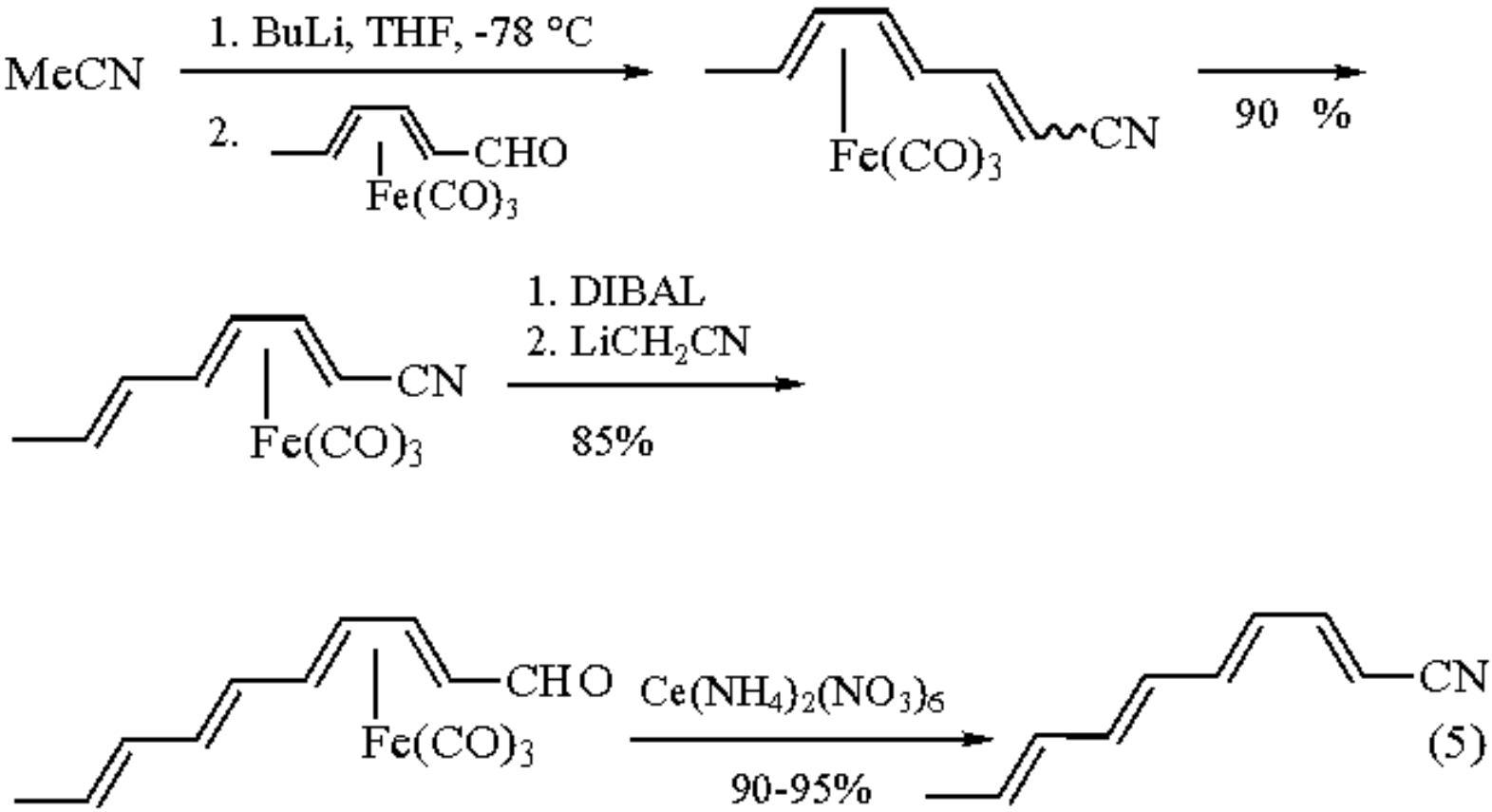

(5)

Kinetically controlled 1,2-addition to α,β-unsaturated ketones occurs at -25 to -30 °C and dehydration leads to cyano-substituted dienes.[24] Higher temperatures lead to the thermodynamic 1,4-addition product. The axial selectivity noted in 1,2-additions to cyclohexanones[15a] increases for the addition of nitrile-stabilized carbanions to cyclohexenones[15b,c] and reaches very high levels (136:1) in the reaction of 2-lithiopropionitrile with pulegone.[15b] The 1,2-additions of lithioacetonitrile and 2-lithiopropionitrile to α-oxoketene dithioacetals and cycloaromatization of the intermediate β-hydroxy nitriles with phosphoric acid provides access to substituted pyridines.[25] The reaction of lithioacetonitrile with an α,β-unsaturated ester leads to both 1,2- and 1,4-addition products (for a solution to this problem, see ***Trimethylsilylacetonitrile***).[26] The 1,4-addition of lithioacetonitrile to other Michael acceptors, such as α,β-unsaturated sulfones[27,28] and vinyl sulfonium salts,[29] proceeds as expected.

Reactions with Heteroelectrophiles.

Trapping nitrile-stabilized carbanions with a variety of electrophiles provides access to sulfur-,[30] phosphorus-,[31] or silicon-substituted nitriles.[32]

Additions to C=N Double Bonds.

The addition of lithioacetonitrile to nitrones[33] and 2-aza-1,3-butadienes[34] furnishes hydroxylamines and, following hydrolysis in the latter case, β-amino nitriles (eq 6), respectively.

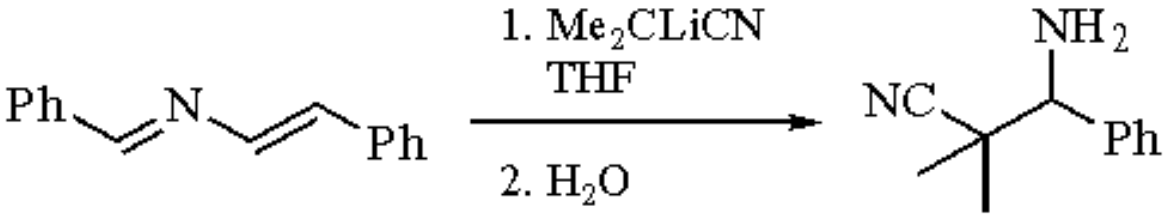

(6)

Addition to η^4-Diene, η^5-Dienyl, and η^6-Arene Metal Complexes.[35]

The addition of nitrile-stabilized anions to diene and dienyl transition metal complexes provides access to various cyano-substituted alkenes, ketones, or dienes. The addition of nitrile-stabilized anions to substituted (η^4-1,3-butadiene)tricarbonyliron complexes furnishes cyano-substituted alkenes[36] as, for example, in the synthesis of 2,2,3,4-tetramethyl-4-pentenenitrile (eq 7).[36b]

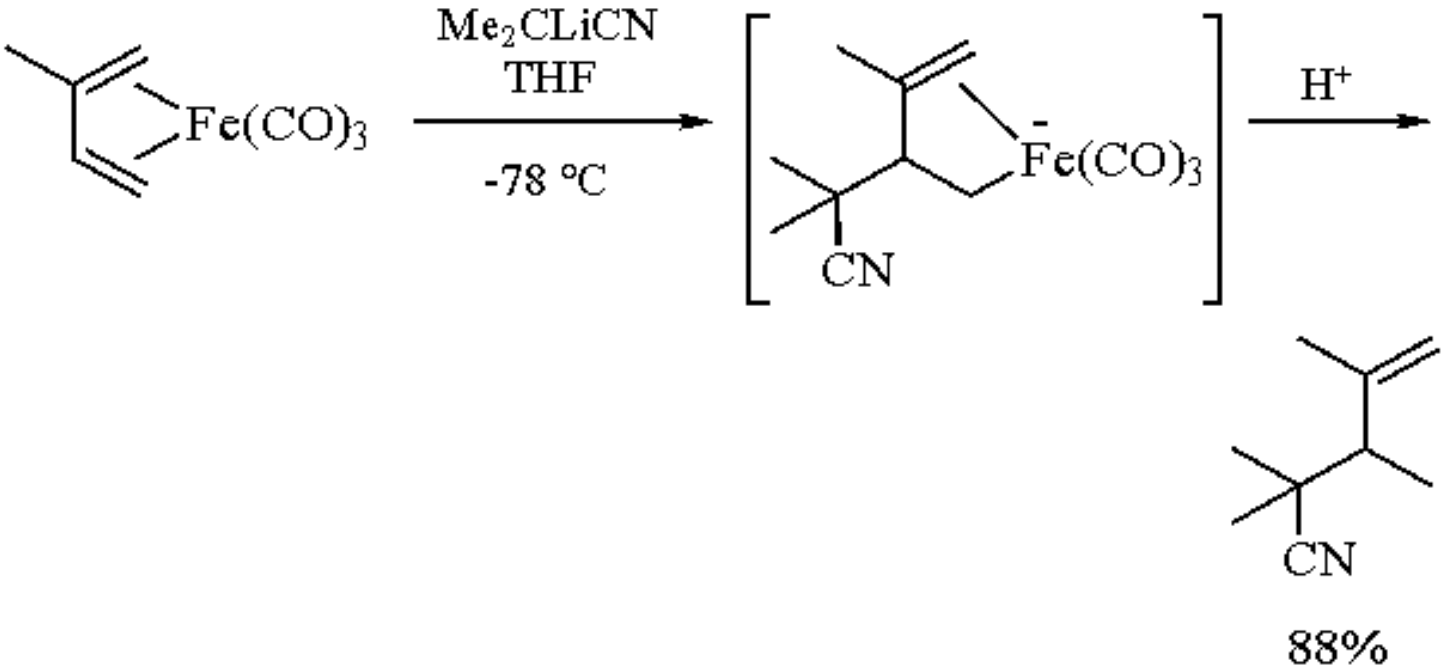

(7)

Trapping the intermediate iron complexes with carbon monoxide leads, in the case of most acylic 1,3-dienes, to cyclopentanones (eq 8),[37] or trapping with carbon monoxide followed by an alkylation gives γ,δ-unsaturated ketones.[38] The addition of 2-lithiobutyronitrile to tricarbonyl(η^5-dienyl)manganese complexes and a subsequent oxidation provides 1,3-dienes (eq 9).[39] The addition of nitrile-stabilized carbanions to various arene-transition metal complexes affords substituted arenes[35a,b] or 1,3-cyclohexadienes[35b,40] (see ***(η^6-Benzene)tricarbonylchromium***). In the case of a methoxy-substituted arene, the addition of 3-lithiobutyronitrile to (η^6-anisole)tricarbonylchromium(0) and the further acid-catalyzed hydrolysis of the intermediate 1-methoxy-1,3-cyclohexadiene provides a substituted cyclohexenone.[40e]

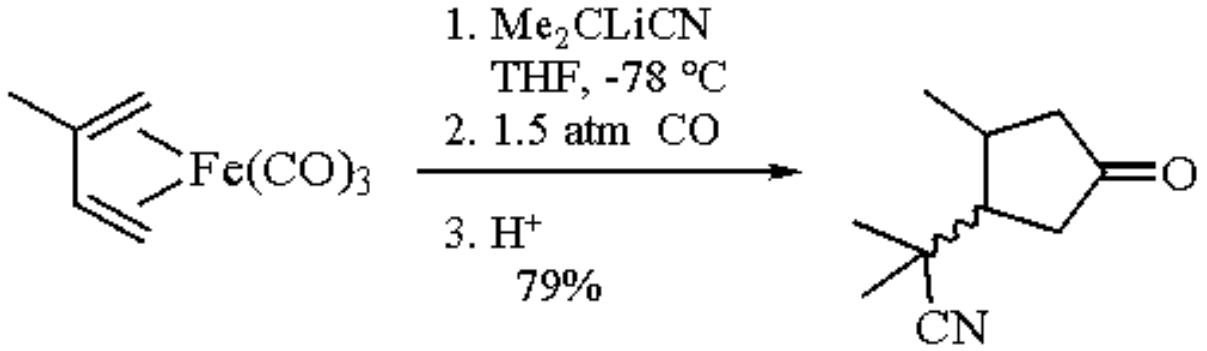

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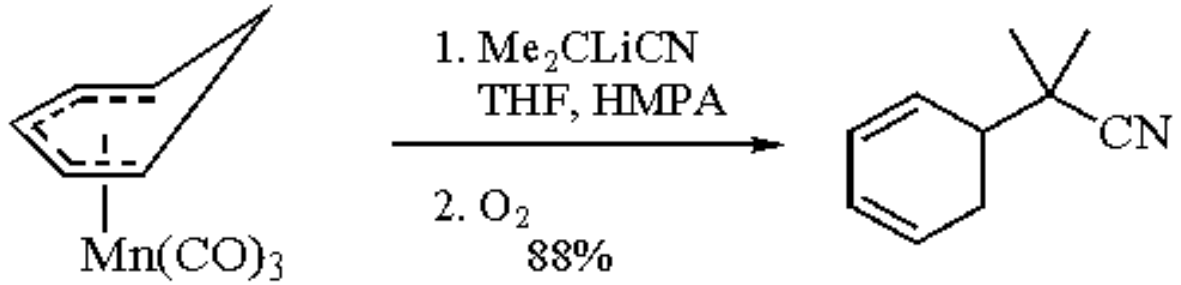

(9)

Related Reagents.

Acetonitrile; ***Cyanoacetic Acid***; ***Ethyl Cyanoacetate***; ***Ethyl Lithioacetate***; ***Pentacarbonyliron***; ***Tricarbonyl(cyclohexadienyl)iron Tetrafluoroborate***; ***Tricarbonyl(pentadienyl)iron Tetrafluoroborate***.

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o-Lithioanisole

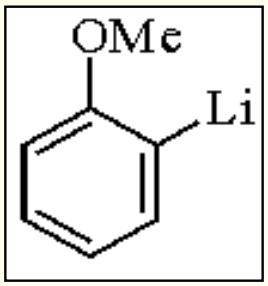

[31600-89-9] · C_7H_7LiO · *o*-Lithioanisole · (MW 114.08)

(strong base/strong nucleophile capable of both nucleophilic addition and nucleophilic substitution)

Physical Data: the pK_a for the *ortho* hydrogens in anisole has been estimated to be 39.0.[4]

Preparative Methods: by metalation of anisole in anhydrous ether with 2 equiv of ***n-Butyllithium*** and 2 equiv of ***N,N,N´,N´-Tetramethylethylenediamine*** at 25 °C for 1-2 h.[1a] Under these conditions a >95% conversion is obtained. If no excess of BuLi or other impurities can be tolerated, then the reagent can be prepared by metal halogen exchange of *o*-bromoanisole and purified by crystallization.[1b] Isolated *o*-lithioanisole is a pyrophoric white powder.

Form Supplied in: the reagent is prepared in situ as needed.

Handling, Storage, and Precautions: must be prepared and handled in an inert atmosphere, as for other organolithium reagents.

o-Lithioanisole as a Reagent.

Several factors influence the site and extent of metalation of an aromatic system containing a substituent group (DMG) that directs metalation.[2] The methoxy group of anisole was the earliest such group to be identified.[3] The important factors affecting the intrinsic (structural) effectiveness of such groups are: (1) the coordinating ability of the heteroatom in the DMG, (2) the electron-withdrawing (*o*-hydrogen-acidity enhancing) ability of the DMG,[4] and (3) the size of the ring structure resulting from the formation of the coordinated *o*-lithio intermediate.[5] The methoxy group occupies an intermediate position in the ranking of DMGs to direct metalation.

Early investigations of this reaction reported conversions of only 50-65% to the *o*-lithio intermediate.[6,7] Later work revealed that the reaction could be accelerated by sonication,[9] and by addition of a stoichiometric amount of ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA),[8] with a yield of 73% of the *o*-trimethylsilyl derivative being reported. A better procedure, that affords 95% (GC yield) of the *o*-trimethylsilyl derivative,[1] involves use of 2 equiv

each of ***n-Butyllithium*** and TMEDA. Concentration also plays a role; solutions of anisole in the 1M range appear to be best. Significantly lower amounts of TMEDA are nearly as effective in promoting the metalation. For highest yields the reaction is run at 25 °C in ether solvent for about one hour.

o-Lithioanisole formally contains only a four-membered coordinated ring system, although more elaborated structures involving the organolithium oligomer allow a pseudo five-membered ring to be drawn.[5] Crystal structures of isolated complexes of *o*-lithioanisole[10,11] exhibit tetrameric unit cells supporting the idea of a pseudo five-membered coordinated ring structure.[12] For metalation solutions containing TMEDA, indirect NMR evidence and MNDO calculations favor an *n*-BuLi dimer-TMEDA-anisole interaction.[5b] Other efforts to understand the mechanism of the *o*-lithiation of anisole have been published.[13,14]

Two separate thermochemical studies have determined that *o*-lithioanisole is more stable than *p*-lithioanisole by either 15[15] or 35 kJ mol^{-1}.[16] That the stability of the coordinated intermediate is important, or that interference with the ability to form such an intermediate is important in the transition state, can be adduced from several studies involving steric effects.[6,17-19] The ability to generate the *o*-lithio intermediate for PhOR, where R is Me, Et, *i*-Pr, and *t*-Bu, falls off through the series.[6,17]

As stated earlier, the methoxy group is intermediate in its directing ability. A study of a series of *p*-substituted anisoles established the order CONHR, SO_2NHMe, SO_2NMe_2, CH_2NMe_2 > OMe > F, CF_3, $CH_2CH_2NMe_2$.[20] Subsequent reports added $CONEt_2$[21] and oxazoline[22] to the stronger- and SMe[23] to the weaker-than-methoxy directing categories. Some additional ordering within the categories has been established as well as certain other directing groups added to each of the categories.[1,2]

A number of other monosubstituted anisoles have been metalated. Varying yields of product derived from metalation *ortho* to the methoxy group have been obtained from *p*-F,[24-27] *p*-Cl,[24,28] *p*-Br,[24] and *p*-I[24] anisole. The best yields that can be obtained from these systems lie in the 50-60% range because of the opportunities for various side reactions involving the halogens. *p*-Methylanisole has been metalated in about 30% yield[29] and 1,4-dimethoxybenzene in about 75% yield.[8] The latter compound, by the addition of TMEDA to the metalation system, can be made to form a 2,5-dilithio intermediate.

Two interesting and potentially useful reversals of the site of metalation have been developed. For *p*-methoxydimethylbenzylamine the preferred site of metalation with *n*-BuLi is that *ortho* to the dimethylaminomethyl group. However, when TMEDA is added to the metalation system, the preferred site of metalation is *ortho* to the methoxy group.[30] Both *o*-and *p*-fluoroanisole can be made to exhibit the same phenomenon. With *n*-BuLi, metalation occurs exclusively *ortho* to the methoxy group,[26,27] while at -78 °C with *n*-BuLi/***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine***, metalation takes place *ortho* to the fluoro substituent.[26]

Disubstituted benzenes exhibiting an *ortho*- or *meta*-orientation of directing substituents can be successfully metalated. 1,2-Dimethoxybenzene easily affords the 3-substituted product of metalation while 1,3-dimethoxybenzene undergoes metalation specifically at the 2-position.[8] Similarly, 3-fluoroanisole, if metalated at -78 °C, provides derivatives at the 2-position.[31] For the hydroxyanisoles, mixtures were obtained for the metalation of the 1,2- and 1,3-isomers, but fairly regiospecific metalation *ortho* to the methoxy group was obtained for the 1,4-isomer.[32]

1-Methoxynaphthalene upon treatment with *n*-BuLi/TMEDA affords 2-metalation; with ***t-Butyllithium***/pentane, 8-metalation is achieved.[33] 2-Methoxynaphthalene undergoes metalation at the 3-position.[34] Certain methoxy heterocycles have also undergone successful directed metalation, although the yields are usually modest. 2-

Methoxypyridine has been derivatized in the 3-position using a novel metalating system: ***Methyllithium*** catalyzed by a small amount of ***Diisopropylamine***. This mixture of a kinetic and thermodynamic base avoids the competition of addition of RLi to the pyridine system.[35] 3-Methoxythiophene has been metalated in the 2-position[36] and 2,4-dimethoxypyrimidine in the 5-position using ***Lithium Diisopropylamide*** or ***Lithium 2,2,6,6-Tetramethylpiperidide***.[37] Methoxyferrocene is metalated with *n*-BuLi in the 2-position.[38]

A number of directing groups related to the methoxy group also provide good yields of the *o*-lithio intermediate. These include the methoxymethoxy group (OCH_2OMe),[39] the carbamate group ($OC(O)NEt_2$)[2,40] the methoxyethoxy group (OCH_2CH_2OMe),[41,44] the 2-(trimethylsilyl)ethoxymethoxy system ($OCH_2OCH_2CH_2SiMe_3$),[42] and the dimethylaminoethoxy group ($OCH_2CH_2NMe_2$).[43,44] Some of these derivatives can be transformed into the phenol upon hydrolysis or other suitable treatment. Lastly, phenol itself can undergo *o*-lithiation.[45] For the first three of the above-named directors the yields of *o*-lithiation are good.

More complex examples of the *o*-lithiation of substituted anisoles illustrate the utility of the reaction for synthesis. In the preparation of a series of phenethylamines the key precursor, 5-methoxybenzonorbornadiene, was generated from *m*-fluoroanisole (eq 1).[46] Using a one-pot lithiation/oxygenation procedure (***s-Butyllithium***, TMEDA; then ***Oxygen***) a series of methoxyphenols was prepared by direct hydroxylation in modest yields (eq 2).[47] Veratrole can be metalated and alkylated cleanly (eq 3).[48] Double metalation of anisole has led to a trisubstituted aryloxazoline (eq 4).[49] A centrally acting dopaminergic and serotoninergic agonist was synthesized by metalation/hydroxylation of a methoxytetralin (eq 5).[50] A total synthesis of the naturally occurring sesquiterpene, aplysin, in its racemic modification was accomplished by a surprisingly regiospecific metalation of a bromoanisole (eq 6). [51] Cram and co-workers have utilized the *o*-lithiation of a dimethoxybiphenyl in the synthesis of cavitands and caviplexes (eq 7).[52]

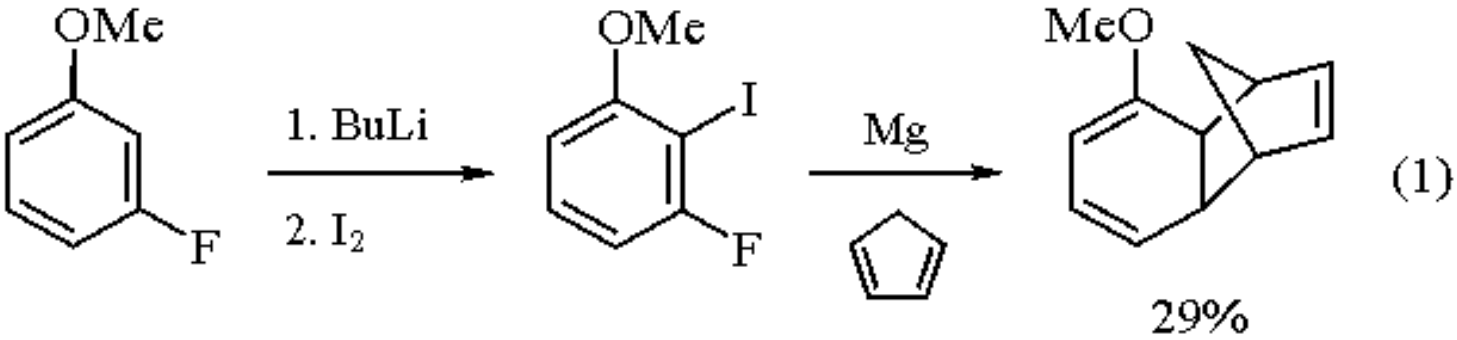

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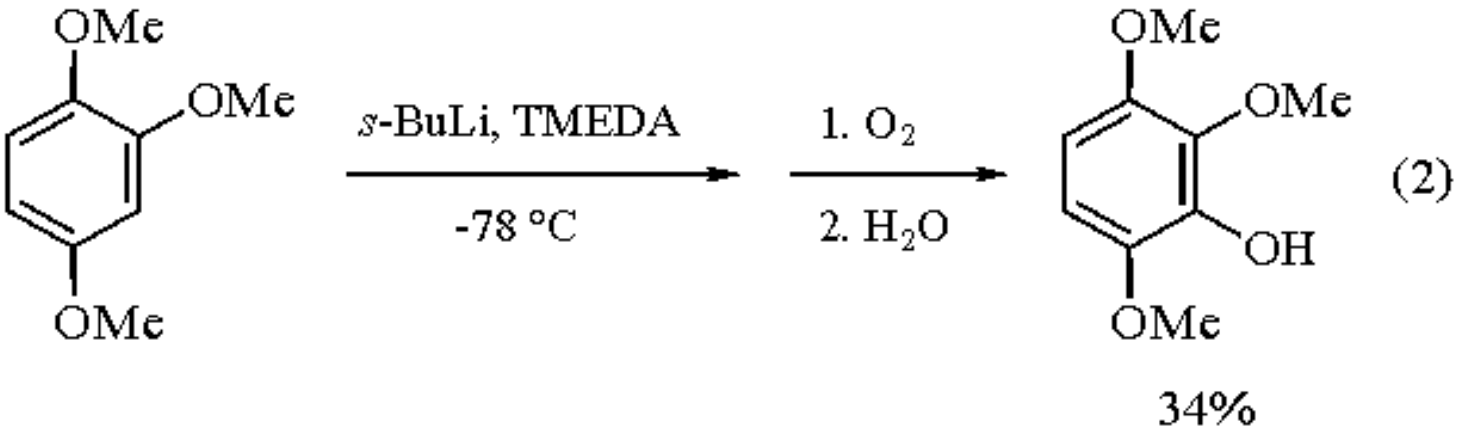

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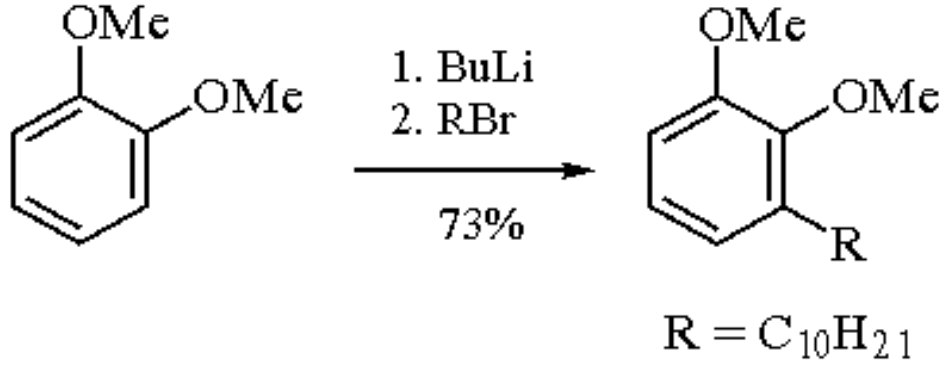
OMe
OMe
1. BuLi
2. RBr
73%
OMe
OMe
R
R = C10H21

(3)

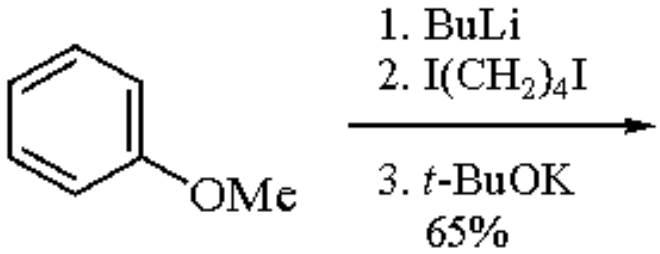
OMe
1. BuLi
2. I(CH2)4I
3. t-BuOK
65%

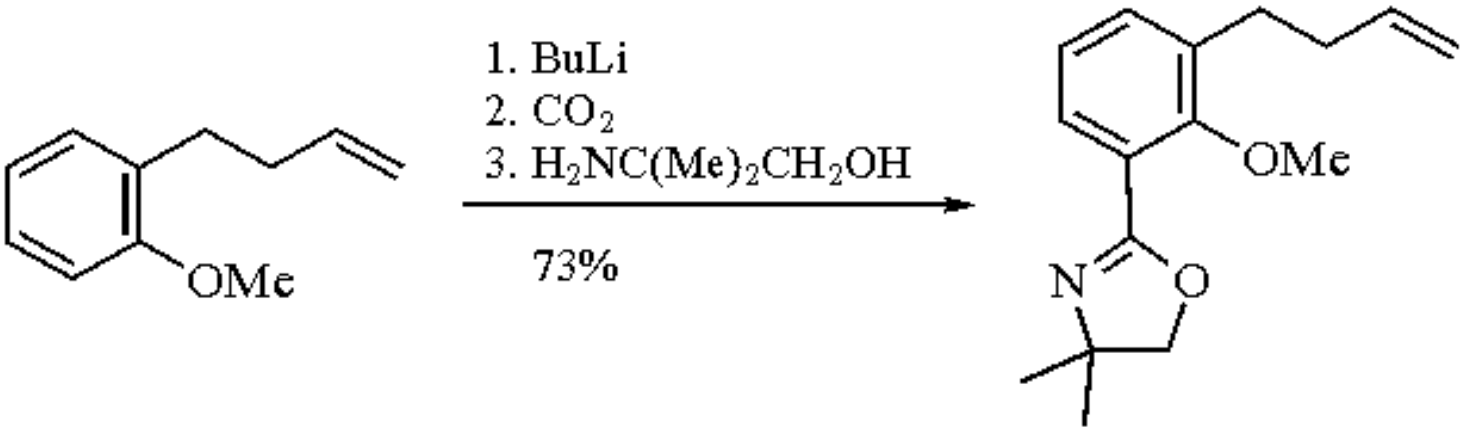
OMe
1. BuLi
2. CO2
3. H2NC(Me)2CH2OH
73%
OMe
N
O

(4)

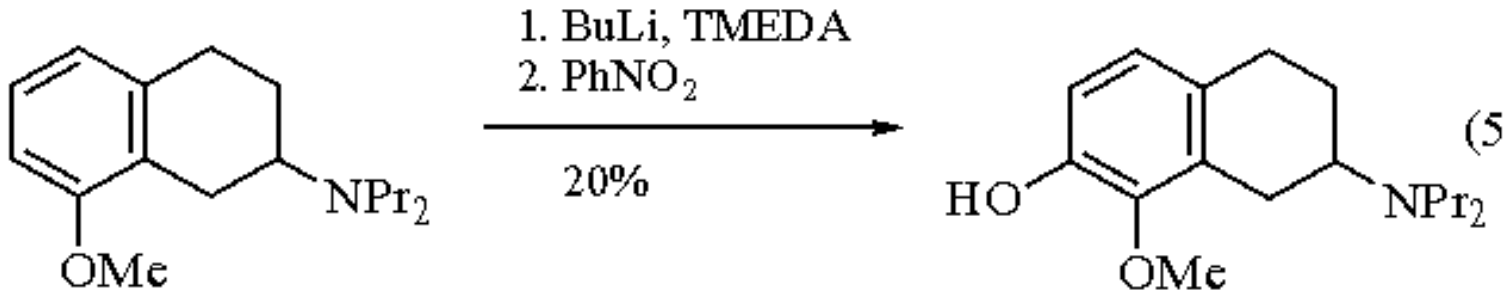
NPr2
OMe
1. BuLi, TMEDA
2. PhNO2
20%
HO
NPr2
OMe

(5)

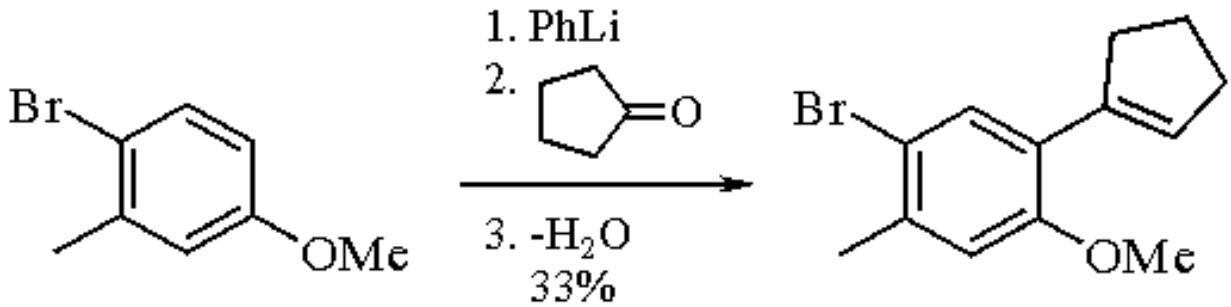
Br
OMe
1. PhLi
2.
O
3. -H2O
33%
Br
OMe

(6)

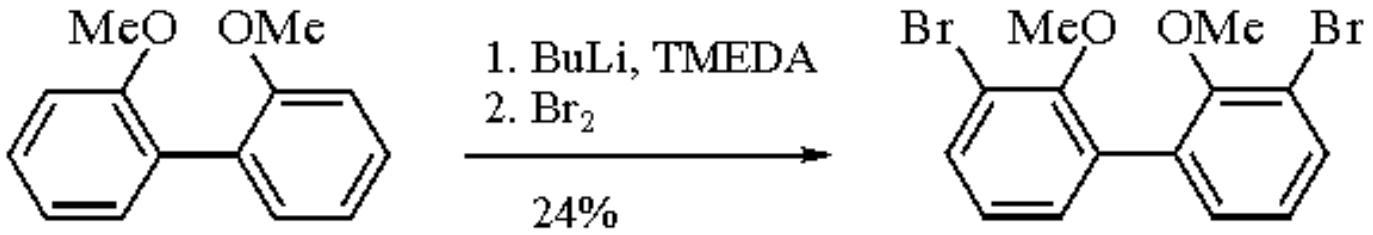

(7)

Examples of the utility of directing groups related to the methoxy group can also be found in the literature. A bipyridine derivative has been used to synthesize orelline, a toadstool metabolite. A test reaction established a fairly efficient bis-metalation of the bipyridine (eq 8).[53] In order to avoid lateral metalation of the methyl group, the methoxymethoxy group was utilized in the first step of a synthesis of anthramycin (eq 9).[54]

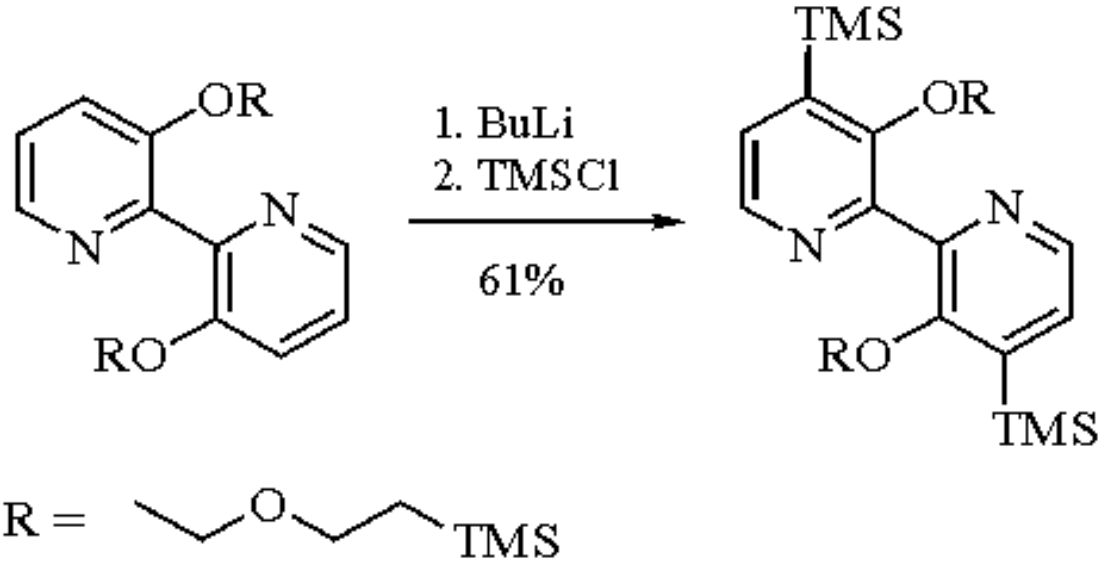

(8)

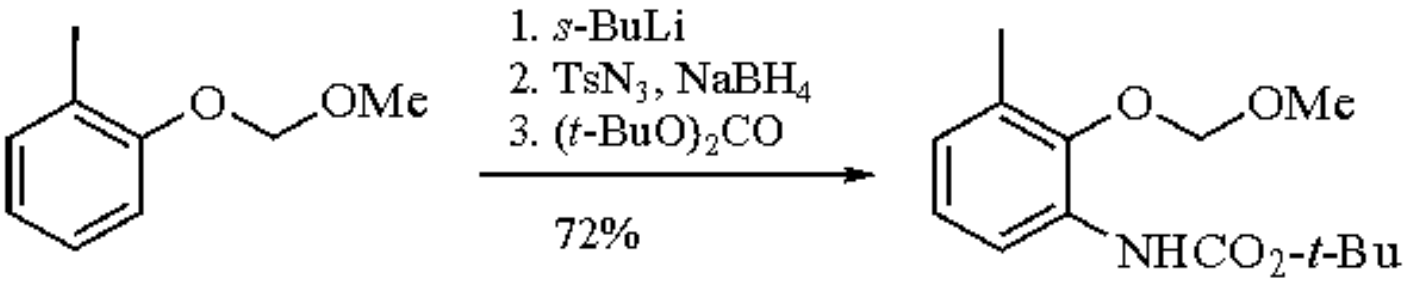

(9)

Regiospecific metalation of tamoxifen, an antiestrogenic agent currently employed in the treatment of breast cancer, has been utilized to synthesize an *o*-iodo derivative (derived from the *o*-Sn precursor); this technique has the potential of introducing a radioactive label (eq 10).[55] Utility of the carbamate group has recently been reviewed.[2b]

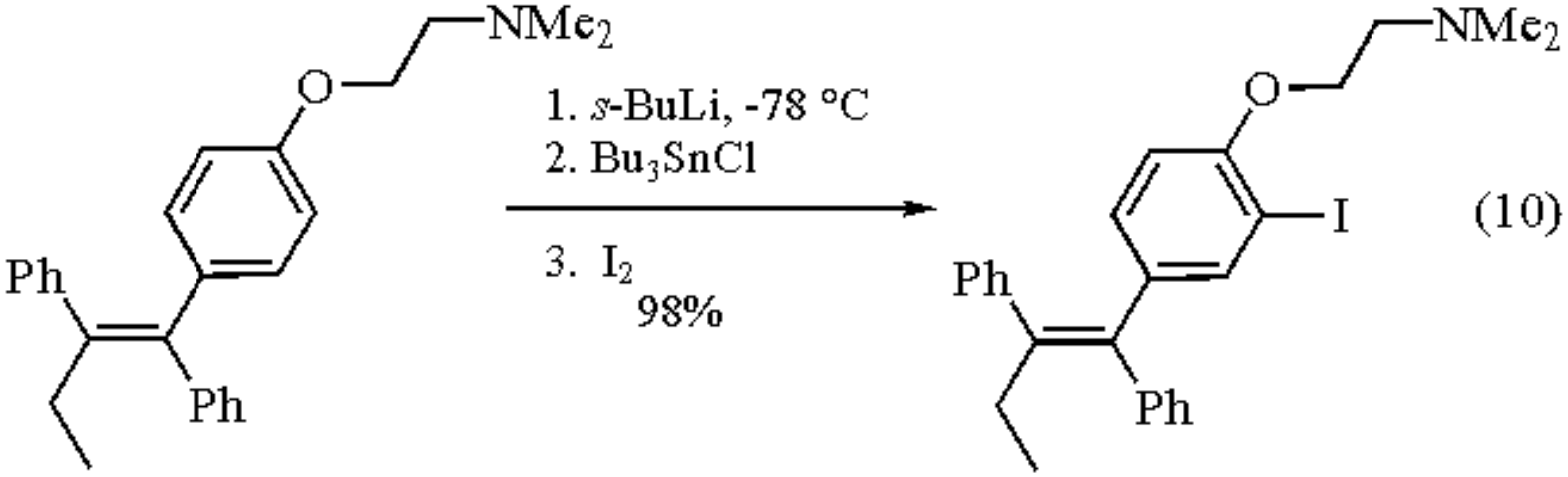

(10)

Related Reagents.

Lithium 2-Lithiophenoxide; ***Phenyllithium***.

---

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2-Lithio-3,3-diethoxy-1-propene[1]

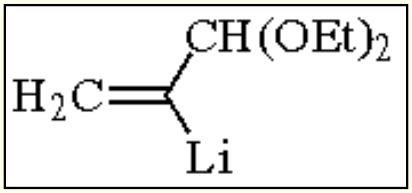

[54780-30-2] · $C_7H_{13}LiO_2$ · 2-Lithio-3,3-diethoxy-1-propene · (MW 136.12)

(is able to transfer a masked acrolein unit to various electrophiles such as carbon dioxide,[1] aldehydes,[2] ketones,[2] and amides;[3] the corresponding cuprate also allows 1,4-addition to conjugated enones,[4] coupling with allylic halides,[4b] and 1,2-opening of 3,4-epoxycycloalkenes[5])

Alternate Names: 3,3-diethoxy-1-propen-2-yllithium; 3,3-diethoxy-2-lithio-1-propene.

Preparative Method: under nitrogen, ***n-Butyllithium*** (2 molar in hexane, 0.95 equiv) is slowly added at -70 °C to 2-bromo-3,3-diethoxy-1-propene in dry THF (1.6 mL $mmol^{-1}$ of bromoacrolein acetal).[2d]

Handling, Storage, and Precautions: this solution of a vinyllithium should be held under nitrogen at low temperature (the upper limit for the thermal stability has been estimated to be approx. -40 °C), kept out of oxygen and moisture, and used immediately for best results.

Organolithium Reagent.

Addition of ketones[2] or aldehydes[2,6] to the title organolithium (**1**) in THF at -70 °C leads to the corresponding β-hydroxy-α-methylene acetals in respectively 50 and 80% yields (eq 1). 1,2-Addition is also observed with conjugated enones[7] or enals. These secondary allylic alcohols can be stereoselectively transformed into trisubstituted functionalized alkenes.[2,8]

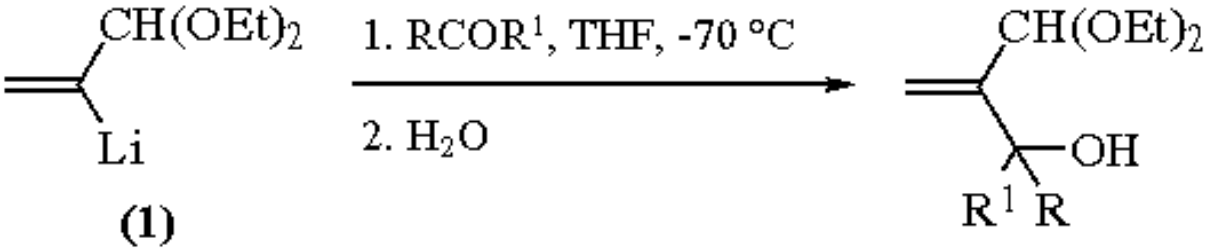

(1)

$$R, R^1 = H,\ R = H,\ R^1 \neq H \text{ or } R, R^1 \neq H$$

Reaction of (**1**) with enantiomerically pure 2,3-*O*-isopropylidene-D-glyceraldehyde gives the diastereoisomer adducts (*erythro*:*threo* = 2:1) in 70% yield (eq 2).[2c] These are precursors of C-2 branched chain pentoses, α-methylenelactones, or

2,4-disubstituted furans.[8b,9]

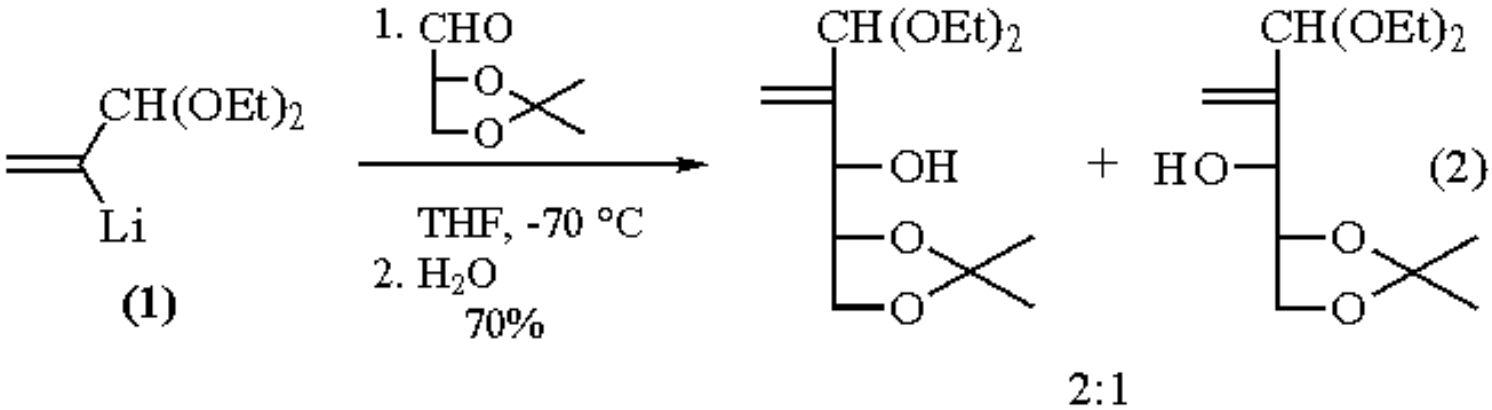

The reagent also reacts with other electrophiles such as ***Carbon Dioxide***,[1] ***Chlorotrimethylsilane***, and amides[3] (eq 3). In the latter case, α-methylene-β-oxoacetals are obtained in about 70% yield, except for R = H or Me (20-30% yield). These adducts lead to substituted β-keto enol ethers by addition of ***Lithium Dimethylcuprate***.[10]

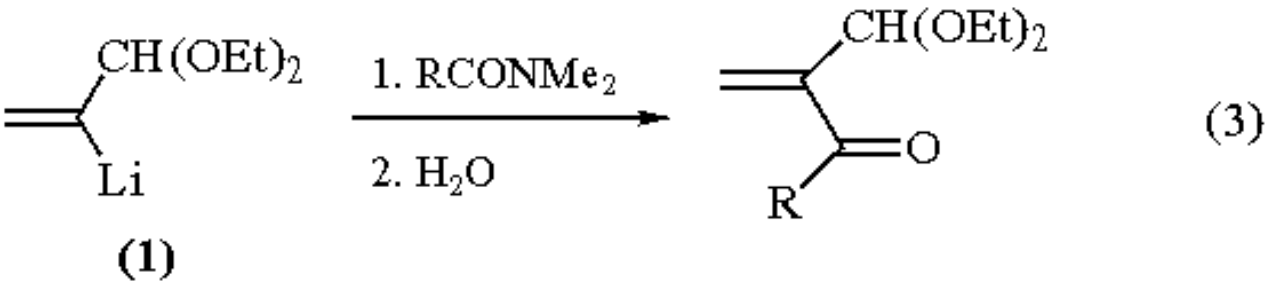

Synthetic equivalents of 2-lithiopropenal[11] and of its diethyl acetal[12] (eqs 4 and 5) have also been reported.

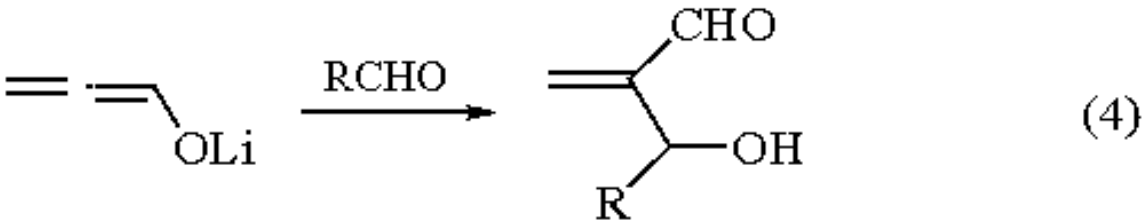

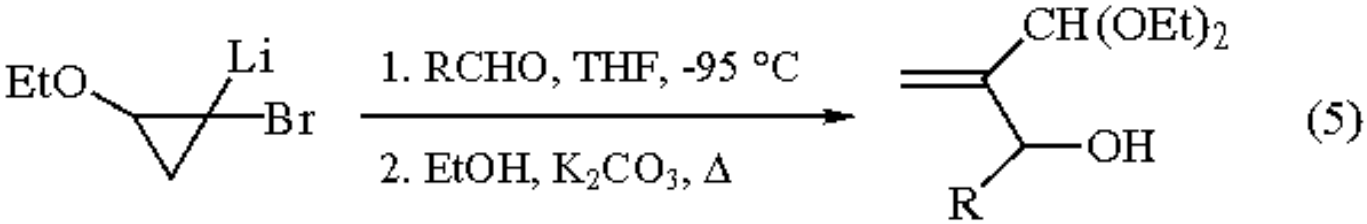

Organocopper Reagents.

(**1**) can be transformed into other organometallic species such as vinylcopper (**2**),[4b] homogeneous diorganocuprates (**3**),[4a] and mixed diorganocuprates such as phenylthio-,[4b,c] alkynyl-,[4,5] or cyanocuprate (**4**)[5]

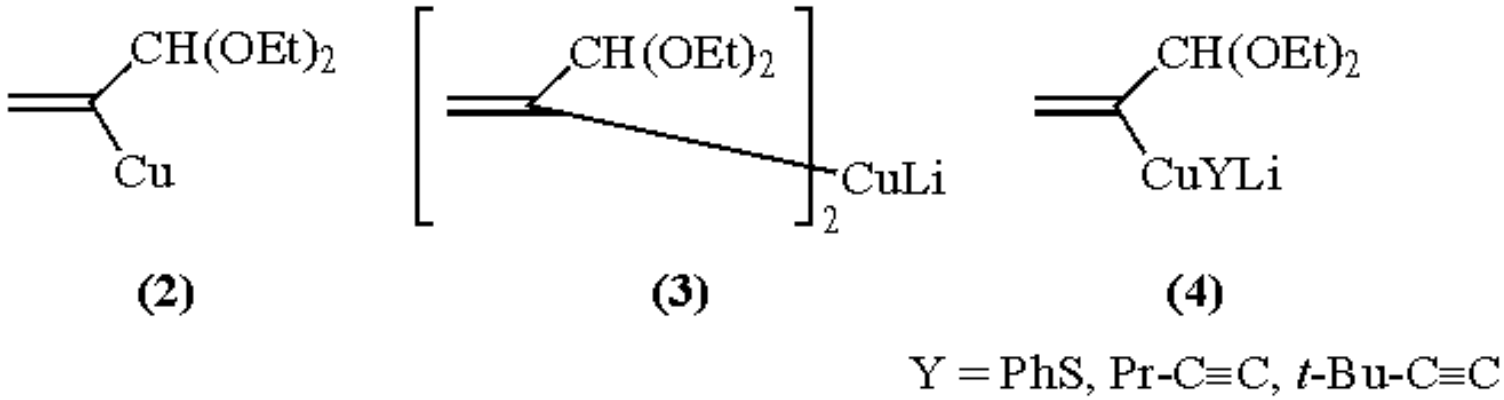

The (α-diethoxymethyl)vinylcopper reacts with allylic halides and gives only 1,2-addition reactions with conjugated enones.[4b] Homogeneous[4a,13] and mixed[4c] diorganocuprates react with a variety of α,β-unsaturated ketones to afford 1,4-adducts in moderate to excellent yields, depending upon steric hindrance in the enone (eq 6). These adducts have been shown to be suitable precursors to α-methylene-γ-lactones.[4c] Mixed diorganocuprates also allow coupling with allylic halides[4b] and allylic epoxides[5] (eqs 7 and 8), but not with vinyl or saturated halides.

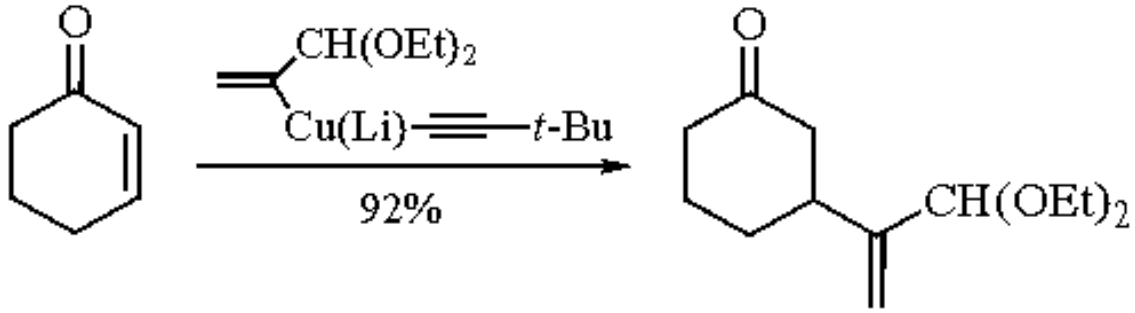

(6)

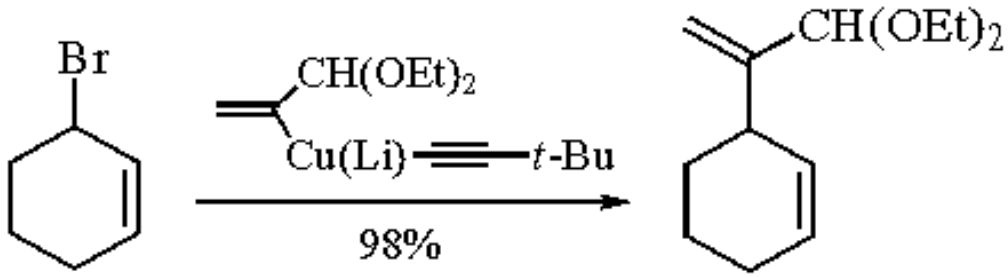

(7)

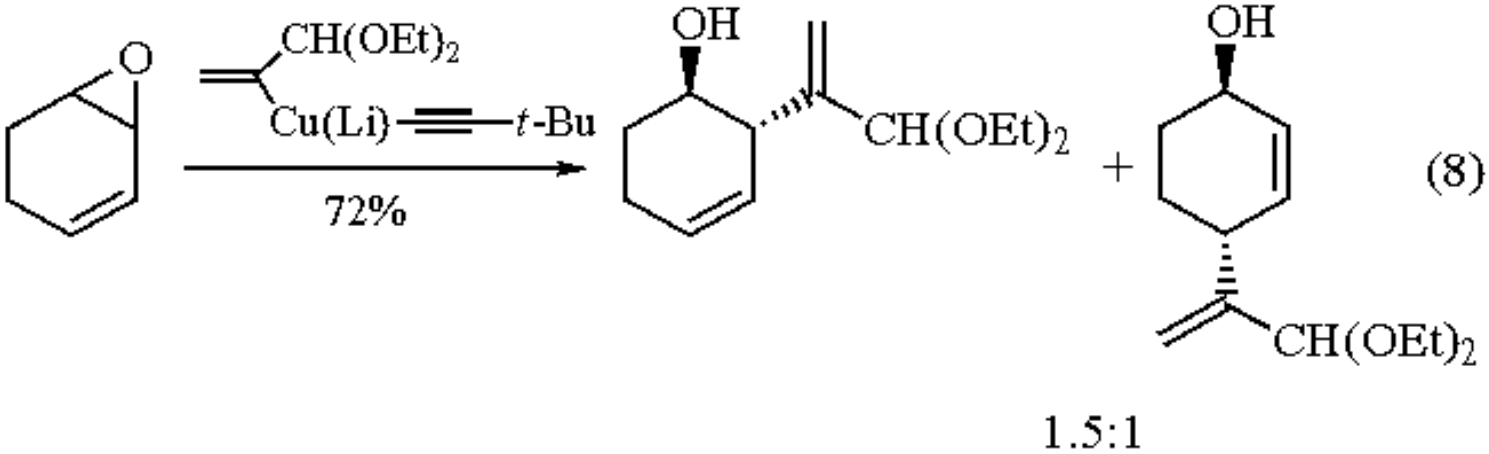

(8)

Related Reagents.

Cyclic analogs (**5**)-(**7**) of the vinyllithium with a β-acetal function[14] have also proved useful in a variety of synthetic schemes.

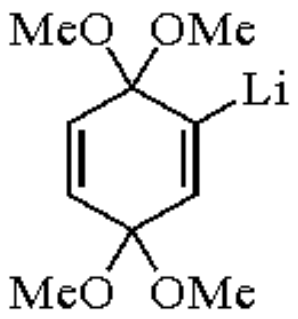

(5)

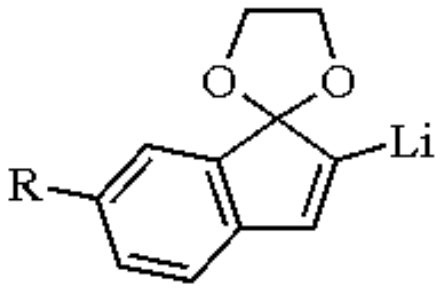

(6) R = H, OMe

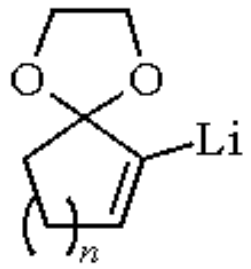

(7) $n = 1, 2$

Acrylate anion analogs such as orthoesters (**8**)[15] and (**9**)[16] and esters (**10**),[17] (**11**),[16] and (**12**)[18] have been described (Table 1). Cuprate (**10**) reacts with allylic and propargylic halides,[17,19] but in contrast to most organocuprate reagents, (**10**) reacts at low temperature with conjugated enones to yield predominately 1,2-addition products.[7,20]

Table 1 Acrylate Anion Analogs of **(1)**

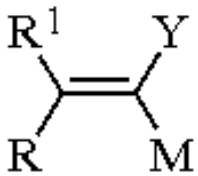

	R	R^1	Y	M
(8)	H	H	$C(OEt)_3$	Li
(9)	H	H	$C(OEt)_3$	Cu(Li)CN
(10)	H	H	CO_2Et	Cu(Li)C≡CBu
(11)	Me	H	CO_2Et	Cu(Li)C≡CBu
(12)	H	$GeMe_3$	CO_2Me	Li

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2-Lithio-*N,N*-diethylbenzamide

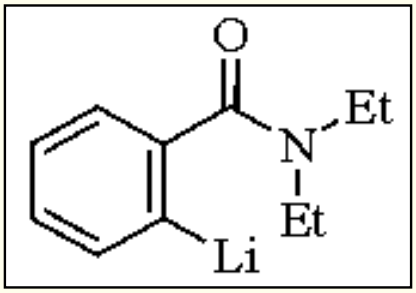

[81380-82-7] · $C_{11}H_{14}LiNO$ · 2-Lithio-*N,N*-diethylbenzamide · (MW 183.179)

(reagent used for production of highly substituted benzene derivatives)

Preparative Method: solutions of the title compound can be obtained by deprotonation of *N,N*-diethylbenzamide using ***s-Butyllithium*** in THF/TMEDA at -78 °C.

General Considerations.

A variety of benzamides have been deprotonated at the *ortho* position to give the corresponding lithiated species which then undergo reaction with electrophiles (eq 1).

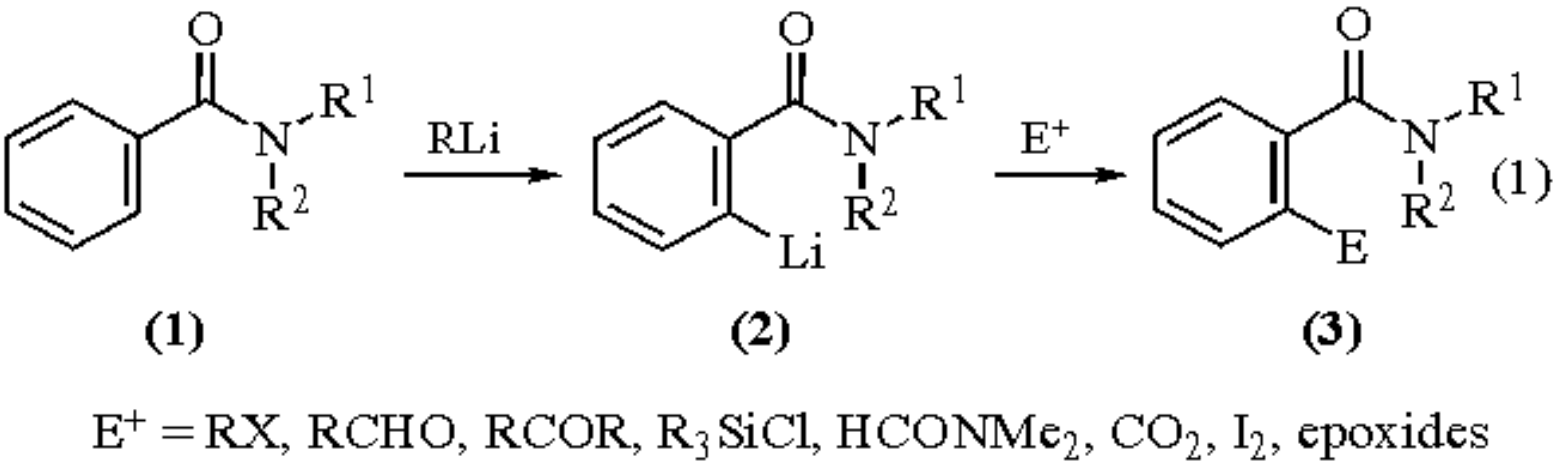

(1) **(2)** **(3)**

$E^+ = RX, RCHO, RCOR, R_3SiCl, HCONMe_2, CO_2, I_2$, epoxides

A large amount of data in this area has been compiled by Snieckus[1] and represents the state of the art in the use of (**2**) and related reagents. Two derivatives of (**1**) which undergo clean deprotonation and reaction with electrophiles are the *N,N*-diethyl and *N,N*-diisopropyl amides. Both can be converted near quantitatively to the corresponding *o*-lithio reagents with *s*-BuLi in THF/TMEDA at -78 °C. Both react with a variety of electrophiles in high yield.

Manipulation of Alkylated Products.

Although *N*,*N*-dialkylbenzamides are quite stable to acidic or basic hydrolysis, some adducts undergo replacement of the *N*,*N*-dialkyl group quite easily as a consequence of proximal functionality. Thus, adducts of the *o*-lithio species with aldehydes and ketones can be cyclized to phthalides (**6**) with acid (eq 2).[2] The phthalides in turn have been converted to anthraquinones (**7** -> **8**) (eq 3).[3] Anthraquinones may also be prepared without going through phthalide intermediates. After addition of the aryllithium to a benzaldehyde (**9**), the alkoxide (**10**) can be further metalated to (**11**), which closes to (**12**). Oxidation gives the anthraquinone (eq 4).[4]

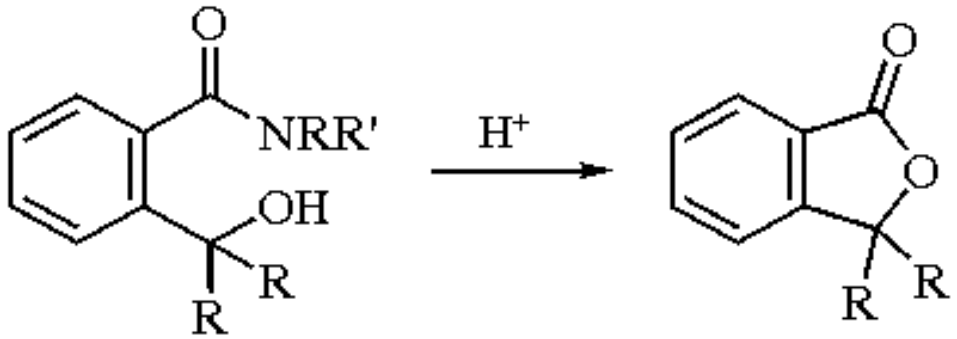

(2)

(5) (6)

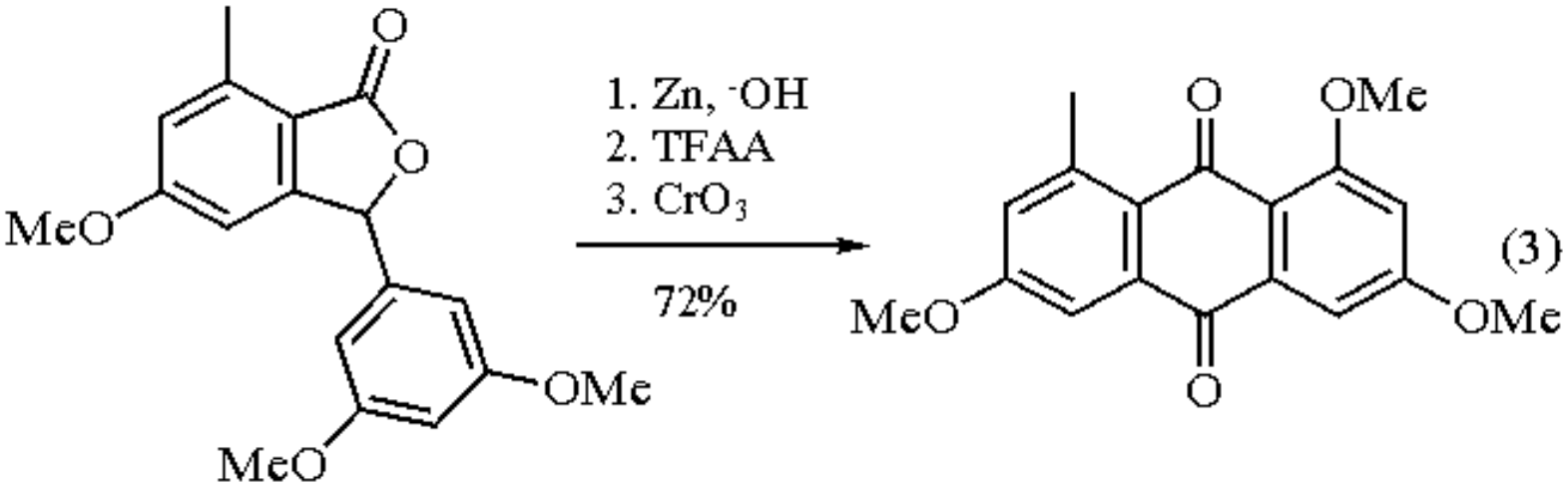

(3)

(7) (8)

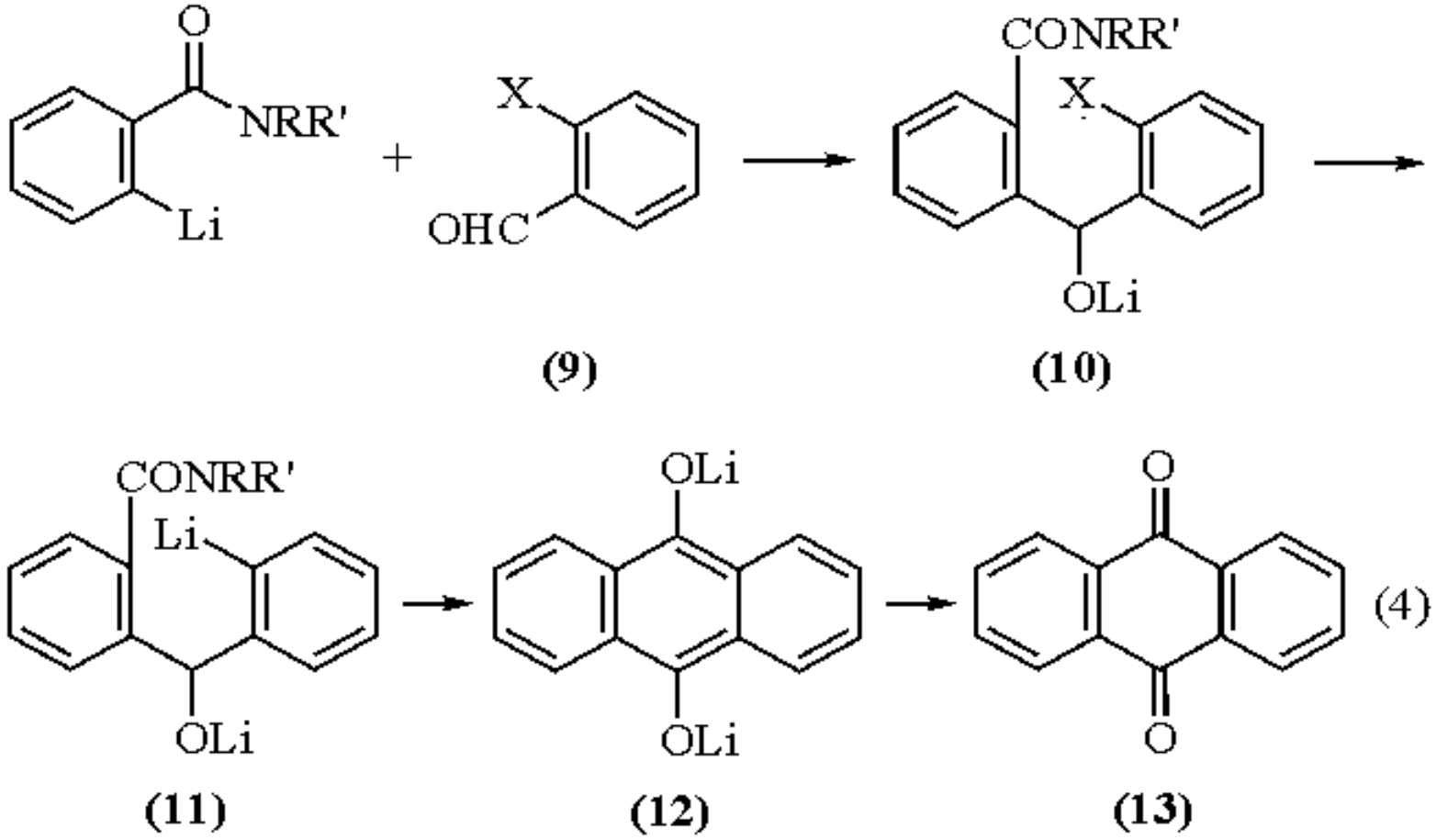

Cross Coupling via Boronic Acids.

Ortho-lithiated benzamides can be converted to *o*-substituted boronic acids (**14**). These can be coupled with aryl halides in a palladium-catalyzed process leading to a general synthesis of biaryls.[5] This is only the beginning of a versatile synthetic method. The presence of the amide in (**15**) enables further metalation and elaboration to a diverse array of aromatic compounds.

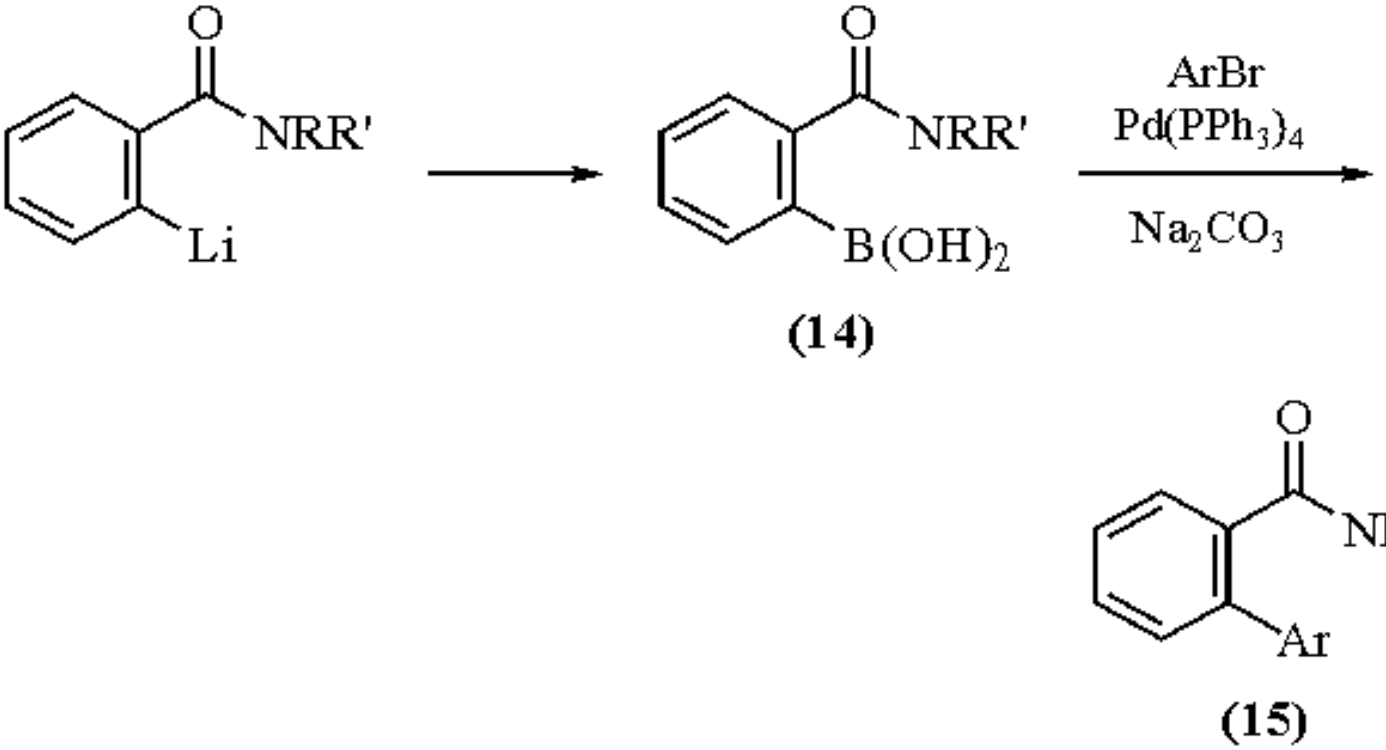

Related Reagents.

o-Lithioanisole; ***3-Lithiofuran***; ***2-Lithiopyridine***; ***Phenyllithium***.

---

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5-Lithio-2,3-dihydrofuran[1]

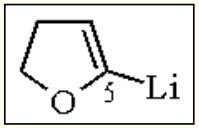

[75213-94-4] · C_4H_5LiO · 5-Lithio-2,3-dihydrofuran · (MW 76.02)

(nucleophilic nonbasic carbanion,[1] formally equivalent to a cyclic acyl anion,[2] which may be interacted readily with many electrophiles[3])

Physical Data: ^{13}C NMR chemical shifts[4] (22.6 MHz, 308 K, THF/hexane, TMS): δ (ppm) = 30.7 (C-3), 66.0 (C-2), 109.6 (C-4), 202.3 (C-5).

Solubility: sol ether, THF.

Form Supplied in: prepared in situ and used directly.

Preparative Methods: the easy deprotonation of 2,3-dihydrofuran (commercially available) at position 5 by strong bases has been known for some time[5] and extensively studied by several groups. While the original procedures described for the title reagent (**1**) employed a stoichiometric amount of ***t-Butyllithium*** in a minimum quantity of THF at low temperature,[1,2] it since has been reported that the deprotonation reaction takes place with mixtures of ***n-Butyllithium*** and ***N,N,N´,N´-Tetramethylethylenediamine*** in hexane at 0 °C[3] or *n*-BuLi in ether at 0 °C.[6,7] A representative procedure consists of the addition of 0.8 equivalent of *t*-BuLi (1.8 M in pentane) to a THF solution of freshly distilled 2,3-dihydrofuran at -40 °C for 0.5 to 1 h.[3] An alternative deprotonation method uses a 1:1:1 mixture of *n*-BuLi, ***Potassium t-Butoxide***, and TMEDA in hexane for 15 min at -30 °C.[8] (**1**) can be used in THF solution or in ether after evaporation of the original solvents.[3,9] The THF solution is stable for at least a few hours at room temperature.[1] However, lithiodihydrofuran in THF partly decomposes after 24 h at 25 °C into lithium alkynolate and ethylene.[10] This reaction in the presence of excess base and silylating reagent leads to bis(silyl)ketenes (eq 1).[10]

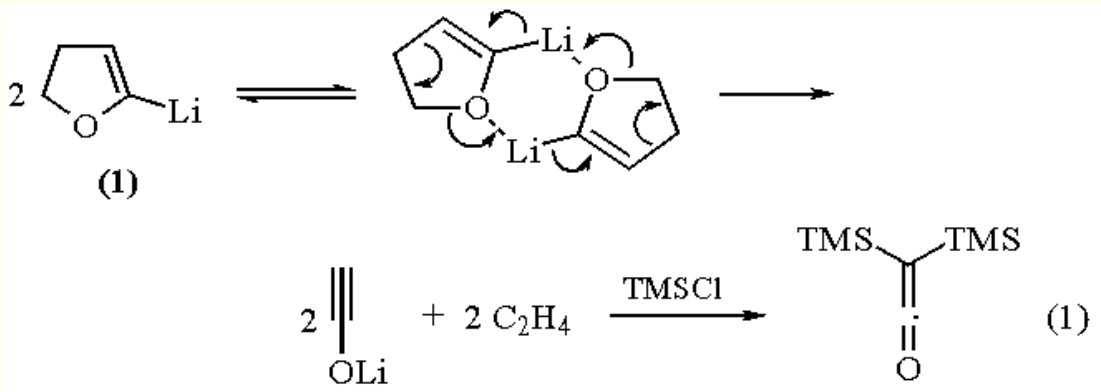

The deprotonation is regioselective, no allylic metalation having been observed to date, a result explained on the ground of orbital calculations as well as steric and electronic considerations.[11] The carbon-13 NMR spectrum of the lithiated compound exhibits a large downfield shift for the two carbon atoms of the double bond.[4]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture.

Reactivity.

(**1**) reacts readily with a variety of electrophiles, providing the expected substitution product in good to excellent yields. Some examples of its addition to ketones have been reported.[1,12] ***Acetone*** gives the expected carbinol in 78% yield.[1] ***Cyclobutanone*** yields a cyclobutanol derivative which rearranges quantitatively with ring expansion in the presence of Dowex-50X at room temperature (eq 2).[12b] Reiteration of this addition-ring expansion process gives access to belted spirocyclic tetrahydrofurans, which behave as potent ionophoric polyethers with extraction equilibrium constants close to those of ***12-Crown-4***.

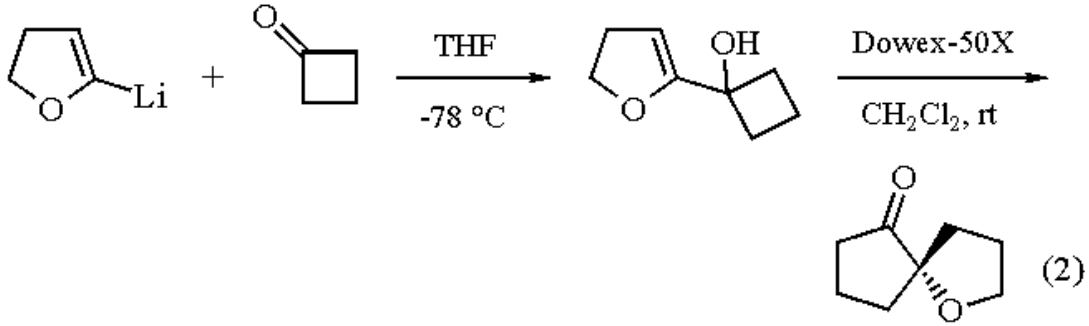

(2)

Similarly, 1,2-addition of an unsaturated nitrile has been shown to yield an imine[13] and interaction with silyl (as well as germanyl and stannyl) chlorides afforded the expected 5-silylated[3,4,14] (germanylated[14b,c] and stannylated[3,15]) 2,3-dihydrofuryl derivatives. A related reaction with disulfides leads to cyclic ketene thioacetals.[8]

Alkylation Reactions: Stereoselective Synthesis of Homoallylic Alcohols.

Alkylations represent a major application of reagent (**1**). The early demonstration of the reactivity of (**1**) toward primary alkyl bromides or iodides[2] followed by the mild hydrolysis of the product illustrates the utility of 5-lithio-2,3-dihydrofuran as a protected substituted acyl anion (eq 3). While the first alkylation reactions have been conducted at moderate temperatures (-78 to 20 °C) in a THF/HMPA mixture,[1,2] later experiments have used THF only, sometimes at temperatures up to 50 °C (eq 3).[3,16]

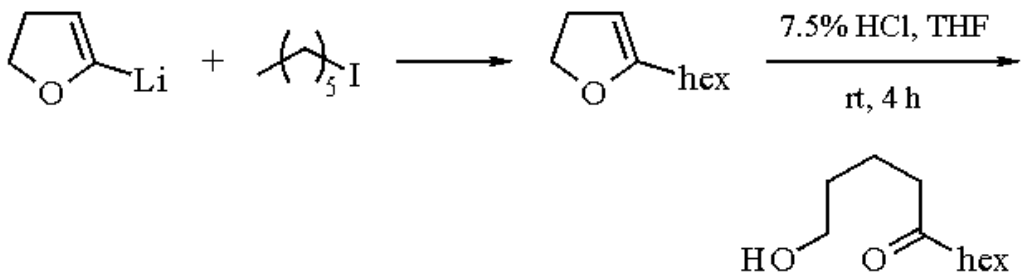

(3)

The alkylation products easily rearrange, placing the double bond into the exocyclic position, as noticed at room temperature in deuteriochloroform (eq 4).[3,17]

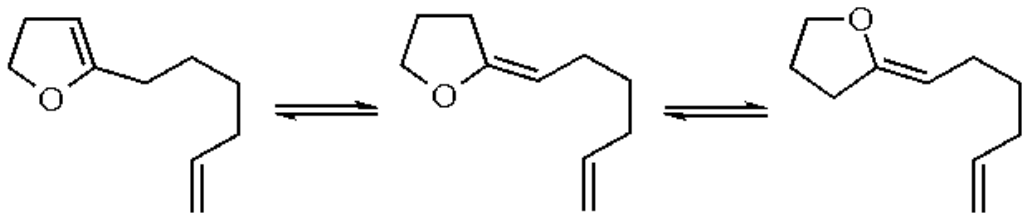

(4)

This reaction has since been applied extensively to the preparation of 5-alkyldihydrofurans whose Ni^0-catalyzed coupling with Grignard reagents leads with high stereocontrol to homoallylic alcohols.[18a] Among the

numerous examples and applications to the stereoselective synthesis of trisubstituted alkenes,[3,9,16,19] an especially attractive example is the coupling with MeMgBr. This yields a useful isoprenoid structure well suited for the iterative approach to the terpene series adopted by Kocienski and colleagues.[19c] In this work, (**1**) is alkylated by 1-iodo-4-methylpent-3-ene in THF at -30 °C to provide the 5-substituted 2,3-dihydrofuran. The latter compound then is coupled with ***Methylmagnesium Bromide*** in benzene in the presence of a catalytic amount of a Ni^0 complex, providing efficient (89%) access to homogeraniol with almost total control (>97%) of the stereochemistry of the double bond. Conversion of this alcohol into the iodo compound provides the substrate for the next iteration, viz alkylation of (**1**), Ni^0-catalyzed coupling with MeMgBr, and iodination (see ***Iodine***). A third iteration is then applied, leading in excellent overall 46% yield (9 steps) to homogeranylgeraniol (eq 5).

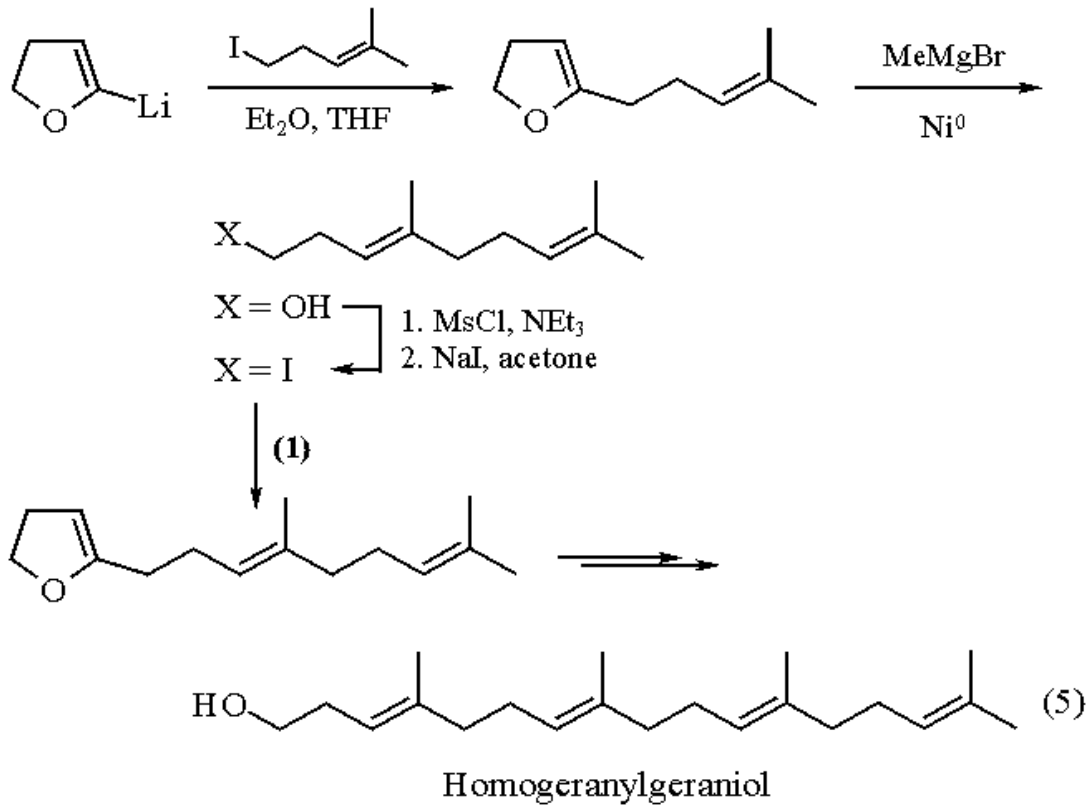

The reaction, however, is restricted to Grignard reagents. On coupling of 5-(trimethylsilyl)- or 5-(trimethylstannyl)dihydrofuran with methylmagnesium bromide a versatile vinyl silane is obtained,[3] which, for instance, could be brominated with complete stereochemical inversion (eq 6).

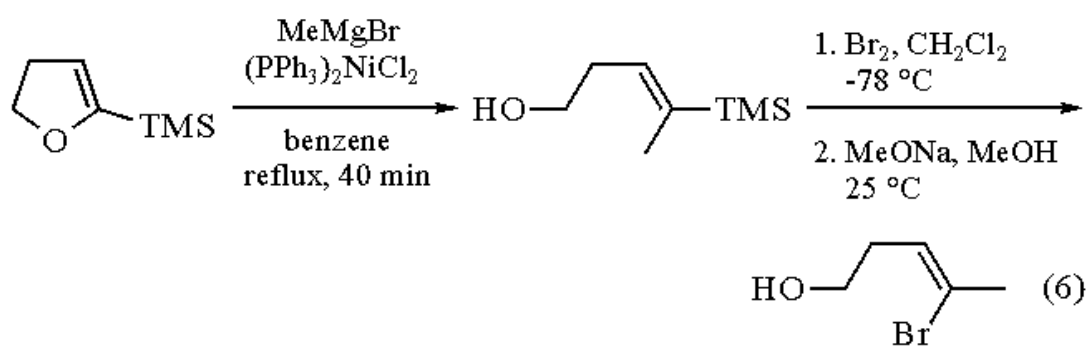

The stereoselective access to (*E*)-disubstituted alkenes is within this methodology's reach.[3,18,20] The use of a Grignard reagent bearing β-hydrogen(s) involves a reduction reaction competing with the coupling

reaction,[18a] supposedly through a β-hydride elimination process and formation of nickel hydride complexes. The observed stereoselectivity depends strongly on the nature of the Ni ligands.[3,20] A recent application of this reduction process is the stereoselective synthesis of the macrolactonic fungal metabolite (±)-recifeiolide.[20]

The title compound can undergo double C-5 substitution. This reaction has been reported to proceed with copper catalysis,[15,19a,21] but has been observed also in the absence of any transition metal.[7] The dihydrofuran moiety is exposed to two successive reactions, first with a nucleophilic (Grignard or organolithium) reagent and then with an electrophilic partner, in a one-pot procedure.[7,15] The copper-catalyzed coupling reaction has been proposed to involve higher or lower order cuprate intermediates, followed by a 1,2-alkyl migration or a dyotropic rearrangement (eq 7).[15,19d]

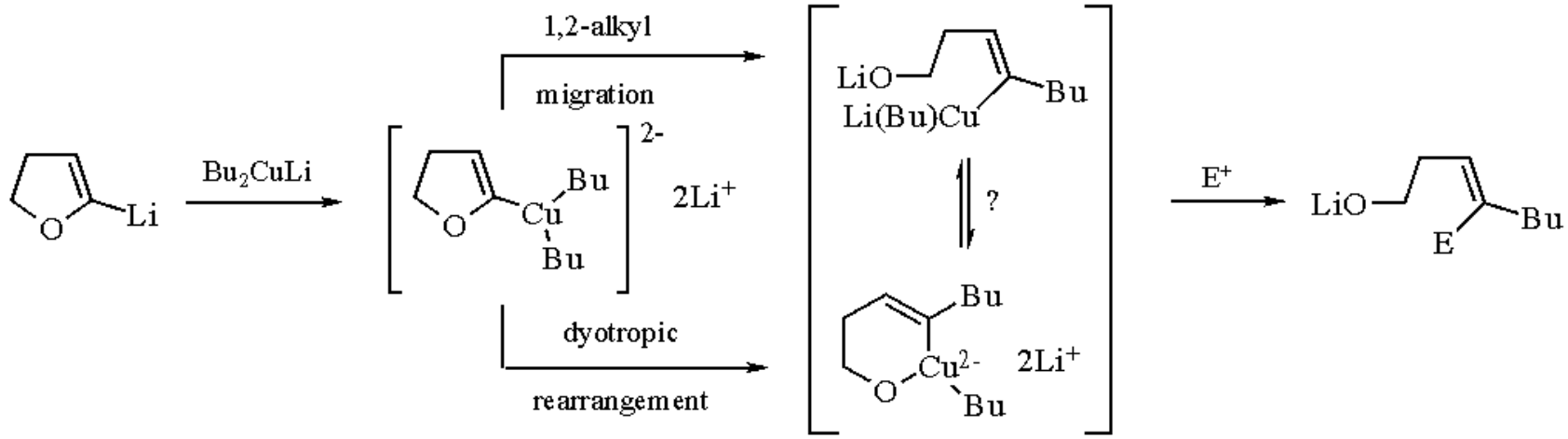

(7)

Depending on the alkyllithium partner, this reaction may become catalytic in copper, a feature explained through a catalytic cycle involving ligand exchange at the metal.[19d]

Unlike the reaction of Grignard reagents with 2,3-dihydrofuran under Ni^0 catalysis[18,22] (coupling with retention of configuration), the corresponding Cu^I-catalyzed reaction appears to proceed with inversion of configuration, leading to di- or trisubstituted homoallylic alcohols (*E* &egt; 97% stereoselectivity). In the absence of any alkyl ligand on copper, this reaction leads to the self coupling of the enol ether, providing spiroacetals.[19d] The first application to natural product chemistry derived from this methodology is the synthesis of the antihypotensive agent lacrimin A.[23] In the case of the uncatalyzed reaction, an addition-elimination mechanism with a dilithiated intermediate has been proposed (eq 8).[7]

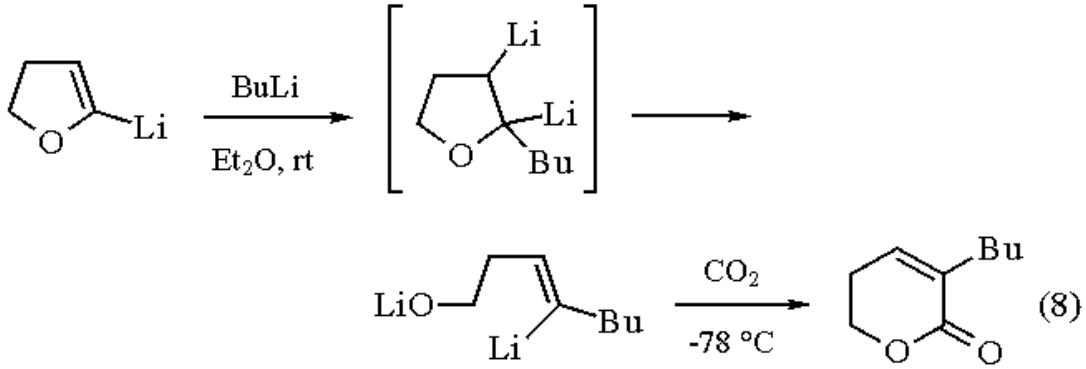

(8)

Other Transmetalation Reactions.

Only a few examples have been described. It has been shown that the low temperature addition of the THF solution of (**1**) to trialkylaluminum in hexane leads to the corresponding dihydrofuranyl triorganoaluminates.[24] These add to electrophiles such as cyclohexene oxide in the presence of a stoichiometric amount of ***Boron Trifluoride Etherate*** to yield the substituted cyclohexanols with a good diastereoselectivity. A 1,2-alkyl migration is proposed to explain this unexpected reactivity. On the other hand, the ring-opened product is obtained by treatment with the same Lewis acid in the absence of any

electrophile,[24] a reaction resembling the copper-catalyzed coupling described above (eq 9).[19d]

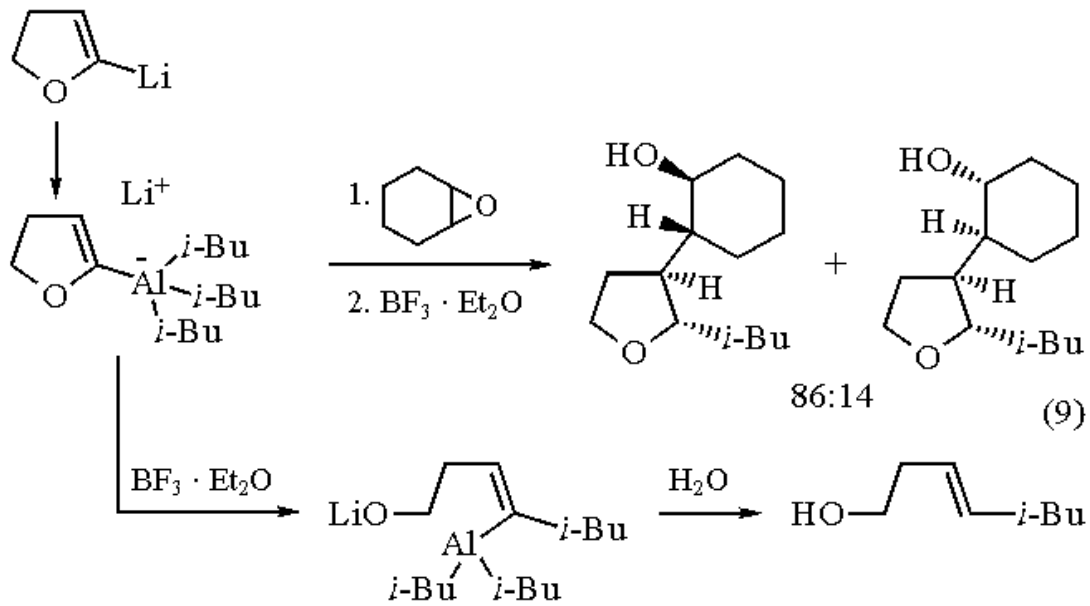

Dihydrofuranyl nickel(II) complexes have been prepared[6] starting from (**1**) and have been shown to yield Ni carbene complexes. Some of them could be crystallized.[6,25]

Related Reagents.

1-Ethoxyvinyllithium; ***6-Lithio-2,3-dihydro-4H-pyran***.

---

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19. (a) Kociénski, P.; Wadman, S.; Cooper, K. *TL* **1988**, *29*, 2357. (b) Kocienski, P.; Love, C.; Whitby, R.; Roberts, D. A. *TL* **1988**, *29*, 2867. (c) Kocienski, P.; Wadman, S.; Cooper, K. *JOC* **1989**, *54*, 1215. (d)

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6-Lithio-2,3-dihydro-4*H*-pyran[1]

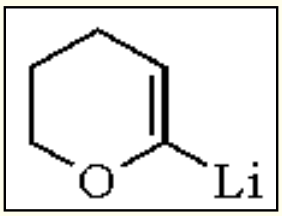

[72081-15-3] · C_5H_7LiO · 6-Lithio-2,3-dihydro-4*H*-pyran · (MW 90.05)

(acyl anion equivalent which reacts with a variety of carbon and other electrophiles via substitution and 1,2-addition;[2-6] after conversion to other organometallics via conjugate addition[7] and Pd^0-catalyzed coupling,[5] the resulting adducts are utilized for the preparation of substituted cyclopentenones and cyclohexenones and polycyclic spiro acetals[2,8,9])

Alternate Name: 6-lithio-3,4-dihydro-2*H*-pyran.

Physical Data: white to off-white, highly moisture and air sensitive solid which may be pyrophoric.[10] ^{13}C NMR (22.625 MHz in d_8 THF): δ 201.2, 111.1 ($^1J_{^{13}C-^1H}$ = 154.8 Hz), 62.8, 24.71, 20.99.[10]

Solubility: sol anhydrous THF, anhydrous ether, and mixtures of saturated hydrocarbons and THF; insol pure hydrocarbons. At high concentrations (> ca. 1M), the reagent will sometimes precipitate from THF-pentanes at -78 °C.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: the extent of metalation can be assessed by deuteration of an aliquot and ^1H NMR analysis of the recovered 2,3-dihydropyran,[10] or by direct observation using ^1H NMR.[2,11] The concentration of solutions of the reagent can be determined by titration.[12]

Preparative Methods: three basic preparative methods have been described: metalation with the *t*-BuLi-2THF complex (lemon yellow) in pentane at about -10 °C;[2] metalation with *n*-BuLi or *t*-BuLi in hexane or pentane containing a catalytic amount of TMEDA at 0 °C to room temperature or slightly above (the reagent precipitates from solution);[10,13] or metalation with *n*-BuLi in hexanes at 50-60 °C for several hours (also results in a precipate of the lithium reagent).[14] For difficult cases, the Schlosser base (*n*-BuLi/KO-*t*-Bu) has been used, usually followed by trapping with chlorotrialkylstannanes and transmetalation of 6-trialkylstannyl-2,3-dihydro-4*H*-pyran and substituted derivatives thereof with *n*-BuLi in THF at -78 °C,[8,15-21] or by palladium-catalyzed coupling of chlorotrialkylstannanes with enol triflates derived from δ-lactones.[22]

Purification: none is normally required; the reagent is used as prepared.

Handling, Storage, and Precautions: the reagent is customarily utilized shortly after preparation. Solvents and reagents should be anhydrous and free of oxygen. Commercial 2,3-dihydropyran is distilled before use. Solutions of the reagent must be protected from air and moisture utilizing standard inert atmosphere/syringe techniques.

Metalation of 2,3-Dihydro-4*H*-pyran (2) and Related Substituted 2,3-dihydro-4*H*-pyrans.

Recommended Procedure for (1).

Metalation of the parent 2,3-dihydro-4*H*-pyran (***3,4-Dihydro-2H-pyran***) (**2**) proceeds smoothly under a variety of reaction conditions to afford exclusively the 6-lithio derivative (**1**) (eq 1).[2] The preferred procedure employs the yellow 2*t*-BuLi-THF complex prepared by treatment of ***t-Butyllithium*** in pentane with a minimum amount (~2 equiv) of THF.[2,11] On a substantial scale, care must be taken to avoid localized heating owing to the heat of solvation which can cause loss of *t*-BuLi.[23] Thus it is advisable to provide efficient stirring and cooling, and to precool the THF to be added. Addition of dihydropyran at -78 °C and slow warming to ca. -10 to 0 °C results in decolorization of the yellow color and the formation of a colorless homogeneous solution of the metalated pyran (**1**). Since metalation is significantly exothermic and does not proceed rapidly at temperatures below -10 °C, when working at concentrations above ~0.25 M it is advisable to add a precooled solution of the dihydropyran to the solution of 2*t*-BuLi-THF complex dropwise at about -10 to 0 °C with efficient stirring.[2,11] Solutions of (**1**) are typically diluted with additional anhydrous THF and recooled to -78 °C prior to use (at higher concentrations, the reagent will sometimes precipitate from solution).

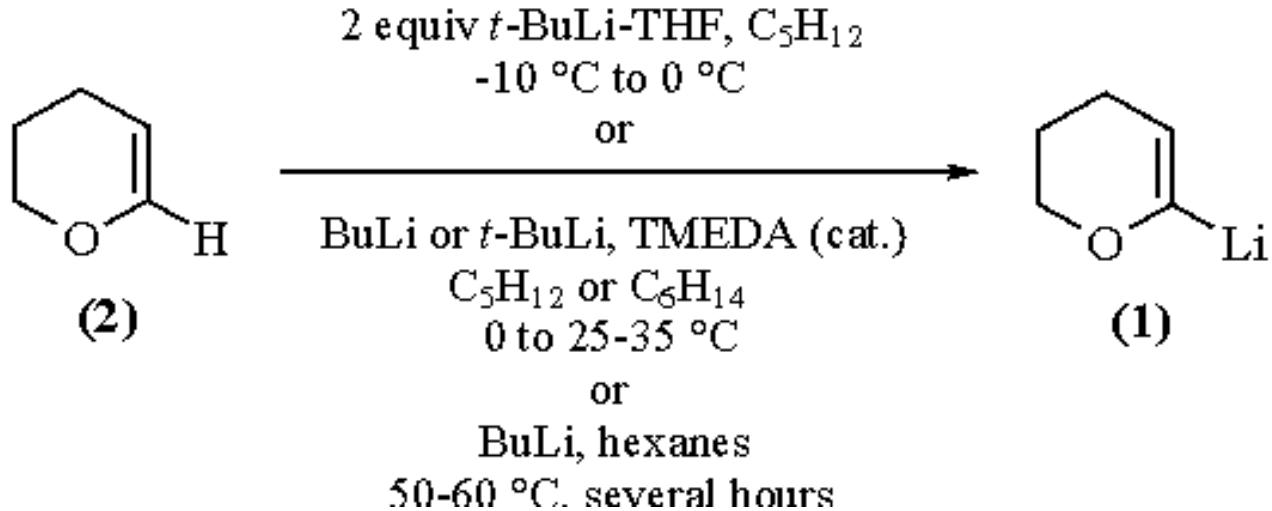

(1)

This procedure is suitable for use with many substituted dihydropyrans, and dihydrofurans, provided there are not additional remote coordinating heteroatoms present. In the absence of remote heteroatom substituents, the rates of metalation are related to the type of substitution at the β-position of the vinyl ether double bond.[2,11] Electron-deficient substituents and substituents containing heteroatoms suitably positioned to assist metalation by coordination of the metalating agent, and/or stabilize the metalated species by chelation, accelerate metalation (e.g. Cl, $(CH_2)_n$OR (n = 1,2)) and alkyl substituents retard it, although examples of successful metalation of a β-methyl substituted

system have been reported.[2,3,24]

Other Procedures.

Less reactive metalating agents such as ***n-Butyllithium*** can only be employed in saturated hydrocarbon solvents since complete metalation requires 1-2 h at 50-60 °C (incompatible with ethereal solvents), affording (**1**) as a precipitate.[14] Either *n*-BuLi at rt to ~30-40 °C or *t*-BuLi at 0 °C to rt can also be employed in the presence of a catalytic amount of ***N,N,N´,N´-Tetramethylethylenediamine*** to assist deaggregation of the alkyllithium metalation reagent, also affording (**1**) as a precipitate.[10,13]

In the cases where metalation fails with the usual procedures, successful metalation can often be achieved by use of the Schlosser base ***n-Butyllithium-Potassium t-Butoxide***.[25,26] Although the species formed can, in principle, be reacted directly with electrophiles, often the basicity of the species is such that clean reactions do not result. In these instances, trapping with chlorotrialkylstannanes cleanly affords the trialkylstannane from which the required lithiopyran can be regenerated by transmetalation with *n*-BuLi (eq 2).[8,15-21] In the presence of heteroatom substituents, use of excess *t*-BuLi with or without subsequent stannylation (eq 3)[2,20,27] or the Schlosser base/stannylation procedure is generally required.[2,8,15-21] The choice of protecting groups for oxygen and nitrogen is crucial to the success of the metalation. Generally, simple alkyl ether, MOM,[19] and TIPS[21] protecting groups are suitable, but benzyl ethers are not owing to competing metalation of the aromatic ring.[16] Oxygenated dihydropyrans bearing TBDMS protecting groups have been metalated,[27,28] but sometimes competing metalation of the methyl groups on the silicon occurs.[29-31] If the system undergoing metalation is exceedingly sterically congested, loss of regiospecificity during metalation has been observed.[32]

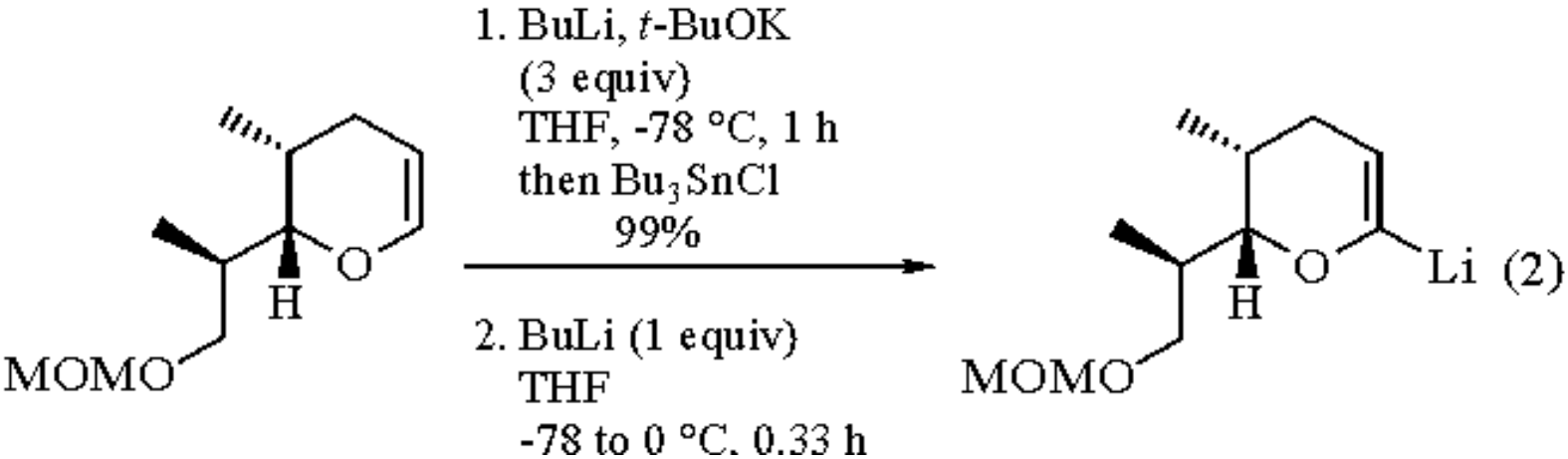

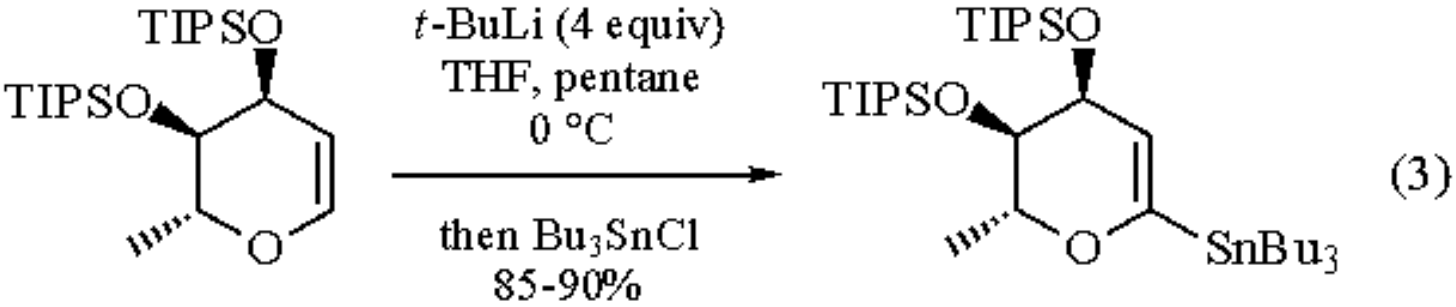

Addition of (1) and Related Systems to Carbonyl

Derivatives and Activated Alkenes.

Addition of lithiopyran (**1**) to all manner of carbonyl electrophiles generally occurs cleanly and in excellent yield (eqs 4-9),[2,6,36,37] although extensive purification of the resulting adducts is not advisable owing to their acid sensitivity.[2,3,13,33] Lithiopyran (**1**) behaves in all respects like a typical strongly nucleophilic and basic organolithium reagent in that multiple addition occurs to acid halides, esters, and related acylating agents, and 1,2-addition occurs exclusively in conjugated carbonyl compounds, including (*E*)-β-trimethylsilylacrolein which affords the corresponding ketone upon oxidation.[2,34] Successful addition of lithiopyran (**1**) exclusively 1,2 to a quinone monoacetal has also been reported.[35] Even complex aldehydes prone to epimerization and β-elimination undergo smooth addition.[36] Addition of lithiopyran (**1**) to acylsilanes followed by Brook rearrangement, ring opening, and silylation affords allenolsilanes very efficiently.[15] Amides, oxalic ester amides, nitriles, and γ-lactones can be employed to afford aldehydes, imines, ketones, and α-ketoamides.[2,3,37-39] Carboxylation affords the corresponding acid and the derived esters.[3,18] 1,4-Addition of (**1**) has been observed to an unsaturated sulfone.[6] Addition of (**1**) to fluoroacetylene (prepared in situ by metalation/elimination of 1,1-difluoroethylene at -110 °C) followed by elimination of fluoride also occurs.[6] These carbanions function as masked acyl anion equivalents and have been employed to prepare a variety of cyclopentenones, cyclohexenones, and 4- and 5-oxo esters.[2]

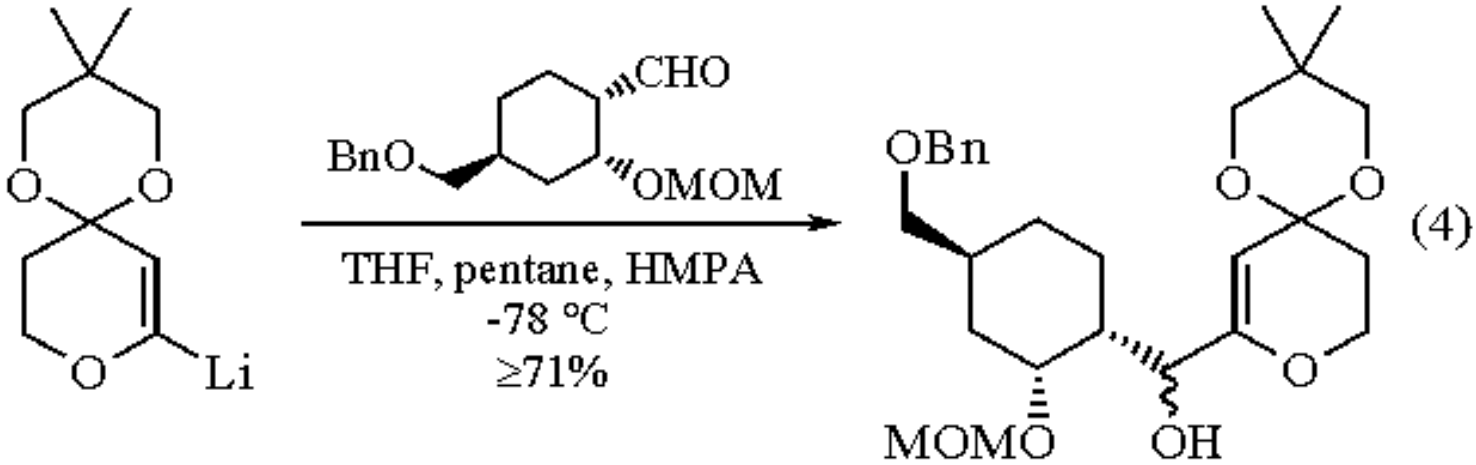

(4)

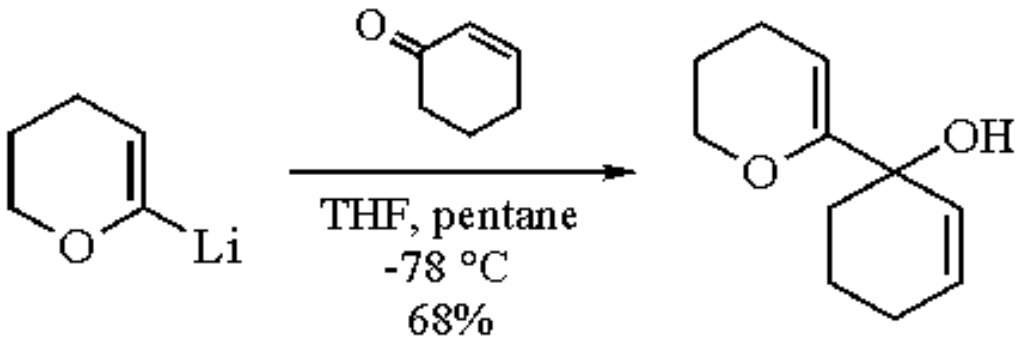

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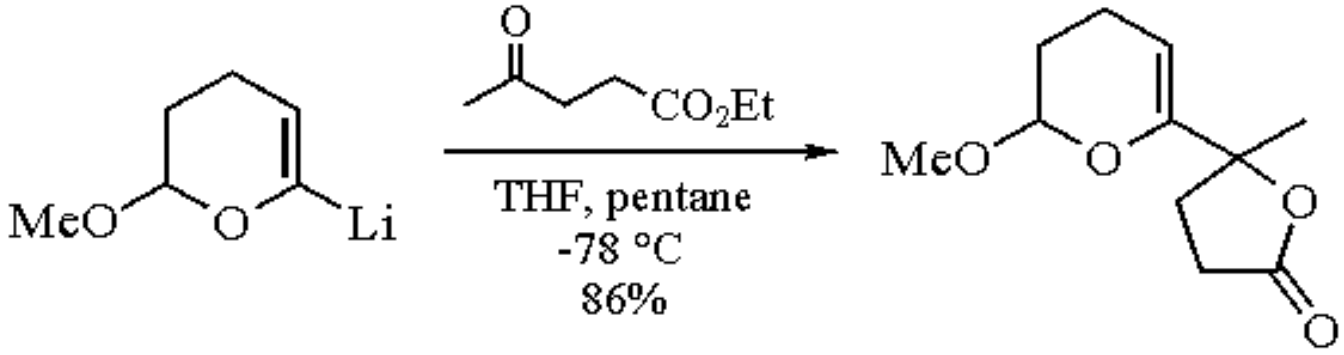
MeO
O
Li
O
CO2Et
THF, pentane
-78 °C
86%
MeO
O
O
O

(6)

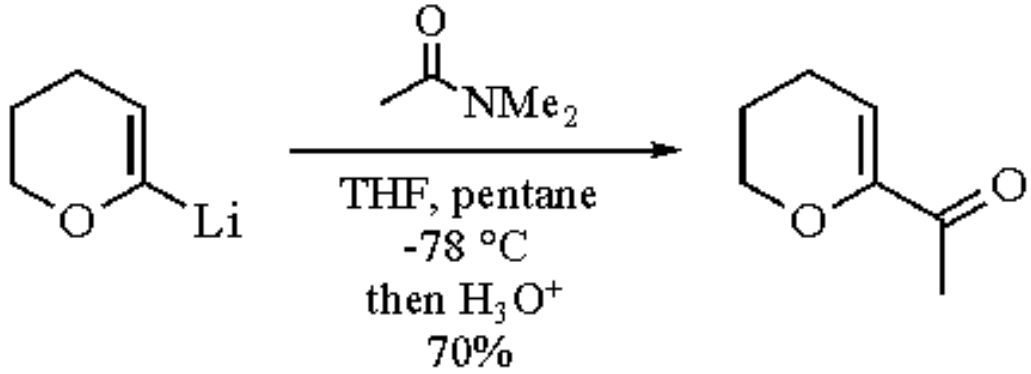
O
Li
O
NMe2
THF, pentane
-78 °C
then H3O+
70%
O
O

(7)

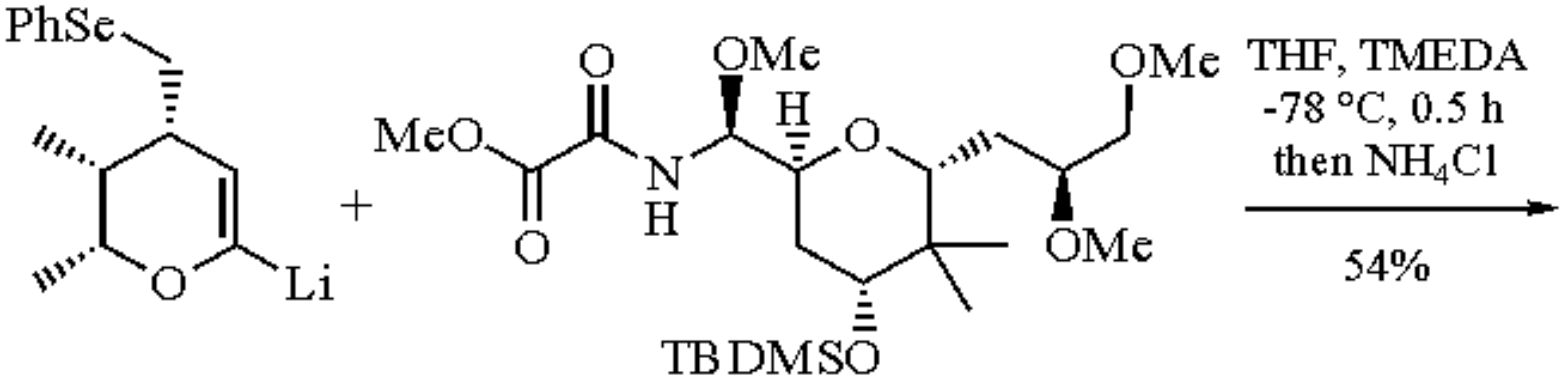
PhSe
O
Li
+
MeO
O
O
N
H
OMe
H
O
OMe
OMe
TBDMSO
THF, TMEDA
-78 °C, 0.5 h
then NH4Cl
54%

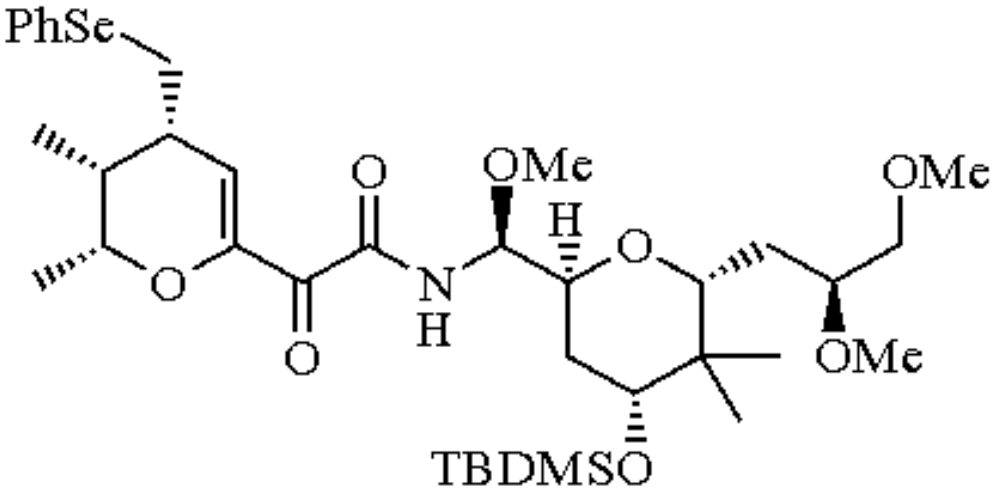
PhSe
O
O
O
N
H
OMe
H
O
OMe
OMe
TBDMSO

(8)

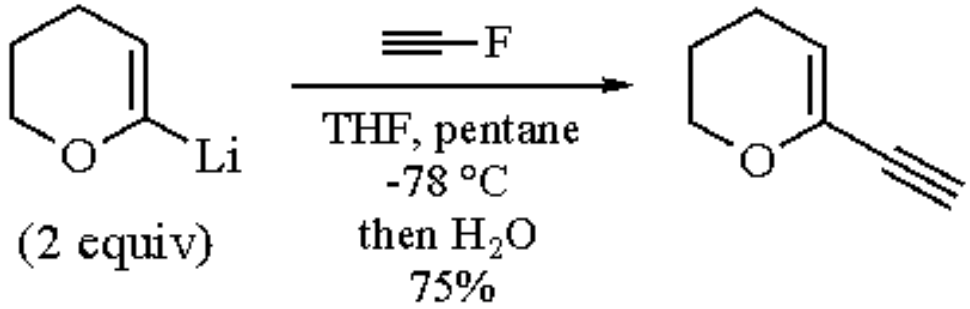

(9)

Alkylation and Related Substitution Reactions of (1) and Related Systems.

Lithiopyran (**1**) undergoes smooth alkylation by ***Iodomethane*** as well as a variety of primary saturated and homoallylic alkyl bromides and iodides, including examples containing protected oxygen functions and remote unsaturation (eqs 10-13).[2-4,8,14,19,40-48] Alkylation of (**1**) by primary and secondary allylic and benzylic bromides, as well as occasionally chlorides, has been reported to occur in good yield in many cases,[2,13,20] but sometimes α-metalation of the allylic halide competes.[2] To overcome this limitation, (**1**) has been converted to its less basic organocopper derivative for reaction with allyl iodide.[27] As is usual for hard organolithium reagents, (**1**) and its derivatives react poorly with epoxides,[2] and other organometallic derivatives are used (see below). Of course, (**1**) and related systems react readily with trialkylsilyl and trialkylstannyl halides, disulfides, and even sources of positive halogen such as NBS to afford the expected substitution products.[2,5,8,19-22,29,49-51] A conceptually related process involving alkylation-elimination of 2-phenylsulfonylpyrans has also been described.[52]

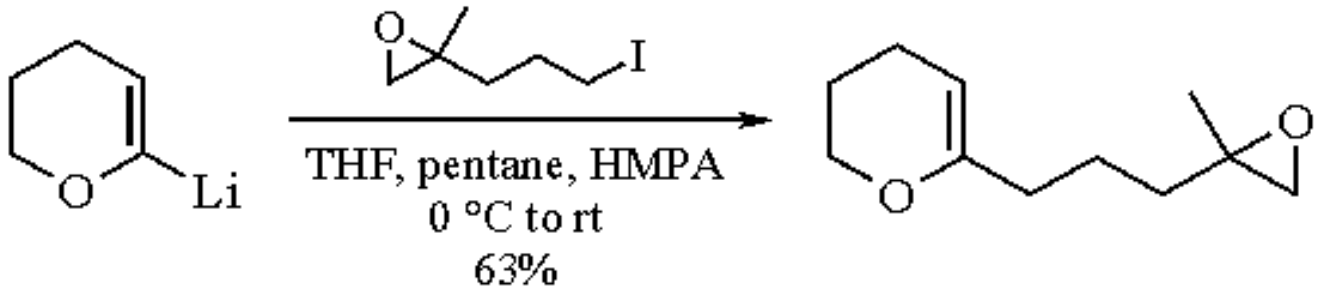

(10)

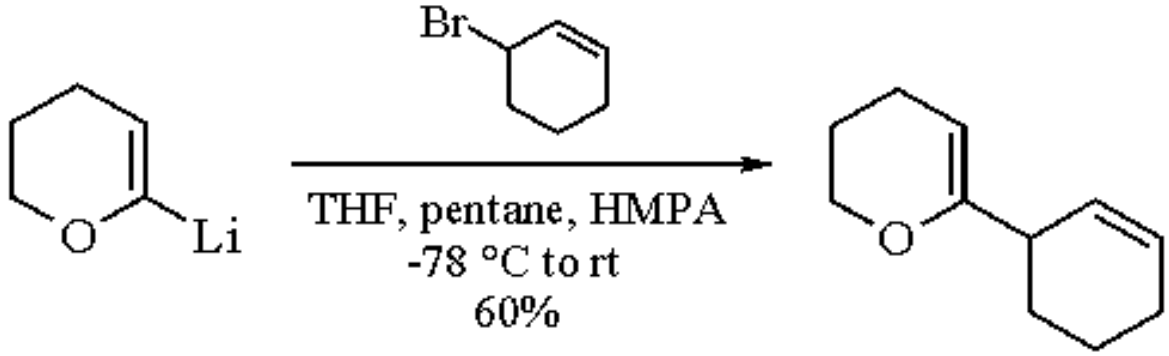

(11)

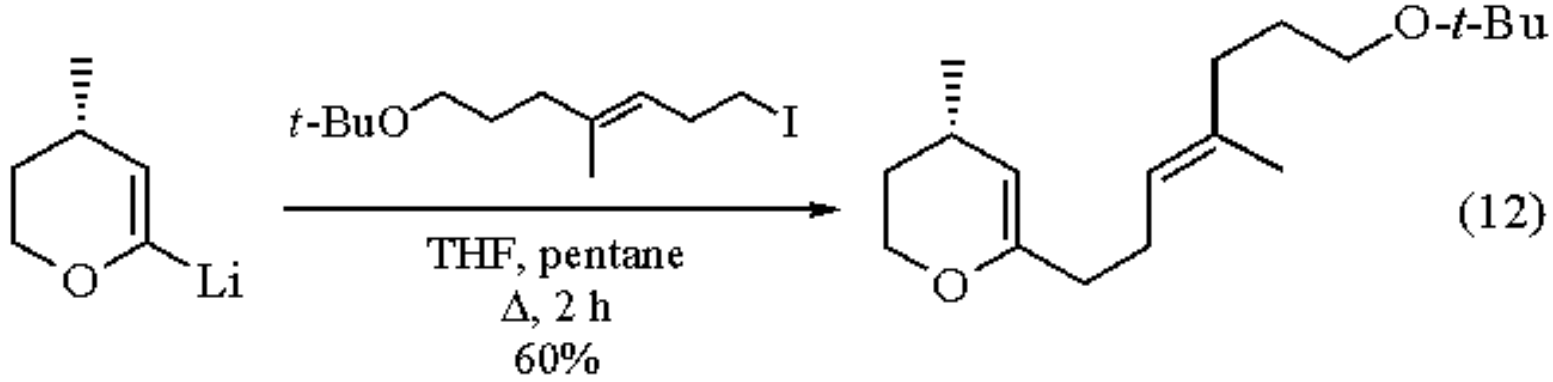

(12)

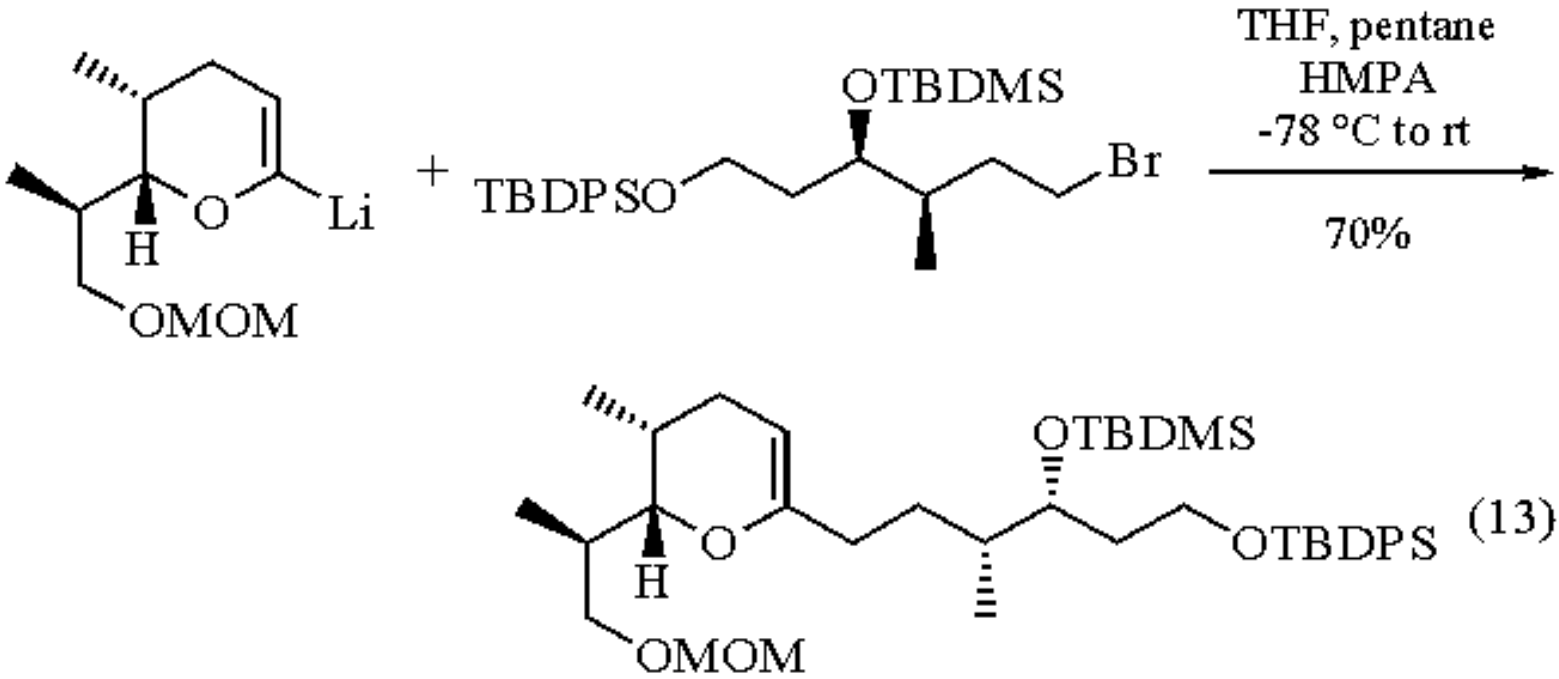

(13)

Conversion of (1) and Related Systems to Other Organometallic Derivatives and Subsequent Reactions.

In order to effect opening of epoxides in high yield, conversion of (**1**) and related systems to mixed diorganocuprate reagents is generally required (eq 14).[53-55] In highly functionalized systems, ***Boron Trifluoride Etherate*** has been employed as an additional Lewis acid to assist the opening.[56]

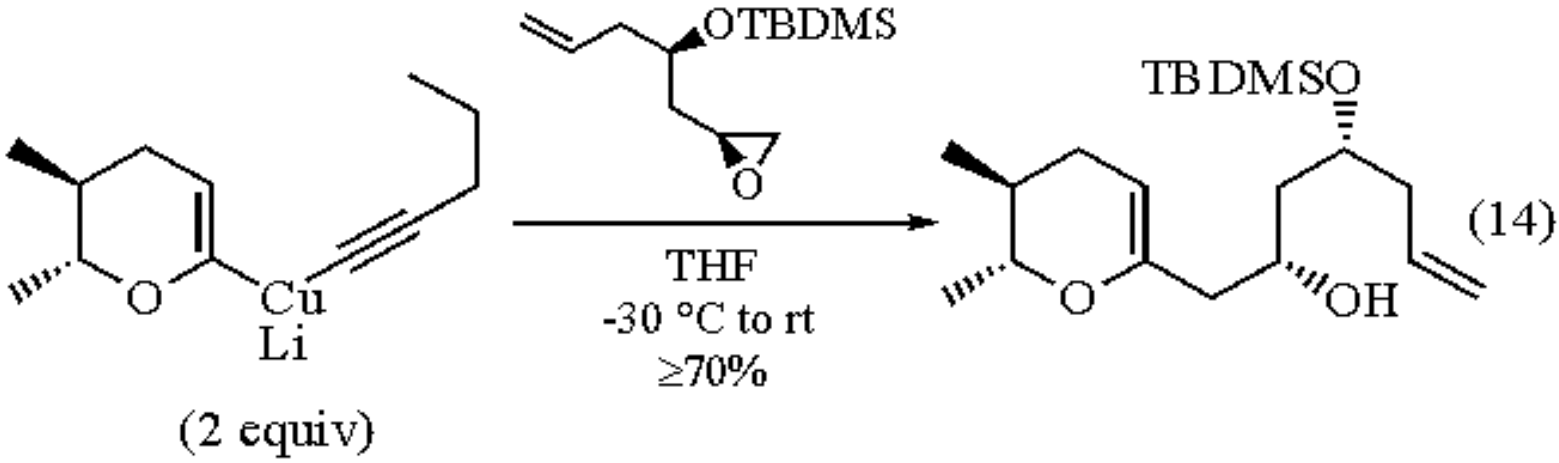

Lithiopyran (**1**) and related systems upon reaction with mixed cyanocuprate reagents at 0 °C and above afford stereoselectively (*E*) disubstituted and trisubstituted alkenic alcohols arising from ring cleavage by apparent substitution at the α-alkenic center by the alkyllithium reagent in an overall inversion at the α-alkenic carbon (eq 15).[53] This process may proceed by way of one of several mechanisms.[55] A conceptually similar reaction is observed between vinyl ethers and Grignard reagents catalyzed by nickel(II) complexes.[24] Lithiopyran (**1**) and related systems have also been found to react directly with simple alkyllithium derivatives to give the same spectrum of products with the same stereoselectivity upon quenching with protons, CO_2, and alkyl halides as occurs with the cyanocuprate derivatives of (**1**) and related systems.[57] The latter reaction does not occur with acyclic analogs of (**1**).

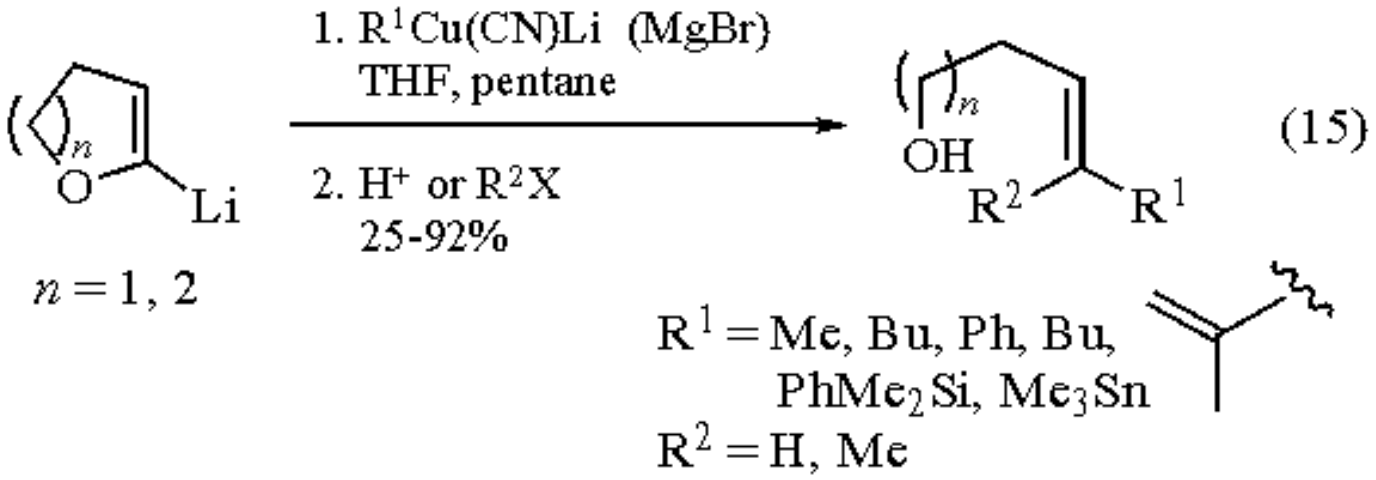

A derivative of (**1**) has been converted to a *C*-glycoside derivative by Pd^0-catalyzed coupling of the zinc derivative with an aryl iodide (eq 16).[28] Furthermore, aluminates formed from (**1**) undergo a novel 1,2-migration reaction upon treatment with benzaldehyde in the presence of $BF_3.Et_2O$, affording *trans*-2-methyl-3-(1-hydroxy-1-phenylmethyl)tetrahydropyrans and -furans (eq 17).[57]

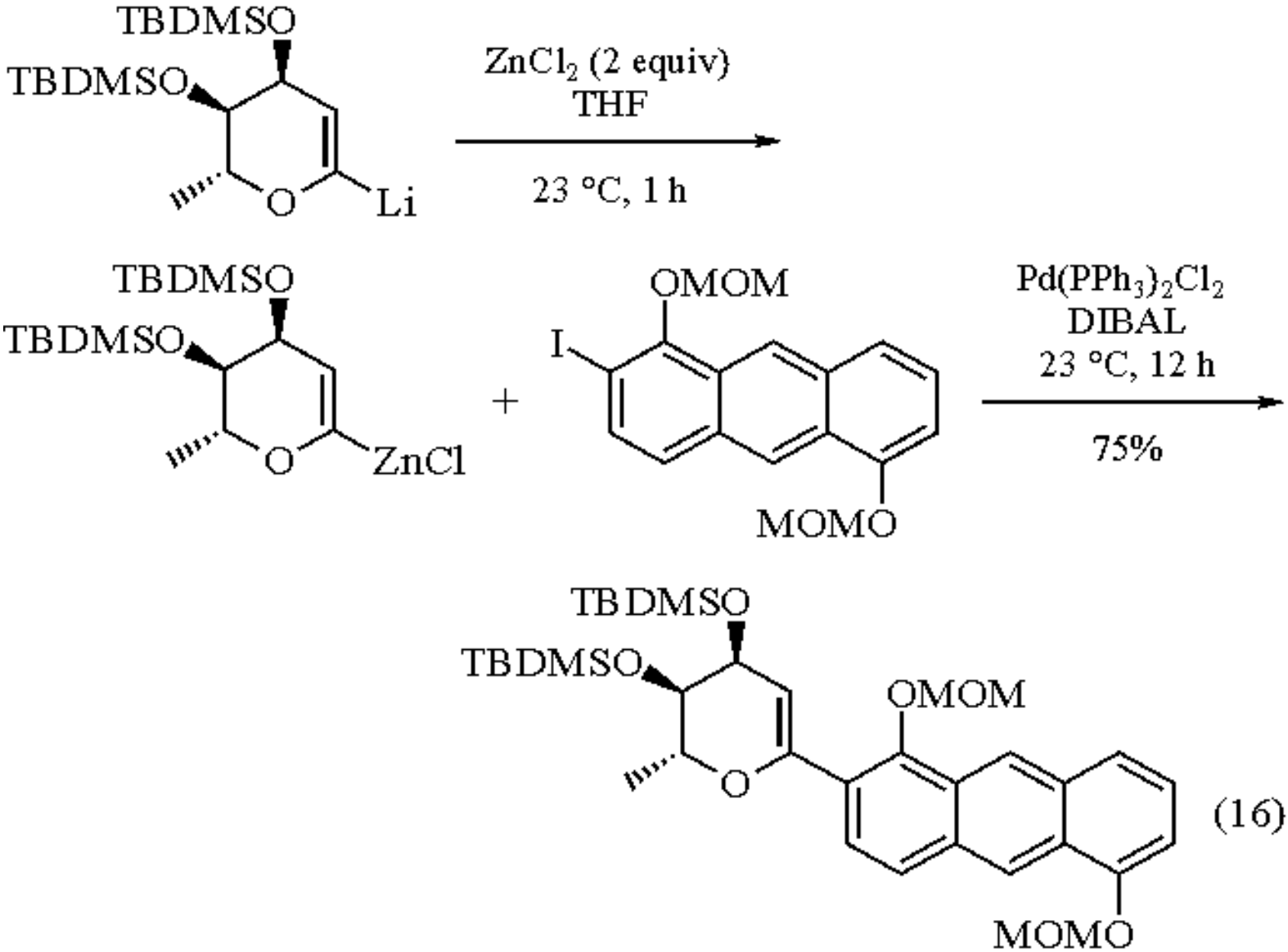

(16)

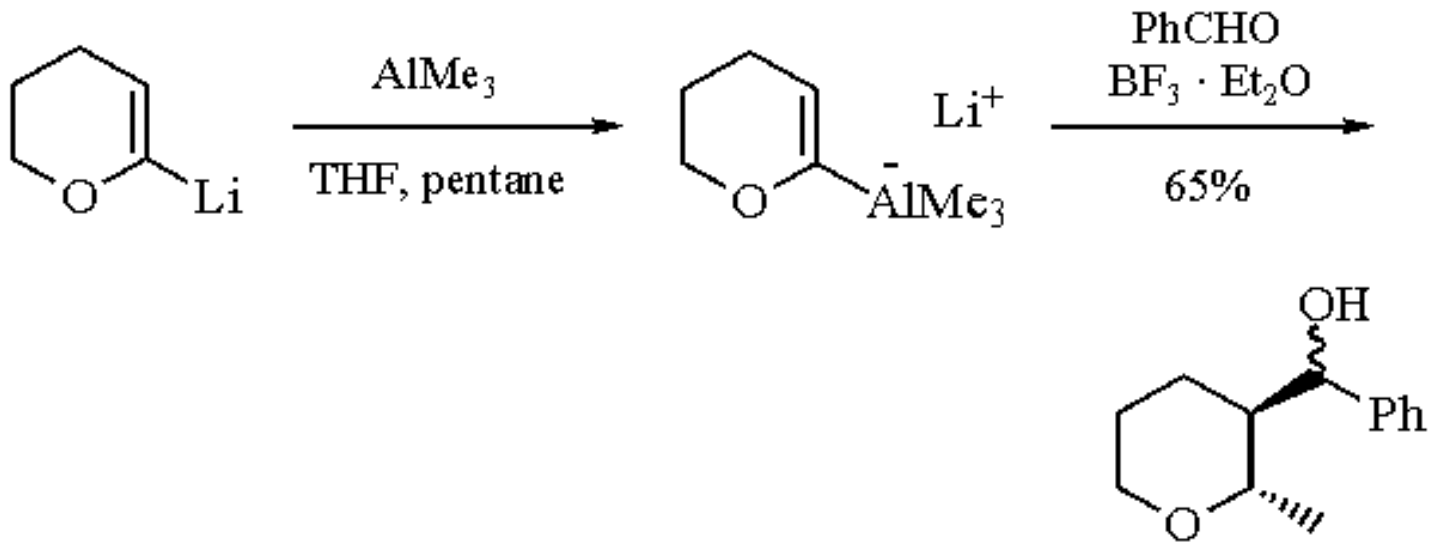

(17)

Finally, in reaction with sterically hindered ketones, conversion to the dichlorocerium reagent by transmetalation of (**1**) and related derivatives with anhydrous ***Cerium(III) Chloride*** minimizes enolization of the substrate (eq 18).[58]

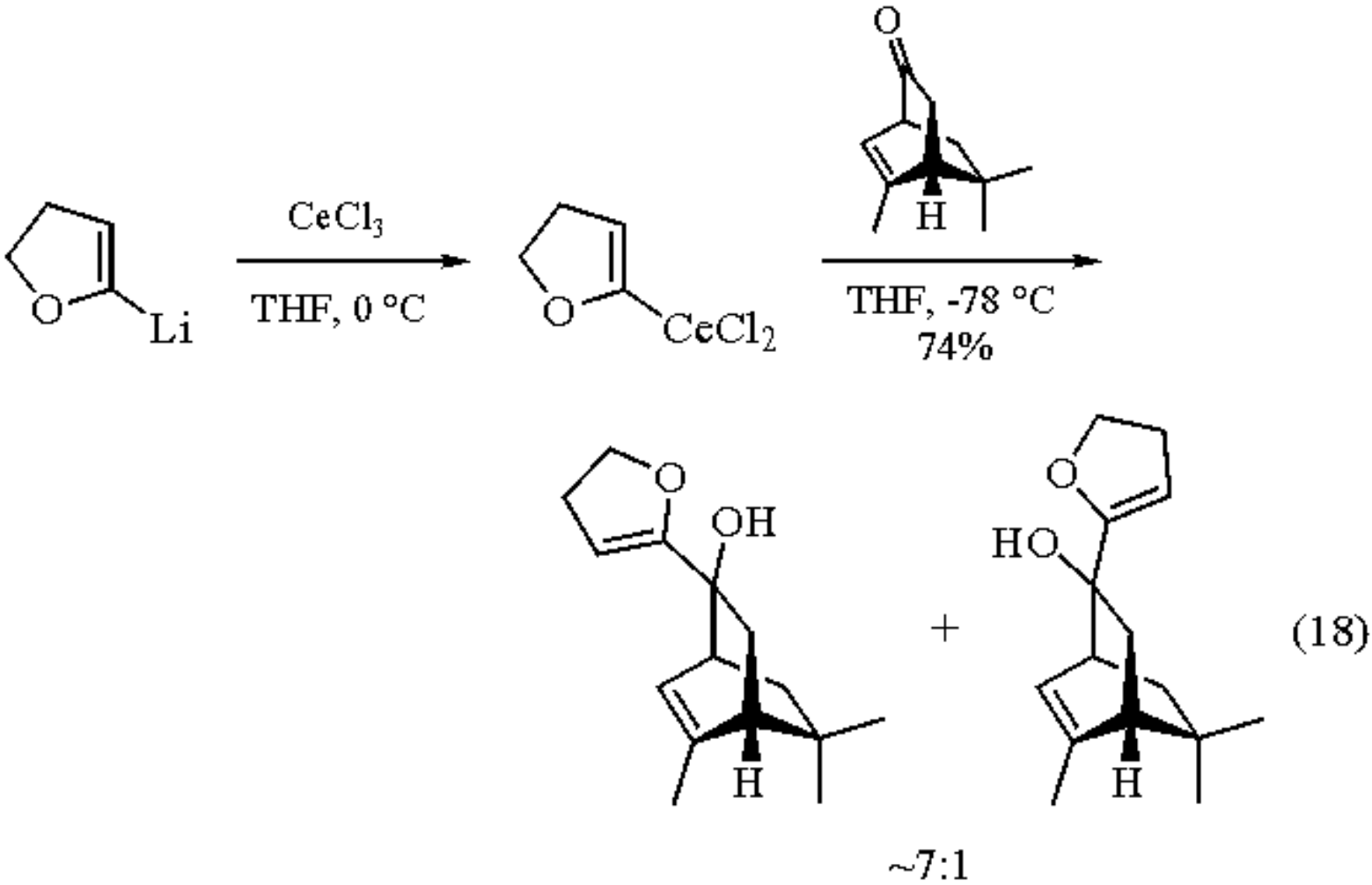

Conversion of (1) and Related Systems to Trialkylstananes and Regeneration of the Lithium Derivative or Direct Palladium-Catalyzed Crossed Coupling.

In addition to the aforementioned methods involving stannylation of lithiopyran (**1**) and related systems by reaction with chlorotrialkylstannanes (eqs 2 and 3),[5,8,16,18,20,21,51] a route from six- or seven-membered ring lactones is available (eq 19).[22] The method fails for five- and eight-membered rings owing to the inability to form the required enol triflates under the usual conditions.[22] These stannane derivatives are precursors for the lithium species by transmetalation (eq 2),[8,16,18,37,51] as well as undergoing direct Pd^0-catalyzed coupling with aryl, allyl, benzyl, and acyl halides (eqs 20 and 21).[5,20,21,50] The oxidative dimerization of the parent alkylstannane, derived from (**1**), catalyzed by $Cu(NO_3)_2$ has also been reported.[59]

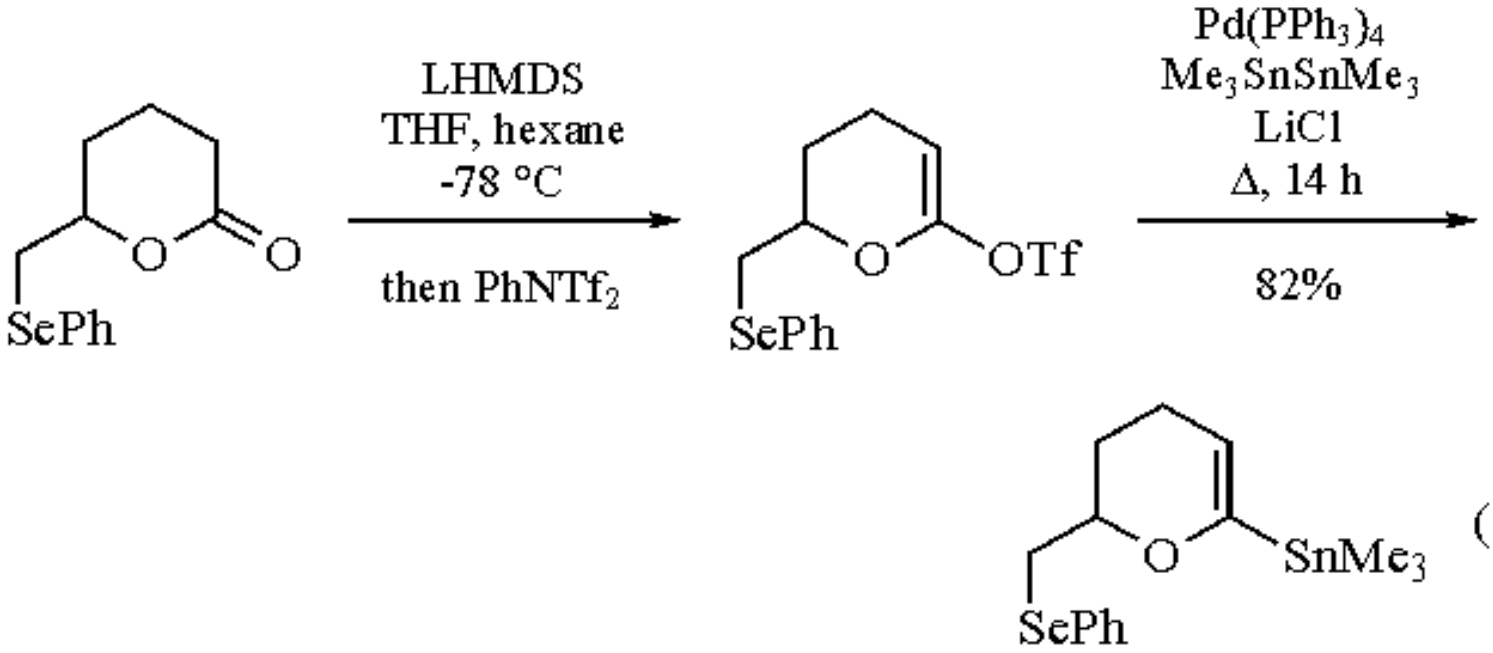

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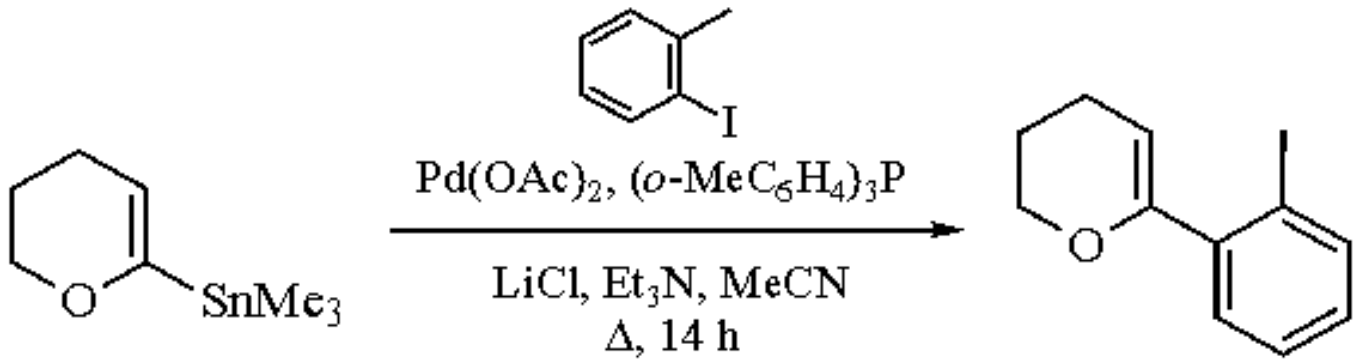

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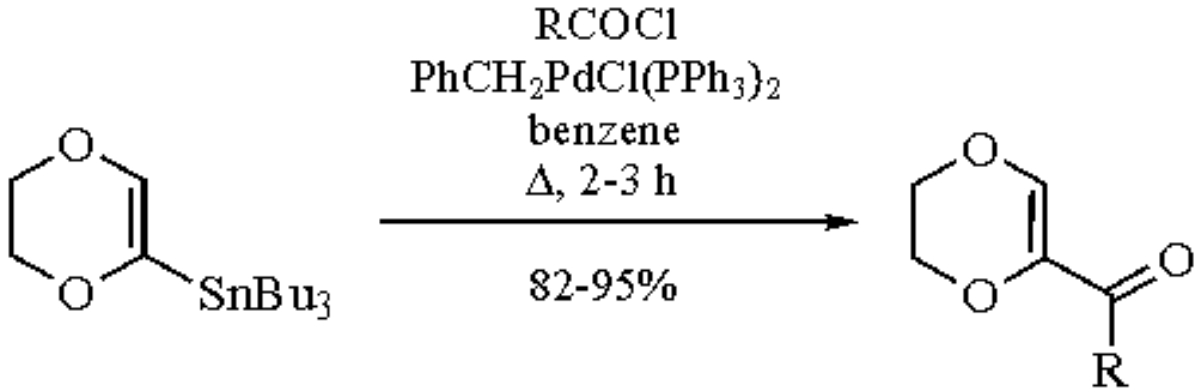

(21)

R = Me, *i*-Bu, Ph, 4-$MeOC_6H_4$
4-$NO_2C_6H_4$, 2-furyl

Metalation and Reactions of Other Cyclic and Acyclic Vinyl Ethers.

Dihydrofurans[2,19,60,61] and the parent dihydrooxepin[10] afford the analogous α-lithio derivatives. Metalation of 1,4-dioxene derivatives has also been reported, although loss of metalation regiospecificity has been noted in hindered systems.[32,50] Metalation of acyclic vinyl and dienyl ethers has also been reported where metalation regiospecificity can be controlled by use of MOM ethers.[62-66] Selectivity for metalation of the α-vinyl H vs. allylic metalation is also observed and a theoretical model has been proposed.[67,68] Reactions of these lithiated ethers parallel those of lithiodihydropyran (**1**).[2,4,5,10,19,21,24,38,44,48,49,57,58,62,64,69-71]

Related Reagents.

(Z)-2-Ethoxyvinyllithium; ***1-Ethoxyvinyllithium***; ***5-Lithio-2,3-dihydrofuran***; ***1-Methoxyvinyllithium***.

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Lithio-*N,N*-dimethylacetamide

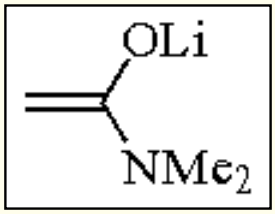

[55259-70-6] · C_4H_8LiNO · Lithio-*N,N*-dimethylacetamide · (MW 93.05)

(relatively stable enolate;[1] used for aldol condensations[1,2] and conjugate addition;[3] reacts with epoxides;[1] can be alkylated[1,2] and silylated[4])

Physical Data: white solid; ^{1}H NMR (pyridine): 3.15 (d, 1H), 2.93 (d, 1H), 2.63 (s, 6H).

Preparative Methods: by deprotonation of *N,N*-dimethylacetamide with a variety of bases, most efficiently with ***Lithium Diisopropylamide*** in THF at -78 °C or at 0 °C.

Handling, Storage, and Precautions: air and moisture sensitive; solid can be stored for several weeks in sealed bottle; THF solutions are stable for at least several hours at 65 °C.

Aldol Condensations.

Lithio-*N,N*-dimethylacetamide reacts with a variety of aldehydes or ketones to give β-hydroxy amides in generally good yields,[2,5] especially at -78 °C.[1] Superior yields, compared to related ester enolates, were obtained with a hindered ketone (eq 1).[5b]

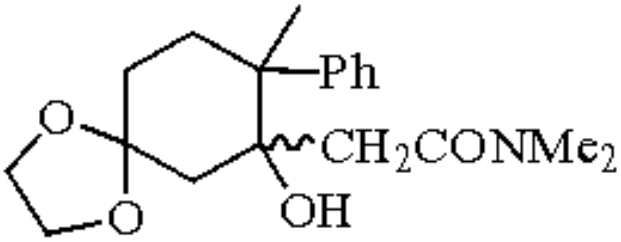

(1)

Asymmetric induction (up to 99% ee) has been reported for condensations with a chiral sulfoxide adjuvant.[5c] Condensation with an aldehyde imine has been described.[5d]

Conjugate Addition.

Conjugate addition of the reagent has been reported for nitrostyrenes,[3a] unsaturated thioamides,[3b,c] and a vinyl sulfone.[3d]

Reaction with Epoxides.

The reagent reacts with epoxides in refluxing THF to give γ-hydroxy amides.[1] Reaction of epoxides with related ester enolates gave lower yields, presumably because of the lesser stability of these enolates.

Alkylation and Silylation Reactions.

The reagent reacts with primary and secondary organic halides to give *C*-alkylated products without competing dialkylation.[1,2] The reagent gives primarily the *C*-silylated product with ***Chlorotrimethylsilane*** and a mixture of *O*- and *C*-silylated products with ***t-Butyldimethylchlorosilane***.[4]

Related Reagents.

t-Butyl α-Lithioisobutyrate; ***Dilithioacetate***; ***N,N-Dimethyl-2-(trimethylsilyl)acetamide***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***.

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2-Lithio-1,3-dithiane[1]

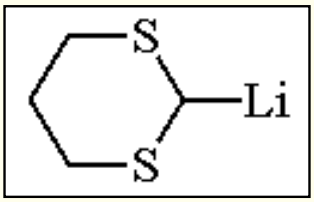

[36049-90-8] · $C_4H_7LiS_2$ · 2-Lithio-1,3-dithiane · (MW 126.19)

(umpolung; C-C bond formation)

Physical Data: pK_a values for several 1,3-dithianes;[1e,2] measurements/calculations on relative acidity of axial vs. equatorial C-2 hydrogens;[3] crystal structure for 2-methyl- and 2-phenyl-2-lithio-1,3-dithiane;[4] low-temperature ^{13}C NMR spectra of ^{6}Li- and ^{13}C-labeled reagent.[5]

Solubility: sol ether, THF; slightly sol pentane.

Analysis of Reagent Purity: solutions of the reagent are colorless, with the exception of solutions of the 2-vinyl- and 2-phenyl-substituted analogs, which are yellow; solutions of the reagent should be titrated before use by one of the standard methods, e.g. MeOD quenching studies (NMR).

Preparative Methods: the parent compound is most conveniently prepared from commercially available ***1,3-Dithiane*** by metalation with one equivalent of ***n-Butyllithium*** at -20 °C in THF.[6] 2-Lithio-1,3-dithianes with a substituent at C-2 can be prepared similarly; the reaction time for metalation varies.[6] Alternatively, Sn/Li transmetalation (LDA or MeLi) of 2-trimethylstannyl- or 2,2-bis(trimethylstannyl)-1,3-dithiane[7] is a much faster process than the direct metalation and occurs within a minute at -78 °C. This allows preparation of substituted 2-lithio-1,3-dithianes, in which the substituent has electrophilic sites, which otherwise would not survive the metalation process.[7] Some sodium[8] and potassium[9] analogs have been reported.[1e] A comprehensive review on the preparation of dithianes is covered under ***1,3-Dithiane***.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen or moisture; solutions in THF are stable for weeks at -20 °C; at room temperature, 2-lithio-1,3-dithiane does not decompose via a carbenoid pathway, but abstracts a proton from the solvent.[1f] Handle in a fume hood.

Alkylation.

On treatment with primary, secondary, or allylic alkyl halides, or primary sulfonates, the corresponding substituted dithianes are obtained, generally in good yield (eq 1).[1b -f,10,11]

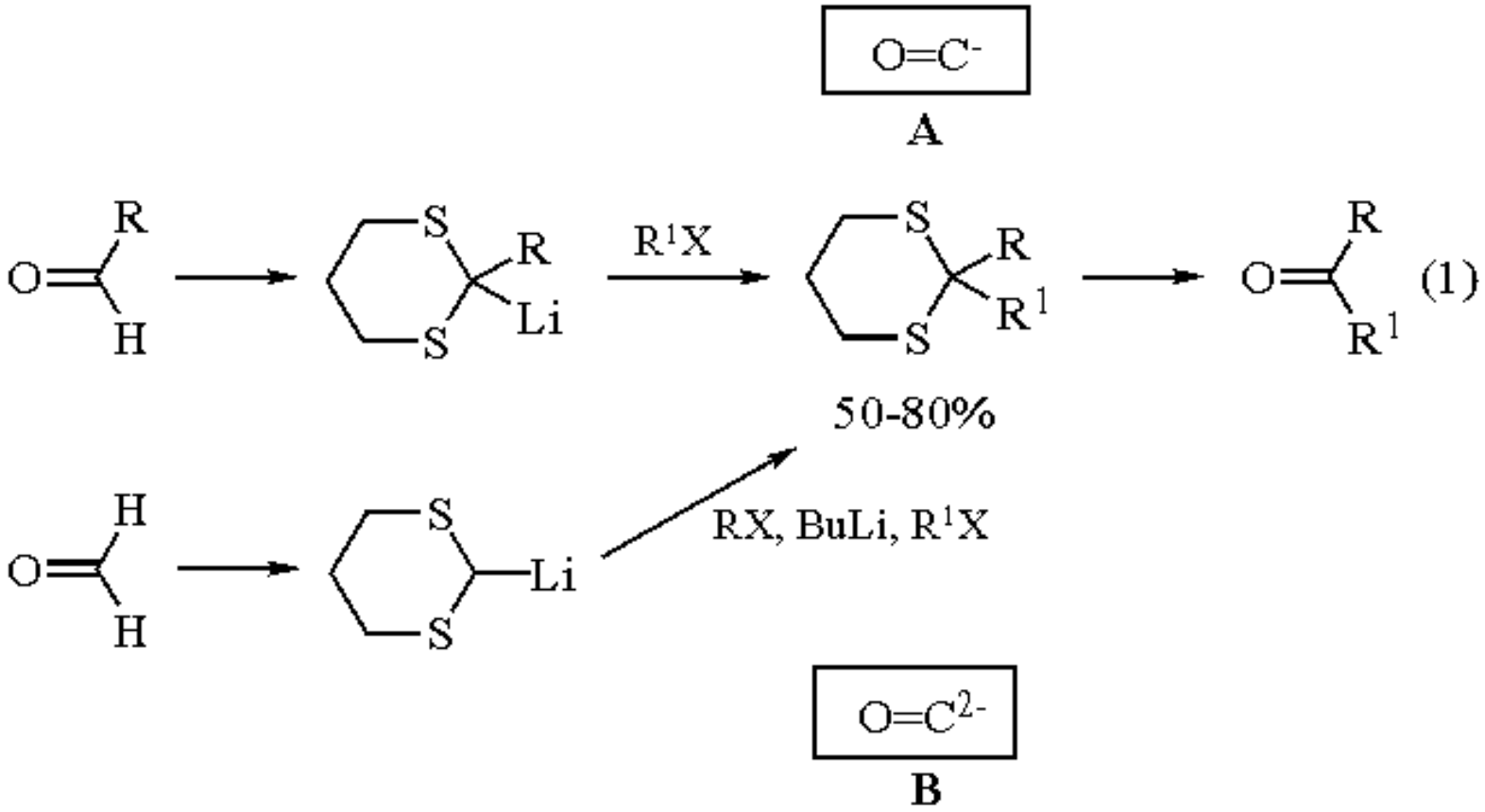

Formally, these transformations give access to ketones from aldehydes (or aldehydes from ***Formaldehyde***, R = H),[12] i.e. the dithiane moiety here functions in a reactivity umpolung mode,[13] as acyl anion **A** or acyl dianion equivalent **B**.

Allylic alcohols, after appropriate in situ activation, can be used as alternatives to the alkyl halides (eq 2).[14]

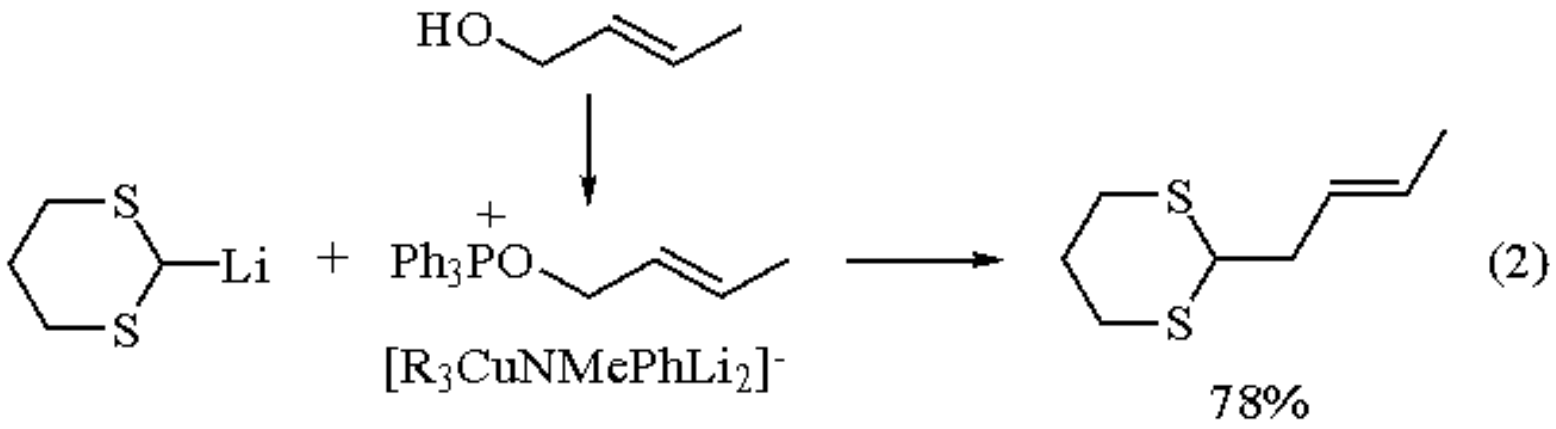

Considerable chemoselectivity is observed in reactions with multifunctionalized electrophiles,[1b-f] e.g. epoxide vs. primary halide (eq 3),[15] or allylic vs. nonallylic halide,[16] or iodide vs. allylic mesylate (eq 6).[17]

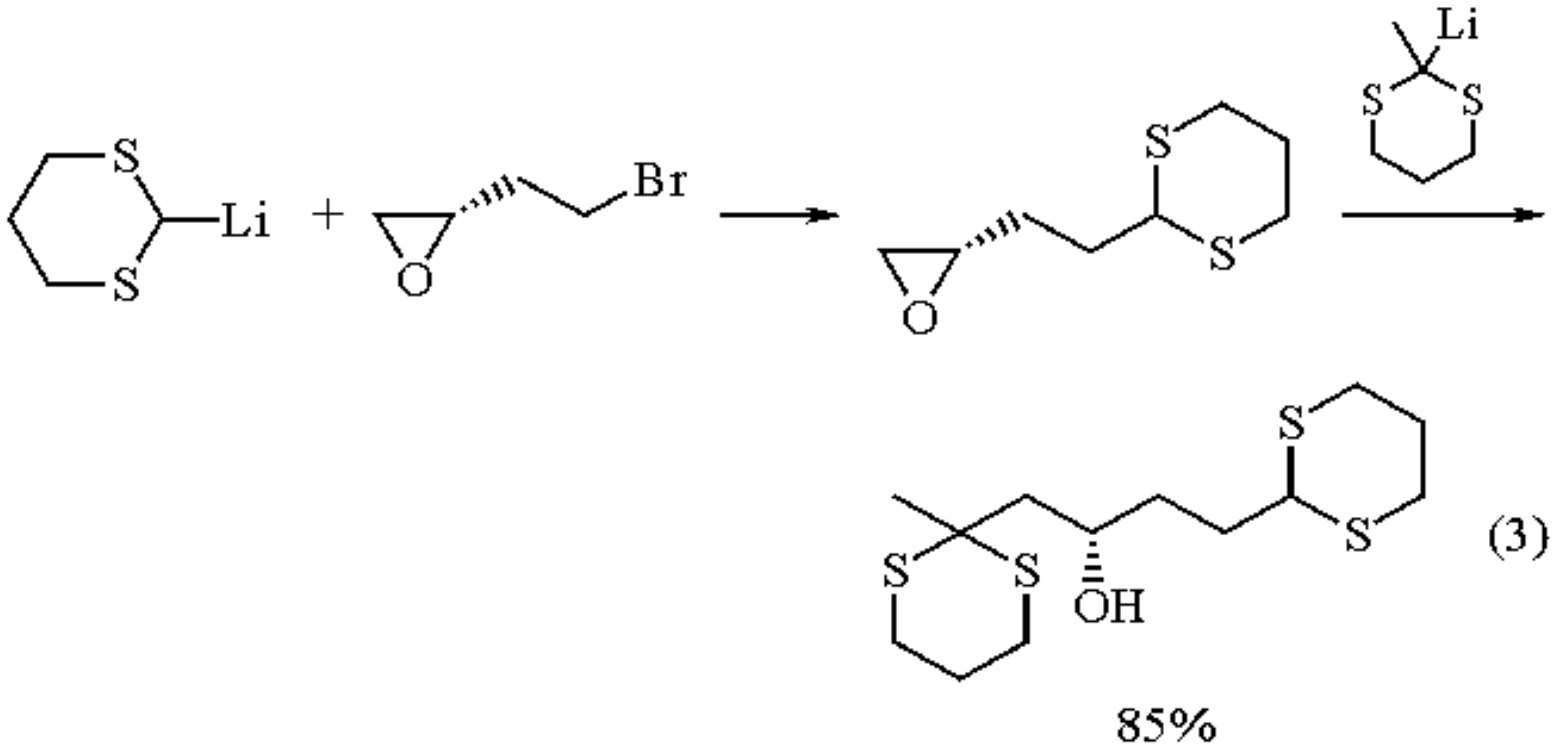

Cycloalkylation products can be obtained from reactions with bifunctional electrophiles, an approach which has found use in the preparation of a variety of macrocycles (acyl dianion equivalent **B**, eq 4).[1b-f] Alternatively, dialkylation with the appropriate electrophiles can also be used for the straightforward preparation of large-ring compounds (eq 5)[1e,f,18] or to set the stage for the synthesis of polycyclic structures (eq 6).[17,19] More recent examples of alkylation of 2-lithio-1,3-dithianes include the preparation of backbone-rigid diamides,[20] the synthesis of (-)-ε-cadinene,[21] methyl ketones which undergo asymmetric reduction in the presence of the dithiane moiety,[22] aminoalkynyldithianes,[23] and dioxaspiro[5.5]undecane ring systems.[24]

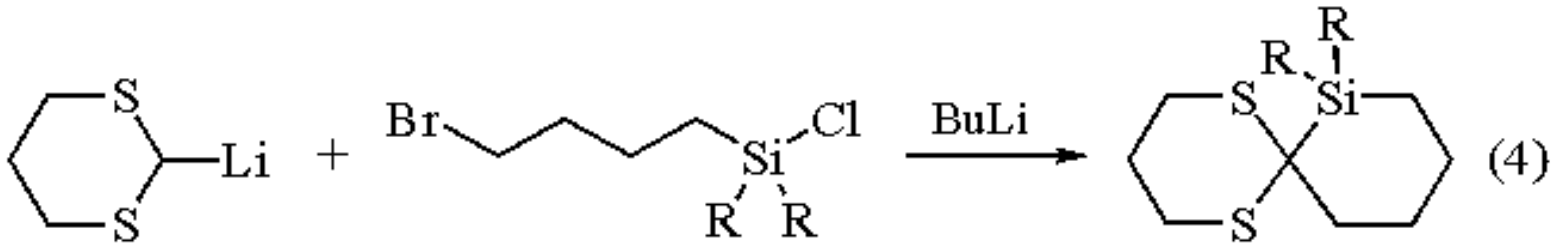

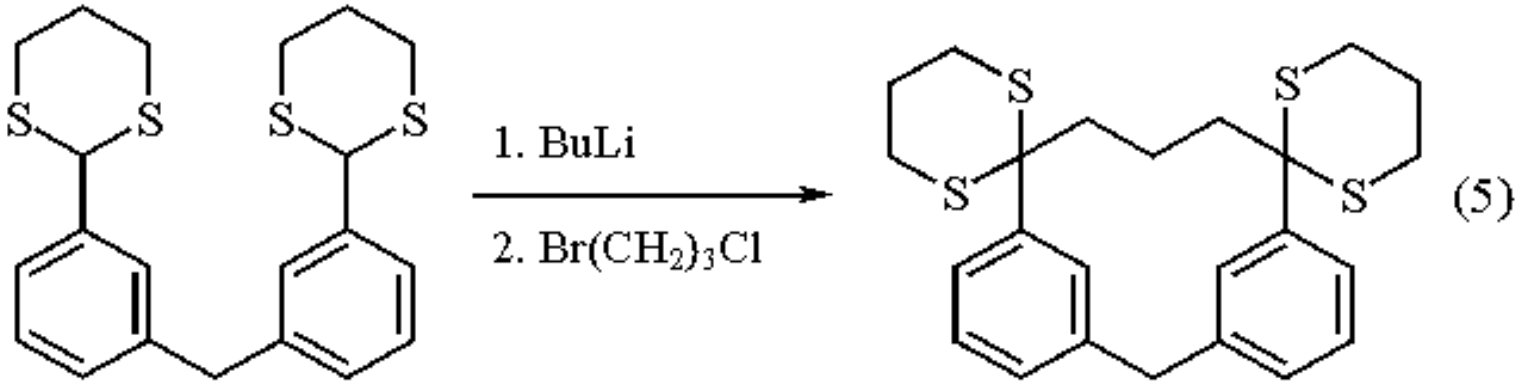

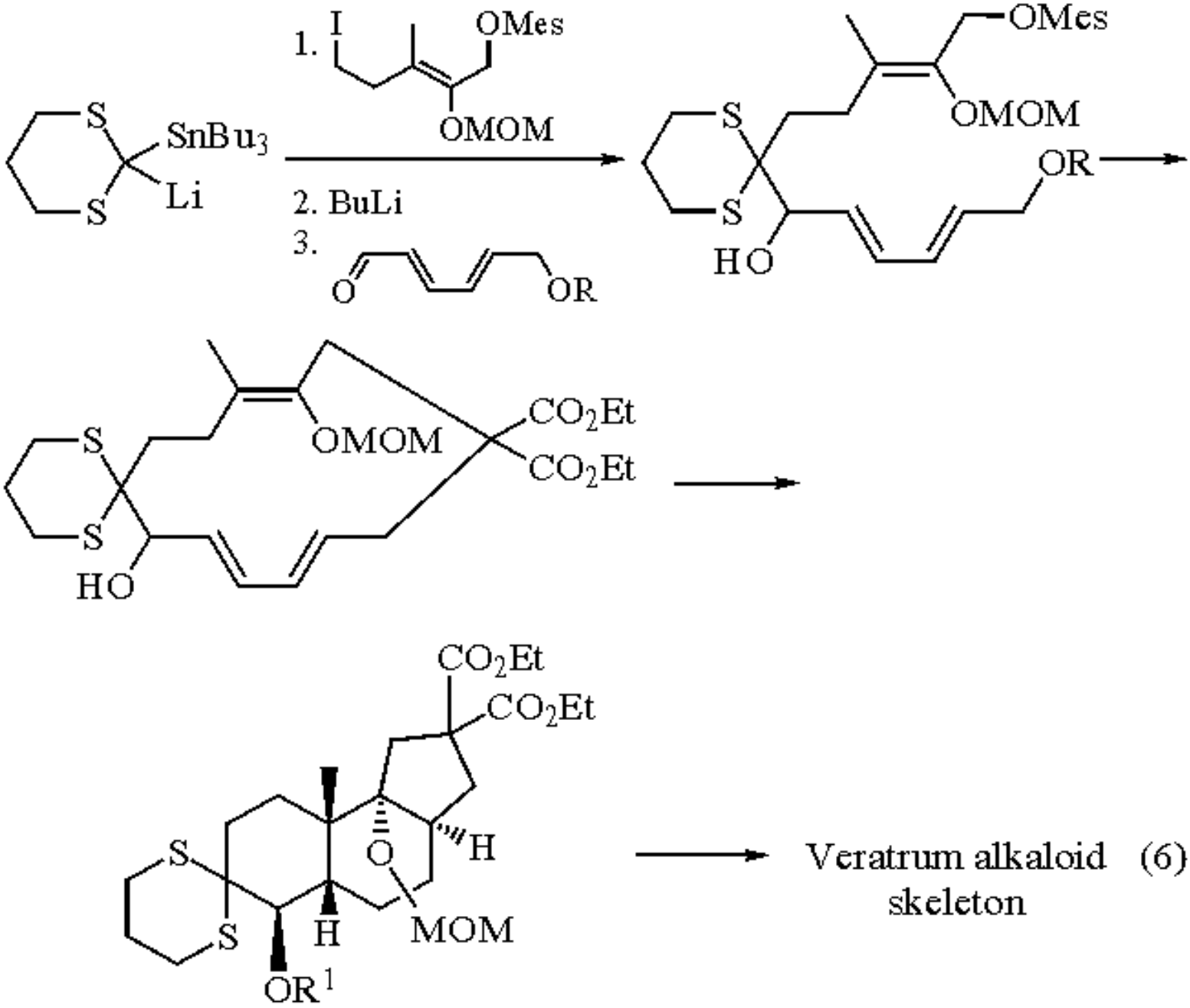

2-Lithio-1,3-dithiane reacts with arene-metal complexes to give the corresponding arene substituted derivatives (eq 7).[25] Some regiochemical control can be achieved; side products often limit the utility of these reactions.[26]

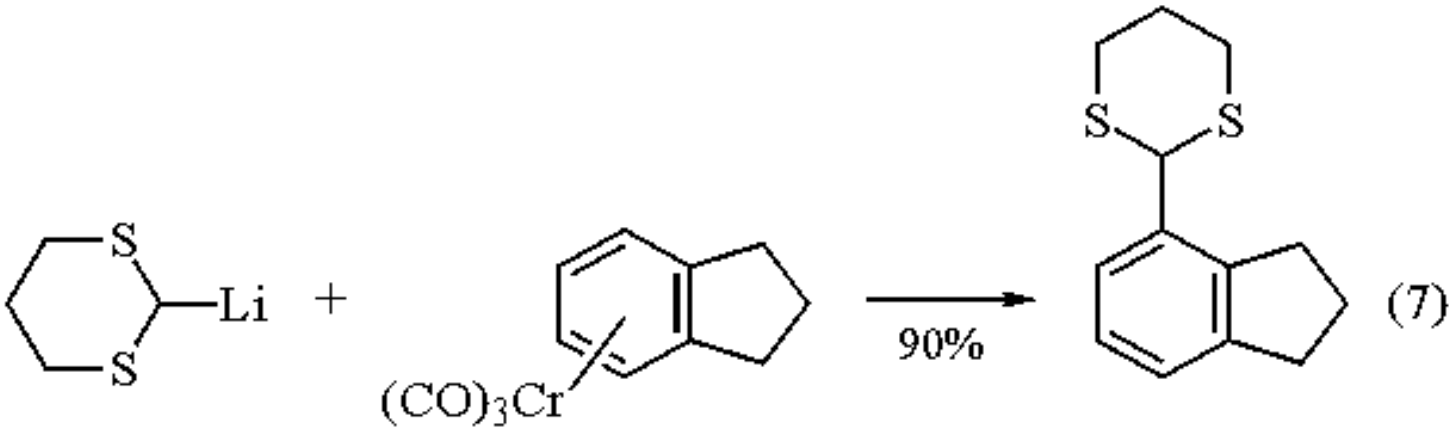

Nitroalkenes (eq 8), as do nitroarenes, react with 2-lithio-1,3-dithianes by conjugate addition.[27] Vinyl sulfones, as described for an oxygenated cyclopentene (eq 9)[28] and an α,β-(phenylseleno)vinyl selenoxide[29] example, display a similar reactivity pattern.

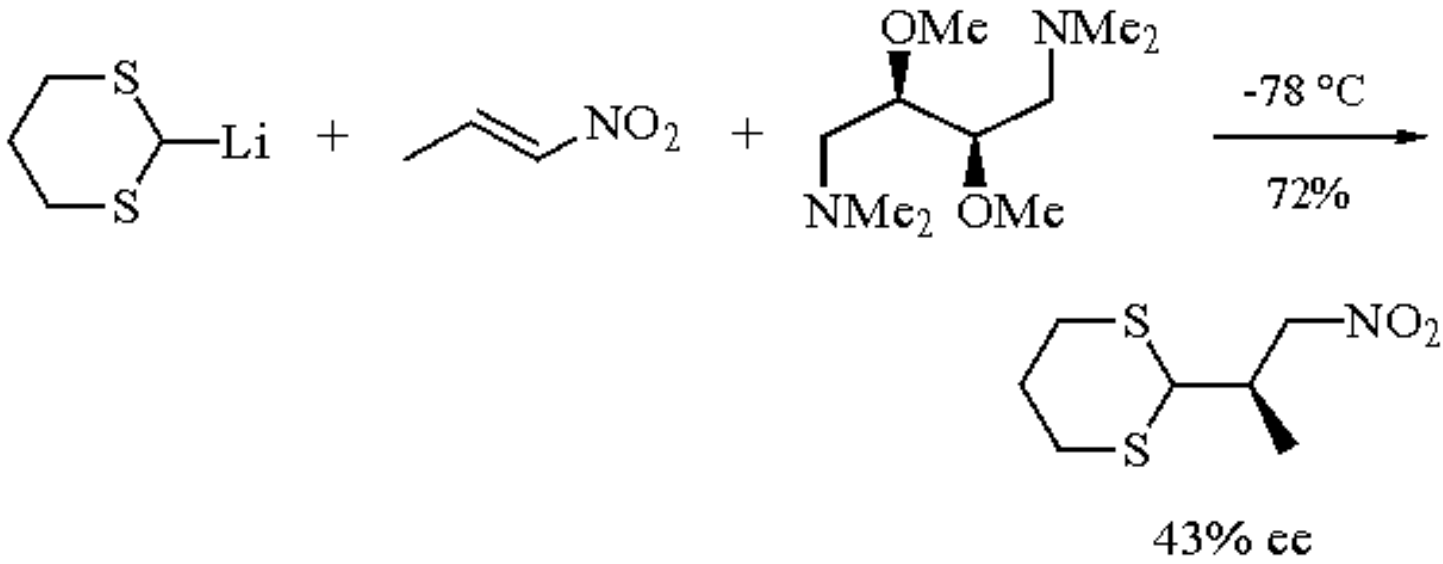

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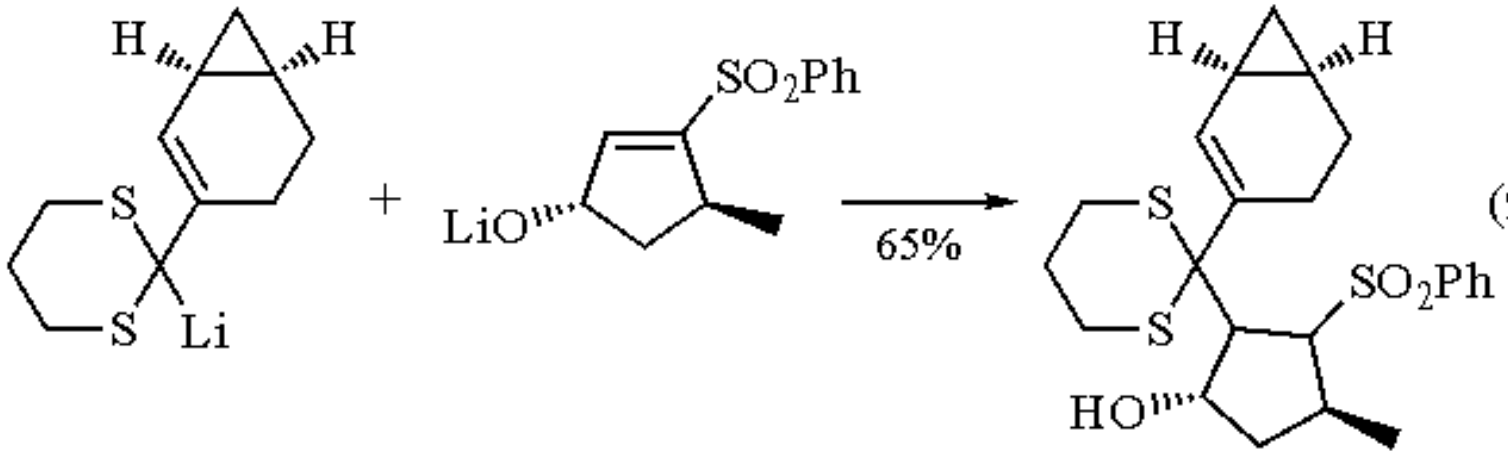

(9)

Vinylphosphonium salts react with 2-lithio-1,3-dithiane to form the β-phosphonio substituted derivative. The inherent properties of the dithiane moiety then allow for the preparation of β-phosphinyl carboxylic acids (eq 10)[30] or other functionalized phosphorus compounds,[31] valuable building blocks in organic synthesis.

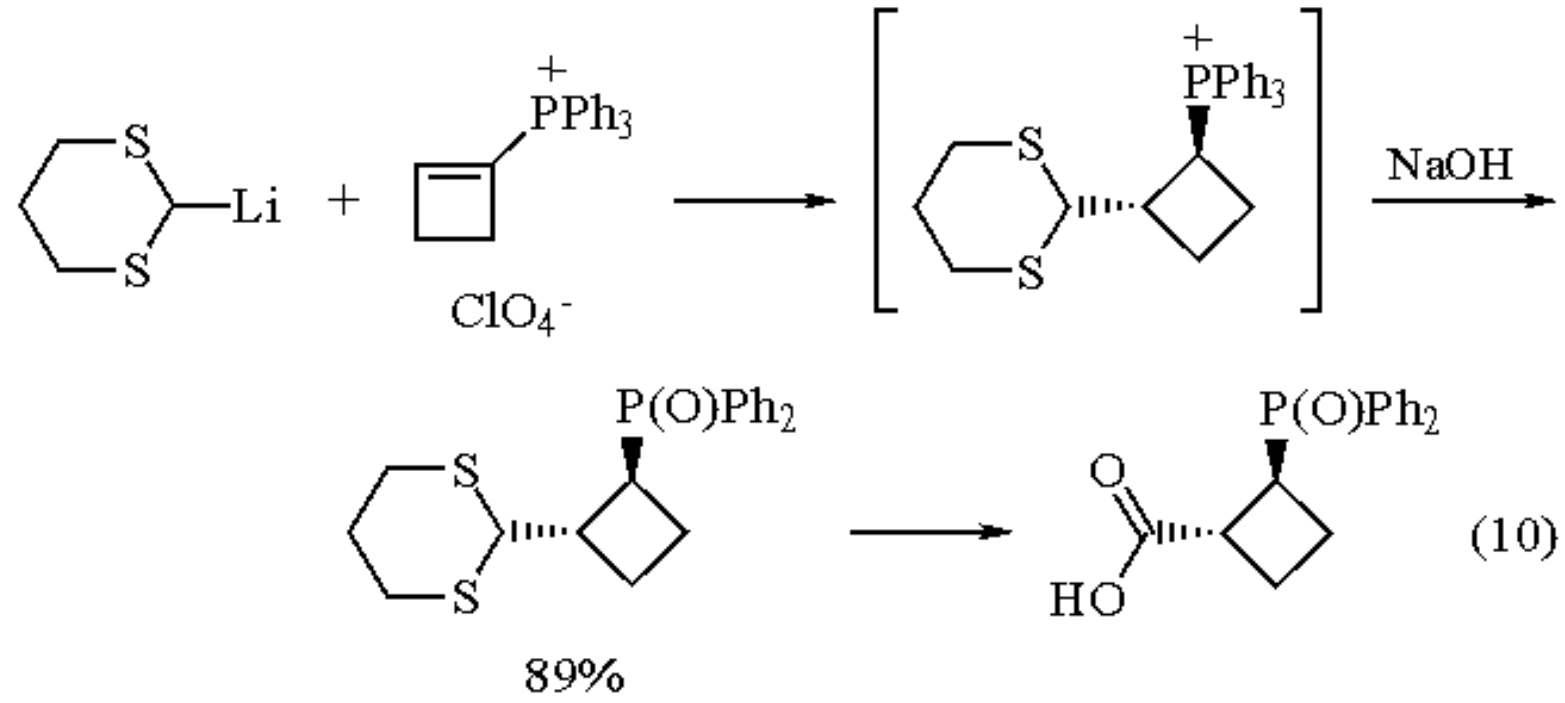

α/β-Aminoalkylation.

The reagent reacts with activated imines to afford the corresponding α-aminoalkylated derivatives (eq 11). Typical reaction partners are phenylazirines (eq 12)[32] or iminium salts.[33] In the case of the former, only the C-2 substituted reagent gives the α-aminoalkylated compound; the parent reagent will afford β-aminoketene dithioacetals instead (eq 13).[32a] Recently, the reaction with *N*-tosylated aziridines has been reported, which leads to the β-amino substituted ketone derivatives.[34] 1-Methyl-4-quinolone as reaction partner gives the α-aminoalkylated product, which in this case derives from a 1,4-addition reaction (see also α-Hydroxyalkylation/γ-Ketoalkylation below).[35]

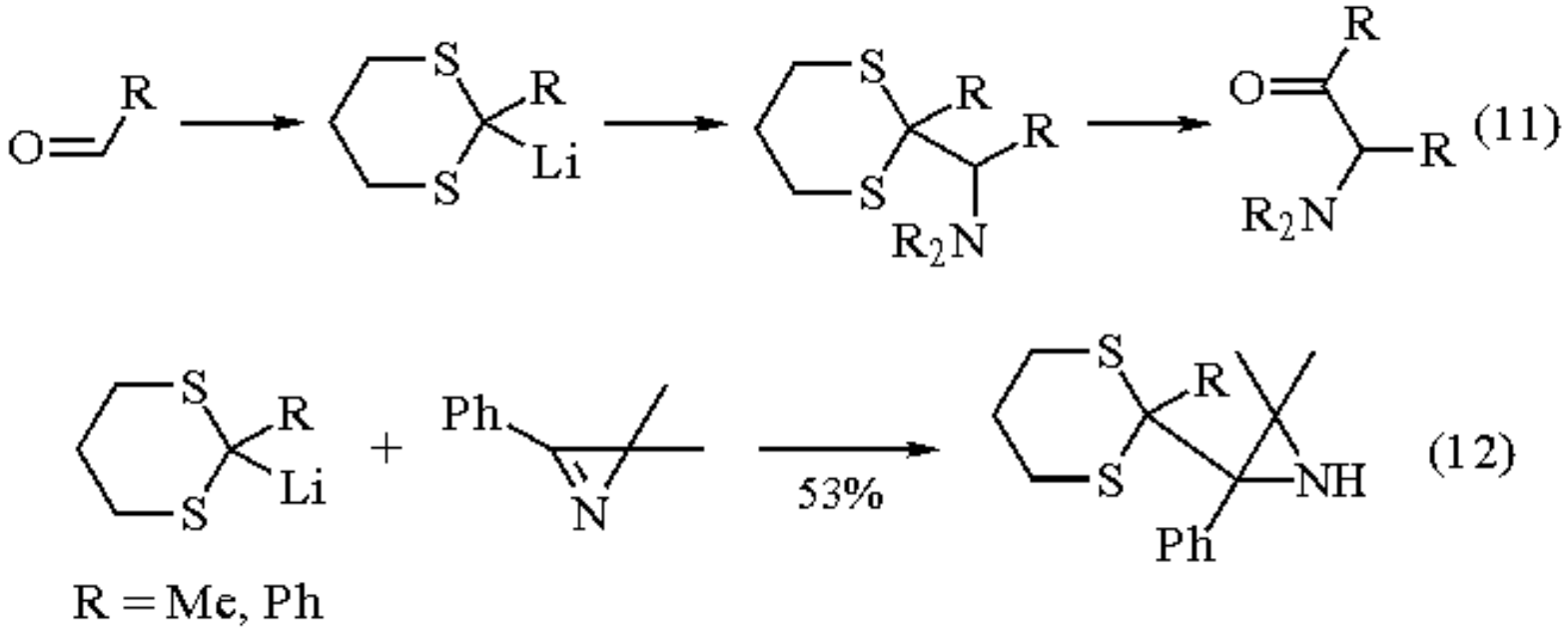

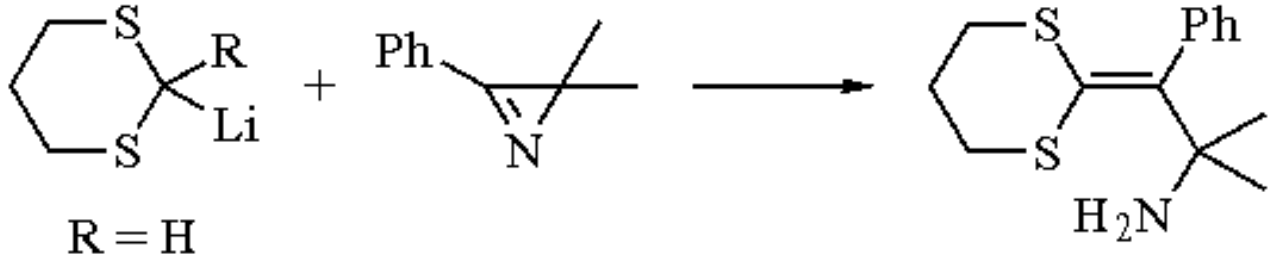

(13)

β-Hydroxyalkylation.

Epoxide ring opening with 2-lithio-1,3-dithianes proceeds in general with good regio- and stereochemical control, following the rules for S_N2-type processes, and affording the β-hydroxyalkylated products in good to excellent yield, routinely exceeding 80% (eq 14).[1b-f]

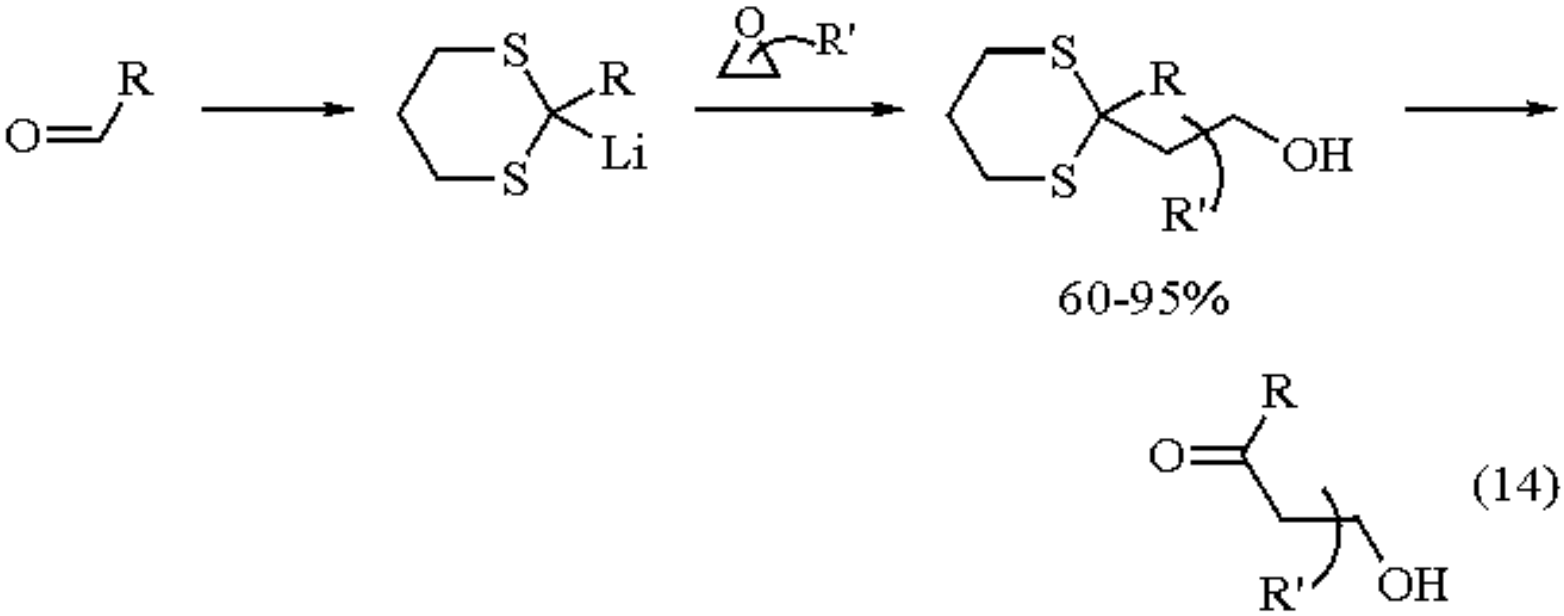

(14)

More recent examples include stereoselective epoxide opening to access enantiomerically pure hydroxylated compounds,[36] e.g. propanal-type aldol products.[37] This reaction sequence also proved to be useful for the synthesis of C-3 formyl sugar derivatives,[38] chiral 4-hydroxycyclopentenones from glucose,[39] and was employed as a key feature in the construction of the Kishi intermediate[40] for aplysiatoxin (eq 15).[41] Noteworthy is the high chemoselectivity displayed by the reagent in these reactions.

2-Lithio-1,3-dithiane

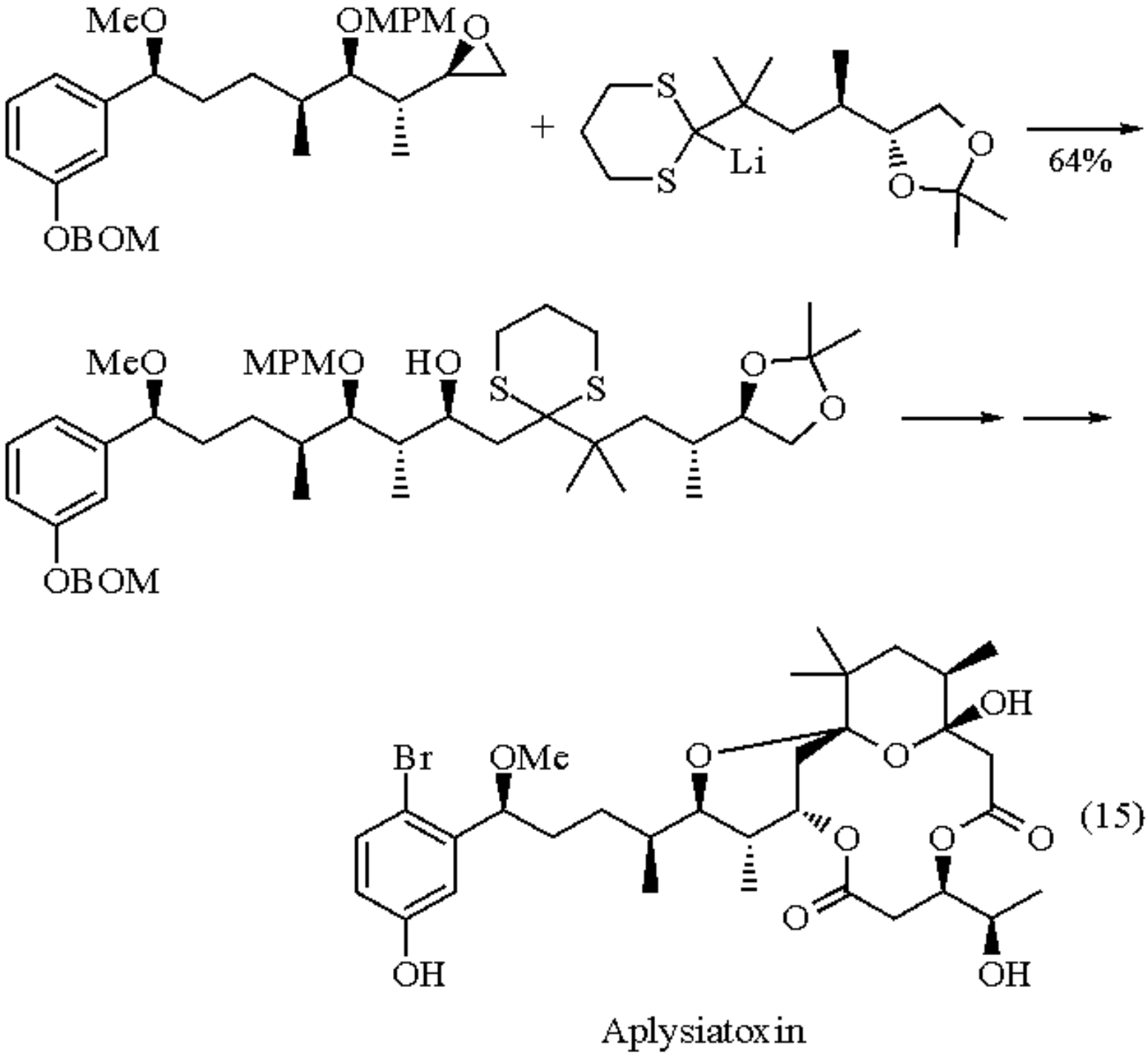

(15)

An unusual example, in which the reagent reacts preferentially with a fulvene functionality over epoxide opening, has been reported (eq 16).[42]

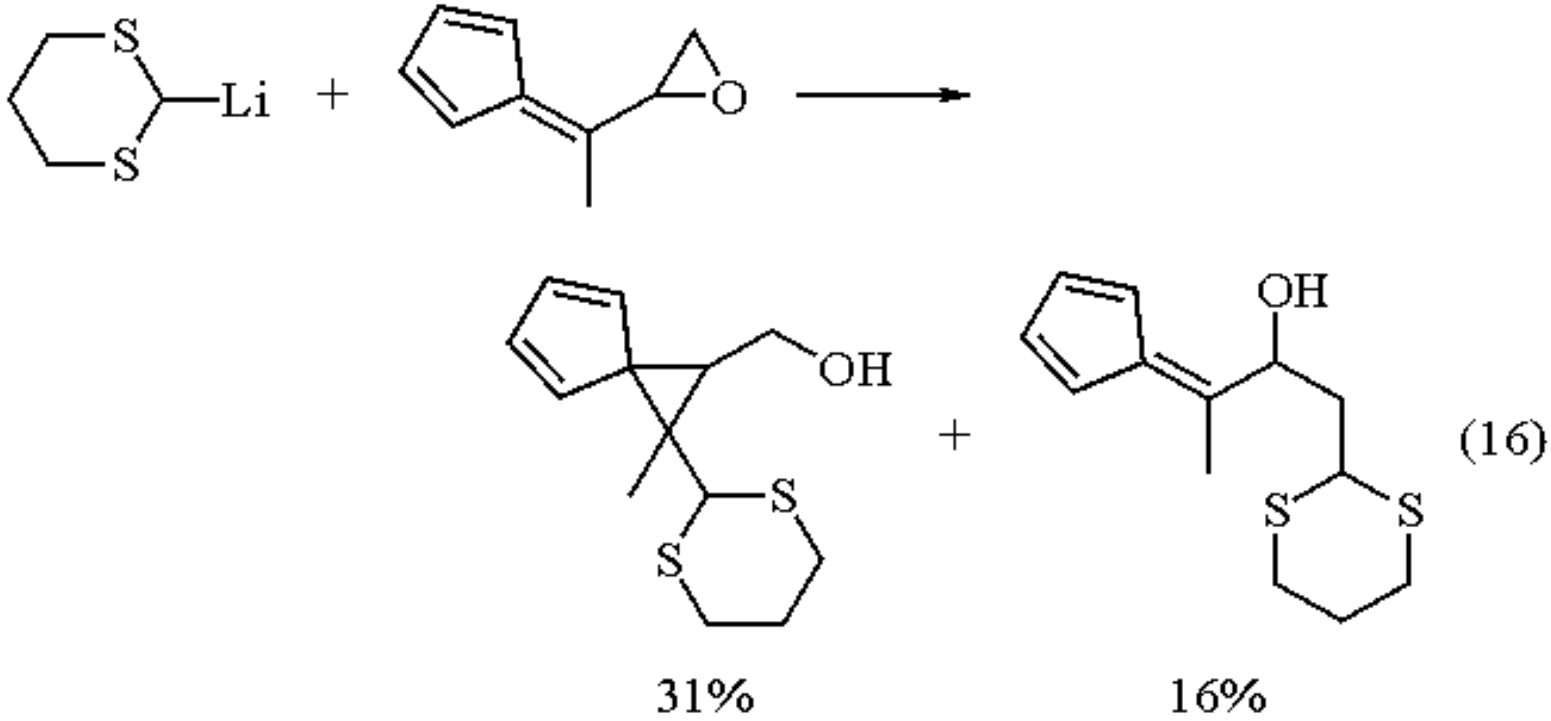

α-Hydroxyalkylation/γ-Ketoalkylation.

Both types of product, obtained from the addition of 2-lithio-1,3-dithianes to aldehydes and ketones, or to the conjugate unsaturated analogs, represent one of the unique features available from the reactivity pattern of the reagent. By virtue of its role as acyl anion equivalent **A**, this reaction allows establishment of a 1,2-arrangement of oxygen functional groups, not so readily achieved by using classical reagents (eq 17). It is this feature of umpolung[1d] of the normal carbonyl reactivity pattern, which earned 2-lithio-1,3-dithianes so much attention in synthetic organic chemistry, and accounts for a significant proportion of all reactions involving the use of the reagent.[1b-f] The yields observed for these addition reactions are in general very good; product formation in the 70-90% range is not uncommon.

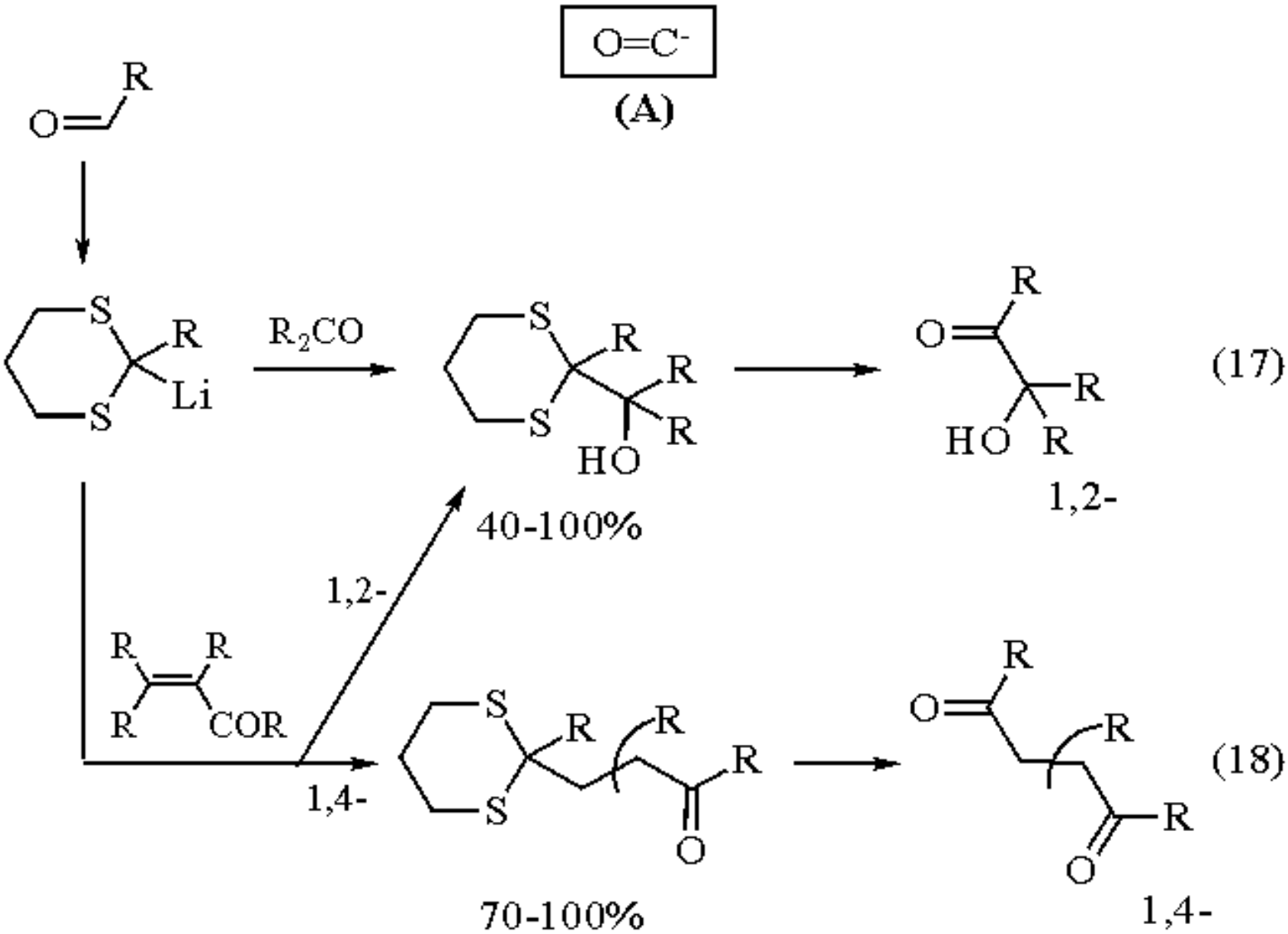

The scope of the reagent was broadened after a thorough investigation established the factors which influence the regioselectivity of the addition of the reagent to α,β-unsaturated aldehydes and ketones.[1d] As a complement to the standard 1,2-addition mode described above, 2-lithio-1,3-dithianes can also be used deliberately to establish a 1,4-arrangement of oxygen functional groups (eq 18), again by functioning as an acyl anion equivalent **A**.[1b-f,35,43] The outcome of the addition to enones can be influenced not only by the choice of solvent,[1d] but also with the help of alkene-complexing agents, as has been demonstrated for the tricarbonyl(tropone)iron complex.[44]

Recent literature reports the addition reaction of 2-lithio-1,3-dithiane to aldehydes for assembling the C(10)-C(19) moiety of FK506,[45] and the possibility of achieving asymmetric induction in this reaction sequence has been investigated (eq 19).[46]

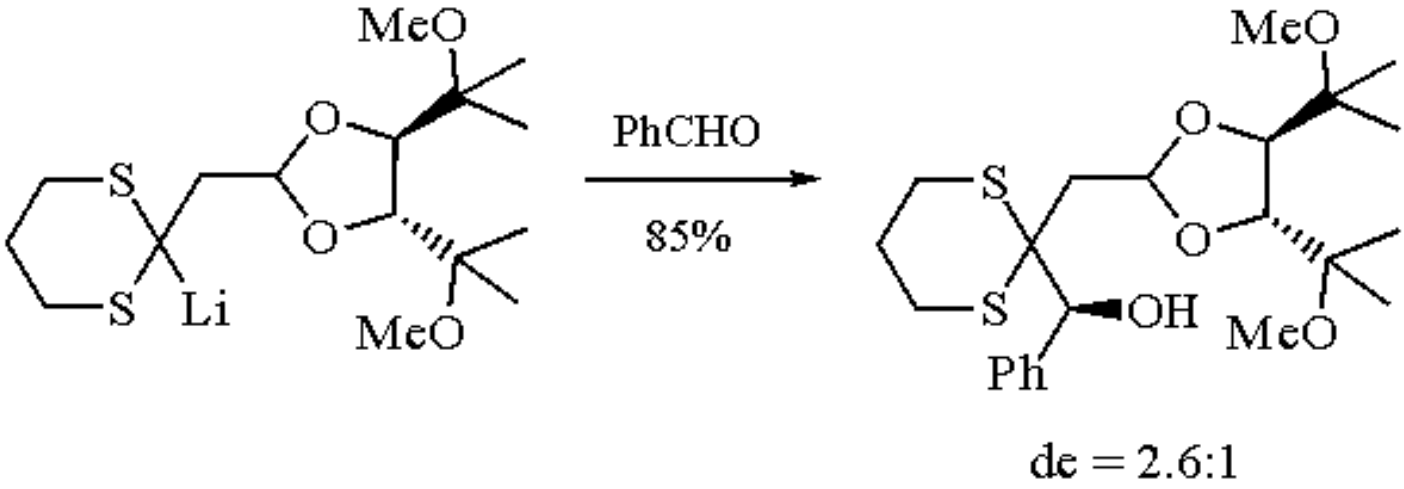

(19)

Cyclic hemiacetals can be used in place of the free carbonyl compound with equal success.[47] The stereoselectivity of the reaction can be influenced by neighboring polar groups, as illustrated in the example with (*R*)-pantolactone (eq 20).[47]

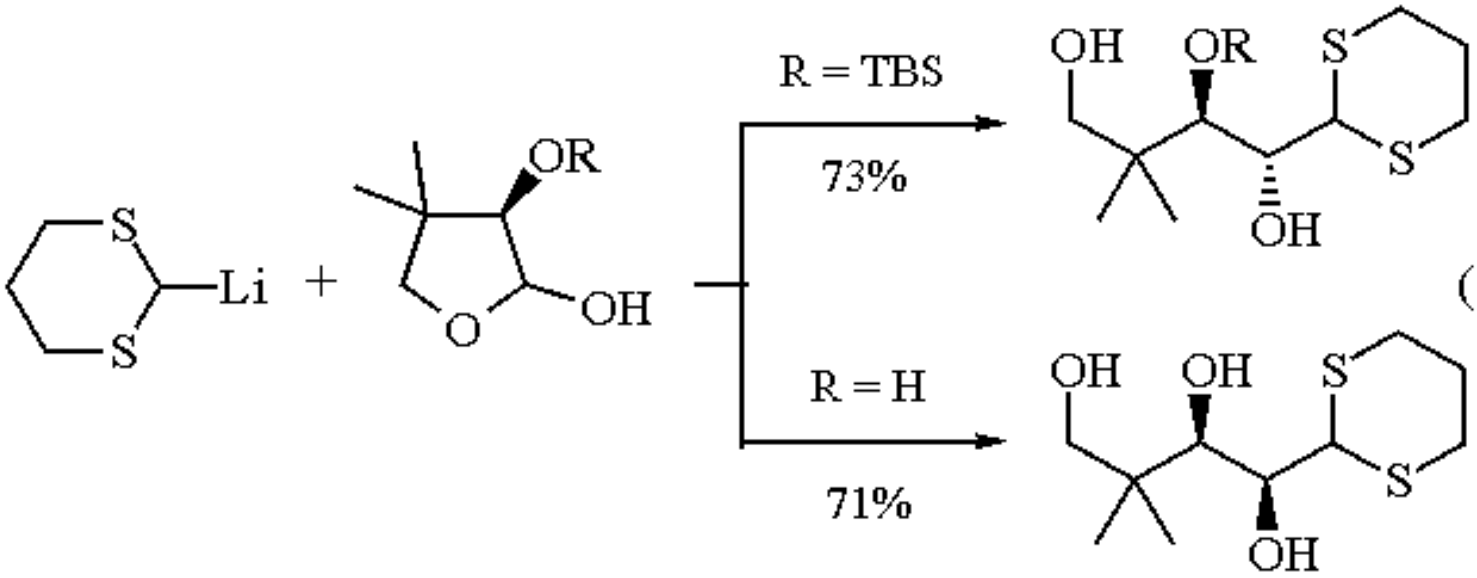

(20)

Acylation.

The characteristic features of the reagent, as indicated in the foregoing section on addition reactions to carbonyl derivatives, also dominate the reactivity pattern observed for the reaction with carboxyl derivatives. The role of 2-lithio-1,3-dithianes as acyl anion equivalent **A**, establishing a 1,2-relationship between the functional groups, is the dominating feature (eq 21).

2-Lithio-1,3-dithiane reacts with acyl derivatives, such as esters or lactones, amides or aziridinones,[48] to afford the corresponding acyl dithiane in variable yield (eq 21).[1b-f] Little investigation has yet been carried out into the regioselectivity for the reaction with the corresponding α,β-unsaturated derivatives.[49,50] With an electron releasing substituent on C-2 the reagent reacts with butenolides in a 1,4-conjugated fashion (eq 22), a scheme specifically exploited in several syntheses of steganin lignans.[49] Also, unsaturated amides, thioamides, and nitriles are reported to react with the reagent in the 1,4-mode indicated in eq 22.[50c-f]

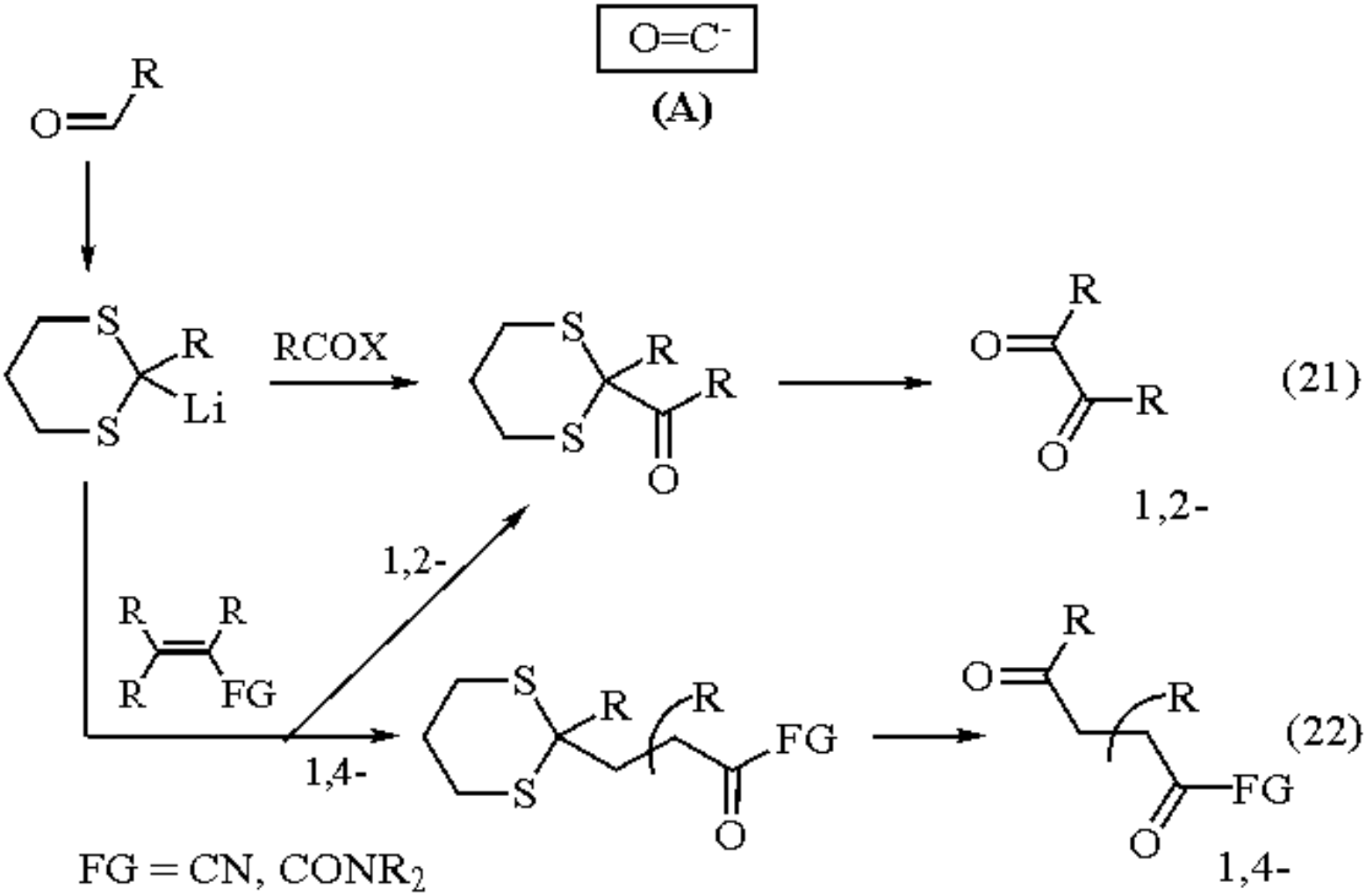

Acid chlorides will give the double addition carbinol product (eq 25),[51] nitriles afford either amino ketene dithioacetals (eq 24)[52,53] or ketones (eq 23),[54] nitrile oxides lead to oxime derivatives (eq 26), activated imides can be opened regioselectively (eq 29),[55] activated ketene acetals give the corresponding enol-type compound (eq 30),[56] and isocyanides afford the cyano substituted dithiane (eq 27).[57]

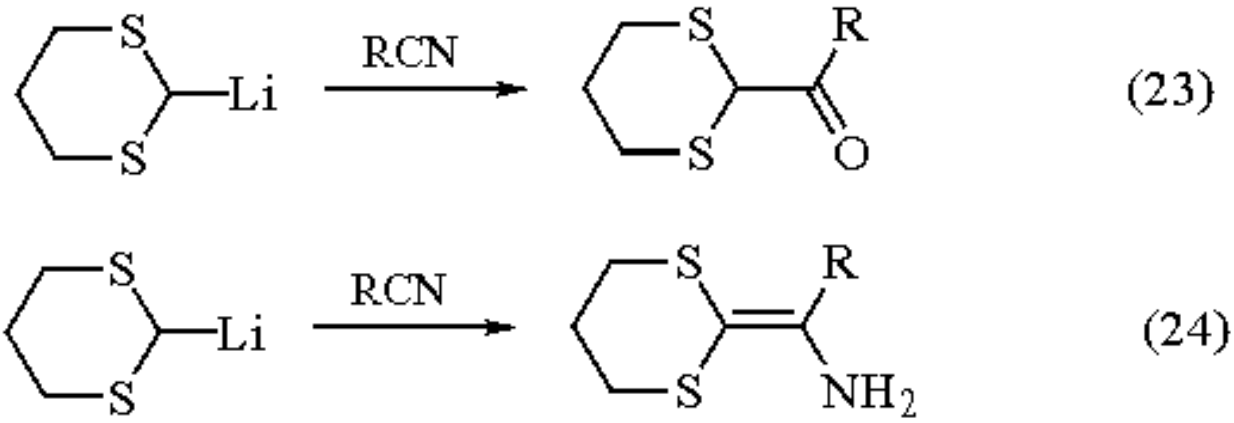

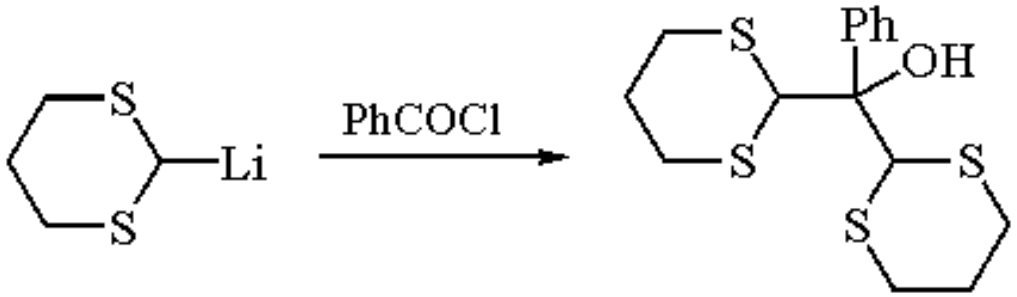

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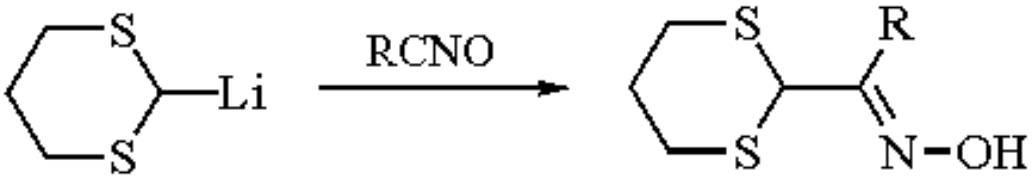

(26)

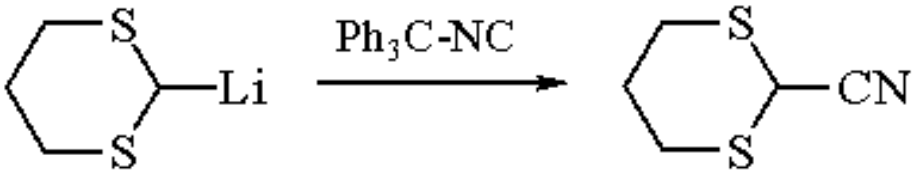

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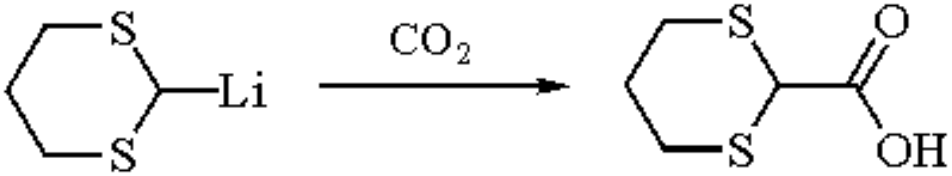

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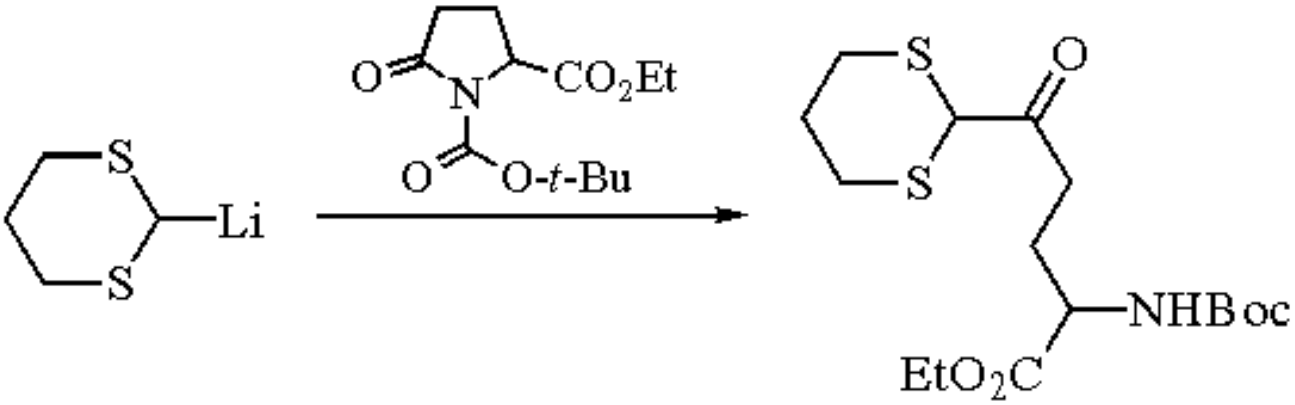

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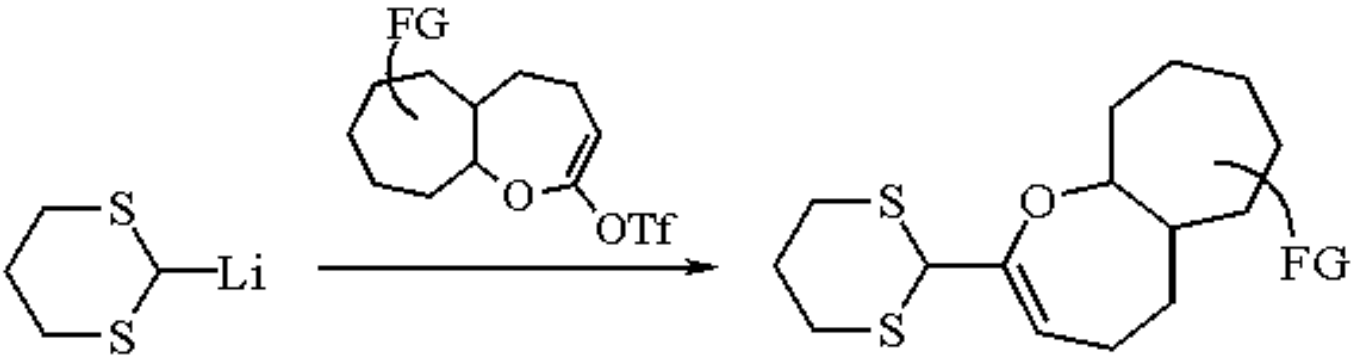

(30)

Carboxylation by reaction with ***Carbon Dioxide*** proceeds in excellent yield (eq 28).[1d,e,58] The reaction products find use as intermediates in a notable lactone synthesis.[59]

The reaction of 2-lithio-1,3-dithiane with carboxyl derivatives can be reversed. This result allows a synthetically useful C-C bond cleavage (eq 31).[1e]

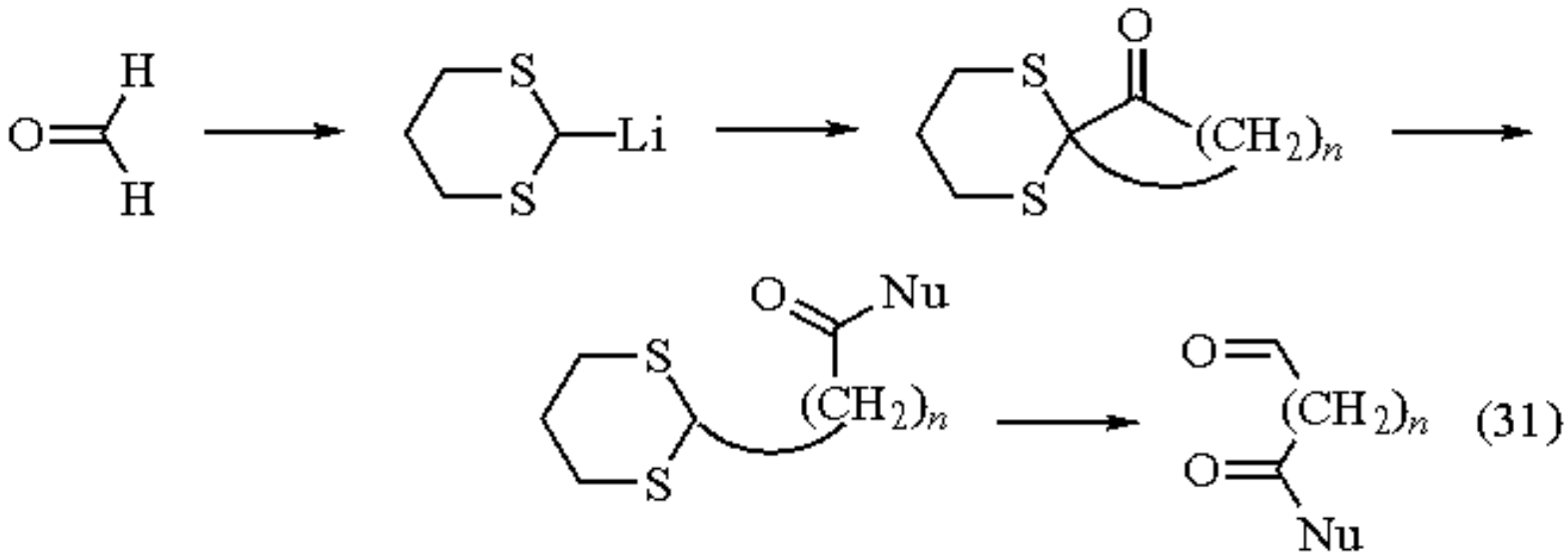

2-P, Sn, Si, Ge, and Ti Derivatives.

The versatility of 2-lithio-1,3-dithiane as an acyl anion **A** or acyl dianion equivalent **B** is further amplified by the possibility of preparing the phosphorus,[60] tin,[1f,7] silicon,[60,61] germanium,[1f,62] or titanium[63] analogs, e.g. on simple treatment with the corresponding chlorides. The phosphorus and silicon analogs deserve special attention, as they allow a convenient entry to ketene dithioacetals (see below). Also, the silicon analog was used in the preparation of formyl-[61] and acylsilanes.[11] The tin and germanium, as well as silicon, derivatives react with acid chlorides to give 2-acyl-1,3-dithianes.[62] The special role of the tin derivative has been outlined already (see Preparation above);[7] the titanium analog was found to be more stable than the reagent, and as a consequence more selective.[63]

Ketene Dithioacetals.

The lithio derivative obtained from deprotonation of ***2-Trimethylsilyl-1,3-dithiane*** deserves special mention. On reaction with carbonyl compounds, ketene dithioacetals are obtained, compounds which are responsive to both electrophilic as well as nucleophilic attack. Other methods for the synthesis of ketene dithioacetals have been reviewed.[60] In addition to their normal reactivity pattern, these derivatives offer an exceptionally broad umpolung-type reactivity pattern, i.e. acyl anion **A**, enolate carbanion **C**, homoenolate anion **D**, and chemistry of the homolog **E** becomes available (eq 32). The

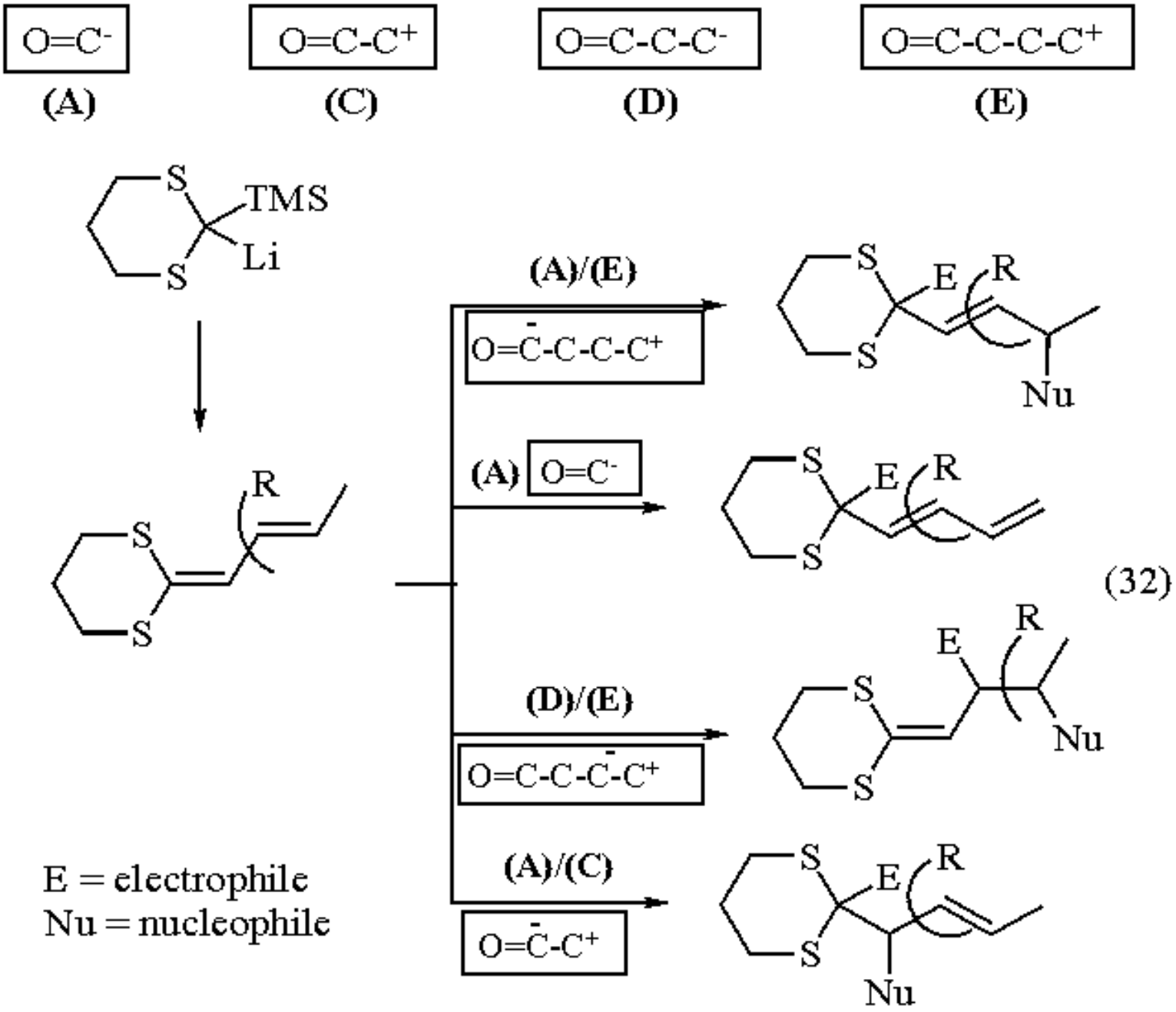

richness offered by this class of compounds in terms of their potential as strategical and useful intermediates in organic synthesis is documented amply, and reference to review articles have to suffice in this context.[1a,60]

Related Reagents.

Bis(methylthio)(trimethylsilyl)methane; ***Bis(phenylthio)methane***; ***N,N-Diethylaminoacetonitrile***; ***1-Ethoxyvinyllithium***; ***RL031-***; ***Methoxy(phenylthio)methane***; ***1-Methoxyvinyllithium***.

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3-Lithiofuran

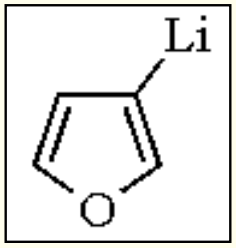

[53101-93-2] · C_4H_3LiO · 3-Lithiofuran · (MW 74.007)

(nucleophilic organolithium reagent useful for alkylation; addition to ketones, acid chlorides, aldehydes, amides, lactones, carbon dioxide, nitrones, epoxides, sulfinate esters, boronic esters, metal carbonyls, borates, metal halides; affords intermediates for organometallic coupling reactions)

Alternate Name: β-furyllithium.

Preparative Methods: metalation of ***Furan*** at the 3-position requires a metal-halogen[1-7] or metal-metal exchange[8] since deprotonation of furan occurs preferentially at the 2-position. 3-Lithiofuran (**1**) (eq 1)[1-3] is prepared by the treatment of 3-iodofuran (**2a**) with ***n-Butyllithium*** in ether or THF (-78 °C);[4,5] by the treatment of 3-bromofuran (**2b**) with *n*-butyllithium in THF (-78 °C);[6,7] or by the reaction of 3-tri-*n*-butylstannylfuran (**2c**) with *n*-butyllithium in THF (-78 °C).[8]

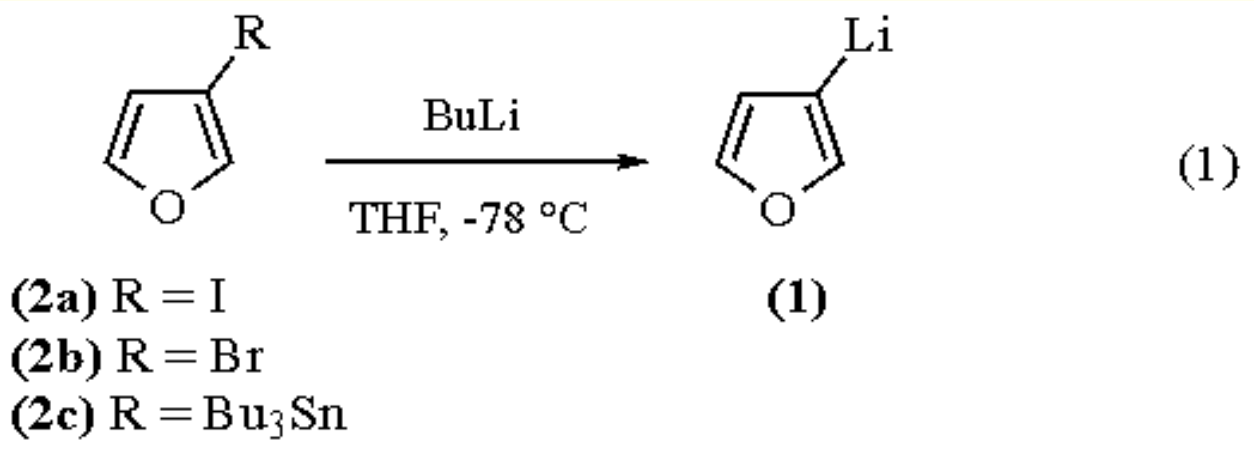

Handling, Storage, and Precautions: the reagent is generated in situ, under anhydrous conditions in an inert atmosphere at low temperatures (<=-40 °C), and used shortly after preparation. The ability to store the reagent is not clear. As *n*-BuLi is employed, the precautions for preparation and use would mirror those of *n*-BuLi and related organometallic reagents. It has been demonstrated that good temperature control is important to the regiochemical integrity of the reagent. Temperatures exceeding -40 °C during the course of reagent generation and use permit isomerization of 3-lithiofuran to the more thermodynamically stable 2-lithiofuran (eq 2).[7]

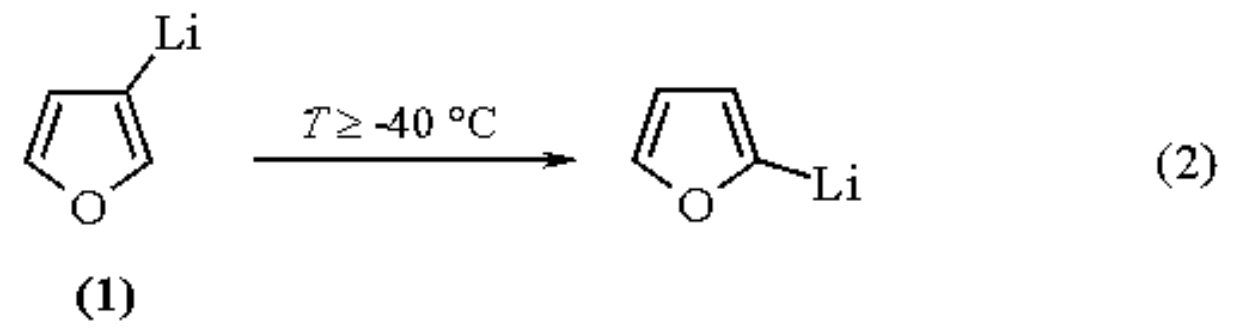

Alkylation.

3-Lithiofuran (**1**) reacts readily with allylic halides and primary alkyl halides, in the presence of ***Hexamethylphosphoric Triamide***, to give 3-substituted furans (eq 3).[7]

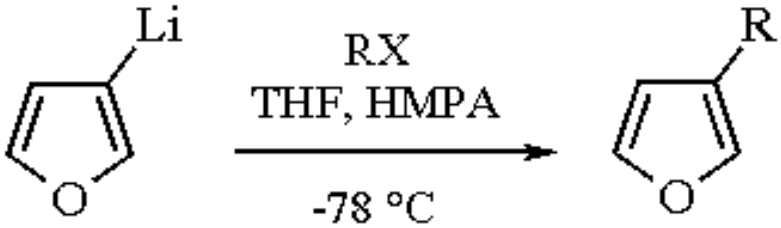

(3)

RX	R	Yield
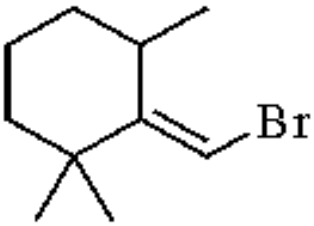	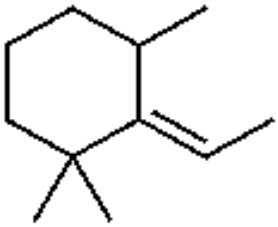	82%
$THPO(CH_2)_3I$	$THPO(CH_2)_3$	79%

Addition to Carbonyl Compounds.

3-Lithiofuran (**1**) adds to acid chlorides to give furyl ketones (eq 4),[5] to aldehydes (eq 5),[7,9,10] and to ketones (eq 6)[11] to give carbinols. The reaction of 3-lithiofuran (**1**) with lactones affords the related lactols (eq 7).[12] ***Carbon Dioxide*** reacts with 3-lithiofuran (**1**) to provide 3-furoic acid.[8,13] Although 3-lithiofuran is considered to be relatively unreactive, it will add to amides to give amines via the reduction of an intermediate enamine (eq 8).[14,15]

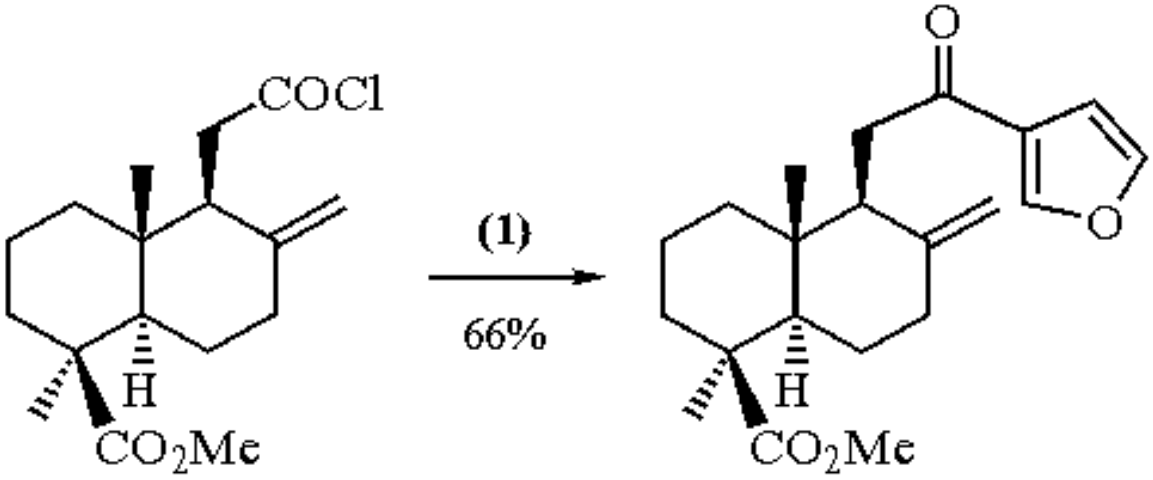
COCl
(1)
66%
O
O
H
CO2Me
H
CO2Me

(4)

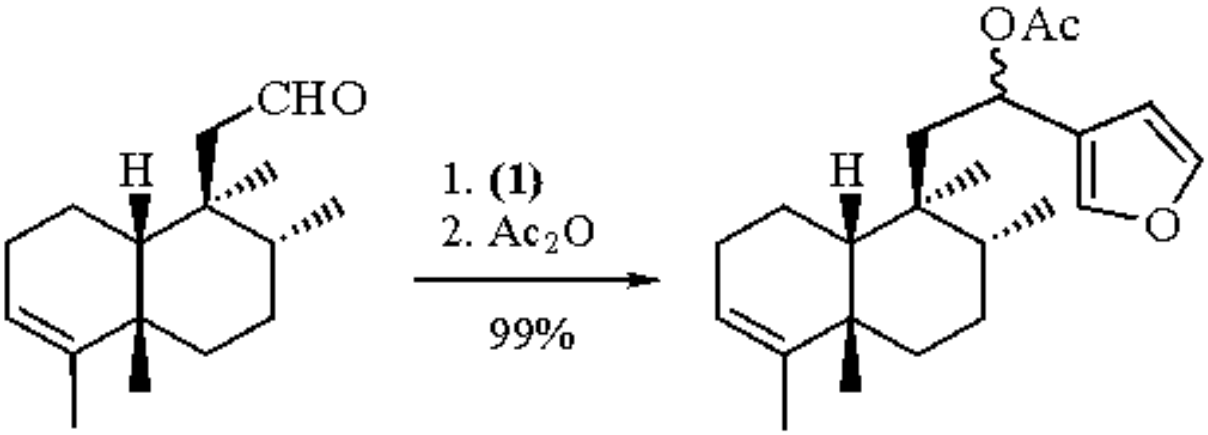
CHO
H
1. (1)
2. Ac2O
99%
OAc
H
O

(5)

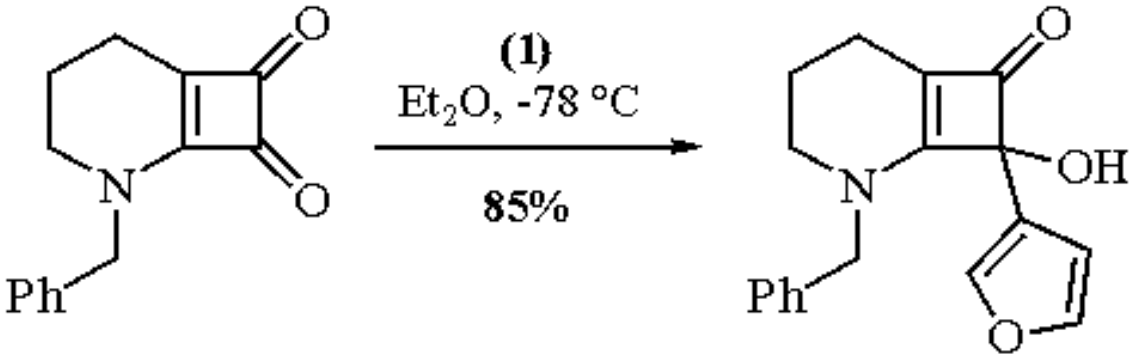
O
O
N
Ph
(1)
Et2O, -78 °C
85%
O
OH
N
Ph
O

(6)

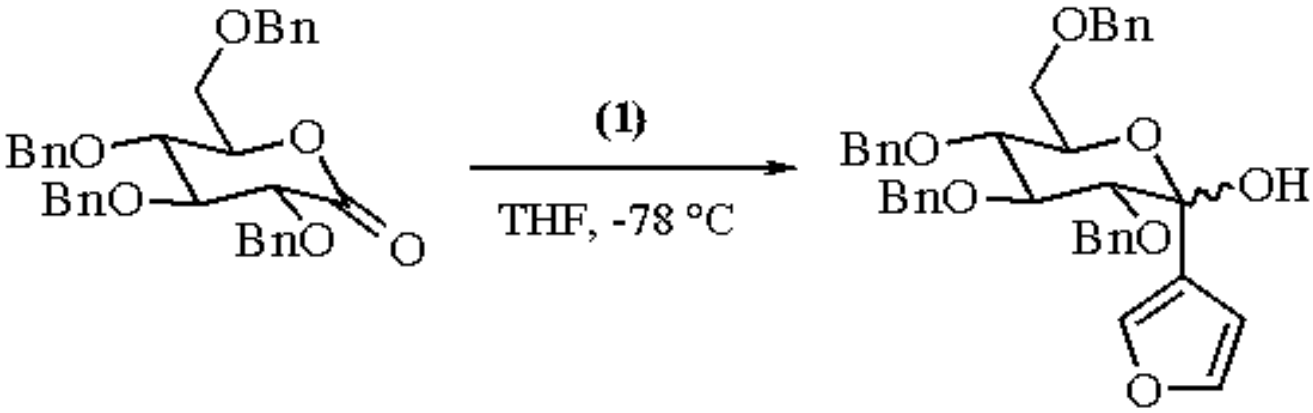
OBn
BnO
BnO
O
BnO
O
(1)
THF, -78 °C
OBn
BnO
BnO
O
OH
BnO
O

(7)

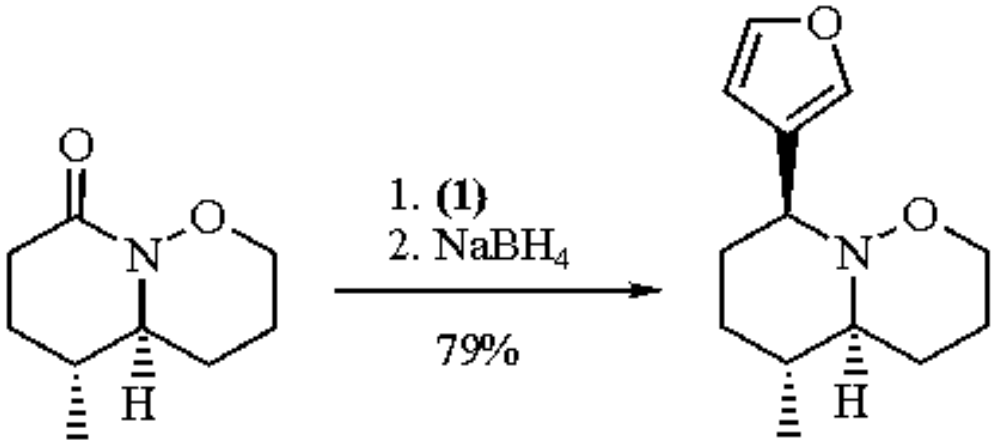

(8)

Reaction with Electrophiles.

Treatment of 3-lithiofuran (**1**) with $CuBr.SMe_2$ (see ***Copper(I) Bromide***) and 2-lithiofuran affords a higher order cuprate which adds to epoxides, giving carbinols (eq 9).[16] 3-Lithiofuran (**1**) affords branched hydroxylamines upon reaction with nitrones (eq 10).[17] (-)-(*S*)-Menthyl *p*-toluenesulfinate,[18] an optically pure boronic ester (see ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***),[19] and ***Hexacarbonylchromium***[20] also react with 3-lithiofuran (**1**) to provide an optically pure furyl sulfoxide (eq 11), an optically pure borinic ester (eq 12), and a furyl-substituted chromium carbene (eq 13), respectively.

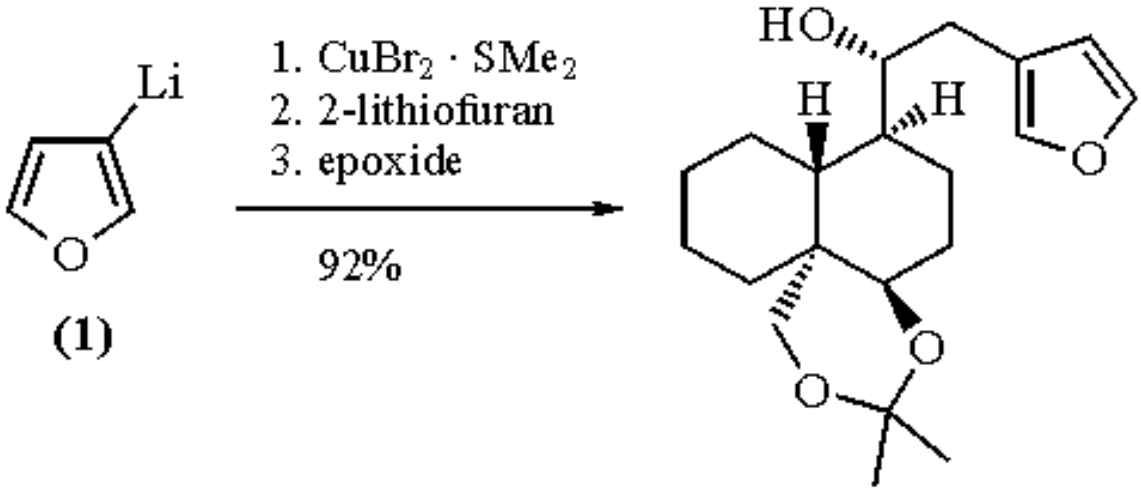

(9)

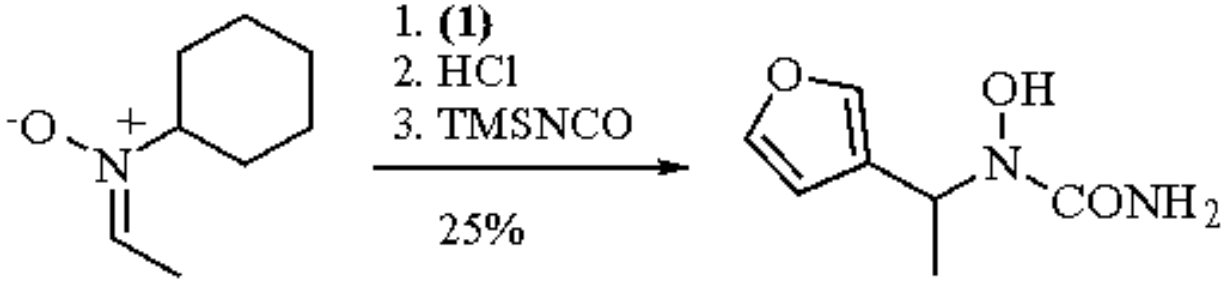

(10)

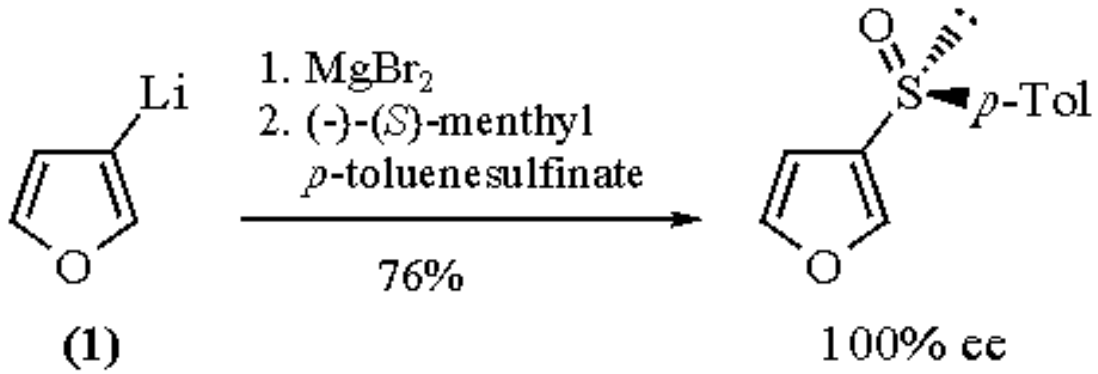

(11)

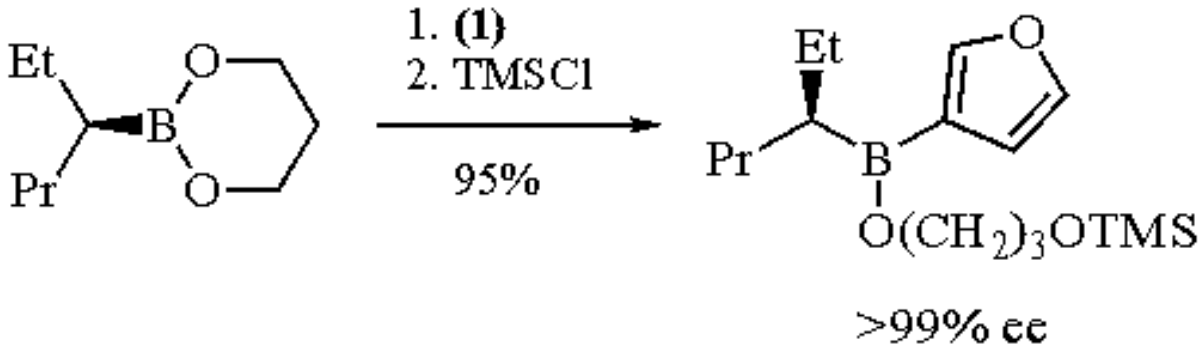

(12)

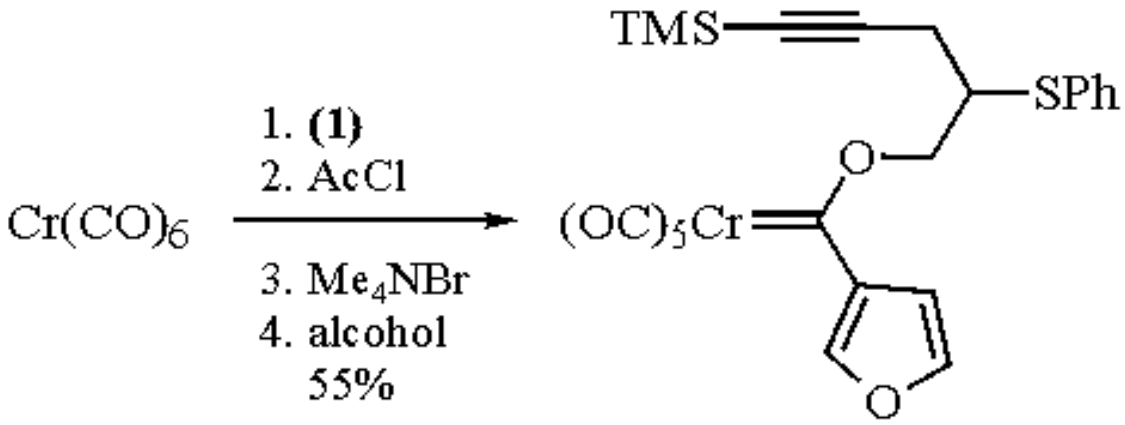

(13)

Analogous Reagents.

A variety of substituted 3-lithiofurans has been prepared by metal halogen exchange [(**3**),[21] (**4**),[22] (**5**),[23] (**6**)[24]]. However, when blocking [(**7**),[25] (**8**)[26]] and/or coordinating groups at the 4-position (**9**)[27] are present, metalation reactions provide an effective path to 3-lithiofurans. 3-Lithiofurans (**8**) and (**9**) have undergone metal-metal exchange to afford the bromozinc[26] and tin reagents,[28] respectively. These reagents, as well as a boronic acid produced from (**9**),[27] have been employed in palladium-catalyzed carbon-carbon bond forming reactions.

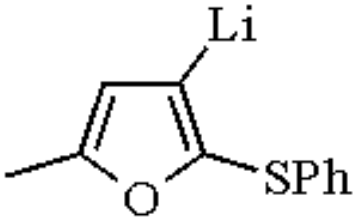

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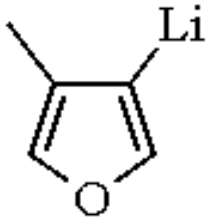

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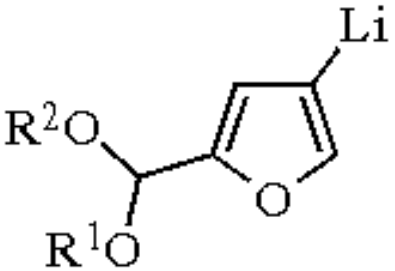

(5) $R^1, R^2 = -CH_2C(Me)_2CH_2-$
(6) $R^1, R^2 = Et$

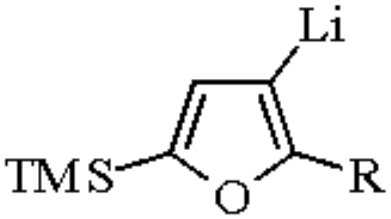

(7) $R = CO_2Li$
(8) R = 4,4-dimethyloxazolinyl

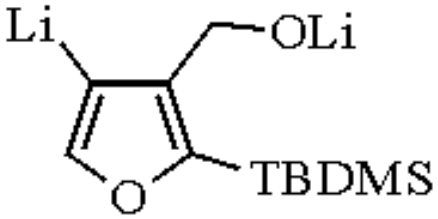

(9)

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The Upjohn Company, Kalamazoo, MI, USA

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1-Lithio-1-methoxycyclopropane[1]

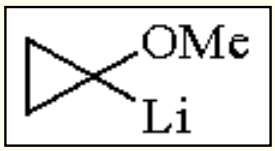

[75697-62-0] · C_4H_7LiO · 1-Lithio-1-methoxycyclopropane · (MW 78.05)

(synthesis of 2-vinylcyclobutanones,[2] which are intermediates in the synthesis of higher-membered rings via ring expansion[3])

Solubility: sol THF, in which solvent it is prepared.

Preparative Methods: from 1-methoxy-1-phenylthiocyclopropane[4] via reductive lithiation with ***Lithium 4,4´-Di-t-butylbiphenylide*** (LDBB) or ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN) in THF at -78 °C.[5] Alternatively, a similar reagent, 1-ethoxy-1-lithiocyclopropane, is obtained by lithium-tin and lithium-bromine exchange reactions of 1-ethoxy-1-(tri-*n*-butylstannyl)cyclopropane and 1-bromo-1-ethoxycyclopropane, respectively.[6]

Handling, Storage, and Precautions: presumed to be unstable and is used immediately for further transformations. α-Metalated ethers undergo Wittig rearrangement[7] and/or carbenoid reactions.[8]

Reactions of 1-Lithio-1-methoxycyclopropane.

1-Lithio-1-methoxycyclopropane reacts at -78 °C with aldehydes to give the expected addition products in high yields (eq 1).[9]

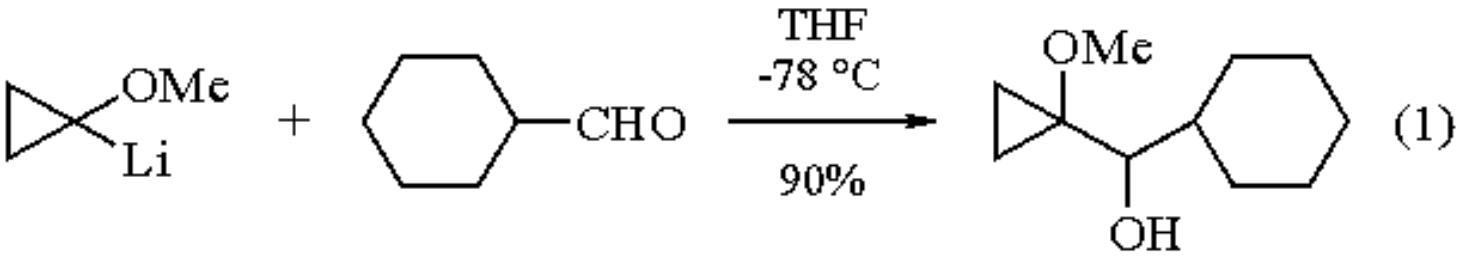

(1-Methoxycyclopropyl)alkyl alcohols are usually not isolated and the crude reaction products are directly subjected to acid-catalyzed rearrangement to 2-substituted cyclobutanones (eq 2).

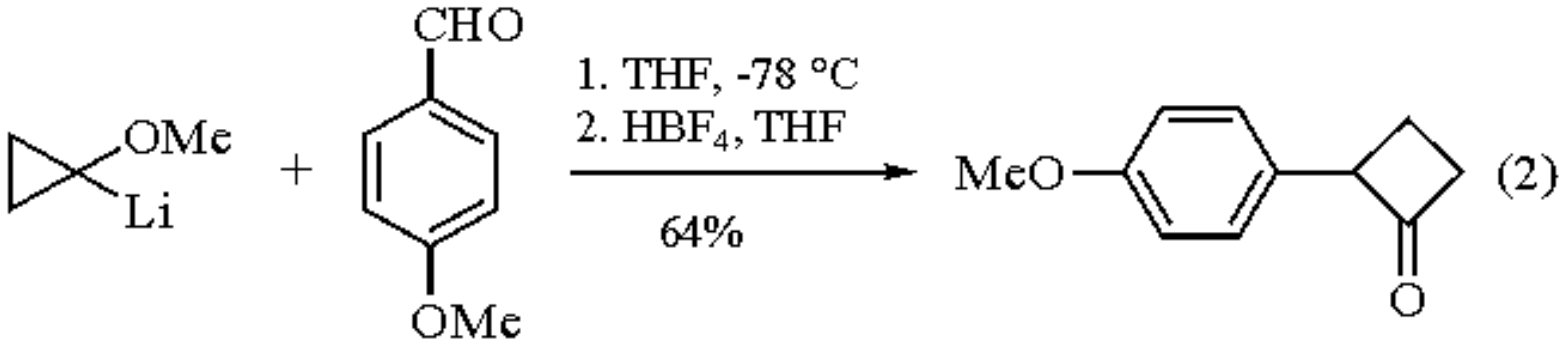

From a synthetic point of view, preparation of 2-vinylcyclobutanones is the most interesting application of the above procedure. Several different sets of conditions have been elaborated to accomplish the rearrangement of the intermediate secondary or tertiary cyclopropylalkyl alcohols. In most cases, a solution of 48% aqueous ***Tetrafluoroboric Acid*** in THF or ether was found to be most effective.[2] Vinylcyclobutanones are prepared from α,β-unsaturated aldehydes and ketones (eqs 3 and 4).[10]

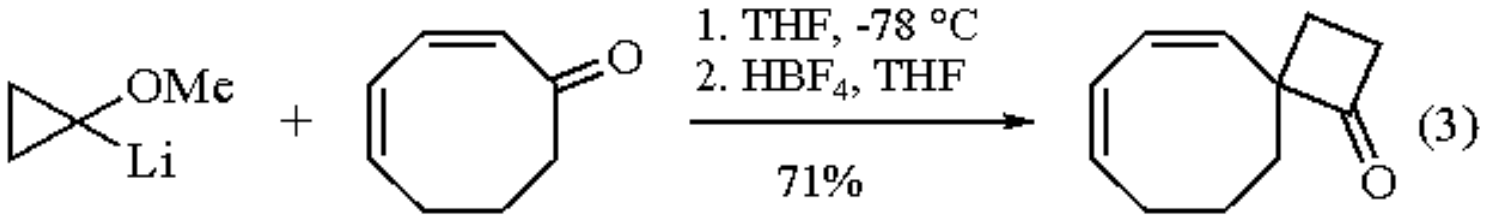

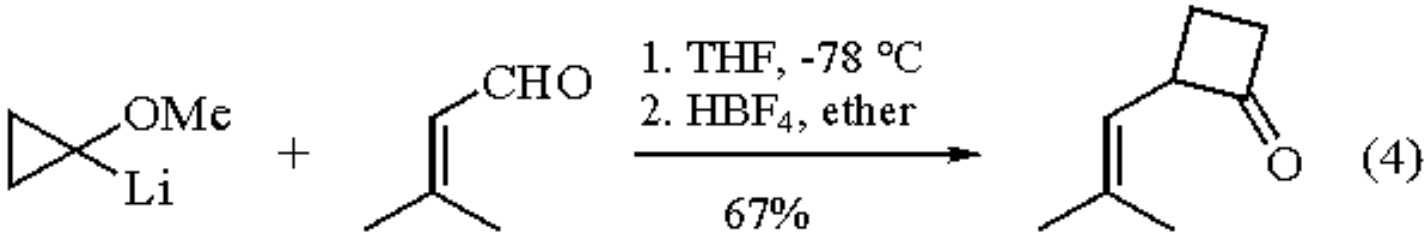

In the case of acid sensitive molecules, the rearrangement can be conducted under neutral conditions by using ***Trifluoromethanesulfonic Anhydride*** in the presence of a hindered base, 2,6-di-*t*-butyl-4-methylpyridine (eq 5).[5]

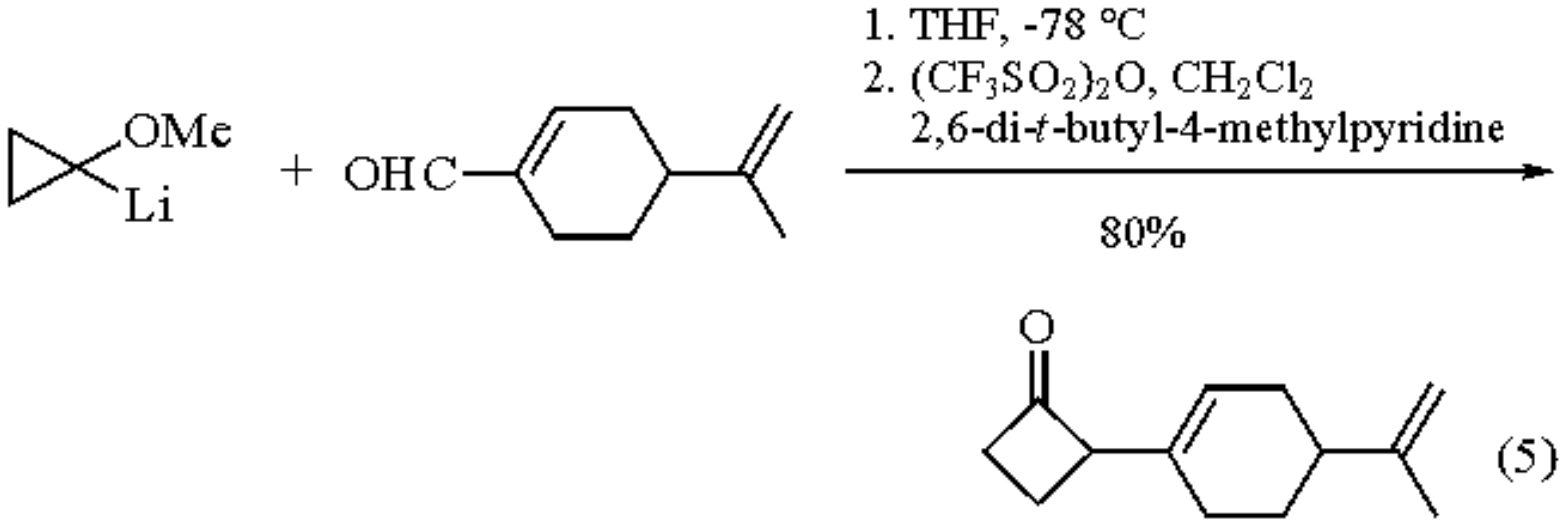

Synthetic Utility of 2-Vinylcyclobutanones.

2-Vinylcyclobutanones are important synthetic intermediates since they undergo ring expansion reactions under a variety of conditions. Thermal,[5] acid catalyzed,[3] alkoxide accelerated,[11] or trimethylsilyl cyanide promoted[12] rearrangements lead to the formation of five-, six-, and eight-membered ring systems.

Synthesis of 2-vinylcyclobutanones from 1-lithio-1-methoxycyclopropane rivals the method of Trost,[13] which employs 1-lithio-1-phenylthiocyclopropane. In the latter method, substantial experimentation leading to different reaction conditions for each case is necessary to obtain good yields in the rearrangement step.[4b]

Related Reagents.

Cyclobutanones can also be prepared from 1-methylseleno-,[14] 1-phenylseleno-,[14] and 1-bromocyclopropyllithium reagents[15] (see ***1-Bromo-1-lithio-2-phenylcyclopropane***).

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2-Lithio-*N*-phenylsulfonylindole

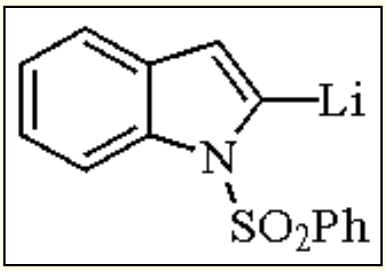

[40900-03-6] · $C_{14}H_{10}LiNO_2S$ · 2-Lithio-*N*-phenylsulfonylindole · (MW 263.26)

(nucleophilic organolithium reagent useful for addition to ketones, aldehydes, esters, lactones, acid chlorides, anhydrides, nitriles, methyl iodide, halogen sources, and sulfur dioxide; employed in the synthesis of 2-substituted indoles and alkaloids)

Preparative Methods: by deprotonation of *N*-phenylsulfonylindole[1] with ***t-Butyllithium*** in ether (-12 °C to room temperature),[1] by treatment of *N*-phenylsulfonylindole with ***n-Butyllithium*** in THF (-70 °C),[2] and by deprotonation of *N*-phenylsulfonylindole with ***Lithium Diisopropylamide*** in THF (-70 to 5 °C) (eq 1).[3]

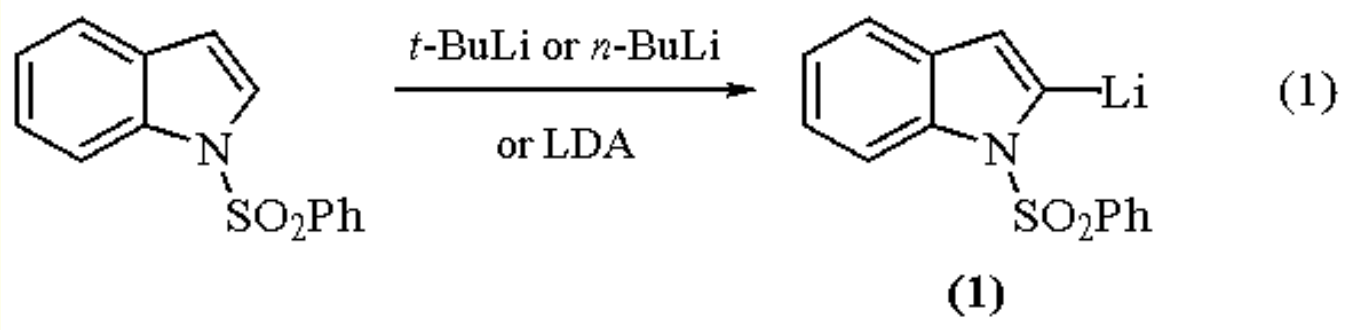

Handling, Storage, and Precautions: the reagent is generated in situ, under anhydrous conditions, in an inert atmosphere, and used shortly after preparation. The stability in storage is unknown. Precautions for preparation and use are as for other reactive organolithium reagents.

Synthesis of 2-Substituted Indoles.

Heteroaromatic compounds such as ***Furan*** and thiophene are readily metalated at an α-position and the resulting organometallic reagents can be captured by a variety of electrophiles.[4a] *N*-Unsubstituted indoles and pyrroles suffer removal of the acidic N-H, affording ambident nucleophiles[4a] which give rise to mixtures of *C*- and *N*-substituted products upon reaction with electrophiles.[4b] 1-Methylindole can be lithiated at the 2-position to provide 1,2-disubstituted indoles after capture by an electrophile.[5] Difficulties associated with *N*-dealkylation restrict this method to the preparation of 1,2-disubstituted indoles.[1] Substitution at the 1-position of the indole moiety with a readily removable group provides access to 2-substituted indoles. *N*-Phenylsulfonylindole is readily deprotonated (eq 1) to give 2-lithio-*N*-phenylsulfonylindole (**1**)

which reacts with electrophiles (eq 2) such as aldehydes,[1] ketones,[1] acid chlorides,[1] ***Carbon Dioxide***,[1] anhydrides,[1,6] arylsulfonyl chloride,[7] ***Cyanogen Bromide***,[7] ***Iodine***,[7] and ***Sulfur Dioxide***[2] to give *N*-phenylsulfonyl substituted indolyl-2-carbinols (from aldehydes, ketones), 2-ketones (from acid chlorides, anhydrides), 2-carboxylic acid (from carbon dioxide), 2-sulfones (from arylsulfonyl chlorides), 2-bromide (from cyanogen bromide), 2-iodide (from iodine), and 2-sulfonic acid salt (from sulfur dioxide) in reasonable yields (25-85%). 2-Lithio-*N*-phenylsulfonylindole (**1**) appears to react poorly with alkyl halides. The reaction of (**1**) with ethyl benzoate gives 2-indolyl phenyl ketone (26%), a product of in situ phenylsulfonyl cleavage.[1] Similarly, the reaction of (**1**) with benzonitrile also yields 2-indolyl phenyl ketone (30%).[1] Cleavage of the *N*-phenylsulfonyl group to generate the target 2-substituted indole is readily accomplished with 2N ***Sodium Hydroxide*** in methanol (reflux, eq 3)[1] or ***Potassium Carbonate*** in methanol/water (3:1) at reflux (eq 4).[6]

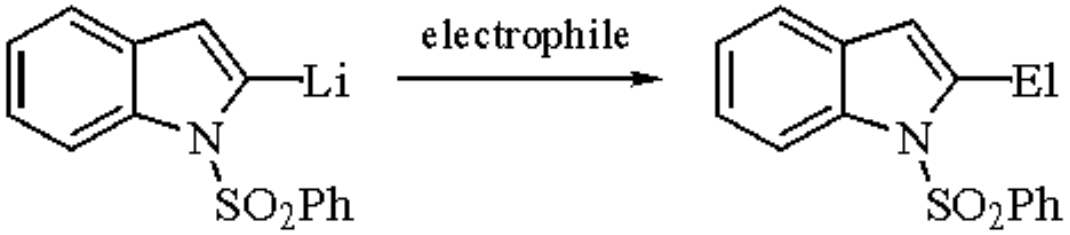

(2)

(1)

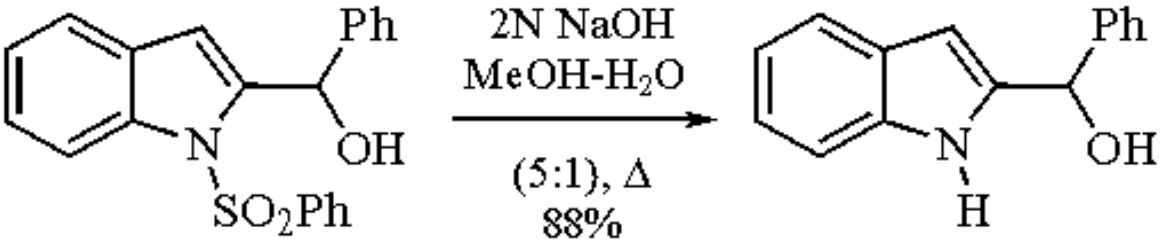

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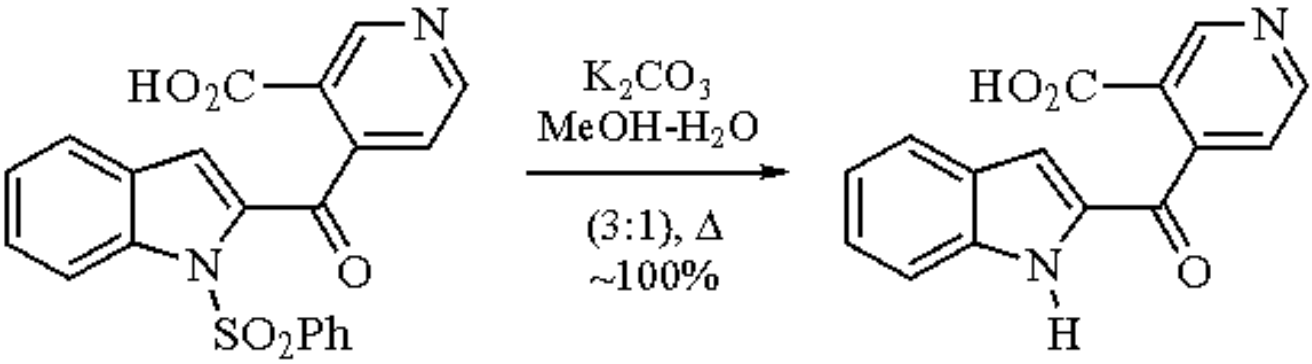

(4)

Alkaloid Synthesis.

Indole alkaloids such as ellipticine (eq 5)[6] and the genotoxic amine TrpP-1 (eq 6)[8] have been prepared from 2-lithio-*N*-phenylsulfonylindole (**1**).

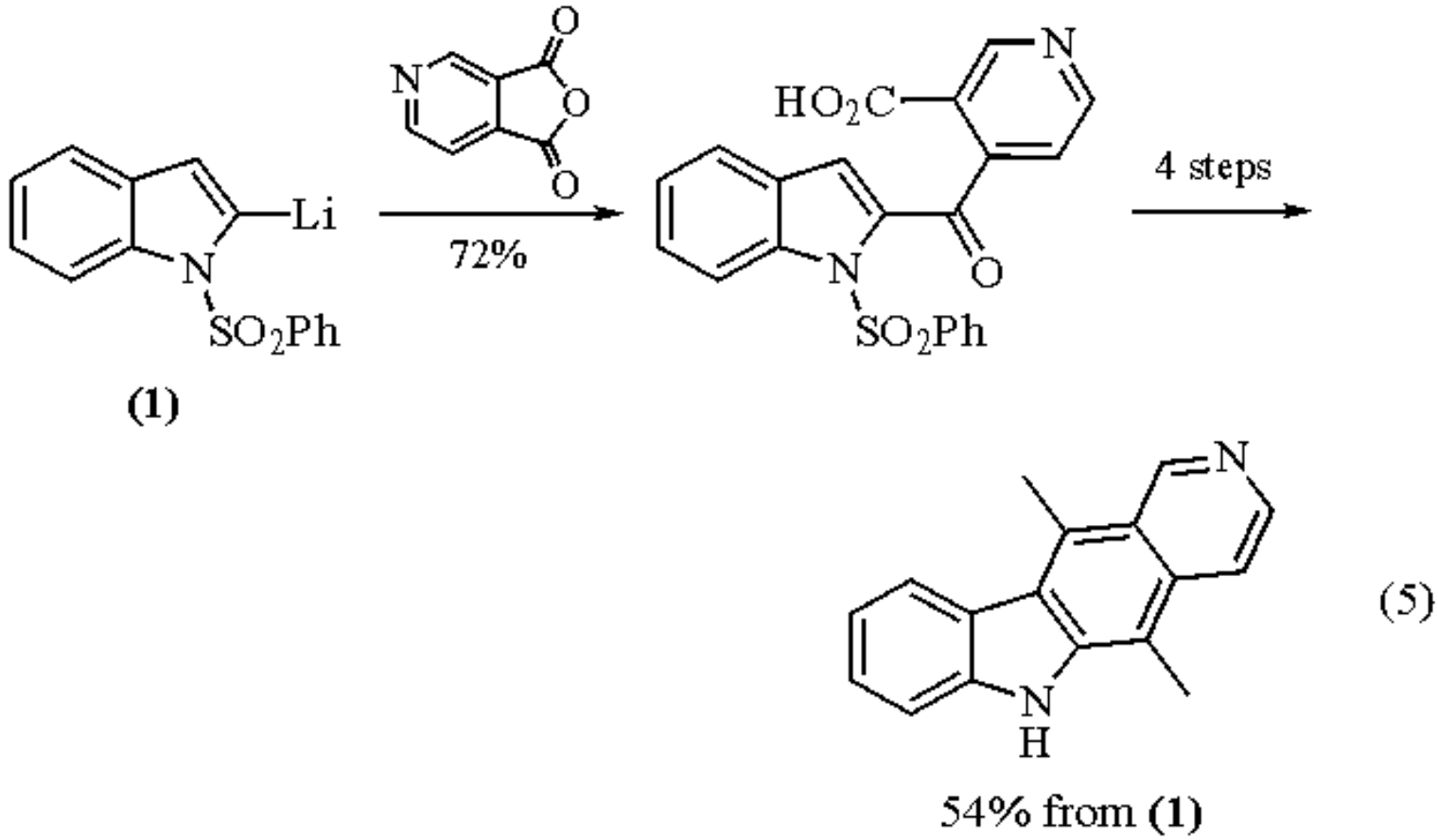

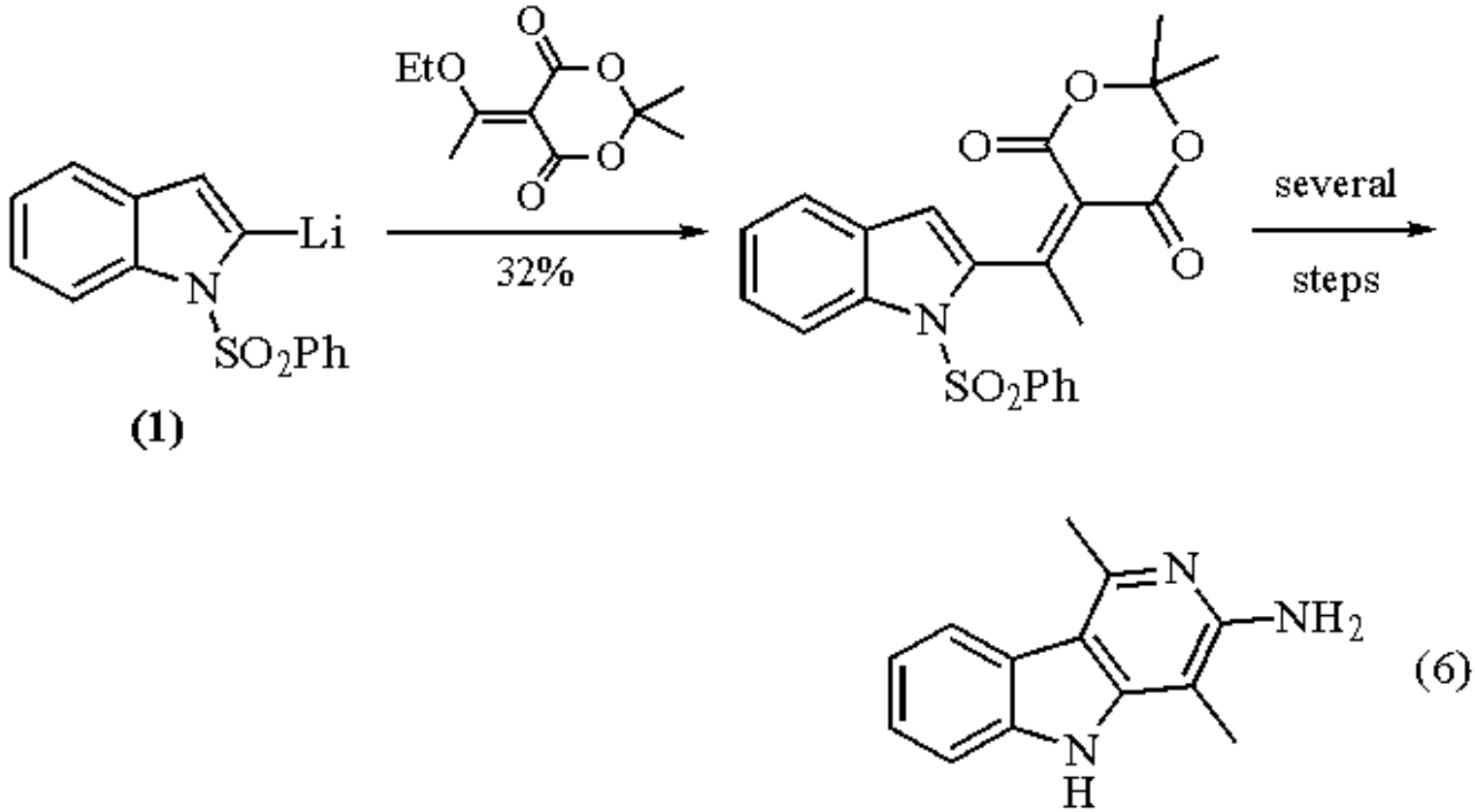

Related Reagents.

A number of indole *N*-protecting groups have been reported to afford variants of 2-lithio-*N*-phenylsulfonylindole which lead to the preparation of 2-substituted products amenable to further synthetic transformation. Table 1 shows a number of removable nitrogen blocking groups in the indole and pyrrole series. In the indole series, (**2a-g**)[1-3,9a-i] readily provide *N*-deprotected 2-substituted indoles. Indolyllithium reagents (**2g**)[1] and (**2h**)[1] are less well explored. In the pyrrole series, (**3a**)[9a] and (**3g**)[10g,h] are problematic due to competitive desulfonylation (**3a**) and silicon migration (**3g**). Pyrrolyllithiums (**3b**),[9a,10a] (**3c**),[9d,10b-d] (**3d**),[10e] and (**3e**)[9h] provide satisfactory yields of 2-substituted pyrroles, although (**3b**)[9a] has been reported to be thermally labile and (**3c**)[9d,10b-d] requires carefully controlled deprotection conditions. Pyrrolyllithium (**3f**) has not been widely examined.[10f]

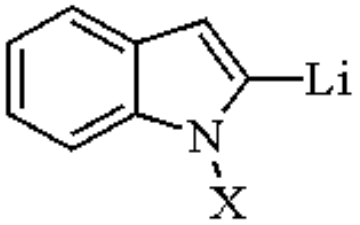

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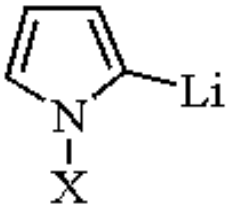

(3)

X = removable *N*-blocking group

Table 1 *N*-Blocked 2-Lithioindoles and *N*-Blocked 2-Lithiopyrroles

(2)	X	Ref.	(3)	X	Ref.
a	SO_2Ph	1 3	**a**	SO_2Ph	9a
b	CO_2-*t*-Bu	9a c	**b**	CO_2-*t*-Bu	9a, 10a
c	SEM	9d	**c**	SEM	9d, 10b d
d	CO_2^-	9e g	**d**	CO_2^-	10e
e	CON(*t*-Bu)Li	9h	**e**	CON(*t*-Bu)Li	9h
f	CH_2NMe_2	9i	**f**	NMe_2	10f
g	CH_2OMe	1	**g**	SiR_3	10g,h
h	SiR_3	1			

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2-Lithiopyridine[1]

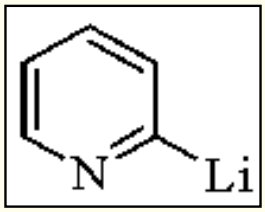

[17624-36-1] · C_5H_4LiN · 2-Lithiopyridine · (MW 85.03)

(convenient 2-pyridinyl building block; can react with a variety of electrophiles[1])

Preparative Methods: lithiation of pyridine with simple lithio bases is difficult; addition across the C=N bond predominates with alkyllithiums,[2] whereas lithium amides give rise to bipyridyls.[3] However, pyridine can be regioselectively metalated by treatment with a complex of ***n-Butyllithium-Potassium t-Butoxide*** under carefully controlled conditions (eq 1).[4] Use of 2-3 equiv of the base is necessary and the excess has to be destroyed by reaction with the solvent (THF) at -25 °C prior to addition of the electrophile. *Ortho* deprotonation of pyridine can be facilitated by formation of a complex with hexafluoroacetone,[5] tricarbonylchromium(0),[6] or, more simply, with a Lewis acid like ***Boron Trifluoride*** (eq 2).[7] Another popular approach to 2-lithiopyridine utilizes an exchange reaction of 2-bromopyridine (eq 3).[8] The choice of method for the preparation of this reagent can depend upon the electrophile with which it is to be used. For instance, BF_3-complexed 2-lithiopyridine gives excellent yields with carbonyl compounds but reacts poorly with alkyl halides.[7]

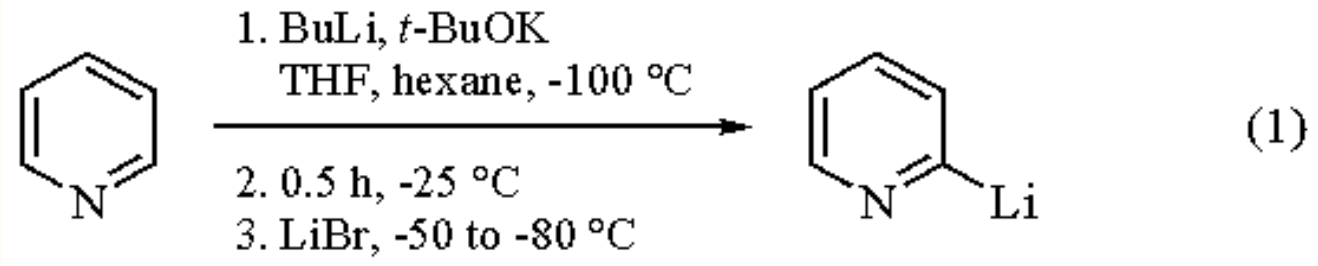

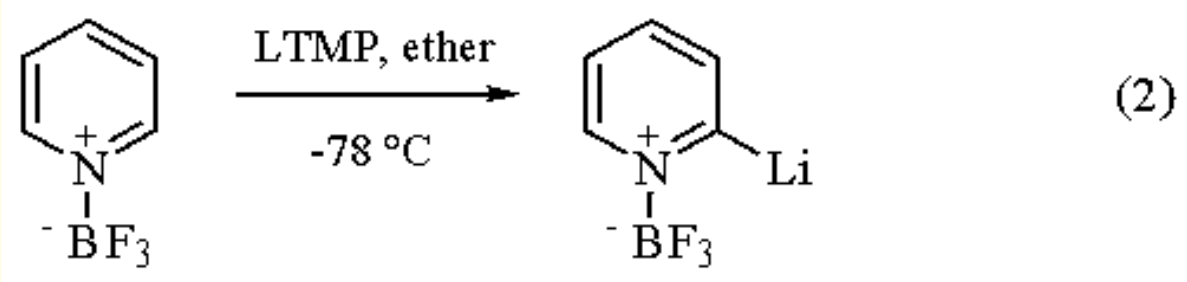

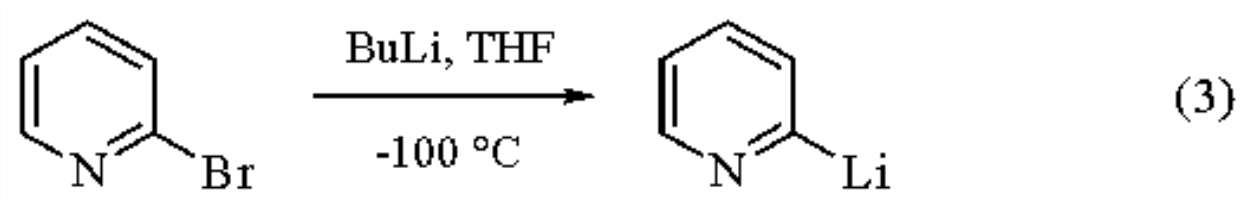

(3)

Handling, Storage, and Precautions: should be prepared and handled in a moisture-free inert atmosphere and used immediately. Use in a fume hood.

Reaction with Electrophiles.

Reaction of 2-lithiopyridine with aldehydes and ketones gives α-pyridinyl alcohols cleanly (eq 4),[7] whereas use of carboxylic acid derivatives leads to the corresponding ketones (eq 5).[9] Treatment of the reagent with ***Copper(I) Iodide*** promotes 1,4-addition with α,β-unsaturated carbonyl compounds (eq 6).[8b]

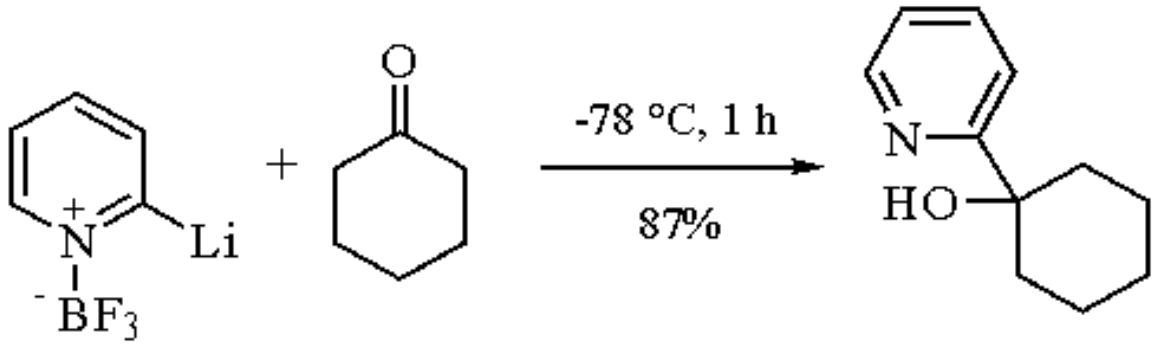

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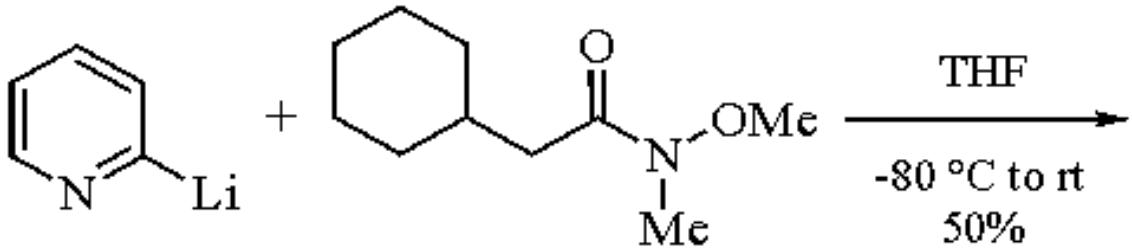

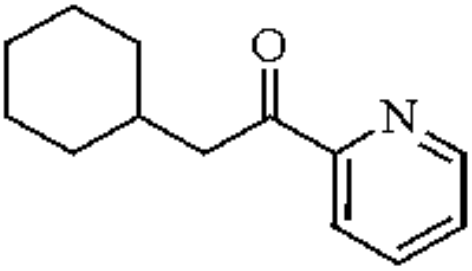

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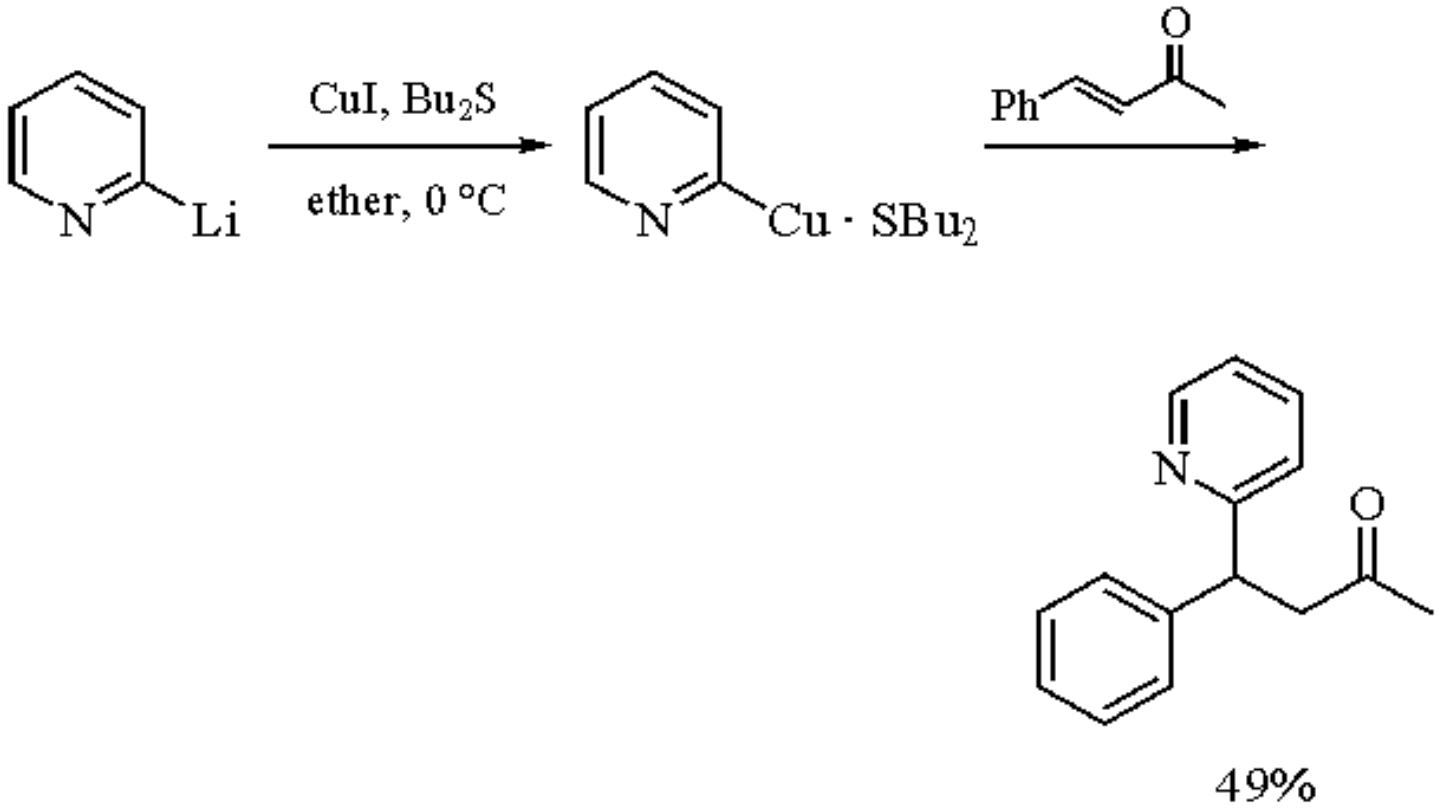

(6)

Other electrophiles which react with 2-lithiopyridine include MeOD (eq 7),[4a] ***Chlorotrimethylsilane*** (eq 8),[4a] ***Iodine***,[4a] ***Dimethyl Disulfide***,[4a] 1,2-dibromo-1,1,2,2-tetrachloroethane (eq 10),[5] ***Iodomethane*** (eq 9),[6] and methyl benzoate.[8a]

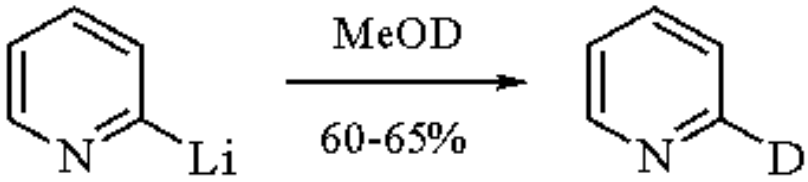

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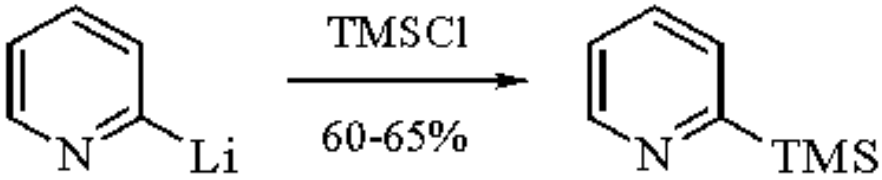

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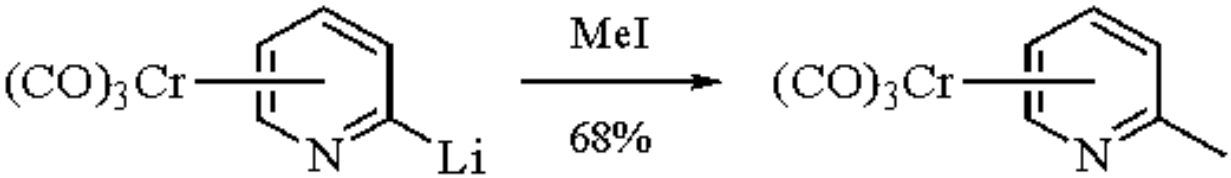

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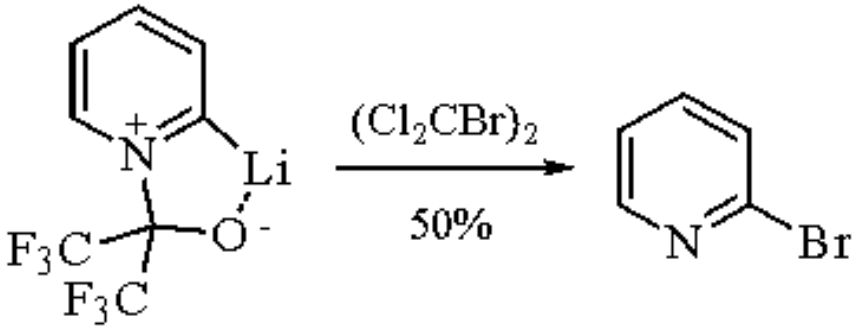

(10)

Related Reagents.

Polar solvents favor 4-metalation of pyridine by the BuLi-*t*-BuOK mixed base.[4] Both 2- and 3-lithiopyridines can be obtained from the corresponding bromides through exchange reaction with BuLi.[8] Pyridines carrying *ortho* directing groups like alkoxy,[10] fluoro,[11b] chloro,[11] bromo,[11] carboxamido,[12] oxazoline,[13] pivaloylamino,[14] and diethylcarbamate[15] can be lithiated regioselectively.

---

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(*E*)-1-Lithio-2-tributylstannylethylene

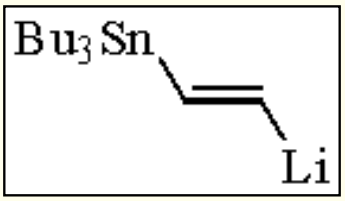

[119119-56-1] · $C_{14}H_{19}LiSn$ · (*E*)-1-Lithio-2-tributylstannylethylene · (MW 323.01)

(precursor of functionalized *trans*-substituted vinylic organometallics or vinylic halides; precursor of *trans*-1-lithio-2-trimethylsilylethylene;[2] synthesis of vinylstannanes; alkylation or condensation products undergo further palladium-catalyzed coupling;[5,9,12] mixed cuprates[1,12] or higher order cyanocuprates[13] couple with halides;[5] epoxide opening;[13b] conjugate addition;[1,13a,15] ethynyl equivalent[1])

Solubility: sol THF, DME, ether, ether/hexane.

Analysis of Reagent Purity: ^{1}H NMR (kinetics of transmetalation); GLC of a quenched aliquot from the transmetalation reaction

Handling, Storage, and Precautions: generated in situ; stable at low temperature and even for several hours in THF at rt; usual handling procedures for sensitive organometallics; no data available for toxicity (usual precautions for handling tin compounds). Use in a fume hood.

Preparation and Reactivity with Electrophiles.

Treatment of (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene with ***n-Butyllithium*** in THF at -78 °C generates cleanly the title lithium reagent (**1**).[1] Attempts to prepare *trans*-1,2-dilithioethylene were unsuccessful (eq 1).[2]

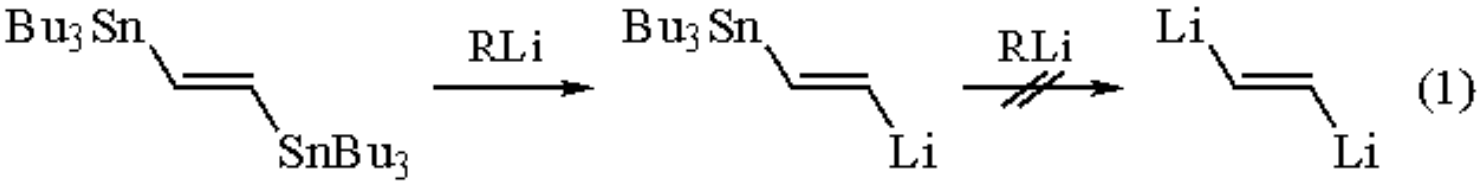

(1)

The transmetalation reaction is known to be an equilibrium process[3] and to occur with complete retention of configuration about the C=C bond.[4] Reaction of the monolithiated species with Me_3SiCl is competitive with transmetalation so that *trans*-1,2-bis(trimethylsilyl)ethylene is formed in variable amounts depending on reaction conditions. (*E*)-1-Lithio-2-tributylstannylethylene can also be generated at -78 °C in THF by using ***Methyllithium***,[5]

and conveniently at room temperature with *n*-BuLi in THF.[2] (*E*)-1-Tributylstannyl-2-trimethylsilylethylene is isolated in 58-63% yield, from which *trans*-1-lithio-2-trimethylsilylethylene is formed very cleanly by reaction with *n*-BuLi in THF (at -78 °C or rt) affording exclusively *trans* substituted products with different electrophiles. Efficient one-pot successive transmetalations and reactions with two different electrophiles have also been reported (eq 2).[2]

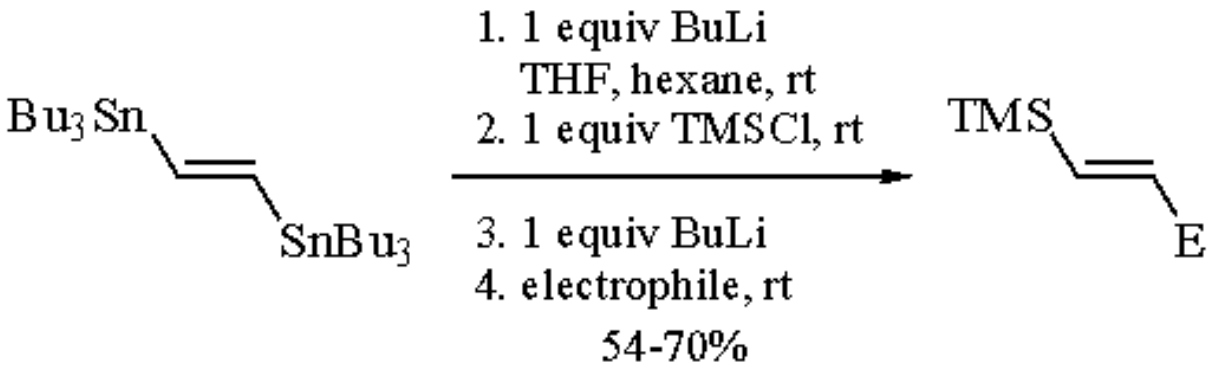

(2)

Ethyl (*E*)-3-(tributylstannyl)propenoate is prepared in 59% yield by reaction of (**1**) with ***Ethyl Chloroformate***. The product was used in a palladium-catalyzed coupling with an acid chloride.[5]

Reagent (**1**) reacts with aldehydes to yield stereospecifically *trans*-β-stannylated allylic alcohols. This route is preferred over the hydrostannylation of propargylic alcohols (protected or not), which under appropriate conditions (excess ***Tri-n-butylstannane*** radical initiator) yield mixtures of (*E*) and (*Z*) isomers (usually in a 5/1 to 10/1 ratio) and some nonterminal stannylated product (eq 3).[6,7a]

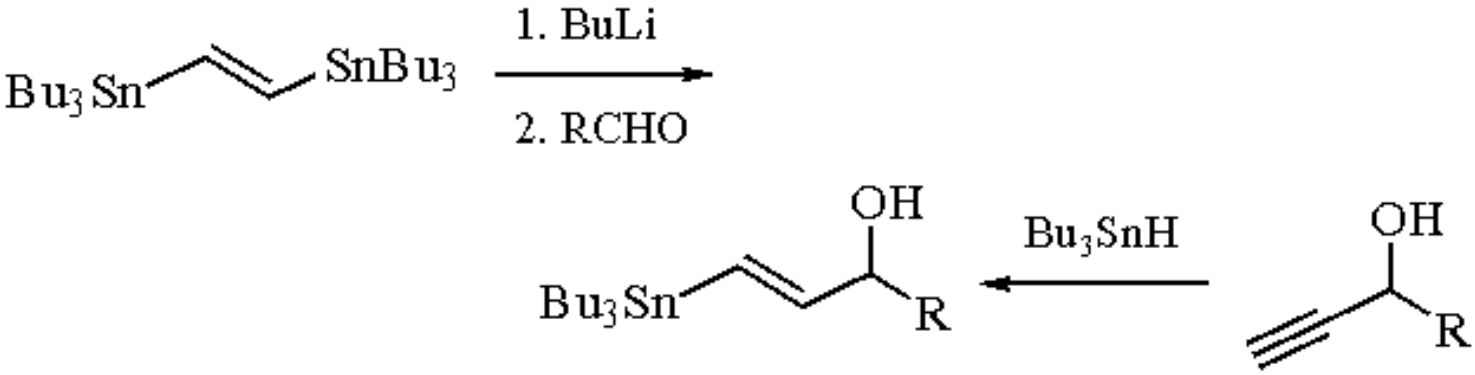

(3)

Such racemic *trans*-β-stannylated allylic alcohols undergo efficient kinetic resolution under Sharpless asymmetric epoxidation conditions and, after vinylic C-Sn bond cleavage with iodine, afford optically active vinyl iodides in high yield and enantiomeric excess.[7] Selective condensation of (**1**) with o-aldehyde esters gives the corresponding racemic β-stannylated allylic secondary alcohols,[7b,c] which were also resolved by the same methodology.[7b]

The lithio reagent (**1**) is not strongly basic, as shown by its reaction with a deconjugated aldehyde (eq 4),[8] or with an α-epoxy aldehyde (eq 5).[9] Thus the reaction of (**1**) with (3*Z*)-nonenal afforded the racemic alcohol in 70% yield, which also underwent an efficient Sharpless kinetic resolution and was further converted into the monochiral vinyl iodide.[8] Functionalized monochiral vinylstannanes were also prepared by reaction with the appropriate α-epoxy aldehyde. The products were coupled with halogenated isocoumarins with palladium catalysis, in a convergent stereospecific synthesis of monocillin I and monorden.[9]

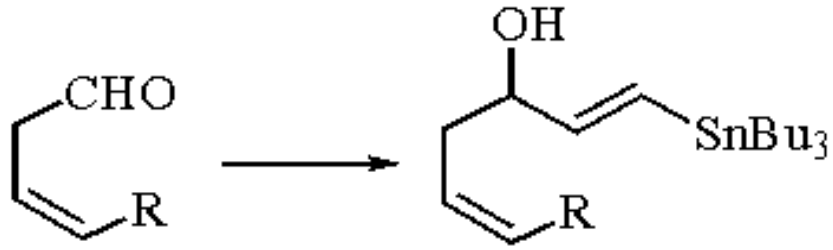

(4)

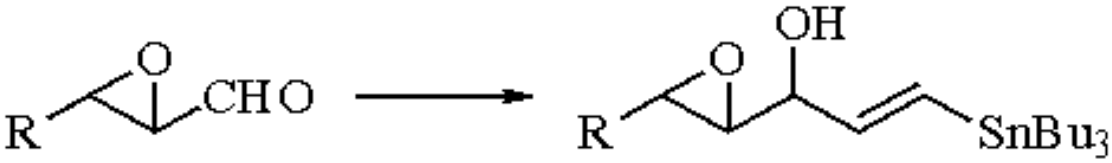

(5)

The addition of (**1**) to several 17-keto steroids has also been reported.[10] The 17α-(*E*-tributylstannylvinyl) adducts can be destannylated in high yields with various electrophiles.[10a] Reaction with $Na^{125}I/AcONa\text{-}AcOH/H_2O_2$ produced ^{125}I-radiolabeled (*E*)-17α-iodovinylestradiol in high isolated radiochemical yield, with a radiochemical purity >98%, at the no-carrier-added level.[10b-e]

The addition of organolithium reagents to pyrylium salts gives (2*Z*,4*E*)-dienals with high stereoselectivity; the reaction with (**1**) is slow, however, and affords the desired trienal in moderate yield (eq 6).[11]

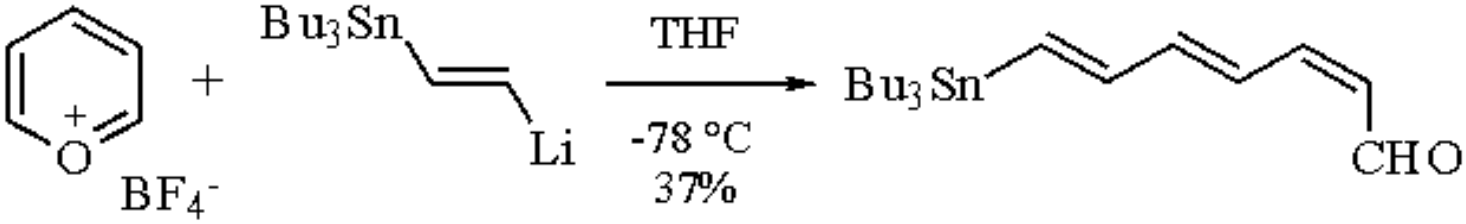

(6)

Derived Mixed Cuprate Reagents.

The mixed cuprate (**2**) is formed rapidly and cleanly when a solution of (**1**) in THF is treated with pentynylcopper in the presence of 2.7 equiv of HMPA. The reaction of the brown, soluble cuprate reagent with enones proceeds with excellent selectivity to afford the β-vinylstannyl ketones in good yields (85-93%). Treatment of these adducts with ***Lead(IV) Acetate*** in acetonitrile, at rt, affords the corresponding β-ethynyl ketones. This two-step procedure is therefore an alternative to the unreactivity of ethynyl Gilman reagents (eq 7).[1]

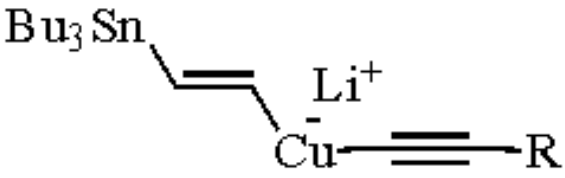

(2)

(E)-1-Lithio-2-tributylstannylethylene

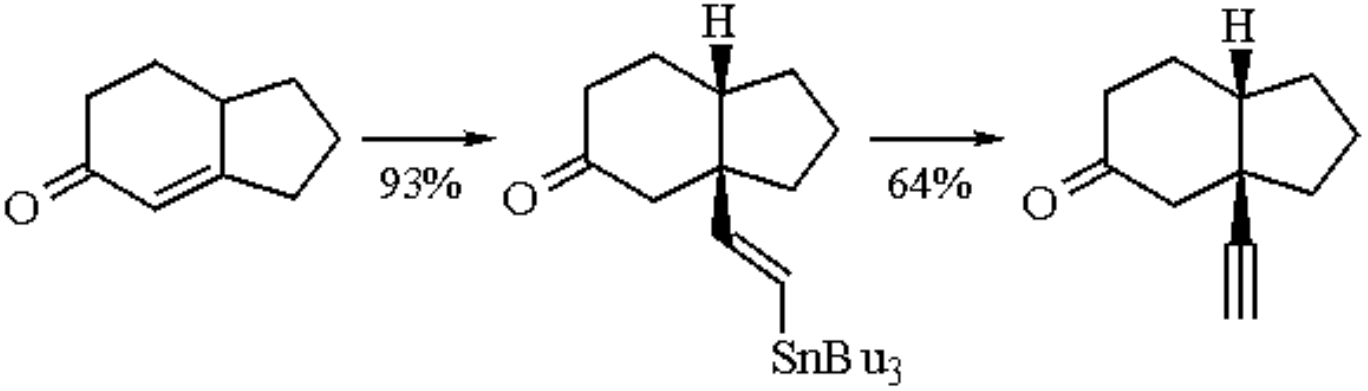

(7)

An analogous mixed cuprate which was formed with *n*-hexynylcopper in THF (with no added HMPA) reacted with 3-furfuryl bromide to give (*E*)-1-(tributylstannyl)-2-(3-furfuryl)ethylene in 73% yield, which further underwent a palladium-catalyzed coupling with a vinyl triflate.[12]

Higher-Order Cyanocuprates.

Reaction of (*E*)-1,2-bis(tributylstannyl)ethylene with 1 equiv of $Me_2Cu(CN)Li_2$ in THF, at rt, leads to the quantitative formation of the mixed higher order cyanocuprate (**3**) (R = Me) and tri-*n*-butyl(methyl)tin. This mixed higher-order cuprate reagent adds by 1,4-addition to cyclohexenone in high yield (93%), with high selectivity for vinylstannyl over methyl transfer.[13a]

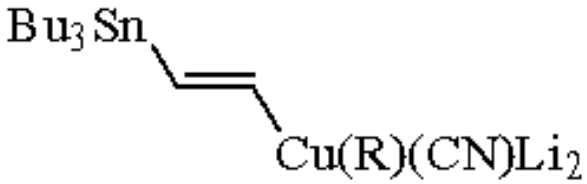

(3) R = Me, 2-thienyl

In situ cuprate formation from (*E*)-1,2-bis(tributylstannyl)ethylene and Me(2-thienyl)$Cu(CN)Li_2$ (1 equiv), from commercially available (2-thienyl)Cu(CN)Li and MeLi, generates (2-thienyl)($Bu_3SnCH{=}CH$)$Cu(CN)Li_2$. The in situ formation of the desired higher-order cuprate (dark red solution in THF-ether) and tributyl(methyl)tin can be monitored by gas chromatographic analysis of a quenched aliquot.[13b] Pure β-hydroxy-(*E*)-vinylstannanes are obtained in good yields (50-74%) by the reaction of this higher-order mixed reagent with mono- or disubstituted terminal epoxides, with excellent regiochemical control of the opening. This route has the advantage of yielding stereochemically pure (*E*)-vinylstannanes when compared to hydrostannylation of the corresponding alkynes, which is difficult and affords (*E*/*Z*) mixtures (eq 8).[6a,13b,14]

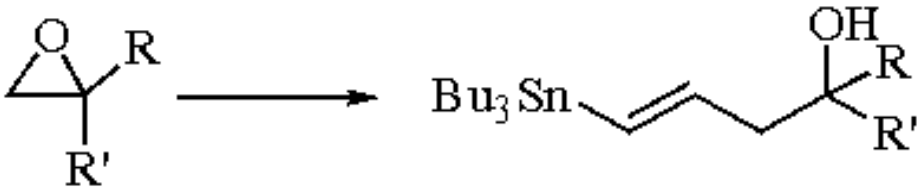

(8)

On the other hand, reactions of the higher-order cuprate (**3**) (R = 2-thienyl) with 1,2-disubstituted epoxides were not

useful, in the presence or absence of ***Boron Trifluoride Etherate***.[13b] The BF_3-catalyzed conjugate addition of $(Bu_3SnCH{=}CH)(2\text{-thienyl})Cu(CN)Li_2$ to an unsaturated lactone in excellent yield and high diastereoselection has been used in the synthesis of (+)-lepicidin A.[15]

Related Reagents.

The (*E*)- and (*Z*)-trimethylstannyl-2-alkenoates (**4**) can be prepared with a high stereoselectivity by the reaction of α,β-alkynic esters with a suitable (trimethylstannyl)copper(I) reagent. However, the intermediate vinylic organocopper adducts react only with proton donors, other electrophiles fail.[16] Hence, a two-step methodology has been developed for the stereospecific conversion of α,β-alkynic esters to stereochemically defined synthons of general interest. Reaction of (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates with MeLi results in the selective transmetalation of the α-$SnMe_3$ group, to provide a vinylic lithio derivative nucleophilic enough to react with alkylating agents or carbonyl compounds to afford a pure geometric isomer in good yields (eq 9).[17] Such synthons should have a high potential for further elaboration.

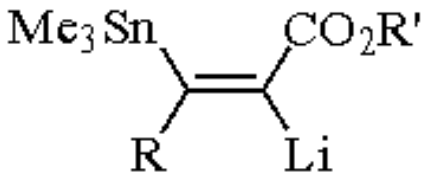

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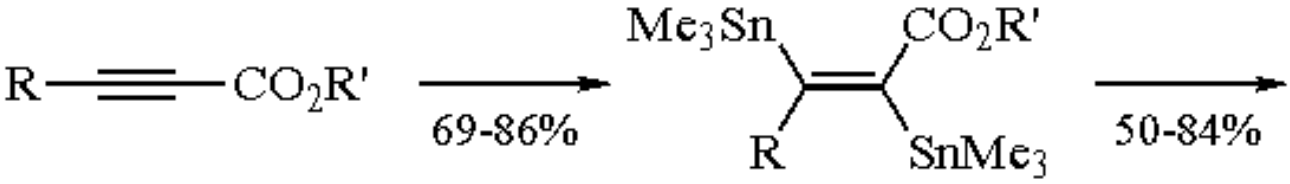

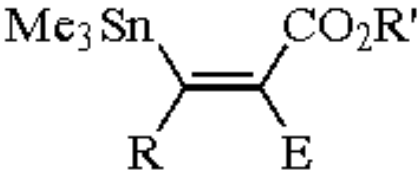

(9)

The reaction of $Bu_3SnCu(Me)(CN)Li_2$ with some simple unactivated alkynes, affords stereochemically pure cuprates (**5**), which are nucleophilic enough to react with Me_3SiCl, Bu_3SnCl, Br_2, I_2, MeI, AcCl, or even ethylene oxide. Conjugate addition with cyclohexenone and methyl crotonate was also reported.[18]

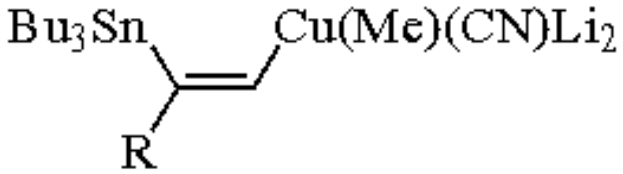

(5) R = H, alkyl

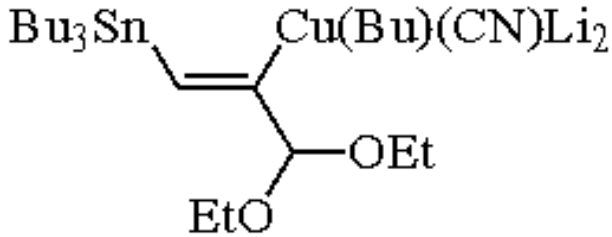

(6)

Stannocupration of 3,3-diethoxypropyne by $Bu_3SnCu(Bu)(CN)Li_2$ affords a vinylic cuprate (**6**) which reacts with electrophiles such as MeOH, I_2, allyl bromide or methyl propynoate to yield isomerically pure products in good yields (70-95%).[19]

1,1-Bis(trimethylstannyl)-1-alkenes readily undergo transmetalation with MeLi to give strongly basic α-stannylvinyllithiums (**7**). These thermally labile lithio derivatives exist almost exclusively in the (*E*) form when R = *t*-Bu or Ph, but otherwise as an (*E*/*Z*) mixture (R = Me, *n*-Bu, Cy). For R = *t*-Bu or Ph, reactions with electrophiles (MeOD, MeI, Me_2SO_4, Me_3SiCl) were reported as highly stereoselective (more than 95/5). 1,2-Addition occurred with aldehydes or nonsterically hindered aromatic ketones, but enolizable ketones gave only the protonation product. With α,β-unsaturated ketones, conjugate addition was observed.[20] Formation of α-trimethylplumbylvinyllithiums has also been reported, these species being more stable and apparently less basic than the corresponding α-stannyl lithio derivatives.[21]

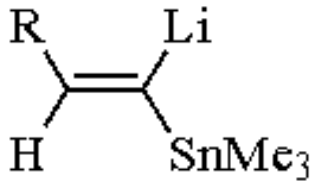

(7) R = *t*-Bu, Ph

See also ***trans-1,2-Bis(tributylstannyl)ethylene***, ***1-(Trimethylsilyl)vinyllithium***, ***Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate***, ***Lithium (1-Pentynyl)(2-tri-n-butylstannylvinyl)cuprate***, and ***(E)-1-Tri-n-butylstannyl-2-trimethylsilylethylene***.

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3-Lithio-1-triisopropylsilyl-1-propyne

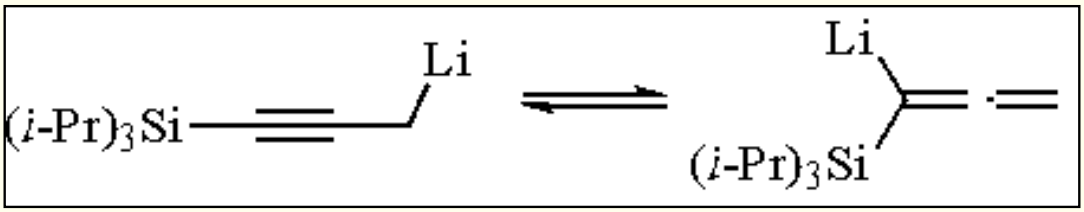

[82192-58-3] · $C_{12}H_{23}LiSi$ · 3-Lithio-1-triisopropylsilyl-1-propyne · (MW 202.38)

(functionalized nucleophilic C_3 building block; forms C-C bonds with many carbon electrophiles[1])

Alternate Name: 3-triisopropylsilyl-2-propynyllithium.

Physical Data: (precursor) bp 100-101 °C/5 mmHg; *d* 0.813 g cm^{-3}.

Solubility: good sol ether, THF.

Introduction.

The title reagent (**1**) was conceived as an improved version of TMS-C&tbond;C-CH_2Li.[2,3] The bulky triisopropylsilyl (TIPS) group provides efficient screening of the carbon atom to which it is attached, and (**1**) therefore usually forms propargylic rather than allenic products.[2,4] The TIPS group is much more inert in basic and nucleophilic reaction mixtures than the widely used TMS group. At the same time, TIPS (in contrast to tri-*t*-butylsilyl) is commercially available, easily introduced, and readily cleaved (F^-) from the product.

Reagent (**1**) is made by deprotonation of 1-TIPS-propyne[2] using ***n-Butyllithium*** in ether, better without than with TMEDA added,[5] or ***t-Butyllithium*** in ether/pentane, or preferably *n*-BuLi in THF (-20 °C, 15 min). 1-TIPS-propyne can be prepared from propyne by silylation of either its lithio derivative using TIPS triflate[2] or of the bromomagnesium derivative using TIPS chloride;[6] it is also commercially available.

Homopropargylic Alcohols.

Reagent (**1**) smoothly reacts with aldehydes and ketones (eqs 1-3).[2,7]

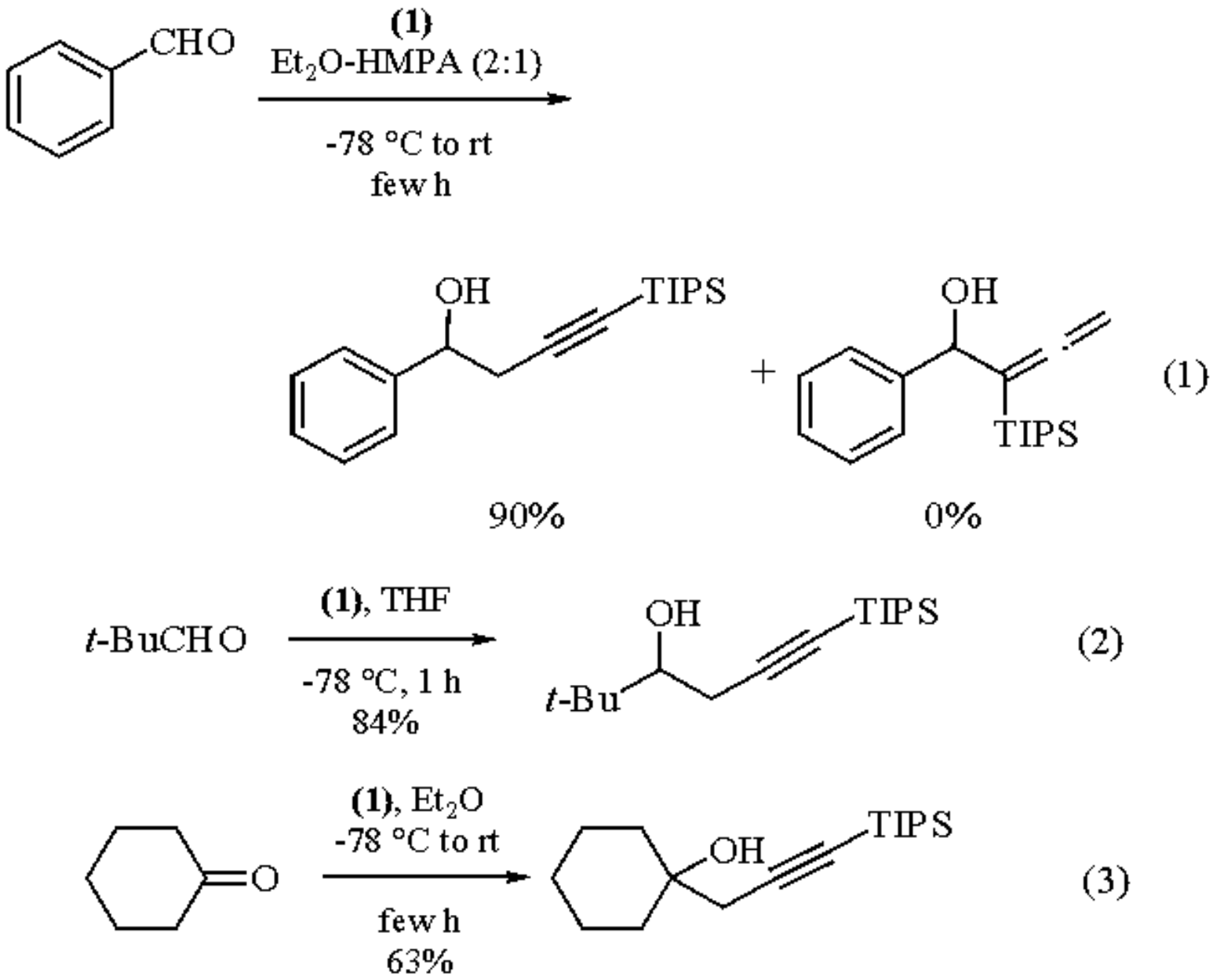

The reaction in eq 1, when performed in ether, gave rise to a 2:1 mixture of the same products. The TMS analog gave none of the corresponding adducts at all in ether/HMPA; in ether it produced both allenic and propargylic major products.

Conjugate Addition.

Reagent (**1**) in THF adds in 1,2-fashion to α,β-unsaturated ketones, whereas in THF/HMPA, 1,4-addition is observed as result of kinetic control (eq 4).[2] The hindered α,β-unsaturated ketone isophorone gave smooth 1,2-addition in THF (89%), while in THF/HMPA, 1,2- and 1,4-addition occurred (1:1) in low conversion. 1,2-Addition of (**1**) to ***Acrolein*** afforded a building block for bongkrekic acid.[8a] 1,4-Addition of (**1**) to η^4-(dienyl)$Fe(CO)_3$ substituted alkylidene malonates is highly stereoselective.[8b]

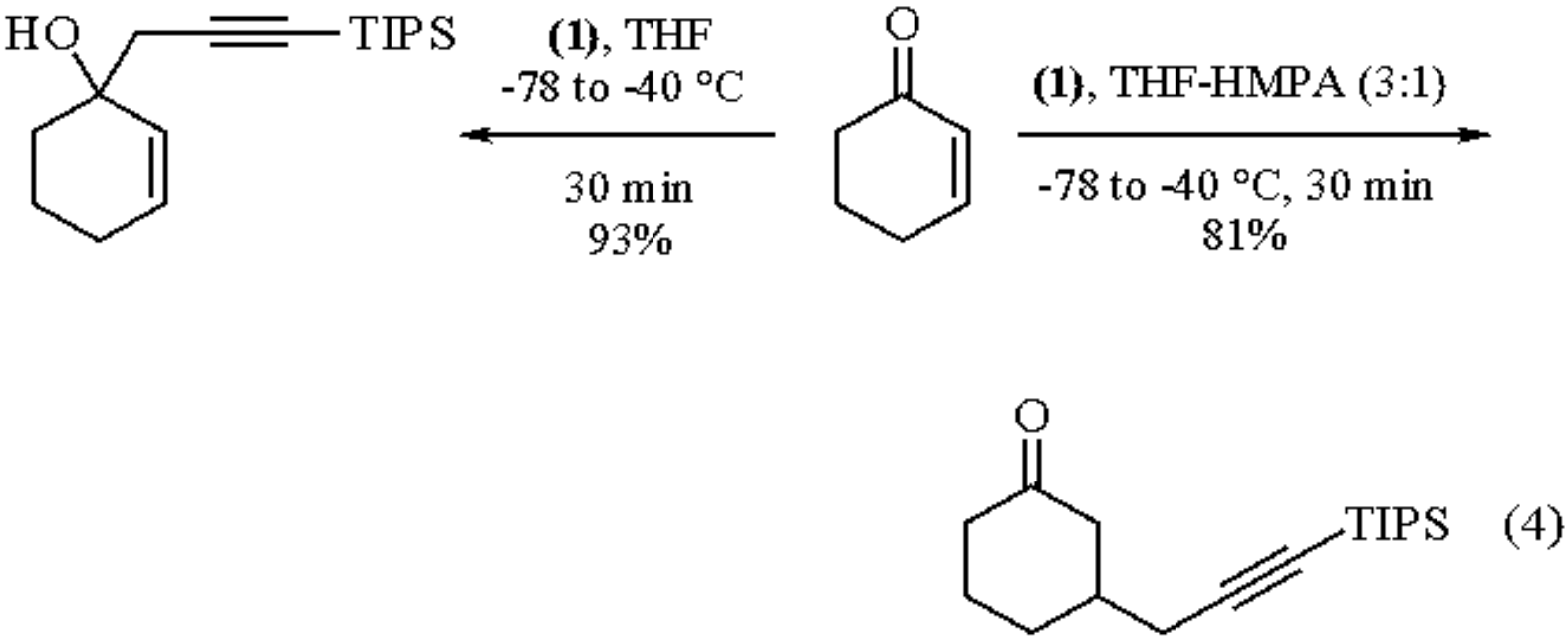

Reactions of similar organoalkynyl/allenyl silanes containing various metals with carbonyl compounds to give propargylic products have been reported.[9-11] Conjugate addition of allenyl stannanes to α,β-unsaturated carbonyl compounds to give propargylic products can be effected in the presence of ***Titanium(IV) Chloride***.[12]

Chain Elongation of Activated Halides or Phospates.

Reagent (**1**) displaces halide ion from benzyl and allyl halides (eqs 5 and 6).[2] The TMS analog reacted less selectively and gave lower yields.[13]

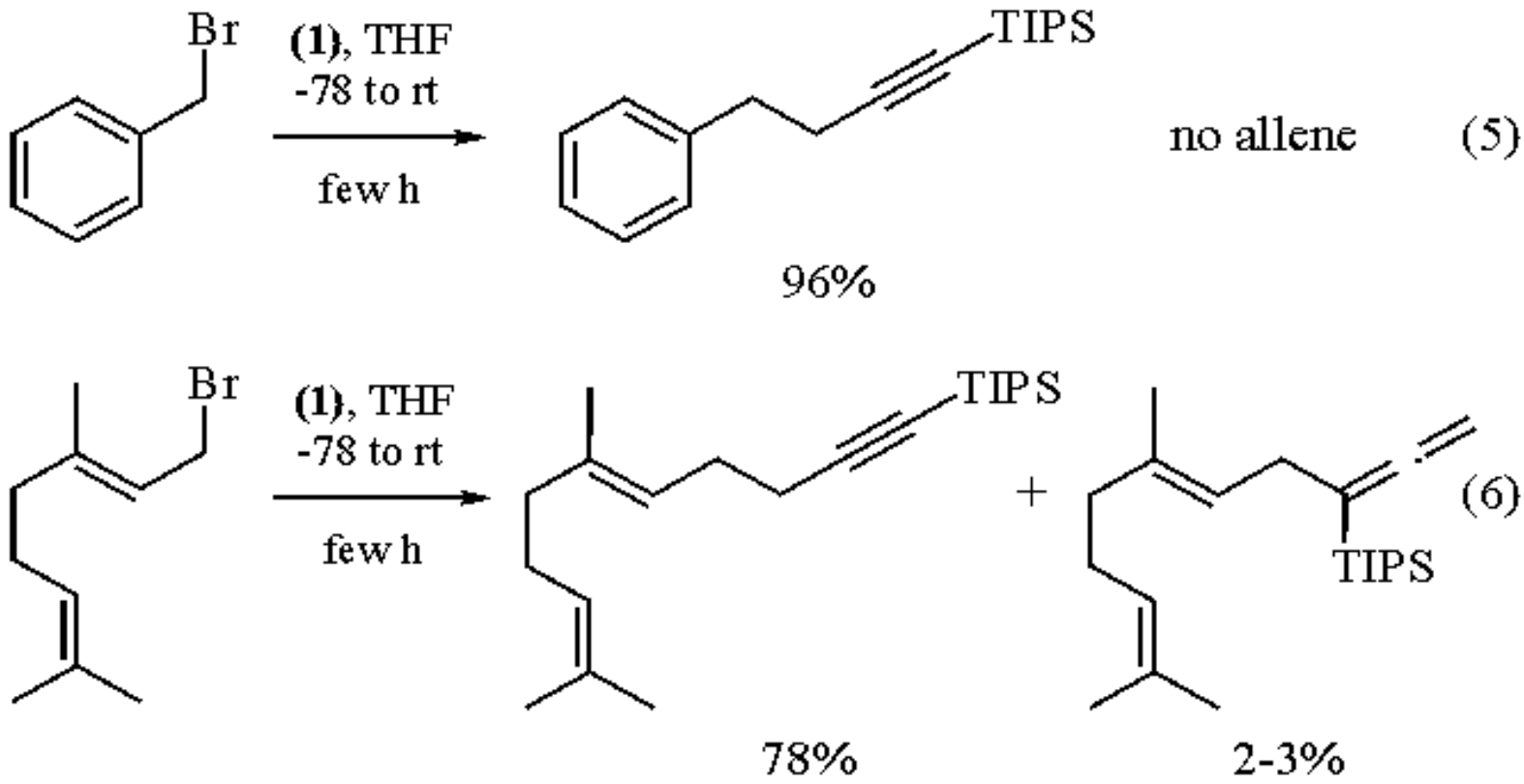

This type of coupling was routinely used by Marshall (allyl chlorides or phosphates) in the synthesis of cembranoids, employing a cuprate made from the bromomagnesium analog TIPS-C&tbond;C-CH_2MgBr (**2**), which is prepared from TIPS-C&tbond;C-CH_2Br.[14] As a rule, with these allylic electrophiles, S_N2' reaction is not observed. An OH function does not interfere if protected as its bromomagnesium salt,[14g] silyl ether,[14c,d] or even acetate.[14e,g]

Epoxide Opening and Cyclopropane Formation.

Reagent (**1**) cleanly opens epoxides (eq 7; S_N2).[2]

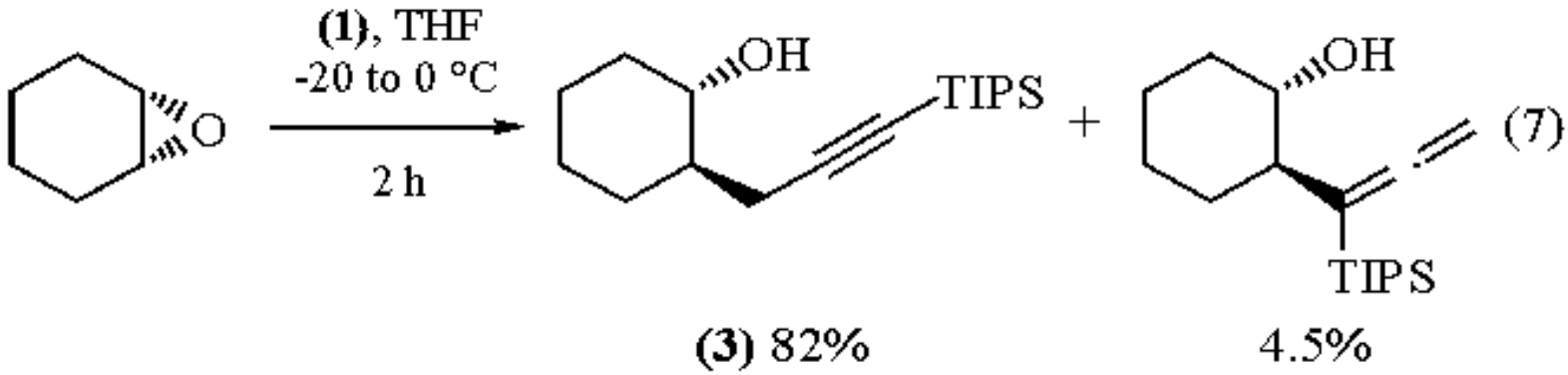

In vinyl epoxides, both exclusive S_N2 and exclusive S_N2' reactions were observed for similar reagents, depending on the substrate (eqs 8 and 9).[5,14a,b] In eq 9, the TMS analog gives a mixture of propargylic and allenic products.

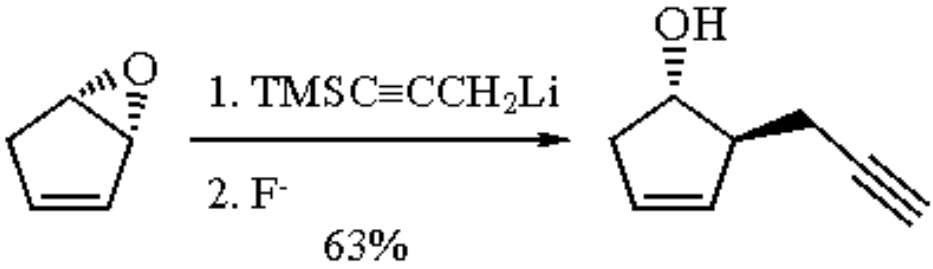

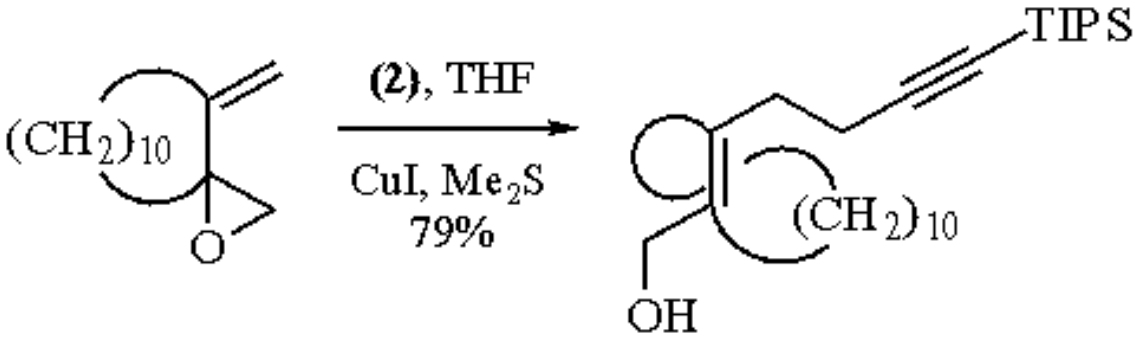

The products of epoxide opening by (**1**) can be transformed into cyclopropanes (eq 10). The TMS analog gave 75% in the cyclization step.

3-Lithio-1-triisopropylsilyl-1-propyne

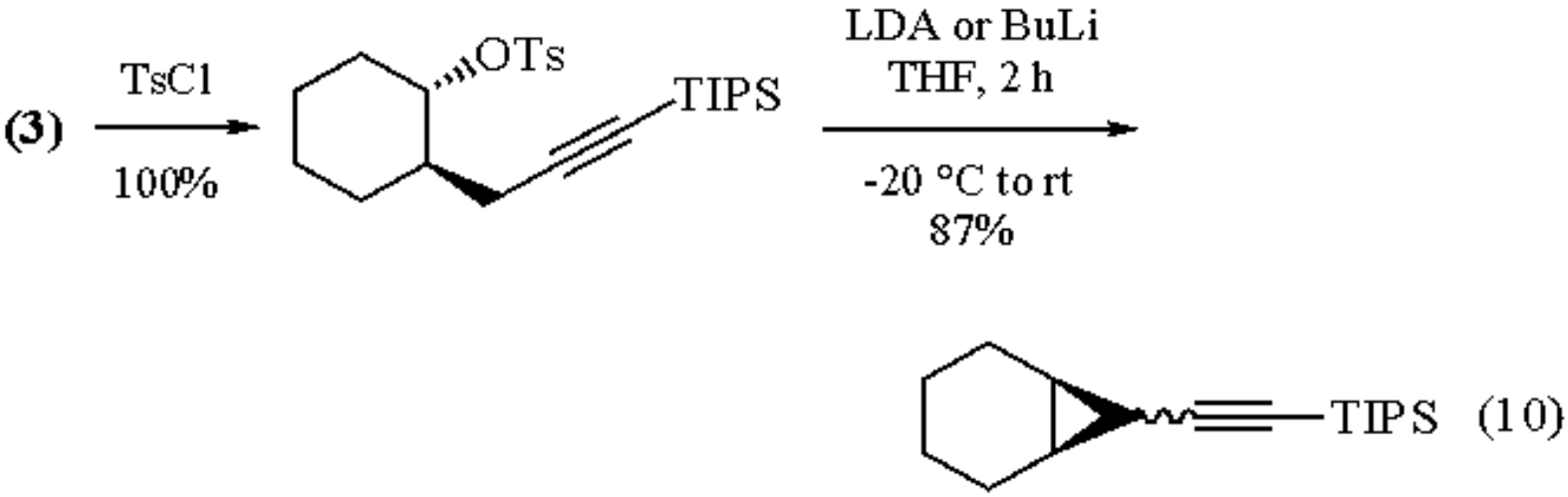

This method was triply used in the preparation of a carbocyclic *cis*-tris-σ-homobenzene (eq 11).[15]

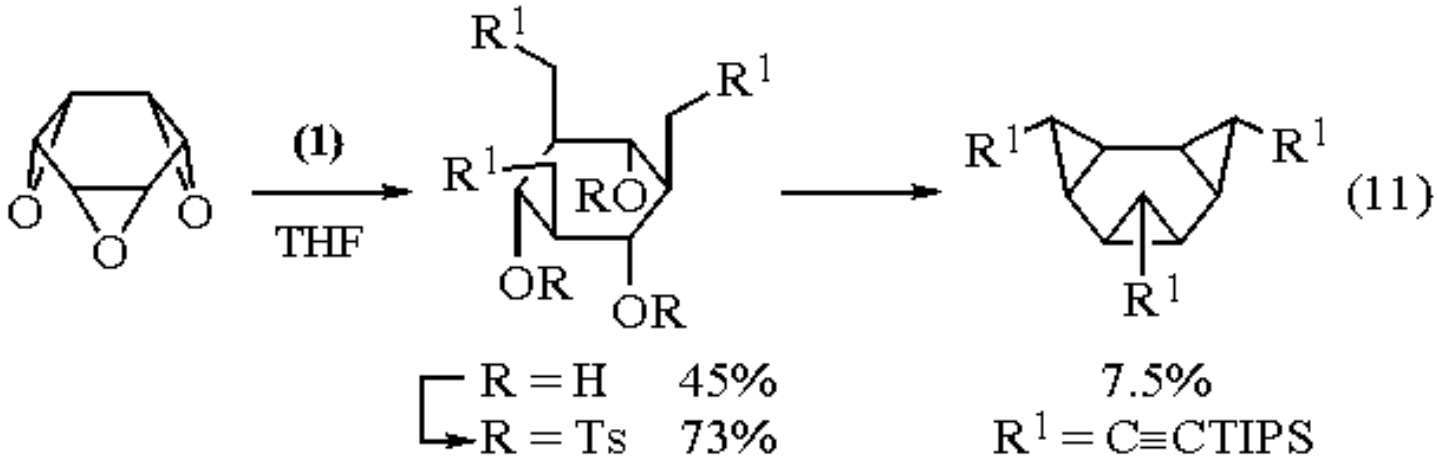

The triple epoxide opening gave higher yields (up to 67%) when organocuprates were used.[16,17] The TMS analog of this tris adduct could not be obtained, due to uncontrolled desilylation reactions.

Transformations of the C&tbond;C-TIPS Group.

The C&tbond;C-TIPS group is cleaved by the action of various fluoride reagents, but not by the $AgNO_3$/KCN procedure employed for cleavage of C&tbond;C-TMS. Corey and Rücker describe other useful transformations.[2] The deprotected propargyl group may be further degraded to an acetic acid moiety by decarboxylative oxidation using RuO_2/$NaIO_4$ in CCl_4/MeCN/H_2O, as in the preparation of *cis*-tris-σ-homobenzenes (eq 12).[17]

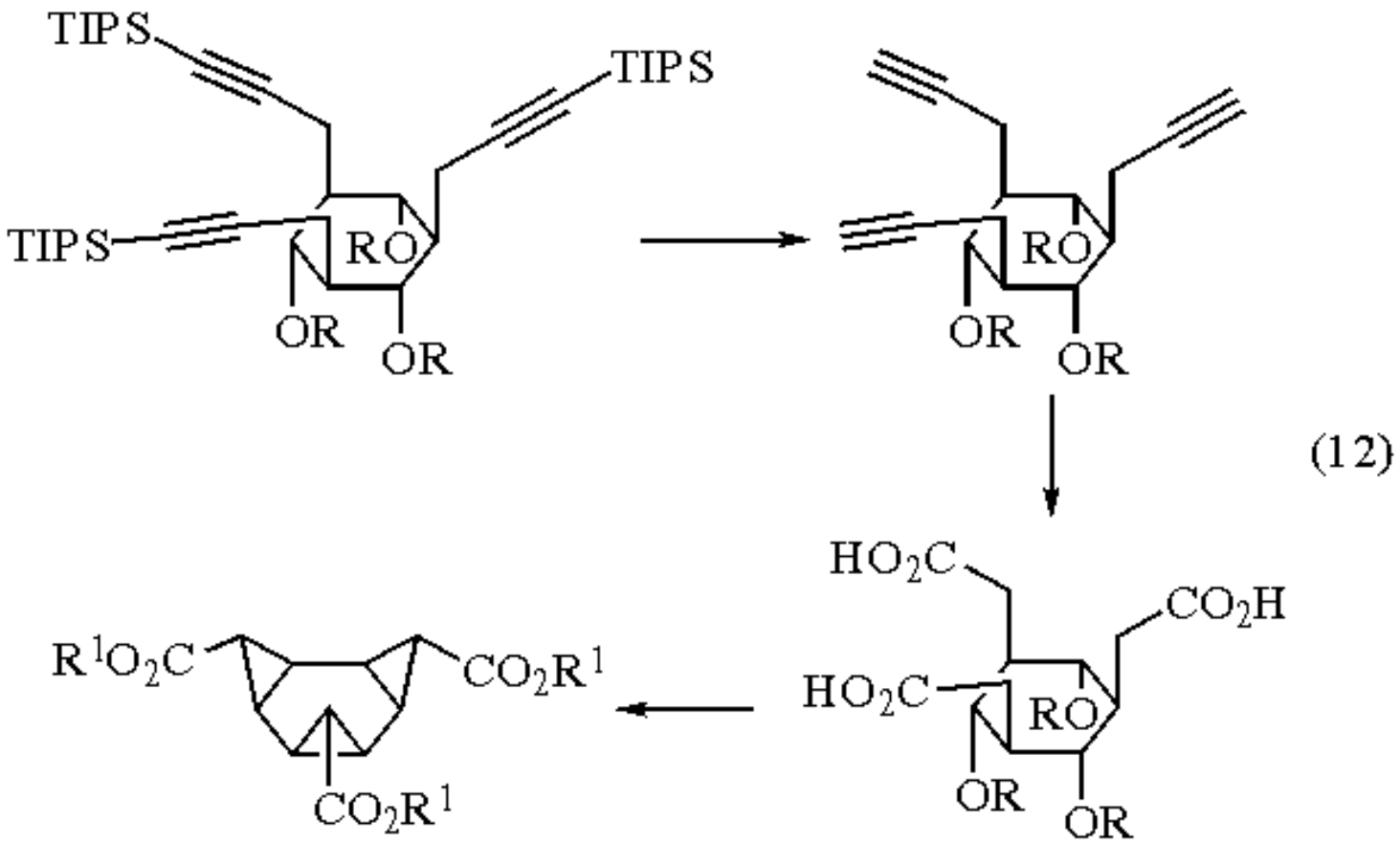

Oxidation of the products by ***Ruthenium(VIII) Oxide*** with the TIPS group still in place gives a mixture of carboxylic acid and an α-keto acyl silane (silyl α-diketone; (eq 13),[7] an otherwise rare class of compounds;[18] compare the oxidation of disubstituted alkynes to 1,2-diketones by RuO_4[19] and the ***Osmium Tetroxide-t-Butyl Hydroperoxide*** oxidation of TMS-alkynes.[20]

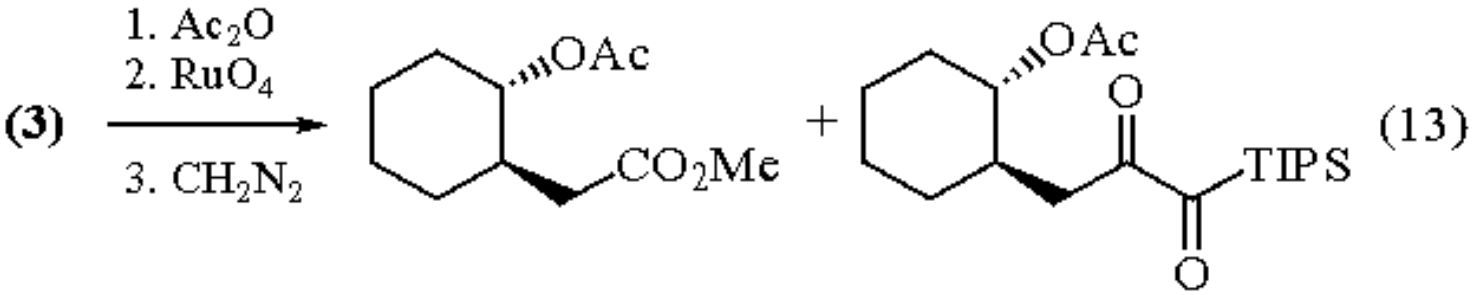

TMS-alkynes are oxidized at the terminal carbon to carboxylic acids by hydroboration/oxidation (dicyclohexylborane/NaOH, H_2O_2). This does not work with TIPS-alkynes.[14b] Instead, TIPS-alkynes are cleanly monohydroborated at the internal carbon by ***9-Borabicyclo[3.3.1]nonane*** to give (*Z*)-β-borylvinylsilanes.[6] These can be oxidized in high yields to α-silyl ketones, or cross coupled with a bromide R^1Br (R^1 = aryl, benzyl, dimethylvinyl) in the presence of NaOH and ***Tetrakis(triphenylphosphine)palladium(0)*** to give β,β-disubstituted vinylsilanes (Suzuki reaction; eq 14).[21a] The same nucleophilic substituted vinylsilane can be added to an aromatic aldehyde to provide access to (*E*)-3-silyl allyl alcohols.[21b]

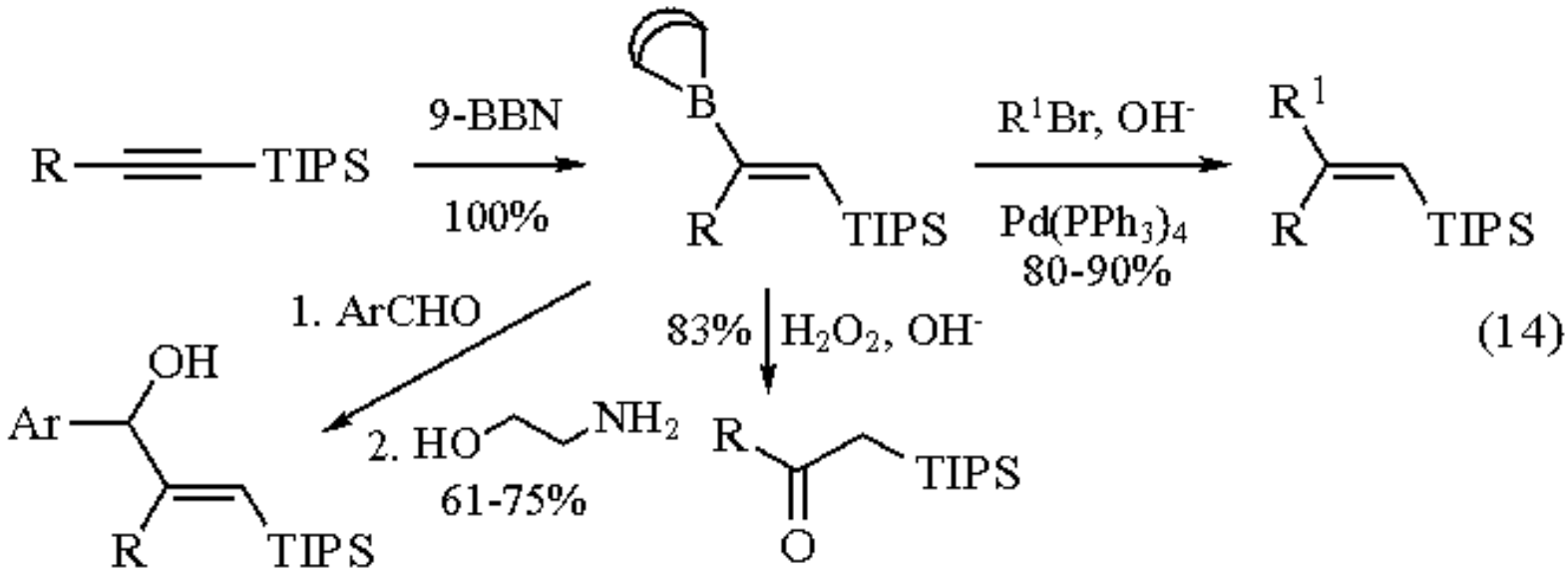

Propargyl Ketones.

The cyanocuprate derived from (**1**) reacts with esters to form propargyl ketones, even in the presence of epoxide functionality (eq 15).[16]

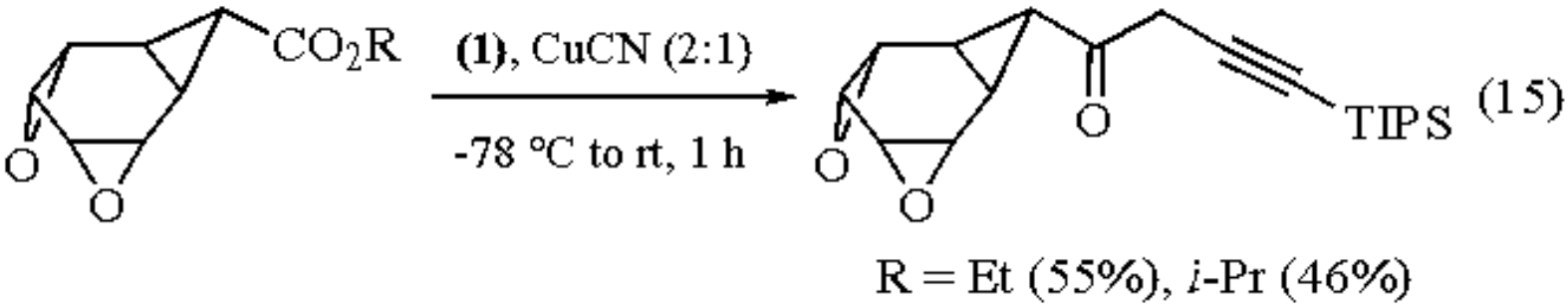

Bis(silyl)propynes.

Reaction of (**1**) with silylating agents affords 1,3-bis(silyl)propynes, valuable Peterson reagents (eq 16) (see ***1,3-Bis(triisopropylsilyl)propyne***).[2]

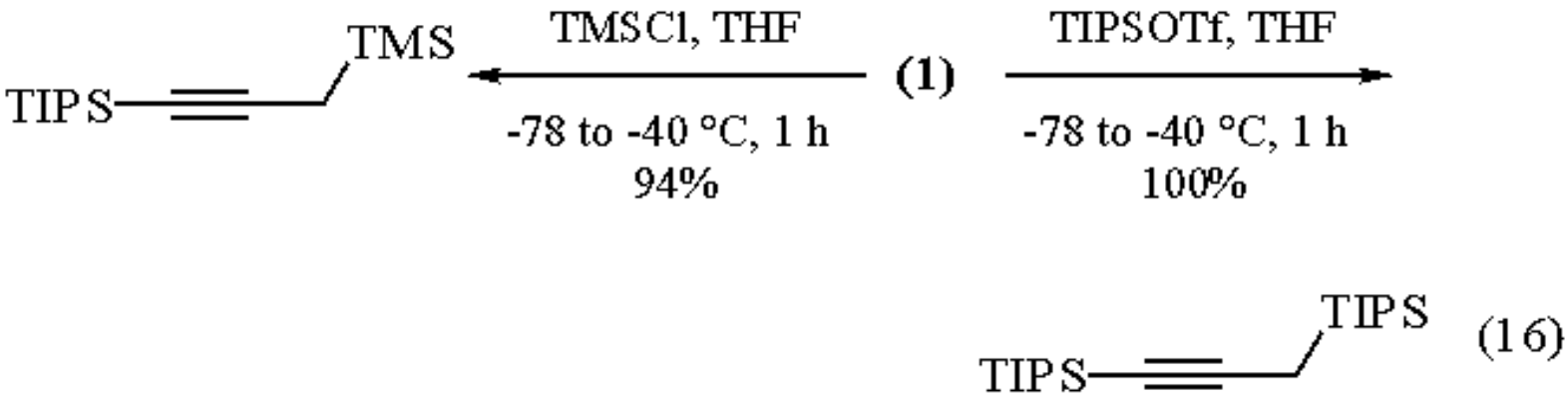

Isomeric Species.

The isomeric substituted lithium acetylide LiC&tbond;C-CH_2TIPS (**4**), from 3-TIPS-propyne,[22] was silylated to 1-TMS-3-TIPS-propyne.[23] Compound (**4**) isomerizes to (**1**) in THF/HMPA solution at rt, as shown by isolation of pure 1-TIPS-propyne after quenching a solution of (**4**) with H_2O.[7]

---

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N-Lithio-*N,N´,N´*-trimethylethylenediamine

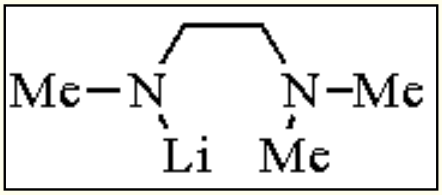

[-] · $C_5H_{13}LiN_2$ · *N*-Lithio-*N,N´,N´*-trimethylethylenediamine · (MW 108.14)

(reagent for the in situ formation of α-amino alkoxides, which are effective directing groups for *ortho* lithiation[1])

Alternate Name: LTMDA.

Preparative Methods: prepared in situ by adding *n*-BuLi to *N,N,N´*-trimethylethylenediamine in anhydrous solvents.

Handling, Storage, and Precautions: highly flammable; should be kept under a nitrogen or argon atmosphere. Handle in a fume hood.

The title reagent (**1**) is an excellent reagent for in situ protection of aldehydes.[1] Low temperature *ortho* lithiation/alkylation of aryl aldehydes can be achieved via an α-amino alkoxide intermediate generated by treating the aldehyde with LTMDA. The use of reagent (**1**) results in better yields of *ortho*-substituted products as compared to other reagents like ***Lithium N-Methylpiperazide*** and ***Lithium Morpholide***.[1] The *ortho*-lithiated intermediates can be trapped with various electrophiles (eq 1).[2]

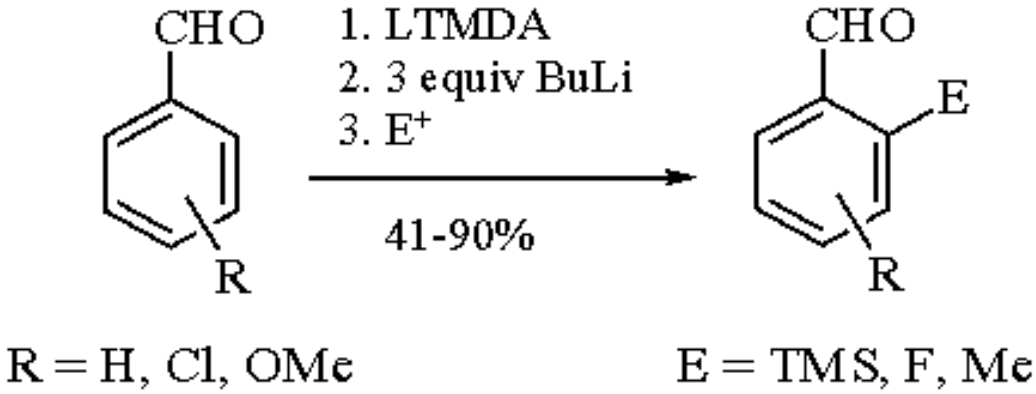

(1)

The effectiveness of the *ortho* lithiations is attributed to an intramolecular TMEDA-like assisted metalation leading to a chelated intermediate such as (**2**) (eq 2).[2] A similar methodology has been used for metalating benzylic carbons (eq 3).[3]

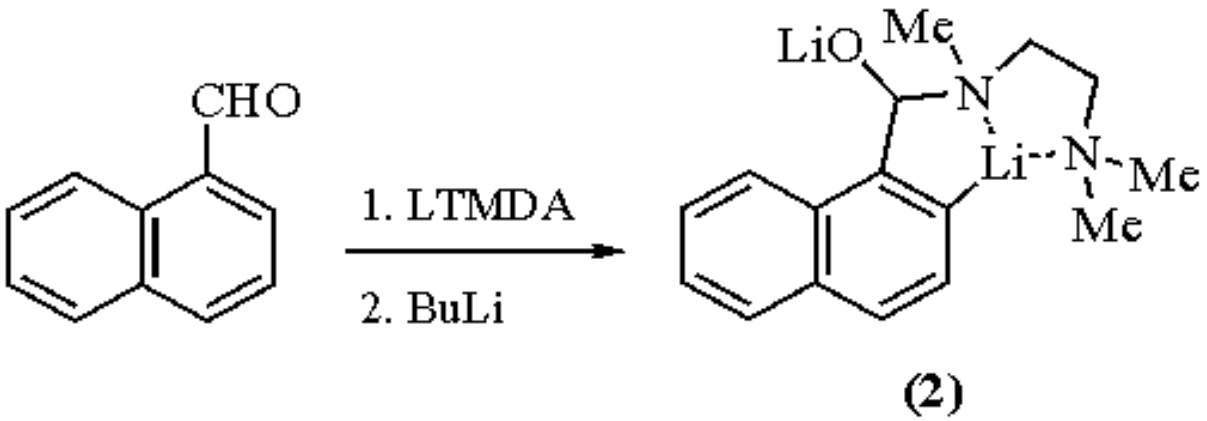

(2)

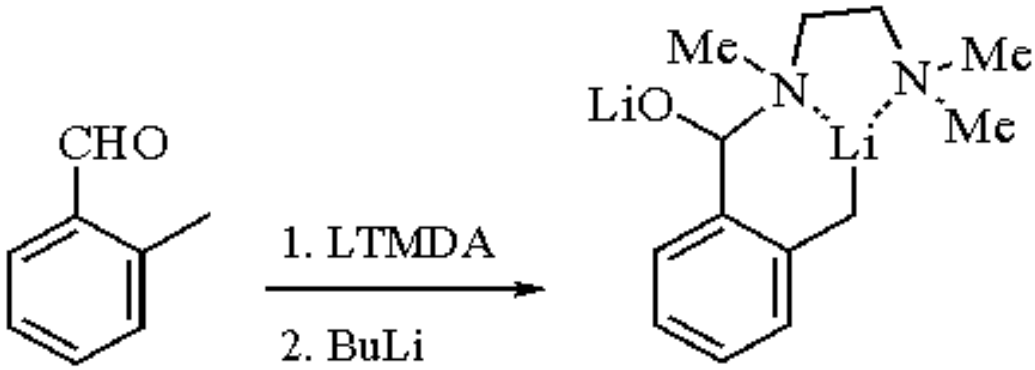

(3)

The versatility of reagent (**1**) has been demonstrated in the regioselective lithiation of various heterocycles.[1] Thiophene-2-carbaldehyde and 2-furaldehydes undergo regioselective *ortho* substitution via *ortho*-lithiated LTMDA-derived α-amino alkoxides (eq 4).[4]

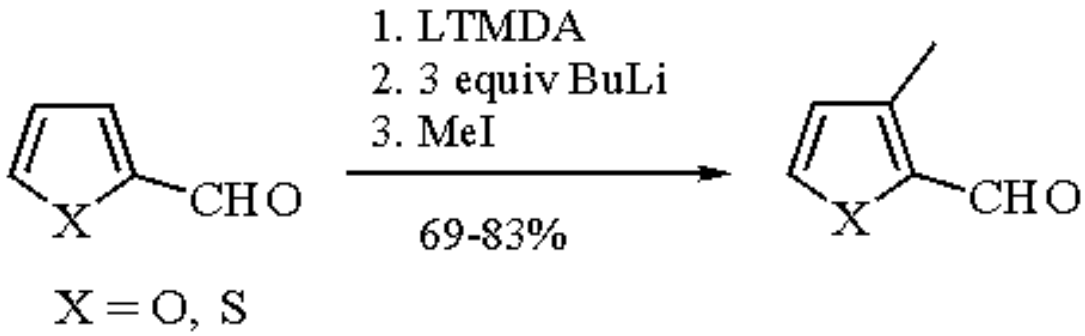

(4)

The scope of this reaction has been established by regioselectively metalating other regioisomers of the above mentioned aldehydes in excellent yields.[4] Indole-2-carbaldehyde behaved in a similar manner.[4] Interestingly, the *N*-methyl group of *N*-methylpyrrole-2-carbaldehyde underwent metalation with LTMDA/***n-Butyllithium*** (eq 5).[4]

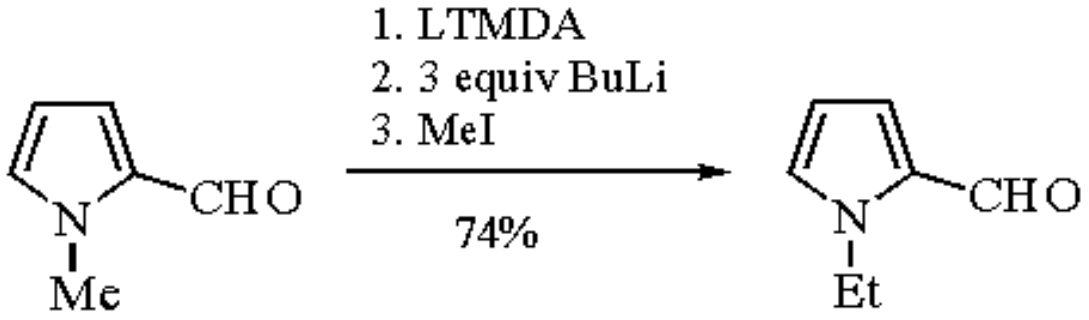

(5)

Under similar reaction conditions, *N*-methylindole-2-carbaldehyde is known to give products resulting from ring-lithiated and *N*-methyl-lithiated intermediates.[5] This selectivity problem was solved by using 3-chloro-*N*-methylindole-2-carbaldehyde, which gave exclusive *N*-methyl lithiation.[5] Regioselective lithiation of α-amino alkoxides prepared from methoxypyridinecarbaldehydes can be achieved in good yield (Scheme 1).[6] Regioselective substitution of a 1-(Boc)-3-formyl-1,4-dihydropyridine has been carried out using (**1**) and ***Mesityllithium*** as the base.[7]

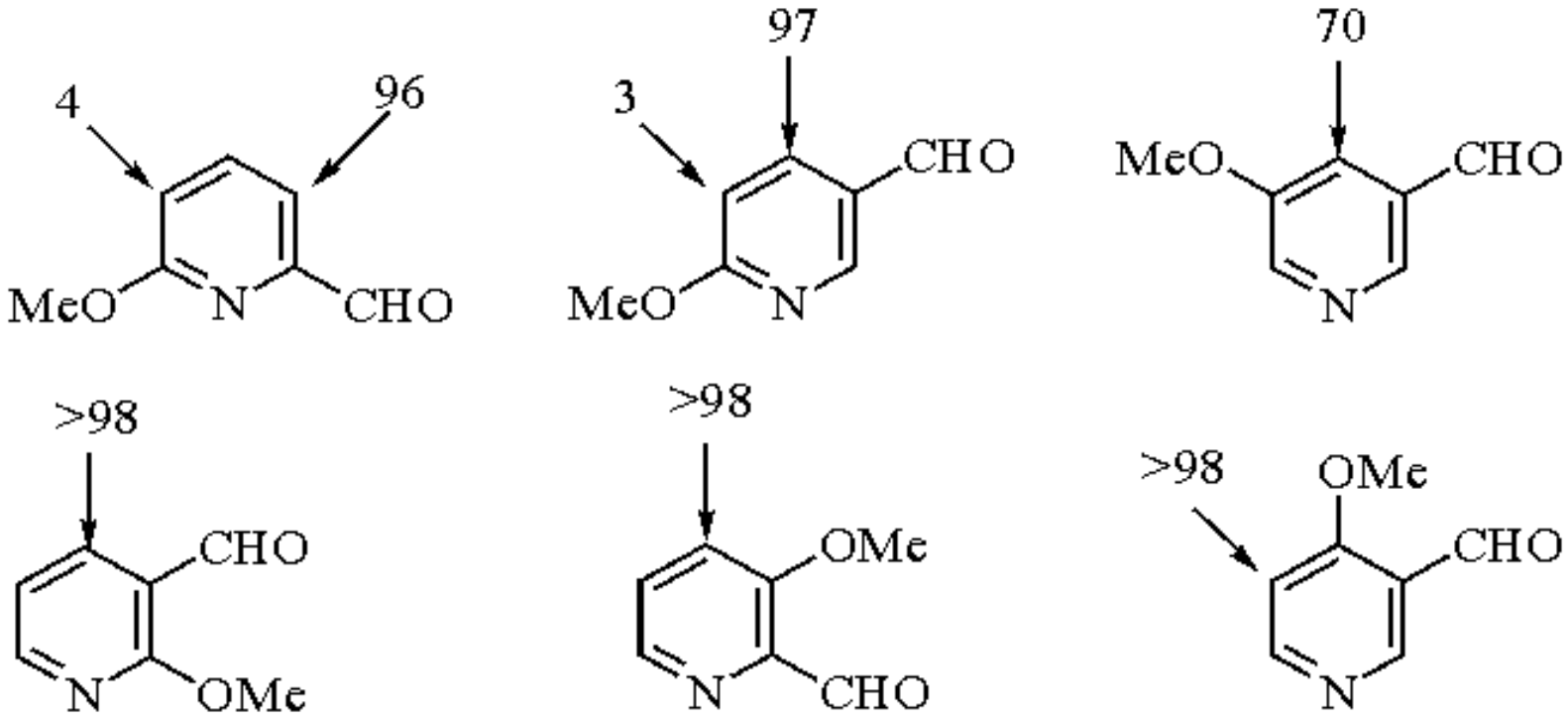

Scheme 1

LTMDA has been successfully utilized in the synthesis of schumanniophytine, isoschumanniophytine,[8a] and maxonine.[8b] A directed lithiation using an LTMDA-derived α-amino alkoxide was a key step in a short, asymmetric synthesis of (*S*)-camptothecin.[9] For another reagent similar to LTMDA, see ***Lithium N-Methylpiperazide***.[1]

---

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1-Lithio-3-trimethylsilyl-1-propyne

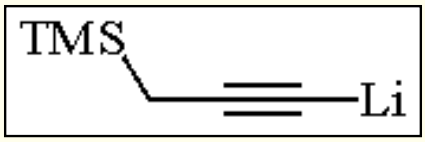

[67965-43-9] · $C_6H_{11}LiSi$ · 1-Lithio-3-trimethylsilyl-1-propyne · (MW 118.20)

(powerful nucleophilic source of 3-trimethylsilylpropynyl unit for many electrophiles)

Solubility: sol THF, toluene.

Preparative Methods: prepared in situ under nitrogen by reaction of commercially available propargyltrimethylsilane[1] with ***n-Butyllithium*** in THF at -78 °C[2] or by reaction of 3,3-dichloroallyltrimethylsilane and *n*-BuLi in THF at -90 °C.[3]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture; stable at room temperature.

Additions to Carbonyl Compounds.

Paraformaldehyde reacts with 1-lithio-3-trimethylsilyl-1-propyne (**1**) at room temperature to give the hydroxymethylated product. Oxidation gave the alkynic aldehyde, which served as a synthetic equivalent for the butadienyl carbenium ion.[4] Reduction with ***Lithium Aluminum Hydride*** gave the allylic alcohol which was used to protect carboxylic acids as esters which could be deprotected under mild palladium-catalyzed conditions (eq 1).[5] Secondary and tertiary alcohols were prepared for hydrostannylation studies by addition of (**1**) to a range of aldehydes and ketones (eq 2).[2] 1,4-Benzoquinones were prepared by thermolysis in refluxing xylene of the adducts of cyclobutenediones and (**1**) (eq 3).[6] Addition to ethyl acetate, in the presence of ***Boron Trifluoride Etherate***, provided the alkynic ketone in superior yield to addition to acetaldehyde and oxidation, due to the low yield in the latter step (eq 4).[7]

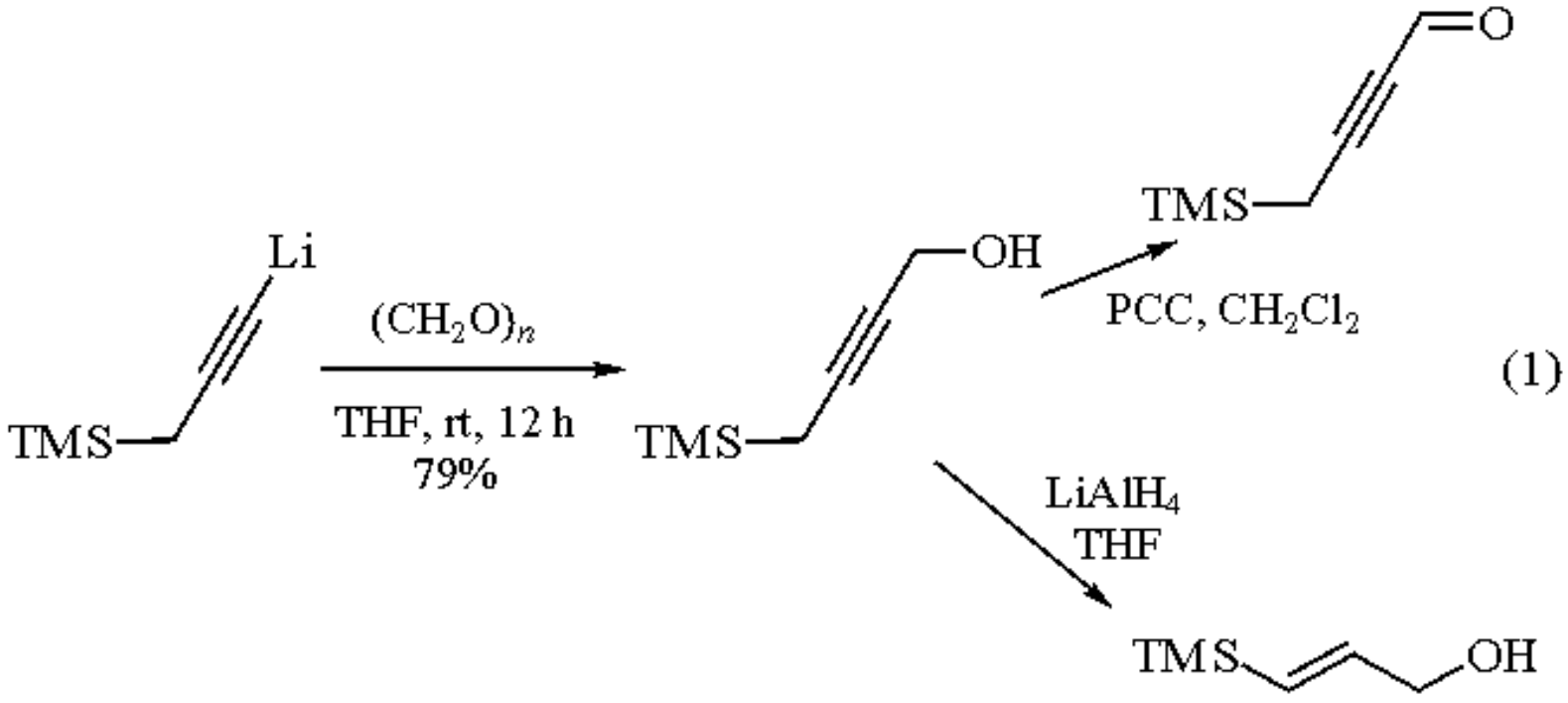
Li
TMS
$(CH_2O)_n$
THF, rt, 12 h
79%
OH
TMS
O
TMS
PCC, CH_2Cl_2
$LiAlH_4$
THF
TMS
OH

(1)

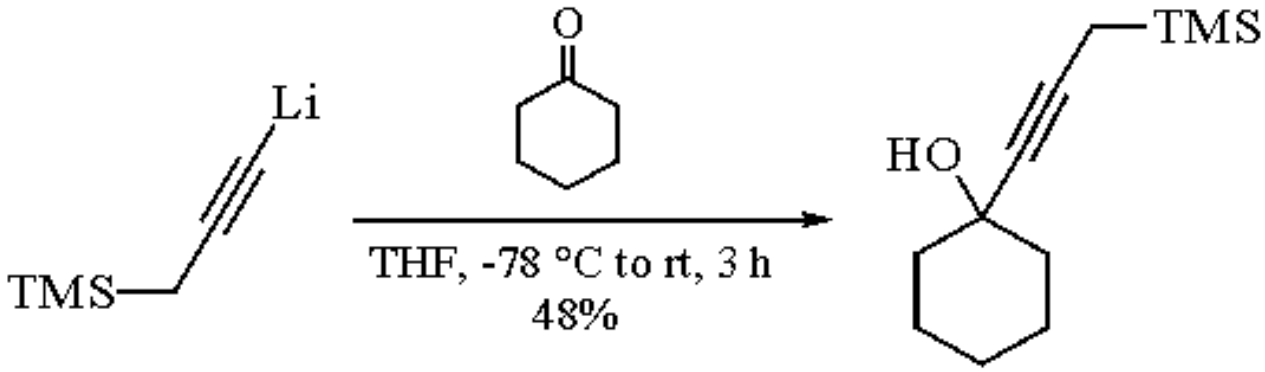
Li
TMS
O
THF, -78 °C to rt, 3 h
48%
TMS
HO

(2)

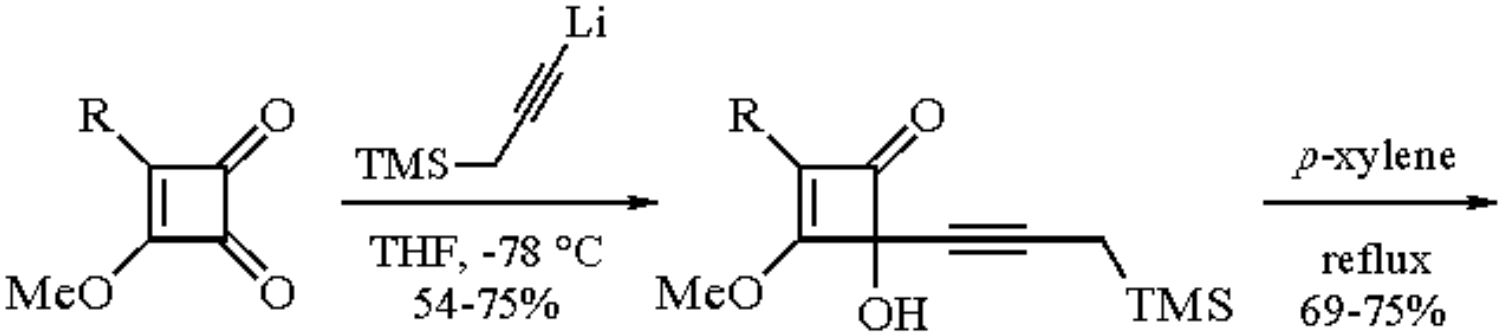
R
O
MeO
O
Li
TMS
THF, -78 °C
54-75%
R
O
MeO
OH
TMS
p-xylene
reflux
69-75%

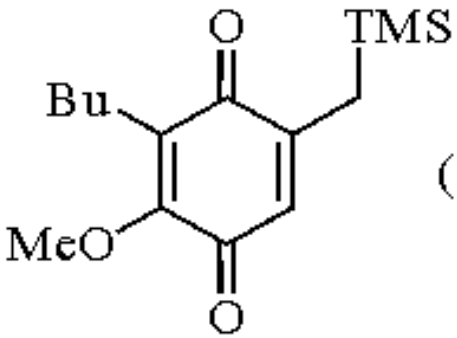
O
TMS
Bu
MeO
O

(3)

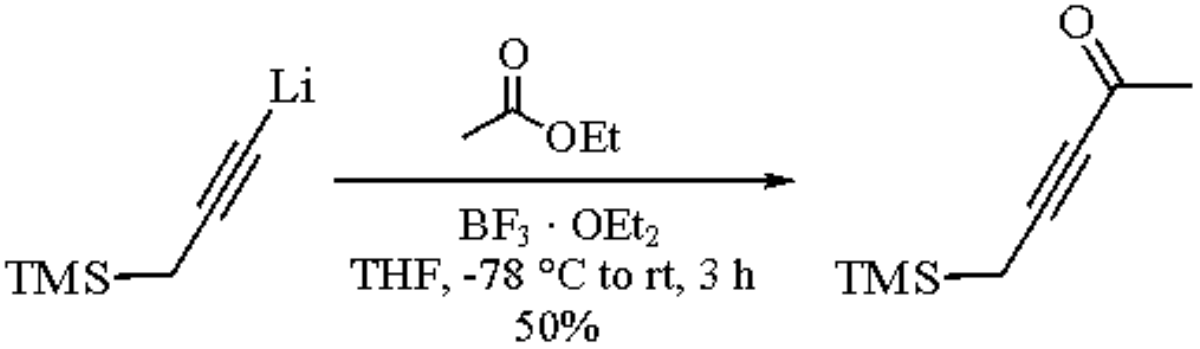

(4)

Alkylations of Alkyl Halides.

Methylation of (**1**) with ***Iodomethane*** in THF/HMPA required extended time at reflux (eq 5).[2] Alkylation of THP-protected linear iodo alcohols was achieved in modest yield at rt in the same solvent system (eq 6).[8] ***(Iodomethyl)trimethylsilane*** reacted well in refluxing THF alone to give 1,4-bis(trimethylsilyl)-2-butyne.[9]

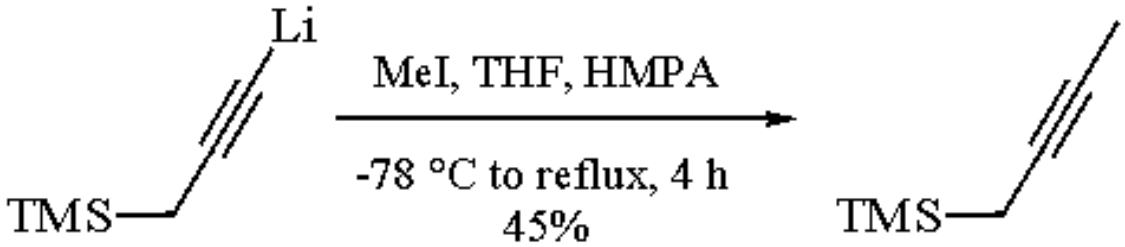

(5)

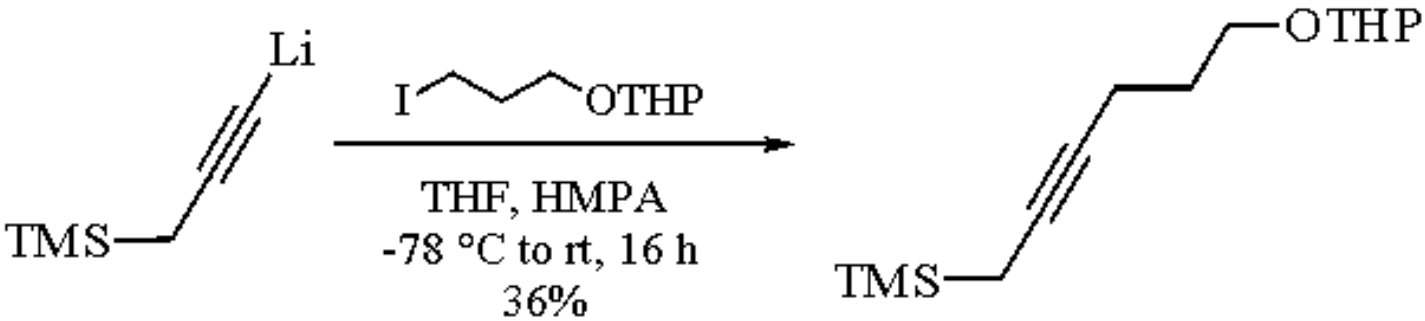

(6)

Additions to Epoxides.

1-Lithio-3-trimethylsilyl-1-propyne reacts well with epoxides only in the presence of Lewis acids. ***Diethylaluminum Chloride*** in toluene was used to promote addition to ***Ethylene Oxide***[10] (eq 7) while boron trifluoride etherate in THF at low temperature ensured high regioselectivity in additions to monosubstituted epoxides (eq 8).[11]

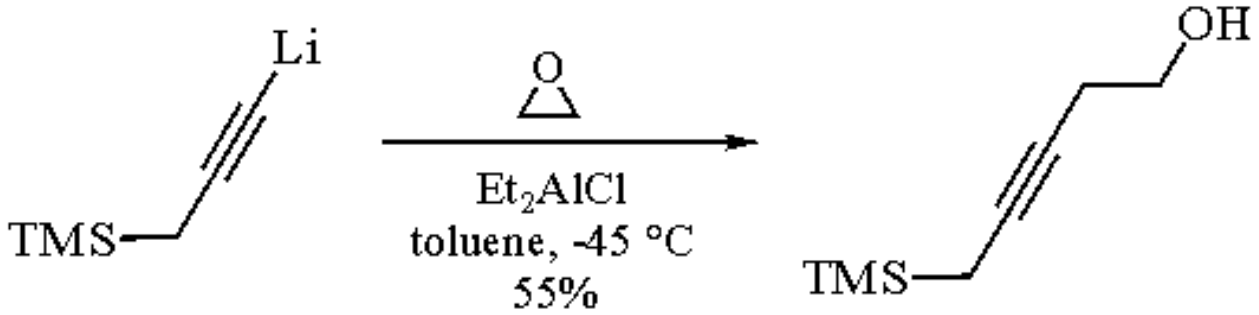

(7)

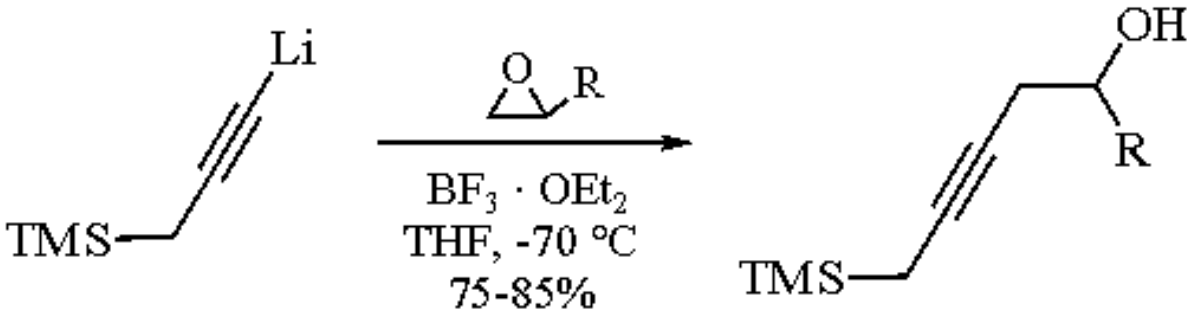

(8)

Reactions with Other Electrophiles.

n-Butyllithium deprotonates the vinyl proton of 3,3-dichloroallyltrimethylsilane in THF, which leads to elimination of lithium chloride, and subsequent metal-halogen exchange produces 1-lithio-3-trimethylsilyl-1-propyne in situ (eq 9). If excess *n*-butyllithium is present, further metalation occurs to give a dilithium species as confirmed by addition of ***Chlorotrimethylsilane*** (eq 10).[3] 1,3-Bis(trimethylsilyl)-1-propyne may be obtained by metalation of propargyltrimethylsilane with butyllithium and reaction with chlorotrimethylsilane (eq 11).[12] Lithium 3-trimethylsilyl-1-propynyltributylborate, formed by addition of 1-lithio-3-trimethylsilyl-1-propyne to ***Tri-n-butylborane***, reacted with ***Trimethylsilylmethyl Trifluoromethanesulfonate*** followed by protonolysis to give the bisallylsilane (eq 12).[13]

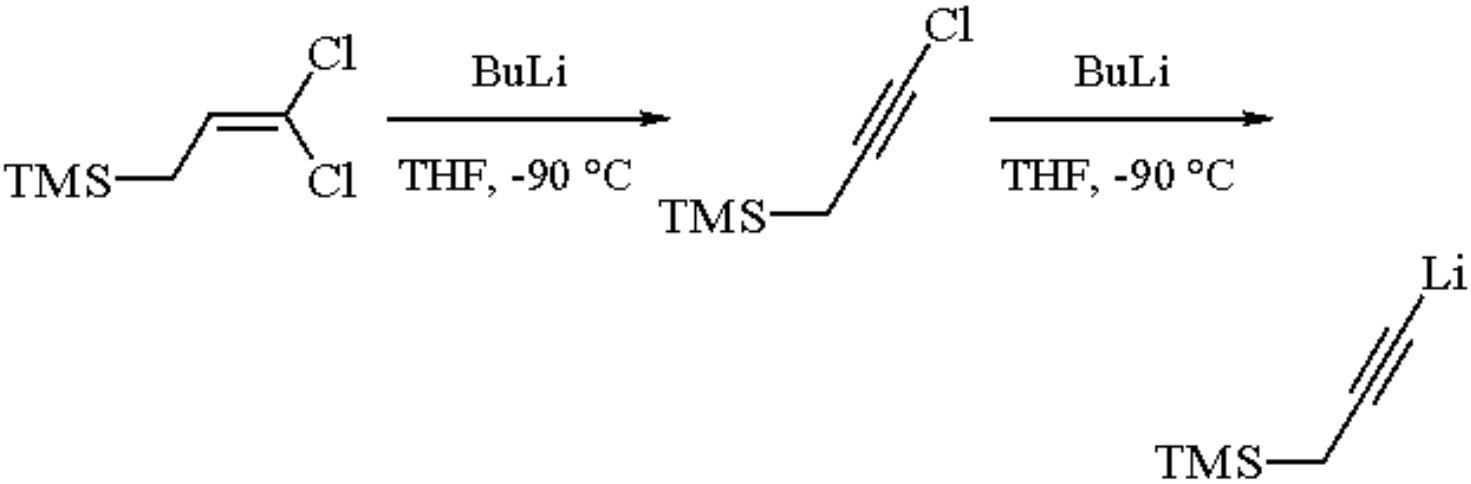

(9)

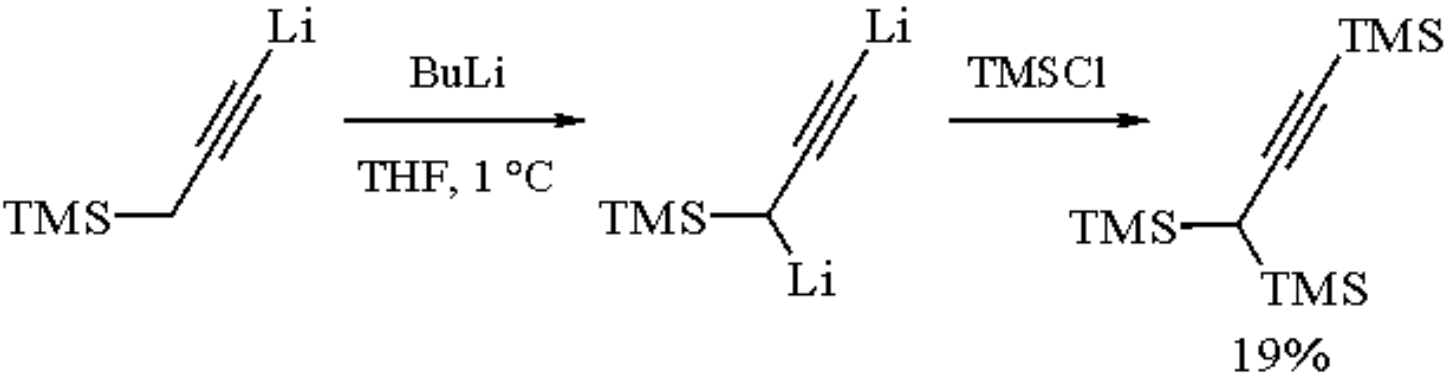

(10)

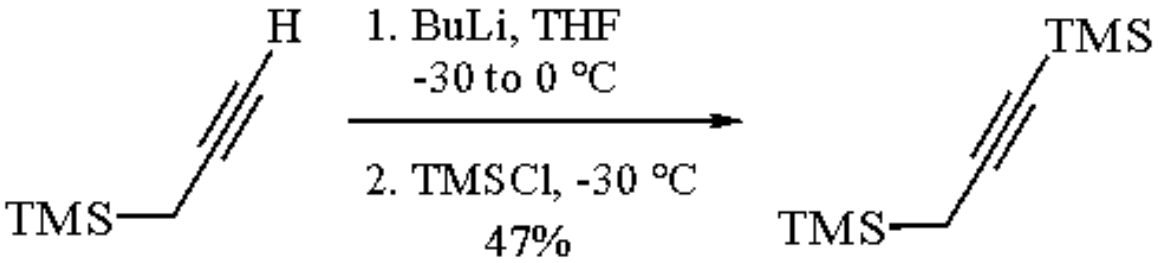

(11)

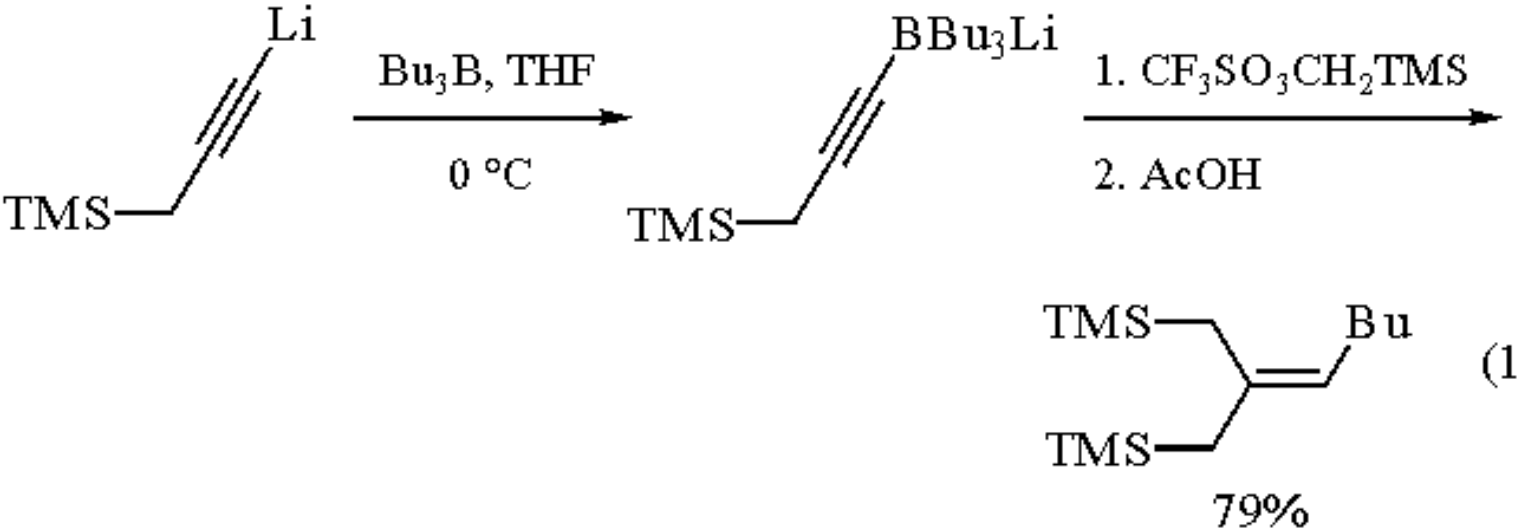

(12)

Related Reagents.

3-Chloro-1-propynyllithium; ***Lithium (Trimethylsilyl)acetylide***; ***Propynyllithium***.

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1. Slutsky, J.; Kwart, H. *JACS* **1973**, *95*, 8678.
2. Nativi, C.; Taddei, M. *JOC* **1988**, *53*, 820.
3. Seyferth, D.; Mammarella, R. E. *JOM* **1978**, *156*, 299.
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Lithium[1]

Li

[7439-93-2] · Li · Lithium · (MW 6.94)

(powerful reducing agent;[1] used for partial reduction of aromatics and conjugated polyenes;[1e,m-o] conversion of alkynes to *trans*-alkenes;[1a,h] stereoselective reduction of hindered ketones;[1l] enone reduction and regioselective alkylation;[1f,j] reductive cleavage of polar single bonds[1a])

Physical Data: mp 180.5 °C; bp 1327 ± 10 °C; *d* 0.534 g cm^{-3}. Natural isotopic composition: ^{7}Li (92.6 %); ^{6}Li (7.4 %).

Solubility: 10.9 g/100 g NH_3 at -33 °C (= 74.1 g/L NH_3); 36.5 g/L $MeNH_2$ at -23 °C.

Form Supplied in: under Ar, as solid in the form of wire, ribbon, rod, foil, shot, ingot, or as a powder; in mineral oil, as wire, shot, or as 25-30 wt % dispersions.

Purification: commercially available in up to 99.97% purity. In general, lithium is not further purified except for cutting off the surface coating.

Handling, Storage, and Precautions: best stored under mineral oil in airtight steel drums and handled under Ar or He. Dispersions in mineral oil segregate on storage and uniformity is restored by stirring. The mineral oil is washed off under Ar with pentane or hexane, and the metal is either dried in an Ar stream or rinsed with the reaction solvent. Dry Li powder is extremely reactive towards air, H_2O vapor, and N_2. The metal reacts rapidly with moist air at 25 °C, but with dry air or dry O_2 only at higher temperatures (>100 °C). A slight blow can initiate violent burning. Reaction with N_2 already occurs at 25 °C, but is inhibited by traces of O_2. Li reacts readily with H_2O, but does not spontaneously ignite as the other alkali metals do. It reacts rapidly with dil HCl and H_2SO_4 and vigorously with HNO_3. Ready reaction occurs with halogens.

Reducing Systems.

For reductions with Li, liquid ***Ammonia*** or primary amines are most often the solvents of choice. Li dissociates in these solvents more or less completely into Li^+ and solvated electrons, producing deep-blue metastable solutions.[2] Ethereal solvents (peroxide-free!) such as THF or DME may be used alone, but are usually used as cosolvents with NH_3 or amines. Li solutions in HMPA are quite unstable in contrast to ***Sodium*** solutions, but are stabilized by THF.[3] Reduction occurs by a sequence of single electron and proton transfers to the organic substrate, leading to saturation of multiple bonds or fission of single bonds.[1a,i,4]

Li-NH_3.

Li has a higher normal reduction potential[5] and molar solubility[6] in liquid NH_3 than Na or ***Potassium*** (see Table 1). This permits the use of larger quantities of cosolvents for substrates that are less soluble in NH_3. The concentrations of Li in NH_3 used in reactions vary widely, from 0.1 to 3 g Li/100 mL NH_3. Concentrations near saturation form a second, less dense, bronze-colored phase which is normally avoided.[7]

Table 1 Solutions of Alkali Metals in Liquid Ammonia

Metal	Solubility[6] at - 33 °C (g metal/100 g NH_3) (g-atom M/mol NH_3)	Normal reduction potential[5] at - 50 °C (V)
Li	10.9 (0.26)	- 2.99
Na	24.5 (0.18)	- 2.59
K	47.8 (0.21)	- 2.73

Reductions are performed either in the absence or presence (Birch conditions[1h]) of a proton source, depending on the desired products.[1a,i,4b] An added proton source can effect reductions which do not occur in its absence (e.g. benzene reduction). It can lead to higher saturation (e.g. in enone reduction) or suppress dimerization and base-catalyzed transformations of primary products. EtOH and *t*-BuOH are the most common proton donors. Primary alcohols protonate the intermediate anions more rapidly, but tertiary alcohols react more slowly with the metal. Other proton donors are NH_4Cl, H_2O, and various amines.[1a,e,4b]

The order of adding the reagents can influence the product distribution.[1g] Most often, Li is added last, until the blue color of the solution persists. For less reactive substrates, alcohol addition is delayed (Wilds-Nelson modification).[5b] The reaction is concluded by quenching excess Li mildly and efficiently with sodium benzoate[8] or with excess EtOH and then NH_4Cl, and NH_3 is allowed to evaporate.

Distillation of NH_3 from Na or through a BaO column removes moisture and iron impurities. The latter catalyze the reaction of alkali metals with the added alcohol and NH_3.[2] The Li-NH_3-ROH system is less sensitive to traces of iron than Na-NH_3-ROH, which accounts in many instances for its superiority.[9] ***Lithium Amide*** is less soluble in NH_3 than ***Sodium Amide*** and ***Potassium Amide***, and base-catalyzed formation of side products is less frequent.[1g,i] Nevertheless, in many cases similar results are obtained with Li and Na in NH_3; Li is preferred for less reactive substrates and Na when overreduction is a problem.[1]

Lithium/Primary Amines.

Li forms stronger, but less selective, reducing agents with primary amines (Benkeser reduction).[1d,h,k] The higher reactivity is probably caused by higher reaction temperatures[1i,k] and possibly also by smaller electron solvation.[2] The reactivity can be modified by addition of alcohols.[1h] The Li-amine solutions seem more sensitive to catalytic decomposition than Li in NH_3.[10] The choice of the amine is limited by the solubility of Li; ethylamine and ethylenediamine are most common. Na is hardly soluble in amines (e.g. more than 100 times less soluble in ethylenediamine at room temperature than Li).[11] Reactions of calcium in amines have been described.[12]

Reduction of Aromatic Compounds.[1,13]

Benzene and its derivatives are reduced to 1,4-cyclohexadienes with Li-NH_3 in the presence of a proton source (see also ***Sodium-Ammonia***). Derivatives with electron-donating substituents lead to 1-substituted cyclohexadienes. Thus reduction of anisole derivatives furnishes 1-methoxycyclohexa-1,4-dienes (eq 1).[9]

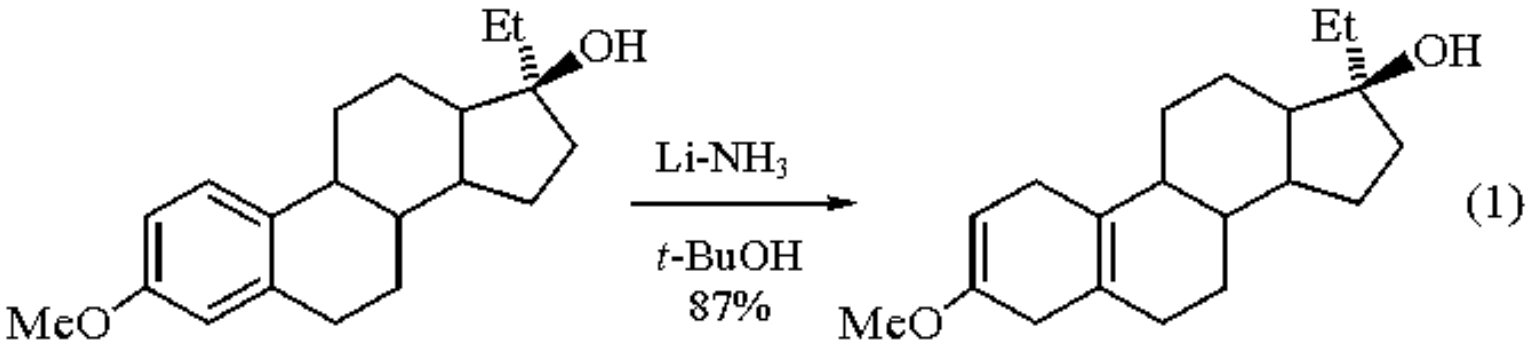

Hydrolysis of such dienol ethers to cyclohex-3-enones or with isomerization to cyclohex-2-enones has found wide application in syntheses of steroids, terpenoids, and alkaloids.[1f,m] Li is superior to Na for the more difficult reductions of 1,2,3-substituted anisole derivatives,[5b] though sometimes even excess Li gives poor results.[14] Anisoles are more readily reduced than phenols (eq 2),[15] but higher concentration of Li in NH_3 may effect phenol reduction to cyclohexenols (eq 3).[16]

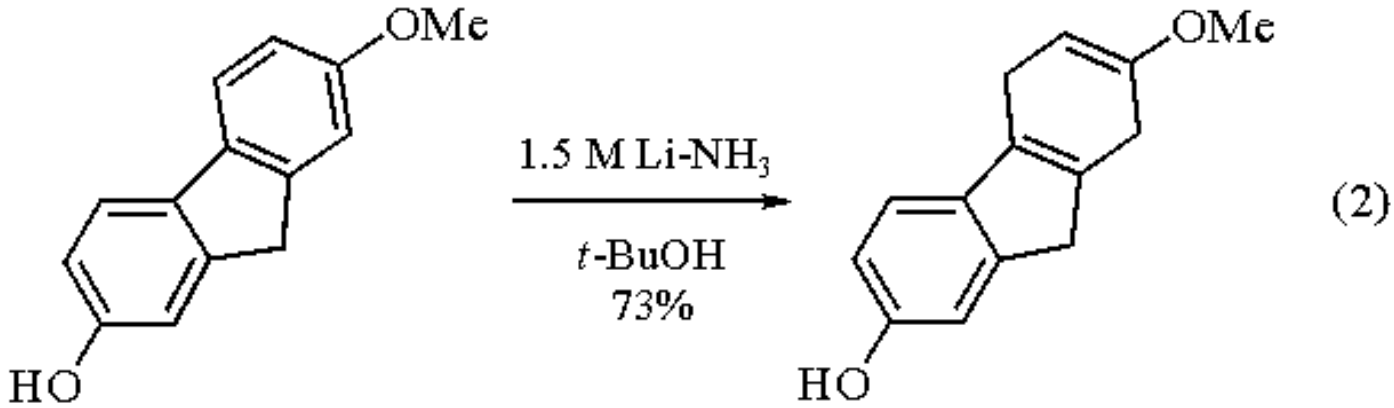

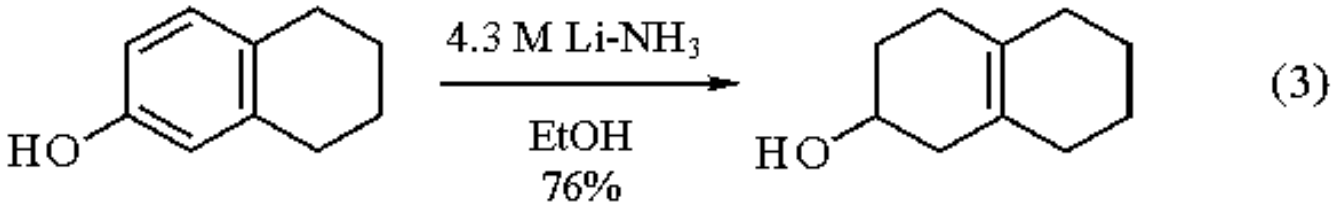

Electron-acceptor substituents enhance reduction rates and promote 1,4-reduction at the substituted carbon atoms, irrespective of alkoxy, amino, or alkyl substituents. Benzoic acid derivatives are readily reduced to the 1,4-dihydro derivatives. The presence of an alcohol is not necessary, in contrast to the derivatives with electron-releasing substituents. It can even result in overreduction, as the lithium alcoholate facilitates isomerization of the 1,4-dihydro product to the 3,4-dihydro isomer (eq 4).[17]

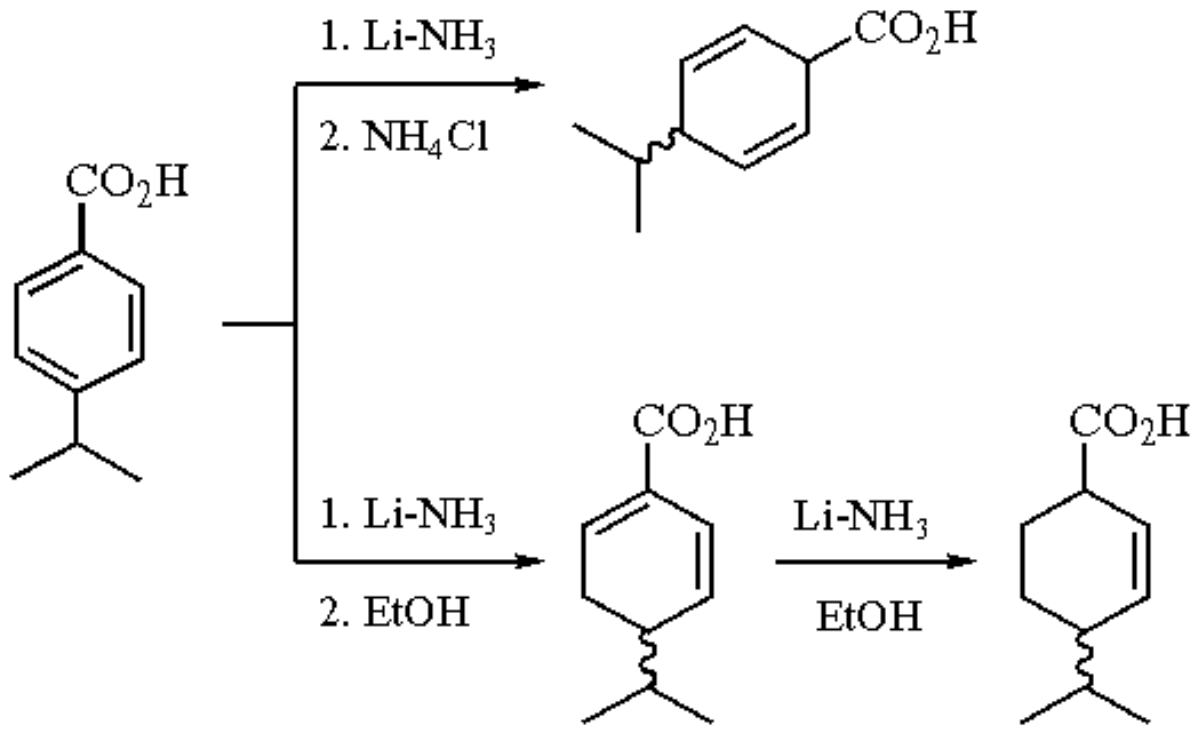

(4)

The dienolate formed during the reduction can be alkylated in situ with alkyl halides,[18,19] epoxides,[19] or α,β-unsaturated esters (eq 5)[20] to give 1-substituted dihydrobenzoic acids. Rearomatization provides alkyl-substituted aromatic compounds.

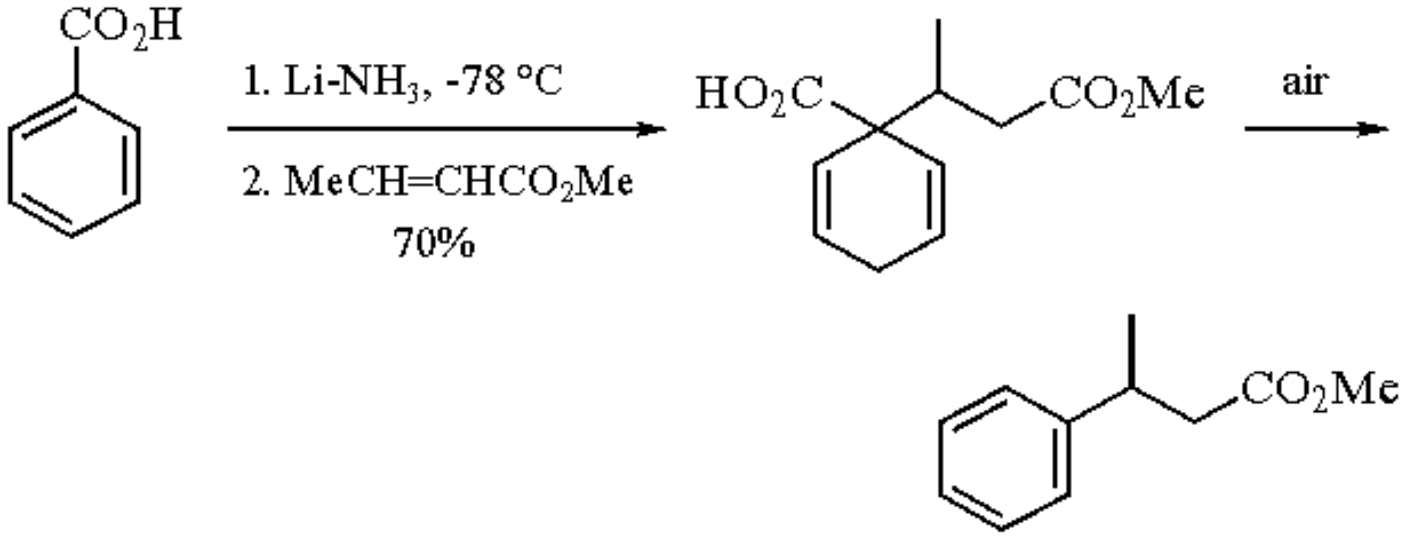

(5)

Benzamides and alkyl benzoates can be reduced to the 1,4-dihydro amides and esters, respectively, with Li-NH_3-*t*-butanol, but K-NH_3-*t*-butanol appears superior.[13] However, Li may be better for in situ reductive alkylations, or K^+ may be exchanged with Li^+ before the alkylation step.[21] Reductive methylation of *N*-benzoyl-L-prolinol derivatives afforded excellent diastereoselectivities, irrespective of the use of Li, Na, or K (eq 6).[22]

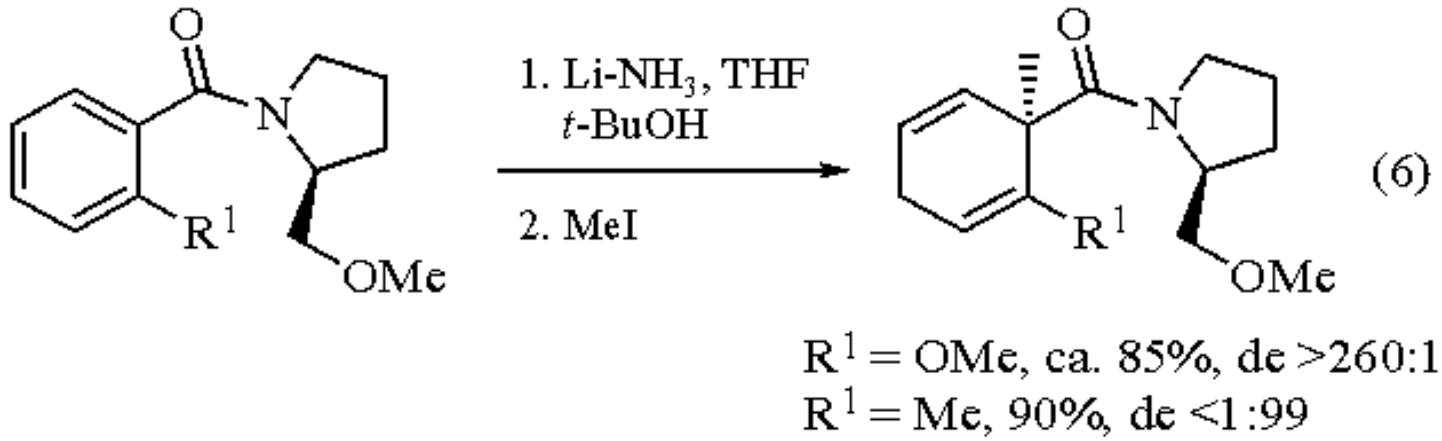

(6)

The strongly activating and easily removable trimethylsilyl group has been used to direct the regioselectivity of reduction (eq 7).[23]

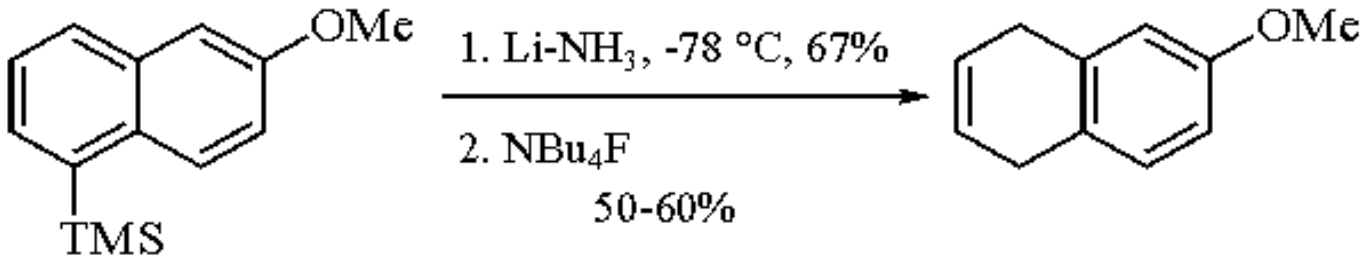

(7)

The Li-amine-alcohol reagents also reduce benzene derivatives to cyclohexadienes, and are usually applied when reduction in NH_3 fails.[1h,k] Thus reduction of dehydroabietic acid with Li-NH_3-*t*-BuOH afforded 35% of diene while Li-EtNH_2-*t*-$C_5H_{11}OH$ gave 81% (eq 8).[24] The importance of the nature of the proton source is demonstrated by the fact that neither Li-NH_3-EtOH nor Li-EtNH_2-EtOH gave any appreciable amount of reduction product.

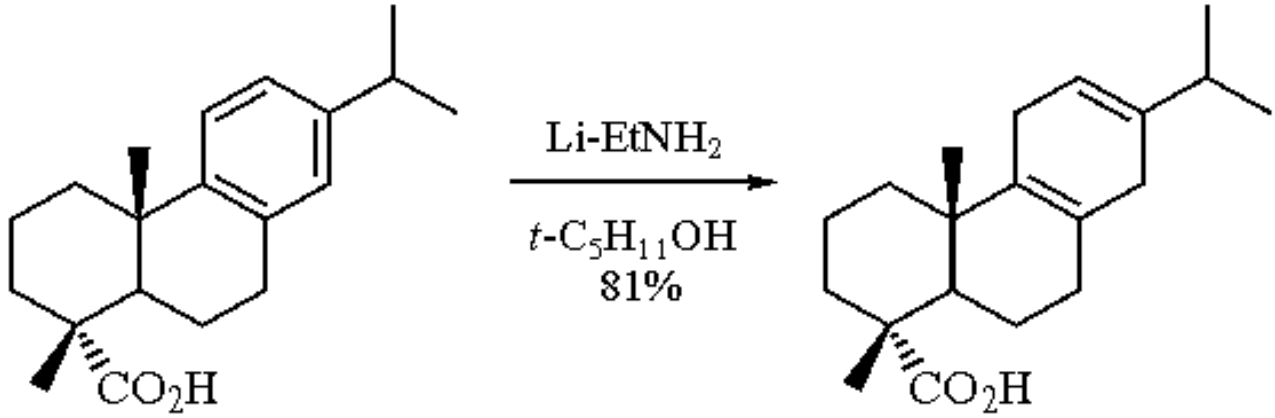

(8)

Reduction with Li-amine gives mainly cyclohexenes due to isomerization of the initially formed 1,4-diene by the strong alkylamide base.[1h,i] Mixtures of regioisomers are formed, and best results favoring the most stable isomer are obtained with mixtures[1h] of primary and secondary amines (eq 9).[25]

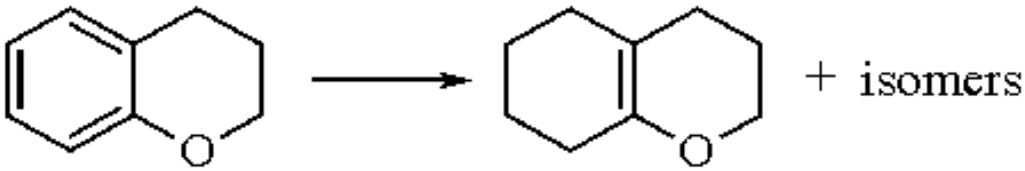

(9)

Li-EtNH$_2$	79%, 87:13
Li-EtNH$_2$-Me$_2$NH (1:1)	88%, 96:4

Condensed aromatic hydrocarbons are reduced more easily than those in the benzene series. Carefully chosen reaction conditions lead to the selective formation of different products.[1b] Most extensive reductions are achieved with Li-ethylenediamine,[26] while Na-NH$_3$ is one of the mildest reagents.[27] Birch and Slobbe discuss the reduction of heterocyclic aromatics.[4b]

Lithium-induced cyclization of 1,1´-binaphthalenes followed by oxidation of the dianion affords perylenes.[28] 3,10-Dimethylperylene was obtained in 95% (eq 10a).[28a] Cyclizations to tetrasubstituted perylenes proceeded in 36-40%,[28b] while similar reactions with K seem somewhat higher yielding.[29a] However, the synthesis of an 1-alkylated perylene was only successful with Li (eq 10b).[29b]

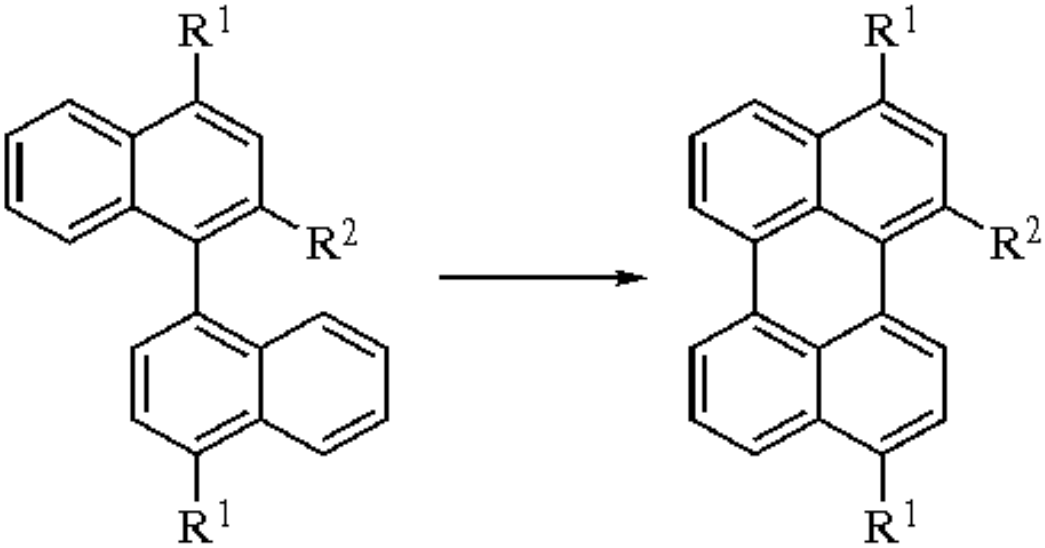

(10)

(a) $R^1 = Me$, $R^2 = H$	1. Li, THF, Δ; 2. O_2; 95%
(b) $R^1 = H$, $R^2 = (CH_2)_5Me$	1. Li, DME, Δ; 2. $CdCl_2$; 30%
	1. K, DME, 25 °C; 2. $CdCl_2$; <5%

Reduction of Alkynes.[1b,h]

Internal alkynes are reduced to *trans*-alkenes with Li-NH$_3$ or stoichiometric amounts of Li in amines. Excess Li in amines leads to alkanes. Li-EtNH$_2$-*t*-BuOH efficiently reduced an alkyne precursor of sphingosine to the *trans*-alkene with simultaneous *N*-debenzylation, while triple bond reduction was incomplete with Na-NH$_3$ and Li-NH$_3$ (eq 11).[30]

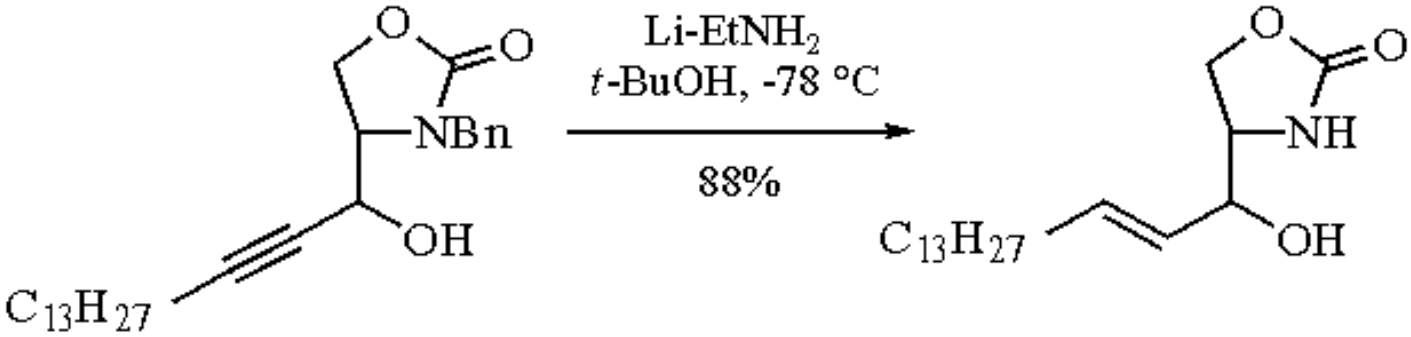

(11)

Dissolving metal reduction is the method of choice for the reduction of triple bonds in the presence of nonconjugated carboxyl groups,[31] where ***Lithium Aluminum Hydride***$_4$ in THF fails. Li-NH_3 afforded higher amounts of *trans*-alkenes in the reduction of some cyclic alkynes compared with Na-NH_3.[32] Terminal triple bonds are protected against reduction with Li-NH_3 by deprotonation with alkali amide, but are completely reduced to double bonds by Li (or Na)-NH_3-$(NH_4)_2SO_4$ or by Li in amines.[1c] Suitably located carbonyl groups give rise to cyclization, yielding vinylidenecycloalkanols,[33] e.g. eq 12.[33a] However, the use of K[33a,34a] or electrochemical reduction[34b] may give better results.

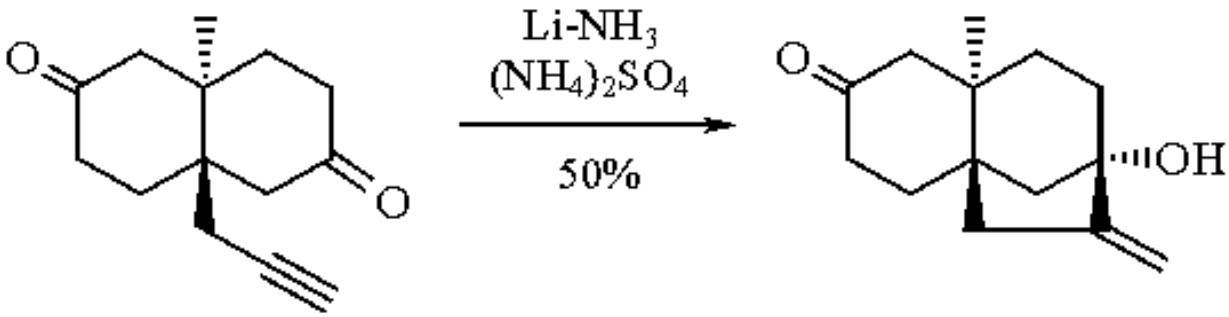

(12)

Reduction of Ketones.[1a,b,l,35]

Li-NH_3-EtOH reduces sterically hindered cyclic ketones to equatorial alcohols (eq 13)[36] and has been widely applied in the syntheses of 11α-hydroxy steroids.[37] This method is complementary to complex hydride reductions, which mainly afford the axial alcohols. Bicyclo[2.2.1]heptanones are reduced predominantly to the *endo*-alcohols. Similar results have been found with Na, K, and Ca.[35]

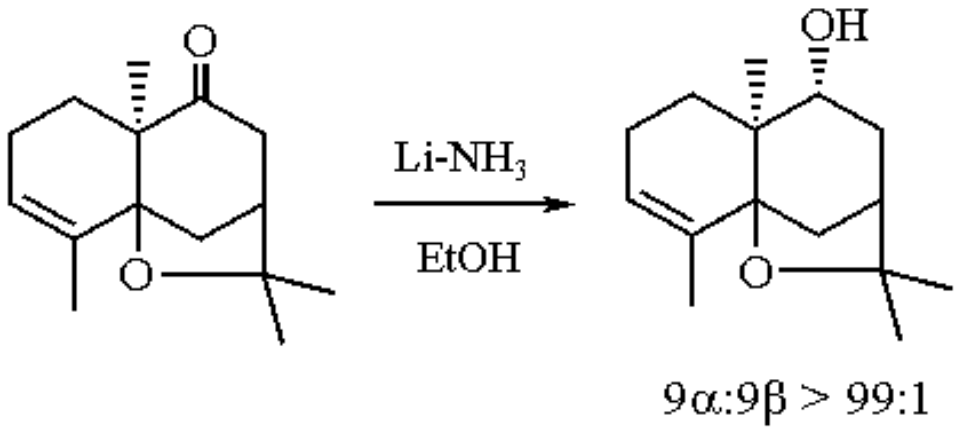

(13)

α,β-Unsaturated ketones are reduced to the ketone by Li-NH_3.[1j] In fused ring enones the relative configuration at the ring

junction is determined by protonation at the β-carbon.[38] Regioselective alkylation is achieved by trapping the intermediate enolate with an alkyl halide,[39a] a strategy also applied to enediones (eq 14).[39b] In the presence of a proton source, reduction to the saturated alcohols occurs.[40] Li-$EtND_2$-*t*-BuOD reduction gives high yields of saturated ketones and has been used for the stereoselective deuteriation at the β-carbon.[41] Conversion to alkenes is accomplished by phosphorylation of an enolate formed by Li-NH_3 reduction and subsequent hydrogenolysis with Li-$EtNH_2$-*t*-BuOH (eq 15).[42]

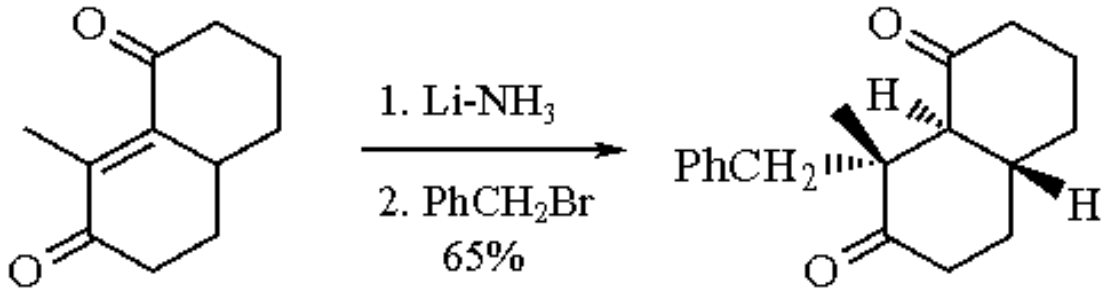

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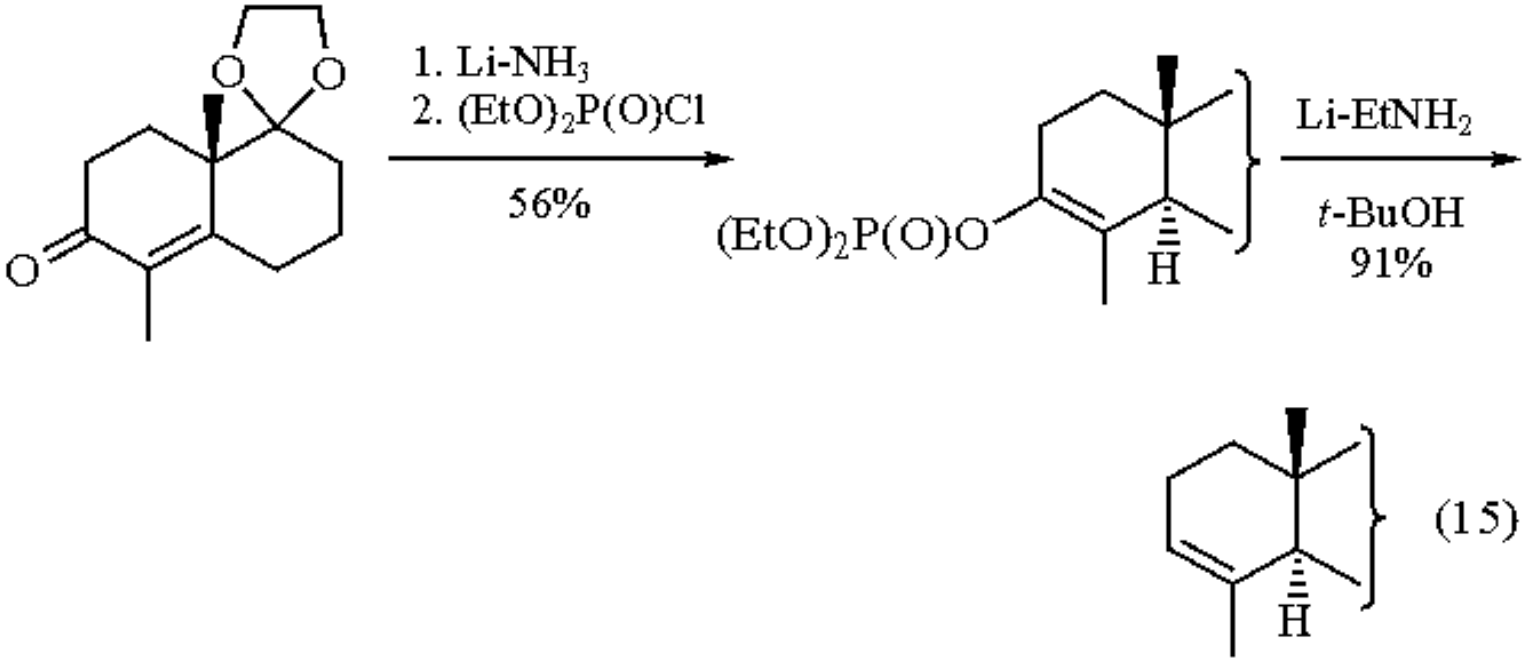

(15)

Reductions of aromatic ketones are complicated by possible pinacol formation, reduction of the aromatic ring, and hydrogenolysis of the C-O bond. Depending on the reaction conditions, 1-tetralone is reduced to tetralin or 1-tetralol (eq 16);[43a] in fact, seven different products can be produced.[43b]

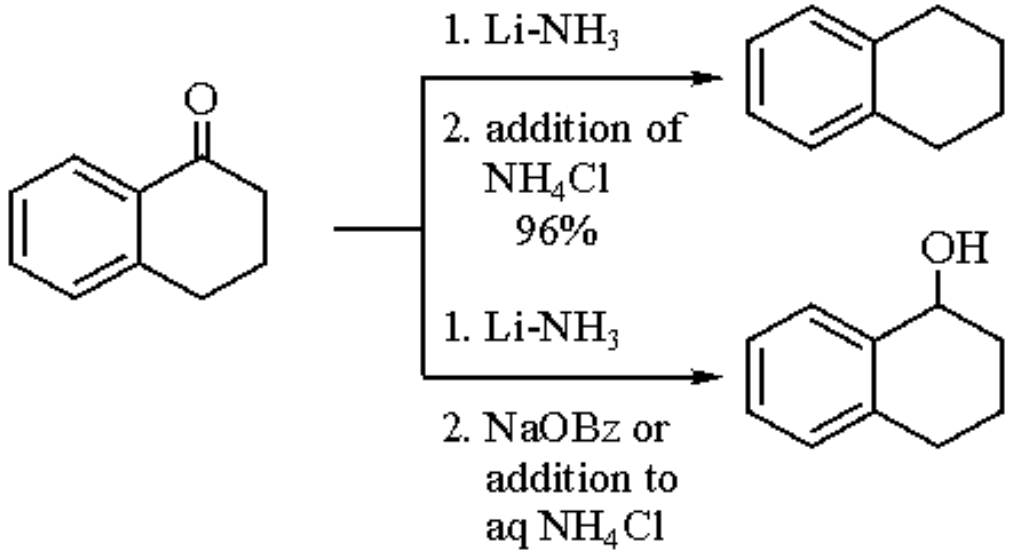

(16)

Aromatic aldehydes and ketones are alkylated and deoxygenated in a one-pot procedure using alkyl- or aryllithium, followed by Li-NH_3 (eq 17).[44]

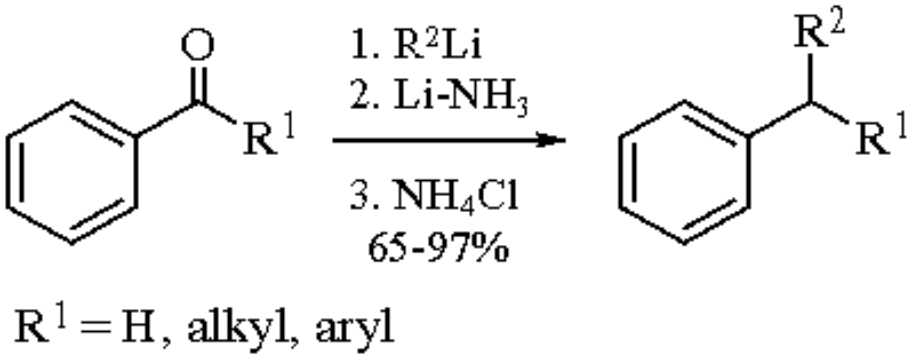

(17)

Aliphatic Carboxylic Acids.

Simple straight chain carboxylic acids are reduced by Li-$MeNH_2$ or Li-NH_3 to an intermediate imine which can either be hydrolyzed to the aldehyde or catalytically reduced to the amine.[45]

Reductive Cleavage of Polar Single Bonds.[1a]

Li in various solvents provides effective reagents for the cleavage of polar single bonds. The cleavage tendency decreases in the order C-I > C-Br > C-Cl > C-S > C-O > C-N > C-C. Polyhalo compounds are completely reduced with Li and *t*-BuOH in THF (Winstein procedure).[46] Allylic, geminal, bridgehead, and vinylic halogen atoms are removed, the latter stereospecifically. NH_3 and amines have been avoided as solvents due to potential reaction with the alkyl halides by elimination or substitution.[1a,47a] However, Li-NH_3 systems successfully reduce vinylic, bridgehead, and cyclopropyl halides[47b,c] and sometimes give better results than the Winstein-Gassman procedures (eq 18).[47c]

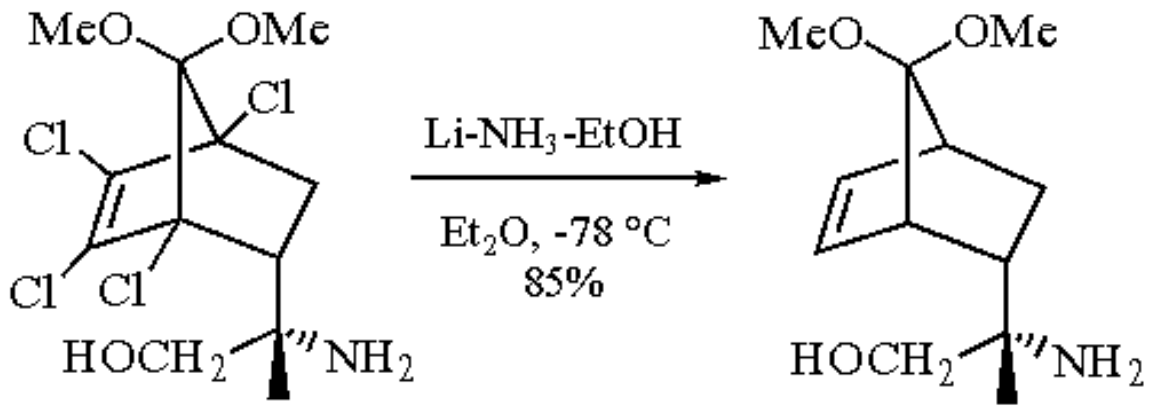

(18)

Alkyllithium reagents nowadays often replace Li for the preparation of organolithium compounds from alkyl or aryl bromides.[48] Li has been used to couple alkyl and aryl halides in Wurtz or Wurtz-Fittig-type reactions,[49] though the use of Na is much more important. Reduction of monosubstituted alkyl halides or selective reduction of geminal dihalides are best carried out with metal or complex hydrides or by catalytic hydrogenation.[1b]

Sulfides, sulfoxides, and sulfones are reductively cleaved with lithium.[50] Reduction of sulfides in THF is improved with catalytic naphthalene. Li-$EtNH_2$ gave better results than ***Sodium Amalgam*** for the cleavage of the C-S bond in sulfones (eq 19),[51a,b] and than ***Raney Nickel*** for some sulfide cleavage.[51c] Selenides are cleaved similarly.[52] Thio- and selenoacetals are reduced to alkanes.

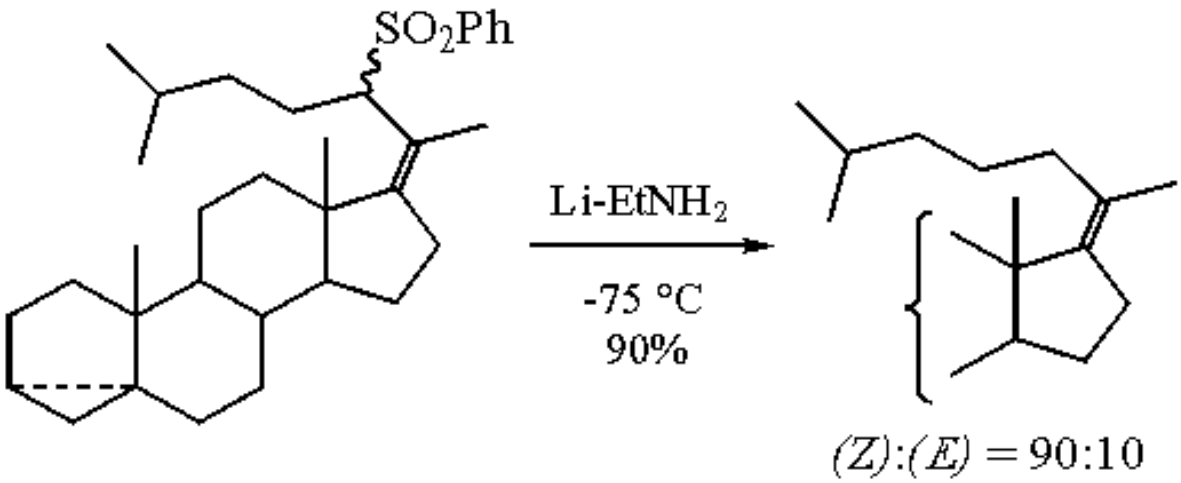

(19)

Allyl, benzyl, and aryl ethers are cleaved by Li in NH_3 or amines.[1a,b] Sterically hindered steroid epoxides, which are not cleaved with $LiAlH_4$, are converted into axial alcohols by Li-$EtNH_2$.[1b] Li-ethylenediamine efficiently cleaves sterically hindered epoxides to tertiary alcohols (eq 20).[53]

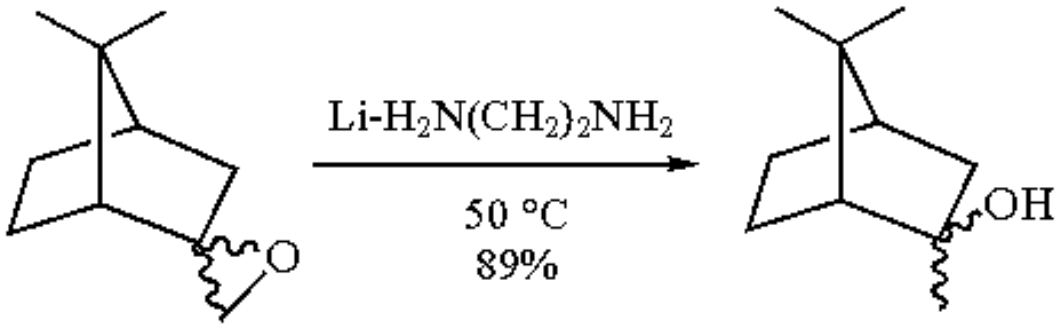

(20)

Li promoted reductions of allyloxy and benzyloxy esters[54a] and esters of sterically hindered secondary and tertiary alcohols[54b] give rise to carboxylate cleavage, thus presenting a means of indirect deoxygenation of alcohols. Further reductive cleavages have been found with activated cyclopropanes,[55] *N*-oxides,[56] and sulfonamides.[57]

Li (and K) promoted reduction of $TiCl_3$ in the McMurry reaction has been reported to be more reliable than the $TiCl_3/LiAlH_4$ reagent.[58]

Related Reagents.

Calcium; ***Lithium-Ethylamine***; ***Potassium***; ***Sodium***; ***Sodium-Alcohol***; ***Sodium-Ammonia***.

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Lithium Acetylide

HC&tbond;CLi

[1111-64-4] · C_2HLi · Lithium Acetylide · (MW 31.97) (ethylenediamine complex)

[6867-30-7] · $C_4H_9LiN_2$ · Lithium Acetylide-Ethylenediamine · (MW 92.09)

(reagent for addition of acetylene to ketones,[1] opening of epoxides,[2] and ethynylation of alkyl halides[3])

Solubility: sol THF; LiC&tbond;CH.EDA sol alkyl amines, slightly sol THF.

Form Supplied in: lithium acetylide.EDA is supplied as a powder.

Preparative Method: monolithium lithium acetylide is prepared by treating a THF solution of ***Acetylene*** with ***n-Butyllithium*** at 78 °C (eq 1).[1]

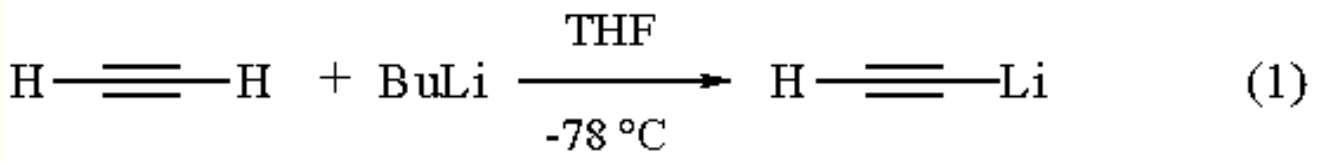

It is critical to keep the temperature at -78 °C. The concentration should be 0.5 M or less. At higher concentrations and temperatures, a white precipitate forms (presumably ***Dilithium Acetylide***) and yields of addition product fall appreciably. Properly formed, lithium acetylide in THF should be a clear, colorless solution.

Handling, Storage, and Precautions: lithium acetylide/THF solution must be used immediately after preparation. It decomposes above -78 °C. A saturated solution of THF/acetylene should not be used during the preparation of lithium acetylide since this may lead to an acetylene atmosphere above the THF. *n*-Butyllithium dropping through the acetylene atmosphere may react violently. Lithium acetylide is air and moisture sensitive.

Addition to Ketones.

Lithium acetylide rapidly adds to a variety of aldehydes and ketones (eq 2).[1]

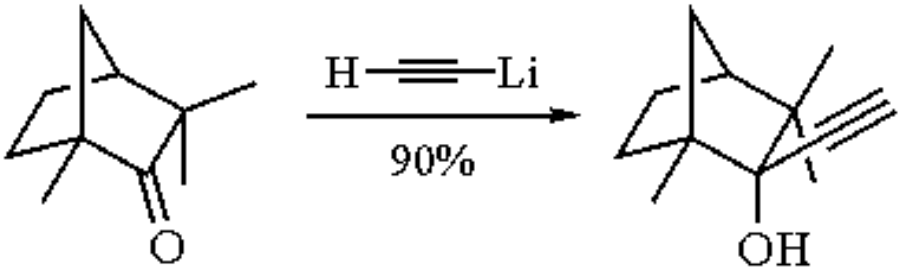

(2)

Hindered ketones such as di-*t*-butyl ketone give best results if an excess of reagent is used. The reagent freshly prepared in THF generally gives better results than lithium acetylide.EDA[4] or lithium acetylide in ammonia.[5] In the case of easily enolizable ketones, the cerium reagent works well (eq 3).[6]

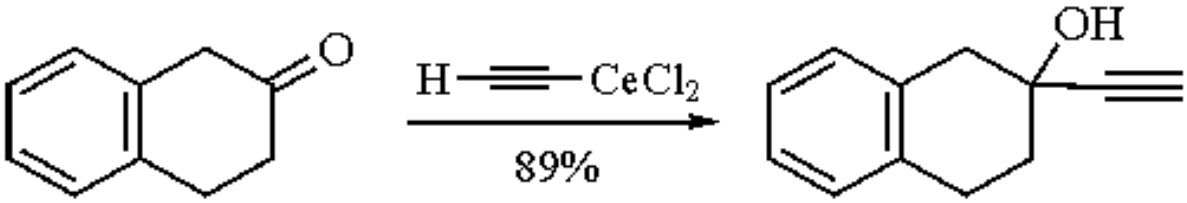

(3)

The TMS cerium acetylide reportedly gives better results than the unsubstituted cerium regent (eq 4).[7]

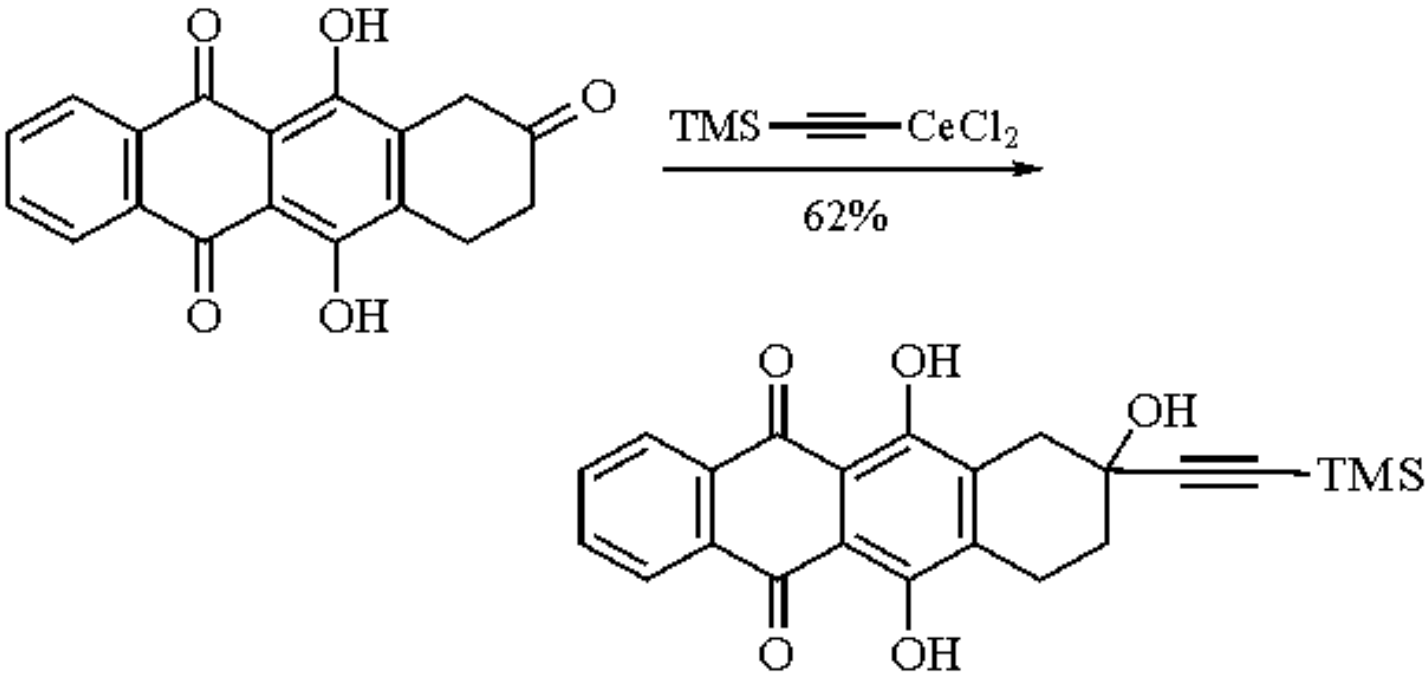

(4)

Reaction with Epoxides.

Lithium acetylide in THF decomposes before it can react with epoxides. However, in the presence of ***Boron Trifluoride Etherate*** epoxides are readily opened (eq 5).[2]

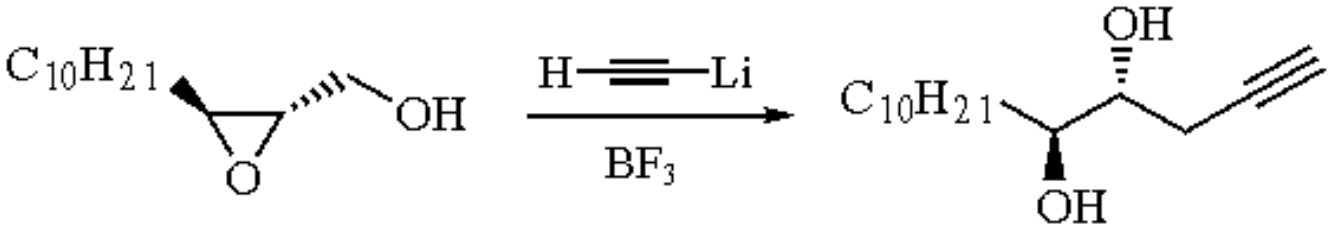

(5)

Lithium acetylide.EDA in THF/HMPA[8] or DMSO[9] may also be used to open epoxides (eq 6).

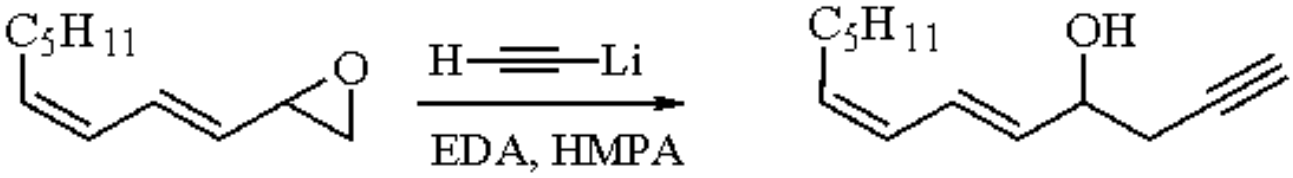

(6)

Ethynylation of Alkyl Halides.

Lithium acetylide.EDA in DMSO can be used to convert alkyl halides and sulfates into terminal alkynes (eq 7).[3]

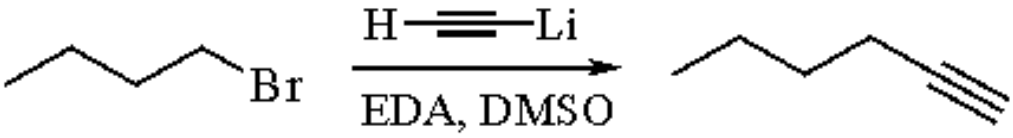

(7)

Monolithium acetylide in THF in the presence of HMPA is stable at 0 °C. This reagent may also be used to ethynylate alkyl halides (eq 8).[10]

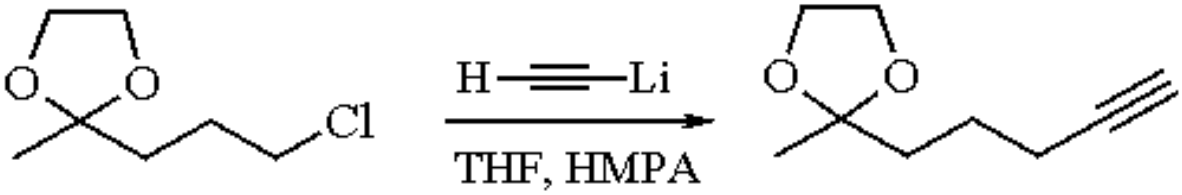

(8)

An alternative route to terminal alkynes involves iodination of lithium ethynyl trialkylborates (eq 9).[11] These are prepared by treating a trialkylborane with lithium acetylide.EDA. This method retains the stereochemistry of the boron-carbon bond.

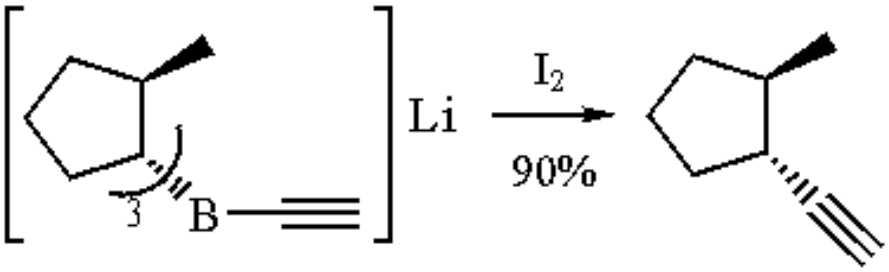

(9)

Related Reagents.

Dilithium Acetylide; ***Ethynylmagnesium Bromide***; ***Lithium Chloroacetylide***; ***Lithium (Trimethylsilyl)acetylide***; ***Propynyllithium***.

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Lithium Aluminum Hydride[1]

$LiAlH_4$

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride · (MW 37.96)

(reducing agent for many functional groups;[1] can hydroaluminate double and triple bonds;[2] can function as a base[3])

Alternate Name: LAH.

Physical Data: mp 125 °C; *d* 0.917 g cm^{-3}.

Solubility: sol ether (35 g/100 mL; conc of more dil soln necessary); sol THF (13 g/100 mL); modestly sol other ethers; reacts violently with H_2O and protic solvents.

Form Supplied in: colorless or gray solid; 0.5-1 M solution in diglyme, 1,2-dimethoxyethane, ether, or tetrahydrofuran; the $LiAlH_4$.2THF complex is available as a 1 M solution in toluene.

Analysis of Reagent Purity: Metal Hydrides Technical Bulletin No. 401 describes an apparatus and methodology for assay by means of hydrogen evolution. See also Rickborn and Quartucci.[39a]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be stored in the absence of moisture. Cans or bottles of $LiAlH_4$ should be flushed with N_2 and kept tightly sealed to preclude contact with oxygen and moisture. Lumps should be crushed only in a glove bag or dry box.

Functional Group Reductions.

The powerful hydride transfer properties of this reagent cause ready reaction to occur with aldehydes, ketones, esters, lactones, carboxylic acids, anhydrides, and epoxides to give alcohols, and with amides, iminium ions, nitriles, and aliphatic nitro compounds to give amines. Several methods of workup for these reductions are available. A strongly recommended option[4] involves careful successive dropwise addition to the mixture containing *n* grams of $LiAlH_4$ of *n* mL of H_2O, *n* mL of 15% NaOH solution, and 3*n* mL of H_2O. These conditions provide a dry granular inorganic precipitate that is easy to rinse and filter. More simply, solid Glauber's salt ($Na_2SO_4.10H_2O$) can be added portionwise until the salts become white.[5] In certain instances, an acidic workup (10% H_2SO_4) may prove advantageous because the inorganic salts become solubilized in the aqueous phase.[6] Should water not be compatible with the product, the use of ethyl acetate is warranted since the ethanol that is liberated usually does not interfere with the isolation.[4] Although the stoichiometry of $LiAlH_4$ reactions is well established,[1] excess amounts of the reagent are often employed (perhaps to make accommodation for the perceived presence of adventitious moisture). This practice is wasteful of reagent, complicates workup, and generally should be avoided.

The reduction of amides can be adjusted in order to deliver aldehydes. Acylpiperidides,[7] *N*-methylanilides,[8] aziridides,[9] imidazolides,[10] and *N,O*-dimethylhydroxylamides[11] have proven especially serviceable. All of these processes generate products that liberate the aldehyde upon hydrolytic workup. The powerful reducing ability of $LiAlH_4$ allows for its application in the context of other functional groups. Alkanes are often formed in good yield upon exposure of alkyl halides (I > Br > Cl; primary > secondary > tertiary)[12] and tosylates[13] to $LiAlH_4$ in ethereal solvents. Chloride reduction is an S_N2 process, while iodides enter principally into single electron transfer chemistry.[14] Benzylic[15] and allylic halides[16] behave comparably, although the latter can react in an S_N2' fashion as well (eq 1).[17] Select aromatic halides can be reduced under forcing conditions (e.g. diglyme, 100 °C),[18] but chemoselectivity as in eq 2 can often be achieved.[19] Vinyl,[20] bridgehead,[20] and cyclopropyl halides (eqs 3 and 4)[20,21] have all been reported to undergo reduction. The SET mechanism is also believed to operate in the latter context.[22]

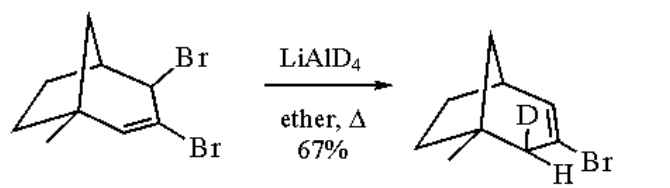

(1)

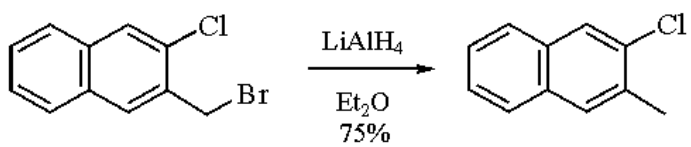

(2)

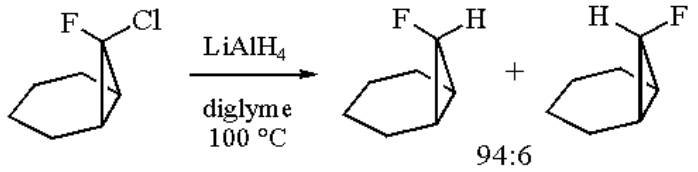

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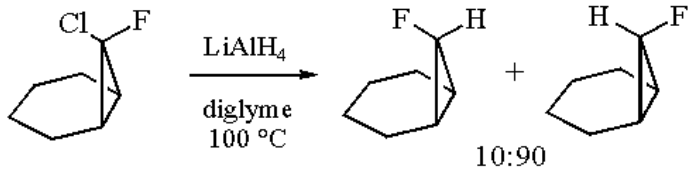

(4)

$LiAlH_4$ is normally unreactive toward ethers.[1] Unsaturated acetals undergo reduction with double bond migration (S_N2'); in cyclic systems, the usual stereoelectronic factors often apply (eq 5).[23] Orthoesters are amenable to attack, giving acetals in good yield (eq 6).[24] The susceptibility of benzylic acetals to reduction can be enhanced by the co-addition of a Lewis acid (eq 7).[25]

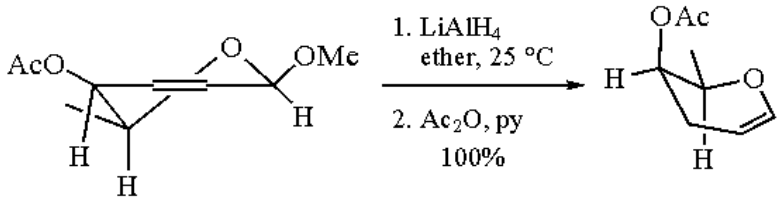

(5)

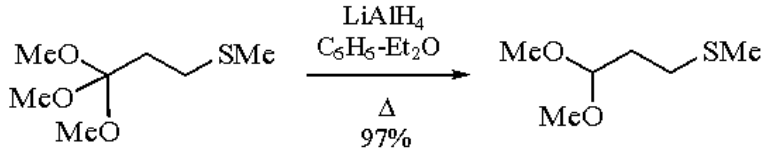

(6)

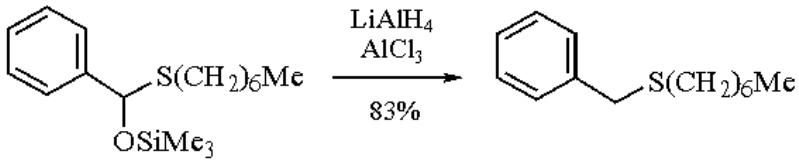

(7)

When comparison is made between $LiAlH_4$ and related reducing agents containing active Al-H and B-H bonds, $LiAlH_4$ is seen to be the most broadly effective (Table 1).[1h] Its superior reducing power is also reflected in its speed of hydride transfer.

Table 1 Comparison of the Reactivities of Hydride Reducing Agents toward the More Common Functional Groups

	Reduction products[a]						
Reagent/functional group	Aldehyde	Ketone	Acyl halide	Ester	Amide	Carboxylate salt	Iminium ion
$LiAlH_4$	Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol	Amine
$LiAlH_2(OCH_2CH_2OMe)_2$	Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol	
$LiAlH(O\text{-}t\text{-}Bu)_3$	Alcohol	Alcohol	Aldehyde	Alcohol	Aldehyde	NR	
$NaBH_4$	Alcohol	Alcohol		Alcohol	NR	NR	Amine
$NaBH_3CN$	Alcohol	NR		NR	NR	NR	Amine
B_2H_6	Alcohol	Alcohol		NR	Amine	Alcohol	
AlH_3	Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol	
$[i\text{-}PrCH(Me)]_2BH$	Alcohol	Alcohol		NR	Aldehyde	NR	
$(i\text{-}Bu)_2AlH$	Alcohol	Alcohol		Aldehyde	Aldehyde	Alcohol	

[a] NR indicates that no reduction is observed.

Hydroalumination Agent.

Ethylene has long been known to enter into addition with $LiAlH_4$ when the two reagents are heated under pressure at 120-140 °C; lithium tetraethylaluminate results.[2] Homogeneous hydrogenations of alkenes and alkynes to alkanes and alkenes, respectively, performed in THF or diglyme solutions under autoclave pressure, are well documented.[26] Such reductions are greatly facilitated by the presence of a transition metal halide ranging from Ti to Ni.[27] Replacement of the hydrolytic workup by the addition of appropriate halides constitutes a useful means for chain extension (eq 8).[28] 1-Chloro-1-alkynes are notably reactive toward $LiAlH_4$, addition occurring regio- and stereoselectively to give alanates that can be quenched directly (MeOH) or converted into mixed 1,1-dihaloalkenes (eq 9).[29]

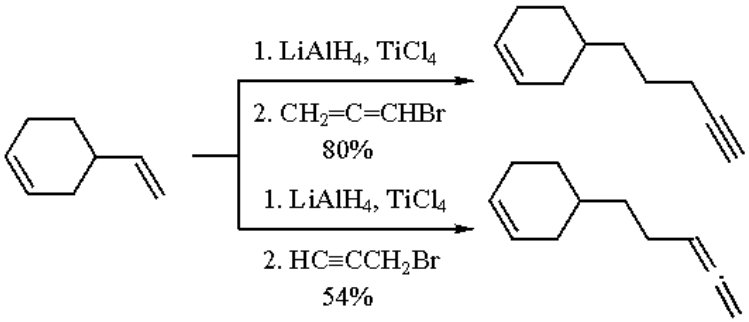

(8)

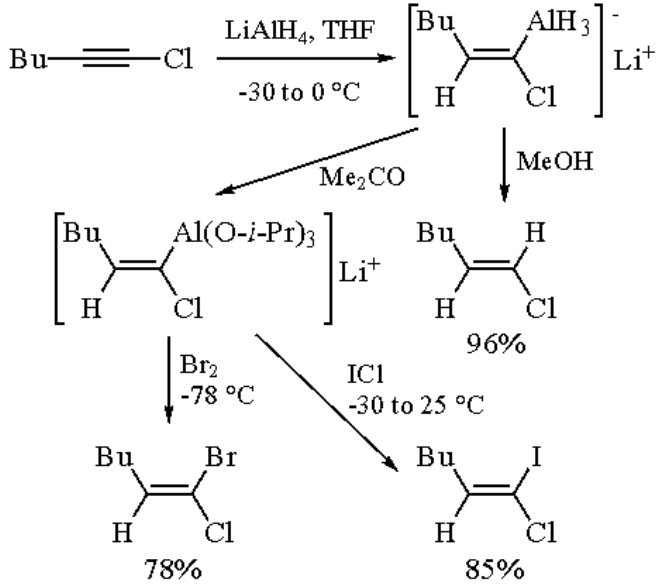

(9)

A pronounced positive effect on the ease of reduction of C=C and C&tbond;C bonds manifests itself when a neighboring hydroxyl group is present. In such cases, $LiAlH_4$ is used alone because reduction is preceded by formation of an alkoxyhydridoaluminate capable of facilitating hydride delivery (eqs 10-12).[30-32] The regio- and stereoselectivities of these reactions, where applicable, appear to be quite sensitive to the substrate structure and solvent.[33] Generally, the use of THF or dioxane results in exclusive *anti* addition. When ether is used, almost equivalent amounts of *syn* and *anti* products can result. Considerable attention has been accorded to synthetic applications of the alanate intermediates produced upon reduction of propargyl alcohols in this way. Simple heating occasions elimination of a δ-leaving group to generate homoallylic[34] and α-allenic alcohols (eqs 13 and 14).[35] Other variants of this chemistry have been reported.[36] The addition at -78 °C of solid iodine to alanates formed in this way greatly accelerates the elimination (eq 15).[37] Solutions of iodine in THF give rise instead to vinyl iodides.[38]

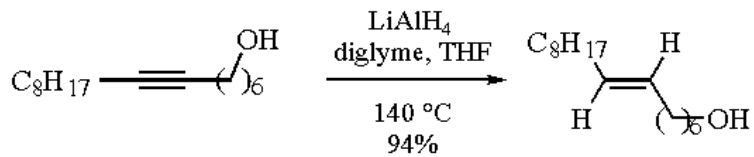

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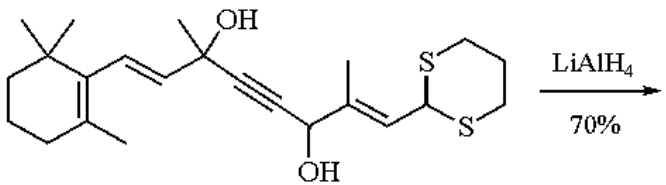

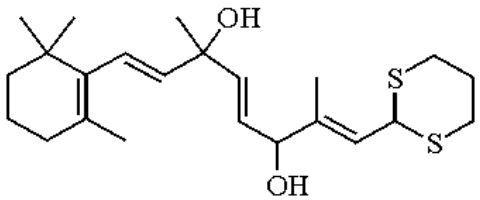

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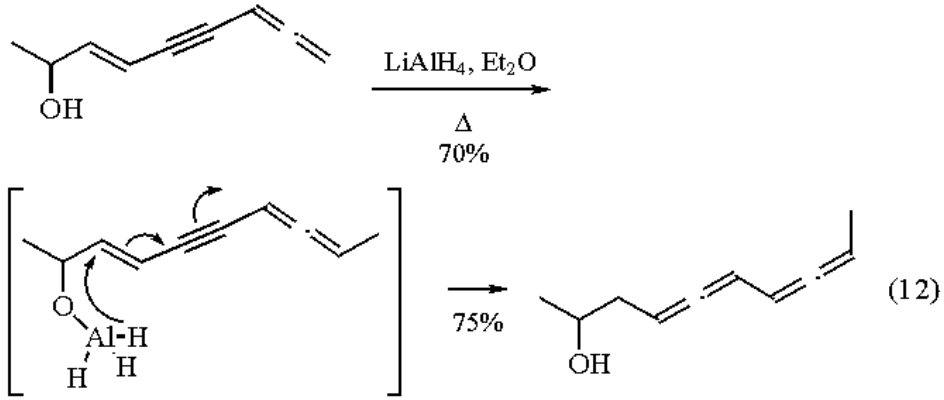

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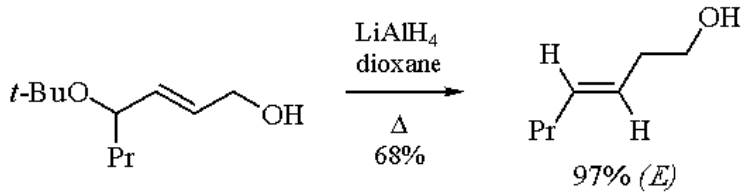

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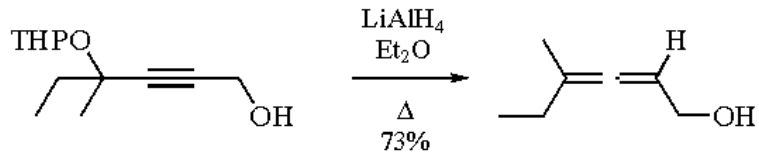

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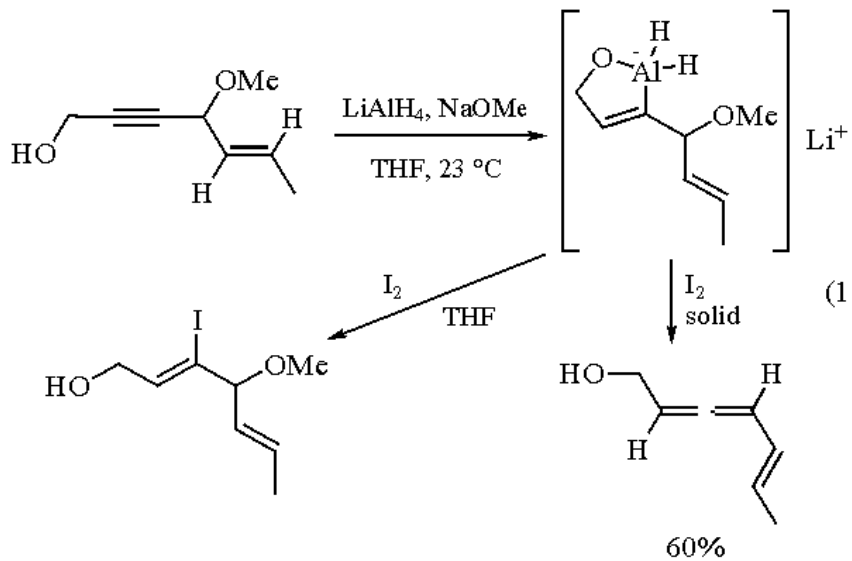

(15)

Epoxide Cleavage and Aziridine Ring Formation.

Epoxides are reductively cleaved in the presence of $LiAlH_4$ with attack generally occurring at the less substituted carbon.[1g] 1,2-Epoxycyclohexanes exhibit a strong preference for axial attack (eqs 16 and 17).[39] In general, *cis* isomers are more reactive than

their *trans* counterparts; ring size effects are also seen and these conform to the degree of steric inhibition to backside attack of the C-O bond.[40] Vinyl epoxides often suffer ring opening by means of the S_N' mechanism (eq 18).[41]

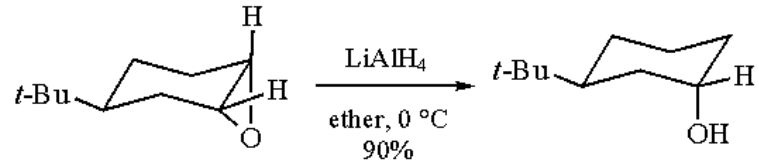

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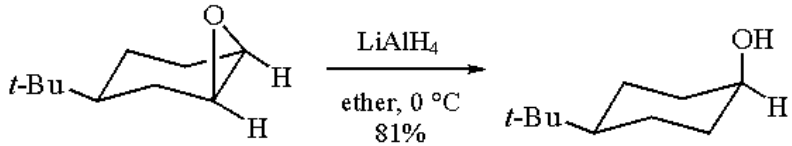

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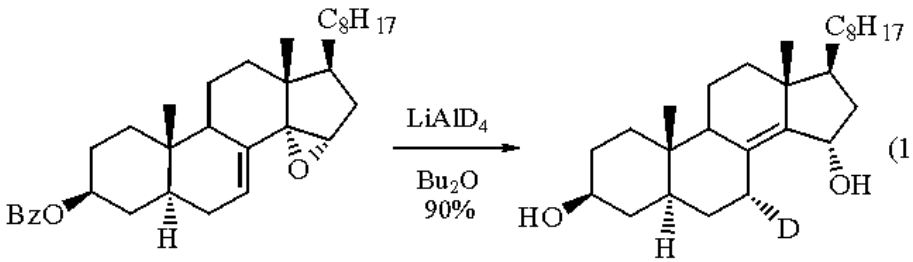

(18)

Two types of oximes undergo hydride reduction with ring closure to give aziridines. These are ketoximes that carry an α- or β-aryl ring and aldoximes substituted with an aromatic group at the β-carbon (eqs 19 and 20).[42]

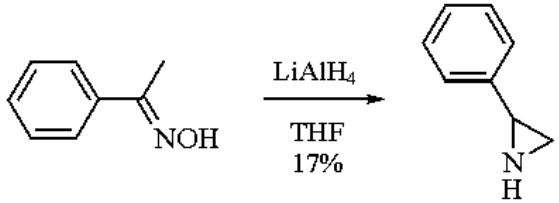

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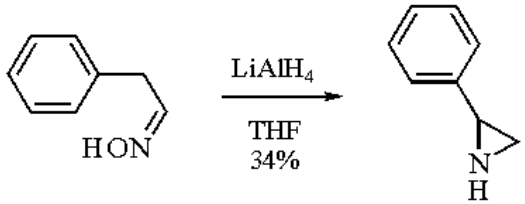

(20)

Use as a Base.

Both 1,2- and 1,3-diol monosulfonate esters react with $LiAlH_4$ functioning initially as a base and subsequently in a reducing capacity (eqs 21 and 22).[3,43]

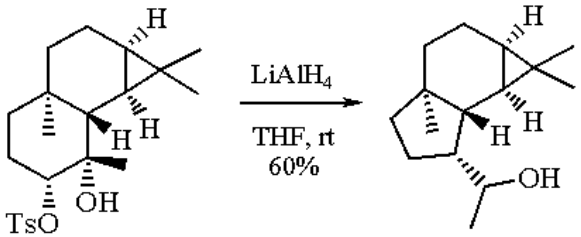

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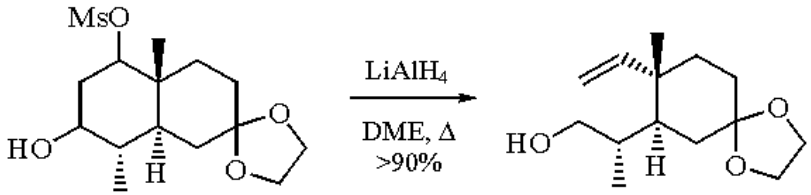

(22)

Reduction of Sulfur Compounds.

Sulfur compounds react differently with $LiAlH_4$ depending on the mode of covalent attachment of the hetero atom and its oxidation state. Reductive desulfurization is not often encountered.[44] Arylthioalkynes undergo stereoselective *trans* reduction (eq 23)[45] and α-oxoketene dithioacetals are transformed into fully saturated *anti* alcohols under reflux conditions (eq 24).[46] While $LiAlH_4$ catalyzes the fragmentation of sulfolenes to 1,3-dienes,[47] the lithium salts of sulfolanes are smoothly ring contracted when heated with the hydride in dioxane (eq 25).[48]

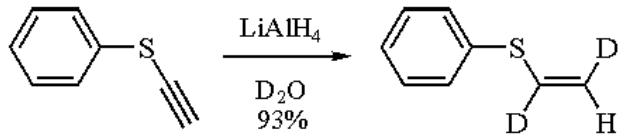

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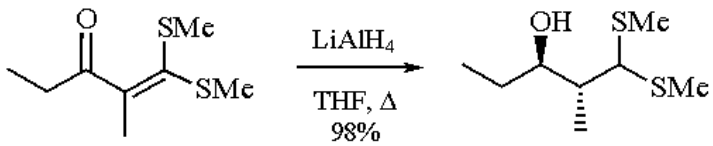

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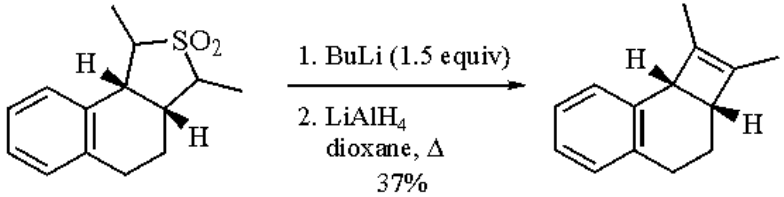

(25)

Stereoselective Reductions.

The reduction of 4-*t*-butylcyclohexanone and (**1**) by $LiAlH_4$ occurs from the axial direction to the extent of 92%[49] and 85%,[50] respectively. When a polymethylene chain is affixed diaxially as in (**2**), the equatorial trajectory becomes kinetically dominant (93%).[50] Thus, although electronic factors may be an important determinant of π-facial selectivity,[51] steric demands within the ketone cannot be ignored. The stereochemical characteristics of many ketone reductions have been examined. For acyclic systems, the Felkin-Ahn model[52] has been widely touted as an important predictive tool.[53] Cram's chelation transition state proposal[54] is a useful interpretative guide for ketones substituted at C_α with a polar group. Cieplak's explanation[55] for the stereochemical course of nucleophilic additions to cyclic ketones has received considerable scrutiny.[56]

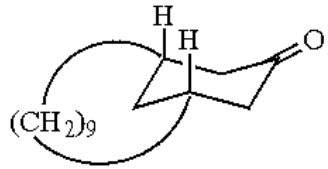

(1)

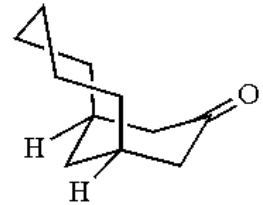

(2)

Useful levels of diastereoselectivity can be realized upon reduction of selected acyclic ketones having a proximate chiral center.[57] The contrasting results in eq 26 stem from the existence of a chelated intermediate when the benzyloxy group is present and its deterrence when a large silyl protecting group is present. In the latter situation, an open transition state is involved.[58,59] In eq 27, $LiAlH_4$ alone shows no stereoselectivity, but the co-addition of ***Lithium Iodide*** gives rise to a *syn*-selective reducing agent as a consequence of the intervention of a Li^+-containing six-membered chelate.[60]

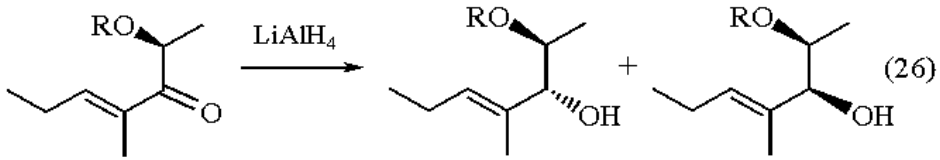

R = Bn, ether, -10 °C 98:2
R = TBDMS, THF, -20 °C 5:95

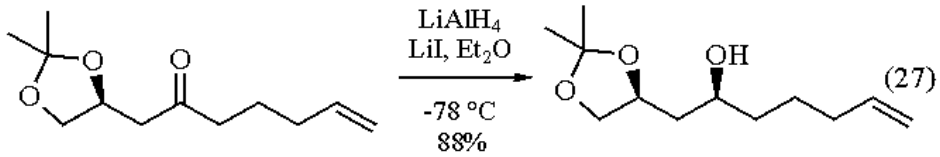

syn:*anti* = 95:5

The reduction of amino acids to 1,2-amino alcohols can be conveniently effected with $LiAlH_4$ in refluxing THF.[61] The higher homologous 1,3-amino alcohols have been made available starting with isoxazolines, the process being *syn* selective (eq 28).[62,63] The *syn* and *anti* *O*-benzyloximes of β-hydroxy ketones are reduced with good *syn* and *anti* stereoselectivity, respectively.[64] However, when NaOMe or KOMe is also added, high *syn* stereoselectivity is observed with both isomers (eq 29).[65]

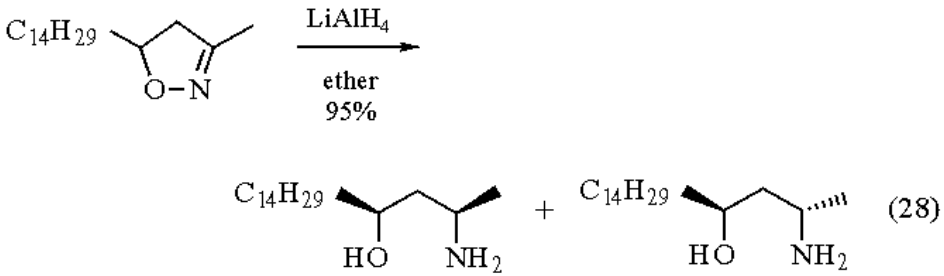

88:12

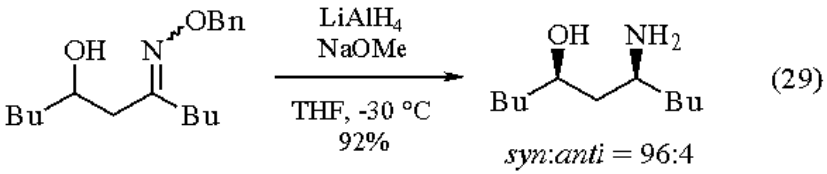

syn:*anti* = 96:4

Addition of Chiral Ligands.

If a chiral adjuvant is used to achieve asymmetric induction, it should preferentially be inexpensive, easily removed, efficiently recovered, and capable of inducing high stereoselectivity.[53] Of these, 1,3-oxathianes based on (+)-camphor[66] or (+)-pulegone,[67] and proline-derived 1,3-diamines,[68] have been accorded the greatest attention.

Extensive attempts to modify $LiAlH_4$ with chiral ligands in order to achieve the consistent and efficient asymmetric reduction of prochiral ketones has provided very few all-purpose reagents.[1f,69] Many optically active alcohols, amines, and amino alcohols have been evaluated. One of the more venerable of these reagents is that derived from DARVON alcohol.[70] The use of freshly prepared solutions normally accomplishes reasonably enantioselective conversion to alcohols.[71] As the reagent ages, its reduction stereoselectivity reverses.[70] This phenomenon is neither understood nor entirely reliable, and therefore recourse to the enantiomeric reagent[72] (from NOVRAD alcohol) is recommended.[73] The highest level of enantiofacial discrimination is usually realized with $LiAlH_4$ complexes prepared from equimolar amounts of (*S*)-(-)- or (*R*)-(+)-2,2´-dihydroxy-1,1´-binaphthyl and ethanol.[74] Often, optically pure alcohols result, irrespective of whether the ketones are aromatic,[74] alkenic,[75] or alkynic in type.[76] A useful rule of thumb is that (*S*)-BINAL-H generally provides (*S*)-carbinols and (*R*)-BINAL-H the (*R*)-antipodes when ketones of the type R_{unsat}-C(O)-R_{sat} are involved (eq 30).[74]

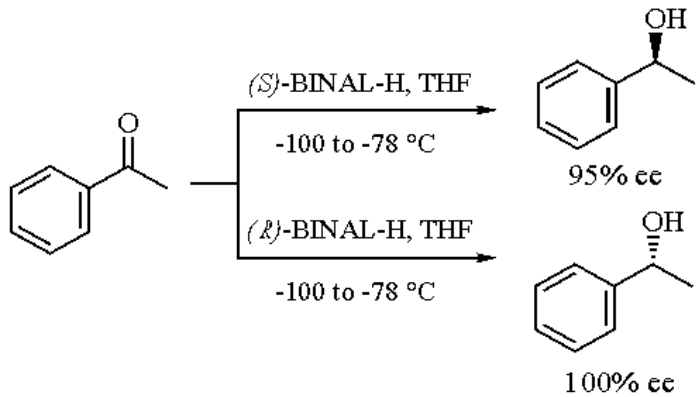

(30)

For a more detailed discussion of asymmetric induction by this means, see also the following entries that deal specifically with $LiAlH_4$/additive combinations.

Related Reagents.

Lithium Aluminum Hydride-(2,2´-Bipyridyl)(1,5-cyclooctadiene)nickel; ***Lithium Aluminum Hydride-Bis(cyclopentadienyl)nickel***; ***Lithium Aluminum Hydride-Boron Trifluoride Etherate***; ***Lithium Aluminum Hydride-Cerium(III) Chloride***; ***Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl***; ***Lithium Aluminum Hydride-Chromium(III) Chloride***; ***Lithium Aluminum Hydride-Cobalt(II) Chloride***; ***Lithium Aluminum Hydride-Copper(I) Iodide***; ***Lithium Aluminum Hydride-Diphosphorus Tetraiodide***; ***Lithium Aluminum Hydride-Nickel(II) Chloride***; ***Lithium Aluminum Hydride-Titanium(IV) Chloride***; ***Titanium(III) Chloride-Lithium Aluminum Hydride***.

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Lithium Aluminum Hydride-(2,2´-Bipyridyl)(1,5-cyclooctadiene)nickel[1]

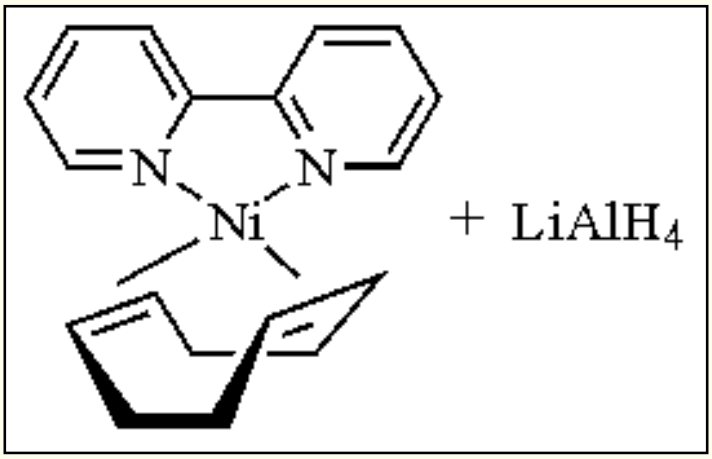

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-(2,2´-Bipyridyl)(1,5-cyclooctadiene)nickel · (MW 37.96) ((bipy)(cod)Ni)

[55425-72-4] · $C_{18}H_{20}N_2Ni$ · Lithium Aluminum Hydride-(2,2´-Bipyridyl)(1,5-cyclooctadiene)nickel · (MW 323.09)

(reagent for desulfurization)[1]

Physical Data: see entry for ***Lithium Aluminum Hydride***. A crystal structure of (2,2´-bipyridyl)(cod)Ni has been reported.[3d]

Solubility: sol THF.

Preparative Methods: as a red-violet solution[1a] by addition of an equimolar quantity of $LiAlH_4$ to a solution of the nickel complex in THF at rt with production of a mole of hydrogen. The nickel complex can be prepared according to literature procedures.[2]

Handling, Storage, and Precautions: highly flammable hydrogen is liberated during the formation of the complex. Solutions should be protected from open flames, moisture, and oxygen under an atmosphere of argon. Nickel and nickel salts are reputed to be carcinogenic and should be handled with due precautions. $LiAlH_4$ is highly flammable as the solid or in solution.

Homogeneous Desulfurizing Agent.

$LiAlH_2$-$(THF)_n$-$C_{10}H_8N_2$-Ni (**1**), resulting from addition of $LiAlH_4$ to (2,2´-bipyridyl)(1,5-cyclooctadiene)Ni, is a powerful desulfurizing agent for some aromatic sulfur heterocycles. For example, desulfurization[3] of dibenzothiophene was achieved with two molar equivalents of the reagent (**1**) (eq 1).[1a]

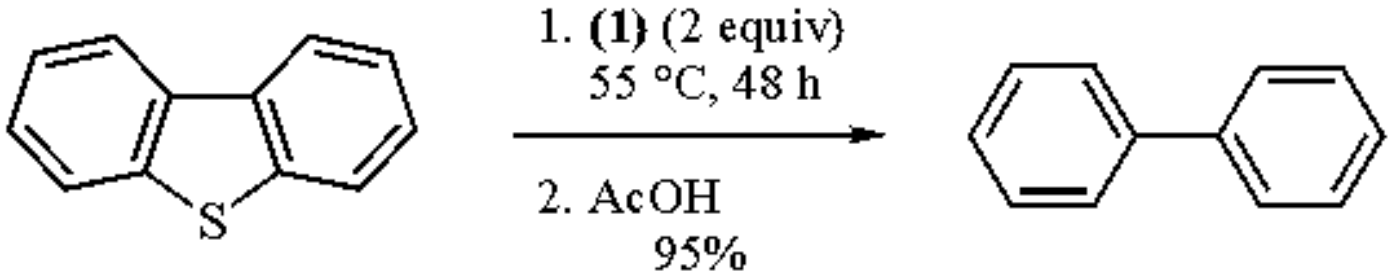

(1)

Phenothiazine (X = NH), phenoxathiine (X = O), and thianthrene (X = S) can be desulfurized under the same conditions (eq 2).[1a] Note that for thianthrene, good chemoselectivity is obtained as only one sulfur atom is removed.

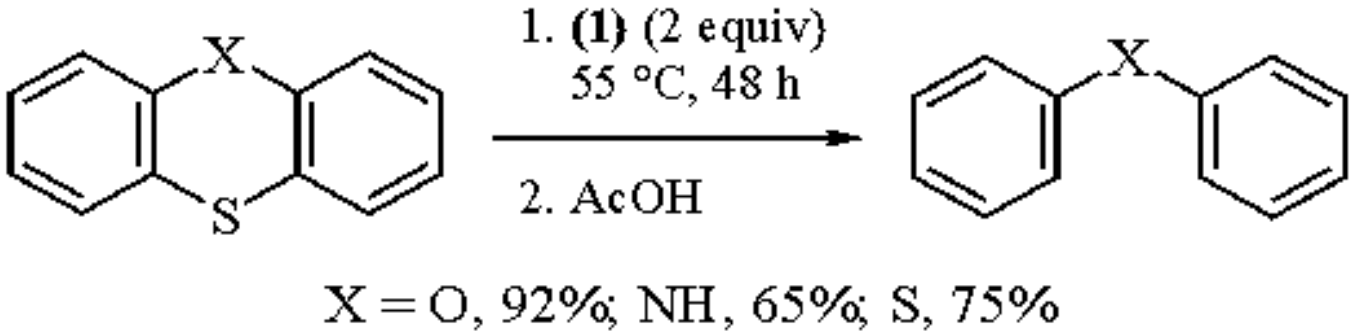

(2)

The use of $LiAlD_4$ resulted in only minor incorporation of deuterium, while quenching with DOAc provided almost no incorporation of the label. Other amine ligands such as ethylenediamine, HMPA, TMEDA, or pyridine (2 equiv), instead of 2,2´-bipyridyl, proved equally effective. Only the limited number of systems described above[1a] have been studied and the generality of this reagent has not been demonstrated. Other reports of homogeneous desulfurizing agents related to (**1**) have appeared in the literature and show broader applicability.[3]

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Lithium Aluminum Hydride-Bis(cyclopentadienyl)nickel

$LiAlH_4$-$NiCp_2$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Bis(cyclopentadienyl)nickel · (MW 37.96)
($NiCp_2$)

[1271-28-9] · $C_{10}H_{10}Ni$ · Lithium Aluminum Hydride-Bis(cyclopentadienyl)nickel · (MW 188.90)

(desulfurization reagent for thiols, thioethers,[1,2] thioacetals,[1] sulfoxides, and sulfones;[2] used as a homogenous catalyst for catalytic hydrogenation[3])

Physical Data: see ***Lithium Aluminum Hydride***.

Solubility: see ***Lithium Aluminum Hydride***. Reactions using the mixture are run in THF.

Form Supplied in: prepared in situ from commercially available components.

Preparative Methods: bis(cyclopentadienyl)nickel is added as a THF solution to an equimolar amount of $LiAlH_4$ at rt under nitrogen, resulting in the formation of a dark brown solution after 15 min. A THF solution of the organic substrate is then added to the mixture dropwise. Each carbon-sulfur bond requires at least 1 equiv of the reagent. Catalytic hydrogenation is performed in the presence of 1-5 mol % of the reagent.

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride***.

Desulfurization.

The mixture of lithium aluminum hydride-bis(cyclopentadienyl)nickel has been used for reductive carbon-sulfur bond cleavage as a homogeneous alternative to the more common reagent, ***Raney Nickel***.[4] It has been found to desulfurize thiols, thioethers, and thioacetals effectively (eqs 1-3).[1,2]

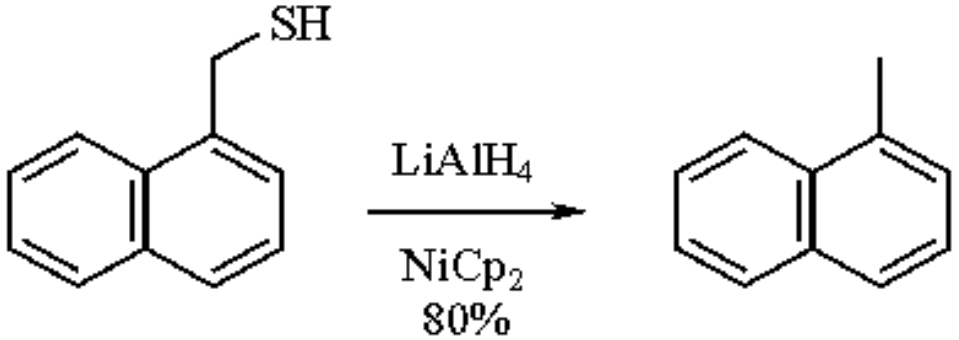

(1)

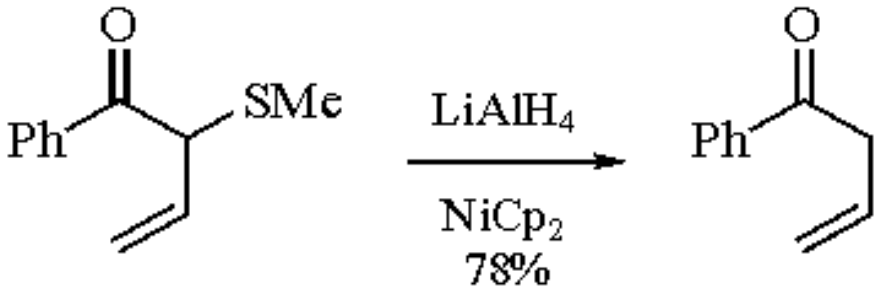

(2)

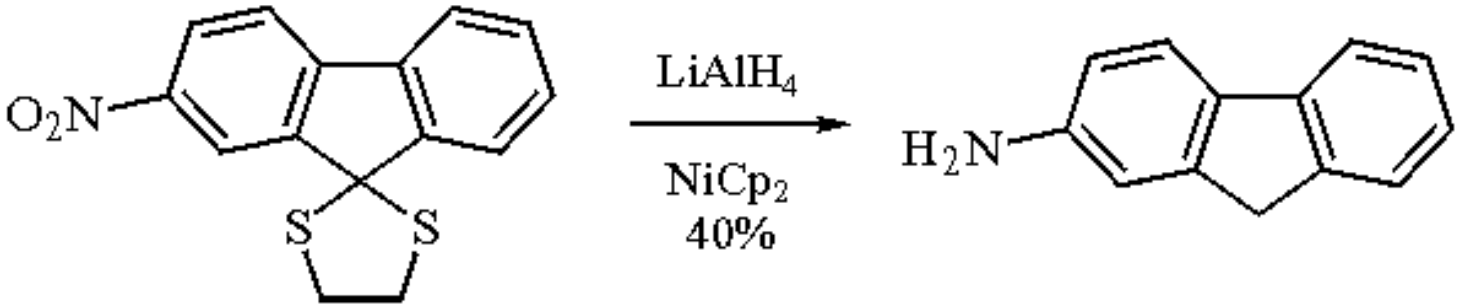

(3)

Benzylic, α-acyl substituted, and aryl carbon-sulfur bonds were found to be easily reduced with this reagent, whereas alkyl carbon-sulfur bonds required more vigorous conditions, resulting in lower yields. Carbonyl groups, esters, and alkenes are stable to the reaction conditions, however, similar to Raney nickel,[4] and nitro groups are reduced to the corresponding primary amines. In addition, sulfoxides and sulfones can also be desulfurized with this reagent. Longer reaction times and an excess of the reagent are required in order to prevent simple deoxygenation of the sulfoxide or sulfone and achieve complete reduction.[2]

Catalytic Hydrogenation.

Alkenes and alkynes can also be hydrogenated in the presence of a catalytic amount of $LiAlH_4$-$NiCp_2$.[3] This reagent shows selectivity for disubstituted alkenes and conjugated polyenes (eq 4), whereas trisubstituted and sterically hindered alkenes (eq 5) are inert to the reaction conditions. Alkynes may be fully or partially reduced to the corresponding alkanes or alkenes, respectively, giving rise to products derived from *cis* and *trans* addition in the latter case.

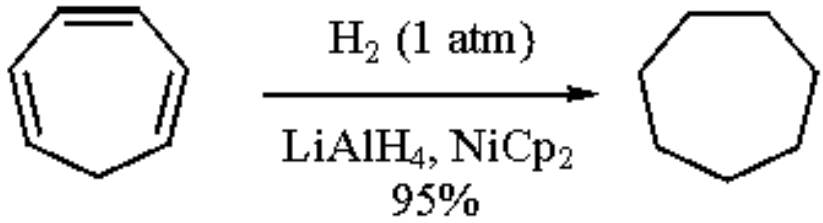

(4)

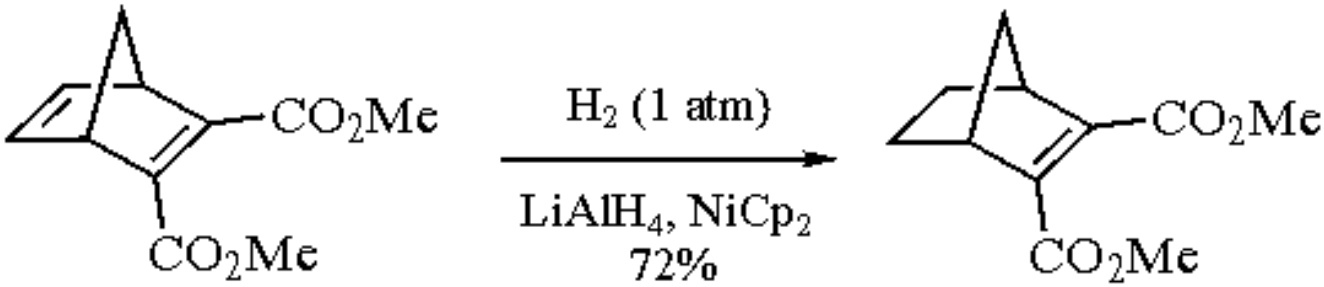

(4)

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Lithium Aluminum Hydride-Boron Trifluoride Etherate[1]

$LiAlH_4$-BF_3.Et_2O

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Boron Trifluoride Etherate · (MW 37.96)
(BF_3.Et_2O)

[109-63-7] · $C_4H_{10}BF_3O$ · Lithium Aluminum Hydride-Boron Trifluoride Etherate · (MW 141.95)

(reducing agent for esters,[2] thiol esters,[3] acetals, and ketals;[4] also a reagent for hydroboration of alkenes[5])

Physical Data: see ***Lithium Aluminum Hydride*** and ***Boron Trifluoride Etherate***

Solubility: most reactions are performed in ether or THF.

Preparative Methods: for reductions, a solution of the carbonyl compound and BF_3.Et_2O in ether is added to a cooled suspension of $LiAlH_4$ in ether.[2] For hydroborations, BF_3.Et_2O is added to a solution of the alkene in ether or THF followed by the addition of $LiAlH_4$ in ether at 0 °C.[5]

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride*** and ***Boron Trifluoride Etherate***.

Reduction of Esters.

The direct reduction of esters and lactones to ethers can be accomplished by employing a reagent prepared from lithium aluminum hydride and boron trifluoride etherate. When 30 mol of BF_3.Et_2O and 2 mol of $LiAlH_4$ per mol of ester is used, a γ-lactone is converted to the tetrahydrofuran in good yield (eq 1).[6]

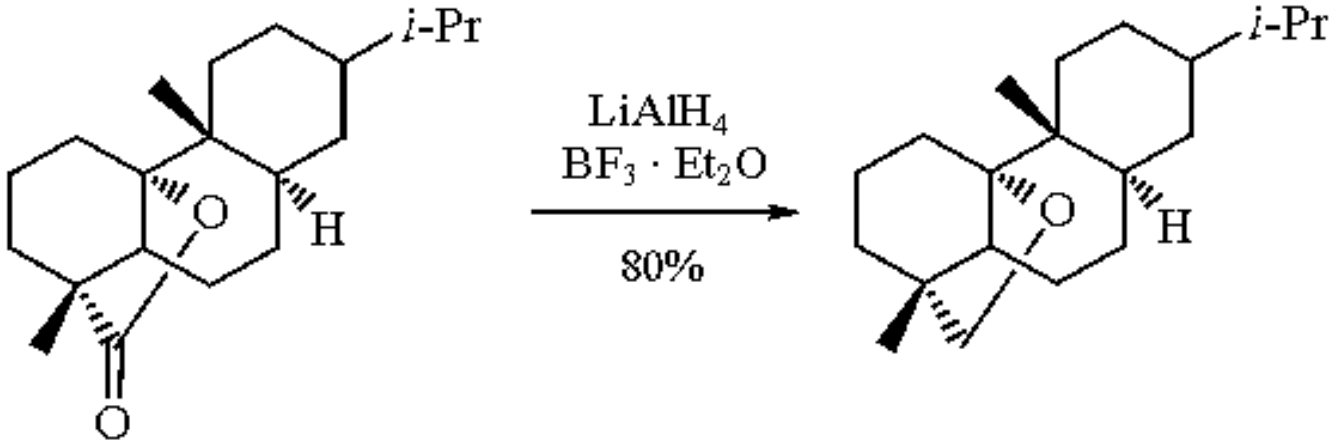

(1)

Also, the yield of ether appears to increase as the alcohol portion of the ester goes from primary to tertiary, as seen in the three isomeric butyl esters (**1a**), (**1b**), and (**1c**) (eq 2).[7] This reagent has also been used to generate crown ethers from crown lactones (eq 3).[8]

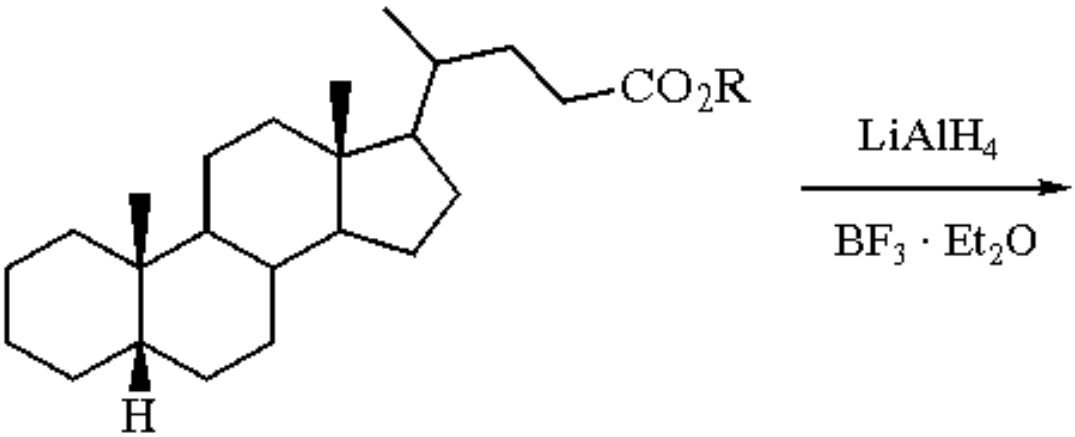

(1a) R = Bu
(1b) R = *s*-Bu
(1c) R = *t*-Bu

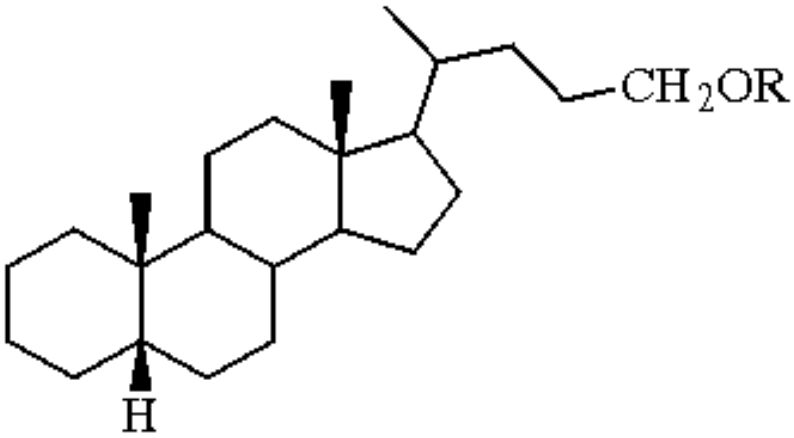

(2)

(2a) R = Bu, 7%
(2b) R = *s*-Bu, 41%
(2c) R = *t*-Bu, 71%

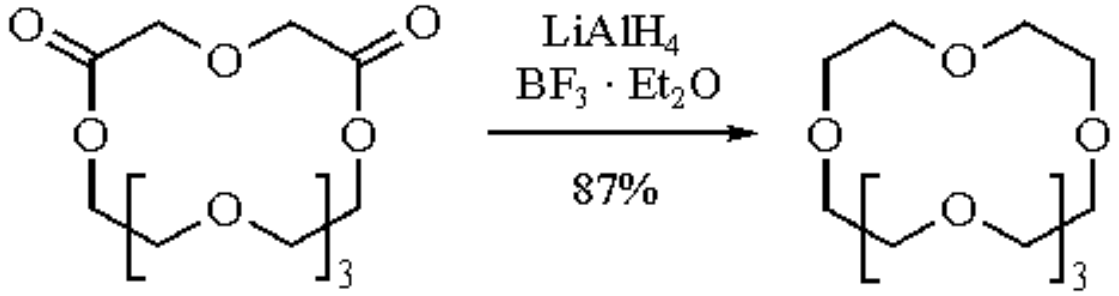

(3)

Reduction of Thiol Esters.

The combination of $LiAlH_4$ and a large excess of $BF_3.Et_2O$ will reduce thiol esters to sulfides. This reaction is similar to the reduction of esters to ethers. Thus cyclohexyl thiolacetate, when treated with $LiAlH_4$-$BF_3.Et_2O$, gives the corresponding sulfide (eq 4).[3]

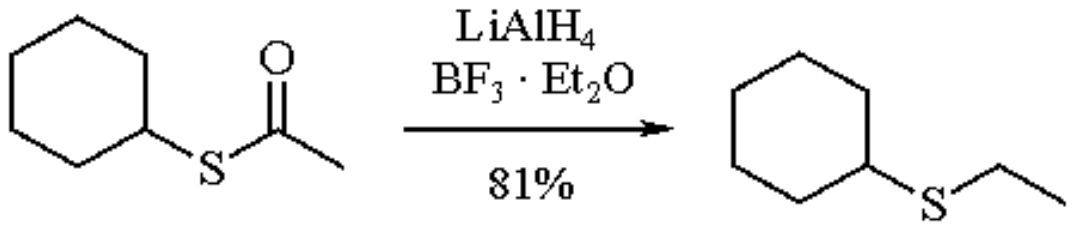

(4)

Reduction of Acetals.

Acetals are inert to $LiAlH_4$, and are normally used as protecting groups for ketones and aldehydes. However, when the reagent prepared from $LiAlH_4$-$BF_3.Et_2O$ is employed, they are reduced to ethers. Lithium aluminum hydride and ***Aluminum Chloride*** also reduces acetals, but $LiAlH_4$-$BF_3.Et_2O$ is preferred because the yields are slightly better and $BF_3.Et_2O$ is less troublesome during the workup. When treated with this reagent, acetal (**3**) gives the corresponding diether (eq 5).[4]

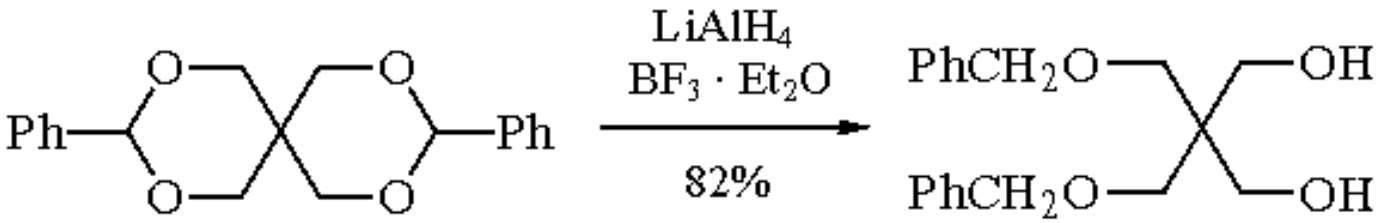

(3)

(5)

Hydroboration of Alkenes.

Diborane can be generated in situ by adding $LiAlH_4$ to $BF_3.Et_2O$, which upon oxidative workup hydrates alkenes to alcohols. For example, when alkene (**4**) reacts with this reagent, it gives the corresponding alcohol (eq 6).[9] Yet, when treated with diborane generated from ***Sodium Borohydride***-$BF_3.Et_2O$, the alcohol is formed in a 55% yield and 40% of starting alkene is recovered. This method cannot be used in the presence of acetals and esters.

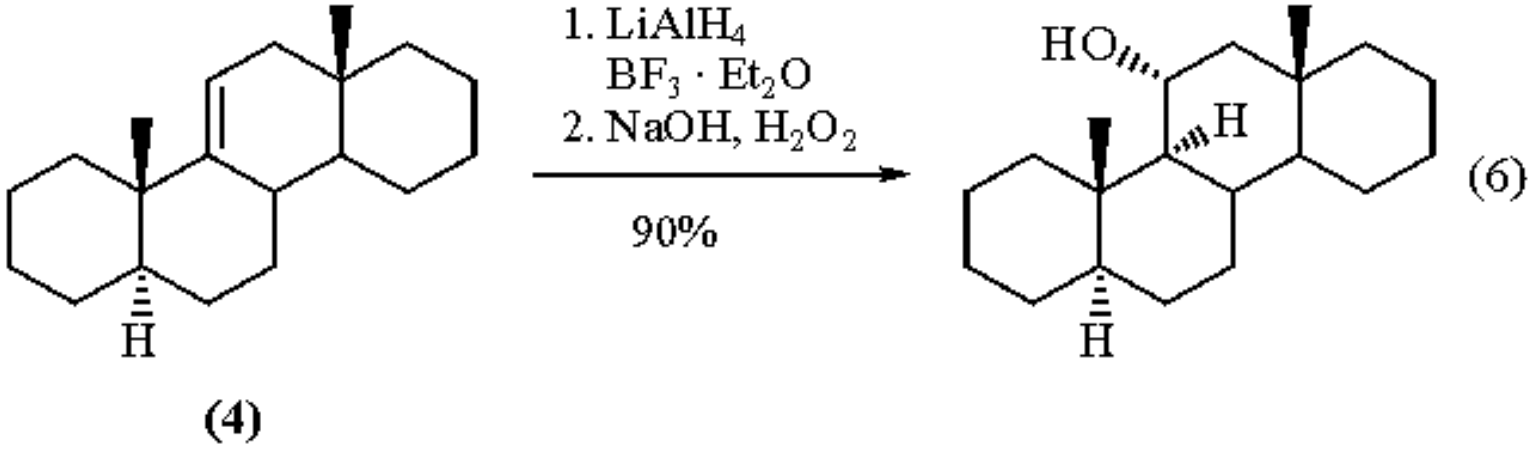

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Lithium Aluminum Hydride-Cerium(III) Chloride

$LiAlH_4$-$CeCl_3$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Cerium(III) Chloride · (MW 37.96) ($CeCl_3$)

[7790-86-5] · $CeCl_3$ · Lithium Aluminum Hydride-Cerium(III) Chloride · (MW 246.47) ($CeCl_3.7H_2O$)

[18618-55-8] · $CeCl_3H_{14}O_7$ · Lithium Aluminum Hydride-Cerium(III) Chloride · (MW 372.61)

(reducing agent for alkyl halides and phosphine oxides;[1] in combination with $NaBH_4$ is a system used to prepare phosphine boranes;[2] catalyst for the isomerization and dimerization of alkenes[3,4])

Physical Data: see ***Lithium Aluminum Hydride*** and ***Cerium(III) Chloride***.

Solubility: see ***Lithium Aluminum Hydride*** and ***Cerium(III) Chloride***; reactions using this reagent system typically use THF or DME as solvent.

Form Supplied in: formed in situ from widely available reagents.

Preparative Method: the organic substrate (1 equiv) and lithium aluminum hydride (4.5 equiv) are added to a suspension of dried cerium(III) chloride (1.5 equiv) in THF.[1]

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride*** and ***Cerium(III) Chloride***.

Reduction of Fluorides and Chlorides.

Alkyl fluorides and chlorides are reduced to their alkane counterparts upon treatment with lithium aluminum hydride-cerium(III) chloride. Despite the relatively inert nature of alkyl (eq 1) and aryl fluorides, they are reduced as readily as chlorides (eqs 2 and 3).[1] The hard Lewis acid character of the cerium cation is believed

to perturb the halogen to an extent such that reduction is easily effected by lithium aluminum hydride. Furthermore, a radical mediated process has been postulated in which hydrogen abstraction from the solvent (THF or DME) is operational.[1]

$$Me(CH_2)_{10}CH_2F \xrightarrow[\text{90\%}]{LiAlH_4,\ CeCl_3,\ THF,\ reflux} Me(CH_2)_{10}Me \qquad (1)$$

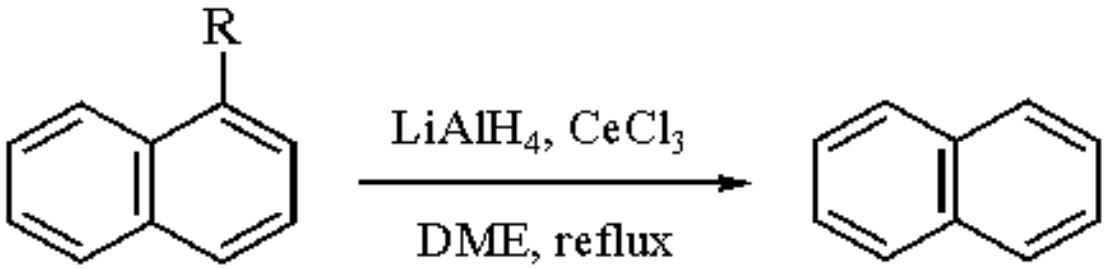

(2)

R = F, 94%
R = Cl, 95%

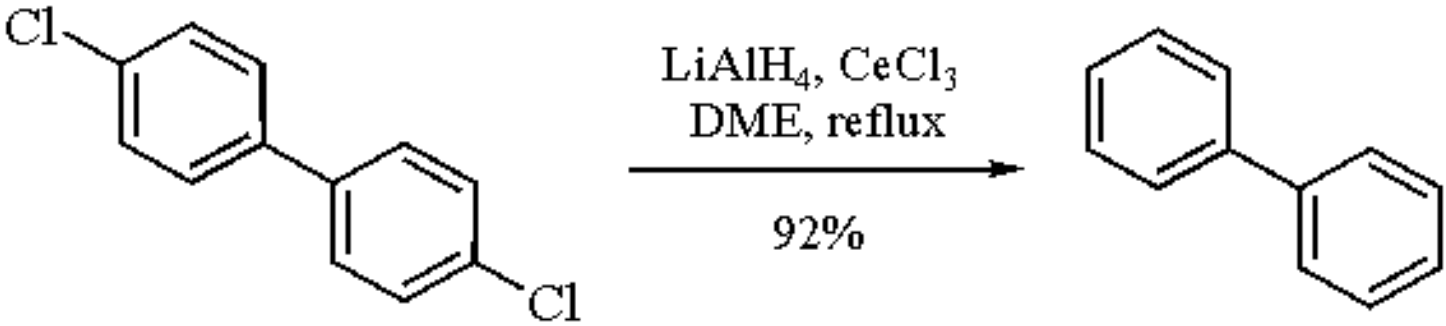

(3)

Reduction of Phosphine Oxides.

Worthy of increased attention is the use of this reagent system in the reduction of phosphine oxides (eq 4).[1] The results from these reductions are general, and sterically hindered phosphine oxides are no exception (eq 5).[1] Unfortunately, racemization is observed in cases where the phosphine oxide is optically active.

$$Ph_3P{=}O \xrightarrow[\text{95\%}]{LiAlH_4,\ CeCl_3\ (2{:}1.5),\ THF,\ 40\ ^\circ C} PPh_3 \qquad (4)$$

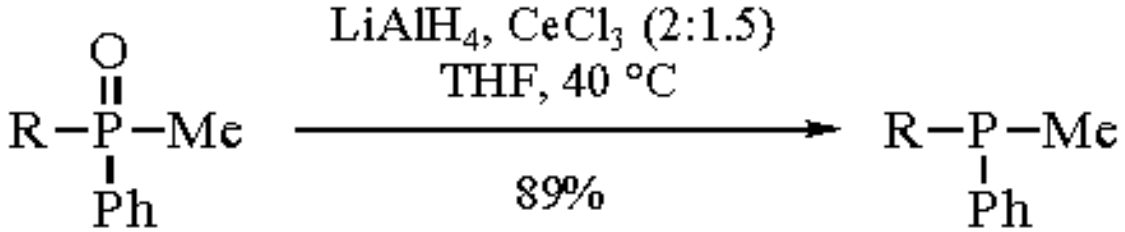

(5)

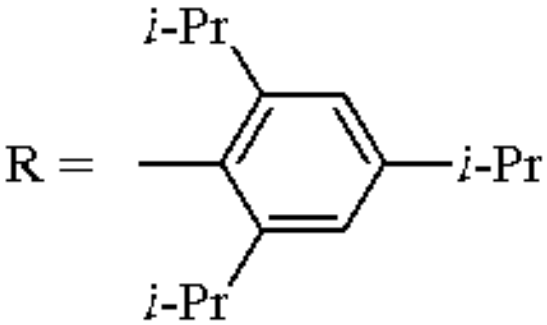

Formation of Phosphine Boranes.

The scope of the lithium aluminum hydride-cerium(III) chloride reduction of phosphine oxides is broadened when the reagents are used in conjunction with ***Sodium Borohydride***. Tertiary and secondary phosphine oxides are transformed into their respective phosphine boranes with great facility (eqs 6 and 7).[2] Further manipulations of these phosphine boranes provide access to a variety of useful phosphine and tethered phosphine derivatives. The borane protecting/activating group is easily removed with retention of configuration when assisted by ***Triethylamine***. The utility of this reagent has been demonstrated through the synthesis of optically pure ligands for use in catalytic asymmetric hydrogenation such as (*S*,*S*)-1,2-ethanediylbis[(*o*-methoxyphenyl)phenylphosphine].[2]

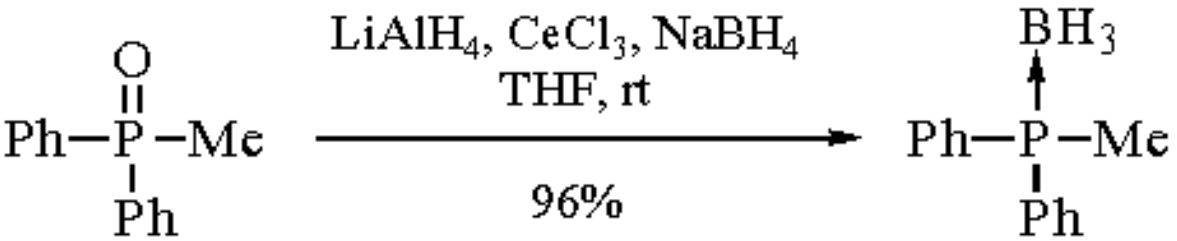

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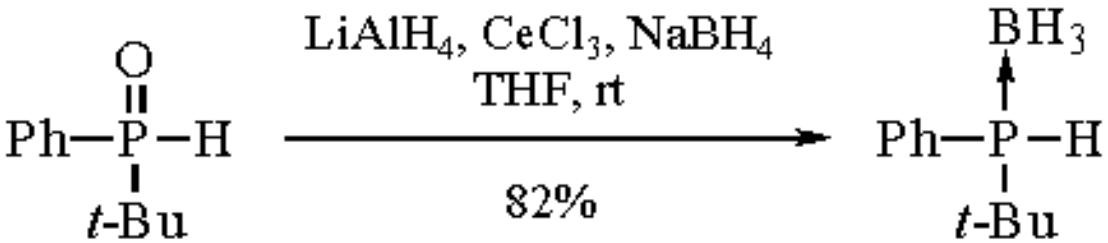

(7)

Isomerization and Dimerization of Alkenes.

The title reagent system is also known to promote the isomerization of alkenes. Bicyclo[3.2.1]oct-2-ene was synthesized in a single maneuver from 4-vinylcyclohexene in 48% yield.[3] Similar activity of the reagent system was realized in the dimerization of 2-alkenes.[4] It should be noted, however, that the use of the reagent in this manner is of limited synthetic value due to the harsh conditions necessary to effect the transformations.

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4. Stapp, P. R. U.S. Patent 3 414 633, 1968 (*CA* **1969** *70*, 46 798q).

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Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl

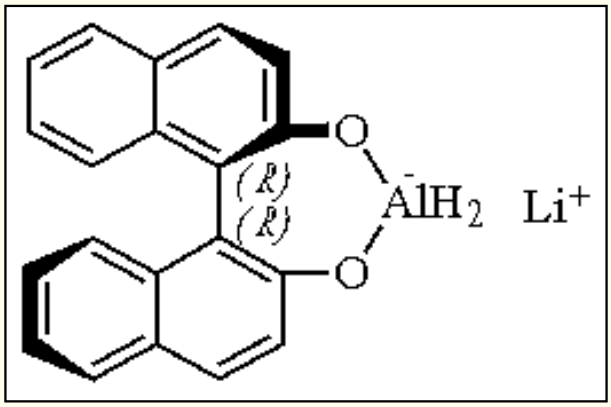

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl · (MW 37.96) ((*R*)-BINAL)

[18531-94-7] · $C_{20}H_{14}O_2$ · Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl · (MW 286.34) ((*S*)-BINAL)

[18531-99-2]

(used for enantioselective reduction of prochiral ketones to alcohols[1])

Alternate Name: BINAL-H.

Physical Data: BINAL: white solid, mp 208-210 °C. Also see ***Lithium Aluminum Hydride***.

Solubility: sol THF.

Preparative Methods: prepared in situ from commercially available lithium aluminum hydride and BINAL.

Handling, Storage, and Precautions: sensitive to moisture (see ***Lithium Aluminum Hydride***).

Overview and General Considerations.

This article will cover the title reagent and other chiral reducing agents derived from lithium aluminum hydride and chiral additives, with initial emphasis on the title reagent. The enantioselective reduction of prochiral ketones is a reaction of

considerable importance to the synthetic organic chemist and can now be accomplished by a variety of methods and reagents.[1,2] Particularly the use of chiral oxazaborolidines for the catalytic asymmetric reduction of ketones has received much recent interest. This method has been shown to be useful for the preparation of a variety of chiral alcohols with high optical purities. This transformation can also be realized using catalytic hydrogenation with a chiral catalyst or by use of chiral borane reducing agents such as ***(R,R)-2,5-Dimethylborolane*** and ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane***. Enzyme-catalyzed transformations, for example ***Baker's Yeast*** reductions of carbonyl compounds, can also provide access to a range of chiral alcohols with high optical purities.

The use of complexes of lithium aluminum hydride (LAH) with various chiral ligands to achieve the enantioselective reduction of prochiral ketones has been extensively studied for over 40 years.[1] However, this method, with some exceptions, has not found widespread use due to a number of limiting factors. These factors vary from moderate to poor enantioselectivities, often observed in these reductions, to ready availability of only one antipode of a desired chiral ligand. The recovery of the often expensive chiral ligand that is used in stoichiometric quantities to form the LAH complex is obviously an important experimental concern. Also, in some cases the LAH complex with the chiral ligand may disproportionate to achiral reducing species under the reaction conditions, resulting in poor optical purities of the desired products. Further, no single complex appears to have a sufficiently broad substrate specificity. Aromatic and unsaturated ketones are in general the better substrates and they can be reduced with good enantioselectivities using this method. A useful article comparing the merits of some of the more promising asymmetric reducing agents known for ketones has been published.[3]

Chiral Alcohol Modifying Agents.

Complexes of a variety of chiral alcohols (see Figure 1) with LAH have been prepared in situ and examined for their ability to effect enantioselective reduction of prochiral carbonyl compounds. However in most cases, the optical purities of the products obtained have not been satisfactory. This is in part due to the tendency of these chiral ligand-hydride complexes to disproportionate under reaction conditions yielding achiral reducing agents. An exception is the complex of LAH and (-)-menthol (**1**) which has been used to reduce α and β-aminoketones with good enantioselectivities.

The reduction of carbonyl compounds with LAH complexes of a number of chiral diols derived from carbohydrates and terpenes has been studied. In general, the enantioselectivities observed with such reagents have been low to moderate. Acetophenone, which is the model substrate in many of these reduction studies, is reduced by a complex of LAH and the glucose-derived diol (**2**) in about 71% ee under optimized conditions.

The reagent (*R*)- or (*S*)-BINAL-H, (**7**) developed by Noyori, is undoubtedly the most useful LAH complex reported so far for the asymmetric reduction of a variety of carbonyl compounds.[4] The reagent is prepared from (*R*)- or (*S*)-2,2´-dihydroxy-1,1´-binaphthyl (**3**) (BINAL). Both enantiomers of BINAL are commercially available, although they are somewhat expensive. The chiral ligand, however, can be recovered after the reduction and reused. Equimolar quantities of BINAL and LAH are initially mixed together to form a LAH complex that has a C_2 axis of symmetry, which makes the two hydrogens on the aluminum homotopic. It is interesting to note that the 1:1 complex of BINAL and LAH is a reducing agent that exhibits extremely low enantioselectivity as seen in the case of acetophenone (2% ee). Replacement of one of the hydrogens with an alcohol, like methanol or ethanol, gives a single reducing agent (**7**), which exhibits much higher specificity in the reduction of prochiral ketones. Another useful observation is that reduction of carbonyls with the (*R*)-BINAL-H reagent tends to give the (*R*)-alcohol while the (*S*)-reagent gives the (*S*)-alcohol. The use of lower reduction temperatures enhances optical purities of the product alcohols, but lowers the yields. Optimized conditions for reductions involve reaction of a ketone with 3 equiv of the reagent formed from LAH, BINAL, and ethanol (1:1:1) in THF for 1 h at -100 °C and then at -78 °C for 2 h.

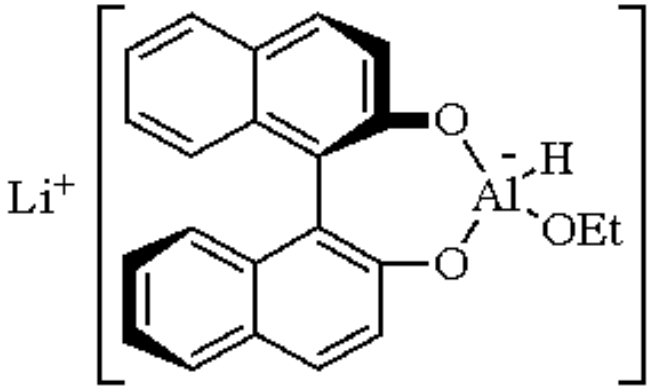

(*R*)-(7)

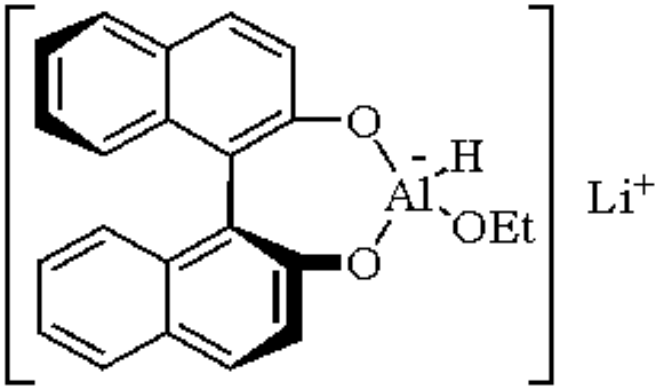

(*S*)-(7)

A number of structurally diverse ketones have been reduced using BINAL-H. Some of the results are summarized in Table 1.[5] Aryl alkyl ketones, alkynic ketones, and α,β-unsaturated ketones are reduced to alcohols with good to excellent % ee, while aliphatic ketones give products with lower optical purities. The asymmetric reduction of a number of acylstannanes with (**7**) gives synthetically valuable α-alkoxystannanes with high optical purities after protection of the initially formed unstable alcohols as their MOM or BOM ethers.[6]

Table 1 Reduction of Ketones with (**7**)

Ketone	(7)	Yield (%)	ee (%)	Product
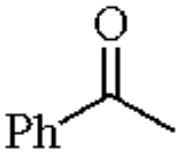	(*R*)	61	95	(*R*)
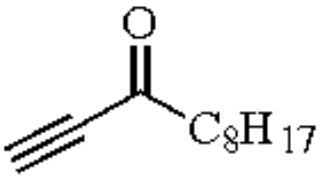	(*S*)	74	90	(*S*)
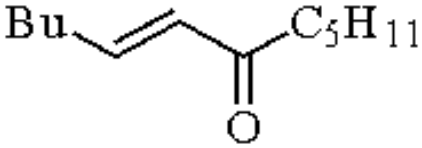	(*R*)	91	91	(*R*)
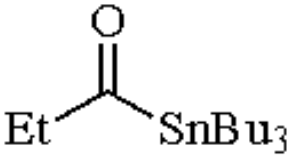	(*S*)	69	96	(*R*)
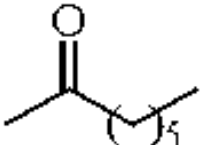	(*S*)	67	24	(*R*)

BINAL-H has been used to prepare deuterated primary alcohols with high optical purities. For example, benzaldehyde-*1-d* is reduced in 59% yield and 87% optical purity. β-Ionone is reduced with this reagent to the corresponding alcohol in 100% ee and 87% yield. Simple cyclic enones like 2-cyclohexenone are not reduced by the BINAL-H reagent under standard reduction conditions.[5]

The chiral nonracemic enone (**8**) is reduced with (*S*)-(**7**) to give the (15*S*)-alcohol in 100% de and 88% yield. The product is a valuable intermediate in the synthesis of prostaglandins.[5]

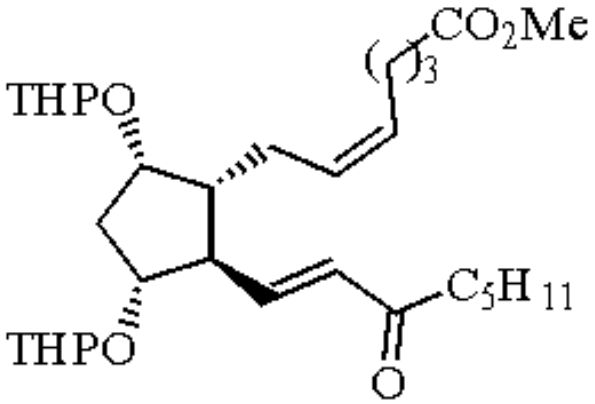

(8)

The asymmetric reduction of lactone (**9**) to give predominantly one atropoisomer can be achieved using 10 equiv of a complex prepared from LAH and BINAL (1:1) at -40 °C.[7] This reduction gives an 88:12 ratio of (**10a**):(**10b**) in good yield (80%). Reduction of the same substrate with 8 equiv of a complex of LAH with (*S*)-(+)-2-(anilinomethyl)pyrrolidine in ether at -40 °C leads to opposite stereochemical results (38:62 ratio of **10a**:**10b**).

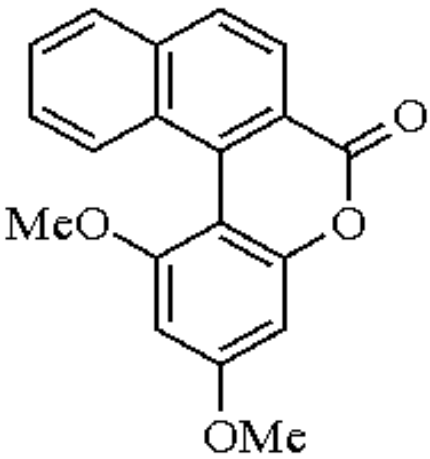

(9)

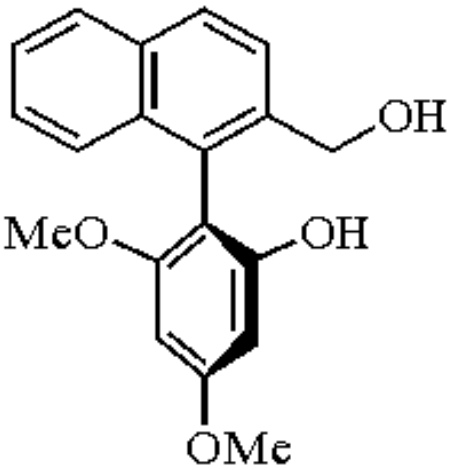

(10a)

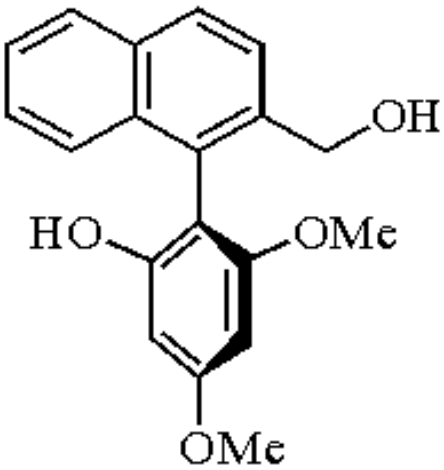

(10b)

BINAL-H has also been used for the asymmetric reduction of methylaryl- and methylalkylphosphinylimines to the corresponding phosphinylamines in high % ee (Table 2).[8] Similar to the reduction of ketones, reduction of the imines with (*S*)-(**7**) produces the (*S*)-amine and reduction with (*R*)-(**7**) gives the (*R*)-amine.

Table 2 Reduction of Imines with (7)

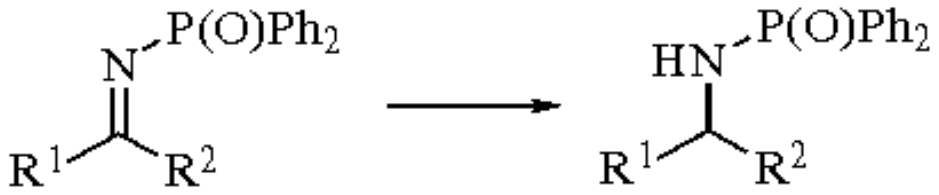

R^1	R^2	(7)	Yield (%)	ee (%)	Product
Me	Ph	(*R*)	20	100	(*R*)
Me	Et	(*S*)	38	93	(*S*)
Me	C_5H_{11}	(*S*)	83	64	(*S*)

The complex of the biphenanthryl diol (**4**) with LAH has been prepared and its reduction properties have been examined.[9] This reagent gives excellent enantioselectivity in the reduction of aromatic ketones. For example, acetophenone is reduced in 75% yield with 97% ee. As with Noyori's reagent, reductions with the (*S*)-reagent give (*S*)-alcohols and aliphatic ketones are reduced with low enantioselectivity. Both enantiomers of this auxiliary can be readily prepared and can also be recovered for reuse at the end of the reduction.

The LAH complex of the chiral spirodiol (**5**) has recently been prepared. This complex exhibits excellent enantioselectivity in the reduction of some aromatic ketones.[10] Acetophenone is reduced at -80 °C in 98% ee and 80% yield. Reduction of other aryl alkyl ketones also gives excellent stereoselectivity, but the use of this reagent with a variety of ketones has not been studied. The chiral auxiliary can be recovered and reused.

Recently, the preparation of the chiral biphenyl (**6**) and its use as a modifying agent with LAH has been reported.[11] A complex of LAH-(**6**)-EtOH (1:1:1) at -78 °C gives the best enantioselectivities in the reduction of prochiral ketones. Similar to Noyori's reagent, use of the LAH complex with (*S*)-(**6**) leads to the (*S*)-alcohol. Enantioselectivity is usually high for aromatic ketones (acetophenone 97% ee, 93% yield). This reagent reduces 2-octanone in higher enantioselectivity (76% ee) than 3-heptanone (36% ee).

Chiral Amino Alcohol Modifying Agents.

A number of chiral amino alcohols have been examined as ligands for the preparation of chiral LAH reducing agents (Figure 2). The complex of (-)-*N*-methylephedrine (**11**) with LAH has been widely studied and has shown promise for the asymmetric reduction of prochiral ketones. It has been found that addition of an achiral component such as 3,5-dimethylphenol (DMP), *N*-ethylaniline (NEA), or 2-ethylaminopyridine (EAP) to the complex of LAH with (**11**) can enhance the enantioselectivity observed in these reductions. Both enantiomers of (**11**) are commercially available and the ligand can be recovered subsequent to the reaction and reused.

Vigneron and co-workers have observed that a complex of LAH, (-)-(**11**), and DMP (1:1:2), in ether at -15 °C, appears to show the highest enantioselectivity in the reduction of a series of aromatic and alkynyl ketones to the corresponding (*R*)-alcohols (Figure 3).[12] Interestingly, the optical purities of the products obtained were lower both at higher and lower reaction temperatures.

The complex of LAH, (-)-(**11**), and DMP has also been used to reduce stereoselectively a steroidal alkynic ketone. Reduction of the alkynic ketone (**16**) with 3 equiv of the complex at -15 °C gave a 17:1 ratio of the two diastereomers (22*R*/22*S*) in 94% yield, to provide a key intermediate for the synthesis of a vitamin D_2 metabolite.[13]

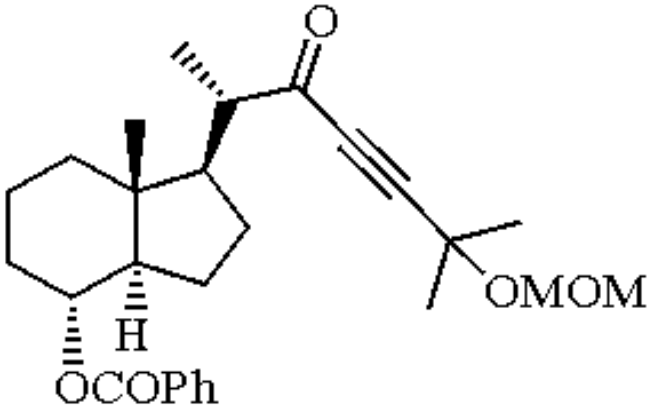

(16)

The enantioselective reduction of cyclic conjugated enones may be best accomplished using a complex of LAH with (**11**) to which EAP has been added.[14,15] Optimum conditions for these reductions involve treatment of the ketone with 3 equiv of a 1:1:2 complex of LAH-(-)-(**11**)-EAP in ether at -78 °C for 3 h (Table 3). However, under these conditions, acetophenone is reduced to the (*R*)-alcohol in only 54% ee.

Table 3 Reduction of Ketones with LAH/(-)- **(11)**/EAP to give (*R*)-Alcohols

Ketone	Yield (%)	ee (%)
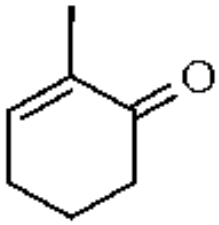	82	96
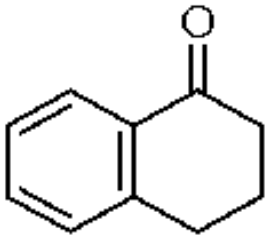	93	96
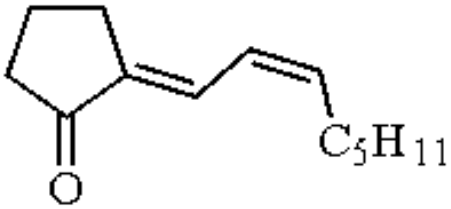	91	96

It has been found that the addition of 2 equiv of NEA to a 1:1 complex of LAH and (-)-(**11**) in ether produces a reagent capable of reducing some α,β-unsaturated ketones to the (*S*)-alcohols in good optical purities at -78 °C (Table 4).[16] It is interesting to note that, with this reagent, the (*S*)-alcohol is the product that is formed preferentially.

Table 4 Reduction of Ketones with LAH/(-)- **(11)**/NEA to give (*S*)-Alcohols

Ketone	Yield (%)	ee (%)
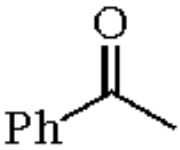	87	86
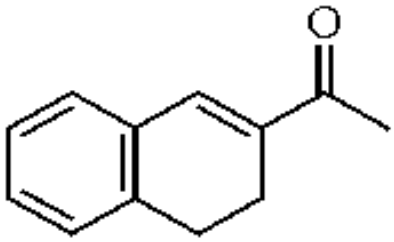	100	>90
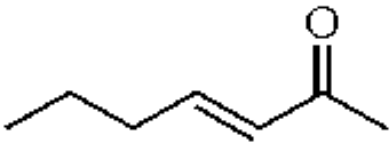	92	88
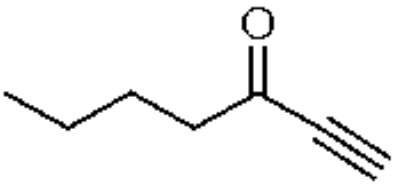	88	76
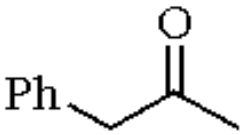	90	41

The preparation and use of a polymer supported LAH-ephedrine-DMP reducing reagent has been reported.[17] In preparing this reagent, ephedrine is attached to a 1% crosslinked polystyrene backbone prior to mixing with LAH and DMP. Careful control of the degree of functionalization of the polymer gives a reducing reagent comparable in efficacy to the analogous nonpolymeric complex.

The use of the complex formed between LAH and Chirald (often called Darvon alcohol in the literature) (**12**) for the reduction of conjugated enones and ynones was first reported by Yamaguchi and Mosher.[18] The mode of preparation of the complex, its age, and the precise experimental conditions of the reduction all appear to have significant impact on the enantioselectivities obtained using this reagent. Thus when 1.5 equiv of a freshly prepared complex of LAH and Chirald (1:2.3) is used to reduce acetophenone at 0 °C, the (*R*)-alcohol is obtained in 68% ee and nearly quantitative yield. If however, the reagent is allowed to stir overnight, or is refluxed in ether prior to the addition of the ketone, the (*S*)-

enantiomer is obtained in 66% ee and 43% yield. Unfortunately, this observed reversal in stereochemical outcome is not predictable. Hence, it may be preferable to use the complex of LAH with the enantiomer of Chirald to reverse the stereoselectivity of the reduction.[19]

A number of alkynic ketones have been reduced with the complex of LAH and (**12**) (1.1:2.5 equiv, ether, -78 °C, 30-60 min) to give the corresponding (*R*)-alcohols (Table 5).[20,21] Johnson and co-workers have reported[22] the reduction of ynone (**17**) to the (*R*)-alcohol in 84% ee and 95% yield with the LAH-Chirald complex. The resulting alcohol was an intermediate in an enantioselective synthesis of 11α-hydroxyprogesterone.[22] The thiophene ketone (**18**) is reduced by the same reagent in ether at -70 °C for 16 h to give the (*R*)-alcohol in 85-88% ee and 80-90% yield.[23] The resulting alcohol has been used in the synthesis of LY248686, an inhibitor of serotonin and norepinephrine uptake carriers.

Table 5 Reduction of Alkynic Ketones with LAH/(-)-**(12)** to give (*R*)-Alcohols

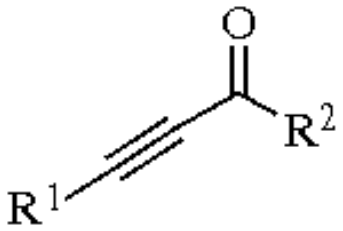

R^1	R^2	Yield (%)	ee (%)
H	C_5H_{11}	96	72
TMS	C_5H_{11}	96	66
C_5H_{11}	C_5H_{11}	97	62

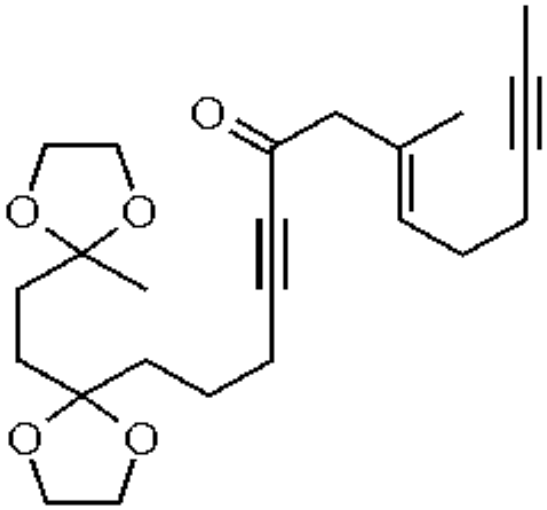

(17)

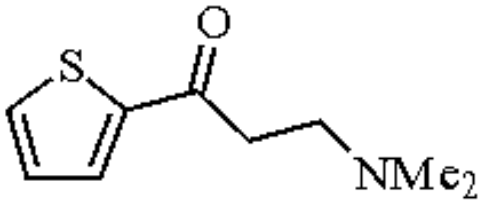

(18)

A macrocyclic alkynic ketone has been protected as the Co derivative and then reduced with the complex of LAH with (**12**)

(eq 1). Deprotection gave the (*R*)-alcohol (71% ee) which was an important intermediate in a synthesis of (+)-α-2,7,11-cembratriene-4,6-diol.[24]

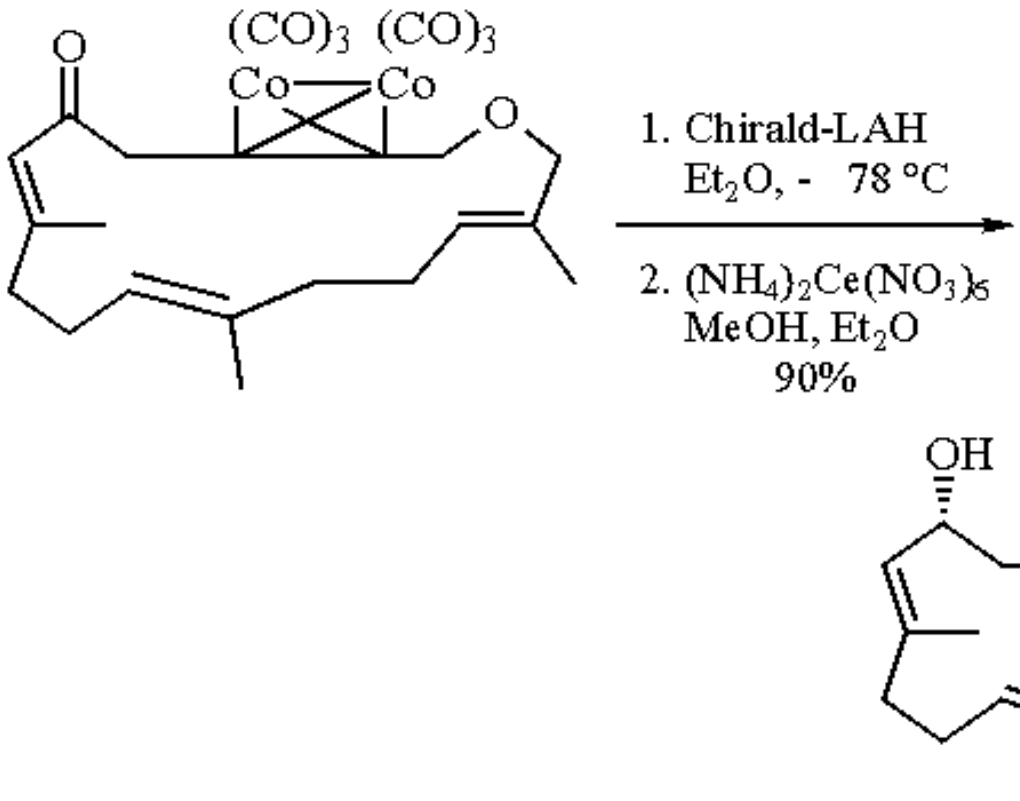

(1)

In general, structural variations to the backbone of the Chirald ligand have not led to the development of more selective or reliable LAH complexes for use in asymmetric reductions.[25] Other complexes of amino alcohols with LAH have been studied for their ability to achieve enantioselective reduction of prochiral ketones. However, in most cases the selectivities observed have been moderate.[26] The complex of LAH with the amino alcohol (**15**) reduces some enones, such as cyclohexenone and cyclopentenone, to the corresponding (*S*)-alcohols in high optical purities (100% and 82% ee, respectively).[27]

Chiral Amine Modifying Agents.

Some chiral amine additives (Figure 4) have also been studied for their potential to give useful chiral LAH reagents, but the results so far have not been very promising. An exception to this is the complex of LAH with the chiral aminopyrrolidine (**19**) (R = Me), which reduces aromatic ketones in good ee.[28] This reagent reduces acetophenone in 95% ee and 87% chemical yield. LAH complexes of diamine ligands (**20**), analogs of BINAL-H, have also been prepared and examined.[29] In general, the optical purities obtained with this reagent are significantly lower than those observed for BINAL-H in the reduction of aryl ketones.

---

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Lithium Aluminum Hydride-Chromium(III) Chloride[1]

$LiAlH_4$-$CrCl_3$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Chromium(III) Chloride · (MW 37.96) ($CrCl_3$)

[10025-73-7] · Cl_3Cr · Lithium Aluminum Hydride-Chromium(III) Chloride · (MW 158.35)

(reducing agent for reductive dimerization of allylic halides,[2] halide reduction,[2,3] and reductive alkylation of carbonyls[2,4,5])

Physical Data: see ***Lithium Aluminum Hydride***.

Solubility: sol THF, DMF, HMPA.

Form Supplied in: prepared in situ from commercially available compounds.

Preparative Method: by adding lithium aluminum hydride to anhydrous chromium(III) chloride suspended in THF at 0 °C under an argon atmosphere. A small amount of zinc metal helps solubilize the chromium(III) chloride. A 2:1 molar ratio of chromium(III) chloride to lithium aluminum hydride yields the most effective reagent.[2]

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride***. Bottles of the lithium aluminum hydride-chromium(III) chloride reagent should be refrigerated and stored under argon.

Reductive Dimerization of Allylic Halides.

Chromium(II) Chloride is commercially available but expensive and susceptible to oxidation.[6] One method of generating Cr^{II} ions in situ is through reduction of chromium(III) chloride with lithium aluminum hydride. Allylic and benzylic halides are reduced by this reagent to give mainly head-to-head coupling products (eq 1).[2]

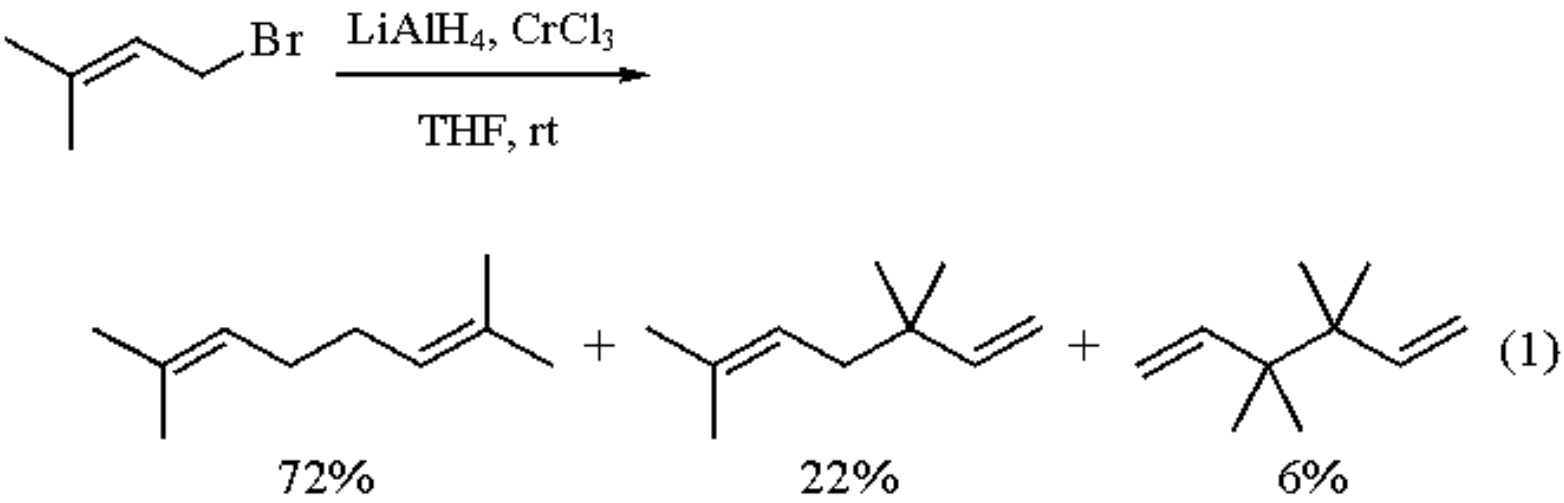

Halide Reduction.

gem-Dibromocyclopropanes are reduced by the title reagent to give allenes (eq 2).[2] Propargylic alkynes are also reduced to form allenes. Addition of HMPA favors allene formation over alkyne formation (eq 3).[3] α-Bromo ketones are reduced to ketones (eq 4).[2]

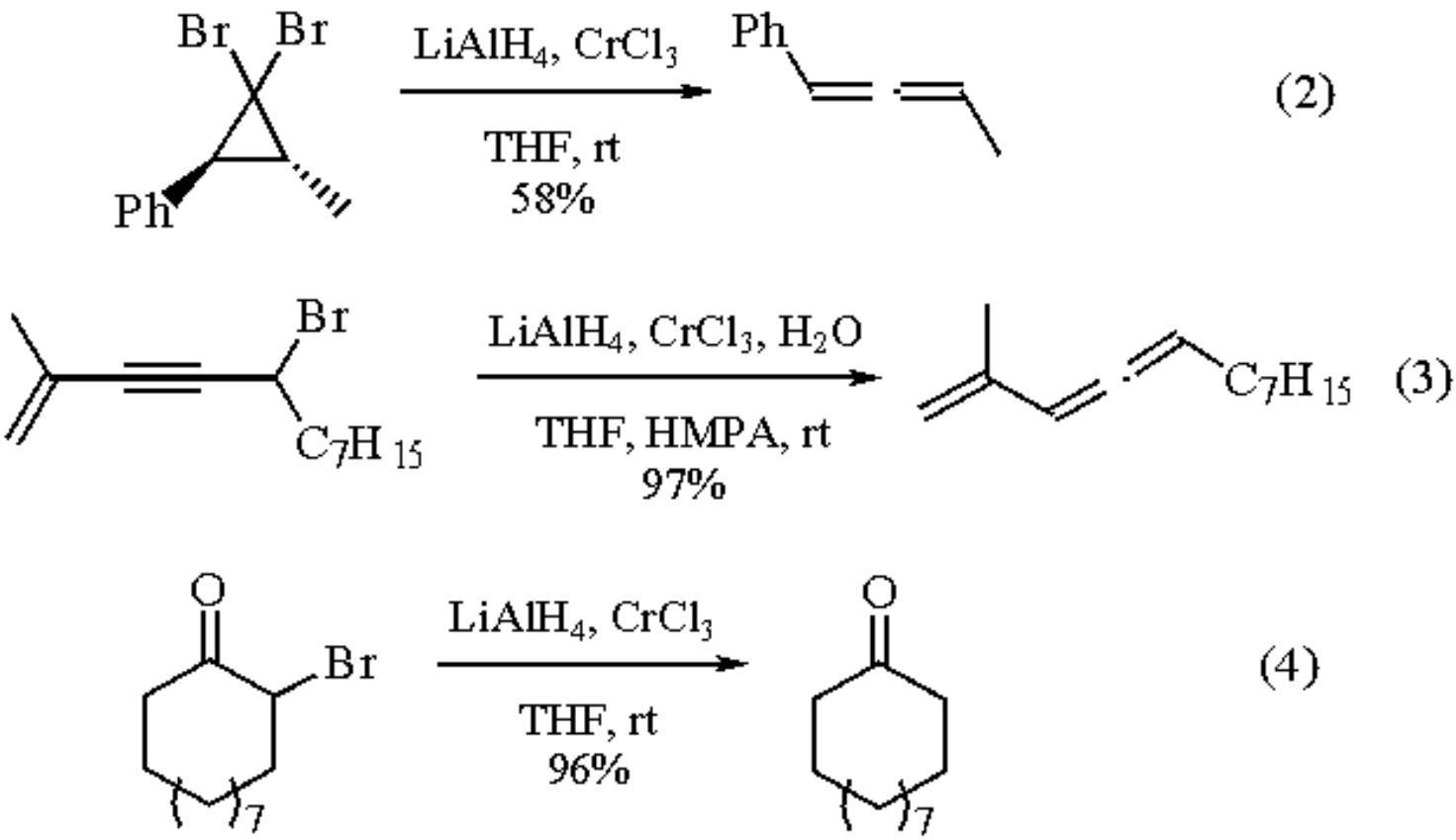

Reductive Alkylation of Carbonyls.

Treatment of aldehydes and ketones with allylic halides in the presence of $LiAlH_4$-$CrCl_3$ gives carbonyl addition products (eq 5). Generally, the more substituted carbon of the allylic halide adds to the carbonyl carbon, affording

homoallylic alcohols.[7] Acetals, esters, and nitriles are not affected by the reagent and aryl, vinyl, and alkyl halides are not reduced. Aldehydes are more reactive than ketones, and 1,2-addition occurs with α,β-unsaturated carbonyls.[2]

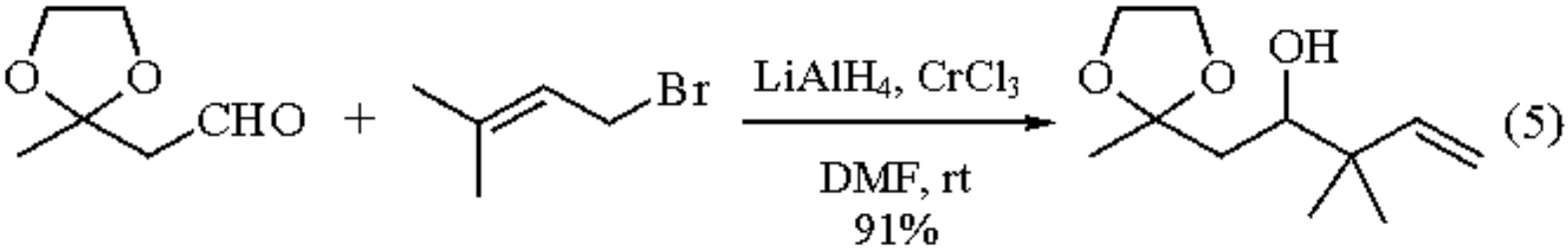

Chiral α-substituted aldehydes frequently give low asymmetric induction, but in some cases, chiral allylic halides (eq 6)[8] and chiral aldehydes (eq 7)[9] have given excellent diastereoselectivity.[10]

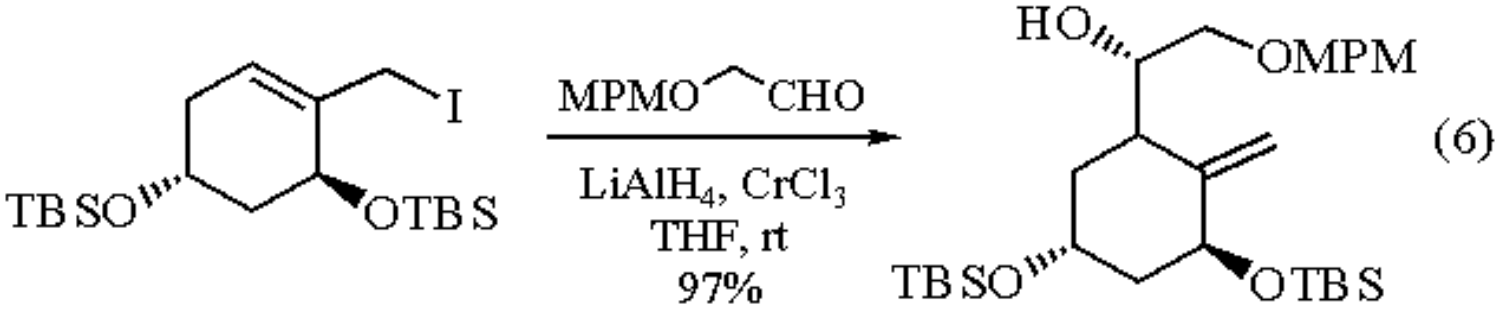

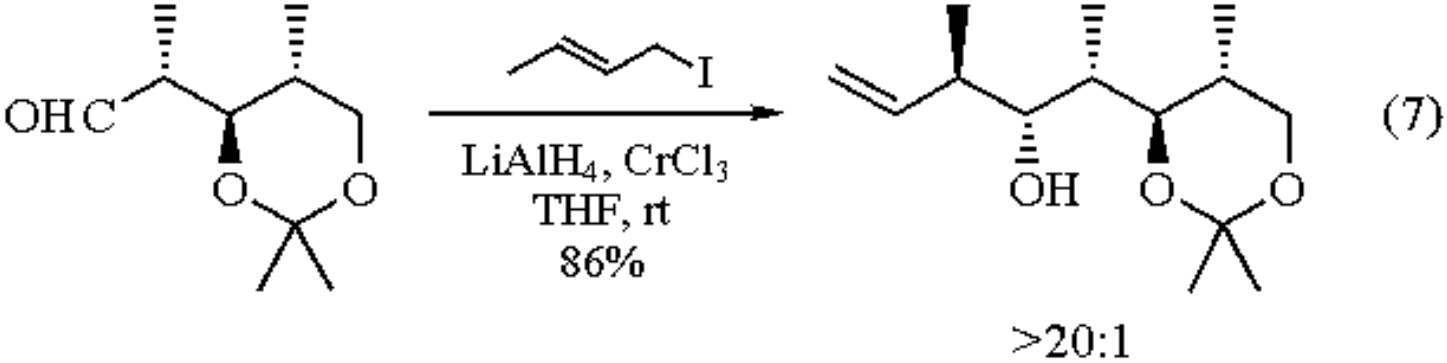

Intramolecular addition of allylic halides to aldehydes is useful for large ring formation (eq 8).[11]

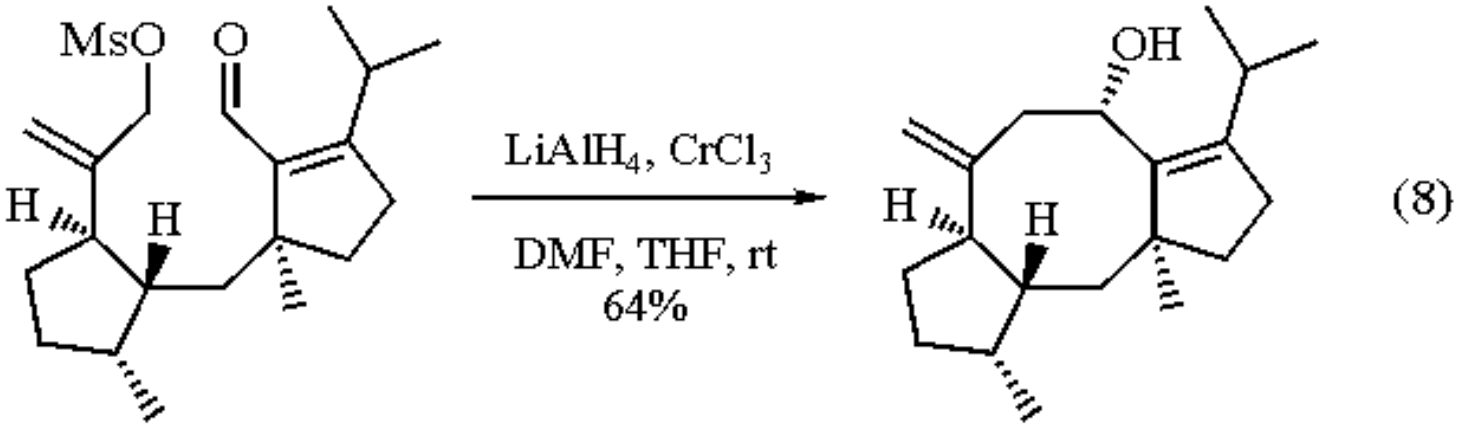

Treatment of aldehydes and ketones with propargyl bromide and $LiAlH_4$-$CrCl_3$ gives allenic alcohols (eq 9).[5]

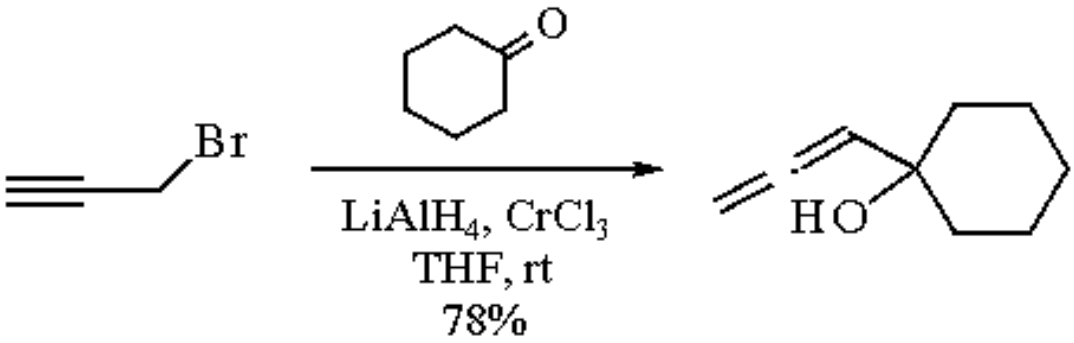

(9)

Alkynyl halides have been coupled with aldehydes using $LiAlH_4$-$CrCl_3$. 1,2-Addition predominates with α,β-unsaturated aldehydes but ketones are unaffected (eq 10).[4]

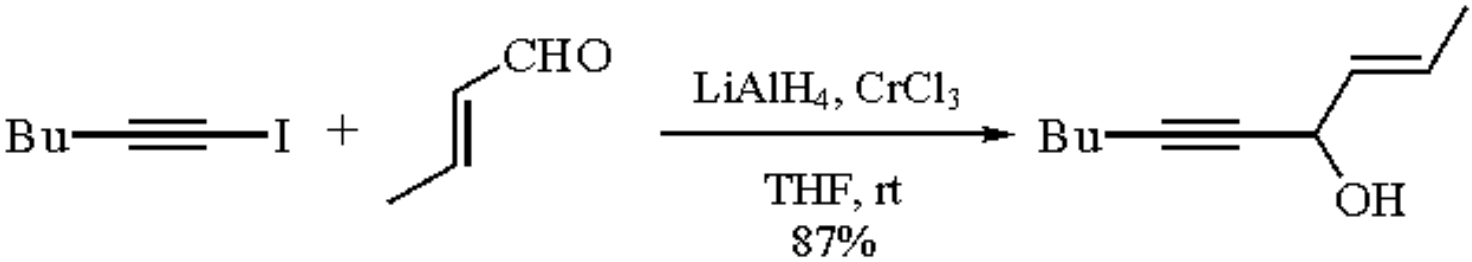

(10)

Aldehydes have been coupled with 2-phenylsulfonyl allylic bromides to give mainly *syn*-homoallylic alcohols (eq 11).[12]

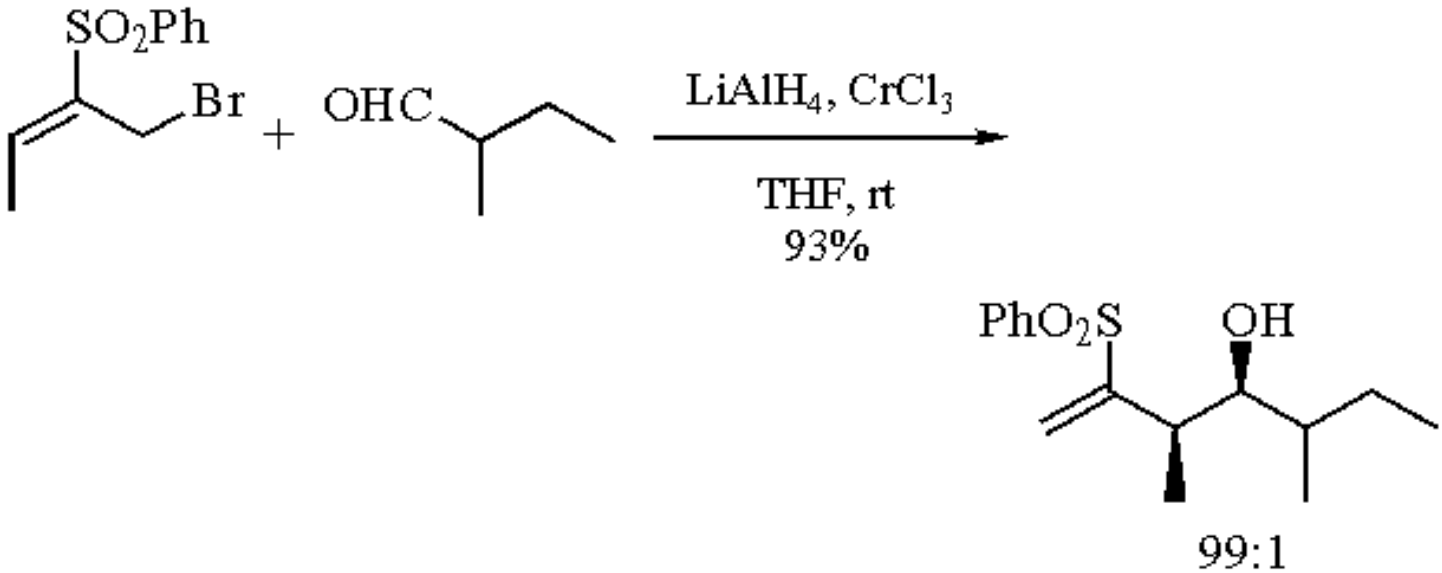

(11)

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Lithium Aluminum Hydride-Cobalt(II) Chloride

$LiAlH_4$-$CoCl_2$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Cobalt(II) Chloride · (MW 37.96) ($CoCl_2$)

[7646-79-9] · Cl_2Co · Lithium Aluminum Hydride-Cobalt(II) Chloride · (MW 129.83)

(reducing agent for alkenes,[1,2] alkynes,[1,2] halides,[1,3,4] and tosylates;[3] catalyst for the reduction of arenes[5])

Physical Data: see ***Lithium Aluminum Hydride*** and ***Cobalt(II) Chloride***

Solubility: see ***Lithium Aluminum Hydride*** and ***Cobalt(II) Chloride***; reactions using this reagent system typically utilize THF as solvent.

Form Supplied in: formed in situ from widely available reagents.

Preparative Method: the organic substrate (1 equiv) in THF is transferred via syringe into a cold (-40 °C) flask containing dry cobalt(II) chloride (1 equiv for stoichiometric use, 0.1 equiv for catalytic use). To this mixture is slowly added the calculated amount of lithium aluminum hydride (1 equiv) in THF solution, which is accompanied by a color change to black, concomitant with the evolution of gas.[1]

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride*** and ***Cobalt(II) Chloride***.

Reduction of Alkenes and Alkynes.

Reduction of alkenes by lithium aluminum hydride alone has historically proven to be an inefficient manipulation. Addition of $CoCl_2$ to the system dramatically overcomes most obstacles to this process. 1-Octene is reduced by $LiAlH_4$-$CoCl_2$ when using the transition metal chloride in either stoichiometric or catalytic amounts (eq 1).[1] Yields in excess of 90% are not atypical for the reduction of mono-, di-, and trisubstituted carbon-carbon double bonds. Eq 2 is illustrative of the efficiency of this reagent.[2] Benzene is reported to have been fully reduced in 76% yield in the presence of hydrogen.[5]

$$Me(CH_2)_5CH{=}CH_2 \xrightarrow{LiAlH_4,\ CoCl_2} Me(CH_2)_6Me \qquad (1)$$

stoichiometric $CoCl_2$, 100%;
catalytic $CoCl_2$, 98%

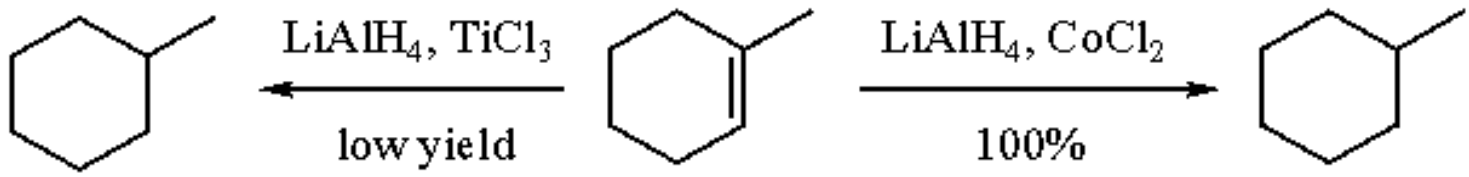

(2)

Alkynes may be reduced to alkenes in similar fashion. Terminal alkynes are reduced to the alkene oxidation state without event (eq 3).[1] However, reduction of aryl-substituted or internal alkynes is typically a low yield process.[1,2] Reduction of these π-systems is postulated to proceed through a metal-hydride reducing agent.[2]

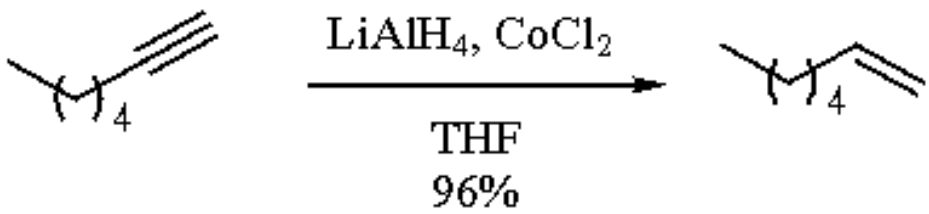

(3)

Reduction of Halides and Tosylates.

The title reagent system is perhaps of most use in the reduction of halides and tosylates. Alkyl halides are reduced in high yield irrespective of the halogen (eq 4).[1,3] Furthermore, *n*-octyl tosylate was reduced in quantitative yield using the catalytic variation of this system. Secondary and tertiary bromides are reduced easily when stoichiometric quantities of the transition metal chloride are used (eq 5).[1,3]

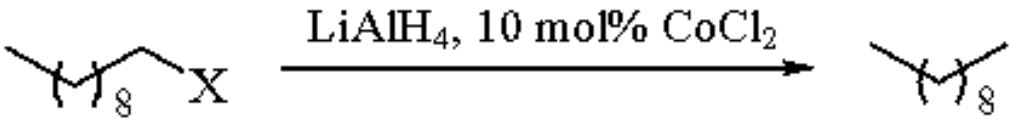

(4)

X = I, 100%; Br, 98%; Cl, 98%; F, 100%

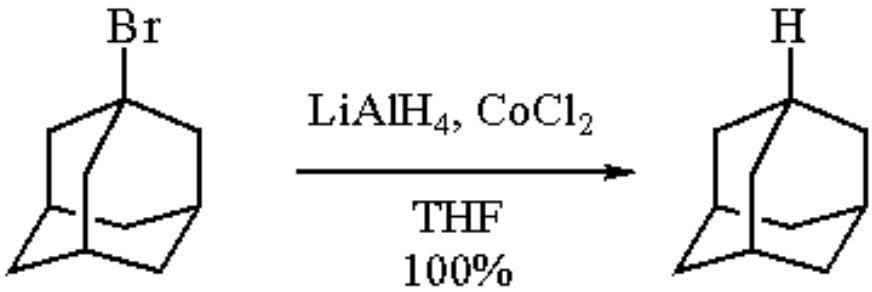

(5)

Replacement of bromine by hydrogen in triarylvinyl bromides, with concomitant loss of stereochemical integrity where applicable, has been achieved in high yield.[4] Similarly, phenyl bromide and iodide are reduced to benzene in 74% and 98% yield, respectively, when stoichiometric amounts of $CoCl_2$ are utilized.[3]

The use of ***Nickel(II) Chloride*** as the transition metal chloride provides a reagent that behaves similarly to the cobalt(II) chloride system, often giving higher yields.[3]

---

1. Ashby, E. C.; Lin, J. J. *TL* **1977**, *18*, 4481.
2. Ashby, E. C.; Lin, J. J. *JOC* **1978**, *43*, 2567.
3. Ashby, E. C.; Lin, J. J. *JOC* **1978**, *43*, 1263.
4. Obafemi, C. A.; Lee, C. C. *CJC* **1990**, *68*, 1998.
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Lithium Aluminum Hydride-Copper(I) Iodide

AlH_2I

[58602-50-9] · AlH_2I · Lithium Aluminum Hydride-Copper(I) Iodide · (MW 155.90)

(in situ prepared hydridoaluminum reagent; 1,4-reduction of enones[1,2])

Alternate Name: aluminum hydride iodide.

Physical Data: (.2THF): mp 165-166 °C.[3]

Preparative Methods: an anhydrous THF solution of ***Lithium Aluminum Hydride*** (1 mmol) is added dropwise to a suspension of dry ***Copper(I) Iodide*** (4 or 2 mmol)[1] in THF maintained at 0 °C under an inert atmosphere. A deep black color is immediately produced with hydrogen gas evolution. After stirring for 3-20 min at 0 °C, the substrate (1 mmol) is added and stirring is continued for 15-60 min. The reaction is quenched with water and treated with a saturated aqueous ammonium chloride solution. Ether is added and the organic layer is dried.[4]

Modifications.

An important modification of the method utilizes HMPA as the co-solvent and a reaction temperature of -78 °C. In this case, the reactive agent is thought to be LiHCuI.[2] Copper(I) iodide can be replaced with ***Copper(I) Bromide***,[5-7] ***Copper(I) t-Butoxide***, or ***Mesitylcopper(I)***.[8]

The alane $HAl[N(i\text{-}Pr)_2]_2$ as well as the boron derivative HBI_2 are effective at conjugate reduction of α,β-unsaturated ketones.[9]

Enones.

The reagent prepared in THF at 0 °C is AlH_2I and not CuH or $CuAlH_4$.[1] This reagent reduces α- and β-substituted ketones in high yield (eqs 1-4). The *cis* analog of (**1**) is reduced to (**2**), albeit at a much slower rate. Cyclohexen-2-one is not reduced to cyclohexanone in THF at 0 °C;[4] however, the enone is readily reduced at -78 °C when HMPA is added.[2] This method is used to reduce *trans*-hex-2-enal to hexanal in 63% yield, along with 12% of the 1,2-reduced product.

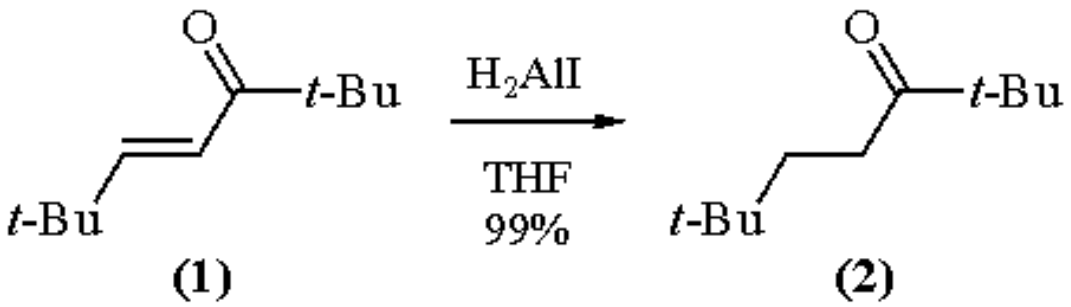

(1)

(2)

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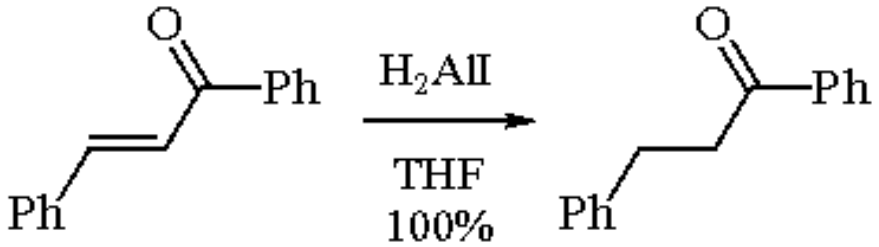

(4)

The HMPA-THF method was used to reduce α,β-unsaturated ester (**3**),[10] the unsaturated ketone (**4**),[11] and the bicyclic enone (**5**) (eq 5).[12] This method was used for other 1,4-reductions of enones.[13-16] Interestingly, the cyclohexenone (**6**) was reduced by the $LiAlH_4$-CuI-THF method. This reduction required 6 equiv of $LiAlH_4$ and 24 equiv of CuI to produce ketone (**7**) in 40% yield (eq 6). The corresponding triene diols were also isolated.[17]

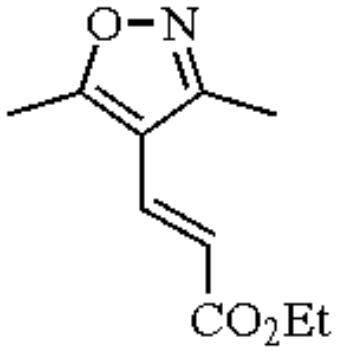

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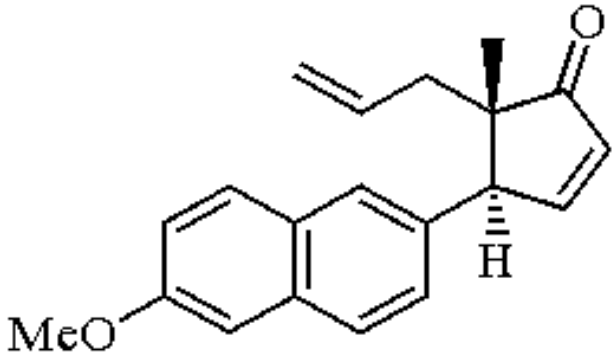

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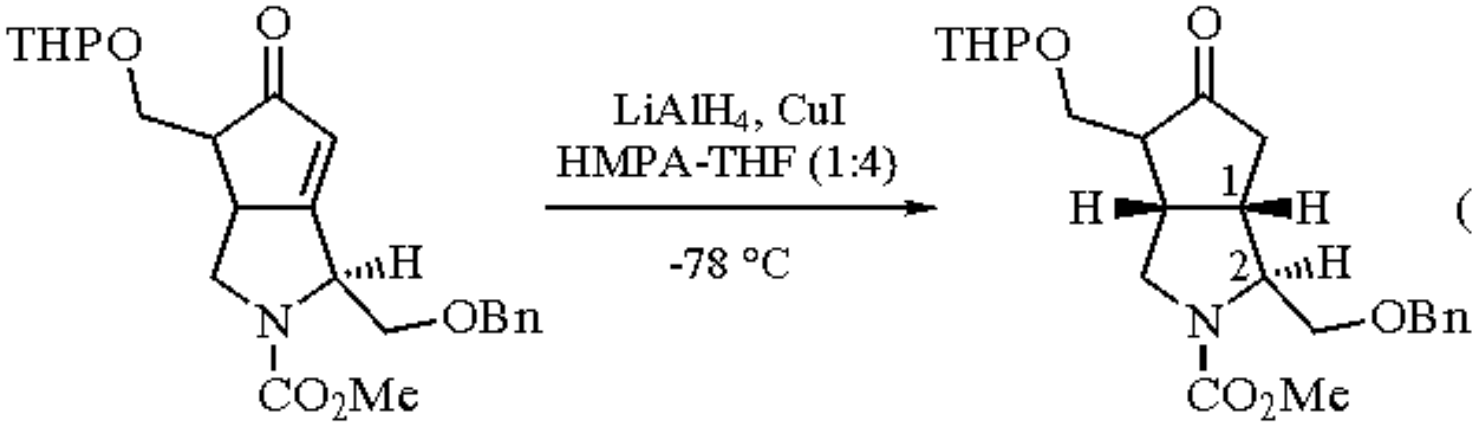

(5)

(5)

60%
plus *cis*-1,2 isomer
10%

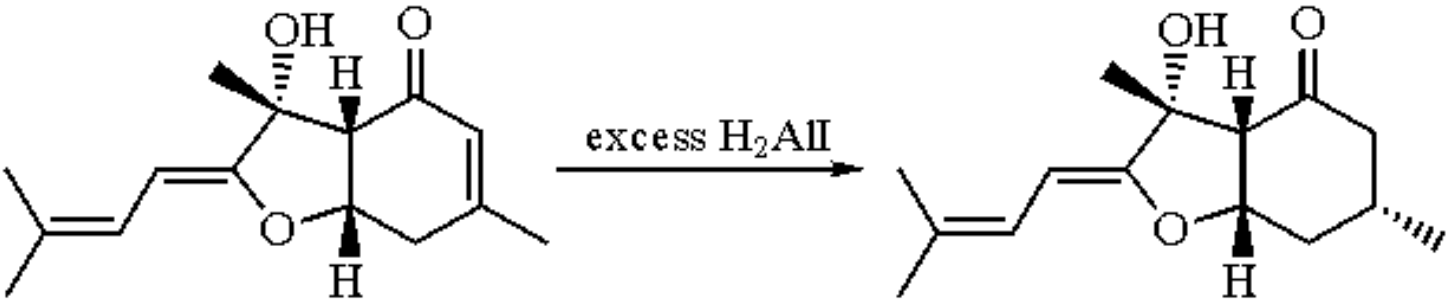

(6)

(6)

(7)

Limitation.

Treatment of enone (**8**) with $LiAlH_4$-CuI-THF produced only the alcohol (**9**), whereas the ***Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride*** method produced the desired ketone (**10**) (eq 7).[18]

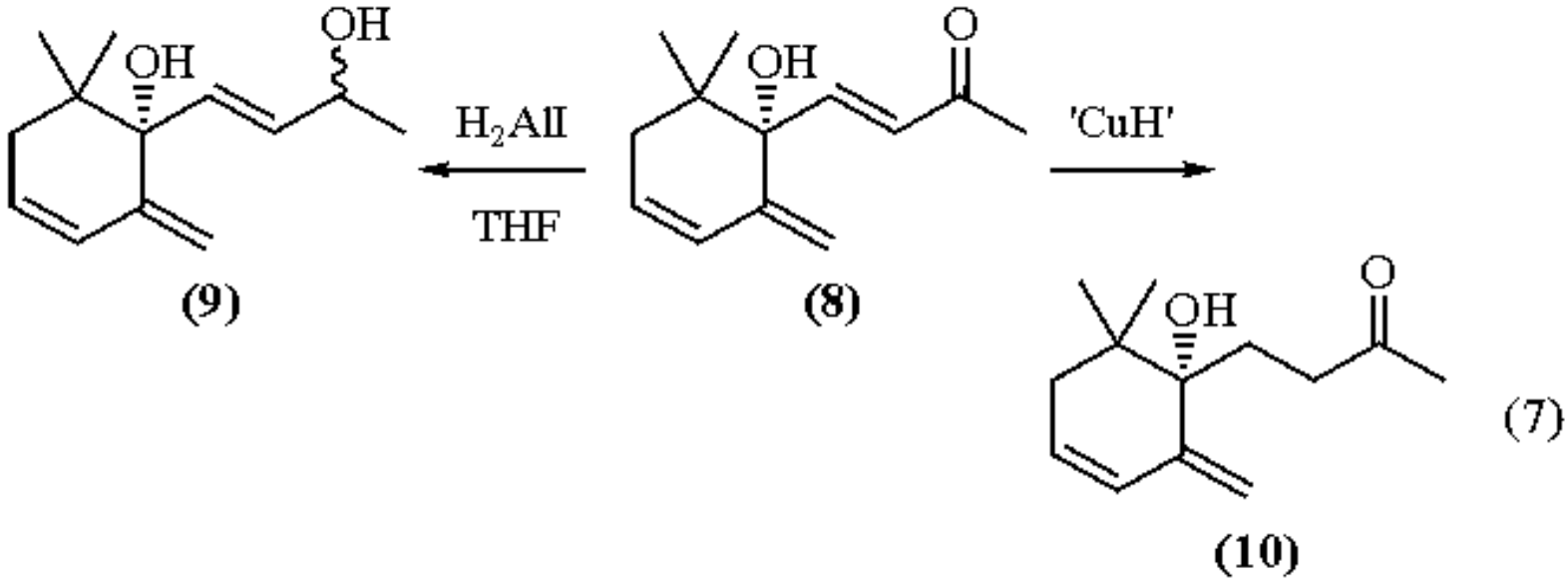

Alternative Methods.

For a discussion on alternative methods of 1,4-reduction of enones, see ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***.

---

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Lithium Aluminum Hydride-Diphosphorus Tetraiodide

$LiAlH_4$-P_2I_4

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Diphosphorus Tetraiodide · (MW 37.96) (P_2I_4)

[13455-00-0] · I_4P_2 · Lithium Aluminum Hydride-Diphosphorus Tetraiodide · (MW 569.54)

(reducing system for converting aromatic ketones to hydrocarbons)

Physical Data: see ***Lithium Aluminum Hydride***. Diphosphorus tetraiodide: mp 125-128 °C.

Form Supplied in: see ***Lithium Aluminum Hydride***. Diphosphorus tetraiodide: orange needles (recrystallized from methylene chloride); available commercially or can be prepared from PCl_3 and KI.[1]

Analysis of Reagent Purity: see ***Lithium Aluminum Hydride***.

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride***. Diphosphorus tetraiodide: should be protected from light, and stored under nitrogen.

Reductions of Aromatic Ketones to Hydrocarbons.

This combination of reagents (1:1 ratio) reduces aromatic ketones to hydrocarbons in refluxing benzene solvent (eqs 1-3).[2] The process may be used to introduce deuterium via use of $LiAlD_4$ (eq 4).[3]

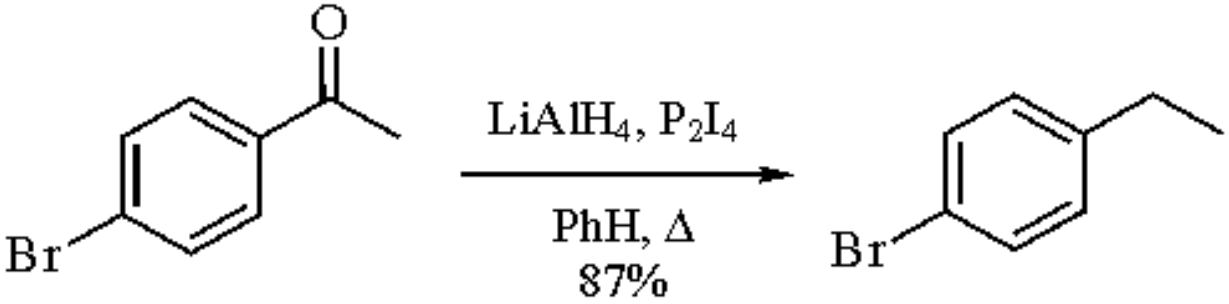

(1)

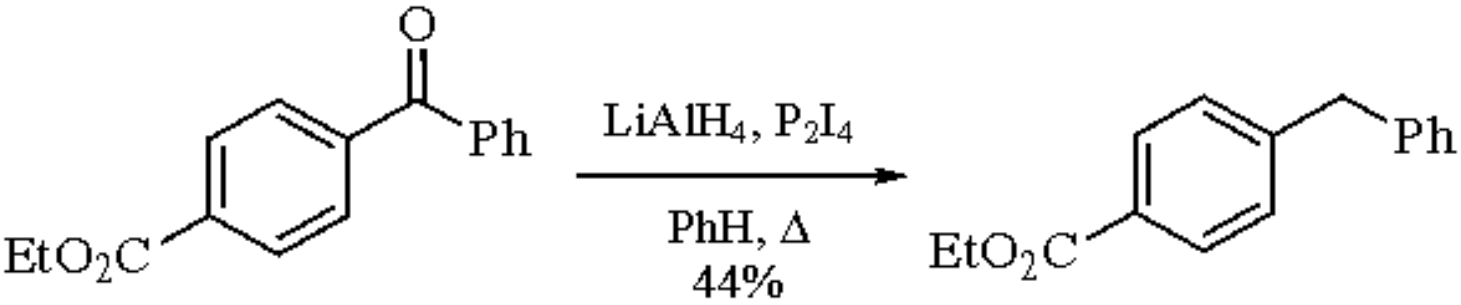

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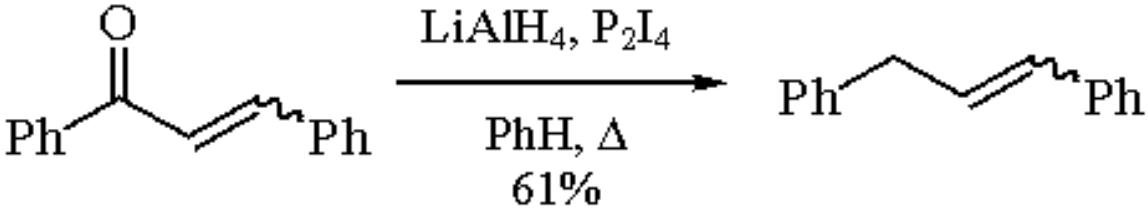

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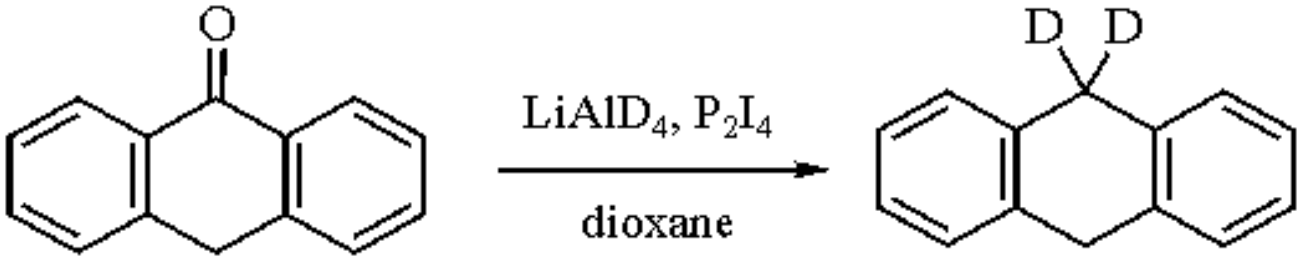

(4)

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Lithium Aluminum Hydride-Nickel(II) Chloride[1]

$LiAlH_4$-$NiCl_2$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Nickel(II) Chloride · (MW 37.96) ($NiCl_2$)

[7718-54-9] · Cl_2Ni · Lithium Aluminum Hydride-Nickel(II) Chloride · (MW 129.59)

(reducing agent for alkenes, alkynes,[2,3] and organic halides;[2,4] can effect N-O bond cleavage and open epoxides.[5])

Physical Data: see ***Lithium Aluminum Hydride*** and ***Nickel(II) Chloride***.

Solubility: see ***Lithium Aluminum Hydride*** and ***Nickel(II) Chloride***; reactions using the mixture are run in THF.

Form Supplied in: prepared in situ from commercially available components.

Preparative Method: nickel(II) chloride (1 equiv for stoichiometric reactions and 0.1 equiv for catalytic reactions) is placed in the reaction vessel at -40 °C and the organic substrate (1 equiv) in THF is added using a syringe. Lithium aluminum hydride (1 equiv) in THF is added slowly, resulting in a black color and gas evolution.

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride*** and ***Nickel(II) Chloride***.

Halide Reductions.

Reductions of organic halides using lithium aluminum hydride and nickel(II) chloride are more efficient than reductions using lithium aluminum hydride alone.[2,4] This mixed reagent converts primary chlorides, bromides, iodides, and tosylates into the corresponding alkanes in near quantitative yields using only a catalytic amount of the nickel species (eq 1). High yields are also realized using stoichiometric amounts of metal halide in the reduction of secondary, tertiary, and aryl chlorides, bromides, and iodides (eqs 2 and 3). These reductions may also be carried out with similar results using ***Iron(II) Chloride***, ***Cobalt(II) Chloride***, or ***Titanium(III) Chloride*** as the metal halide.

$$Me(CH_2)_7I \xrightarrow[NiCl_2]{LiAlH_4} Me(CH_2)_6Me \qquad (1)$$

98%, cat $NiCl_2$

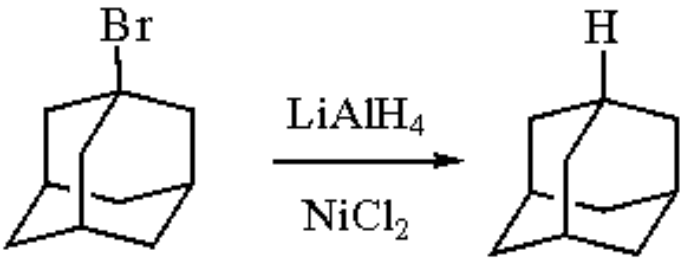

(2)

100%, stoich. $NiCl_2$

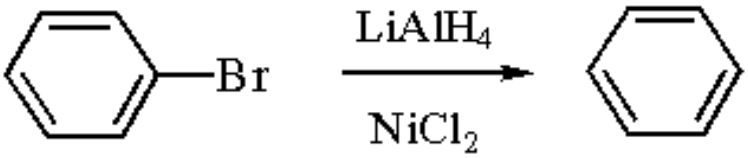

(3)

87%, cat. $NiCl_2$
100%, stoich. $NiCl_2$

Furthermore, triarylvinyl halides can be reduced to the corresponding hydrocarbons using $LiAlH_4$-$NiCl_2$ at temperatures below 0 °C (eq 4).[6]

$$Ph_2C{=}C(Br)Ph \xrightarrow[95\%]{} Ph_2C{=}C(H)Ph \qquad (4)$$

The strong reducing nature of this reagent has limited its use in synthesis, as many other functional groups do not survive the conditions. For example, esters are reduced faster than tertiary halides (eq 7).[7]

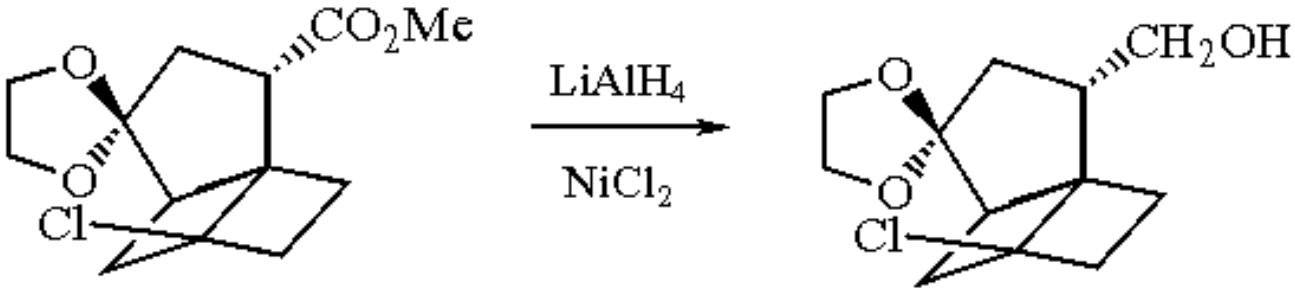

(5)

Reduction of Carbon-Carbon Double and Triple Bonds.

The admixture of lithium aluminum hydride-nickel(II) chloride has been used to efficiently reduce alkenes to the corresponding alkanes and to effect the partial reduction of an alkyne to an alkene.[2,3] Such transformations require only catalytic amounts of the nickel species for monosubstituted alkenes or alkynes, but higher orders of substitution require stoichiometric amounts of nickel(II) chloride (eqs 6-8). Cobalt(II) chloride works equally well when used as the metal halide species for these reductions.

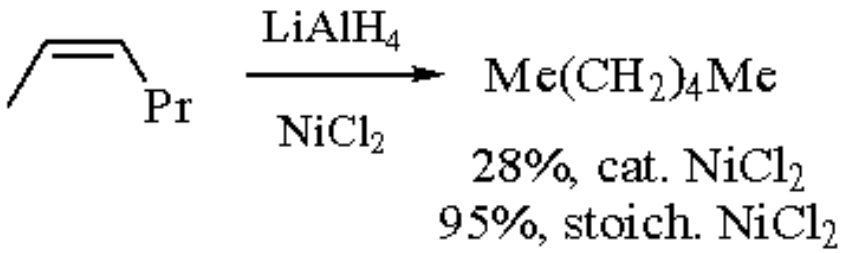

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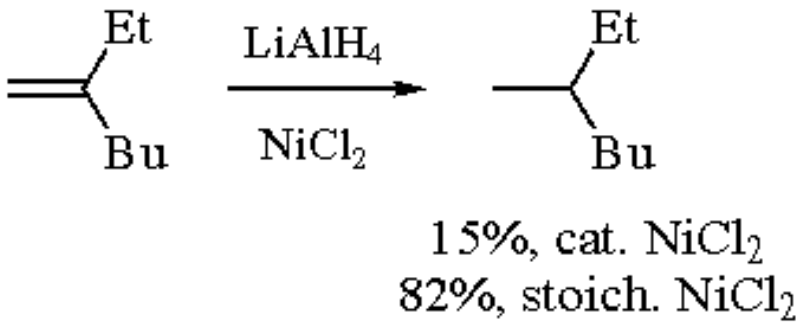

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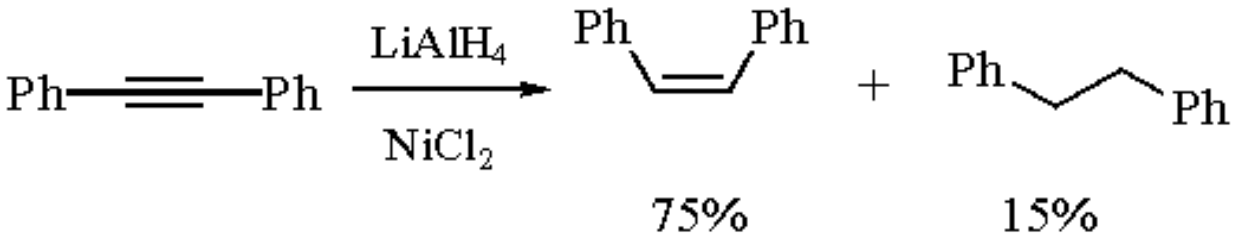

(8)

This mixed reagent has been used to reduce alkenes in the presence of ethers and acetals (eq 9),[8] but fails to selectively reduce triple bonds in the presence of esters.[9]

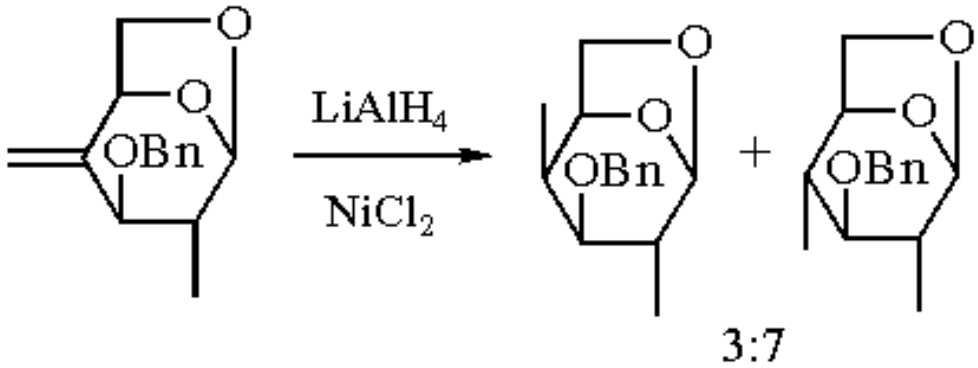

(9)

Cleavage of N-O Bonds and Epoxide Opening.

Amino alcohols have been prepared in high yield from isoxazolidines with $LiAlH_4$-$NiCl_2$ (eq 10). This mixed reagent

has also been used to open epoxides to alcohols.[5] This admixture reacts with styrene oxide to yield β-phenylethanol (eq 11). In contrast, use of lithium aluminum hydride alone gives α-phenylethanol.

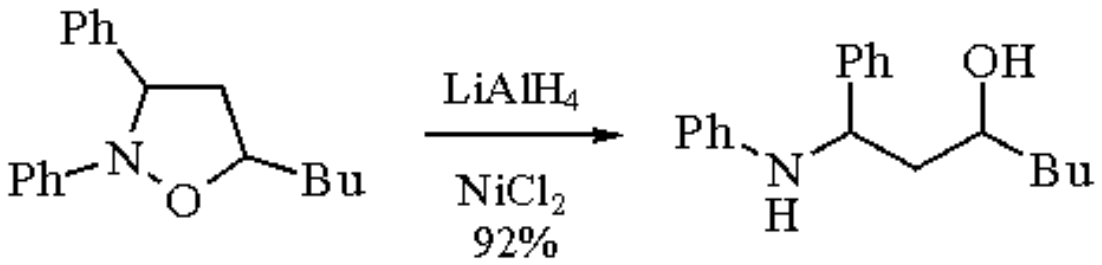

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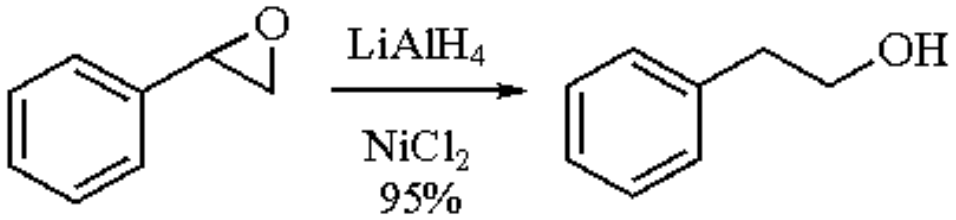

(11)

Reduction of an N-O bond with lithium aluminum hydride-nickel(II) chloride has been used in an approach to anatoxin *a* (eq 12).[5] Initial N-O bond cleavage gives an epoxide which is opened by the reducing agent to give an alcohol.

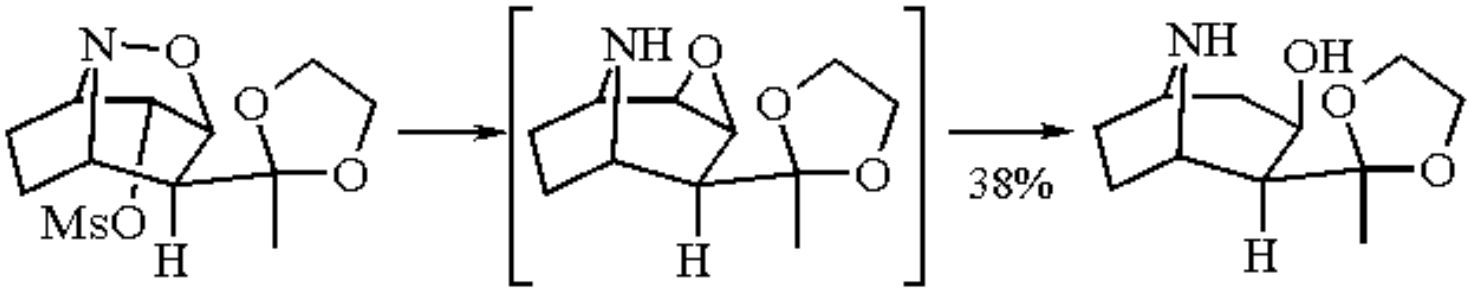

(12)

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Lithium Aluminum Hydride-Titanium(IV) Chloride[1]

$LiAlH_4$-$TiCl_4$

($LiAlH_4$)

[16853-85-3] · AlH_4Li · Lithium Aluminum Hydride-Titanium(IV) Chloride · (MW 37.96) ($TiCl_4$)

[7550-45-0] · Cl_4Ti · Lithium Aluminum Hydride-Titanium(IV) Chloride · (MW 189.68)

(generation of dihalocarbenes;[2,3] hydrogenolysis of allylic alcohols;[4] deoxygenation of oxygen-bridged compounds[9,10] and *N*-oxides;[12] preparation of alkenes;[15] reducing agent for sulfoxides,[17] alkenes, alkynes,[18] and 3-amido ketones;[20] catalyst for hydroaluminations of alkenes and alkynes[22])

Physical Data: see ***Lithium Aluminum Hydride*** and ***Titanium(IV) Chloride***.

Solubility: see ***Lithium Aluminum Hydride*** and ***Titanium(IV) Chloride***; reactions using the mixture are run in anhydrous THF or diethyl ether.

Form Supplied in: for most applications, the reagent is prepared in situ from commercially available components.

Preparative Method: for applications involving the initial formation of low-valent titanium, lithium aluminum hydride (1 equiv) is added under nitrogen to a cooled (0 °C) solution of titanium(IV) chloride (1 equiv) in anhydrous THF, resulting in a black suspension with gas evolution.[13] The molar ratio of $LiAlH_4$ and $TiCl_4$ can vary and the addition of various organic tertiary amine bases following the addition of $LiAlH_4$ is also common.

Handling, Storage, and Precautions: see ***Lithium Aluminum Hydride*** and ***Titanium(IV) Chloride***. Use in a fume hood.

Generation of Dihalocarbenes.

Carbon tetrachloride reacts with $LiAlH_4$-$TiCl_4$ in the presence of alkenes to provide *gem*-dichlorocyclopropanes (eq 1).[2] The reaction conditions are slightly acidic, in contrast to other methods that require strongly basic conditions. 1-Chloro-1-fluorocyclopropanes can be prepared in good yields using $CFCl_3$ and low-valent titanium (eq 2).[3] Other methods of generating chlorofluorocarbene in the presences of alkenes give lower yields.

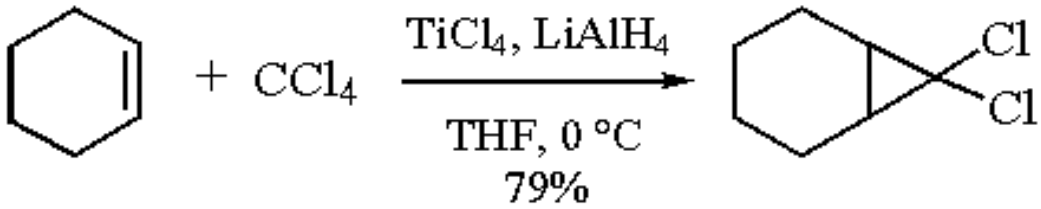

(1)

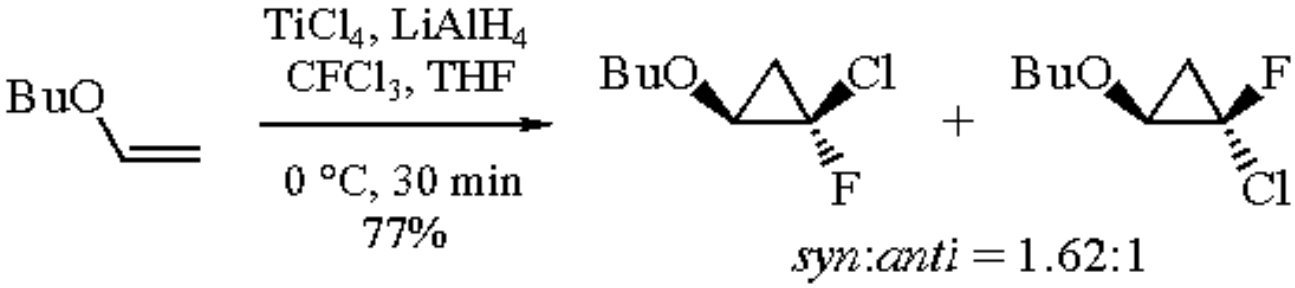

(2)

Deoxygenations.

Secondary allylic alcohols react with $LiAlH_4$-***Aluminum Chloride*** and $LiAlH_4$-$TiCl_4$ in a similar fashion to provide hydrogenolysis products in fair yields.[4] However, upon reaction with $LiAlH_4$-$AlCl_3$, tertiary allylic alcohols undergo dehydration whereas $LiAlH_4$-$TiCl_4$ gives the expected hydrogenolysis product (eq 3). In some cases, double bond migration occurs via a reductive S_N2' reaction. In a related reaction, reductive demethoxylation of allyl methyl ethers using low-valent titanium is accompanied by double bond migration, providing predominantly the (*Z*)-alkene from either the (*E*)- or (*Z*)-allyl ethers (eq 4).[5]

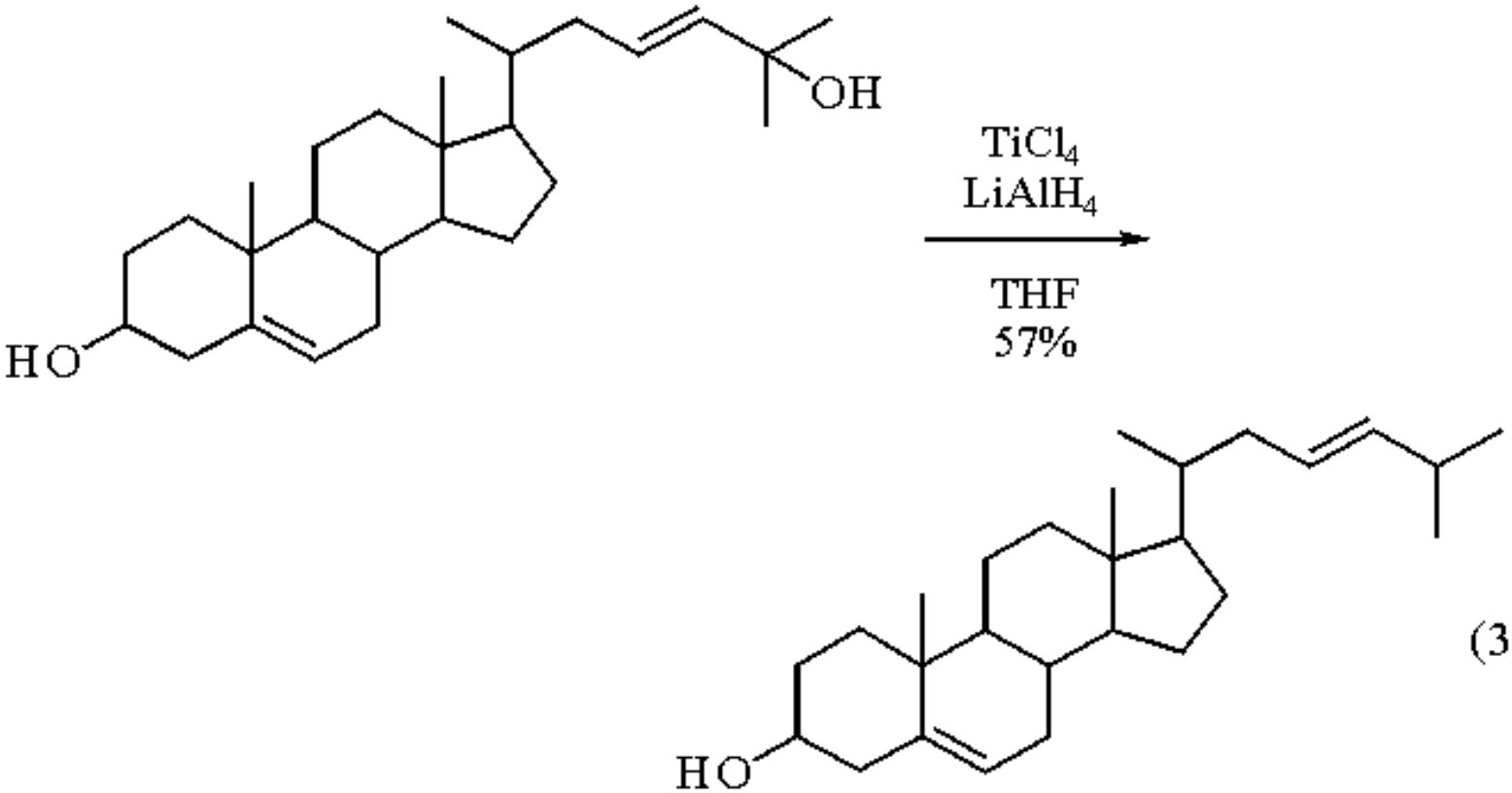

(3)

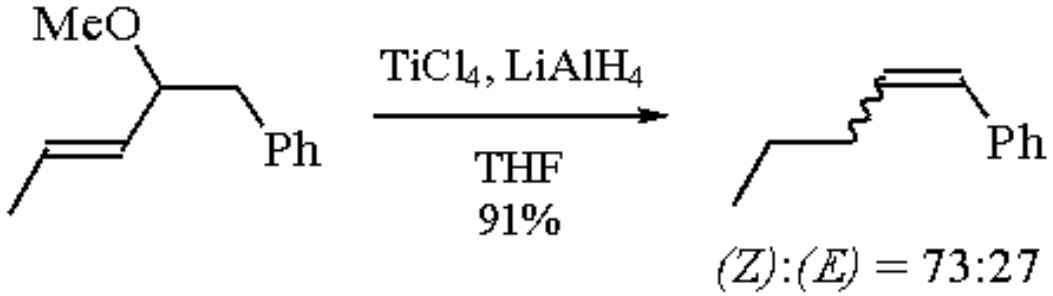

(4)

Photooxygenation of (-)-β-pinene followed by reduction of the resulting peroxide to the corresponding alcohol and then treatment with low-valent titanium provides a simple route to (-)-α-pinene via hydrogenolysis of the allylic alcohol (eq 5).[6] The peroxide also provides (-)-α-pinene upon treatment with low-valent titanium.

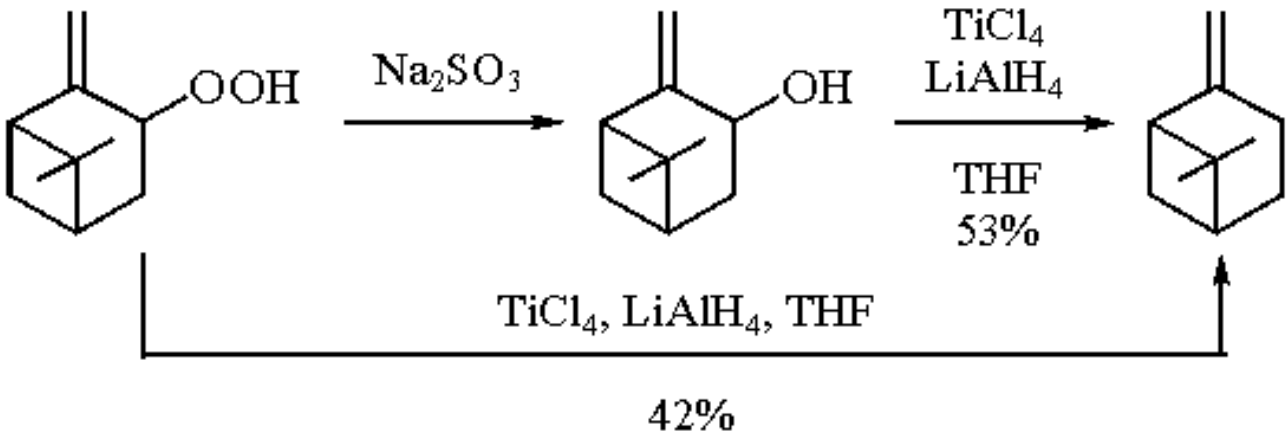

(5)

Alkenes can be prepared from epoxides with low-valent titanium generated from ***Titanium(III) Chloride*** and $LiAlH_4$.[7] The same reduction with $TiCl_4$ in the presence of ***Triethylamine*** has been used to prepare a key intermediate in the synthesis of *trans*-γ-irone (eq 6).[8]

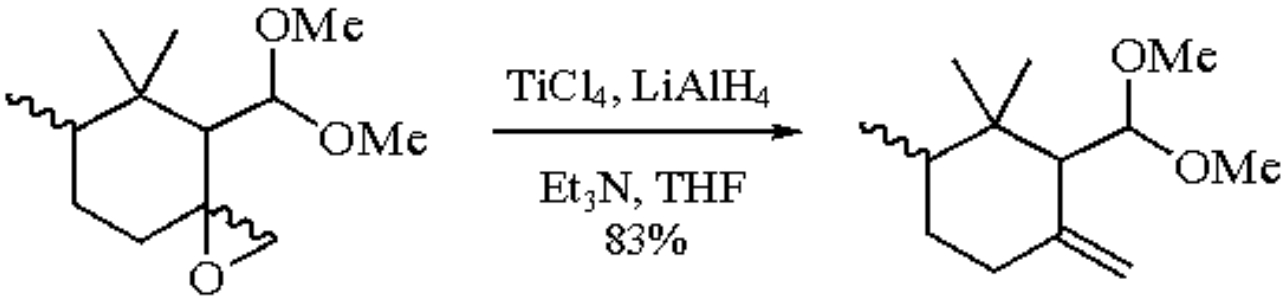

(6)

Low-valent titanium has been used to deoxygenate furan cycloadducts in the preparation of arenes (eq 7).[9] Substituted furan adducts provide substituted benzenes with $LiAlH_4$-$TiCl_4$ in the presence of triethylamine, while in the absence of triethylamine, 1,3-cyclohexadienes are obtained (eq 8).[10]

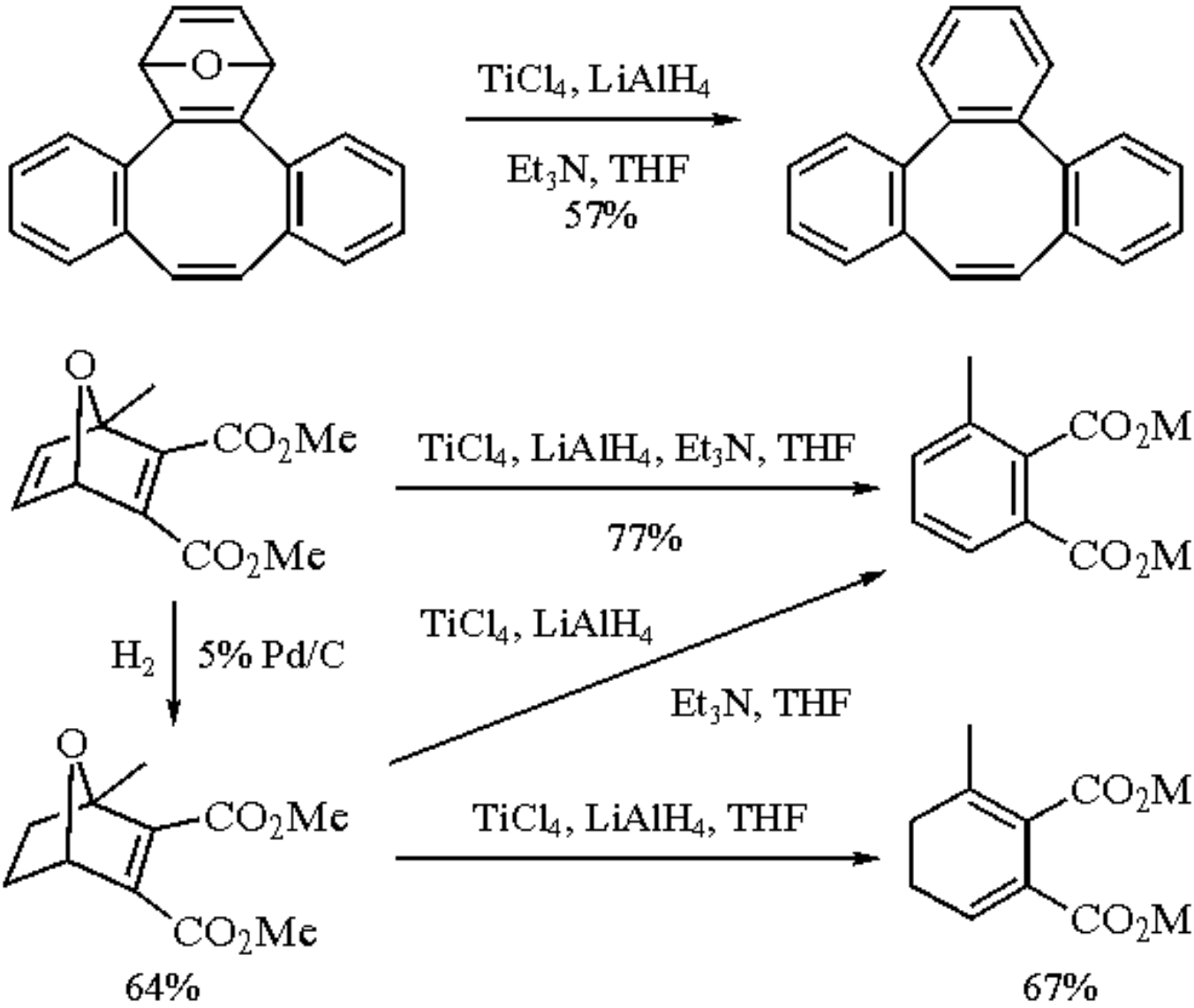

A third pathway involves the presence of small amounts of triethylamine and results in reduction of the enedicarboxylate portion of the molecule without deoxygenation (eq 9).[11] Isolated double bonds are not reduced using low-valent titanium, but $LiAlH_4$-$TiCl_4$ does reduce diethyl maleate to diethyl succinate in 59% yield.

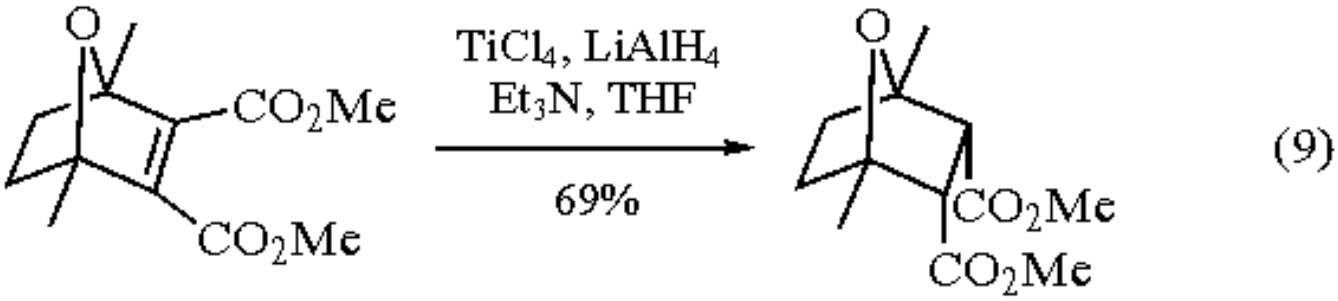

Aromatic *N*-oxides, typically resistant to deoxygenation, can be reduced under mild conditions using low-valent titanium.[12] These conditions have been used to reduce heteroaromatic *N*-oxides with labile halogen atoms *ortho* and *para* to the ring nitrogen (eq 10).[13] These compounds do not undergo dehalogenation, but it has been reported that 1-chloronaphthalene is reduced to naphthalene in 83% yield under similar conditions.[14]

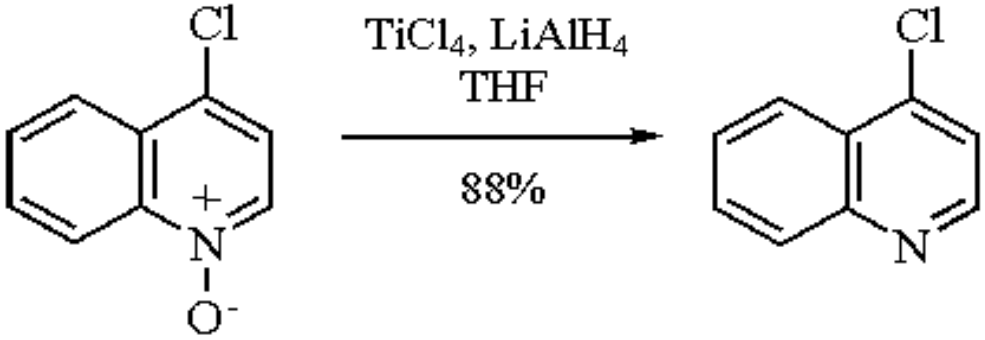

(10)

Reductive Couplings.

Upon treatment with low-valent titanium in the presence of tertiary amines, carbonyl compounds undergo reductive dimerization in high yields to produce symmetrical alkenes (eq 11).[15] Acetals of aromatic aldehydes and ketones couple to provide pinacol ethers or alkenes in high yields (eq 12), while dialkyl acetals derived from aliphatic aldehydes and ketones provide ethers as a result of reductive dealkoxylation (eq 13).[16]

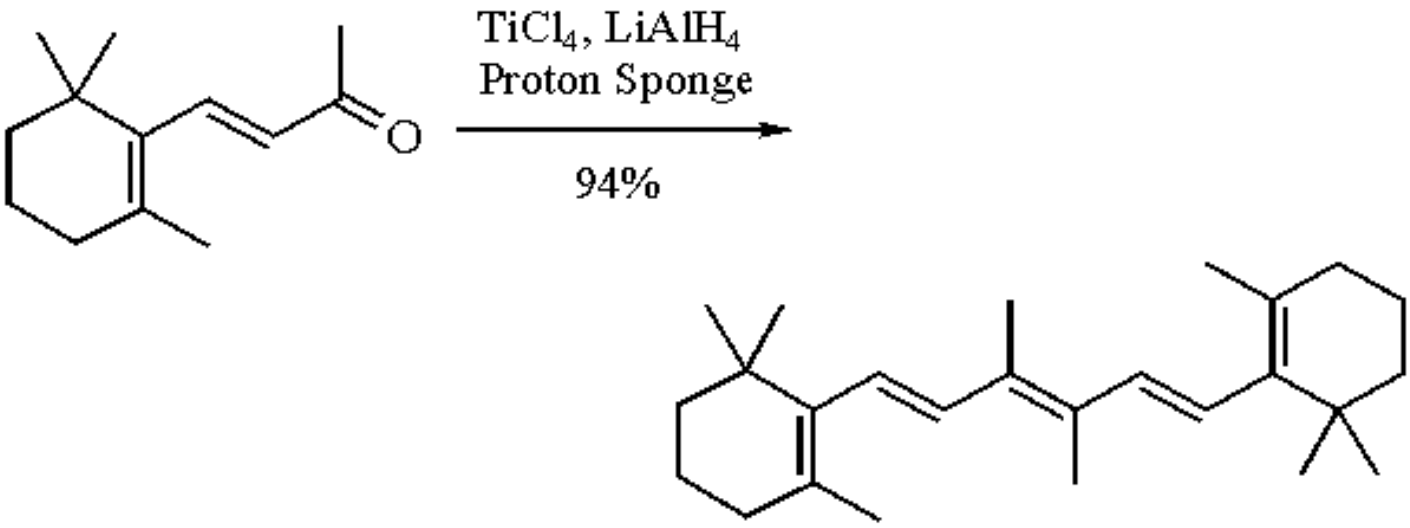

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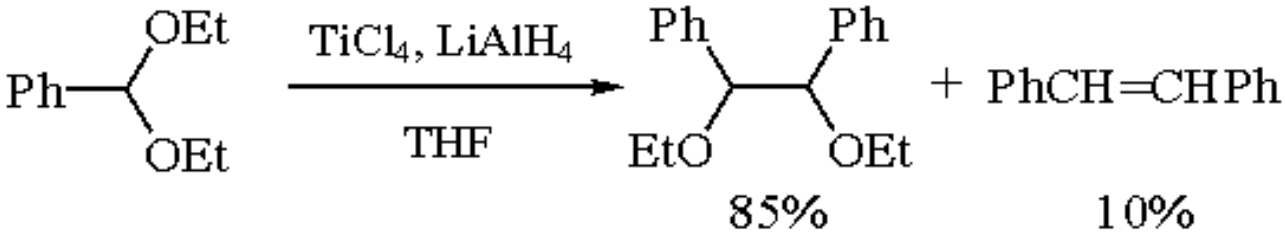

(12)

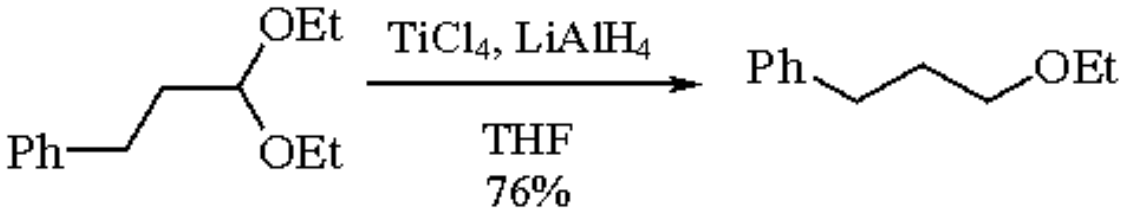

(13)

Miscellaneous Reductions.

Lithium aluminum hydride/titanium(IV) chloride provides a mild method for the reduction of sulfoxides to the corresponding sulfides (eq 14).[17] Yields are generally higher than when $LiAlH_4$ is used alone and reductions are complete within 2 h at or below room temperature. Complex formation between the metal ion and the sulfinyl oxygen has been invoked to explain the effect that $TiCl_4$ has in facilitating this reduction.

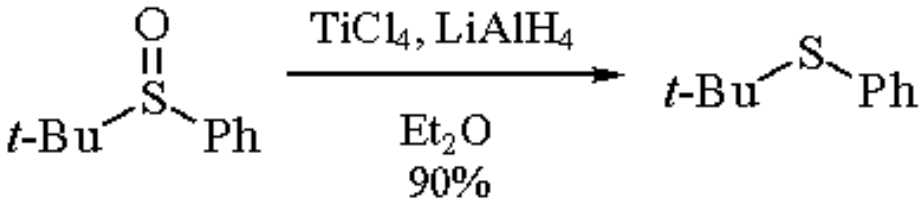

(14)

Sulfides are reduced to the corresponding hydrocarbons in good yield with $TiCl_4$-$LiAlH_4$ in THF at reflux.[14] Terminal alkenes and alkynes are reduced to the corresponding alkanes in good yields using equamolar quantities of $LiAlH_4$ and $TiCl_4$.[18] Disubstituted double bonds are only partially reduced, while internal alkynes give predominately the *cis*-alkene in good yield.

Stereoselective Reductions.

Reduction of 1,3-dicarbonyl compounds with lithium aluminum hydride in the presence of chelating agents such as $TiCl_4$ provides 1,3-diols with good diastereoselectivity (eq 15).[19] Cyclic models have been used to explain the course of reductions (eq 16). It has been suggested that the major isomer is formed via addition of hydride to both carbonyls from the least hindered side.

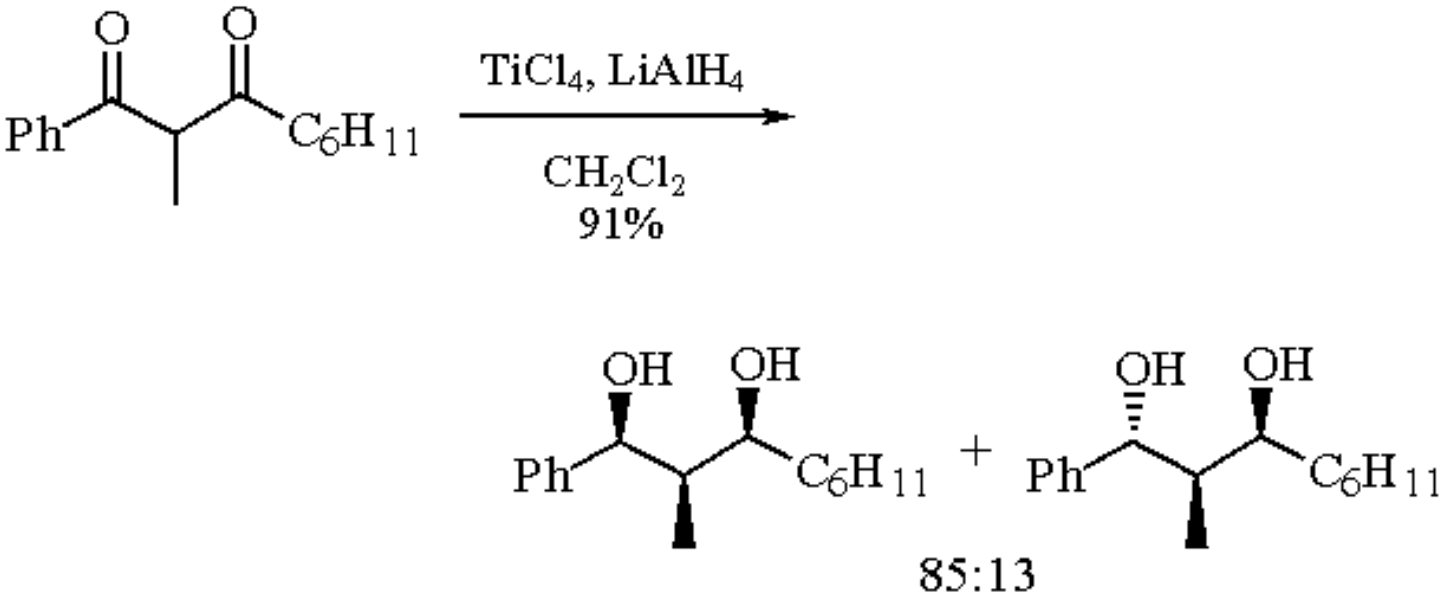

(15)

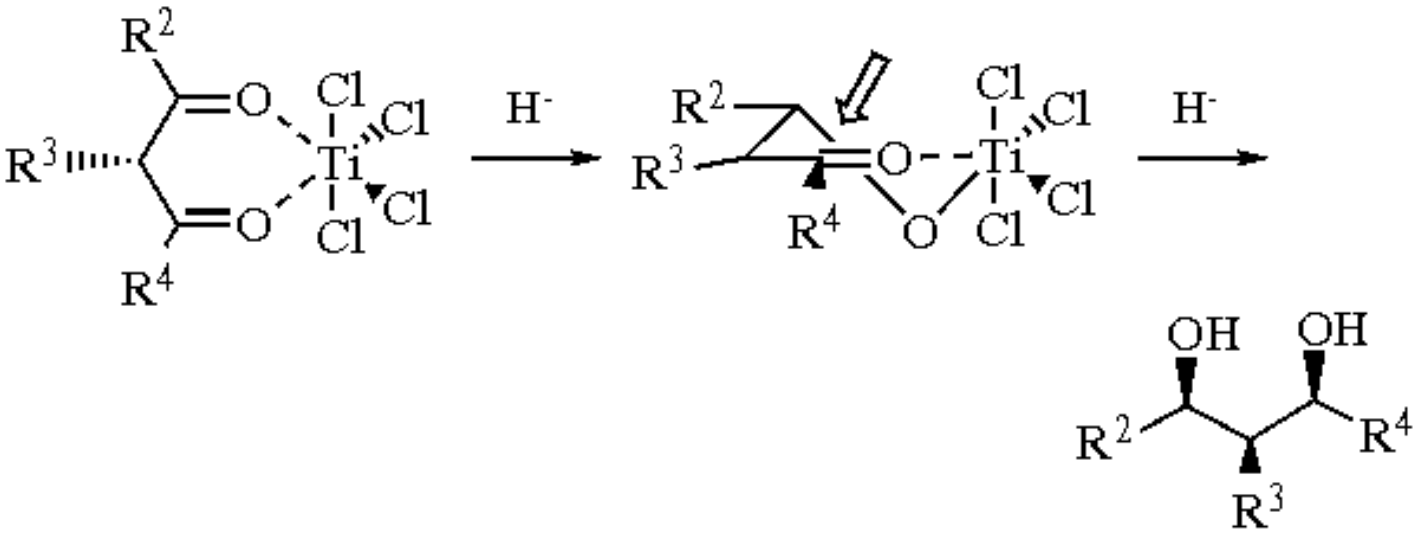

Chelation control with $TiCl_4$ has been applied to the stereoselective synthesis of 1,3-amino alcohols from *anti*-3-amido ketones (eq 17).[20,21] Again the stereochemical results are explained by a rigid cyclic transition state.

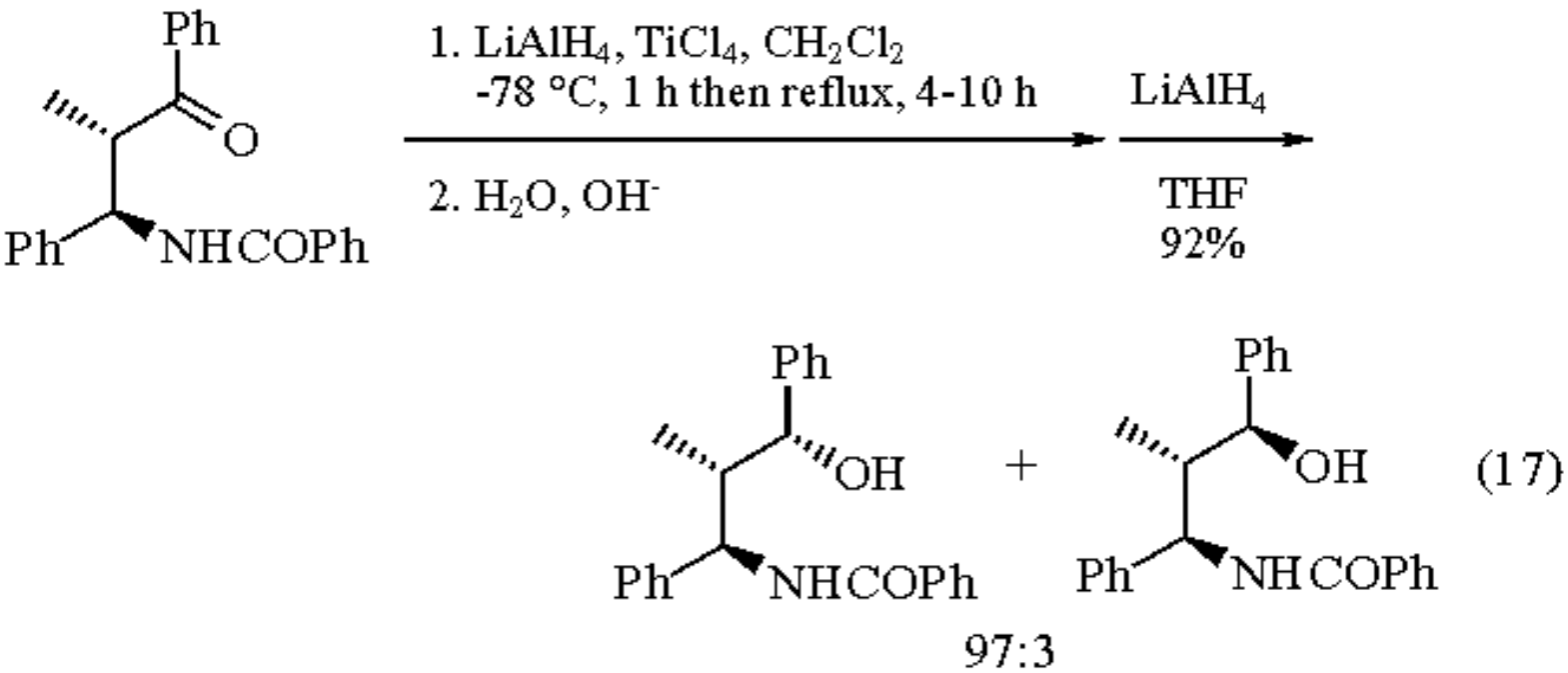

Hydroaluminations.

Titanium(IV) chloride catalyzes the addition of lithium aluminum hydride to alkenes to provide the corresponding organoaluminates in high yields under mild conditions.[22] The relative rates of reaction decrease with increased substitution on the alkene, and with nonconjugated alkenes, $LiAlH_4$ selectively adds to the least hindered double bond. Organoaluminates provide a convenient route to primary acetates,[23] alkyl halides (eq 18),[22,24] and alcohols,[22] terminal allenes[25] and alkynes,[26] alkanes,[22] and trialkenylboranes.[27] Coupling reactions between organoaluminates and allylic halides can be accomplished in the presence of copper(I) salts.[28]

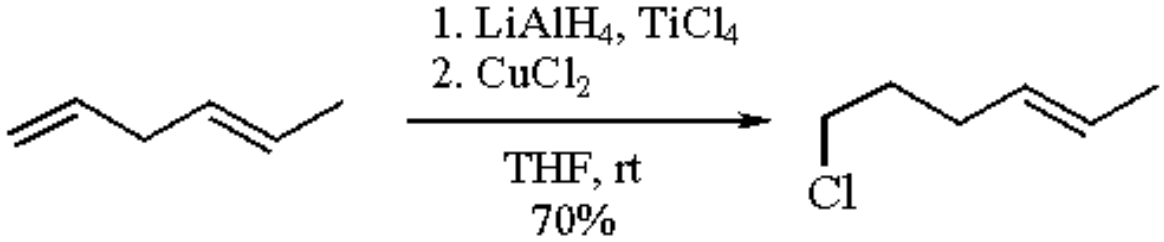

(18)

Methylenation of Carbonyl Compounds.

β-Elimination of 2-(phenylthio)ethanols, prepared via reaction of ketones with phenylthiomethyllithium, occurs with $TiCl_4/LiAlH_4$ in the presence of a tertiary amine to provide the terminal alkene in high yield.[29]

Related Reagents.

Titanium(III) Chloride-Lithium Aluminum Hydride.

---

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24. (a) Sato, F.; Mori, Y.; Sato, M. *CL* **1978**, 833. (b) Sato, F.; Sato, S.; Sato, M. *JOM* **1977**, *131*, C26.
25. Sato, F.; Oguro, K.; Sato, M. *CL* **1978**, 805.
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Lithium Amide[1]

$LiNH_2$

[7782-89-0] · H_2LiN · Lithium Amide · (MW 22.97)

(strong base; used in *N*-alkylation of aromatic amines,[5,6] Claisen condensations,[7] α-alkylations of carbonyl compounds,[13] eliminations[21] and isomerizations,[26] synthesis of ethynyl compounds[16] and alkynyl carbinols[30])

Physical Data: mp 380-400 °C; *d* 1.178 g cm^{-3}.

Solubility: sl sol liq NH_3, ethanol; insol ether, benzene, toluene.

Form Supplied in: gray-white powder; widely available.

Analysis of Reagent Purity: several titration procedures are available.[2]

Preparative Method: in a typical procedure[3] for the preparation of lithium amide in ammonia, a small piece of ***Lithium*** metal is added to commercial anhyd liquid NH_3 with stirring; after the almost immediate appearance of a blue color, a few crystals of iron(III) nitrate are added, followed by small portions of lithium metal; after about 20 min the blue color disappears and a gray suspension of lithium amide is formed.

Handling, Storage, and Precautions: the dry solid is flammable, air- and moisture-sensitive, and must be stored in tightly stoppered bottles; in water, it decomposes slowly when in lumps, faster in smaller particle sizes; like other alkali metal amides, the reagent must be guarded against air oxidation to prevent the formation of potentially explosive substances;[4] samples which develop a yellow or green or darker color should be properly disposed of; if left open for minimal periods during weighing, the titer remains fairly constant; contact with skin causes burns; use in a fume hood.

N-Alkylation of Amines.

Lithium amide has been employed as a powerful base in the *N*-alkylation of heterocyclic aromatic amines.[5] A variety of *N*-substituted 2-aminopyridines, 2-aminopyrimidines, and 2-aminolepidines have been prepared by treating the respective amine with 2 equiv $LiNH_2$ and the alkyl halide (eq 1).[6] Lithium amide is more easily handled than ***Sodium Amide*** and is therefore the reagent of choice in these reactions.

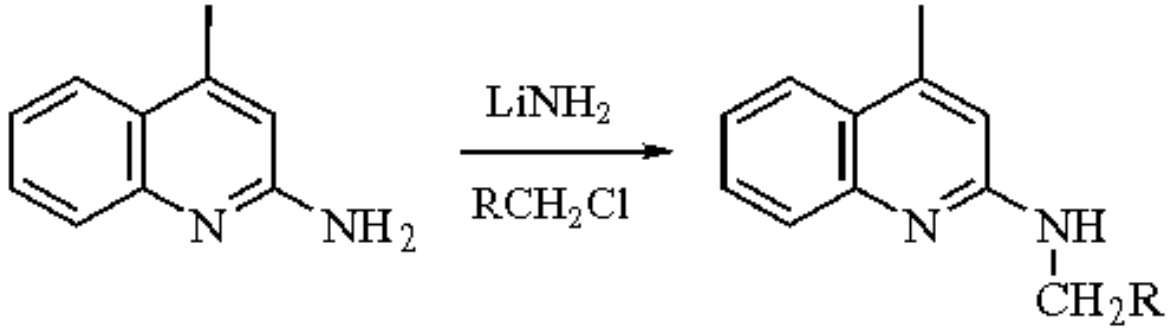

(1)

Condensations of Esters with Carbonyl Compounds.

Hauser and Puterbaugh found $LiNH_2$ superior to sodium amide in condensations of *t*-butyl acetate with ketones (eq 2).[7] Condensations with acetophenone, *p*-nitrocaprophenone, benzaldehyde, acetone, and cyclohexanone proceeded in good yields (53-76%).

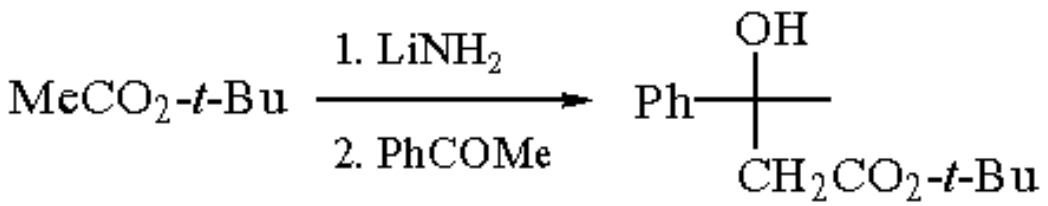

(2)

This condensation method is a useful alternative to the Reformatsky reaction, and in certain cases compares favorably in terms of yields and practicality. Later studies simulated a Reformatsky-type reaction employing *t*-butyl acetate instead of an α-halo ester.[8] It was found that this type of aldol condensation may be effected more conveniently and in higher yields by means of $LiNH_2$, and that the use of ***Zinc Chloride*** was unnecessary in this case. Use of $NaNH_2$ under similar conditions failed to give β-hydroxy esters. Hauser and Lindsay further reported[9] that when ethyl acetate was employed instead of *t*-butyl acetate, self-condensation of the ester could be circumvented by using 2 equiv $LiNH_2$. Under these conditions, even benzophenone could be condensed with ethyl acetate. It is suggested that the extra equivalent of $LiNH_2$ coordinates with the monolithio salt of ethyl acetate, as in (**1**), or in a dimer or trimer. Some sort of coordination is indicated, since an extra equivalent of $LiNH_2$ retards the self-condensation of EtOAc; $NaNH_2$, which should coordinate to a smaller degree, fails to exhibit such a retarding effect under similar conditions.[3,10]

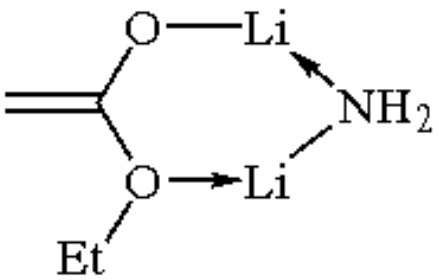

(1)

Ethyl 3-alkoxy-2-butenoates have been condensed with aldehydes in the presence of $LiNH_2$ at the γ-position to give dihydropyrones which, under the basic conditions employed, give rise to 3-alkoxy-*cis*-2-*trans*-4-unsaturated acids (eq 3).[11]

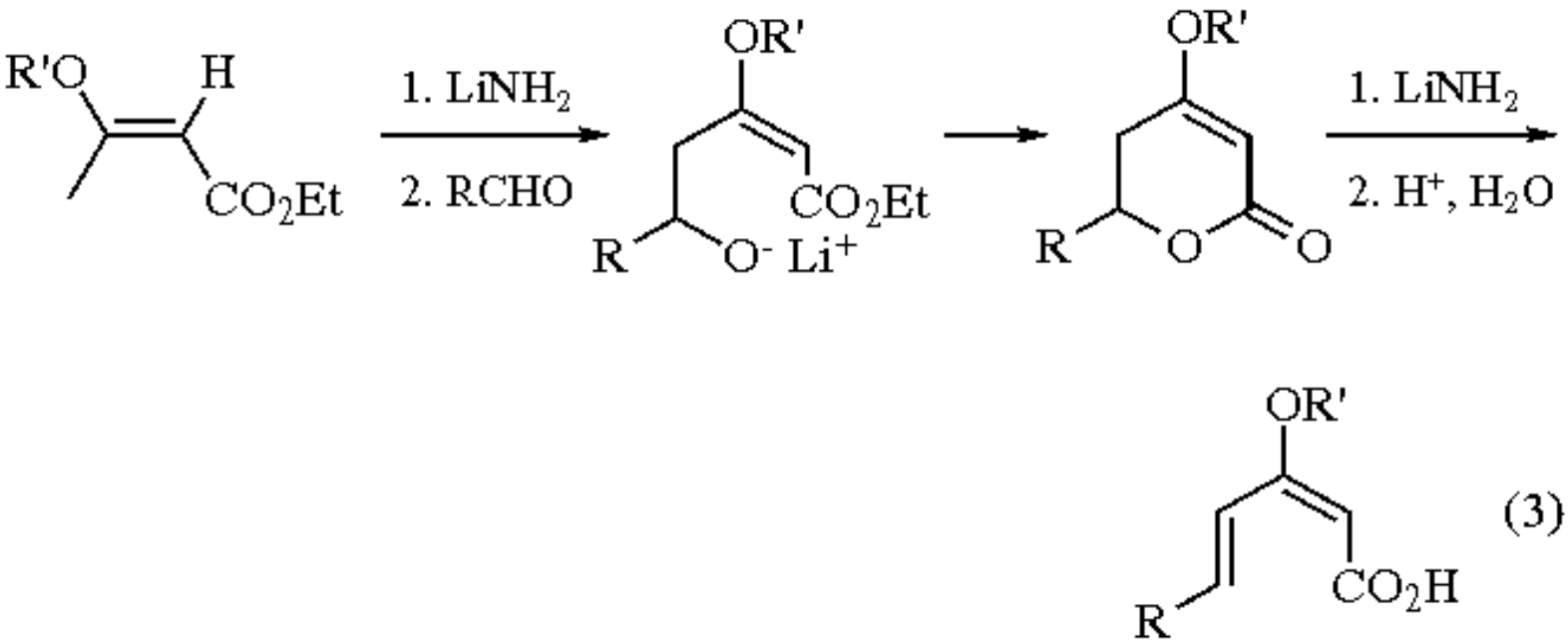

(3)

Along similar lines, enol silyl ethers are alkylated in high yields with lithium amide and alkyl halides.[12] When alkylation of (**2**) is attempted with ***Methyllithium*** and 3-bromopropionitrile, E2 elimination predominates, yielding polyacrylonitrile and cyclohexanone; the same reaction using $LiNH_2$ instead results in a 48% yield of the alkylated product (eq 4).

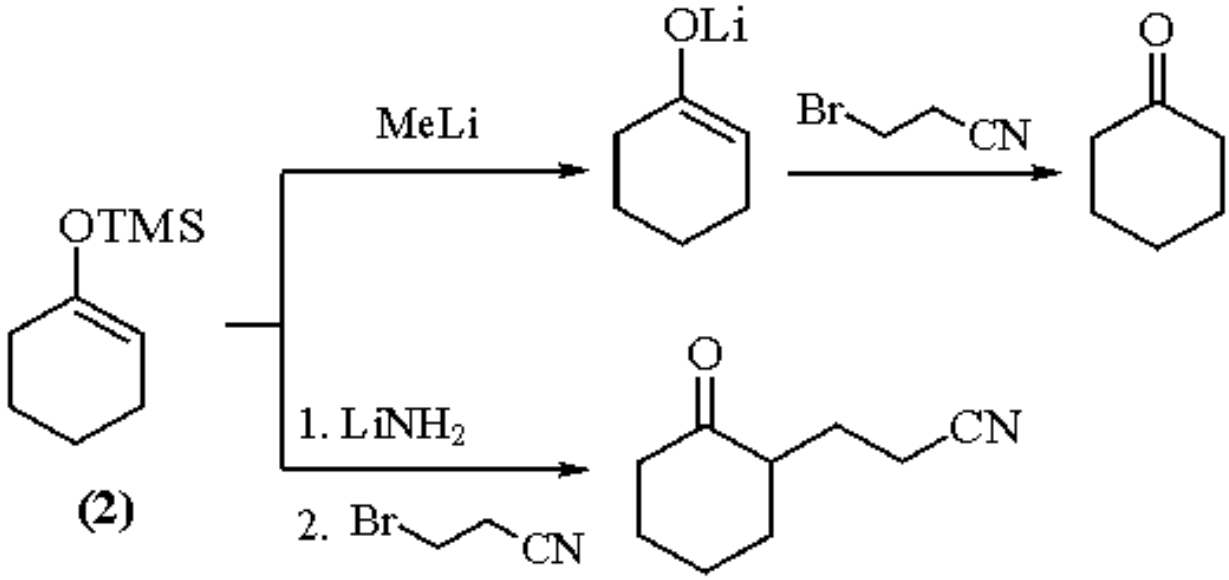

(4)

Alkylation of *t*-Butyl Esters with Organic Halides.

The direct alkylation of *t*-butyl acetate is a valuable alternative to the malonic ester method for preparing mono- and dibasic carboxylic acids. Monoalkylation is observed with various alkyl or alkenyl halides in very good yields using $LiNH_2$ (eqs 5 and 6);[13] in contrast, $NaNH_2$ gives rise to dialkylated products under the same conditions. *t*-Butyl propionate and *n*-butyrate have also been alkylated in excellent yields using $LiNH_2$. With 1,4-dibromobutane, suberic acid was obtained in quantitative yield after saponification. 1,2-Dibromoethane gave succinic acid in moderate yield,

whereas use of $NaNH_2$ in the latter case did not provide any product.

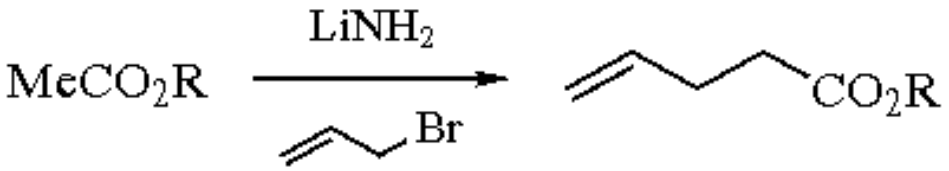

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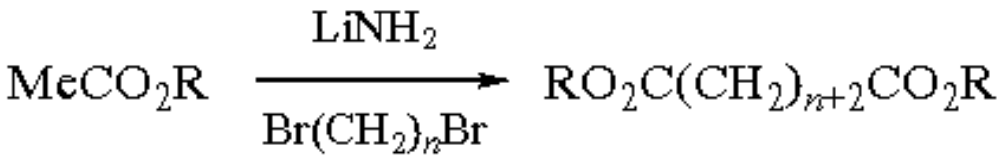

(6)

Treatment of *t*-butyl acetate with $LiNH_2$ and 1,4-dibromo-2-butene gave the diester of 4-octenedioic acid (eq 7). α,β-Unsaturated esters furnished α-mono- and α,α-dialkylation products with $LiNH_2$ (eq 8); no γ-alkylated products were formed in these reactions.[14]

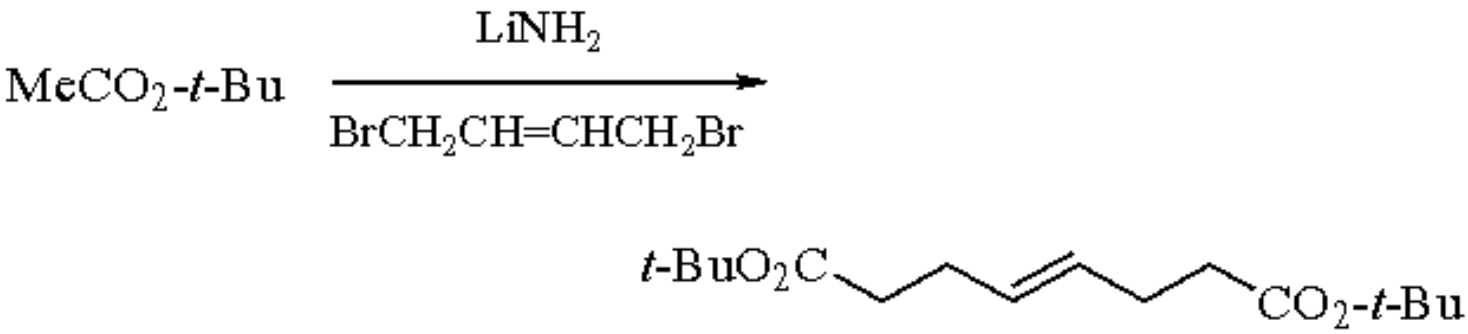

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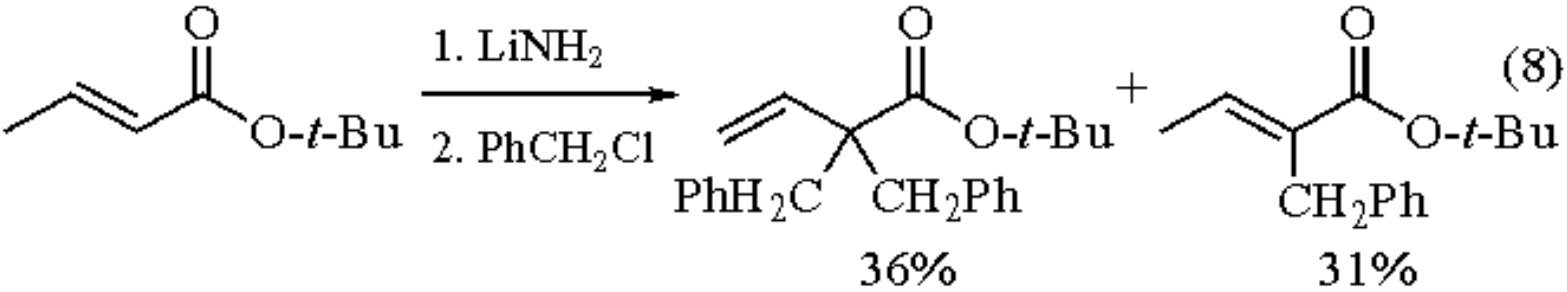

(8)

Alkylation and Condensation of Substituted Succinic Acid Derivatives.

Both monoester isomers of 2-alkyl- or arylsuccinic acids were alkylated exclusively on the carbon adjacent to the ester function (see **3**) using 2 equiv $LiNH_2$.[15] In contrast, the anion obtained from diethyl 2-methylsuccinate gave on methylation a mixture of alkylated esters, including the diesters of 2,2-dimethylsuccinic and 2,3-dimethylsuccinic acids.

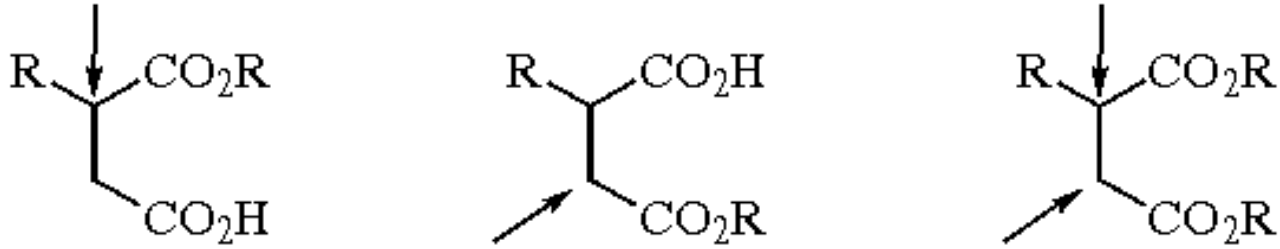

(3) (4) (5)

Condensation of monoester dianions with ketones or benzaldehyde similarly took place at the carbon α to the ester group, but only when the methylene group was not substituted (i.e. **4**). Condensation products were not obtained from the isomer (**3**).

Reactions with Alkyne Derivatives.

Alkynes carrying functional groups such as NHR or OH can be alkylated in high yields in the presence of lithium amide (eqs 9 and 10).[16-20] 1-Alkyn-o-ols are alkylated by primary or secondary alkyl halides in 50-80% yields, and it is not necessary to protect the alcohols.

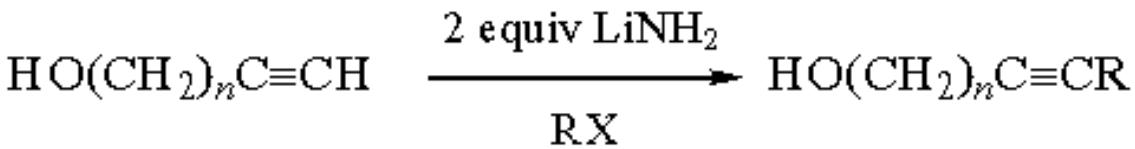

(9)

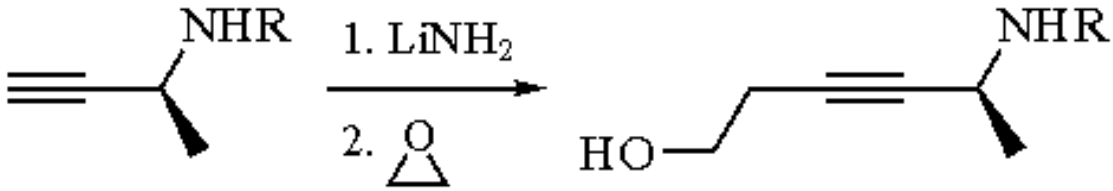

(10)

Eliminations and Isomerizations.

$LiNH_2$ has been found superior to sodium amide in dehydrohalogenations of γ-methallyl chloride and α-methallyl chloride to give 3-methylcyclopropene and 1-methylcyclopropene, respectively (eqs 11 and 12).[21-23] ***Potassium Amide***, on the other hand, isomerizes the α-isomer to methylenecyclopropane.[24]

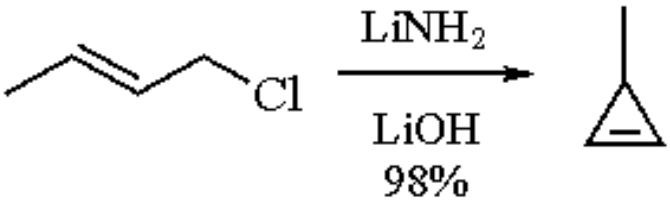

(11)

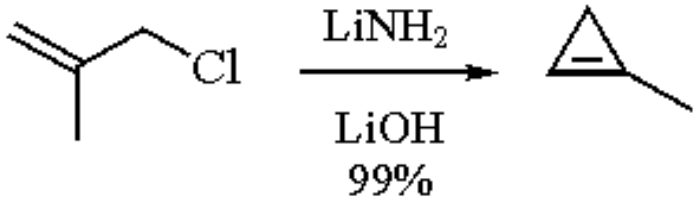

(12)

In the dimerization of cyclopropene in the presence of alkali amides (eq 13), two opposing factors influence the course of the reaction.[25] On the one hand, the rate of cyclopropenylcyclopropane formation is retarded in the presence of stronger base (KNH_2) due to lower concentrations of unmetalated cyclopropene. On the other hand, increasing base strength favors the equilibrium between (**6**) and (**7**) in favor of (**7**), thus securing a greater yield of bicyclopropylidene (**8**). The best yields of (**8**) were obtained using $LiNH_2$ in liquid NH_3, albeit with much longer reaction times (4 weeks at -50 °C) than with $NaNH_2$.

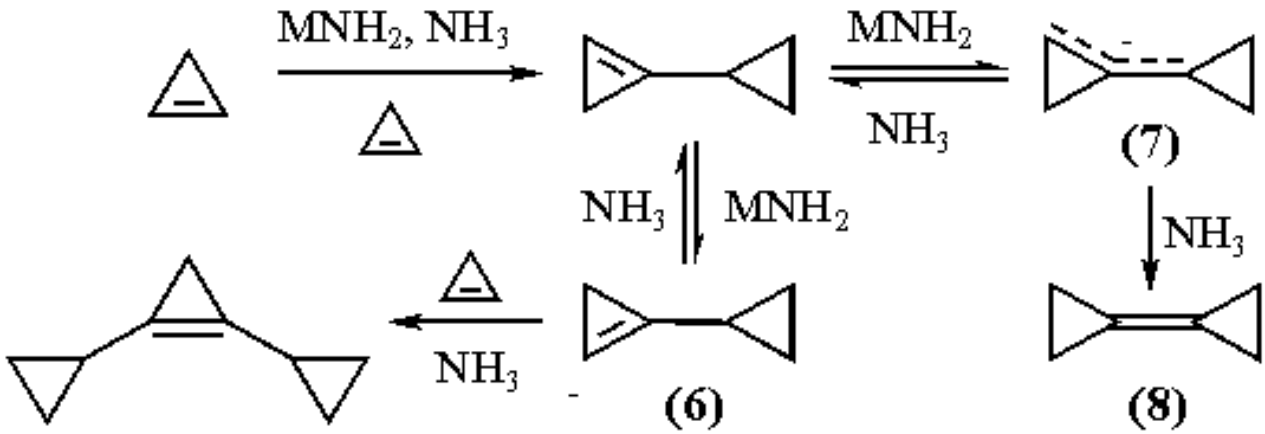

(13)

The propargyl sulfides (**9**) and (**10**) have been isomerized in good yields to the corresponding allenes with $LiNH_2$ in liquid NH_3 (eqs 14 and 15).[26-28]

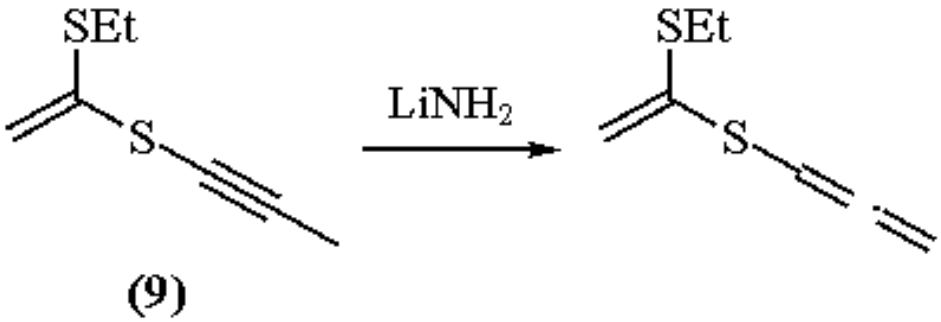

(14)

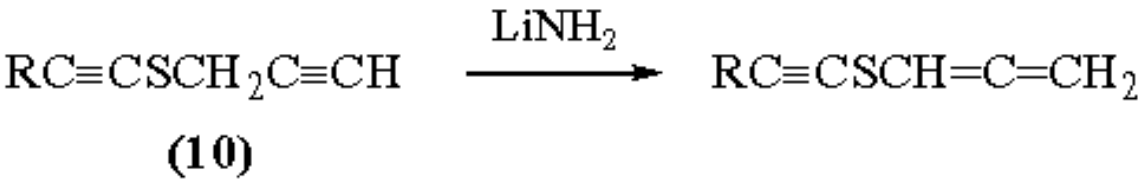

(15)

Chiral propargyl alcohols can be prepared[29] from allylic alcohols by Sharpless asymmetric epoxidation,[30] conversion of the alcohol product into the corresponding chloride, and treatment with $LiNH_2$ in liquid NH_3 (eq 16). Use of ***Lithium Diisopropylamide*** (LDA) gives comparable yields. The same reaction with ***n-Butyllithium*** in THF at -33 °C

results in mixtures of the chlorovinyl alcohol, propargyl alcohol, and starting material. It appears that *n*-BuLi reacts indiscriminately with both the epoxy chloride and the chlorovinyl alcohol formed during the reaction.

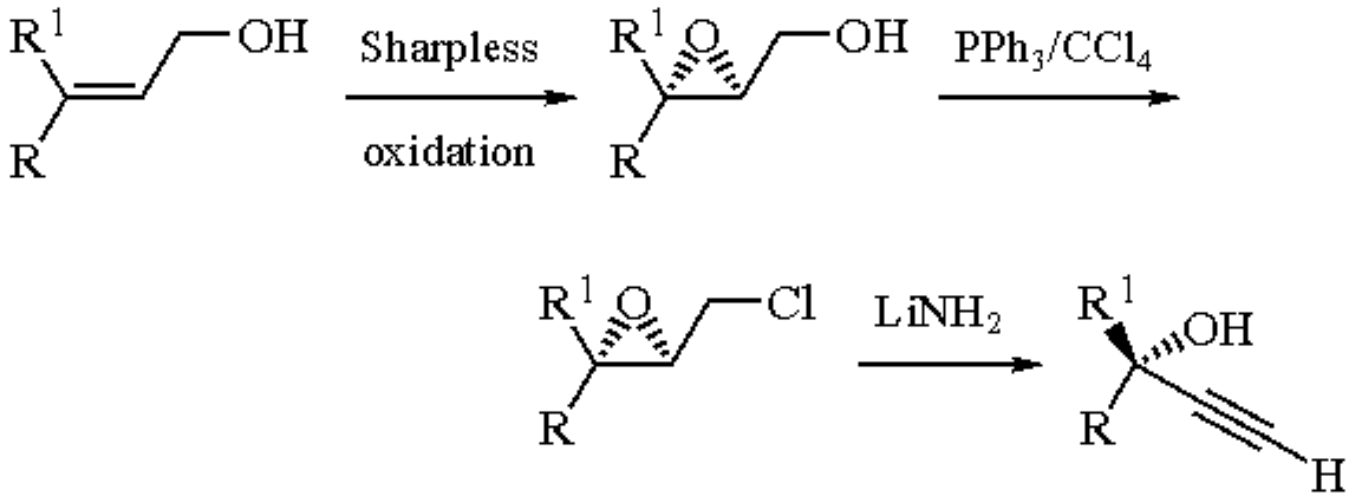

(16)

2-Chloromethyltetrahydrofuran undergoes ring opening followed by dehydrochlorination with 3 equiv of $LiNH_2$.[31] The lithio acetylide (**11**) formed in situ can be alkylated to give 4-alkynyl alcohols (eq 17).

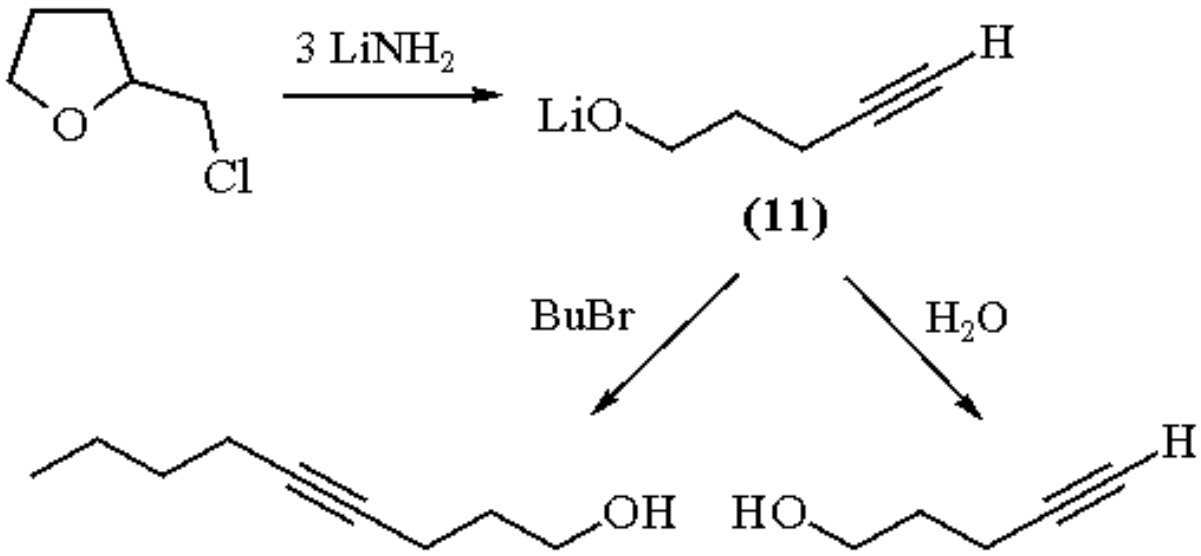

(17)

This reaction has been employed in the synthesis of chiral alkynyl compounds from simple carbohydrate precursors (eq 18).[32] The elimination reaction here is chemoselective, since the other isopropylidene group in the substrate remains unaffected.

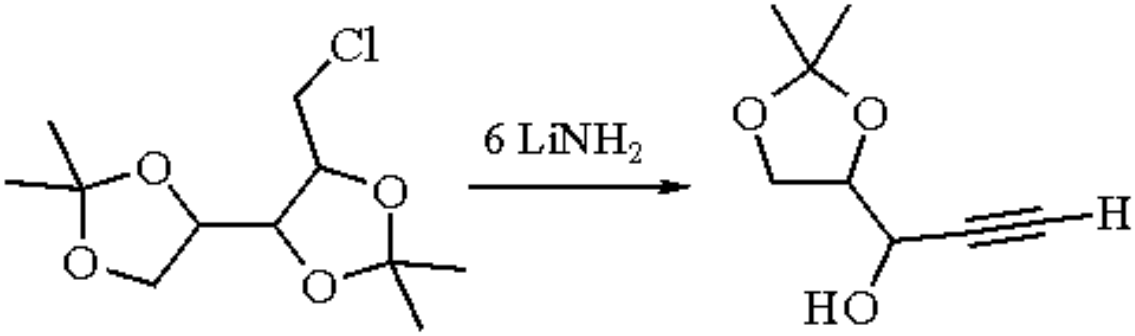

(18)

Related Reagents.

Lithium Diethylamide; ***Lithium Diisopropylamide***; ***Lithium Hexamethyldisilazide***; ***Lithium Piperidide***; ***Lithium Pyrrolidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***; ***Potassium Amide***; ***Sodium Amide***.

---

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Lithium *N*-Benzyltrimethylsilylamide

$LiN(SiMe_3)CH_2Ph$

[113709-50-5] · $C_{10}H_{16}LiNSi$ · Lithium *N*-Benzyltrimethylsilylamide · (MW 185.31)

(less-basic lithium amide capable of regioselective conjugate addition to α,β-unsaturated esters;[1] amide cuprates have increased selectivity and reactivity toward enoates[2])

Alternate Name: LSA.

Solubility: sol THF.

Preparative Method: to a solution of freshly distilled *N*-benzyltrimethylsilylamine (0.2 mL, 1.0 mmol)[3] in THF at -78 °C is slowly added a solution of ***n-Butyllithium*** (0.61 mL, 1.64 M in hexane, 1.0 mmol) under Ar; a pale yellow solution of lithium *N*-benzyltrimethylsilylamide in THF is obtained after stirring for several min at -78 °C.[1]

Handling, Storage, and Precautions: is moisture- and air-sensitive, and should thus be handled under inert atmosphere; prepare just prior to use; use in a fume hood.

Conjugate Additions.

Lithium dialkylamides (e.g. ***Lithium Diisopropylamide***, LDA) with weak nucleophilicity are commonly used as strong bases for deprotonation. However, lithium *N*-benzyltrimethylsilylamide acts as a nucleophile with a basicity weaker than LDA. For example, the reaction of LSA with (*E*)-crotonates affords the conjugate adducts, β-amino esters, in high yields without formation of 1,2-adducts (amides) or products arising from deprotonation at the γ-position of the enoates (eq 1).[1] On the other hand, the reaction of LDA with (*E*)-methyl crotonate gives a mixture of the conjugate adduct and deprotonation product (eq 2).[1,4] The reaction of lithium benzylamide gives the 1,2-adduct as a major product. The (*E*) geometry of α,β-unsaturated esters is essential for conjugate addition, since the treatment of (*Z*)-methyl 2-decenoate with LSA gives the deconjugated ester, methyl 3-decenoate, in high yield.[5] Since the N-Si bond is cleaved easily under weak acidic conditions, purification of the conjugate adduct (see eq 1) by silica gel column chromatography provides desilylated benzylamino esters.

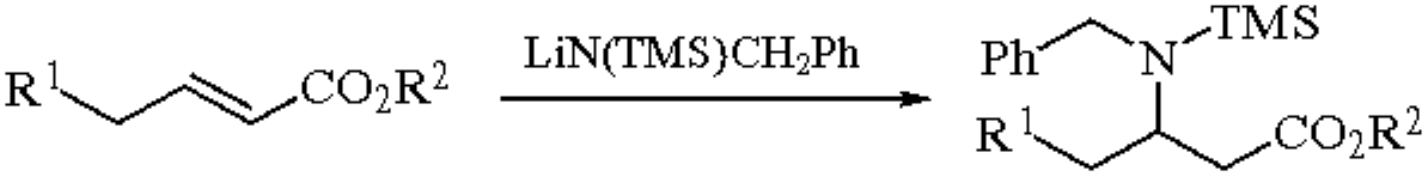

(1)

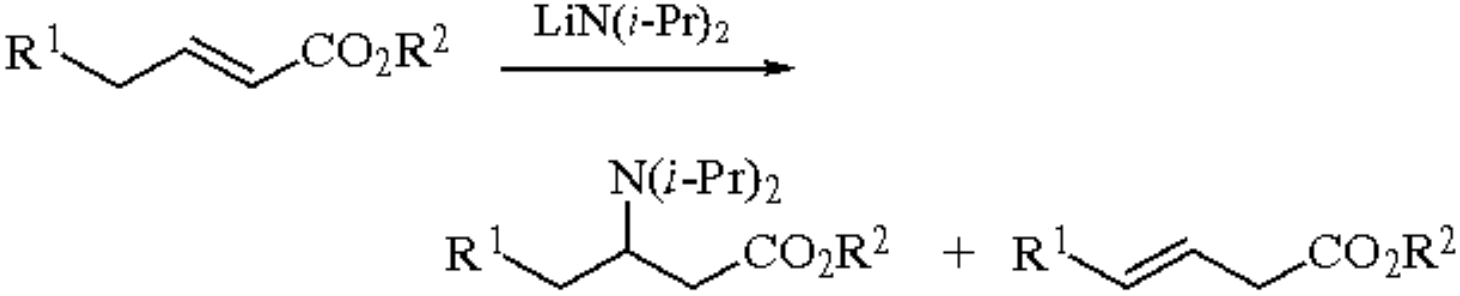

(2)

The conjugate addition of LSA to methyl crotonate followed by trapping of the resulting enolate with ***Chlorotrimethylsilane*** affords the (*Z*)-ketene silyl acetal nearly exclusively (*Z*:*E* = 99:1) (eq 3). On the other hand, if the conjugate addition reaction is quenched with methanol, deprotonation of the resulting β-amino ester with LDA followed by treatment with Me_3SiCl gives the (*E*)-ketene silyl acetal with very high stereoselectivity (*Z*:*E* = 2:98) (eq 4). Accordingly, the stereodivergent synthesis of (*Z*)- or (*E*)-enolates of β-amino esters is achieved via the direct conjugate addition of LSA or the two-step procedure, respectively.[6]

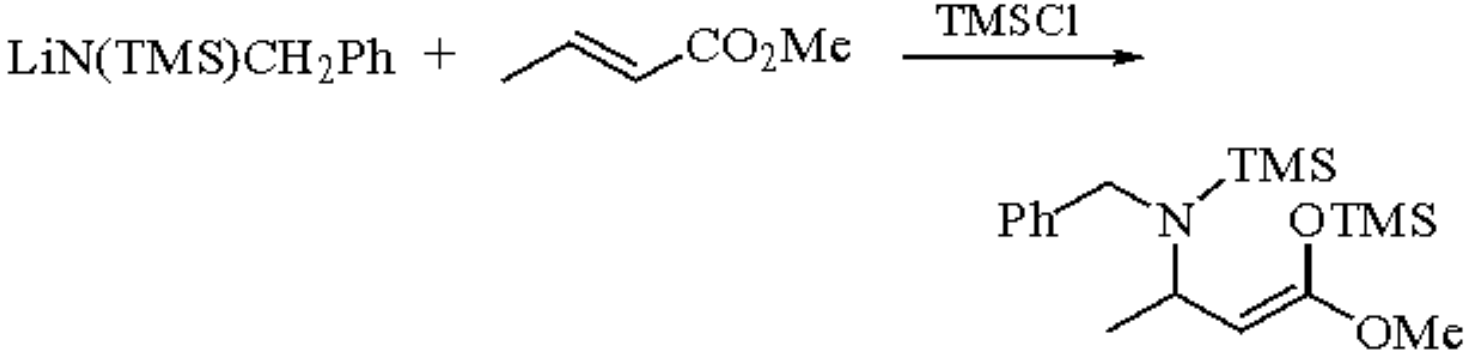

(3)

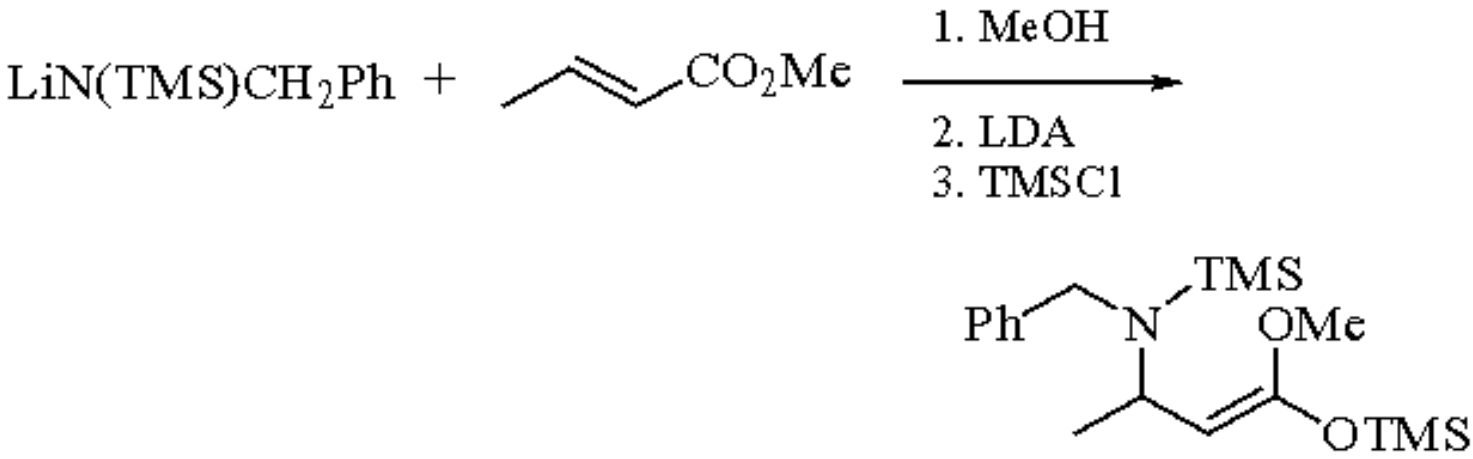

(4)

The conjugate addition of LSA to enoates followed by trapping with alkyl halides gives α-alkyl-β-amino esters, which are converted to α-alkylated α,β-unsaturated esters upon deamination with silica gel.[1] The reaction of the

enolates with aldehydes produces β-amino-β´-hydroxy esters, which are converted to β-lactams having a 1-hydroxyalkyl group at the C-3 position (eq 5). Thus the β-lactam skeleton is prepared stereoselectively and expeditiously via a three-component coupling reaction.[6] The amide cuprate reagents, prepared from 2 equiv LSA and ***Copper(I) Cyanide***, react effectively with α,β,γ,δ-unsaturated esters to give the corresponding β-amino esters. Based upon this procedure, asymmetric syntheses of β-lactams have been accomplished (eq 6).[2]

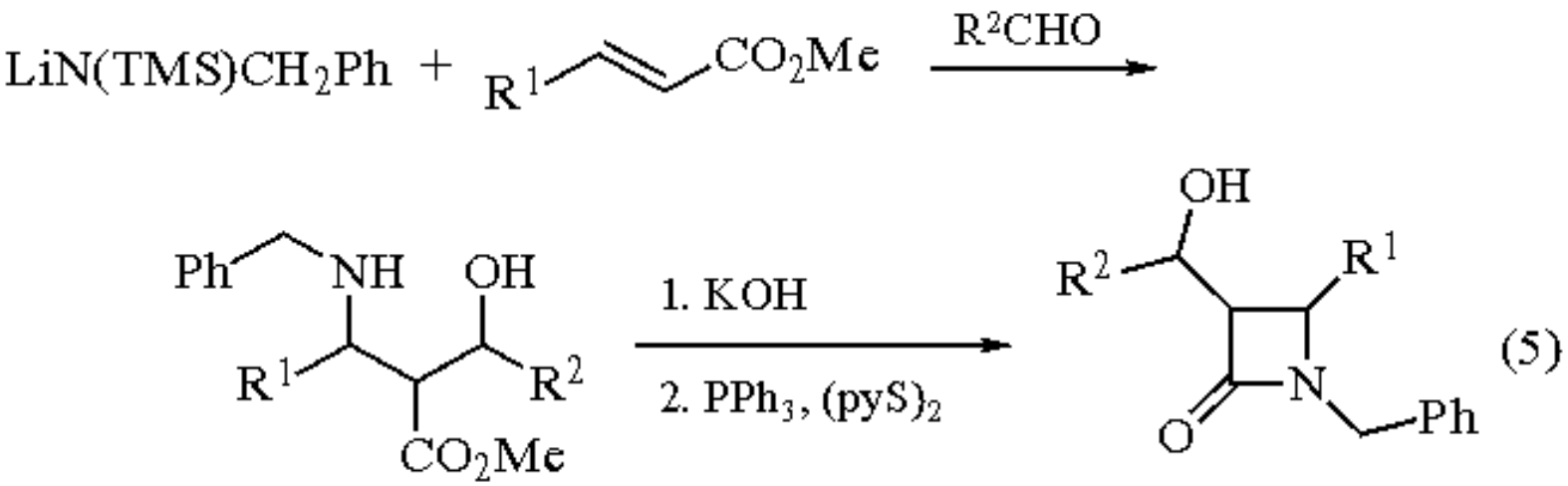

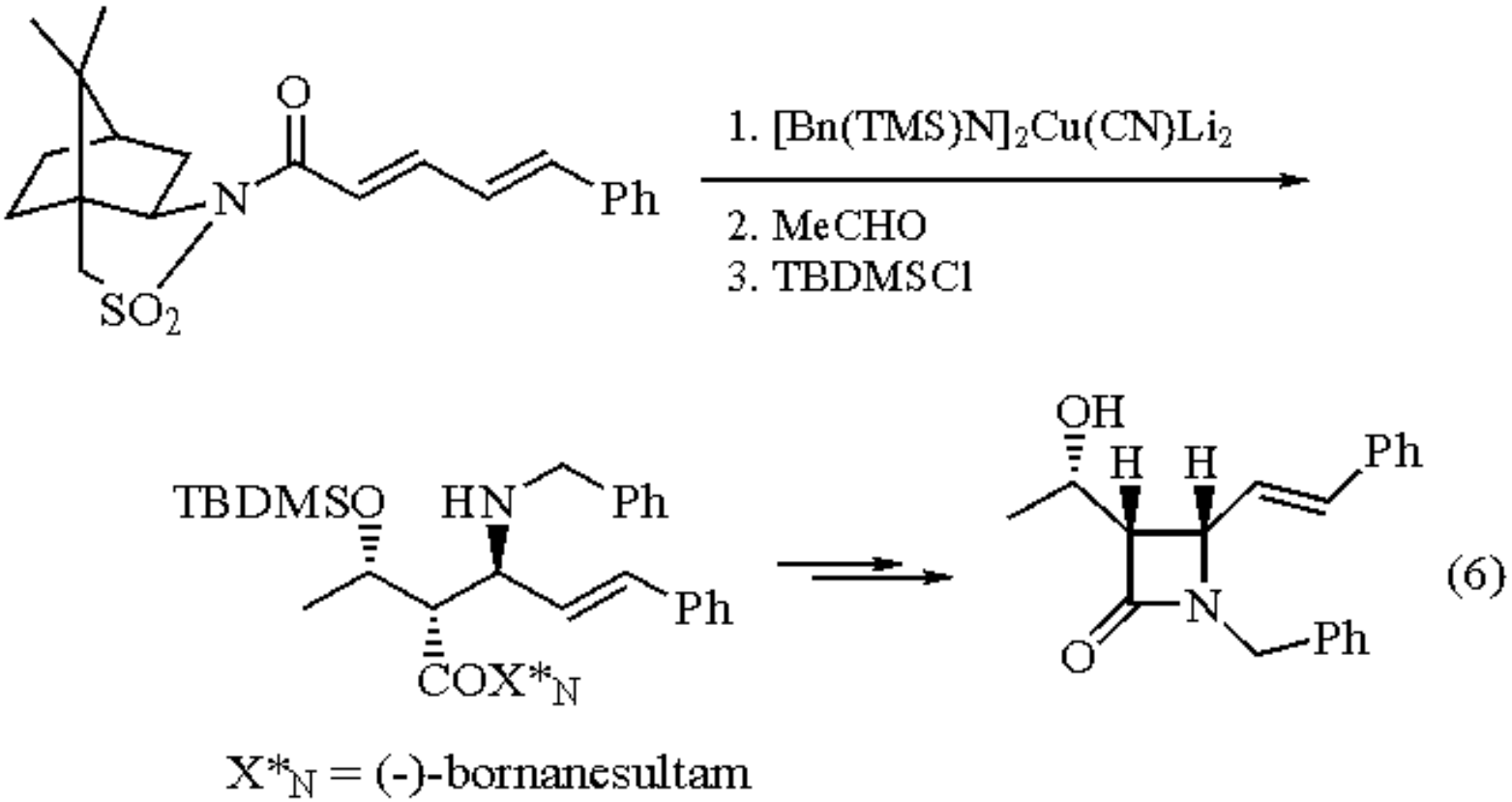

The reaction of LSA with o-halo-α,β-unsaturated esters produces cyclization products.[5] In the case of α,β,χ,ψ-unsaturated dioic acid esters, tandem conjugate additions occur stereoselectively; this cyclization strategy has been applied to the synthesis of racemic cyclopentane monoterpenes.[5]

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Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate

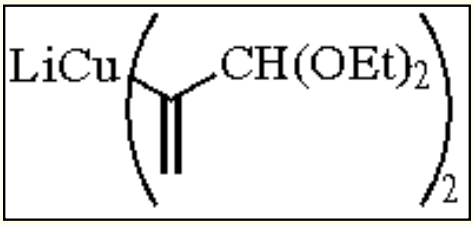

[58384-87-5] · $C_{14}H_{26}CuLiO_4$ · Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate · (MW 328.85)

(organocopper reagent for the transfer of a protected acrolein group to allyl halides, vinyl epoxides, and carbonyl compounds; reagent for the construction of α-methylene-γ-butyrolactones)

Physical Data: thermally unstable organocuprate generated between -60 and -70 °C; stable and reactive at temperatures below -40 °C.

Solubility: sol THF at -40 °C or below.

Preparative Method: from the reaction of ***2-Lithio-3,3-diethoxy-1-propene***[2] with Me_2S complex of ***Copper(I) Bromide*** at -60 to -70 °C in THF.

Handling, Storage, and Precautions: should be generated in the absence of O_2 and moisture at low temperatures under an N_2 or Ar atmosphere.

Conjugate Additions to Enones.

The generation of the title reagent (**1**)[1] is straightforward at -70 °C (eq 1). In addition to the homocuprate (**1**) a mixed cuprate containing a *t*-butyl-alkynyl ligand may also be prepared at -40 °C.[1]

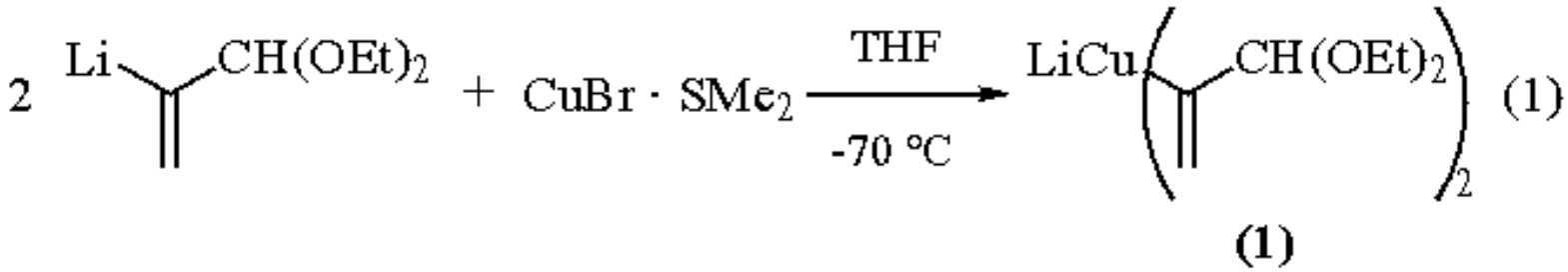

This cuprate (**1**) is the one organometallic reagent in the highest oxidation state capable of adding an acrolein and hence

an acrylate unit in a conjugate addition to enones. In a typical example, (**1**) adds 1,4 to carvone at -70 °C to produce the adduct (**2**) (eq 2). Hydrolysis of (**2**) and mild oxidation with ***Silver(I) Oxide*** produces the acrylic acid (**3**) (eq 3).[1]

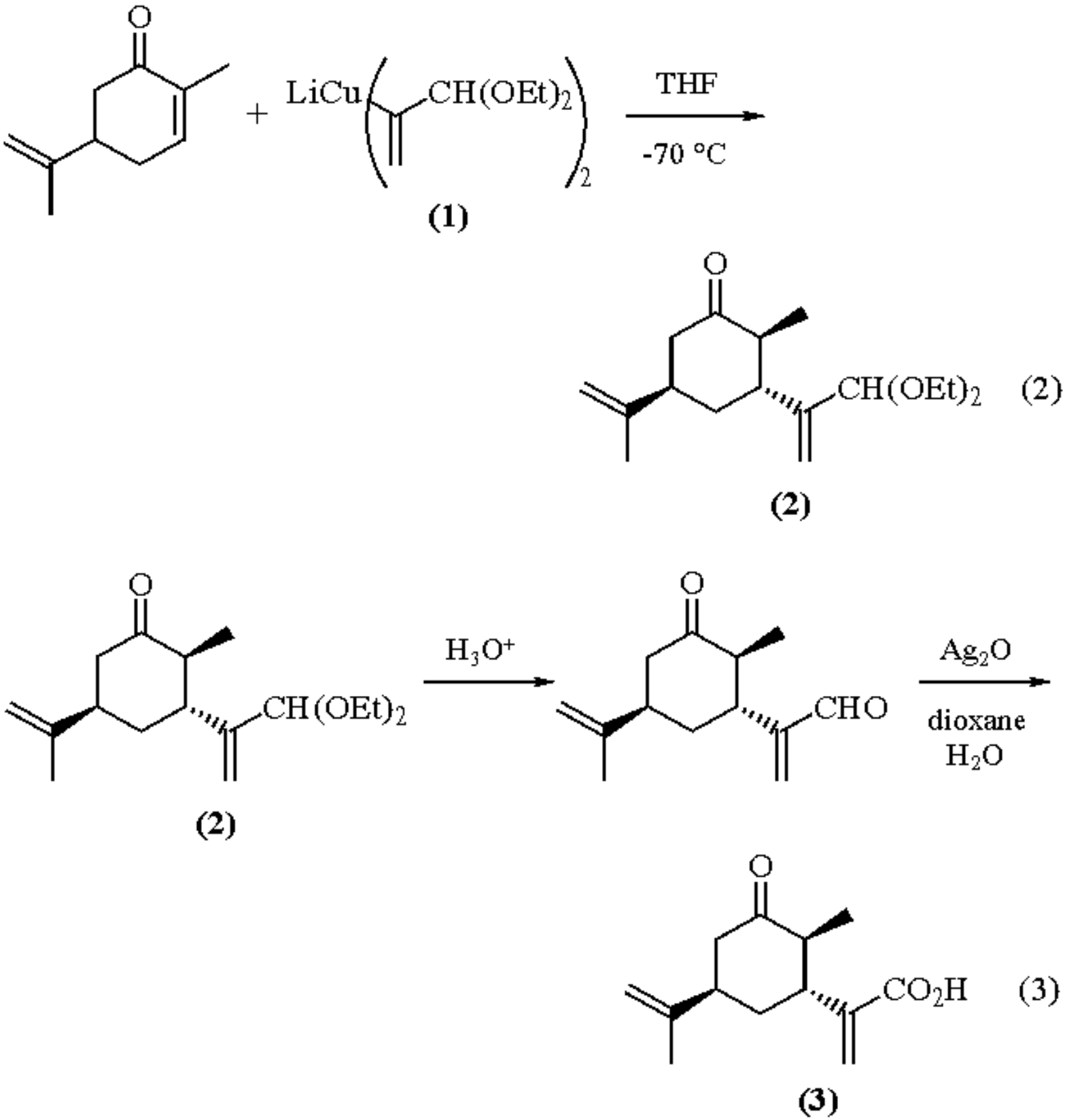

In a total synthesis of (+)-hanegokedial, a modified version of reagent (**1**) was added in a 1,4-manner to the cycloheptenone (**4**) to prepare a 2:1 mixture of stereoisomers of adduct (**5**) in 84% yield. In this example the copper enolate intermediate was trapped with gaseous ***Formaldehyde*** (eq 4).[3]

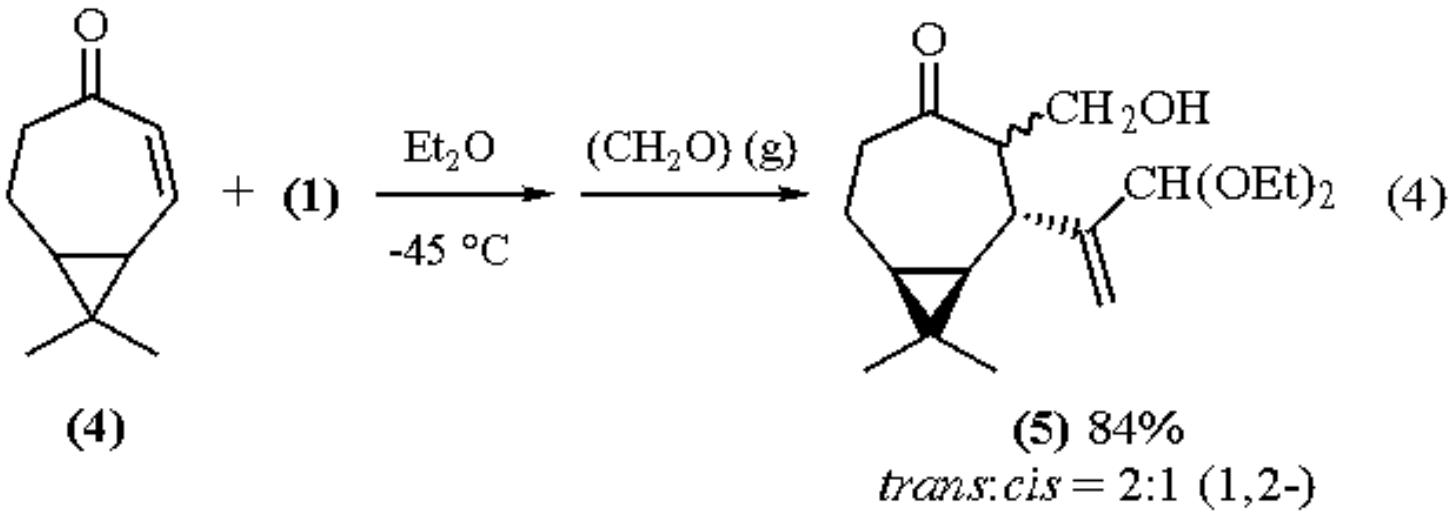

Additions to Cyclic Allylic Halides.

The direct alkylation of 3-bromocycloheptene with (**1**) produces the adduct (**6**) in 60% yield at -40 °C. The adduct (**6**) was a convenient precursor to an acrylic acid (**7**) and iodolactone (**8**) (eq 5).[4]

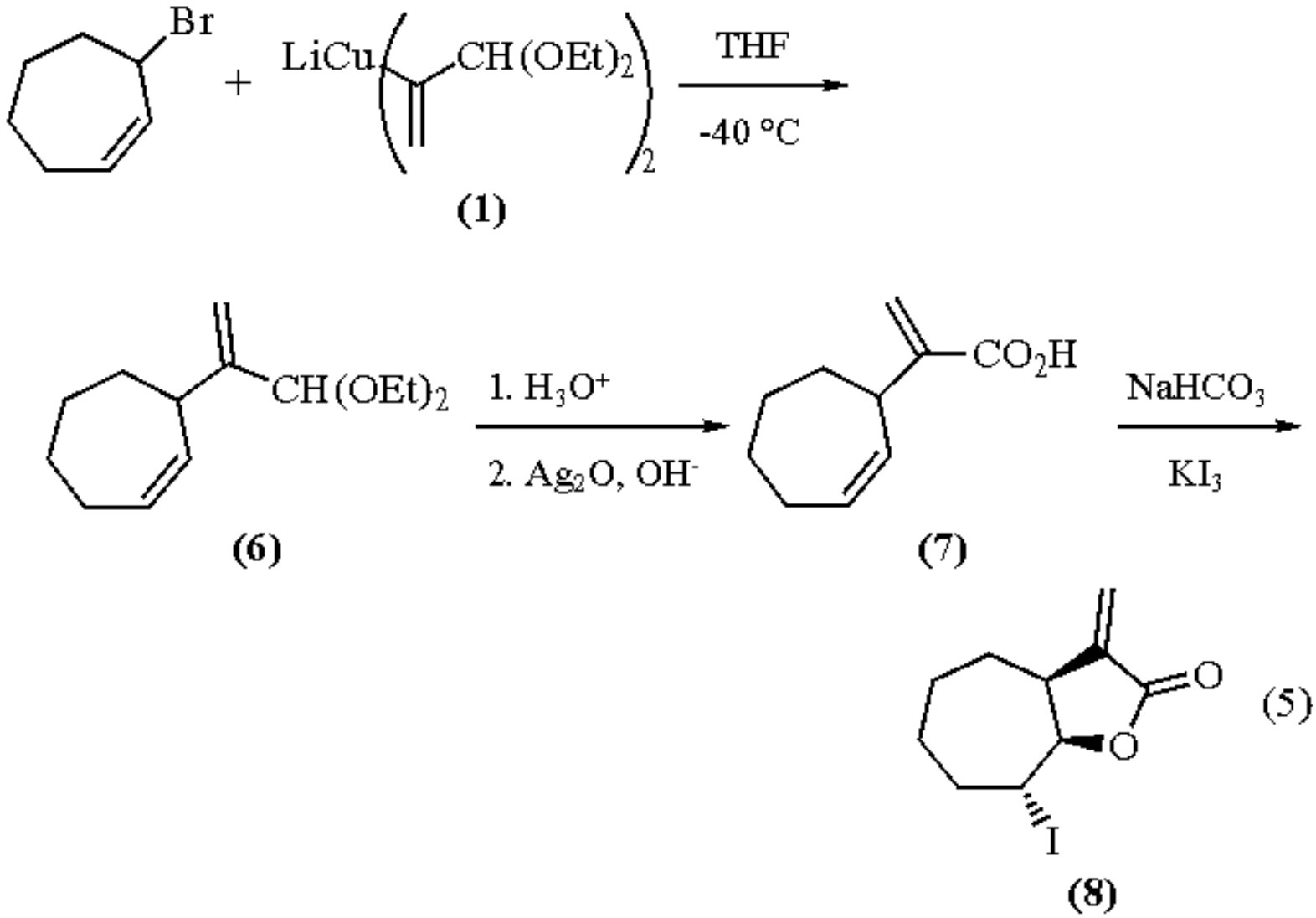

While the title reagent reacted well with allylic halides, it did not react with allylic acetates. All attempts to open simple epoxides with (**1**) also failed at various temperatures below 0 °C.[4]

Additions to Cyclic Vinyl Epoxides.

Reactions of the cuprate (**1**) with monoepoxides of cyclic 1,3-dienes yielded mixtures of 1,2 and 1,4 ring-opened products, with the former as the major products.[5] The ratio of 1,2 to 1,4 products varied slightly depending on whether THF or ether was used as a reaction solvent. In the case of cyclopentadiene monoepoxide in THF, the yield of adducts was 87% with a 1,2:1,4 ratio of 7:3 (eq 6).

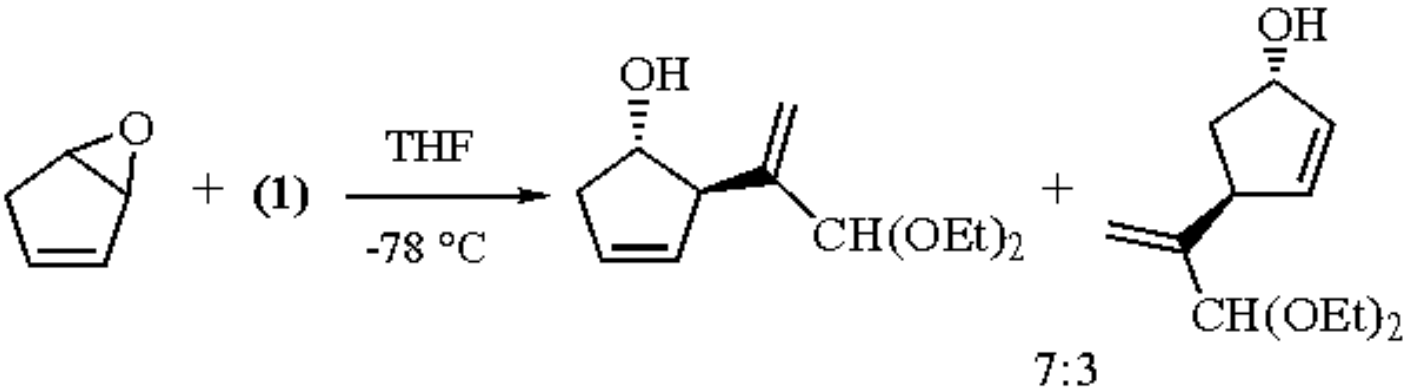

(6)

The best regioselectivity found for an epoxide opening was for the cycloheptadiene monoepoxide system which produced a 1,2:1,4 ratio of 3:1 in THF and 6:1 in diethyl ether (eq 7).

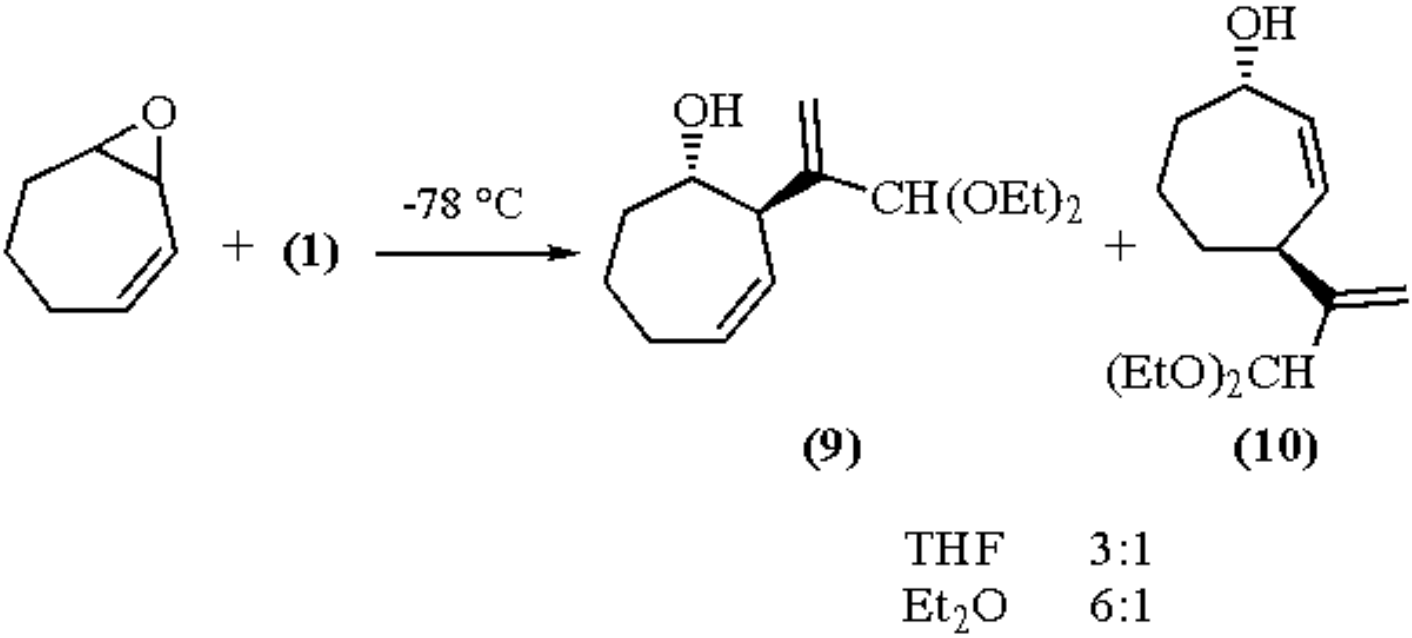

(7)

The 1,2-adduct (**9**) could be transformed into a *trans*-α-methylenebutyrolactone (**11**) or a *cis*-α-methylenebutyrolactone (**12**) (eq 8).[5]

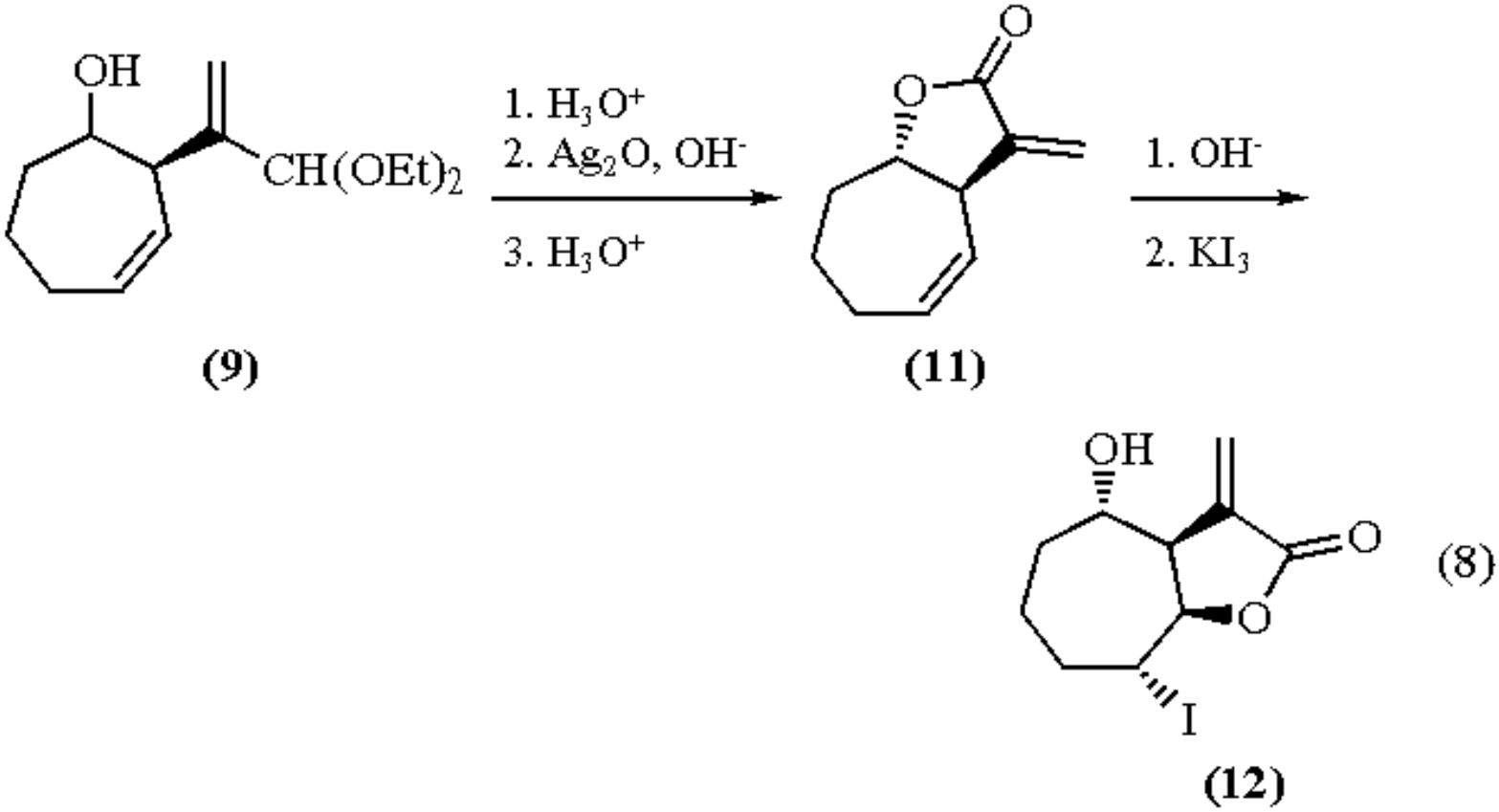

Related Reagents.

3,3-Diethoxy-1-propen-2-ylcopper; ***Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate***.

---

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4. Farina, J. S., PhD Thesis, University of Michigan, 1978.
5. Marino, J. P.; Farina, J. S. *JOC* **1976**, *41*, 3213.

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Lithium Bis(*N,N*-diethylcarbamoyl)cuprate

$(Et_2NCO)_2CuLi$

[71435-48-8] · $C_{10}H_{20}CuLiN_2O_2$ · Lithium Bis(*N,N*-diethylcarbamoyl)cuprate · (MW 270.76)

(carbamoylation of organic halides[1,2])

Alternate Name: lithium bis[(diethylamino)carbonyl]cuprate.

Solubility: sol THF, HMPA.

Preparative Method: prepared in situ under N_2; an equimolar reaction of ***Copper(I) Chloride*** and ***Lithium Diethylamide*** in a mixed solvent of THF and HMPA (4:1) at -20 °C produced a precipitate of $CuNEt_2$, which was dissolved by an additional 1 equiv of $LiNEt_2$; 2 equiv ***Carbon Monoxide*** were absorbed by this homogeneous solution under ambient conditions; the resulting solution was used in the carbamoylation directly.[1]

Handling, Storage, and Precautions: stable below 80 °C, decomposes partly at 100 °C; air- and moisture-sensitive; handle in a fume hood under inert gas (Ar or N_2);[1] the hazards of HMPA and CO are well-documented.[3]

Carbamoylation.

Various organic halides can be carbamoylated by this reagent. The active allyl halide gave a 45% yield of *N,N*-diethyl-3-butenamide (based on $LiNEt_2$), with concomitant evolution of CO nearly equivalent to copper; the yield was 76% under a CO pressure of 50 kg cm^{-2}. Reaction with acid bromides took place smoothly under mild conditions to produce α-keto amides, but for some less reactive chlorides a higher reaction temperature was required.[1] This reaction with acid halides provides an effective method of preparing α-ketoamides (eq 1); several other reagents utilized for direct carbamoylation did not give this functionality.[4,5] Lithium *N,N*-dimethylcarbamoylnickel carbonylate,[5f] which is effective for the carbamoylation of vinylic and aromatic halides, reacted with acid halides to produce the corresponding amides instead of α-ketoamides. *N,N*-Diisopropylcarbamoyllithium[5c,5e] and *N,N*-dimethylcarbamoyllithium react with aldehydes and ketones readily, but their reaction with acid halides has not been reported.

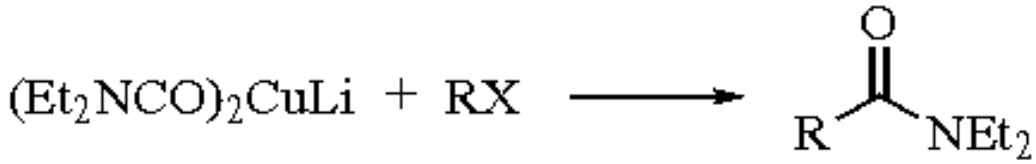

(1)

R = Me, $H_2C{=}CHCH_2$, MeCO
X = Br, Cl

Under palladium catalysis, the carbamoylation of iodobenzene was optimized.[2] A related reagent, ***Lithium Bis(N-methyl-N-phenylcarbamoyl)cuprate***, reacts with iodobenzene with relatively higher yield under the same catalysis conditions (eq 2).

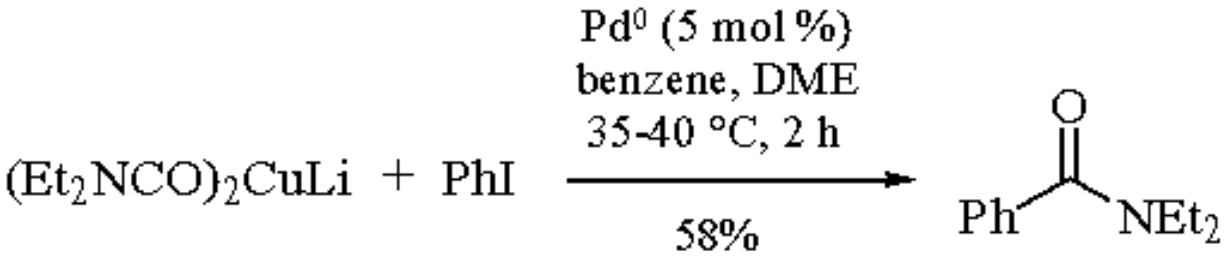

(2)

The title reagent undergoes conjugate addition with methyl vinyl ketone to give *N*,*N*-diethyllevulinamide in 78% isolated yield, but reaction with cyclohexenone was not successful (eq 3).[1]

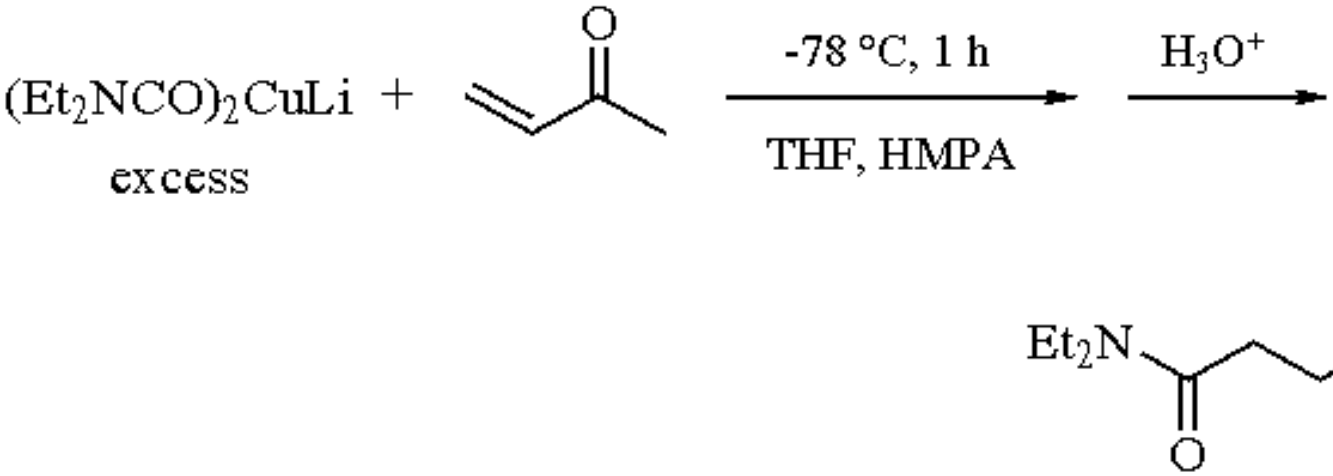

(3)

Conversion to Oxamide and Carbamate Derivatives.

Under suitable conditions, lithium bis(*N*,*N*-diethylcarbamoyl)cuprate can be converted to the corresponding oxamide, oxamic acid, and carbamate (eqs 4-6).[2]

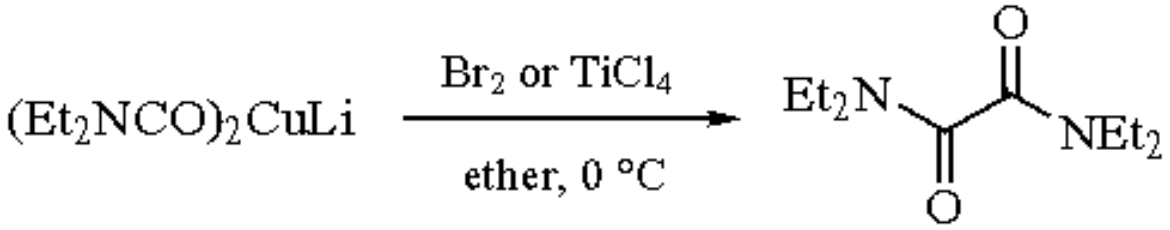

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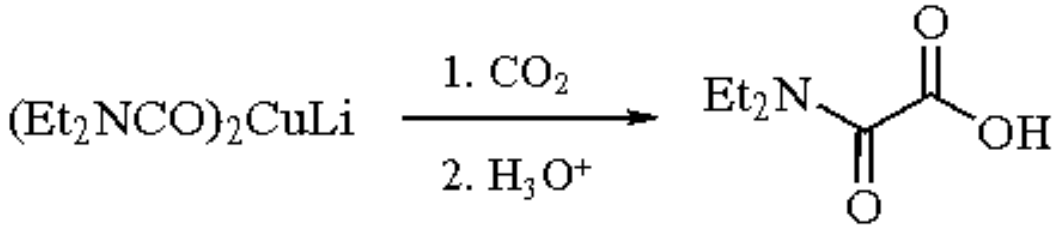

(5)

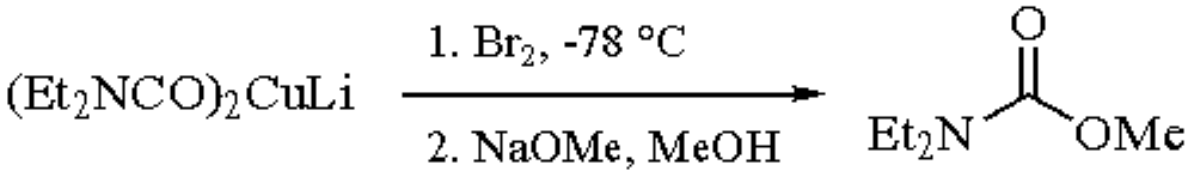

(6)

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Lithium Bis[dimethyl(phenyl)silyl]cuprate[1]

$(PhMe_2Si)_2CuLi$

[75583-57-2] · $C_{16}H_{22}CuLiSi_2$ · Lithium Bis[dimethyl(phenyl)silyl]cuprate · (MW 341.01)

(dimethyl(phenyl)silyl nucleophile for making Si-C bonds by reaction with α,β-unsaturated carbonyl compounds, alkynes, allenes, and allylic acetates)

Physical Data: typically a 0.6M, dark, reddish-brown solution in THF.

Analysis of Reagent Purity: the silyllithium solution can be double-titrated for active reagent using ***Allyl Bromide***, but the cuprate is usually used without further checks; NMR (of the cuprate made with CuCN in THF-d_8): ^{1}H δ 0.09; ^{13}C δ 5.1; ^{29}Si δ -24.4; ^{7}Li δ -3.33.[2]

Preparative Methods: the silyl cuprate is prepared[1] from the corresponding silyllithium reagent (***Dimethylphenylsilyllithium***); commercially available ***Chlorodimethylphenylsilane*** is stirred with ***Lithium*** shot, wire, or powder under Ar or N_2 in THF at 0 °C for 4-12 h; the silyllithium solution may also be prepared, free of halide ion, by cleaving tetramethyldiphenyldisilane with lithium and ultrasound irradiation;[2] the silyllithium solution (2 equiv), after assay, is transferred by syringe on to anhyd ***Copper(I) Iodide***, ***Copper(I) Bromide***, or ***Copper(I) Cyanide*** (1 equiv), kept under argon or nitrogen at 0 °C, stirred at this temperature for 20 min, and then used immediately.

Handling, Storage, and Precautions: must be kept free of O_2 and H_2O; while somewhat more stable thermally than alkyl cuprates, surviving for a few hours at 0 °C, it is best used immediately after its preparation; the copper salts, and especially copper(I) cyanide, are toxic; the solutions should therefore be handled in a fume hood wearing impermeable gloves, and the aqueous washings disposed of appropriately, immediately after use.

Introduction.

Because dimethyl(phenyl)silyllithium is much easier to prepare than ***Trimethylsilyllithium***, the most commonly used silyl cuprate reagent is derived from this silyl group. The reagent can be prepared using CuI, $CuBr.SMe_2$, or CuCN. The three reagents appear to be very similar in their reactivity, except for the higher regioselectivity of the cyanide-derived reagent with terminal alkynes. The dimethyl(phenyl)silyl group in products like allyl- and vinylsilanes appears to impart very similar reactivity to that imparted by the trimethylsilyl group, and it has an advantage over the trimethylsilyl group in that the presence of the phenyl group allows the dimethyl(phenyl)silyl group to be converted into a hydroxyl group with retention of configuration at carbon (eq 1). This transformation requires first a reaction with an electrophile, such as a proton,[3] bromine, or the mercury(II) cation,[4] to remove the phenyl ring and place a

nucleofugal group X on the silicon atom. This step is followed by treatment either with peracid or with ***Hydrogen Peroxide*** and a base. The two steps may be combined in one pot;[4] bromine itself does not have to be used, since the ***Peracetic Acid*** oxidizes bromide ion to bromine in situ.

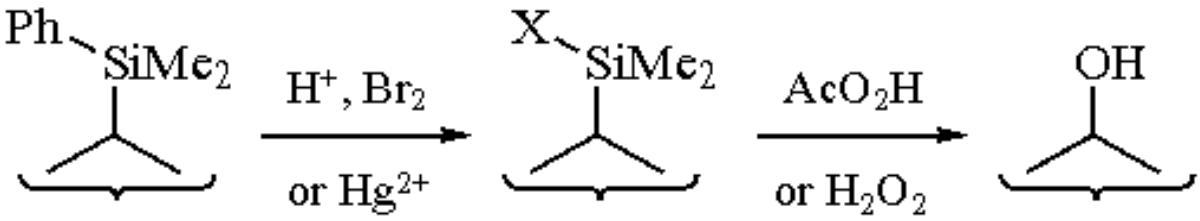

(1)

This capacity of the dimethyl(phenyl)silyl group cannot be drawn upon, however, when there is a C=C double bond in the molecule; no matter which electrophile is used, it attacks the double bond more rapidly than it removes the phenyl ring from the silyl group. This limitation has been overcome using the corresponding diethylamino(diphenyl)silyl-[5] and 2-methylbut-2-enyl(diphenyl)silylcuprate[6] reagents.

A mixed cuprate, [dimethyl(phenyl)silyl]methyl(or-butyl)cuprate,[7] containing one silyl and one alkyl group, has some advantages. Only the silyl group is transferred to the substrate, and hence only one silyl group is needed, and the byproduct of the silyl-cupration step, methane or butane, is volatile. Yields in silyl-cupration reactions carried out with only 1:1 stoichiometry are apt not to be quite so good, however. Other silyl copper reagents and cuprates with more specific or limited applications are (*t*-butyldimethylsilyl)butylcuprate,[8] triphenylsilylcopper,[9] the bis(*t*-butyldiphenylsilyl)cuprate,[10] and the bis[tris(trimethylsilyl)silyl]cuprate.[11]

Reaction with α,β-Unsaturated Carbonyl Compounds.

Although silyllithium reagents add kinetically at the β-position of α,β-unsaturated ketones,[12] the reactions are better with the cuprate when the enone is hindered.[13] The cuprate, unlike the lithium reagent, also reacts with α,β-unsaturated aldehydes, esters (eq 2), amides, and nitriles[13] and with vinyl sulfoxides.[14] With esters, the intermediate enolates, which have the (*E*) geometry (**1**), may be used directly in highly stereoselective reactions with alkyl halides and aldehydes.[15,16] The β-hydroxy esters, such as (**2**), can be used in the synthesis of allylsilanes.[17]

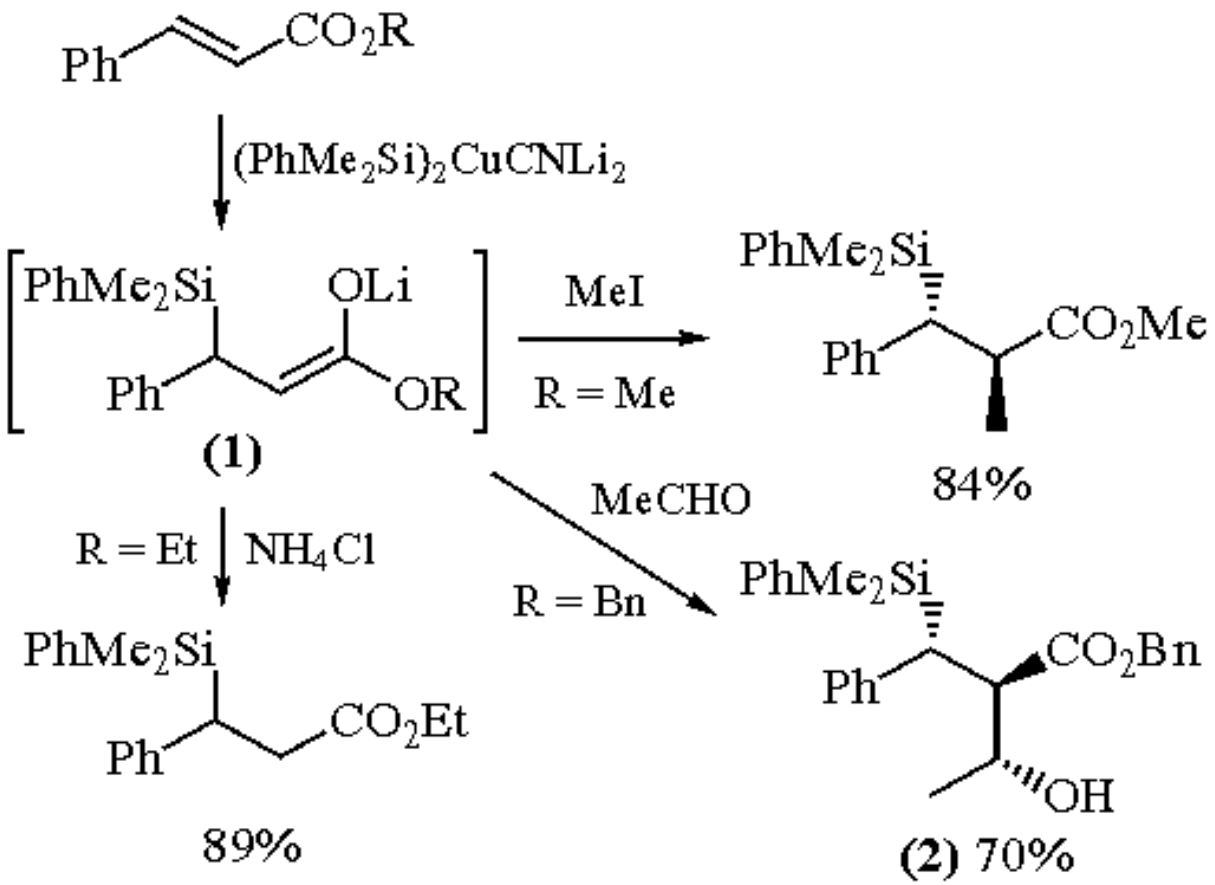

(2)

α,β-Unsaturated carbonyl compounds attached to a homochiral auxiliary, such as Koga's lactam or Oppolzer's sultam, give products with a stereogenic center carrying a silyl group having high levels of enantiomeric purity.[18,19]

Reaction with Alkynes.

The silyl cuprate reacts with alkynes by *syn* stereospecific metallo-metallation (eq 3). Provided that the cuprate is derived from copper cyanide, the regioselectivity with terminal alkynes is highly in favor of the isomer with the silyl group on the terminus. The intermediate vinyl cuprate (**3**) reacts with many substrates, familiar in carbon-based cuprate chemistry, to give overall *syn* addition of a silyl group and an electrophile to the alkyne.[20] A curious feature of this reaction is that the intermediate (**3**), although uncharacterized, has the stoichiometry of a mixed silicon-carbon cuprate, and yet it transfers the carbon-based group to most substrates, in contrast to the behavior of mixed silyl alkyl cuprates.

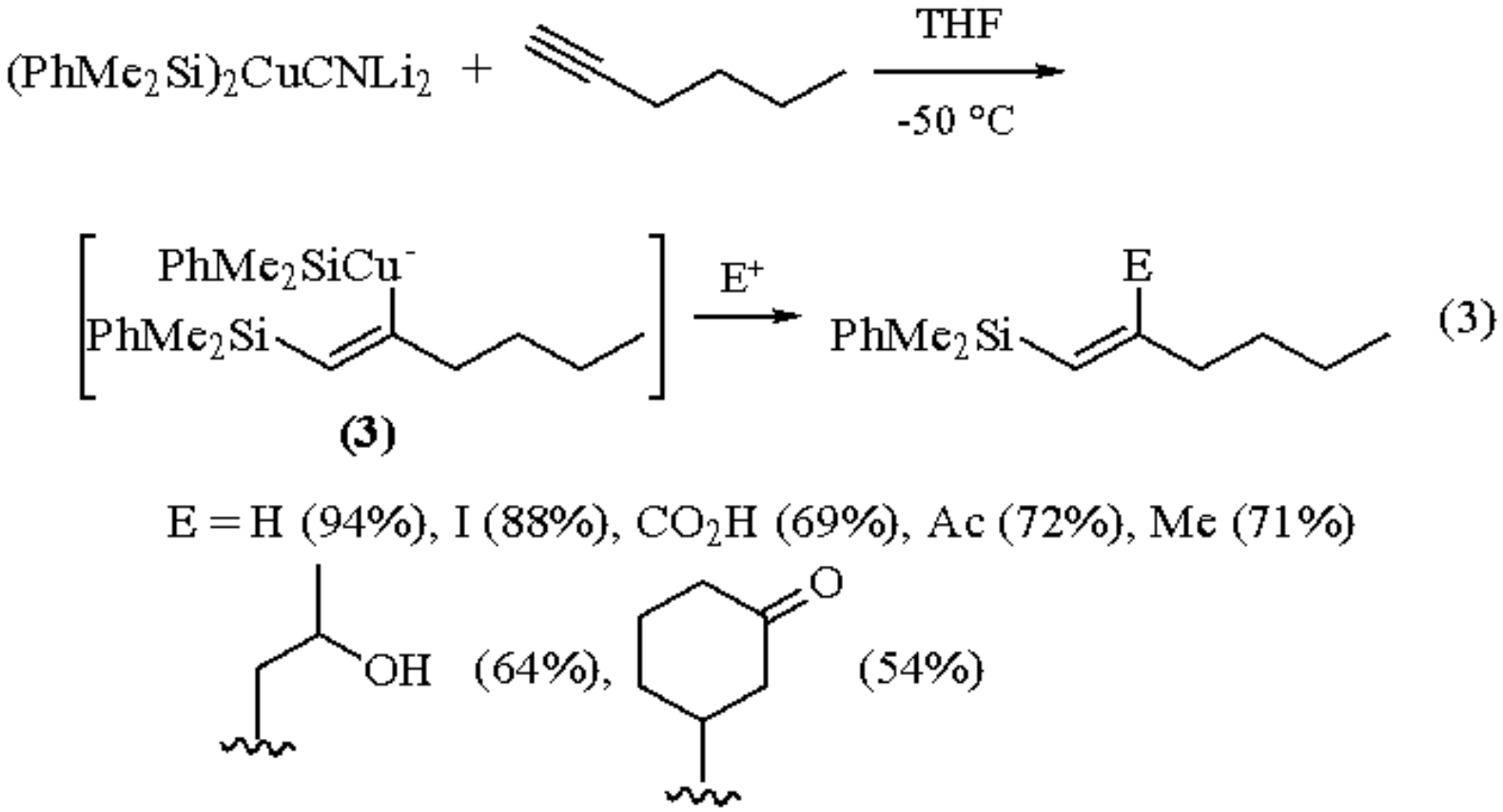

Disubstituted alkynes also react, and, if the two substituents are well differentiated sterically, as with a methyl group on one side and a branched chain on the other, the regioselectivity is highly in favor of the silyl group appearing at the less hindered end.

Reaction with Allenes.

Allenes react with the silyl cuprate at low temperature. The regiochemistry with allene itself places the silyl group on the central carbon atom and the added electrophile at the terminus (eq 4).[21] One surprising exception to this rule is with iodine as the electrophile, when the product (**5**) has the opposite regiochemistry even from that of the reaction with chlorine. Since the iodide (**5**) can be converted into a lithium reagent [and a cuprate that is not identical with (**4**)], it is possible to achieve overall either regiochemistry in additions to allene. Monosubstituted allenes give mixtures of regioisomers,[21,22] and disubstituted and trisubstituted allenes give largely allylsilanes whatever electrophile is used. The metallo-metallation step is stereospecifically *syn*.[23]

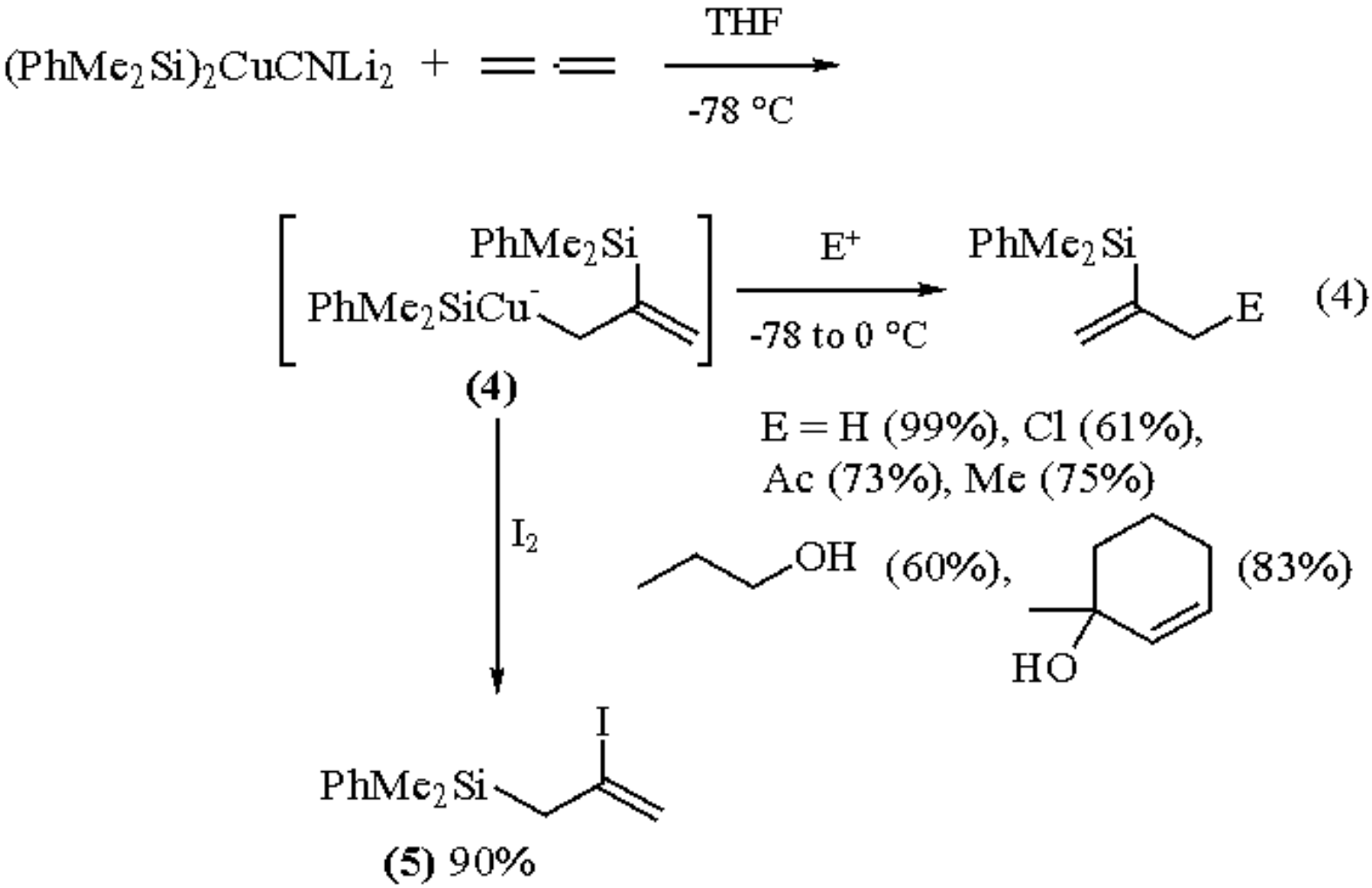

Reaction with Allylic Acetates.

Silyl cuprates react with allylic acetates to give allylsilanes directly (eqs 5-7). Allylic acetates that are secondary at both ends are apt to give both regioisomers. Some control of the regiochemistry is possible, however, by using a *cis* double bond; this encourages reaction with allylic shift, especially when the silyl group is delivered to the less-hindered end of the allylic system (eq 5).[24] An alternative protocol, assembling a mixed silyl cuprate on a carbamate group, is even better in controlling the regioselectivity, usually giving complete allylic shift (eq 6).[24,25] Tertiary acetates, on the other hand, are very well behaved regiochemically, giving only the product with the silyl group at the less-substituted end of the allylic system (eq 7).[25,26] Allylsilanes have many uses as carbon nucleophiles in organic synthesis.[27]

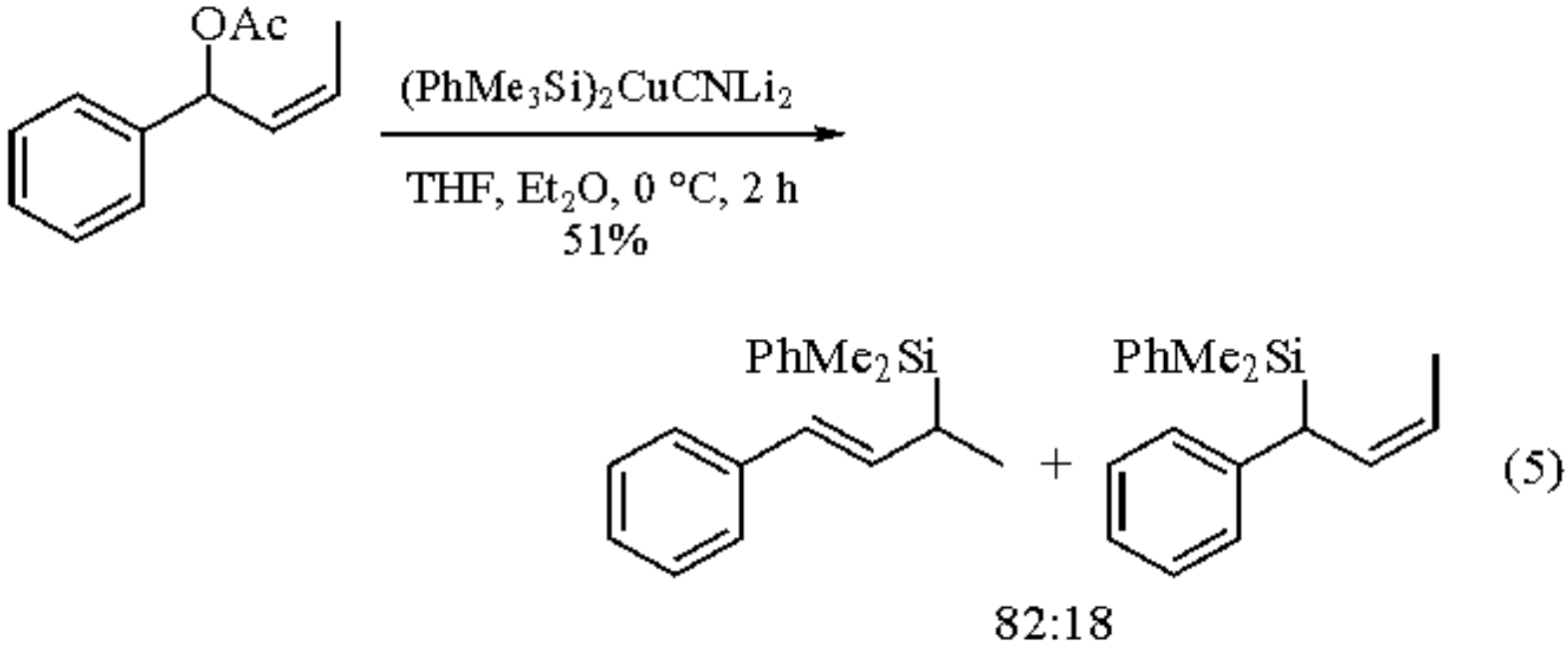

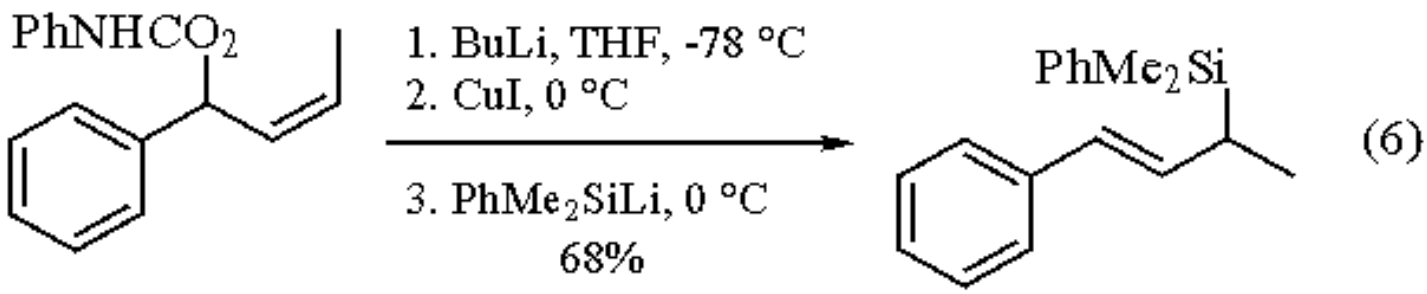

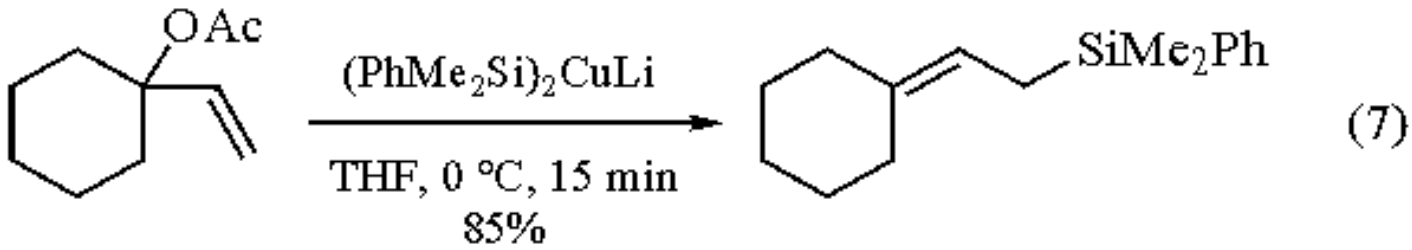

The acetate reaction (eq 5) and the carbamate alternative (eq 6) are complementary in their stereochemistry, the former taking place stereospecifically *anti* and the latter stereospecifically *syn*.[24,25]

Other Reactions.

Other substrates that have been found to react with silyl-copper reagents and with silyl cuprates are allyl chlorides,[28] an alkyl bromide,[29] epoxides,[8,22] acid chlorides,[9,30] propargyl acetates[31] and sulfides,[32] a vinyl iodide,[9] an aminomethyl acetate,[33] ethyl tetrolate,[34] and some strained allylic ethers.[35]

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Lithium Bis(*N*-methyl-*N*-phenylcarbamoyl)cuprate

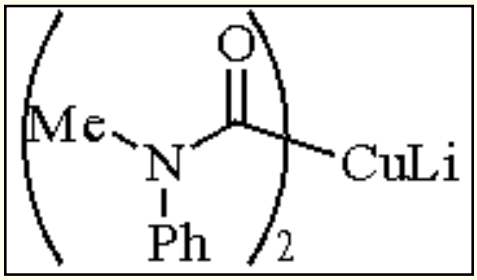

[85138-79-0] · $C_{16}H_{16}CuLiN_2O_2$ · Lithium Bis(*N*-methyl-*N*-phenylcarbamoyl)cuprate · (MW 338.80)

(carbamoylation of organic halides[1])

Alternate Name: lithium bis[(methylphenylamino)carbonyl]cuprate.

Preparative Method: prepared in situ: a solution of 18.7 mmol of *N*-methylaniline in 45 mL of anhyd ether was placed in a reaction flask equipped with a balloon; ***n-Butyllithium*** in hexane (12 mL of a 15% solution) was added with stirring at 0 °C; the resulting pale yellow solution was stirred for 1 h and exposed to ***Carbon Monoxide*** for 0.5 h at 0 °C to inactivate excess *n*-BuLi; a homogeneous solution was formed after adding 9.35 mmol of purified ***Copper(I) Iodide*** at 0 °C; after reaction with CO at 0 °C for 3.5 h, the reagent formed as a white precipitate.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive; handle under dry N_2; irritant; the hazards of CO are well-documented.[2]

Carbamoylation.

This reagent behaves very similarly to ***Lithium Bis(N,N-diethylcarbamoyl)cuprate***, a carbamoylation reagent reactive towards organic halides.[1,3,4] The reaction with ***Benzyl Bromide*** and iodobenzene gave carbamoylation products (**5**) and (**6**) in low yield (eq 1). *N,N´*-Dimethyl-*N,N´*-diphenylethanediamide (**7**), formed as a byproduct, proved to be an oxidative dimerization product arising from the organic group in the CO-containing copper complex. Reaction with ***N-Bromosuccinimide*** gave *N,N´*-dimethylcarbanilide in 46% yield. The similar reaction with 1,2-epoxyethylbenzene gave the expected 3-hydroxy-*N*-methyl-*N*-phenyl-3-

phenylpropanamide (**10**) in 52% yield.[1]

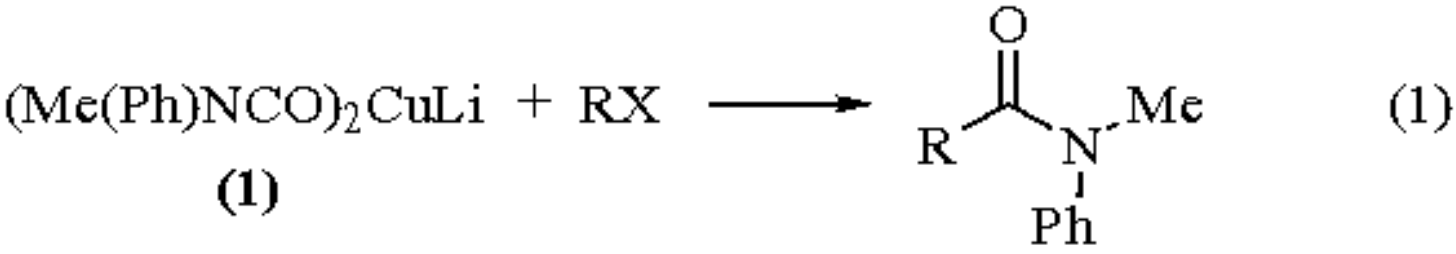

R	Yield (%)	
Me	71	**(2)**
$CH_2{=}CHCH_2$	88	**(3)**
MeCO	72	**(4)**
CH_2Ph		**(5)**
Ph		**(6)**
CON(Me)Ph		**(7)**
NHPh		**(8)**
N(Me)Ph		**(9)**
$CH_2CH(OH)Ph$		**(10)**

The reaction with iodobenzene could be optimized under the catalysis of palladium; otherwise, the yield was less than 5% (eq 2).[1,3]

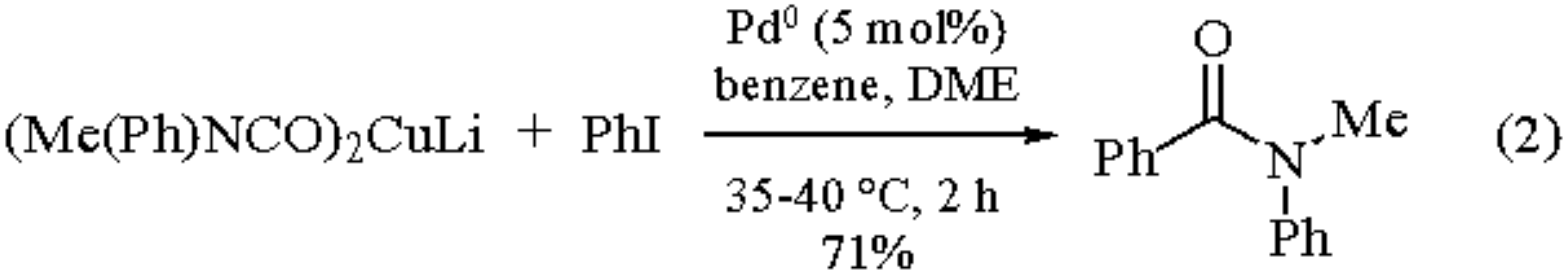

Conversion to Oxamide and Carbamate Derivatives.

Like lithium bis(*N*,*N*-diethylcarbamoyl)cuprate, lithium bis(*N*-methyl-*N*-phenylcarbamoyl)cuprate can also be converted to the corresponding oxamide by treatment with ***Bromine*** or ***Titanium(IV) Chloride*** (eq 3).[3] Formation of the corresponding oxamic acid was accomplished by reaction with ***Carbon Dioxide*** and warming with dilute acid (eq 4). Its carbamate was produced on treatment with bromine and then with

Sodium Methoxide in methanol (eq 5).[3]

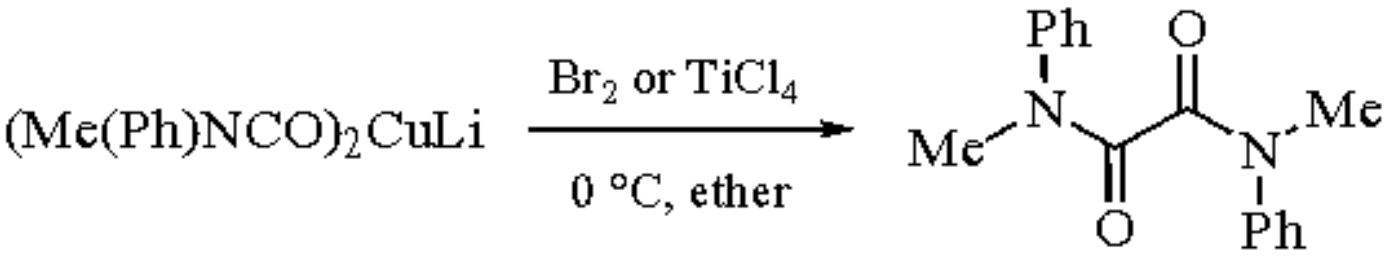

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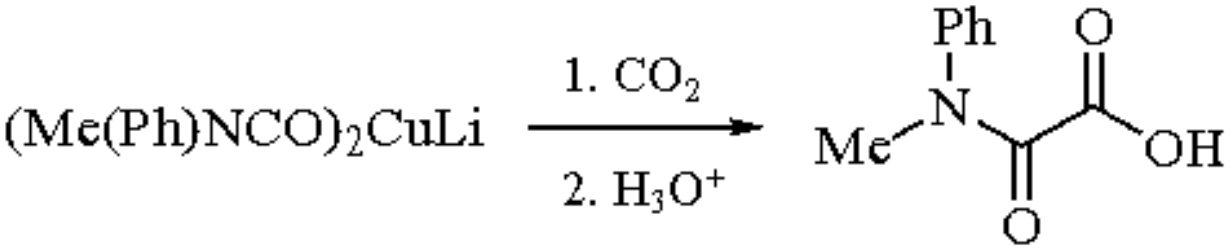

(4)

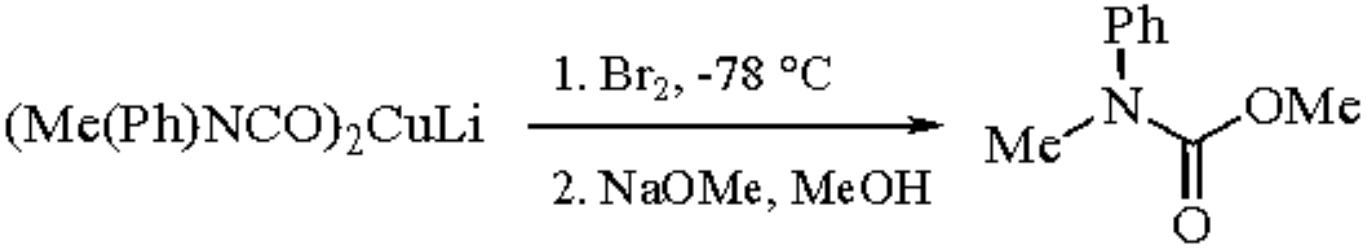

(5)

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4. Tsuda, T.; Miwa, M.; Saegusa, T. *JOC* **1979**, *44*, 3734.

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Lithium Bis(3-trimethylsilyl-1-propen-2-yl)cuprate

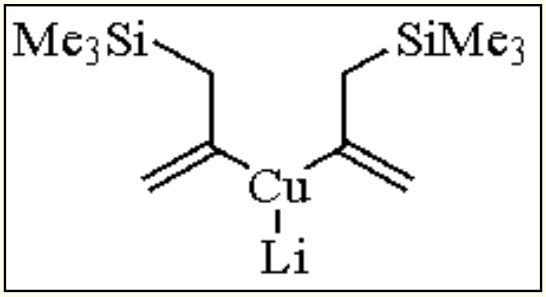

[-] · $C_{12}H_{26}CuLiSi_2$ · Lithium Bis(3-trimethylsilyl-1-propen-2-yl)cuprate · (MW 297.05)

(precursor to diene used in tandem Diels-Alder reactions)

Preparative Method: ***2-Bromo-3-trimethylsilyl-1-propene*** is lithiated with ***n-Butyllithium*** in ether at -78 °C, followed by addition of 0.5 equiv ***Copper(I) Iodide***[1].

Handling, Storage, and Precautions: air- and moisture-sensitive; use in a fume hood.

Lithium bis(3-trimethylsilyl-1-propen-2-yl)cuprate (**1**) has been used to prepare 2,3-[bis(trimethylsilyl)methyl]-1,3-butadiene (**2**) via an oxidative dimerization reaction promoted by ***Copper(II) Chloride*** (eq 1). Reaction of (**2**) with ***Dimethyl Acetylenedicarboxylate*** afforded the cyclohexadiene (**3**) in 82% yield. Oxidative bis-desilylation of (**3**) and reaction with ***N-Phenylmaleimide*** provided the linear tricycle (**4**) in moderate yield (eq 2). Additional examples of the tandem Diels-Alder sequence with a variety of dienophiles are also given.[1]

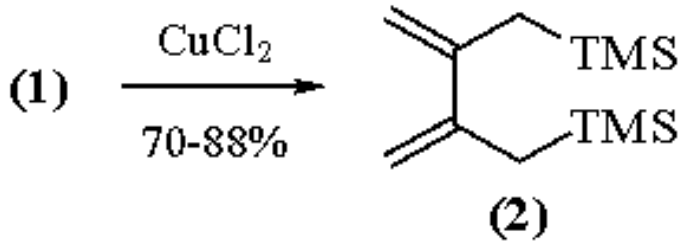

(1)

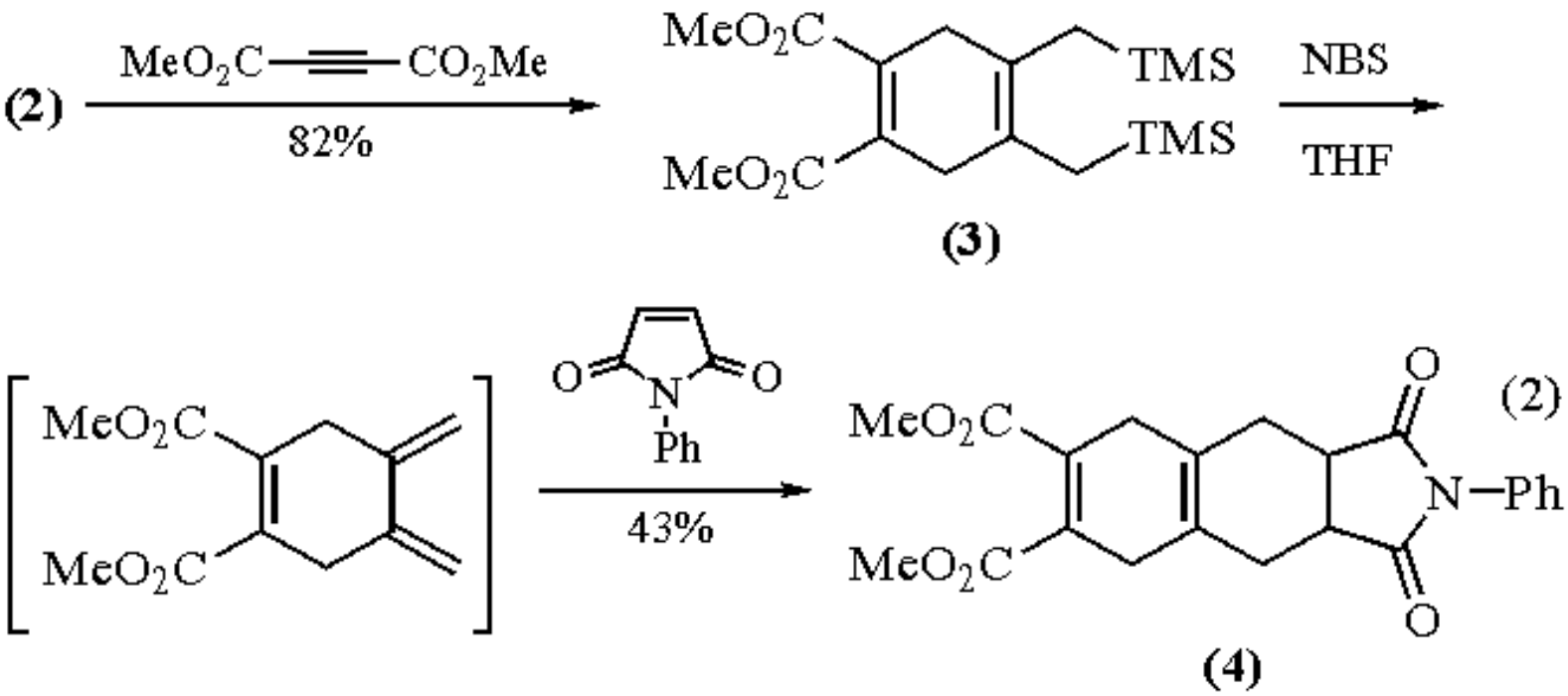

Related Reagents.

Lithium Diallylcuprate.

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1. Trost, B. M.; Shimizu, M. *JACS* **1982**, *104*, 4299.

Matthew E. Voss

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Lithium Bis(2-vinylcyclopropyl)cuprate

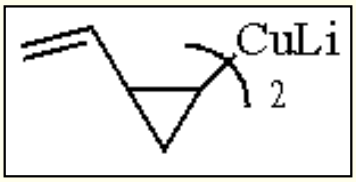

[61863-88-5] · $C_{10}H_{14}CuLi$ · Lithium Bis(2-vinylcyclopropyl)cuprate · (MW 204.73)

(organometallic reagent for the introduction of a vinylcyclopropyl unit via conjugate additions to enones and ynones; useful for the construction of divinylcyclopropane and vinylcyclopropane systems as precursors to 1,3-cycloheptadiene and cyclopentenes, respectively)

Solubility: sol THF-ether (2:1) at -78 °C.

Preparative Method: prepared at -78 °C by adding a solution (THF-ether; 2:1) of 2-vinylcyclopropyllithium to 0.5 equiv of $CuBr.SMe_2$ (see ***Copper(I) Bromide***); the cyclopropyllithium intermediate can be generated by the metal-halogen exchange of 2-vinylcyclopropyl bromide with ***t-Butyllithium*** at -95 °C (eq 1).[1]

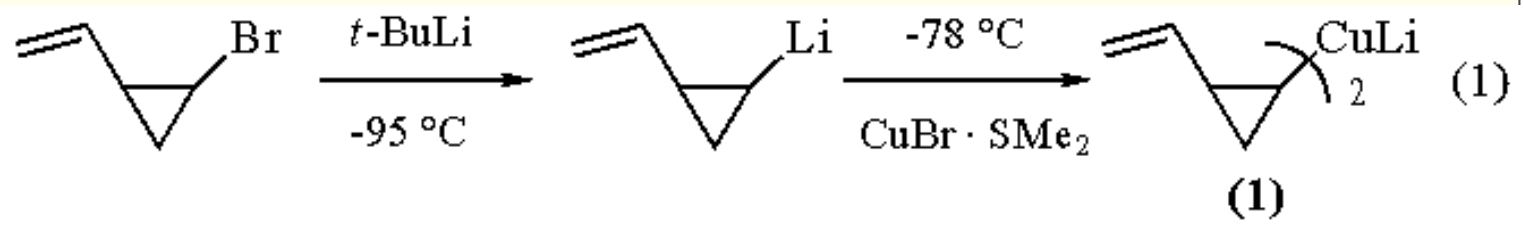

Handling, Storage, and Precautions: thermally unstable; must be generated in the absence of H_2O and O_2 at -78 °C; reactions with (**1**) and unsaturated carbonyl compounds should be carried out at -78 °C.

Conjugate Additions to Unsaturated Carbonyl Compounds.

The major utility of lithium bis(2-vinylcyclopropyl)cuprate (**1**) is its reaction with α,β-alkynic esters and ketones in order to construct the divinylcyclopropane system. The 1,4-addition of (**1**) to the alkynic ketone (**2**) to produce an 8:1 mixture of the divinylcyclopropane (**3**) and the rearranged product (**4**) in 90% yield is illustrated in eq 2.[2]

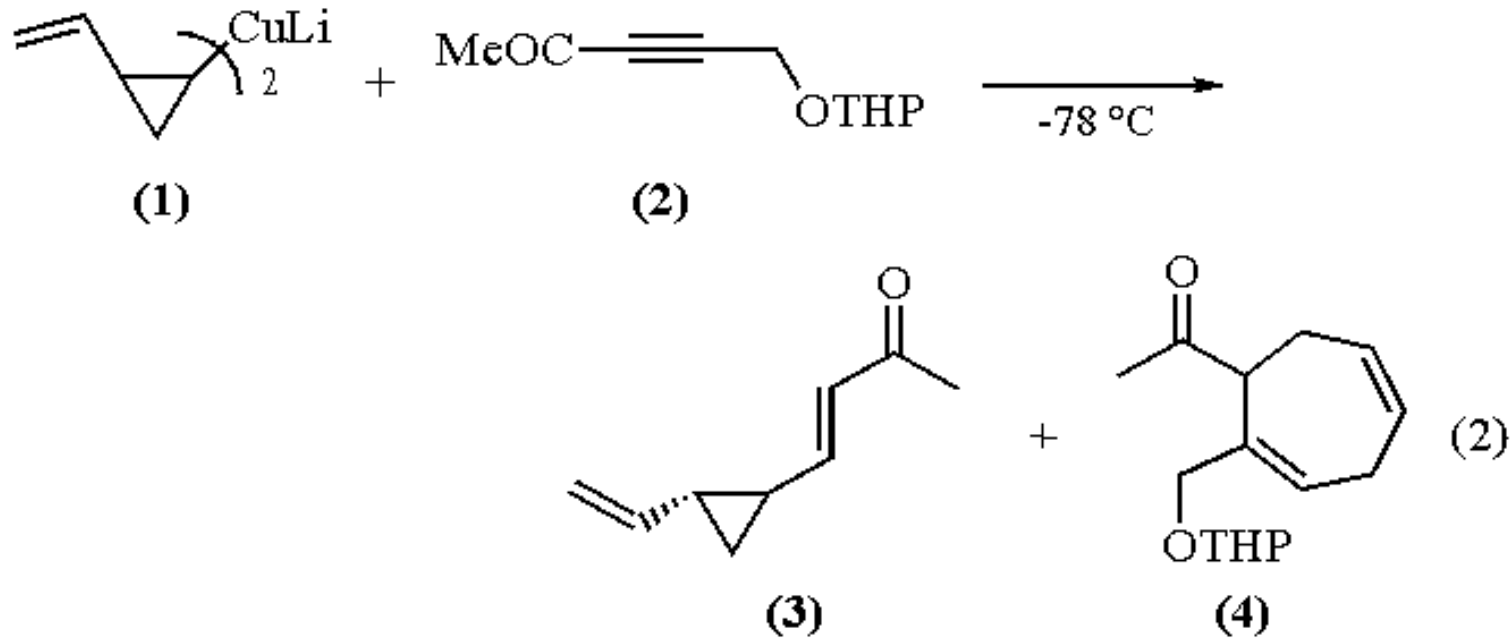

The 1,3-cycloheptadiene product (**4**) is the result of the facile 3,3-sigmatropic rearrangement of the *cis*-(2-vinylcyclopropyl)enone isomer. In fact, the *trans* isomer also rearranges at higher temperatures (140-150 °C) to the same cycloheptadiene (**4**).

In studies directed towards the synthesis of ring-fused cycloheptadienes,[2,3] an analogous cuprate containing a phenylthio ligand (see ***Lithium Phenylthio(2-vinylcyclopropyl)cuprate***) has been added 1,4 in an addition/β-elimination process to a β-iodocyclohexenone (**5**) (eq 3). Subsequent rearrangement of adduct (**6**) leads to a ring-fused 1,3-cycloheptadiene (**7**).

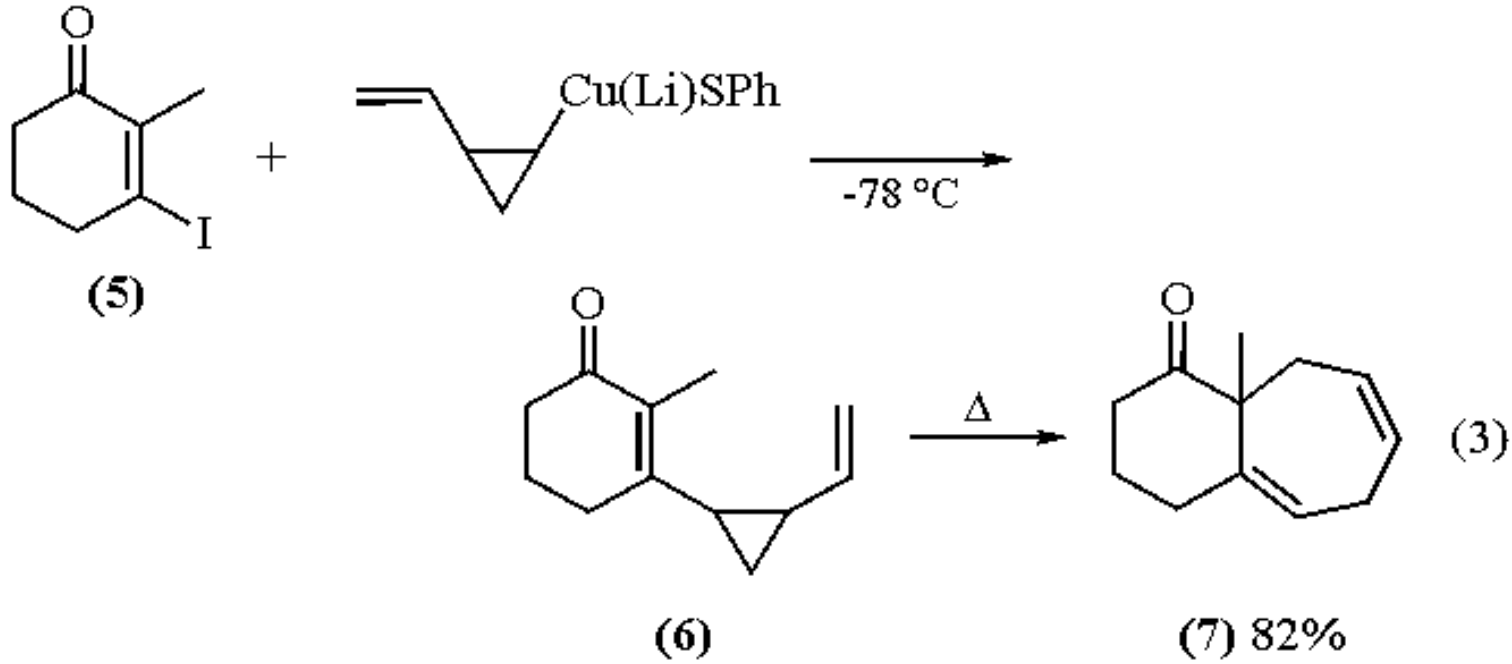

Other variants[4] of eq 3 have led to the synthesis of spirocycloheptadienes (**8**) (eq 4) after thermal rearrangement of the divinylcyclopropane.

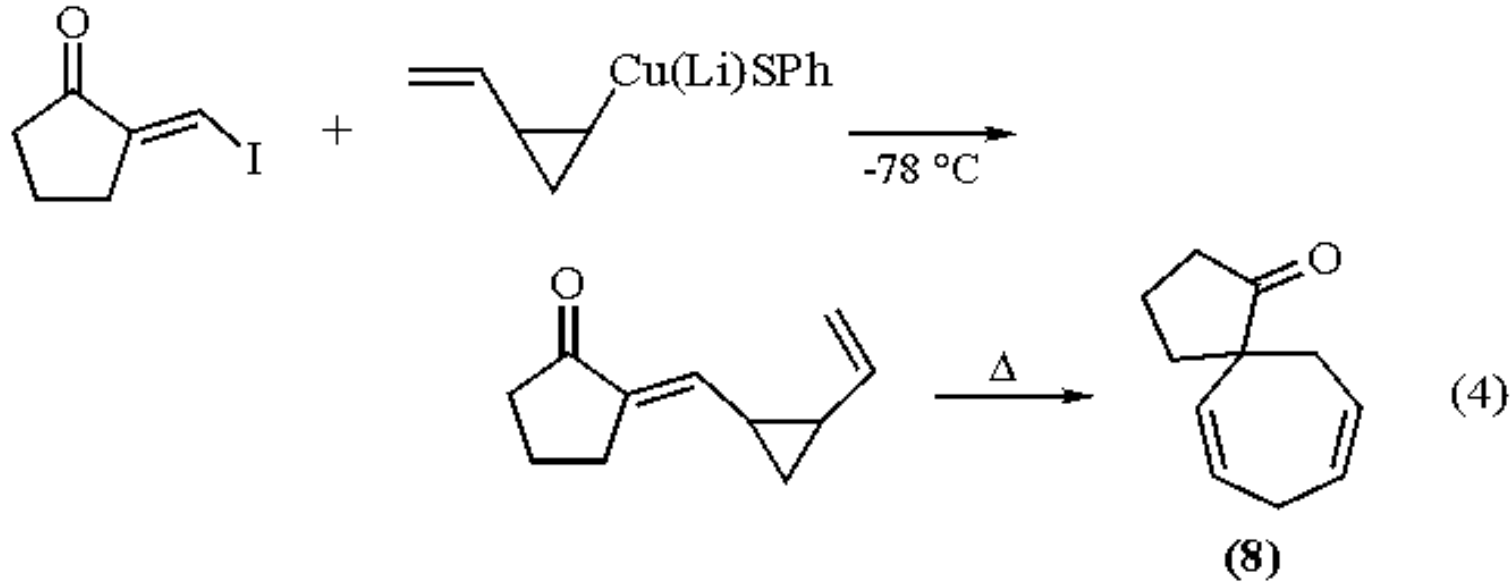

2-Vinylcyclopropylcuprates also undergo rapid acylations with acid chlorides to produce 2-vinylcyclopropyl ketones such as (**9**) (eq 5). Ketone (**9**) may also be converted to a divinylcyclopropane system via its enol ether (**10**), and then to a spirocycloheptadiene (**11**) (eq 6).[5]

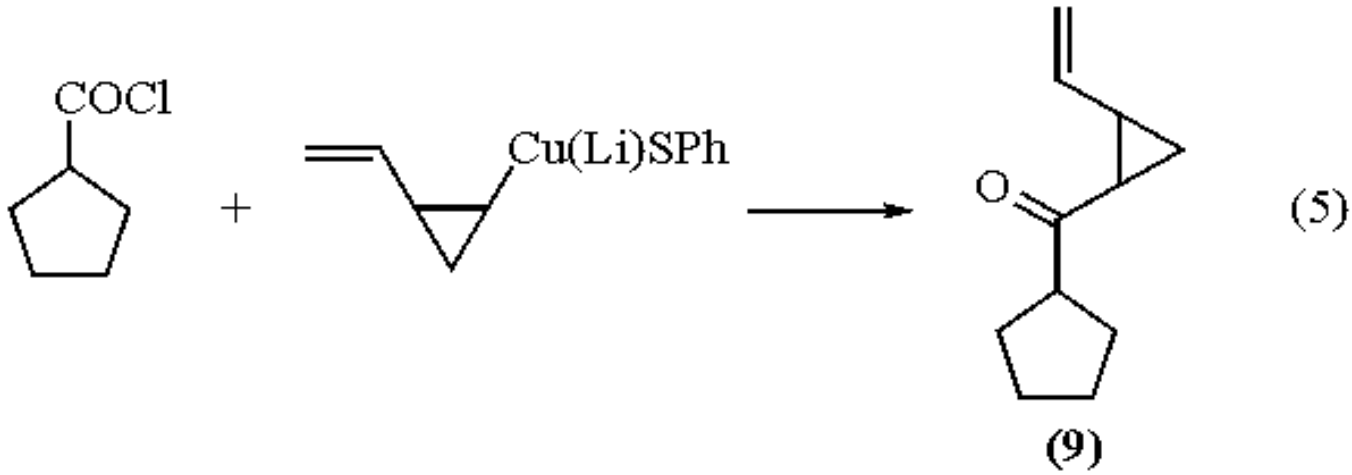

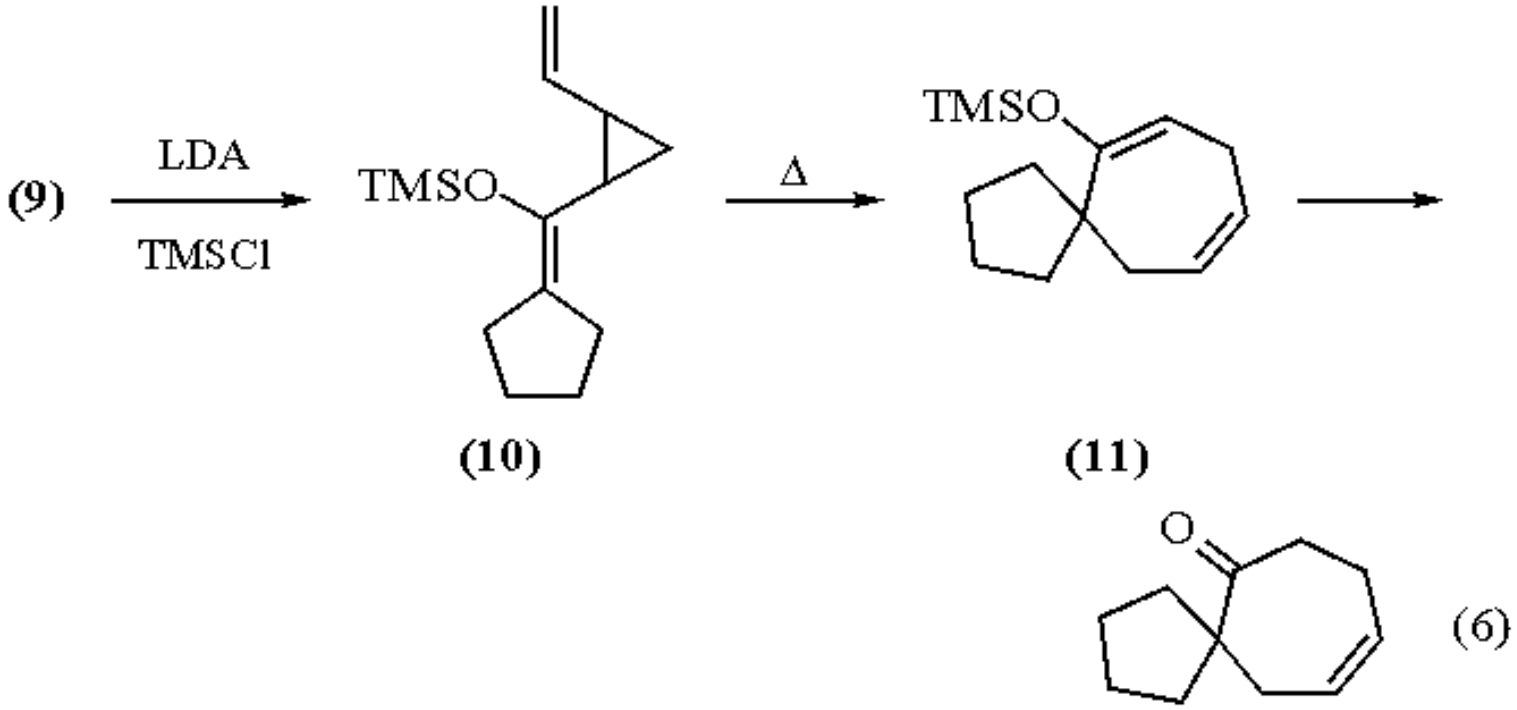

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3. Piers, E.; Nagakura, I. *TL* **1976**, 3237.
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Lithium 9-boratabicyclo[3.3.1]nonane[1]

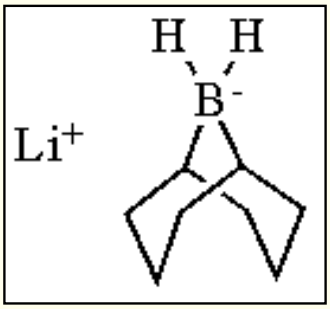

[76448-08-3] · $C_8H_{16}BLi$ · Lithium 9-boratabicyclo[3.3.1]nonane · (MW 129.99)

(selective reducing agent for esters, aldehydes, ketones, primary halides and tosylates, epoxides, aromatic nitriles, and tertiary amides; catalyst for $LiBH_4$ reduction of esters; with 9-BBN-H, reduces carboxylic acids to aldehydes)

Alternate Name: Li(H_2-9-BBN).

Physical Data: colorless in THF solution.

Solubility: sol THF; evolves H_2 in protic solvents.[2]

Form Supplied in: 1.0 M solution in THF.

Analysis of Reagent Purity: ^{11}B NMR resonance in THF at δ -17.4 (t, *J* = 72.1 Hz) ppm.[2a]

Handling, Storage, and Precautions: THF solutions of the reagent are stable indefinitely at 25 °C when stored under N_2; exposure to O_2, H_2O, or protic solvents results in its potentially dangerous rapid oxidation and/or the exothermic generation of H_2; its generation and use involves handling air-sensitive reagents (i.e. LiH, ***9-Borabicyclo[3.3.1]nonane***); use in a fume hood.[1]

Selective Reductions.

The reagent is conveniently prepared from an excess of LiH and 9-BBN in THF (48 h, 65 °C)[2] and is omnipresent as a byproduct from the reaction of alkyllithium reagents with 9-BBN.[3] Its reactivity with representative compounds containing different functional groups has been surveyed.[2b] Primary alcohols, phenols, and aliphatic and aromatic thiols react with excess reagent in THF at 25 °C with rapid and quantitative H_2 evolution. However, *n*-hexylamine is unreactive, and secondary and tertiary alcohols react very slowly under these conditions. The reagent reduces acid chlorides, esters, lactones, aldehydes, and even highly substituted ketones to the corresponding alcohols (eq 1), but

anhydrides are only reduced to an equimolar mixture of alcohol and carboxylate. Cinnamaldehyde undergoes clean 1,2-reduction to produce cinnamyl alcohol. Epoxides are reductively opened from the least substituted side while acetals and orthoesters are inert to the reagent. Treatment of primary amides with Li(H_2-9-BBN) leads only to slow H_2 evolution, whereas caprolactam is reduced slowly and tertiary amides are reduced to the corresponding amines (24 h, 25 °C). Aromatic nitriles are also reduced to the amine under these conditions, but aliphatic nitriles react sluggishly. Isocyanates are reduced to formamides while treatment of oximes results only in H_2 evolution. Azobenzene is essentially inert to the reagent, while pyridine, azoxybenzene, and nitropropane are partially reduced. Nitrobenzene and pyridine *N*-oxide are reduced, but the actual products have not been determined. Disulfides are reduced to thiolates, while sulfoxides, sulfones, sulfonic acids, and sulfides are inert. The reduction of *n*-alkyl derivatives follows the order: I > OTs > Br >> Cl, whereas secondary bromides and tosylates are not effectively reduced at 25 °C. *B*-Halo-9-BBN derivatives are also conveniently reduced to 9-BBN by the reagent.[4]

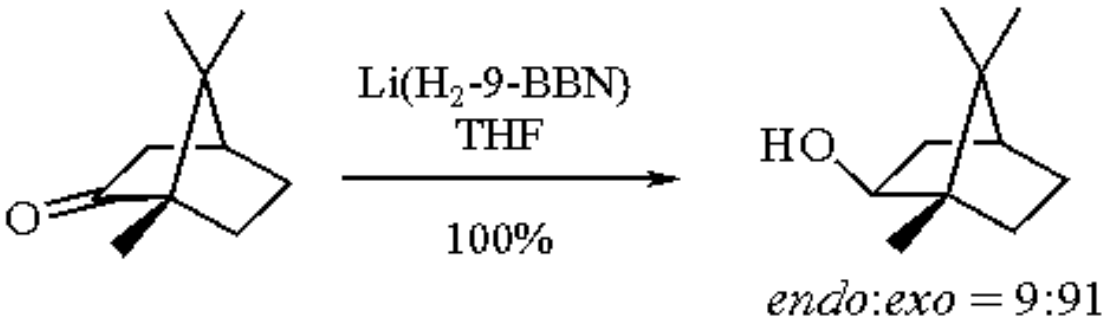

(1)

Catalyst for the $LiBH_4$ Reduction of Esters.

The reduction of ethyl caproate by Li(H_2-9-BBN) is rapid in THF (1 h, 25 °C), while its reduction by ***Lithium Borohydride*** is significant slower (ca. 50% in 8 h, 25 °C). With 10 mol % of Li(H_2-9-BBN) or *B*-MeO-9-BBN as well as other organoboranes as catalysts, a markedly enhanced rate of reduction of esters by $LiBH_4$ in THF (8 h, 25 °C) or ether (eq 2) is observed.[5] A modest catalytic effect is observed for epoxides and primary tosylates, and the reduction of benzonitrile by $LiBH_4$ is observed only with added catalyst. *n*-Octyl bromide is not reduced under catalytic conditions, but is reduced slowly by using stoichiometric amounts of Li(H_2-9-BBN) (6 h, 25 °C). This reagent may be the active species in these catalytic reductions.

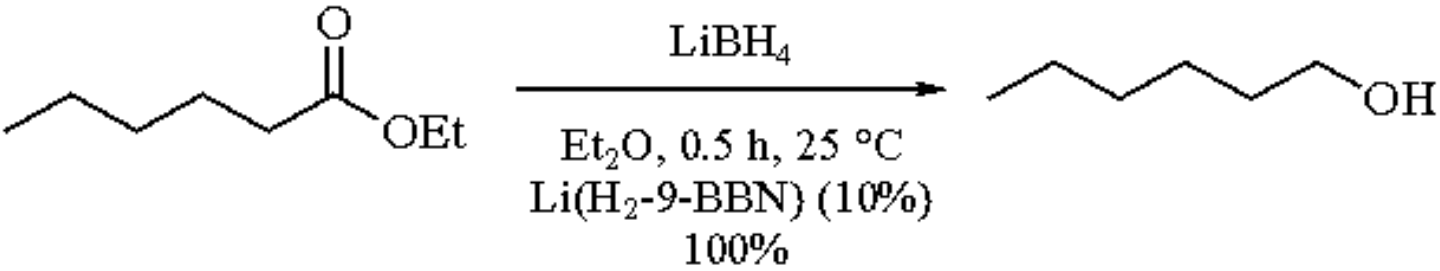

(2)

Aldehydes from Carboxylic Acids.[6]

The reaction of 9-BBN with carboxylic acids evolves H_2, producing the corresponding acyloxy-9-BBN derivative which, upon treatment with Li(H_2-9-BBN) at room temperature, gives high yields of the corresponding aldehydes (76-99%). The procedure is widely applicable, being effective for both aromatic and aliphatic substrates (eq 3). Dicarboxylic acids are also reduced to dialdehydes efficiently (eq 4), and the process tolerates aromatic functionality

(e.g. Cl, NO_2, OMe).

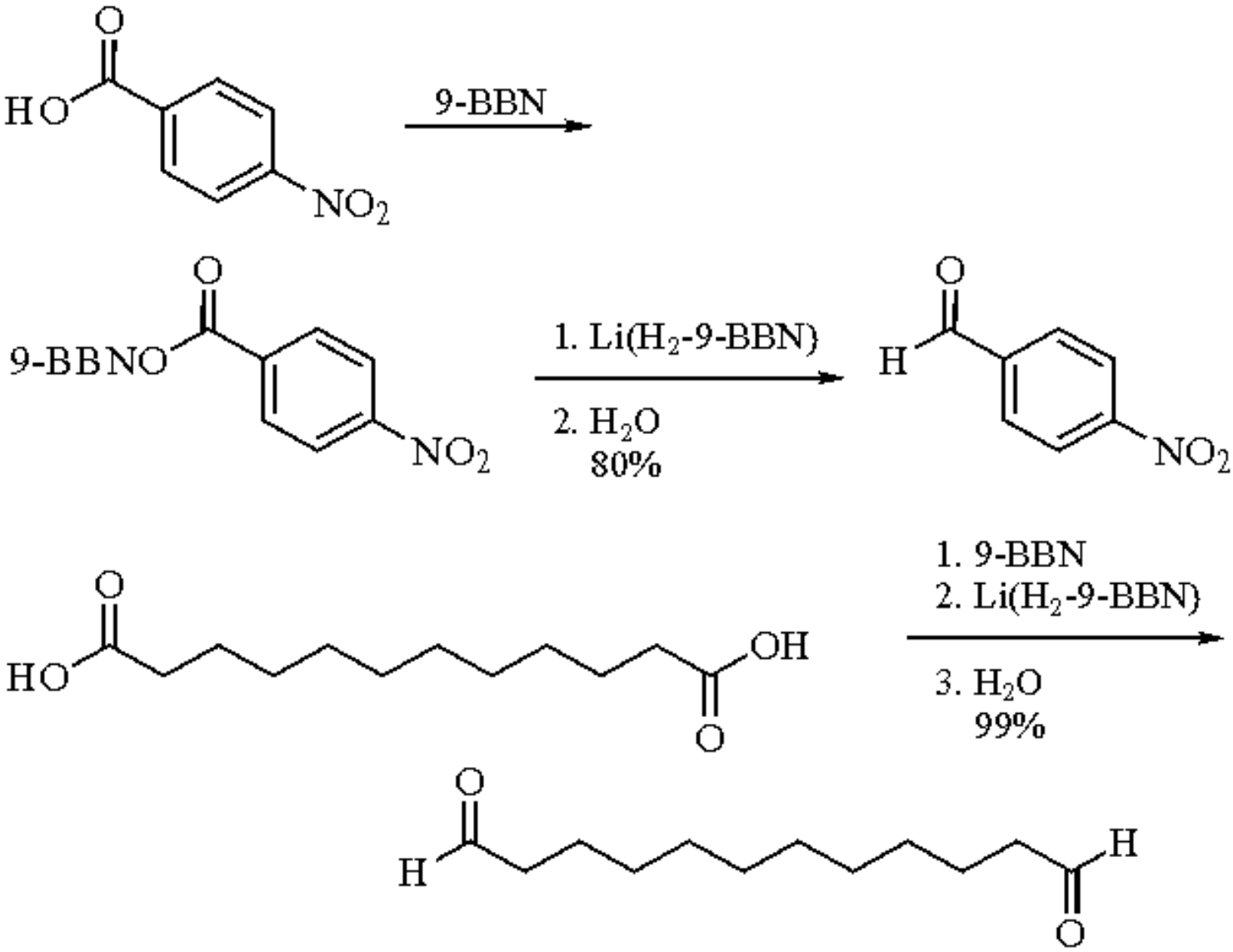

(3)

(4)

Related Reagents.

Lithium Borohydride; ***Lithium 9,9-Dibutyl-9-borabicyclo[3.3.1]nonanate***; ***Potassium 9-Siamyl-9-boratabicyclo[3.3.1]nonane***.

---

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4. Brown, H. C.; Kulkarni, S. U. *JOM* **1981**, *218*, 299.
5. (a) Brown, H. C.; Narasimham, S. *JOC* **1982**, *47*, 1604. (b) Brown, H. C.; Narasimham, S. *JOC* **1984**, *49*, 3891.
6. Cha, S. S.; Kim, J. E.; Oh, S. Y.; Kim, J. D. *TL* **1987**, *28*, 4575.

Lithium Borohydride[1]

$LiBH_4$

[16949-15-8] · BH_4Li · Lithium Borohydride · (MW 21.78)

(reducing agent for esters and lactones,[1,2a,b] acyl chlorides,[2c] epoxides,[1] aldehydes and ketones;[1,2a,b,d] precursor of other borohydrides;[1] catalyst for hydroborations[3])

Physical Data: mp 284 °C (dec); *d* 0.666 g cm^{-3}.

Solubility: sol ethers (3 g/100 mL Et_2O, 25 g/100 mL THF),[4] lower primary amines ($MeNH_2$, $EtNH_2$, *i*-$PrNH_2$),[5] diglyme[6] (9 g/100 mL);[4] sol (with reaction) alcohols[7] (1.6 g/100 mL MeOH, 3 g/100 mL *i*-PrOH);[4] solution in absolute EtOH shows no appreciable decomposition after 2-4 h at about 0 °C;[7] solution in *i*-PrOH shows no decomposition after 24 h;[4] sol (with slow decomposition) water.

Form Supplied in: off-white solid; 2.0 M solution in THF.

Analysis of Reagent Purity: hydrolysis with dilute acid and titration for boron;[8] ethereal or THF solutions can be titrated with 2 N HCl-THF (1:1).[4]

Purification: recrystallization from Et_2O; the purified material is pumped free of ether at 90-100 °C for 2 h.[8]

Handling, Storage, and Precautions: both solutions and (especially) the solid[9] are flammable and must be stored under N_2 in the absence of moisture; the solid is capable of creating a dust explosion; $LiBH_4$ reacts with water and acids, generating flammable and/or explosive gas (H_2 and borane), and is incompatible with strong oxidizing agents.

Reduction of Functional Groups.

Lithium borohydride is more reactive as a reducing agent than ***Sodium Borohydride*** and less reactive than ***Lithium Aluminum Hydride***.[1] In THF, $LiBH_4$ readily reduces aldehydes and ketones to alcohols at room or even ice-bath temperature,[9] whereas esters and lactones require higher temperatures and prolonged reaction times to give the corresponding alcohols and diols. Thus selective reductions are possible. Epoxides are reduced by $LiBH_4$, while carboxylic acids, carboxylic acid salts, tertiary amides, nitriles, nitro compounds, alkenes, and halogeno derivatives do not usually react.[1]

The chief advantage of $LiBH_4$ over $LiAlH_4$ is its much greater chemoselectivity, while the chief advantage over $NaBH_4$ is its higher solubility in ethereal solvents. The different reactivity of the two lithium hydrides ($LiBH_4$ and $LiAlH_4$) is essentially due to the different hardness of the two hydride-delivering anions, while the different reactivity of the two borohydrides ($LiBH_4$ and $NaBH_4$) is essentially due to the different Lewis acidity of the associated cation, rather than to differences in solubility.[6,10]

Lithium borohydride reactivity is greatest in media of low dielectric constant: increasing the polarity decreases reactivity.[4] The order of reactivity is $LiBH_4$ in Et_2O > THF &AApprox; diglyme > 2-propanol; this trend is exactly reversed for $Ca(BH_4)_2$.

Several papers have dealt with the effects of solvent,[4,6,11] concentration,[10a] added salt,[6] and added cation complexing agents[10] both on the reaction rate and the regiochemistry of $LiBH_4$ reductions, regarding essentially ester reduction.

Since carbonyl compounds are rapidly reduced by $LiBH_4$ alone, less attention has been devoted to this reaction. Nevertheless, it has been shown that the rate of the reduction of acetone in *i*-PrOH[11] ($k = 50.3 \times 10^{-4}$ L mol^{-1} s^{-1}) is not appreciably affected by the addition of ***Triethylamine***, while addition of ***Lithium Chloride*** accelerated the reduction. The added lithium salt probably has a double effect: on one hand, it can modify the nature of the ionic cluster; on the other, it can activate the carbonyl group. In contrast, $NaBH_4$ reductions are almost unaffected by added ***Sodium Iodide*** and accelerated by Et_3N. Reaction rates for reduction of some aliphatic and aromatic ketones with borohydrides in various solvents have been reported.[12]

In the reduction of cyclic ketones, $LiBH_4$ generally attacks more from the more hindered side than $LiAlH_4$;[13] stereochemical aspects of cyclic ketone reduction by complex borohydrides have been widely discussed in some reviews.[14] In the reduction of conjugated cyclic enones[1,10,13] $LiBH_4$ usually gives more 1,4-attack than does $LiAlH_4$. This tendency is enforced by the presence of a lithium-complexing agent, such as [2.1.1]cryptand: when lithium cation is removed from the reaction medium, the reaction rate of 1,2-attack is decreased more than that of 1,4-attack, probably because of different influence of Li^+ on the carbonyl LUMO and on reducing agent HOMO levels, so that 1,4-attack becomes predominant.[10b] For example, cyclohexen-3-one is reduced to give predominantly the corresponding allylic alcohol by $LiBH_4$ alone, while in the presence of [2.1.1]cryptand the saturated ketone and alcohol are largely predominant (eq 1). Results comparable to that reported in eq 1 have also been obtained using ***Tetra-n-butylammonium Borohydride*** in several aprotic solvents.[15]

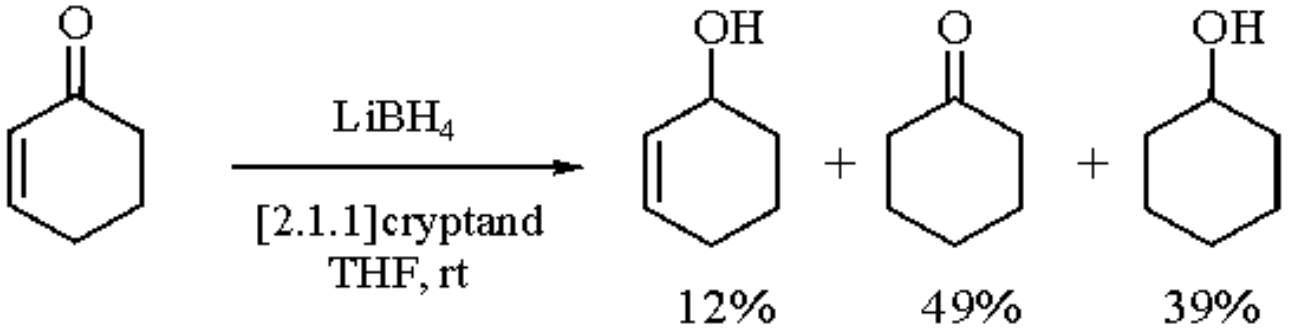

(1)

Regio- and diastereoselective reductions of steroidal ketones have been achieved by using $LiBH_4$.[7,16a] Stereoselective reduction of a polyfunctionalized ketone, intermediate in the synthesis of oleandomycin, was realised via $LiBH_4$ reduction (THF-MeOH, -78 °C) of the dibutylboron aldolate derived from reaction of the ketone itself with dibutylmethoxyborane.[16b]

More studies have been devoted to the reduction of esters, regarding the solvent and possible additives. Different solvents can be used: Et_2O, THF, diglyme, or *i*-PrOH, although in the latter case a large excess of $LiBH_4$ is required to compensate the loss due to the side reaction with the solvent.[5] A clean procedure to reduce esters in high yield using an essentially stoichiometric amount of $LiBH_4$ in Et_2O or THF has been reported.[4] Under these reaction conditions, hindered esters, such as ethyl adamantanecarboxylate, and lactones are also readily reduced, while other functional groups, such as alkyl and aryl halides, nitro groups, ethers, and nitriles remain unaffected. Diesters have been reduced to the corresponding diols using $LiBH_4$,[4,17] while reduction of ***Ethyl Acetoacetate*** has been reported to give rise to some problems, due to the formation of a borate complex, from which the reduction product cannot be isolated.[9]

The reducing ability of $LiBH_4$ has been found to be greatly enhanced in mixed solvents containing methanol, and to be dependent on the amount of added alcohol.[18] Using the $LiBH_4$-Et_2O-MeOH (1 equiv with respect to $LiBH_4$) reducing system, esters, lactones, and epoxides are selectively reduced, even at room temperature, with respect to nitro groups, aryl halides, primary amides, and carboxylic acids. By employing the $LiBH_4$-diglyme (or THF)-MeOH (4 equiv with respect to $LiBH_4$) systems, a further enhancement of reducing capabilities is observed: nitro compounds and nitriles are reduced to amines, and carboxylic acids are reduced to alcohols, while amides show different behaviors depending on substitution. Tertiary amides are reduced essentially to alcohols, through C-N bond fission, while primary amides are cleanly reduced to amines, via C-O bond fission. Secondary amides show different behavior depending on nitrogen substituent.

The chemoselective reduction of an ester moiety in the presence of a carboxylic acid, using $LiBH_4$, or vice versa, using diborane, has been applied in the stereoselective synthesis of both (*R*)- and (*S*)-mevalonolactone.[19a] The chemoselective reduction of an ester with respect to an amide using $LiBH_4$ in THF has been reported in carbohydrate chemistry.[19b] Sterically hindered acyloxazolidinones have been reduced to the corresponding primary alcohols using $LiBH_4$ in Et_2O containing water (1 equiv) in better yields than using $LiBH_4$ or $LiAlH_4$ alone.[19c]

An interesting stereoselective 1,4 reduction of an acetoxy unsaturated nitrile has been realized by using $LiBH_4$ in THF, probably through the intermediate formation of an alkoxyhydride; the same reaction has been realized on a preparative scale using $LiAlH_4$ in THF.[20a] Sparse reports on the reduction of other functional groups (carbazole derivatives of carboxylic acids to aldehydes,[20b] hydrazides to hydrazines,[20c] cyclic anhydrides to lactones,[20d] acyl chlorides to alcohols[2b]) using $LiBH_4$ in various nonhydroxylic solvents have appeared.

Reactivity of $LiBH_4$ towards *n*-octyl chloride has been found to be extremely low; ***Lithium Triethylborohydride*** is 10^4 times more efficient in carrying out the reduction to *n*-octane.[21a] Alkyl tosylates are almost inert towards $LiBH_4$, while they are readily reduced by $LiEt_3BH$.[21b]

Epoxides are smoothly reduced by $LiBH_4$,[18,22] with attack occurring mainly at the less hindered site and *cis* epoxides being reduced more rapidly than *trans* ones. 2,3-Epoxy alcohols and their derivatives can be regioselectively reduced to 1,2-diols by using a suspension of $LiBH_4$ in hexane at ambient temperature;[23] results are superior to that obtained using completely dissolved $LiBH_4$ in THF or a ***Titanium Tetraisopropoxide***-$LiBH_4$ system (see below).

Addition of Lewis Acids.

In the effort to tune up the selectivity of lithium borohydride, several combinations of the reducing agent with a variety

of Lewis acids have been assayed.

Addition of boranes or alkoxyboranes greatly enhances the reactivity of $LiBH_4$ towards esters in Et_2O or THF;[24] a particularly high catalytic effect is shown by *B*-MeO-9-BBN and ***Trimethyl Borate***. Many other additives that generate a borane species under the reaction conditions (e.g. $LiEt_3BH$, $LiEt_3BOMe$, ***Tri-n-butylborane***) show a catalytic effect. These additives also exert a catalytic effect on epoxide reductions, but have little if any influence on the reduction of carboxylic acids, tertiary amides [which can be reduced by *n*-Bu_4NBH_4 or by $NaBH_4$-***Titanium(IV) Chloride*** (see under ***Sodium Borohydride***)], nitriles, sulfur compounds, and pyridine. ***Borane-Tetrahydrofuran*** and ***Boron Trifluoride Etherate*** are ineffective as catalysts. Alkenes, although normally inert to the action of $LiBH_4$, are hydroborated (see below) by this reagent in the presence of esters, with concomitant enhancement of the ester reduction rate: as a consequence, unsaturated esters are transformed into a mixture of regioisomeric diols.

Lithium borohydride combined with ***Chlorotrimethylsilane*** generates a more powerful reducing system.[25] Amino acids can be reduced to amino alcohols, with retention of optical purity; primary, secondary, and tertiary amides, as well as nitriles, are reduced to amines, and sulfoxides to sulfides; a nitrostyrene derivative is reduced to the corresponding saturated amine, in better yield than with alternative reducing systems ($LiAlH_4$ or catalytic hydrogenation). These reactions are believed to proceed through the formation of a borane-THF complex.

Lithium borohydride combined with ***Europium(III) Chloride*** in MeOH-Et_2O has given the best result in regio- and diastereoselective reduction of a polyfunctionalized conjugated enone intermediate in the synthesis of palytoxin.[26] Inferior results were obtained with other reducing systems.

Lithium borohydride combined with titanium tetraisopropoxide in THF, benzene, or CH_2Cl_2 reduces 2,3-epoxy alcohols regioselectively to 1,2-diols in high yield.[27a,b] Good 1,2 regioselectivity is shown also by ***Diisobutylaluminum Hydride*** (DIBAL) in benzene, while 1,3-diols can be regioselectively obtained by using Red-Al (***Sodium Bis(2-methoxyethoxy)aluminum Hydride***) in THF.[27c,d] The $LiBH_4$-Ti(*i*-PrO)$_4$ system is effective in *syn* diastereoselective reduction of β-hydroxy ketones to 1,3-diols,[27e] although other hydrides ($LiAlH_4$, $NaBH_4$) combined with different additives [Ti(*i*-PrO)$_4$, Ti(OEt)$_4$, $TiCl_4$, LiI] show the same trend and often give better results.

The addition of titanium tetrachloride reverses the diastereoselectivity of the $LiBH_4$ reduction of 3,3-dimethyl-2,4-pentanedione,[28] so that *meso*-2,4-pentanediol is obtained as the main product.

Lithium borohydride (but also $LiAlH_4$ and $NaBH_4$) combined with boron trifluoride etherate in Et_2O, THF, or THF-diglyme reduces cyclic lactones to cyclic ethers.[29]

Addition of Grignard Reagents.

Synthesis of secondary alcohols from esters can be realised by combining $LiBH_4$ with Grignard reagents via formation of an intermediate ketone, which is reduced by $LiBH_4$ much more rapidly than the ester.[30a] When 2-alkoxy esters are used, stereoselective formation of *anti* 1,2-diols is observed, especially when THF is used as solvent.[30b] The reversed diastereoselectivity is observed when DIBAL is added to the ester, with formation of an intermediate aldehyde, before adding the Grignard reagent.

Addition of Chiral Ligands.

N-Benzoylcysteine, a chiral ligand available in both enantiomeric forms, is highly effective in enantioselective $LiBH_4$ reductions of alkyl aryl ketones in THF-*t*-BuOH (ee up to 92%).[31a] Analogous results are obtained using the dimer *N*,*N*-dibenzoylcystine,[31b] which also reduces a conjugated enone to the corresponding chiral allyl alcohol.[31b] The $LiBH_4$-*N*,*N*-dibenzoylcystine system has also been used to enantioselectively reduce β-keto esters,[31c] β-chloro ketones[31d] (which are precursors of optically active oxetanes), acetylpyridines, and α- and β-amino ketones.[31e]

Other Reductions.

In an attempt to reduce the ester moiety of some functionalized 2-methylthiopyrimidines, it has been found that $LiBH_4$ (and also $LiAlH_4$) in THF reduces the heteroaromatic ring, leaving almost unaffected the ester and other functional groups, so that differently substituted 1,6-dihydroxypyrimidines can be obtained in good yields (eq 2).[32] Differently functionalized pyrimidines are similarly reduced by $LiBH_4$ in DMF. It should be emphasized that a tertiary amide like DMF can be a suitable solvent for $LiBH_4$ (see above for discussion of amide reductions).

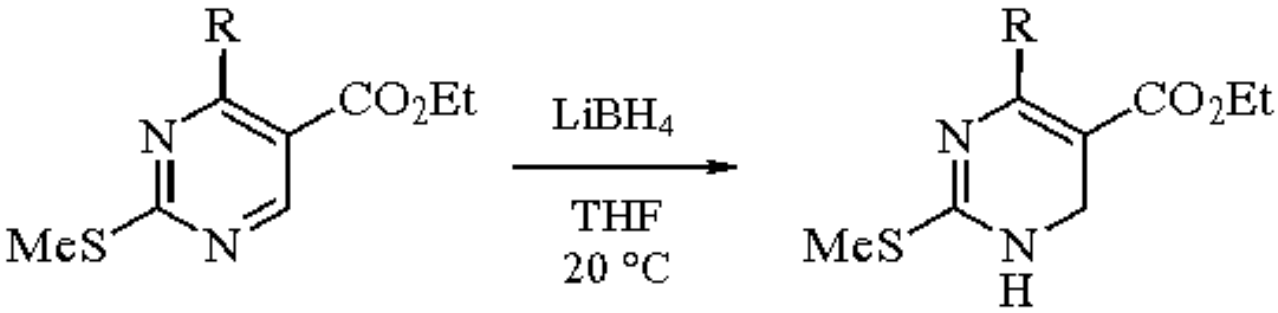

(2)

R = Me, CN, Cl, CH=NOH

Alkyl- and arylhalostibines can be reduced to hydrides, having general formula R_nSbH_{3-n}, both by $LiBH_4$ and other complex hydrides ($LiAlH_4$, $NaBH_4$).[2e]

Hydroboration.

Lithium borohydride is an effective catalyst for the hydroboration of alkenes with ***Catecholborane*** at rt in THF.[3] This method is superior to that employing ***Chlorotris(triphenylphosphine)rhodium(I)*** as catalyst, since trisubstituted and even tetrasubstituted ethylenes can also be almost quantitatively hydroborated. Other borohydrides ($LiBEt_3H$ in THF, $NaBH_4$ in diglyme) were tested and found to be less effective as catalysts.

Preparation of Other Borohydrides.

Lithium borohydride has been used to synthesize other borohydrides,[5] particularly aluminum borohydride (a volatile, liquid source of borohydride groups) through the metathesis between ***Aluminum Chloride*** and $LiBH_4$ (eq 3). For this process, $LiBH_4$ is superior to $NaBH_4$, both for a more pronounced reactivity and for a more favorable equilibrium position, so that lower temperatures and a much smaller excess of $AlCl_3$ are required.

$$AlCl_3 + 3\,LiBH_4 \rightleftharpoons Al(BH_4)_3 + 3\,LiCl \qquad (3)$$

Miscellaneous.

The addition of $LiBH_4$ in the carbonylation of trialkylboranes not only has the effect of stopping the reaction after the transfer of only one alkyl group, but also enhances the rate of the uptake of ***Carbon Monoxide***[2f,33] (see also ***Potassium Triisopropoxyborohydride***). Aldehydes or alcohols are obtained, depending on workup conditions (eq 4).

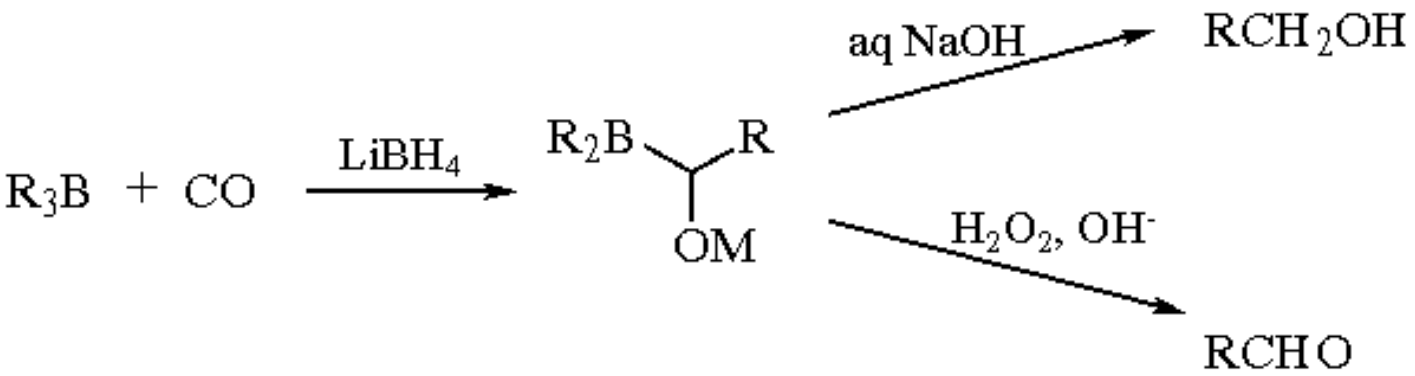

(4)

Lithium borohydride has been used in the degradation of peptides, in order to determine the terminal carboxylic groups.[1f]

Isotopically labelled lithium borohydrides, $LiBD_4$ and $LiBT_4$, have been used in reaction mechanism studies.[2g,20a]

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Lithium Bromide[1]

LiBr

[7550-35-8] · BrLi · Lithium Bromide · (MW 86.85)

(source of nucleophilic bromide;[2] mild Lewis acid;[1] salt effects in organometallic reactions;[1] epoxide opening[1])

Physical Data: mp 550 °C; bp 1265 °C; *d* 3.464 g cm^{-3}.

Solubility: 145 g/100 mL H_2O (4 °C); 254 g/100 mL H_2O (90 °C); 73 g/100 mL EtOH (40 °C); 8 g/100 mL MeOH; sol ether, glycol, pentanol, acetone; slightly sol pyridine.

Form Supplied in: anhyd white solid, or as hydrate.

Purification: dry for 1 h at 120 °C/0.1 mmHg before use; or dry by heating in vacuo at 70 °C (oil bath) for 24 h, then store at 110 °C until use.

Handling, Storage, and Precautions: for best results, dry before use in anhyd reactions.

Alkyl and Alkenyl Bromides.

LiBr has been extensively used as a source of bromide in nucleophilic substitution and addition reactions. Interconversion of halides[2] and transformation of alcohols to alkyl bromides via the corresponding sulfonate[3] or trifluoroacetate[4] have been widely used in organic synthesis. Primary and secondary alcohols have been directly converted to alkyl bromides upon treatment with a mixture of ***Triphenylphosphine***, ***Diethyl Azodicarboxylate***, and LiBr.[5]

(*Z*)-3-Bromopropenoates and -propenoic acids have been synthesized stereoselectively by the reaction of LiBr and propiolates or propiolic acid (eq 1).[6]

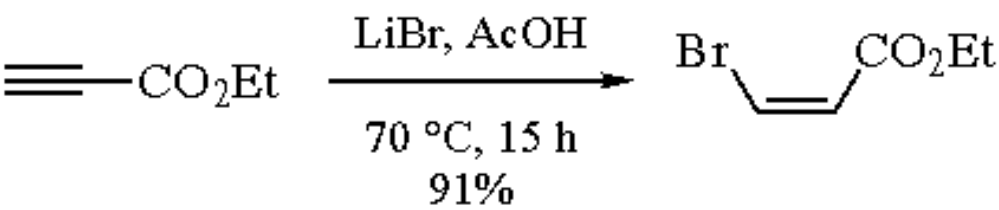

(1)

Heterolytic Cleavage of C-X Bonds.

In the presence of a Lewis acid, LiBr acts as a nucleophile in the opening of 1,2-oxiranes to produce bromohydrins (eq 2).[7] In the absence of an external Lewis acid or nucleophile, epoxides generally give rise to products resulting from ring-contraction reactions (eq 3).

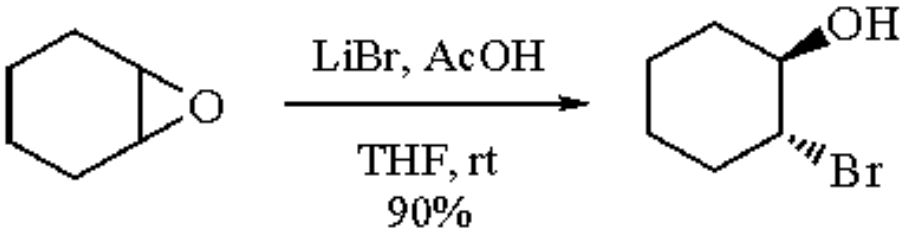

(2)

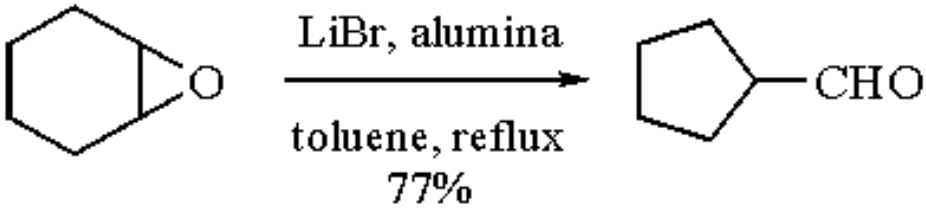

(3)

LiBr-mediated decomposition of dioxaphospholanes results in the exclusive formation of the epoxide, whereas the thermal decomposition produces a mixture of products (eq 4).[8]

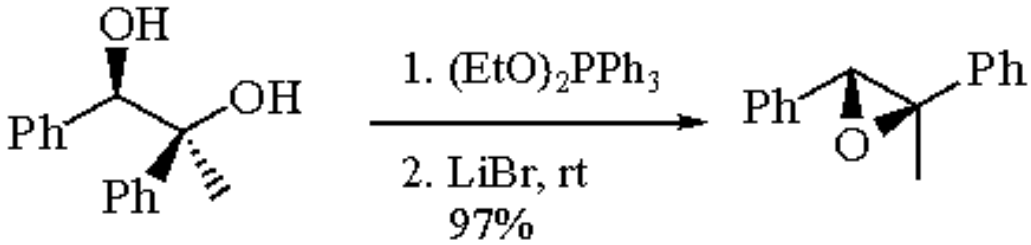

(4)

Protection of alcohols as their MOM ethers can be achieved using a mixture of ***Dimethoxymethane***, LiBr, and ***p-Toluenesulfonic Acid***.[9]

Bifunctional Reagents.

Activated α-bromo ketones are smoothly converted into the corresponding silyl enol ethers when treated with a mixture of LiBr/R_3N/***Chlorotrimethylsilane***.[10] Aldehydes are converted into the corresponding α,β-unsaturated esters using ***Triethyl Phosphonoacetate*** and ***Triethylamine*** in the presence of LiBr (eq 5).[11,12] Similar conditions were extensively used in the asymmetric cycloaddition and Michael addition reactions of *N*-lithiated azomethine ylides (eq 6).[13]

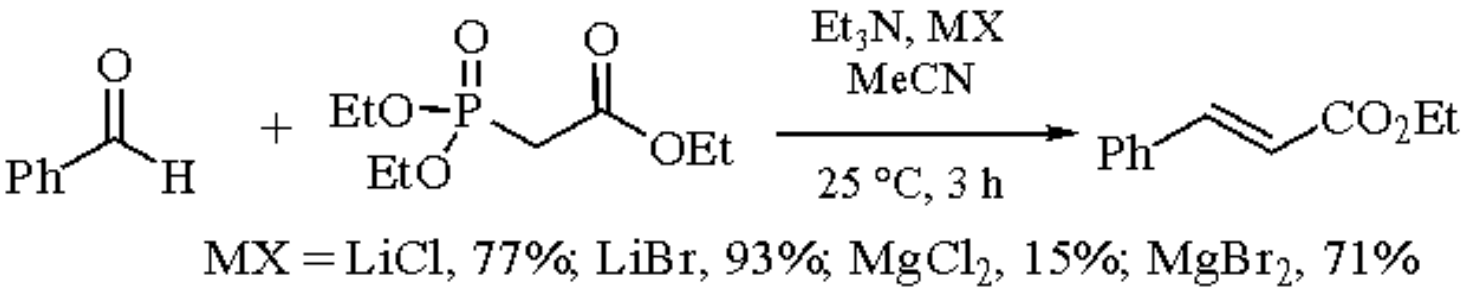

(5)

MX = LiCl, 77%; LiBr, 93%; $MgCl_2$, 15%; $MgBr_2$, 71%

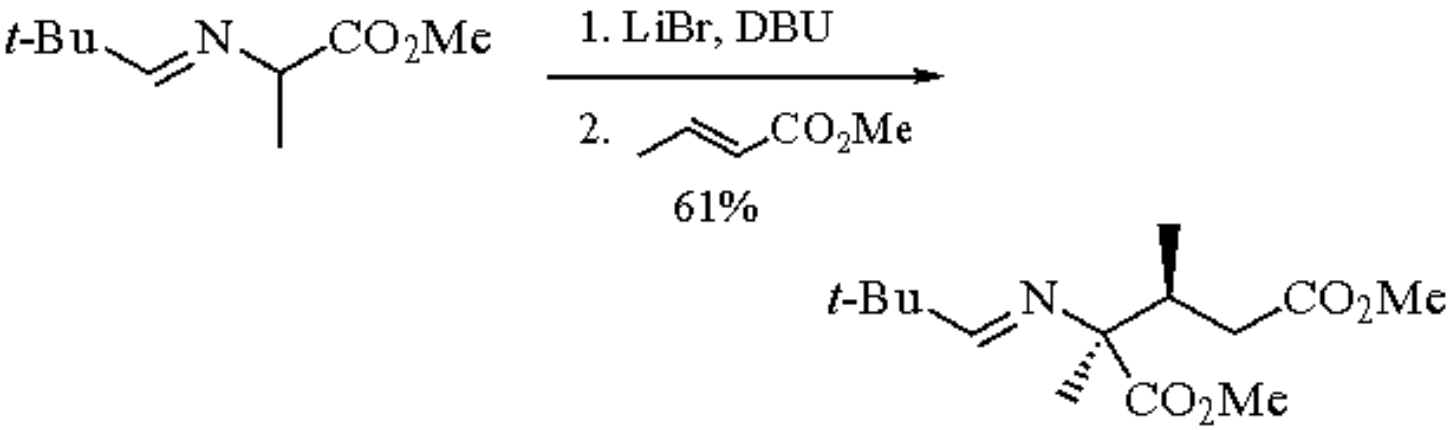

(6)

Additive for Organometallic Transformations.

The addition of LiBr and ***Lithium Iodide*** was shown to enhance the rate of organozinc formation from primary alkyl chlorides, sulfonates, and phosphonates, and ***Zinc*** dust.[14] Beneficent effects of LiBr addition have also been reported for the Heck-type coupling reactions[15] and for the nickel-catalyzed cross-couplings of alkenyl and α-metalated alkenyl sulfoximines with organozinc reagents.[16] The addition of 2 equiv of LiBr significantly enhances the yield of the conjugate addition products in reactions of certain organocopper reagents (eq 7).[17]

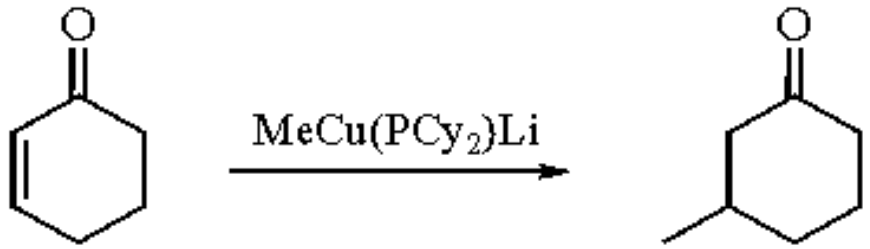

(7)

LiBr (0 equiv), 61%
LiBr (2 equiv), 96%

Finally, concentrated solutions of LiBr are also known to alter significantly the solubility and the reactivity of amino acids and peptides in organic solvents.[18]

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Lithium *t*-Butoxide

***t*-BuOLi**

[1907-33-1] · C_4H_9LiO · Lithium *t*-Butoxide · (MW 80.07)

(weakly basic and nucleophilic metal alkoxide)[1]

Physical Data: crystalline solid, subl over 170-205 °C/760 mmHg; dec above 250 °C.[2]

Form Supplied in: commercially available as a white powder.

Preparative Methods: the crystalline material is prepared using a Schlenk apparatus by reaction of *t*-BuOH with a small excess of ***Lithium*** sand in PhMe at rt for 24 h;[2] the excess metal is removed by filtration and the solvent is removed in vacuo; the remaining solid is sublimed at 110-120 °C/0.01 mmHg. In situ preparation is accomplished by adding a solution of anhyd *t*-BuOH in THF to 1.6 M ***n-Butyllithium*** in hexane,[1a] or by slowly adding a 1.55 M solution of *n*-BuLi in hexane to an excess of the anhyd alcohol under N_2;[1b] the reaction is exothermic, and a water bath should be used to keep the temperature of the mixture near rt.

Handling, Storage, and Precautions: use same procedure as for ***Potassium t-Butoxide***, i.e. handle and conduct reactions in a fume hood under an inert atmosphere; for critical experiments, it is recommended that the reagent be freshly prepared.

Preparation of *t*-Butyl Esters.

t-BuOLi reacts with acid chlorides of hindered carboxylic acids to give the corresponding *t*-butyl esters in high yields (eq 1).[1] The ester product shown in eq 1 is not obtained by the more conventional method of reacting the acid chloride with *t*-BuOH in the presence of $PhNMe_2$.[3]

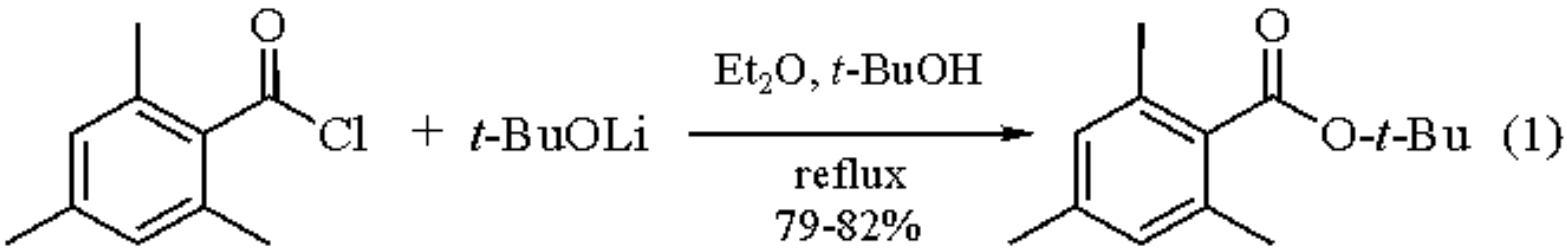

Oxidation of Alcohols.

Alkoxymagnesium bromides of secondary alcohols and allylic and benzylic alcohols are oxidized to the corresponding ketones or aldehydes with ***N-Chlorosuccinimide*** in the presence of *t*-BuOLi.[4] The method is ineffective for primary saturated and some unsaturated alcohols, but oxidations of the former substrates to aldehydes occur readily if ***t-Butoxymagnesium Bromide*** is substituted for *t*-BuOLi.[5] Secondary alcohols (eq 2) and primary benzylic (eq 3) and allylic alcohols are oxidized to the corresponding carbonyl compounds in good yields using 2-3 equiv of a 1:1 mixture of ***Copper(II) Bromide***-*t*-BuOLi in THF at rt.[6] However, the reagent is not effective for the conversion of primary aliphatic alcohols to aldehydes.

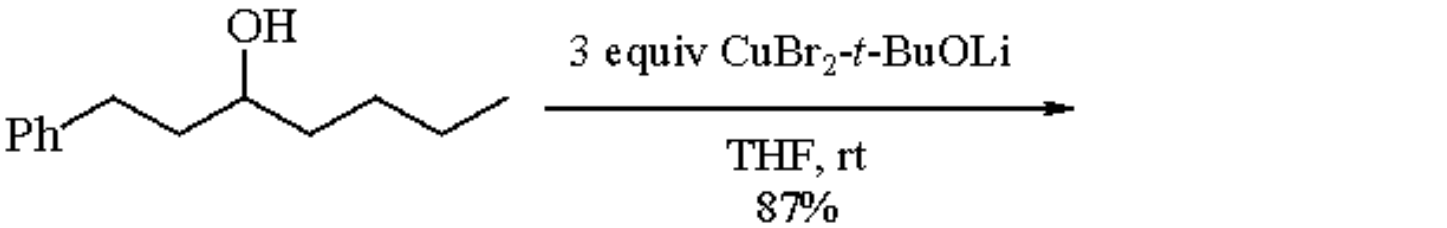

(2)

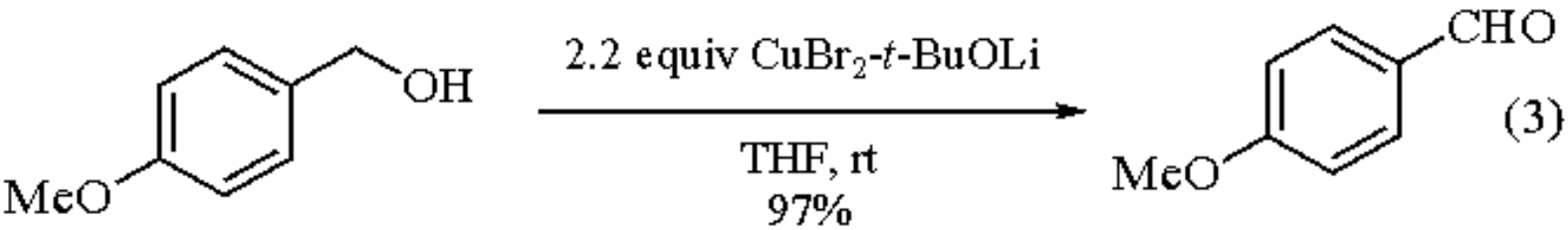

(3)

Condensation Reactions.

In the presence of dipolar aprotic additives, e.g. ***Hexamethylphosphoric Triamide*** (eq 4) or ***12-Crown-4***, which reduce the degree of aggregation, *t*-BuOLi catalyzes the Michael addition of methyl cyanoacetate to benzylideneacetophenone.[7] A similar yield of the Michael adduct is obtained if *t*-BuOK is used as the base, and no additive is required.

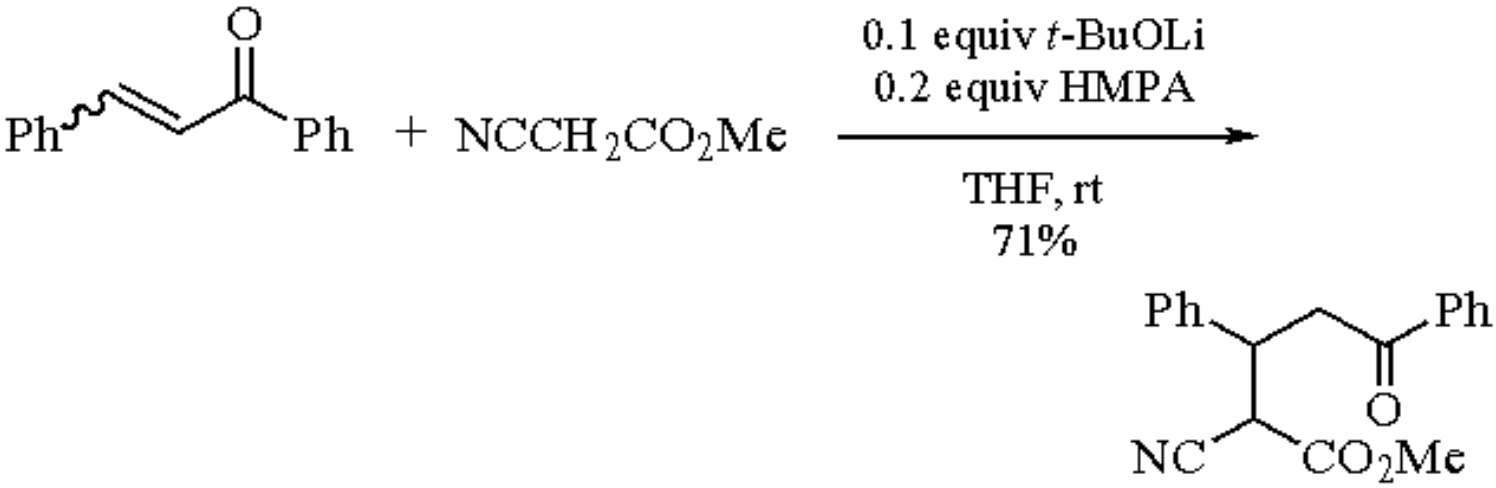

(4)

Additions to Hindered Ketones.

In the absence of various additive salts, the reaction of *i*-Pr_2Mg with *t*-Bu_2CO leads mainly to simple reduction of the carbonyl group.[8] In the presence of *t*-BuOLi, addition to the carbonyl group occurs in good yield (eq 5).[8] *t*-BuOLi, MeOK, and $(Me_2CH)_2CHOK$ are more effective than MeONa or quaternary ammonium salts in preventing the reduction process. The exact role of the additive in favoring addition to the hindered ketone over reduction is unknown.

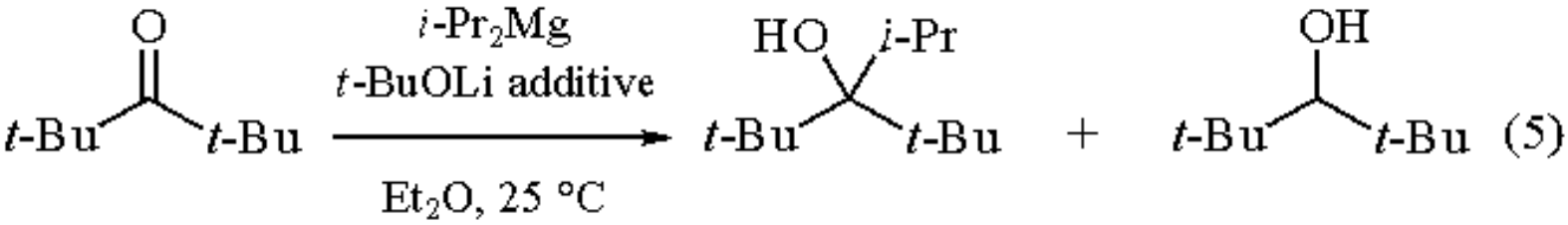

t-BuOLi (1.0-2.0 equiv)	81-84%	0%
no additive	1.3%	88%

β-Elimination Reactions.

1-Methoxyacenaphthene undergoes loss of MeOH via an E1cB mechanism.[9] *t*-BuOLi/*t*-BuOH favors exchange and elimination of the proton *syn* to the methoxy group much more than do other alkali metal alkoxides. It has been suggested that the strong tendency of the lithium cation of the base ion pair (or an aggregate) to coordinate with the ether oxygen of the substrate accounts for this.[9]

---

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Lithium *t*-Butoxy(*t*-butyl)cuprate[1]

***t*-BuCu(O-*t*-Bu)Li**

[41655-91-8] · $C_8H_{18}CuLiO$ · Lithium *t*-Butoxy(*t*-butyl)cuprate · (MW 200.71)

(heterocuprate of greater thermal stability than analogous homocuprate;[2] capable of nucleophilic additions[2] and substitutions[3])

Solubility: sol THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl; the yield of PhCO(*t*-Bu) is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: ***Lithium t-Butoxide*** is prepared[2] under N_2 by dropwise addition of 1.00 equiv of ***n-Butyllithium*** in hexanes to a solution of dry *t*-BuOH in dry THF[3b] (***Potassium t-Butoxide*** should not be substituted for the lithium salt); a stirred suspension of 1.00 equiv of ***Copper(I) Iodide***[5] in dry THF at rt under N_2 is treated with the *t*-BuOLi solution dropwise; after 15 min, the resulting cloudy, green-brown suspension is cooled to -78 °C and then treated with 1.00 equiv ***t-Butyllithium*** in pentane; the product, a cloudy, brown mixture, is ready for use after stirring for 5 min at -78 °C (alternative methods also may be acceptable; high-purity *t*-BuOLi is commercially available).[6,7]

Handling, Storage, and Precautions: best results are obtained with high-purity copper(I) salts,[5,8] dry, oxygen-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides;[9] the *t*-BuLi used to prepare the reagent is pyrophoric[10] and due care must be exercised in its handling; use in a fume hood; thermal decomposition occurs at &egt;-30 °C, but the reagent is stable for one or more h at <=-50 °C.

Introduction.

The title reagent is representative of the heterocuprate class of organocopper reagents. The *t*-Bu group is reactive as a nucleophile, whereas the *t*-BuO group is not; such nontransferable groups are called dummy ligands.[11] For *t*-Bu heterocuprates, *t*-BuO, PhO, and especially PhS dummy ligands are found to provide thermal stability compared to the parent homocuprate, $(t\text{-Bu})_2CuLi$.[12] Heterocuprates generally exhibit less nucleophilic reactivity than corresponding homocuprates;[13] however, increased thermal stabilities coupled with greater efficiency in use of the

transferable ligand[12] make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Nucleophilic Substitutions of Halides.

The thermal stability of the cuprate typically results in higher chemical yields using highly reactive substrates such as ***Benzoyl Chloride*** (eq 1);[12] in contrast, copper(I)-catalyzed reactions with *t*-BuLi or *t*-BuMgX are unsatisfactory. The low temperatures at which the reactions proceed allow for other, less reactive, functional groups to be present (eq 2).[12]

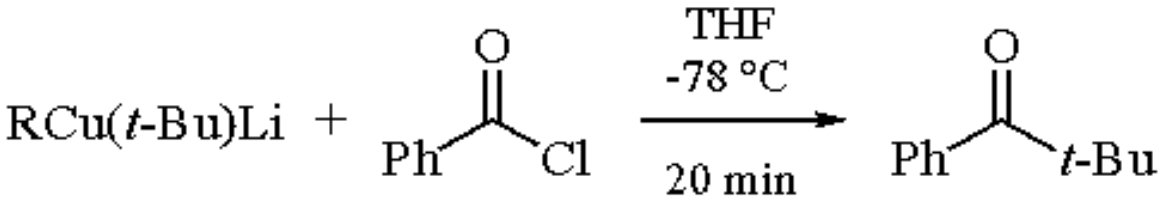

(1)

R = *t*-BuO 98%
R = *t*-Bu 76%

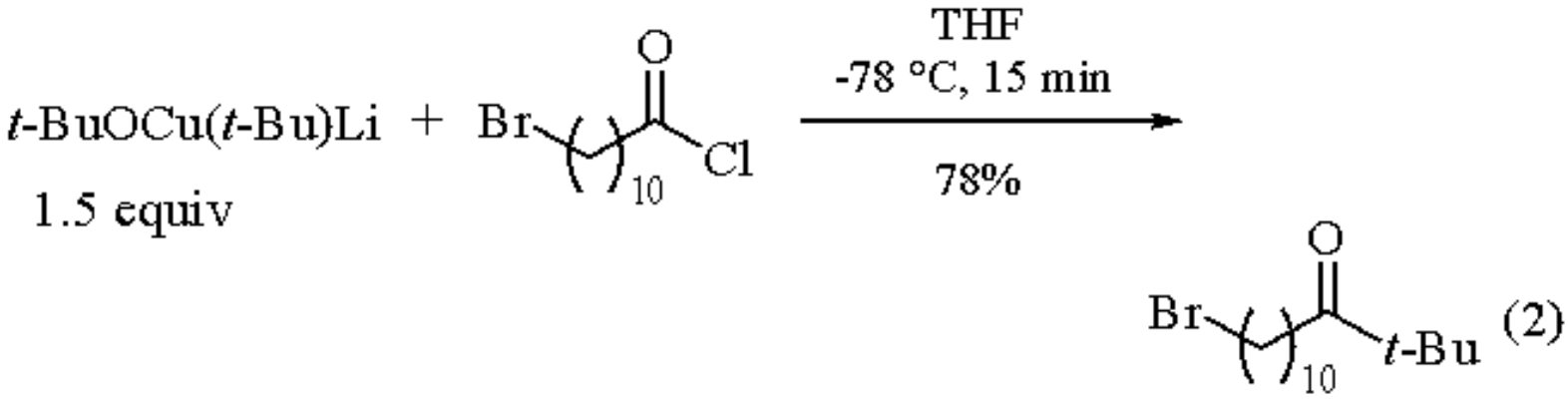

(2)

Reaction with α,α´-dibromo ketones provides a regioselective, efficient route to α-tertiary and α-secondary alkylations of ketones (eq 3);[5a,12,14] α-*t*-Bu alkylations using enolates or enolate equivalents generally are difficult and yields may be unsatisfactory. A related report indicates that the reagent is not effective when α-chlorophosphonates are used as substrates.[15]

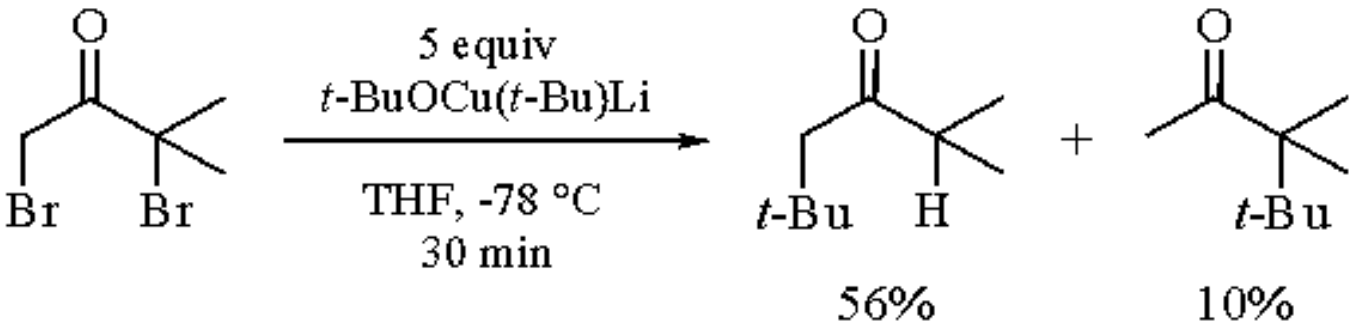

(3)

56% 10%

The reagent has been used to effect simple S_N2 reactions of iodoalkanes;[12] it follows normal trends, providing good chemical yields for primary substrates only. Secondary *exo*-norbornenyl tosylates react to provide 2-*t*-butylnortricyclanes in good yield.[16]

1,4-Additions to 2-Alkenones.

While apparently not as effective as mixed homocuprates of general formula RC&tbond;CCu(*t*-Bu)Li, the reagent does act as a conjugate donor, undergoing slow 1,4-addition to 2-cyclohexenone (eq 4).[11]

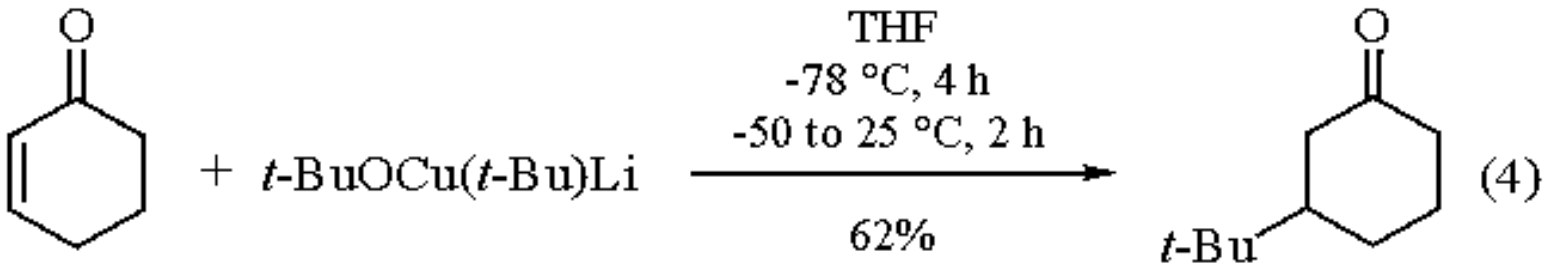

Related Reagents.

See also ***Lithium Di-t-butylcuprate***; for related heterocuprates, see, e.g. ***Lithium Methyl(phenylthio)cuprate***; for discussion of lithium dialkylcuprates, see ***Lithium Dimethylcuprate***.

---

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Lithium Butyl(cyano)cuprate

***n*-BuCuCNLi**

[41742-63-6] · C_5H_9CuLiN · Lithium Butyl(cyano)cuprate · (MW 153.62)

(organometallic reagent for the addition of an *n*-butyl group to enones, vinyl epoxides, simple epoxides, vinyl sulfones, and allylic halides)

Solubility: sol diethyl ether, THF at -78 °C.

Preparative Method: the title reagent, like other alkyl or arylcyanocuprates, is prepared at -78 °C from the addition of the alkyl- or aryllithium precursor to 1 equiv anhyd ***Copper(I) Cyanide***.[1]

Handling, Storage, and Precautions: thermally unstable organocuprate; generated at -78 °C in the absence of moisture and oxygen.

Additions to Epoxides.

The ring-opening reactions of the title reagent (**1**) with epoxides are typical of most organocuprates in that the less hindered carbon of an epoxide is attacked selectively. The cyclohexene epoxide of eq 1 illustrates this reactivity.[2]

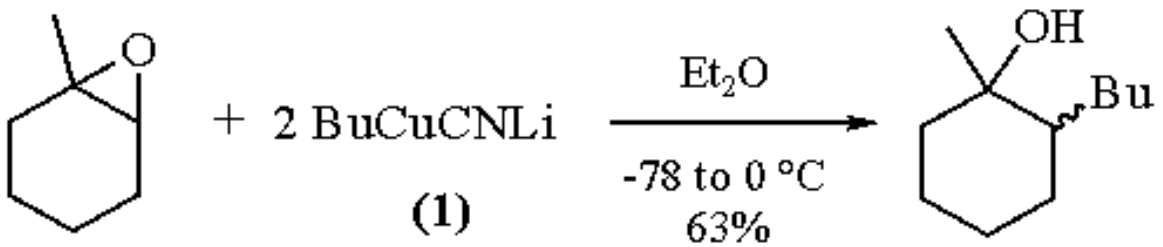

(1)

In the case of the more activated epoxy ester (**2**), the reagent delivers an *n*-butyl group α to the ester (eq 2).[2]

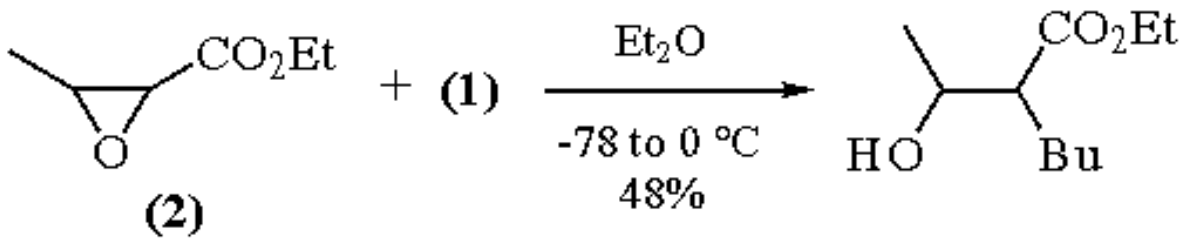

(2)

The real uniqueness of the cyano reagent (**1**) is evidenced by its reactions with vinyl epoxides. In reactions with cyclic

vinyl epoxides[1] such as 1,3-cyclohexadiene monoepoxide and 1,3-cycloheptadiene monoepoxide, 1,4-addition predominates in ether at -78 °C (eq 3).[1,3] These selectivities are possible only in the less polar ether solvent, as illustrated for the latter epoxide.

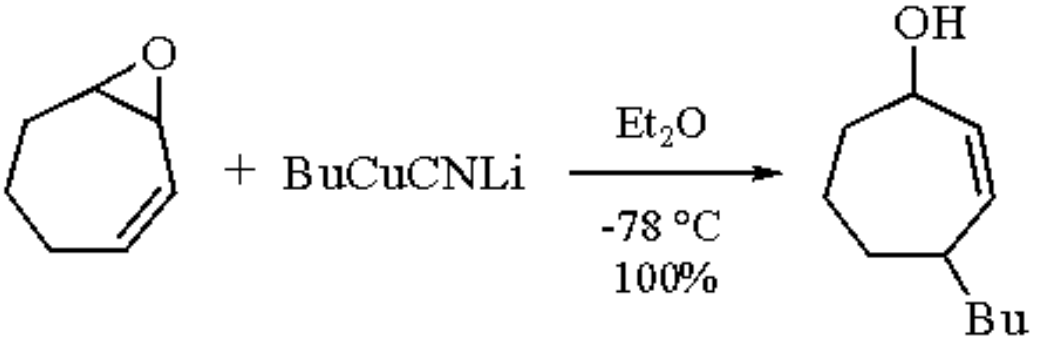

(3)

In a similar fashion, exocyclic vinyl epoxides such as the cyclohexenyl epoxide (**3**) react regiospecifically with (**1**) to produce the tertiary alcohol (**4**) (eq 4).[4,5]

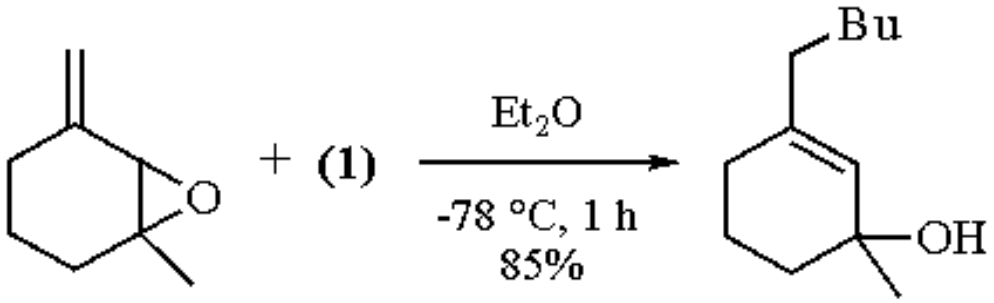

(4)

(3) (4)

When enol ethers of keto epoxides are employed as the vinyl epoxide system, the higher alkyl- and arylcyanocuprates, such as (**1**), add in a *trans*-1,4-manner for cyclohexyl and cyclopentyl systems. In eq 5 a silyl enol ether of the cyclohexenone epoxide (**5**) reacts with (**1**) to produce the adduct (**6**).[6]

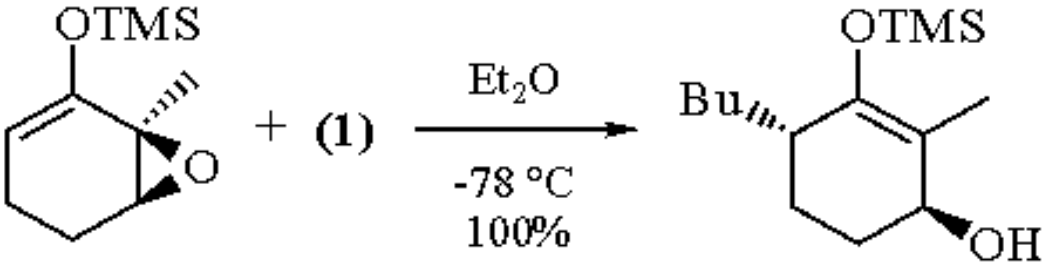

(5)

(5) (6)

In the cyclopentenone epoxide system, both the silyl enol ether (**7**) and the enol phosphate epoxide (**8**) yield the 1,4-*trans*-adduct (**9**) with (**1**) (eqs 6 and 7).[7]

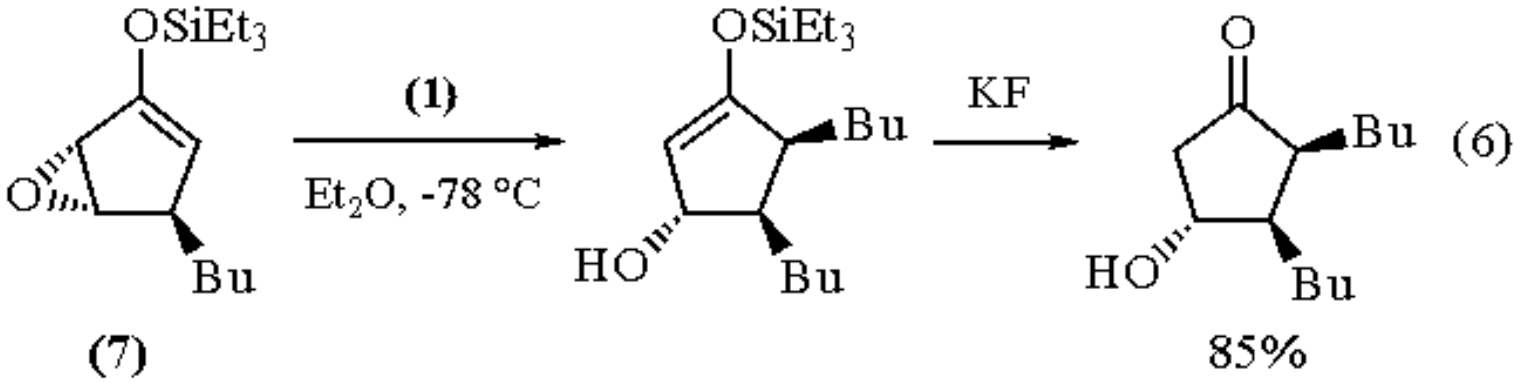

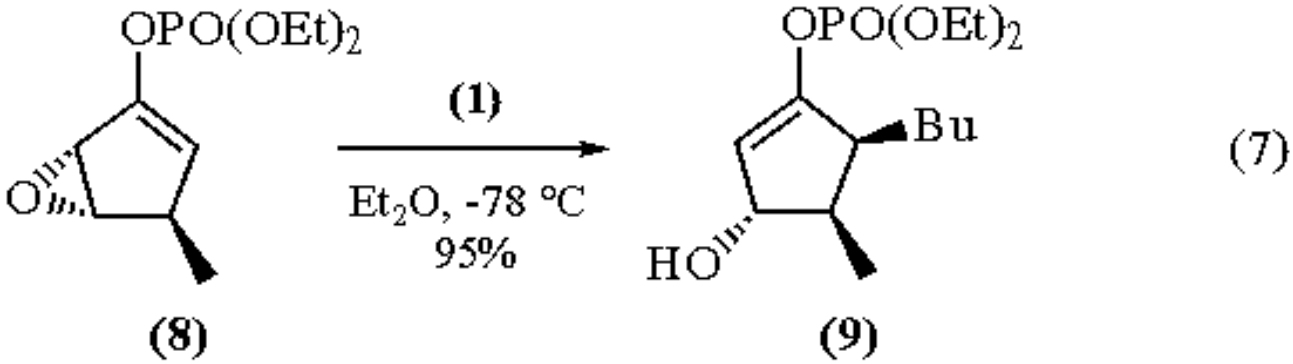

Vinyl epoxides which are disubstituted at the terminus of the alkene often react selectively in a 1,2-ring opening, as is the case for the epoxyvinyl sulfone (**10**) (eq 8).[8]

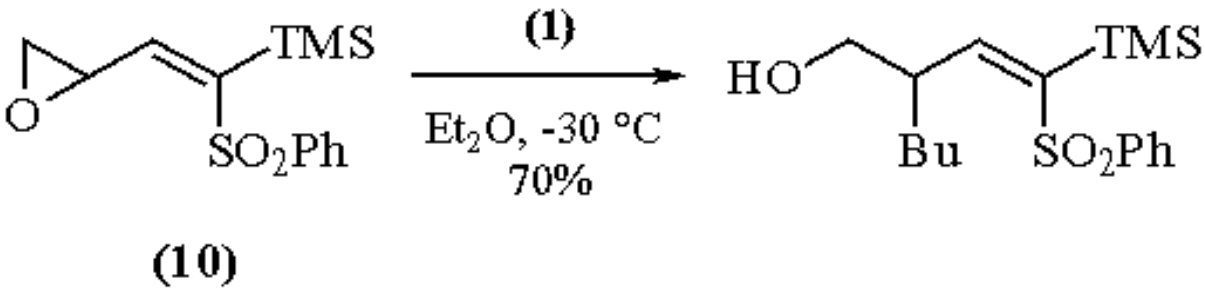

Lithium Cyano(isohexyl)cuprate.

By analogy with the *n*-butylcyanocuprate reagent (**1**), the isohexyl reagent (**11**) is easily prepared from the isohexyllithium precursor and 1 equiv of anhyd copper(I) cyanide at -78 °C in ether. A direct application of (**11**) to the synthesis of the side chain of cholesterol involves the 1,4-addition of (**11**) to the *exo*-vinyl epoxide (**12**) (eq 9).[9]

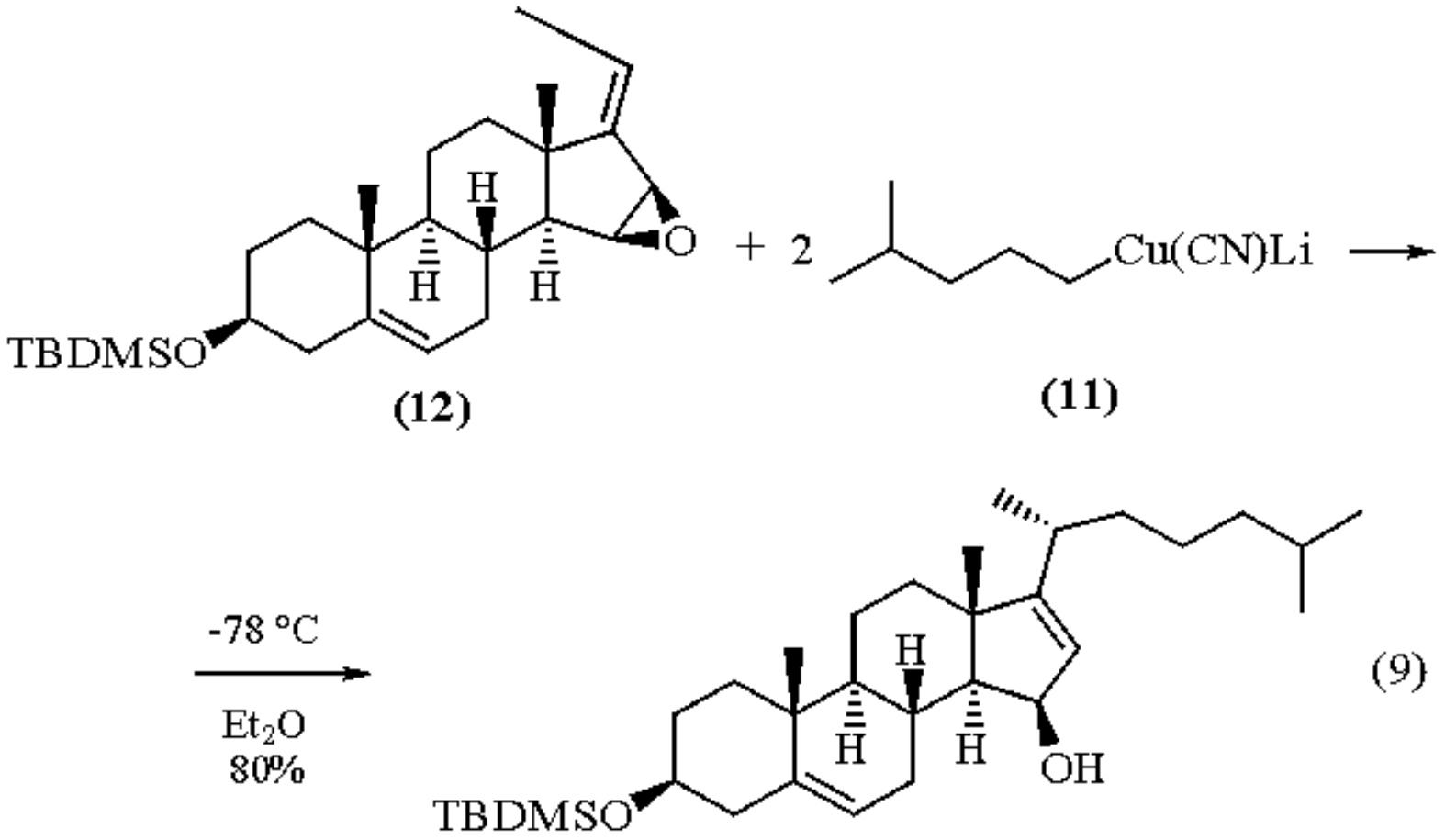

In a synthetic application for the preparation of the side chain of α-tocopherol, the isohexylcyanocuprate (**11**) was added in a 1,4-manner to a (*Z*)-alkenyl butyrolactone (**13**) in high yield (eq 10).[10]

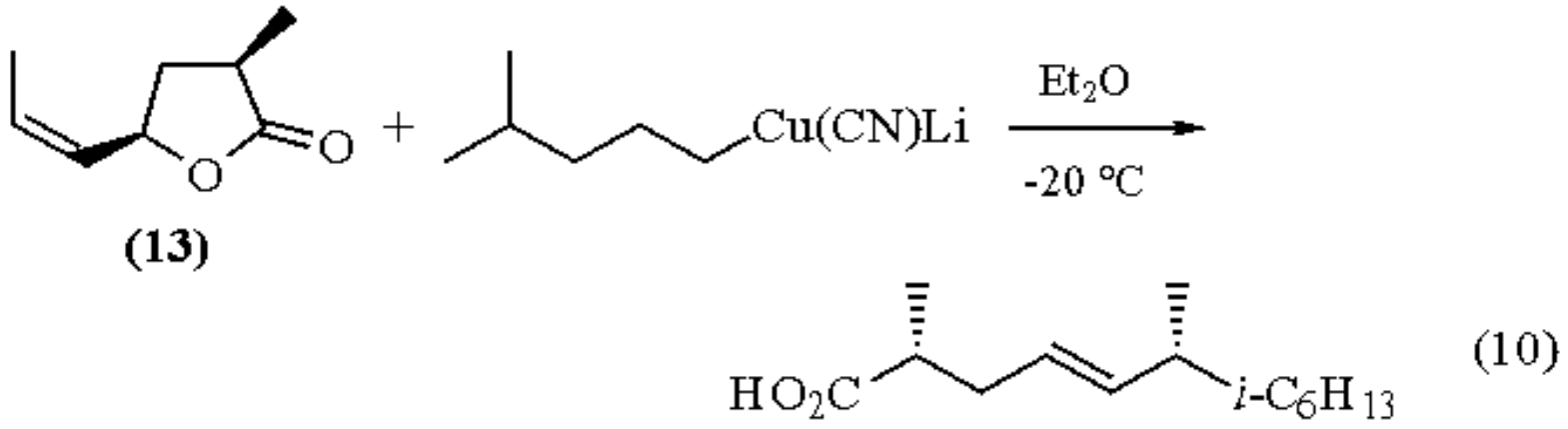

Lithium Cyanophenylcuprate.

As a further extension of the cyanocuprate reagents, the lithium cyanophenylcuprate reagent (**14**) was easily prepared by adding commercially available ***Phenyllithium*** to anhyd copper(I) cyanide at -78 °C in ether. This reagent is usually more thermally stable than the higher alkylcyanocuprates and, therefore, reactions can be performed at temperatures as high as 0-25 °C. The regioselectivity of cyanocuprates towards vinyl epoxides is, by and large, maintained for the cyanophenylcuprate (**14**). In the case of the *exo*-vinyl epoxide (**15**), the 1,4-addition occurs selectively to give (**16**) in 75% yield (eq 11).[4]

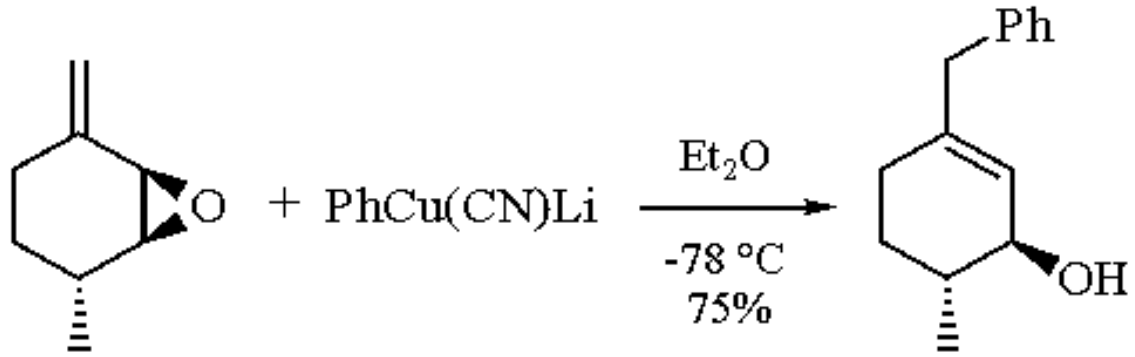

(11)

(15) (14) (16)

Other examples involving enol ether epoxides are shown in eqs 12 and 13.[6,7] In the case of the enol phosphate of the cyclopentenone epoxide, the regioselectivity is skewed towards the 1,2-product to the extent of 2:1.[7]

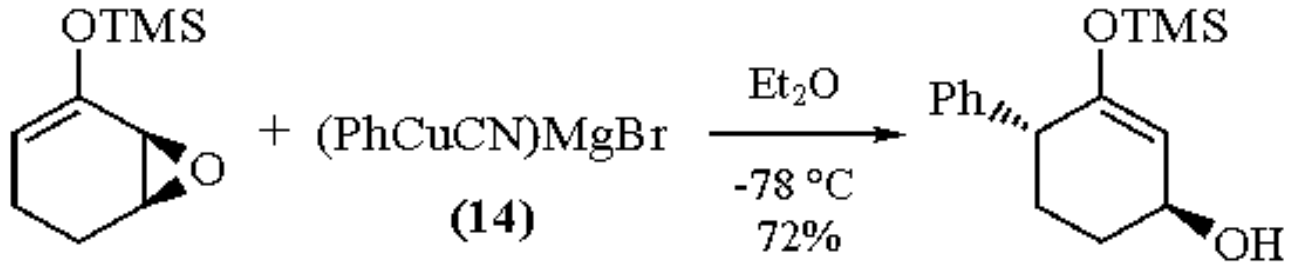

(12)

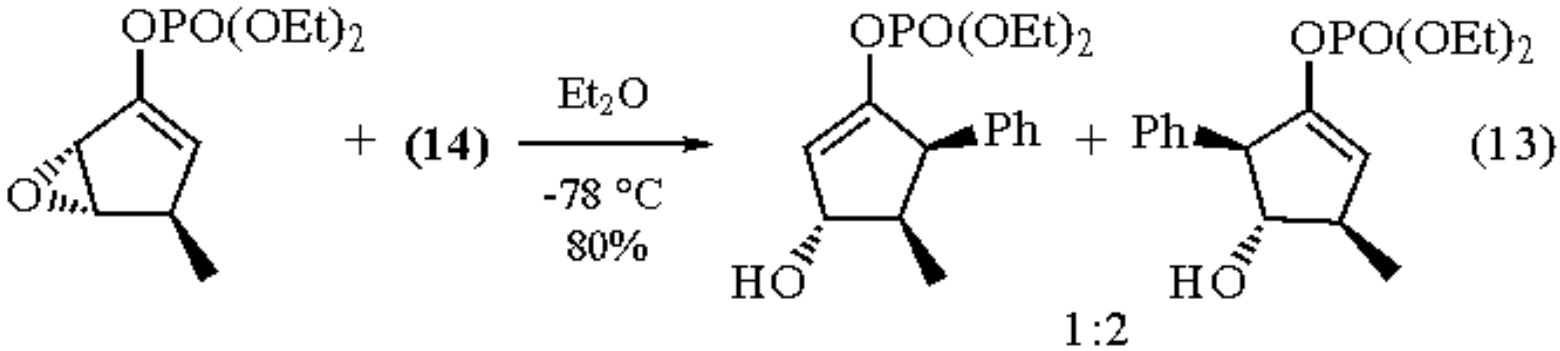

(13)

In summary, both the *n*-butylcyanocuprate reagent (**1**) and the isohexylcyanocuprate (**11**) behave consistently in their 1,4-regioselectivity towards cyclic vinyl epoxides. Only the phenylcyanocuprate (**14**) exhibits mixed selectivity with the enol ethers of cyclopentenone epoxides.

Related Reagents.

Lithium Cyano(dimethylphenylsilyl)cuprate; ***Lithium Cyano(methyl)cuprate***; ***Lithium Di-n-butylcuprate***.

---

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Lithium *t*-Butyl(diisobutyl)aluminum Hydride

$LiAlH(i\text{-}Bu)_2(t\text{-}Bu)$

[62779-60-6] · $C_{12}H_{28}AlLi$ · Lithium *t*-Butyl(diisobutyl)aluminum Hydride · (MW 206.28)

(sterically hindered and mild reducing agent for aldehydes, ketones, α,β-unsaturated ketones, esters, and lactones[1-5])

Physical Data: see ***Diisobutylaluminum Hydride*** and ***t-Butyllithium***.

Solubility: see ***Diisobutylaluminum Hydride*** and ***t-Butyllithium***; reactions using the title reagent sol THF, toluene, hexane.

Preparative Method: prepared in situ by dropwise addition of equimolar amounts of *t*-butyllithium in hexane to a solution of diisobutylaluminum hydride in hexane at -78 °C followed by dilution with THF at 0 °C; a suspension is formed when toluene is used in place of THF.[4]

Handling, Storage, and Precautions: see ***Diisobutylaluminum Hydride*** and ***t-Butyllithium***.

Stereoselective Reductions.

This mixed reducing reagent provides a convenient method for converting sterically hindered ketones into alcohols (eq 1).[1] Exceptionally high stereoselectivity is reported, even with an unhindered bicyclic ketone such as norcamphor (eq 2).[1b] Reduction of conformationally rigid and hindered bicyclic ketones such as decalin derivatives has been reported to give a single stereoisomer in quantitative yield (eq 3).[2]

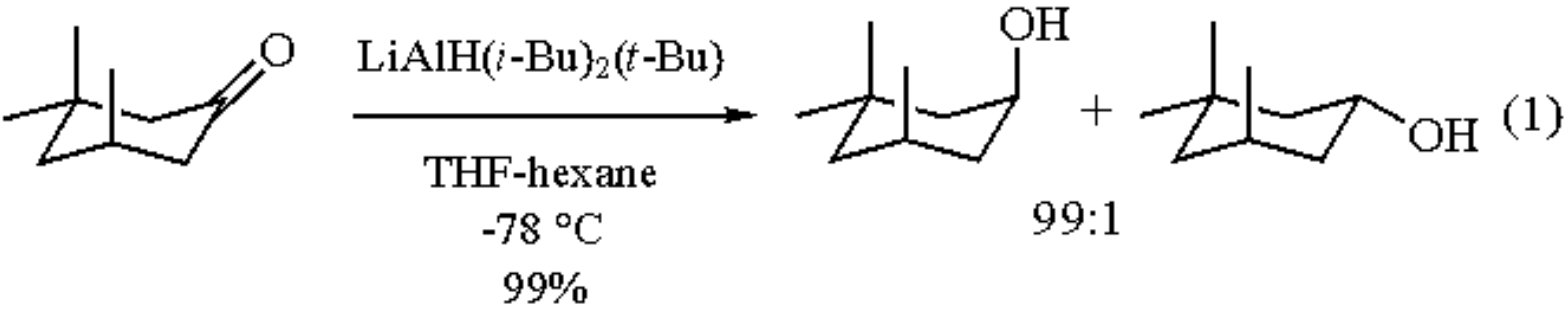

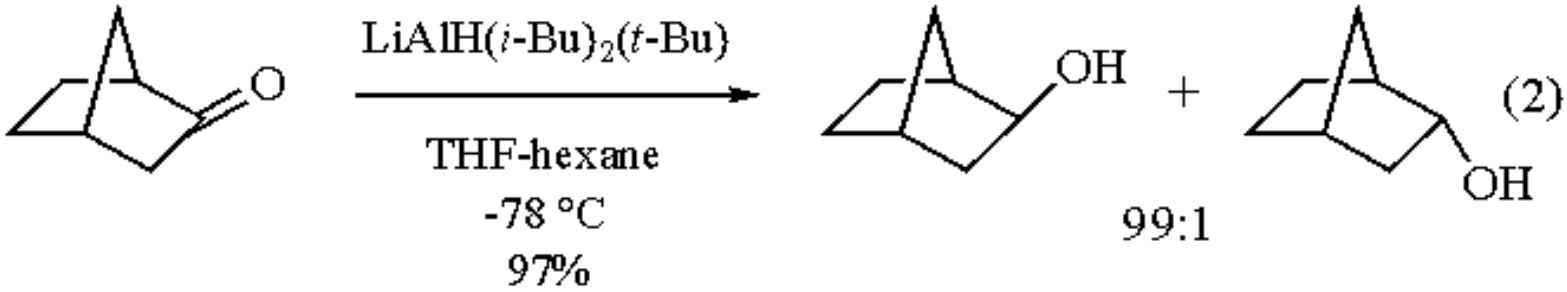

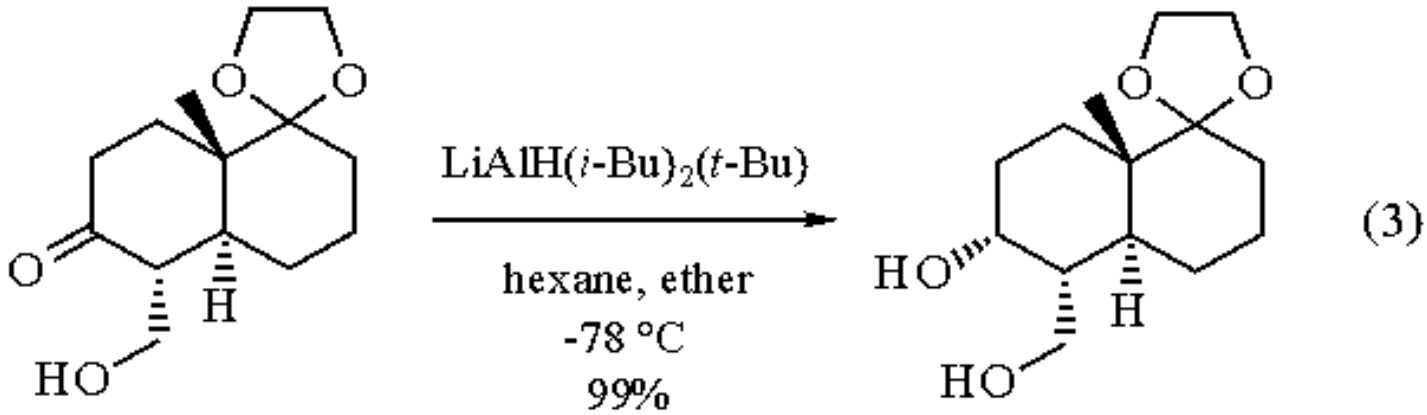

Regioselective Reductions.

This mixed reagent has been used effectively to reduce a lactone in the presence of an ester in good yield (eq 4).[3] The absence of overreduction under the reaction conditions is notable.

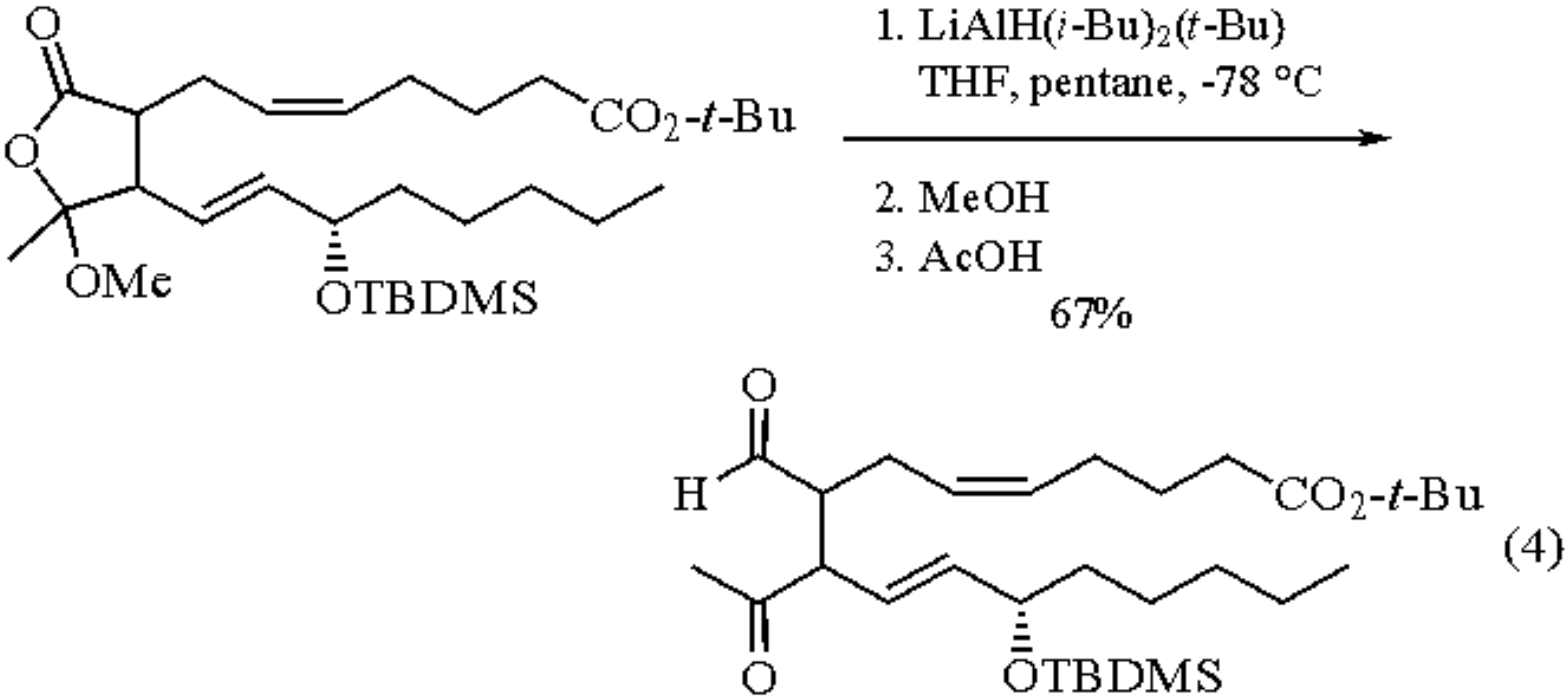

Lithium n-Butyl(diisobutyl)aluminum Hydride, which is similar to the title reagent, reduces α,β-unsaturated ketones to allyl alcohols.[4] The reduction of enones by the title reagent in the presence of ***Methylaluminum Bis(2,6-di-t-butyl-4-***

methylphenoxide) (MAD) results in reversal of the selectivity (eq 5).[5]

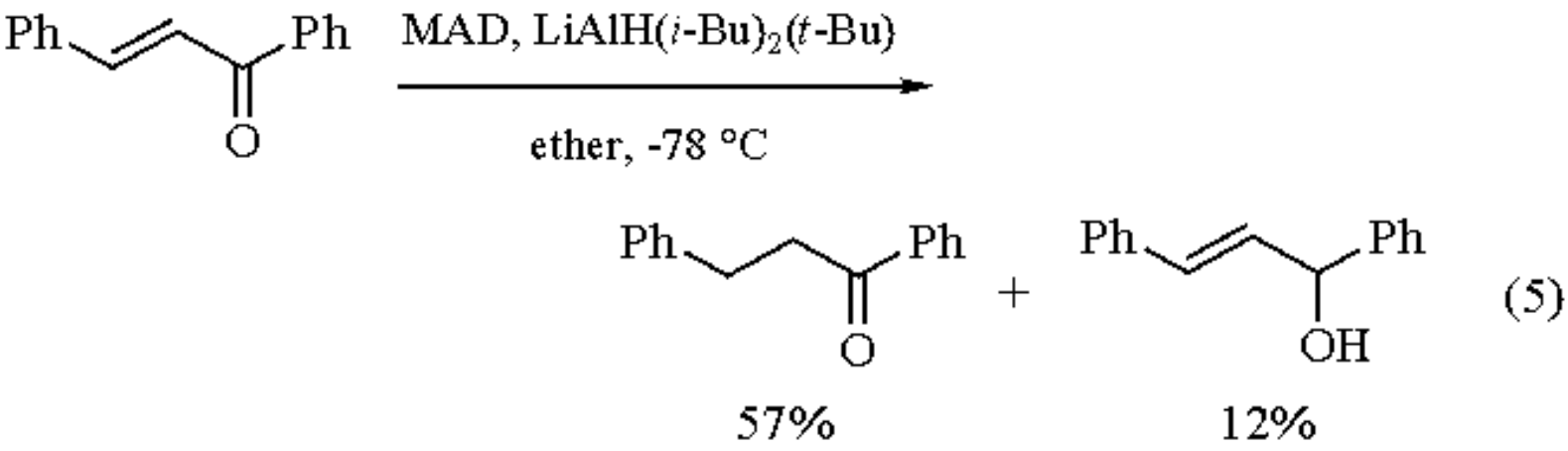

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Lithium *n*-Butyl(diisobutyl)aluminum Hydride[1]

Li(*n*-Bu)(*i*-Bu)$_2$AlH

[62779-58-2] · $C_{12}H_{28}AlLi$ · Lithium *n*-Butyl(diisobutyl)aluminum Hydride · (MW 206.28)

(reducing system for selectively converting conjugated enones and esters to allylic alcohols, esters, lactones, and acid chlorides to alcohols, acid anhydrides to alcohols and carboxylic acids, tertiary amides to aldehydes, primary, benzylic, and allylic halides to hydrocarbons, epoxides to alcohols, and disulfides to thiols)

Preparative Method: the reagent system (ate complex) is prepared and utilized in either hexane/THF or hexane/toluene solutions from equal molar quantities of ***Diisobutylaluminum Hydride*** (DIBAL) in hexane and ***n-Butyllithium*** in hexane and diluted with either THF or toluene;[2a] such combinations have been described as lithium trialkylaluminum hydrides, although the exact structures are unknown.[2b-e]

Analysis of Reagent Purity: by analysis of the reduction product of 4-*t*-butylcyclohexanone.[2a]

Handling, Storage, and Precautions: use in a fume hood; see also ***n-Butyllithium*** and ***Diisobutylaluminum Hydride***.

Reduction of Enones to Allylic Alcohols.

This reagent system is effective for the selective 1,2-reduction of acyclic and cyclic α,β-unsaturated enones to allylic alcohols (eqs 1 and 2[2a and 3]), particularly in hexane/toluene media.[2a] Small amounts (1-10%) of saturated ketones and/or saturated alcohols are observed with cyclic enones and β-phenyl enones.[2a] On the other hand, prior complexation of enones with ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD) and subsequent reduction with Li(*n*-Bu)(*i*-Bu)$_2$AlH affords high yields of the corresponding saturated ketones resulting from 1,4-reduction (eq 3),[4] except when the enone is substituted at the β position; in this case, 1,2- or a mixture of 1,2- and 1,4-reduction is obtained.[4]

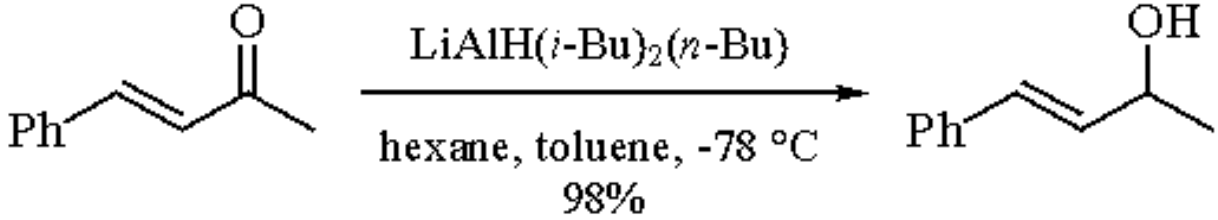

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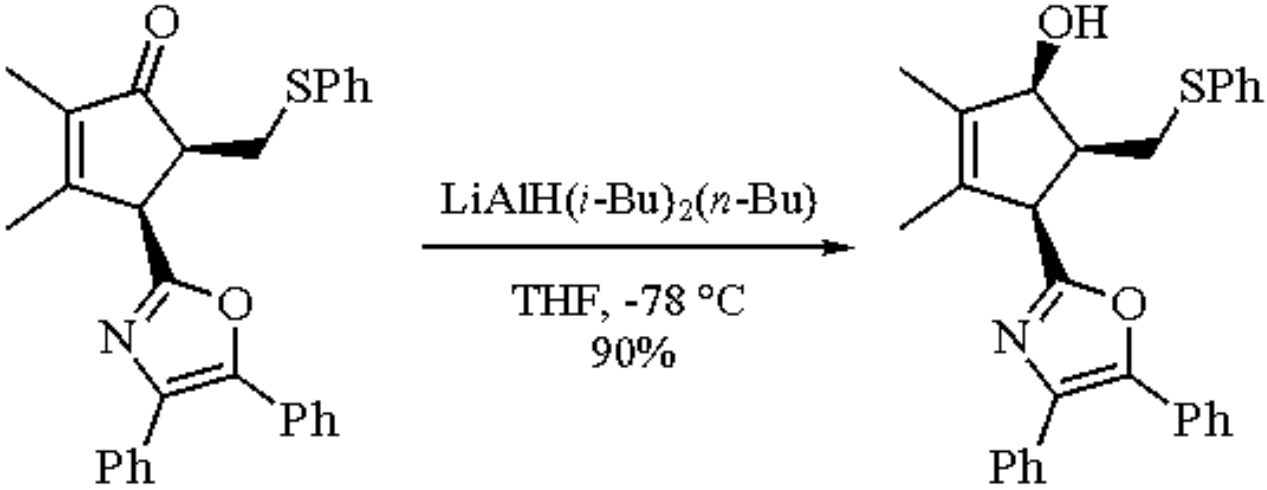

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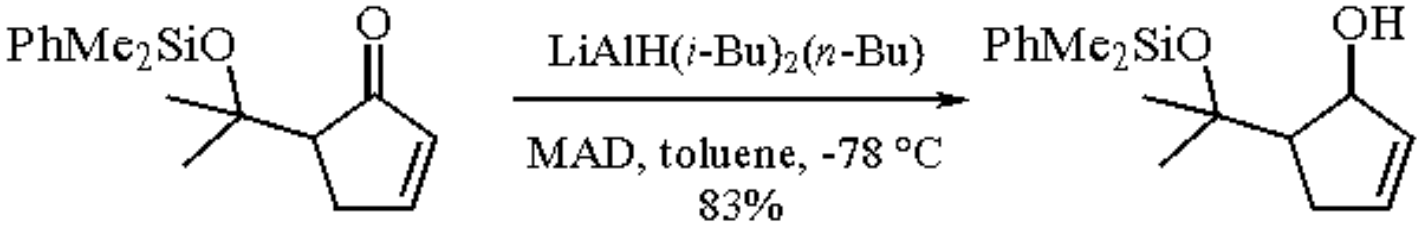

(3)

Reduction of Esters to Aldehydes and Alcohols.

At low temperatures (-78 °C), Li(*n*-Bu)(*i*-Bu)$_2$AlH reduces esters, including lactones and conjugated examples, to the corresponding aldehydes and/or alcohols as mixtures (eqs 4 and 5[6 and 7a]).[2a,5-7] Often, the mixtures are further reduced with borohydride[7c,d] to give alcohols or oxidized to the aldehydes.[5,7a,b] The process appears selective for the reduction of methyl esters in the presence of *t*-butyl derivatives (eq 5).

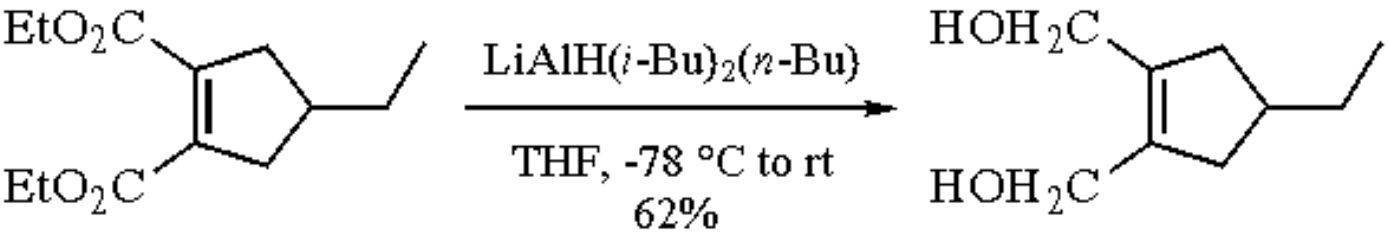

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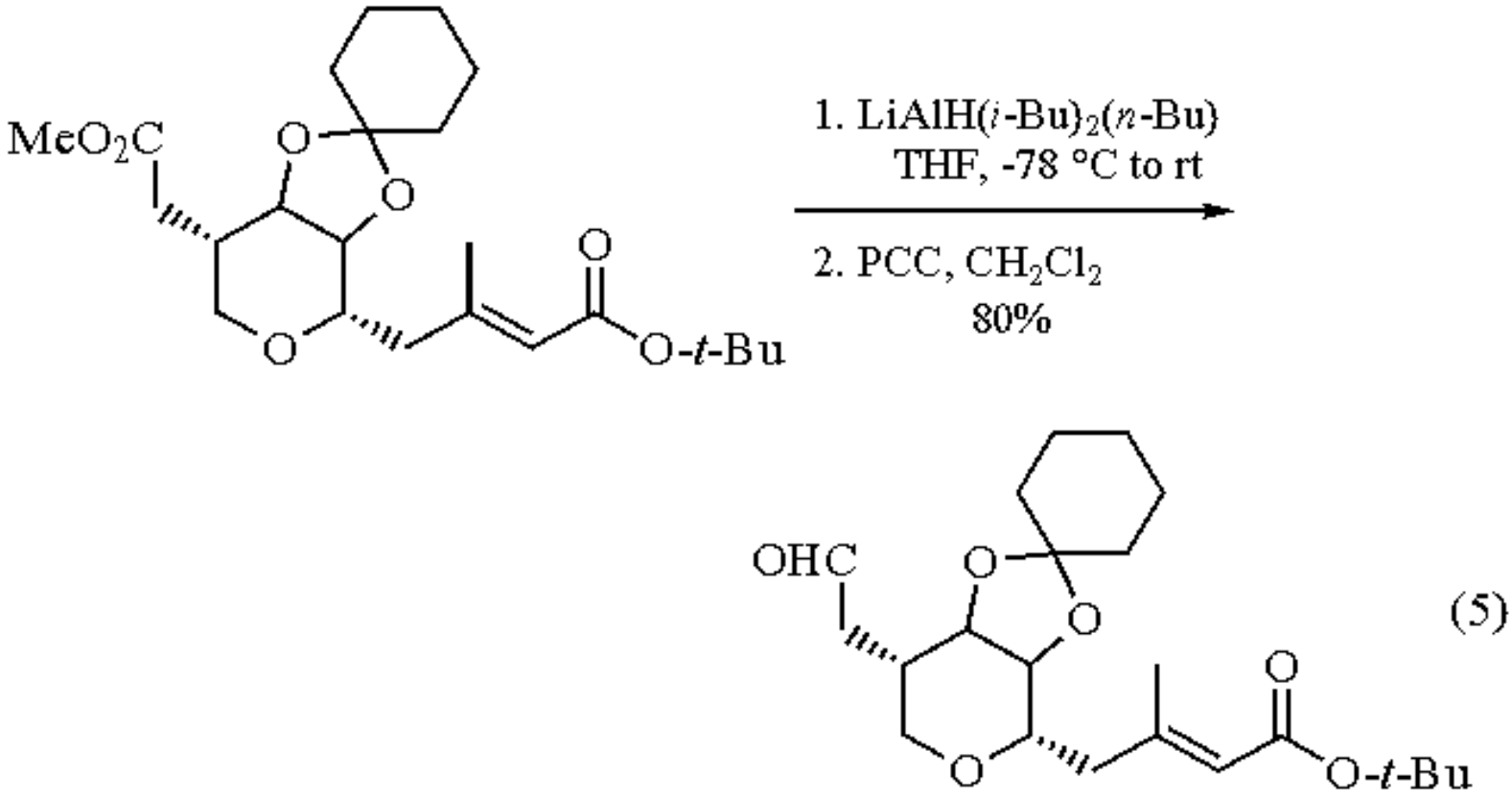

Reduction of *t*-Amides to Aldehydes and Alcohols.

Although primary and secondary amides are inert to Li(*n*-Bu)(*i*-Bu)$_2$AlH, tertiary derivatives are reduced to mixtures of aldehydes and alcohols (eq 6[8a]).[2a,8]

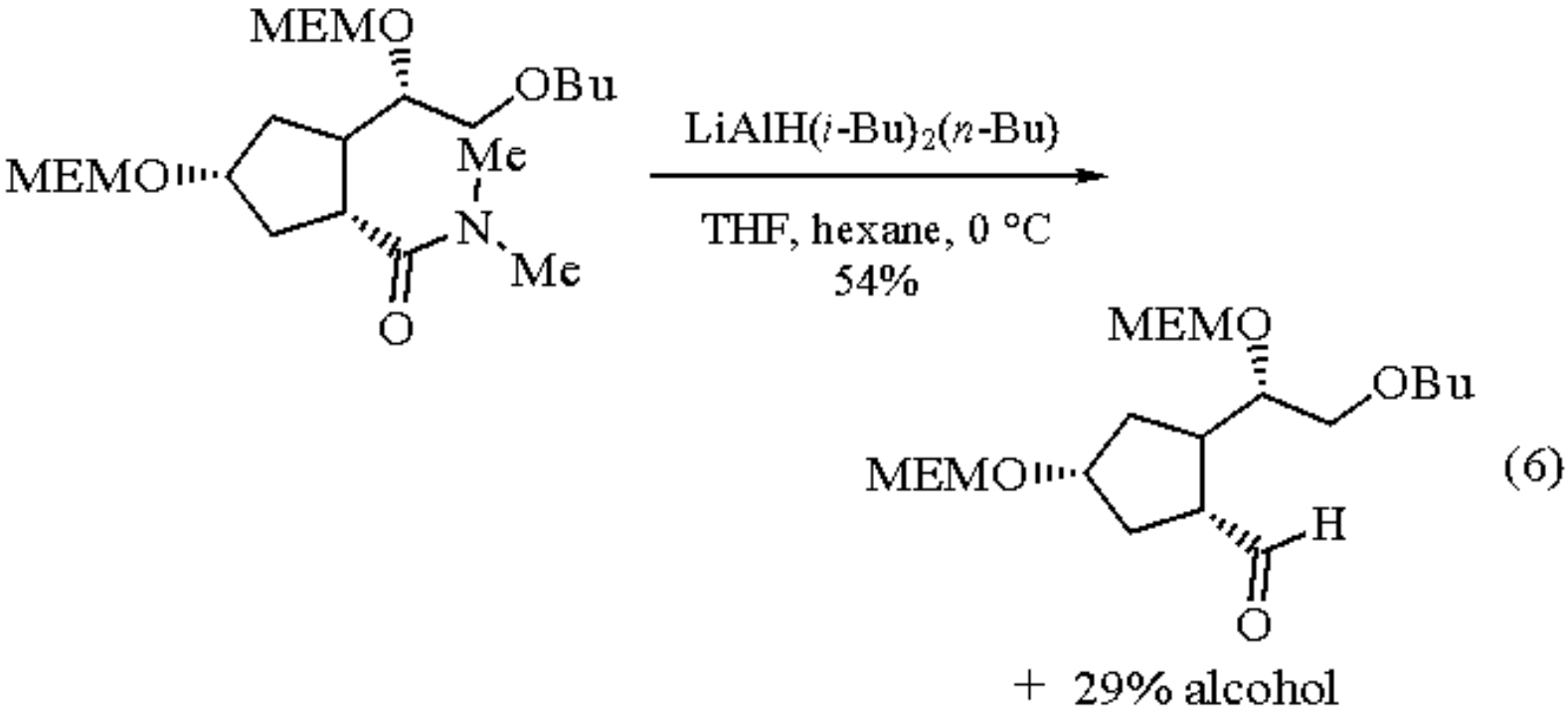

Reduction of Other Functional Groups.

This reagent system reduces acid chlorides to alcohols (eq 7), anhydrides to alcohols and acids (eq 8), primary alkyl iodides to hydrocarbons (eq 9), epoxides to alcohols (eq 10) and disulfides to thiols (eq 11).[2a] Chemoselectivity is possible, as illustrated in eq 12.[2a]

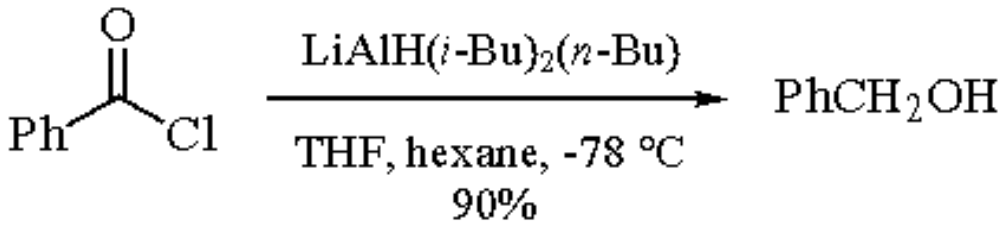

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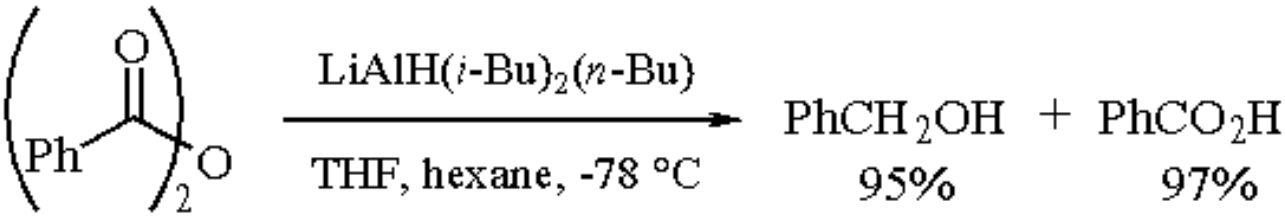

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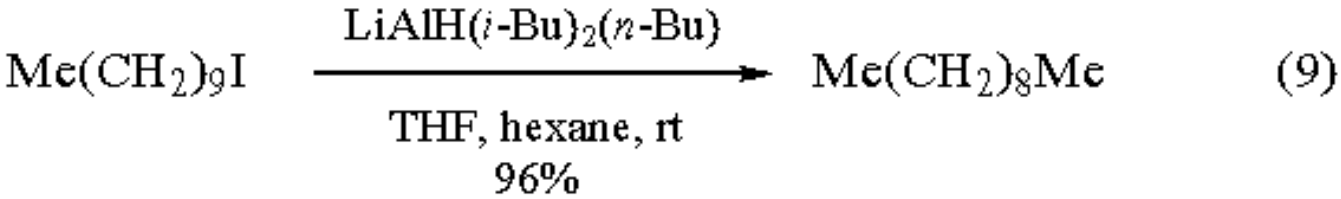

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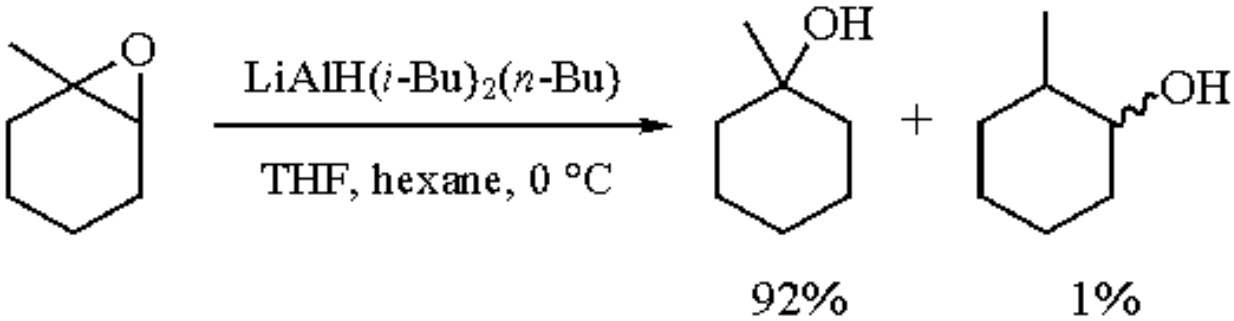

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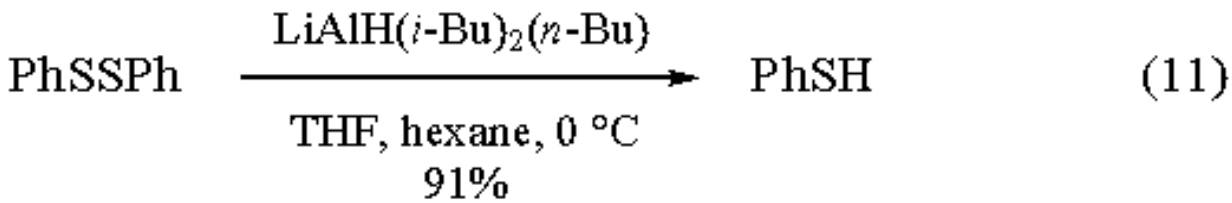

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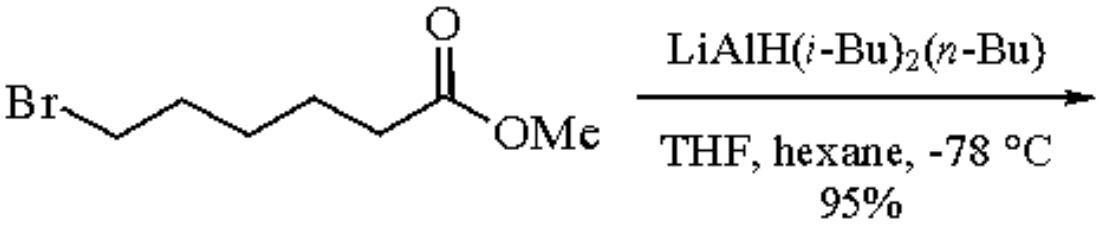

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Lithium *n*-Butyl(hydrido)cuprate[1]

LiCuH(*n*-Bu)

[53093-27-9] · $C_4H_{10}CuLi$ · Lithium *n*-Butyl(hydrido)cuprate · (MW 128.63)

(in situ hydrido copper reagent; reductive removal of halogen, mesyloxy, or tosyloxy groups; reduction of aldehydes or ketones to alcohols; 1,4-reduction of enones[2])

Preparative Method: copper(I) hydride (4 mmol, prepared by the method of Whitesides[3]) is placed in a round-bottom flask at -50 °C under an inert atmosphere, washed with -50 °C ether (4 times), and then treated with -40 °C ether before the addition of cold ***n-Butyllithium*** in hexane (4 mmol); the resulting dark brown solution (reagent partially insoluble) is stirred for 10 min, an ethereal solution of the substrate (1 mmol) is added, and the reaction mixture is allowed to warm to rt; after 2 h stirring time, the mixture is poured into saturated aqueous ammonium chloride solution, the aqueous phase is extracted with ether, and the combined organic phase is dried.[2]

Primary, secondary, and tertiary halides as well as mesylates and tosylates are reduced by lithium butyl(hydrido)cuprate in 70-100% yield (Table 1). Although aldehydes and ketones are reduced to their corresponding alcohols, α,β-unsaturated ketones are only reduced to their ketones (eqs 1-3). The *n*-butyl group is not incorporated into the product.

Table 1 Reductions with Lithium Butyl(hydrido)cuprate

Substrate	Product	Yield (%)
1-Bromoadamantane	Adamantane	70
2-Bromononane	*n*-Nonane	95
1-Bromonaphthalene	Naphthalene	95
n-Octanyl tosylate	*n*-Octane	80
Cyclohex-3-enyl tosylate	Cyclohexene	75
Ethyl 12-bromostearate	Ethyl 12-stearate	85
Heptanal	Heptan-1-ol	100
Cyclohexanone	Cyclohexanol	100

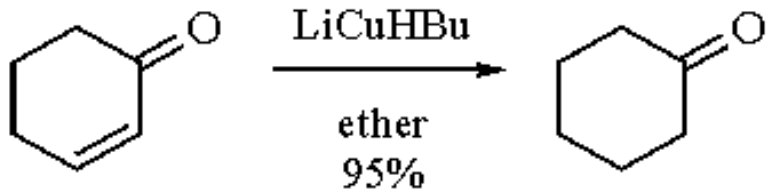

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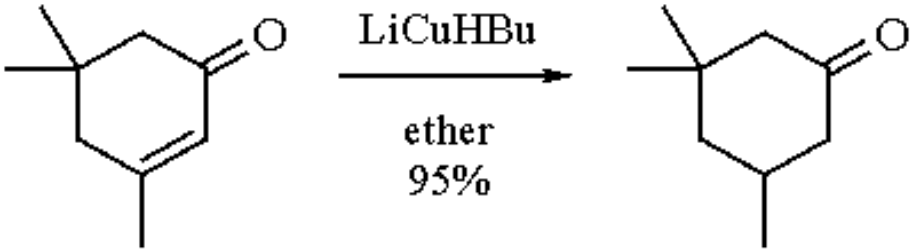

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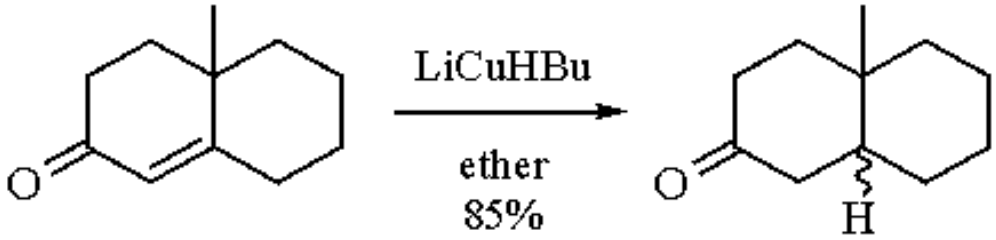

cis:*trans* = 7:3

(3)

Modifications.

Other ate complexes of the general formula LiCuHR (where R = *t*-Bu,[2] *i*-Pr,[2] 1-pentynyl,[2,4] *O*-*t*-butyl,[4] or PhS[4]) were prepared. The *n*-butyl ate complex is the most reactive hydride reducing agent. The use of THF as solvent provides no advantage,[2] whereas THF/HMPA is an effective solvent.[4]

Alternative Methods.

For a discussion of alternative methods for reductive removal of halogen, hydroxy, mesyloxy, or tosyloxy groups, see ***Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride***.

For a discussion of alternative methods for reduction of aldehydes or ketones to alcohols, see ***Lithium Aluminum Hydride*** and related reagents, or ***Sodium Borohydride*** and related reagents.

For a discussion of alternative methods for 1,4-reduction of enones, see ***Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride***.

---

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Lithium *n*-Butyl(3-methoxy-3-methyl-1-butynyl)cuprate

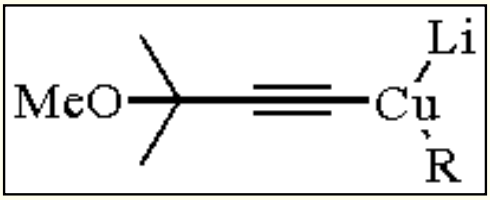

(**1**; R = *n*-Bu)

[66777-74-0] · $C_{10}H_{18}CuLiO$ · Lithium *n*-Butyl(3-methoxy-3-methyl-1-butynyl)cuprate · (MW 224.77) (**2**; R = *t*-Bu)

[66777-76-2]

(mixed cuprate butyl transfer agents)

Preparative Methods: these reagents are prepared in situ by deprotonation of 3-methoxy-3-methyl-1-butyne with ***n-Butyllithium***, followed by addition of ***Copper(I) Iodide*** and then either ***t-Butyllithium*** or *n*-butyllithium.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive; use in a fume hood.

Butyl Transfer Agents.

The less expensive 3-methoxy-3-methyl-1-butyne was introduced as an alternative to *t*-butylacetylene for mixed cuprate reactions. Cuprates synthesized using this reagent maintain the same solubility profile, thermal stability, and ligand transfer preferences as obtained using *t*-butylacetylene. Lithium *n*-butyl(3-methoxy-3-methyl-1-butynyl)cuprate (**1**) underwent displacement reactions with cyclohexyl iodide and cinnamyl bromide in moderate yield, but produced a quantitative yield upon 1,4-addition to 2-cyclohexen-1-one. The much more sterically hindered lithium *t*-butyl(3-methoxy-3-methyl-1-butynyl)cuprate (**2**) also underwent 1,4-addition to 2-cyclohexen-1-one in excellent yield (eqs 1-4).[1]

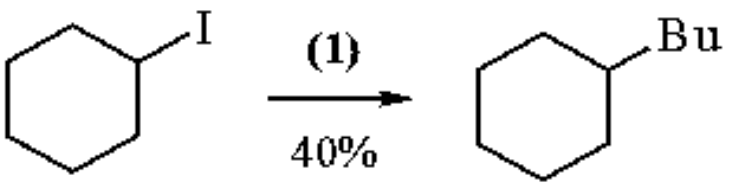

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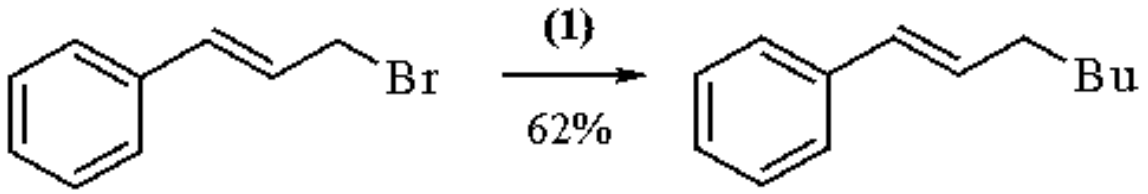

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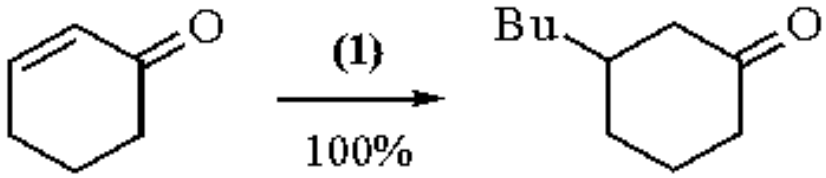

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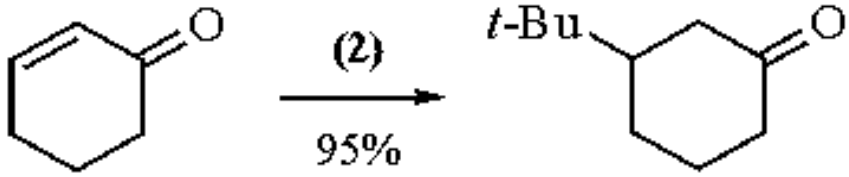

(4)

Reagent (**1**) was used to study the reaction of cuprates with α-oxoketene dithioacetals.[2] Reaction of (**1**) with (**3**) gave a 92:8 (*E*)/(*Z*) ratio of addition products (**4**) in 55% yield, along with a 12% yield of reduction product (**5**) and 38% recovered (**3**) (eq 5). When (**1**) was reacted with the α-oxoketene dithioacetal (**6**) only the addition product (**7**) (89:11 *E*/*Z*) was obtained in 93% yield (eq 6).

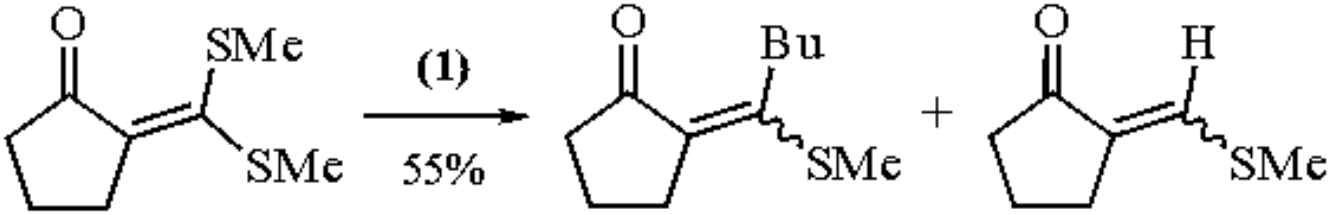

(5)

(3) **(4)** **(5)** 12%

(E):*(Z)* = 92:8

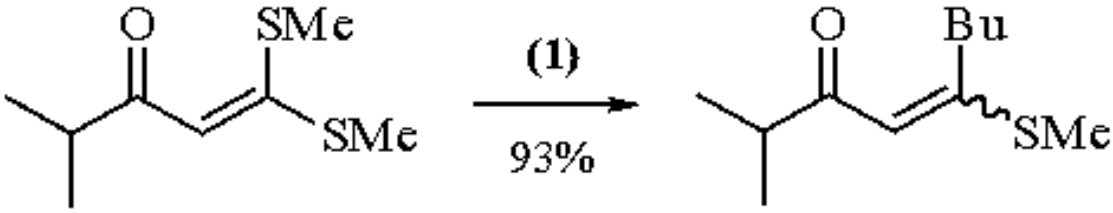

(6)

(6) **(7)**

(E):*(Z)* = 89:11

During a study of the effects of trimethylsilyl halides on the structure and reactivity of higher order (HO) cuprates, it was discovered that addition of 2 equiv ***Chlorotrimethylsilane*** irreversibly transformed the HO cuprate (**8**) (R = Me) into the lower order (LO) cuprate (**9**) and 1 equiv ***Cyanotrimethylsilane*** and LiCl (eq 7).[3] To determine if (**9**) was the

reactive intermediate, TMSCl, TMSCN, and LiI were added to a solution of (**1**). 1,2-Addition to aldehyde (**10**) produced alcohols (**11**) and (**12**) in a 10-12:1 (*syn*:*anti*) ratio in high chemical yield (eq 8). This is analogous with the results obtained from reaction of (**10**) with HO cuprates using TMSX (X = Cl, Br, I, OTf) as an additive. No reaction between (**1**) and TMSCl could be detected by ^{1}H, ^{7}Li, or ^{29}Si NMR, leaving the role of TMSX in these reactions somewhat elusive.

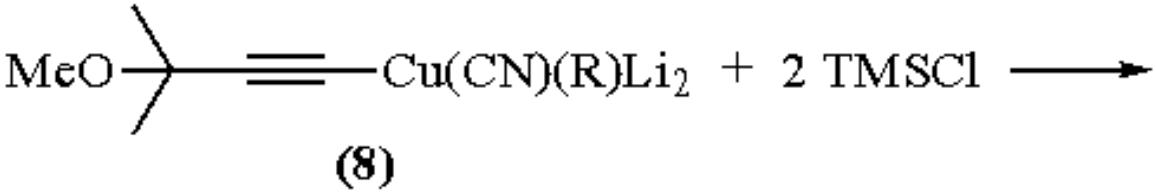

(8)

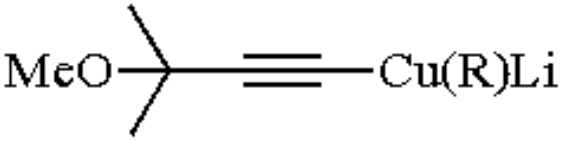

(7)

(9)

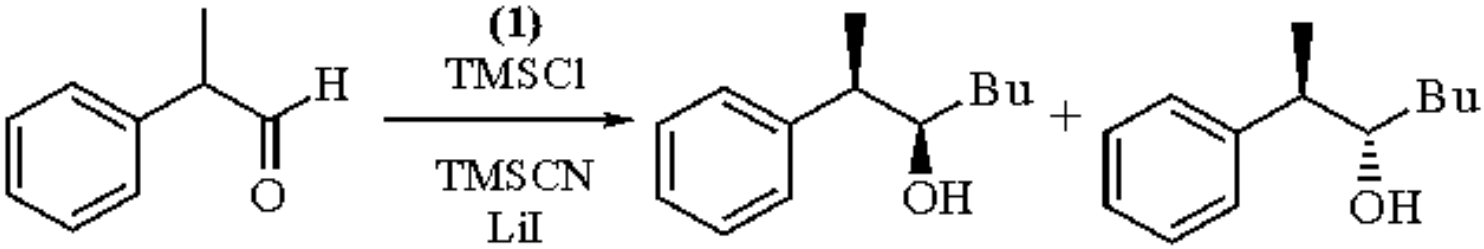

(8)

(10) 96-100% (11) 10-12:1 (12)

Related Reagents.

3,3-Dimethyl-1-butynylcopper(I); ***(3-Methoxy-3-methyl-1-butynyl)copper(I)***.

---

1. Corey, E. J.; Floyd, D.; Lipshutz, B. H. *JOC* **1978**, *43*, 3418.
2. Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E. *JACS* **1985**, *107*, 4679.
3. Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J.; Shirazi, A. *TL* **1988**, *29*, 6677.

Matthew E. Voss

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Lithium *t*-Butyl-*t*-octylamide

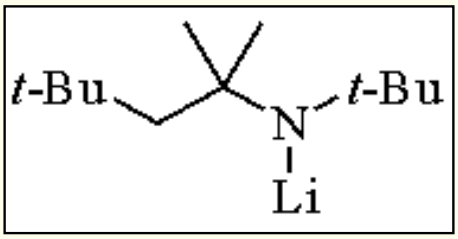

[90702-60-6] · $C_{12}H_{26}LiN$ · Lithium *t*-Butyl-*t*-octylamide · (MW 191.33)

(relatively accessible hindered amide base)

Alternate Name: LOBA.

Preparative Methods: a variety of di-*t*-alkylamines which are more hindered than the commercially available ***2,2,6,6-Tetramethylpiperidine*** can be prepared by multistep routes;[1-4] the precursor to LOBA, 1,1,3,3-tetramethylbutyl-*t*-butylamine, is obtained in three steps from commercially available materials in an overall yield of 73%;[4] LOBA is prepared by metalation of this amine with ***Methyllithium***; metalation with BuLi occurs sluggishly, if at all.

Handling, Storage, and Precautions: lithium amide bases are reactive to air and water; use in a fume hood.

Selective Enolate Formation.

In a comparison with ***Lithium Diisopropylamide***, LOBA exhibits greater regioselectivity (eq 1) and greater stereoselectivity (eq 2) in the formation of ketone and ester enolates, as judged by an in situ quenching procedure using ***Chlorotrimethylsilane*** (TMSCl).[5,6]

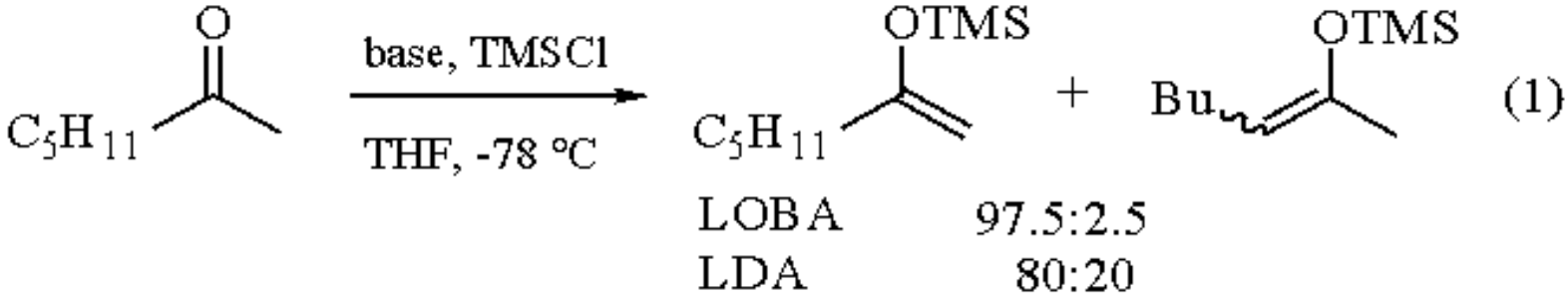

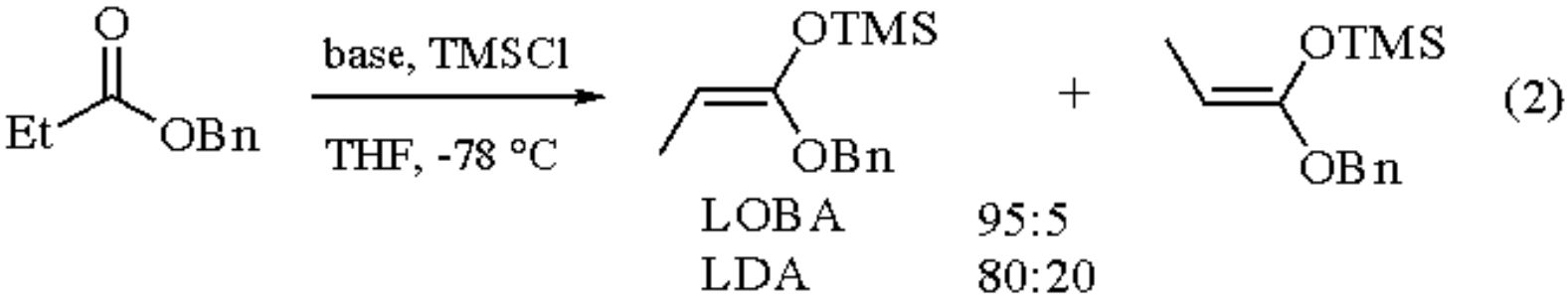

Ester (**1**), an intermediate in a synthesis of pseudomonic acid C,[7] is converted by the Ireland-Claisen rearrangement,[8] using LDA, into a 4:1 mixture of epimers (**2**) and (**3**) (eq 3). ***Lithium 2,2,6,6-Tetramethylpiperidide*** and LOBA give higher selectivities (6:1 and 7:1, respectively) but the yield is much lower (<30%).

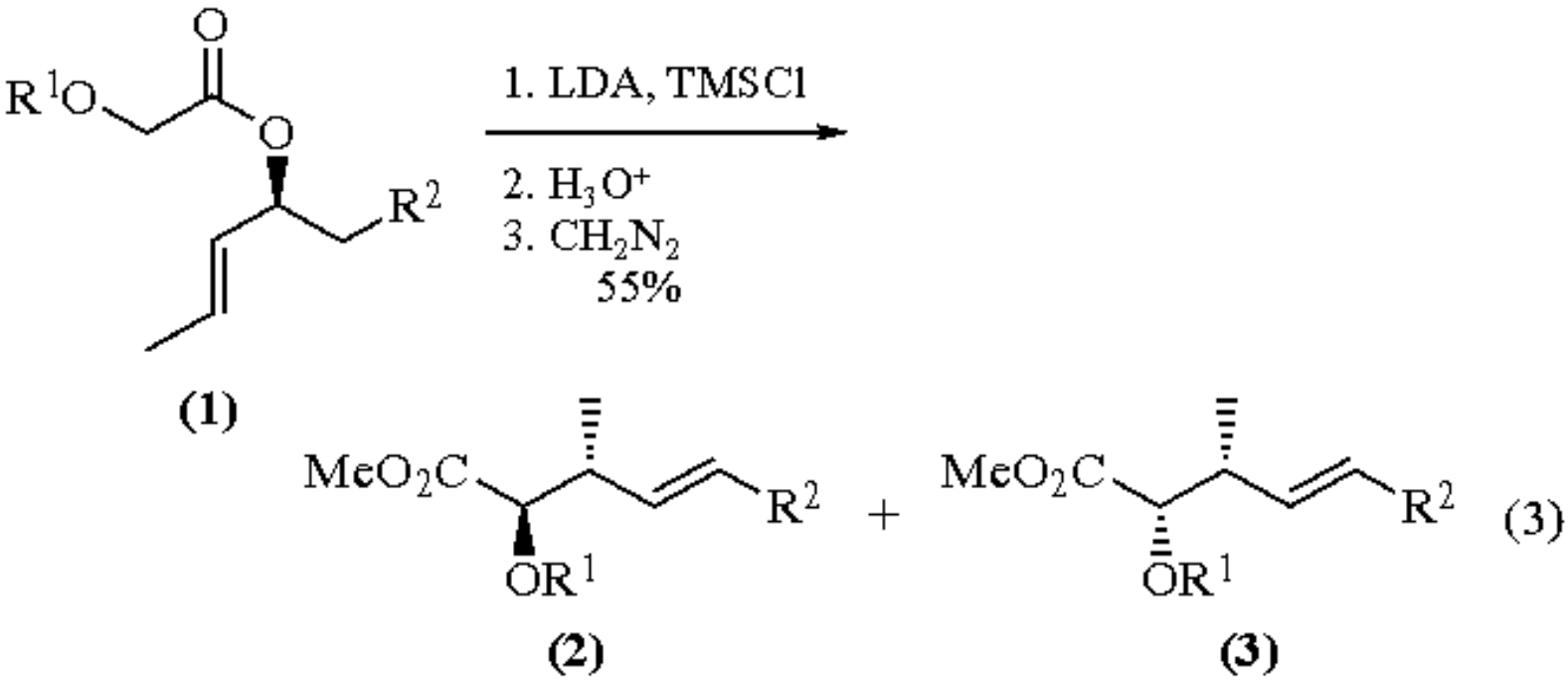

Related Reagents.

See entries for similar amide bases, e.g. ***Lithium Amide***, ***Lithium Diethylamide***, ***Lithium Diisopropylamide***, ***Lithium 2,2,6,6-Tetramethylpiperidide***, ***Potassium Diisopropylamide***.

---

1. Schwartz, M. A.; Hu, X. *TL* **1992**, *33*, 1689.
2. Klusener, P. A. A.; Tip, L.; Brandsma, L. *T* **1991**, *47*, 2041.
3. Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *JOC* **1980**, *45*, 4616.
4. Corey, E. J.; Gross, A. W. *TL* **1984**, *25*, 491.
5. Corey, E. J.; Gross, A. W. *TL* **1984**, *25*, 495.
6. For an explanation of the changes in selectivity observed with in situ quenching compared to external quenching in related systems, see: Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *JACS* **1991**, *113*, 9571.
7. Barrish, J. C.; Lee, H. L.; Mitt, T.; Pizzolato, G.; Baggiolini, E. G.; Uskokovic, M. R. *JOC* **1988**, *53*, 4282.
8. Ireland, R. E.; Mueller, R. H.; Willard, A. K. *JACS* **1976**, *98*, 2868.

Lithium *n*-Butyl(phenylthio)cuprate[1]

***n*-BuCu(SPh)Li**

[53128-68-0] · $C_{10}H_{14}CuLiS$ · Lithium *n*-Butyl(phenylthio)cuprate · (MW 236.80)

(primary heterocuprate capable of nucleophilic additions and substitutions[2])

Solubility: sol THF, ether.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[3] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl, and the yield of PhCO(*n*-Bu) is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: 1.0 equiv of ***n-Butyllithium*** is added dropwise to a 0.2 M, 0 °C THF solution of ***Thiophenol*** in a three-neck flask equipped with N_2 inlet, solid addition funnel, and rubber septum; after stirring for 10 min, 1.0 equiv of ***Copper(I) Iodide*** is added via the addition funnel; stirring for an additional 15 min provides a clear, yellow solution which is cooled to -78 °C; 1.0 equiv of *n*-BuLi is then added dropwise via syringe;[4,5] after 1 h, the light brown, opaque solution is ready for use. Alternate sources of PhSCu may be acceptable; PhSCu in purities of 95->98% is commercially available.[6]

Handling, Storage, and Precautions: use in a fume hood; best results are obtained with high-purity copper(I) salts,[7] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides;[8] *n*-BuLi is pyrophoric,[9] and due care must be exercised in its handling; the reagent has greater stability in THF than in ether; thermal decomposition is minimal at or below -25 °C but is substantial at 0 °C.[3b]

This primary alkyl organometal reagent is representative of the heterocuprate class of organocopper reagents.[10] The *n*-Bu group is nucleophilically reactive, whereas the SPh group is not. Such nontransferable groups are called dummy ligands;[11] the SPh dummy ligand in particular provides enhanced thermal stability and solubility compared with the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium *n*-butyl(phenylthio)cuprate has been used in nucleophilic substitution reactions of arenesulfonyl fluorides,[12] allylic acetates,[13] 9-BBN,[14] propargylic carbamates,[15] and bromoalkenes,[16] as well as in nucleophilic additions to

acetoxyepoxides.[17] It is a good choice for 1,4-addition of an *n*-Bu group, having been used in 1,4-addition-elimination reactions of α-oxoketene dithioacetals[4] and 3-halo-2-cycloalkenones,[18] and in tandem vicinal dialkylation reactions of 5-methyleneoxazolones[19] and alkynes.[20] A typical example is the use of the reagent in the stereospecific synthesis of (*Z*)-2-heptenoic acid from acetylene (eq 1).[20a]

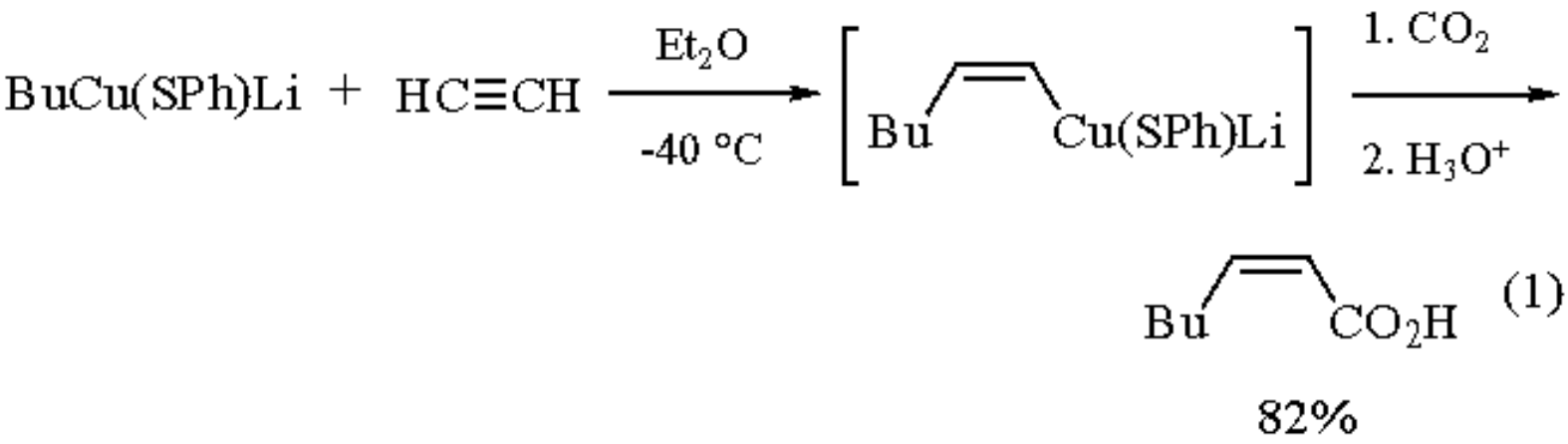

Related Reagents.

For related heterocuprates, see ***Lithium Methyl(phenylthio)cuprate***; for discussion of lithium dialkylcuprates, see ***Lithium Dimethylcuprate***.

---

1. (a) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
2. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992. (b) Kozlowski, J. A. *COS* **1991**, *4*, 169. (c) Hulce, M.; Chapdelaine, M. J. *COS* **1991**, *4*, 237. (d) Chapdelaine, M. J.; Hulce, M. *OR* **1990**, *38*, 225. (e) Posner, G. H. *OR* **1975**, *22*, 253. (f) Posner, G. H. *OR* **1972**, *19*, 1.
3. (a) Bertz, S. H.; Dabbagh, G. *CC* **1982**, 1030. (b) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *JACS* **1982**, *104*, 5824.
4. Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E. *JACS* **1985**, *107*, 4679.
5. (a) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *S* **1974**, 662. (b) For a detailed preparation of the corresponding *t*-Bu heterocuprate, see Posner, G. H.; Whitten, C. E. *OSC* **1988**, *6*, 248.
6. Corey, E. J.; Boger, D. L. *TL* **1978**, *39*, 4597.
7. Purification methods: (a) Posner, G. H.; Sterling, J. J. *JACS* **1973**, *95*, 3076. (b) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed; Pergamon: New York, 1988; p 322. (c) Lipshutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *TL* **1986**, *27*, 4273.
8. Corey, E. J.; Naef, R.; Hannon, F. J. *JACS* **1986**, *108*, 7114.
9. Wakefield, B. J. *Organolithium Methods*; Academic: New York, 1988; pp 11-15.
10. Posner, G. H.; Whitten, C. E.; Sterling, J. J. *JACS* **1973**, *95*, 7788.
11. Lipshutz, B. H. *SL* **1990**, 119.
12. Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *JOC* **1992**, *57*, 697.
13. Kal'yan, Yu. B.; Krimer, M. Z.; Smit, V. A.; Moiseenkov, A. M.; Lutsenko, A. I. *IZV* **1985**, 2092 (*CA* **1986**, *105*, 97 193n).
14. Whiteley, C. G.; Zwane, I. *JOC* **1985**, *50*, 1969.

15. Pirkle, W. H.; Boeder, C. W. *JOC* **1978**, *43*, 1950.
16. Miller, R. B.; McGarvey, G. *JOC* **1979**, *44*, 4623.
17. Amos, R. A.; Katzenellenbogen, J. A. *JOC* **1977**, *42*, 2537.
18. (a) Piers, E.; Cheng, K. F.; Nagakura, I. *CJC* **1982**, *60*, 1256. (b) Christie, R. M.; Gill, M.; Rickards, R. W. *JCS(P1)* **1981**, 593.
19. Schulz, G.; Gruber, P.; Steglich, W. *CB* **1979**, *119*, 3221.
20. (a) Alexakis, A.; Normant, J.; Villiéras, J. *TL* **1976**, 3461. (b) Furber, M.; Taylor, R. J. K.; Burford, S. C. *TL* **1985**, *26*, 2731.

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Lithium Carbonate

Li_2CO_3

[554-13-2] · CLi_2O_3 · Lithium Carbonate · (MW 73.89)

(base for dehydrohalogenation reactions and halide displacements; reagent for regioselective alkylations)

Physical Data: mp 723 °C; bp 1310 °C; *d* 2.11 g cm^{-3}.

Solubility: sol cold (1 g/78 mL), hot H_2O (1 g/140 mL); insol alcohol, acetone.

Form Supplied in: white powder; widely available. *Drying:* details are available.[1]

Dehydrohalogenation.

Lithium carbonate in refluxing DMF is an excellent base for dehydrohalogenation reactions. LiCl in DMF caused rearrangement of the alkene to the more substituted α,β-position.[2] Treatment with a stronger base, lithium carbonate, led to good yields of the less substituted enone (eq 1). Substituted tropones have been prepared in a similar manner from alkyl-substituted tribrominated cycloheptanones (eq 2).[3]

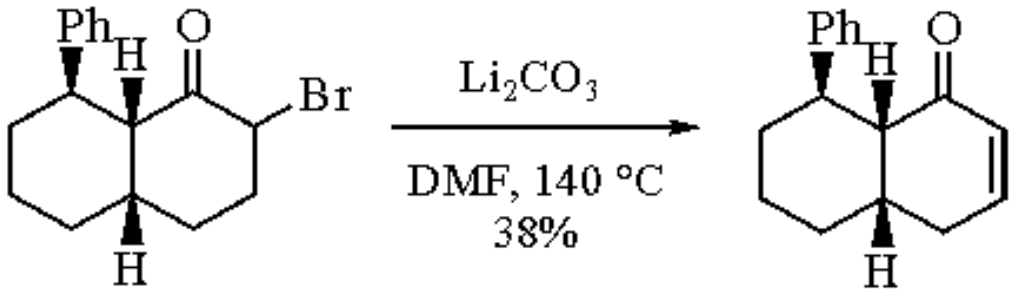

(1)

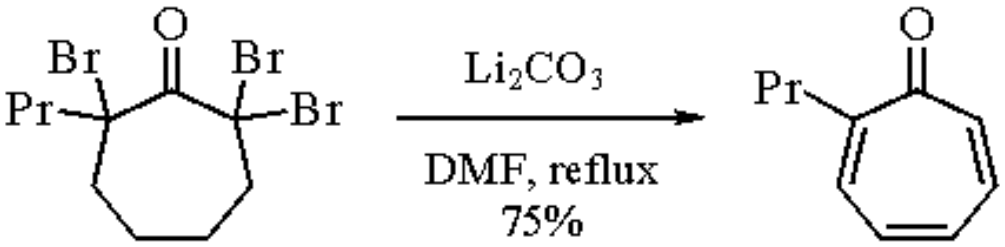

(2)

Halide Displacement.

A preparation of steroidal oxetanones has been reported using Li_2CO_3 in refluxing DMF. It was found that either the *cis* or the *trans* bromides can give the α-oxetanone in good yield (eq 3).[4]

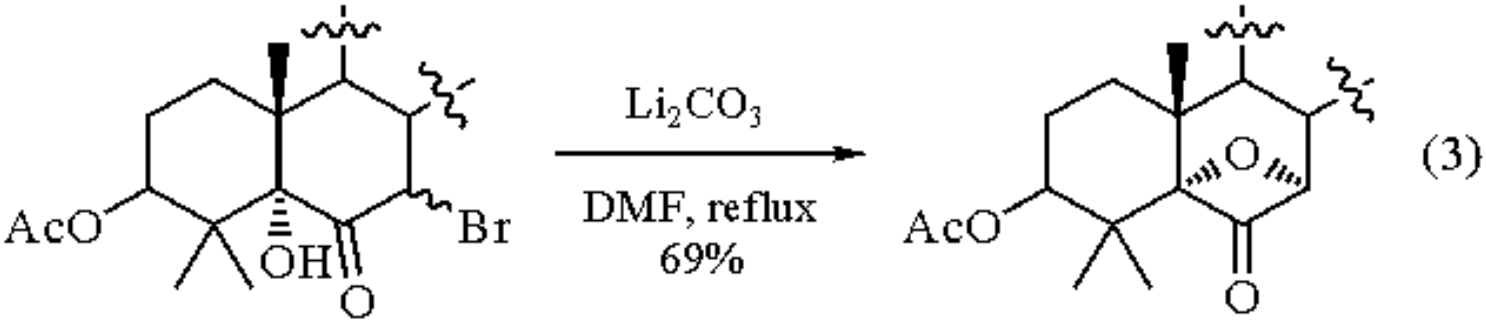

Alkylations.

Lithium carbonate used in conjunction with DMF and various alkylating agents has been found to regioselectively alkylate bisphenolic, 1,3-dicarbonyl, and thiol substrates that contain hydrogens that are more acidic than phenol (pK_a &AApprox; 8).[5] It has been determined that phenolic compounds containing electron-withdrawing groups alkylate at either the *ortho* or *para* positions exclusively (eq 4). Attempts to use other bases such as ***Potassium Carbonate*** or ***Sodium Carbonate*** showed a loss of selectivity. Using more reactive alkylating agents such as propargyl bromide (see under ***Propargyl Chloride***) or ***Benzyl Bromide*** also reduces the selectivity of alkylation. This sequence has been used to differentiate between the two hydroxyl groups present in alizarin (eq 5).[5]

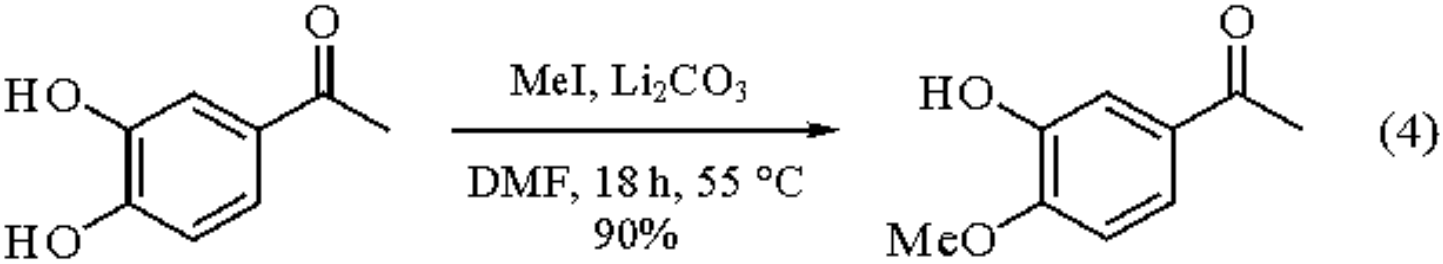

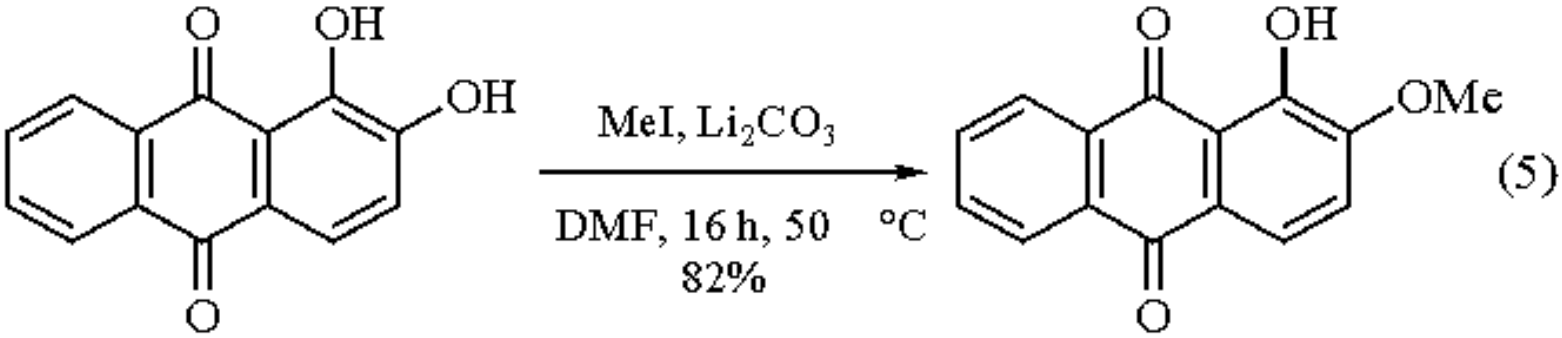

1,3-Dicarbonyl compounds such as β-keto esters or β-diketones are sufficiently acidic to alkylate as well (eq 6).[5]

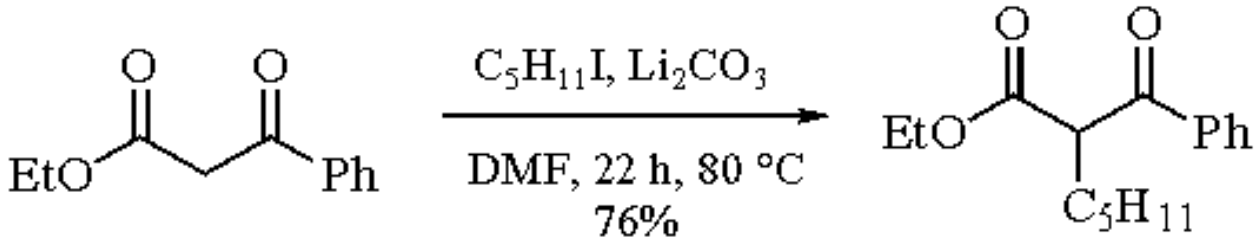

(6)

Thiophenoxyphenols have shown selectivity of alkylation with lithium carbonate. The more acidic S-H can be preferentially alkylated in deference to a phenolic O-H bond.[5] Using potassium carbonate in the same alkylation scheme gives only 4% of the desired product.

Base Assistance.

Spirocyclic ethers can be generated via intramolecular nucleophilic attack of hydroxide upon π-(allyl)palladium complexes (eq 7). The attack of an external nucleophile can then be directed for either *cis* or *trans* addition, depending on the concentration of nucleophile present.[6] In the presence of 3 equiv of Li_2CO_3, *cis* migration of acetate was the only reaction observed. Conversely, the addition of 1.8 equiv of chloride ion causes chloride to be added from the face opposite the metal.

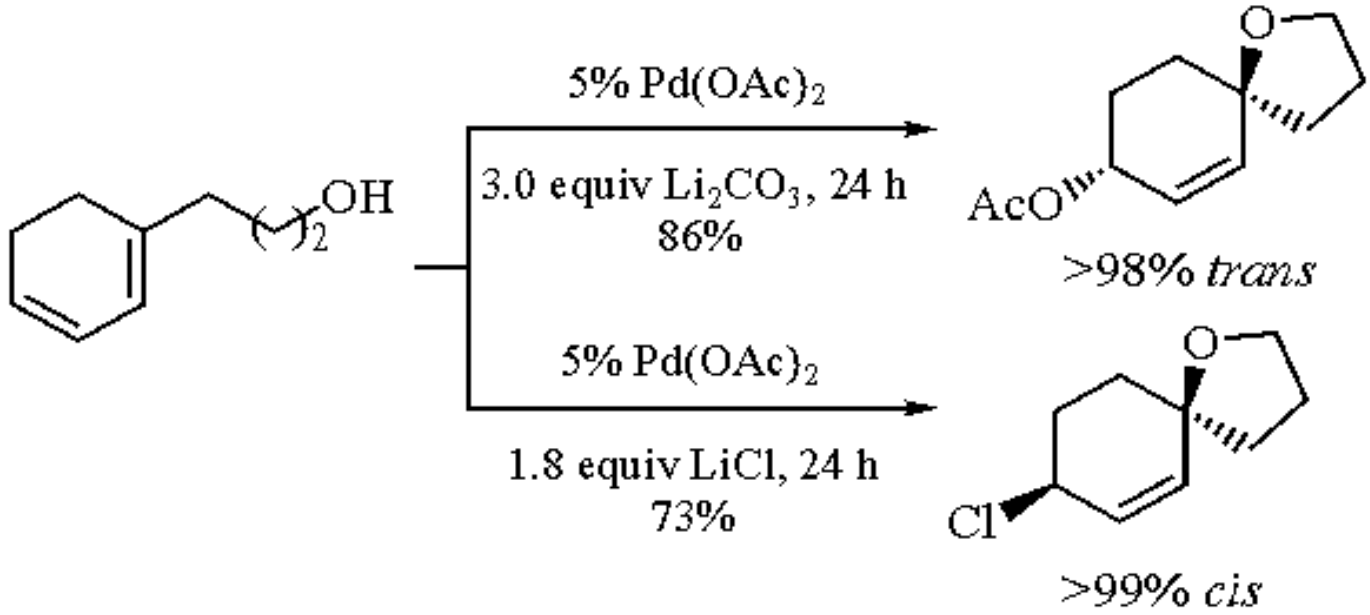

(7)

Related Reagents.

Lithium Carbonate-Lithium Bromide; ***Potassium Carbonate***; ***Sodium Carbonate***.

---

1. *Inorg. Synth.* **1939**, *1*, 1.
2. House, H. O.; Bashe, R. W. II. *JOC* **1965**, *30*, 2942.
3. (a) Jones, G. *JCS(C)* **1970**, 1230. (b) Collington, E. W.; Jones, G. *JCS(C)* **1969**, 2656. (c) Collington, E. W.; Jones, G. *CC* **1968**, 958.

4. (a) Hanna, R.; Maalouf, G.; Muckensturm, B. *T* **1973**, *29*, 2297. (b) Rowland, A. T.; Bennett, R. J.; Shoupe, T. S. *JOC* **1968**, *33*, 2426.
5. Wymann, W. E.; Davis, R.; Patterson, J. W.; Pfister, J. *SC* **1988**, *18*, 1379.
6. Bäckvall, J. E.; Andersson, P. G. *JOC* **1991**, *56*, 2274.

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Lithium Carbonate-Lithium Bromide

Li_2CO_3-LiBr

(Li_2CO_3)

[554-13-2] · CLi_2O_3 · Lithium Carbonate-Lithium Bromide · (MW 73.89) (LiBr)

[7550-38-8] · BrLi · Lithium Carbonate-Lithium Bromide · (MW 86.85)

(reagent for dehydrohalogenation of α-halo ketones)

Physical Data: see ***Lithium Carbonate*** and ***Lithium Bromide***.

Dehydrohalogenations.

The combination of lithium carbonate and lithium bromide has been found to be a powerful reagent for effecting the dehydrohalogenations of α-halo ketones.[1] A typical procedure involves heating of the halo ketone with a 1:1 mixture of lithium carbonate-lithium bromide in refluxing DMF. Frequently this procedure is used for the introduction of a conjugated alkene. This method has been shown in certain cases to be superior to other dehydrohalogenation methods. An interesting example is given by the dehydrobromination of dibromoacetoxyetiocholane (eq 1).[1]

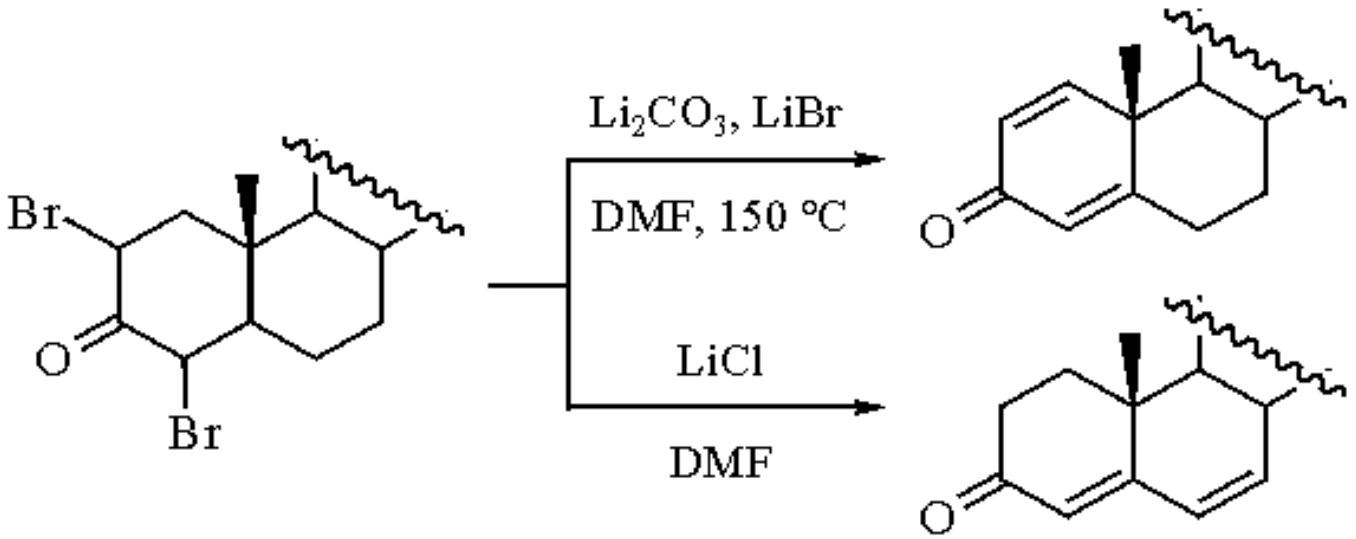

(1)

Excellent yields (96%) of the 1,4-dienone were obtained using the carbonate-bromide pair. However, when ***Lithium Chloride*** in DMF was used as the base, a mixture of the 1,4- and 1,6-dienones was obtained. The same investigators have also observed that the use of shorter reaction times allows for the isolation of the monodebrominated compound

in lower yield without contamination from the didebrominated product (eq 2).[2]

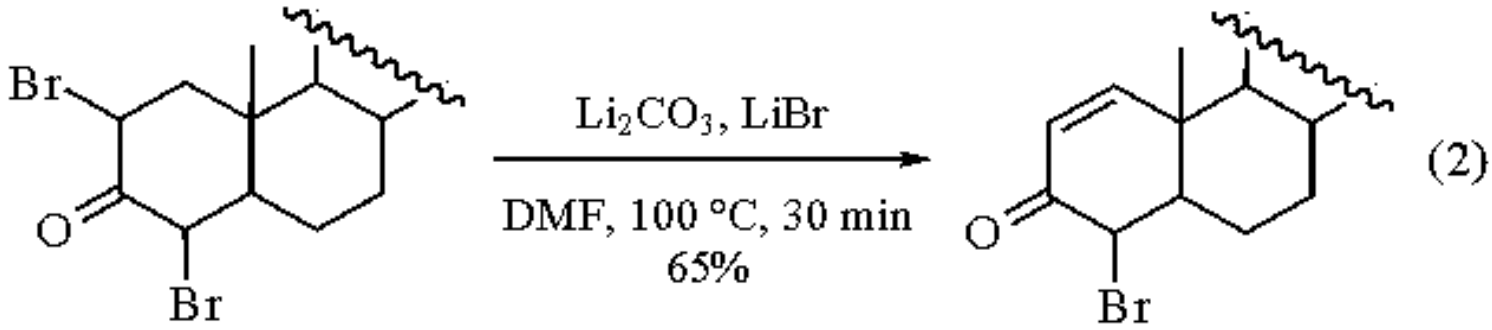

This procedure was utilized by Grieco to prepare a key dienophile for a synthesis of quassin (eq 3).[3] The octalone is selectively brominated at the more substituted position and then dehydrobrominated to furnish the enone in excellent overall yield. A similar dehalogenation procedure was also attempted using collidine as the base, producing the enone in 40% yield.

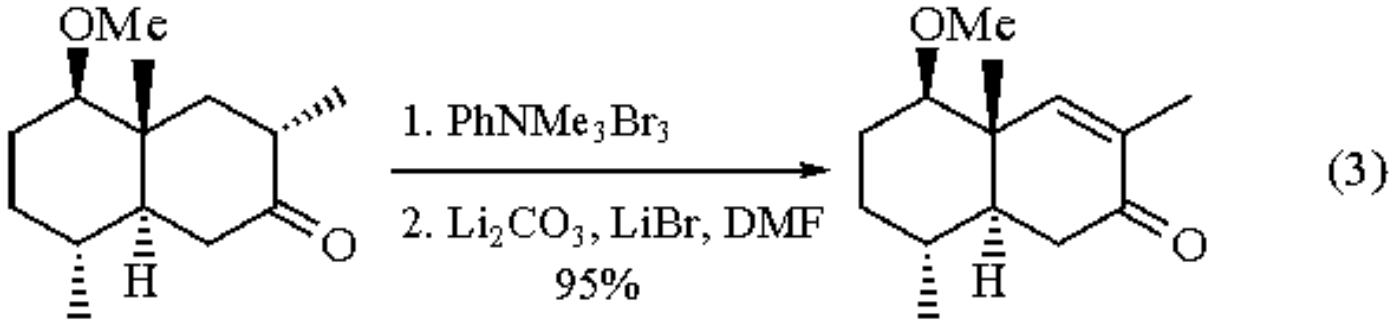

This reaction has been employed in the synthesis of tuberiferin.[4] Selective bromination of the less substituted α-position, followed by treatment of the crude bromide with lithium carbonate-lithium bromide, produced the enone in good overall yield (eq 4).

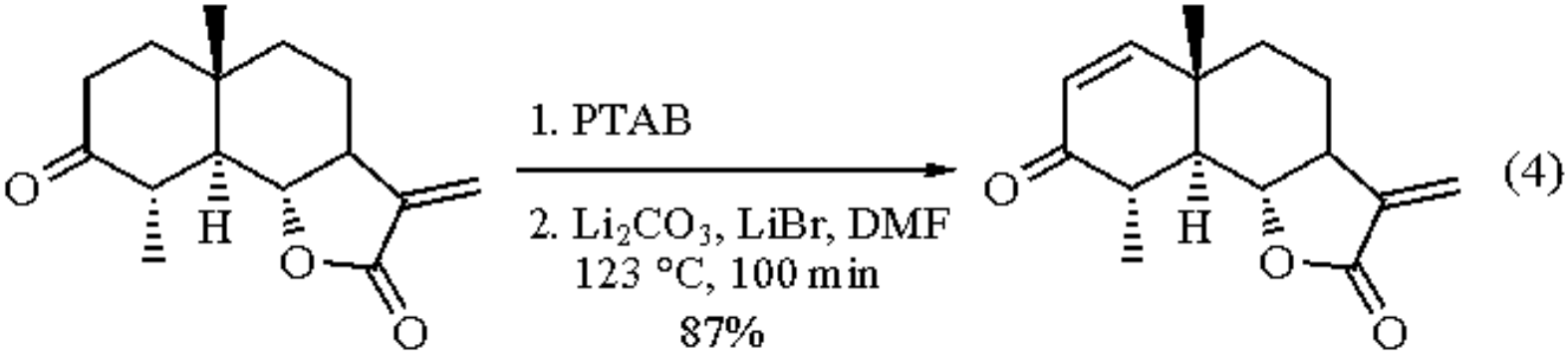

This combination of reagents also proved to be valuable for the synthesis of dienones from enone precursors. A two-step sequence of halogenation-dehydrohalogenation was engaged to produce substituted cyclohexadienones (eq 5).[5] Bromination of the enone through its enol acetate, followed by base-induced bromide elimination, yields the dienone in 85% isolated yield. When the dehydrobromination was attempted using collidine, the dienone was produced in an attenuated 40% yield.

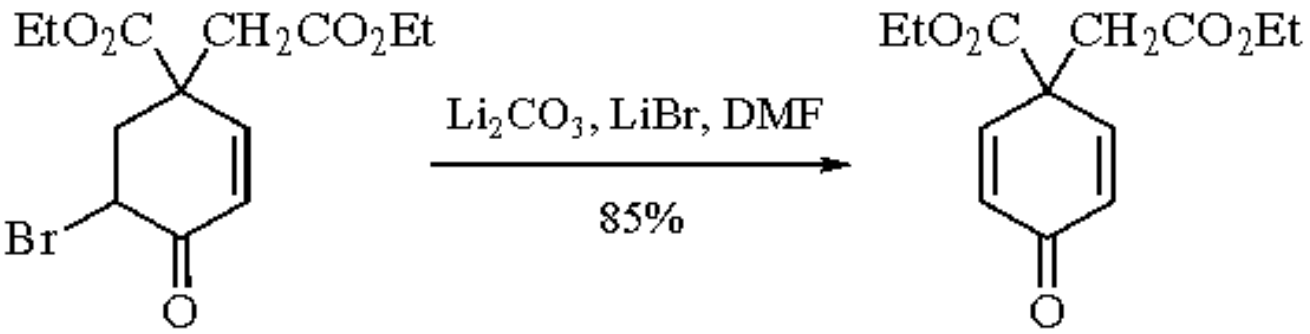

(5)

Paquette has recently applied this methodology towards an intermediate found useful for the synthesis of 18-oxo-3-virgenene (eq 6).[6] The overall yield for the sequential bromination-dehydrobromination was 71%.

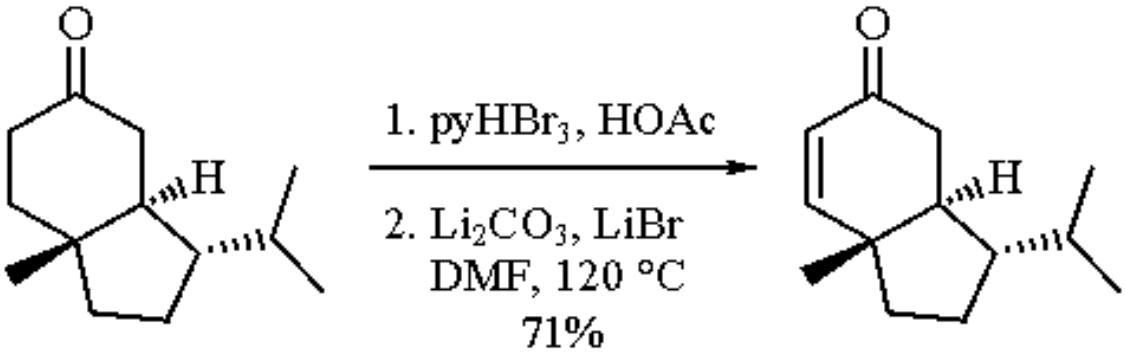

(6)

Certain dienones can be prepared directly from ketones: dibromination of the ketone followed by bis-dehydrohalogenation yields the dienone. This methodology proved valuable in a synthesis of substituted homotropones (eq 7).[7]

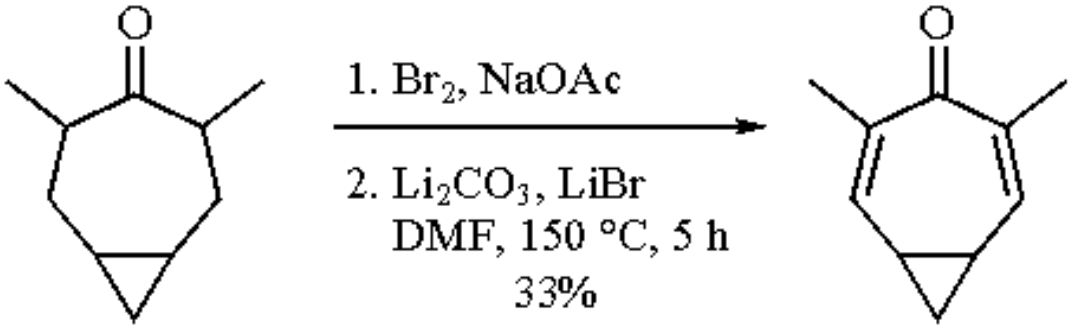

(7)

A key dienone for the construction of linear tetraquinane intermediates used in the synthesis of fusiccosin and ophiobolin natural products was prepared by a similar protocol. Bromination of the enone with elemental bromide followed by exposure to the carbonate-bromide combination produced the dienone in acceptable yield (eq 8).[8]

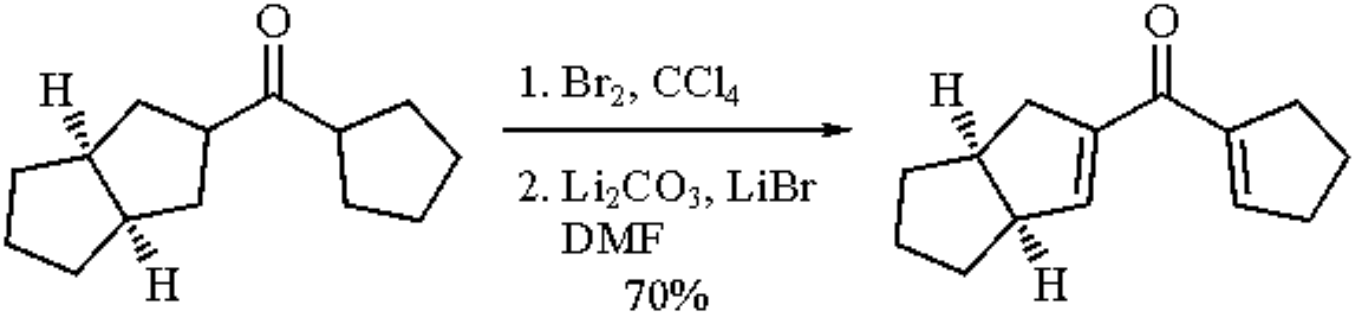

(8)

This dehalogenation procedure has been documented to work effectively on α-chloro ketones as well. The protocol was employed in a synthesis of dihydrojasmone (eq 9).[9]

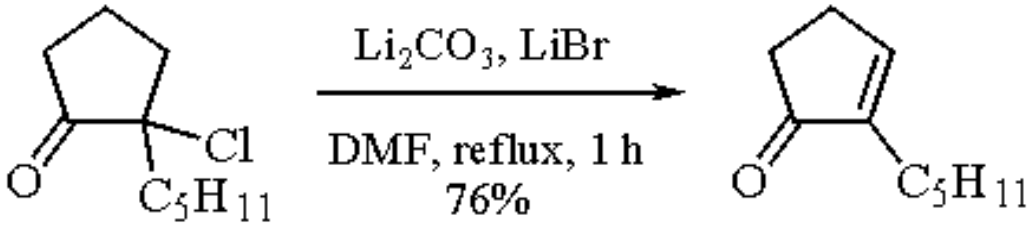

(9)

Related Reagents.

2,4,6-Collidine; ***1,5-Diazabicyclo[4.3.0]non-5-ene***; ***1,8-Diazabicyclo[5.4.0]undec-7-ene***; ***Lithium Carbonate***.

---

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Lithium Chloride

LiCl

[7447-41-8] · ClLi · Lithium Chloride · (MW 42.39)

(source of Cl^- as nucleophile and ligand; weak Lewis acid that modifies the reactivity of enolates, lithium dialkylamides, and other Lewis bases)

Physical Data: mp 605 °C; bp 1325-1360 °C; *d* 2.068 g cm^{-3}.

Solubility: very sol H_2O; sol methanol, ethanol, acetone, acetonitrile, THF, DMF, DMSO, HMPA.

Form Supplied in: white solid, widely available. *Drying:* deliquescent; for most applications, drying at 150 °C for 3 h is sufficient; for higher purity, recrystallization from methanol, followed by drying at 140 °C/0.5 mmHg overnight, is recommended.

Handling, Storage, and Precautions: of low toxicity; take directly from the oven when dryness is required.

Source of Chloride Nucleophile.

The solubility of LiCl in many organic dipolar solvents renders it an effective source of nucleophilic chloride anion. Lithium chloride converts alcohols to alkyl chlorides[1] under Mitsunobu conditions,[2] or by way of the corresponding sulfonates[3] or other leaving groups.[4] This salt cleanly and regioselectively opens epoxides to chlorohydrins in the presence of acids and Lewis acids such as ***Acetic Acid***,[5] Amberlyst 15 resin,[6] and ***Titanium(IV) Chloride***.[7] In the presence of acetic acid, LiCl regio- and stereoselectively hydrochlorinates 2-propynoic acid and its derivatives to form the corresponding derivatives of (*Z*)-3-chloropropenoic acid.[8] Oxidative decarboxylation of carboxylic acids by ***Lead(IV) Acetate*** in the presence of 1 equiv of LiCl generates the corresponding chlorides.[9]

In wet DMSO, LiCl dealkoxycarbonylates various activated esters (eq 1).[10,11] If the reaction is performed in anhyd solvent the reaction generates a carbanion intermediate, which can undergo inter- or intramolecular alkylation or elimination. Other inorganic salts (NaCN, NaCl, ***Lithium Iodide***) and other dipolar aprotic solvents (HMPA, DMF) can also be employed. Under similar conditions, lithium chloride cleaves alkyl aryl ethers having electron-withdrawing substituents at the *ortho* or *para* positions.[12]

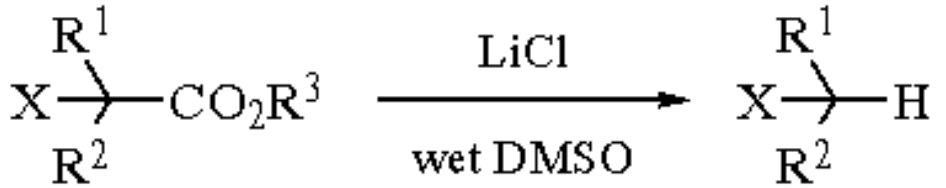

(1)

$X = CO_2R$, COR, CN, SO_2R; $R^3 = Me$, Et

Source of Chloride Ligand.

In palladium-catalyzed reactions, LiCl is often the reagent of choice as a source of chloride ligand. Lithium chloride is a necessary component in palladium-catalyzed coupling and carbonylative coupling reactions of organostannanes and vinyl triflates.[13,14] Lithium chloride has a dramatic effect on the stereochemical course of palladium-catalyzed 1,4-additions to 1,3-dienes.[15] Treatment of 1,3-cyclohexadiene with ***Palladium(II) Acetate*** and LiOAc and the oxidizing agents ***1,4-Benzoquinone*** and ***Manganese Dioxide*** affords 1,4-*trans*-diacetoxy-2-cyclohexene (eq 2). In the presence of a catalytic quantity of LiCl, the *cis* isomer is formed (eq 3). If 2 equiv LiCl are added, the *cis*-acetoxychloro compound forms (eq 4). These methods are general for both cyclic and acyclic dienes, and have recently been extended to the stereospecific formation of fused heterocycles.[16] Lithium chloride is also used in the preparation of ***Dilithium Tetrachloropalladate(II)***[17] and zinc organocuprate reagents.[18]

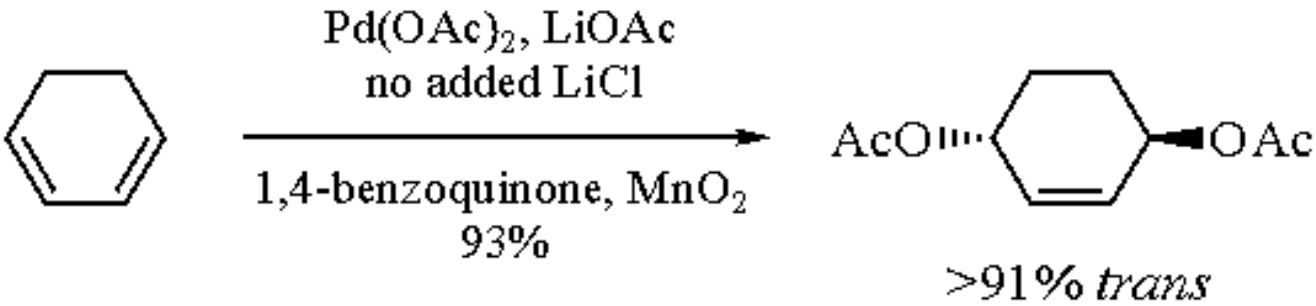

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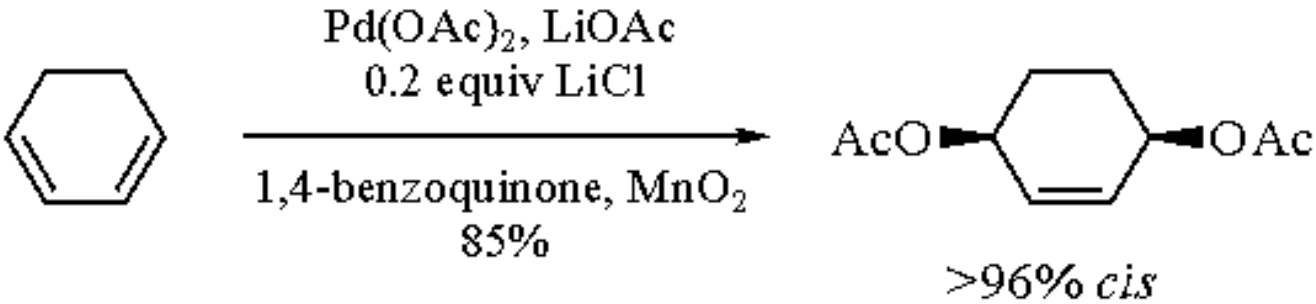

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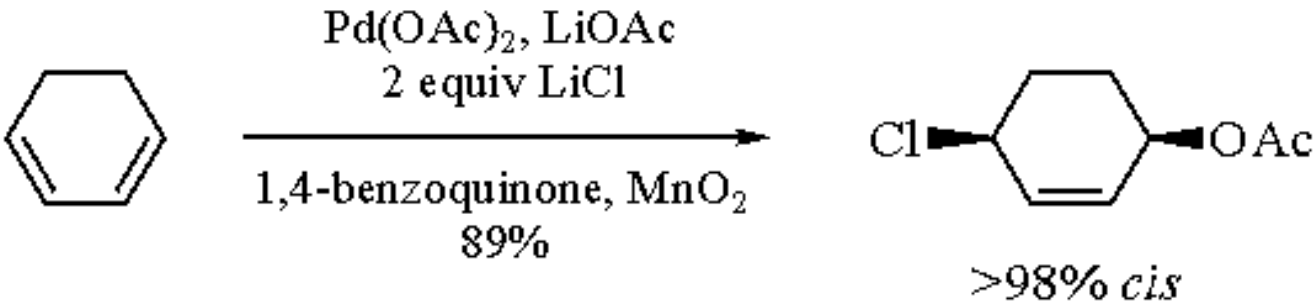

(4)

Weak Lewis Acid.

Lithium chloride is a weak Lewis acid that forms mixed aggregates with lithium dialkylamides, enolates, alkoxides, peptides, and related hard Lewis bases.[19] Thus LiCl often has a dramatic effect on reactions involving these species. In the deprotonation of 3-pentanone by ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LTMP), addition of 0.3 equiv LiCl increases the (*E*)/(*Z*) selectivity from 9:1 to 52:1 (eq 5).[20] Enhancement in the enantioselectivity of deprotonation of prochiral ketones by a chiral lithium amide has also been reported.[21] Lithium chloride stabilizes anions derived from α-phosphonoacetates, permitting amine and amidine bases to be used to perform Horner-Wadsworth-Emmons reactions on base-sensitive aldehydes under exceptionally mild conditions.[22] Lithium chloride and other lithium salts disrupt peptide aggregation and increase the solubilities of peptides in THF and other ethereal solvents, often by 100-fold or greater.[23] These effects render LiCl a useful additive in the chemical modification of peptides (e.g. by the formation and alkylation of peptide enolates).[19,24] Lithium chloride has also shown promise as an additive in solid-phase peptide synthesis, increasing resin swelling and improving the efficiencies of difficult coupling steps.[25]

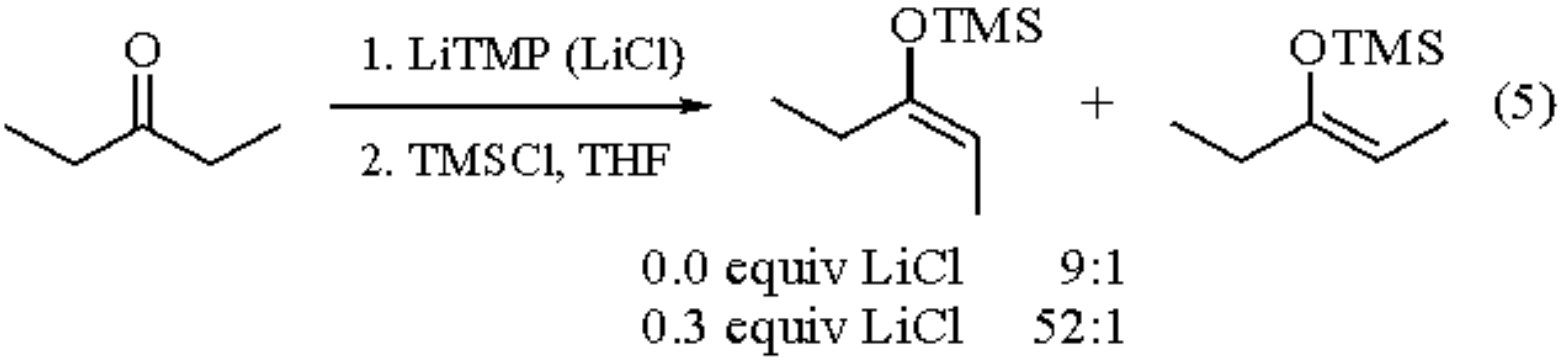

Related Reagents.

Lithium Chloride-Diisopropylethylamine; ***Lithium Chloride-Hexamethylphosphoric Triamide***.

---

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Lithium Chloride-Diisopropylethylamine

LiCl-*i*-Pr_2NEt

(LiCl)

[7447-41-8] · ClLi · Lithium Chloride-Diisopropylethylamine · (MW 42.39) (*i*-Pr_2NEt)

[7087-68-5] · $C_8H_{19}N$ · Lithium Chloride-Diisopropylethylamine · (MW 129.28)

(lithium salt-amine base combination for Horner-Wadsworth-Emmons alkenation; alkylation of β-keto esters; palladium-catalyzed cross-couplings)

Physical Data: see ***Lithium Chloride*** and ***Diisopropylethylamine***.

Handling, Storage, and Precautions: the combination reagent is prepared in situ; use in a fume hood; see ***Lithium Chloride*** and ***Diisopropylethylamine*** for handling of each reagent.

Horner-Wadsworth-Emmons Alkenation.

The combination of LiCl and DIPEA (1:1 molar ratio) finds utility in the Horner-Wadsworth-Emmons alkenation involving base-sensitive compounds.[1] Treatment of aliphatic, α,β-unsaturated, and aromatic aldehydes with ***Triethyl Phosphonoacetate*** and LiCl-DIPEA (or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***) in acetonitrile leads to high yields of (*E*) isomeric unsaturated esters (eq 1).

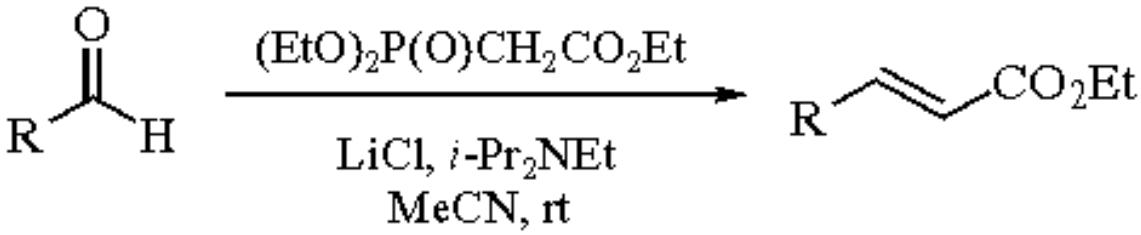

(1)

R	yield (%)	(*E*):(*Z*)
i-Pr	97	50:1
MeCH=CH	85	20:1
Ph	87	100:1

Treatment of the base-sensitive phosphonate (**1**) and aldehyde (**2**) with LiCl-DIPEA in acetonitrile at rt for 24 h affords the ketone (**3**) in high yields, with no evidence of epimerization at the α-position or self-condensation of the aldehyde (eq 2). Use of ***Sodium Hydride*** or ***Potassium t-Butoxide*** leads to much lower yields (0-34%).

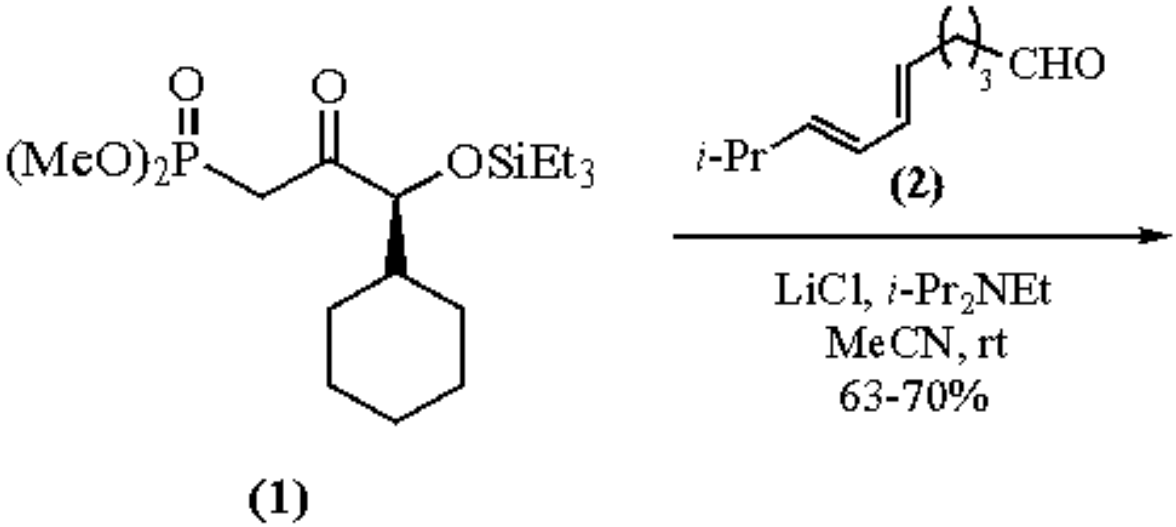

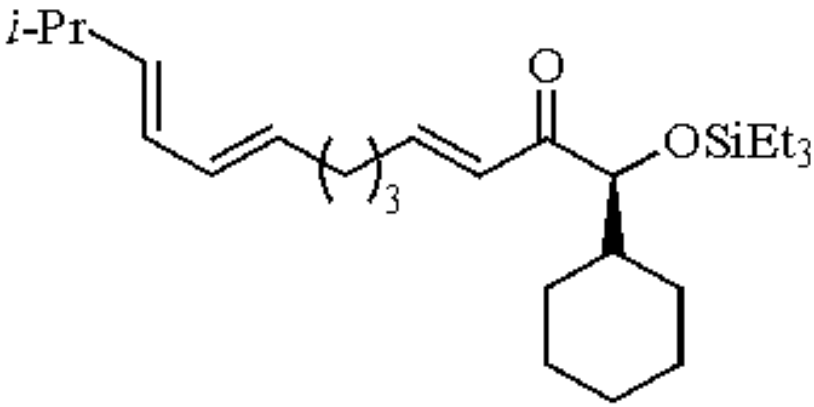

(2)

(3)

β-Keto Ester Alkylations.

Ethyl Acetoacetate and ***Diethyl Malonate*** are monoalkylated in high yields using a 1:2 mixture of LiCl-DIPEA with ***Benzyl Bromide*** (1 equiv) in refluxing THF (eq 3).[2] The presence of the lithium cation is critical for a successful alkylation. Replacement of the lithium salt by NaCl or KCl leads to no alkylation products.[3] *O*-Alkylation does not take place under these reaction conditions; however, dialkylation occurs using acetonitrile as solvent. Acetylacetone does not alkylate under these reaction conditions.

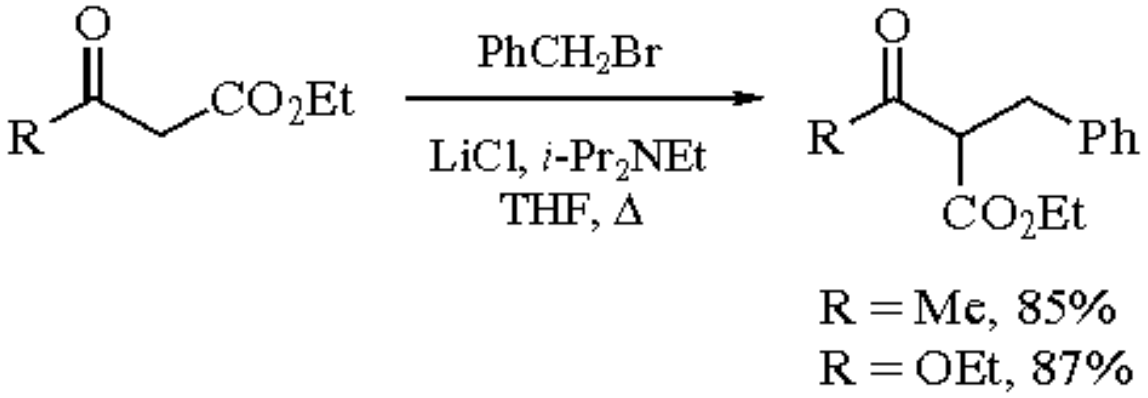

(3)

Cross-Couplings.

The optimal conditions for a successful palladium-catalyzed cross-coupling between aryl halides and unsaturated epoxides involve 10% ***Palladium(II) Acetate***, *n*-Bu_4NCl (1 equiv), lithium formate (3 equiv), and the combination of LiCl (1 equiv) and DIPEA (3 equiv) at 50 °C in DMF. Following these optimized reaction conditions, the cross-coupling of iodobenzene and 4,5-epoxy-1-hexene (**4**) leads to a 79:21 mixture of (*E*):(*Z*) allylic alcohols (**5**) in 78% yield (eq 4).[4] The mechanism involves a palladium migration process.

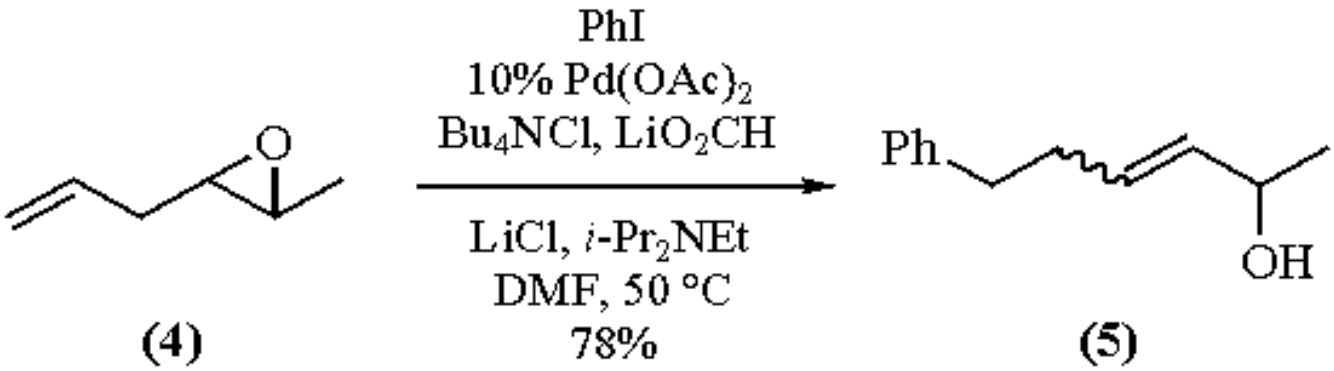

(4)

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Lithium Chloride-Hexamethylphosphoric Triamide[1]

$LiCl\text{-}(Me_2N)_3PO$

(LiCl)

[7447-41-8] · ClLi · Lithium Chloride-Hexamethylphosphoric Triamide · (MW 42.39) (HMPA)

[680-31-9] · $C_6H_{18}N_3OP$ · Lithium Chloride-Hexamethylphosphoric Triamide · (MW 170.24)

(chloride displacement reactions, dehydrohalogenation reactions, and decarboxylative alkylations)

Physical Data: see ***Lithium Chloride*** and ***Hexamethylphosphoric Triamide***.

Chloride Displacement.

In an early example, S_N2 attack of chloride ion on an (*S*)-tosylate produced the (*R*)-alkyl chloride in 62% yield with nearly complete inversion of stereochemistry (98% ee) without rearrangement of the neopentyl group (eq 1).[2] Allylic chlorides can be easily prepared from the corresponding allylic alcohols (eq 2).[3] Attempts to use a mesitoate nucleophile failed under these conditions.[4] In situ generation of the allylic tosylate and subsequent displacement by chloride led to good yields of allylic chlorides that were further used for Grignard coupling reactions. Utilization of these conditions precluded any formation of the tertiary halide via S_N2'-like reactions.

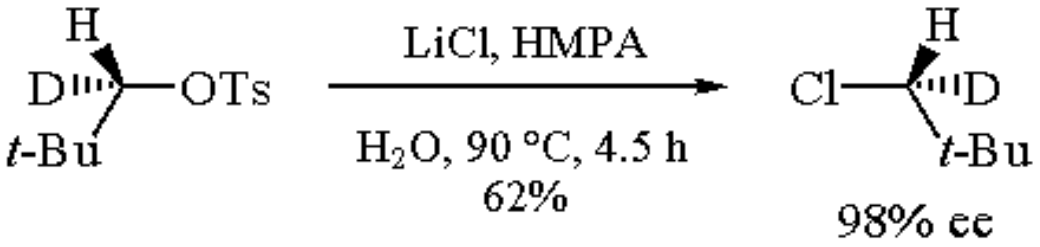

(1)

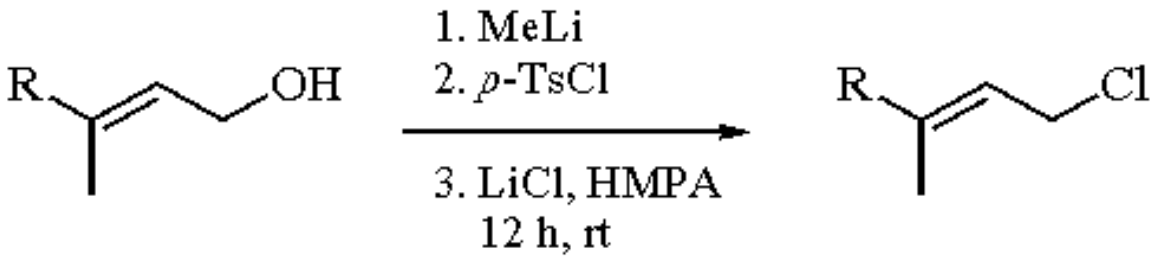

(2)

$R = CH_2CH_2CH(OMe)_2$

Dehydrohalogenation.

Lithium chloride, with HMPA as solvent and ***Lithium Carbonate*** as a buffer, has been used for large-scale dehydrobromination reactions to prepare 1,3-cyclohexadiene (eq 3).[5] The same reaction sequence has been used to prepare a mixture of two deuterium-labeled cyclohexadienes that have been further reacted with ***Maleic Anhydride*** to prepare labeled Diels-Alder adducts (eq 4).[5]

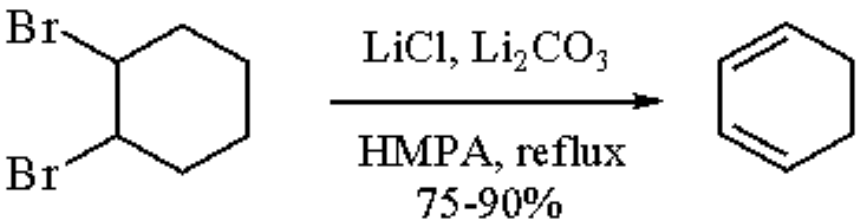

(3)

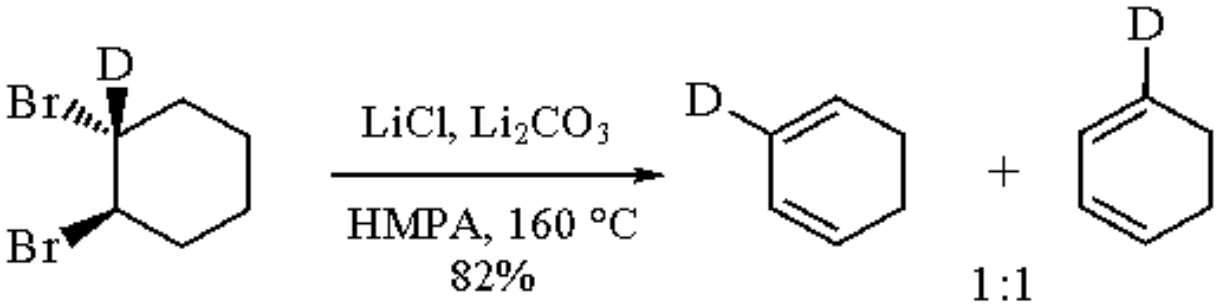

(4)

A similar protocol has been used in more substituted examples to provide substrates that can be utilized for bis-epoxidation (eq 5).[6] Diepoxide compounds of this type are novel antitumor agents.

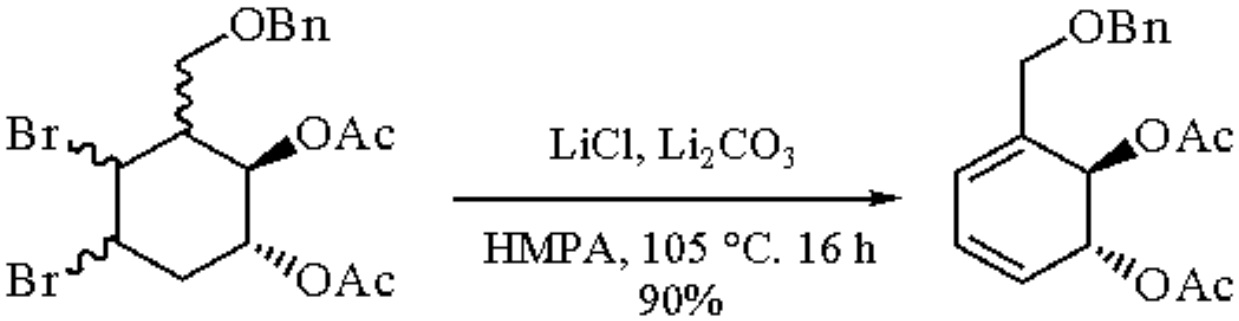

(5)

Decarboxylative Alkylation.

It has been reported that the decarboxylation of β-diesters with LiCl and HMPA provided evidence that it was possible to alkylate the putative anion with various electrophiles such as ***Benzyl Bromide***.[7] Further, it was shown that replacement of HMPA with ***Dimethyl Sulfoxide*** as the solvent retarded the rate of the reaction. The use of any base other than LiCl gave poorer yields.[8] β-Vetivone has been prepared utilizing an intramolecular alkylation via an anion derived from the induced decarboxylation of a β-keto ester (eq 6).[9] Similar results can be achieved using ***1-Methyl-2-pyrrolidinone***, but replacement of this solvent with ***N,N-Dimethylformamide*** resulted in a substantial reduction in yield.

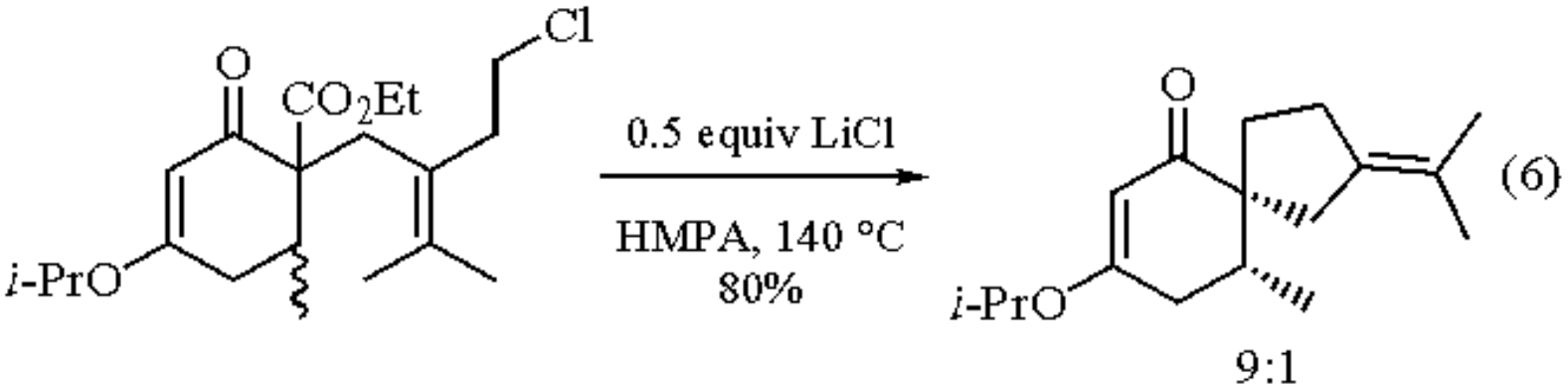

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Lithium Chloroacetylide[1]

Cl-C&tbond;C-Li

[6180-21-8] · C_2ClLi · Lithium Chloroacetylide · (MW 66.41)

(nucleophilic organolithium reagent capable of reacting with a variety of electrophiles[2,3])

Alternate Name: chloroethynyllithium.

Solubility: sol ether.

Preparative Method: prepared in ether solution under anhyd conditions by treatment of *cis*- or *trans*-1,2-dichloroethylene with 2 equiv ***Methyllithium*** at 0 °C under N_2.[2]

Handling, Storage, and Precautions: dry lithium chloroacetylide is explosive (as are the other metal haloacetylides), but may be safely handled and kept in the solution in which it is prepared under N_2.

Lithium chloroacetylide reacts with aldehydes and ketones in good yield to form chloroethynyl substituted carbinols (eq 1).[1-3] Alkylations, silylations, and stannylations all proceed well.[1] Other electrophiles such as ***Carbon Dioxide*** and α-naphthyl isocyanate also produce the expected addition products.[2]

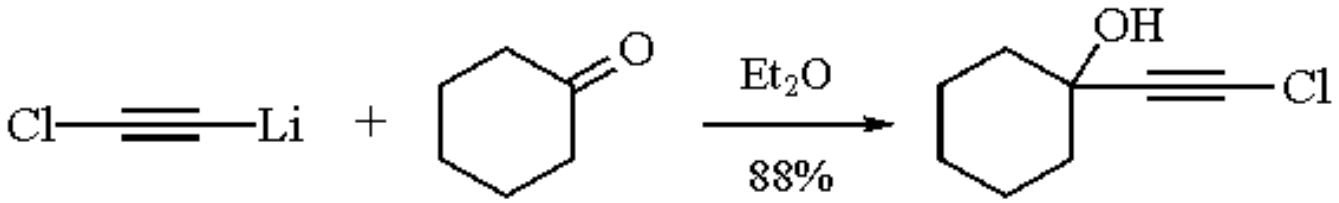

(1)

A protected tetrahydroxylactone is reported to give the monoaddition product (eq 2).[4] Reaction with ***Methyl Chloroformate*** at -78 °C can be used to prepare methyl chloropropiolate (eq 3).[2,5] In this reaction, explosions have occurred in more than one instance, possibly due to the formation of tris(chloroethynyl)carbinol.[5,6]

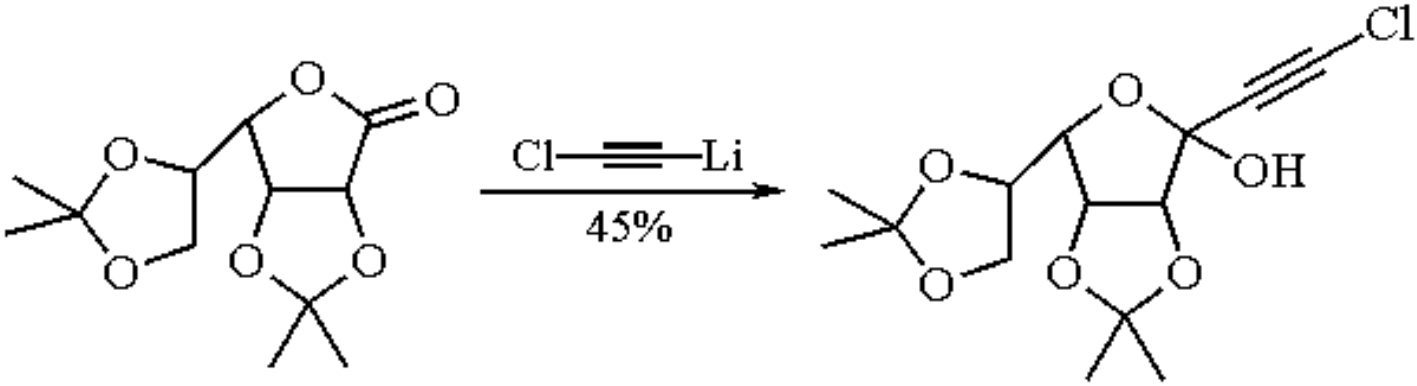

(2)

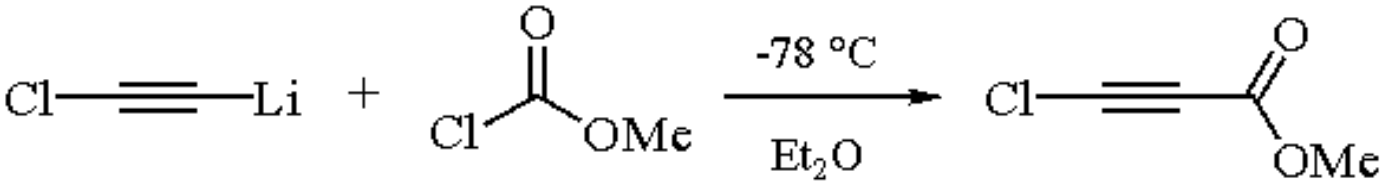

(3)

Lithium chloroacetylide has been used in coupling reactions. In the presence of ***Copper(I) Iodide***, coupling to ***Allyl Bromide*** was observed (eq 4).[7] When treated with cyclohexenylzinc bromide, lithium chloroacetylide gives 2-cyclohexenylacetylene (43%) and 1,1-bis(2-cyclohexenyl)ethylene (16%), in analogy to its reactions with other allylic organozinc compounds (eq 5).[8]

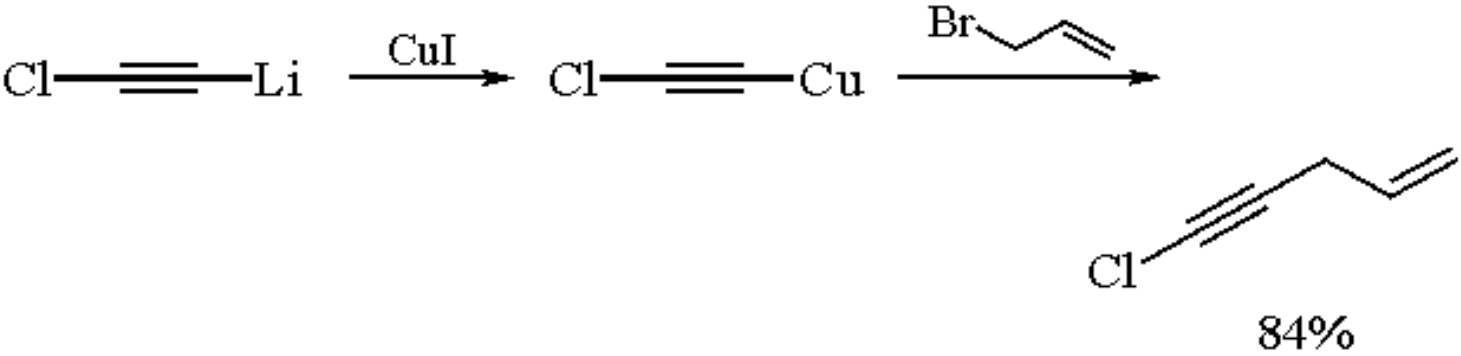

(4)

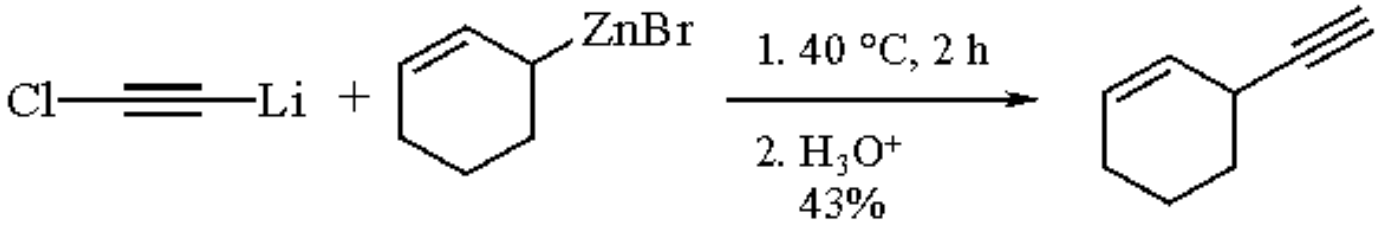

(5)

The chloroacetylides of Na, K, and Ca have also been prepared, as well as some bromo and fluoro analogs.[9] All these chloroacetylides react with the organohalides of Al, Sn, Pb, As, Sb, or Bi to exchange the metal (e.g. eq 6)[3,10]

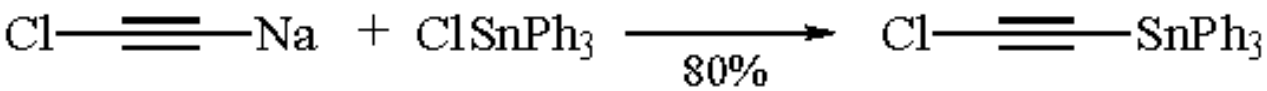

(6)

Suzuki et al.[11] have used lithium chloroacetylide to prepare lithium 2-chloroethynyltrialkylborates, which react with ***Iodine*** to give the corresponding symmetric alkynes (eq 7).

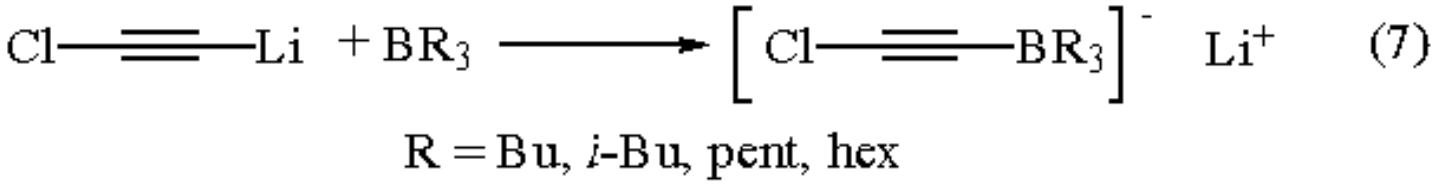

Related Reagents.

Dilithium Acetylide; ***Dipotassium Acetylide***; ***Ethynylmagnesium Bromide***; ***Lithium Acetylide***; ***Lithium (Trimethylsilyl)acetylide***.

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Lithium Cyanide

LiCN

[2408-36-8] · CLiN · Lithium Cyanide · (MW 32.96)

(synthesis of nitriles from halides, alcohols, aldehydes, ketones; synthesis of cyanohydrins; deoxygenation of ketones)

Physical Data: mp 160 °C, *d* 1.025 g cm^{-3};[1] hygroscopic solid.

Solubility: sol H_2O, DMF, THF.

Form Supplied in: solid or 0.5 M solution in DMF.

Preparative Methods: from ***Lithium*** metal and ***Silver(I) Cyanide***,[2] from lithium hydride and ***Hydrogen Cyanide***,[3] or, more conveniently, from ***Acetone Cyanohydrin*** and lithium hydride.[4]

Handling, Storage, and Precautions: moisture-sensitive; like ***Sodium Cyanide*** and ***Potassium Cyanide***, LiCN is highly toxic; use in a fume hood.

Nitriles (from Halides).

Nitriles can be prepared from halides (Br or I) under nonaqueous conditions using LiCN in refluxing THF for 1 h (seven examples; >90% yields).[5] A simple alkyl chloride gave only a 50% yield after 18 h (one example).

Nitriles (from Alcohols).

The quantitative conversion of a tosylate to a nitrile (one example) in refluxing THF has been reported.[5]

Manna et al. have reported the conversion of alcohols to nitriles using LiCN under Mitsunobu conditions (***Diethyl Azodicarboxylate*** and ***Triphenylphosphine***; two examples, 50% yields).[6]

β-Hydroxynitriles (from Epoxides).

Ciaccio et al. have reported the preparation of β-hydroxynitriles from epoxides using LiCN in 60-88% yield (10 examples; eq 1).[7] Cycloalkene oxides gave exclusively the *trans*-hydroxynitriles. Monosubstituted epoxides were

reported to give exclusive attack at the less substituted carbon. Acetals, alkenes, and *t*-butyldimethylsilyloxy groups were shown to be stable to the reaction conditions. After an aqueous extractive workup or passage through a plug of Florisil, the crude compounds are reported to be pure by TLC, IR, and ^{1}H and ^{13}C NMR analysis.

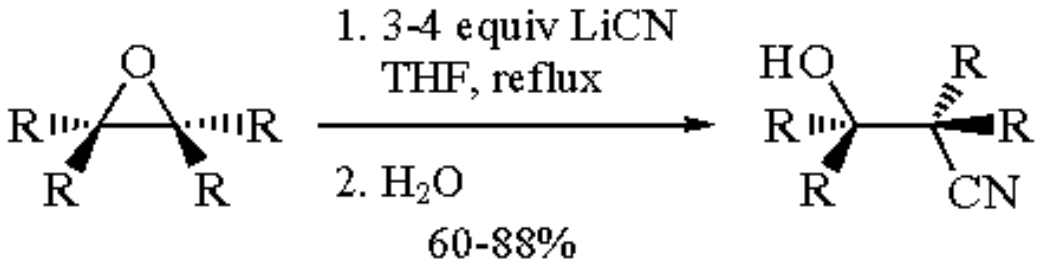

(1)

Previously, in a synthesis of a dideoxynucleoside, Matsuda et al. reported the opening of an epoxide with LiCN in refluxing THF; however, LiCN in DMF gave intractable mixtures.[8]

Alkylsilyl Cyanides.

LiCN is reported to be the method of choice for the preparation of alkylsilyl cyanides from the corresponding chlorides.[4,9] Both dialkylsilyl[9] and trialkylsilyl[4,9] cyanides have been reported.

Cyanohydrins.

Yoneda et al. have reported the preparation of trialkylsilyl cyanohydrins and acyl cyanohydrins from aldehydes and ketones.[10,11] Addition of LiCN to a THF solution of the carbonyl compound and ***Benzoyl Chloride*** (nine examples),[10] ***Acetyl Chloride*** (five examples),[10] ***Chlorotrimethylsilane*** (six examples),[10] or ***t-Butyldimethylchlorosilane*** (eight examples),[11] followed by stirring at rt, results in the appropriate cyanohydrin (eq 2). Yields ranged from 47 to 100% (generally >80%; distillation or column chromatography).

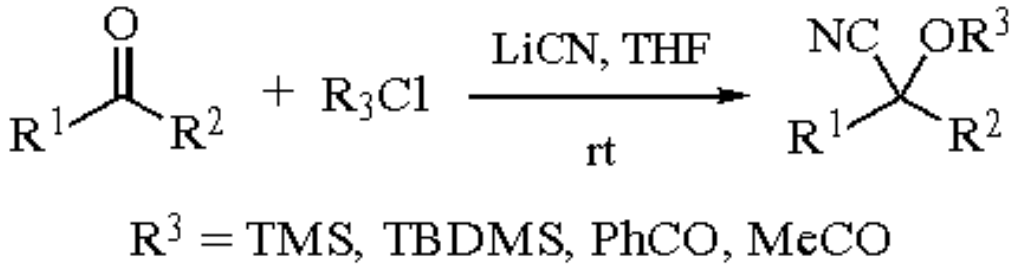

(2)

Conjugate Additions.

Treatment of 4-cholesten-3-one with lithium cyanide (THF, 16 h, reflux) gives 5-cyanocholestan-3-one (80%, 5α:5β-cyano = 3:1).[5]

Cyanophosphates.

Aldehydes and ketones react rapidly with LiCN and ***Diethyl Phosphorocyanidate*** (DEPC) in THF to form

cyanophosphates (eq 3).[12] These cyanophosphates can serve as intermediates in the synthesis of structurally diverse nitriles. These syntheses are discussed in the appropriate sections below.

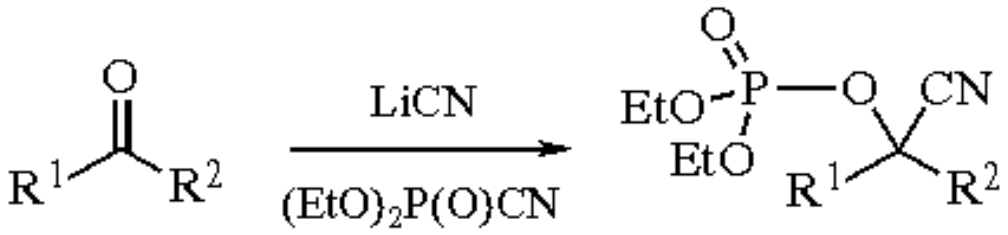

(3)

α,β-Unsaturated Nitriles.

Several procedures have appeared for the preparation of α,β-unsaturated nitriles using LiCN as a reagent (e.g. eq 4; six examples; 61-94%; column chromatography).[12] A cyanophosphate when treated with ***Boron Trifluoride Etherate*** will undergo elimination to form the α,β-unsaturated nitrile. However, in the compounds examined, this elimination only occurs if R^1 is an aromatic group. If R^1 is an alkyl group, the cyanophosphate does not eliminate. This reaction has been used in the synthesis of lysergic acid and related compounds.[13,14]

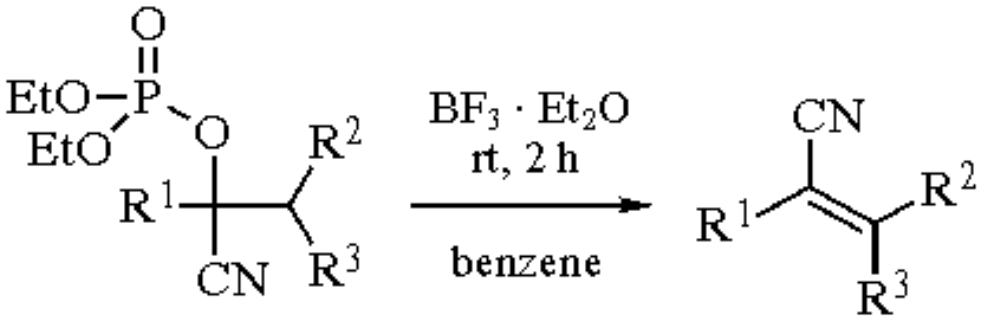

(4)

A second synthesis of α,β-unsaturated nitriles, also from ketones, has been reported (eq 5).[15] Reaction of a ketone to form the vinyl trifluoromethanesulfonate is followed by treatment of the triflate with LiCN, ***Tetrakis(triphenylphosphine)palladium(0)***, and ***12-Crown-4*** to give the α,β-unsaturated nitrile. This procedure may provide an alternative to the procedure of Harusawa, since an aromatic ketone is not required. Eight examples (all cycloalkyl ketones) were given, including one β-keto ester and two α,β-unsaturated ketones. Isolated yields (chromatography or distillation) were 59-87%.

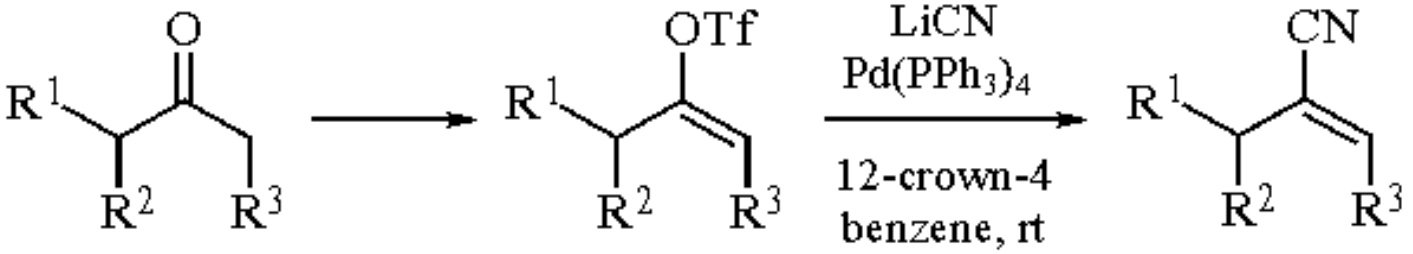

(5)

A similar transformation on an *O*-triflyl imidate has been reported to occur without the need for transition metal catalysis (eq 6).[16]

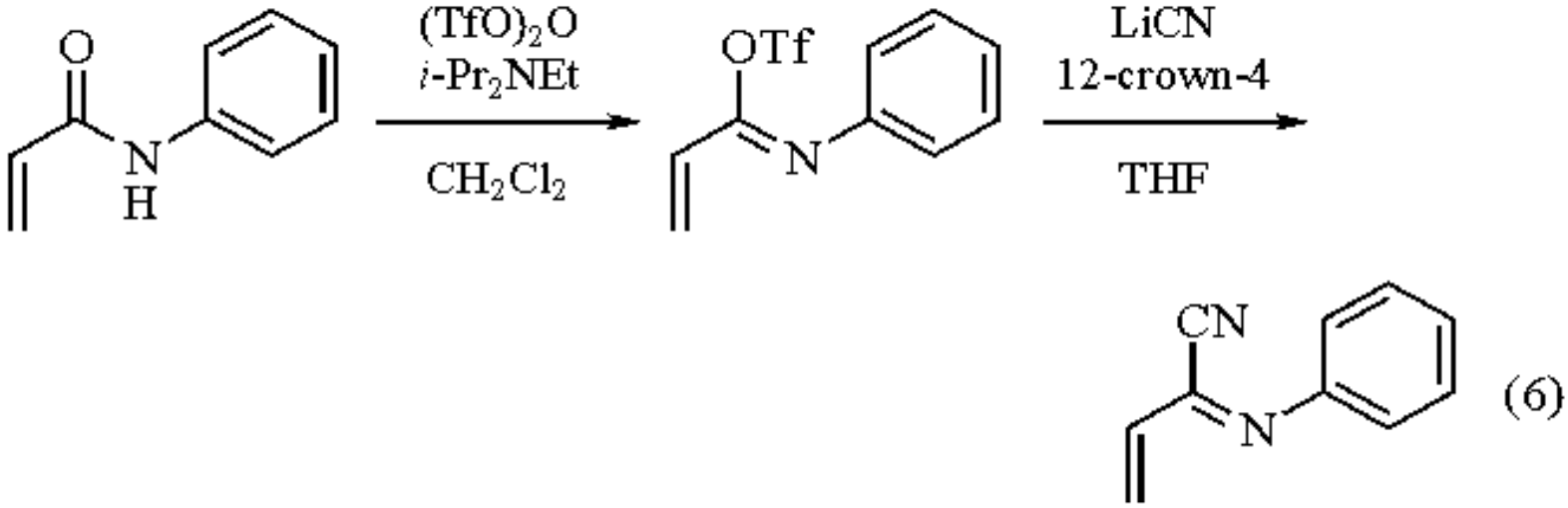

A synthesis of α-methylenenitriles has been reported (eq 7).[17] Treatment of an *N*-(*p*-tolylsulfonyl)vinylsulfoximine with LiCN in DMF for 1 h at rt gave 63-81% yields of the α-methylenenitriles (three examples).

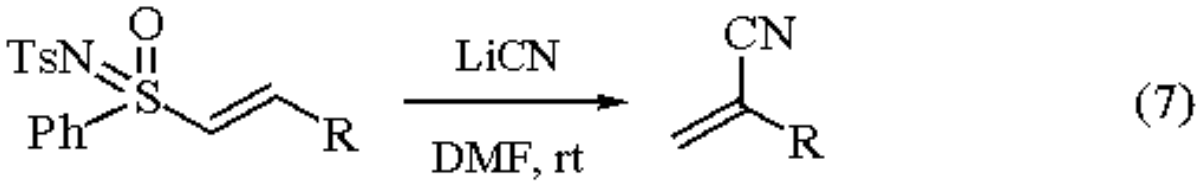

β,γ-Unsaturated Nitriles.

Aldehydes and ketones can be transformed into β,γ-unsaturated nitriles.[18] Treatment of the cyanophosphate derived from the carbonyl compound with ***Samarium(II) Iodide*** in THF gives the β,γ-unsaturated nitrile in 60-94% yield (eq 8; column chromatography; 14 examples).

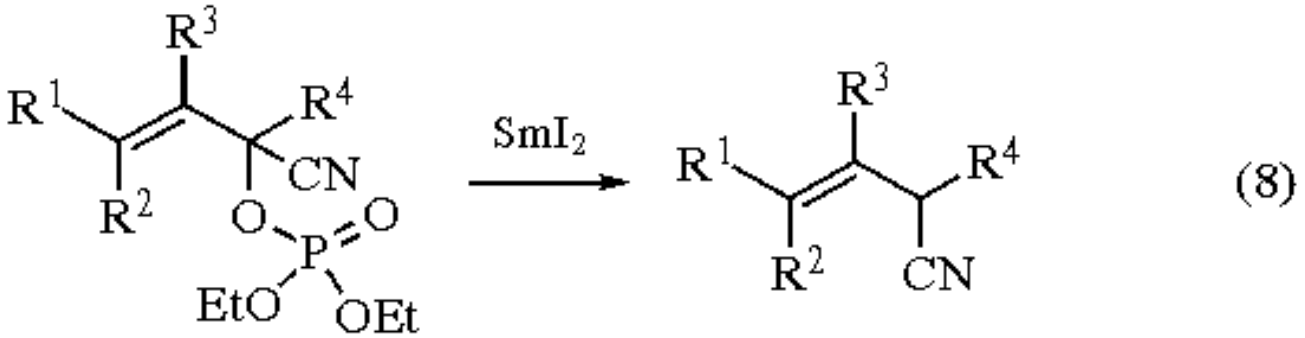

Nitriles (from Carbonyl Compounds).

Cyanophosphates can be used to prepare nitriles by treating them with either lithium in liquid ammonia (seven examples; 72-91% yields; column chromatography)[19] or samarium iodide (12 examples; 61-95%; column chromatography) (eq 9).[18] The Li/NH_3 reduction should be carried out at -78 °C; when the reaction is done in refluxing NH_3, reduction of the cyanophosphate to a methylene group can be the major product (see below).[20]

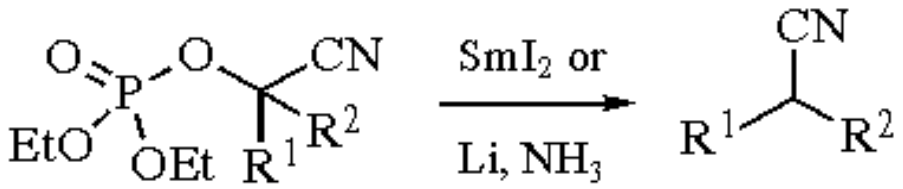

(9)

If one of the R groups is aromatic, then hydrogenation with a Pd catalyst will also give nitriles (two examples; 75, 81%).[21]

Deoxygenation of Ketones.

Cyanophosphates have also been used for the deoxygenation of α,β-unsaturated ketones and aromatic ketones (eq 10; five examples; 80-99%; no chromatography) by treatment with lithium in liquid ammonia.[20] As noted above, this reaction should be carried out in refluxing NH_3; at lower temperatures, reduction to the nitrile predominates. The reduction to the alkene is reported to be free of double bond isomerization or migration.

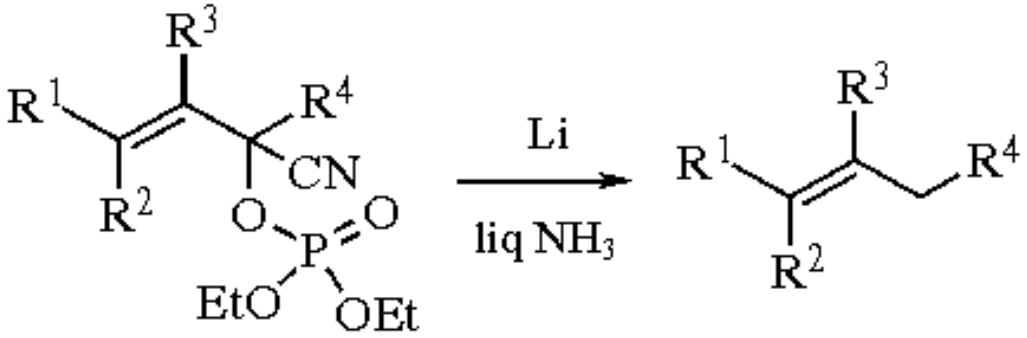

(10)

Allenic Nitriles.

Treatment of a cyanophosphate (derived from an α,β-alkynyl ketone) with a higher-order cuprate gives trisubstituted allenes (eq 11; three ketone and one aldehyde examples; five cuprate examples; 32-87%; column chromatography).[22]

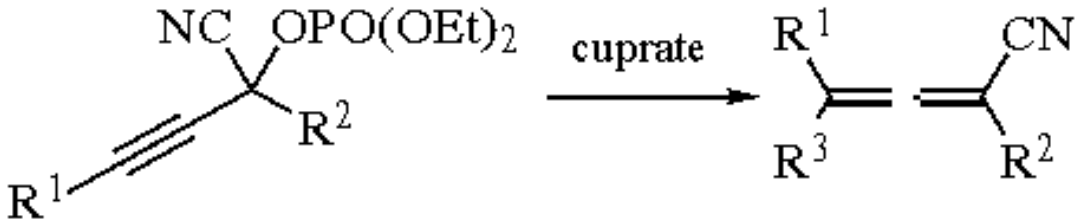

(11)

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Lithium Cyano(dimethylphenylsilyl)cuprate

$Me_2PhSiCuCNLi$

[75583-56-1] · $C_9H_{11}CuLiNSi$ · Lithium Cyano(dimethylphenylsilyl)cuprate · (MW 231.79)

(organometallic reagent for the silylcupration of enones, alkynes, and strained alkenes)

Solubility: sol ether, THF from -78 to 25 °C.

Preparative Method: the title reagent (**1**), as well as lithium cyano(trimethylsilyl)cuprate *[81802-36-0]*, can be prepared from the corresponding silyllithium species and 1 equiv ***Copper(I) Cyanide*** in ether or THF at -78 to -5 °C;[1,2] the precursor silyllithium (**2**) is generated by the reaction of ***Chlorodimethylphenylsilane*** with ***Lithium*** metal in THF or ether (eq 1).

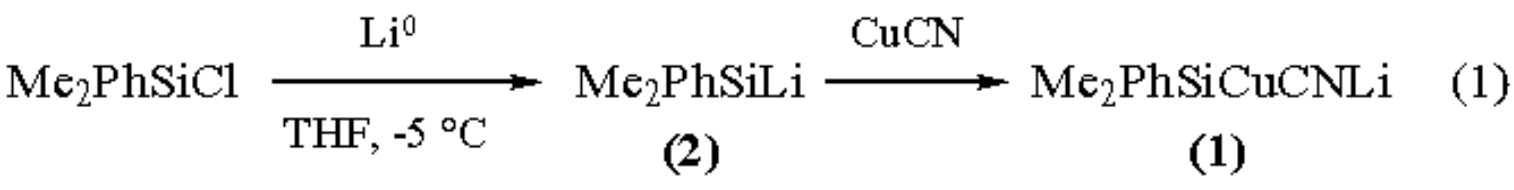

Handling, Storage, and Precautions: thermally stable up to ambient temperatures; oxygen- and moisture-sensitive; use in a fume hood.

Structure and Properties.

Low-temperature ^{29}Si, ^{13}C, and ^{1}H NMR spectroscopic techniques have been used to probe the structure of (**1**),[2] which is referred to as a lower-order cuprate. When 2 equiv of the silyllithium (**2**) are combined with 1 equiv copper(I) cyanide, a new reagent, referred to as a higher-order cuprate, is generated (see ***Dilithium Cyanobis(dimethylphenylsilyl)cuprate***).[3] Evidence for the different cuprate structures comes from separate signals in the ^{29}Si and ^{13}C spectra.[2]

Conjugate Additions to Enones.

Reagent (**1**) effectively adds the dimethylphenylsilyl group to α,β-unsaturated ketones, esters, and alkynic analogs. In a typical case, (**1**) adds to cyclohexenone in ether at -78 °C in 58% yield (eq 2).[2]

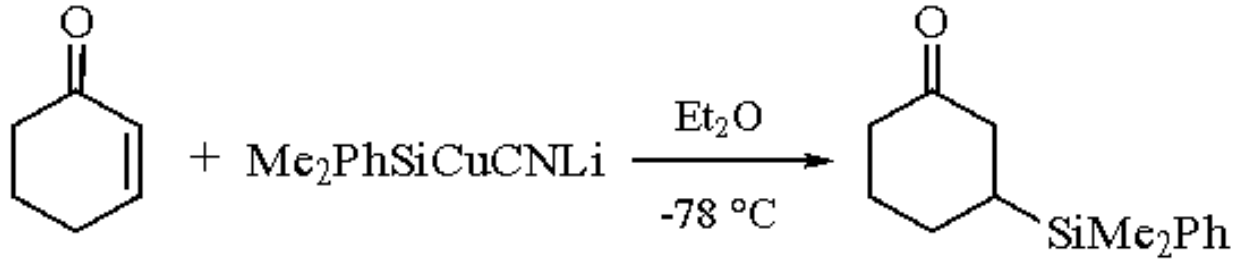

(2)

The analogous trimethylsilylcuprate (**3**) adds to ethyl-2-butynoate at 0 °C to give a mixture of stereoisomers, while the higher-order species reacts at -78 °C to yield a single geometrical isomer (eq 3).[4]

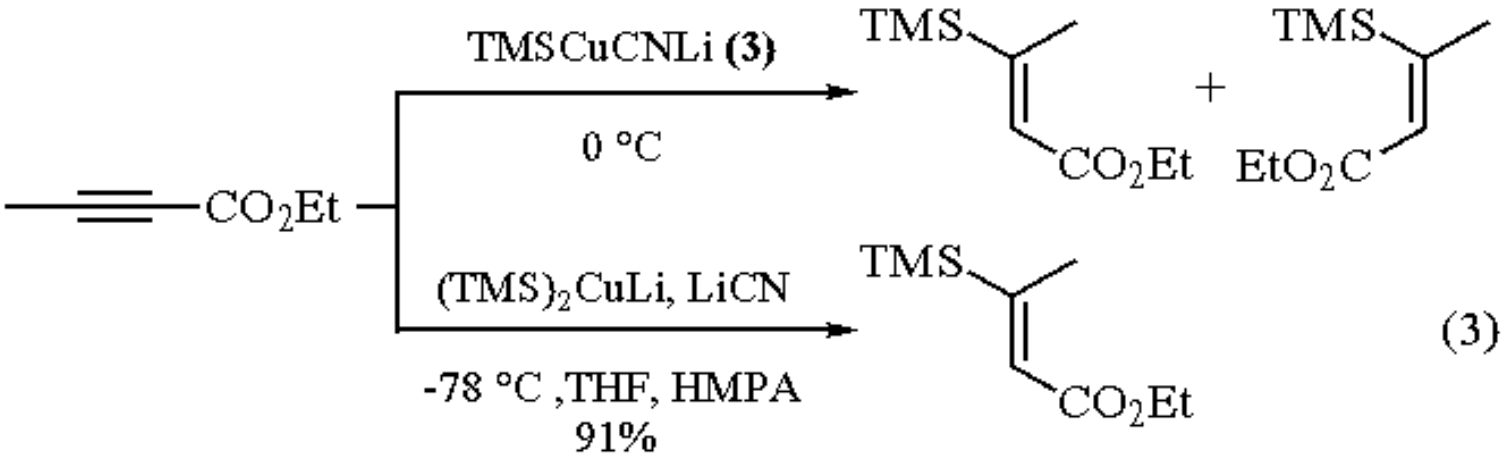

(3)

The lower-order silyl cuprates are apparently less reactive than the higher-order cuprates in conjugate addition reactions. Reagent (**1**) has been added in an addition-elimination sequence to an alkylidenemalonate system as a route to vinylsilanes (eq 4).[5]

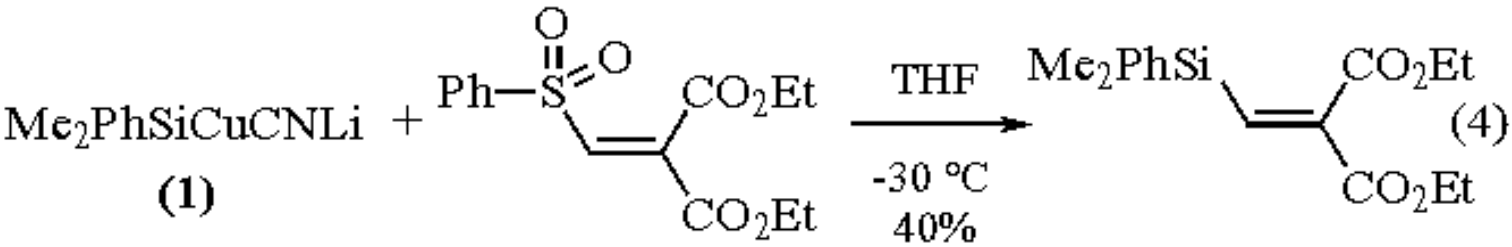

(4)

This reaction was a prelude to a more elaborate scheme for producing more substituted vinylsilanes. The product of eq 4 further reacted with a geminal diorganometallic species to yield an (*E*)/(*Z*) (86:14) mixture of a vinylsilane (eq 5).

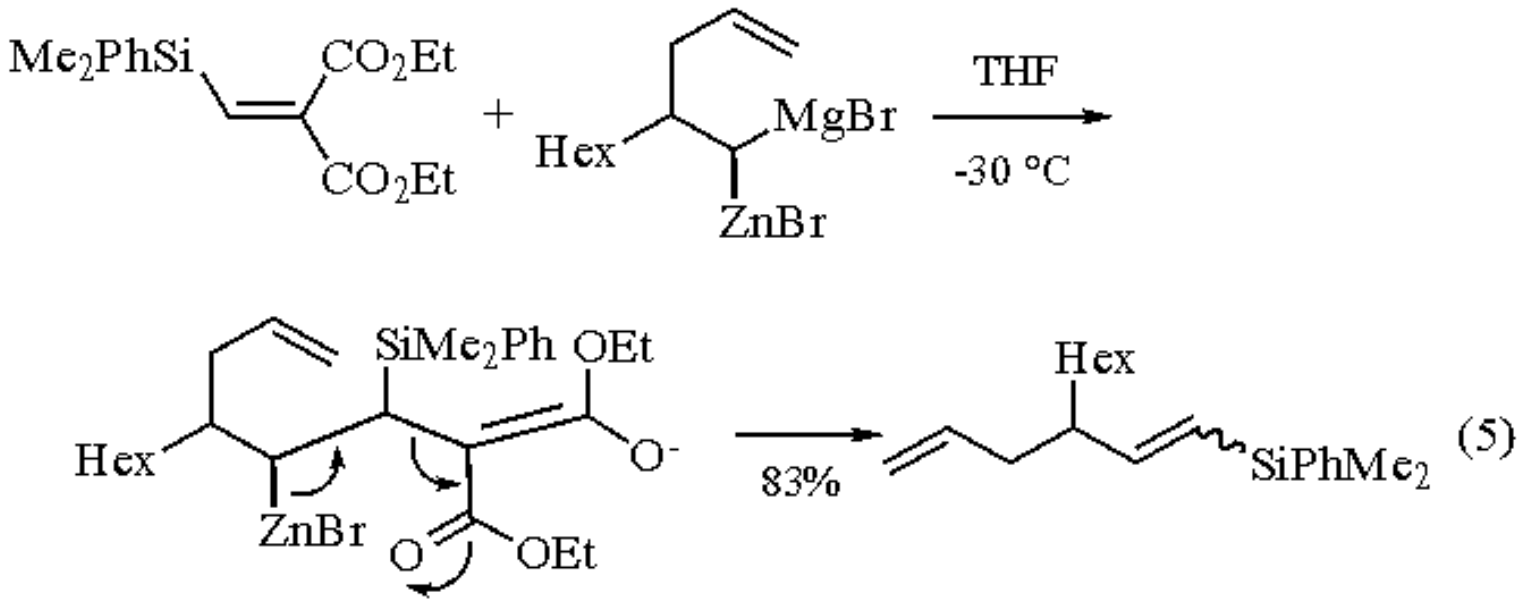

Alkylations with Allyl Halides.

The enhanced reactivity of allyl halides is reflected in the reactions of both (**1**) and (**3**). Thus (**1**) reacts with 2-*t*-butylsulfonylallyl bromide at low temperatures (eq 6).[6]

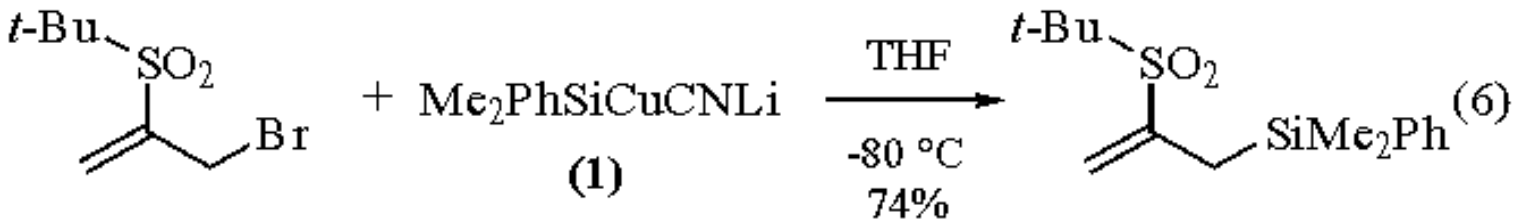

Reagent (**3**) can be employed in the preparation of the 2-bromoallylsilane (eq 7).[7]

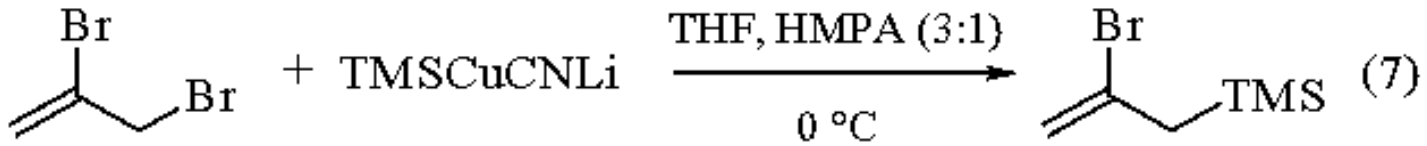

Silylcuprations of Unsaturated Systems.

Carbocupration of alkynes is a major synthetic route to substituted alkenes. With (**1**), additions to terminal alkynes usually lead to regioisomeric vinylsilanes (eq 8).[2,8] In contrast to the lower-order cuprates, the corresponding higher-order cuprates generally are regioselective for the generation of the 1-silyl-substituted vinylsilanes (98:2 ratio).

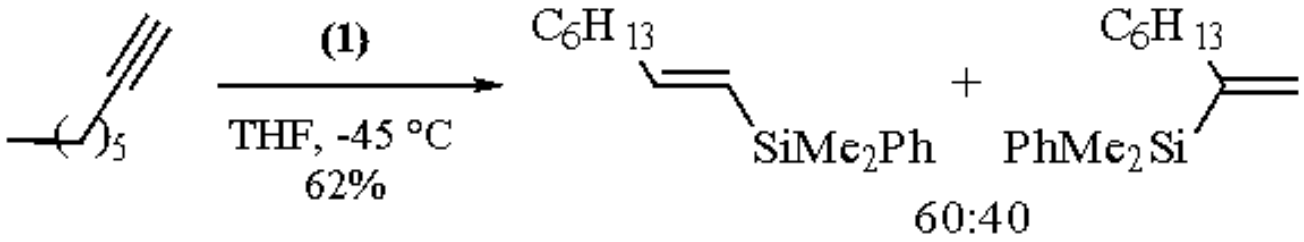

(8)

The regioselectivity of the addition of the title reagent (**1**) to 1,2-allenes, such as 1,2-undecadiene, is much more favorable for silylation at the 1-carbon atom. In fact, the major regio- and stereoisomer produced is the (*Z*)-1-dimethylphenylsilyl-2-undecene (eq 9).[9]

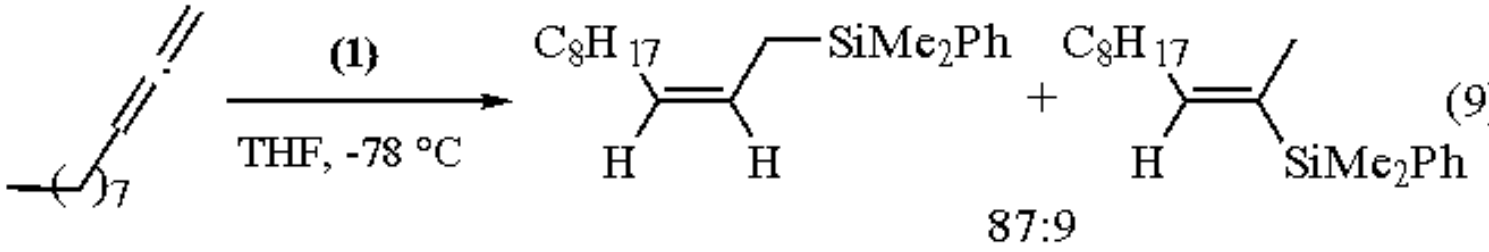

(9)

In general, (**1**) does not add to unactivated alkenes. However, strained bicyclic alkenes do undergo silylcupration with the reagent. The [2.2.1] bicyclic ethers (**4**) react with (**1**) at 0 °C, ultimately giving substituted 1,3-cyclohexadienes (**7**) via intermediates (**5**) and (**6**). The latter intermediate undergoes a Peterson alkenation to give (**7**) (eq 10).[10]

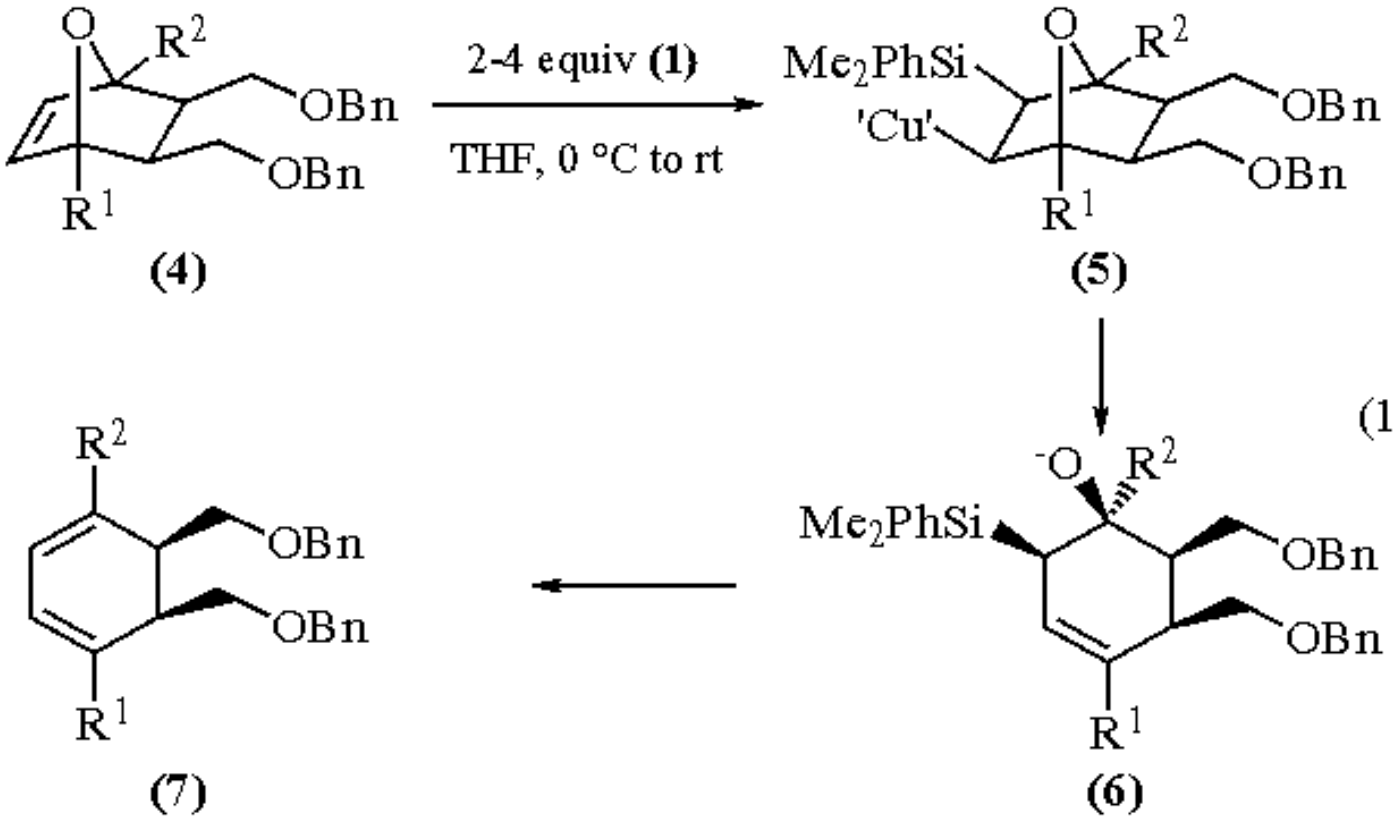

(10)

$R^1 = Me$, $R^2 = H$ (81%)
$R^1 = Me$, $R^2 = Me$ (83%)

Silylcupration of the oxabicyclic ketone (**8**) takes a different course, in that the bridged oxygen system is not cleaved.

Instead, the initial *exo* adduct (**9**) produces a cyclobutanol product (**10**) exclusively (eq 11).[11]

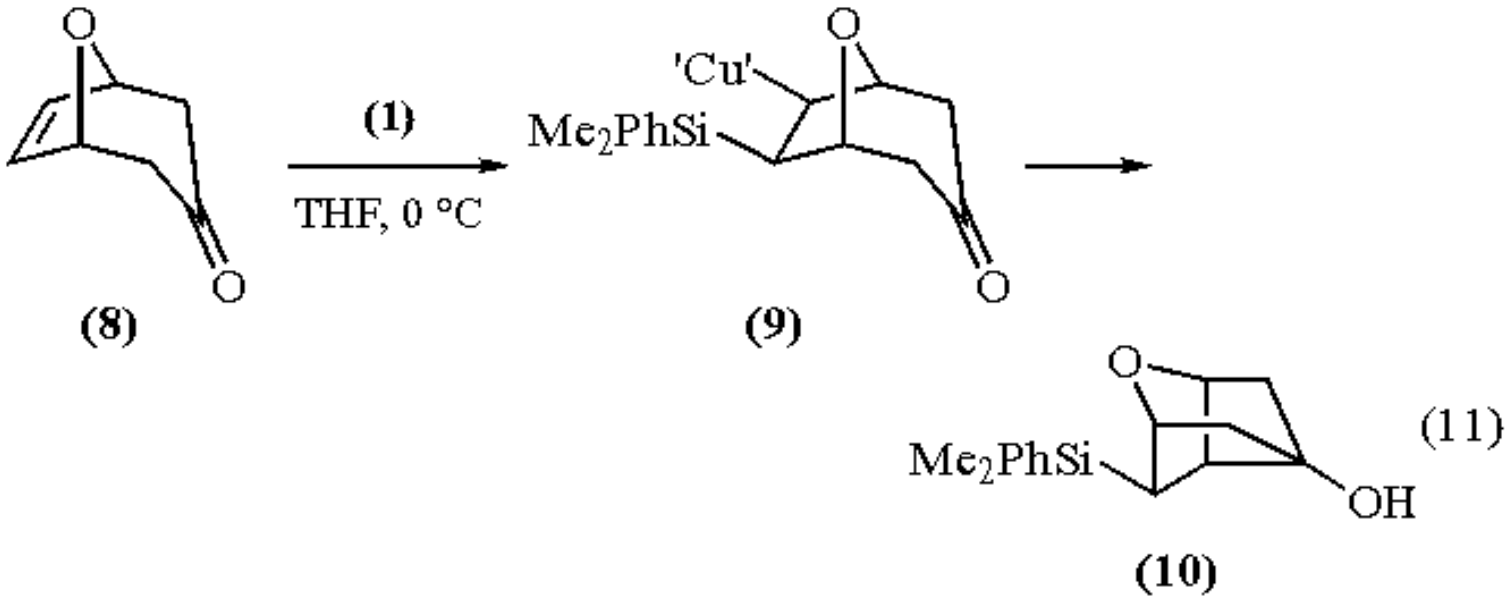

In the same [3.2.1] bicyclic ether system with methyl substitution α to the carbonyl, (**1**) adds to the double bond without cyclobutanol formation (eq 12). With the monomethylated ketone (**11**) an 8:1 mixture of regioisomers is produced, with (**12**) predominating.

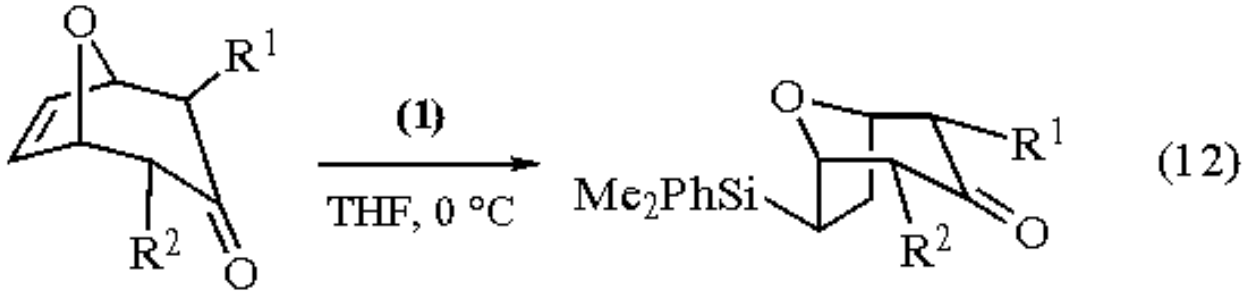

(11) $R^1 = Me$, $R^2 = H$ **(12)** $R^1 = Me$, $R^2 = H$

By allowing the above reaction to proceed for extended periods of time, the corresponding cyclobutanol product derived from (**11**) is favored, while with the dimethyl ketone (**13**) ($R^1 = R^2 = Me$), no cyclobutanols are formed. Intermediate cuprates (**9**) derived from higher-order cuprate additions may be trapped with ***Iodomethane***, acid, or hydroxyl groups (eq 13).

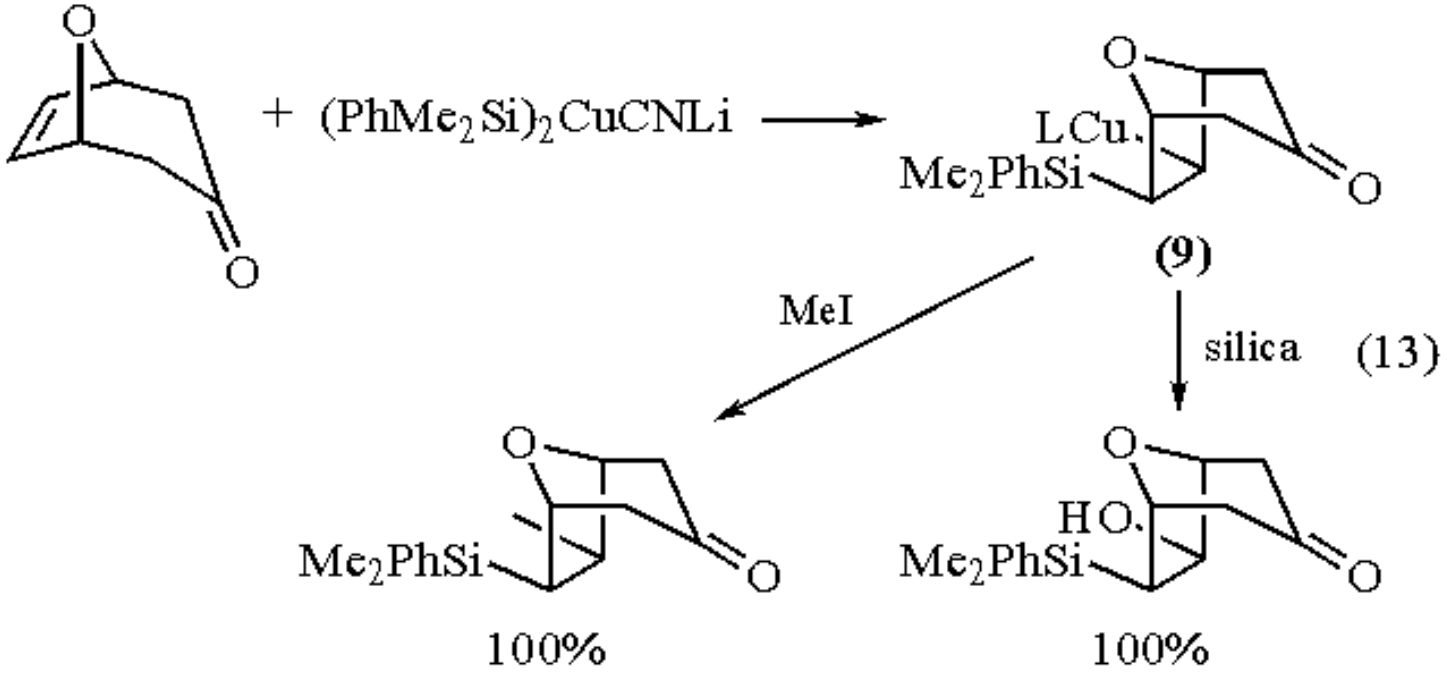

In summary, the lower-order cyanotrialkylsilylcuprates (**1**) and (**3**) react as do most carbon-based cuprates in conjugate additions and carbocupration processes. These reagents are less basic than higher-order cyanocuprates, and less reactive with some less electrophilic partners.

Related Reagents.

Dilithium Cyanobis(dimethylphenylsilyl)cuprate; ***Dimethylphenylsilyllithium***; ***Dimethylphenylsilyl(methyl)magnesium***.

---

1. (a) Fleming, I.; Marchi, D. *S* **1981**, 560. (b) Fleming, I.; Terrett, N. K. *JOM* **1984**, *264*, 99.
2. Sharma, S.; Oehlschlager, A. C. *JOC* **1991**, *56*, 770.
3. Fleming, I.; Rowley, M. *T* **1989**, *45*, 413.
4. Audia, J. E.; Marshall, J. A. *SC* **1983**, *13*, 531.
5. Tucker, C. E.; Rao, S. A.; Knochel, P. *JOC* **1990**, *55*, 5446.
6. Auvray, P.; Knochel, P.; Normant, J. F. *T* **1988**, *44*, 4495.
7. Trost, B. M.; Chan, D. M. T. *JACS* **1982**, *104*, 3733.
8. Fleming, I.; Roessler, F. *CC* **1980**, 276.
9. Singh, S. M.; Oehlschlager, A. C. *CJC* **1991**, *69*, 1872.
10. Lautens, M.; Ma, S.; Belter, R. K.; Chiu, P.; Leschziner, A. *JOC* **1992**, *57*, 4065.
11. Lautens, M.; Belter, R. K.; Lough, A. J. *JOC* **1992**, *57*, 422.

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Lithium Cyano(methyl)cuprate

MeCuCNLi

[41753-78-0] · C_2H_3CuLiN · Lithium Cyano(methyl)cuprate · (MW 111.55)

(regioselective organocuprate reagent for the 1,4-addition of a methyl group to vinyl epoxides and enones)

Solubility: sol ether at -20 °C; precipitates from solution at -78 °C.

Preparative Method: an ether solution of low-halide ***Methyllithium*** is added to 1 equiv of anhyd ***Copper(I) Cyanide*** at -78 °C;[1] in order to maximize the 1,4-addition mode of lithium cyano(methyl)cuprate to vinyl epoxides, commercial methyl lithium with no halide present should be used.

Handling, Storage, and Precautions: thermally stable up to a temperature of about 0 °C; more stable than most organocuprates at rt or 0 °C; oxygen- and moisture-sensitive.

Ring Opening Reactions of Epoxides.

One of the first reports of the use of the cyano ligand in cuprates came from the work of Acker[2] in the ring opening of simple epoxides (eq 1). As predicted, the cuprates added regiospecifically to the less-substituted carbon atom of the epoxide.

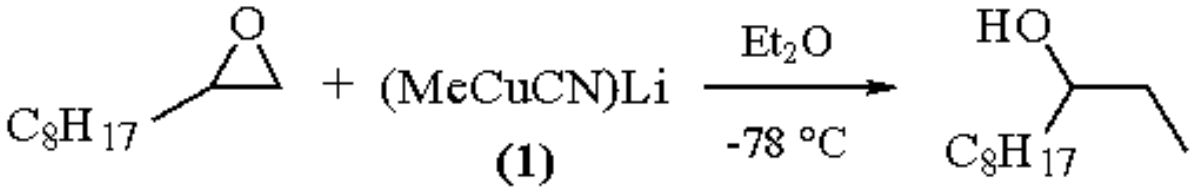

(1)

The regioselectivity of cyanocuprates can be further demonstrated with the reaction of the reagent (**1**) with the bis-epoxide (**2**).[3] With 1 equiv of reagent at -78 °C, the less-hindered pendent epoxide is opened selectively to form (**3**), which can then undergo intramolecular ring openings of the cyclic oxirane to produce the bicyclic ether (eq 2).

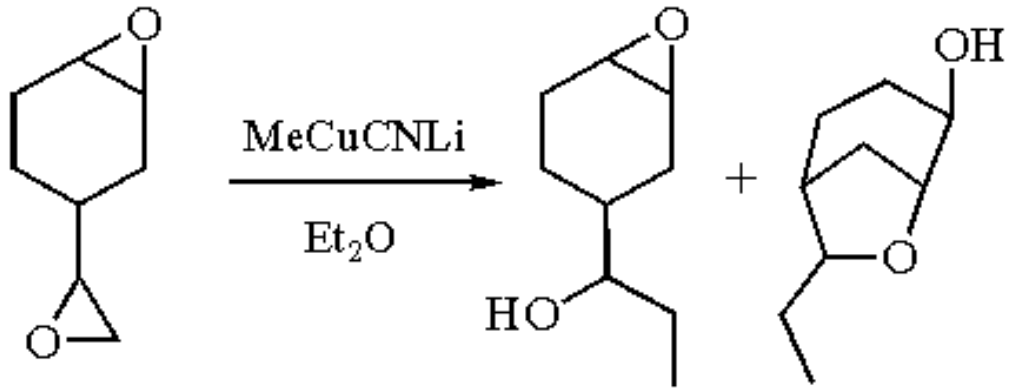

(2)

(2) (3) 58% 38%

In an interesting ring opening of an epoxide derived from an allylic alcohol, 3 equiv of (**1**) reacted with the epoxy alcohol (**4**) to produce the diol (**5**), which was an intermediate in the synthesis of (+)-*exo*-brevicomin (eq 3).[4]

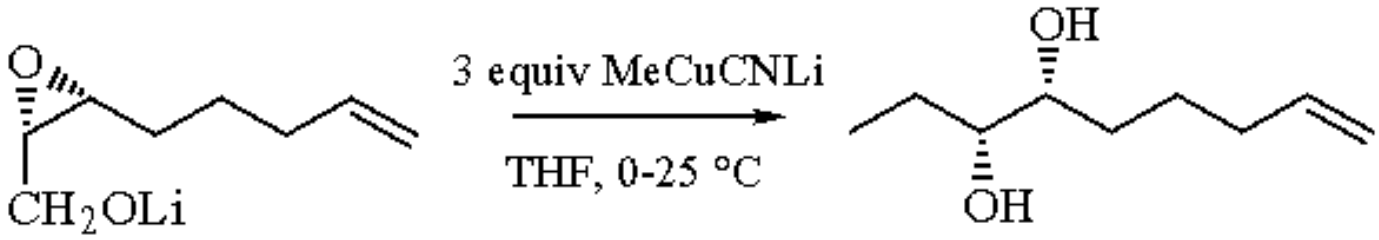

(3)

(4) (5)

While it had been well known that homoorganocuprates add in a 1,4-manner to acyclic vinyl epoxides,[5] reactions of ***Lithium Dimethylcuprate*** with cyclic vinyl epoxides gave mixtures of 1,2 and 1,4 ring-opened products.[6] The greater reactivity of cyclic vinyl epoxides usually resulted in the competitive 1,2 ring opening. In 1979 it was recognized that the cyanoalkylcuprates in ether regioselectively added 1,4 to cyclic vinyl epoxides.[1] A typical example of this selectivity is shown for the reaction of (**1**) with 1,3-cycloheptadiene monoepoxide (eq 4). These reactions must be done in ether and not THF in order to observe the selective 1,4-addition.

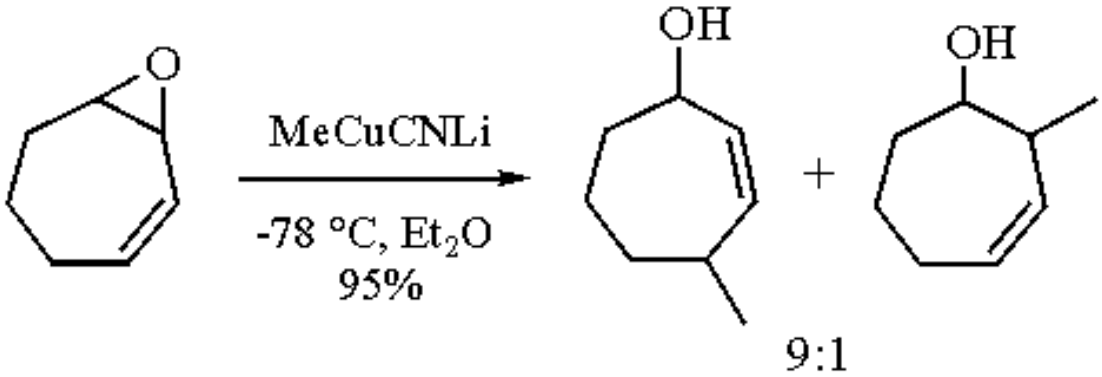

(4)

In the case of the 1,3-cyclohexene monoepoxide, only the 1,4-adduct is observed with *trans* stereochemistry. Lithium methyl acrylate cuprates transfer a methyl group to these epoxides with even greater regioselectivity (97:3). The conclusion reached is that the strongly electron-withdrawing cyano and acrylate ligands are responsible for this enhanced regioselectivity.[1] This ligand effect exhibited by the cyano group is general for all cyanoalkylcuprates.

Other examples of the 1,4-addition of (**1**) include the *exo*-methylene epoxide (**6**) (eq 5).[7] The product of this reaction (**7**) was used as an intermediate in the synthesis of the pheromone α-multistriatin.[8]

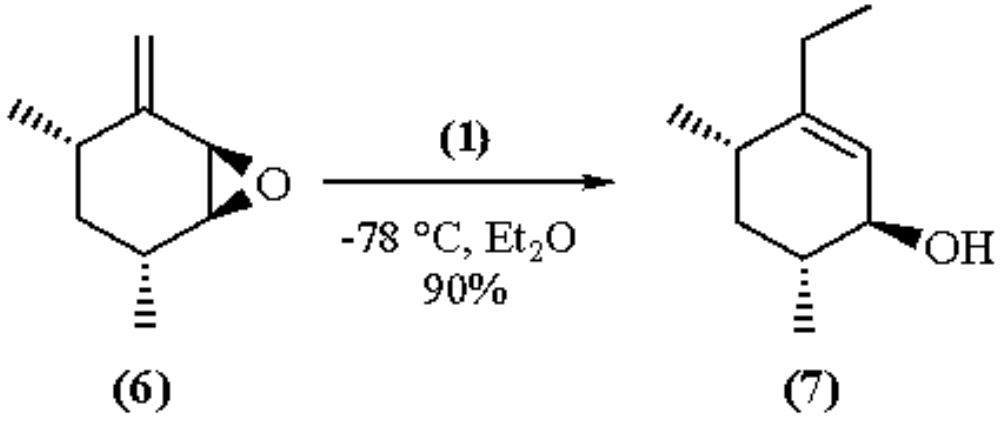

(5)

The unique ability of the cyano group to direct the ring openings of cyclic vinyl epoxides in a *trans*-1,4 manner provided new methodology for the synthesis of chiral molecules. The reiterative sequence of cyclohexadiene monoepoxides reacting with cyanocuprates allowed for the introduction of three stereocenters within the cyclohexene ring, as outlined in eq 6.[9]

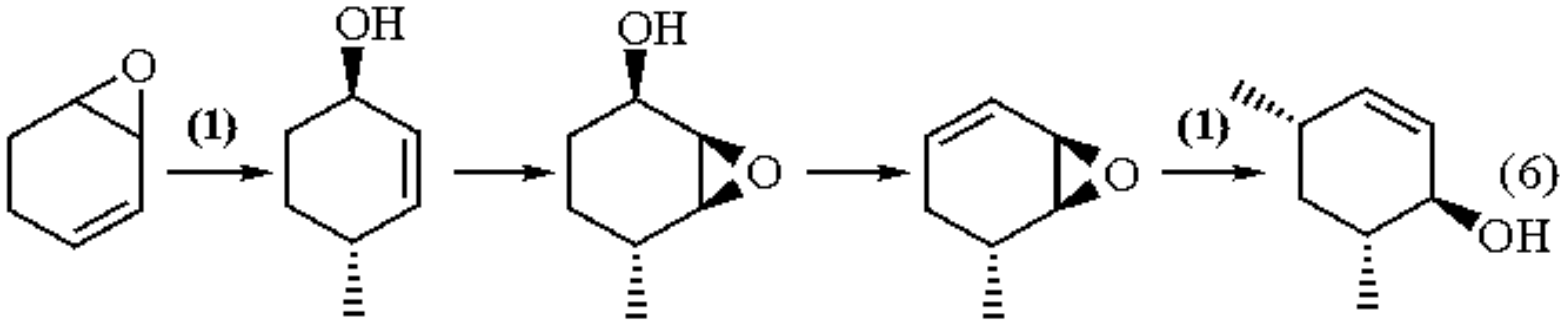

(6)

A further variation in the 1,4-additions of cyanocuprates to vinyl epoxides comes from the use of enol ethers derived from α,β-epoxy ketones as the vinyl component of the vinyl epoxide system.[9] This strategy places an alkyl group α to a ketone in an umpolung manner, as illustrated for α,β-epoxycyclohexanones in eq 7.[10]

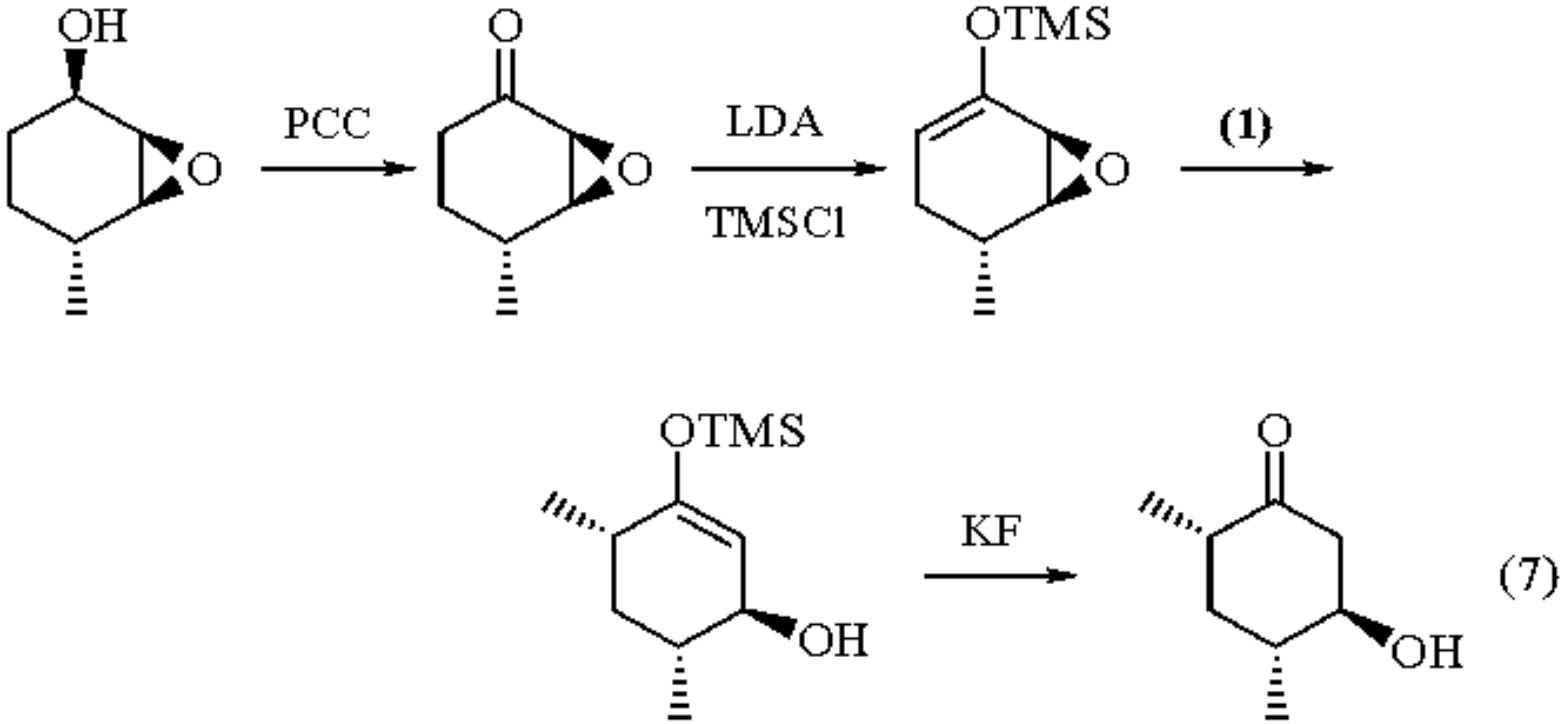

The use of a silyl enol ether in a cyclopentanone epoxide system was the basis for a synthesis of prostaglandins.[11] A simple version of this ring opening is shown in eq 8 for (**1**) and enol ether epoxide (**8**) to give the hydroxycyclopentanone (**9**).

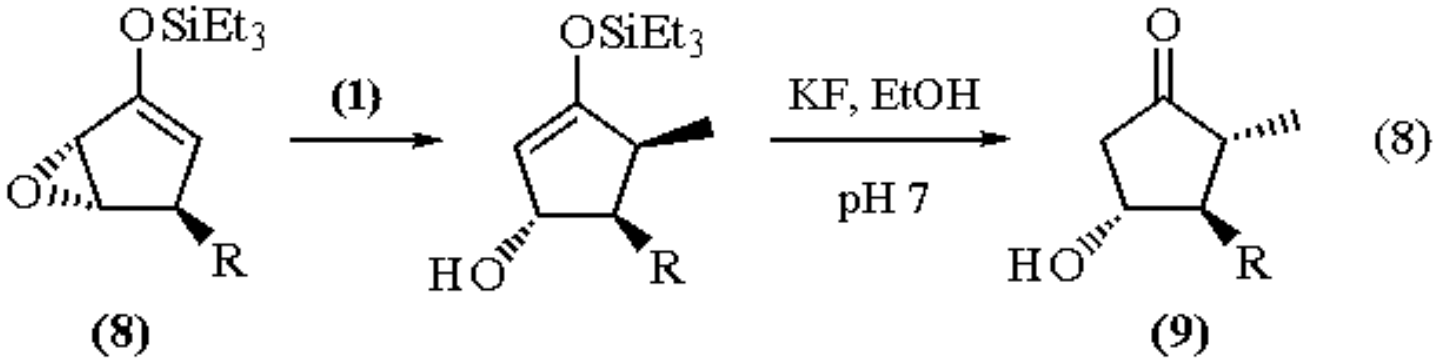

In addition to the silyl enol ethers of ketones, enol phosphates of epoxy ketones undergo the regioselective 1,4 ring openings with (**1**).[11] In the epoxycyclopentanone system, the enol phosphate (**10**) is prepared from the ketone with ***Lithium Diisopropylamide*** and ***Diethyl Phosphorochloridate*** at -78 °C. Reaction of (**10**) with (**1**) gives exclusively the 1,4-product (**11**) in 94% yield (eq 9).

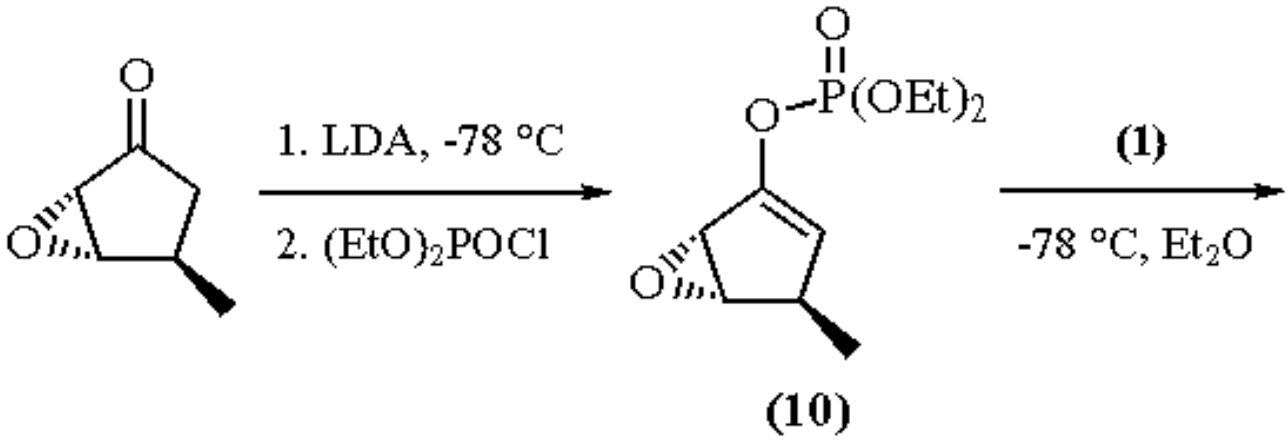

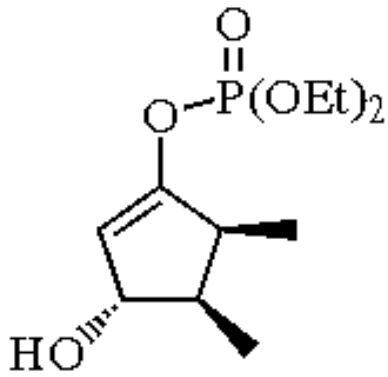

(9)

An additional advantage of the enol phosphates is that the phosphate unit may be reductively removed to produce an alkene.[8] This last process was used in the synthesis of α-multistriatin via intermediate (**12**) (eq 10).

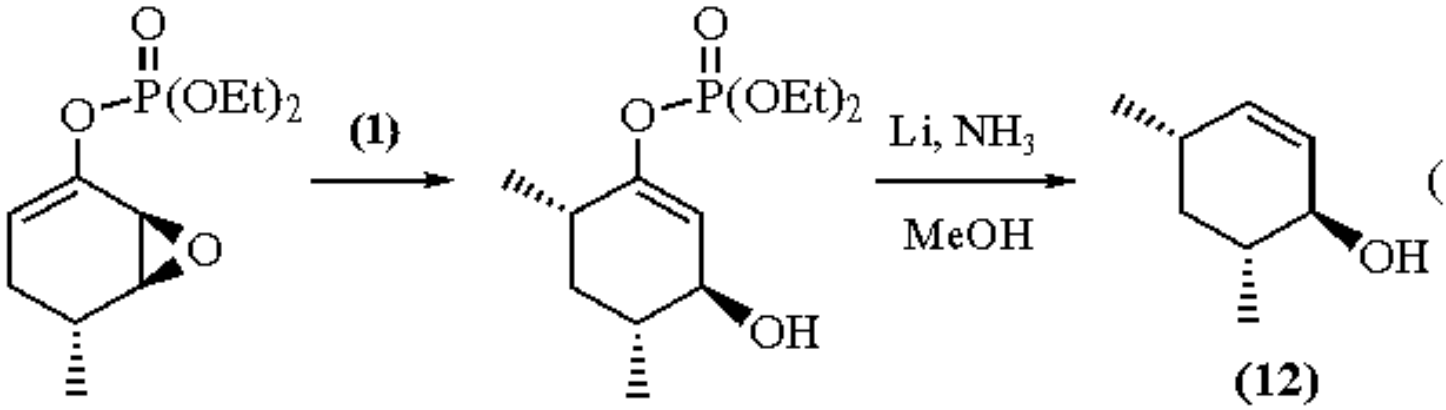

(10)

Reactions with Allylic Acetates.

The reagent (**1**) is also very effective in the allylations of allylic acetates and benzoates in an S_N2' sense. The reaction of (**1**) with the allyl acetate (**13**) proceeds in high yield to produce a mixture of the substituted enyne (**14**) and the allene (**15**) (eq 11).[12] The latter product results from addition of the cyanocuprate to the propargyl acetate system.

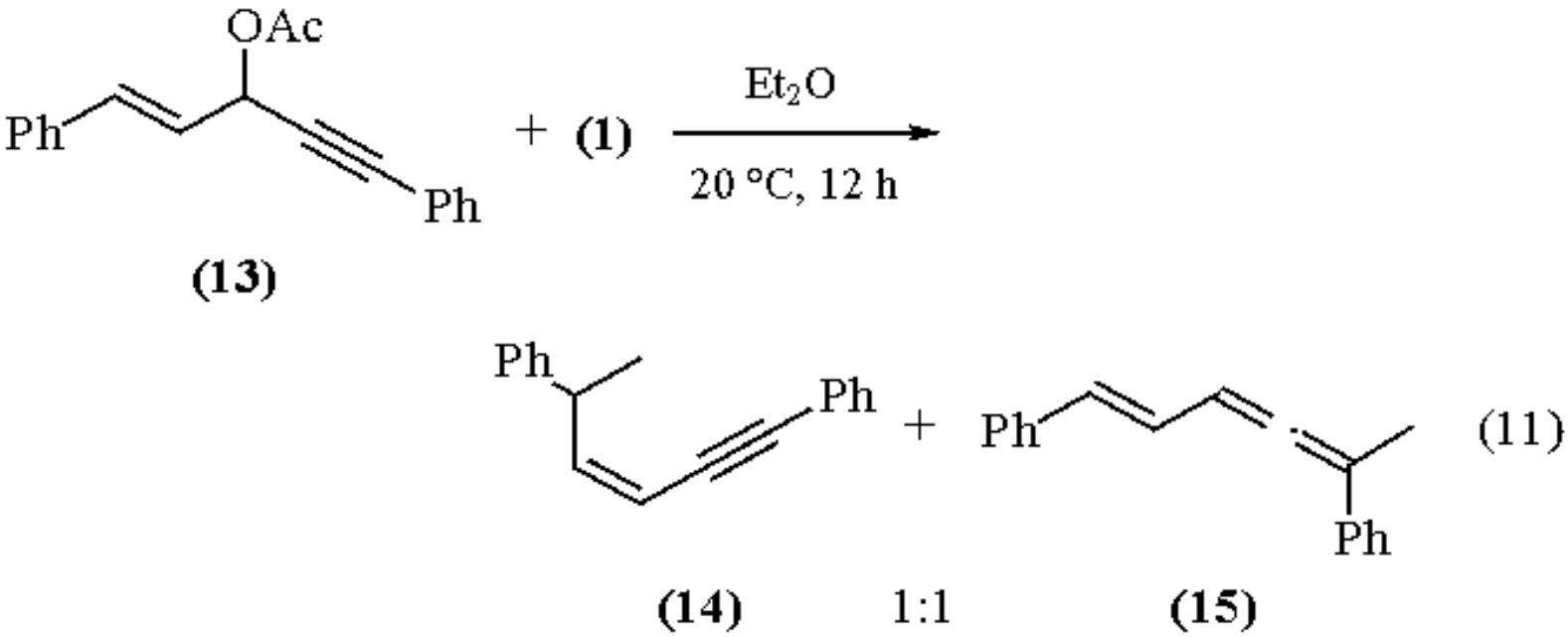

In another example, (**1**) added cleanly to the bis-allyl benzoate (**16**) to give the diene (**17**) (eq 12).[13]

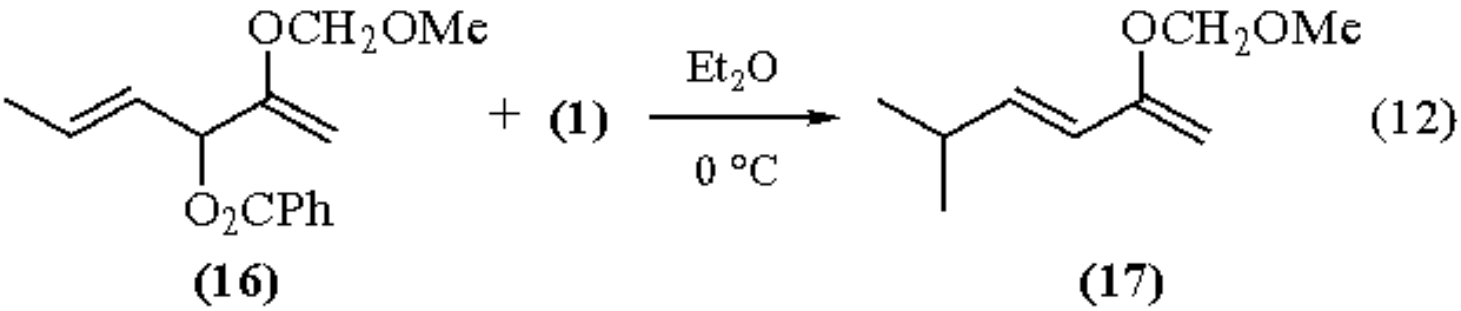

An example of the cyanocuprate (**1**) undergoing a conjugate addition to an allenyl sulfone is shown in eq 13. The allenyl *p*-tolyl sulfone is converted to the allyl sulfone (**18**) in good yield.[14]

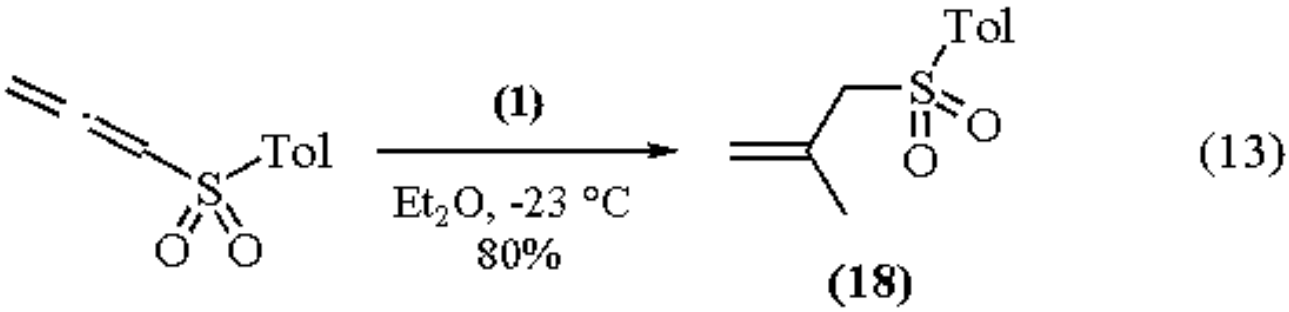

Related Reagents.

Lithium Butyl(cyano)cuprate; ***Lithium Cyano(dimethylphenylsilyl)cuprate***.

1. Marino, J. P.; Floyd, D. M. *TL* **1979**, 675.
2. Acker, R.-D. *TL* **1977**, 3407.
3. Acker, R.-D. *TL* **1978**, 2399.
4. Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *CC* **1988**, 356.
5. Anderson, R. J. *JACS* **1970**, *92*, 4978.
6. Staroscik, J.; Rickborn, B. *JACS* **1971**, *93*, 3046.
7. Marino, J. P.; Abe, H. *S* **1980**, 872.
8. Marino, J. P.; Abe, H. *JOC* **1981**, *46*, 5379.
9. Marino, J. P.; Hatanaka, N. *JOC* **1979**, *44*, 4467.
10. Marino, J. P.; Jaén, J. C. *JACS* **1982**, *104*, 3165.
11. Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *JOC* **1987**, *52*, 4898.
12. Keinan, E.; Bosch, E. *JOC* **1986**, *51*, 4006.
13. Newman, M.; Hussain, N. S. *JOC* **1982**, *47*, 2837.
14. Berlan, J.; Koosha, K. *JOM* **1978**, *153*, 107.

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Lithium Cyclopropyl(phenylthio)cuprate[1]

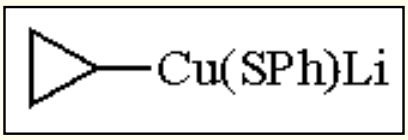

[84180-46-1] · $C_9H_{10}CuLiS$ · Lithium Cyclopropyl(phenylthio)cuprate · (MW 220.72)

(heterocuprate useful in 1,4-addition-elimination reactions[2] and annulations[3])

Solubility: sol THF; less sol ether.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl, and the yield of cyclopropyl phenyl ketone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Method: cyclopropyllithium[5,6] is prepared by cooling a 0.25 M THF solution of bromocyclopropane under Ar to -78 °C; dropwise addition of 1.0 equiv of a solution of ***s-Butyllithium*** is followed by stirring for 2 h; this cyclopropyllithium solution is transferred by cannula to a stirred, -78 °C THF slurry of ***Phenylthiocopper(I)***[7] under Ar; the resultant mixture is warmed to -20 °C; a clear, light brown solution of cuprate forms after stirring for 20 min; it is cooled to -78 °C and is used directly.[8]

Handling, Storage, and Precautions: best results are obtained with PhSCu prepared from high purity Cu^I salts,[9] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides;[10] *s*-BuLi is pyrophoric;[11] care must be exercised in its handling, and a fume hood should be used; the reagent is more stable than lithium dicyclopropylcuprate, which decomposes upon prolonged standing at -78 °C.[5]

This cyclopropyl organometal reagent is representative of the heterocuprate class of organocopper reagents.[12] The cyclopropyl group is nucleophilically reactive, whereas the SPh group is not. The nontransferable SPh group, or dummy ligand,[13] provides enhanced thermal stability and solubility compared with the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when higher reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium cyclopropyl(phenylthio)cuprate has been used in 1,4-addition-elimination reactions with α-oxoketene dithioacetals[14] and 3-halo-2-alkenones.[8,15] The latter substrates yield 3-cyclopropyl-2-alkenones which undergo high-yield thermal ring expansions, providing a two-step, five-membered ring annulation method.[8] Bicyclo[4.3.0]-1-nonen-2-ones (eq 1) and bicyclo[3.3.0]-1-octen-2-ones of use in the synthesis of zizaene-type sesquiterpenoids can be

prepared.[8] Spiro[4.5]-1-decen-6-ones and spiro[4.4]-1-nonen-6-ones, which provide access to vetivane-type sesquiterpenoids, also can be prepared.[15]

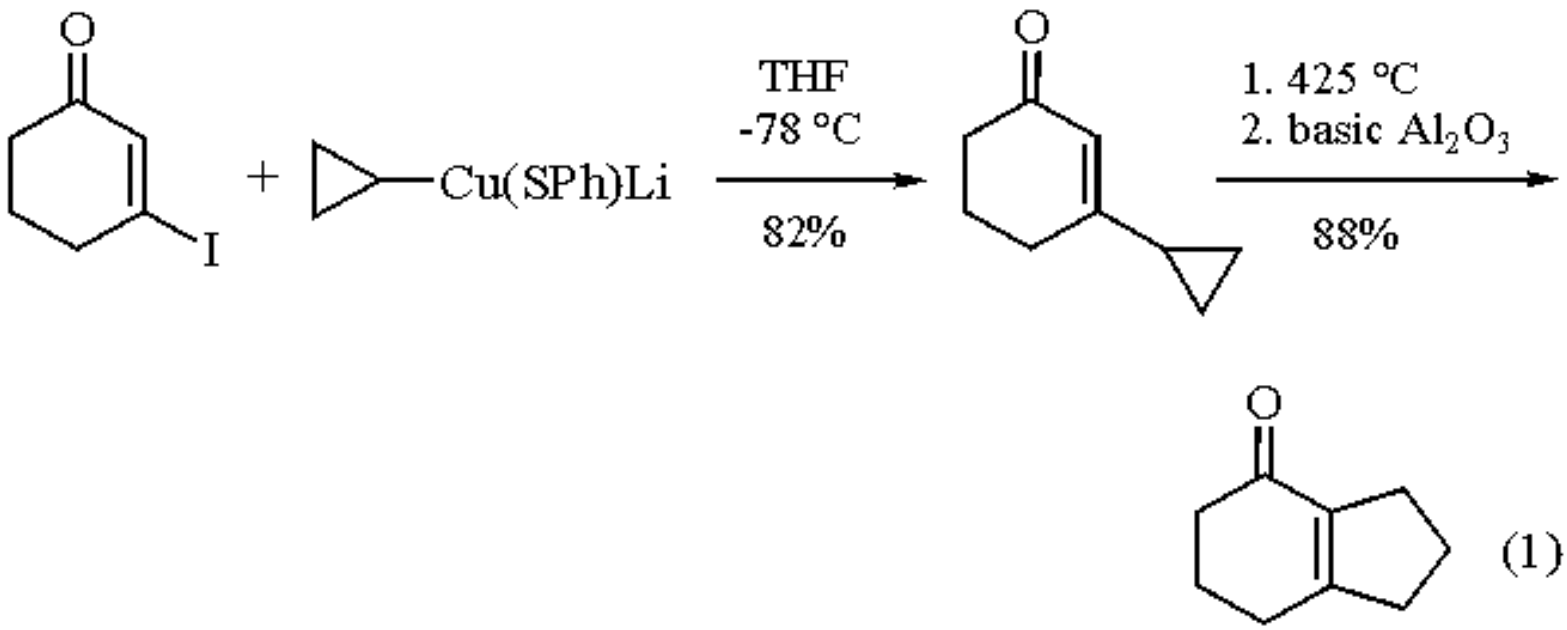

(1)

Related Reagents.

For related heterocuprates, see ***Lithium Methyl(phenylthio)cuprate*** for discussion of lithium dialkylcuprates, see ***Lithium Dimethylcuprate***.

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Lithium Diallylcuprate[1]

$(CH_2{=}CHCH_2)_2CuLi$

[21500-57-2] · $C_6H_{10}CuLi$ · Lithium Diallylcuprate · (MW 152.63)

(allylating reagent; undergoes conjugate addition reactions[1a,b,d] and substitution reactions[1a,c,d])

Alternate Name: lithium di(2-propenyl)cuprate.

Physical Data: ^{13}C NMR δ 150, 91, 24.[2b]

Solubility: sol THF, Et_2O.

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***[2a,3a] or $CuI.SBu_2$[3b]) under N_2 or argon atmosphere (see ***Lithium Dimethylcuprate***) and ***Allyllithium***[3a,3c] which is prepared from ***Allyltributylstannane*** or ***Tetraallylstannane*** and ***Phenyllithium*** or ***n-Butyllithium***.

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Introduction.

Lithium diallylcuprate displays the characteristic reactivity patterns of lithium diorganocuprates (see e.g. ***Lithium Di-n-butylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***). The very high reactivity of $(CH_2{=}CHCH_2)_2CuLi$ is sometimes problematic, and allylcopper reagents can be more effective (see ***Allylcopper***).[3a]

Addition Reactions.

Lithium diallylcuprate reacts with α,β-alkenyl ketones (eq 1),[1,9] lactones,[4] esters,[5] nitriles,[6] lactams (eq 2),[7] and phosphonates[8] with conjugate transfer of the allyl ligand. Addition of ***Chlorotrimethylsilane*** can accelerate the conjugate addition reaction and results in improved yields.[9]

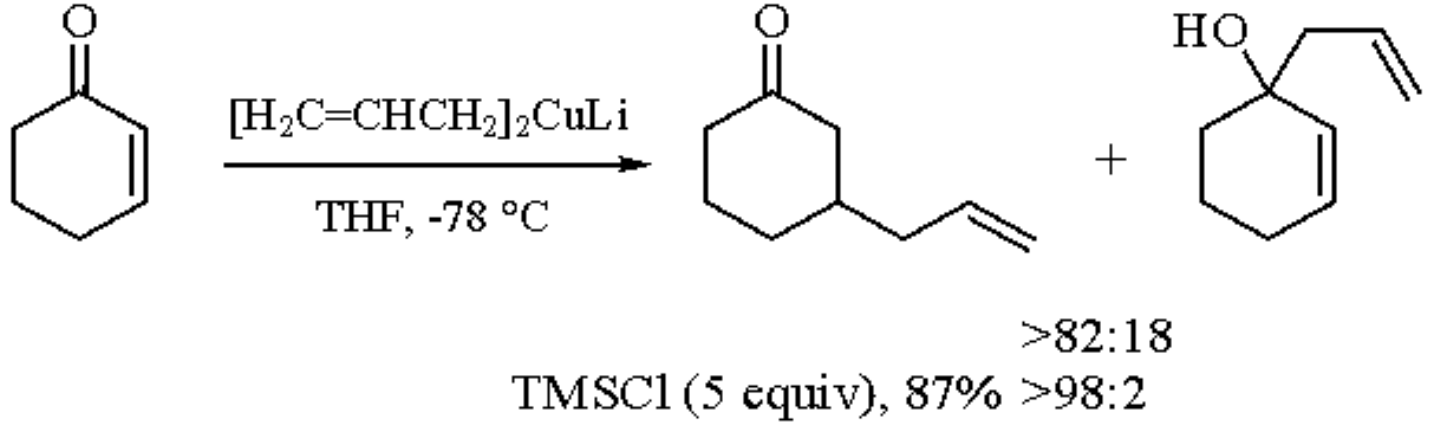

(1)

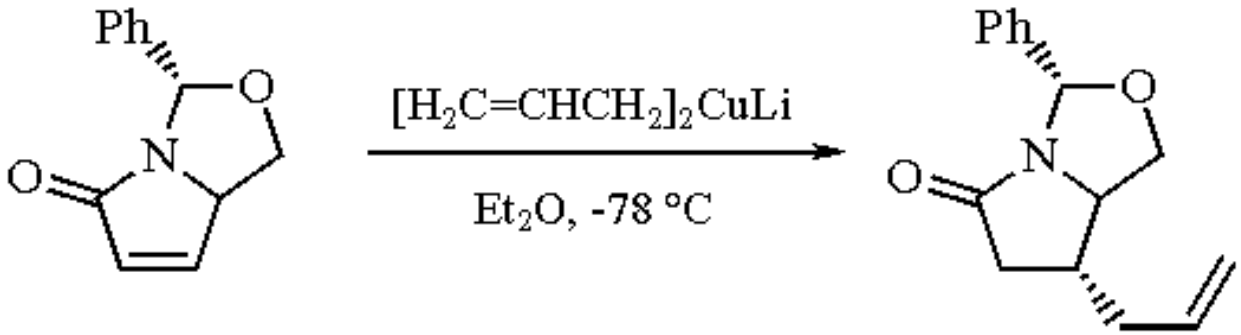

(2)

The reagent adds stereoselectively (*cis* addition) to α,β-alkynoates, affording 2,5-dienoates (eq 3).[10] Dienyl esters and dienyl nitriles exclusively afford 1,6-addition products in good yields.[6] Diethyl 2-vinyl-1,1-cyclopropanedicarboxylate gives mixtures of 1,5- and 1,7-addition products.[11] Tandem conjugate addition-enolate trapping is a powerful synthetic method, although additives[12] and solvent changes are sometimes required. Conjugate addition of the reagent to ketoketenimines affords β-enamino ketones under mild reaction conditions.[13] 1-Alkoxycarbonylpyridinium halides undergo both 1,2- and 1,4-addition reactions, leading to regioisomeric dihydropyridines (eq 4).[14] Lithium diallylcuprate reacts with α,β-enals in the presence[15] of TMSCl to give the 1,2-addition products regioselectively.

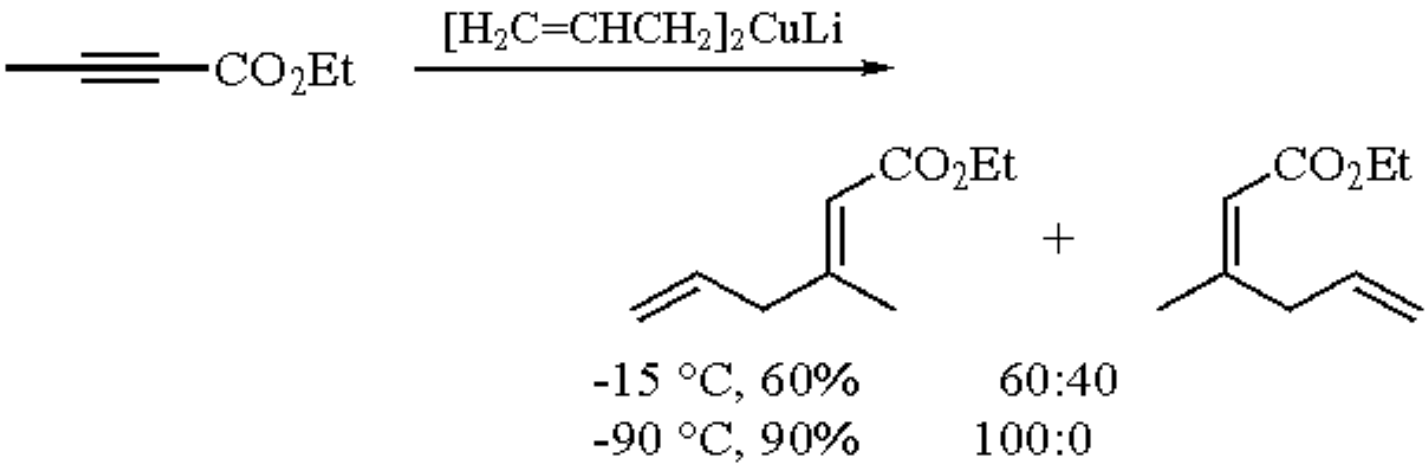

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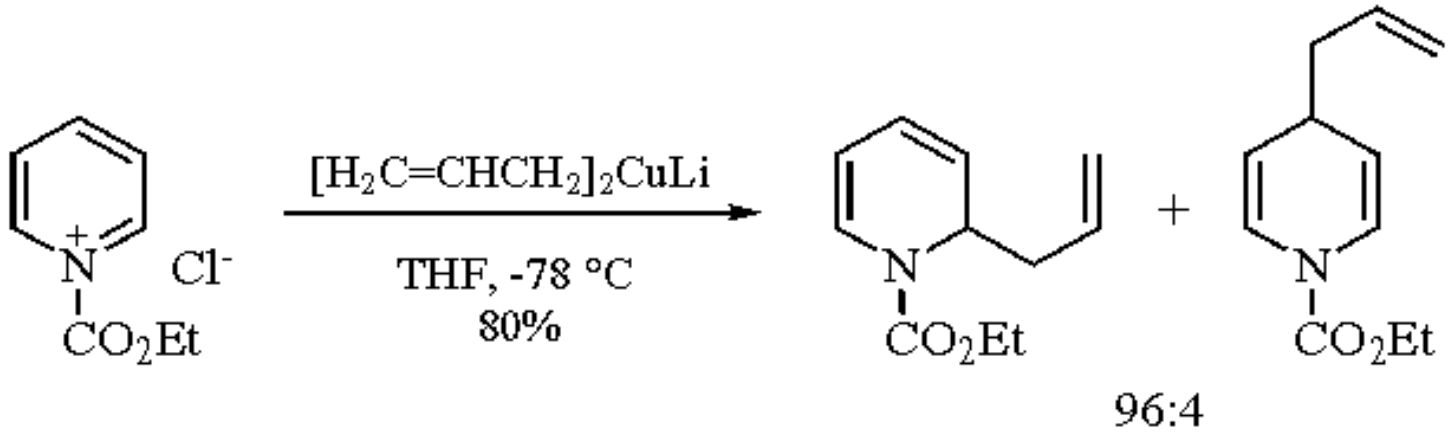

Substitution Reactions.

Lithium diallylcuprate participates in substitution reactions with alkyl halides,[2a] carboxylates,[16] and sulfonate esters.[17] Secondary tosylates undergo the substitution reaction with clean inversion of configuration; the reaction is greatly facilitated when a heteroatom (e.g. O, S) is proximate to the nucleofugal substituent and elimination pathways are minimized (eq 5).[18] 4-Bromo-2-butenyltributylphosphonium salts undergo substitution reactions with the reagent, with formation of an ylide which can react with aldehydes to afford dienes.[19] Allylic ammonium salts participate in *syn*-S_N2' pathways with good stereo- and regioselectivity (eq 6).[20]

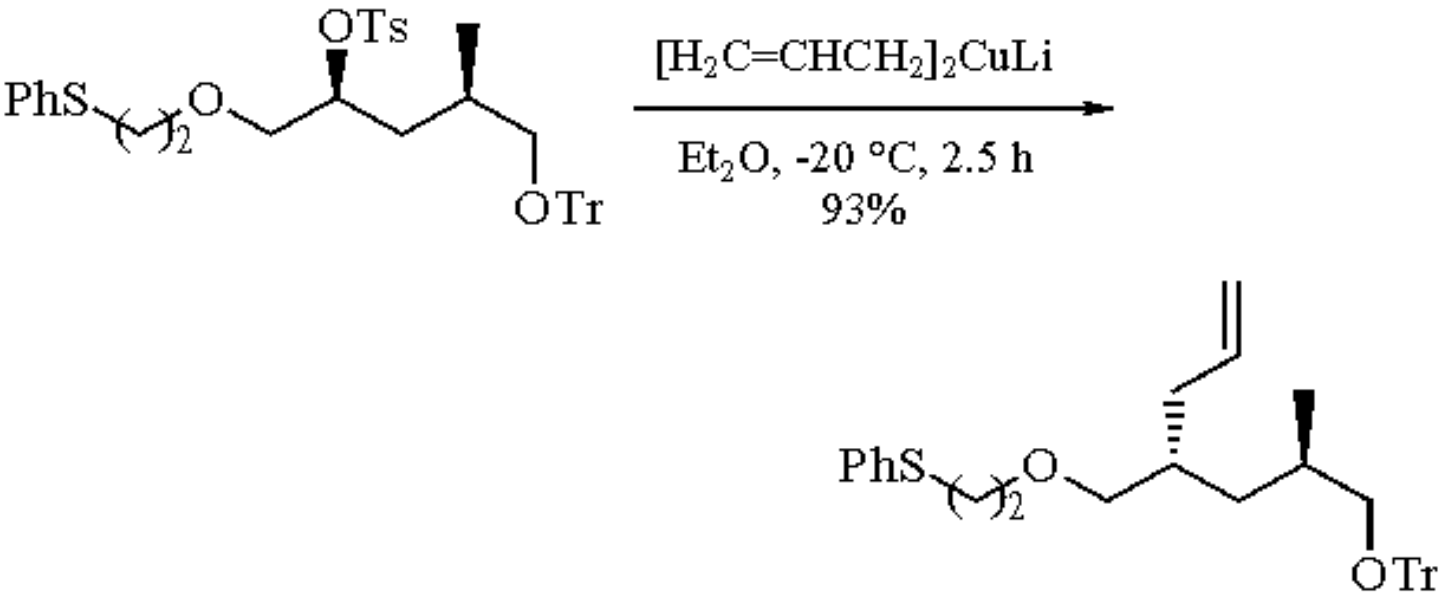

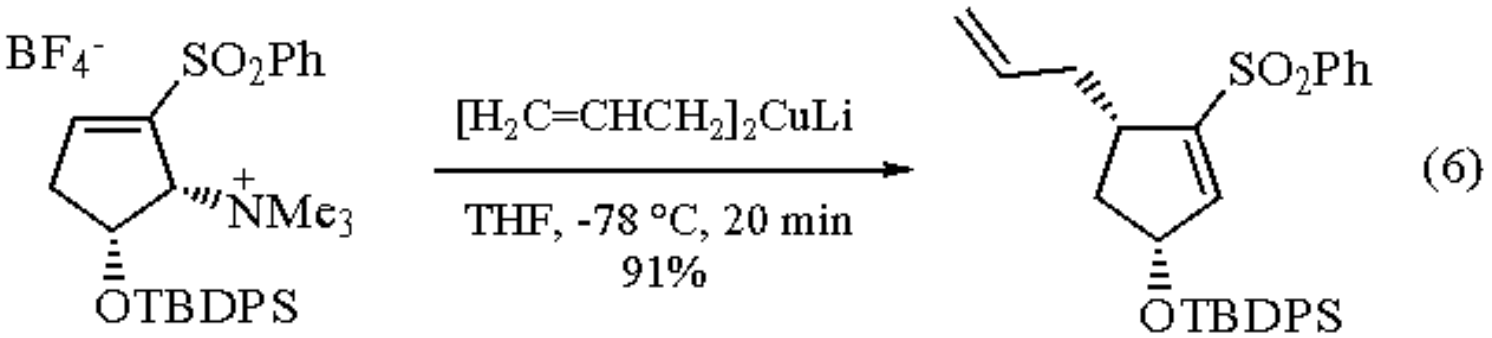

Miscellaneous Reactions.

1-Cyclooctenyl phenyl sulfones fail to undergo conjugate addition with lithium diallylcuprate, instead affording reduction products.[21]

Related Reagents.

Lithium Bis(1-ethoxyvinyl)cuprate; ***Lithium Diisopropenylcuprate***; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Di-(E)-1-propenylcuprate***; ***Lithium Divinylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

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Lithium 4,4´-Di-*t*-butylbiphenylide[1]

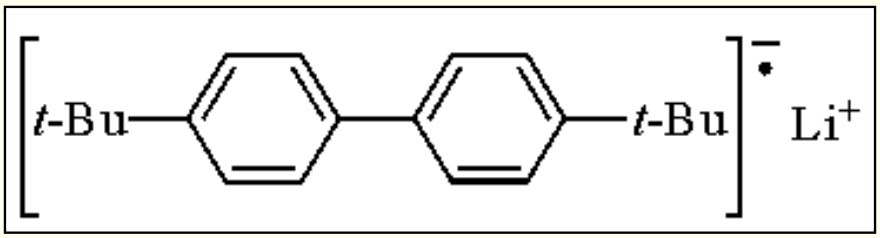

[61217-61-6] · $C_{20}H_{26}Li$ · Lithium 4,4´-Di-*t*-butylbiphenylide · (MW 273.40)

(reductive lithiations of thiophenyl ethers,[11] carbonyl groups,[23] phosphinates;[25] generation of alkyllithiums,[2] α-lithio ethers,[3] allyllithiums,[17,18] β-,γ-,δ-lithio alkoxides;[19] propellane bond cleavage[22])

Alternate Name: LDBB.

Solubility: sol THF

Preparative Methods: anhydrous THF and 4,4´-di-*t*-butylbiphenyl (DBB) are cooled to 0 °C under a blanket of argon and stirred with a glass-coated stirring bar; ***Lithium*** foil (or ribbon) is added in portions and the mixture is stirred for 5 h at 0 °C; the appearance of the deep blue-green radical anion appears within 5 min.

Handling, Storage, and Precautions: LDBB will slowly decompose at room temperature.

Reductive Lithiation.

There are several advantages for using LDBB over the traditional ***Lithium Naphthalenide*** or ***Sodium Naphthalenide*** (LN, NaN). LDBB is a more powerful reducing agent than the alkali naphthalenides and the resulting carbanion will be trapped as an organolithium. The high steric environment of the *t*-butyl groups lead preferentially to electron transfer and to little or no radical combination. This is in contrast to LN, where alkylation of naphthalene is frequently observed. Another advantage is the ease in separation of nonvolatile DBB from the reaction mixture.[2]

LDBB has been used in place of ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN), leading to slightly higher yields of the desired products or when reaction conditions dictate.[3]

Alkyllithiums.

The conversion of alkyl halides to alkyllithiums is highly effective with LDBB. The corresponding hydrocarbons can be formed in high yields upon the addition of H_2O (eq 1).[2]

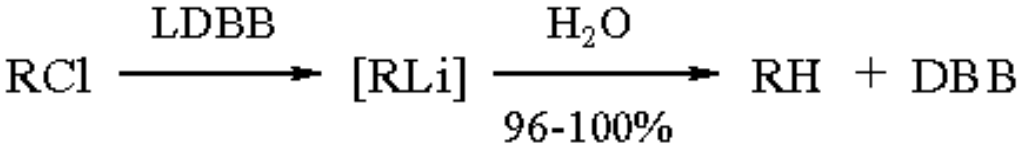

(1)

The alkyllithiums can be trapped by a variety of electrophiles including aldehydes (eq 2),[4] carbon dioxide (eq 3)[5] and aryl groups (eq 4).[6] The use of LDBB to generate the organolithium in the latter example proved critical since other methods (***n-Butyllithium***, ***t-Butyllithium***, ***s-Butyllithium***, and ***Methyllithium***) led to lower yields and longer reaction times. One possible reason for the enhancement in organolithium activity may be a result of lowered aggregation.[6]

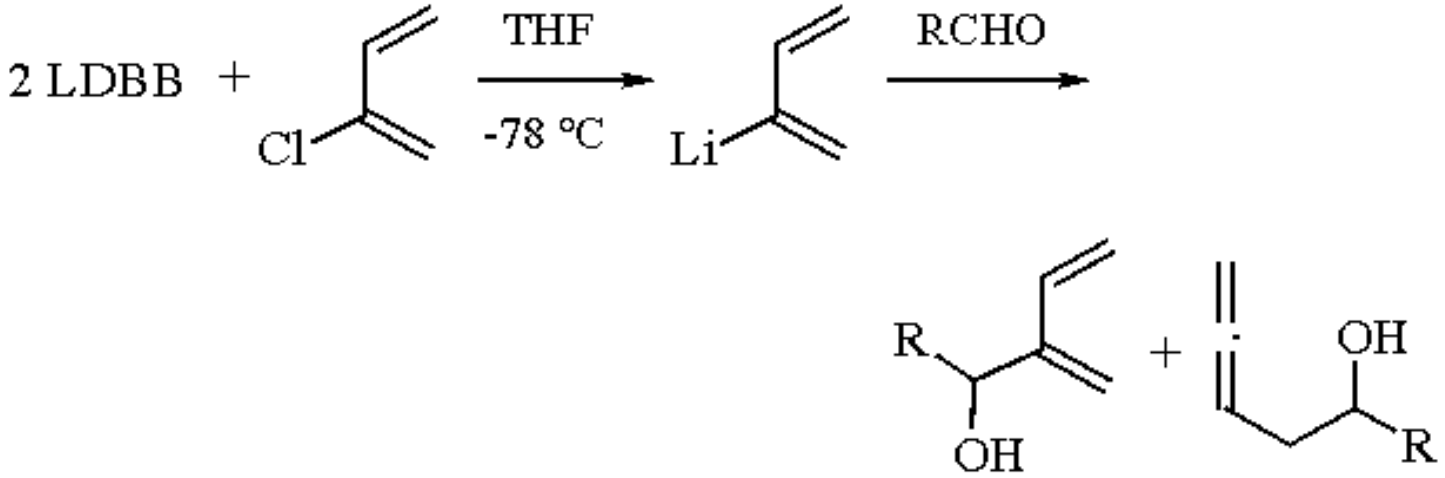

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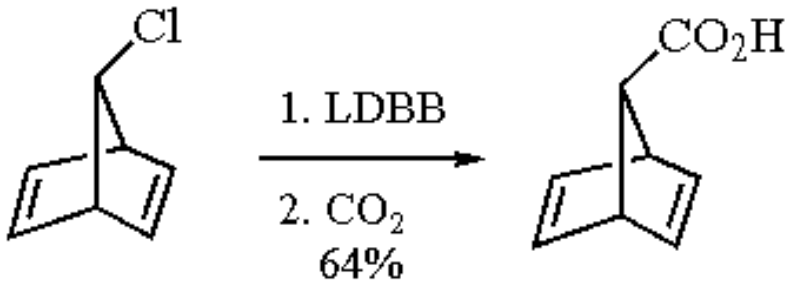

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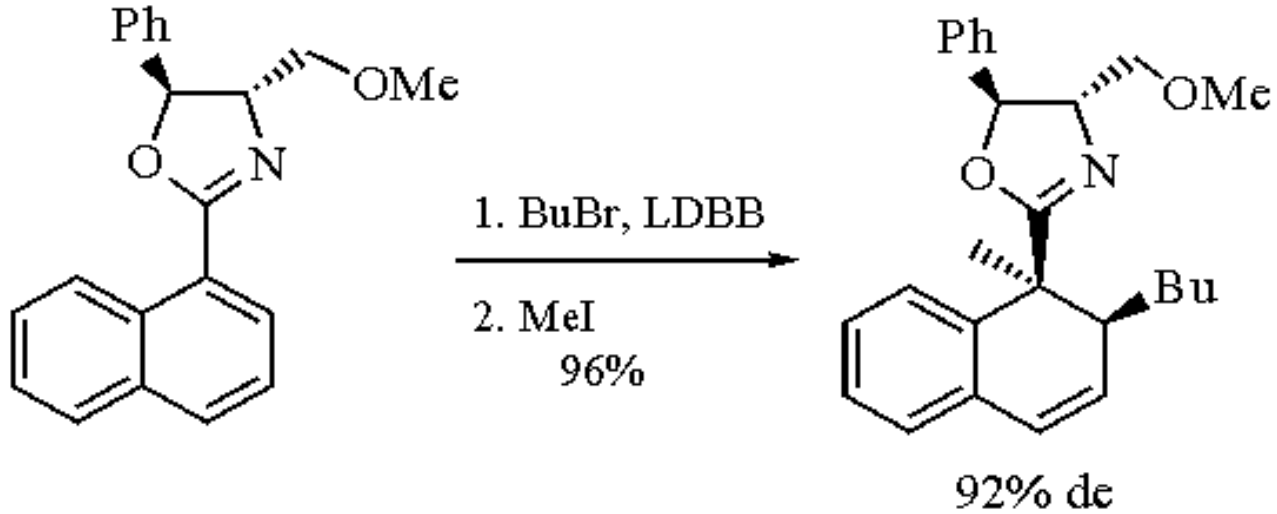

(4)

The geminal dilithio species can also be generated and trapped with electrophiles in good yields (eqs 5 and 6).[7]

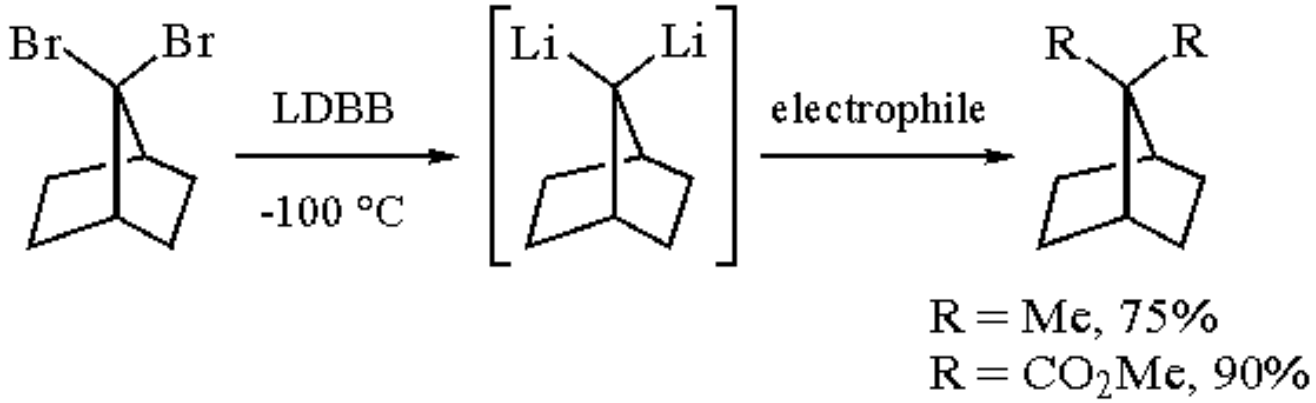

(5)

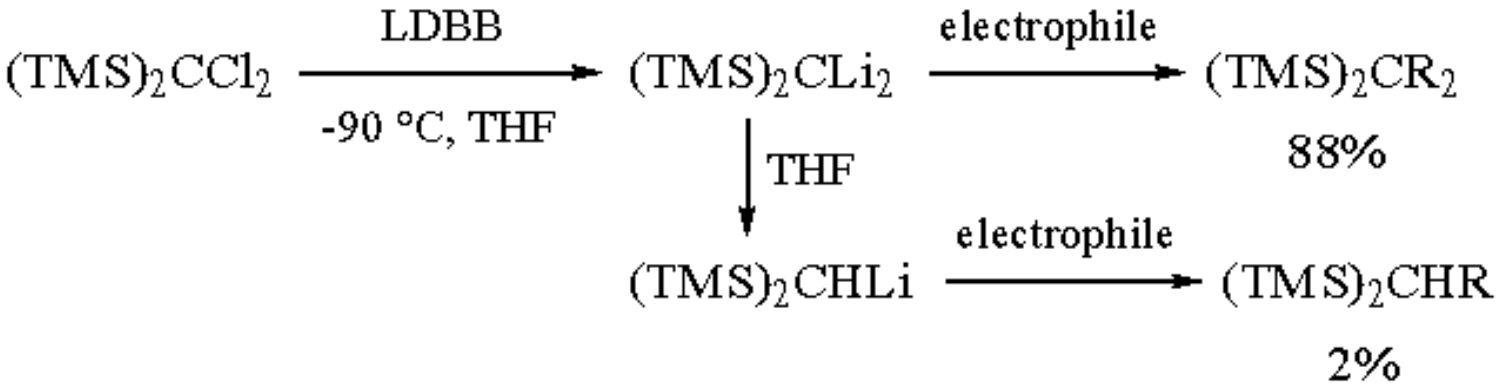

(6)

The generation of alkyllithium (**1**) proved pivotal in the enantioselective synthesis of spiculisporic acid.[8] Derived from the corresponding alkyl bromide, this homoenolate equivalent could not be made from lithium metal and the corresponding Grignard reagent led to the wrong isomer.

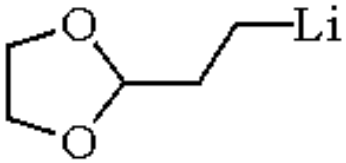

(1)

Reductive Lithiation of Thiophenyl Ethers.

A variety of thiophenyl ethers are reduced with LDBB and can be trapped with electrophiles, leading to 1-substituted bicyclo[1.1.1]pentanes[9] and vinyl substituted compounds (eqs 7 and 8).[10] The latter procedure to generate the alkenyllithium is a better and more cost efficient route than the Bond modification of the Shapiro reaction. The cuprate reagent from both the bicyclo[1.1.1]pentane and alkenyl compounds can be generated and reacted with electrophiles.

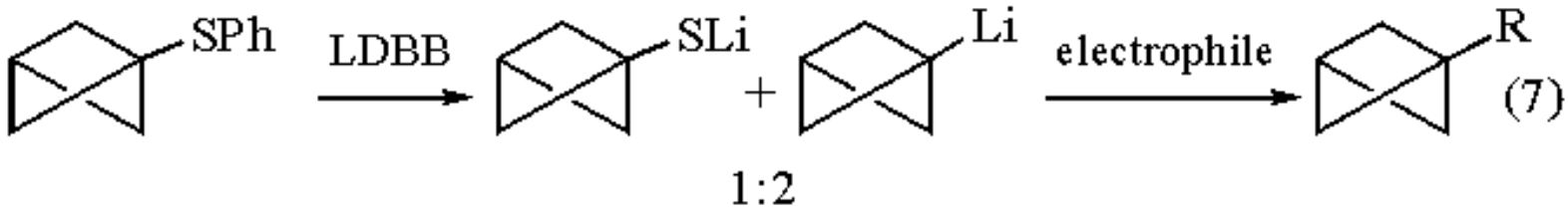

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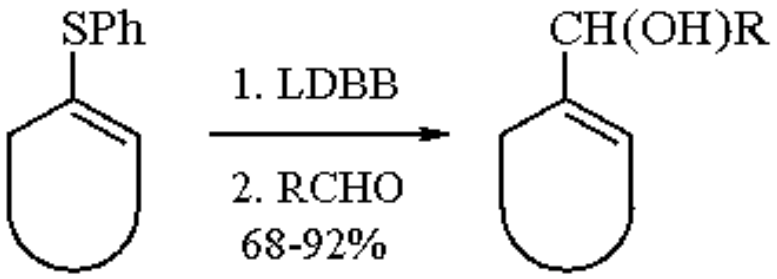

(8)

Homoenolate (**2**) is produced from the reductive lithiation of the corresponding phenylthio derivative and can be reacted with many electrophiles in high yields (72-83%).[11]

(2)

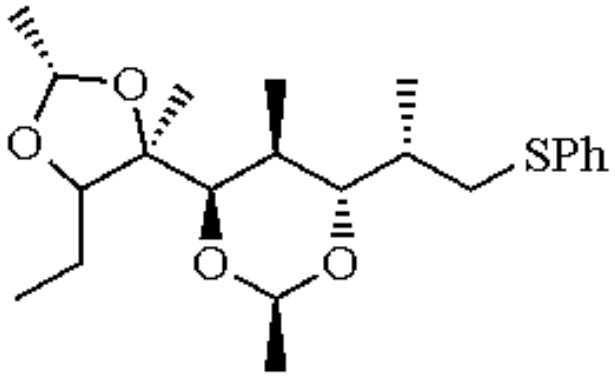

(3)

The use of LDBB was advantageous in the total synthesis of (+)-(9*S*)-dihydroerythronolide A, converting the thiophenyl group in (**3**) to an alkyllithium and then to a Grignard reagent.[12]

An unusual 1,4 O -> C silicon shift was observed when a tris(trimethylsilyl) ether was treated with LDBB to yield the *scyllo*-tris(trimethylsilylmethyl)cyclohexanetriol.[13]

α-Lithio Ethers.

The generation of α-lithio ethers can be performed using LDBB followed by trapping with electrophiles. The α-lithio ethers of 1-methoxy-1-phenylthiocyclopropanes are reacted with conjugated aldehydes or ketones to yield 1-cyclopropylallyl alcohols. The addition of ***Trifluoromethanesulfonic Anhydride*** led, after rearrangement, to 2-vinylcyclobutanones (eq 9).[3a] Previous investigations of these cyclopropanes used LDMAN for reductive lithiation, which led to lower yields of the alcohol and, for acid sensitive compounds, significant drops in yield.

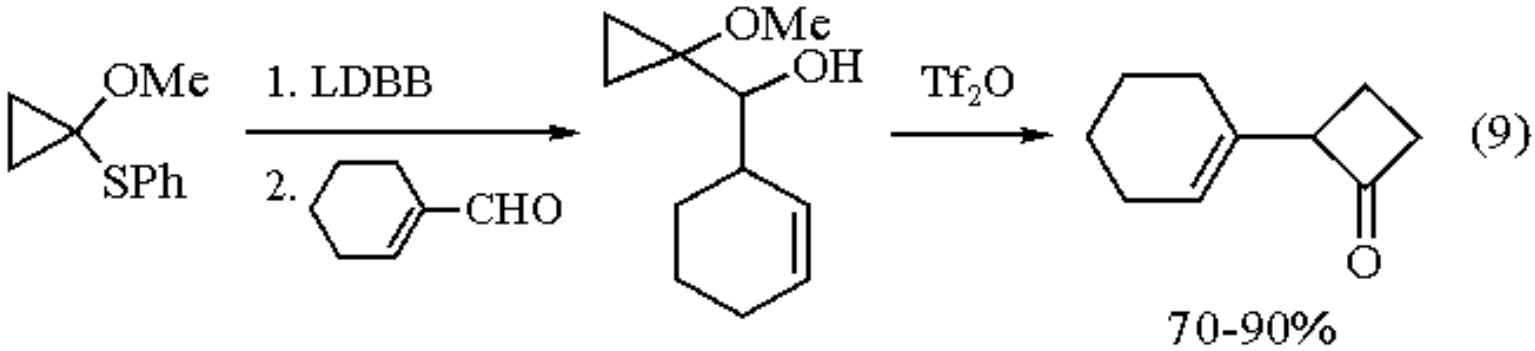

The reductive lithiation of 2-(phenylthio)tetrahydropyrans led selectively to the axial 2-lithio species which, upon equilibration, could be converted to the more thermodynamic equatorial α-lithio ether. Treatment with electrophiles such as acetone led to good yields of products (eq 10).[3b] The use of LDBB led to higher yields and cleaner reductions compared with LDMAN or LN.

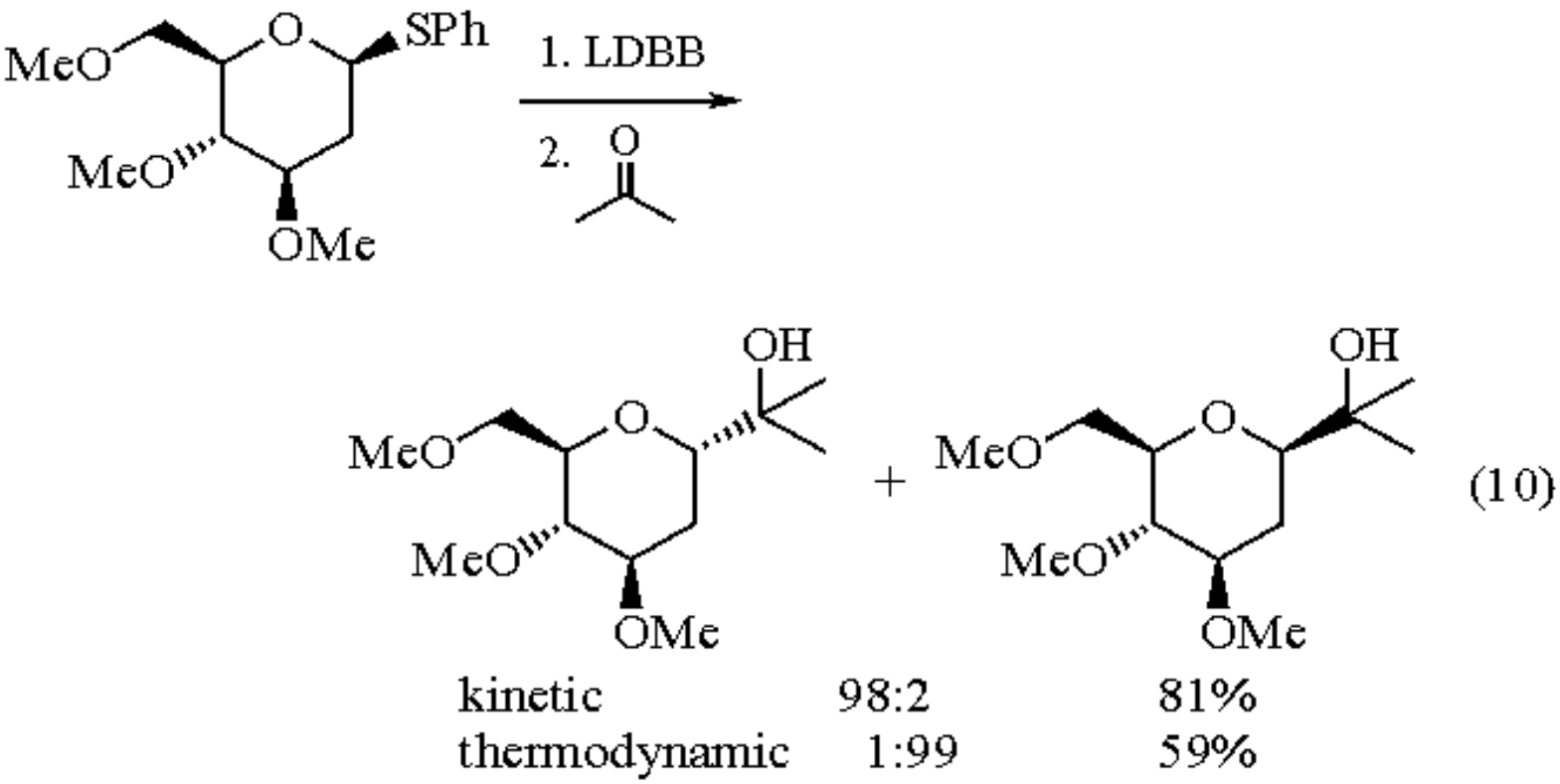

The placement of a vinyl group at the 6-position on the tetrahydropyran moiety and addition of LDBB leads to competing [1,2] and [2,3] Wittig rearrangements, with inversion of configuration at the lithium bearing carbon (eq 11).[14] A *t*-butyl group at position 4 significantly changes the reaction course, leading to a small amount of [2,3] Wittig rearranged product. The major product is derived from a 1,4-transannular H-transfer to the lithium-bearing carbon, with inversion of configuration.[15]

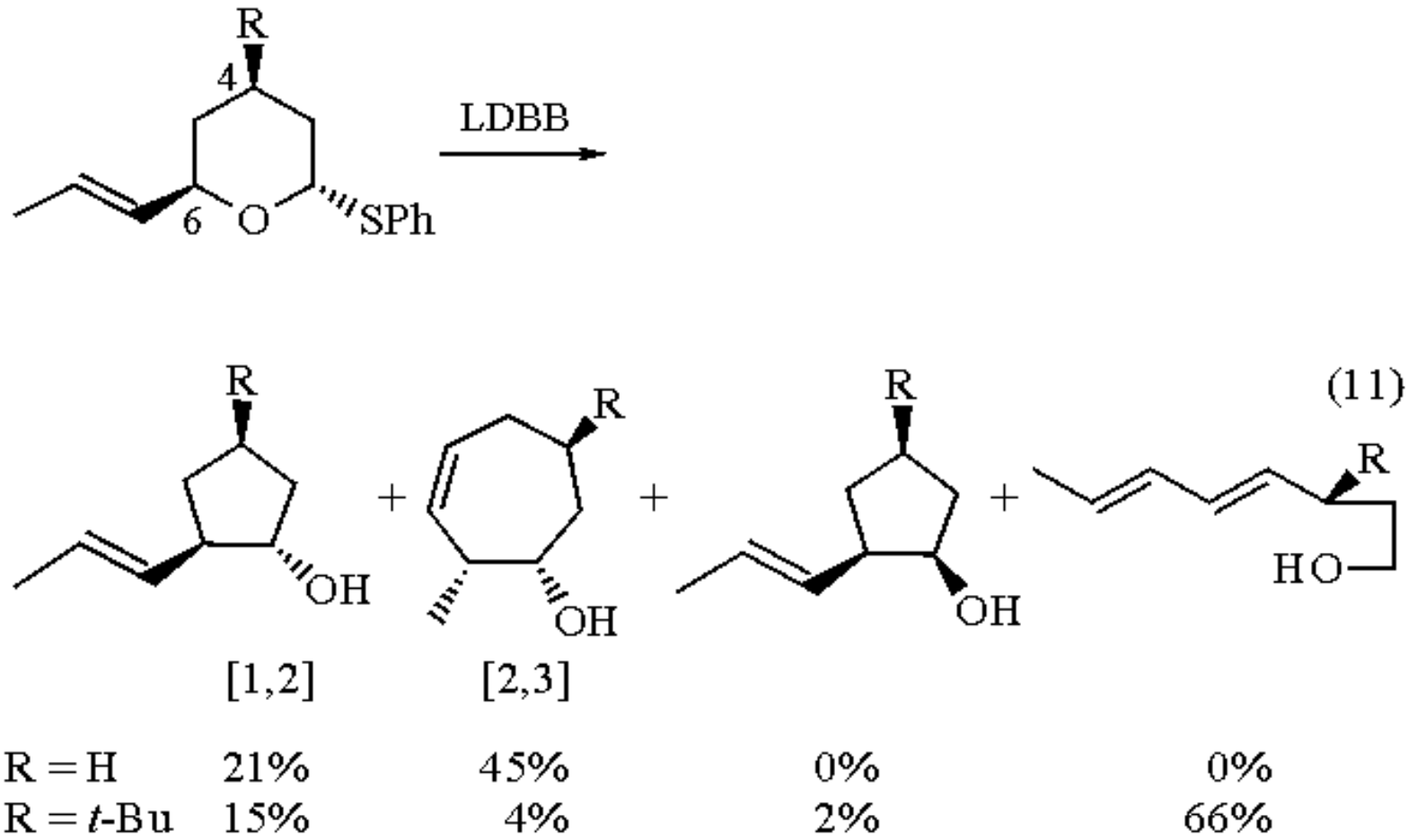

(Dialkoxymethyl)lithium compounds can be generated from the corresponding phenylthio derivative and reacted with aldehydes and ketones (eq 12).[16] The cyclic lithium reagent could be generated from LN, while the acyclic required LDBB.

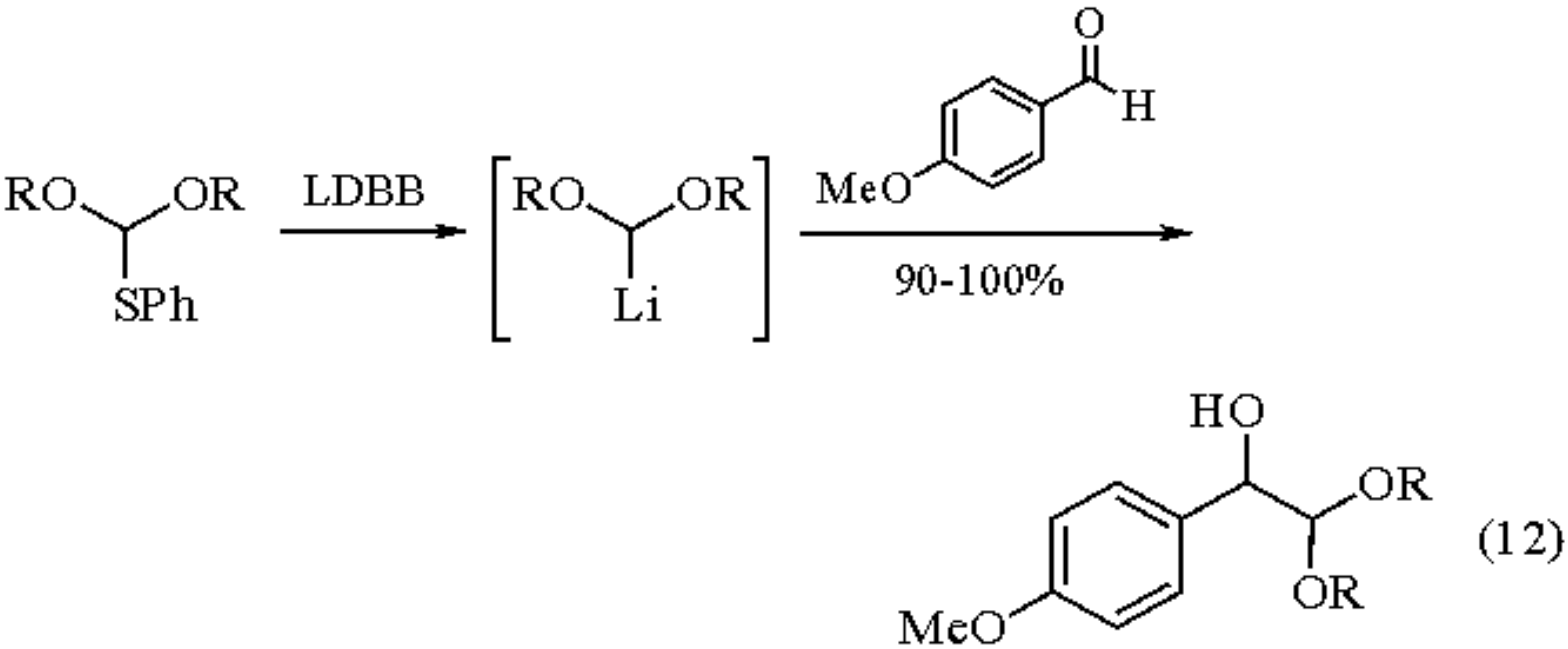

Allyllithiums.

The treatment of allyl phenylthio ethers with ***Lithium 1-(Dimethylamino)naphthalenide*** leading to allyllithiums has been performed. Allyllithiums derived from treatment with LDBB can be converted to the allylcerium reagent and trapped with unsaturated aldehydes. Homoallylic alcohols were obtained by 1,2-addition with attack by the least substituted terminus of the allyl anion (eq 13).[17] Regiocontrol of the double bond is attained by a slight temperature modification.

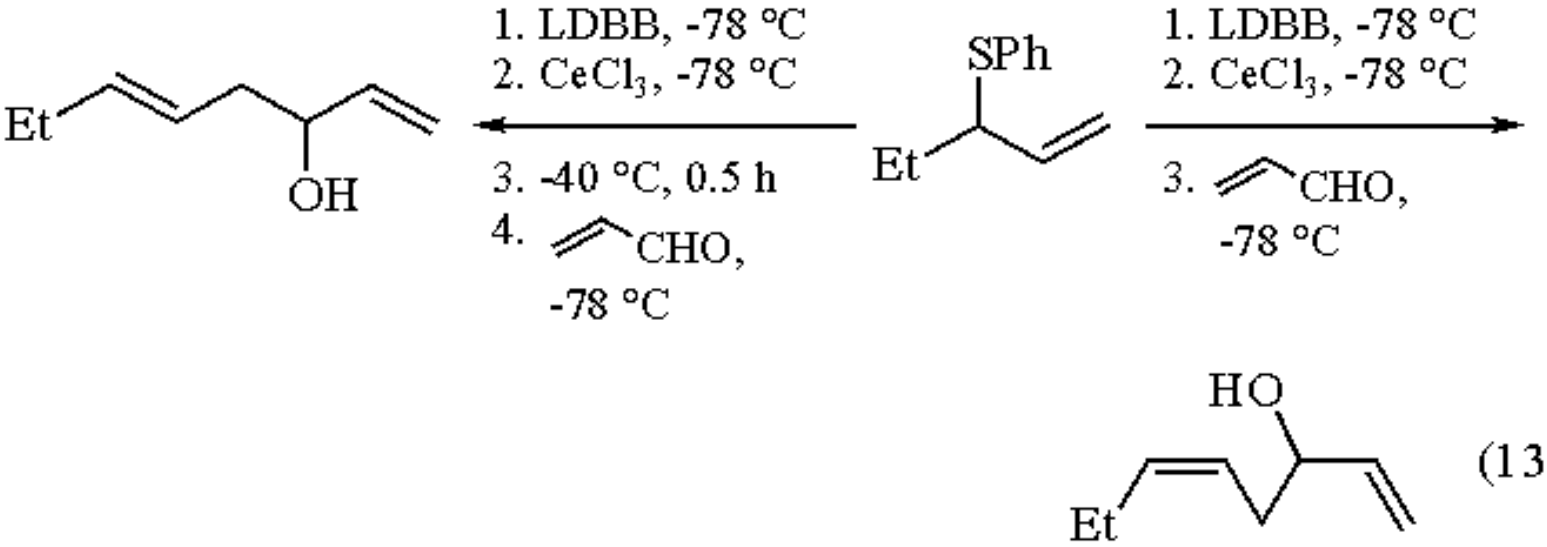

(13)

The ability to control the regiochemistry of allyllithium terminus and double bond geometry led to a one-pot synthesis of the Comstock mealy bug sex pheromone in a 45% yield, and a four-step synthesis of the California red scale pheromone in 23% yield.[18]

β-,γ-,δ-Lithio Alkoxides.

The treatment of epoxides with LDBB leads to β-lithio alkoxides which can be reacted with an aldehyde or ketone to yield varying amounts of a diol and an alcohol.[19] The diol is obtained from cleavage of the least substituted carbon oxygen bond, while the other alcohol arrives via a hydride transfer (eq 14). Reductive lithiation of vinyloxiranes led to ring opening in the opposite direction. The allylic anions could be treated with Ti^{IV} or Ce^{III} and added to aldehydes at the most or least substituted terminus, respectively.

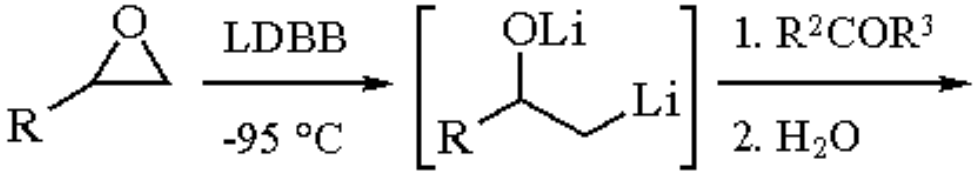

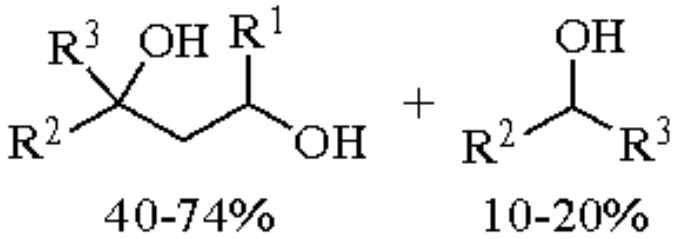

(14)

The generation of γ-lithio alkoxides from the corresponding oxetanes require higher temperatures (0 °C) than epoxide ring opening with LDBB.[20] γ-Lithio alkoxides can be trapped by electrophiles in modest yields. The addition of trialkylaluminums yields the lithium trialkylaluminates, which react with electrophiles in modest yields (eq 15).

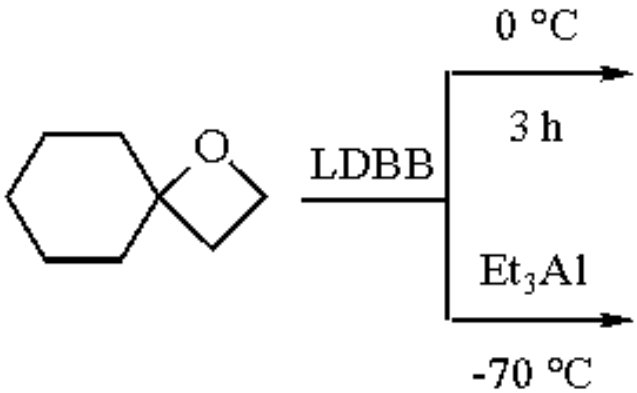

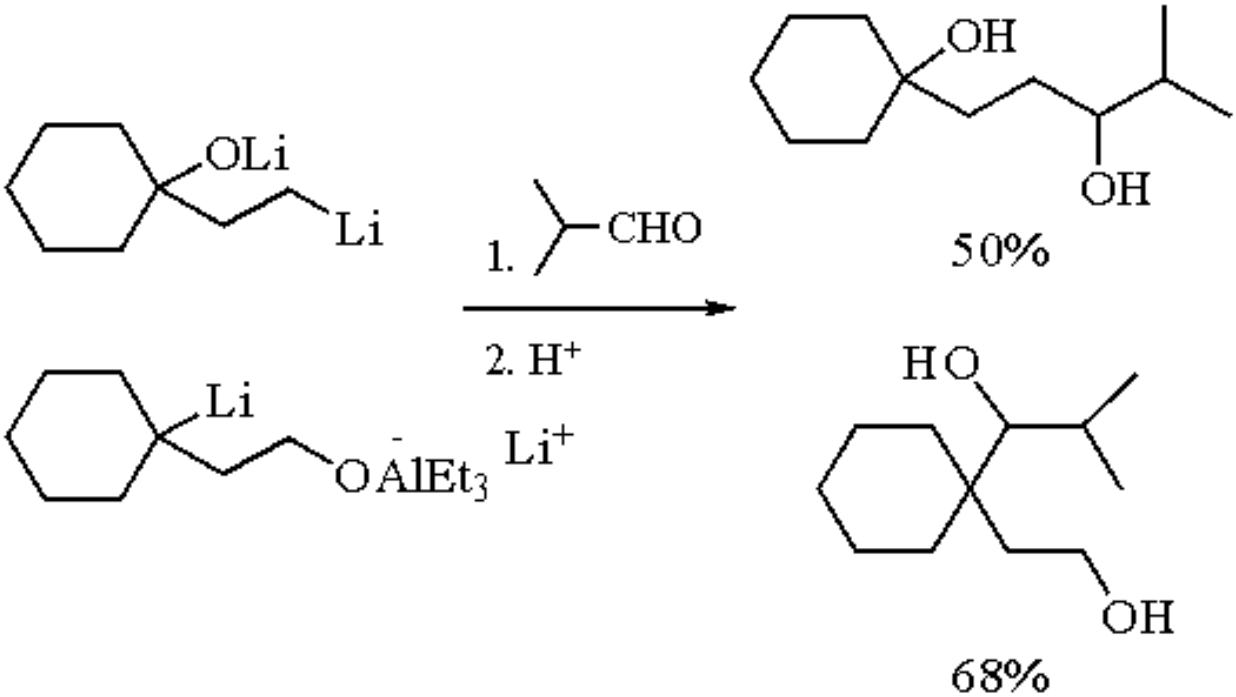

(15)

68%

The next higher analog, δ-lithio alkoxides, can be obtained by LDBB reductive lithiation in the presence of ***Boron Trifluoride Etherate***.[21] The Lewis acid helps stabilize the resulting open-chain oxyanion. Treatment with various electrophiles led to products in high yields and is a good protocol for the preparation of the synthetically useful [5.*n*] spiroacetal units (eq 16). The most branched alcohol is obtained upon cleavage of substituted epoxides and oxetanes, while the opposite regioselectivity is observed for THF.

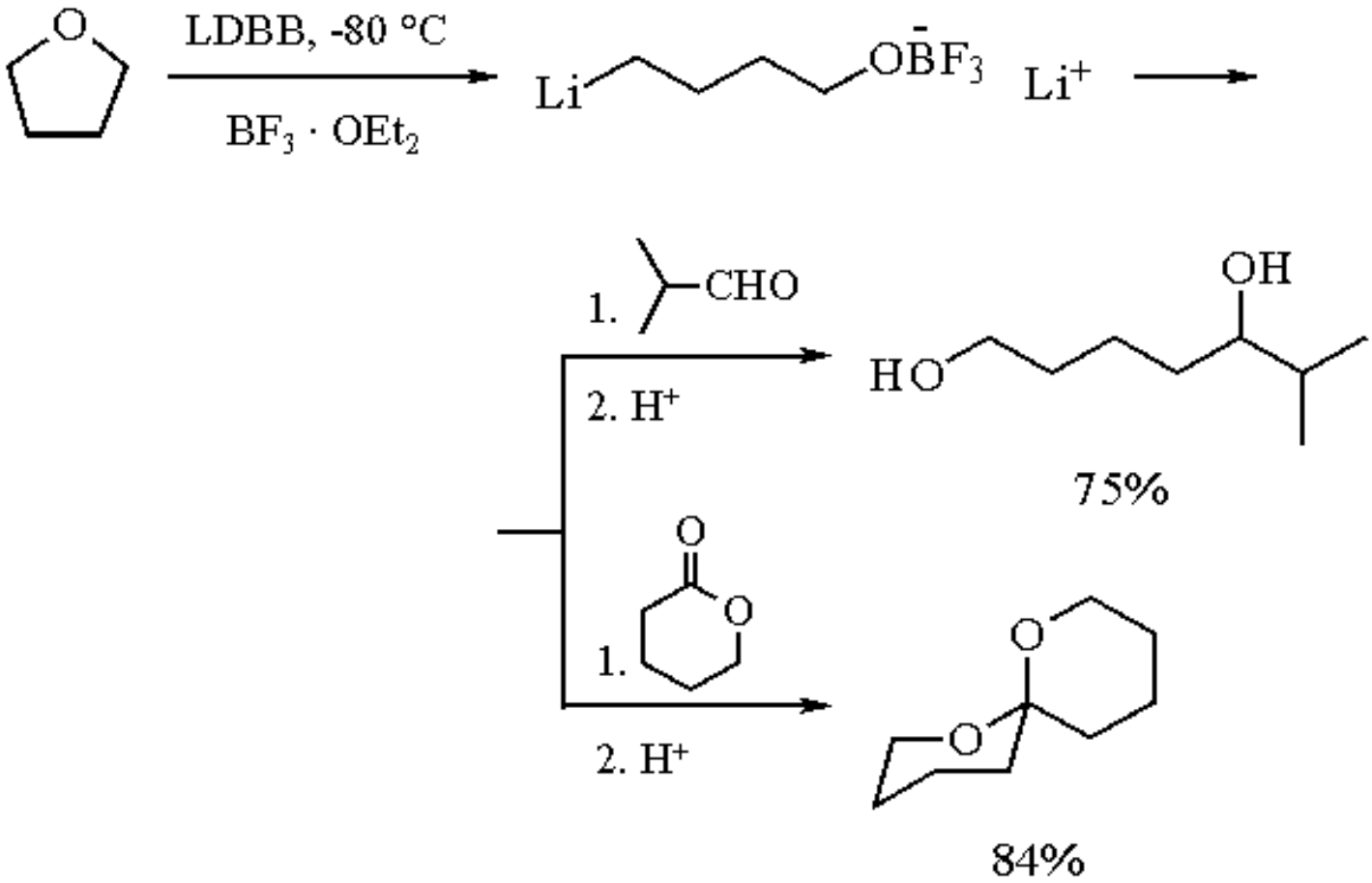

(16)

Propellanes.

The central bond in [1.1.1]propellanes can be reductively cleaved to the corresponding dilithio species, which can be trapped by electrophiles to make bicyclo[1.1.1]pentane derivatives (eq 17).[22]

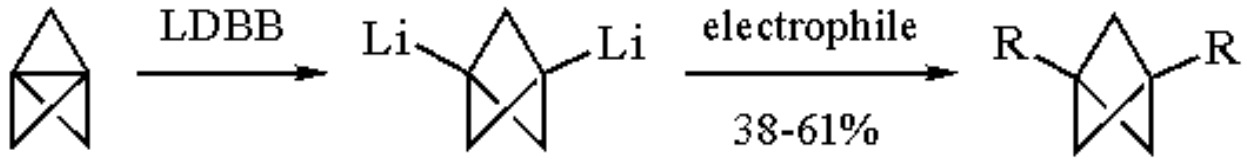

(17)

Carbonyl groups.

Aromatic ketones, benzylic alcohols, and ethers can be converted to the dilithio species with lithium and a catalytic

amount of DBB followed by trapping with electrophiles (eq 18).[23] The generation of aliphatic ketones in good yield from the corresponding esters proceeds with LDBB (eq 19), whereas sodium leads to high yields of the acyloin product.[24]

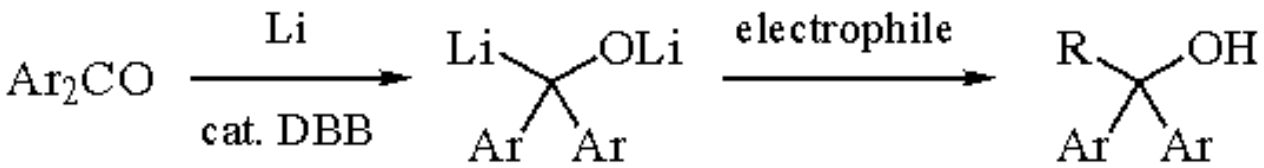

(18)

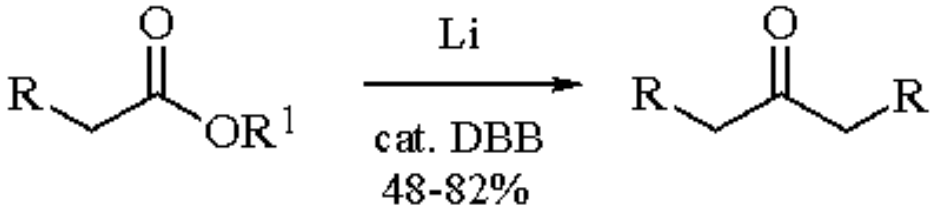

(19)

Phosphinates.

Reduction of diastereomerically pure menthyl phosphinate with LDBB followed by treatment with alkyl halides yields the phosphine oxides in good yield with high optical purity (eq 20).[25]

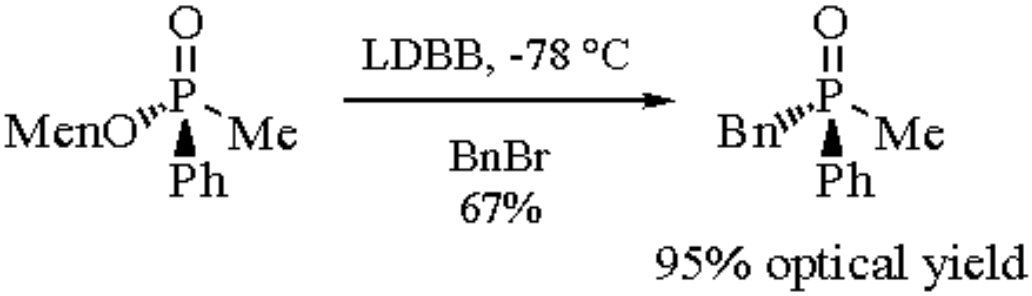

(20)

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Lithium 9,9-Dibutyl-9-borabicyclo[3.3.1]nonanate[1]

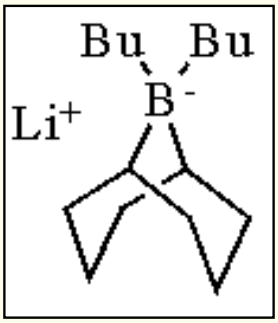

[56050-29-4] · $C_{16}H_{32}BLi$ · Lithium 9,9-Dibutyl-9-borabicyclo[3.3.1]nonanate · (MW 242.23)

(mild, selective reagent for the reduction of tertiary, allyl, and benzyl chlorides and bromides,[2] aldehydes and ketones,[3] and epoxides[4])

Physical Data: white gelatinous solid in hexane (reagent generated in situ).

Solubility: insol to sparingly sol hexane; sol MeOH, THF, benzene.[2-5]

Preparative Methods: a slurry of the reagent (**1**) is prepared by the dropwise addition of ***n-Butyllithium*** (14.4 mL of 1.39 M, 20.0 mmol) in hexane to *B*-Bu-9-BBN (3.76 g, 20.0 mmol) in hexane (25 mL) at 0 °C under a nitrogen atmosphere.[2]

Analysis of Reagent Purity: exhibits a single resonance in its ^{11}B NMR (THF) spectrum at δ -18.5 (s) ppm.[5]

Handling, Storage, and Precautions: the generation of (**1**) involves handling air-sensitive reagents which can be pyrophoric (i.e. BuLi, *B*-Bu-9-BBN) and consequently should be performed in a well ventilated hood. Individuals should thoroughly familiarize themselves with the special handling techniques required for such reagents prior to using (**1**).[1]

Selective Reduction of Halides.

Exhibiting unique behavior among organoborane-based reducing agents, (**1**) serves as an α-hydride source reducing allylic, benzylic, and tertiary halides to hydrocarbons with the accompanying rearrangement of the bicyclo[3.3.1]nonanate skeleton to *cis*-bicyclo[3.3.0]oct-1-yl(dibutyl)borane (**2**) (eqs 1, 2).[2-5] Although significantly more reactive than other common tetraalkylborates, the reagent fails to reduce primary, secondary, or aryl halides, a feature which can be utilized in selective reductions. These reductions, which are thought to involve carbocationic

rather than radical intermediates,[2b] are carried out in hexane, a medium in which (**1**) is only sparingly soluble.

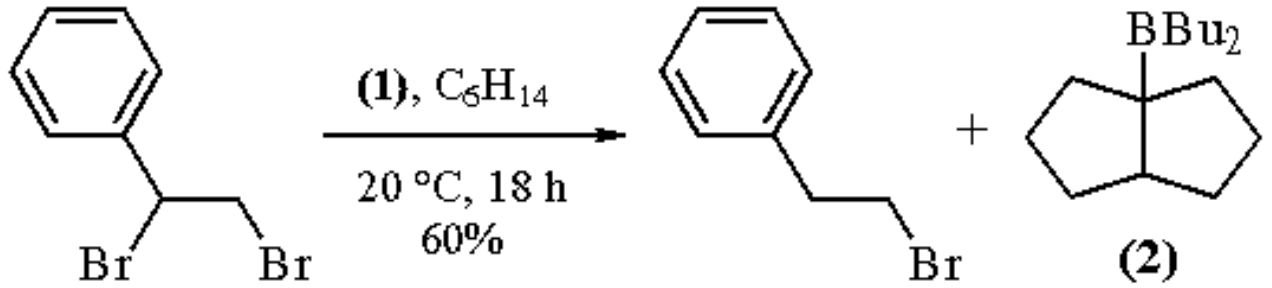

(1)

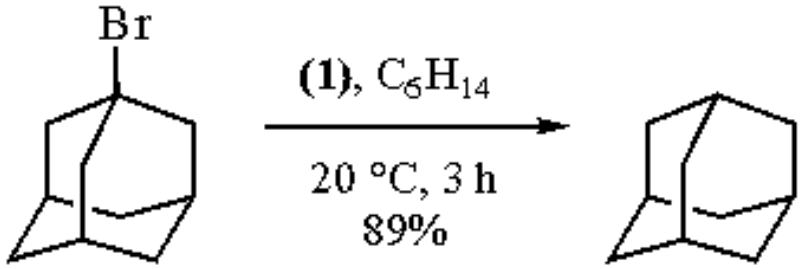

(2)

Selective Reduction of Carbonyl Compounds.[3]

In THF solution, the reduction of acetyl chloride occurs at low temperature to produce ethyl acetate and (**2**).[5a] The reagent reduces neither esters nor nitriles. While useful for the reduction of both aldehydes and ketones, the former are reduced selectively in admixtures. Moreover, methyl ketones are reduced faster than their straight or branched chain isomers, and also faster than aryl ketones (eqs 3-5).

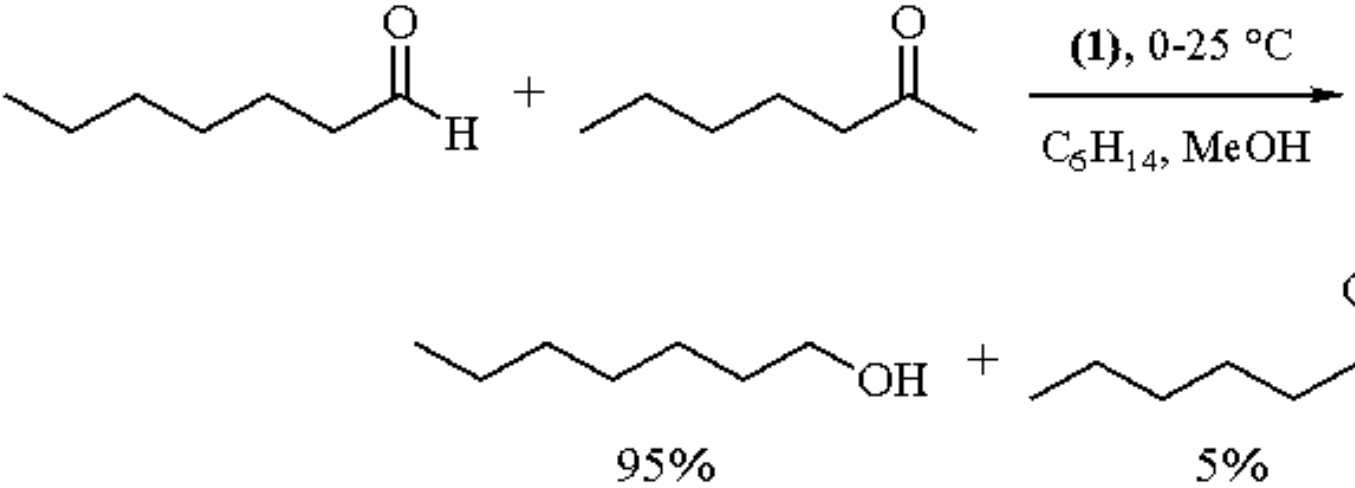

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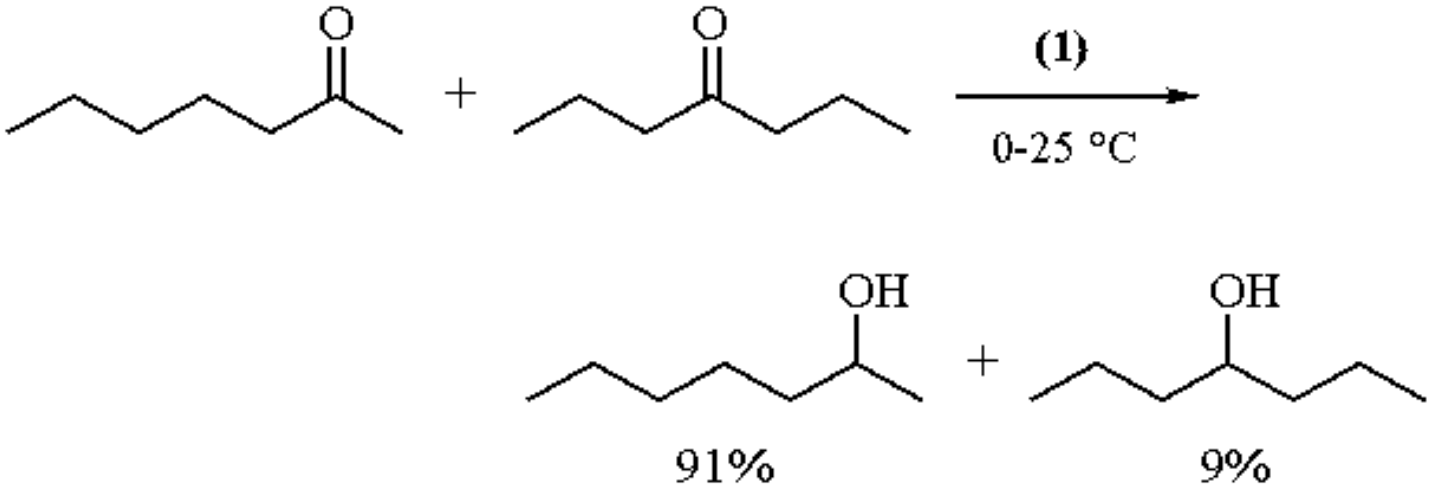

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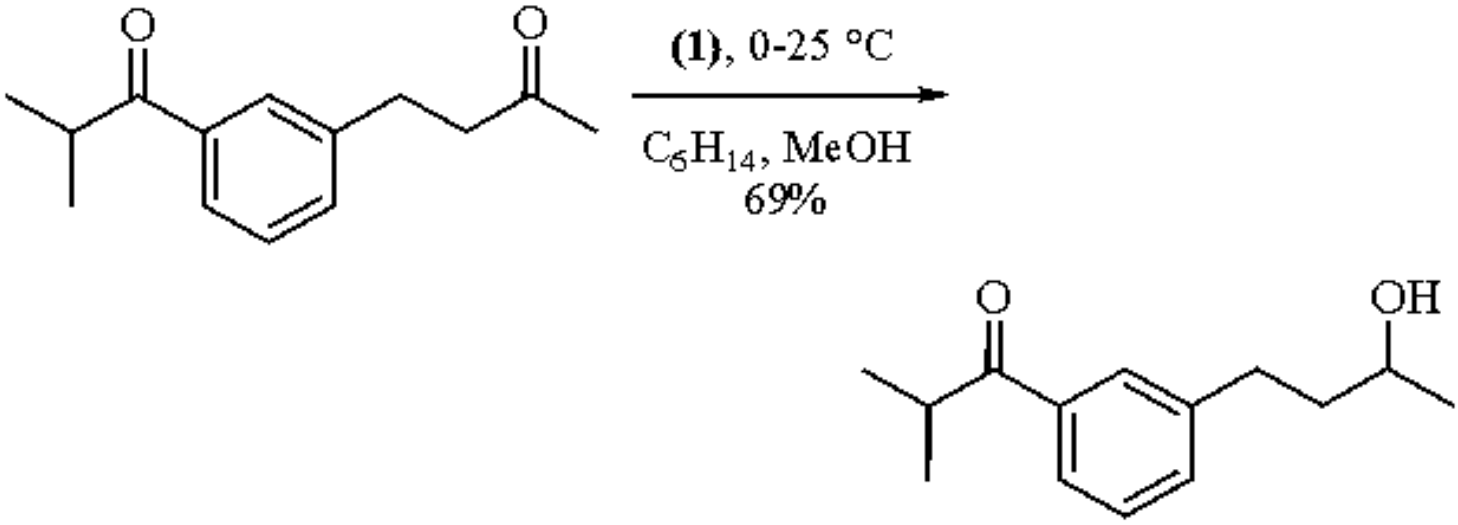

(5)

Cycloalkanones are reduced from their least hindered face to give *cis*-cyclohexanols, a process enhanced with added MeOH to suppress equilibration. However, with added lithium salts (i.e. LiOMe, LiBr) or excess ketone in the absence of MeOH, a Meerwein-Ponndorf-Verley type equilibration occurs to give the more thermodynamically favored isomer (eq 6). Methanol is thought to inhibit the formation of alkoxyborate complexes while lithium ions are believed to function as Lewis acids, making the carbonyl a better hydride acceptor.

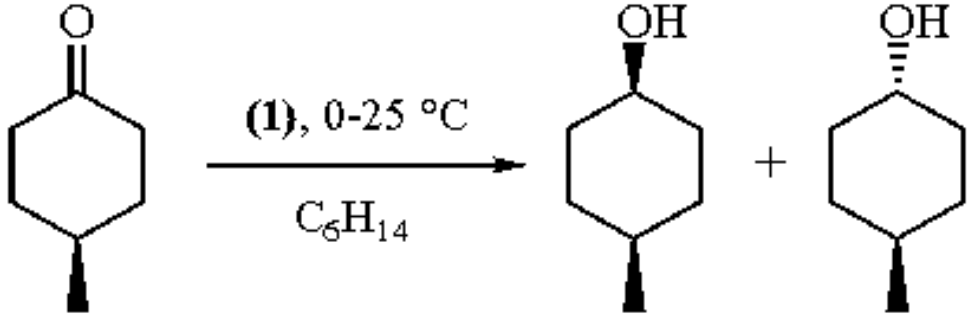

(6)

Additive		
none	47	53
MeOH	84	16
LiOMe	10	90

Selective Reduction of Epoxides.[4]

Unsymmetrical epoxides are reduced by (**1**) in a regioselective manner, the course of which is determined by the nature of the substituents. Aromatic derivatives give primary alcohols whereas aliphatic derivatives exhibit the opposite selectivity, suggesting that a steric basis for the regiochemistry is more important in these substrates (eq 7).

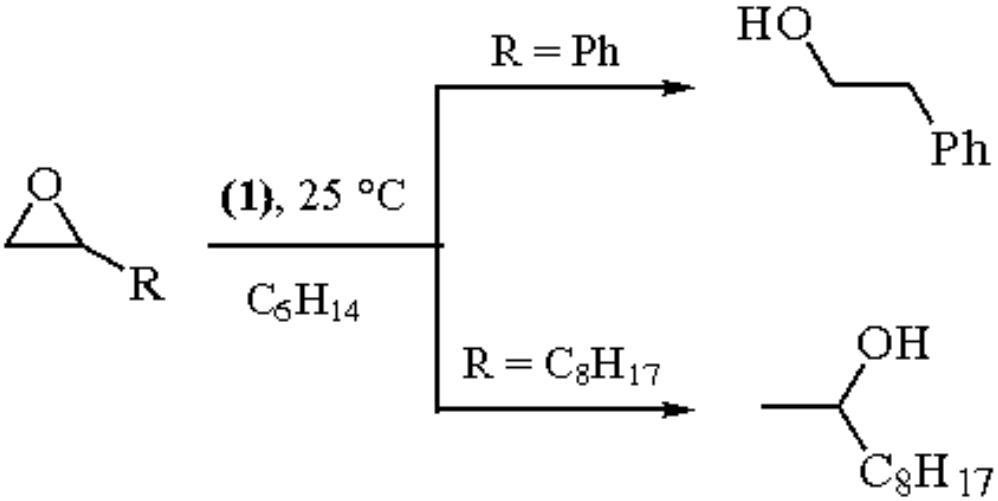

(7)

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Lithium Di-*n*-butylcuprate[1]

***n*-Bu_2CuLi**

[24406-16-4] · $C_8H_{18}CuLi$ · Lithium Di-*n*-butylcuprate · (MW 184.75)

(butylating reagent; undergoes conjugate addition reactions,[1a,b,e,f] 1,2-addition reactions,[1e,2] substitution reactions with alkyl, vinyl, aryl, and allylic substrates,[1a,c,e] reduction of carbon-heteroatom bonds,[3] oxidative dimerization,[4a] and oxidative coupling with amines[4b])

Physical Data: ^1H NMR (Et_2O) δ -6.99 to -7.14 ppm (t, *J* = 7.0 Hz, 2 H, -60 to +20 °C); (C_5H_{12}) δ -7.29 to -7.32 ppm (-50 to +35 °C).[5]

Solubility: sol THF, Et_2O.

Preparative Methods: prepared in situ from Cu^I salts under N_2 or argon atmosphere.[1a] Rate of cuprate formation is temperature- and Cu^I salt-dependent; reagent prepared from Cu^I halides may contain free BuLi.[6a] Dark-colored solutions are indicative of decomposition (see ***Lithium Dimethylcuprate*** for purification of CuI and CuBr). Colorless solutions of Bu_2CuLi can be prepared from BuCu obtained by low-temperature centrifugation.[1b] Polymer-bound *n*-Bu_2CuLi can be prepared.[7]

Handling, Storage, and Precautions: stable in solution for several hours below 0 °C (10% decomposition at 0 °C for 30 min)[6b] and is very sensitive to O_2. Use in a fume hood.

Addition Reactions.

Reaction of Bu_2CuLi with α,β-alkenyl ketones (eq 1),[1,8] aldehydes,[9] esters,[1] lactones,[1] sulfoxides,[10a] sulfones,[10b] sulfoximines,[10c] *N*-tosylamides,[11a] nitriles,[11b] *N*-nitroso[11c] and nitro[11d] compounds, phosphonates,[12a] phosphine oxides,[12b] phosphinates,[1a] and phosphonium salts (eq 2)[12c] results in conjugate addition of the butyl ligand; ligand transfer can be facilitated by bis-activation[1,13] of the alkene (e.g. alkylidene malonates). Bis-activated cyclopropanes[1d] afford products of homoconjugate addition, and dienyl systems[14,15] generally yield 1,6-addition products. Byproducts consistent with an equilibrium presence of *n*-BuLi[6a] are sometimes observed.[15] The reagent is compatible with transition metal carbonyls (eq 1)[8] and nitroalkanes[16] under appropriate conditions.

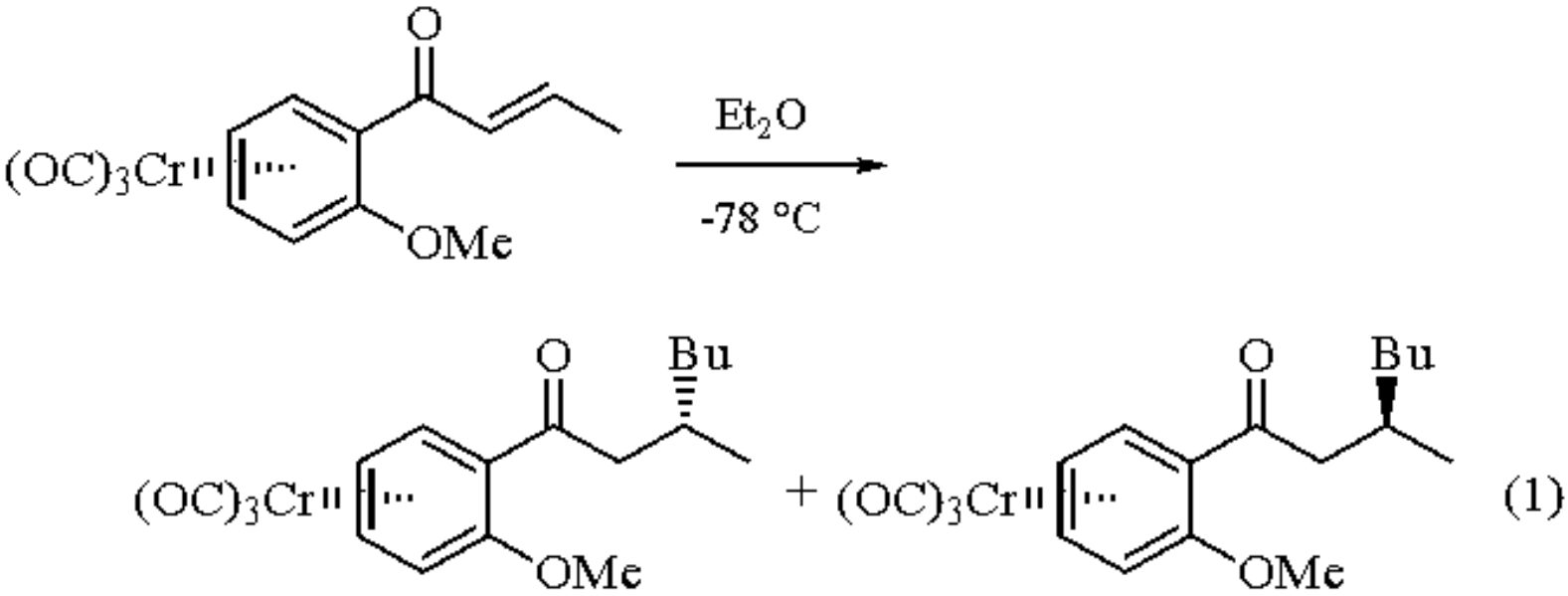

Bu_2CuLi	98%	76:24
$Bu_2CuCNLi_2$	98%	80:20
$BuCu \cdot BF_3$	96%	8:92

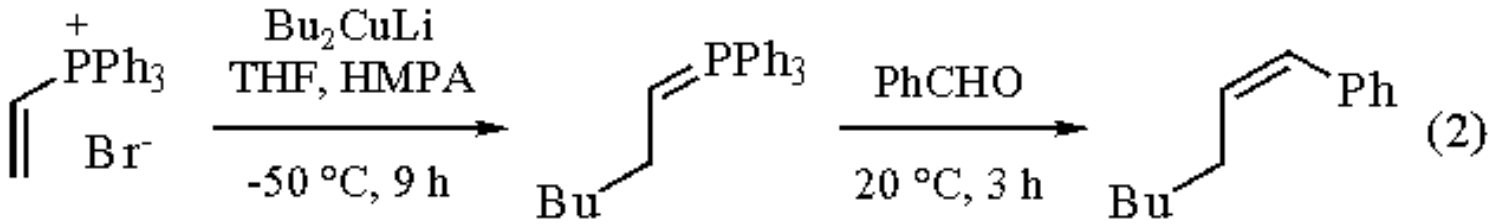

80%
$(E):(Z) = 3:97$

Exploitation of the anion resulting from conjugate addition[17] provides for powerful synthetic opportunities (eq 2).[12c] β-Nucleofuge-substituted α,β-unsaturated systems undergo substitution with varying degrees of stereoselectivity (eq 3).[18] Procedures for achieving absolute asymmetric conjugate addition of Bu_2CuLi are available.[19]

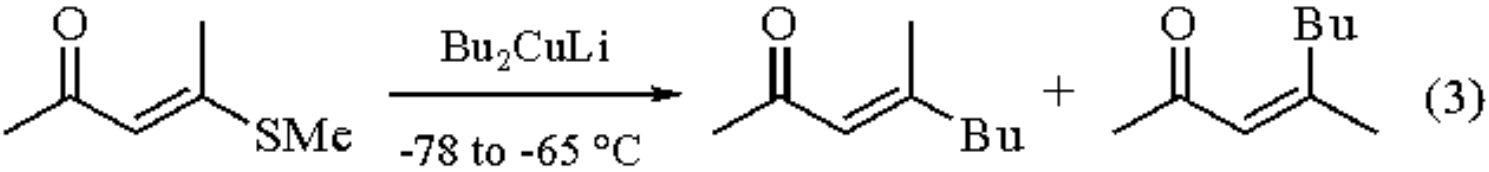

THF, DMS	93%	97:3
Et_2O	97%	5:95

Although Bu_2CuLi effects carbocupration of alkynes more readily than Me_2CuLi, copper-catalyzed Grignard additions are more efficient and widely employed.[1a]

Addition of ***Chlorotrimethylsilane*** facilitates 1,2-addition of Bu_2CuLi to ketones[2] and to aldehydes with increased Cram selectivity,[2,20a] while addition of crown ethers favors formation of anti-Cram[20b] products. 1,2-Addition of Bu_2CuLi to *N*-silylformamides affords imines.[20c]

Substitution Reactions.

Bu_2CuLi participates in substitution reactions with alkyl (e.g. halides (eq 4),[21] carboxylates, sulfonate esters) and alkenyl substrates (e.g. enol triflates and phosphates); the reaction is very general.[1a,c] Substitution reactions occur with β-lactones[22] and often proceed with good regio- and stereocontrol with oxiranes[1] (eq 5)[23] and tosylated aziridines.[24] Acylation of Bu_2CuLi with thiol esters provides a good route to ketones.[25]

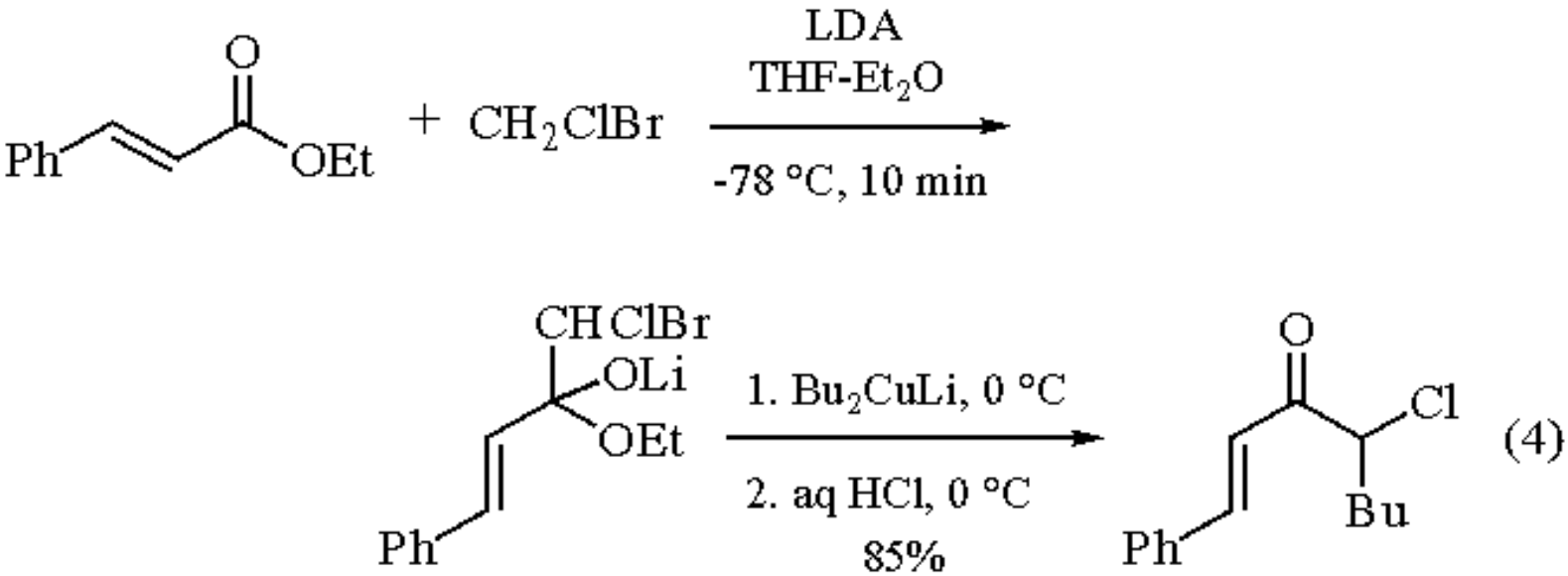

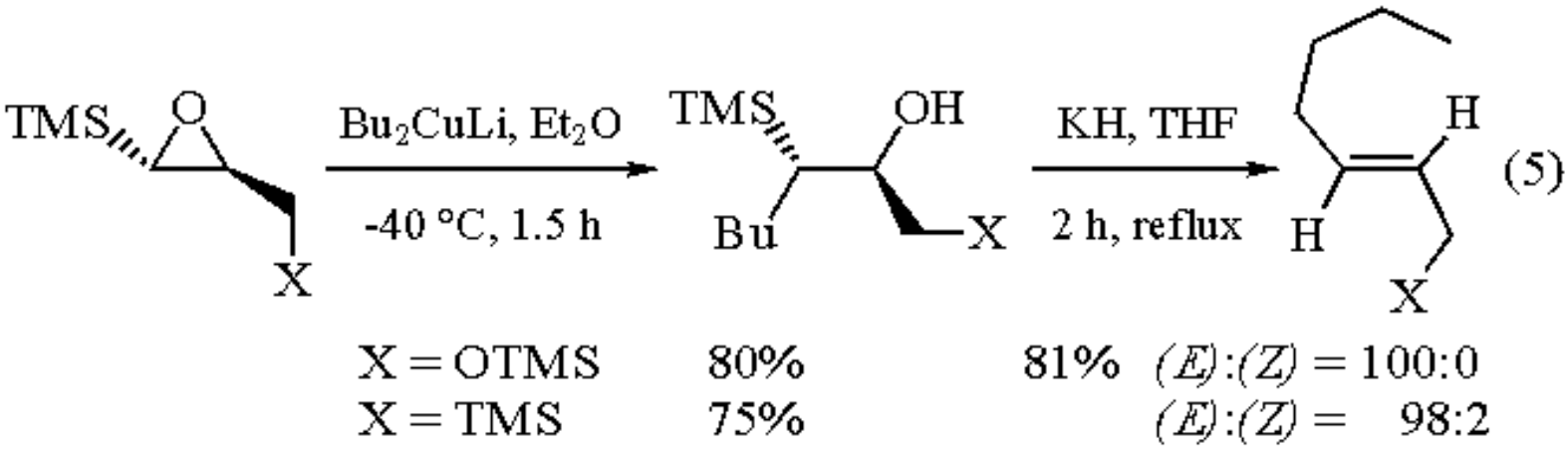

Although the preference of allylic substrates (e.g. halides, sulfonimides, carboxylates, oxiranes, sulfones, carbamates, and nitro compounds[26]) for *anti*-S_N2' pathways is synthetically useful, steric effects, leaving groups, and substrate structure can alter regiochemistry and stereochemical integrity can be lost by isomerization pathways.[27] Propargyl substrates generally give substitution with rearrangement (eq 6).[28]

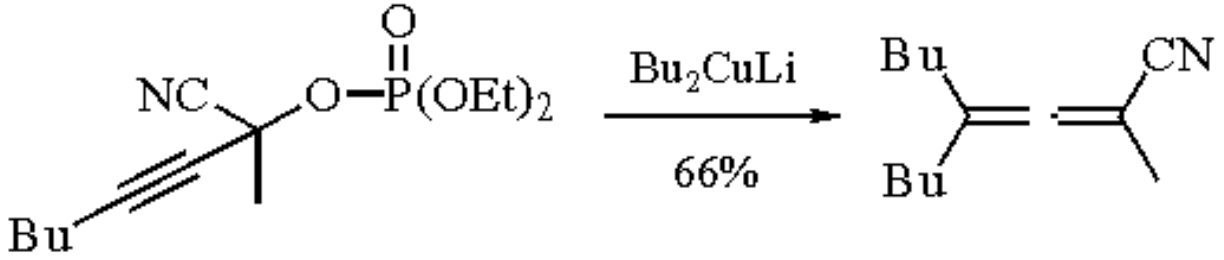

(6)

Miscellaneous Reactions.

Bu_2CuLi will reduce a variety of carbon-heteroatom bonds, and the reaction can be exploited synthetically.[1a,d] Reduction of cyclopropyl halides gives an intermediate copper species that can be alkylated or acylated (eq 7)[3] with some stereocontrol. Oxidative dimerization[4a] of Bu_2CuLi affords octane; an oxidative coupling reaction can be used to prepare butylated amines (eq 8).[4b]

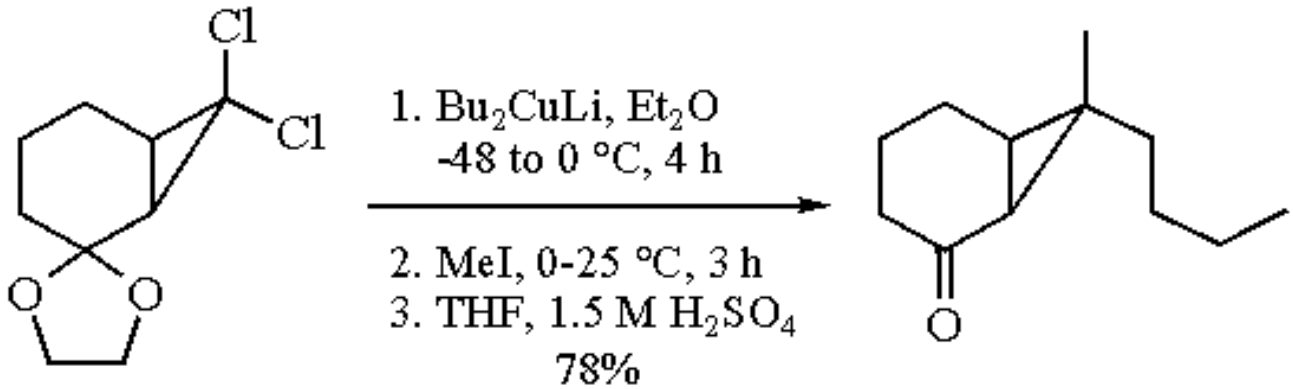

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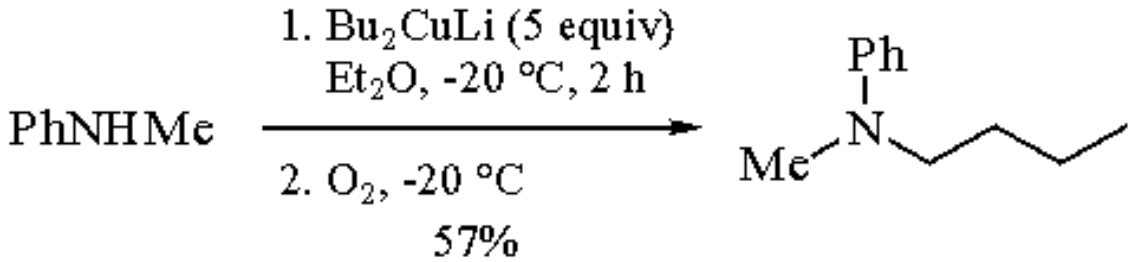

(8)

Related Reagents.

Lithium Diethylcuprate; ***Lithium Dimethylcuprate***; ***Lithium Diphenylcuprate***; ***Lithium Di-n-propylcuprate***.

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1. (a) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (b) Posner, G. H. *OR* **1972**, *19*, 1. (c) Posner, G. H. *OR* **1975**, *22*, 253. (d) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980. (e) Faust, J.; Froböse, R. In *Gmelin Handbook of Inorganic Chemistry*; Springer: Berlin, 1983; Copper, Part 2. (f) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
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Lithium Di-*t*-butylcuprate[1]

***t*-Bu_2CuLi**

[23402-75-7] · $C_8H_{18}CuLi$ · Lithium Di-*t*-butylcuprate · (MW 184.75)

(*t*-butylating reagent which undergoes conjugate addition reactions,[1,2] 1,2-addition reactions,[3] substitution reactions,[2b,4,5] carbocupration of alkynes,[6] and oxidation reactions[7])

Physical Data: dark red-brown to black solution; decomposes at 25 °C.[1b]

Solubility: sol Et_2O, THF, pentane-Et_2O-Me_2S (1:1:1).

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***,[1b,5] ***Copper(I) Bromide***[1b]) and complexes ($CuBr.SMe_2$[8a] and ***Copper(I) Iodide-Tributylphosphine***[7a]) under an inert atmosphere of N_2 or argon in Et_2O or THF. Polymer-supported *t*-Bu_2CuLi can be prepared.[9] Preparation, stability and reactivity of organolithium- and organomagnesium-derived cuprate reagents and mixed hetero-*t*-butylcuprate reagents have been noted.[1,4c,10,11] See ***Lithium Dimethylcuprate*** for purification of Cu^I salts.

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Introduction.

Lithium di-*t*-butylcuprate displays the typical reactivity patterns of lithium diorganocuprates (see, e.g. ***Lithium Di-n-butylcuprate***, ***Lithium Diethylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***, ***Lithium Di-n-propylcuprate***).

Addition Reactions.

t-Bu_2CuLi reacts with α,β-alkenyl ketones[1,2,9] (mechanistic studies[8]), chiral esters[12] (in the presence of ***Chlorotrimethylsilane***) (eq 1), sulfoxides,[13] *N*-tosyl-1-azoalkenes,[14] ketoketenimines,[15] and vinylphosphonium salts[16] with conjugate transfer of the *t*-butyl ligand. Stereoselective *cis* addition can be achieved in the reaction of *t*-Bu_2CuLi with α,β-alkynyl sulfones.[17] Reaction of α,β-alkynyl trifluoromethyl ketones[18] with *t*-Bu_2CuLi affords mixtures of 1,2- and 1,4-addition products with modest regiocontrol; regioselective control can be obtained with the cyanocuprate reagent. Systems with extended conjugation, such as 3-alkynyl-2-cycloalkenones, undergo 1,6-addition.[19]

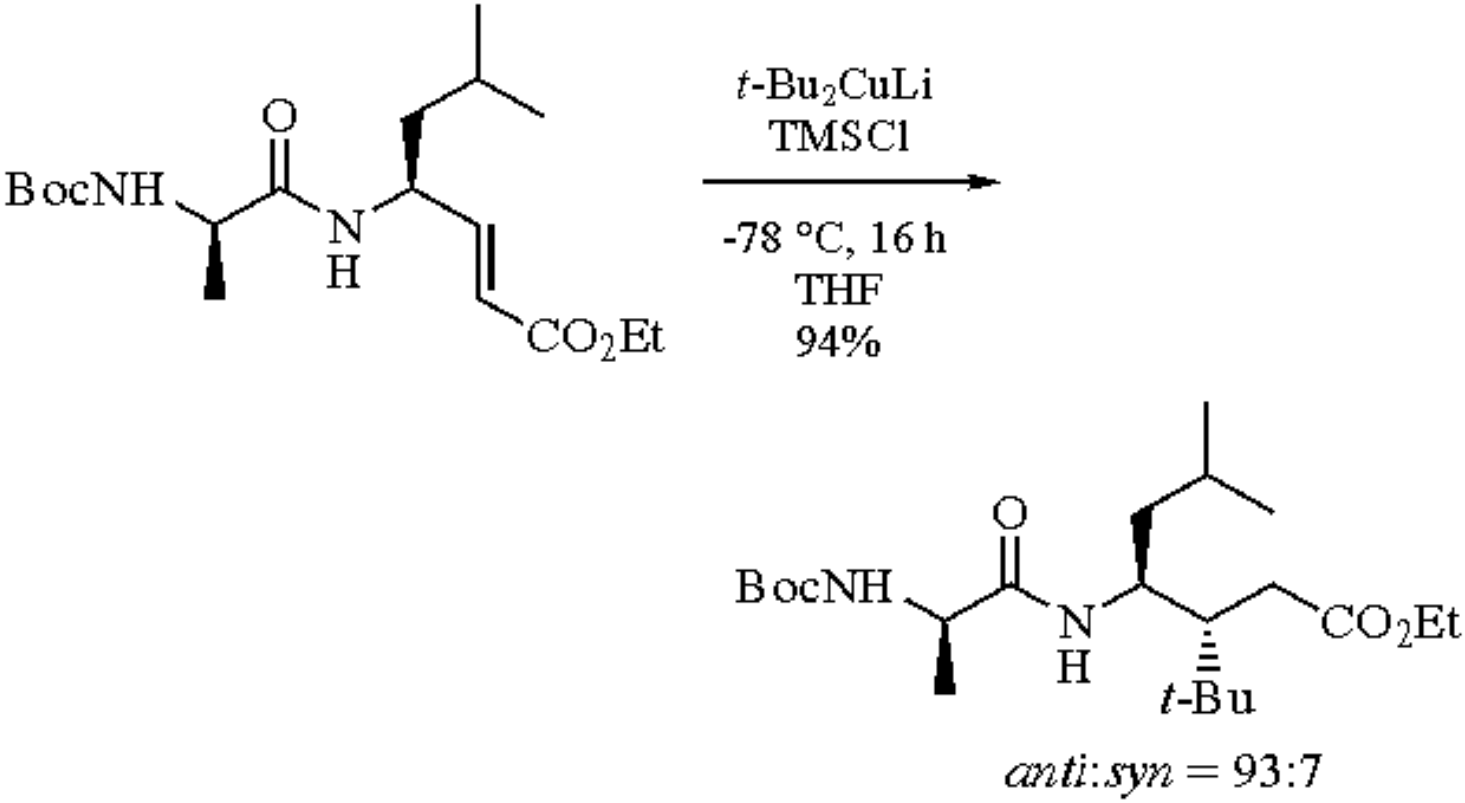

(1)

1,2-Addition of *t*-Bu_2CuLi to a chiral γ-alkoxy-α,β-enal[3] occurs with vinylogous Cram stereoselectivity in the presence of ***t-Butyldimethylchlorosilane***. Alkylated 3,4-dihydro-β-carbolines[20] can be synthesized by 1,2-addition of *t*-Bu_2CuLi to BF_3 iminium salts.

Substitution Reactions.

t-Bu_2CuLi effects substitution reactions with alkyl halides,[2b,4,9] α-halo ketones,[4b,21] alkyl tosylates,[2b,4c,5,9] acetates,[22] arene sulfonyl fluorides,[23] and alkenyl substrates (e.g. vinyl triflates[24] in the presence of ***Boron Trifluoride Etherate*** and enol phosphates[25]). Simple[26a] and alkenyl oxiranes[11,26b-d] undergo substitution reactions (eq 2); however, reactions of oxiranes with *t*-Bu_2CuLi can be complicated by the formation of reduction products[11] and mixtures of S_N2- and S_N2'-type products.[26c,d]

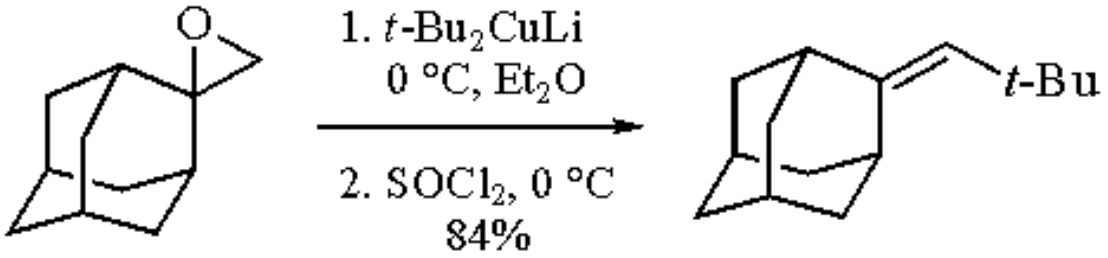

(2)

Chiral α,β-alkenyl oxazolidines[27] undergo allylic substitution reactions with *t*-Bu_2CuLi. β´-Aminocyclopentenyl sulfones[28] participate in stereoselective *syn*-S_N2' substitution with *t*-Bu_2CuLi in modest yield (eq 3). Acyl halides[4b] and *S*-2-pyridyl thioates[7c] participate in nucleophilic acyl substitution reactions with *t*-Bu_2CuLi to give ketones.

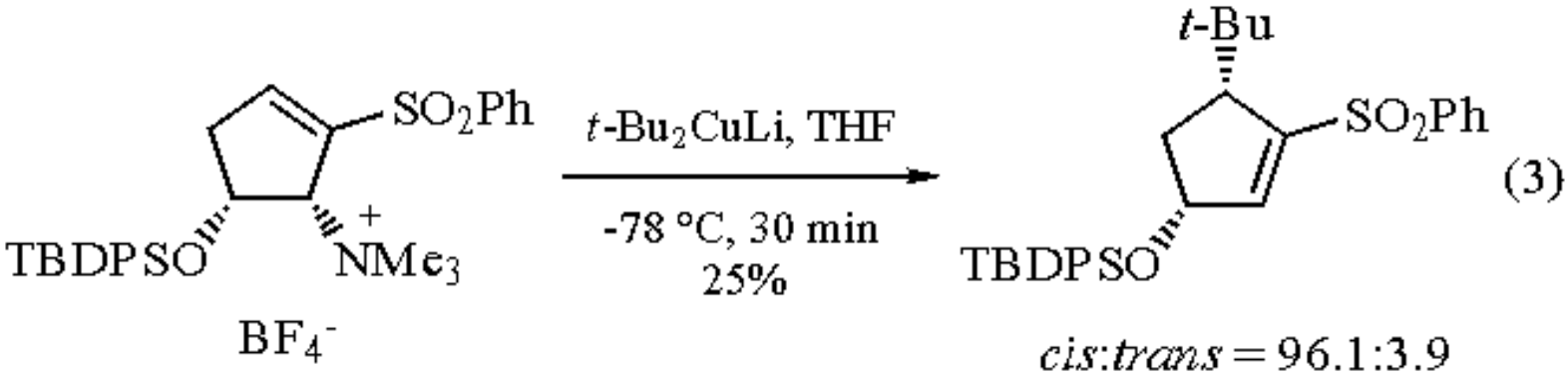

Carbocupration.

Acetylene undergoes a stereoselective *syn* carbocupration[6] with *t*-Bu_2CuLi and can be manipulated further in subsequent additions to α,β-alkenyl sulfones[29] with retention of double bond configuration.

Oxidation Reactions.

Oxidative dimerization of *t*-Bu_2CuLi proceeds poorly.[7a] Oxidative coupling of amines[7b] with *t*-Bu_2CuLi affords *t*-butylated amines. Reaction of *t*-Bu_2CuLi with *S*-2-pyridyl thioates[7c] in the presence of O_2 gives esters.

Miscellaneous Reactions.

Reduction of 1,3-thiazole-5(4*H*)-thiones by electron transfer pathways can occur with *t*-Bu_2CuLi.[30] A vinylic bromide[31] undergoes reduction-elimination reactions with *t*-Bu_2CuLi. *t*-Bu_2CuLi reduces *gem*-dihalocyclopropyl[32] derivatives to give an intermediate copper species that can be alkylated. o-Halo-1-phenylalkynes[33] are reduced by *t*-Bu_2CuLi, affording an organocopper intermediate that can undergo intramolecular carbocupration (eq 4).

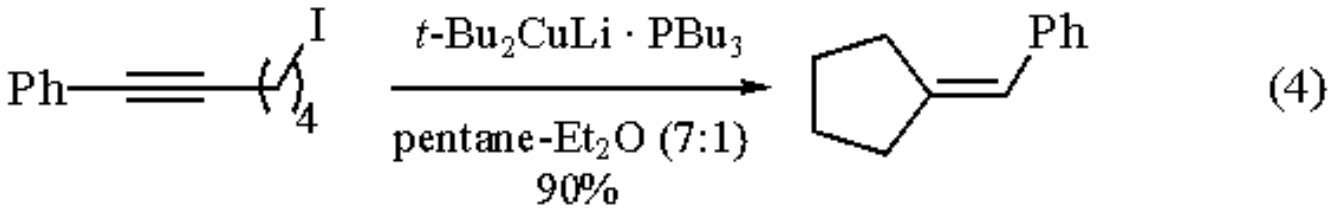

Related Reagents.

Copper(I) Iodide-Tributylphosphine; ***Lithium t-Butoxy(t-butyl)cuprate***.

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Lithium Dicyclohexylamide

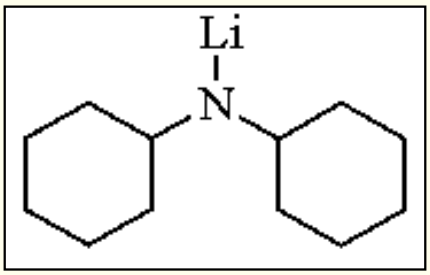

[4111-55-1] · $C_{12}H_{22}LiN$ · Lithium Dicyclohexylamide · (MW 187.29)

(performs as a strong base, allowing deprotonation of ketones,[1] esters,[2] aryl[3] and allyl[4,5] halides, alkyl dihalides,[6] allenes,[7] alkylboron reagents,[8] azulene and methylazulenes;[9] used for the formation of formamides, glyoxylamides, oxomalonamides, and tartronamides[10])

Physical Data: IR (solution/suspension in benzene, 3000-2400 cm^{-1}): 2916s, 2880s, 2850s, 2831s, 2757m, 2620w, 2572w; 635s and 270s also reported.[11]

Solubility: partially sol benzene, hexanes; sol THF.

Preparative Methods: from the reaction of dicyclohexylamine with ***n-Butyllithium*** in hexanes and benzene at 0 °C; solvent can then be removed under reduced pressure and the resulting free flowing solid dissolved in THF.[12]

Handling, Storage, and Precautions: both solution and solid are pyrophoric and air- and moisture-sensitive; also the solid is spontaneously flammable in air. The reagent is corrosive and extremely destructive to tissues of the mucous membranes and the upper respiratory tract, eyes, and skin. Note that dicyclohexylamine is a suspected carcinogen and may cause chemical pneumonitis and pulmonary edema.[13] Use in a fume hood.

Introduction.

The title reagent (Cy_2NLi) has generally been used as a base in the formation of organolithium substrates in a similar way to ***Lithium Diisopropylamide*** and related lithium amides. It is reported, however, to be a stronger base than LDA, ***Lithium Diethylamide***, and lithium isopropylcyclohexylamide (LiN(*i*-Pr)Cy).[14] Also the conjugate acid (Cy_2NH) has been shown to be a weaker acid than diisopropylamine, isopropylcyclohexylamine, and diethylamine.[14]

As a general note, a number of different methods for the removal of the dicyclohexylamine byproduct have been developed because of the formation of a precipitate with HCl workups. Use of HCl will cause the formation of a precipitate, which has been removed by filtration and the filtrate then subjected to standard workup.[9] Citric acid[1,3] and ammonium chloride[4] have been used without any problems of precipitation (the former used specifically to prevent this problem). In one case, the amine has been removed by distillation. Both MeI and $BF_3.Et_2O$ have been used to precipitate the amine followed by

filtration and subsequent standard workup of the filtrate.[5]

Deprotonation of Carbonyl Compounds.

In the formation of β-keto esters from unsaturated ketones, Cy_2NLi was found to give better results than the other bases examined (LDA, ***Sodium Hydride***, ***Potassium t-Butoxide***) (eqs 1 and 2).[1] It was reported that Cy_2NLi overcomes the problems of substrate self-condensation side-products and nucleophilic attack of base on diethyl carbonate. It has also been used in condensation reactions between ethyl 2-(trimethylsilyl)acetate and a number of ketones (eq 3).[2]

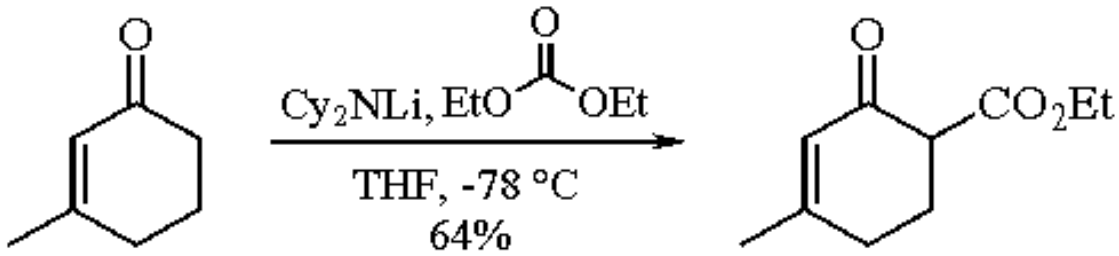

(1)

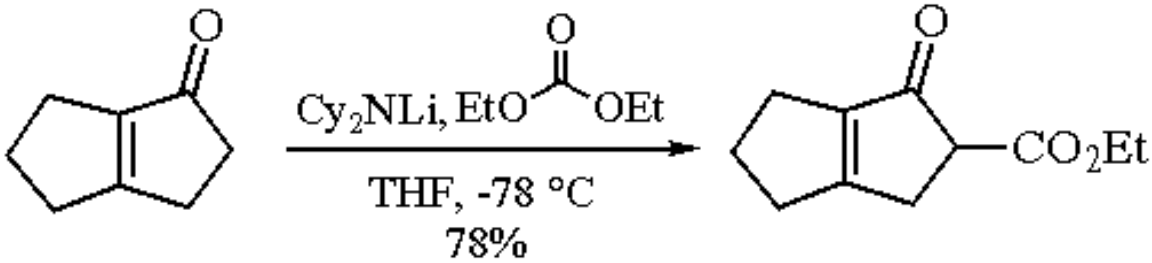

(2)

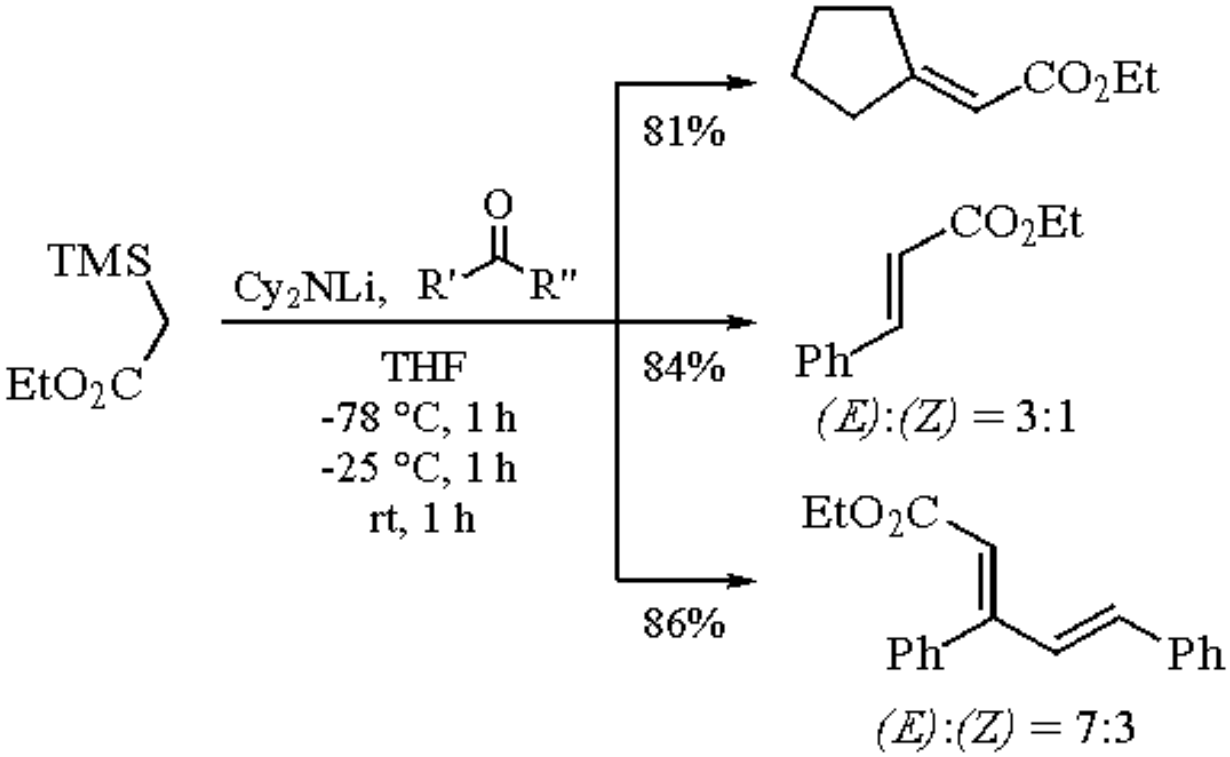

(3)

Deprotonation of Allenes.

Normally the deprotonation of alkoxyallenes leads to α-lithiation;[15] however, in conjunction with bulky alkoxy groups on alkoxyallenes, the steric size of Cy_2NLi has been used to give selective γ-deprotonation of alkoxyallenes (eq 4).[7]

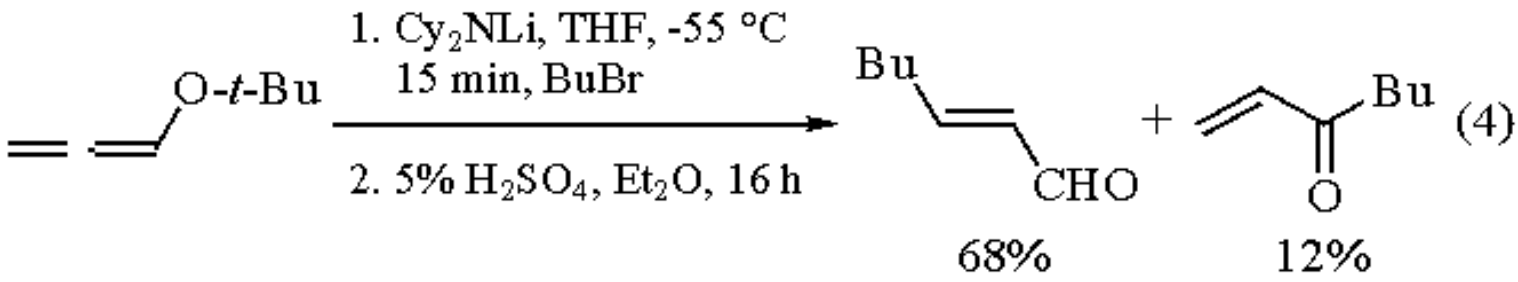

Deprotonation of Alkyl Halides.

In studies of the deprotonation of mono- and dihaloalkyl and -aryl compounds, the choice of base has been found to be crucial for the deprotonation of substrates that contain sites more reactive towards nucleophilic attack (eq 5).[6] In one example, the dihalomethylhydroxy product of the condensation of dihalolithiomethane with a carbonyl has been used to obtain the ring expanded ketone (eq 6).[16]

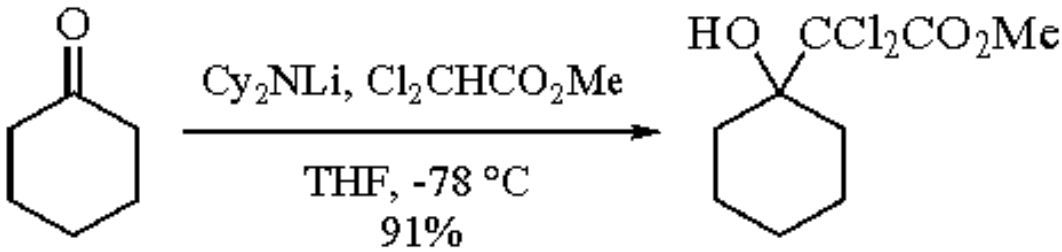

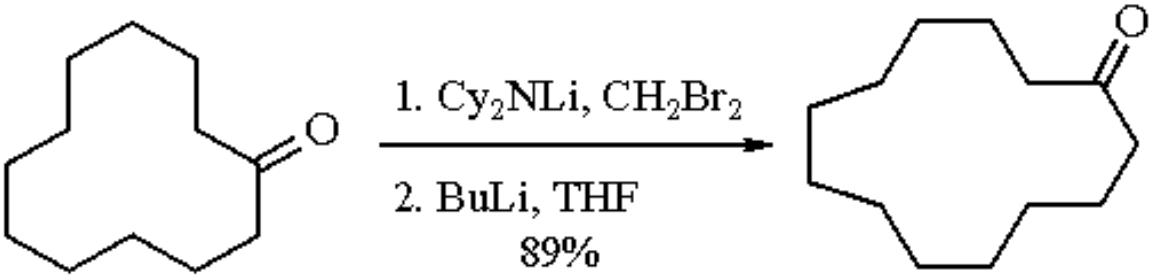

For the formation of carbenes via deprotonation of aryl halides (eq 7), a number of bases have been investigated including Cy_2NLi.[3] These studies also looked at the formation of benzyne intermediates from *o*-chloroanisole (eq 8).

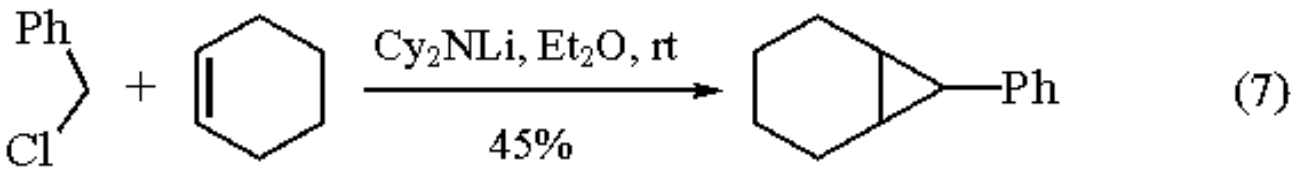

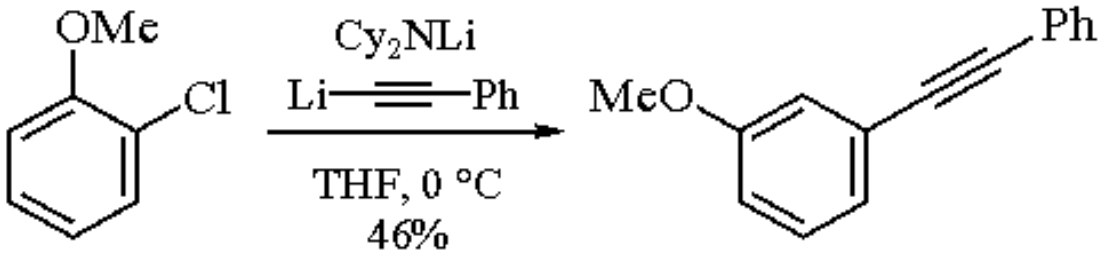

(8)

While Cy_2NLi was found to give consistently better results than LDA, LiN(*i*-Pr)Cy, and $LiNEt_2$, ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LiTMP) was reported to be the best reagent for these processes.

Deprotonation of allyl chlorides with Cy_2NLi gives a lithiated carbenoid intermediate which has been silylated to give an allyl halosilane, which can subsequently be used in reactions with carbonyl and acetal substrates (eq 9).[4] Allylsilanes can be used in a number of synthetically useful transformations.[17]

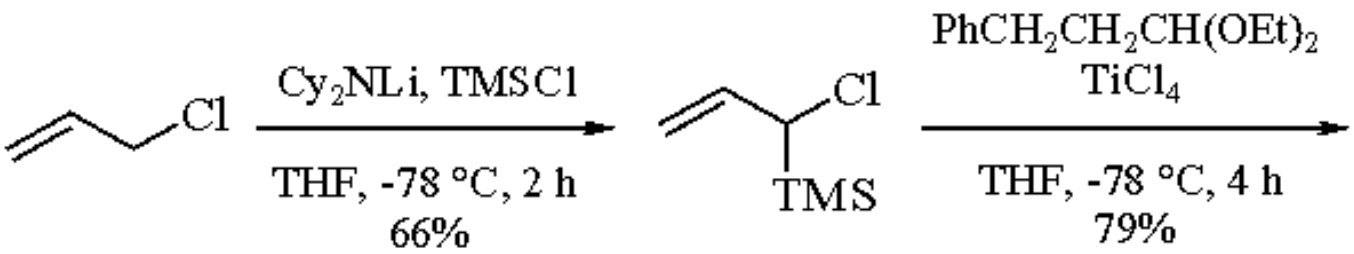

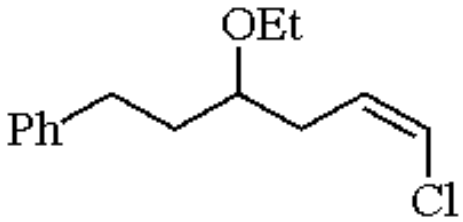

(9)

$(Z):(E) = 10:1$

More recently the carbenoid intermediate, prepared from allyl chloride and Cy_2NLi, has been reacted with 9-methoxy-9BBN to give the homologous boron product (**1**) (eq 10). This can in turn undergo a number of transformations to give cyclooctane derivatives (eqs 11-13).[5]

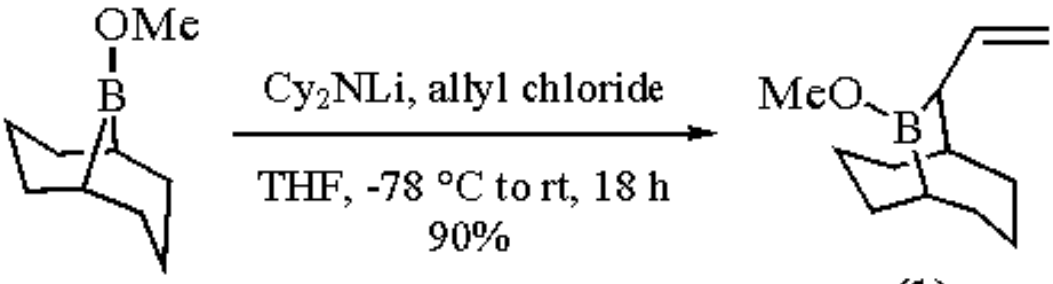

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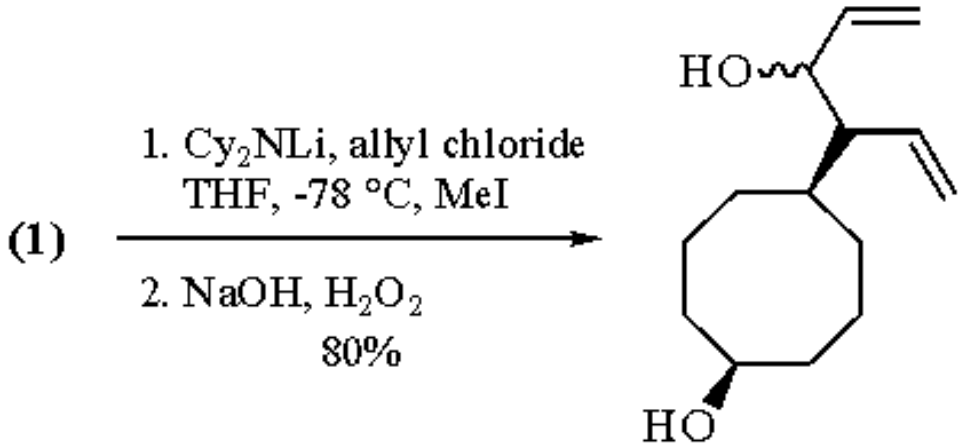

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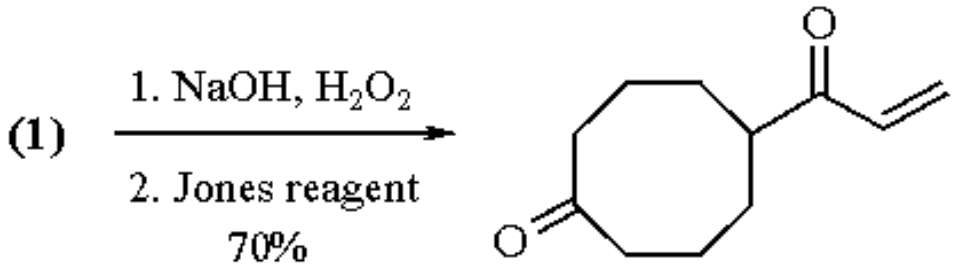

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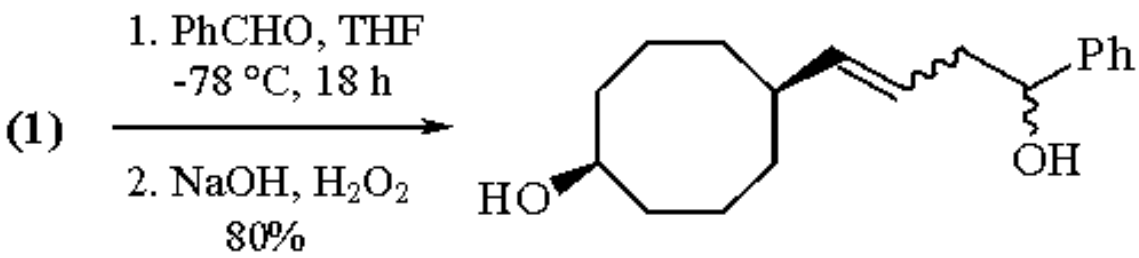

(13)

In these transformations, Cy_2NLi was the reagent of choice as other bases ($LiNEt_2$, ***Lithium Pyrrolidide***, $LiN(t\text{-}Bu)SiMe_3$) gave reduced yields due to the problems of nucleophilic displacement of the methoxy group from the boron atom.

Deprotonation of Alkyl Boron Compounds.

Lithium dicyclohexylamide has been used in the formation of α-boron anion intermediates, the reactions of which have been extensively studied (eqs 14-17).[8,12] In the coupling of the α-boron anion with metal compounds, a number of reagents and metals have been used, with $HgCl_2$ giving the lowest yields.

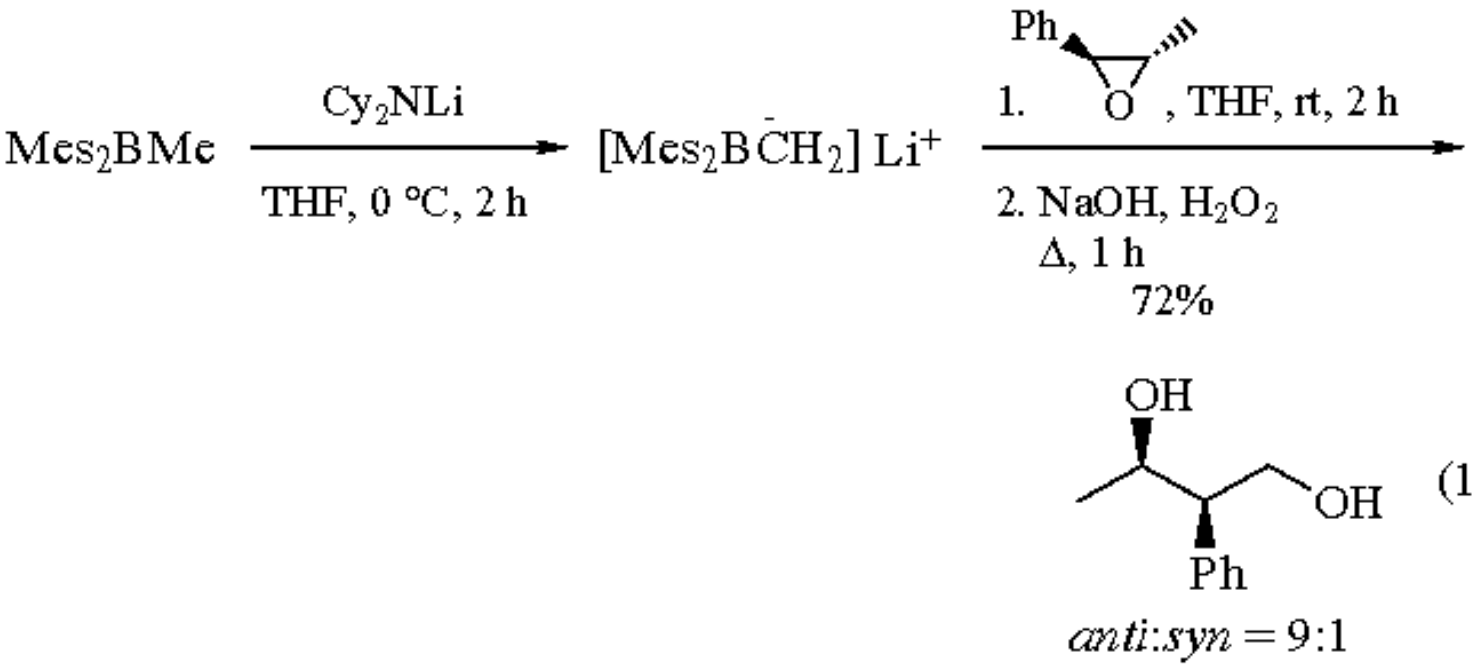

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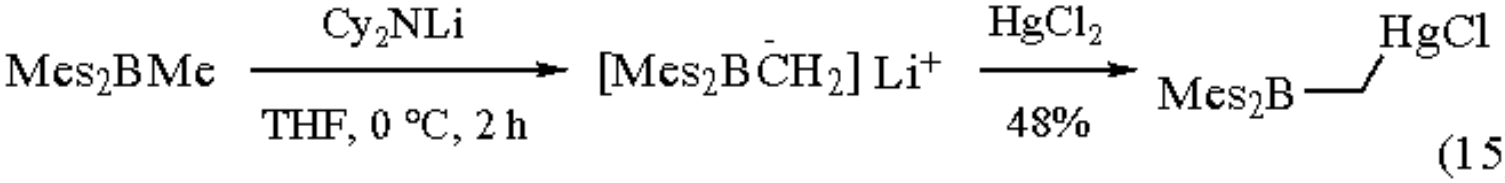

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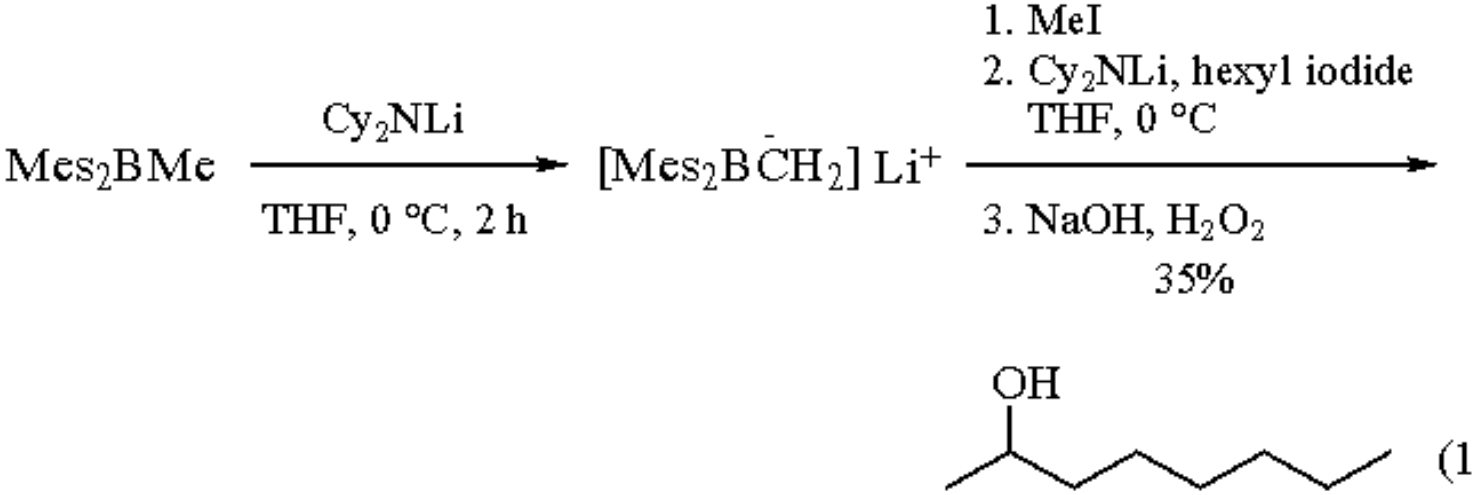

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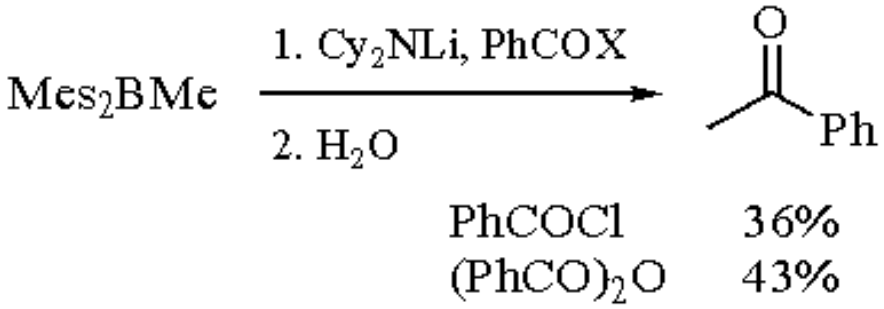

(17)

In these studies, good yields were obtained with Cy_2NLi, although ***Mesityllithium*** gave more consistent results. LiTMP has

also been used in studies in this area.[18]

Miscellaneous.

Extensive studies of the reaction of lithium amides with carbon monoxide at atmospheric pressure have led to the formation of formamides (**2**), glyoxylamides (**3**), tetraalkylureas (**4**), tartronamides (**5**) and oxomalonamides (**6**) with good selectivity depending on the conditions of the reaction and workup (eq 18) (Table 1).[10,14]

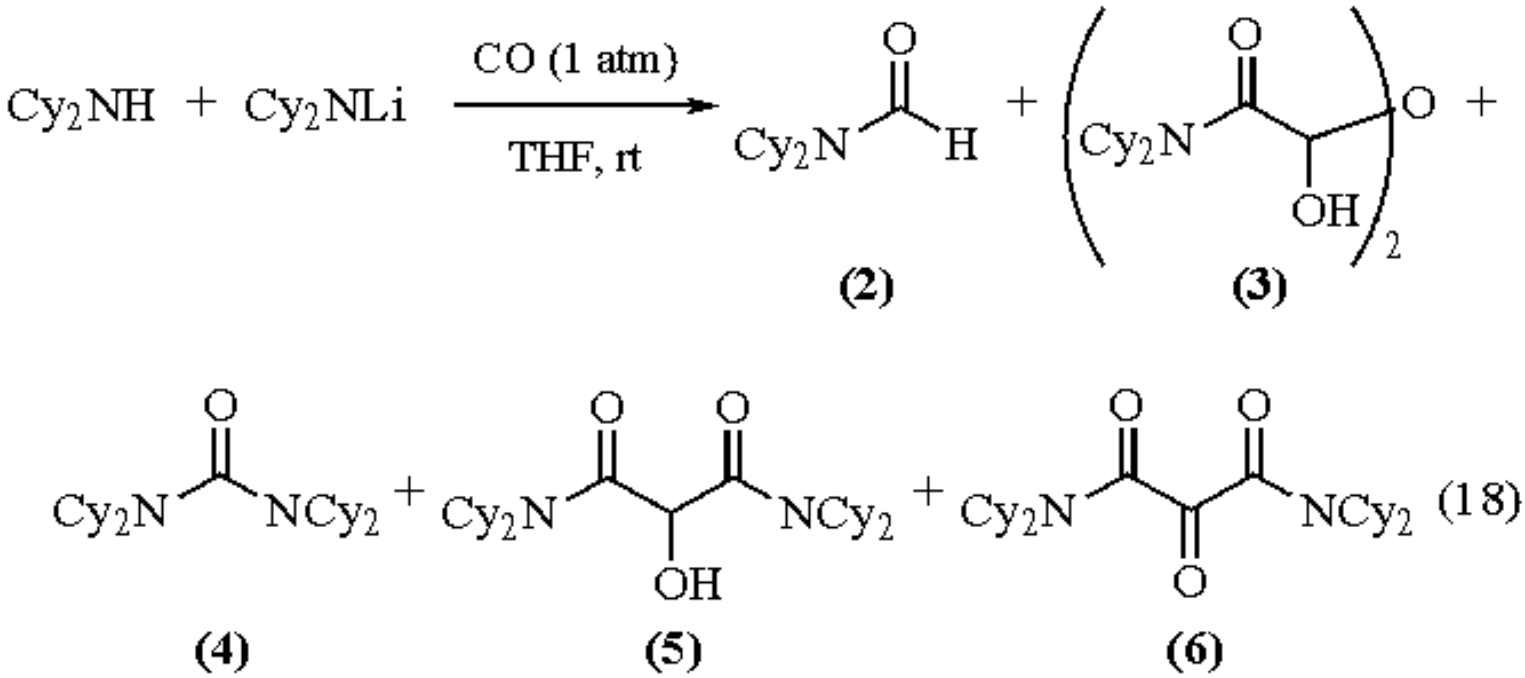

Table 1 Conditions and Yields for Reaction with CO

Ratio NLi:NH	Product (2)	(3)	(4)	(5)	(6)
5:4[a]	91	8		1	
5:1[a]		10		90	
5:4[b]		3	66		31
5:1[b]		4			96

[a] LiBr cat.; H_2O workup. [b] LiBr cat.; O_2, $NaHCO_3$, H_2O workup.

One example of the use of Cy_2NLi in studies with nonbenzenoid aromatic compounds has been reported. These results examined the deprotonation and carbonylation of a variety of azulenes (eqs 19 and 20). Good yields of the monocarboxy

products were obtained, although the di- and triesters were also formed with azulene.[9]

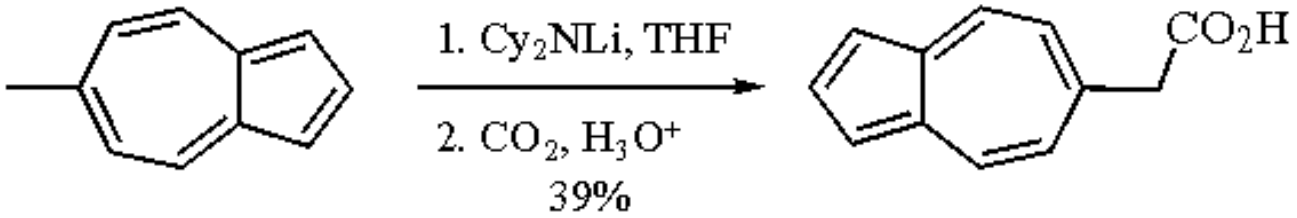

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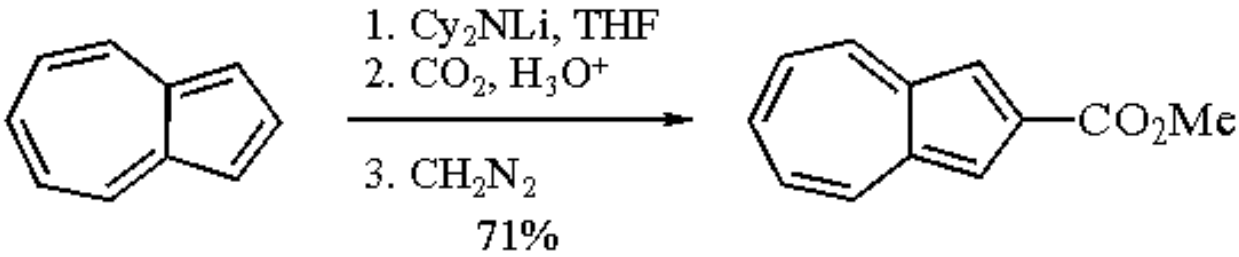

(20)

One example of the use of Cy_2NLi for dehydrochlorination has also been reported, giving the selective formation of *trans*-cyclodecene (eq 21) (cf. *t*-BuOK, eq 22).[19]

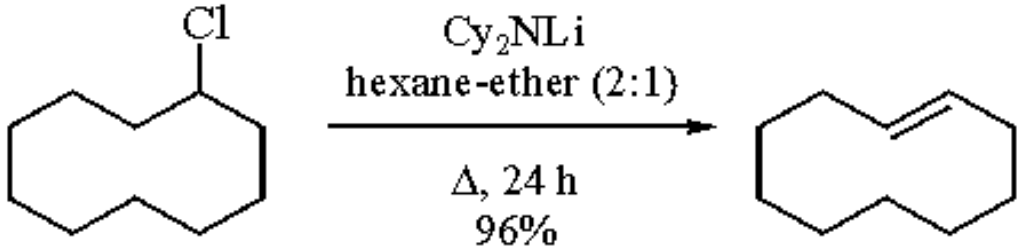

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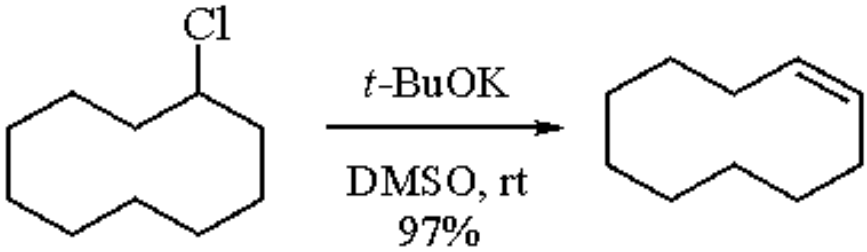

(22)

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Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate

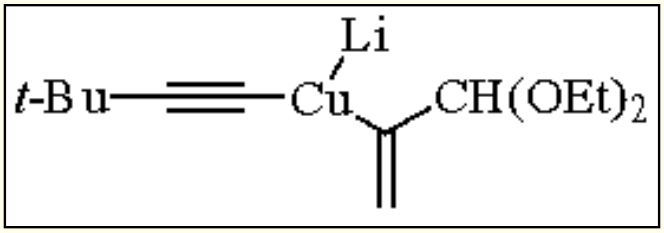

[58419-23-1] · $C_{13}H_{22}CuLiO_2$ · Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate · (MW 280.84)

(mixed organocuprate; acrolein and acrylate equivalent)

Preparative Methods: prepared in situ from ***3,3-Dimethyl-1-butynylcopper(I)*** and ***2-Lithio-3,3-diethoxy-1-propene*** at -78 °C; ether or a mixture of ether/THF can be used as solvent.

Handling, Storage, and Precautions: air- and moisture-sensitive; use in a fume hood.

Mixed Cuprate Acrolein Equivalent.

Lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate (**1**) has been used primarily as an α-acrolein and α-acrylate anion equivalent (eq 1). The *t*-butyl acetylide ligand has proven to be superior over other typical mixed cuprate ligands due to improved solubility, increased thermal stability, and higher yields. The 3,3-diethoxypropenyl unit is cleanly transferred in 1,4-additions to enones (eq 2), though the reaction was reported to be slower and the yields moderate when β-substituents of increasing bulk were introduced.[1,2] The addition of (**1**) to cyclic γ-hydroxy enones provides useful intermediates for the synthesis of α-methylene-γ-lactones (eq 3).[2] The reagent will not react with primary or vinyl halides but will add to allylic halides in excellent yield (eq 4).[2]

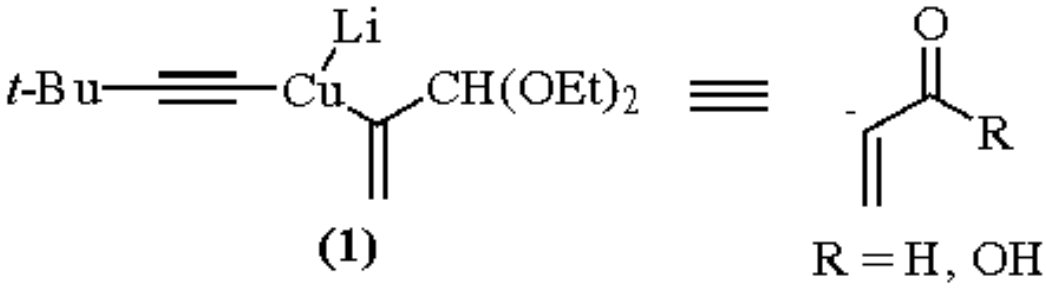

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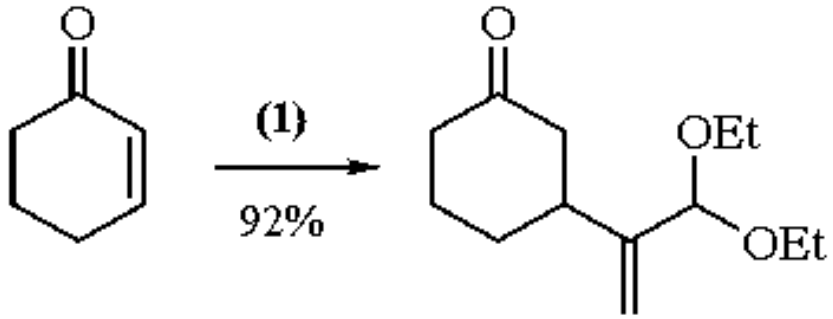

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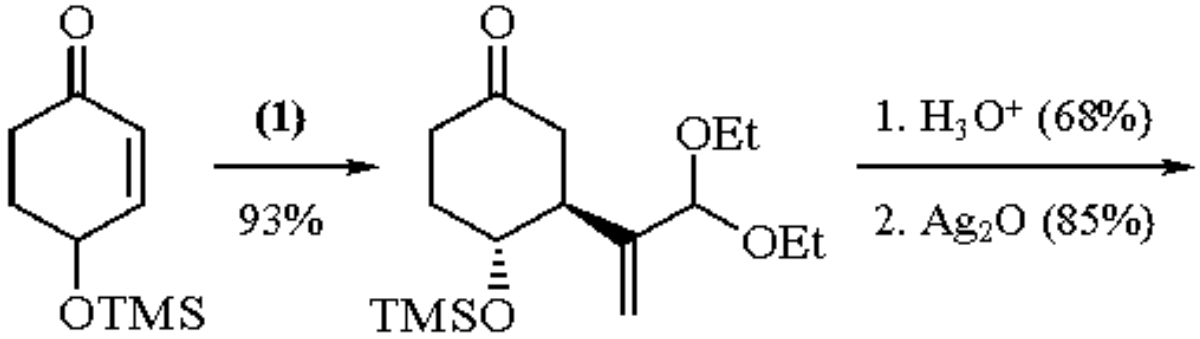

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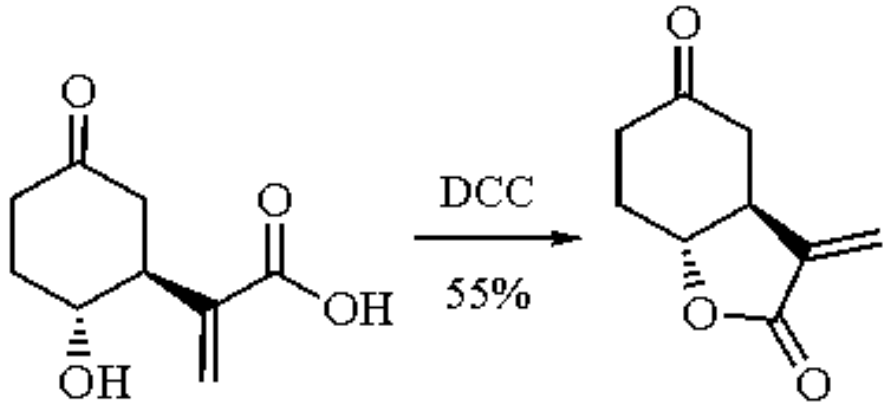

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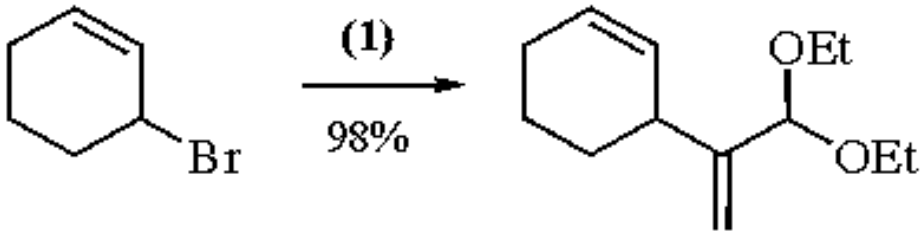

(7)

(4)

The addition of (**1**) to cyclic allylic epoxides was shown to give predominantly 1,2-addition vs. 1,4-addition.[3] Maximum yields were obtained at -40 °C, giving exclusively *trans* addition products (eq 5). Hydrolysis of acetals (**8**) and (**9**) was followed by oxidation to give the mixture of acids (**10**) and (**11**). If this mixture was treated with ***1,3-Dicyclohexylcarbodiimide*** (conditions a), only the acid with the proximal hydroxy group

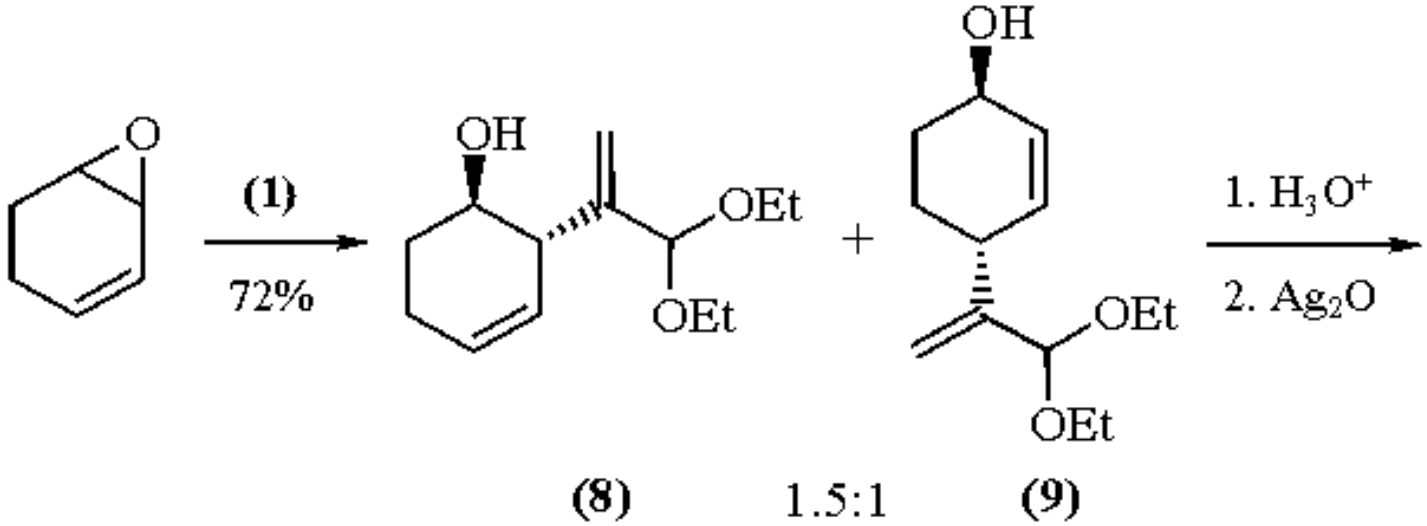

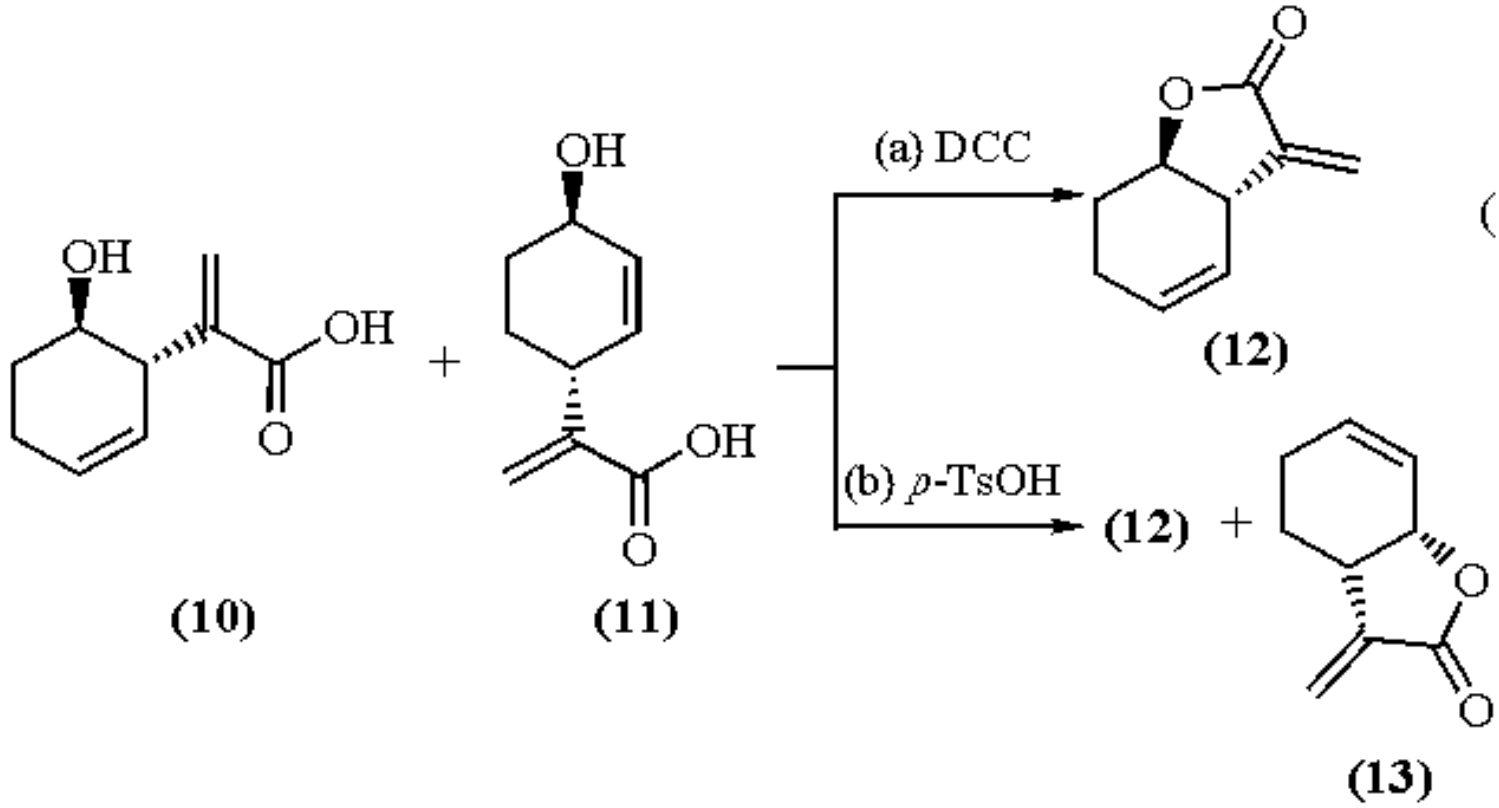

(5)

cyclized to give *trans*-α-methylenelactone (**12**). When the mixture of (**10**) and (**11**) was refluxed in benzene in the presence of ***p-Toluenesulfonic Acid*** (conditions b), (**12**) was isolated along with the *cis*-α-methylenelactone (**13**).

Related Reagents.

3,3-Dimethyl-1-butynylcopper(I); ***3,3-Diethoxy-1-propen-2-ylcopper***; ***Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate***; ***Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate***.

---

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Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate[1]

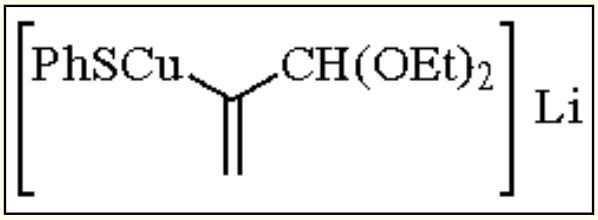

[57428-24-7] · $C_{13}H_{18}CuLiO_2S$ · Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate · (MW 308.87)

(α-bromoacrolein-derived heterocuprate capable of nucleophilic additions and substitutions;[2] useful in the preparation of α-methylene-γ-butyrolactones[3])

Alternate Name: lithium [(α-diethoxymethyl)vinyl](phenylthio)cuprate.

Solubility: prepared as a solution in ether; presumably can also be prepared in THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl. The yield of phenyl ketone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: preparation of the heterocuprate[5] requires synthesis of 2-bromo-3,3-diethoxypropene,[6] which can be obtained from the widely available diethyl acetal of acrolein via bromination-dehydrobromination. Under an inert atmosphere of nitrogen or argon, a 0 °C solution of distilled ***Thiophenol*** in anhydrous ether is treated with 1 equiv of ***n-Butyllithium***. The resultant solution is transferred to a room-temperature suspension of 1 equiv of ***Copper(I) Iodide*** in anhydrous ether under nitrogen or argon, to provide a yellow suspension of ***Phenylthiocopper(I)***; this suspension is cooled to -78 °C. In a separate flask under nitrogen or argon at -78 °C, 1 equiv of 2-bromo-3,3-diethoxypropene in anhydrous ether is treated dropwise with 1 equiv of *n*-BuLi; the 3,3-diethoxy-2-lithiopropene[7] that results is added dropwise to the -78 °C solution of PhSCu. The heterocuprate that forms is typically reacted with electrophiles at -78 °C with subsequent warming to -40 °C. Modifications using other sources of PhSCu may be acceptable.[8]

Handling, Storage, and Precautions: best results are obtained with high purity copper(I) salts,[9] dry, oxygen-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[10] *n*-BuLi is used to prepare the intermediate reagents lithium thiophenoxide and 3,3-diethoxy-2-lithiopropene, and is pyrophoric;[11] due care must be exercised in its handling. Thermal decomposition occurs at &egt;-40 °C. Use in a fume hood.

Introduction.

This vinylic organometallic reagent is representative of the heterocuprate class of organocopper reagents. The vinylic group is reactive as a nucleophile, whereas the SPh group is not. Such nontransferable groups are called dummy ligands;[12] the SPh dummy ligand in particular is typically found to provide enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Lithium (3,3-diethoxy-1-propen-2-yl)(phenylthio)cuprate can be used to prepare a variety of 2-substituted propenoic acid derivatives, especially α-methylenelactones. The reagent, along with cognate mixed homocuprate reagents, is generally considered to be superior to analogous (ethoxycarbonyl)vinylcuprate reagents. These latter reagents usually undergo 1,2- as opposed to expected 1,4-additions to α,β-unsaturated carbonyl compounds.[13]

Nucleophilic Substitutions of Halides.

Although unreactive with benzyl bromide and vinyl iodides, lithium (3,3-diethoxy-1-propen-2-yl)(phenylthio)cuprate undergoes clean substitutions with allylic bromides[5] to afford 1,4-dienes (eq 1). The mixed homocuprate ***Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate*** provides similar results.[14]

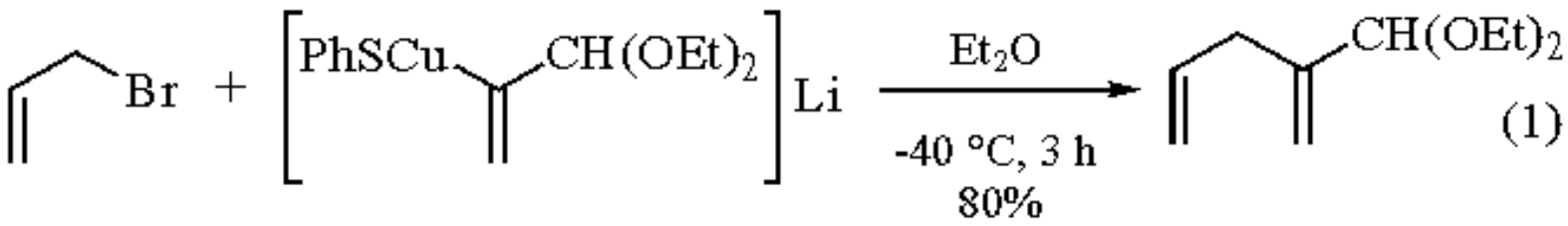

(1)

1,4-Additions to 2-Alkenones.

The reagent undergoes 1,4-addition to cyclohexenone, cyclopentenone, and 3-penten-2-one in 50-80% chemical yields in diethyl ether; the use of THF greatly diminishes formation of 1,4-adducts.[5] A comparative study indicates that mixed homocuprates, especially lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate, are the reagents of choice in 1,4-additions (eq 2).[14]

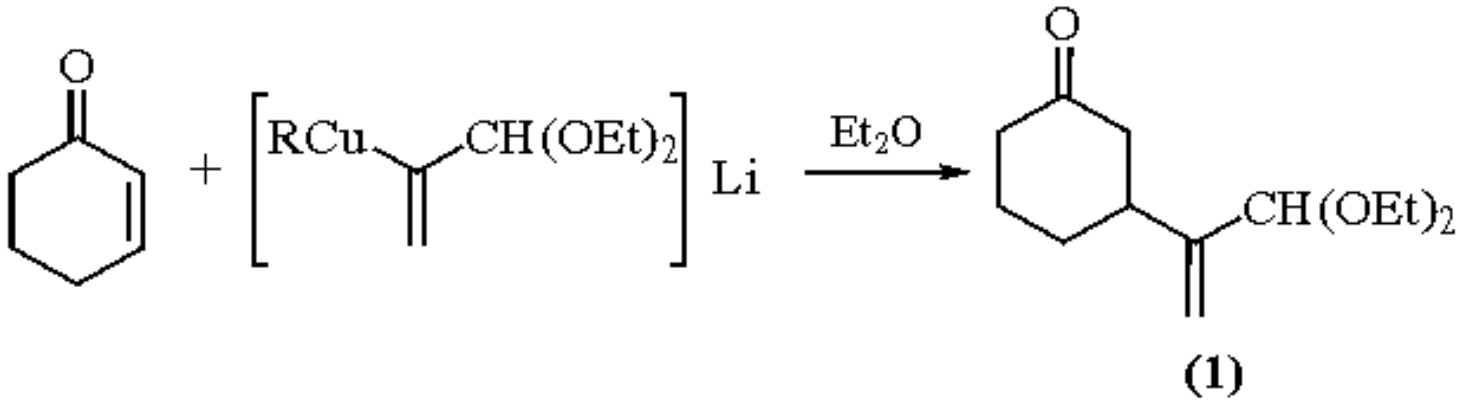

R = SPh	50%
R = Pr—≡	65%
R = *t*-Bu—≡	92%

1,4-Adduct (**1**) has been used to prepare α-methylene-δ-valerolactones (eq 3),[5] common structural motifs in marine cembranolides.[3a] If a 4-trimethylsilyloxy- or 4-*t*-butyldimethylsilyloxy-2-cycloalkenone is used as substrate for the 1,4-addition, *trans*-α-methylene-γ-butyrolactones can be prepared;[14] this strategy utilizes the steric control effect of the 4-silyloxy substituent, which causes the nucleophile to attack at the opposing face of the double bond.

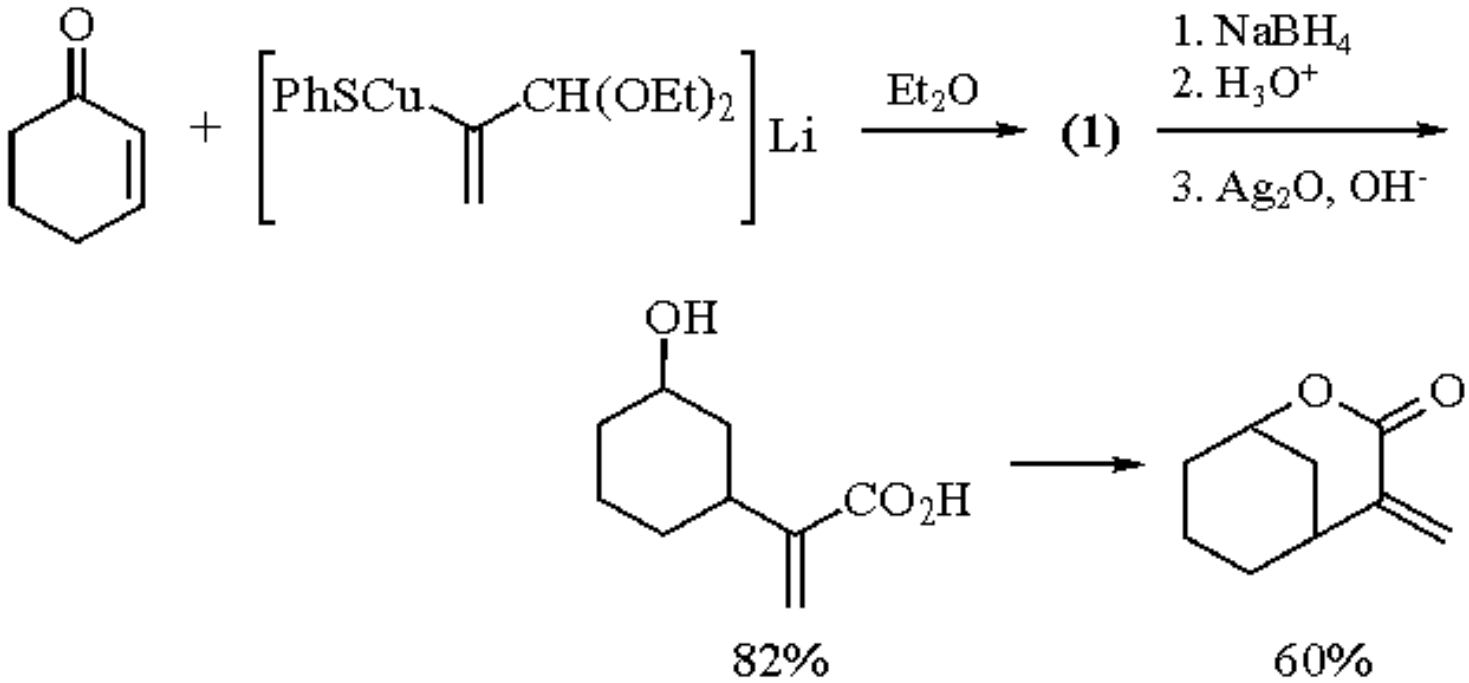

Additions to Epoxides.

Although the phenylthiocuprate is reported to be unreactive with cyclohexene epoxide, the homocuprate ***Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate*** and mixed homocuprate lithium (3,3-diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate undergo both 1,2- and 1,4-additions to cycloalkadiene monoepoxides (eq 4).[15] 1,4-Addition is distinctly favored when diethyl ether is used as solvent. The hydroxyacetal adducts can be used in the stereospecific construction of α-methylene-γ-butyrolactones of 1,3-diols. For example, when (**2**) is isolated from (**3**) by vacuum

distillation, transacetalization affords a cyclic mixed acetal. Upon oxidation with Jones reagent, the corresponding *trans*-α-methylene-γ-butyrolactone is isolated (eq 5). If 1,4-adduct (**3**) is hydrolyzed, the resultant aldehyde can be oxidized to its corresponding acid; iodolactonization provides a *cis*-α-methylene-γ-butyrolactone (eq 6).

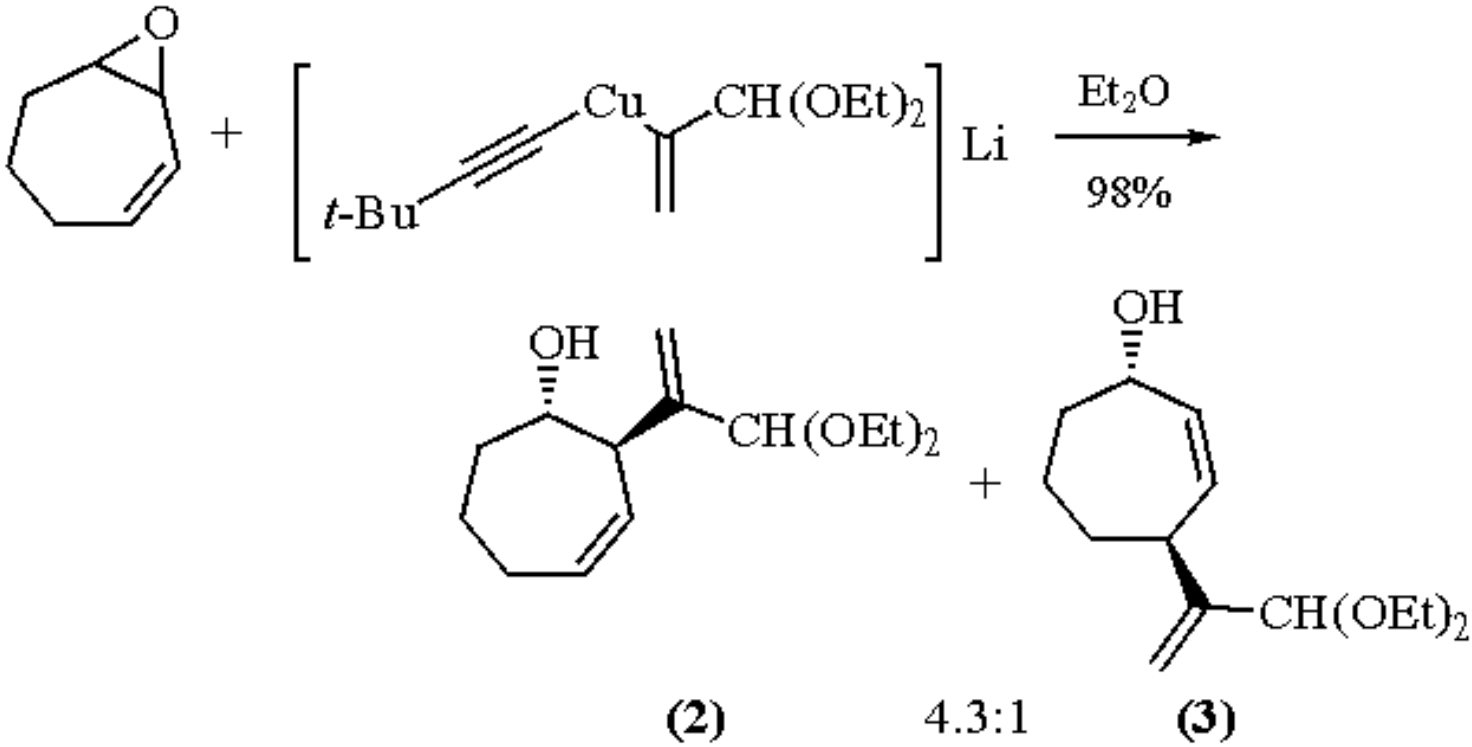

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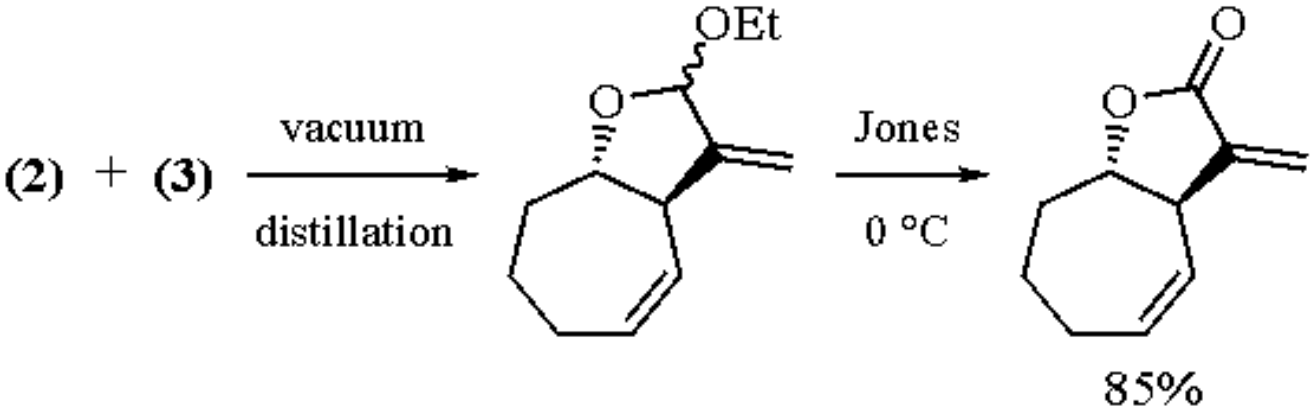

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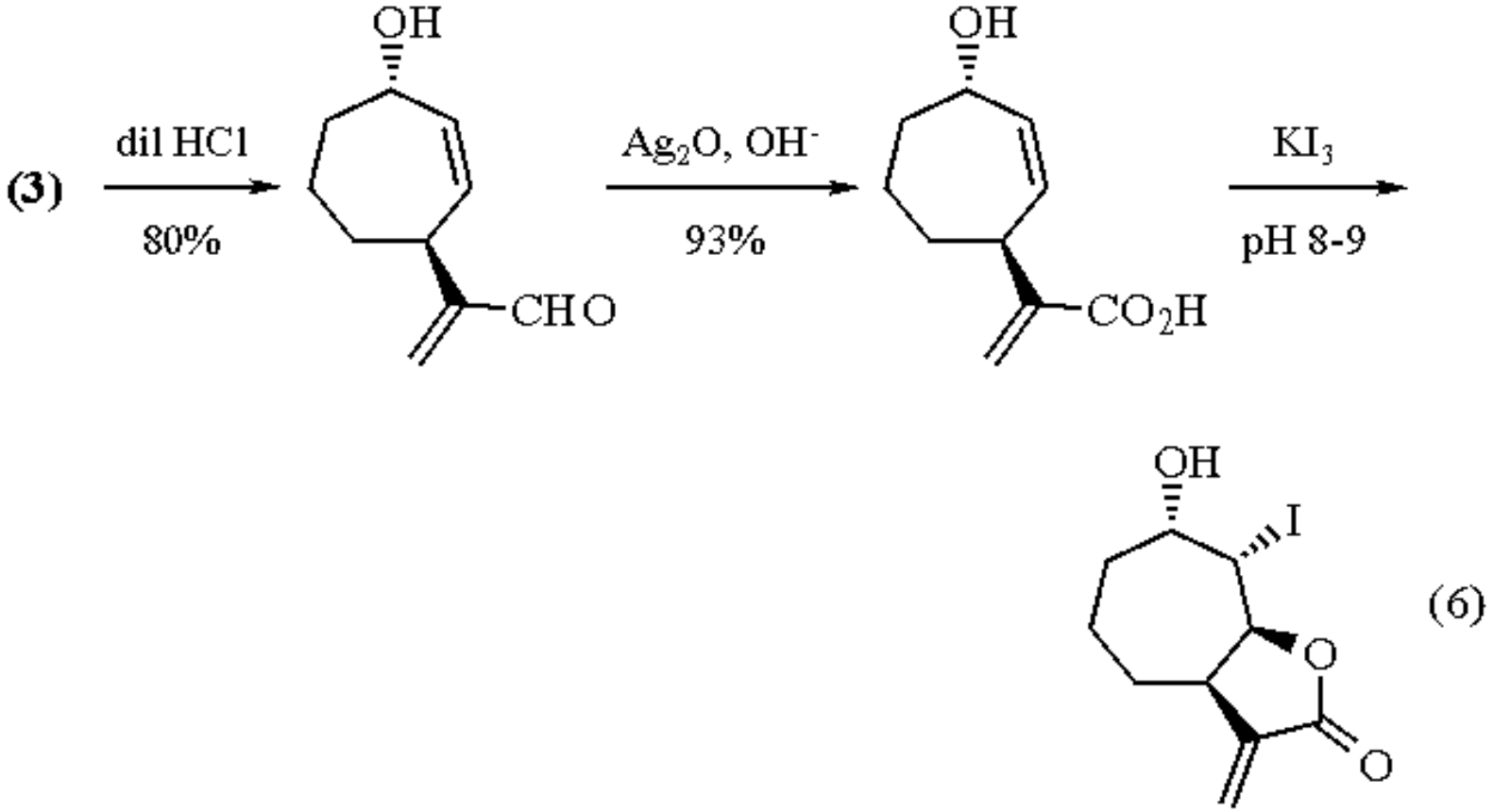

Other potential methods to prepare 2-substituted propenoic acid derivatives include Pd-catalyzed formylation of vinyl iodides and vinyl triflates[16] and hydrocupration of alkyl propiolates using ***Hexa*-μ-*hydrohexakis(triphenylphosphine)hexacopper***.[17]

Related Reagents.

3,3-Diethoxy-1-propen-2-ylcopper; ***Lithium Bis(3,3-diethoxy-1-propen-2-yl)cuprate***; and ***Lithium (3,3-Diethoxy-1-propen-2-yl)(3,3-dimethyl-1-butynyl)cuprate***; for related heterocuprates, see ***Lithium Methyl(phenylthio)cuprate***; for discussion of lithium dialkylcuprates, see ***Lithium Dimethylcuprate***.

---

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Lithium Bis(1-ethoxyvinyl)cuprate[1,2]

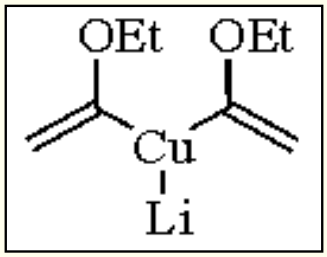

[123206-02-0] · $C_8H_{14}CuLiO_2$ · Lithium Bis(1-ethoxyvinyl)cuprate · (MW 212.71)

(vinylcuprate reagent and acyl anion equivalent which undergoes 1,4-addition reactions,[3] 1,2-addition reactions,[4] and substitution reactions[3])

Physical Data: homogenous, red solution displaying some temperature sensitivity; dec. estimated between -35 and -25 °C.[3]

Solubility: sol THF.

Preparative Methods: prepared under an inert atmosphere of argon by the rapid addition of 2 equiv of ***1-Ethoxyvinyllithium***[5] in THF at -78 °C to a suspension of purified ***Copper(I) Iodide*** at -78 °C, which is stirred at -30 °C for 1 h to afford a deep red solution.[3]

Handling, Storage, and Precautions: air- and moisture-sensitive reagent prepared in situ. Use in a fume hood.

Addition Reactions.

Lithium bis(1-ethoxyvinyl)cuprate affords transfer of the 1-ethoxyvinyl ligand, an acyl anion equivalent,[6] via conjugate addition to α,β-alkenyl ketones[7] (25-91% yield)[3] (eqs 1 and 2). This reaction is sensitive to steric hindrance resulting from substitution in the α,β-enone, especially at the β-position, resulting in slow 1,4-addition. Use of excess reagent can sometimes overcome this limitation. The *n*-propynyl mixed cuprate reagent can be used effectively to give conjugate transfer of the 1-ethoxyvinyl ligand to 2-cyclohexen-1-one (83% yield).[3]

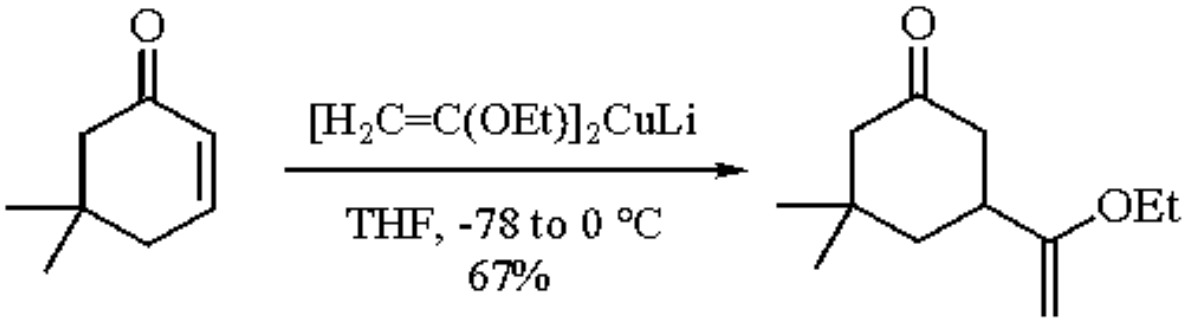

(1)

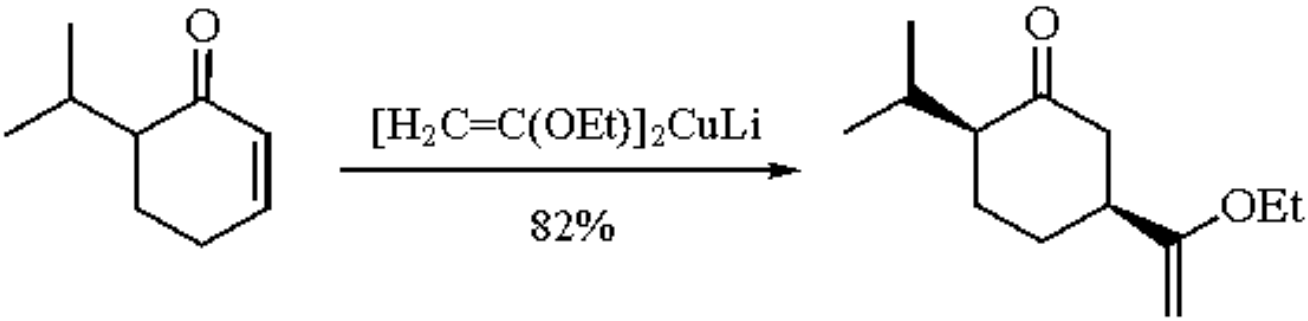

(2)

Employment of ***Boron Trifluoride Etherate*** in conjunction with lithium bis(1-ethoxyvinyl)cuprate gives an enhancement of reagent efficiency as well as improved control over the regioselectivity in the reaction, preventing 1,2-addition (eq 3).[8]

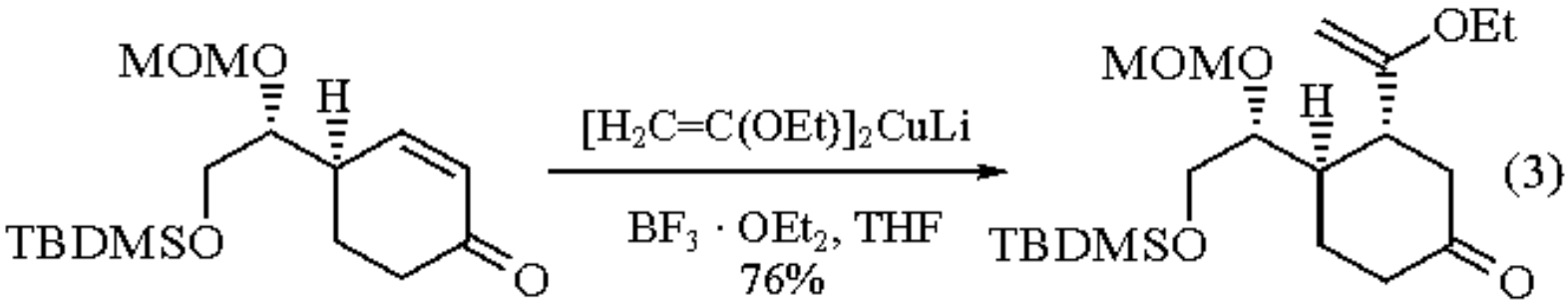

(3)

A lithium bis(1-ethoxyvinyl)cyanocuprate reagent can be prepared by the transmetalation of the vinylstannane with lithium dimethylcyanocuprate to give effective conjugate addition of the 1-ethoxyvinyl ligand to an α,β-enone.[9] The resulting vinyl ether 1,4-adducts can be readily hydrolyzed under mildly acidic conditions (0.1 N HCl/ether, 0.1 N oxalic acid/MeOH, or SiO_2 in wet benzene) to afford 1,4-diketones in 57-95% yield.[3]

Chemoselective 1,2-addition of lithium bis(1-ethoxyvinyl)cuprate to an aldehyde can be achieved in moderate yield (eq 4).[4]

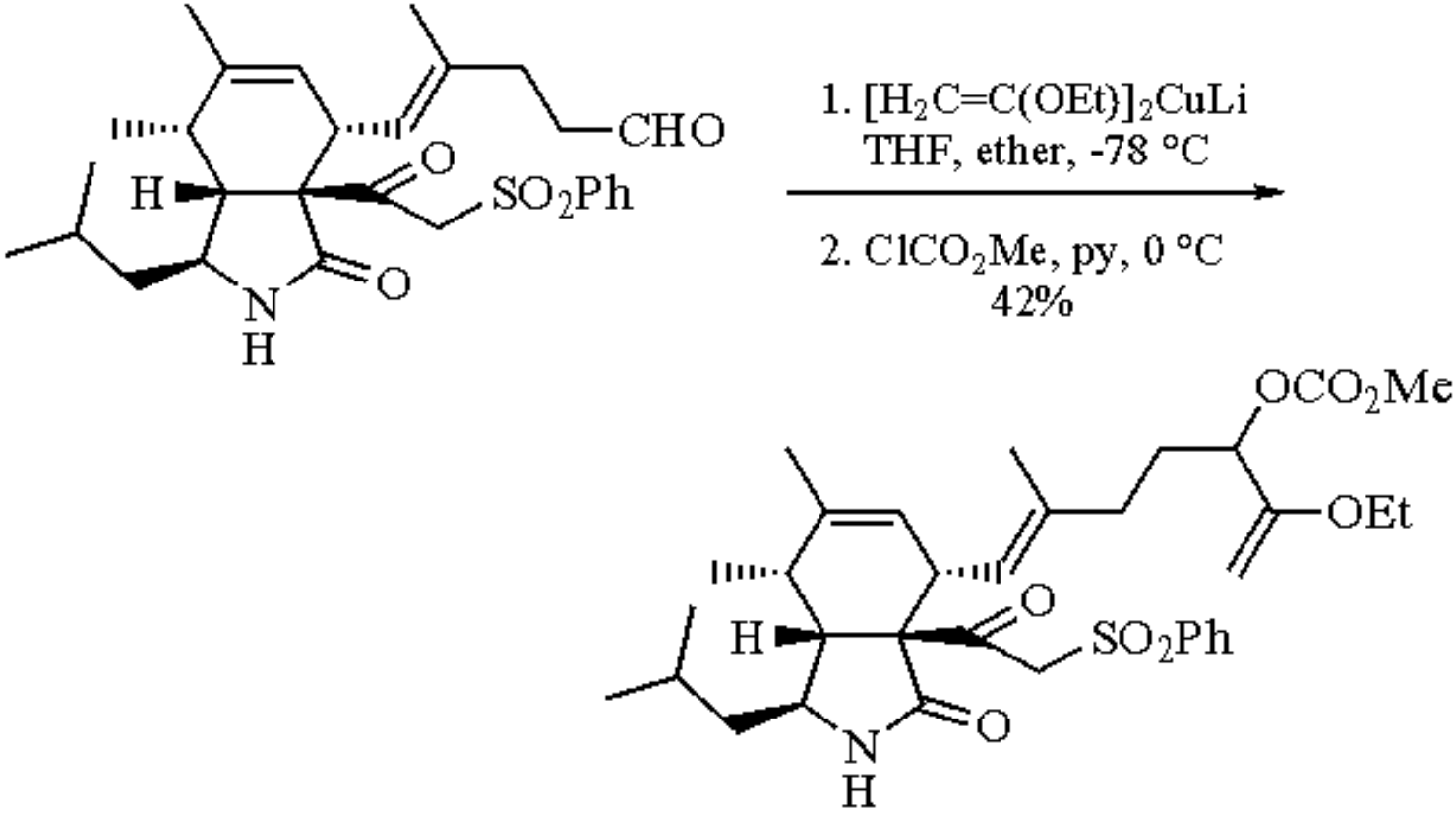

(4)

Substitution Reactions.

Coupling of lithium bis(1-ethoxyvinyl)cuprate with allylic bromides occurs in good yield (eq 5).[3,10] However, this reagent fails to give desired coupling products with saturated primary and secondary alkyl bromides, affording cuprate reagent self-coupling products; attempted opening of oxiranes was also unsuccessful.[3]

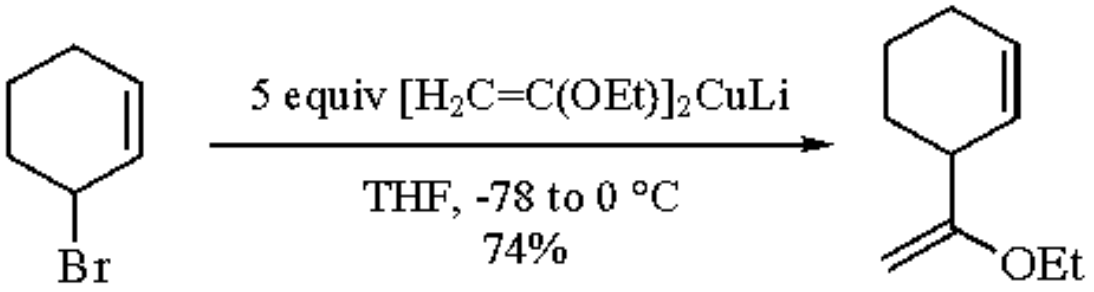

(5)

Related Reagents.

1-Ethoxyvinyllithium; ***Lithium (Z)-Bis(2-ethoxyvinyl)cuprate***; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Divinylcuprate***.

---

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Lithium (*Z*)-Bis(2-ethoxyvinyl)cuprate[1]

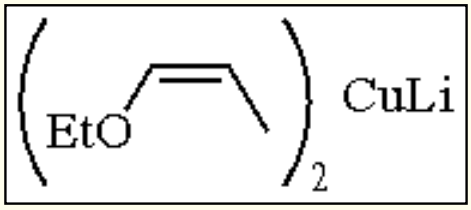

[64823-09-2] · $C_8H_{14}CuLiO_2$ · Lithium (*Z*)-Bis(2-ethoxyvinyl)cuprate · (MW 212.71)

(a lower order cuprate reagent, prepared in situ, which undergoes conjugate addition reactions and substitution reactions[2])

Solubility: sol THF.

Preparative Methods: ***1-Ethoxy-2-tributylstannylethylene*** is prepared by the hydrostannation of ***Ethoxyacetylene***, which is then reacted with 1.1 equiv of ***n-Butyllithium*** in THF at -78 °C for 1 h to afford ***(Z)-2-Ethoxyvinyllithium***. To this solution is added 0.5 equiv purified ***Copper(I) Iodide*** and 2.0 equiv ***Dimethyl Sulfide*** in THF. The mixture is stirred for 1 h, affording lithium bis(2-ethoxyvinyl)cuprate, a red-brown solution.[2]

Handling, Storage, and Precautions: air- and moisture-sensitive reagent prepared and used in situ. Use in a fume hood.

1,4-Addition Reactions with α,β-Unsaturated Carbonyl Compounds.

Lithium bis(2-ethoxyvinyl)cuprate undergoes 1,4-addition to α,β-alkenyl and α,β-alkynyl ketones by conjugate transfer of the 2-ethoxyvinyl ligand (eqs 1 and 2).[2]

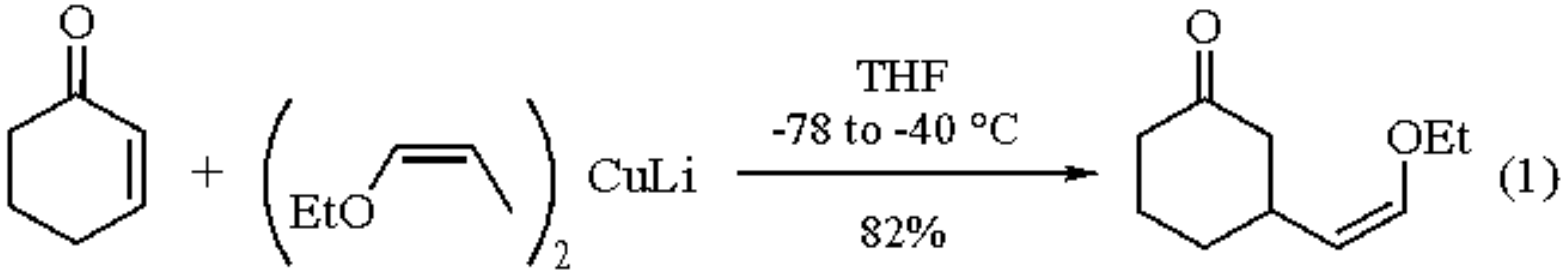

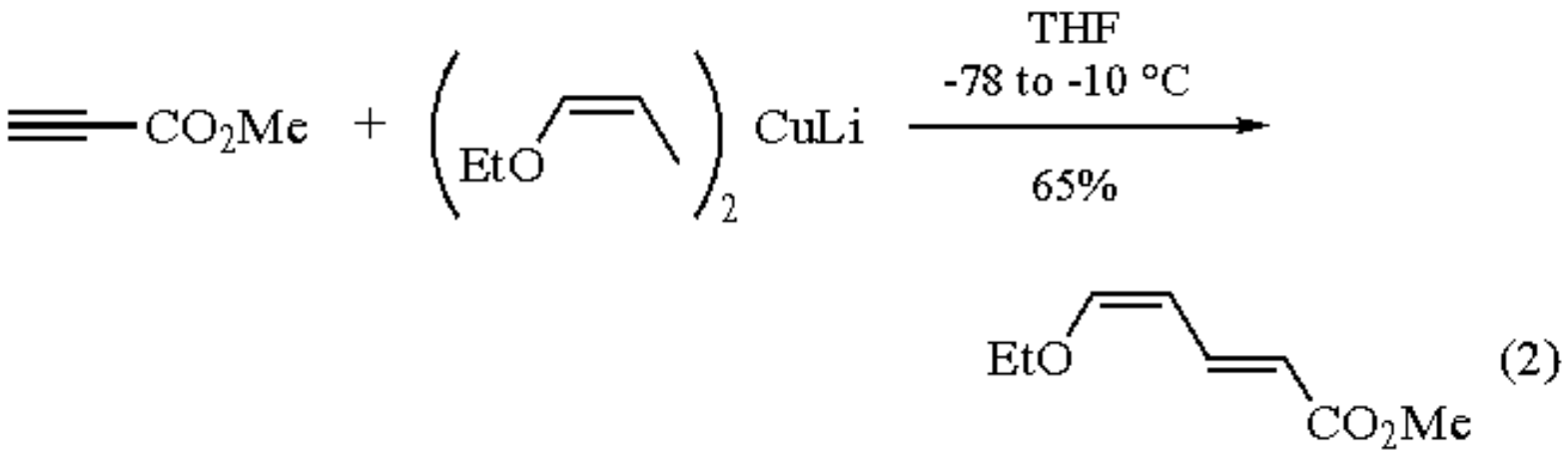

Substitution Reactions.

Lithium bis(2-ethoxyvinyl)cuprate reacts with alkyl halides in substitution reactions (eq 3).[2]

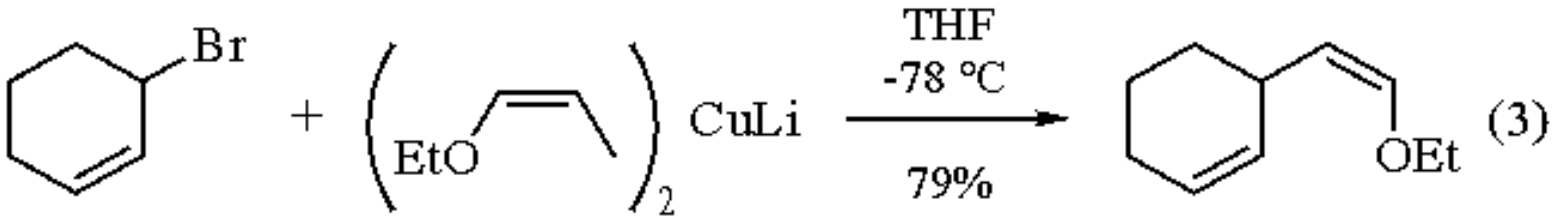

In reactions of enantiomerically pure alkyl bromide, substitution occurs with inversion of configuration at carbon. If the halogen is iodine, the reaction affords racemic product.[3]

Related Reagents.

1-Ethoxyvinyllithium; ***Lithium Bis(1-ethoxyvinyl)cuprate***; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Divinylcuprate***.

---

1. Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135.
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Lithium Diethylamide

$LiNEt_2$

[816-43-3] · $C_4H_{10}LiN$ · Lithium Diethylamide · (MW 79.09)

(strong base; nitrogen nucleophile)

Physical Data: pK_a = 31.7.[1]

Solubility: sol THF, Et_2O, Et_2O-hexane mixtures, Et_2O-benzene mixtures; insol hydrocarbon solvents.

Form Supplied in: white solid.

Preparative Methods: by treating diethylamine with ***Phenyllithium*** or ***n-Butyllithium*** or, alternatively, by treating diethylamine with ***Lithium*** metal in the presence of ***Hexamethylphosphoric Triamide***[2] or an electron acceptor.[3]

Handling, Storage, and Precautions: reacts with water vigorously and ignites spontaneously in air. When heated to decomposition, it emits toxic fumes of NO_x. Should be kept and handled under argon. Use in a fume hood.

Lithium Diethylamide as Base.

Lithium diethylamide is a strong base whose use may be complementary to ***Lithium Diisopropylamide***. For example, $LiNEt_2$ serves to abstract the o-proton of sorbic acid to generate a lithium trienolate which undergoes regioselective condensation with aldehydes and ketones (eq 1),[4] and to prepare carbocyclic nitriles by a sequential inter- and intramolecular alkylation route (eq 2).[5] $LiNEt_2$ has been employed with a sterically hindered lactam for an α-deprotonation-cyclization reaction as part of the synthesis of (-)-δ-*N*-normethylskytanthine, an alkaloid from *Tecoma arequipensis* (eq 3).[6] $LiNEt_2$ may be a superior base to LDA for enolate formation.[7]

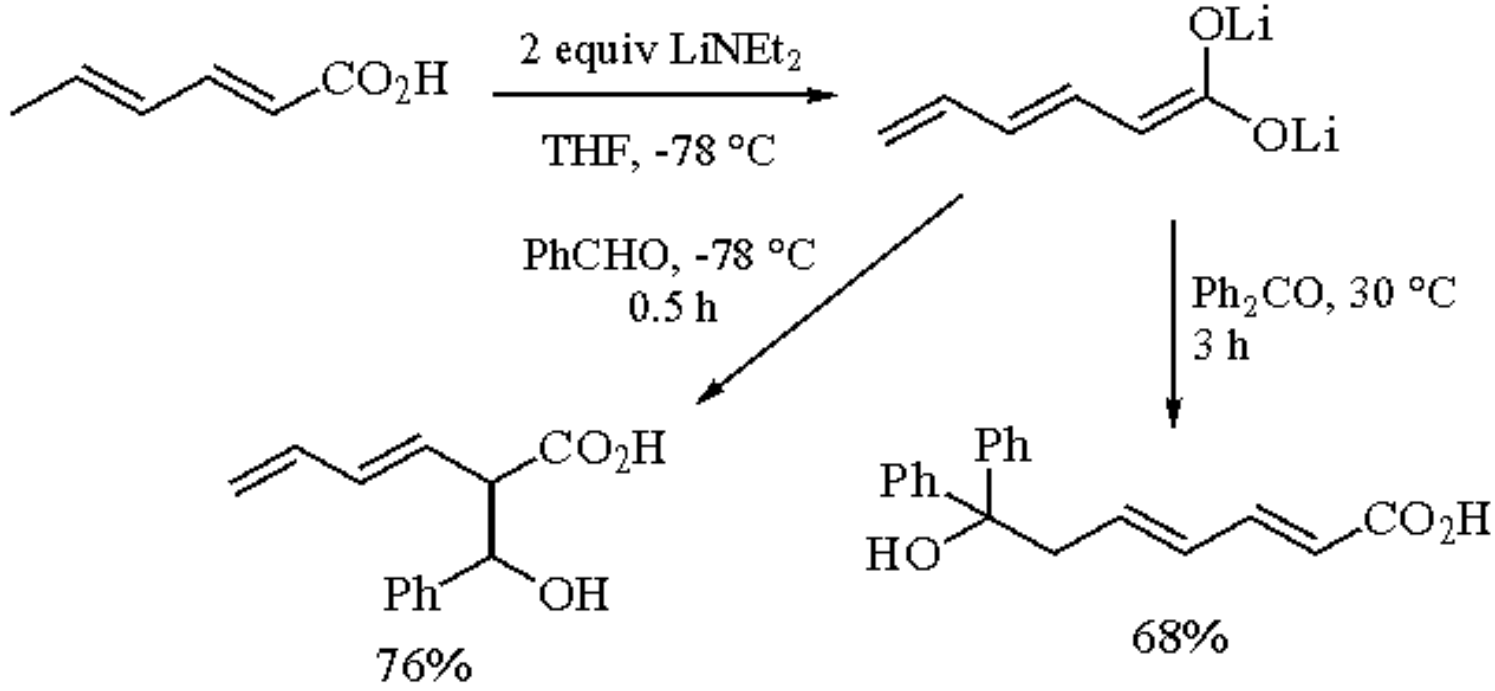
CO2H
2 equiv LiNEt2
THF, -78 °C
OLi
OLi
PhCHO, -78 °C
0.5 h
Ph2CO, 30 °C
3 h
CO2H
Ph
OH
76%
Ph
Ph
HO
CO2H
68%

(1)

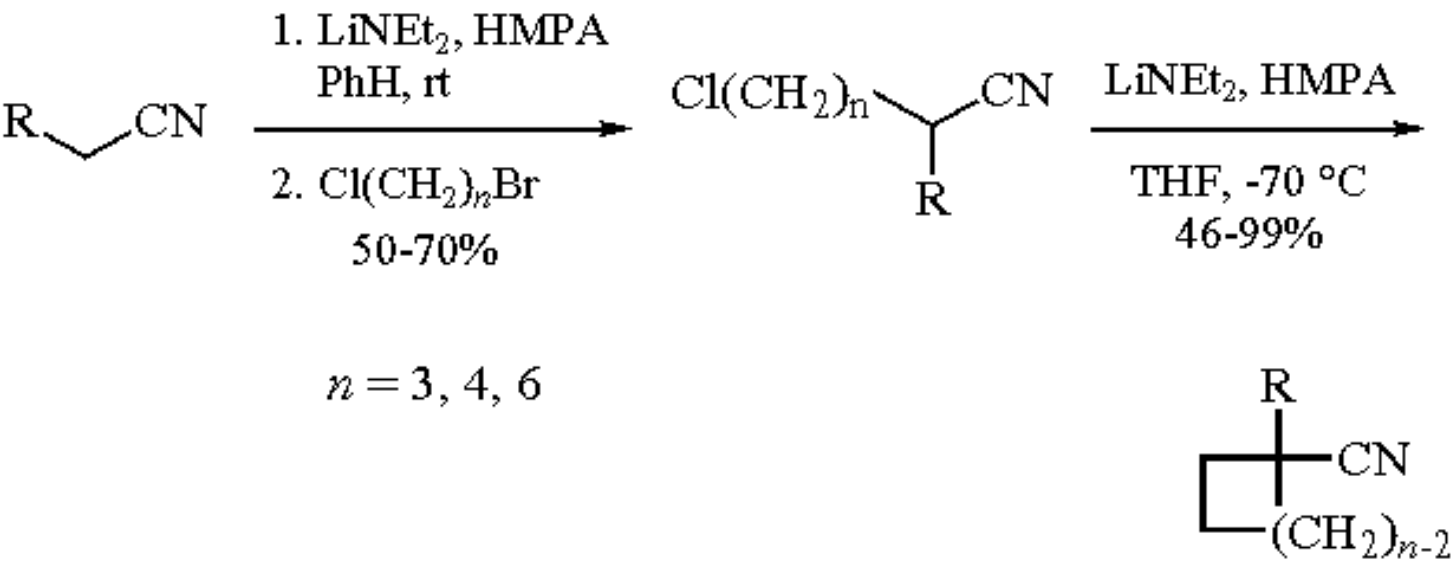
R
CN
1. LiNEt2, HMPA
PhH, rt
2. Cl(CH2)nBr
50-70%
Cl(CH2)n
CN
R
LiNEt2, HMPA
THF, -70 °C
46-99%
n = 3, 4, 6
R
CN
(CH2)n-2

(2)

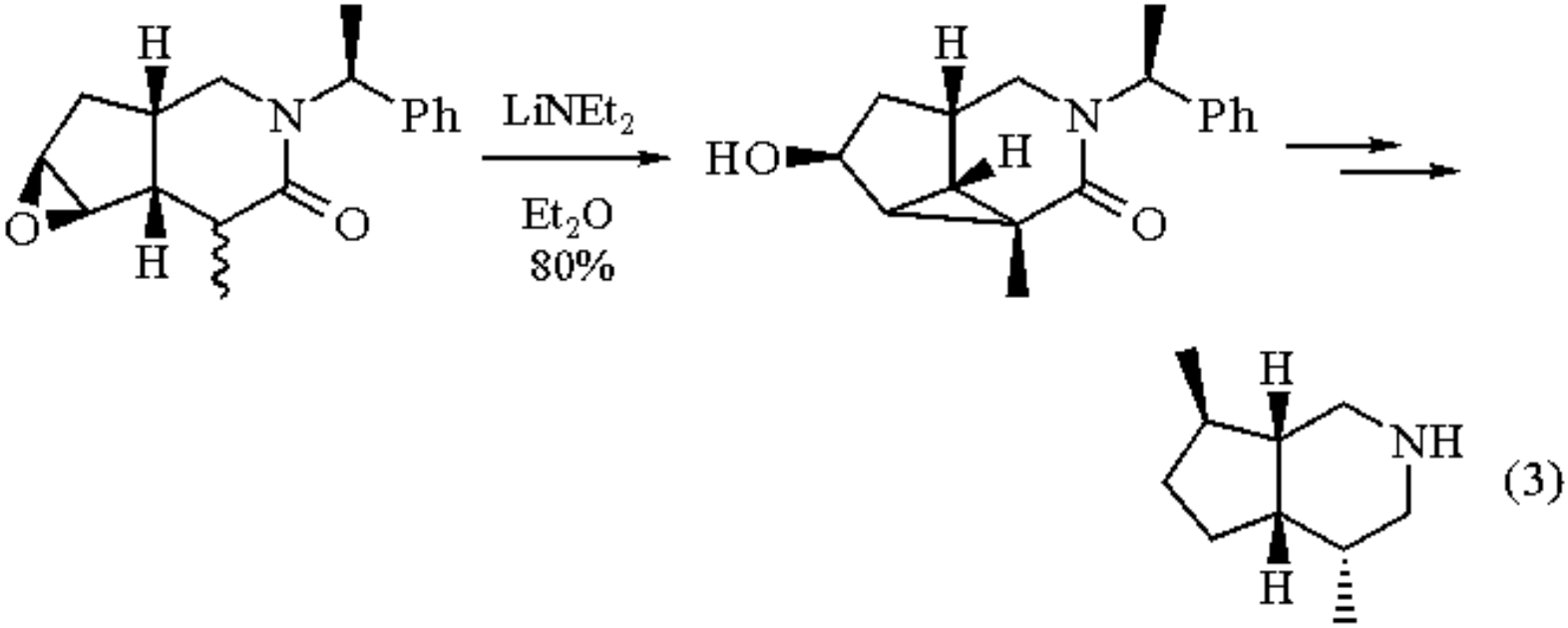

(3)

(-)-δ-*N*-Normethylskytanthine

Lithium diethylamide is widely used for base-induced epoxide opening to allylic alcohols and rearrangement via carbenoids.[8] Two reaction pathways are observed: β-*syn*-elimination[8c] to afford an allylic alcohol (eq 4) and α-elimination to generate a carbenoid followed by C-H insertion (eqs 5 and 6). Allylic deprotonation followed by intramolecular epoxide ring opening has been observed (eq 6). The β-elimination process is often highly stereoselective and therefore has synthetic value.[8h]

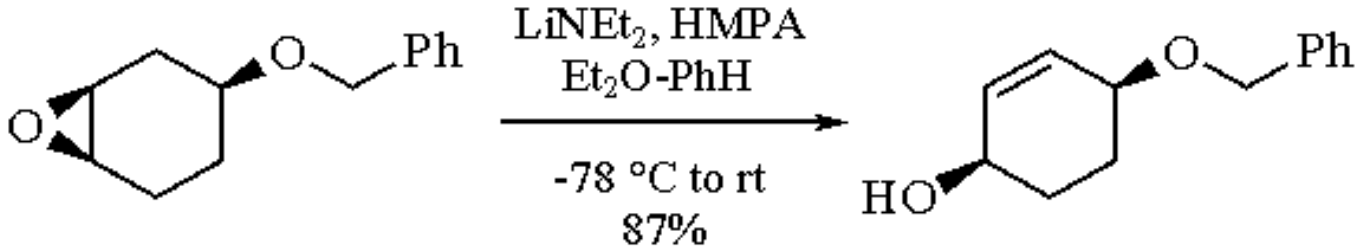

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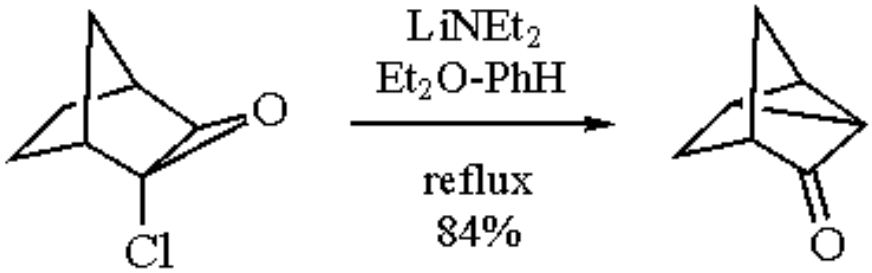

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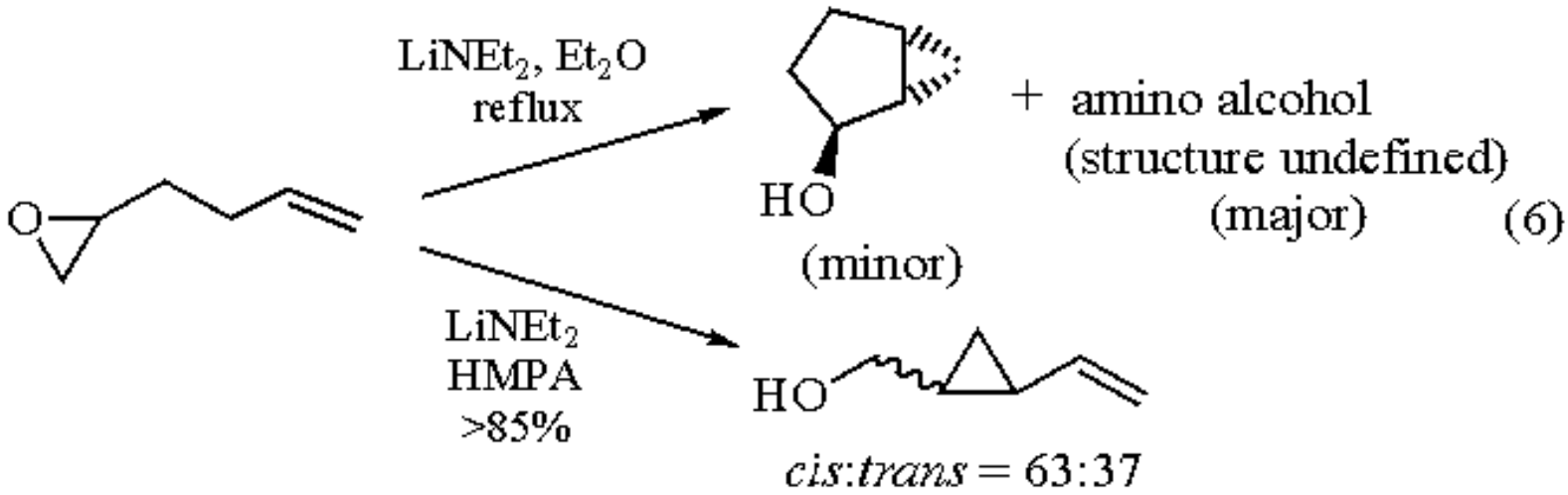

$LiNEt_2$ is sufficiently basic to effect α-deprotonation of allenic ethers. Subsequent reaction with ketones followed by acid treatment affords 3-furanones (eq 7).[9]

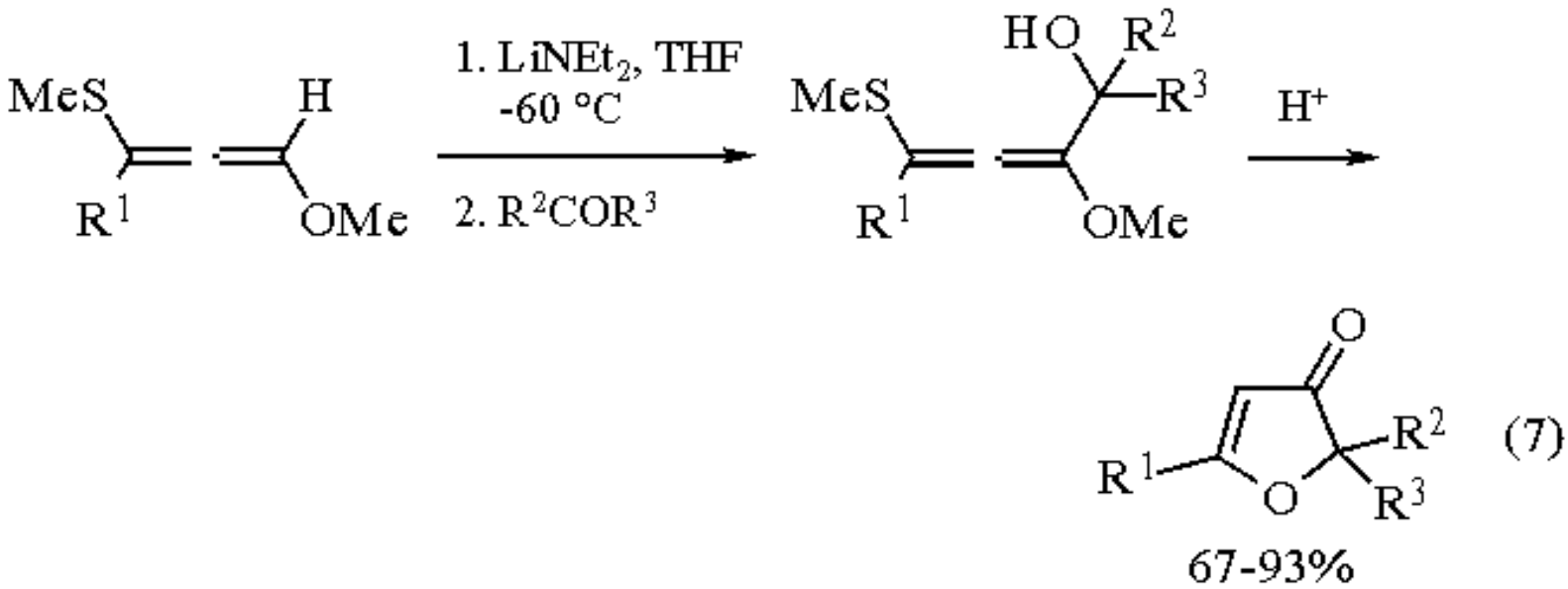

Treatment of tetraphenylphosphonium bromide with $LiNEt_2$ leads to 9-phenyldibenzophosphole[10] which may be further transformed into Wittig-Horner reagents (eq 8), useful for highly stereoselective synthesis of alkenes.

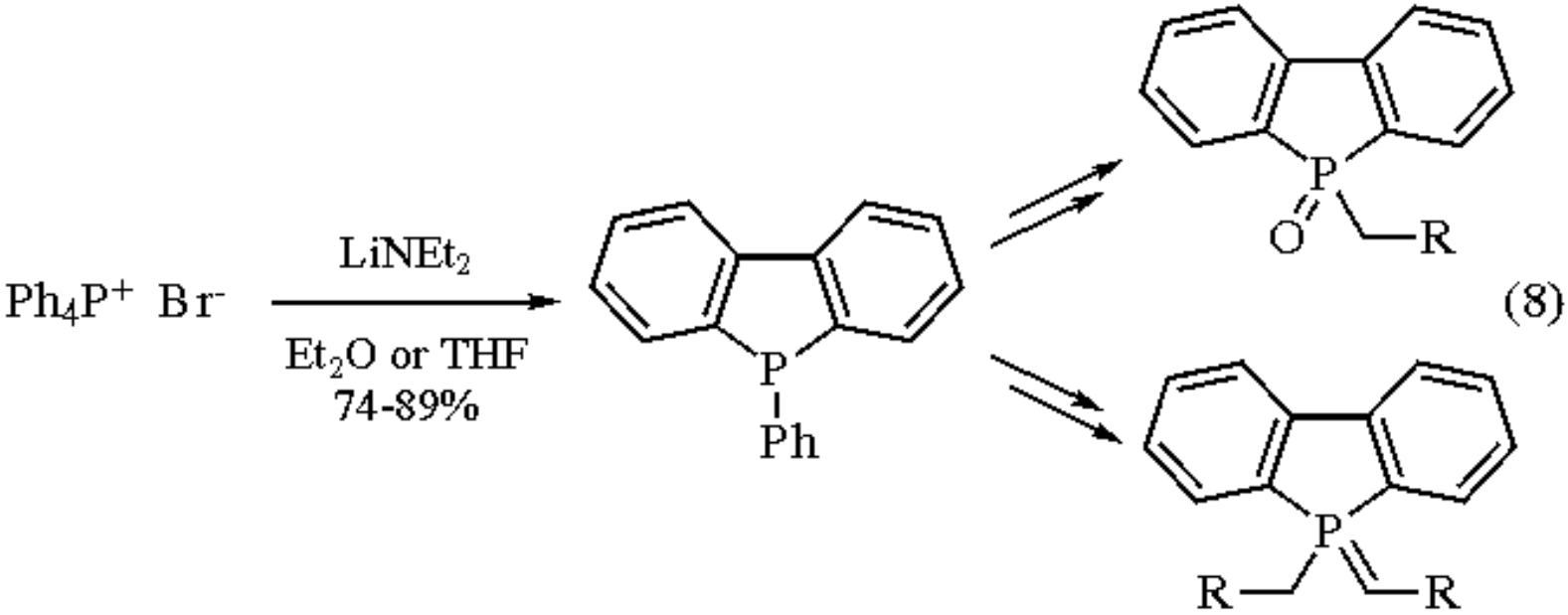

Lithium Diethylamide as Nucleophile.

Treatment of aldehydes with a $LiNEt_2$-***Titanium Tetraisopropoxide*** complex generates α-amino alkoxides which undergo reaction with Grignard reagents to afford tertiary amines (eq 9).[11] $LiNEt_2$ attacks THP ethers of 2,4-alkadien-1-ols regioselectively at C-5 to furnish amino dienes with predominately (*E*,*E*) stereochemistry (eq 10).[12] Treatment of perfluorinated alkanes with $LiNEt_2$ results in β-elimination to provide terminal alkenes (eq 11).[13] Further treatment with $LiNEt_2$ leads to addition and fluoride elimination to give enamines which, after hydrolysis, produce perfluorinated amides. Similarly, chloroalkynes lead to ynamines (eq 12).[14]

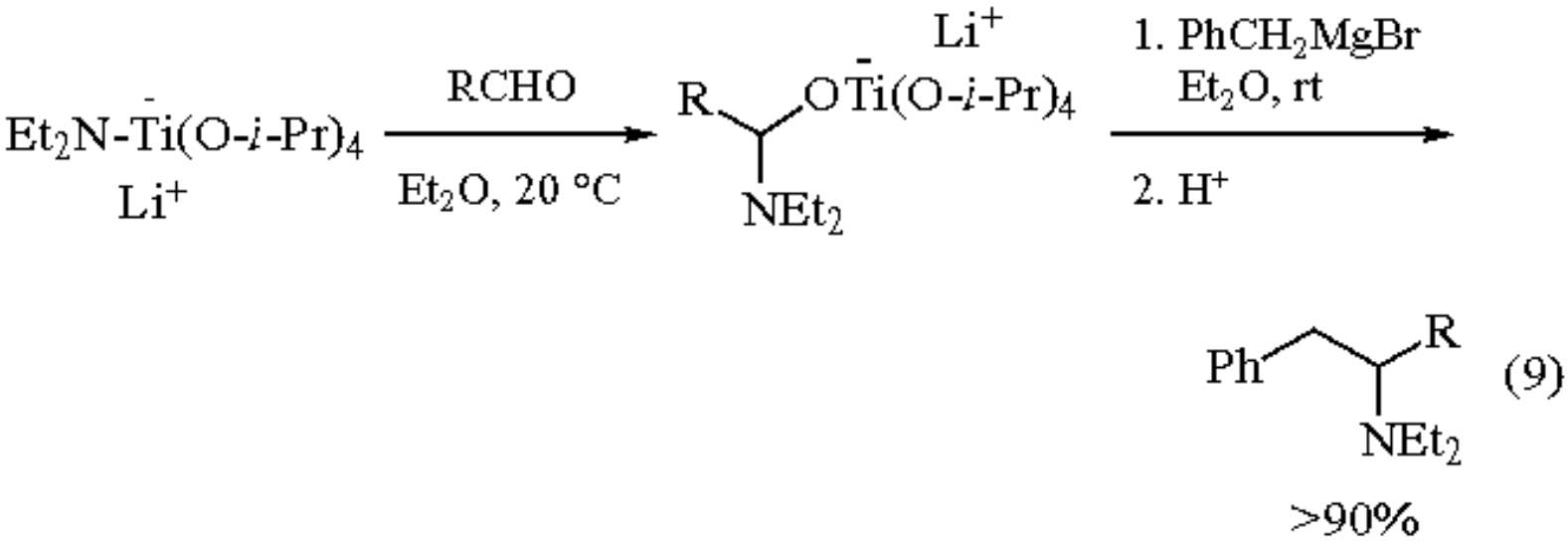

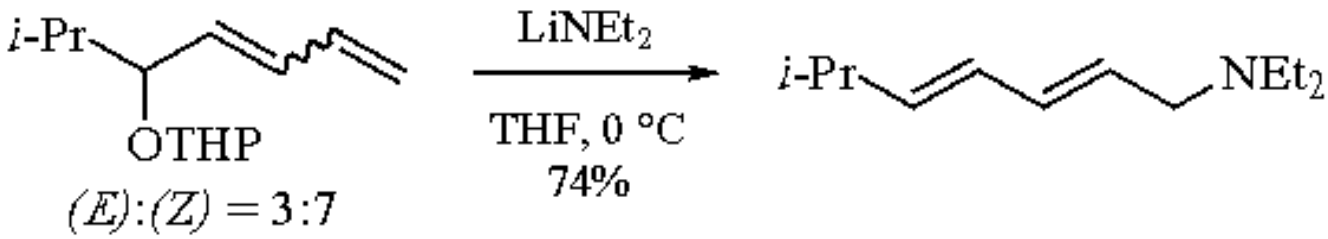

(10)

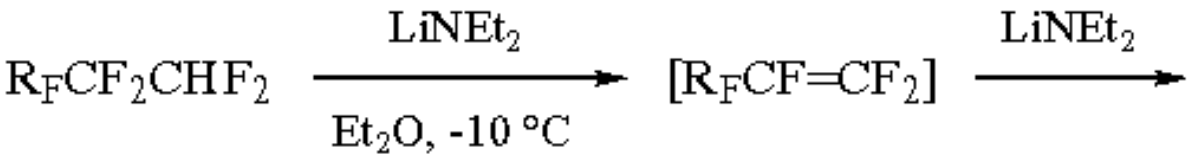

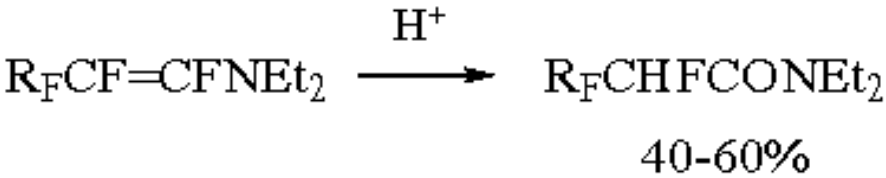

(11)

$R_F = CF_3(CF_2)_3$-, $PhCH_2O(CF_2)_4$-, etc.

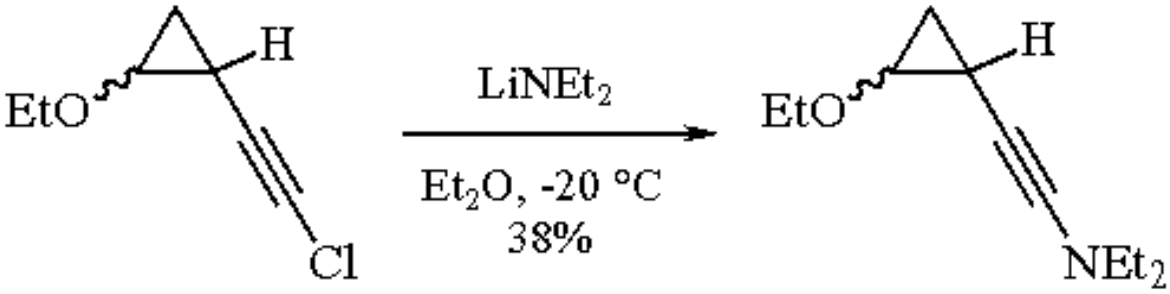

(12)

Related Reagents.

Lithium Diisopropylamide; ***Lithium Hexamethyldisilazide***; ***Lithium Piperidide***; ***Lithium Pyrrolidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***.

---

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Lithium Diethylcuprate[1]

Et_2CuLi

[38297-20-0] · $C_4H_{10}CuLi$ · Lithium Diethylcuprate · (MW 128.63)

(ethylating reagent; undergoes conjugate addition reactions,[1a,b,d] substitution reactions,[1a,c,d] and carbocupration[1])

Physical Data: black solution (prep. from CuI).[2]

Solubility: sol THF, Et_2O

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***,[2,3a] ***Copper(I) Iodide-Tributylphosphine***[3b]) under N_2 or argon atmosphere (see ***Lithium Dimethylcuprate***).

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Introduction.

Lithium diethylcuprate displays the characteristic reactivity patterns of lithium diorganocuprates (see ***Lithium Di-n-butylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***).

Addition Reactions.

Lithium diethylcuprate reacts with α,β-alkenyl ketones (eq 1),[1,4] esters,[5] and amides[6] with conjugate transfer of the ethyl ligand. Conjugate addition of Et_2CuLi to the enol tosylate of an α-dione followed by elimination of the tosylate group affords the substituted α-dione (eq 2).[7] The reagent adds stereoselectively (*cis* addition) to α,β-alkynoates[8a] and alkynamides (eq 3),[8b] affording alkenyl esters and amides.

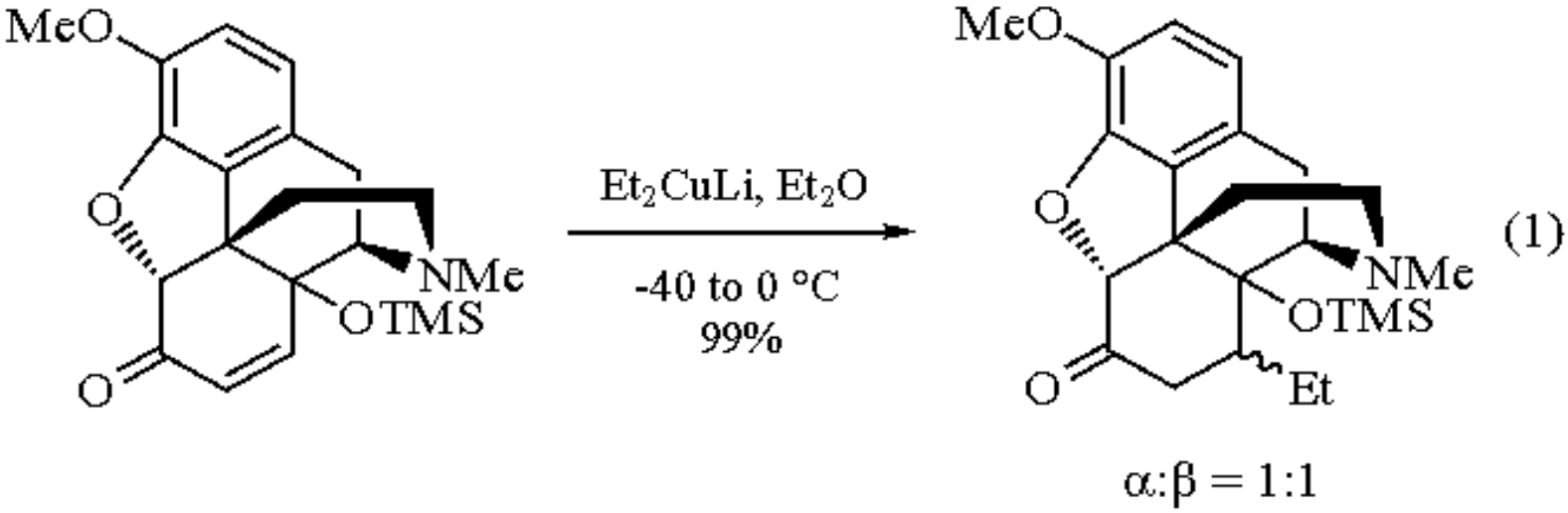

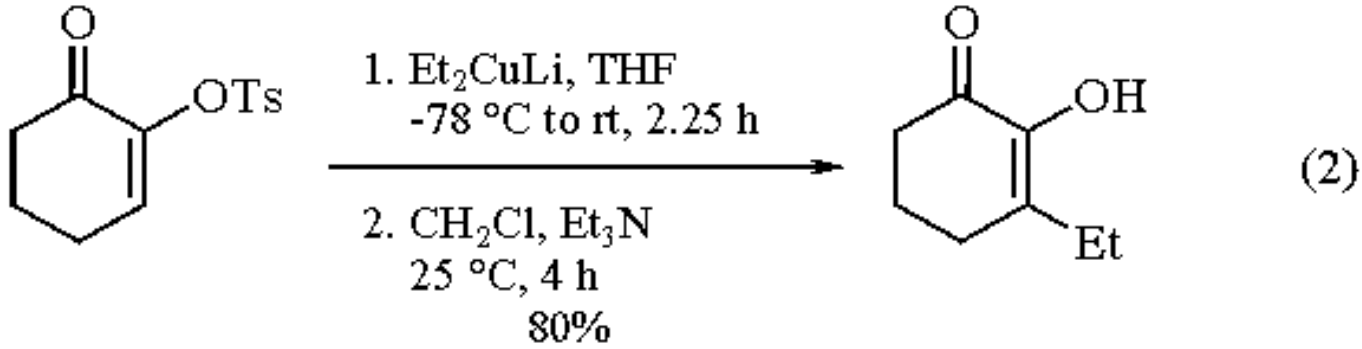

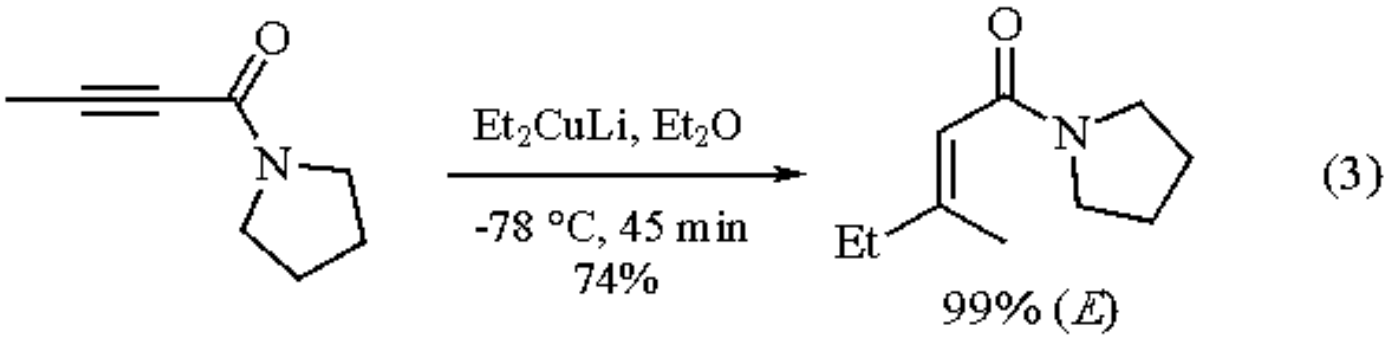

Dienones undergo a 1,6-addition reaction.[9] Reaction of Et_2CuLi with thiones[10] and aldehydes[11] affords 1,2-addition products.

Substitution Reactions.

Lithium diethylcuprate participates in substitution reactions with alkyl halides,[12] carboxylates,[13] tosylate esters,[2b,12a,14] sulfinate esters,[15] and thioesters.[9] Reaction of Et_2CuLi with acyl halides[16] results in nucleophilic acyl substitution, providing a useful route to ketones. Vinyl bromides[17] couple with Et_2CuLi to afford substitution products; the reaction proceeds with retention of configuration. Vinyl triflates[18] derived from β-dicarbonyl compounds afford substitution products that may result from addition-elimination reaction pathways.

Carbocupration.

Carbocupration of alkynes with Et_2CuLi affords alkenylcopper compounds which can react with alkyl halides,[19] enones,[20] and oxiranes[21] to give substitution, 1,4-addition, and ring-opened products, respectively. Carbocupration of acetylene with Et_2CuLi followed by addition of a 1-alkyne affords a dienylcuprate that can undergo reactions with various electrophiles (eq 4).[22] Carbocupration of methoxyallenes has been reported.[23]

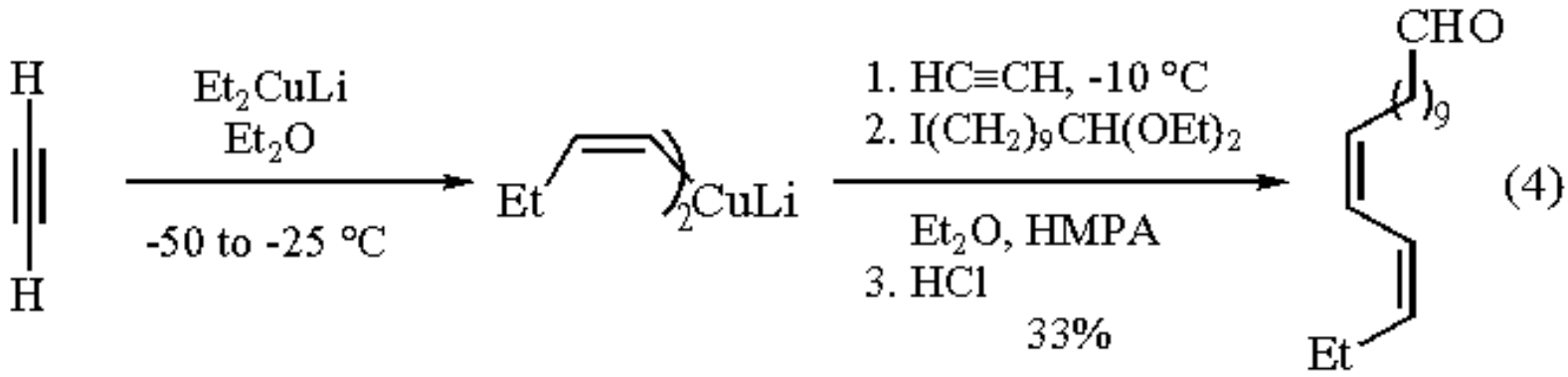

(4)

Miscellaneous Reactions.

Reaction of this reagent with aziridines affords ring-opened products.[24] Propargylic halides (eq 5),[3a] α,β-alkenyl acetals,[25] and vinyl lactones (eq 6)[26] undergo S_N2' reactions. Vinyl oxiranes[27] participate in *anti*-stereoselective S_N2' pathways. Propargylic oxiranes[28] give α-allenic alcohols upon reaction with Et_2CuLi.

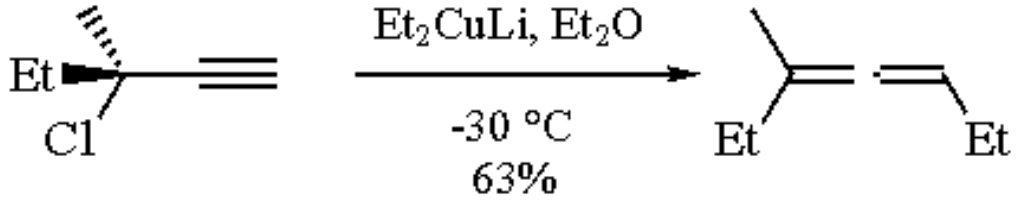

(5)

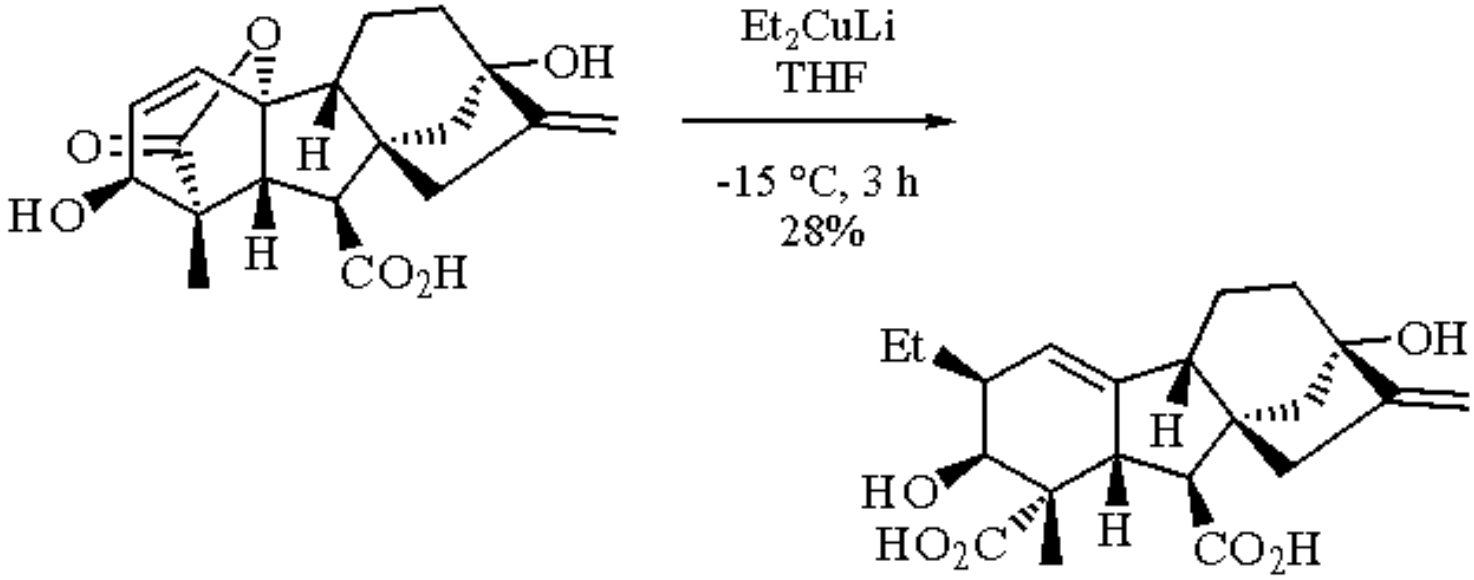

(6)

Related Reagents.

Lithium Diethylcuprate-Tributylphosphine.

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Lithium Diethylcuprate-Tributylphosphine[1]

$Et_2CuLi.(n\text{-}Bu)_3P$

(Et_2CuLi)

[38297-20-0] · $C_4H_{10}CuLi$ · Lithium Diethylcuprate-Tributylphosphine · (MW 128.63)
(Bu_3P)

[998-40-3] · $C_{12}H_{27}P$ · Lithium Diethylcuprate-Tributylphosphine · (MW 202.36)

(representative phosphine-ligated homocuprate for 1,4-addition,[2] nucleophilic substitution,[3] and reductive metalation[4])

Solubility: sol ether, THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[5] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl. The yield of propiophenone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: the following general procedure has been used to prepare a variety of $R_2CuLi.P(n\text{-}Bu)_3$ reagents:[6] a round-bottom flask equipped with magnetic stirring bar and rubber septum is charged with ***Copper(I) Iodide-Tributylphosphine***.[7] Under a nitrogen atmosphere, ether or THF is added. After cooling the resultant solution to -78 °C, 2.0 equiv of the appropriate RLi reagent is added dropwise. Formation of a colorless, pale pink, or yellow cuprate is immediate. Alternate preparations by addition of 1.0 equiv of ***Tri-n-butylphosphine*** to an ether or THF slurry of ***Copper(I) Iodide*** before addition of two equiv of RLi or by use of $CuBr[(n\text{-}Bu)_3P]_2$[8] may be possible.

Handling, Storage, and Precautions: best results are obtained with high purity Cu^I salts,[9] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[10] Like most alkyllithium reagents, ***Ethyllithium***[11] is pyrophoric;[12] care must be exercised in its

handling. Homocuprates are stabilized in the presence of stoichiometric quantities of $(n\text{-Bu})_3P$; there is no noticeable decomposition at -78 °C.[6] Use in a fume hood.

General Discussion.

Phosphine-ligated homocuprates were introduced early in the development of organocopper chemistry.[6,13] The $(n\text{-Bu})_3P$ ligand solubilizes the homocuprate in ether solvents, increasing its reactivity, and also retards thermal decomposition. Generally, the presence of stoichiometric quantities of the ligand makes reaction workup unsatisfactory;[6,13a,14] for this reason, various heterocuprates[15] have found wider application in organic chemistry. Eq 1 provides a typical comparison.[15]

$$x\,(t\text{-Bu})\text{CuRLi}\cdot\text{L} + \text{C}_5\text{H}_{11}\text{Br} \xrightarrow{\text{THF}} t\text{-Bu}\text{C}_5\text{H}_{11} \qquad (1)$$

x	R	L	
5	*t*-Bu	Bu_3P	92%
2	SPh	-	98%

Lithium diethylcuprate-tributylphosphine has been essentially unused in organic synthesis. Phosphine-ligated organocopper reagents, however, have found recent applications in tandem vicinal dialkylation reactions leading to prostaglandins.[16] Other reports suggest that the presence of a phosphine ligand during organocopper-mediated epoxide openings is important in promoting reductive metalation of substrate.[4,8]

Related Reagents.

Lithium Diethylcuprate; ***Lithium Dimethylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

---

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Lithium Diisobutyl(methyl)aluminum Hydride[1]

Li[(*i*-Bu)$_2$(Me)AlH]

[17034-29-6] · $C_9H_{22}AlLi$ · Lithium Diisobutyl(methyl)aluminum Hydride · (MW 164.23)

(used to hydroaluminate triple bonds[2,3] and to reduce α,β-unsaturated carbonyl compounds regioselectively in conjuction with MAD[4])

Physical Data: see ***Diisobutylaluminum Hydride*** and ***Methyllithium***.

Solubility: reactions using the title reagent are conducted in ether or glyme.

Preparative Methods: prepared in situ by adding methyllithium in ether to diisobutylaluminum hydride in ether or glyme while maintaining the temperature below 25 °C or at 0 °C.[2]

Form Supplied in: prepared in situ from commercially available reagents.

Handling, Storage, and Precautions: see ***Diisobutylaluminum Hydride*** and ***Methyllithium***.

Hydroalumination of Alkynes.

Lithium diisobutyl(methyl)aluminum hydride hydroaluminates symmetrical disubstituted alkynes in a *trans* fashion.[2] On the other hand, *cis* hydroalumination takes place if diisobutylaluminum hydride (DIBAL) and methyllithium are introduced sequentially.[5] The later sequence also hydroaluminates monosubstituted triple bonds to generate vinylalanate complexes with the aluminum adding exclusively to the alkyne terminus (eq 1).[5]

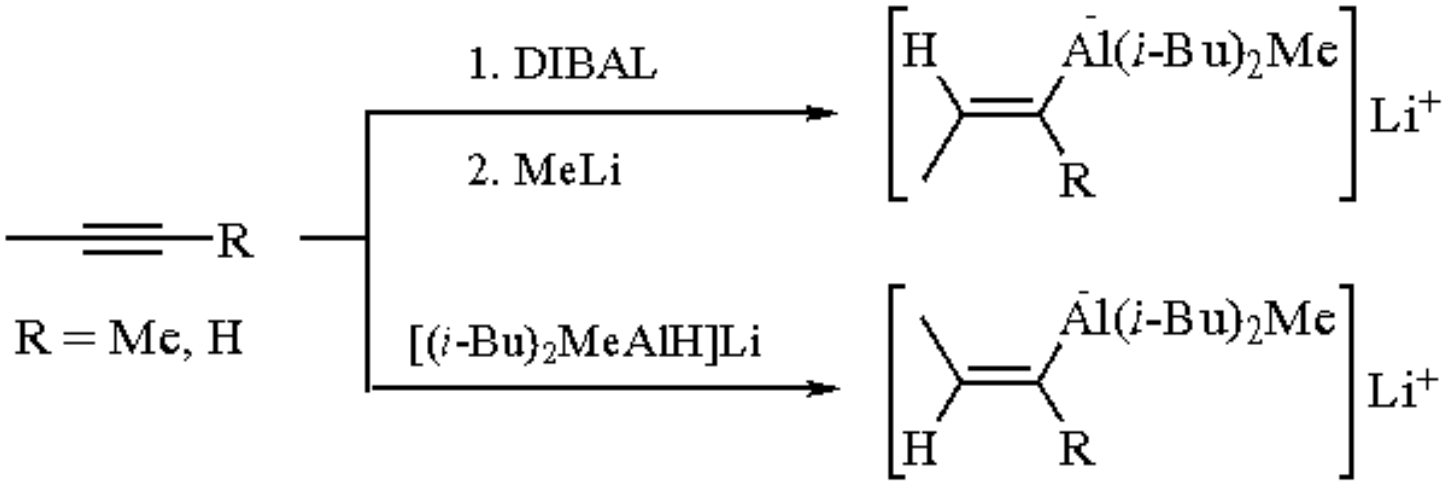

(1)

Studies on the hydroalumination of conjugated diyne systems revealed that the addition occurs in a *trans* fashion, with the aluminum attacking exclusively the less hindered side. The reaction stops at the enyne stage even when an excess of the hydride complex is used (eq 2).[3]

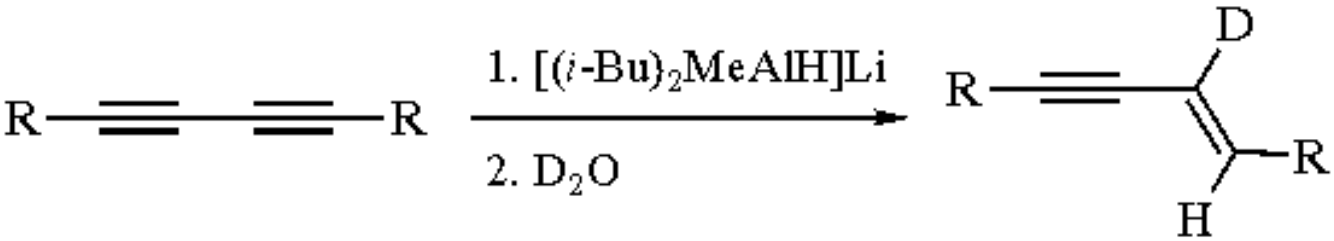

(2)

R	Yield (%)	Geometrical purity (%)
n-Bu	92	99
i-Bu	89	98
i-C_6H_{11}	91	98
t-Bu	80	96

The hydroalumination products have been captured by various electrophiles including carbon dioxide,[2] halogens,[6] and cyanogen,[8] with retention of double bond geometry (eq 3). This provides a method to prepare isomerically pure α,β-unsaturated acids, nitriles, and vinyl halides.

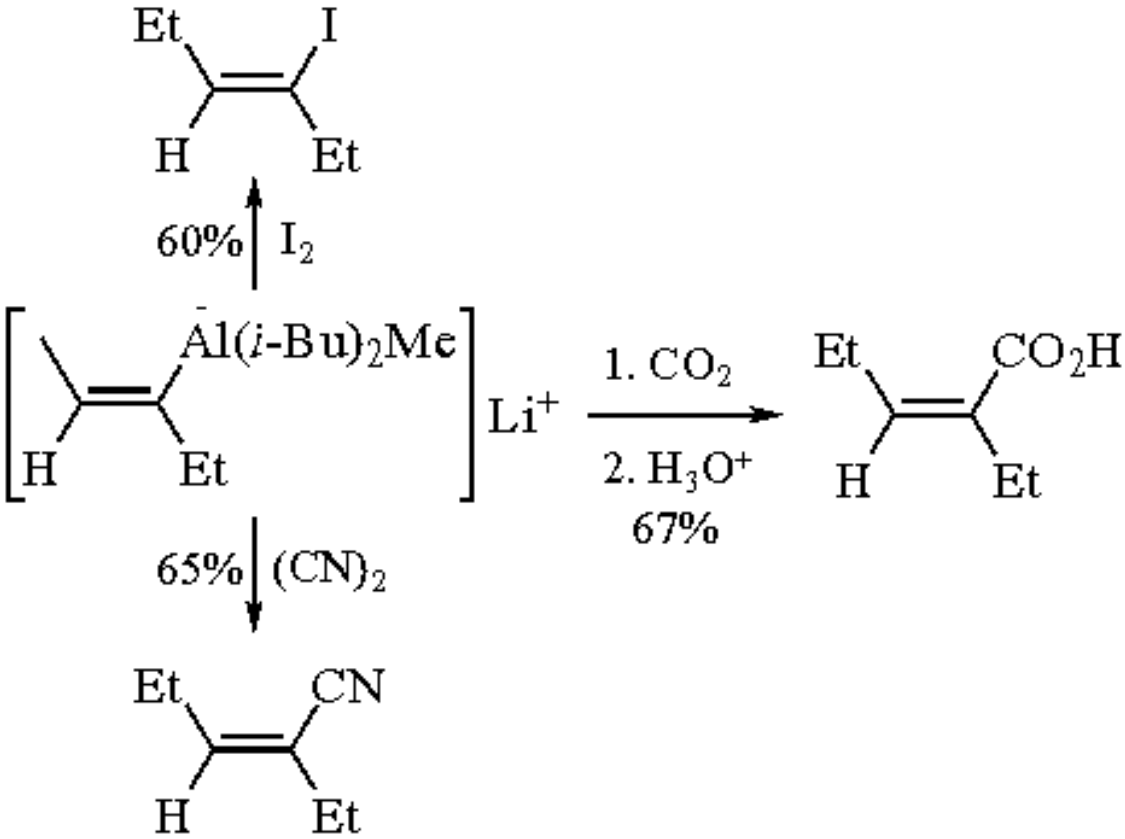

(3)

Condensation of vinylalanates with aldehydes affords an efficient route to allylic alcohols (eq 4).[7,8]

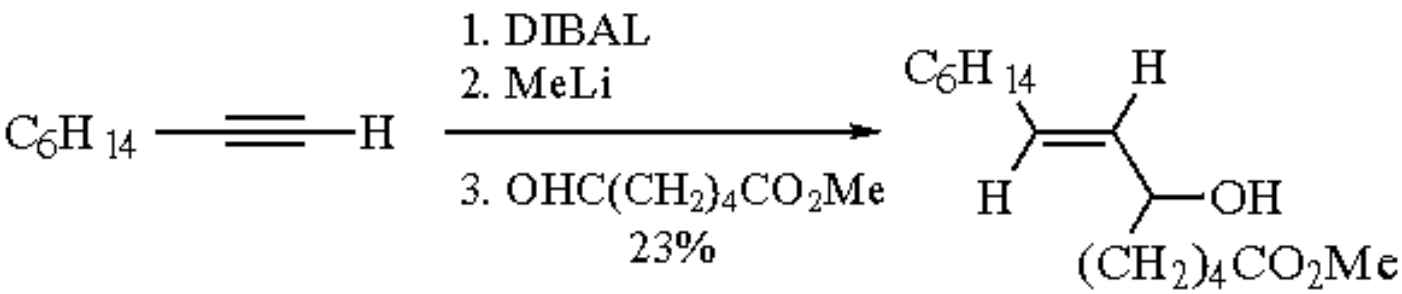

(4)

The reaction of the aluminum ate complex with an allylthiosulfonate provides a strategy for preparing a thioether of (*Z*) stereochemistry about the vinyl moiety. The method serves as a general route to stereodefined thioethers as precursors for thio-Claisen rearrangements (eq 5).[9]

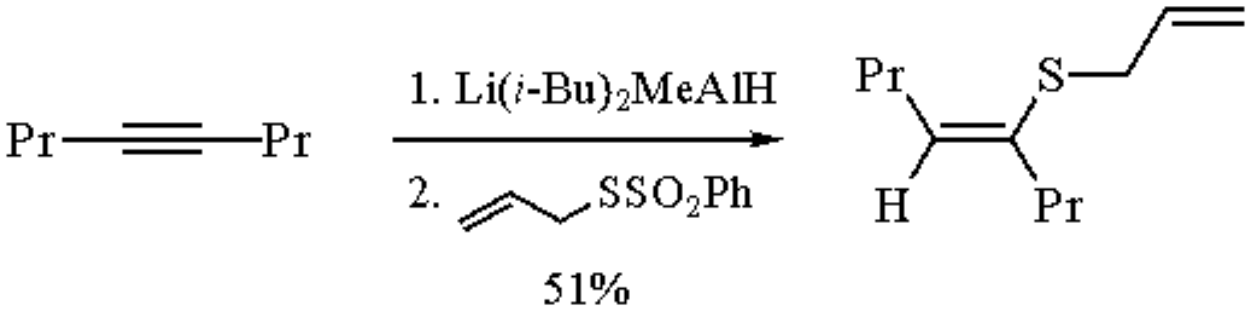

(5)

The vinyl ligand of the ate complex has also been added in a 1,4-manner to α,β-unsaturated ketones. No 1,2-addition

was observed, and no reaction occurred at the ester group (eq 6).[10]

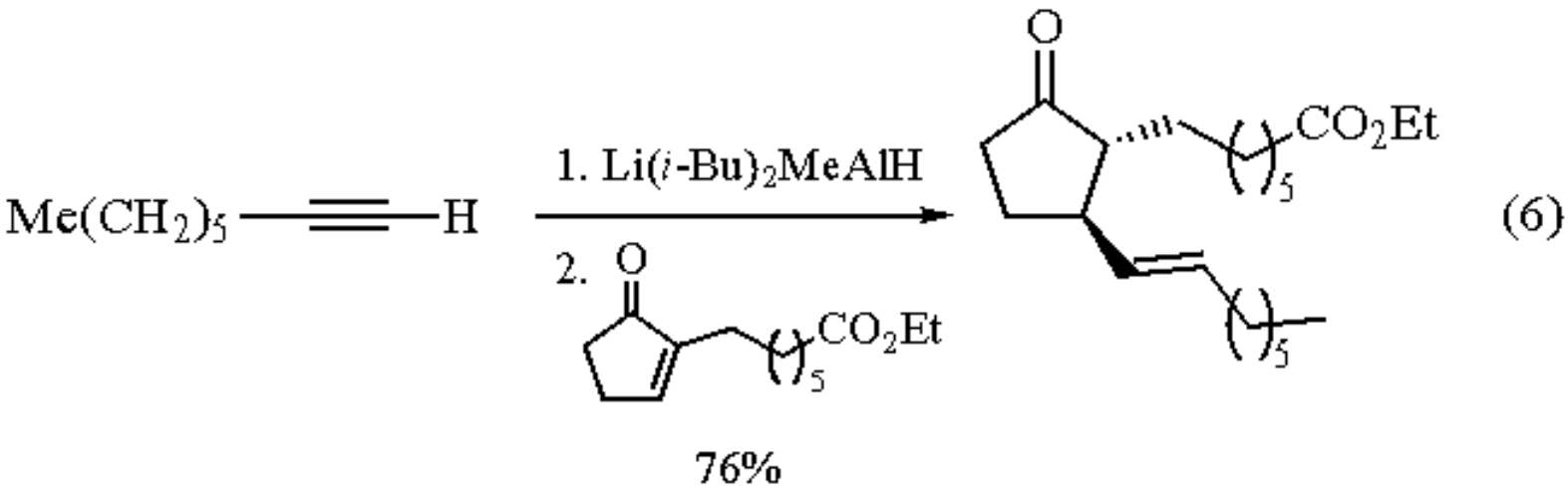

Selective Reduction.

It was reported that Li(R)(i-Bu)$_2$AlH (R = n-Bu, t-Bu, Me) can accomplish 1,4-reduction of α,β-unsaturated ketones in combination with ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD) (eq 7).[4]

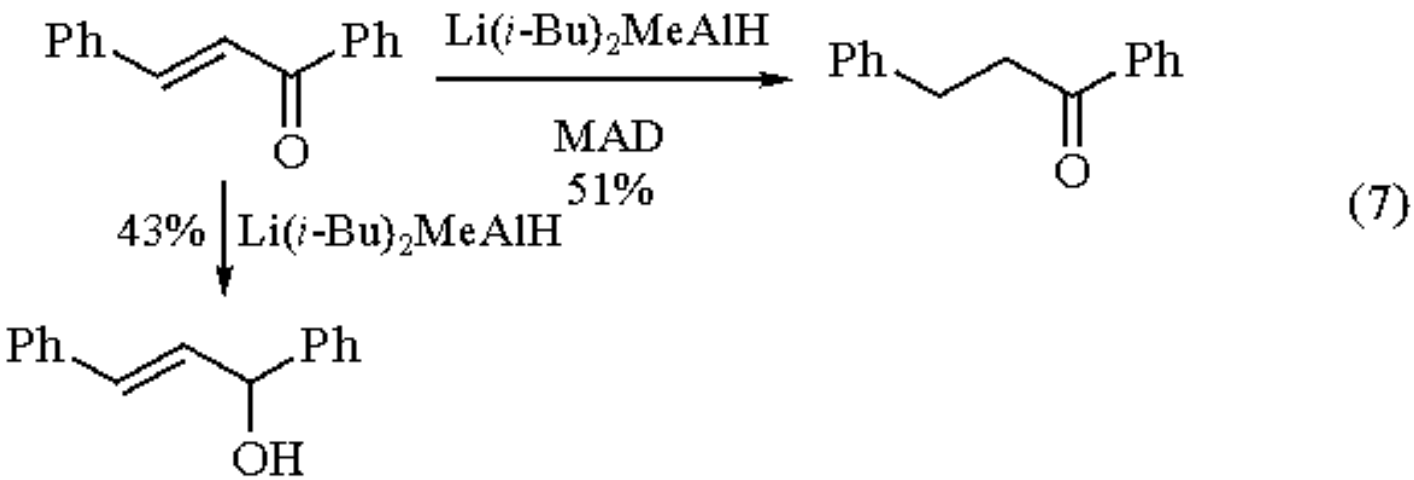

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Lithium Diisopropenylcuprate[1,2]

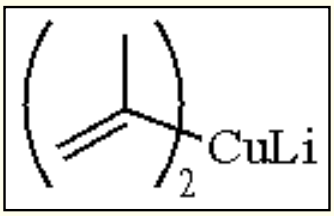

[21329-14-6] · $C_6H_{10}CuLi$ · Lithium Diisopropenylcuprate · (MW 152.65)

(isopropenylating reagent; undergoes conjugate addition reactions,[1a] 1,2-addition reactions,[3] substitution reactions with oxiranes[4] and alkyl, vinyl, and aryl substrates,[1e] carbocupration of alkynes,[5] and acylation reactions[1e])

Physical Data: chocolate-brown slurry in Et_2O at -78 °C.[2]

Solubility: sol THF, Et_2O.

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide*** or $CuBr.SMe_2$ (see ***Copper(I) Bromide***)) under N_2 or argon atmosphere.[2] Rate of cuprate formation is temperature- and Cu^I salt-dependent, and reagent prepared from Cu^I halides is critically dependent on the purity of the salt used (see ***Lithium Dimethylcuprate*** for purification of CuI and CuBr). Dark-colored solutions are indicative of decomposition.

Handling, Storage, and Precautions: stable in solution for several h below -60 °C; however, at elevated temperatures of 0 °C to -15 °C, thermal dimerization occurs and only 2,3-dimethyl-1,3-butadiene can be detected.[2] Air and moisture sensitive.

Introduction.

Lithium diisopropenylcuprate (**1**) displays the characteristic reactivity patterns of lithium diorganocuprates (see ***Lithium Di-n-butylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***).

Addition Reactions.

Reaction of (**1**) with α,β-alkenyl ketones (eq 1),[1,6] esters,[1e] and lactones[7,8] results in 1,4-transfer of the isopropenyl ligand. Several natural product syntheses employ this particular methodology as a key step.[6,7,9] A homoconjugate addition reaction of (**1**) with 1-(arylsulfonyl)bicyclobutanes (eq 2) has been observed.[10] The resultant substituted

cyclobutane derivative arises from addition across the central bond of the bicyclobutane from the *endo* side. Acylvinylcyclopropanes also afford homoconjugate addition products, and dienyl systems generally yield 1,6-addition products (eq 3).[11] 2-Pyrones can be converted to 2-siloxypyrylium salts,[12] which undergo regioselective addition at the 4-position (eq 4).

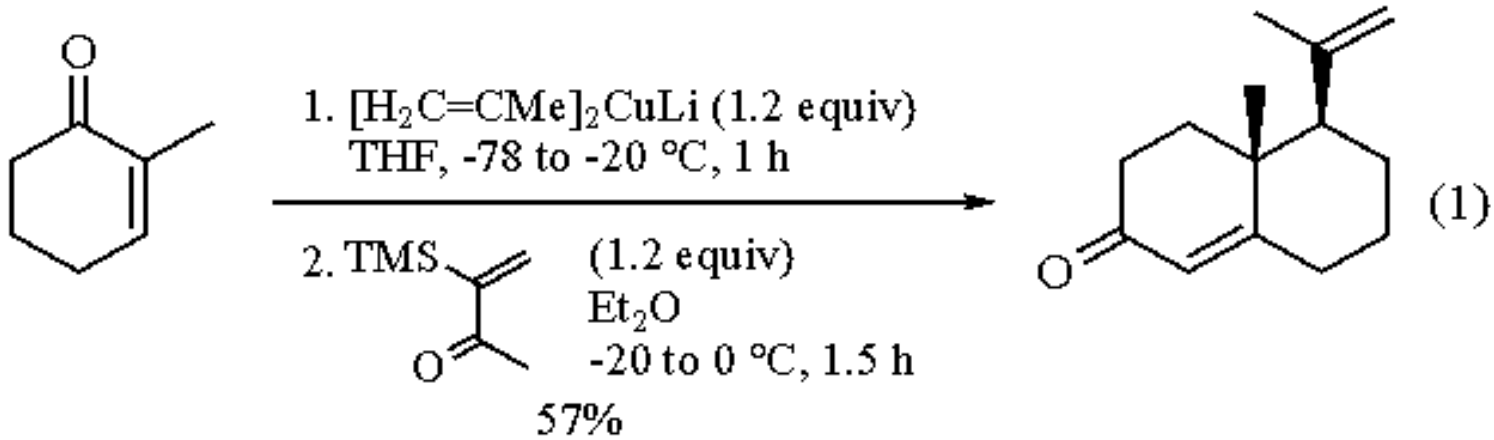

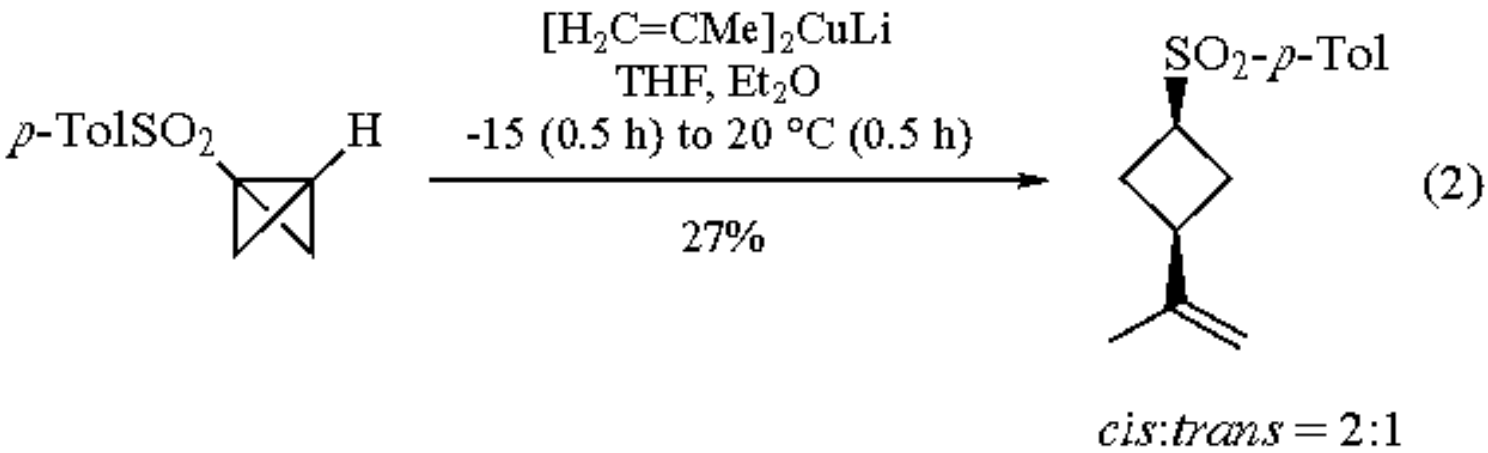

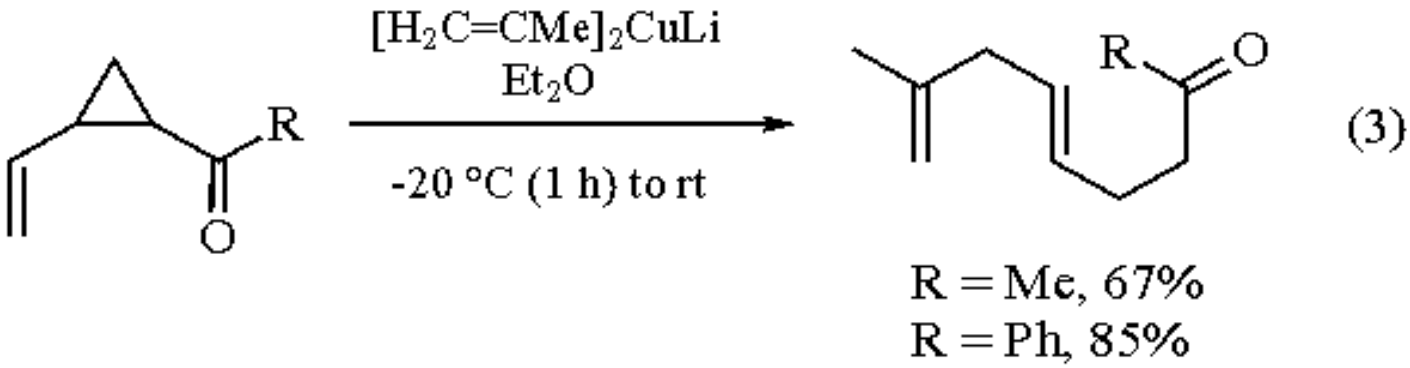

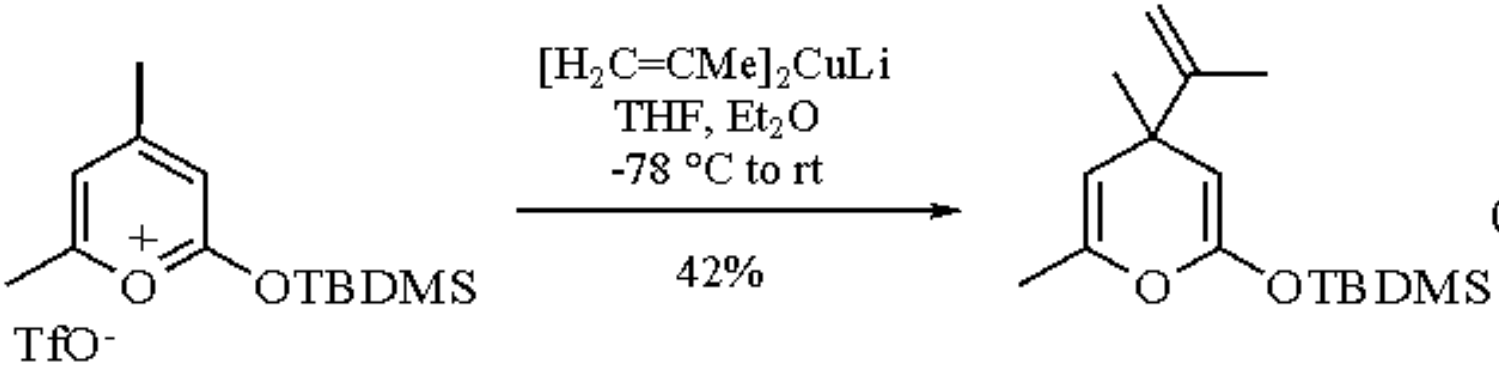

(4)

The key step in the synthesis of the C(7)-C(13) subunit of erythronolide B involved the reaction of (**1**) with (*R*)-3-benzyloxy-2-methylpropionaldehyde to afford the 1,2-addition product.[3] The stereochemistry of addition was controlled by chelation effects.

$[CH_2{=}C(Me)]_2CuLi$ effects carbocupration of acetylene in good yield. Generally, only those vinylic cuprates having a substituent geminal to copper afford satisfactory yields.[5]

Substitution Reactions.

Although isopropenyl transfers in epoxide substitutions are rare, (**1**) reacts with β,γ-epoxy alcohols[4] and epoxy esters (eq 5).[13] Reaction regioselectivity and yields are temperature dependent, and Cu^I-catalyzed Grignard additions are preferred. Cyanocuprates [e.g. $(CH_2{=}C(Me))CuCNLi$ and 2 $(CH_2{=}C(Me))Li$ + CuCN] afford better results in oxirane cleavage reactions.

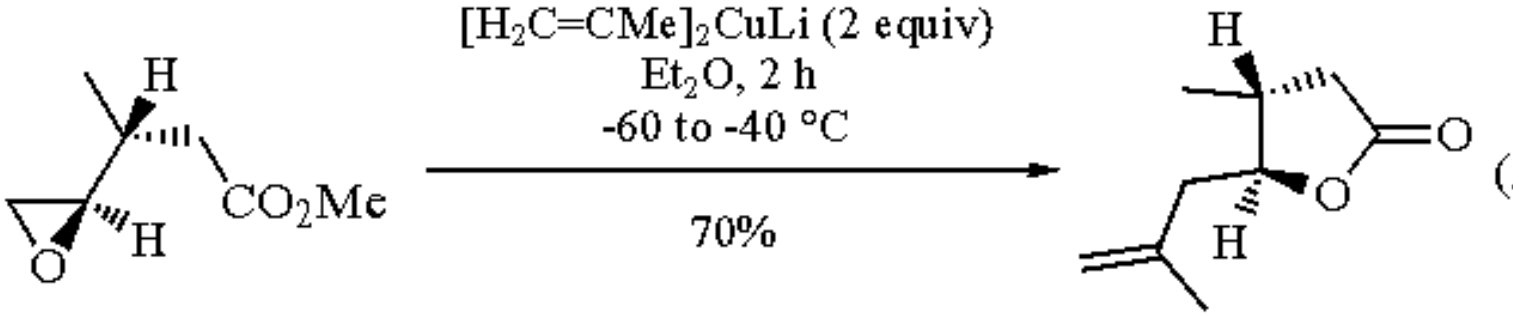

(5)

The title reagent participates in general substitution reactions with alkyl (e.g. halides[14,15] and tosylates[15]), vinyl (eq 6),[16] and aryl (eq 7)[14] substrates.[1a,e] Acylation of (**1**) with acid chlorides is a poor synthetic route to 1-methylvinyl ketones.[2] Mixtures result from conjugate addition of the organocopper reagent to the product α,β-enone.

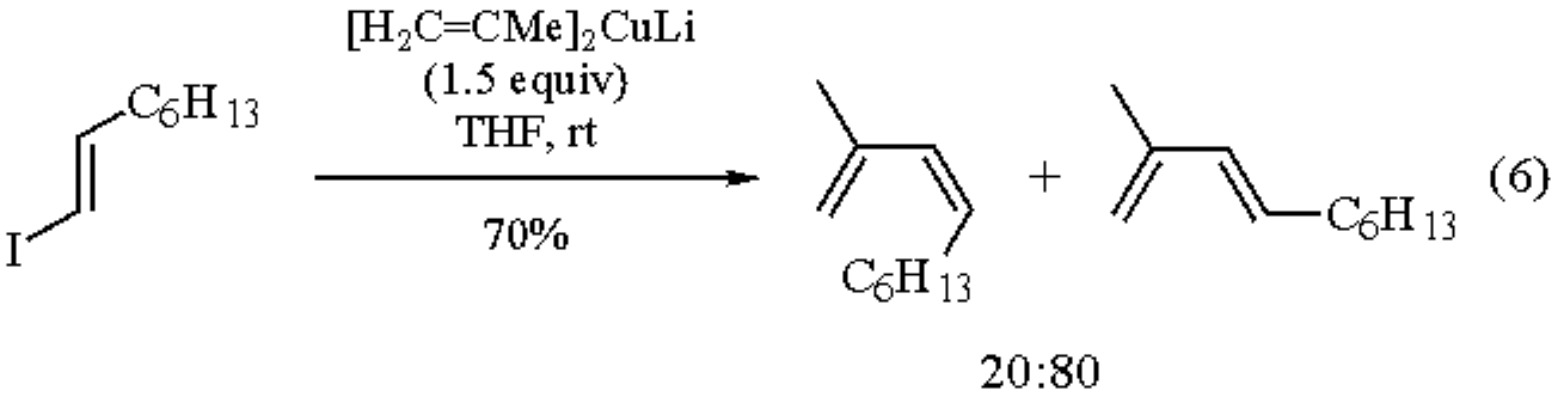

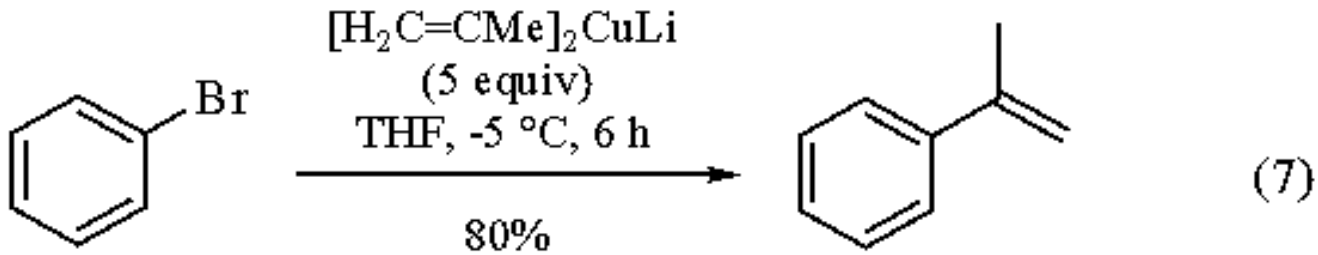

Related Reagents.

Lithium Diallylcuprate; ***Lithium Bis(1-ethoxyvinyl)cuprate***; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Di-(E)-1-propenylcuprate***; ***Lithium Divinylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

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Janice W. Dieter & R. Karl Dieter

Lithium Diisopropylamide[1,2]

***i*-Pr$_2$NLi**

[4111-54-0] · $C_6H_{14}LiN$ · Lithium Diisopropylamide · (MW 107.15)

(hindered nonnucleophilic strong base used for carbanion generation, especially kinetic enolates,[4] α-heteroatom, allylic,[5,6] and aromatic and heteroaromatic carbanions;[7-9] unavoidable in organic synthesis)

Alternate Name: LDA.

Physical Data: powder, melts with decomposition; pK_a = 35.7 in THF.[3]

Solubility: sol Et_2O, THF, DME, HMPA; unstable above 0 °C in these solvents; stable in hexane or pentane (0.5-0.6 M) at rt for weeks, when not cooled or concentrated;[10] the complex with one molecule of THF is soluble in alkanes like cyclohexane and heptane.

Form Supplied in: solid; 2.0 M solution in heptane/THF/ethylbenzene stabilized with Mg(*i*-Pr$_2$N)$_2$; 10 wt % suspension in hexanes; LDA.THF complex, 1.5 M solution in cyclohexane and 2.0 M in heptane.

Analysis of Reagent Purity: several titration methods have been described.[120]

Preparative Methods: generally prepared directly before use from anhydrous ***Diisopropylamine*** and commercially available solutions of ***n-Butyllithium***. Another process, especially useful for the preparation of large quantities, is the reaction of styrene with 2 equiv of ***Lithium*** and 2 equiv of *i*-Pr$_2$NH in Et_2O.[11]

Handling, Storage, and Precautions: very moisture- and air-sensitive, and should always be kept in an inert atmosphere; irritating to the skin and mucous membranes; therefore contact with skin, eyes, and other tissues and organs should be avoided; proper protection is necessary. Use in a fume hood.

Enolates.

LDA is undeniably the first-choice base for the quantitative formation of enolates in general and kinetic (usually less substituted) enolates in particular. It was first used for this purpose by Hamell and Levine;[12] now it is a rare day (or night) that a chemist does not use or a graduate student does not propose LDA for a carbanionic transformation. Its advantages (fast, complete, and regiospecific enolate generation, unreactivity to alkyl halides, lack of interfering products) over earlier developed bases (e.g. ***Sodium Hydride***, ***Triphenylmethyllithium***)[13] are no longer noted. Except for enolates of aldehydes, which are very reactive and undergo self-aldol condensation reactions,[14] the derived lithio

enolates can be used for a broad spectrum of reactions including *O*- and *C*-alkylations and acylations, transmetalation to other synthetically useful metallo enolates,[15] and a multitude of carbanion-based condensations and rearrangements. The trapping of kinetically derived lithio enolates with ***Chlorotrimethylsilane*** as silyl enol ethers[16] (e.g. eqs 1 and 2),[17] originally used for separation from minor regioisomers and regeneration (with ***Methyllithium*** or ***Lithium Amide***) for the purpose of regiospecific alkylation, has been superseded in general by methods of their direct alkylation under Lewis acid catalysis.[18]

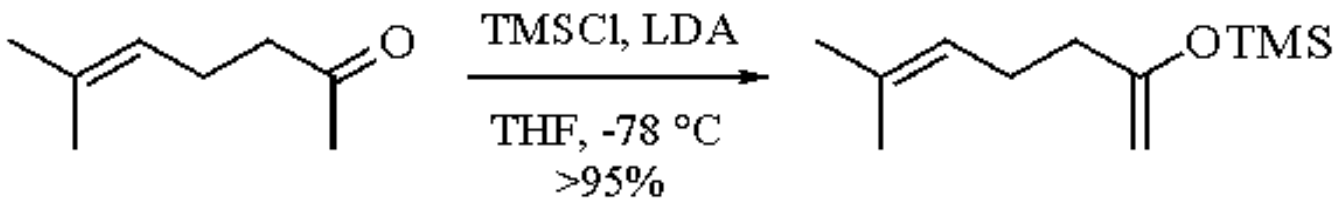

(1)

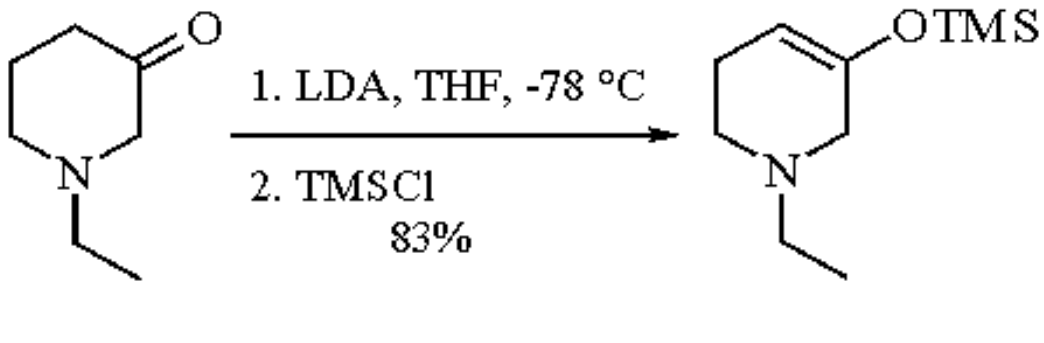

(2)

Consonant with its pK_a, LDA is used to derive a variety of α-stabilized carbanions, e.g. ketones (eqs 1 and 3),[19,20] α-amino ketones,[21] o-bromo ketones (eq 4),[10] imines (eqs 6 and 7),[22-24] imino ethers (eq 8),[25] carboxylic acids (eq 9),[26] carboxylic esters,[27] lactones,[28] amides,[29] lactams,[30] imides,[31] and nitriles[32] which may be alkylated or used in aldol condensations. Enolates of methyl ketones may be *O*-alkylated with ***Diethyl Phosphorochloridate*** to give enol phosphates which, upon β-elimination, afford terminal alkynes in high yields (eq 5).[33]

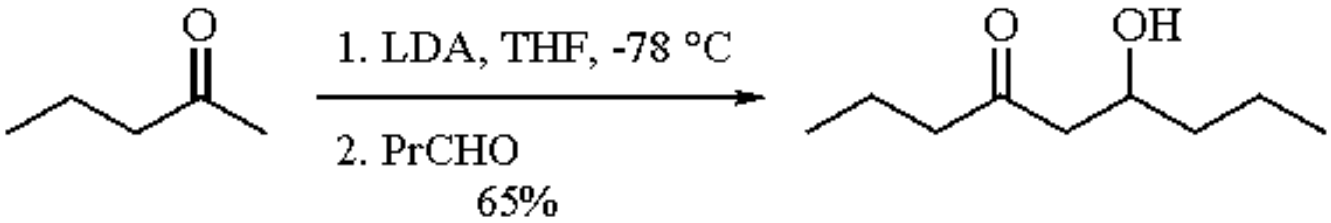

(3)

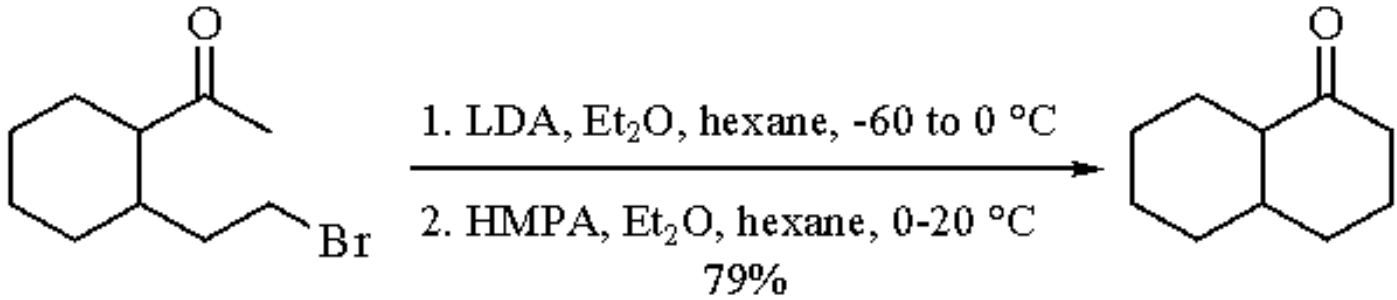

(4)

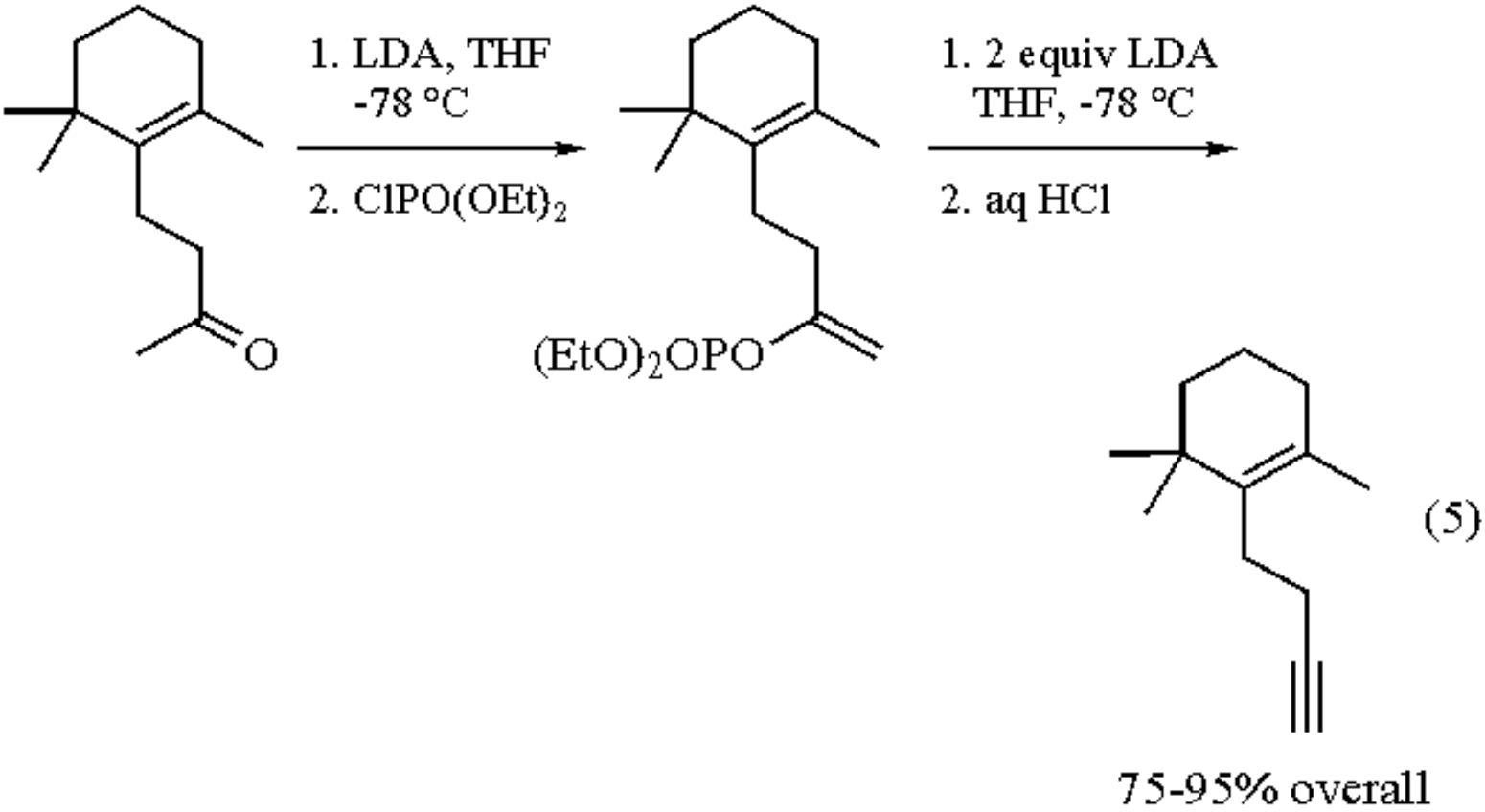
1. LDA, THF
-78 °C
2. ClPO(OEt)2
1. 2 equiv LDA
THF, -78 °C
2. aq HCl
O
(EtO)2OPO
(5)
75-95% overall

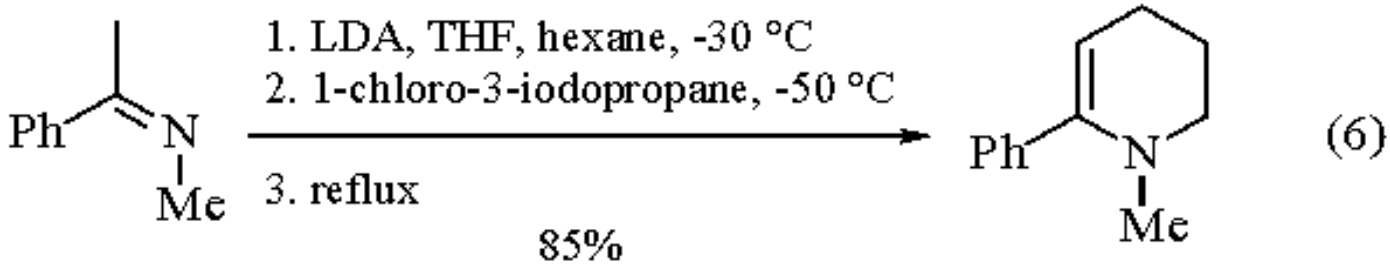
1. LDA, THF, hexane, -30 °C
2. 1-chloro-3-iodopropane, -50 °C
3. reflux
85%
Ph
N
Me
(6)

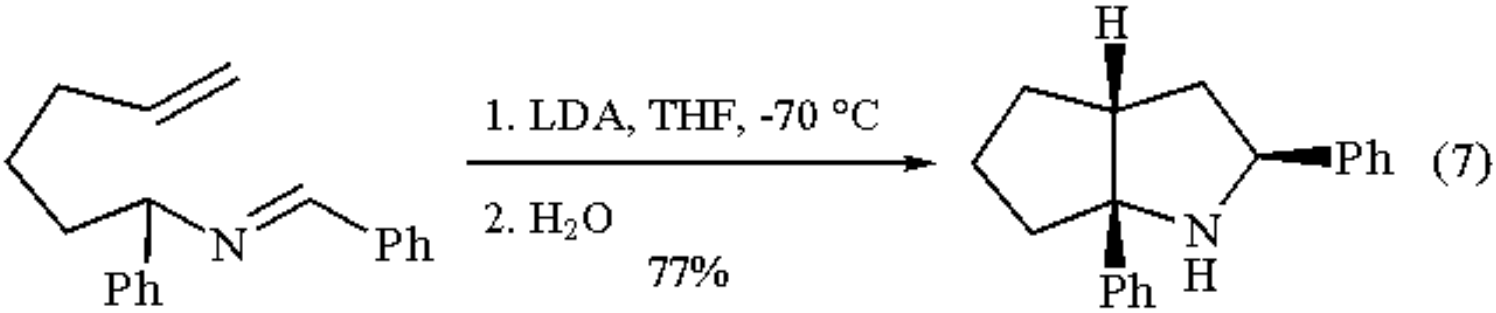
1. LDA, THF, -70 °C
2. H2O
77%
Ph
N
H
(7)

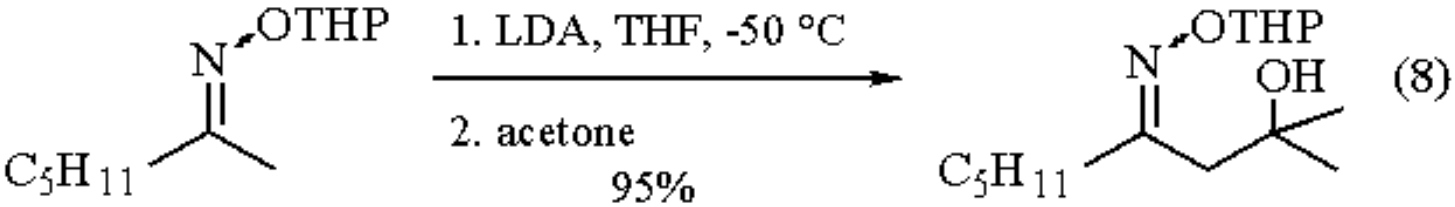
OTHP
N
C5H11
1. LDA, THF, -50 °C
2. acetone
95%
OH
(8)

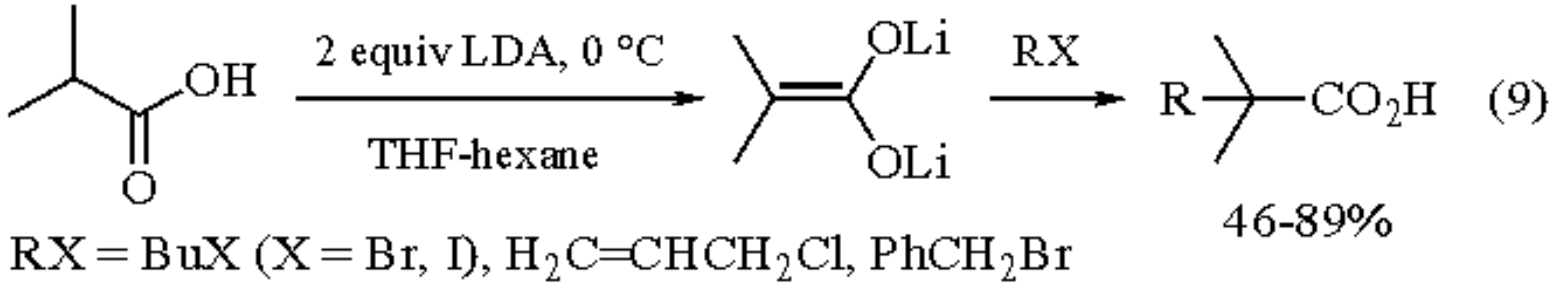

The (*Z*)/(*E*) stereoselectivity of enolate formation is dictated by the structure of the starting carbonyl compound and the base used for deprotonation. Compared to LDA, ***Lithium 2,2,6,6-Tetramethylpiperidide*** usually favors (*E*)-enolates whereas ***Lithium Hexamethyldisilazide*** preferentially leads to (*Z*)-enolates (eq 10).[34] With a *caveat* for any generalization, enolate configuration usually determines the stereochemical result in the product; for example, using a hindered ester and a bulky aldehyde combination, excellent stereoselectivities in aldol reactions are observed (eq 11).[27]

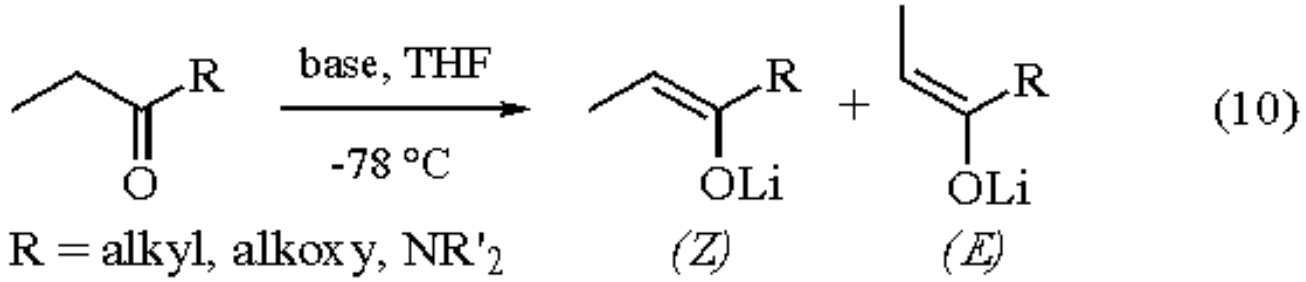

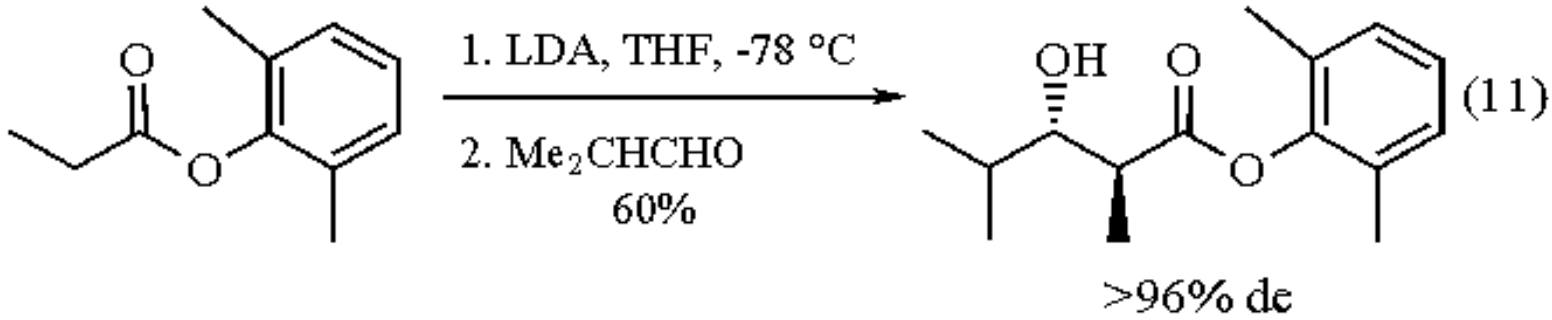

A useful reaction of ketone enolates is their oxidative coupling,[35] e.g. in the formation of a tricyclic intermediate towards the synthesis of the diterpene cerorubenic acid-III (eq 12).[36]

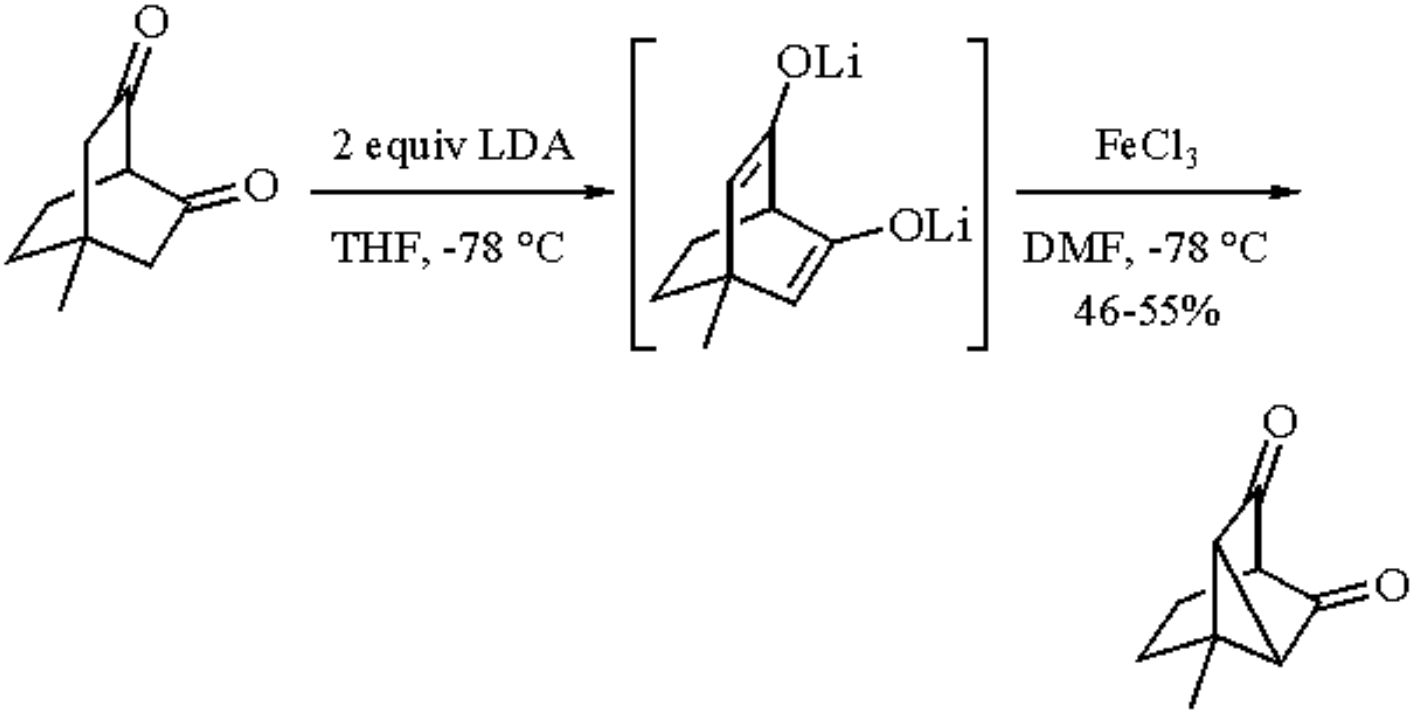

(12)

Alkylation of β-lactone enolates proceeds with high stereoselectivity dictated by strong stereocontrol from the C-4 R substituent (eq 13).[28] A similar result is obtained with the lithium enolates of diarylazetidinones which, on reaction with aldehydes, alkylate with high *cis* diastereoselectivity (eq 14).[30]

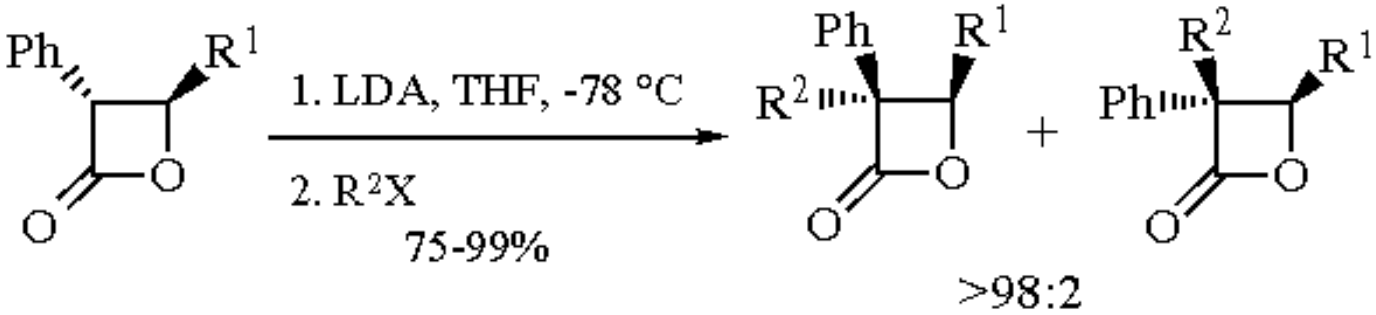

(13)

$R^1 = t\text{-Bu}$, $R^2 = \text{Me, Et, CH}_2\text{Ph, CH}_2\text{CO}_2\text{Me}$
$R^1 = i\text{-Pr}$, $R^2 = \text{Me, CH}_2\text{CH=CH}_2\text{, CO}_2\text{Me, CH}_2\text{C}\equiv\text{CH, COPh}$

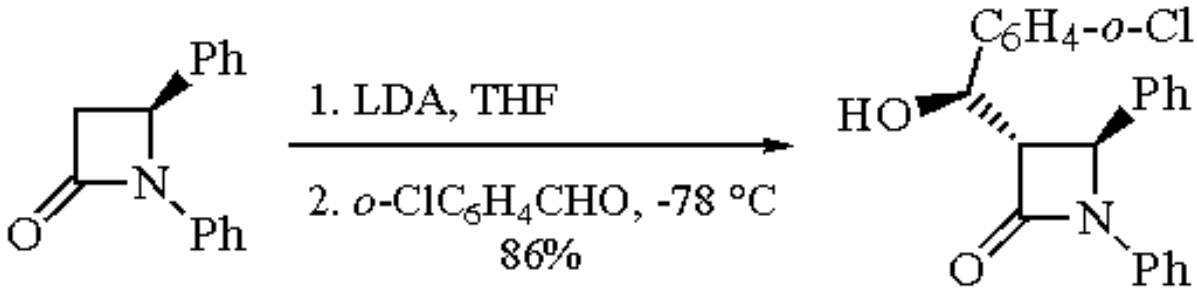

(14)

Sarcosine (*N*-methylglycine)-containing tripeptides and hexapeptides are poly-deprotonated in the presence of excess ***Lithium Chloride*** to give amide enolates which give *C*-alkylated sarcosine products with ***Iodomethane***, ***Allyl Bromide***, and ***Benzyl Bromide*** (eq 15).[29] With (*S*) configuration amino acids, the newly formed stereogenic center tends to have

the (*R*) configuration. α-Nitrile carbanions are generally useful in alkylation and other reactions with electrophiles, e.g. eq 16.[32]

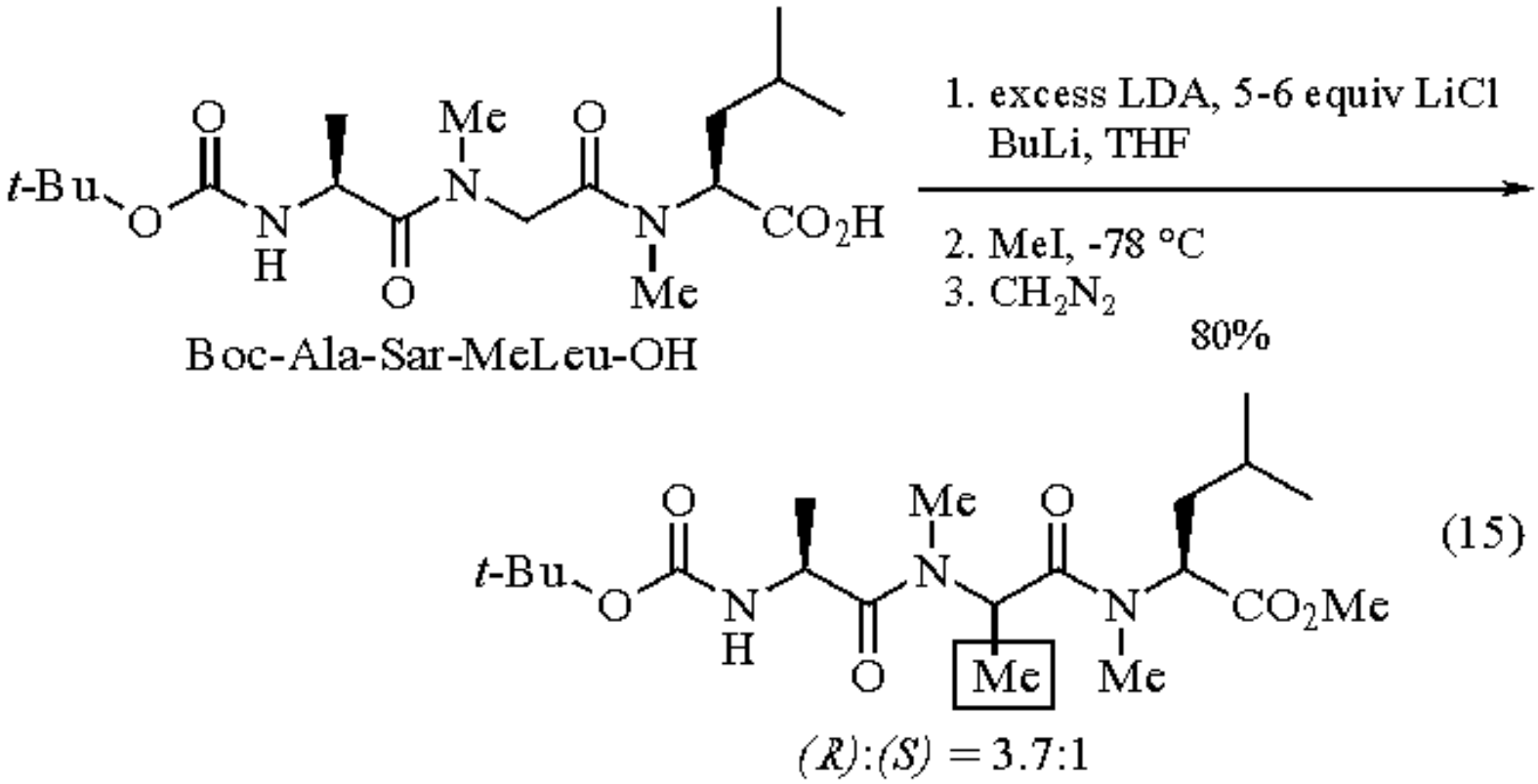

(15)

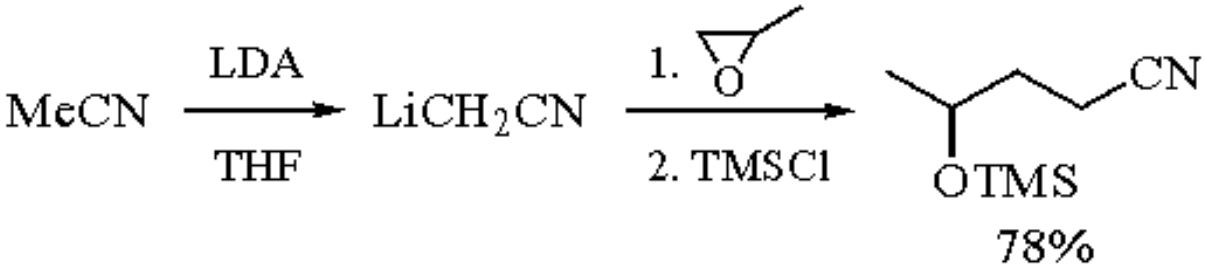

(16)

α,β-Unsaturated Carbonyl Compounds.

Of particular synthetic value is the generation of kinetic enolates of cyclic enones which may be alkylated (e.g. eq 17)[37] or undergo more demanding processes, e.g. double Michael addition (eq 18).[38] Imines of α,β-unsaturated aldehydes and ketones with δ-acidic hydrogens undergo clean deconjugative α-alkylation (eq 19).[23,39]

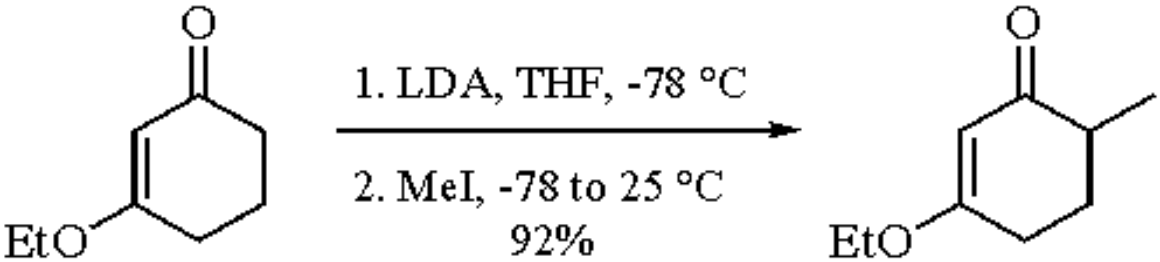

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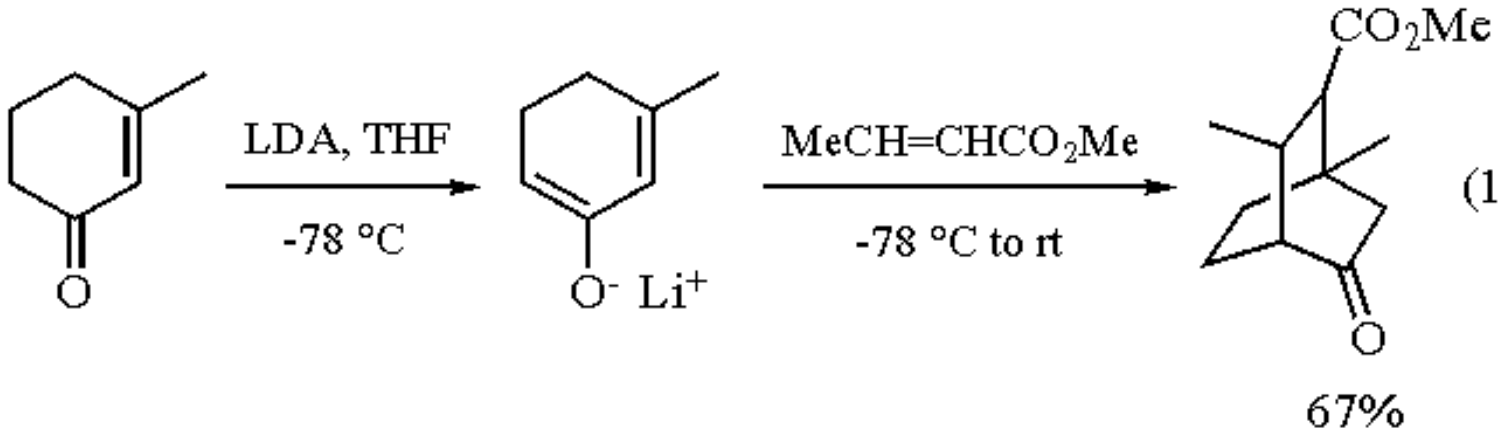

(18)

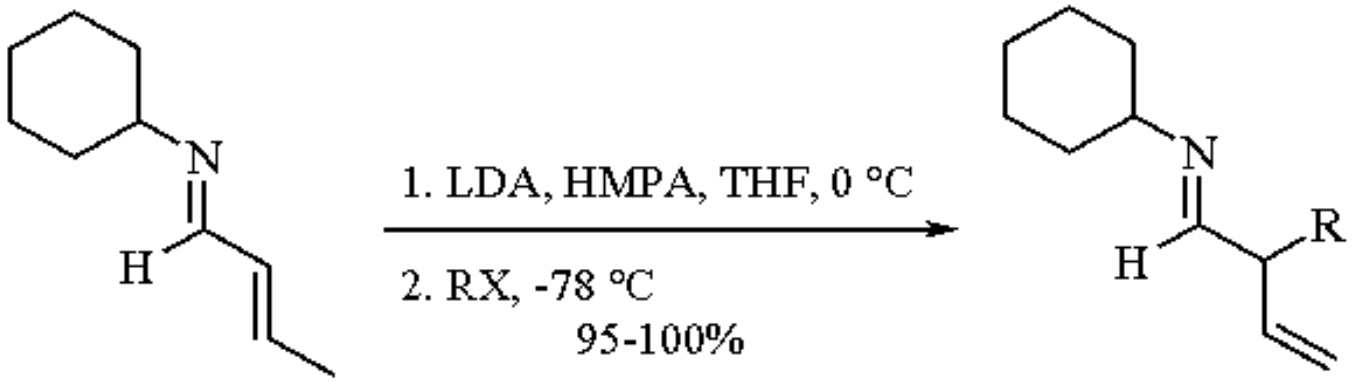

(19)

R = Me, $H_2C{=}CHCH_2$, $HC{\equiv}CCH_2$, $PhCH_2$, *i*-Pr, Bu
X = I, Br

Copper dienolates of α,β-unsaturated acids, prepared by ***Copper(I) Iodide*** transmetalation, can be selectively γ-alkylated with allylic halides; the use of nonallylic electrophiles leads mainly to α-alkylation (eq 20).[40] Copper enolates of α,β-unsaturated esters[41] and amides[42] show similar behavior.

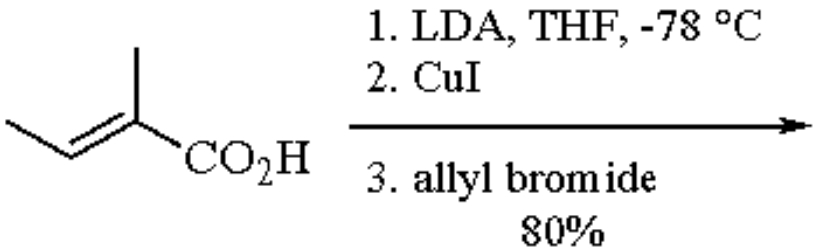

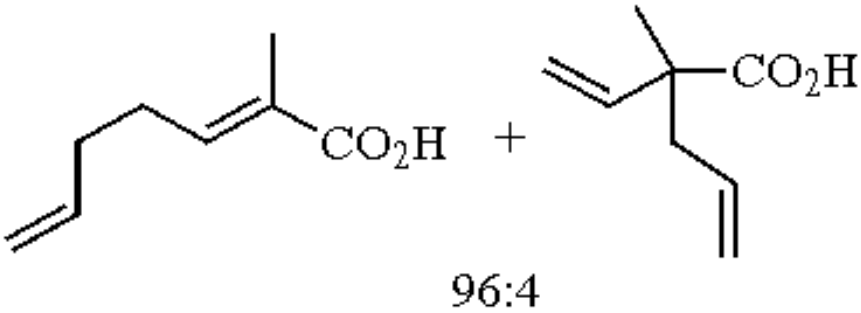

(20)

Enolates with Chiral Auxiliaries.

Enantioselective alkylation of carbonyl derivatives encompassing chiral auxiliaries constitutes an important synthetic process. The anions derived from aldehydes,[43] acyclic ketones,[44,45] and cyclic ketones with ***(S)-1-Amino-2-methoxymethylpyrrolidine*** (SAMP)[46] are used to obtain alkylated products in good to excellent yields and high enantioselectivity (e.g. eq 21).[46]

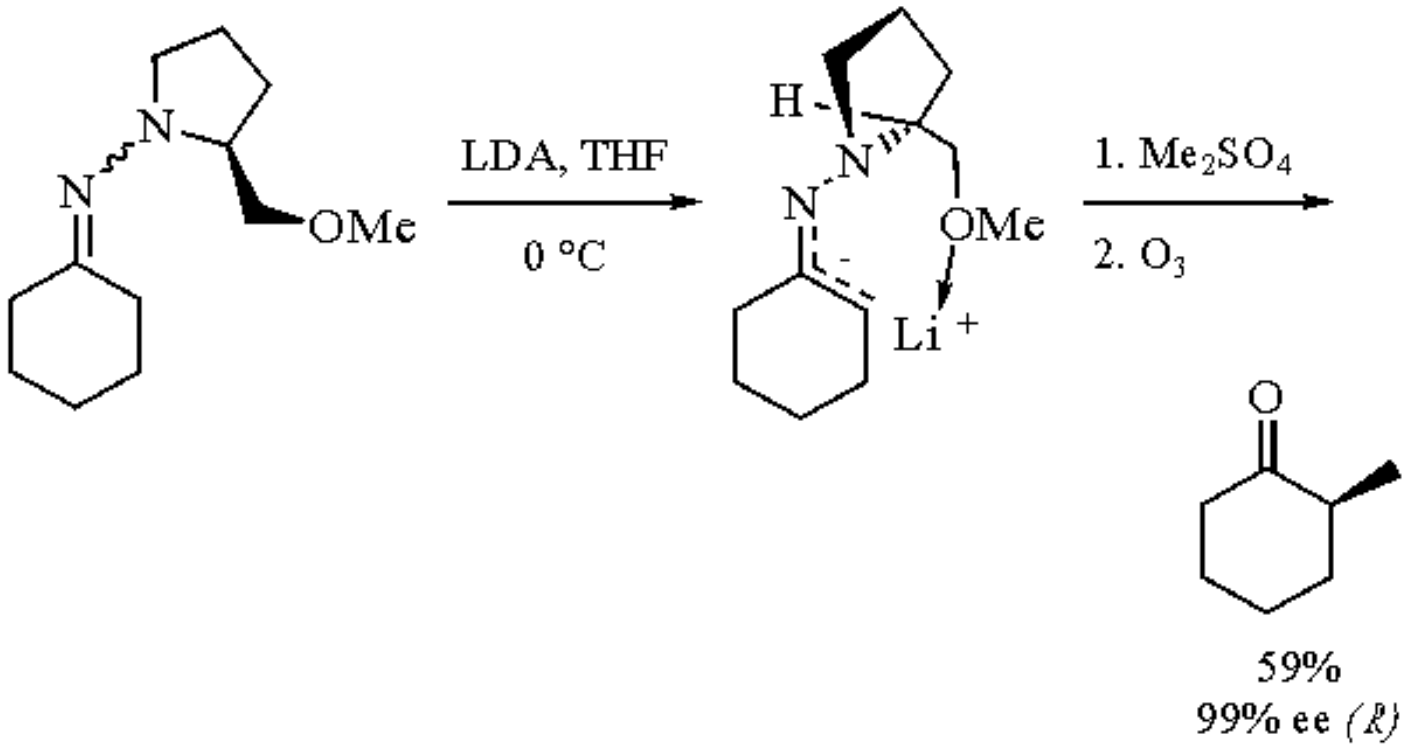

(21)

Metalation[47,48] of chiral oxazolines, derived from (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol, followed by alkylation and hydrolysis, leads to optically active dialkylacetic acids, e.g. eq 22,[49] 2-substituted butyrolactones and valerolactones,[50] β-hydroxy and β-methoxy acids,[51] 2-hydroxy carboxylic acids,[52] and 3-substituted alkanoic acids (eq 23).[53]

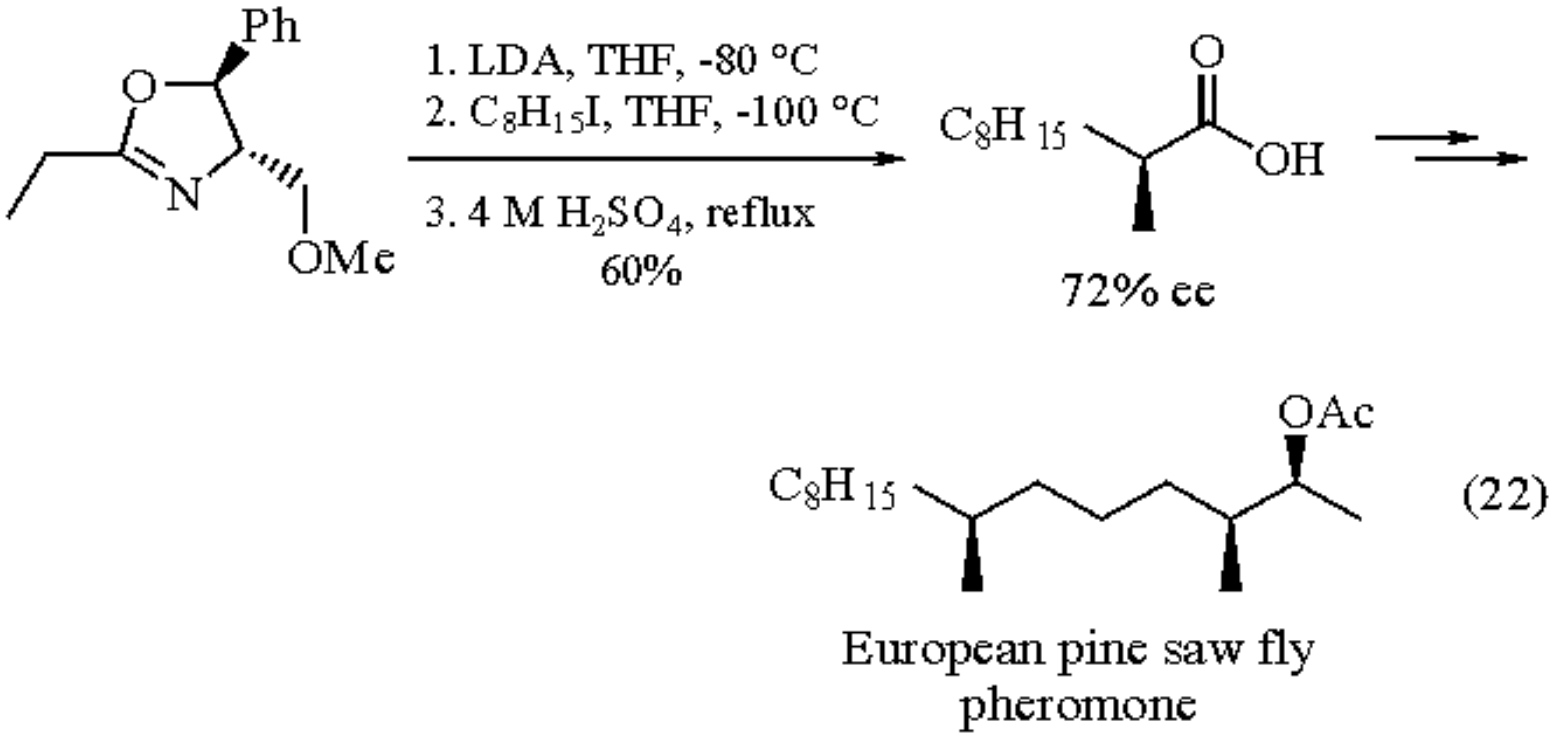

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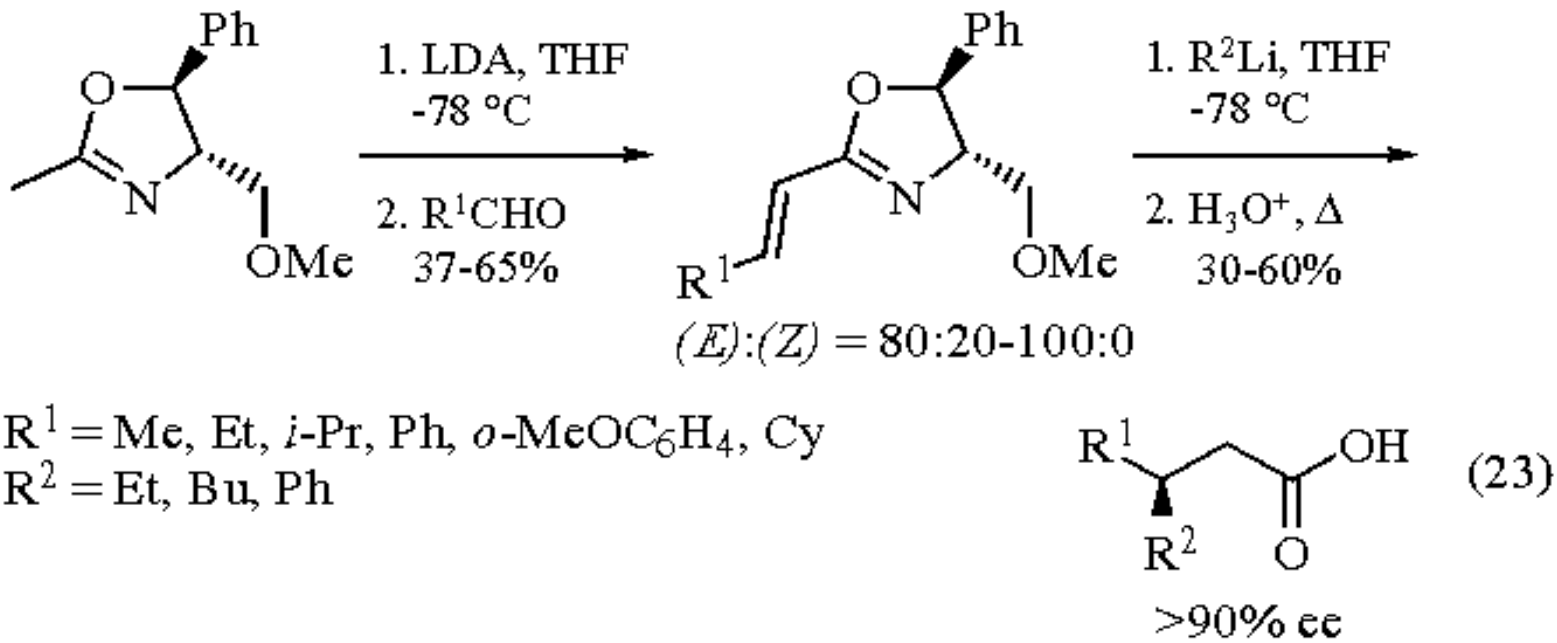

(23)

Imide enolates derived from (*S*)-valinol and (1*S*,2*R*)-norephedrine and obtained by either LDA or ***Sodium Hexamethyldisilazide*** deprotonation (eq 24)[54] exhibit complementary and highly diastereoselective alkylation properties. Mild and nondestructive removal of the chiral auxiliary to yield carboxylic acids, esters, or alcohols contributes to the significance of this protocol in small- and large-scale synthesis.[55,56]

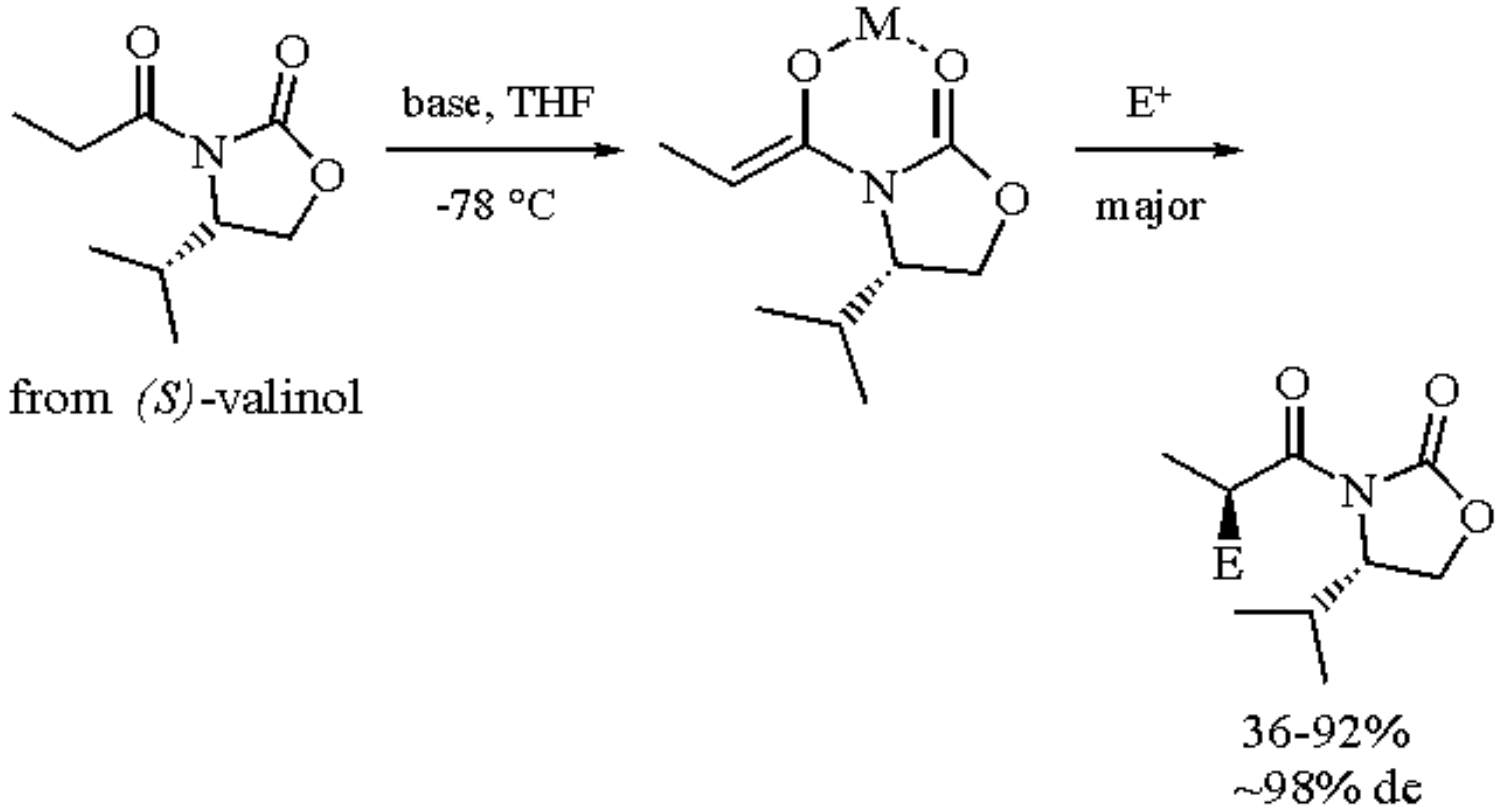

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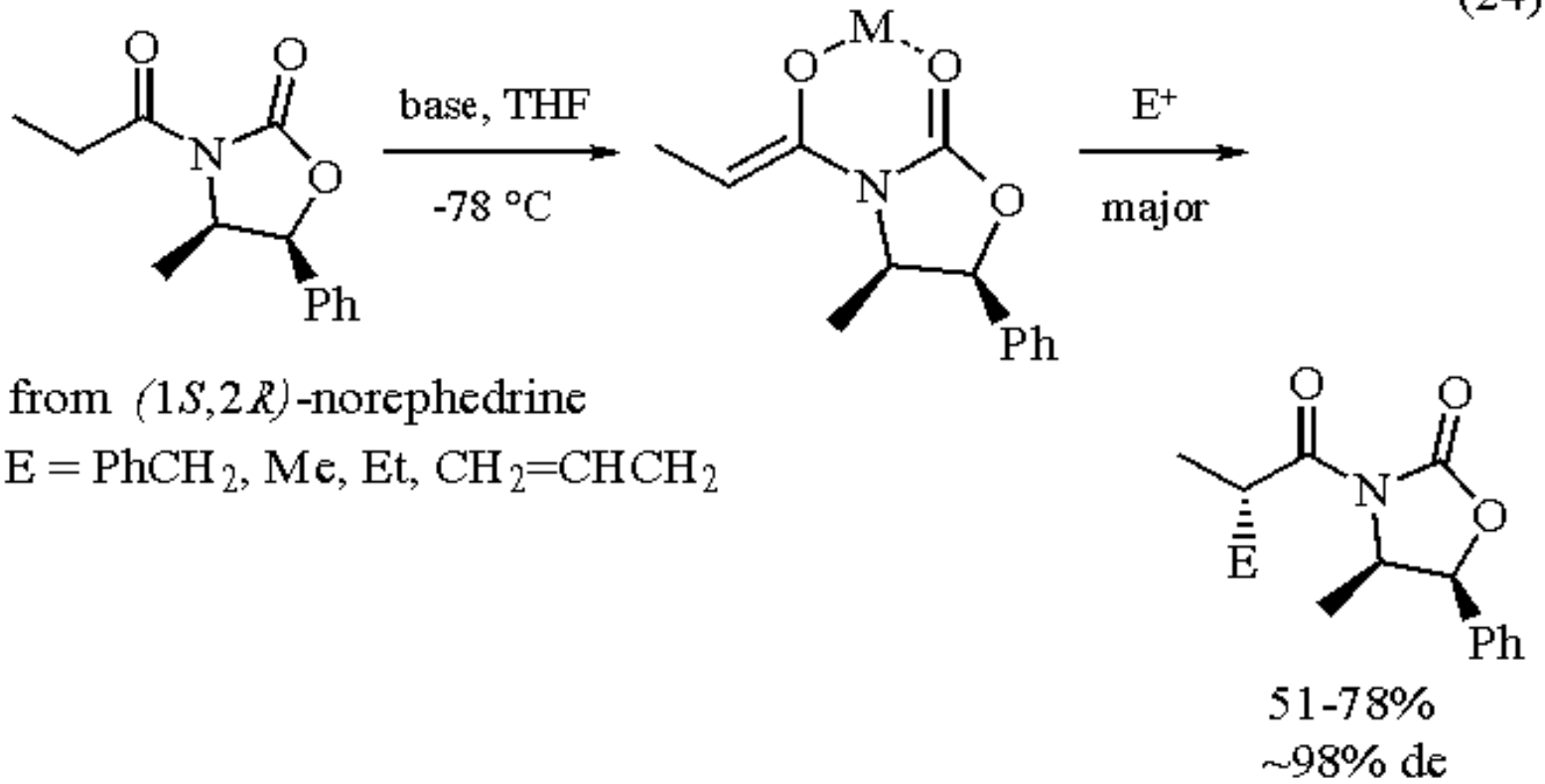

Metalated *t*-butyl 2-*t*-butyl-2,5-dihydro-4-methoxyimidazole-1-carboxylate is alkylated in good yields and with high *trans* diastereoselectivity (>99:1); hydrolysis of the resulting adducts liberates the α-amino acid methyl esters in high yields (eq 25).[57] Using this method, the (*S*)-*t*-butyl 2-*t*-butylimidazole derivative gave, upon isopropylation and hydrolysis, the L-valine methyl ester with 81% ee.

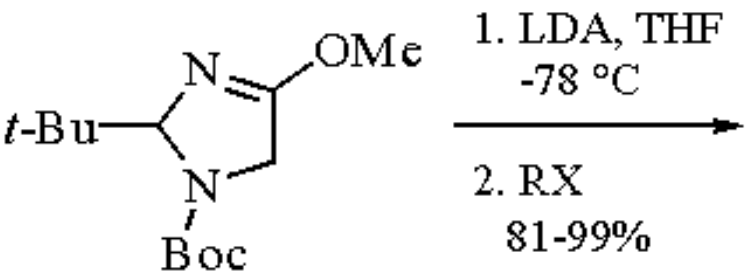

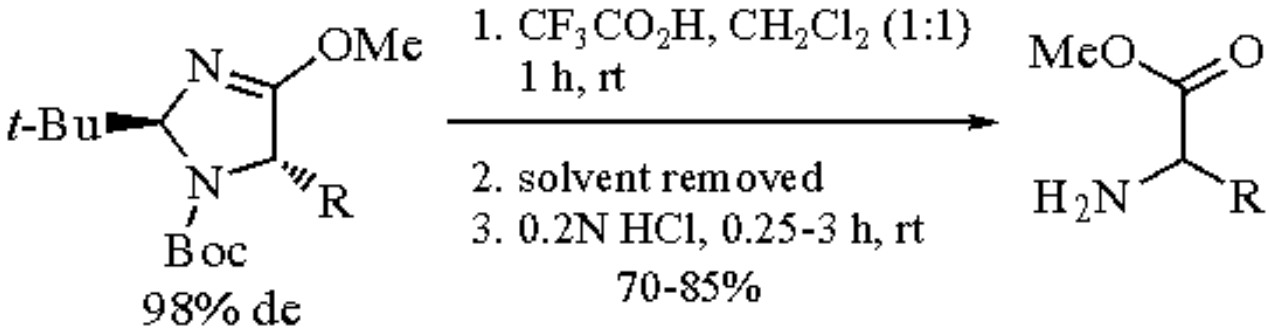

(25)

RX = MeI, EtI, $H_2C{=}CHCH_2Br$, *i*-PrI, $PhCH_2Br$

Alkylations and aldol condensations of aldehydes and ketones with enolates of chiral dioxolanes proceed generally with high diastereoselection, e.g. eq 26[58,59] and eq 27.[60] The magnesium enolate of *S*-(+)-2-acetoxy-1,1,2-triphenylethanol generated by transmetalation with ***Magnesium Bromide*** has enjoyed considerable success in aldol condensations, e.g. eq 28.[61]

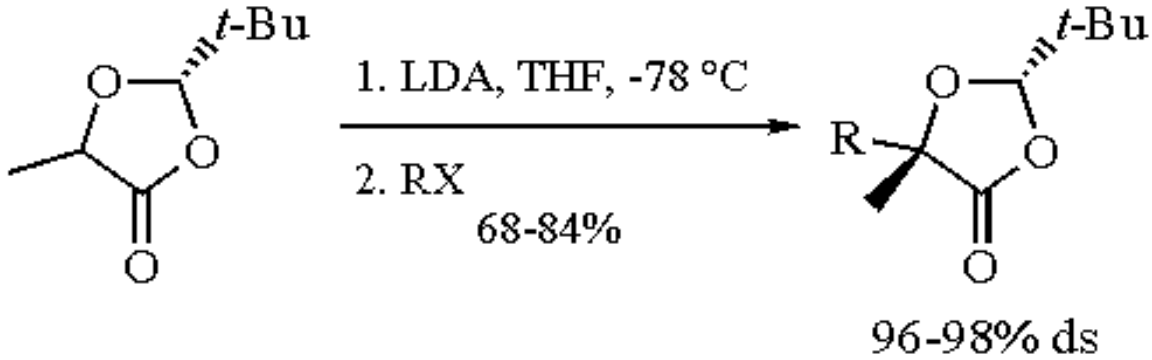

(26)

RX = EtI, PrI, BuI, $C_7H_{15}I$, $H_2C{=}CHCH_2Br$, $PhCH_2Br$

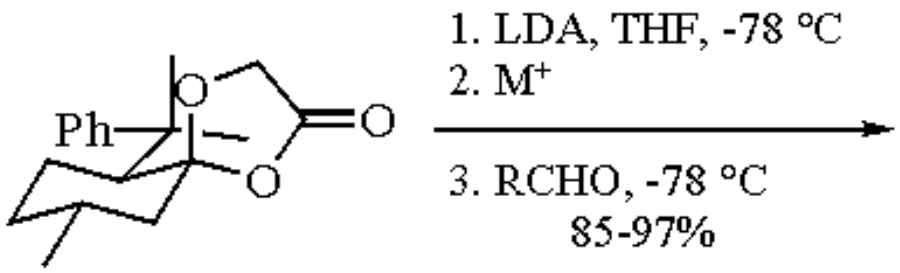

R = Ph, Pr, *i*-Pr

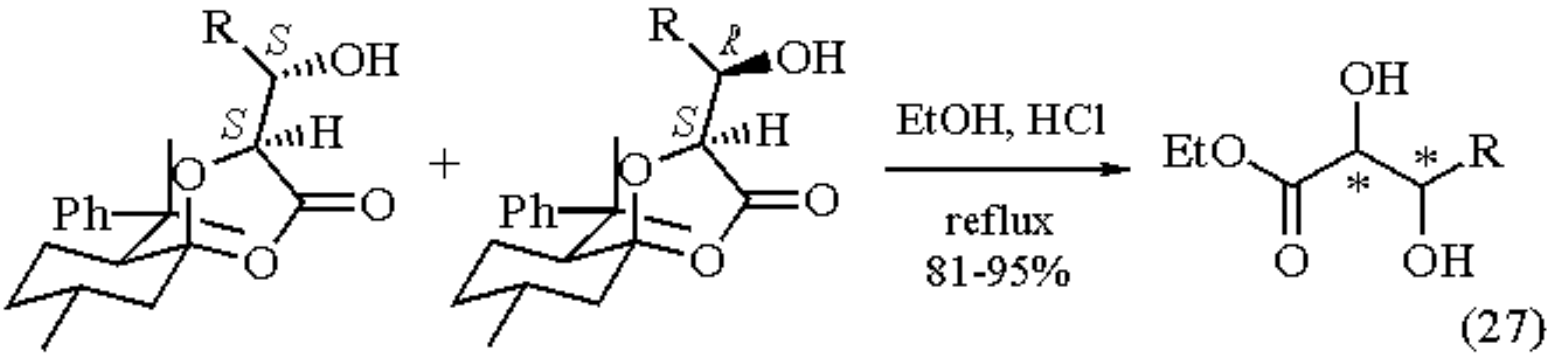

(27)

$M^+ = Li^+$	68:32-96:4
$M^+ = Mg^{2+}$	73:27-90:10
$M^+ = Zr^{4+}$	45:55-19:81

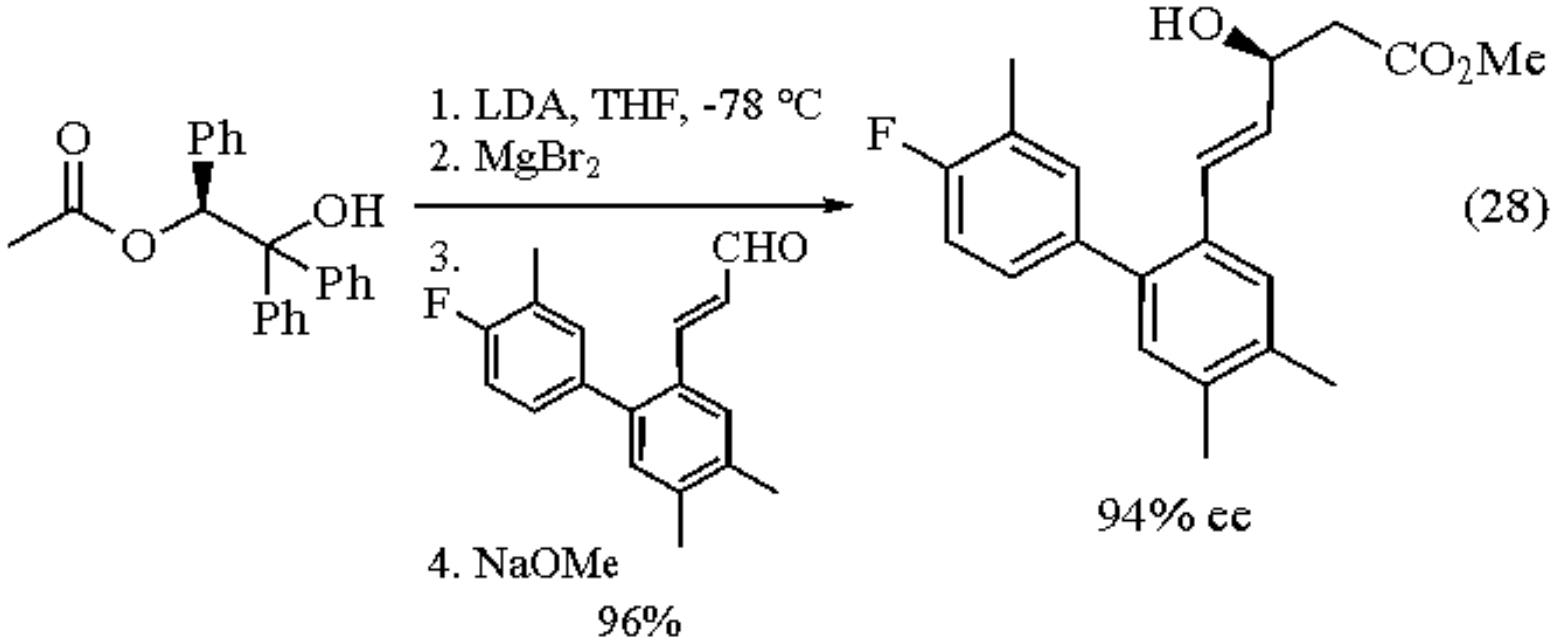

(28)

β-Lactams with high ee values[62] result from the condensation of lithium enolates of 10-diisopropylsulfonamide isobornyl esters with azadienes (eq 29).[63,64]

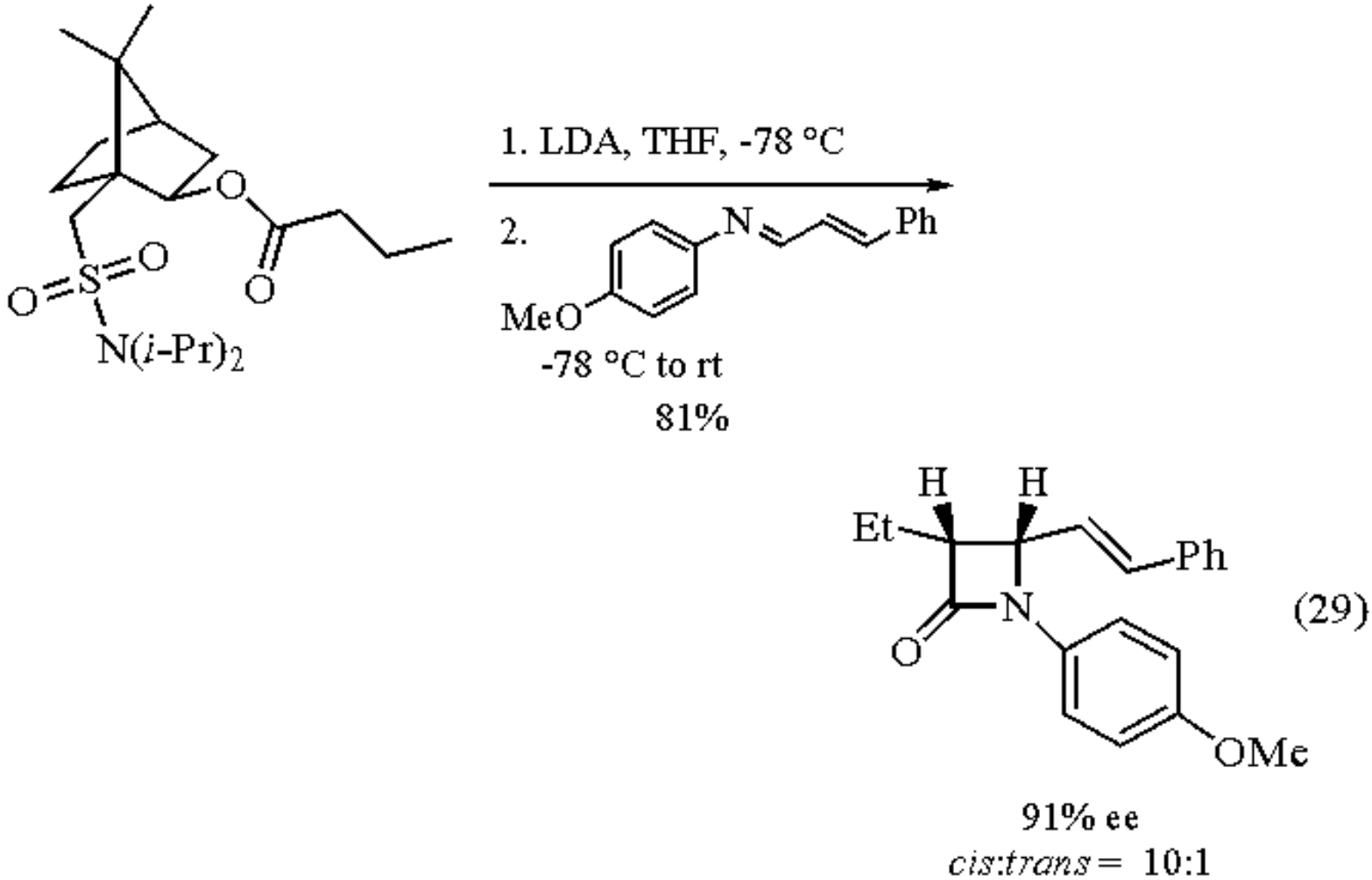

(29)

Enolate Rearrangements.

Ireland-Claisen Rearrangement.[65,66]

Silyl enol ethers of allyl esters undergo highly stereoselective Ireland-Claisen rearrangement to afford 4-pentenoic acids.[67] The structure of the ester and the reaction conditions dictate the stereoselectivity. It has seen wide synthetic application, e.g. the construction of unnatural (-)-trichodiene (eq 30).[68]

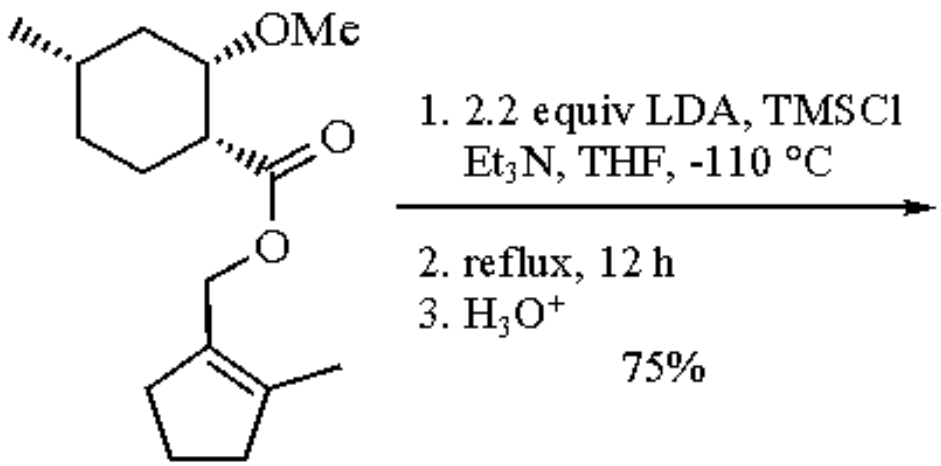

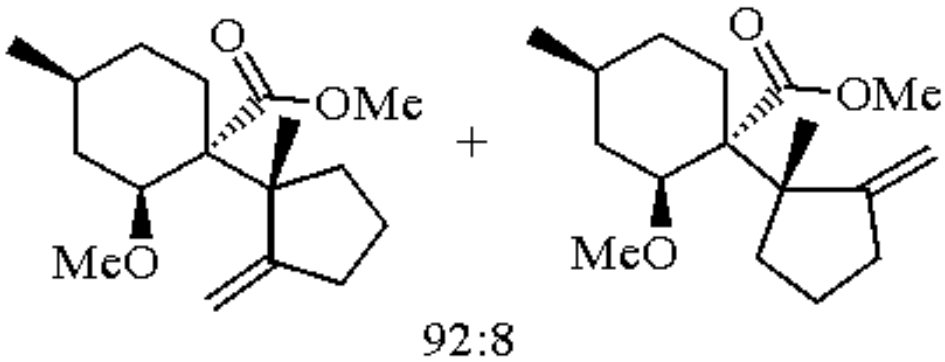

(30)

Wittig Rearrangements.[69]

Enolates derived from chiral propargyloxyacetic acids lead to chiral allenic esters, via a rapid diastereoselective [2,3]-Wittig rearrangement followed by esterification (eq 31).[70] Analogous rearrangements are feasible with carbohydrate derivatives[71] and steroids (eq 32).[72] In some cases, improved enantioselectivities resulted when the lithium enolate was transmetalated with ***Dichlorobis(cyclopentadienyl)zirconium***.[73] Benzylic, allylic, propargylic, and related lithio derivatives of cyanohydrin ethers undergo the [2,3]-Wittig rearrangement to afford ketones, e.g. eq 33.[74,75] Lithiated *N*-benzyl- and *N*-allylazetidinones lead, via [1,2]-Wittig rearrangement exhibiting radical character, to pyrrolidones (eq 34).[76]

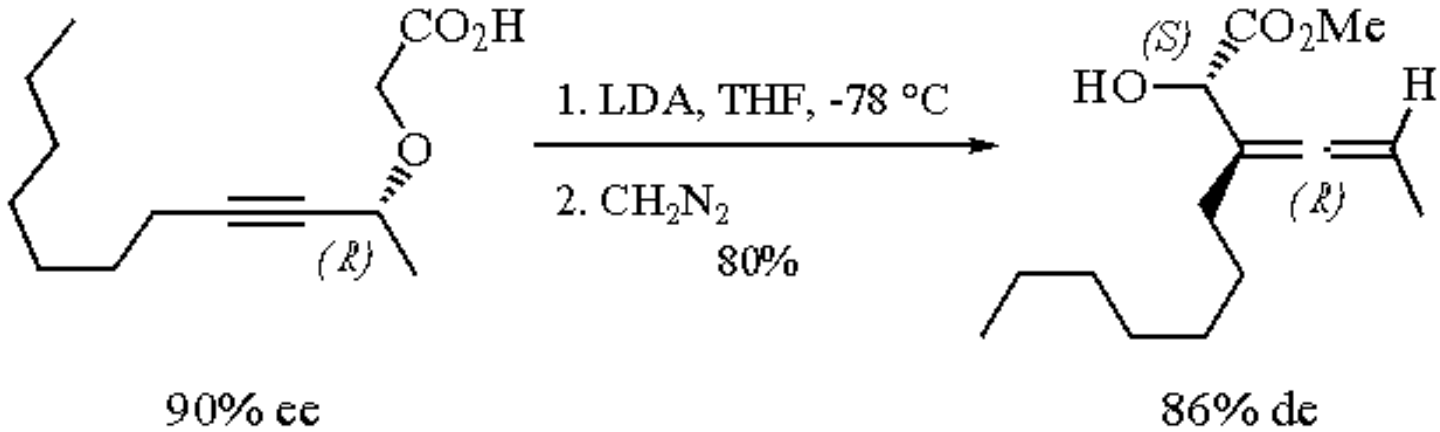

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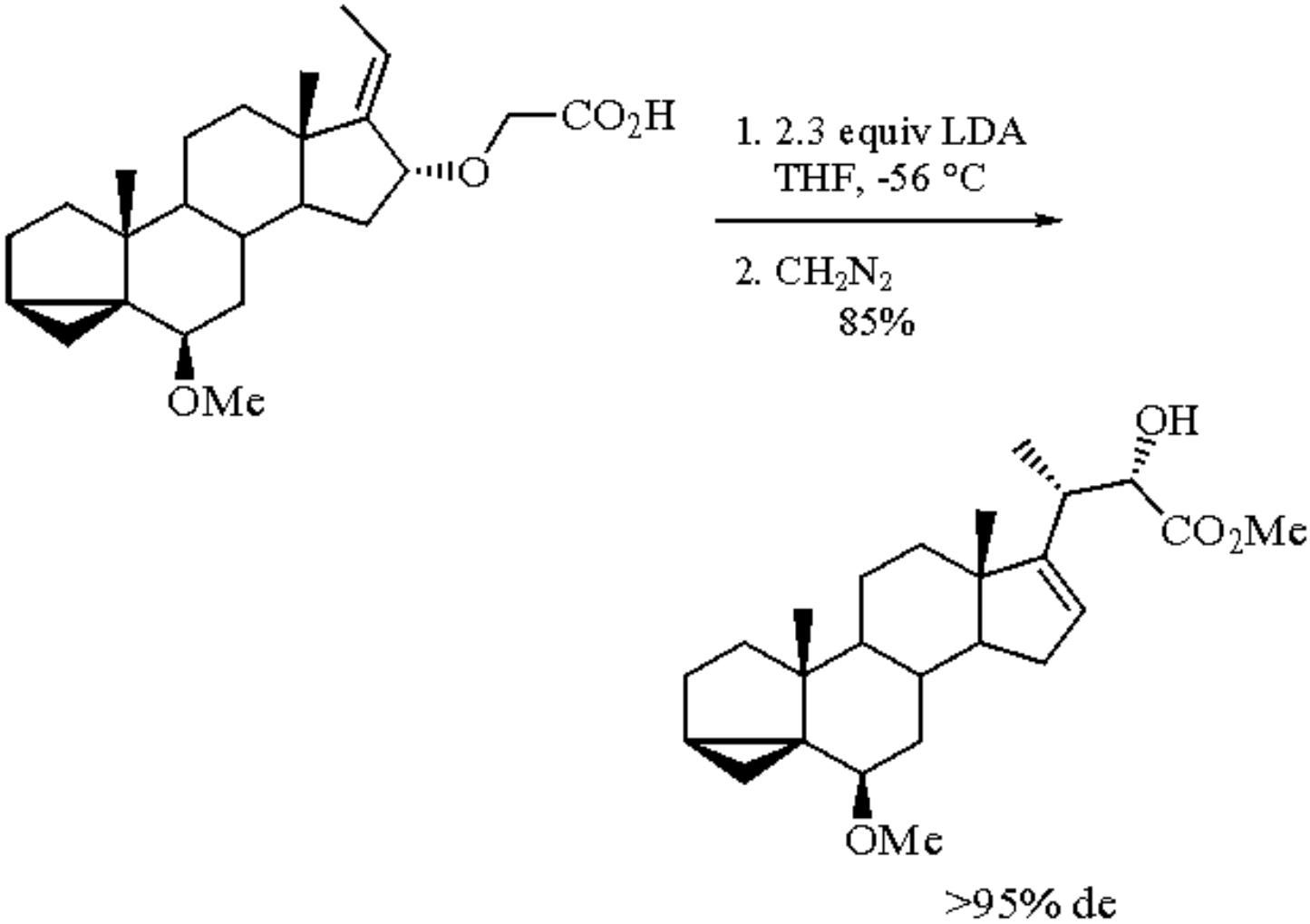

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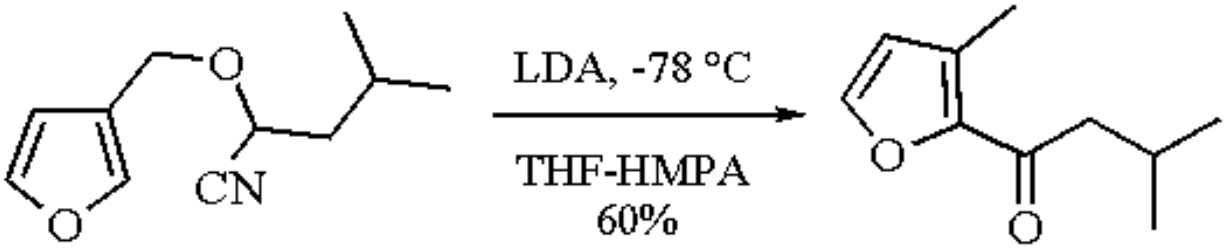

(33)

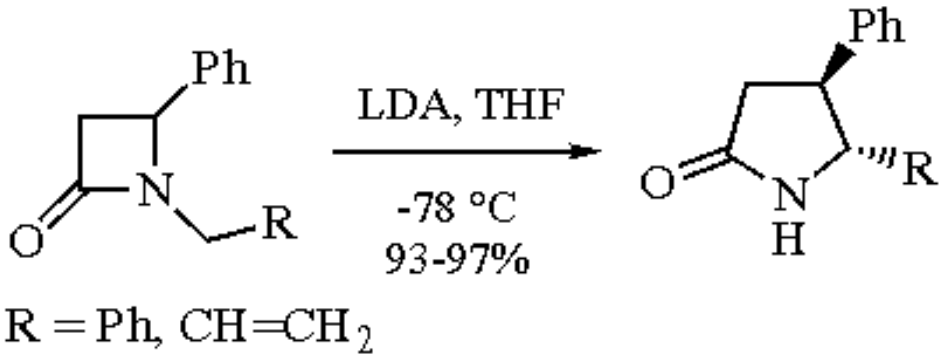

(34)

Stevens Rearrangement.

Ammonium ylides undergo a stereoselective Stevens [2,3]-rearrangement when treated with LDA to afford *N*-methyl-

2,3-disubstituted piperidines (eq 35).[77]

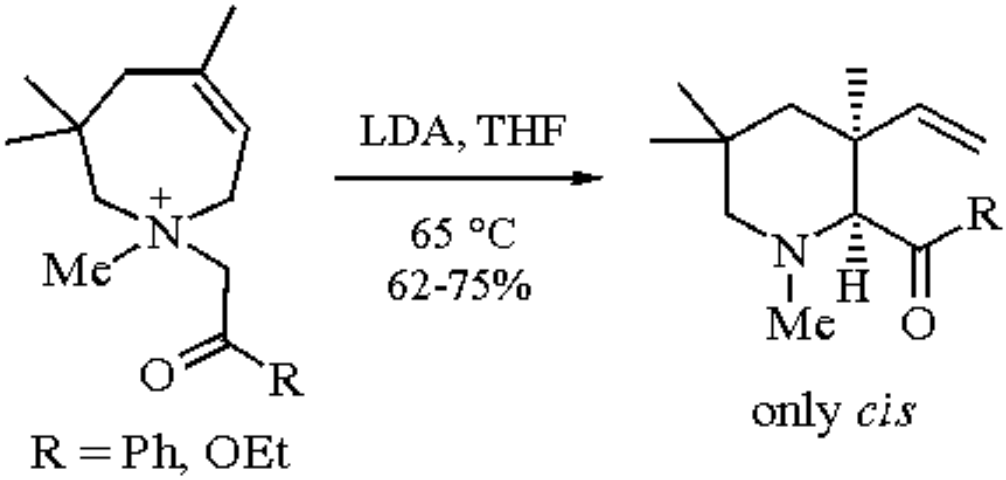

(35)

Heteroatom-Stabilized Carbanions.

Heteroatom-stabilized and allylic carbanions serve as homoenolate anions and acyl anion equivalents,[5,78] e.g. α-anions of protected cyanohydrins of aldehydes and α,β-unsaturated aldehydes are intermediates in general syntheses of ketones and α,β-unsaturated ketones (eq 36).[79] Allylic anions of cyanohydrin ethers may be α-alkylated (eq 37)[80,81] or, if warmed to -25 °C, may undergo 1,3-silyl migration to cyanoenolates which may be trapped with TMSCl.[82] Metalated α-aminonitriles of aldehydes are used for the synthesis of ketones and enamines (eq 38).[83] Similarly, allylic anions from 2-morpholino-3-alkenenitriles undergo predominantly α-*C*-alkylation to give, after hydrolysis, α,β-unsaturated ketones (eq 39).[84]

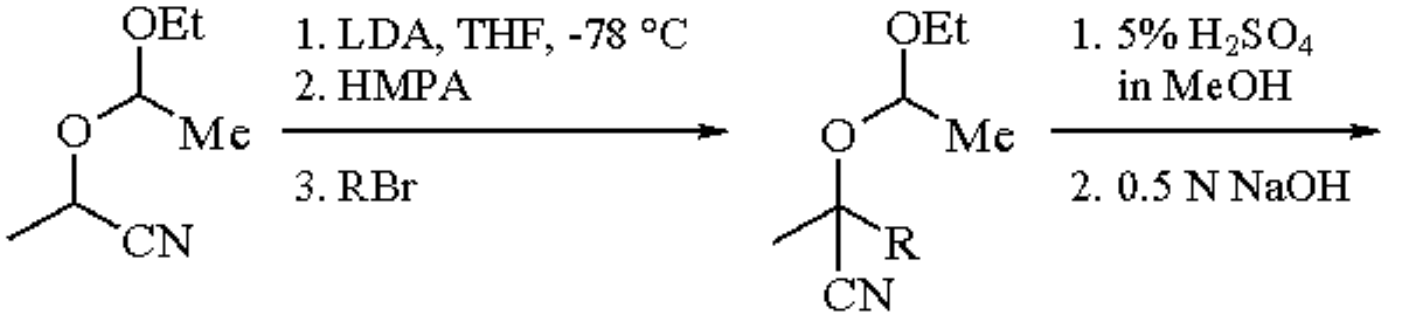

(36)

R = Bu, Hex, Dec	80-85%
R = *i*-Pr, *c*-Pent, *c*-Hex	41-80%
R = $H_2C{=}CHCH_2$	76%

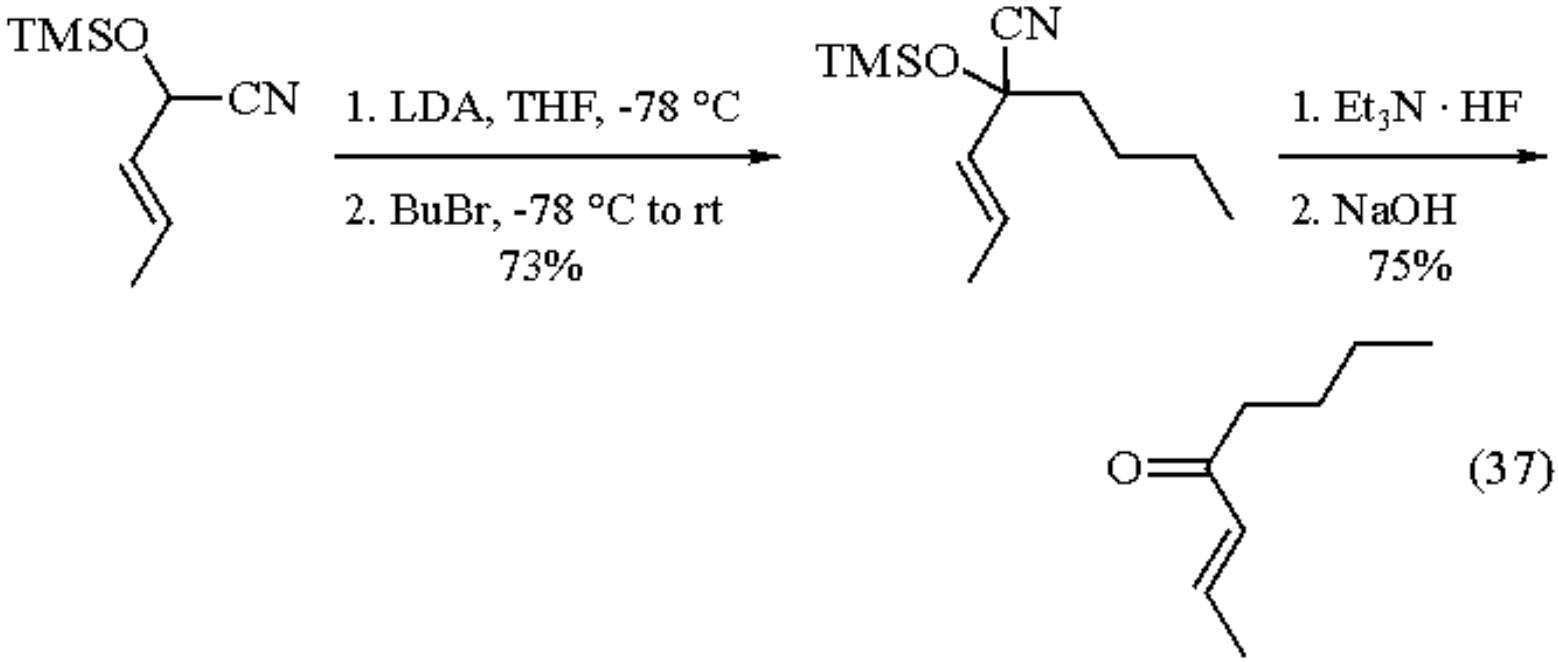

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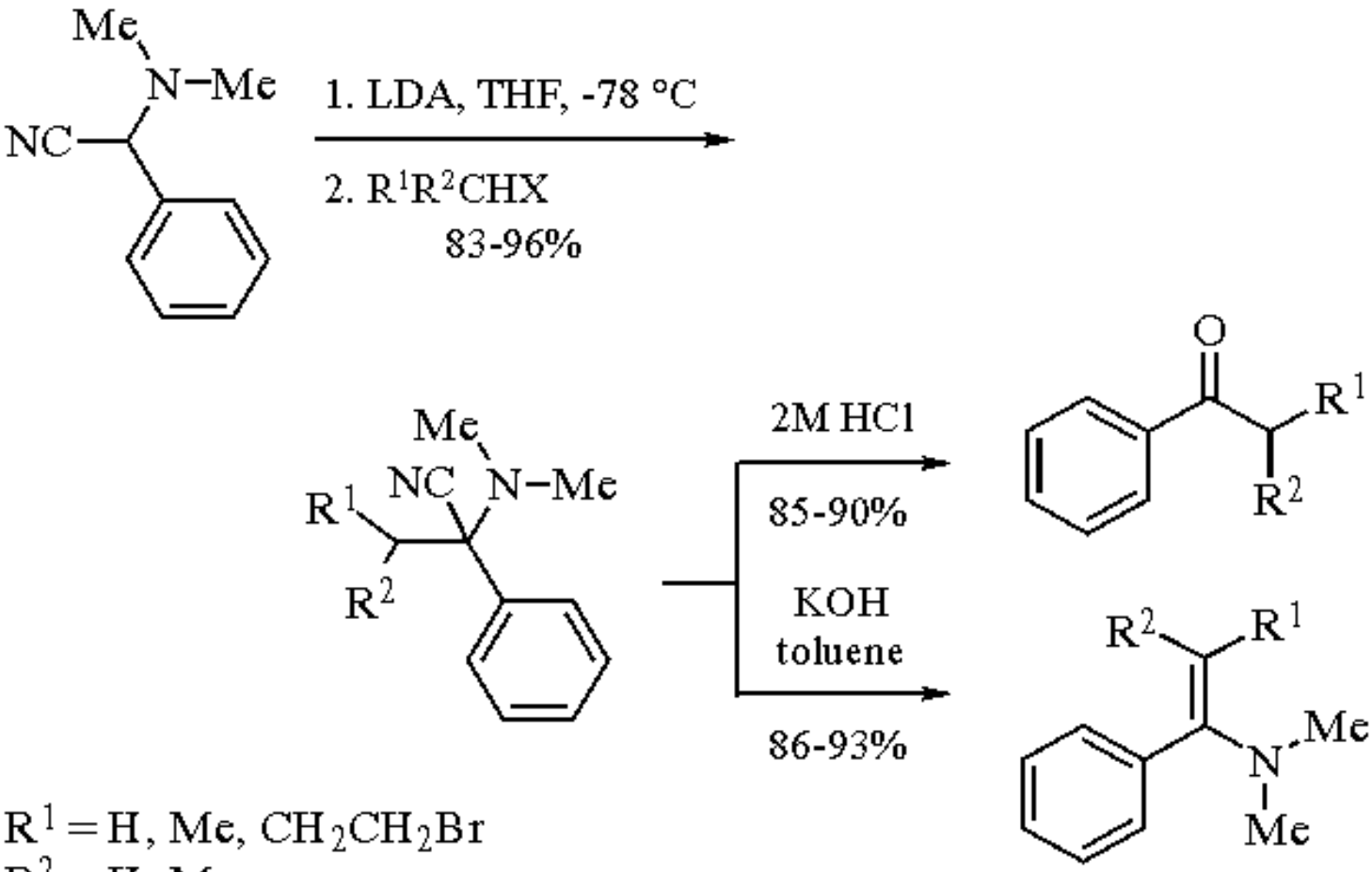

(38)

$R^1 = H, Me, CH_2CH_2Br$
$R^2 = H, Me$

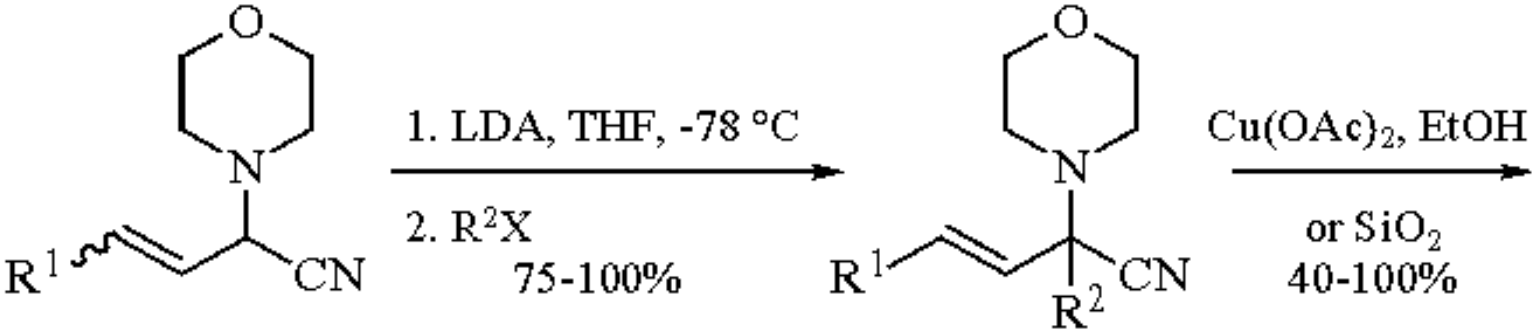

R^1 = Me, Ph; R^2 = Me, Et, hexyl

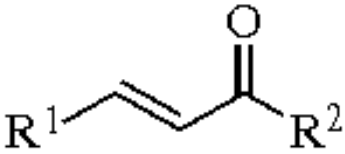

(39)

α-Sulfoxide- and sulfone-stabilized carbanions are highly useful synthetic intermediates, e.g. α-lithiated (+)-methyl *p*-tolyl (*R*)-sulfoxide reacts with α,β-unsaturated aldehydes to give, after dehydration, enantiomerically pure 1-[*p*-tolylsulfinyl]-1,3-butadienes (eq 40),[85] metalation of phenyl 3-tosyloxybutyl sulfone leads to efficient cyclopropane ring formation (eq 41),[86] and precursors for the Ramberg-Bäcklund rearrangement are prepared via α-lithiated cyclic sulfones (eq 42).[87]

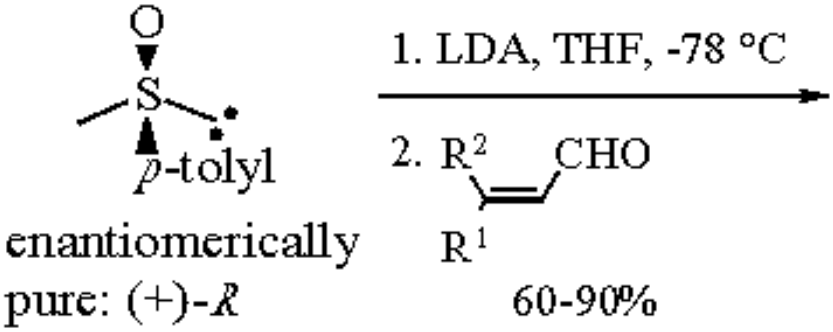

R^1 = Me, Et, Ph, 2-$MeOC_6H_4$
R^2 = H, Me

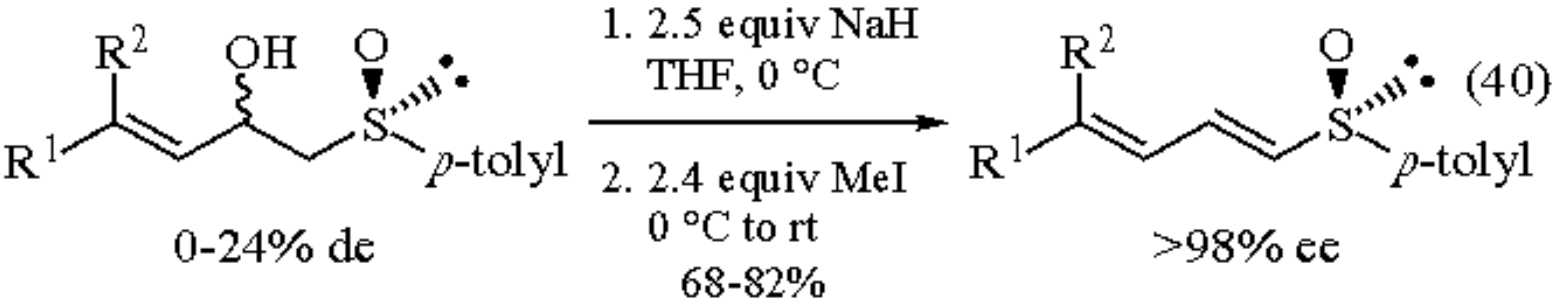

(40)

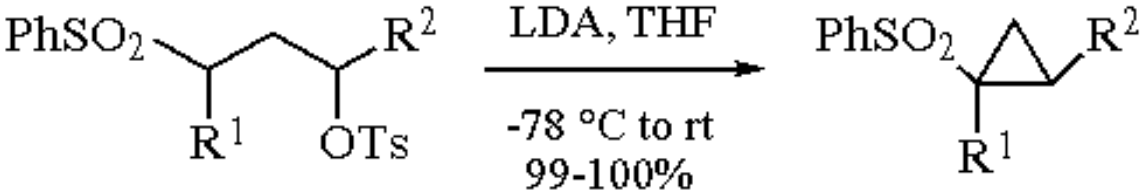

(41)

$R^1 = Ph, Hex; R^2 = H$
$R^1 = H; R^2 = H, Me$

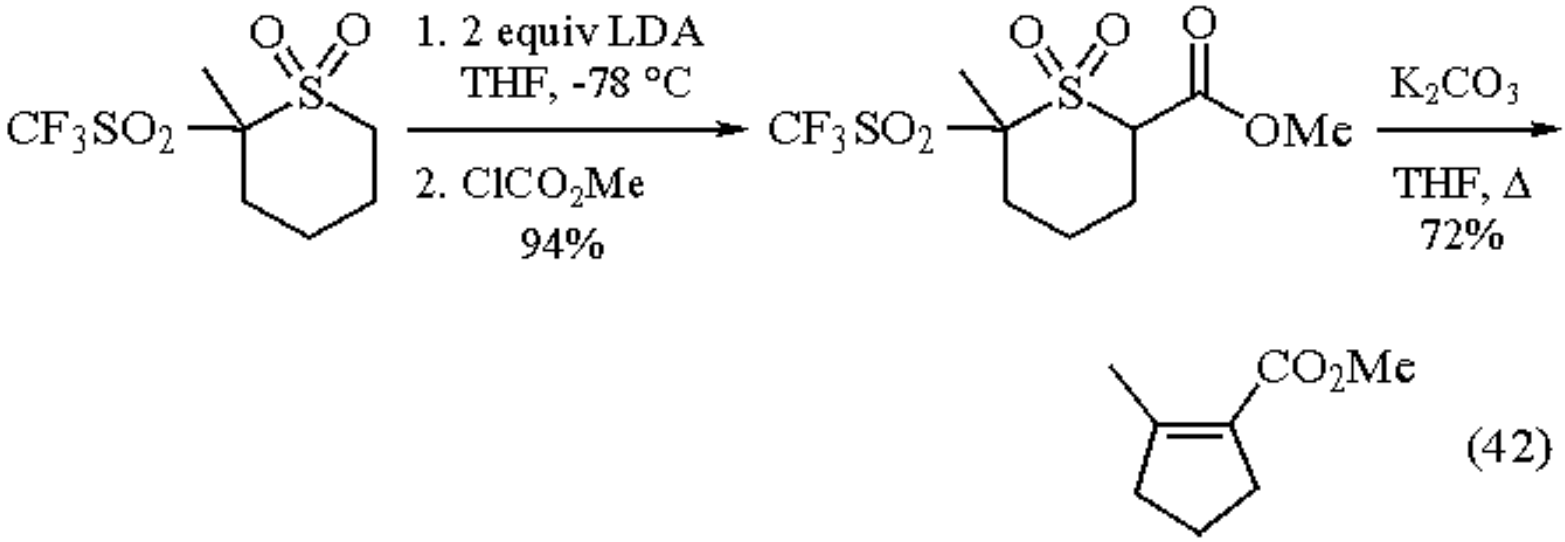

(42)

Lithiated allylic sulfoxides may be α-alkylated and the resulting products subjected to [2,3]-sigmatropic rearrangement induced by a thiophile to give allylic alcohols (eq 43).[6,88] In contrast, alkenyl aryl sulfoxides produce α-lithiated species which are alkylated with MeI or PhCHO in good yields (eq 44).[89,90] LDA has also been used to metalate allylic[91] and propargylic selenides[92,93] as well as aryl vinyl selenides.[94]

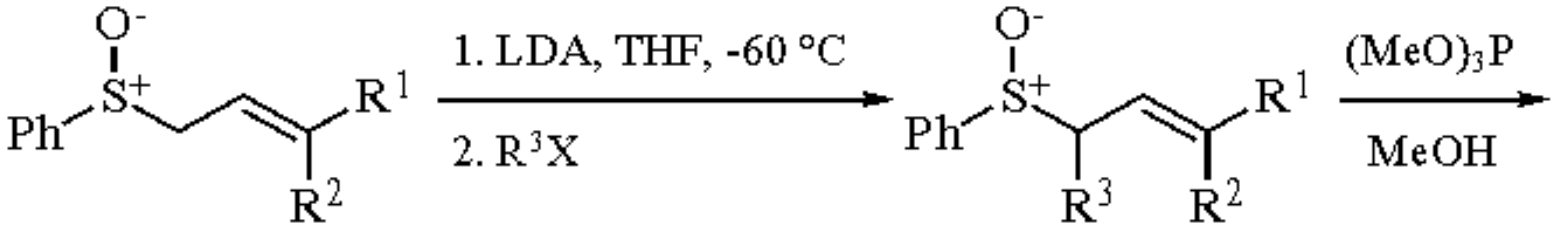

$R^1 = H, Me; R^2 = H, Me$ $R^3 = Me, Et, H_2C{=}CHCH_2$

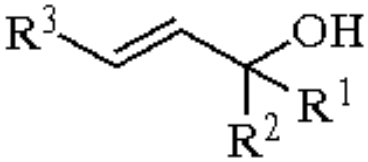

(43)

50-85% overall

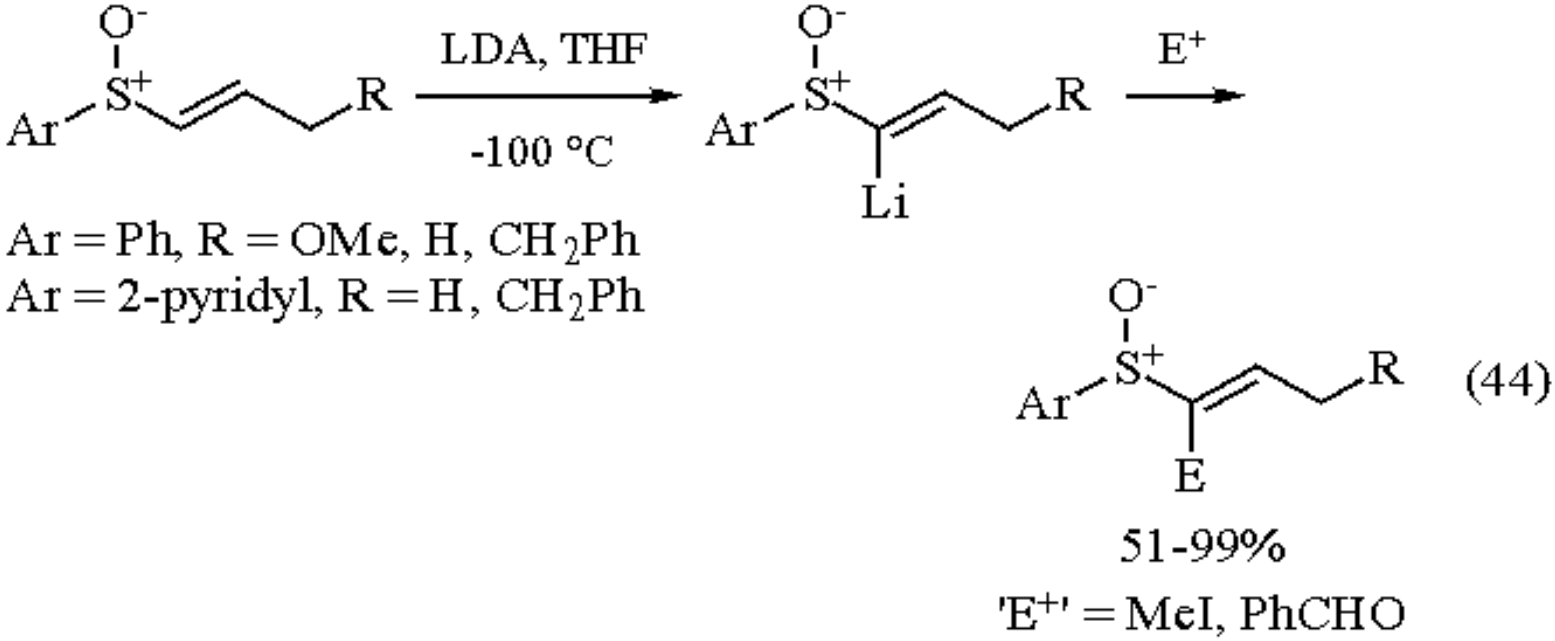

Aromatic and Heteroaromatic Metalations.

Aromatics.

The utility of LDA for kinetic deprotonation of aromatic substrates is compromised by its insufficient basicity compared to the alkyllithiums.[8] Selective lateral deprotonation may be achieved which complements the *ortho*-metalation process (eq 45).[95]

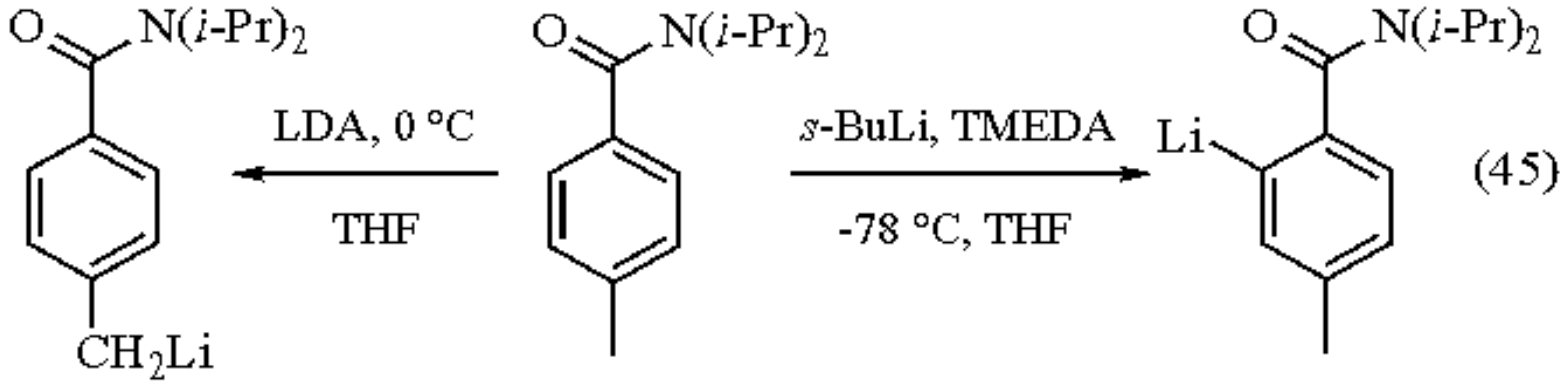

Of considerable synthetic utility is the LDA-induced conversion of bromobenzenes into benzynes. Thus low-temperature deprotonation of *m*-alkoxyaryl bromides followed by warming to rt in the presence of furan gives cycloadducts (eq 46);[96] the lithio species may also be trapped with CO_2 at -78 °C to give unusual aromatic substitution patterns. Treatment of aryl triflates with LDA leads to *N*,*N*-isopropylanilines in good yield (67-98%).[97]

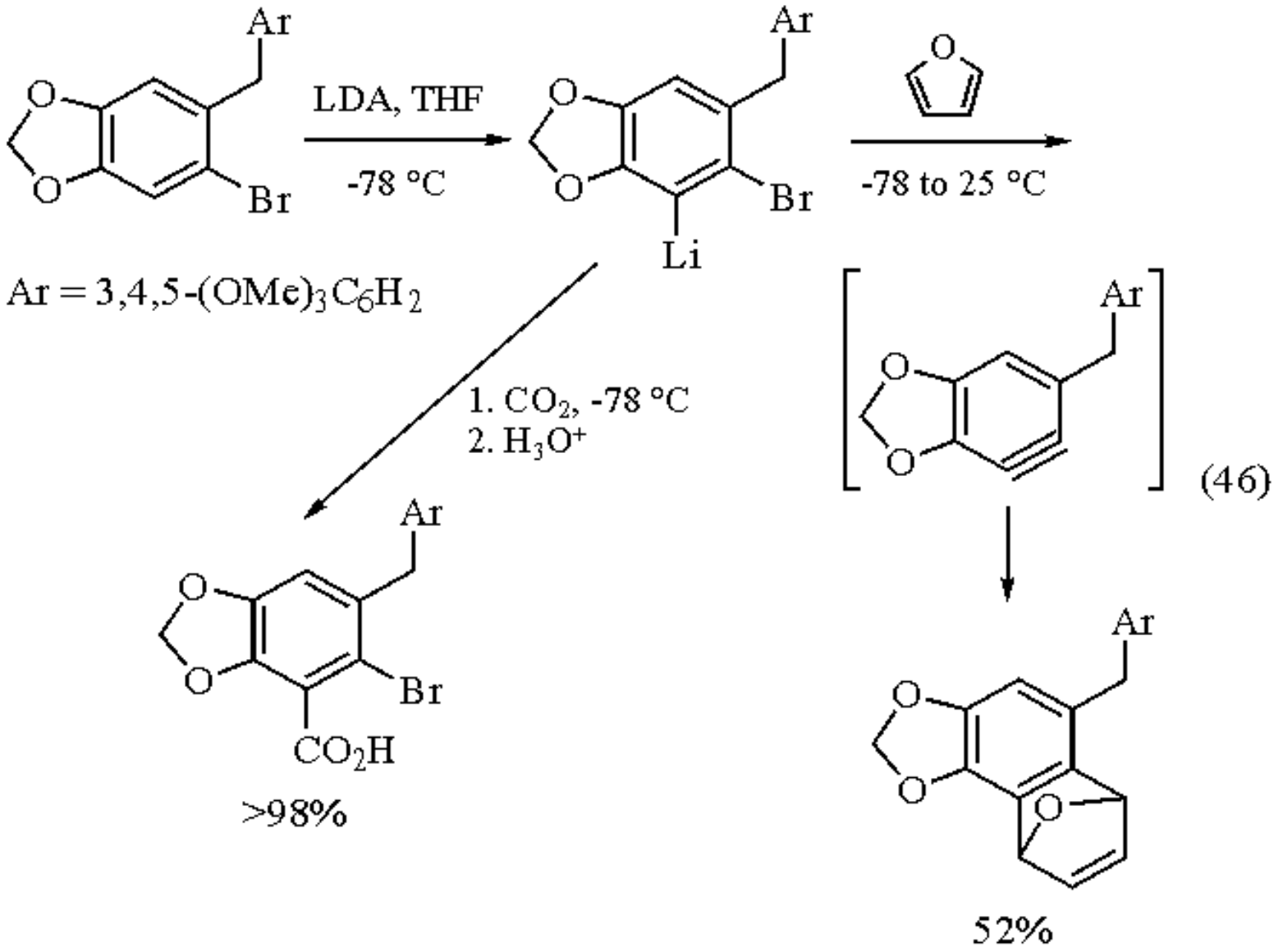

Remote metalation of biaryls and *m*-teraryls provides a general synthesis of substituted and condensed fluorenones (eq 47).[98] Similarly, biaryl *O*-carbamates undergo remote metalation and anionic Fries rearrangement to 2-hydroxy-2´-carboxamidobiaryls, which are efficiently transformed into dibenzo[*b*,*d*]pyranones.[99]

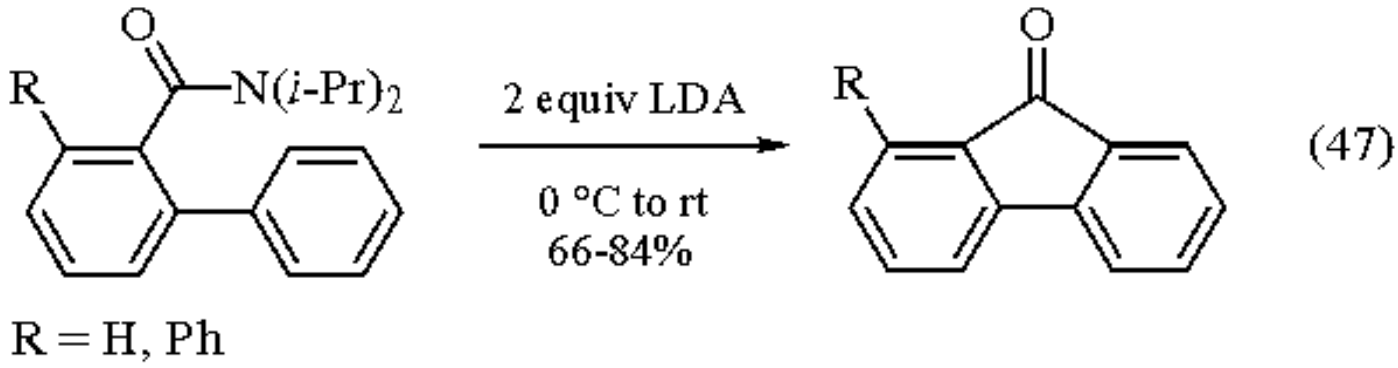

Lateral Lithiation.[7]

Laterally metalated *o*-toluic acids (eq 48),[100] esters (eq 49),[101] and amides (eq 50)[102] are important intermediates for chain extension and carbo- and hetero-ring annulation. Remote lateral lithiation of 2-methyl-2´-carboxaminobiaryls constitutes a general regiospecific synthesis of 9-phenanthrols (eq 51).[103-105]

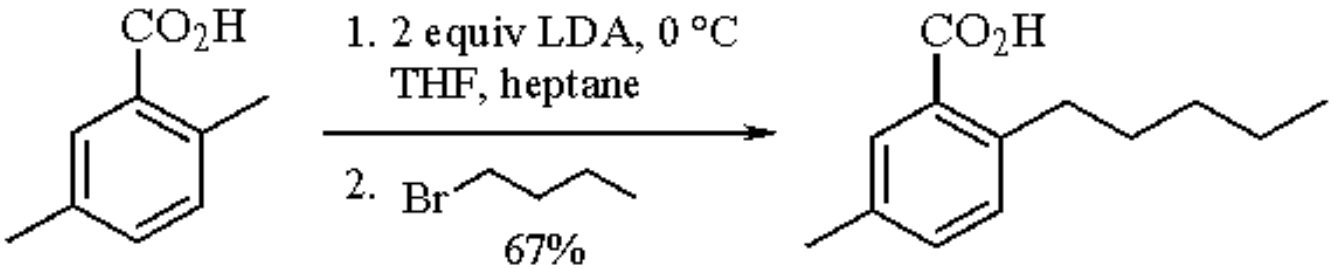

(48)

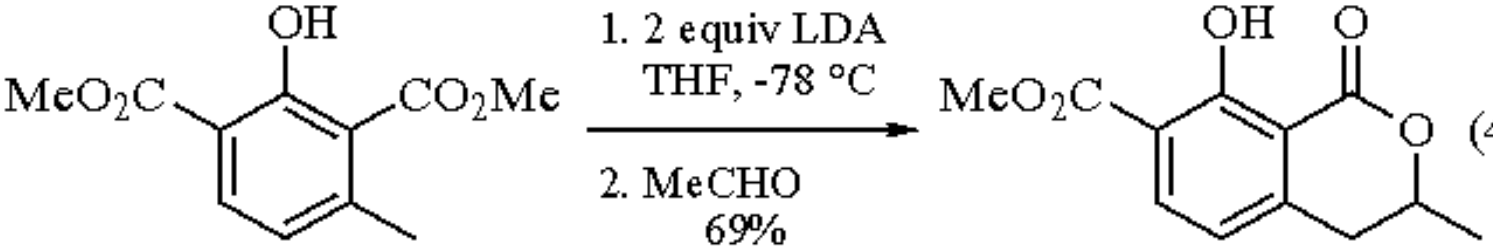

(49)

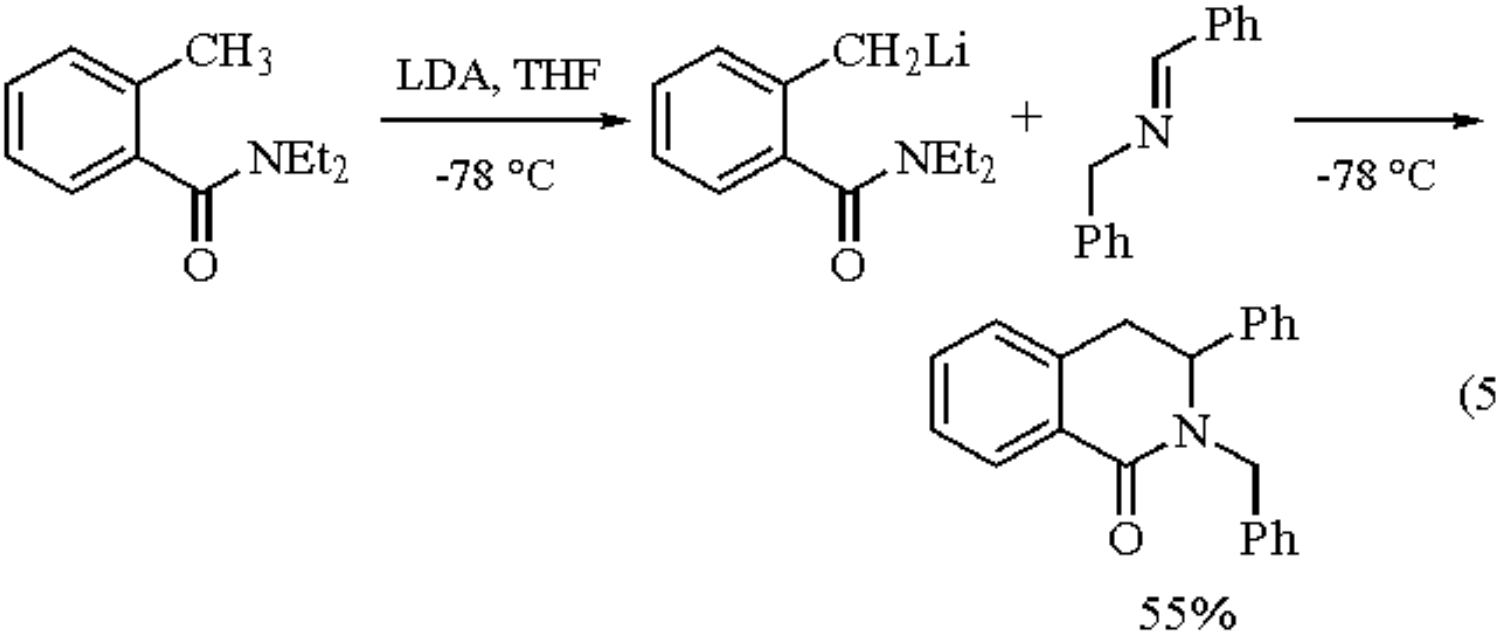

(50)

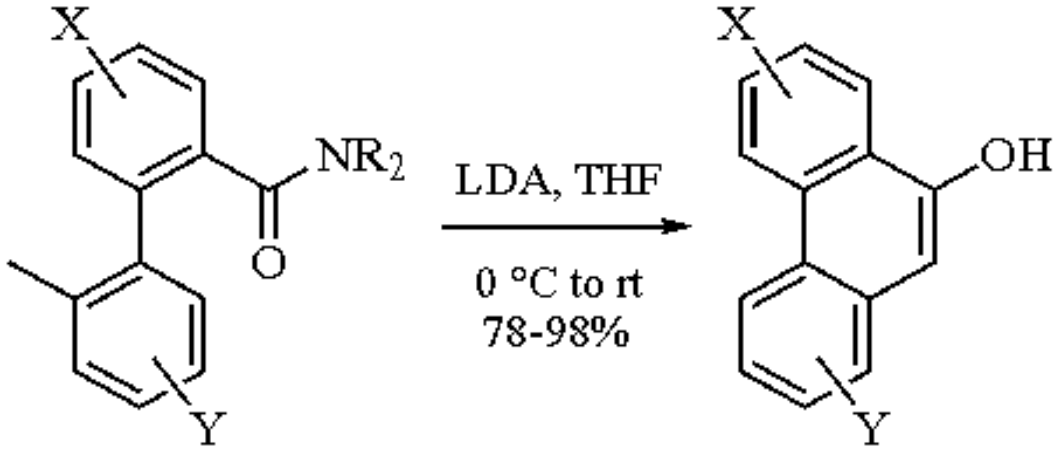

(51)

α-Lithiated *o*-tolyl isocyanides may be alkylated and, following a second metalation with LiTMP, converted into 3-substituted indoles, e.g. eq 52.[106] Michael addition of α-lithiated 3-sulfonyl- and 3-cyanophthalides to α,β-unsaturated ketones and esters initiates a regioselective aromatic ring annulation process to give naphthalenes, e.g. eq 53.[107] Lithiated 3-cyanophthalides also undergo reaction with in situ-generated arynes to give anthraquinones (eq 54).[108] Similarly, aza-anthraquinones are obtained using 3-bromopyridine as the 3,4-pyridyne precursor.[109]

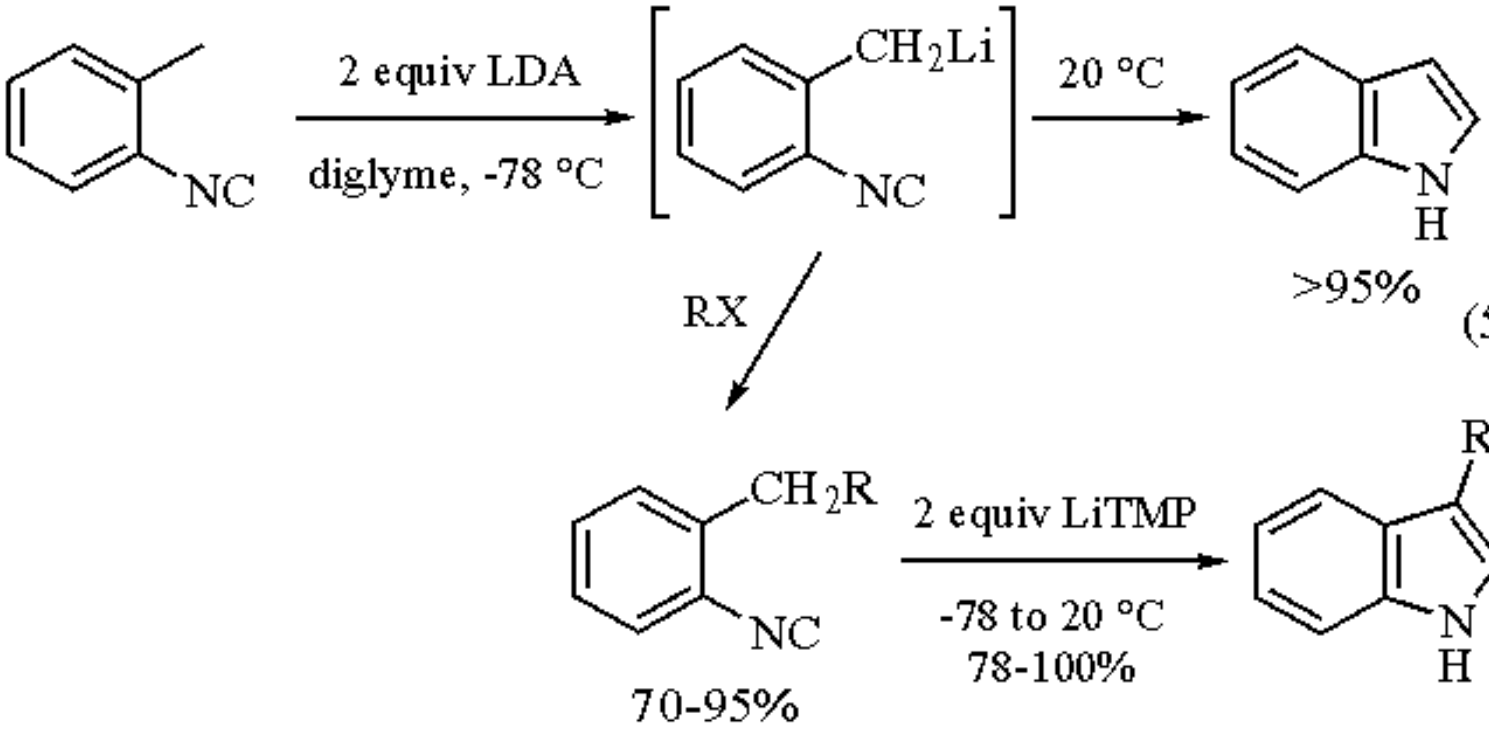

(52)

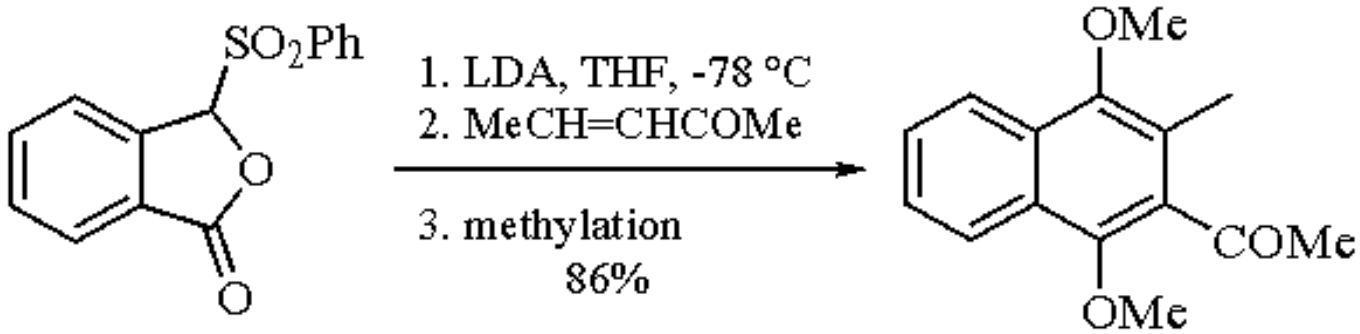

(53)

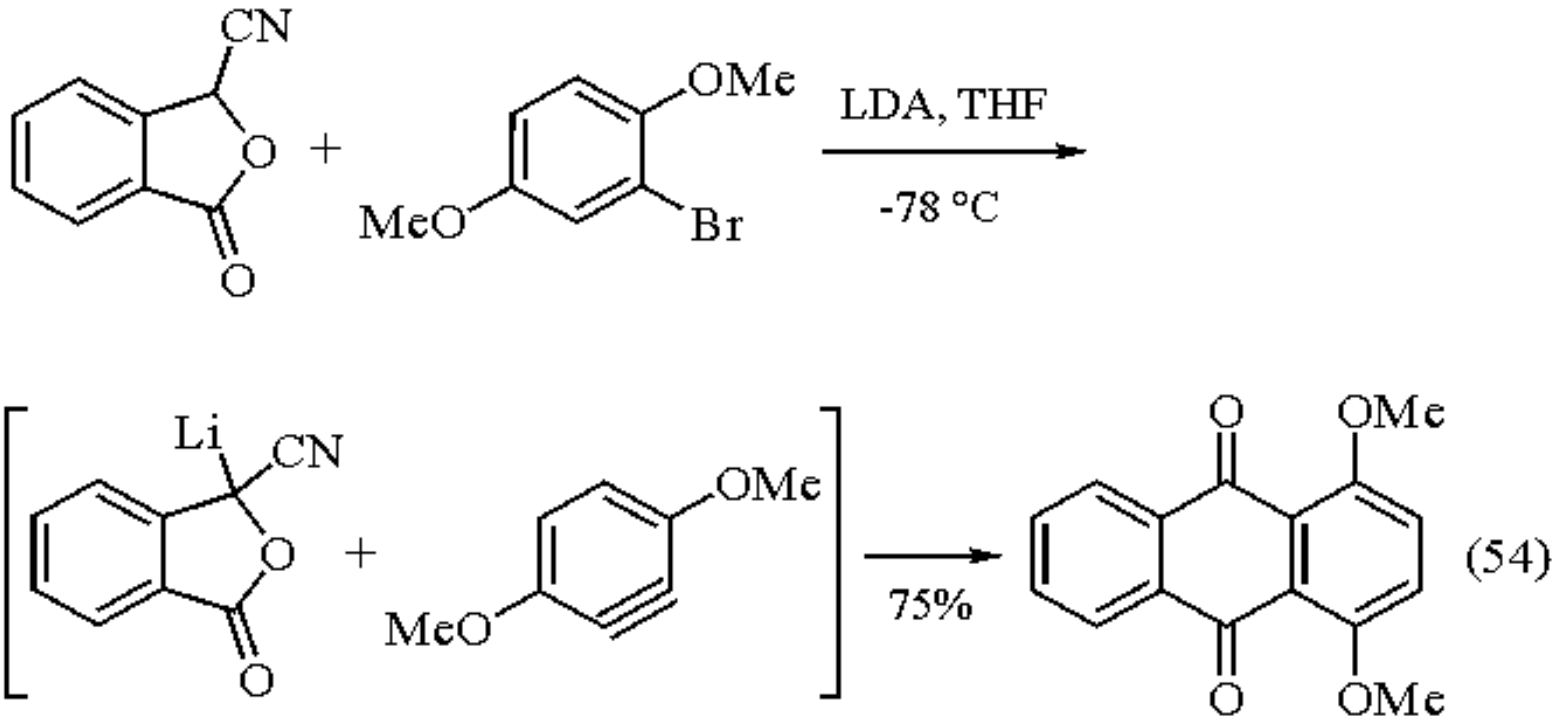

Heteroaromatics.[9]

LDA (and LiTMP) are advantageous bases for the directed *ortho*-metalation chemistry of pyridines[110,111] and, to a much lesser extent, pyrimidines.[112] Several halopyridines can be lithiated *ortho* to the halo substituent and trapped with various electrophiles (eq 55).[113]

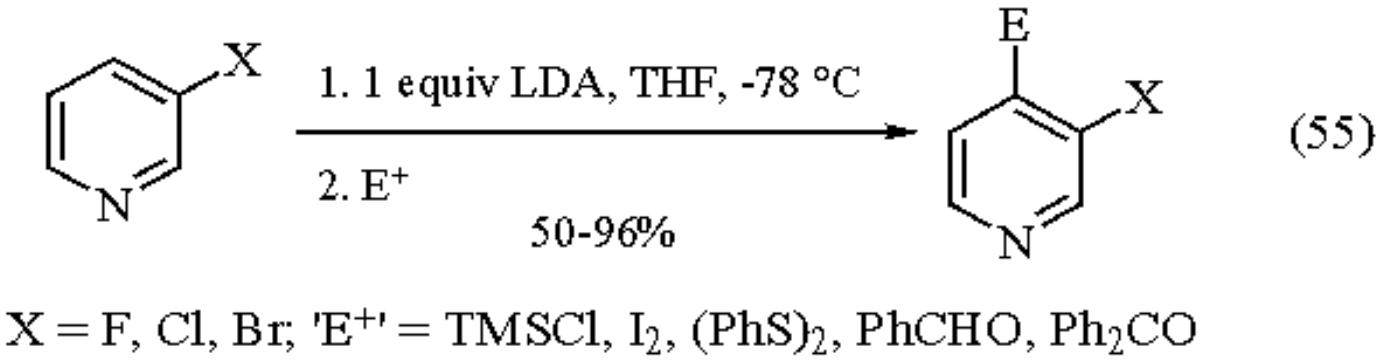

Lithiated furan- and thiophenecarboxylic acids (eq 56),[114,115] indoles (eq 57),[116] indole-3-carboxylic acids (eq 58),[117] benzofurancarboxylic acids,[118] and thiazole- and oxazolecarboxylic acids[119] serve well in heteroaromatic synthesis.

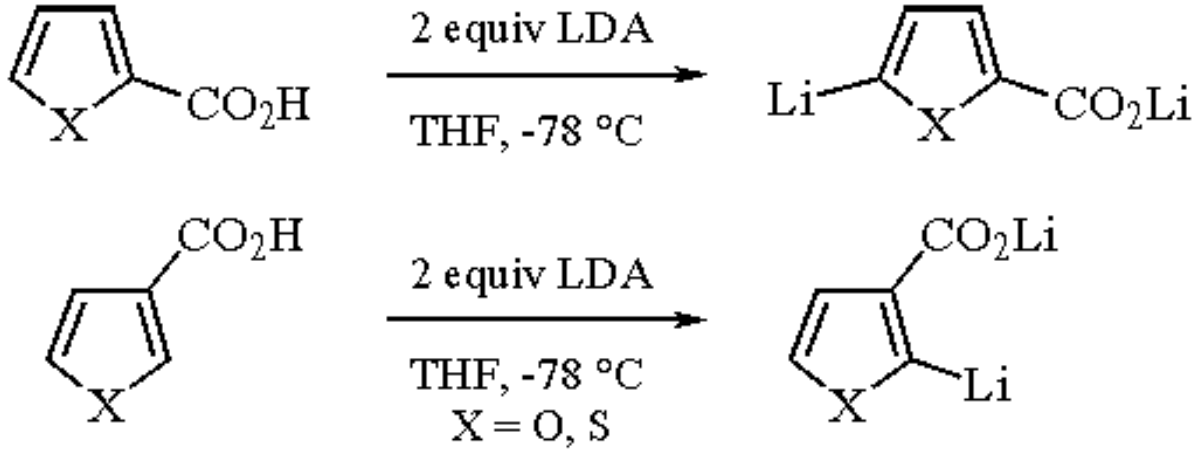

(56)

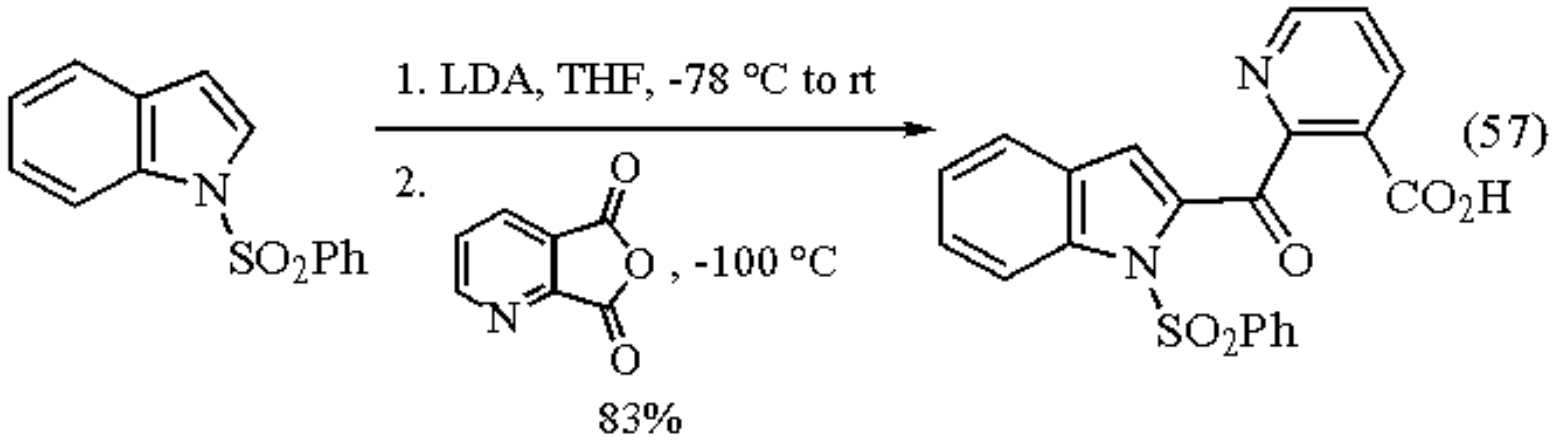

(57)

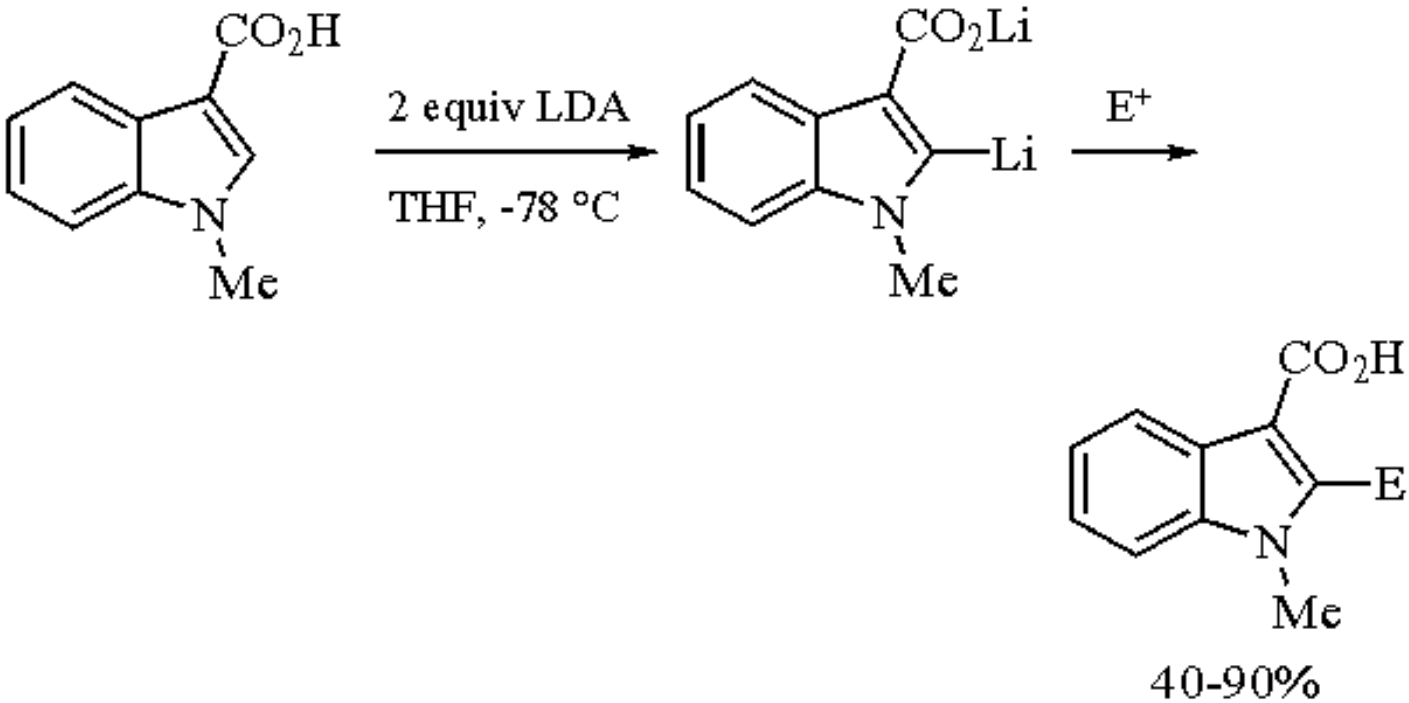

(58)

E = TMS, Me, PhCH(OH), PrCH(OH), Ph_2COH
PhC(OH)Me, Me_2COH

Related Reagents.

Lithium Amide; ***Lithium Hexamethyldisilazide***; ***Lithium Diethylamide***; ***Lithium Piperidide***; ***Lithium Pyrrolidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***; ***Potassium Diisopropylamide***.

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Lithium Bis(1-methoxyvinyl)cuprate[1,2]

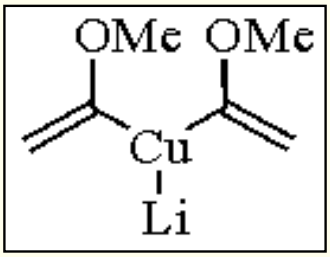

[56646-93-6] · $C_6H_{10}CuLiO_2$ · Lithium Bis(1-methoxyvinyl)cuprate · (MW 184.65)

(vinylcuprate reagent and acyl anion equivalent which undergoes 1,4-addition reactions,[3] substitution reactions,[3] and reductive elimination reactions[4])

Physical Data: yellow mixture, prepared in situ.

Solubility: sol THF.

Preparative Methods: by the slow addition of a -40 °C solution of ***1-Methoxyvinyllithium***[5,6] to a solution of purified ***Copper(I) Iodide*** in a ***Dimethyl Sulfide***-THF mixture (1:4 mole ratio of CuI:Me_2S) at -40 °C; stirring for 30 min gives a yellow mixture.[3]

Handling, Storage, and Precautions: air- and moisture-sensitive reagent prepared in situ. Use in a fume hood.

Addition Reactions.

Lithium bis(1-methoxyvinyl)cuprate affords transfer of the 1-methoxyvinyl ligand, an acyl anion equivalent,[7] via conjugate addition to α,β-alkenyl ketones (eq 1).[3] This cuprate reaction is sensitive to the substitution patterns of the α,β-enone, especially at the C-3 and C-5 positions of cyclohexenone derivatives. The vinyl ether 1,4-adducts can be efficiently converted to either 1,4-diketones under dilute acidic conditions [0.025 N HCl/MeOH-H_2O (4:1)] or 1,4-keto esters by ozonolysis in CH_2Cl_2-MeOH (9:1) at -60 °C.[3]

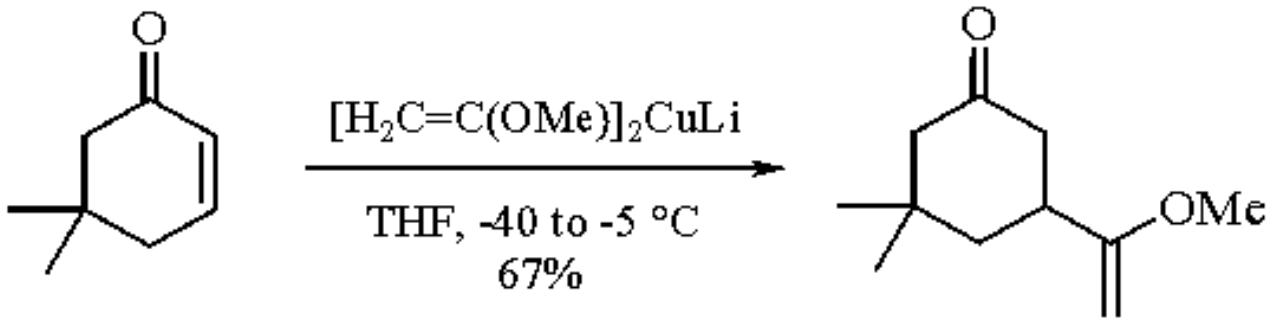

(1)

Substitution Reactions.

Lithium bis(1-methoxyvinyl)cuprate couples with ***Benzyl Bromide*** to afford a substitution product that, upon hydrolysis, yields 1-phenyl-2-propanone (eq 2). This reaction failed with 2-bromooctane.[3]

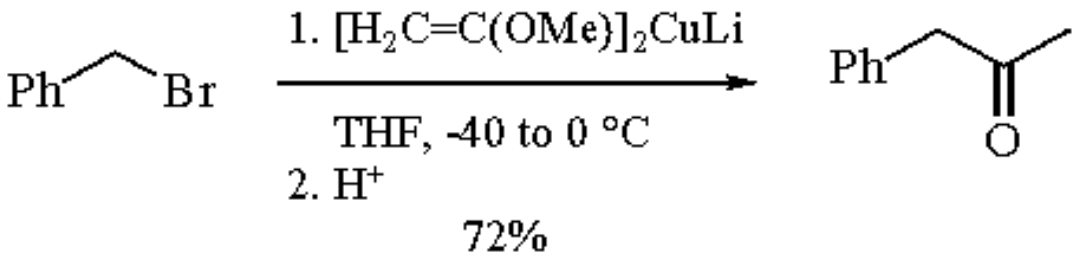

(2)

A lithium bis(1-methoxyvinyl)cyanocuprate reagent prepared from tetrakis(α-methoxyvinyl)tin reacts with ***Allyl Bromide*** to afford the coupling product in 60% yield.[8]

An allylic epoxide undergoes reaction with lithium bis(1-methoxyvinyl)cuprate to yield a substituted allylic alcohol (eq 3).[9]

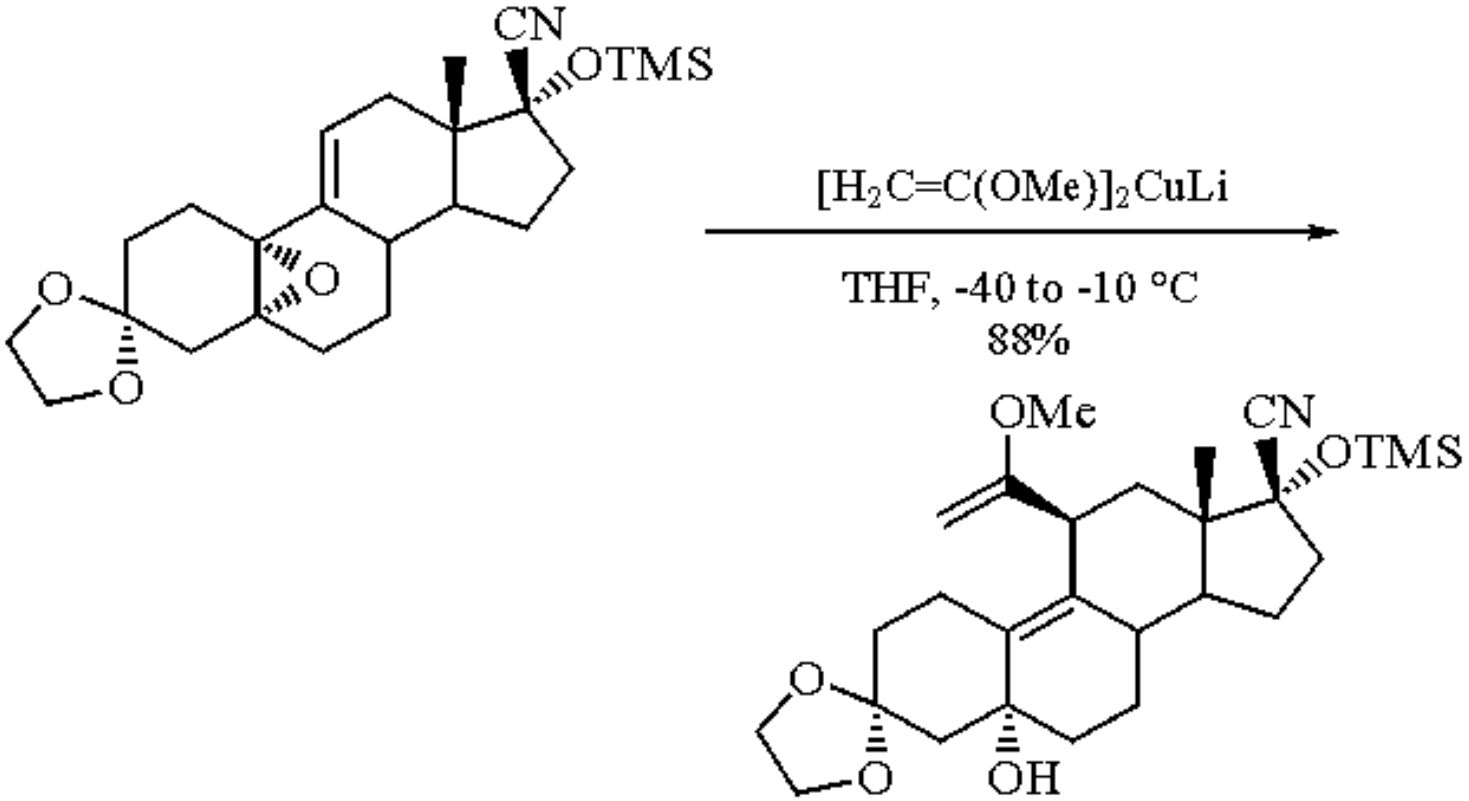

(3)

Miscellaneous.

γ-Mesyl-α,β-enoates undergo reductive elimination with either lithium bis(1-methoxyvinyl)cuprate.BF_3 or lithium bis(1-methoxyvinyl)cyanocuprate.BF_3.2LiCl to afford β,γ-enoates (eq 4) in excellent yield.[4]

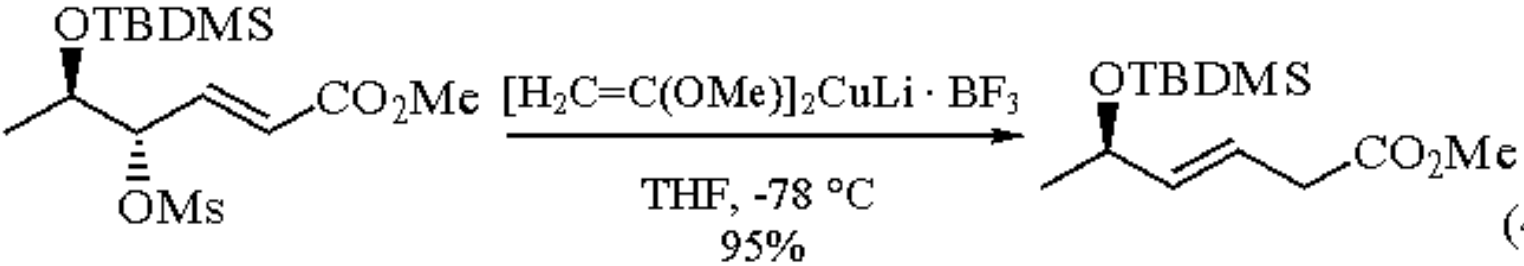

(4)

Related Reagents.

1-Ethoxyvinyllithium; ***Lithium Bis(1-ethoxyvinyl)cuprate***; ***Lithium (Z)-Bis(2-ethoxyvinyl)cuprate***; ***Lithium Divinylcuprate***.

---

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Lithium 1-(Dimethylamino)naphthalenide[1]

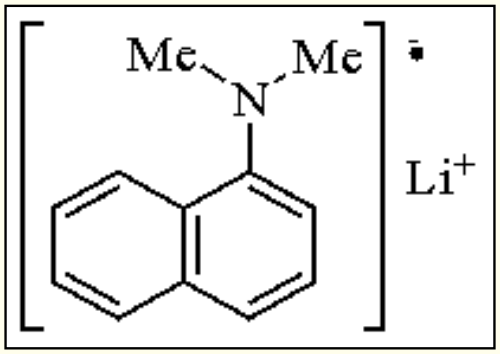

[74379-76-3] · $C_{12}H_{13}LiN$ · Lithium 1-(Dimethylamino)naphthalenide · (MW 178.20)

(reductive lithiations of thioacetals;[2] generation of α-lithio ethers,[3] α-lithio silanes;[6] synthesis of α-trialkylsilyl ketones;[7] generation of allyllithiums;[1b] desulfurization[10])

Alternate Name: LDMAN.

Solubility: generated in THF

Preparative Methods: anhydrous THF and lithium metal ribbon are cooled to between -40 and -55 °C by use of a 1-hexanol/dry ice bath; 1-(dimethylamino)naphthalene is added slowly; the appearance of the dark green radical anion is evident within 10 min but complete conversion to LDMAN takes 3.5-4 h at -45 °C.

Handling, Storage, and Precautions: LDMAN must be prepared and stored below -45 °C. No method of titration has been developed.

Reductive Lithiation.

The major advantage of LDMAN for reductive lithiation over ***Lithium Naphthalenide*** is the ease in removal of the byproduct dimethylaminonaphthalene (DMAN) from the reaction mixture by extraction with dilute acid.[2]

Thioacetals.

Cyclopropane dithioacetals undergo reductive lithiation leading to cyclopropyllithium species which can be trapped by various electrophiles in high yields (eq 1).[2] Ketene phenyl thioacetals can also be used under these conditions to yield vinyl substituted thioethers (eq 2).[2]

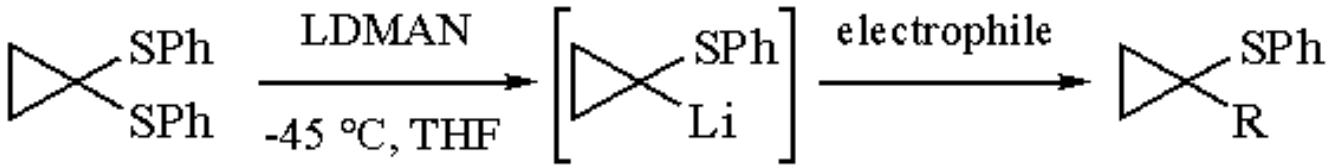

R = H (90%), TMS (81%), Me (88%)

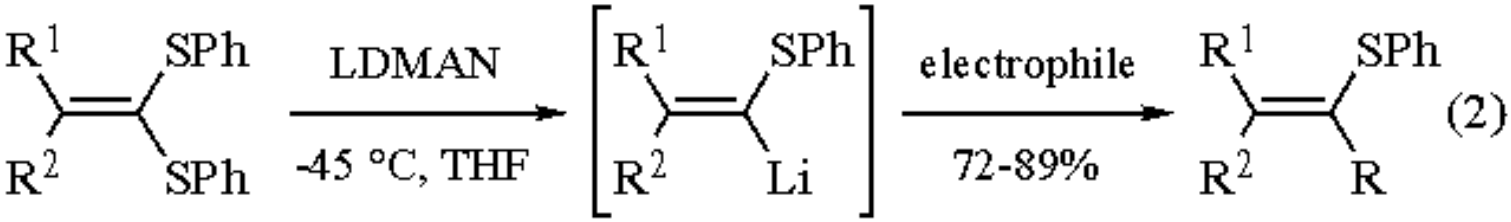

α-Lithio Ethers.

The generation of stabilized and unstabilized α-lithio ethers can be prepared and subsequently reacted with a variety of electrophiles (eq 3).[3] Treatment of 1-methoxy-1-phenylthiocyclopropanes with LDMAN followed by 1,2-trapping with conjugated aldehydes or ketones yields 1-cyclopropylallyl alcohols. These alcohols rearrange to the corresponding 2-vinylcyclobutanones upon the addition of acid (eq 4).[4] It was observed that ***Lithium 4,4´-Di-t-butylbiphenylide*** (LDBB) was a better reagent for this transformation when the alkoxy cyclopropyl vinyl carbinols are acid sensitive.[4b]

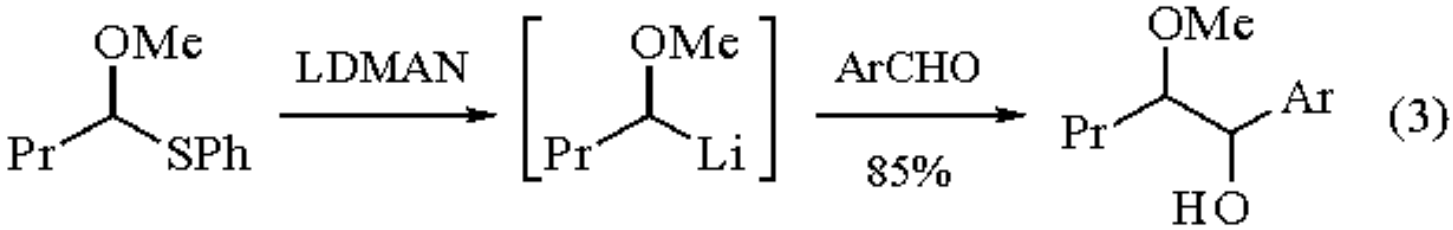

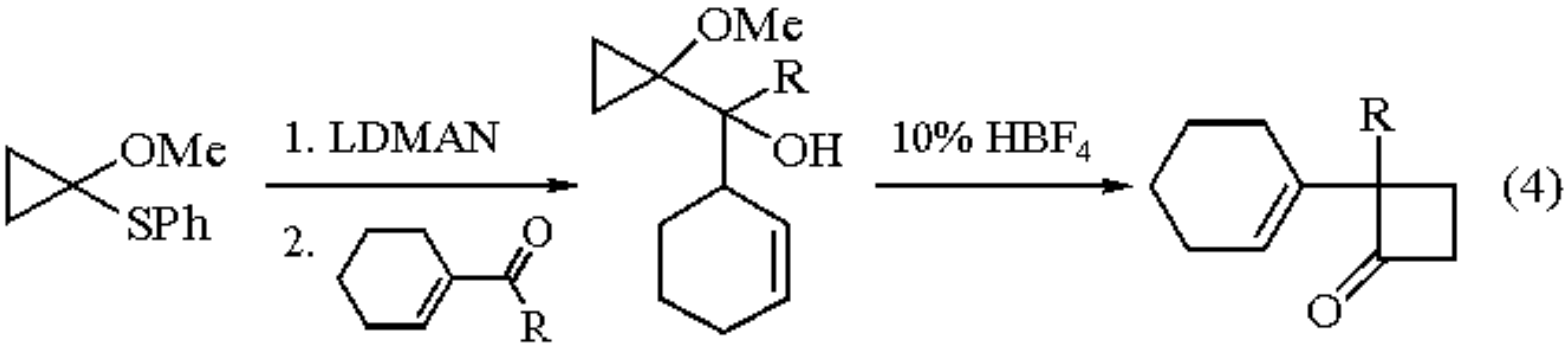

The α-lithio derivatives of substituted tetrahydrofurans and tetrahydropyrans can be generated and reacted with aldehydes (eq 5).[5] This approach led to the first stereoselective synthesis of (±)-*trans*-rosoxide. The organolithium derived for the tetrahydropyran was axial and could be equilibrated to the more stable equatorial species. A two-flask synthesis of brevicomin was performed with the α-lithio ether of a dihydropyran (eq 6).[3]

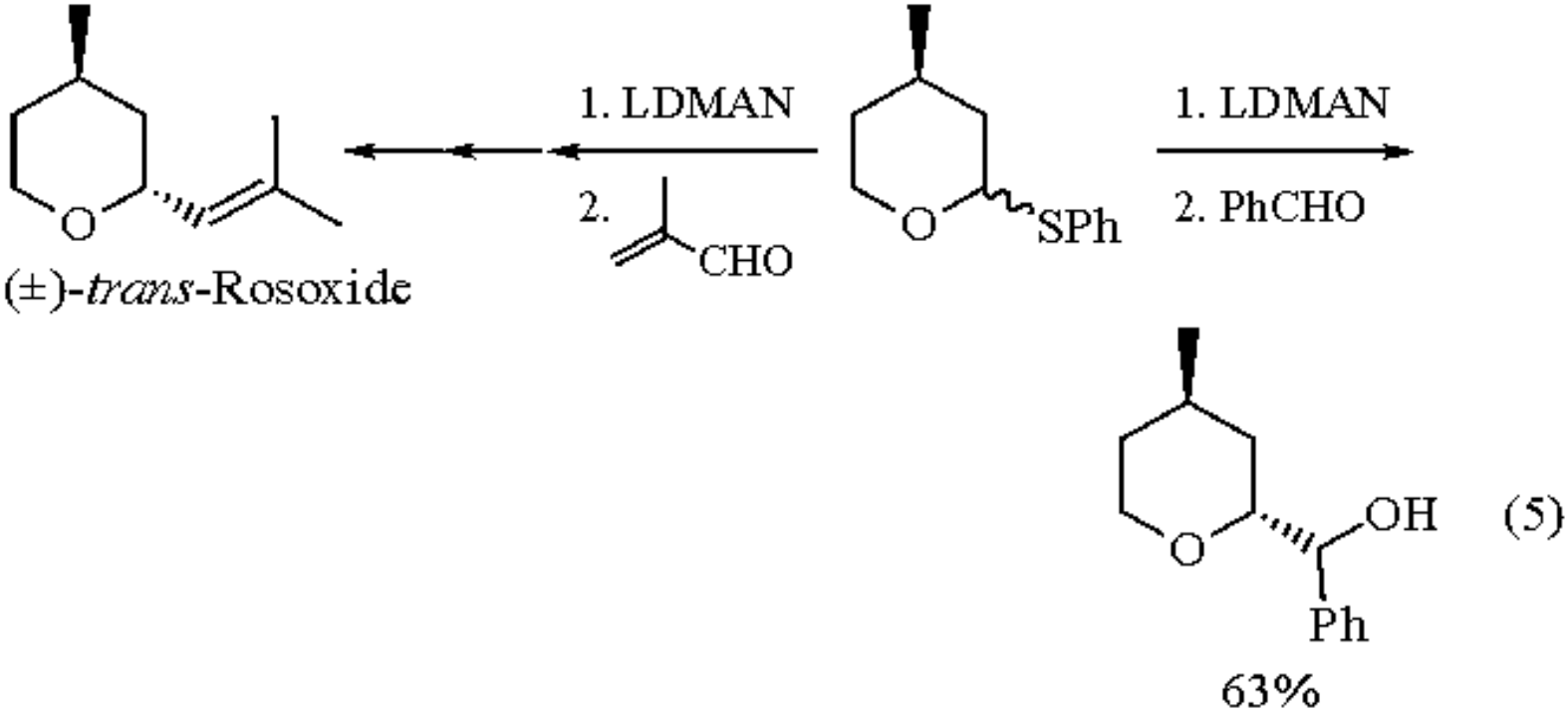

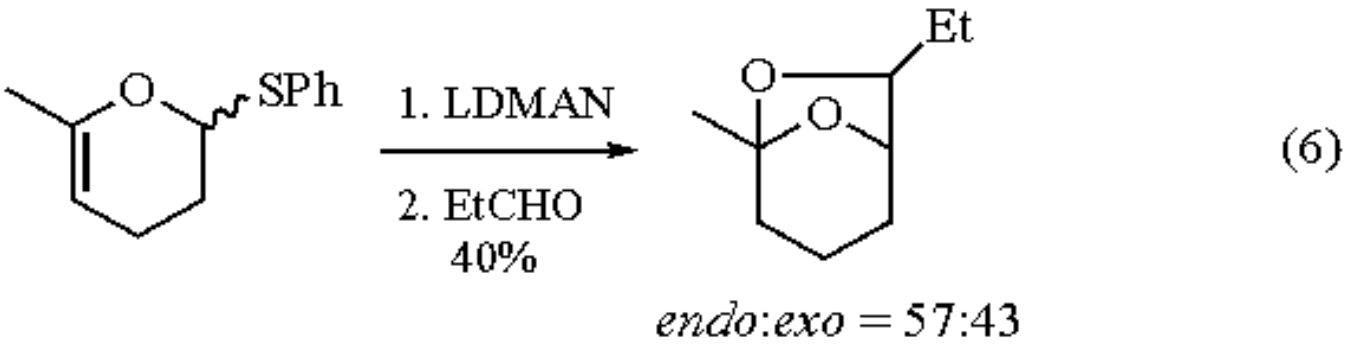

α-Lithio Silanes.

The use of α-lithio silanes is an excellent protocol for the Peterson alkenation.[6] Diphenyl thioacetals are treated with LDMAN, ***Chlorotrimethylsilane***, and LDMAN again, followed by trapping with an aldehyde or ketone leading to high yields of the β-silyl carbinol (eq 7). Elimination to the alkene can be accomplished with ***Potassium Hydride*** on the carbinol.[6a] An improved one-pot synthesis involves treatment of the lithium alkoxide with ***Potassium t-Butoxide***.[6b] This route has led to the synthesis of a variety of synthetically versatile alkylidene- and allylidenecyclopropanes.[6]

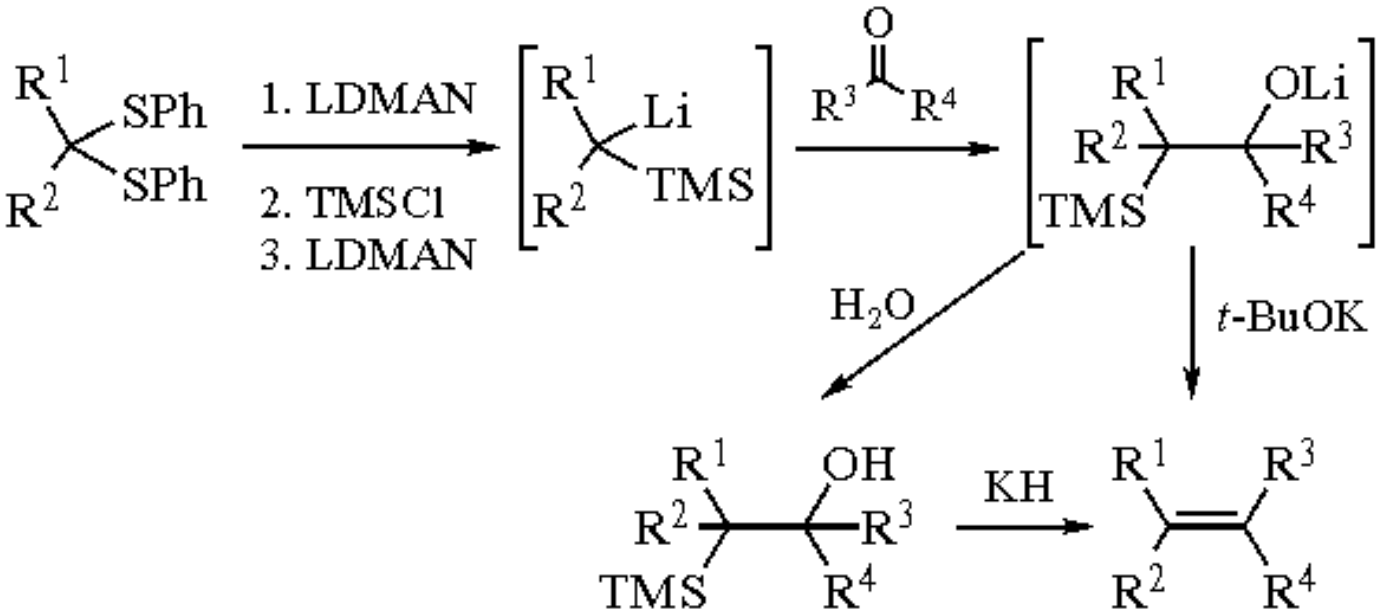

(7)

α-Trialkylsilyl Ketones.

LDMAN cleaves selectively the weak C-Se bond of silyl enol ethers of α-phenylseleno ketones.[7] The corresponding α-trialkylsilyl ketones were obtained in good yields after rearrangement of the trialkylsiloxyvinyllithium (eq 8). Modest yields were obtained for the acyclic analogs accompanied by the formation of alkynic compounds, which presumably arise via β-elimination of the siloxyvinyllithium species.

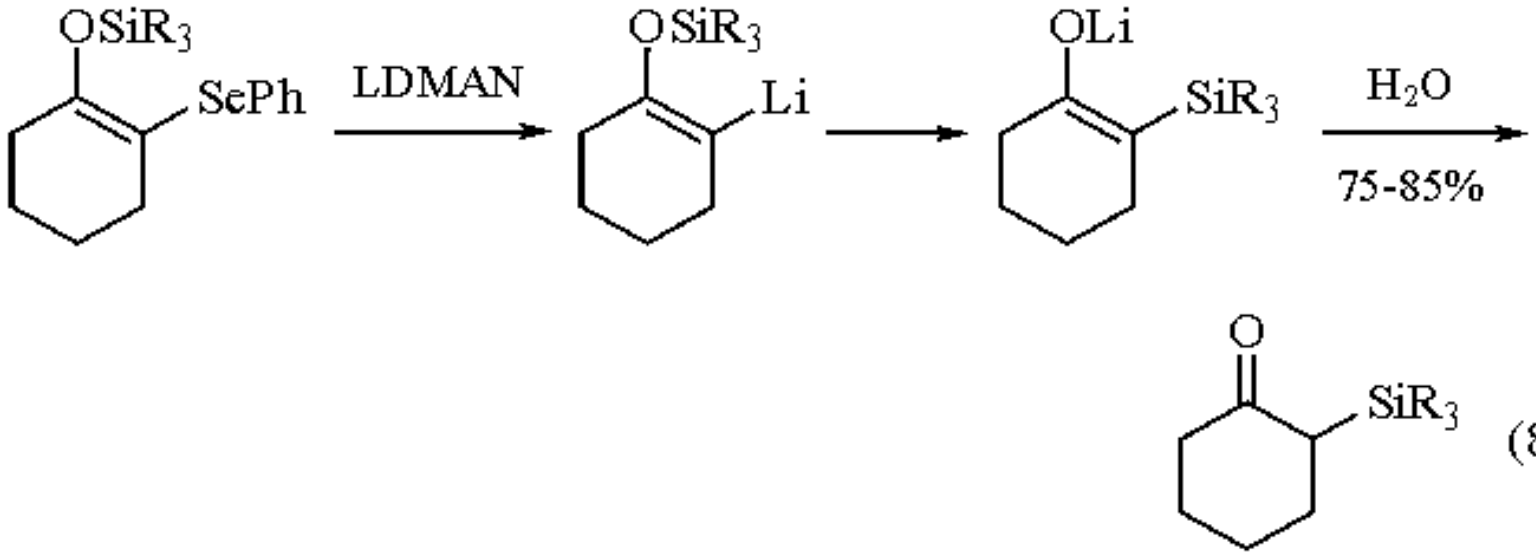

(8)

Allyllithiums.

The use of LDMAN provides a general route to the preparation of hydrocarbon allyl anions.[1b] The treatment of allylphenylthio ethers with LDMAN followed by reacting with ***Crotonaldehyde*** leads to a mixture of regioisomers (eq 9). A slight preference for attack at the more substituted allyl terminus was observed. Transmetalation of the allyllithium with Ti^{IV} leads selectively to the 1,2-addition product (derived from the more substituted terminus) as a 9:1 mix of diastereomers in high yield.

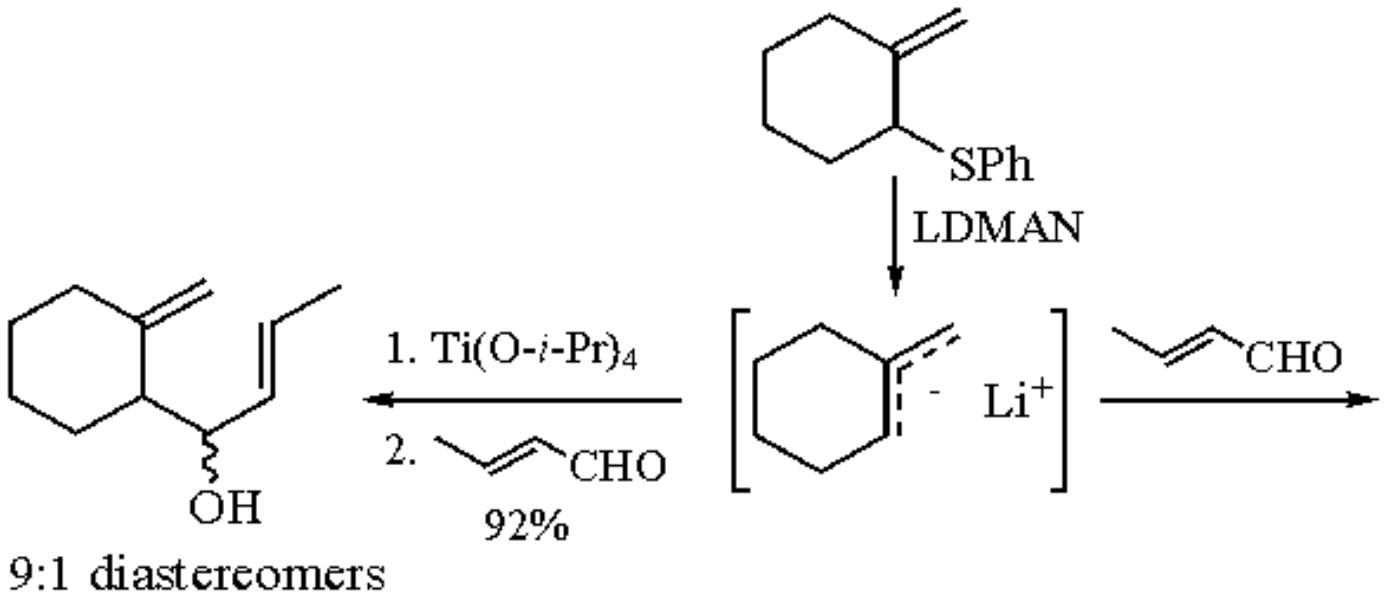

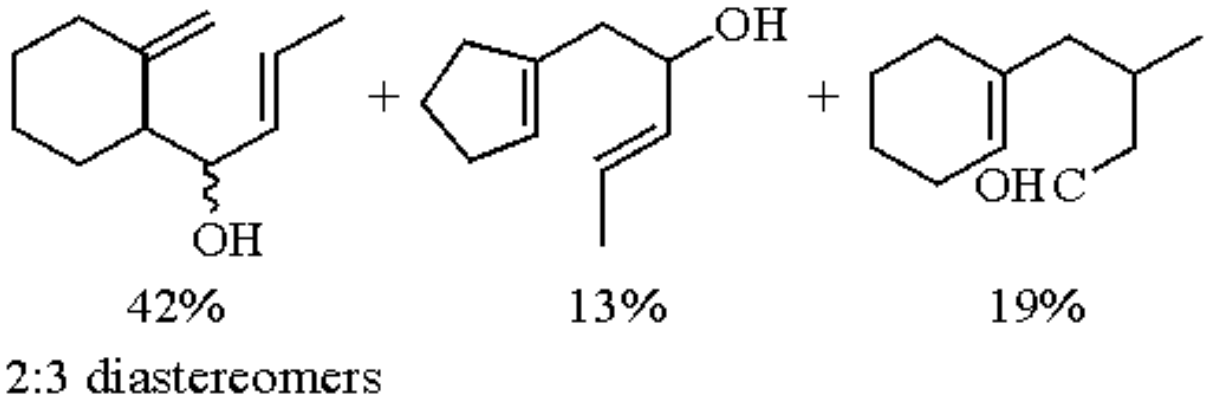

(9)

The regioselectivity of the allyl system can be reversed to favor the least substituted position by transmetalation with Ce^{III} leading to *cis*- or *trans*-homoallylic alcohols (eq 10).[8]

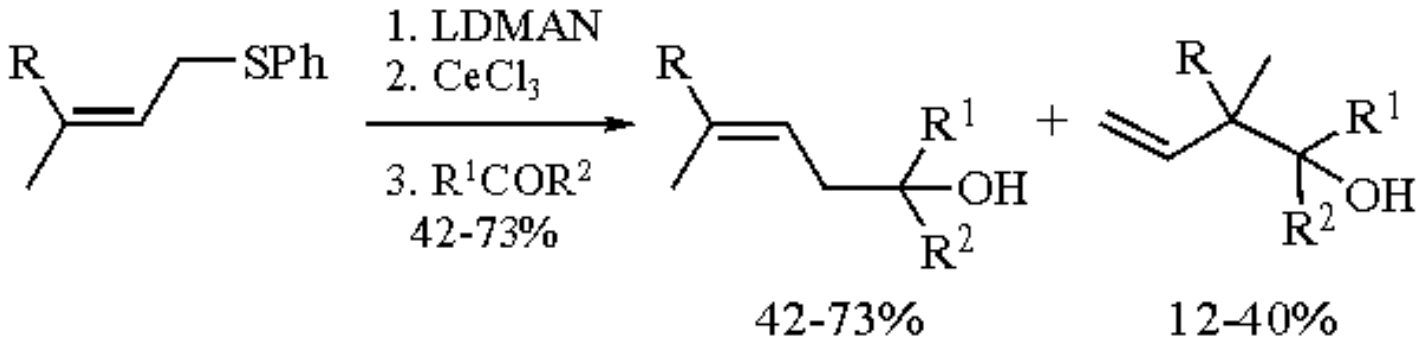

(10)

Synthesis of the elusive (1,1,3,3-tetramethylallyl)lithium was accomplished via LDMAN reductive lithiation.[9]

Desulfurization.

LDMAN has been used to remove the phenylthio group of substituted cyclobutanones (eq 11).[10] This method proved

superior to ***Raney Nickel***, which led to desulfurization and ketone reduction; lithium in ammonia led to an amide via ring cleavage.

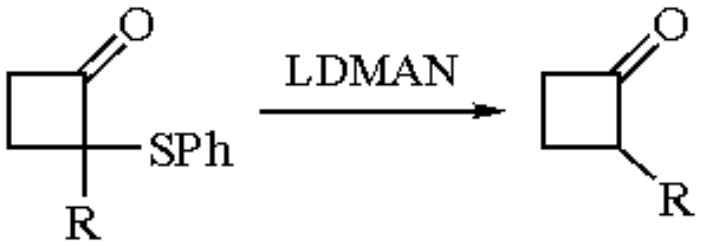

(11)

Removal of the phenylthio group in 2-substituted 2-(phenylthio)cyclopropanecarboxamides led to high yields of the *trans*-substituted products (eq 12).[11]

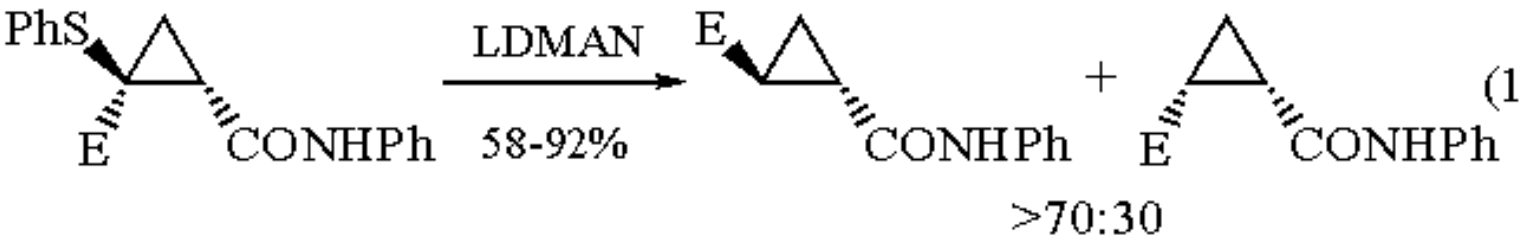

(12)

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1. (a) Cohen, T.; Bhupathy, M. *ACR* **1989**, *22*, 152. (b) Cohen, T.; Guo, B.-S. *T* **1986**, *42*, 2803. (c) Cohen, T.; Matz, J. R. *Organomet. Synth.* **1986**, *3*, 361.
2. Cohen, T.; Matz, J. R. *SC* **1980**, *10*, 311.
3. Cohen, T.; Matz, J. R. *JACS* **1980**, *102*, 6900.
4. (a) Cohen, T.; Matz, J. R. *TL* **1981**, *22*, 2455. (b) Cohen, T.; Brockunier, L. *T* **1989**, *45*, 2917.
5. Cohen, T.; Lin, M.-T. *JACS* **1984**, *106*, 1130.
6. (a) Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *JACS* **1984**, *106*, 3245. (b) Cohen, T.; Jung, S.-H.; Romberger, M. L.; McCullough, D. W. *TL* **1988**, *29*, 25. (c) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Selim, M. R. *TL* **1987**, *28*, 693.
7. Kuwajima, I.; Takeda, R. *TL* **1981**, *22*, 2381.
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Lithium (3,3-Dimethyl-1-butynyl)methylcuprate

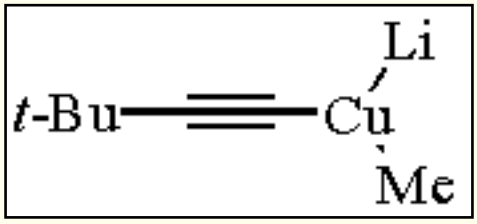

[41602-02-2] · $C_7H_{12}CuLi$ · Lithium (3,3-Dimethyl-1-butynyl)methylcuprate · (MW 166.68)

(mixed cuprate methyl transfer agent)

Alternate Name: lithium (*t*-butylethynyl)methylcuprate

Preparative Methods: by the addition of ***Methyllithium*** to ***3,3-Dimethyl-1-butynylcopper(I)*** at -40 °C in ether or THF.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Methylating Agent.

House and Umen demonstrated that lithium (3,3-dimethyl-1-butynyl)methylcuprate (**1**) would transfer a methyl group to the relatively unreactive isophorone (**2**) in 76% yield with a 12% recovery of starting material.[1] The reaction rate was significantly slower than the rate of methyl transfer from the homocuprate ***Lithium Dimethylcuprate*** to (**2**). While Me_2CuLi reacted slowly with enone (**4**), there was no reaction with mixed cuprate (**1**) (eqs 1 and 2).

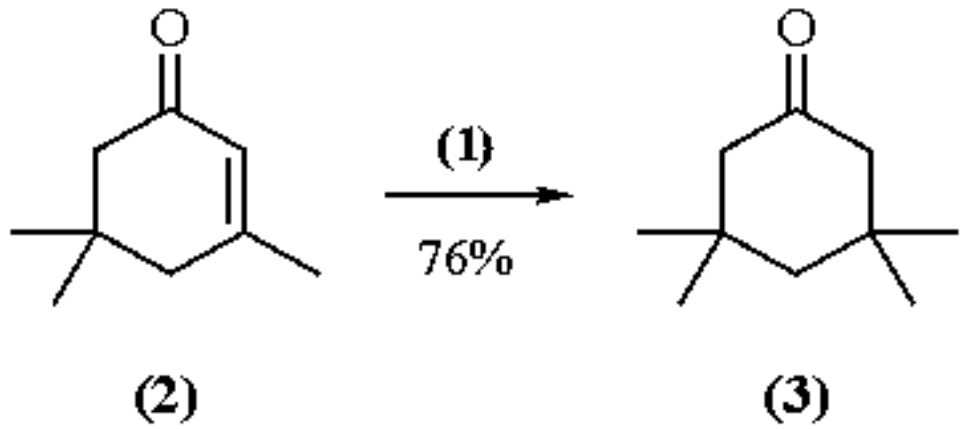

(1)

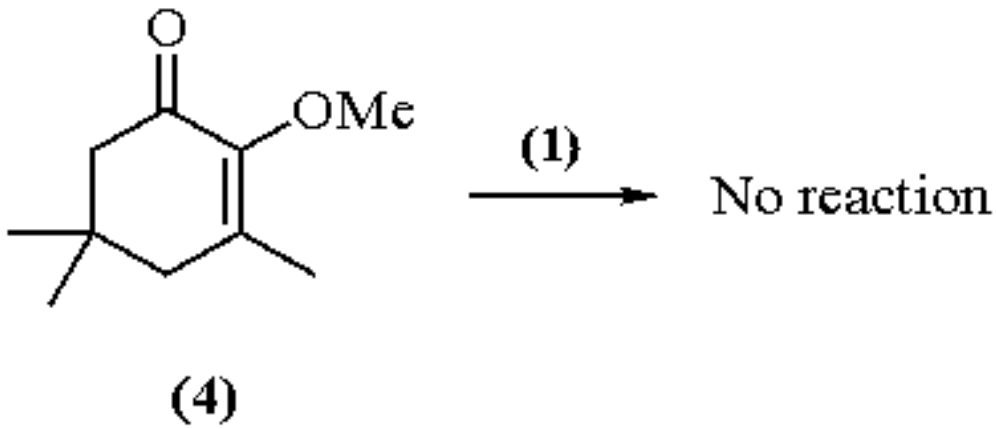

(2)

A study designed to evaluate the electron transfer abilities of several organocuprates showed that mixed cuprate (**1**) effectively converts keto-mesylate (**5**) into cyclopropyl ketone (**6**). Reaction of (**1**) with (**5**) at -78 °C in THF produced a 50% yield of (**6**), and at 0 °C the yield of (**6**) improved to 95% (eq 3).[2]

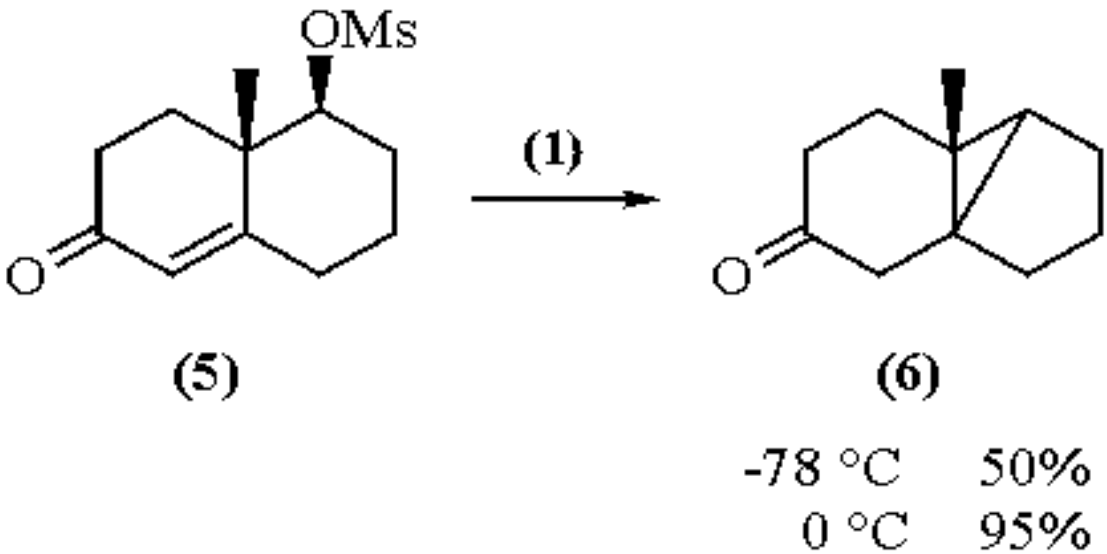

(3)

Related Reagents.

3,3-Dimethyl-1-butynylcopper(I); ***Lithium (3,3-Dimethyl-1-butynyl)vinylcuprate***; ***Lithium Dimethylcuprate***.

---

1. House, H. O.; Umen, M. J. *JOC* **1973**, *38*, 3893.
2. Hannah, D. J.; Smith, R. A. J.; Teoh, I.; Weavers, R. T. *AJC* **1981**, *34*, 181.

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Lithium (3,3-Dimethyl-1-butynyl)vinylcuprate

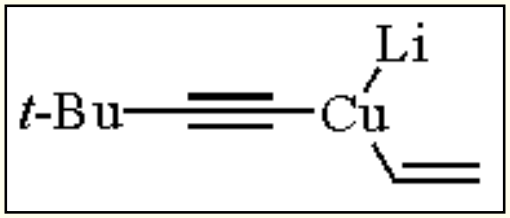

[41602-03-3] · $C_8H_{12}CuLi$ · Lithium (3,3-Dimethyl-1-butynyl)vinylcuprate · (MW 178.69)

(mixed cuprate vinyl transfer agent)

Alternate Name: lithium (*t*-butylethynyl)vinylcuprate.

Preparative Methods: prepared in situ by addition of ***Vinyllithium*** to ***3,3-Dimethyl-1-butynylcopper(I)*** in ether at -40 °C.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Vinyl Transfer Agent.

Lithium (3,3-dimethyl-1-butynyl)vinylcuprate (**1**) is thermally more stable than ***Lithium Divinylcuprate*** and has been shown to transfer the vinyl group preferentially in 1,4-addition to enones (eq 1). Reaction of (**1**) with isophorone (**2**) is sluggish but will proceed, even though partial decomposition of the cuprate was reported.[1]

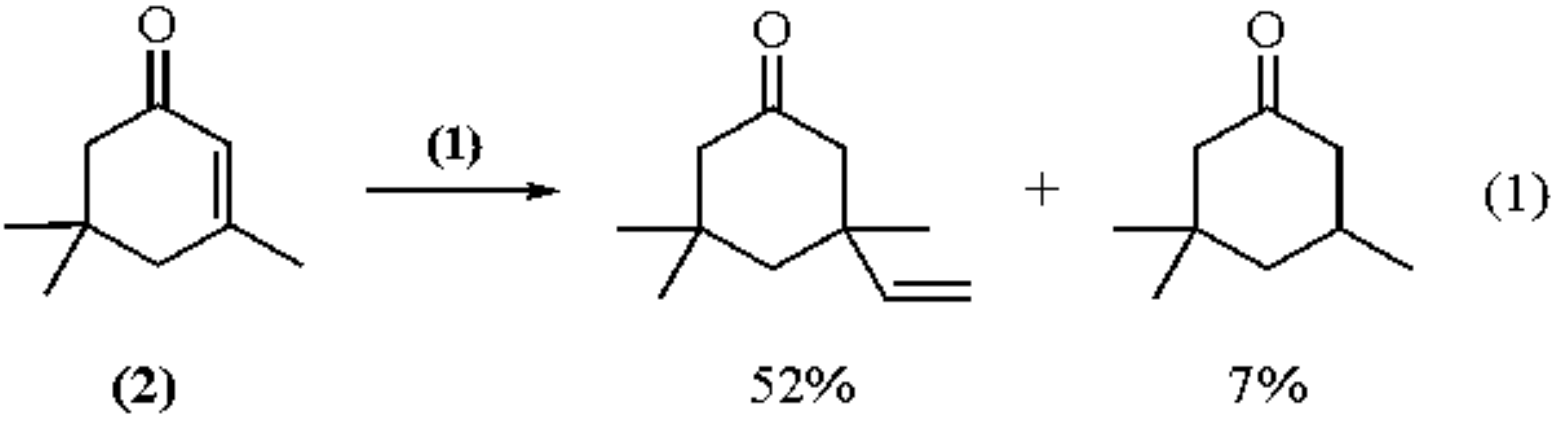

Related Reagents.

3,3-Dimethyl-1-butynylcopper(I); ***Lithium (3,3-Dimethyl-1-butynyl)methylcuprate***; ***Lithium Dimethylcuprate***; ***Lithium Divinylcuprate***.

---

1. House, H. O.; Umen, M. J. *JOC* **1973**, *38*, 3893.

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Lithium Dimethylcuprate[1]

Me_2CuLi

[15681-48-8] · C_2H_6CuLi · Lithium Dimethylcuprate · (MW 100.57)

(methylating reagent; undergoes conjugate addition reactions,[1a,b,e,f] 1,2-addition reactions,[2] substitution reactions with alkyl, vinyl, and allyl substrates,[1a,c,e,f] carbocupration of alkynes,[1a] and reduction of carbon-heteroatom bonds[3])

Physical Data: colorless solution in THF or Et_2O; ^1H NMR (Et_2O) δ -1.46 to -1.55 ppm (at 25 to -70 °C);[4,5] ^7Li NMR δ 0.75 to -0.38 ppm (at 25 to -70 °C for Me_2CuLi) and δ 0.495 to -0.38 ppm (at 25 to -70 °C for Me_2CuLi + LiI);[5] X-ray scattering measurements;[4] molecular association data.[4,6]

Solubility: sol THF, Et_2O

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***, ***Copper(I) Bromide***, ***Copper(I) Trifluoromethanesulfonate***, ***Copper(I) Chloride***) and ***Methyllithium*** under N_2 or argon.[1a] Impurities present in CuI or CuBr can promote decomposition of the reagent. Pure, light tan CuI is obtained by dissolving crude CuI in boiling NaI(aq) followed by cooling, precipitation of CuI by addition of H_2O, filtration, sequentially washing the solid with H_2O, EtOH, EtOAc, Et_2O, and pentane, and then drying in vacuo for 24 h.[7] CuBr can be purified in a similar manner[8] with NaBr (aq) or by dissolving in 48% HBr, precipitating with H_2O, sequentially washing the solid with H_2O, EtOH, and Et_2O, and drying in vacuo.[9] CuI has also been purified by continuous extraction with THF in a Soxhlet extractor (12 h) followed by drying in vacuo.[10] Me_2CuLi free of LiI can be prepared from isolated ***Methylcopper***,[8] and the reagent can also be prepared in the presence of complexing agents from $CuI.SBu_2$,[8] ***Copper(I) Iodide-Tributylphosphine***,[8] or $CuBr.SMe_2$.[11] Polymer-supported Me_2CuLi is also available.[12]

Handling, Storage, and Precautions: air- and moisture-sensitive; handle under inert atmosphere in a fume hood.

Organocuprate Reagents.

Organocuprate reactivity and thermal stability are functions of Cu^I precursor,[1a,11b,13] solvent,[1,14] temperature,[1b] cuprate composition,[5,11b] cation (e.g. Li,[1a] Mg,[1a] Zn,[15a] Mn[15b]), and alkyl[1b] ligand. Experimental evidence for ligand and metal lability has been interpreted in terms of a dynamic equilibrium between Me_2CuLi, MeLi, and Me_3Cu_2Li.[5]

Me_2CuLi is formulated as a dimer, and since cuprate reactivity is a function of composition (e.g. Me_3Cu_2Li, $Me_5Cu_3Li_2$[16]), stoichiometric considerations are important in preparing the reagent. For any given application the reactivity profile of Me_2CuLi should be compared with a range of mixed homocuprates (e.g. MeCuC&tbond;CRLi, ***Lithium Cyano(methyl)cuprate***, and $Me_2CuCNLi_2$ or $Me_2CuCN.LiCN$),[17] mixed heteroatom alkylcuprates (i.e. amido,[10,18] phosphido ,[18] thioxy,[10] and alkoxy[10]), and methylcopper in the presence of additives (e.g. TMEDA/TMSCl,[19] TMSI,[20] and TMSCl + LiI[20]).

Conjugate Addition Reactions.

Me_2CuLi transfers the methyl ligand in a 1,4-fashion to a wide range of α,β-unsaturated substrates which include enones,[1,21,22b] enals,[22] enoates,[1,14d,23] ynones,[24a] ynoates,[24b] and α,β-unsaturated lactones,[25] imides,[26] and phosphonates.[27] α,β-Alkenyl sulfoxides,[28] sulfones,[29] and phosphine oxides,[30] α,β-allenyl phosphine oxides,[31a] sulfoxides, sulfones,[31b] and ketones,[31c,d] ketoketenimines,[31e] and α,β-alkynyl sulfones[32] also undergo 1,4-addition of methyl upon reaction with Me_2CuLi. These reactions proceed most readily in nonpolar solvents (Et_2O, PhMe, CH_2Cl_2, pentane), since good donor solvents (e.g. THF, DME, HMPA) diminish cuprate reactivity toward conjugate addition.[1,14] Less reactive substrates can often be activated toward conjugate addition by use of Lewis acid additives[1] and by solvent modifications (eq 1[14d]).[14] Utilization of low temperatures and nonpolar solvents[22] gives, with the more reactive enals,[22] better ratios of 1,4-/1,2-addition products, and $Me_5Cu_3Li_2$[16] is generally more effective than Me_2CuLi (see ***Dilithium Pentamethyltricuprate***).

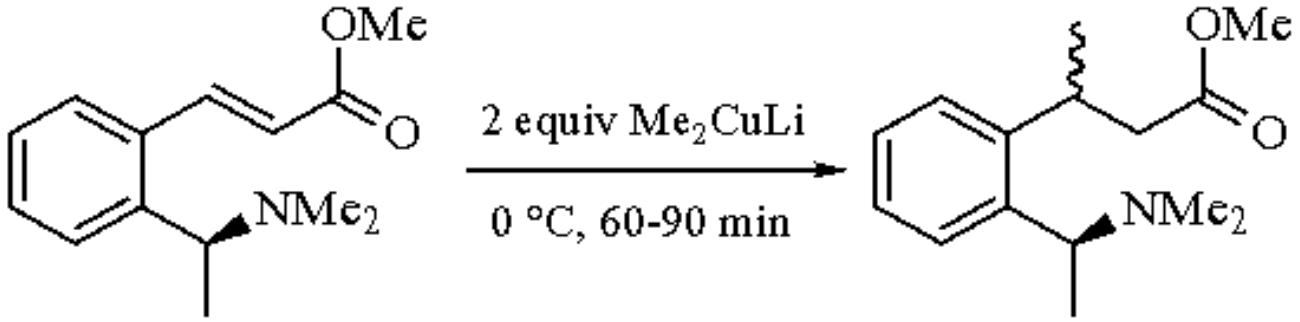

(1)

Solvent	% Yield	% de
THF	<1	-
Diethyl ether	18	68
Diethyl ether, TMSI	83	0
Toluene	91	82
Dichloromethane	94	69-79

Conformational (eq 2)[33] and steric factors often control diastereoselectivity, although electronic[34] effects have been observed and stereodivergent pathways (eq 3)[35a] can sometimes be achieved by use of Lewis acid additives. Stereocontrol in conjugate addition to γ-heteroatom substituted α,β-unsaturated substrates is a function of heteroatom identity and substitution patterns (eq 4).[35b]

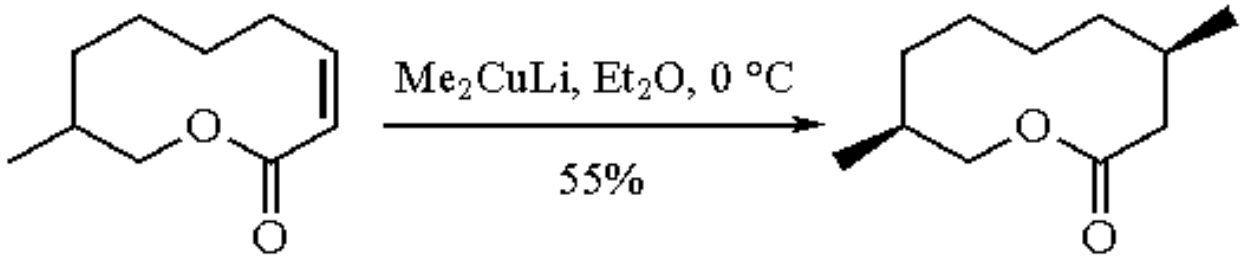

(2)

cis:*trans* = 80:20

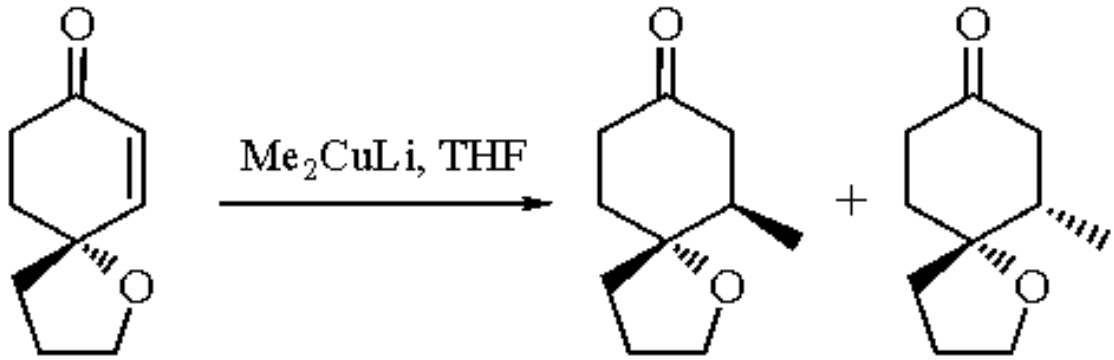

(3)

-78 to 0 °C	61%	8:92
TMSCl, -78 °C	70%	99:1

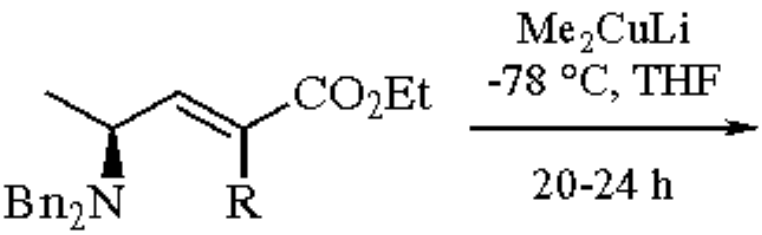

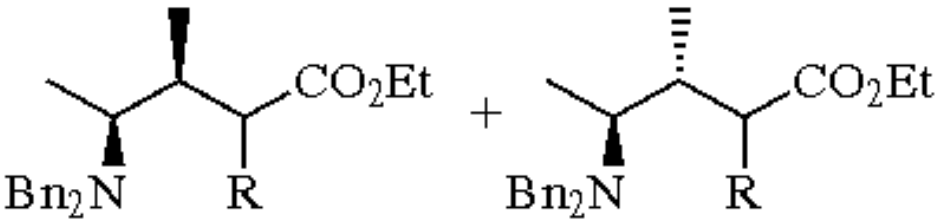

(4)

R = H	TMSCl	80%	94:6
R = CO_2Et	-	68%	21:79

The conjugate addition reaction is compatible with alkyl bromide[36] and nitroalkane (eq 5)[37] functionality, although substitution of mesylates is competitive[36] with conjugate addition. Substrates with extended conjugation generally afford products of 1,6- or 1,8-addition.[38] Reaction of Me_2CuLi with ynenoates gives nonconjugated allenyl esters upon careful protonation of the enolate (eq 6).[38c] Bis-activation (e.g. alkylidenemalonates (eq 4), perhydro-1,4-oxazepine-5,7-diones,[39a] malononitriles,[39b] α-keto sulfoxides,[39c] and 2-acyl- or 2-alkoxycarbonyl-4-chromones[39d]) of the alkene facilitates conjugate addition, allowing participation of normally unreactive functionality (e.g. α,β-unsaturated nitriles

and 4-chromones).

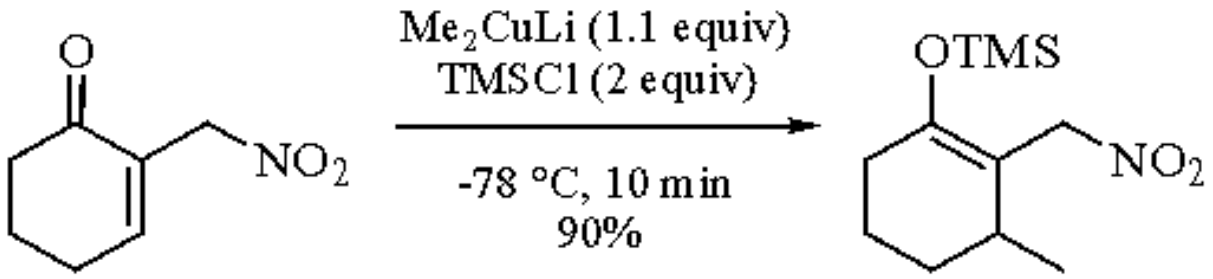

(5)

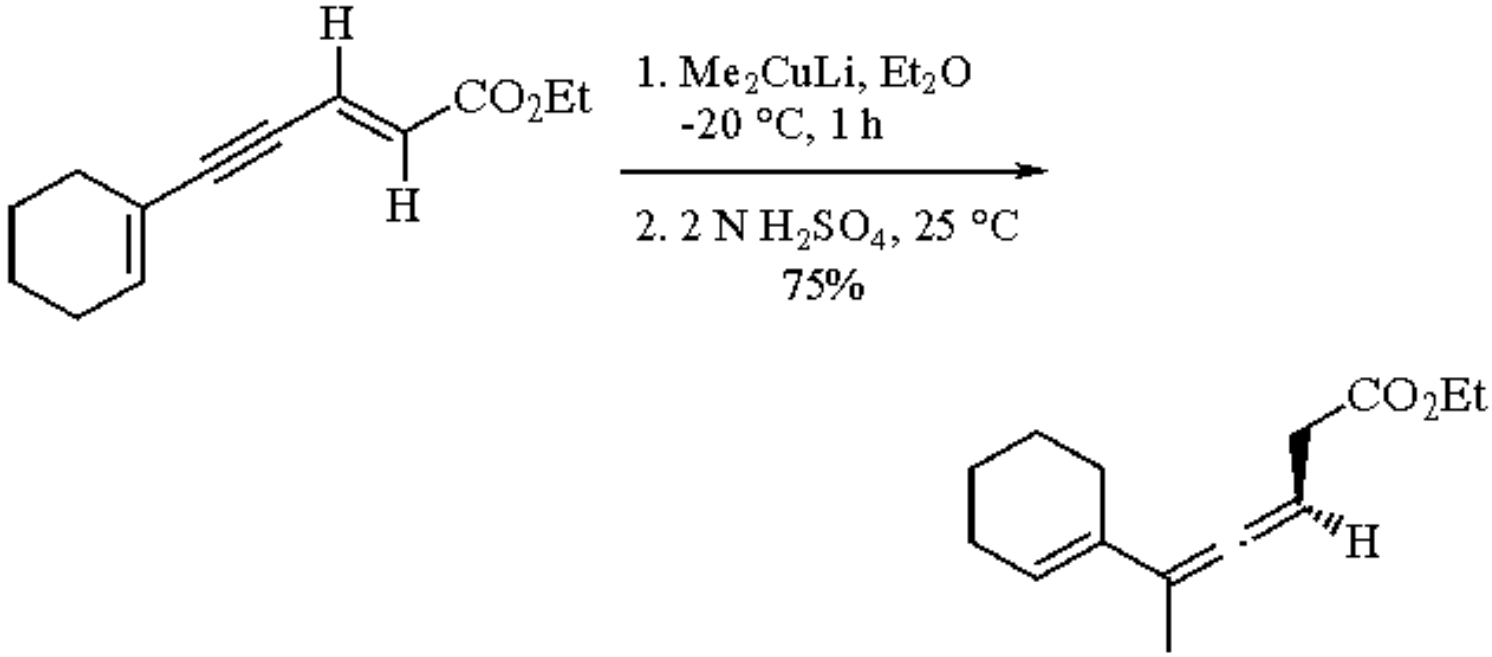

(6)

Transition metal-alkene complexes undergo conjugate addition (eq 7),[40a] and Me_2CuLi and MeLi can effect different[40b] regioselectivities. Reaction at metal carbonyls can be a side reaction, and the efficiency of cuprate conjugate addition is dependent upon the ligands attached to the metal.[40b]

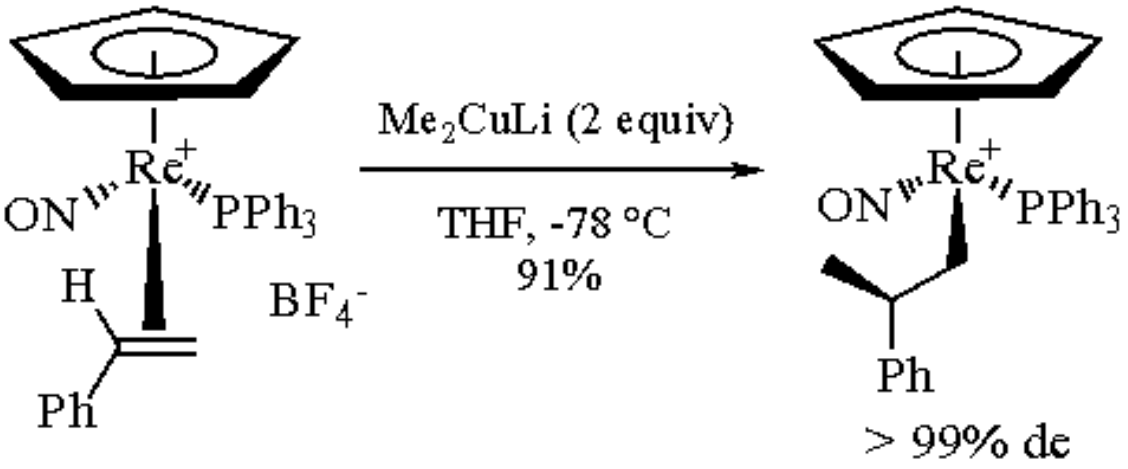

(7)

The enolate resulting from conjugate addition can be trapped with a variety of electrophiles (e.g. alkyl halides, halosilanes (eq 5), acid chlorides, formaldehyde, sulfenyl halides, selenenyl halides, aldehydes, Mannich salts,

triflating agents, CO_2, and chlorophosphates), although solvent modifications and use of additives (e.g. HMPA, ***Zinc Chloride***) are sometimes required.[41] The wide range and variability of reaction conditions required for successful tandem conjugate addition-enolate trapping reflect the complexity of these reaction mixtures and the generally diminished reactivity of the enolate, although enolates generated by conjugate addition of Me_2CuLi to γ-methylenebutenolides[42a] and simple butenolides[42b] participate in conjugate addition reactions with the starting lactone. Although acylation of these enolates is often problematic,[43a] *O*- vs. *C*-acylation can be controlled by use of ***Methyl Cyanoformate***[43b] in either Et_2O or THF (eq 8). A powerful application of cuprate 1,4-addition lies in the generation of regiospecific enolates which can undergo subsequent chemistry such as Dieckmann cyclization (eq 9)[23a] or Claisen rearrangement (eq 10).[44]

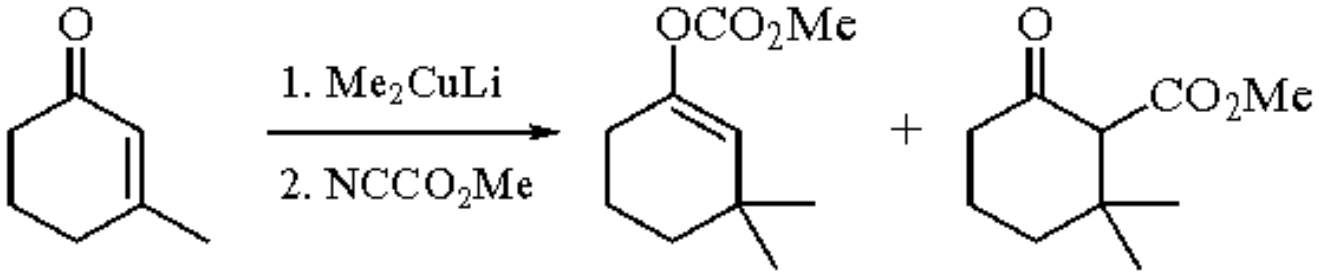

(8)

THF	89%	95:5
Et_2O	84%	7:93

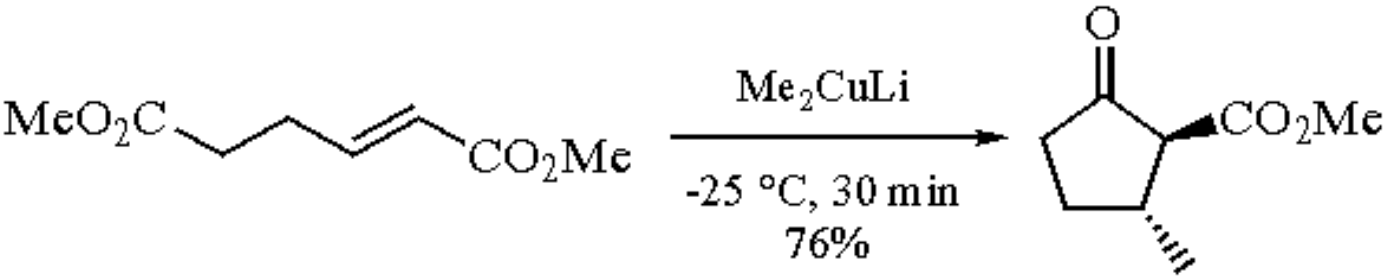

(9)

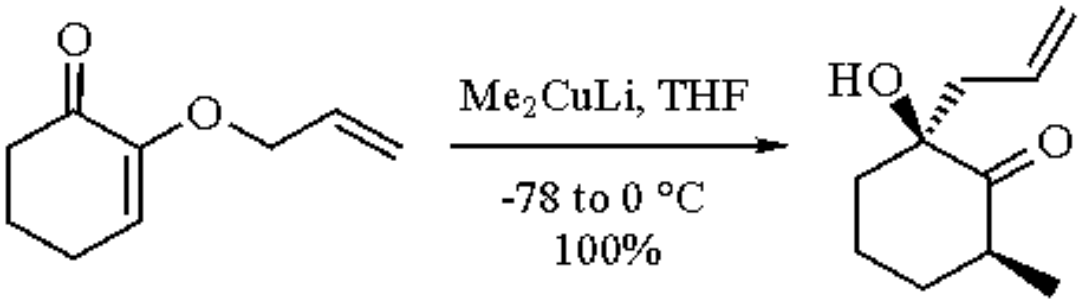

(10)

α,β-Unsaturated substrates containing a good leaving group (e.g. halide, alkoxycarbonyl, sulfonate esters, phosphonate esters, alkyl- or arylthioxy, alkoxy) on the β-carbon atom undergo substitution reactions,[45] and tandem addition-elimination-addition pathways[46] can be designed (eq 11)[46b] for substrates with an α-CH_2L substituent; ***Chlorotrimethylsilane*** is necessary to prevent elimination of the nitro group in the reaction of Me_2CuLi with an α-nitromethylenone[37] (eq 5).

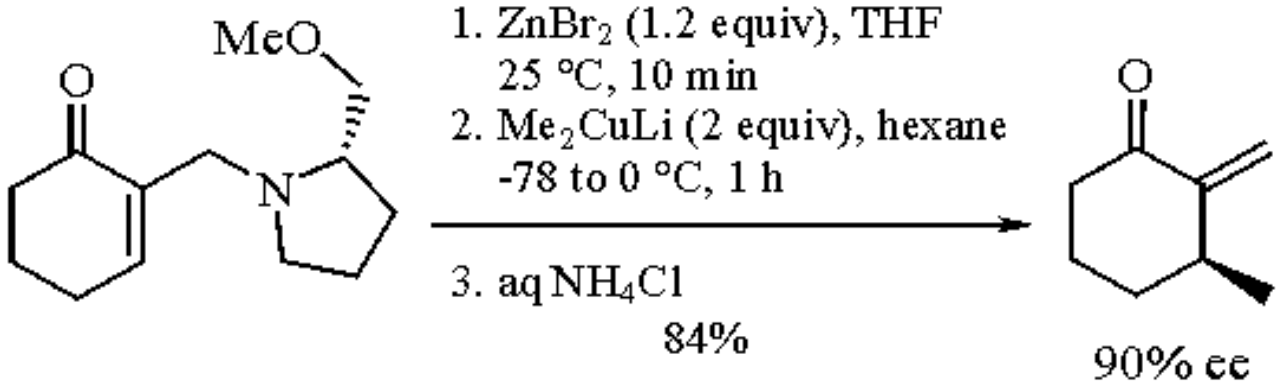

(11)

Several scalemic substrates[26,37,39a,47] (eqs 11 and 12[46b and 47c]) afford good to excellent asymmetric induction in the conjugate addition reaction, while more modest ee's have been achieved with chiral coordinating[47a] ligands.

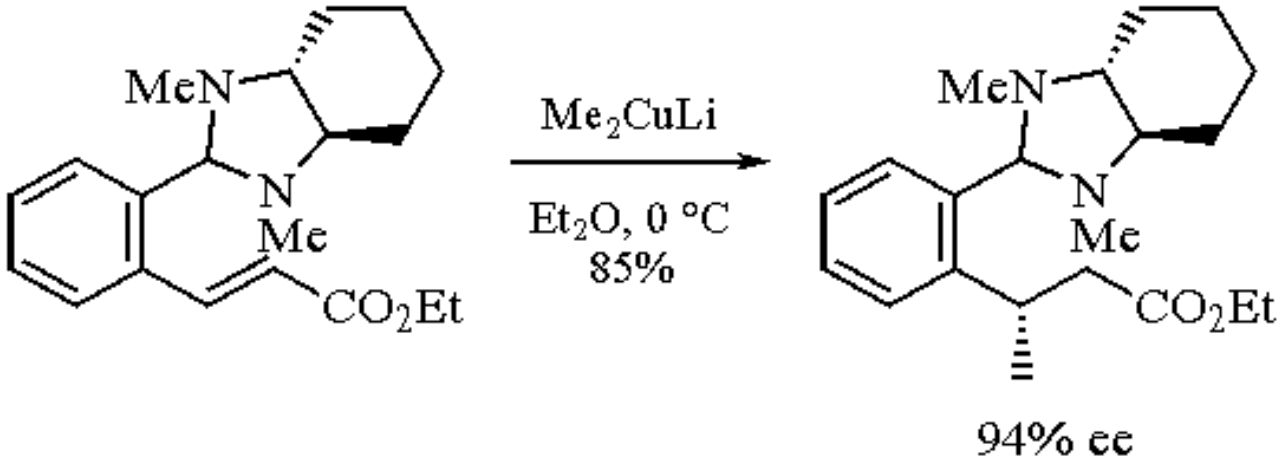

(12)

Although simple cyclopropyl ketones do not react with Me_2CuLi, 1,1-bis-activated cyclopropanes (e.g. cyclopropylmalonates,[48a] β-keto esters,[48a] β-keto phosphonates[48b]) undergo a homoconjugate addition reaction (eq 13),[48a] and methylenecyclopropyl ketones[48c] participate in 1,5-additions.

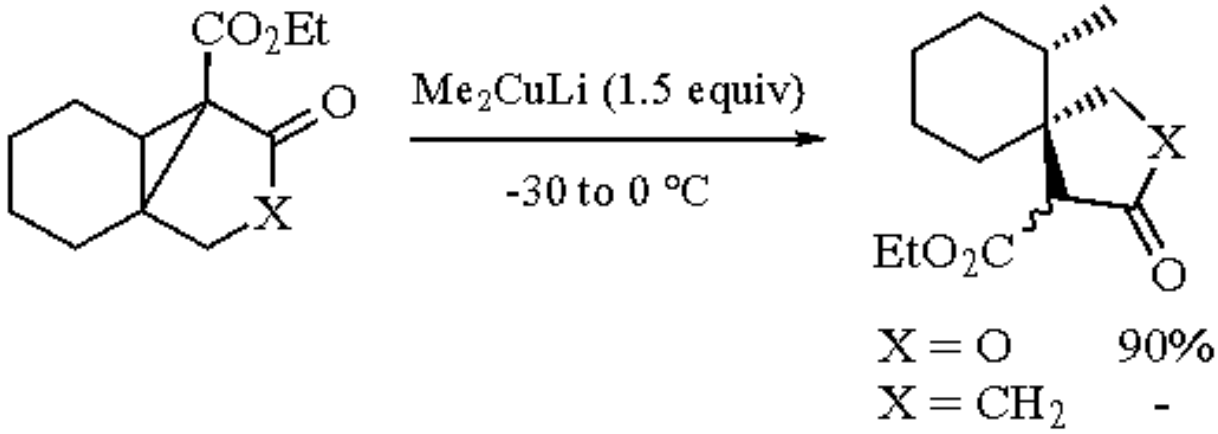

(13)

Carbonyl Additions.

1,2-Addition of Me_2CuLi to ketones is generally limited to alkyl aryl[49a] and diaryl[49b] ketones, although an α,α´-

dialkoxy ketone (eq 14)[49c] gave good yields of the 1,2-addition product. Although enals preferentially react in a 1,4-fashion, 1,2-addition is often a serious side reaction and is favored by addition of TMSCl (which also facilitates 1,2-addition to ketones[2]); this additive also increases Cram stereoselectivity.[2,50]

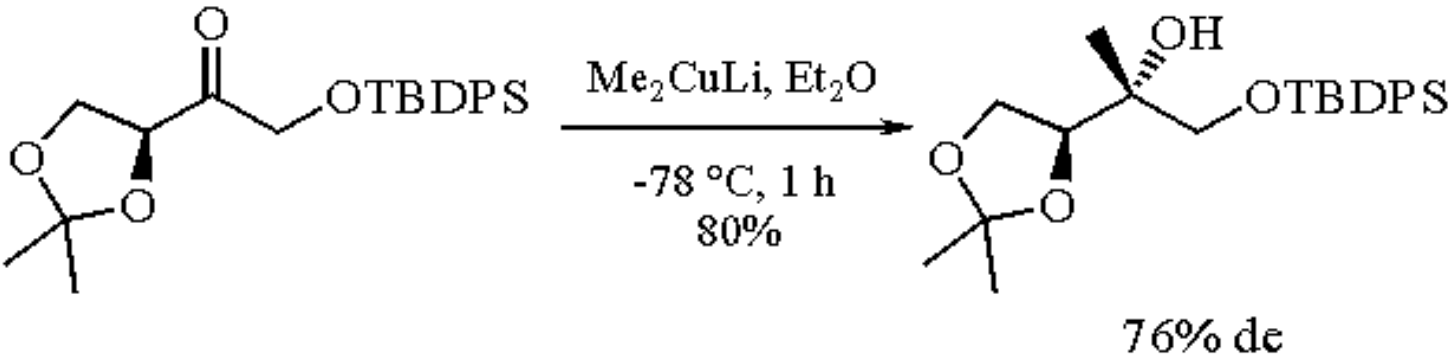

(14)

Carbocupration.

Carbocupration of alkynes with Me_2CuLi appears limited to propynal diethyl acetal;[51a] the reaction fails with a higher homolog. Carbocuprations of 1-methoxyallene[51a] and of cyclopropene derivatives (eq 15)[51b] have been reported.

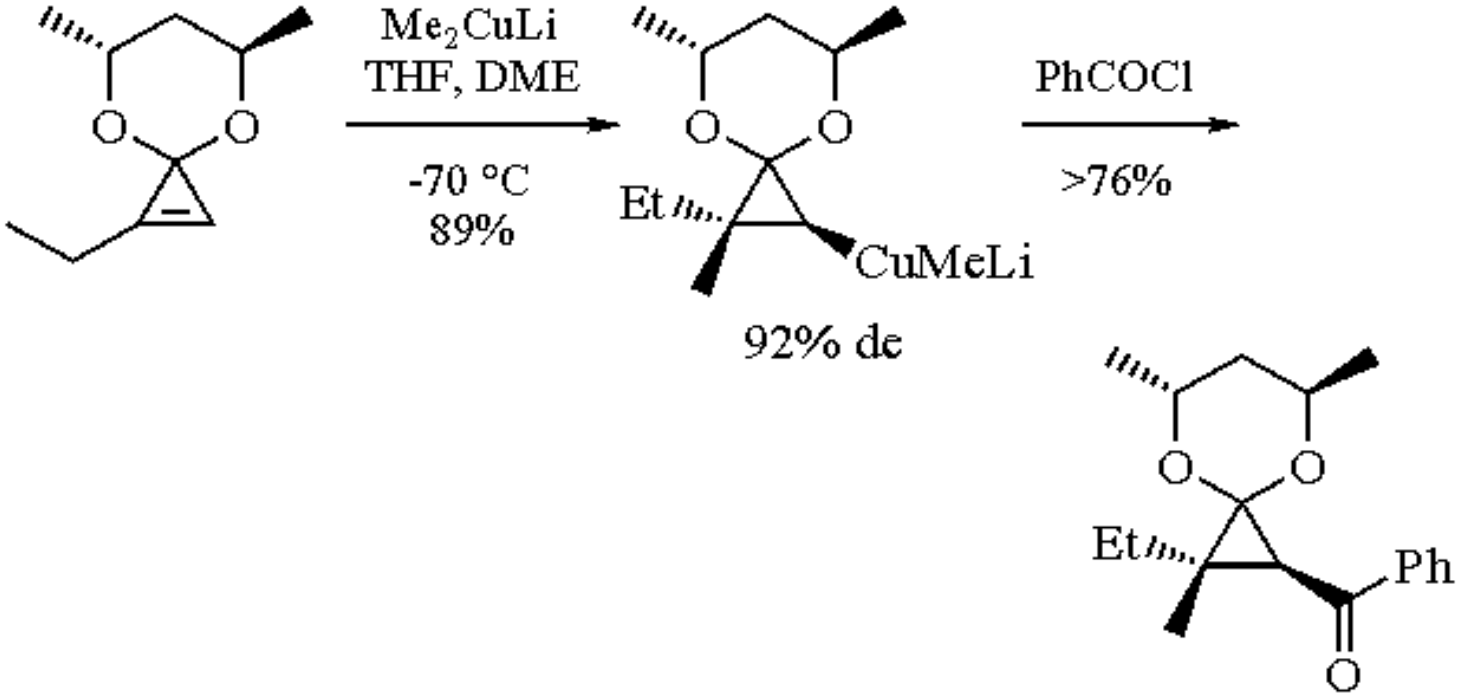

(15)

Substitution Reactions.

Me_2CuLi participates in S_N2-type substitution reactions[1a,c,e] with alkyl halides[8,52] (e.g. α-halo ketones[52a] and β-alkoxy-β-OLi intermediates[52b]), sulfonate esters,[53] oxiranes (epoxides),[54] tosylated aziridines,[55a] oxetanes,[55b] cyclic sulfinates,[56a] trifluoromethyl sulfonimides,[56b] β-lactones,[57] and with vinyl halides,[58a] triflates,[58b,c] and selenones.[58d] 1,1-Dibromocyclopropanes[59] can undergo a double substitution reaction with Me_2CuLi. Proximate heteroatoms facilitate the reaction of secondary tosylates.[53b] Alkyl substrates generally react with inversion of configuration, while

substitution on alkenyl substrates (eq 16)[58a] proceeds with retention of configuration. Although Me_2CuLi reacts with iodobenzene, it is unreactive towards aryl triflates and bromides and thus the reaction[8] is unsatisfactory for effecting aryl substitution.

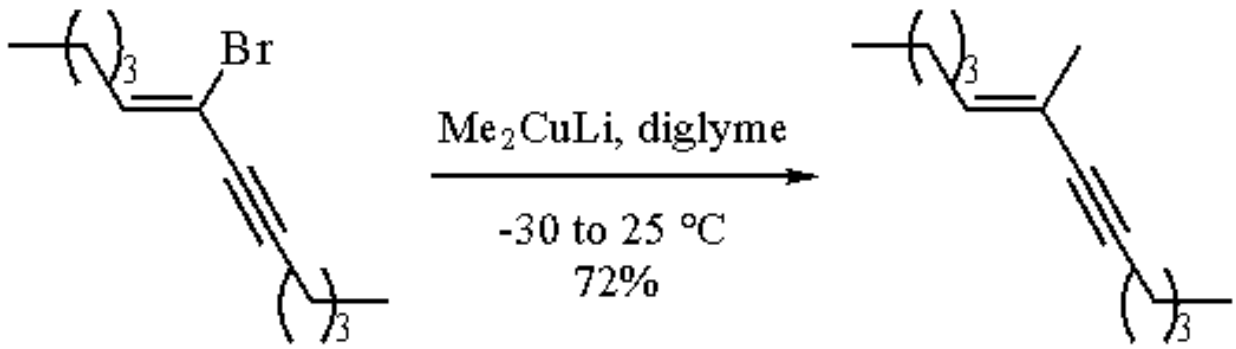

(16)

Regioselective cleavage of oxiranes is a powerful synthetic method.[1a,c,e] Me_2CuLi cleaves epoxides at the least substituted center; 1,2-disubstituted epoxides afford mixtures of regioisomers. Regiocontrol is possible in 2,3-epoxy acids,[54a] esters,[54b,c] and 4-alkyl-substituted 2,3-epoxy alcohols,[54d] and regiocontrol is enhanced by solvent effects with 2,3-epoxy alcohols[54e] lacking a C-4 substituent.

Allylic substrates react with (S_N2') or without (S_N2) rearrangement via a π-allyl copper complex, with the *anti* S_N2' pathway predominating. Regio- and stereochemistry is generally governed by steric factors, although stereoelectronic effects may also operate.[1a] Allylic carbamates display high *syn* S_N2' stereo- and regioselectivity (eq 17[60a]).[60] Propargyl substrates uniformly give S_N2' substitution.[1a] Vinyloxetanes,[61] vinyloxiranes (eq 18),[62a] and allylic sulfoxides and sulfones[62b] undergo S_N2' substitutions, and the vinyloxiranes react with good diastereoselectivity.

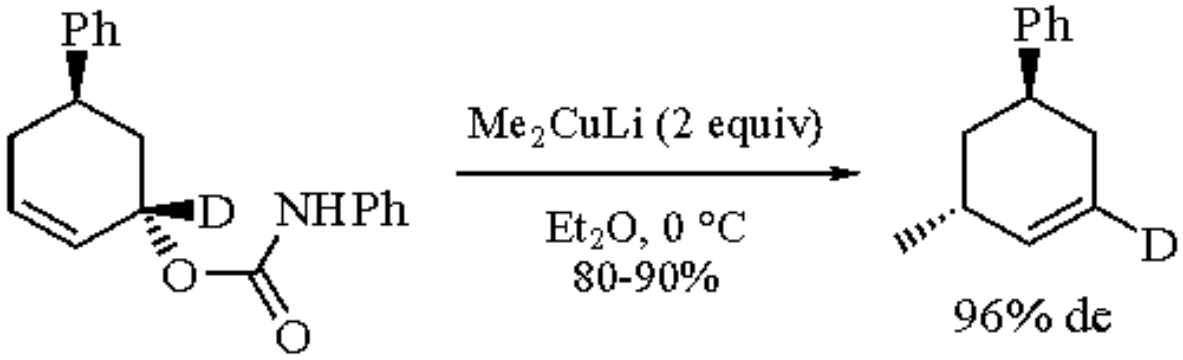

(17)

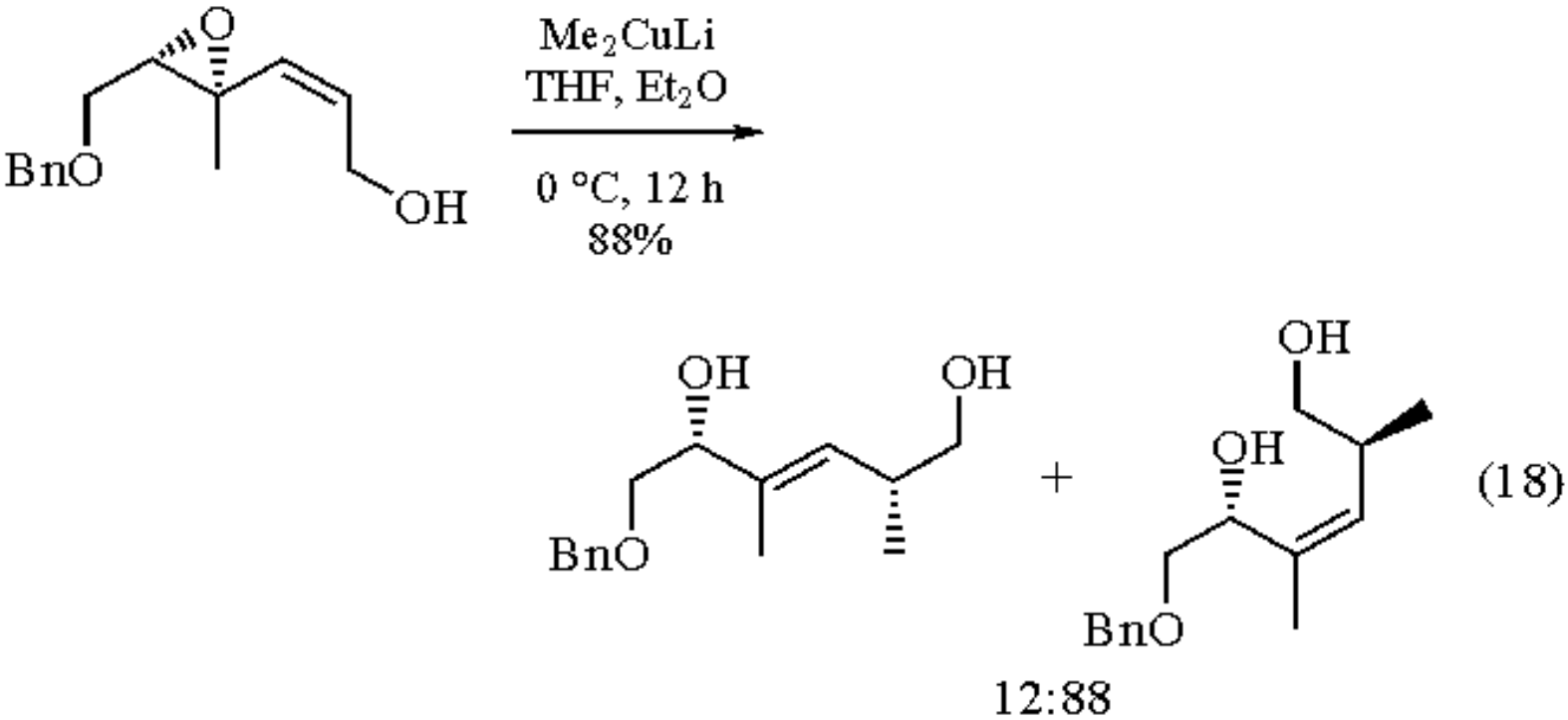

Reaction of Me_2CuLi with acyl halides[1c] or thiol esters[63] results in nucleophilic acyl substitution, providing a useful route to ketones. Substitution reactions also occur between Me_2CuLi and sulfonium salts,[64] and via benzyne[65] intermediates.

Miscellaneous Reactions.

The reagent adds to 1-acylpyridinium salts[66] and to transition metal carbene complexes.[67] Me_2CuLi can reduce α-halo[3a] and α-acetoxy ketones[3a] and α,β-epoxy[3b] ketones. Reduction of α,β-epoxy sulfoxides affords enolates.[68] Me_2CuLi reacts with α,α´-dibromo ketones to afford α-methyl ketones via a cyclopropanone intermediate (eq 19).[36a,68] Reaction of Me_2CuLi with α´-nucleofuge α,β-enones leads to mixtures of reduction and substitution products.[70] Chiral allenes have been prepared by reaction of Me_2CuLi with allylic sulfinyl mesylates.[71]

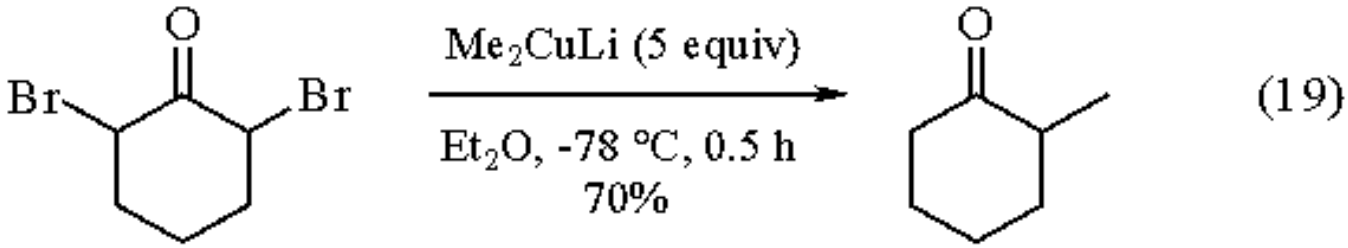

Related Reagents.

Lithium Diallylcuprate; ***Lithium Di-n-butylcuprate***; ***Lithium Diethylcuprate***; ***Lithium Diethylcuprate-Tributylphosphine***; ***Lithium Dimethylcuprate-Boron Trifluoride***; ***Lithium Diphenylcuprate***; ***Lithium Di-n-propylcuprate***; ***Lithium Di-p-tolylcuprate***; ***Lithium Divinylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

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Lithium Dimethylcuprate-Boron Trifluoride[1]

Me_2CuLi-BF_3

(Me_2CuLi)

[15681-48-8] · C_2H_6CuLi · Lithium Dimethylcuprate-Boron Trifluoride · (MW 100.57) (BF_3)

[7637-07-2] · BF_3 · Lithium Dimethylcuprate-Boron Trifluoride · (MW 67.81) ($BF_3.Et_2O$)

[109-63-7] · $C_4H_{10}BF_3O$ · Lithium Dimethylcuprate-Boron Trifluoride · (MW 141.95)

(methylating reagent that undergoes accelerated conjugate addition reactions,[1] 1,2-addition reactions,[2] substitution reactions with alkyl[1,3] and allylic substrates,[1,4] and reduction reactions[4])

Physical Data: clear solution in THF; ^1H NMR data for Me_2CuLi + 2 $BF_3.Et_2O$ at -80 °C is suggestive of a four-component system: Me_2CuLi (δ -1.57 ppm) + Me_3Cu_2Li (δ -1.31 and -0.35 ppm) + $MeLi.BF_3$ (δ 0.16 ppm) + BF_3.[1b]

Solubility: sol THF, Et_2O

Preparative Methods: addition of 2 equiv of ***Boron Trifluoride Etherate*** to ***Lithium Dimethylcuprate*** prepared from Cu^I salts and ***Methyllithium*** at -78 °C gives a clear solution in THF; warming the solution from -78 to -60 °C over 10 min generates a solution of Me_3Cu_2Li + BF_3 + $MeLi.BF_3$.[1b] The reagent can also be prepared by addition of ***Boron Trifluoride*** to Me_2CuLi, although use of $BF_3.Et_2O$ is more convenient and affords identical results.[3b]

Handling, Storage, and Precautions: air- and moisture-sensitive; handle under inert atmosphere in a fume hood.

Addition Reactions.

Addition of $BF_3.Et_2O$ to solutions of Me_2CuLi affords a reagent and reaction conditions in which conjugate transfer of the methyl ligand to α,β-alkenyl ketones (eq 1[5b]),[5] enoates,[6] lactones[5b,7] and alkylidenemalonates[6a,8] is accelerated relative to Me_2CuLi. The reagents $MeCu.BF_3$ and $Me_2Cu(CN)Li_2/BF_3$ can also be used, and the relative effectiveness of each reagent is generally substrate dependent. γ-Silyloxy- (eq 2)[6a] and γ-amino-α,β-enoates[6b] as well as γ-

alkoxyalkylidenemalonates[6a] undergo conjugate addition reactions with these reagents with varying degrees of stereoselectivity and yield. The reagent has often been used on substrates with reduced reactivity resulting from substitution and steric factors. This reagent combination has been effectively used in a homoconjugate addition reaction with a cyclopropyl ketone (eq 3).[9]

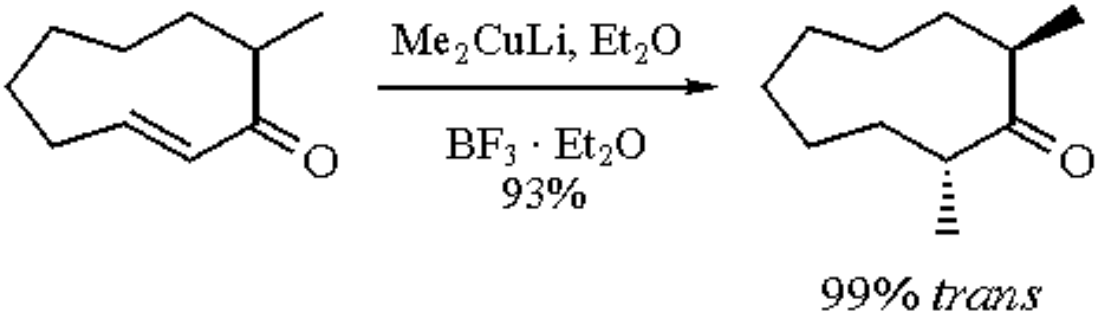

(1)

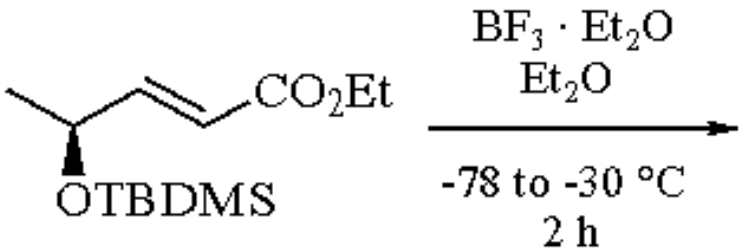

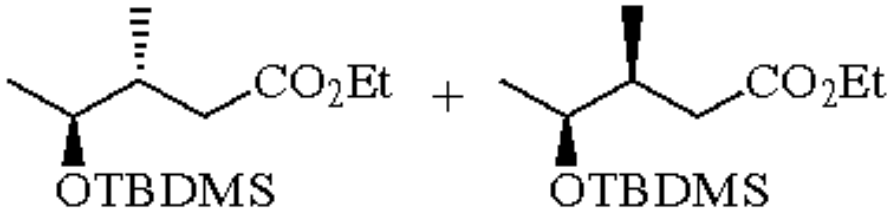

(2)

MeCu	68:32	6%
Me_2CuLi	73:27	26%
$Me_2Cu(CN)Li_2$	92:8	92%

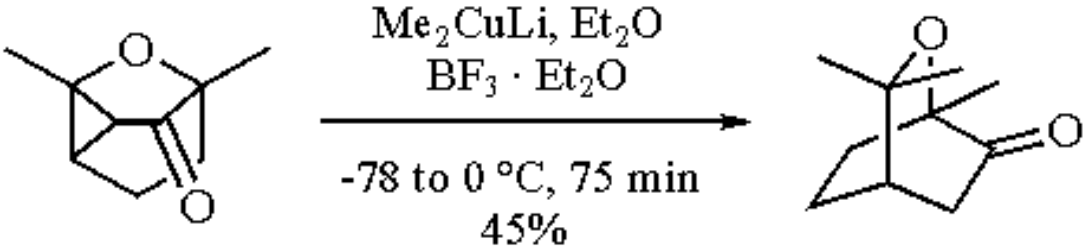

(3)

1,2-Addition of $Me_2CuLi/BF_3.Et_2O$ to chiral imines provides a synthetic route to chiral amines that is stereodivergent relative to the 1,2-addition reactions of organolithium and organocerium reagents (eq 4).[2]

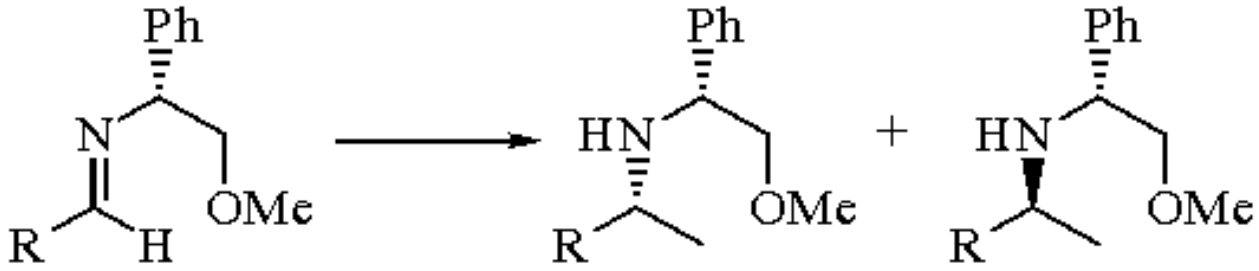

(4)

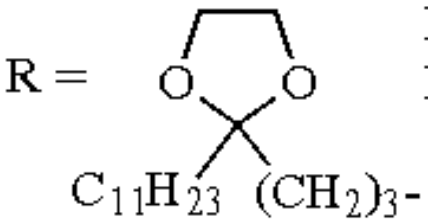

Me_2CuLi, BF_3 (from CuI)	14:86	52%
Me_2CuLi, BF_3 (from $CuBr \cdot SMe_2$)	10:90	56%
MeLi	95:5	66%
$MeCeCl_2$	97:3	65%

Substitution Reactions.

Addition of $BF_3.Et_2O$ to solutions of Me_2CuLi provides a reagent and reaction conditions that can effect substitution reactions on substrates, such as aziridines (eq 5)[10] and acetals,[3] that are normally unreactive toward Me_2CuLi alone. Although ***Titanium(IV) Chloride*** can also be employed, superior yields are generally obtained with $BF_3.Et_2O$ (eq 6).[3b] A β-bromobutenolide undergoes a substitution reaction with varying combinations of Me_2CuLi, MeLi, and $BF_3.Et_2O$ (eq 7).[11]

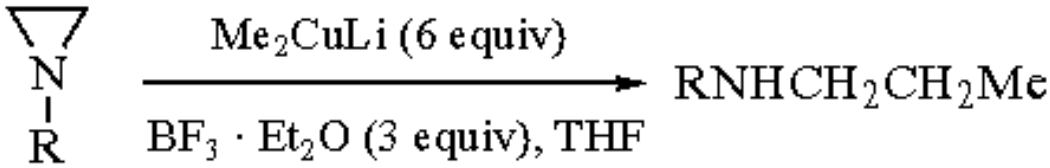

(5)

$R = PhCH_2$	80%
$R = (4\text{-}MeOC_6H_4)_2CH$	97%

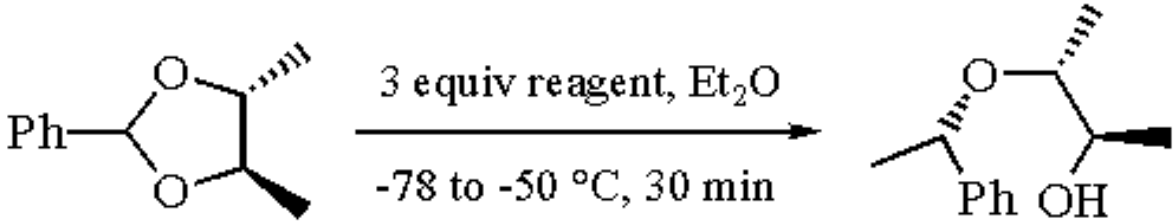

(6)

Me_2CuLi, BF_3	95%	67% de
Me_2CuLi, $TiCl_4$	48%	88% de
MeCu, BF_3	50%	72% de

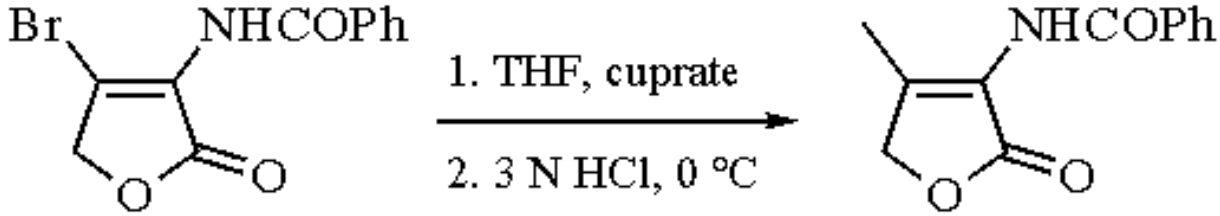

(7)

Me_2CuLi (1.5 equiv), 0 °C, 2 h	26-29%
Me_2CuLi, $MeBF_3Li$ (1.5 equiv), 0 °C, 2 h	57%
$MeBF_3Li$ (2 equiv), then Me_2CuLi (2 equiv) 0 °C, 30 min	78%

Allylic acetals[12] and oxazolidines[13] undergo reaction with Me_2CuLi/BF_3 to afford mixtures of rearranged (S_N2') and unrearranged (S_N2) substitution products, while allylic acetals[12] afford, exclusively, substitution products via S_N2' pathways. Chiral allylic oxazolidines give substitution products with very modest asymmetric induction.[13] Good asymmetric induction has been achieved with chiral γ-sulfonyloxy-α,β-enoates, which undergo preferential allylic substitution (eq 8).[4]

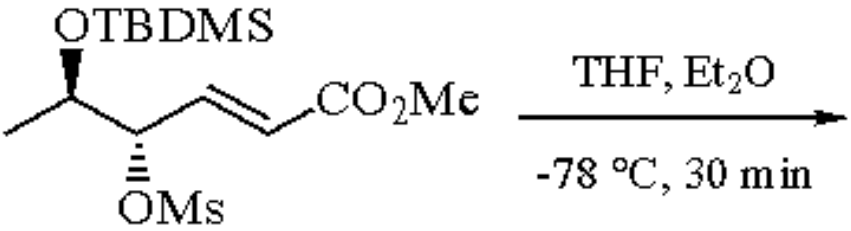

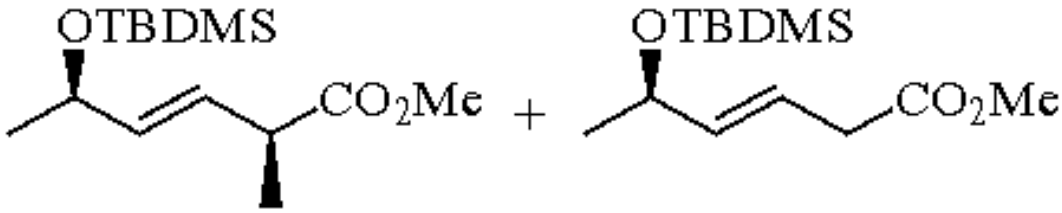

(8)

Me_2CuLi, BF_3	61%	>99% de	25%
$Me_2Cu(CN)Li_2$	78%	>99% de	11%
$Me_2Cu(CN)Li_2$, BF_3	96%	>99% de	-

Reduction Reactions.

γ-Acyloxy-α,β-enoates[4] undergo reduction upon treatment with Me_2CuLi/BF_3, in contrast to the γ-alkoxy derivatives,[6a] which undergo conjugate addition, and the γ-mesyloxy derivatives,[4] which undergo allylic substitution. $BF_3.Et_2O$ as an additive attenuates the electron transfer properties of Me_2CuLi.[14]

Related Reagents.

Lithium Cyano(methyl)cuprate; ***Lithium Dimethylcuprate***; ***Methylcopper***; ***Methylcopper-Boron Trifluoride Etherate***.

---

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Lithium Diphenylcuprate[1]

Ph_2CuLi

[23402-69-9] · $C_{12}H_{10}CuLi$ · Lithium Diphenylcuprate · (MW 224.71)

(phenylating reagent; undergoes conjugate addition reactions,[1a,b,d] substitution reactions with alkyl, vinyl, and allylic substrates,[1a,c,d] oxidative coupling,[2] and addition to benzynes[3])

Physical Data: $Ph_2CuLi.0.4Et_2O$ isolated as white crystals or yellow powder when dry; [$Ph_2CuLi.3.25LiBr.4.2C_4H_8O_2$] precipitated from dioxane;[4a] X-ray structure of [$Ph_2CuLi.Et_2O$] prepared from $CuI.PBu_3$;[4b] ^{13}C NMR (DMS) of Ph_2CuLi prepared from CuBr: δ 163.1, 143.6, 128.1, 127.0 ppm; ^6Li NMR δ -0.57 ppm.[4c]

Solubility: sol THF, Et_2O, benzene, hexane.

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***, ***Copper(I) Bromide***, $CuBr.SMe_2$ or ***Copper(I) Iodide-Tributylphosphine***) under N_2 or argon atmosphere (see ***Lithium Dimethylcuprate***).[1a] Polymer-supported Ph_2CuLi can be prepared.[5]

Handling, Storage, and Precautions: dry crystals are stable at 25 °C, but the reagent decomposes in solution. Air and moisture sensitive. Use in a fume hood.

Addition Reactions.

Ph_2CuLi reacts with α,β-alkenyl ketones, aldehydes,[6] esters,[7] lactones,[8] malonates,[9] sulfones, and *N*-tosyl-1-azoalkenes[10] with conjugate transfer of the phenyl ligand.[1] α,β-Ynones,[11a] ynoates,[11b] and ynoic acids[11b] also participate in 1,4-additions with Ph_2CuLi, while yields vary widely[1d] with nitroalkenes. Appropriate location of nucleofuge substituents, including σ-complexed transition metals,[12a] can result in addition-elimination[12b,c] or addition-elimination-addition (eq 1)[12d] reactions. Subsequent exploitation of chemo- (eq 2)[7b] or regioselectively generated enolate anions represents a powerful dimension of cuprate conjugate addition reactions (eq 3[7c]).[13] Acylvinylcyclopropanes undergo 1,6-addition[14a] and 1,1-diactivated cyclopropanes undergo homoconjugate addition.[14b]

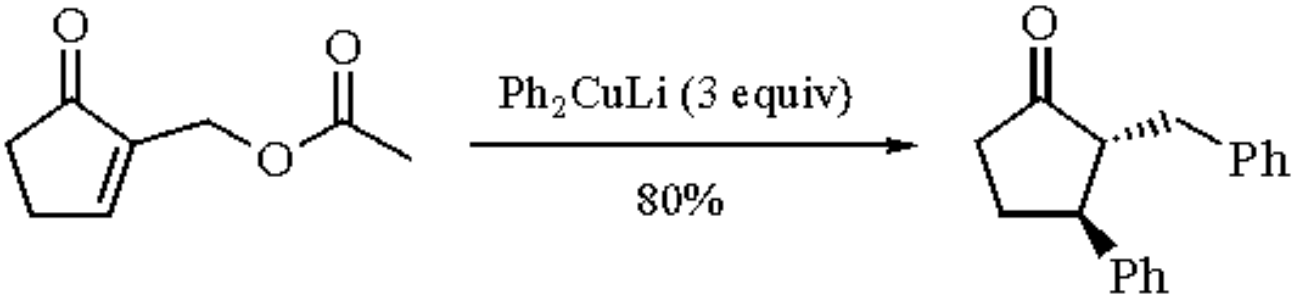

(1)

trans:*cis* = 95:5

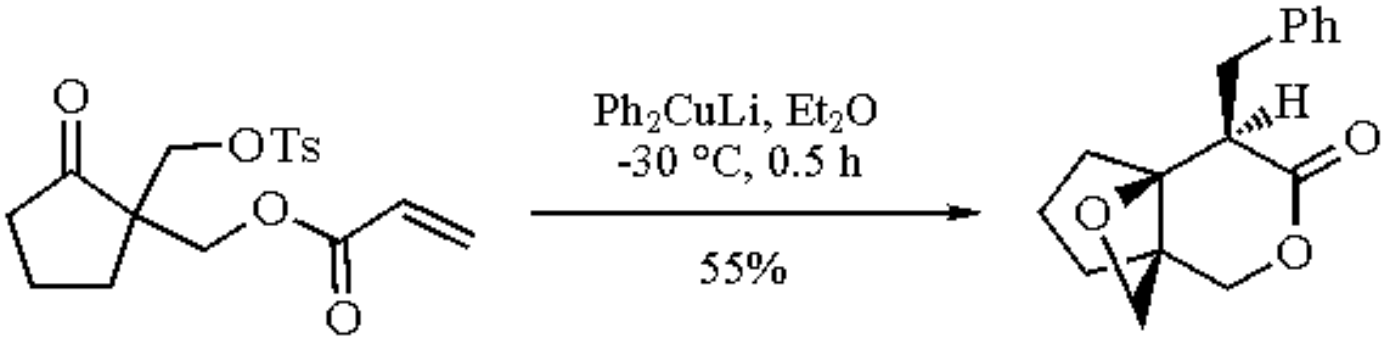

(2)

α-H:β-H = 7:1

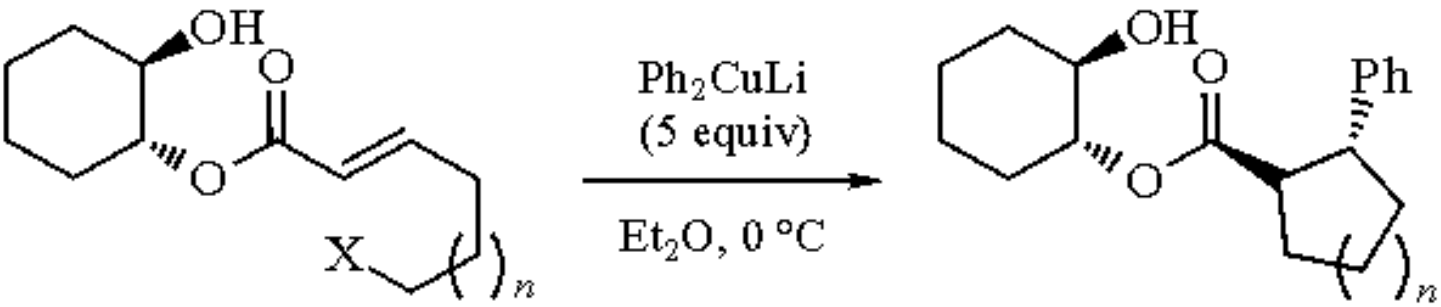

(3)

n = 1, X = Cl, 50%, 76% de
n = 2, X = I, 61%, 78% de

1,2-Addition of Ph_2CuLi to a chiral γ-alkoxy-α,β-enal occurs with vinylogous Cram selectivity in the presence of ***Chlorotrimethylsilane*** despite the general preference of this reagent to add 1,4 to enals.[15] Although carbocupration of acetylene has been achieved with Ph_2CuLi, the generality of the reaction has not been established.[1d]

Substitution Reactions.

Ph_2CuLi participates in substitution reactions with alkyl halides,[1] sulfinates,[16] and sulfonate esters (eq 4).[17] Vinyl halides,[18] triflates,[19a,b] and phenyl(vinyl)iodonium salts (eq 5)[19c] afford good yields of substitution products with retention of configuration, which is in marked contrast to the poor participation of aryl halides.[1] Anhydrides,[20a] thiol esters,[20b] and acyl halides[1d] react with Ph_2CuLi to afford aryl ketones.

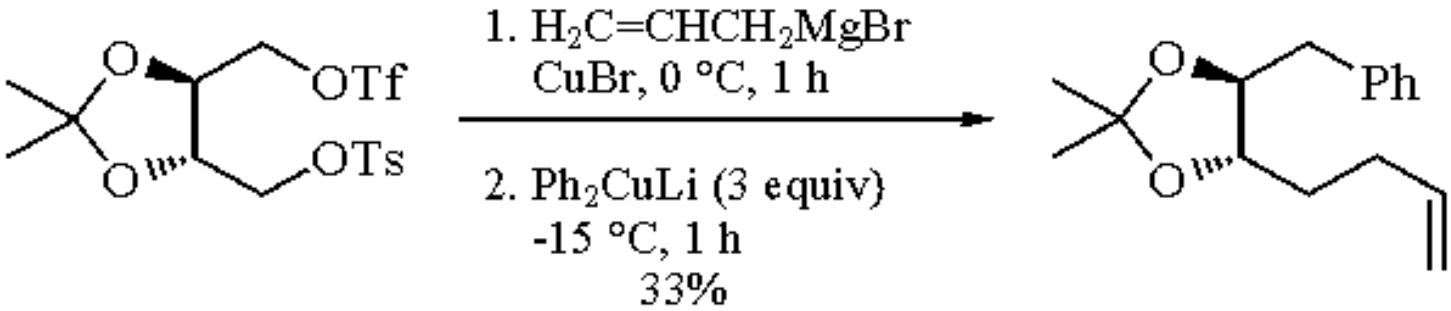

(4)

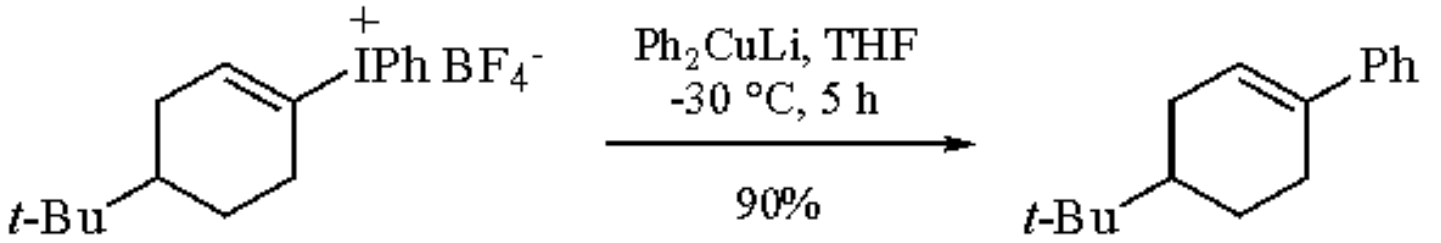

(5)

Allylic halides (eq 6),[21] oxiranes (eq 7),[22] carboxylates, oxazolidines,[23] sulfonimides,[24] and ammonium salts[25] participate in *anti*-S_N2' pathways, although regio- and stereochemistry can vary.[1]

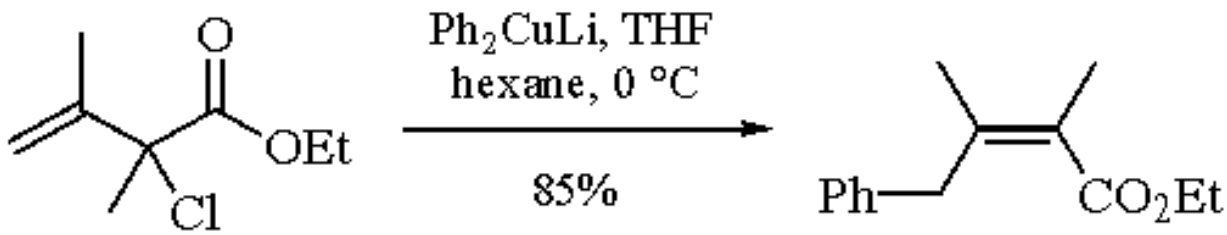

(6)

(*E*):(*Z*) = 92:8

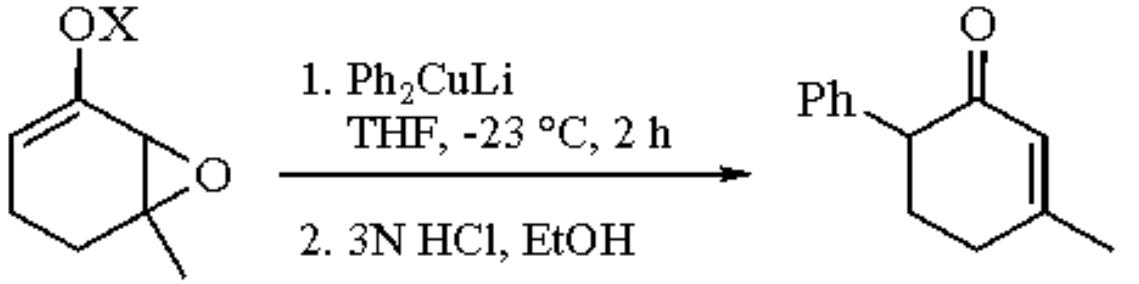

(7)

X = TMS, 95%
X = Li, 72%

Miscellaneous Reactions.

Ph_2CuLi undergoes oxidative dimerization[2a] and oxidative coupling[2b] with amines. Reaction of Ph_2CuLi with α,α´-dibromo ketones[26] leads to α-phenyl ketones via cyclopropanone intermediates; the reagent also adds to benzynes.[3]

Related Reagents.

Lithium Dimethylcuprate; ***Lithium Di-p-tolylcuprate***.

---

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R. Karl Dieter

Lithium Di-(*E*)-1-propenylcuprate[1]

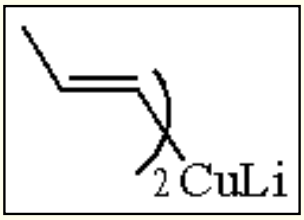

[33462-38-3] · $C_6H_{10}CuLi$ · Lithium Di-(*E*)-1-propenylcuprate · (MW 152.65)

(propenylating reagent; undergoes conjugate addition reactions,[2-4] 1,2-addition reactions to aldehydes,[5,6] substitution reactions with alkyl[7] and vinyl substrates,[8] and oxidative dimerization[9])

Physical Data: colorless solution in Et_2O with CuI;[7] ink-blue color with CuI.P(OMe)$_3$.[4]

Solubility: sol Et_2O, THF.

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***)[7] or complexes (***Copper(I) Iodide-Tributylphosphine***[5,9] and ***Copper(I) Iodide-Trimethyl Phosphite***[4]) in Et_2O or THF at -78 °C under argon[1c] by the addition of *trans*-1-propenyllithium.[7] See ***Lithium Dimethylcuprate*** for purification of Cu^I salts.

Handling, Storage, and Precautions: air- and moisture-sensitive; use in a fume hood.

Introduction.

Lithium di-(*E*)-1-propenylcuprate displays the typical reactivity patterns of lithium diorganocuprates (see ***Lithium Dimethylcuprate***).

Addition Reactions.

Lithium di-(*E*)-1-propenylcuprate undergoes 1,4-addition to simple α,β-alkenyl ketones[2] with retention of alkene configuration by conjugate transfer of the (*E*)-1- propenyl ligand. This reaction has been applied to the synthesis of (±)-dechloromycorrhizin A (eq 1).[10] 1,4-Additions have been achieved with ethyl acrylate and ethyl propiolate in limited yields.[4] In the synthesis of aucantene, 1,4-addition to an α,β-alkenyl aldehyde[3] was achieved (eq 2). Diastereoselective 1,2-additions of lithium di-(*E*)-1-propenylcuprate to aldehydes can be performed in good yields[5] and in the presence of ***Magnesium Bromide*** etherate, which facilitates chelation control (eq 3).[6]

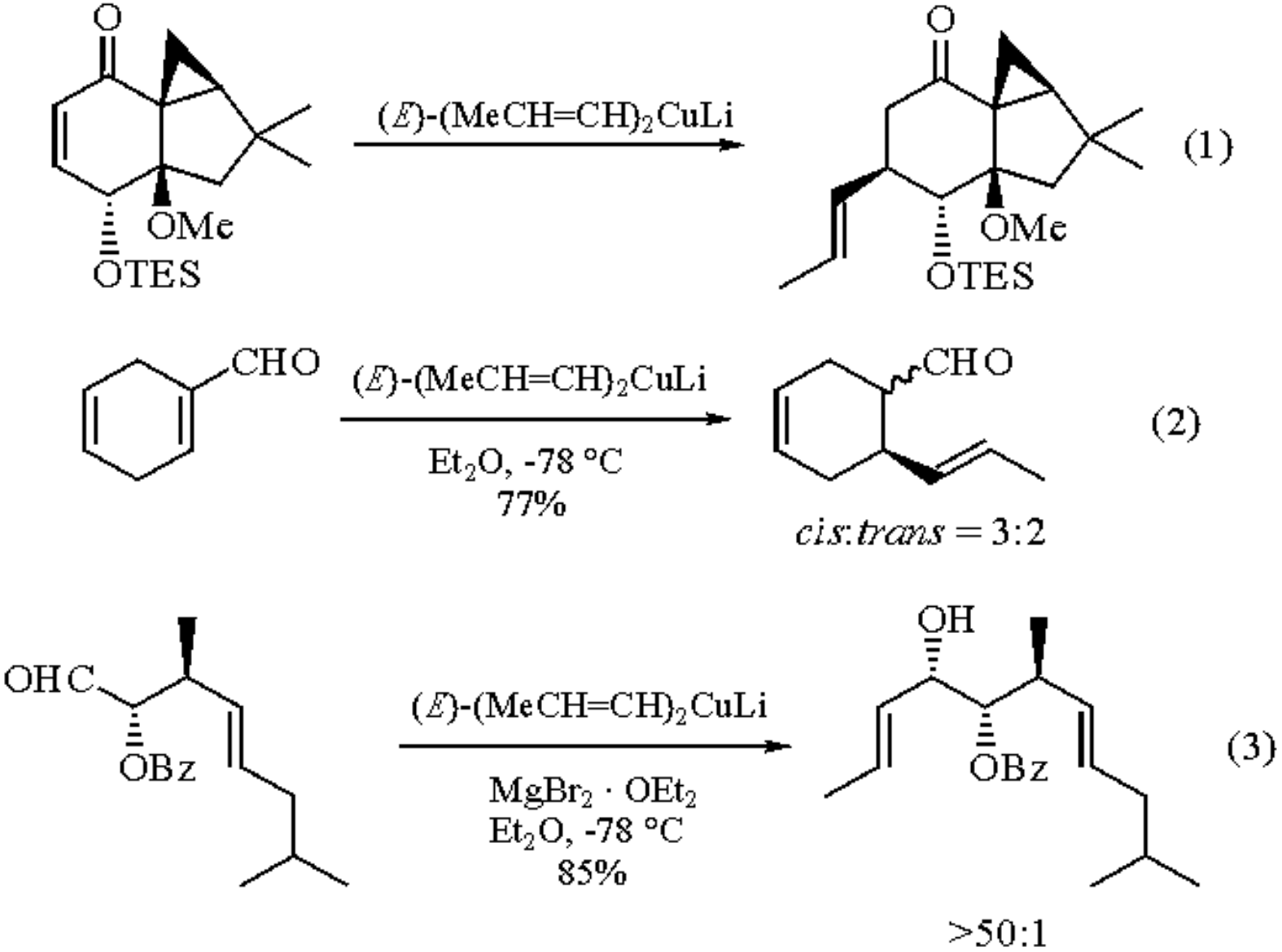

Substitution Reactions.

Lithium di-(*E*)-1-propenylcuprate reacts with alkyl halides and tosylates in high-yield substitution reactions, with and without HMPA additive, in Et_2O or THF.[7] Coupling of lithium di-(*E*)-1-propenylcuprate with a vinyl chloride was used in the synthesis of fulvoplumieren (eq 4).[8]

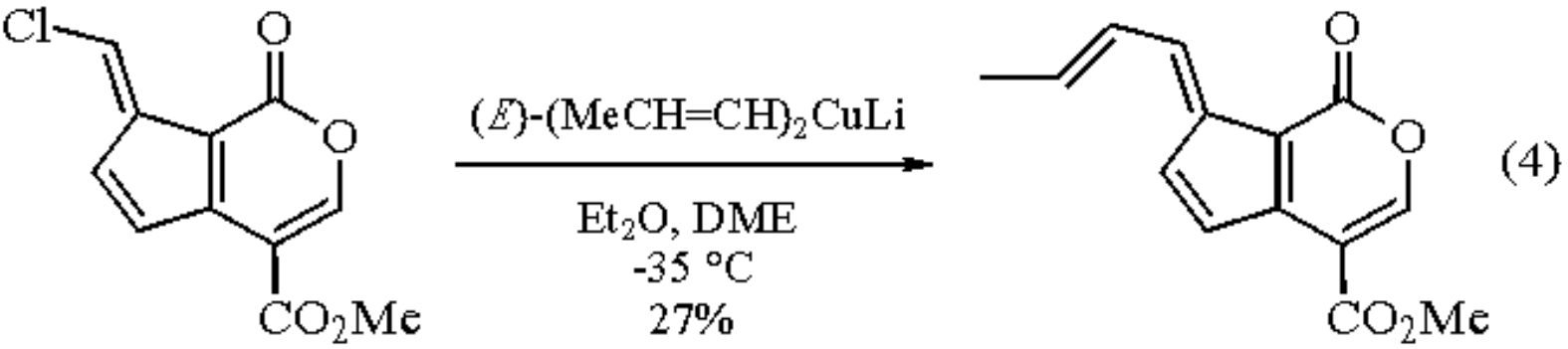

Oxidation Reactions.

Oxidative dimerization of a copper(I) ate complex prepared from *trans*-1-propenyllithium affords a good yield of the dimer *trans*,*trans*-2,4-hexadiene, without loss of stereochemical integrity (eq 5).[9]

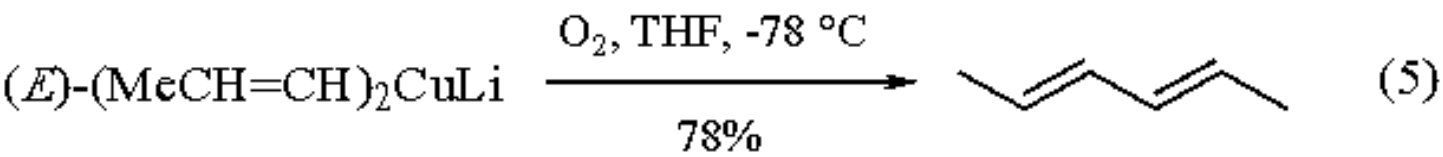

Related Reagents.

Lithium Diallylcuprate; ***Lithium Bis(1-ethoxyvinyl)cuprate***; ***Lithium Diisopropenylcuprate***; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Divinylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

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Lithium Di-*n*-propylcuprate[1]

***n*-Pr_2CuLi**

[43093-17-0] · $C_6H_{14}CuLi$ · Lithium Di-*n*-propylcuprate · (MW 156.69)

(propylating reagent; undergoes conjugate addition reactions,[1a,b,e] epoxide addition reactions,[1a,e] substitution reactions with alkyl and vinyl substrates,[1a,c,e] carbocupration with alkynes,[1e] and acylation reactions[1e])

Physical Data: dark suspension in Et_2O at 0 °C;[2] brown-black solution in THF between -20 and -10 °C.[3]

Solubility: sol THF, Et_2O.

Preparative Methods: prepared in situ from Cu^I salts (CuI or CuBr.SMe_2) under N_2 or argon atmosphere.[4] Rate of cuprate formation is temperature- and Cu^I salt-dependent, and reagent prepared from Cu^I halides is critically dependent on the purity of the Cu^I salts used (see ***Lithium Dimethylcuprate*** for purification of CuI and CuBr).

Handling, Storage, and Precautions: stable in solution for several hours below -60 °C; cuprate reactions are generally carried out at -78 °C. Air- and moisture-sensitive; use in a fume hood.

Introduction.

Lithium di-*n*-propylcuprate displays the characteristic reactivity patterns of lithium diorganocuprates (see ***Lithium Di-n-butylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***).

Addition Reactions.

n-Pr_2CuLi reacts with α,β-alkenyl ketones,[1e,4,5] esters,[1e,6,7,8] lactones,[8] and 1,3-dioxin-4-ones (eq 1)[2] with 1,4-transfer of the propyl ligand. *n*-Pr_2CuLi undergoes 1,6-addition to dienyl amides[9] and 1,8-addition to trienyl ketones and esters (eq 2).[10] Conjugate addition to 2-alkynoic esters proceeds in an exclusively *cis* manner (eq 3).[11]

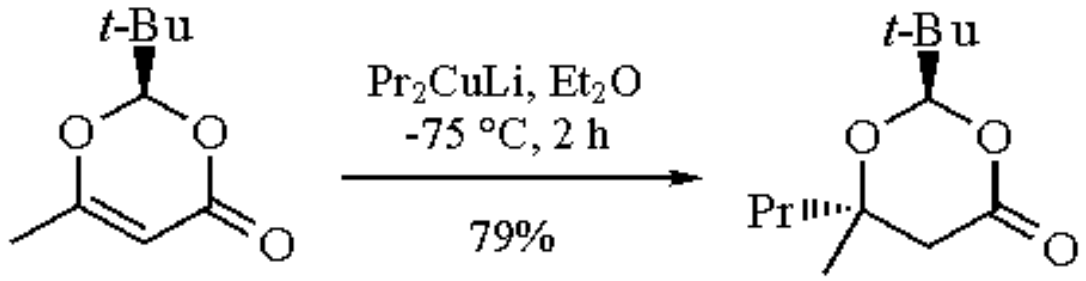

(1)

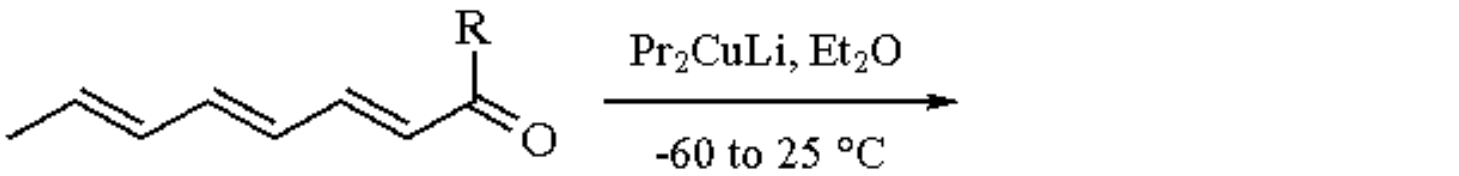

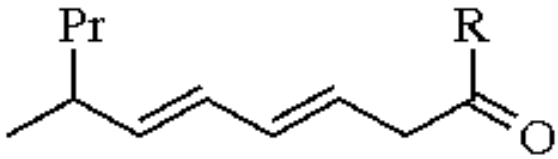

(2)

R = Me, 52%
R = OEt, 61%

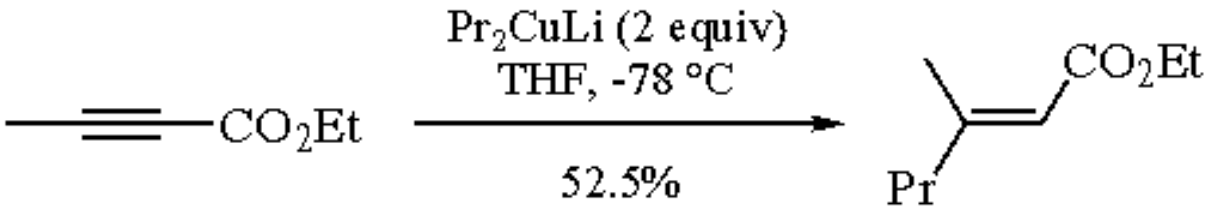

(3)

(*E*):(*Z*) = 93:7

Substitution Reactions.

n-Pr_2CuLi participates in substitution reactions with alkyl halides[1a,e,12-14] and sulfonate esters.[1a,e,12a,c,d,13,15-17] Several natural product syntheses employ this coupling methodology as the key step.[12,13,15-17] Vinyl iodides (eq 4)[11b] afford good yields of substitution products with retention of configuration. 2-Trimethylsilylpentanoyl chloride[1e] and γ-bromobutanoyl chloride react with *n*-Pr_2CuLi to afford the corresponding propyl ketones.

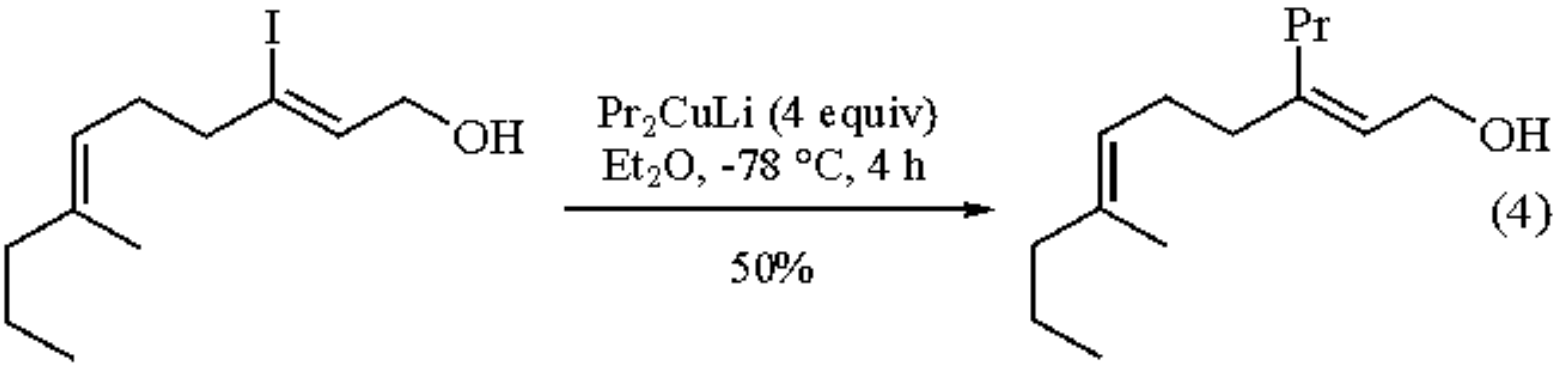

α,β-Epoxysilanes (eq 5),[18] alkenyl lactones,[3] and alkynyl carboxylates[1e] participate in *anti*-S_N2' pathways, although regio- and stereochemistry can vary.[1] Reaction of α,β-unsaturated oxazolidines with *n*-Pr_2CuLi (eq 6)[19] also proceeds in an S_N2' manner. The steric course can be reversed and the diastereoselectivity enhanced by salt and/or solvent effects.

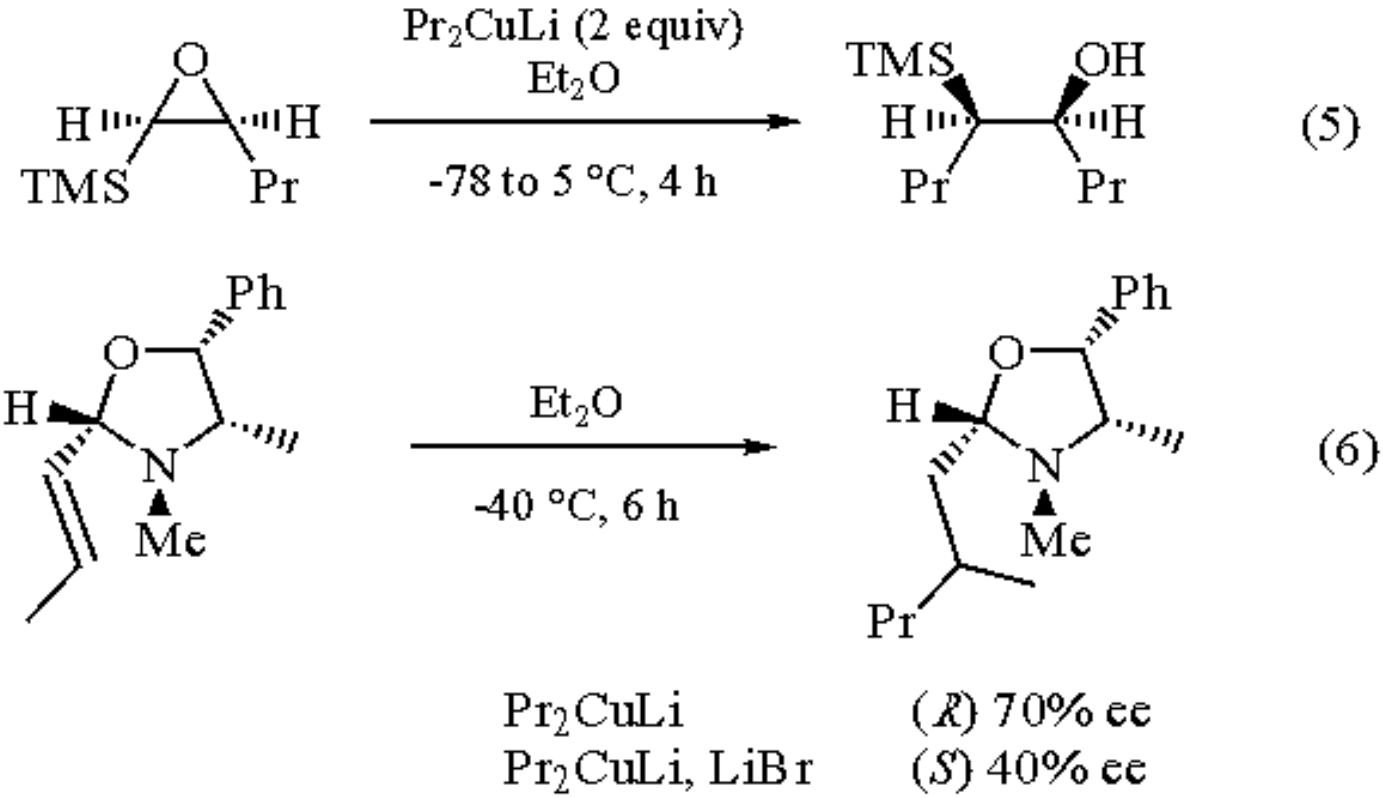

Miscellaneous Reactions.

n-Pr_2CuLi reacts with ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) to afford *B*-alkyl-9-BBN.[20] This procedure can be extended to prepare mixed organoboranes.

---

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Lithium Diselenide

Li_2Se_2

[65027-50-1] · Li_2Se_2 · Lithium Diselenide · (MW 171.80)

(an excellent nucleophilic agent for synthesis of organic diselenides; can be used for synthesis of bis(trimethylsilyl) selenide[1])

Alternate Name: dilithium diselenide.

Solubility: sol H_2O; mod sol THF, HMPA, DMF, ethanol.

Form Supplied in: brownish-red solid, or suspension in THF.

Preparative Methods: reduction of ***Selenium*** with 1 equiv ***Lithium Triethylborohydride***[2] or with ***Lithium*** in THF in the presence of diphenylacetylene or naphthalene as catalyst.[1,3]

Handling, Storage, and Precautions: Li_2Se_2 is unstable in air and decomposes with separation of Se. It can be stored for a limited period of time under an inert gas atmosphere in a refrigerator. It should be used directly as prepared, without isolation. Use in a fume hood.

Lithium diselenide reacts with many carbon electrophiles. It is a more reactive nucleophile than K_2Se_2 and ***Sodium Diselenide***.[1] Substitution of halogens, mesyl, tosyl, or diazonium groups takes place to form bisaryl or bisalkyl diselenides in fair yields (eq 1).[1,4] In some cases, aromatic and heteroaromatic diselenides are accompanied by minor amounts of selenides as byproducts.[1]

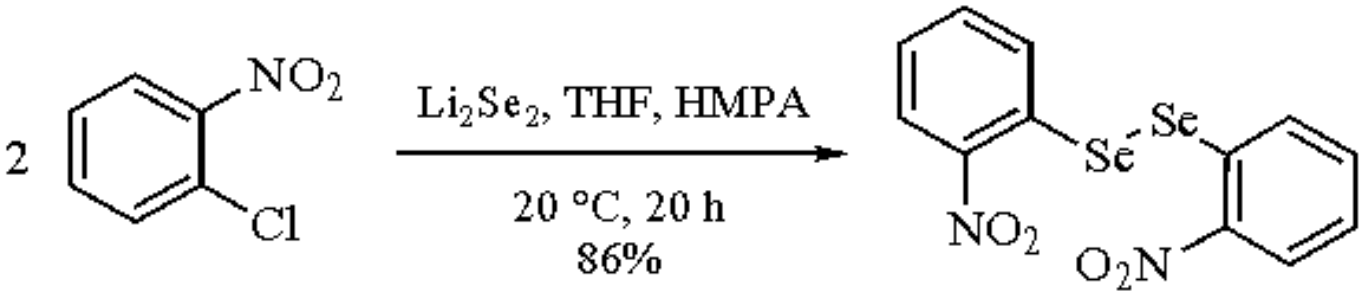

(1)

The electrophilic carbon atoms of the oxirane or the lactone ring are attacked by the diselenide anion formed from Li_2Se_2 and ring opening leads to bis(β-hydroxyalkyl) diselenides (eq 2) or bis(carboxyalkyl) diselenides (eq 3).[1]

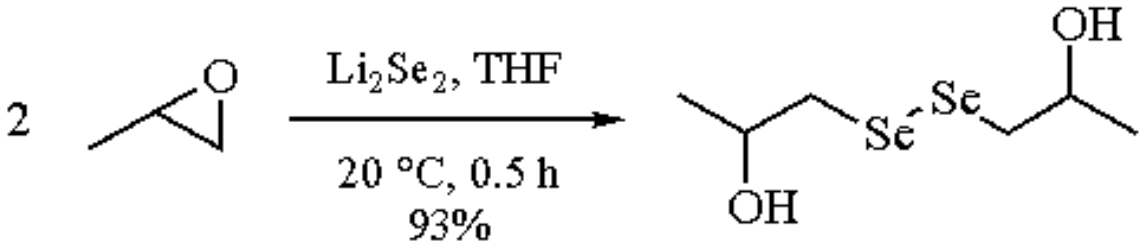

(2)

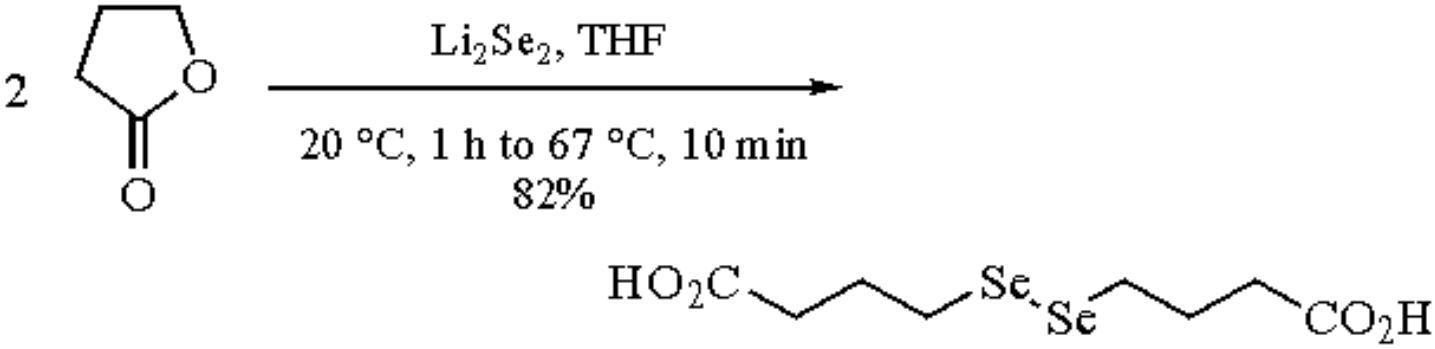

(3)

Bis(trimethylsilyl) Selenide is obtained when ***Chlorotrimethylsilane*** is treated with Li_2Se_2 (eq 4).[1]

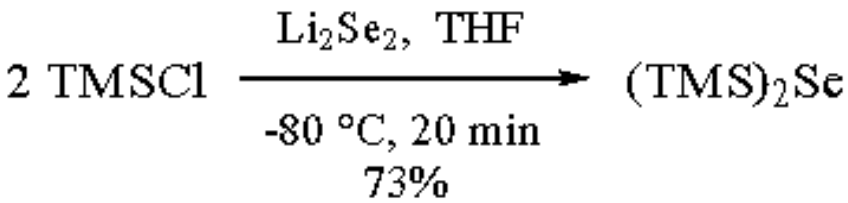

(4)

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Lithium Di-*p*-tolylcuprate[1]

(p-$MeC_6H_4)_2CuLi$

[54747-02-3] · $C_{14}H_{14}CuLi$ · Lithium Di-*p*-tolylcuprate · (MW 252.77)

(tolylating reagent which undergoes conjugate addition reactions,[2] addition reactions to pyrylium[3,4] and pyridinium salts,[5] and substitution reactions[6,7])

Physical Data: a clear yellow solution results from the reaction of a 1:1 mixture of $(p\text{-}MeC_6H_4)_4Cu_4$ and $p\text{-}MeC_6H_4Li$ in Et_2O, from which dimeric and tetrameric species have been isolated. Cryoscopic molecular weight determinations in C_6H_6 support a $(p\text{-}MeC_6H_4)_4Cu_2Li_2.2OEt_2$ composition. This complex is stable up to 135 °C. ^1H NMR (C_6D_6) δ = 0.64 (t, OCMe), 2.08 (s, *p*-Me), 2.72 (q, OCH_2), 7.0 (d, H-3), 8.20 (d, H-2, $J_{2,3}$ = 7.5 Hz). If prepared in C_6H_6, an unsolvated complex is formed which decomposes at ~110 °C.[1c,8]

Solubility: sol Et_2O, THF.

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***,[5,6] ***Copper(I) Bromide***[9]) under an inert atmosphere of N_2 or argon in Et_2O, THF, or C_6H_6.[1c,8] See ***Lithium Dimethylcuprate*** for purification of Cu^I salts.

Handling, Storage, and Precautions: extremely sensitive to moisture and oxygen; ignites spontaneously in air. Use in a fume hood.

Lithium di-*p*-tolylcuprate displays the typical reactivity patterns of lithium diorganocuprates (See ***Lithium Dimethylcuprate***).

Addition Reactions.

Lithium di-*p*-tolylcuprate transfers the *p*-tolyl ligand in a 1,4-addition to enantiomerically pure 3-methyl-2-(*p*-tolylsulfinyl)cyclopentenones to give 3,3-disubstituted cyclopentanones (eq 1) with a high degree of enantioselectivity.[2] 2,4,6-Trimethyl-[3] and 2-siloxypyrylium salts (eq 2)[4] also undergo 1,4-addition to give 4*H*-pyrans with good to high regioselectivity. There are some differences in yield and reactivity between organolithium and Grignard-derived cuprate reagents. 1-Acylpyridinium salts, prepared in situ from ***Pyridine*** and ***Methyl Chloroformate***, react with lithium di-*p*-tolylcuprate to afford 4-substituted 1,4-dihydropyridine

derivatives[5] with high regioselectivity (eq 3).

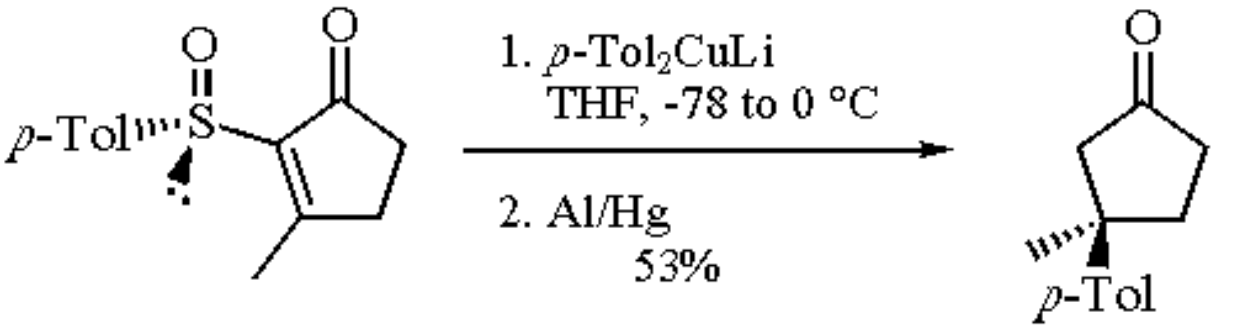

(1)

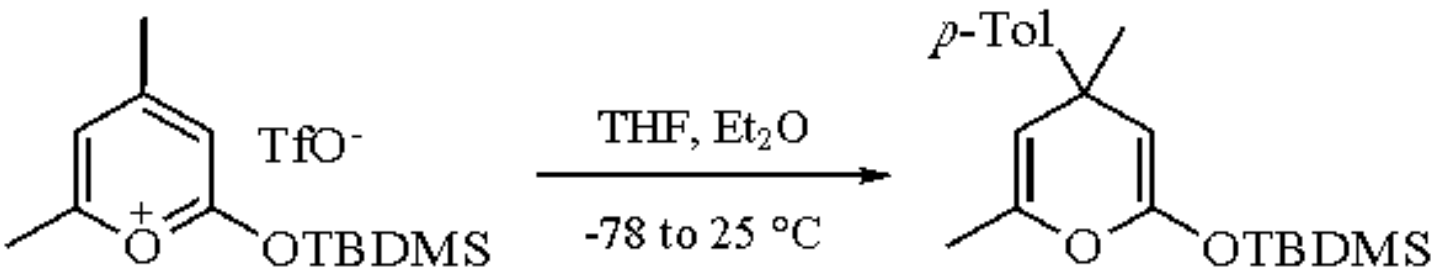

(2)

p-Tol_2CuLi, 65%; *p*-$Tol_2CuMgBr$, 28%

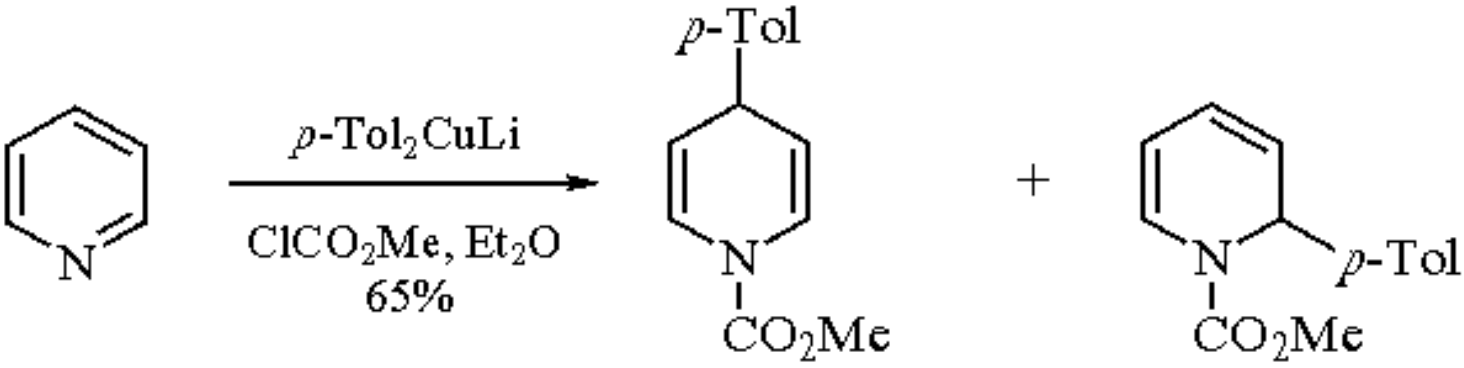

(3)

92:8

Substitution Reactions.

Lithium di-*p*-tolylcuprate participates in substitution reactions with alkyl (eq 4)[6] and aryl halides.[7] Aryl coupling with 1,8-diiodonaphthalene occurs to give 1,8-di-*p*-tolylnaphthalene.[7]

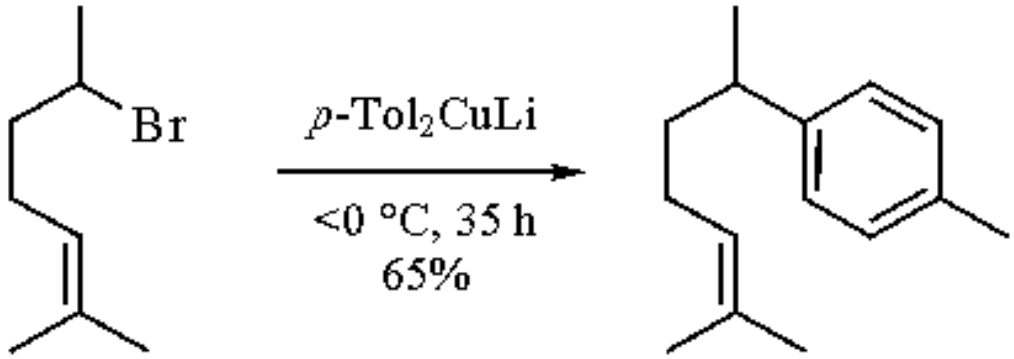

(4)

Miscellaneous Reactions.

A transmetalation reaction with diborane[9] can be effected to give aryl boron compounds which can be manipulated to give phenols, aryl amines, and triaryl boron complexes in limited yields. The reagent (p-$MeC_6H_4)_4Cu_2Li_2$ reacts with rhodium(I) complexes[10] under a carbon monoxide, nitrogen, or ethylene atmosphere to give 4,4´-bitolyl and 4,4´-ditolyl ketone. The product ratios and yields vary with reactant stoichiometry, and minor byproducts are formed.

Related Reagents.

Lithium Dimethylcuprate; ***Lithium Diphenylcuprate***.

---

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Lithium Divinylcuprate[1]

$(CH_2{=}CH)_2CuLi$

[22903-99-7] · C_4H_6CuLi · Lithium Divinylcuprate · (MW 124.59)

(vinylating reagent; undergoes conjugate addition reactions[1a,b,d] and substitution reactions[1a,c,d])

Physical Data: clear yellow (prep. from $CuI.PBu_3$[2a]) or light gray solution (prep. from $CuBr.SMe_2$)[2b]

Solubility: sol THF, Et_2O

Preparative Methods: prepared in situ from Cu^I salts (***Copper(I) Iodide***,[2b] ***Copper(I) Bromide***.SMe_2,[3,2b] ***Copper(I) Iodide-Tributylphosphine***[2a]) and ***Vinyllithium*** under N_2 or argon atmosphere (see ***Lithium Dimethylcuprate***).

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Introduction.

Lithium divinylcuprate displays the characteristic reactivity patterns of lithium diorganocuprates (see ***Lithium Di-n-butylcuprate***, ***Lithium Dimethylcuprate***, ***Lithium Diphenylcuprate***).

Addition Reactions.

Lithium divinylcuprate reacts with α,β-alkenyl ketones,[1] esters (eq 1),[4] lactones,[5] nitro compounds,[6] and aldehydes[7] with conjugate transfer of the vinyl ligand (see ***Vinylcopper***). Addition of ***Chlorotrimethylsilane*** can accelerate the conjugate addition reaction and promote increased stereoselectivity (eq 2).[8]

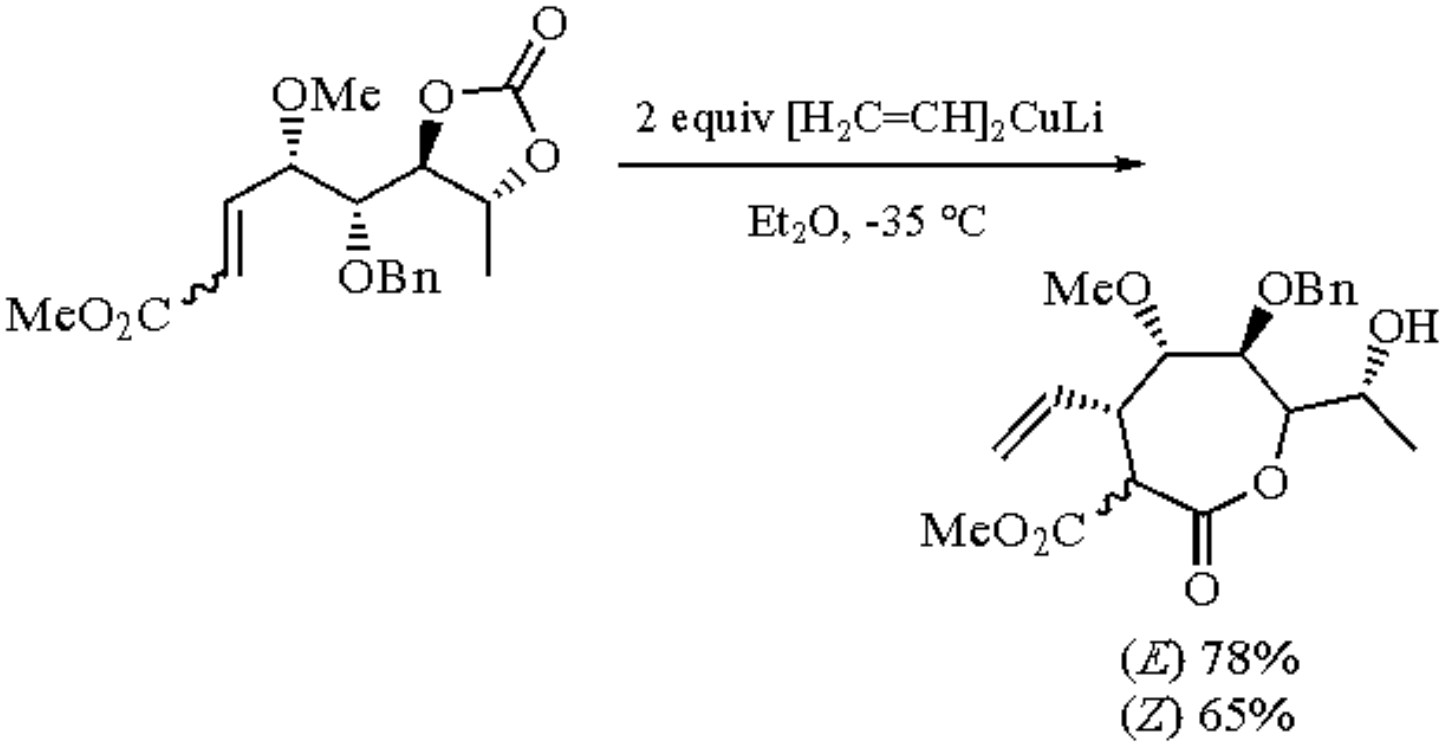

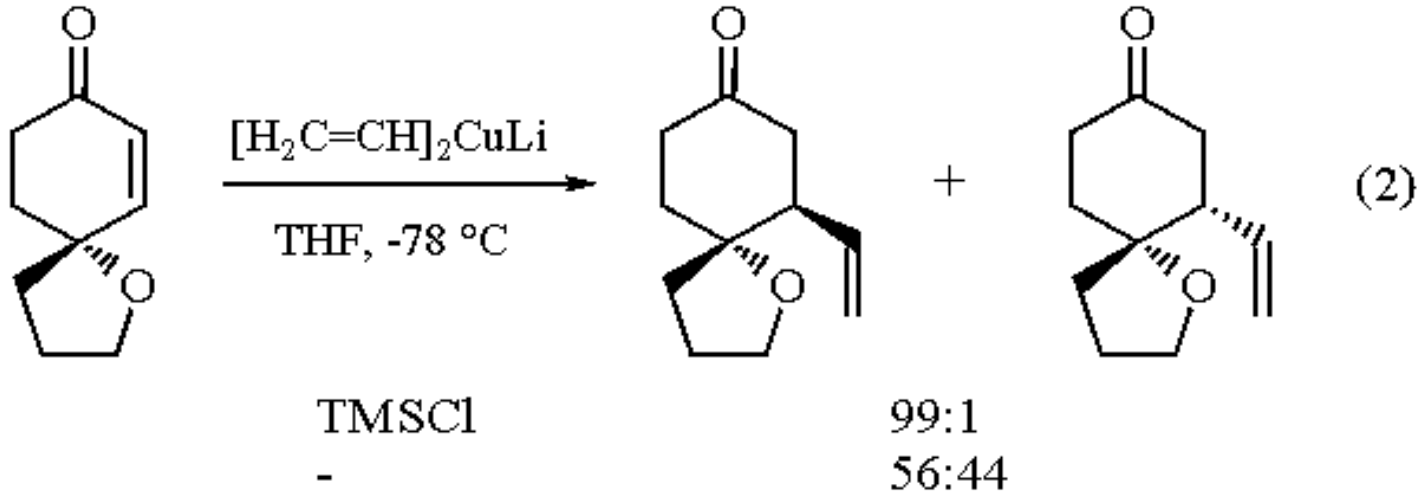

The reagent adds stereoselectively (*cis* addition) to α,β-alkynoates, affording 2,4-dienoates.[9] Dienyl esters exclusively afford 1,6-addition products.[10] Tandem conjugate addition-enolate trapping is a powerful synthetic method (eq 3).[11] The reagent adds to vinyltriphenylphosphonium bromides to provide phosphoranes which can generally be exploited in subsequent chemistry.[12] 2-Siloxypyrylium salts undergo 1,4-addition, leading to 4-substituted 4*H*-pyrans.[13] 1,1-Diactivated cyclopropanes undergo a homoconjugate addition reaction with $(CH_2{=}CH)_2CuLi$.[14]

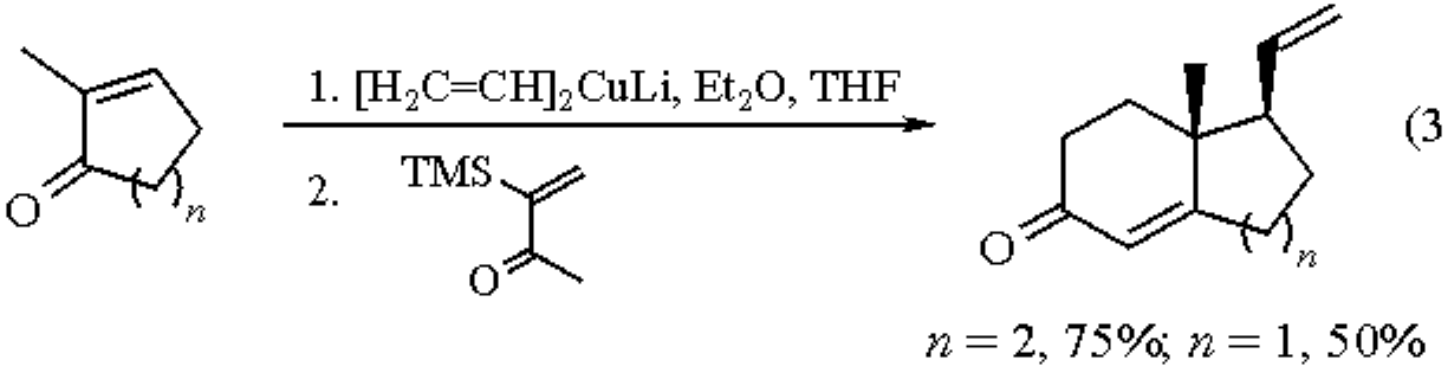

Substitution Reactions.

Lithium divinylcuprate participates in substitution reactions with alkyl halides[3c,15] and carboxylates.[3b,16] Vinyl triflates derived from β-dicarbonyl compounds afford substitution products that may result from addition-elimination reaction pathways (eq 4).[17] *gem*-Dibromocyclopropanes give mono- and disubstituted products, depending upon the reaction temperature.[18] Allylic ammonium salts participate in *syn*-S_N2' pathways with good stereo- and regioselectivity.[19]

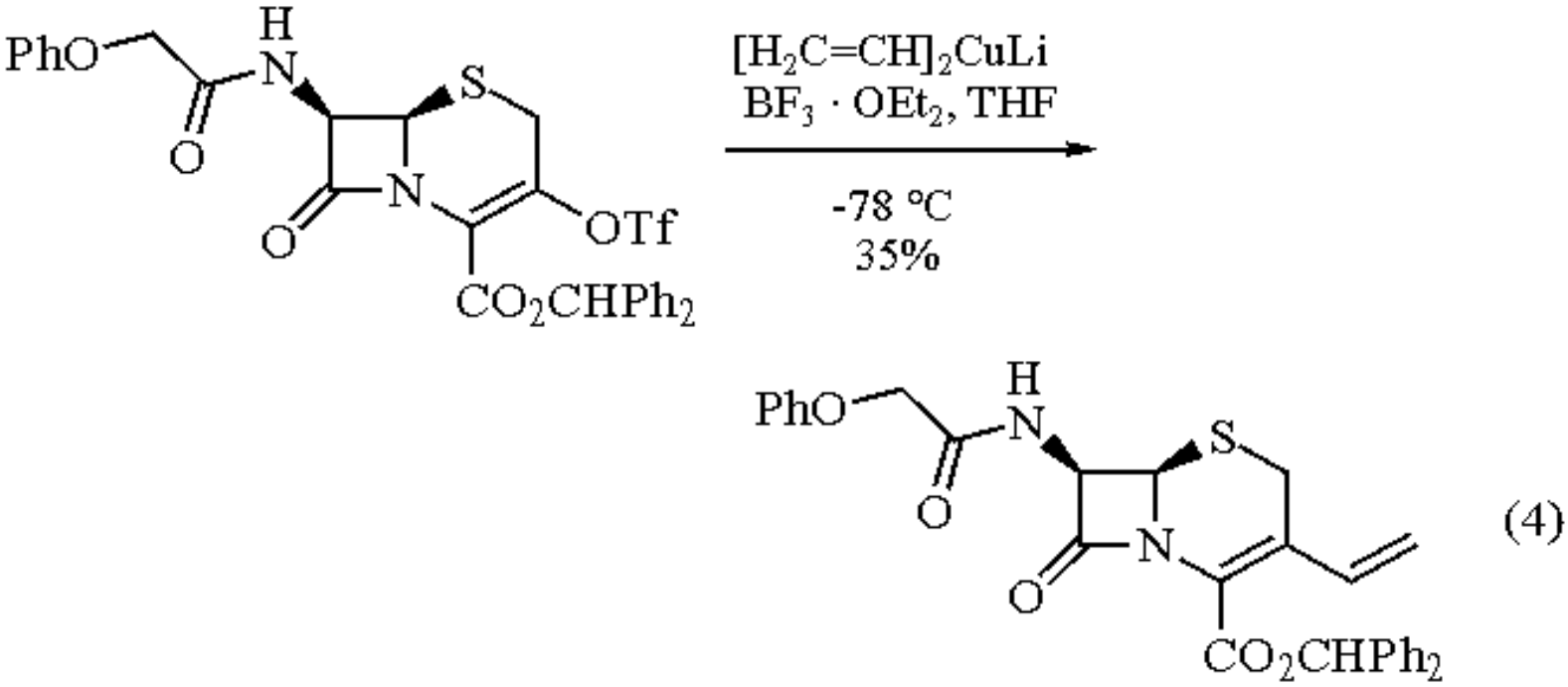

Miscellaneous Reactions.

Alkylation of a tricarbonylcyclohexadienyliron salt with lithium divinylcuprate gives moderate yields.[20] Reaction of this reagent with oxiranes (eq 5; iodide from CuI),[21] 2-alkenyl oxetanes (eq 6),[22] activated cyclopropanes,[23] and aziridines[24] affords ring-opened products. Carbocuprations of cyclopropene derivatives have been reported.[25] Arylmercurials couple with this reagent, giving fair to good yields of cross-coupled products.[26]

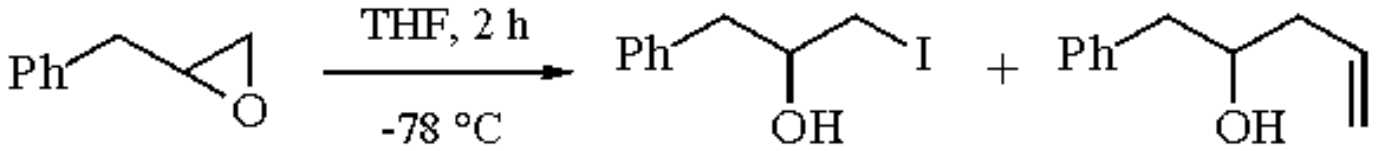

(5)

$[H_2C{=}CH]_2CuLi + 2\ BF_3$	93%	75:18
$[H_2C{=}CH]_3Cu_2Li + 2\ BF_3$	97%	95:2
$[H_2C{=}CH]_2CuLi$	28%	0:100
$[H_2C{=}CH]_3Cu_2Li$	28%	0:100
$[H_2C{=}CH]Cu + BF_3$	100%	72:28

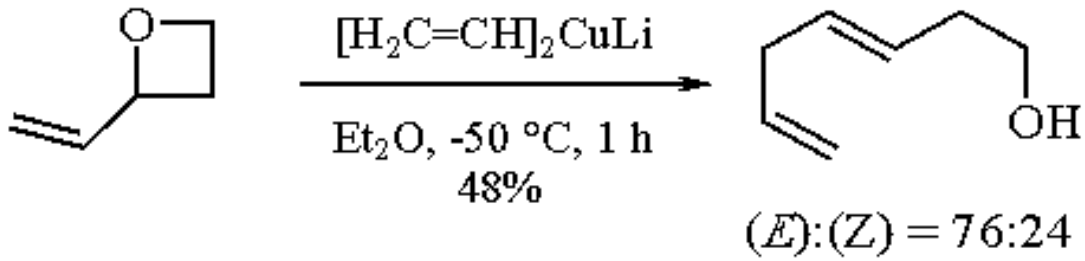

(6)

Related Reagents.

Lithium Bis(1-ethoxyvinyl)cuprate; ***Lithium Bis(1-methoxyvinyl)cuprate***; ***Lithium Diallylcuprate***; ***Lithium Diisopropenylcuprate***; ***Lithium Di-(E)-1-propenylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***.

---

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Lithium Divinylcuprate-Tributylphosphine[1]

$(CH_2{=}CH)_2CuLi.n\text{-}Bu_3P$

[24743-97-3] · $C_{16}H_{33}CuLiP$ · Lithium Divinylcuprate-Tributylphosphine · (MW 326.95)

(phosphine-ligated divinylcuprate for 1,4-addition[2] and nucleophilic substitution[3])

Physical Data: see entries for ***Lithium Divinylcuprate***, ***Tri-n-butylphosphine***.

Solubility: sol ether, THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl. The yield of phenyl vinyl ketone is measured by GC, the response of which is calibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: a round-bottom flask equipped with magnetic stirring bar and rubber septum is charged with ***Copper(I) Iodide-Tributylphosphine***.[5-7] Under a nitrogen atmosphere, THF is added and the flask cooled to -78 °C; to the resultant cold solution is slowly added 2.0 equiv of ***Vinyllithium***[8] in THF. A blue-black mixture forms, which can be used immediately. Alternate preparations, by addition of 1.0 equiv of $n\text{-}Bu_3P$ to a THF slurry of CuI before addition of 2 equiv of vinyllithium, or by use of $CuBr(n\text{-}Bu_3P)_2$,[9] may be possible.

Handling, Storage, and Precautions: best results are obtained with high purity Cu^I salts,[10] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[11] Like most alkyllithium reagents, vinyllithium is pyrophoric;[12] care must be exercised in its handling. Homocuprates are stabilized in the presence of stoichiometric quantities of $n\text{-}Bu_3P$; there is no noticeable decomposition at -78 °C.[6] Use in a fume hood.

Phosphine-ligated homocuprates were introduced early in the development of organocopper chemistry.[6,13] The $n\text{-}Bu_3P$ ligand solubilizes the homocuprate in ether solvents, increasing its reactivity, and also retards thermal decomposition. Generally, the presence of stoichiometric quantities of the ligand make reaction workup unsatisfactory;[6,13a,14] for this reason, various heterocuprates[15] have found wider application in organic chemistry.

Lithium divinylcuprate-tributylphosphine undergoes efficient substitution reactions with primary iodoalkanes when

used in excess.[6] It is more commonly found as a reagent in 1,4-additions to 2-alkenones, and has found application in the stereocontrolled synthesis of 1,3,5-triols[16] and 11-substituted 11-deoxyprostaglandins.[17] A typical example is the 1,4-addition to isophorone (eq 1);[5] the thermal stability of the reagent allows normally sluggish 3,3-disubstituted 2-alkenones to be used as substrates. The isolated chemical yield (60%), when compared to GC analysis of the crude product (85%), is indicative of the difficulty that can be encountered in efficiently separating the phosphine from the product.

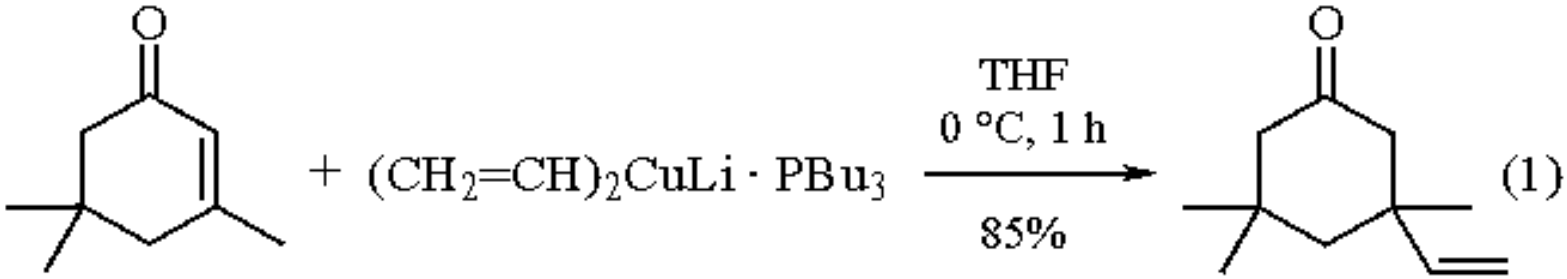

Related Reagents.

Lithium Diethylcuprate-Tributylphosphine; ***Lithium Dimethylcuprate***; ***Lithium Divinylcuprate***; ***Tri-n-butylphosphine***.

---

1. (a) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (b) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
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Lithium α-Ethoxycarbonylvinyl(1-hexynyl)cuprate

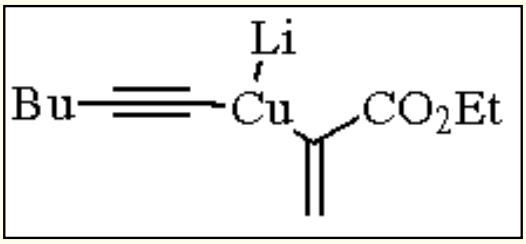

[54111-85-2] · $C_{11}H_{16}CuLiO_2$ · Lithium α-Ethoxycarbonylvinyl(1-hexynyl)cuprate · (MW 250.76)

(organometallic reagent for the introduction of an acrylate unit onto allylic halides, vinyl epoxides, and carbonyl compounds; also effective for the synthesis of α-methylene-γ-butyrolactones from allylic halides)

Physical Data: thermally unstable organocuprate generated at -78 °C in the absence of moisture and oxygen.

Solubility: sol diethyl ether and THF at temperatures approaching -78 °C.

Preparative Methods: generated at -78 °C in ether by the metal-halogen exchange reaction of ethyl α-bromoacrylate and lithium 1-hexynyl(methyl)cuprate.[1]

Handling, Storage, and Precautions: must be prepared in the absence of moisture and oxygen at -78 °C. Diethyl ether should be freshly distilled from lithium aluminum hydride. Reaction temperatures should be maintained below -60 °C.

Generation and Reactivity of α-Alkoxycarbonylvinylcuprates.

In general, α-alkoxycarbonylvinylic cuprates have been generated in situ from the conjugate additions of organocopper reagents to alkynic esters and acids.[2-4] The unsubstituted title reagent can best be prepared by the reaction of methylcuprates with ethyl α-bromoacrylate (eq 1).[1] This metal-halogen exchange was first observed by Klein and Levene for substituted α-alkoxycarbonylvinylcuprates.[5] While oxidation, protonation, and iodination of the vinylcuprates have met with success, alkylations with simple alkyl halides other than methyl iodide have not been reported.[4]

The parent α-ethoxycarbonylvinylcuprate selectively reacts with allyl halides and propargyl halides to produce 1,3-dienes (**2**) and 1,3-enynes (eq 2).[1] The adduct (**3**) of the title reagent with 3-bromocyclohexene produces the acrylic acid

(**4**) after basic hydrolysis (eq 3). Iodolactonization of acid (**4**) and subsequent deiodination with ***Tri-n-butylstannane*** yields the α-methylene-γ-butyrolactone (**6**) (eq 4).[1]

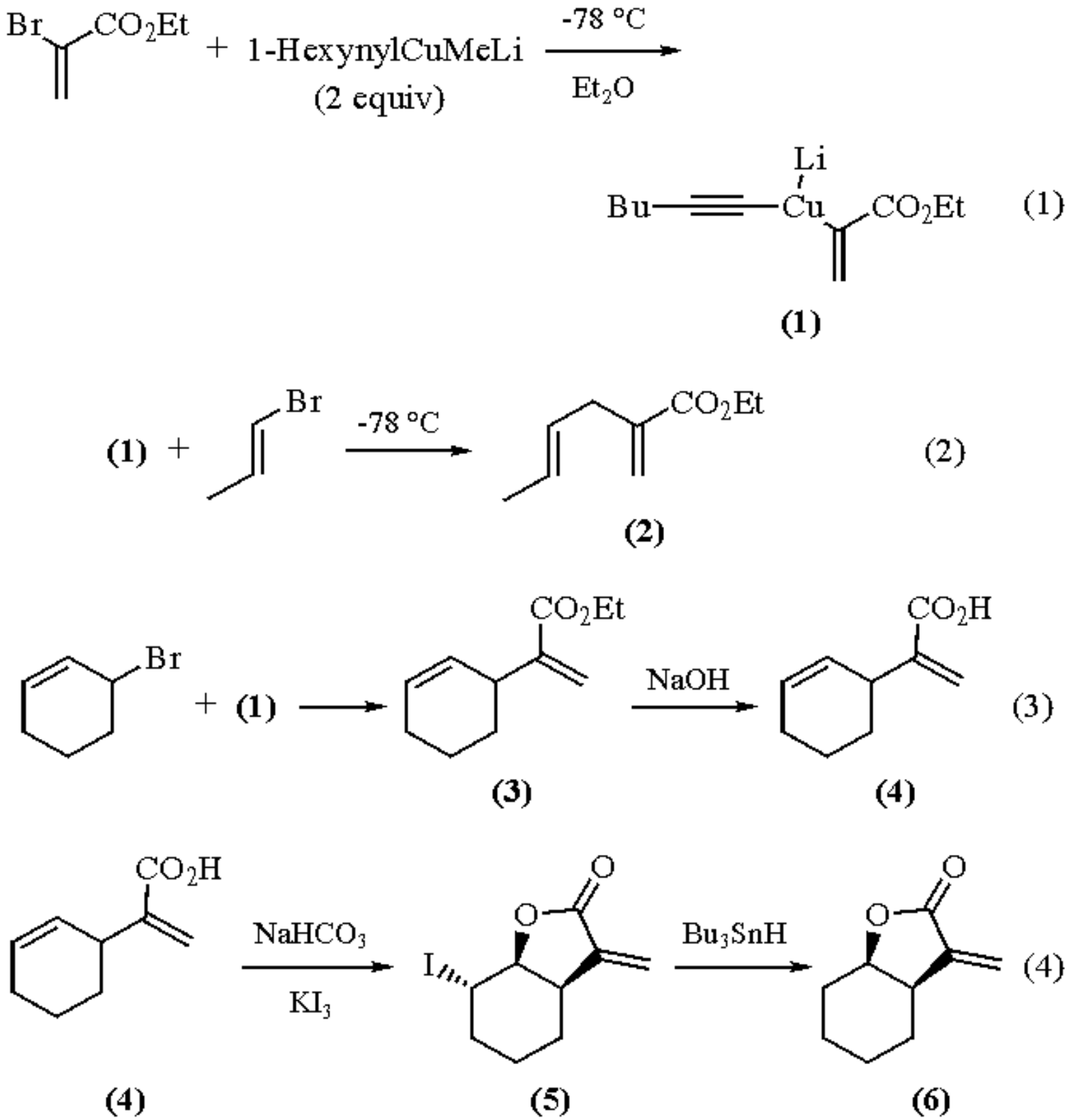

An application of cuprate (**1**) in the synthesis of swazinecic acid dilactone[6] is provided in eq 5 for the allylation of halide (**7**).

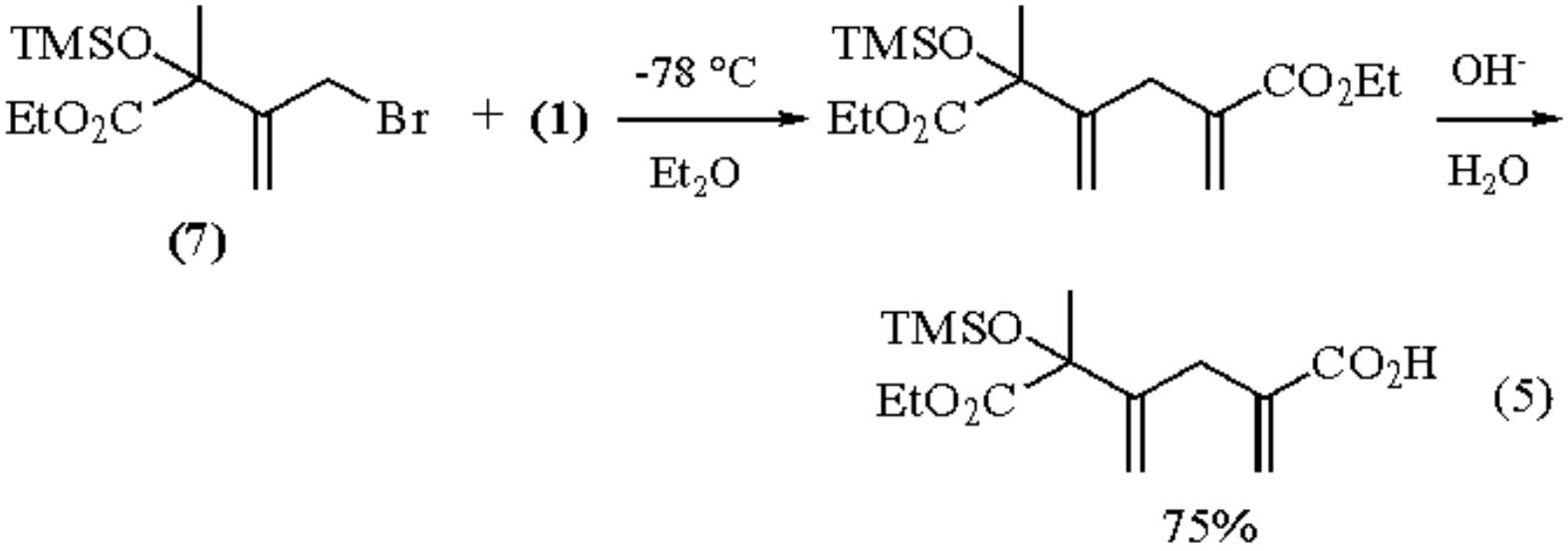

Reactions with Carbonyl Compounds.

By analogy to reagent (**1**), α-methoxycarbonylvinylcuprate (**8**) was prepared from methyl α-bromoacrylate according to the aforementioned procedure.[1] A study of the reactivity of reagent (**8**) with ketones and α,β-unsaturated ketones was carried out. Unlike most organocuprates, reagent (**8**) added in a 1,2-manner to the carbonyl group of a series of cyclic ketones at -78 °C in high yield (eq 6).[7]

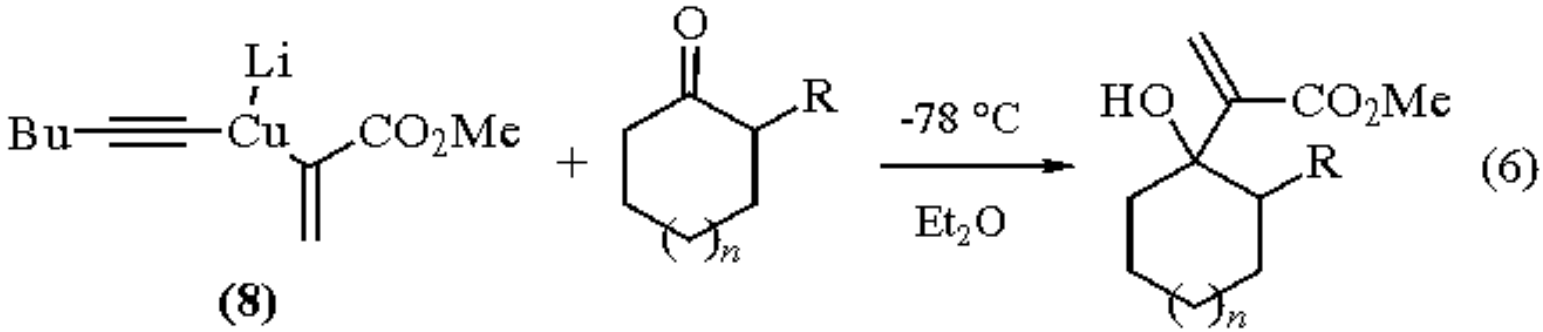

$n = 1$, R = Me	100%
$n = 2$, R = H	100%
$n = 1$, R = OAc	80%

More unusual is the fact that cuprate (**8**) preferentially adds 1,2 and not 1,4 to a variety of enones.[7] Cyclohexenone, cyclohexenecarbaldehyde, and acylcyclohexenes all gave 1,2-adducts exclusively with cuprate (**8**) (eqs 7 and 8). Only the reaction of (**8**) with methyl vinyl ketone resulted in the 1,4-adduct being the major product (eq 9).

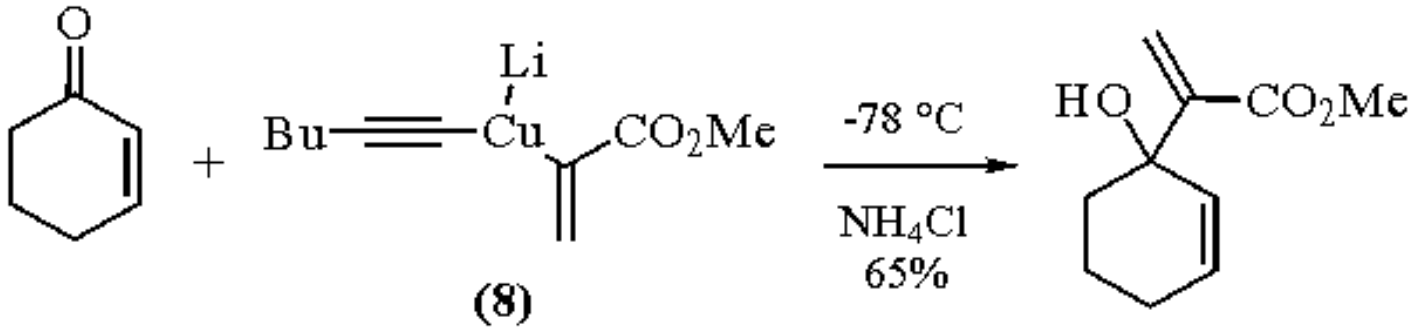

(7)

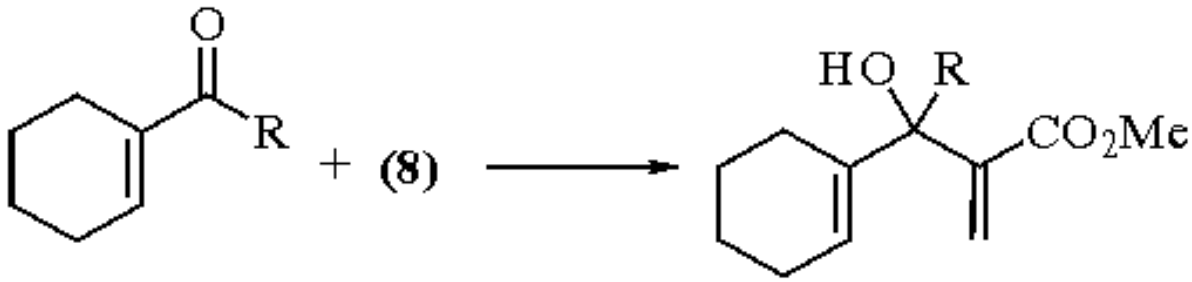

(8)

R = H 80%
R = Me 92%
R = *i*-Pr 90%

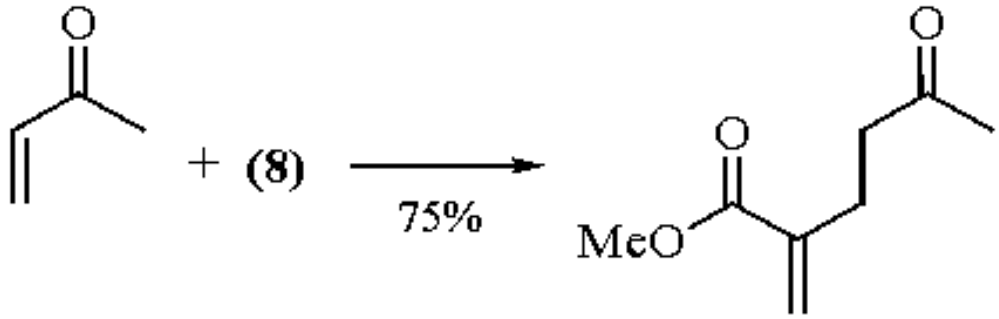

(9)

This reactivity profile suggested that the α-alkoxycarbonylvinylcuprates are structurally indicative of an allenoate species. Evidence for the allenoate-type structure (**9**) comes from IR data[5] and trapping of substituted α-alkoxycarbonylvinylcuprates generated in the conjugate addition of alkylcuprates to ethyl propiolate (eq 10).[8] After the addition of ***Lithium Dimethylcuprate*** to ethyl propiolate at -78 °C, the reaction mixture was quenched with ***Chlorotrimethylsilane*** in triethylamine. The *O*-silylated allene (**10**) was isolated and characterized by IR and NMR.

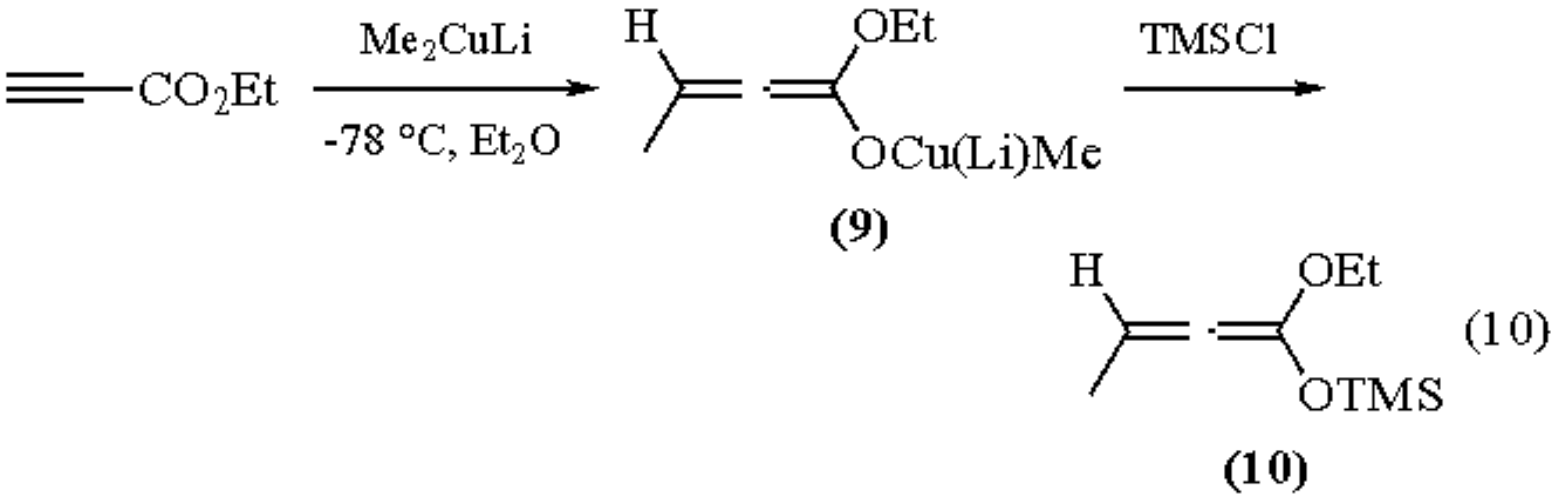

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Lithium-Ethylamine[1]

Li-EtNH$_2$

(Li)

[7439-93-2] · Li · Lithium-Ethylamine · (MW 6.94) (EtNH$_2$)

[75-04-7] · C_2H_7N · Lithium-Ethylamine · (MW 45.10)

(powerful reducing agent;[1] used for (partial) reduction of aromatics;[1a-d,f] conversion of alkynes to *trans*-alkenes and alkanes;[1a,f] stereoselective reduction of hindered ketones[1a,e,13b] and oximes;[16] reductive cleavage of polar single bonds[1a,b,d,f,19,27a])

Physical Data: Li: mp 180.5 °C; bp 1327 ± 10 °C; *d* 0.534 g cm^{-3}. EtNH$_2$: mp -81 °C; bp 16.6 °C; *d* 0.689 g cm^{-3}.

Form Supplied in: see ***Lithium***; ethylamine, 99% anhydrous, packaged in steel cylinders fitted with stainless steel valves.

Purification: see ***Lithium***; ethylamine can be purified by distillation from sodium under exclusion of H_2O and CO_2.

Handling, Storage, and Precautions: see ***Lithium***. Ethylamine is a toxic, colorless, and highly flammable gas with a low flash point (-16 °C). It should be handled in a well-ventilated hood, only after having eliminated all potential sources of ignition. It is corrosive to Cu, Al, Sn, Zn, and their alloys, but is stored satisfactorily in stainless steel.

Lithium-Ethylamine Solutions.

Lithium dissolves in EtNH$_2$ to give deep-blue solutions due to solvated electrons.[2a-d] Similar solutions are obtained with Li in other primary amines.[2a,b] EtNH$_2$ and ethylenediamine (EDA) are the most common solvents, but methylamine, propylamine, isopropylamine, and butylamine have also been used for reductions. The other alkali metals are less soluble in these amines and rarely used for reductions in amines. For instance, the solubilities in EDA at room temperature are 2.9×10^{-1} mol L^{-1} (Li), 2.4×10^{-3} (Na), 1.0×10^{-2} (K), 1.3×10^{-2} (Rb), and 5.4×10^{-2} (Cs).[2e] However, the solubilities can dramatically be increased by using crown ether and cryptand complexants.[2a,b] In contrast to the Li-amine solutions, the amine solutions of K, Rb, and Cs contain, besides solvated electrons, the metal anion as major species, while Na-amine solutions contain only the metal anion and are in general not blue at all.[2a,b] More recently, methylamine-assisted solubilization of Li and Li-Na mixtures (up to 1:1) in several amine and ether solvents,

in which the metals alone are not or only slightly soluble, has been reported.[3]

The reducing agents formed by Li in amines (Benkeser reduction) are more powerful but less selective than Li in NH_3.[1a,4] The higher reactivity is caused by higher reaction temperatures and possibly also by a smaller degree of electron solvation; the better solubility of many organic compounds in amines is also advantageous. The reactivity can be modified by using lower reaction temperatures and by addition of alcohols and secondary amines. Li-amine solutions are more sensitive to catalytic decomposition than Li in NH_3,[5] and clean solvents are mandatory.

Experimental.

Detailed procedures are available,[1b,c] as are details for reaction assemblies.[6] Reduction occurs by a sequence of single electron and proton transfers to the substrate, resulting in saturation of multiple bonds or fission of single bonds (see also ***Lithium***).

Reduction of Aromatic Compounds.

Li-$EtNH_2$ reduces benzene and its derivatives to cyclohexenes.[1a-d] Monoalkylbenzenes give mixtures of regioisomers. More selective formation of the Δ^1-ene is achieved when the reaction is performed in a mixture of primary and secondary amines.[1a] With excess Li and at higher temperatures, further reduction to cyclohexanes can occur (eq 1).[4]

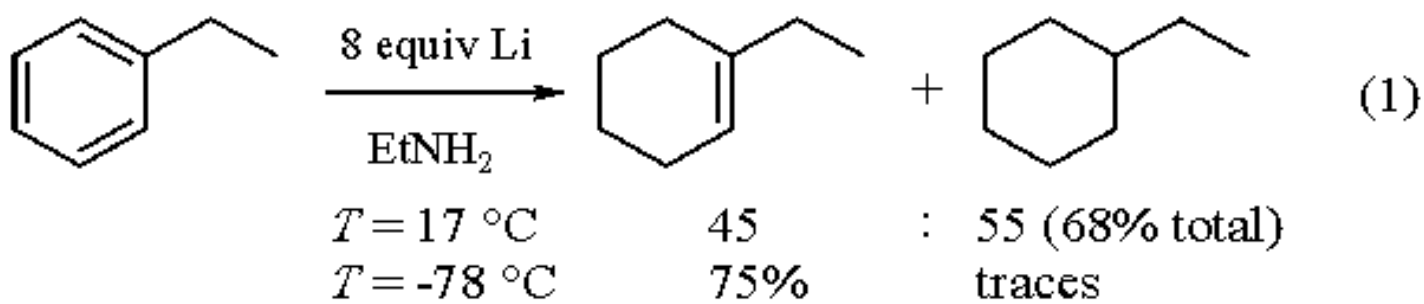

Li-$EtNH_2$ affords, in the presence of alcohols (alcohol:-Li > 1:1), Birch reduction products, i.e. 1,4-cyclohexadienes.[1a,d] This procedure is more powerful than the Birch method (eq 2) and useful for the reduction of highly substituted benzene rings.[7] Li-EDA reductions of benzene derivatives have been performed (eq 2),[7b,8a,b] but Li-$EtNH_2$ appears to be superior for cyclohexene formation, probably due to the presence of *N*-lithioethylenediamine in refluxing EDA.[7b] Cyclohexenes and cyclohexa-1,4-dienes are formed in high yields by electrolysis of benzene derivatives with LiCl in $MeNH_2$ in a divided or undivided cell, respectively.[1a]

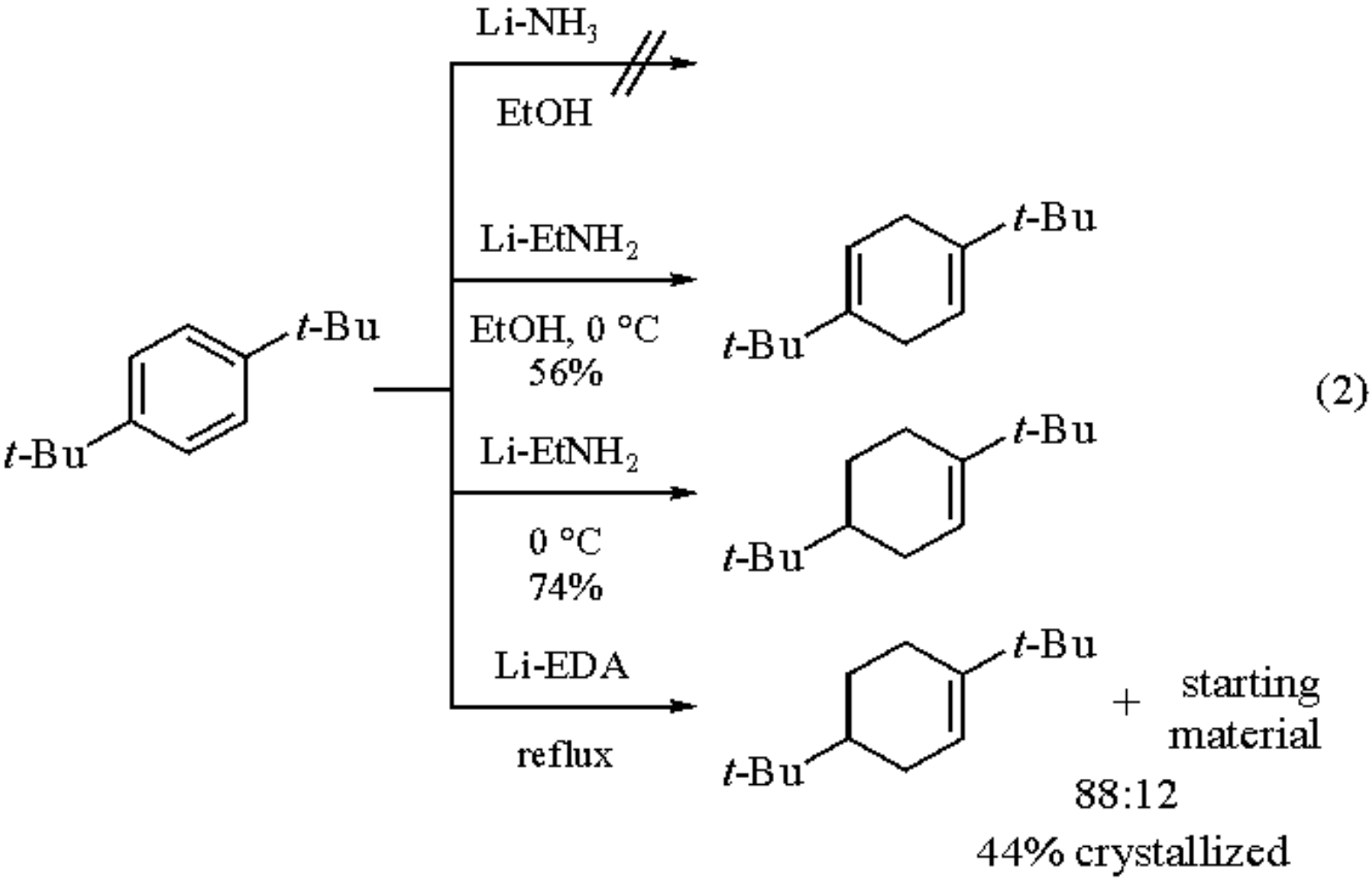

Reduction of polycyclic aromatic compounds is complex, and the products delicately depend on the exact reaction conditions. Most extensive reductions have been achieved with Li-EDA.[1f] Ferrocenes have been reductively cleaved with Li-propylamine in 35-77% yield.[9]

Alkenes.

Terminal[10a-c] and internal double bonds may be reduced by Li-amine; however, the latter react more slowly.[1a,b,d] Strained cyclic alkenes are more easily reduced, and ring size effects are observed. Na-*t*-BuOH-HMPA is more powerful and reduces even nonterminal alkenes in nearly quantitative yields.[10d]

Alkynes.

Internal alkynes are rapidly reduced to *trans*-alkenes by stoichiometric amounts of Li in amines.[1a] Excess Li leads to alkanes.[11] Ca in $MeNH_2$/EDA (1:1) has been used for similar reductions.[12] Li-$EtNH_2$-*t*-BuOH efficiently reduced an alkyne precursor of sphingosin, while triple bond reduction was incomplete with Na- and Li-NH_3.[6b] For the conversion of 1-alkynes to 1-alkenes, Na-NH_3-$(NH_4)_2SO_4$ is the system of choice.[1a] Li-EDA reduction of 1-alkynes usually gives alkanes.

Ketones.

Steroidal and triterpenoid ketones have been selectively reduced to the equatorial alcohols by Li-EDA in high yields.[10b,13] Stereoselective reduction of an α,β-unsaturated ketone to the (20*R*)(β)-alcohol was achieved with Li-EDA, while ***Sodium Borohydride*** led to a mixture of the (20*R*)(β)-alcohol and the Δ^{16}-(20*S*)-alcohol (eq 3).[14] Li-$EtND_2$-*t*-BuOD reduces α,β-unsaturated ketones to the saturated ketones in high yields and deuteriates the β-C-atom stereoselectively.[15] Li-$EtNH_2$ reduction of 3-oximino steroids is apparently the best procedure to prepare 3β-amino steroids.[16]

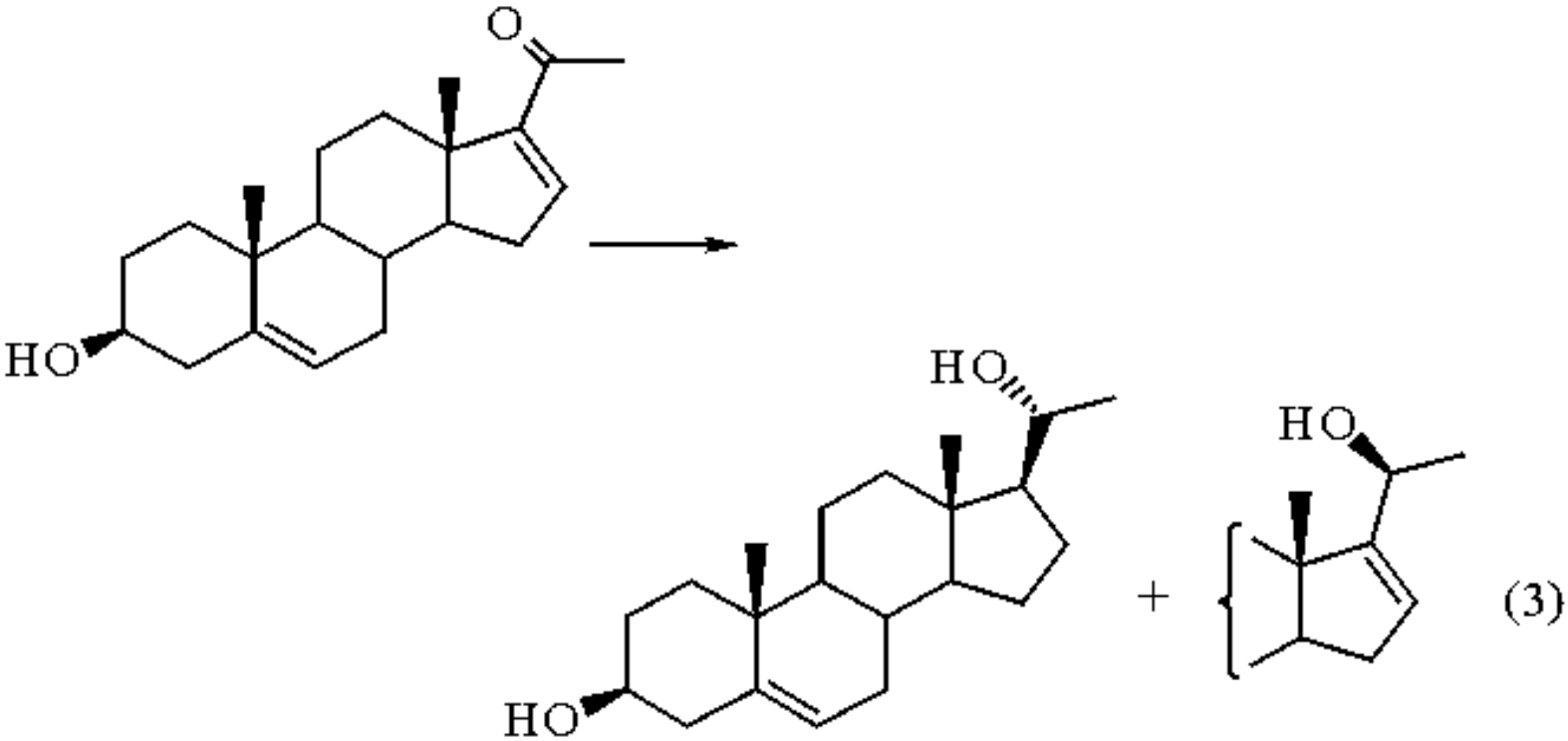

Li-EDA, reflux, 2 h	95%	-
$NaBH_4$, MeOH, py, rt, 100 h	45%	47%

Carboxylic Acids and Derivatives.

Li-$MeNH_2$ or -$EtNH_2$ reduce aliphatic saturated acids to aldehydes or imines in 53-84% yield, depending on the workup procedure.[17] Tertiary carboxamides are cleaved to aldehydes.[18] A major limitation is the substantial formation of transamidation byproducts. *N*-Proline peptide bonds have been cleaved to an extent of 50-70 %.[18a]

Reductive Cleavage of C-S and C-Se Bonds.[19]

Mainly sulfones,[20] but also sulfoxides,[21] sulfides,[22] and dithioacetals[23] have been desulfurized by Li in amines, most often in $EtNH_2$, but also in EDA[20g,h] and $MeNH_2$.[20f] As an excess of reducing agent is normally used, functional groups sensitive to SET may be reduced. Li-$EtNH_2$ cleaves allylic C-S bonds generally without side-reactions and has

thus proven to be especially useful in terpene synthesis for the reductive removal of sulfur-containing functional groups.[20a-c,22a,b]

Allylic aryl sulfones were converted to the alkenes by Li-$EtNH_2$ in 77-98 % yield,[20a-c] while ***Sodium Amalgam*** caused double bond migration (eq 4)[20a] or (*E*)/(*Z*) isomerization.[20b] However, in some cases, extensive double bond migration using Li-$EtNH_2$ or Li-EDA has been observed.[20d]

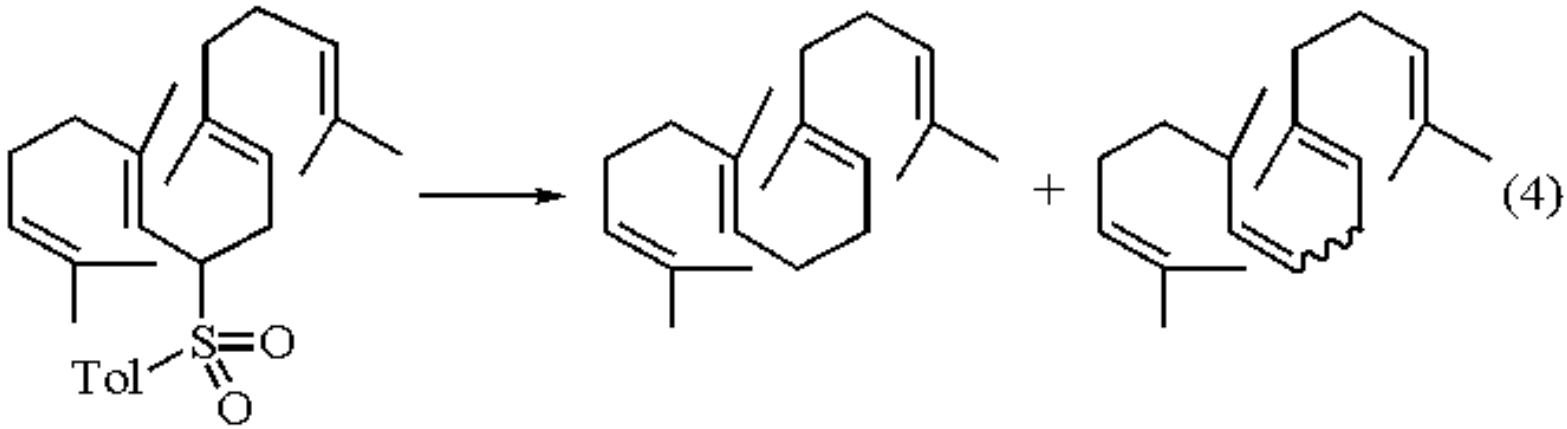

Li-$EtNH_2$, 0 °C, 30 min	77%		-
$Na(Hg)_x$, EtOH, 1.5 h	9	:	4 (90%)

Vinyl sulfones have been hydrogenolyzed to 2-alkenes by Li-$EtNH_2$ or C_8K in Et_2O with extensive isomerization of the *cis* double bond, forming *cis*/*trans* mixtures, while ***Aluminum Amalgam*** gave no reduction at all.[20e] Besides arylsulfonyl groups, some alkylsulfonyl groups have also been reductively removed by Li-$EtNH_2$ or -$MeNH_2$.[20c,f] Allylic alcohols survived the reductive cleavage of a sulfoxyl group by Li-$EtNH_2$ at -78 °C, whereas the double bond was simultaneously reduced when ***Raney Nickel*** was used.[21] While unsatisfactory results were obtained from attempts to desulfurize a 4-thiacyclohexene with Raney Ni, stepwise reduction using Li-$EtNH_2$, followed by Raney Ni to reduce the intermediate Li thiolate, yielded the alkene in 55-70%.[22c] Li-$EtNH_2$ reductively cleaves allylic *N*,*N*-dimethyldithiocarbamates that have been employed in the synthesis of disubstituted alkenes, in 90-95% yield.[24] Selenides and diselenoacetals are reduced to the corresponding alkanes by Li-$EtNH_2$ or Raney Ni in good yields.[25]

Epoxides.

Sterically hindered steroid and triterpenoid epoxides are reductively opened to the axial alcohols by Li-$EtNH_2$[26a] and Li-EDA.[26b] Thus Li-EDA reduced 3α,4α-epoxyfriedelan to the 4α-alcohol (eq 5), while ***Lithium Aluminum Hydride*** did not give any reduction at all, and the 3β,4β-isomer to the 3β-alcohol (eq 6).[26b] Reductive opening of other tri- and tetrasubstituted epoxides with Li-$EtNH_2$[26c-e] and Li-EDA[26f] are high yielding, but depending on the substrate, mixtures of alcohols are encountered.[26d-g] Reductions with Li in propylamine and butylamine seem to give more side-products.[26e]

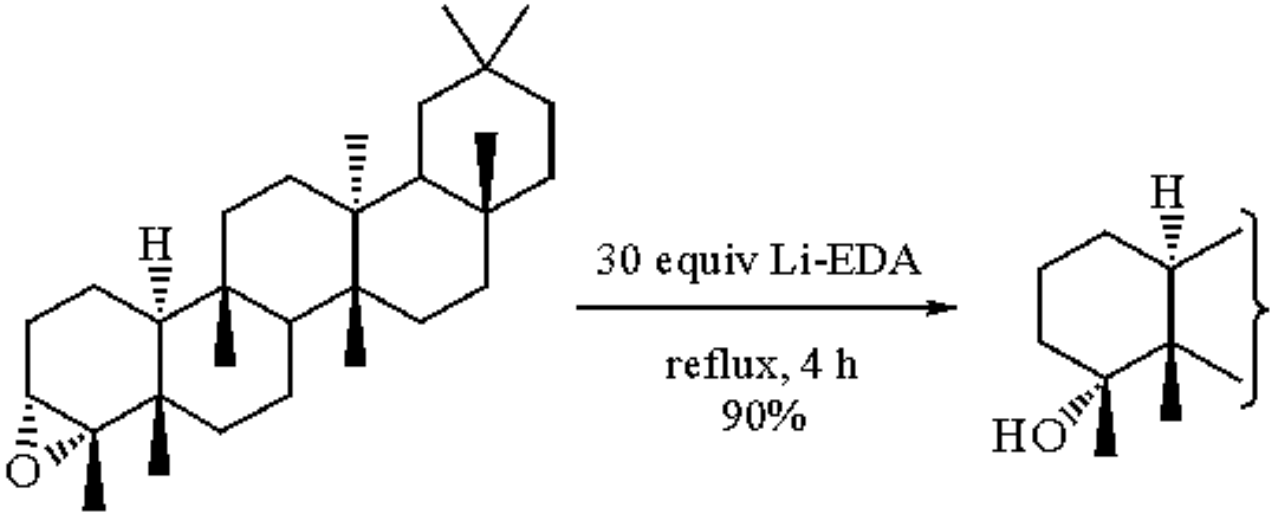

(5)

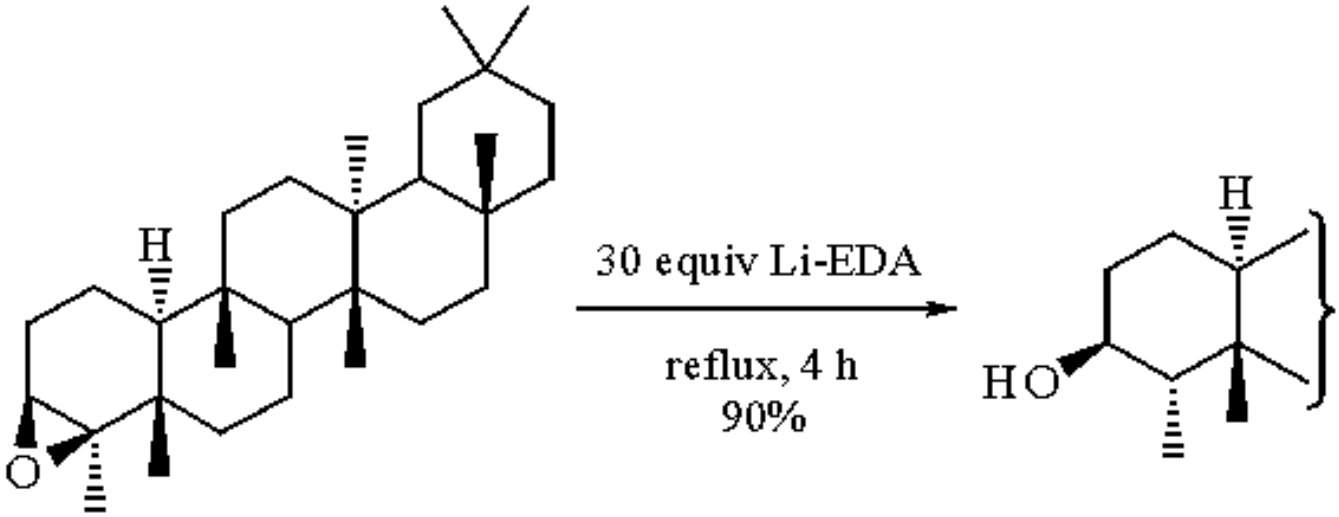

(6)

Li-EDA[27a,b] and Ca-EDA[27a] are excellent reductants for epoxides of bicyclic compounds which react sluggishly and often undergo rearrangements with $LiAlH_4$ (eq 7)[27b] ***Lithium Triethylborohydride*** has proven to be a powerful reductant for bicyclic and tri- and tetrasubstituted oxiranes and is in some instances superior to Li-EDA.[27c]

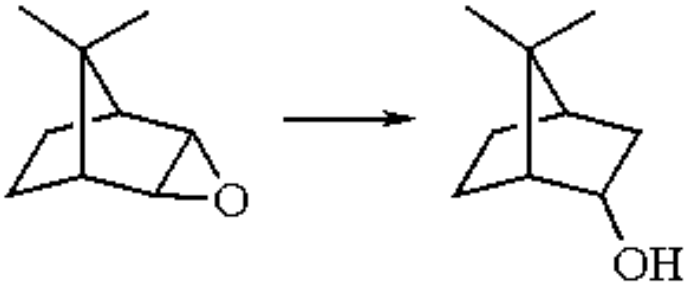

		+ starting material	+ rearranged alcohols	(7)
Li-EDA, 50 °C, 1 h	87%			
$LiAlH_4$, diglyme 100 °C, 24 h	47%	19%	(44%)	

Reductive Cleavage of Miscellaneous Single Bonds.

Allyl and benzyl ethers are cleaved by Li-$MeNH_2$ or -$EtNH_2$ in fair to good yields[28] (eqs 8 and 9[28d,e]).

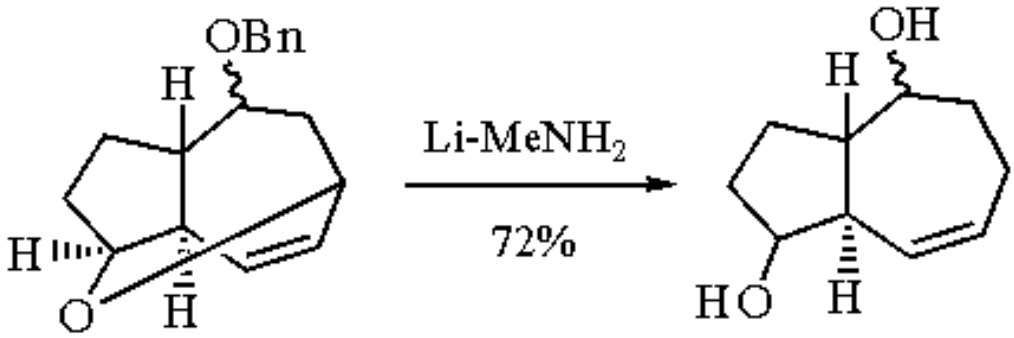

(8)

Similarly, the reductive cleavage of the *O*-alkyl bonds of esters of allylic alcohols is effected by Li-$EtNH_2$;[28e] allylic alcohols are normally not efficiently cleaved unless they are sterically hindered (eq 9).[28e]

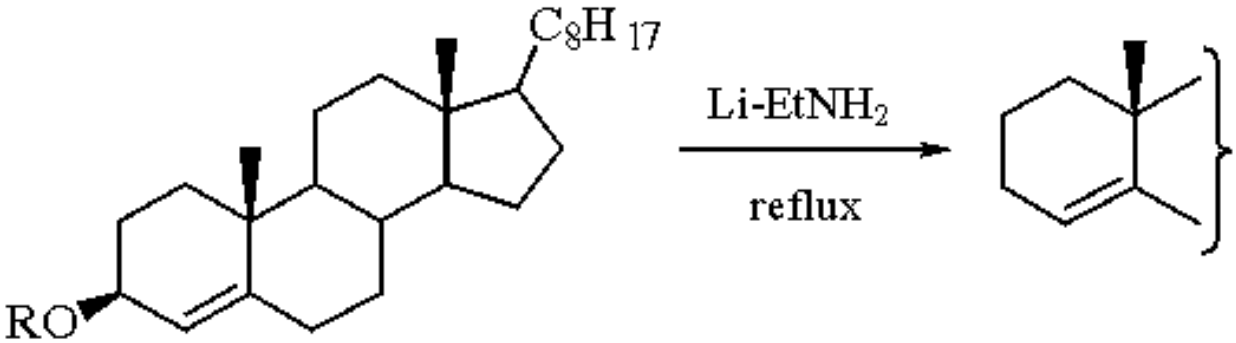

(9)

R = Ac, 15 equiv Li	94%
R = Me, 30 equiv Li	84%
R = H, 22 equiv Li	15% + 61% S.M.

Esters of tertiary and sterically hindered secondary alcohols are cleaved to the corresponding alkanes and carboxylates by Li-$EtNH_2$[29a] and Li-EDA,[29b], whereas the parent alcohol is regenerated from nonhindered esters. This allows the selective deoxygenation of suitable diesters (eq 10).[29a]

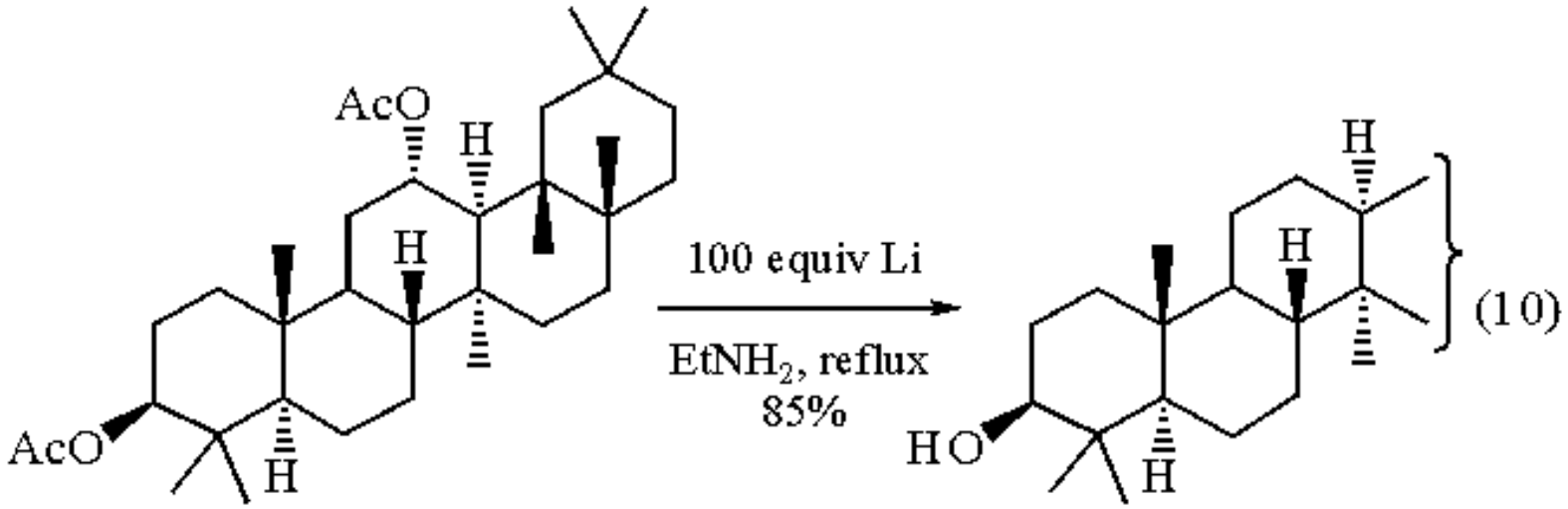

Esters of moderately hindered secondary alcohols often give mixtures of alkane and alcohol. Using ***Potassium 18-Crown-6*** in ***t-Butylamine***, the alkane:alcohol ratio seems to be somewhat higher.[29a] ***Sodium-Hexamethylphosphoric Triamide***-*t*-butanol is another efficient system for the transformation of hindered esters to alkanes.[29c] K-Na eutectic solubilized with 18-crown-6 in *t*-butylamine and THF deoxygenates hindered and nonhindered esters.[29a] Alcohol regeneration by Li in refluxing $EtNH_2$ seems to be essentially due to transacylation, leading to *N*-ethylamides, while at low temperature the Bouveault-Blanc reaction predominates.[29a] Methyl esters of bulky carboxylic acids have been converted to the acids by Li in refluxing EDA.[29d]

Phosphorodiamidates are cleaved to alkanes by Li-$EtNH_2$, providing another indirect method for the deoxygenation of alcohols (eq 11).[30]

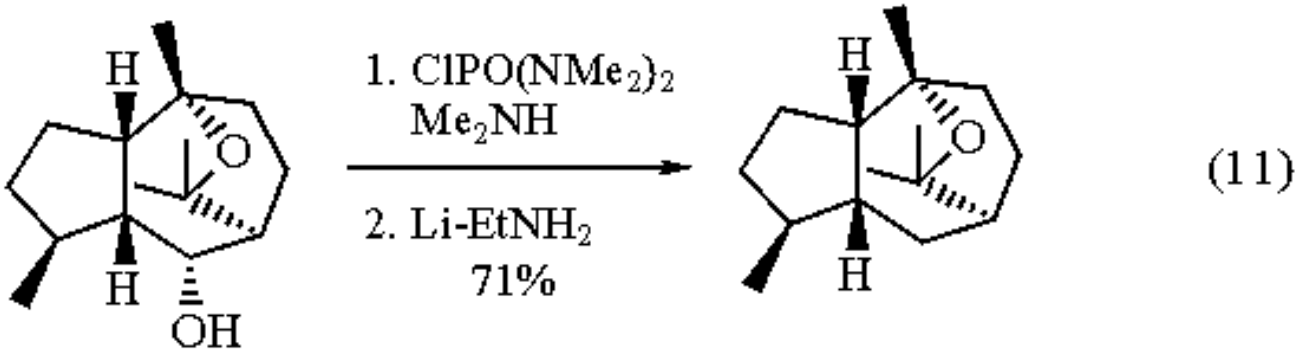

Li-amine reagents have been used for the cleavage of vinyl phosphates to alkenes,[31] of oxetanes,[32] of bicyclobutanes,[33] and of allylic *N*,*N*′-diacylhydrazines.[34] Li-EDA cleaves glycosyluronic acid-containing oligosaccharides specifically at the site of the acid residue.[35]

Related Reagents.

Lithium; ***Potassium***; ***Sodium***; ***Sodium-Ammonia***.

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Lithium Fluoride[1]

LiF

[7789-24-4] · (MW 25.94)

(mild base;[2] can replace other halogens with fluorine;[3] desilylation reagent for forming reactive azomethine ylides;[4] stereoselective oxidative desulfurization when used with MeI and Li_2CO_3[5])

Physical Data: mp 848 °C; bp 1681 °C; *d* 2.639 g cm^{-3}.

Solubility: sol 0.27 g per 100 g water at 18 °C.

Form Supplied in: white solid; fused pieces and random crystals; widely available.

Handling, Storage, and Precautions: avoid breathing dust and contact with eyes, skin, or clothing.

Fluorination Agent.

Lithium fluoride can be used to exchange other halogens with fluorine. The reactivity of lithium fluoride is weaker than ***Potassium Fluoride*** and it cannot displace less reactive halogens, such as aryl chlorides or bromides. Glycerol chlorohydrin can be converted to the corresponding fluorohydrin in moderate yield (eq 1).[3] Treatment of dichloroboranes with lithium fluoride in ether gives the corresponding difluoroboranes in good yield (eq 2).[6] Lithium fluoride can also exchange with chlorine atoms[7] and trifluoromethanesulfonyloxy groups[8] on silicones to give the corresponding fluorinated silane derivatives (eqs 3 and 4).

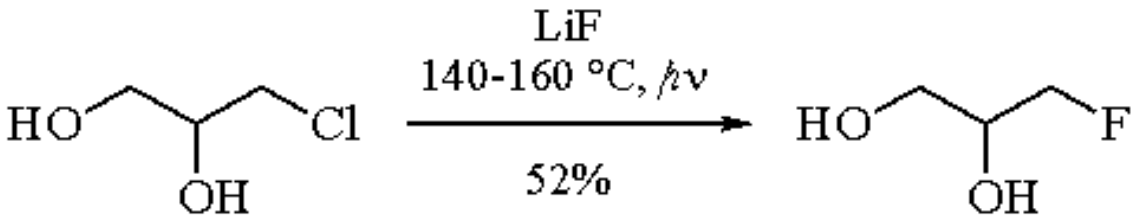

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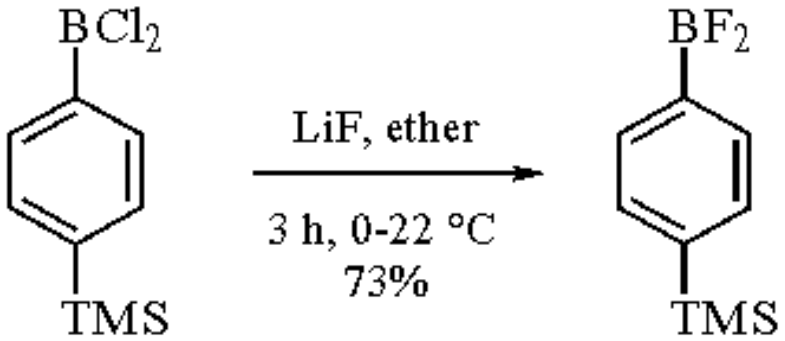

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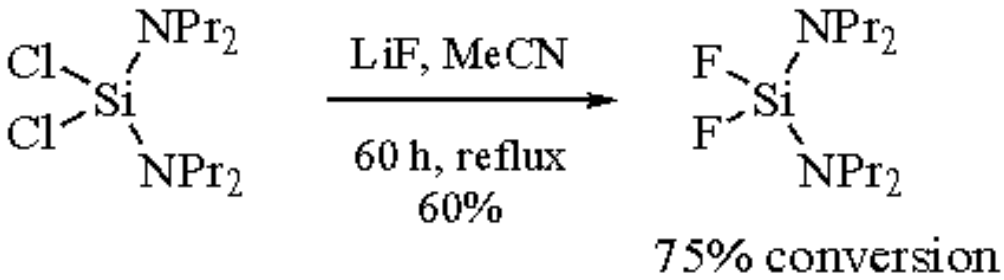

75% conversion

(3)

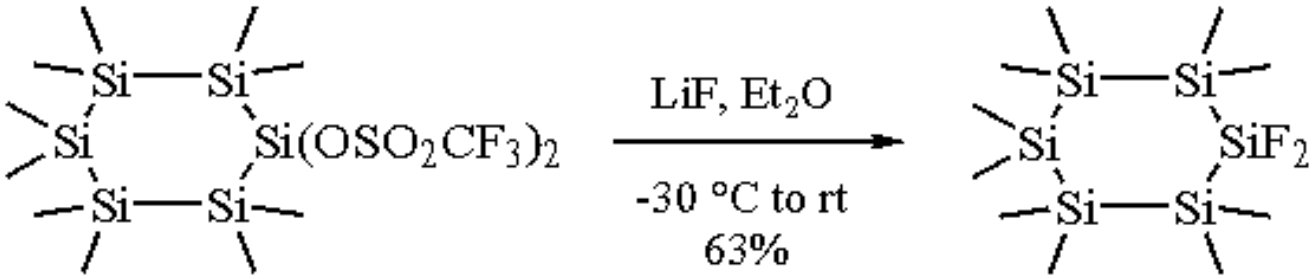

(4)

Desilylation Agent.

Lithium fluoride has been found to be the most effective desilylating reagent for *N*-[(trimethylsilyl)methyl]amino ethers in the formation of azomethine ylides which can undergo 1,3-dipolar cycloaddition reactions with reactive dipolarophiles in high yield.[4] This is a very useful method for the preparation of pyrrolidines. A mixture of *N*-benzyl-*N*-methoxymethyl-*N*-(trimethylsilyl)methylamine and *N*-phenylmaleimide with LiF in anhydrous acetonitrile was sonicated for 3 h to give the cycloadduct in 72-75% yield (eq 5).[9] The cycloaddition proceeded with complete stereospecificity with dimethyl maleate and fumarate, giving rise to *cis* (eq 6) and *trans* (eq 7) cycloadducts, respectively. This cycloaddition did not take place with methyl propiolate; instead, the reaction gave the conjugate addition product (eq 8).

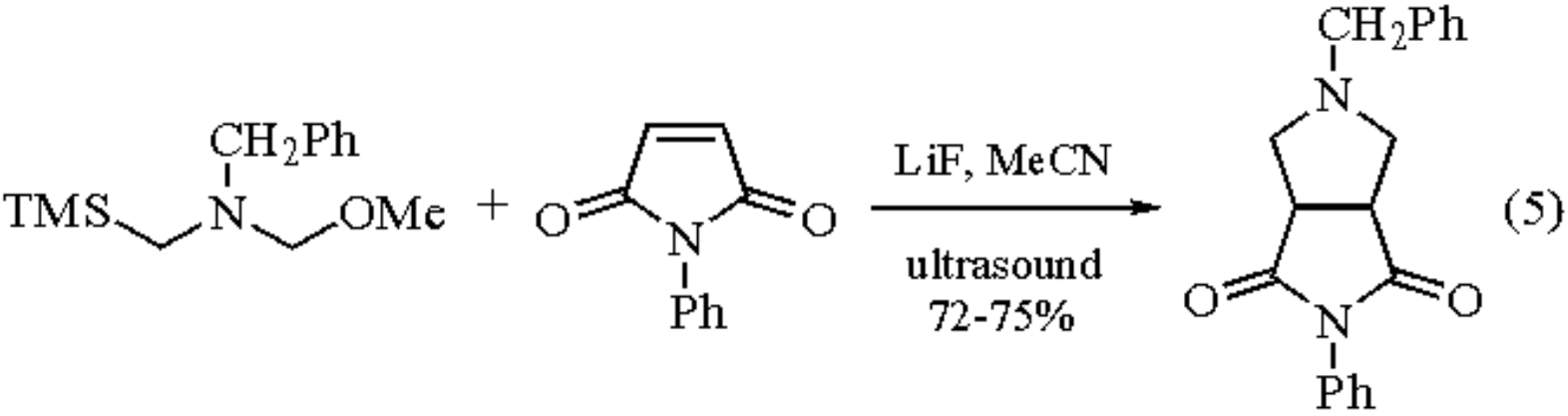

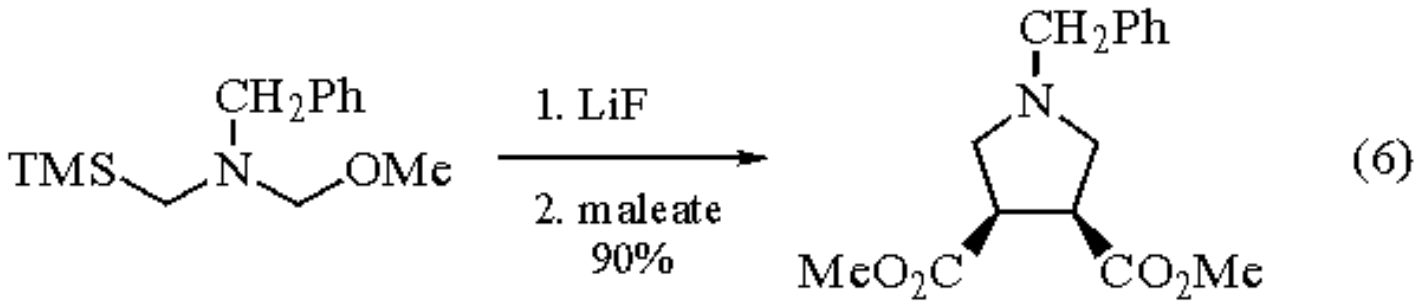

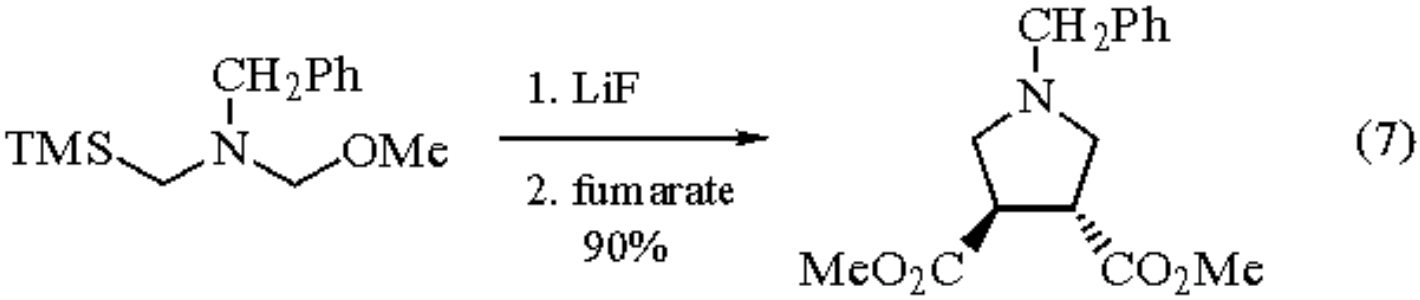

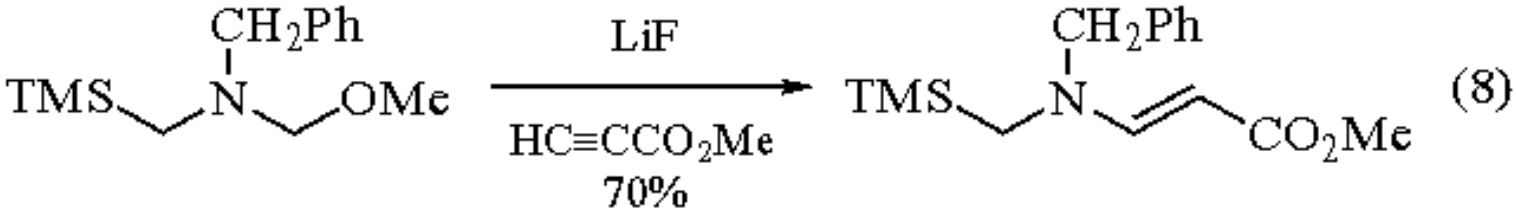

Desulfurization.

A mixture of lithium fluoride, ***Iodomethane*** and ***Lithium Carbonate*** is an effective reagent for the desulfurization of allylic dithiocarbamates.[5] All-*trans*-2,4,6,8-decatetraene was prepared in 75-80% yield (eq 9).[10] Terminal silyl derivatives can undergo this oxidative desulfurization regioselectively to form the terminal double bond, leaving the existing double bonds intact (eq 10).[11]

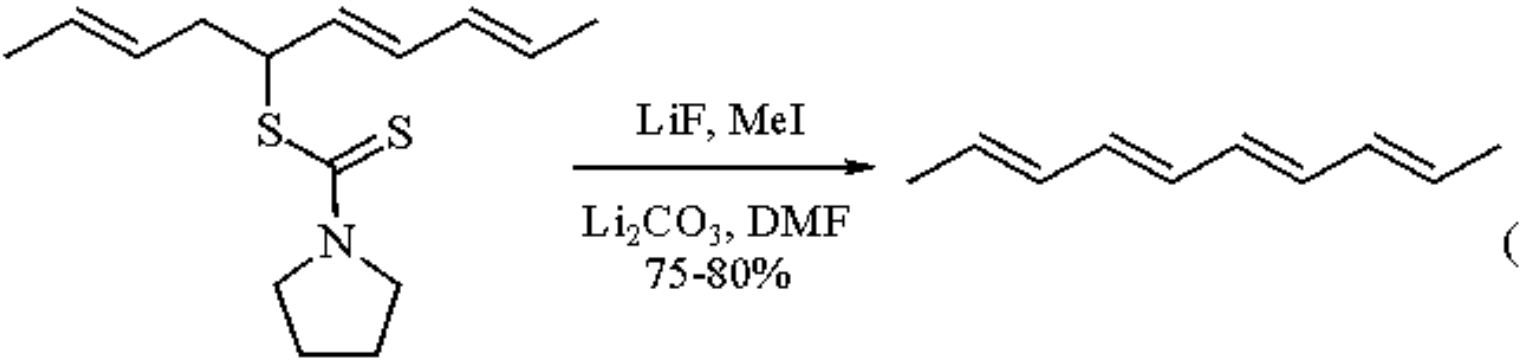

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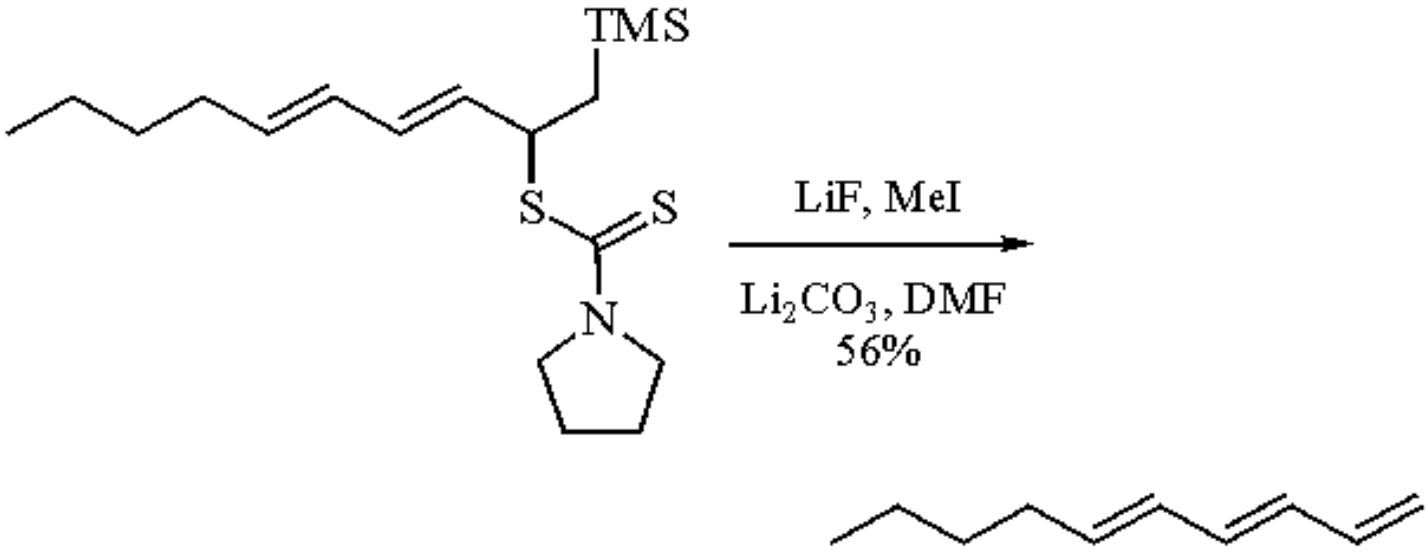

(10)

Related Reagents.

Potassium Fluoride; ***Potassium Fluoride-Alumina***; ***Potassium Fluoride-Celite***.

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Lithium Hexamethyldisilazide

$(Me_3Si)_2NLi$

[4039-32-1] · $C_6H_{18}LiNSi_2$ · Lithium Hexamethyldisilazide · (MW 167.37)

(strong nonnucleophilic base)

Alternate Names: LHMDS; lithium bis(trimethylsilyl)amide.

Physical Data: distillable low-melting solid; mp 70-72 °C, bp 115 °C/1 mmHg.[2] LHMDS is a cyclic trimer in the solid state,[3] whereas in benzene solution it exists in a monomer-dimer equilibrium.[4] LHMDS is less soluble, less basic, more stable, and much less sensitive to air compared to ***Lithium Diisopropylamide***. pK_a 29.5 (THF, 27 °C).[1]

Solubility: sol most nonpolar solvents, e.g. aromatic hydrocarbons, hexanes, THF.

Form Supplied in: colorless crystalline solid, 1 M solution in THF or hexanes, 1.3 M solution in THF, 1 M solution in THF/cyclohexane.

Preparative Methods: conveniently prepared by the reaction of ***Hexamethyldisilazane*** with ***n-Butyllithium*** in hexane. For most uses the hexane is then evaporated and replaced with THF.[5]

Handling, Storage, and Precautions: a flammable, moisture sensitive solid; stable in a nitrogen atmosphere. Use in a fume hood.

Ketone Enolates.

A high yielding synthesis of 6-aryl-4,6-dioxohexanoic acids, precursors to antiinflammatory agents, is achieved using LHMDS (eq 1).[6] This process is applicable to large scale and involves relatively high reaction temperatures. The use of LDA gives reduced yields and small amounts of a diisopropylamide byproduct.

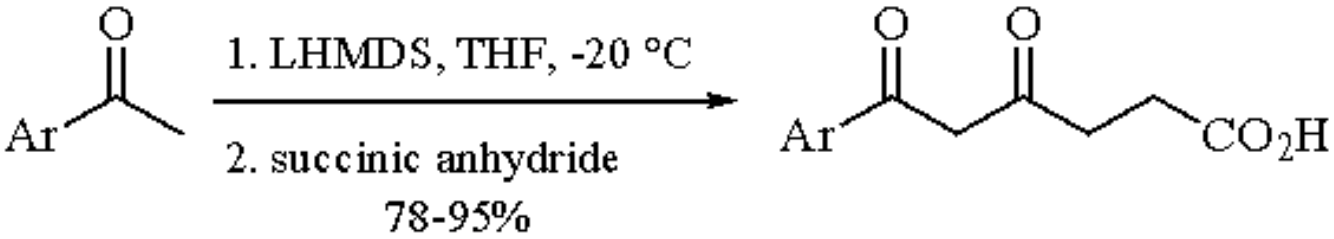

(1)

Ar = 4-ClC_6H_4, 2-thienyl, 3-pyridyl, 4-MeC_6H_4

Ester Enolates.

Enantiomerically pure amino acids may ultimately be prepared via stereospecific ester enolate generation using an oxazolidine chiral auxiliary (eq 2).[7] Moderate diastereoselectivity is observed using ***Potassium Hexamethyldisilazide***.

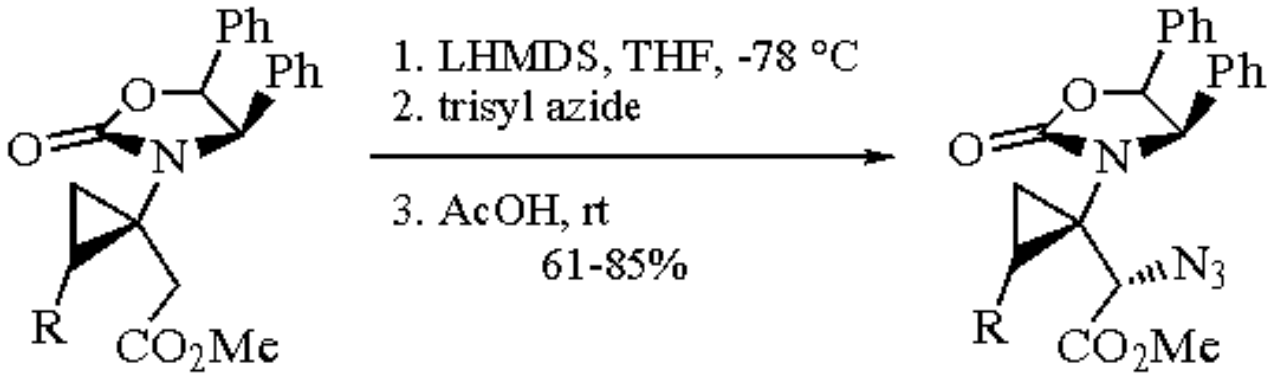

(2)

trisyl = 2,4,6-triisopropylbenzenesulfonyl

Lithio ethyl acetate is prepared in quantitative yield by reaction of LHMDS with ethyl acetate in THF at -78 °C.[8a] Reaction with carbonyl compounds leads to condensation products in high yield (eqs 3 and 4).[8] No racemization of the α-silyloxy esters occurs (eq 4).

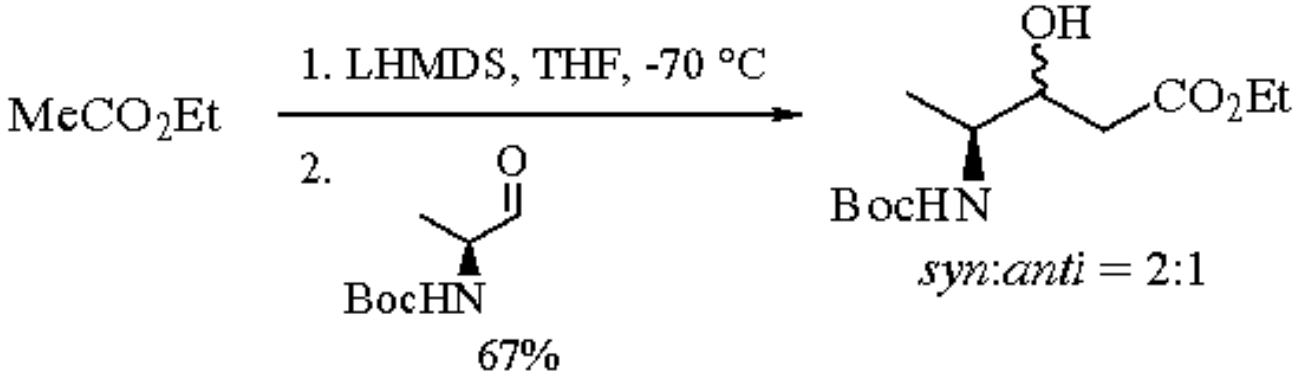

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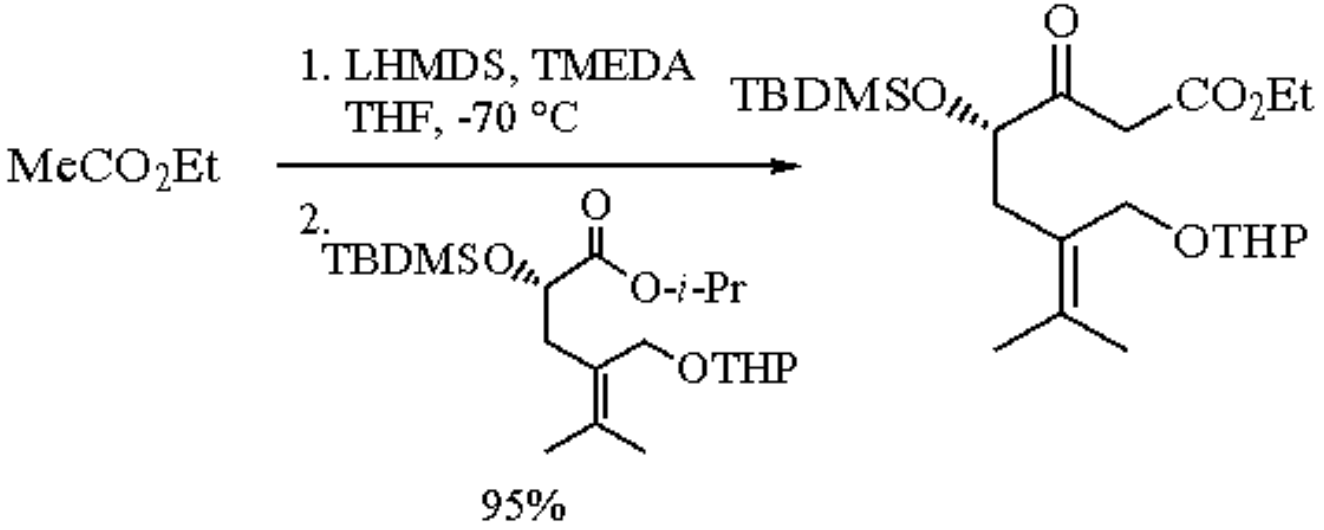

(4)

Kinetic Enolates.

LHMDS is the recommended base for the generation of kinetic enolates. The resulting enolates are more regiostable than those generated with the corresponding sodium base, ***Sodium Hexamethyldisilazide***. Thus reaction of Δ^4-3-keto steroids with LHMDS yields 2,4-dienolate ions which can be methylated at C-2 or trapped as 2,4-dienolsilyl ethers (eq 5).[9] Use of ***Potassium t-Butoxide***/*t*-BuOH produces the thermodynamically more stable 3,5-dienolate. Acid-catalyzed conditions yields the 3,5-enol ether. Enolates generated with LHMDS may serve as ketone protecting groups during metal hydride reductions (eq 6).[10]

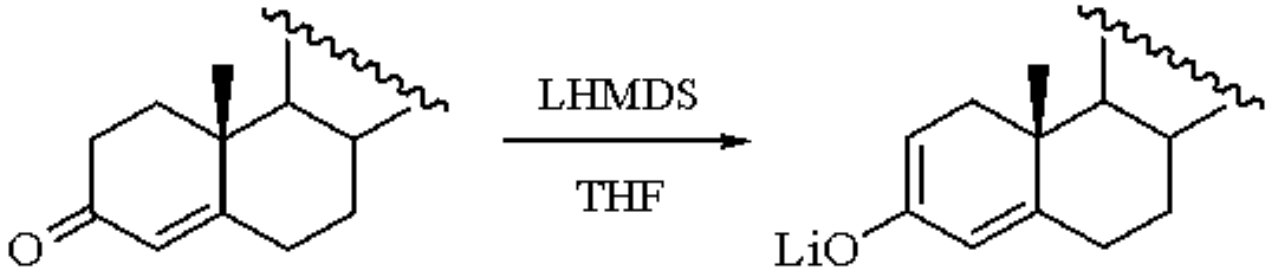

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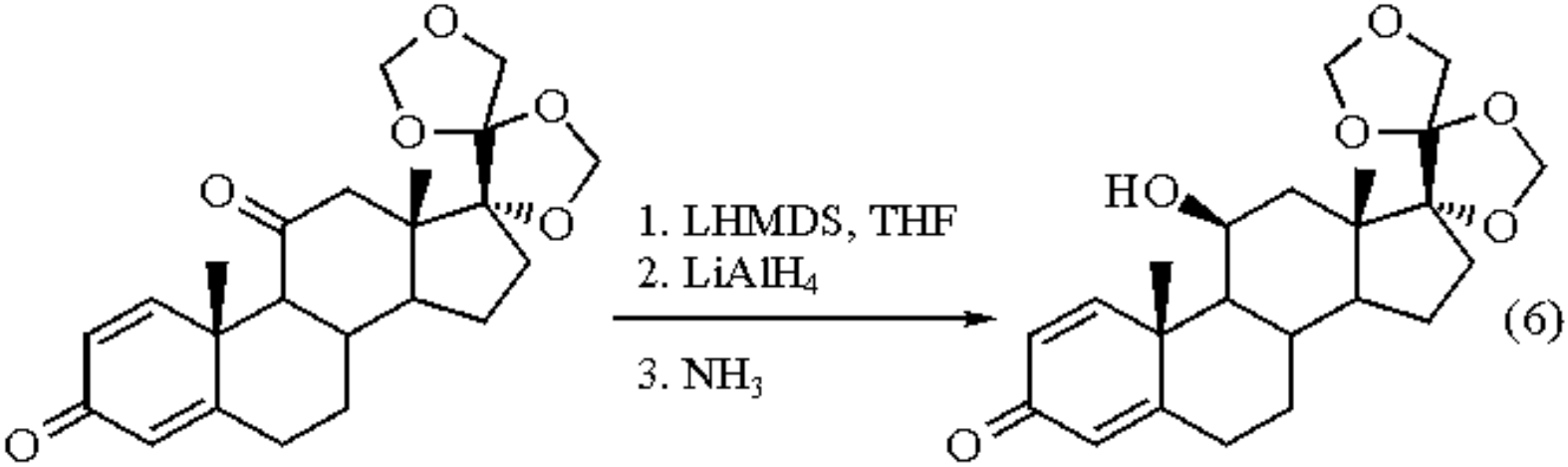

(6)

LHMDS has also been used in directed aldol condensations. The compatibility of the base with a silyl ether moiety is of note in the synthesis of (±)-[6]-gingerol (eq 7).[11]

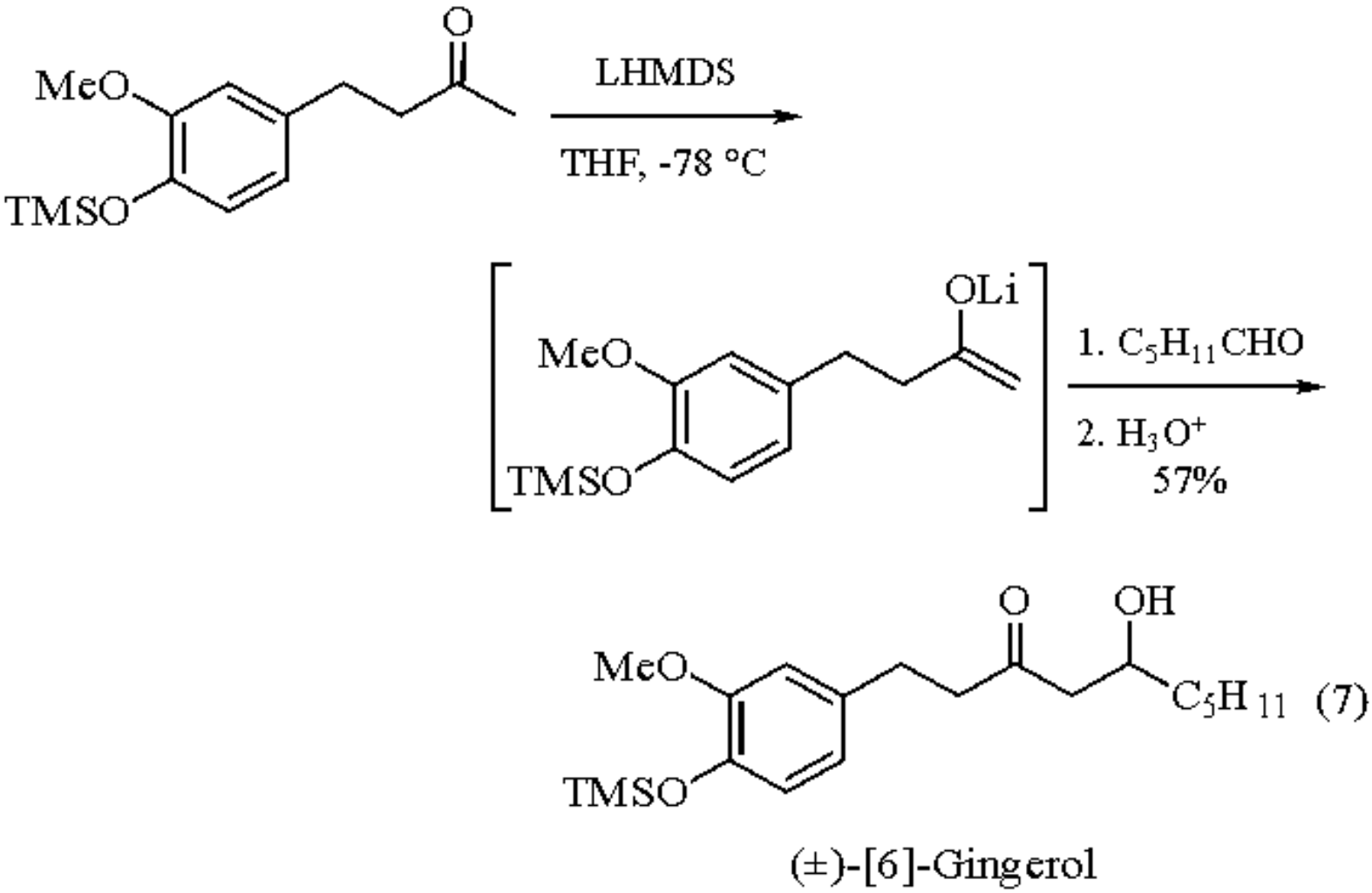

Darzens Condensation.

The Darzens reaction invariably fails with aldehydes due to competing base-catalyzed self-condensation reactions.[12] With LHMDS as base, even acetaldehyde provides the desired glycidic ester products in high yield (eq 8).[13]

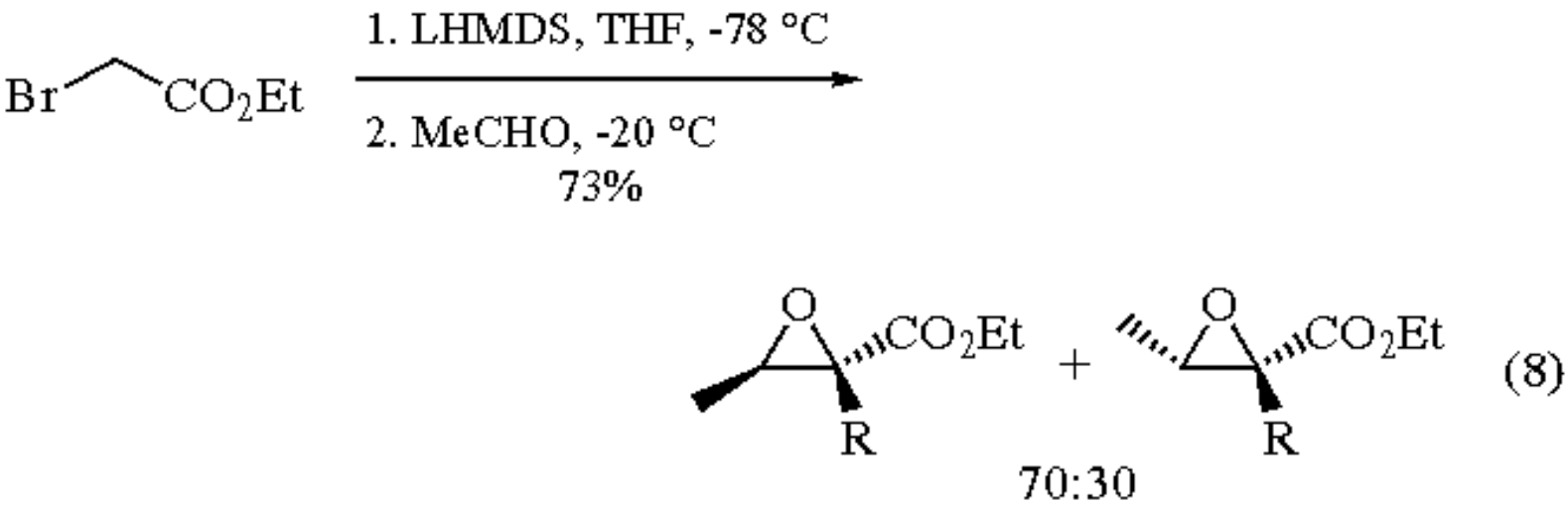

Intramolecular Cyclizations.

LHMDS-mediated intramolecular cyclizations have been demonstrated (eq 9).[14] The choice of counter cation has a dramatic effect on the stereochemistry of the cyclization.

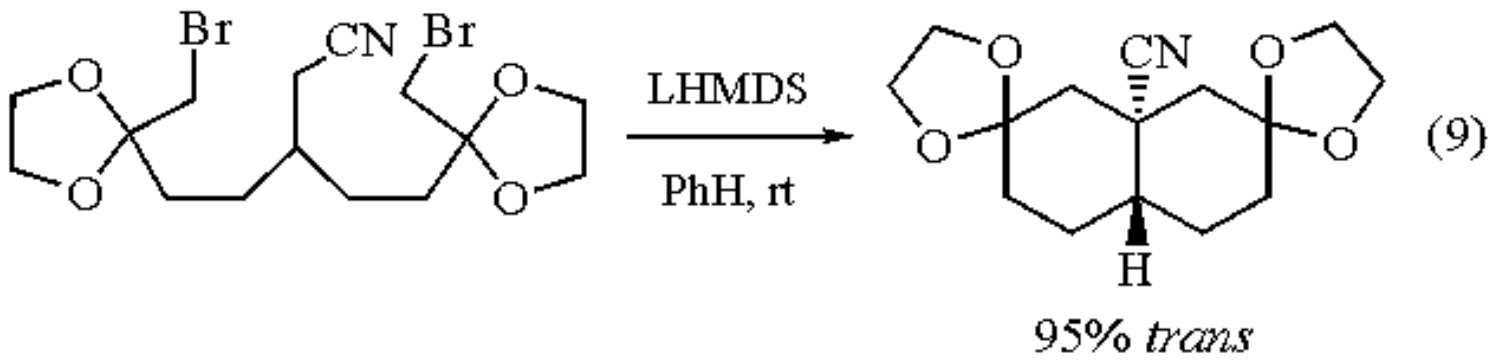

Ester Enolate Claisen Rearrangement.

LHMDS is comparable to LDA for the stereoselective Ireland-Claisen rearrangement of ester enolates (eq 10).[15]

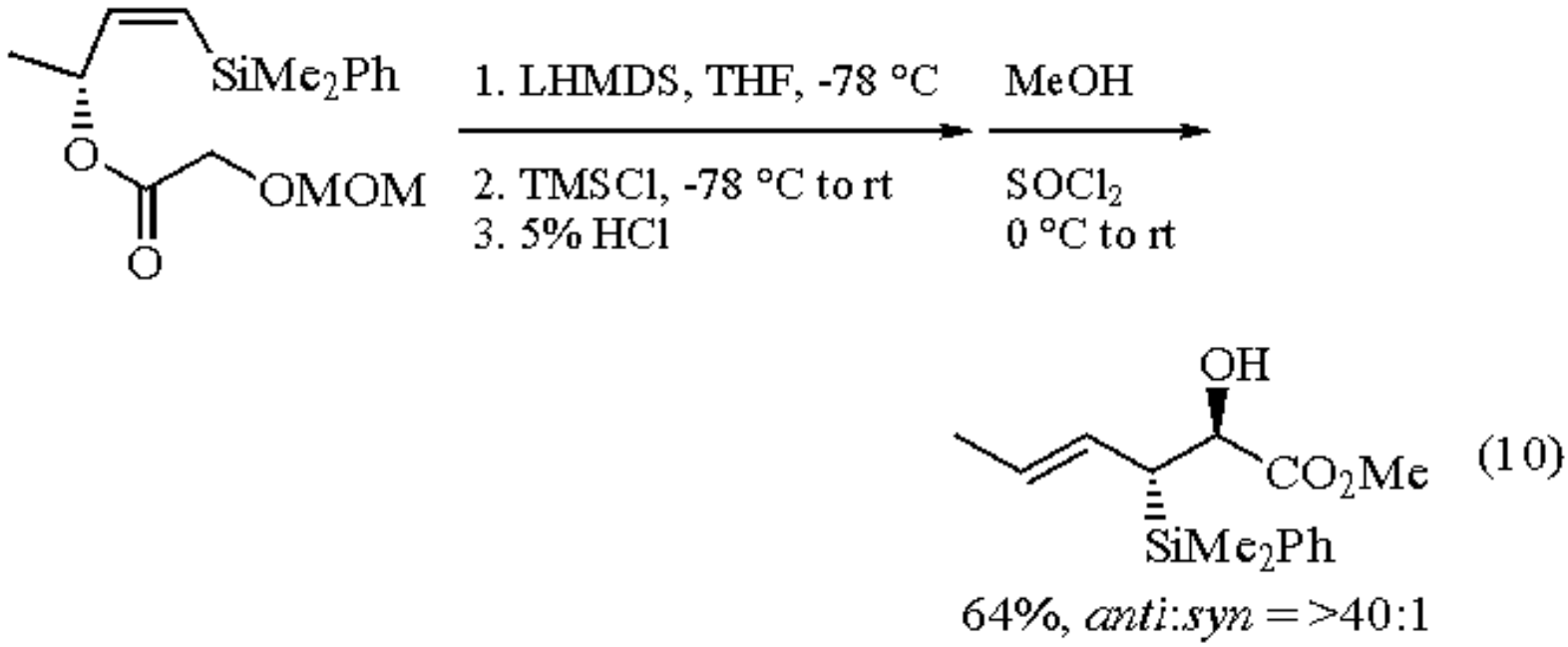

Intramolecular Double Michael Addition.

LHMDS-mediated sequential Michael reactions constitute the key component of a total synthesis of the diterpene alkaloid atisine (eq 11).[16]

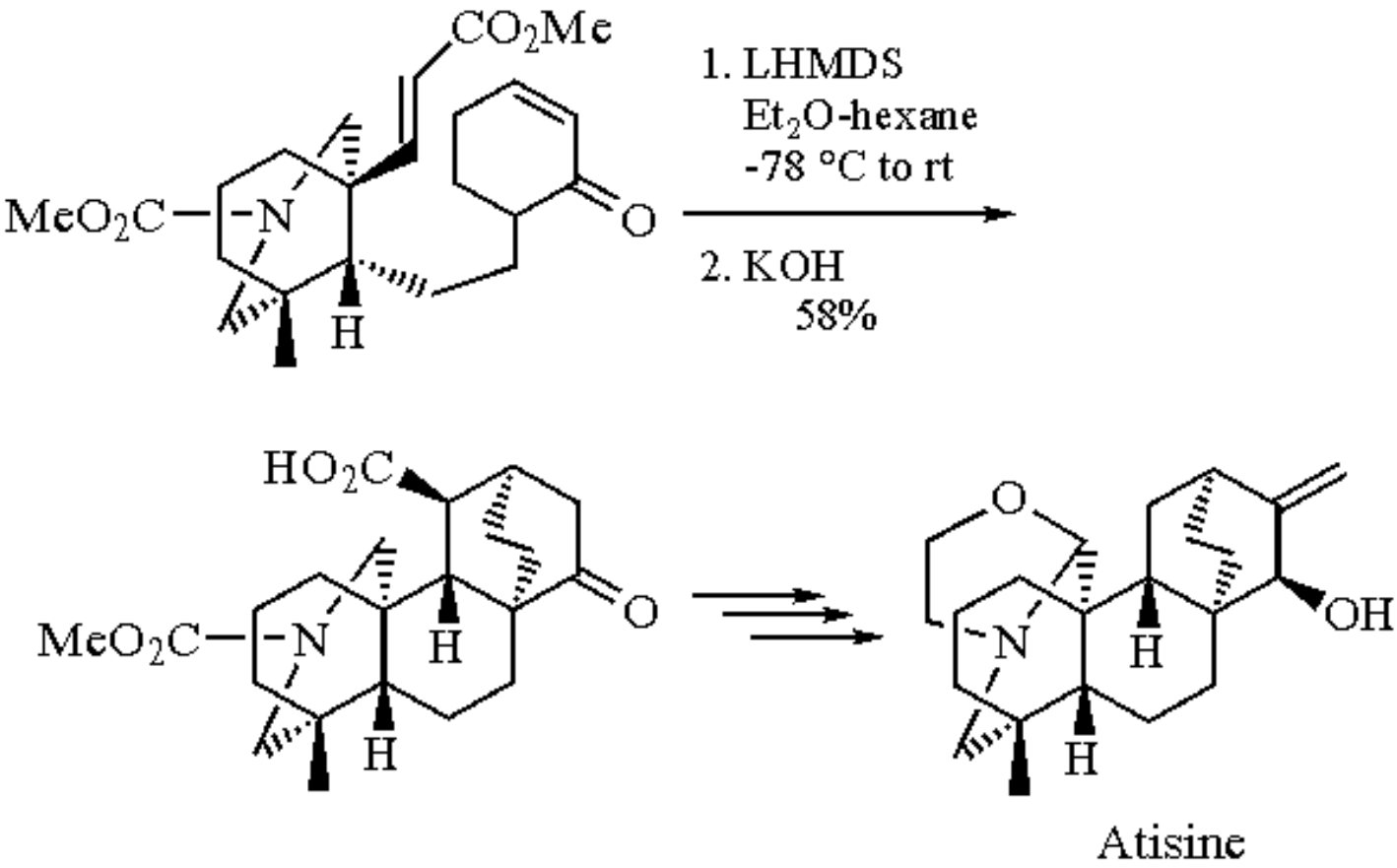

(11)

Synthesis of Primary Amines.

N,*N*-Bis(trimethylsilyl)methoxymethylamine, formally a $^{+}CH_2NH_2$ equivalent, is obtained in high yield by treating chloromethyl methyl ether with LHMDS. Treatment of the bis-silylamine with organometallic reagents followed by mild solvolysis gives primary amines in good to excellent yield (eq 12).[17]

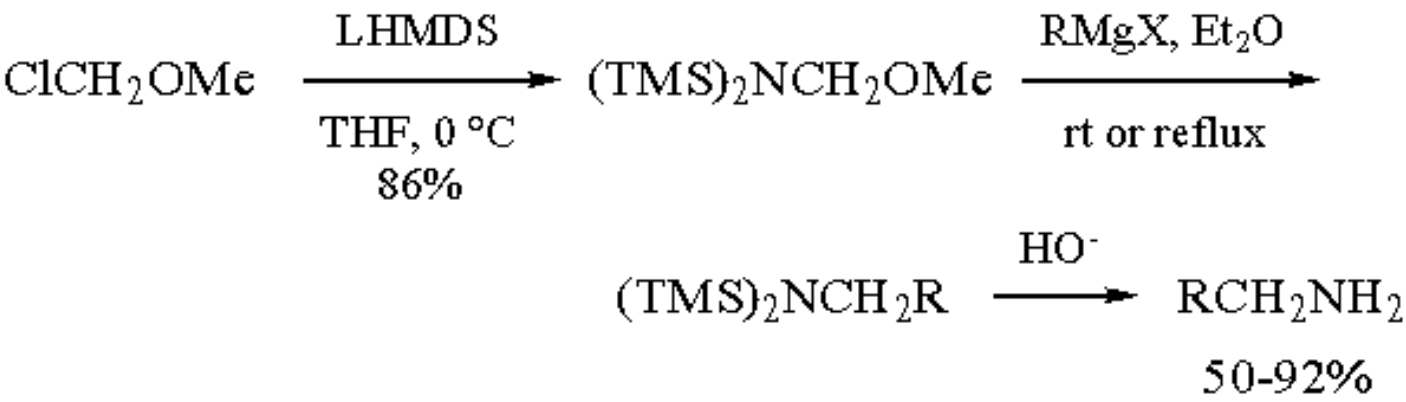

(12)

N-Trimethylsilylaldimines.

Aldehydes, even enolizable ones, undergo Peterson reactions with LHDMS to give *N*-trimethylsilylaldimines (eq 13),[18] which are valuable intermediates for a variety of systems, including primary amines,[18a,19] β-lactams,[18] and α-methylene-γ-lactams (eq 14).[20] Extension of this chemistry to include α-keto ester substrates allows for the preparation of α-amino esters.[21]

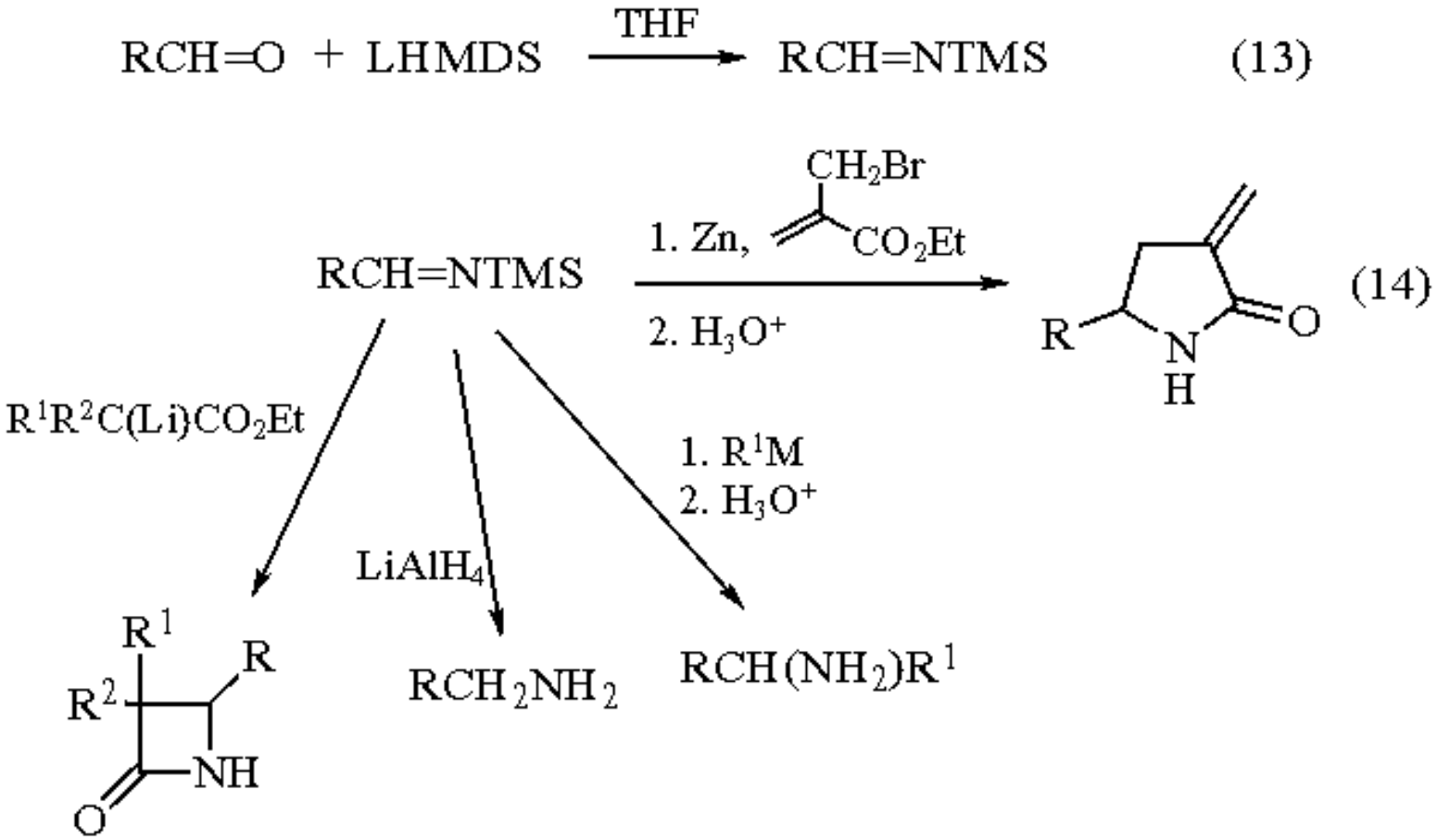

N,N-Bis(trimethylsilyl)aminomethyl Acetylide.

The reaction of LHMDS with propargyl bromide constitutes a straightforward route to a γ-amino lithium acetylide, a useful precursor to a wide variety of unsaturated protected primary amines (eq 15).[22]

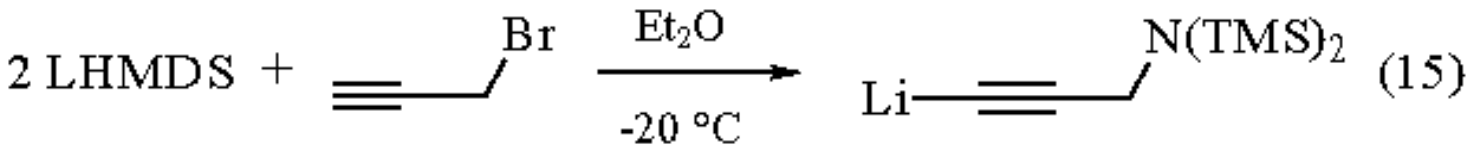

For example, reaction with aromatic aldehydes gives α-alkynyl amino alcohols, which can be trapped as their silyl ethers. Base-catalyzed isomerization to an allenic isomer followed by hydrolysis and concomitant cyclization affords 2-substituted pyrroles (eq 16).[22]

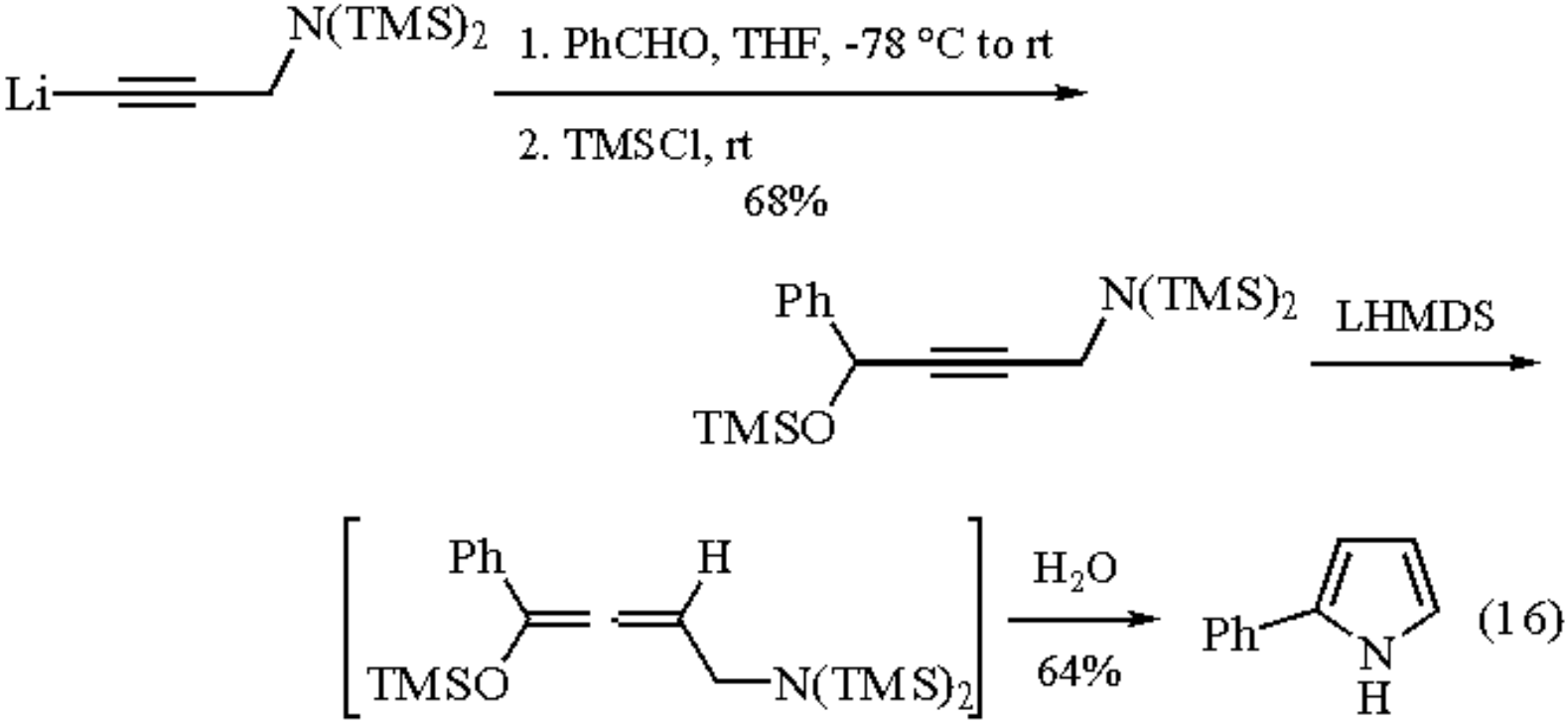

β-Ketosilanes.

β-Ketosilanes may be prepared from α-bromo ketones using LHMDS to generate intermediate silyl enol ethers followed by metal-halogen exchange (eq 17).[23] They undergo facile rearrangement to silyl enol ethers and are also substrates, after carbonyl reduction, for overall Peterson alkenation.

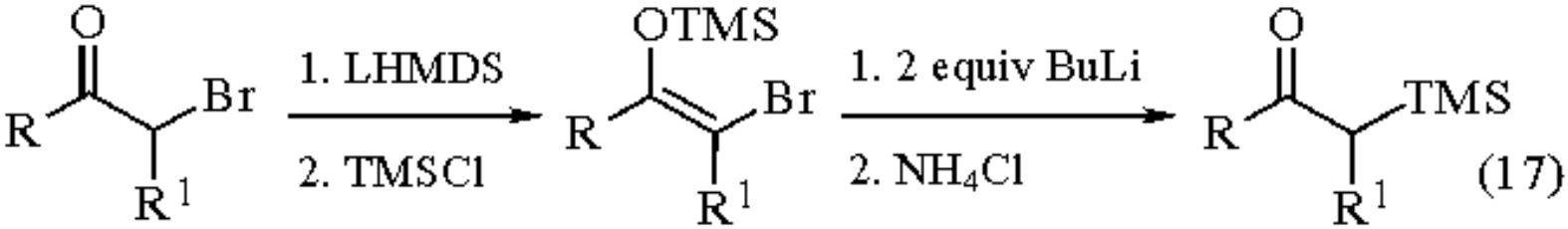

Related Reagents.

Lithium Diethylamide; ***Lithium Diisopropylamide***; ***Lithium Piperidide***; ***Lithium Pyrrolidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***.

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Lithium (1-Hexynyl)(2-tri-*n*-butylstannylvinyl)cuprate

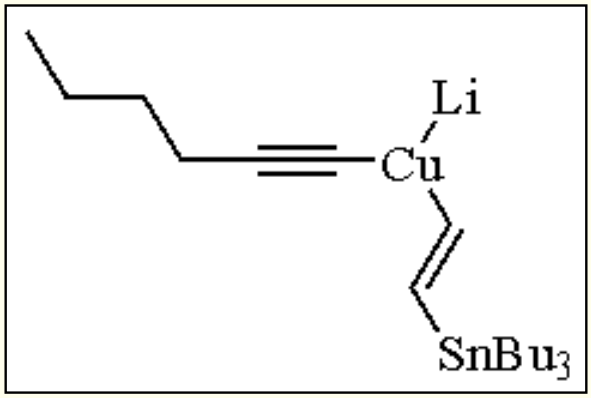

[91158-78-0] · $C_{20}H_{38}CuLiSn$ · Lithium (1-Hexynyl)(2-tri-*n*-butylstannylvinyl)cuprate · (MW 467.78)

(mixed organocuprate; introduces vinylstannane group)

Preparative Methods: prepared in situ from ***1-Hexynylcopper(I)*** and ***(E)-1-Lithio-2-tributylstannylethylene***.[1]

Handling, Storage, and Precautions: air and moisture sensitive; use in a fume hood.

Lithium (1-hexynyl)(2-tri-*n*-butylstannylvinyl)cuprate (**1**) provided a *trans* ethylene dianion equivalent in the total synthesis of pleraplysillin-I. Addition of (**1**) to 3-furfuryl bromide (**2**) gave the furanylstannane (**3**). Palladium-catalyzed coupling of (**3**) with triflate (**4**) in the presence of ***Lithium Chloride*** provided pleraplysillin-I in two steps with complete retention of the *trans* alkene stereochemistry (eq 1).

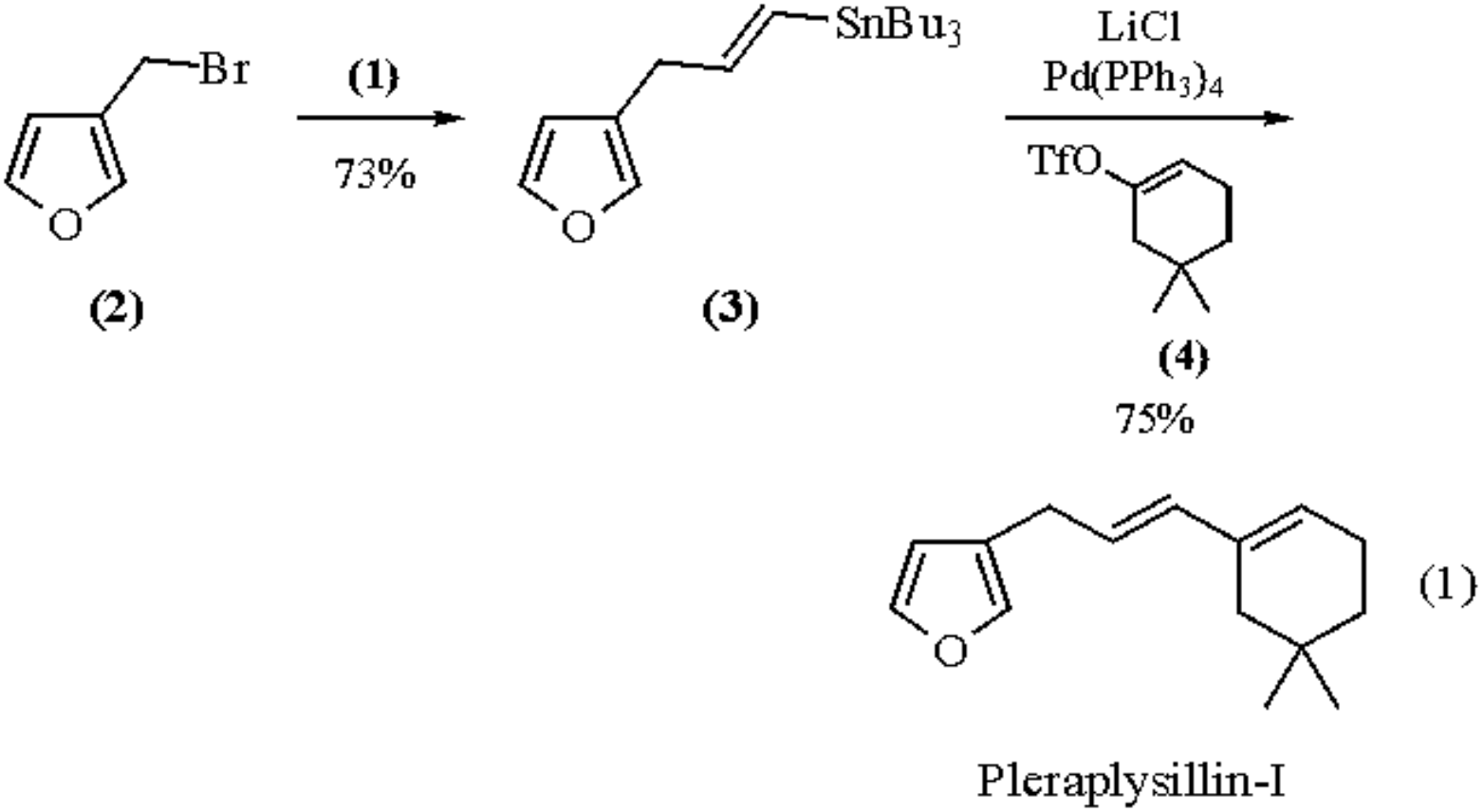

Related Reagents.

1-Hexynylcopper(I); ***Lithium (1-Pentynyl)(2-tri-n-butylstannylvinyl)cuprate***; ***1-Pentynylcopper(I)***; ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***.

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Matthew E. Voss

The Du Pont Merck Pharmaceutical Company, Wilmington, DE, USA

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Lithium Hydroperoxide

LiOOH

[23594-83-4] (.H_2O)

[54637-08-0] · $HLiO_2$ · Lithium Hydroperoxide · (MW 39.95)

(nonbasic hydrolysis of imides, amides, and esters; nondestructive recovery of chiral auxiliaries[3])

Physical Data: hydrate: white crystalline solid; *d* 1.69 g cm^{-3}.

Solubility: sol THF/H_2O (3:1), dioxane.

Preparative Methods: prepared in situ from ***Lithium Hydroxide*** and aq. ***Hydrogen Peroxide***.

Handling, Storage, and Precautions: reagent is typically generated in situ immediately prior to use. The hydrate can be prepared in an inert atmosphere from ethanolic LiOEt and 30% H_2O_2.[1] Extended storage over desiccants such as P_2O_5 leads to the formation of Li_2O_2. LiOOH.H_2O reacts spontaneously with atmospheric CO_2 to form Li_2CO_3 and O_2, and gradually decomposes on standing at room temperature to LiOH.H_2O.

Cleavage of *N*-Acyloxazolidones and Related Imides.

Effective use of the high diastereoselectivity realized from enolate chemistry of optically active *N*-acyloxazolidones,[2a-d] or Diels-Alder cycloaddition[2e] reactions of their α,β-unsaturated derivatives, depends upon clean removal of the chiral auxiliary in a regioselective fashion and without racemization at any acidic chiral centers. Lithium hydroperoxide was originally introduced as an alternative to reductive cleavage of sensitive β,γ-unsaturated *N*-acyloxazolidones with ***Lithium Borohydride***, and showed exceptional regioselectivity for attack at the exocyclic carbonyl with no epimerization or double bond conjugation (eq 1).[3]

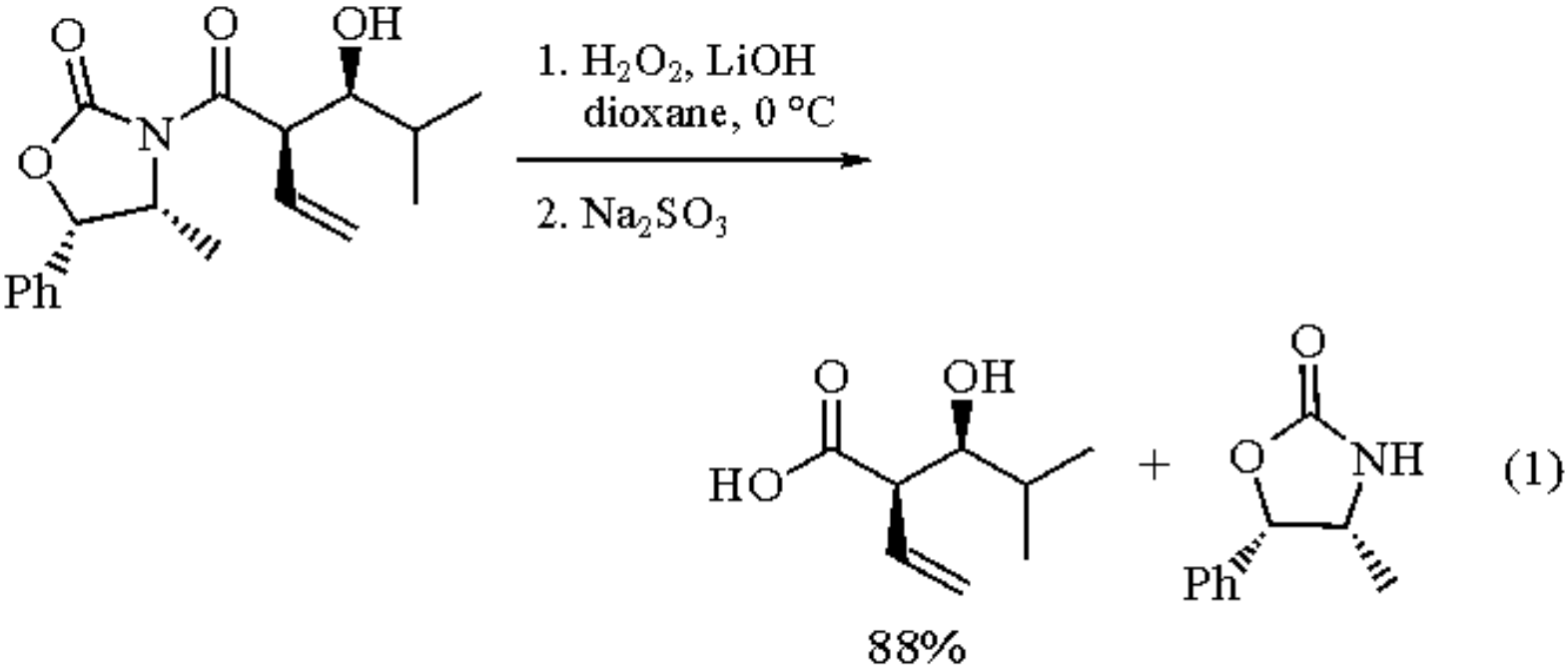

In a subsequent, more complete study, lithium hydroperoxide was demonstrated to be the reagent of choice for regioselective cleavage of a variety of sterically hindered *N*-acyloxazolidones which underwent competing oxazolidone ring opening with LiOH or $LiOCH_2Ph$ (eq 2).[4] Similarly high selectivity for attack at the more hindered carbonyl group was also seen with an acyclic imide (eq 3). The reaction is usually carried out in aqueous THF and is typically quenched with aqueous Na_2SO_3 to reduce the peracid intermediate and consume unreacted LiOOH. Recent examples include the use of this cleavage step in the synthesis of amino acid derivatives,[5a] the calyculins,[5b-c] macbecin,[5d] baclofen,[5e] and polyketide intermediates in the biosynthesis of nargenicin.[5f]

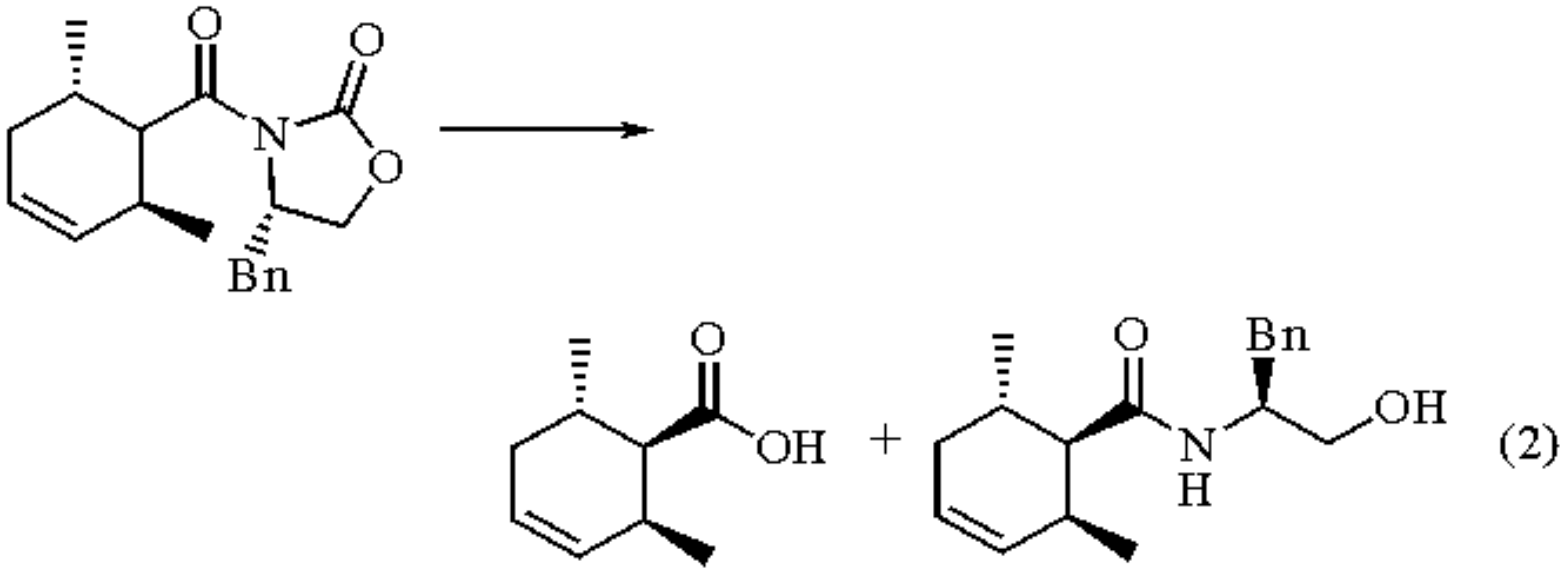

1. LiOOH, aq THF, 0 °C 2. Na_2SO_3	76%	16%
LiOH, aq THF, 0 °C	0%	100%

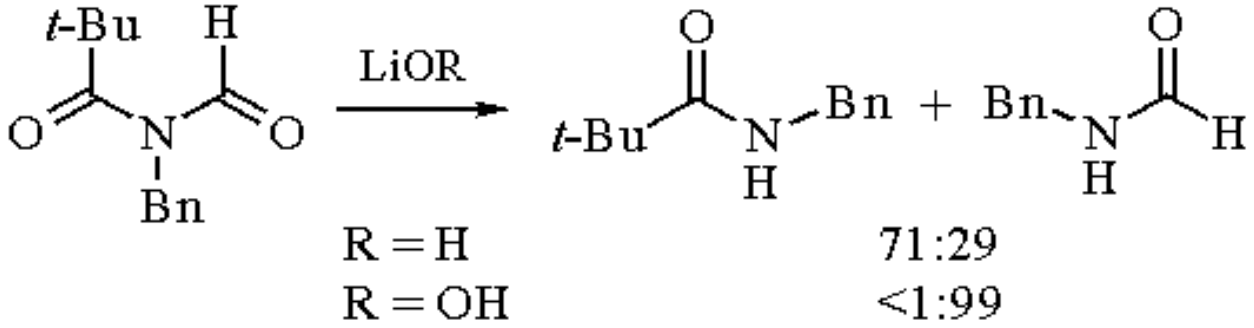

(3)

In a route to optically active α-alkylsuccinates, LiOOH proved to be highly chemoselective for imide cleavage, with no competing cleavage of a methyl ester also present.[6] In a recent approach to β-amino acids, regioselective cleavage of an intermediate in the synthesis of thienomycin was found to require the addition of DMF (3:3:1 DMF/THF/H_2O) as a cosolvent (eq 4).[7] Importantly, this reagent can be used in the presence of α-phenylselenyl groups with no competing oxidation of the selenide.[8]

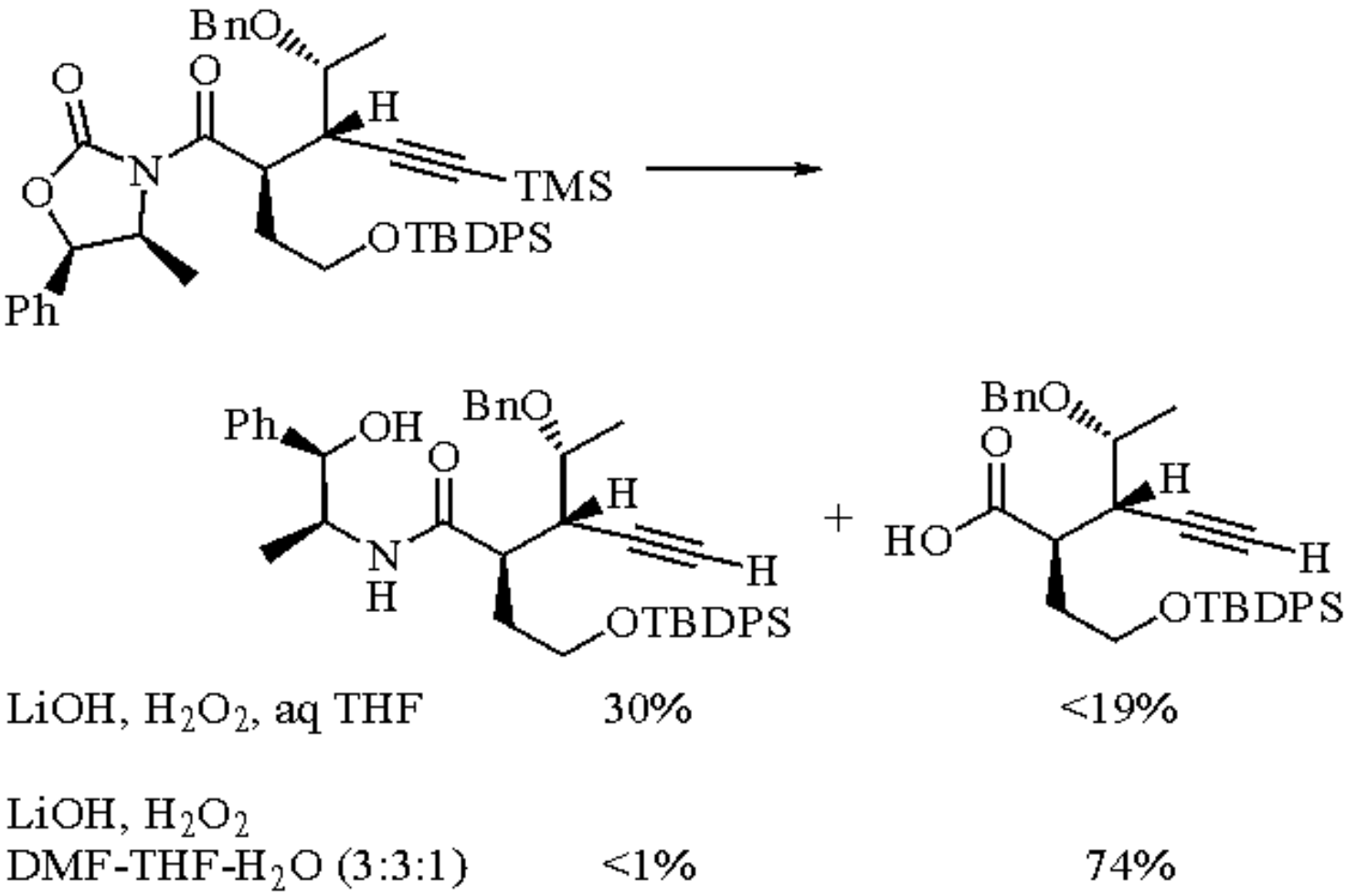

(4)

Other examples (shown in **1**-**6**) include the cleavage of *N*-acylbenzoxazolinones,[9] carbohydrate-derived *N*-acyloxazolidones,[10] camphor-derived *N*-acyloxazolidonethiones,[11] camphor-derived imides,[12] *N*-acylpiperidone derivatives of Kemp's triacid,[13] and chiral *N*-acylpyrimidones.[14] Also, cleavage of *N*-acyl and *N*-carbamoyl derivatives of an oxazolidone obtained from *endo*-borneol has been described as a method for resolving racemic carboxylic acids or alcohols.[15]

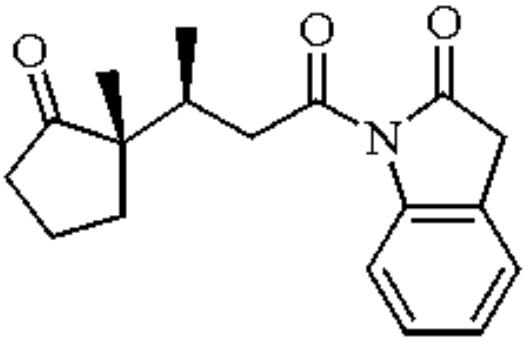

(1)

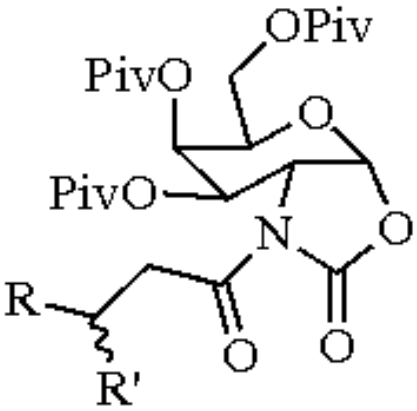

(2)

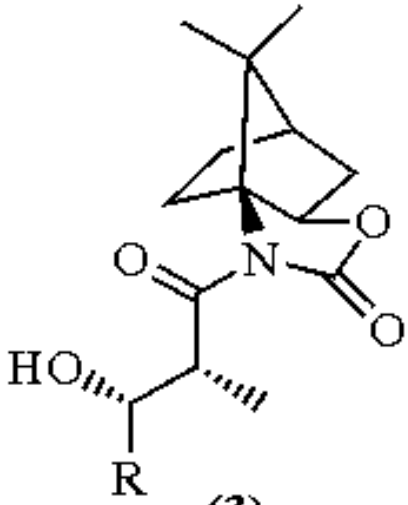

(3)

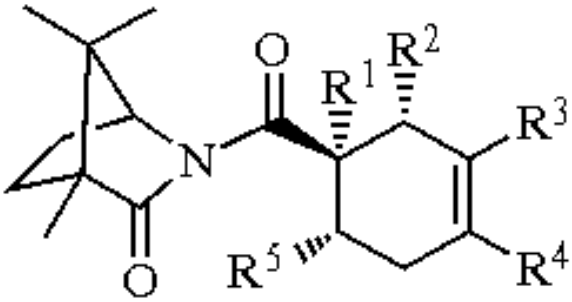

(4)

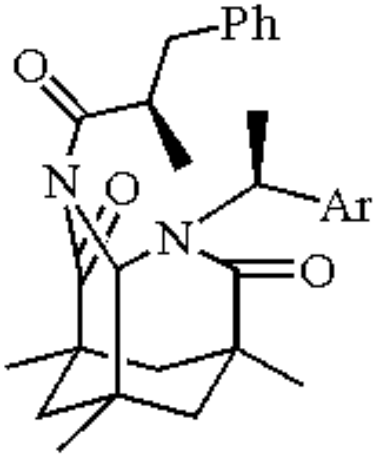

(5)

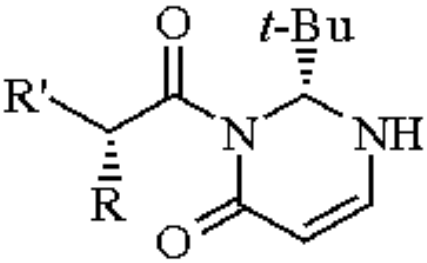

(6)

Cleavage of *N*-Acylsultams.

In addition to imide carbonyls, optically active *N*-acylsultams can be cleaved using LiOOH. Following either asymmetric alkylation[16a] or conjugate addition,[16b] bornanesultam chiral auxiliaries can be removed with good recovery and without racemization of the resulting carboxylic acids (eq 5). This cleavage method was also used in the preparation of a toluenesultam chiral auxiliary.[16c]

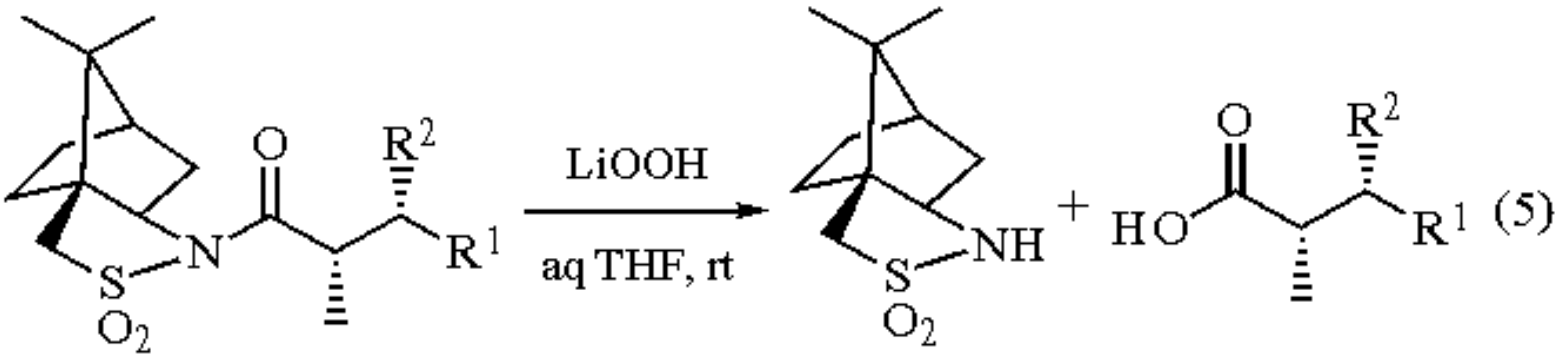

(5)

Cleavage of Esters and Amides.

Notwithstanding the previously noted chemoselectivity for imides,[6] LiOOH has been used to saponify esters under mild conditions. For example, in a synthesis of a bifunctional chelate molecule, an ethyl ester was cleaved in high yield using LiOOH.[17] Also, in the synthesis of a heparin analog, simultaneous deprotection of a series of primary and secondary acetates and two methyl esters was effected via LiOOH without the intervention of undesired β-elimination.[18] LiOOH was also used to cleave a methyl ester in a recent total synthesis of the leukotriene precursor (15*S*)-HPETE (eq 6).[19] Interestingly, cycloheptene was used to reduce the resulting peroxy acid selectively in the presence of an allylic hydroperoxide. Finally, deprotection of an *N*-formylamino polyol was carried out using LiOOH/THF.[20] The authors noted that stabilization of the THF with BHT was desirable to suppress side reactions involving radicals.

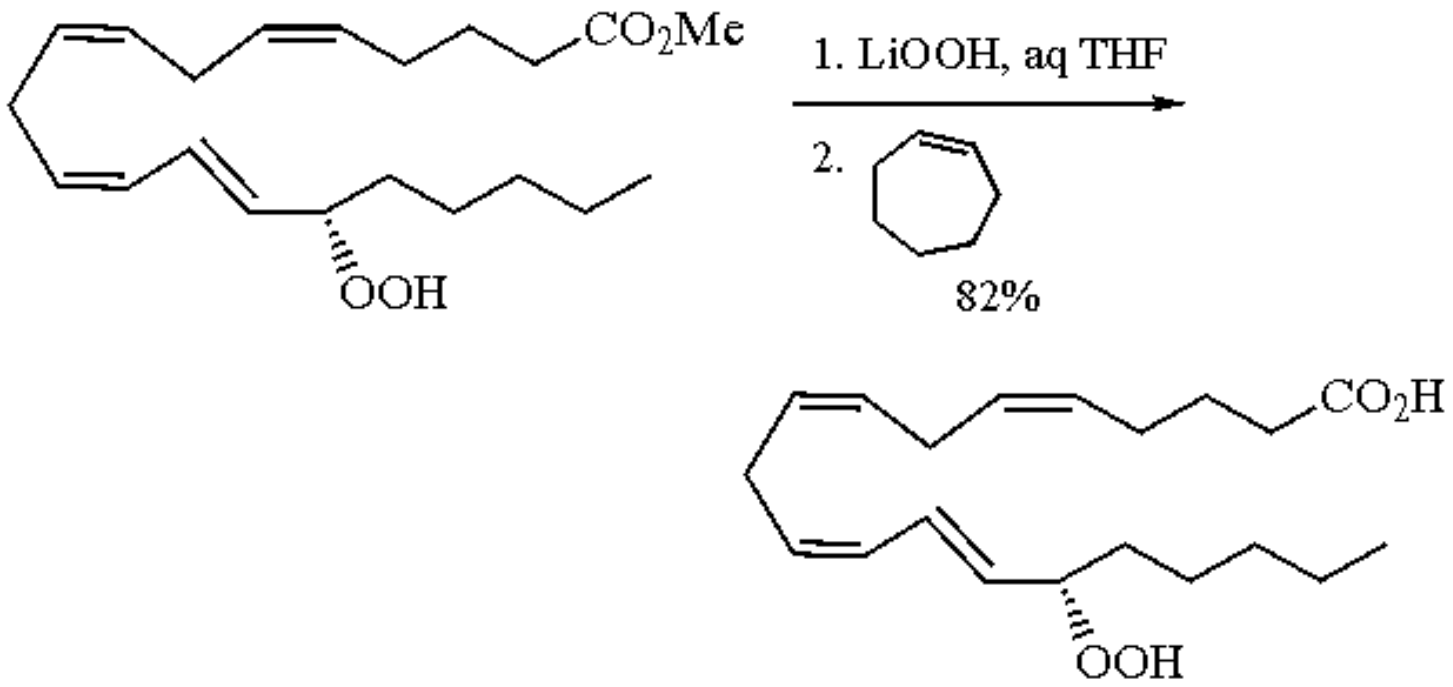

(6)

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Lithium Hydroxide

LiOH

[1310-65-2] · HLiO · Lithium Hydroxide · (MW 23.95) (.H_2O)

[1310-66-3] · H_3LiO_2 · Lithium Hydroxide · (MW 41.97)

(very strong alkali; reacts readily with acids and is used as a base as well as a nucleophile in organic reactions, particularly in the hydrolysis of esters and amides)

Physical Data: d (anhyd.) 2.54 g cm^{-3}; (monohyd.) 1.51 g cm^{-3}; mp (anhyd.) 471 °C.

Solubility: sol water: (w/w) 10.7% at 0 °C, 10.9% at 20 °C, 14.8% at 100 °C; pH of 1.0 N soln. about 14; slightly sol ethanol.

Form Supplied in: the commercially available material is the monohydrate: small, white monoclinic crystals.

Handling, Storage, and Precautions: corrosive. Harmful if swallowed, inhaled, or absorbed through skin. Toxicity in rat: LD_{50} 365 mg kg^{-1} (oral dose). Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin. Inhalation may be fatal; do not breathe dust. Avoid contact with eyes, skin, and clothing. Incompatible with strong oxidizing agents and strong acids. Absorbs moisture and CO_2 from air. Hygroscopic; store in a cool dry place. Wash thoroughly after handling.

Hydrolysis of Esters.

The methyl ester of the 9,11-azo analog of prostaglandin endoperoxide PGH_2 (**1**) was hydrolyzed under mild conditions using 0.15 N LiOH in 2.5:1 THF-H_2O at 0 °C for 2.5 h to give the 9,11-azo analog of PGH_2 (**2**) in 99% isolated yield (eq 1).[1]

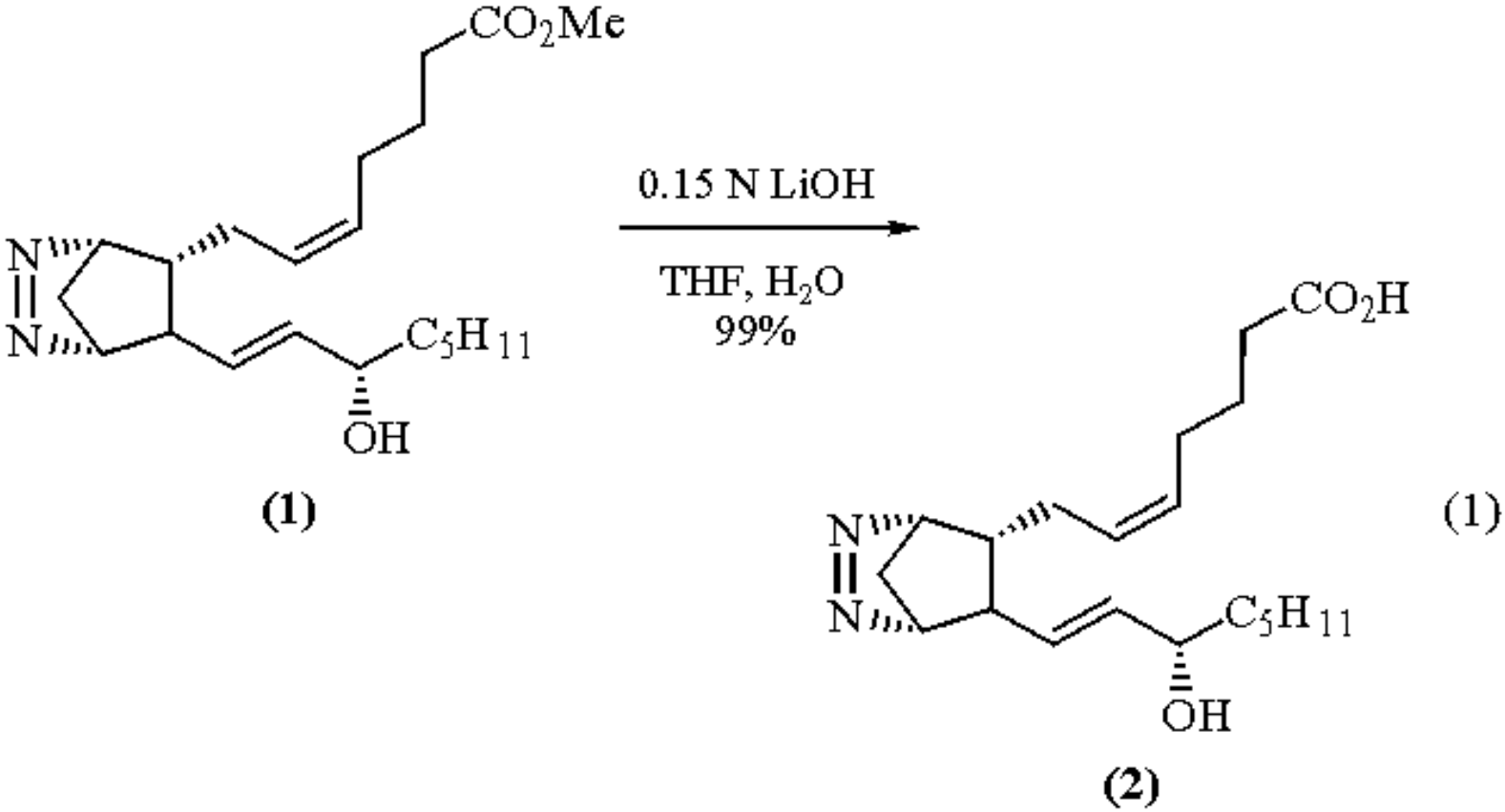

Hydrolysis of Urethanes to Alcohols.

The *p*-phenylphenylcarbamoyl group served as a protecting group for the C-11 alcohol and also as a directing group to control the stereochemistry of the carbonyl reduction at C-15 in the synthesis of the prostaglandin synthon (**3**). This protecting group was removed following the ketone reduction by treating (**3**) with 1 M aq LiOH at 120 °C for 72 h to afford (**4**) in >90% yield.[2]

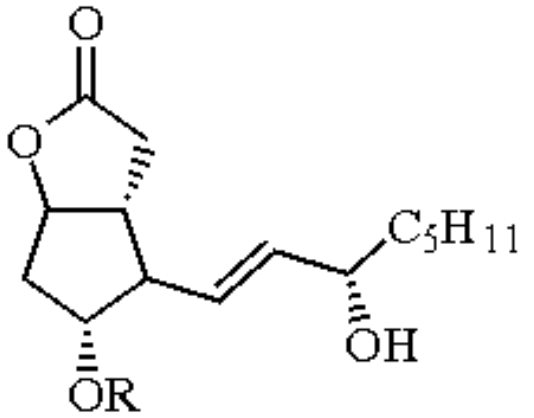

(3) R = *p*-PhC$_6$H$_4$NHCO-
(4) R = H

Hydrolysis of Bile Acid Methyl Esters.

Bile acid methyl esters were hydrolyzed under mild conditions with LiOH in aq. methanol at 25 °C to the bile acids. This procedure gave higher yields (80-98%) compared to conventional ***Sodium Hydroxide*** or ***Potassium Hydroxide*** hydrolysis reactions (48-55%). The procedure caused no racemization or elimination side reactions, e.g. (23*R*)-methyl 3α,7α,23α-trihydroxy-5β-cholan-24-oate (**5**) gave the corresponding acid (**6**) in 96% isolated yield (eq 2).[3]

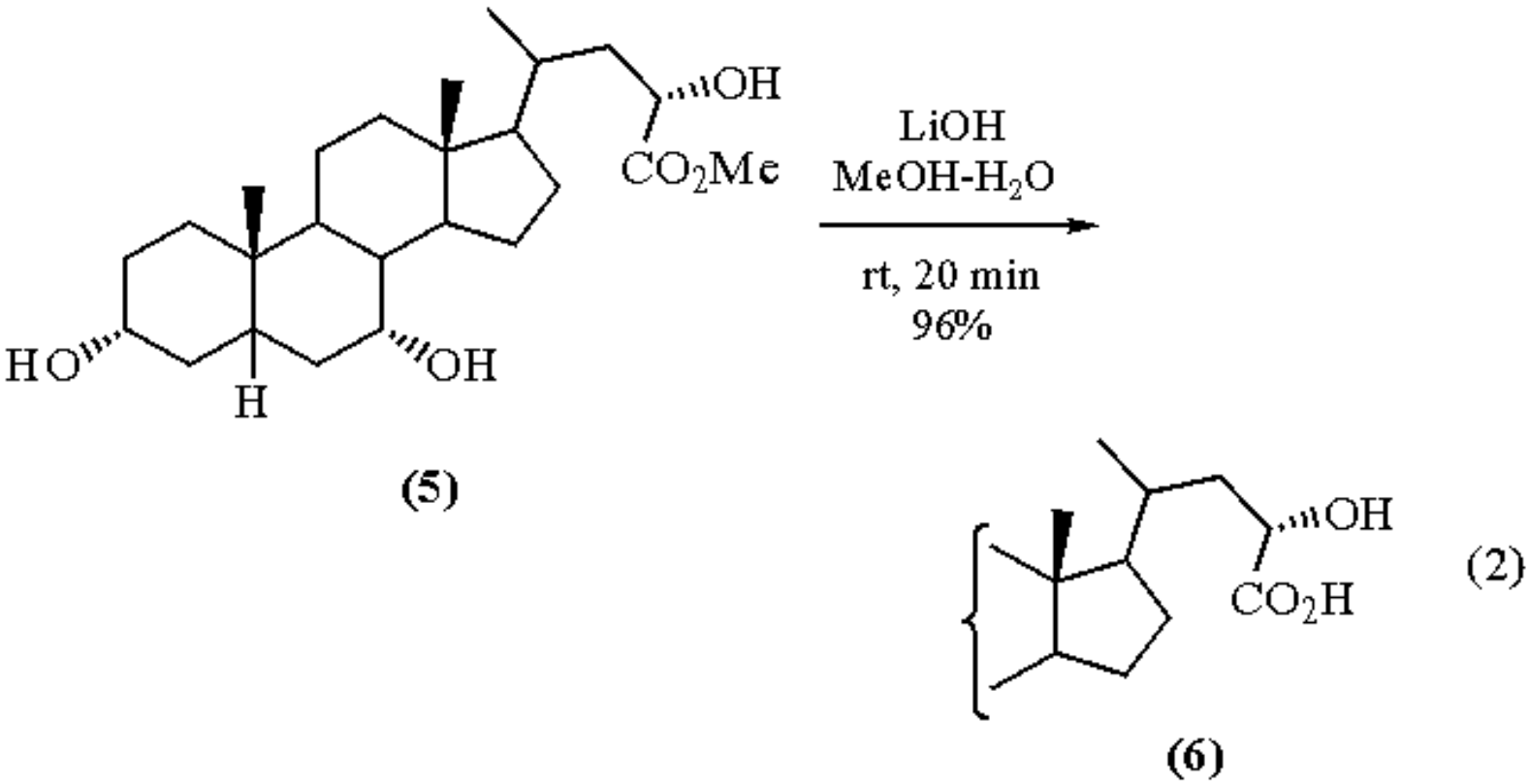

Hydrolysis of *N*-Boc Lactams and *N*-Boc Secondary Amides.

N-Boc derivatives of lactams were regioselectively hydrolyzed with LiOH in aq. THF to the corresponding o-amino acids. For example, *N*-Boc valerolactam was hydrolyzed with 3.0 equiv of LiOH in aq. THF at rt to give the *N*-Boc-δ-aminovaleric acid in 90% yield (eq 3). The reaction conditions are very mild and provide the o-amino group in a protected form, thus permitting further elaboration of the carboxylic acid residue. The procedure was applied successfully to the hydrolysis of *N*-Boc secondary amides to the corresponding acids.[4]

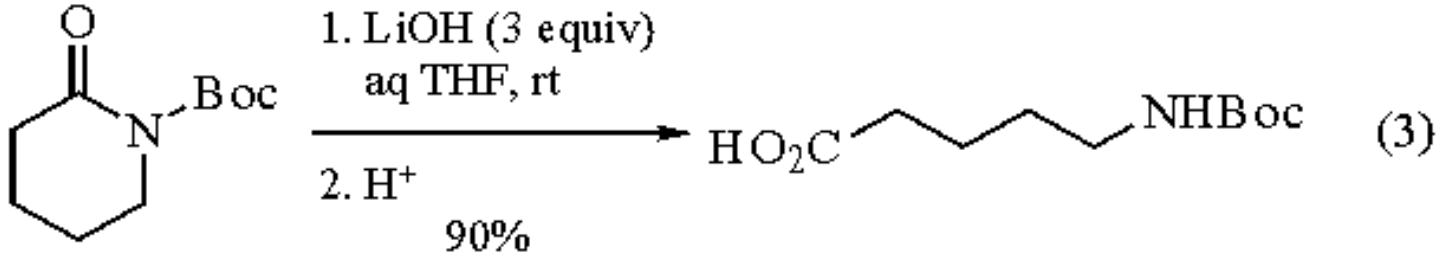

Cleavage of 2-Oxazolidinone Chiral Auxiliaries.

The hydrolysis of the *N*-(α-azidoacyl)- and *N*-[α-((+)-MTPA-amino)acyl]-2-oxazolidinone derivatives (**7**) with LiOH (2 equiv) in THF-H_2O (3:1) for 30 min at 0 °C afforded the corresponding α-amino acid synthons (**8**) in 95-100% yields (eq 4). No detectable racemization was observed when R = Bn and about 1% racemization occurred with the phenylglycine synthons (R = Ph).[5]

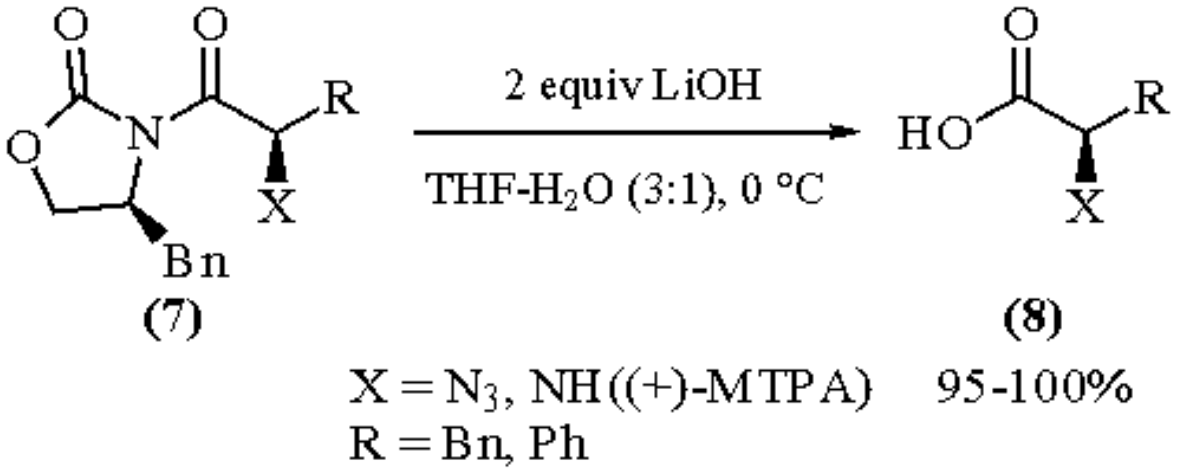

(4)

Regioselective Hydrolysis of Carboximide Derivatives.

The regioselective hydrolysis of the carboximide derivative (**9**) was achieved with excess 2 N aq LiOH in dioxane at rt overnight to give the desired β-hydroxy-α-amino acid (**10**) and a byproduct (**11**) (eq 5) in isolated yields of 83% and 17% respectively (a 5:1 ratio). The products (**10**) and (**11**) are the result of endocyclic and exocyclic carbonyl attack by the hydroxide ion, respectively. The success of this procedure was based on the selection of the sterically demanding *N*-protecting Boc group, which largely directed the regioselectivity of the attack by the hydroxide ion to the less hindered oxazolidinone carbonyl.[6]

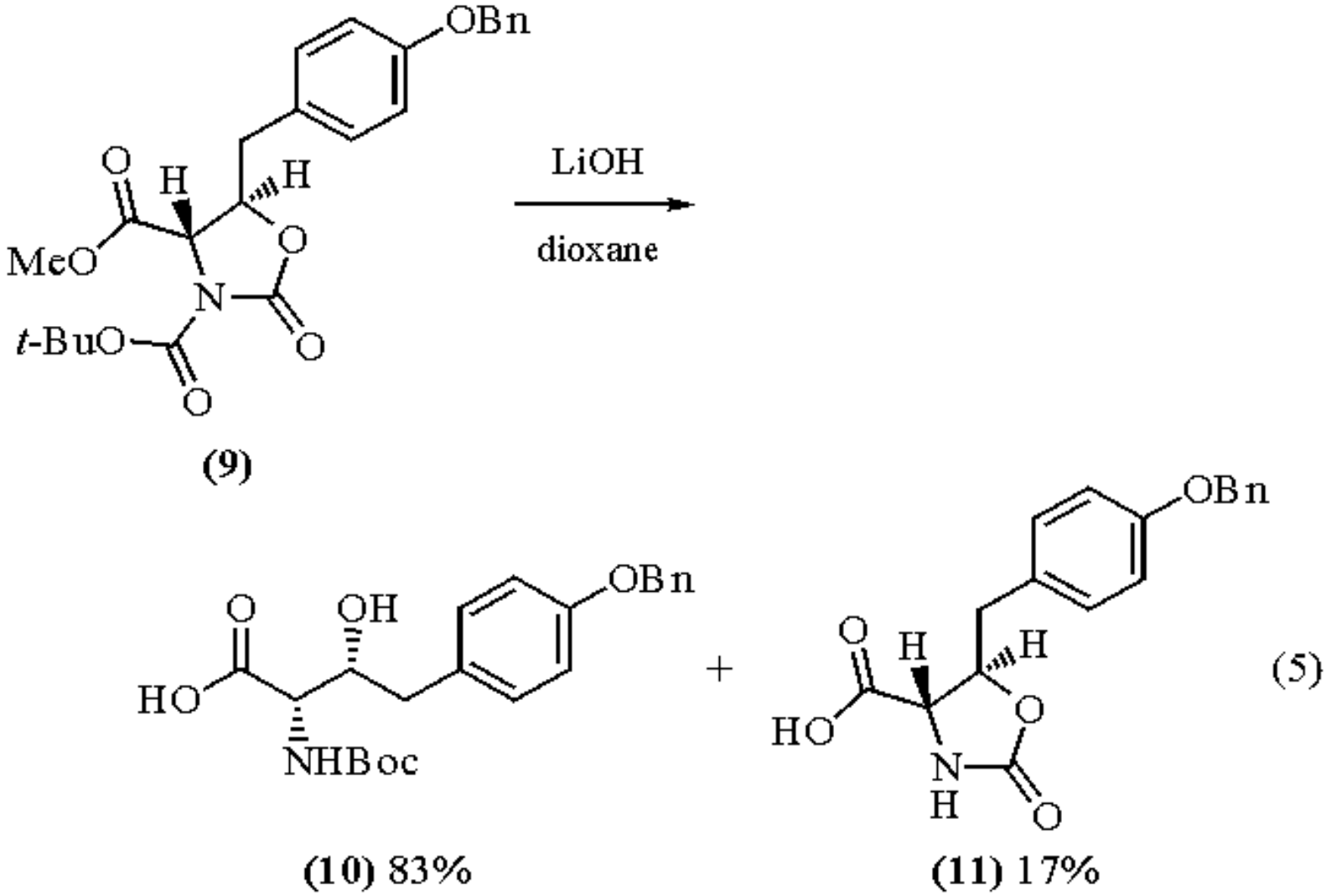

If, on the other hand, the hydrolysis was to be directed towards the exocyclic carbonyl of a highly branched *N*-acyl oxazolidinone derivative, a complementary procedure was developed employing lithium hydroperoxide to achieve that regioselectivity.[7]

Hydrolysis of *N*-Monosubstituted Amides via Acetoxypivalimides.

Hydrolysis of *N*-monosubstituted amides under mild conditions without epimerization at the α-position was accomplished in two steps. The amides (**12**) were first converted into the *N*-acetoxypivaloyl derivatives (**13**) (eq 6). These derivatives were then treated with LiOH in THF to give the carboxylic acids (**15**) in good yields. The procedure takes advantage of the easier hydrolysis of imides than amides and the intramolecular nucleophilic attack by the acetoxy oxygen on the imide carbonyl (eq 7) causing an *N*-*O* acyl migration to form the intermediate acyloxypivalamide (**14**). Further hydrolysis of (**14**) gave the desired carboxylic acids (**15**) and *N*-alkylhydroxypivalamides (**16**).[8]

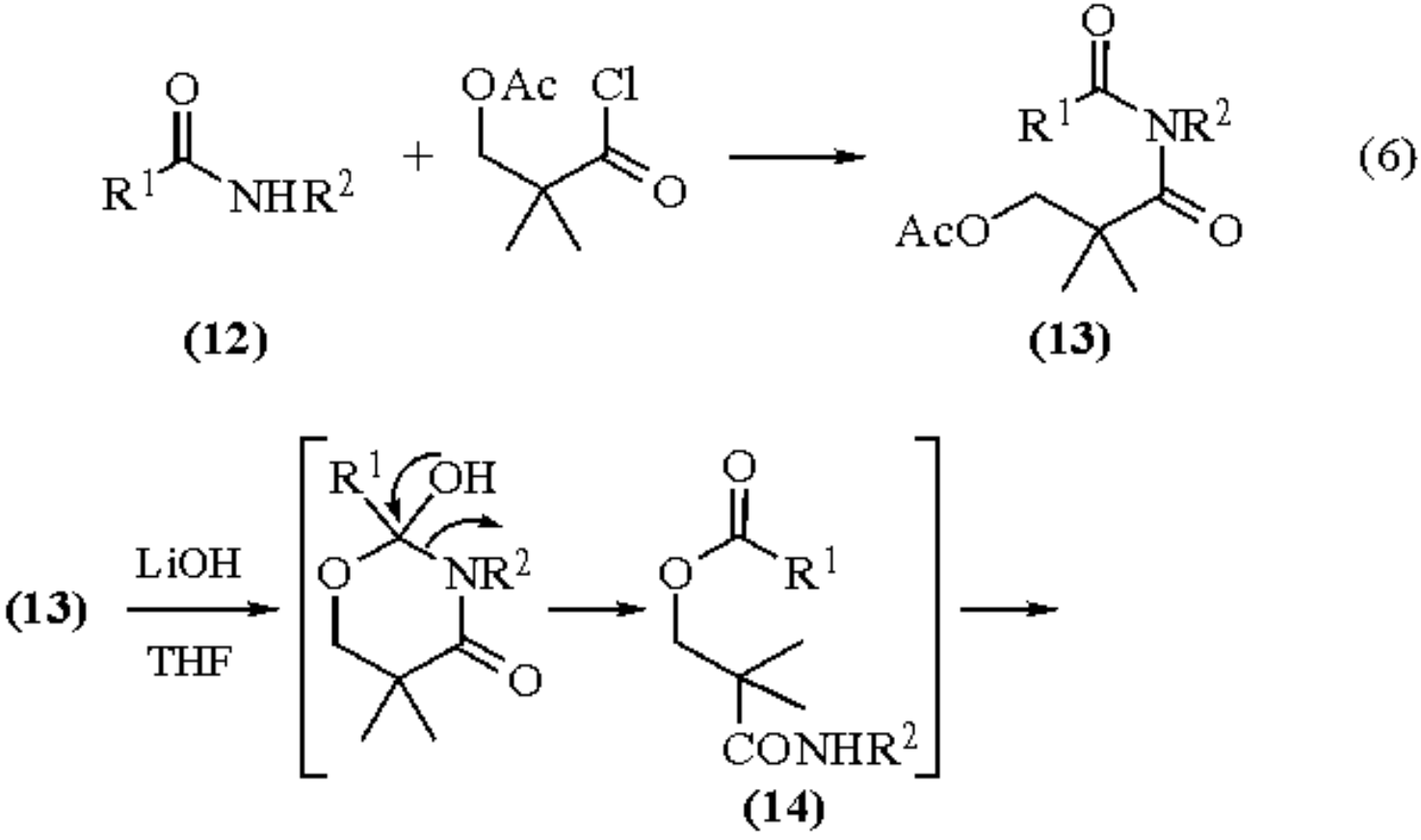

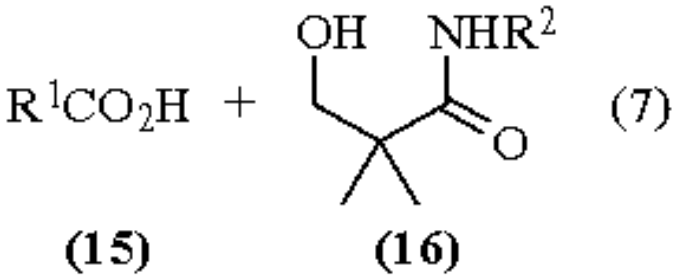

The method is mild enough to use with *N*-butyl-(2*S*,3*S*)-dimethyl-4-pentenamide to give (2*S*,3*S*)-dimethyl-4-pentenoic acid in 76% yield with practically no epimerization (eq 8).[8]

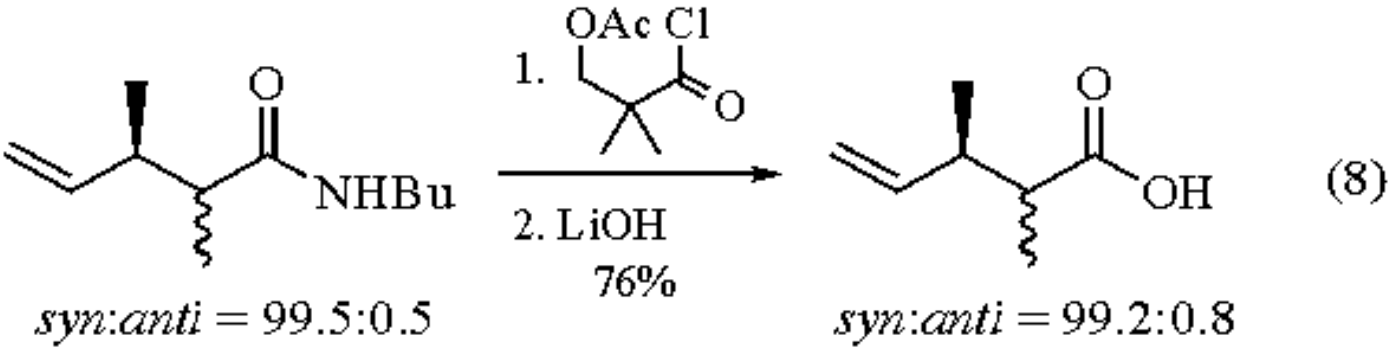

Selective *O*-Acetyl Hydrolysis of *N,O*-Diacetylhydroxamates.

Treatment of *N*-acetoxy-*N*-{1-[4-(phenylmethoxy)phenyl]ethyl}acetamide (**17**) with LiOH in 2:1 *i*-PrOH-H_2O selectively hydrolyzed the *O*-acetyl to give the hydroxamic acid (**18**) (eq 9). The procedure was described as part of a two-step conversion of hydroxylamines into hydroxamic acids.[9]

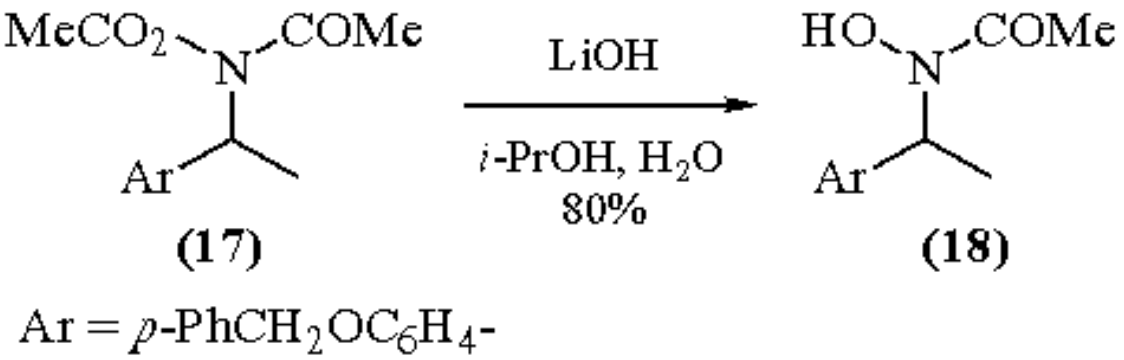

(9)

Selective *O*-Deacetylation in Carbohydrates.

The *O*-acetyl groups in the penta-*O*-acetyl tri-*N*-acyl disaccharide (**19**) (eq 10) were selectively hydrolyzed with 0.6 M LiOH for 1 h at rt to give, after purification and recrystallization, the pentahydroxy tri-*N*-acyl disaccharide (**20**) in 92% yield.[10]

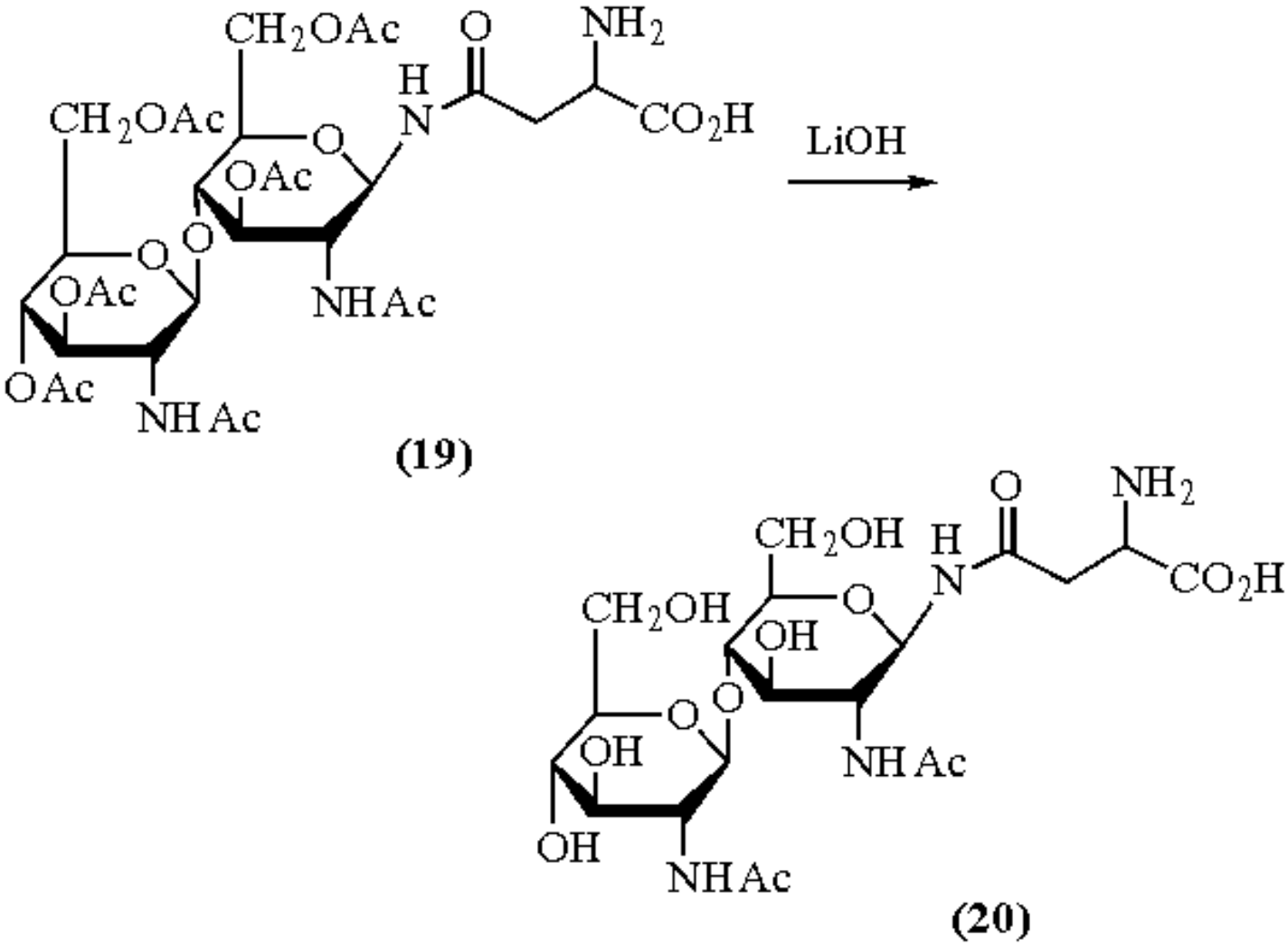

(10)

Dihydroquinoxalones from Ethyl Alkylglycidates.

The reactions of *o*-phenylenediamine with ethyl 2,3-epoxycrotonate (**21a**), ethyl 2,3-epoxypentenoate (**21b**), or ethyl 2,3-epoxy-3,3-dimethylacrylate (**21c**) were catalyzed by LiOH and gave the dihydroquinoxalones (**22a-c**) (eq 11). The initial nucleophilic attack occurred on the α-carbon of (**21**) followed by intramolecular aminolysis to give the cyclized product. When unsubstituted epoxyacrylates and cinnamates were used, the initial attack occurred on the β-carbon and gave the uncyclized hydroxyamino esters.[11]

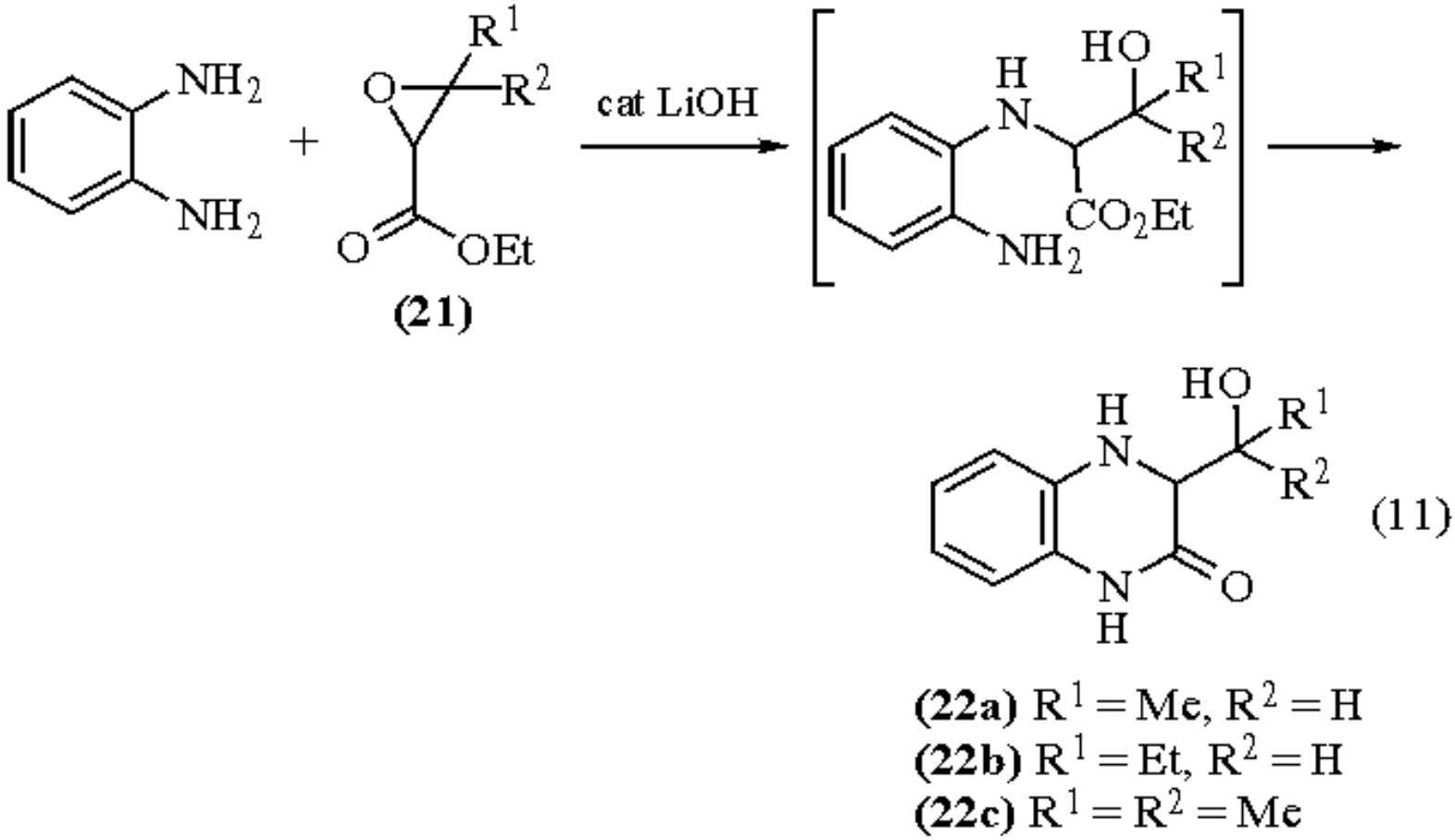

Synthesis of 3-Hydroxybenzo[*b*]thiophene-2-carboxylates.

Substituted methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylates (**24**) were prepared in yields ranging from 50 to 85% by the LiOH-catalyzed reaction of substituted methyl *o*-nitrobenzoates (**23**) and methyl thioglycolate in dry DMF (eq 12). Under the reaction conditions the activated nitro group was displaced by the thiolate anion, followed by cyclization.[12]

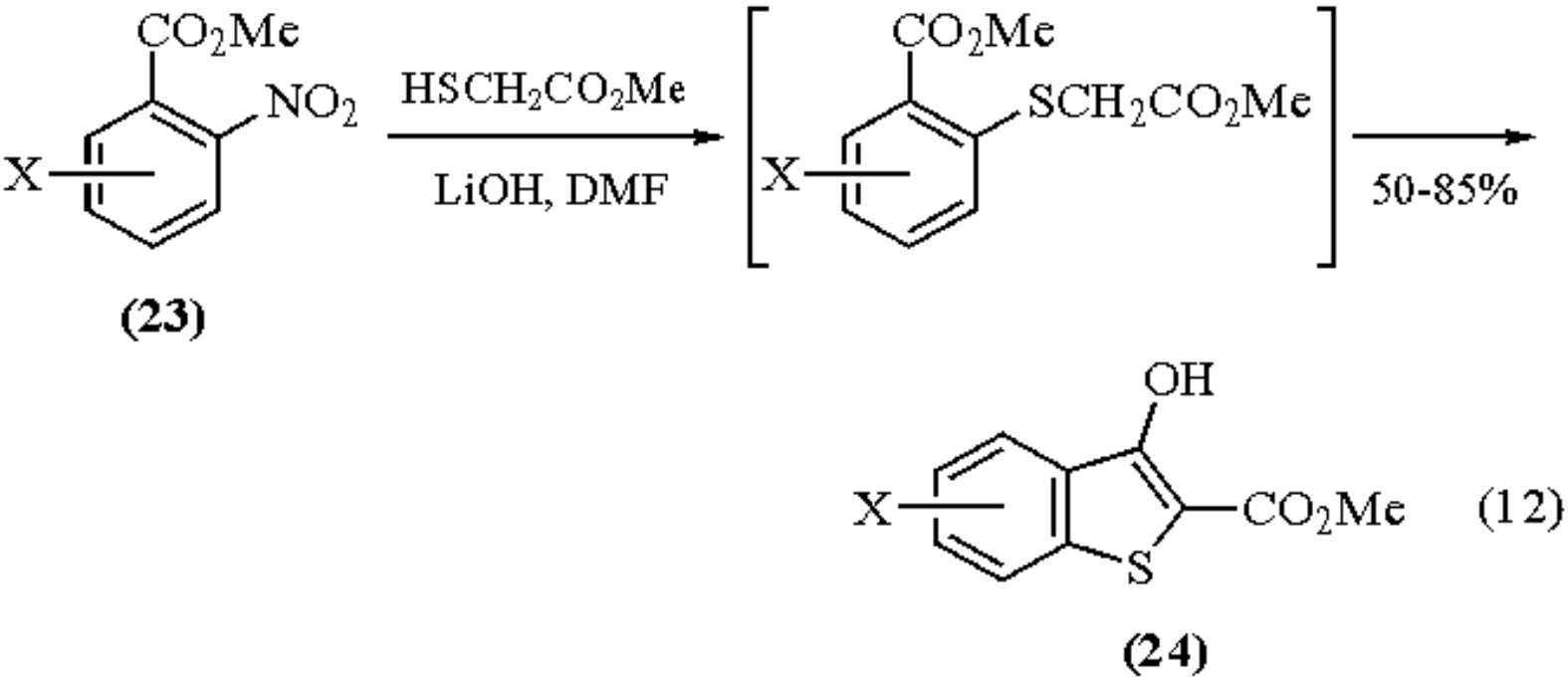

(12)

Stereochemical Control in Conversion of Diols to Epoxides.

The intermediate 22-tosyloxy-23-pivaloxy steroid (**25**) was prepared from the corresponding diol and then treated with LiOH in dioxane-H_2O at rt for 8 h to give the 22,23-epoxy steroid (**26**) in 92% yield (eq 13).[13]

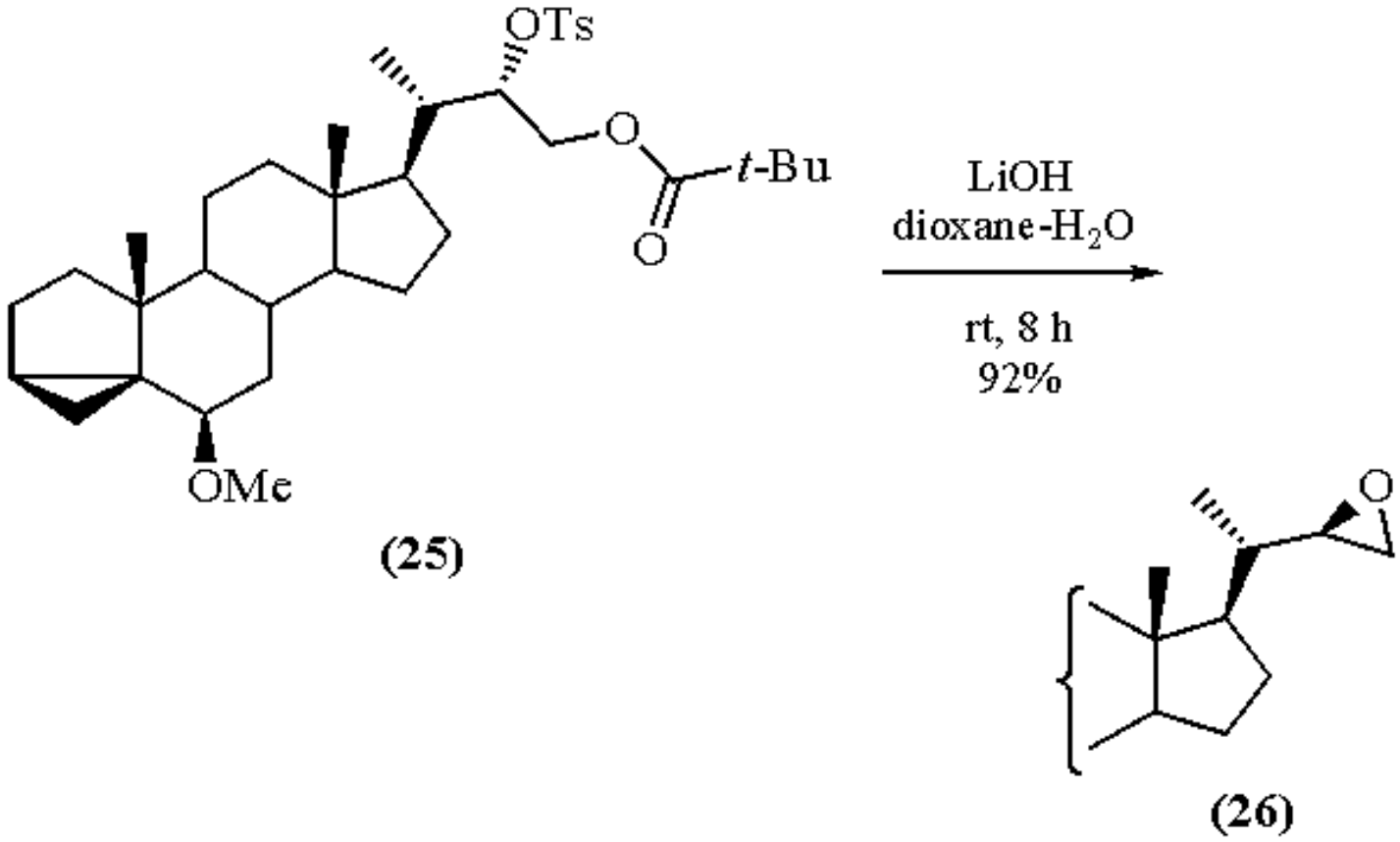

(13)

Oxetane Formation from 3,4-Epoxy Alcohols.

Treatment of the 3,4-epoxy alcohol (**27**) with LiOH, NaOH, or KOH in aq DMSO at 140-150 °C gave a mixture of the oxetane (**28**) in 49% yield and the 1,2,4-triol (**29**) in 32% yield (eq 14). Reaction times were 15, 45, and 90 min for LiOH, NaOH, and KOH, respectively. The procedure was presented as a nonphotochemical synthesis of oxetanes.[14]

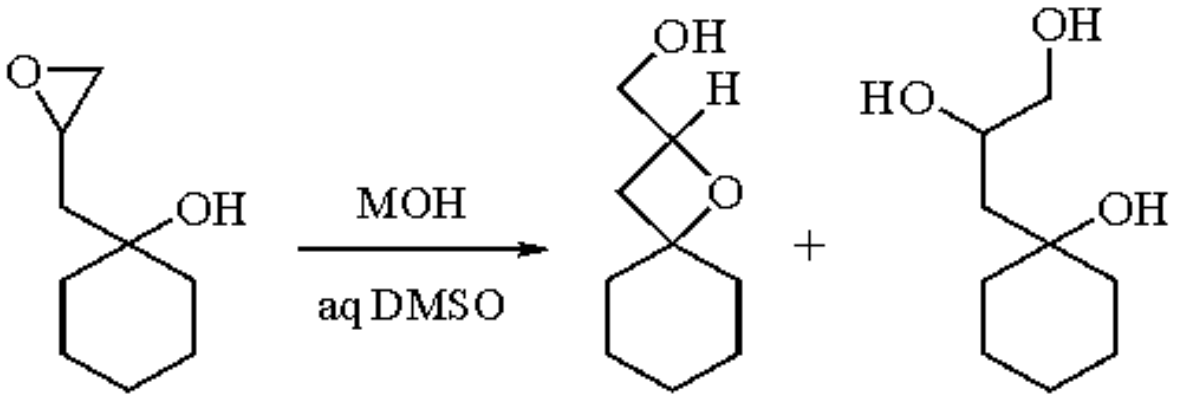

(14)

(27) **(28)** **(29)**

M = Li, Na or K

Formation of *trans*-Hydrindanones.

Treatment of 8-oxo-2-methyl-6-nonenal (**30**) with LiOH in MeOH gave a 4:1 mixture of *trans*- and *cis*-hydroxyhydrindanones (**32**). The reaction proceeded via consecutive intramolecular Michael and aldol addition reactions. The stereochemical control was greatly improved by using the better chelating Zr^{IV} *n*-propoxide in benzene to effect the initial Michael addition, yielding the monocyclic ketoaldehyde (**31**), and then adding LiOH/MeOH to effect the aldol addition step (eq 15). This modification gave the desired hydroxyhydrindanone (**32**) in 90% yield as a 40:1 mixture of the *trans* and *cis* isomers.[15]

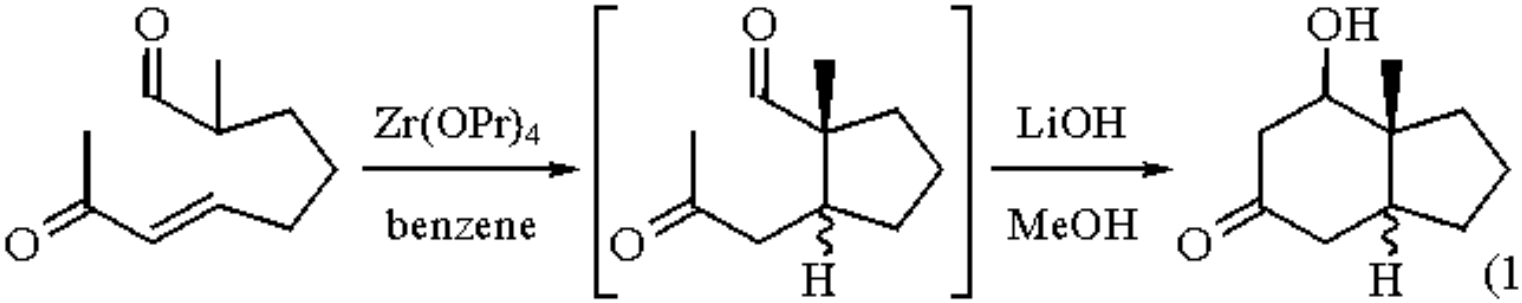

(15)

(30) **(31)** **(32)**

trans:*cis* = 40:1

Synthesis of 1-Deoxy-D-*erythro*-2-pentulose.

Treatment of a solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**33**) in ether with an aq. soln. of LiOH and vigorously stirring the two-phase system at 20 °C for 16 h gave 3,5-*O*-benzylidene-1-deoxyketo-D-*erythro*-2-pentulose (**34**) in 55% isolated yield (eq 16).[16]

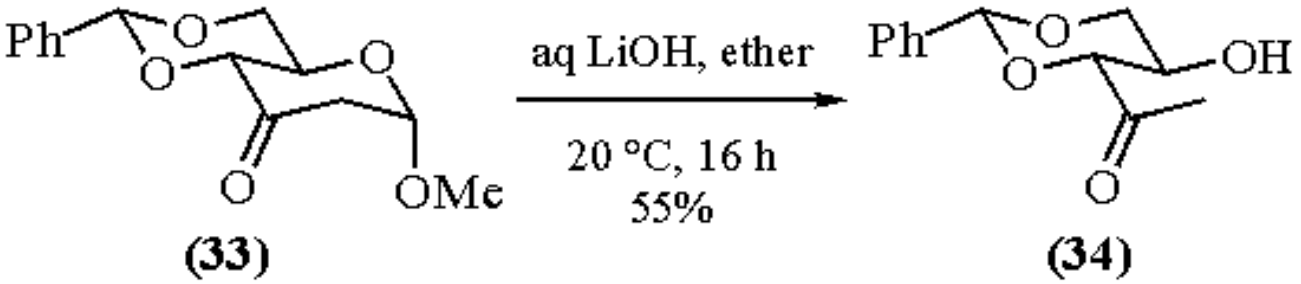

(16)

Conversion of Mixed Phosphoric Acid Triesters to Mixed Phosphoric Acid Diesters.

In a three-step sequence for the conversion of bis(*p*-nitrophenyl) hydrogen phosphate to dialkyl phosphates (**36**), the intermediate dialkyl *p*-nitrophenyl phosphates (**35**) were selectively hydrolyzed with 1N LiOH in acetonitrile at rt to give the desired dialkyl phosphates under mild conditions (eq 17). Various mixed dialkyl phosphates were prepared in good overall yields without isolation of any synthetic intermediate.[17]

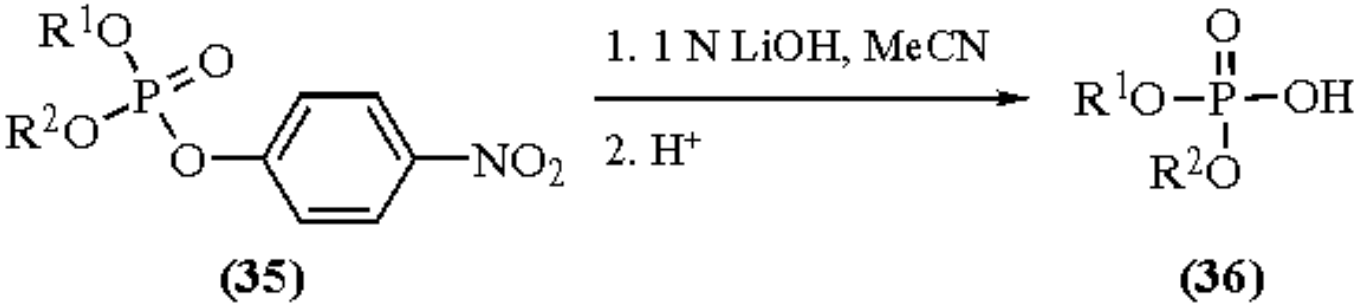

(17)

R^1	R^2	overall yield
$Ph(CH_2)_2$	$MeO(CH_2)_2$	80%
$Ph(CH_2)_2$	≡—CH_2	76%
$MeO(CH_2)_2$	≡—CH_2	75%

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Lithium Iodide[1]

LiI

[10377-51-2] · ILi · Lithium Iodide · (MW 133.84)

(ester cleavage and decarboxylation;[2] source of nucleophilic iodide;[3] mild Lewis acid;[1] salt effects in organometallic reactions;[1] epoxide opening[4])

Physical Data: mp 449 °C; bp 1180 °C; *d* 4.076 g cm^{-3}.

Solubility: 165 g/100 mL H_2O (20 °C); 433 g/100 mL H_2O (80 °C); 251 g/100 mL EtOH (20 °C); 343 g/100 mL MeOH (20 °C); 43 g/100 mL acetone (18 °C); very sol NH_4OH.

Form Supplied in: anhydrous white solid or as the hydrate.

Preparative Methods: the anhydrous salt of high purity can be prepared from lithium hydride and iodine in ether.[5]

Purification: crystallized from hot H_2O (0.5 mL g^{-1}) by cooling in $CaCl_2$-ice or from acetone. LiI is dried for 2 h at 120 °C (0.1 mmHg, P_2O_5) before use.

Handling, Storage, and Precautions: for best results, LiI should be dried prior to use in anhydrous reactions.

Heterolytic C-X Bond Cleaving Reactions.

In the presence of amine bases, LiI has been extensively used as a mild reagent for the chemoselective cleavage of methyl esters (eq 1).[6] Decarboxylation of methyl esters usually occurs when an electron-withdrawing group is present at the α-position of the ester (eq 2).[7] Ester-type glycosyl linkages of acidic tri- and diterpenes can also be selectively cleaved under these conditions.[8] Aryl methyl ethers can be demethylated to afford the corresponding phenols upon heating with LiI and *s*-collidine.[9]

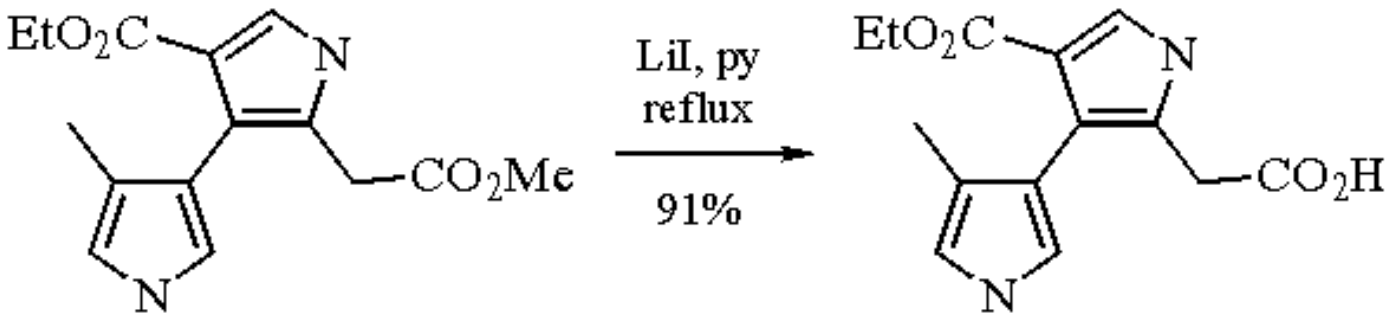

(1)

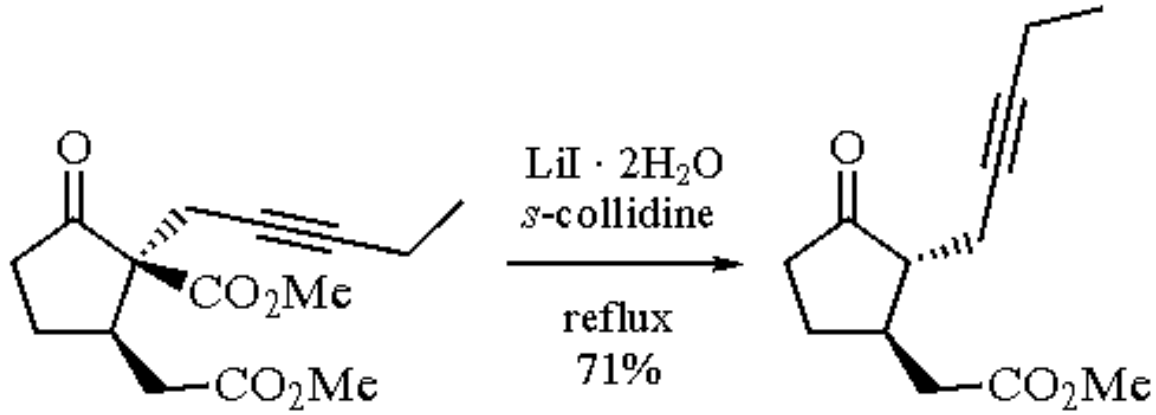

(2)

1,2-Oxiranes are readily opened by LiI and a Lewis acid to produce iodohydrins (eq 3).[4] Conversely, 1-oxaspiro[2.2]pentanes and 1-oxaspiro[3.2]hexanes give rise to bond migration products.[10] β-Vinyl-β-propiolactone is efficiently opened by LiI to produce the corresponding substituted allyl iodide (eq 4).[11]

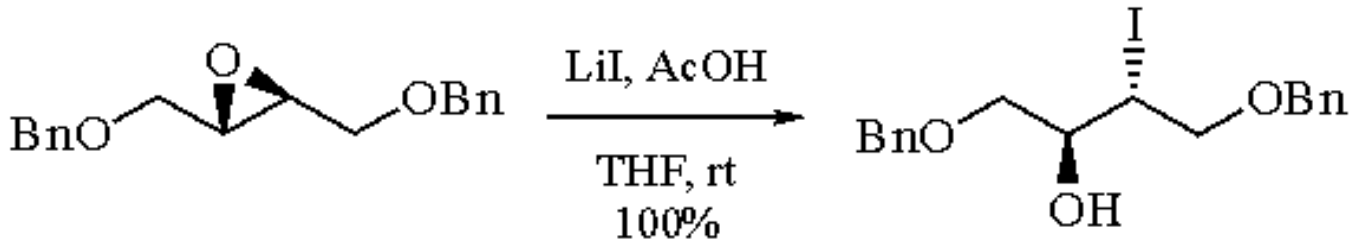

(3)

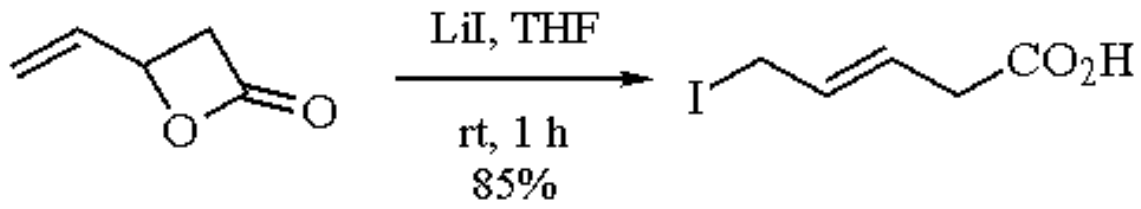

(4)

Alkyl and Alkenyl Iodides.

LiI has been used as a source of iodide in nucleophilic substitution and addition reactions. Primary alcohols have been directly converted to alkyl iodides upon treatment with a mixture of ***Triphenylphosphine***, ***Diethyl Azodicarboxylate***, and LiI.[3] Tertiary alcohols can be converted into tertiary alkyl iodides upon treatment with ***Hydrogen Iodide*** in the presence of LiI.[12]

(*Z*)-3-Iodopropenoates and -propenoic acids have been synthesized stereoselectively by the reaction of LiI and

propiolates or propiolic acid.[13]

C-C Bond Forming Reactions.

LiI was shown to efficiently catalyze the Michael addition of β-dicarbonyl compounds,[14] and the intramolecular allylsilane addition to imines to produce 4-methylenepiperidine derivatives (eq 5).[15]

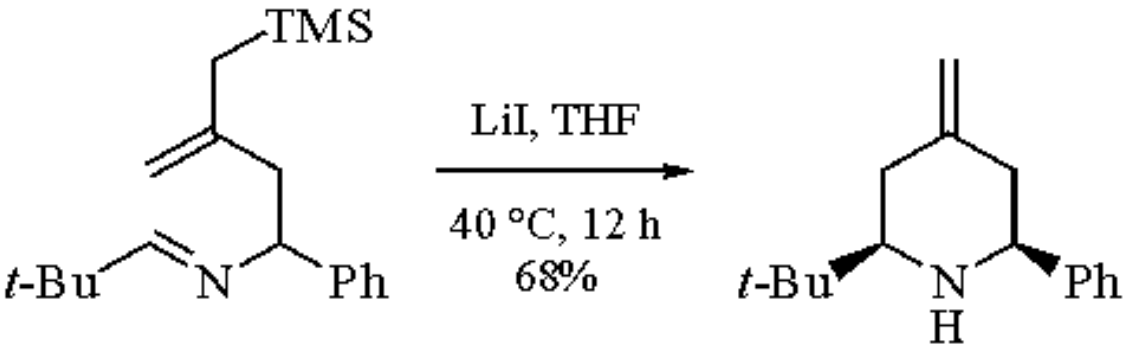

(5)

LiI as an Additive for Organometallic-Mediated Transformations.[16]

The *syn*/*anti* selectivity in the reduction of β-alkoxy ketones is drastically increased by the addition of LiI (eq 6).[17]

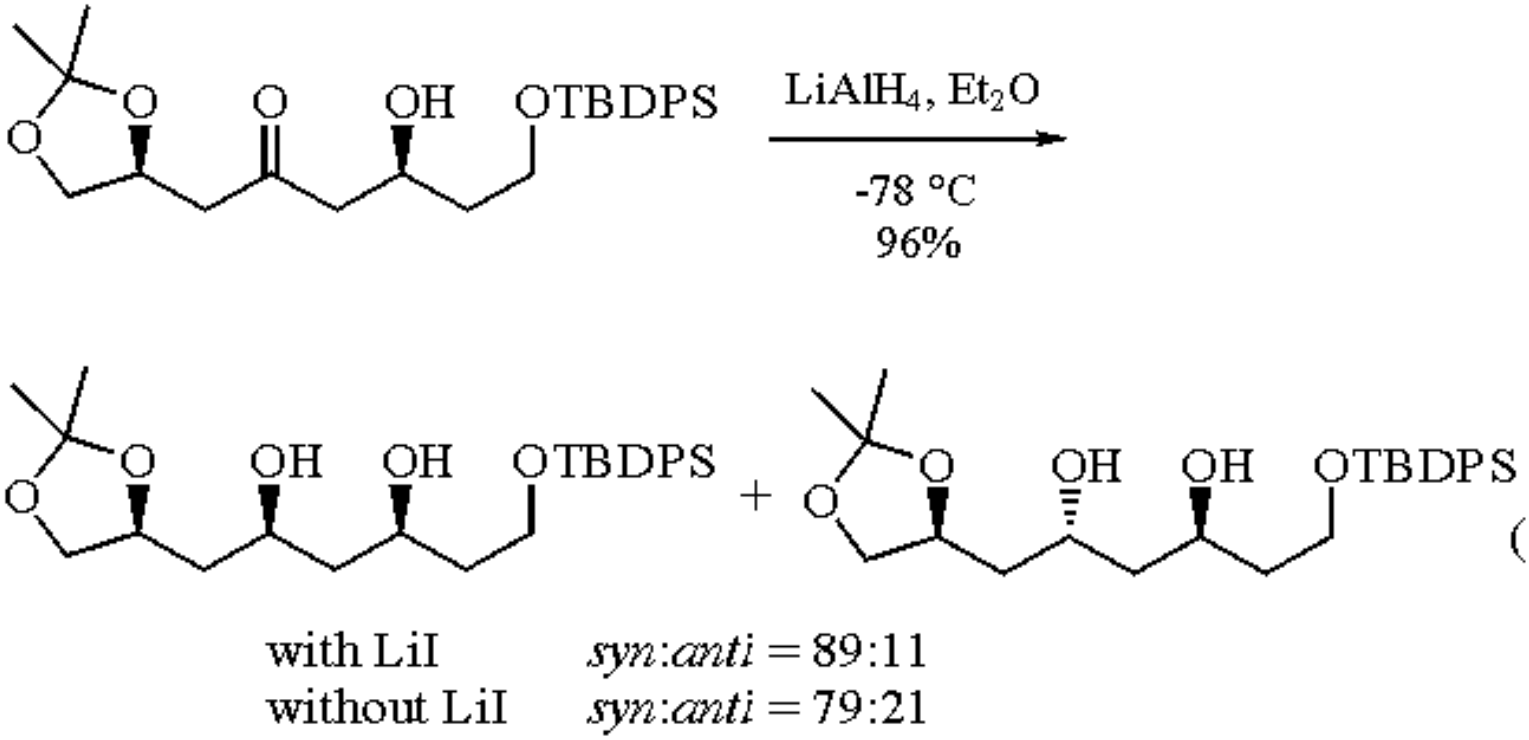

(6)

The addition of ***Lithium Bromide*** and LiI was shown to enhance the rate of organozinc formation from primary alkyl chlorides, sulfonates, and phosphonates, and zinc dust.[18] Beneficial effects of LiI addition have also been reported for Heck-type coupling reactions[19] and in conjugate addition to chiral vinyl sulfoximines.[20]

The (*E*)/(*Z*) alkenic ratio in Wittig-type alkenations was shown to be dependent on the amount of Li salt present.[21]

Reduction of α-Alkoxycarbonyl Derivatives.

α-Halo ketones are reduced to the corresponding ketones upon treatment with a mixture of LiI and ***Boron Trifluoride Etherate***.[22]

---

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Lithium 2-Lithiobenzenethiolate

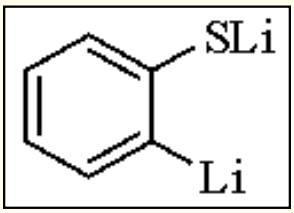

[117526-82-6] · $C_6H_4Li_2S$ · Lithium 2-Lithiobenzenethiolate · (MW 122.05)

(reagent for preparation of *ortho*-substituted thiophenols[1])

Preparative Methods: easily prepared in the form of a white viscous slurry by stirring ***Thiophenol*** with 2 equiv ***n-Butyllithium*** and 2 equiv ***N,N,N´,N´-Tetramethylethylenediamine*** in dry cyclohexane in a nitrogen atmosphere for 20 h.[1] No purification of the crude product is generally required. It is stable in the absence of air and moisture.

Handling, Storage, and Precautions: the title reagent (**1**) is best made as needed and should be handled and stored under nitrogen in a fume hood. Both preparation and decomposition of (**1**) on exposure to moisture release the foul smelling, toxic thiophenol. Great care should be taken in disposing of (**1**) and cleaning apparatus exposed to (**1**). Excess thiophenol or reagent (**1**) should be destroyed in a good fume hood using an oxidizing agent such as sodium hypochlorite solution (see ***Thiophenol***).

Reaction with Electrophiles.

Diverse thiophenols can be prepared by trapping 2-LiC_6H_4SLi (**1**) with various electrophiles, as illustrated in eq 1 and Table 1.

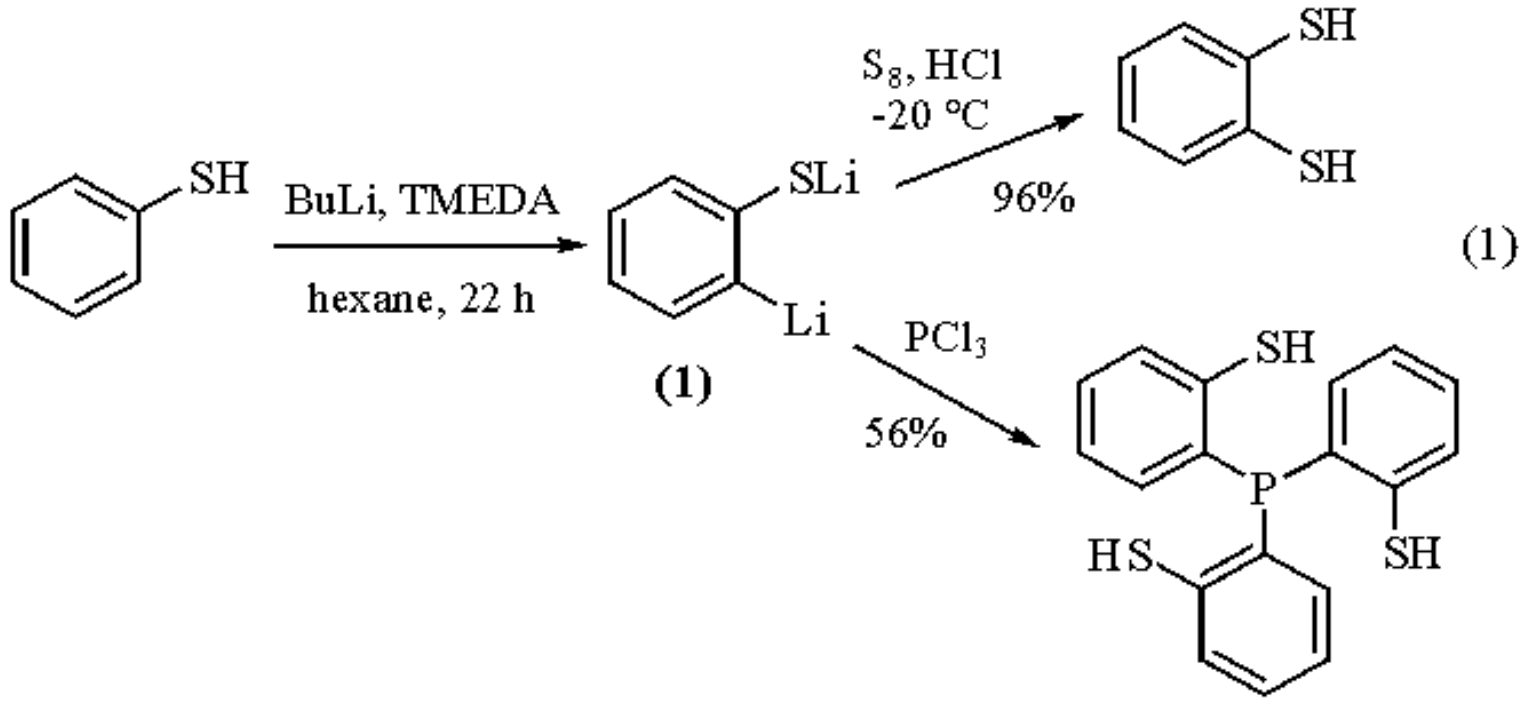

Table 1 Thiophenols formed by Reaction of Lithium 2-Lithiobenzenethiolate with Electrophiles

Electrophile	Product	Yield (%)	Ref.
D_2O	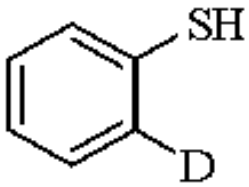	97	1a
S_8	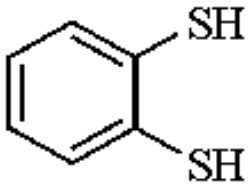	96	1b
$[i\text{-}Pr_2NC(S)S]_2$	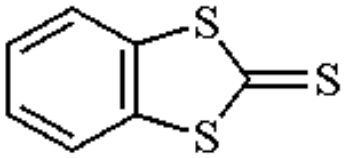	67	1c
CO_2	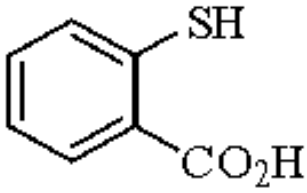	61	1a

Me_2CO			61	1a
R_3SiCl	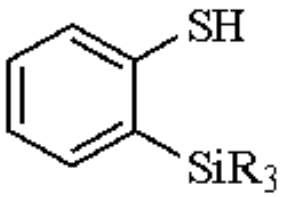	R = Me R = Et R = Ph R = *t*-BuMe$_2$	92 79 43 28	1b, c
Me_2SiCl_2	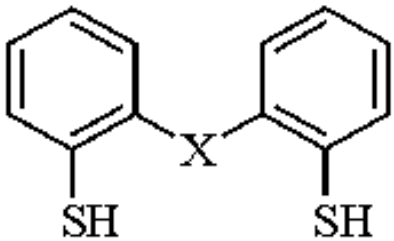	X = $SiMe_2$ X = $[SiMe_2]_2$ X = $[SiMe_2$-$CH_2]_2$	44 40 33	1b
Ph_2XCl	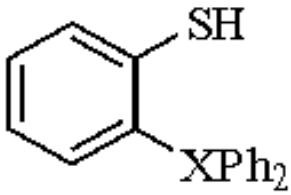	X = P X = P=O	65 67	6
$PhXCl_2$	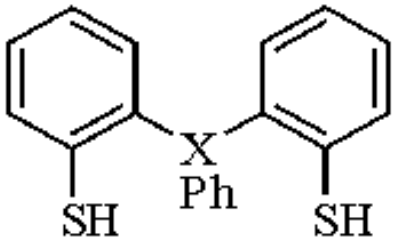	X = P X = P=O	76 63	6
XCl_3	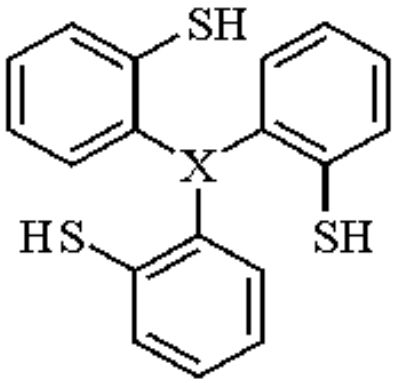	X = P X = P=O X = SiH	56 67 11	6, 4

DMF, $MeCOCH_2Cl$ 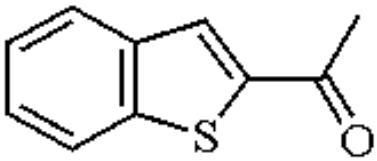 75 9

If 2-LiC_6H_4SLi is treated with elemental sulfur[1b] followed by acid,[5] 1,2-benzenedithiol is formed in 96% yield. 1,2,3-Benzenetrithiol can be prepared in 35% yield by extension of this procedure.[1b] This reaction represents the method of choice to prepare 1,2-benzenedithiol. If 2-LiC_6H_4SLi is coupled with chlorophosphines or phosphonic chlorides, a variety of 2-phosphino- or 2-phosphinylbenzenethiols results.[6] These two classes of compounds have utility as multidentate ligands for metals such as Ni,[7a] Os,[7b] and Tc[7c] and have been used in the synthesis of a cyclophane phosphine.[7] With ***Chlorotrimethylsilane***, chlorotriethylsilane, chlorotriphenylsilane, and chloro(*t*-butyl)dimethylsilane, the products were the corresponding 2-[tris(organosilyl)]benzenethiols in 92, 79, 43, and 28% yields, respectively.[1b] Multiple silylation could be used to prepare 2,6-bis(trimethylsilyl)benzenethiol in 55% overall yield from 2-LiC_6H_4SLi. With dichlorosilanes or dichlorodisilanes, various bis(thiophenols) could be prepared.[1b] These thiophenols are useful as hindered ligands.[2,3] Through reaction of 2-LiC_6H_4SLi with ***Trichlorosilane***, a novel cyclophane silane was prepared.[4]

This procedure can be used with substituted thiophenols,[1b] with 2-naphthalenethiol,[1b] and with 2-mercaptopyridine.[8] 2-Acetylbenzo[*b*]thiophene, a key intermediate in the synthesis of the 5-lipoxygenase inhibitor zileuton, has been prepared in 75% overall yield from thiophenol via condensation of lithium 2-lithiobenzenethiolate with DMF followed by chloroacetone (eq 2).[9] If 0.5 equiv of iodine is used instead of chloroacetone, the product is 2,2´-dithiobisbenzaldehyde, a stable precursor to 2-mercaptobenzaldehyde.[9]

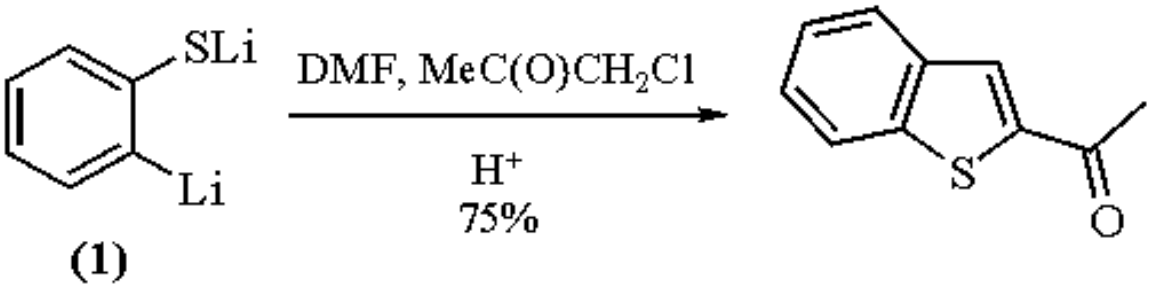

1. (a) Figuly, G. D.; Loop, C. K.; Martin, J. C. *JACS* **1989**, *111*, 654. (b) Block, E.; Eswarakrishnan, V.; Gernon, M.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *JACS* **1989**, *111*, 658. (c) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *JACS* **1989**, *111*, 665.
2. (a) Block, E.; Kang, H.; Ofori-Okai, G.; Zubieta, J. *ICA* **1989**, *156*, 27. (b) Block, E.; Kang, H.; Ofori-Okai, G.; Zubieta, J. *ICA* **1990**, *167*, 147.
3. (a) Block, E.; Gernon, M.; Kang, H.; Ofori-Okai, G.; Zubieta, J. *IC* **1989**, *28*, 1263. (b) Block, E.; Brito, M.; Gernon, M.; McGowty, D.; Kang, H.; Zubieta, J. *IC* **1990**, *29*, 3172.
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6. Block, E.; Ofori-Okai, G.; Zubieta, J. *JACS* **1989**, *111*, 2327.
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9. Basha, A.; Brooks, D. W. *JOC* **1993**, *58*, 1293.

Lithium 2-Lithiomethyl-2-propenolate[1]

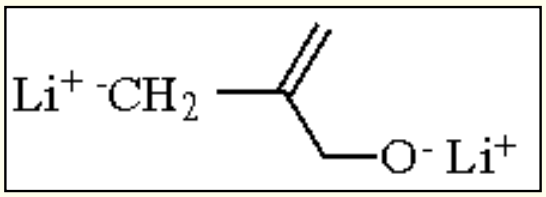

[-] · $C_4H_6Li_2O$ · Lithium 2-Lithiomethyl-2-propenolate · (MW 83.98)

(nucleophilic reagent for the generation of functionalized isoprenoid compounds through alkylation or addition reactions)

Physical Data: gold colored solid.

Solubility: insol hexane.

Preparative Methods: metalation of methallyl alcohol with ***n-Butyllithium-Potassium t-Butoxide***.

Handling, Storage, and Precautions: air, water, and temperature (greater than 0 °C) sensitive.

The allylic dianion is prepared by the action of *t*-BuOK/*n*-BuLi (i.e. Schlosser's base) in hexane on methallyl alcohol.[1] The active reagent is formed immediately upon the completion of the alcohol addition (0 °C). The yield of allylic anion formed appears to be extremely sensitive to reaction conditions (e.g. fresh *n*-BuLi,[1] solvent[2]).

The methallyl alcohol dianion can be alkylated with alkyl halides (eq 1)[3] or epoxides (eq 2),[4] silylated (eq 3),[2,5] or undergo addition reactions with aldehydes or ketones (eq 4).[1] This carbon-carbon bond-forming process introduces a functionalized isoprenoid unit.

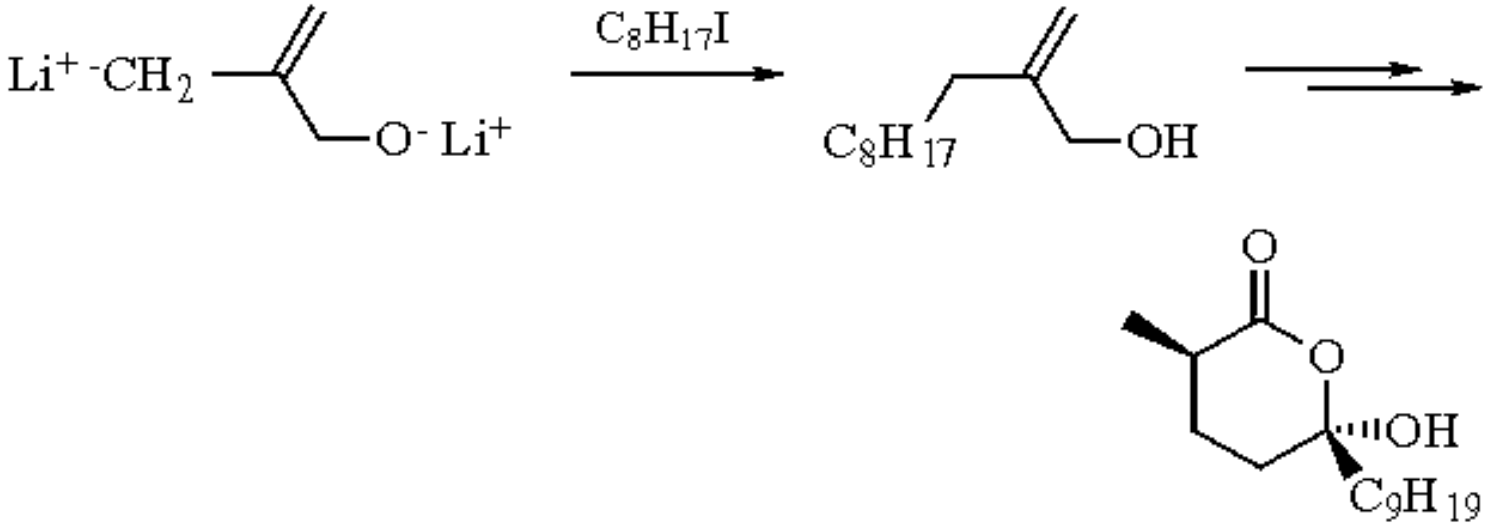

(1)

Malynolide

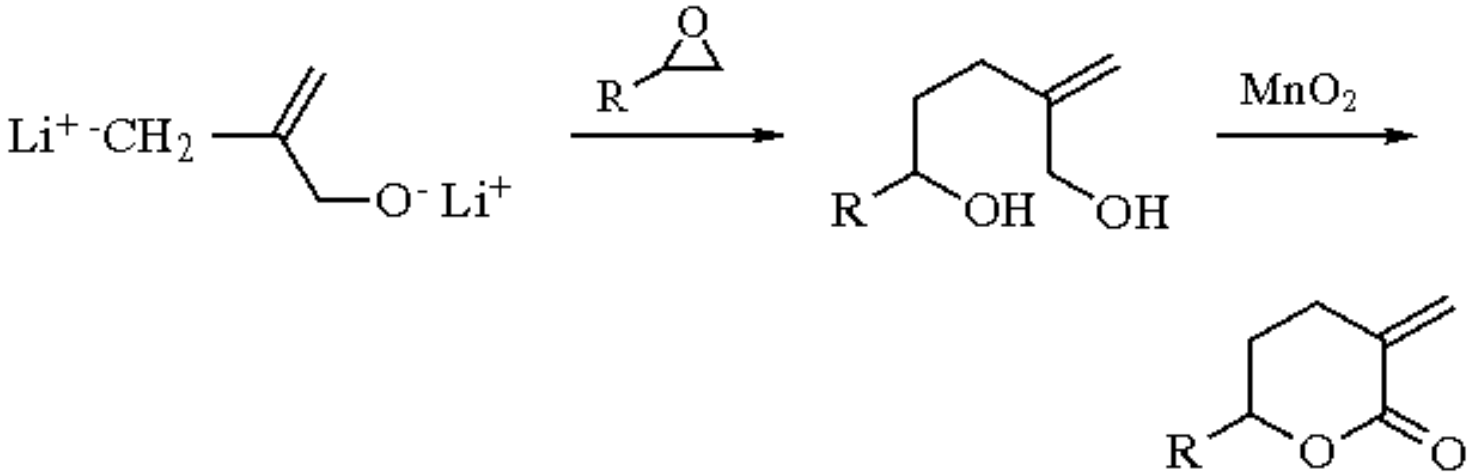

(2)

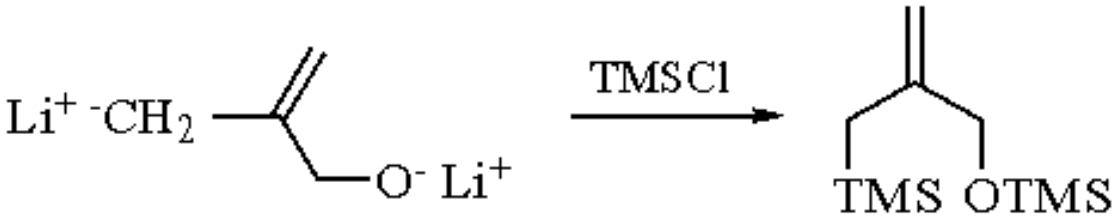

(3)

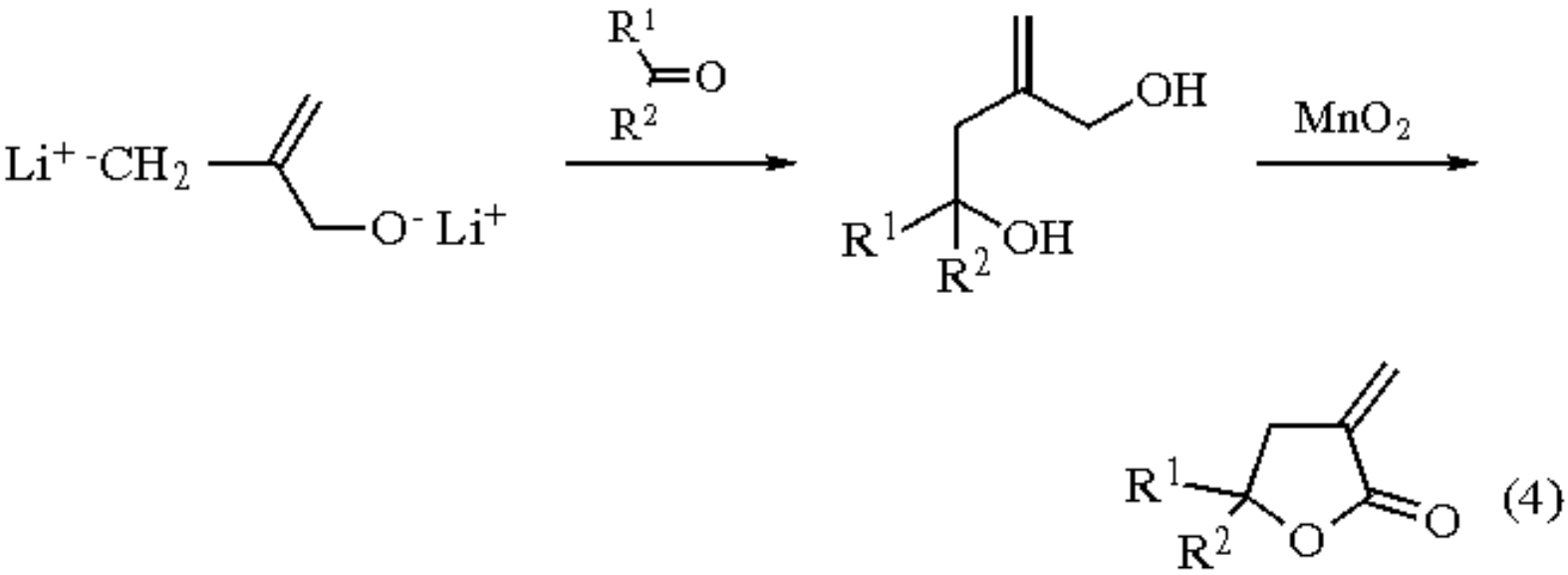

Related Reagents.

A similar transformation is observed with 2-ethylallyl alcohol derived from commercially available 2-ethylacrolein (eq 5). The observed addition products are mixtures of 1,4-diols derived from attack on both the primary and secondary carbons. Oxidation with activated ***Manganese Dioxide*** gives the α-methylene- and (*Z*)-α-ethylidenebutyrolactones (eq 5).[6] See also ***Methallyllithium***.

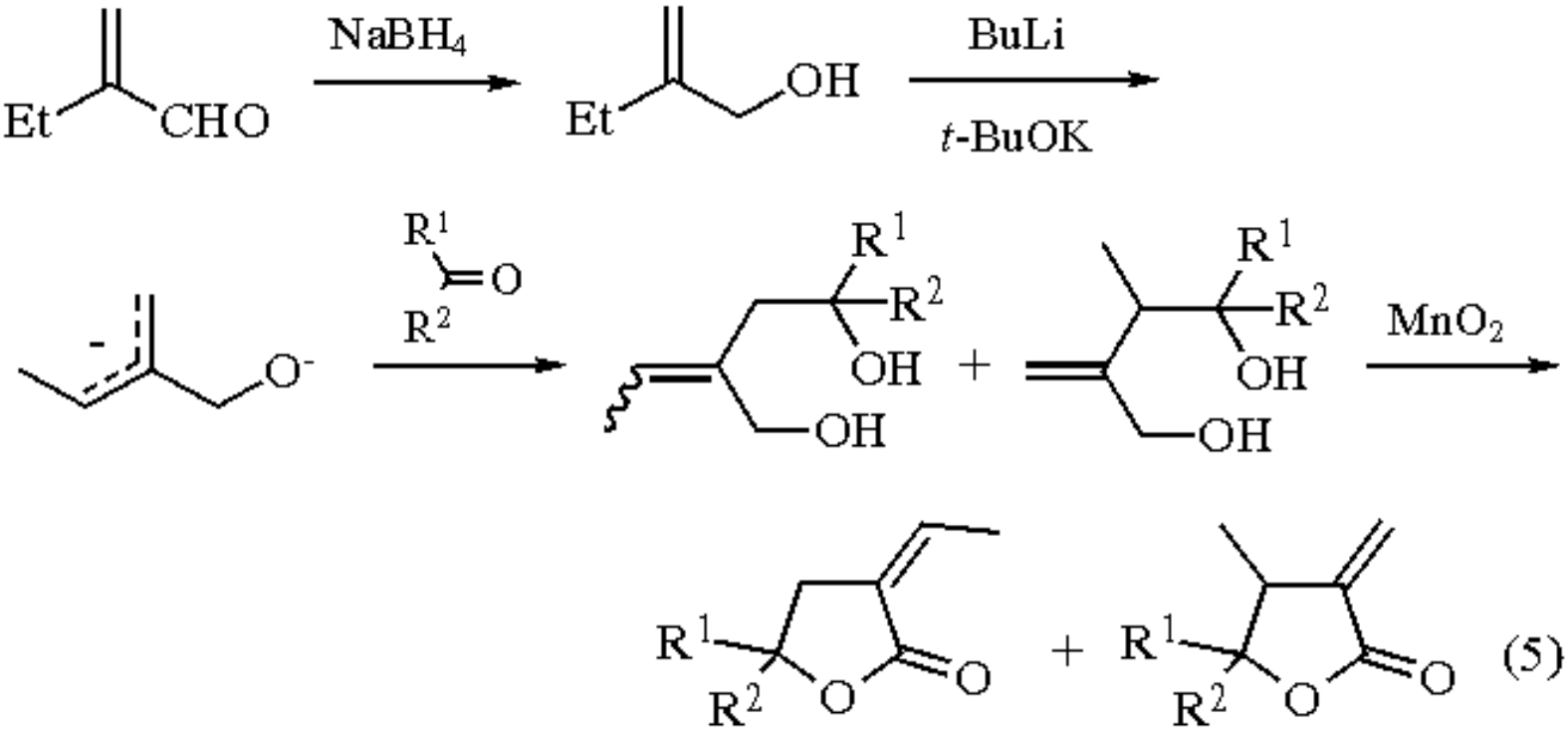

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1. Carlson, R. M. *TL* **1978**, 111.
2. Trost, B. M.; Chan, D. M. T. *JACS* **1983**, *105*, 2315.

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Lithium 2-Lithiophenoxide

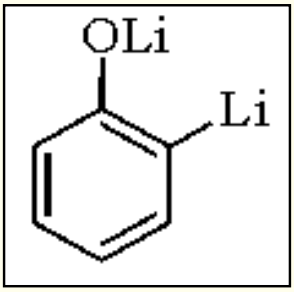

[55274-02-7] · $C_6H_4Li_2O$ · Lithium 2-Lithiophenoxide · (MW 105.98)

reacts with electrophiles to give substituted phenols

Solubility: sol ethereal solvents.

Preparative Methods: conveniently prepared and used in situ by one of two methods. The first reported preparation[1] involves the treatment of *o*-bromophenol with ***n-Butyllithium*** at 25 °C to generate the dilithio species (eq 1). A subsequent report[2] described an alternative preparation by directed *ortho* deprotonation of phenol with ***t-Butyllithium*** (eq 2).

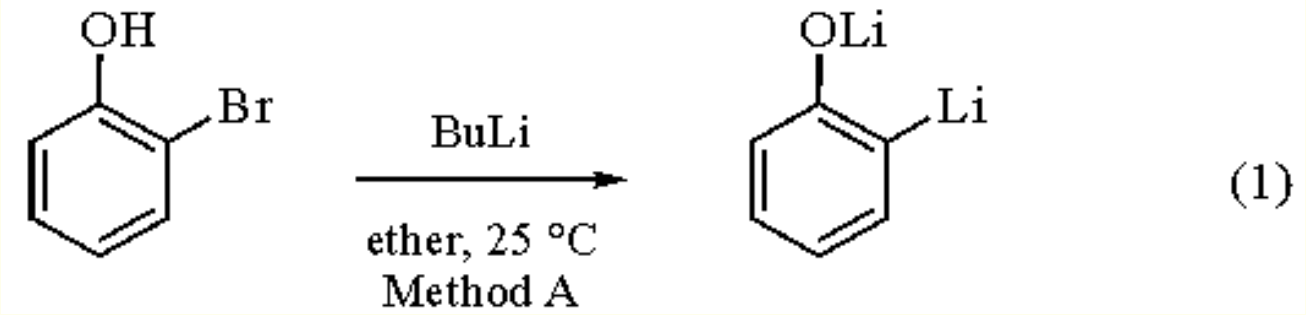

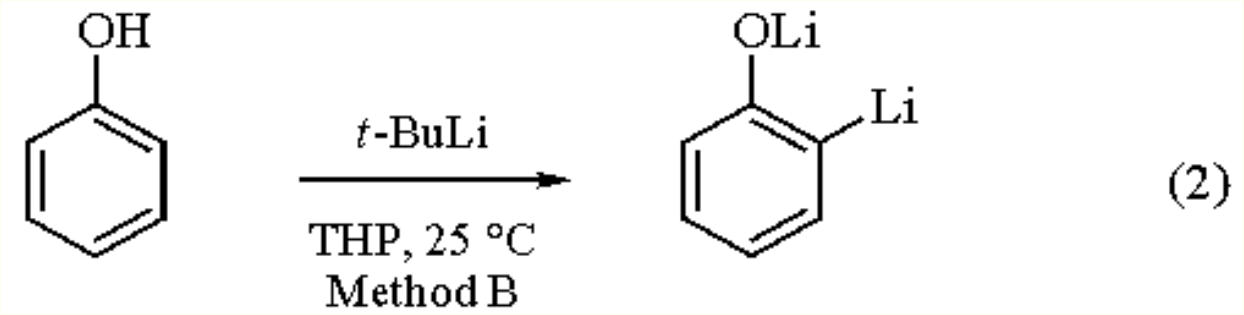

Handling, Storage, and Precautions: moisture sensitive; freshly prepare before use. Long term stability has not been determined. Reactions should be run under an inert atmosphere.

Reactions.

The reagent prepared by either route has been shown to react with electrophiles at the *ortho* carbon (eqs 3 and 4).[3] The electrophiles studied included hindered ketones and enolizable aldehydes and ketones.

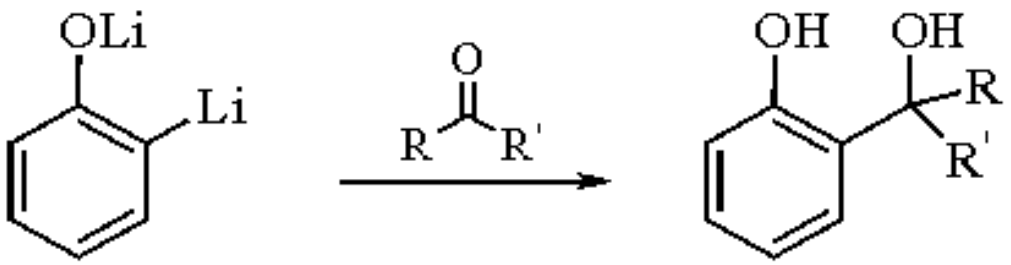

(3)

Method	R	R'	Yield
A	Ph	Ph	75%
"	Ph	H	88%
"	Me	Me	80%
"	CH_2=CH	Me	80%
"	CH_2=CH	H	88%

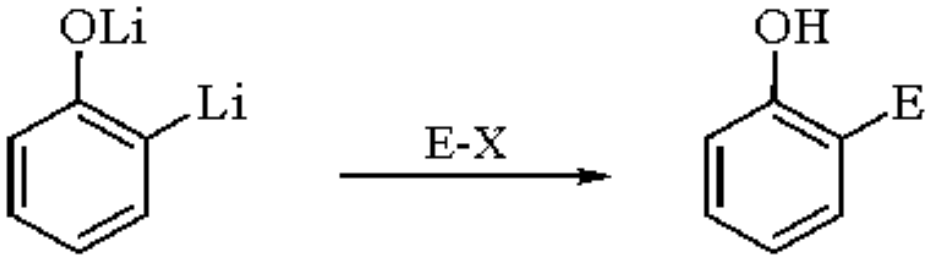

(4)

Method	E-X	E	Yield
B	MeI	Me	44%
"	CO_2	CO_2H	42%
"	$PhCO_2H$	PhCO	48%
"	CBr_4	Br	46%
"	TMSCl	TMS	67%

The corresponding *meta*[4] and *para* isomers are prepared by the halogen-metal exchange route with *t*-BuLi. The dilithio species (both *meta* and *para* isomers) react with a variety of electrophiles including aldehydes, ketones (eq

5), and amides.

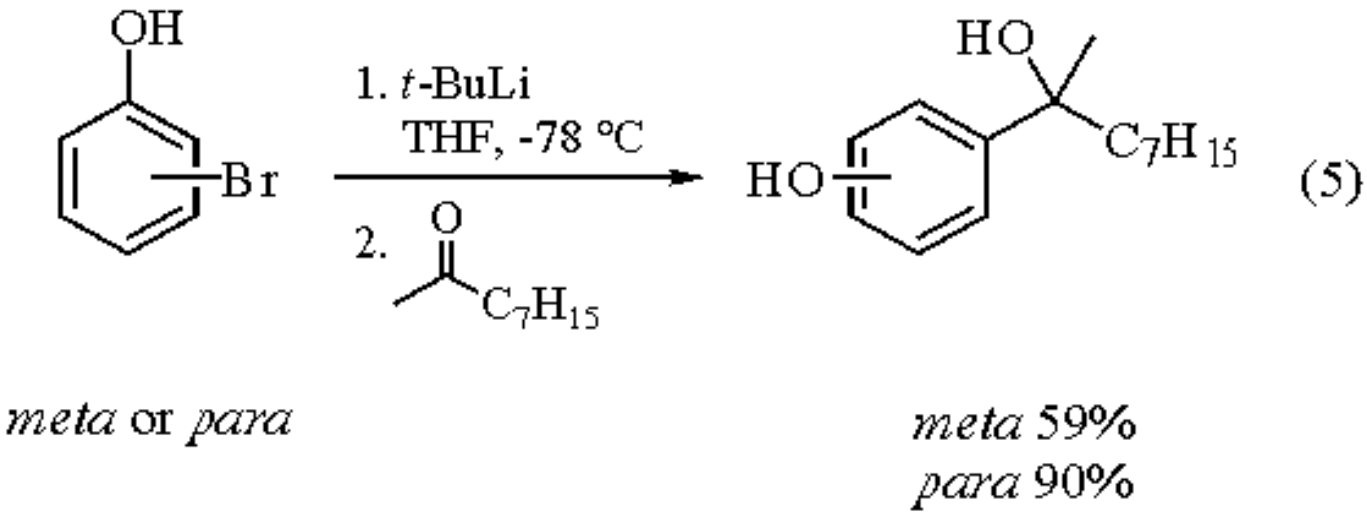

Related Reagents.

The corresponding sulfur analogs are prepared similarly to the phenolic examples.[5] Treatment of thiophenol with *n*-BuLi at room temperature in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** gives rise to the lithium 2-lithiothiophenoxide in solution which can be trapped with electrophiles (eq 6).

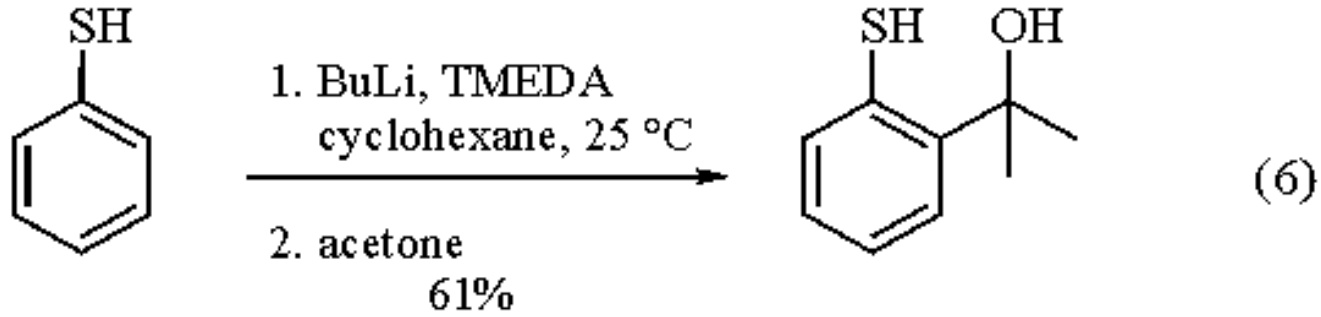

The *meta* and *para* isomers are prepared by the halogen-metal exchange route and have been shown to react with acylating reagents (eq 7).[4]

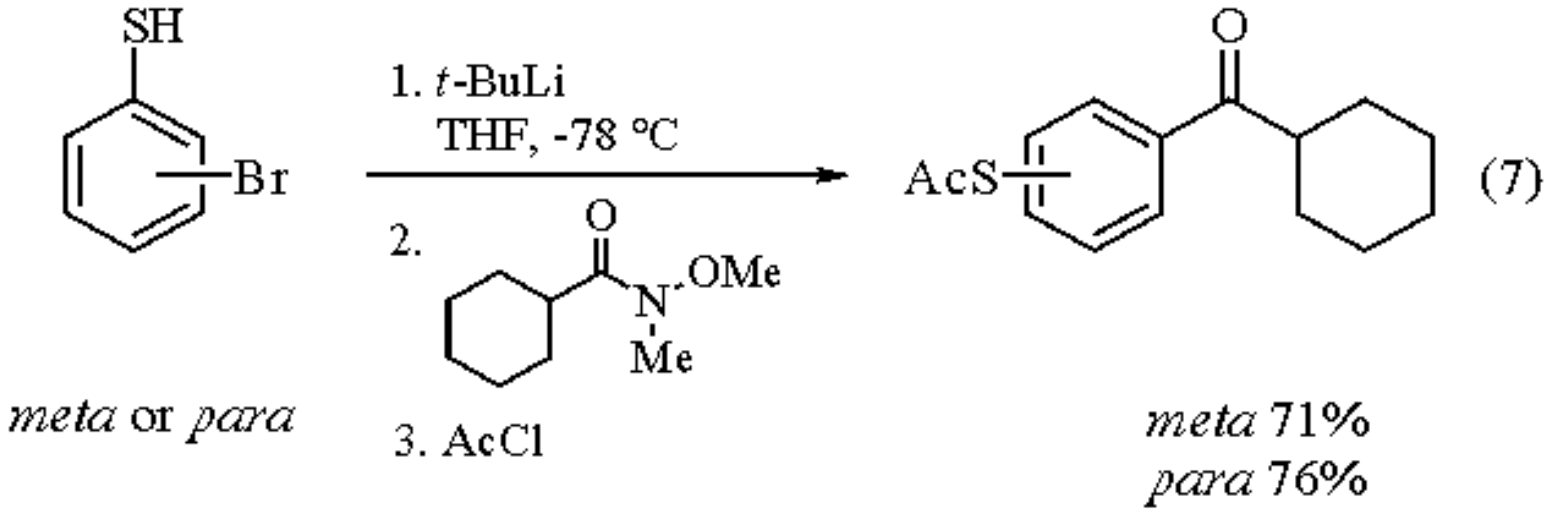

Similar reagents in which the phenolic oxygen is protected (methyl or silyl ether) prior to lithiation have been reported.[6] An example in the synthesis of thromboxane A2 antagonists is shown (eq 8). See also ***o-Lithioanisole***.

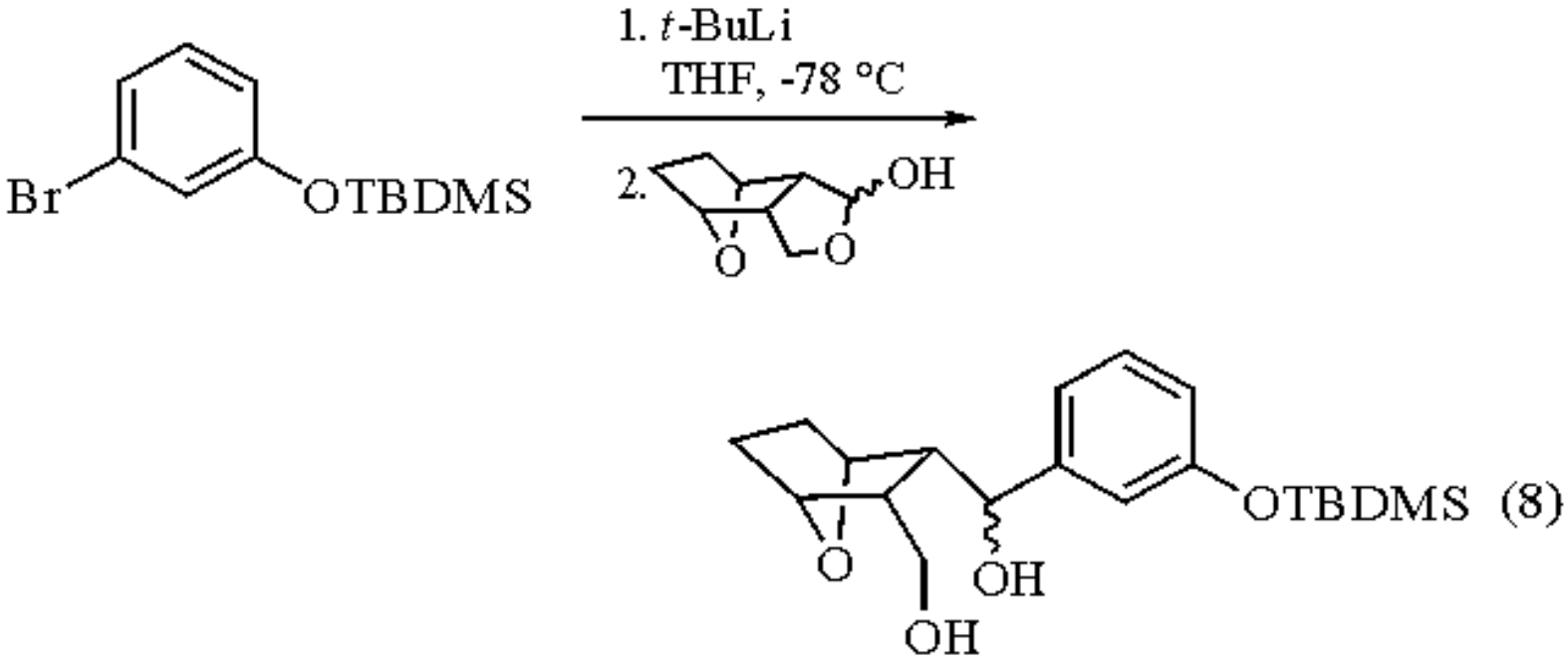

It is also possible to generate related *C,O,O*-trilithiated species by the halogen-metal exchange strategy (eq 9).[7] Higher temperatures and sonication appear to be necessary for trianion formation.

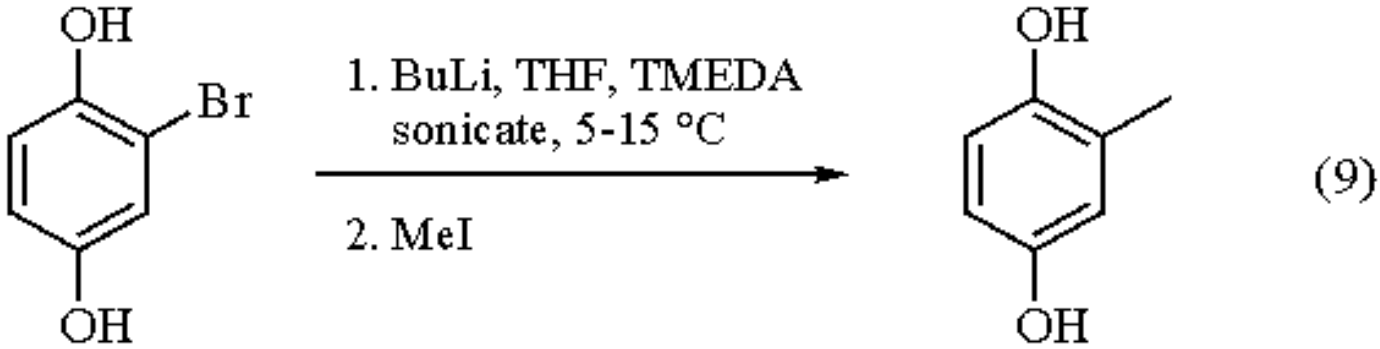

1. (a) Gilman, H.; Arntzen, C. E.; Webb, F. J. *JOC* **1945**, *10*, 374. (b) Gilman, H. *OR* **1951**, *6*, 339.
2. Posner, G. H.; Canella, K. A. *JACS* **1985**, *107*, 2571.
3. (a) Talley, J. J.; Evans, I. A. *JOC* **1984**, *49*, 5267. (b) Talley, J. J. *JOC* **1985**, *50*, 1695. (c) Heinicke, J.; Tzschach, A. *JPR* **1983**, *325*, 232.
4. Selnick, H. G.; Bourgeois, M. L.; Butcher, J. W.; Radzilowski, E. M. *TL* **1993**, *34*, 2043.
5. (a) Masson, S.; Saint-Clair, J.; Saquet, M. *S* **1993**, 485. (b) Block, E.; Ofori-Okai, G.; Zubieta, J. *JACS* **1989**, *111*, 2327. (c) Figuly, G. D.; Loop, C. K.; Martin, J. C. *JACS* **1989**, *111*, 654. (d) Smith, K.; Lindsay, C. M.; Pritchard, G. J. *JACS* **1989**, *111*, 665.
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7. Saá, J. M.; Morey, J.; Suñer, G.; Frontera, A.; Costa, A. *TL* **1991**, *32*, 7313.

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Lithium 3-Lithiopropionate

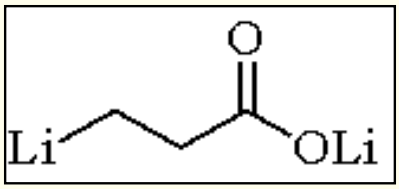

[117951-86-7] · $C_3H_4Li_2O_2$ · Lithium 3-Lithiopropionate · (MW 85.95)

(useful for the synthesis of γ-lactones from aldehydes and ketones[1])

Form Supplied in: 3-bromopropionic acid, mp 61-63 °C, is commercially available; hexane solutions of *n*-butyllithium are commercially available in several concentrations; naphthalene, mp 80-82 °C, is commercially available.

Preparative Method: for the in situ preparation of the reagent, ***n-Butyllithium*** (10.40 mL of a 1.73 M solution in hexane) is added dropwise with stirring under nitrogen over ca. 30 min to a solution of 2.75 g (18 mmol) of 3-bromopropionic acid in 75.0 mL anhydrous THF at -70 °C. The resulting solution of lithium 3-bromopropionate is held at -70 °C and added dropwise with rapid stirring to a solution containing 30 mmol of ***Lithium Naphthalenide*** in 100 mL of anhydrous THF at -70 °C until the dark green color of the solution changed to dark brown.

Handling, Storage, and Precautions: n-butyllithium is pyrophoric and moisture sensitive; 3-bromopropionic acid is corrosive; lithium naphthalenide is air and moisture sensitive. Avoid contact of all ingredients and the reagent itself with the eyes, skin, and clothing. Prepare and handle the reagent under an inert nitrogen or argon atmosphere. It is recommended that the reagent be prepared immediately prior to use.

In recent years there has been a great deal of interest in the preparation and reactions of metal homoenolates and homoenolate equivalents.[2,3] The conversion of 3-bromopropionic acid into its lithium salt provides protection of the carboxyl group so that bromine-lithium exchange can occur with lithium naphthalenide to give the parent lithium homoenolate system. Under the reaction conditions the homoenolate system does not rearrange into the more thermodynamically stable lithium enolate of the carboxylate. Treatment of 3-bromopropionic acid with 2.2 equiv of *n*-butyllithium at -70 to -100 °C provides a very low yield of the reagent.[1] Instead, heptanoic acid, which results from an unusually facile Wurtz coupling of the lithium 3-bromocarboxylate and *n*-butyllithium, is obtained.

The addition of carbonyl compounds to solutions of the reagent at -70 °C followed by warming to rt and neutralization of the reaction mixture produces γ-hydroxy acids, which produce γ-lactones in moderate yields upon mild acid treatment. Saturated aliphatic and aromatic aldehydes (eq 1) yield the corresponding γ-monosubstituted γ-lactones.[1] Unconjugated unsaturated aldehydes also react similarly (eq 2).[4]

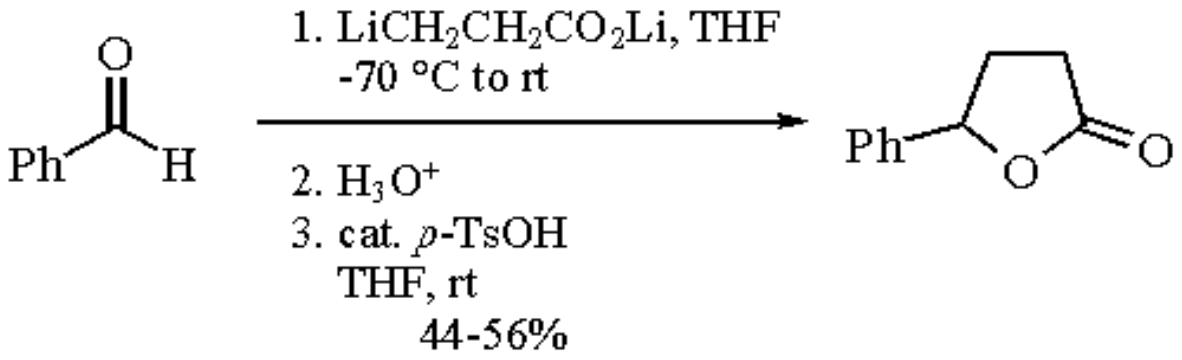

(1)

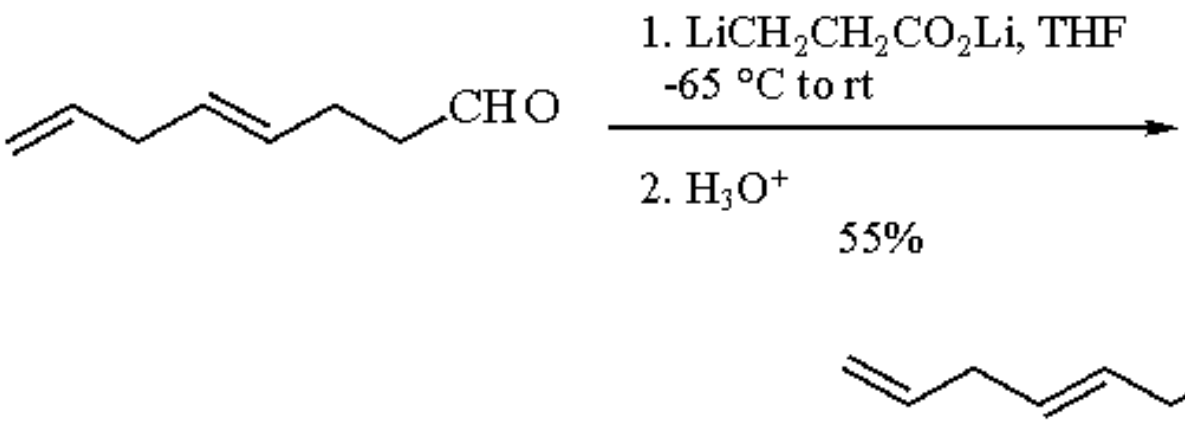

(2)

Acyclic and cyclic saturated ketones yield γ,γ-disubstituted or spirocyclic γ-lactones upon treatment with the reagent. The reagent adds to 4-*t*-butylcyclohexanone from the equatorial direction with low stereoselectivity to produce the *syn* spirolactone as the major product (eq 3).[1] Interestingly, the *anti* spirolactone is produced with high stereoselectivity in the SmI_2-induced coupling of 4-*t*-butylcyclohexanone with ethyl acrylate.[5]

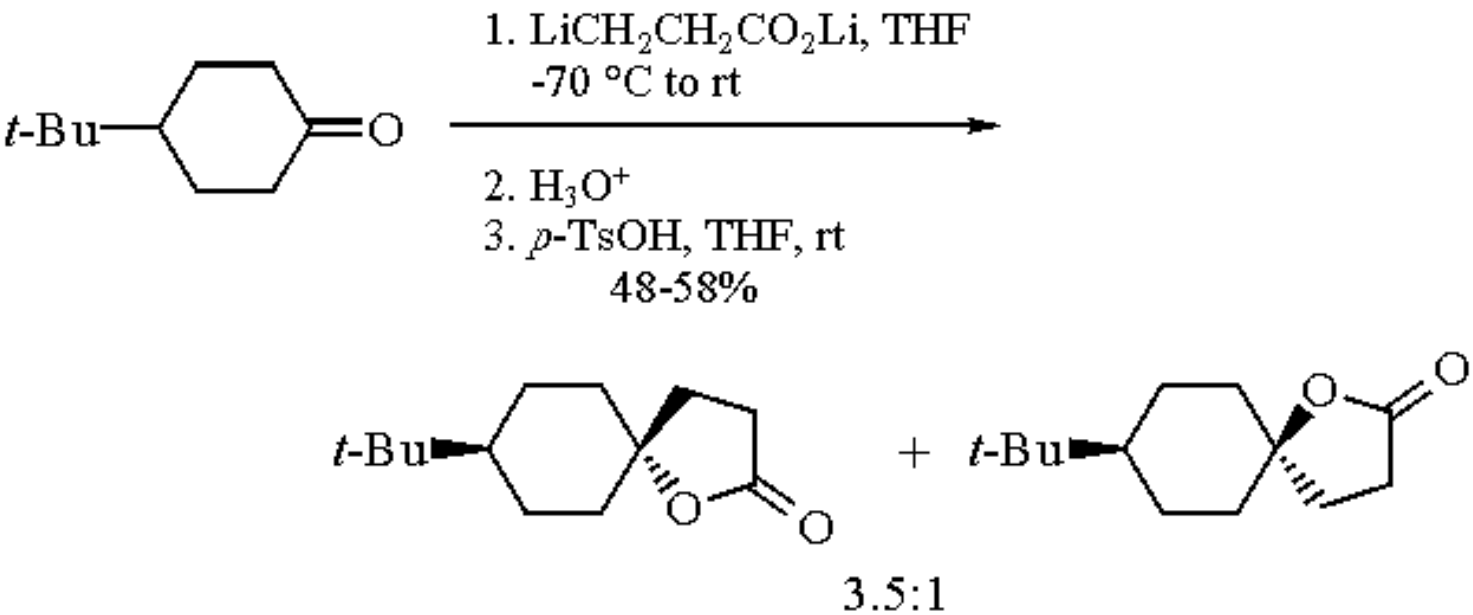

(3)

The reagent also reacts with α,β-unsaturated ketones, e.g. isophorone, to provide a direct route to allylic spirolactones (eq 4).[6] A more lengthy synthesis of the allylic spirolactone shown in eq 4 was reported recently.[7]

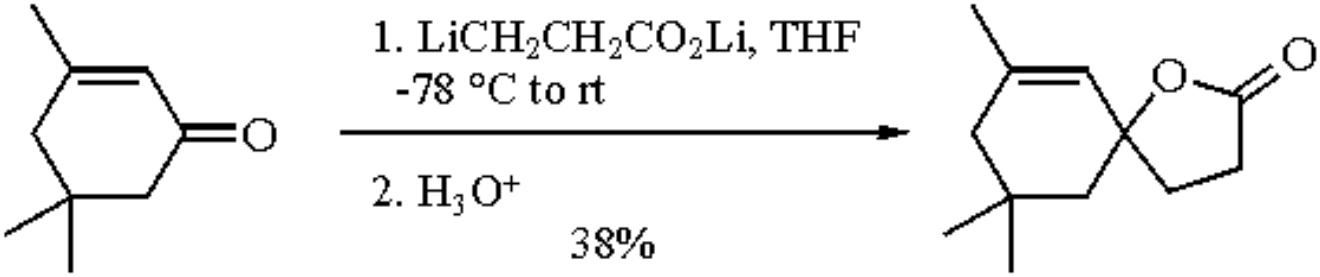

(4)

A variety of other metal homoenolate reagents are capable of converting carbonyl compounds into γ-lactones in a straightforward manner. Some of these include the dilithium dianion prepared from treating 3-tri-*n*-butylstannylpropionamide with 2.0 equiv *n*-BuLi at low temperature,[8a,b] trichlorotitanium homoenolates of propionate esters prepared from treatment of 1-alkoxy-1-trimethylsilylcyclopropanes with ***Titanium(IV) Chloride***,[8c,d] esters of zinc homoenolates mediated by titanium(IV) reagents,[8e] and esters of lanthanoid homoenolates.[8f] ***Samarium(II) Iodide***-promoted couplings of carbonyl compounds with α,β-unsaturated[5] and 3-halopropionate esters[9] also provide useful direct routes to γ-lactones.

See also ***1-Ethoxy-1-(trimethylsilyloxy)cyclopropane***.

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Lithium 1-Methyl-2-(2-methyl-1-(*E*)-propenyl)cyclopropyl(phenylthio)cuprate

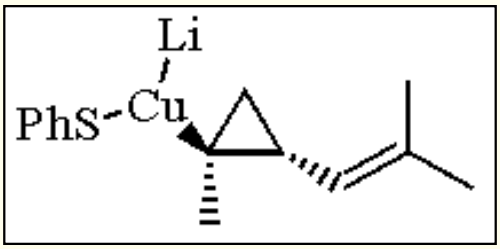

(*E*)

[87084-08-0] · $C_{14}H_{18}CuLiS$ · Lithium 1-Methyl-2-(2-methyl-1-(*E*)-propenyl)cyclopropyl(phenylthio)cuprate · (MW 288.88)

(intermediate for the synthesis of natural products, terpenes, and substrates for Cope rearrangement, divinylcyclopropane and [3,3]-sigmatropic shift studies)

Preparative Methods: to a stirred solution of 1.03 g (5.4 mmol) of 1-bromo-1-methyl-2-(2-methyl-1-propenyl)cyclopropane in 50 mL of dry THF-ether (1:1) at -78 °C under nitrogen was added dropwise a solution of ***t-Butyllithium*** (10.8 mmol) in pentane. After the pale yellow solution had been stirred at -78 °C for 30 min, 0.93 g (5.4 mmol) of ***Phenylthiocopper(I)*** was added from a bent tube attached to the reaction flask. The suspension was warmed to -20 °C and stirred for 30 min, which gave a red brown solution of the cuprate. The solution was cooled to -78 °C for addition to the iodo enone.[2]

Handling, Storage, and Precautions: best used immediately following its preparation. THF and ether need to be anhydrous (distill from sodium benzophenone). Air and moisture should be excluded.

The title reagent (**4m**) and the related reagents (**1-5**) shown in Table 1[2-12] are generally used to prepare divinylcyclopropanes that undergo Cope rearrangements to form seven-membered rings (eq 1). Formation and rearrangement of (**7**) is nearly quantitative, yielding a single product (**8**), which was converted to (±)-β-himachalene. In this case, the *trans* cuprate gave excellent results, but in certain other cases a *cis* cuprate is desirable[1,7] (see below).

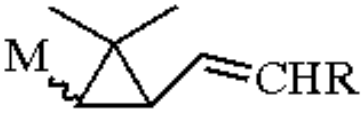

(1h) R = H
(1m) R = Me
(1s) R = SPh

(2)

M = Li, MgBr, PhSCuLi or CuLi (dimer) (see Table 1)

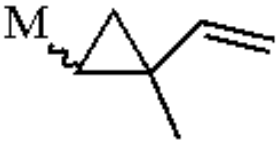

(3)

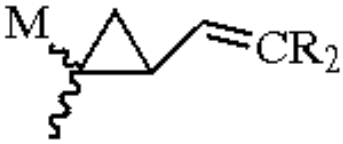

(4h) R = H
(4m) R = Me

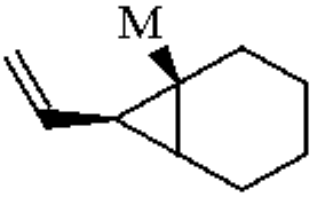

(5)

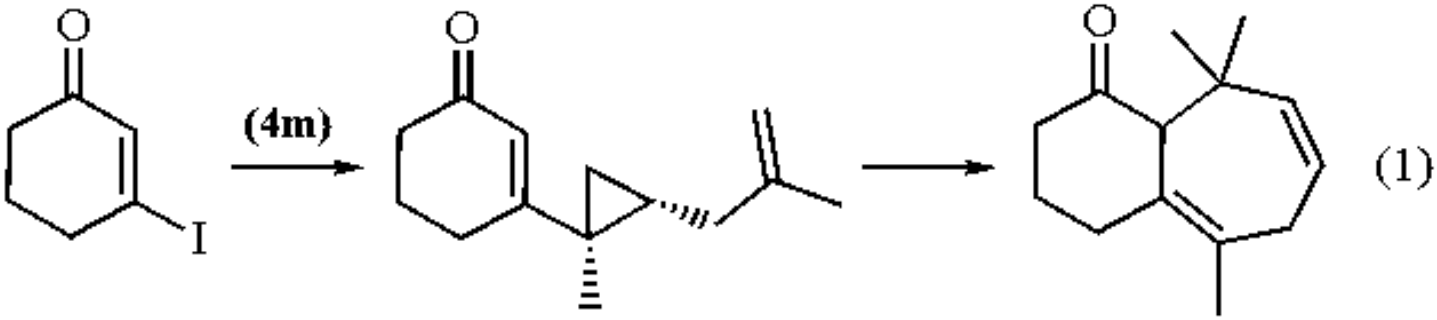

(1)

(6) **(7)** **(8)**

Table 1 Lithium 1-Methyl-2-(2-methyl-1-(*E*)-propenyl)cyclopropyl-(phenylthio)cuprate and Related Reagents

Cmpd.	Bromide precursor	Reagent type	*cis*:*trans* or (*Z*):(*E*)[a]	Ref.
(**1h**)	19879-92-6	Li		3
	15136-02-4 (*trans*)	CuLi	1:4	4, 5
	15136-01-3 (*cis*)	PhSCuLi	7:3, 5:1[b]	6 9
(**1m**)	64434-67-9 (*E*)	CuLi	1:8[c]	4, 5
(**1s**)		Li	1:4[d]	4, 5
(**2c**)	67885-78-3 (*cis*)	PhSCuLi	20:1	7, 10
(**2t**)	67885-79-4 (*trans*)	PhSCuLi	*trans*	7, 10
(**3**)	60288-35-9 (*Z*)	MgBr	(*Z*)	11
(**4h**)	61782-54-5 (*Z*)	CuLi	45:55	4
	61782-53-4 (*E*)			
(**4m**)	87084-08-0 (*E*)	PhSCuLi	13:87	2
(**5**)	76886-06-1	Li	(*Z*)	12

[a] Stereochemistry of cyclopropyl ring (*Z*:*E* refers to **3**, **4m**, and **5**). [b] 73 from reduction with *n*-Bu_3SnH, 5:1 from reduction with Zn/ether HOAc.[6] [c] Double bond stereochemistry 4:1 *cis*/*trans*. [d] Double bond stereochemistry 3:5 *cis*/*trans*.

Preparation of Vinylcyclopropyl Bromides and their Organolithium Derivatives.

The bromides corresponding to reagents (**1h**) and (**4h**) were prepared by adding the dibromocarbene to butadiene and then replacing one bromide (eq 2). Treatment of (**9**) with *t*-butyllithium and then either ***Hydrogen Bromide*** or ***Iodomethane*** gives mixtures of products with the *trans* isomer predominating[4,5] (see Table 1 for ratios). The *cis* and *trans* bromides are separable by spinning band distillation. Dibromide reduction with ***Tri-n-butylstannane*** or ***Zinc-Acetic Acid*** gives mixtures with the *cis* isomer predominating.[6-9] The reaction of (**10**) with *t*-butyllithium produces (**1h**) and (**4h**) (M = Li) which can then be converted to the cuprate using $CuBr_2.SMe_2$ or PhSCu. Starting with 2-methylbutadiene leads to (**3**) in the same

way.[11] The lithium reagent (**3**) (M = Li) was converted to the more selective MgBr variant by treatment with ***Magnesium Bromide***.

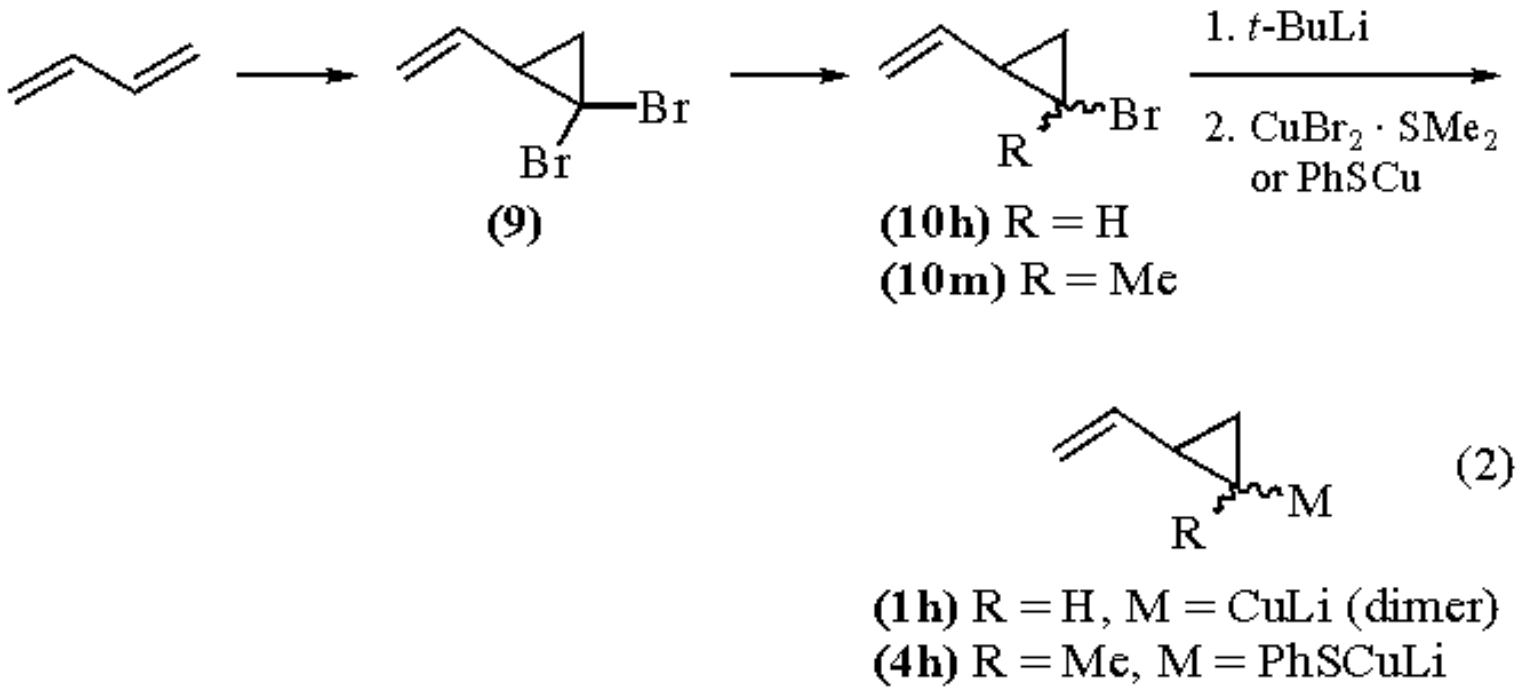

(2)

To obtain a substituted vinyl group,[4,5] acrolein acetal (**11**) was converted to the dibromide (**12**), which reacts with ethylidenetriphenylphosphorane or ***Diethyl Phenylthiomethylphosphonate*** to form (**13**) (eq 3). Treatment with *t*-butyllithium followed by HBr formed the monobromide and then reaction with *t*-butyllithium produced (**1m**) or (**1s**).

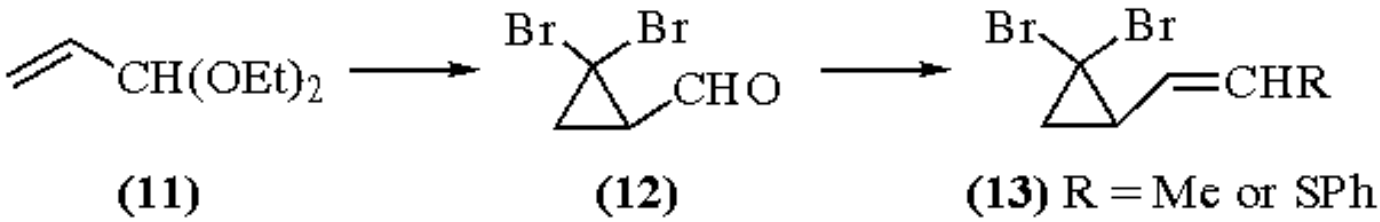

(3)

A highly stereoselective synthesis[7] of (**2c**) and (**2t**) starts with dibromocarbene addition to the THP derivative of 3-methyl-2-buten-1-ol to produce (**14**) (eq 4). Hydrolysis of the THP ether, ***Pyridinium Chlorochromate*** oxidation, and Wittig alkenation results in (**15b**), which undergoes Zn/acetic acid reduction to selectively form *cis*-bromide (**16**). Treatment of (**14**) with *n*-BuLi gives only *trans*-bromide (**17**), which was converted to *trans*-bromide (**19**) by hydrolysis, PCC oxidation, and Wittig reaction. Both (**16**) and (**19**) were converted to thiophenylcuprates in the same way as the title compound.

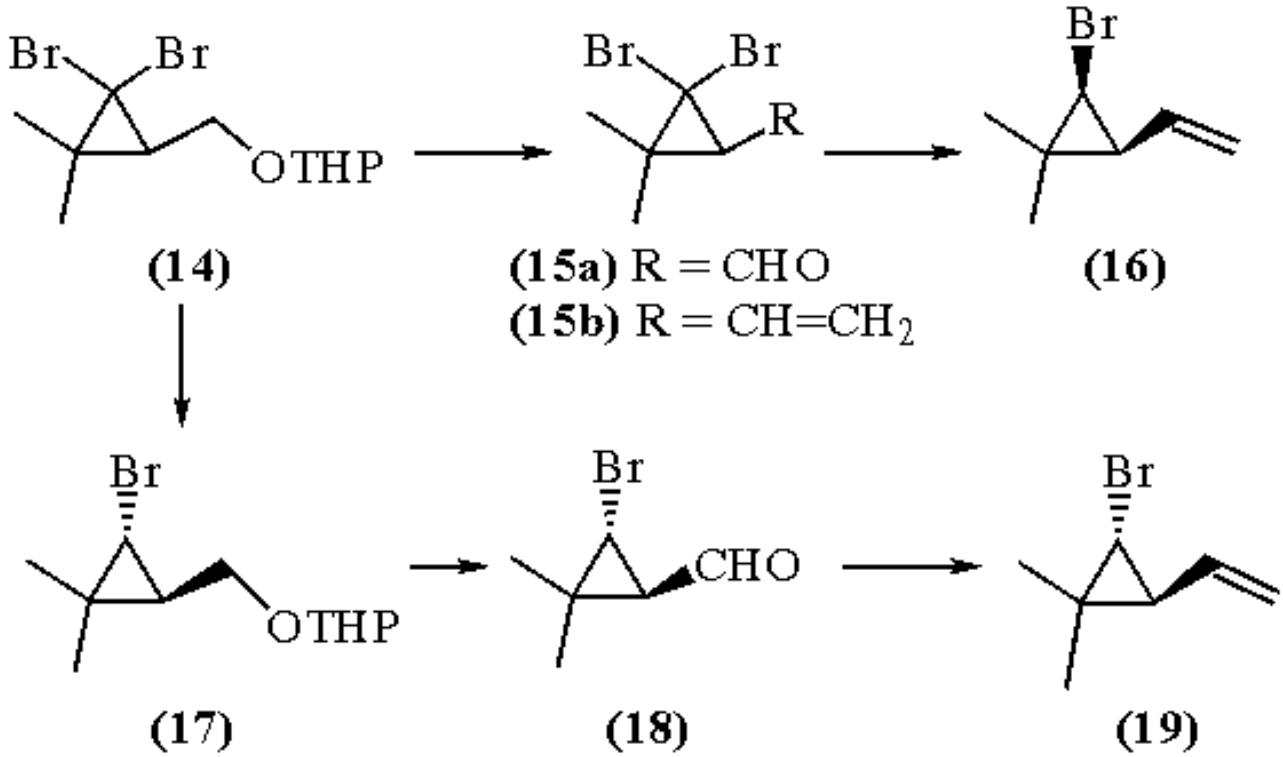

(4)

In a similar way (eq 5),[2] acetal (**20**) was transformed into (**21**) which was treated with *n*-BuLi/MeI in HMPA-THF to selectively make (**22**). The mixture (ca. 90% *trans*) could be separated by chromatography and crystallization. Hydrolysis of the acetal in formic acid followed by Wittig reaction with ***Isopropylidenetriphenylphosphorane*** generated the bromide needed to produce the *trans* cuprate (**4m**) (M = PhSCuLi).

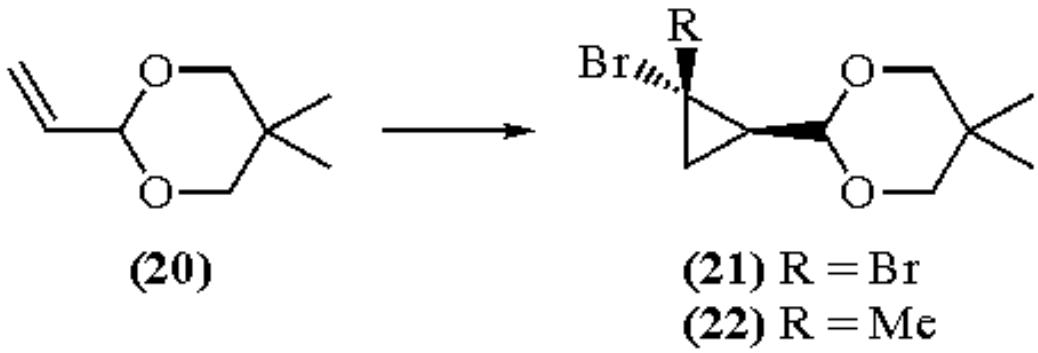

(5)

Bromoenone (**23**) and $Me_2SCH_2CO_2Et$ have been combined[12] to form (**24**) (eq 6), which was elaborated to (**25**) by a five-step sequence. Bromide (**25**) was converted to (**5**) (M = Li) using *t*-butyllithium.

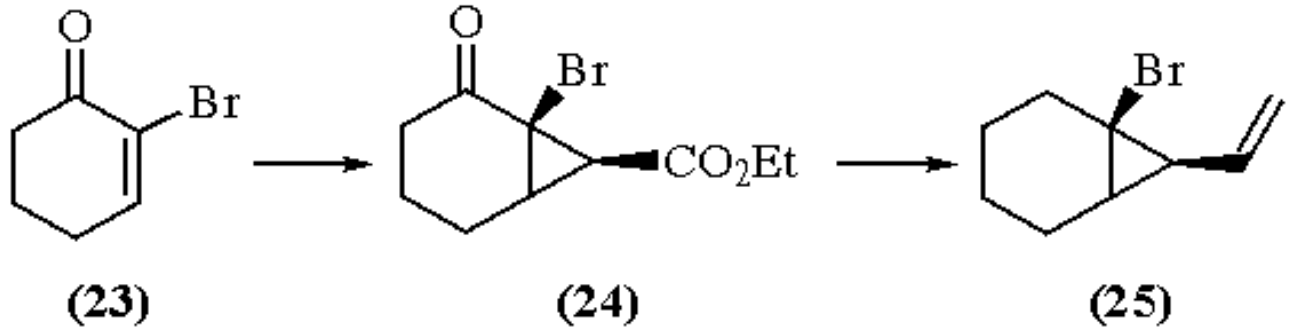

(6)

Stereochemistry of Divinylcyclopropane Rearrangements.

For reagents (**1**)-(**5**), the *cis* isomers lead to the *cis*-divinylcyclopropanes that are excellent substrates for the Cope rearrangement. However, in many cases the *trans*-divinylcyclopropane works sufficiently well that separating *cis* and *trans* isomers is not necessary.[1] In certain compounds where the Cope rearrangement is disfavored by steric factors, *cis* to *trans* isomerization and 1,5-shifts compete with the Cope rearrangement.[7] In one such case (eq 7), an ingenious simultaneous photolysis/thermolysis overcame these side reactions and gave a high yield of Cope product from a *cis*/*trans* mixture.[13]

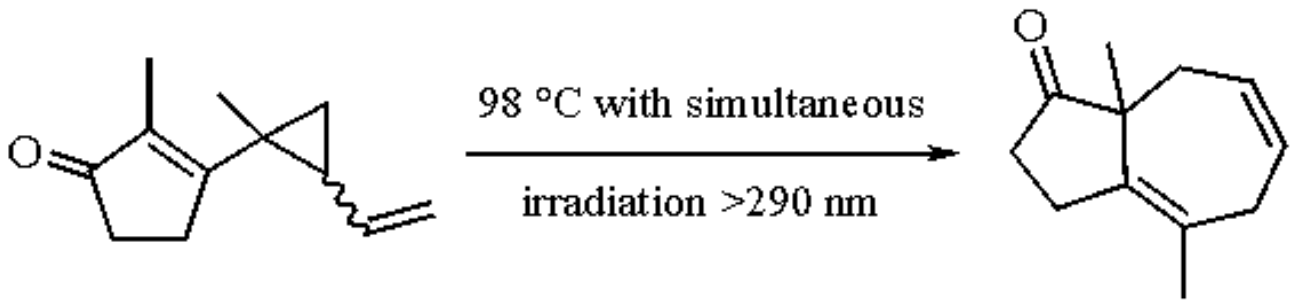

(7)

Choice of Organometallic Reagent.

The cuprate reagents (**1**), (**2**), and (**4**) have been used effectively for coupling reactions with β-iodoenones,[2,7,9,10] e.g. (**6**) or 2-iodomethylenecyclohexanone, acyl chlorides[6,8] (followed by conversion to the silyl enol ether), propargyl ketones,[5] and propargyl esters.[5] The phenylthiocuprates are efficient for transfer of secondary and tertiary cyclopropyl compounds and are readily made from ***Phenylthiocopper(I)***.[14] The lithium reagents add in 1,2-fashion to β-alkoxy enolates[3,5,15] to form some of the same compounds available from the cuprate route exemplified in eq 1. For example (eq 8), 3-methoxy-2-methylcyclopentanone gives products similar to (**7**).

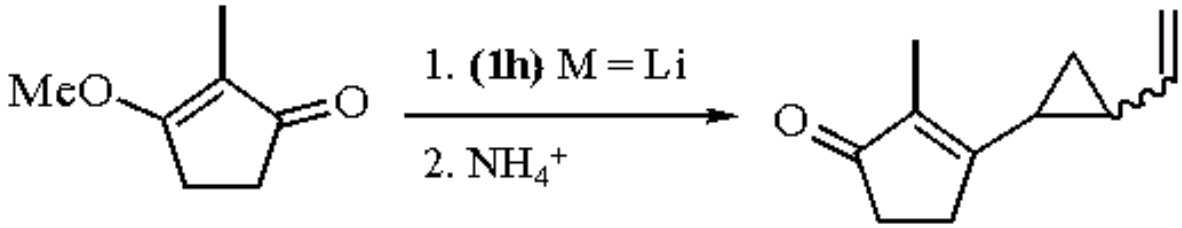

(8)

They can also be used to add to aldehydes or ketones (eq 9); the resultant alcohol group can then be used to form the second vinyl group. Scopadulcic acid-B has been prepared[11] using this approach with (**3**) (M = MgBr). The lithium reagent (**3**) (M = Li) was found to attack the aryl iodide of the starting aldehyde. Some of the lithium reagents have also been used to prepare chromium carbene complexes.[16]

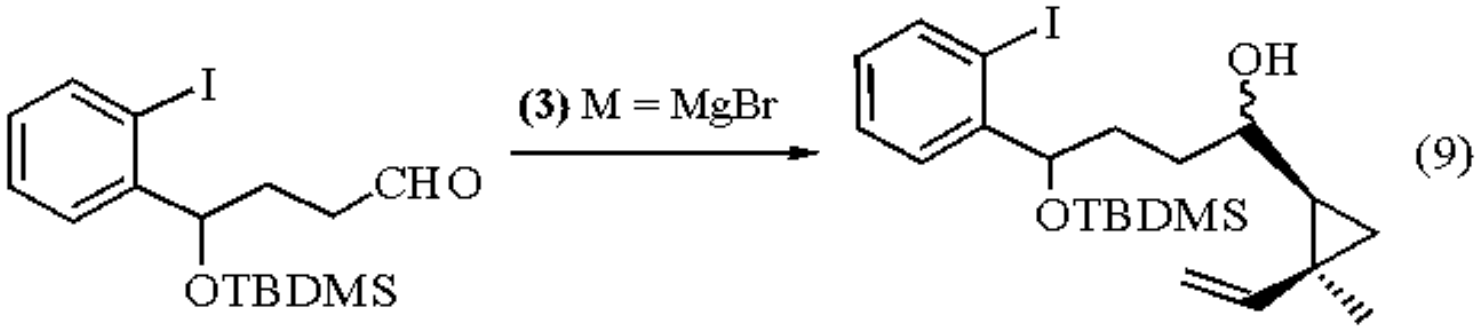

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Lithium Methyl(phenylseleno)cuprate[1]

MeCu(SePh)Li

[91365-06-9] · $C_7H_8CuLiSe$ · Lithium Methyl(phenylseleno)cuprate · (MW 241.60)

(heterocuprate designed for 1,4-addition-elimination reactions[2] with aryl β-(phenylseleno)vinyl sulfones[3])

Solubility: sol ether, THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl; the yield of acetophenone is measured by GC, precalibrated using authentic product and *n*-dodecane as internal standard.

Preparative Methods: ***Phenylselenocopper(I)*** is prepared by portionwise addition of 1.0 equiv ***Diphenyl Diselenide*** to a mechanically stirred, rt solution of 2.0 equiv ***Sodium Borohydride*** in 1:1 2 M aqueous NaOH:EtOH. The resultant yellow suspension is heated at reflux under N_2 for 30 min; a clear solution results. Cooling to 0 °C and acidification to pH 5-6 using conc HCl is followed by addition of 1.0 equiv Cu_2O in one portion. The mixture is heated at reflux under N_2 for 18 h. Cooling is followed by filtration and washing of the brownish-yellow precipitate with ethanol and water; drying overnight in vacuo provides the selenide.[3]

MeCu(PhSe)Li is prepared by stirring a 0 °C suspension of 1.0 equiv PhSeCu in THF under N_2 and adding 1.0 equiv of an ether solution of ***Methyllithium*** dropwise. After 15 min the resultant clear green-brown solution is cooled to -78 °C and is ready for use.

Handling, Storage, and Precautions: best results will be obtained with PhSeCu prepared from high purity Cu_2O, dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[5] MeLi is pyrophoric;[6] care must be exercised in its handling. The reagent appears to have thermal stability equal to that of ***Lithium Methyl(phenylthio)cuprate***. Use in a fume hood.

Lithium methyl(phenylseleno)cuprate is a novel representative of the heterocuprate class of organocopper reagents.[7] The methyl group acts as a nucleophile, while the SePh group does not. This latter nontransferable or dummy ligand[8] provides enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when higher reaction temperatures are required, or when the organolithium used to form the cuprate is difficult or expensive to prepare.

Designed for 1,4-addition-elimination reactions with aryl β-(phenylseleno)vinyl sulfones, these cuprates offer specific advantages over the corresponding homocuprates and alkyl(phenylthio)cuprates (eq 1).[3] Applications include stereospecific net *anti* addition of R-H to alkynes via a selenosulfonation/1,4-addition-elimination/reductive sulfurization[9] sequence complementary to traditional *syn* carbocupration,[10] and the synthesis of marine sterols.[11]

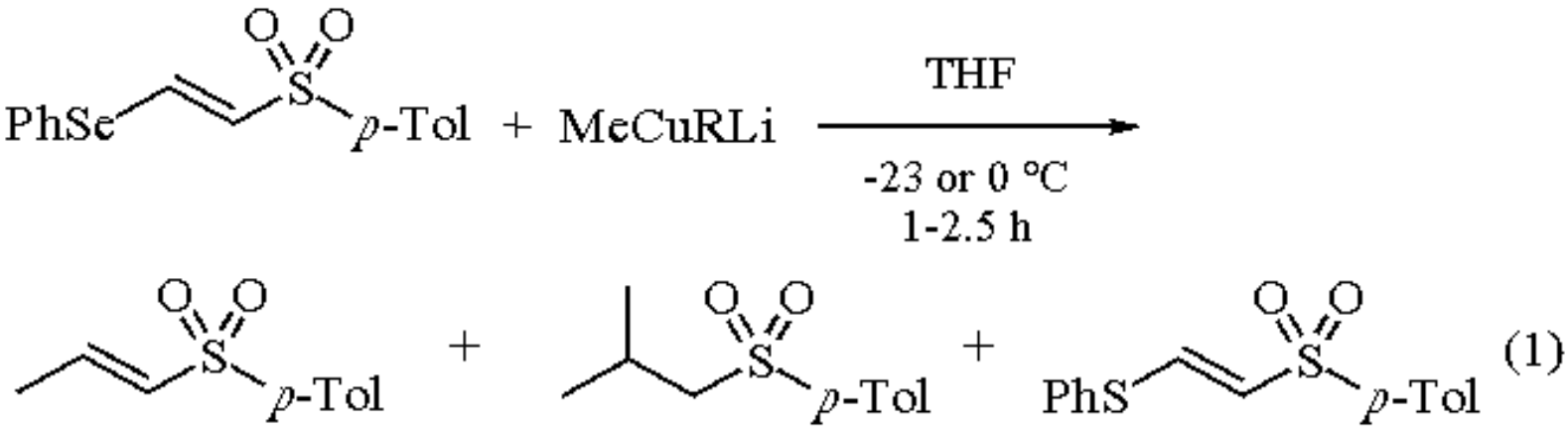

R			
Me	68%	20%	-
PhS	31%	-	55%
PhSe	90%	-	-

Related Reagents.

Lithium t-Butoxy(t-butyl)cuprate; ***Lithium Dimethylcuprate***; ***Lithium Methyl(phenylthio)cuprate***.

---

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Lithium Methyl(phenylthio)cuprate[1]

MeCu(SPh)Li

[56831-21-1] · C_7H_8CuLiS · Lithium Methyl(phenylthio)cuprate · (MW 194.71)

(heterocuprate, useful in 1,4-additions,[2] carbocuprations,[3] and substitutions[4])

Solubility: sol ether, THF.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[5] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl; the yield of acetophenone is measured by GC, after calibration using authentic product and *n*-dodecane as internal standard.

Preparative Method: from ***Phenylthiocopper(I)*** prepared in situ: 1.0 equiv of ***n-Butyllithium*** is added dropwise to a 0.2 M, 0 °C THF solution of ***Thiophenol*** in a three-neck flask equipped with N_2 inlet, solid addition funnel, and rubber septum. After stirring for 10 min, 1.0 equiv of ***Copper(I) Iodide*** is added via the addition funnel. Stirring for an additional 15 min provides a clear, yellow solution, to which 1.0 equiv of a solution of ***Methyllithium*** is added dropwise via syringe. After 15 min, the brown solution is ready for use.[6] Alternate sources of PhSCu may be acceptable.[7]

Handling, Storage, and Precautions: best results are obtained with high purity Cu^I salts,[8] dry, O_2-free solvents, and methyllithium solutions free of contaminating alkoxides or hydroxides.[9] MeLi is pyrophoric;[10] due care must be exercised in its handling. Thermal decomposition of the reagent is minimal at or below room temperature.[11] Use in a fume hood.

Lithium methyl(phenylthio)cuprate is representative of the heterocuprate class of organocopper reagents.[6] The Me group is nucleophilically reactive, whereas the SPh group is not. These nontransferable groups are called dummy ligands;[12] the SPh group in particular provides enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when relatively high reaction temperatures are required, when the organolithium used to form the cuprate is difficult or expensive to prepare, or when overalkylation using the homocuprate is observed.

The reagent has been used in nucleophilic substitution reactions of allylic acetates[13] and 9-BBN,[14] as well as in conjugate additions to α-oxoketene dithioacetals[15] and α,β-unsaturated oxazolidines[16] and ketones.[17] Good results

have been reported in carbocupration reactions using alkynes (eq 1)[18] and cyclopropenes;[19] the analogous lithium methyl(methylthio)cuprate is used to synthesize tertiary thiols from dithio esters.[20] On the other hand, cross coupling with organomercury reagents is unsatisfactory.[11] Preferential transfer of the phenylthio group[21] has been observed; this behavior is substrate dependent and should not normally be anticipated.

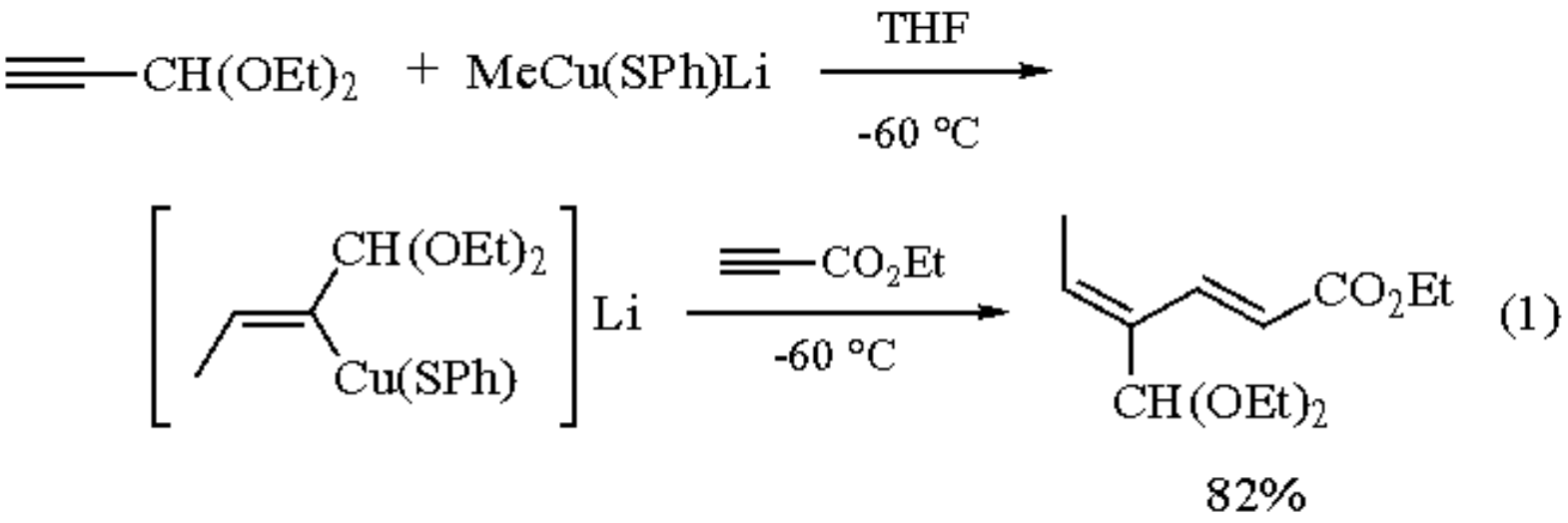

Related Reagents.

Lithium t-Butoxy(t-butyl)cuprate; ***Lithium n-Butyl(phenylthio)cuprate***; ***Lithium Cyclopropyl(phenylthio)cuprate***; ***Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate***; ***Lithium Methyl(phenylseleno)cuprate***.

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Lithium *N*-Methylpiperazide

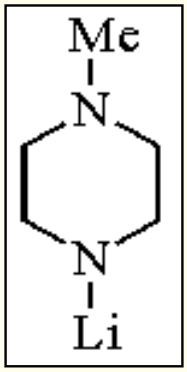

[105563-31-3] · $C_5H_{11}LiN_2$ · Lithium *N*-Methylpiperazide · (MW 106.12)

(in situ protection of aryl aldehydes via α-amino alkoxide formation; α-amino alkoxides can direct or block *ortho*-lithiation[1])

Alternate Name: LNMP.

Preparative Method: prepared in situ by adding ***n-Butyllithium*** to *N*-methylpiperazine in anhydrous solvents.

Handling, Storage, and Precautions: highly flammable; should be kept under a nitrogen or argon atmosphere.

Lithium *N*-methylpiperazide is conveniently used as a reagent for in situ protection of aryl aldehydes through α-amino alkoxide formation.[1] Stability of LNMP-derived α-amino alkoxides to alkyllithium reagents and their solubility in organic solvents are reasons why LNMP is preferred over similar reagents.[1] The α-amino alkoxides obtained in situ from substituted benzaldehydes are not easily *ortho*-lithiated; however, refluxing a benzene solution of the α-amino alkoxide and excess ***n-Butyllithium*** for 3-12 h effects *ortho*-metalation. Addition of excess electrophile followed by aqueous workup gives moderate to good yields of the desired *ortho*-substituted aryl aldehydes (eq 1).[2]

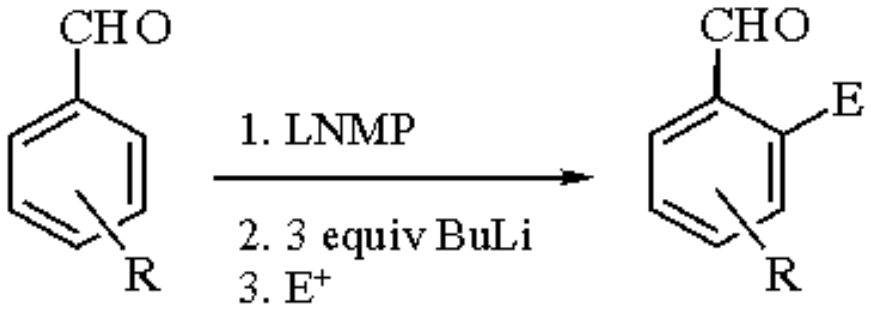

(1)

Regioselective substitution of bis-activated benzaldehydes can be achieved by lithiation/alkylation of an α-amino alkoxide obtained from LNMP. *p*-Anisaldehyde, on treatment with LNMP and ***s-Butyllithium*** in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** and subsequent quenching with ***Iodomethane***, gives 4-methoxy-3-methylbenzaldehyde (eq 2).[3] This is in sharp contrast to the analogous reaction using ***N-Lithio-N,N´,N´-trimethylethylenediamine*** (LTMDA) in place of LNMP, where 4-methoxy-2-methylbenzaldehyde is produced in good yield.[1] Under the same reaction conditions, *o*- and *m*-anisaldehydes give C-3 and C-4 lithiated products, respectively. Both 3,5- and 2,4-dimethoxybenzaldehydes can be metalated between the methoxy substituents in excellent yield using LNMP, *s*-BuLi, and TMEDA.

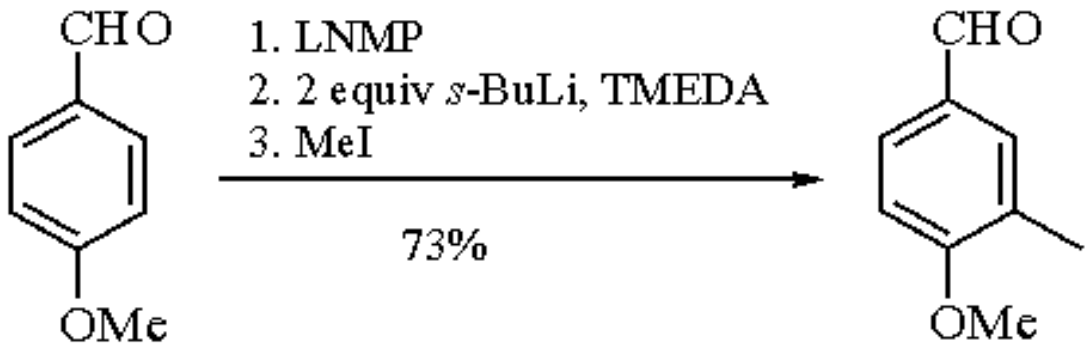

(2)

Heterocyclic aldehydes can be metalated regioselectively using similar methodology to that described above.[4] For example, 2-thiophenecarbaldehyde on reaction with LNMP, *n*-BuLi, and TMEDA and subsequent quenching with iodomethane, gives 5-methyl-2-thiophenecarbaldehyde in 77% yield (eq 3).

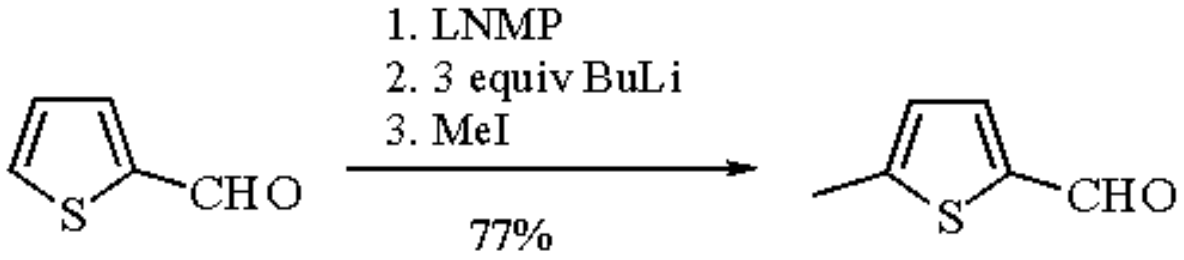

(3)

When LTMDA is used instead of LNMP, a mixture of 3- and 5-methyl-2-thiophenecarbaldehydes is obtained. However, 3-thiophenecarbaldehyde and LNMP under similar reaction conditions give a mixture of C-5 and C-2 substituted products in a ratio of 83:17. Alkylation of 2-furaldehyde occurs exclusively at the 5-position when treated with LNMP, *n*-butyllithium, and iodomethane.[4] In a similar manner, 3-furaldehyde gives mainly C-2 alkylation, but 2-methyl-3-furaldehyde, on treatment with LNMP, *n*-BuLi, and iodomethane, gives 2,5-dimethyl-3-furaldehyde in 50% yield. Using similar reaction conditions, *N*-methylpyrrole-2-carbaldehyde and *N*-methylindole-2-carbaldehyde give the corresponding C-5 and C-3 substituted products on reaction with LNMP, *n*-BuLi, TMEDA, and iodomethane.[4] Interestingly, methoxypyridinecarbaldehydes, on treatment with LNMP, alkyllithium, and TMEDA, give metalation *ortho* to the methoxy group (Scheme 1).[5] This is in sharp contrast to LTMDA-assisted metalations, where substitution occurs *ortho* to the aldehyde group.

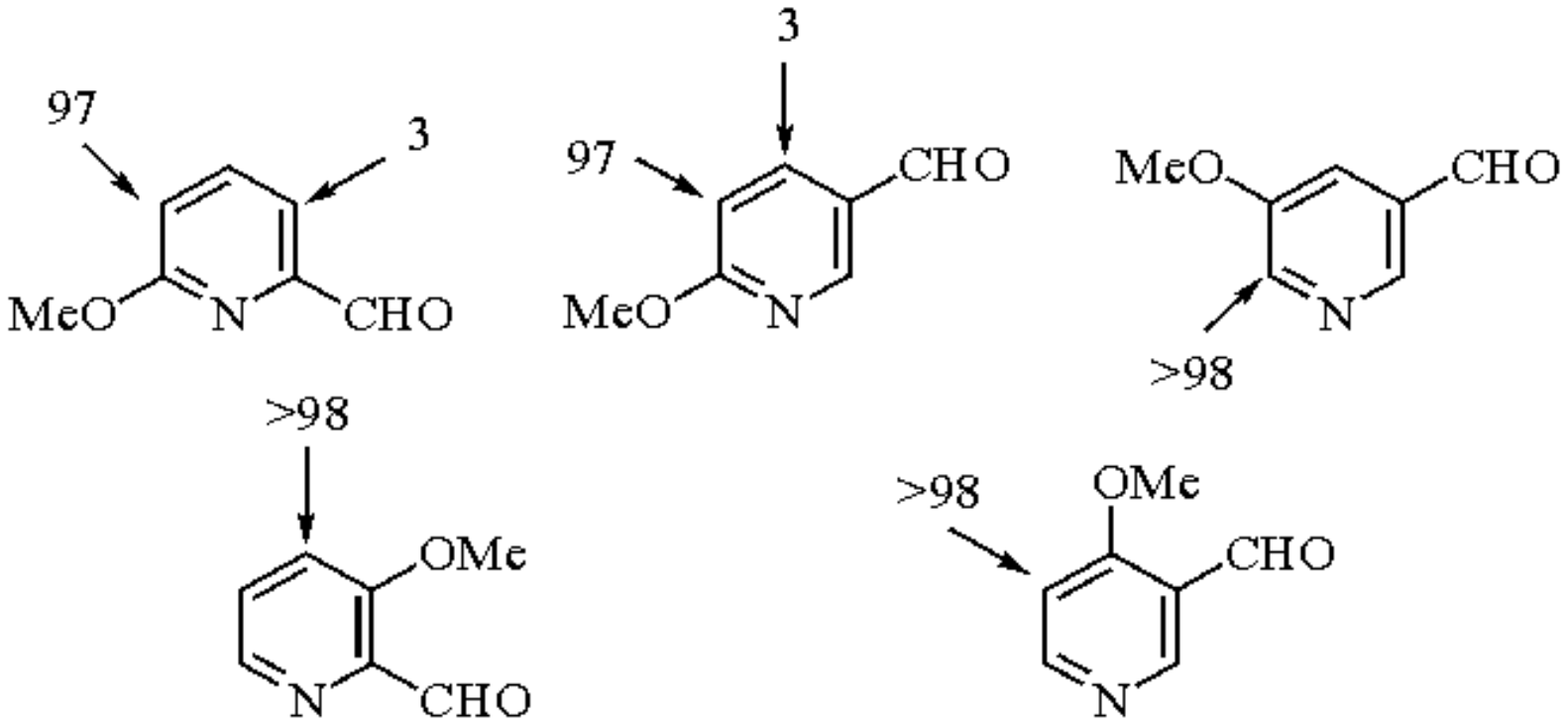

Scheme 1

A regioselective lithiation/alkylation of a 1-Boc-3-formyl-1,4-dihydropyridine has been effected using LNMP and ***Mesityllithium*** as the base.[6] Dealkylation of several *o*-alkoxyaryl aldehydes can be achieved via the corresponding α-amino alkoxides prepared with LNMP.[7]

Related Reagents.

N-Lithio-N,N´,N´-trimethylethylenediamine; ***Lithium Morpholide***.

---

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Lithium Methylsulfinylmethylide[1]

$LiCH_2SOMe$

[57741-62-5] · C_2H_5LiOS · Lithium Methylsulfinylmethylide · (MW 84.08)

(a strong base and nucleophile, very useful for the introduction of the methylsulfinylmethyl group[1])

Alternate Names: lithium dimsylate; dimsyllithium; LiDMSO.

Solubility: sol DMSO; sparingly sol THF.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: titration with formanilide using triphenylmethane as indicator.[2]

Preparative Methods: by the reaction of alkyllithiums or ***Lithium Amide*** with ***Dimethyl Sulfoxide*** in DMSO or ethereal solvents.[2,3] May also be prepared by the reaction of freshly prepared (but not commercial) LiH.[4]

Handling, Storage, and Precautions: best prepared as needed, although synthesis and storage procedures similar to those used in some preparations of ***Sodium Methylsulfinylmethylide*** (NaDMSO) would probably result in long shelf life.[5] Complexes of LiDMSO with ethereal solvents have been isolated and characterized. Solvent-free LiDMSO is shock sensitive.[6] Hydrogen gas or hydrocarbon may be emitted during the preparation of this reagent and due caution should be exercised in its preparation, particularly on a large scale. Problems encountered in the preparation of NaDMSO may be relevant to LiDMSO.[7]

Dimethyl sulfoxide is a weakly acidic compound (pK_a = 35) whose conjugate base is both a strong nucleophile and base. The sodium and potassium salts of DMSO have found considerable use in synthesis (see ***Potassium Methylsulfinylmethylide*** and ***Sodium Methylsulfinylmethylide***) and much of the chemistry of those reagents is shared with lithium methylsulfinylmethylide. This reagent was introduced nearly contemporaneously with NaDMSO, though the latter has seen more application.[2]

Lithium Methylsulfinylmethylide as Base.

Carbanion Accelerated Claisen Rearrangement.

LiDMSO, particularly in the presence of excess ***Lithium Chloride***, serves as the best base for inducing the anionic Claisen rearrangement of (**1**) (eq 1).[8] With NaDMSO and KDMSO, 1-(*p*-tolylsulfonyl)-2-butanone is formed as a side product in 24% and 65% yield, respectively. The side reaction leading to this elimination product is completely suppressed with LiDMSO in the presence of LiCl and leads to the conclusion that undesired reactions mediated by powerfully basic reagents might be minimized through the use of added lithium and other metal salts (see, for example, ***Cerium(III) Chloride***).

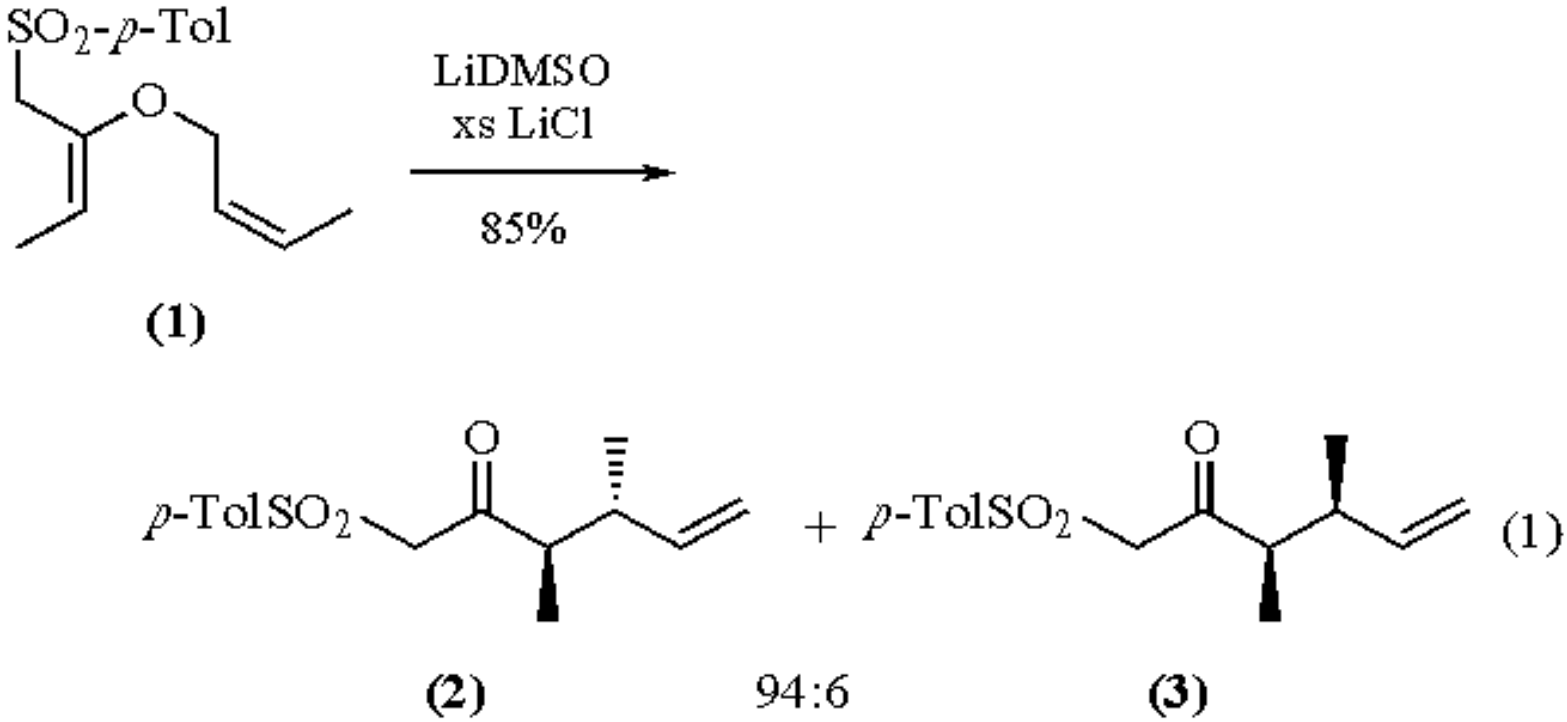

Ether Synthesis.

The modification of polysaccharides via alkylation of free hydroxy groups (Hokomori reaction) has been performed using LiDMSO as base.[9] Glycoprotein glycans have been similarly modified to facilitate their handling and analysis.[10] The superiority of LiDMSO as a reagent for this reaction vis-à-vis NaDMSO has been reported.

Lithium Methylsulfinylmethylide as Nucleophile.

Reactions with Acid Derivatives.

The condensation of dimsyl anions with acid derivatives, almost exclusively esters, leads to the formation of β-keto sulfoxides, whose rich chemistry makes them versatile and useful intermediates (eqs 2 and 3).[11,12] For example, the conversion of (**4**) to (**5**), an intermediate in a synthesis of vindoline, occurs via a Pummerer reaction followed by cyclization and carbocation rearrangement. Many other transformations of β-keto sulfoxides are known.[13] A one-pot conversion of carboxylic acids to β-keto sulfoxides has been developed.[13]

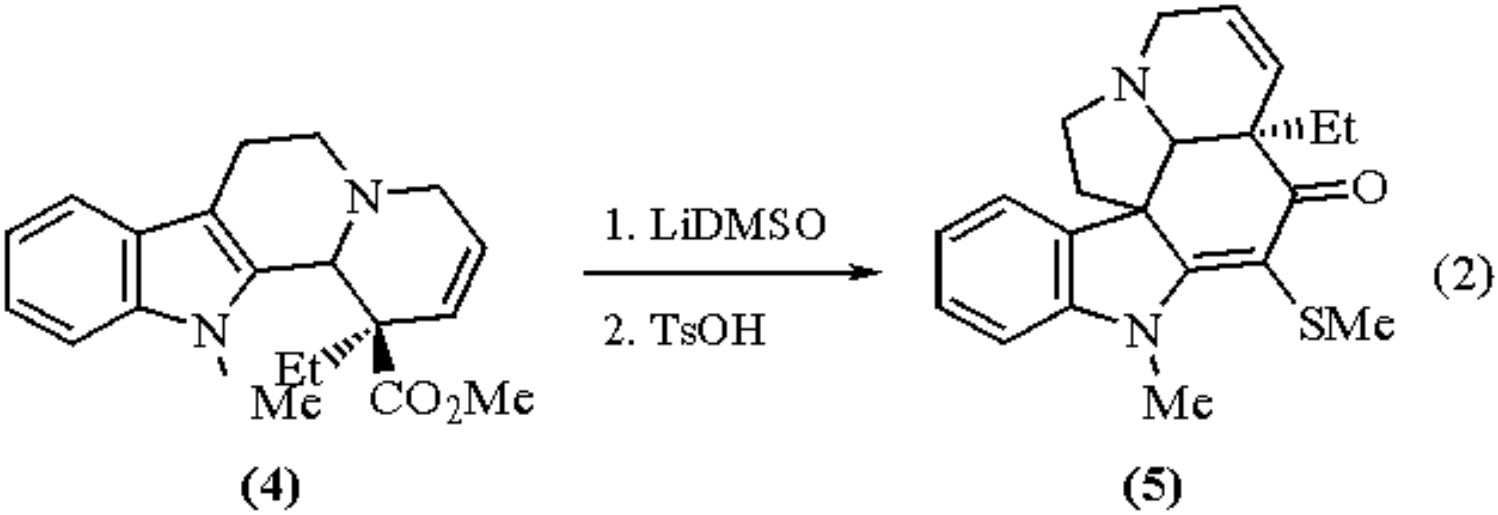

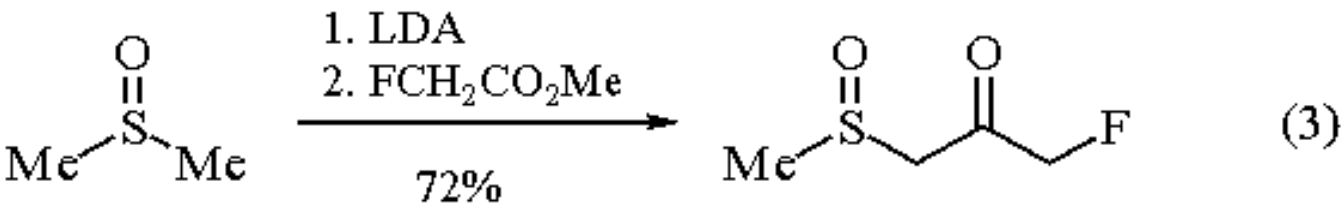

Reaction of a carboxylic acid with ***N,N´-Carbonyldiimidazole*** leads to acyl imidazolides which give β-keto sulfoxides upon reaction with LiDMSO (eq 4). β-Enamino sulfoxides can be prepared by condensation of amines with the adduct from the reaction of LiDMSO and DMF (eq 5).[14] Finally, methylsulfinylketene dithioacetals are formed stereoselectively when LiDMSO is reacted with dialkyl thiocarbonates and the resulting lithium salts are quenched with alkyl halides (eq 6).[15] With NaDMSO, mixtures of (*E*) and (*Z*) isomers are produced.

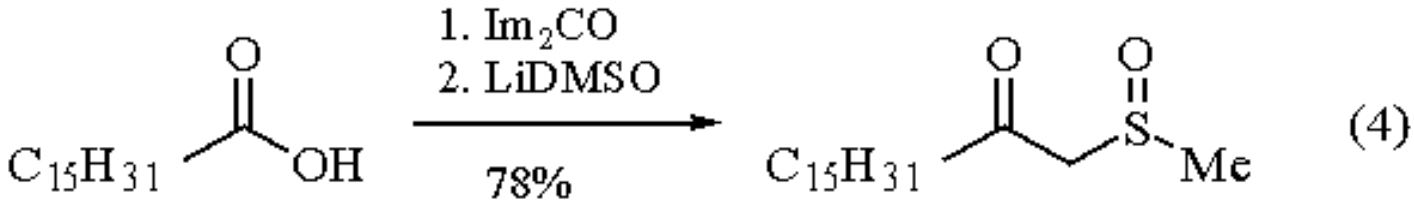

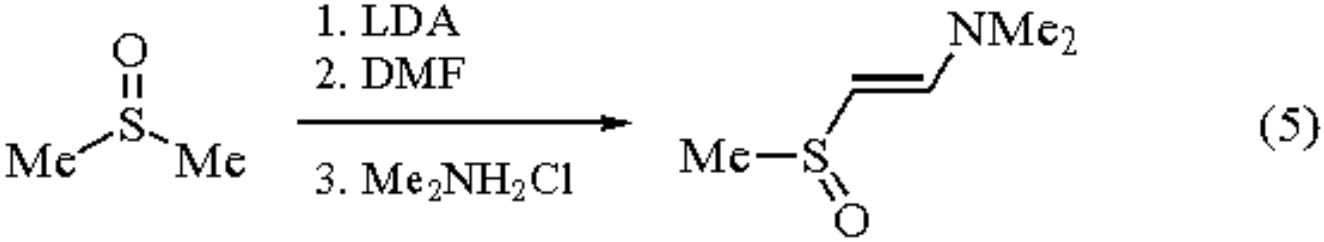

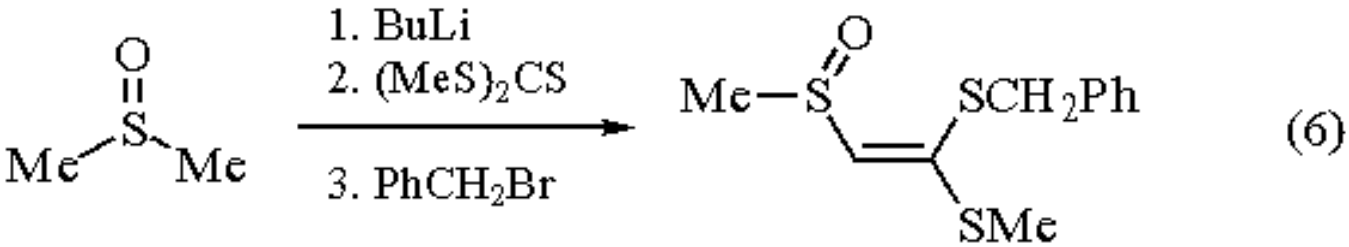

Reactions with Aldehydes and Ketones.

Non-enolizable ketones and aldehydes react successfully with dimsyl anions.[1] An interesting route to naphthols was reported involving the nucleophilic addition of LiDMSO to an indenone followed by a ring expansion (eq 7).[16] Reaction with a cyclohexadienone has also been reported (eq 8).[17]

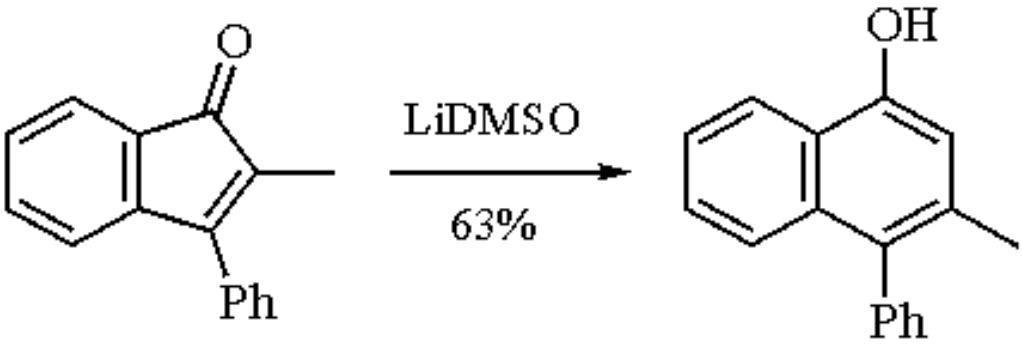

(7)

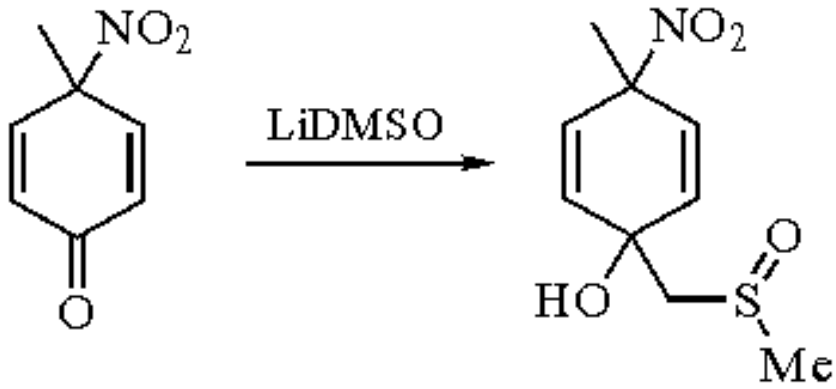

(8)

A one-pot synthesis of alkenes from non-enolizable ketones begins with a carbonyl addition reaction, the product of which is treated with a chlorophosphite. Decomposition of the adduct gives the alkene in high yield (eq 9).[18]

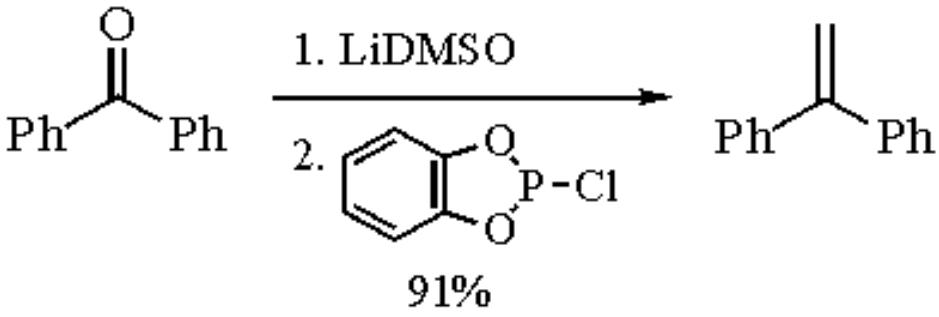

(9)

The reaction of LiDMSO with cyclohexanone is reported to give a 45% yield of the addition product along with 51% of recovered starting material, arising from competitive enolization of the ketone. This compares favorably with NaDMSO, with which the same products are formed in 17 and 80% yields, respectively. This is another example of the potential of LiDMSO in circumventing untoward reactions precipitated by the potent basicity of dimsyl anions.

Reaction with Imines and Related Compounds.

As with NaDMSO, the addition of LiDMSO to aromatic nitrogenous heterocycles has been examined. A recent report describes a tandem addition to quinoxaline to give an annulated product in fair yield (eq 10).[19]

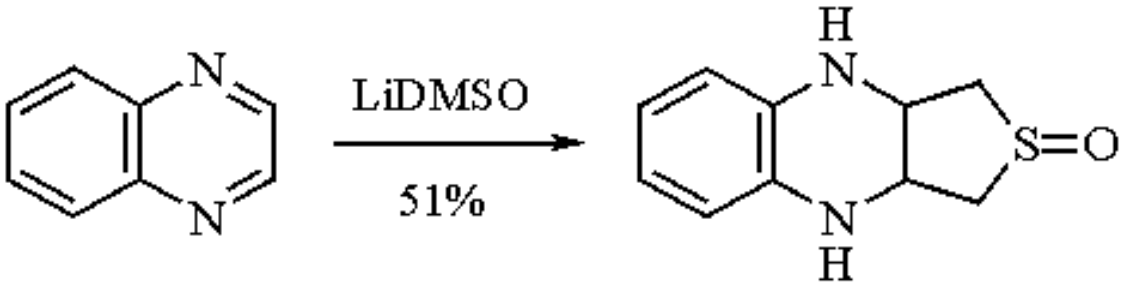

(10)

Reaction with Halides.

LiDMSO reacts with chloromethyl alkyl ethers to give substitution products in poor to fair yields.[20]

Reaction with Michael Acceptors.

α,β-Unsaturated thioamides react in a 1,4-fashion with LiDMSO (eq 11).[21] No information on the diastereoselectivity of this reaction was reported.

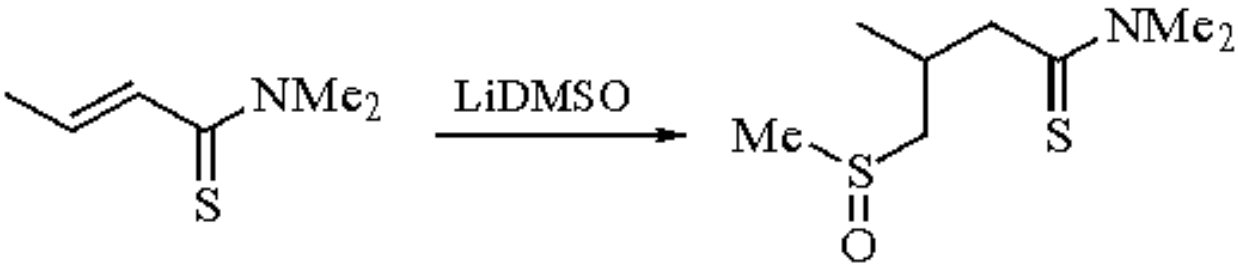

(11)

Reaction with Sulfur Electrophiles.

Optically active β-disulfoxides are available from the reaction of optically pure menthyl sulfoxides and LiDMSO.[22]

Other Applications.

The use of DMSO as a dummy ligand in cuprate chemistry has been reported.[23] The reaction of LiDMSO with

Copper(I) Iodide followed by reaction with an alkyllithium (RLi) gives a cuprate ($MeSOCH_2$)RCuLi. Subsequent reactions including conjugate additions, ketone formation from acid chlorides, S_N2' reactions, and coupling with primary iodides and tosylates result in selective transfer of the alkyl group. This inexpensive and readily available dummy ligand should find considerable application in cuprate chemistry.

---

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Lithium Morpholide

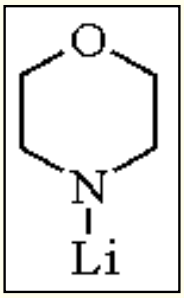

[37828-58-3] · C_4H_8LiNO · Lithium Morpholide · (MW 93.07)

(in situ protection of aromatic aldehydes via α-amino alkoxides;[1] nucleophile capable of adding to activated triple bonds[6-8])

Preparative Methods: prepared in situ by adding ***n-Butyllithium*** to ***Morpholine*** in anhydrous organic solvents at -40 °C.

Handling, Storage, and Precautions: highly flammable; should be kept under a nitrogen or argon atmosphere. Use in a fume hood.

Lithium morpholide (**1**) is conveniently used for in situ protection of aldehydes as α-amino alkoxides.[1a] This method has been used to regioselectively alkylate substituted benzaldehydes (eq 1)[2] and furaldehydes. Better solubility of (**1**) and the corresponding α-amino alkoxide in THF at low temperature makes (**1**) more convenient to use than other reagents such as lithium *N*-methylanilide and ***Lithium Piperidide***.[2]

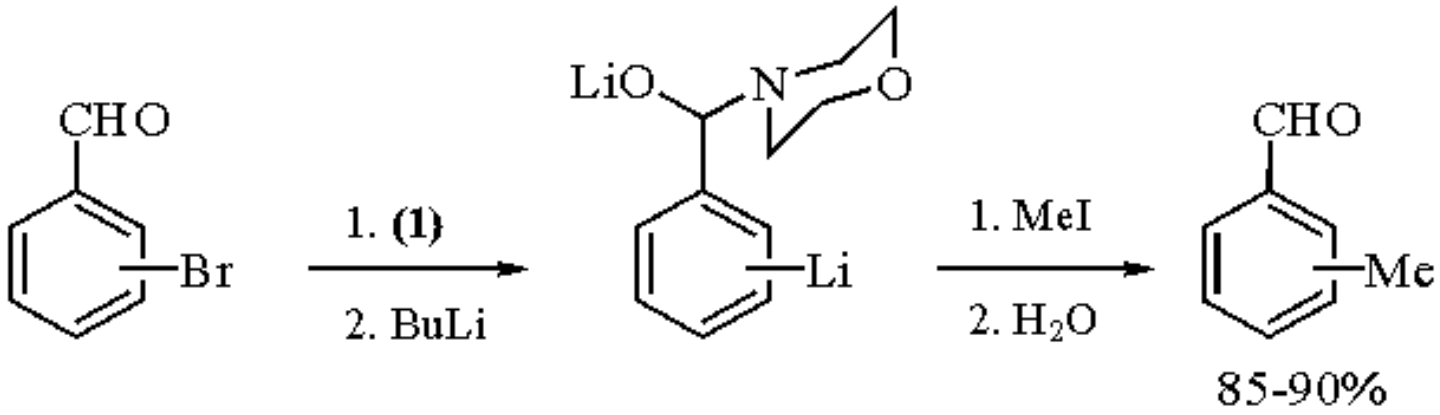

(1)

N-Formylmorpholine can be prepared by reacting (**1**) with ***Carbon Monoxide*** in THF.[3,4] Electrochemically, (**1**) can react with THF to give the aminotetrahydrofuran (**2**) (eq 2).[5]

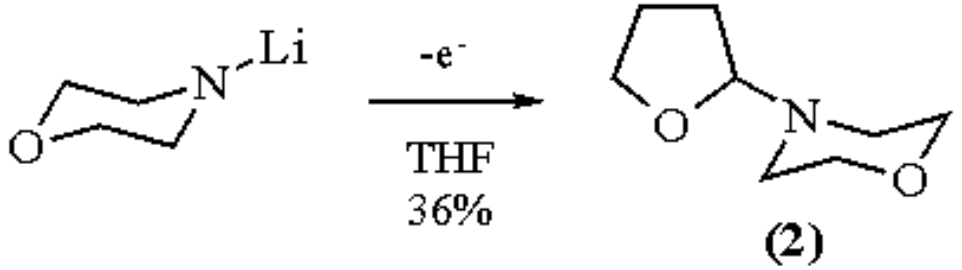

(2)

Like other lithium amides, lithium morpholide adds to various activated triple bonds to give vinyllithiums (**3**) (eq 3)[6] or allenes (**4**) (eq 4).[7]

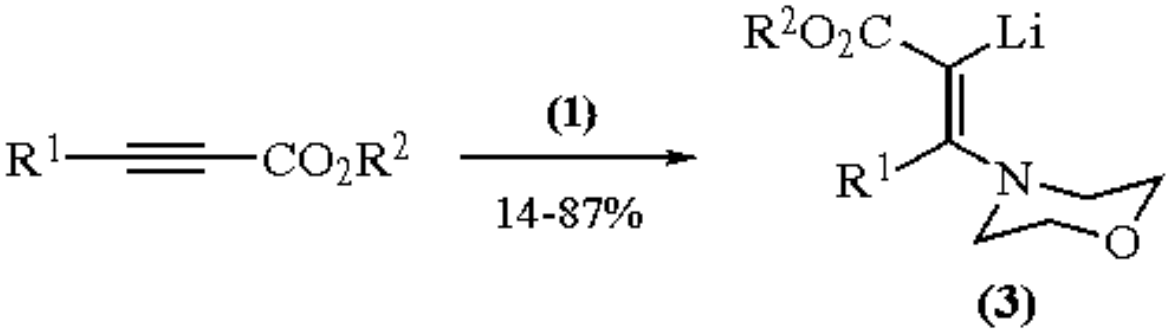

(3)

(3)

$R^1 = H, CO_2R; R^2 = Me, Et$

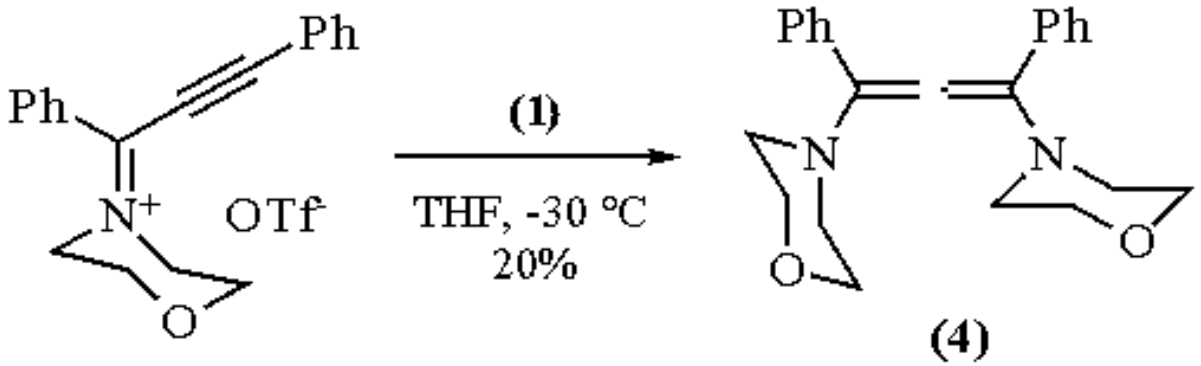

(4)

(4)

The morpholyl imine (**5**) is the product from the reaction of triethoxyacetonitrile with lithium morpholide (**1**) (eq 5).[8]

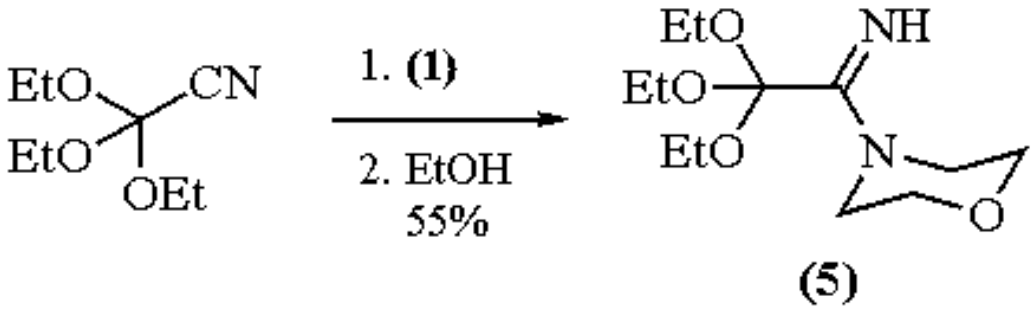

(5)

(5)

N-(α-Cyanoacetyl)morpholine is prepared by the nucleophilic substitution of ethyl cyanoacetate with lithium morpholide.[9] Dimerization resulting in bimorpholine has been observed when (**1**) is treated with ***Copper(I) Chloride***.[10]

Related Reagents.

N-Lithio-N,N´,N´-trimethylethylenediamine; ***Lithium N-Methylpiperazide***; ***Lithium Piperidide***.

---

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Lithium Naphthalenide[1]

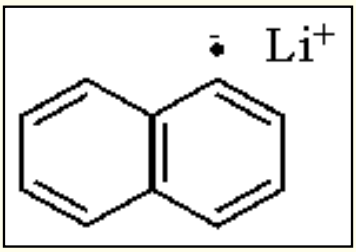

[7308-67-0] · $C_{10}H_8Li$ · Lithium Naphthalenide · (MW 134.12)

(reductive metalation reactions;[1c] reduction of metal salts;[27] initiation of polymerization reactions[28])

Alternate Name: LN.

Physical Data: no data on the isolated material; only available in solution.

Solubility: sol ether, benzene, THF; reacts with protic solvents and THF at elevated temperatures.[2]

Preparative Methods: made by addition of freshly cut ***Lithium*** metal to a solution of naphthalene in THF. Preparation can be accelerated by ultrasonication.[3]

Analysis of Reagent Purity: two titration methods have been described;[4] the more convenient[4b] involves conversion of 1,1-diphenylethylene by lithium naphthalenide to an intensely red-colored dianion, which is then titrated against *s*-butanol.

Handling, Storage, and Precautions: can be stored in solution up to several days; must be protected from air and moisture; can be used to ambient temperature.

Reductive Metalation.

The powerful reductive nature of this reagent makes it an important tool for lithium-heteroatom exchange reactions. Thus, it was established early on that (phenylthio)alkanes can be converted into their requisite alkyllithium species.[5] This has become the method of choice over generation by lithium metal alone. The resultant alkyllithium species can either be quenched with a proton source (eq 1),[6] or intercepted with an electrophile. This has subsequently evolved into a powerful technique, since the reaction is general for all chalcogens (eq 2)[7] and halides (eq 3).[8]

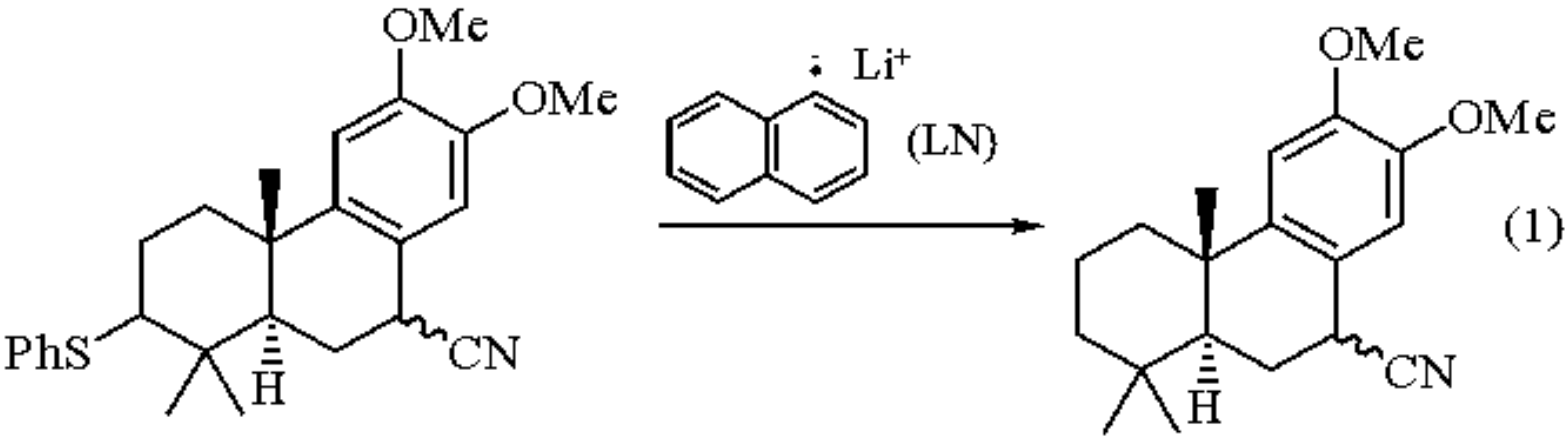

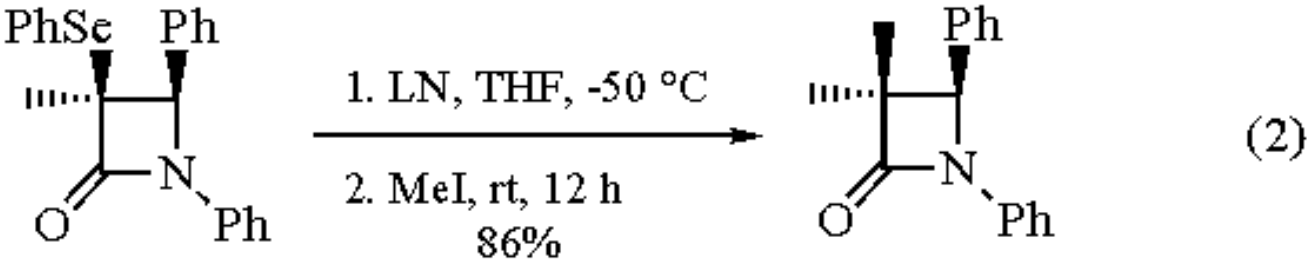

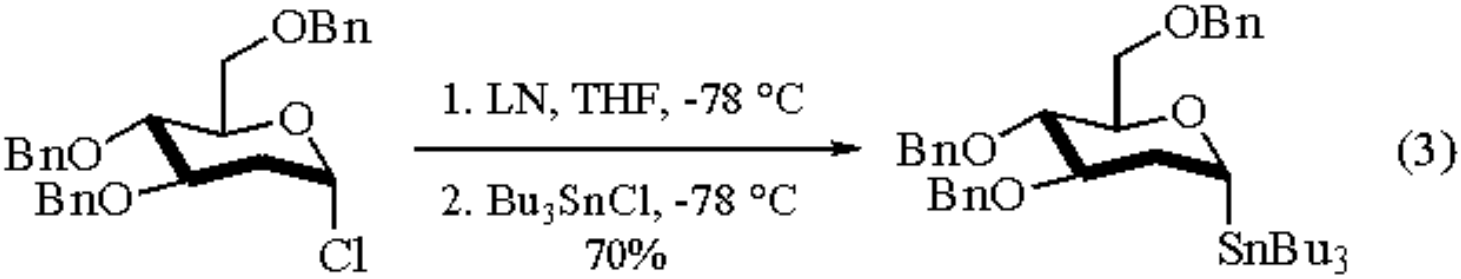

Metal-heteroatom exchange can also be persuaded to occur with a variety of other systems, resulting in allyl-[9] and vinyllithium[10] species, as well as α-lithio ethers (eq 3),[1c,8,11] α-lithio thioethers,[1c,12] α-lithio amines,[11b] and α-lithio silanes.[1c,12b,13] The latter class provides useful intermediates for the Peterson alkenation reaction (eq 4).[13a]

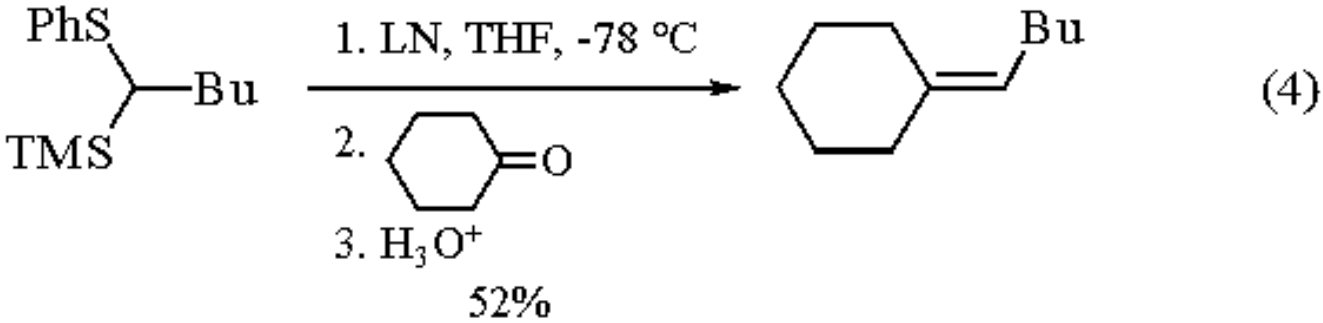

In some cases, however, it may be advantageous to proceed via either ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN), or ***Lithium 4,4´-Di-t-butylbiphenylide*** (LDBB).[1c] With the former reagent, the byproduct formed, (dimethylamino)naphthalene, is more easily removed than is naphthalene from product mixtures. In the latter case, the greater reduction potential of di-*t*-butylbiphenyl appears to lead to more efficient halogen-lithium exchange.[8b]

Dianion Generation.

Lithium naphthalenide efficiently deprotonates β-alkynyloxy[14] and carboxylate anions (eq 5).[15] In addition, the previously mentioned phenomenon of reductive metalation has been exploited to access dianions from halohydrins,[16] β-halo carboxylic acids,[17] and β-halo carboxamides,[18] and even trianions from β,o´-dihalo alcohols.[19] A major pathway for the polyanionic species is β-elimination (eq 6);[16a,19] when such processes can be avoided, the polyanions react according to Hauser's rule (eq 7).[16a,20]

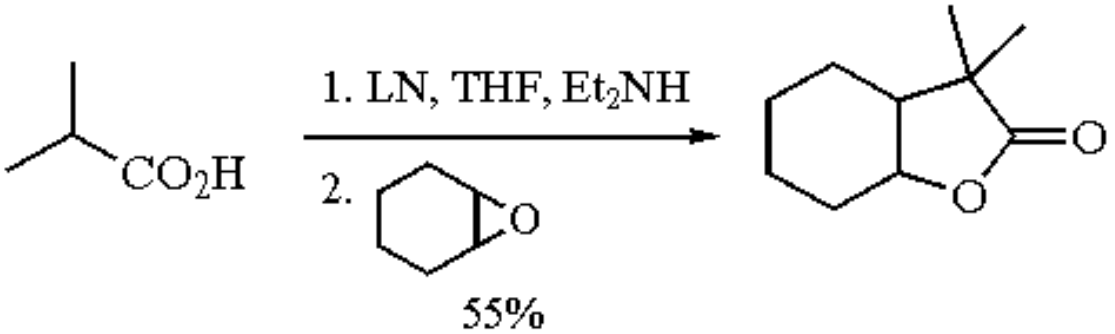

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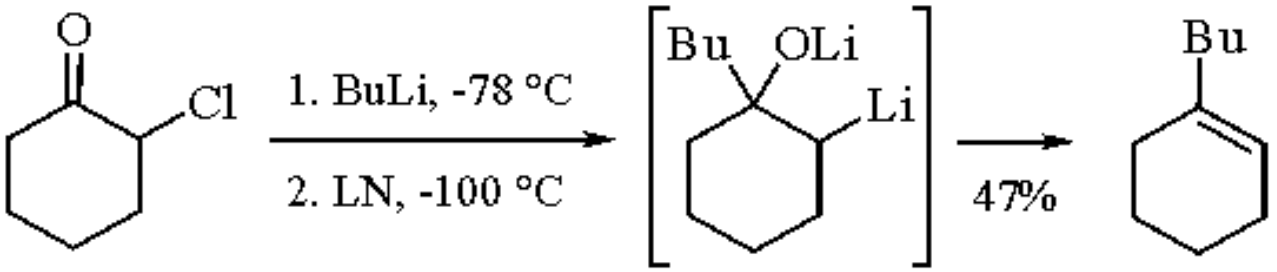

(6)

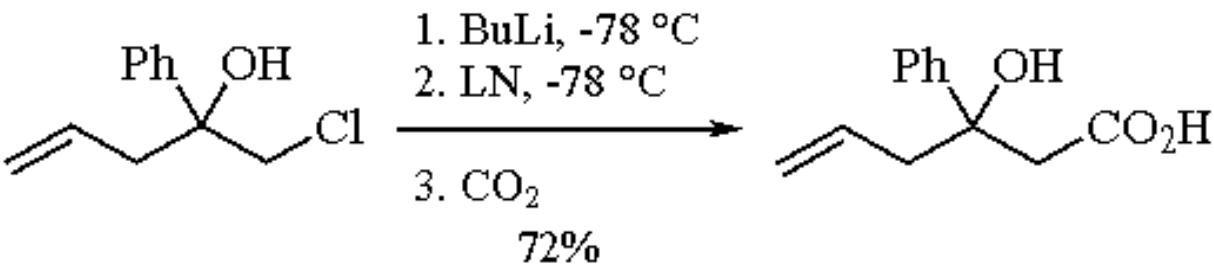

(7)

Dehalogenation Reactions.

Since lithium naphthalenide is a particularly effective initiator for halogen-metal exchange, it has found widespread use for the conversion of dihalides to unsaturated species. Thus, 1,2-dichlorodisilanes have been converted to silenes (eq 8)[21] and diphosphiranes to phosphacumulenes.[22] In a related field, silicon cages[23] have been constructed from trichlorodisilanes.

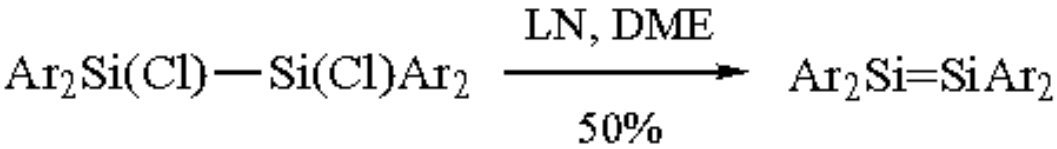

(8)

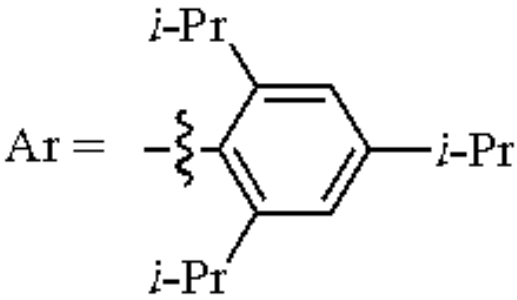

Metal Redox Reactions.

Lithium naphthalenide is a convenient reducing agent for a variety of metals, and shows great promise in the synthetic area. Thus, Cu^{I} complexes have been reduced to Cu^{0}; the resultant highly reactive species adds in an oxidative fashion across the carbon-halogen bond.[24] As a consequence, the well known organocuprate addition chemistry can be carried out in one step from halocarbons, without having to initially prepare the organolithium species (eq 9). In addition to the reduction of Cu^{I}, lithium naphthalenide reduces Si^{IV} to Si^{II},[25] Sn^{IV} to Sn^{II} (eq 10),[26] and various lanthanide compounds.[27]

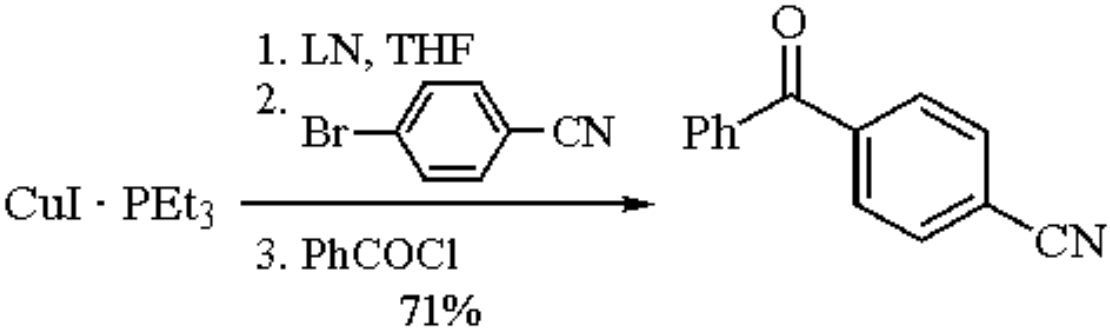

(9)

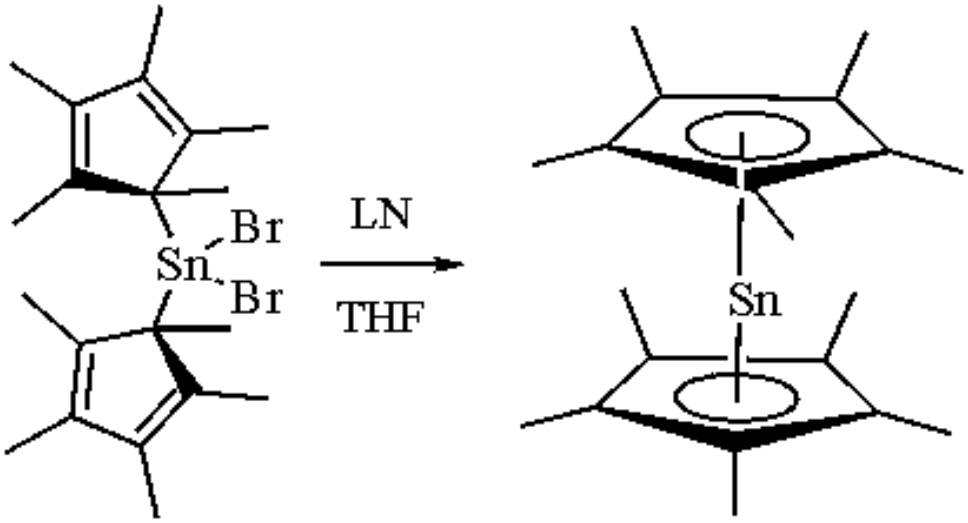

(10)

Oligomerization Reactions.

Lithium naphthalenide has long been a convenient initiator for anionic living polymerization reactions.[28] Thus, styrenes, acrylates, dienes, and other monomers have been polymerized using lithium naphthalenide as an anionic initiator. In some circumstances, however, oligomerization can be controlled to furnish only dimers (eq 11).[29] Also, in the presence of a secondary amine, 1,3-dienes can be persuaded to react in a formal 1,4-fashion to produce allyl amines (eq 12).[30]

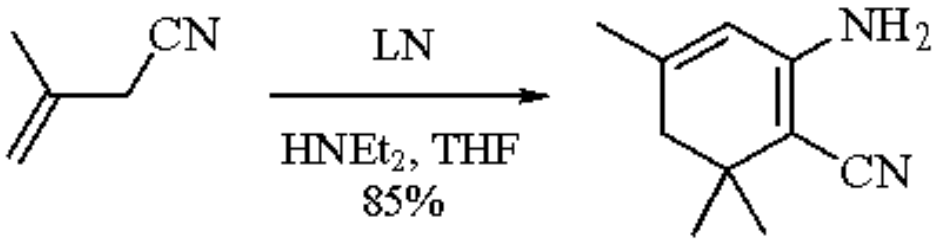

(11)

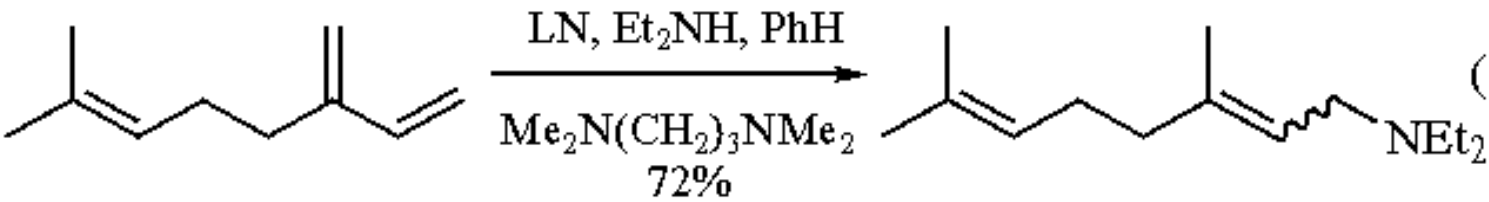

(12)

Interesting approaches toward functional polymers have recently been detailed,[31] wherein previously described chemistry involving lithium naphthalenide is conducted on suitably substituted polystyrene derivatives (eq 13).

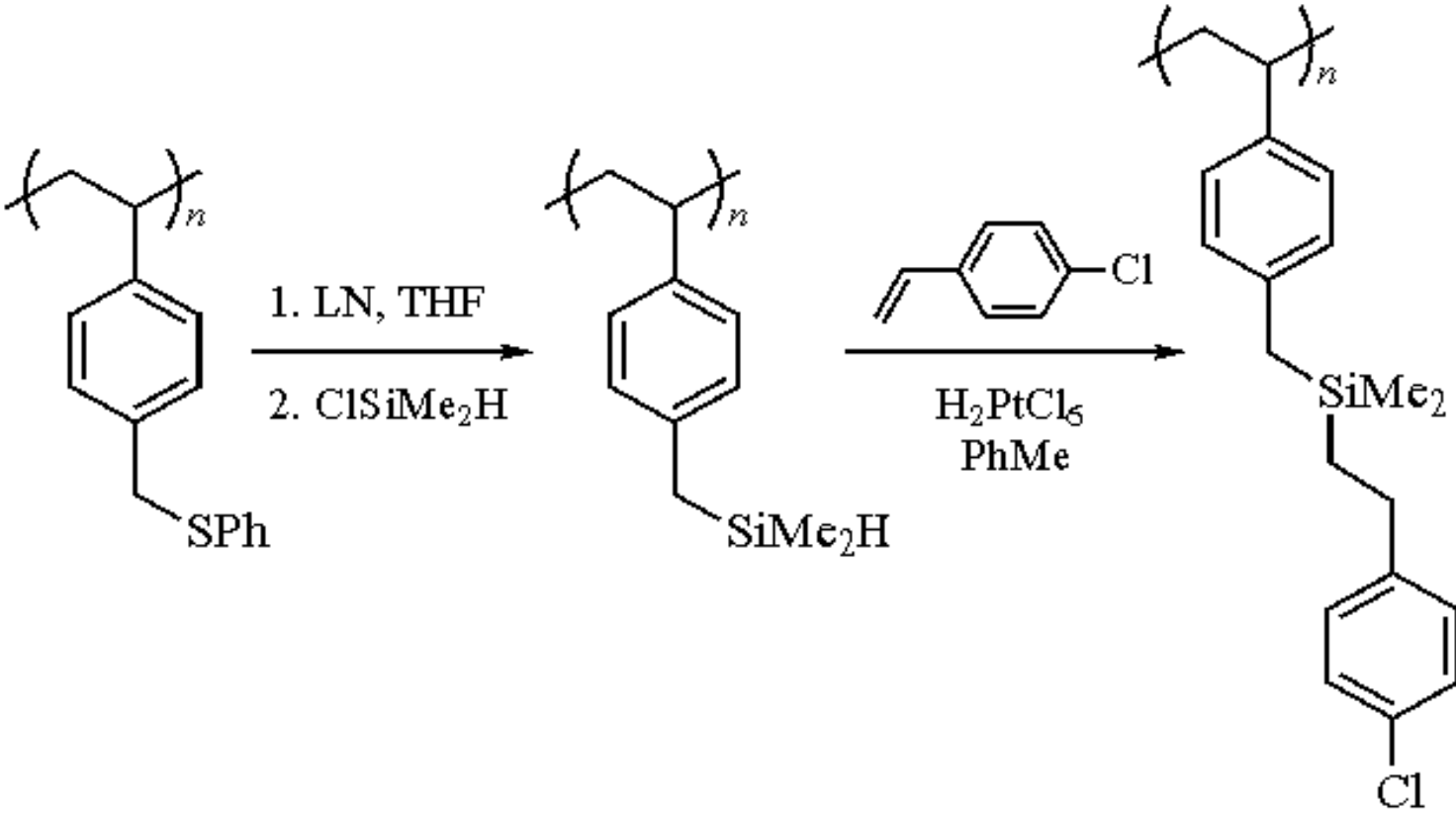

(13)

Related Reagents.

Copper(I) Iodide-Triethylphosphine-Lithium Naphthalenide; ***Lithium 4,4´-Di-t-butylbiphenylide***; ***Lithium 1-(Dimethylamino)naphthalenide***; ***Potassium Naphthalenide***; ***Sodium Anthracenide***; ***Sodium Naphthalenide***; ***Sodium Phenanthrenide***.

---

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Lithium (1-Pentynyl)(3-tetrahydropyran-2´-yloxy-1-propenyl)cuprate

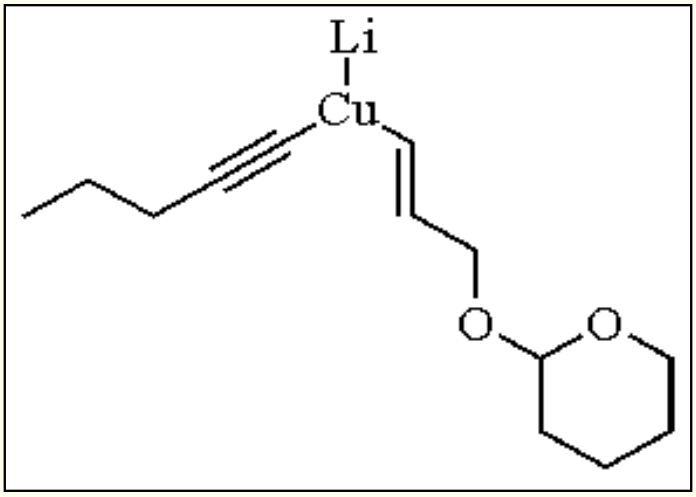

[66915-91-1] · $C_{13}H_{20}CuLiO_2$ · Lithium (1-Pentynyl)(3-tetrahydropyran-2´-yloxy-1-propenyl)cuprate · (MW 278.82)

(mixed organocuprate useful in the synthesis of *trans*-allylic alcohols)

Preparative Methods: prepared in situ by lithiation of *trans*-3-tetrahydropyran-2´-yloxy-1-(tri-*n*-butylstannyl)-1-propene with ***n-Butyllithium*** in THF. The resulting lithium reagent is then added to ***1-Pentynylcopper(I)*** in the presence of ***Hexamethylphosphorous Triamide*** at -40 °C.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Lithium (1-pentynyl)(3-tetrahydropyran-2´-yloxy-1-propenyl)cuprate (**1**) allows the synthesis of *trans*-allylic alcohols from α,β-enones. For example, reaction of (**1**) with 2-cyclohexen-1-one affords the conjugate addition adduct (**2a**) in 85% yield (eq 1).[1] The utility of the intermediates generated by reaction of (**1**) with enones has been demonstrated (eq 2). Reaction with 2-cyclopenten-1-one followed by deprotection, mesylation, and base treatment provides vinylcyclopropane (**4**), which is thermolyzed at 600 °C to provide bicyclic ketone (**5**). Compound (**5**) is reduced with ***Sodium Borohydride*** and the alkene is oxidatively cleaved with ***Sodium Periodate-Osmium Tetroxide***; methanolysis in the presence of a catalytic amount of ***Boron Trifluoride Etherate*** is followed by epimerization with base to afford aldehyde (**6**). The transformation of (**6**) to 11-deoxyprostaglandin E_2 (**7**) had been previously reported.[2]

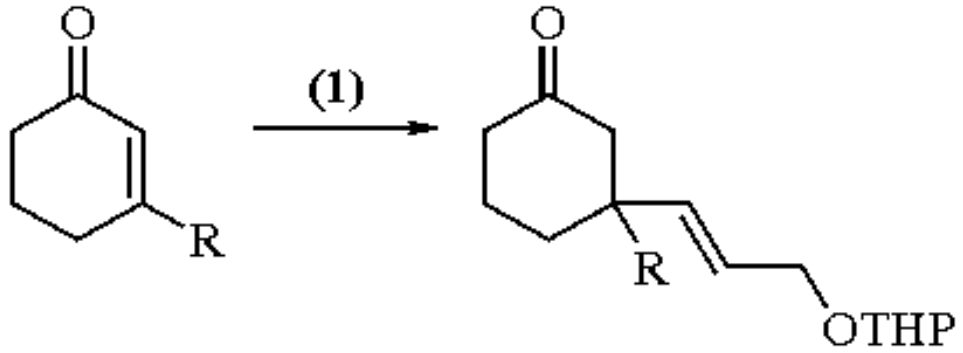

(1)

(2a) R = H, 85%
(2b) R = Me, 84%

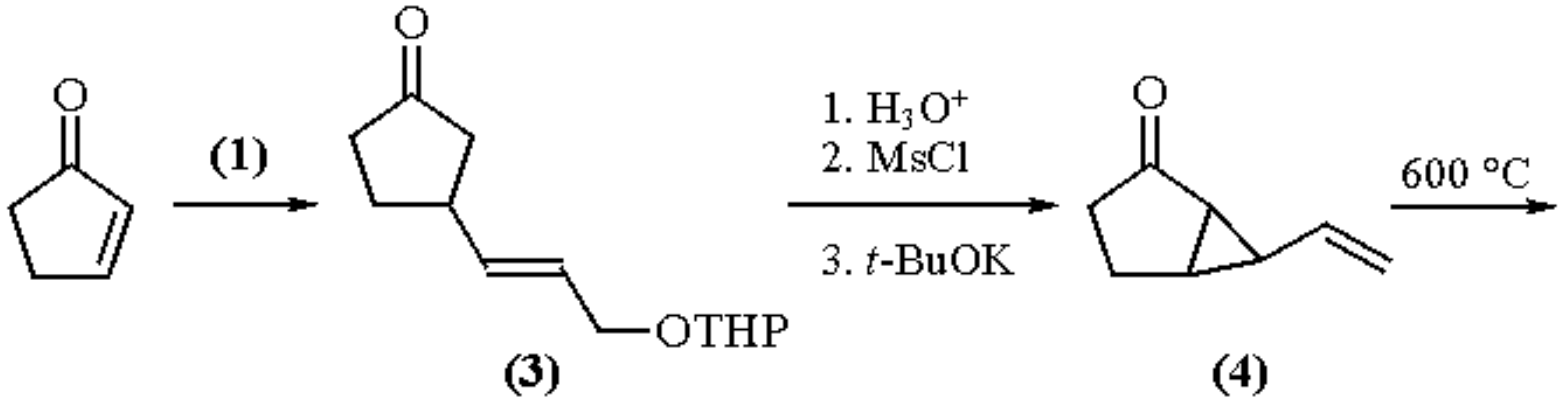

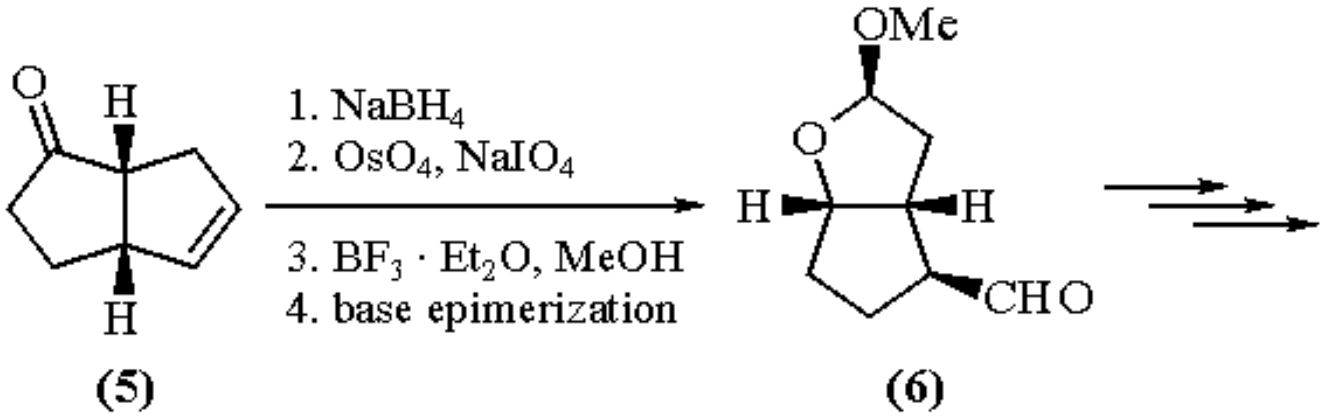

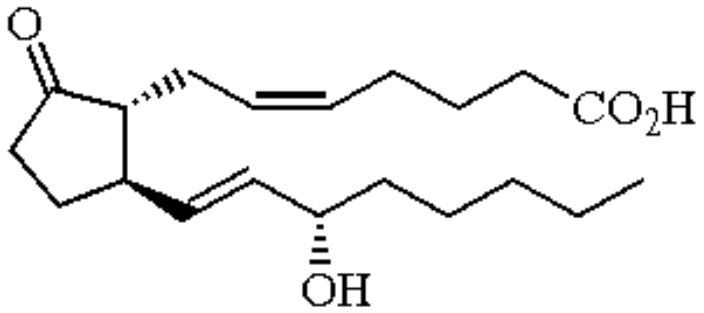

(2)

(7)

A report in the patent literature (eq 3) utilizes (**1**) to prepare the prostaglandin analog (**9**).[3] Starting with 2-cyclopenten-1-one, the intermediate anion is trapped with $MeO_2C(CH_2)_5COCl$ to provide cyclopentanone (**8**) in 49% yield. Hydrolysis of the THP group and saponification gives the desired analog (**9**) in ~30% overall yield.

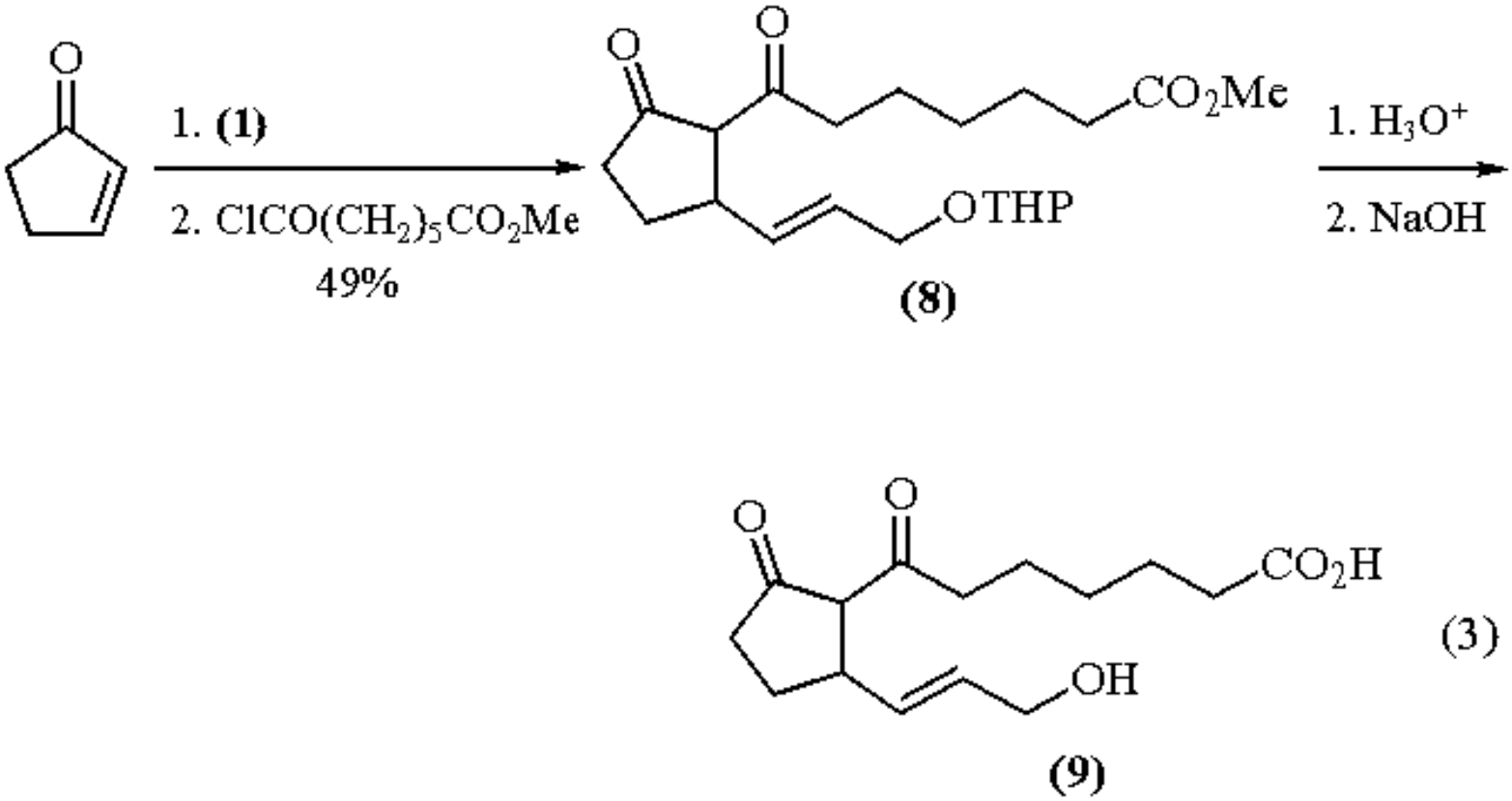

(3)

Related Reagents.

1-Hexynylcopper(I); ***Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate***; ***Lithium (1-Pentynyl)(2-tri-n-butylstannylvinyl)cuprate***; ***1-Pentynylcopper(I)***; ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***.

---

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2. Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *JACS* **1969**, *91*, 5675.
3. Toru, T.; Kurozumi, S.; Kobayashi, M.; Hashimoto, Y. *Jpn. Patent* 78 23 954, 1978 (*CA* **1978**, *89*, 23 837e).

Matthew E. Voss

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Lithium (1-Pentynyl)(2-tri-*n*-butylstannylvinyl)cuprate

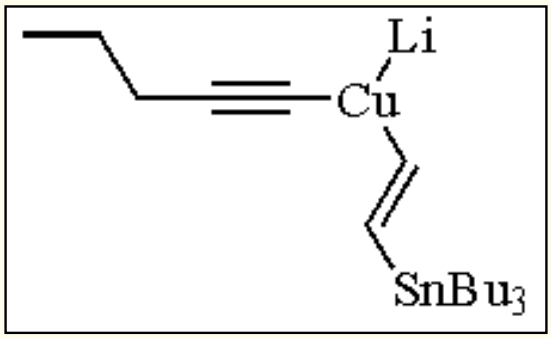

[-] · $C_{19}H_{36}CuLiSn$ · Lithium (1-Pentynyl)(2-tri-*n*-butylstannylvinyl)cuprate · (MW 453.75)

(mixed organocuprate; introduces angular acetylene equivalent to enones via vinylstannanes)

Preparative Method: prepared in situ by first monolithiating ***trans-1,2-Bis(tributylstannyl)ethylene*** with ***n-Butyllithium*** in THF at -78 °C, then transferring the anionic solution via cannula to a mixture of ***1-Pentynylcopper(I)*** and ***Hexamethylphosphorous Triamide*** at -40 °C.[1]

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Lithium (1-pentynyl)(2-tri-*n*-butylstannylvinyl)cuprate (**1**) undergoes 1,4-addition to α,β-enones in high yields.[1] The resulting addition products can then be readily transformed into terminal alkynes with ***Lead(IV) Acetate*** in acetonitrile. This sequence provides a two-step method for the introduction of angular acetylenes (eqs 1 and 2).

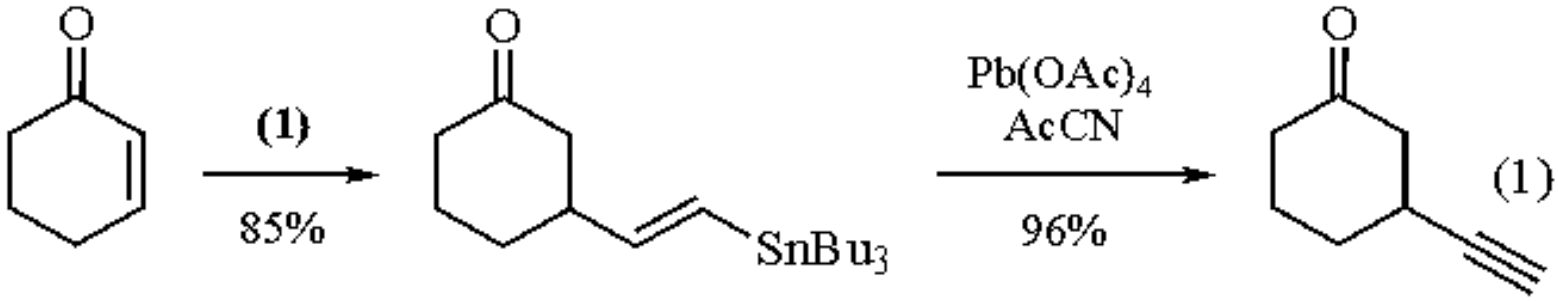

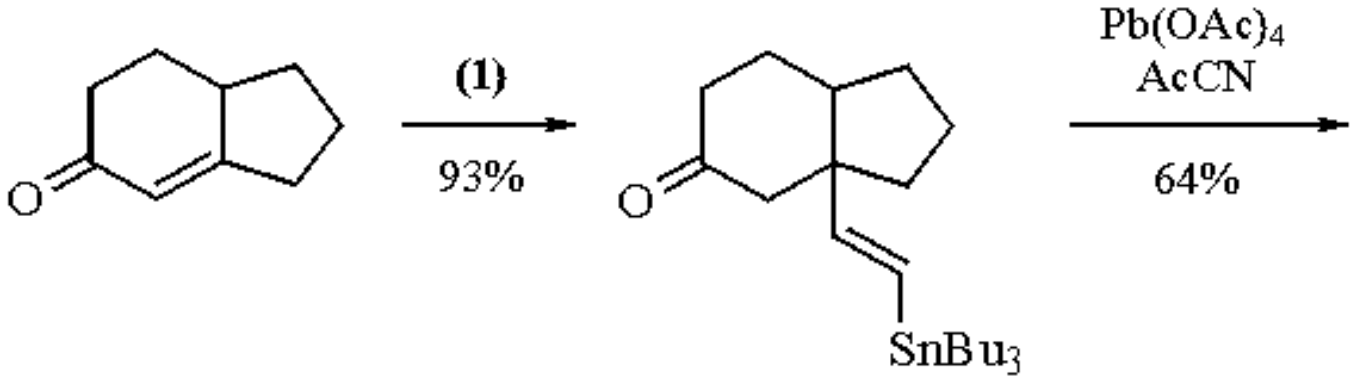

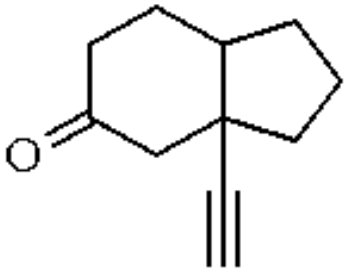

(2)

Related Reagents.

1-Hexynylcopper(I); ***Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate***; ***1-Pentynylcopper(I)***; ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***.

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1. Corey, E. J.; Wollenberg, R. H. *JACS* **1974**, *96*, 5581.

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Lithium Perchlorate[1]

$LiClO_4$

[7791-03-9] · $ClLiO_4$ · Lithium Perchlorate · (MW 106.39)

(mild Lewis acid[1] for cycloaddition reactions,[2] conjugate additions,[3] ring opening of epoxides,[4] and ring expansion of cyclopropanes[5])

Physical Data: mp 236 °C; bp 430 °C (dec); *d* 2.428 g cm^{-3}.

Solubility: 60 g/100 mL H_2O (25 °C); 150 g/100 mL H_2O (89 °C); 152 g/100 mL EtOH (25 °C); 137 g/100 mL acetone (25 °C); 182 g/100 mL MeOH (25 °C); 114 g/100 mL ether.

Form Supplied in: white solid; widely available in anhydrous form or as the trihydrate; it is usually used in solution in ether or MeOH.

Purification: anhydrous lithium perchlorate is prepared by heating the commercially available anhydrous material or its trihydrate at 160 °C for 48 h under high vacuum (P_2O_5 trap).

Handling, Storage, and Precautions: the anhydrous material should be used as prepared for best results. The decomposition of lithium perchlorate starts at about 400 °C and becomes rapid at 430 °C, yielding lithium chloride and oxygen. Perchlorates are potentially explosive and should be handled with caution.

Lewis Acid Catalyst for Cycloaddition Reactions and Carbonyl Addition Reactions.

This reagent, usually prepared as a 5.0 M solution in diethyl ether, produces a dramatic rate acceleration of Diels-Alder reactions (eq 1). Evidence shows that this rate acceleration, which was initially thought to be a result of high internal solvent pressure, is due to the Lewis acid character of the lithium ion.[6]

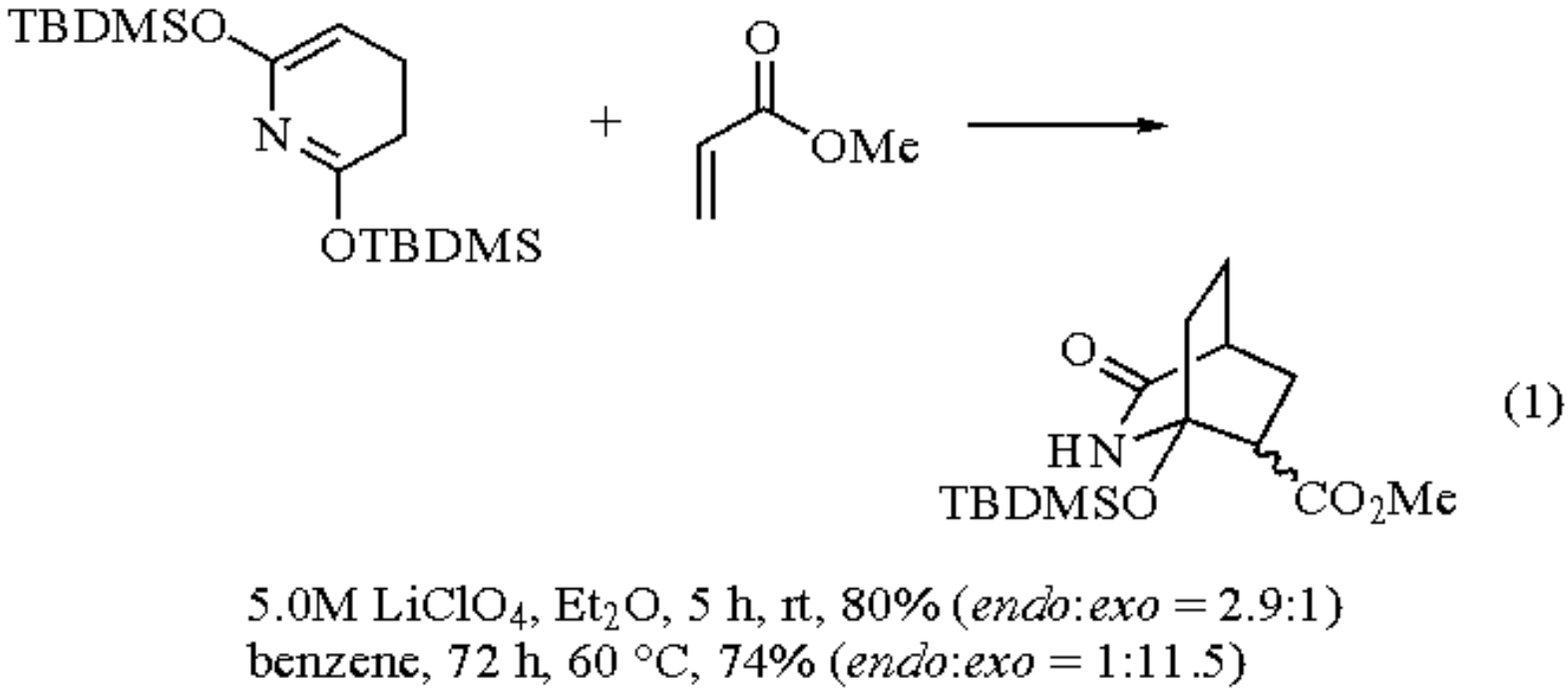

Under these conditions, reasonable levels of diastereoselectivity have been observed in the reaction between a chiral diene and ***N-Phenylmaleimide*** (eq 2).[7] An interesting protecting group dependence of diastereoselectivities has also been observed in the hetero-Diels-Alder reaction of *N*-protected α-amino aldehydes with 1-methoxy-3-*t*-butyldimethylsilyloxybutadiene to produce dihydropyrones (eqs 3 and 4).[8]

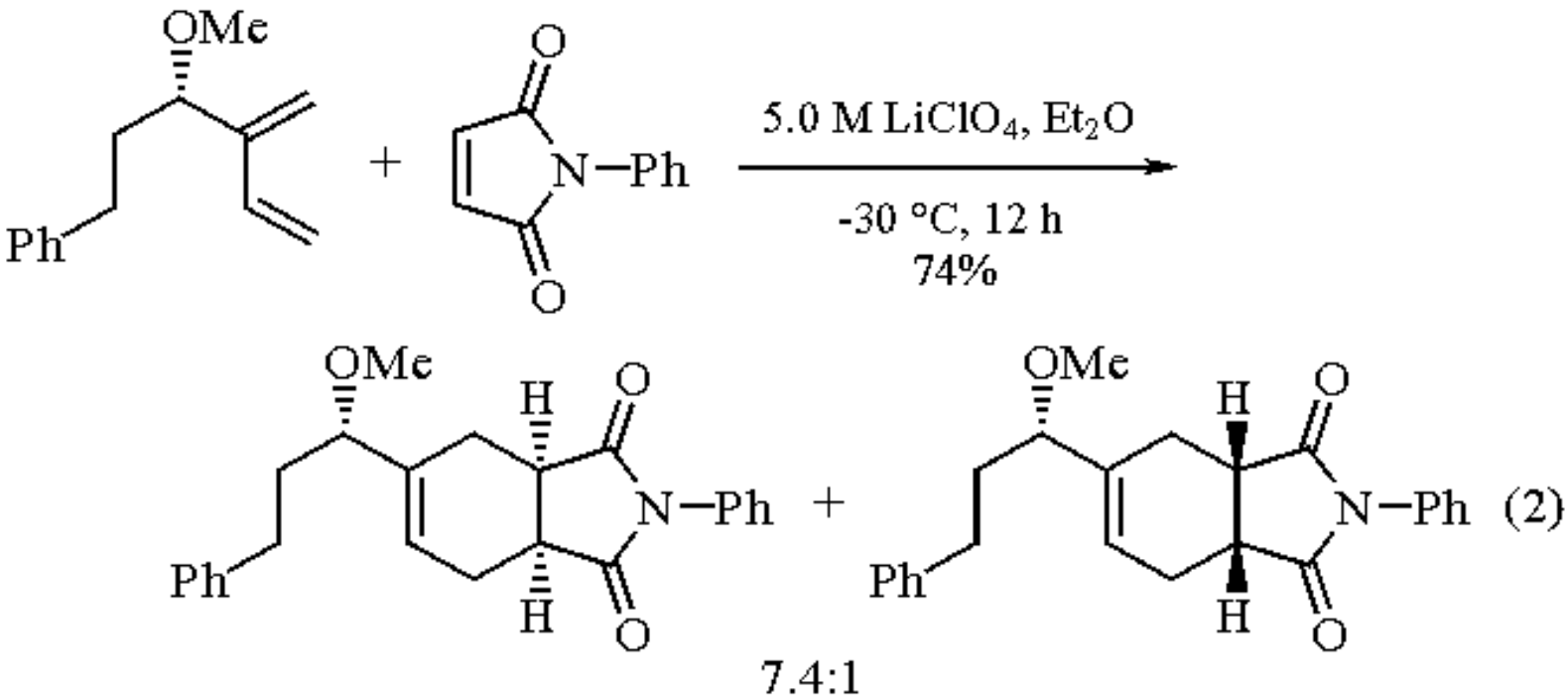

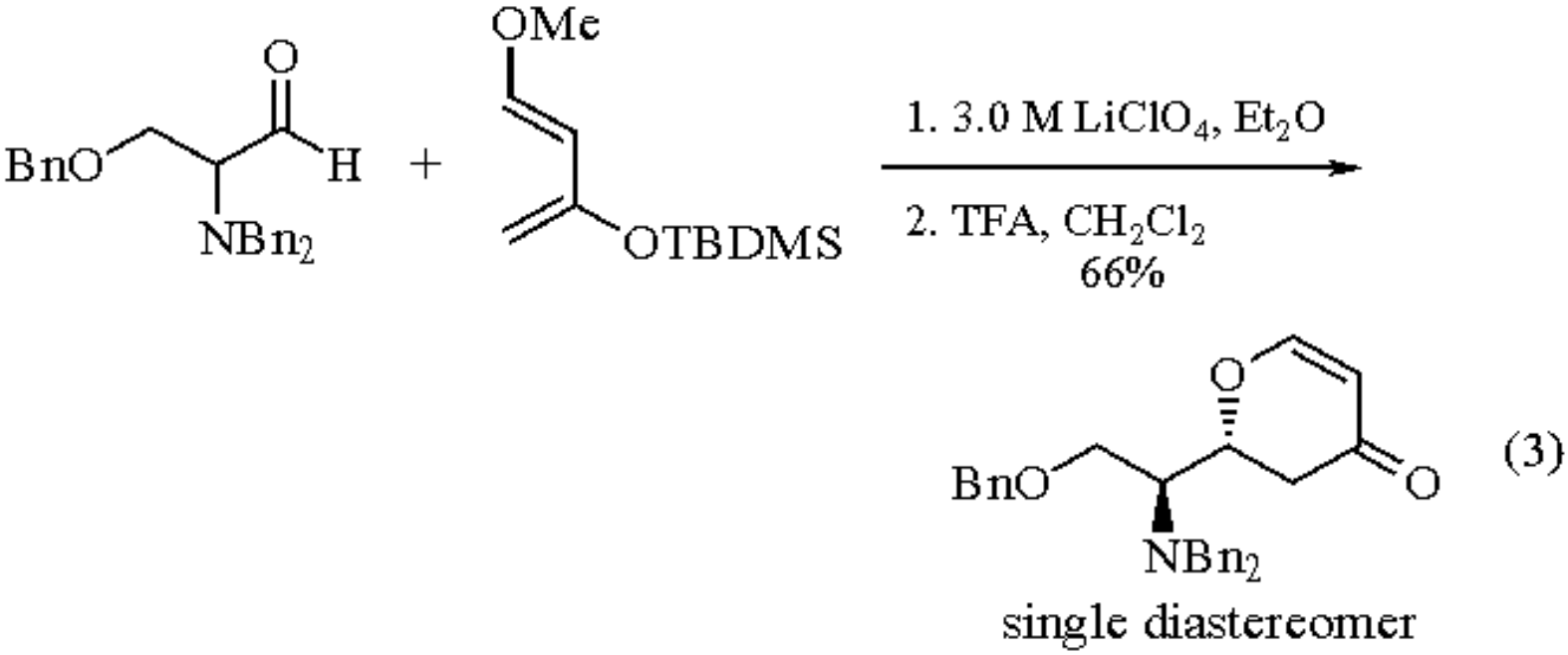

(3)

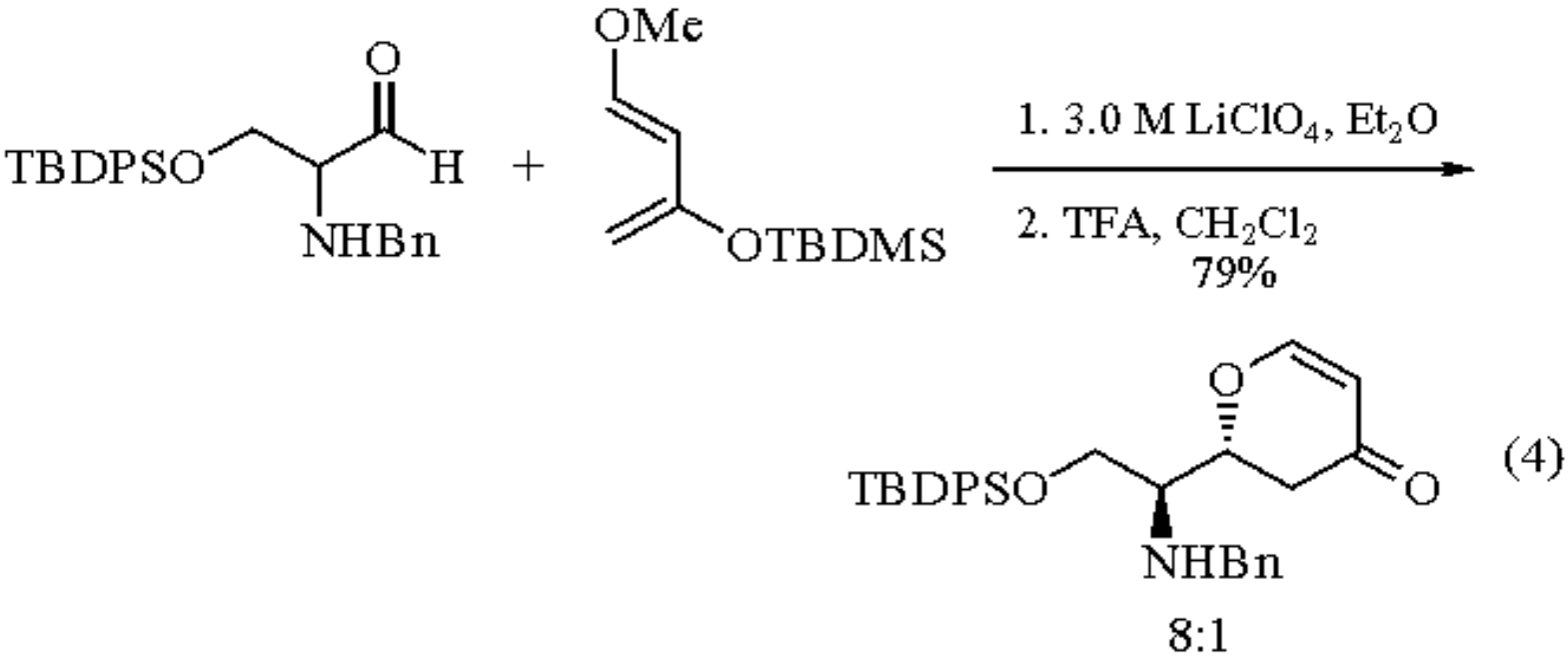

(4)

O-Silylated ketene acetals undergo 1,4-conjugate addition to hindered α,β-unsaturated carbonyl systems[3] and quinones[9] in the presence of $LiClO_4$.

[1,3]-Sigmatropic Rearrangements.

In contrast to the [3,3]-sigmatropic rearrangement observed under thermal conditions, allyl vinyl ethers undergo [1,3]-sigmatropic rearrangements at rt when submitted to 1.5-3.0 M $LiClO_4$ in Et_2O (eq 5).[10]

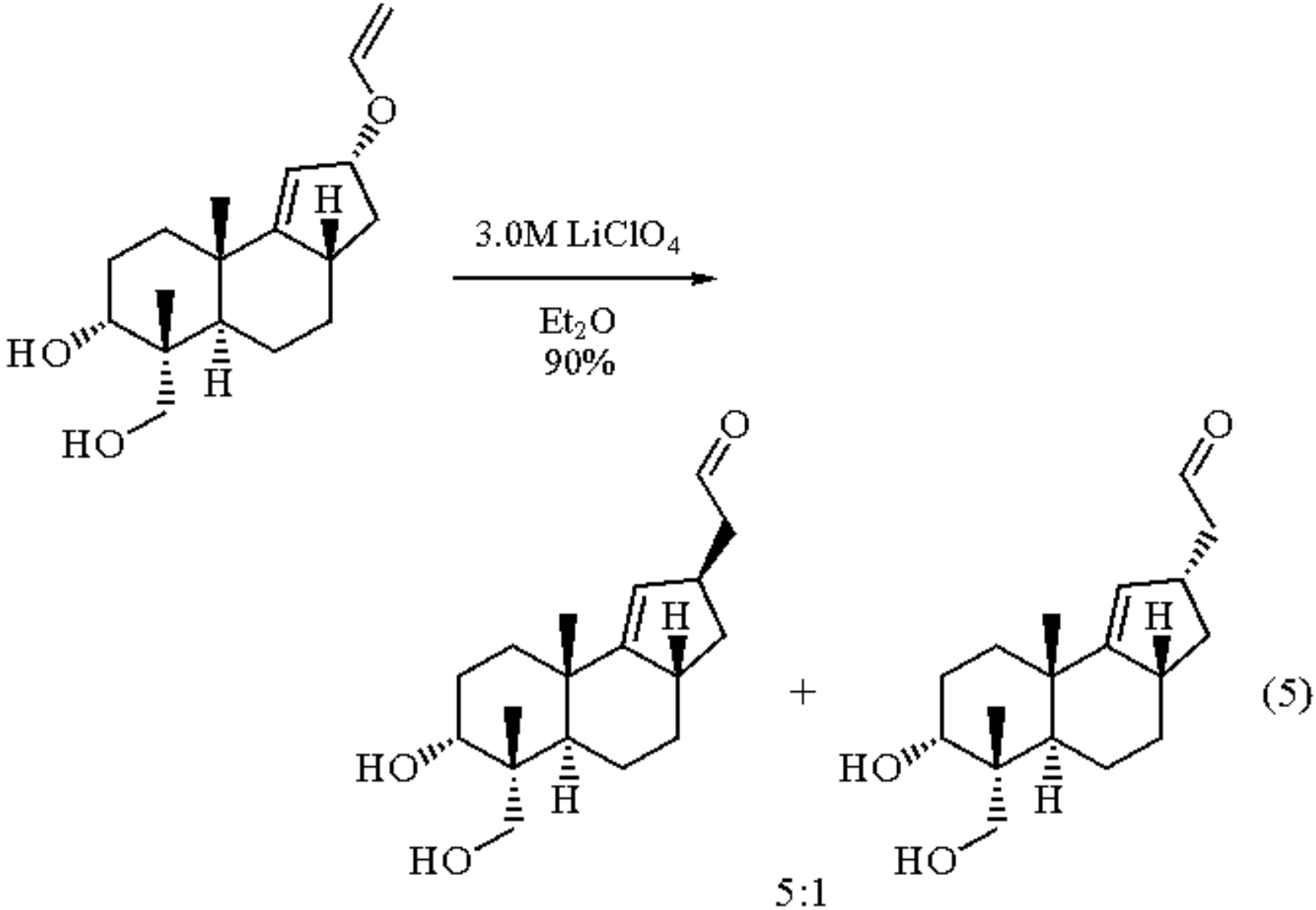

(5)

Epoxide Opening.

$LiClO_4$ is an efficient promotor for the regioselective nucleophilic opening of oxiranes with amines,[11] cyanide,[12] azide,[13] thiols,[14] halides,[15] and lithium acetylides.[16] The regioselective opening of oxiranes with lithium enolates derived from ketones has also been observed in the presence of $LiClO_4$ (eq 6).[17]

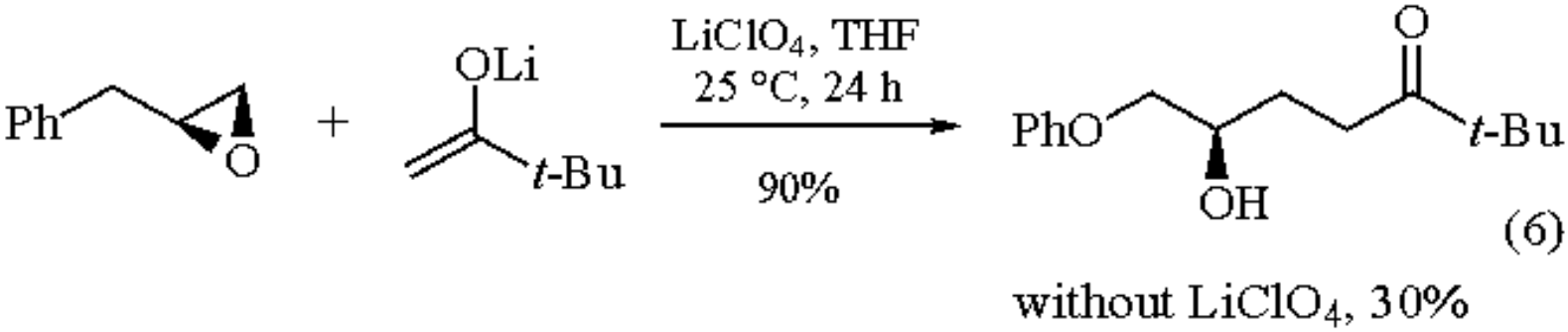

(6)

Ring Expansion.

The condensation of aldehydes and ketones with diphenylsulfonium cyclopropylide produces oxaspiropentanes which undergo ring expansion to produce cyclobutanones upon treatment with lithium perchlorate.[18]

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Lithium Phenylethynolate

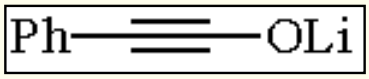

[57015-19-7] · C_8H_5LiO · Lithium Phenylethynolate · (MW 124.07)

(ambident nucleophile producing ketenes or alkynol esters in reactions with acid chlorides;[1] intermediate reagent in carboxylic acid homologation;[2] starting reagent in the synthesis of silyl ynol ethers[3])

Physical Data: the pK_a of phenylethynol is estimated to be less than 2.8.[4]

Solubility: THF; reacts with water and protic solvents.

Form Supplied in: prepared in situ and used directly.

Preparative Methods: four methods can be used for the preparation of lithium phenylethynolate and other lithium alkynolates: reaction of α,α-dibromo ketones with alkyllithium reagents (eq 1);[1,2] a multistep, one-pot synthesis from ethyl esters (eq 2);[2] reaction of isoxazole with ***n-Butyllithium*** (eq 3);[5] and oxidation of lithium phenylacetylide by lithium *t*-butyl peroxide (eq 4).[6] The first two reactions (eqs 1 and 2) are the most general and usually give the best results in the preparation of a variety of lithium alkynolates.[2,3] The other two methods (eqs 3 and 4) lack generality and have only limited application. All these methods are used for the preparation of lithium alkynolates in situ; no attempts to isolate pure compounds have been reported.

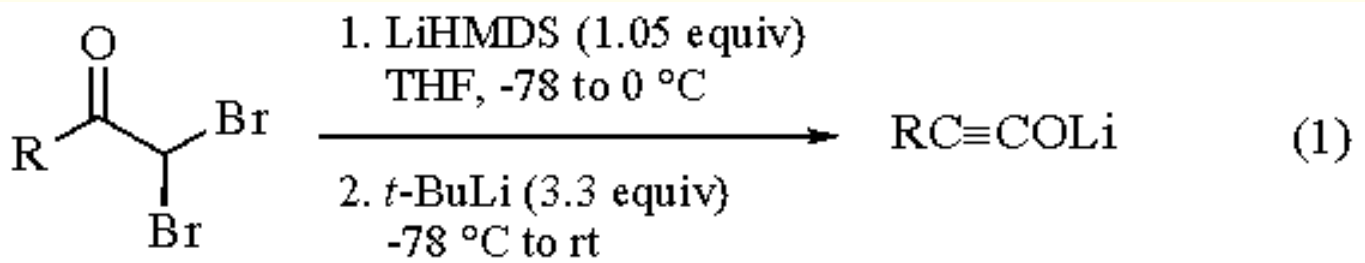

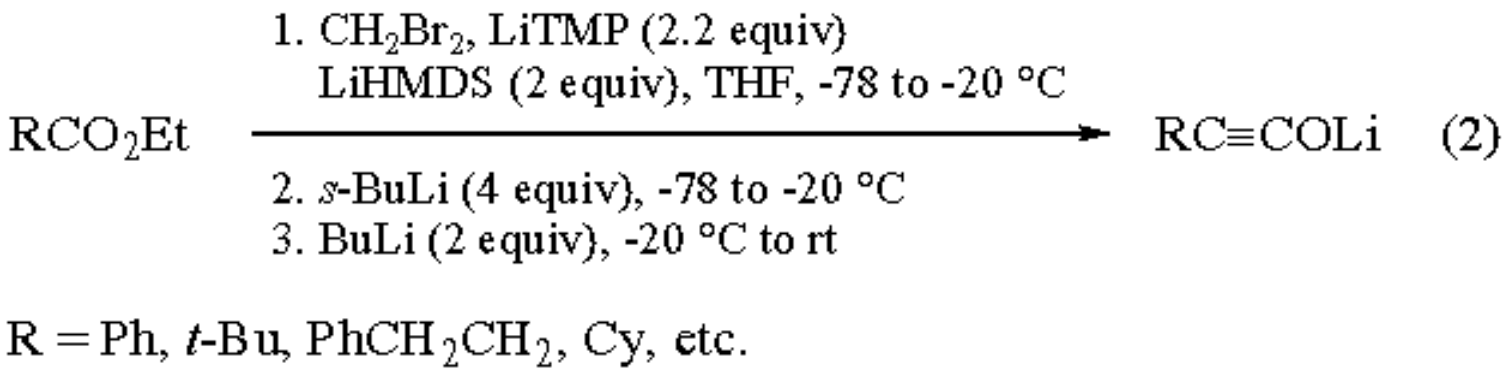

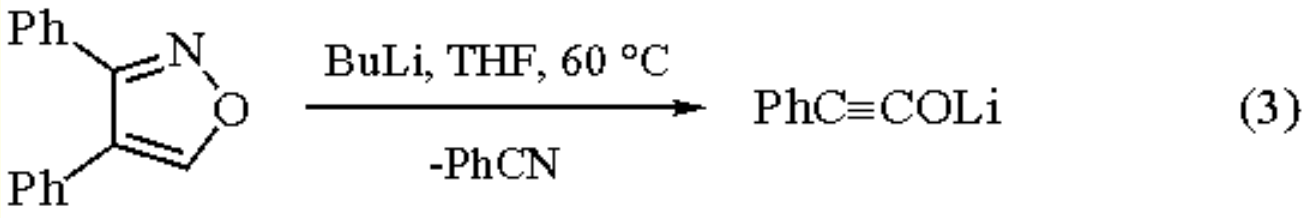

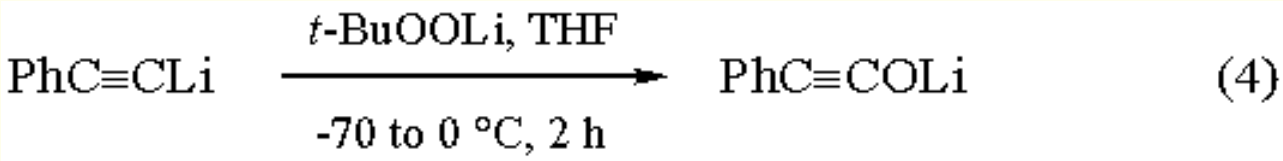

Handling, Storage, and Precautions: must be prepared and handled under inert gas (Ar or N_2) to exclude moisture. Solutions in THF are stable for several hours at room temperature.

Reactions with Acid Chlorides.

Lithium alkynolates are ambiphilic nucleophiles and can form products of both *O*- and *C*-attack in reactions with electrophilic reagents. Reaction of lithium alkynolates with dialkyl chlorophosphates affords alkynyl phosphate esters as the major products (eq 5). However, reactions with acyl chlorides under similar conditions results in both the alkynyl benzoate *O*-acylation product and the corresponding ketene due to *C*-acylation (eq 6).[1]

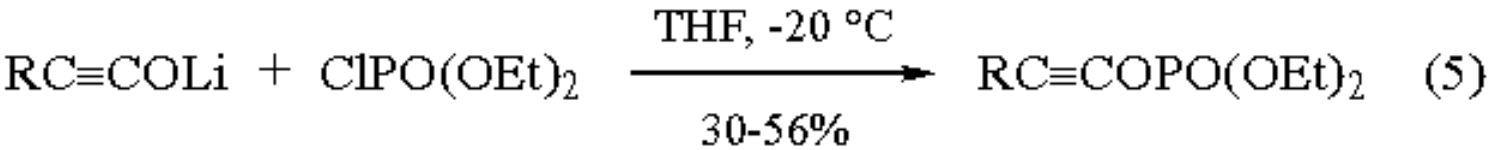

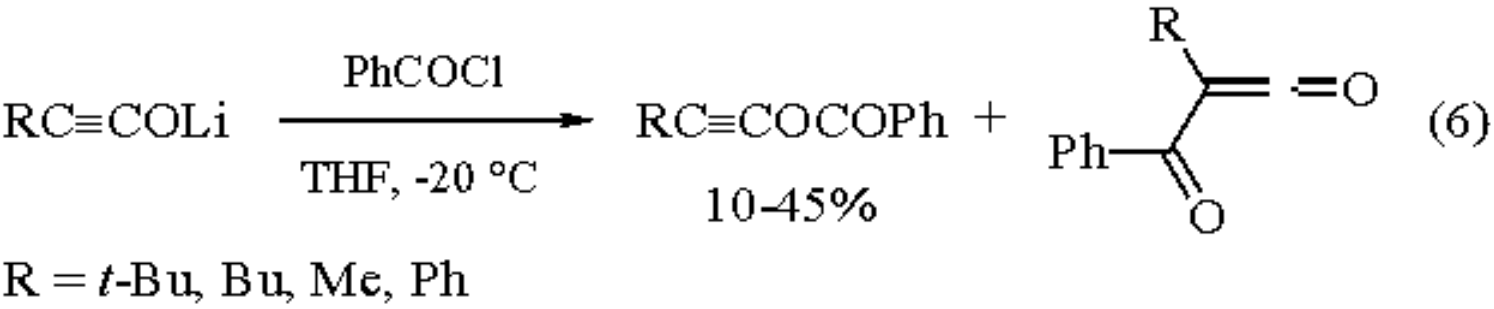

Reactions with Ketones and Aldehydes.

Carbon electrophiles such as ketones and aldehydes react with alkynolates, forming exclusively products of *C*-attack. Addition of phenylethynolate to cyclohexanone affords a spirolactone resulting from the cyclization of the originally formed ketene (eq 7). Similarly, the reaction of lithium alkynolates with benzaldehyde can be rationalized by the intermediate formation of ketene (eq 8); however, the final product in this case is the unsaturated acid, not a lactone.[2a]

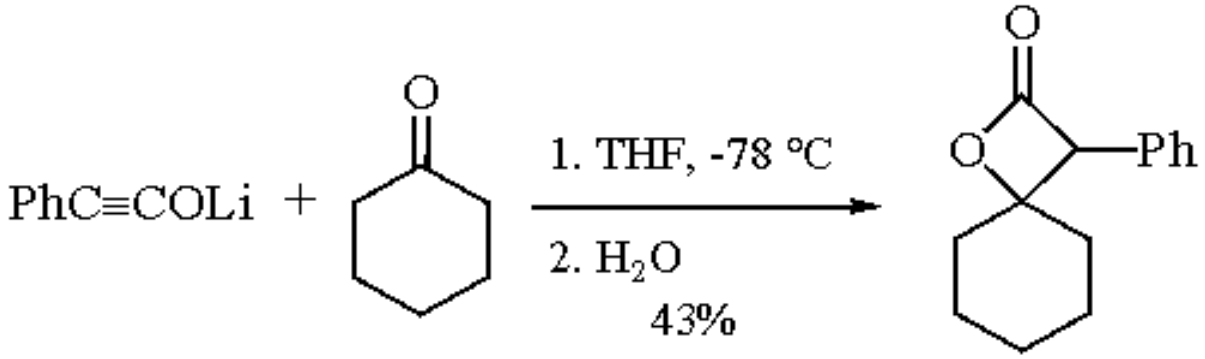

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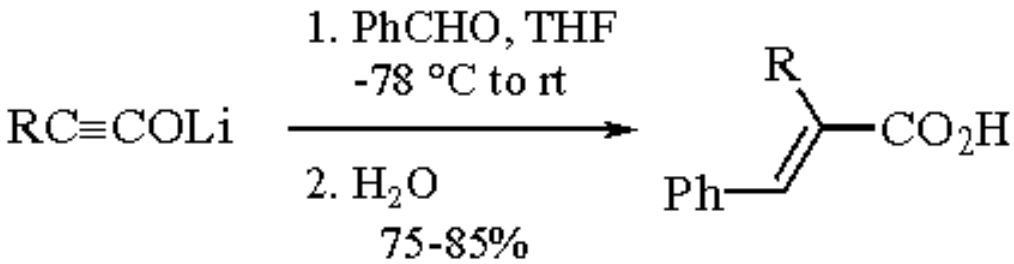

(8)

R = Ph, *t*-Bu

Reactions with Alcohols.

Alcoholysis of lithium alkynolates yields esters (eq 9).[2] This reaction is especially useful in organic synthesis as a method of ester homologation. In this case, ethyl esters of carboxylic acids are used for the generation of lithium alkynolates in situ (eq 2). Subsequent ethanolysis of lithium alkynolates in the presence of HCl gives homologated esters in good yield.[2]

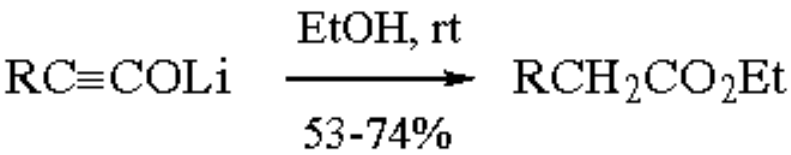

(9)

R = Ph, Cy, BuC≡C, PhCH=CH, $PhCH_2CH_2$, etc.

Preparation of Silyl Ynol Ethers.

Silylation of lithium alkynolates with trialkylchlorosilanes can be used for the preparation of silyl ynol ethers.[3] However, this method gives good yields only in reactions of sterically hindered alkynolates (eq 10).[3c] The analogous reaction of lithium alkynolates with trialkylgermanium and trialkyltin chlorides results in the exclusive formation of the corresponding ketenes.[3a]

$$RC{\equiv}COLi + R'_3SiCl \xrightarrow[50\text{-}93\%]{THF,\ -78\ ^\circ C\ to\ rt} RC{\equiv}COSiR'_3 \quad (10)$$

$R = Ph,\ t\text{-}Bu,\ s\text{-}Bu,\ Cy,\ PhCH_2CH_2,\ etc.$
$SiR'_3 = Si(i\text{-}Pr)_3$ or $Si(t\text{-}Bu)Me_2$

---

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Lithium Phenylthio(trimethylstannyl)cuprate

$Me_3SnCu(SPh)Li$

[69608-62-4] · $C_9H_{14}CuLiSSn$ · Lithium Phenylthio(trimethylstannyl)cuprate · (MW 343.50)

(trimethyltin transfer to the β-carbon of α,β-unsaturated carbonyl compounds[1-5] and α,β-alkynic carboxylic acid derivatives[6-12])

Physical Data: prepared in situ; the THF solution is dark red.

Solubility: sol THF.

Preparative Methods: lithium (phenylthio)(trimethylstannyl)cuprate (**2**) is prepared by the addition of solid ***Phenylthiocopper(I)***[14] to a THF solution of ***Trimethylstannyllithium*** (**1**)[15] (eq 1).

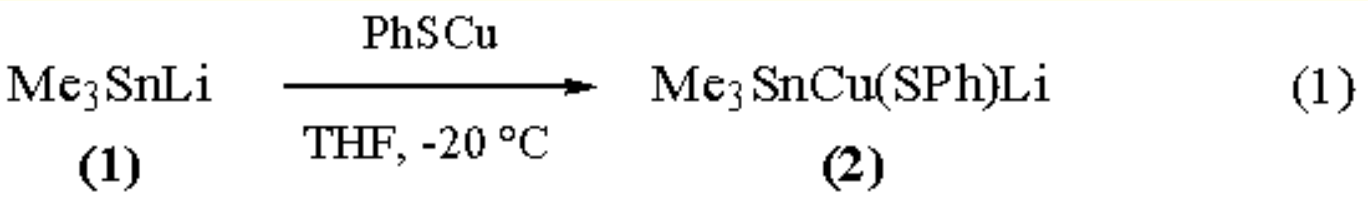

Handling, Storage, and Precautions: should be prepared in dry solvent and used under an inert atmosphere. Since organotin compounds are toxic,[13] reaction workup should be carried out in a fume hood.

Reaction With α,β-Unsaturated Carbonyl Systems.

Reagent (**2**) readily effects conjugate addition of the Me_3Sn moiety to a variety of α,β-unsaturated carbonyl compounds, including enones,[1,2] β-iodo enones,[1,2] and β-trifluoromethanesulfonyl enoates[3] (eqs 2-4). Notably, the intermediate enolate anion derived from the reaction of (**2**) with (*R*)-(-)-5-methyl-2-cyclohexen-1-one can be trapped with ***Iodomethane*** to give, stereoselectively, the ketone (**3**) (eq 5).[4,16] It is pertinent to mention that the conjugate additions of reagents (**1**) and (**2**) to bicyclic enones are stereochemically complementary. For example, reaction of (**4**) with (**1**) affords the *trans*-fused substance (**5**), while reagent (**2**) converts (**4**) into the *cis*-isomer

(6).[5,17]

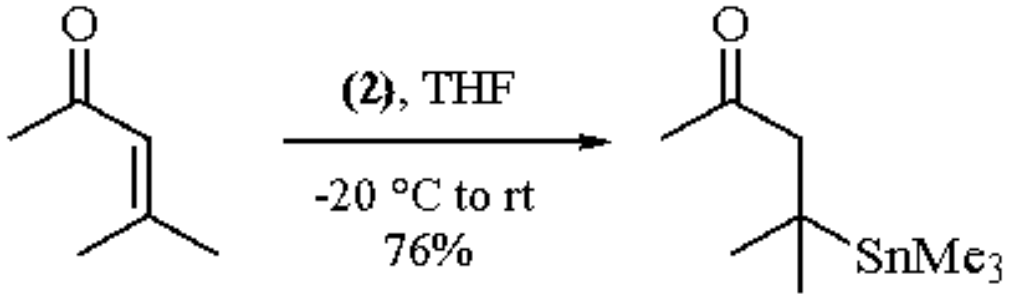
(2), THF
-20 °C to rt
76%
SnMe3

(2)

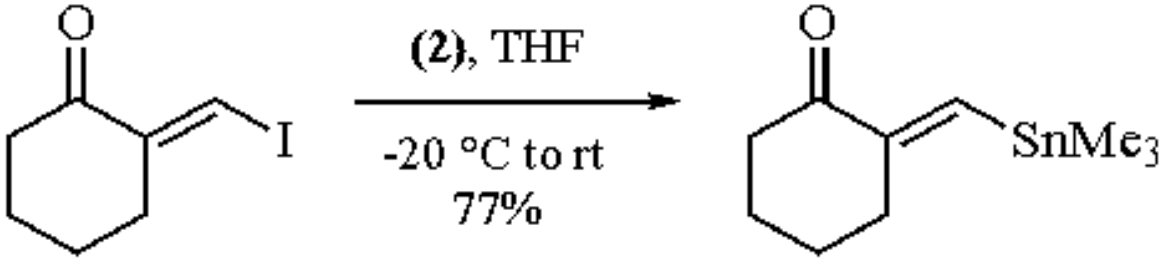
(2), THF
-20 °C to rt
77%
I
SnMe3

(3)

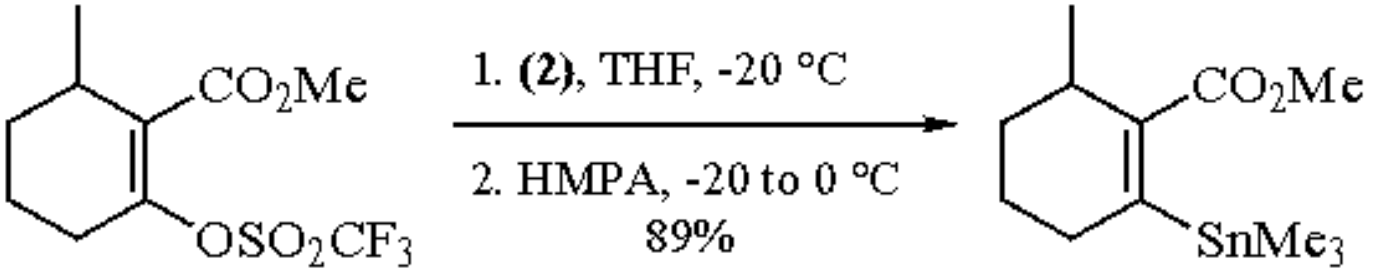
1. (2), THF, -20 °C
2. HMPA, -20 to 0 °C
89%
CO2Me
OSO2CF3
CO2Me
SnMe3

(4)

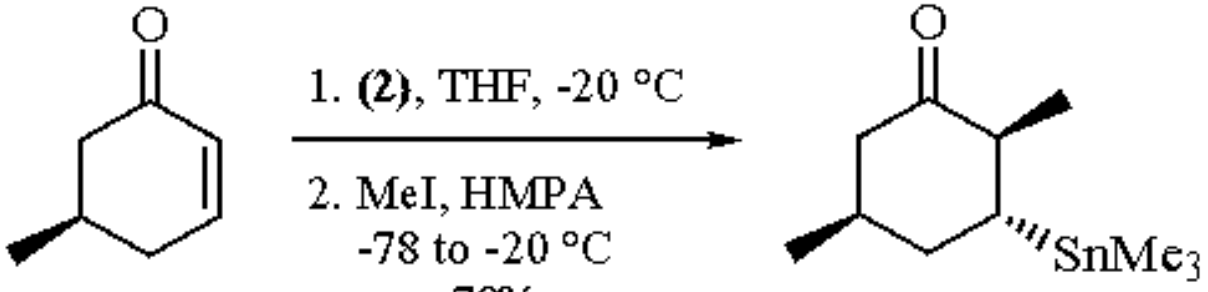
1. (2), THF, -20 °C
2. MeI, HMPA
-78 to -20 °C
78%
SnMe3

(3)

(5)

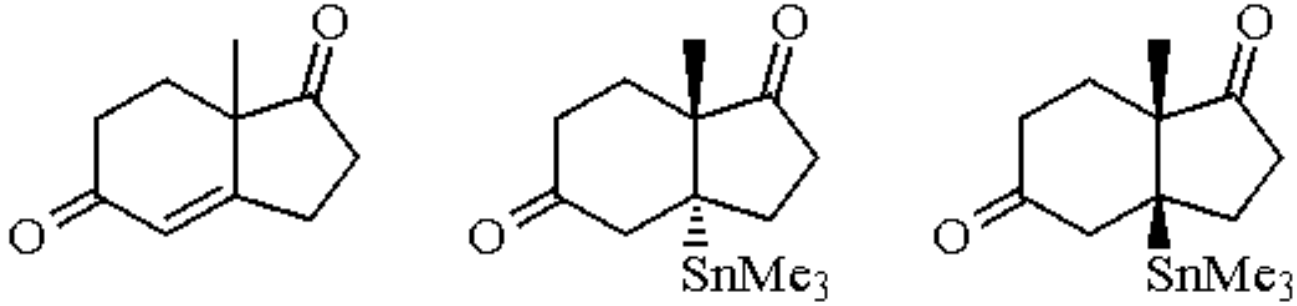

(4) (5) (6)

Reaction With α,β-Alkynic Carboxylic Acid Derivatives.

The stereochemical outcome of the regioselective addition of the elements of Me_3Sn-H across the triple bond of α,β-alkynic esters by reagent (**2**) can be controlled simply by varying the reaction conditions. Thus, reaction at -78 °C in the presence of a proton source provides alkyl (*E*)-3-trimethylstannyl-2-alkenoates (eq 6),[6-8] while use of the reaction conditions outlined in eq 7 produces the corresponding (*Z*)-isomers.[6-8,10-12,18] Similar stereochemical control can be accomplished with α,β-alkynic *N*,*N*-dimethylamides as substrates.[9] Alkyl (*E*)- and (*Z*)-3-trimethylstannyl-2-alkenoates have been shown to be useful synthetic intermediates in a range of contexts, including natural product syntheses.[6,8,10,12,16b,19]

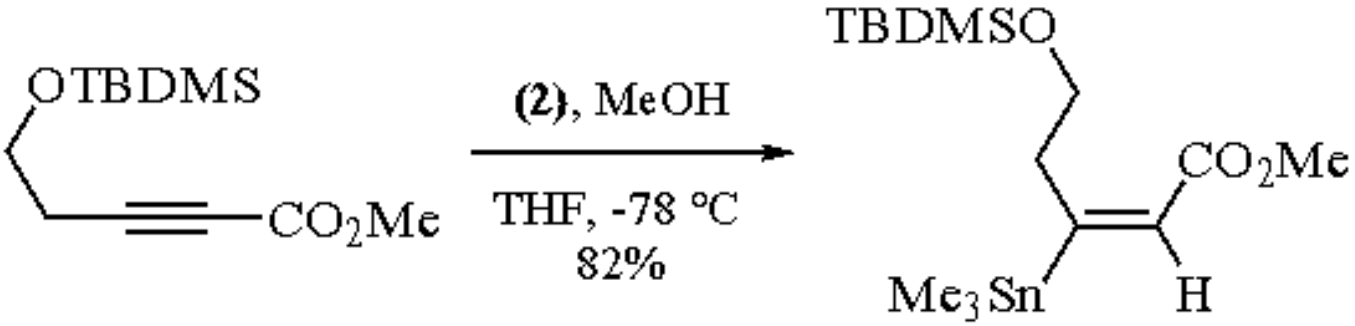

(6)

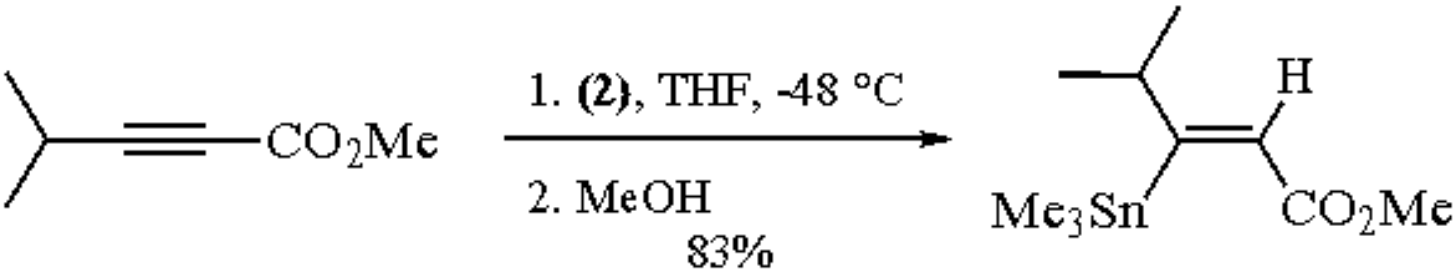

(7)

Related Reagents.

A number of lower order heterocuprates related in composition to (**2**) have been reported. These include $Me_3SnCu(Y)Li$ (Y = C&tbond;$CCMe_2OMe$[2,7,20] and CN[2,18]) and $Bu_3SnCu(Y)Li$ (Y = SPh[2,21] and CN[22-24]). To date, these reagents have been employed primarily in reactions similar to some of those described above for (**2**).

A recent report describing the use of $Bu_3SnCu(CN)Li$ for the preparation of (*Z*)-1-tributylstannyl-1-alken-3-ynes (eq 8)[24] is noteworthy.

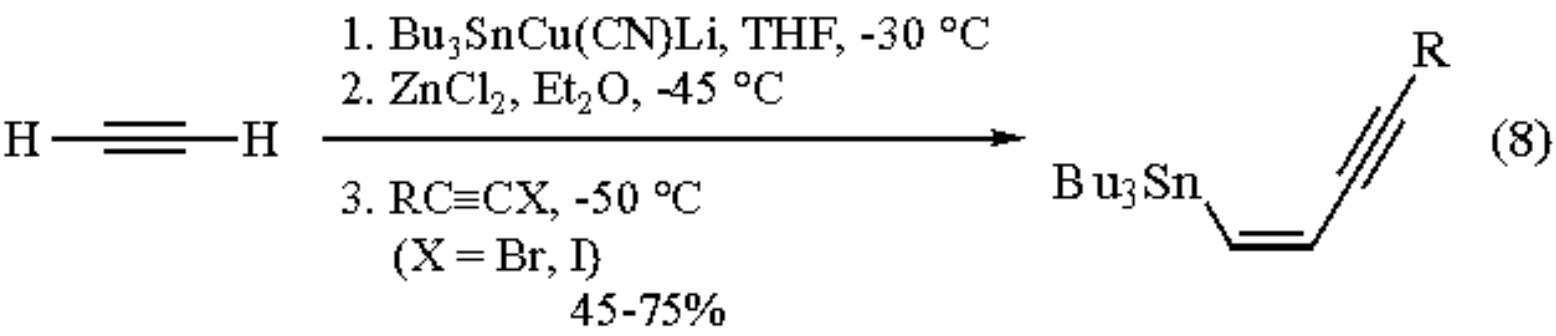

See also ***2,3-Bis(trimethylstannyl)-1,3-butadiene***; ***4-Chloro-2-trimethylstannyl-1-butene***; ***(E)-1-Lithio-2-tributylstannylethylene***; ***Methyl Tributylstannyl Sulfide***; ***trans-1,2-Bis(tributylstannyl)ethylene***; ***Tri-n-butylstannylacetylene***; ***Tri-n-butylstannylcopper***; ***Tri-n-butylstannyllithium***; ***Trimethylstannylcopper-Dimethyl Sulfide***; ***2-Trimethylstannylmethyl-1,3-butadiene***; ***Trimethylstannyllithium***; and ***(Triphenylstannylmethyl)lithium***.

---

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Lithium Phenylthio(2-vinylcyclopropyl)cuprate[1]

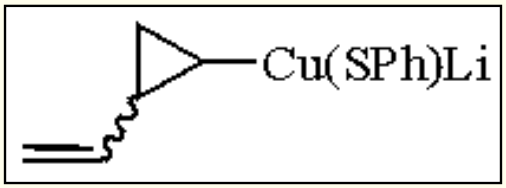

[61754-34-5] · $C_{11}H_{12}CuLiS$ · Lithium Phenylthio(2-vinylcyclopropyl)cuprate · (MW 246.79) (*cis*)

[71647-04-6] (*trans*)

[102511-64-8]

(heterocuprate useful in 1,4-addition-elimination reactions[2] and annulations[3])

Solubility: sol THF; less sol ether.

Analysis of Reagent Purity: an assay to determine relative thermal stabilities[4] can be used to estimate reagent quality and concentration: a sample of known volume and temperature is quenched with excess PhCOCl; the yield of 2-vinylcyclopropyl phenyl ketone is measured by GC or HPLC, the response of which is calibrated using authentic product and an appropriate internal standard.

Preparative Method: 2-vinylcyclopropyllithium[5] is prepared by cooling a 0.25 M ether or THF solution of 1-bromo-2-vinylcyclopropane[6] under Ar to -78 °C. Dropwise addition of 1.1-1.4 equiv of a solution of ***t-Butyllithium*** is followed by stirring for 2 h. One equiv of ***Phenylthiocopper(I)***[7] is added, and the resultant slurry is diluted with 5 mL THF per mmol of cyclopropane. The reaction is warmed to -20 °C; a clear, light brown solution of cuprate forms after stirring for 20 min. It is cooled to -78 °C and is used directly.

Handling, Storage, and Precautions: best results are obtained with PhSCu prepared from high purity Cu^{I} salts,[8] dry, O_2-free solvents, and alkyllithium solutions free of contaminating alkoxides or hydroxides.[9] *t*-BuLi is pyrophoric;[10] care must be exercised in its handling. Use in a fume hood.

This cyclopropyl organometallic reagent is representative of the heterocuprate class of organocopper reagents.[11] Only the cyclopropyl group, and not the SPh group, is nucleophilically reactive. The nontransferable SPh group, or dummy ligand,[12] provides enhanced thermal stability and solubility compared to the analogous homocuprate. Heterocuprates generally exhibit less nucleophilic reactivity than the corresponding homocuprates; however, increased thermal stabilities coupled with greater efficiency in use of the transferable ligand make them reasonable alternative reagents. This is particularly true when higher reaction temperatures are required, or when the organolithium used to form the

cuprate is difficult or expensive to prepare.

Lithium phenylthio(2-vinylcyclopropyl)cuprate has been used in acylations[3] and 1,4-addition-elimination reactions with 3-halo-2-alkenones.[13] The products of these reactions undergo high-yield thermal ring expansions (see ***Lithium Cyclopropyl(phenylthio)cuprate***), providing a two-step, seven-membered ring annulation method. 4-Cycloheptenones and various seven-membered ring bicycloalkadienones and spiroalkadienones (eq 1)[13] can be prepared.

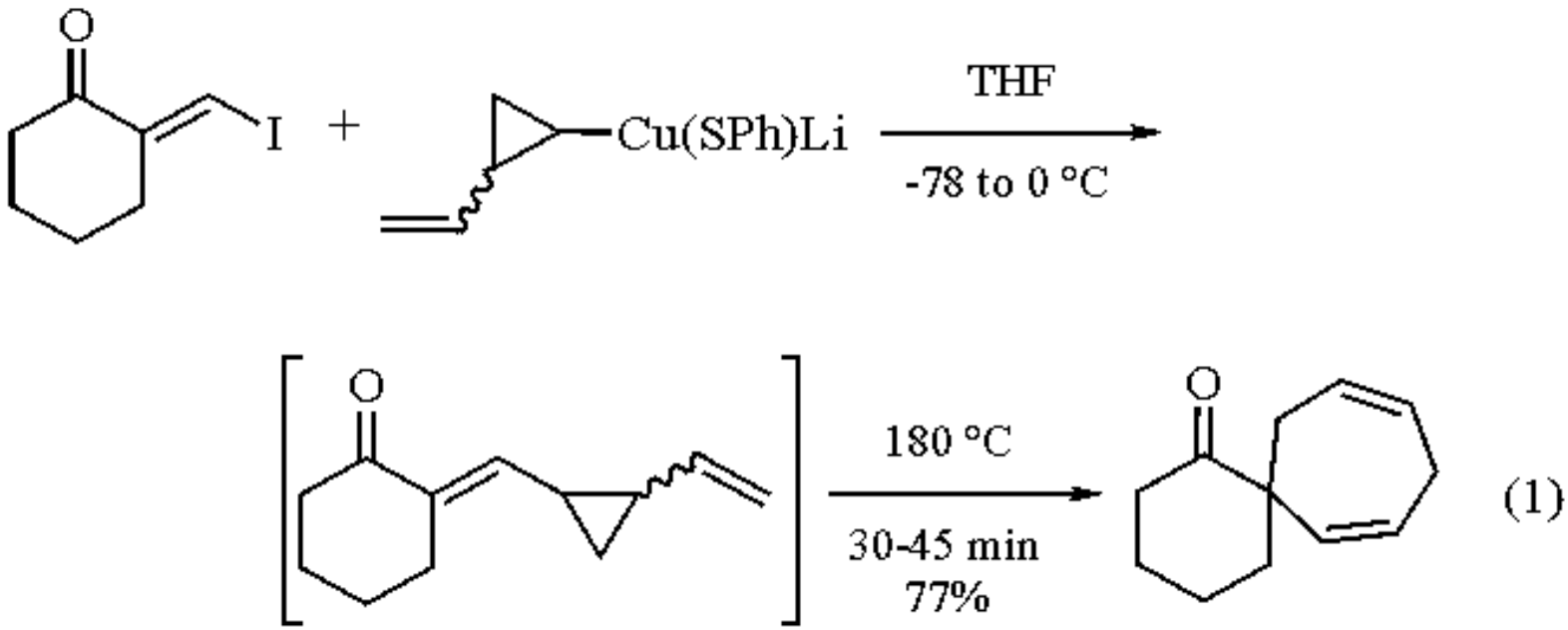

Either the *cis*- or *trans*-isomer or a mixture of isomeric 1-bromo-2-vinylcyclopropanes can be used in the reaction, although rearrangement is more facile with the *cis*-isomer. The method has been used in a convergent total synthesis of the sesquiterpene β-himachalene to assemble the 7,6-fused ring core of the natural product.[14]

Related Reagents.

Lithium Bis(2-vinylcyclopropyl)cuprate; ***Lithium Dimethylcuprate***; ***Lithium Methyl(phenylthio)cuprate***.

---

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Lithium Piperidide

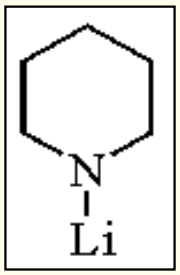

[4442-11-9] · $C_5H_{10}LiN$ · Lithium Piperidide · (MW 91.10)

(nucleophilic base used to probe aromatic substitution and benzyne-type reactions;[1-7] useful base to effect elimination of dihalocarbenoids to prepare α-halo ketones,[8] dichloro alkenes,[9] and chloro alkynes[9])

Physical Data: white solid,[10] unstable in air, pK_a 30.7 (THF at 30 °C).[11]

Solubility: sol THF,[10] DME,[1] Et_2O;[1] insol hexane[10] (at 0 °C).

Preparative Method: lithium piperidide in piperidine is prepared by adding a calculated amount of standardized ***Phenyllithium*** or ***n-Butyllithium*** in hexane to a solution of ***Piperidine*** (dried over KOH or activated alumina and distilled from KOH or sodium) in DME or Et_2O at 0 °C under an inert atmosphere.[1]

Handling, Storage, and Precautions: best prepared in situ prior to use. Use in a fume hood.

Nucleophilic Aromatic Substitution.

In 1956, Wittig[2] used lithium piperidide to explore benzyne formation. Its dual properties of strong basicity and nucleophilicity have led to the use of lithium piperidide as a probe for exploring nucleophilic aromatic substitution via the addition-elimination and benzyne pathways on a range of systems (haloimidazoles,[3] -pyridines,[4] -quinazolines,[5] -benzenes[6]); for example, substitution of 1- and 3-bromo-10-methylacridones[1] (eq 1) is not accompanied by rearrangement and presumably proceeds entirely by the addition-elimination mechanism (Table 1).

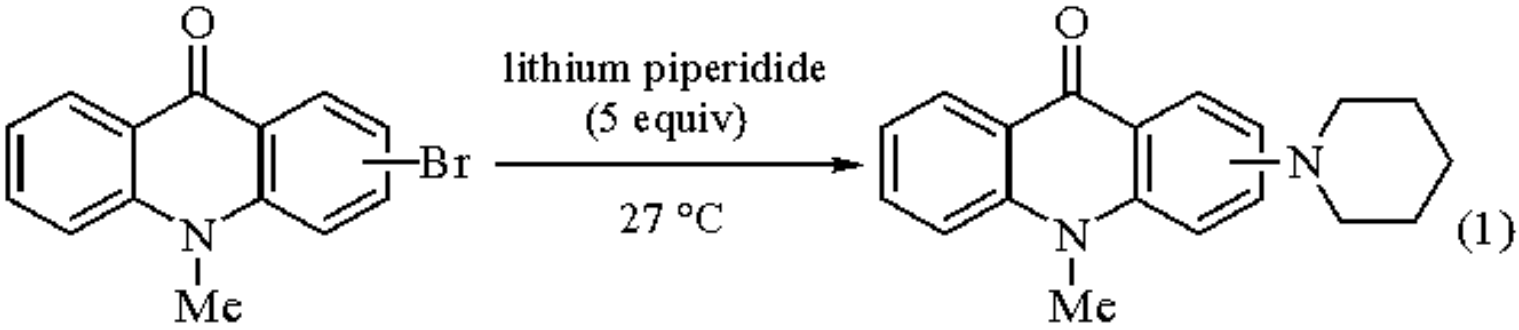

Table 1 Products from Reaction of Bromo-10-methylacridones with Lithium Piperidide in Piperidine at 27 °C[a]

Starting material	Reaction after 10 min (%)	1-Pip	2-Pip	3-Pip	4-Pip
1-Bromo	65	74	0	0	0
2-Bromo	9	1	72	10	0
3-Bromo	39	0	0	73	0
4-Bromo	46	0	0	31	0

[a] Yields based on unrecovered starting material.[1]

2-Bromo-10-methylacridone reacts with lithium piperidide in piperidine at 27 °C much more slowly than the 1- and 3-isomers to give rearrangement products, indicating the intermediacy of arynes (**1**) and (**2**); the direction of addition is controlled by the inductive effect of the heterocyclic nitrogen atom and the carbonyl group.

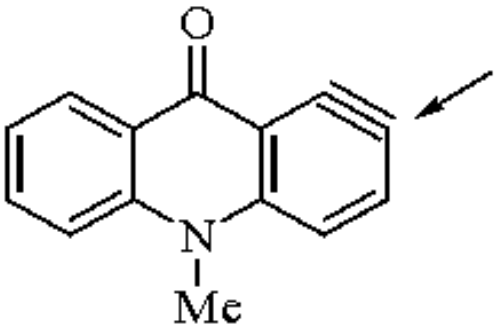

(1)

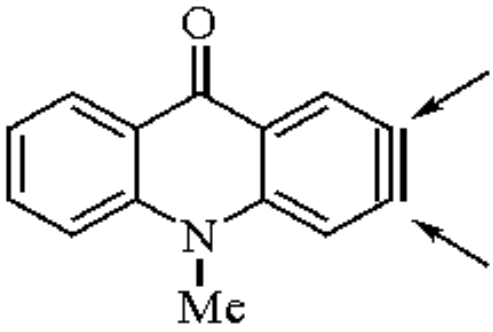

(2)

Reaction of lithium piperidide with methoxy aromatics in refluxing THF leads to products resulting from direct *ipso* substitution (eq 2).[7]

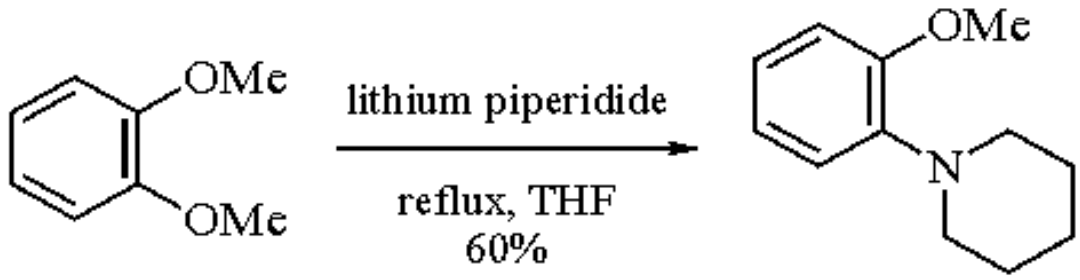

(2)

Preparation of α-Halo Ketones,[8] Dichloro Alkenes,[9] and Chloro Alkynes[9] via Elimination of Dichloro Carbenoids.

Lithium β-alkoxy carbenoids are quite unstable even at -120 °C and undergo α-elimination.[8] A subsequent migration of a group from the neighboring alkoxy carbon to the carbenoid center leads to the formation of an α-bromo enolate and constitutes a facile one-step preparation of α-halo ketones (eq 3). It is particularly suitable for the synthesis of C_{n+1} chlorocyclanones from C_n cyclanones (eq 4) (superior yields compared with *n*-BuLi).

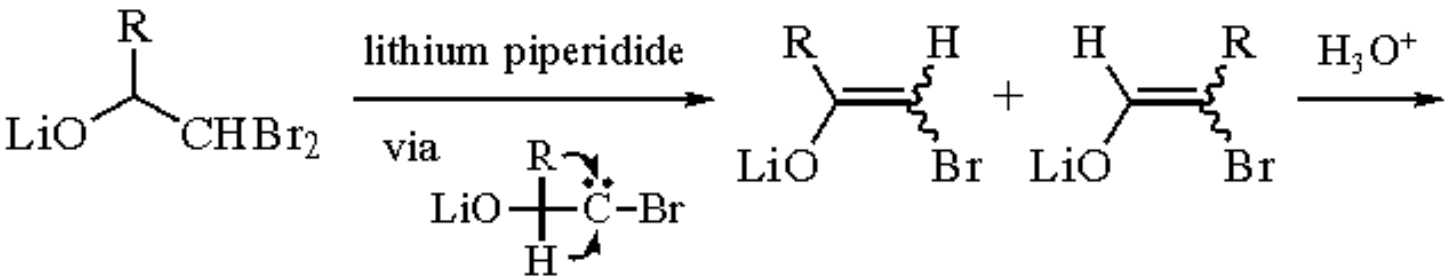

$RCOCH_2Br + RCHBrCHO$ (3)

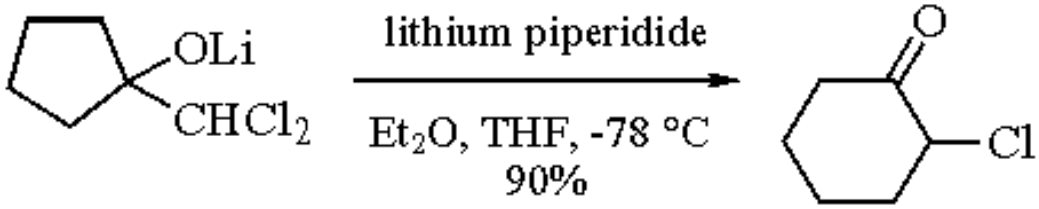

(4)

β-Silyloxy carbenoids,[9] however, generally undergo β-elimination, leading to the formation of dihalo alkenes which, with excess base, undergo elimination to halo alkynes in good yields (eq 5).

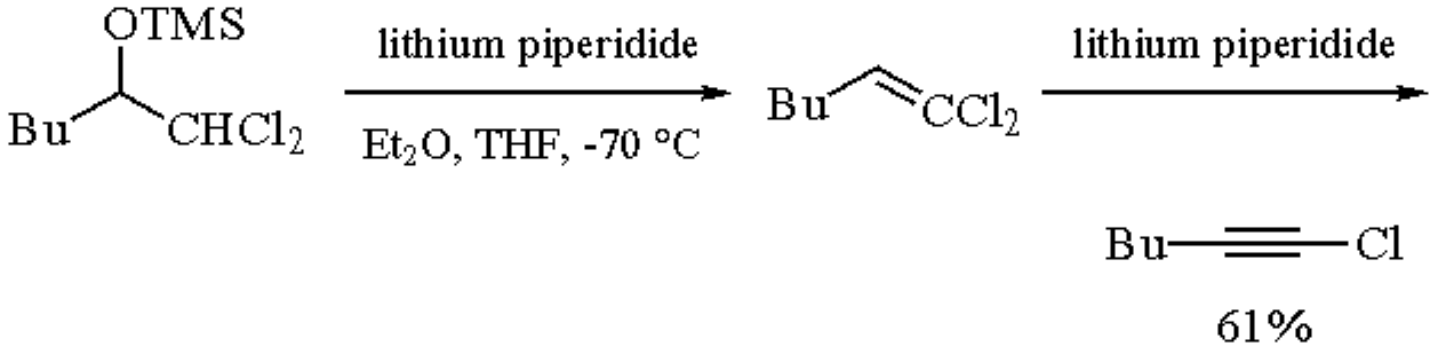

(5)

Carbonylation.

Carbamoyl- and acyllithium species are potentially useful intermediates, but their instability has prompted an extensive search for their synthetic equivalents. Widdowson[12] has shown that the carbamoyl anions, produced by bubbling carbon monoxide into a solution of lithium piperidide in THF (-78 °C), can be bottled as the corresponding carbamoyltin reagents (eq 6). These are useful in Stille[13] cross-coupling reactions, yielding a variety of aroyl, alkenoyl, and hetaroyl amides in good yields (eq 7). This may be useful for the synthesis of ^{11}C-labeled compounds for biological and clinical studies, such as positron emission tomography.[14]

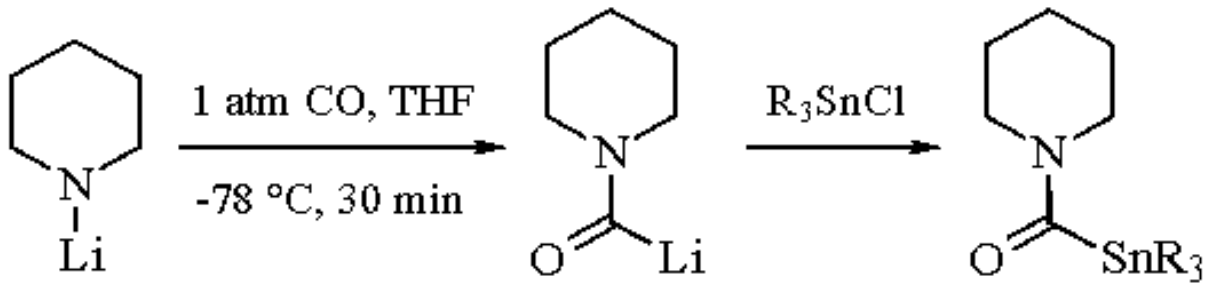

(6)

R = Me (61%), Bu (87%), Ph (53%)

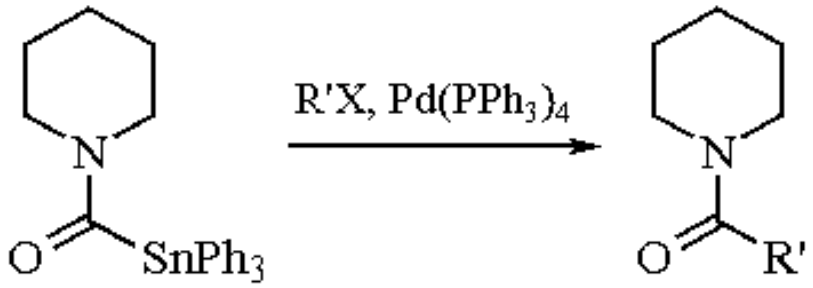

(7)

R'X = PhI (72%), 4-$MeOC_6H_4I$ (72%), *(E)*-$C_5H_{11}CH{=}CHI$ (64%)
(E)-PhCH=CHI (77%), 2-iodofuran (84%)
2-bromothiophene (57%), 3-bromopyridine (63%)

Related Reagents.

Lithium Diethylamide; ***Lithium Diisopropylamide***; ***Lithium Hexamethyldisilazide***; ***Lithium Pyrrolidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***.

---

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Lithium 1-Propanethiolate

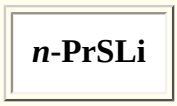

[16203-40-0] · C_3H_7LiS · Lithium 1-Propanethiolate · (MW 82.11)

(cleavage of the alkyl-oxygen bond of methyl esters under mild conditions;[1] lithium thiolates have also been used for selective demethylation of aryl methyl ethers[2] and quaternary ammonium salts[3])

Preparative Methods: a 5.0 M stock solution in HMPA is typically used. Addition of ***n-Butyllithium*** to a stirred solution of freshly distilled 1-propanethiol in dry hexane at 0 °C is followed by stirring for 10 min. The resulting suspension is then concentrated in vacuo to dryness at 0 °C and dissolved in the appropriate amount of HMPA.[4]

Handling, Storage, and Precautions: the reagent is stored under argon at 0 °C. Contact with oxygen results in rapid oxidation of the thiolate. Propanethiol must be handled with care and used in a hood due to its strong odor. For most applications the reagent is prepared and stored in HMPA, a potent carcinogen; therefore due caution should be exercised when handling this reagent. Note that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (***N,N´-Dimethylpropyleneurea***; DMPU) has been used as a substitute for the more hazardous HMPA in applications of this reagent.[5]

Demethylation of Methyl Esters.

Lithium propanethiolate was introduced as a reagent for the mild deprotection of methyl esters in 1970.[1] The reagent readily cleaves the alkyl-oxygen bond by an S_N2 process.[6] Due to this mechanism, the reagent offers advantages over conventional hydrolytic processes, particularly when the substrate carboxylate is sterically hindered or has additional functionality which is sensitive toward acid or base. For example, the sterically hindered ester methyl *O*-methylpodocarpate is readily cleaved to *O*-methylpodocarpic acid in quantitative yield at 25 °C in 1.5 h (eq 1). Additionally, methyl 3β-acetoxy-Δ^5-etienate which contains both a hindered ester and a hydrolytically sensitive acetate functionality, is readily cleaved to the etianic acid in high yield without concomitant acetate cleavage (eq 2).[1] It should be noted that the lithium thiolate in HMPA is superior to the sodium thiolate in DMF for methyl ester cleavage. Bartlett and Johnson report a rate enhancement for the cleavage of methyl mesitoate by a factor of 57.[1]

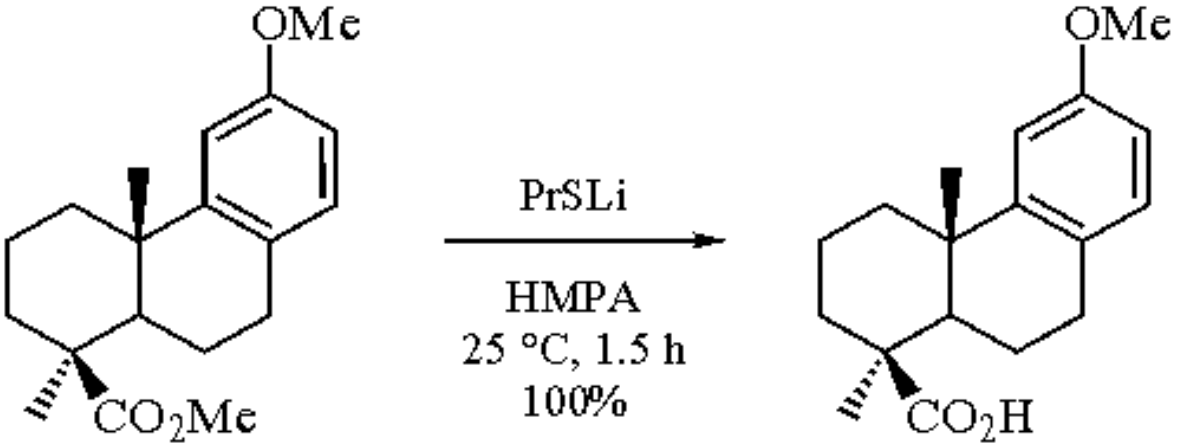

(1)

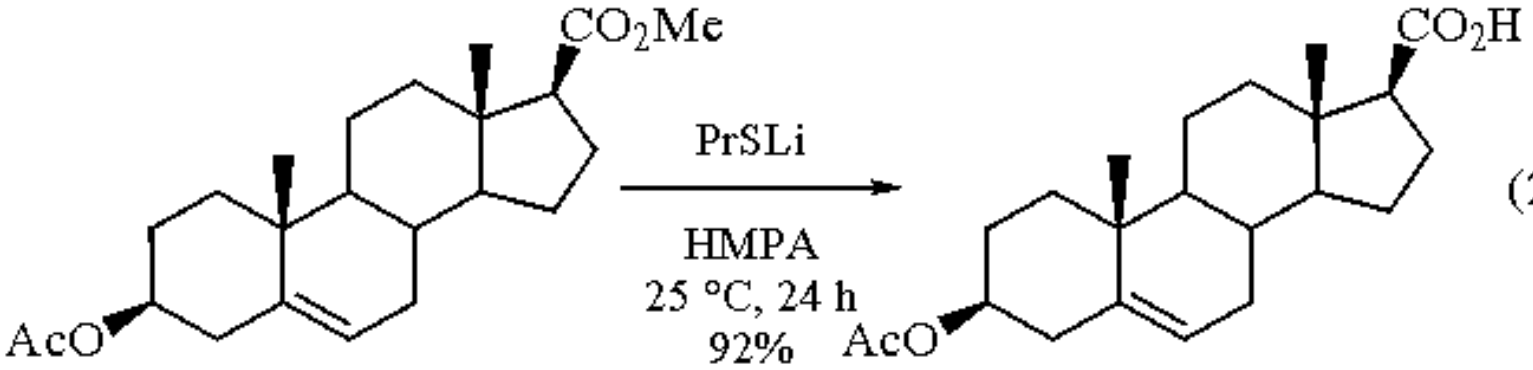

(2)

Additional examples include the cleavage of an acid-sensitive methyl gibberellate to afford gibberellic acid in high yield (eq 3),[7] and the selective cleavage of a sterically hindered bridgehead ester in the presence of a pyridyl methyl ether to afford a late intermediate in the synthesis of (*Z*)-huperzine A (eq 4).[8] Lithium propanethiolate will also selectively cleave vinylogous methyl esters in the presence of alkyl methyl esters. For example, in work related to the synthesis of chlorothricolide, the selective cleavage of a butenolide ester gave the corresponding ester acid in 79% yield (eq 5).[4] This methodology has also been used to prepare tetronic acid analogs of thiolactomycin, and it is reported to be superior to other demethylating agents such as ***Iodotrimethylsilane***[9] and dilute acid hydrolysis.[10]

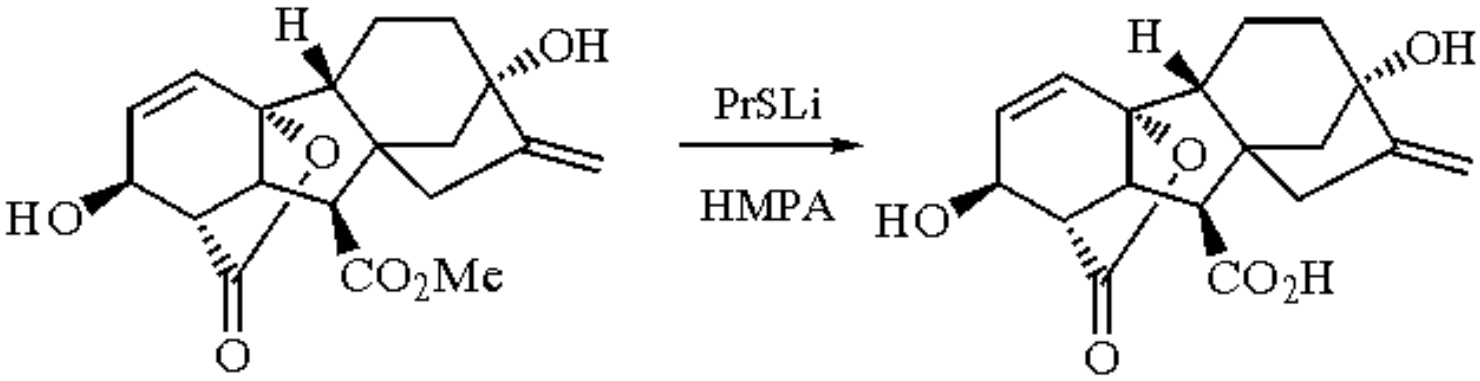

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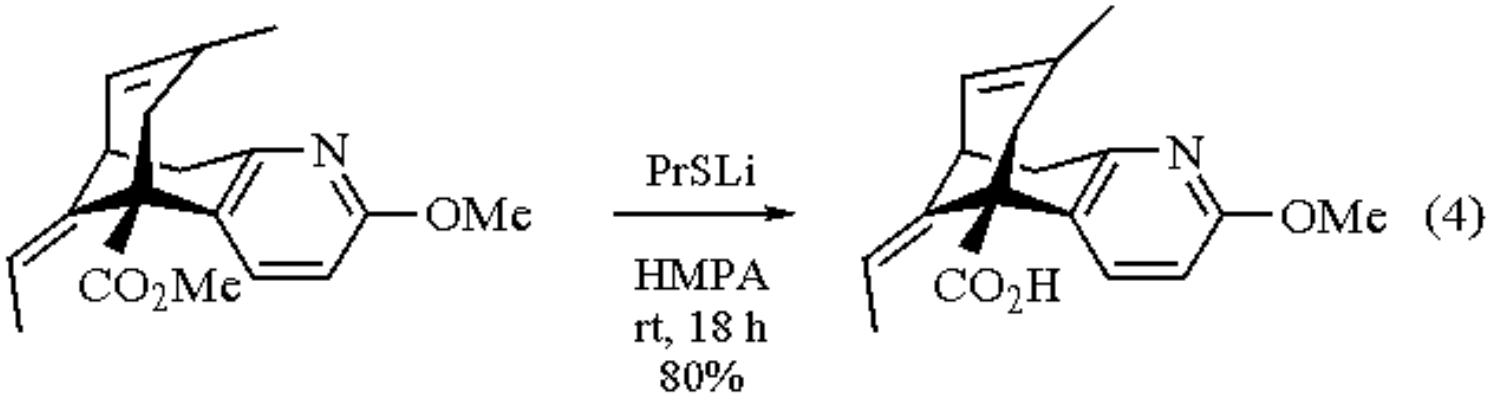

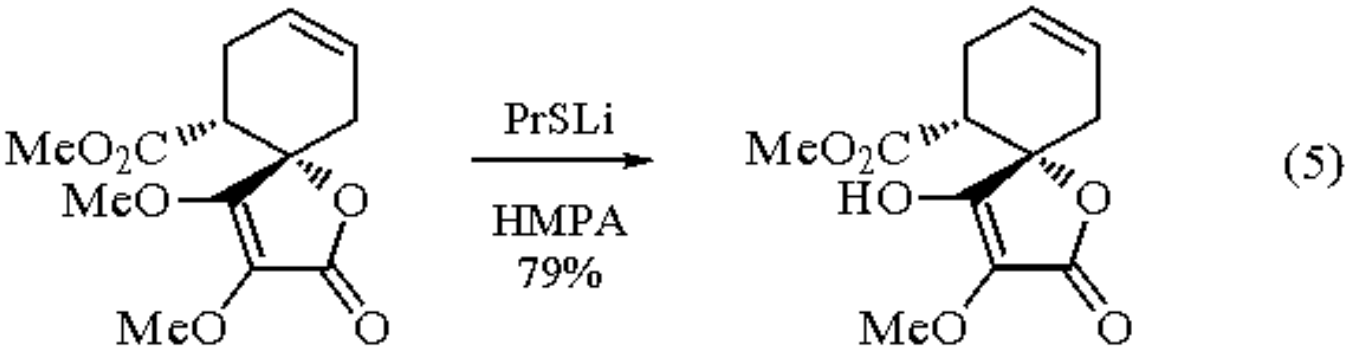

Demethylation of Aryl Methyl Ethers.

The demethylation of aryl methyl ethers using thiolate ion was also reported in 1970; a variety of anisoles were demethylated using sodium ethanethiolate in hot DMF to afford high yields of the corresponding phenols.[2] Lithium propanethiolate has been used for this purpose; however, there appears to be no advantage over the sodium thiolate reagents as is seen with the cleavage of methyl esters. For example, the aryl methyl ether of *O*-methylpodocarpic acid (see eq 1) can be removed with lithium propanethiolate, but only at elevated temperatures.[1] Another example for this class of reagents is the cleavage of a 7-methoxyindole using lithium butanethiolate in HMPA at 110 °C to afford the corresponding phenol in 88% yield (eq 6).[11]

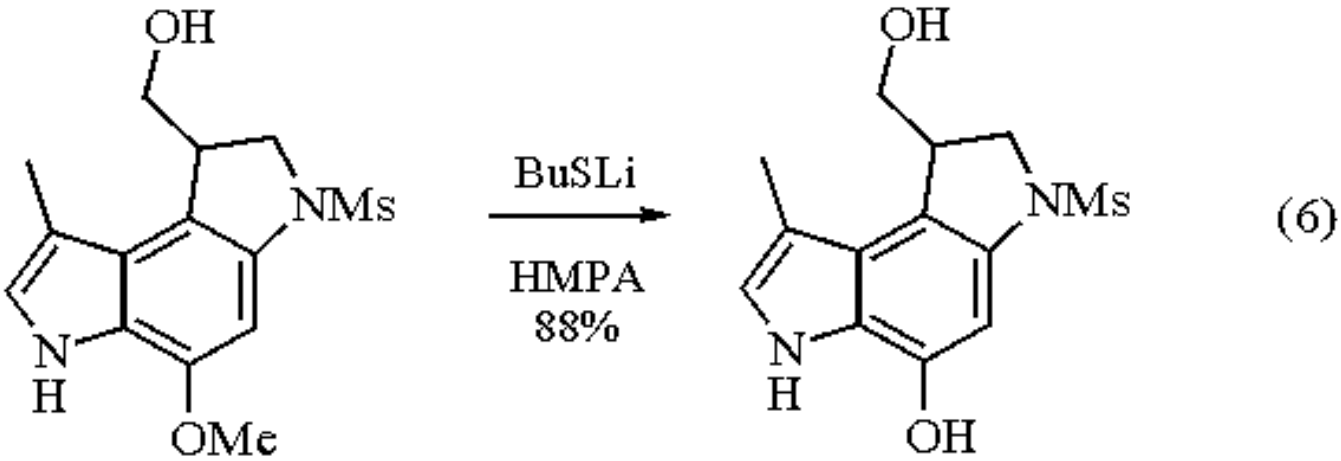

Demethylation of Quaternary Ammonium Salts.

The selective demethylation of quaternary ammonium salts has also been accomplished using lithium propanethiolate.[3] The method has been used to prepare a variety of unsymmetrical tertiary amines and is reported to give superior yields and selectivity over other reagents used for this purpose such as ***Lithium Aluminum Hydride***, ***Sodium-Ammonia***, thiophenoxide anion, or ***Lithium Iodide***. For example, *n*-dodecyldimethylpropylammonium iodide is readily demethylated using lithium propanethiolate in HMPA at 50 °C after 3 h to afford *n*-dodecylmethylpropylamine in 99% yield (eq 7).

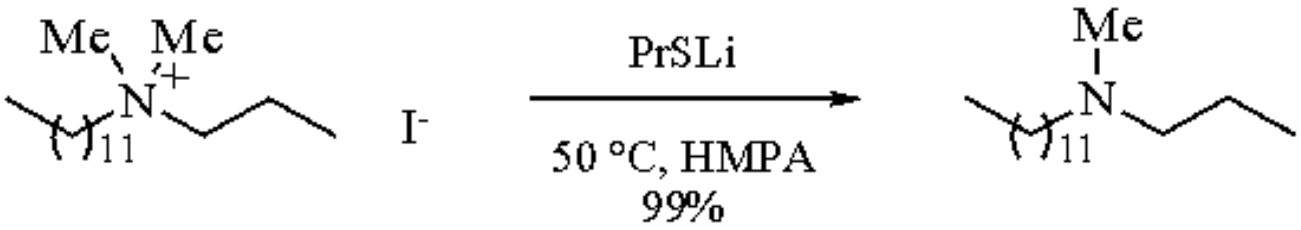

(7)

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Lithium Pyrrolidide

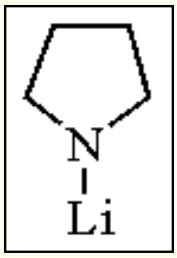

[4439-90-1] · C_4H_8LiN · Lithium Pyrrolidide · (MW 77.07)

(reduction of nonenolizable ketones;[3] carbonylation;[5] nucleophilic additions[6,8] and substitutions[4,9])

Physical Data: white, amorphous solid, $[(CH_2)_4NLi]_n$; mp 150 °C (dec); X-ray structures of $[((CH_2)_4NLi)_3.PMDETA]_2$ and $[((CH_2)_4NLi)_2.TMEDA]_2$ have been reported.[1]

Solubility: sol THF, Et_2O; insol pentane, hexane (at rt).

Preparative Method: prepared from ***Pyrrolidine*** (dried over and distilled from CaH_2) and ***Methyllithium*** or ***n-Butyllithium*** in Et_2O or THF usually at 0 °C for 30 min.[3,4]

Handling, Storage, and Precautions: unstable in THF solution at rt, forming LiH after a short period of time.[2] Best prepared in situ immediately prior to use. Use in a fume hood.

Reduction.

In 1971, Wittig[3] reported that treatment of nonenolizable ketones with lithium pyrrolidide (2 equiv) leads to alcohols in good yields (eq 1).

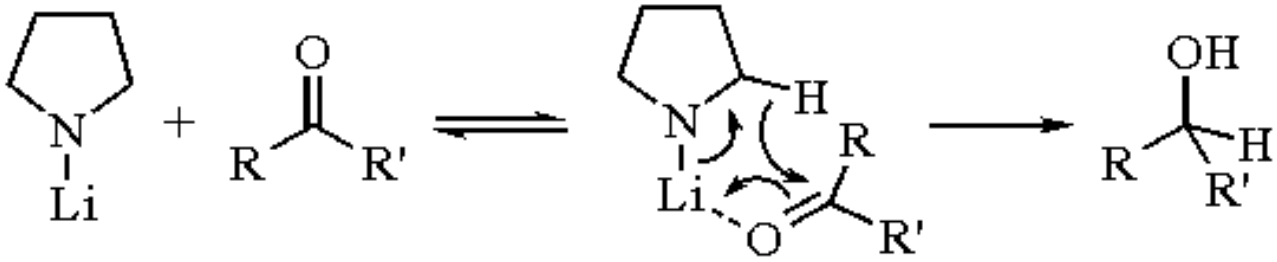

R	R'	Temp. (°C)	Time (min)	Yield (%)
Ph	1-Naphthyl	0	10	95
Ph	CPh_3	0	10	95
Ph	Ph	20	180	74
t-Bu	*t*-Bu	0	10	77

Carbonylation.

Treatment of lithium pyrrolidide with CO at atmospheric pressure leads to a carbamoyllithium species which, when quenched with R_3SnCl, affords amidostannanes (eq 2).[5] These may be cross-coupled with alkenyl, aryl, and heteroaryl halides under Pd^0 catalysis to give acylpyrrolidines. Trimethyltin derivatives are the most effective cross-coupling partners. This procedure was developed for the introduction of ^{11}C (from ^{11}CO) into molecules for biological and clinical studies.

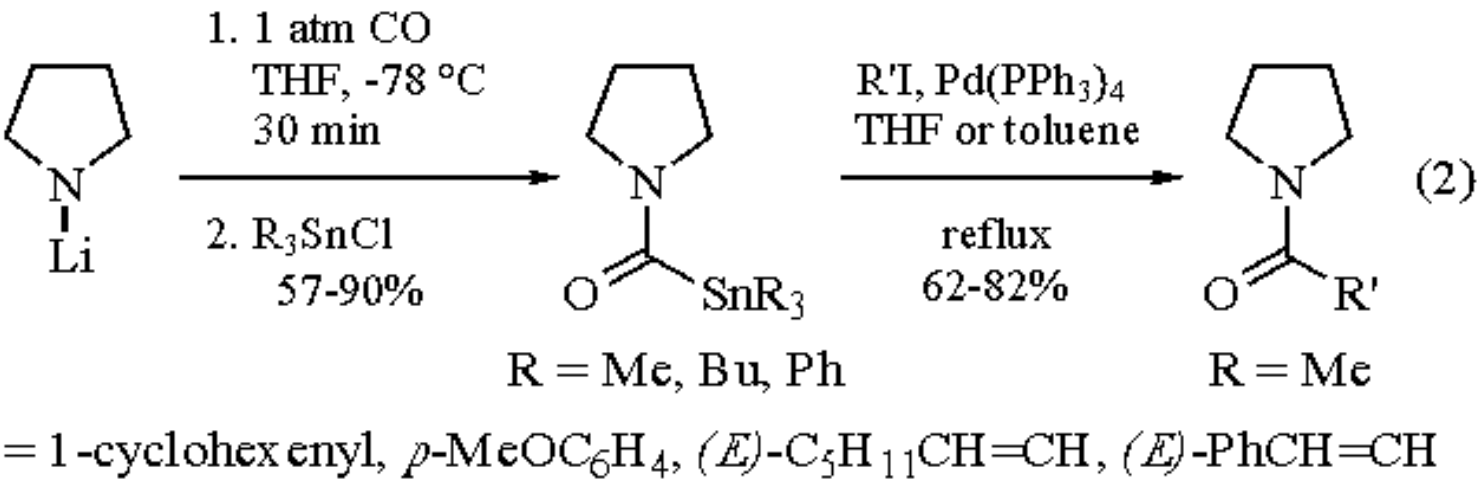

Nucleophilic Addition.

Treatment of 1-chloro-2-phenylacetylene with lithium pyrrolidide yields 1-(1-pyrrolidinyl)-2-phenylacetylene (eq 3), which may be used as an electron-rich partner in [2 + 2] cycloaddition reactions with heterocyclic compounds.[6] In general, ynamines are versatile reagents.[7]

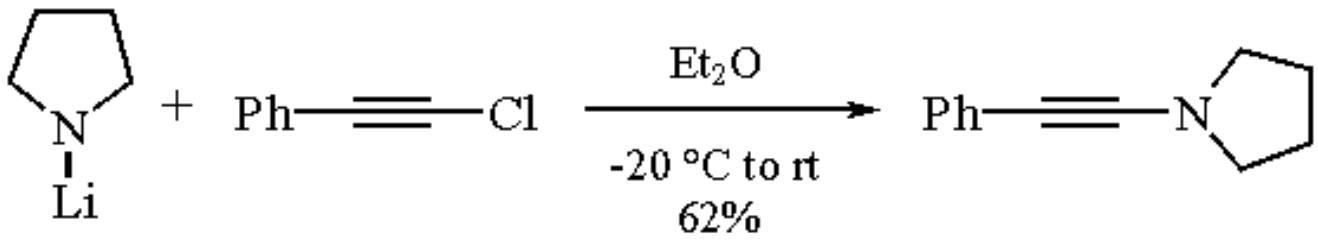

(3)

Addition of lithium pyrrolidide to activated alkynes leads to (*Z*)/(*E*) mixtures of synthetically useful vinyllithium species (eq 4).[8] Yields given correspond to the protonated products obtained by quenching with MeOH.

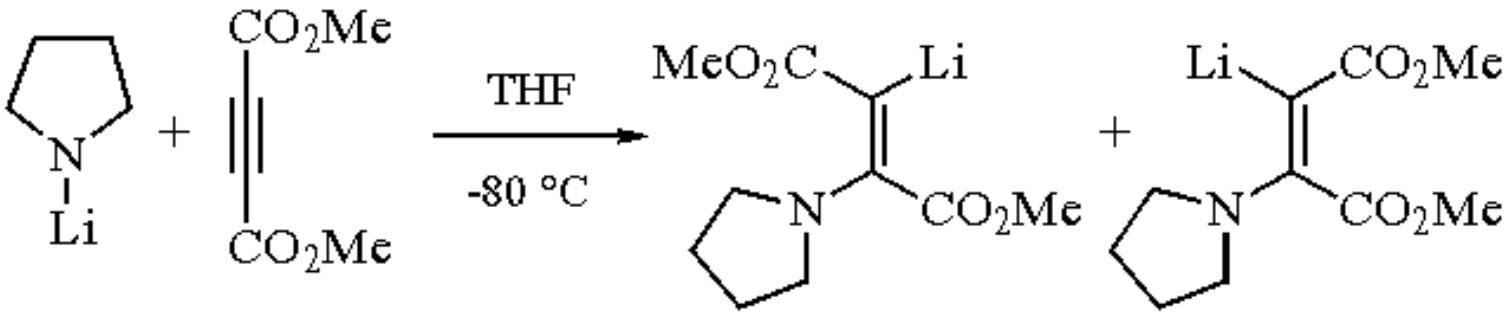

(4)

2 equiv	12%	69%
0.75 equiv	0%	100%

Nucleophilic Substitution.

The reaction of lithium pyrrolidide with ***Dimethyl Disulfide*** in pentane gives the corresponding sulfenamide (eq 5).[9] This reaction fails in THF. Sulfenamides have been used as sulfenyl-group transfer reagents.[10]

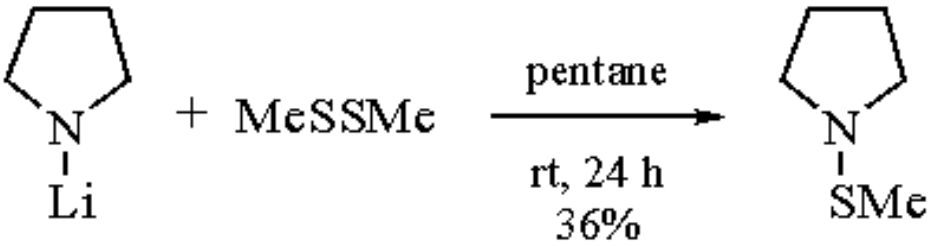

(5)

Treatment of 1,2-dimethoxybenzene with lithium pyrrolidide leads to displacement of only one methoxy group (eq 6)[4] in a reaction which appears not to proceed via a benzyne intermediate.

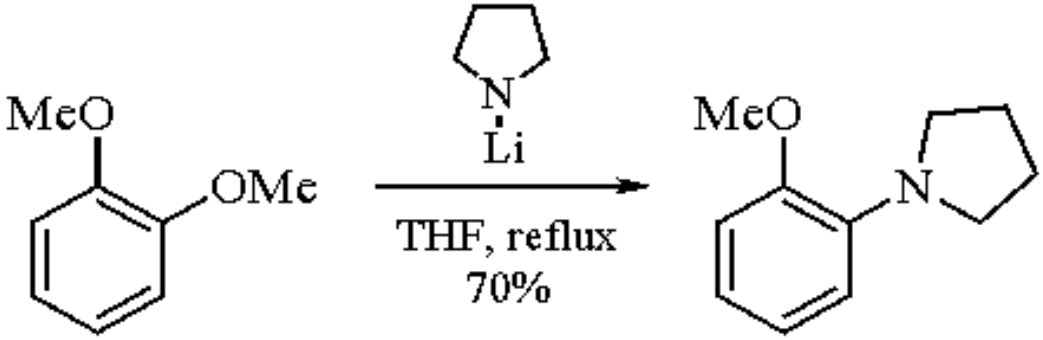

(6)

Related Reagents.

Lithium Diethylamide; ***Lithium Diisopropylamide***; ***Lithium Hexamethyldisilazide***; ***Lithium Piperidide***; ***Lithium 2,2,6,6-Tetramethylpiperidide***.

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Lithium Selenide

Li_2Se

[12136-60-6] · Li_2Se · Lithium Selenide · (MW 92.84)

(nucleophilic agent for synthesis of organic selenides[1,2])

Physical Data: d 2.91 g cm^{-3}; red-brown solid or milky white crystalline suspension in THF.

Solubility: sol water; sparingly sol THF.

Preparative Methods: reduction of ***Selenium*** with ***Lithium*** in liquid ammonia produces red-brown Li_2Se after NH_3 evaporation.[3] Reaction of Se with 2 equiv ***Lithium Triethylborohydride*** in THF gives a suspension of Li_2Se. The method is somewhat limited by scale and produces flammable byproducts.[1] For large-scale preparations, reduction of Se with Li in THF in the presence of naphthalene as a catalyst is safe and more economical.[2]

Handling, Storage, and Precautions: should be used directly as prepared. Use in a fume hood.

The reaction of Li_2Se with alkyl halides gives dialkyl selenides in high yields. It is less reactive than K_2Se or ***Sodium Selenide***.[1,2] Benzyl, 4-chlorobenzyl, 2-phenylethyl, and pentyl bromides give selenides in yields of above 54% (eq 1), but no selenide is obtained when 2-octyl bromide is used as a substrate.[1,2] Bis(trialkylsilyl) selenides are obtained when trialkylchlorosilanes are treated with Li_2Se (eq 2).[4,5]

$$2\ PhCH_2Br \xrightarrow[80\%]{Li_2Se,\ THF\ 0\text{-}5\ ^\circ C,\ 1.5\ h} (PhCH_2)_2Se \qquad (1)$$

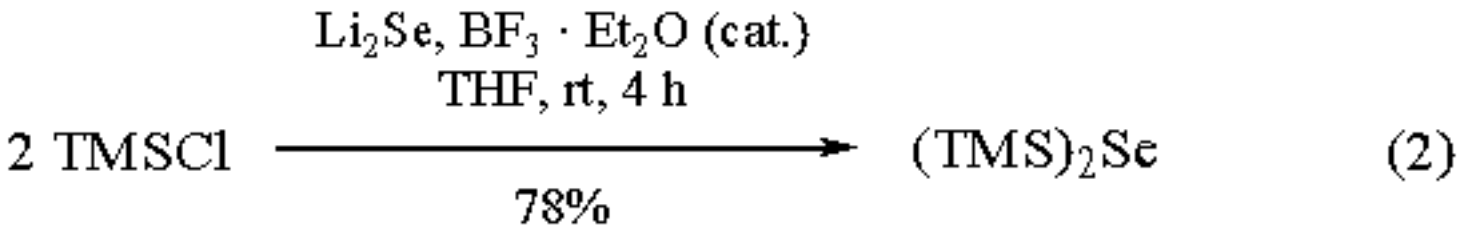

Related Reagents.

Hydrogen Selenide; ***Sodium Hydrogen Selenide***; ***Sodium Selenide***.

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Lithium Tetrafluoroborate[1]

$LiBF_4$

[14283-07-9] · BF_4Li · Lithium Tetrafluoroborate · (MW 93.75)

(fluoride source for cleavage of silyl ethers;[2] mild Lewis acid capable of promoting acetal hydrolysis,[3] rearrangement of oxaspiropentanes,[4] facilitating the addition of arenesulfenyl chlorides to alkenes;[5] catalysis of Diels-Alder cycloadditions;[6] used as an electrolyte in oxidative cleavage of 2-oxo-1-cyclohexanones[7])

Physical Data: mp 5 °C.

Solubility: sol methanol, acetonitrile.

Form Supplied in: anhydrous white solid; also available as a 1 M solution in acetonitrile. *Drying:* anhydrous material is obtained by overnight drying in an oven at 80-90 °C.[1]

Handling, Storage, and Precautions: extremely hygroscopic; should be handled and stored under an inert atmosphere; contact irritant.

Cleavage of Ethers.

$LiBF_4$ is an effective reagent for the removal of silyl ethers.[2,8,9] An excess of the salt in acetonitrile at ambient temperature effects cleavage of *t*-butyldimethylsilyl ethers (eqs 1-3).

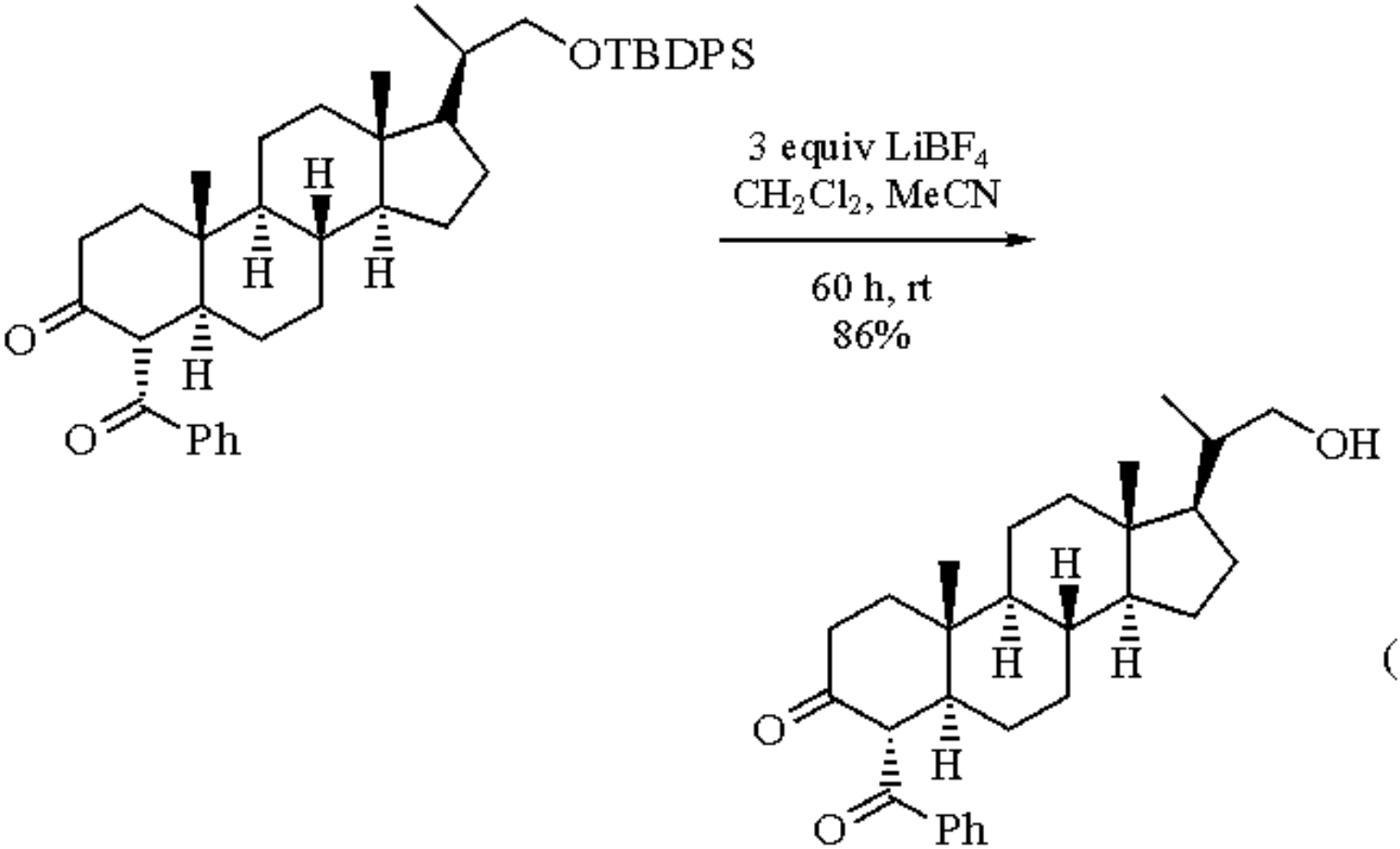
OTBDPS
3 equiv LiBF4
CH2Cl2, MeCN
60 h, rt
86%
OH
Ph
H
O

(1)

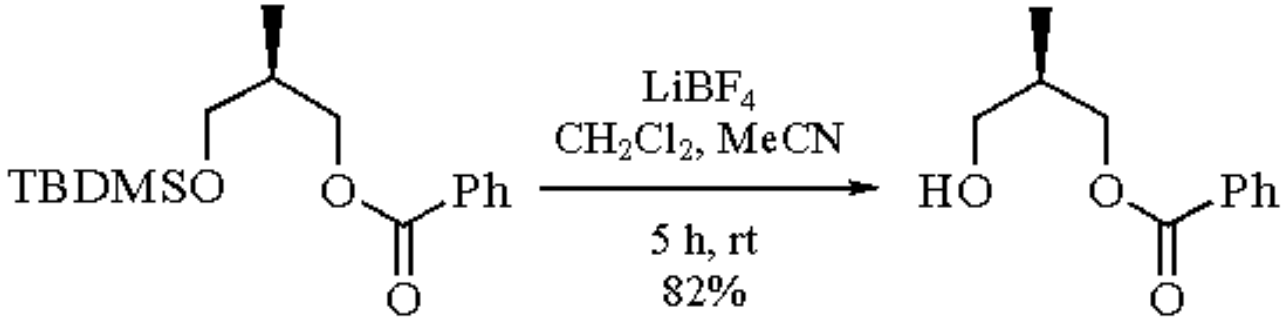
TBDMSO
Ph
LiBF4
CH2Cl2, MeCN
5 h, rt
82%
HO
O

(2)

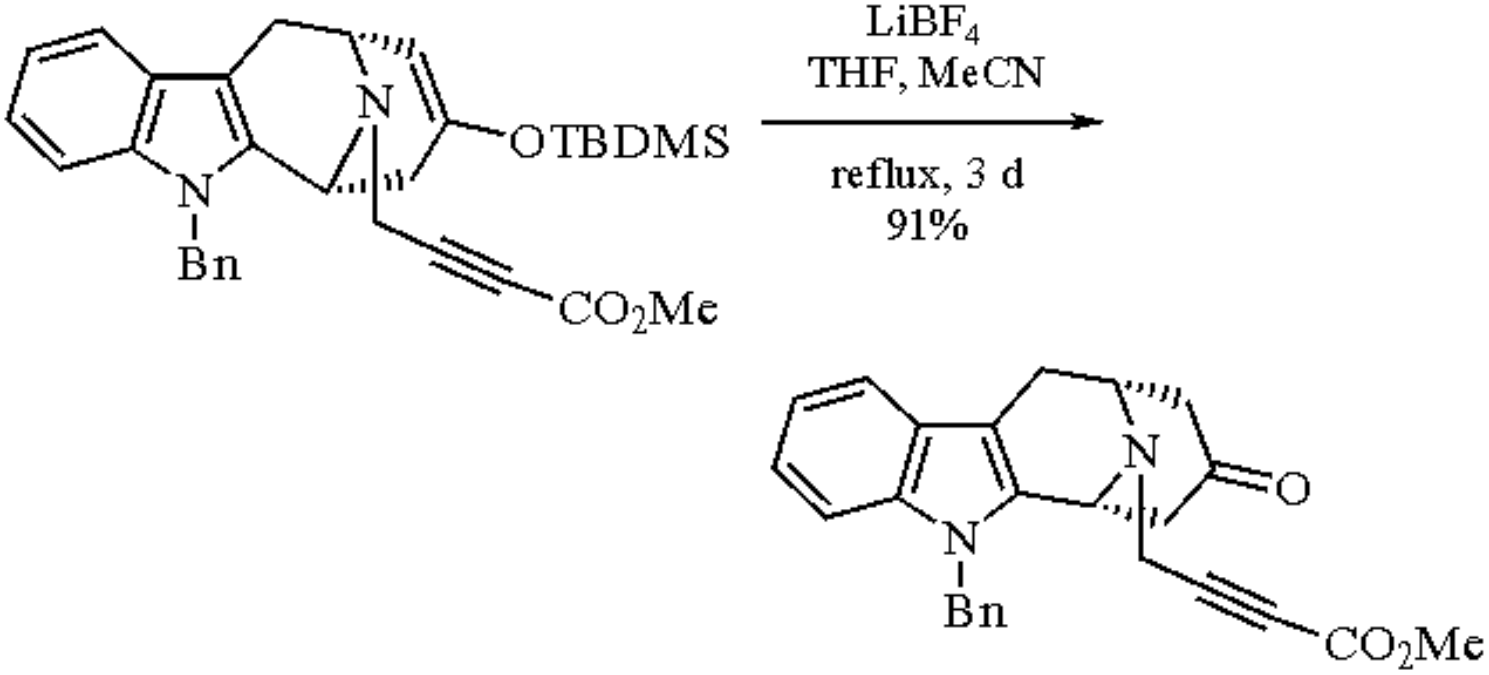

Use of this reagent under more vigorous conditions results in removal of (trimethylsilyl)ethoxymethyl (SEM) ethers and methoxymethyl (MOM) ethers (eqs 4, 5).[11]

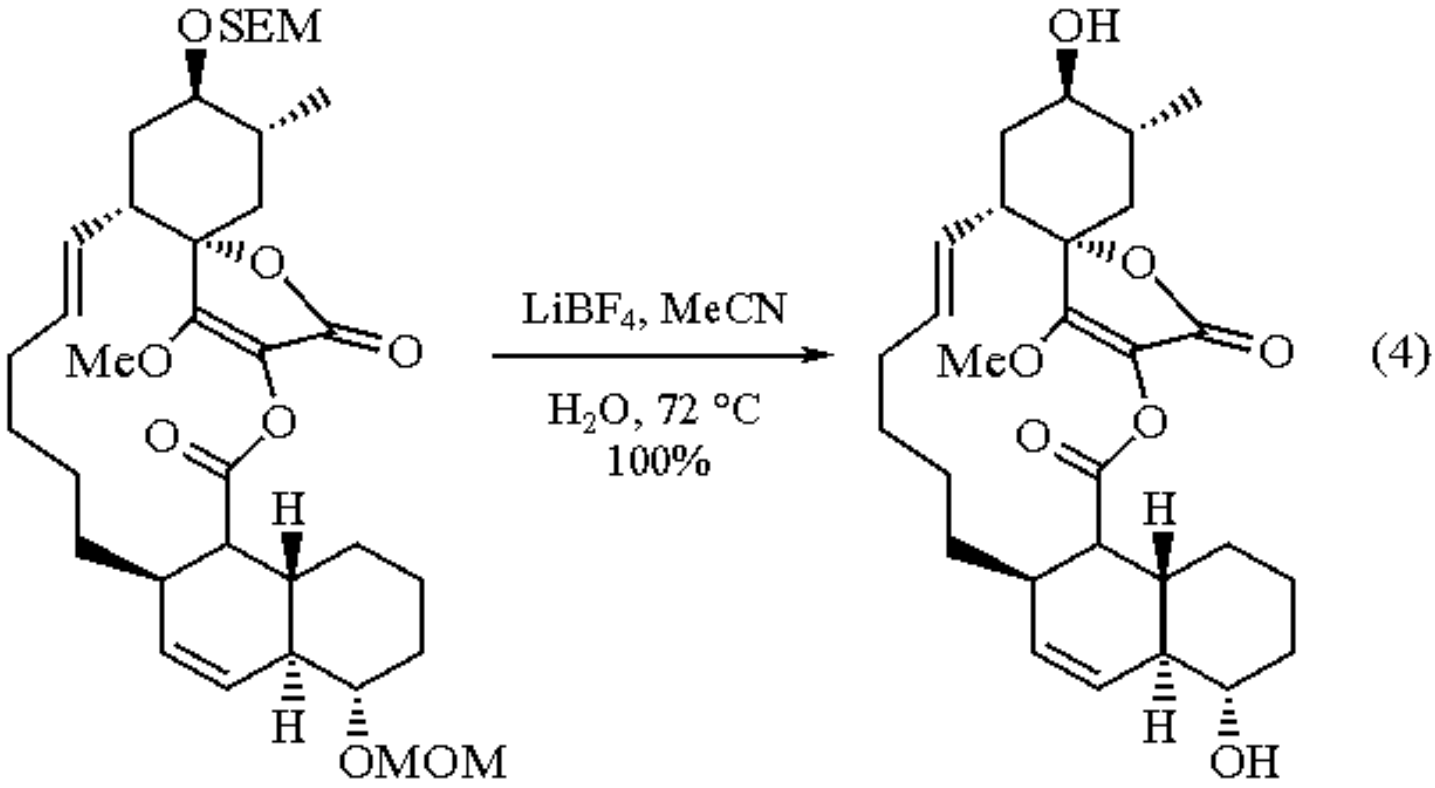

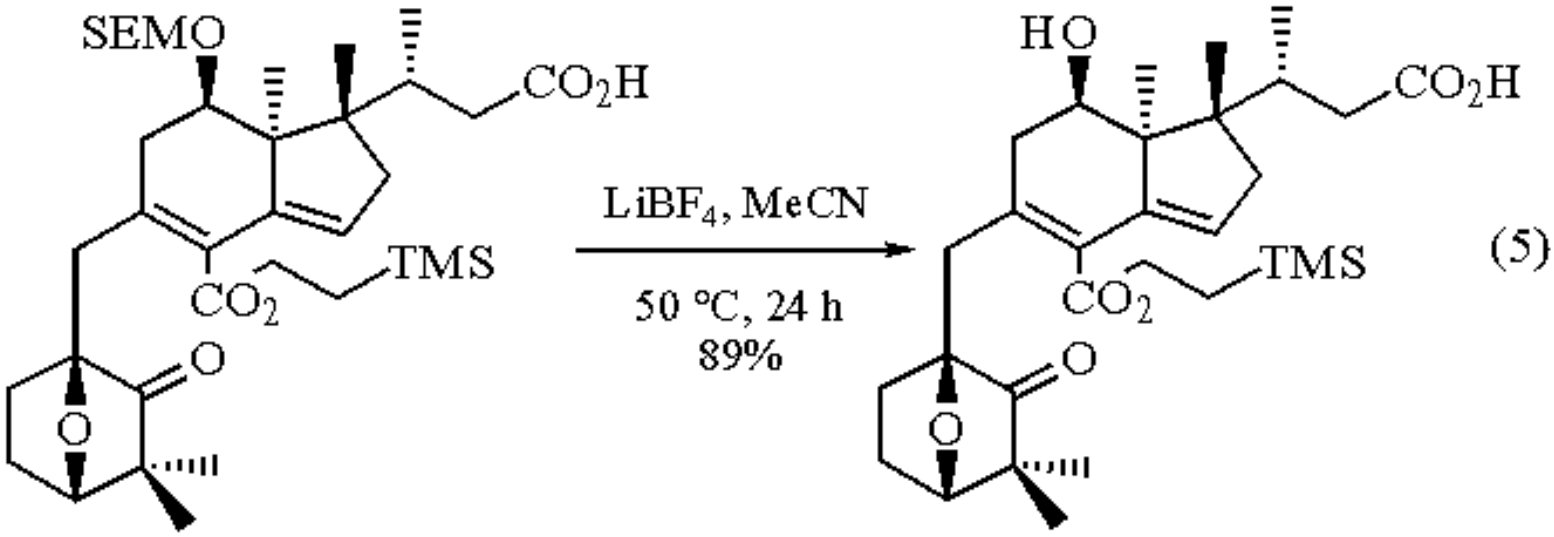

$LiBF_4$ is particularly effective in the deprotection of β-trimethylsilylethyl protected glycosides (eq 6).[12] Notably, the β-anomers undergo hydrolysis more rapidly than the corresponding α-anomers. Benzylidene acetals are cleaved under these conditions (eq 7).

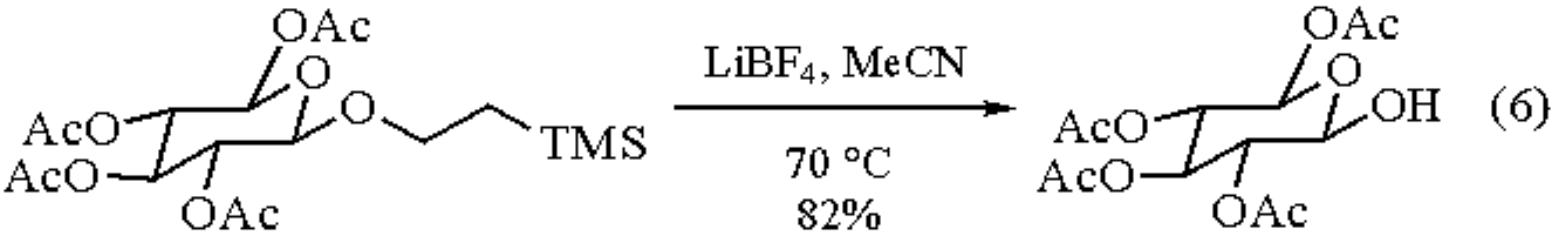

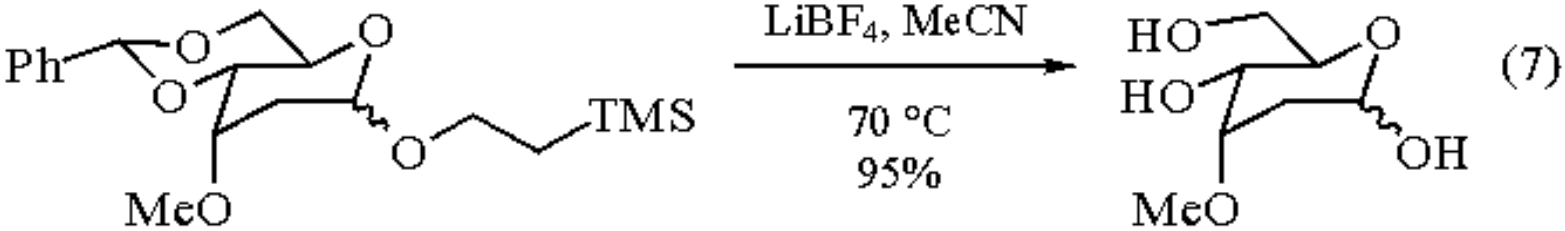

Hydrolysis of Acetals.

Treatment of acetals with $LiBF_4$ in wet acetonitrile provides carbonyl compounds in moderate yield.[3] Aliphatic acetals (eq 8) give the corresponding carbonyl products in near quantitative yield. Cyclic dioxolane derivatives are hydrolyzed at a slower rate (eq 9). Substitution of the dioxolane further hinders the reaction (eq 10). Aliphatic aldehydes protected as 1,3-dioxanes are inert to these hydrolysis conditions.

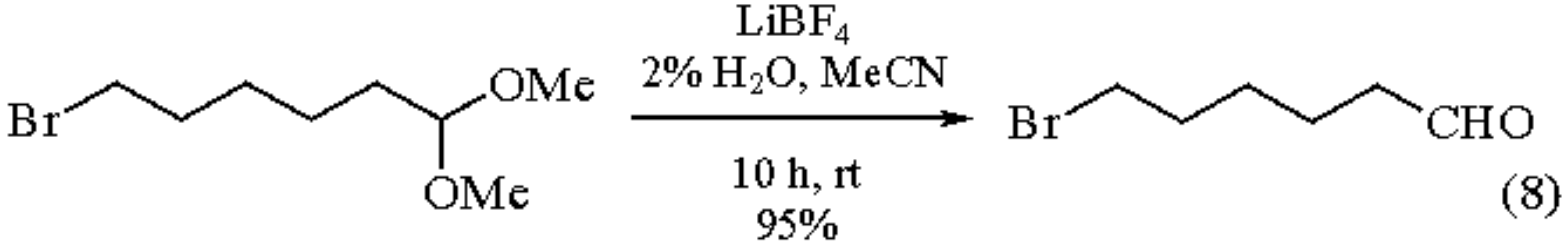

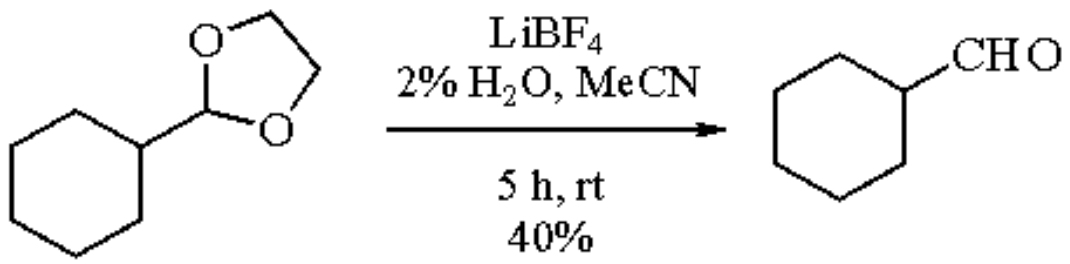

(9)

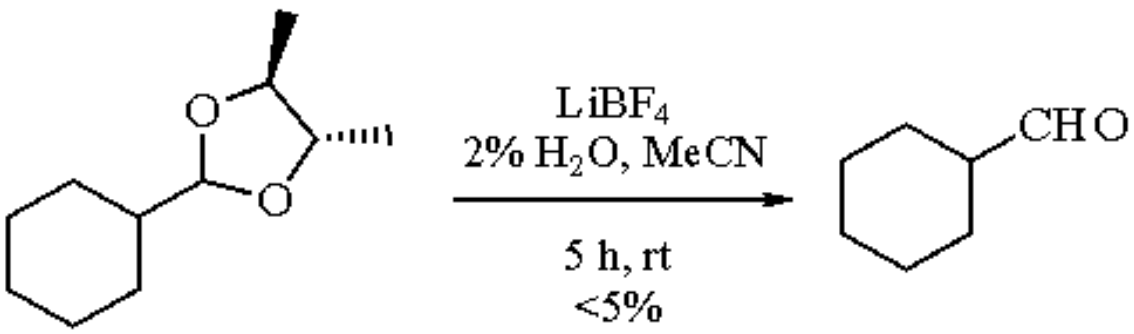

(10)

Lewis Acid Promoted Reactions.

$LiBF_4$ promotes a high yielding rearrangement of oxaspiropentanes to cyclobutanones (eq 11).[4] In this regard, $LiBF_4$ is reported to be superior to ***Lithium Perchlorate***.

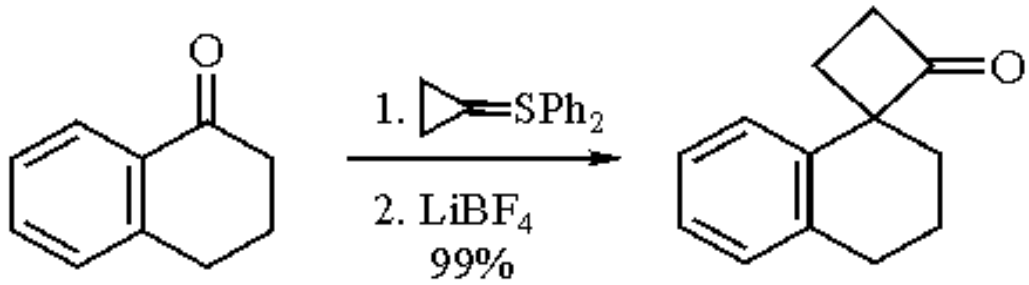

(11)

$LiBF_4$ is an effective catalyst for the intramolecular Diels-Alder reaction. A single *cis*-fused cycloadduct was obtained in quantitative yield from the triene (eq 12).[6] The use of other Lewis acids gives poor selectivity and lower yields of the bicyclic product.

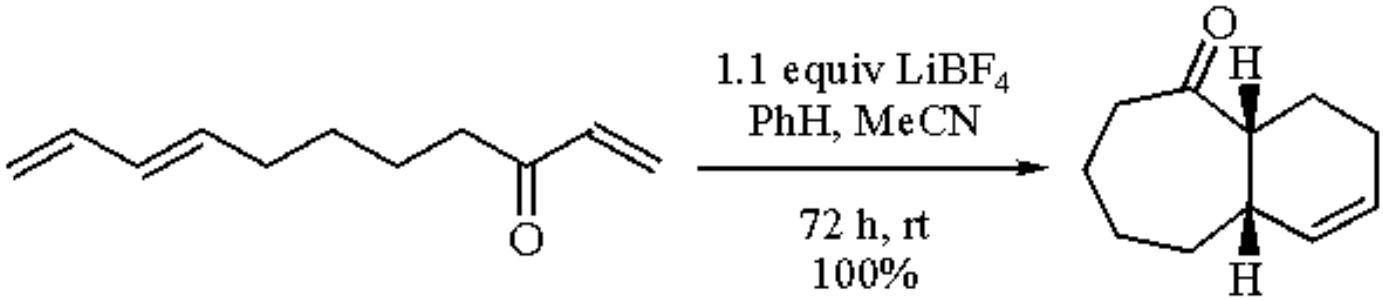

(12)

$LiBF_4$ has been employed as an electrolyte in the oxidative cleavage of 2-oxy-1-cyclohexanones, which gives good

yields of the ring-opened dicarbonyl compound (eq 13).[7]

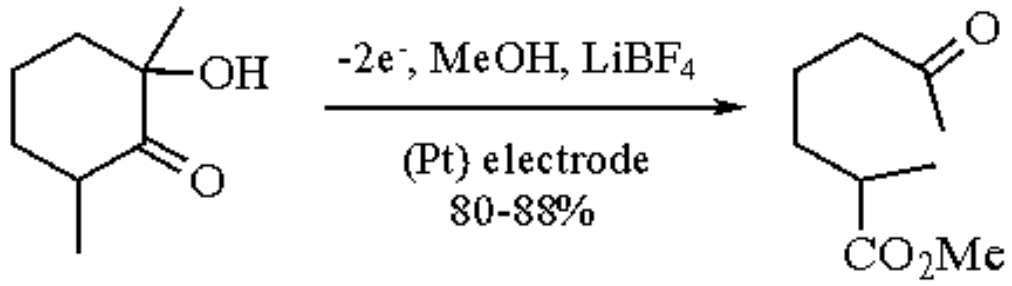

(13)

The Lewis acid character of $LiBF_4$ enhances the electrophilicity of arenesulfenyl chlorides in their additions to carbon-carbon double bonds.[5] In appropriately disposed bicyclic systems (eq 14), transannular bond formation is observed.

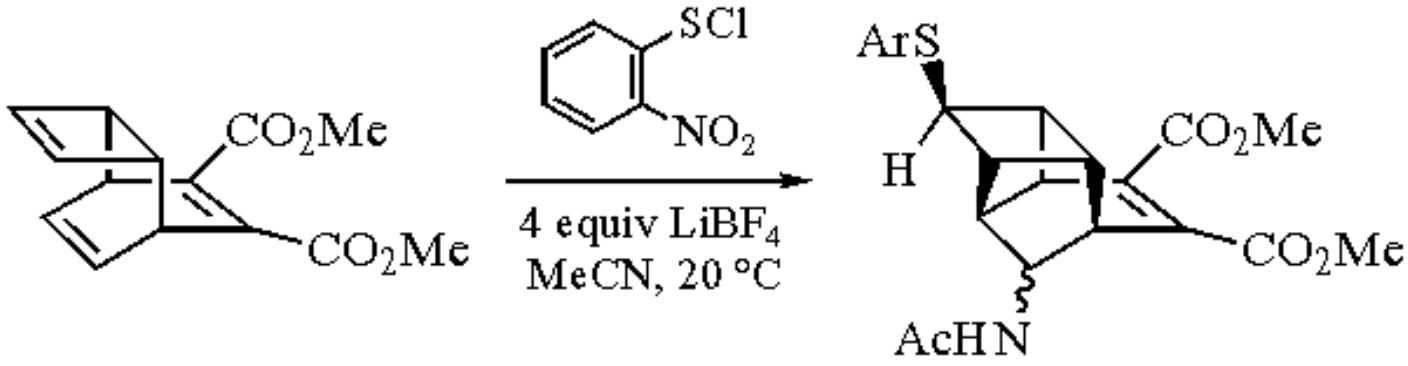

(14)

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Lithium 2,2,6,6-Tetramethylpiperidide

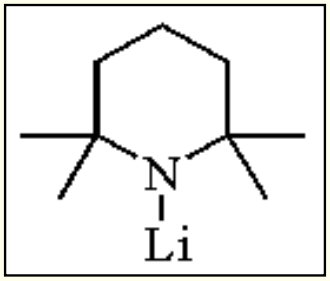

[38227-87-1] · $C_9H_{18}LiN$ · Lithium 2,2,6,6-Tetramethylpiperidide · (MW 147.22)

(strong, highly hindered, nonnucleophilic base (pK_a = 37.3)[1] capable of selective deprotonation of aromatics, heteroaromatics, and aliphatic C-H acidic sites in the presence of a variety of functional groups; also compatible with several electrophiles for in situ quenching of kinetically derived lithiated species[2-5])

Alternate Names: LiTMP; LTMP.

Physical Data: exists in THF solution as a dimer-monomer equilibrium mixture; additives such as HMPA increase monomer concentration.[6,7] X-ray structure determination shows that LiTMP crystallizes as a tetramer from hexane/pentane mixtures.[8]

Solubility: sol most organic solvents including THF, Et_2O, hexane.

Preparative Method: prepared in Et_2O or THF solutions immediately before use by treatment of commercially available dry ***2,2,6,6-Tetramethylpiperidine*** with ***n-Butyllithium*** (1:1). Tetramethylpiperidine is dried by heating a mixture of the base with CaH_2 at reflux for 4 h in a preflamed flask, followed by distillation at atmospheric pressure (bp 152 °C). It should be stored in a septum sealed bottle.

Handling, Storage, and Precautions: LiTMP solutions are pyrophoric, can cause severe burns, and should always be handled and transferred under an inert atmosphere. Solutions of LiTMP show a loss of activity (50% in THF; 60% in Et_2O) after 12 h at 24 °C.[9] Use in a fume hood.

Benzyne Formation.

The earliest uses of LiTMP as a base involved the deprotonation of benzyl chloride to give phenylcarbene and of 2-chloroanisole to give 3-methoxybenzyne.[10] LiTMP may also be used for heteroaryne generation; for example, treatment of 1,3-bis(TMS)isobenzofuran with 3-bromopyridine in the presence of LiTMP gives the corresponding cycloaddition product (eq 1).[11]

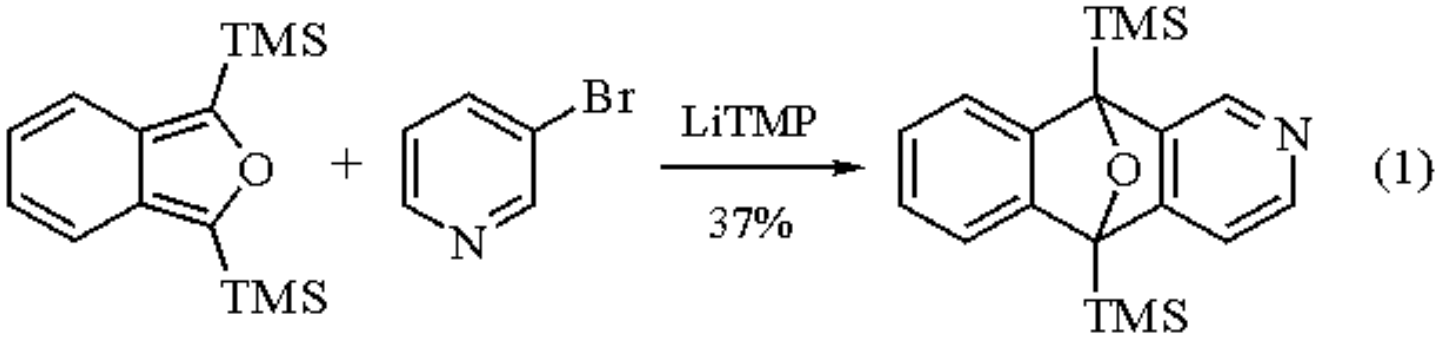

In situ Compatibility with Electrophiles.

Martin first demonstrated that the low nucleophilicity of LiTMP makes it compatible, at low temperatures, with certain electrophiles, e.g. ***Chlorotrimethylsilane***, ***Trimethyl Borate***.[2a] This allows the preparation of 2- and 2,6-silylated benzoates and benzonitriles by equilibrium controlled *ortho*-lithiation processes (eq 2). The distribution of mono- and disilylated products may be controlled by the number of equivalents of LiTMP; these products may be converted into corresponding bromo and iodo derivatives by *ipso*-halodesilylation.[2a,12] Similar ***Lithium Diisopropylamide***-TMSCl compatibility has been demonstrated.[5,13]

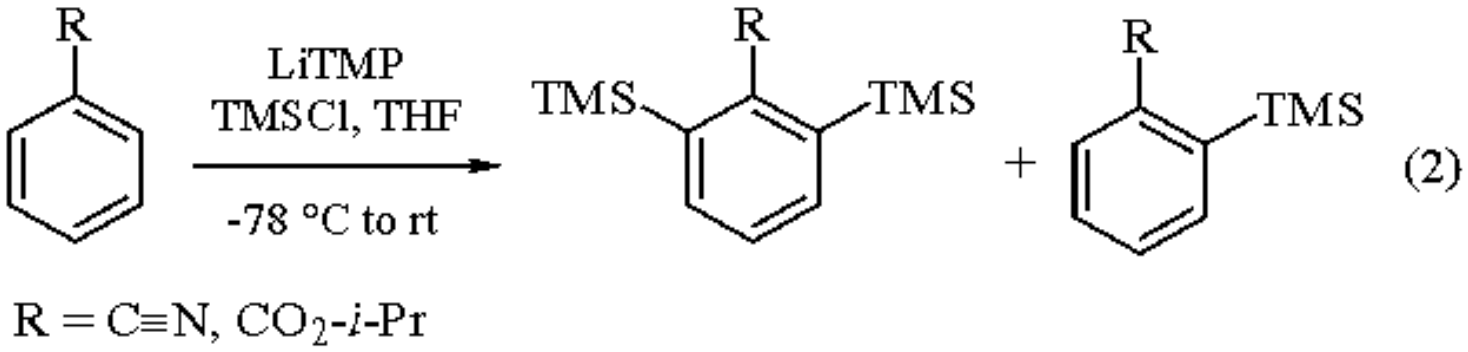

Analogous use of the LiTMP-***Mercury(II) Chloride*** combination allows selective functionalization of cubanecarboxamides (eq 3) and cyclopropanecarboxamides (eq 4),[14,15] presumably as a consequence of the high s character of the C-H bonds in these systems.

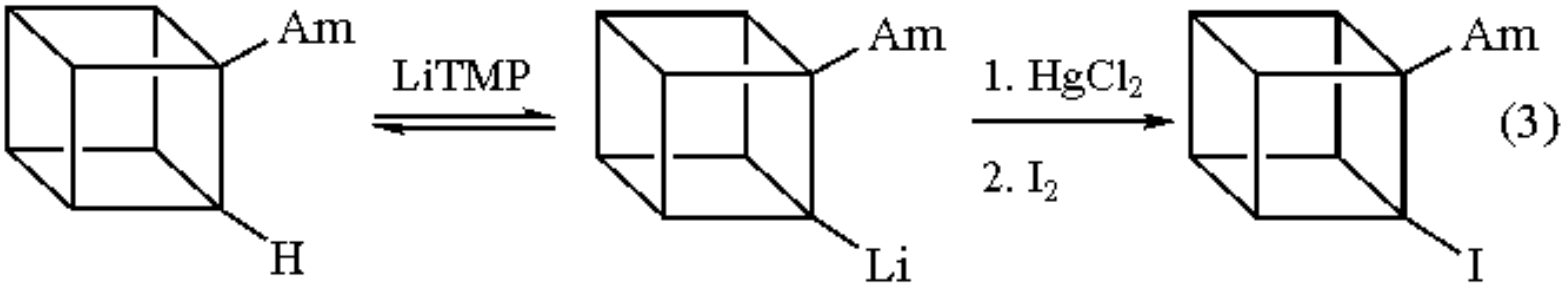

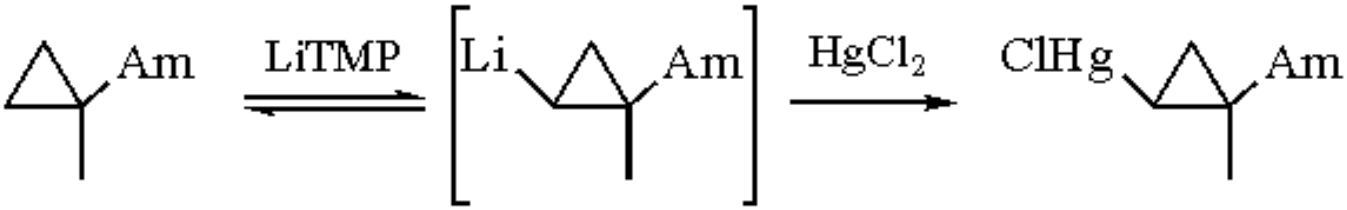

(4)

Am = CON(*i*-Pr)$_2$

Application of Martin's conditions to *N*,*N*-dimethylbenzamide leads, surprisingly, to α,α´-disilylation in good yield (eq 5).[16] Further treatment with LiTMP/TMSCl gives the *ortho*-silylated product. The bis-TMS derivative serves as a useful directed metalation group and may be readily converted to benzoic acid, benzaldehyde, and benzyl alcohol derivatives.

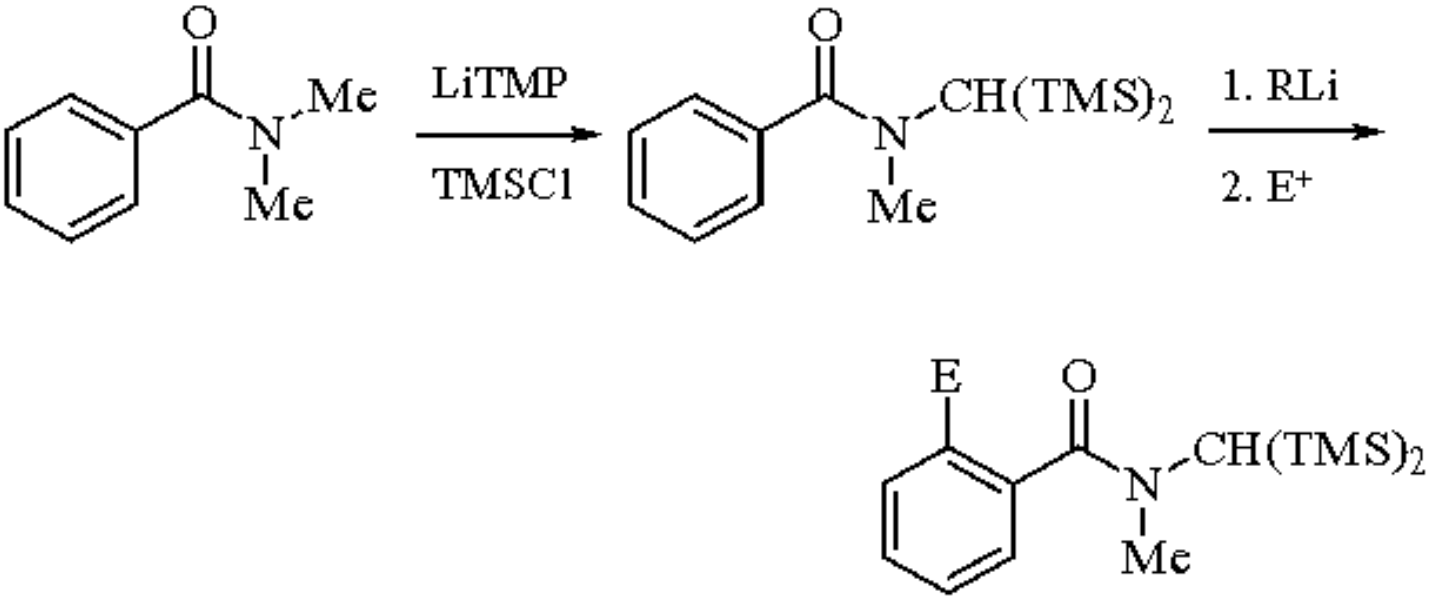

(5)

Remote Metalation.

LiTMP may be used interchangeably with LDA to effect conversion of diaryl amides into fluorenones by virtue of a complex induced proximity effect (eq 6).[17] This general route complements Friedel-Crafts chemistry for the preparation of fluorenones.

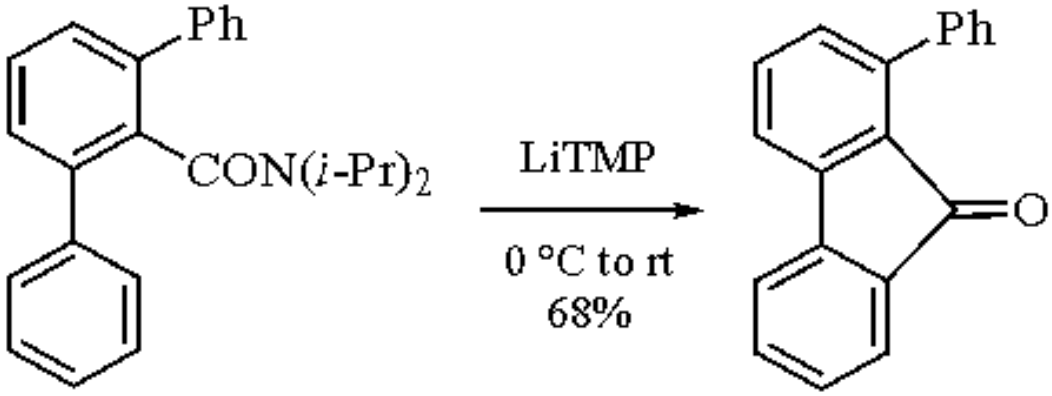

(6)

Directed *ortho* Metalation.

N-*t*-Boc-pyrrole undergoes clean deprotonation with LiTMP.[18] Low-temperature LiTMP lithiation of pyrazinecarboxamide followed by deuteration leads to isomeric products reflecting the temperature at which the reaction is quenched (eq 7).[3] This is rationalized by the thermodynamic stability of the *ortho*-amido lithiated species at the higher temperature.

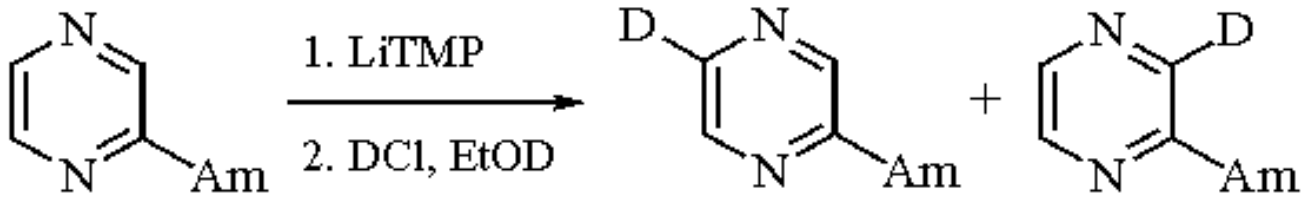

(7)

Am = CONH-*t*-Bu	0 °C	0%	75%
	-70 °C	40%	25%

The use of LiTMP in heterocyclic directed *ortho*-metalation chemistry is advantageous. For example, pyridine amide and oxazoline derivatives are smoothly deprotonated and lead, after electrophile quench, to 4-substituted products (e.g. eq 8),[19] which may be used for the synthesis of natural products (e.g. eq 9) and pharmaceuticals.[20-22] In contrast to LDA and, of course, alkyllithiums, no nucleophilic attack of the pyridine ring is observed.[19] The considerable C-H acidity of methylpyridines allows deprotonation-condensation reactions which are of general synthetic value (eq 9).[20]

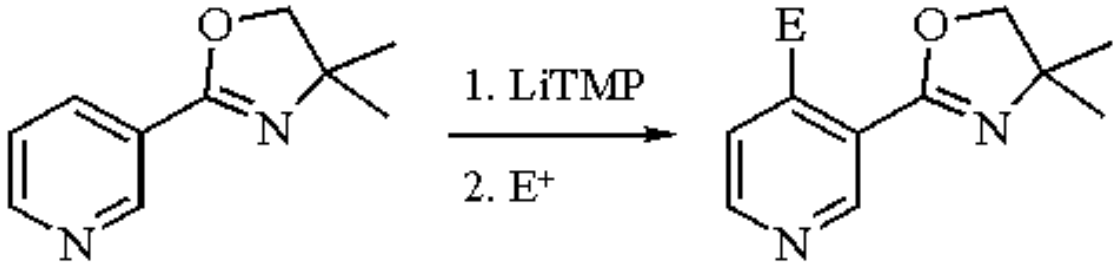

(8)

$E^+ = D_2O$, 70%; PhCHO, 50%; Et_2CO, 52%; MeI, 80%; BuI, 9%

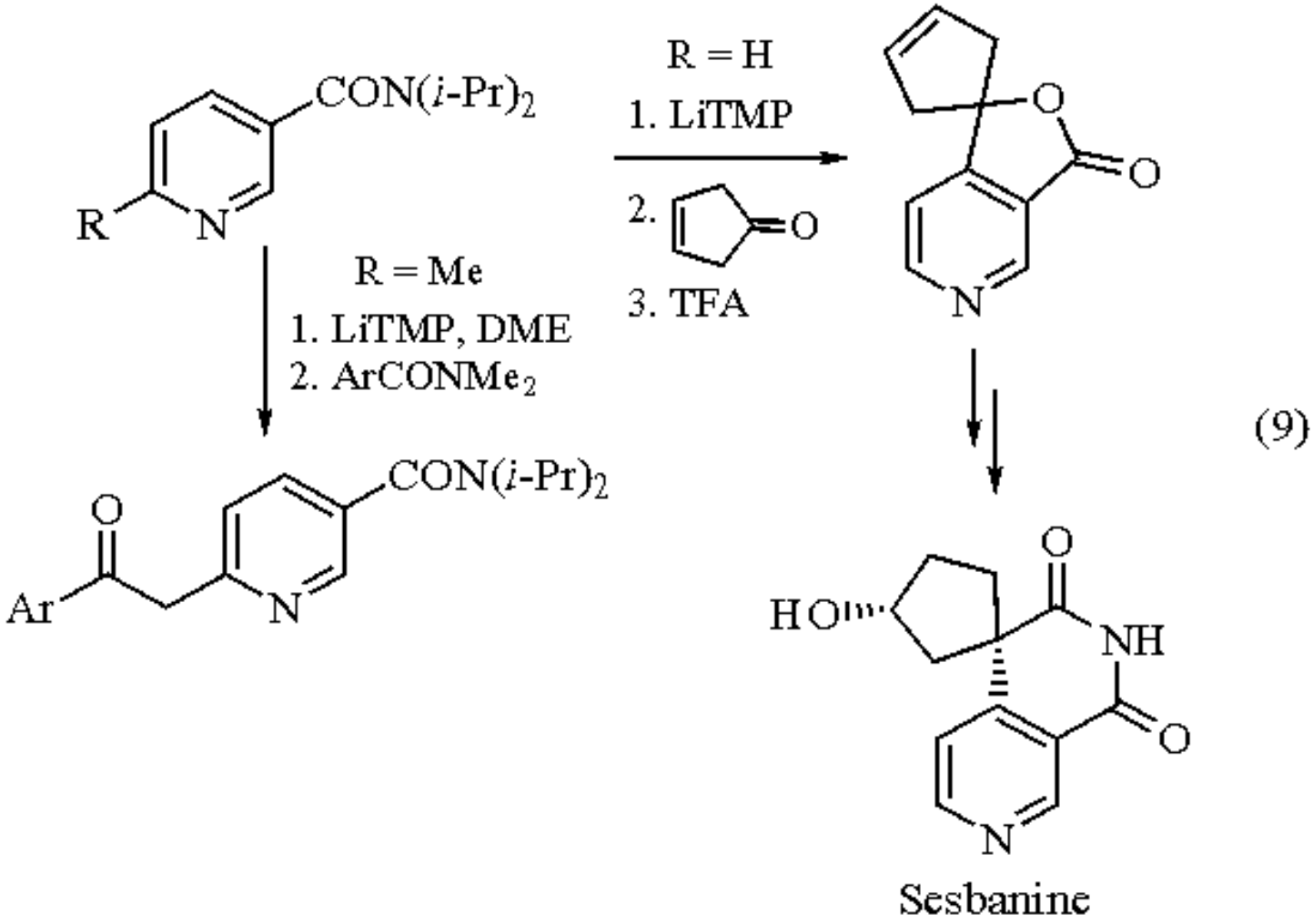

(9)

In some cases, LiTMP complements the metalation regioselectivity of LDA. For example, LDA metalation of 2,4-dichloropyrimidine gives the 5-substituted product whereas LiTMP affords mainly the product of 6-substitution (eq 10).[23]

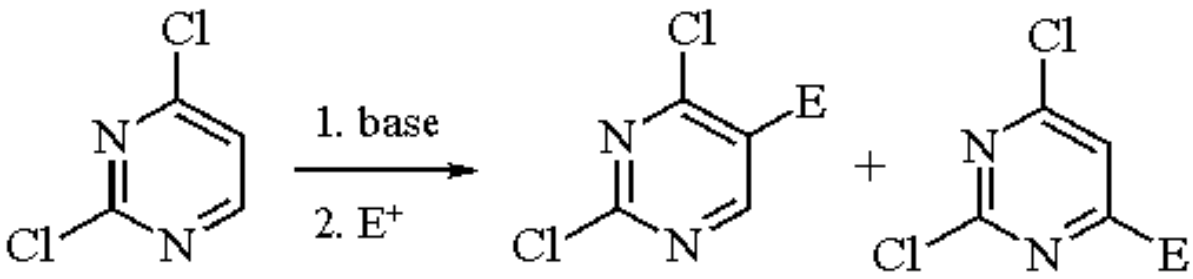

(10)

base =		
LDA	100	0
TMP	35	65

Enolate Formation.

LiTMP is widely used to generate α-stabilized carbanions. For example, in the synthesis of paniculide A, the use of LiTMP is critical; LDA fails to give the required product (eq 11).[24]

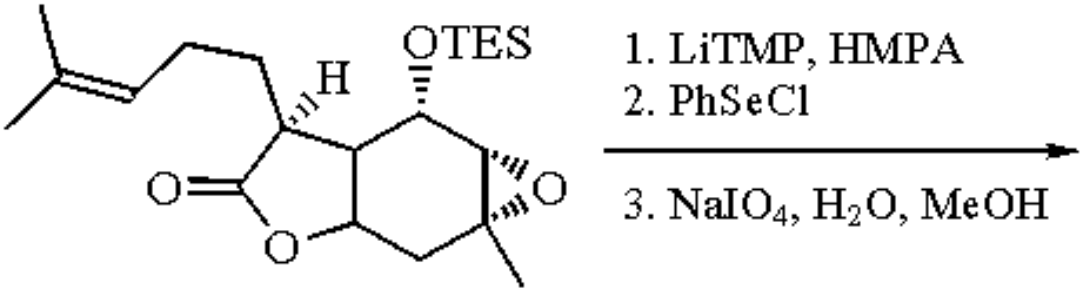

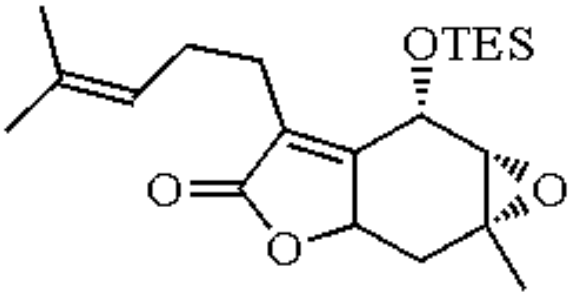

(11)

LiTMP is especially useful in cases where the reactants are sensitive to nucleophilic attack (e.g. eq 12) (cf. 66% yield with LDA).[10]

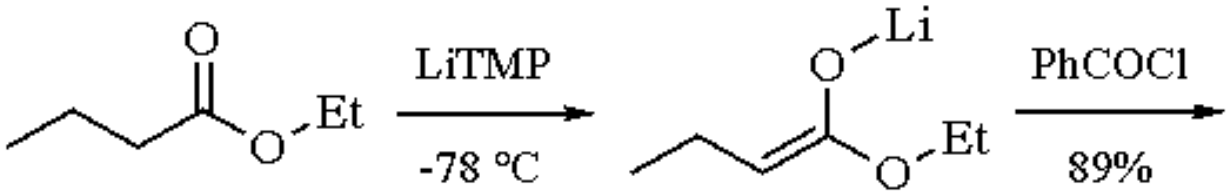

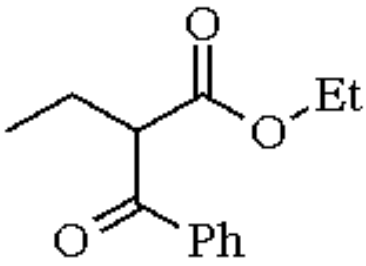

(12)

LiTMP is also used to deprotonate nonenolizable sites. For example, bridgehead deprotonation of (-)-camphenilone is followed by self-condensation to give a high yield of dimeric product (eq 13).[25]

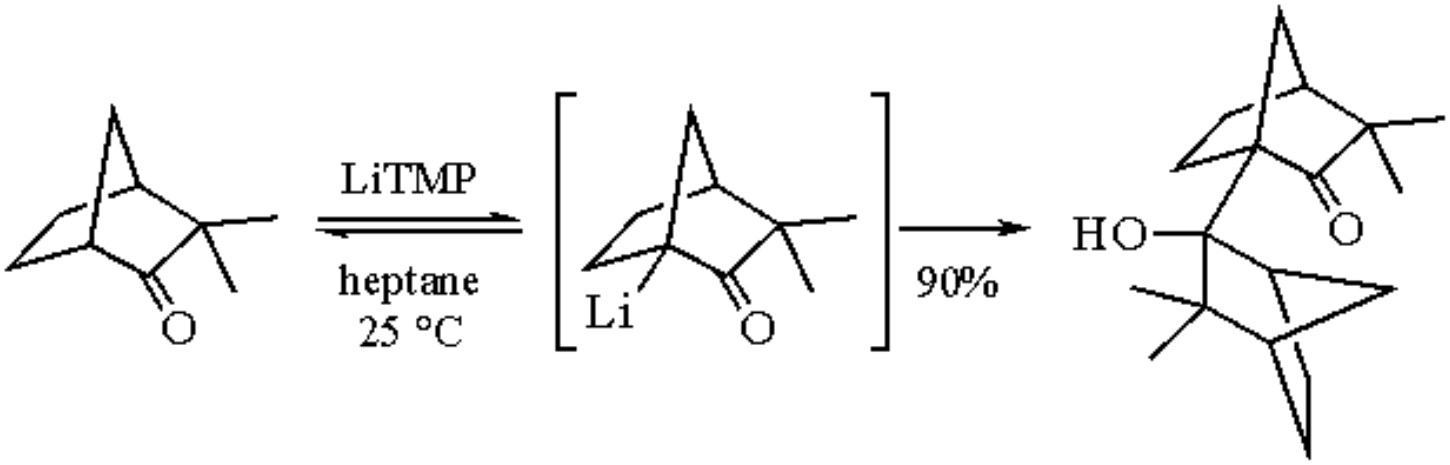

(13)

Under similar conditions, LiTMP generates the acyllithium of a nonenolizable aldehyde which undergoes self-condensation to give an acyloin (eq 14).[25]

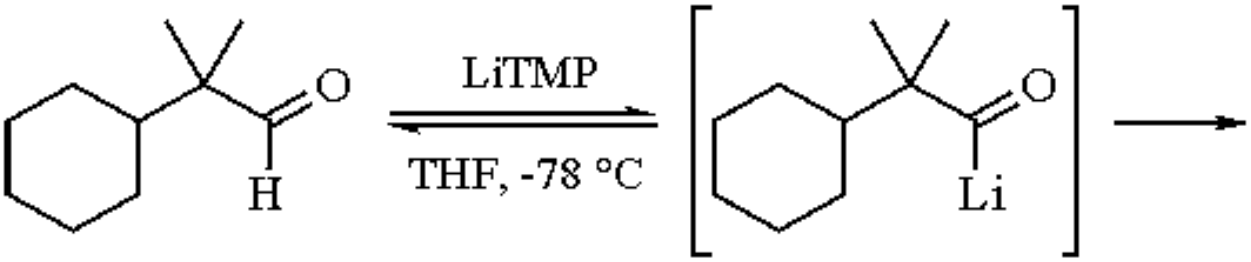

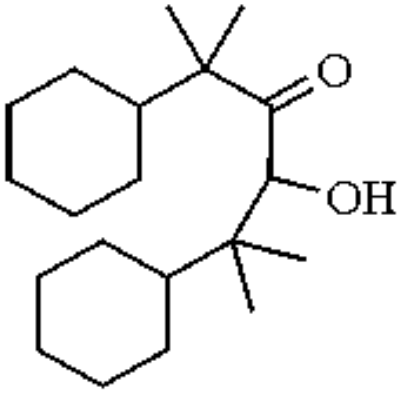

(14)

The primary reservation concerning the use of LiTMP in synthesis, particularly on a large scale, is the cost of tetramethylpiperidine relative to other amine bases. However, an aqueous acid extraction of the reaction mixture allows the recovery of tetramethylpiperidinium salt from which the free base can be obtained by neutralization and distillation. This recovery method is dependent on the acid stability of the reaction products.

Related Reagents.

Lithium Diethylamide; ***Lithium Diisopropylamide***; ***Lithium Hexamethyldisilazide***; ***Lithium Piperidide***; ***Lithium Pyrrolidide***.

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Lithium Tri-*t*-butoxyaluminum Hydride[1]

$LiAlH(OR)_3$

(R = *t*-Bu)

[17476-04-9] · $C_{12}H_{28}AlLiO_3$ · Lithium Tri-*t*-butoxyaluminum Hydride · (MW 254.32) (R = Et_3C)

[79172-99-9] · $C_{21}H_{46}AlLiO_3$ · Lithium Tris(3-ethyl-3-pentoxy)aluminum Hydride · (MW 380.59) (R = Et)

[17250-30-5] · $C_6H_{16}AlLiO_3$ · Lithium Triethoxyaluminum Hydride · (MW 170.14) (R = Me)

[12076-93-6] · $C_3H_{10}AlLiO_3$ · Lithium Trimethoxyaluminum Hydride · (MW 128.05)

(reducing agent for many functional groups; cleaves cyclic ethers)

Physical Data: R = *t*-Bu: mp 300-319 °C (dec); sublimes at 280 °C/2 mmHg. All the other reagents are unstable and are prepared in situ.

Solubility: R = *t*-Bu: (at 25 °C) diglyme (41 g/100 mL), THF (36 g/100 mL), DME (4 g/100 mL), ether (2 g/100 mL).

Form Supplied in: R = *t*-Bu: solid; 0.5 M or 1.0 M solutions in diglyme or THF. The other reagents are prepared in situ just prior to use.

Preparative Methods: for R = Me,[2] Et,[3] or 3-ethyl-3-pentyl,[4] in situ preparation can be carried out as follows: addition of 3 mol of the desired alcohol to 1 mol of standardized ***Lithium Aluminum Hydride*** solution in ether, THF, or diglyme results in the formation of the corresponding trialkoxyaluminohydride reagent. The *t*-Bu[5] derivative can also be prepared in situ by this method.

Analysis of Reagent Purity: standardization of $LiAlH(O\text{-}t\text{-}Bu)_3$ solutions is best carried out by reduction of cyclohexanone and with GC and/or spectroscopic analysis to measure the extent of reaction. Iodometric titrations are not suitable in this case.[6]

Handling, Storage, and Precautions: the dry solid and solutions are corrosive and/or highly flammable and must be stored in the absence of moisture. While the *t*-BuO compound appears to have long term stability in terms of storage, the MeO compound degrades in its reactivity within one week. Therefore it is advised to use freshly prepared reagent solutions.[2a]

Functional Group Reductions.

The high reactivity for reduction exhibited by $LiAlH_4$ can be attenuated by modifying this reagent. Altered reagents can be prepared by the addition of an alcohol such that a 3:1 complex of alcohol:$LiAlH_4$ is formed. The reactivity of these new trialkoxyaluminohydride reagents can be modulated by the selection of the appropriate alcohol. In terms of relative reactivity one can rank[7] hydride reagents as follows: $LiAlH_4$ > $LiAlH(OMe)_3$ > $LiAlH(O\text{-}t\text{-}Bu)_3$ > $NaBH_4$. Table 1 provides a comparison of the aluminum based reagents with various functional groups. For a detailed discussion of the reduction properties of $LiAlH_4$, see ***Lithium Aluminum Hydride***.

Table 1 Comparison of the Reactivities of Aluminohydride Reducing Agents

Reaction	$LiAlH_4$	$LiAlH(OMe)_3$	$LiAlH(O\text{-}t\text{-}Bu)_3$
Aldehyde to alcohol	+	+	+
Ketone to alcohol	+	+	+
Acid chloride to alcohol	+	+	+
Lactone to lactol	+	+	slow
Epoxide to alcohol	+	slow	slow
Ester to alcohol	+	+	slow
Carboxylic acid to alcohol	+	+	-
Carboxylic acid salt to alcohol	+	+	-
t-Amide to amine	+	+	-
Nitrile to amine	+	+	-
Nitro to amine	+	-	-
Alkene	-	-	-

This observation of diminished reactivity of the trialkoxyaluminohydrides is opposite to that observed with $NaBH_4$ and its alkoxy analogs (see ***Sodium Borohydride*** and ***Sodium Trimethoxyborohydride***). The stoichiometry for the reaction can be determined from the theoretical number of hydrides required for the reduction based on the observation that the trialkoxyaluminohydrides can be considered to be the source of one hydride. For example, the reduction of an aldehyde or ketone theoretically requires one hydride and so one equivalent of the reagent is needed for this reduction.

The differential reducing abilities of these reagents allows selective reduction of one functional group in the presence of another. While simple saturated aldehydes can be reduced by both $LiAlH(OMe)_3$ and $LiAlH(O\text{-}t\text{-}Bu)_3$ as rapidly as by $LiAlH_4$ at 0 °C, cyano aldehydes can be reduced at low temperature to the corresponding alcohol derivatives (eq 1).[8]

Aldehyde lactones can also be reduced chemoselectively (eq 2).[9]

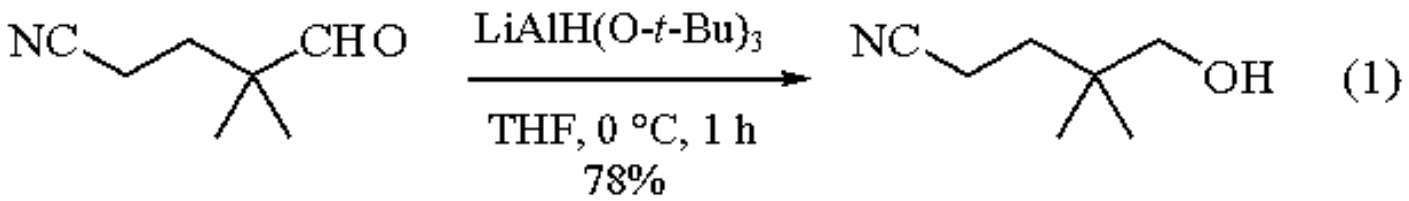

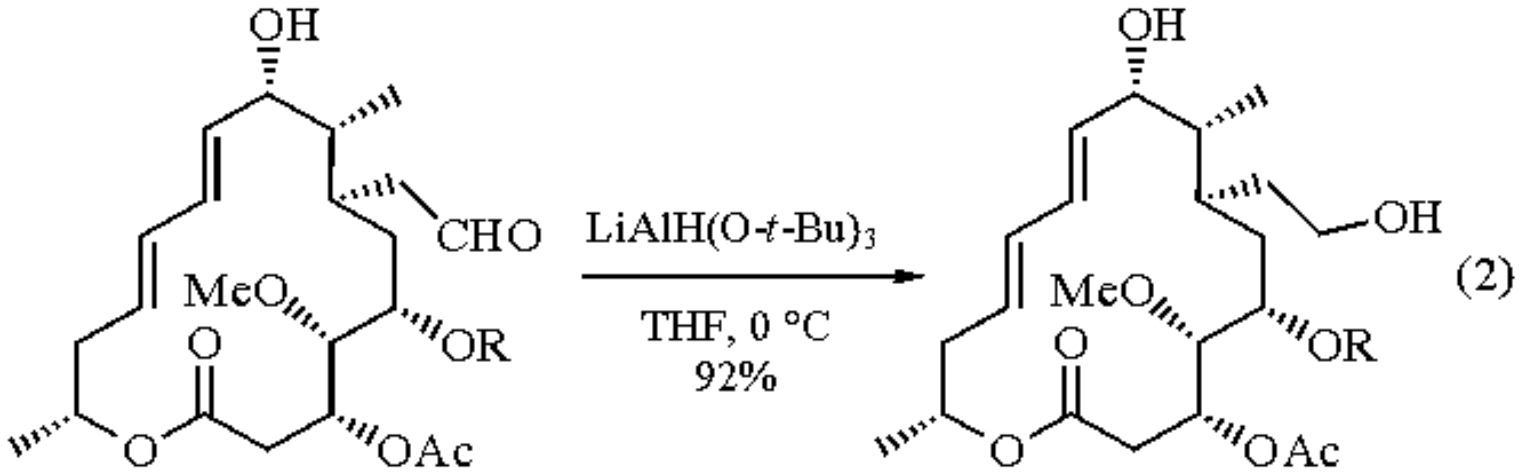

The reduction of aldehyde esters can lead to the formation of lactones with or without subsequent acidic workup (eqs 3 and 4).[10,11] Aldehydes can also be reduced preferentially in the presence of ketones (eq 5).[4]

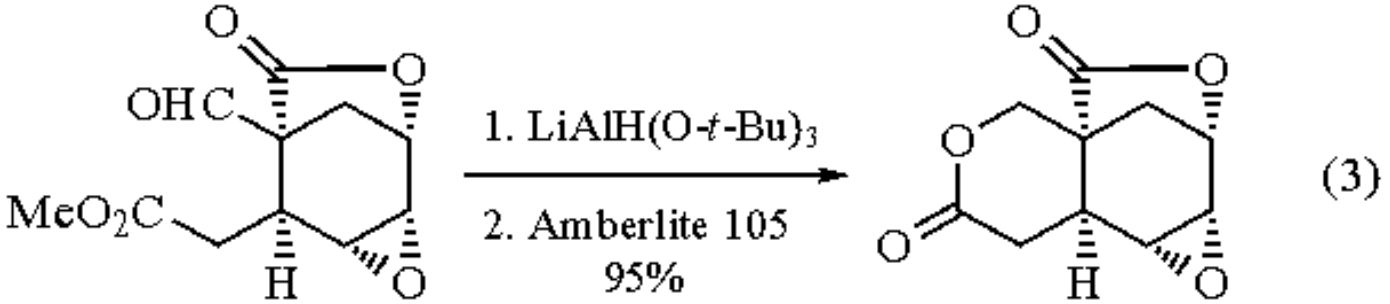

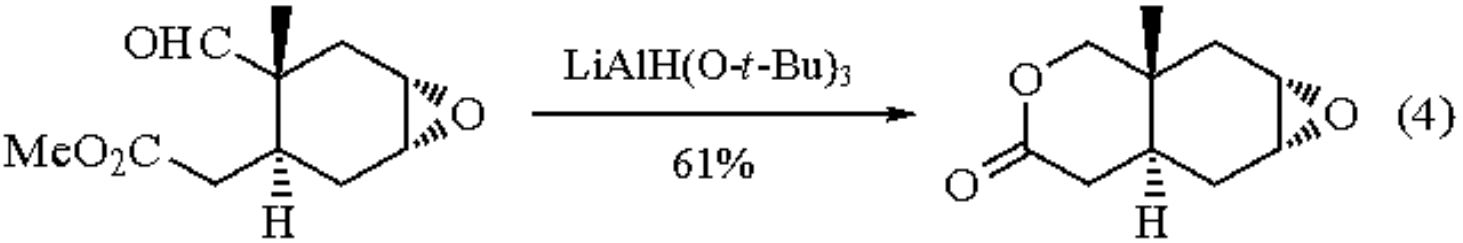

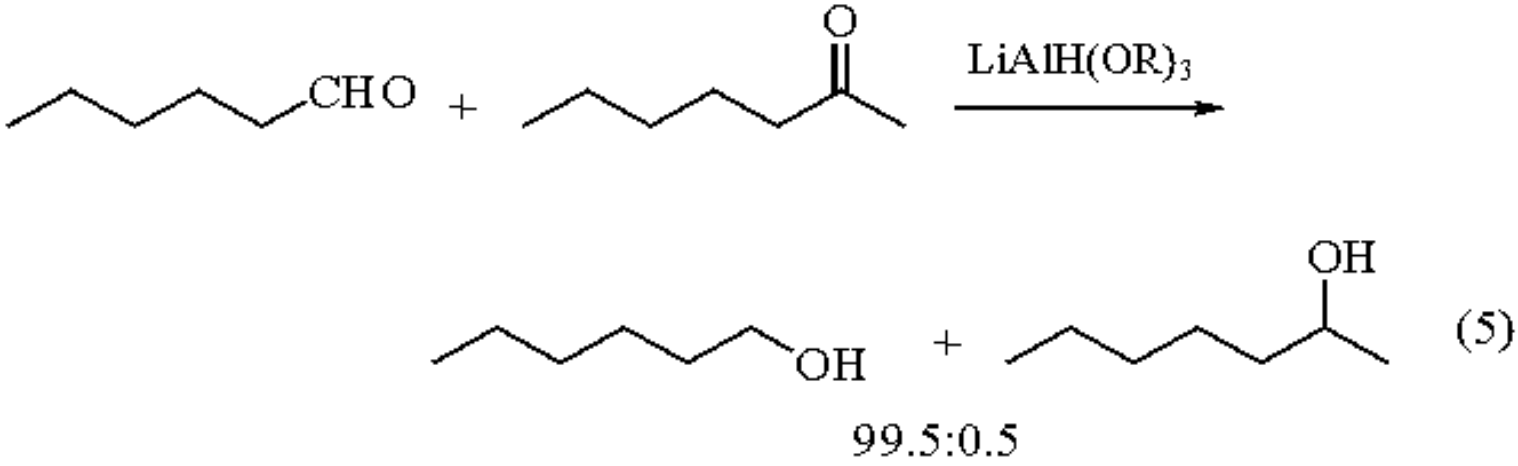

With unsaturated aldehydes such as cinnamaldehyde, LiAlH(O-*t*-Bu)$_3$ gives the corresponding allylic alcohol, whereas LiAlH(OMe)$_3$ affords the saturated alcohol. This difference in reactivity can be exploited (eq 6).[12] The course of the reduction can be changed if a copper species is also used (eq 7).[13]

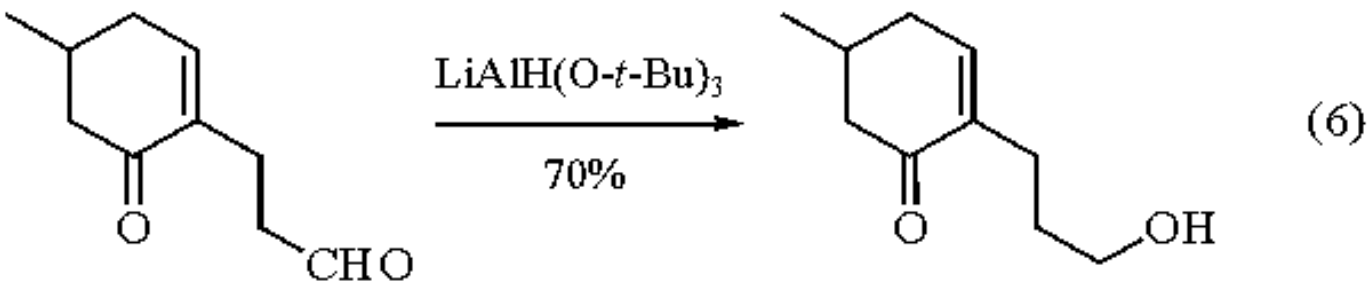

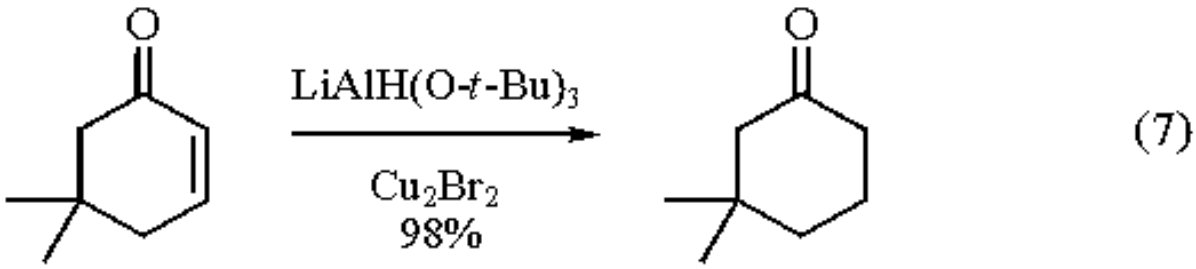

Similarly, ketones can be reduced with LiAlH(O-*t*-Bu)$_3$ in the presence of esters,[14a] lactones,[14b] amides,[5] halogens,[15] epoxides,[5] *O*-alkyl oximes,[5] azides,[16] and cyano groups.[5] A ketone can be reduced in the presence of an aldehyde, provided the aldehyde is first masked as an aldimine, for example. The reduction of an acid halide to the corresponding alcohol can be carried out with LiAlH(O-*t*-Bu)$_3$ at 0 °C, while the corresponding aldehyde can be obtained if the reduction is performed at -80 °C in diglyme.[17] Aldehydes can also be obtained by the reduction of nitriles[3a] or tertiary amides[3b] if LiAlH(OEt)$_3$ is used as the reductant.

In addition to the differences in relative functional group reactivities that LiAlH(OR)$_3$ has over LiAlH$_4$, these reagents also exhibit improved stereoselectivities in these reductions.[18] For example, the reduction of norbornanone to give the *endo*-alcohol proceeds with greater control (eq 8).[2b] Further examples of this stereoselectivity are illustrated in eqs 9-11.[19-21] The use of LiAlH$_4$-***Lithium Iodide*** in the reaction depicted in eq 11 results in complete inversion of stereochemistry (*syn*:*anti* = 5:95). Therefore the choice of reagents allows preparation of either diastereomer.

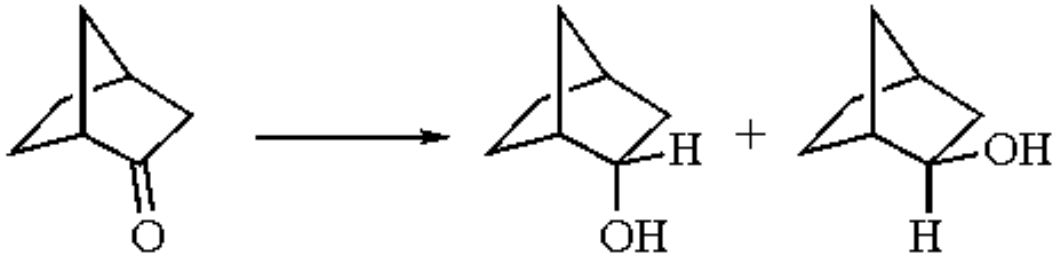

(8)

$LiAlH_4$	89:11
$LiAlH(OMe)_3$	98:2

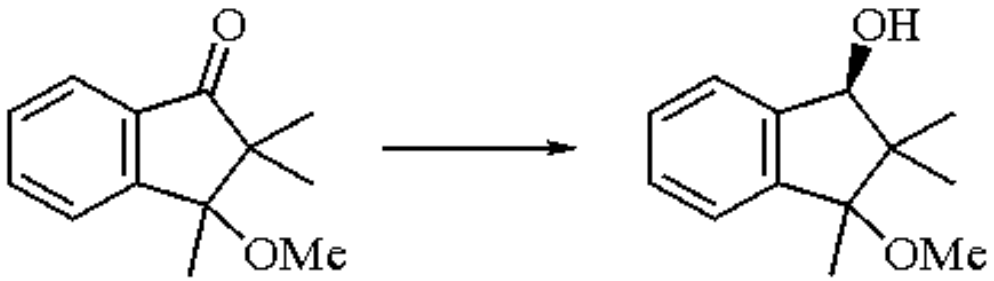

(9)

$LiAlH_4$	*trans*:*cis* = 32:68
$LiAlH(O\text{-}t\text{-}Bu)_3$	*trans*:*cis* = 90:10

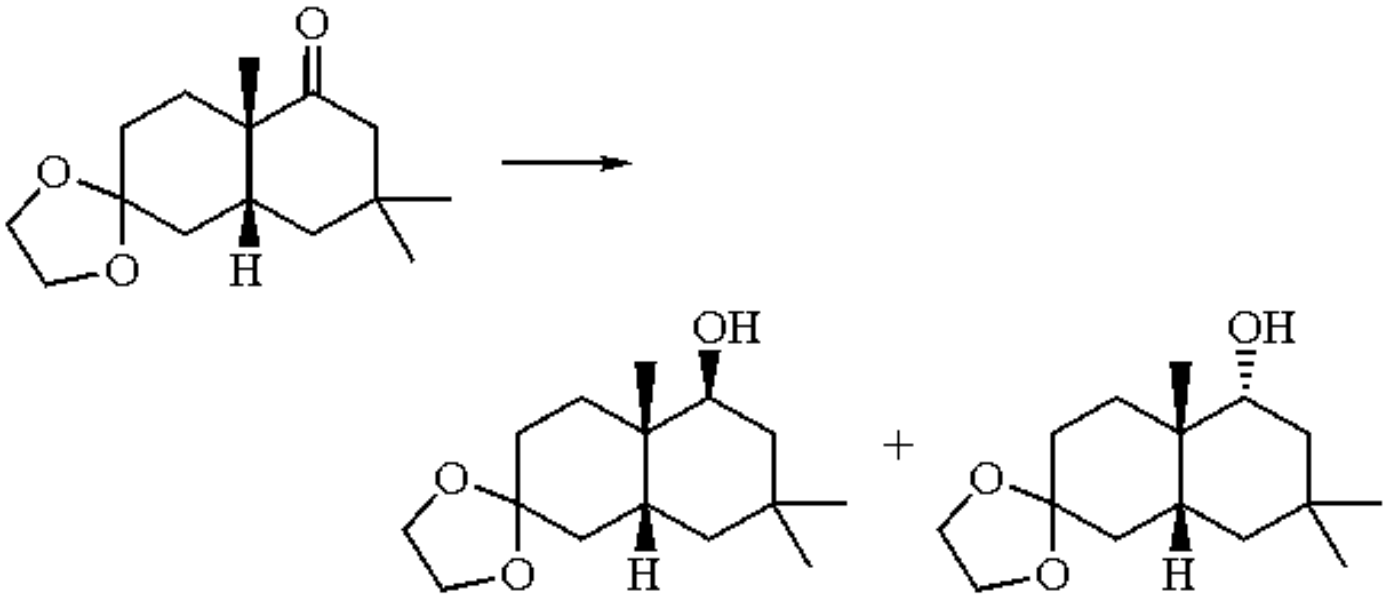

(10)

$LiAlH_4$	60:40
$LiAlH(OCMe_2Et)_3$	100:0

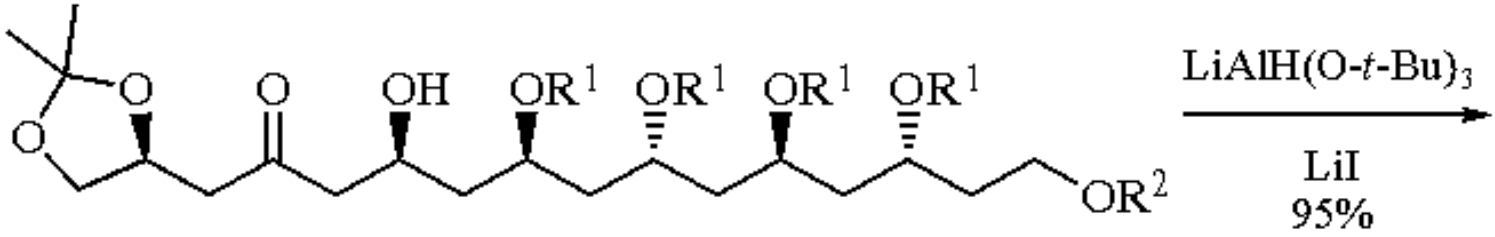

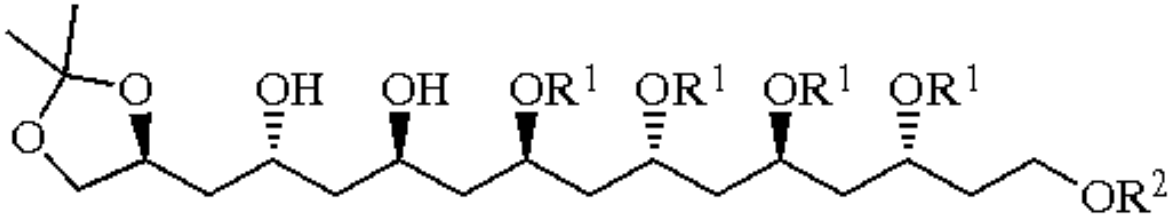

(11)

anti:*syn* = 95:5

Enantioselective reductions are also possible if the alcohol used to form the trialkoxyaluminohydride is optically active. For example, treating $LiAlH_4$ with MeOH and BINAL-H[22] in a mole ratio of 1:1:1 in dry THF generates an optically active hydride[23] reagent which can reduce ynones with good enantioselectivity, as shown in eq 12. The (*R*)-antipode of BINAL-H results in the isolation of the (*R*)-propargylic alcohol. See ***Lithium Aluminum Hydride-2,2´-Dihydroxy-1,1´-binaphthyl*** for additional examples of this type.

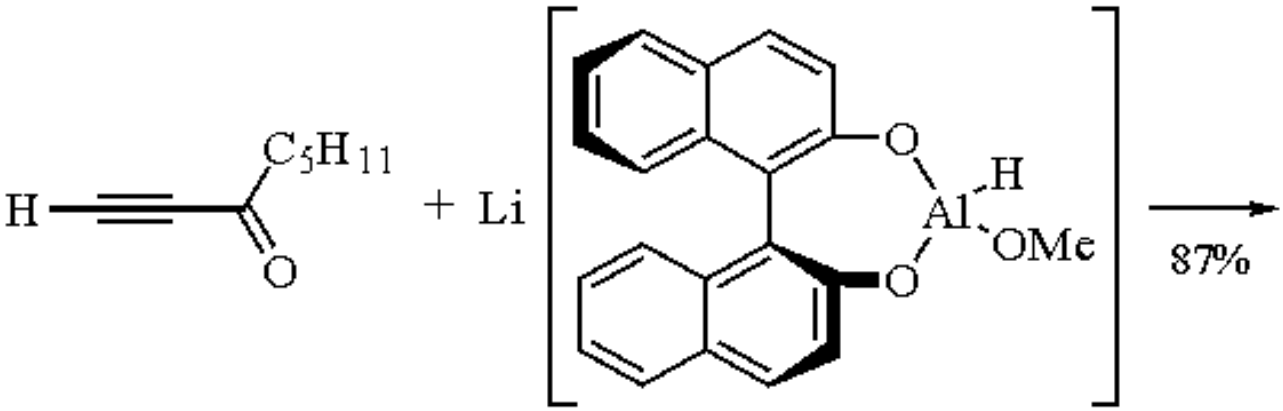

(*S*)-BINAL-H

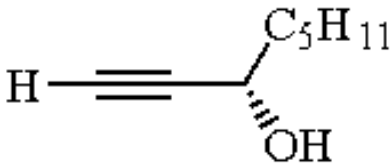

(12)

84% ee

While unsubstituted lactams are reduced to the corresponding amines, the intermediates in these reductions can be diverted into other reactions when the substrate is suitably functionalized. One example is shown in eq 13.[24] The trialkoxyaluminohydrides are capable of reducing most nitrogen based functional groups; however, imides do not react. This attribute has been used in a diastereoselective synthesis of D-*threo*-sphingamine (eq 14).[25] Oximes react with these

reagents only to generate hydrogen. No reduction is observed. *N*-Methylamines are formed by the reduction of isocyanates with $LiAlH(OMe)_3$,[2a,26] while $LiAlH(O\text{-}t\text{-}Bu)_3$ gives formamides (eq 15).[5b,27] Unsaturated isocyanates are also reduced to the corresponding vinylic formamide (eq 16).[28] Thiocyanates are inert to $LiAlH(O\text{-}t\text{-}Bu)_3$.[29]

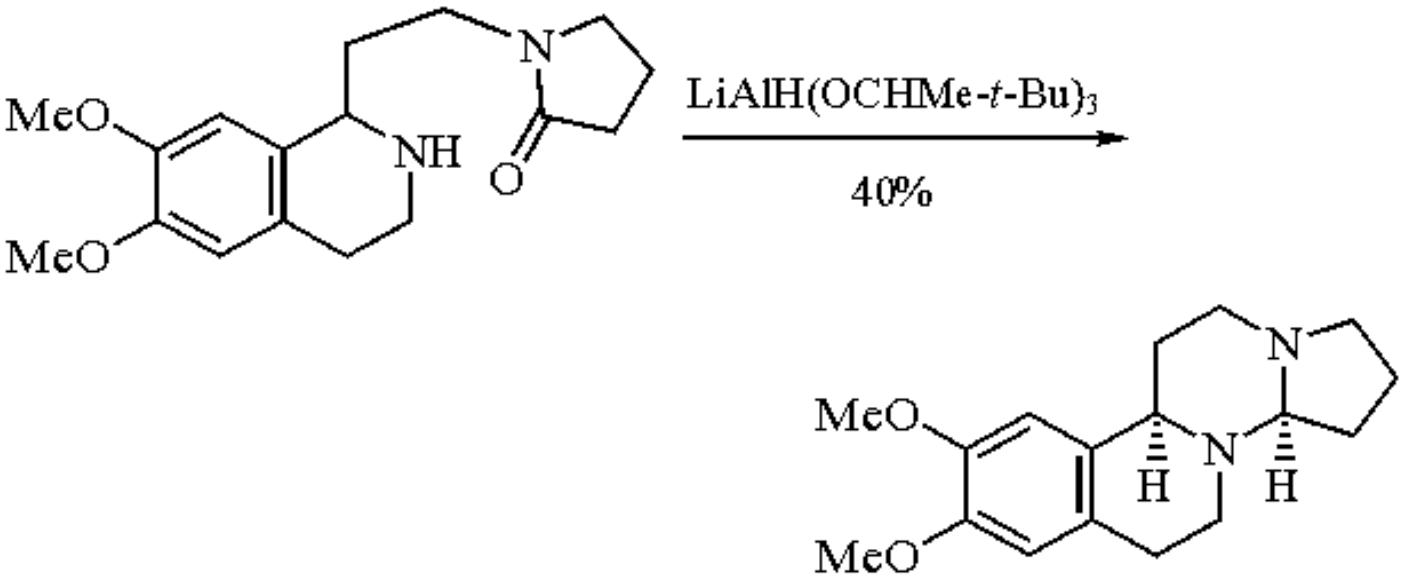

(13)

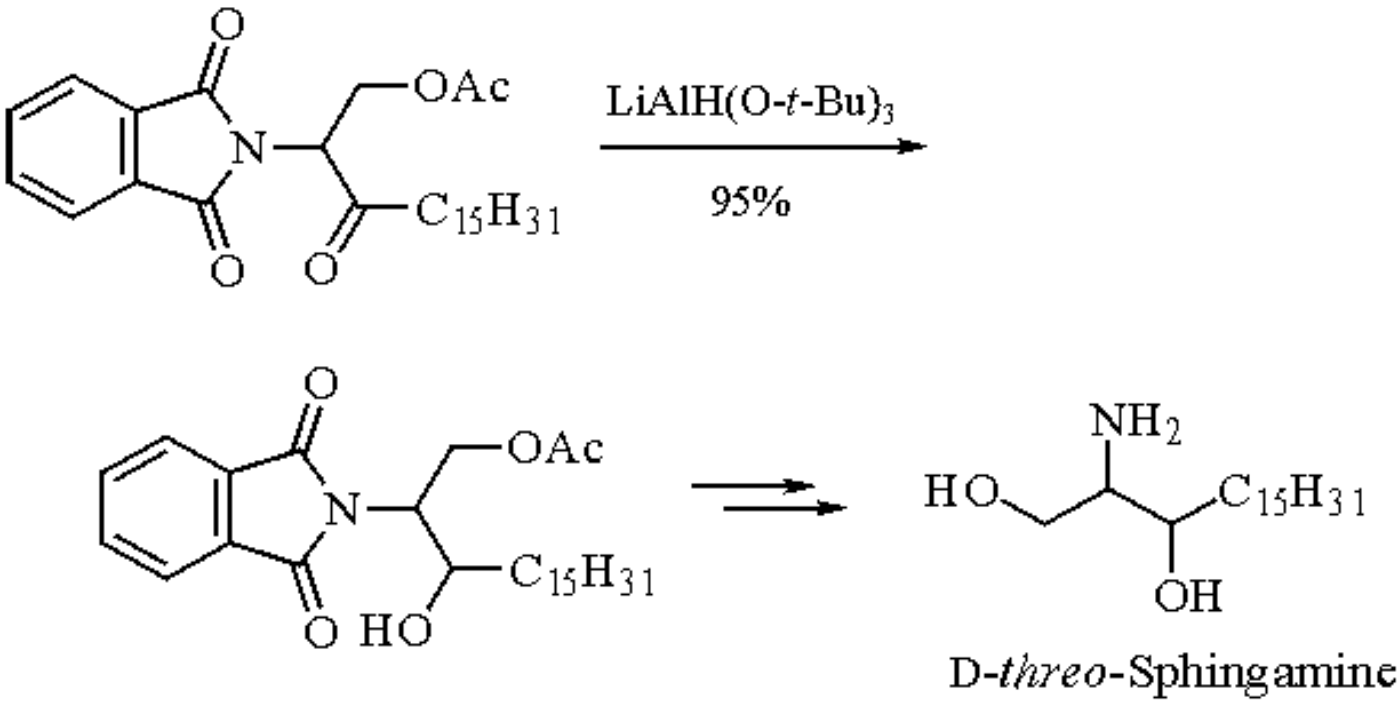

(14)

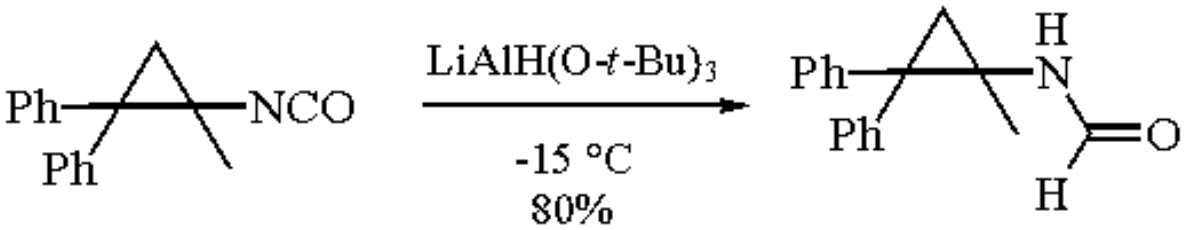

(15)

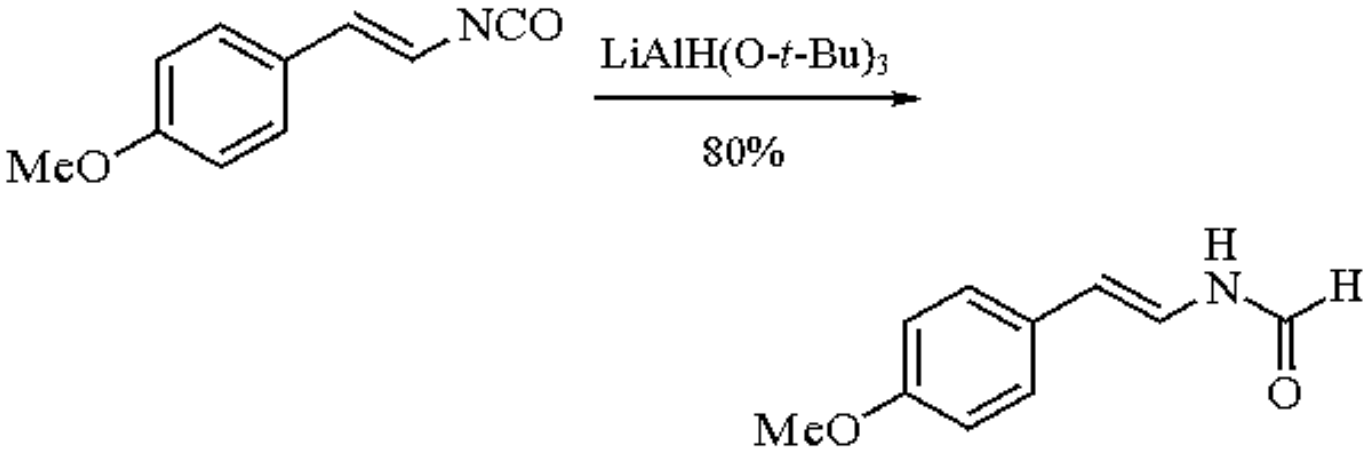

(16)

The trialkoxyaluminohydrides generate 1 equiv of hydrogen upon exposure to thiols and are inert to dialkyl and/or aryl sulfides, while disulfides are reduced to thiols (eq 17).[30] Alkyl 1-alkynyl sulfides are reduced to the corresponding alkyl *cis*-1-alkenyl sulfides when the reaction is carried out in the presence of ***Copper(I) Bromide*** (eq 18).[31] The *trans*-isomer is obtained with $LiAlH_4$. Two equivalents of hydride are required to reduce sulfoxides by $LiAlH(OMe)_3$,[2a,26] while $LiAlH(O\text{-}t\text{-}Bu)_3$[32] is unreactive to sulfoxides. Sulfones do not react with these reagents.[2a,5b,26] While alkyl mesylates and tosylates are inert to the trialkoxyaluminohydrides, $LiAlH(OMe)_3$ can reduce acetylenic mesylates to the corresponding allene in an *anti* fashion to maintain chirality (eq 19).[33]

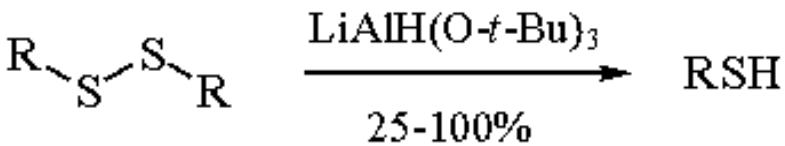

(17)

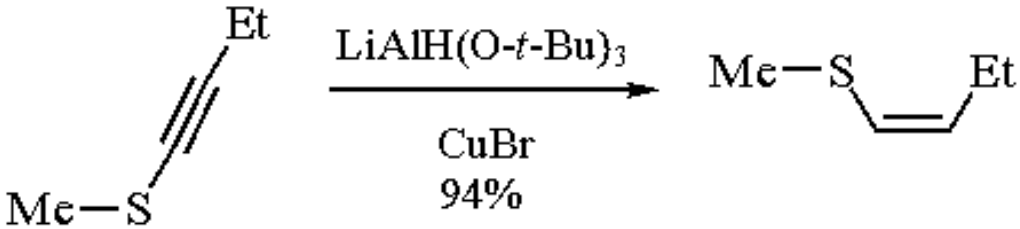

(18)

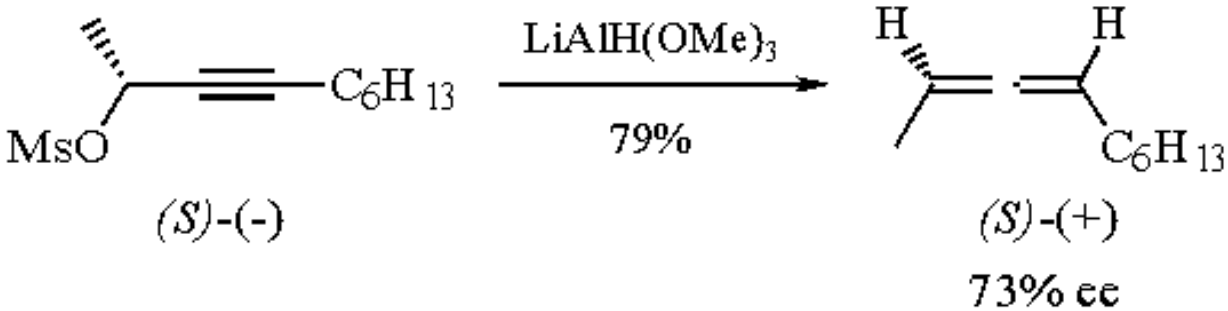

(19)

A related reagent is $NaAlH_2(OCH_2CH_2OMe)_2$, which is abbreviated to SMEAH or Red-Al, and has in some cases comparable reactivity and chemistry and in other cases complementary activity (see ***Sodium Bis(2-methoxyethoxy)aluminum Hydride***).

Reductive Cleavage of Ethers.

Dialkyl ethers, alkyl aryl ethers, diaryl ethers, and cyclic ethers react very slowly with these reductants, if at all. However, the addition of ***Triethylborane***, in varying amounts, produces a complex which is capable of ring opening some cyclic ethers (eqs 20 and 21).[34] Epoxides also react very slowly with $LiAlH(O\text{-}t\text{-}Bu)_3$,[26] which allows for differentiating functional groups during their reduction. Formation of a complex with BEt_3 now can be used to open the epoxide (eq 22).[29,35] A mixture of $LiAlH(OMe)_3$ and ***Copper(I) Iodide*** can also be used to open epoxides (eq 23).[36]

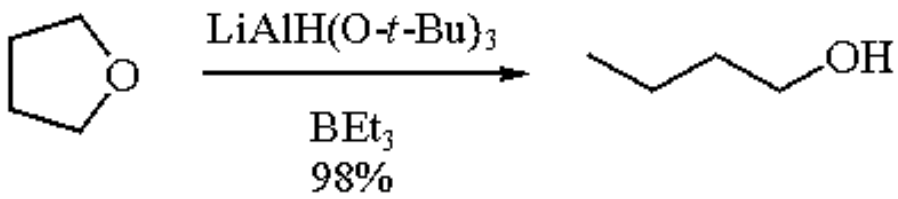

(20)

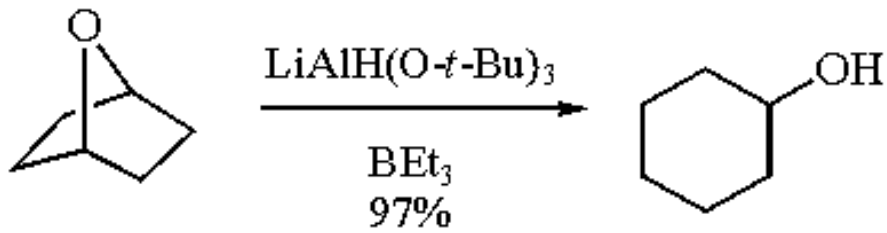

(21)

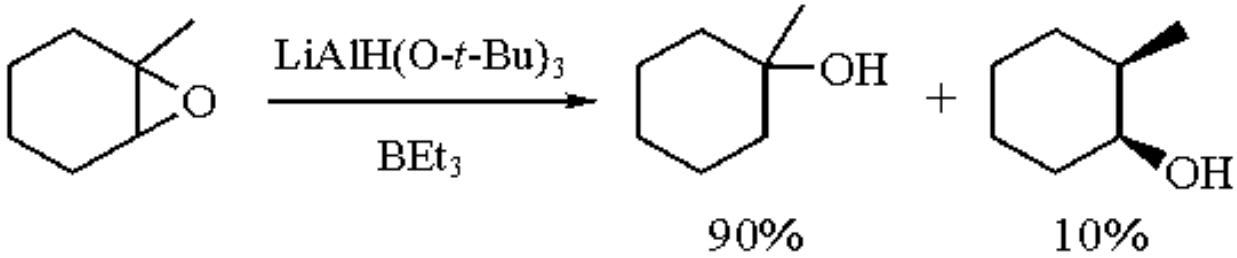

(22)

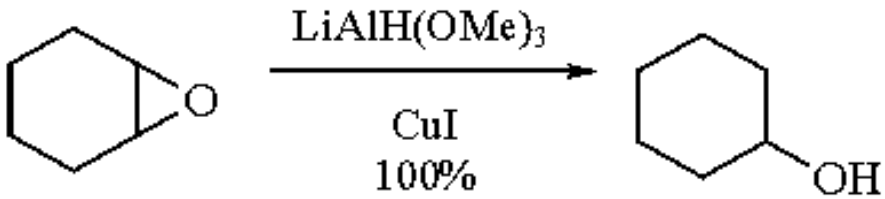

(23)

Reduction of Halogenated Compounds.

The reduction of 1-iodoalkanes with $LiAlH(OMe)_3$ is comparable to reduction by $LiAlH_4$, while the reactivity with bromo and chloro compounds is very low. There is no reaction of $LiAlH(O\text{-}t\text{-}Bu)_3$ with chloro compounds. As a result, one can reduce aldehydes in the presence of chloro groups. The mixture of CuI and $LiAlH(OMe)_3$ provides a species which is capable of reducing primary chlorides, and primary and secondary bromides.[5b,37]

Related Reagents.

Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride; ***Copper(I) Iodide-Lithium Trimethoxyaluminum Hydride***.

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Lithium Tri-*s*-butylborohydride[1]

$LiBH(s\text{-}Bu)_3$

[38721-52-7] · $C_{12}H_{28}BLi$ · Lithium Tri-*s*-butylborohydride · (MW 190.15)

(reducing agent for various functional groups;[2] selective reducing agent;[3-6] stereoselective reducing agent for ketones[7,8] and other functional groups;[5,9,10] regioselective reducing agent for cyclic anhydrides;[11] used for conjugate addition and alkylation of α,β-unsaturated esters or ketones[12] and for Michael-initiated ring closure reactions;[13] reduces (2-arylprop-1-en-3-yl)trimethylammonium iodides to 2-arylpropenes;[14] hydroborates substituted styrenes;[15] reacts with carbon monoxide in the presence of free trialkylborane[16])

Alternate Name: L-Selectride®.

Physical Data: not isolated; prepared and used in solution.

Solubility: solubility limits have not been established. The reagent is normally used as a 1.0 M solution in THF or Et_2O. Use of a solution in toluene is reported and one method of preparation results in a THF-pentane solvent mixture.

Form Supplied in: 1.0 M solution in THF (L-Selectride®).

Analysis of Reagent Purity: solutions of pure reagent exhibit doublets (*J* &AApprox; 70 Hz) centered in the range δ -6.3 to δ -6.7 in the ^{11}B NMR spectrum.[17-20] Concentration of hydride is determined by hydrolysis of aliquots and measurement of the hydrogen evolved or by quenching aliquots in excess 1-iodooctane and analysis of the octane formed by GLC.[17] Concentration of boron is verified by oxidizing aliquots using alkaline hydrogen peroxide and analyzing the 2-butanol formed by GLC.[21]

Preparative Methods: direct reaction of tri-*s*-butylborane with LiH is not suitable, proceeding only to about 10% completion after 24 h in refluxing THF.[17] The preferred methods are reaction of the organoborane with ***Lithium Aluminum Hydride*** in the presence of ***1,4-Diazabicyclo[2.2.2]octane***[18] or with ***t-Butyllithium***.[19] Reaction with lithium trimethoxyaluminum hydride is effective but leads to byproducts not easily separated from the reagent.[20]

Handling, Storage, and Precautions: solutions are air- and water-sensitive and should be handled in a well-ventilated hood under an inert atmosphere using appropriate techniques.[22] Potentially pyrophoric *s*-Bu_3B is a byproduct of reductions; thus standard organoborane oxidation[21] is recommended as part of the workup.

Functional Group Reductions.

Alkanes are formed from primary and some secondary alkyl halides via S_N2 processes with potential chemoselectivity based on relative ease of displacement (I > Br > Cl).[2a] The corresponding reaction for tosylates has not been investigated thoroughly.[2b] Dealkylation of quaternary ammonium halides yields the corresponding amines, demethylation being strongly favored.[2c] Rates and regioselectivities for reduction of various epoxides have been determined.[2d] Reduction of conjugated nitroalkenes gives nitroalkanes[2e] or ketones,[2f] depending on the workup used (eq 1).

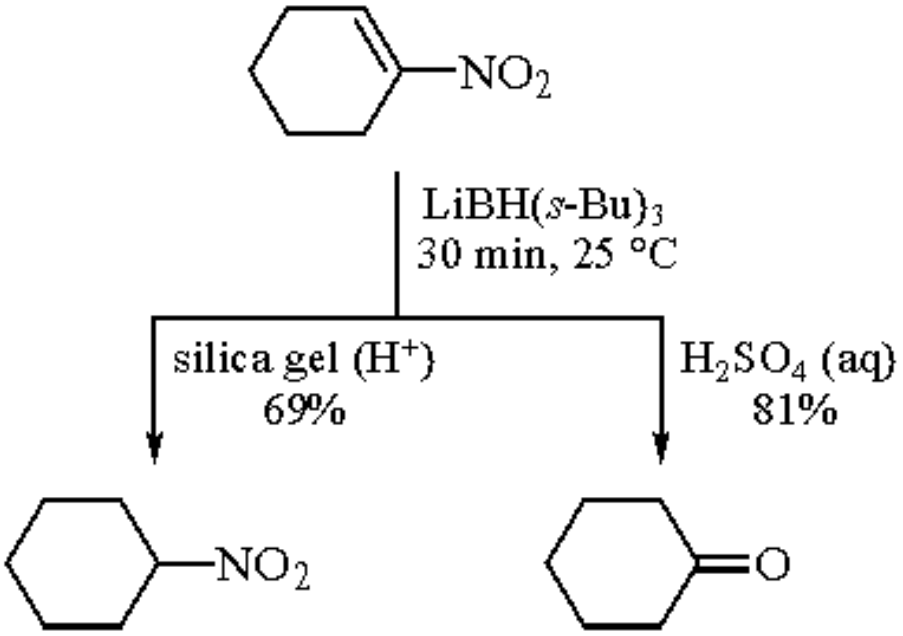

(1)

Certain γ-keto esters undergo reduction-lactonization[2g] which, in some cases, is followed by reduction of the γ-lactones to the γ-lactols (eq 2).[2h] Some esters of Δ^2-isoxazolinylcarboxylates are reduced to the corresponding primary alcohols (no yields given).[2i]

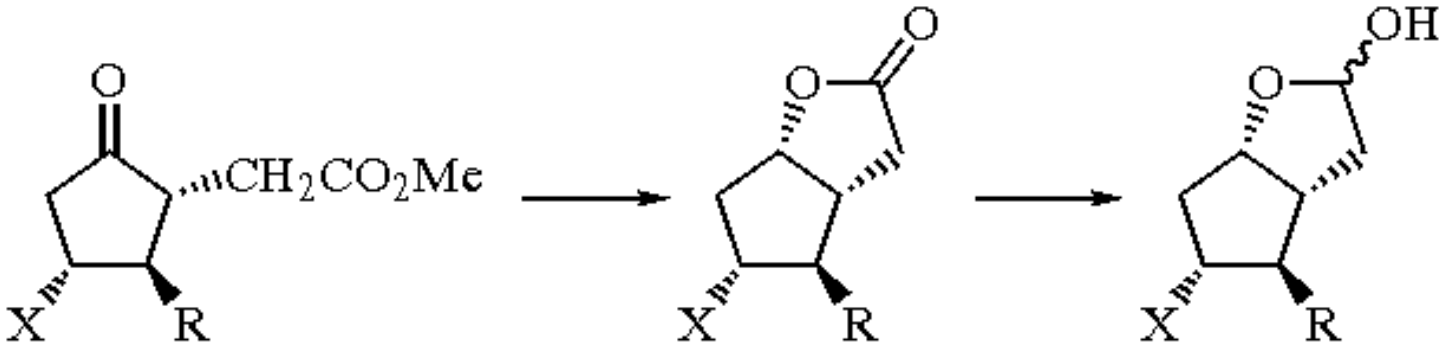

(2)

The reagent is ineffective compared to *t*-butylmagnesium chloride as a hydride source for a hydrozirconation procedure.[2j]

Selective Reductions.

Ketones are reduced selectively in the presence of other functional groups: carboxylic acids;[3a] esters,[3b -n] including γ-lactones[3j,k] and 1,3-dioxolan-4-ones;[3e] amides,[4] including benzenesulfonamides[4a,b] and 2-acetyl β-lactams;[4f,g] and internal epoxides.[31] An enamine is reduced selectively in the presence of a sulfoxide.[5]

Diastereospecific 1,2-reduction of a conjugated enone occurs in the case of 2β-*t*-butyldimethylsilyloxycyperone (eq 3).[6a] The corresponding 2α-silyloxy diastereomer requires $LiAlH_4$ for reduction, also yielding the 3β-ol. A conjugated enone undergoes 1,2-reduction while a lactone (both functions in the same 14-membered ring) remains untouched (see below).[12o]

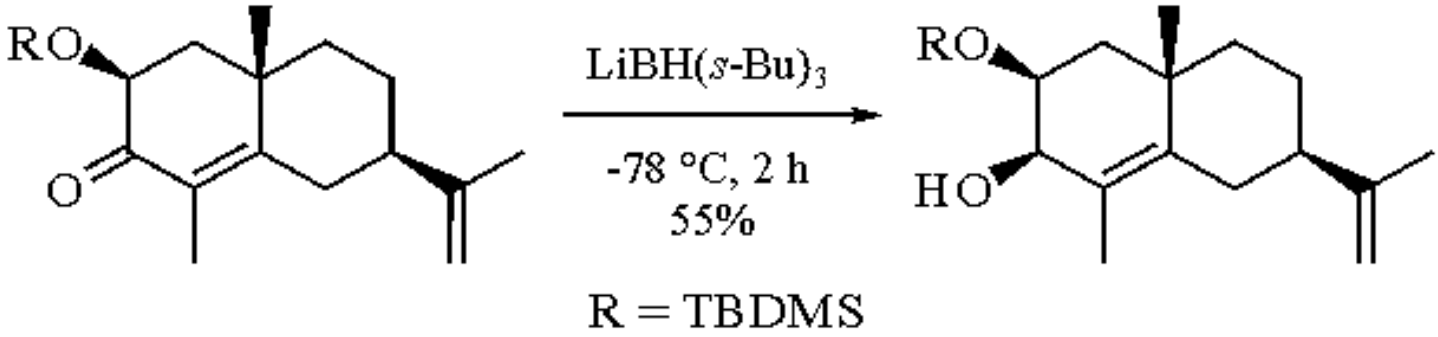

(3)

Amides are reduced to aldehydes in the presence of other readily reducible functional groups by first treating with ethyl trifluoromethanesulfonate (EtOTf) or MeOTf in CH_2Cl_2, removing the solvent, dissolving the residue in THF, and treating with L-Selectride (eq 4).[6b] In all cases, some unreacted starting material is recovered. K-Selectride® (***Potassium Tri-s-butylborohydride***) gives a lower yield; other hydrides give byproducts.

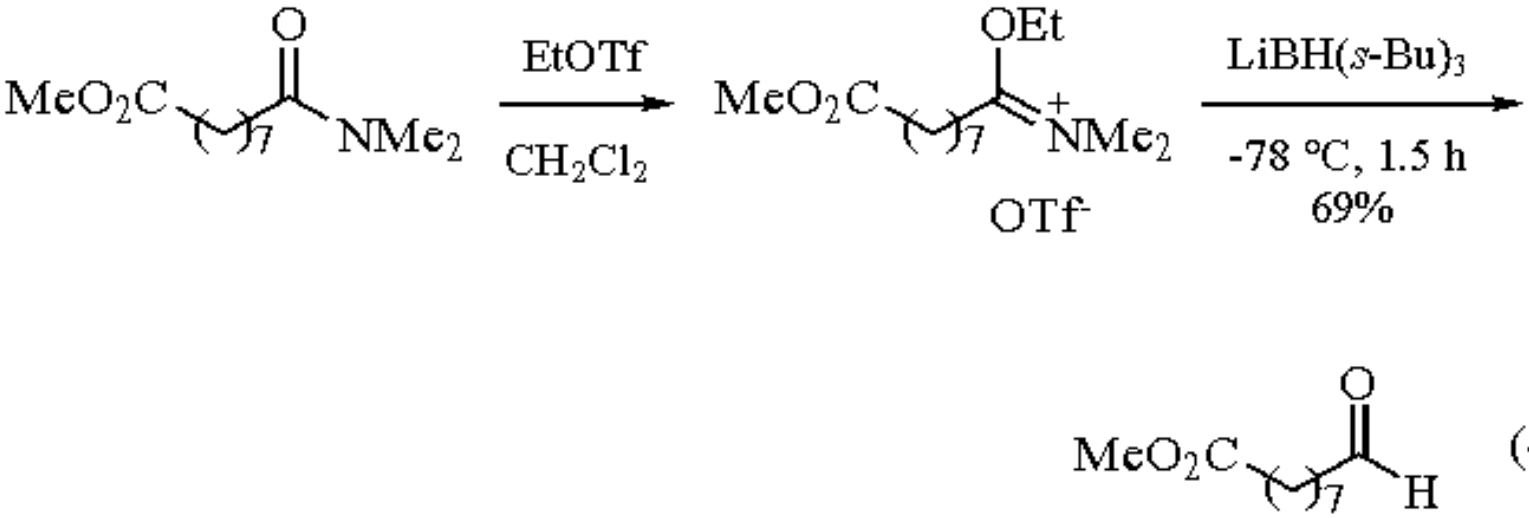

(4)

A keto aldehyde is reduced selectively (eq 5).[6c] The resulting hydroxy ketone is in equilibrium with its cyclic hemiacetal.

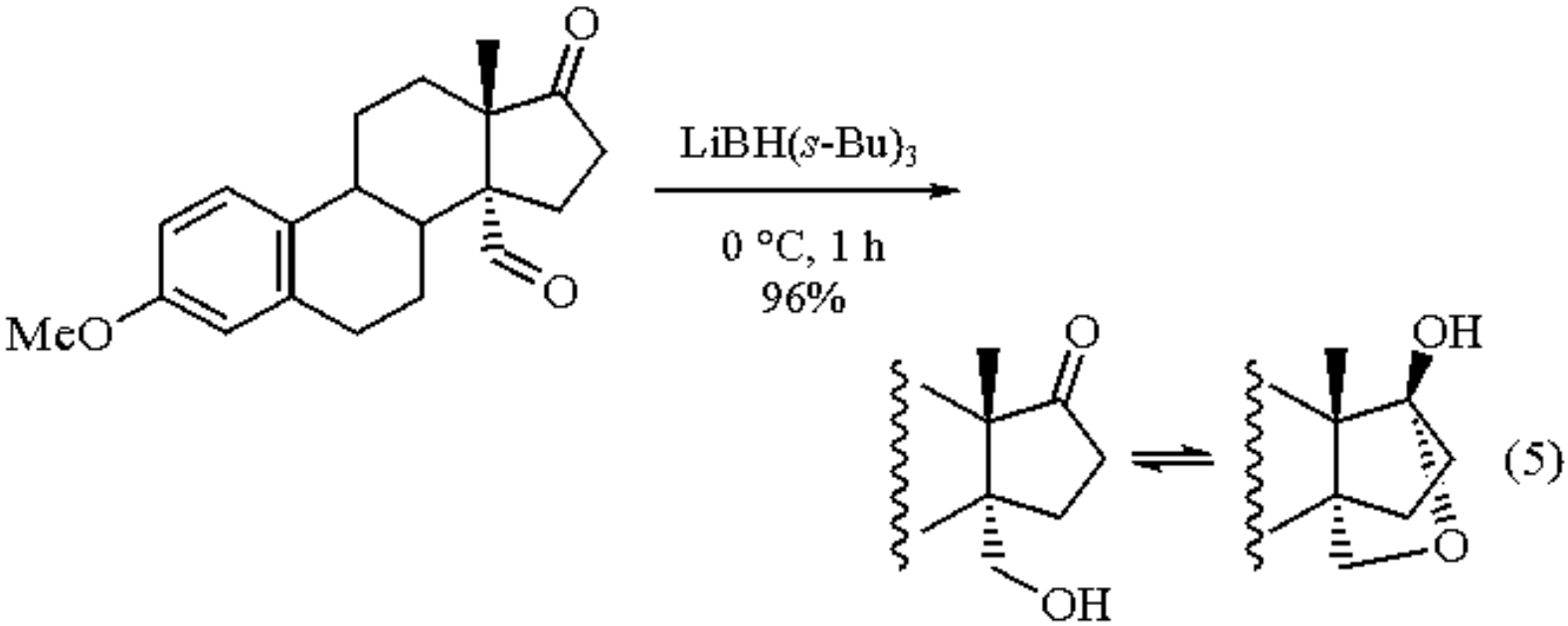

Stereoselective Reductions.

The synthetic use that first brought attention to L-Selectride was the diastereoselective reduction of alkyl-substituted cyclic ketones to alcohols.[20] Numerous applications for cyclic[7,11m] and acyclic[8,23c] ketones have now been reported, including various ketocarboxylate[3] and ketonamide[4] systems.

Various theoretical models are used to rationalize observed diastereoselectivity.[23] In simple cases, the bulk of the reagent appears to dictate that hydride approach from the less sterically hindered face of the carbonyl (eq 6).[20] However, complexation effects, including those of heteroatoms,[7b] crown ethers,[3i,8u] and cryptands,[8u] may reverse the direction of approach. It is also observed that varying the coordinating ability of the solvent influences the ratio of diastereomers.[3e]

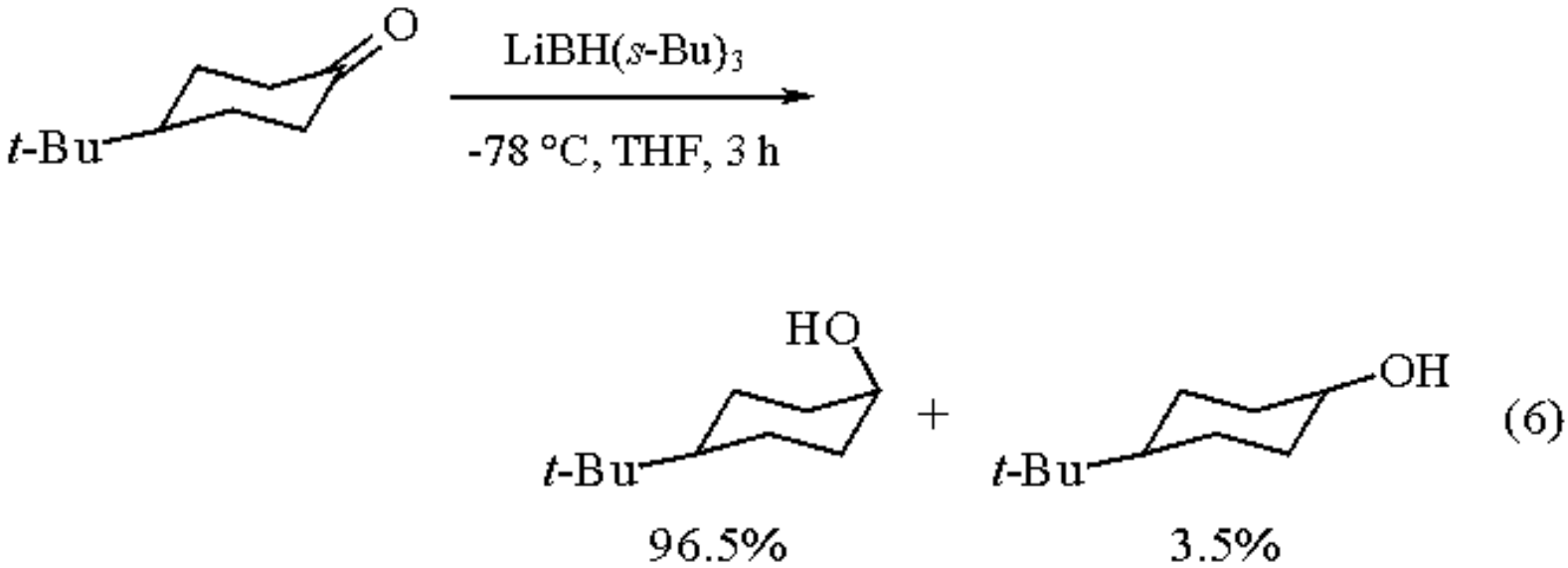

In most cases, imines can be reduced stereoselectively to amines (eq 7).[9a-e] However, some 2-substituted imines resist reduction and require using the more reactive ***Lithium Triethylborohydride***. Enamino sulfoxides are also

stereoselectively reduced to amines.[5] Chiral β-imino sulfoxides are reduced stereoselectively but in poor yield.[9f] Reduction of a tartarimide gives >99% stereoselection in the formation of the corresponding hydroxylactam (eq 8).[10]

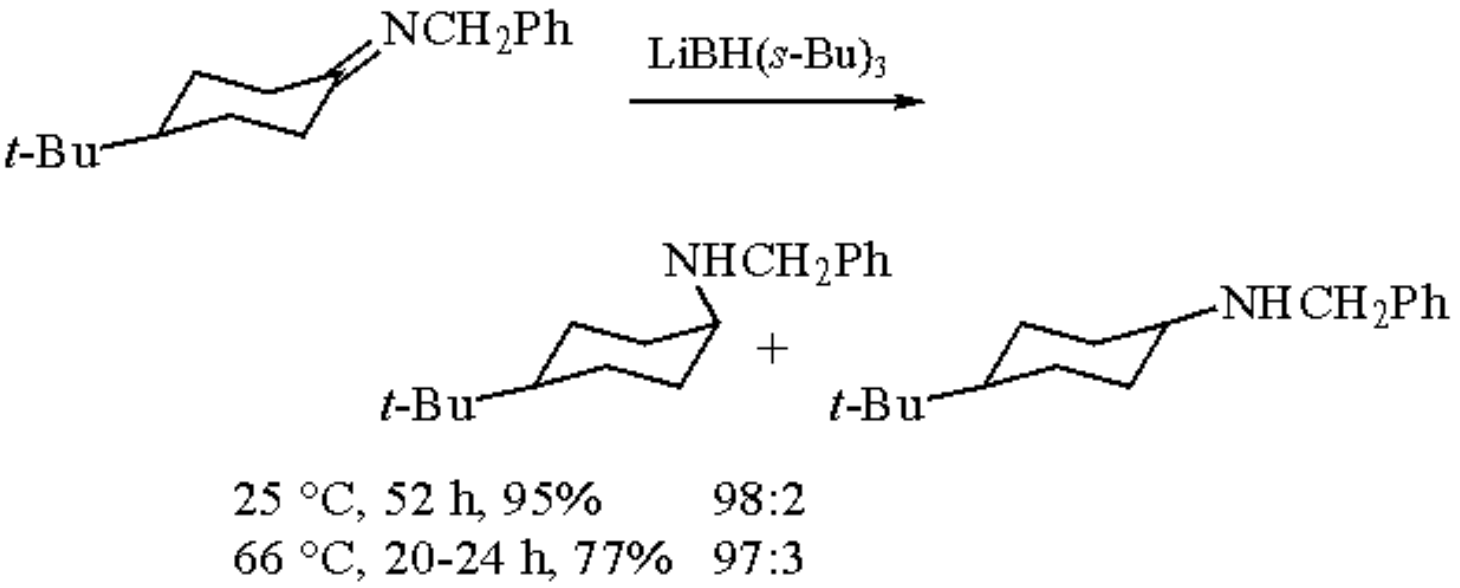

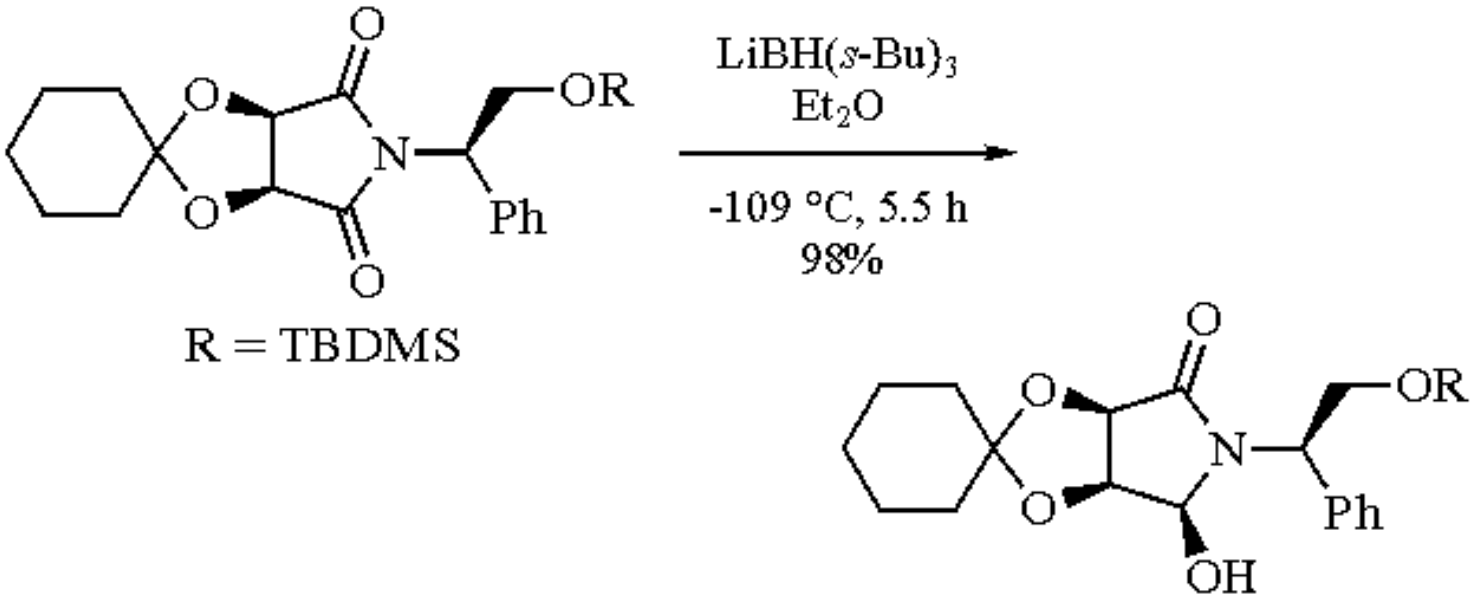

Regioselective Reduction of Cyclic Anhydrides.

Various succinic and phthalic anhydrides are reduced to lactones.[11] With certain exceptions (eq 9),[11d] reduction occurs preferentially at the less hindered carbonyl function. A mechanistic interpretation of the results has been proposed.[11d,e]

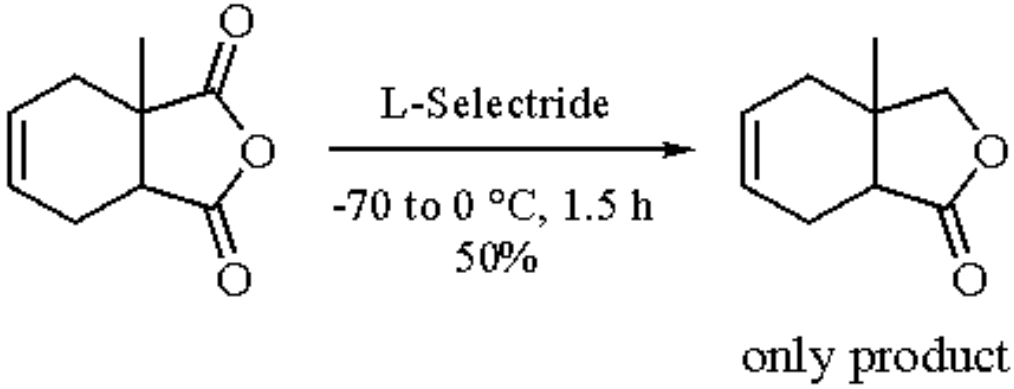

(9)

Reduction of Enones and Enoates.

Following the first reported stereoselective reduction of an acyclic enone to an allylic alcohol,[12a] a reasonably systematic study using K- and L-Selectride was conducted.[12b] With certain exceptions, results for the latter are comparable to those for the former:

- 1)whereas one equivalent of K-Selectride gives exclusively 1,2-addition with 3,5-dimethyl-2-cyclohexenone, L-Selectride gives a 1:1 mixture of 1,2- and 1,4-addition products;
- 2)in reductive alkylation of enones use of L- rather than K-Selectride leads to higher yields of monoalkylated products;
- 3)while attempted reduction of α,β-unsaturated esters with K-Selectride leads to Claisen condensation products, slowly adding a mixture of ester and *t*-butyl alcohol to a THF solution of L-Selectride at -70 °C gives the saturated ester cleanly.

Replacing *t*-butyl alcohol with various electrophiles in the procedure of (3) allows reductive alkylation, although Claisen condensation product also forms if the enoate lacks α- or β-substitution.

Other reports confirm that stereoselective 1,2-reduction is likely with both acyclic enones[12c,d] and β-substituted cyclic enones.[12e-g] However, in one case, treating the latter first with ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** followed by L-Selectride (2 equiv, -78 °C, 30 min) gives the 1,4-reduction product in quantitative yield.[12g] Terminal acyclic enones undergo 1,4-reduction with predominant formation of the *s-trans* enolate, the exact ratio *s-trans*:*s-cis* depending on the relative bulk of *R* and *R´* (eq 10).[12h] Systems with extended conjugation, such as a phenyldienone, resist conjugate addition and undergo stereoselective 1,2-reduction.[12i] Unlike simpler substrates, a complex methyl enoate is reduced to the corresponding allylic alcohol.[12j]

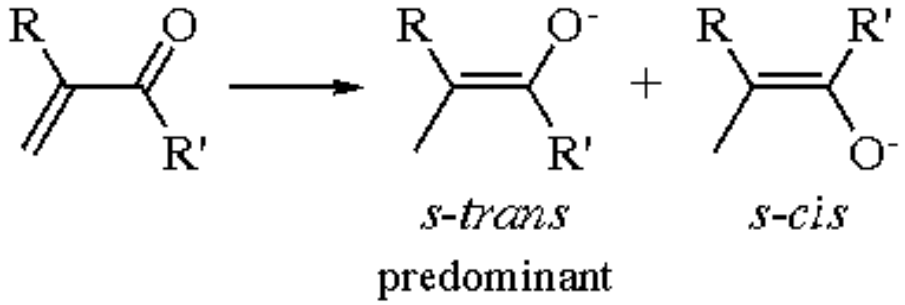

(10)

Cyclic enones without β-substituents often undergo 1,4-reduction,[12k-m] which may be followed by alkylation;[12k,m,n]

the alkylation may be stereoselective.[12k,m] In some cases, mixtures of 1,2- and 1,4-reduction products are obtained,[12o,p] in contrast to 1,2-reduction only for K-Selectride.[12o] Vinyl triflates may be produced from enones if 1,4-reduction is facile.[12q] In the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2 (1*H*)-pyrimidinone, a conjugated cyclic dienone is reduced to the conjugated enone.[12r]

α,β-Alkynic esters tend toward nearly exclusive 1,2-reduction with formation of propargylic alcohols.[12b] Likewise, α,β-alkynic ketones yield only propargylic alcohols.[8e,f]

Michael Initiated Ring Closure (MIRC) Reactions.

Formation of five- and six-membered rings results from treatment of o-alkylidenemalonates with L-Selectride, but better yields are realized with nucleophiles other than hydride.[13a] A MIMIRC procedure using 2-cyclohexenone and ***Vinyltriphenylphosphonium Bromide*** (VTB) is highly successful (eq 11).[13b] The 1-*t*-butyl 9-methyl diester of (*E*,*E*)-(*S*)-2,4-dimethyl-2,7-nonadienedioic acid is converted to a cyclohexane diester as a single stereoisomer (eq 12).[13c]

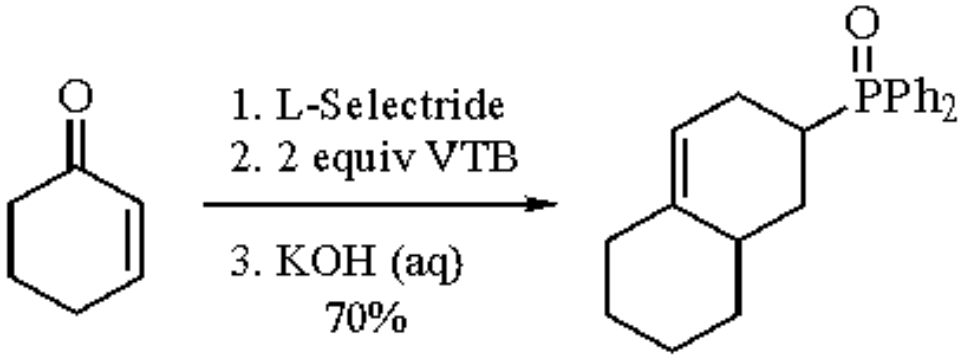

(11)

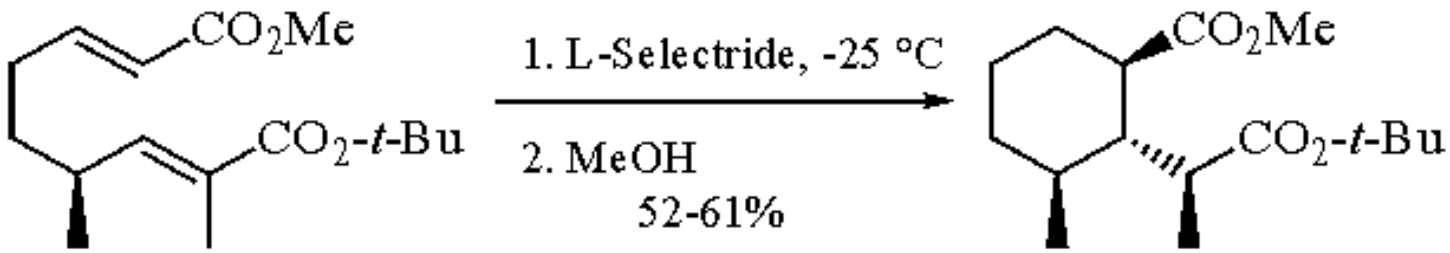

(12)

Reduction of (2-Arylprop-1-en-3-yl)trimethylammonium Iodides.

Treatment of [2-(4-methoxyphenyl)prop-1-en-3-yl]trimethylammonium iodide with L-Selectride results in addition of hydride with displacement of Me_3N, giving 2-(4-methoxyphenyl)propene in virtually quantitative yield (eq 13).[14] This reaction may be applicable for derivatives containing a wide variety of aryl groups.

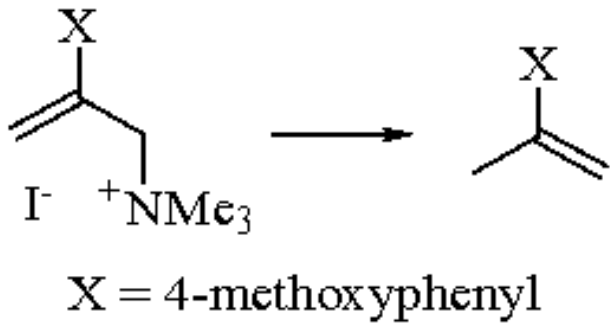

(13)

Hydroboration of Styrenes.

This reaction is quantitative with ***Lithium Triethylborohydride*** but proceeds to the extent of less than 40% with L-Selectride, polymerization of styrene being the predominant result.[15]

Reaction with Carbon Monoxide.

Carbonylation of LiBH-(*s*-Bu)$_3$ followed by treatment with refluxing aqueous NaOH gives 2-methyl-1-butanol.[16a] Since LiBH(*s*-Bu)$_3$ is an intermediate in hydride-induced carbonylation of *s*-Bu$_3$B using LiAlH(OMe)$_3$,[16b,20] different workup procedures yield 2-methylbutanal[16c] or 3,5-dimethyl-4-heptanol.[16d]

Related Reagents.

Lithium Aluminum Hydride; ***Lithium Triethylborohydride***; ***Lithium Trisiamylborohydride***; ***Potassium Tri-s-butylborohydride***.

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Lithium Tri-*t*-butylzincate

t-Bu_3ZnLi

[63676-98-2] · $C_{12}H_{27}LiZn$ · Lithium Tri-*t*-butylzincate · (MW 243.72)

(1,4-addition to enones;[1] halogen-zinc exchange reactions)

Alternate Name: tri-*t*-butylzinclithium.

Solubility: sol ether, THF.

Preparative Methods: lithium triorganozincates (R_3ZnLi) such as lithium tri-*t*-butylzincate are prepared by the reaction of RLi (3 equiv) with ***Zinc Chloride*** or by the treatment of R_2Zn with RLi in ether or THF.[1-4]

Handling, Storage, and Precautions: like other polar organometallics, lithium tri-*t*-butylzincate is very sensitive to oxygen and moisture. It is best generated in situ and should be stored at low temperature.

Halogen-Zinc Exchange Reactions.

Lithium tri-*t*-butylzincate is a highly efficient reagent for performing bromine-zinc exchange reactions with various types of 1,1-dibromoalkanes,[5] 1,1-dibromoalkenes,[6,7] and 1,1-dibromocyclopropanes.[8,9] The initial halogen-zinc exchange reaction is followed by a 1,2-migration of the *t*-butyl group, leading to a zinc reagent which can be trapped with various electrophiles (eqs 1-3).[5,6,9] Other primary and secondary lithium triorganozincates behave in a similar way.[5-9] Interestingly, the halogen-zinc exchange proceeds with a high stereoselectivity and, in the case of β-disubstituted 1,1-dibromoalkenes, the Br/Zn exchange takes place preferentially at the sterically more hindered bromine atom (eq 4).[7] This constitutes an excellent method for the stereospecific preparation of alkenyl halides (eq 5).[7]

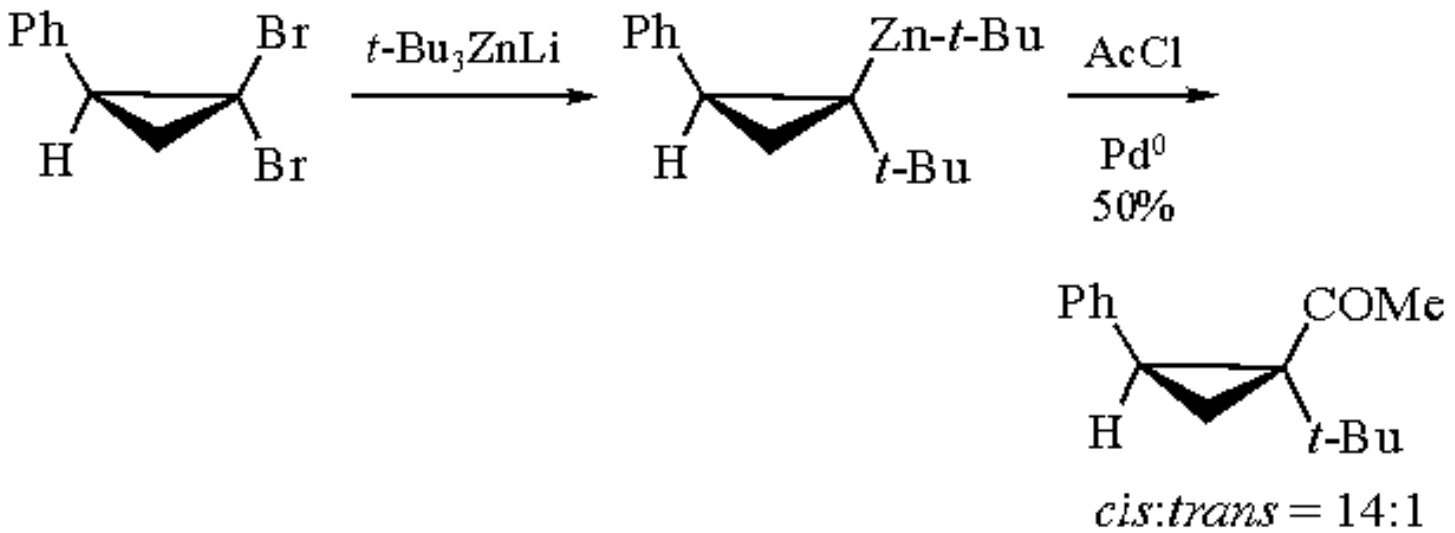
Ph
Br
H
Br
t-Bu3ZnLi
Ph
Zn-t-Bu
H
t-Bu
AcCl
Pd0
50%
Ph
COMe
H
t-Bu
(1)
cis:trans = 14:1

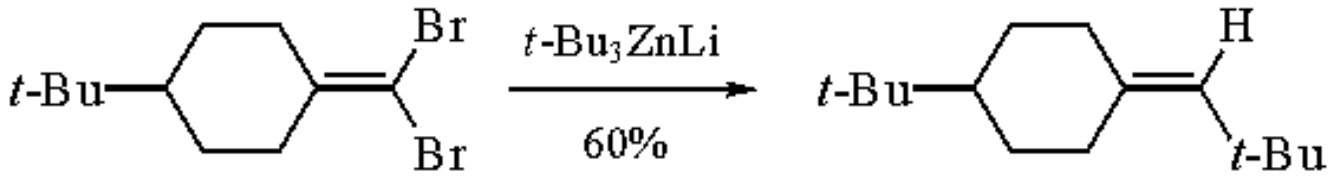
t-Bu
Br
Br
t-Bu3ZnLi
60%
t-Bu
H
t-Bu
(2)

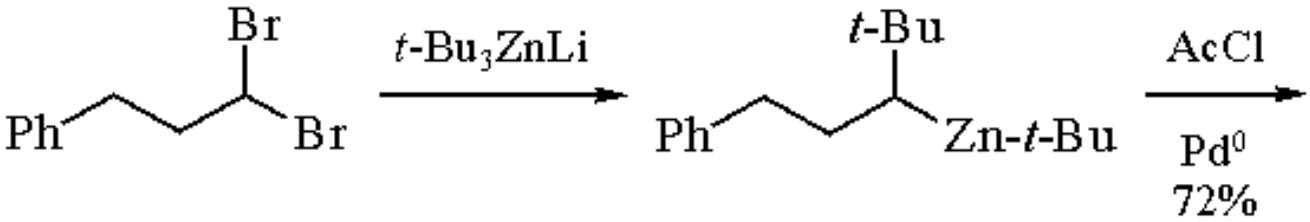
Br
Ph
Br
t-Bu3ZnLi
t-Bu
Ph
Zn-t-Bu
AcCl
Pd0
72%

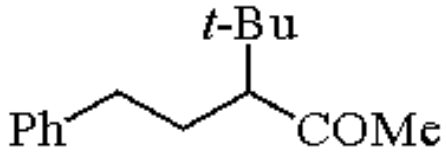
t-Bu
Ph
COMe
(3)

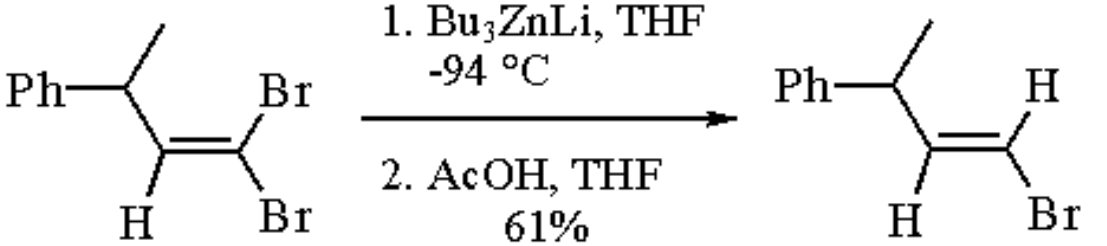
Ph
Br
H
Br
1. Bu3ZnLi, THF
-94 °C
2. AcOH, THF
61%
Ph
H
H
Br
(4)

(Z):(E) = 31:69

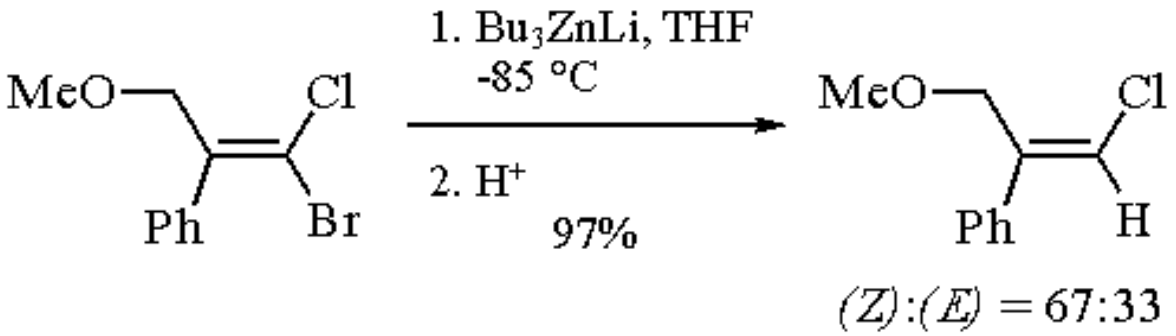

(5)

Michael Addition Reactions.

Lithium tri-*t*-butylzincate undergoes a Michael addition to enones (eq 6).[1] A similar reaction is observed with magnesium tri-*t*-butylzincate (eq 7).[4] If mixed trizincates are used, the *t*-butyl group is transferred with moderate selectivity (eq 8).[4] In strong contrast, an *n*-butyl group is transferred with a high chemoselectivity (eq 9).[4,10-12] Related mixed heterozincates, R_2(O-*t*-Bu)ZnMgBr.TMEDA, prepared by the reaction of $ZnCl_2$.TMEDA, *t*-BuOK, and RMgX (2 equiv), add readily to enones to provide the 1,4-adducts in satisfactory yields. By using chiral TMEDA analog ligands, moderate optical yields (5-14% ee) are obtained.[13-15] The addition of Bu_3ZnLi to nitrostyrene in the solvent mixture pentane-(*S*,*S*)-1,4-dimethylamino-2,3-dimethoxybutane (DDB) affords the Michael adduct in optically active form (eq 10).[3]

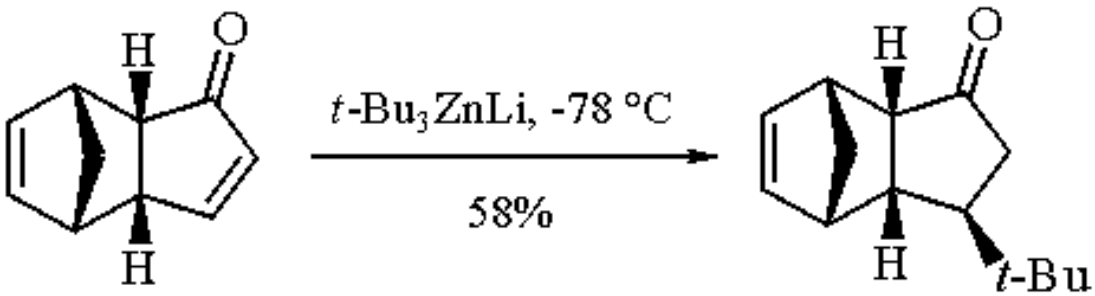

(6)

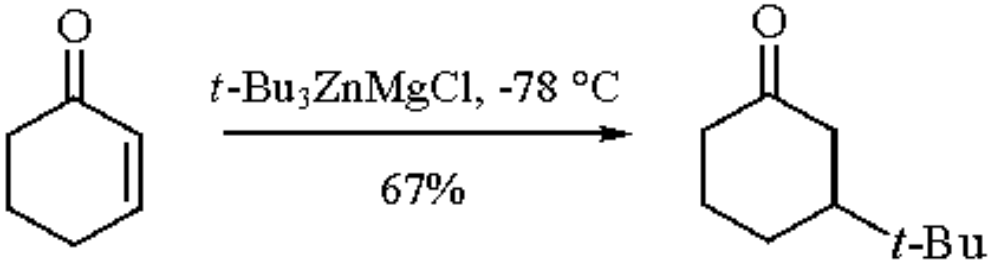

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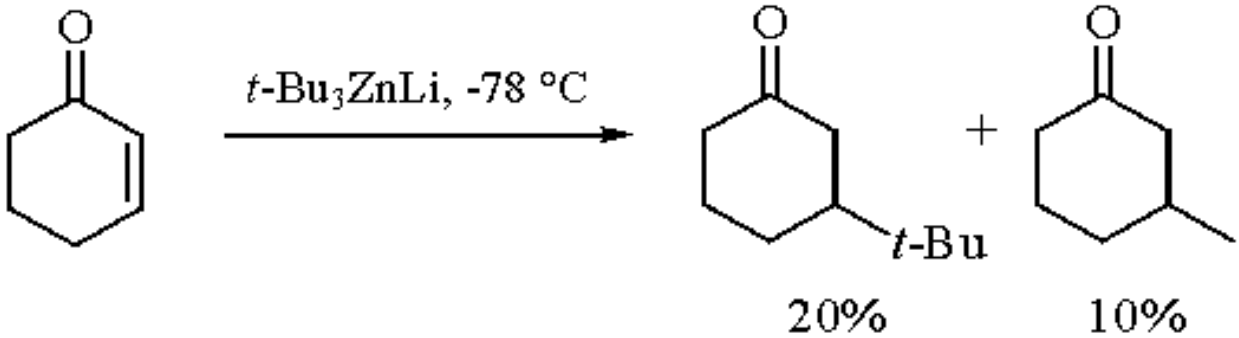

(8)

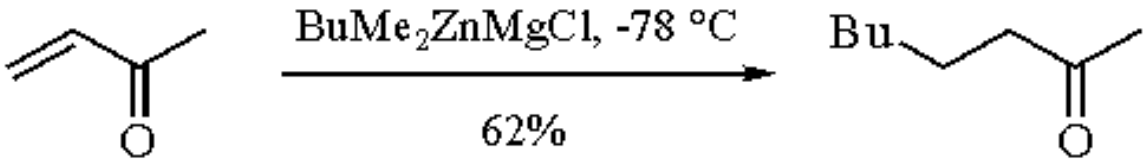

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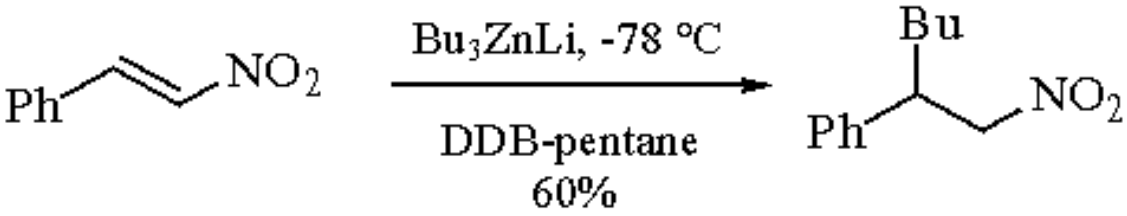

(10)

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Lithium Tricarbonyl(*n*-pentanoyl)nickelate

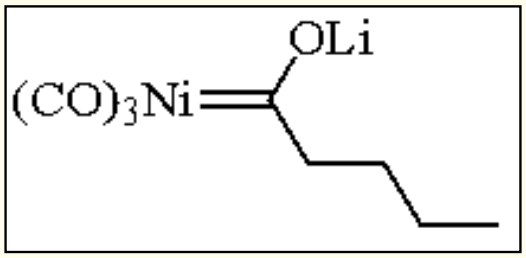

[26402-51-7] · $C_8H_9LiNiO_4$ · Lithium Tricarbonyl(*n*-pentanoyl)nickelate · (MW 234.80)

(acyl anion equivalent in alkylations;[1] acylation of vinyl halides,[3] conjugate additions[3,5])

Physical Data: the pure reagent has not been isolated, but solutions have been characterized by ^{1}H NMR, ^{13}C NMR, and IR.[1a]

Solubility: the reagent has been used in diethyl ether and THF.

Preparative Methods: solutions of the title reagent can be prepared by adding *n*-BuLi to $Ni(CO)_4$ in THF at -78 °C.[1b]

Handling, Storage, and Precautions: the reagent is oxygen sensitive and is best used directly after preparation. NMR studies, however, indicate stability from +20 °C to -78 °C over a period of 8 h.[1a] See ***n-Butyllithium*** and ***Tetracarbonylnickel*** for handling of these reagents.

General Considerations.

The title reagent is the most studied of a family of reagents prepared by addition of nucleophiles to tetracarbonylnickel. Other members of this family include lithium tricarbonyl(dimethylcarbamoyl)nickelate,[2d] lithium *t*-butoxycarbonyl(tricarbonyl)nickelate,[3a] lithium tricarbonyl(methoxycarbonyl)nickelate,[3a] and selected lithium aroyl(tricarbonyl)nickelates.[2c] This article will focus on reactions of the title reagent, but will discuss the behavior of this family of reagents in general terms. For additional information on these reagents, see ***Tetracarbonylnickel***.

Nickel acylate complexes are synthesized from the reaction of an anionic compound, such as an alkyl- or aryllithium, an amide, or an alkoxide, with tetracarbonylnickel in an ether solvent.[1-3] The alkoxide reactions are often performed with the corresponding alcohol as the solvent. The complexes are usually formed as the lithium salt, but some sodium salts, especially for the alkoxides, are also known.

The structure of the alkyl nickel acylate complex generated in THF is monomeric; however, there is some controversy about the structure of the alkyl acylate complex when it is generated in Et_2O.[1] Both the monomeric structure[3] and a

dimeric structure[2] have been proposed for this complex. In contrast, the structures of the amido and alkoxy acylate complex are monomeric regardless of the solvent used.[2]

Oxidation, Hydrolysis, and Thermolysis of the Alkyl or Aryl Nickel Acylate Complex.

The oxidation of the acylate complex is easily accomplished by the addition of an oxidant, such as oxygen, iodine, or ferrocenium ion, to give a variety of diketones and keto esters. It has been shown with an alkyl acylate complex that a 17-electron intermediate is formed initially and that this then decomposes to give the observed organic products (eq 1).[1] Similar types of products are obtained upon thermolysis of an acylate complex, but the mechanism of this reaction is not known.[2]

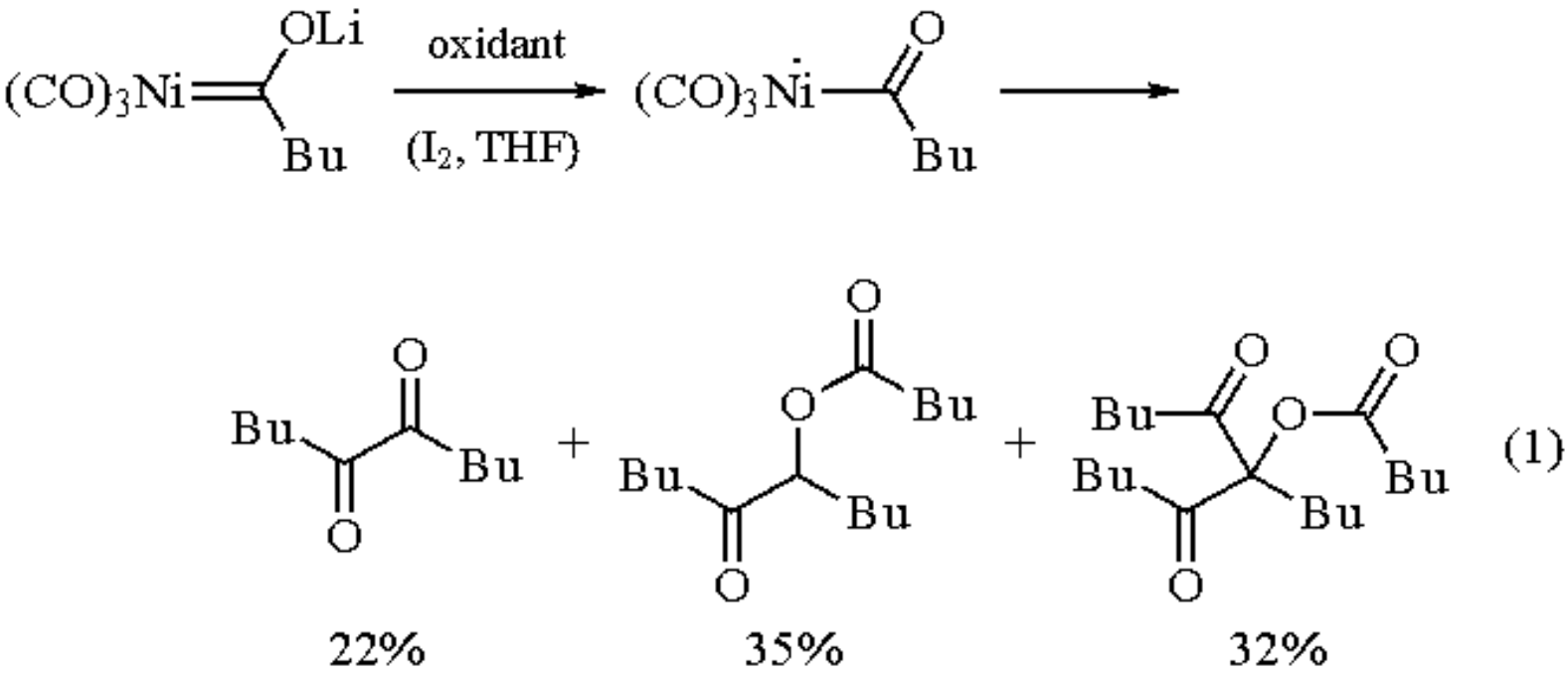

When the alkyl acylate complex is treated with water or a mineral acid, an acyloin derivative is generated (eq 2).[1,2] The formation of an acyloin is in contrast to the results obtained from the reaction of an acid with an iron, chromium, molybdenum, or tungsten acylate complex, which gives an aldehyde upon hydrolysis.[4] The nickel acylate complex will not add to the carbonyl of a simple ketone; however, it will deprotonate a ketone which has a pK_a of 16 or less.

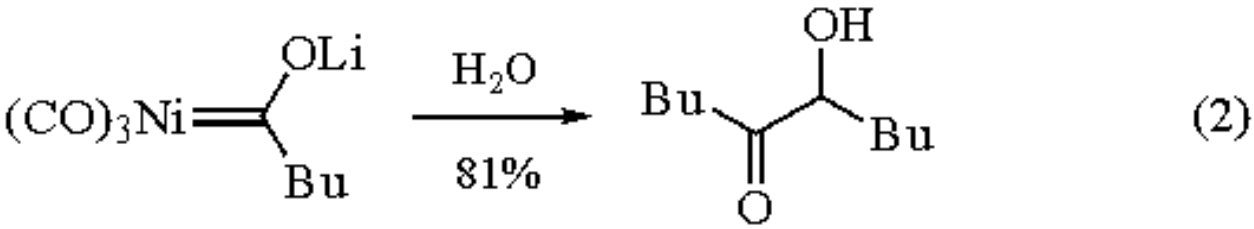

Alkyl and aryl acylate complexes react with alkyl halides. One of the cleanest and fastest reactions is with ***Allyl Bromide***. This is a very efficient synthesis of β,γ-unsaturated ketones (eq 3).[3] Using Et_2O as the solvent, the highest yields are obtained when the solution is kept below -30 °C;[3] however, in THF the reaction can be done either cold or at

room temperature in about an hour.[1]

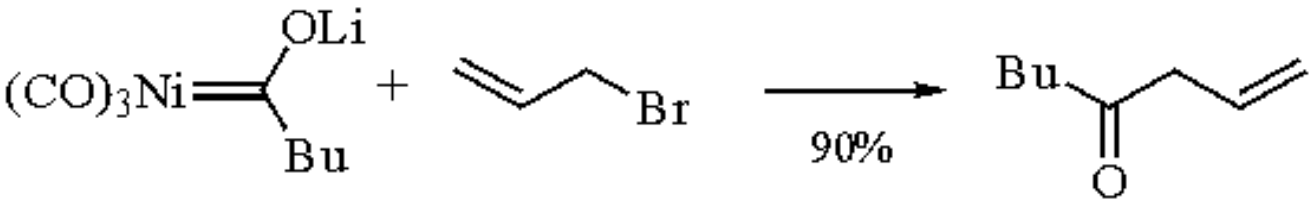

(3)

In contrast, ***Iodomethane*** reacts with a nickel acylate complex rather slowly. The reaction, which may be done using either Et_2O or THF as the solvent, requires overnight at rt. Another major difference in the reaction with iodomethane, in comparison to the reaction with allyl bromide, is that here, after protonation, an acyloin derivative is generated and not the simple ketone (eq 4). It is believed that this product results from attack of the acylate complex on a first-formed nickel complex. This attack is possible when using iodomethane, but not with allyl bromide, due to the much slower rate of the former compared to the latter reaction.[1,3]

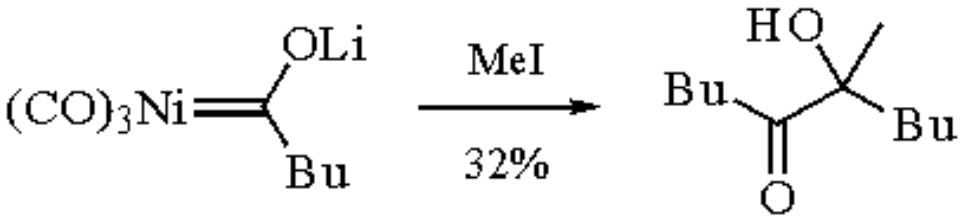

(4)

The rate of the reaction of an alkyl or aryl nickel acylate complex with ***Benzyl Bromide***, qualitatively, is between that found for the reaction with allyl bromide and that for the reaction with iodomethane. Consistent with this observation is the formation of a mixture of the ketone and the acyloin derivatives.[1,2]

An alkyl and aryl acylate complex also will react with a terminal alkyne to generate a 1,4-diketone (eq 5).[2]

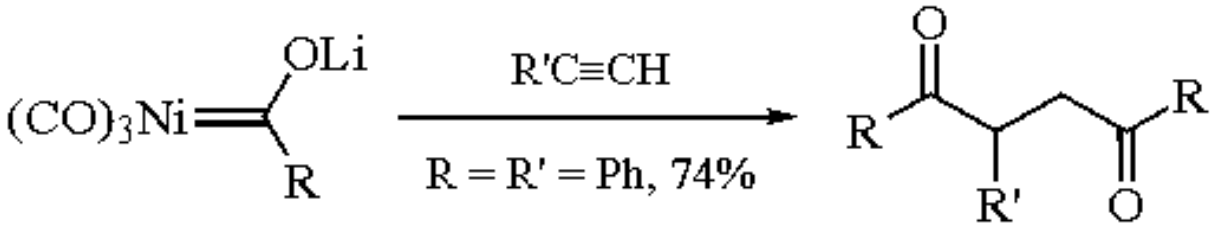

(5)

Also, in contrast to the acylate complexes of iron, chromium, molybdenum, and tungsten, a nickel acylate complex reacts readily with a vinyl halide, such as bromostyrene. The major product is a 1,4-diketone. In addition, smaller amounts of an α,β-unsaturated ketone, the proposed first formed intermediate, are generated (eq 6).[3] This discovery led to the development of the use of nickel acylate complexes for Michael additions to α,β-unsaturated ketones and esters.

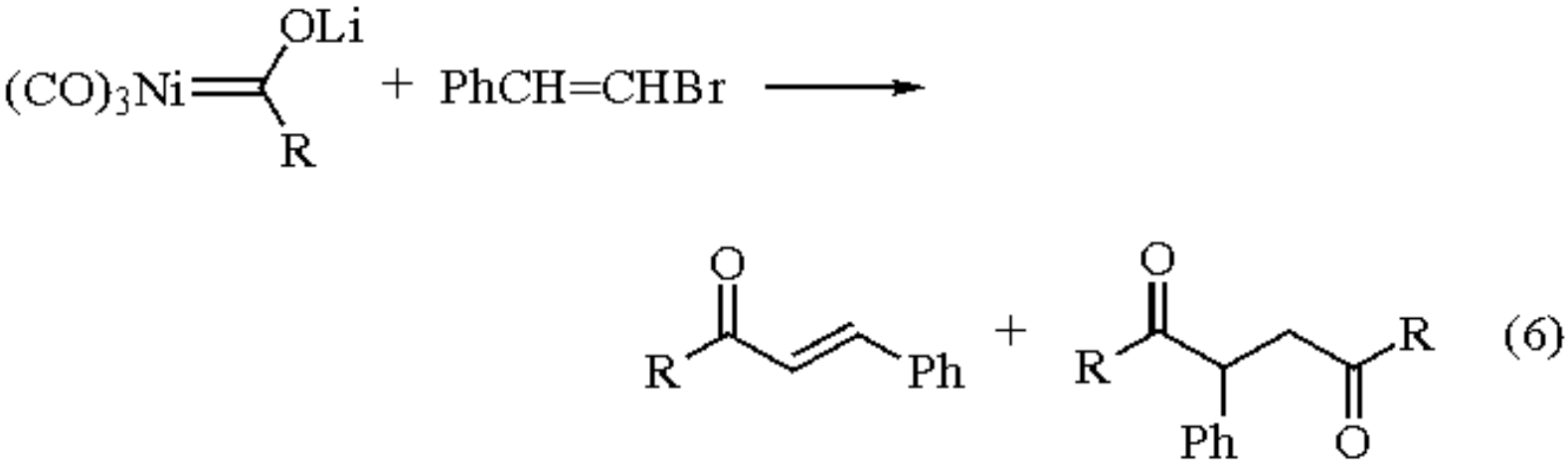

Michael Additions of Alkyl and Aryl Nickel Acylate Complexes.

As just mentioned, a nickel acylate complex will undergo a Michael addition to an α,β-unsaturated ketone. This reaction also works very well with an α,β-unsaturated ester. In fact, the cleanest reactions of the alkyl and aryl nickel acylate complexes are these Michael additions (eq 7).[3]

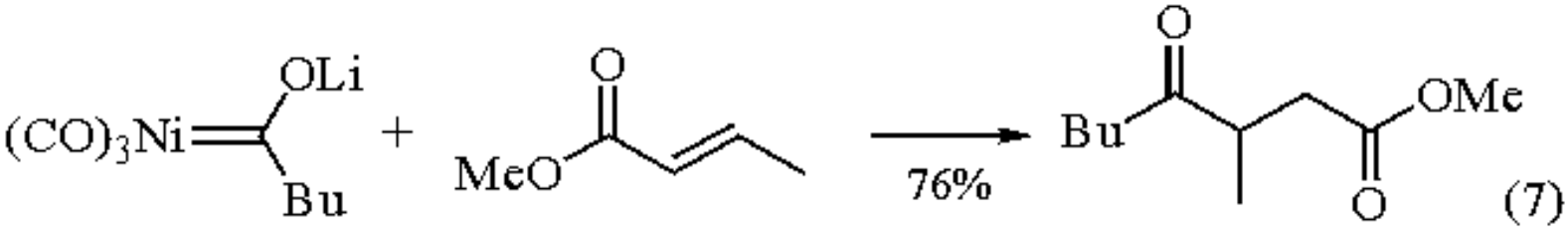

Michael additions of acylate complexes have been used for the synthesis of natural products such as naphthoquinone antibiotics (eq 8).[5]

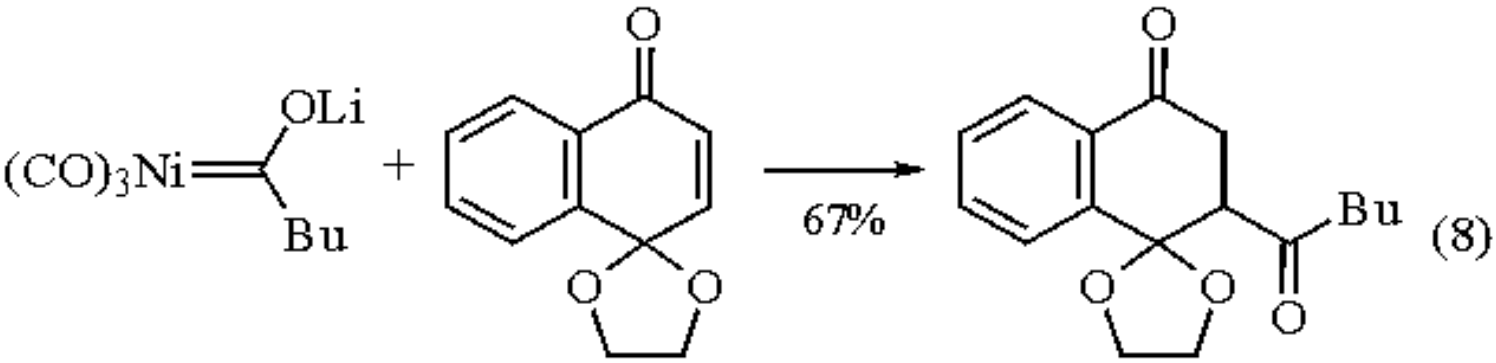

Heteroatom Nickel Acylate Complexes.

The synthesis of nickel acylate complexes is not restricted to the attack of an alkyl- or aryllithium reagent on tetracarbonylnickel. As mentioned in the introduction, a dialkyl amide also reacts with tetracarbonylnickel to form an

amido nickel acylate complex, using either Et_2O or THF as the solvent. This acylate complex reacts readily with allyl bromide, a vinyl halide, an aryl halide, or with a terminal alkyne to generate a large variety of organic compounds (eq 9).[2,3]

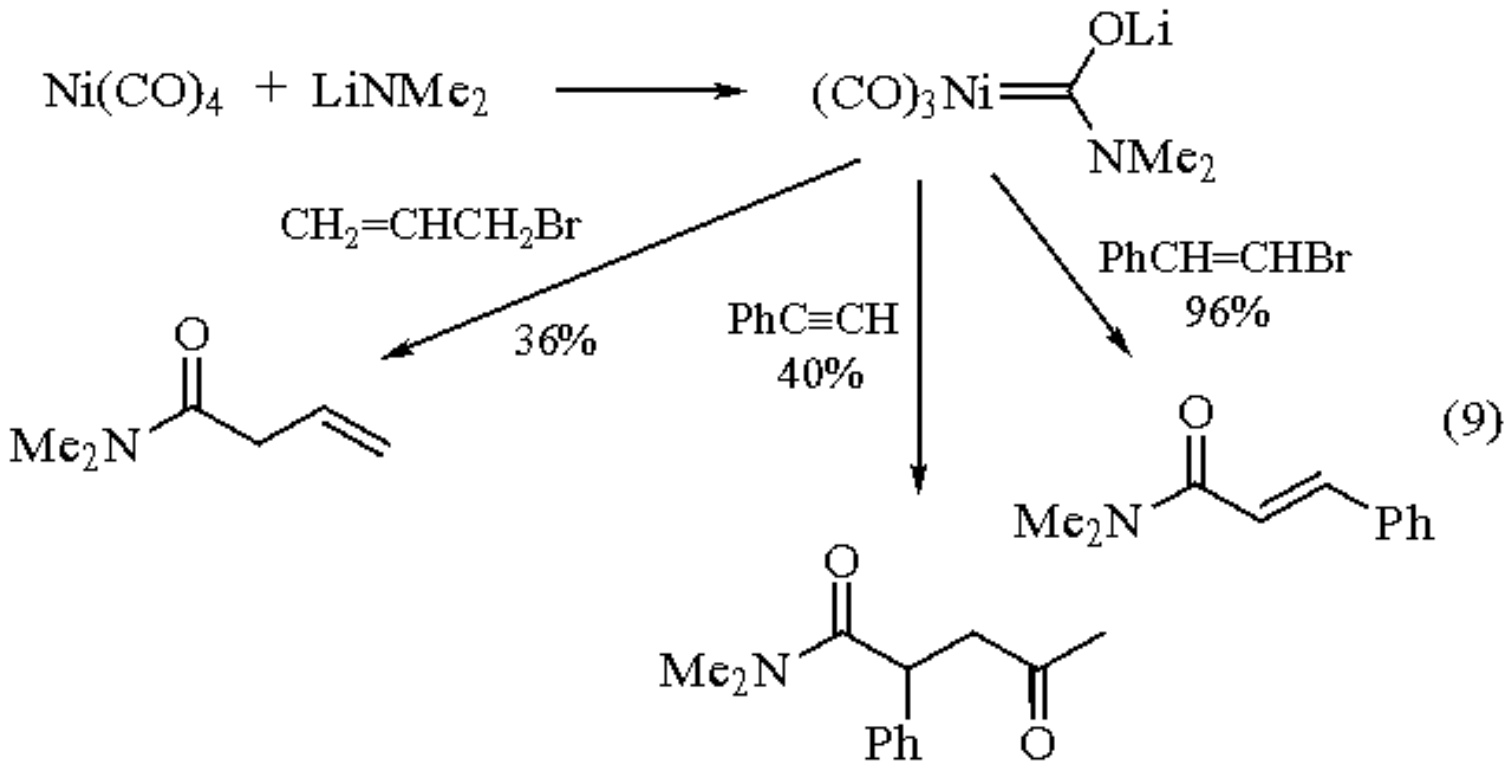

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4. See for example: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
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Lithium Trichloropalladate

$LiPdCl_3$

[22587-92-4] · Cl_3LiPd · Lithium Trichloropalladate · (MW 219.71)

(catalyst for alkylation and arylation of alkenes by organomercurials;[1-12] catalyst for heteroannulation reactions;[13-16] catalyst for coupling of organometallics with aryl and alkyl halides[17-20])

Solubility: prepared and used in acetonitrile; THF, DMSO, HMPA, H_2O have been used as solvent additives in reactions.

Preparative Methods: usually prepared as a solution in acetonitrile by stirring anhydrous ***Palladium(II) Chloride*** with a small excess of anhydrous ***Lithium Chloride*** overnight at rt,[1] or by refluxing for 30-60 min.[5-8] Obviously, this reagent exists as a complex with the solvent.

Handling, Storage, and Precautions: the solution of $LiPdCl_3$ in acetonitrile is usually used immediately after preparation. No data are available for the toxicity of this compound.

Arylation and Alkylation of Alkenes with Organomercurials.

Organomercury compounds react with $LiPdCl_3$ (see also ***Dilithium Tetrachloropalladate(II)***) to give organopalladium compounds that undergo the alkene insertion-elimination process to give aryl(alkenyl)-substituted alkenes (eq 1).[1] This reaction is sometimes called the Heck reaction.

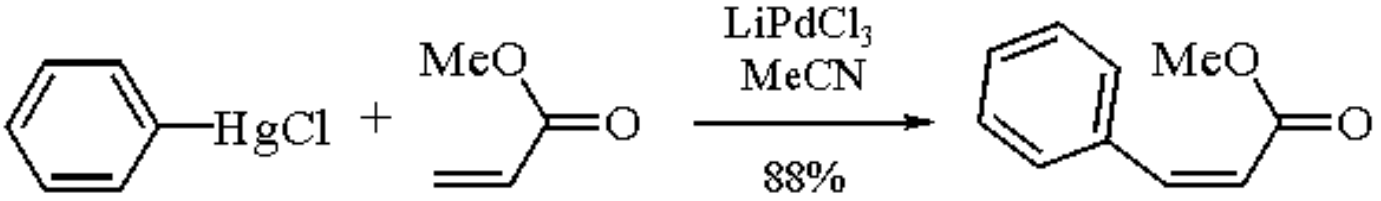

(1)

Palladium is readily reoxidized under the reaction conditions by mercury(II) salts (or ***Copper(II) Chloride***) and thus only catalytic amounts are required.[1,3,4,9] Practically any arylmercury(II) salt will function as an arylating agent in this reaction. In general, strong electron-donating groups (*p*-methoxy, *o*-hydroxy, *p*-diethylamino) decrease the yields, while good coordinating groups, for example amino groups, retard or even completely stop the reaction because they form stable, unreactive complexes with palladium.[1] The rates of reaction and the regioselectivity depend on both steric

and electronic factors.[1,2] The less sterically hindered the alkene, the greater the rate, and the new C-C bond is formed at the least sterically hindered or at the most electron-deficient carbon atom. The regioselectivity is highest when a strong electron-withdrawing group such as CN, CO_2Me, or Ph is attached to the double bond and therefore styrene, acrylonitrile, acrolein, and methyl acrylate are the most useful alkenes in the Heck reaction.[1-9] Quinones can be also used as substrates for arylation.[11] Several interesting examples of heterocyclic mercury salts have been used as arylation agents, including porphyrins,[5,12] substituted pyrroles,[8] and sydnones.[7] Utilization of vinyl mercurials gives conjugated dienes.[3,4]

Heteroannulation.

A variety of oxygen- and nitrogen-containing heterocycles can be prepared from π-allylpalladium compounds bearing carboxylic acid,[14,15] phenol,[14,16] alcohol,[14] amide,[14] and amino[13] functionality. Addition of base liberates an oxygen or nitrogen nucleophile that displaces the palladium with the formation of the carbon-heteroatom bond. Usually these π-allylpalladium compounds are prepared in situ by reaction of alkenes or dienes, as well as vinylcyclopropanes, with organomercurials and $LiPdCl_3$. Functional groups necessary for further cyclization can be attached either to the organomercurial (eq 2)[14,16] or the alkene (eq 3).[15] The shortcoming of this procedure is the need to use equal amounts of the palladium salt and organomercurial.

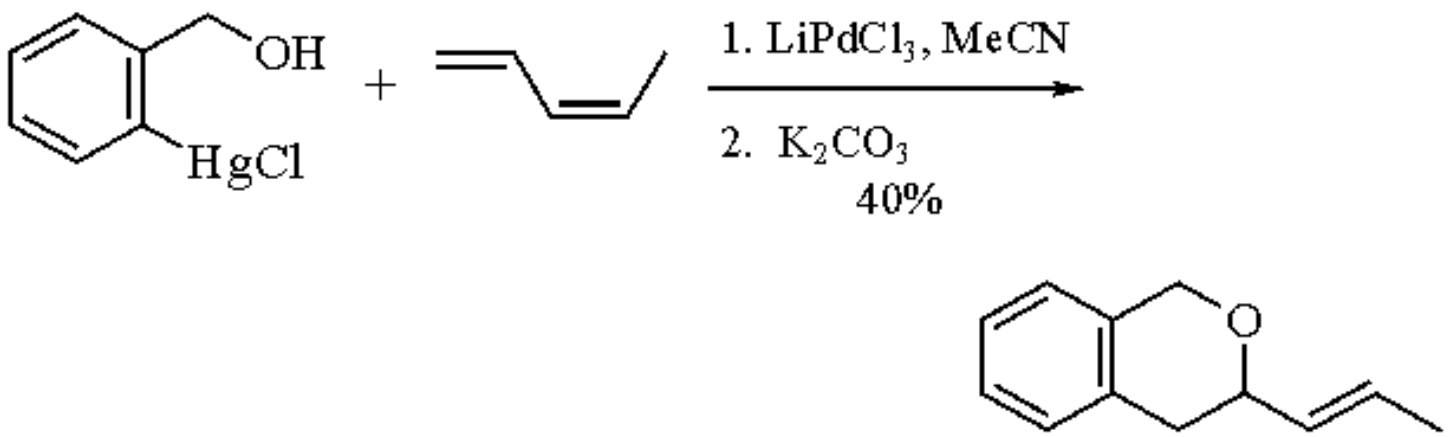

(2)

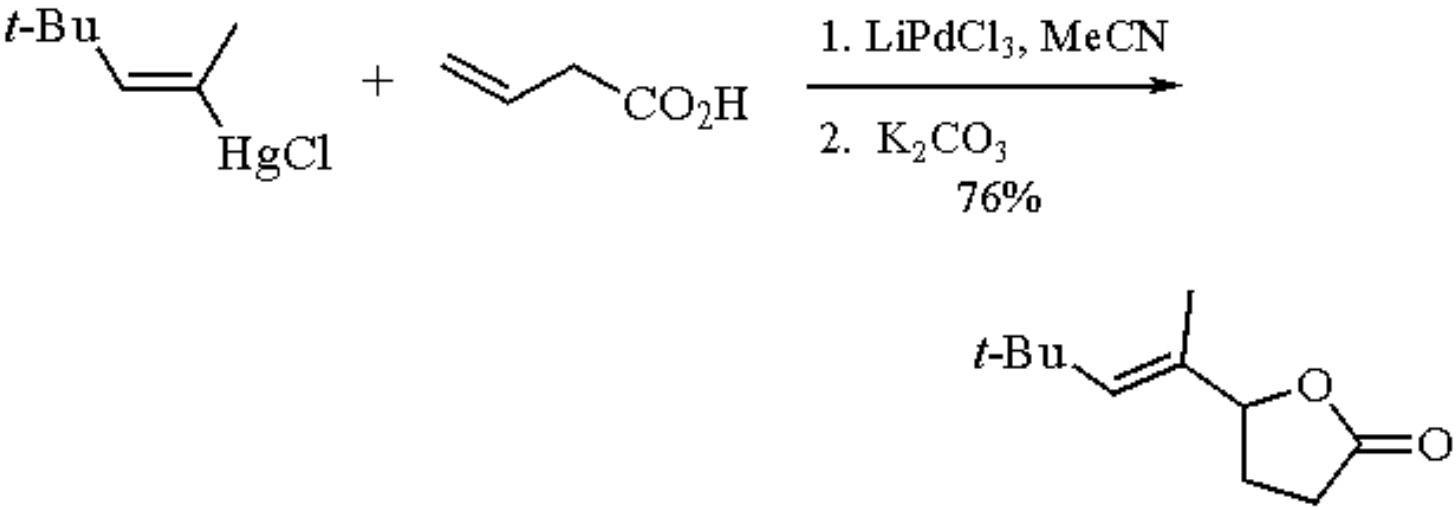

(3)

Arylation of Unsaturated Compounds.

Arylmercurials react with allylic halides in the presence of $LiPdCl_3$ and $CuCl_2$ (as reoxidant) at room temperature in acetonitrile to produce allyl aromatic derivatives (eq 4). A wide variety of allyl aromatic compounds can be obtained by this procedure, even ones containing nitro, ester, and aldehyde groups.[17] Catalytic amounts of $LiPdCl_3$ and 10-30 mol% of $CuCl_2$ generally must be used to obtain optimum yields.

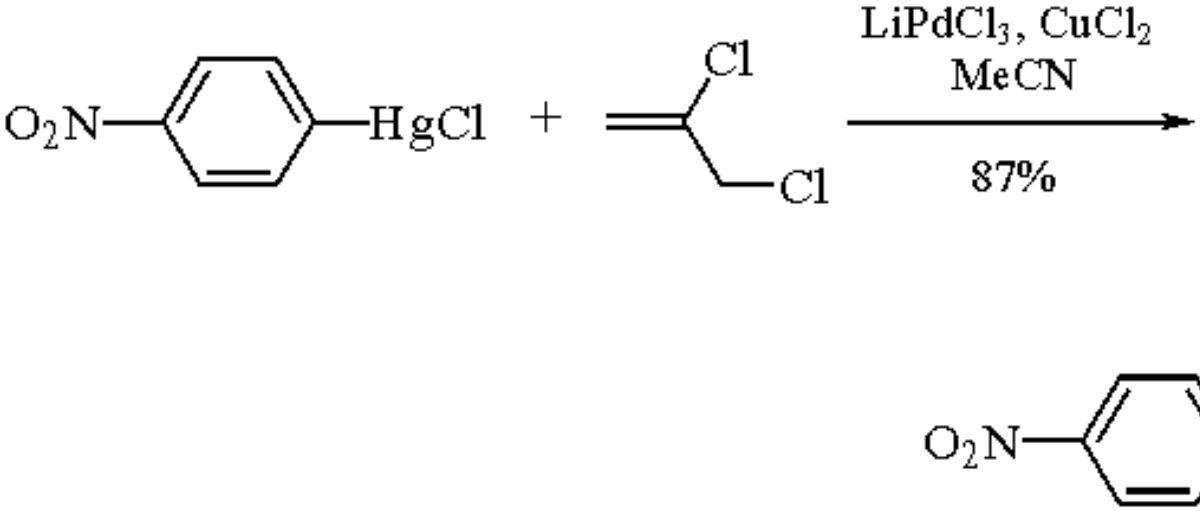

(4)

$LiPdCl_3$ has also been used, among other palladium catalysts, for cross-coupling reactions of organometallic compounds with aryl halides.[18-20]

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Vladimir V. Popik

Lithium Triethylborohydride[1]

$LiBHEt_3$

[22560-16-3] · $C_6H_{16}BLi$ · Lithium Triethylborohydride · (MW 105.97)

(exceptionally powerful nucleophile in S_N2 displacement reactions with super hydride activity; powerful and selective reducing agent)

Alternate Name: Super Hydride®.

Physical Data: mp 66-67 °C;[2] *d*420 0.920 g cm^{-3} for 1 M solution in THF.

Solubility: sol THF, benzene; reacts violently with water.

Form Supplied in: 1 M solution in THF.

Preparative Methods: prepared by the reaction of ***Triethylborane*** with ***t-Butyllithium***,[3a] lithium hydride,[2,3b] or ***Lithium Aluminum Hydride*** in the presence of triethylenediamine.[3c]

Analysis of Reagent Purity: IR: 2060 cm^{-1} (BH). ^{11}B NMR (THF) δ, ppm, -12.2 (d, J_{B-H} = 61 Hz).[3a] Active hydride is determined by hydrolysis of an aliquot and measuring the hydrogen evolved according to the standard procedure.[4] Low concentrations may be determined by iodometric titration.[5]

Handling, Storage, and Precautions: corrosive flammable liquid. Handle and store under nitrogen or argon in a cool dry place. Avoid contact with skin and clothing. Use in a fume hood.

Reduction of Functional Groups.

Lithium triethylborohydride shows super hydride activity. Its reactivity in comparison to other nucleophiles is given in Table 1.[6] The reduction of representative functionalities by the reagent under standard conditions has been described.[7]

Table 1 Reactivity of Et_3BH^- in Comparison to Other Nucleophiles

Reagent	Relative Nucleophilicity
Et_3BH^-	9 400 000
n-BuS^-	680 000
PhS^-	470 000
AlH_4^-	230 000
I^-	3 700
EtO^-	1 000
BH_4^-	940
Br^-	500
PhO^-	400
NO_3^-	1

Alkyl Halides.

Lithium triethylborohydride is the reagent of choice for dehalogenation of alkyl halides (eq 1).[6,8] Primary iodides are the most reactive. Fluorides are reduced at slower rates (eq 2).[9] Secondary halides may give elimination products in some cases. Mechanistic aspects of the reaction have been studied.[10]

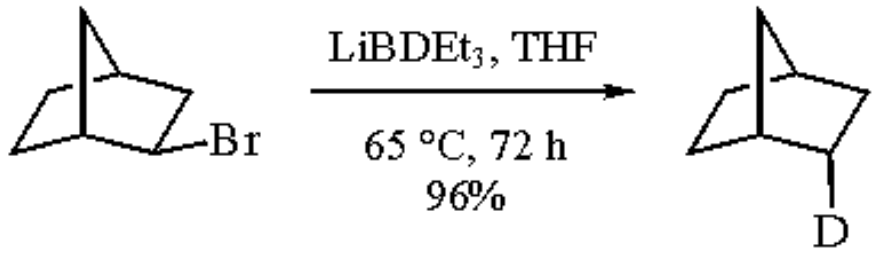

(1)

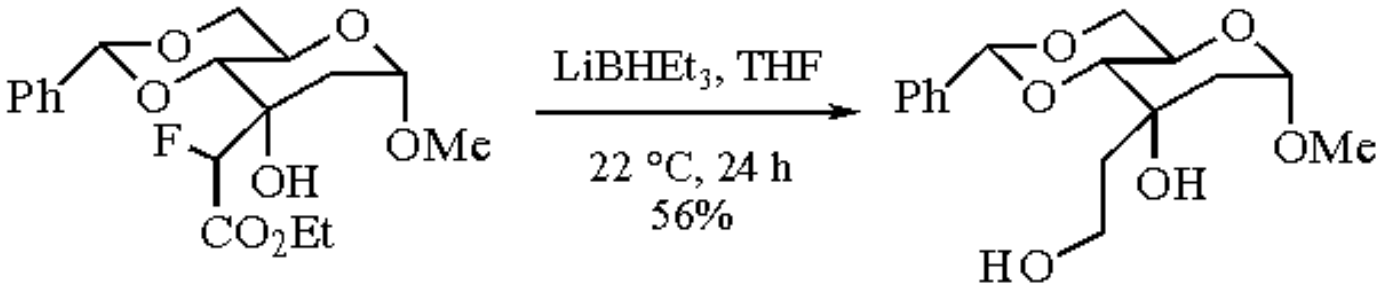

(2)

Deoxygenation of Alcohols.

Tosylates,[11] mesylates,[12] and alkoxytris(dimethylamino)phosphonium salts[13] of primary alcohols are cleanly reduced to hydrocarbons. Tosylates of secondary alcohols may undergo elimination reactions. Even in such cases the reduction may be synthetically useful (eq 3).[11f] Differences in the reactivity of tosylates and alkylsulfonates have been observed.[11e]

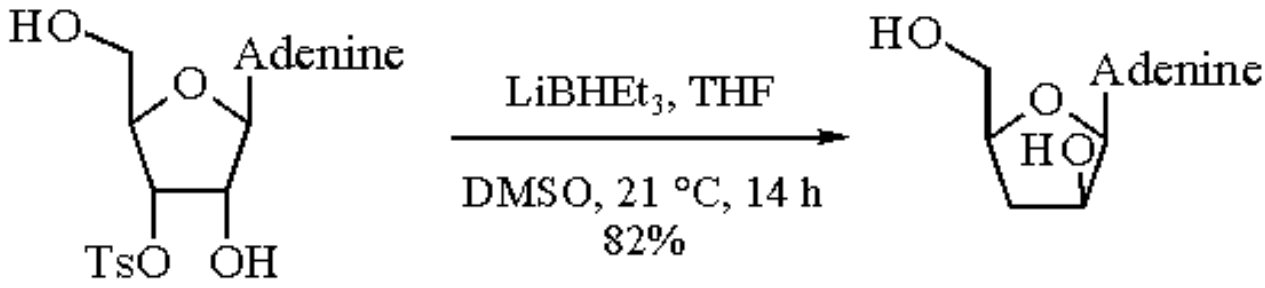

(3)

Allylic Derivatives.

Allylic groups such as -OR, -SR, -SO_2R, -SeR, and -OTBDMS undergo reductive cleavage by lithium triethylborohydride catalyzed by palladium compounds (eq 4).[14a] Squalene (*E*/*Z* = 97:3) has been prepared using this reaction as a key step.[14b]

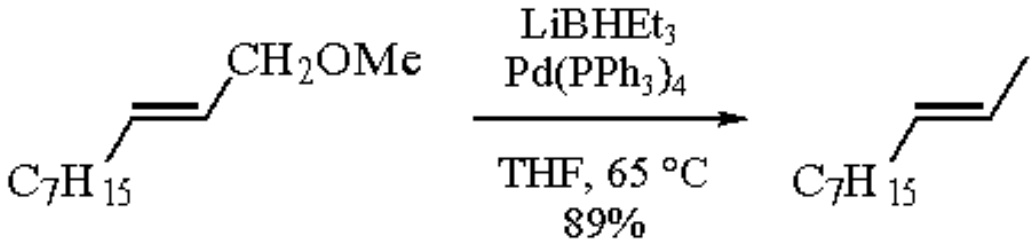

(4)

(*E*):(*Z*):terminal = 94:3:3

Epoxides and Oxetanes.

The reduction of epoxides by the reagent is quite facile, yielding exclusively the Markovnikov product.[5,7,15] Its advantage is evident in the reduction of labile epoxides prone to electrophilic rearrangements (eq 5).[16] Oxetanes are opened in a similar fashion.[17] Conjugated epoxides may undergo 1,4-reduction.[18]

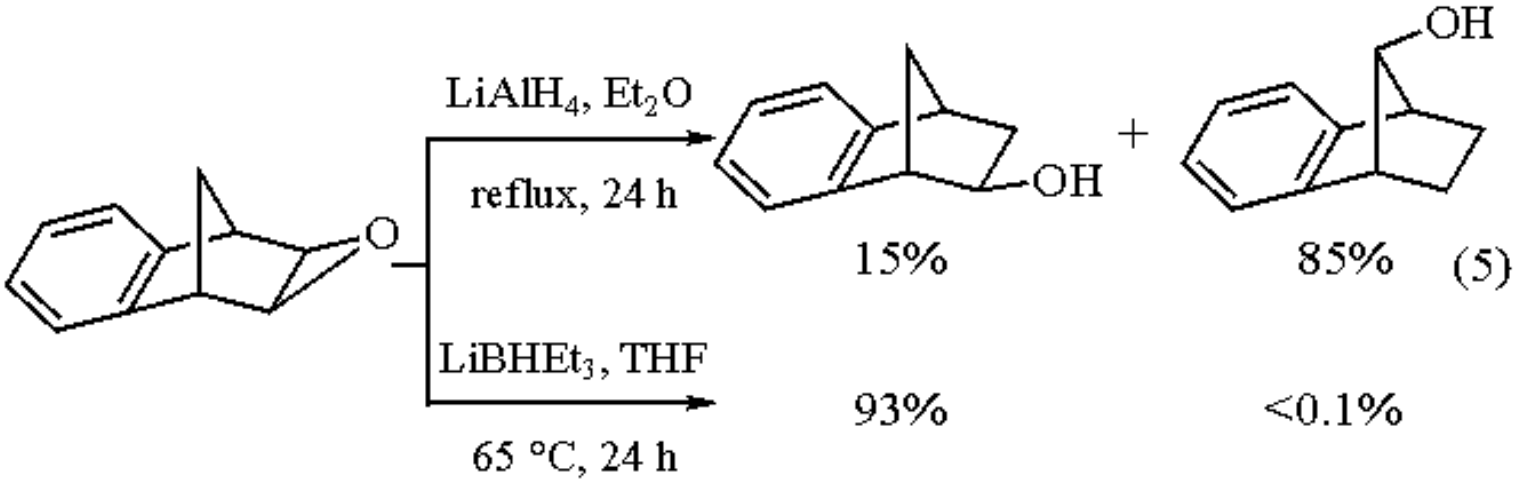

Ketones and Derivatives.

Aldehydes and ketones are reduced by lithium triethylborohydride rapidly and quantitatively to the corresponding alcohols, even at -78 °C.[7] Enthalpies of these reactions have been estimated.[19] Selective reduction of a keto group in the presence of an electron-rich aldehyde group has been achieved.[20a] Although the stereoselectivity of the reagent is lower as compared to other trialkylborohydrides containing bulky sterically demanding groups, several α-, β-, or γ-substituted ketones undergo reduction with high selectivity.[20b-j] α,β-Unsaturated ketones and esters undergo 1,4-additions.[21] *N*-Alkylimines derived from cyclic ketones are reduced to the corresponding secondary amines which can be transformed into primary amines.[22]

The reduction of α-trityl ketones with lithium triethylborohydride proceeds with cleavage of the trityl group. Stereoselective aldol reaction, combined with the reduction, provides access to stereodefined acyclic 1,3-diols[23] (eq 6).[23b] Trityl alkynic ketones are cleaved without affecting the triple bond.[24] Acetals are stable to the reagent and can be used as protective groups (eq 2).[7,9,11c,d] However, acetals are cleaved in the presence of ***Titanium(IV) Chloride***.[25]

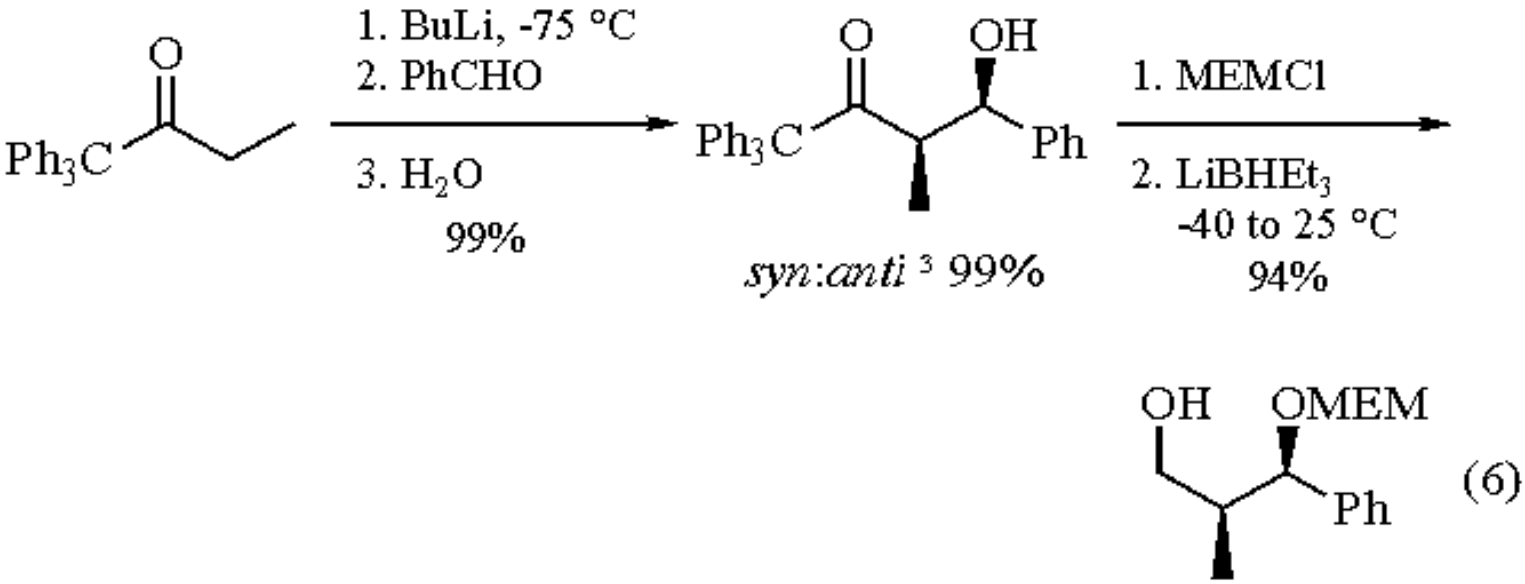

Carboxylic Acid Derivatives.[7]

The inertness of carboxylic acids to the reagent is noteworthy. Anhydrides are reduced to alcohols and acids. Cyclic

anhydrides can be transformed into the corresponding lactones via intermediate hydroxy acids. The reactivity of lithium triethylborohydride toward ester groups is exceptionally high. Even esters of aromatic carboxylic acids are selectively reduced to alcohols in the presence of other functional groups (eq 7).[26] Selective reduction of the less hindered MEM ester groups of a diester has been achieved.[27a] The reduction of esters with ***Lithium Borohydride*** is catalyzed by lithium triethylborohydride.[27b]

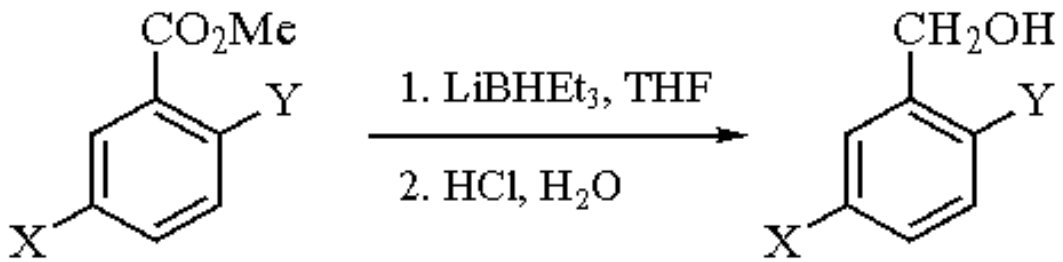

(7)

X = H, Y = NH_2, 82.5%
X = H, Y = NO_2, 99.7%
X = Cl, Y = OMe, 94.4%

Unlike most other hydride reducing agents, lithium triethylborohydride reduces tertiary amides to the corresponding alcohols.[7,28] Benzonitrile cleanly gives benzylamine with an excess of the reagent. With an equimolar ratio of the reactants, an 85-97% yield of benzaldehyde is obtained.[7] Aliphatic nitriles give lower yields of the corresponding amines.

Other Functionalities.

The formation of ethylbenzene in the reaction of lithium triethylborohydride with diphenyl sulfone illustrates a general reactivity pattern of trialkylborohydrides with aromatic sulfones (eq 8).[29]

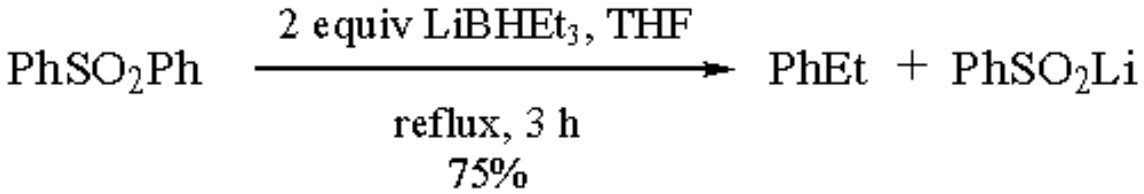

(8)

α,β-Unsaturated nitro compounds are transformed into lithium nitroalkanes.[30a] In the presence of borane, *N*-ethylamine derivatives are formed (eq 9).[30b] 1,2-Iodo thiocyanates[31a] and vinylthiophthalimides[31b] yield thiiranes (eq 10). The reagent is useful for selective demethylation of quaternary ammonium salts containing at least two methyl groups.[32] It also finds application in the synthesis of di- and trialkyldihydronaphthalenenes.[33a] Pyridine is reduced to tetrahydropyridine.[7,33b]

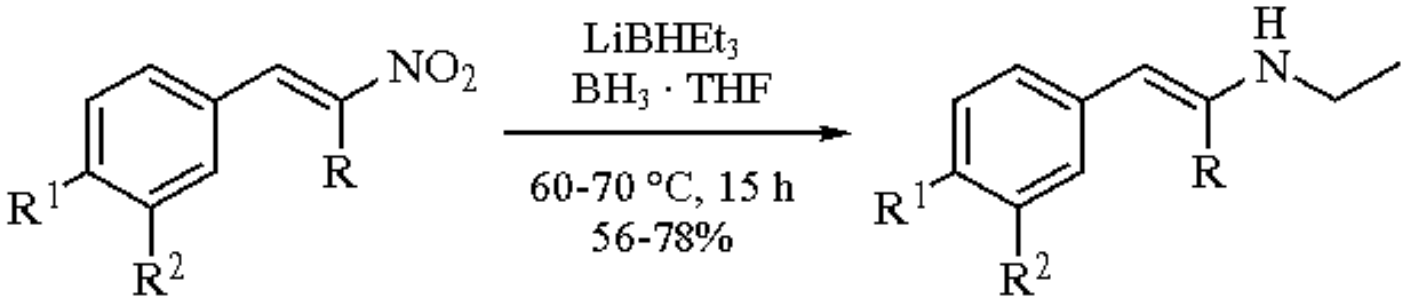

(9)

R	R^1	R^2
H	H	H
Me	H	H
H	Br	H
Me	EtO	EtO

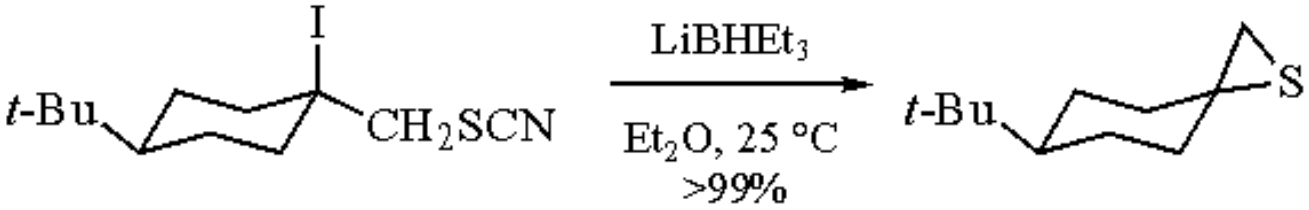

(10)

Hydroboration.

The reagent hydroborates aromatically conjugated alkenes in a Markovnikov fashion (eq 11).[34] Substituents that decrease the electron density of the double bond increase the rate of reaction. Lithium triethylborohydride promotes hydroboration of alkenes by dialkoxyboranes; the addition is anti-Markovnikov.[35]

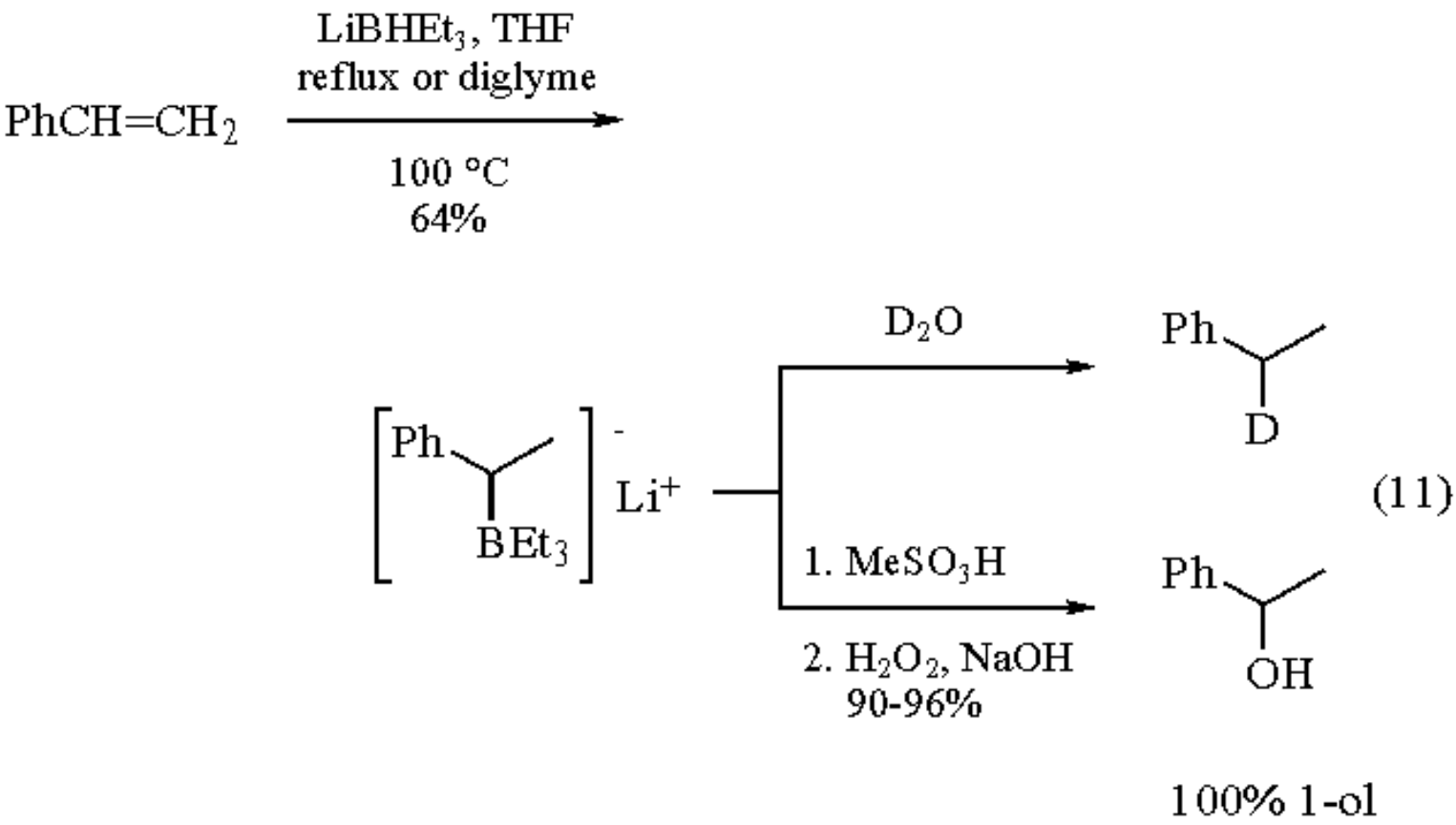

(11)

Synthesis of Borates and Boronates.

The reagent promotes the reaction of alcohol with borane to give borates in high yields[36] (see also ***Borane-Dimethyl Sulfide***). Ethyl boronates can be conveniently prepared by the reaction with 1,2-diols.[37]

Organometallic Synthesis.[38]

Lithium triethylborohydride is recommended for the generation of chloro(cyclopentadienyl)hydrozirconium (Schwartz hydrozirconation reagent).[39] The reagent is used for the reduction of other transition metal halide complexes.[40] The major area of its application in transition metal chemistry involves metal-metal and metal-metalloid bond cleavage[38,41] and formation of anionic and neutral formyl complexes.[38,42] It finds various other applications.[43-45]

Related Reagents.

Potassium Triethylborohydride.

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Lithium Trimethylmanganate[1]

Me_3MnLi

[105870-26-6] · C_3H_9LiMn · Lithium Trimethylmanganate · (MW 107.00)

(less expensive, more stable[2] cuprate[3] analog that undergoes nucleophilic additions,[4] conjugate additions,[5] and substitutions[6])

Solubility: sol THF; sol ether if prepared from MnI_2.

Preparative Methods: can be prepared as an ether solution from MnI_2 and ***Methyllithium***, or as a THF solution from ***Manganese(II) Chloride*** or Li_2MnCl_4 and MeLi. For instance, to prepare Me_3MnLi in THF from MeLi, charge a dry, N_2-purged round-bottom flask equipped with magnetic stirring bar, N_2 inlet, and septum stopper with 1.0 equiv of high purity, (>99%) dried (2 h at 180 °C) $MnCl_2$ and add sufficient dry, O_2-free THF to form a ca. 0.2 M slurry. Cool the slurry to -10 to 0 °C and add 3.0 equiv of a solution of MeLi dropwise. After the addition is complete, stir the reaction at room temperature for 30 min. A brownish-red to clear yellow solution results and can be used directly.[7]

Handling, Storage, and Precautions: best results are obtained with high purity, dry, O_2-free solvents and manganese salts. MeLi is pyrophoric;[8] due care must be exercised in its handling. The reagent has greater thermodynamic stability when prepared in THF than in ether.

Originally prepared from MnI_2 and MeLi in ether,[9] the formulation of the reagent as Me_3MnLi is a convenience only and this may not be the reactive species in solution. There is considerable evidence that, over a wide range of reagent ratios, the reaction equilibrium favors formation of $Li_2[MnMe_3]_4$; $[MnMe_3]^-$ species form only as intermediates.[10]

Trialkylmanganates are sufficiently nucleophilic to react with good electrophiles, such as phenyl isocyanate, in good yield (eq 1).[3] Conjugate additions to 2-alkenones are more problematic: relatively rare β-reductive dimerization[5] (eq 2) is sometimes observed in addition to β-alkylation[11] (eq 2). Dimerization is, however, substrate specific;[7] it may be possible to improve yields using catalytic or stoichiometric amounts of Cu^I salts.[12]

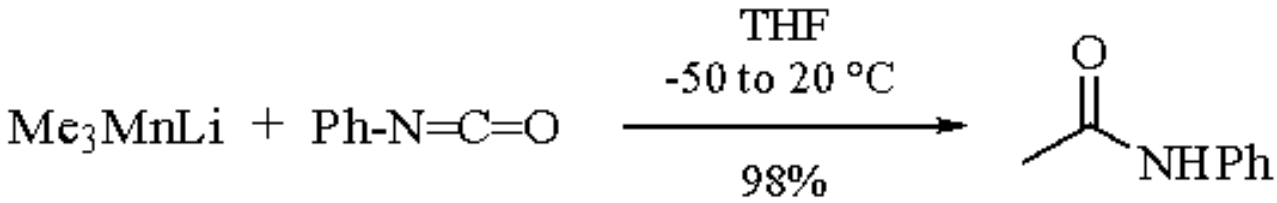

(1)

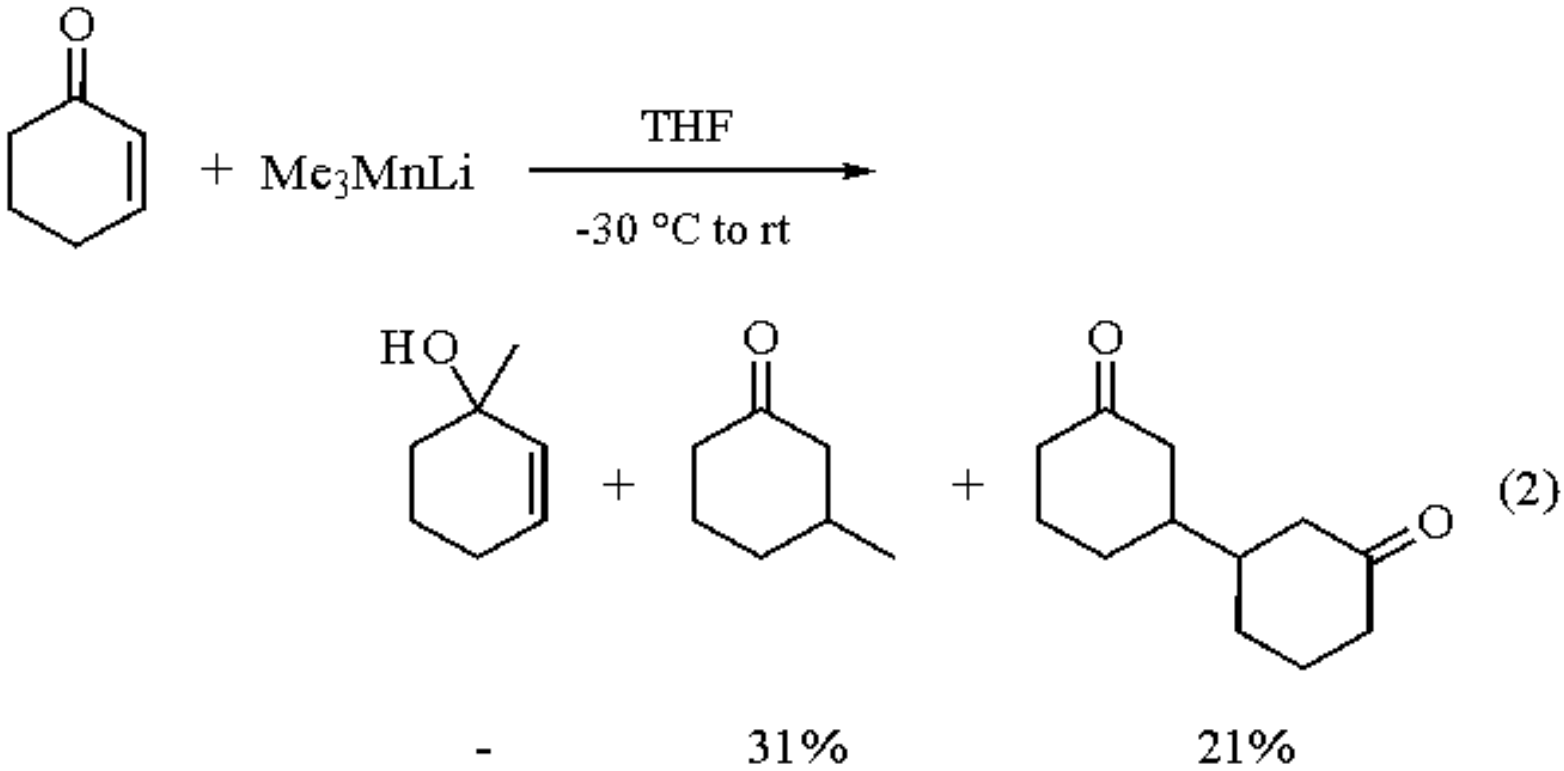

Although cuprate reagents generally are found to be superior in nucleophilic substitution reactions with haloalkanes, trialkylmanganates provide the same products, usually in good yields.[6] Primary iodoalkanes, allylic halides (eq 3), and vinylic halides are satisfactory substrates; secondary and tertiary haloalkanes are not. Cross-coupling reactions between trialkylmanganates and enol phosphates are catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)***; Li_2MnCl_4 catalyzes similar coupling between Grignard reagents and enol triflates, presumably via formation of an R_3MnLi species.[13]

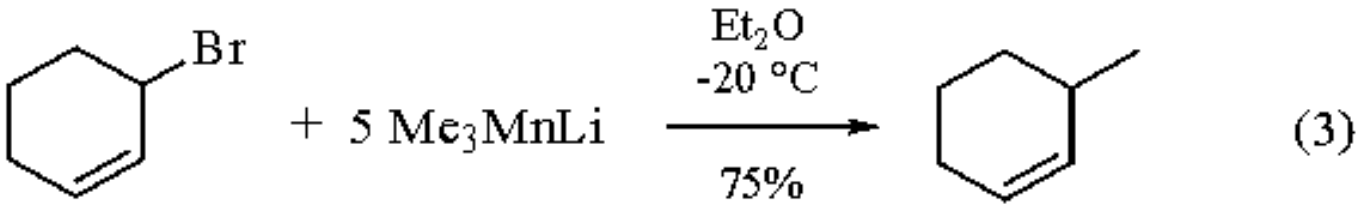

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Lithium (Trimethylsilyl)acetylide

Me_3SiC&tbond;CLi

[54655-07-1] · C_5H_9LiSi · Lithium (Trimethylsilyl)acetylide · (MW 104.17)

(synthesis of unsymmetrically disubstituted alkynes, where use of the silyl protecting group ensures selective monofunctionalization of the acetylide anion; the reaction products can be deprotected by cleavage of the Si-C bond, or the silicon group can be displaced with other electrophiles)

Form Supplied in: solution in THF (0.5 M).

Preparative Methods: most often prepared in situ by treatment of ***Trimethylsilylacetylene***[1] with ***n-Butyllithium***,[2] ***Lithium Diisopropylamide***,[3] or ***Ethyllithium-Lithium Bromide***.[4] It can also be prepared by monodesilylation of ***Bis(trimethylsilyl)acetylene*** with MeLi-LiBr complex (see ***Methyllithium***).[5]

Transmetalation.

Lithium (trimethylsilyl)acetylide can be transmetalated to enhance reactivity. Reaction with $CuBr.SMe_2$ (see ***Copper(I) Bromide***) provides the lithium (trialkynyl)cuprate, which can undergo electrophilic amination to provide 1-alkynylamines.[6] Transmetalation to cerium using ***Cerium(III) Chloride*** allows superior yields of addition products with cyclic ketones (eq 1).[7,8]

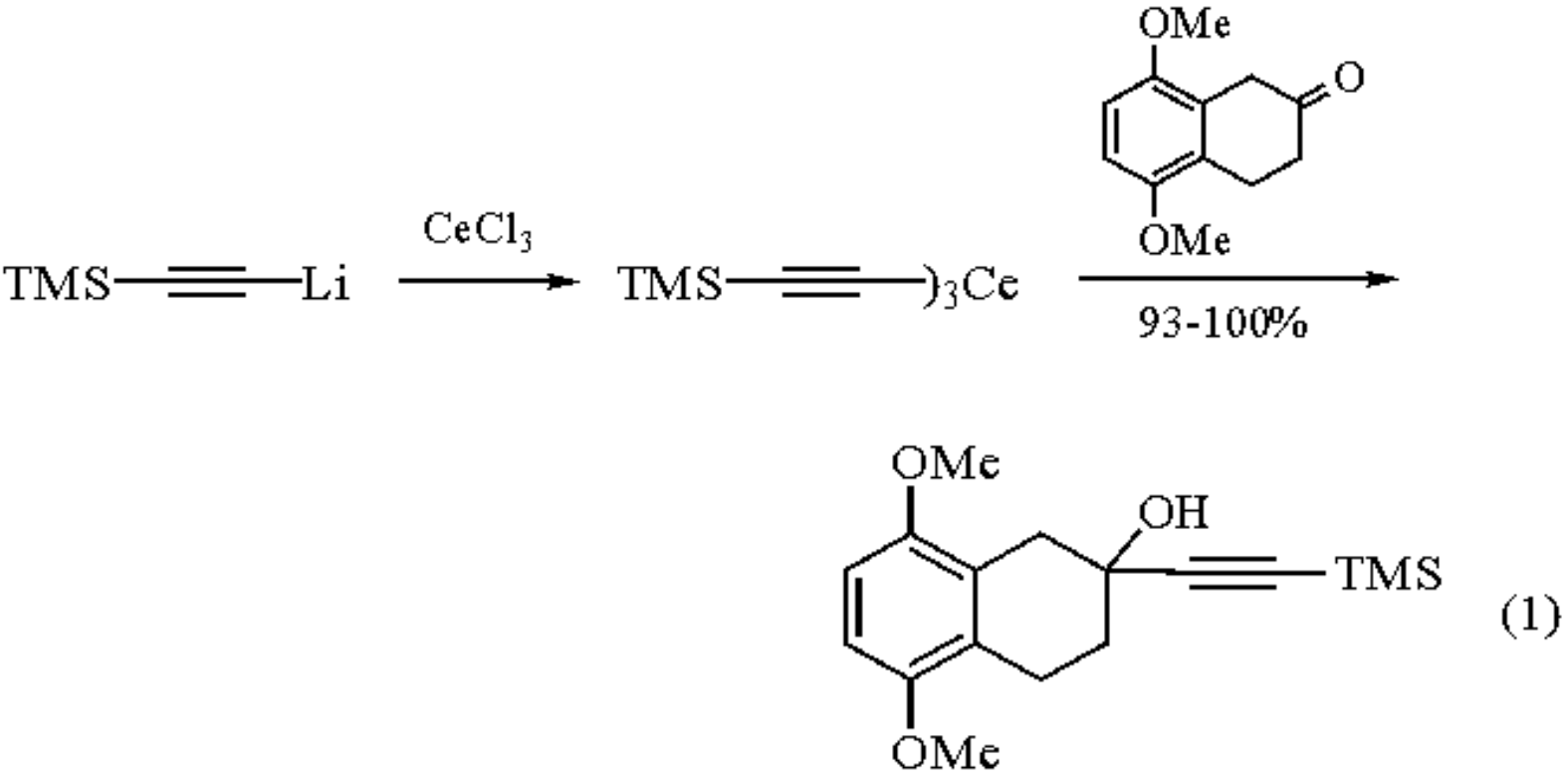

Addition to Carbonyl Compounds.

The title compound reacts with a variety of aldehydes[5,9-12] and ketones[13,14] to provide propargylic alcohol derivatives. Other carbonyl compounds used as substrates include quinones[2a] and quinone monoacetals,[15] alkynyl aldehydes[16] and ketones,[17] and dialkyl squarates (eq 2).[18] The propargylic alcohol products can be stereospecifically reduced to (*E*)-vinylsilanes, with ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al®).[19]

The reagent has been added to α-chiral aldehydes[20,21] and ketones,[22-25] with moderate to good stereoselectivity, although in one case the Grignard reagent proved superior to the lithium acetylide.[23a] Alternatively, optical activity can be introduced by employing a chiral ligand.[26]

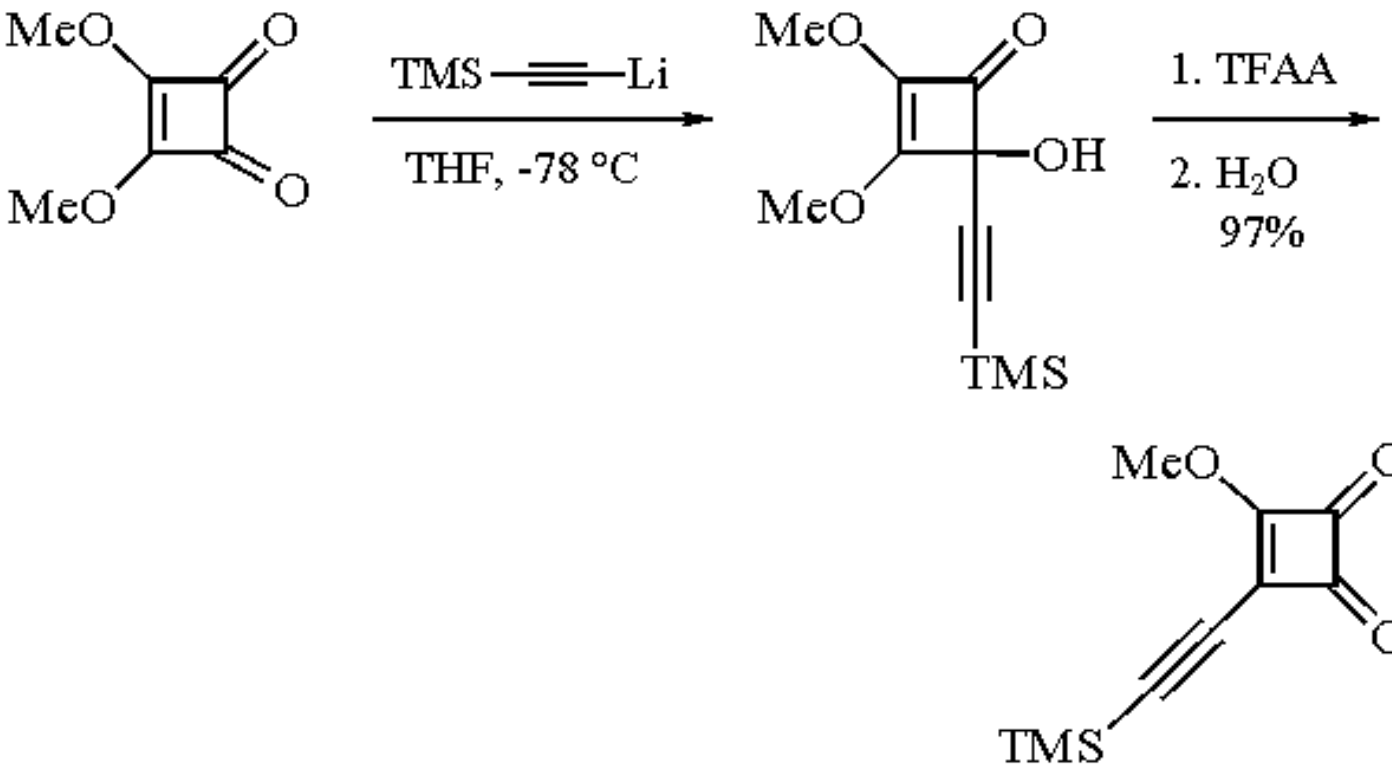

(2)

Addition to Epoxides.

Lithium (trimethylsilyl)acetylide has been used to open terminal epoxides in the presence of Lewis acids such as $GaMe_3$[27] or ***Boron Trifluoride Etherate*** (eq 3).[28]

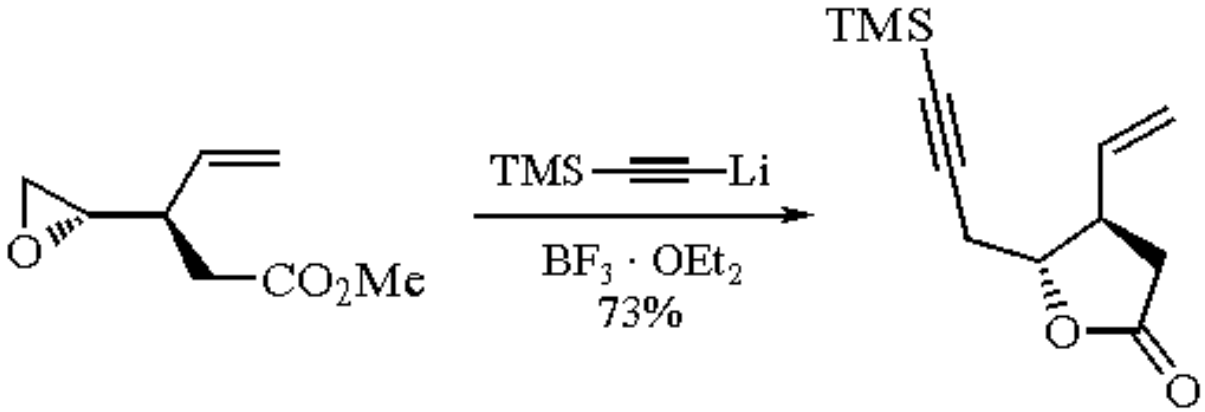

(3)

Alkynyl Ketones.

Treatment of a Weinreb amide[29] (see ***N,O-Dimethylhydroxylamine***) or an isoxazolidide[30] with the title compound provides good to excellent yields of α,β-ynones (eq 4).

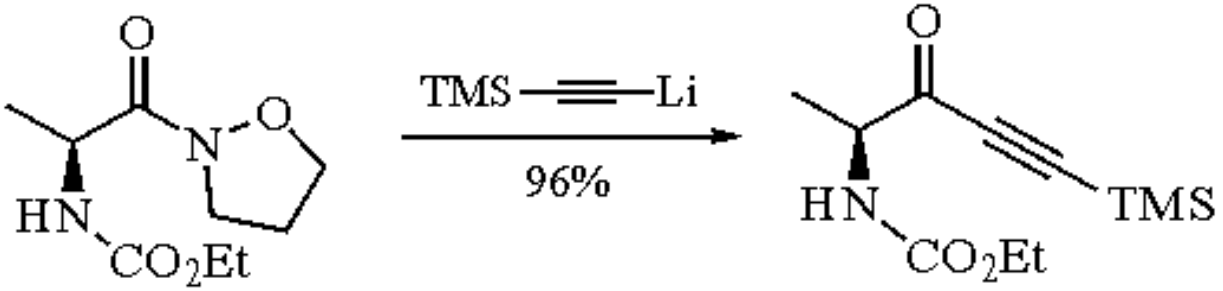

(4)

Miscellaneous.

Lithium (trimethylsilyl)acetylide has been employed in the nucleophilic displacement of bromides[10] and iodides[31] and the Grignard analog in aryl chloride substitution.[32] The reaction of lithium (trimethylsilyl)acetylide with 2-chloroethyl thiocyanate is an efficient route to 1-vinylthioacetylene.[33] Trisubstituted vinylsilanes can be prepared from the reaction of lithium (trimethylsilyl)acetylide with trialkylboranes and electrophiles.[34] The title reagent has been added to *N*-acyl imines to form α,α´-disubstituted amino acid bis-amides.[35] Excellent stereocontrol has been observed in addition reactions of lithium (trimethylsilyl)acetylide to 3-thiazolines (eq 5)[3] and β´-aminocyclopentenyl sulfones (eq 6).[36]

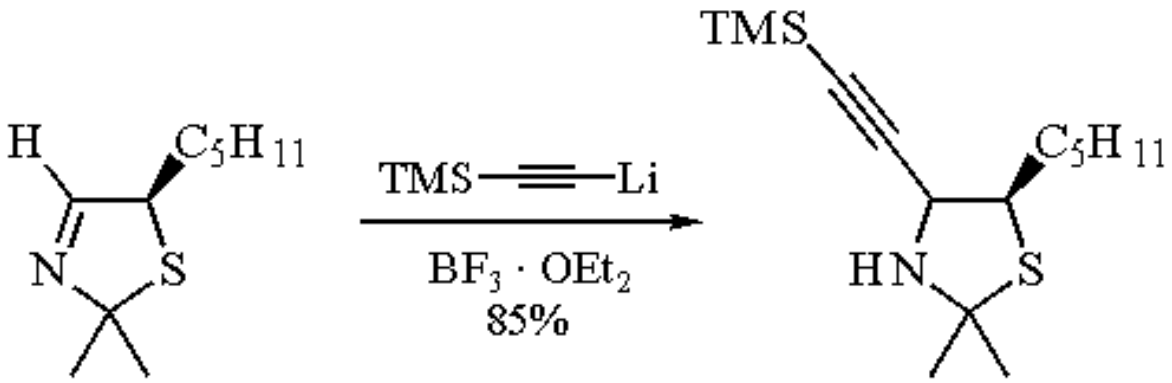

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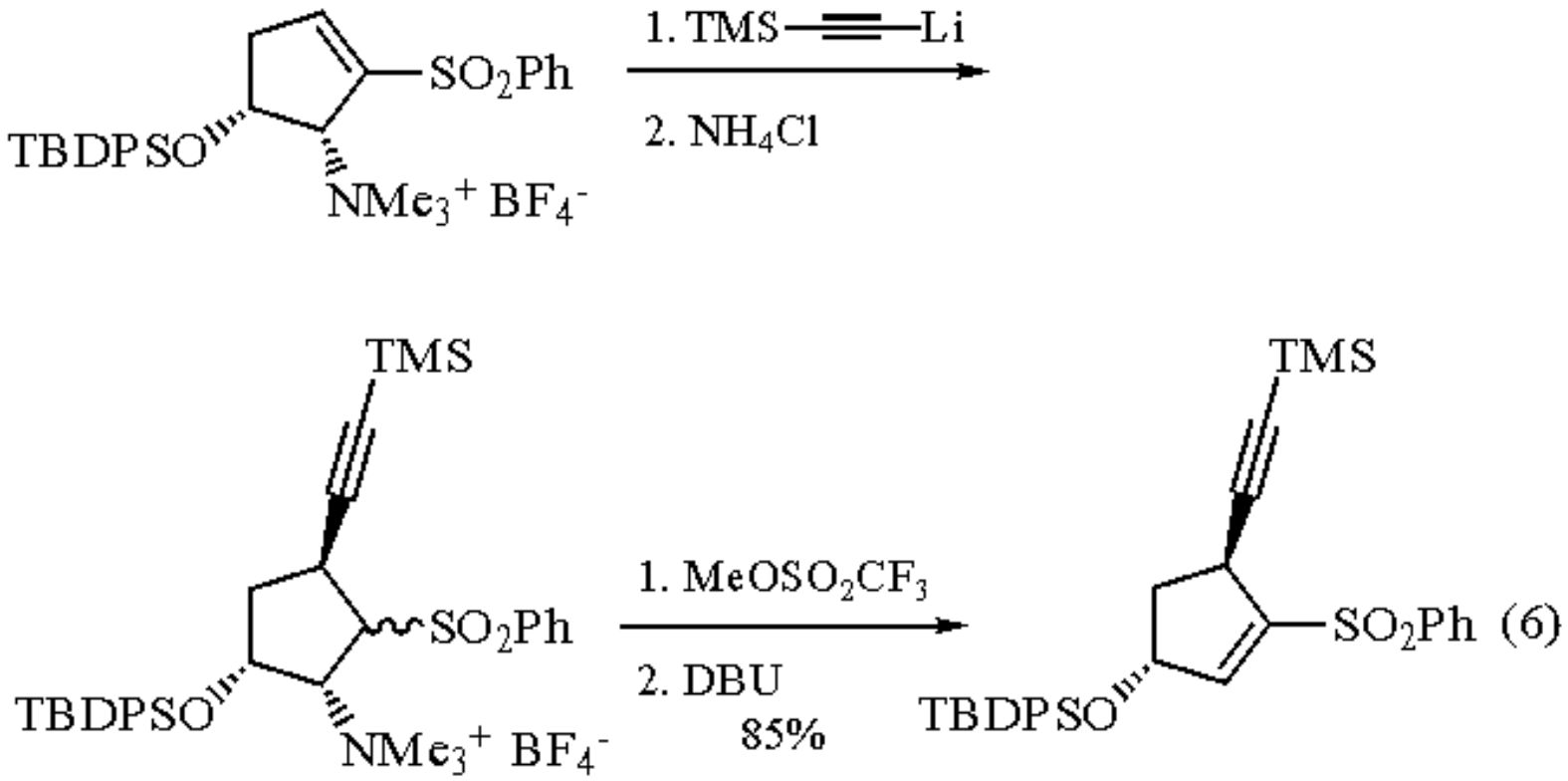

Related Reagents.

Dilithium Acetylide; ***Ethynylmagnesium Bromide***; ***Lithium Acetylide***; ***Lithium Chloroacetylide***; ***Propynyllithium***.

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Lithium Trimethylzincate

Me_3ZnLi

[52196-05-1] · C_3H_9LiZn · Lithium Trimethylzincate · (MW 117.45)

(strong nucleophile; undergoes 1,4-additions to enones;[1-6] can be used for performing halogen-zinc exchange reactions[8,9])

Solubility: sol ether, THF; reacts with H_2O, protic solvents, and oxygen.

Preparative Methods: THF or ether solutions can be prepared by the reaction of ***Methyllithium*** (3 equiv) with ***Zinc Chloride*** or by the treatment of Me_2Zn with MeLi.[1-4]

Handling, Storage, and Precautions: should be handled under an inert atmosphere; like organolithiums, it may react with THF; best generated in situ and used rapidly.

Michael Additions.

Lithium trimethylzincate, like most lithium or magnesium triorganozincates, undergoes 1,4-additions to enones with high chemoselectivity (see ***Lithium Tri-t-butylzincate***). The nature of the lithium salts present in the reaction mixture strongly influences the yield obtained (eq 1).[1] It must also be noted that lithium trimethylzincate is one of the least reactive triorganozincates and that the transfer of a methyl group proceeds generally with moderate yield (eq 2).[4] This has been exploited synthetically by preparing mixed alkyldimethylzincates which were shown to transfer selectively the alkyl group in the Michael addition (alkyl = *n*-Bu, *i*-Pr, *t*-Bu, *i*-Bu, Ph, vinyl, Me_2PhSi; eqs 3 and 4).[4,5] If the addition of lithium trimethylzincate to cyclohexenone is performed in a chiral solvent like (+)-1,4-dimethylamino-2,3-dimethoxybutane (DDB), the resulting 3-methylcyclohexane is obtained in low enantioselectivity.[3] α,β-Unsaturated epoxides react rapidly affording a mixture of S_N2 and S_N2' substitution products (eq 5).[6] Lithium trimethylzincate adds with moderate stereoselectivity to 4-*t*-butylcyclohexanone, producing a mixture of axial and equatorial alcohols (70:30).[7]

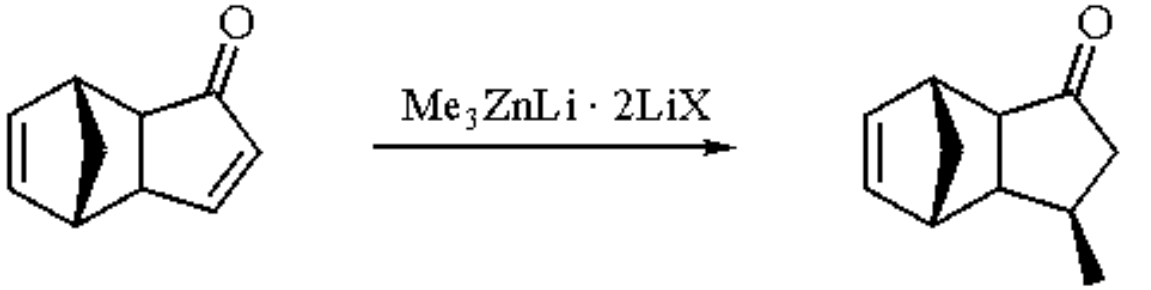

(1)

X = Cl, 92%
X = Br, 76%
X = I, 68%

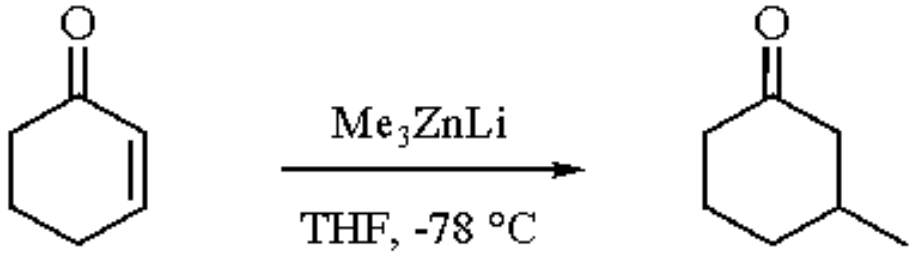

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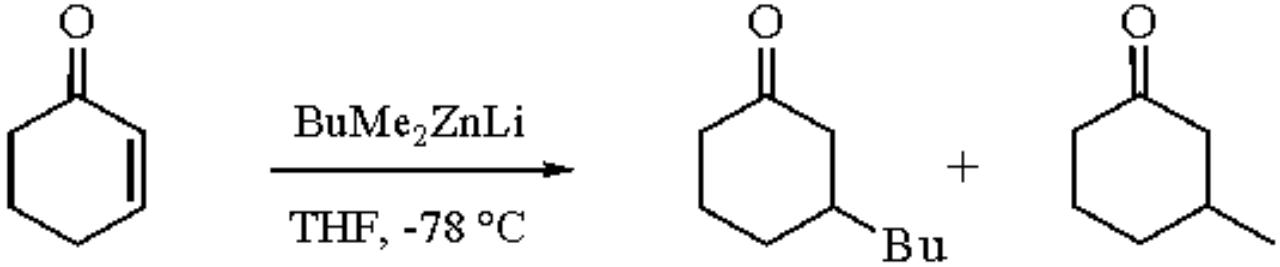

(3)

92% 3%

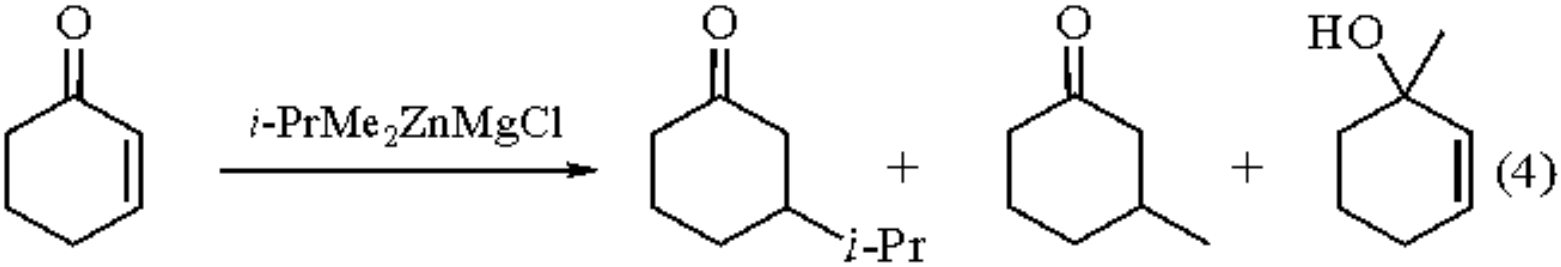

(4)

85% 0-2% 0-2%

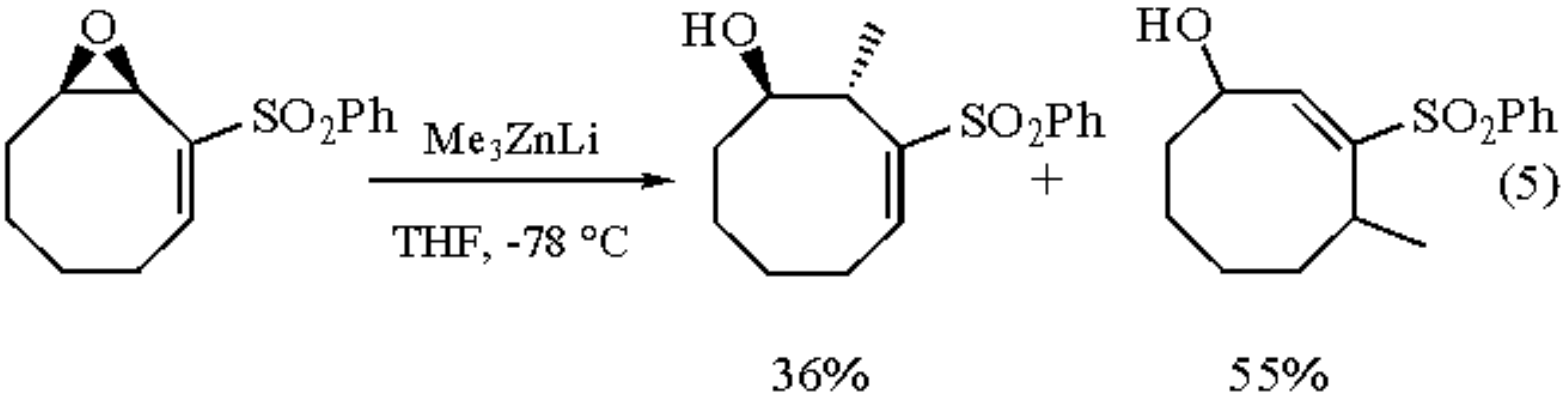

Halogen-Zinc Exchange Reactions.

Interestingly, lithium triorganozincates can be used for performing halogen-zinc exchange reactions.[8,9] 1,1-Dibromoalkanes such as (**1**) react readily with Me_3ZnLi at -85 °C, providing the corresponding zinc carbenoid (**2**) which undergoes 1,2-migration[10,11] upon warming to 0 °C to afford the organozinc reagent (**3**); after protonolysis, this gives the cyclopropane derivative (**4**) (eq 6).[8] The reaction can be extended to acyclic 1,1-dibromoalkanes, thus offering unique homologation possibilities (eq 7).[9]

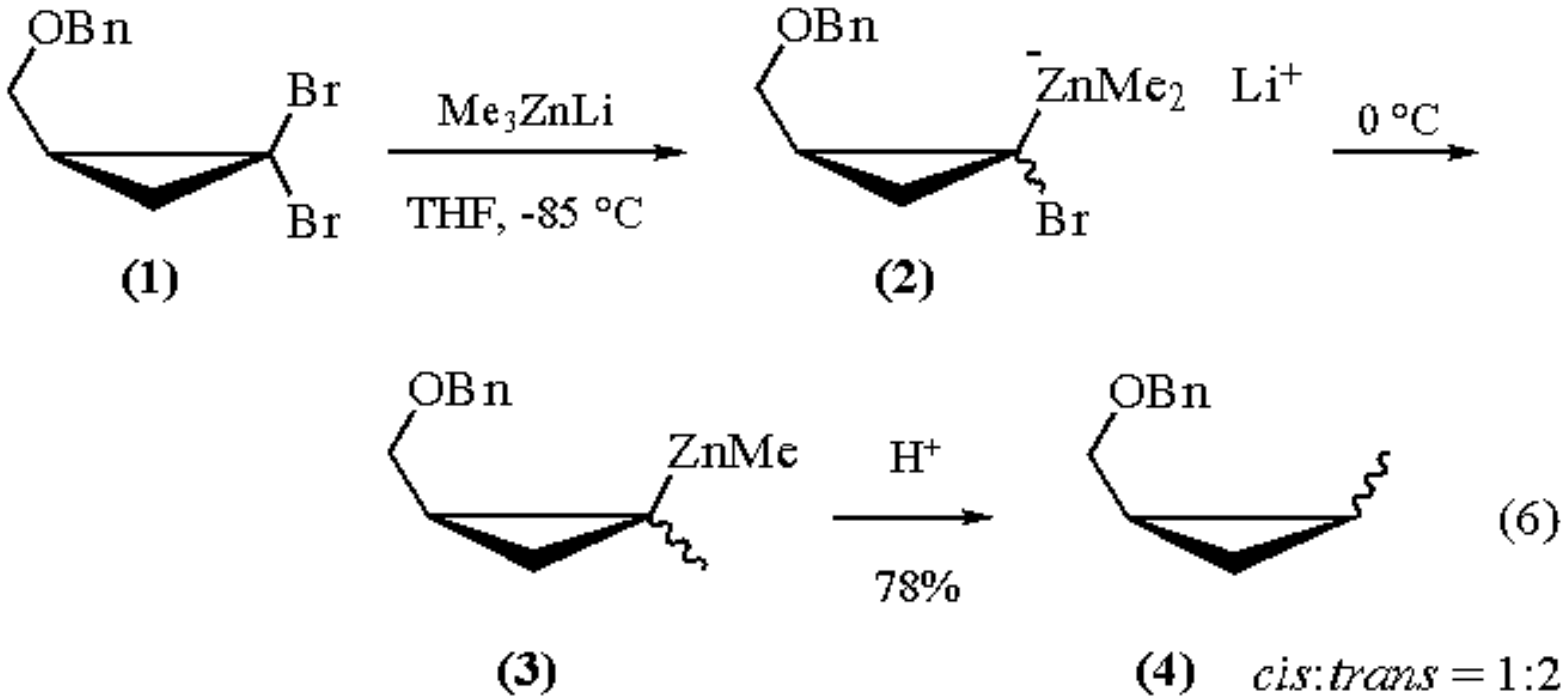

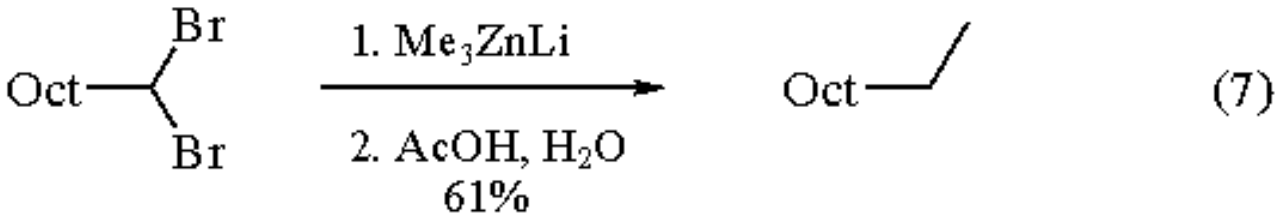

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Lithium Trisiamylborohydride

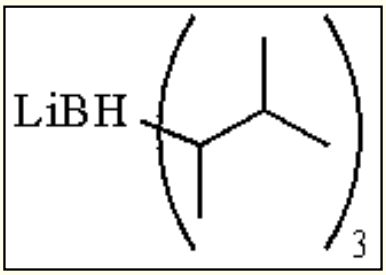

[60217-34-7] · $C_{15}H_{31}BLi$ · Lithium Trisiamylborohydride · (MW 232.19)

(highly chemo- and stereoselective reducing agent)

Alternate Name: LS-Selectride®.

*Physical Data: d*420 = 0.903 for 1 M solution in THF.

Solubility: sol THF, diethyl ether.

Form Supplied in: 1 M solution in THF.

Preparative Methods: by the reaction of ***t-Butyllithium*** with trisiamylborane,[1] of ***Lithium Aluminum Hydride*** with trisiamylborane in the presence of triethylenediamine,[2] or of lithium trimethoxyaluminohydride with trisiamylborane.[3]

Analysis of Reagent Purity: ^{11}B NMR (THF), δ, ppm, two pairs of doublets, -12.5 (d, *J* = 78 Hz), -13.9 (d, *J* = 79 Hz) area 3:1;[1] IR: 2150 cm^{-1}. Active hydride is determined by hydrolysis and measuring the hydrogen evolved according to the standard procedure.[4]

Handling, Storage, and Precautions: air- and moisture-sensitive, flammable liquid. Reacts violently with water. Handle and store under nitrogen or argon. Use in a fume hood.

Lithium trisiamylborohydride ($LiBSia_3H$) is a highly hindered trialkylborohydride containing three bulky β-methyl-substituted secondary alkyl groups. The reagent reduces, rapidly and quantitatively, unhindered cyclic and bicyclic ketones with exceptional steric control. Thus, 2-, 3-, and 4-methylcyclohexanones are all reduced at -78 °C in >99% stereoselectivity to give the less stable isomer of the corresponding methylcyclohexanol (Table 1). Attack from the less hindered side is also favored for the alkaloid and steroidal ketones.[6-8]

Table 1 Reduction of Representative Cyclic Ketones with Lithium Trisiamylborohydride and Other Trialkylborohydrides[1]

Ketone	Product alcohol (%)			
	Less stable isomer	LiB-Sia_3H	LiB-$(s\text{-Bu})_3H$	Other hydrides
2-Methylcyclopentanone	*cis*	98.5	98.5	75[a], 79.2[b]
2-Methylcyclohexanone	*cis*	99.7	99.3	
3-Methylcyclohexanone	*trans*	99.6	95.0	
4-Methylcyclohexanone	*cis*	99.0	90.0	
4-*t*-Butylcyclohexanone	*cis*	99.4	96.5	99.2[c], 20[b]
Norcamphor	*endo*	>99.5	99.6	
Camphor	*exo*	99.3	99.0	

[a]$LiBEt_3H$.[5a] [b]$KBEt_3H$.[5b] [c]$KBSia_3H$.[5c]

Conjugate reduction of the macrocyclic keto lactone occurs only as a minor side-reaction, accounting for 10% of the reaction product, whereas with L-Selectride (***Lithium Tri-s-butylborohydride***) (but not with K-Selectride (***Potassium Tri-s-butylborohydride***)), 53% of the product is the saturated ketone (eq 1).[9] Both L- and K-Selectrides reduce α,β-enones and α,β-enoates in a conjugate fashion.[10]

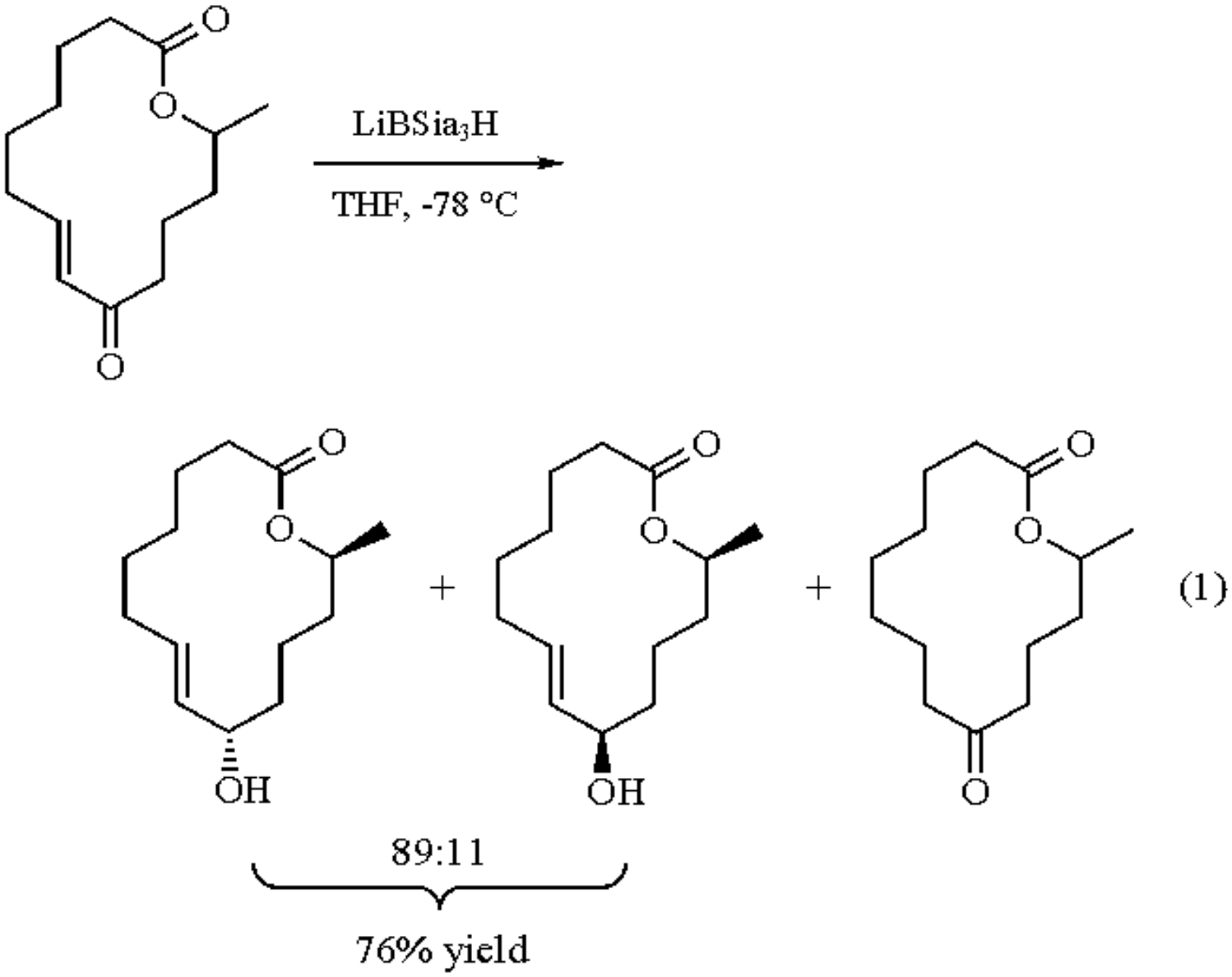

High stereoselectivity is also observed in the reduction of acyclic ketones with LS-Selectride. Thus, the α,β-dialkoxy ketone is reduced with 97% *syn* diastereoselectivity (eq 2).[11] The reagent is the most stereoselective among the borohydrides used for the reduction of (-)-menthyl phenylglyoxalate and (-)-menthyl pyruvate (eq 3).[12] Only lithium trialkoxyaluminohydrides derived from very hindered tertiary alcohols show higher stereoselectivity in this reaction (86-90% de).[12]

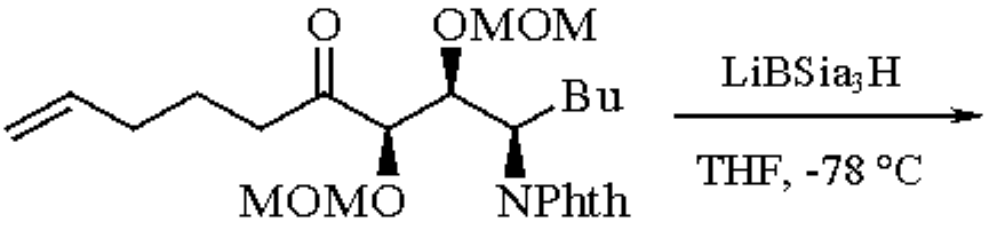

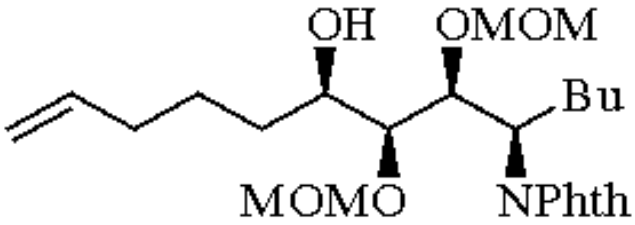

(2)

67%, 97% *syn*
83%, 98% *syn* (L-Selectride)

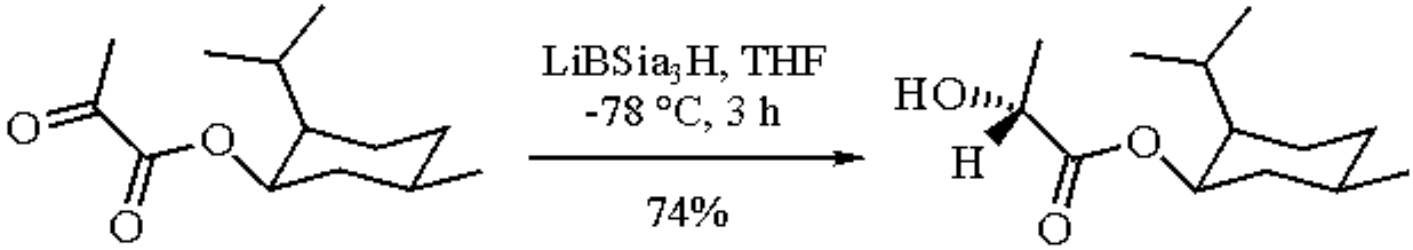

(3)

74% de

Chemoselective reduction of a tertiary amide to an aldehyde in the presence of an ester group is possible with LS-Selectride, but L-Selectride gives better results.[13] Unsymmetrical cyclic anhydrides are reduced to lactones at the less hindered carbonyl group. In contrast, other less bulky hydrides attack the anhydride preferentially at the more hindered carbonyl group (eq 4).[14-16]

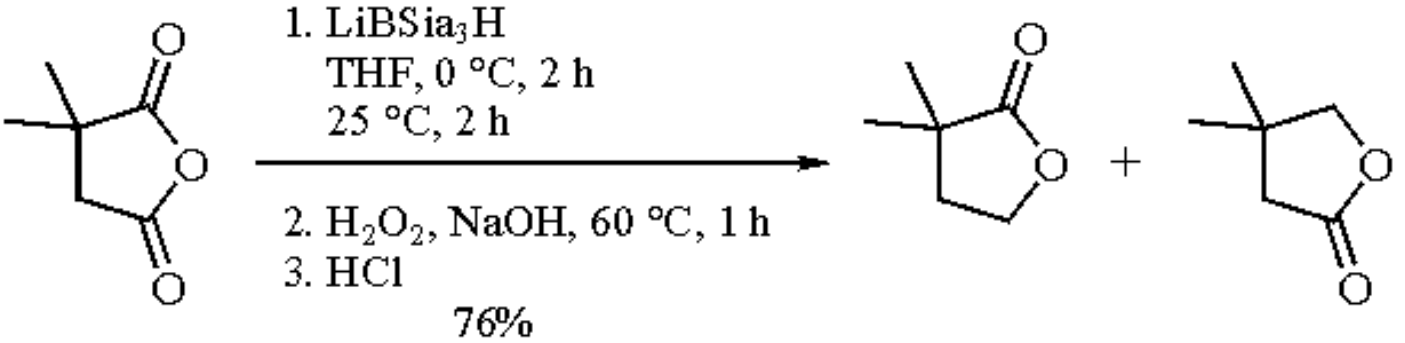

(4)

	92%	8%
$LiAlH_4$[15]	5%	95%
$NaBH_4$[16]	0%	100%

1. (a) Krishnamurthy, S.; Brown, H. C. *JACS* **1976**, *98*, 3383. (b) Brown, H. C.; Kramer, G. W.; Hubbard, J. L.; Krishnamurthy, S. *JOM* **1980**, *188*, 1.
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Purdue University, West Lafayette, IN, USA

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2,6-Lutidine

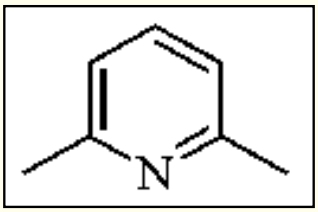

[108-48-5] · C_7H_9N · 2,6-Lutidine · (MW 107.17)

(basic reagent/catalyst for silylation of alcohols,[2-10] for Rosenmund reduction,[14] and for preparation of boron enolates[15])

Physical Data: colorless oily liquid with an odor of pyridine and peppermint; bp 144.0 °C/760 mmHg, 79 °C/87 mmHg; mp -5.9 °C; *d* (20 °C) 0.9252 g cm^{-3}; *n*20D 1.49797. The major synthetic applications reported for 2,6-lutidine exploit its weakly nucleophilic nature (a result of steric crowding at the ring nitrogen) but moderately basic character (pK_a of its conjugate acid is 6.7).

Solubility: sol common organic solvents (e.g. ether, THF, DMF, alcohol); shows considerable water solubility (ca. 27% (w/w) at 45 °C).

Form Supplied in: a widely available article of commerce. Redistilled (99+ % purity) is available commercially. *Drying:* commonly dried by treatment with KOH or sodium followed by distillation, or by refluxing with, followed by distillation from, BaO[1] or CaH_2.[2]

Purification: both 3- and 4-picolines are common contaminants which can be removed by distillation from $AlCl_3$ (14 g/100 mL 2,6-lutidine, which also removes traces of water), or by addition of BF_3 (4 mL/100 mL of 2,6-lutidine) to anhydrous, fractionally distilled 2,6-lutidine, followed by redistillation.[1]

Handling, Storage, and Precautions: toxic flammable liquid; should be handled with caution in a fume hood.

Alcohol Protection Reactions.

The protection of alcohols as hindered silyl ethers proceeds in >90% yield using the appropriate trialkylsilyl triflate in the presence of anhydrous 2,6-lutidine as an acid scavenger. ***Triisopropylsilyl Trifluoromethanesulfonate***/2,6-lutidine in CH_2Cl_2 (-78 °C to 0 °C) allows for the protection of primary and secondary (but not tertiary) alcohols (eq 1).[2,3] Tertiary alcohols can be protected as the somewhat less crowded *i*-$PrEt_2Si$ ether (*i*-$PrEt_2SiOTf$/2,6-lutidine, CH_2Cl_2, rt).[4] The silylation of tertiary and unreactive secondary alcohols can also be achieved using ***t-Butyldimethylsilyl Trifluoromethanesulfonate***/2,6-lutidine in CH_2Cl_2 (0-25 °C);[2,5] silylation at -78 °C allows for the selective protection

of a secondary alcohol in the presence of a secondary allylic alcohol (eq 2).[6] The silylation of secondary allylic alcohols as the bulky tribenzylsilyl ether or tri-*p*-xylylsilyl ether can be accomplished using the appropriate tris(arylmethyl)chlorosilane/2,6-lutidine in DMF at -20 °C.[7] The bis-protection of 1,2-, 1,3-, and 1,4-diols as the corresponding dialkylsilylene derivatives can be achieved in high yield using ***Diisopropylsilyl Bis(trifluoromethanesulfonate)*** or ***Di-t-butylsilyl Bis(trifluoromethanesulfonate)*** at rt in $CDCl_3$ in the presence of 2,6-lutidine (eq 3);[8] interestingly, 2,6-lutidine was found to retard the 3´,5´-protection of nucleosides in DMF solution.[9] Protection of a 1,3-diol as its methylene acetal can be achieved using ***Trimethylsilyl Trifluoromethanesulfonate***/2,6-lutidine in $MeOCH_2OMe$ (0 °C, 15 min, 79%).[10]

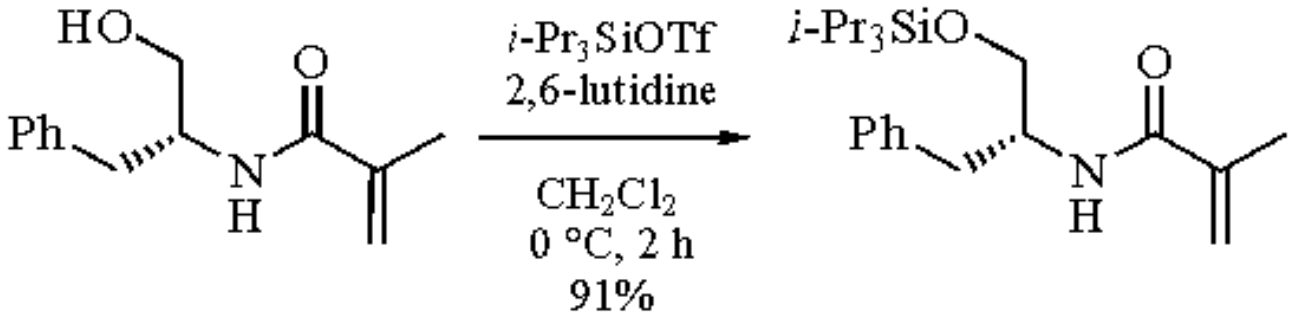

(1)

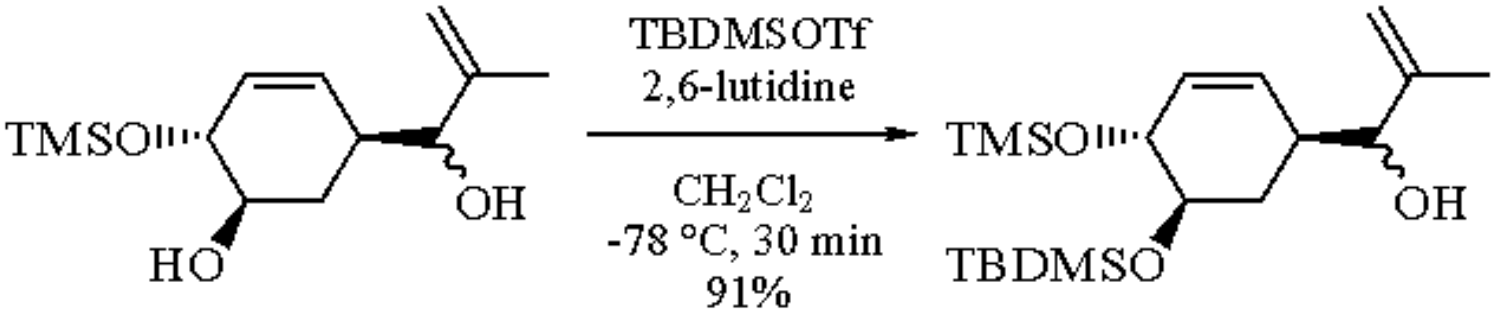

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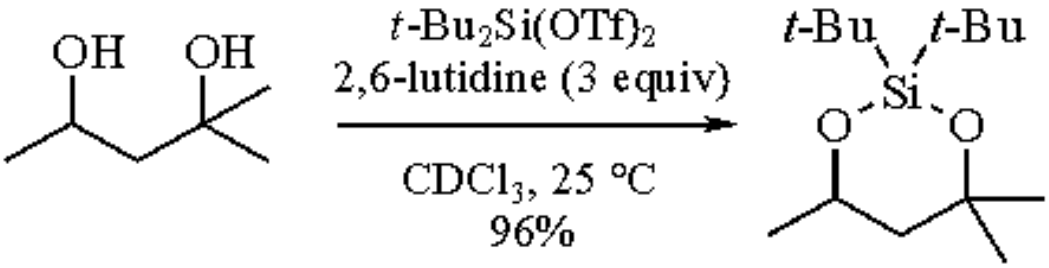

(3)

Other Protection/Deprotection Reactions.

2,6-Lutidine is more effective than ***Silver(I) Carbonate*** or other amine bases at mediating the conversion of a 2-acetylpyranosyl bromide to an orthoester (eq 4).[11] Side reactions are minimized due to the lower acidity of the conjugate acid of 2,6-lutidine (pK_a 6.7) when compared to the other substituted pyridines examined. *Exo* stereoselectivity is maximized when using 2,6-lutidine rather than silver carbonate. 2,6-Lutidine considerably accelerates bond cleavage during the triarylamine radical cation-mediated oxidative cleavage of primary and secondary benzyl[12] and *p*-methoxybenzyl[13] ethers to the corresponding alcohols.

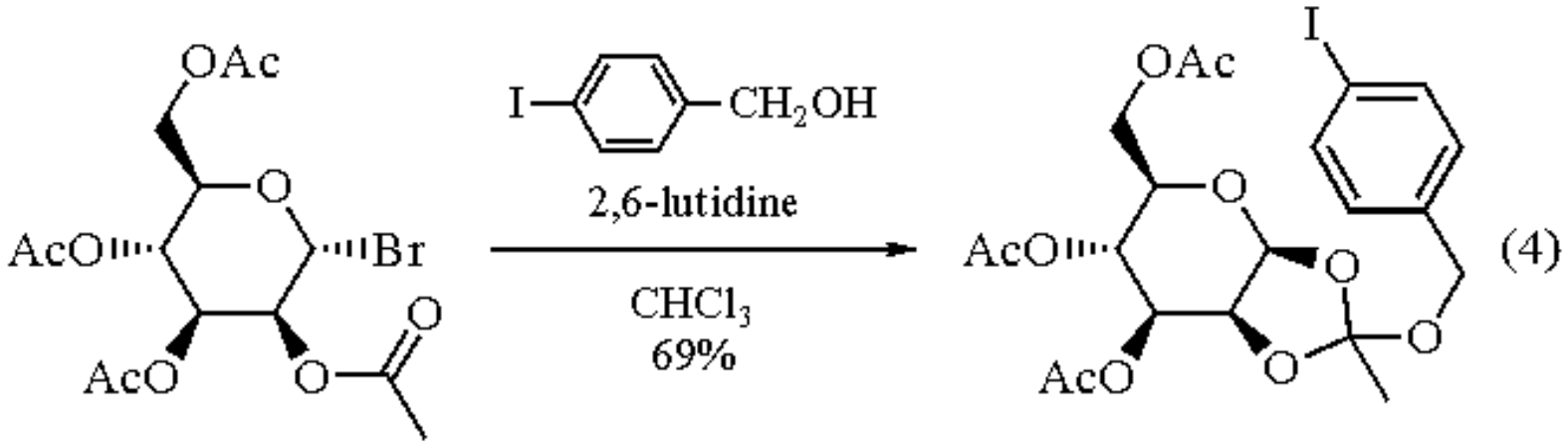

Rosenmund Reduction.

2,6-Lutidine is usefully employed as an HCl scavenger in the catalytic hydrogenation of aliphatic acyl chlorides to aldehydes (Rosenmund reduction) (eq 5).[14] These reactions are run in THF at <0.25 M in substrate to prevent poisoning of the Pd catalyst. 2,6-Lutidine is far superior to other basic additives (e.g. ***Diisopropylethylamine***, *N*,*N*-dimethylaniline, NaOAc). This method can tolerate ketone and ester functionality, proceeds on both unhindered and crowded acyl chlorides, and is especially suitable for the preparation of sensitive aldehydes. These reactions are faster and superior to those performed under classical Rosenmund reduction conditions (no added base), where high reaction temperatures are required and where the HCl byproduct can mediate side reactions.

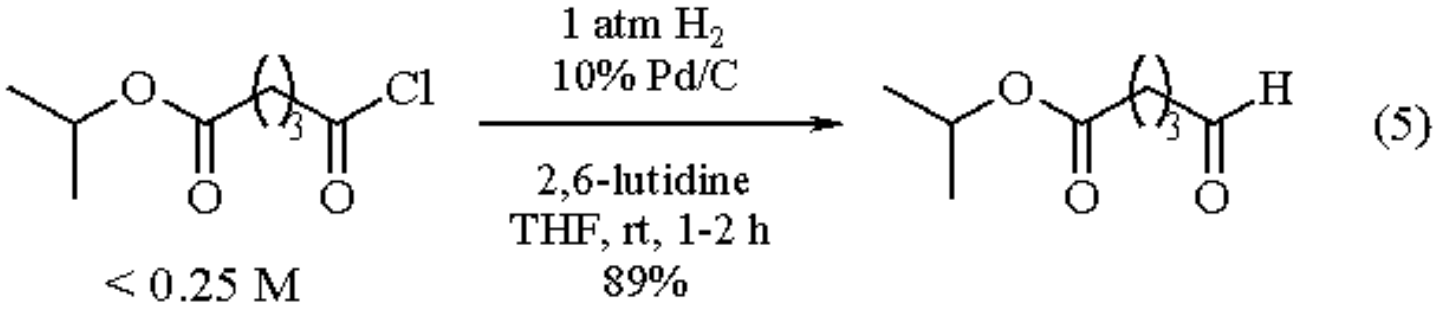

Preparation of Boron Enolates.

Dialkylboryl triflates react with ketones in the presence of a hindered tertiary amine base (typically 2,6-lutidine or ***Diisopropylethylamine***) to afford boron enolates that are useful in stereoselective directed aldol condensation reactions.[15] 2,6-Lutidine is superior to other tertiary amines for the regioselective formation of the more stable 9-BBN boron enolate from alkyl methyl ketones using ***9-Borabicyclononyl Trifluoromethanesulfonate*** (eq 6).[15b,16,17] The 2,6-lutidinium triflate byproduct is presumably sufficiently acidic to facilitate enolate equilibration, resulting in thermodynamically controlled enolate formation.[15b,17] Interestingly, alkyl ethyl ketones are converted under apparently identical conditions to the less substituted boron enolate[18] with relatively high (>10:1) (*Z*) stereoselectivity (eq 7);[17,18] these reactions presumably proceed under kinetic control.[17] An opposite sense of regiocontrol has been observed when preparing dibutylboron enolates rather than 9-BBN enolates from alkyl methyl ketones using ***Di-n-butylboryl Trifluoromethanesulfonate***/2,6-lutidine,[17] although use of the more hindered and basic diisopropylethylamine in place of 2,6-lutidine affords much higher levels of regiocontrol.[17] Poor (*Z*)-dibutylboron enolate stereoselectivity is observed with alkyl ethyl ketones using 2,6-lutidine under kinetic control;[19,20] somewhat improved (>3:1) (*Z*) selectivity is

achieved under thermodynamic control.[20] Much higher (*Z*) stereoselectivity is achieved under strictly kinetic control using diisopropylethylamine as base.[17,19,20]

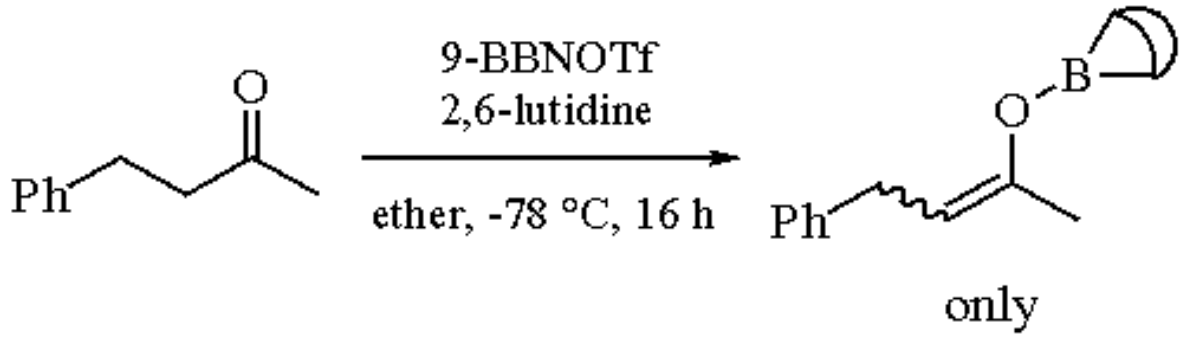

(6)

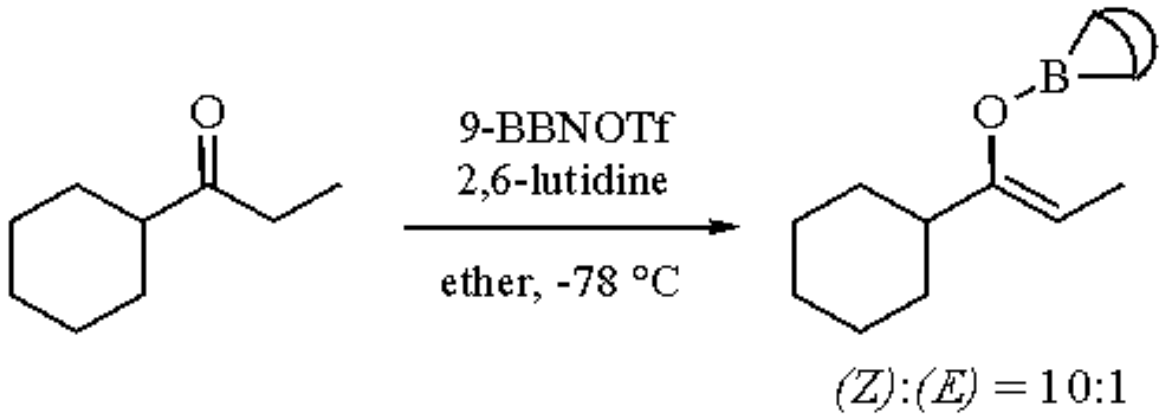

(7)

Radical Cyclopentannulation Reactions.

Zinc*/*Chlorotrimethylsilane-mediated cyclopentannulation reactions, involving the addition of an α-siloxy radical to an alkene or alkyne, are best performed in the presence of 2,6-lutidine, which prevents proton and $ZnCl_2$-catalyzed elimination of the tertiary siloxy group in the immediate product (eq 8).[21]

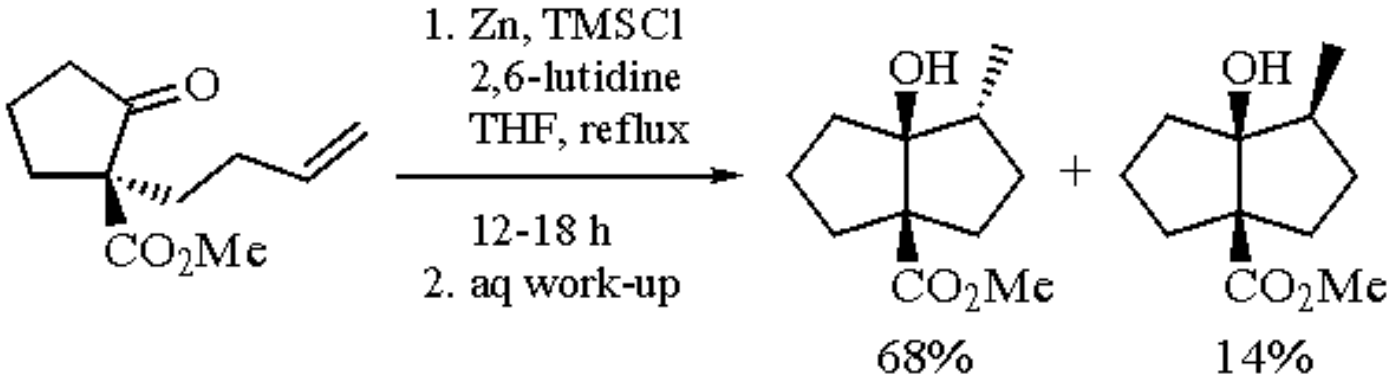

(8)

Oxidation of Allylic Alcohols.

2,6-Lutidine is added to prevent HCl-mediated side reactions during the ruthenium(II)-catalyzed oxidation of allylic alcohols (including labile allylic alcohols such as retinol) to α,β-unsaturated aldehydes using molecular oxygen (eq

9).[22] Other less hindered pyridine derivatives poison the catalyst and are ineffective.

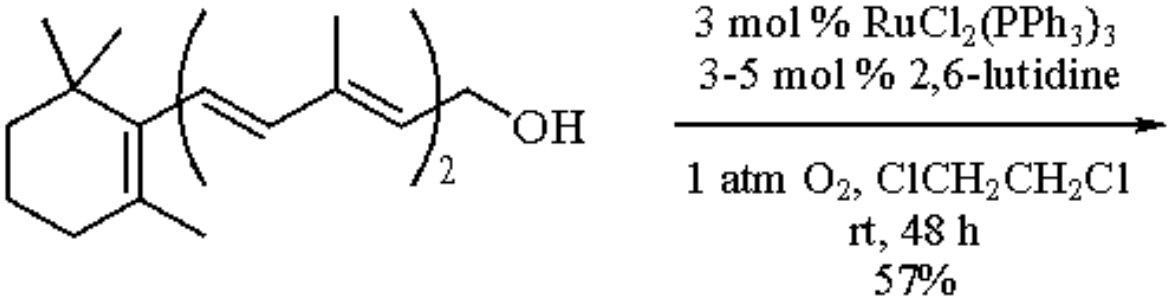

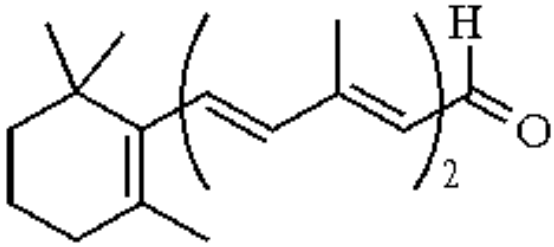

(9)

Bromination of Sensitive Allylic Alcohols.

Preparation of highly labile allyl bromides can be achieved using ***Thionyl Bromide***/2,6-lutidine (eq 10).[23] Virtually no bromide is formed in the absence of 2,6-lutidine.

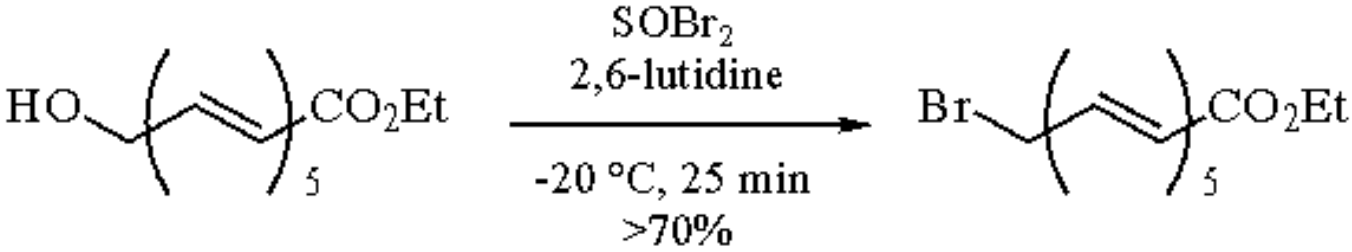

(10)

Related Reagents.

2,4,6-Collidine; ***1,5-Diazabicyclo[4.3.0]non-5-ene***; ***1,8-Diazabicyclo[5.4.0]undec-7-ene***; ***Diisopropylethylamine***; ***Pyridine***; ***Quinoline***; ***Triethylamine***.

---

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Magnesium[1]

Mg

[7439-95-4] · Mg · Magnesium · (MW 24.31)

(formation of organomagnesium compounds; reduction of metal halides; reduction of organic functional groups)

Physical Data: mp 651 °C; bp 1107 °C; *d* 1.74 g cm^{-3}.

Preparative Methods: widely commercially available in forms (most commonly turnings and powders) and in purity (98-99.95%) suitable for many applications in organic synthesis. For some applications magnesium powder or activated magnesium is freshly prepared via the reduction of a magnesium(II) salt or the evaporative deposition of magnesium metal. The commercially available magnesium-anthracene adduct *[86901-19-1]* also provides a highly reactive form of magnesium metal.

Handling, Storage, and Precautions: most freshly prepared magnesium powders and organomagnesium compounds are pyrophoric.

Formation and Reactions of Organomagnesium Compounds.

The carbon-carbon bond forming reactions of organomagnesium (Grignard) reagents via their reaction with carbon electrophiles constitute one of the cornerstones of organic synthesis (eq 1). Much is known about this most famous of organometallic reactions. The mechanisms of Grignard formation[2-13] and reaction[14,15] have been studied extensively. Structural[16,17] and thermochemical[18] data of the organomagnesium compounds have been reported.

$$RX + Mg \longrightarrow [RMgX] \xrightarrow{E^+} RE \qquad (1)$$

Many novel organomagnesium compounds have been prepared. These include dimetallic species[19,20] such as methylenedimagnesium dibromide (see also ***Magnesium Amalgam***)[21] and 1,*n*-(dimagnesio)alkanes such as 1,4-bis(bromomagnesio)pentane, an intermediate which has been used for the stereoselective conversion of esters to *trans*-1,2-disubstituted cyclopentanols (eq 2).[22] Remarkably, even a soluble trimagnesium compound was recently prepared under relatively routine reaction conditions (eq 3).[23]

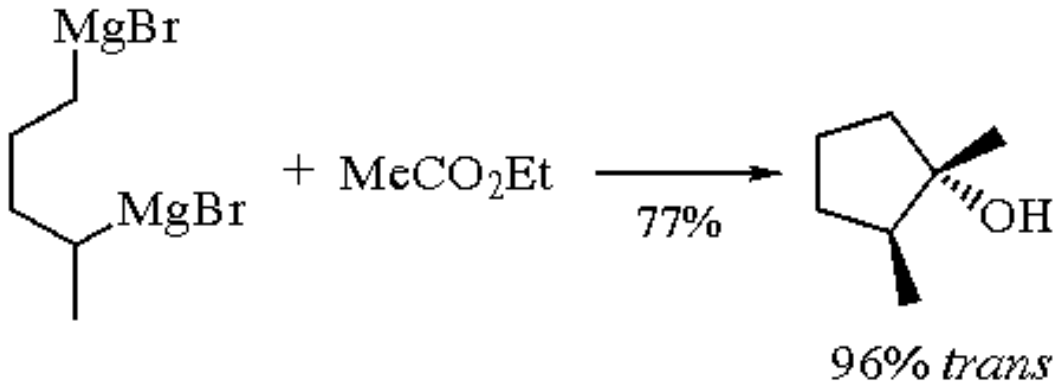

(2)

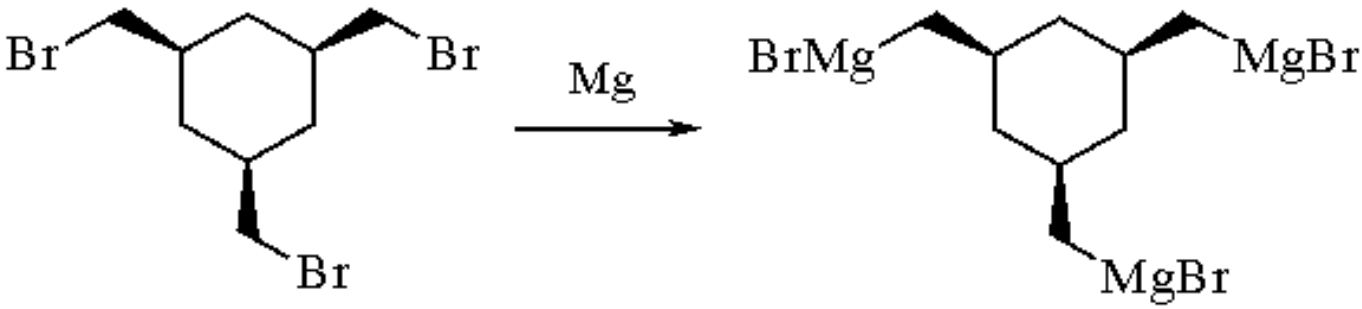

(3)

The form of the magnesium metal employed is often critical to the successful formation of the organomagnesium reagent. For simple primary or secondary alkyl bromides or iodides, and simple aryl or vinyl bromides or iodides, commercially available magnesium turnings or powders of modest purity (>98%) are often suitable. If necessary, activating the surface of the magnesium with iodine,[1,24] dibromoethane,[1,25] or ultrasound[26] treatment, or employing ultrapure magnesium metal,[27] is usually sufficient to facilitate Grignard reagent formation with such substrates. In the case of many organochlorine or organofluorine compounds, as well as unreactive bromides and iodides, a more reactive form of magnesium must be employed. Three practical methods have been developed for the preparation of highly reactive magnesium (active magnesium) for use in organic synthesis. A highly reactive magnesium slurry is prepared via the evaporative deposition of magnesium in THF using a relatively simple preparative apparatus.[28-30] Magnesium halides are reduced by ***Potassium*** metal,[31,32] or better ***Lithium Naphthalenide***,[33,34] to afford an active magnesium powder often referred to as Rieke magnesium. Magnesium metal can be activated by treatment with anthracene,[35] or the magnesium-anthracene adduct,[36] which is in equilibrium with the finely divided metal powder, can be used directly.

The formation of allyl or benzylic Grignard species is often accompanied by dimerization of the allylic or benzylic halide. Indeed, this reductive dimerization can be preparatively useful using the classical Grignard-forming reaction conditions,[37] but to avoid it, an active magnesium is typically employed.[38,39] Oppolzer[40] reported a comparison of the three methods discussed above in a 1984 study of the metallo-ene reaction. The magnesium variant of the metallo-ene reaction[41] features the formation and subsequent cycloisomerization of an allylmagnesium chloride from an allylic chloride. As shown in eq 4, magnesium-mediated cyclization and trapping with the electrophilic oxygen source ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** (i.e. MoOPH) proceeds in 55% yield with magnesium slurry prepared by evaporative deposition, in 55% yield with Rieke magnesium, and in 56% yield with magnesium-anthracene.

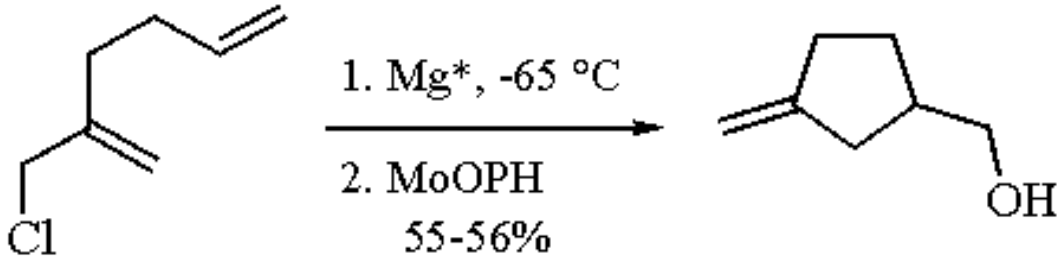

(4)

The extent to which these activated forms of magnesium have expanded the range of substrates suitable for formation of organomagnesium species cannot be overemphasized. For example, alkyl fluorides are very poor substrates for the classical Grignard conditions. In contrast, treatment of octyl fluoride with Rieke magnesium[32,34] affords the corresponding organomagnesium reagent which reacts with ***Carbon Dioxide*** in 89% yield (eq 5). The chloride shown in eq 6 is benzylic, thus prone to dimerization with classical magnesium sources, and requires formation of a dianionic intermediate. Magnesium powder is reported to afford the diorganomagnesium species in only 43% yield. In contrast, the dichloride reacts with magnesium-anthracene in 92% yield.[36,42] Cyclopropylmethyl compounds are prone to rearrange via ring opening to the *n*-butenyl isomers. Formation of the Grignard reagent from cyclopropylmethyl bromide under classical conditions followed by trapping with carbon dioxide affords 4-pentenoic acid (eq 7). In contrast, treatment of cyclopropylmethyl bromide at -78 °C with the magnesium slurry prepared via evaporative deposition affords mostly cyclopropylacetic acid (92% of the product mixture, 78% yield) after trapping with carbon dioxide.[28]

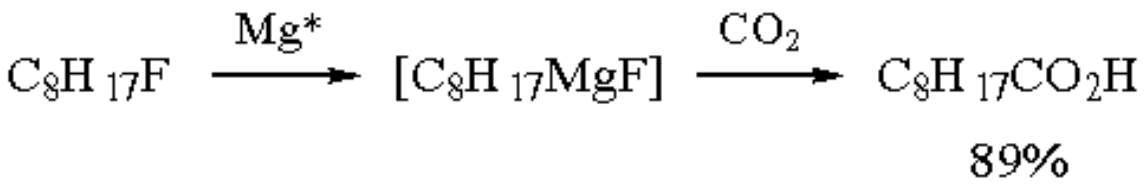

(5)

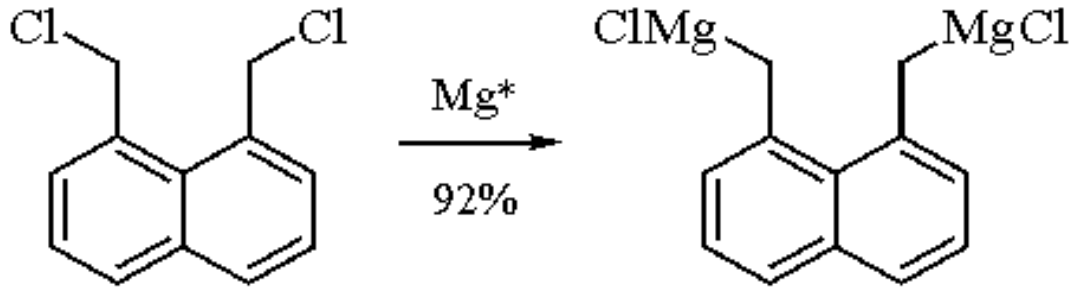

(6)

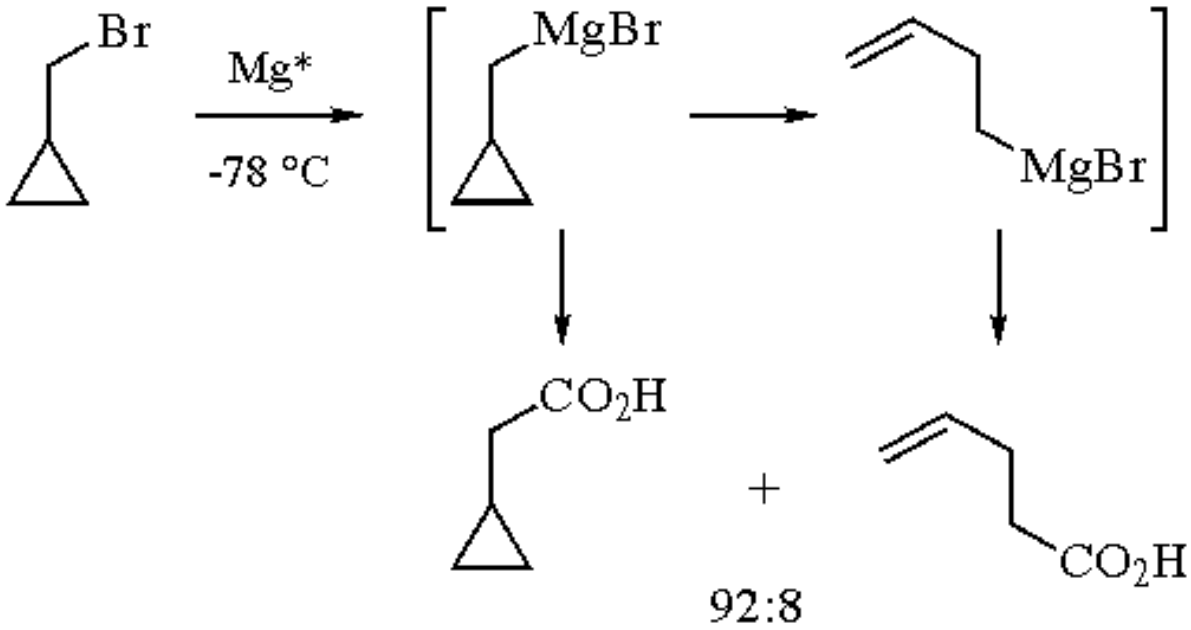

(7)

The chemistry of organomagnesium compounds is extraordinarily rich and diverse. It is impossible to detail comprehensively their many reactions with classical organic electrophiles (e.g. aldehydes, ketones, carboxylic acid derivatives, carbon dioxide, C-N multiple bonds, epoxides, alkyl halides, etc.) within the space limitations here. Fortunately, several standard texts give a good account of these procedures.[43,44] The following paragraphs highlight several of the many less routine uses of these reagents. For example, in addition to the reaction with traditional carbonyl electrophiles, organomagnesium reagents add efficiently to certain mixed orthoformates to afford acetals. For example (eq 8), *n*-butylmagnesium bromide adds to phenyl diethyl orthoformate in 90% yield.[45]

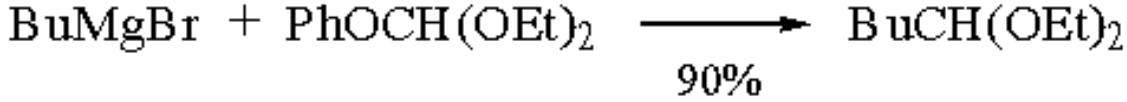

(8)

The one-pot combination of alkyl halide, magnesium metal, and carbon electrophile is often referred to as the Barbier reaction.[46] This strategy is particularly appropriate for the cyclization of substrates containing both reacting partners within their structure. The intramolecular reaction of halo ketones can afford cyclized products, but often in only modest-to-good yield with magnesium.[47] For example (eq 9), the cycloheptanone derivative cyclizes to the hydroazulene ring skeleton in 54% yield. Lithium/ultrasound,[48,49] ***Lithium***, ***Tin(II) Chloride***,[50] and ***Samarium(II) Iodide***[51] may offer suitable alternative reagents for such cyclizations.

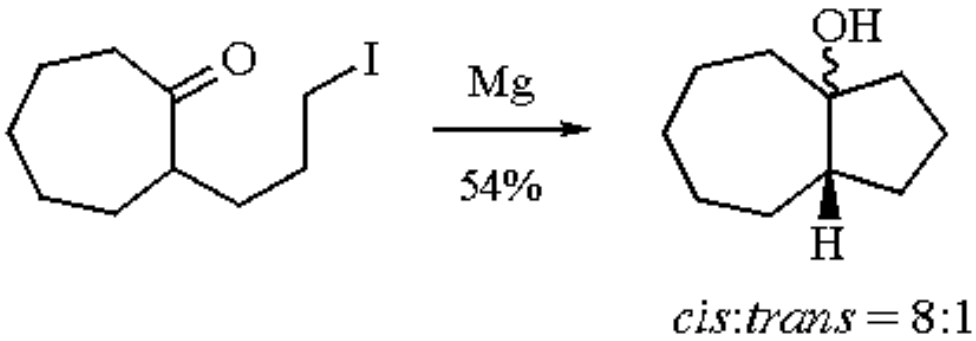

(9)

The complementary magnesium-mediated cyclizations of cyanoiodoalkanes can be an efficient reaction. For example, the iodonitrile shown (eq 10) undergoes magnesium-mediated cyclization to form the relatively sterically congested 2,2-

disubstituted cyclohexanone in 71% yield.[52]

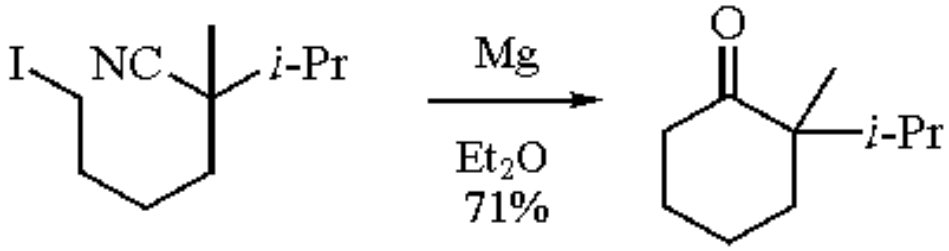

(10)

Magnesium is an alternative to zinc metal for effecting the Reformatsky reaction and has been used in the synthesis of β-keto esters.[53] For example (eq 11), *t*-butyl bromoacetate is condensed with cyclohexanone in 80% yield.[54]

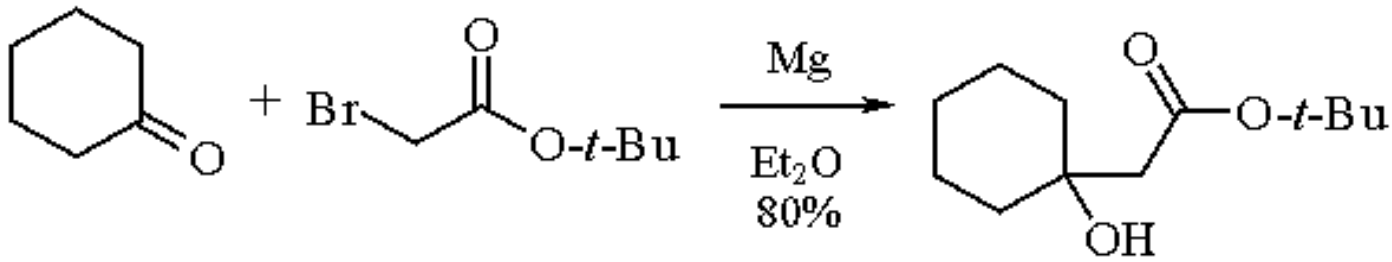

(11)

Organomagnesium species can effect the carbometalation of alkenes and alkynes.[55,56] The more common variants, however, are the copper-catalyzed reactions, a subject which has been comprehensively reviewed by Lipshutz and Sengupta.[57] For example (eq 12), the ***Ethylmagnesium Bromide*/*Copper(I) Bromide*** combination effects net *syn* addition across 1-octyne. The resulting alkenyl metal species can be stereospecifically trapped by a variety of electrophiles, including ***Allyl Bromide*** (85%) and 1-heptene oxide (94%).[58] This reaction constitutes a useful stereoselective alkene synthesis. ***Dichlorobis(cyclopentadienyl)titanium*** also catalyzes the net *syn* addition of organomagnesium reagent across alkynes.[59] (See also the corresponding organolithium and organocopper compounds for alternative reagents.[57])

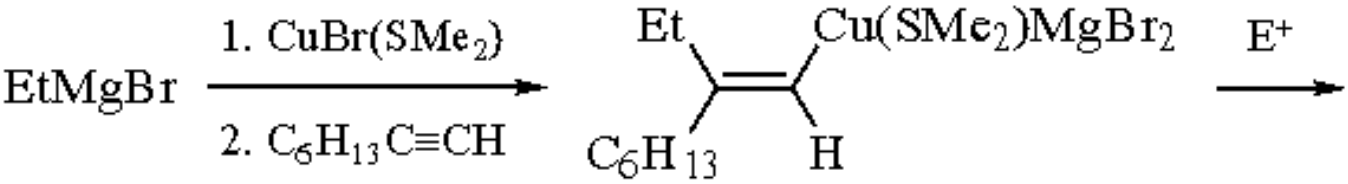

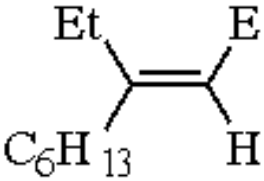

(12)

$E = CH_2CH{=}CH_2$ (85%)
$CH_2CH(OH)C_5H_{11}$ (94%)

Organomagnesium reagents undergo efficient copper-catalyzed conjugate addition reactions.[57] For example (eq 13), *n*-butylmagnesium bromide undergoes CuBr-Me_2S-catalyzed addition to acrolein in the presence of ***Chlorotrimethylsilane*** and ***Hexamethylphosphoric Triamide*** (HMPA) to afford the (*E*)-silyl enol ether in 89% yield (96% *E*).[60]

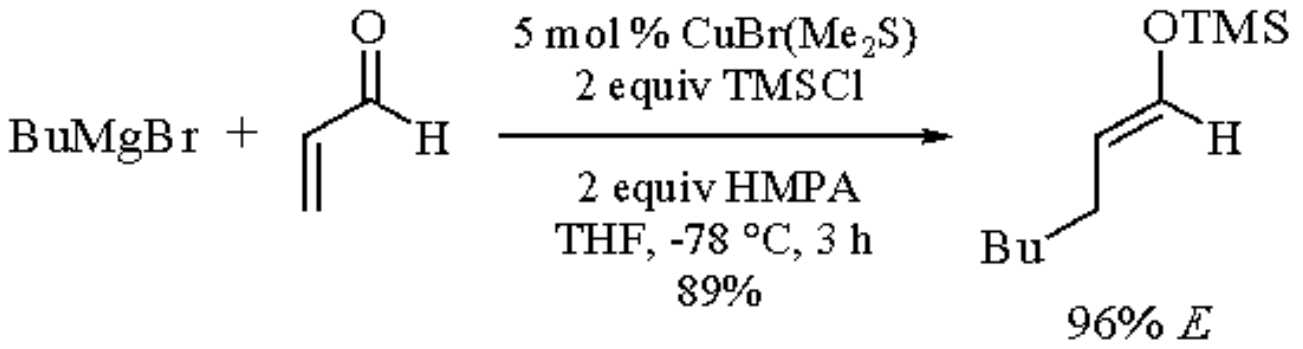

(13)

Organomagnesium reagents undergo copper-catalyzed reaction with alkyl, allyl, vinyl, and aryl halides or sulfonates, and with epoxides.[57] For example (eq 14), *n*-butylmagnesium bromide undergoes copper-catalyzed substitution of the propargyl methyl ether to afford an allene.[61] The substitution proceeds in high chemical yield and with good stereochemical control.

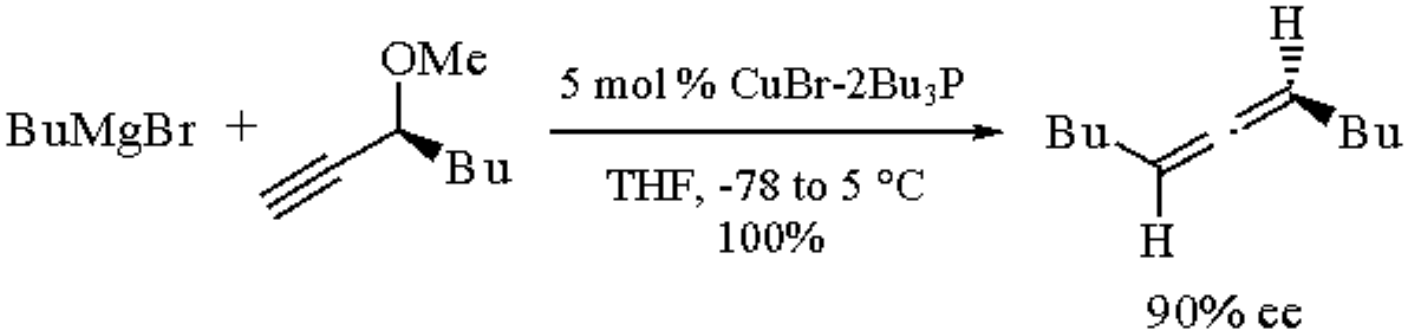

(14)

A number of other transition metals catalyze interesting reactions of organomagnesium reagents.[59,62] Of particular novelty is the titanium-catalyzed hydromagnesiation of alkenes. For example (eq 15), vinylcyclohexanol transmetalates with ethylmagnesium bromide in the presence of catalytic Cp_2TiCl_2 to afford, after capture by carbon dioxide, the γ-lactone shown in 58% yield.[63-65]

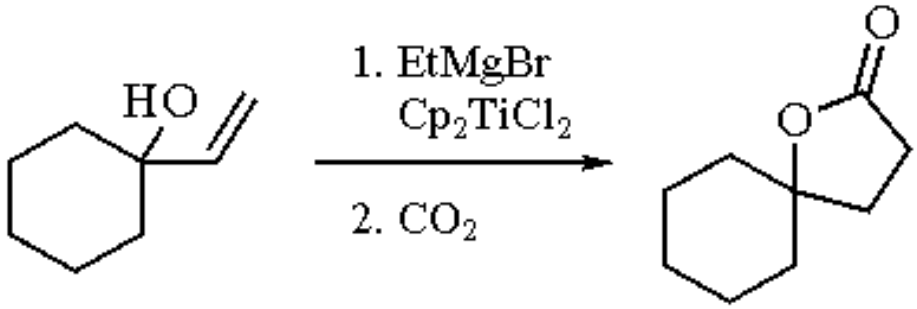

(15)

Reductions with Magnesium.

Magnesium is a common agent for reducing a variety of transition metal salts,[66-68] for example the reduced titanium reagent (***Titanium(IV) Chloride***-Mg) used widely in carbonyl coupling reactions.[69] Magnesium itself effects the reductive dimerization (pinacol coupling) of ketones[70] and enones[71] (see also ***Magnesium Amalgam*** and $TiCl_4$-Mg). Magnesium effects the reductive dimerization of organotin oxides[72] (eq 16) and dialkylantimony bromides (eq 17).[73]

$$(i\text{-Bu})_3\text{SnOSn}(i\text{-Bu})_3 \xrightarrow[82\%]{\text{Mg, THF}} (i\text{-Bu})_3\text{SnSn}(i\text{-Bu})_3 \qquad (16)$$

$$2\ \text{Bu}_2\text{SbBr} \xrightarrow{\text{Mg, THF}} \text{Bu}_2\text{SbSbBu}_2 \qquad (17)$$

Magnesium has been used for the reduction of 1,1-dibromoalkanes,[74] although reductive dimerization has been found to compete in some cases,[75,76] and in the formation of $Ph_3P{=}CCl_2$ from triphenylphosphine and carbon tetrachloride.[77] Magnesium has been used as an alternative to ***n-Butyllithium*** or lithium amalgam for the conversion of 1,1-dibromoalkenes to alkynes (eq 18).[78]

$$\text{RCHO} \xrightarrow[\text{CBr}_4]{\text{Ph}_3\text{P}} \text{RCH}{=}\text{CBr}_2 \xrightarrow[\substack{65\ ^\circ\text{C}\\ 75\text{-}95\%}]{\text{Mg, THF}} \text{RC}{\equiv}\text{CH} \qquad (18)$$

Magnesium reacts with amines to form magnesium amides,[79] and with alcohols to form magnesium alkoxides. In the latter context, magnesium has been used as a drying agent for alcohols,[80] but the combination of magnesium-methanol has also found significant utility as a selective reducing agent for certain organic functional groups (e.g. conjugated ketones, esters, nitriles, amides).[81] The combination of ***Cadmium Chloride***-magnesium in aqueous THF also shows interesting selective functional group reductions, e.g. the selective 1,2-reduction of enones (eq 19) and the selective reduction of an epoxide in the presence of an allylic acetate (eq 20).[82,83]

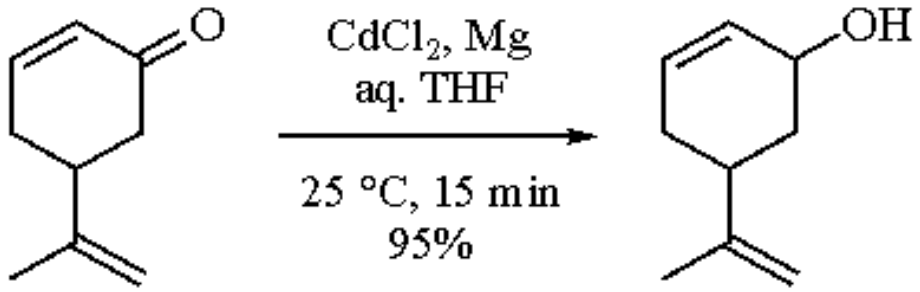

(19)

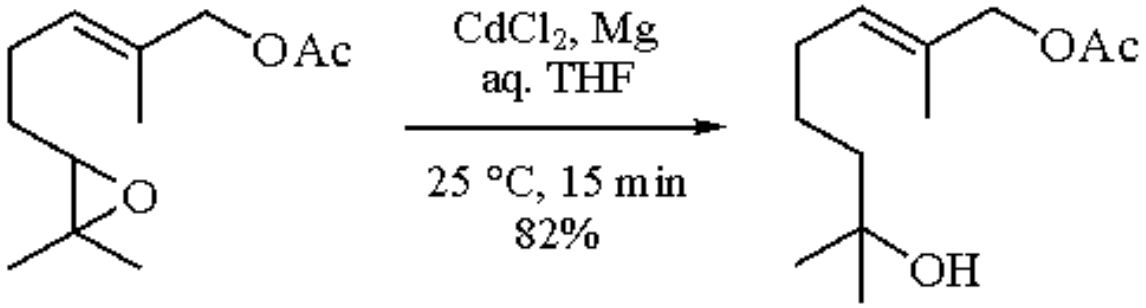

(20)

The combination of magnesium-***Chlorotrimethylsilane*** has been used for the reductive silylation of 1,1-dibromides,[84]

conjugated trienes,[85] heterocycles,[86] and, as shown in eq 21, certain chloro-substituted enynes.[87] Magnesium has been also used as a reactive metal electrode in an electroreductive silylation of alkenes.[88]

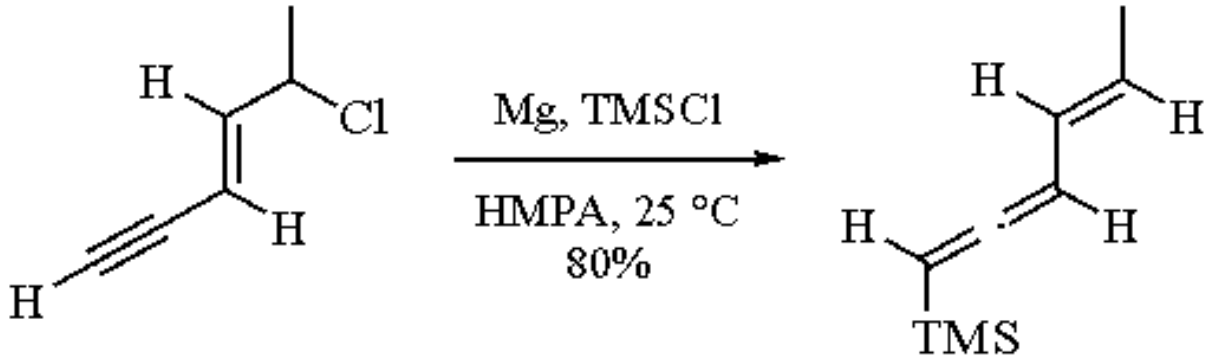

(21)

1,3-Dienes form reactive complexes with magnesium.[89] In this capacity, active magnesium has been used for the reductive silylation and dialkylation of certain conjugated 1,3-dienes. For example (eq 22), treatment of 1,4-diphenyl-1,3-butadiene with Rieke magnesium affords the magnesium-diene complex. Addition of ***Dichlorodimethylsilane*** affords the *cis*-diphenylsilacyclopentene in 66% yield.[90]

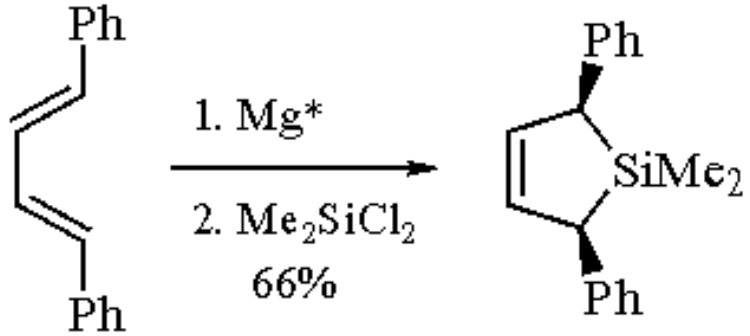

(22)

Related Reagents.

Tetrachloro(*η^5*-cyclopentadienyl)niobium-Magnesium.

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Magnesium Amalgam

Mg(Hg)

[37237-15-3] · Mg · Magnesium Amalgam

(reduction of metal halides, particularly for the synthesis of organometallic compounds; preparation of a reduced titanium species from $TiCl_4$ that is useful for the reductive dimerization of ketones, aldehydes, their derived imines, and the chemoselective reduction of nitro groups; preparation of bis(bromomagnesio)methanes; reductive dimerization of germane derivatives; deoxygenation of epoxides)

Preparative Methods: prepared fresh, or generated in situ, from ***Magnesium*** metal and typically 1-3 mol % of a mercury(II) salt such as ***Mercury(II) Chloride*** in THF or aromatic hydrocarbon solvent.

Handling, Storage, and Precautions: mercury salts are toxic. Proper disposal is required.

Reductions and Reductive Dimerizations.

Mg(Hg) is the classical reagent for the reductive dimerization of acetone to form pinacol,[1] and still finds occasional use in that regard.[2,3] More recently, the pinacol coupling has been effected by the combination of ***Titanium(IV) Chloride*** and 2 equiv of Mg(Hg).[4] For example, using the latter mixture, cyclohexanone is dimerized in 93% yield (eq 1). The intramolecular dimerization can be facile, as illustrated by the reductive cyclization of 2,5-hexanedione to the *cis*-cyclobutanediol (eq 2), and the intramolecular ketoaldehyde cross coupling illustrated in eq 3. Other reagents for pinacol-type coupling of carbonyl derivatives include a variety of reduced titanium reagents,[5-7] ***Samarium(II) Iodide***,[8] Niobium Trichloride,[9] and ***Aluminum Chloride-Zinc-Acetic Acid***.[10]

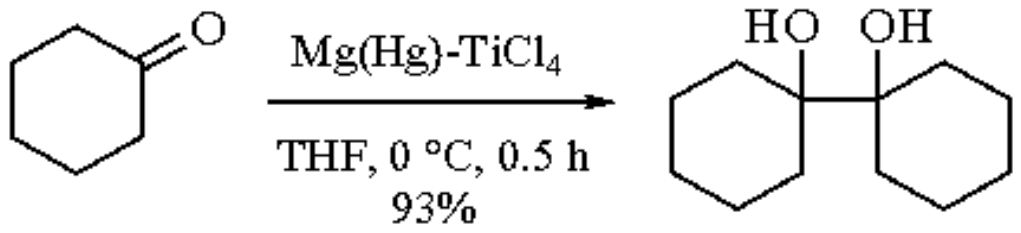

(1)

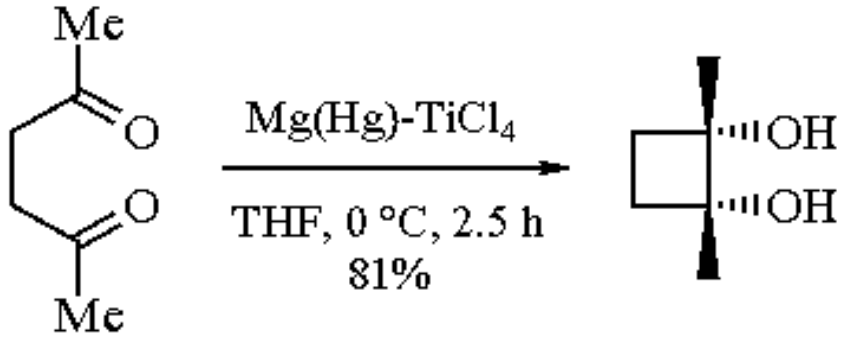

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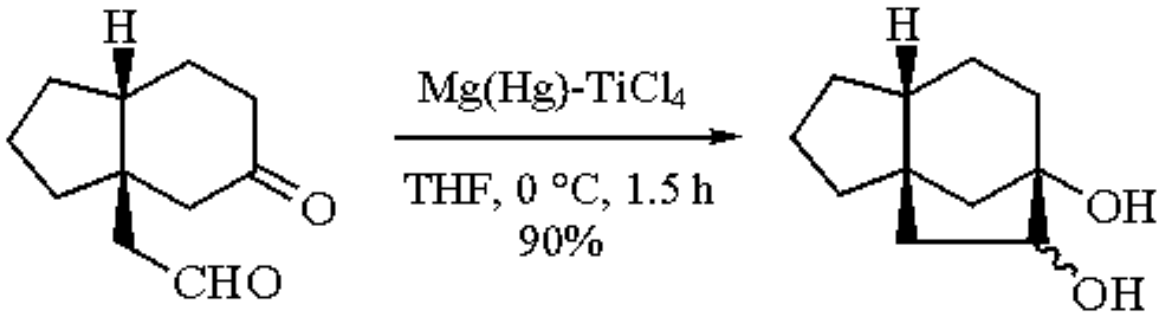

(3)

The Mg(Hg)-$TiCl_4$ mixture is also an effective reagent for the stereoselective reductive dimerization of aldimines to 1,2-diamines.[11,12] For example (eq 4), treatment of the aldimine derived from benzaldehyde leads to a 80:20 mixture of *syn* (±) and *anti* (*meso*) isomers in 63% yield. Simple reduction of the aldimine competes with the dimerization. Similarly, the *N*-benzylimine derived from acetaldehyde affords a 90:10 *syn*:*anti* mixture in 67% yield. Other reagents for the reductive dimerization of imines include $TiCl_4$-Mg,[13] SmI_2,[14,15] ***Niobium(IV) Chloride***,[16] ***Indium***,[17] ***Ytterbium(0)***,[18] and ***Zinc***.[19]

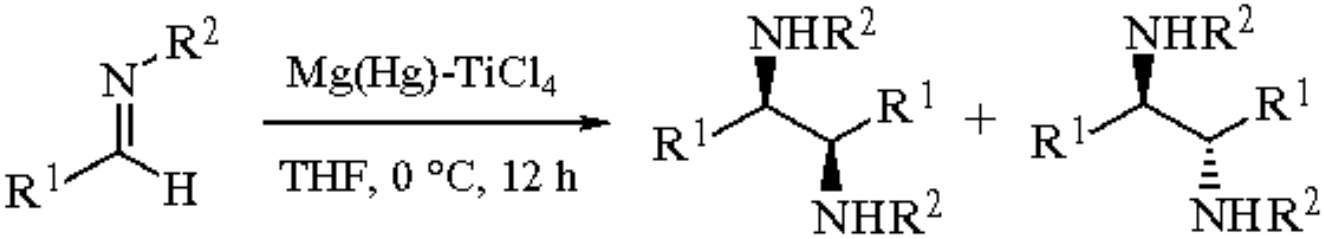

(4)

(a) R = Ph, R^2 = Me (63%)
(b) R^1 = Me, R^2 = CH_2Ph (67%)

syn (±) *anti (meso)*

Rivière and Satge[20] reported the Mg(Hg)-mediated reductive dimerizations of organogermanes. For example (eq 5), treatment of phenylchlorogermane with Mg(Hg) (THF, 20 °C) affords the diphenyl-1,2-digermane in 75% yield. Similarly, diphenylchlorogermane affords tetraphenyl-1,1,2,2-digermane in 73% yield.

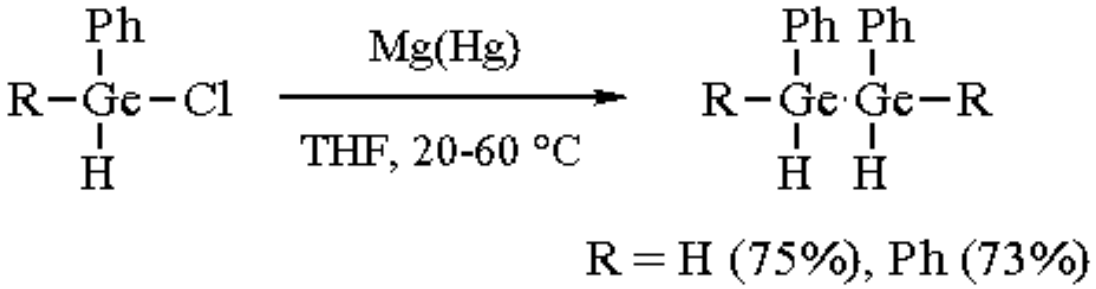

The Mg(Hg)-$TiCl_4$ mixture is an effective reagent for the chemoselective reduction of the nitro group.[21] For example (eq 6), chloro-, cyano-, and carboxy-substituted nitro aromatics are each reduced in high yield by the Mg(Hg)-$TiCl_4$ mixture (THF-*t*-butanol, 0 °C, 1 h). Aliphatic nitro compounds are also efficiently reduced. Others have used this procedure successfully.[22 -24] Other reagents for this transformation include ***Titanium(III) Chloride***,[25] $TiCl_4$-Te(*i*-Bu)$_2$,[26] $TiCl_4$-***Sodium Borohydride***,[27] ***Palladium on Carbon-Ammonium Formate***,[28] ***Raney Nickel-Hydrazine***,[29] ***Chromium(II) Chloride***,[30] ***Tin(II) Chloride***,[31] and ***Nickel Boride*** (Ni_2B).[32]

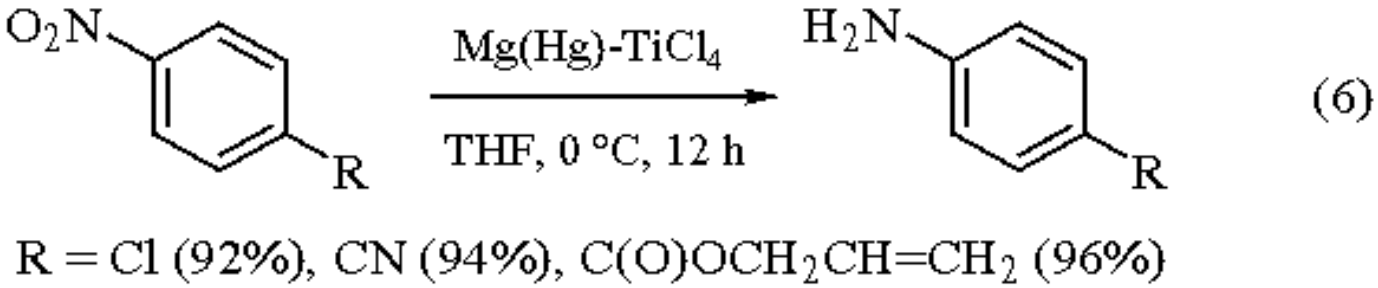

Mg(Hg) has been used occasionally for the reduction of 1,2-dihalides[33] and enones,[34] and has been extensively used for the preparation of reduced organometallic complexes.[35-40]

Preparation of 1,1-Diorganometallic Reagents.

Mg(Hg) has been widely used for the preparation of 1,1-dimagnesium reagents[41] by reaction with methylene dibromides and diiodides. For example (eq 7), Cainelli and co-workers[42] found that treatment of ***Dibromomethane*** or ***Diiodomethane*** with Mg(Hg) affords a solution of organomagnesium reagent. Bis(bromomagnesio)methane reacts with CO_2 to afford the malonic acid and with aldehydes and ketones to give alkenes. This reagent has found use in organic synthesis[43-47] and offers an alternative to ***Methylenetriphenylphosphorane***, ***Trimethylsilylmethyllithium***, ***Trimethylsilylmethylmagnesium Chloride***, the Tebbe reagent (μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***), dimethyltitanocene (***Bis(cyclopentadienyl)dimethyltitanium***),[48] CH_2I_2-$CrCl_2$,[49] CH_2I_2-Zn-Me_3Al,[50] CH_2I_2-Zn-$TiCl_4$,[51,52] and $CH_2(AlR_2)_2$,[53] reagents. Similarly, Mg(Hg) has been used for the preparation of the 1,1-dimagnesium species bis(bromomagnesio)trimethylsilylmethane[54] and bis(bromomagnesio)bis(trimethylsilyl)methane.[55]

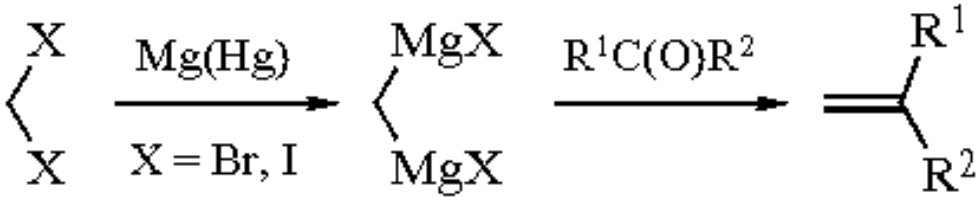

(7)

$R^1 = C_{11}H_{23}$, $R^2 = H$ (65%)
$R^1 = Ph$, $R^2 = H$ (70%)
$R^1, R^2 = -(CH_2)_5-$ (68%)

Bickelhaupt and co-workers[56] reported the use of bis(bromomagnesio)methane as a reagent for the preparation of 1,3-dimetallacyclobutanes. For example (eq 8), treatment of bis(bromomagnesio)methane (prepared using Mg(Hg) as described above) with Cp_2TiCl_2 and ***Dichlorodimethylsilane*** affords the novel mixed 1,3-dimetallacyclobutane in quantitative yield.

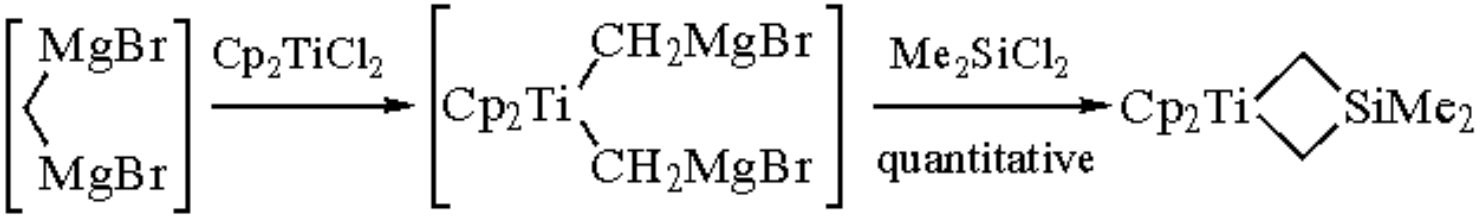

(8)

Miscellaneous.

Mg(Hg) has been used in combination with ***Magnesium Bromide*** as a reagent for the deoxygenation of epoxides.[57] Yields are typically modest, for example 50% for the formation of cyclohexene from cyclohexene oxide, and several good alternative reagents are available for this transformation.[58]

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Magnesium Bromide

$MgBr_2$

($MgBr_2$)

[2923-28-6] · Br_2Mg · Magnesium Bromide · (MW 184.11) ($MgBr_2.6H_2O$)

[13446-53-2] · $H_{12}Br_2MgO_6$ · Magnesium Bromide · (MW 292.23) ($MgBr_2.OEt_2$)

[29858-07-9] · $C_4H_{10}Br_2MgO$ · Magnesium Bromide Diethyl Etherate · (MW 258.25)

(Lewis acid capable of catalyzing selective nucleophilic additions,[1] cycloadditions,[2] rearrangements,[3] coupling reactions;[4] effective brominating agent[5])

Physical Data: mp 165 °C (dec) (etherate >300 °C; fp 35 °C).

Solubility: sol alcohol, H_2O; etherate sol common organic solvents.

Form Supplied in: white solid, widely available; etherate gray solid.

Preparative Method: the etherate is easily prepared from reacting a slight excess of ***Magnesium*** turnings with ***1,2-Dibromoethane*** in anhydrous diethyl ether.[13]

Handling, Storage, and Precautions: etherate is flammable and moisture sensitive; freshly prepared material is most reactive and anhydrous. Irritant.

Nucleophilic Additions.

$MgBr_2$ has been shown to form discrete bidentate chelates with various species,[6] particularly α- and/or α,β-alkoxy carbonyl compounds,[7] and thus functions as a diastereofacial control element in many nucleophilic addition reactions. In many cases, its inclusion completely reverses the nonchelation-controlled stereochemistry observed with nonchelating Lewis acids such as ***Boron Trifluoride Etherate***. Highest diastereoselectivity is observed with α-substituted aldehydes (eq 1).[8] High selectivities are observed for β-alkoxy aldehydes as well, including cases where three contiguous chiral centers are defined during the reaction (eq 2).[9]

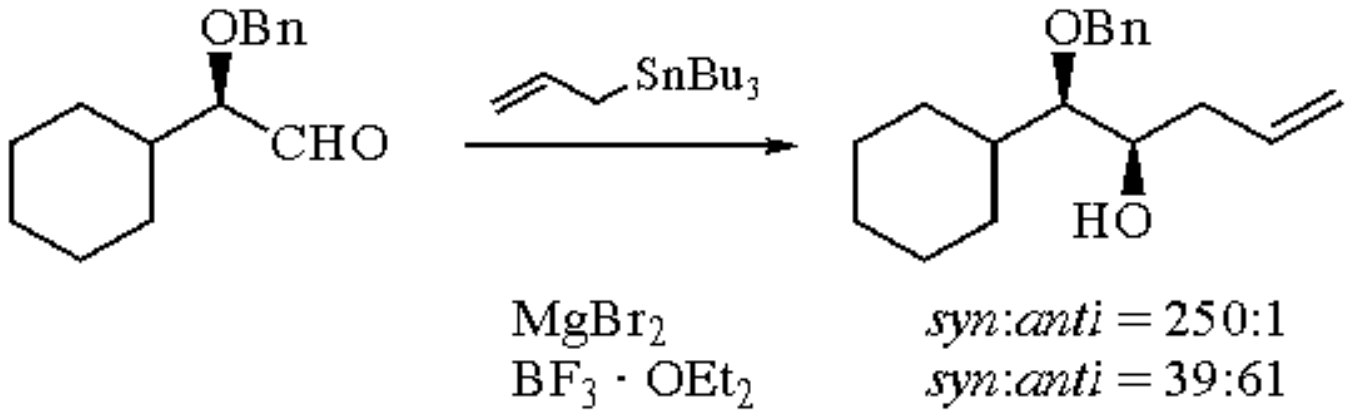

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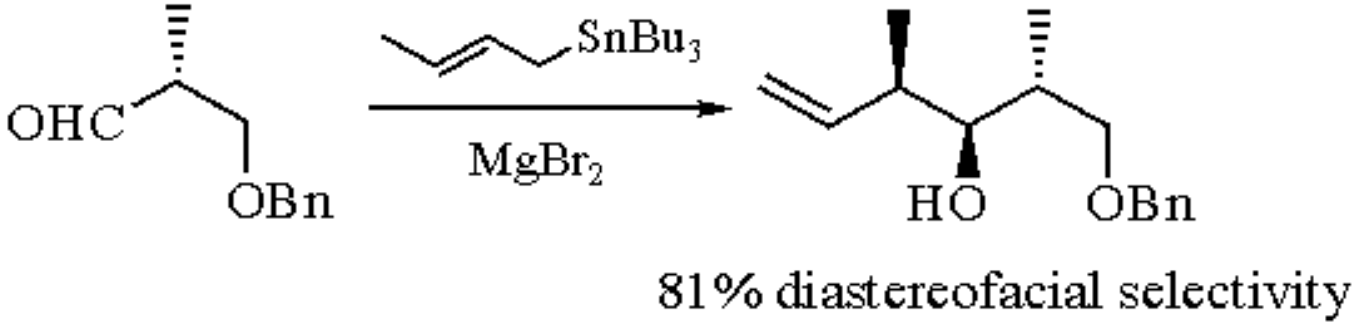

(2)

Nucleophilic additions to α,β-dialkoxy aldehydes via allyl silanes (eq 3)[10] or silyl ketene acetals (Mukaiyama reaction) (eq 4)[11] exhibit similarly high selectivities. α-Thio aldehydes also react under $MgBr_2$-catalyzed Mukaiyama conditions with efficient stereocontrol (eq 5).[1]

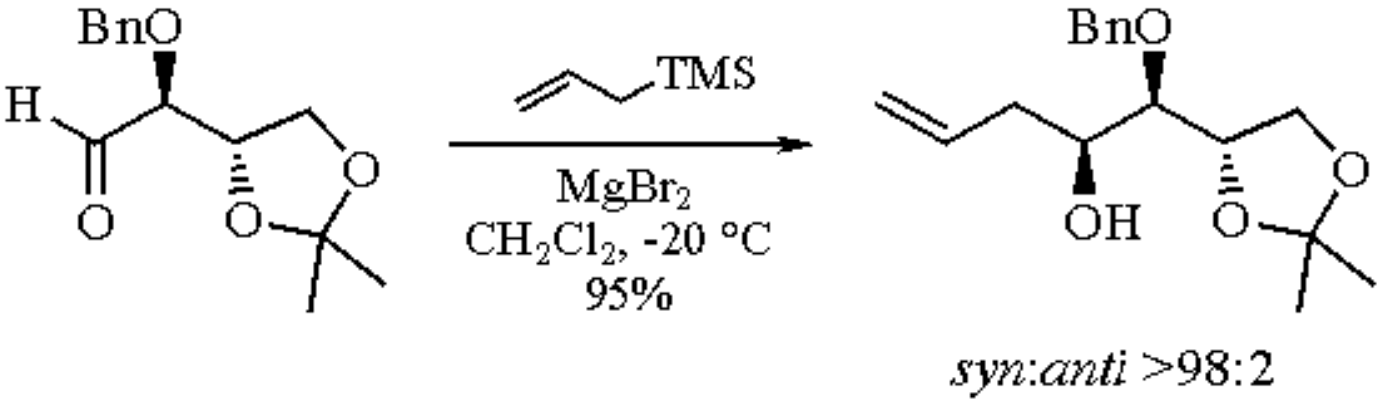

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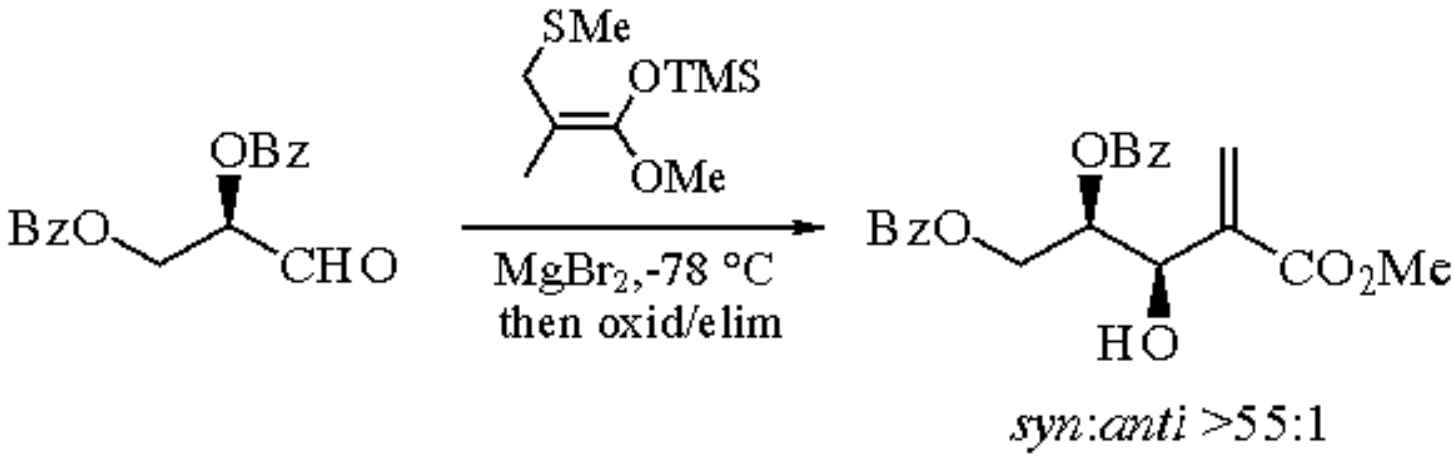

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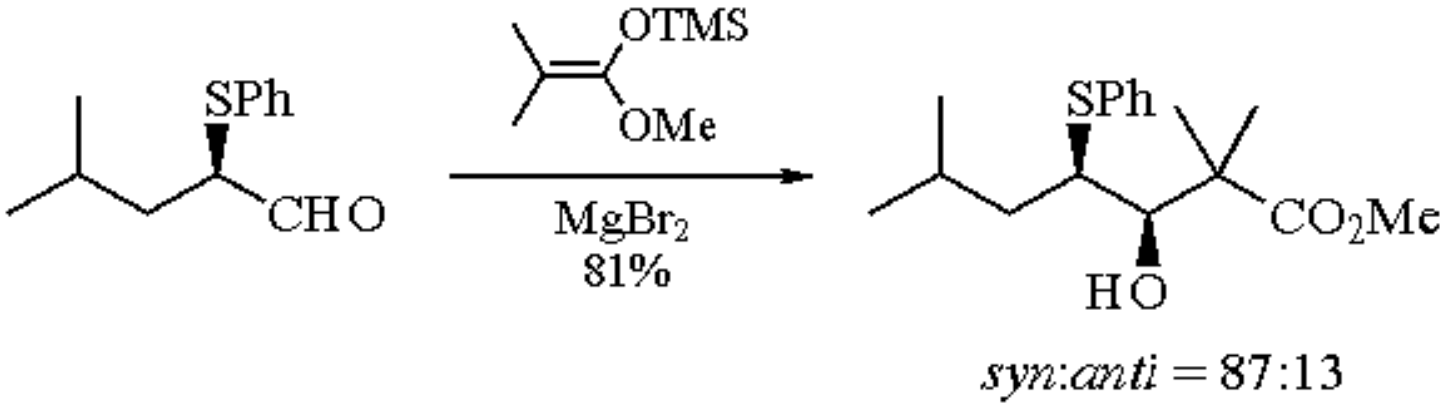

(5)

Rearrangements.

The oxophilic nature of $MgBr_2$ renders it effective in mediating many rearrangements wherein polarization of a C-O bond initiates the process. A classic application involves the conversion of an epoxide to an aldehyde (eq 6).[12]

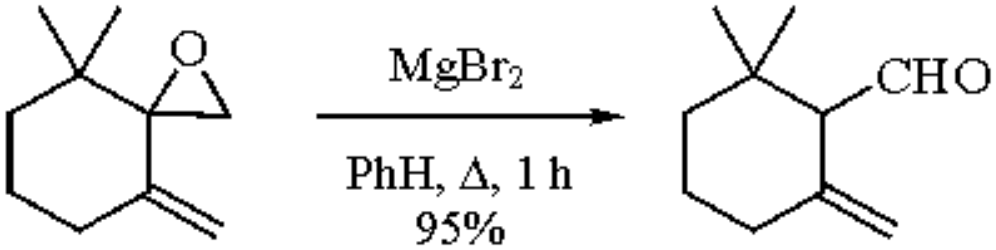

(6)

β-Lactones, when treated with $MgBr_2$, undergo ionization with further rearrangement to afford either butyrolactones or β,γ-unsaturated carboxylic acids (eq 7).[3] The reaction course is dependent upon whether the cation resulting from lactone ionization can rearrange to a more or equivalently stable cation, in which case ring expansion is observed. If the β-lactone bears an α-chloro substituent, ring expansion is accompanied by elimination of HCl to afford butenolides (eq 8).[13]

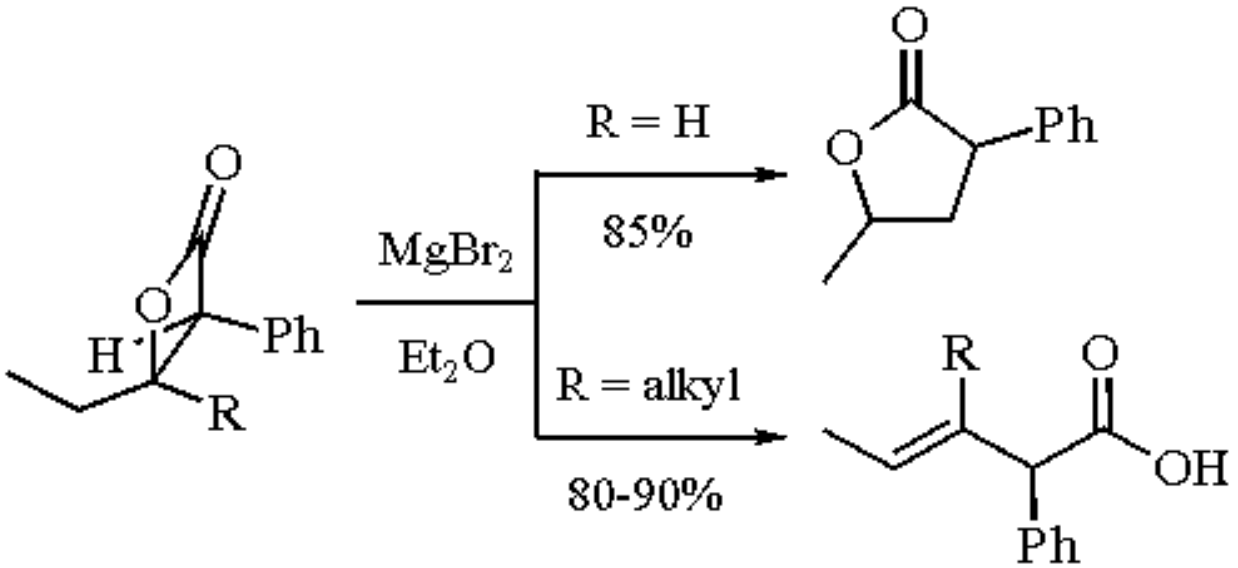

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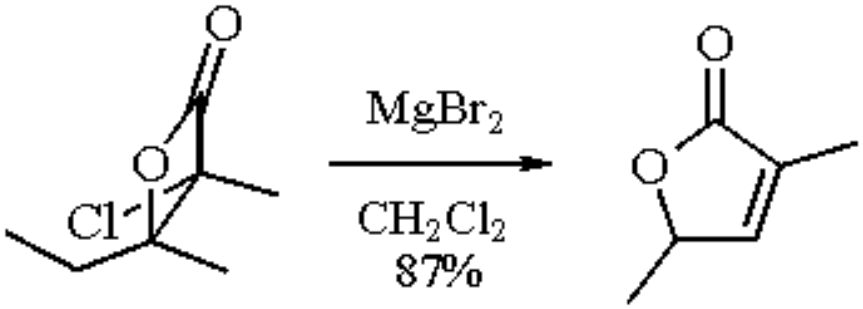

(8)

Cycloadditions.

The $MgBr_2$-mediated cyclocondensation of a Danishefsky-type diene with chiral α-alkoxy aldehydes affords a single diastereomer, which reflects a reacting conformer in which the alkoxy group is *syn* to the carbonyl, which is then attacked from its less-hindered face (eq 9).[2] The cycloaddition of ynamines with cycloalkenones occurred selectively at the carbonyl, while in the absence of $MgBr_2$ reaction at the alkene C=C bonds was observed (eq 10).[14]

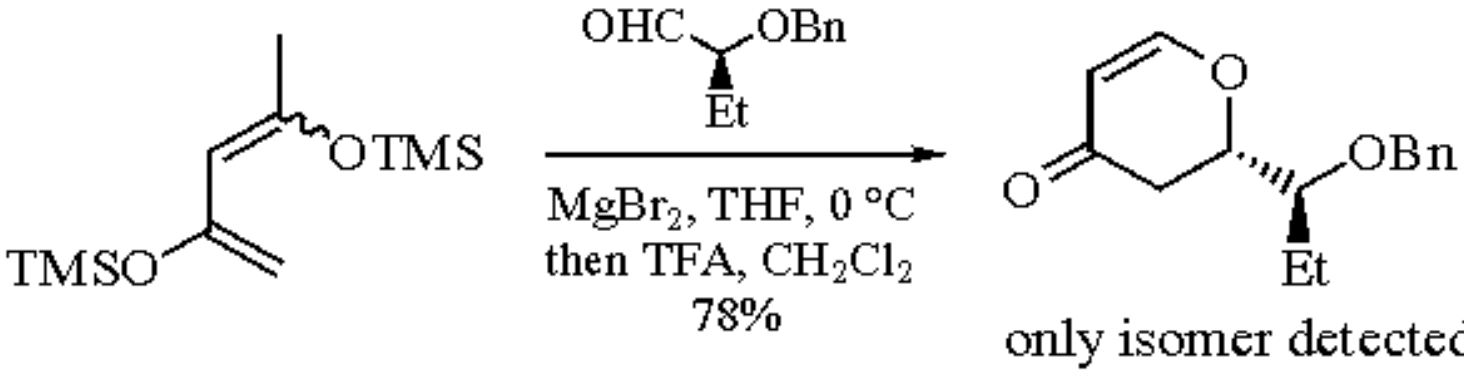

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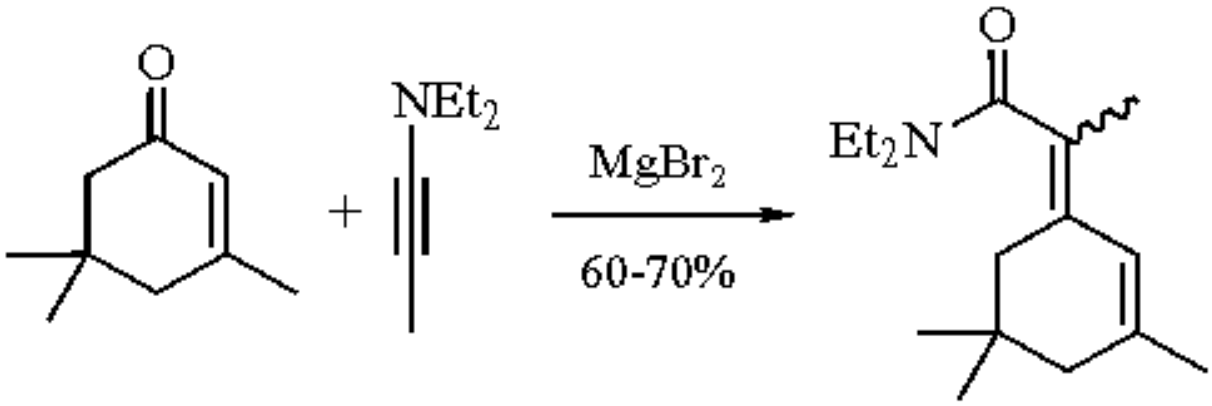

(10)

Organometallic Reactions.

$MgBr_2$ often increases the yields of Grignard reactions, as in the synthesis of cyclopropanols from 1,3-dichloroacetone (eq 11).[15] It also serves to form Grignard reagents in situ via first lithiation followed by transmetalation with $MgBr_2$. This technique enables the formation of vinyl Grignards from vinyl sulfones (eq 12),[16] and of α-silyl Grignard reagents from allyl silanes (eq 13).[17] In the latter case, the presence of $MgBr_2$ provided regioselectivity at the α-position; without it, substitution at the γ-position was predominant.

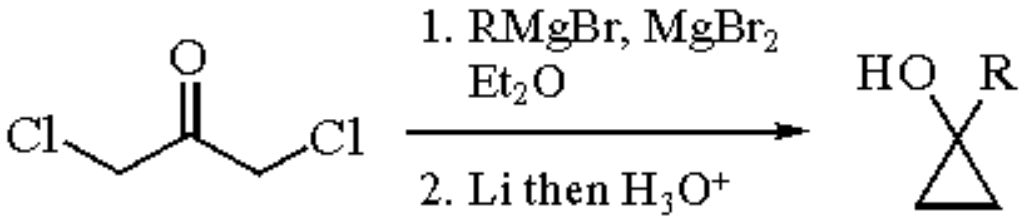

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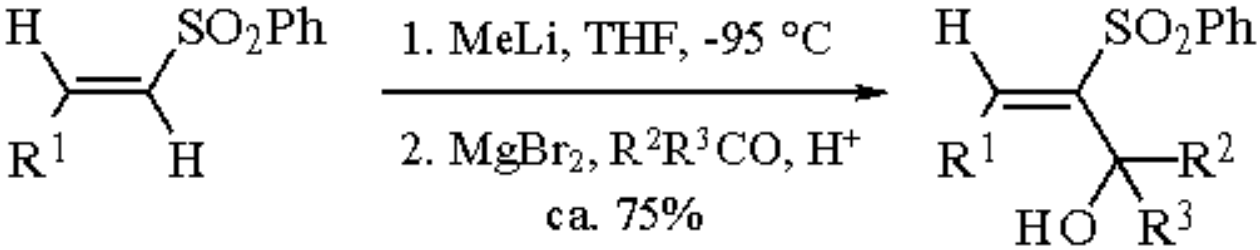

(12)

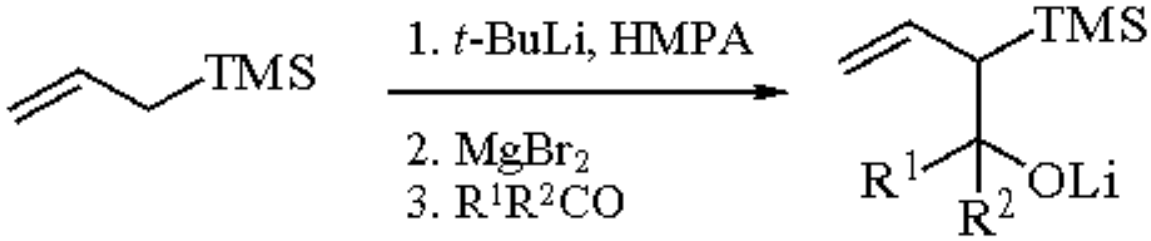

(13)

Bromination.

Magnesium bromide serves as a source of bromide ion, for displacement of sulfonate esters under mild

conditions and in high yield. The reaction is known to proceed with complete inversion at the reacting carbon center when backside attack is possible (eq 14).[5] Even bromination of highly congested bridgehead positions is possible via triflate displacement, although the reaction requires high temperatures, long reaction times, and activation via ultrasound (eq 15).[18]

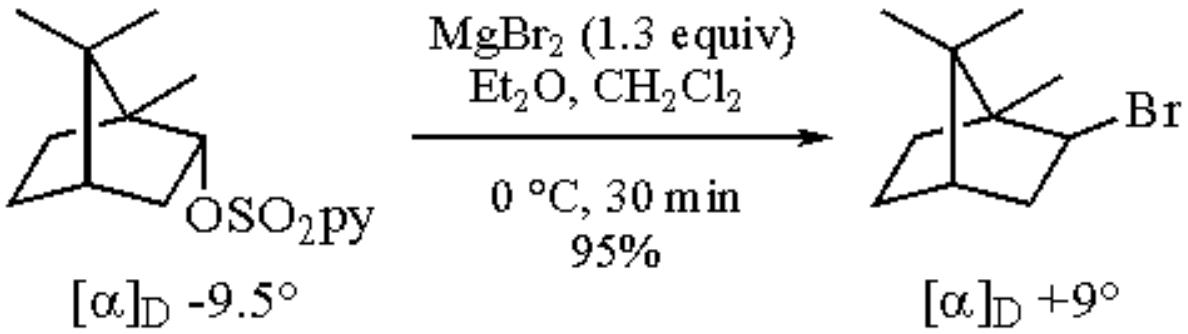

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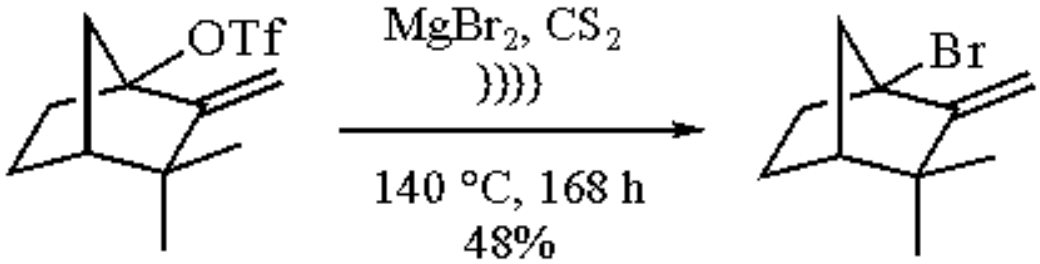

(15)

Epoxides are also converted regiospecifically to bromohydrins by $MgBr_2$.[19]

Carbonyl Condensations.

Bis- or tris-TMS ketenimines condense with ketones, mediated by $MgBr_2$, to produce an intermediate that loses hexamethylsiloxane, affording 2-alkenenitriles in high yield with high (*E*) selectivity (eq 16).[20] $MgBr_2$ also enables the use of very mild bases like ***Triethylamine*** in Horner-Wadsworth-Emmons reactions, enabling the synthesis of unsaturated esters from aldehydes or ketones without the need for strongly basic conditions (eq 17).[21]

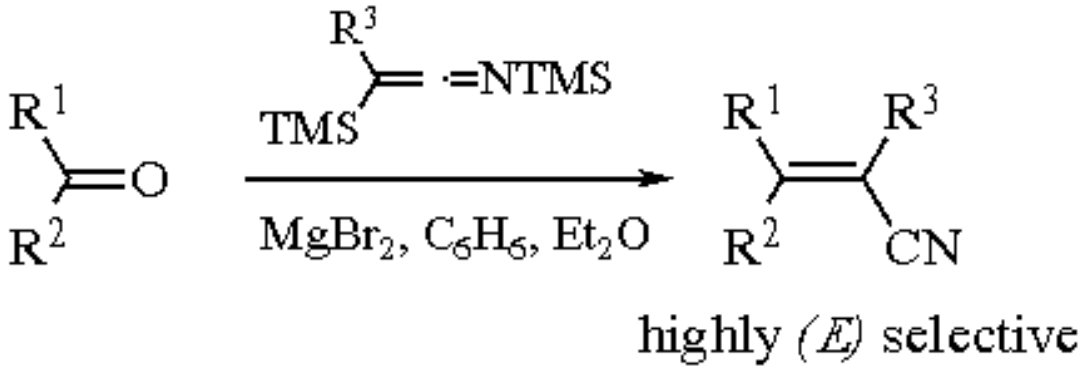

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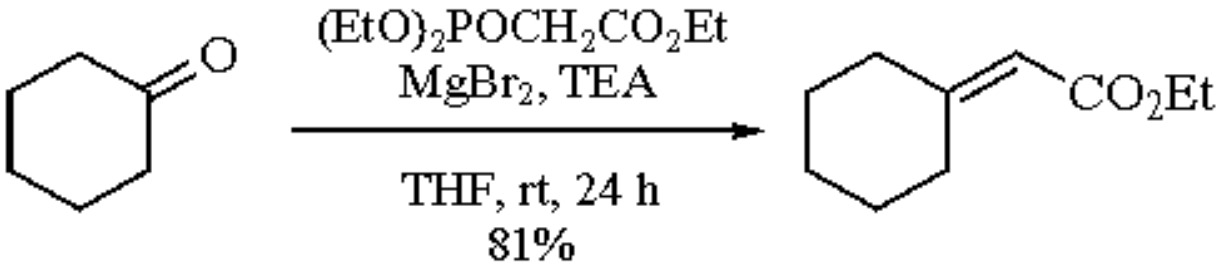

(17)

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Magnesium Ethyl Malonate[1]

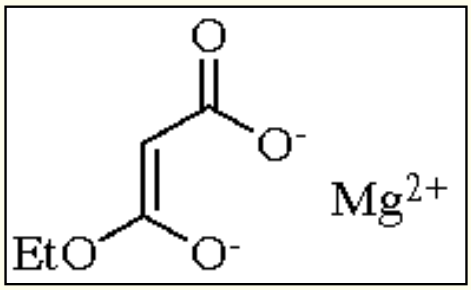

[64679-38-5] · $C_5H_6MgO_4$ · Magnesium Ethyl Malonate · (MW 154.42)

(reagent for conjugate addition to α,β-unsaturated carbonyl compounds followed by in situ decarboxylation to give 1,5 keto-esters;[2] conjugate addition to other functionality;[2] acylation of active esters[1,3])

Alternate Name: MEM.

Physical Data: high melting solid salt; ethanol complex.

Solubility: sol DMF; slightly sol THF.

Form Supplied in: off-white solid or slurry in THF.

Analysis of Reagent Purity: ^{1}H NMR. *Drying:* azeotrope with benzene or toluene; high vacuum.

Handling, Storage, and Precautions: hygroscopic solid; stable for at least several weeks as a solid or slurry in dry THF.

Introduction.

Magnesium ethyl malonate (**1**) undergoes conjugate addition reactions with α,β-enones and other activated alkenes,[2] as well as acylation of active esters.[1,3] Decarboxylation occurs upon neutralization with acetic acid or during workup, affording a single-step addition of an acetic ester residue. ***Ethyl Malonate*** reacts with magnesium metal turnings in ethanol to give (**1**), a basic salt, complexed with 1 equiv of ethanol (eq 1) or with isopropylmagnesium bromide to form a bromide complex.[1]

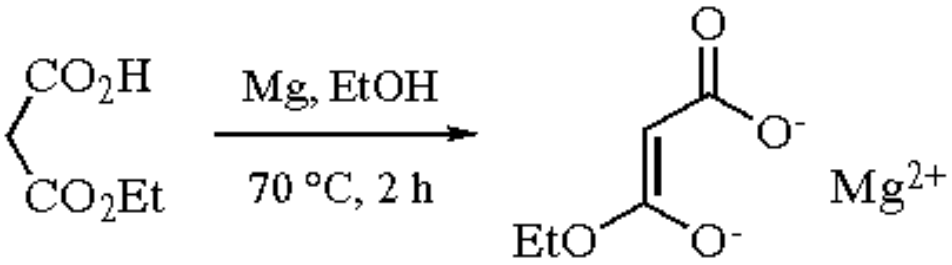

(1)

(1)

Dilithio ethyl malonate undergoes alkylation with alkyl halides and subsequent decarboxylation (eq 2).[4] Little or no reaction occurs with ketones or enones.

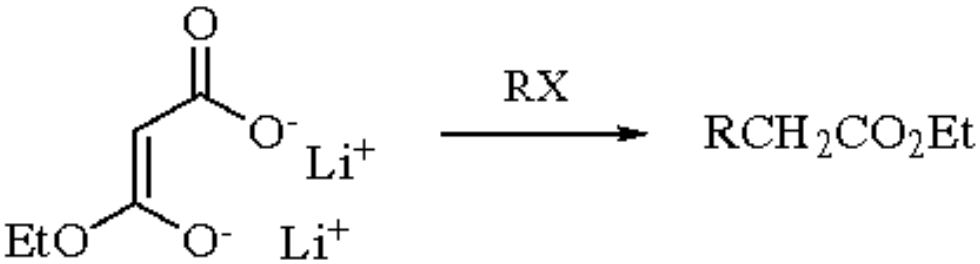

(2)

Conjugate Additions.

As the magnesium salt, (**1**) gives exclusive conjugate, 1,4 addition to α,β-enones, probably due to the reversibility of 1,2-addition (eq 3).[2] Steric hindrance at either the α- or β-position can inhibit addition of (**1**) and starting material is then recovered.[2] Conjugate addition of (**1**) to 6-methyl-2-cyclohexenone occurs with stereoselection (axial attack) (eq 4).[5] Other α,β-unsaturated electron-withdrawing groups give conjugate addition with (**1**) (eqs 5-7).[2,6]

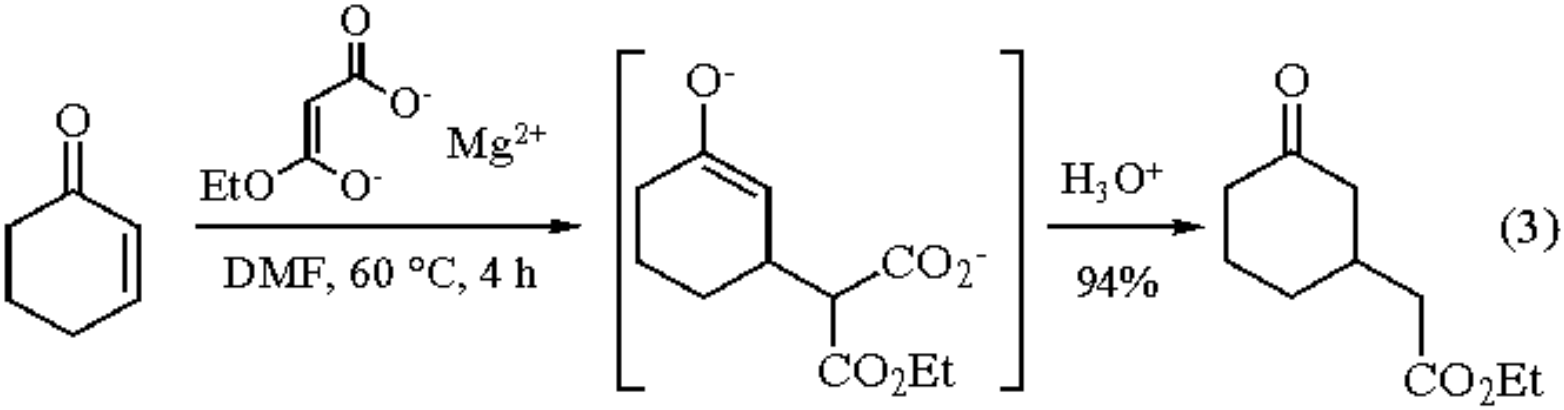

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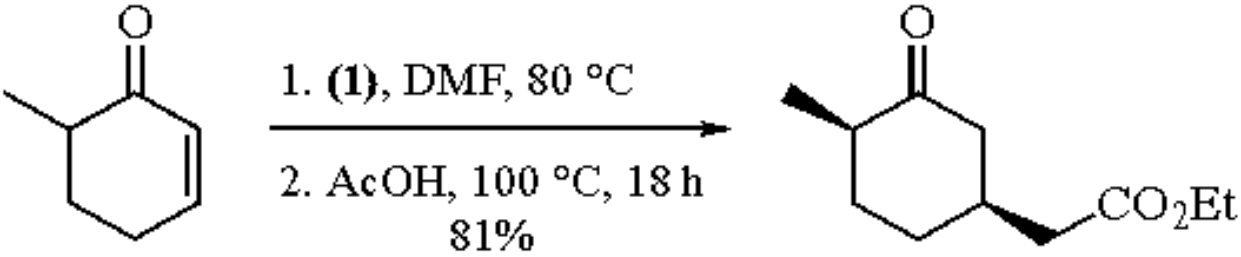

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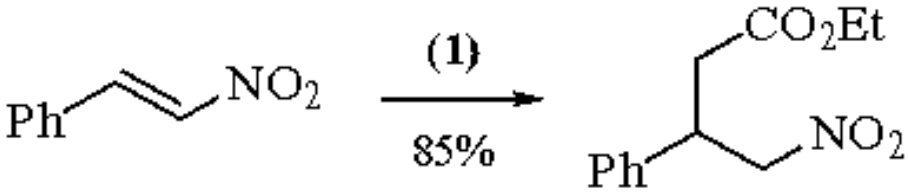

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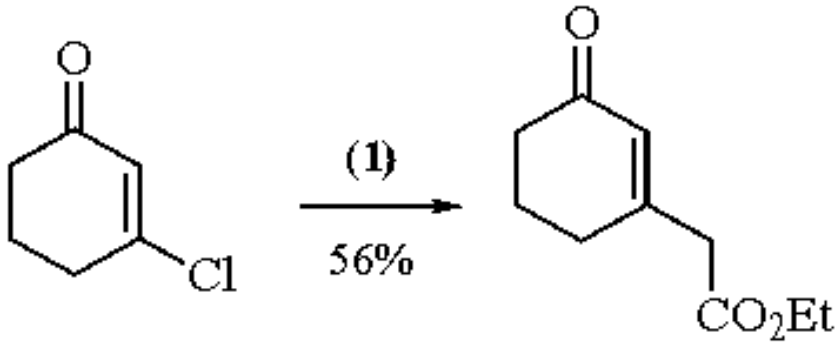

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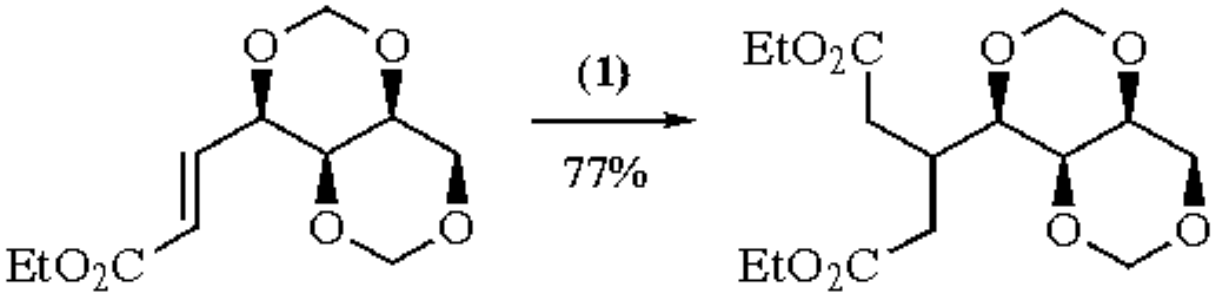

(7)

Acylations.

Magnesium ethyl malonate adds the acetic ester residue to activated carboxylic acid derivatives, acid chlorides (eq 8),[1,3a] acyl imidazolides (eqs 9-12),[1,3b-f] and mixed anhydrides (eq 11).[3b] Decarboxylation is more facile after acylation with (**1**) than after conjugate addition and does not require prolonged treatment after neutralization with acetic acid.

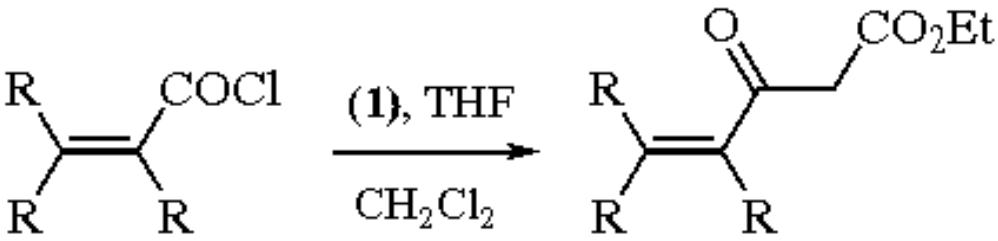

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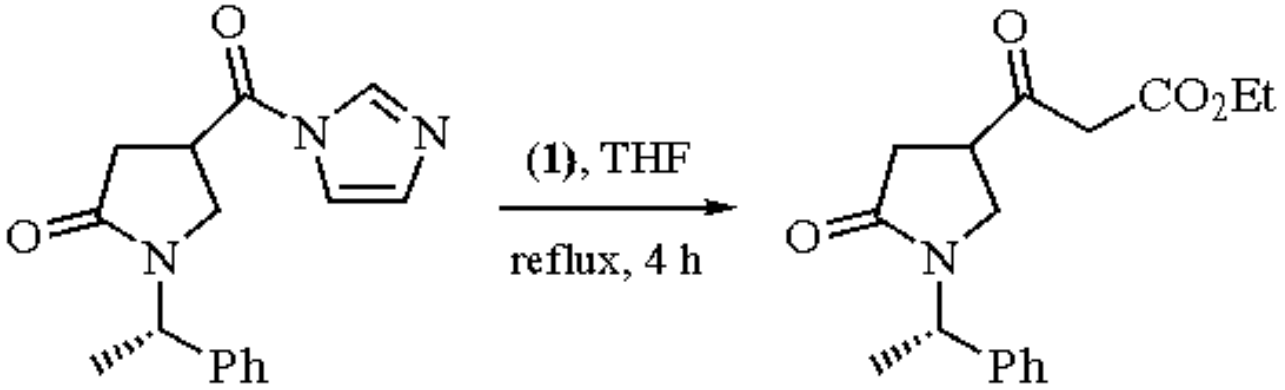

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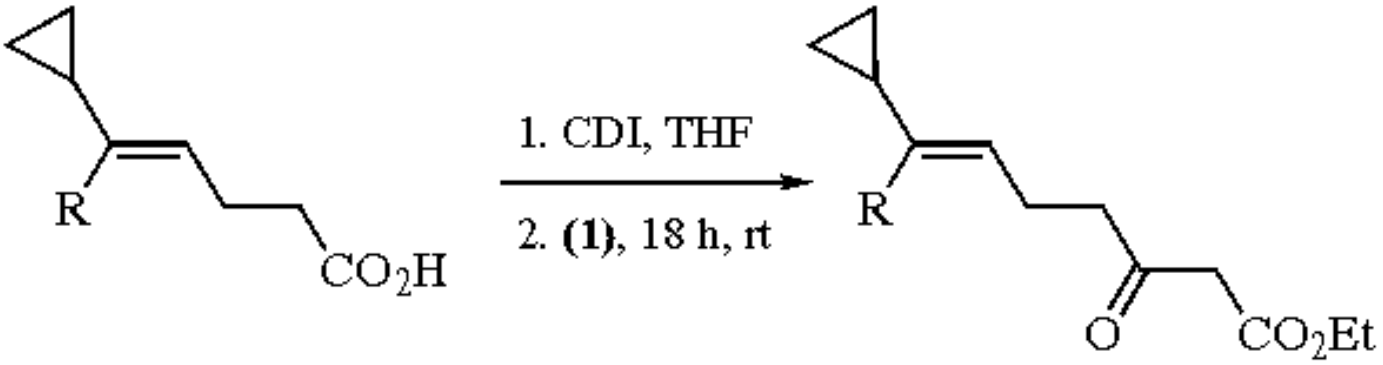

(10)

R = H (91%), Ph (78%)

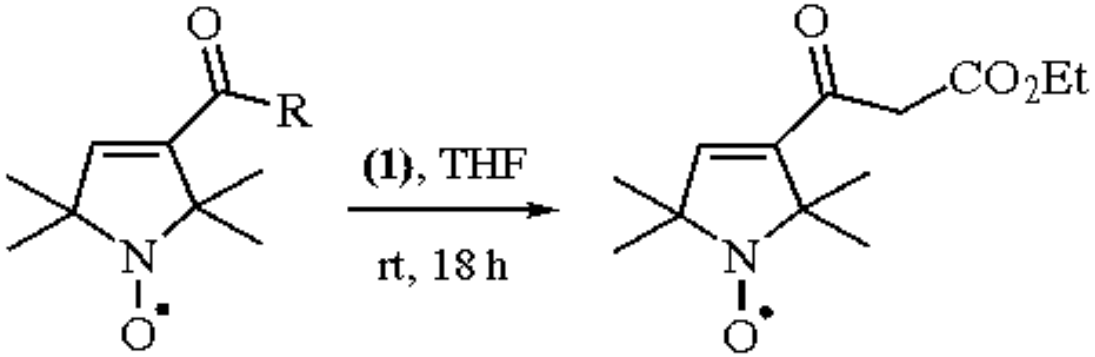

(11)

R = OCO_2Et (50%), (73%)

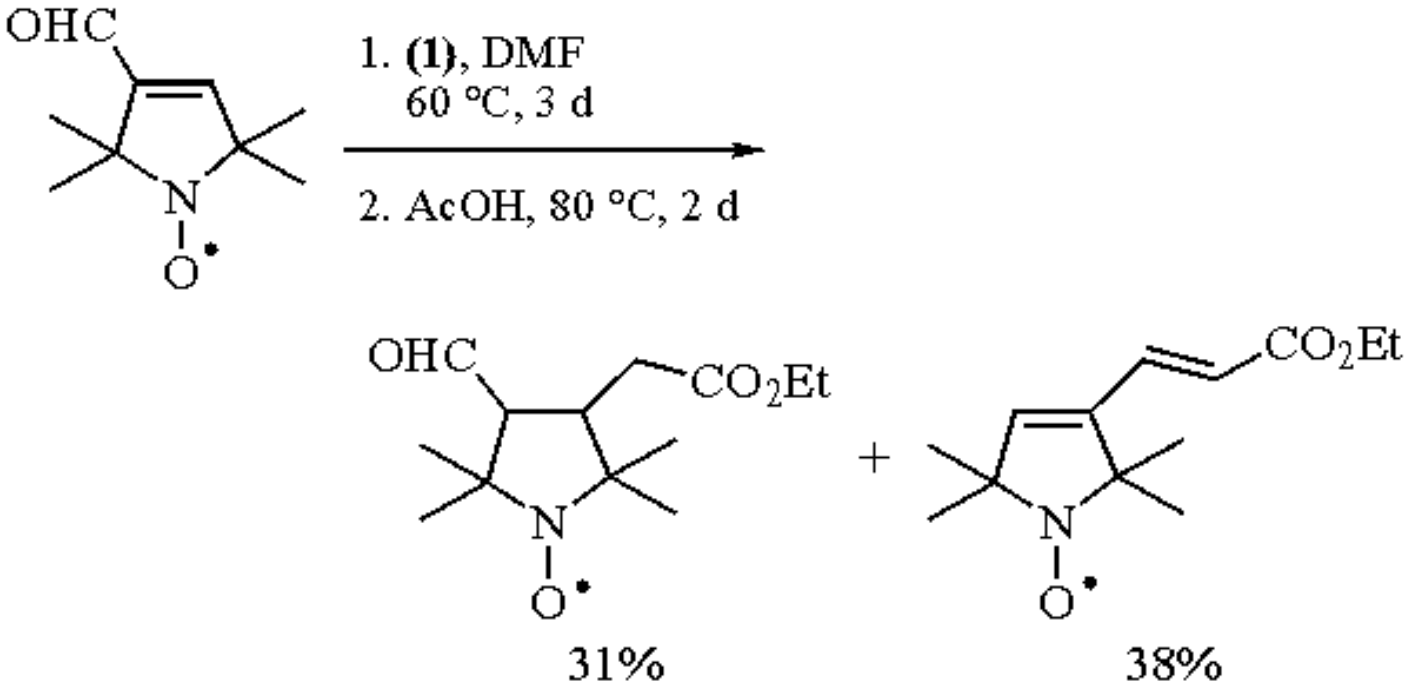

(12)

Electrophiles such as (methylthio)alkylideniminium salts react with (**1**) to give the expected addition products (eq 13).[7]

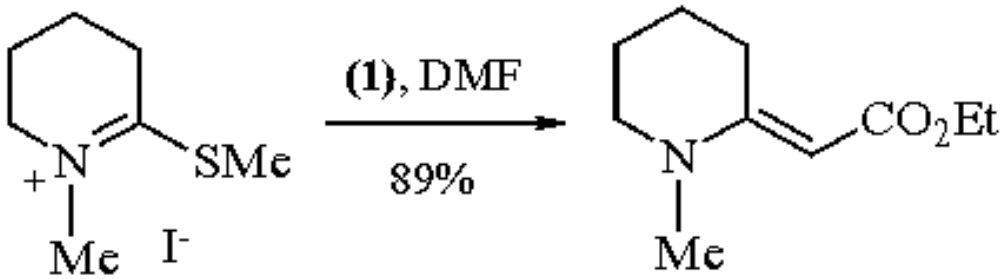

(13)

Analogous Magnesium Malonates.

The neutral magnesium carboxylate salt of *S*-thioethyl methylthiomalonate has been prepared and added to acyl imidazolides (eq 14).[8] The methyl ester analog of (**1**) is also reactive (eq 15).[8]

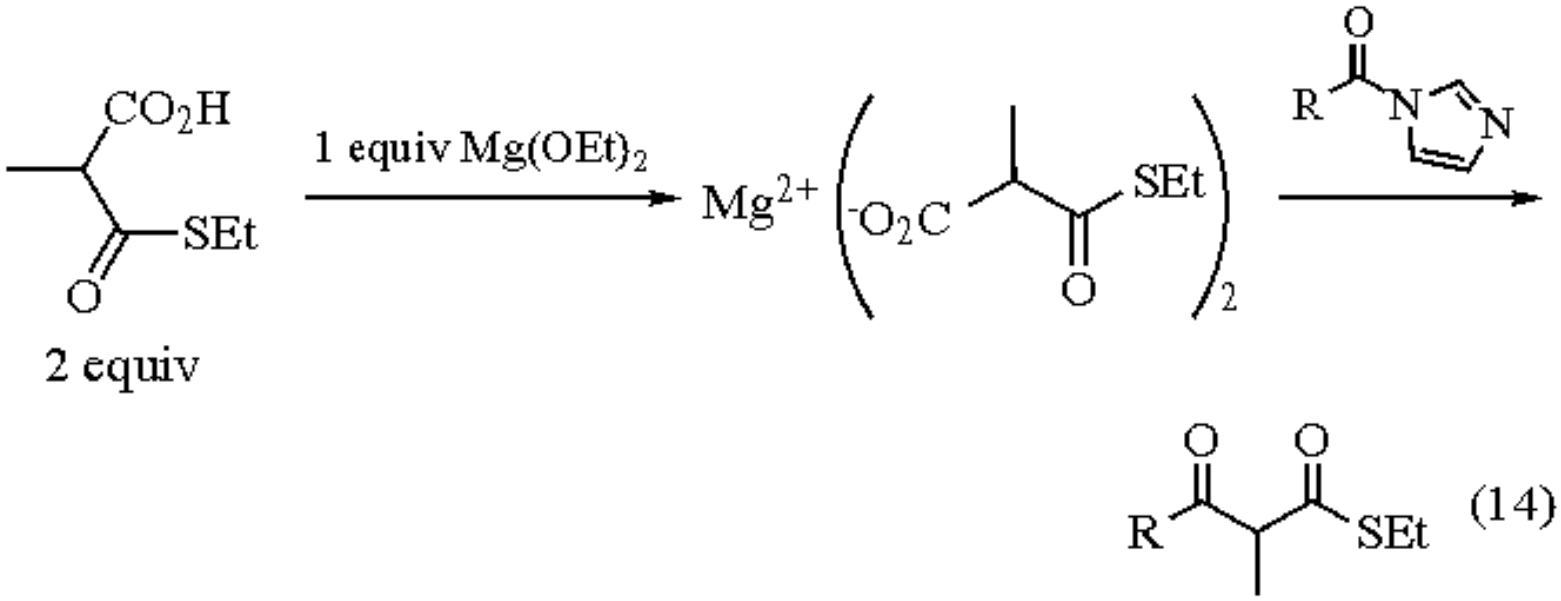

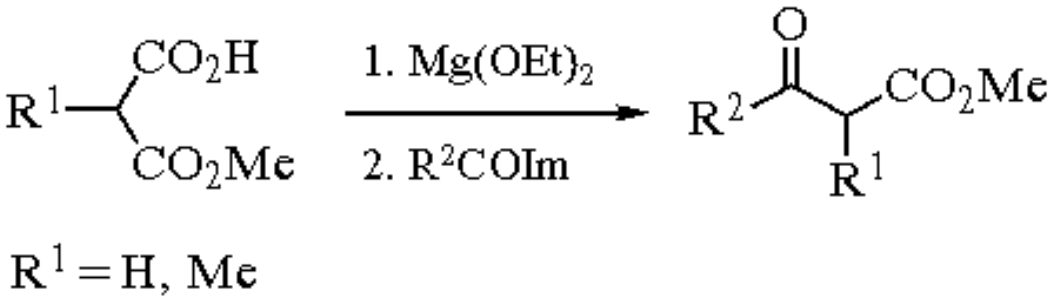

(15)

Related Reagents.

Bis(trimethylsilyl) Malonate; ***Diethyl Ethoxymagnesiomalonate***; ***Diethyl Malonate***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl Malonate***; ***Ethyl Trimethylsilylacetate***; ***Ethyl Trimethylsilyl Malonate***.

---

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Magnesium Hydride-Copper(I) Iodide

CuH.HMgI

(MgH_2)

[7693-27-8] · H_2Mg · Magnesium Hydride-Copper(I) Iodide · (MW 26.33) (CuI)

[7681-65-4] · CuI · Magnesium Hydride-Copper(I) Iodide · (MW 190.45)

(in situ prepared hydridocopper reagent; reduces alkynes stereoselectively to *cis*-alkenes[1])

Physical Data: prepared in situ.

Preparative Method: a slurry of MgH_2 (4 mmol)[1,2] in THF is added via syringe into a mixture of alkyne (1 mmol) and ***Copper(I) Iodide*** (4 mmol) at -78 °C under an inert atmosphere. The cooling bath is removed and the reaction temperature is allowed to warm slowly to rt. The mixture becomes a deep black color with slight effervescence. After stirring for 24-48 h the reaction is quenched with water and the aqueous layer is extracted with THF. The combined organic extract is dried over $MgSO_4$.

Reactions.

The reagent reduces terminal alkynes to the corresponding alkenes (alkanes were not detected) with 100% selectivity in 80-98% yield. Internal alkynes are reduced only to the *cis*-alkene (no *trans*-alkene or alkane detected) in 80-95% yield (Table 1).

Table 1 Reduction of Alkynes by Magnesium Hydride Copper(I) Iodide

Alkyne	Product	Yield (%)
1-Hexyne	1-Hexene	80
1-Octyne	1-Octene	84
Phenylacetylene	Styrene	98
2-Hexyne	*cis*-2-Hexene	80
Diphenylacetylene	*cis*-Stilbene	95

Modifications.

Copper(I) t-Butoxide can be substituted for copper(I) iodide.[1]

Alternative Methods.

The reduction of alkynes to *cis*-alkenes can be accomplished by many other methods, such as catalytic hydrogenation,[3,4] dialkylaluminum hydride,[5,6] or ***Hexa-μ-hydrohexakis(triphenylphosphine)hexacopper***.[7] See also ***Copper(I) Bromide-Lithium Trimethoxyaluminum Hydride***.

---

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Magnesium Iodide

MgI_2

[10377-58-9] · I_2Mg · Magnesium Iodide · (MW 278.11)

(mild Lewis acid for Diels-Alder reaction;[12] enol acetylation of ketones;[14] deoxygenation of oxiranes;[1] iodination and opening of epoxides and cyclopropylmethanols[8,9])

Physical Data: mp (dec) <637 °C; *d* 4.43 g cm^{-3}.

Solubility: sol water (1.48 g mL^{-1} of H_2O at 18 °C); slightly sol alcohols, ethers, ammonia.

Preparative Method: mostly prepared in situ from ***Magnesium*** turnings and ***Iodine*** in refluxing ether.

Handling, Storage, and Precautions: toxicity data not available. May be harmful by inhalation, ingestion, or skin contact.

MgI_2 is used in the deoxygenation of oxiranes to the corresponding alkenes via iodohydrins with retention of configuration in high yields.[1]

Vinyl[2] and bridgehead triflates[3] are converted into the corresponding iodides by reaction with MgI_2, generally in nonpolar solvents such as CS_2 (eq 1).

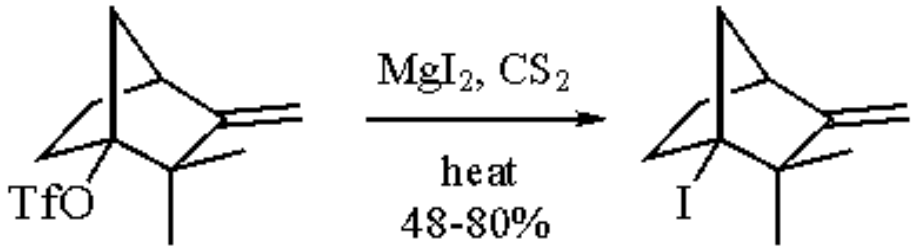

(1)

MgI_2 can effect the transformation of cyclopropylcarbinols into homoallylic iodides in refluxing Et_2O (eq 2).[4,5] Tertiary and benzylic alcohols are more reactive than secondary. MgI_2 can also be used in the regioselective opening of 2,3-epoxy alcohols and β,γ-epoxy sulfones, leading to the corresponding 3-iodo-1,2-diols (eq 3) and β-hydroxy sulfones (eq 4), respectively.[6,7]

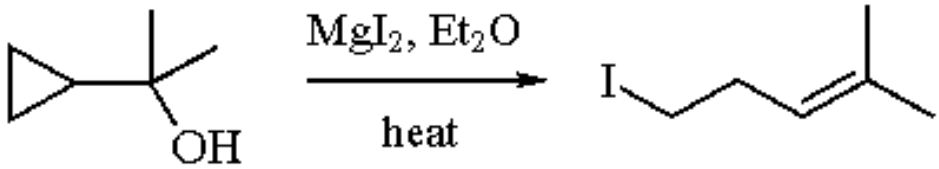

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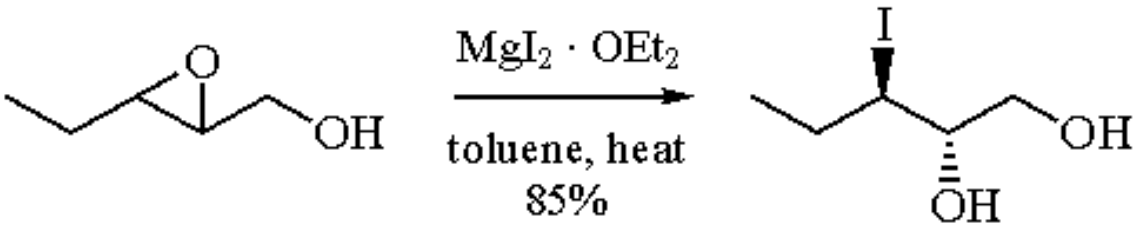

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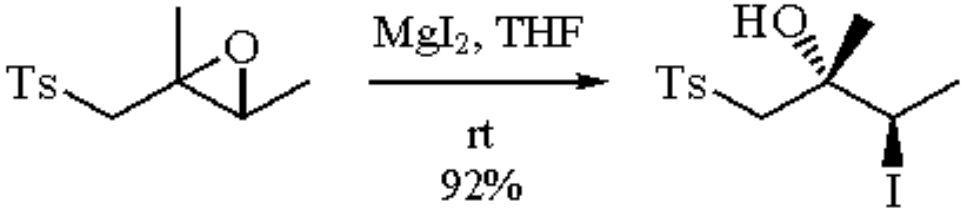

(4)

Treatment of silyloxiranes[8] and glycidic esters[9] with MgI_2 results in their rearrangement to the corresponding silyl ketone (eq 5) and α-keto esters.

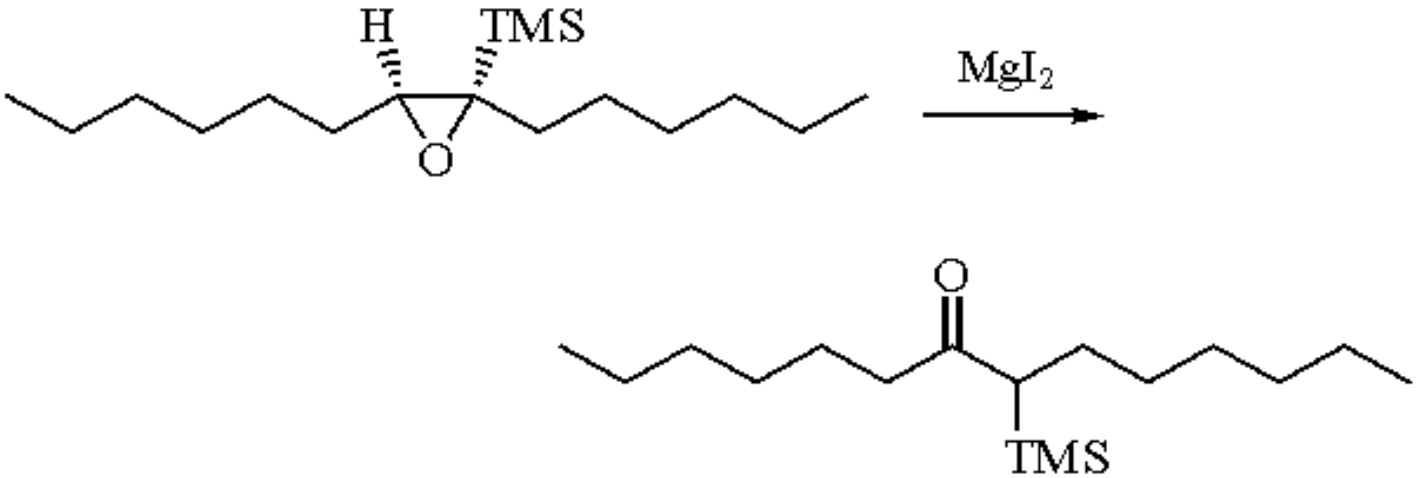

(5)

Carboxylic esters can be hydrolyzed with MgI_2 in aprotic solvents like CS_2 and toluene.[10] It can also be used to demethylate a methoxy group *ortho* to an acyl group under mild conditions without isomerization of an isopropenyl group (eq 6).[11]

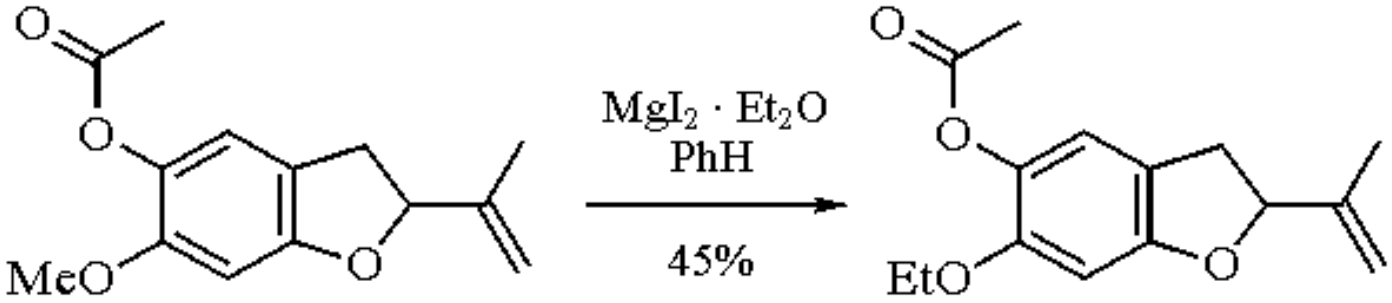

(6)

As a Lewis acid, MgI_2 has been shown to increase the regioselectivity, having equal but opposite effect to that of ***Boron Trifluoride Etherate*** in Diels-Alder reactions of perihydroxylated naphthoquinones with 1-methoxy-3-methyl-1,3-butadiene (eq 7).[12]

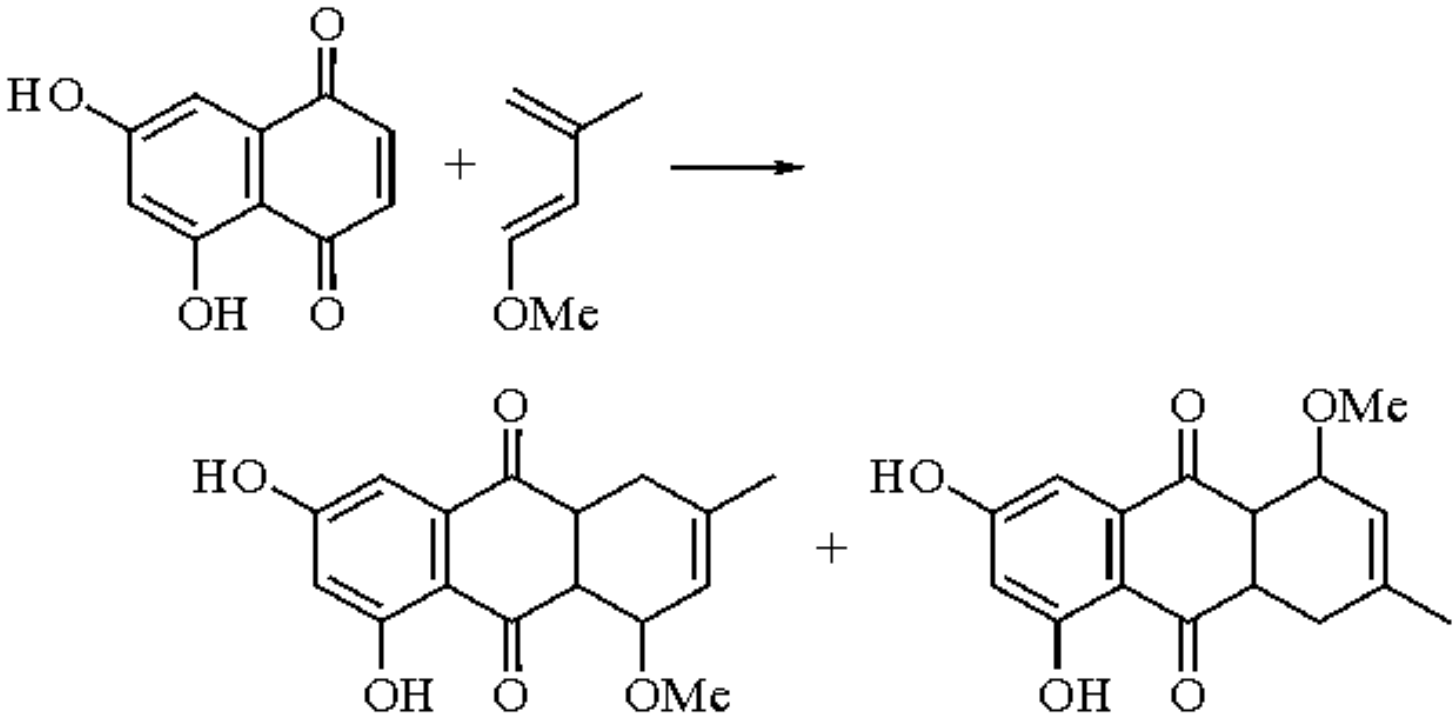

25 °C	45%	55%
MgI_2	[2]25%	[3]95%
$BF_3 \cdot Et_2O$	[3]95%	[2]25%

(7)

Radical-mediated reduction of α-iodo-β-alkoxy esters with ***Tri-n-butylstannane*** in the presence of catalytic MgI_2 results in excellent *erythro* selectivity. *Threo* selectivity is seen in the absence of a Lewis acid.[13]

$MgI_2.Et_2O$ can be used as a mild Lewis acid catalyst for the enol acetylation of ketones.[14]

---

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Magnesium-Methanol

Mg-MeOH

(Mg)

[7439-95-4] · Mg · Magnesium-Methanol · (MW 24.31) (MeOH)

[67-56-1] · CH_4O · Magnesium-Methanol · (MW 32.05)

(reducing system for α,β-unsaturated nitriles, amides, esters, ketones, imines, halides, sulfones, and azides)

Physical Data: Mg: mp 651 °C; bp 1107 °C; *d* 1.74 g cm^{-3}. MeOH: bp 64.65 °C; *d* 0.796 g cm^{-3}.

Form Supplied in: Mg: powder, ribbon, chips, shavings; widely available. MeOH: anhydrous and reagent grade widely available.

General Reductions.

Reductions with ***Magnesium*** in methanol are usually accomplished simply by stirring the reactants at ambient temperature using an excess (5-40-fold) of magnesium. There is often an induction period, probably needed to cleanse the surface of the magnesium for efficient reaction. The ensuing reaction with methanol is exothermic, and may or may not require cooling in an ice bath.[1-8]

Carbon-Carbon π-Bond Reductions.

The dissolving metal reducing system generated by this reagent combination provides convenient electron transfer/protic source reductions of α,β-unsaturated nitriles[1] (eq 1),[1d] amides[2] (eq 2),[2c] and esters[3] (eq 3)[3b] to the saturated derivatives. Conjugated alkynic esters (but not acids) also afford saturated products (eq 4),[4] while α,β-unsaturated ketones and imines give the corresponding saturated alcohols or amines, respectively, resulting from concomitant reduction of the carbonyl or imine group.[5] However, α,β-unsaturated ketones further conjugated to furan rings are selectively converted to the saturated ketones (eq 5)[6] without affecting the carbonyl.[6] Deuterium may be introduced by using MeOD as the solvent (eq 4).[3b,4] Isolated double and triple bonds are not affected[4,1d,2,3c] unless conjugated to two (but not one) phenyl groups (eq 6).[4,7]

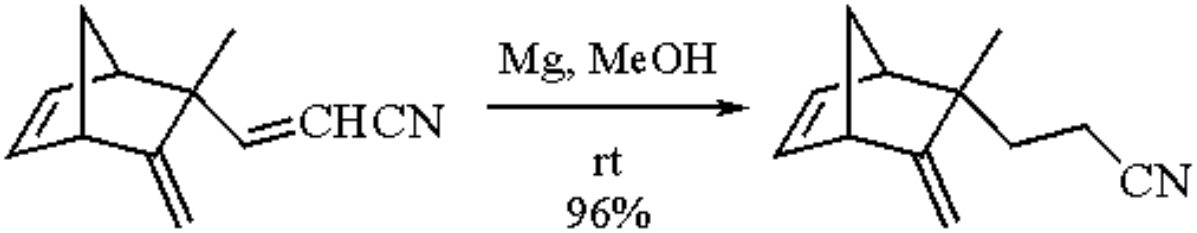
CHCN
Mg, MeOH
rt
96%
CN

(1)

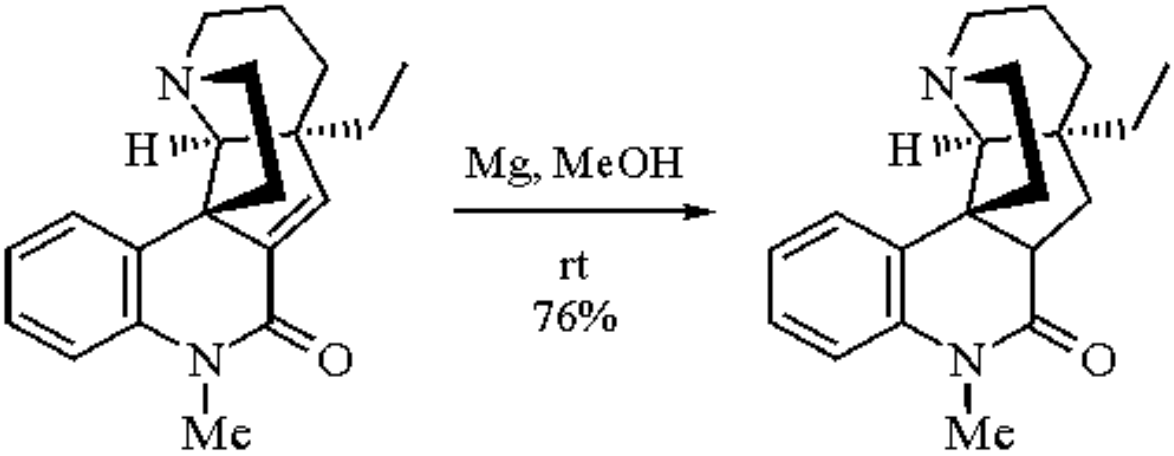
N
H
N
O
Me
Mg, MeOH
rt
76%
N
H
N
O
Me

(2)

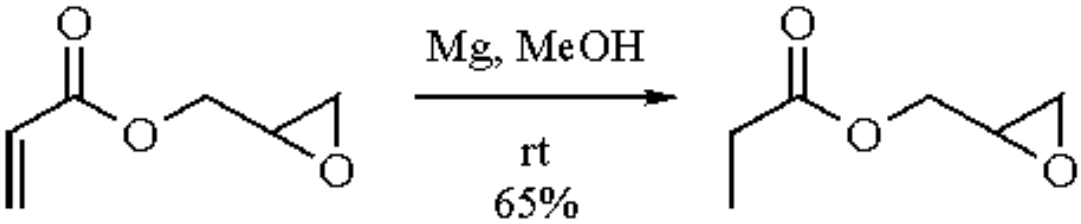
O
O
O
Mg, MeOH
rt
65%
O
O
O

(3)

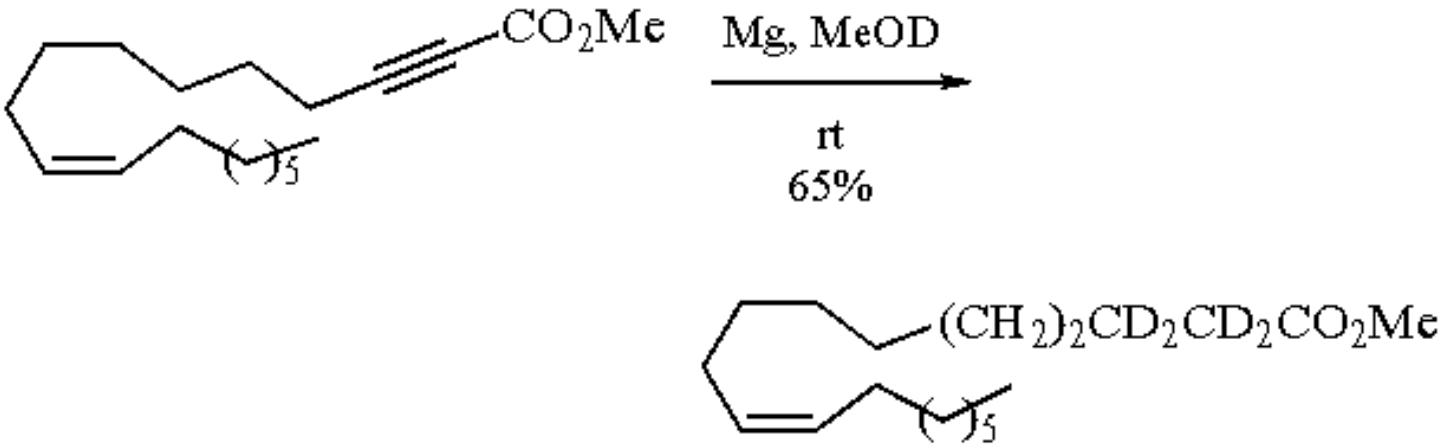
CO2Me
5
Mg, MeOD
rt
65%
(CH2)2CD2CD2CO2Me
5

(4)

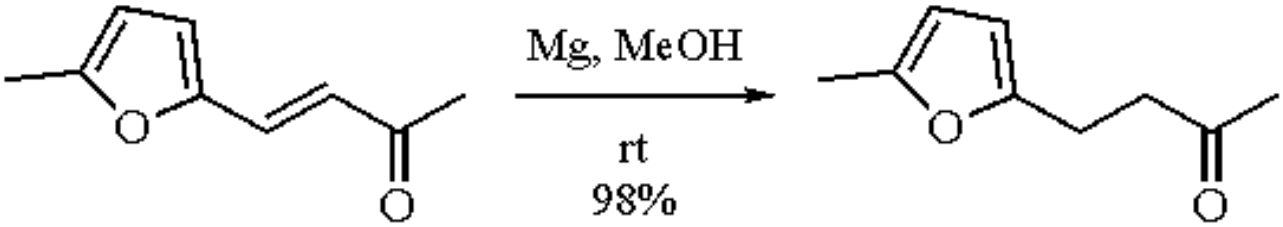
O
O
Mg, MeOH
rt
98%
O
O

(5)

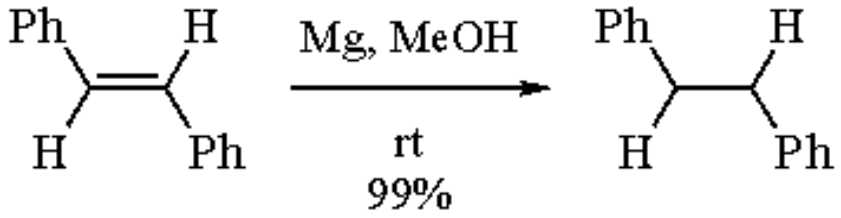

(6)

Functional Group Reductions.

The reagent system effectively and selectively reduces alkyl and aryl iodides and bromides to hydrocarbons.[5a,8a] Vinyl bromides are reduced if conjugated to an aromatic ring, while only benzylic and allylic chlorides are reduced (eq 7).[8a] Deuterium may be incorporated using MeOD as the solvent (eq 8).[8a] Aryl chlorides convert to hydrocarbons using a similar system involving magnesium powder and isopropanol in refluxing decahydronaphthalene.[8b]

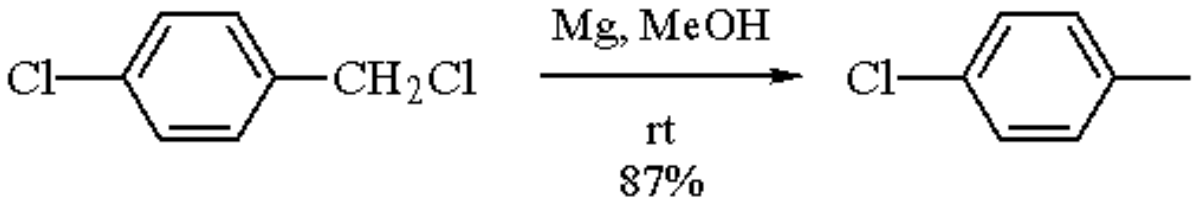

(7)

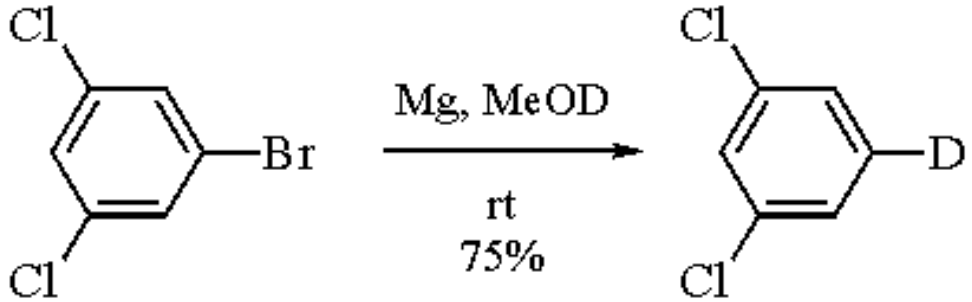

(8)

Mono- and bisulfones are effectively desulfonated with magnesium-methanol to afford mostly alkenes (with 1,2-disulfones, eq 9)[9] or hydrocarbons (with 1,1-disulfones or monosulfones, eq 10).[9] In these cases, the magnesium was preactivated by treatment with dilute HCl.

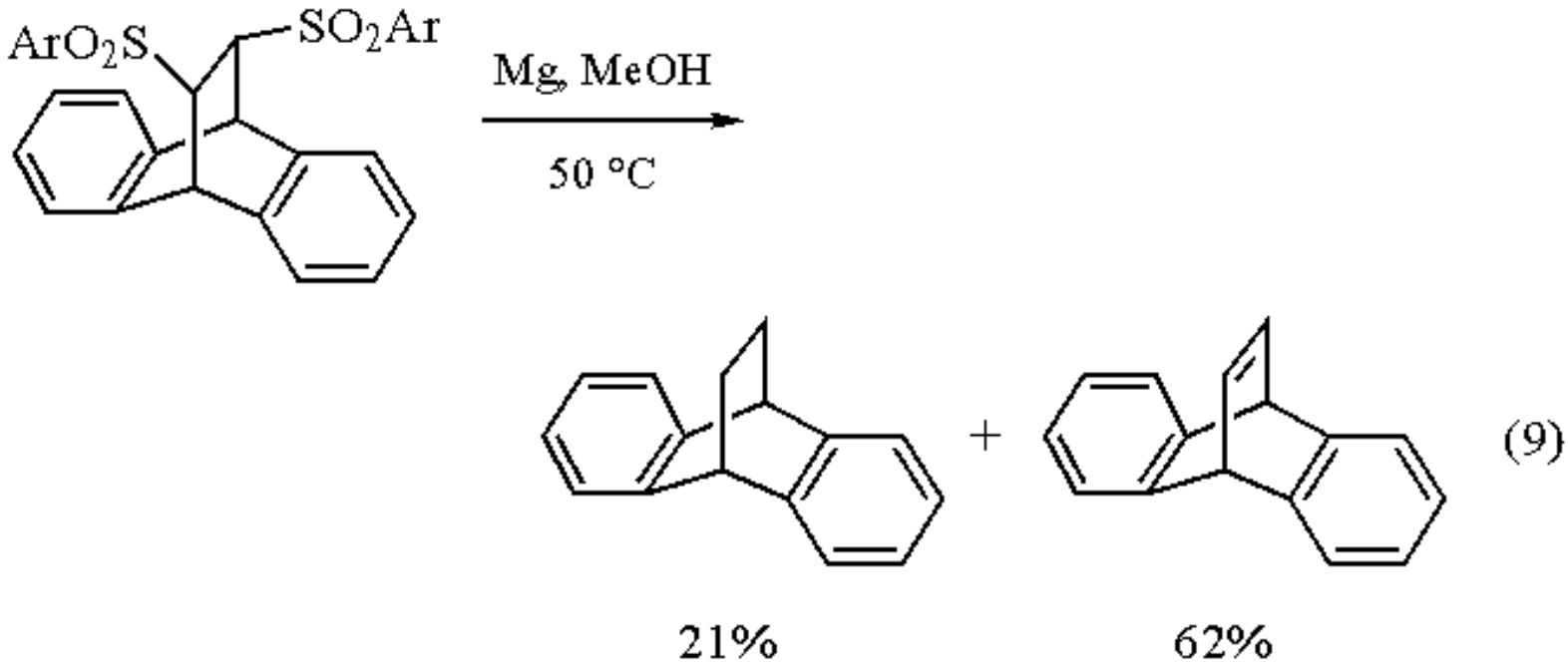

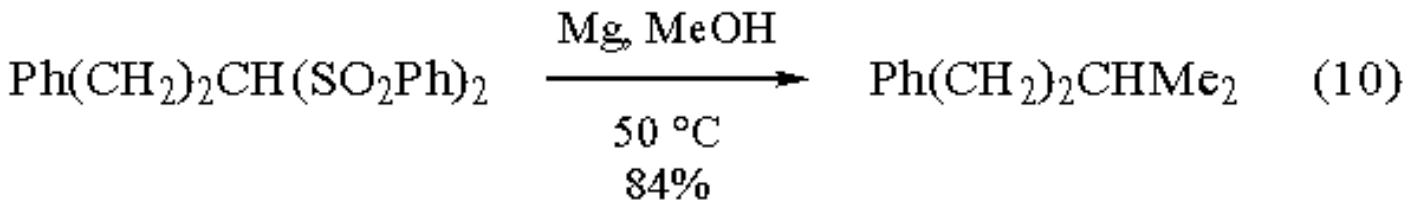

Alicyclic, benzylic, and allylic azides are efficiently reduced to the corresponding amines with magnesium powder in methanol (eq 11).[10] Aromatic nitro compounds are reduced to mixtures of azo and azoxy derivatives.[5a] Reduction of an *N*-magnesium imine to the amine has been reported.[11]

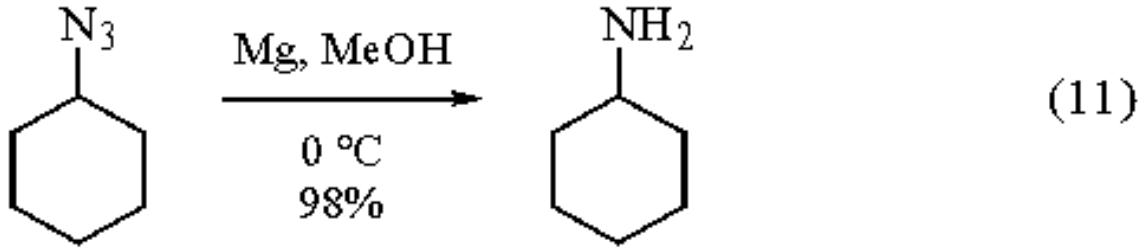

This reagent combination provides a convenient, mild, chemoselective, and inexpensive dissolving metal process for reduction of double bonds in conjugated esters, nitriles, and amides and for selective reductions of alkyl and aryl iodides and bromides.

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Magnesium Methoxide

$(MeO)_2Mg$

[109-88-6] · $C_2H_6MgO_2$ · Magnesium Methoxide · (MW 86.39)

(weakly basic metal alkoxide; forms stable chelates with enolizable carbonyl compounds[1])

Solubility: slightly sol MeOH, EtOH, DMF.

Form Supplied in: commercially available as neat white powder or as 8 wt % solution in MeOH.

Preparative Method: by addition of small batches of ***Magnesium*** metal to anhydrous MeOH.[1]

Handling, Storage, and Precautions: use same precautions as for other metal alkoxides (see ***Potassium t-Butoxide***); avoid contact with eyes and clothing; handle and conduct reactions under an inert atmosphere. For critical experiments, it is recommended that the reagent be freshly prepared. Use in a fume hood.

Preparation of Magnesium Methyl Carbonate.

The reaction of $(MeO)_2Mg$ with CO_2 in DMF solution leads to the formation of $MeOMgOCO_2Me$ (eq 1).[2] This reagent is very useful for the carboxylation of α-methylene ketones, lactones, nitro compounds, etc. (see ***Methyl Magnesium Carbonate*** (MMC)).[2]

$$(MeO)_2Mg + CO_2 \xrightleftharpoons[\text{DMF}]{} MeOMgOCO_2Me \qquad (1)$$

Carbonyl Condensation Reactions.

Because of the ability of the magnesium cation to form stable chelates with carbonyl compounds, $(MeO)_2Mg$ is a useful base for the promotion of a variety of carbonyl condensation reactions. The reagent catalyzes the condensation of triacetic acid lactone methyl ether with aromatic aldehydes to yield styryl monopyrone methyl ethers (eq 2).[3] The condensation of 2,2-dimethoxy-3-butanone with benzaldehyde in the presence of $(MeO)_2Mg$ leads to a magnesium chelate of the initially formed α-diketone condensation product, which undergoes intramolecular Michael addition to form 4-phenylcyclopentane-1,2-dione (eq 3).[4] Dimethyl oxalate reacts with 2,2-dimethoxy-3-butanone under similar conditions to give 2,5-dimethoxy-*p*-benzoquinone.[4] The use of other bases such as sodium alkoxides, tertiary amines,

or quaternary ammonium salts in these reactions leads to unidentified products. Treatment of cyclohexenone with dimethyl 2-methoxycarbonylglutarate in the presence of $(MeO)_2Mg$ in MeOH results in a Michael addition followed by an aldol condensation to yield a decalin-1,8-dione derivative which exists primarily in its tautomeric enol forms (eq 4).[5]

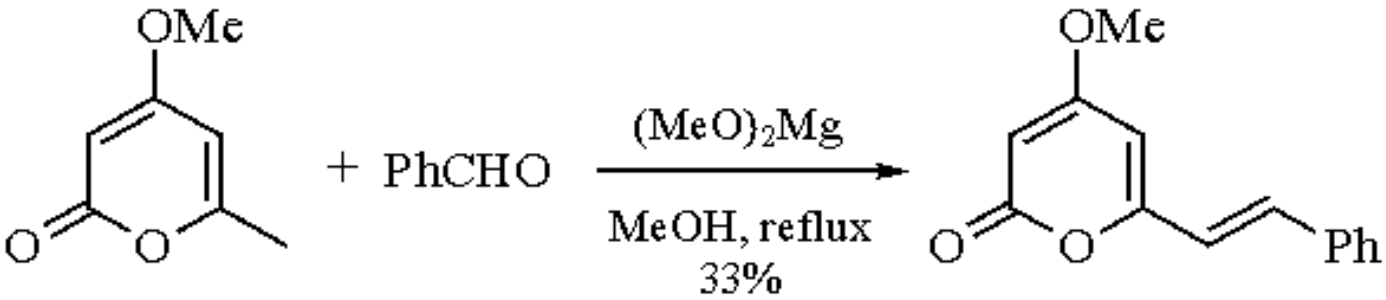

(2)

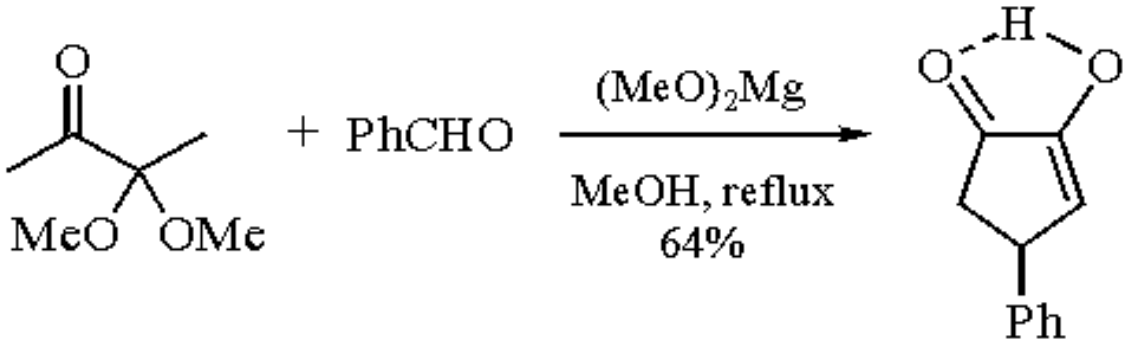

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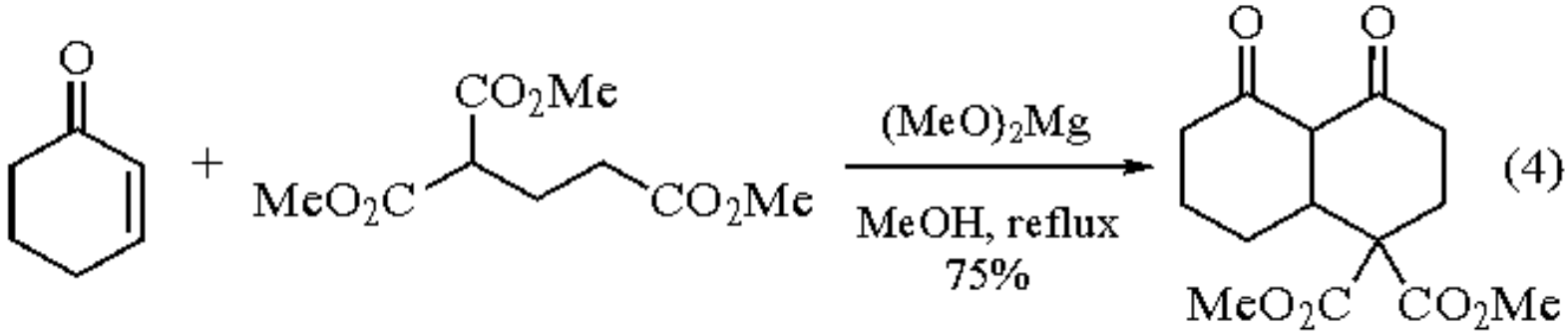

(4)

A mixture of diastereomers of 6-isopropyl-9-methylbicyclo[4.3.0]nonen-3-one is obtained by a tandem Michael-aldol reaction of an appropriate acyclic unsaturated keto aldehyde using $(MeO)_2Mg$ as the base (eq 5).[6] The reaction is reasonably stereoselective for the *trans*-fused ring system, but it is somewhat more stereoselective and the overall yield is considerably higher when ***Zirconium Tetraisopropoxide*** is used as the base. The ability of the zirconium cation to form even stronger chelates than the magnesium cation presumably accounts for this.[6b] A good yield of the cyclization products is also obtained with ***Sodium Methoxide***, but the stereoselectivity is low.

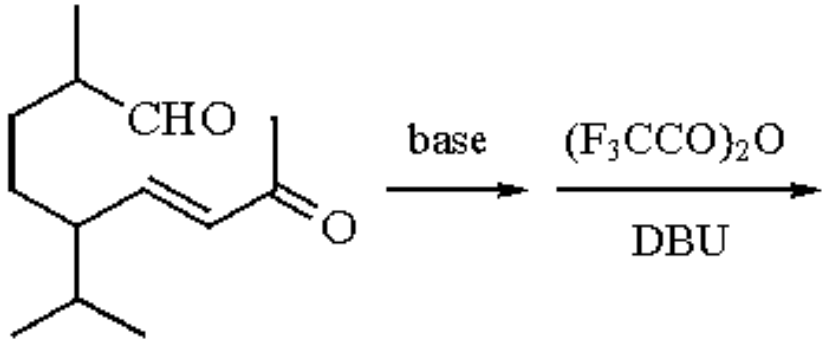

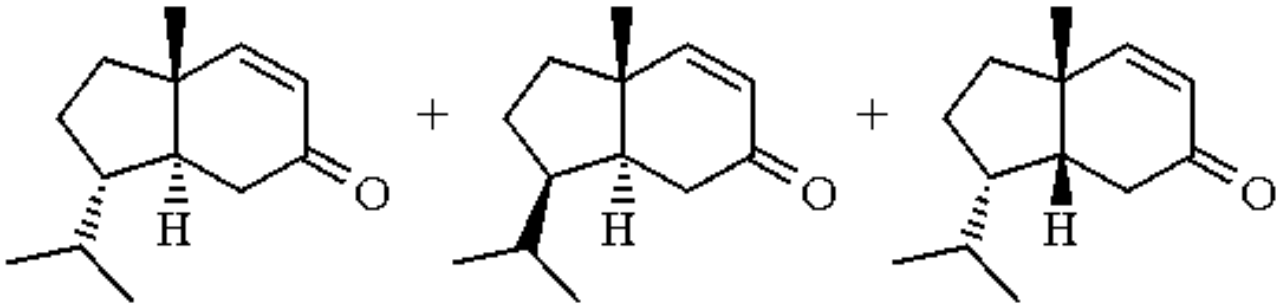

(5)

$(MeO)_2Mg$	10:1.5:1	51%
$(i\text{-}PrO)_4Zr$	10:1:1	80%
MeONa	3.4:1.2:1	80%

The methyl ester of phenylsulfinylacetic acid condenses with aliphatic aldehydes to give γ-hydroxy-α,β-unsaturated esters directly (eq 6).[7] The α-phenylsulfinyl-α,β-unsaturated ester, which is obtained by dehydration of the aldol product, undergoes deconjugation of the double bond to the β,γ-position. Then, a [2,3]-sigmatropic rearrangement of the sulfoxide group occurs, followed by cleavage of the sulfenate. A two-step process which involves the use of ***Sodium Hydride/Zinc Chloride*** catalyst to effect the aldol condensation and dehydration followed by treatment with an amine base yields the same types of products.

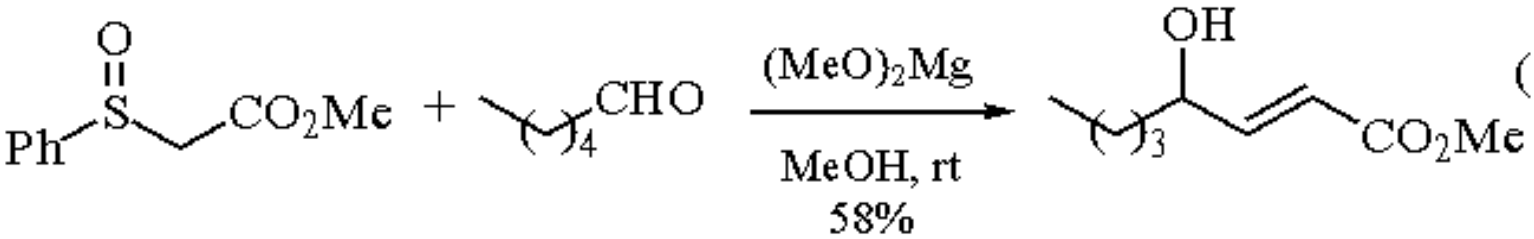

(6)

The Darzens condensation of methyl chloroacetate with benzaldehyde occurs relatively slowly in the presence of $(MeO)_2Mg$ in MeOH.[8] These conditions allow the isolation of methyl 2-chloro-3-hydroxy-3-phenylpropanoate and methyl 2-hydroxy-3-methoxy-3-phenylpropanoate, as well as the products of the Cannizzaro reaction of benzaldehyde, in addition to the expected methyl 2,3-epoxy-3-phenylpropanoate (glycidic ester).

Since the magnesium cation has a high affinity to form stable chelates with β-dicarbonyl compounds, the course of cyclizations of polyketonic-polyenolic systems may change significantly in going from alkali metal alkoxide bases to $(MeO)_2Mg$.[3b,9,10] For example, dimethyl 2,4-diacetylglutaconate cyclizes to an acyl pyrone in relatively high yield upon treatment with &egt;2.0 equiv of MeONa in MeOH/PhH (eq 7).[9a] The same pyrone is formed if the diester is

treated with 1.0 equiv of $(MeO)_2Mg$, but when &egt;2.0 equiv of this reagent is used, a phenol derivative and a resorcinol derivative are also formed. Apparently, the chelate of the initially formed acyl pyrone undergoes ring opening with the excess base to form the chelate of a glutaconic ester dianion, which undergoes an intramolecular Michael or aldol reaction to form a phenol derivative or an intramolecular Claisen condensation to form a resorcinol derivative.[9a] Also, bispyrones undergo ring openings to triketo esters followed by aldol cyclizations, sometimes accompanied by decarboxylations to mixtures of resorcinol derivatives upon treatment with KOH in MeOH (eq 8),[10] but phloroglucinol derivatives, which apparently arise via Claisen condensation of open chain magnesium bischelates, are obtained in low yields with excess $(MeO)_2Mg$ (eq 9).[3b,9a]

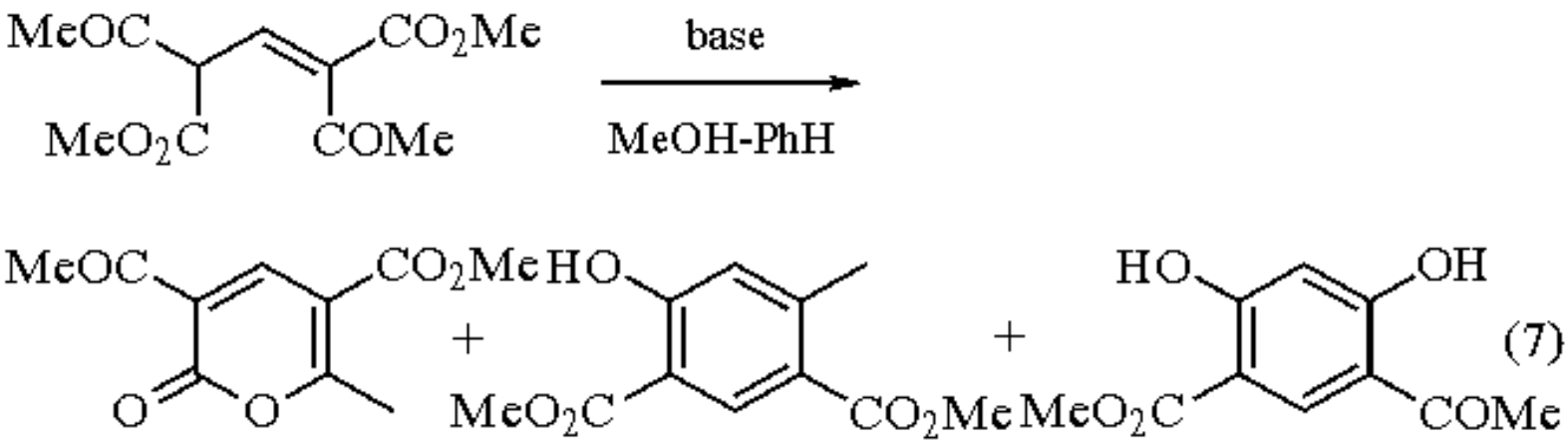

2.0 equiv $(MeO)_2Mg$	-	55%	26%
2.0 equiv MeONa	81%	-	-

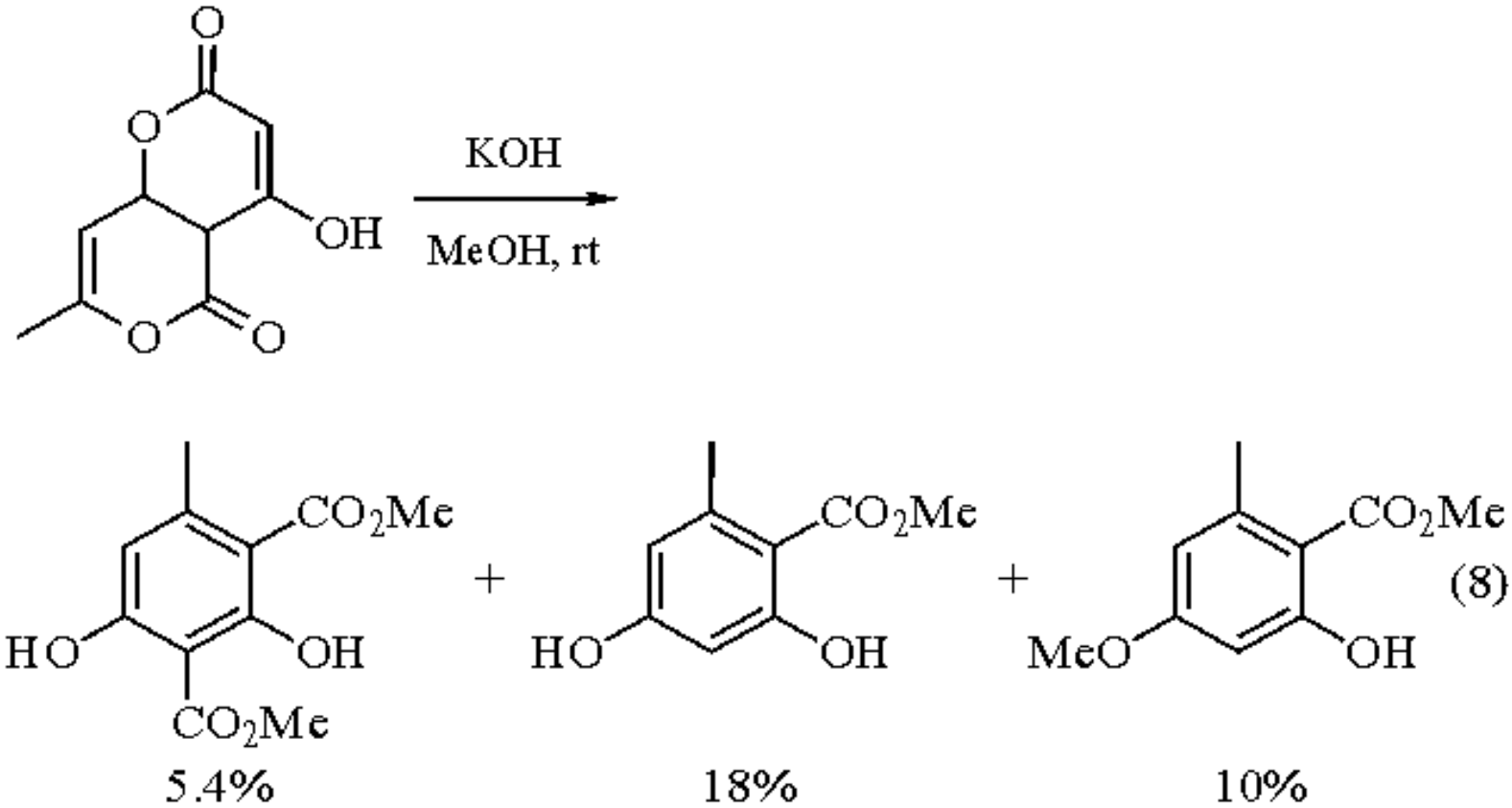

(8)

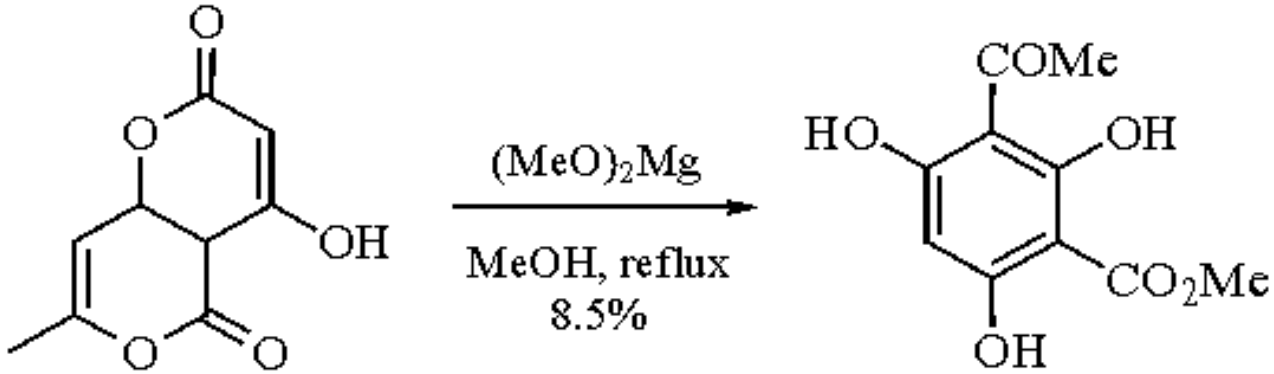

(9)

Triacetic acid methyl ester is conveniently prepared by treating dehydroacetic acid with $(MeO)_2Mg$ in MeOH (eq 10).[11] The ring opening reaction occurs more slowly when MeOLi or MeONa are employed as the bases.

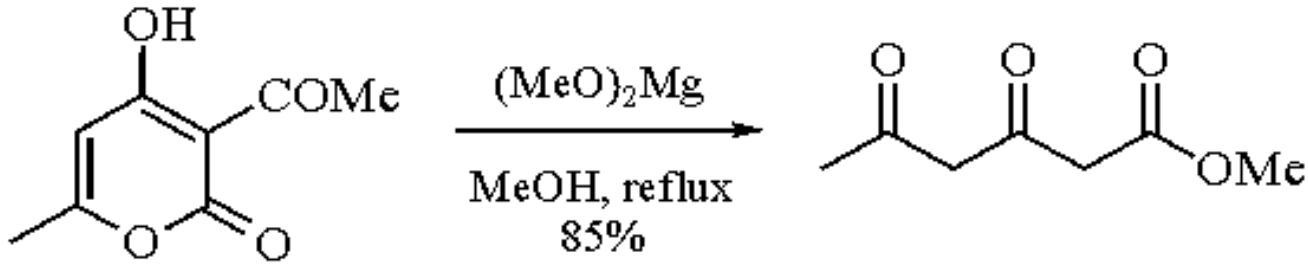

(10)

Related Reagents.

Sodium Ethoxide; ***Sodium Methoxide***.

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Magnesium Oxide

MgO

[1309-48-4] · MgO · Magnesium Oxide · (MW 40.31)

(dehydrohalogenation;[1] reductions;[2,6-8] alkene synthesis;[3] oxidations;[9] epoxide opening;[10] acylations[12,13])

Physical Data: mp 2852 °C; bp 3600 °C; *d* 3.58 g cm^{-3}.

Solubility: sol water (0.0086 g/100 mL at 30 °C).

Form Supplied in: white powder.

Preparative Method: dehydration of $Mg(OH)_2$ at 1100 °C for 2 h.

Handling, Storage, and Precautions: tumorigenic (olfactory and respiratory system); avoid breathing dust; incompatible with strong oxidizing agents; air and moisture sensitive. May react violently on mixing with phosphorus pentachloride, chlorine trifluoride, or bromine pentafluoride.

Reactions with Aldehydes and Ketones.

α,β-Unsaturated ketones can be prepared from α-bromo ketones when treated with magnesium oxide in DMF (eq 1).[1]

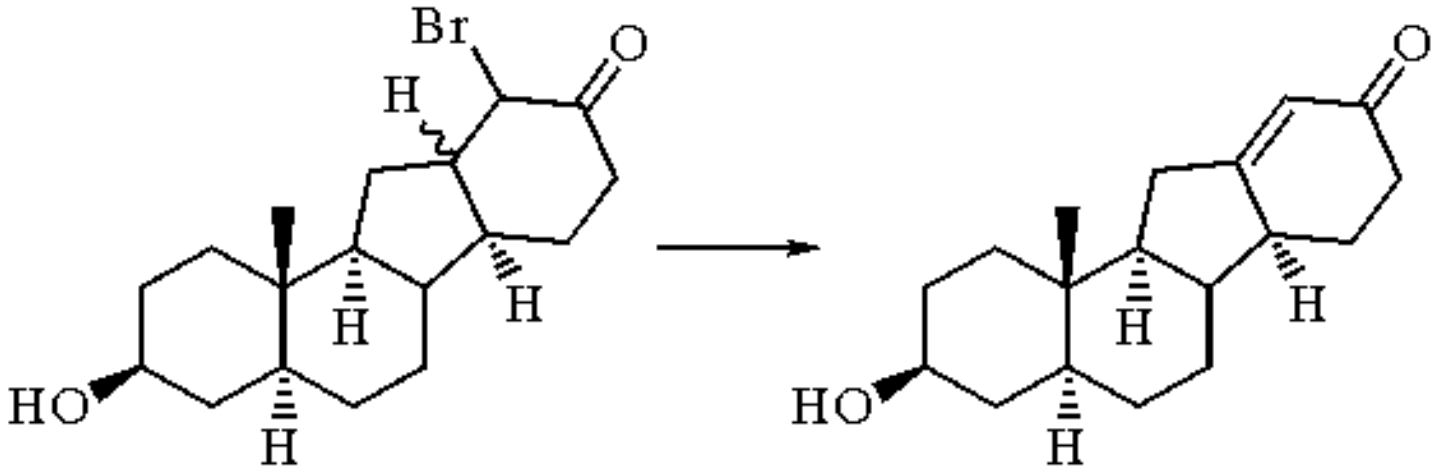

(1)

In the presence of a hydrosilane, magnesium oxide catalyzes the conversion of carbonyl compounds to silyl alcohols (eq 2).[2]

$$R_2CO + (EtO)_3SiH \longrightarrow R_2CH\text{-}OSi(OEt)_3 \qquad (2)$$

Aldehydes are converted to alkenes in a biphasic solid-liquid system with magnesium oxide via Wittig-Knoevenagel or Wittig-Horner reactions (eq 3).[3]

$$PhCHO + NC\text{-}CH_2PPh_3Cl \xrightarrow[87\%]{MgO} PhCH{=}CHCN \qquad (3)$$

$$PhCHO \xrightarrow[\substack{MgO \\ 94\%}]{NCCH_2CN} PhCH{=}C(CN)_2$$

Allylic silylcyanohydrins can be prepared in excellent yields upon treatment of an α,β-unsaturated ketone with ***Cyanotrimethylsilane*** and magnesium oxide. In most cases, less than 1% of the 1,4-adduct was detected (eq 4).[4]

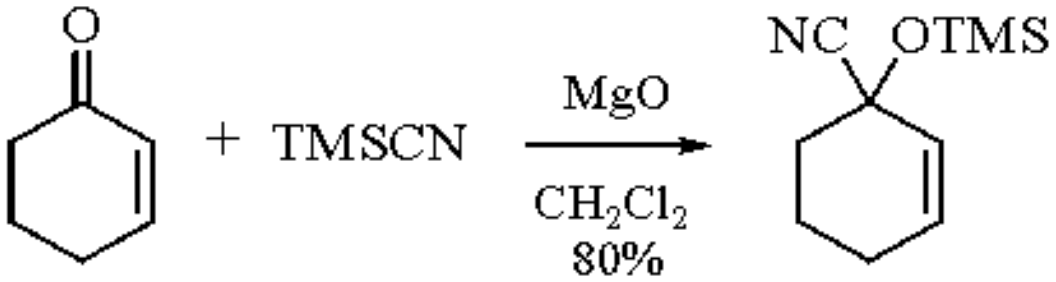

(4)

Reaction with Alkynes.

Both 1 and 2-butyne can be isomerized at low temperature (<100 °C) to yield 1,3-butadiene.[5]

Reductions, Hydrogenolyses, and Dehydrogenation.

As a reduction catalyst, magnesium oxide aids in the dechlorination of dichloropyrimidines to yield pyrimidines.[6] 1,3-Butadiene is converted to *cis*-2-butene under similar conditions.[7] In a unique modification of the Meerwein-Pondorf-Verley reduction, α,β-unsaturated ketones are converted to allylic alcohols in moderate yield (eq 5).[8]

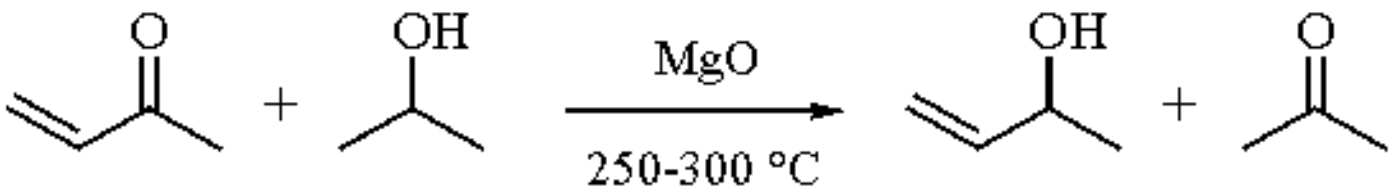

(5)

Conversely, magnesium oxide serves as a dehydrogenation catalyst. Primary amines are converted to nitriles in good yield (eq 6).[9]

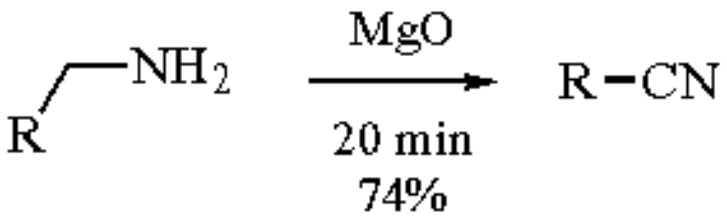

(6)

Miscellaneous.

Epoxides are opened regioselectively by cyanotrimethylsilane in the presence of magnesium oxide (eq 7).[10]

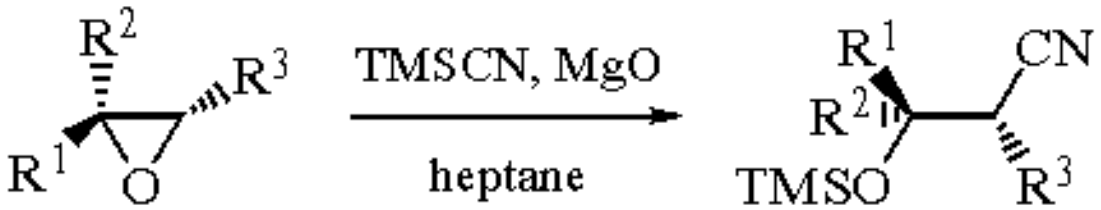

(7)

This reagent also serves as an efficient acid scavenger during the *N*-protection of α-amino acids with benzyloxycarbonyl chloride (***Benzyl Chloroformate***).[11] In acylation reactions, magnesium oxide can be used to *C*-acylate malonates[12] and *N*-acylate anilines.[13]

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Maleic Anhydride[1]

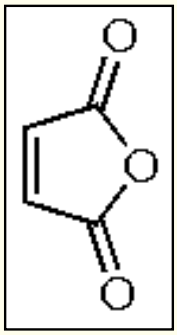

[108-31-6] · $C_4H_2O_3$ · Maleic Anhydride · (MW 98.06)

(reactive dienophile and dipolarophile; undergoes thermal and photochemical [2 + 2] cycloadditions; alkylating and acylating agent)

Alternate Name: MA.

Physical Data: mp 54-56 °C; bp 200 °C; *d* 1.314 g cm^{-3}.

Solubility: sol ether, acetone, chloroform, ethyl acetate, benzene, toluene, carbon tetrachloride, petroleum ether, dioxane.

Form Supplied in: white solid; widely available. *Drying:* at 100 °C.

Purification: recrystallization from acetone/petroleum ether or from hot water. Alternatively sublimed.

Handling, Storage, and Precautions: toxic, an irritant, and corrosive. Avoid inhalation. Store in a tightly sealed brown bottle; avoid exposure to moisture.

Cycloadditions.

Maleic anhydride has served as an excellent dienophile in a variety of Diels-Alder cycloadditions.[2] The use of purified maleic anhydride in the Diels-Alder reaction is recommended in order to remove trace amounts of maleic acid, which may lead to polymerization or diene isomerization. Of historical significance, the first [4 + 2] cycloaddition reported by Otto Diels and Kurt Alder employed maleic anhydride as a dienophile and butadiene as the diene component. Since the initial report, many variations on the cycloaddition process have been published. Reaction conditions vary from below rt to greater than 250 °C. As a representative example, the Diels-Alder reaction of ***Cyclopentadiene*** and MA proceeds at rt to provide the *endo* product in quantitative yield (eq 1).[3] Heterosubstituted dienes typically undergo *endo* selective cycloaddition reactions with maleic anhydride (eqs 2-4).[4] Maleic anhydride also reacts stereoselectively with *ortho*-

quinodimethanes. For example, photoenolization of *o*-tolualdehyde stereoselectively generates an (*E*)-dienol, which is trapped by MA (eq 5).[5]

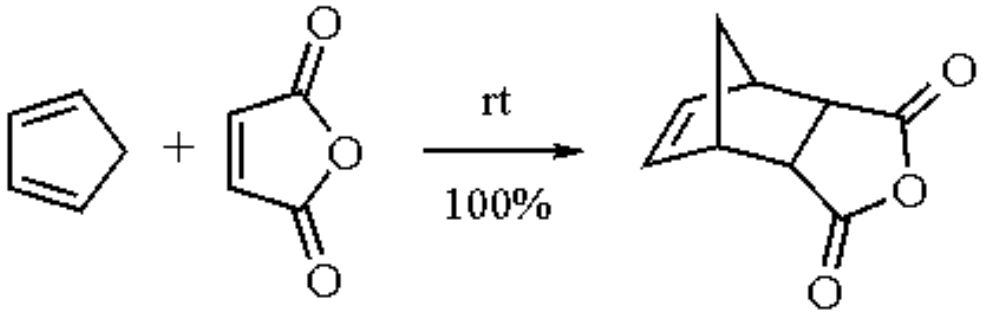

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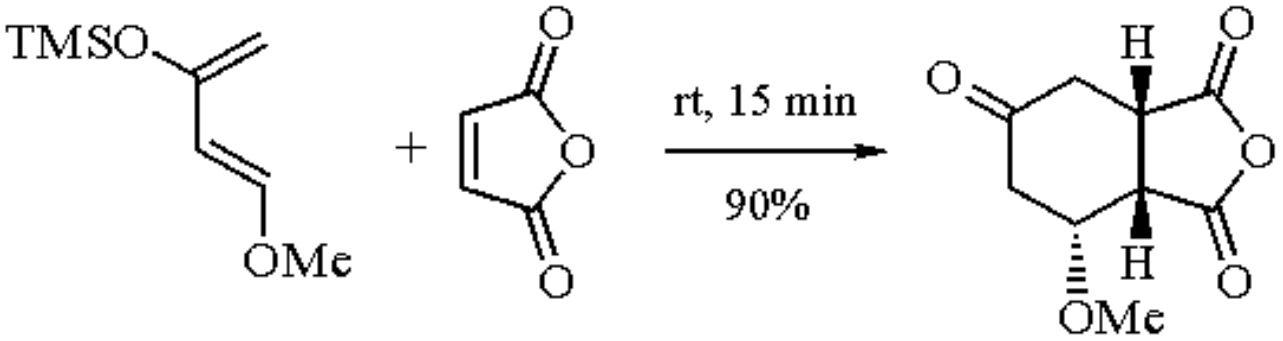

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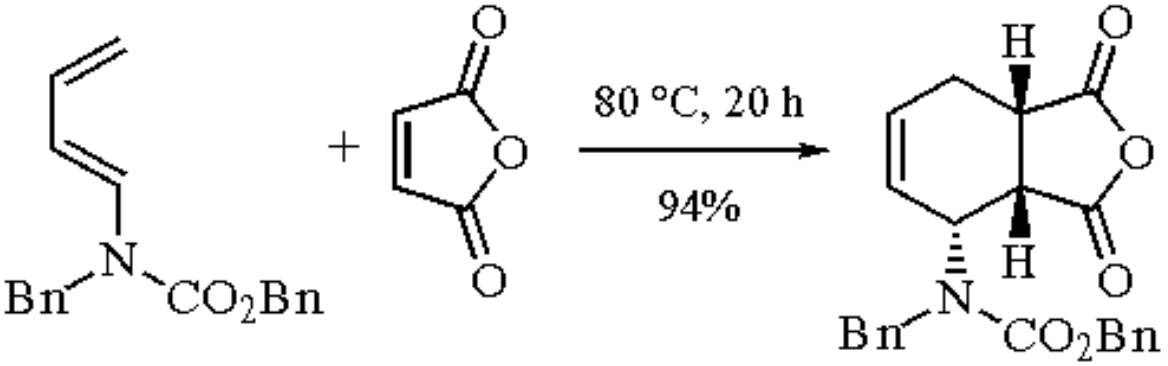

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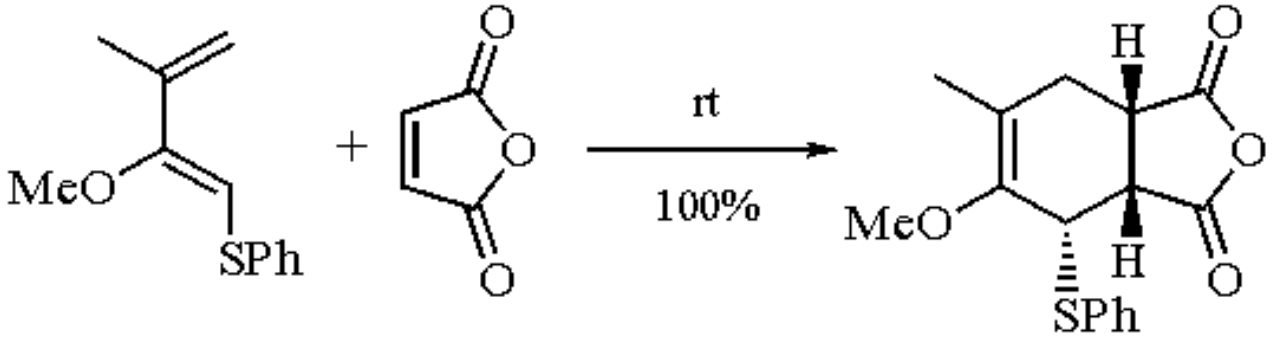

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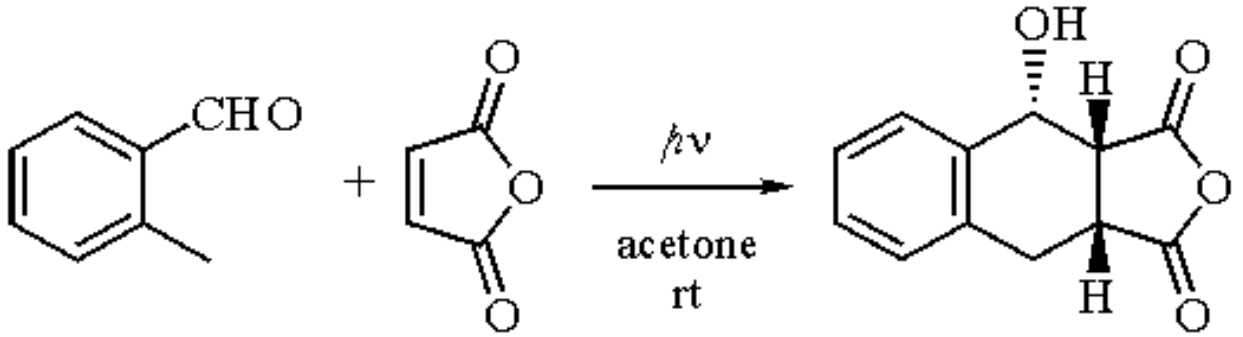

(5)

A number of maleic anhydride derivatives have been examined in the Diels-Alder reaction. For example, the conjugate addition of thiophenol to maleic anhydride followed by chlorination and finally dehydrochlorination affords 2-(phenylthio)maleic anhydride in good overall yield (eq 6). 2-(Phenylthio)maleic anhydride reacts with cyclopentadiene at rt to provide the corresponding Diels-Alder adduct in 83% yield.[6] Maleic anhydride readily undergoes Diels-Alder reactions with furan. However, the Diels-Alder reaction of furan with dimethylmaleic anhydride fails due to the rapid reversion of the Diels-Alder adduct to starting material. On the other hand, the dihydrothiophene derivative of maleic anhydride reacts with furan at high pressure to produce a 20:80 mixture of *endo* and *exo* Diels-Alder adducts in good yield (eq 7).[7] Subsequent ***Raney Nickel*** desulfurization produces the dihydro version of the Diels-Alder adduct corresponding to the dimethylmaleic anhydride product.

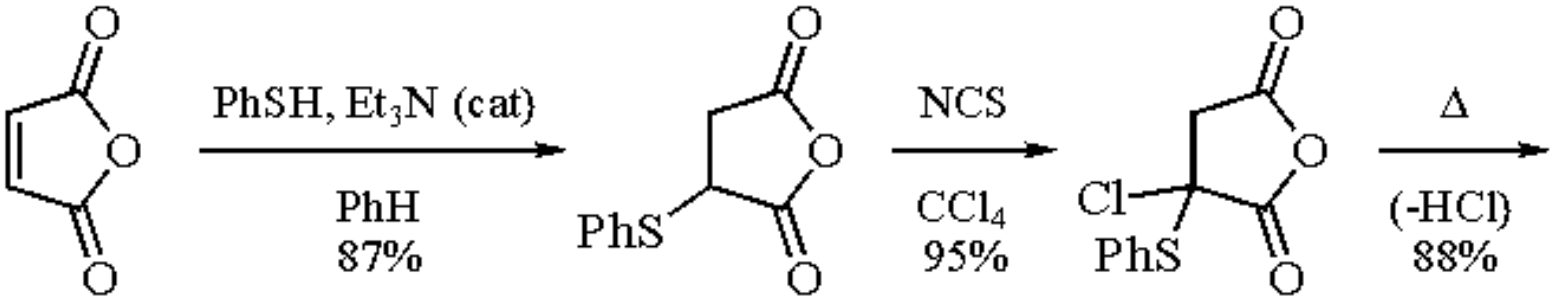

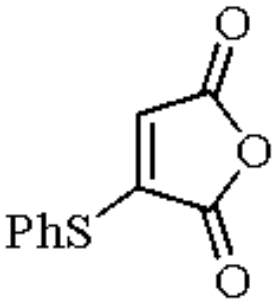

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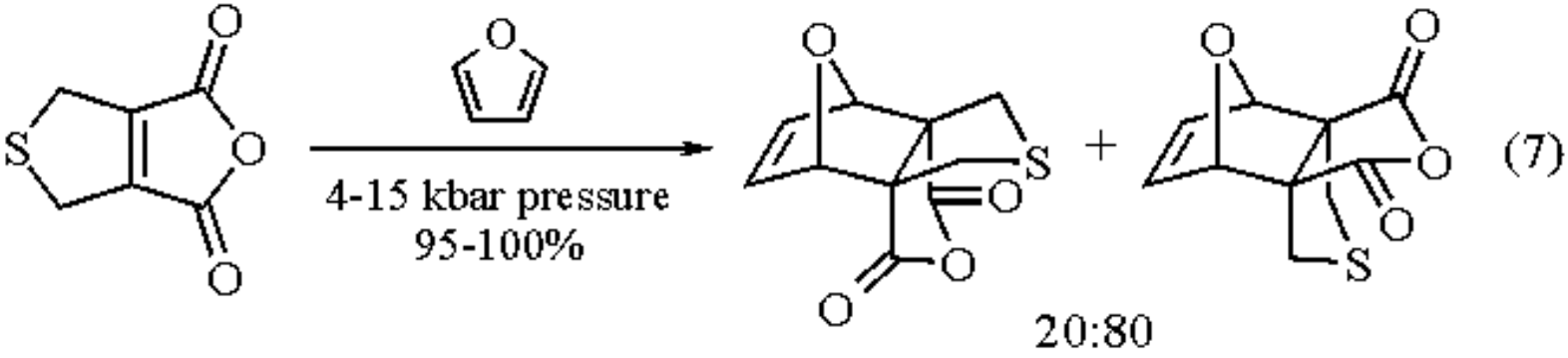

Maleic anhydride undergoes [2 + 2] photocycloadditions with a variety of substrates. Aromatic species (eq 8),[8] isolated alkenes (eq 9),[9] and alkynes (eq 10)[10] readily undergo sensitized photochemical cycloadditions with maleic anhydride. Photochemical [2 + 2] cycloadditions usually employ benzophenone as a sensitizer; however, other sensitizers such as acetophenone, propiophenone, benzaldehyde, and diacetylbenzene have also been utilized. For example, irradiation of a solution of benzene and maleic anhydride in the presence of benzophenone produces a 2:1 maleic anhydride/benzene adduct, which presumably arises from a photochemical [2 + 2] photocycloaddition followed by a Diels-Alder reaction of the resulting diene with a second equivalent of maleic anhydride (eq 8). Irradiation of a solution of maleic anhydride in acetone produces the Paterno-Büchi product in good yield (eq 11).[11] Maleic anhydride can also undergo thermal [2 + 2] cycloadditions. For example, thermolysis of a mixture of allene and maleic anhydride produces the corresponding cyclobutane in 22-26% yield (eq 12) (also see ***Dimethyl Maleate***).[12]

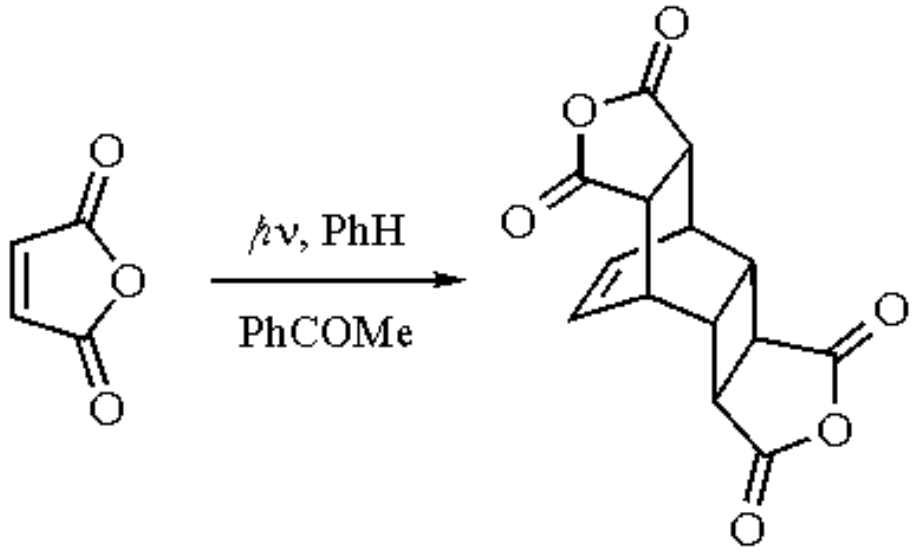

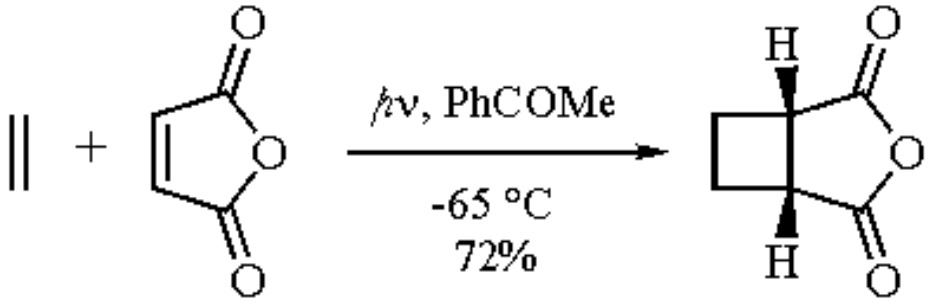

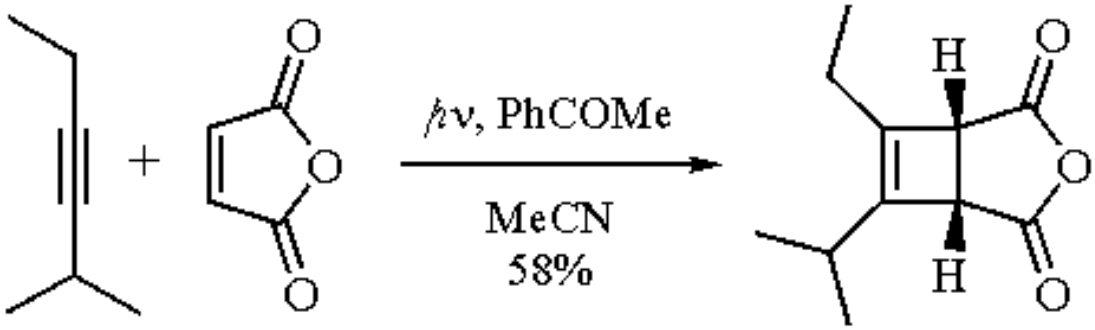

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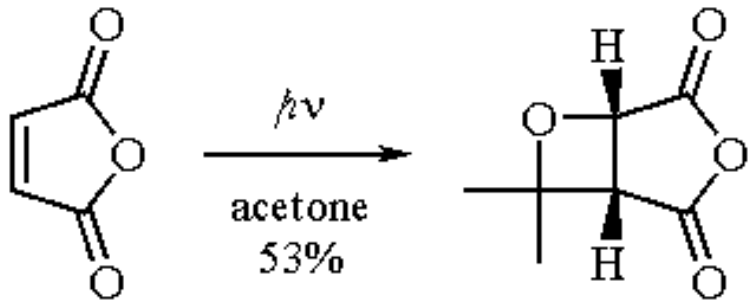

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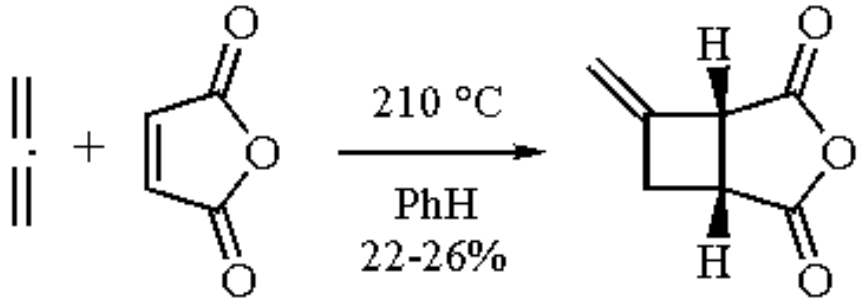

(12)

Maleic anhydride reacts with a variety of dipoles to produce the corresponding cycloadducts in good to excellent chemical yield. For example, cycloadditions with nitrones,[13] diazo compounds,[14] nitrile oxide,[15] and azomethine ylides[16] have been reported (eqs 13-16).

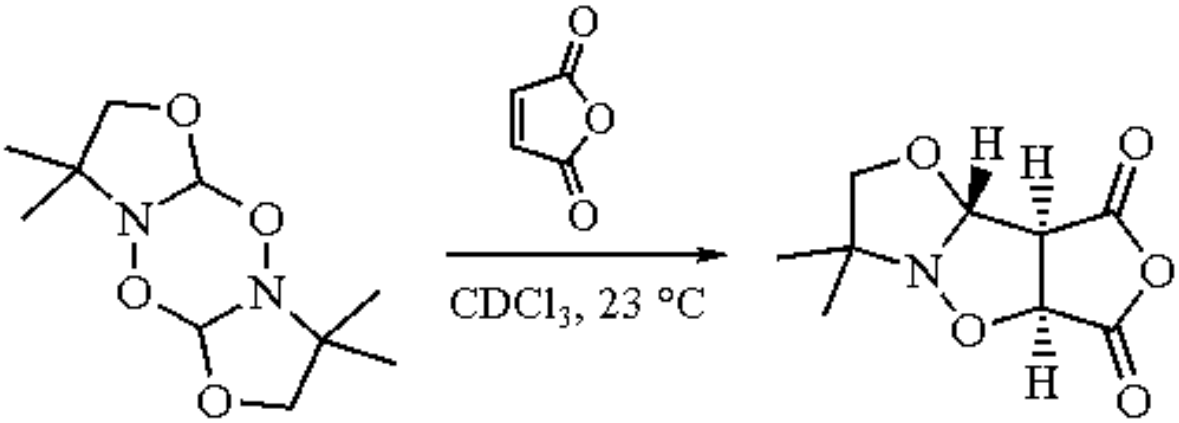

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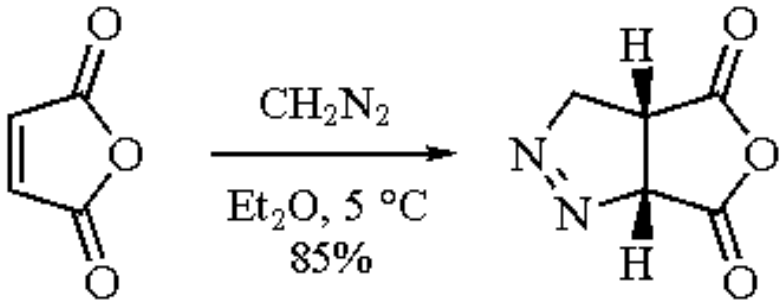

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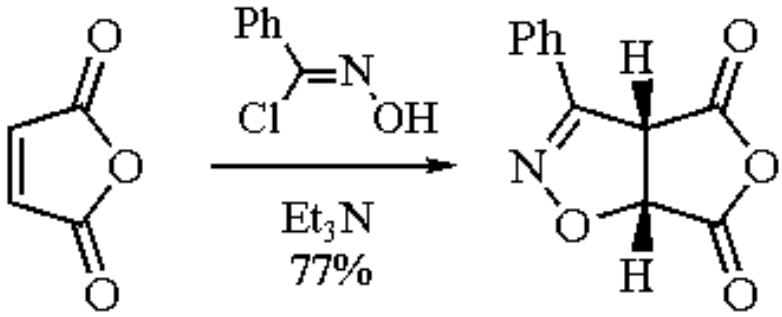

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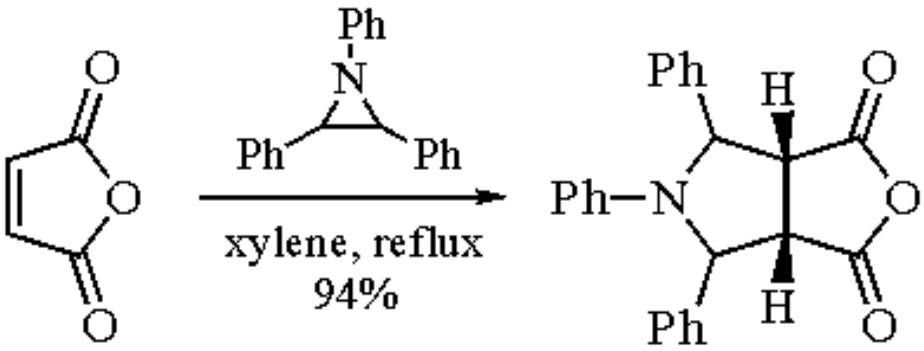

(16)

Acylations and Alkylations.

Maleic anhydride acylates aromatic ring systems under Friedel-Crafts acylation conditions.[17] A typical example is the acylation of benzene (eq 17) to provide β-benzoylacrylic acid in 80-85% yield.[18] The useful quinone naphthazarin can be prepared from dihydroxybenzene and MA under rigorous reaction conditions (eq 18).[19] Substituted aryl-1,3-dioxocarboxylic acids have been prepared by the generation of enolates from aryl ketones followed by acylation with MA (eq 19).[20]

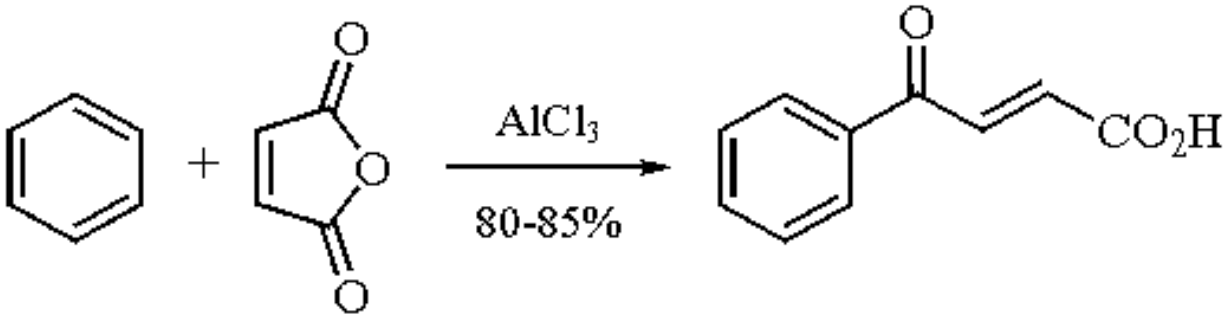

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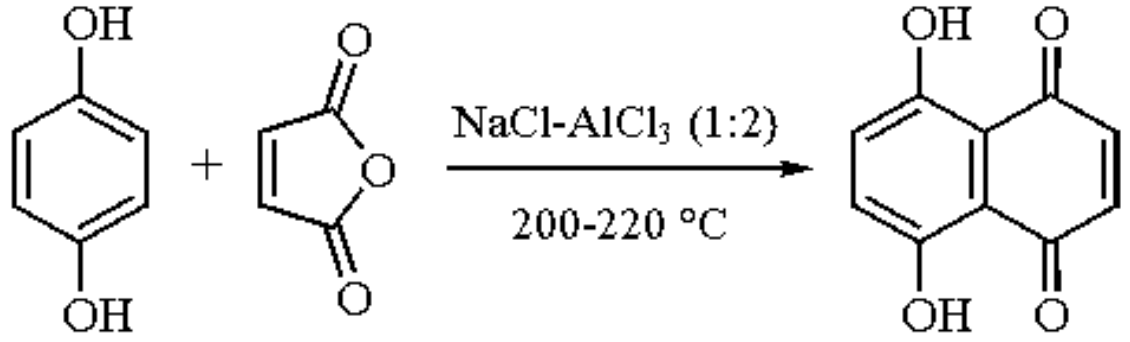

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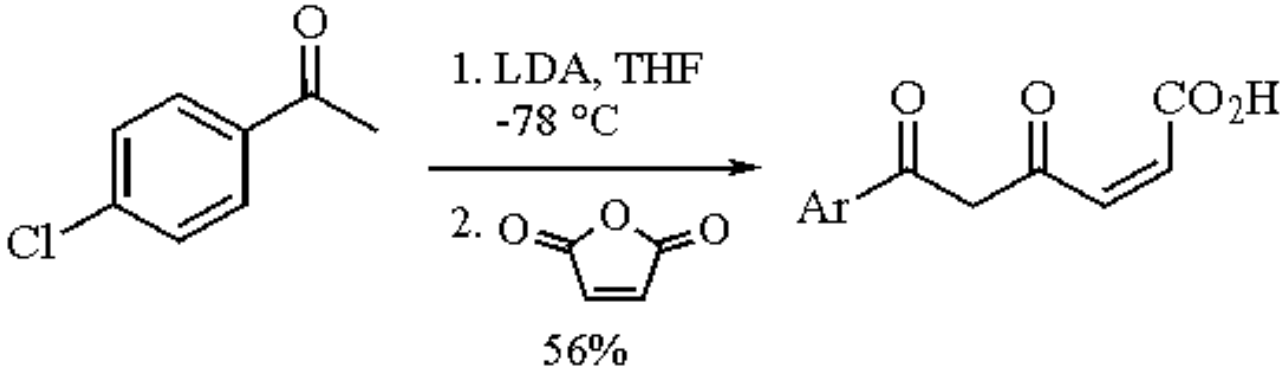

(19)

Maleic anhydride can also partake in Michael-type reactions. As previously described, thiophenol adds in a conjugate fashion to maleic anhydride (eq 6).[6] On the other hand, amines undergo acylation with maleic anhydride to afford the corresponding amides (eqs 20 and 21).[21] It should be mentioned that maleic anhydride is a poor radical acceptor relative to other commonly used radical traps (see ***Dimethyl Fumarate*** and ***Dimethyl Maleate***) due to competing polymerization. For example, benzyl radicals generated by heating a mixture of dibenzylmercury and MA at 100 °C produce only 22% of benzylsuccinic anhydride (eq 22).[22]

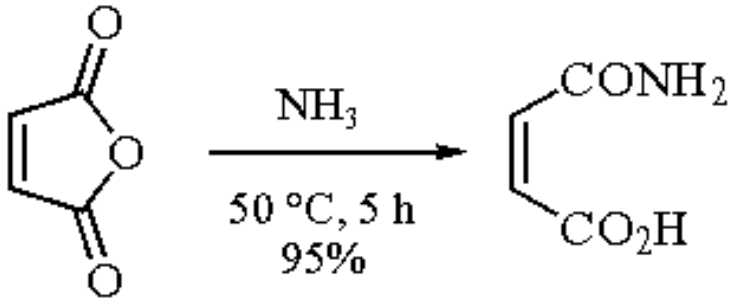

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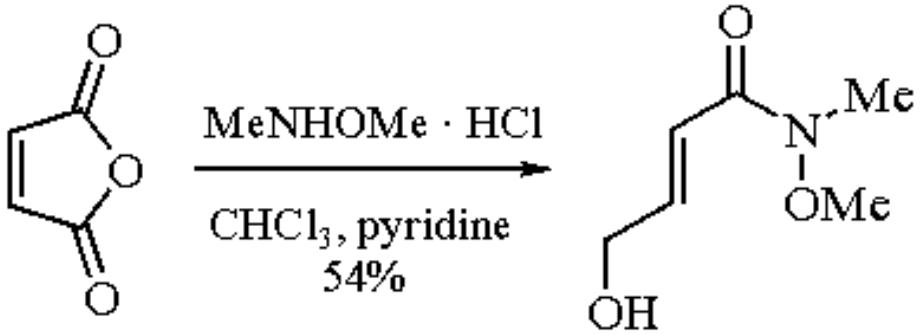

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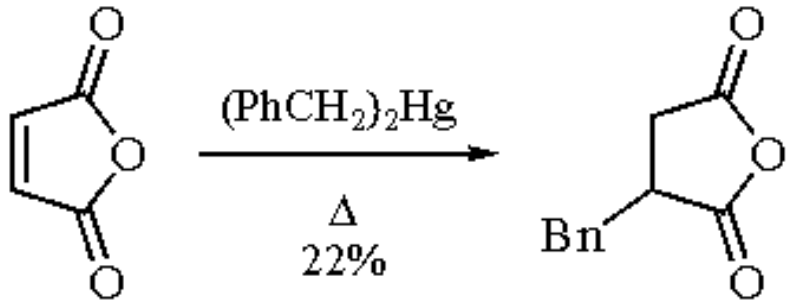

(22)

Miscellaneous.

Under thermal conditions, alkenes bearing an allylic hydrogen will undergo an ene reaction with maleic anhydride. Historically, the first reported ene reaction employed maleic anhydride as the enophile component. This reaction has proven to be quite general and typically requires elevated temperatures to occur (eqs 23 and 24). As an alternative to harsh thermal conditions, high pressure has been reported to induce the ene reaction. For example, maleic anhydride reacts with β-pinene at elevated temperatures to afford the corresponding ene adduct (eq 23), while the same reaction occurs at ambient temperature utilizing 4000 MPa pressure to afford the same adduct in 74% yield.[23]

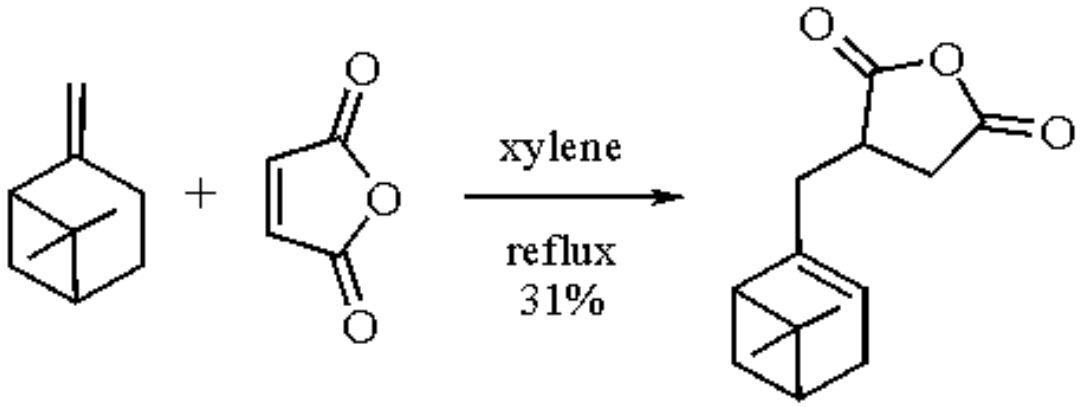

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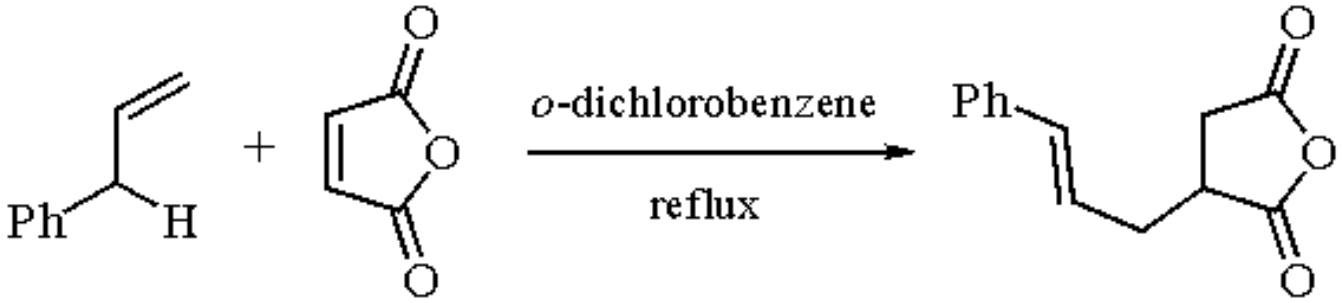

(24)

Maleic anhydride has been utilized as a ligand in a coupling reaction between an alkenylzirconium(IV) complex and a (η^3-allylic)palladium chloride dimer to produce a 1,4-diene (eq 25).[24] In contrast, the overall rate of the coupling reaction was retarded by the addition of a phosphine ligand.

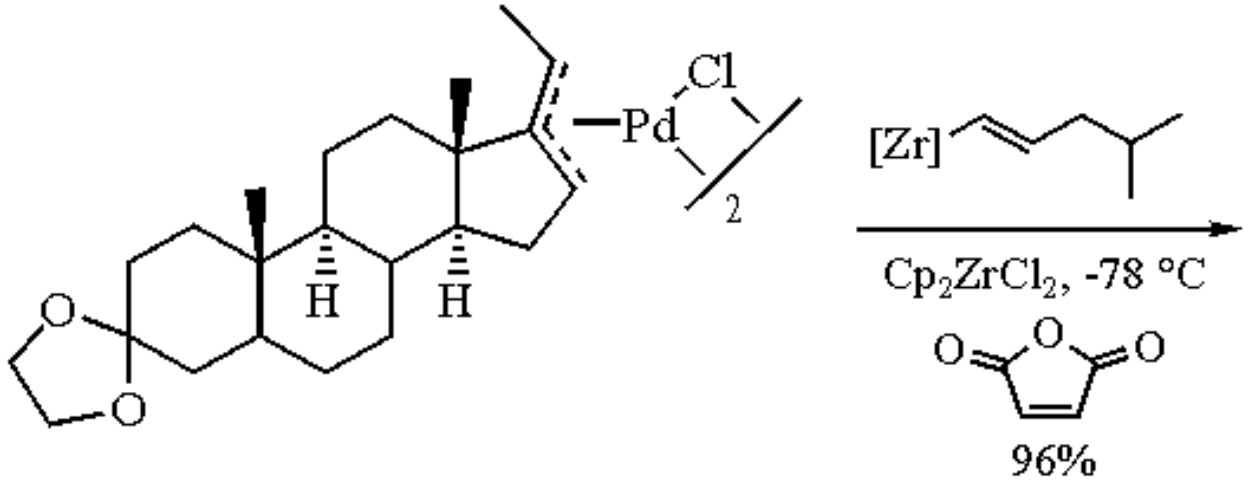

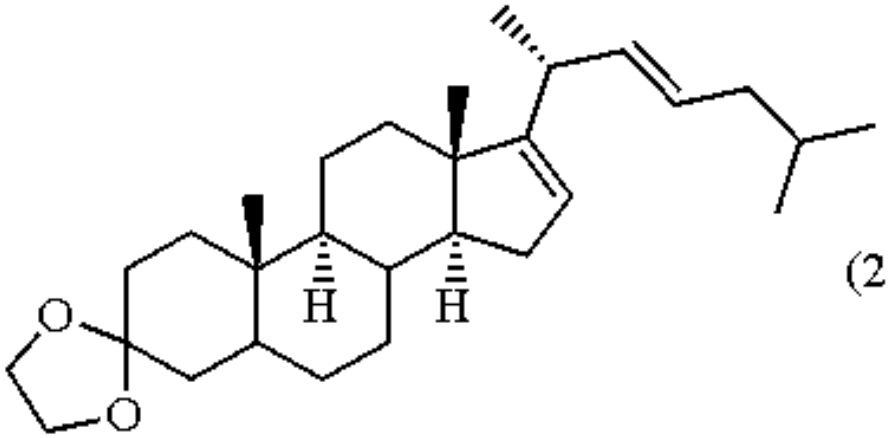

(25)

Related Reagents.

Diethyl Malonate; ***Methylthiomaleic Anhydride***; ***N-Phenylmaleimide***.

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(Maleic anhydride)bis(triphenylphosphine)palladium

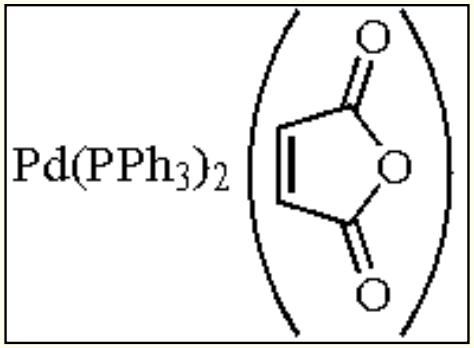

[17830-50-1] · $C_{40}H_{32}O_3P_2Pd$ · (Maleic anhydride)bis(triphenylphosphine)palladium · (MW 729.08)

(zerovalent palladium complex which catalyzes the dimerization of 1,3-dienes and 1,2-dienes[5-9])

Alternate Name: bis(triphenylphosphine)(maleic anhydride)palladium.

Physical Data: mp 147-151 °C (dec).[1]

Solubility: sol THF, acetone, chloroform; low sol benzene.

Form Supplied in: not widely available.

Analysis of Reagent Purity: ^{1}H NMR in $CDCl_3$,[1] benzene-d_6;[2] IR.[2]

Preparative Methods: reaction of ***Tetrakis(triphenylphosphine)palladium(0)*** with ***Maleic Anhydride*** at rt in benzene,[1] benzene/THF,[2,3] or THF[3] yields the title complex as a stable monomeric species, which is purified by crystallization from methanol/hexane.[2] The title reagent has also been synthesized from the putative bis(triphenylphosphine)palladium.[4]

Handling, Storage, and Precautions: stable in air for many hours in the solid state.[2]

Dimerization of Conjugated Dienes.

(Maleic anhydride)bis(triphenylphosphine)palladium (**1**) is a zerovalent palladium complex that has been used extensively as a catalyst for the dimerization of conjugated dienes.[5-7] For example, complex (**1**) efficiently promotes the coupling of ***1,3-Butadiene*** to form linear dimers (eq 1).[5] These reactions are most commonly carried out in

benzene, THF, and acetone. In the presence of protic nucleophiles such as MeOH or ***Morpholine***, the dimerizations take place with addition of the protic component (eq 2). Further studies have demonstrated that (**1**) catalyzes the reaction of 1,3-dienes with acyloin derivatives to yield mainly the product of *O*-alkylation (eq 3).[6]

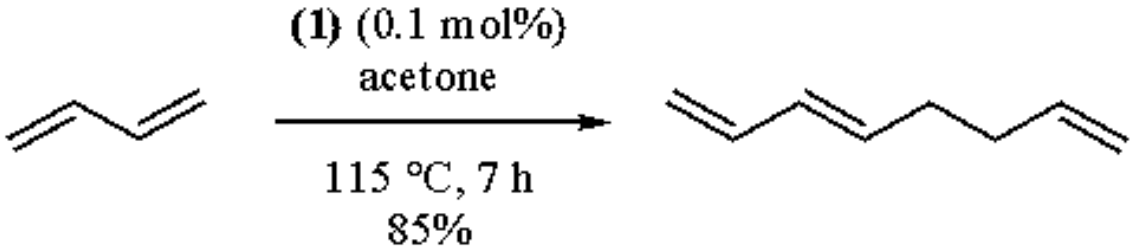

(1)

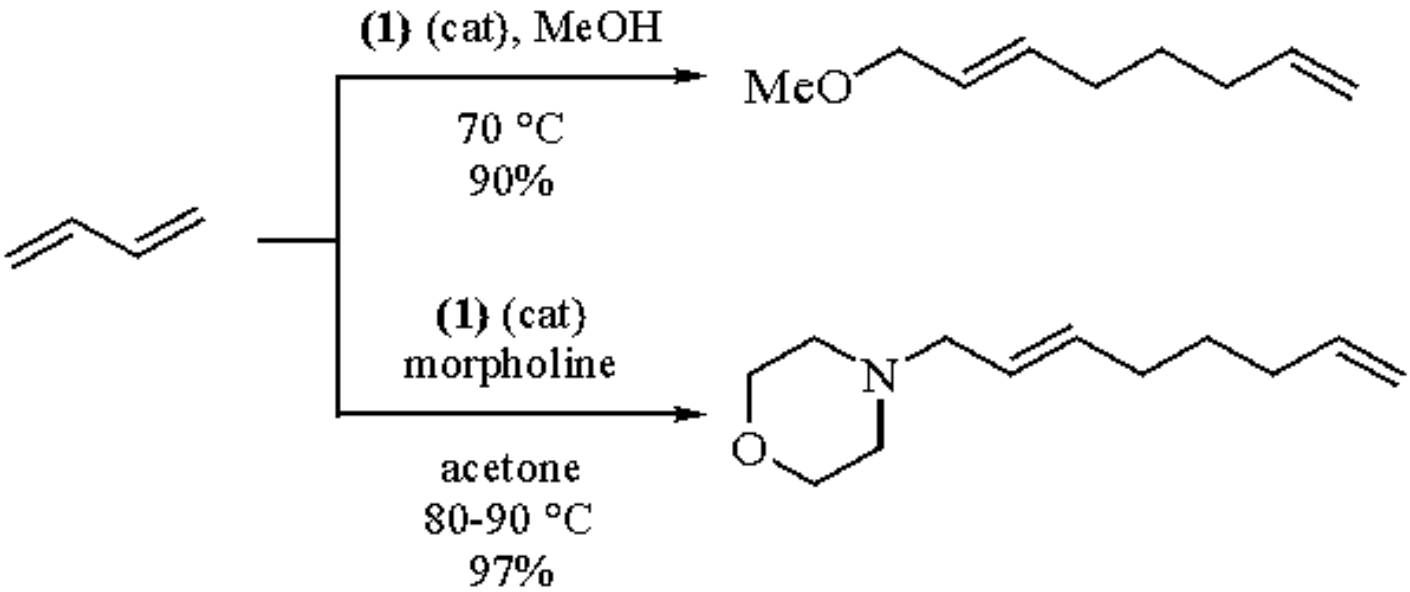

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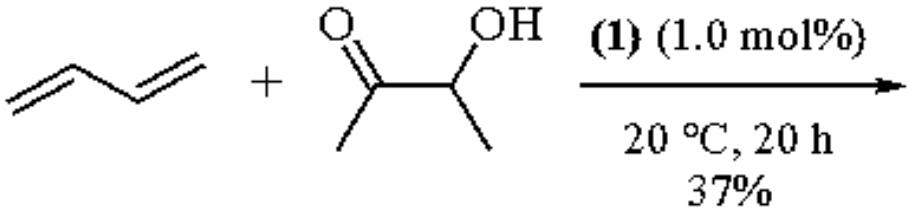

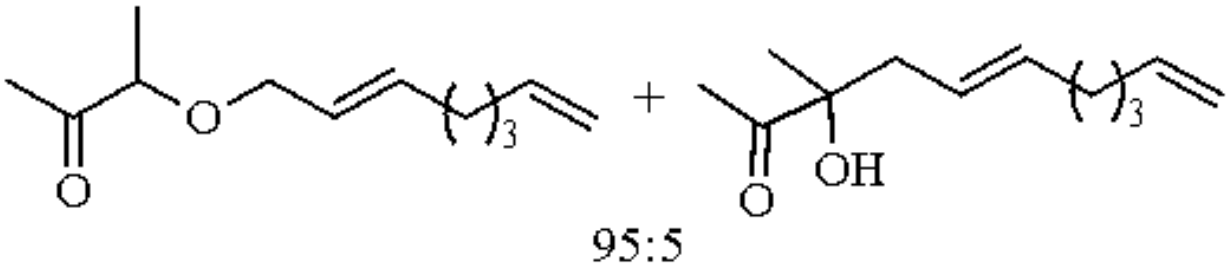

(3)

The title reagent promotes the co-cyclization of conjugated dienes with isocyanates (eq 4).[7]

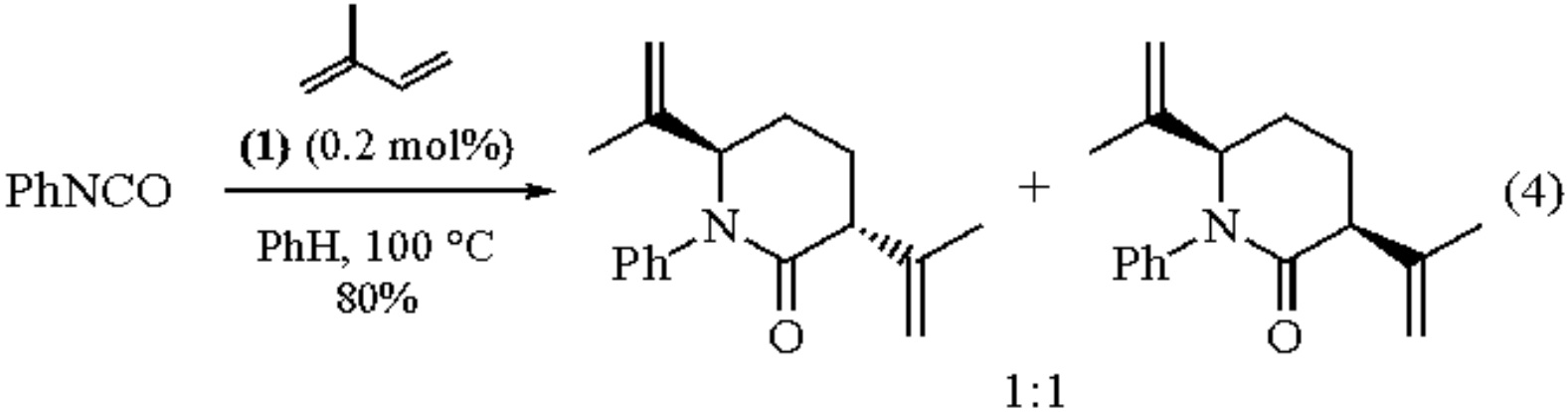

Reaction of Allenes.

Allenes can be condensed with dienes,[8] amines, enamines, and activated methylenes,[9] using reagent (**1**). Secondary amines react efficiently with allenes in the presence of 0.2 mol % of (**1**) to provide substituted 1,3-dienes (eq 5). Primary amines give the corresponding bis(dienyl)amines, albeit in lower yields. Carbon acids also react with allenes in the same way to yield substituted dienes (eq 6). In all these reactions, complex (**1**) was the palladium reagent of choice due of its ease of preparation, good stability, and high reactivity.[9]

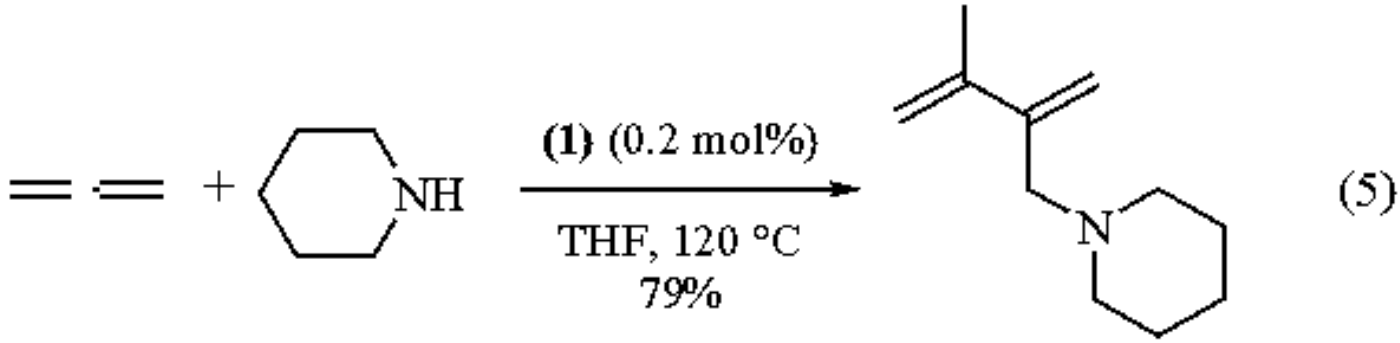

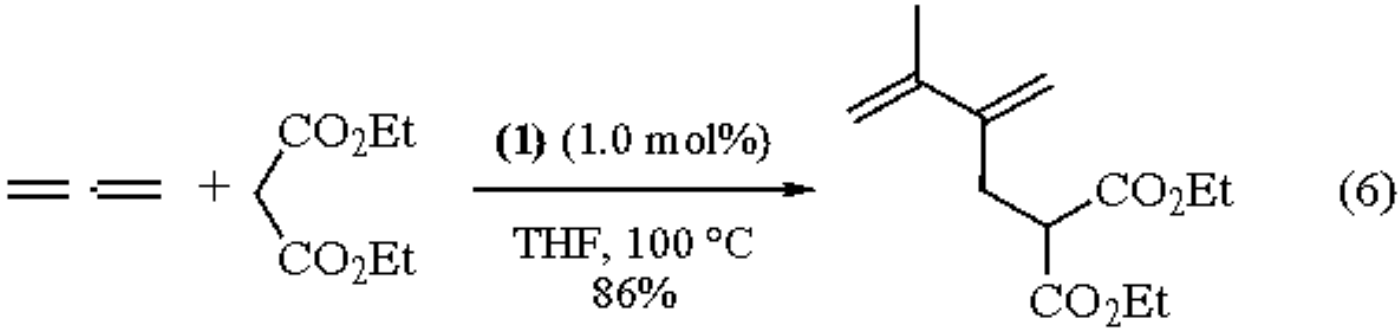

Miscellaneous.

In the presence of an acid catalyst, reagent (**1**) promotes the addition of cyclic amines to homoconjugated dienes such as norbornadiene (eq 7).[10]

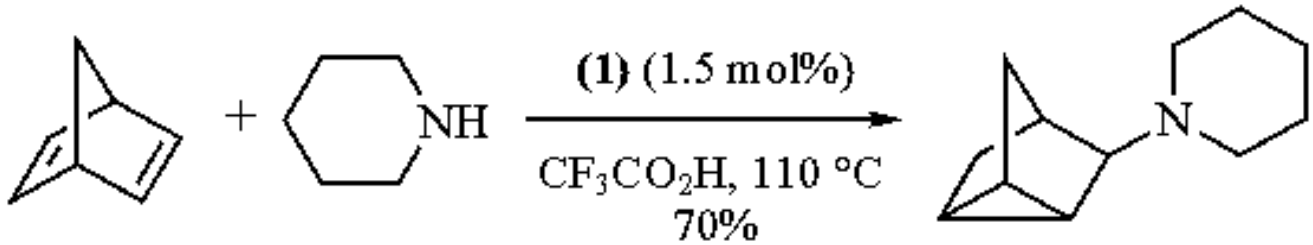

(7)

Reagent (**1**) catalyzes the hydrosilation of allenes and dienes. The reaction between allene and triethylsilane gives the 1:1 addition product, allyltriethylsilane, in 48% yield.[9] The analogous reaction with 1,3-dienes yields the linear dimer of the diene (eq 8).[11] Catalysis of a Si-Si/Si-Si metathesis reaction, which proceeds very slowly at 200 °C, can be catalyzed by reagent (**1**) (eq 9).[12]

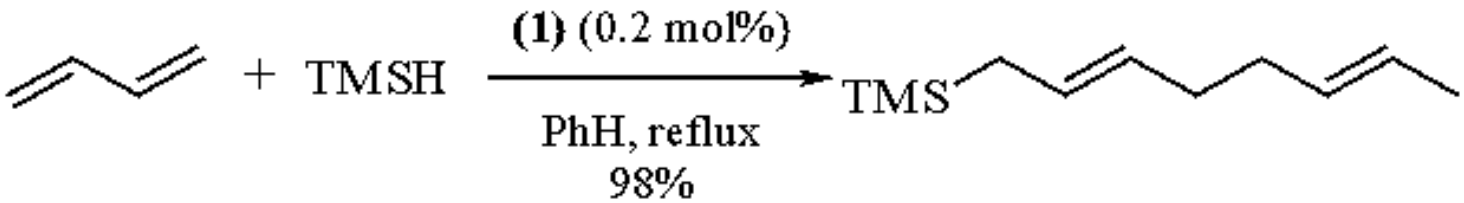

(8)

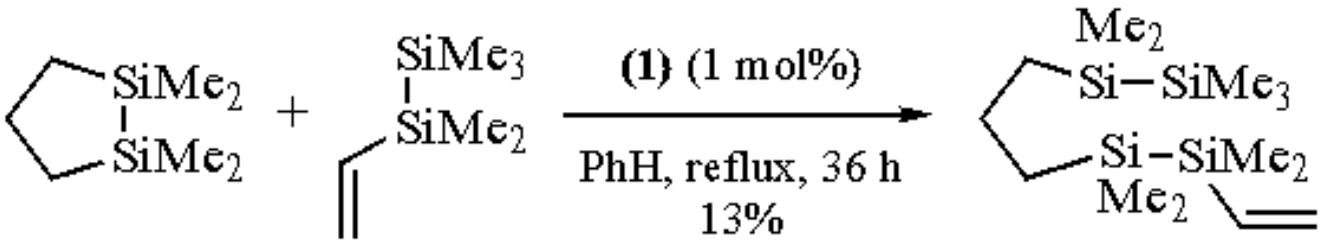

(9)

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Malondialdehyde[1]

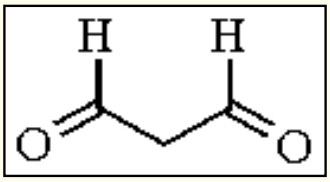

[542-78-9] · $C_3H_4O_2$ · Malondialdehyde · (MW 72.07)

(behaves as multifunctional compound;[1] aldehyde reactions;[2-4] forms both cyclic and acyclic acetals;[5] may react as vinylog of formic acid;[6-8] chelates with metal ions as β-dialdehyde;[8] behaves as push-pull alkene[9])

Alternate Names: MDA; malonaldehyde; 1,3-propanedial.

Physical Data: free aldehyde: hygroscopic needles; mp 72-74 °C; sodium salt: mp 245 °C (dec); UV λ_{max} (0.1 N HCl) 245 nm (ε 12 800), (0.1 N NaOH) 267 nm (ε 29 400); ^{1}H NMR (D_2O) δ 5.73 (t, 1H, J = 10.1 Hz), 9.08 (d, 2H, J = 10.1 Hz); ^{13}C NMR (D_2O) δ 110.3, 193.6; pK_a (H_2O) = 4.5.[1]

Solubility: sodium salt: sol EtOH, MeOH, H_2O; moderately sol CH_2Cl_2; insol ether.

Form Supplied in: can be generated in situ from commercially available malondialdehyde bis(dimethyl acetal) *[102-52-3]* or bis(diethyl acetal) *[122-31-6]*. However, it is unstable and is best handled as its sodium salt.

Handling, Storage, and Precautions: unstable and easily polymerizes. The generation of MDA in situ from the hydrolysis of its bis-acetals results in the formation of a number of side products, including β-alkoxyacrolein, 3,3-dialkoxypropionaldehyde, and fluorescent condensation polymers of MDA. Crystalline sodium MDA, which is much more stable than MDA, is the recommended synthetic reagent. Sodium MDA, if stored under nitrogen in a refrigerator, is stable for months.

Preparation of Sodium Malondialdehyde.

This reagent is most conveniently prepared by the acid hydrolysis of malondialdehyde bis(dimethyl acetal) with 1 N HCl and then conversion of the released MDA to its sodium salt by treatment with 5 N NaOH (pH 10).[1] Sodium MDA crystallizes from ethanol-ether as white needles.

Derivatives of Malondialdehyde.

A number of 2-substituted derivatives of MDA are known, including alkyl, aryl, halo, nitro, amino, cyano, diazo, formyl, and methylene compounds.[10-15]

Structure of Malondialdehyde.

MDA exists almost entirely in its enolic form. There are three possible tautomeric forms of enolic MDA, all of which are interconvertible by the processes of tautomerization and carbon-carbon single bond rotation.[3,16-18] In organic solvents such as CCl_4 and $CHCl_3$, the major form is the intramolecularly hydrogen-bonded *cis* form. In polar hydroxylic solvents such as water, MDA exists largely as the *trans* form (eq 1).[3]

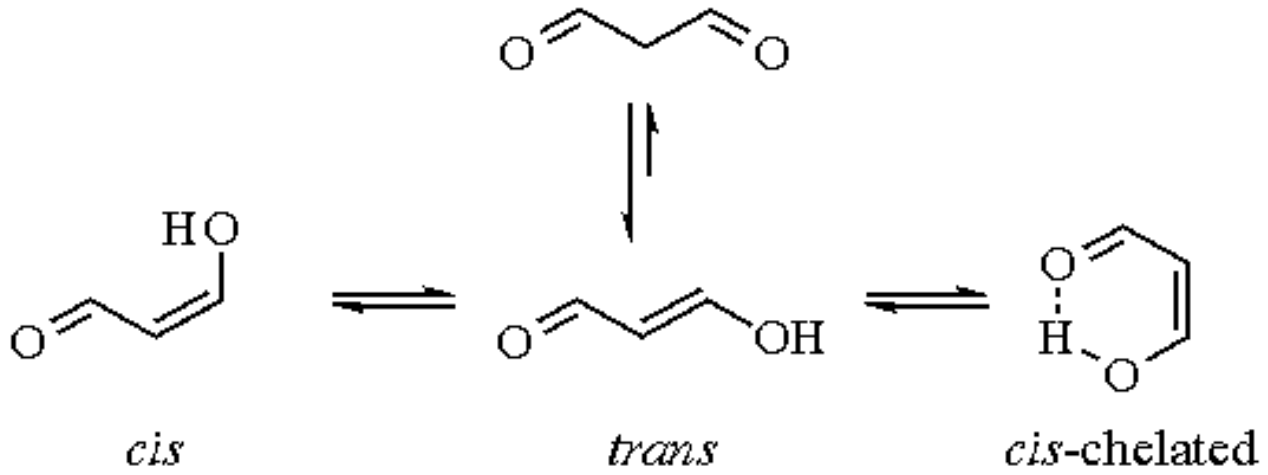

(1)

Reactions of Malondialdehyde.

MDA behaves in some respects as a typical aldehyde. Thus it forms dianils[3] and cyclic and acyclic acetals,[5] and forms chelates with metal ions.[8] MDA may also be looked upon as a vinylog of formic acid in that it undergoes reactions that are typical of carboxylic acids, such as salt formation and conversion to vinylogous esters with diazomethane.[6-8] In some of its reactions, MDA behaves as a push-pull alkene and participates in both nucleophilic and electrophilic substitution reactions.[9] For example, MDA undergoes nucleophilic attack at the terminal positions in its reaction with amines and electrophilic substitution at C-2 in its reaction with bromine (eqs 2 and 3).[3,9,19,20]

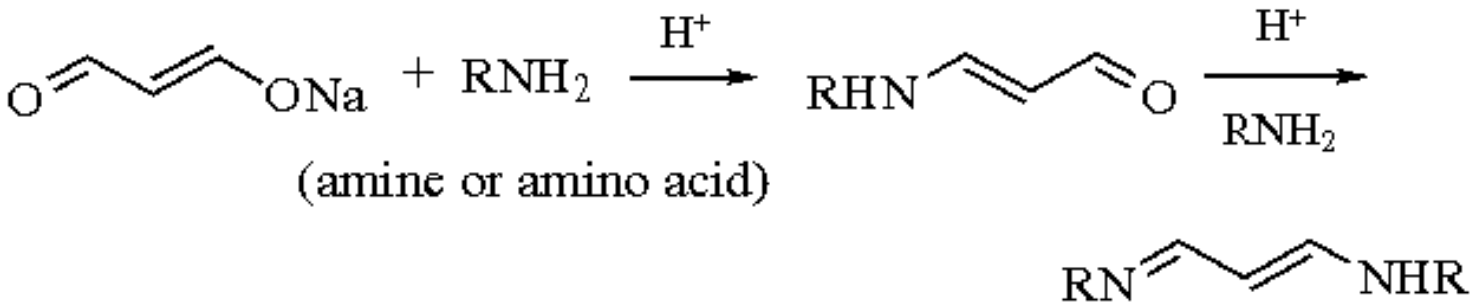

(2)

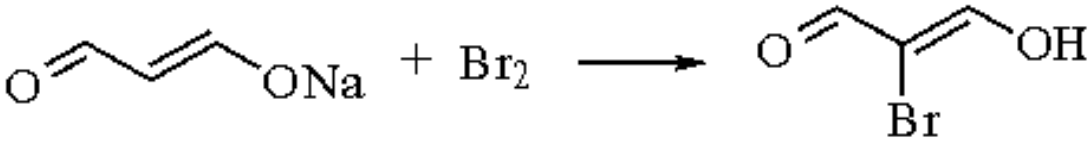

(3)

MDA reacts with dimethyl 3-oxoglutarate to form phenolic or bicyclic adducts, depending on the pH of the reaction.[20] The synthesis of secologanin, a biosynthetic precursor of secoiridoid glycosides, was achieved using sodium MDA in a key step of the synthesis (eq 4).[21]

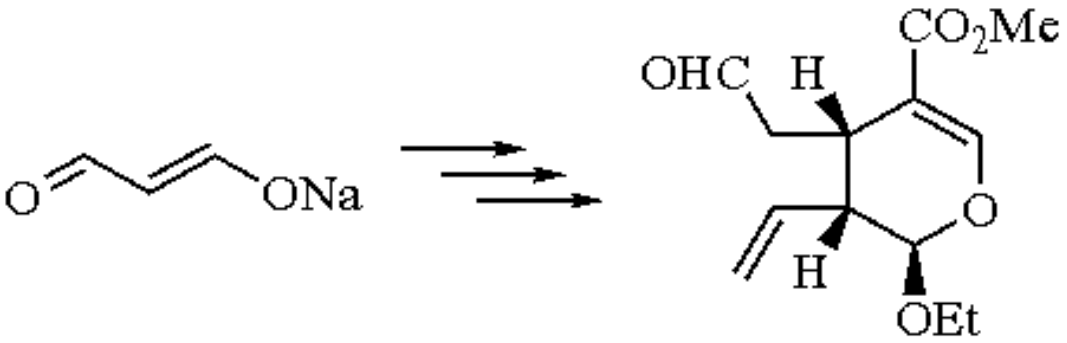

(4)

The thiobarbituric acid (TBA) test is used extensively as a spectrophotometric method for the detection of peroxidation of unsaturated fatty acids.[22] The assay apparently is for the detection of MDA, and the red pigment (TBA-MDA adduct) formed is a mixture of equilibrating structures of the type (**1**).[23]

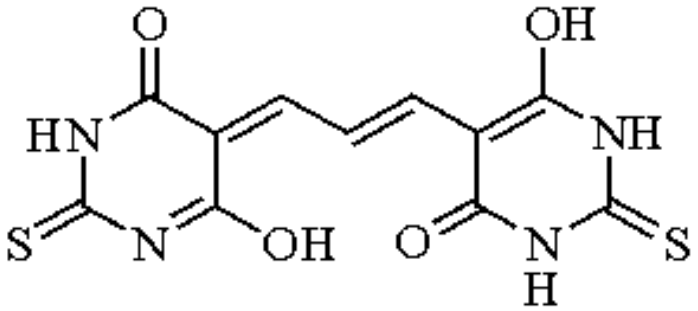

(1)

Nucleic acid bases are modified by MDA. For example, treatment of guanosine or deoxyguanosine with MDA results in the formation of a nucleoside with a tricyclic base as the primary product. Further reaction of this adduct with MDA produces a compound bearing a tetracyclic base moiety (eq 5).[24-27] The modification of other nucleic acid bases has also been studied.[28,29]

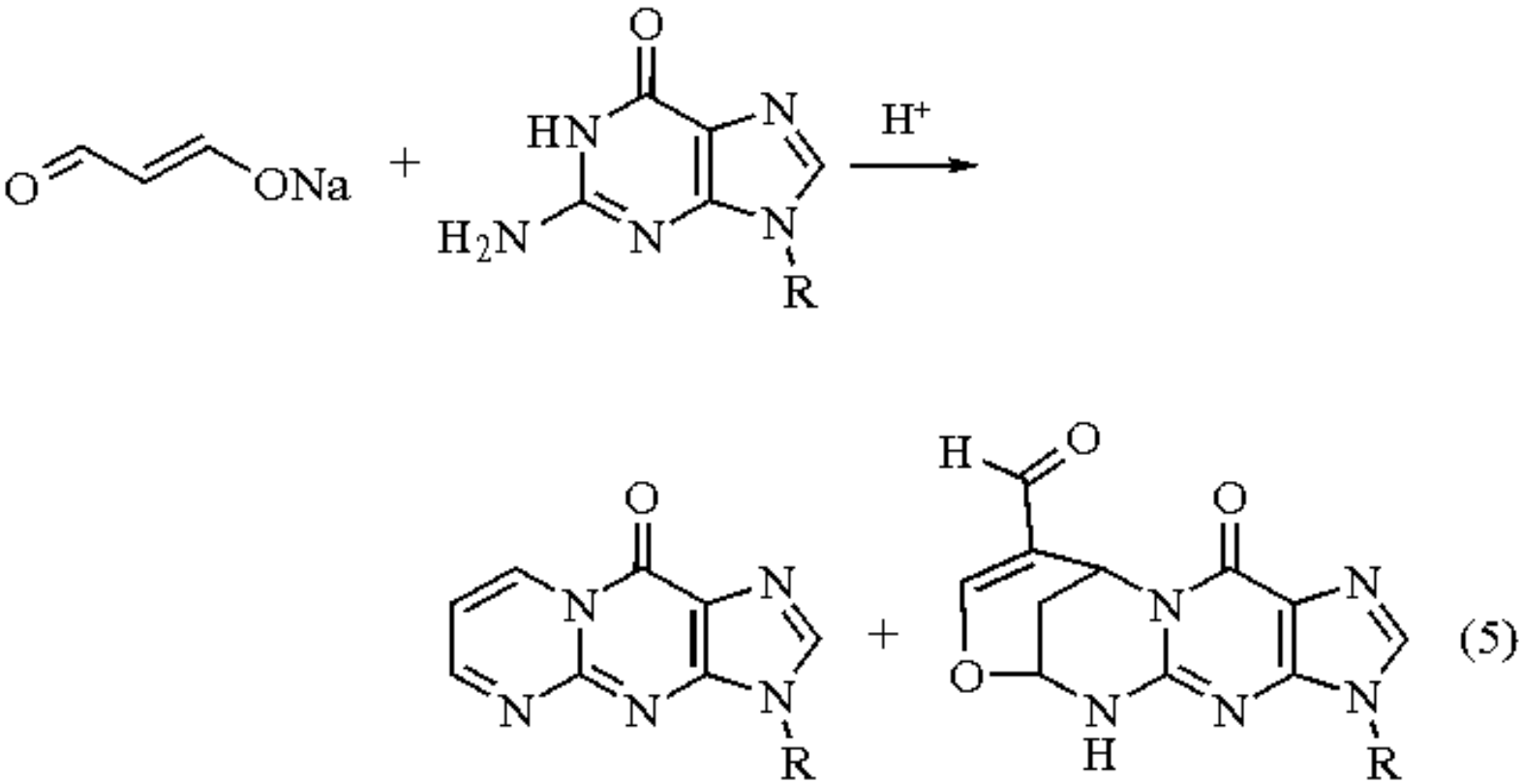

R = ribosyl or deoxyribosyl

Interestingly, MDA reacts with amines and amino acids in the presence of a monoaldehyde to produce highly fluorescent and stable dihydropyridines.[1,30,31] A plausible mechanistic explanation of this transformation involves the condensation of MDA with the amine to form an enaminal (eq 6), and with the additional aldehyde to produce an alkylidene MDA derivative. Subsequent Michael reaction between these two species, followed by cyclization and elimination of water, results in the formation of the dihydropyridine (eq 7).

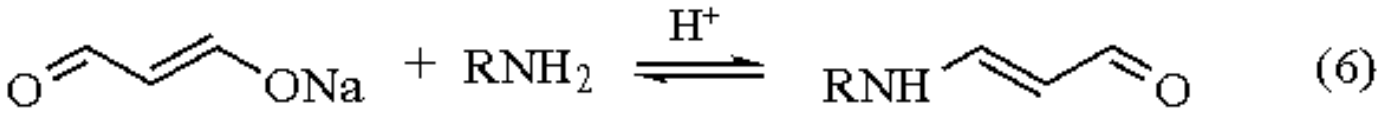

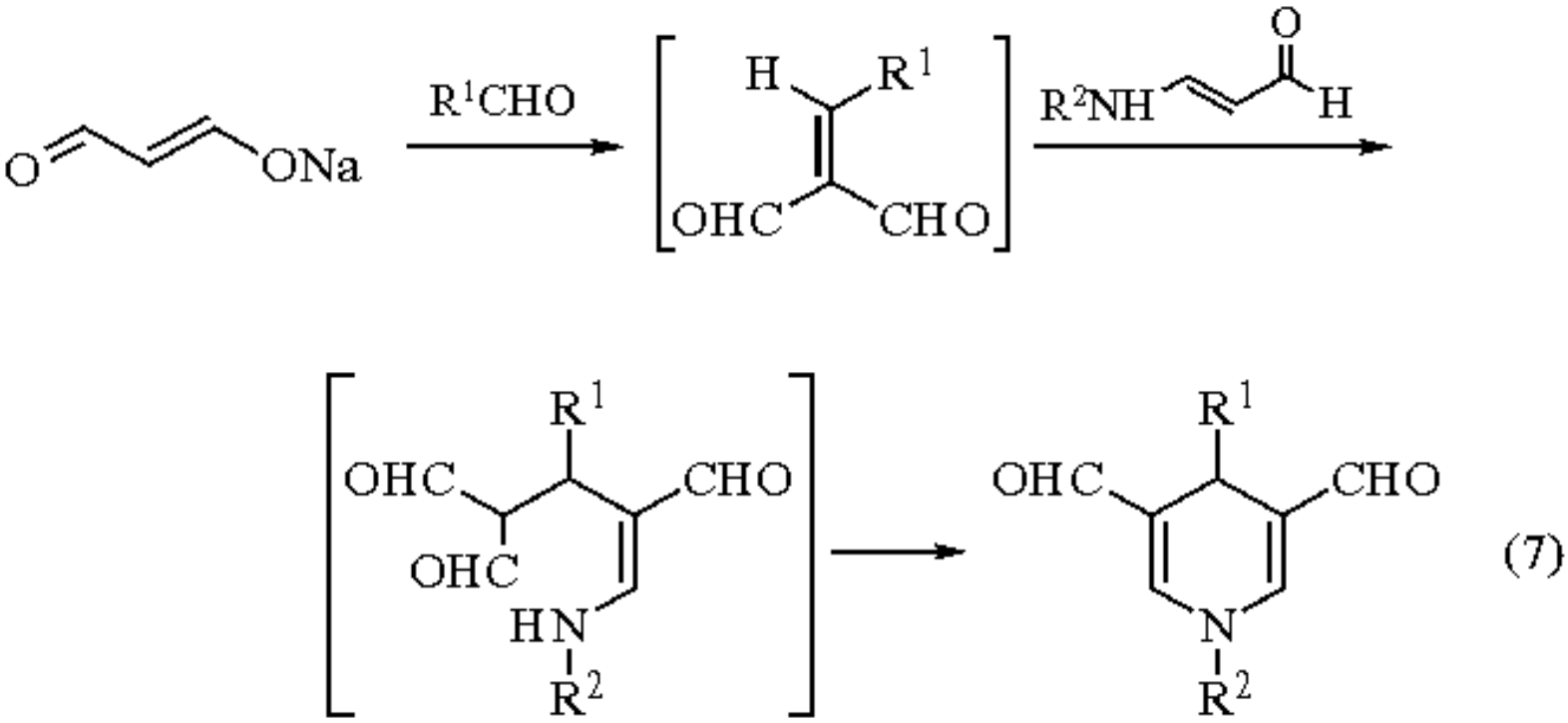

R^1, R^2 = alkyl, aryl

Methylenemalondialdehydes (alkylidenemalondialdehydes), intermediates in the synthesis of the aforementioned dihydropyridines, were first utilized under conditions of in situ generation by Woodward and co-workers in the synthesis of cephalosporin C.[32] Various masked forms of MDA have also been used in synthesis (see, for example, Cho et al.[33]).

Related Reagents.

Formic Acid; ***Glyoxal***; ***Succindialdehyde***.

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Vasu Nair

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Malonic Acid[1]

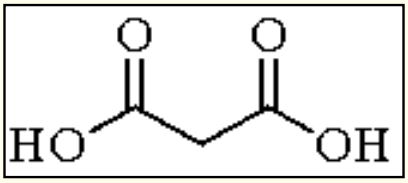

[141-82-2] · $C_3H_4O_4$ · Malonic Acid · (MW 104.07)

(useful reagent for synthesis of cinnamic and acrylic acid derivatives via the Doebner modification[2] of the Knoevenagel condensation[3])

Alternate Name: 1,3-propanedioic acid.

Physical Data: mp 135-137 °C; *d* 1.619 g cm^{-3}; pK_a (H_2O) 2.38 and 5.69.[1a]

Solubility: very sol H_2O; sol Et_2O, EtOH; insol benzene; moderately sol pyridine.

Form Supplied in: white powder; widely available.

Preparative Method: can be prepared from chloroacetic acid;[1c] a number of monosubstituted derivatives are also commercially available.

Handling, Storage, and Precautions: strong irritant; LD_{50} 1310 mg/kg (rat).[1a]

Synthetic Applications.

Malonic acid has been widely used in the Knoevenagel condensation with aldehydes and some ketones.[3] The alkylidene or arylidene malonic acid derivatives can be obtained when ethanolic ammonia or acetic acid is the reaction solvent (eq 1).[4] The Doebner modification, in which pyridine is used as the solvent, generally results in condensation with decarboxylation to provide cinnamic or acrylic acid derivatives.[2,5] Other amines, such as piperidine, or amine salts, such as piperidinium acetate, have also been used to catalyze the reaction. 2,3-Dimethoxycinnamic acid has been prepared in good yield under these conditions (eq 2).[5c] The *trans*-α,β-unsaturated acids are generally obtained. The Doebner conditions are usually the method of choice for the preparation of cinnamic acid derivatives, in comparison with other classical synthetic procedures.[2]

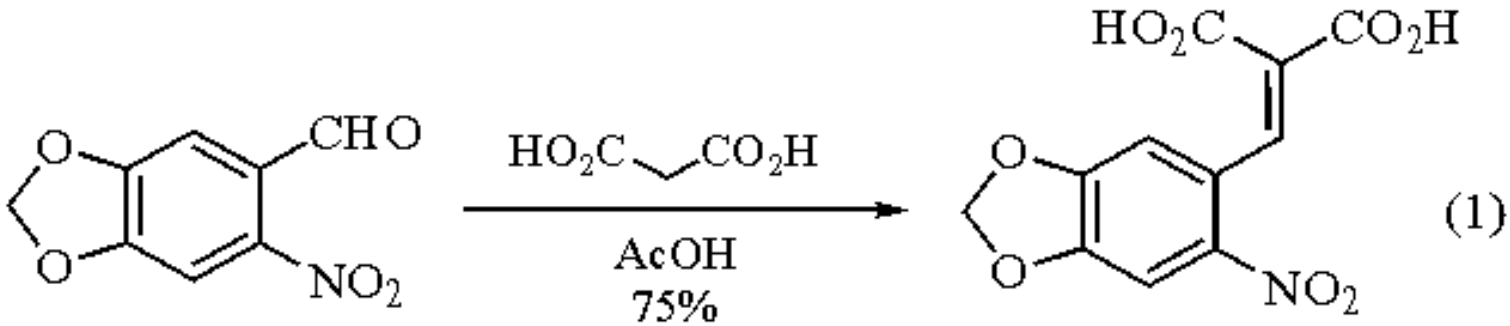

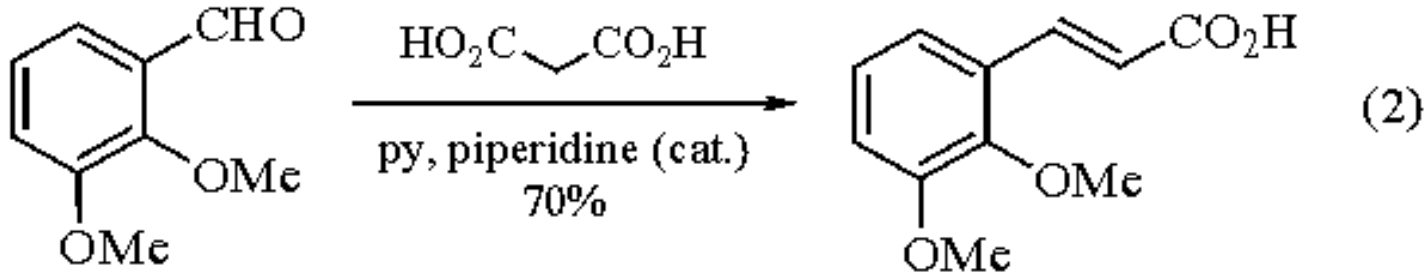

Yields are generally high, and the reaction is usually not complicated by side reactions, such as the Michael addition of a second malonic acid molecule to the product.[3] Monosubstituted malonic acid derivatives also undergo condensation with aldehydes to provide α-alkylcinnamic acids, but the synthetic utility is limited due to steric problems.[3]

The condensation sometimes proceeds inefficiently with aliphatic aldehydes, resulting in low yields or mixtures of the α,β- and β,γ-unsaturated acids. For these reasons, a number of modified or improved Knoevenagel/Doebner procedures for the synthesis of acrylic acid derivatives have been reported.[6] One such modification, in which acrolein is added dropwise to malonic acid in pyridine at 60 °C, provides *trans*-2,4-pentadienoic acid in a higher and more reproducible yield than earlier procedures (eq 3).[5a] The conditions can also be modified to provide *trans*-β,γ-unsaturated acids exclusively in moderate yield.[6a]

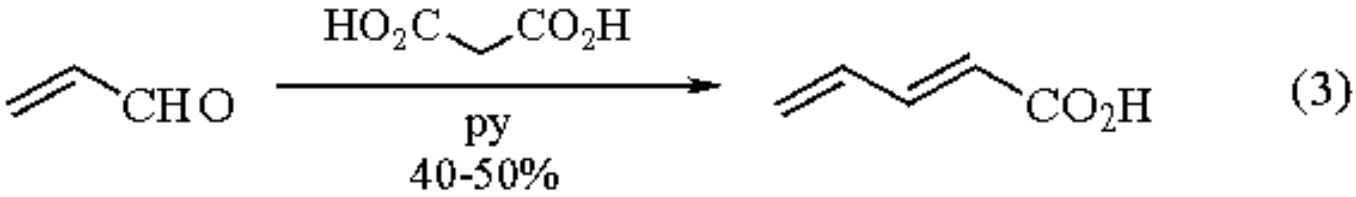

The final step in the synthesis of strychnine (**2**) has been accomplished by treatment of the aldehyde (**1**) with malonic acid.[7] Knoevenagel condensation under these conditions is accompanied by decarboxylation and cyclization to form the final two rings (eq 4).[7]

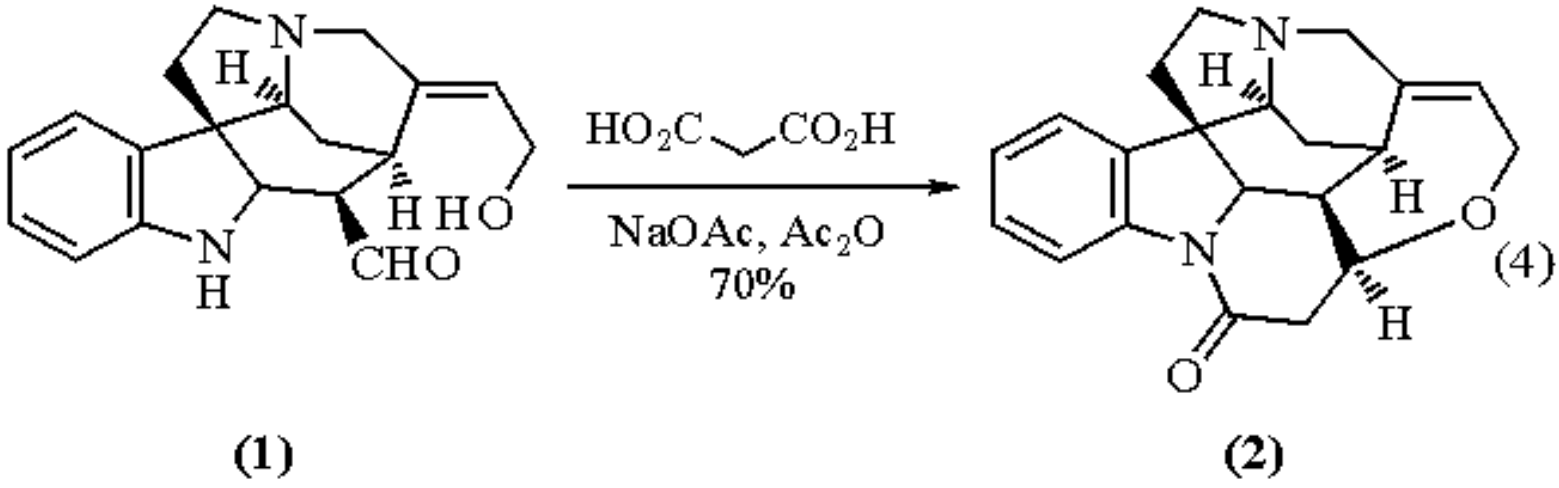

Efforts to effect asymmetric decarboxylation of disubstituted malonic acids have met with some success. Thus enzyme-mediated decarboxylation of prochiral α-methyl-α-phenylmalonic acid led to (*R*)-α-methylphenylacetic acid methyl ester in high yield with 98% ee after esterification (eq 5).[8]

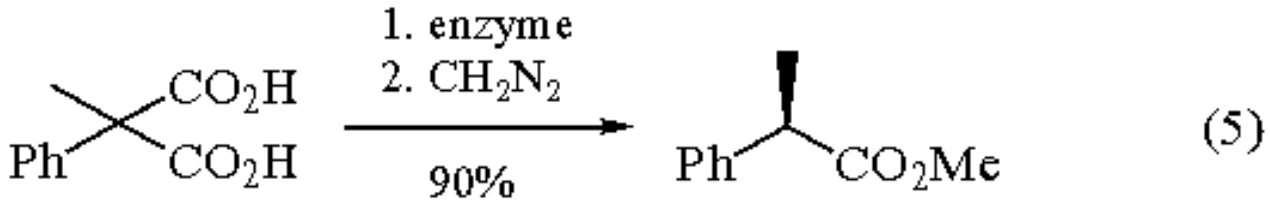

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Parke-Davis/Warner-Lambert Company, Ann Arbor, MI, USA

Malononitrile[1]

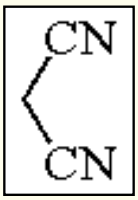

[109-77-3] · $C_3H_2N_2$ · Malononitrile · (MW 66.07)

(active methylene reagent useful for condensation reactions, for preparing synthetic intermediates, and for the synthesis of heterocycles)

Alternate Names: propanedinitrile; dicyanomethane; malonic (acid) dinitrile; propiodinitrile; methylene cyanide; cyanoacetic acid nitrile; malonitrile; malodinitrile; malonodinitrile.

Physical Data: mp 32-34 °C; bp 218-219 °C; *d* 1.191 g cm^{-3}; pK_a 11.

Solubility: sol acetone, benzene, ethanol, ether, water.

Form Supplied in: white crystals; available commercially.

Preparative Methods: prepared from cyanoacetamide.[2,3] The high temperature, continuous, one-step process for the synthesis of malononitrile by Lonza Inc. permits commercial-scale production of high purity reagent.

Purification: crystallization.[4]

Handling, Storage, and Precautions: **caution**: highly toxic irritant and should be stored in a well-ventilated fume hood. Over time, colorless malononitrile becomes dark and eliminates hydrogen cyanide. Inhalation should be avoided. Persons who suffer from a poor sense of smell, heart condition, or blood circulation problems should not be exposed to malononitrile. Above 100 °C, malononitrile may decompose spontaneously.

Introduction.

Fatiadi[1b] in his comprehensive review stated that malononitrile has become the keystone for synthesis of unique heterocyclic systems, fungicides, pharmaceuticals, pesticides, charge-transfer salts that conduct electricity, and solvatochromic dyes. Malononitrile is easily converted to derivatives, including dimers and trimers, which are also valuable in synthesis.[1]

Condensation Reactions with Aldehydes and Ketones.

Malononitrile undergoes the Knoevenagel condensation with aldehydes and ketones. Effective catalysts for the condensation include glycine[5] and β-alanine.[5,6] Benzaldehyde condenses with malononitrile in the presence of a catalytic amount of glycine to give benzalmalononitrile, which is valuable in heterocyclic synthesis, in quantitative yield (eq 1).[5] The condensation of 1,4-cyclohexanedione with malononitrile proceeds almost quantitatively to 1,4-bis(dicyanomethylene)cyclohexane under catalysis by β-alanine (eq 2).[7] 1,4-Bis(dicyanomethylene)cyclohexane is used to prepare the quinomethane electron acceptor 7,7,8,8-tetracyanoquinonedimethane (TCNQ).[7] In general, the Knoevenagel condensation of malononitrile with ketones[8] or esters[9] is efficiently catalyzed by weak bases (β-alanine, ammonium acetate) while stronger bases (KF, KOAc, NaOAc) promote telomerization of malononitrile.[8] Dimethylformamide (DMF) is a useful solvent for a wide variety of Knoevenagel reactions.[10] Dialkylidenemalononitriles having cyclic and terpenoid groups are potential cytostatic and pesticidal agents that may be useful in regulating insect juvenile hormone activity.[11,12]

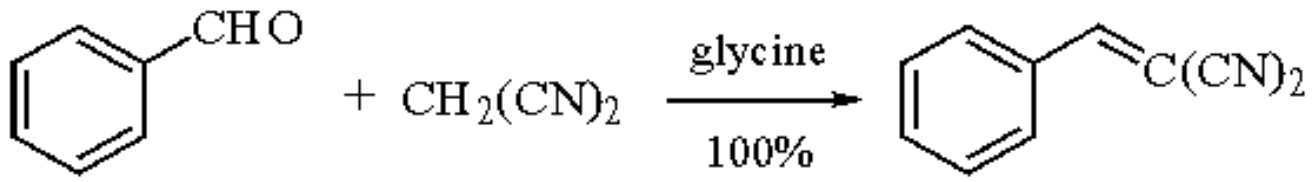

(1)

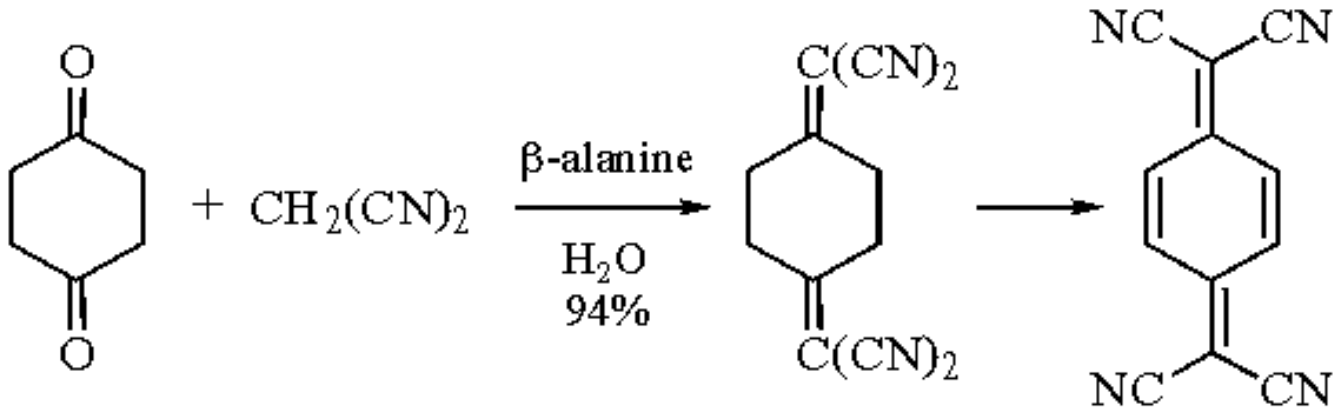

(2)

2,3-Butanedione reacts with malononitrile to produce 4,5-dimethyl-5-hydroxy-2-oxo-3-pyrroline-3-carbonitrile (**1**), 1,5-dimethyl-3,7-dioxo-2,6-diaza-*cis*-bicyclo[3.3.0]octane-4,8-dicarbonitrile (**2**), 3-imino-1,5,9,11-tetramethyl-7-oxo-2,10-dioxa-6-azatetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-4,8-dicarbonitrile (**3**) (eq 3), and the isomeric bislactam 1,5-dimethyl-3,7-dioxo-2,8-diaza-*cis*-bicyclo[3.3.0]octane-4,6-dicarbonitrile (**4**) (eq 4).[13,14] Benzil reacts with malononitrile to give the Knoevenagel product (**5**) or the γ-lactam (**6**) (4-cyano-2,3-diphenyl-5-oxo-3-pyrrolin-2-ylmalononitrile) (eq 5).[15-17]

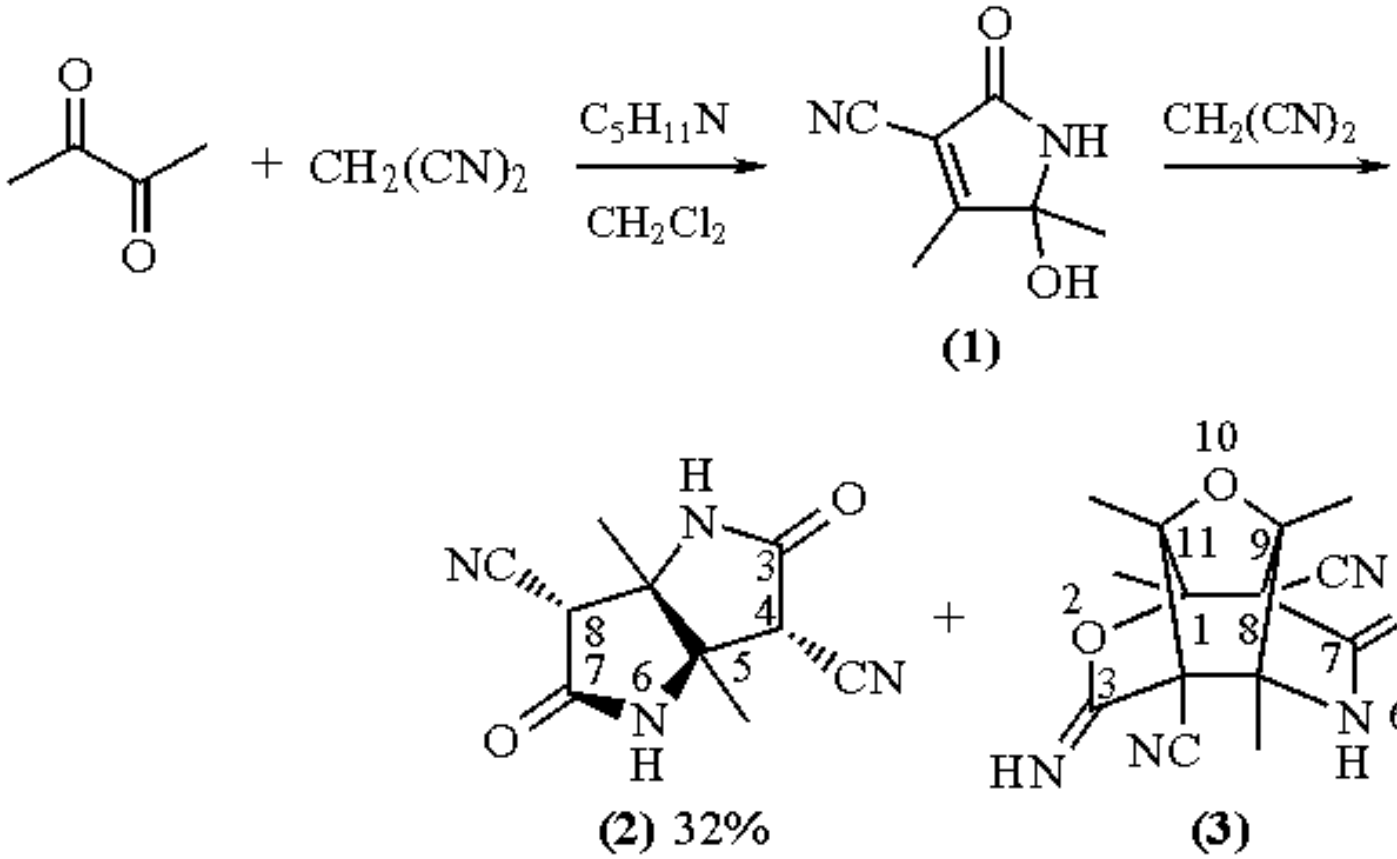

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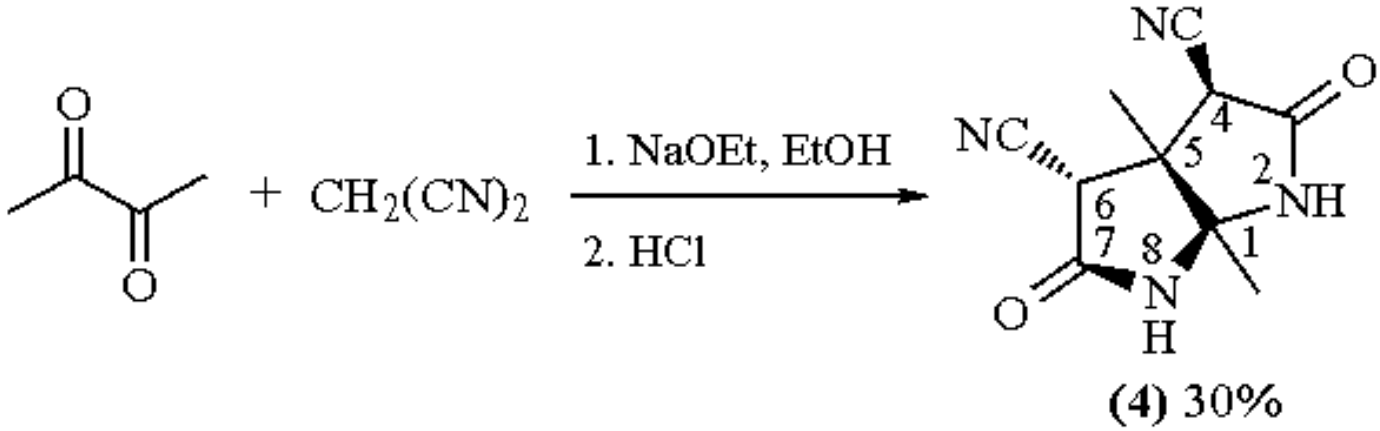

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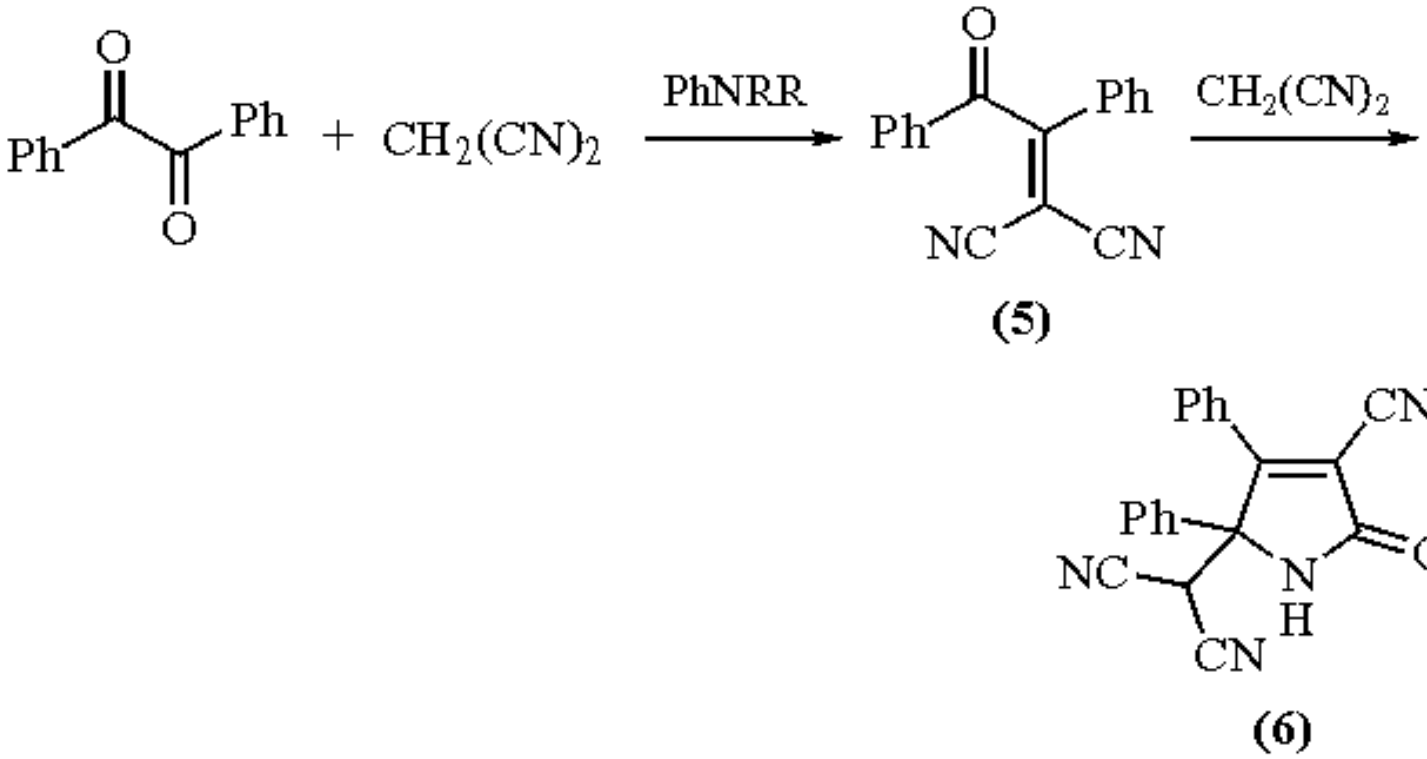

(5)

2-Acetylcyclohexanones react with malononitrile to give a mixture of products including polyhydrobenzo[*c*]pyridines (isoquinolines) and tetrahydronaphthalenes (eq 6).[18-20] The reaction with 2-acetylcyclopentanone proceeds similarly. Enolizable aliphatic and aromatic 1,4-diketones (e.g. 2,5-hexanedione) react with malononitrile in benzene in the presence of ammonium acetate or piperidinium acetate to give an array of products including double Knoevenagel adducts, cyclopentadiene derivatives, and 1-pyrindine derivatives (eq 7).[21-23]

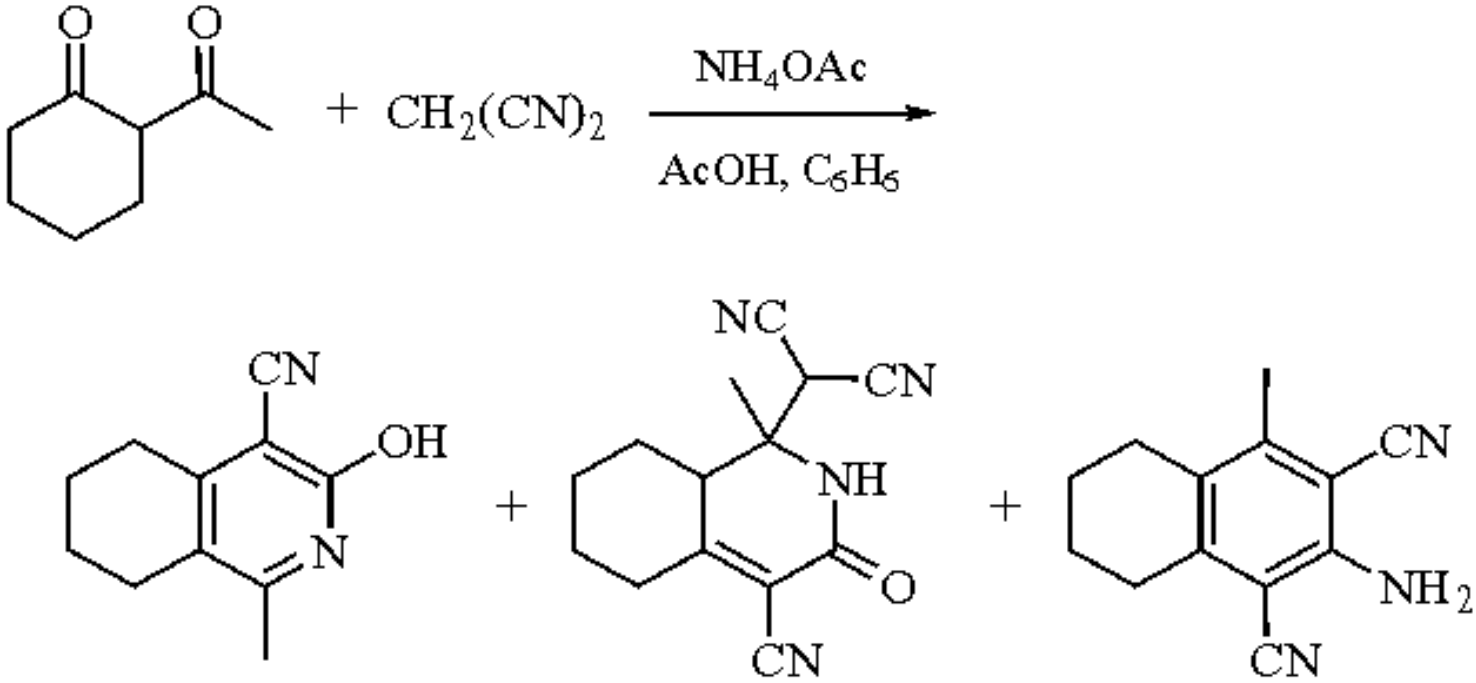

(6)

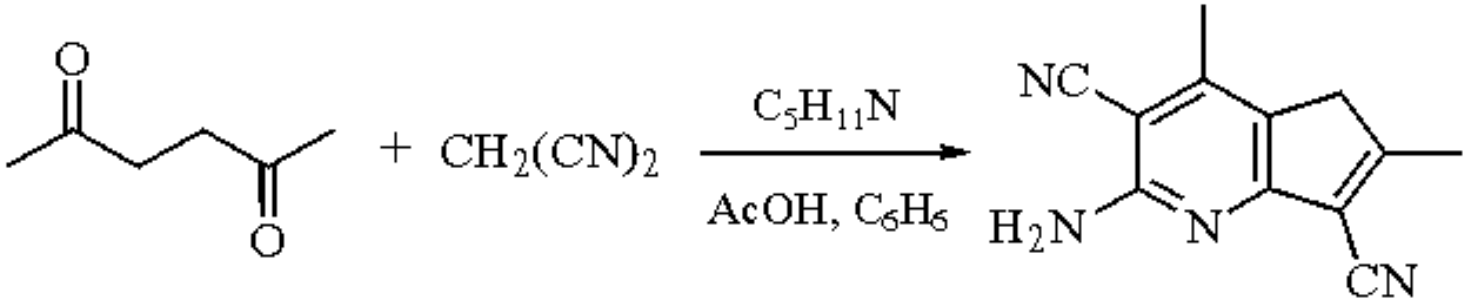

(7)

Condensation Reactions with Esters.

Ethyl pyruvate condenses with malononitrile to yield ethyl 2-dicyanomethylenepropanoate (eq 8), a useful dienophile in the Diels-Alder reaction and in natural products synthesis.[9,24] Ethoxycarbonyl-1-cyclohexanone reacts with malononitrile to give the Knoevenagel condensation product, which rearranges to the tetrahydroisoquinoline (eq 9).[18-20,25,26]

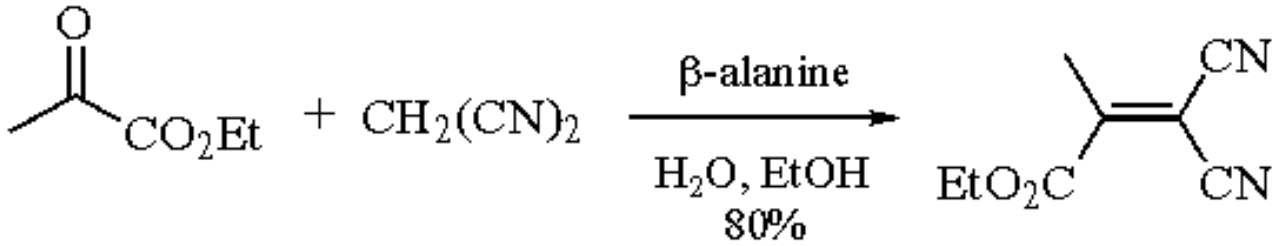

(8)

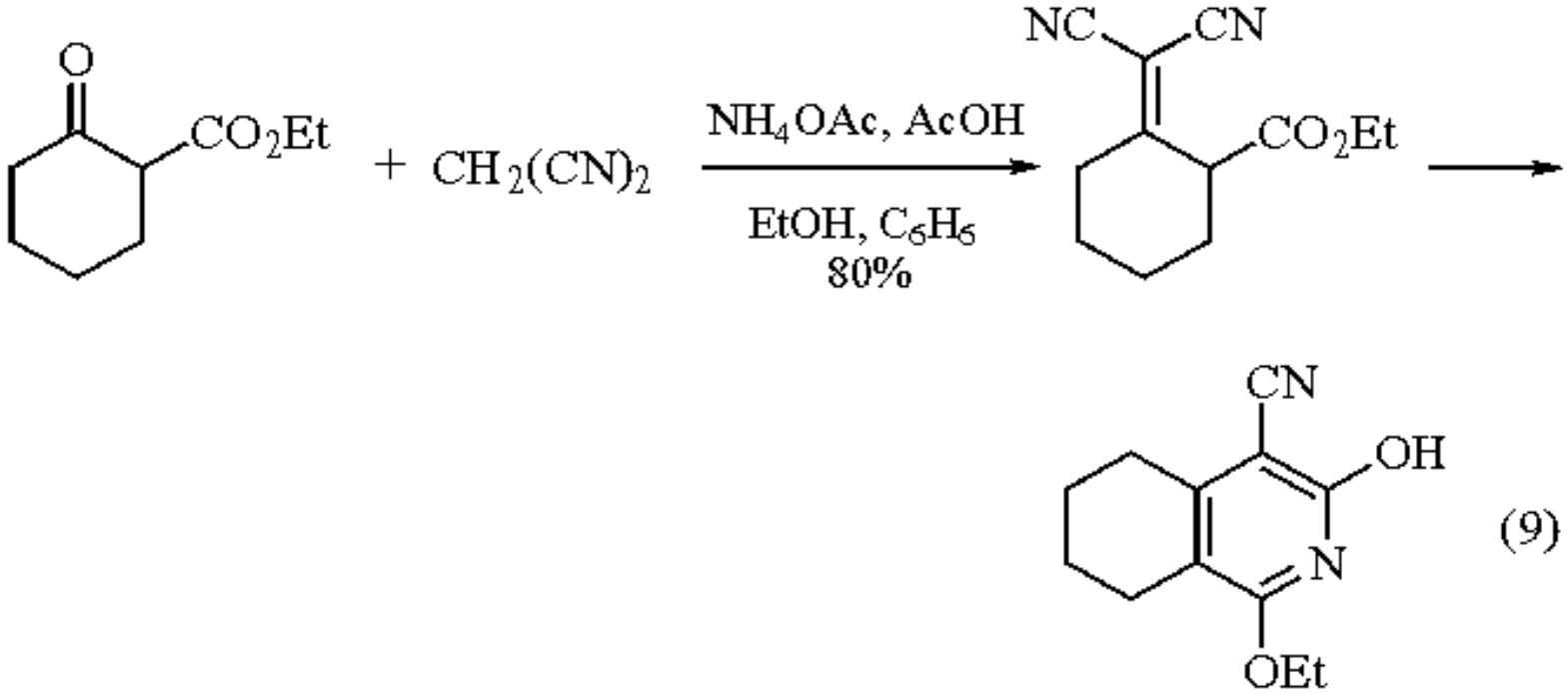

(9)

Reactions with α,β-Unsaturated Carbonyl Compounds.

The Knoevenagel reaction of aliphatic methyl ketones with malononitrile produces 6-alkyl-2,4-diamino-3,5-dicyanopyridines in moderate yield.[27] The Michael reaction between aliphatic α,β-unsaturated ketones and

malononitrile gives 2-amino-3-cyano-4,6-dialkylpyridines.[27] Conjugated aromatic ketones react with malononitrile in the presence of ammonium acetate to give 2-amino-4,6-diarylnicotinonitriles.[28] The Michael addition of malononitrile to α-acetylcinnamamides and chiral α-acylacrylates to form 2-amino-4*H*-pyrans and polyfunctionalized carbocycles,[29,30] and the first asymmetric synthesis of polyfunctionalized 4*H*-pyrans via Michael addition of malononitrile to 2-acyl acrylates, have been reported.[31] Polyfunctionalized 4*H*-pyrans are a common structural unit in a number of natural products.

Reaction with Allene.

Malononitrile reacts with allene in the presence of catalytic Pd^0 complexes, such as ***(Maleic anhydride)bis(triphenylphosphine)palladium***, to afford a 2-(1,1-dicyanoethyl)-3-methyl-1,3-butadiene (eq 10).[32]

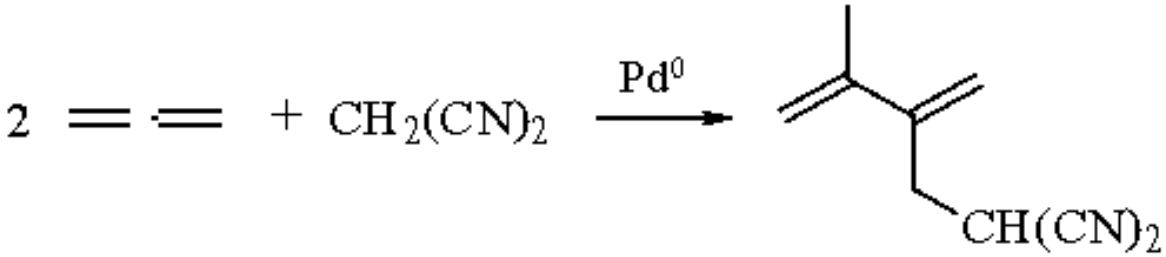

(10)

Reaction with Tetracyanoethylene.

Tetramethylammonium 1,1,2,3,3-pentacyanopropenide, which is useful for preparation of pentacyanopropenide salts of other metals and quaternary ammonium cations by metathesis, is prepared from malononitrile and tetracyanoethylene (eq 11).[33]

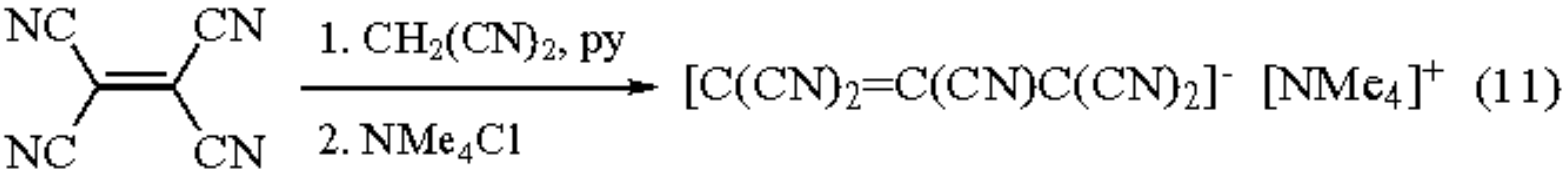

(11)

Reactions with Alkyl- and Cycloalkylureas.

Malononitrile condenses with heptylurea and ethyl triorthoformate to form the 3-heptylureidomethylenemalononitrile, which is a precursor to 3-heptyl-5-cyanocytosine (eq 12).[34] The reaction is effective for preparing 3-alkyl- and 3-cycloalkyl-5-cyanocytosines, but not for 3- and 5-cyanocytosines from arylureas.

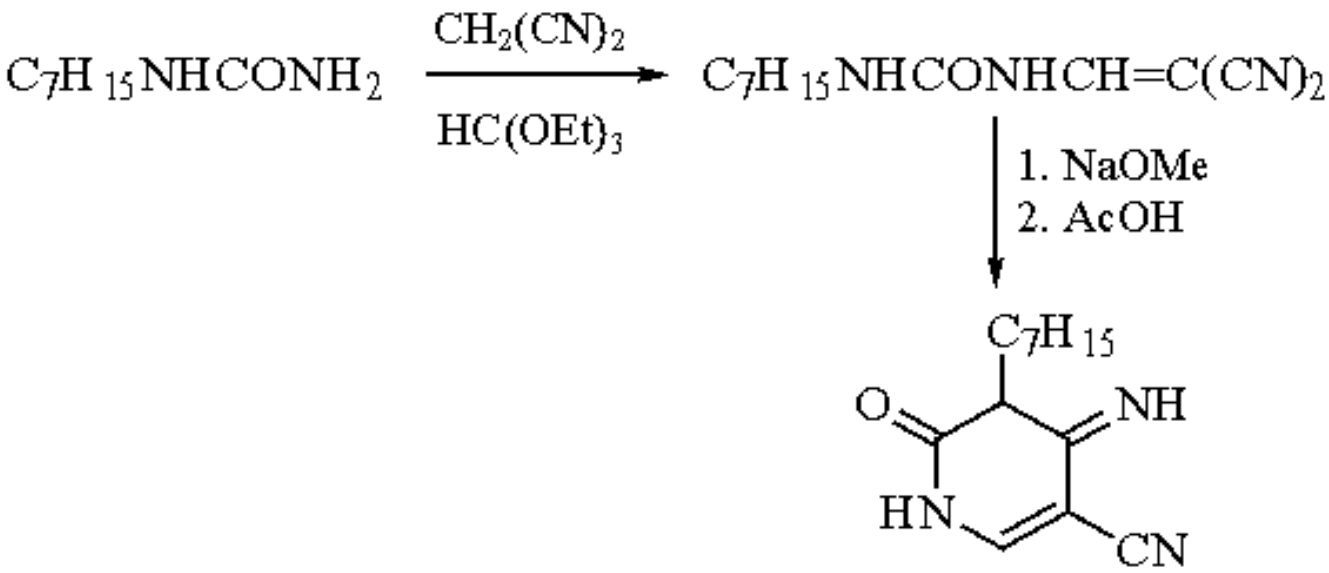

(12)

Reactions with Carbon Disulfide and/or Sulfur.

Malononitrile reacts with carbon disulfide in aqueous ammonia to yield 4,6-diamino-3,5-dicyano-2*H*-1-thiapyran-2-thione (eq 13).[35] Malononitrile reacts with carbon disulfide and sulfur in the presence of secondary or tertiary amines to give 4-cyano-5-amino-1,2-dithiole-3-thione.[36] 2-Amino-3-cyano-4,5-dialkylthiophenes are obtained from malononitrile, ketones, and sulfur.[37] Cholestan-3-one reacts with malononitrile and sulfur in ethanol containing morpholine to produce cholestanothiophene (2´-aminocholest-2-eno[3,2-*b*]thiophene-4´-carbonitrile) (eq 14).[38]

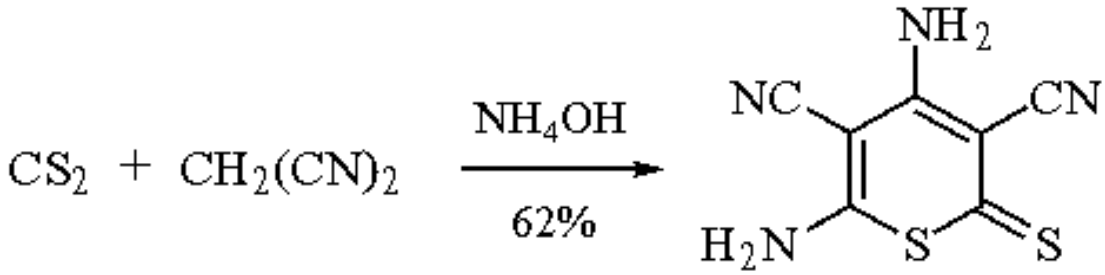

(13)

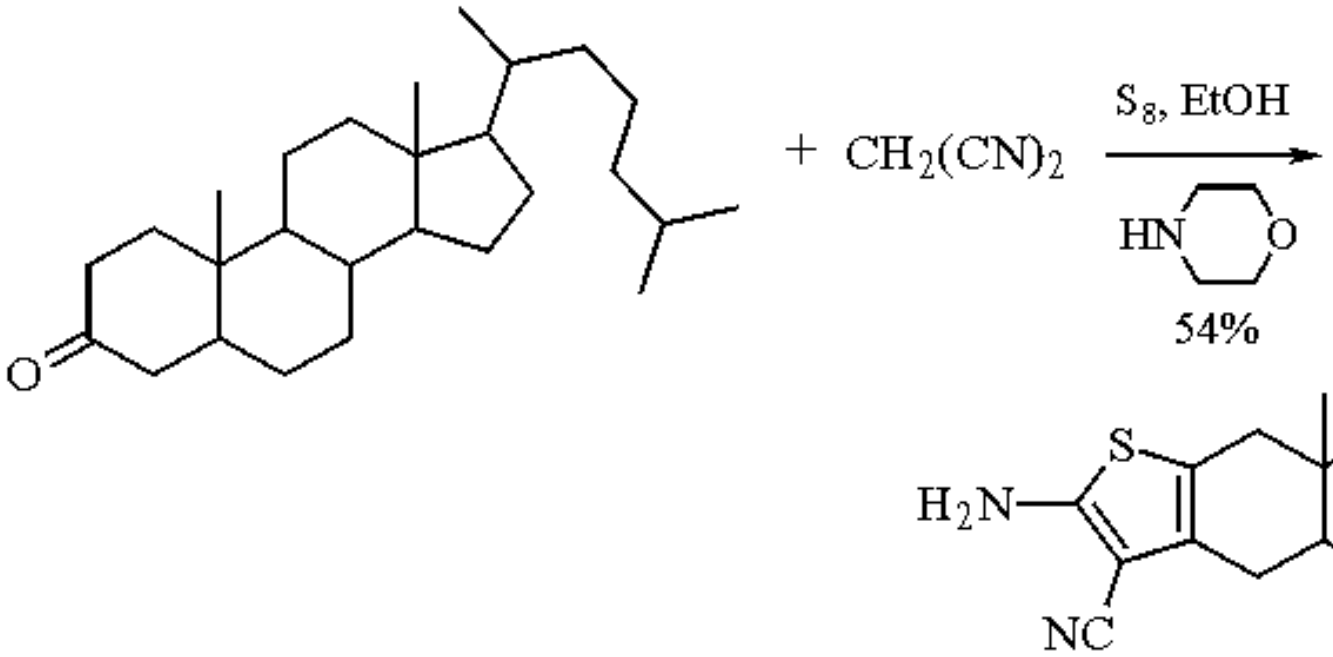

(14)

Other Applications.

Malononitrile forms synthetically useful dimers and trimers[1] and can be alkylated under a variety of experimental conditions.[39,40] Ethyl orthoformate reacts with malononitrile to form ***Ethoxymethylenemalonitrile***.[41] Malononitrile reacts with 2,3-bis(phenylsulfonyl)-1,3-butadiene via a novel 4*H*-annulation to yield 1-sulfonyl-4,4-dicyanocyclopentene.[42] Cholest-1-en-3β-yl esters undergo allylic alkylation with malononitrile in the presence of a palladium catalyst.[43] Malononitrile may be used to prepare adenine,[44,45] aminopyrroles,[46] aminocyanopyrroles,[47] diaminopyrimidines,[48] and many other heterocycles.[1] Malononitrile is converted to aminomalononitrile (aminopropanedinitrile) which is useful in the synthesis of heterocycles including pyrazines,[49,50] *C*-nucleosides,[51,52] dicyanoazomethine ylides,[53] substituted 2-aza-1,3-butadienes,[54] piperazines,[55] and thiazoles.[56] Malononitrile is also an important precursor for dicyanocarbene[57] and for dibromodicyanomethane, which is useful in the synthesis of tetracyanocyclopropanes.[58-61]

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Malonyl Chloride

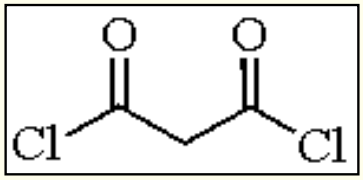

[1663-67-8] · $C_3H_2Cl_2O_2$ · Malonyl Chloride · (MW 140.95)

(reactive acyl chloride/C_3O_2 equivalent;[1] self condensation;[2] reacts with various functional groups to give heterocyclic compounds[3])

Physical Data: colorless liquid, bp 58 °C/26 mmHg; *d* 1.4486 g cm^{-3}.

Solubility: sol most organic solvents; *reacts violently with H_2O and protic solvents*.

Form Supplied in: colorless or red liquid; widely available in differing purity.

Preparative Methods: from ***Malonic Acid*** and ***Thionyl Chloride***.[4]

Handling, Storage, and Precautions: unstable at rt and should be used freshly distilled in vacuo or freshly prepared; however, it can be stored in the cold for several days; lachrymatory; use in a fume hood.

Acylation.

Malonyl chloride may be used as other acyl halides in Friedel-Crafts and related reactions.[5] Thus cyclic hydrocarbons may be prepared by a [3 + *n*] annulation from aromatic compounds (eq 1) and organometallics (eq 2). Similarly, malonyl chloride can be used like other α,ο-carboxylic acid derivatives for the synthesis of macrocycles.[6] In this respect, malonyl chloride behaves identically to C_3O_2 (see ***Carbon Suboxide***), although its reactivity is significantly lower.[1,7]

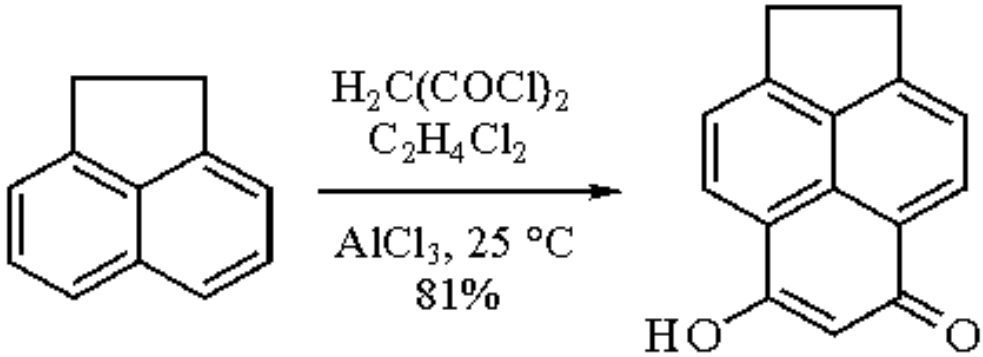

(1)

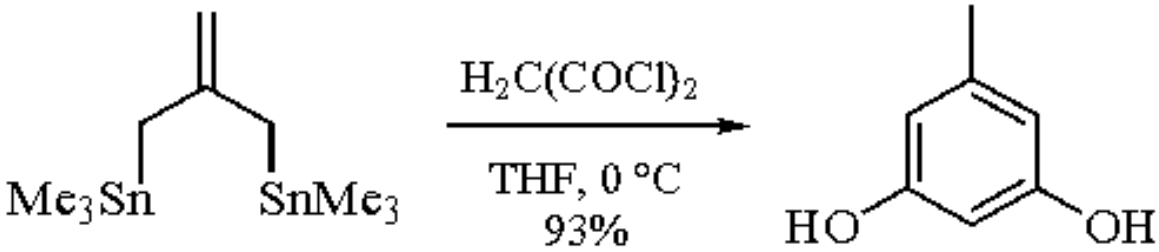

(2)

Preparation of Heterocycles.

Compounds possessing two nucleophilic centers yield heterocycles upon treatment with malonyl chloride. The reaction proceeds via initial HCl elimination from malonyl chloride[8] to give chlorocarbonyl ketenes (**1**) which are stable for the substituted counterparts (see ***(Chlorocarbonyl)ethylketene***). This elimination is even induced by weak bases such as acetone.[2,8] The ketene intermediate may then react with the respective nucleophile or it dimerizes in the case of malonyl chloride in a [4 + 2] fashion to yield 6-chloro-3-chlorocarbonyl-4-hydroxy-2-oxo-2*H*-pyran (**2**) (eq 3).[2]

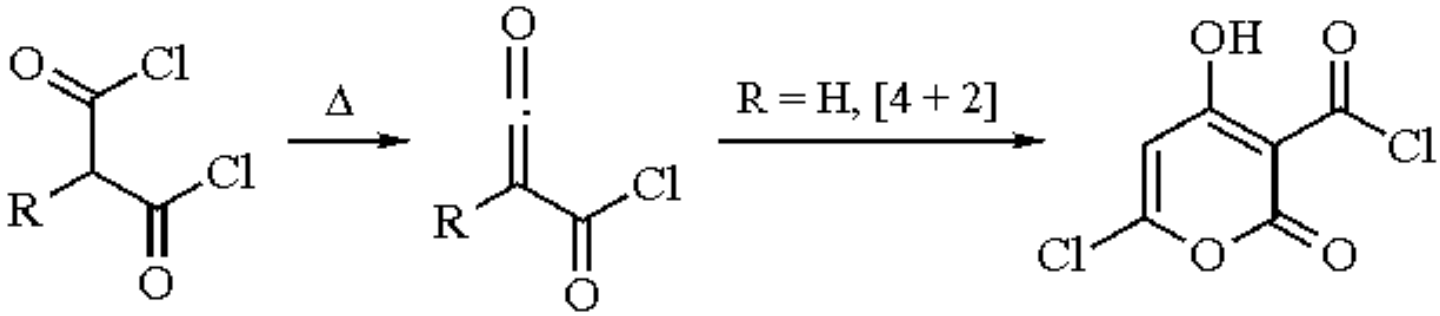

(1) (2) (3)

With enolizable ketones and β-dicarbonyl compounds, pyrones are normally obtained via ketene (**1**). Unsymmetrically substituted diketones give, however, mixtures of isomers.[9] Furthermore, some of the pyrones formed can further add malonyl chloride or ketene (**1**) to give pyrano[4,3-*b*]pyran-2,5-diones (eq 4).[1,10]

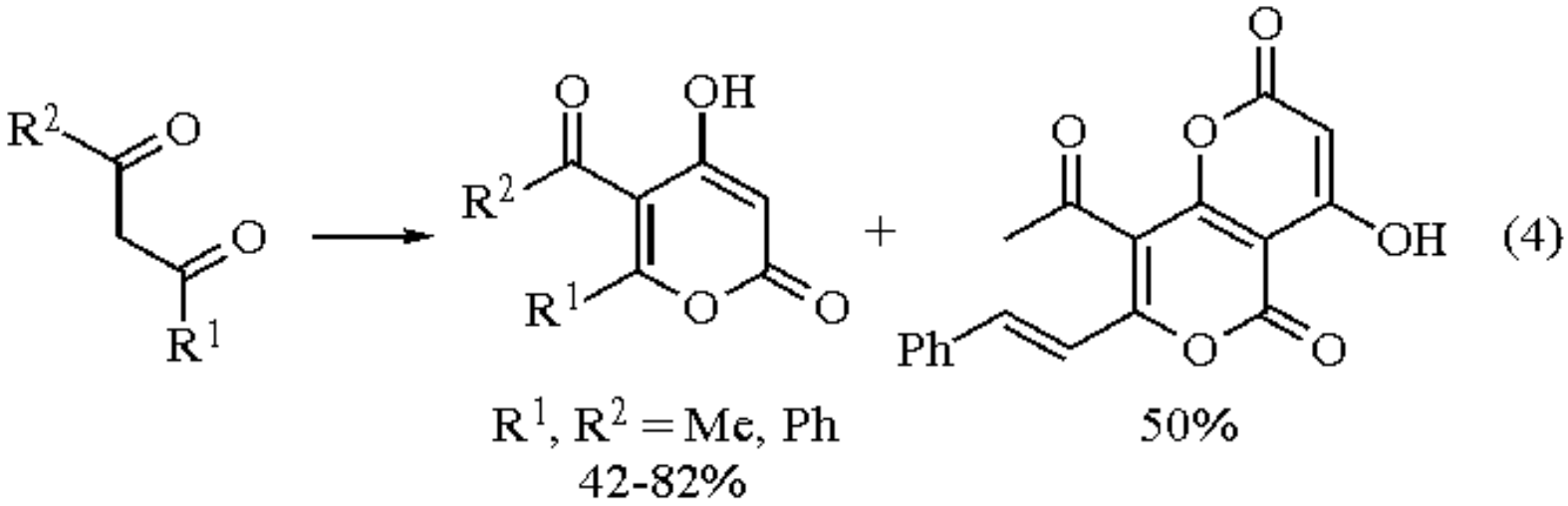

Of the numerous examples reported so far for the condensation of malonyl chloride with 1,2- and 1,3-heteroatom-containing nucleophiles, most of the products are very similar to those obtained from the respective nucleophile and C_3O_2, chlorocarbonyl ketene, or active malonates.[1] Some newer examples for the use of malonyl chloride include the preparation of barbituric acid derivatives from silylated carbodiimides,[11] coumarins from salicylic aldehyde imines,[12] pyridones from ketene *S*,*N*-acetals,[13] diazepines from diamines,[14] and pyranopyrans from malonamides.[15] Amidines and similar nucleophiles condense with malonyl dichloride, chlorocarbonyl ketene, and C_3O_2 to give mesoionic heterocycles (betaines).[3,16] These are synthetically useful compounds since, for example, highly substituted pyridones can be prepared by a cycloaddition reaction (eq 5). Enol ethers that are derived from aldehydes react at low temperature with malonyl chloride via (**1**) to give, after workup with ethanol, 1,3,5-tricarbonyl compounds that can be further converted to otherwise difficult to obtain 6-unsubstituted pyrones (eq 6).[17]

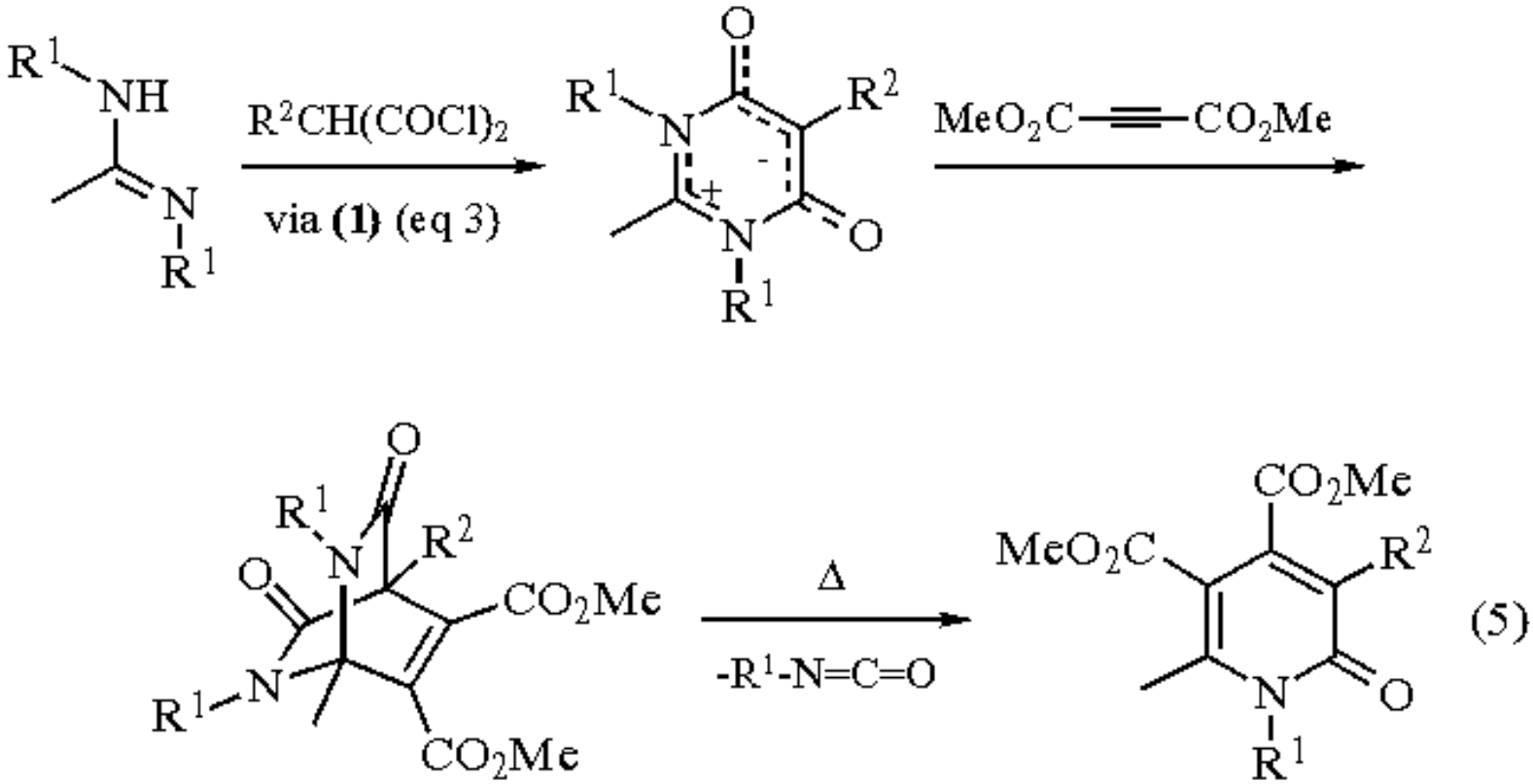

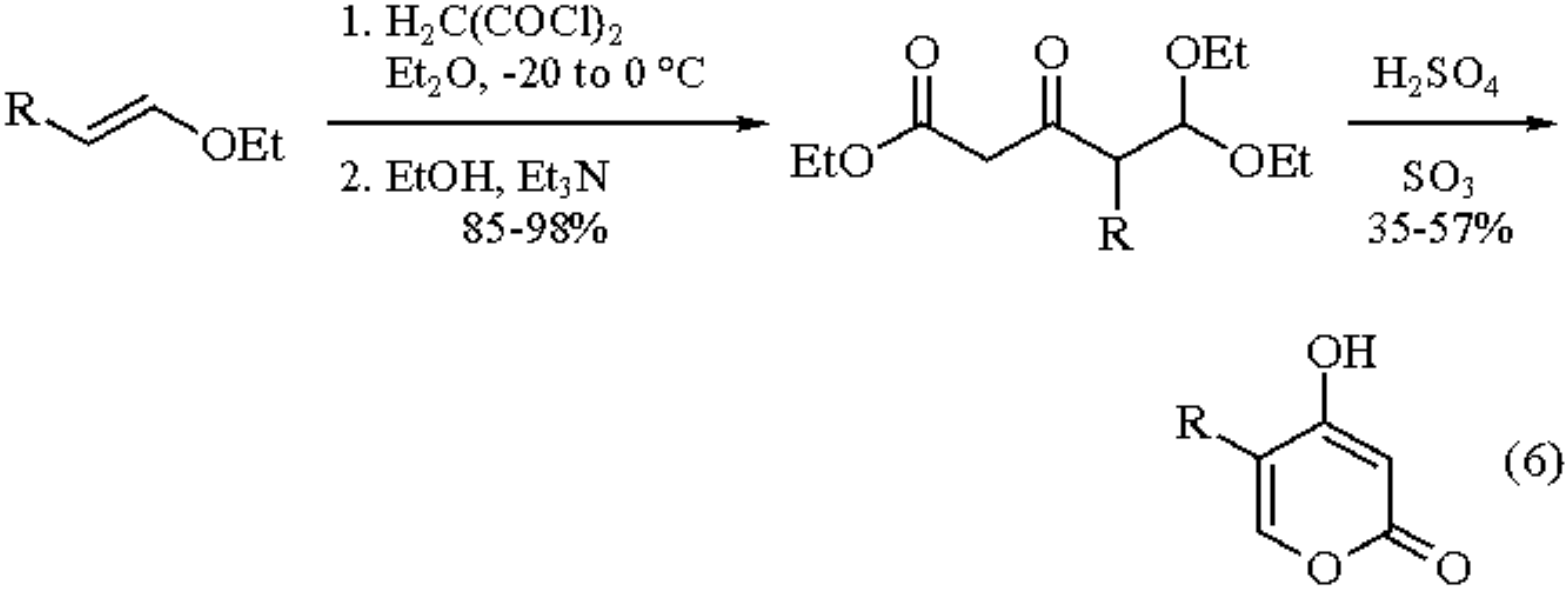

From ketone-derived alkyl and trimethylsilyl enol ethers, mixtures of the corresponding phloroglucinols, cyclophanes, and substituted or methylene-bridged pyrones are produced upon condensation with malonyl chloride (eq 7).[18]

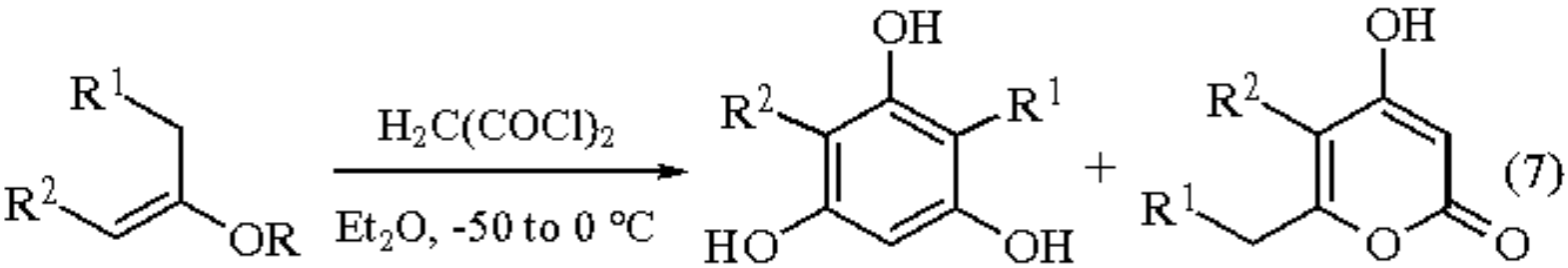

R = Me, Et,	TMS$R^1 = R^2 = H$	52%	43%
	$R^1 = H$, $R^2 = Et$	80%	11%
	$R^1 = R^2 = Me$	53%	30%
	$R^1, R^2 = -(CH_2)_n-$	(n = 2-9, hy)	

Less nucleophilic functional groups like nitriles react with malonyl chloride via the intermediate chlorocarbonyl pyrone (**2**) to give pyrano[3,4-*e*][1,3]oxazines.[19] However, the product distribution depends on the nitrile, the reaction conditions and, if present, on the substituent of the malonyl chloride. Thus oxazinones (eq 8),[20] pyridones (eq 9),[21] and pyrimidones (eq 10)[19] can be obtained as well.

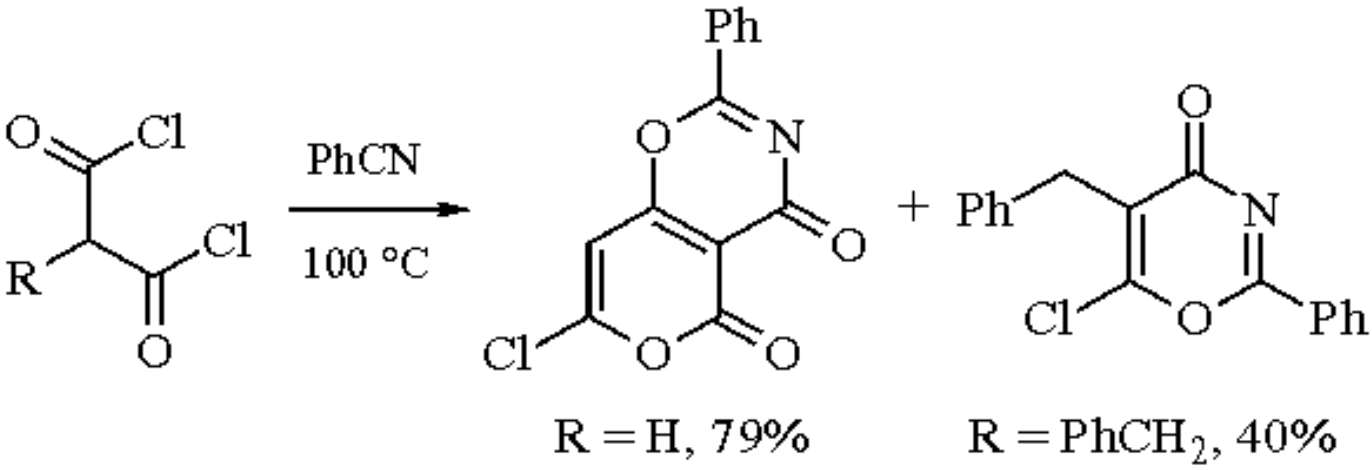

(8)

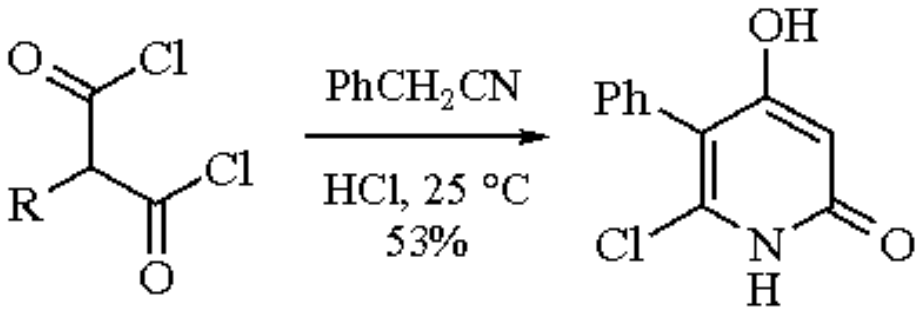

(9)

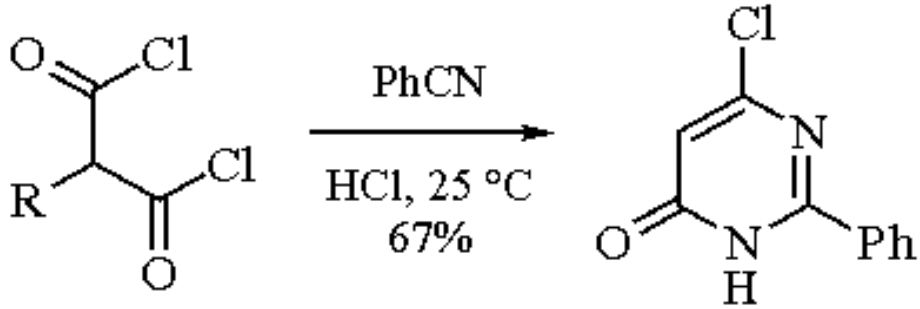

(10)

The condensation of nitriles with malonyl chloride has been reviewed.[1b] Thiocyanates,[22] isothiocyanates,[23,24] and cyanates[24] condense with malonyl chloride in a similar fashion to nitriles via (**2**) to give 2-substituted 7-chloropyrano[3,4-*e*][1,3]oxazine-4,5-diones (eq 11). Similarly, cyanamides yield pyrano[4,3-*d*][1,3]oxazines and pyrano[4,3-*b*]azetidinones, depending on the reaction conditions (eq 12).

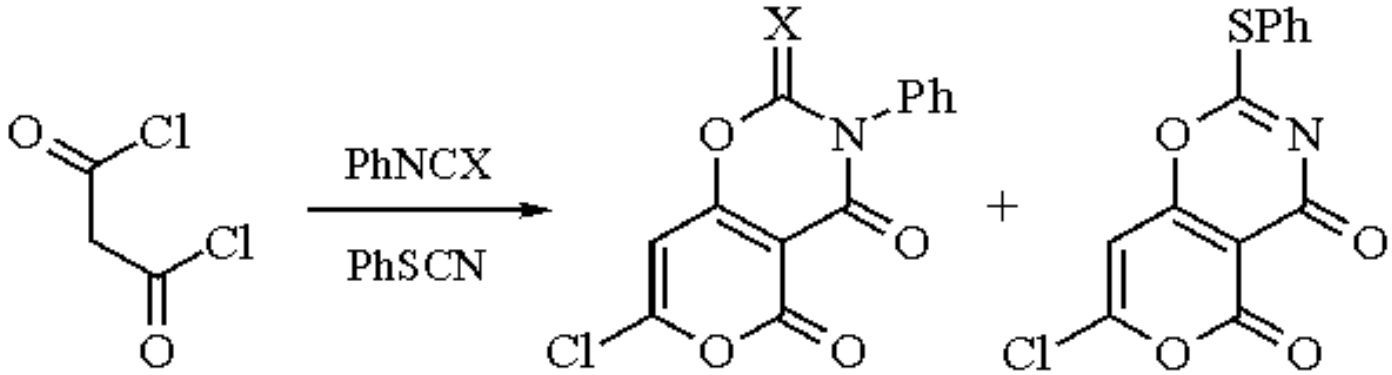

(11)

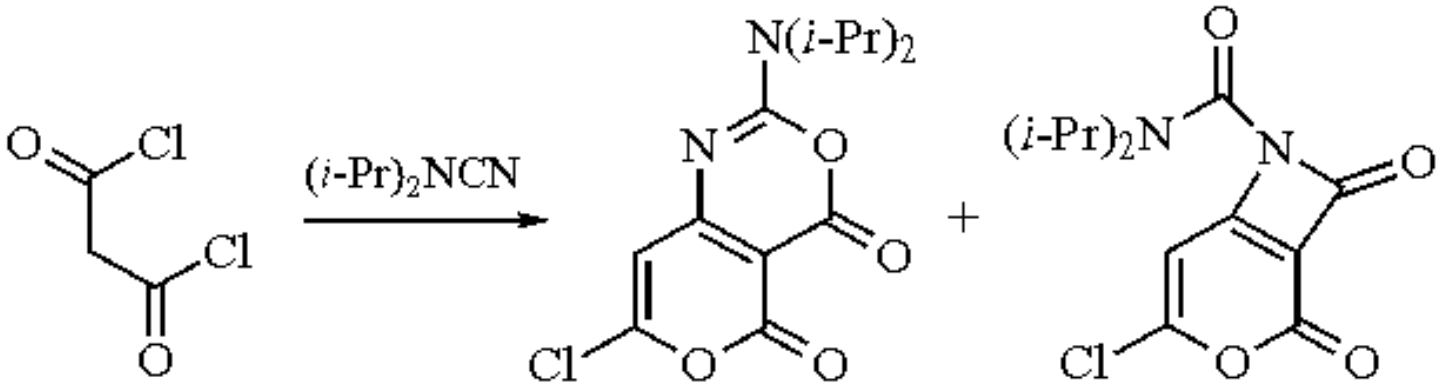

CH_2Cl_2, 50 °C, 25% di oxane, 25 °C, 38%

(12)

Related Reagents.

Bis(2,4,6-trichlorophenyl) Malonate; ***Carbon Suboxide***; ***(Chlorocarbonyl)ethylketene***.

---

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Mandelic Acid

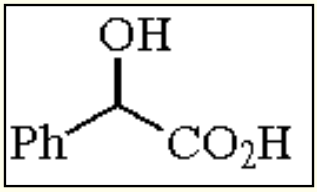

(*S*)-(+)

[17199-29-0] · $C_8H_8O_3$ · Mandelic Acid · (MW 152.16) (*R*)-(-)

[611-71-2]

(useful reagent for the resolution of enantiomeric amines[1] and alcohols;[5] serves as a chiral nonracemic template for asymmetric reductions,[11-14] aldol condensations,[15-17] and Diels-Alder reactions;[18,19] chiral nonracemic starting material[22])

Alternate Names: phenylglycolic acid; α-hydroxyphenylacetic acid.

Physical Data: (*S*)-(+): mp 134-135 °C; [α]20D + 156.6° (H_2O, *c* = 2.9). (*R*)-(-): mp 133-135 °C; [α]20D - 158.0° (H_2O, *c* = 2.5). (±): mp 121-123 °C; *d* 1.341 g cm^{-3}; K_a 4.3 × 10^{-4} (25 °C).

Solubility: sol water (1 g/6.3 mL), ethanol (1 g/mL), acetic acid, chloroform; very sol ether.

Form Supplied in: white crystalline solid; widely available.

Handling, Storage, and Precautions: darkens and decomposes upon prolonged exposure to light.

Resolving Reagent.

Due to the ready availability of both enantiomers of this compound in high enantiomeric purity, mandelic acid is widely used as a reagent for enantiomeric resolutions.[1] It is used in resolving racemic mixtures of amines[1] or diamines[2] as the diastereomeric ammonium salts. Amino esters[3] or amino lactams[4] are resolved by formation of the amides or ammonium salts,[4b] and alcohols[5] are resolved by formation of the corresponding diastereomeric esters[5a,b] or ethers.[5c] Generally, the derivatives are crystalline solids easily purified by recrystallization. In a related application, enantiomeric purity determinations of chiral nonracemic amines by ^1H NMR are obtained using mandelic acid as a solvating agent.[6] As well, absolute configuration determinations of enantiomers can be undertaken using either isomer of mandelic acid in conjunction with CD-ORD,[7] X-ray,[8] and mass spectral analyses.[9] Mandelic acid can also be utilized in enantiomeric chromatography[10] as a chiral nonracemic mobile phase additive[10a] or as a solid support component.[10b]

Asymmetric Reductions.

Acyloxy-alkoxy borohydrides, produced from the reaction of mandelic acid enantiomers and ***Sodium Borohydride***,[11] and aluminum hydride reagents modified with ligands derived from mandelic acid,[12] will reduce ketones with poor stereoselectivity. Reactions of nitriles with a mixture of $NaBH_4$ and mandelic acid followed by alkylation of the intermediate *N*-boryl imine with organometallic reagents provide the corresponding primary amines in good yield but with low stereoselectivity (eq 1).[13] However, catalytic hydrogenations with chiral nonracemic phosphino ligands (**1**),[14b-d] easily derived from mandelic acid (eq 2), with rhodium have given the corresponding products (e.g. amino acids) with high enantiomeric purity (eq 3).[14]

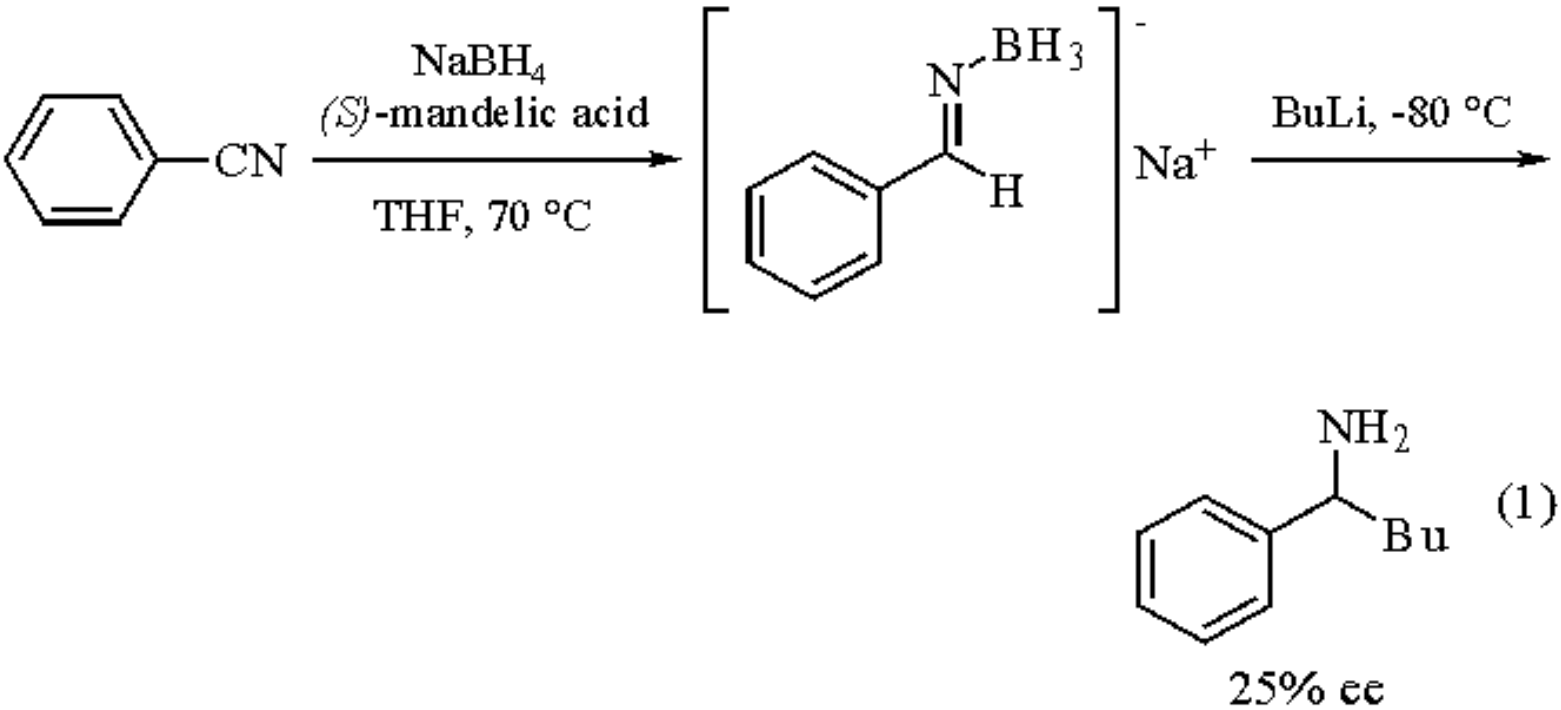

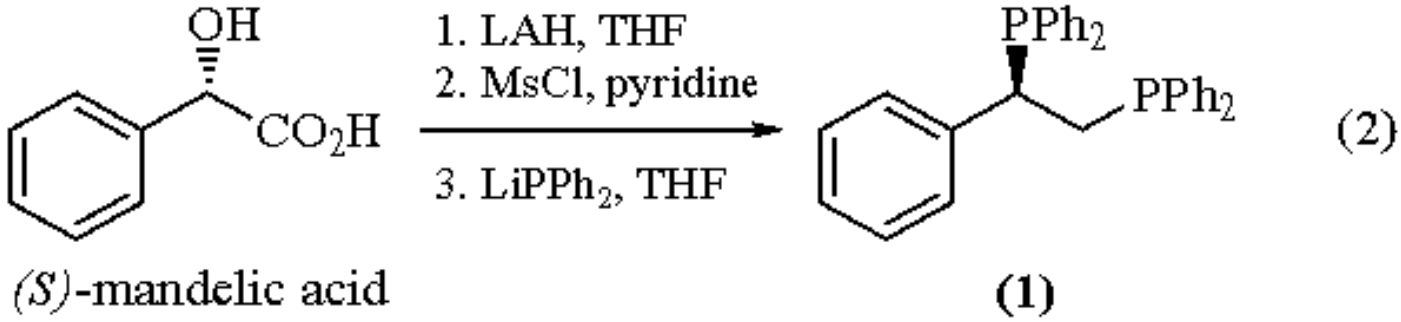

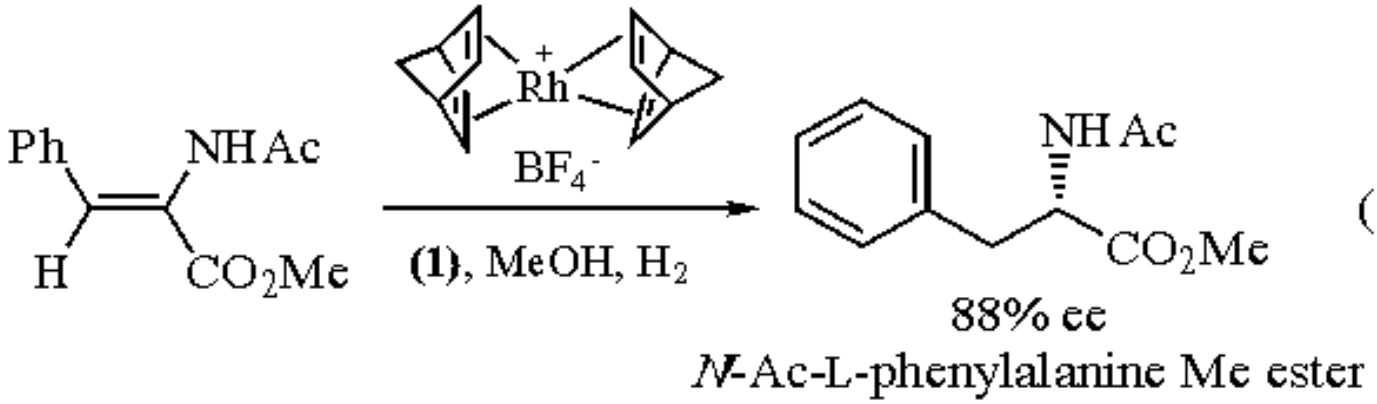

(3)

Aldol Condensations.

Mandelic acid and a variety of easily prepared derivatives serve as excellent chiral nonracemic auxiliaries for aldol condensations, giving products in high diastereoselectivity. Lewis acid mediated condensation of silyl enol ethers or allylsilanes with 1,3-dioxolan-4-ones (**2**), produced from the reaction of mandelic acid with various aldehydes and ketones, gives the corresponding products in up to 86% de (eq 4).[15] The diastereomers are easily separated and the chiral nonracemic auxiliaries are readily removed with ***Lead(IV) Acetate*** without racemization, giving enantiomerically pure aldols or homoallylic alcohols.

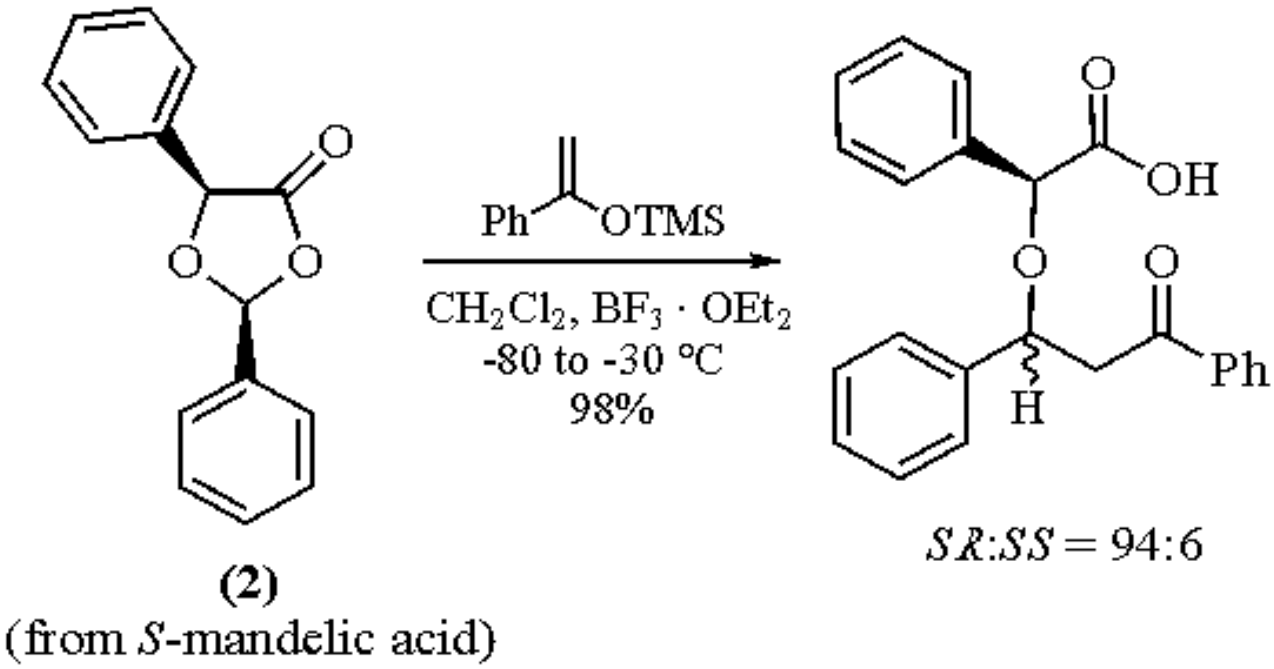

(4)

Chiral nonracemic silyl ketene acetals produced from mandelic acid derived amino alcohols successfully undergo asymmetric Mukaiyama aldol condensations,[16] and the magnesium enolates of acetoxy-1,1,2-triphenylethanols (**3**) derived from mandelic acid (eq 5) condense with aldehydes with high stereoselectivity (eq 6).[17]

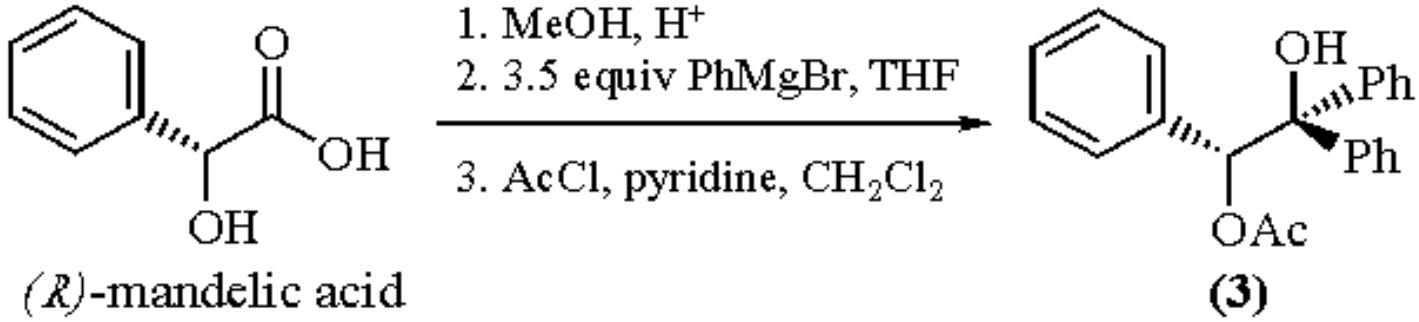

(5)

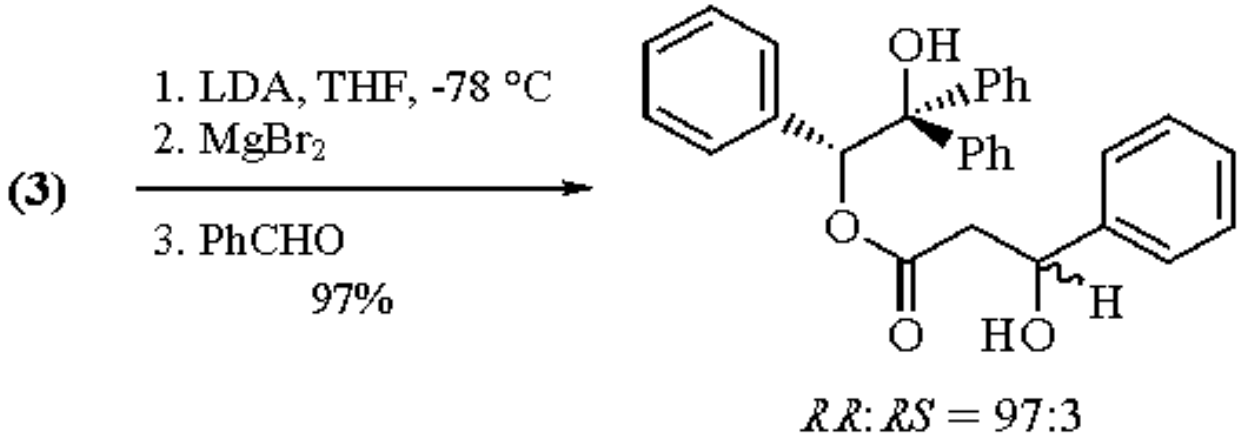

(6)

Diels-Alder Reactions.

Hydroxamic acids of the mandelic acid enantiomers serve as precursors to chiral nonracemic acylnitroso dienophiles (**4**) (eq 7).[18] In most examples the stereoselectivity of the cycloaddition is relatively low. However, in some cases (with double asymmetric induction),[19] significant diastereoselectivities can be achieved (eq 8).

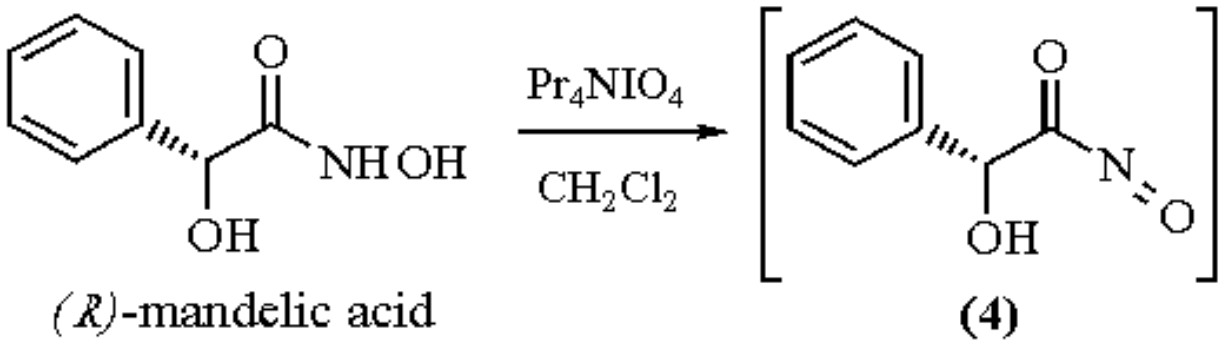

(7)

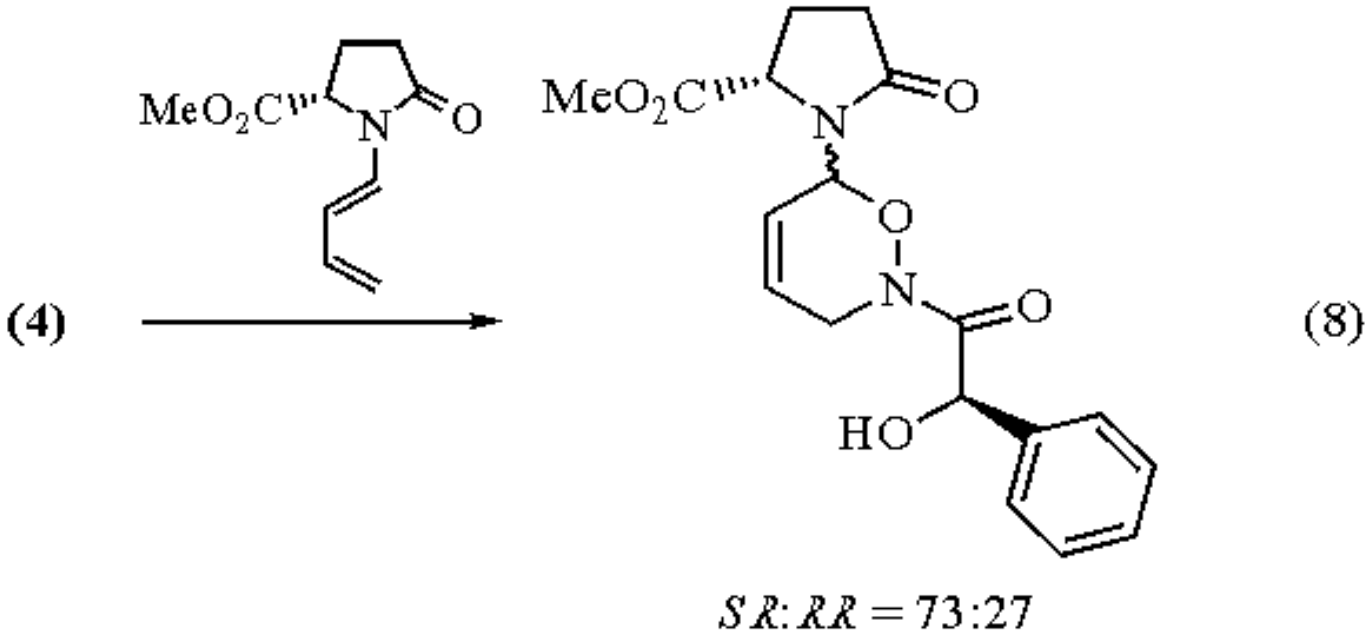

Asymmetric Organometallic Reagents.

Amino derivatives (**5**) of mandelic acid serve as ligands for copper reagents, facilitating conjugate additions to enones with high enantioselectivity (eqs 9 and 10).[20] Lithio benzylmandelate enantioselectively cleaves tricyclic anhydrides to give enantiomers of bicyclic dicarboxylic acids.[21]

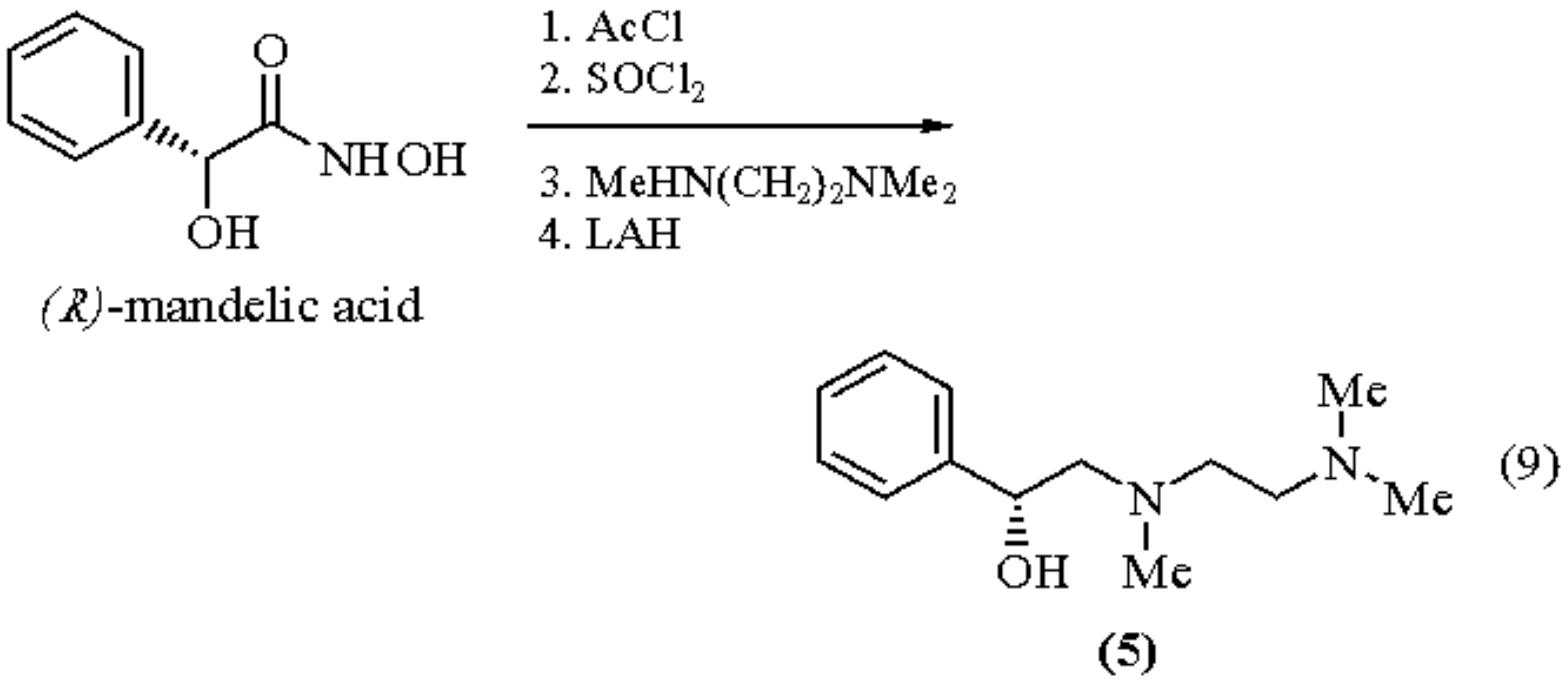

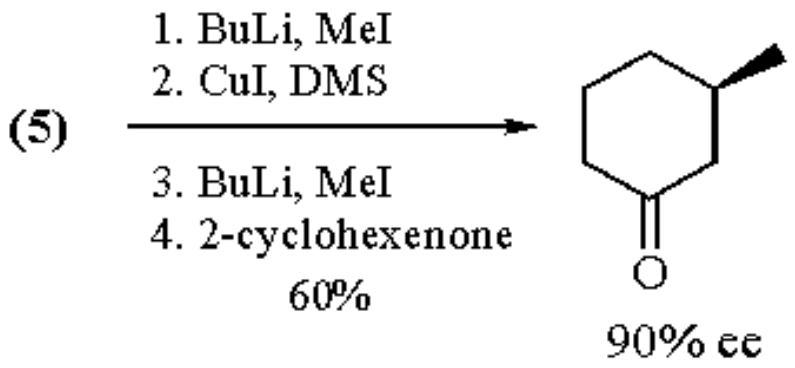

(10)

Chiral Nonracemic Starting Material.

Both (*S*)-(+)- and (*R*)-(-)-mandelic acid are used extensively for enantiomeric syntheses.[22] It is a convenient starting material for enantiomerically pure phenylethanediol and styrene oxide (eq 11).[23] These methodologies are useful in preparing enantiomerically enriched deuterated compounds.[24] Enantiomerically pure benzoins produced from mandelic acid serve as templates for preparing enantiomerically enriched [^{16}O, ^{17}O, ^{18}O] phosphate esters[25] and sulfate esters.[26] The alcohol, acid, or aromatic ring functional groups can be interconverted in a variety of ways, so mandelic acid serves as an excellent chiral nonracemic starting material for numerous categories of compounds, including such complex molecules as macrolide antibiotics.[27]

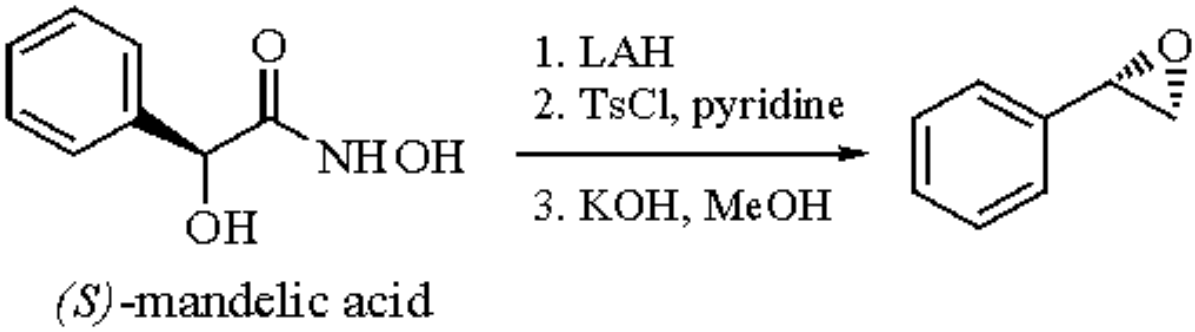

(11)

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Manganese(III) Acetate[1]

$Mn(OAc)_3$

($Mn(OAc)_3$)

[993-02-2] · $C_6H_9MnO_6$ · Manganese(III) Acetate · (MW 232.09) ($Mn(OAc)_3.2H_2O$)

[19513-05-4] · $C_6H_{13}MnO_8$ · Manganese(III) Acetate · (MW 268.13)

(one-electron oxidant used to oxidize acetic acid and β-dicarbonyl compounds to the corresponding radical and for α´-acetoxylation of enones)

Physical Data: the commercially available dihydrate is cinnamon brown. The anhydrous form is dark brown. The crystal structure of the anhydrous form indicates an oxo-centered trimer with bridging acetates.[2]

Solubility: sol acetic acid, ethanol, and a variety of other organic solvents; disproportionates in water.

Preparative Methods: commercially available dihydrate is easily prepared by the reaction of manganese(II) acetate with potassium permanganate in acetic acid at reflux.[1] The anhydrous form is prepared in acetic acid and acetic anhydride.[1]

$Mn(OAc)_3$ has been extensively used for the oxidative addition of acetic acid to alkenes to give γ-butyrolactones.[3,4] The addition of acetic acid to alkenes in acetic acid at reflux is quite general.[1] ***Acetic Anhydride*** and sodium acetate are often used as additives that modify the rate of reaction and ratio of products. With simple carboxylic acids, this reaction is limited to acetic acid and other acids which can be used as solvent. Mechanistic studies[5a] have shown that the rate determining step is formation of a Mn^{III} enolate which rapidly transfers an electron to give the carboxymethyl radical and Mn^{II}. This radical adds to the alkene to give a γ-carboxyalkyl radical that is oxidized by a second equivalent of $Mn(OAc)_3$ to give mixtures of lactone, alkene, and γ-acetoxycarboxylic acid (eq 1), depending on the exact reaction conditions and structure of the alkene.[6]

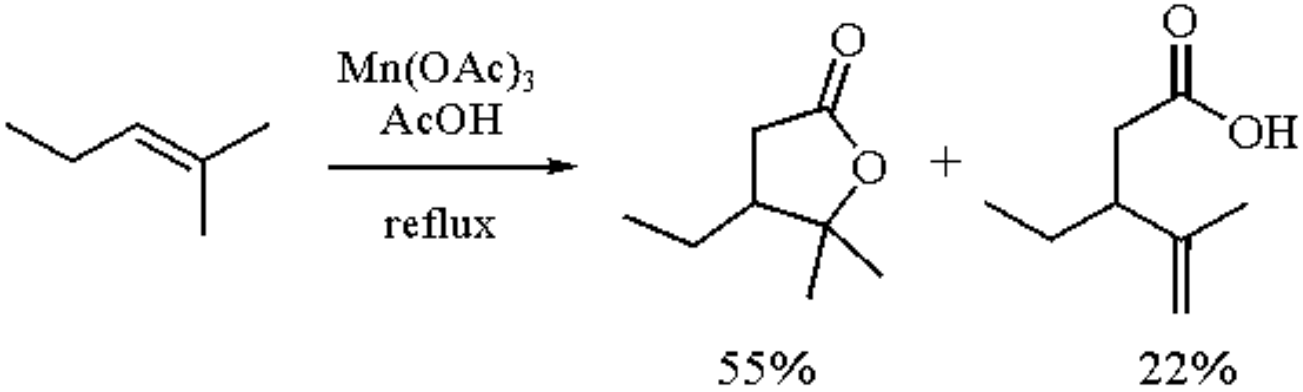

(1)

The lactonization reaction is much more facile with cyanoacetic acid and malonic acid, which undergo the rate-determining enolization more rapidly in acetic acid at rt (eq 2).[1,5,7] Malonic acid gives only bis-lactone 2:1 adducts resulting from the addition to two molecules of alkene (eq 3).[8]

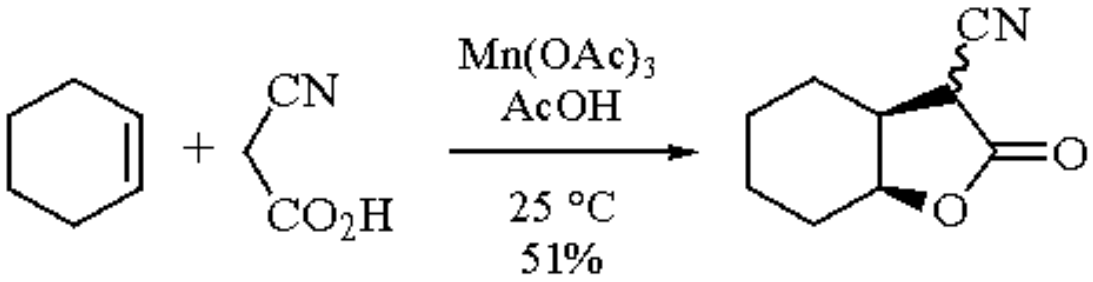

(2)

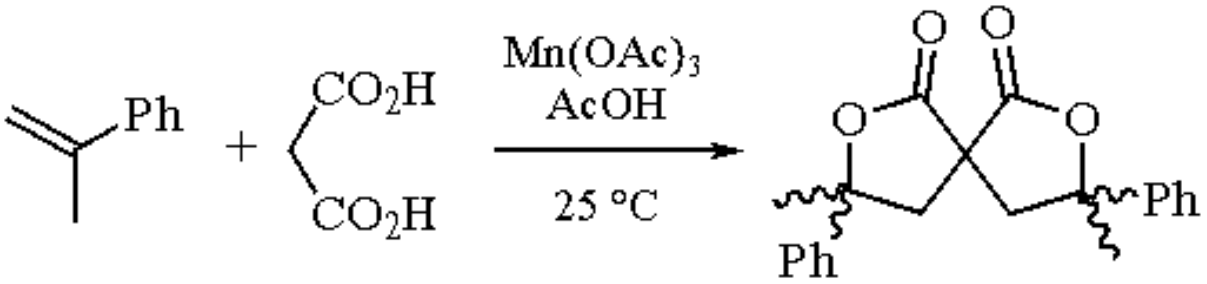

(3)

$Mn(OAc)_3$ oxidizes ketones and aldehydes to α-carbonyl radicals which add to alkenes to give γ-oxo radicals. If these radicals are secondary, they are not oxidized unless ***Copper(II) Acetate*** is used as a co-oxidant (eqs 4 and 5).[9,10] Instead they undergo chain-transfer reactions to give saturated carbonyl compounds. Tertiary radicals give mixtures of saturated and unsaturated carbonyl compounds.

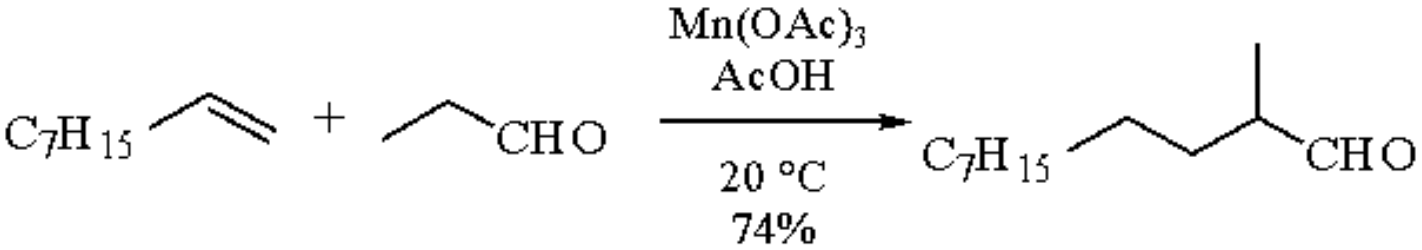

(4)

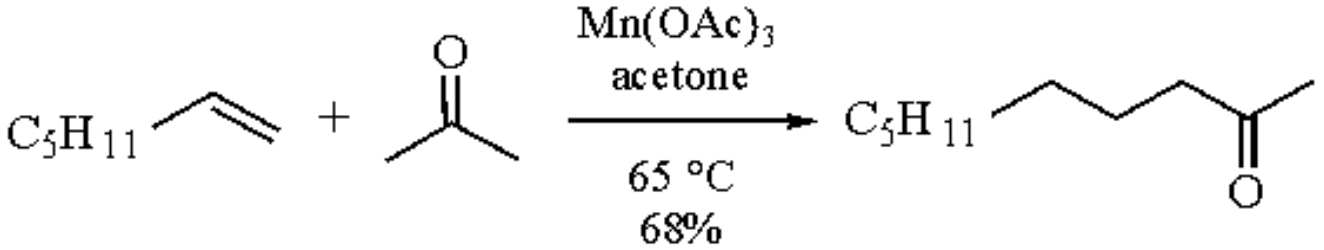

(5)

These reactions proceed in good yield based on oxidant consumed but must be carried out with a large excess of ketone or aldehyde, which is sometimes used as the solvent, since the products are oxidized further to give radicals at about the same rate as the starting carbonyl compound is oxidized.

A wide variety of β-dicarbonyl compounds can be oxidized by $Mn(OAc)_3$ to radicals in the presence of alkenes.[11] Addition of the radical to styrene and other electron-rich alkenes affords dihydrofurans. Addition to enol ethers occurs readily to give 1-alkoxy-1,2-dihydrofurans, which can be hydrolyzed to yield 1,4-diketones or dehydrated to form furans.[12]

Intramolecular versions of these reactions provide an efficient route to cyclic ring systems. Oxidation of unsaturated β-keto acids affords cyclopentanones fused to γ-lactones (eq 6).[13]

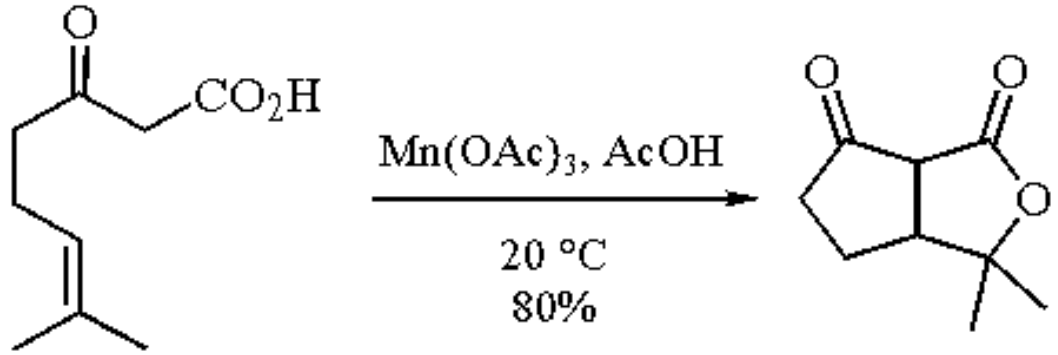

(6)

Oxidation of unsaturated β-keto esters affords α-keto radicals which add to alkenes to give alkyl radicals which are oxidized to alkenes in the presence of $Cu(OAc)_2$ (see ***Manganese(III) Acetate-Copper(II) Acetate***). If the alkyl radical is a 4-phenylbutyl radical, cyclization onto the aromatic ring results in the formation of a tetralin. This reaction occurs stereospecifically, as shown in the synthesis of *O*-methylpodocarpic acid (eq 7).[14]

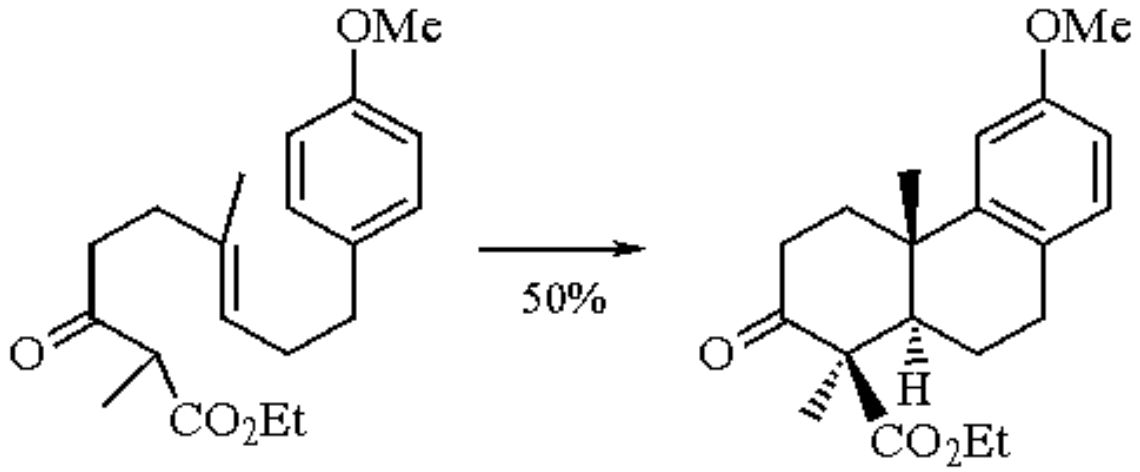

(7)

Haloalkenes are compatible with radical generation by oxidation of β-dicarbonyl compounds with $Mn(OAc)_3$ and can be used to control the regiochemistry of the cyclization (eq 8).[15] Loss of HCl from the intermediate affords the naphthol in 79% yield in one pot. This reaction is compatible with allylic oxygen functionality and has been used for the synthesis of okicenone (eq 9).[16]

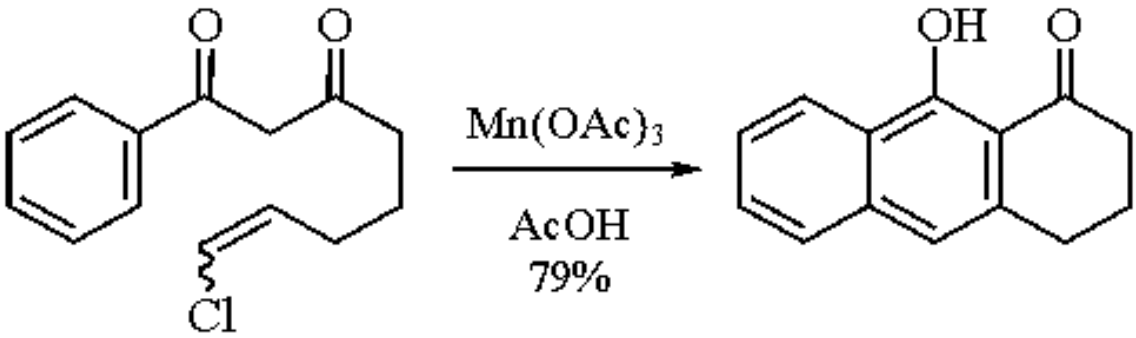

(8)

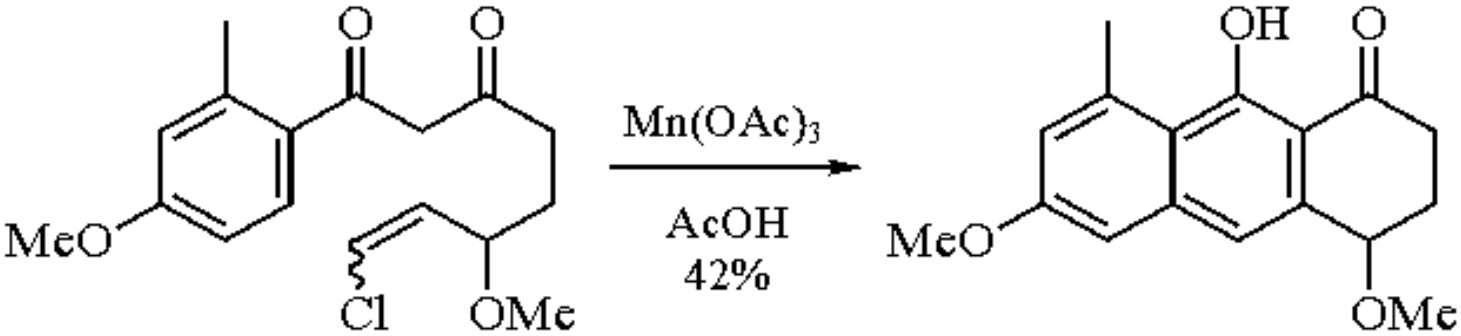

(9)

Oxidation of allylic β-keto amides with $Mn(OAc)_3$ in EtOH affords γ-lactams. The primary radical formed in the cyclization abstracts a hydrogen from the solvent (eq 10).[17] Similarly, saturated γ-lactones can be prepared by oxidation of allylic malonates and acetoacetates.[18]

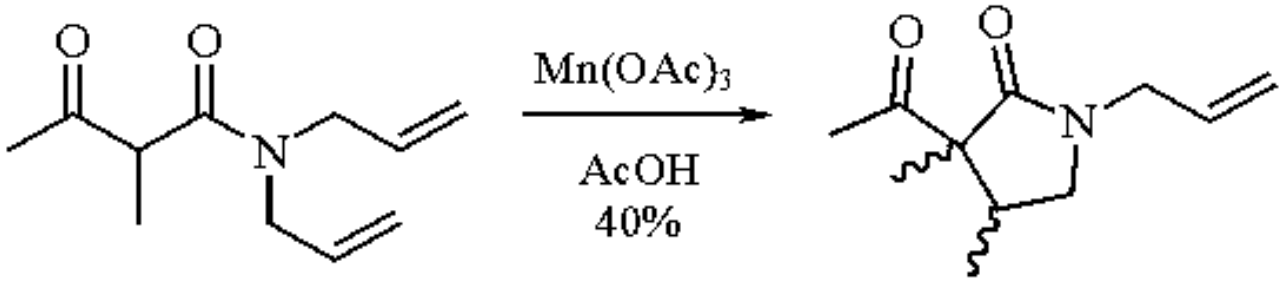

(10)

The radicals formed by oxidation of 1,3-dicarbonyl compounds will add to electron-rich naphthalenes (eq 11).[19] Tetralins and dihydronaphthalenes can be formed by oxidation of diethyl α-benzylmalonate in the presence of an alkene or alkyne (eq 12).[20-22]

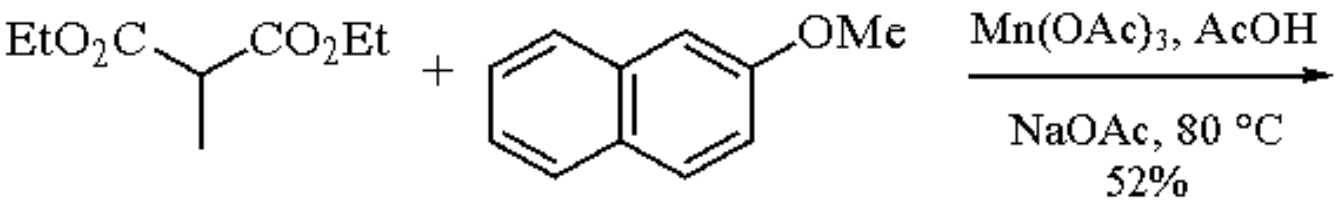

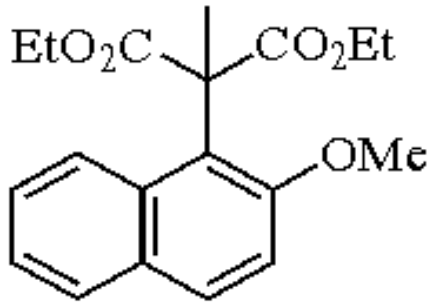

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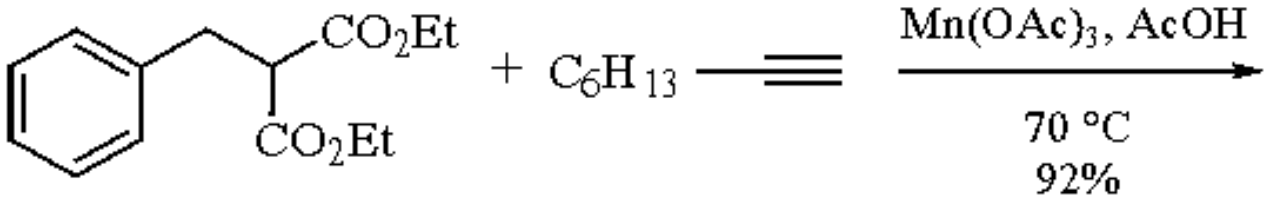

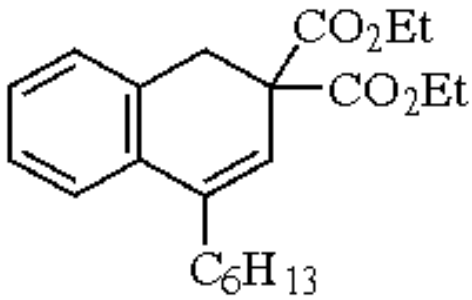

(12)

α´-Acetoxylation of conjugated enones with $Mn(OAc)_3$ in acetic acid proceeds in modest yield.[23] The reaction proceeds in much better yield with well-dried oxidant in refluxing benzene (eq 13).[24] A wide variety of α-esters can be introduced by exchange of carboxylic acids with $Mn(OAc)_3$ in benzene at reflux prior to the addition of the enone.[25] This procedure is applicable to α- and β-alkoxy enones[26] and is suitable for α-acetoxylation of aryl alkyl ketones.[27]

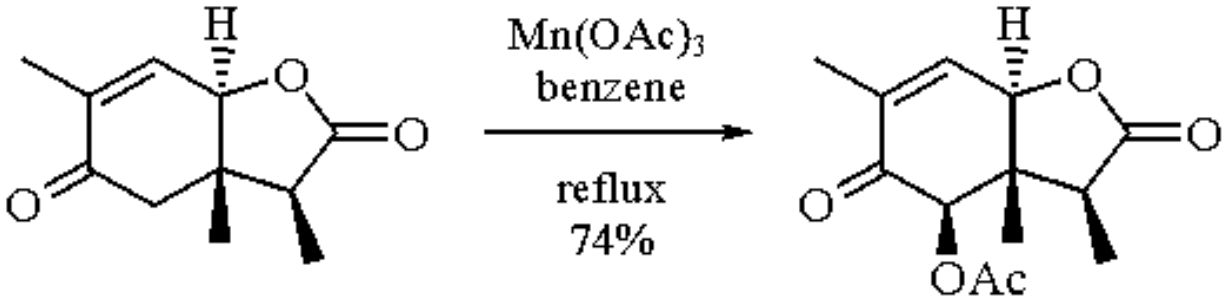

(13)

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Manganese(III) Acetate-Copper(II) Acetate[1]

$Mn(OAc)_3$-$Cu(OAc)_2$

($Mn(OAc)_3$)

[993-02-2] · $C_6H_9MnO_6$ · Manganese(III) Acetate-Copper(II) Acetate · (MW 232.09) ($Mn(OAc)_3.2H_2O$)

[19513-05-4] · $C_6H_{13}MnO_8$ · Manganese(III) Acetate-Copper(II) Acetate · (MW 268.13) ($Cu(OAc)_2$)

[142-71-2] · $C_4H_6CuO_4$ · Manganese(III) Acetate-Copper(II) Acetate · (MW 181.65) ($Cu(OAc)_2.H_2O$)

[6046-93-1] · $C_4H_8CuO_5$ · Manganese(III) Acetate-Copper(II) Acetate · (MW 199.67)

(Mn^{III} oxidizes mono- and β-dicarbonyl compounds to the corresponding radical which adds to alkenes to give an alkyl radical; Mn^{III} oxidizes tertiary radicals to cations but does not oxidize primary and secondary alkyl radicals; thermodynamically weaker oxidant Cu^{II} oxidizes primary and secondary radicals about 350 times faster than Mn^{III} does to give alkenes, rather than cations)

Solubility: oxidations are usually carried out in acetic acid or ethanol, although other organic solvents can be used.[2] $Mn(OAc)_3$ disproportionates in water.

Form Supplied in: $Cu(OAc)_2$ is readily available and can be used as either the hydrate or anhydrous form.

Intermolecular Reactions.

Reaction of 1-octene with ***Manganese(III) Acetate*** in acetic acid containing potassium acetate affords mainly γ-*n*-hexylbutyrolactone.[3] If the reaction is run in acetic acid/acetic anhydride with a catalytic amount of ***Copper(II) Acetate***, the secondary radical reacts more rapidly with Cu^{II} to give the Cu^{III} intermediate, which loses Cu(OAc) and HOAc to give mainly 4-decenoic acid and some 3-decenoic acid (eq 1);[4] 2 equiv of $Mn(OAc)_3$ are still required and $Cu(OAc)_2$ can be used in catalytic amounts since Cu^{I} is reoxidized to Cu^{II} by Mn^{III}.

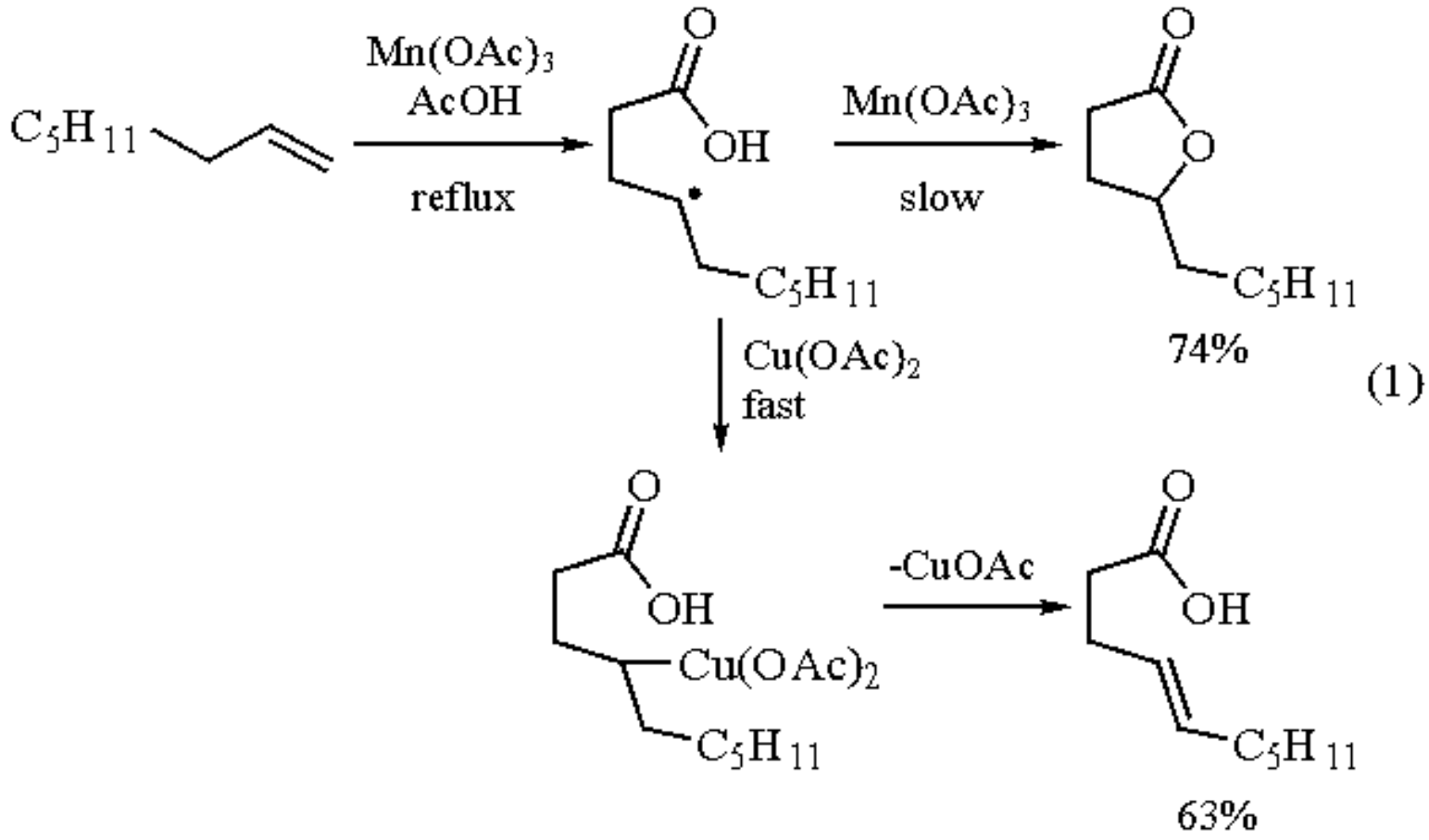

Oxidation of acetone with $Mn(OAc)_3$ in the presence of 1-heptene affords 2-decanone.[5] If $Cu(OAc)_2$ is present, the secondary radical is oxidized to an alkene, affording a mixture of 4- and 5-decenone (eq 2).[5] Similar results are obtained by oxidizing aldehydes with $Mn(OAc)_3$ and $Cu(OAc)_2$ in the presence of alkenes.[6]

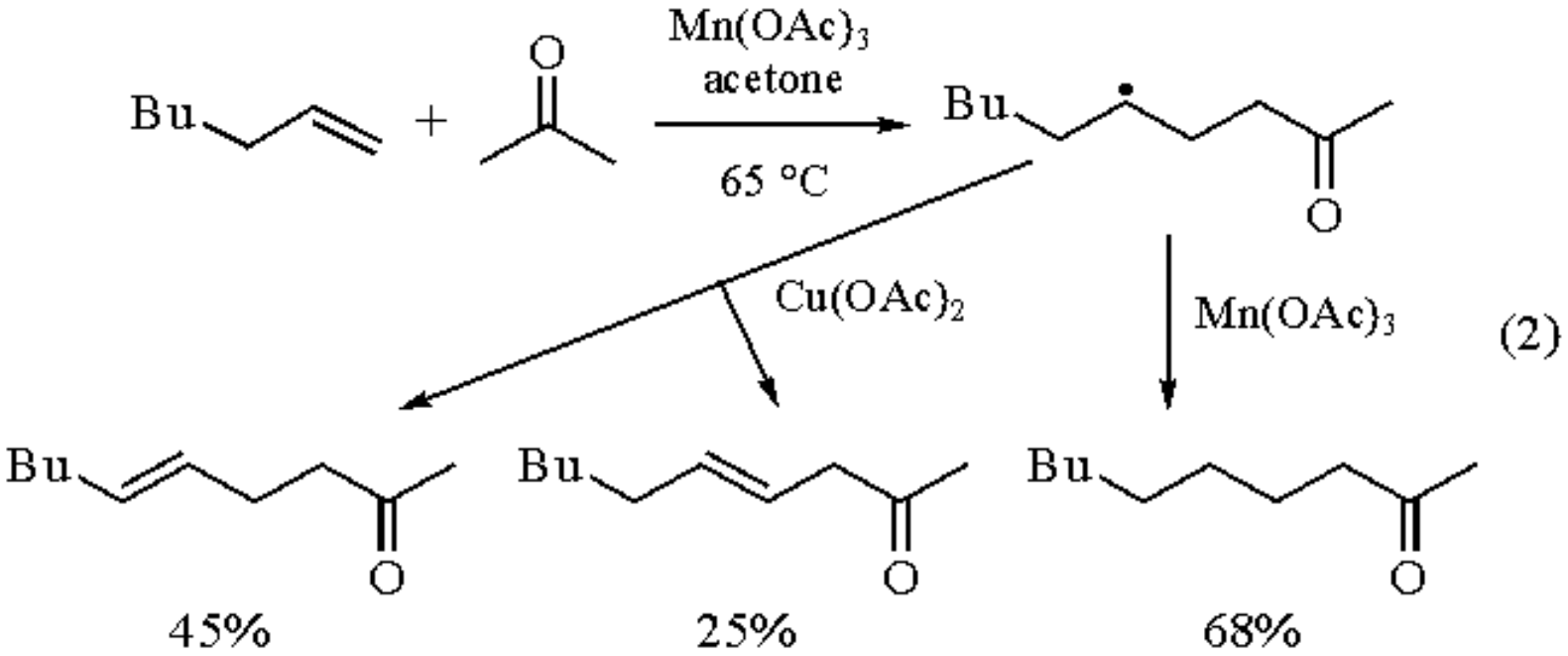

Oxidation of diethyl malonate with $Mn(OAc)_3$ in acetic acid at 90 °C in the presence of 1-heptene affords 50% of diethyl heptylmalonate since the secondary radical abstracts hydrogen faster than it is oxidized by Mn^{III}.[7] If the

reaction is run in the presence of $Cu(OAc)_2$, oxidation of the secondary radical is rapid so that diethyl 2-heptenylmalonate is the only product (eq 3).

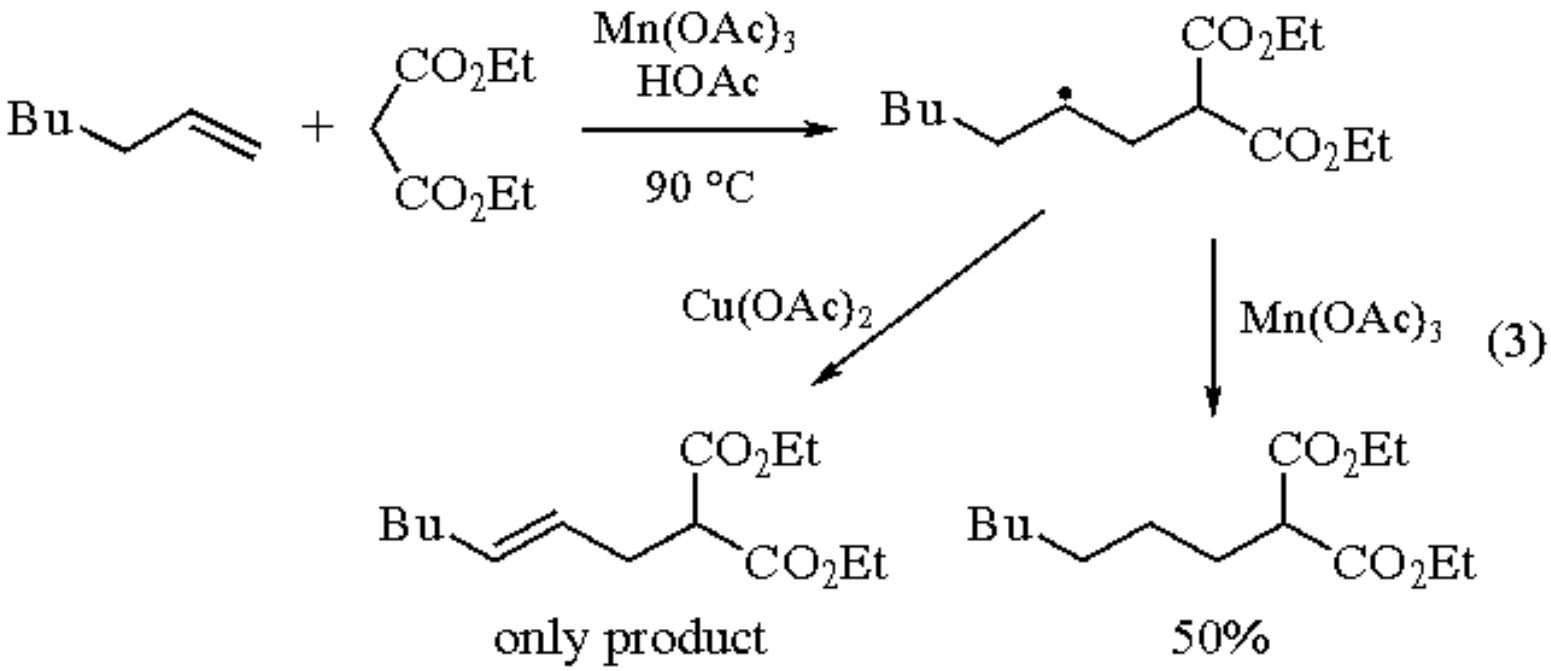

The yields of all of the reactions discussed above are based on oxidant consumed. Since the products are also susceptible to further oxidation, the mono- or 1,3-dicarbonyl compound must be used in large excess. This is practical when the carbonyl compound is a low molecular weight compound such as acetone or acetic acid which can be used as solvent.

Annulations can be carried out by oxidation of diethyl allylmalonate with Mn^{III} and Cu^{II} in the presence of an alkene (eq 4). The radical formed by addition to the alkene cyclizes to the allyl double bond to give a primary radical that is oxidized by Cu^{II} to an alkene.[8]

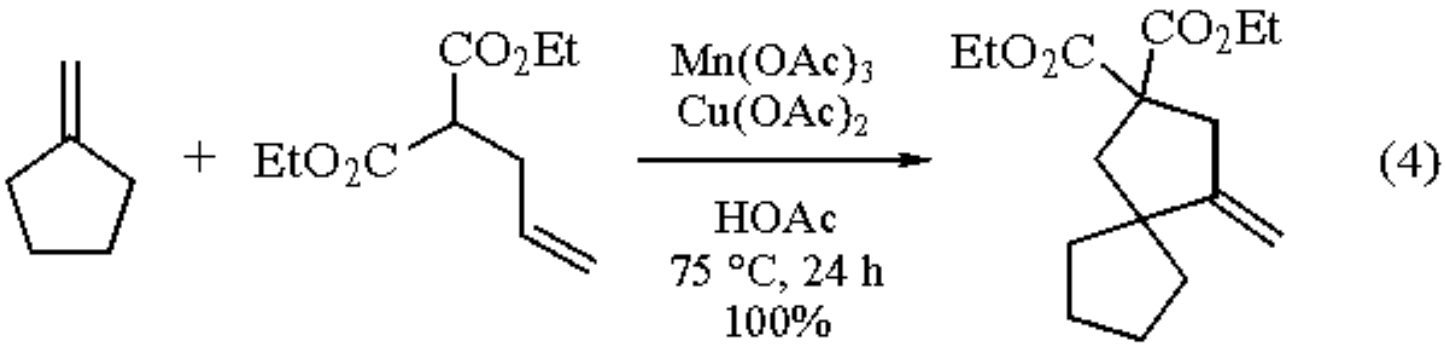

Intramolecular Reactions.

Oxidative cyclizations can be carried out in high yield with substrates containing double bonds and 1,3-dicarbonyl compounds, which are much more easily oxidized than monocarbonyl compounds. Oxidation of (**1a**) with $Mn(OAc)_3$ and $Cu(OAc)_2$ affords 71% of (**2a**) (eq 5).[9,10] However, oxidation of 1,3-dicarbonyl compounds with two α-hydrogens usually proceeds in lower yield since the product can be oxidized further by Mn^{III}. The formation of

38% of (**2b**) and 10% of (**3**), formed by further oxidation of (**2b**), shows that this problem is more serious in the formation of five- than six-membered rings.[10]

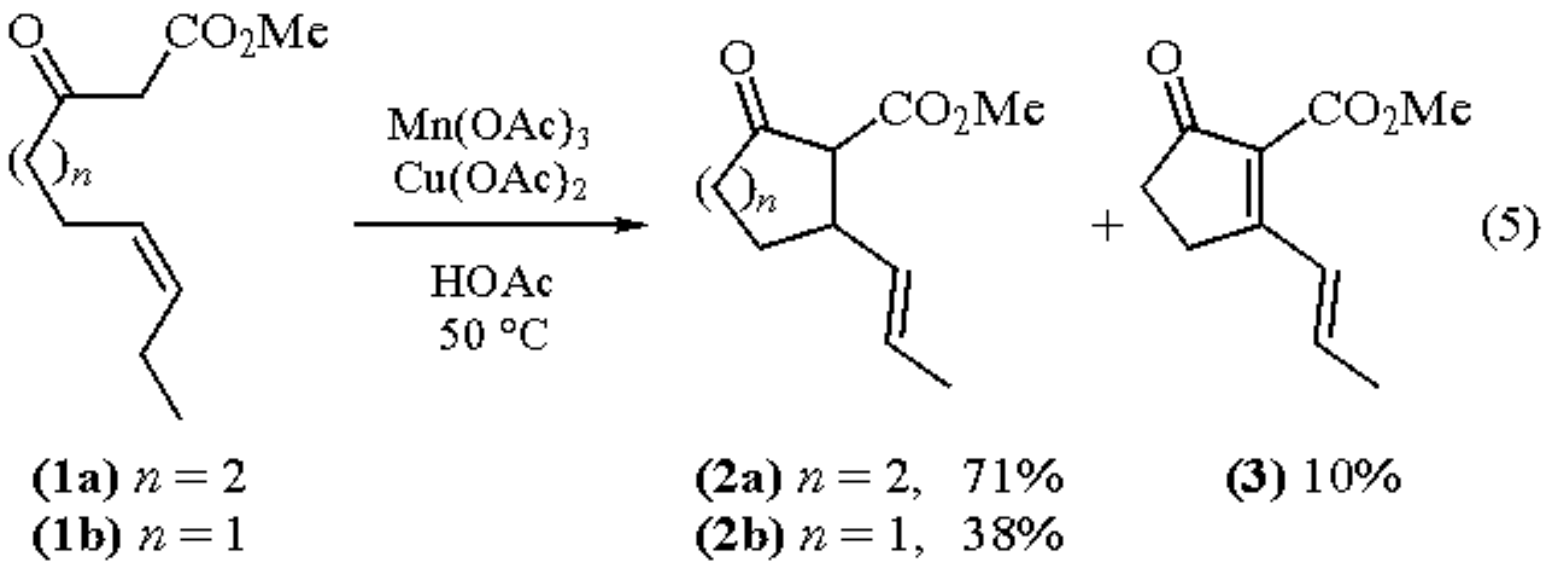

Oxidative cyclization of 1,3-dicarbonyl compounds that contain only a single α-hydrogen typically proceed in good yield and can be used to form five-, six-, seven- and eight-membered rings (eqs 6-9).[10-13]

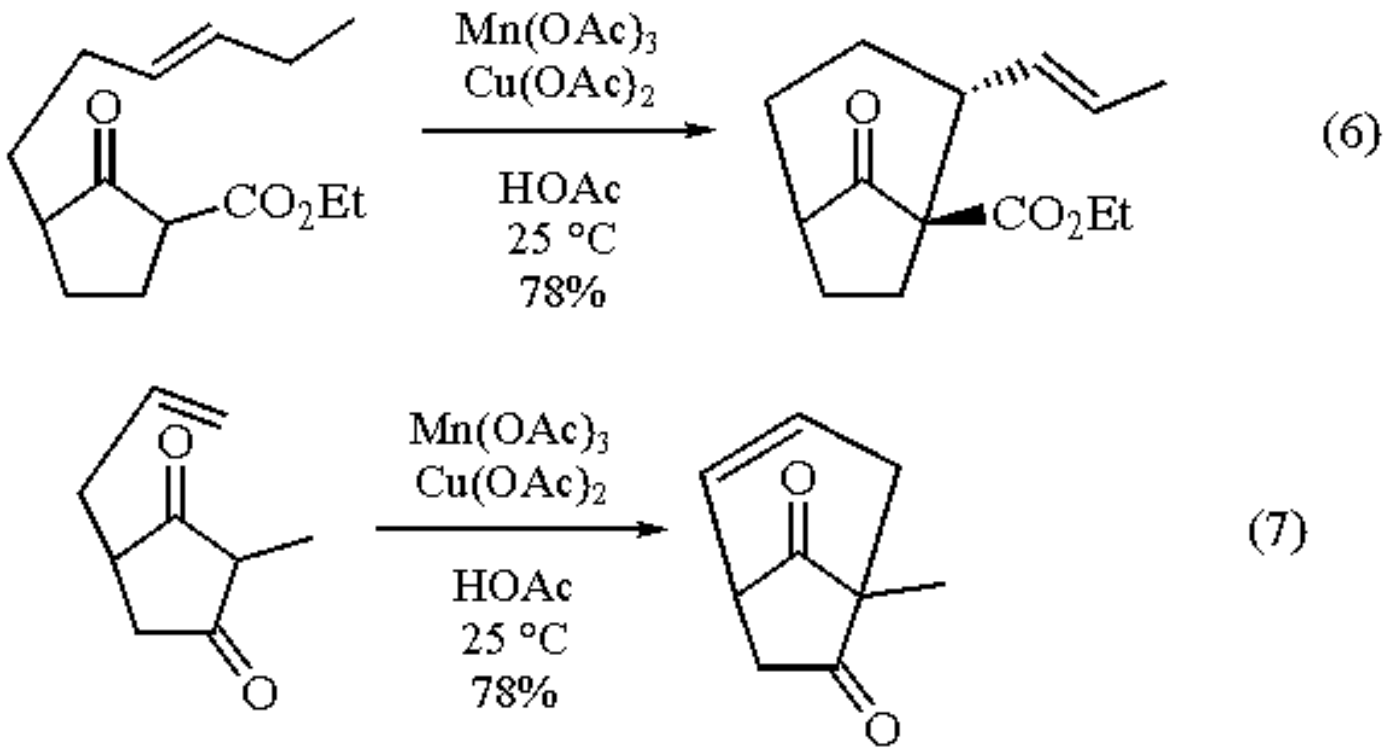

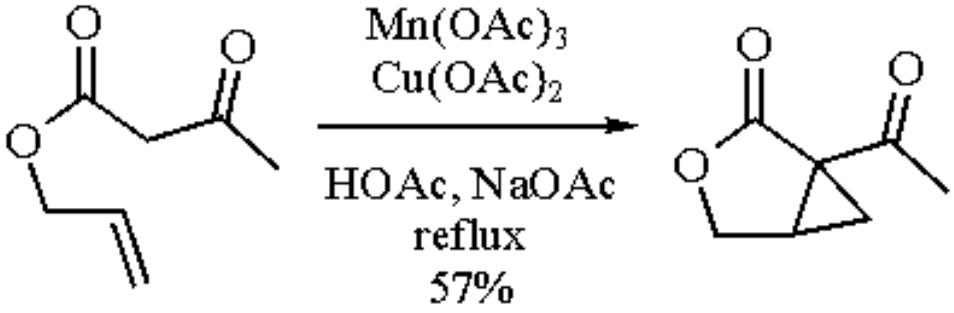

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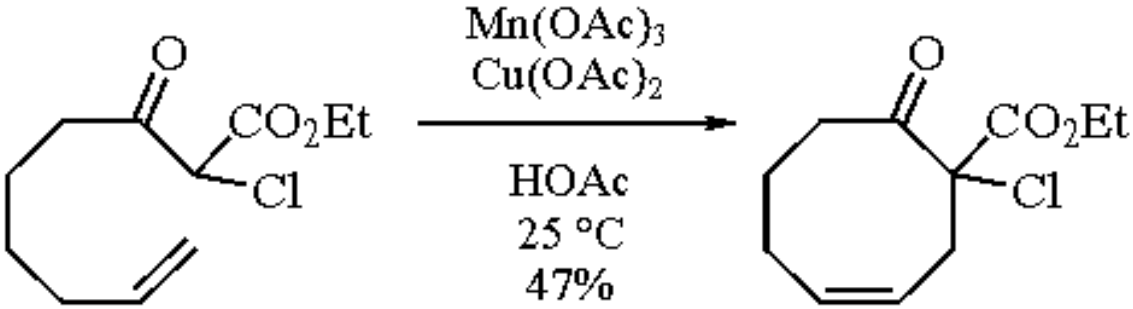

(9)

Oxidation of α-chloro-1,3-dicarbonyl compounds generally proceeds in good yield (eqs 9 and 10).[14] Reduction with zinc removes the chloride, affording the cyclized product with an α-hydrogen. This product usually cannot be obtained directly due to problems with further oxidation as discussed above.[13,15,16]

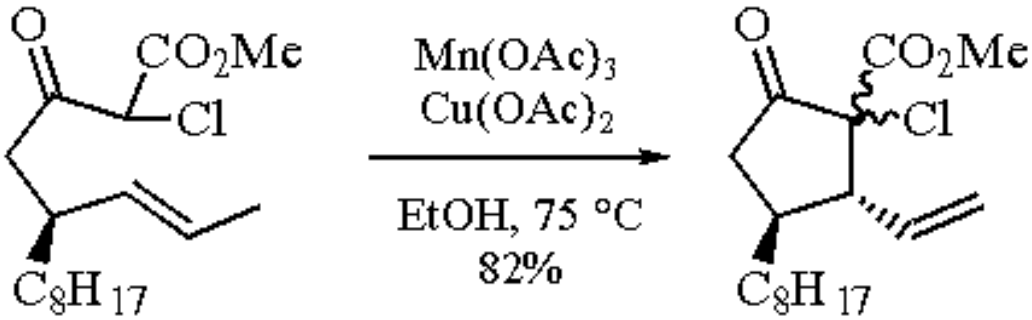

(10)

Oxidation of acetoacetates such as that shown in eq 11 with 4 equiv of Mn^{III} and a catalytic amount of Cu^{II} results in 6-*endo* cyclization and further oxidation to afford methyl salicylate.[17-19] This reaction can be used for the formation of more highly functionalized salicylate derivatives.[19]

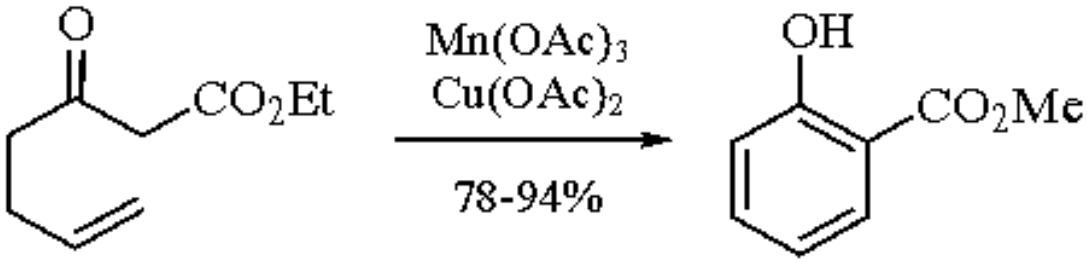

(11)

Tandem,[9,20-26,28] triple,[22] and even quadruple[27] cyclizations can be carried out with multiply unsaturated 1,3-dicarbonyl compounds, as shown in eqs 12-14.[2a,22,24-27] High levels of asymmetric induction can be achieved with phenylmenthyl acetoacetate esters and dimethylpyrrolidine acetoacetamides.[29-31]

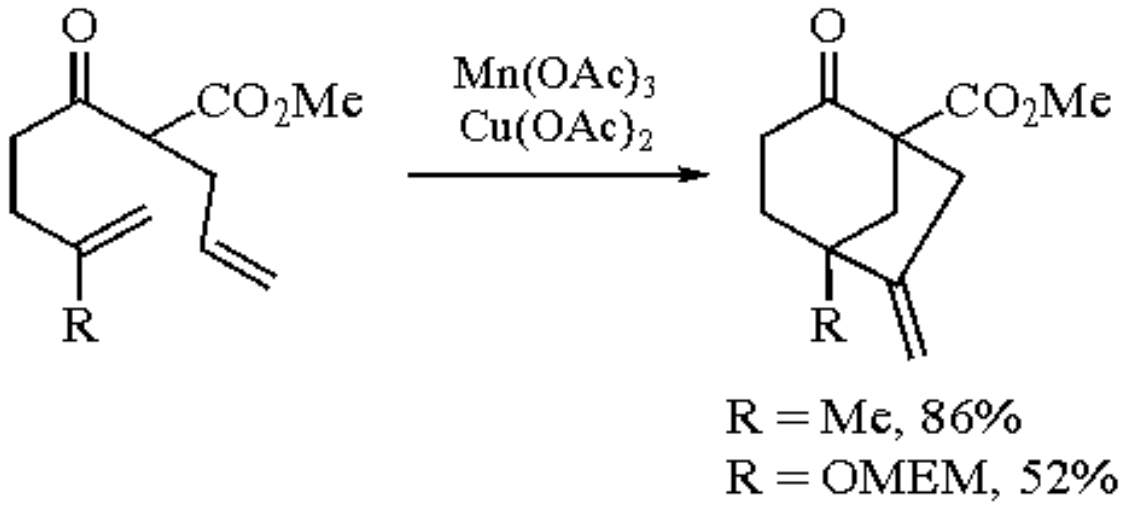

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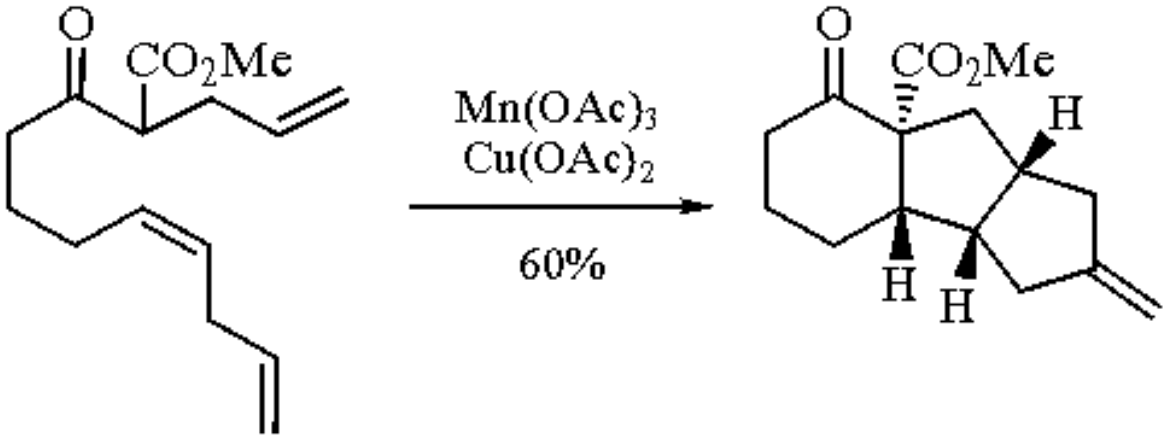

(13)

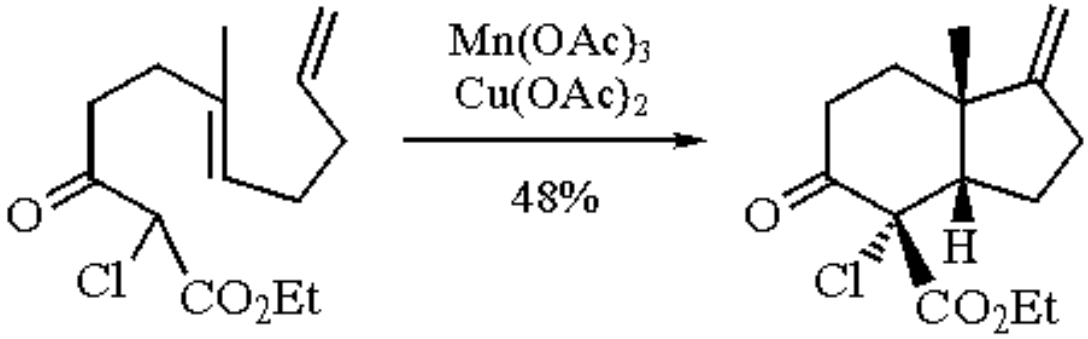

(14)

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Manganese(II) Chloride

$MnCl_2$

($MnCl_2$)

[7773-01-5] · Cl_2Mn · Manganese(II) Chloride · (MW 125.84) ($MnCl_2.4H_2O$)

[13446-34-9] · $Cl_2H_8MnO_4$ · Manganese(II) Chloride · (MW 197.92)

(starting material for preparation of organomanganese chloride reagents;[1] in combination with RLi or RMgX catalyzes reduction of vinyl and aryl halides,[2] stereoselective coupling of vinyl iodides,[3] and alkylation of enol triflates;[4] also used for Mn-Cu-catalyzed conjugate addition of RMgX to enones[5] and for Mn-catalyzed acylation of RMgX by acyl chlorides;[6] in combination with $NaBH_4$ is diastereoselective reducing agent;[7] starting material for the preparation of Mn enolates regio- and stereoselectively[8])

Physical Data: anhydrous material: mp 650 °C; bp 1190 °C; *d* 2.98 g cm^{-3}; hygroscopic. Tetrahydrate: mp 58 °C, *d* 2.01 g cm^{-3}.

Solubility: sol H_2O and some polar organic solvents (DMF, NMP, DMPU, etc.); insol hydrocarbons, ether, THF. $MnCl_2$ can be dissolved in THF as its ate complex $MnCl_4Li_2$. The latter is easily obtained by mixing LiCl (2 equiv) and anhydrous $MnCl_2$ in THF at rt until dissolution (about 1 h). $MnCl_4Li_2$ is generally used in place of $MnCl_2$; it reacts similarly but more rapidly owing to its solubility.[1]

Form Supplied in: pink grayish powder; widely available. *Drying:* for organometallic uses, it is recommended that the commercial anhydrous $MnCl_2$ be dried since the industrial anhydrous material contains 0.1-1% H_2O. The following procedure is convenient: heating at 200 °C under vacuo (10^{-2} mmHg) for 2 h.

Handling, Storage, and Precautions: anhydrous $MnCl_2$ is a very hygroscopic material. It must be handled very quickly and stored in a tightly closed bottle.

Preparation of Organomanganese Reagents.[1]

RMnCl are easily prepared by adding RLi or RMgX to a solution of $MnCl_4Li_2$ (see above) in THF (eq 1):

$$\text{RLi (or RMgX)} + MnCl_2 \xrightarrow{THF} \text{RMnX} \qquad (1)$$

According to the ratio RLi:$MnCl_2$ or RMgX:$MnCl_2$, several other types of organomanganese reagents can be prepared: the symmetrical organomanganeses R_2Mn and the organomanganates R_3MnLi and R_4MnLi_2 or R_3MnMgX and $R_4Mn(MgX)_2$.

In most cases, the transmetalation reaction can be performed between 0 and 20 °C (-20 °C to -10 °C when R = *s*- or *t*-alkyl) and the Li-Mn or Mg-Mn exchange occurs quantitatively and almost instantaneously. RMnCl react with carboxylic acid chlorides to give ketones and with ketones or aldehydes to lead to the corresponding alcohols. In the presence of copper, they also add to conjugated unsaturated ketones, aldehydes, esters, and amides to afford the 1,4-addition products. All these reactions have a large scope and give high yields under mild conditions. It is important to note that RMnCl react chemoselectively and are especially useful in the preparation of multifunctionalized molecules (see ***n-Butylmanganese Chloride***).

Reduction of Vinyl and Aryl Halides.[2]

In the presence of $MnCl_2$, in THF, *i*-PrMgCl reduces vinyl and aryl halides in good yields (eqs 2 and 3). Some functional groups such as ethers or amines are tolerated.

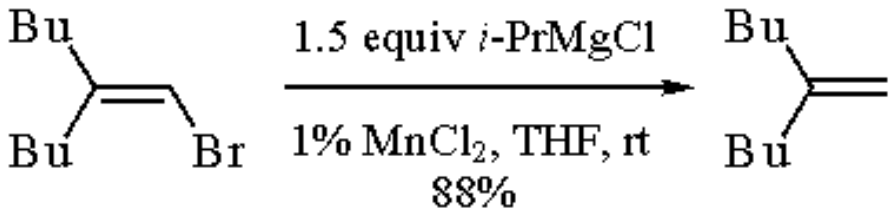

(2)

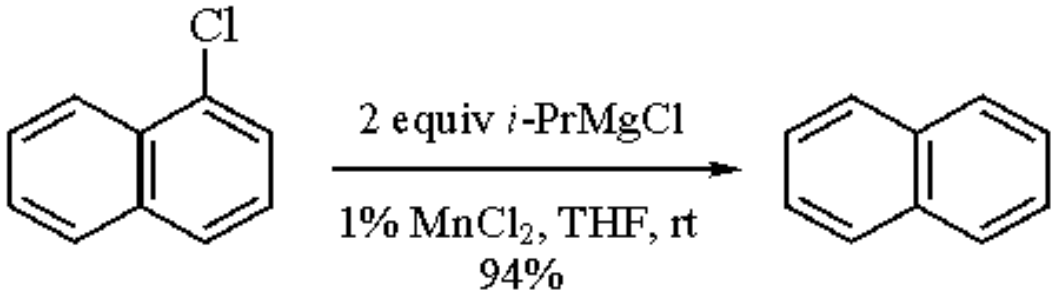

(3)

Stereospecific Symmetrical Coupling of Vinyl Iodides.[3]

In ether, in the presence of $MnCl_2$, MeLi or *n*-BuLi react with vinyl iodides to give stereospecifically the corresponding conjugated dienes in excellent yields (eq 4).

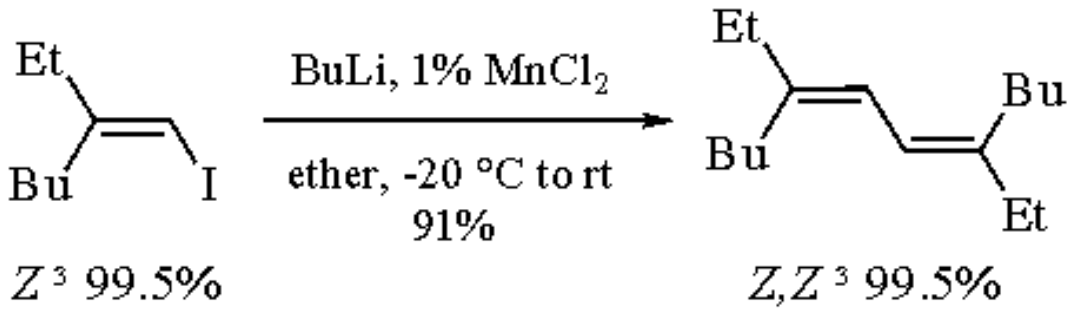

(4)

Alkylation of Enol Triflates.[4]

Organomagnesium compounds react with enol triflates, in the presence of $MnCl_4Li_2$, to give the substituted alkenes (eq 5). However, good yields are obtained only with aryl, benzyl, or allyl Grignard reagents.

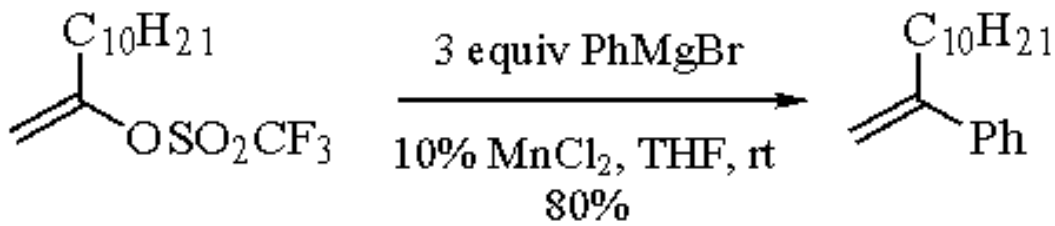

(5)

$MnCl_2$ as Precursor of Mn^0.

$MnCl_2$ is reduced by ***Lithium Aluminum Hydride*** in THF at 0 °C (eq 6) to give a very fine black suspension of Mn^0 (the exact nature of this precipitate has not been established). The subsequent addition of allyl bromide leads to an intermediate species which reacts with aldehydes or reactive ketones to give the corresponding homoallylic alcohols (eq 7).[9]

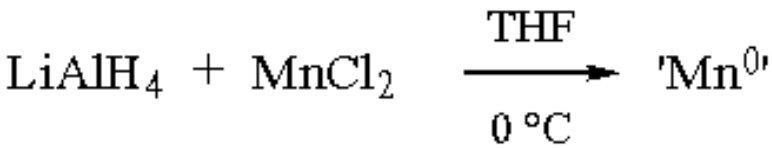

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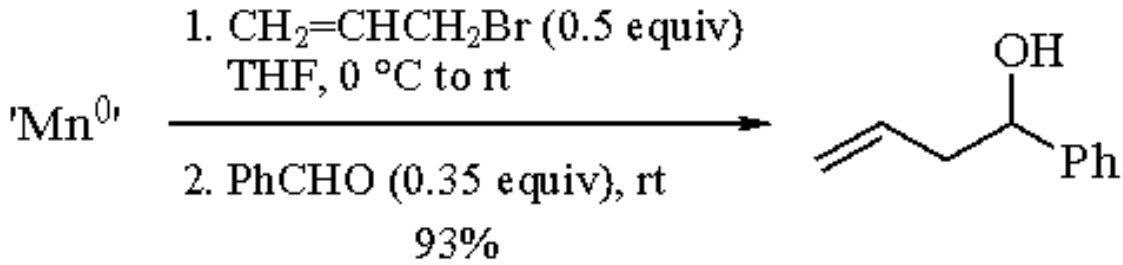

(7)

From a practical point of view, it is interesting to note that such a Mn-mediated Barbier reaction can be more efficiently performed by using commercial manganese metal,[10] a very cheap material. Thus, upon reaction of Mn^0 with allylic halides in EtOAc at 50 °C in the presence of aldehydes or ketones, the 1,2-addition product is obtained in high yields. With functionalized aldehydes or ketones, the chemoselectivity is excellent (eq 8).

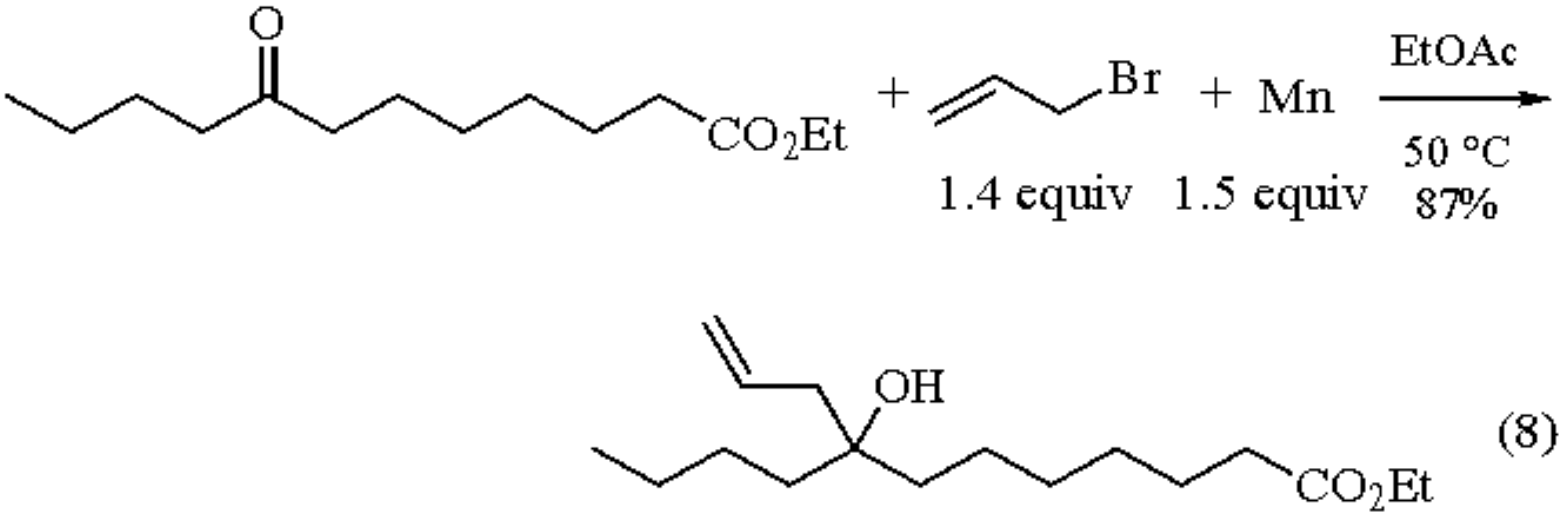

(8)

In THF, the reaction takes place at 60 °C and only in the presence of ***Zinc Chloride***. Even allylic chlorides can be used (eq 9).

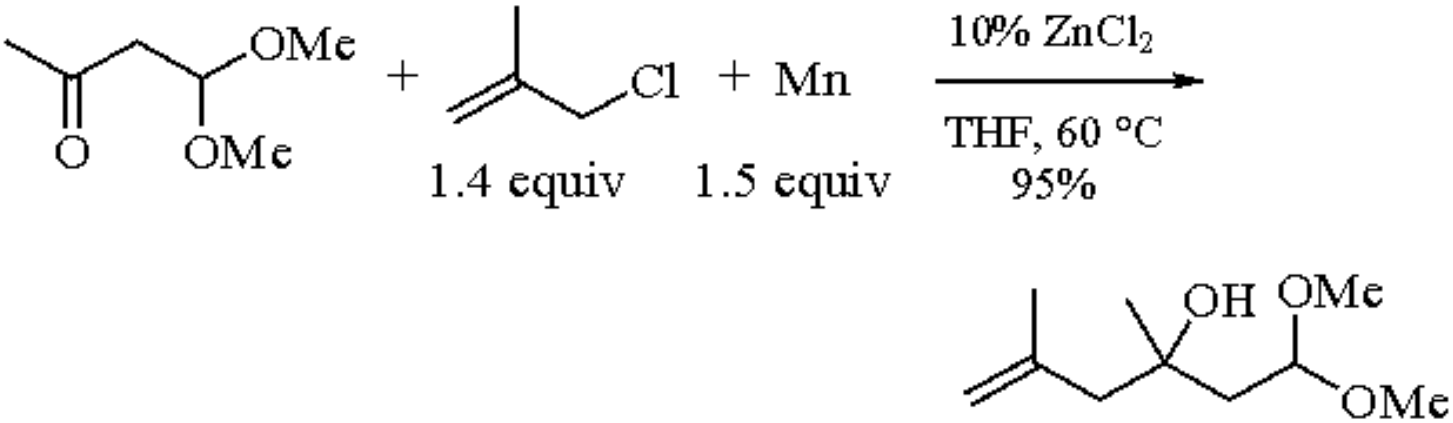

(9)

A Mn-mediated Reformatsky reaction can also be effected in EtOAc in the presence of $ZnCl_2$. The alcoholates resulting from the addition of the intermediate ester Mn-enolates to aldehydes or ketones can be trapped by Ac_2O to give good yields of β-acetoxy esters (eq 10).

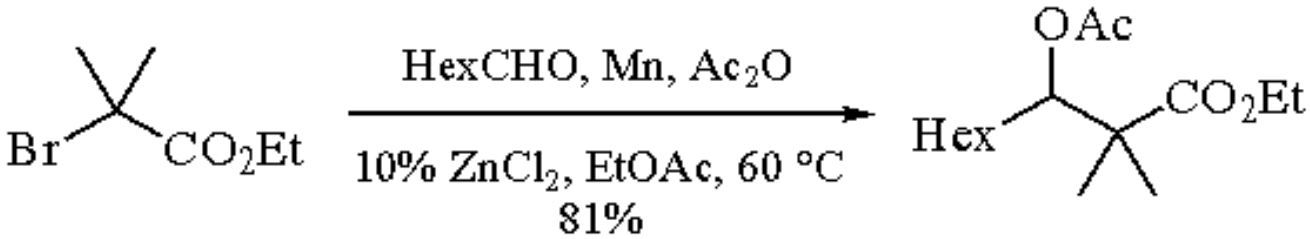

(10)

Mn-Cu-Catalyzed Conjugate Addition of Organomagnesium Reagents to Enones.[5]

RMgX add to enones in the presence of both Mn and Cu chlorides to afford good yields of 1,4-addition products. This procedure is generally superior to the classical Cu-catalyzed conjugate addition of RMgX as well as to the reaction of

organocuprates (eq 11).

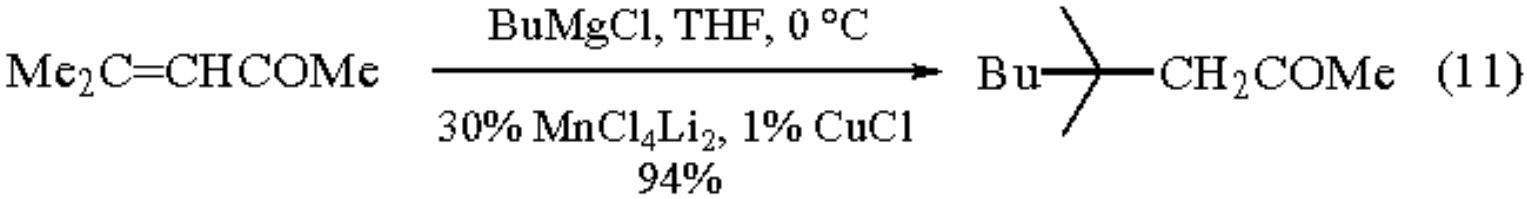

Mn-Catalyzed Acylation of Organomagnesium Reagents by Acyl Chlorides.[6]

In THF, in the presence of $MnCl_4Li_2$, RMgX react with acyl chlorides under mild conditions to give the corresponding ketones in high yield. This procedure is very interesting from both practical and economical points of view. The chemoselectivity is excellent (eq 12).[6]

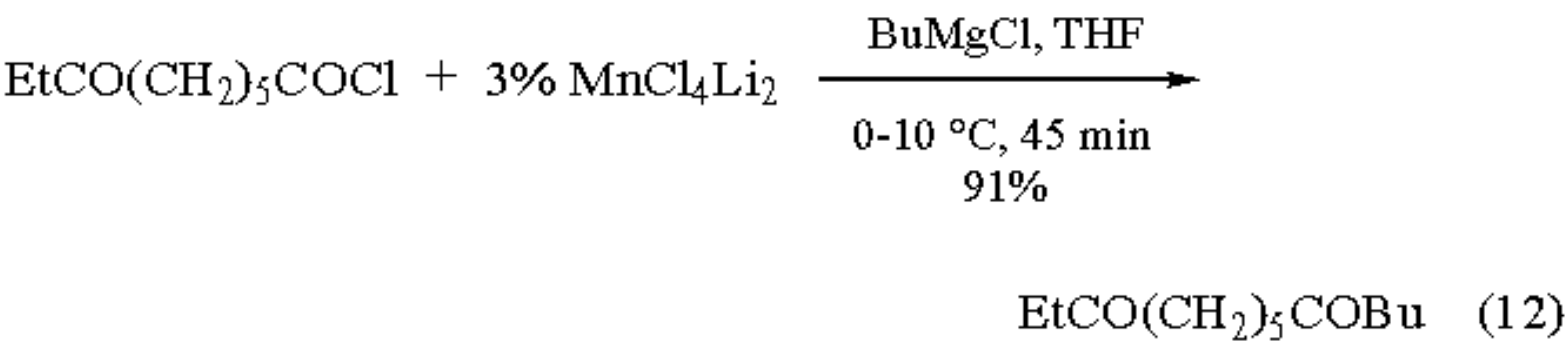

Diastereoselective Reduction of Ketones.[7]

In the presence of $MnCl_2$, the reduction of α-methyl β-keto esters or amides by ***Sodium Borohydride*** leads to the corresponding β-hydroxy esters or amides with an excellent stereoselectivity (eq 13).

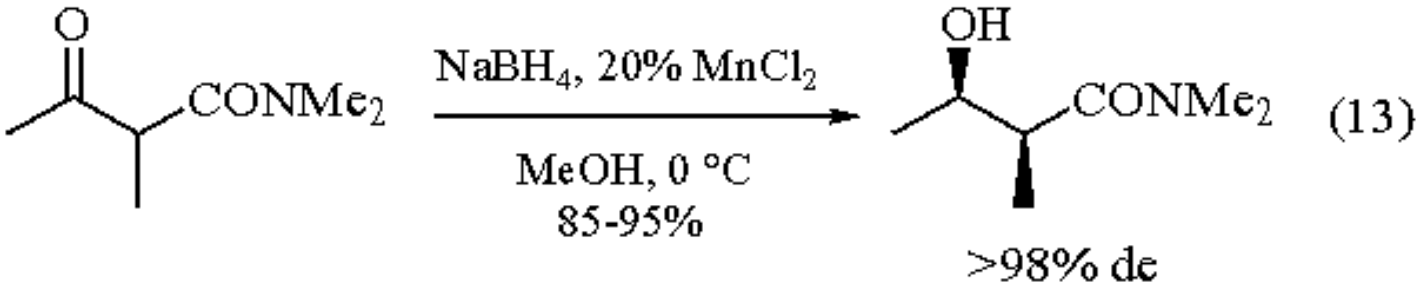

Regioselective and Stereoselective Preparation of Manganese Enolates: Applications in Organic Synthesis.[8]

Mn enolates are easily prepared from Na, Mg, or Li enolates by transmetalation with $MnCl_2$ (or $MnBr_2$). The stereo- and the regiochemistry of the starting enolate is maintained during the reaction.

It is important to note that Mn enolates can also be quantitatively obtained regio- and stereoselectively (>95% of the less hindered (*Z*) isomers) by enolization of ketones with Mn amides prepared from $MnCl_2$. This procedure very often gives better yields and the (*Z*) stereoselectivity is clearly superior.

Mn enolates are regioselectively alkylated in good yields; interestingly, the formation of polyalkylated products is never observed (eq 14). They react regio- and stereospecifically with Me_3SiCl or carboxylic acid anhydrides to give respectively silyl enol ethers and enol esters (95-99% *Z*) in high yields (eq 15). Finally, they add to α,β-ethylenic carbonyl compounds (Michael addition) as well as to aldehydes and reactive ketones (diastereoselective aldolization condensation). In all cases, the reactions give excellent yields and occur regioselectively.

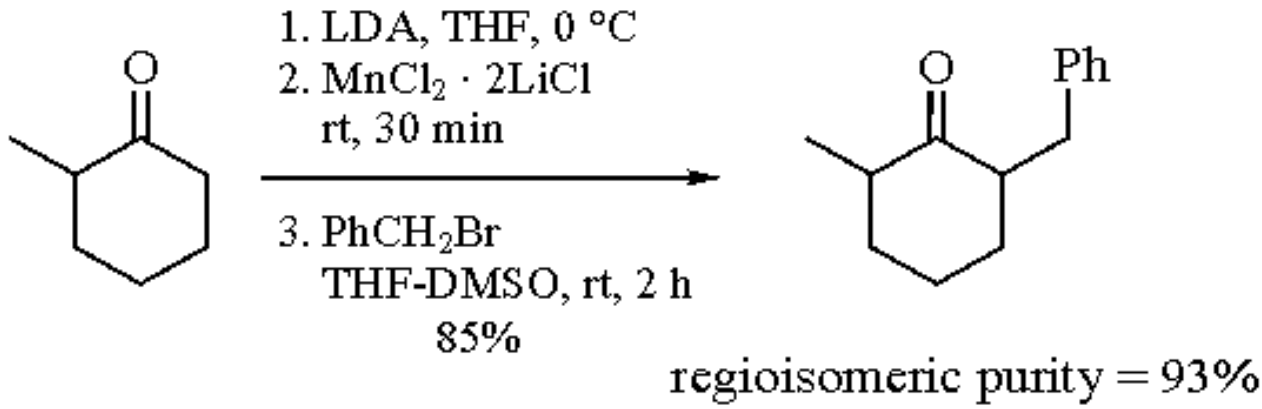

(14)

regioisomeric purity = 93%

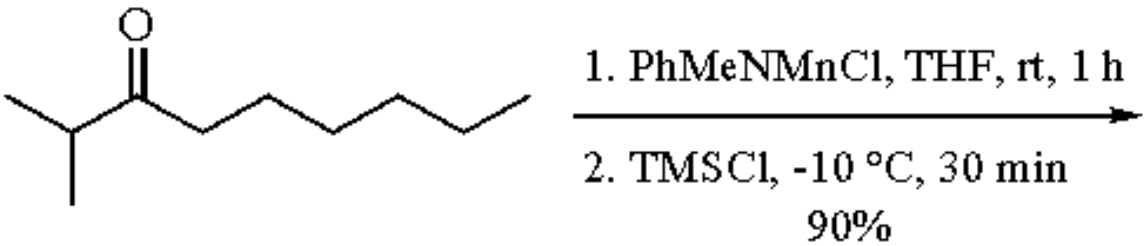

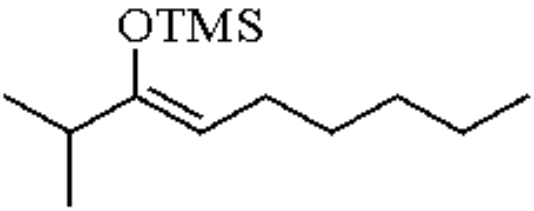

(15)

Z = 97%, regioisomeric purity = 98%

Related Reagents.

n-Butylmanganese Chloride.

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2. Cahiez, G.; Bernard, D.; Normant, J. F. *JOM* **1976**, *113*, 107.
3. Cahiez, G.; Bernard, D.; Normant, J. F. *JOM* **1976**, *113*, 99.
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6. Cahiez, G.; Laboue, B. *TL* **1992**, *33*, 4439.
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8. (a) Cahiez, G. Fr. Patent Appl. 88/15 806, 1988; Eur. Patent Appl. 373 993, 1990 (*CA* **1991**, *114*, 61 550y). (b) Cahiez, G.; Cléry, P.; Laffitte, J. A. Fr. Patent Appl. 90/16 413, 1990 and 91/11 814, 1991; PCT Int. Appl. 93/06 071, 1993 (*CA* **1993**, *118*, 169 340b and **1993**, *119*, 116 519f).
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10. Cahiez, G.; Chavant, P. *TL* **1989**, *30*, 7373.

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Manganese Dioxide[1]

MnO_2

[1313-13-9] · MnO_2 · Manganese Dioxide · (MW 86.94)

(useful selective oxidizing reagent for organic synthesis; oxidation of allylic alcohols to α,β-ethylenic aldehydes or ketones;[2] conversion of allylic alcohols to α,β-ethylenic esters or amides;[3] oxidation of propargylic alcohols,[4] benzylic or heterocyclic alcohols,[5] and saturated alcohols;[6] oxidative cleavage of 1,2-diols;[7] hydration of nitriles to amides;[8] dehydrogenation and aromatization reactions;[9] oxidation of amines to aldehydes, imines, amides, and diazo compounds[10])

Alternate Names: manganese oxide; manganese(IV) oxide.

Physical Data: mp 535 °C (dec); *d* 5.03 g cm^{-3}.

Solubility: insol H_2O and organic solvents.

Form Supplied in: dark brown powder, widely available. The commercial active MnO_2 used as oxidizing reagent for organic synthesis is a synthetic nonstoichiometric hydrated material. The main natural source of MnO_2 is the mineral pyrolusite, a poor oxidizing reagent.

Structure of Active Manganese Dioxide.[1,11,12]

The structure and the reactivity of active manganese dioxides used as oxidizing reagents in organic synthesis closely depends on their method of preparation (see below). Active manganese oxides are nonstoichiometric materials (generally MnO_x; $1.93 < x < 2$) and magnetic measurements reveal the presence of lower valency Mn species, probably Mn^{II} and Mn^{III} oxides and hydroxides. Thermogravimetric analysis experiments show the existence of bonded and nonbonded water molecules (hydrated MnO_2). On the basis of ESR studies and other experiments, a locked-water associated structure (**1**) has been proposed for the apomorphous precipitated MnO_2.[12]

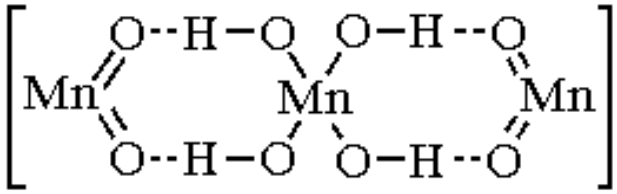

(1)

In addition, variable amounts of alkaline and alkaline earth metal derivatives are detected by atomic adsorption analysis. X-ray studies have shown that the structures of active MnO_2 are quite complex; they are either amorphous or of moderate crystallinity (variable proportions of β- and γ-MnO_2).

Preparation of Active MnO_2, Oxidizing Power, and Reproducibility of the Results.[1,13]

Pyrolusite (natural MnO_2) and pure synthetic crystalline MnO_2 are poor oxidants.[1] The oxidation of organic compounds requires an active, specially prepared MnO_2 and several procedures have been reported.[1,13] According to the method of preparation, the structure, the composition, and therefore the reactivity of active MnO_2 are variable. On this account, the choice of a procedure is of considerable importance to obtain the desired oxidation power and the reaction conditions must be carefully controlled to obtain a consistent activity. The active manganese dioxides described in the literature are generally prepared either by mixing aqueous solutions of $KMnO_4$ and a Mn^{II} salt ($MnSO_4$, $MnCl_2$) between 0 and 70 °C under acid, neutral, or basic conditions[13a-e] or by pyrolysis of a Mn^{II} salt (carbonate, oxalate, nitrate) at 250-300 °C.[13d,f] In this case the activity of the resulting material can be increased by washing with dilute nitric acid.[13f] A similar treatment has also been used to activate pyrolusite (natural MnO_2).[13h] On the other hand, it has been reported that the efficiency of an active MnO_2 depends on the percentage of the γ-form present in the material.[13i] Indeed, active γ-MnO_2 is sometimes clearly superior to the classical active MnO_2 prepared according to Attenburrow.[13j]

It worthy of note that the percentage water content strongly influences both the oxidizing power and the selectivity (oxidation of multifunctional molecules) of active MnO_2. Thus it is well known that the wet material (40-60% H_2O) obtained after filtration must be activated by drying[1,13] (heating to 100-130 °C for 12-24 h[13a-d] or, better, at 125 °C for 52 h).[13e] Indeed, an excess of water decreases the oxidation power[1e,13k] since, according to the triphasic mechanism generally postulated,[12] it would prevent the adsorption of the substrate to the oxidatively active polar site on the surface of MnO_2.[1a,c,e] On the other hand, it is very important not to go past the point of complete activation since the presence of hydrated MnO_2 species is essential to obtain an active reagent. For this reason, the drying conditions must be carefully controlled.[1,13a,d,g,k] Alternatively, the wet material can be activated by azeotropic distillation since this mild procedure preserves the active hydrated species.[131] Thus azeotropic distillation has been used to remove the water produced during the oxidation reaction to follow the rate of MnO_2 oxidations.[13e] Finally, the active MnO_2 mentioned above contains various metallic salts as impurities. According to their nature, which depends on the method of preparation, they can also influence the oxidizing power of the reagent (for instance, permanganate).[13d] Finally, it should be noted that the preparation of active MnO_2 on carbon[13m] or on silica gel[13n] as well as the activation of nonactive MnO_2 (pure crystalline MnO_2) by ultrasonic irradiation[13o] has also been reported. Some typical procedures to prepare active MnO_2 are reported below.

Preparation of Active MnO_2 from $KMnO_4$ under Basic Conditions (Attenburrow).[13a]

A solution of $MnSO_4.4H_2O$ (110 g) in H_2O (1.5 L) and a solution of NaOH (40%; 1.17 L) were added simultaneously during 1 h to a hot stirred solution of $KMnO_4$ (960 g) in H_2O (6 L). MnO_2 precipitated soon after as a fine brown solid. Stirring was continued for an additional hour and the solid was then collected with a centrifuge and washed with water until the washings were colorless. The solid was dried in an oven at 100-120 °C and ground to a fine powder (960 g) before use.

Preparation of Active MnO_2 from $KMnO_4$ under Acidic Conditions.[13k]

Active MnO_2 was made by mixing hot solutions of $MnSO_4$ and $KMnO_4$, maintaining a slight excess of the latter for several hours, washing the product thoroughly with water and drying at 110-120 °C. Its activity was unchanged after storage for many months, but it was deactivated by H_2O, MeOH, thiols, or excessive heat (500 °C). MnO_2 was less active when prepared in the presence of alkali and ineffective when precipitated from hot solutions containing a large excess of $MnSO_4$.

Preparation of Highly Active MnO_2 from $KMnO_4$.[1a]

A solution of $MnCl_2.4H_2O$ (200 g) in H_2O (2 L) at 70 °C was gradually added during 10 min, with stirring, to a solution of $KMnO_4$ (160 g) in H_2O (2 L) at 60 °C in a hood. A vigorous reaction ensued with evolution of chlorine; the suspension was stirred for 2 h and kept overnight at rt. The precipitate was filtered off, washed thoroughly with H_2O (4 L) until pH 6.5-7 and the washing gave a negligible chloride test. The filter cake was then dried at 120-130 °C for 18 h; this gave a chocolate-brown, amorphous powder; yield 195-200 g. Alternatively, the wet cake was mixed with benzene (1.2 L) and H_2O was removed by azeotropic distillation giving a chocolate-brown, amorphous powder; yield 195 g. The last procedure gave a slightly less active material.

Preparation of Active MnO_2 by Pyrolysis of $MnCO_3$.[13f]

Powdered $MnCO_3$ was spread in a one-inch thick layer in a Pyrex glass and heated at 220-280 °C for about 18 h in an oven in which air circulated by convection. The initially tan powder turned darker at about 180 °C, and black when maintained at over 220 °C. No attempt was made to determine lower temperature or time limits, nor the upper limit of temperature. The MnO_2 prepared as above was stirred with about 1 L of a solution made up of 15% HNO_3 in H_2O. The slurry was filtered with suction, the solid was washed on the Buchner funnel with distilled water until the washes were about pH 5, and finally was dried at 220-250 °C. The caked, black solid was readily crushed to a powder which retained its oxidizing ability even after having been stored for several months in a loosely stoppered container.

Preparation of γ-MnO_2.[1a]

To a solution of $MnSO_4$ (151 g) in H_2O (2.87 L) at 60 °C was added, with stirring, a solution of $KMnO_4$ (105 g) in H_2O

(2 L), and the suspension was stirred at 60 °C for 1 h, filtered, and the precipitate washed with water until free of sulfate ions. The precipitate was dried to constant weight at 60 °C; yield 120 g (dark-brown, amorphous powder).

Preparation of Active MnO_2 on Silica Gel.[13n]

$KMnO_4$ (3.79 g) was dissolved in water (60 mL) at rt. Chromatographic grade silica gel (Merck, 70-230 mesh, 60 g) was added with stirring, and the flask connected to a rotary evaporator to strip off the water at 60 °C. The purple solid was ground to fine powder and then added with vigorous stirring to a solution of $MnSO_4.H_2O$ (9.3 g) in H_2O (100 mL). The resulting brown precipitate was filtered with water until no more Mn^{II} ion could be detected in the wash water by adding ammonia. After being dried at 100 °C for 2 h, each gram of this supported reagent contained 0.83 mmol of MnO_2.

As shown above, a wide range of products of various activities are called active MnO_2 and the results described in the literature are sometimes difficult to reproduce since the nature of the MnO_2 which was used is not always well defined. Now, the commercial materials give reproducible results but they are not always convenient to perform all the oxidation reactions described in the literature. In addition, their origin (method of preparation) is not often indicated and comparison with the active MnO_2 described in the literature is sometimes difficult. For all these reasons, the use of activated MnO_2 has been somewhat restricted in spite of the efficiency and selectivity of its reactions since only an empirical approach and a careful examination of the literature allow selection of the suitable activity of MnO_2 and the optimum reaction conditions for a defined substrate.

Oxidation of Organic Compounds with MnO_2: Reaction Conditions.[1,13]

Solvent.

Oxidation of organic compounds with MnO_2 has been performed in many solvents. The choice of the solvent is important; thus primary or secondary alcohols (or water) are unsatisfactory since they can compete with the substrate being adsorbed on the MnO_2 surface and they have a strong deactivating effect.[13k] A similar but less pronounced influence has also been observed with various polar solvents such as acetone, ethyl acetate, DMF, and DMSO. However, these polar solvents, including water,[13p] acetic acid, and pyridine, can be used successfully at higher temperatures. This deactivating influence due to the polarity of the solvent can be used to control the reactivity of active MnO_2 and sometimes to avoid side reactions or to improve the selectivity (for instance, allylic alcohol vs. saturated alcohol). Most of the reactions described in the literature were carried out in aliphatic or aromatic hydrocarbons, chlorinated hydrocarbons, diethyl ether, THF, ethyl acetate, acetone, and acetonitrile (caution: MeCN can react with highly active MnO_2 or with classically activated MnO_2 on prolonged treatment). In the case of the oxidation of benzylic[13f] and allylic[13d] alcohols, the best results have been obtained using diethyl ether (diethyl ether > petroleum ether > benzene). Caution: a spontaneous ignition has been observed when highly active MnO_2 was used in this solvent.[13f]

Temperature and Reaction Time.

At rt, the reaction time can vary from 10 min to several days according to the nature of the substrate and the activity of the MnO_2.[13a,d,e,f,l,p] The reaction times are shortened by heating[13d] but the selectivity is very often much lower.[13q]

Ratio MnO_2:Substrate.

The amount of active MnO_2 required to perform the oxidation of an organic substrate depends on the type of MnO_2, on the substrate, and on the particle size of the MnO_2.[13d,f,g] With a classical material (100-200 mesh), the ratio varies from 5:1 to 50:1 by weight.

Oxidation of Allylic Alcohols.[2]

MnO_2 was used as oxidizing reagent for the first time by Ball et al. to prepare retinal from vitamin A_1 (eq 1).[2a] Since that report, the use of MnO_2 for the conversion of allylic alcohols to α,β-ethylenic aldehydes has been extensively utilized. Interestingly, the configuration of the double bond is conserved during the reaction (eqs 2-4).[2b,c] In some cases a significant rate difference between axial and equatorial alcohols has been observed[2d] (eq 5).[2e]

MnO_2 has been frequently used for the preparation of very sensitive polyunsaturated aldehydes or ketones (eq 6).[2f]

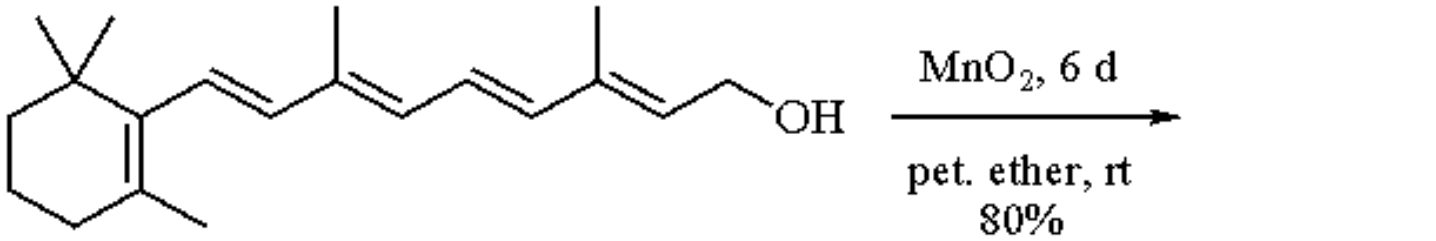

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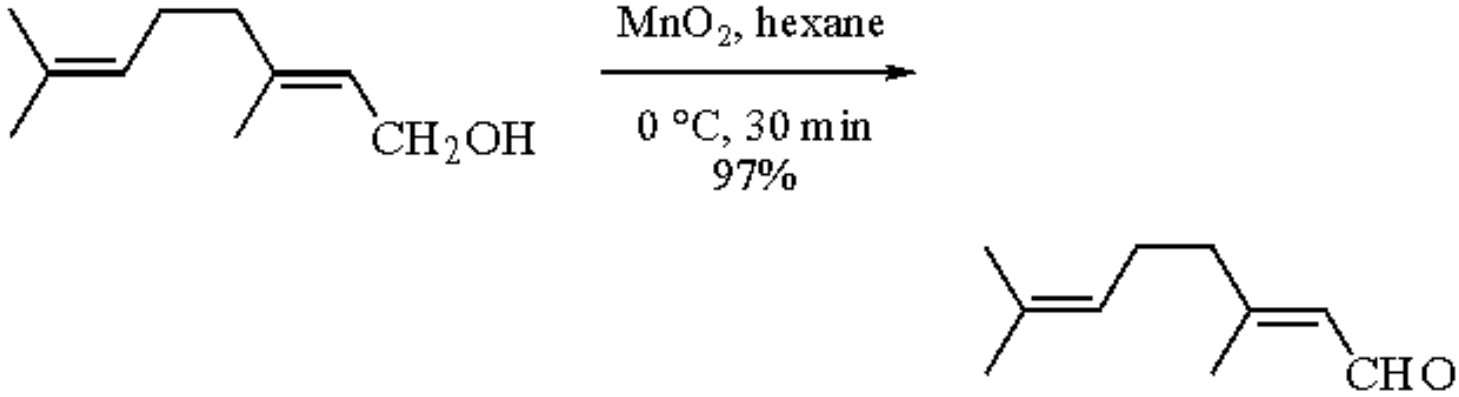

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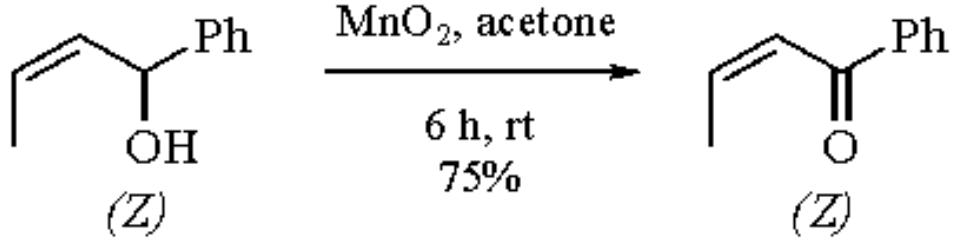
Ph
OH
(Z)
MnO2, acetone
6 h, rt
75%
Ph
O
(Z)

(3)

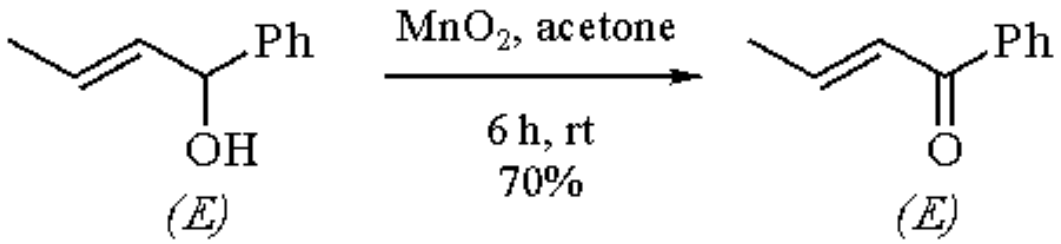
Ph
OH
(E)
MnO2, acetone
6 h, rt
70%
Ph
O
(E)

(4)

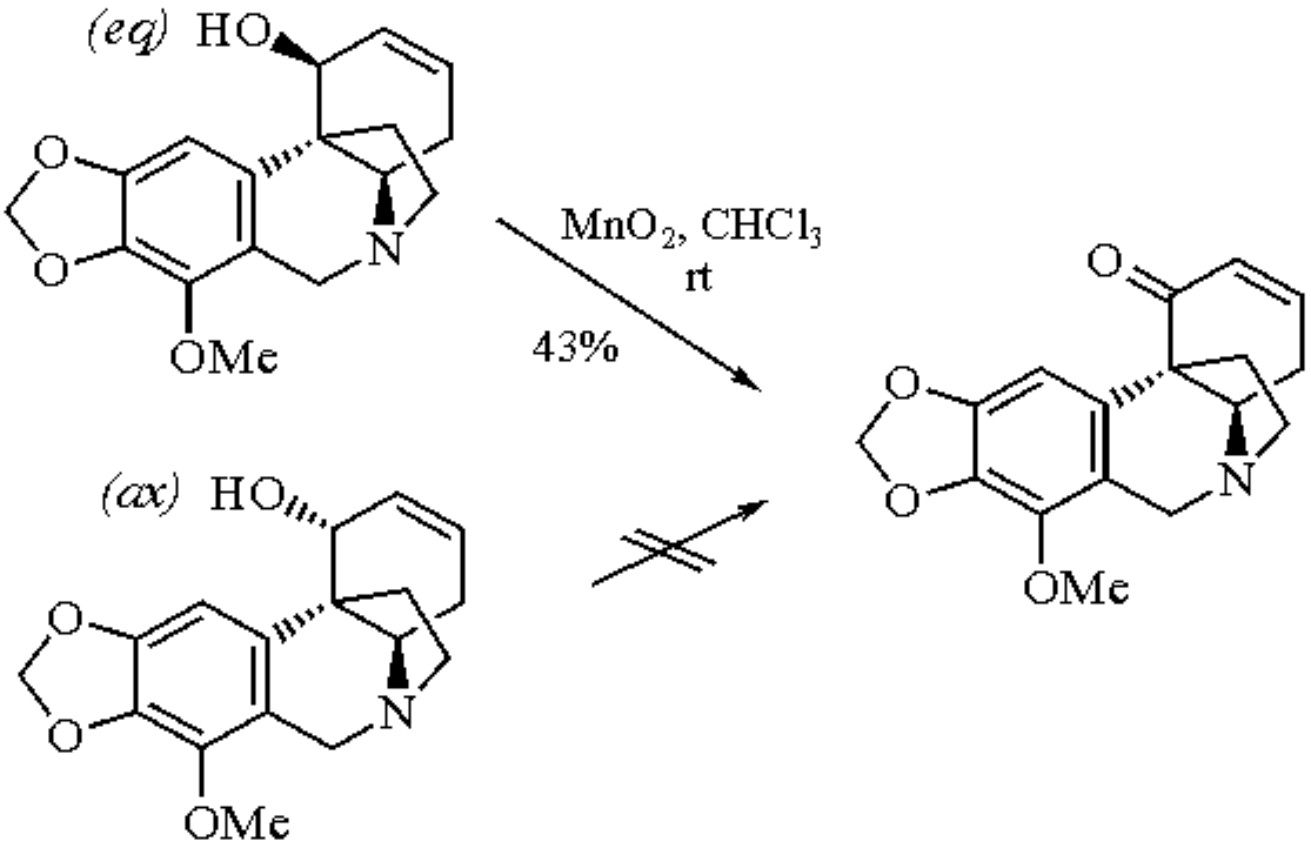
(eq) HO
O
O
N
OMe
MnO2, CHCl3
rt
43%
O
O
O
N
OMe
(ax) HO
O
O
N
OMe

(5)

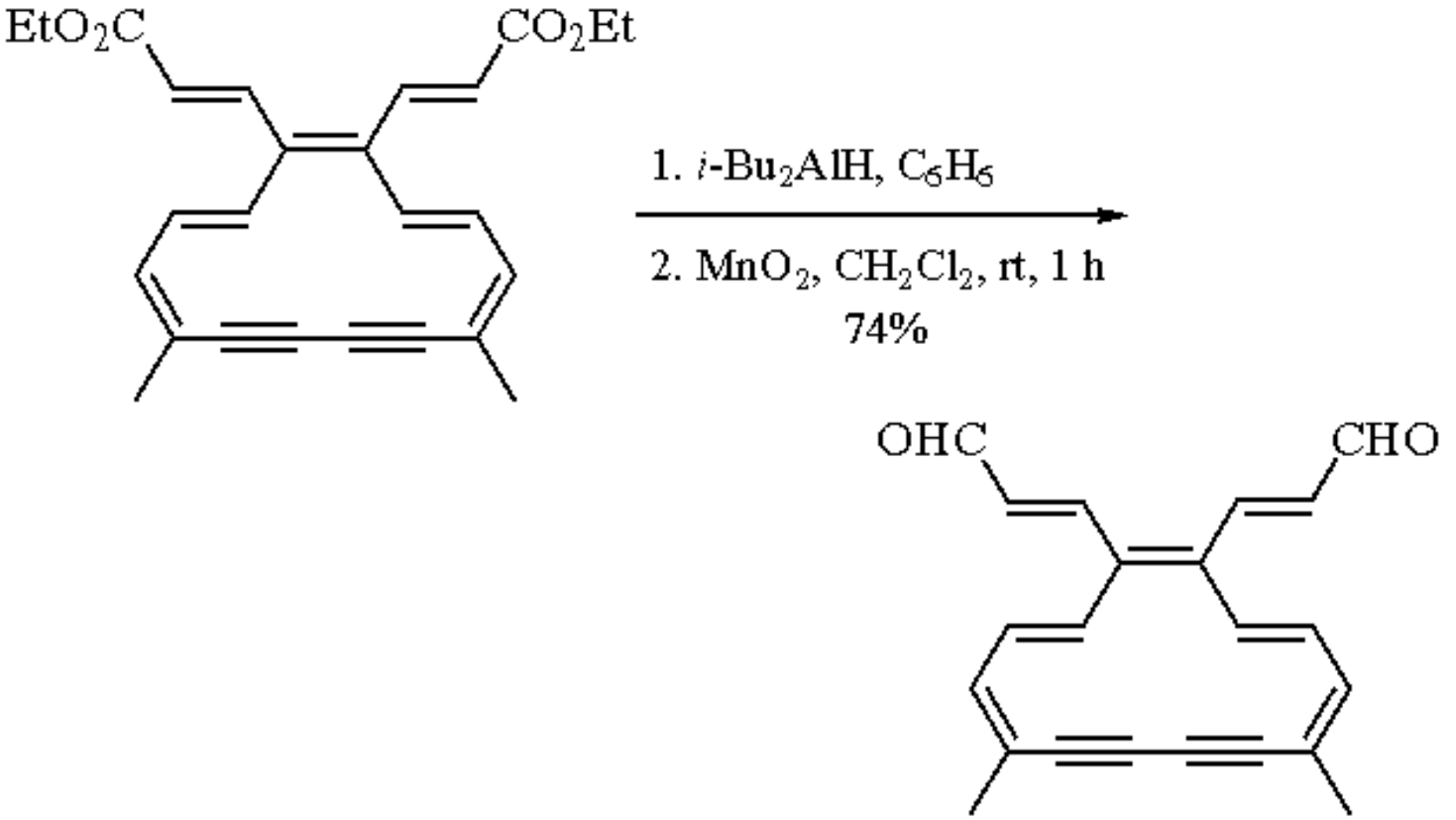

(6)

Numerous functionalized α,β-ethylenic aldehydes are readily obtained by chemoselective oxidation of the corresponding allylic alcohols (eqs 7-11).[2g-k]

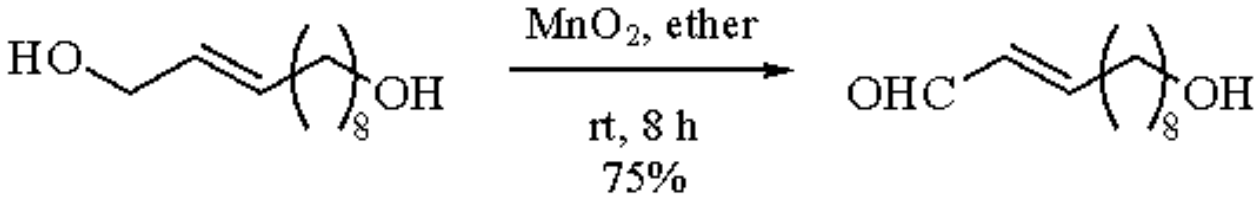

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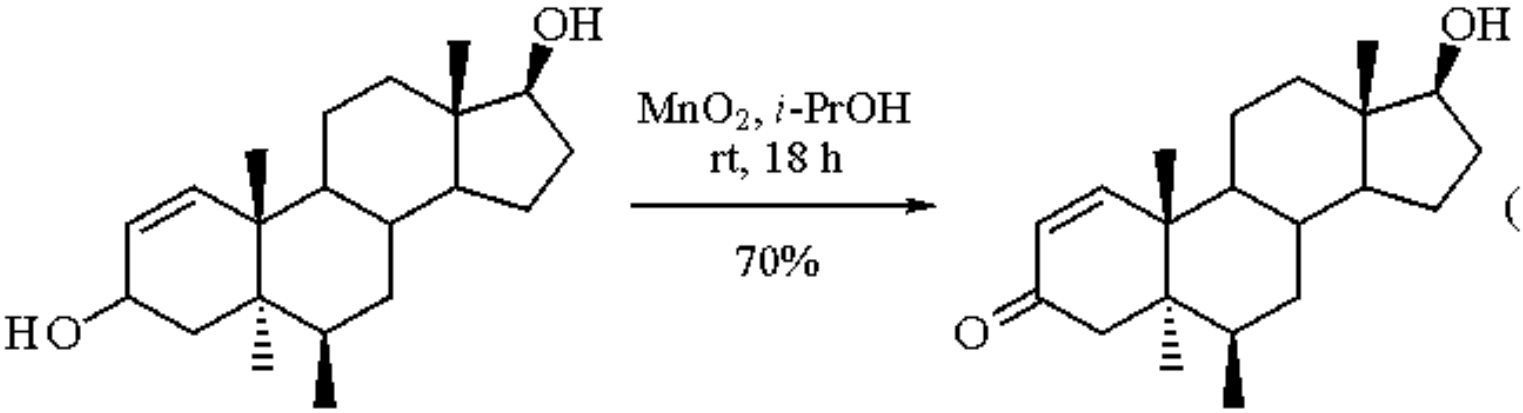

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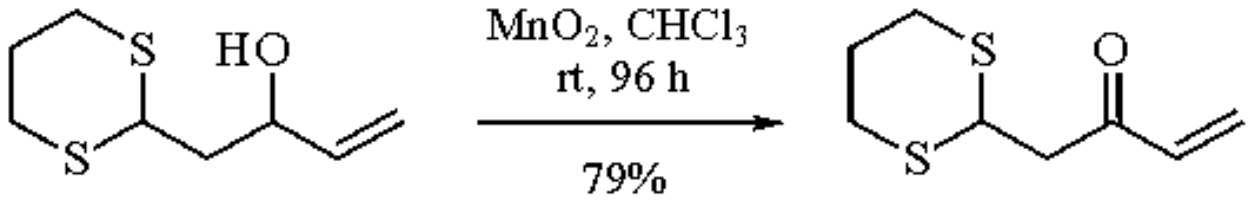

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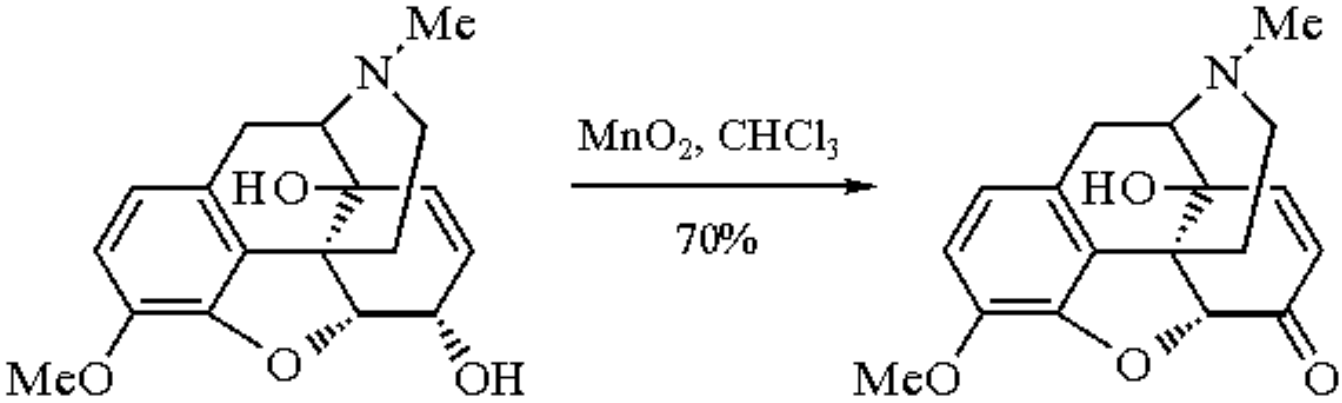

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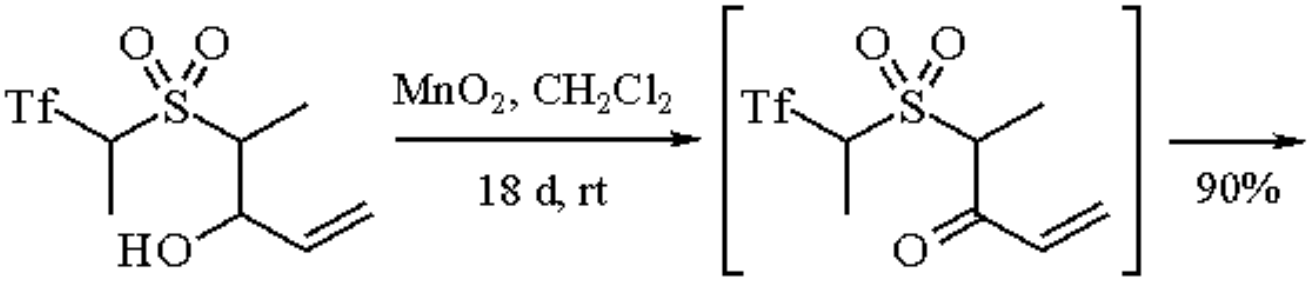

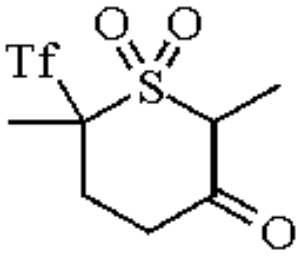

(11)

The α,β-ethylenic ketone obtained by treatment of an allylic alcohol with MnO_2 can undergo an in situ Michael addition (eqs 11 and 12).[21]

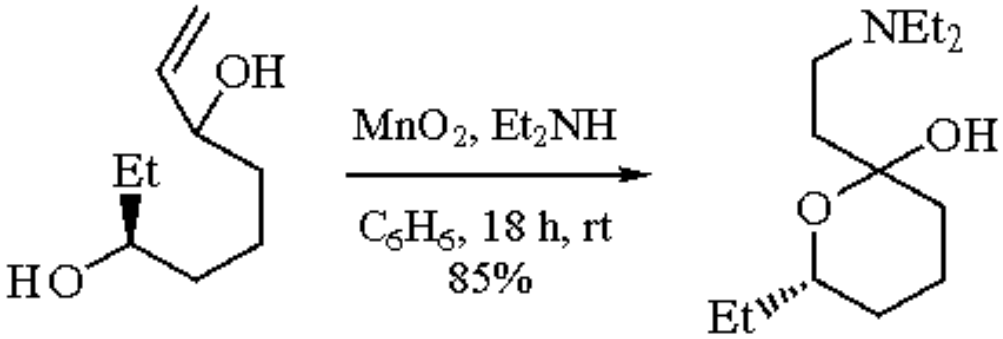

(12)

Conversion of Allylic Alcohols to α,β-Ethylenic Esters and Amides.[2b,3]

This procedure was first described by Corey.[2b,3] The key step is the sequential formation and oxidation of a cyanohydrin. In the presence of an alcohol or an amine the resulting acyl cyanide leads by alcoholysis or aminolysis to the corresponding α,β-ethylenic ester[2b] or amide[3] (eqs 13-15).

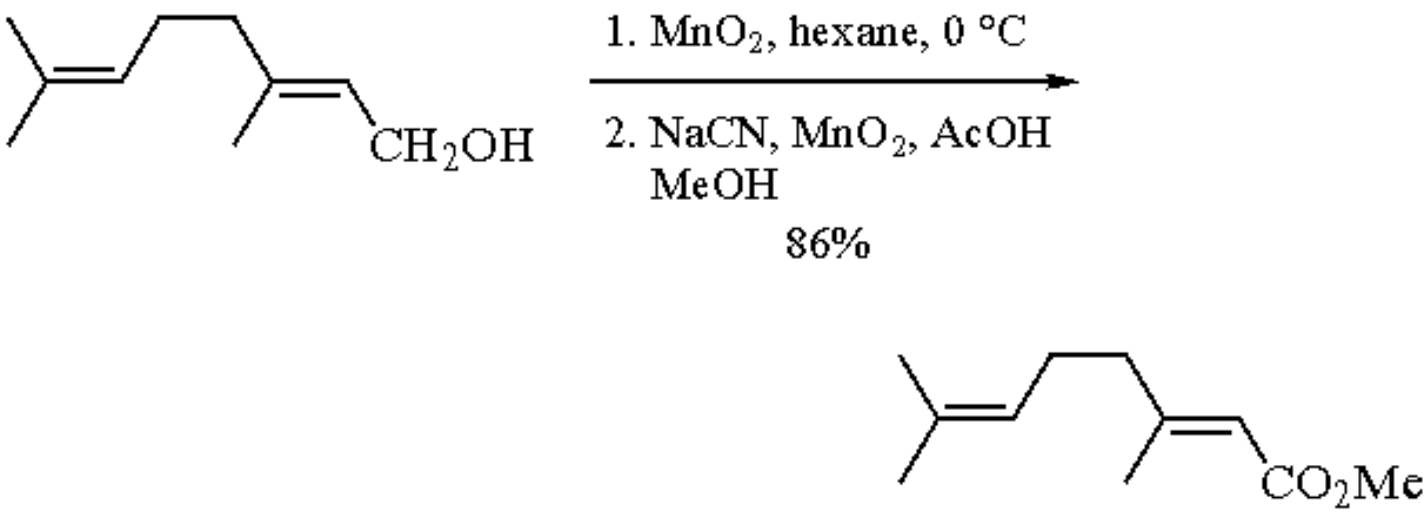

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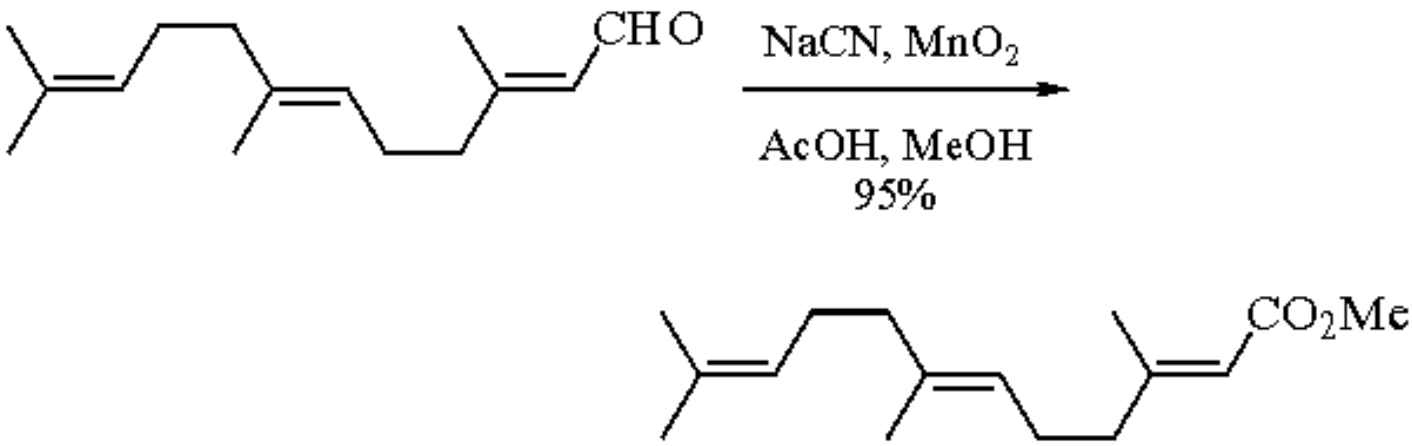

(14)

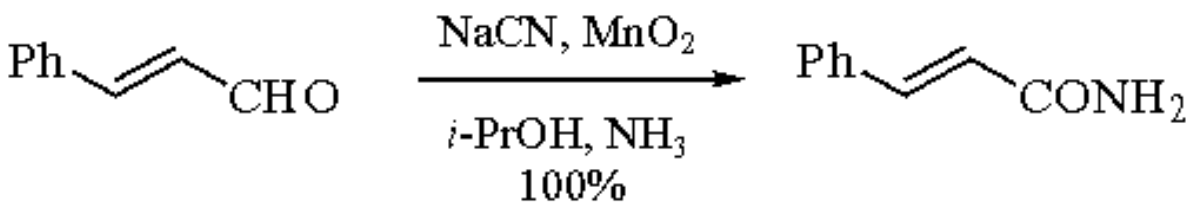

(15)

Oxidation of Propargylic Alcohols.[4]

Propargylic alcohols are easily oxidized by MnO_2 to alkynic aldehydes and ketones (eqs 16-18).[4a-c] In the example in eq 19 the unstable propargyl aldehyde is trapped as a Michael adduct.[4d]

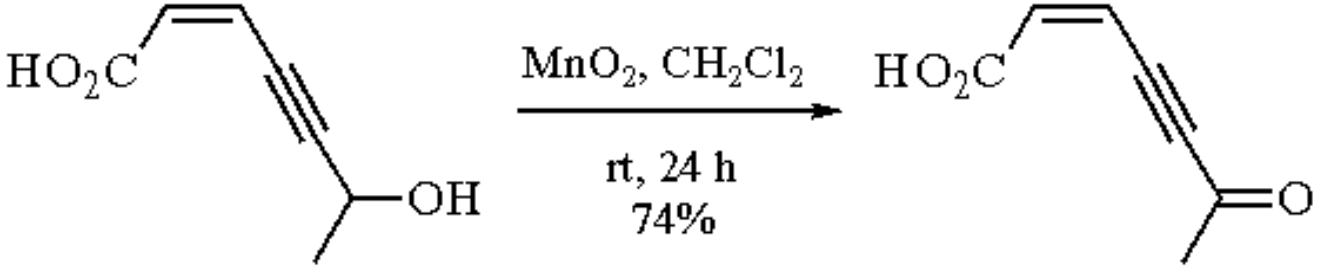

(16)

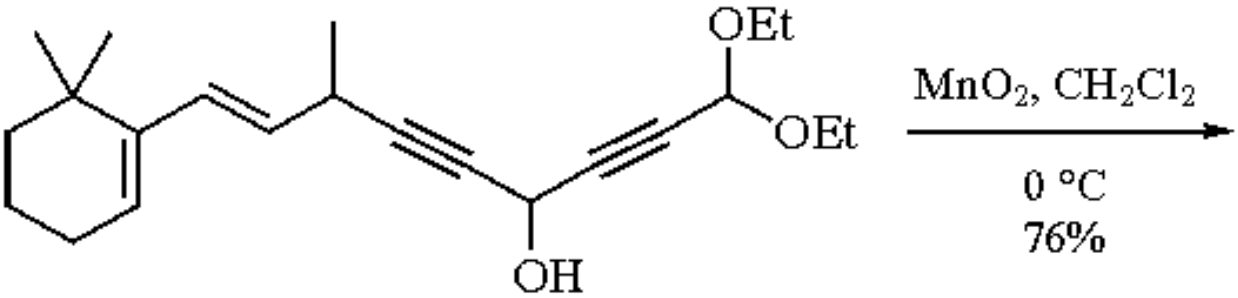

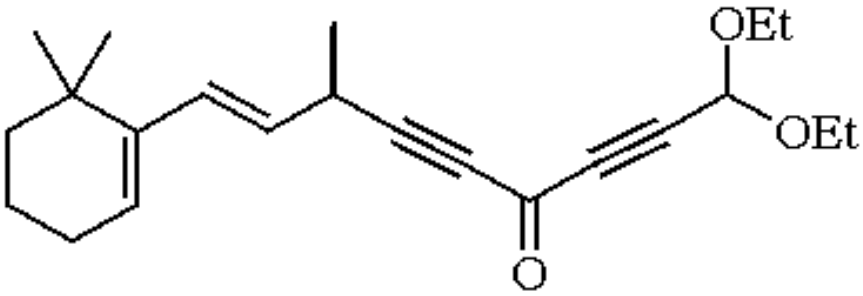

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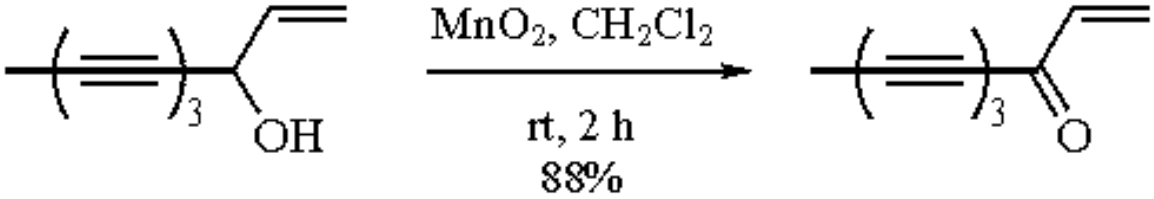

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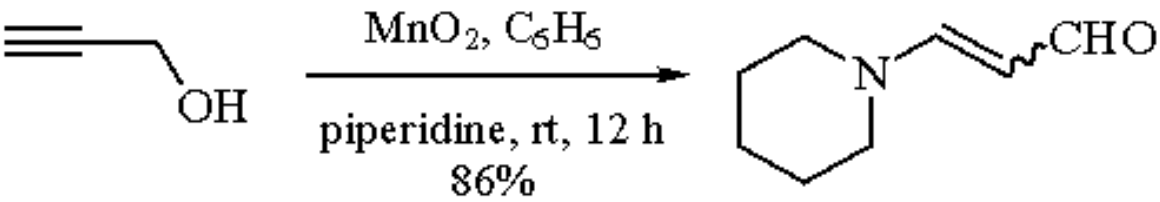

(19)

Oxidation of Benzylic and Heterocyclic Alcohols.[2b,5]

Conjugated aromatic aldehydes or ketones can be efficiently prepared by treatment of benzylic alcohols with MnO_2 (eq 20).[5a] Numerous functional groups are tolerated (eqs 21-24).[5a-c]

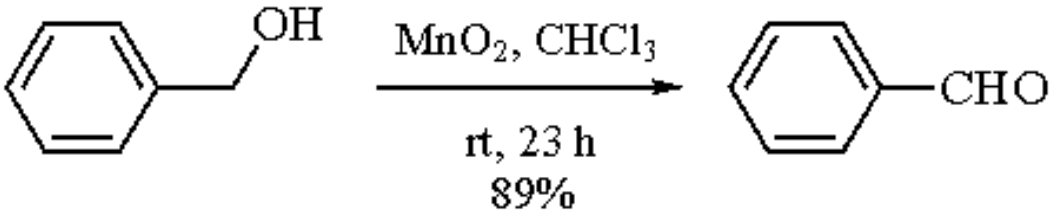
OH
MnO2, CHCl3
rt, 23 h
89%
CHO

(20)

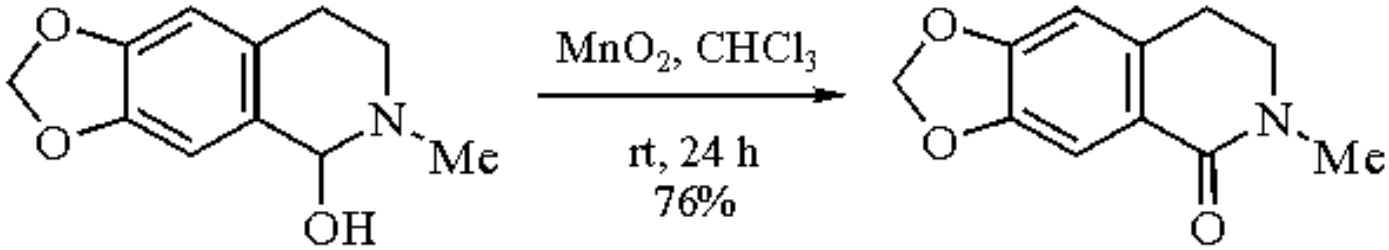
O
O
N
Me
OH
MnO2, CHCl3
rt, 24 h
76%
O
O
N
Me
O

(21)

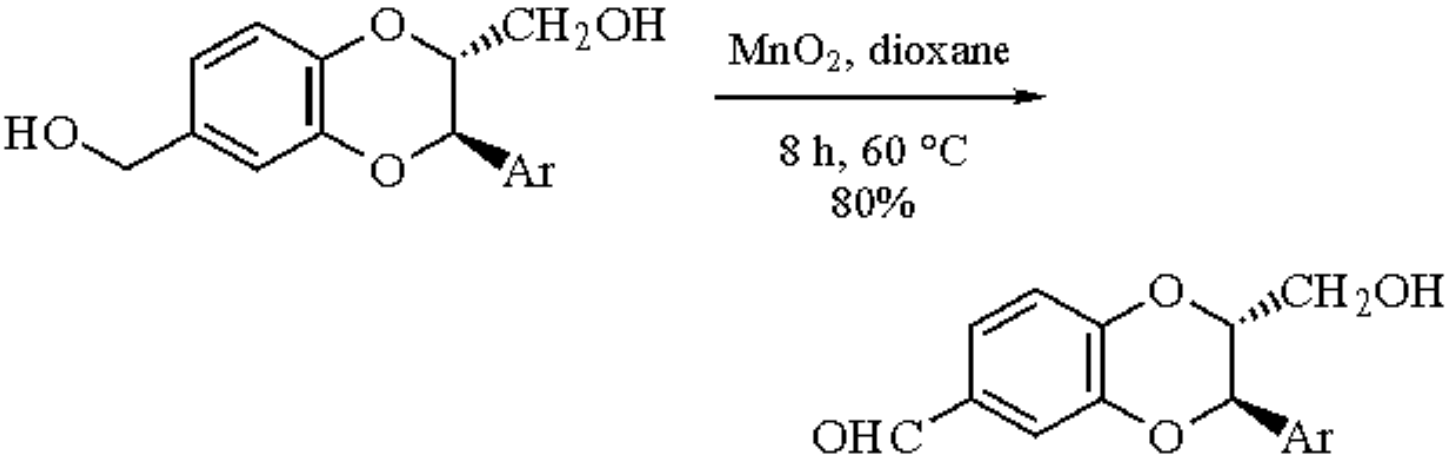
O
CH2OH
HO
O
Ar
MnO2, dioxane
8 h, 60 °C
80%
O
CH2OH
OHC
O
Ar

(22)

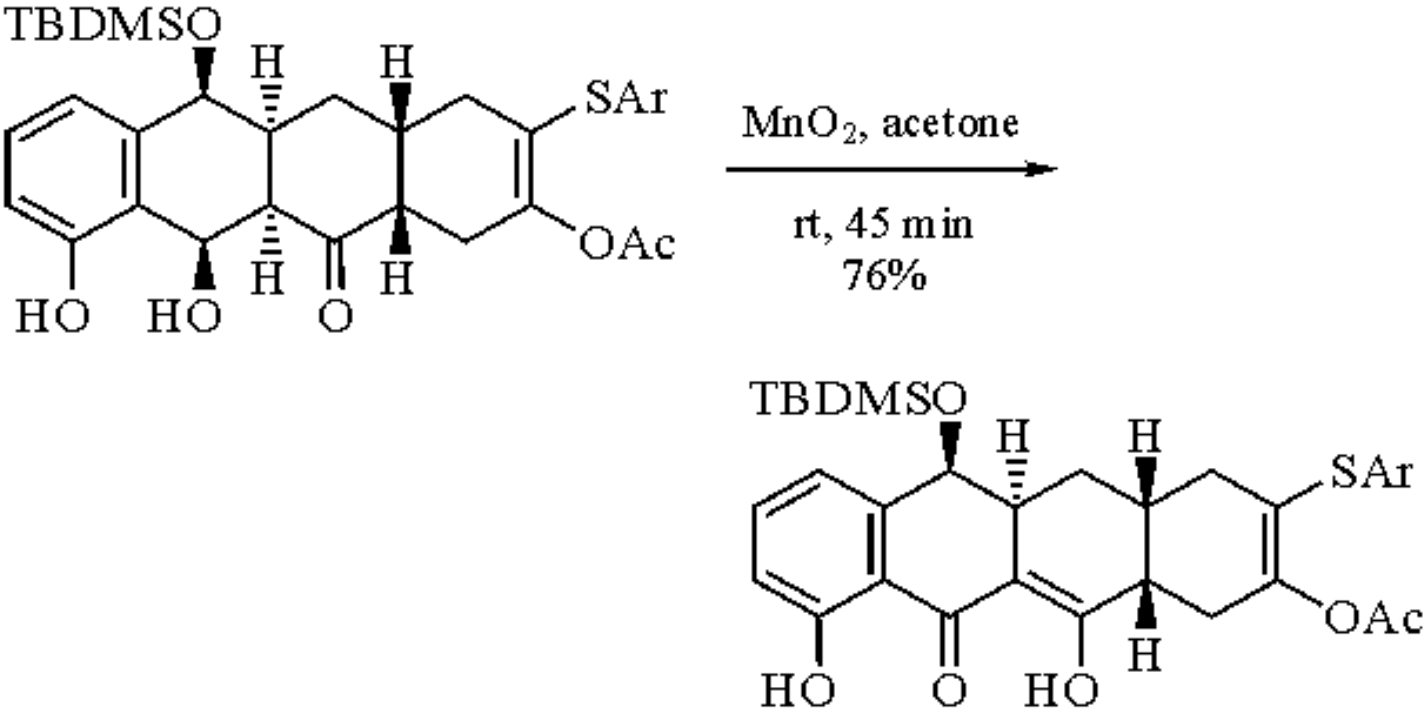
TBDMSO
H
H
SAr
OAc
H
H
HO
HO
O
MnO2, acetone
rt, 45 min
76%
TBDMSO
H
H
SAr
OAc
H
HO
O
HO

(23)

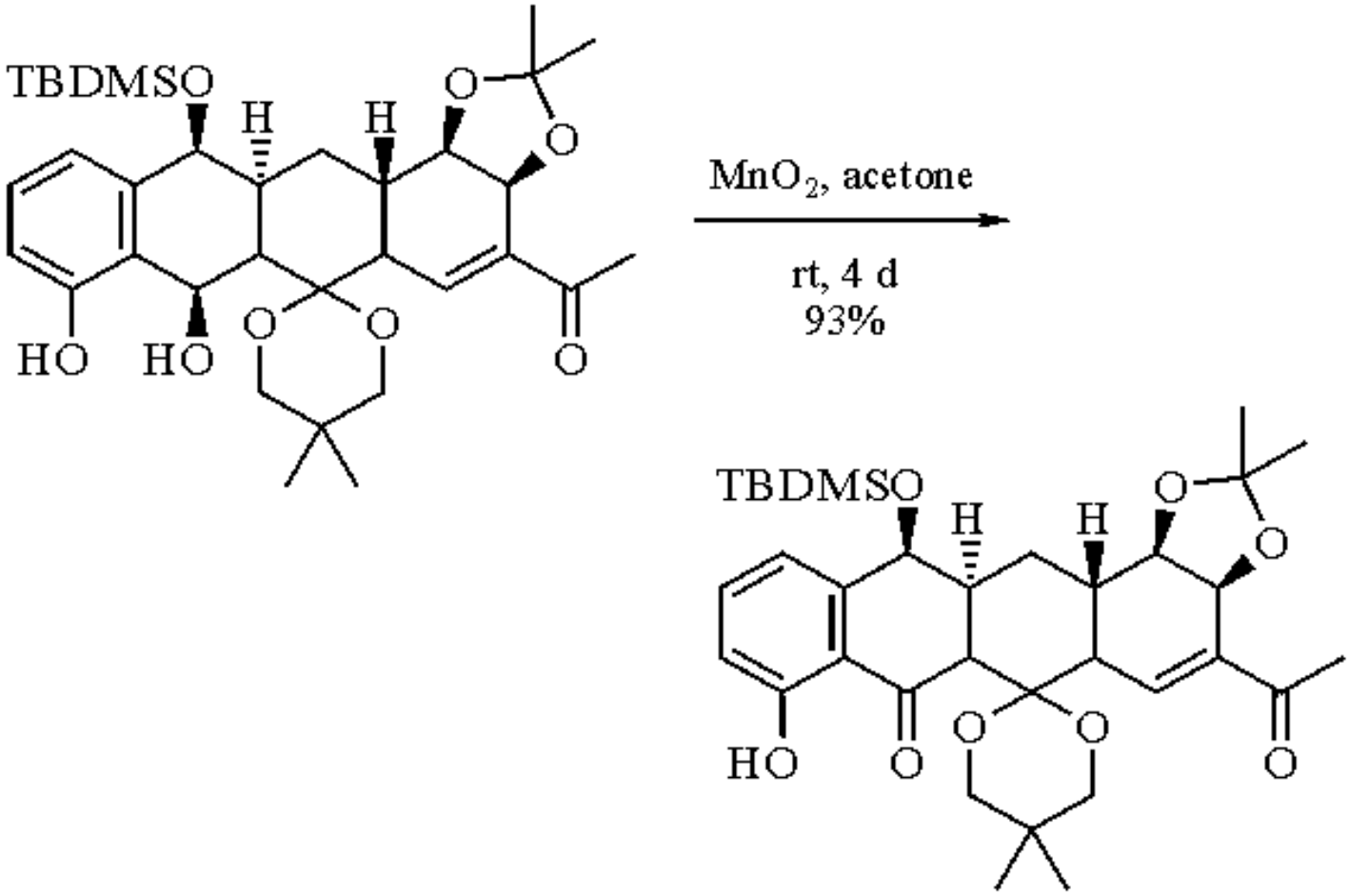

(24)

Benzyl allyl and benzyl propargyl alcohols have been oxidized successfully to ketones (eqs 25 and 26).[5d,e]

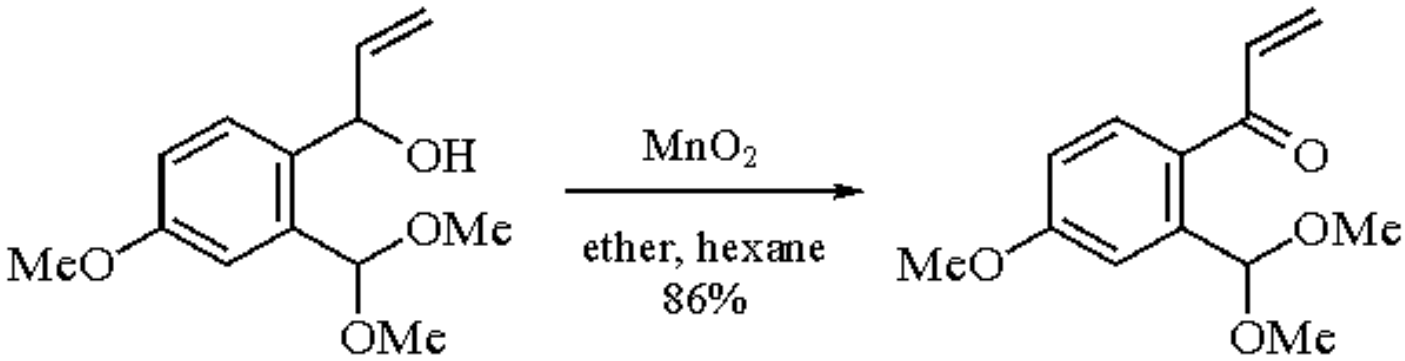

(25)

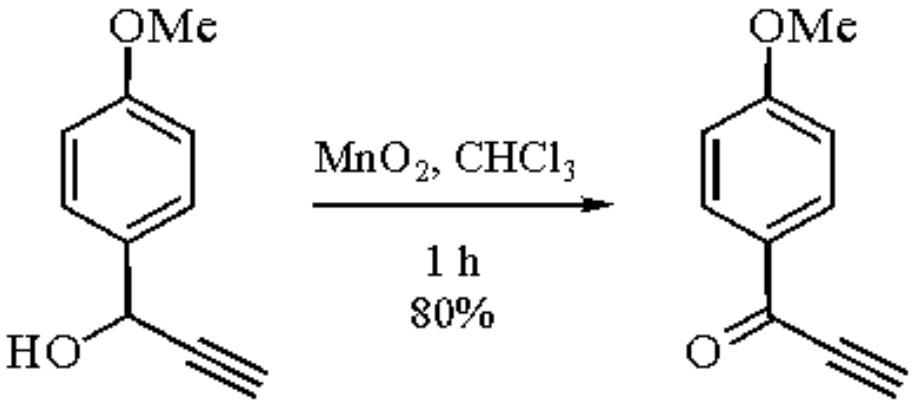

(26)

The oxidation reaction can be extended to heterocyclic alcohols (eq 27)[5f] and the Corey procedure gives the expected esters (eq 28).[2b]

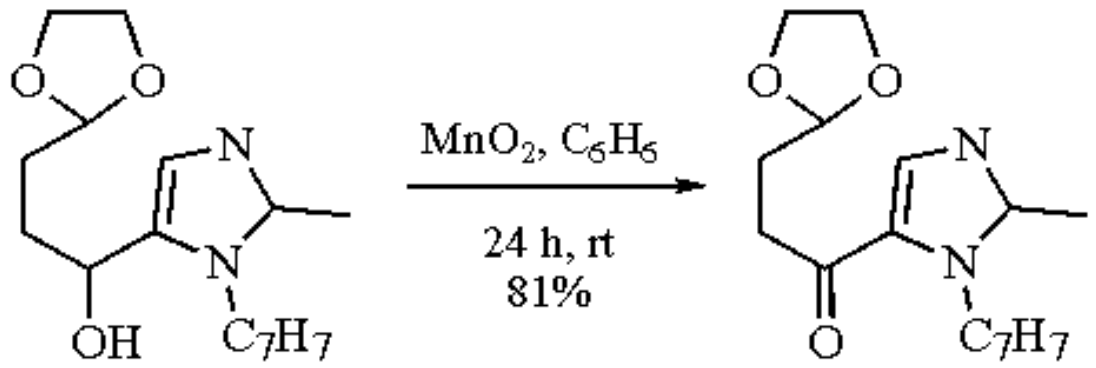

(27)

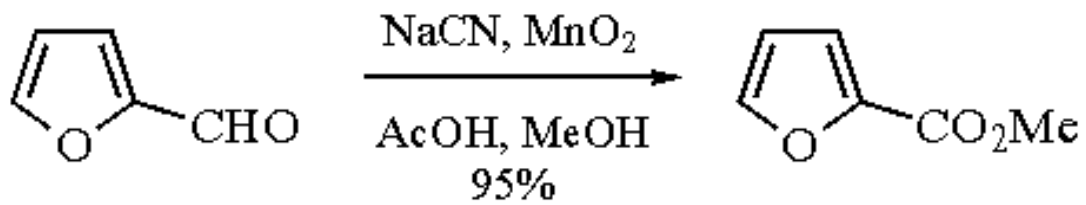

(28)

Oxidation of Saturated Alcohols.[6]

Cyclic and acyclic saturated alcohols react with MnO_2 to give the saturated aldehydes or ketones in good yields (eqs 29-32).[6a,b]

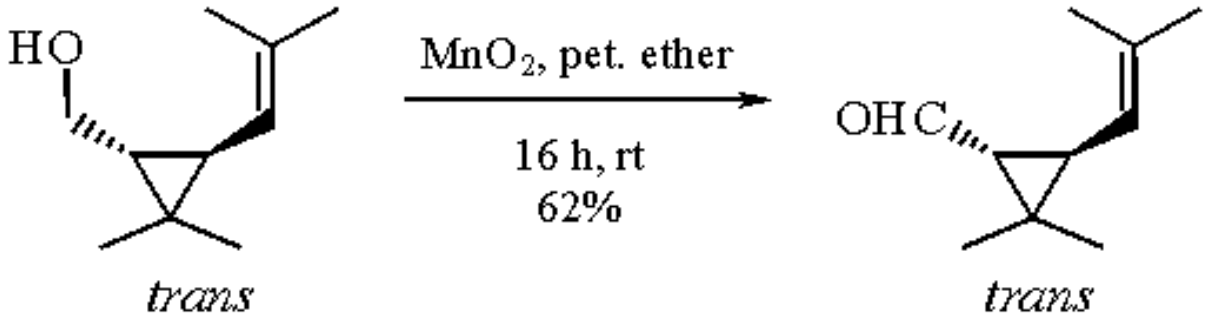

(29)

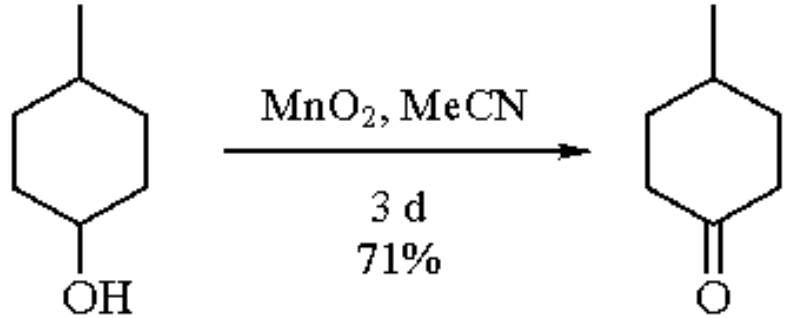

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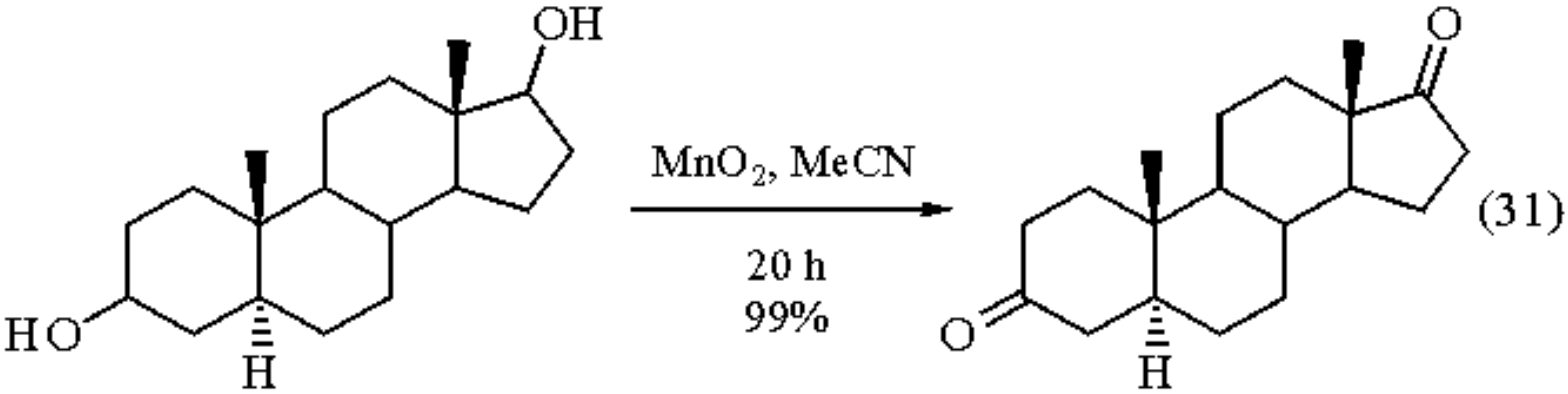

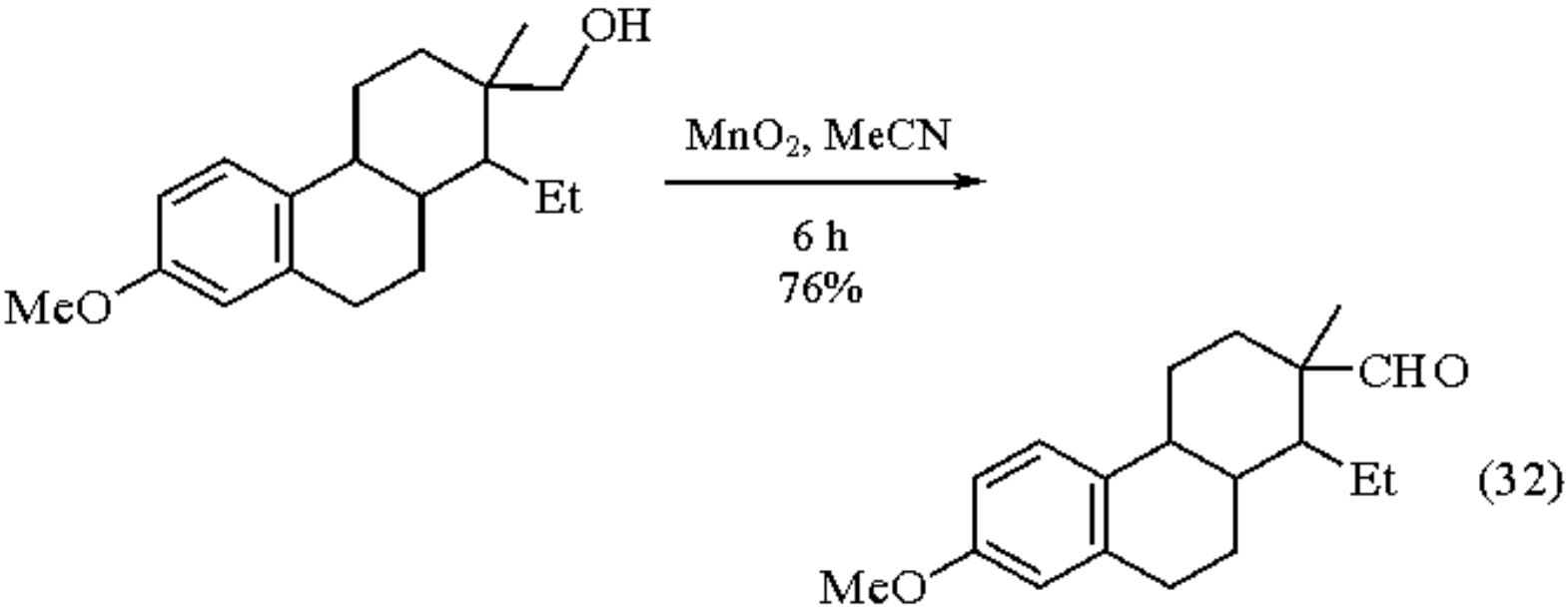

Oxidative Cleavage of 1,2-Diols.[7]

1,2-Diols are cleaved by MnO_2 to aldehydes or ketones. With cyclic 1,2-diols, the reaction leads to dialdehydes or diketones (eqs 33 and 34)[7] and the course of the reaction depends on the configuration of the starting material (eqs 34 and 35).[7]

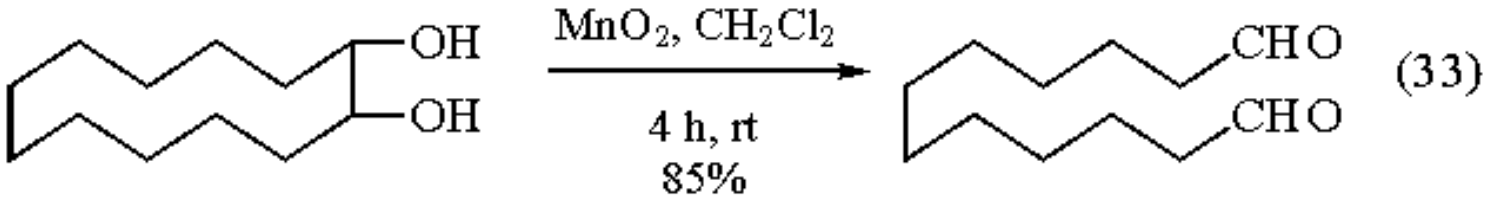

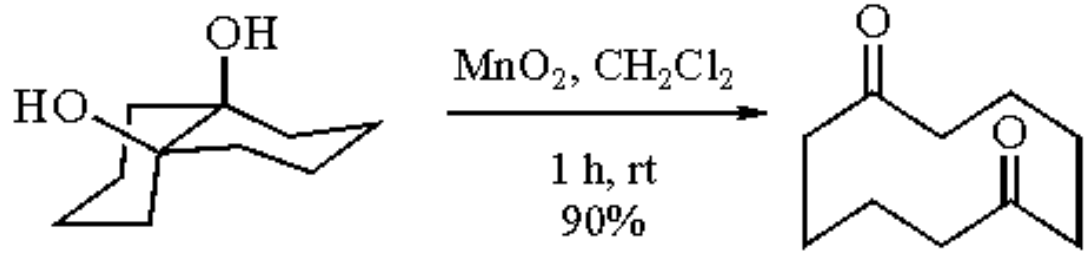

cis-diol

(34)

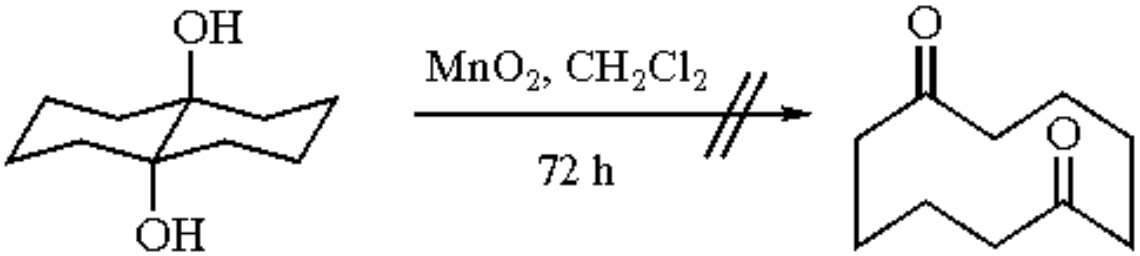

trans-diol

(35)

Hydration of Nitriles to Amides.[8]

By treatment with MnO_2, nitriles are readily converted to amides. MnO_2 on silica gel is especially efficient to perform this reaction (eqs 36 and 37).[8a,b]

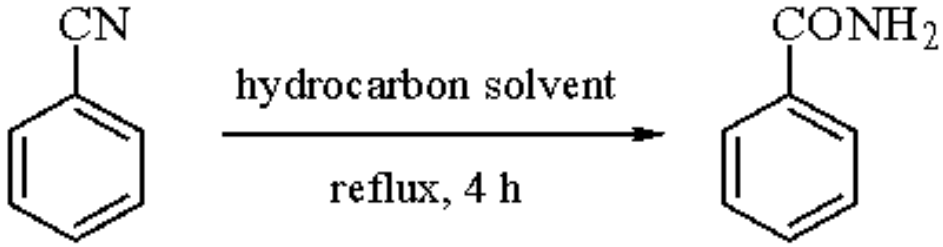

(36)

active MnO_2	30%
MnO_2, SiO_2	100%

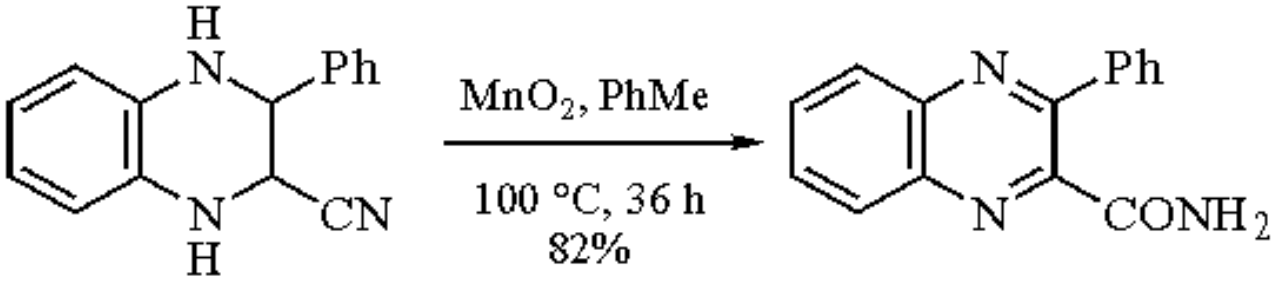

(37)

Dehydrogenation and Aromatization Reactions.[9,13j,q]

MnO_2 has been widely used to carry out various dehydrogenation and aromatization reactions (eqs 38-41).[9a-c] In some

cases the dehydrogenation can occur as a side reaction during, for instance, the hydration of nitriles (eq 37)[8b] or the oxidation of allylic alcohols.[13q]

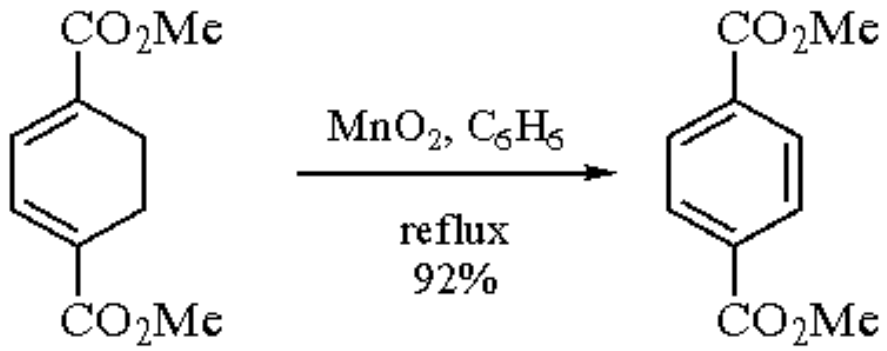

(38)

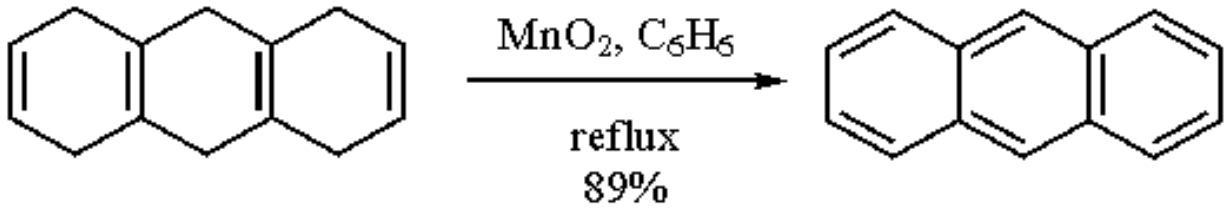

(39)

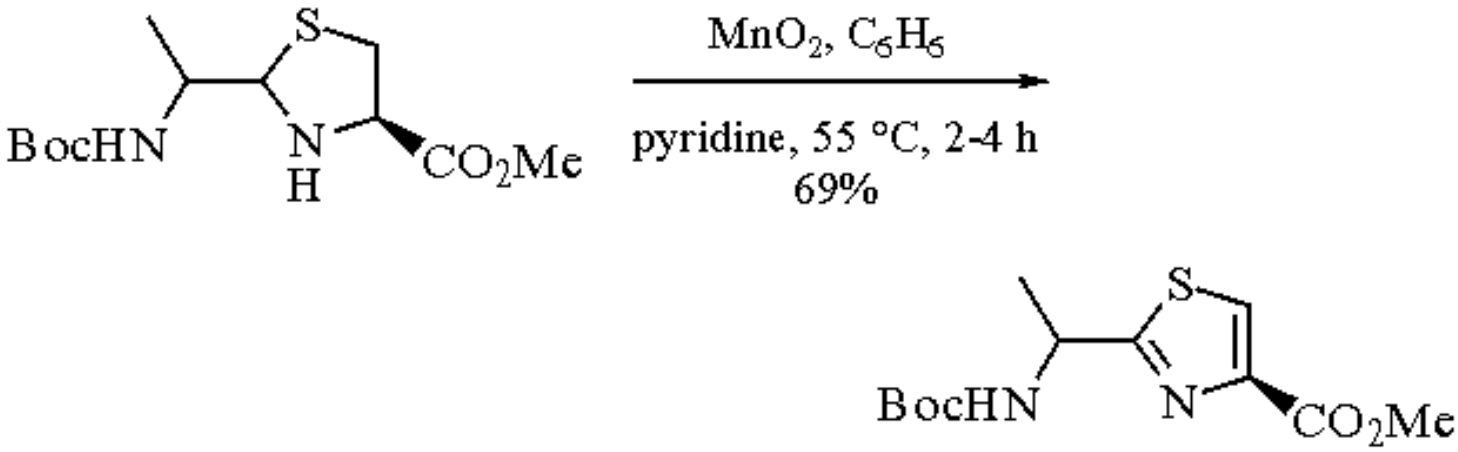

(40)

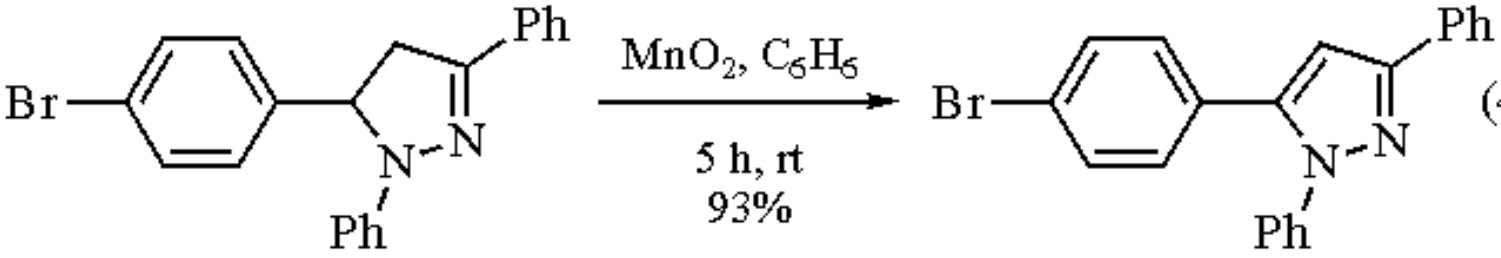

(41)

It is interesting to note that the use of γ-MnO_2 is essential to achieve the following dehydrogenation reactions (eqs 42 and 43).[13j]

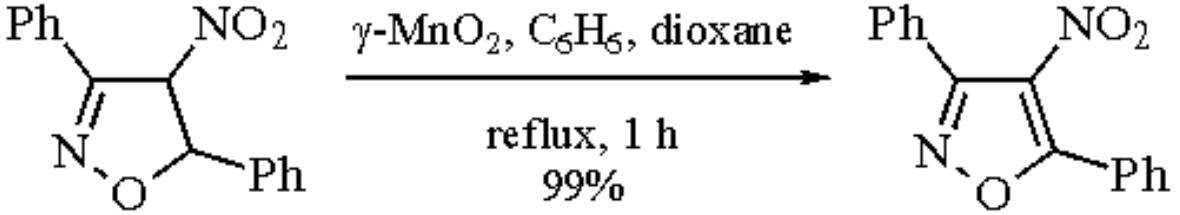

(42)

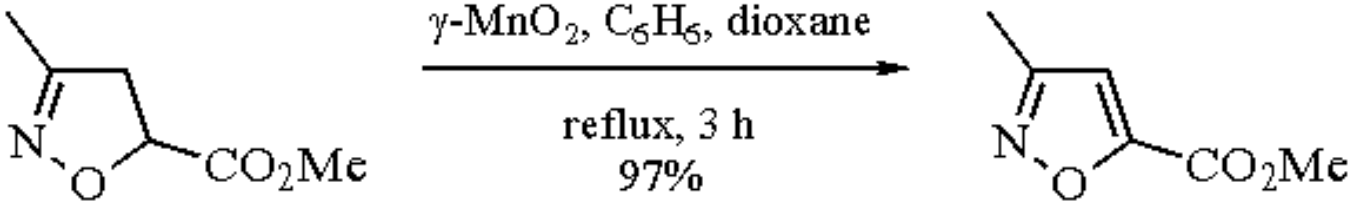

(43)

Oxidation of Amines to Aldehydes, Imines, Amides, and Diazo Compounds.[10,13g,p]

The oxidation of amines by MnO_2 can lead to various products according to the structure of the starting material. Thus the formation of imines (eq 44),[10] formamides (eqs 45 and 46),[13g] and diazo compounds (eq 47)[13p] have all been described.

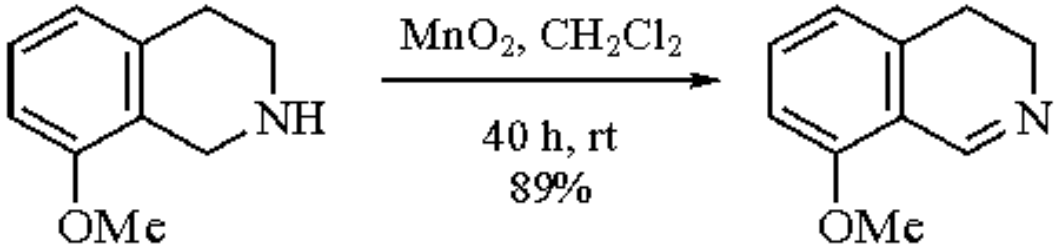

(44)

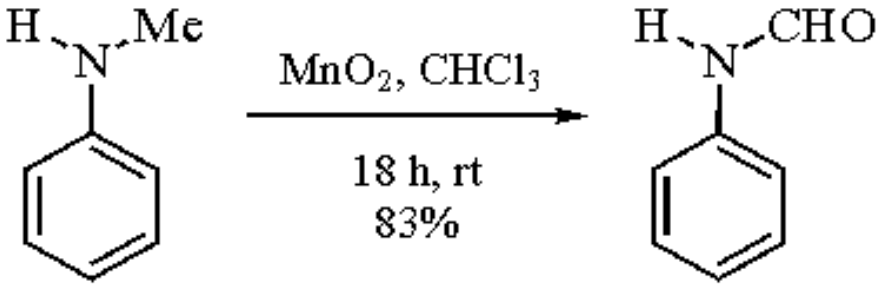

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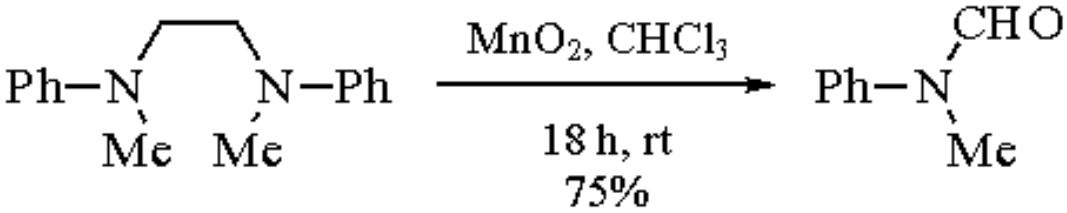

(46)

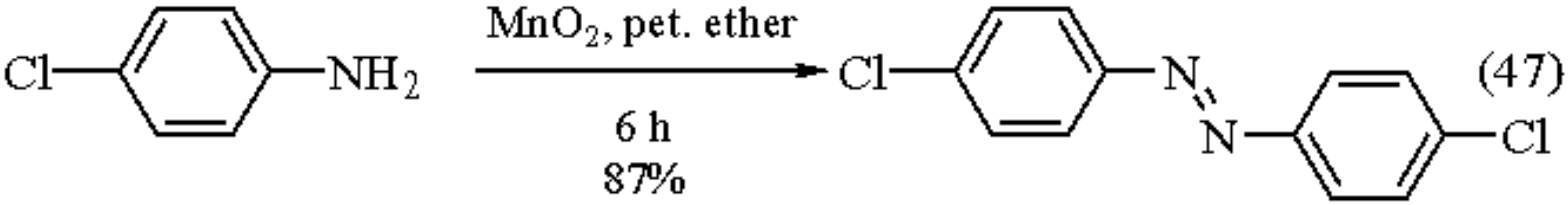

Miscellaneous Reactions.[13p,14]

MnO_2 has also been used to perform various oxidation reactions: the oxidative cleavage of α-hydroxy acids (eq 48),[13p] the oxidative dimerization of diarylmethanes (eq 49),[14a] or their conversion to diaryl ketones (eq 50),[14a] the oxidation of aldehydes to carboxylic acids,[13p] the preparation of disulfides from thiols,[14b] of phosphine oxides from phosphines,[13p] or of ketones from amines.[14c]

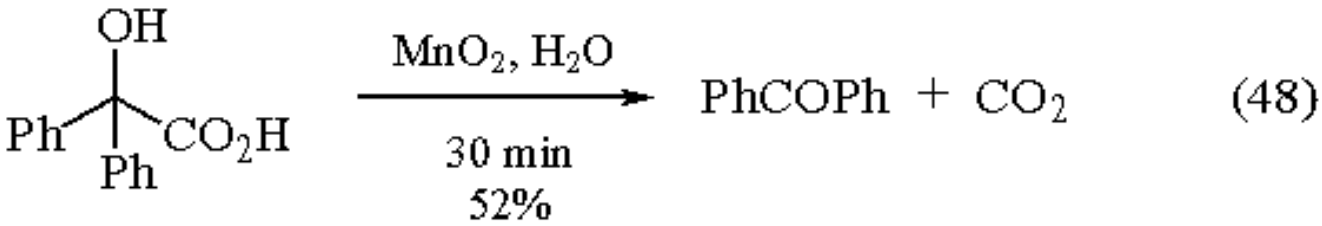

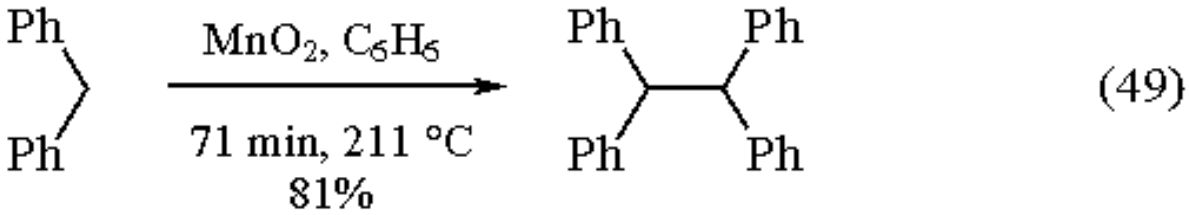

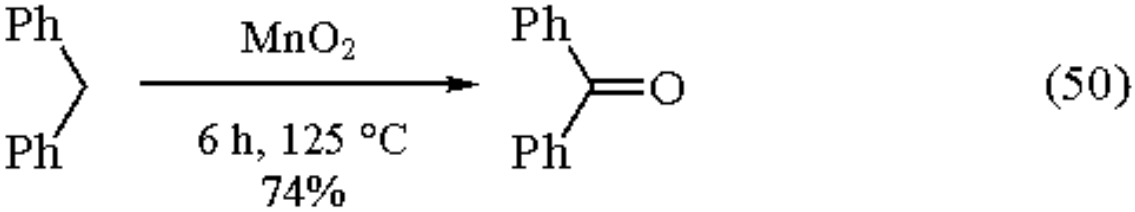

Related Reagents.

Barium Manganate; ***Nickel(II) Peroxide***.

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Manganese(III) Acetylacetonate

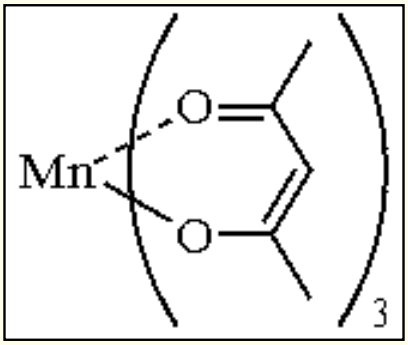

[14284-89-0] · $C_{15}H_{21}MnO_6$ · Manganese(III) Acetylacetonate · (MW 352.30)

(one-electron oxidant used to oxidize phenols, β-dicarbonyl compounds, and thiols to the corresponding radical)

Physical Data: lustrous brown crystalline solid; mp 172 °C.[1]

Solubility: slightly sol water; sol acetone, benzene, chloroform, ether, ethanol, ethyl acetate.[1]

Manganese(III) acetylacetonate, $Mn(acac)_3$, was reported to be the most useful manganese(III) reagent for oxidative coupling of phenols.[2,3] For instance, 2-naphthol is oxidized to 2,2´-binaphthol in 69% yield in acetonitrile or carbon disulfide (eq 1).[2] $Mn(acac)_3$ has been used for the intramolecular oxidative coupling of a series of α,o-bis(3,4-dimethoxyphenyl)alkanes.[4] Anodic oxidation gives somewhat higher yields than $Mn(acac)_3$. Intramolecular oxidative coupling with $Mn(acac)_3$ has been used as a key step in the synthesis of (+)- and (-)-galanthamine (eq 2).[5] $Mn(acac)_3$ induces the oxidative cyclization of a phenolic oxime to give the spiroisoxazoline in 50% yield (eq 3).[6] $Mn(acac)_3$ in carbon disulfide oxidizes aryl, alkyl, and benzyl thiols at rt in 1-2 h to disulfides in 85-99% yield.[7]

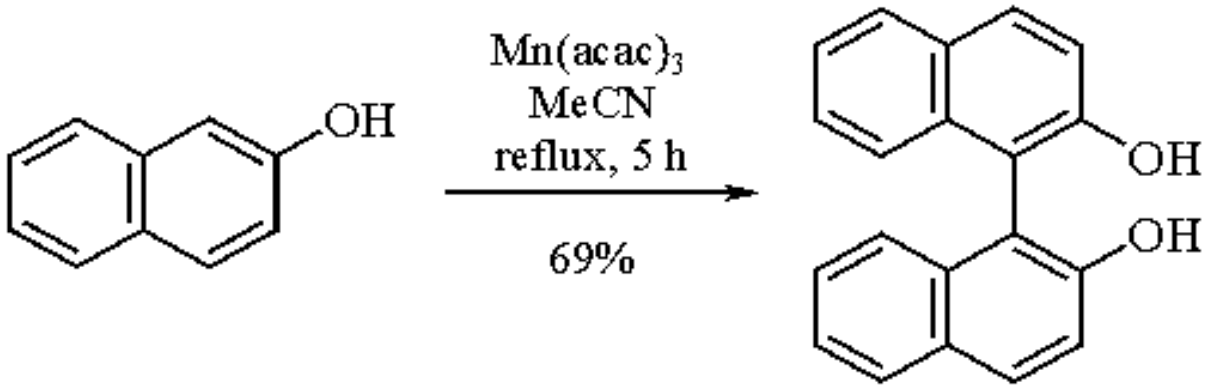

(1)

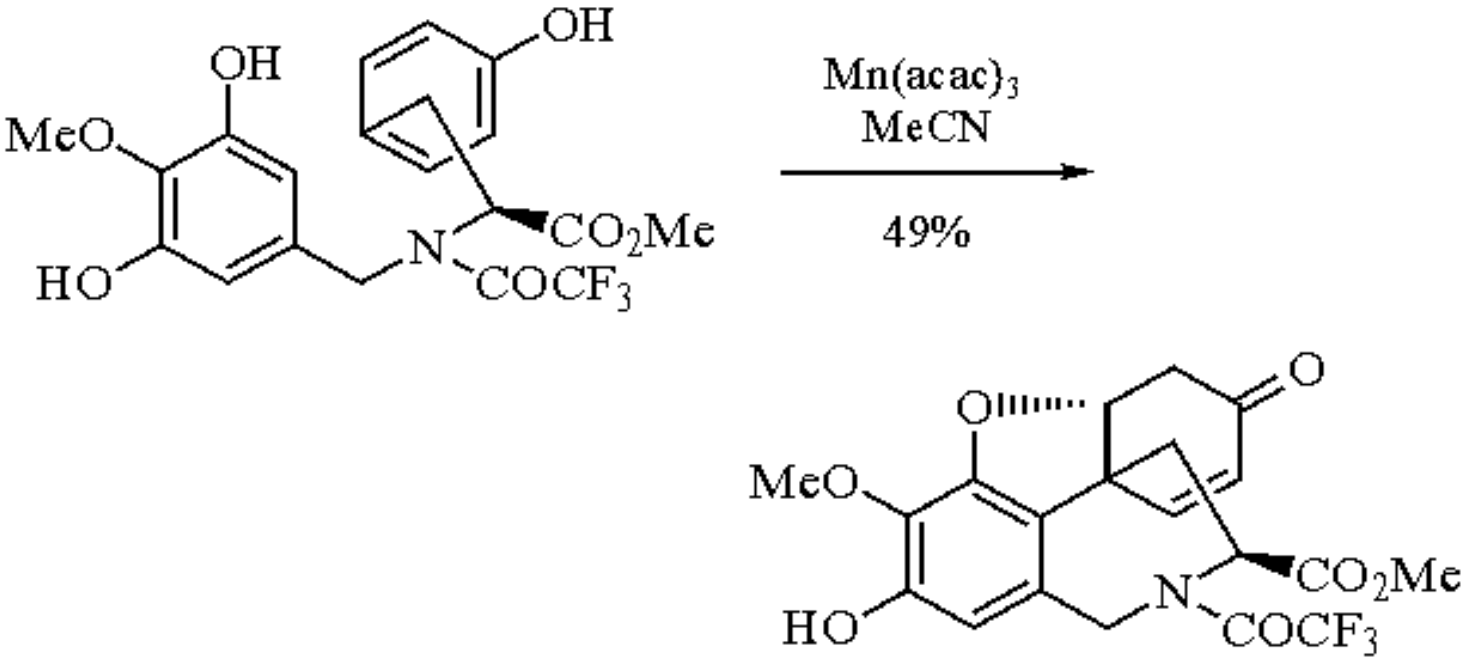

(2)

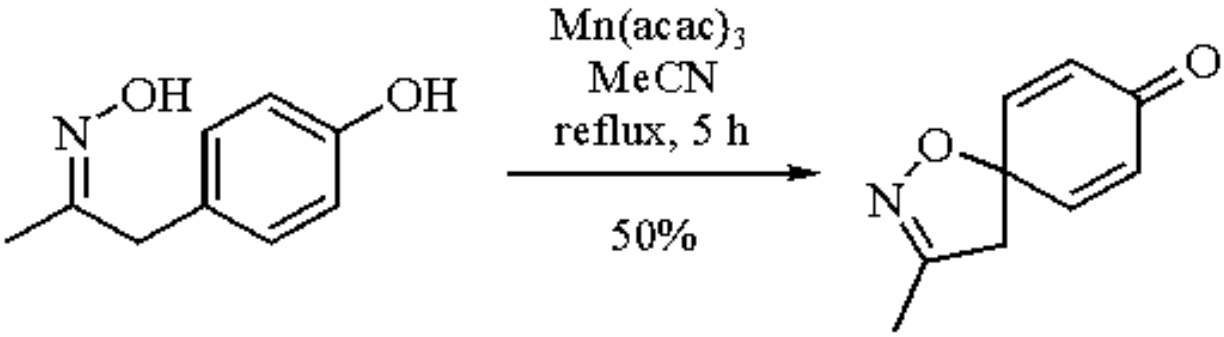

(3)

In the absence of a more readily oxidizable substrate, $Mn(acac)_3$ reacts with alkenes[8,9] and electron-rich arenes[10] to give radicals that are oxidized by $Mn(acac)_3$ to give the final product (eqs 4 and 5). The acetylacetone radical is probably not an intermediate in these reactions.[11]

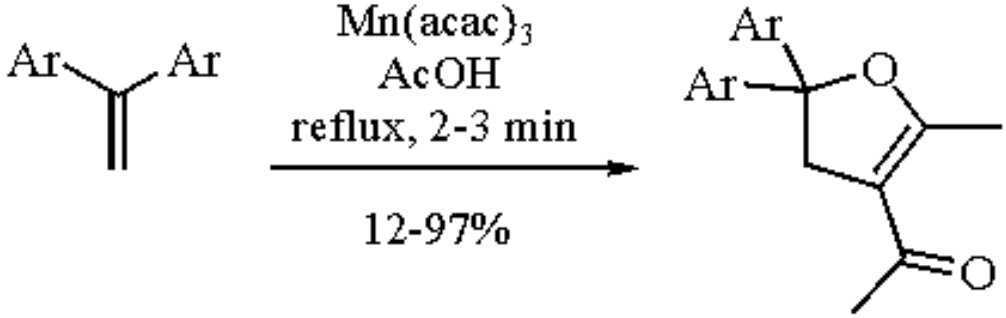

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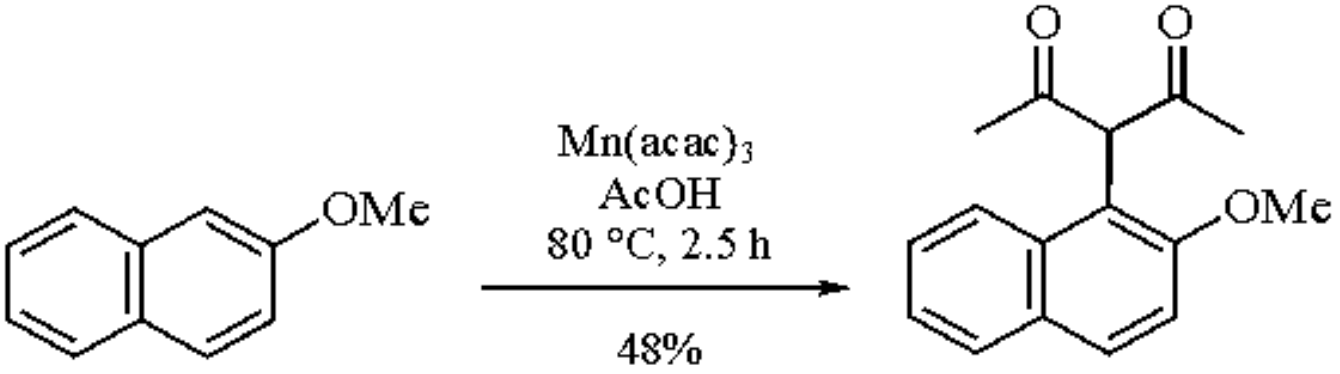

(5)

Peroxy hemiacetals are prepared by oxidative addition of $Mn(acac)_3$ to alkenes in the presence of oxygen (eq 6).[12]

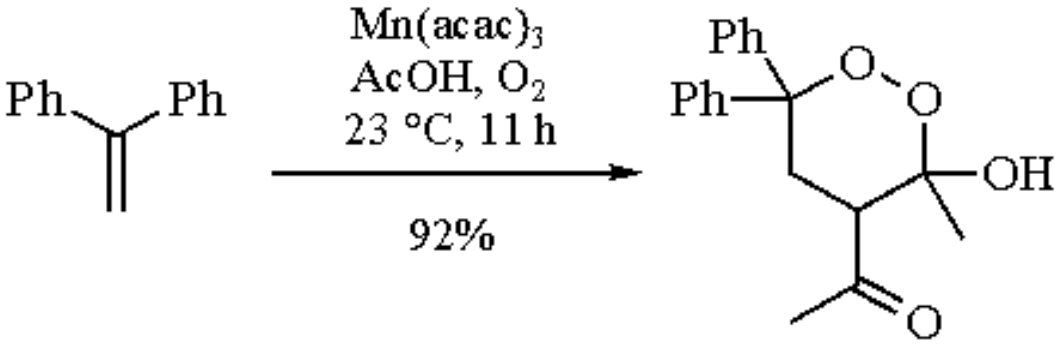

(6)

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(-)-(1*R*,2*S*,5*R*)-Menthyl (*S*)-*p*-Toluenesulfinate

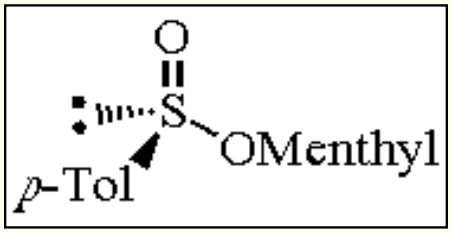

[1517-82-4] · $C_{17}H_{26}O_2S$ · (-)-(1*R*,2*S*,5*R*)-Menthyl (*S*)-*p*-Toluenesulfinate · (MW 294.50)

(agent used for the synthesis of chiral sulfoxides[1,3])

Physical Data: $[\alpha]_D$ = -202° (acetone, *c* = 2.0).

Preparative Method: obtained by reaction of (-)-menthol with *p*-toluenesulfinyl chloride. This esterification showed no particular stereoselectivity, giving an equal amount of the two sulfinate diastereomers.[1] In order to avoid a chromatographic separation, it is possible to epimerize these sulfinate esters in acidic medium and displace the resulting equilibrium towards the less soluble isomer, (-)-menthyl (*S*)-*p*-toluenesulfinate, in 80% yield (eq 1).[2] This procedure was later extended to large scale preparation.[3]

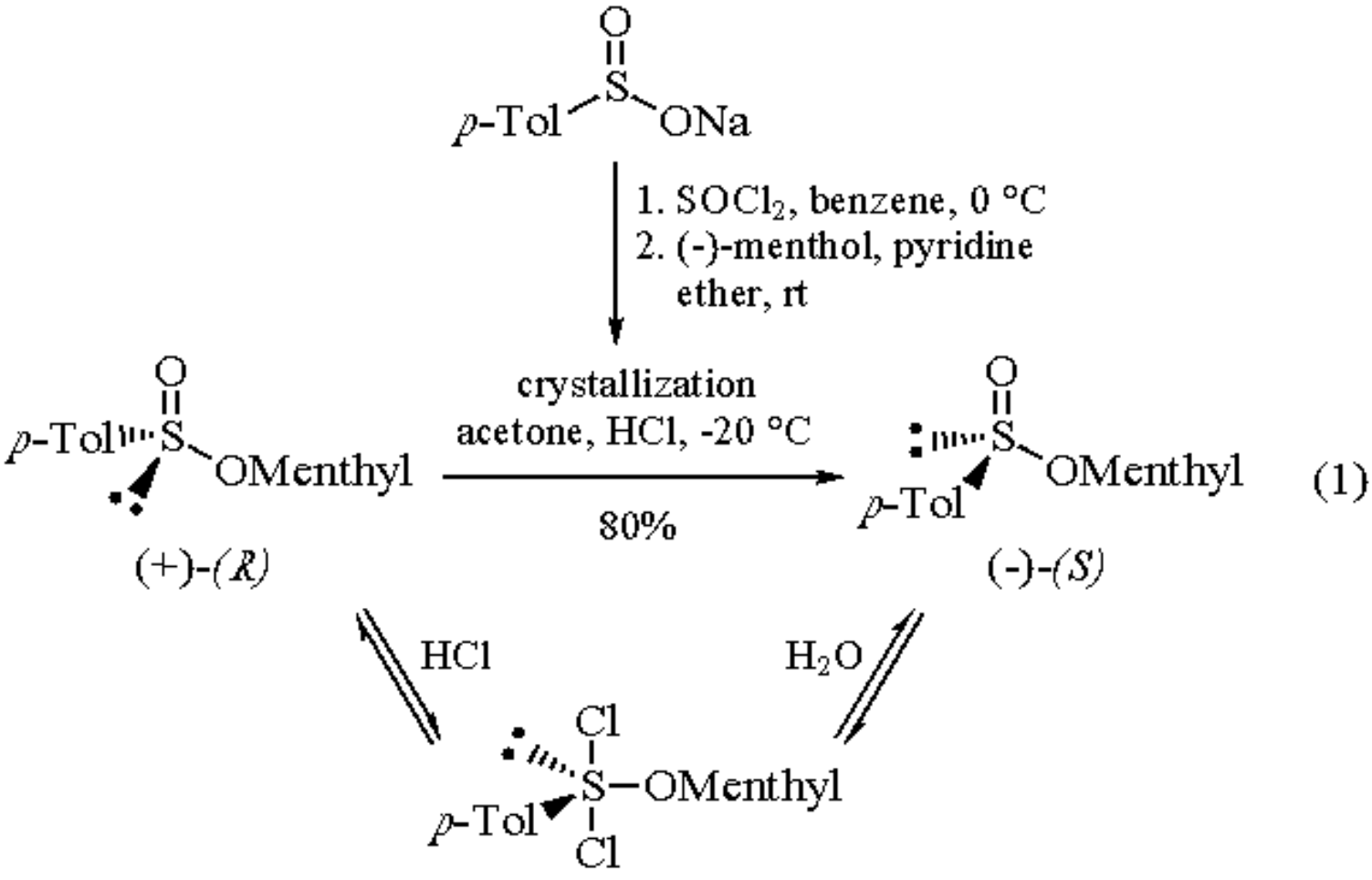

The absolute configuration of (-)-menthyl (*S*)-*p*-toluenesulfinate was established by correlation with (-)-menthyl *p*-iodobenzenesulfinate, known from X-ray diffraction analysis.[4]

Synthesis of Chiral Sulfoxides.

Alkyl Sulfoxides.

Any Grignard reagent reacts with (-)-menthyl (*S*)-*p*-toluenesulfinate and displaces the menthoxy group with complete inversion of configuration at sulfur (eq 2; R = Me,[3,5] Et,[5,6] *n*-C_6H_{13}[7]).

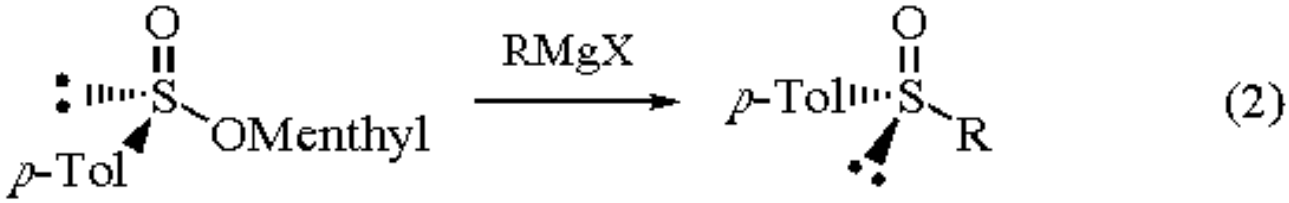

It was also reported that using methyllithium instead of the methyl Grignard could give some racemization of methyl *p*-tolyl sulfoxide as a result of methyl group exchange via a methylene sulfine intermediate.[8]

(*R*)-4-Substituted cyclohexylmethyl *p*-tolyl sulfoxide (**1**)[9] as well as (*R*)-4-hydroxybutyl *p*-tolyl sulfoxide (**2**)[10] and (*R*)-3-butenyl *p*-tolyl sulfoxide (**3**)[11] were also obtained by reaction of (-)-menthyl (*S*)-*p*-toluenesulfinate and the corresponding Grignard reagent.

(1)

R = Me, $MeOCH_2$, $ClCH_2$

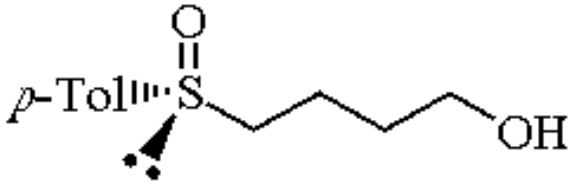

(2)

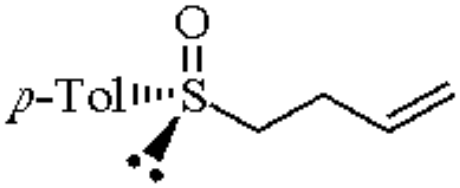

(3)

Vinyl Sulfoxides.

A stereocontrolled preparation of (*E*)-1-alkenyl *p*-tolyl sulfoxide from (-)-menthyl-(*S*) *p*-toluenesulfinate was reported (eq 3).[12a]

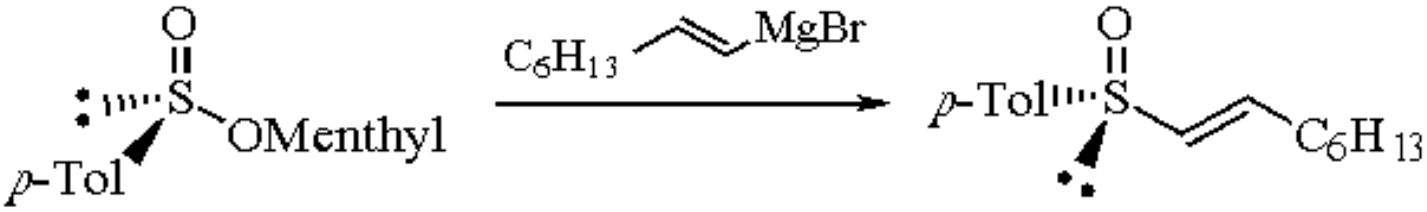

(3)

One example was also reported showing the formation of an (*E*)-alkenyl sulfoxide in the reaction of a vinylic lithium compound on menthyl sulfinate (eq 4).[12b]

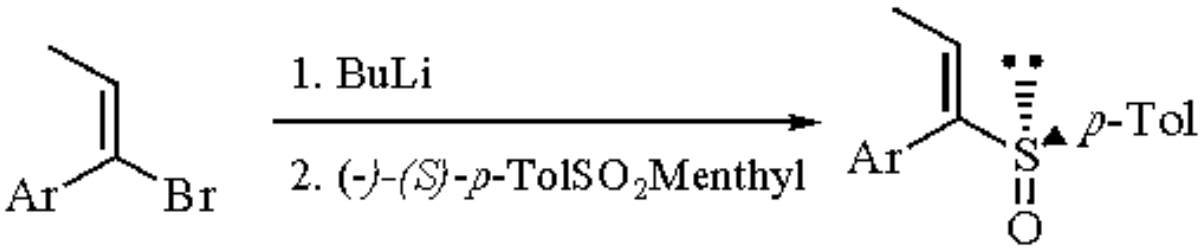

(4)

(+)-(*S*)-2-(*p*-Tolylsulfinyl)-2-cyclopentenone was also prepared by reaction of a vinyllithium derivative and menthyl

sulfinate (eq 5).[13]

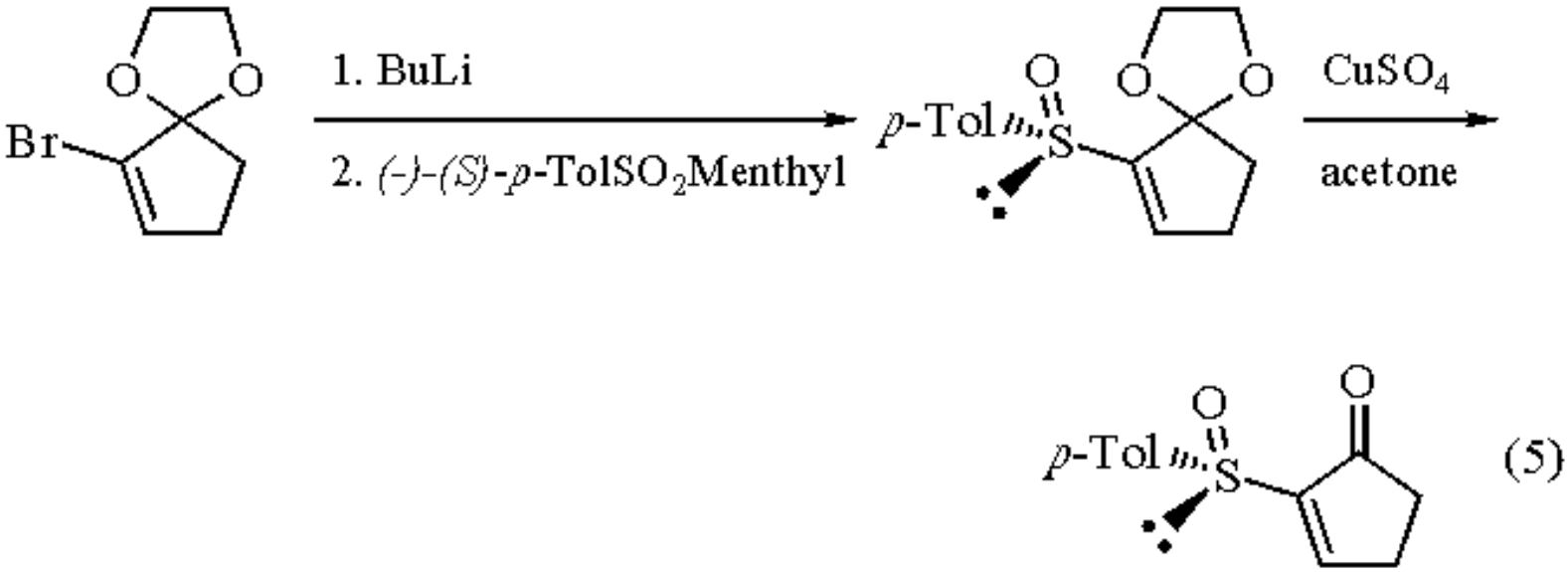

The preparation of optically pure (*E*)- and (*Z*)-1-alkenyl *p*-tolyl sulfoxides was described via stereoselective reduction of 1-alkynyl *p*-tolyl sulfoxides (eq 6).[14]

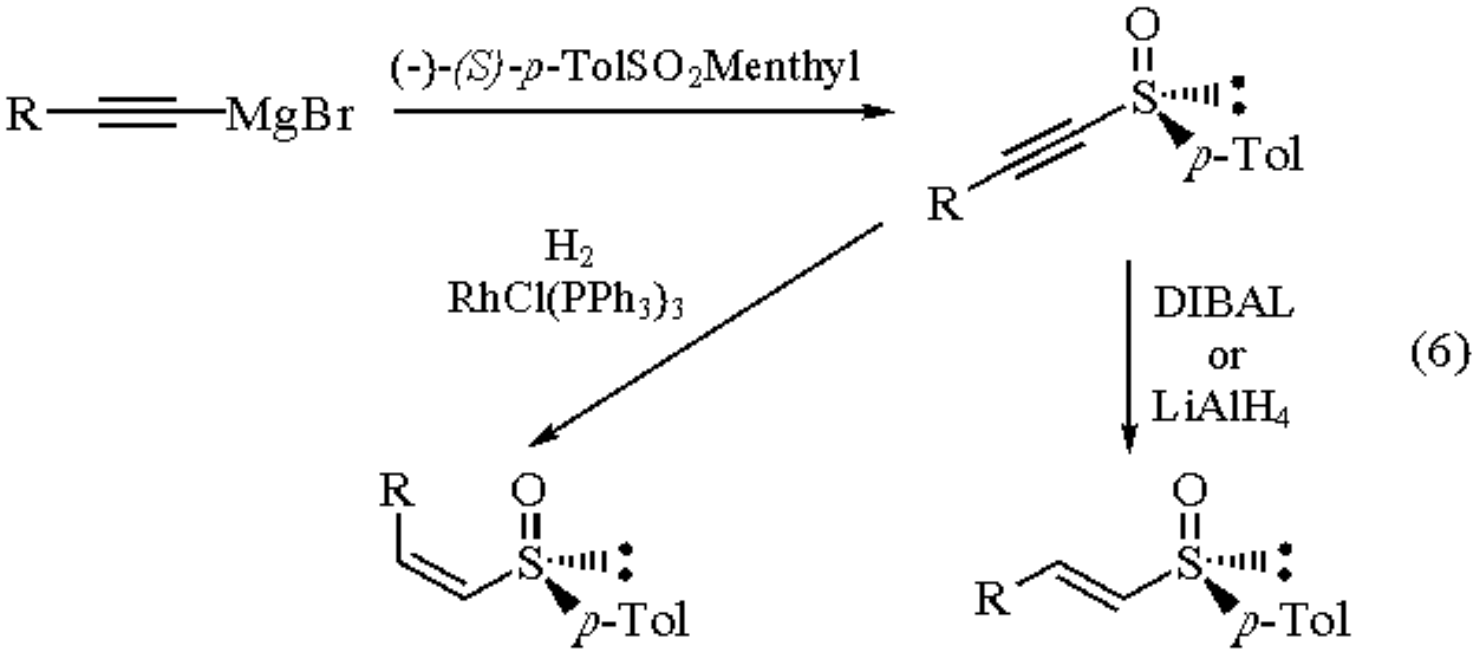

Alkynic sulfoxides have been made from trimethylsilylethynylmagnesium bromide and the resulting alkyne disilylated on silica gel (eq 7).[15]

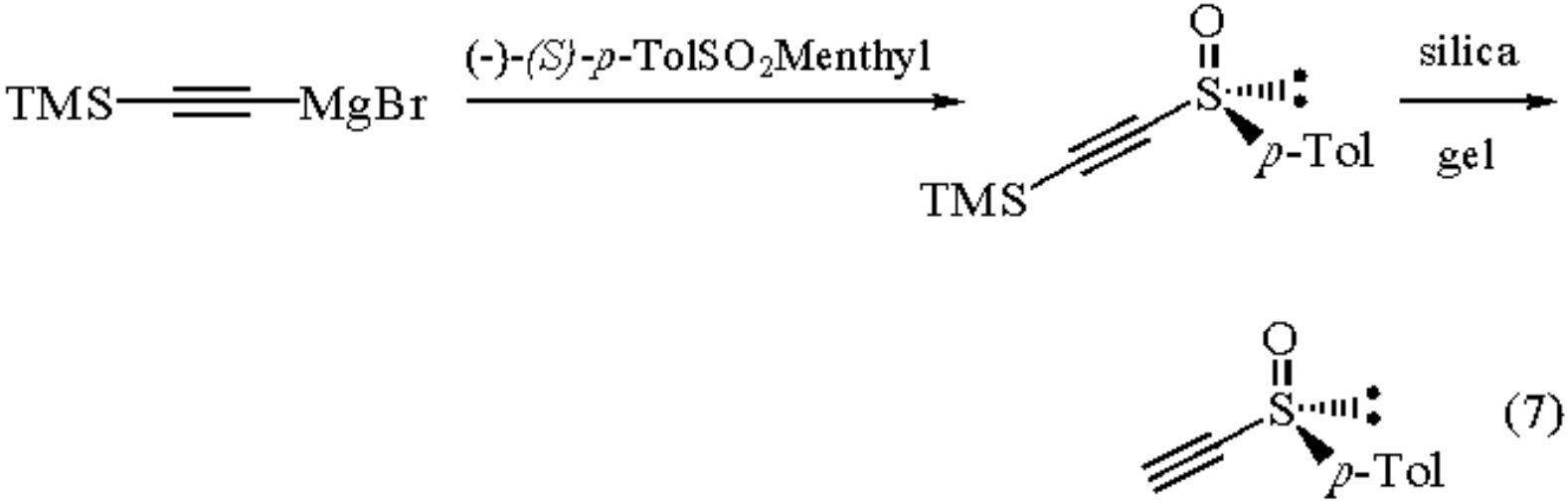

(7)

Chiral vinyl sulfoxides can also be prepared by a Horner-Emmons reaction of carbonyl compounds with α-phosphoryl sulfoxides which are obtained from lithiated dimethyl methylphosphonate and (-)-menthyl (*S*)-*p*-toluenesulfinate (eq 8).[16] However, this reaction applied to carbonyl compounds often gives a mixture of the (*E*) and (*Z*) isomers of the vinylic sulfoxide.

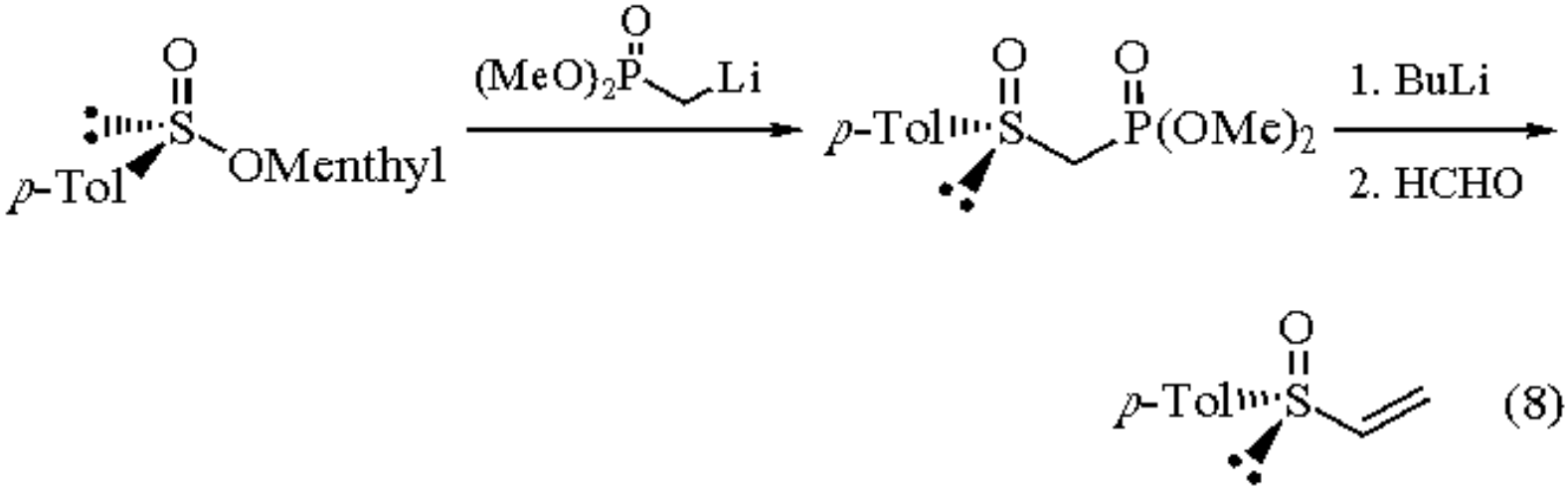

(8)

The reaction of α-phosphoryl sulfoxide with the dimethyl acetal of pyruvic aldehyde allowed the preparation of the corresponding vinylic sulfoxide as a 1:1 mixture of (*E*) and (*Z*) isomers which could be isomerized with ***Lithium Diisopropylamide*** to the lithiated (*E*) isomer, used for the asymmetric synthesis of α-tocopherol (eq 9).[17]

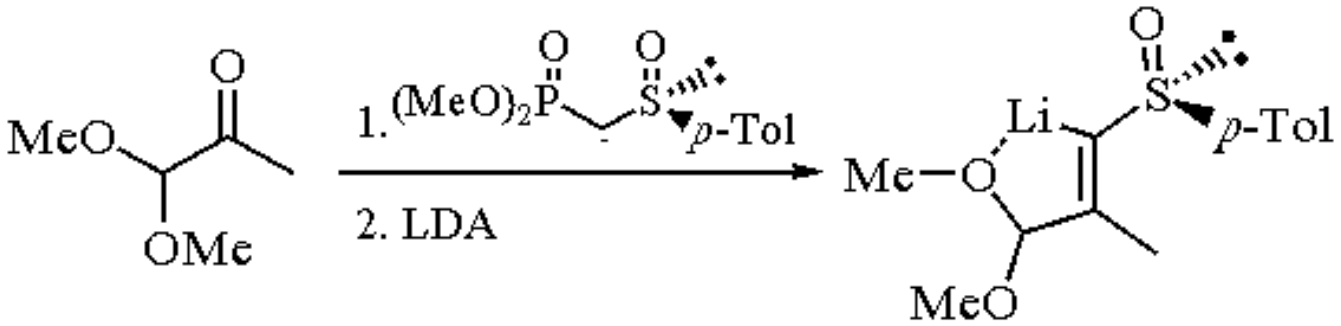

(9)

The Wittig reaction of an optically active sulfinylphosphonium ylide was reported to yield only the (*E*)-vinylic

sulfoxides (eq 10).[18]

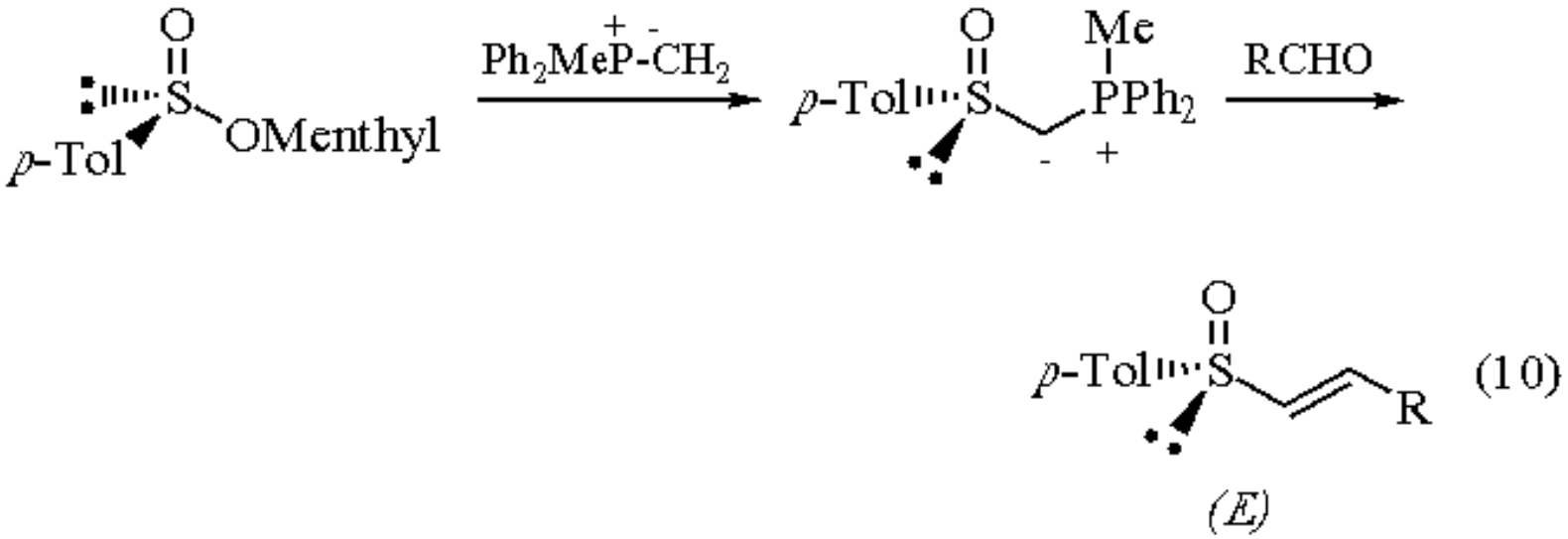

Diaryl Sulfoxides.

Optically active diaryl sulfoxides are prepared by reaction of an aryl Grignard with (-)-menthyl (*S*)-*p*-toluenesulfinate: 2,5-dimethoxyphenyl *p*-tolyl sulfoxide (**4**), a precursor of sulfinyl quinones,[19] and 3-pyridyl *p*-tolyl sulfoxide (**5**), a precursor of sulfinyl dihydropyridines (studied as NADH model compounds)[20] are two typical examples.

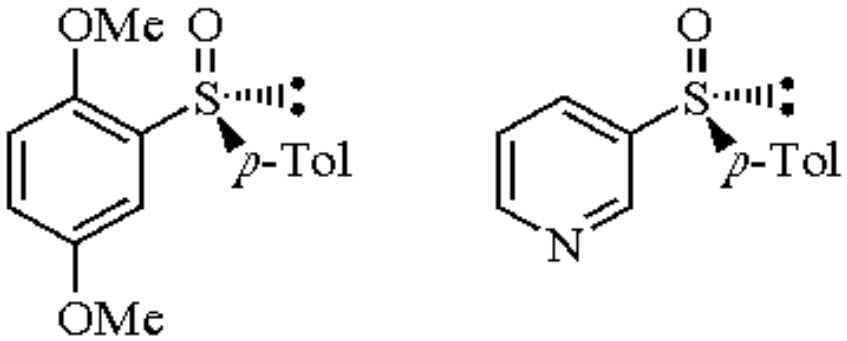

(4) **(5)**

Sulfinyl Esters and Derivatives.

(*R*)-(+)-*t*-Butyl 2-(*p*-tolylsulfinyl)acetate is conveniently prepared by reaction of the magnesium enolate of *t*-butyl acetate (readily made with ***Bromomagnesium Diisopropylamide***) with (-)-menthyl (*S*)-*p*-toluenesulfinate (eq 11).[21]

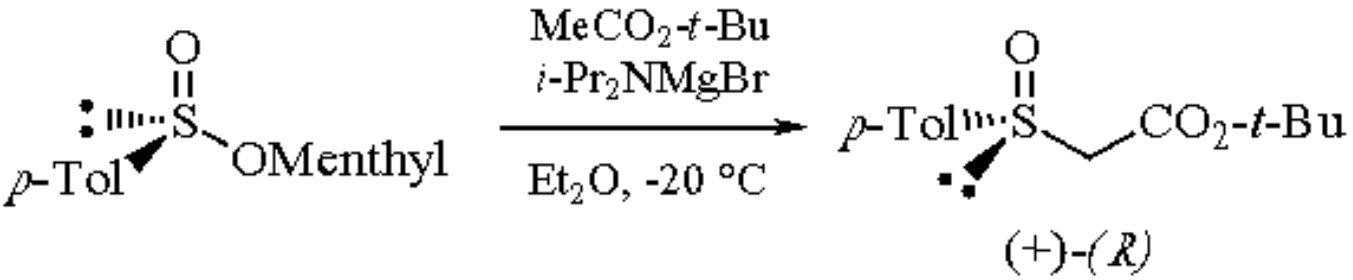

(11)

Substituted sulfinyl esters (**6**) have also been prepared by this reaction using the same base[22a] or lithium cyclohexyl(isopropyl)amide,[22b] which gives higher yields.

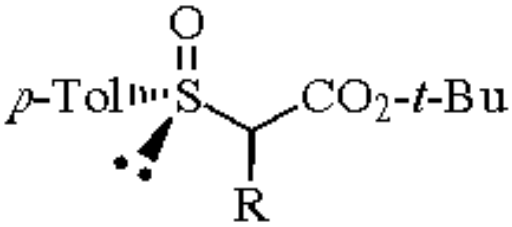

(6) R = Me, Et, $C_{14}H_{29}$

The anion of acetonitrile also reacts with (-)-menthyl (*S*)-*p*-toluenesulfinate to give the corresponding β-sulfinylacetonitrile (eq 12).[23]

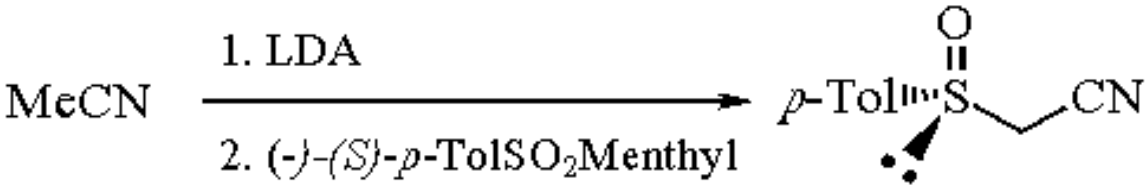

(12)

Similarly, *exo*-metalation with LDA of the racemic 3-methyl-4,5-dihydroisoxazole and reaction with (-)-menthyl (*S*)-*p*-toluenesulfinate afforded the sulfinyl-4,5-dihydroisoxazole as a diastereomeric mixture;[24] lithiated *N*,*N*-dimethylthioacetamide leads to the sulfinyl *N*,*N*-dimethylthioacetamide,[25] and lithiated ethyl *N*-methoxyacetimidate leads to *p*-tolylsulfinylethyl-*N*-methoxyacetimidate (eq 13).[26]

(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate

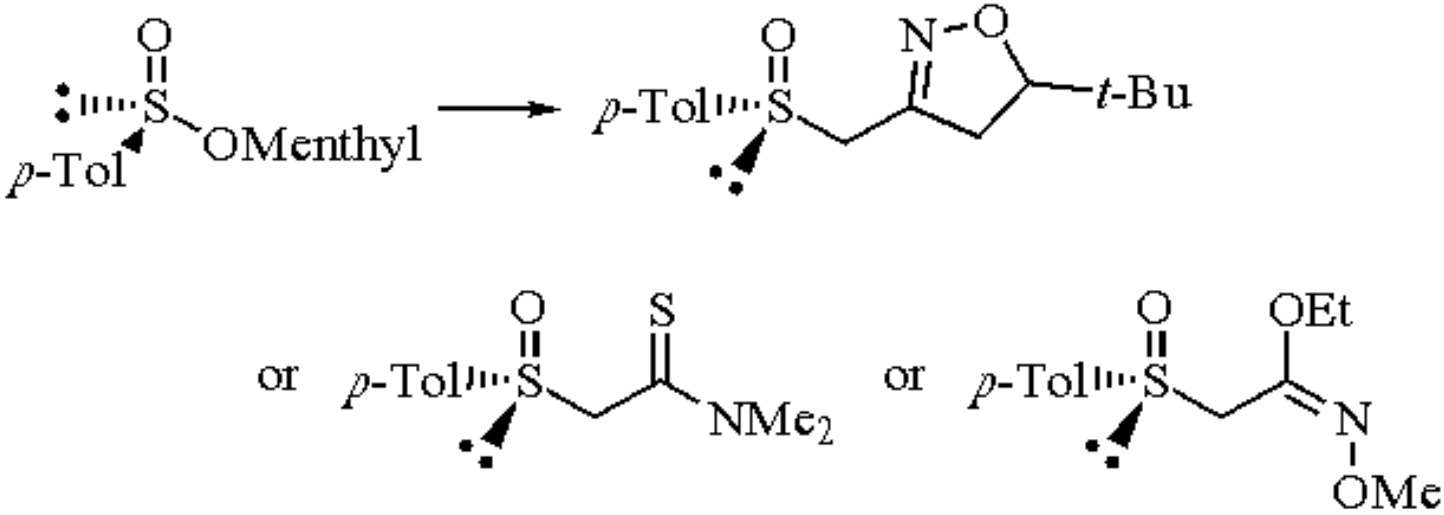

(13)

β-Keto Sulfoxides.

Cyclic β-keto sulfoxides are readily obtained from the magnesium enolate of the ketone and (-)-menthyl (*S*)-*p*-toluenesulfinate[27] as a mixture of diastereomers in which the major epimer has the sulfoxide group in the equatorial orientation (eq 14).

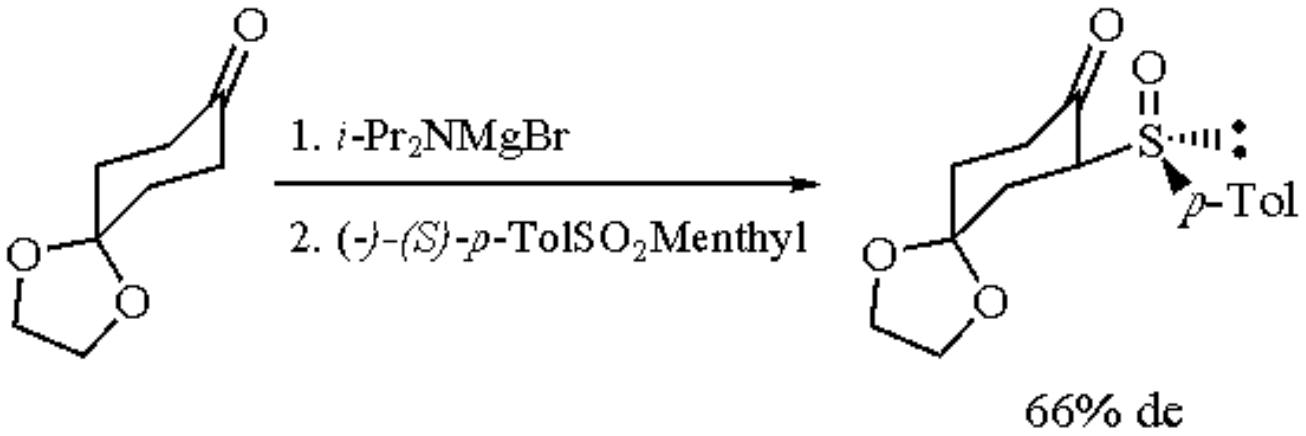

(14)

By condensation of the dianion of *t*-butyl acetoacetate and (-)-menthyl (*S*)-*p*-toluenesulfinate, the corresponding β-keto sulfoxide was obtained in high yield (eq 15) and shown to be an efficient precursor of both enantiomers of β-hydroxybutyric acid via selective reduction of the ketone carbonyl group.[28] β,δ-Diketo sulfoxides were prepared in a similar way from diketone dianions (eq 16).[29]

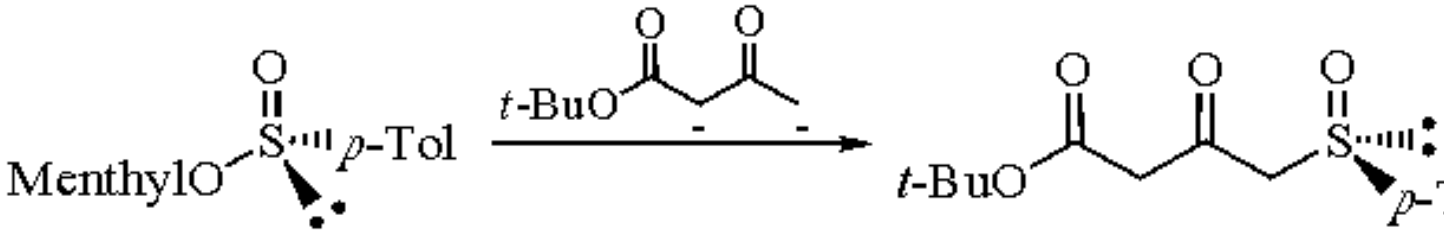

(15)

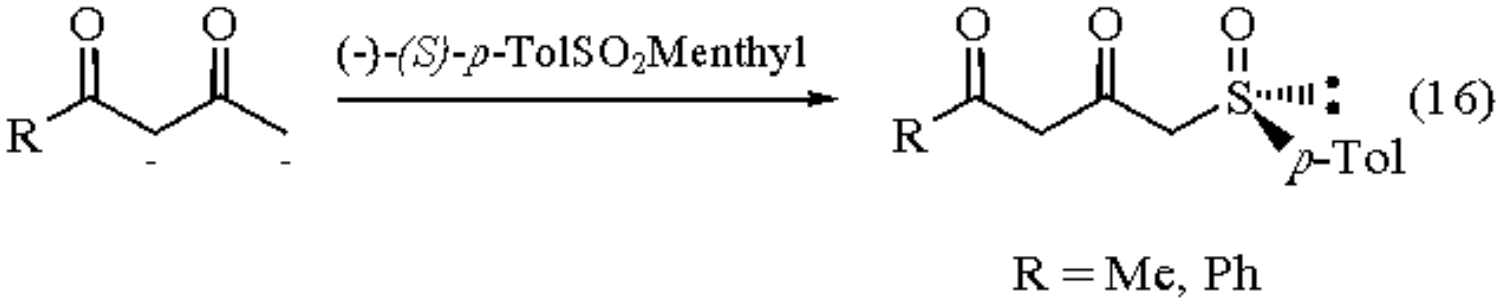

Imino Sulfoxides.

Metalated imines reacted with (-)-menthyl (*S*)-*p*-toluenesulfinate to yield the corresponding sulfinylimines as a diastereoisomeric mixture (eq 17).[30]

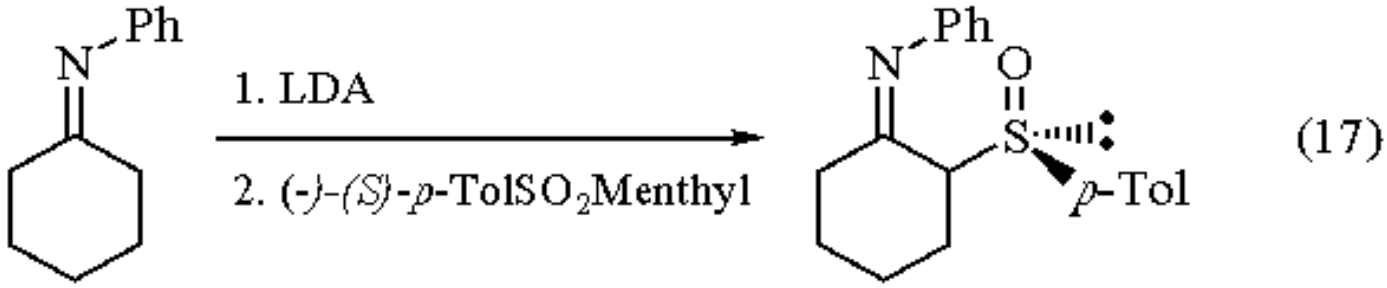

Similarly, *exo*-metalated cyclic imines afforded the sulfinylimines as an alkaloid precursor (eq 18).[31]

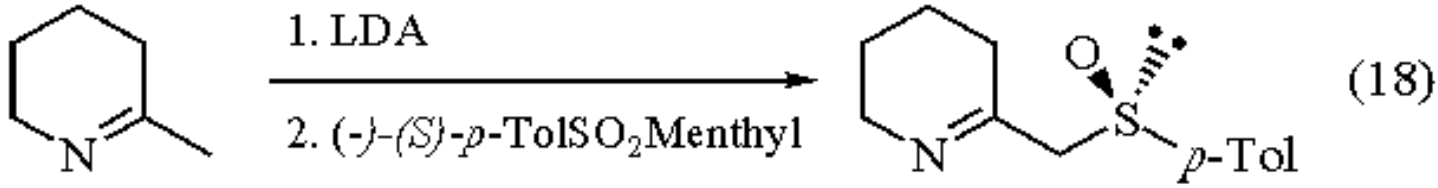

Miscellaneous.

(*S*,*S*)-Bis(*p*-tolylsulfinyl)methane (**7**) is readily prepared from (-)-menthyl (*S*)-*p*-toluenesulfinate and (*R*)-methyl *p*-tolyl sulfoxide.[32] (+) (*S*)-*p*-Tolylsulfinylmethyl *t*-butyl sulfone (**8**) was made from the *t*-butyl methyl sulfone anion and (-)-menthyl (*S*)-*p*-toluenesulfinate.[33]

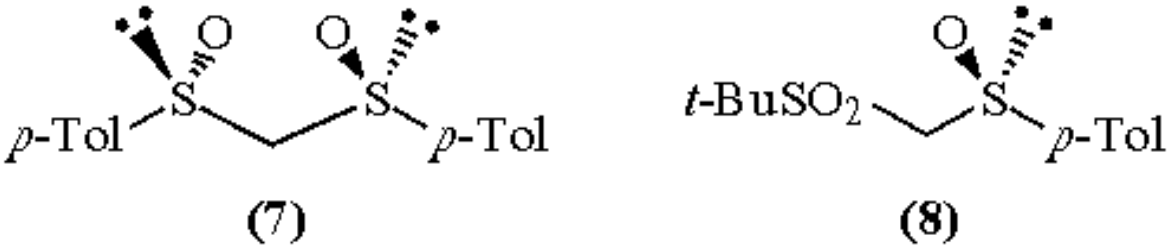

Chiral *N*-benzylidene *p*-toluenesulfinamides were prepared by reaction of benzonitrile with an alkyllithium followed by

addition of (-)-menthyl (*S*)-*p*-toluenesulfinate and converted into optically active amines and amino acids (eq 19).[34]

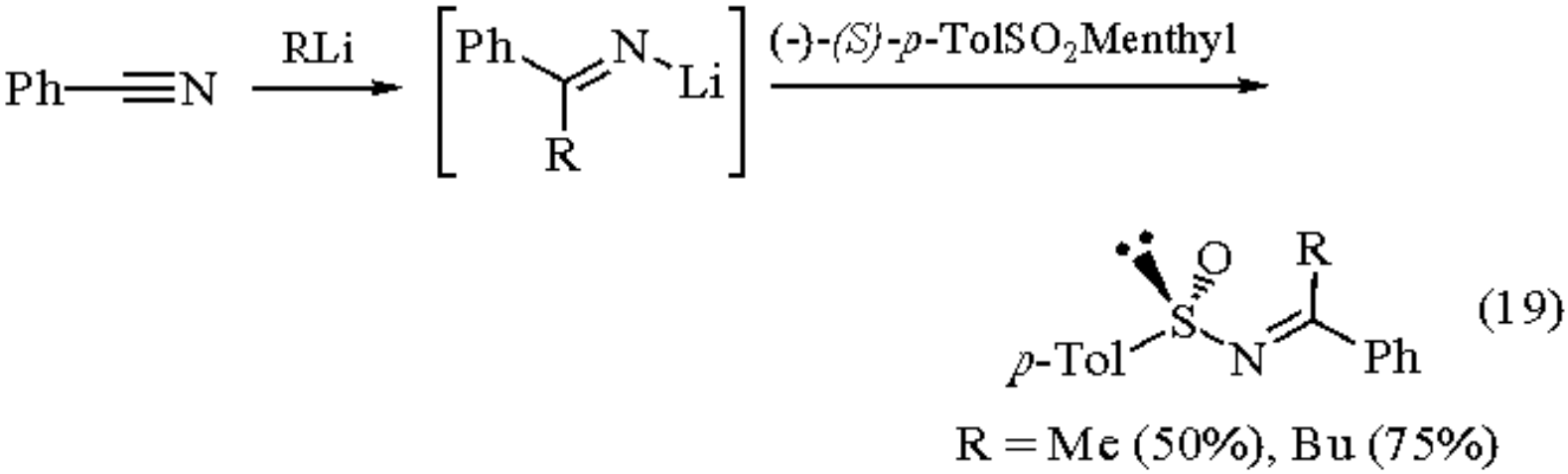

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2-Mercaptoethanol

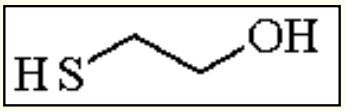

[60-24-2] · C_2H_6OS · 2-Mercaptoethanol · (MW 78.15)

(synthesis of 1,3-oxathiolanes from ketones; reducing agent for fluorimetric assay of amino acids)

Physical Data: bp 157-158 °C; flash point 73 °C; *d* 1.114 g cm^{-3}; *n*20D 1.4996.

Solubility: sol alcohols, Et_2O, benzene; sparingly sol H_2O.

Form Supplied in: liquid; commercially available.

Analysis of Reagent Purity: mp of 2-(2,4-dinitrophenylthio)ethanol is 101-102 °C.[1]

Preparative Methods: by reaction of ethylene chlorohydrin with ***Sodium Hydrogen Sulfide*** or ***Potassium Hydrogen Sulfide***;[2] by treatment of bis(β-hydroxyethyl) disulfide with zinc dust in aqueous alcoholic sulfuric acid at 40 °C;[3] or by reaction of ***Ethylene Oxide*** (2 mol) and ***Hydrogen Sulfide*** (1 mol) in thiodiglycol at 45-60 °C.[4]

Purification: by distillation (bp 157-158 °C).

Handling, Storage, and Precautions: can be stored as colorless, odorous liquid in a refrigerator for several months without significant coloration developing. Toxic by inhalation, in contact with skin and if swallowed. Irritating to eyes, respiratory system, and skin. Stench; can be incinerated neat for disposal. Use in a fume hood.

Synthesis of 1,3-Oxathiolanes from Ketones.[5]

The synthesis of 1,3-oxathiolanes from ketones constitutes one of the principal synthetic applications of 2-mercaptoethanol (eq 1). It was found that using 1 equiv of ***Boron Trifluoride Etherate*** in the reaction gave highest yields of 1,3-oxathiolanes. Reducing the amount of solvent below 750 mL per mol of ketone reduced yields of oxathiolanes and increased yields of polymeric materials.

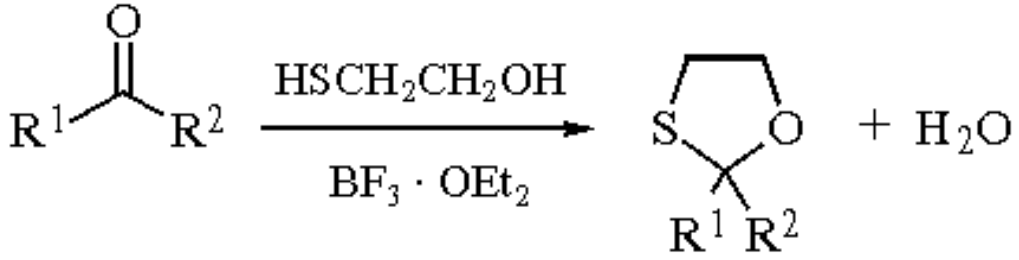

Conversion of Steroidal Ketones to Ethylenehemithioacetals (1,3-Oxathiolanes).

2-Mercaptoethanol was introduced by Djerassi[6] for the conversion of steroidal ketones to ethylenehemithioacetals (1,3-oxathiolanes) (eq 2). These are more readily reconverted to the ketone (using Raney nickel) than the similar ethylene thioacetals. The simplest procedure uses boron trifluoride etherate as catalyst.[7]

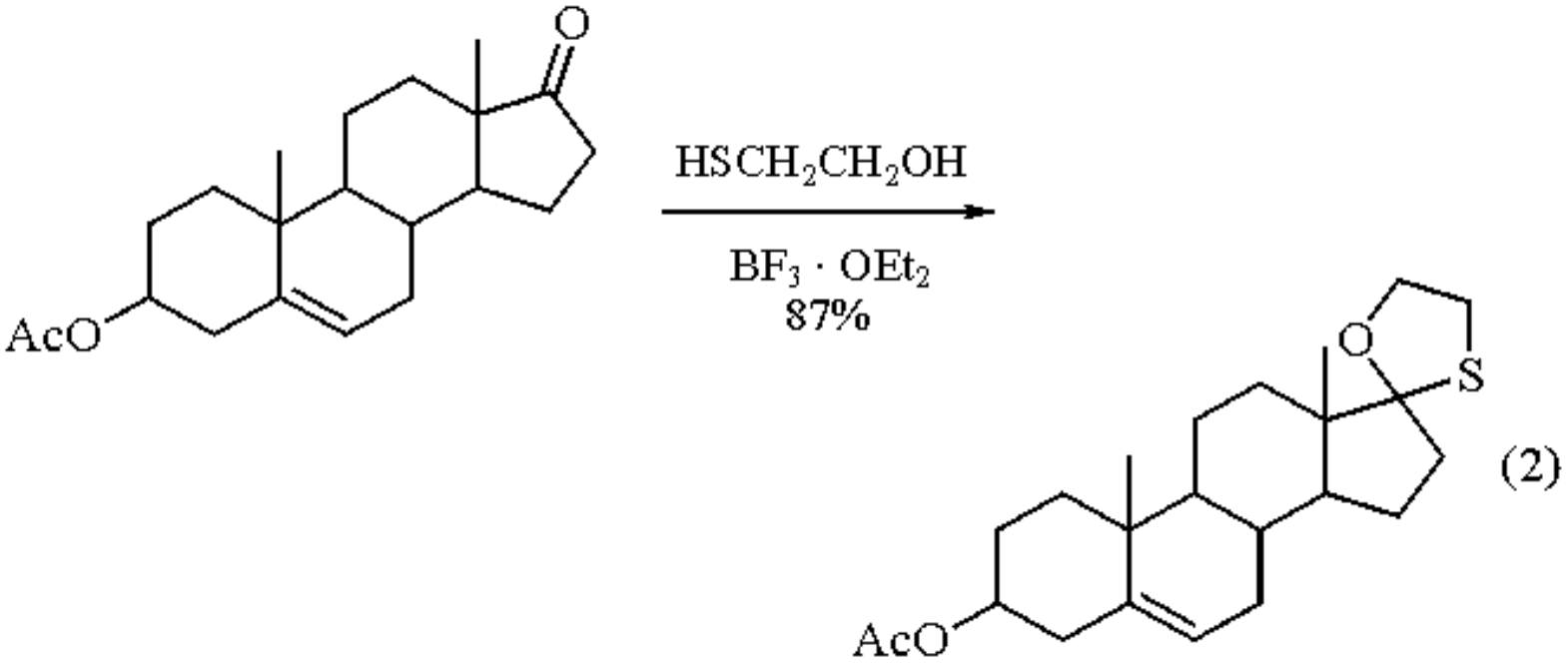

Fluorimetric Assay of Amino Acids.

o-Phthaldialdehyde reacts with amino acids in alkaline medium in the presence of 2-mercaptoethanol, as reducing agent, giving rise to fluorescent compounds.[8] This permits fluorimetric assay of amino acids down to the nanomolar range. The sensitivity is better than with ninhydrin procedures. The amino acids proline and hydroxyproline are not detected by the method.

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Mercury(0)

Hg

[7439-97-6] · Hg · Mercury(0) · (MW 200.59)

(photosensitizer for C-H bond cleavage reactions;[1-6] solvent for metals to give amalgams which can act as selective reducing agents;[8-19] heterogeneous catalyst poison, especially for Group 10 metal catalysts;[22] electrode material in electrosynthesis[24])

Physical Data: mp -38.87 °C; bp 356.6 °C; *d* 13.6 g cm^{-3}.

Solubility: sparingly sol organic solvents and water.

Form Supplied in: silvery liquid; widely available; electronic grade (foreign metals <=1 ppm) and ACS grade (99.9995%) are available, normally making purification unnecessary.

Handling, Storage, and Precautions: as a volatile heavy metal, care must be taken to prevent long term inhalation of the vapor. Carrying out reactions in a fume hood, cleaning up spills, and assuring that the air handling system of the laboratory is operating normally is generally sufficient.

Mercury Photosensitization.

This allows the dehydrodimerization of a variety of volatile organic molecules on a 1 to 50 g scale without a solvent in a simple apparatus which can be put together from standard laboratory photochemical equipment.[1-5] A 254 nm low-pressure mercury lamp is used, together with quartz glassware. The reactive triplet excited state of mercury is usually designated Hg*. The reaction happens in the vapor phase at rt and pressure, but no special precautions have to be taken; the normal vapor pressure of the substrate is usually enough to replenish the vapor above the substrate when reaction has taken place. Mercury is supplied in the form of a small mercury drop in the substrate. Normal laboratory glassware can contain sufficient adsorbed mercury so that Hg photosensitized reactions can occur. To obtain a valid control experiment in the absence of mercury, it is sometimes necessary to anneal the glassware in a glassblower's oven. This implies that care needs to be taken in interpreting the results of what are ostensibly normal or nonmercury photosensitized reactions where special care to remove trace mercury may not have been taken.

The liquid phase is unreactive and this has important effects on the selectivity of the reaction. Dehydrodimerization or functionalization always leads to the condensation of the product, which protects it from further reaction and so the substrate only undergoes one homolysis even if there are several C-H bonds of similar strength. To take a simple example, cyclohexane dimerizes to bicyclohexyl with no further oligomerization. The origin of the nonreactivity of the liquid phase is probably that the very narrow atomic absorption line for vapor-phase mercury is broadened and shifted

when the mercury is dissolved. Perfect matching of the emitter and absorber in the vapor phase, where both are vapor-phase mercury atoms, leads to efficient energy transfer in the vapor; energy transfer is probably poor for dissolved Hg. The use of a high-pressure mercury lamp (or even allowing the temperature of the lamp to become abnormally high) causes the selectivity of the reaction to change sharply for the worse, presumably because absorption can now take place in the liquid phase and so condensation no longer protects the condensate from further reaction.

The absorption coefficient for mercury vapor is so large that all the light is absorbed within a few micrometers of the inside surface of the reactor and so the bulk of the vapor is protected from irradiation. This means that normal organic photochemistry is severely suppressed; essentially all the energy is absorbed by the mercury atoms, leaving none to excite the much more weakly absorbing organic species. Absorption of the 254 nm line is responsible for the chemistry described here, and so the excited state responsible is the $^3P_1$ state of mercury. The quartz glassware is transparent to the 254 nm line, allowing for efficient transmission to the reaction zone.

A useful modification for certain substrates is the use of a reactive atmosphere. In this case, the temperature is typically adjusted so that the vapor pressure of the substrate is 100 Torr. This is necessary so that the reactive gas has a substantial partial pressure (*P*) in the reaction zone; in the case where the substrate has a *P*(substrate) of 100 Torr, the *P*(reactive gas) would be 660 Torr. The two most useful reactive gases are H_2 (Hg*/H_2 conditions)[4] and NH_3 (Hg*/NH_3 conditions).[5] The reason for moving to these reactive gases is that the standard conditions, with reflux under N_2 (Hg* conditions), completely fail when the Hg* attacks a functional group in the substrate. This typically happens for substrates having multiple bonds or N lone pairs. Under Hg*/H_2 or Hg*/NH_3 conditions, H atoms take over from Hg* as the active species, and a much wider range of substrates are reactive. For example, NEt_3 fails to react at all under Hg* conditions, presumably because Hg* attacks the N lone pair, and energy transfer leads to thermal excitation of the substrate but not to productive chemistry. Under Hg*/H_2 conditions the compound undergoes dehydrodimerization at the C-H bond α to N. Arenes seem to work best under Hg* conditions, probably because H atom addition leads to undesired and unselective partial saturation of the aromatic ring. In practice there is little point in attempting to predict what will happen with a given substrate because it is easy to try Hg* conditions first and then move to Hg*/H_2 conditions if the results are unsatisfactory.

In each case, the crude product is collected by removing the volatile starting material by rotary evaporation after the reaction is over. The main limitation is that the substrate be volatile, but compounds with up to 16 nonhydrogen atoms have been successfully dimerized. The reaction proceeds under reduced pressure if this is useful to vaporize the substrate. Another useful modification is to use steam distillation to bring the substrate into the vapor phase; in this variant, water is added to the substrate and the mixture is refluxed. The weakest C-H (or X-H) bond in the molecule is homolyzed and the resulting C-centered (or, in general, X-centered) radicals recombine. That part of the radical pool which disproportionates instead of recombining does not in general lead to lower chemical yield because the H atoms present add to the alkene disproportionation product and re-form the initial radical. Quantum yields of 0.04-0.8 are usual and the majority of substrates have values in the range 0.2-0.6. Chemical yields are good to excellent (40-98%). Conversions depend on photolysis time.

The great advantage of the method is that it allows a number of difficult synthetic transformations to be carried out in one step. The synthesis of a few simple compounds that are otherwise very difficult to make is shown below. In the diamine synthesis, Hg*/NH_3 conditions gave the best results (eq 1).

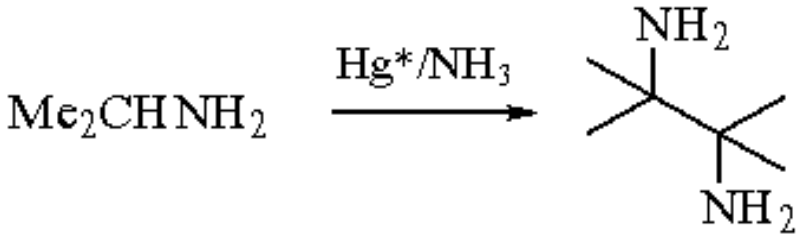

(1)

A variant, hydrodimerization of alkenes, takes place under Hg^*/H_2 conditions (eq 2). The H atoms add to the terminal carbon of the alkene to give the intermediate radical shown.

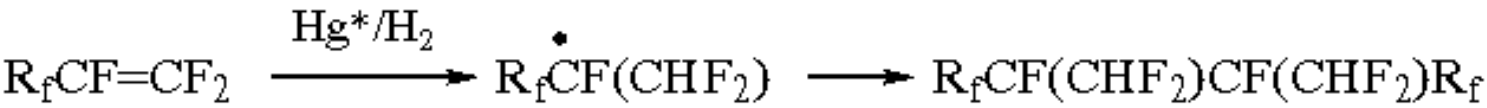

(2)

Another useful feature is the facility with which two different substrates cross dimerize (eq 3).

(3)

In suitable cases, the volatility or polarity differences among the three allow easy separation by distillation or chromatography (eq 4).

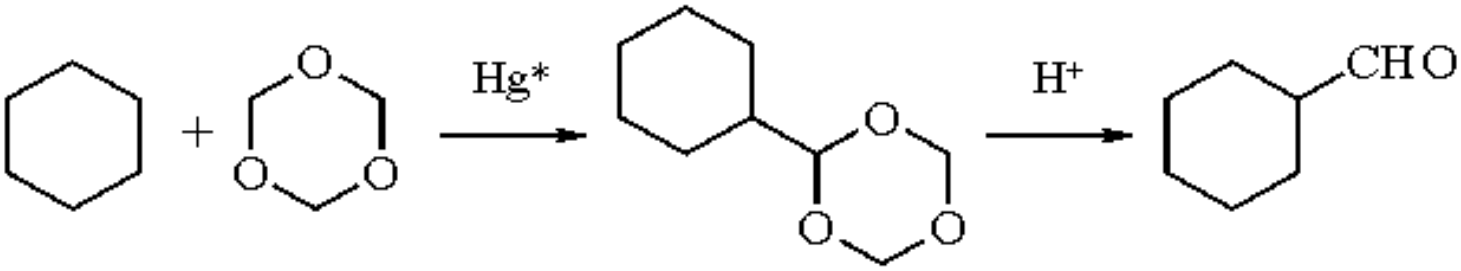

(4)

The intermediate radicals can undergo rearrangement in special cases, as in the case of hexenyl radicals which cyclize. Trapping the intermediate radicals with CO, SO_2, and O_2 has proved possible, giving aldehydes, ketones, sulfonic acids, and hydroperoxides.[6]

Since methane has strong C-H bonds, it only reacts well under Hg^*/NH_3 conditions to give CH_2=NH as product.[5a] Arenes do not undergo cleavage of the strong aryl C-H bonds but benzylic C-H bonds of side chain alkyl groups can be cleaved under Hg* conditions; neither Hg^*/H_2 nor Hg^*/NH_3 conditions seem to be useful for arenes, however, probably because H atoms readily add to arene rings to give a complex mixture of products.

Reduction.

Ultrasonically dispersed mercury reduces α,α´-dibromo ketones to an intermediate that is believed to be a mercurated 2-oxyallyl species which gives a 4-methylene-1,3-dioxolane with acetone.[7]

Amalgams.

This is a traditional and well-established application of Hg^0. Metallic mercury readily forms amalgams with most metals but Na/Hg, Al/Hg, and Zn/Hg are the most useful in organic chemistry. The mercury serves both to keep the surface of the metal clean (because inorganic salts adhere poorly to the amalgam) and to dilute the active metal (and so moderate its thermodynamic reducing potential), which can improve the selectivity of the reduction.

Sodium Amalgam.

Sodium Amalgam is a liquid up to 1%, semisolid at 1.2%, and a pulverizable solid at higher concentrations, except in a narrow range around 40% Na, where the material is a low melting (<30 °C) solid. These materials can be made from elemental Na and Hg (*caution*: much heat is evolved) and analyzed by titration with acid.[8] Na/Hg is useful for the reduction of α,β-unsaturated carboxylic acids to the saturated forms, and for the Emde degradation of a quaternary amine (eq 5).[9] The reduction of aldonolactones to aldoses with Na/Hg is a key transformation in sugar chemistry.[10] Oximes are readily reduced to amines.[11]

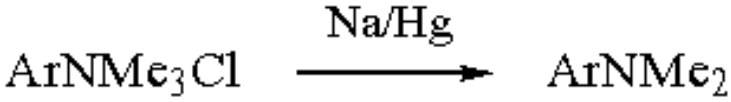

(5)

Aluminum Amalgam.

Aluminum Amalgam, readily prepared[12] by treating base-etched elemental aluminum with aqueous mercury(II) salts, is a useful replacement for Na/Hg when the compound to be reduced is base sensitive. Diethyl oxaloacetate can be reduced to diethyl malate (70-80% yield) (eq 6) and aryl ketones can be reduced to the corresponding pinacols (30-60% yield) (eq 7) in this way.[12] Desulfurization of disulfides is also possible.[13]

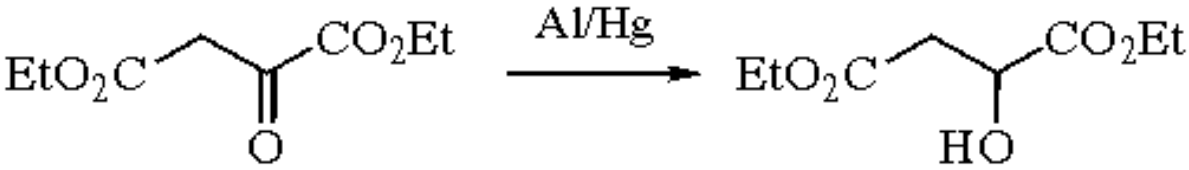

(6)

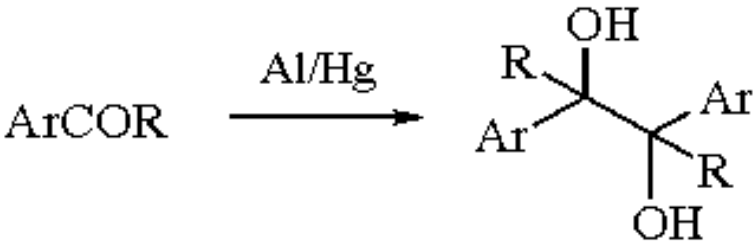

(7)

Dienes undergo what is effectively a 1,4-addition of H_2 to give the monoenes, and cumulenes undergo a 1,2-reduction.[14] The C-S bond in α,β-unsaturated phenyl sulfones can be hydrogenolyzed stereospecifically to give the alkene in excellent yield.[15] Net hydrogenolysis of a P=C bond is involved in the sequence shown in eq 8, in which an acyl halide is converted to a keto ester.[16a]

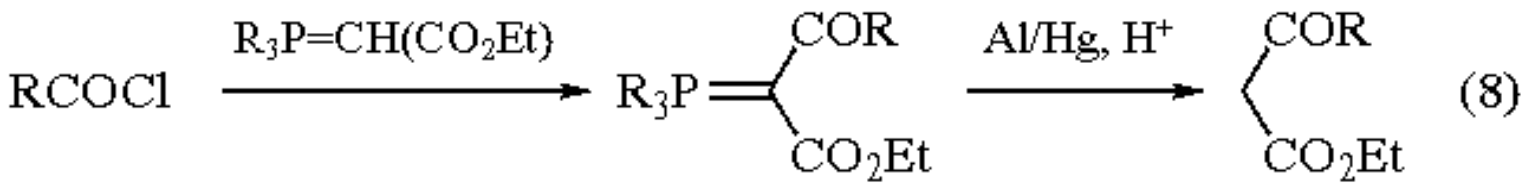

In a recent synthesis of mannostatin A, King and Ganem have shown how the N-O bond of a cyclic acyl-nitroso compound can be hydrogenolyzed by Al/Hg (eq 9).[16b]

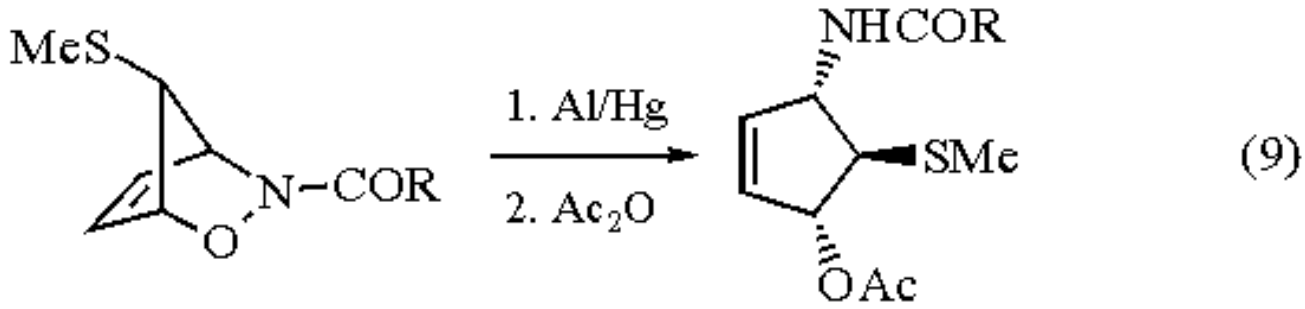

Zinc Amalgam.

The classic use of ***Zinc Amalgam*** is the Clemmensen reduction of ArCOR to $ArCH_2R$.[17] Variants of this method have proved successful for specific substrates.[18] The nitroalkene closure shown in eq 10 is a more recent application of Zn/Hg.[19]

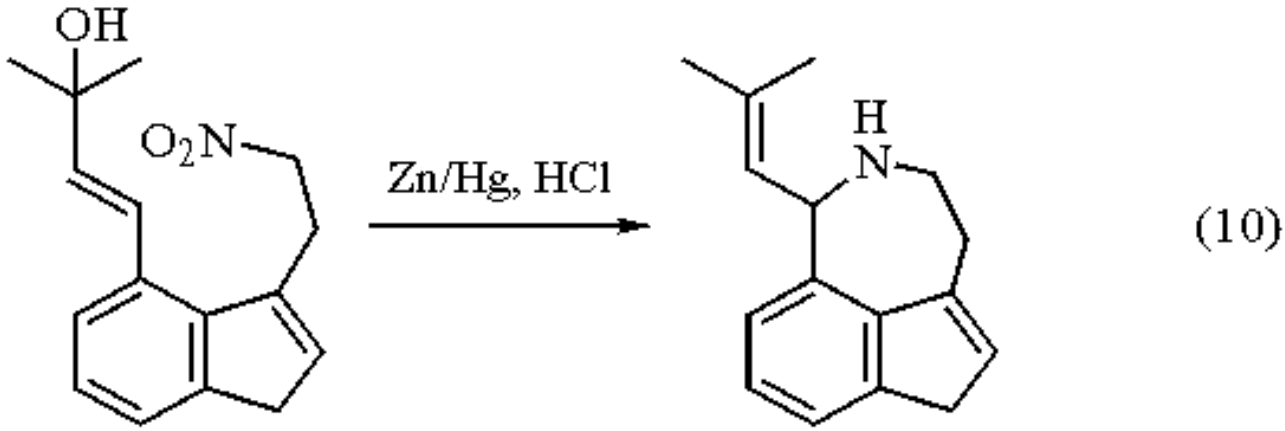

Ultrasound[20] and Rieke[21] methods are increasingly being used as an alternative to Hg amalgamation for activating metals, a trend encouraged by disposal problems of mercury-contaminated wastes.

Catalyst Poison.

Mercury selectively poisons heterogeneous catalysts, particularly of the platinum group metals (PGM). This can be useful when a homogeneous PGM catalyst decomposes with time to give the free metal; in such a case, Hg^0 can suppress the heterogeneous component of the reaction.[22] This can improve selectivity or give mechanistic information about which products are attributable to which pathway.

Potential Route to Organomercury Compounds from Hg^0.

Organomercury compounds are synthetically accessible[23] from metallic mercury by a number of routes, including reaction of elemental mercury with alkenes in acid medium and with acyl and alkyl halides (under thermal or photochemical conditions). Organic synthetic applications of this chemistry seem to be very rare, however.

Electrolysis at Mercury Cathodes.

The high overvoltage of a mercury surface in several electrochemical processes is often used to advantage; for example, proton reduction to H_2 is kinetically disfavored relative to electron transfer to an organic substrate. An example of an organic electrochemical application is provided by reduction of a number of alkyl halides, RX, to the radical, R&bdot;, which dimerizes to R_2, disproportionates to RH and the corresponding alkene, and also leads to the formation of R_2Hg.[24]

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Mercury(II) Acetate

$Hg(OAc)_2$

[1600-27-7] · $C_4H_6HgO_4$ · Mercury(II) Acetate · (MW 318.69)

(inter- and intramolecular oxy-,[1-3] amino-, and amidomercuration[1,40,43,47] of alkenes and alkynes; cleavage of cyclopropanes;[64,65] mercuration of aromatics;[75] *o*-mercuration of phenols;[76] mild oxidation[101,102])

Alternate Name: mercuric acetate.

Physical Data: mp 179-182 °C; bp dec; *d* 3.28 g cm^{-3}.

Solubility: sol CH_2Cl_2, AcOH; slightly sol alcohols; insol benzene, hexane, etc.; sol H_2O (slowly hydrolyzed to HgO).

Form Supplied in: white, hygroscopic crystals. *Drying:* recrystallization from AcOH followed by storage in a desiccator.

Handling, Storage, and Precautions: acute poison. $Hg(OAc)_2$ is easily absorbed through the skin and is corrosive. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Oxymercuration.[1,2]

Electrophilic Hg^{2+} is capable of attacking alkenic double bonds to effect Markovnikov addition,[3] typically with *anti* stereochemistry (eq 1).[4,5] However, *syn* attack can be enforced if the *anti*-face is severely hindered;[4] thus norbornene,[5] *trans*-cyclooctene,[6] and *trans*-cyclononene[6] give *syn* addition products.[6] Solvomercuration occurs in hydroxylic solvents (water or alcohols)[1,7,8] except when *t*-BuOH is utilized.[7] Using Hg^{II} salts with less nucleophilic anions (e.g. $CF_3CO_2^-$) improves the yields of the solvomercuration products.[7] In the presence of Cl_2 or Br_2, the HgX group in the original adduct is replaced by halogen.[7] Peroxymercuration of alkenes occurs in the presence of peroxides.[9] Methoxymercuration of alkynes[10] or allenes[11] in methanol gives mercurated vinyl ethers (eq 2),[10] whereas vinyl acetates are formed in AcOH.[12] Mercury(II) acetate also catalyzes the perborate or MoO_5.HMPA-mediated oxidation of terminal alkynes to α-acetoxy ketones (eq 3).[13]

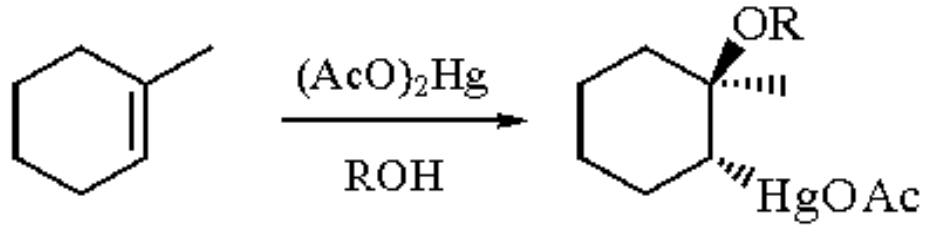

(1)

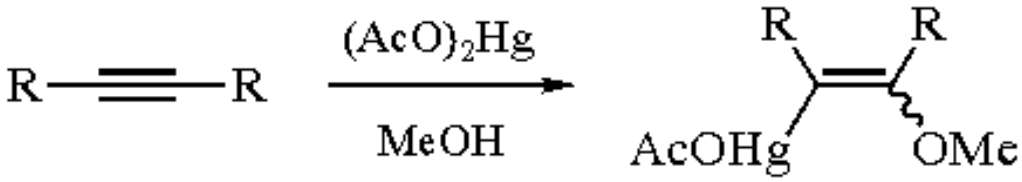

(2)

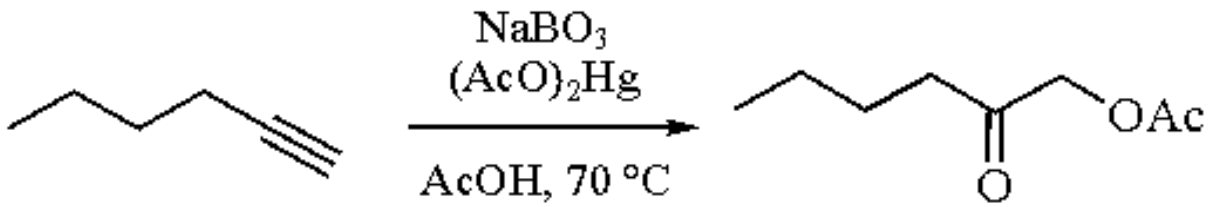

(3)

Although mercuration exhibits features common to most electrophilic additions,[14] it differs in details. Thus the rate-limiting step for mercuration is the cleavage of the intermediate mercuronium ion by a nucleophile; in contrast, bromination proceeds by the rate-limiting formation of the bromonium ion.[15]

Mercuration is very sensitive to steric factors in which it parallels hydroboration.[16] The following reactivity of alkenes has been observed: terminal disubstituted > terminal monosubstituted > internal disubstituted >> trisubstituted > tetrasubstituted (eq 4);[17] *cis*-alkenes are more reactive than their *trans* counterparts[17] and enol ethers are much more reactive than any other alkene.[18] Attempted asymmetric mercuration in the presence of cyclodextrin or in chiral micelles has only been partly successful, giving 3-55% ee; in one case the ee was 96%.[19]

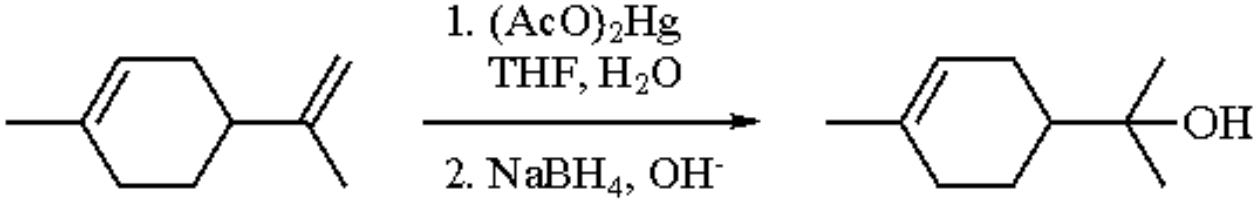

(4)

Neighboring group participation can be employed to construct cyclic structures such as tetrahydrofurans and tetrahydropyrans[3c,20-22] (eqs 5 and 6),[3c,20,21] spiroacetals (eq 7),[23] lactones,[24] and cyclic peroxides,[25] or to introduce a hydroxy group stereoselectively.[26] 4-Pentynoic acid reacts with $(AcO)_2Hg$ to produce α´-angelicalactone (eq 8).[27] A neighboring ether or hydroxy group can steer the approach of Hg^{2+} to the double bond by coordination and thus exercise a relatively high degree of stereocontrol (up to 93% de).[28]

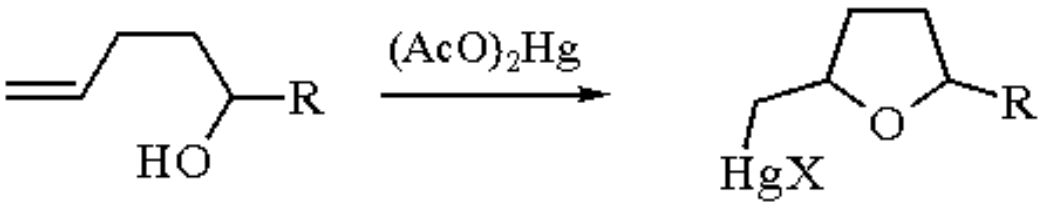

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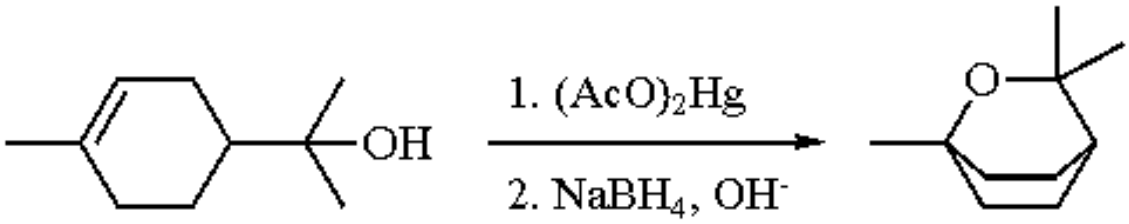

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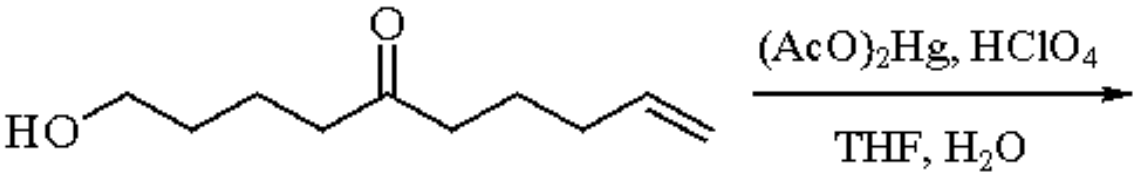

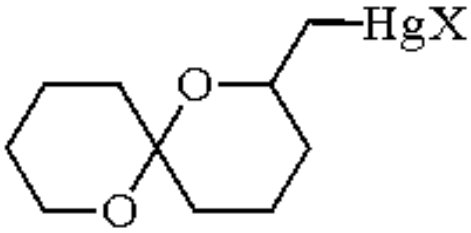

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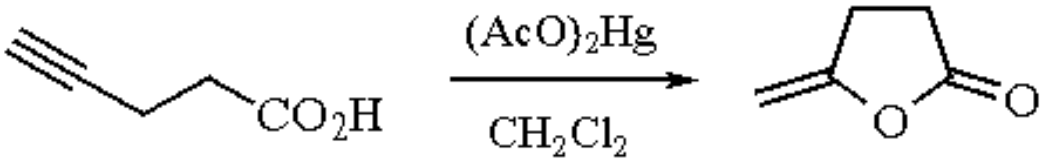

(8)

The adducts can be demercurated by hydrides (e.g. ***Sodium Borohydride***)[1] or sulfur compounds (***1,3-Propanedithiol*** or ***Sodium Trithiocarbonate***)[29,30] so that the method can be used as a formal addition of ROH across a double bond. While the hydride reduction may result in inversion (4:1), predominant retention of configuration (20:1) has been reported for the latter method.[29,30] The hydride reduction proceeds via a C-centered radical which can be trapped in a number of ways, e.g. by addition across an electron-deficient double bond[31-34] (eqs 9 and 10),[31,32] or by oxygen.[35] The latter method (O_2/$NaBH_4$) replaces HgX with OH.[1,36] Transmetalation of organomercurials by palladium is another option.[1,36]

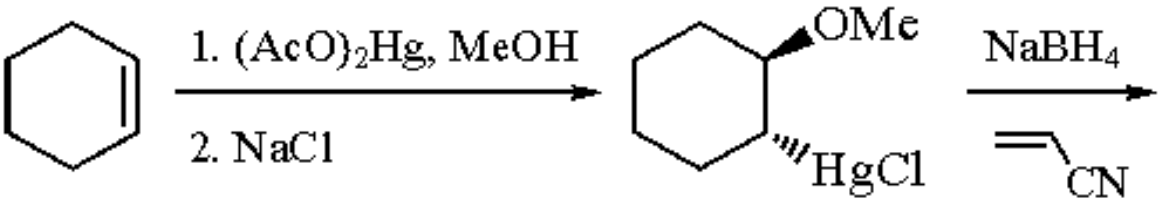

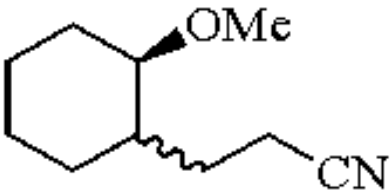

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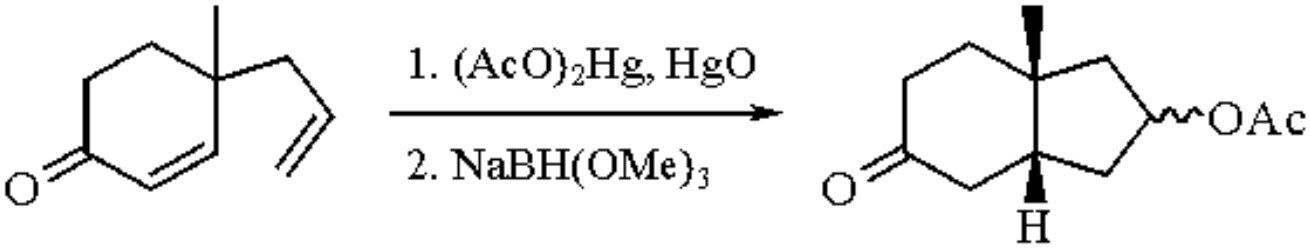

(10)

On treatment with bromine, NBS, NBA, or KBr_3, organomercurials are converted into the corresponding halides[37] (in a nonstereoselective fashion[38]). If applied to α,β-unsaturated acids,[37a,b] this reaction can be employed as a key step for the synthesis of serine or threonine (eq 11).[39]

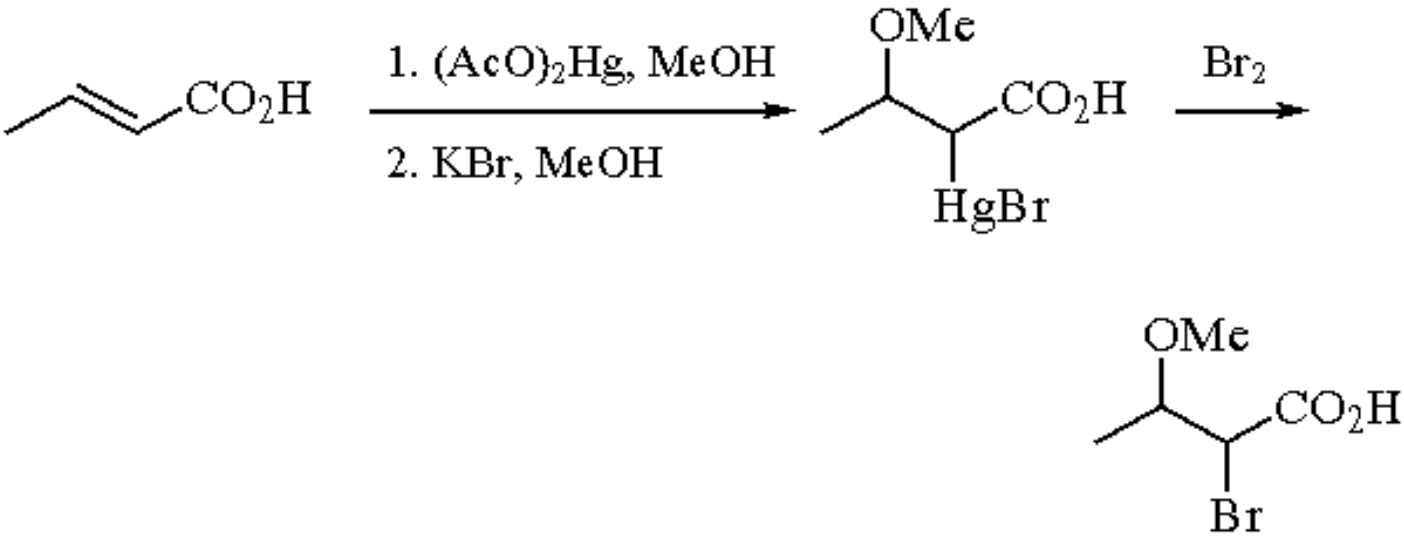

(11)

Amino- and Amidomercuration.

Amino alkenes can similarly be cyclized by $(AcO)_2Hg$ to afford various nitrogen heterocycles[22b,d,e,40] via a 5- or 6-(N)^n-*exo-trig* pathway (eq 12).[41] This method has also been applied to the synthesis of indoles.[42] An interesting intra/intermolecular version has been developed for the stereoselective synthesis of piperidines (eq 13).[43,44]

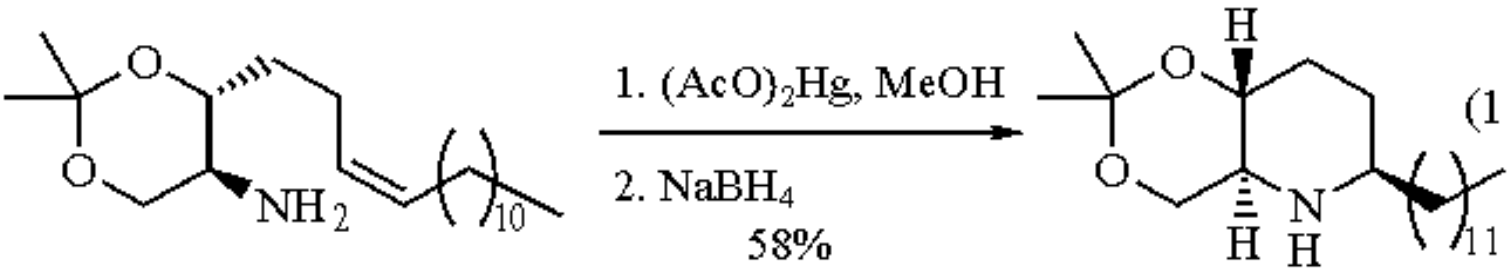

(12)

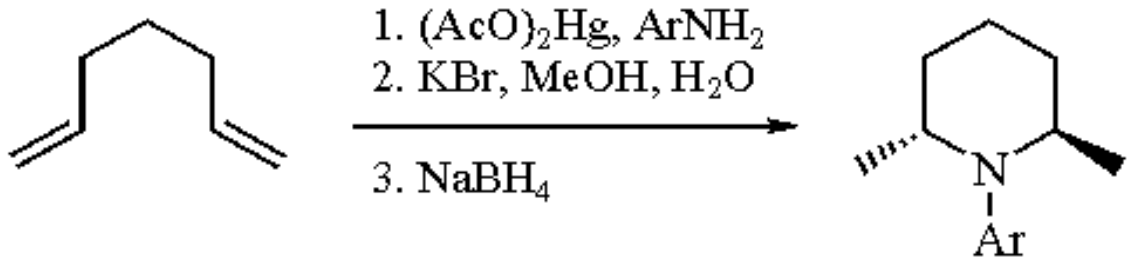

(13)

Intramolecular amidomercuration is another variation on the same theme[32-34,35d,45] which works even with β-lactams (eq 14).[46] Intermolecular amidomercuration can be accomplished in acetonitrile through a Ritter-type reaction.[47]

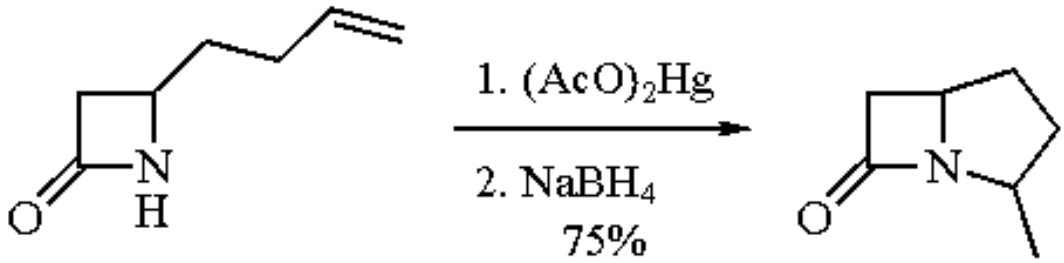

(14)

Unsaturated oximes also undergo a ring-closure reaction on treatment with $(AcO)_2Hg$ to produce nitrones which can be trapped via a [3 + 2] cycloaddition (eq 15).[48]

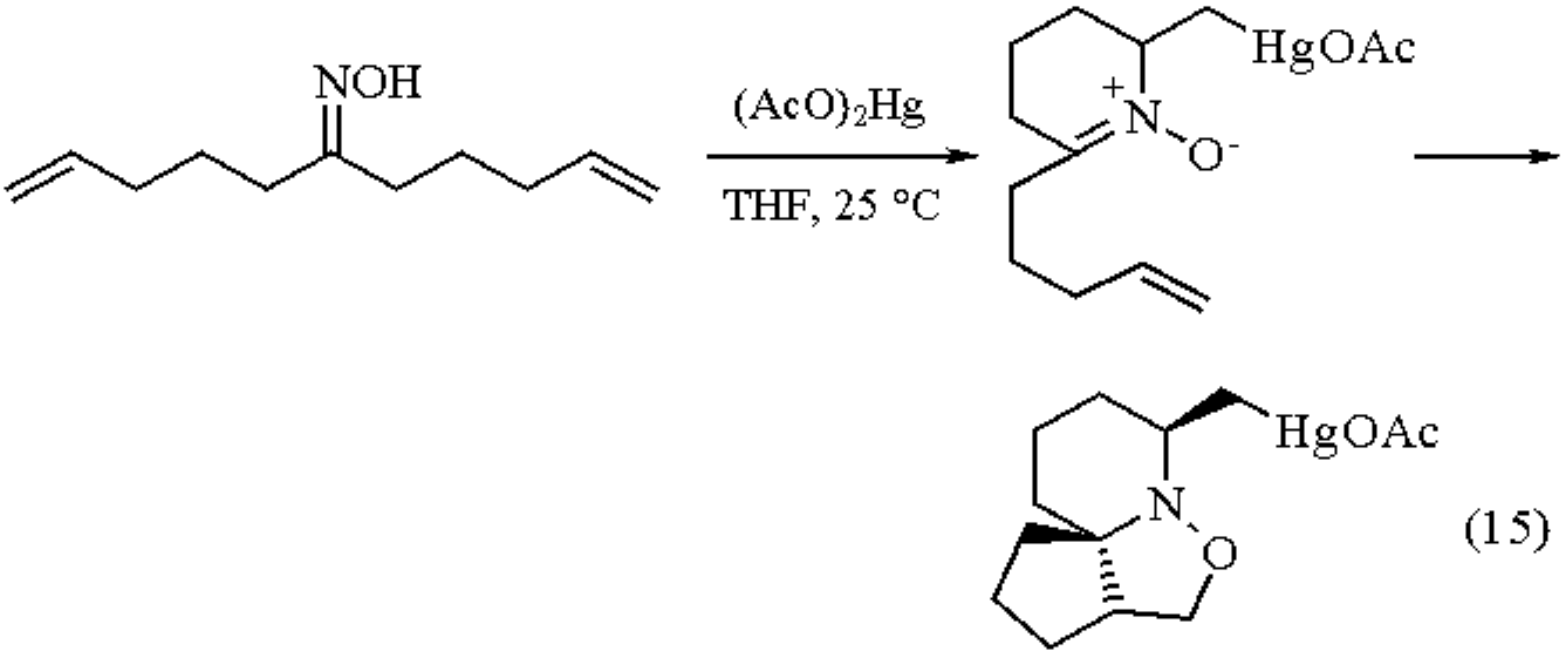

(15)

3-Alken-1-ynes undergo catalytic aminomercuration in the presence of $(AcO)_2Hg$ or HgCl at elevated temperatures to produce enamines.[49] By contrast, propargylic alcohols (HC&tbond;CCH_2OH) undergo oxidative aminomercuration to afford bis-aminated aldehydes, e.g. (*Z*)-PhNHCH=C(NHPh)CH=O.[50] Catalytic aminomercuration of protected propargylic alcohols gives enamines, $CH_2=C(NR^1{}_2)CH_2OR^2$, as the result of a regioselective Markovnikov addition-demercuration.[51] Dipropargyl ethers produce aminofurans.[51]

Polyene Cyclization.

Treatment of dienes or trienes with $(AcO)_2Hg$ triggers cyclization analogous to the Johnson polyene cyclizations.[52,53] The HgX group in the resulting cyclic organomercurial can best be eliminated to afford the corresponding alkene by photochemically induced transmetalation with ***Diphenyl Diselenide*** followed by standard selenoxide elimination.[54] Allenes with another alkenic bond can also be employed in this cyclization.[55] By contrast, 1,4-cyclohexadiene gives a mixture of mono- and bis-methoxymercurated products with no transannular C-C bond formation.[56]

Addition of Alcohols to Vinyl Ethers.

Vinyl ethers such as CH_2=CHOEt undergo a formal exchange reaction with another alcohol in the presence of $(AcO)_2Hg$, which occurs via elimination of EtOH from the intermediate.[1,57] Acetals can also be isolated from this reaction.[18,58] Similar reactions occur with vinyl esters (e.g. vinyl acetate)[59] and vinyl thioethers.[60] Ketone trimethylsilyl enolates give α-mercurio ketones[61] which are capable of the ***Boron Trifluoride Etherate***-catalyzed aldol condensation with aldehydes;[62] the reaction exhibits a high degree of *syn* stereoselectivity, comparable with that obtained from the Zr or Ti enolates.[61]

Mercuration of Enamines.

Enamines react with $(AcO)_2Hg$ in DMF to give intermediate iminium salts ($R^1{}_2N^+$=CHC(HgOAc)R^2R^3), which are reduced with $NaBH_4$ to afford the corresponding tertiary amines $R^1{}_2NCH_2CHR^2R^3$ (50-90%).[63]

Ring Opening of Cyclopropanes.

The cleavage of cyclopropanes with Hg^{II} occurs[34,64] predominantly with inversion of configuration at the carbon attacked by Hg^{2+} (corner opening)[65,66] and nucleophiles such as AcO^- or MeOH are incorporated in the product (eq 16).[65] Peroxides can also be employed as nucleophiles to produce the corresponding organic peroxides.[67] Cyclopropenes are either opened on treatment with $(AcO)_2Hg$ to produce allylic acetates[68] or undergo addition across the C=C bond (if the cleavage is suppressed by an electron-withdrawing group).[69]

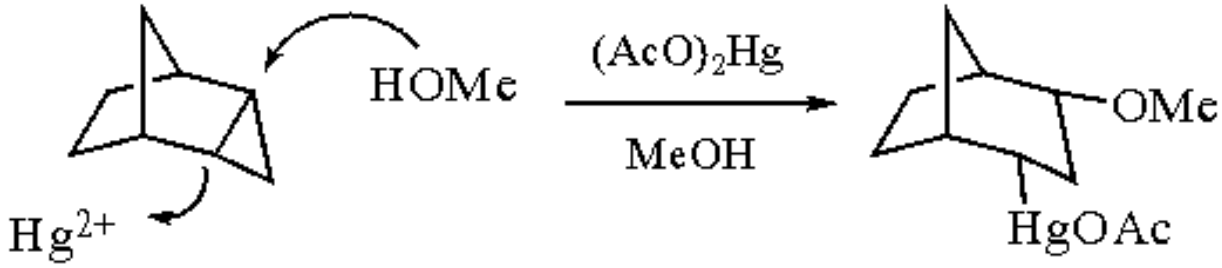

(16)

Allylic Oxidation.

At higher temperatures (typically 70-150 °C), alkenes are oxidized with $(AcO)_2Hg$ to give allylic acetates (eq 17; the Treibs reaction)[70,71] or dienes;[72] the yields vary in the range 20-70%.[73] Similarly, enolizable ketones and carboxylic

acids undergo α-acetoxylation, but the yield seldom surpasses other methods.[70] Certain alkenes are oxidized to α,β-unsaturated ketones.[74]

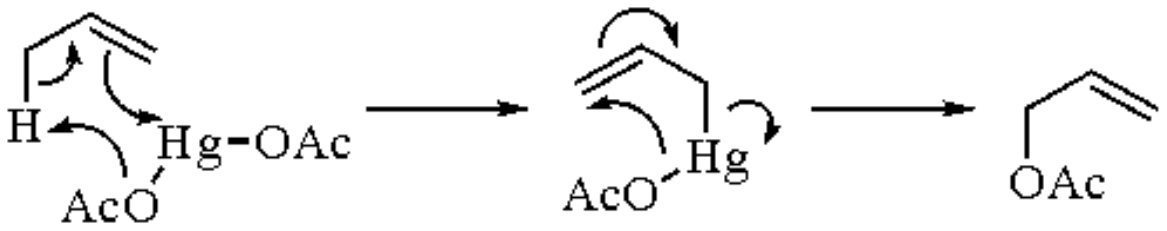

(17)

Mercuration of Aromatics.

Being an electrophile, $(AcO)_2Hg$ effects aromatic electrophilic substitution of reactive aromatics.[75] A strong *o*-directing effect of groups capable of coordination with Hg^{2+} has been observed. Thus, for instance, on treatment with $(AcO)_2Hg$ in boiling water followed by NaCl quenching, phenol affords exclusively *o*-chloromercuriophenol (eq 18).[76] Mercuration of the following aromatics and heteroaromatics[37c,d] has been described: acetanilide[77] and its derivatives,[78] aromatic Schiff bases,[79] 3,4,5-trimethoxybenzoic acid,[80] estradiol,[81] α-phenylpyridine,[82] furan,[83] furfuryl diacetate,[84] pyrrole,[83,85] thiophene,[86] 1,3-thiazole,[87] indole,[88] pyrimidines,[89] pyridazines,[90] diazines,[91] trithiadiazepine,[92] ferrocene,[93] tricarbonyl(η-cyclobutadiene)iron,[94] pentamethylruthenocene,[95] Ni^{II}, Pd^{II}, and Pt^{II} porphyrins,[96] and others.[1] Since organomercurials RHgX are readily converted to the corresponding bromide RBr on reaction with Br_2, Hg^{II} salts can serve as effective catalysts in aromatic bromination.[97] An indirect route to mercurioaromatics ArHgOAc is by transmetalation of the corresponding silyl[98] or stannyl[99] derivatives ($ArSiMe_3$ or $ArSnBu_3$) with $(AcO)_2Hg$.[98] The resulting organomercurials can be further transmetalated with borane.[98,99] Reversed transmetalation of organoboranes with $(AcO)_2Hg$ ($R^1BR^2_2$ -> R^1HgX) has also been described.[100]

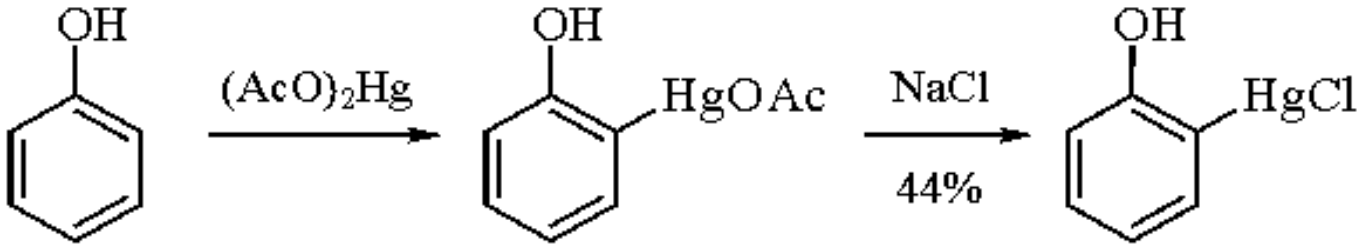

(18)

Mercuriaromatics are coupled to give bisaryl derivatives on catalytic reaction with $PdCl_2$[101] or $[Rh(CO)_2Cl_2]_2LiCl$[102,103] in a process similar to Ullmann coupling.

Dehydrogenation of Tertiary Amines.

Tertiary amines react with Hg^{II} to generate iminium salts (eq 19), which on treatment with base are converted into enamines.[104] Alternatively, the iminium intermediate can be trapped by an internal nucleophile (eq 19).[105] The reaction is improved by adding ethylenediaminetetraacetic acid (EDTA).[106]

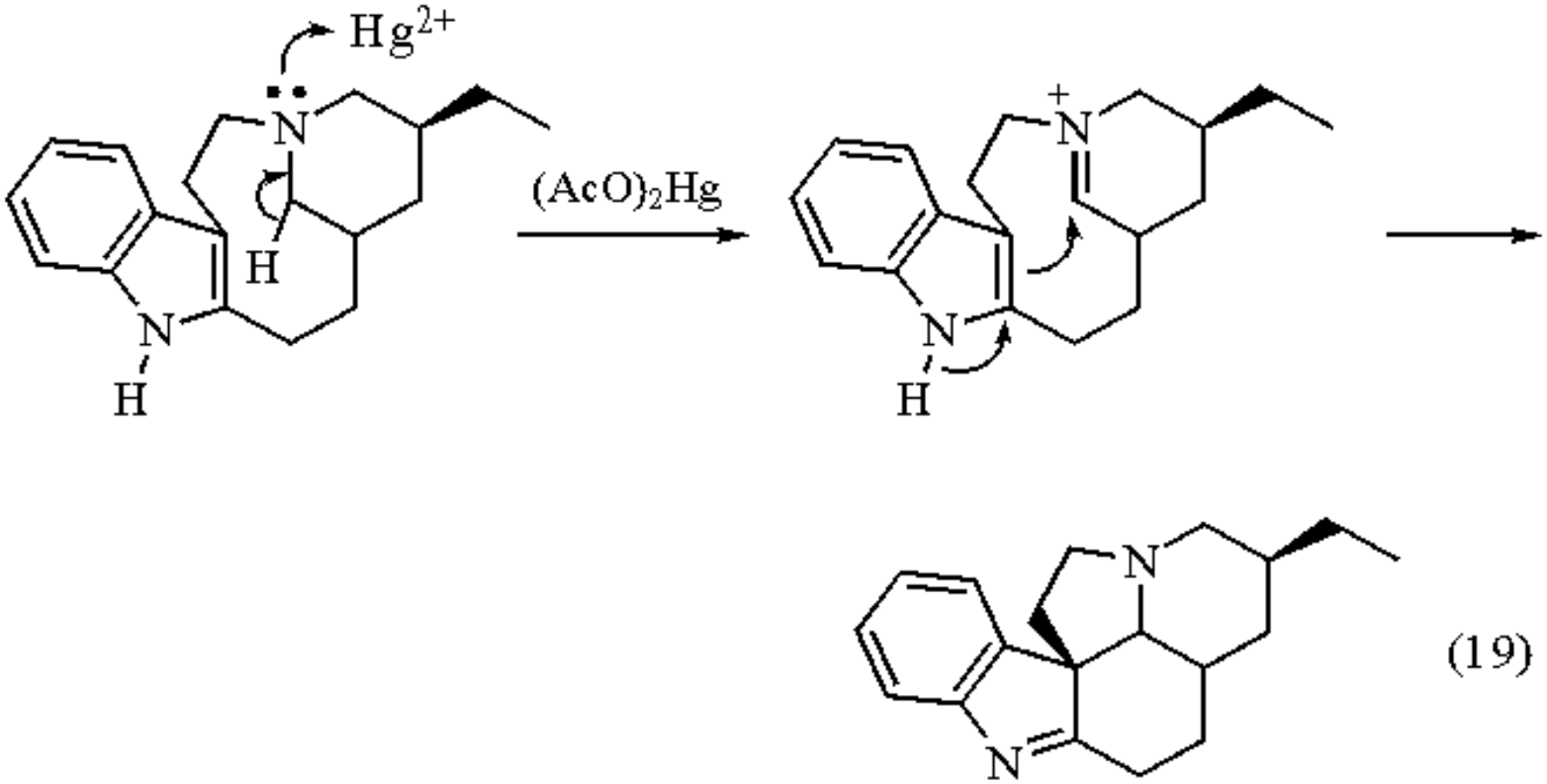

(19)

Miscellaneous Reactions.

$(AcO)_2Hg$ has been found to oxidize α-amino ketones to α-dicarbonyl compounds (50-95%),[107] to effect *cis* -> *trans* isomerization of alkene,[108] to induce hydrolysis of vinyl chlorides to the corresponding ketones (a modification of the Wichterle reaction),[109] to mediate Koenigs-Knorr-type reactions (in analogy to Ag^+),[110] to oxidize β-aminocyclohexenones to *m*-aminophenols,[111] to hydrate nitriles (to give primary amides),[112] to effect oxidative degradation of penicillins,[113] and to mediate Claisen rearrangement.[114] Trialkylboranes R_3B, obtained by hydroboration of alkenes, react with $(AcO)_2Hg$ and I_2 to afford terminal acetates ROAc; this is an alternative to the usual H_2O_2/OH^- oxidation.[115] This B -> Hg -> OAc transformation has also been accomplished with vinylic substrates.[100b] On treatment with $(AcO)_2Hg$ in MeOH followed by demercuration with KSCN, cinnamyl esters $PhCH{=}CHCH_2OCOR$ undergo cleavage to furnish $PhCH(OMe)CH{=}CH_2$ (eq 20). The reaction is catalyzed by HNO_3 (apparently, mercury(II) nitrate is the reactive species) and can be used for protection-deprotection of carboxylic acids.[116]

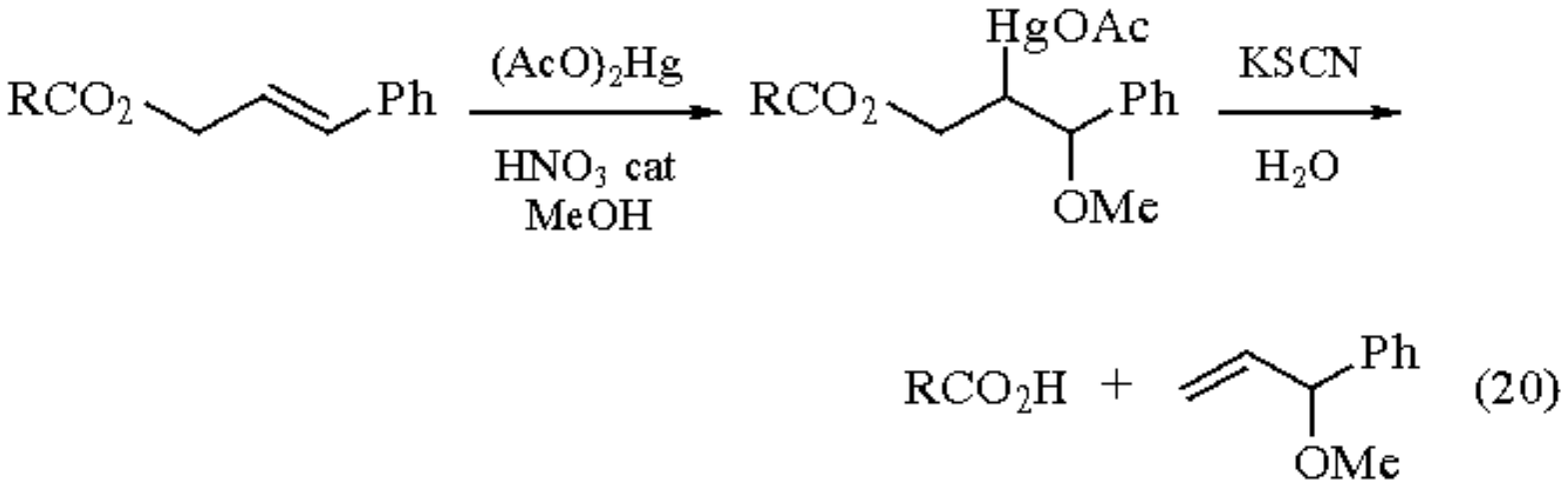

Related Reagents.

Mercury(II) Acetate-Ethylenediaminetetraacetic Acid; ***Mercury(II) Acetate-Sodium Trimethoxyborohydride***; ***Mercury(II) Nitrate***; ***Mercury(II) Perchlorate***; ***Mercury(II) Trifluoroacetate***; ***Thallium(III) Acetate***; ***Thallium(III) Trifluoroacetate***.

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Mercury(II) Acetate-Ethylenediaminetetraacetic Acid

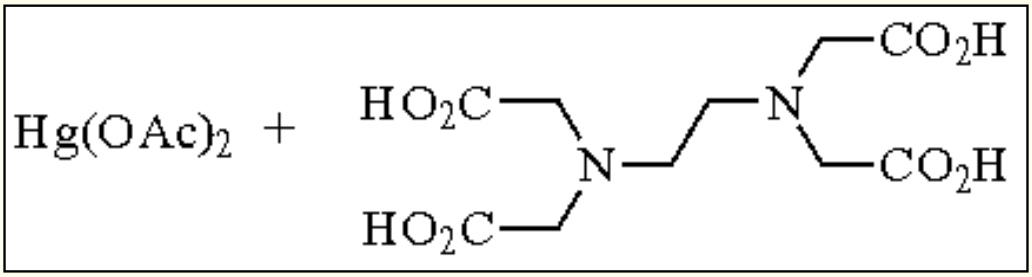

($Hg(OAc)_2$)

[1600-27-7] · $C_4H_6HgO_4$ · Mercury(II) Acetate-Ethylenediaminetetraacetic Acid · (MW 318.69) (EDTA)

[60-00-4] · $C_{10}H_{16}N_2O_8$ · Mercury(II) Acetate-Ethylenediaminetetraacetic Acid · (MW 292.28)

(dehydrogenation of tertiary amines,[2] oxidation of tertiary amines to amides[3])

Physical Data: $Hg(OAc)_2$: mp 179-182 °C. EDTA: mp 250 °C (dec).

Solubility: sol CH_2Cl_2, AcOH; slightly sol alcohols; insol benzene, hexane, etc.

Preparative Method: by simply mixing the two commercially available reagents in an appropriate solvent.

Handling, Storage, and Precautions: acute poison. $Hg(OAc)_2$ is easily absorbed through the skin and is corrosive. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

The addition of EDTA to Hg^{II} salts has a beneficial effect on the selectivity of dehydrogenation of tertiary amines (see also ***Mercury(II) Acetate***).[1] Thus papaverin has been reported to produce a mixture of two dehydrogenated products (eq 1) when treated with equal amounts of $(AcO)_2Hg$ and EDTA. By contrast, in the absence of EDTA, papaverin is cleaved at the methylene bridge.[2] Amine oxidation has also been employed in the construction of ajmalicine (eq 2)[3] and yohimbine.[4] In this case, only 2 equiv of Hg^{II} are required as opposed to 5 equiv if $(AcO)_2Hg$ is used alone.[4]

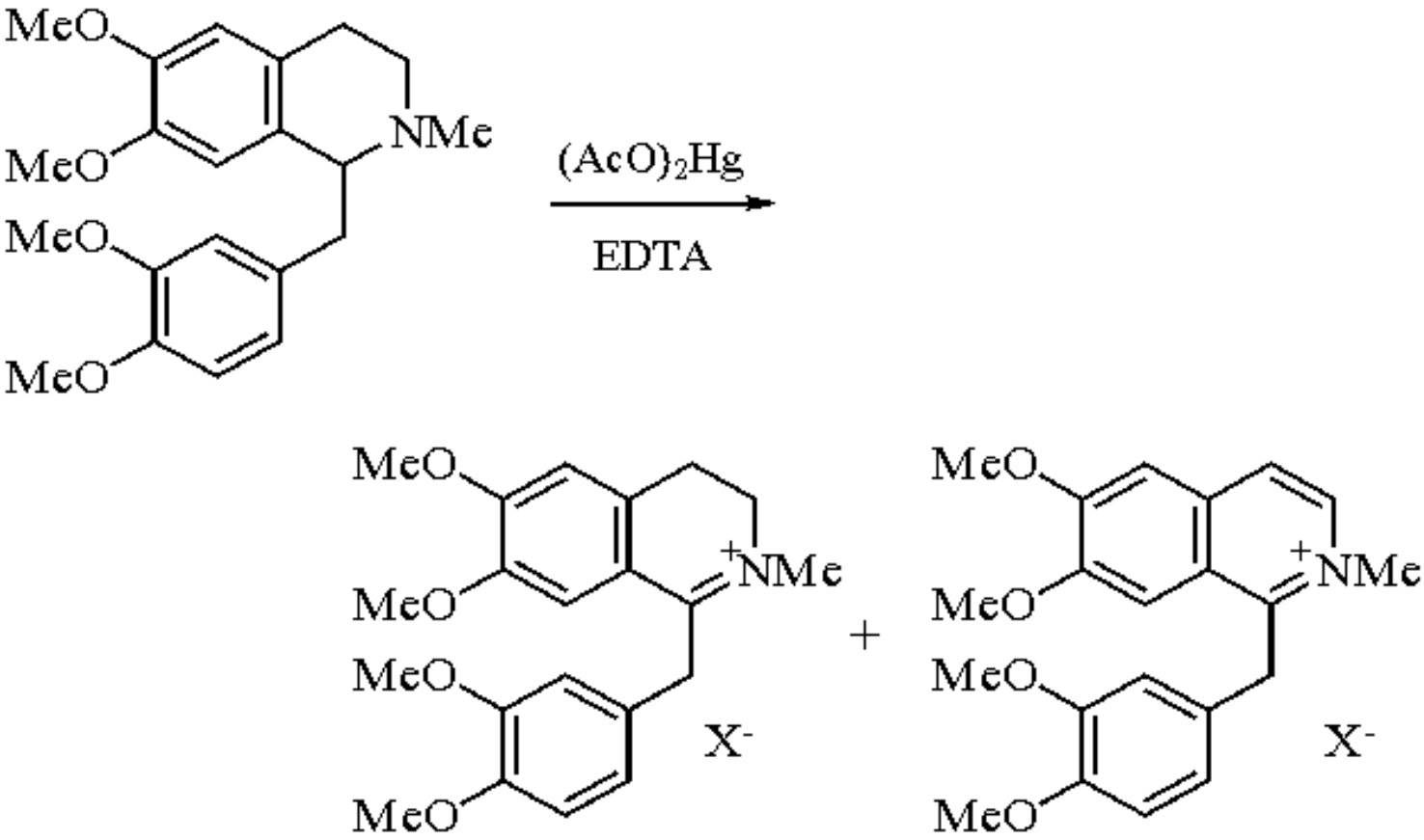

(1)

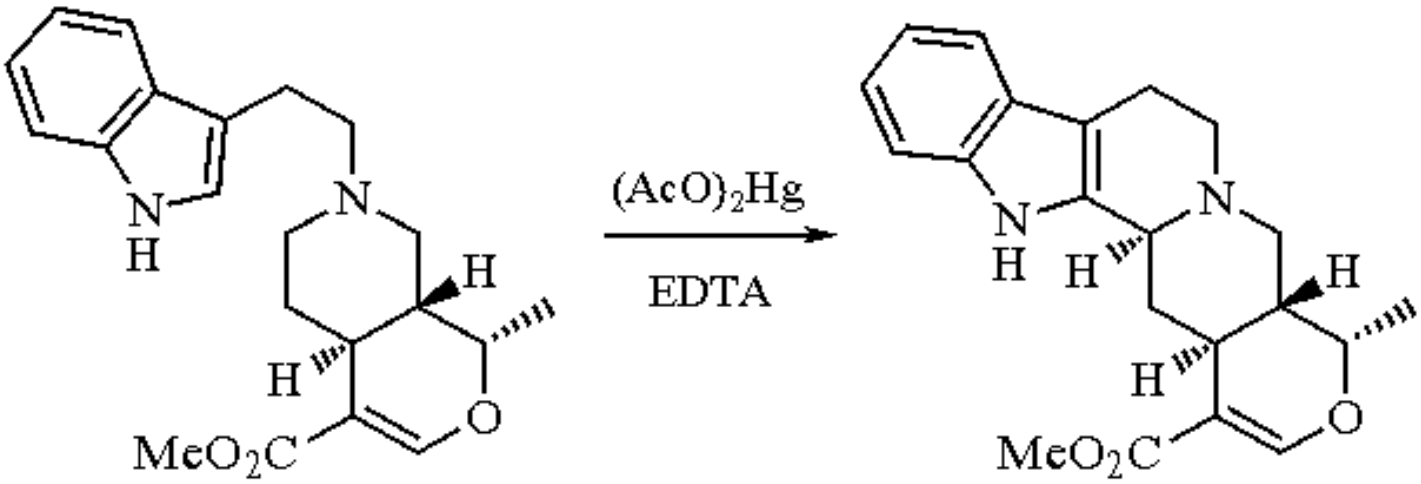

(2)

The mixture of $(AcO)_2Hg$ and EDTA can also convert oxidizable tertiary amines into lactams (eq 3).[5]

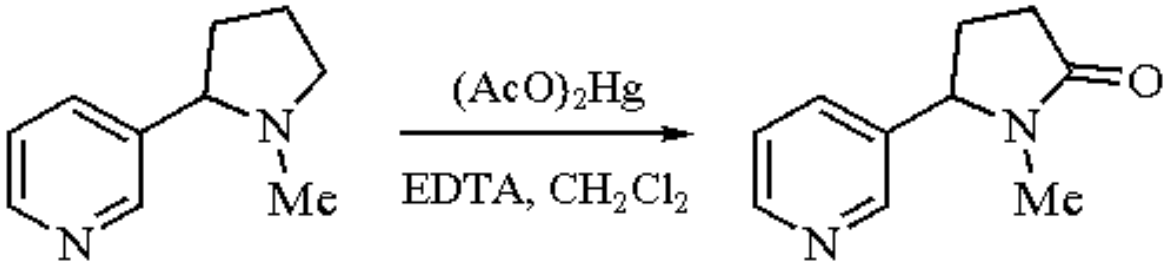

(3)

Related Reagents.

Mercury(II) Acetate; ***Mercury(II) Trifluoroacetate***.

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Mercury(II) Acetate-Sodium Trimethoxyborohydride[1]

$Hg(OAc)_2$-$NaBH(OMe)_3$

($Hg(OAc)_2$)

[1600-27-7] · $C_4H_6HgO_4$ · Mercury(II) Acetate-Sodium Trimethoxyborohydride · (MW 318.69)
($NaBH(OMe)_3$)

[16940-17-3] · $C_3H_{10}BNa$ · Mercury(II) Acetate-Sodium Trimethoxyborohydride · (MW 170.83)

(organomercury acetates are powerful reagents for radical carbon-carbon bond formation in combination with borohydrides[1])

Physical Data: mp 178-180 °C (overheating results in decomposition); *d* 3.27 g cm^{-3}.

Solubility: sol ethanol, methanol, acetic acid, ethylene glycol, hot water; slightly sol acetone, ethyl acetate, water.

Form Supplied in: white solid; widely available.

Purification: recrystallization from a mixture of hot ethanol, water, and acetic acid (10:10:1).

Handling, Storage, and Precautions: mercury(II) acetate has a slight acetic odor; forms white light-sensitive crystals. Keep well closed and protected from light. Inhalation of mercury(II) acetate dust should be avoided: wearing of protecting gloves for handling this compound is recommended. Extremely toxic. Use in a fume hood.

Reduction of Organomercury Acetates.

Reaction of ***Mercury(II) Acetate*** with alkenes, cyclopropanes, ketones, organoboron and metalloorganic compounds leads to organomercury acetates.[2] On reduction with ***Sodium Borohydride*** or ***Sodium Trimethoxyborohydride*** they give organomercury hydrides,[3] which are potential precursors for carbon radicals. In the presence of alkenes, crossed-coupled products are formed in a radical chain process. To achieve high yields, electron-poor alkenes like acrylonitrile, vinyl ketones, acrylates, fumarodinitrile, or maleic anhydrides should be used.[4] Compared with the tin method, the mercury method has the advantages of mild reaction conditions (20 °C), short reaction times (30-60 min), and easy workup procedures (after filtration of the precipitated mercury, distillation of the residual product).

Alkenes.

Alkenes with an electron-rich terminal double bond can be coupled with electron-poor alkenes in a one pot reaction.[5] The reaction proceeds via hydroboration of the alkene, transformation of the boron-carbon into a mercury-carbon bond, and reaction with $NaBH_4$ and alkene. The reaction conditions tolerate substituents like Br, Cl, OH, OAc, OTs, OR, and CO_2R. Alkenes with two different substituted double bonds react regioselectively (eq 1).[5] An example of the high stereoselectivity of this method is demonstrated in the reaction of β-pinene (eq 2).[5]

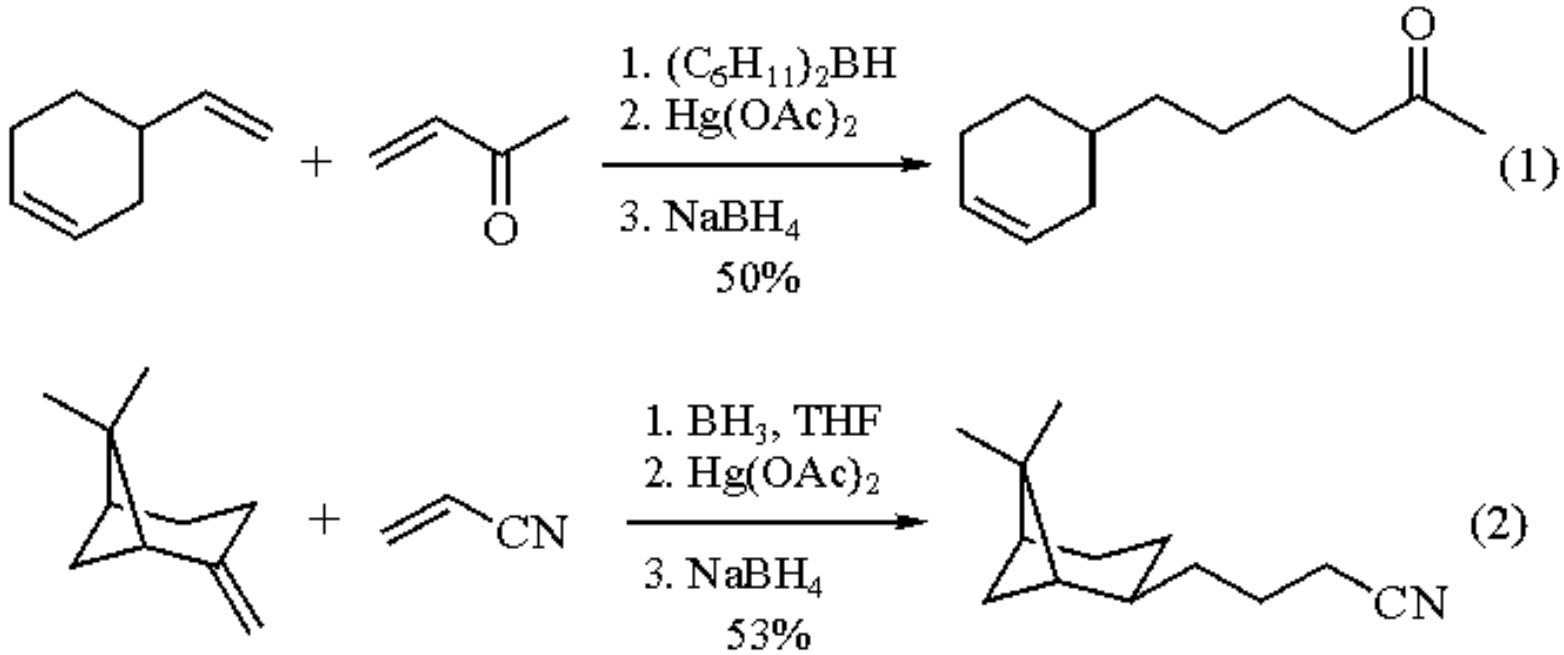

The reaction of mercury salts with electron-rich alkenes yields different β-substituted organomercury acetates via addition of the electrophilic mercury ion to the double bond and subsequent trapping by nucleophilic solvent (water, alcohol, acids).[6] The addition reaction follows the Markovnikov rules (eq 3).[7]

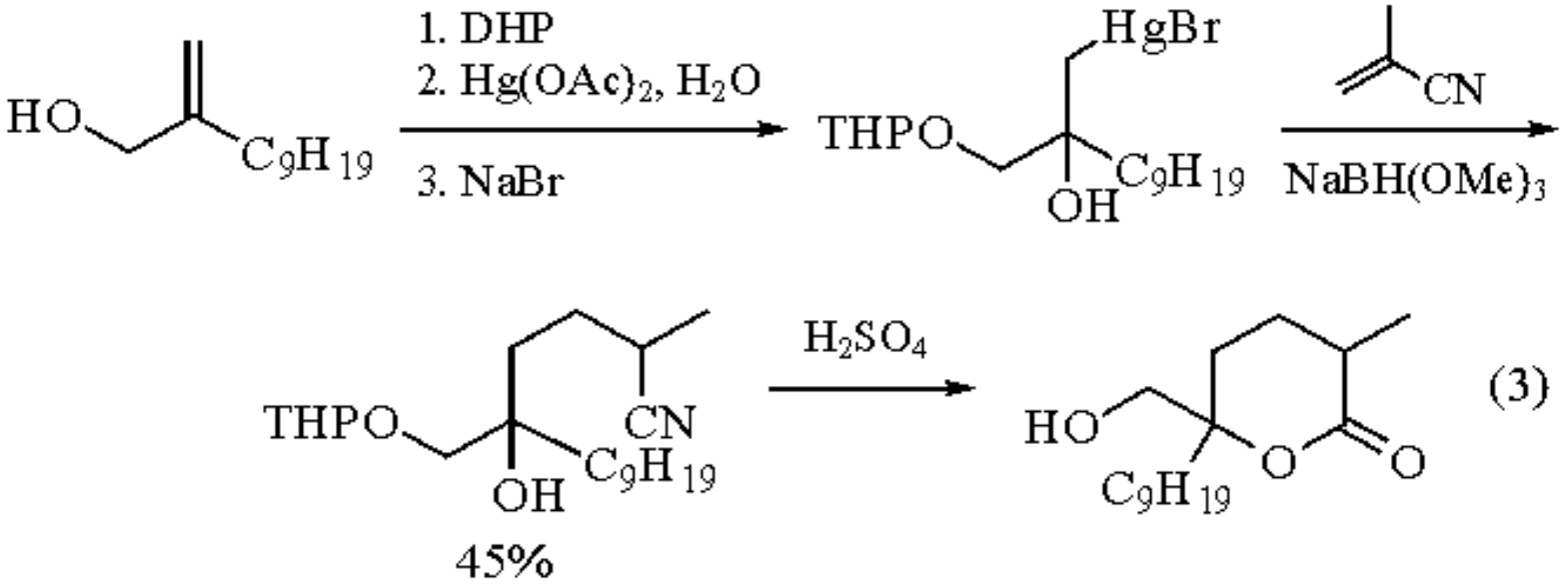

Alkenes with nucleophilic neighboring groups such as alcohols (eq 4), carboxylates (eq 5), amides, amines, and

alkenes, lead to cyclic products in the mercuration/reductive coupling sequence.[8] The nucleophiles act as intramolecular traps for the mercurated alkenes.

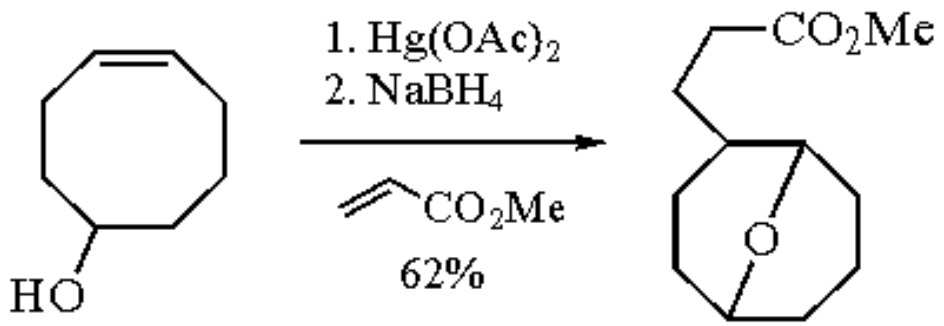

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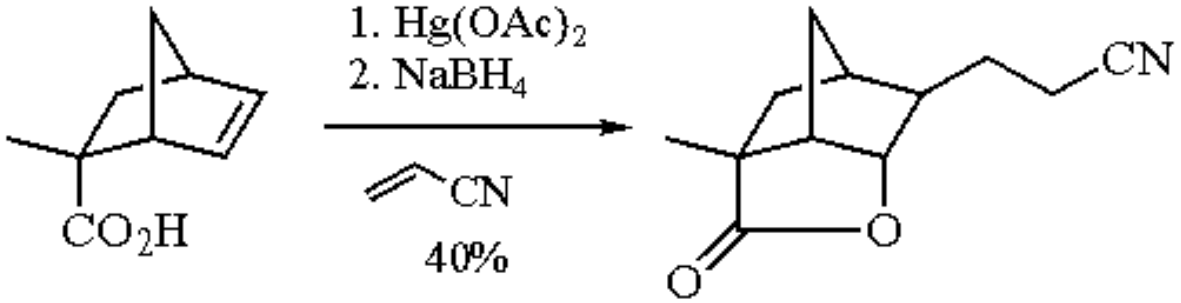

(5)

Cyclopropanes.

The ring opening of cyclopropanes proceeds by attack of mercury acetate at the least substituted ring position and ring opening towards the most substituted position. Different functional groups are introduced into the products by varying solvents (see above).[9] The acyclic organomercury salt can be coupled with an alkene (eq 6).[10]

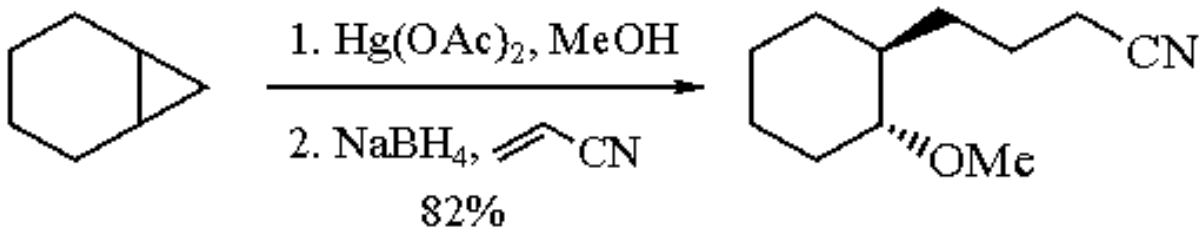

(6)

Carbonyl compounds can act as precursors for cyclopropanes. An aldehyde or ketone is converted to its trimethylsilyl enol ether which is then subjected to the Simmons-Smith cyclopropanation reaction (eq 7).[11]

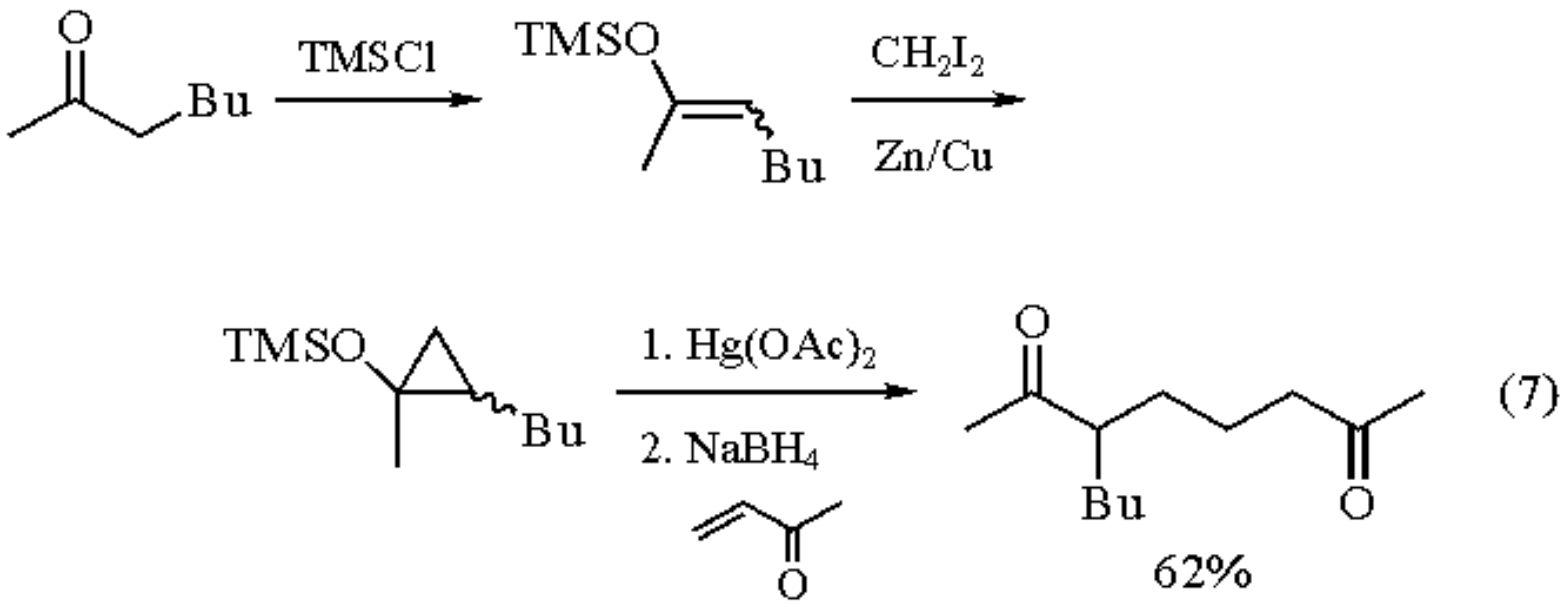

Ketones.

Ketones can be coupled with electron-poor alkenes via hydrazones.[12,13] A large variety of ketones can be used; the bulky *t*-butyl group is tolerated (eq 8).[14] With sterically hindered starting materials or less reactive alkenes, as a side reaction the reduction products are formed.

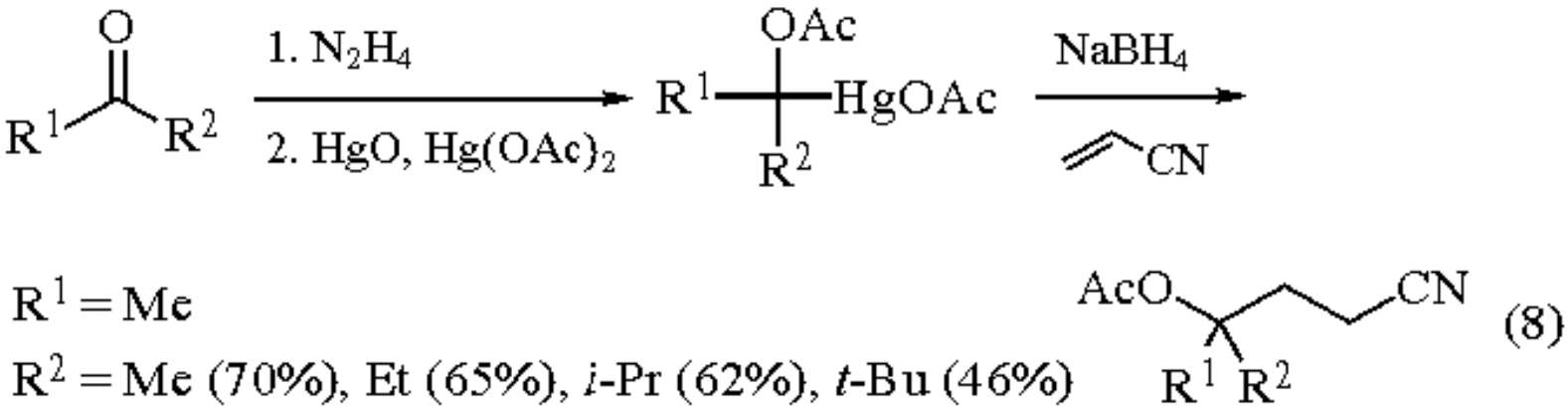

The reactions of norcamphor derivatives illustrate how an electrophilic carbon of a carbonyl group can be coupled with electron-poor alkenes (umpolung) (eq 9).[15]

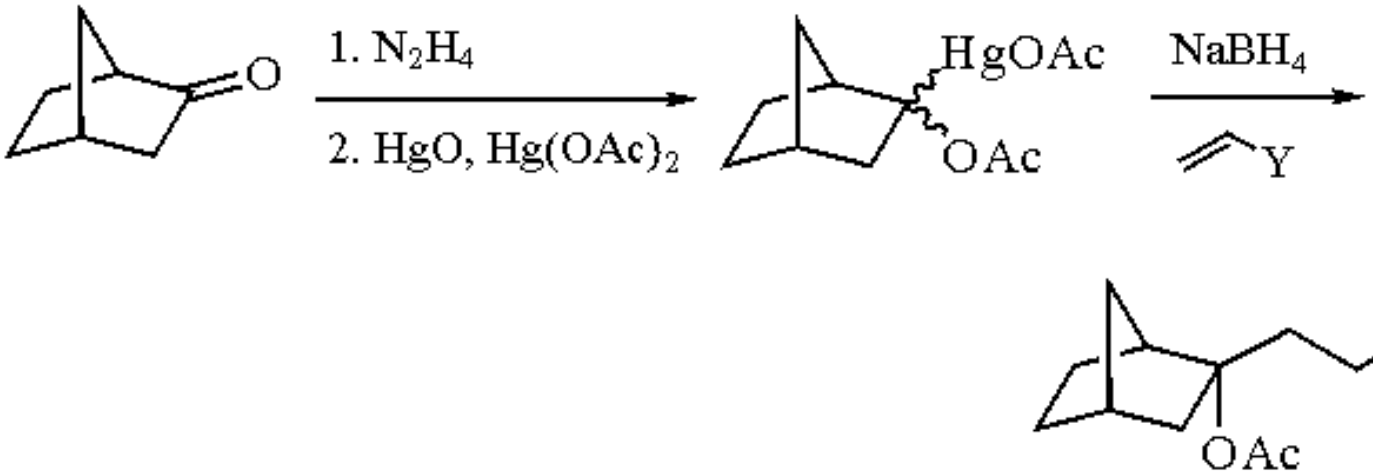

(9)

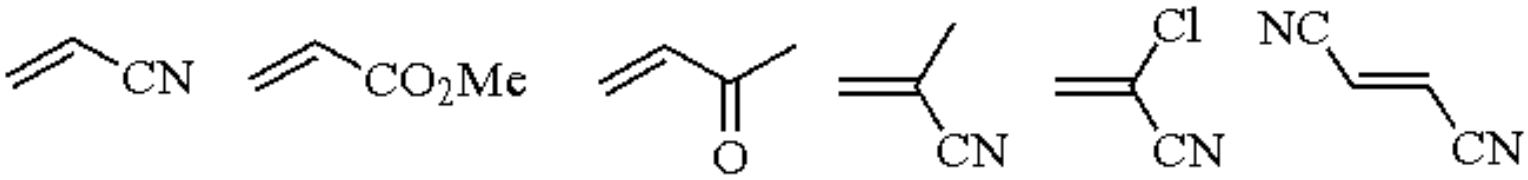

77% 75% 60% 58% 81% 52%

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Bernd Giese & Joachim Dickhaut

University of Basel, Switzerland

Mercury(II) Chloride[1]

$HgCl_2$

[7487-94-7] · Cl_2Hg · Mercury(II) Chloride · (MW 271.49)

(electrophilic mercuration of multiple bonds;[1] cleavage of vinyl sulfides and thioacetals;[17] transmetalation;[1] preparation of amalgams[30-33])

Alternate Name: mercuric chloride.

Physical Data: mp 277 °C; bp 302 °C; *d* 5.440 g cm^{-3}.

Solubility: sol H_2O, alcohol, ether, glycerol, acetic acid, acetone, ethyl acetate; slightly sol benzene, pyridine, CS_2.

Form Supplied in: white rhombic crystals.

Handling, Storage, and Precautions: violent poison; may be fatal if swallowed in 0.2-0.4 g doses. Exposure to any mercury reagent is to be avoided. Teratogen; mutagen; irritant. Reacts violently with K, Na. Releases toxic Hg vapor when heated to decomposition. Handle in a fume hood.

Electrophilic Attack on Multiple Bonds.

Although less electrophilic than other Hg^{II} reagents, $HgCl_2$ has been successfully employed in electrophilic cyclization of various dienes[1,2] (see also ***Mercury(II) Acetate***) (eq 1);[3] an allylic hydroxyl controls the diastereoselectivity of the latter reaction.[3] Aromatization of certain conjugated systems has also been observed on treatment with $HgCl_2$.[4] Similar to Tl^{I} salts,[5] $HgCl_2$ promotes iodocyclization of alkenic alcohols.[6] In the presence of a halogen (Cl_2 or Br_2), $HgCl_2$ facilitates halogenation of a C=C bond.[2]

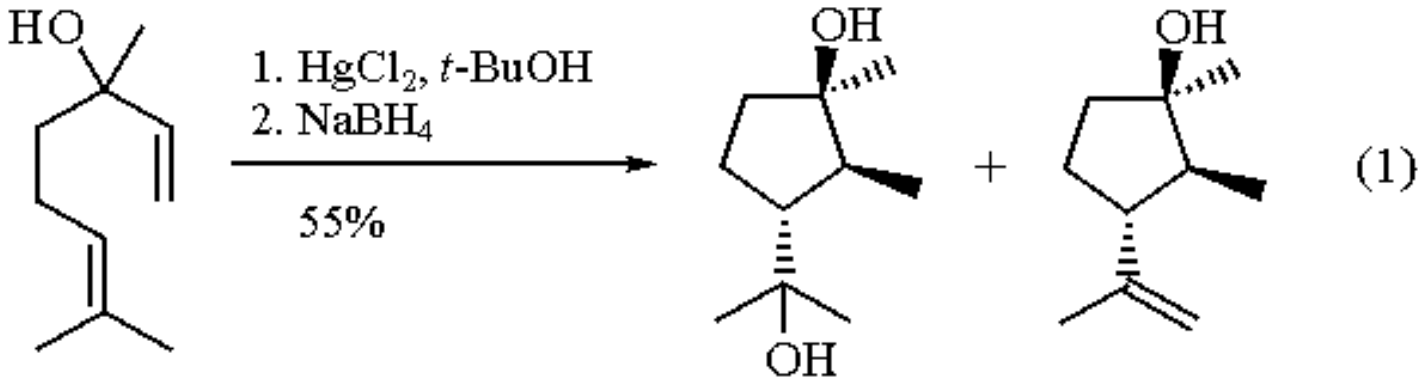

Intramolecular aminomercuration of δ,ε-unsaturated amines has also been accomplished with $HgCl_2$[7,8] (eq 2).[8] The stereochemistry of the reaction is solvent dependent[8] and may be reversible.[9]

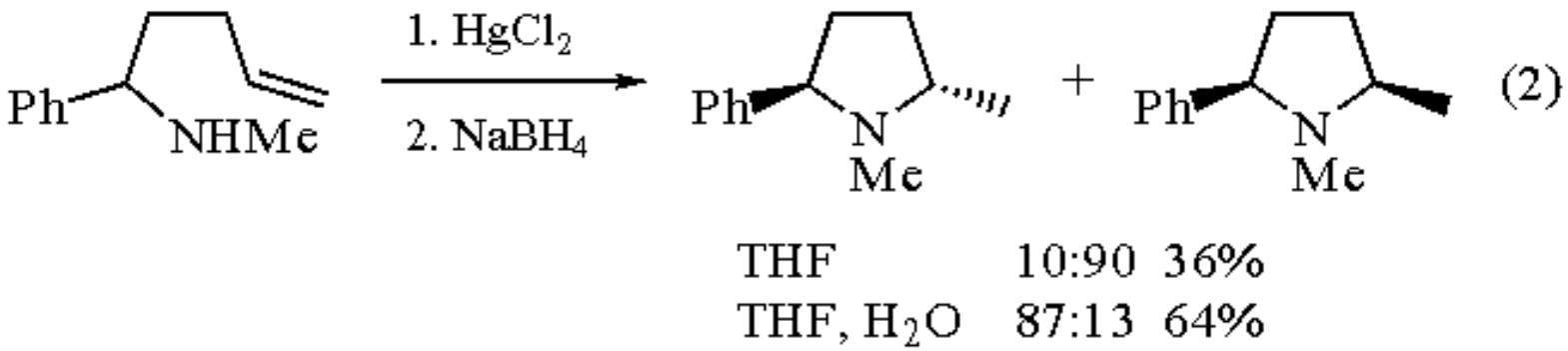

Terminal alkynes (RC&tbond;CH) add MeOH in the presence of ***Triethylamine*** and a catalytic amount of $HgCl_2$ to give enol ethers of the corresponding ketones ($RC(OMe)=CH_2$).[10] This reaction parallels the well-known $HgSO_4$-catalyzed hydration of alkynes, producing ketones. 3-Alken-1-ynes undergo catalytic aminomercuration in the presence of $HgCl_2$ at 70 °C over 3-6 h to produce enamines.[11] By contrast, propargylic alcohols (HC&tbond;CCH_2OH) undergo oxidative aminomercuration to afford bis-aminated aldehydes, e.g. (*Z*)-PhNHCH=C(NHPh)CH=O.[12] Propargyl amines (HC&tbond;C-CH_2NR_2) add $HgCl_2$ in aqueous HCl to give ClCH=C(HgCl)-CH_2NR_2.[13]

Treatment of silyl enol ethers of ε-alkynic ketones or aldehydes with $HgCl_2$ (1.1 equiv) and ***Hexamethyldisilazane*** (0.2 equiv; acid scavenger) induces cyclization (eq 3).[14]

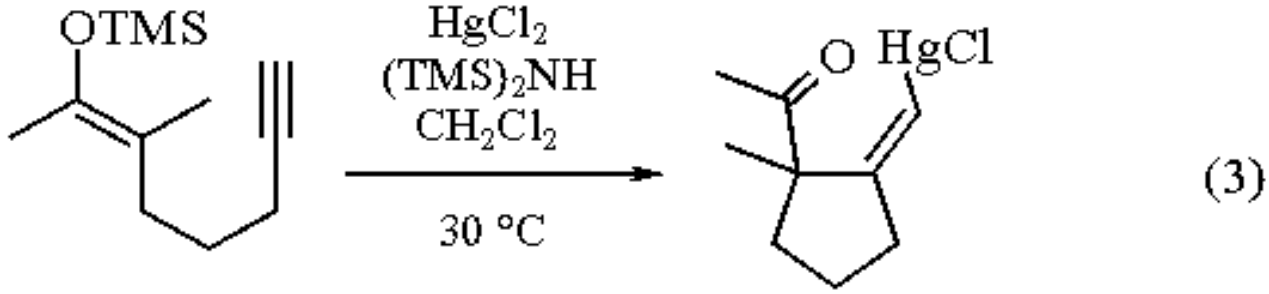

Enol ethers derived from carbohydrates can be readily converted into carbocycles via a $HgCl_2$-mediated reaction which involves an electrophilic attack at the C=C bond to generate the corresponding ketoaldehyde, which cyclizes

spontaneously via an intramolecular aldol condensation (eq 4).[15]

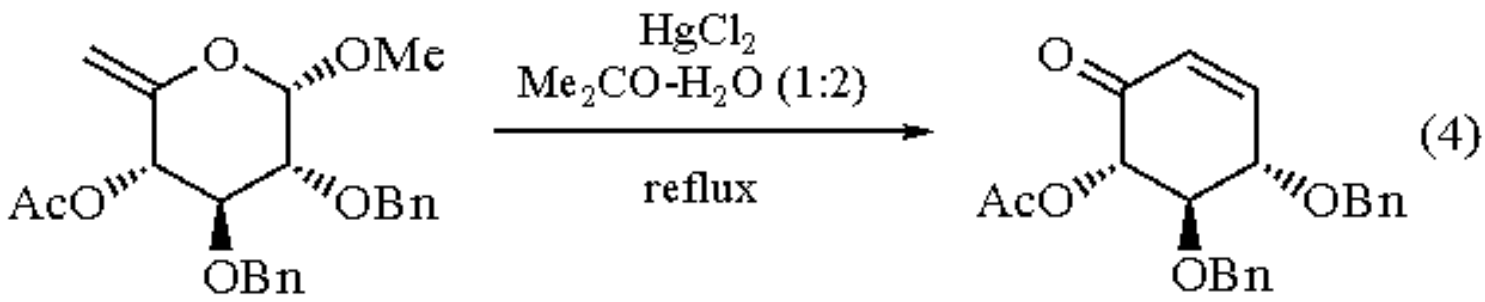

Aldehydes $RCH_2CH{=}O$ (R = Me, Et) afford α,α-bischloromercurated products on treatment with excess $HgCl_2$.[16]

Hydrolysis of Vinyl Sulfides and Thioacetals to Carbonyl Compounds.[17]

Whereas the hydrolysis of vinyl sulfides to ketones works well with a mixture of $HgCl_2$ and an additive (HgO, $CaCO_3$, or $CdCO_3$), the reaction leading to aldehydes often gives unsatisfactory results. In this case, yields can be dramatically improved if HCl is first added across the double bond of the vinyl sulfide (RCH=CHSPh) to generate R-$CH_2CH(Cl)SPh$. The latter intermediate is then quantitatively hydrolyzed by $HgCl_2$ and water to the aldehyde $RCH_2CH{=}O$.[18]

Thioacetals[19,20] and *O*,*S*-acetals[21] are hydrolyzed by means of $HgCl_2$ to the corresponding carbonyl compounds; addition of ***Calcium Carbonate*** usually improves the yields (see also ***Mercury(II) Chloride-Cadmium Carbonate***). This method, involving spontaneous spirocyclization of the resulting keto group, has been employed in the synthesis of talaromycin B (eq 5).[20]

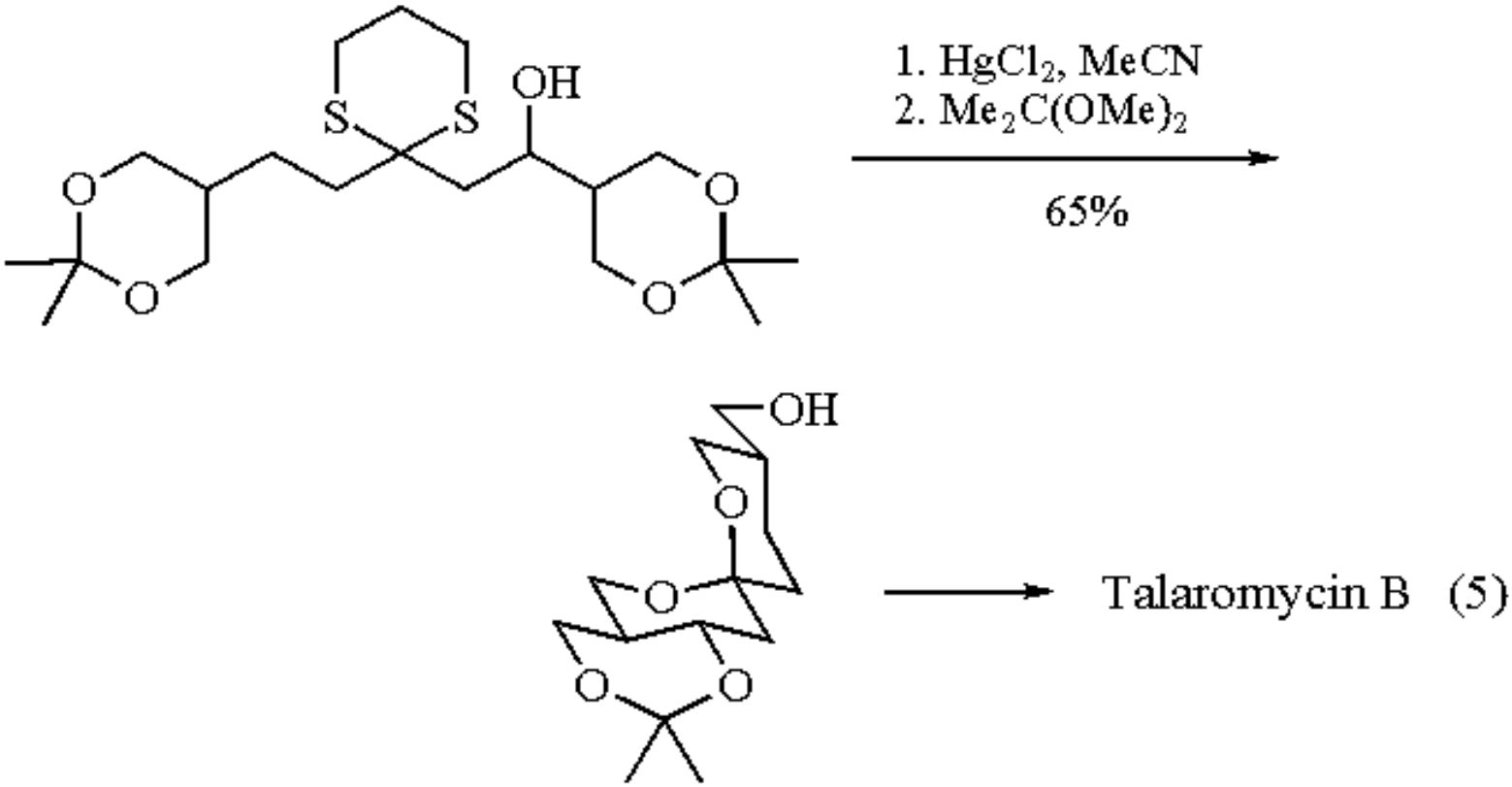

Methylthiomethyl (MTM) ethers can be converted into 2-methoxyethoxy (MEM), methoxymethyl (MOM), or ethoxymethyl (EOM) ethers on reaction with $HgCl_2$ and $MeOCH_2CH_2OH$, MeOH, or EtOH, respectively, in 70-80% yields.[22]

Addition of $HgCl_2$ to boronate ate complexes derived from *O*,*S*-acetals induces B -> C migration. This sequence has been used to obtain optically pure aldehydes (eq 6).[23] Selenoacetals are similarly hydrolyzed by $HgCl_2/CaCO_3$ in acetonitrile.[24]

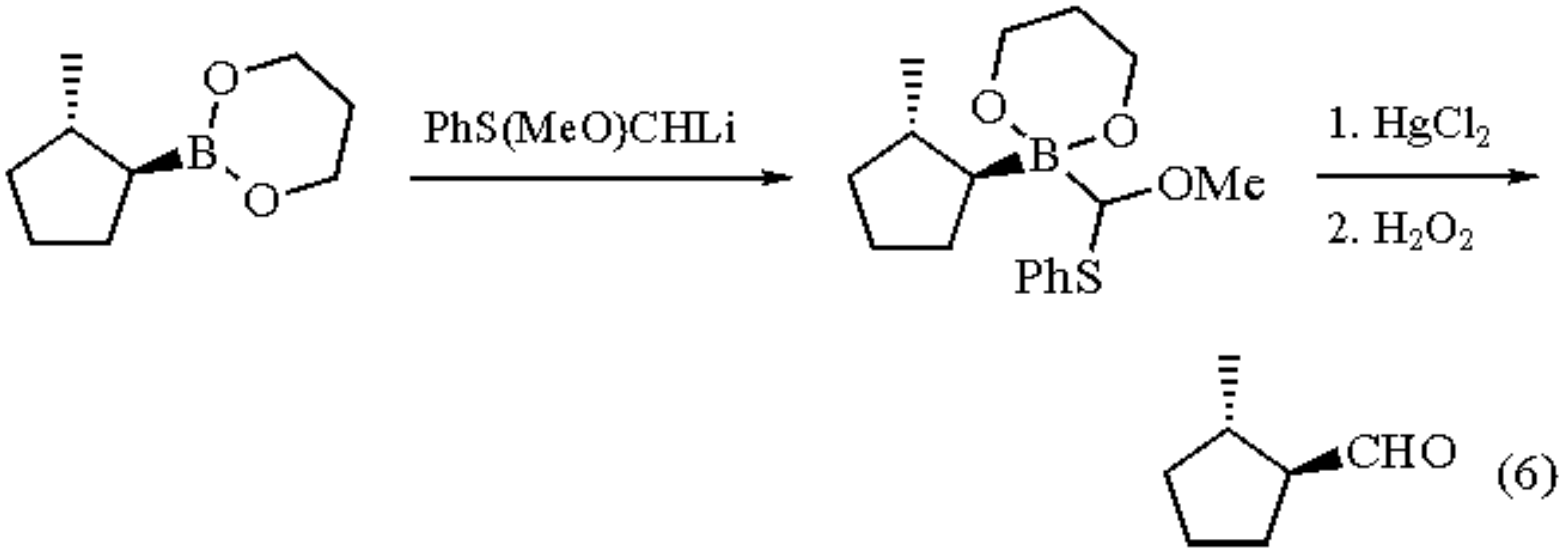

Preparation of Organomercurials by Exchange Reactions.

Among the methods developed for the synthesis of organomercurials is the transmetalation of other organometallics with $HgCl_2$ (e.g. ArLi -> ArHgCl or RMgCl -> RHgCl),[1,25] and reactions of aromatic diazonium salts with $HgCl_2$ and copper (ArN_2^+ Cl^- -> ArHgCl).[26] The yields in the latter methods do not exceed 50%.[25] Sodium *p*-toluenesulfinate is also converted into the corresponding organomercurial (MeC_6H_4HgCl) on reaction with $HgCl_2$.[27] Vinylmercury chlorides (RCH=CH-HgCl) can be prepared by transmetalation of the corresponding vinylalanes, which, in turn, are available from terminal alkynes; the transmetalation occurs with >98% retention of configuration.[28] A stable metalated cubane derivative has been obtained by lithiation of the diisopropylamide of cubanecarboxylic acid with ***Lithium 2,2,6,6-Tetramethylpiperidide*** followed by transmetalation with $HgCl_2$.[29] Reversed transmetalation (cubane-HgCl -> cubane-Li) has also been described.[29]

Amalgams.

Mercury(II) chloride has been extensively utilized for the preparation of a variety of amalgams (e.g. Zn,[30] Mg,[31] and Al)[32,33] to be employed in reductive processes such as Clemmensen reduction (with Zn)[30] or pinacol coupling (Mg),[31] and to prepare, for example, aluminum ethoxide[32] and *t*-butoxide.[33]

Miscellaneous.

Penam derivatives result from the $HgCl_2$-promoted ring closure of azetidin-2-one.[34] Mercury(II) chloride seems to be a reagent of choice for isolation of histidine from a mixture of amino acids in the form of an insoluble complex.[35] In combination with iodine, $HgCl_2$ facilitates α-iodination of enolizable ketones and aldehydes.[36]

Related Reagents.

Mercury(II) Chloride-Cadmium Carbonate; ***Mercury(II) Chloride-Silver(I) Nitrite***.

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Mercury(II) Chloride-Cadmium Carbonate

$HgCl_2$-$CdCO_3$

($HgCl_2$)

[7487-94-7] · Cl_2Hg · Mercury(II) Chloride-Cadmium Carbonate · (MW 271.49) ($CdCO_3$)

[513-78-0] · $CCdO_3$ · Mercury(II) Chloride-Cadmium Carbonate · (MW 172.42)

(hydrolysis of thioacetals;[1-5] glycosylation[10])

Preparative Method: from the components in situ.

Handling, Storage, and Precautions: acute poison. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

The mixture of ***Mercury(II) Chloride*** and ***Cadmium Carbonate*** serves as a mild reagent for the hydrolysis of thioacetals[1-3] and 1,3-dithianes (eqs 1-3).[4-7] This method is particularly suited to the synthesis of chiral ketones from chiral aldehydes (using the umpolung methodology) because only a little racemization occurs at the α-carbon.[4,5]

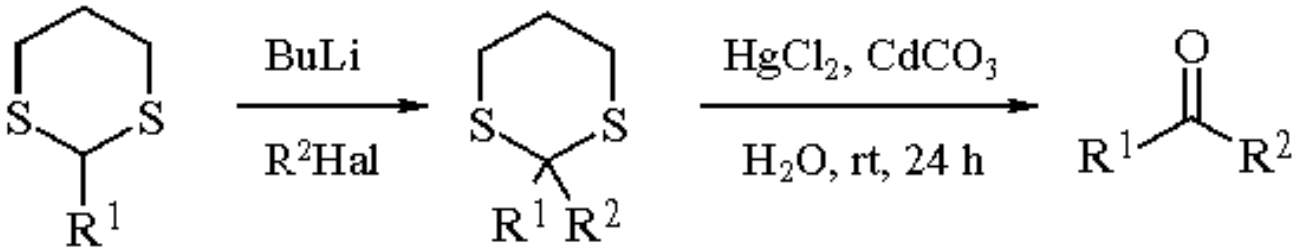

(1)

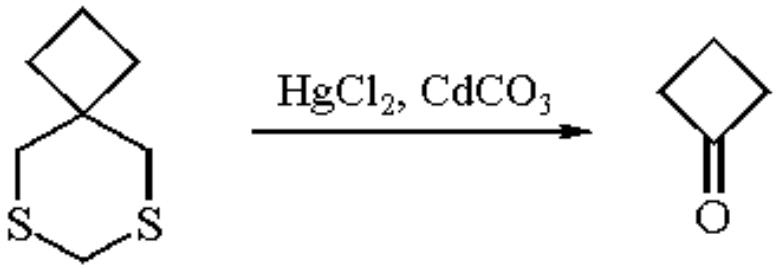

(2)

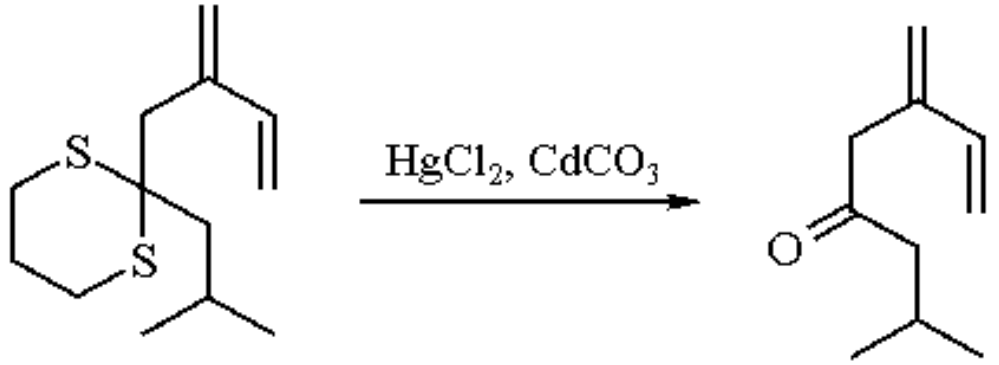

(3)

Thioacetals derived from aldehydes often give lower yields than those made from ketones; in these cases the ***Mercury(II) Oxide/Boron Trifluoride Etherate*** mixture in THF/H_2O is recommended.[8]

Thioglycosides react with alcohols such as cardenolides in the presence of $HgCl_2$ and $CdCO_3$ to give the corresponding glycosides.[9] This reaction is generally nonstereoselective (e.g. both α- and β-glycosides are formed). However, neighboring group participation can ensure that only one anomer is produced in a kinetically controlled reaction (eq 4).[10]

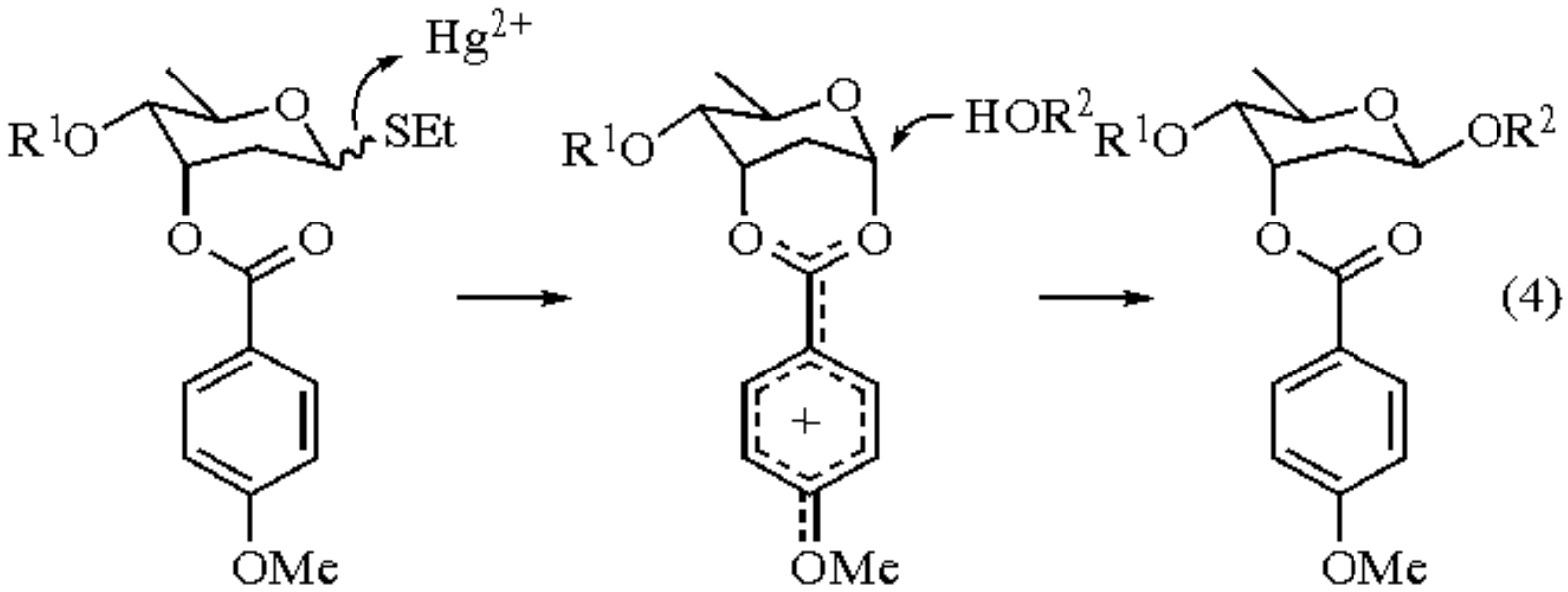

(4)

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Mercury(II) Chloride-Silver(I) Nitrite

$HgCl_2$-$AgNO_2$

($HgCl_2$)

[7487-94-7] · Cl_2Hg · Mercury(II) Chloride-Silver(I) Nitrite · (MW 271.49) ($AgNO_2$)

[7783-99-5] · $AgNO_2$ · Mercury(II) Chloride-Silver(I) Nitrite · (MW 153.88)

(nitromercuration[1-4] and synthesis of nitroalkenes from alkenes[4,5])

Form Supplied in: white, odorless needles or powder (both reagents).

Handling, Storage, and Precautions: acute poison. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Mixing ***Mercury(II) Chloride*** and ***Silver(I) Nitrite*** generates $Hg(NO_2)_2$ in situ, which reacts with alkenes to give nitromercuration products with high regio- and stereoselectivity (eq 1).[1-3] The reaction with norbornene occurs without rearrangement, indicating that carbocationic character in the transition state is little developed. On treatment with a base (NaOH or R_3N), the primary adducts undergo an elimination reaction to afford nitroalkenes (eq 1).[4] This two-step transformation represents a general route to nitroalkenes[4] and has been employed in the synthesis of 3-nitrocycloalkenones[5] and (*E*)-2-nitrovinyltrimethylsilane.[6] However, better yields are usually obtained if $AgNO_2/I_2$ is used instead.[7]

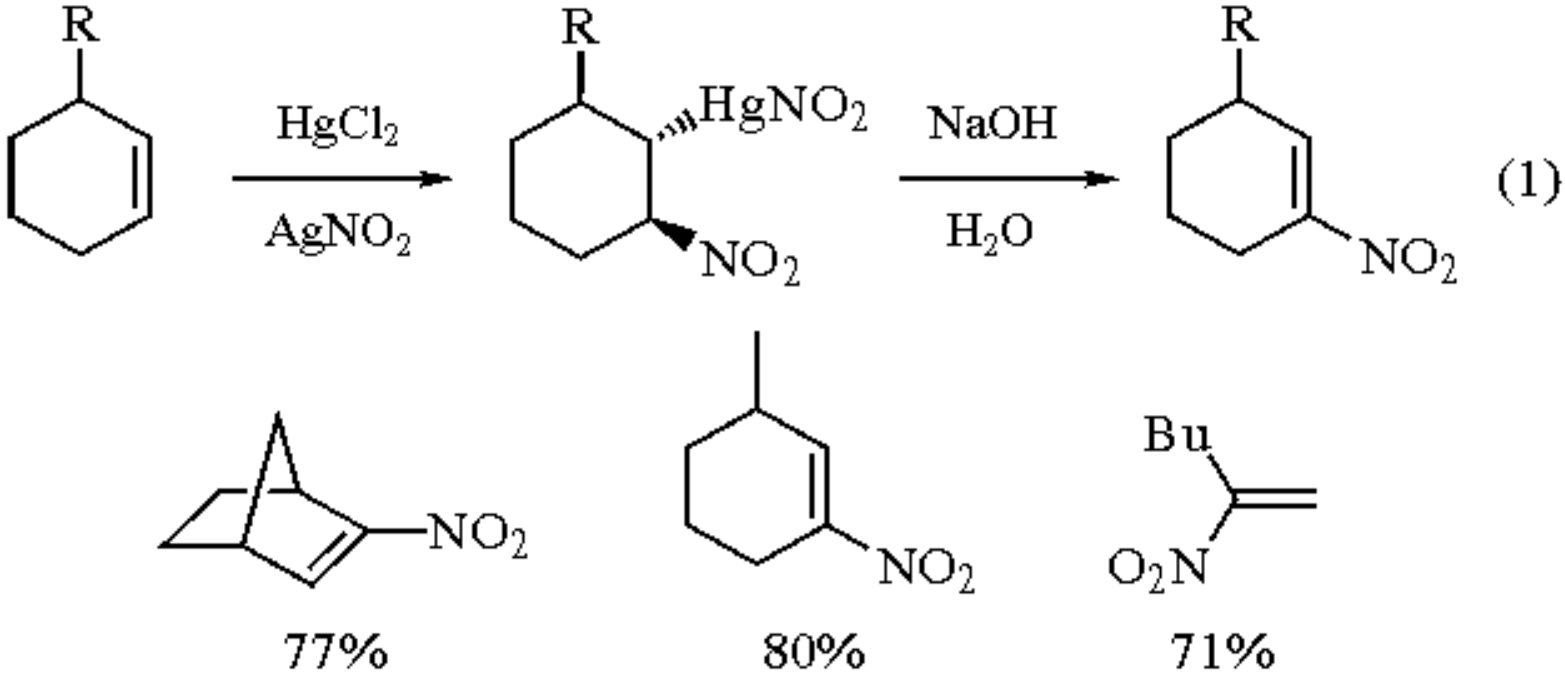

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Mercury(II) Cyanide

$Hg(CN)_2$

[592-04-1] · C_2HgN_2 · Mercury(II) Cyanide · (MW 252.63)

(glycosidation reagent[1])

Alternate Name: mercuric cyanide.

Physical Data: mp 320 °C dec; *d* 3.996 g cm^{-3}.

Solubility: insol benzene; sol H_2O, alcohol, NH_3; slightly sol ether.

Form Supplied in: colorless, odorless, tetragonal crystals or white powder.

Handling, Storage, and Precautions: acute poison. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Mercury(II) cyanide is sometimes superior to Ag_2CO_3 in the formation of glycosides from bromo sugars with isolated yields up to 90%; $MeNO_2$ or CH_2Cl_2 seem to be the best solvents.[1] Evomonoside, a steroidal cardioactive glycoside, has been prepared from digitoxigenin in 44% yield;[2] attempted synthesis with Ag_2CO_3 failed because of an extensive elimination of the 14β-OH of the aglycon.[2] Nucleosides can be obtained from pyrimidine bases and protected halo sugars by heating with $Hg(CN)_2$ in an inert solvent (toluene, MeCN, or $MeNO_2$).[3]

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Mercury(II) Fluoride[1]

HgF_2

[7783-39-3] · F_2Hg · Mercury(II) Fluoride · (MW 238.59)

(fluorinating reagent)

Alternate Name: mercuric fluoride.

Physical Data: mp 645 °C, bp >650 °C, *d* 8.95 g cm^{-3}.

Solubility: hydrolyzes in water; slightly sol MeCN, DMSO.

Form Supplied in: white powder.

Handling, Storage, and Precautions: turns yellow on exposure to moist air; highly toxic.

Metathesis Reactions.

Mercury(II) fluoride has been used to replace chlorine,[2] bromine,[3] and iodine[4] at sp^3 carbon with fluorine, as shown in eqs 1-3. In cases where a typical S_N2 reaction occurs, ***Potassium Fluoride*** in the presence of ***18-Crown-6*** is a better reagent. However, for highly halogenated compounds,[5] HgF_2 is the reagent of choice.

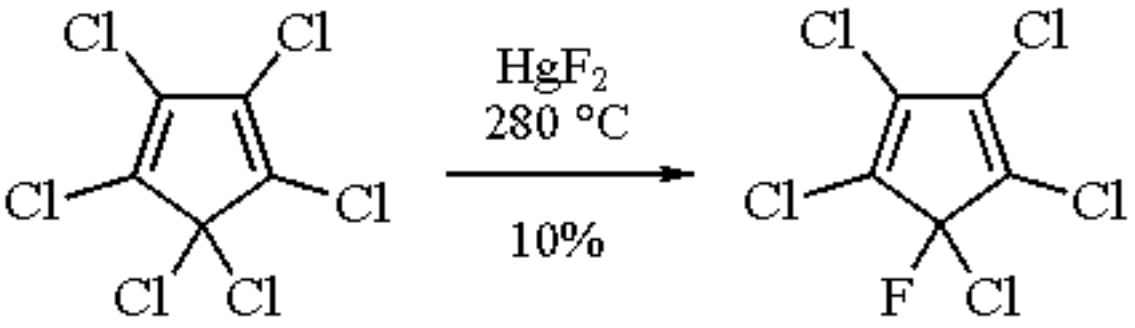

(1)

$$1\text{-}C_8H_{17}Br \longrightarrow \underset{23\%}{1\text{-}C_8H_{17}F} + \underset{27\%}{2\text{-}C_8H_{17}F} \qquad (2)$$

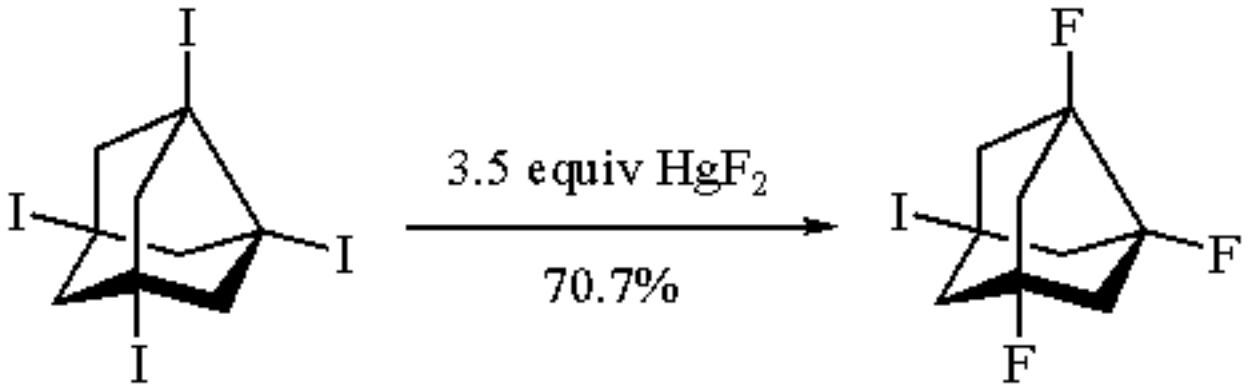

(3)

Addition Reactions.

Alkenes treated with an electrophile in the presence of mercury(II) fluoride add the electrophile and fluoride to give the *trans* product stereoselectively, as shown in eqs 4 and 5.[6,7]

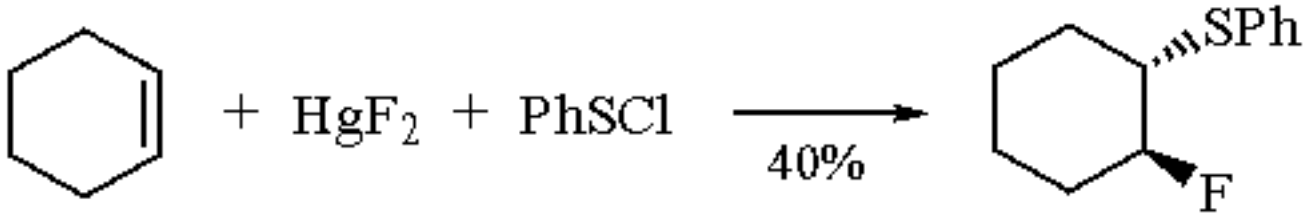

(4)

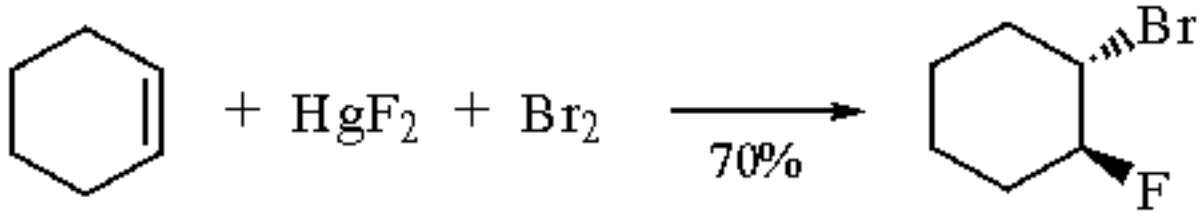

(5)

α-Fluoro Sulfides.

Thioacetals, on treatment with mercury(II) fluoride in acetonitrile, give rise to α-fluoro sulfides, as shown in eq 6.[8] Treatment of sulfoxides with ***N,N-Diethylaminosulfur Trifluoride*** also results in the formation of α-fluoro sulfides.[9]

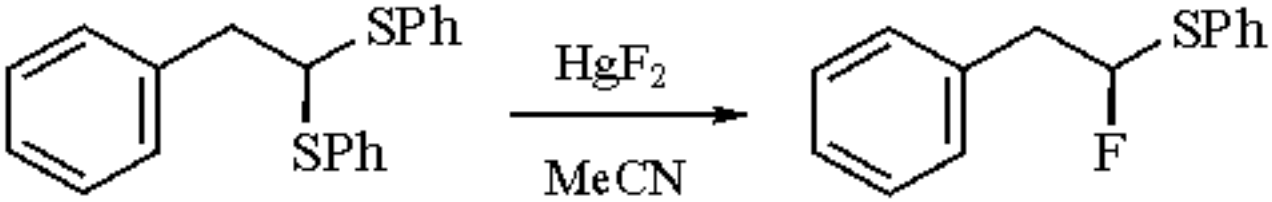

(6)

Selective Photochemical Fluorination.

Triphenylacetic acid, triphenylethylene, and triethyl phosphite have been selectively fluorinated in DMSO/HgF_2 solutions under UV-visible illumination (eqs 7-9).[10]

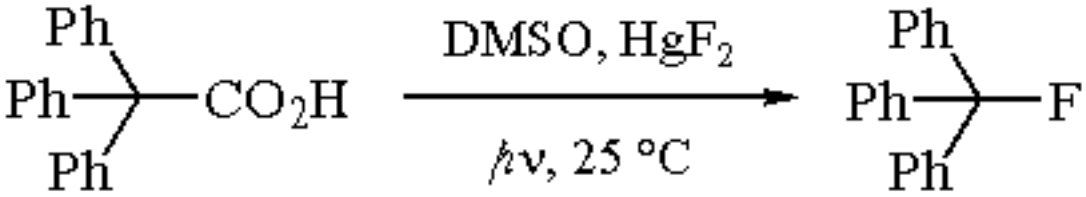

(7)

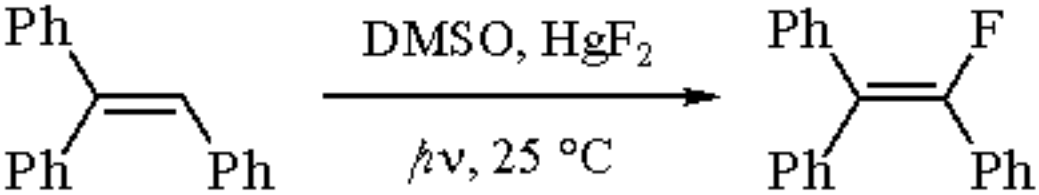

(8)

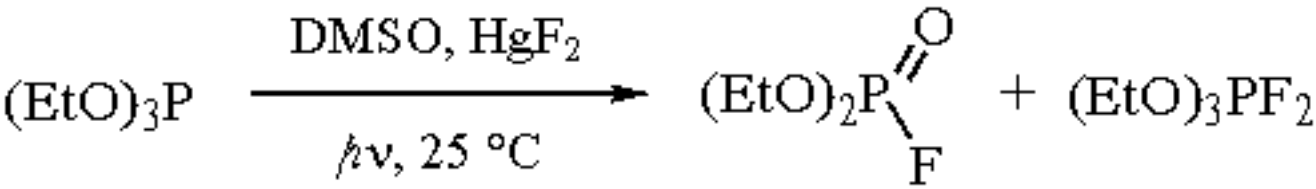

(9)

Fluorodecarboxylations have also been accomplished with ***Xenon(II) Fluoride***.[11] Phosphites can also be oxidatively fluorinated with carbonyl fluoride[12] or ***2H-Hexafluoropropyl Azide***.[13]

---

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Mercury(I) Nitrate[1]

$Hg_2(NO_3)_2.2H_2O$

[7782-86-7] · $Hg_2N_2O_6$ · Mercury(I) Nitrate · (MW 561.24)

(synthesis of alkyl nitrates from alkyl halides[3])

Alternate Name: mercurous nitrate.

Physical Data: mp about 70 °C (dec); bp explodes; *d* 4.785 g cm^{-3}

Solubility: insol alcohol, ether; sol H_2O containing 1% HNO_3 (with H_2O alone, basic salt is formed).

Form Supplied in: dihydrate (usual form); colorless monoclinic crystals, usually with slight odor of HNO_3. *Drying:* dehydration in vacuum; however, heating above 100 °C causes decomposition.[2]

Handling, Storage, and Precautions: acute poison. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

While nitrates are frequently prepared from alkyl halides on reaction with ***Silver(I) Nitrate*** in MeCN, mercury(I) nitrate offers a cheaper alternative (eq 1). Yields are high for primary, allylic, and benzylic bromides and satisfactory for secondary bromides. Tertiary bromides react slowly, whereas α-bromo carbonyl compounds are virtually inert.[3]

$$RBr \xrightarrow[-\,HgBr]{HgNO_3} RONO_2 \qquad (1)$$

Benzyl nitrates ($ArCH_2ONO_2$) synthesized in this way give the corresponding aldehydes (ArCH=O) upon reflux with NaOH in aq MeOH.[4]

---

1. (a) Larock, R. C. *AG(E)* **1978**, *17*, 27. (b) Larock, R. C. *T* **1982**, *38*, 1713. (c) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (d) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*, Springer: Berlin, 1986.
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Mercury(II) Nitrate[1]

$Hg(NO_3)_2.H_2O$

[7783-34-8] · $H_2HgN_2O_7$ · Mercury(II) Nitrate · (MW 342.63)

(oxymercuration;[4-9] amidomercuration;[12,15] cyclopropane cleavage;[17,19] glycosylation[23])

Alternate Name: mercuric nitrate.

Physical Data: mp 79 °C; bp (dec); *d* 4.3 g cm^{-3}.

Solubility: insol alcohol; very sol H_2O (in dilute solutions forms an insol basic salt); sol acetone, THF, DME, dioxane, NH_3, HNO_3, and other dilute acids.

Form Supplied in: transparent, hygroscopic crystals with slight odor of HNO_3. *Drying:* heating of the monohydrate to 55-60 °C/10^{-2} mmHg.[2,3]

Handling, Storage, and Precautions: acute poison. Exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Oxymercuration.

The reactivity of $Hg(NO_3)_2$ is similar to that of other Hg^{II} salts (acetate and trifluoroacetate)[1] so that this reagent can be employed to achieve similar goals such as electrophilic additions. The nitrate is often superior to its relatives (due to its higher electrophilicity) and may exhibit some variations in reactivity.[4] Thus, for instance, conjugated dienes afford products of both 1,4- and 1,2-addition (eq 1).[5,6] By contrast, with $Hg(OAc)_2$, only the 1,2-adduct is formed.[5] In the absence of stronger nucleophiles (in a nonnucleophilic solvent), nitratomercuration has been observed.[7] In the presence of Cl_2 or Br_2, the HgX group in the original adduct is replaced by halogen.[7]

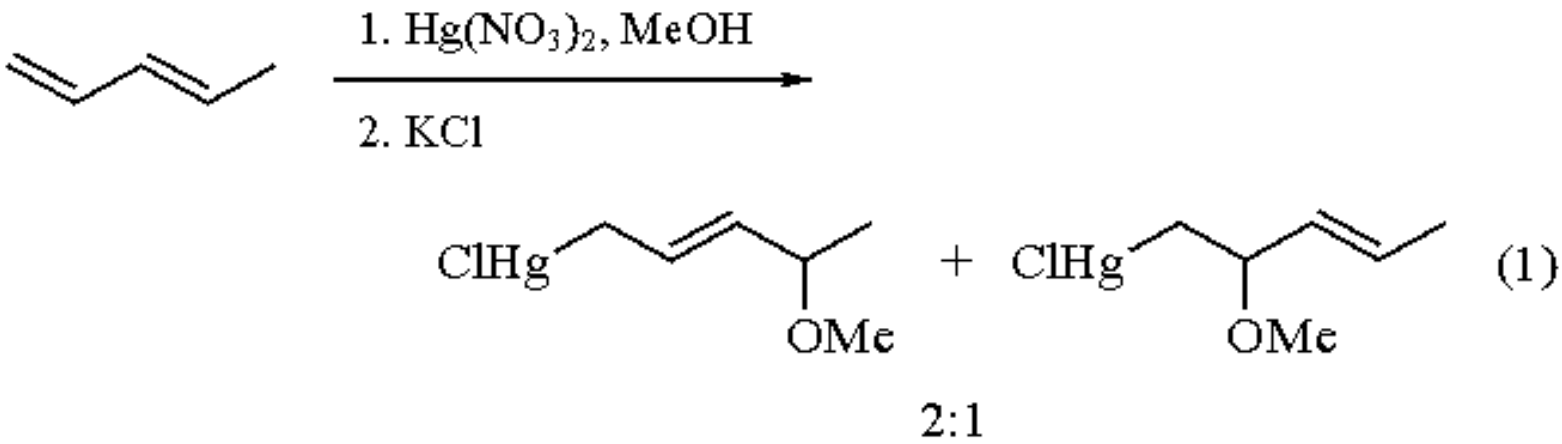

In the presence of ***Hydrogen Peroxide***, alkenes are peroxymercurated[8] on reaction with $Hg(NO_3)_2$ as a result of H_2O_2 being a stronger nucleophile than NO_3^-.

Like other Hg^{II} salts, mercury(II) nitrate effects intramolecular alkoxymercuration of unsaturated alcohols to produce oxygen heterocycles (eq 2).[9] Similar to other electrophilic additions, oxymercuration is a priori a reversible reaction. It has been shown that selecting the method of quenching is crucial to minimize the reversion. Thus, oxymercuration products with rigid, antiperiplanar arrangement of the C-HgX and C-O bonds (eq 2) immediately revert back to the starting material upon treatment with sources of hard halogen anion (NaCl, KBr, $CuCl_2$, etc.). By contrast, quenching with soft reagents (e.g. CuCl) reliably affords the stable chloromercurio compound. Excess of strong acids should be avoided as H^+ catalyzes reversion.[9,10]

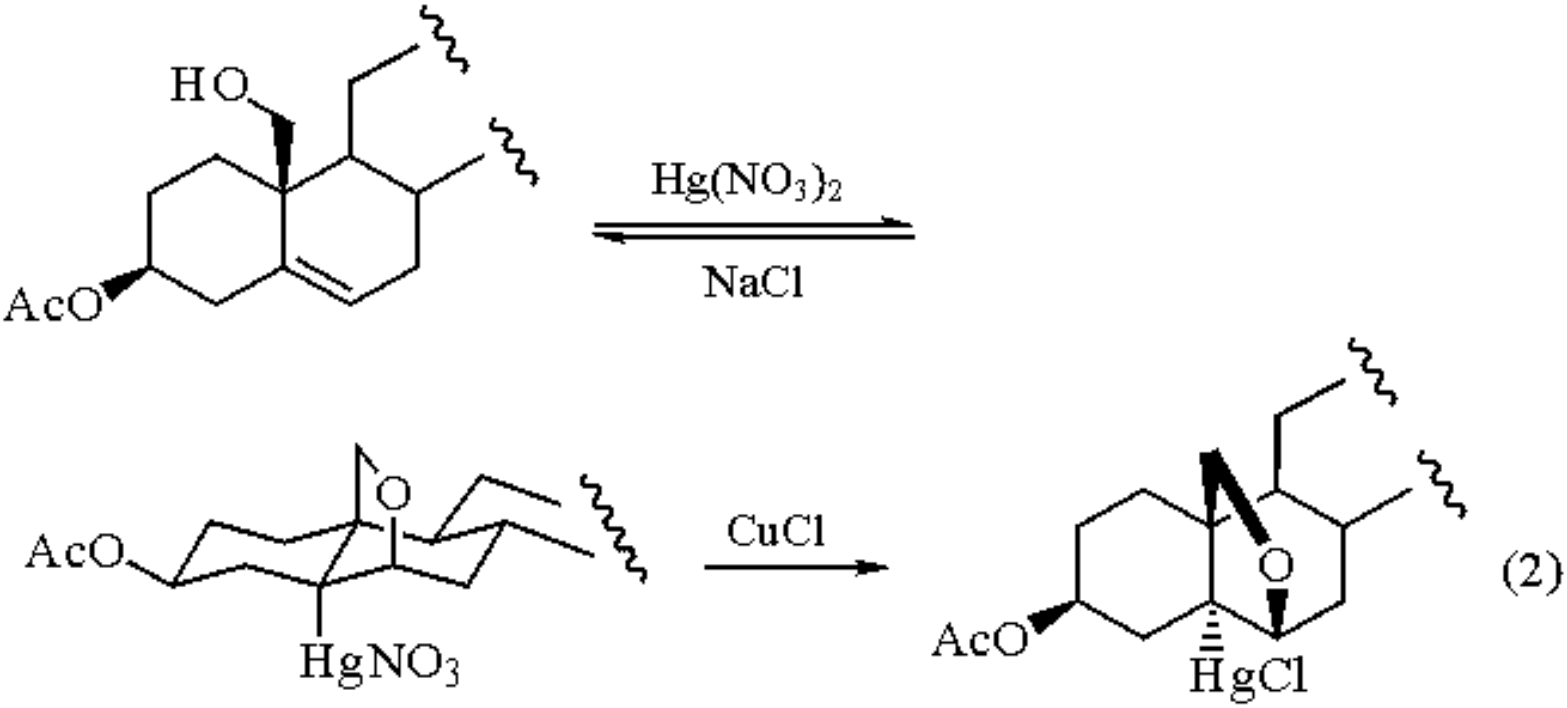

In a close analogy to alkenic alcohols, unsaturated hydroperoxides react with $Hg(NO_3)_2$ to give cyclic peroxides which can be further elaborated.[8,11]

Amidomercuration.[12]

The mercuration of terminal or cyclic alkenes with $Hg(NO_3)_2$ in MeCN[2,13,14] affords amides via the Ritter reaction (eq 3).[13] In contrast to the original, strong acid-mediated reaction, this modification is less prone to rearrangements as it proceeds via a mercuronium ion.[13,14] The reaction works with mono- and disubstituted double bonds but fails with trisubstituted alkenes.[14] Other Hg^{II} salts, namely $(AcO)_2Hg$ and $(CF_3CO_2)_2Hg$, are not satisfactory,[13] apparently owing to their lower electrophilicity.

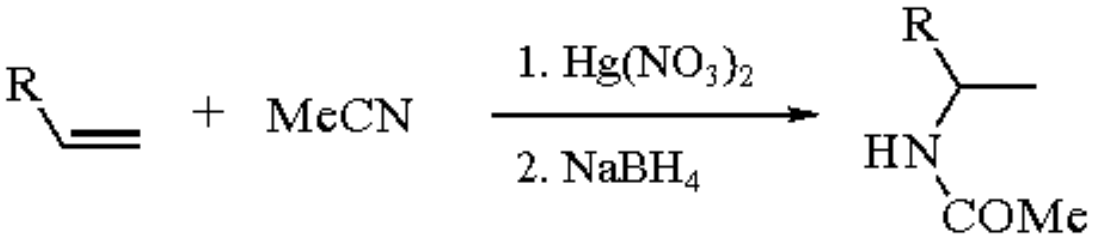

(3)

Primary amides and $TsNH_2$ similarly add across alkenic double bonds to give the corresponding tosylamides.[15] Asymmetric, intramolecular amidomercuration employing chiral carbamates has also been described (eq 4).[16]

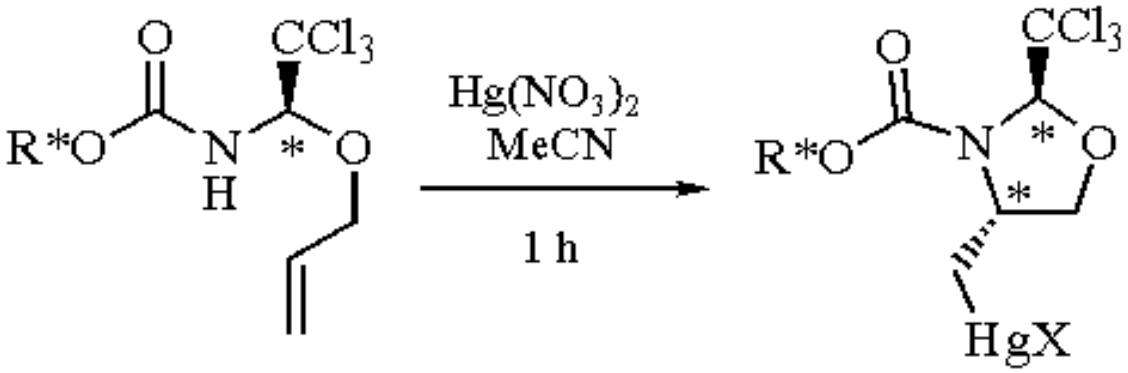

(4)

Cyclopropane Ring Opening.[17-19]

Mercury(II) nitrate appears to be the reagent of choice to accomplish stereospecific corner opening[19] of cyclopropyl derivatives (eqs 5 and 6);[19,20] other Hg^{II} salts are less reactive.[19,21] The reaction is also regioselective: the cleavage occurs between the most and the least substituted carbon.[19] The resulting organomercurials can be transmetalated by transition metals (Pd, Mo, Cu) to accomplish a variety of interesting transformations.[19]

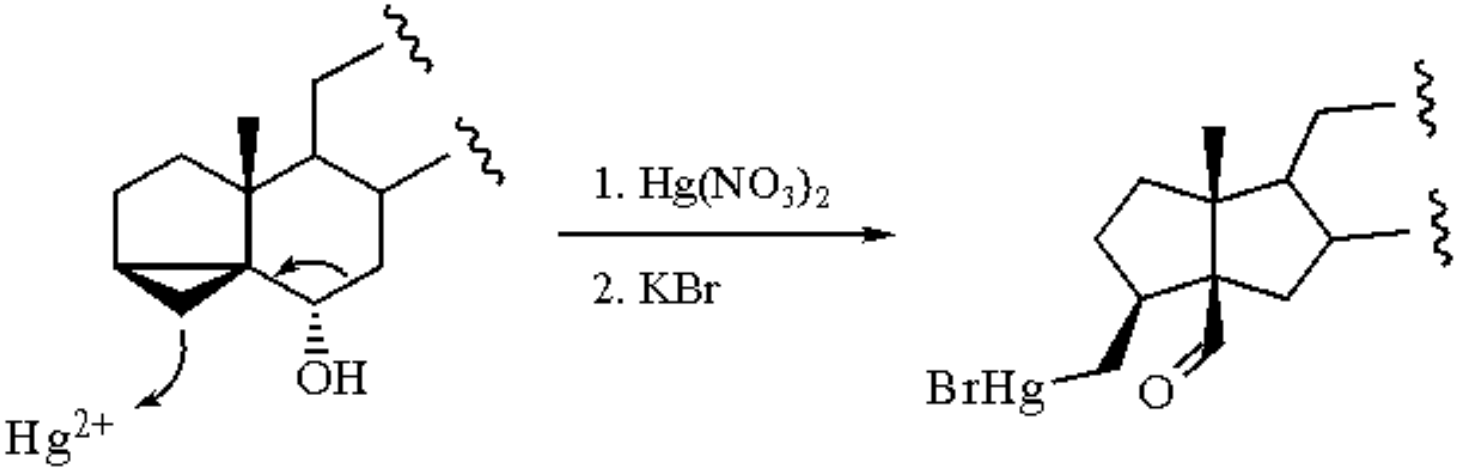

(5)

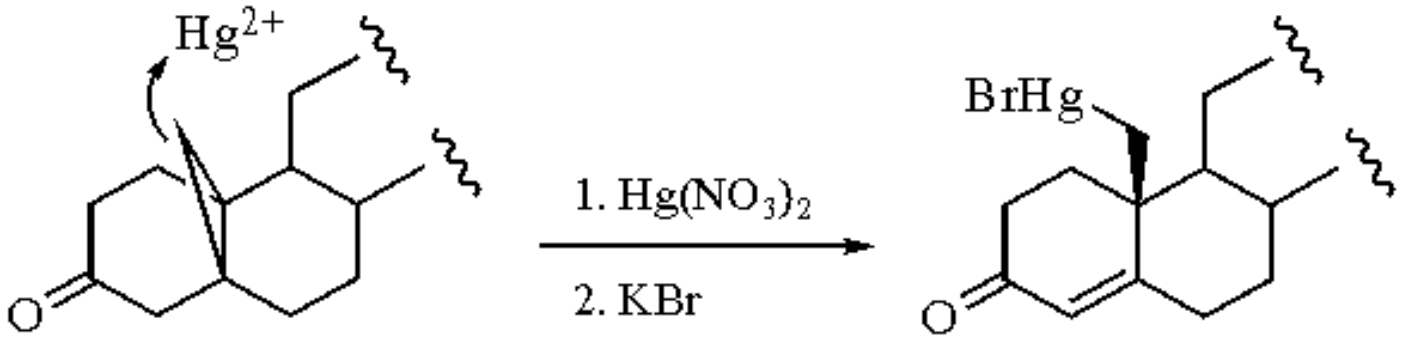

(6)

Glycosylation.

Thioglycosides can be utilized as glycosylating agents in conjunction with anhydrous $Hg(NO_3)_2$ (or $AgNO_3$).[22] Although the reaction normally affords mixtures of α- and β-glycosides,[22] neighboring group participation can render it stereoselective (for discussion and examples, see ***Mercury(II) Chloride-Cadmium Carbonate***).[23]

Miscellaneous.

β-Pinene undergoes a Ritter-type transformation on reaction with $Hg(NO_3)_2$/MeCN[24] to give the starting material for the synthesis of aristoteline[25] and other indole alkaloids (eq 7);[25] the reaction is not enantioselective and gives racemic products.[24,25] Mercuration of enolizable ketones has little synthetic value: thus, for instance, acetone has been found to produce a mixture of nine compounds.[26]

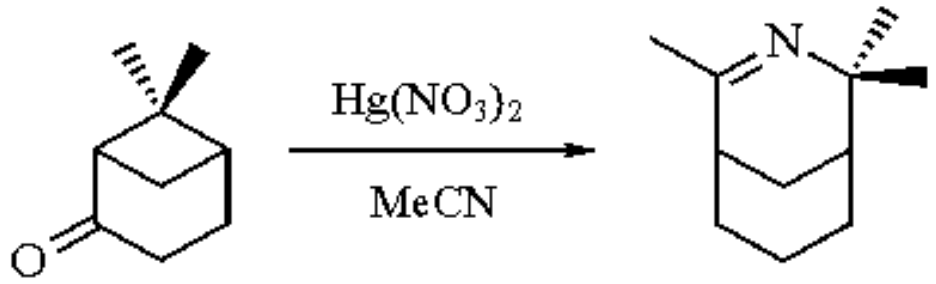

(7)

Related Reagents.

Mercury(II) Acetate; ***Mercury(II) Trifluoroacetate***; ***Mercury(II) Perchlorate***.

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Mercury(II) Oxide[1]

HgO

[21908-53-2] · HgO · Mercury(II) Oxide · (MW 216.59)

(promotion of thio-Claisen rearrangement;[2] deprotection of dithianes, dithiolanes,[3] thioorthoesters;[4] synthesis of tetrahydrofurans;[5] oxidizing agent[6-18])

Alternate Name: mercuric oxide.

Physical Data: mp 500 °C (dec); *d* 11.14 g cm^{-3}.

Solubility: sol dilute HCl, HNO_3; insol water, ethanol.

Form Supplied in: commercially available in both yellow and red crystalline forms.

Handling, Storage, and Precautions: highly toxic; oxidizer; protect from light.

Conversion of Ketones into Unsaturated Aldehydes.

Mercury(II) oxide promotes the Wittig-thio-Claisen rearrangement sequence which converts ketones into unsaturated aldehydes (eq 1).[2] The reaction proceeds via formation of an allyl vinyl sulfide followed by rearrangement to form the α-allyl aldehyde.

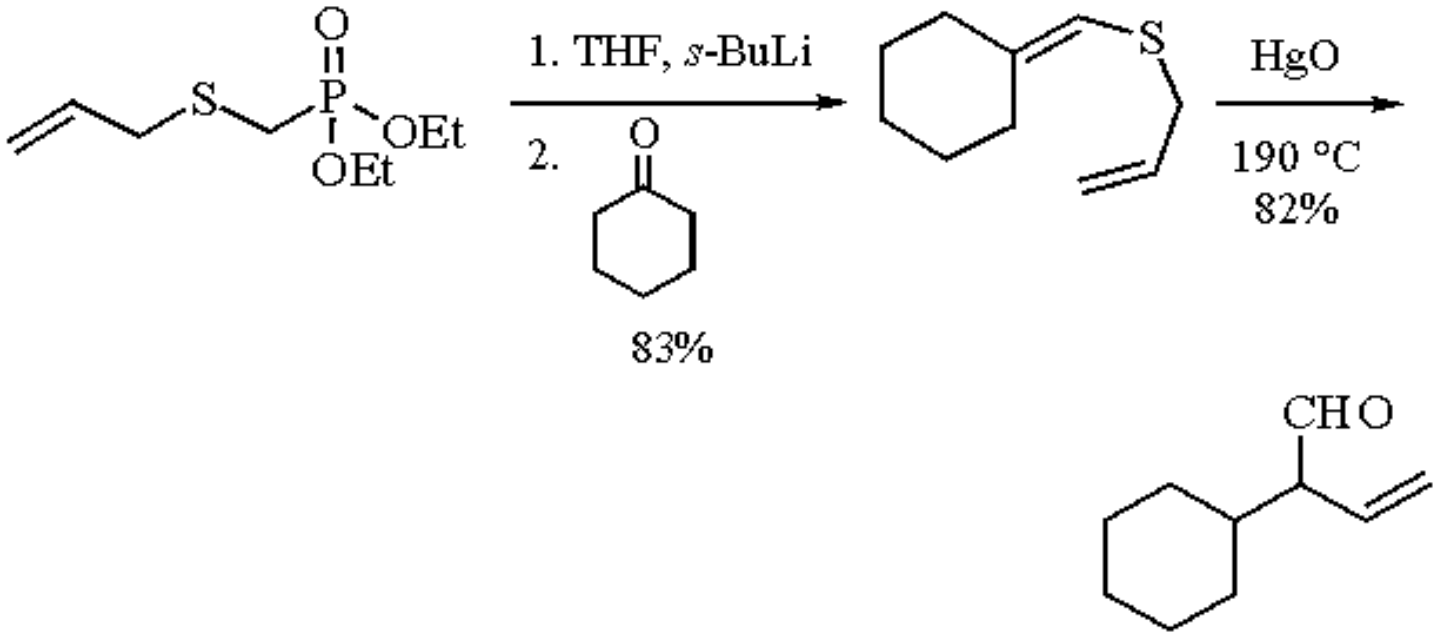

(1)

Preparation of Aldehydes and Ketones by Hydrolysis of Sulfur-Containing Compounds.

A mixture of mercury(II) oxide/35% aqueous ***Tetrafluoroboric Acid***/THF can be used for the hydrolysis of 1,3-benzodithioles (eq 2), 1,3-benzoxathioles (eq 3), 1,3-oxathiolanes (eq 4), 1,3-dithiolanes (eq 5), and 1,3-dithianes (eq 6).[3] These reaction conditions offer an alternative to those reported by Vedejs and Fuchs[19] which use a mixture of mercury(II) oxide/***Boron Trifluoride Etherate***/THF.

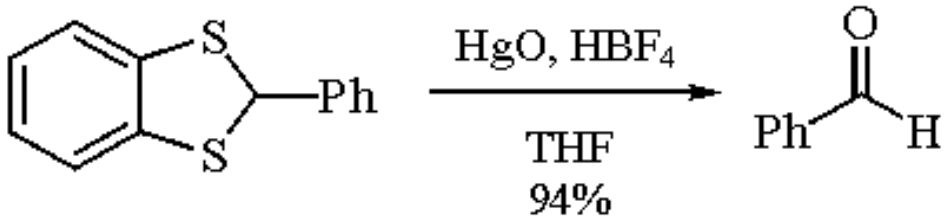

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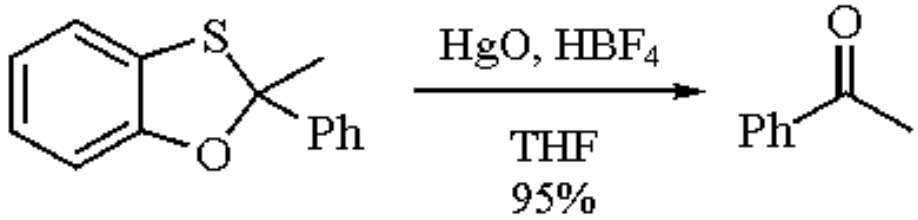

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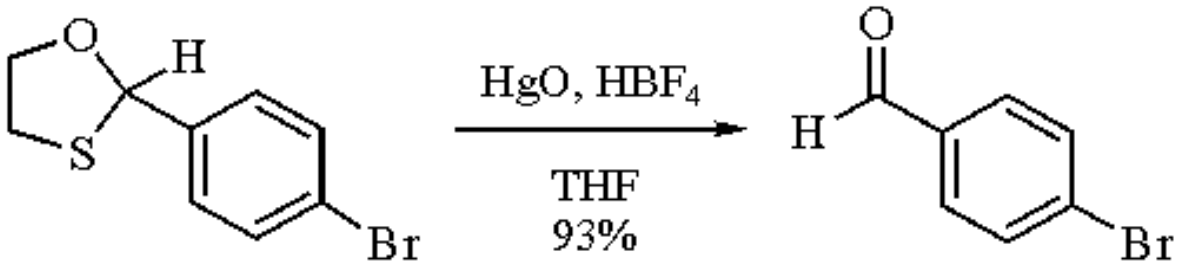

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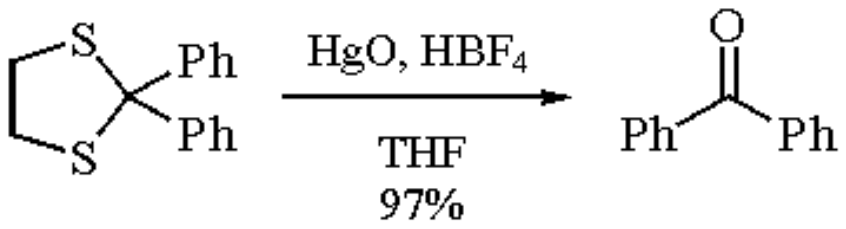

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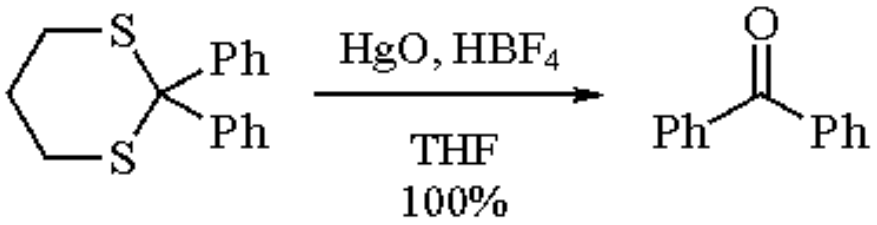

(6)

Synthesis of Esters by Solvolysis of α-Hydroxy Thioorthoesters.

The use of mercury(II) oxide/50% aqueous tetrafluoroboric acid/THF and an alcohol is a fast and mild procedure for the hydrolysis of α-hydroxy thioorthoesters to the corresponding ester (eq 7).[4]

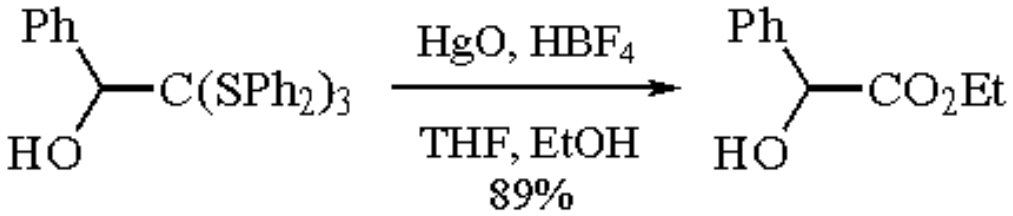

(7)

Cyclization of Primary and Secondary Alcohols to Yield Tetrahydrofurans.

Primary and secondary unbranched aliphatic alcohols are readily converted into the corresponding tetrahydrofuran derivatives using mercury(II) oxide and ***Iodine*** in carbon tetrachloride (eqs 8 and 9).[5]

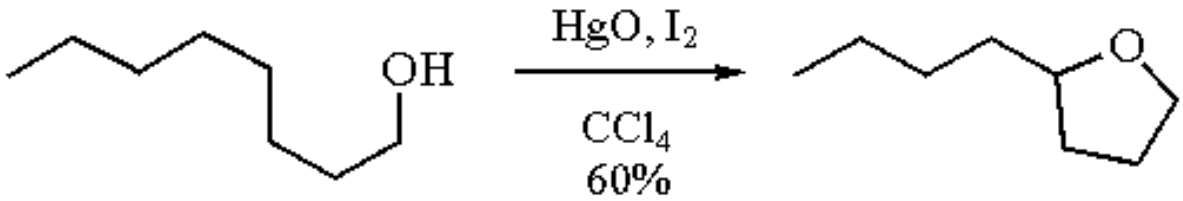

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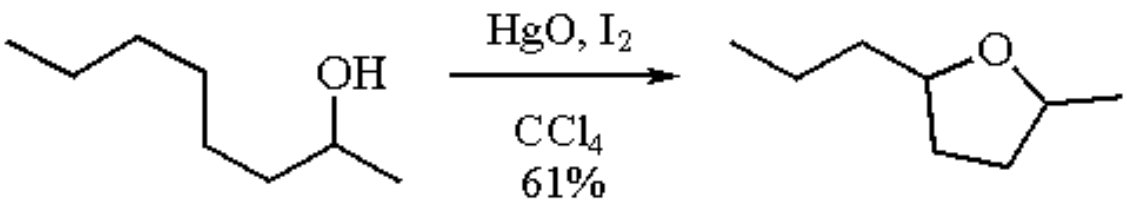

(9)

Synthesis of β-Substituted Polynitroalkyl Vinyl Ethers.

The inherent instability of β-substituted polynitroaliphatic alcohols in acidic and basic media precludes the use of traditional vinyl ether synthesis. The use of mercury(II) oxide/***Trifluoroacetic Acid*** in refluxing dichloromethane permits a one-step, high-yielding synthesis of β-substituted polynitroalkyl ethers (eq 10).[6] The use of mercury(II) oxide alone produces the product in 20-30% yield, whereas the addition of TFA as cocatalyst substantially increases the yield of the desired product.

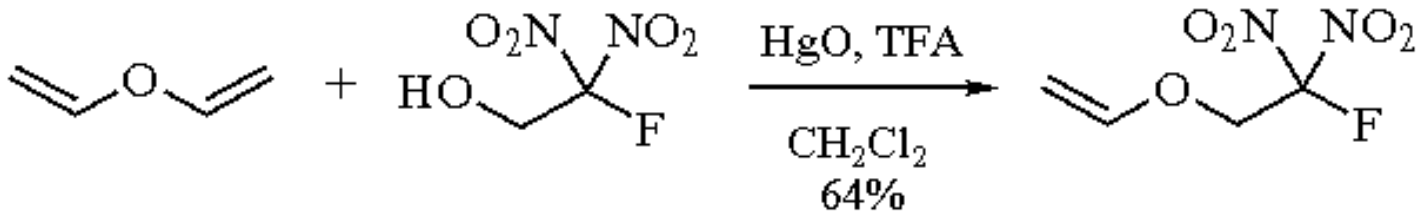

(10)

Synthesis of *trans*-Cinnamyl Ethers.

Oxidation of allylbenzene using mercury(II) oxide/tetrafluoroboric acid and alcohols in THF forms exclusively *trans*-cinnamyl ethers (eq 11).[7]

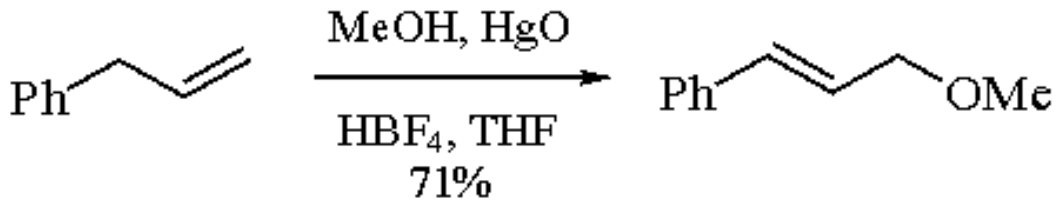

(11)

Diamination of Alkenes.

The mercuration of alkenes using mercury(II) oxide and tetrafluoroboric acid in the presence of excess amine leads to the formation of 1,2-diamines (eq 12).[8] Presumably, the reaction takes place via formation of a β-aminomercury(II) tetrafluoroborate which undergoes nucleophilic attack of an amine.

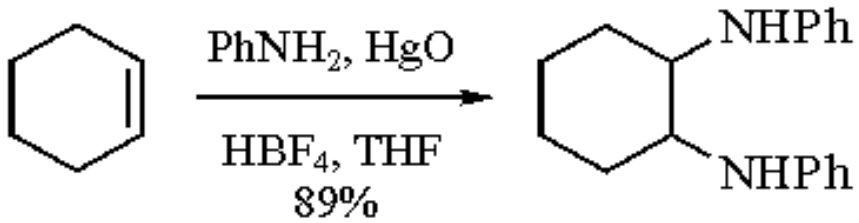

(12)

Hydroxy(alkoxy)phenylamination of Alkenes.

A one-pot procedure for hydroxy(alkoxy)phenylamination of alkenes has been developed using mercury(II) oxide and tetrafluoroboric acid (eq 13).[9] The reaction proceeds through the formation of the aminomercurial from the alkene

followed by reaction with water or alcohol. The ratio of products depends on the substitution pattern on the alkene. For terminal alkenes, the rearranged isomer predominates and cyclic alkenes afford *trans* products (eq 14).[9]

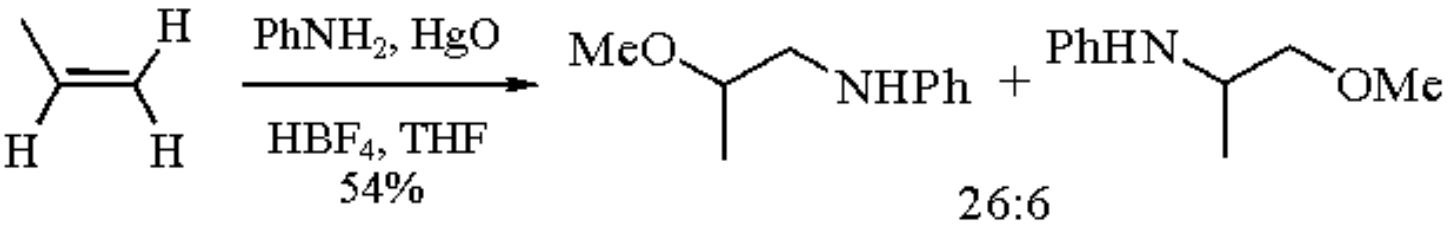

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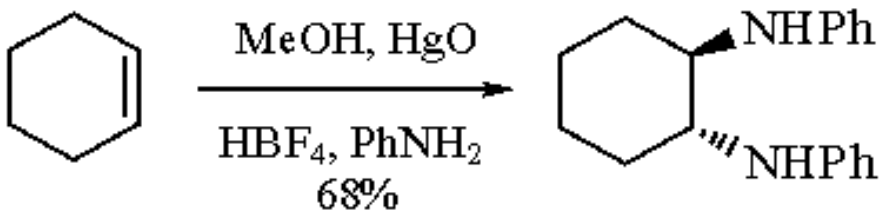

(14)

Cyclization of Alkynecarboxylic Acids.

A variety of γ-methylenebutyrolactones have been successfully synthesized by cyclization of the appropriate alkynecarboxylic acid with mercury(II) oxide as catalyst (eqs 15 and 16).[10] In some instances the reaction must be run neat; in other cases, solvents such as chloroform, acetone, benzene, dioxane and even refluxing DMF are necessary.

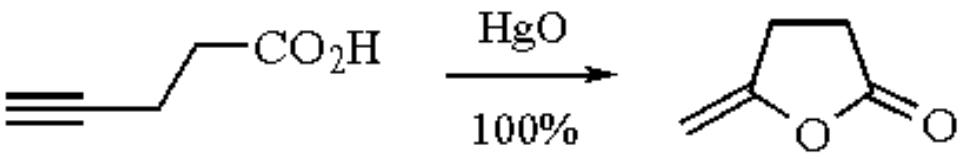

(15)

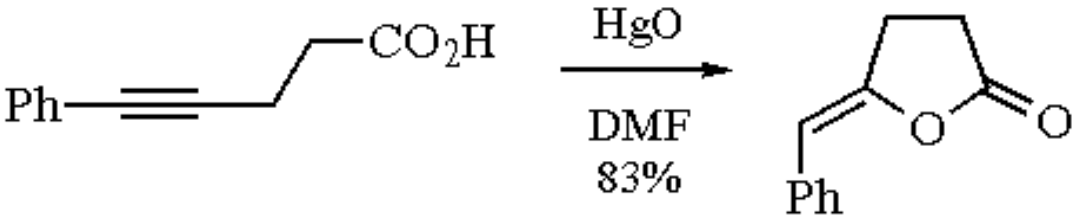

(16)

In a similar approach, mercury(II) oxide has also been used to catalyze the cyclization of γ-allenic acids into γ-ethylenic δ-lactones (eq 17).[11]

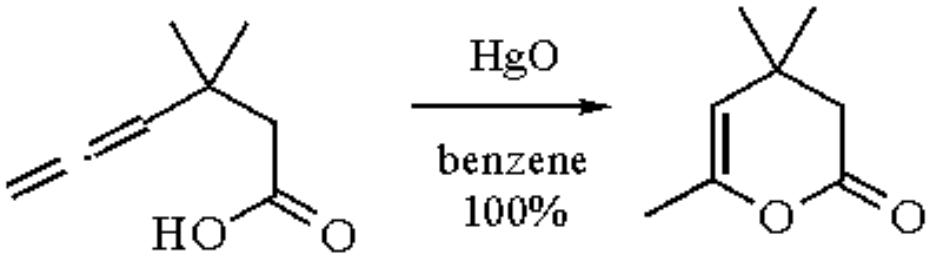

(17)

Preparation of Alkyl Halides.

Alkanes react with a mixture of ***Bromine*** and mercury(II) oxide to afford the corresponding alkyl bromide in good yield (eqs 18 and 19).[12] This combination of reagents is more reactive than bromine or ***N-Bromosuccinimide***. The mechanism has been postulated to proceed through the formation of bromine monoxide in situ as the brominating agent.[12] Primary and secondary alkyl bromides are readily formed, but tertiary bromides and benzylic bromides are rather problematic.

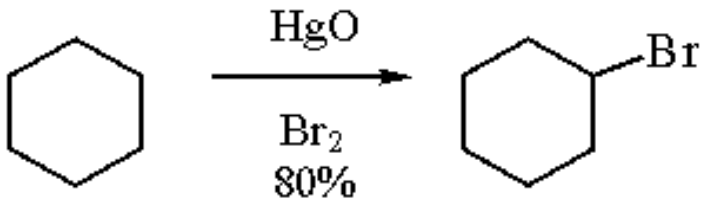

(18)

$$CH_2Cl_2 \xrightarrow[\substack{Br_2 \\ 80\%}]{HgO} CHBrCl_2 \qquad (19)$$

Alkyl and aryl halides can also be synthesized using the Cristol-Firth modification of the Hunsdiecker reaction (eqs 20 and 21).[13,14] Even bridgehead carboxylic acids can be transformed into the corresponding bromide using mercury(II) oxide and bromine. Aromatic acids form insoluble mercury(II) salts which normally lead to lower yields, but it has been found that irradiation of the reaction with a 100 W bulb affords excellent yields.[14] Interestingly, irradiation of reactions of aliphatic acids does not improve the yield and, in some cases, even produces lower yields.

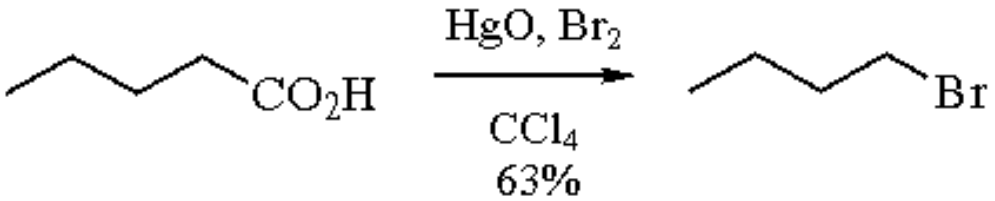

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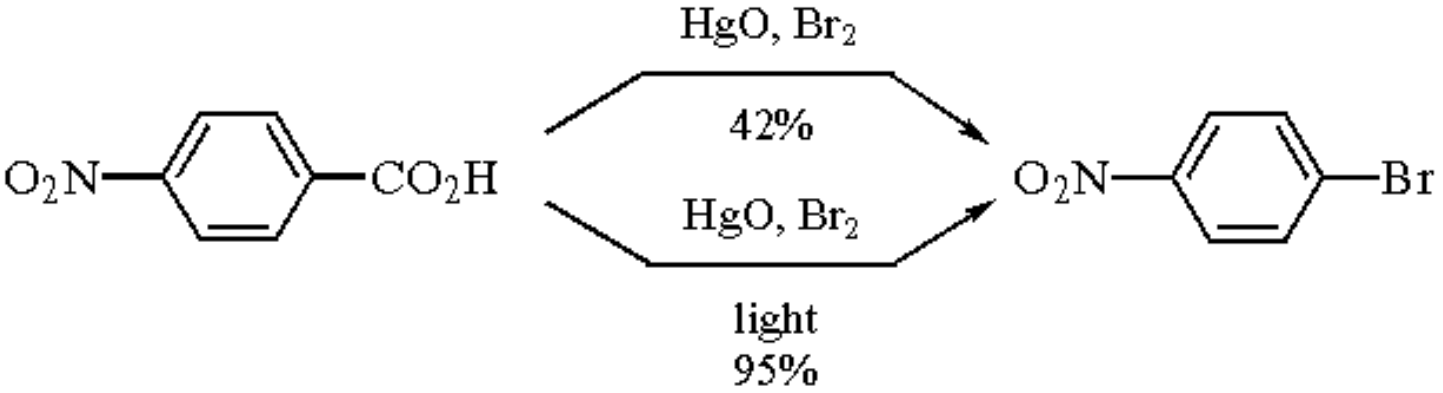

(21)

Decarboxylation of bridgehead carboxylic acids has been accomplished in two steps. The bromide is formed first followed by reduction with ***Tri-n-butylstannane***. The deuterated analog can be made using tributyltin deuteride (eq 22).[15]

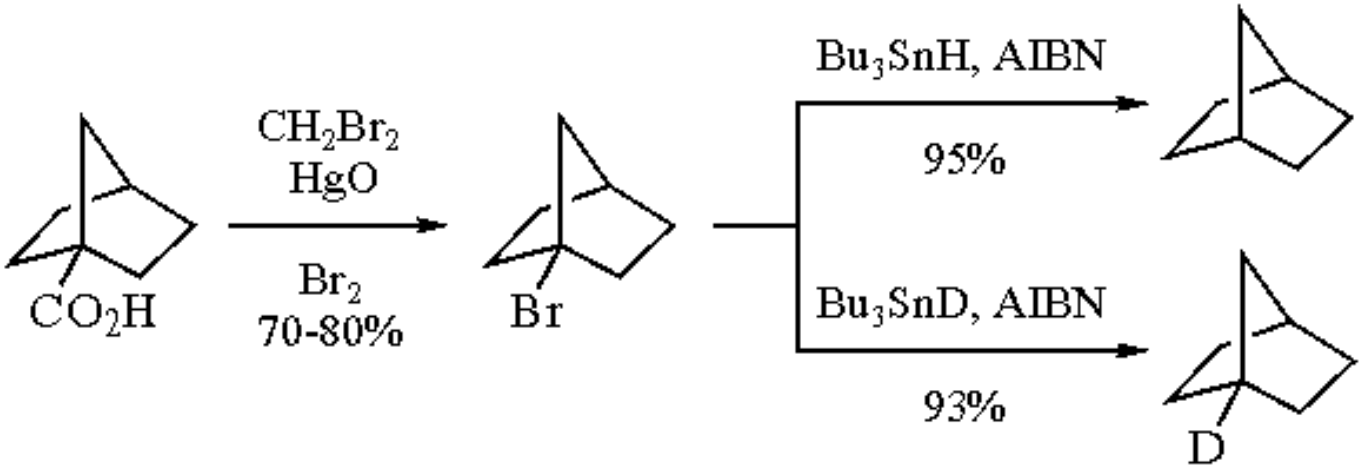

(22)

Oxidation of Phenols and Hydroquinones.

In most cases, mercury(II) oxide can be used instead of ***Mercury(II) Trifluoroacetate*** to oxidize phenols and hydroquinones (eqs 23 and 24).[16] These conditions are attractive in that they do not require the use of an acid scavenger to neutralize the trifluoroacetic acid that is formed during the course of the reaction.

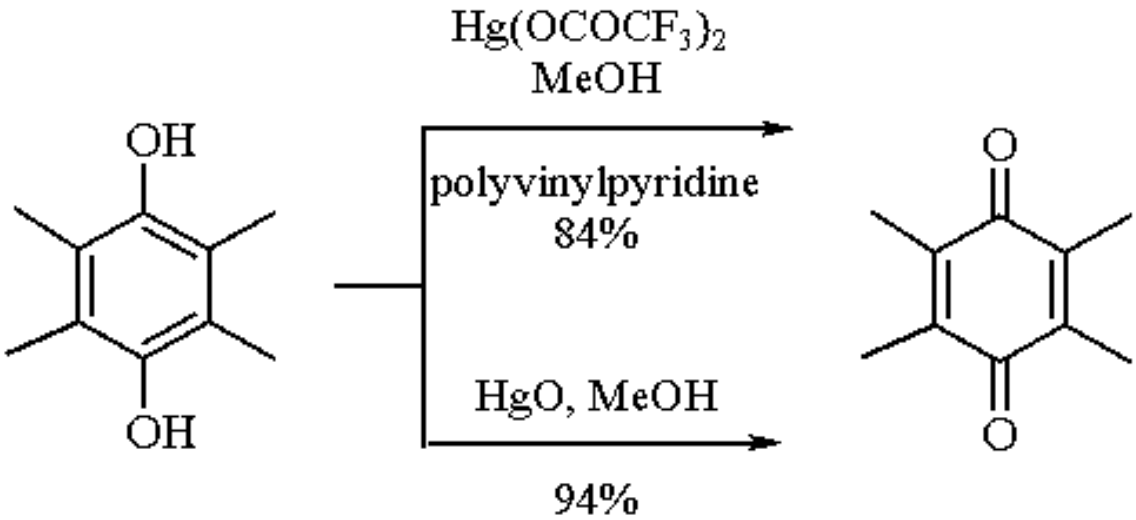

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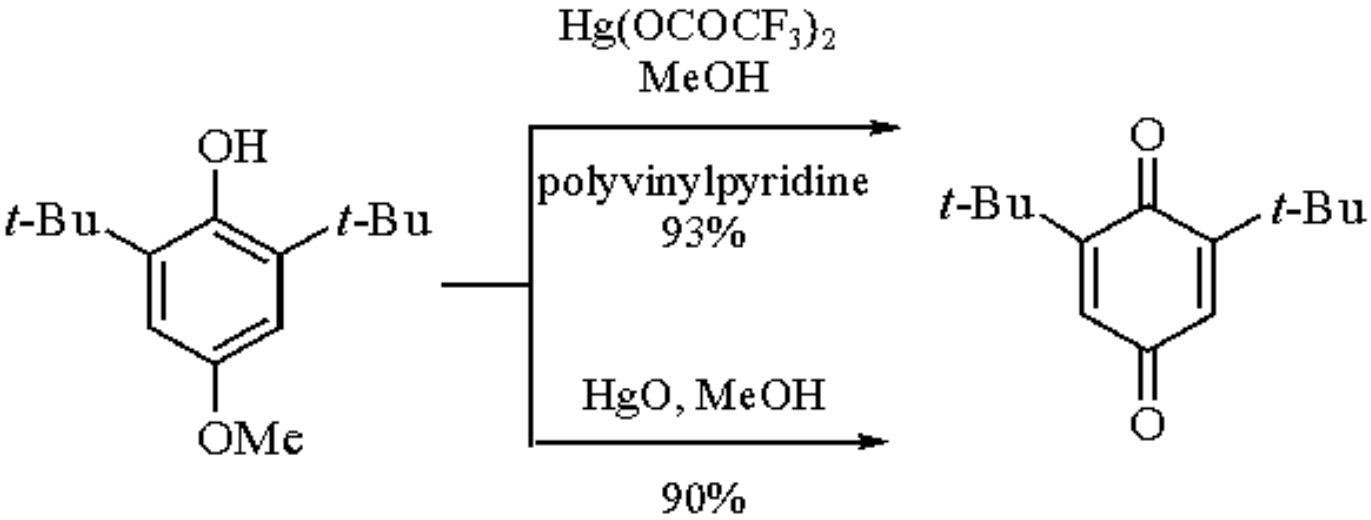

(24)

Oxidation of Hydrazones.

Aliphatic and aromatic hydrazones are oxidized with mercury(II) oxide to afford the corresponding diazo compound (eqs 25-27).[17] Reaction of the monohydrazones derived from α-diketones give α-diazo ketones, which, upon heating, form ketenes (eq 28).[17] Treatment of the bis-hydrazones of α-diketones with mercury(II) oxide at higher temperatures affords alkynes (eq 29).[17] Seven- and eight-membered cycloalkynes as well as even larger cycloalkynes have been synthesized using this methodology (eq 30).[17]

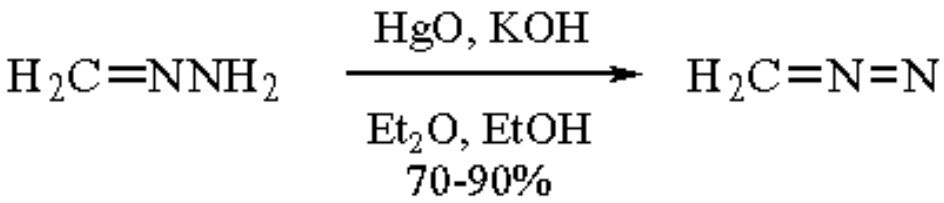

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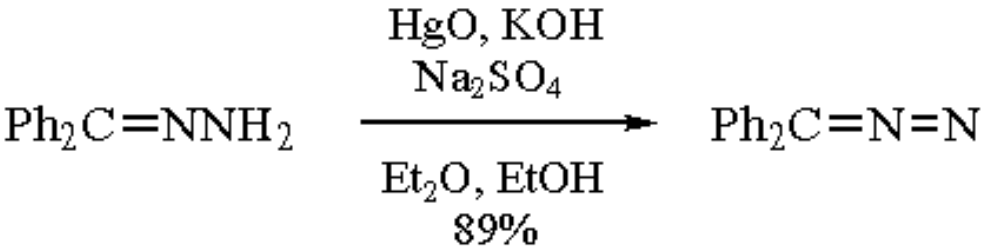

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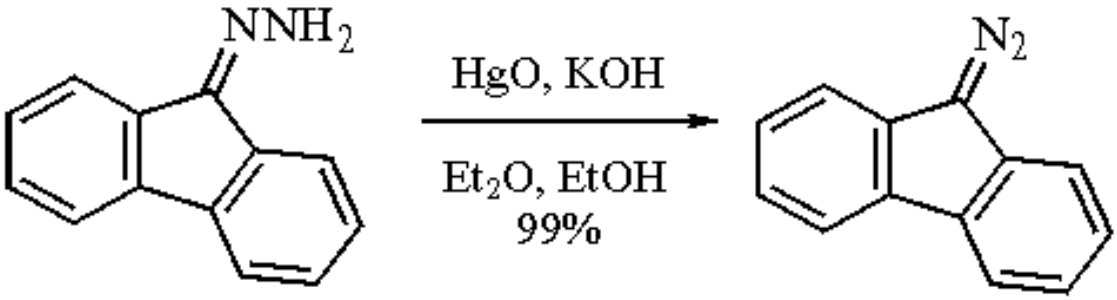

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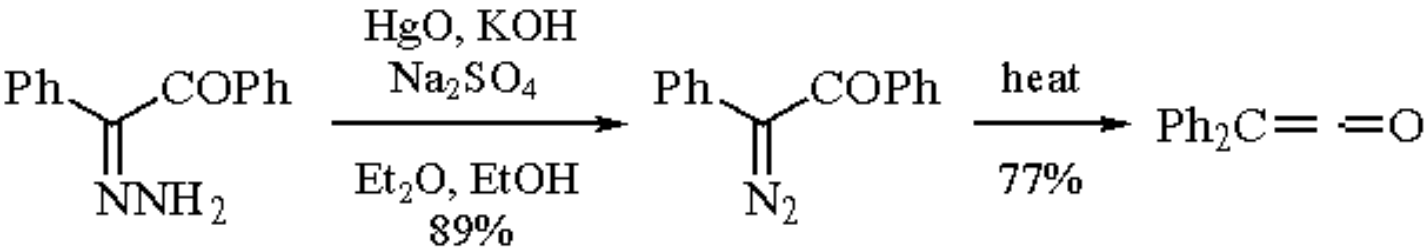

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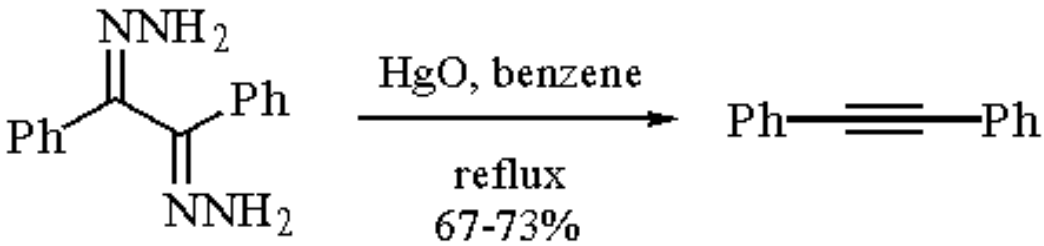

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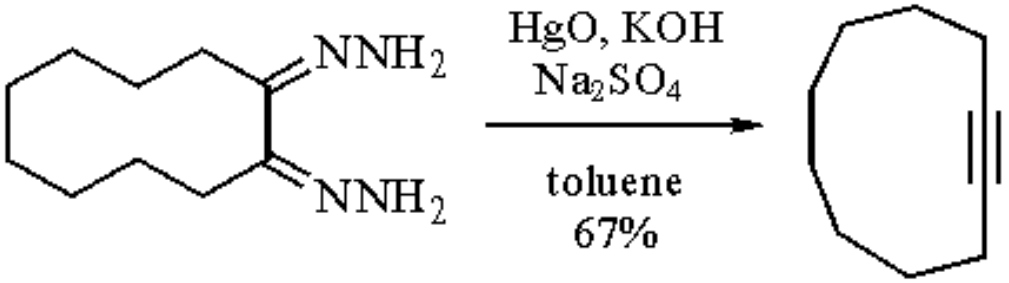

(30)

Hydration of Alkynes.

A mixture of mercury(II) oxide and ***Sulfuric Acid*** effects hydration of alkynes to form the corresponding methyl ketone. This protocol was utilized in the synthesis of some daunomycinone analogs (eq 31).[18]

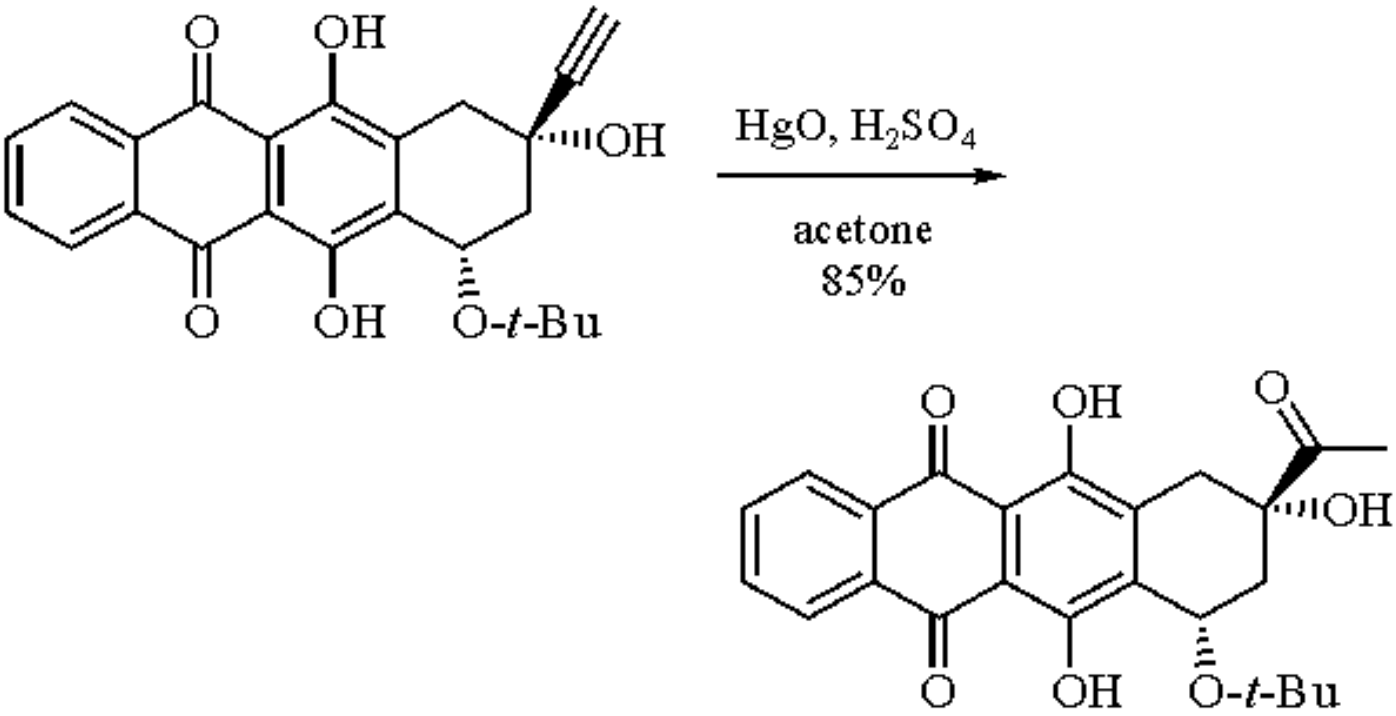

(31)

Related Reagents.

Mercury(II) Oxide-Bromine; ***Mercury(II) Oxide-Iodine***; ***Mercury(II) Oxide-Tetrafluoroboric Acid***.

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Mercury(II) Oxide-Bromine[1]

$HgO\text{-}Br_2$

(HgO)

[21908-53-2] · HgO · Mercury(II) Oxide-Bromine · (MW 216.59) (Br_2)

[7726-95-6] · Br_2 · Mercury(II) Oxide-Bromine · (MW 159.80)

(reagent for the generation of isolable Br_2O,[2] which reacts with alcohols and carboxylic acids to give the corresponding alkyl hypobromites, ROBr,[3] and acyl hypobromites, RCO_2Br,[2c] respectively)

Physical Data: Br_2: mp -7.25 °C; bp 59.5 °C; *d* 3.187 g cm^{-3} (0 °C), 7.59 g dm^{-3} (gas).

Solubility: Br_2: sol water ethanol, ether, chloroform, CS_2.

Handling, Storage, and Precautions: since releasing the used reagent into the environment could be hazardous, one must follow the appropriate regulations. Use in a fume hood.

Reagent for Preparation of Alkyl Hypobromites.[3]

Alkyl hypobromites can be prepared by the reaction of alcohols with this reagent in a manner parallel to the preparation of hypoiodites by the reaction of alcohols with ***Mercury(II) Oxide-Iodine*** (eqs 1 and 2).

$$HgO + 2\,Br_2 \longrightarrow Br_2O + HgBr_2 \qquad (1)$$

$$Br_2O + 2\,ROH \longrightarrow 2\,ROBr + H_2O \qquad (2)$$

The reactive species generated from the combination of ***Mercury(II) Oxide*** and ***Bromine*** is Br_2O, and, in contrast to I_2O from HgO and I_2, it can be isolated.[2] These alkyl hypobromite intermediates dissociate to alkoxyl and bromine radicals upon heating or irradiation with Pyrex-filtered light, as in the case of hypoiodites, and thus can be used for remote functionalization as well as β-scission in a manner similar to that of the hypoiodites. Thus treatment of cedrol with mercury(II) oxide-bromine, followed by irradiation, gives the corresponding cyclic ether (eq 3).[3a] The mechanism is parallel to that for the formation of cyclic ethers from alkyl hypoiodites (see ***Mercury(II) Oxide-Iodine***). An example of the β-scission of an alkoxyl radical generated from alkyl hypobromite is illustrated in eq 4.[3b]

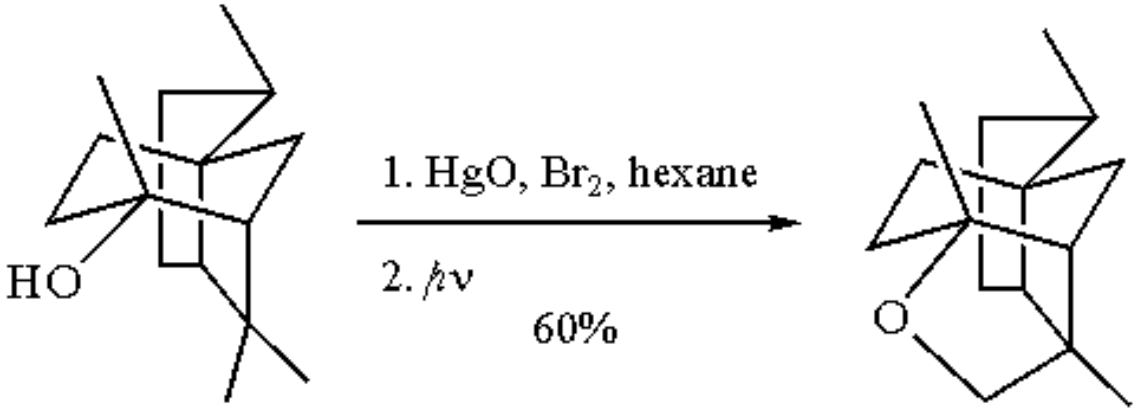

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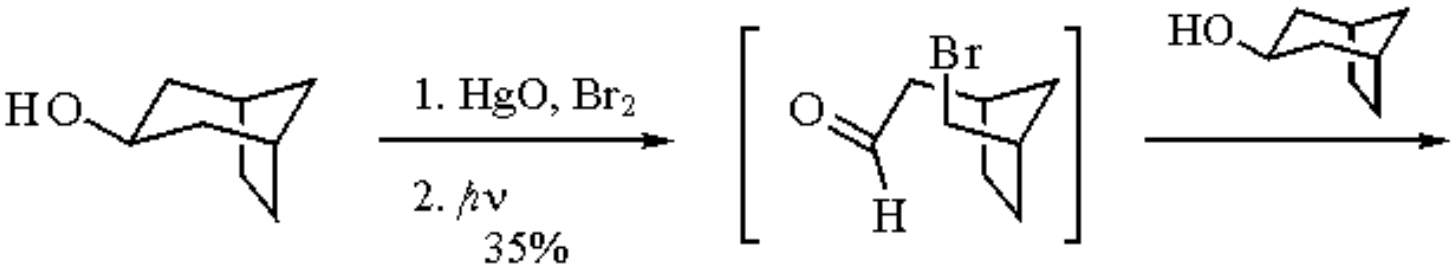

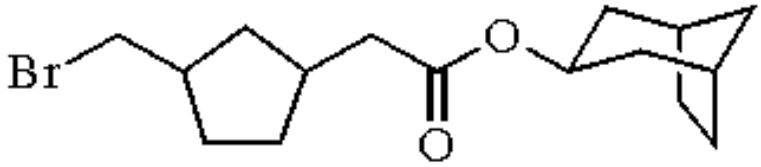

(4)

Reagent for the Modified Hunsdiecker Reaction.[1]

When the silver salt of a carboxylic acid is treated with bromine, the carboxy group is lost as CO_2 and alkyl or aryl bromides are produced. This reaction has been known as the Hunsdiecker reaction.[4] Cristol found that treatment of excess red mercury(II) oxide in a refluxing solution of an aliphatic carboxylic acid in CCl_4 with approximately 1 equiv of Br_2 in the dark gave good yields of the corresponding alkyl bromide (eq 5)[1] (see also ***Mercury(II) Oxide-Iodine***). Subsequently, a number of investigators have reported that the Cristol method is simpler than the original Hunsdiecker method in that it does not require the preparation of the dry silver salt.[5]

$$Me(CH_2)_{16}CO_2H \xrightarrow[\text{2. } \Delta,\ 93\%]{\text{1. HgO, } Br_2\text{, } CCl_4} Me(CH_2)_{16}Br \qquad (5)$$

The reaction involves the formation of RCO_2Br intermediates, followed by the removal of CO_2 via a radical intermediate. Thus cyclopropanecarboxylic acid is converted to bromocyclopropane in 41-46% yield by the treatment of red HgO and bromine in 1,1,2,2-tetrachloroethane (eq 6).[6] 6-Bromo-4-*t*-butylhexanoic acid is converted to 1,5-dibromo-3-*t*-butylpentane (eq 7).[7]

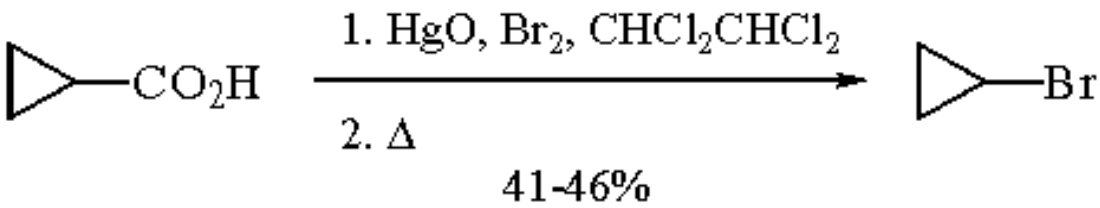

(6)

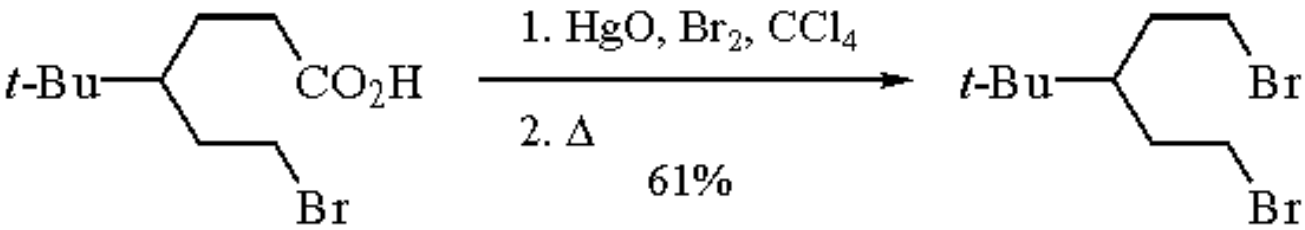

(7)

Bromination of Alkanes.

The combination of bromine and mercury(II) oxide is a reagent for the radical bromination of alkanes. The reagent, which involves Br_2O as the brominating species, is significantly more reactive than ***Bromine*** or ***N-Bromosuccinimide*** and is applicable to a substitution of the primary and secondary C-H bonds (eq 8).[8]

$$2\,RH + 2\,Br_2 + HgO \longrightarrow 2\,RBr + HgBr_2 + H_2O \qquad (8)$$

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Mercury(II) Oxide-Iodine

$HgO-I_2$

(HgO)

[21908-53-2] · HgO · Mercury(II) Oxide-Iodine · (MW 216.59) (I_2)

[7553-56-2] · I_2 · Mercury(II) Oxide-Iodine · (MW 253.80)

(hypoiodite formation; generation of alkoxyl radicals)

Physical Data: see ***Mercury(II) Oxide*** and ***Iodine***.

Solubility: I_2: sol organic solvents (g I_2/100 g solvent, 25 °C): benzene (14.09), CS_2 (16.47), EtOH (21.43), Et_2O (25.20), cyclohexane (2.72), CCl_4 (2.60, 35 °C); sol $CHCl_3$, AcOH, glycerol.

Form Supplied in: both reagents are widely available. HgO: bright red or orange-red solid; yellow when finely powdered. I_2: violet crystals.

Handling, Storage, and Precautions: protect from light. Avoid contact with skin and eyes.

Introduction.

The $HgO-I_2$ combination is widely used for the conversion of an alcohol to a hypoiodite.[1] A nonpolar solvent is generally used for the reaction. Due to the weak RO-I bond (~56 kcal mol^{-1}), hypohalites are generally not isolable but are generated and used in situ. Their subsequent decomposition under thermal or photochemical conditions yields alkoxyl radicals, which are highly reactive and undergo a variety of reactions including H&bdot; abstraction, cleavage of the adjacent C-C bond (β-fragmentation), and addition to unsaturated compounds.

Hydrogen Abstraction.

Intramolecular hydrogen abstraction by an alkoxyl radical is most favored through a six-membered ring transition state (1,5-abstraction) and enables the functionalization of remote unactivated carbons.[2] Interception of the intermediate radical by iodine is then followed by cyclization to give tetrahydrofurans (eq 1).[2a] This Barton-type reaction has been applied extensively in steroid chemistry.[1] Other oxidants, such as ***Lead(IV) Acetate-Iodine*** can also be used, although the $HgO-I_2$ combination has been reported to give a cleaner and higher yielding reaction.[2] An analogous reaction with *N*-nitro amines gives, by way of hydrogen abstraction by a nitrogen-centered radical, *N*-nitropyrrolidines.[3] Although

1,5-hydrogen abstraction is preferred, 1,6-abstraction is possible, particularly in cases where the former is not feasible (eq 2)[2c] or when it leads to stabilized radicals (eq 3).[4] The title reagents have also been used for functionalization at more remote positions,[5] in analogy with the work of Breslow.[6]

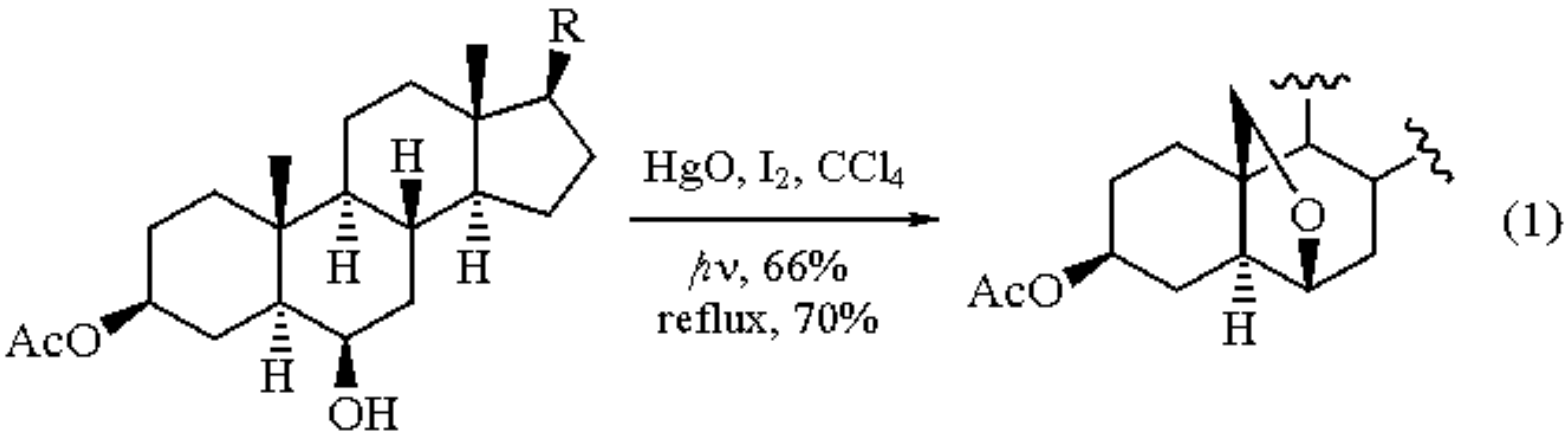

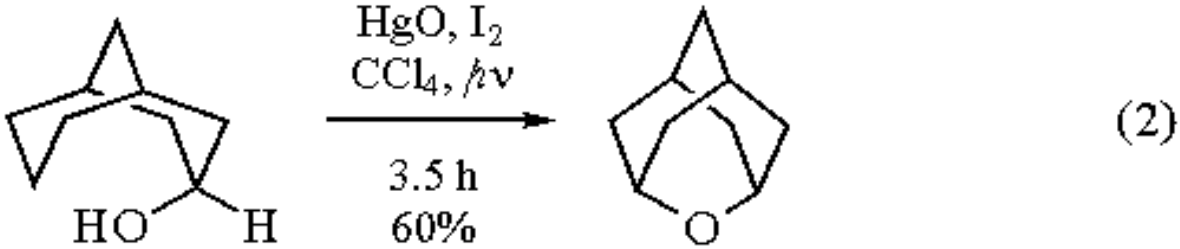

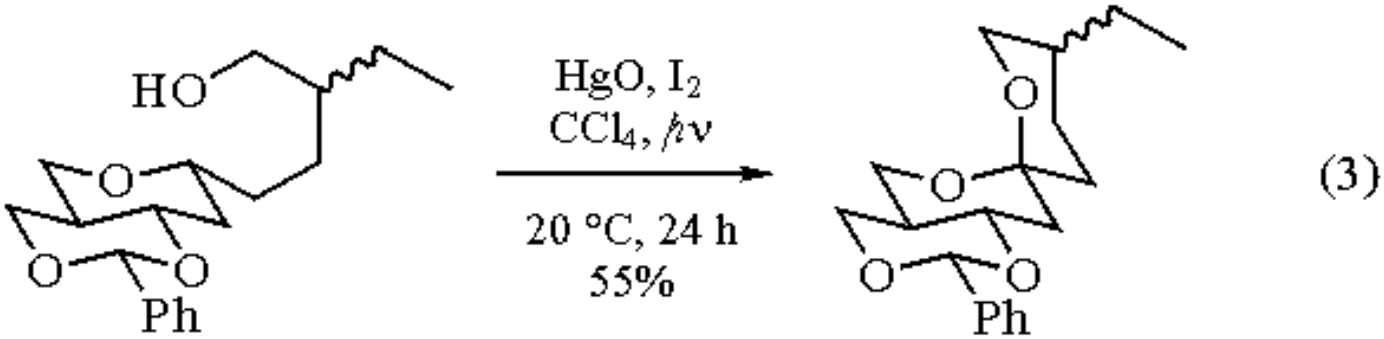

β-Fragmentation.

An important reaction of alkoxyl radicals is the homolytic cleavage of the adjacent C-C bond to yield a carbonyl and (generally) the more stable of the two possible carbon-centered radicals. In an early example, Barton found that irradiation of a mixture of cyclopentanol, HgO, and I_2 gives δ-iodovaleraldehyde.[2a] These fragmentation conditions are quite mild, as evidenced by the degradation of a highly functionalized steroidal alcohol to an aldehyde, presumably through an iodo intermediate (eq 4).[7] The β-fragmentation is particularly advantageous when the hydroxy group is located on a ring junction, since medium or large ring ketones can be formed, sometimes with elimination of the expected iodide (eq 5).[8] The factors that determine whether the central or the side-ring bond is broken are not well understood, although the stability of the resulting radical and relief of ring strain appear to be important (eq 6).[9]

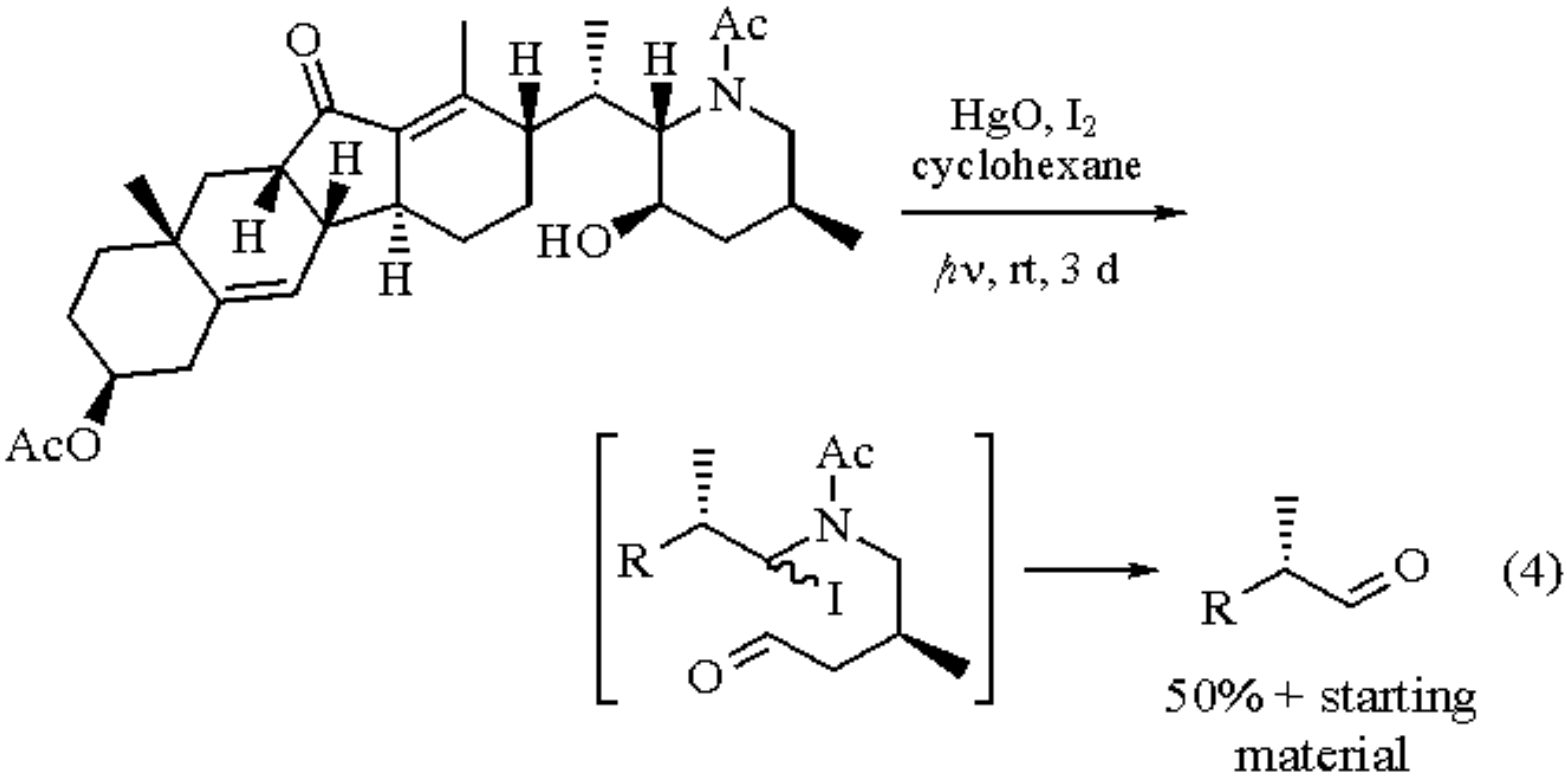

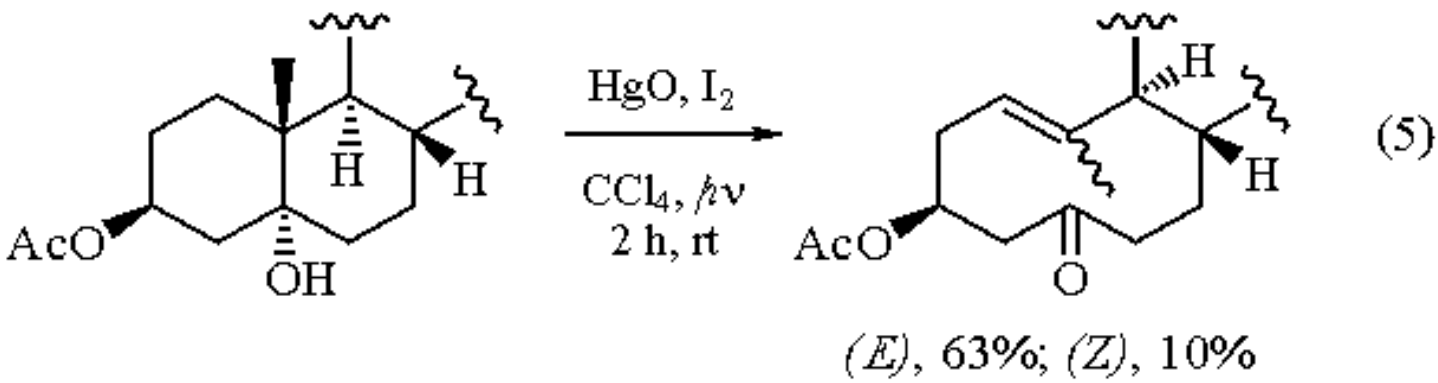

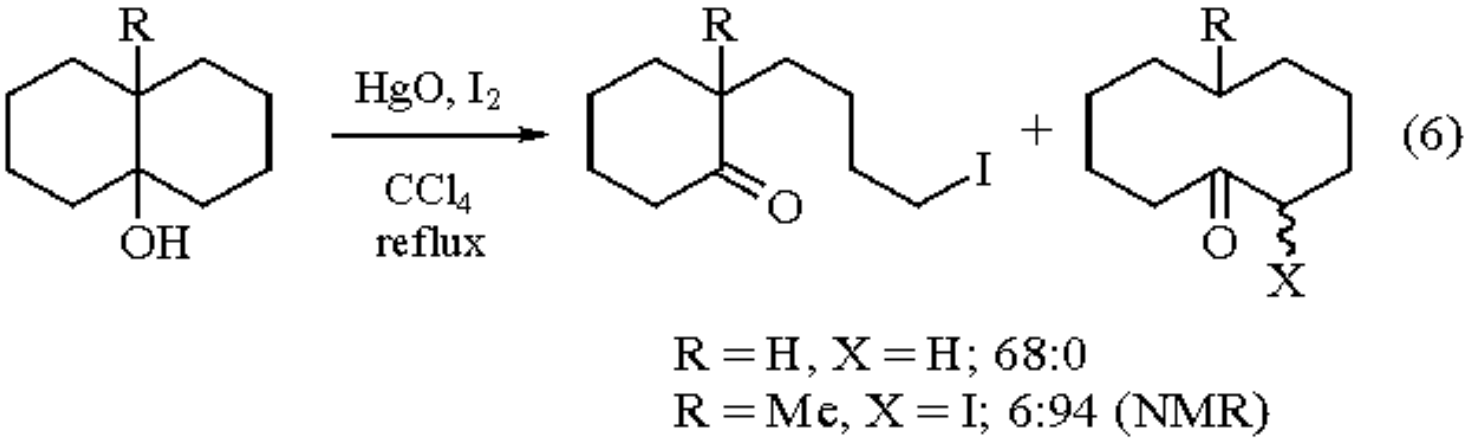

An analogous fragmentation process, involving the reaction of lactol-derived hypoiodites, provides a general route to medium and large ring lactones (eq 7).[10] The HgO-I_2 mediated fragmentation of hydroxy groups on nonbridging carbons gives iodoformates, via oxidative fragmentation of a lactol intermediate. Treatment of adamantan-2-ol under these conditions gives oxaadamantane directly, presumably by way of the lactol (eq 8).[11] Related fragmentations have

been studied extensively and offer a general route to cyclic ethers (eq 9).[12] Vicinal diols have been cleaved to the corresponding aldehydes using this reagent system.[2b]

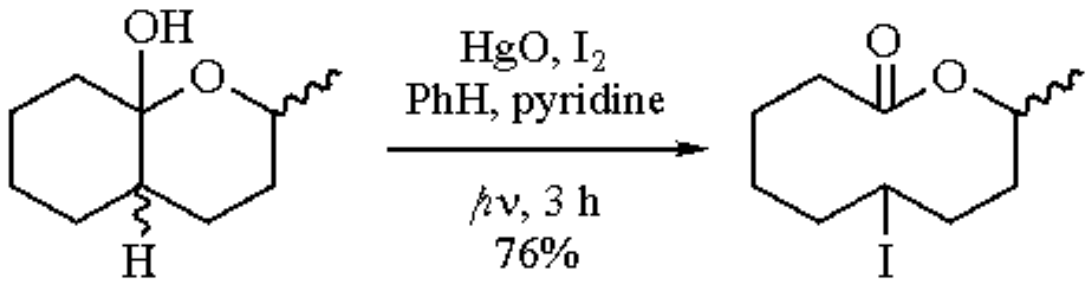

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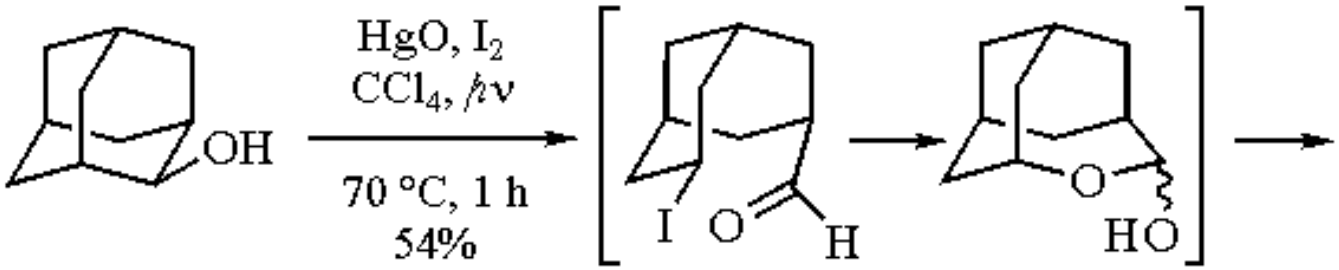

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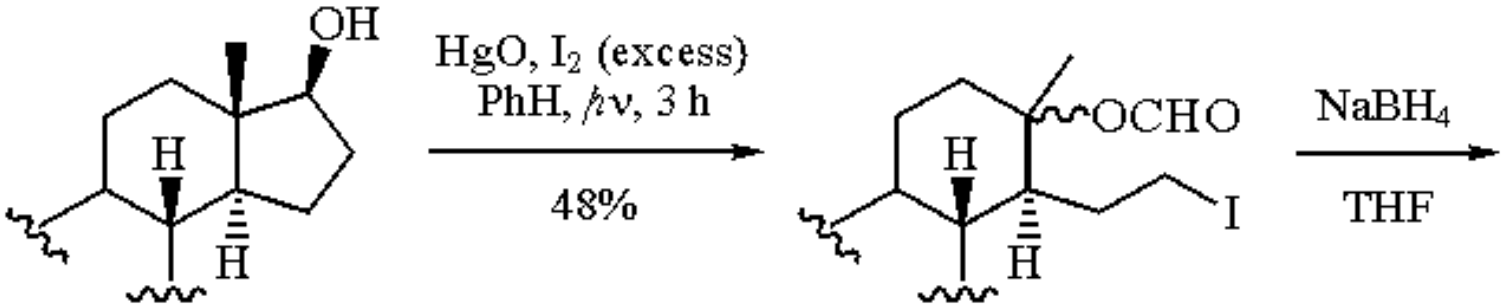

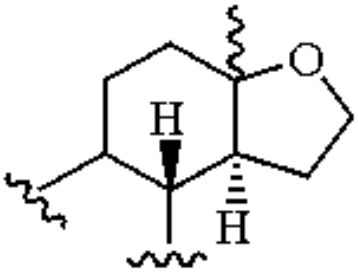

(9)

Additions to Unsaturated Compounds.

The title reagent system effects the addition of alkoxy-iodide to an alkene in an inter- or intramolecular sense (eq 10).[13]

Interestingly, the intramolecular addition is possible even for allylic alcohols and yields α-iodo epoxides (eq 11),[14] which are synthetically useful intermediates.[15] The yield of the iodo epoxide is significantly higher in the presence of a small amount of pyridine.

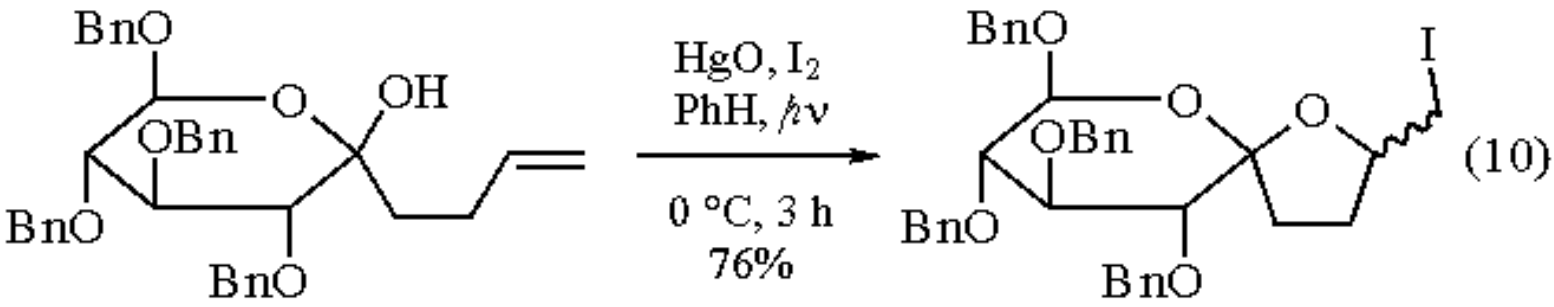

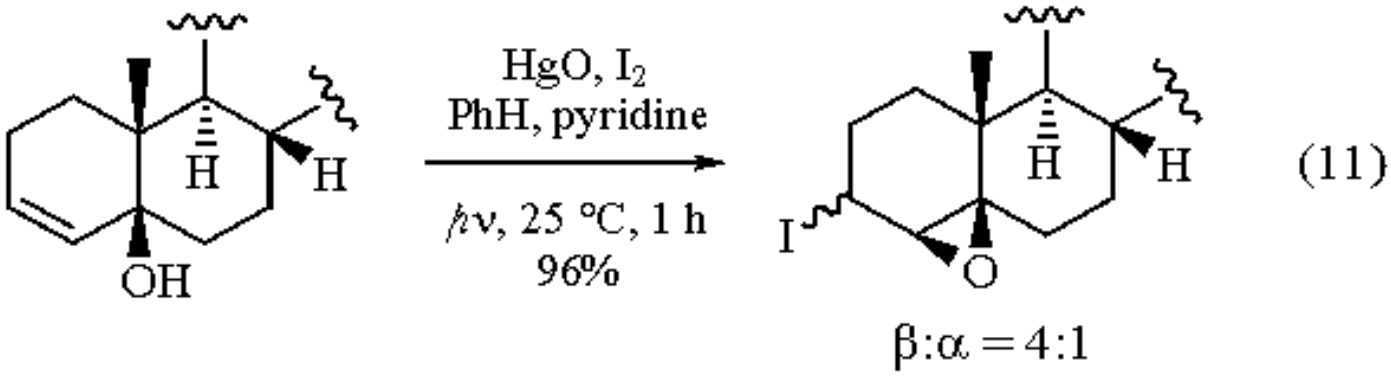

Miscellaneous Reactions.

Advantage has been taken of HgO-I_2 as a source of electrophilic iodide. Thianaphthene can be iodinated using this reagent system (eq 12).[16] Similarly, anisole is iodinated at the *para* position in high yield. The ethylene acetal of *p*-benzoquinone can be made through a two-step sequence in which both steps utilize HgO-I_2, first for electrophilic aromatic iodination and then for the formation of an alkoxyl radical from a hypoiodite intermediate (eq 13).[17]

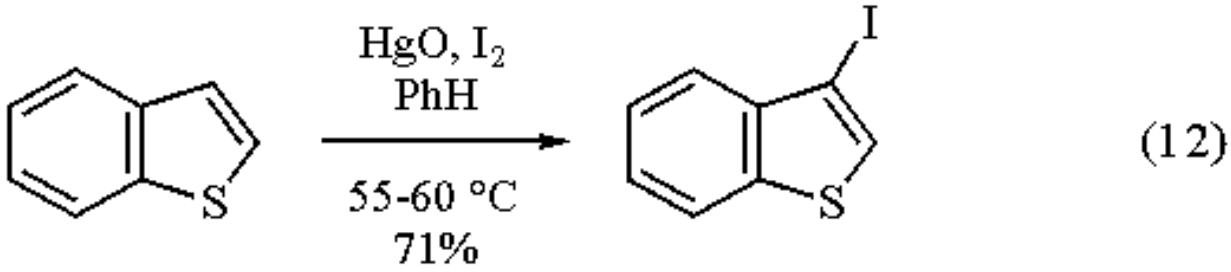

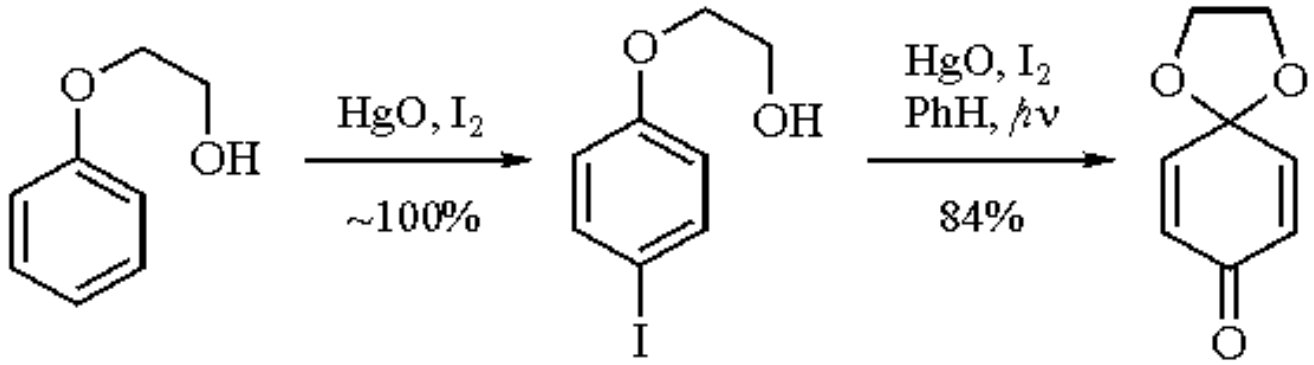

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Mercury(II) Oxide-Tetrafluoroboric Acid

$HgO\text{-}HBF_4$

(HgO)

[21908-53-2] · HgO · Mercury(II) Oxide-Tetrafluoroboric Acid · (MW 216.59) (HBF_4)

[16872-11-0] · BF_4H · Mercury(II) Oxide-Tetrafluoroboric Acid · (MW 87.82)

(capable of diamination[1] and hydroxyamination[2] of alkenes, cycloamination of dienes,[7,8] and of hydrolysis of alkyl bromides;[11] facilitates *m*-iodination of deactivated arenes[9])

Solubility: HBF_4: sol ethereal solvents.

Form Supplied in: HgO: red or yellow precipitate; the yellow form is more finely divided and more reactive than the red form. HBF_4: available as liquid Et_2O or Me_2O complexes.

Preparative Methods: reaction of ***Mercury(II) Oxide*** (red) with ***Tetrafluoroboric Acid*** (Et_2O solution) generates $Hg(BF_4)_2$ in situ.

Handling, Storage, and Precautions: acute poison; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light. Tetrafluoroboric acid is extremely corrosive.

Electrophilic Additions.

Mercury(II) tetrafluoroborate, generated in situ from HgO and HBF_4, appears to be the reagent of choice to promote diamination of alkenes with primary and secondary amines. The reaction occurs in THF at reflux and gives good to excellent yields (eq 1).[1] In the presence of alcohols, hydroxyamination is observed.[2] The structure of the products is consistent with an overall *anti* mechanism, involving aminomercuration followed by replacement of $HgBF_4^-$. The latter step occurs with overall retention,[3] apparently due to the participation of the neighboring nitrogen.[4]

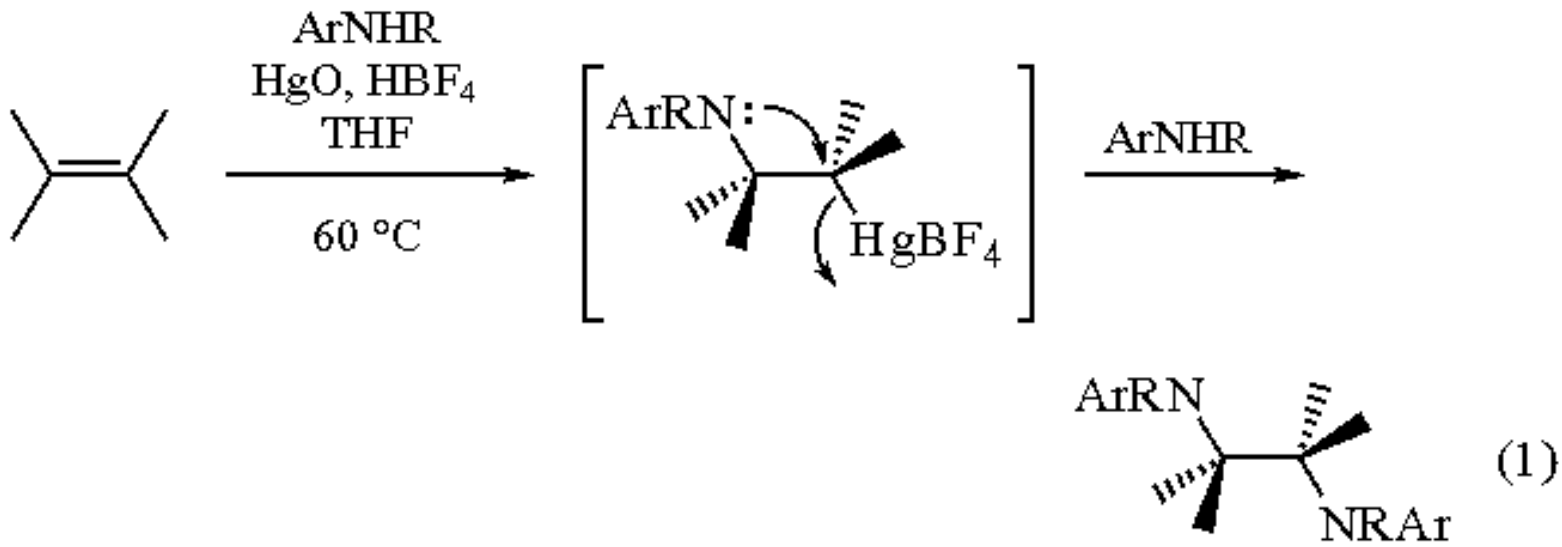

Allylic alcohols are converted into allylic amines with an overall 1,3-rearrangement (eq 2).[5]

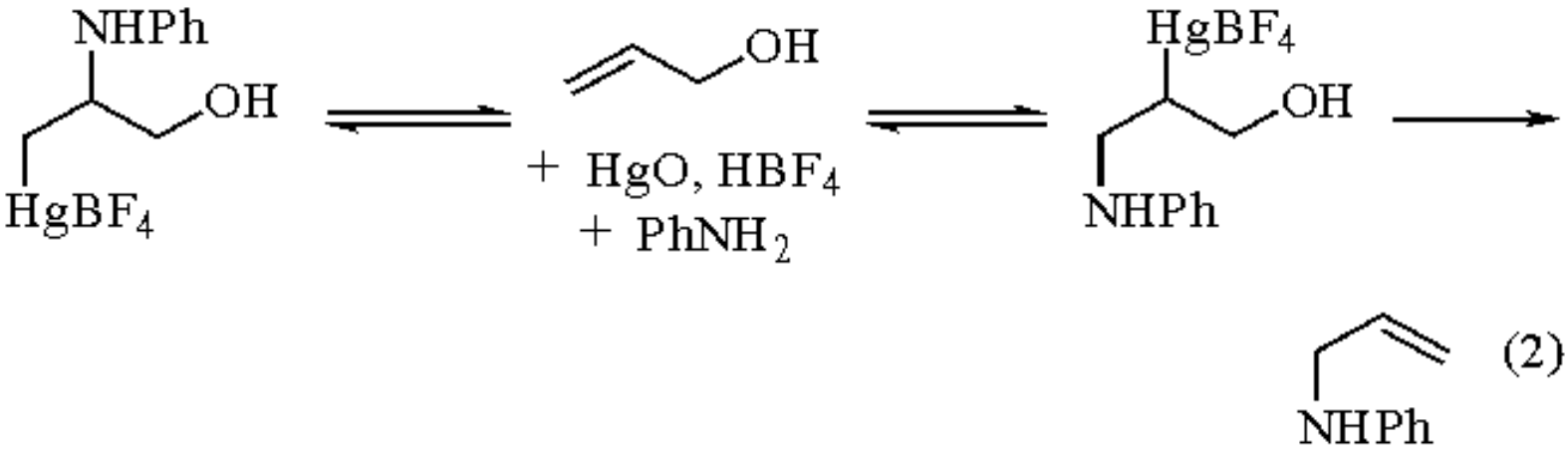

The reagent differentiates between di- and trisubstituted double bonds. Thus, for example, only the methylene group of limonene reacts (eq 3). Due to the nonnucleophilic anion, a variety of nucleophiles can be introduced in this way: H_2O (84% yield), MeOH (87%), AcOH (85%), NaN_3 (80%), and MeCN (80%, Ritter reaction).[6]

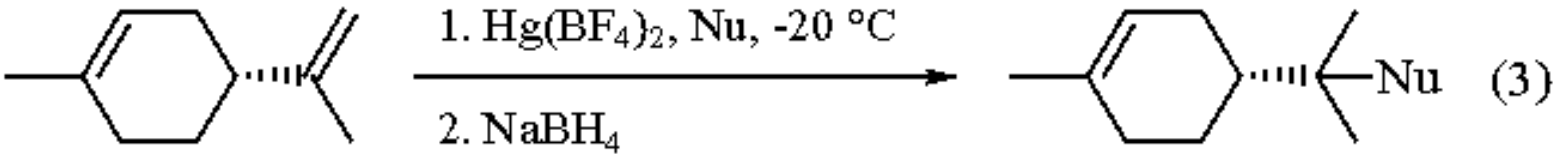

Conjugated dienes react with primary amines in the presence of HgO/HBF_4 to give products of 1,4-addition as reactive intermediates, which are converted to the corresponding pyrrolidine derivatives via an intramolecular S_N2 reaction (eq 4).[7] Nonconjugated dienes react with 2 equiv of $Hg(BF_4)_2$ to afford the corresponding adduct whose -$HgBF_4$ groups can be replaced by heteroatom nucleophiles such as water in a stereospecific manner (eq 5).[8]

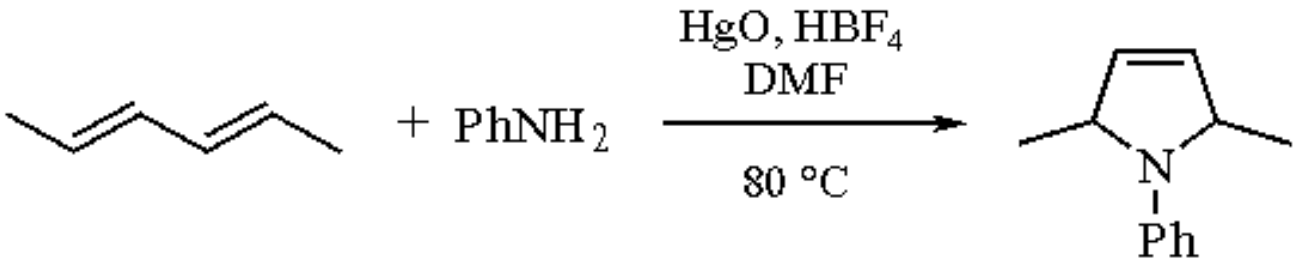

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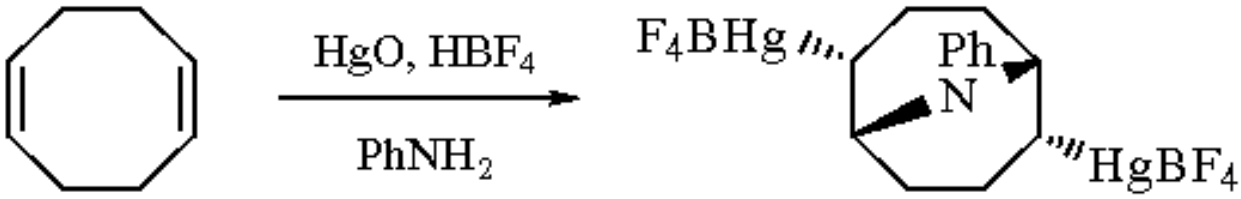

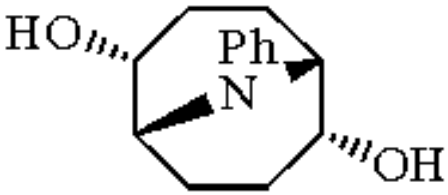

(5)

Allylic Oxidation.

Allylbenzene ($PhCH_2CH{=}CH_2$) is oxidized with HgO/HBF_4 in the presence of alcohols to afford exclusively *trans*-cinnamyl ethers, e.g. $PhCH{=}CHCH_2OMe$.[2a,9]

Aromatic Electrophilic Substitution.

Aromatic compounds can be iodinated by I_2 in the presence of the HgO/HBF_4 reagent. The orientation obeys the rules for aromatic electrophilic substitution: *ortho* attack is favored over *para* substitution with activated arenes. The method appears to be particularly useful for *meta* iodination of deactivated arenes (up to 99% selectivity).[10]

Hydrolysis of Dithioacetals.

The same reagent, generated in situ from HgO and 35% aq HBF_4 in THF, can hydrolyze dithioacetals and hemithioacetals more effectively than $HgO/BF_3.Et_2O$.[11]

Substitution Reactions.

Alkyl bromides are hydrolyzed by HgO/HBF_4 in THF, dioxane, or CH_2Cl_2 to the corresponding alcohols.[12] Similarly, ethers are obtained if stoichiometric amounts of alcohols are used. The yields range from 55 to 95% (eq 6).[12]

$$R^1Br \xrightarrow[HgO,\ HBF_4]{R^2OH} R^1OR^2 \qquad (6)$$

---

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Mercury(II) Perchlorate[1]

$Hg(ClO_4)_2.3H_2O$

[73491-34-6] · Cl_2HgO_8 · Mercury(II) Perchlorate · (MW 453.55)

(can hydrolyze vinyl halogenides[4] and thioacetals;[5] promotes formation of dialkyl ethers by nucleophilic substitution of alkyl bromides with alcohols;[7] cleaves cyclopropanes[8])

Alternate Name: mercuric perchlorate.

Physical Data: d ca. 4 g cm^{-3}.

Solubility: sol CH_2Cl_2, THF, DME; slightly sol alcohols; insol benzene, hexane, etc.

Form Supplied in: colorless lumps; widely available as the trihydrate.

Preparative Methods: can be prepared in situ by heating ***Mercury(II) Oxide*** and 60% aq $HClO_4$ at 40-60 °C for 1-5 min, or at rt by mixing ***Mercury(II) Acetate*** and $HClO_4$ in DME or THF.

Handling, Storage, and Precautions: acute poison; oxidizer; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg and Cl_2 fumes when heated to decomposition. Protect from light.

Like other Hg^{II} salts, the perchlorate facilitates electrophilic additions across alkenic double bonds.[1,2] Whereas oxymercuration normally occurs with *anti* stereoselectivity, products of *syn* addition have been observed for norbornene.[3]

Mercury(II) perchlorate and other Hg^{II} salts (namely sulfate, nitrate, and tetrafluoroborate) promote hydrolysis of vinyl halogenides to ketones (50-90%). The reaction is not catalytic and is believed to involve oxymercuration/dehalogenation (eq 1; X = Cl, Br).[4] Other Hg^{II} salts, such as $HgSO_4$, $Hg(NO_3)_2$, and $Hg(BF_4)_2$, react similarly.[4]

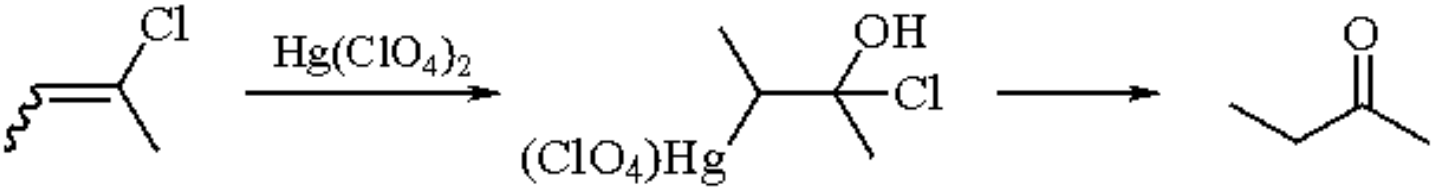

(1)

Monothioacetals of α-diketones can be converted into α-diketones upon oxidation with $Hg(ClO_4)_2$ (eq 2).[5] Analogous reaction with ***Thallium(III) Nitrate*** in MeOH results in the formation of the corresponding dimethyl monoacetal.[6]

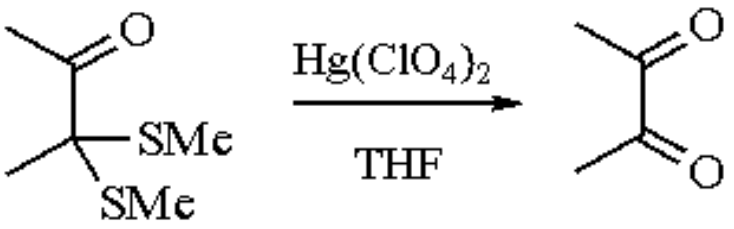

(2)

In the presence of $Hg(ClO_4)_2$, ethers (R^1OR^2) are formed from alkyl bromides (R^1Br) and aliphatic alcohols (R^2OH) via a nucleophilic substitution (R^1, R^2 = Me, Et, $PhCH_2$).[7]

In addition to other Hg^{II} salts, $Hg(ClO_4)_2$ is also very effective in the cleavage of cyclopropanes (eq 3).[8,9]

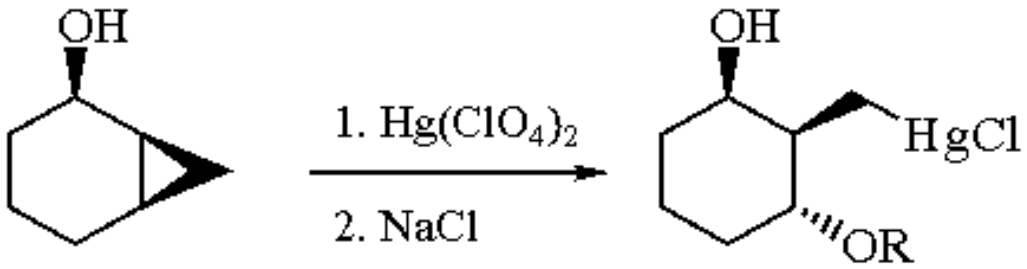

(3)

Related Reagents.

Mercury(II) Acetate; ***Mercury(II) Nitrate***; ***Mercury(II) Trifluoroacetate***.

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1. (a) Larock, R. C. *AG(E)* **1978**, *17*, 27. (b) Larock, R. C. *T* **1982**, *38*, 1713. (c) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (d) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: Berlin, 1986.
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4. Arzoumanian, H.; Metzger, J. *JOM* **1973**, *57*, C1.
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8. (a) Collum, D. B.; Mohamadi, F.; Hallock, J. S. *JACS* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *JACS* **1986**, *108*, 2094.
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Pavel Ko&cbreve;ovský

Mercury(II) Pivalate

$(t\text{-BuCO}_2)_2Hg$

[32276-77-0] · $C_{10}H_{18}HgO_4$ · Mercury(II) Pivalate · (MW 402.87)

(oxymercuration[2])

Alternate Name: mercuric pivalate.

Solubility: sol THF, DME; insol benzene, hexane, etc.

Preparative Methods: see White et al.[2]

Handling, Storage, and Precautions: acute poison; mercury carboxylates are generally easily absorbed through the skin and are corrosive; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Mercury(II) pivalate has similar synthetic applications as the acetate and other Hg^{II} electrophiles.[1,2] In contrast to, e.g. ***Mercury(II) Acetate***, the pivalate has better solubility in THF and exhibits higher regio- and stereoselectivity in oxymercuration reactions.[3] The pivalate has been employed to conduct the intramolecular oxymercuration which afforded isolineatin in 42% yield after hydride reduction of the intermediate organomercurial (eq 1).[2]

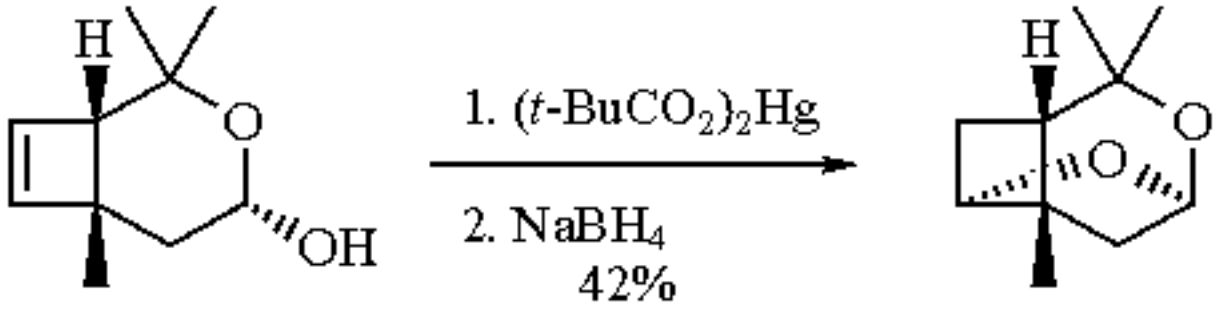

(1)

Related Reagents.

Mercury(II) Acetate; ***Mercury(II) Trifluoroacetate***.

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1. (a) Larock, R. C. *AG(E)* **1978**, *17*, 27. (b) Larock, R. C. *T* **1982**, *38*, 1713. (c) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (d) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: Berlin, 1986.
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Mercury(II) Sulfate

$HgSO_4$

[7783-35-9] · HgO_4S · Mercury(II) Sulfate · (MW 296.66)

(converts alkynes and vinyl halides into ketones;[1-5,9] facilitates conversion of glucals into furan derivatives[7])

Alternate Name: mercuric sulfate.

Physical Data: mp dec; *d* 6.470 or 7.56 g cm^{-3}.

Solubility: insol H_2O (dec into a yellow, basic sulfate); sol HCl, hot dil H_2SO_4, HNO_3, and conc solution of NaCl.

Form Supplied in: white, odorless, monoclinic crystals, granules, or powder.

Handling, Storage, and Precautions: acute poison; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

In combination with strong acids[1-4] or Dowex 50,[4,5] $HgSO_4$ is often employed as a catalyst for effecting hydration of alkynes, which results in the formation of the corresponding ketones (eq 1). This strategy has been used in the synthesis of 19-norprogesterone[6] and histamine.[3b]

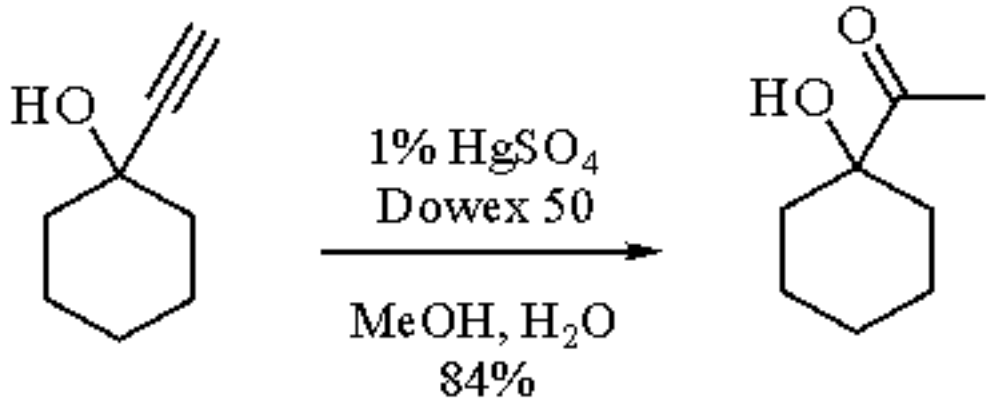

(1)

D-Glucal has been found to produce (2*R*)-(1,2-dihydroxyethyl)furan when treated with $HgSO_4/H_2SO_4$ (eq 2).[7] Other glycals undergo hydration or elimination.[8]

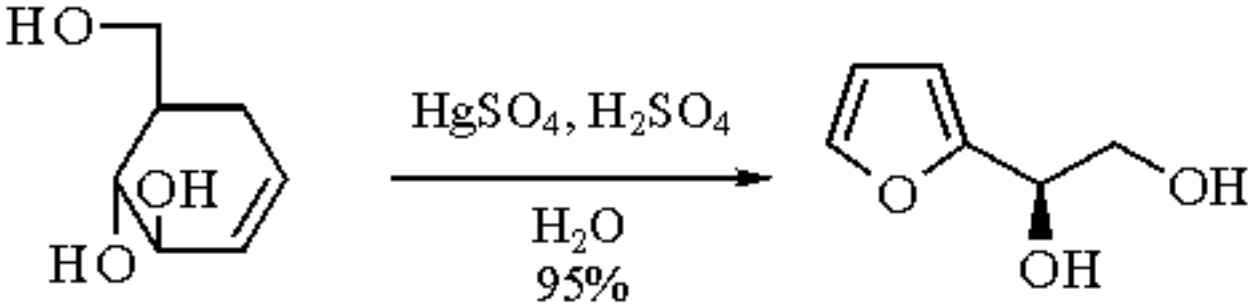

(2)

Similarly to other mercury(II) salts, $HgSO_4$ effects hydrolysis of vinyl halides to ketones[9] and allylic oxidation (Deigès reaction).[10]

Related Reagents.

Mercury(II) Acetate.

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1. (a) Larock, R. C. *AG(E)* **1978**, *17*, 27. (b) Larock, R. C. *T* **1982**, *38*, 1713. (c) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (d) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: Berlin, 1986.
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Mercury(II) Thiocyanate

$Hg(SCN)_2$

[592-85-8] · $C_2HgN_2S_2$ · Mercury(II) Thiocyanate · (MW 316.77)

(catalyst for addition of HSCN to alkynes[1,2])

Alternate Name: mercuric thiocyanate.

Physical Data: mp ca. 165 °C (dec).

Solubility: slightly sol H_2O, alcohols; sol NH_3 and NH_4 salts.

Form Supplied in: white, odorless needles or powder.

Handling, Storage, and Precautions: acute poison; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light.

Mercury(II) salts, e.g. $Hg(SCN)_2$, catalyze addition of thiocyanic acid (HSCN) across the triple bond of a variety of alkynes (eq 1);[1,2] HSCN is formed in situ from $Bu_4N^+SCN^-$ and a strong acid (H_2SO_4, HCl, or HBF_4).[2] $Hg(SCN)_2$ appears to be the catalyst of choice as it suppresses the formation of the corresponding methyl ketones.[2] In the presence of ***Bromine***, $Hg(SCN)_2$ has been reported to effect a formal addition of Br-SCN across a C=C bond (due to the replacement of HgX in the primary adduct by halogen).[3]

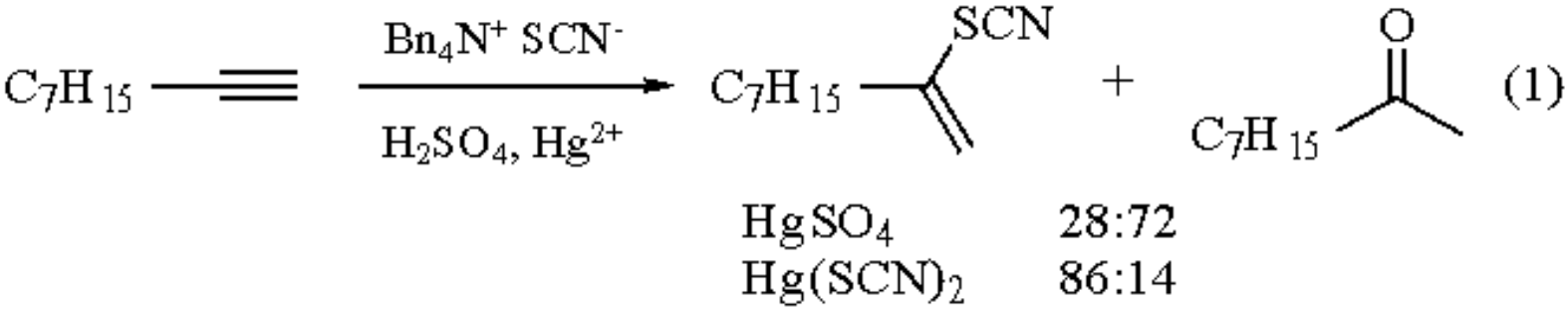

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1. (a) Larock, R. C. *AG(E)* **1978**, *17*, 27. (b) Larock, R. C. *T* **1982**, *38*, 1713. (c) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (d) Larock, R. C. *Solvomercuration/Demercuration Reactions in Organic Synthesis*; Springer: Berlin, 1986.

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Mercury(II) Trifluoroacetate[1]

$(CF_3CO_2)_2Hg$

[13257-51-7] · $C_4F_6HgO_4$ · Mercury(II) Trifluoroacetate · (MW 426.63)

(oxymercuration[3] and aminomercuration[17] of alkenes; polyene cyclization;[21] allylic oxidation;[32] macrolide synthesis[37])

Alternate Name: mercuric trifluoroacetate.

Physical Data: mp 171-173 °C.

Solubility: sol THF, DME, dioxane; insol hexane.

Preparative Methods: can be prepared from ***Mercury(II) Oxide*** in ***Trifluoroacetic Acid***[2-4] or generated in situ from ***Mercury(II) Acetate*** and CF_3CO_2H.[8b]

Form Supplied in: white, hygroscopic crystals.

Handling, Storage, and Precautions: acute poison; is easily absorbed through the skin and is corrosive; exposure to all mercury compounds is to be strictly avoided. Releases toxic Hg fumes when heated to decomposition. Protect from light. Use in a fume hood.

Oxymercuration.[3-5]

The reactivity of mercury(II) trifluoroacetate is similar to that of ***Mercury(II) Acetate*** but exhibits higher electrophilicity.[3] Thus, for instance, while cholesterol and other alkenes with a trisubstituted double bond are normally reluctant to react with $(AcO)_2Hg$ (unless neighboring group participation boosts the reaction), $(CF_3CO_2)_2Hg$ reacts readily with cholesteryl acetate (eq 1).[6] Even α,β-unsaturated esters react with $(CF_3CO_2)_2Hg$; the corresponding adducts are readily transformed into α-bromo derivatives (eq 2).[7] Generally, in the presence of Cl_2 or Br_2, the HgX group in the original adduct is replaced by halogen.[1,5]

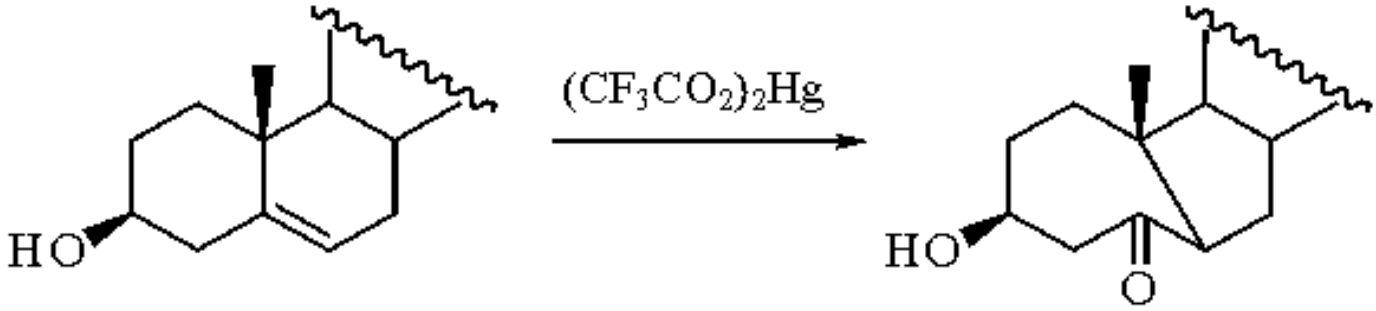

(1)

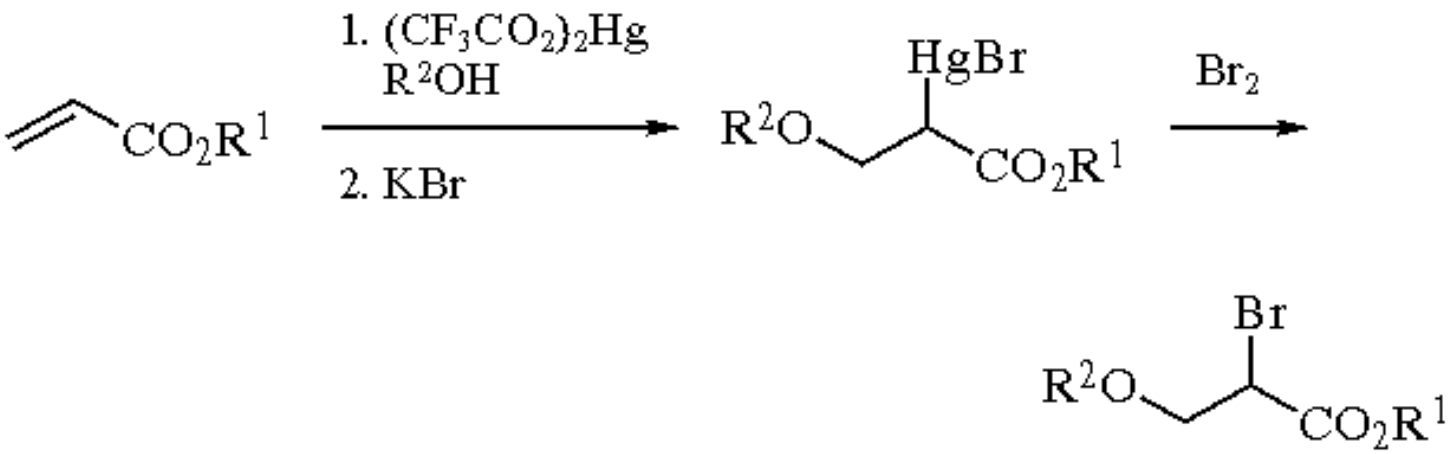

(2)

Increased selectivity in oxymercuration has been observed when $(CF_3CO_2)_2Hg$ and other Hg^{II} salts were generated in situ from HgO and RCO_2H in an inert solvent (CH_2Cl_2, hexane, or aq THF) on sonication.[4]

Whereas oxymercuration normally occurs with *anti* stereoselectivity,[3,4] products of *syn* addition have been observed for norbornene derivatives.[8]

Intramolecular oxymercuration[9] has been extensively utilized for the construction of various oxygen heterocycles, usually with high stereoselectivity (eq 3).[10] Both isolated[9,10] and conjugated[11] double bonds react, and 5-*exo-trig*, 5-*endo-trig*, and 6-*exo-trig* reactions have all been observed.[9-11] Similarly, cyclic peroxides are formed from the unsaturated peroxides.[12]

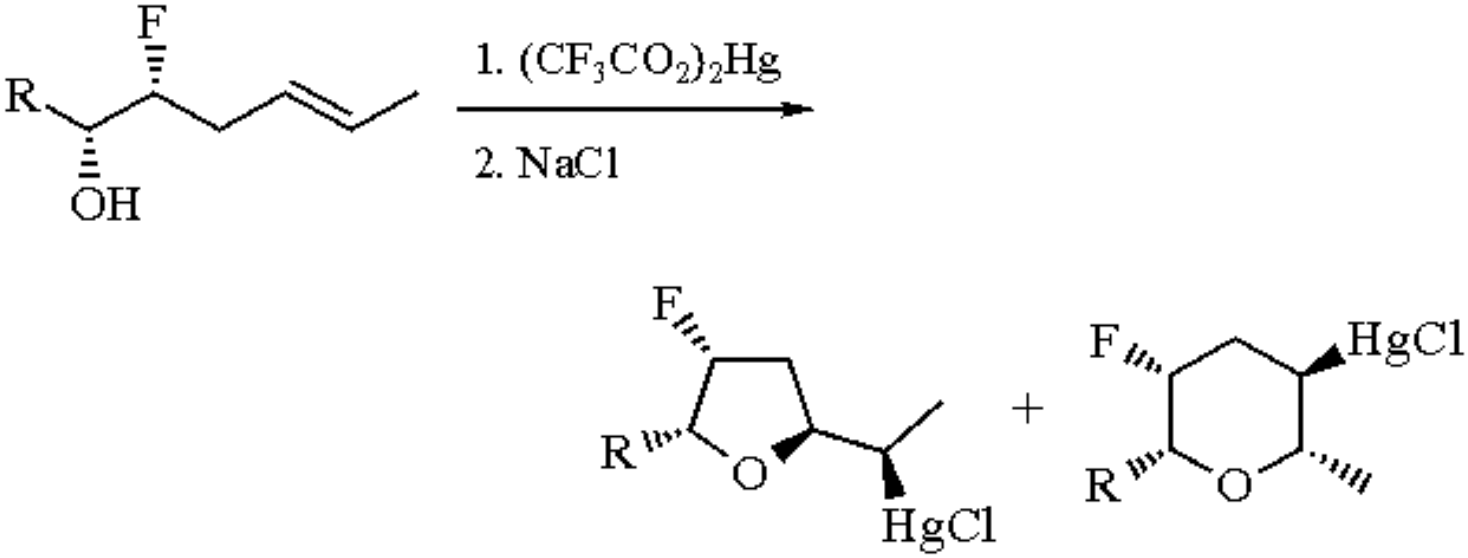

(3)

The relatively stable trichloroacetals derived from allylic alcohols can be utilized as intermediates to accomplish stereo- and regiocontrolled mercuration which gives *cis*-1,2-diols (eq 4).[13] However, this method has the following limitations: (1) the original hydroxy group must be equatorial, (2) the double bond cannot be trisubstituted, (3) the reaction is not regioselective for acyclic allylic alcohols, and (4) the reaction is unsuccessful with homoallylic alcohols.[13]

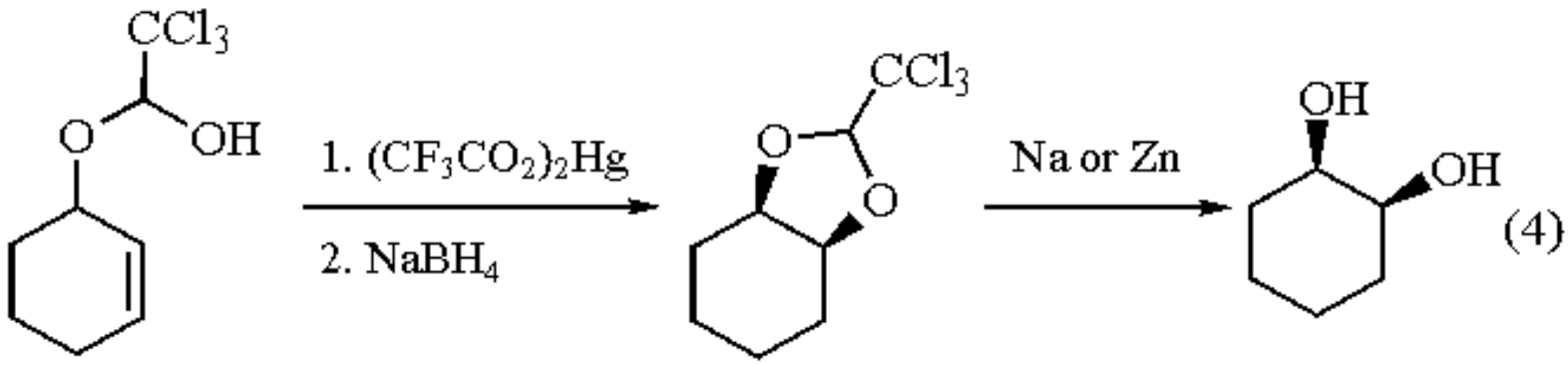

Hydroxy allenes seem to be particularly suitable substrates as the sp^2-bonded mercury can be transmetalated with palladium salts, which expands the versatility of this methodology (eq 5).[14] Alkynic alcohols also produce vinylmercurials (with some preference for (*Z*) isomers)[15] which can be further elaborated, e.g. by conversion into vinyl halides on reaction with sources of electrophilic halogen (***N-Iodosuccinimide***).[16]

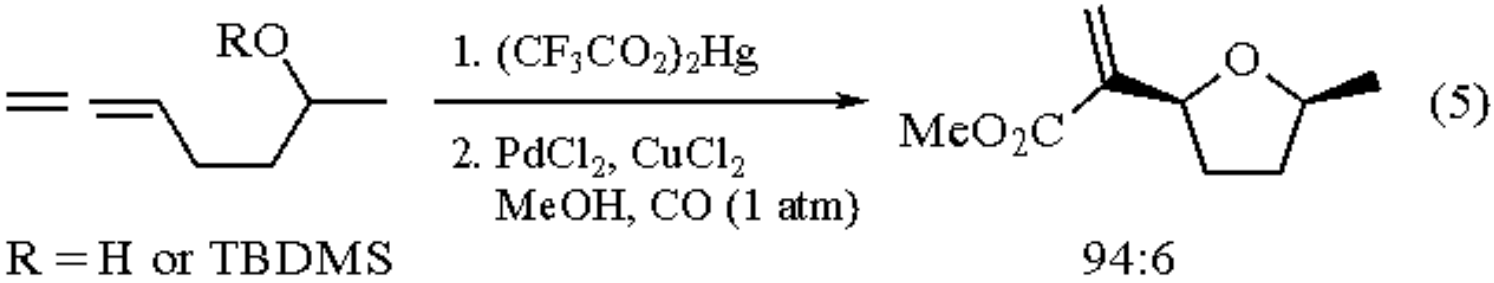

Aminomercuration.

Intramolecular aminomercuration followed by demercuration is a useful method of construction of a variety of nitrogen heterocycles such as aza sugars.[17] Intramolecular amidomercuration, employing $(CF_3CO_2)_2Hg$, has also been reported.[18] It has been shown that the steric course of mercuration can be controlled by a neighboring nitrogen group (eq 6).[19]

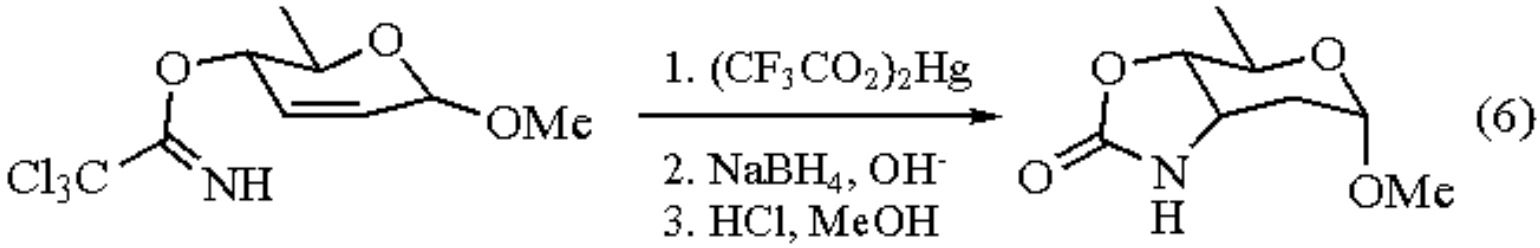

Azidomercuration of an alkenic double bond can be accomplished in quantitative yield (in the case of a

monosubstituted double bond) by the reaction carried out with $(CF_3CO_2)_2Hg$ and ***Sodium Azide*** (3:1) in THF-H_2O (1:1) at 60 °C for 48 h.[20] This method has been utilized for syntheses of amino sugars. By contrast, $(AcO)_2Hg$ gives only 20% in the same case.[20]

Polyene Cyclization.

Acyclic isoprenoids are stereospecifically cyclized on reaction with $(CF_3CO_2)_2Hg$ to afford polycyclic structures (eq 7).[21] An aromatic ring can be used in place of the nucleophilic double bond in a similar type of cyclization.[22]

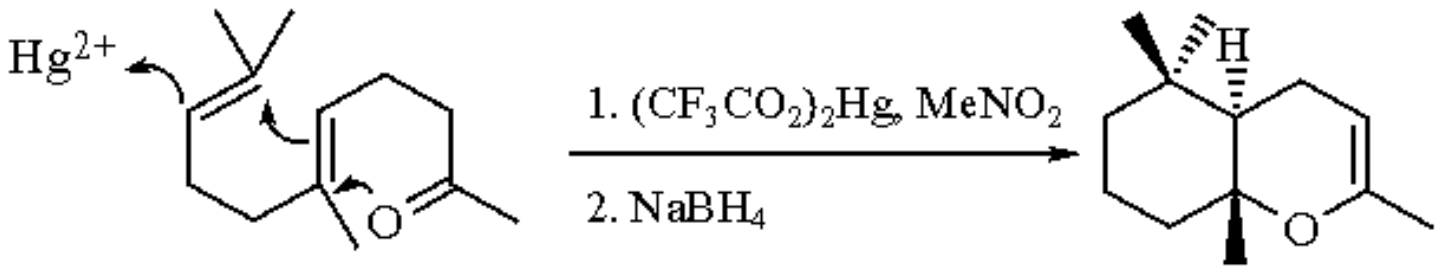

(7)

Cyclopropane Ring Opening.

Mercury(II) trifluoroacetate readily opens up cyclopropane rings.[23] The reaction is usually faster than that with $(AcO)_2Hg$ and slower than for ***Mercury(II) Nitrate***.

Mercuration of Aromatics.

Being a good electrophile, $(CF_3CO_2)_2Hg$ and other Hg^{II} salts also attack aromatic rings.[24,25] Combined with the subsequent reaction with iodine, this method has long served to accomplish iodination in cases where the arene is inert to direct iodination. Polyhaloaromatics can also be synthesized in this way.[26]

[3,3]-Sigmatropic Rearrangements.

Oxy-Cope rearrangement can be initiated at rt by $(CF_3CO_2)_2Hg$ (1 equiv); the intermediate α-mercurio ketone is then demercurated with ***Sodium Borohydride***.[27] The reaction can be carried out with a catalytic amount of Hg^{II} and an excess of lithium triflate or trifluoroacetate.[28] The Claisen rearrangement of allylic carbamates can be best achieved via a suprafacial [3,3]-migration mediated by $(CF_3CO_2)_2Hg$ (eq 8); the reaction is thermodynamically controlled.[29] Using a carbamate derived from an optically active amine, formation one of the diastereoisomers may be preferred; however, this method seems to have a limited value due to the low de.[30]

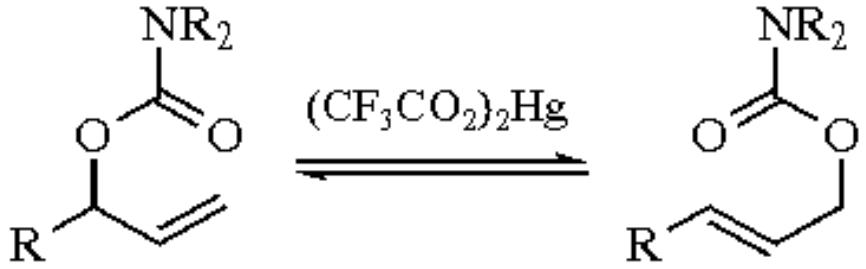

(8)

Allylic Oxidation (Treibs Reaction[31]).[32]

More effective than the acetate, $(CF_3CO_2)_2Hg$ facilitates allylic oxidation[33,34] of alkenes which are generally reluctant to be oxymercurated (namely those with trisubstituted double bonds). Thus, cholesterol and its esters are converted, after hydrolysis, to the 3β,6β-dihydroxy-4-ene at 0 °C in 40-70% yields.[33]

Hydrolysis of Vinyl Chlorides.

The original Wichterle reaction[35] relied on the hydrolysis of vinyl chlorides with H_2SO_4. The improved version utilizing $(CF_3CO_2)_2Hg$ allows the control of regioselectivity by the solvent.[36] Thus, hydrolysis in $MeNO_2$, CH_2Cl_2, or AcOH gives only 1,5-diketone (to be cyclized) in up to 97% yield, whereas hydrolysis in MeOH gives mainly the 1,4-diketone (eq 9).[36]

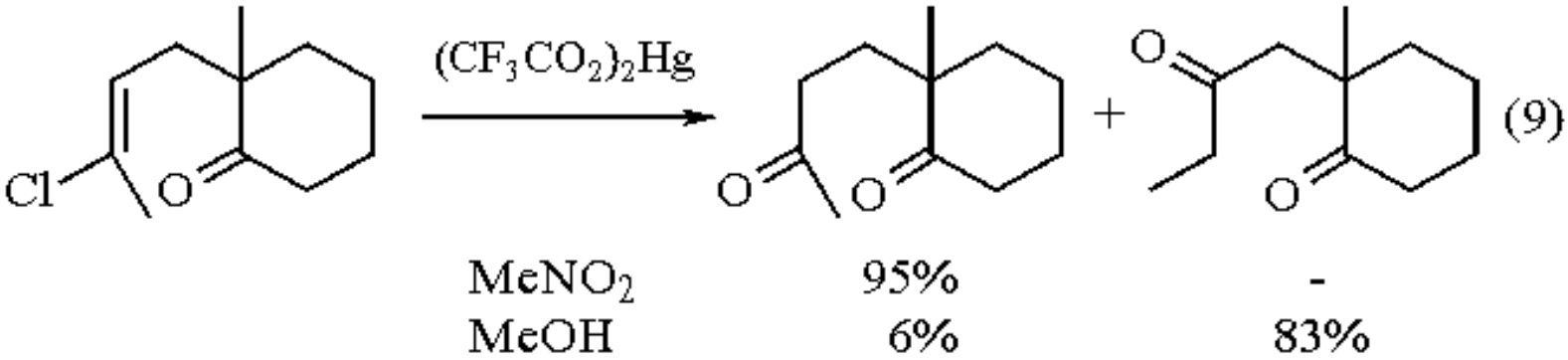

Synthesis of Macrolides.

t-Butyl thioesters are converted to esters on reaction with $(CF_3CO_2)_2Hg$ or $(MeSO_3)_2Hg$. This method is general for synthesis of macrolides (eq 10) but cannot be used for substrates containing electron-rich centers such as double bonds (which undergo oxymercuration); other less electrophilic cations can be employed in those instances (Cu^+, Cu^{2+}, or Ag^+).[37]

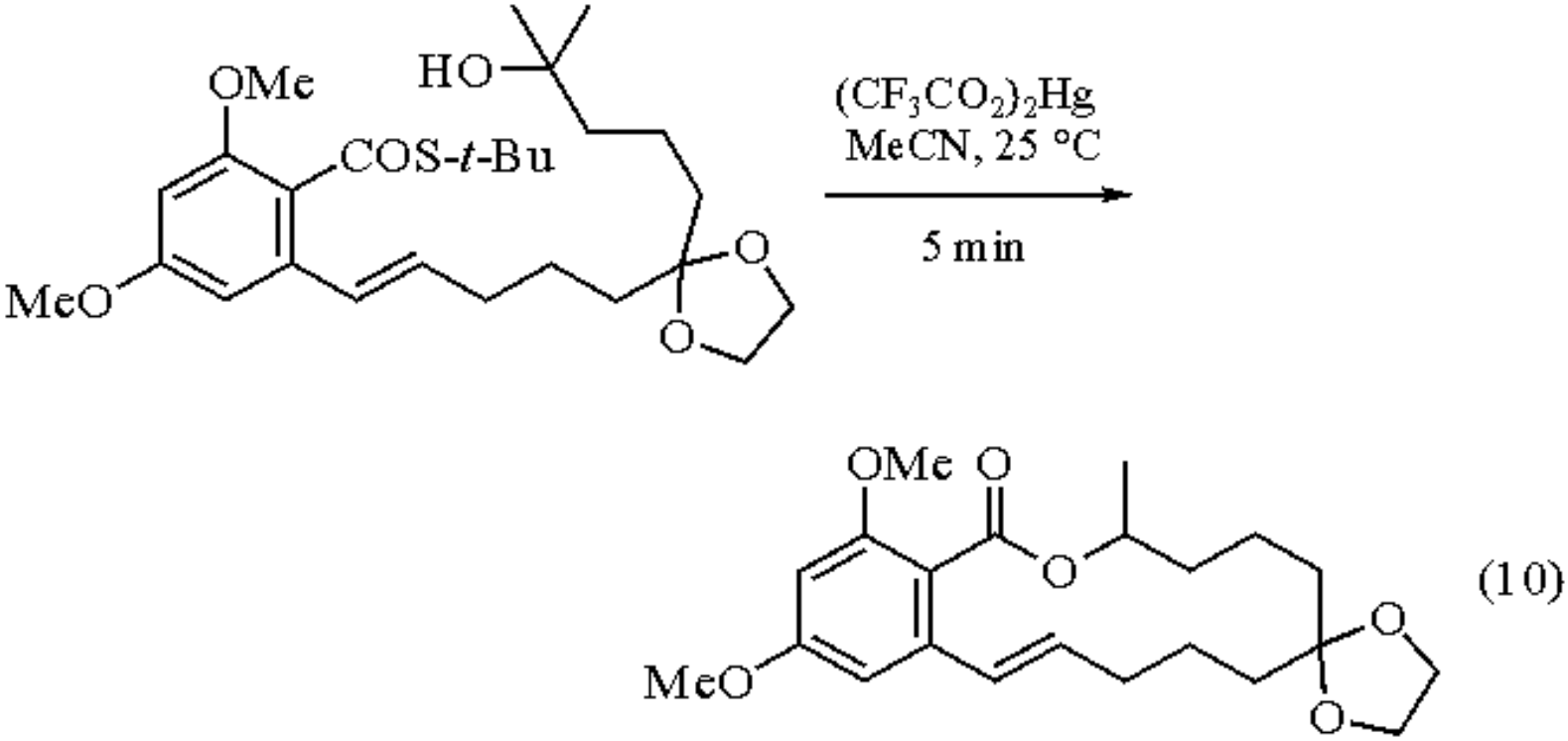

Miscellaneous.

Like HgO or Tl^{III}, mercury(II) trifluoroacetate oxidizes phenols and hydroquinones to quinones in the presence of an acid scavenger.[38] Monohydrazones of α-diketones are oxidized with $(CF_3CO_2)_2Hg$ to give α-diazo ketones.[2] Enol esters, obtained by the reaction of 4-dimethylamino-3-butyn-2-one with o-hydroxy carboxylic acids, react with $(CF_3CO_2)_2Hg$ or ***10-Camphorsulfonic Acid*** to give macrocyclic lactones.[39] 1,3-Dioxolanium salts are converted to α-mercurio derivatives of carboxylic acids on reaction with $(CF_3CO_2)_2Hg$ or $(AcO)_2Hg$.[40] TMS derivatives of tertiary vinyl alcohols undergo Wagner-Meerwein migration on treatment with $(CF_3CO_2)_2Hg$; this can be used as a ring-expansion methodology in cyclic systems.[41]

Related Reagents.

t-Butyldimethylsilyl Hydroperoxide-Mercury(II) Trifluoroacetate; ***Mercury(II) Acetate***.

---

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O-Mesitoylhydroxylamine

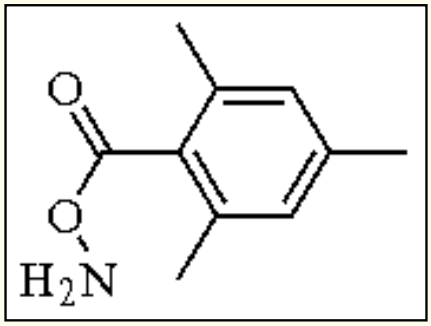

[37477-17-1] · $C_{10}H_{13}NO_2$ · *O*-Mesitoylhydroxylamine · (MW 179.24)

(reagent for electrophilic aminations, H_2N transfers to nucleophiles)

Physical Data: oil; mp of *N*-acetyl-*O*-mesitoylhydroxylamine 128-129 °C.[1]

Preparative Method: a solution of 10.0 g (35.8 mmol) *t*-butyl *N*-mesitoyloxycarbamate in 150 mL of nitromethane was treated with a stream of anhydrous hydrogen chloride for 5-7 min. After standing for 15 min the precipitated solid (**1**) (mp 125-127 °C, dec) was filtered, washed with nitromethane, dried in air and then suspended in 100 mL of water and treated with 1 M sodium bicarbonate solution until gas evolution stopped. The resulting oil was extracted with three 15 mL portions of CH_2Cl_2, the extracts dried over magnesium sulfate, and the solvent removed from a water bath at room temperature under reduced pressure (ca. 12-20 mmHg). *O*-mesitoylhydroxylamine (**2**) remained as a clear, colorless oil; 5.5 g (86%) (eq 1).[2]

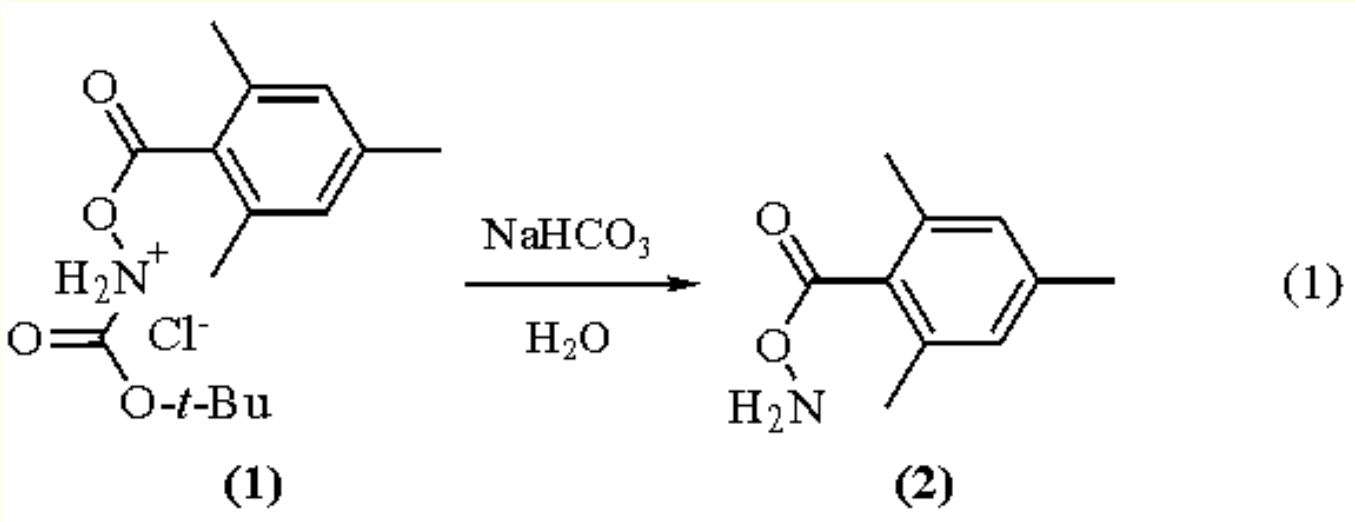

(1)

Handling, Storage, and Precautions: explosions which have been reported for compounds similar to (**2**), e.g. ***O-(Mesitylsulfonyl)hydroxylamine*** or *O*-(*p*-tolylsulfonyl)hydroxylamine,[2] have not been described for (**2**).

Reactions with Amines.

While *O*-(mesitylsulfonyl)hydroxylamine is the reagent of choice for the *N*-amination of heteroaromatic and tertiary amines,[1] it is (**2**) which should be used for the preparation of 1,1-disubstituted hydrazines from secondary amines (Table 1).[1,2a,3] Compound (**2**) is also a good reagent for the amination of anionic nitrogen atoms of amides, pyrroles, and related compounds, as shown in Table 2.[4,5]

Table 1 1,1-Disubstituted Hydrazines from **(2)** and Secondary Amines

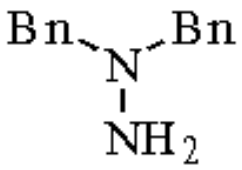

(3) 58%

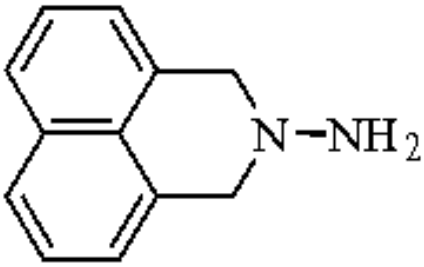

(4) 39%

Table 2 *N*-Amination of 'Anionic' Nitrogen Atoms of Organometallic Compounds RM with **(2)**

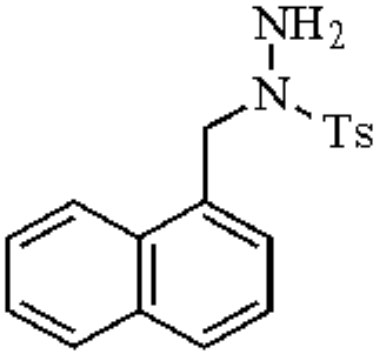

(5) 43% (RNa)

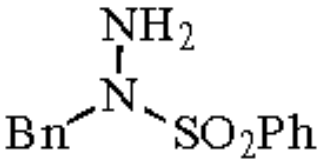

(6) 57% (RNa)

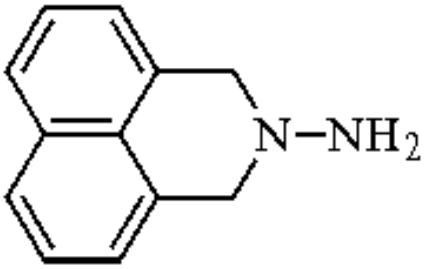

(4) 87% (RNa)

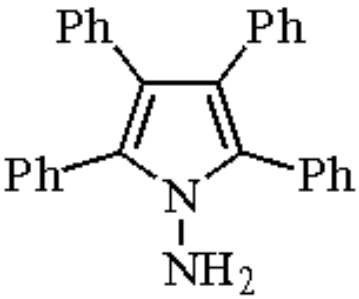

(7) 37% (RNa)

One should mention here that *O*-(2,4-dinitrophenyl)hydroxylamine (**8**) also aminates substrates of this type quite well.[1,6,7] In contrast, *O*-(mesitylsulfonyl)hydroxylamine[1] is not a good reagent for such reactions.

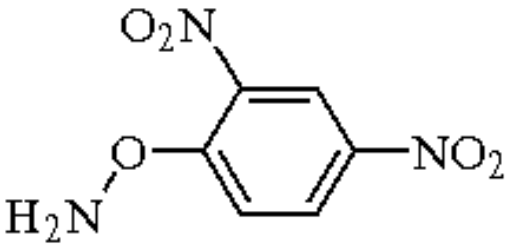

(8)

Miscellaneous Reactions.

O-Mesitoylhydroxylamine (**2**) was used (among others) for the α-amination of dilithiated carboxylic acids, $RCHLiCO_2Li$;[8] however, success was very poor. Other aminating reagents for these and other carbanions turned out to be much better, as excellently described in a recent review.[9]

Makhova et al. used (**2**) for the preparation of diaziridines,[10] a reaction which is also performed with *O*-(mesitylsulfonyl)hydroxylamine.

Finally, (**2**) has been identified as an oxidative inhibitor of cysteine proteinases.[11]

Related Reagents.

O-(Diphenylphosphinyl)hydroxylamine; ***O-(Mesitylsulfonyl)hydroxylamine***.

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Mesitylcopper(I)

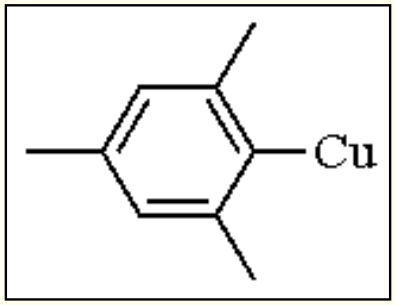

[75732-01-3] · $C_9H_{11}Cu$ · Mesitylcopper(I) · (MW 182.75)

(thermally stable and soluble metalation agent for active hydrogen compounds;[1] nontransferable group of mixed organocuprates;[1] catalyst for conjugate reduction of α,β-unsaturated carbonyl compounds by lithium aluminum hydride[1])

Alternate Name: 2,4,6-trimethylphenylcopper(I).

Physical Data: thermally stable up to ca. 100 °C; exists as a pentamer.

Solubility: sol benzene, ether, THF; partly sol hexane.

Preparative Method: prepared by the metathesis reaction between ***Copper(I) Chloride*** and mesitylmagnesium bromide in THF and can be isolated by precipitating magnesium salts with addition of dioxane.[1]

Handling, Storage, and Precautions: extremely oxygen- and moisture-sensitive. Preparation and reaction should be conducted under rigorously oxygen-free and anhydrous conditions.

Metalation.

Copper(I) t-Butoxide has been known to be a useful metalation agent for a variety of active hydrogen compounds under mild conditions with concomitant quantitative liberation of *t*-butyl alcohol to generate corresponding organic Cu^I compounds. Mesitylcopper(I) is a unique organocopper(I) compound with high thermal stability and solubility, and acts as a more powerful metalation agent than copper(I) *t*-butoxide with concomitant liberation of inert mesitylene and without accompanying salts. For example, mesitylcopper(I) effects the metalation of primary and secondary amines (eq 1),[1,2] which copper(I) *t*-butoxide cannot perform. Metalation of functionalized benzoic acids[3] such as 2-bromobenzoic acid (eq 2) occurs readily, where mesitylcopper(I) is more efficient than 2-tolylcopper(I). Copper(I) 2-bromobenzoate is an intermediate of the Hurtley reaction and cannot be prepared by the conventional ***Copper(I) Oxide*** method. Metalation of perfluoro-*t*-butyl alcohol affords copper(I) perfluoro-*t*-butoxide (eq 3),[4] which is one of the

most volatile copper alkoxides and may be useful for sol-gel and chemical vapor deposition processes. Organic reactions utilizing the excellent thermal stability of mesitylcopper(I) have been reported: formaldehyde insertion into its Cu-C bond[5] and its palladium(0)-catalyzed cross-coupling[6] with aryl iodides in the presence of Bu_4NX (X = Br, I).

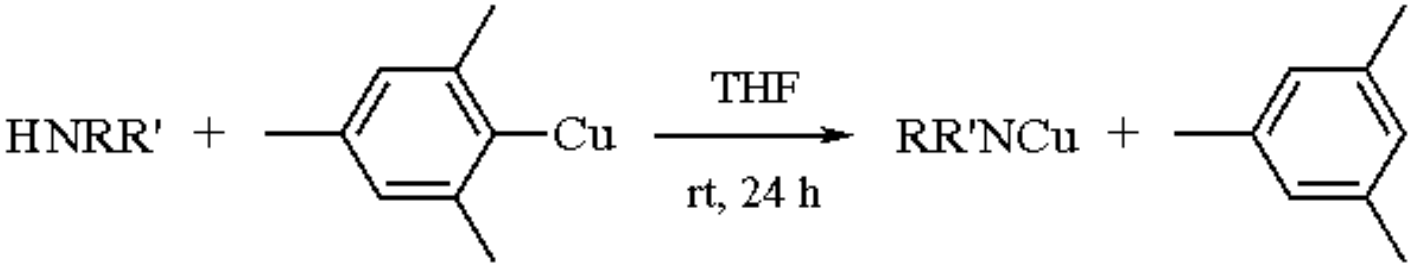

(1)

R, R' = H, Et, Bu, -$(CH_2)_5$-, -$(CH_2)_2O(CH_2)_2$-; R = H, R' = Bu, *t*-Bu, Ph

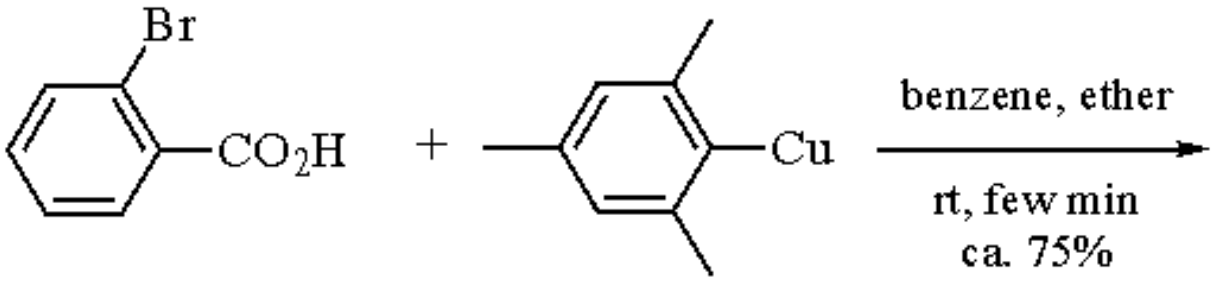

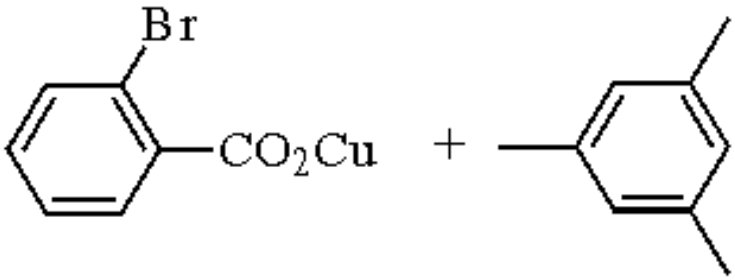

(2)

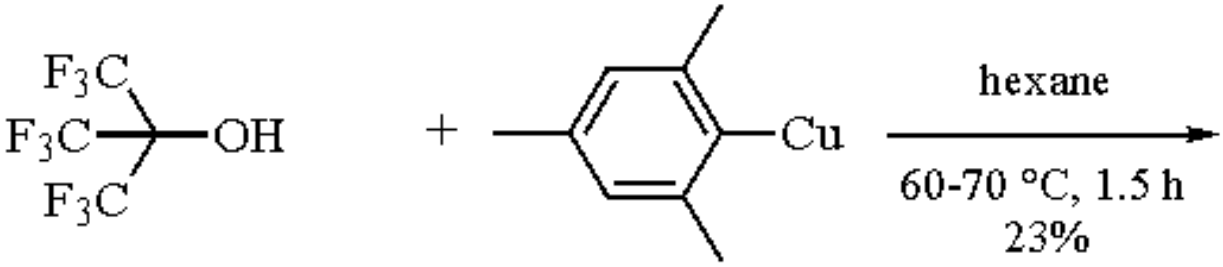

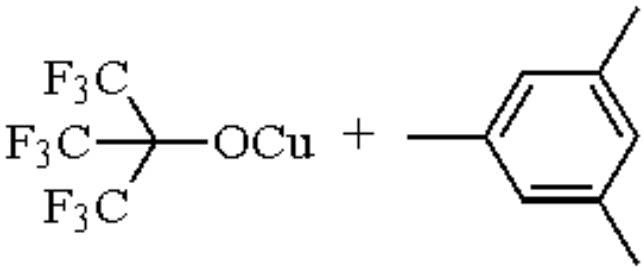

(3)

Nontransferable Group of Mixed Organocuprates.

Nontransferable groups of mixed organocuprates have been developed for stabilizing organocuprate reagents and for saving one organic group of diorganocuprates. Mesitylcopper(I) can be used for a nontransferable group of mixed organocuprates having primary and secondary alkyl groups (eq 4).[1]

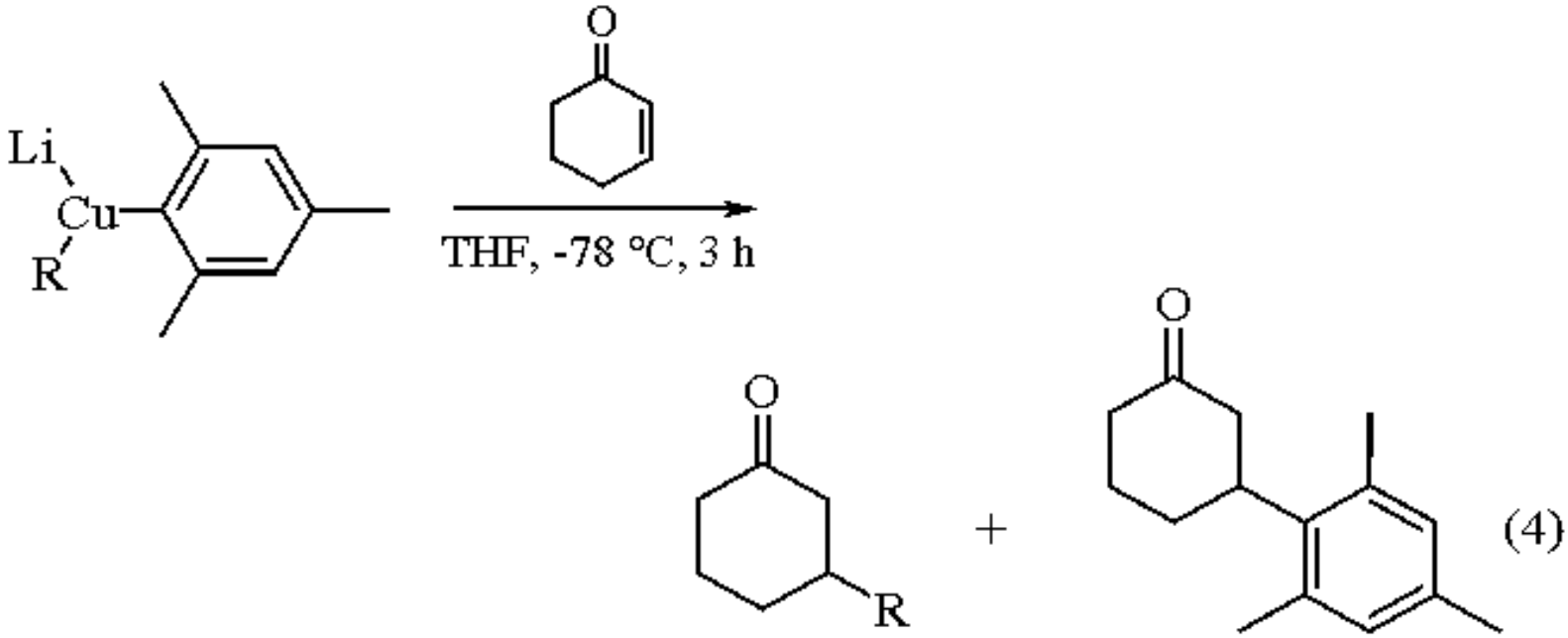

R = Bu	90%	0%
R = *s*-Bu	85%	trace
R = *t*-Bu	26%	19%

Catalyst for Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Lithium Aluminum Hydride.

Mesitylcopper(I) catalyzes conjugate reduction of α,β-unsaturated aldehydes and ketones by ***Lithium Aluminum Hydride*** (LAH) in the presence of ***Hexamethylphosphoric Triamide*** (HMPA) (eq 5).[1] Mesitylcopper(I)/LAH/HMPA has been the basis of the development of the related reagents CuI/LAH/HMPA[7] and $MeCu^{I}$/DIBAL/HMPA,[8] which similarly effect conjugate reduction of α,β-unsaturated carbonyl compounds (see ***Lithium Aluminum Hydride-Copper(I) Iodide***, ***Methylcopper***, and ***Diisobutylaluminum Hydride***).

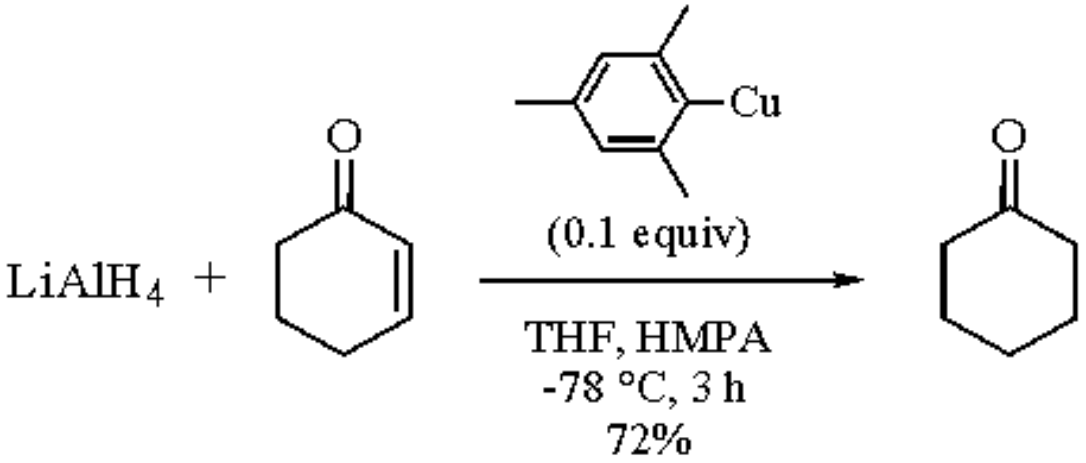

(5)

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Mesitylenesulfonyl Chloride

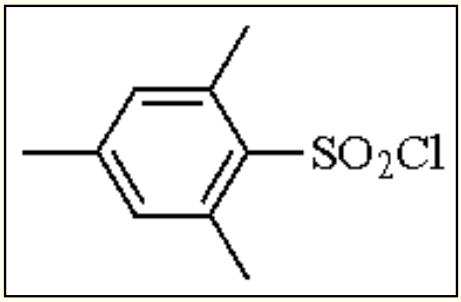

[773-64-8] · $C_9H_{11}ClO_2S$ · Mesitylenesulfonyl Chloride · (MW 218.72)

(preparation of sulfonates;[1] condensing agent in nucleotide synthesis[2])

Alternate Name: 2,4,6-trimethylbenzenesulfonyl chloride.

Physical Data: mp 55-57 °C.

Solubility: sol organic solvents.

Form Supplied in: white crystalline solid; widely available.

Purification: can be recrystallized from hexane or pentane.

Handling, Storage, and Precautions: corrosive; moisture sensitive; handle and store under nitrogen.

Sulfonamide Formation.

Reaction of mesitylenesulfonyl chloride with amines in the presence of ***Pyridine*** or ***Triethylamine*** yields the corresponding sulfonamides (eq 1),[3] which have been used as intermediates in synthesis.

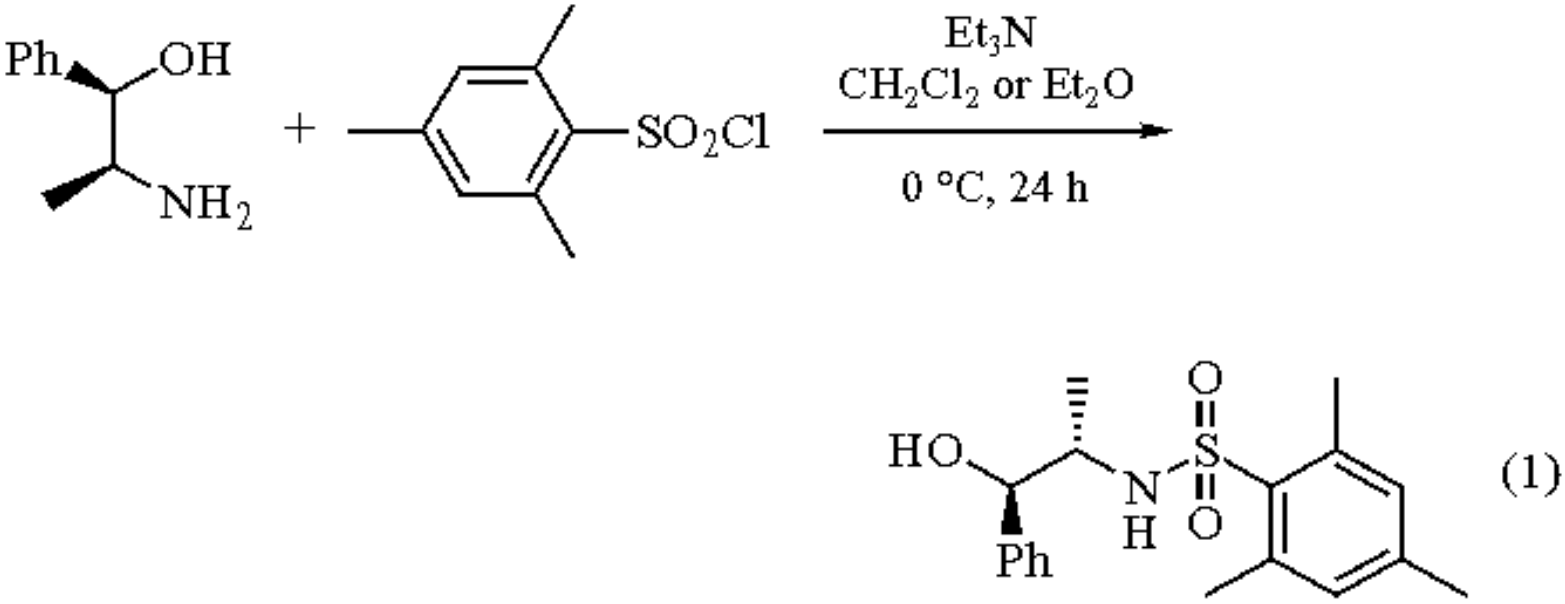

The mesityl group has been used as a protecting group for various amines including amino acids (eq 2)[4] and peptides.[5-7]

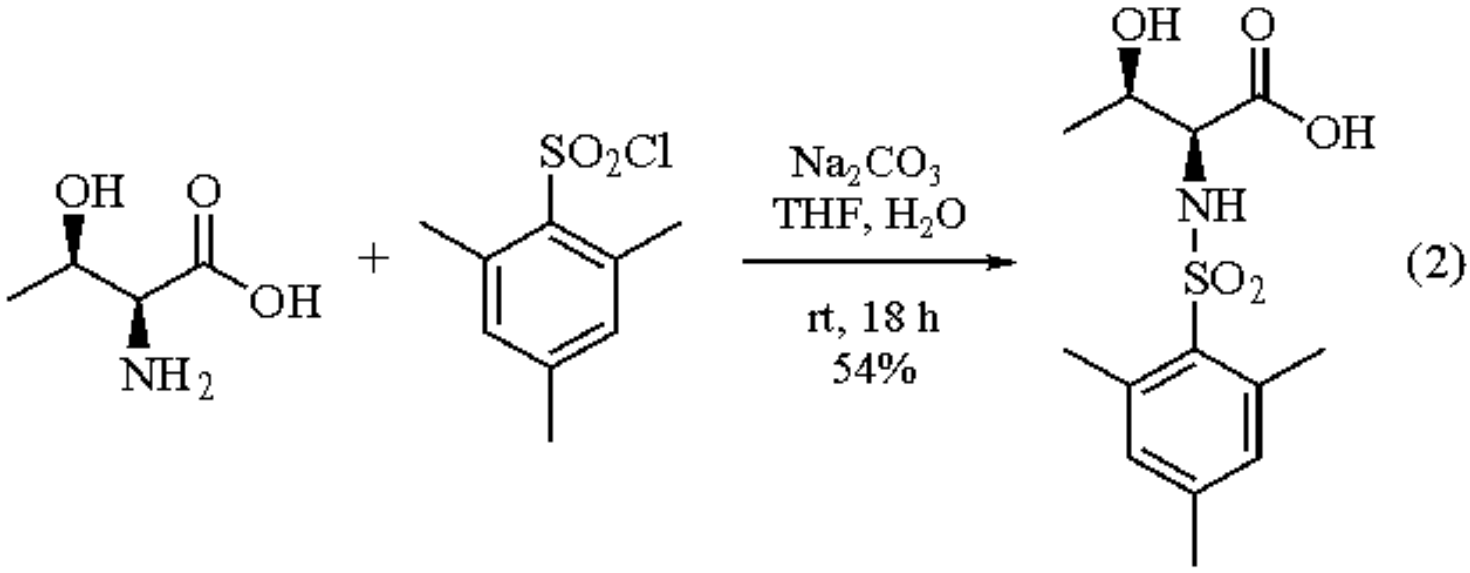

The mesitylsulfonyl-protected amino acids can be deblocked by treatment with ***Hydrogen Bromide*** and ***Acetic Acid***. The stability of the sulfonamide towards both acidic and basic conditions makes it a useful protecting group for peptide synthesis. The mesitylenesulfonyl group has been used to protect the indole group of tryptophan[6] and the guanidine group of arginine.[7] These mesityl derivatives can be cleaved with ***Trifluoromethanesulfonic Acid*** or ***Methanesulfonic Acid***. Partial cleavage of the guanidinomesityl group occurs when treated with HBr/HOAc. The mesitylenesulfonyl group has also been used as a blocking group for other indoles. Boteju et al. reported the formation of the indole sulfonamide by treatment with ***n-Butyllithium*** and mesitylenesulfonyl chloride, but the sulfonamide group was not subsequently removed (eq 3).[8]

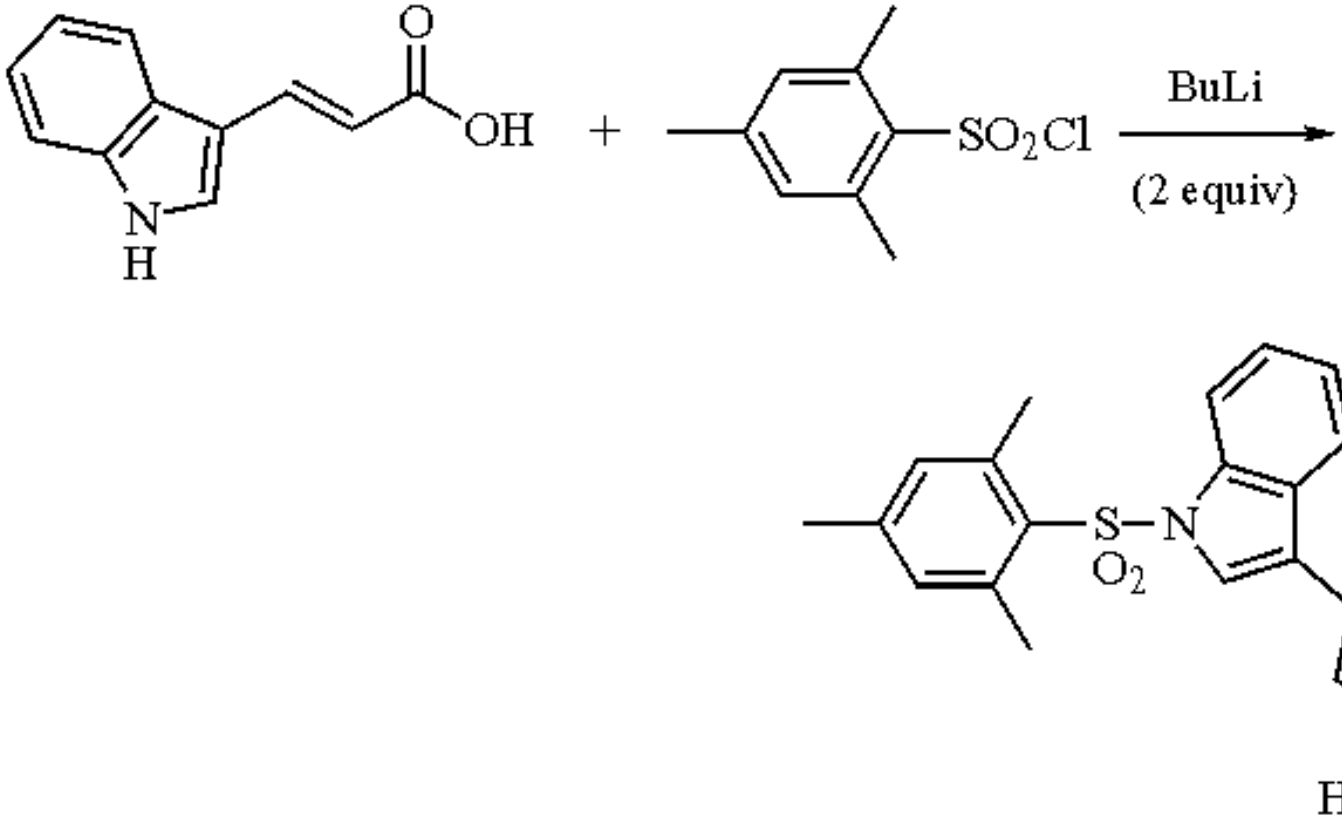

(3)

Sulfonate Formation.

Treatment of alcohols with mesitylenesulfonyl chloride yields the corresponding sulfonates. Mesitylenesulfonyl chloride is particularly useful for the selective sulfonation of polyhydroxylic systems such as carbohydrates (eq 4).[1,9] It is more selective than ***p-Toluenesulfonyl Chloride***, which has been frequently used but gives mixtures of products. Unfortunately, the mesitylenesulfonates are not as reactive as the corresponding tosylates. Numerous 1´-derivatives of sucrose have been synthesized via mesitylenesulfonyl derivatives.[10]

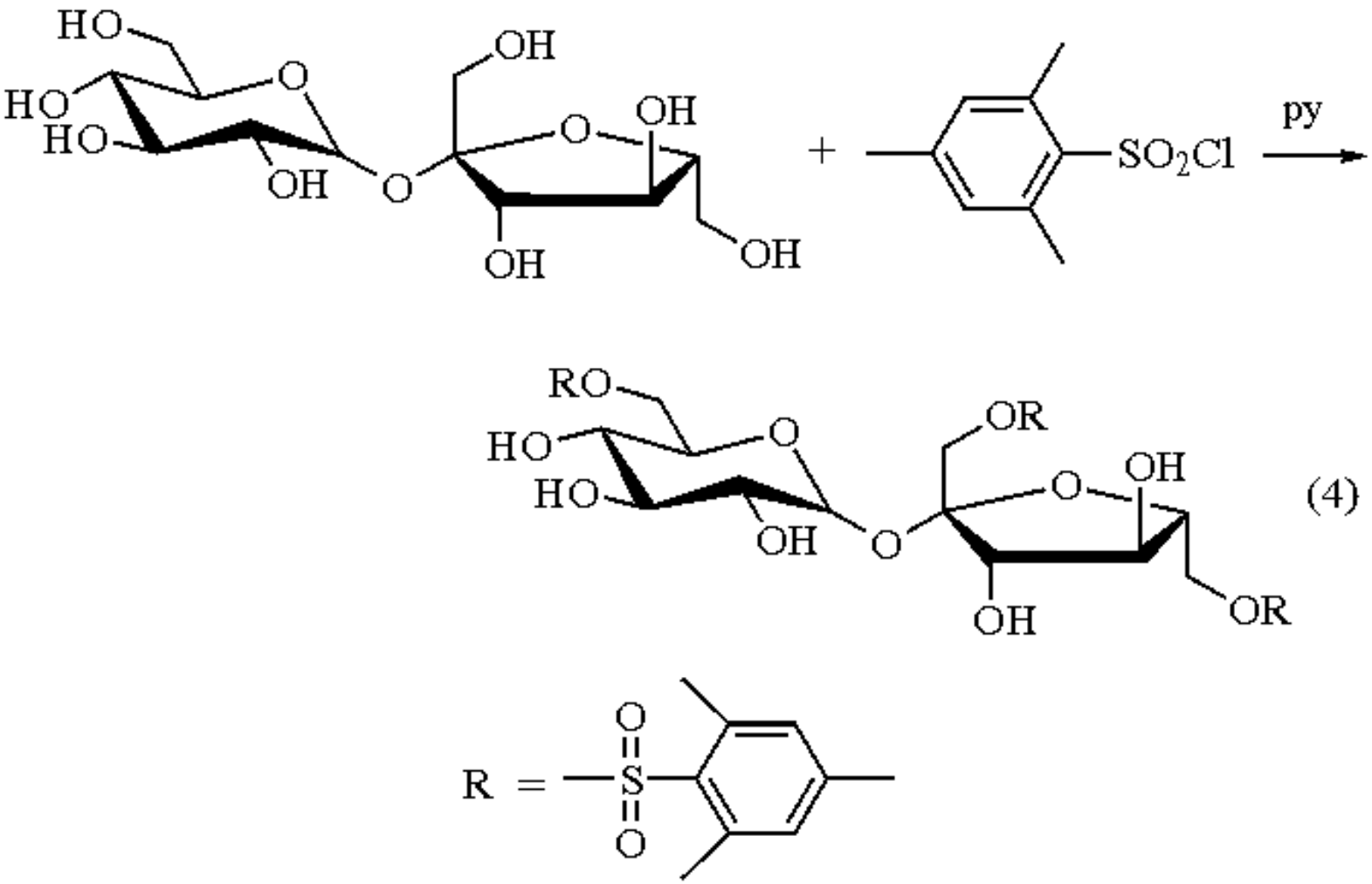

(4)

The selectivity of sulfonation has also been applied to other polyhydroxylic systems such as α- and β-cyclodextrins[11,12] and nucleotides.[13] Monosulfonated products have been reported from the treatment of diols with mesitylenesulfonyl chloride (eq 5).[14,15]

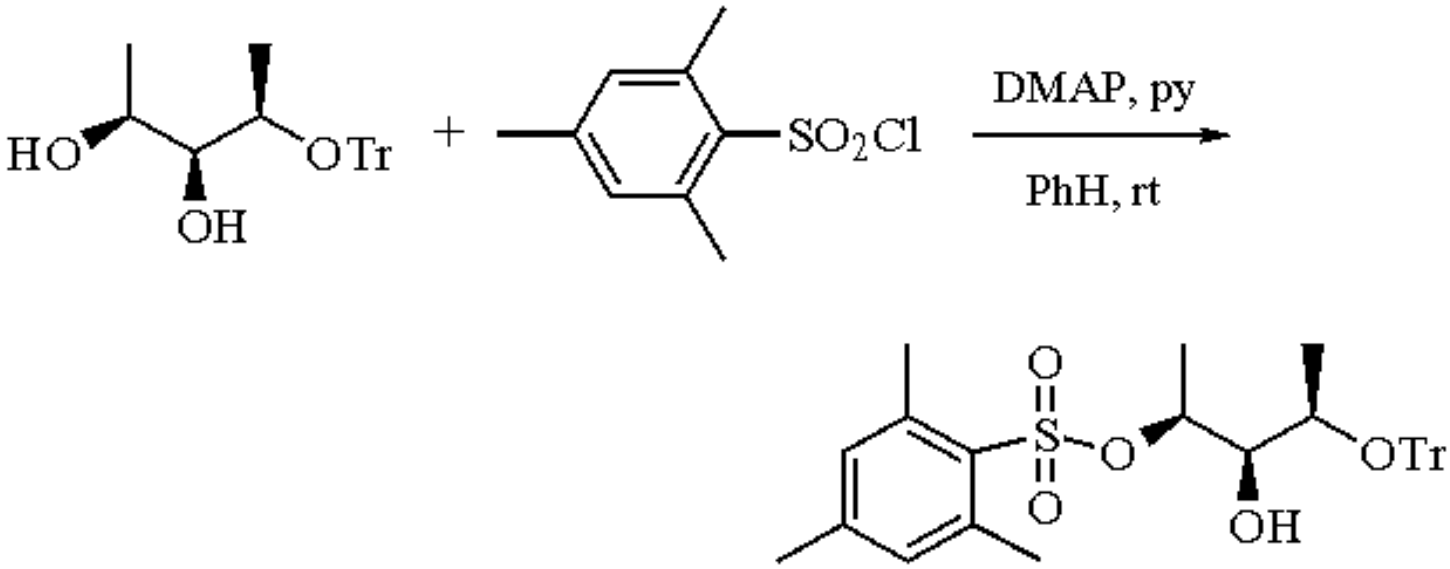

(5)

Mesitylenesulfonyl derivatives which have specific biological activities, such as 2,3-diaziridinyl-1,4-napthoquinone

sulfonates[16] and 1-arenesulfonyloxy-2-alkanones,[17] have also been prepared.

Nucleotide Synthesis.

Mesitylenesulfonyl chloride has been used as a condensing agent in the diester approach to nucleotide synthesis (eq 6).[2] However, it is not effective in the triester approach due to extensive sulfonation of the 5´-hydroxy group.[18] Other condensing agents include ***1,3-Dicyclohexylcarbodiimide*** (DCC), benzenesulfonyltriazole (BST), (1-mesitylyl-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT), ***Mesitylsulfonyl-1H-1,2,4-triazole*** (MST), *p*-nitrobenzenesulfonyltriazole (*p*-NBST), *p*-toluenesulfonyltriazole (TST), and triisopropylbenzenesulfonyl chloride (TPS).

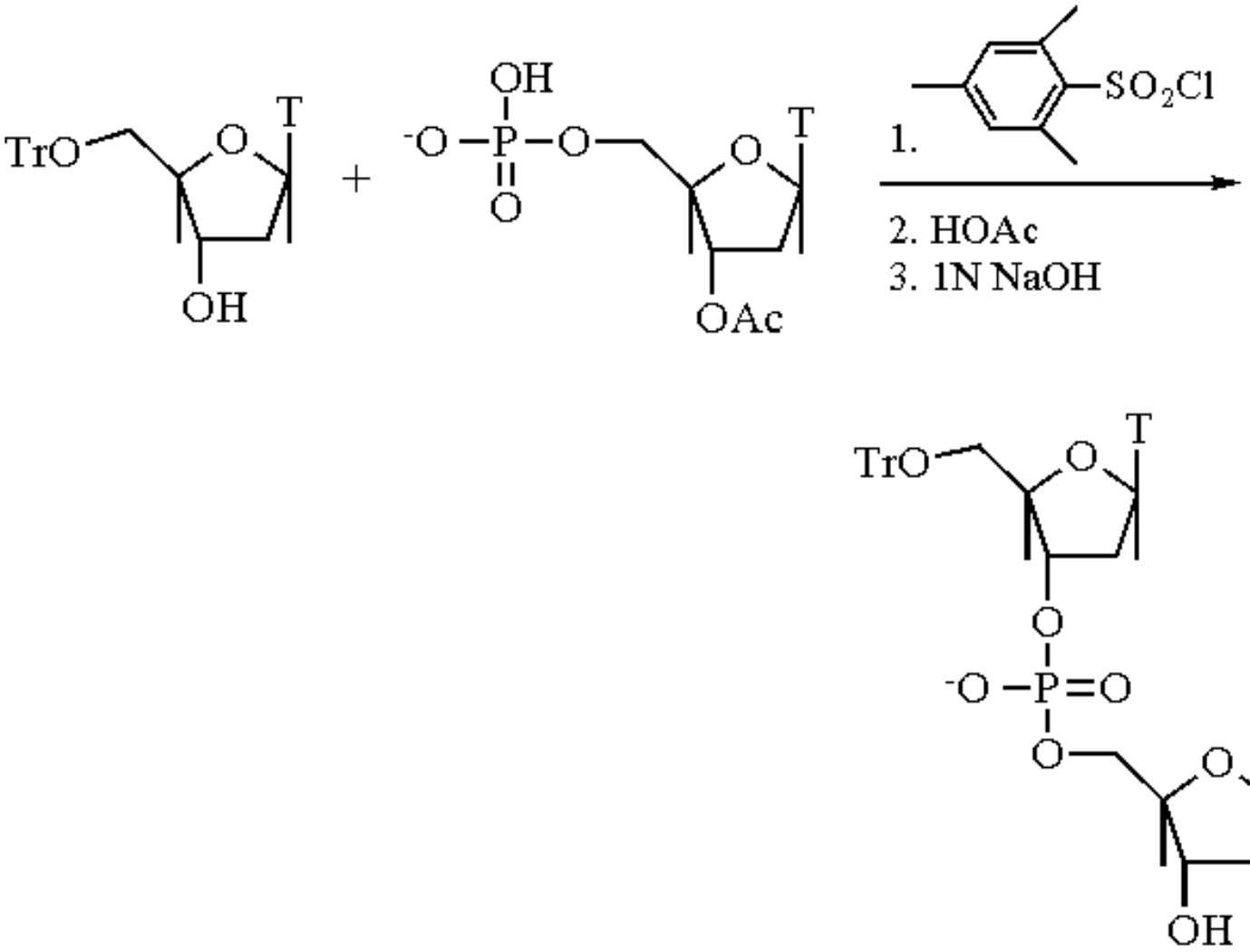

(6)

Condensation Reactions.

Mesitylenesulfonyl chloride has also been employed as a condensing agent for the preparation of esters in the synthesis of nonactin (eq 7),[19] *N*-methylmaysenine,[20] and maysine.[21]

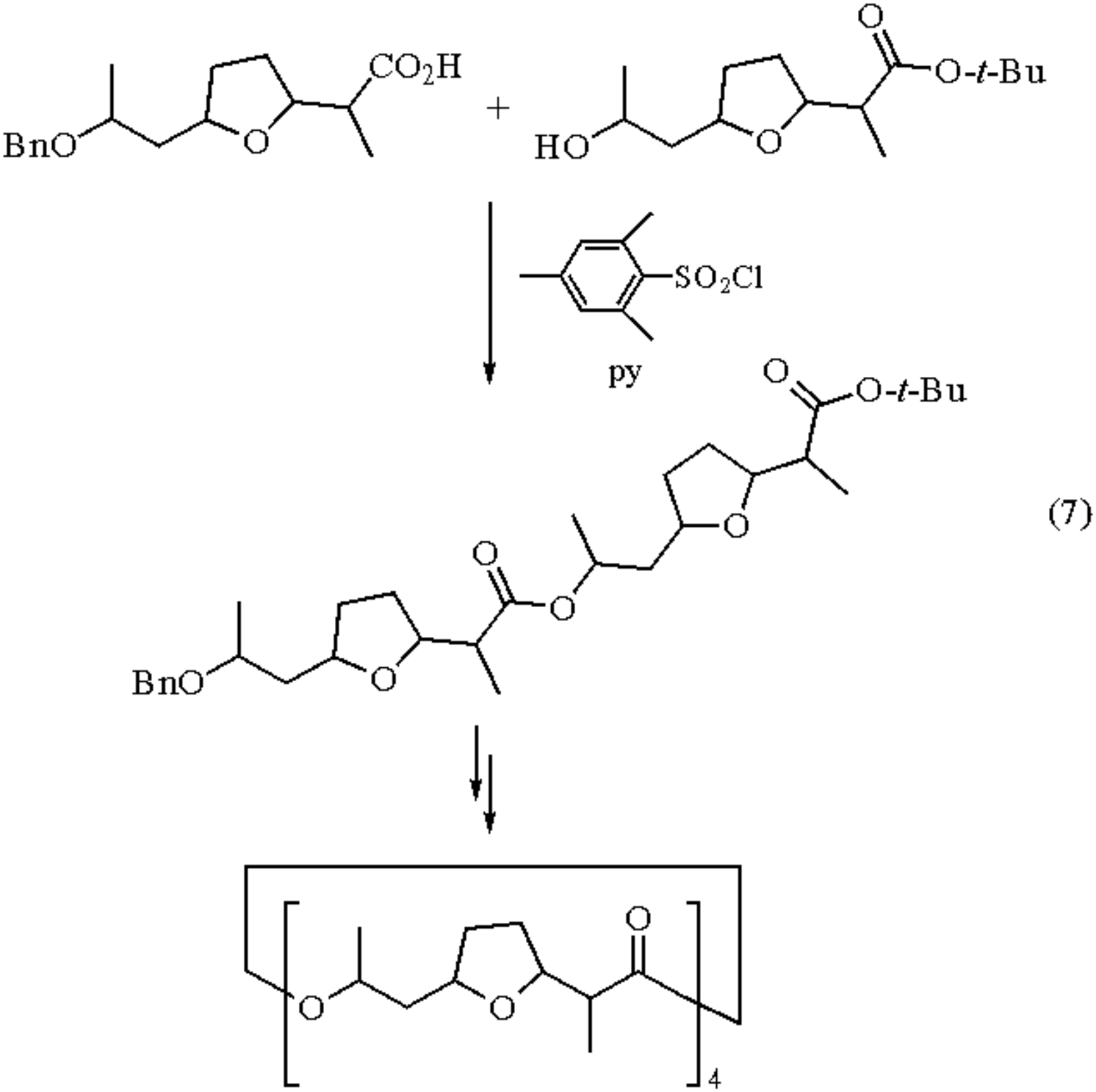

Sulfinate Ester Synthesis.

Sulfinate esters of menthol can be prepared via reaction of mesitylenesulfonyl chloride (as well as other sulfonyl chlorides) with menthol using ***Trimethyl Phosphite*** (eq 8).[22] Sulfinate esters of menthol are used for the preparation of optically active sulfoxides. See also ***10-Camphorsulfonyl Chloride*** and ***p-Toluenesulfonyl Chloride***.

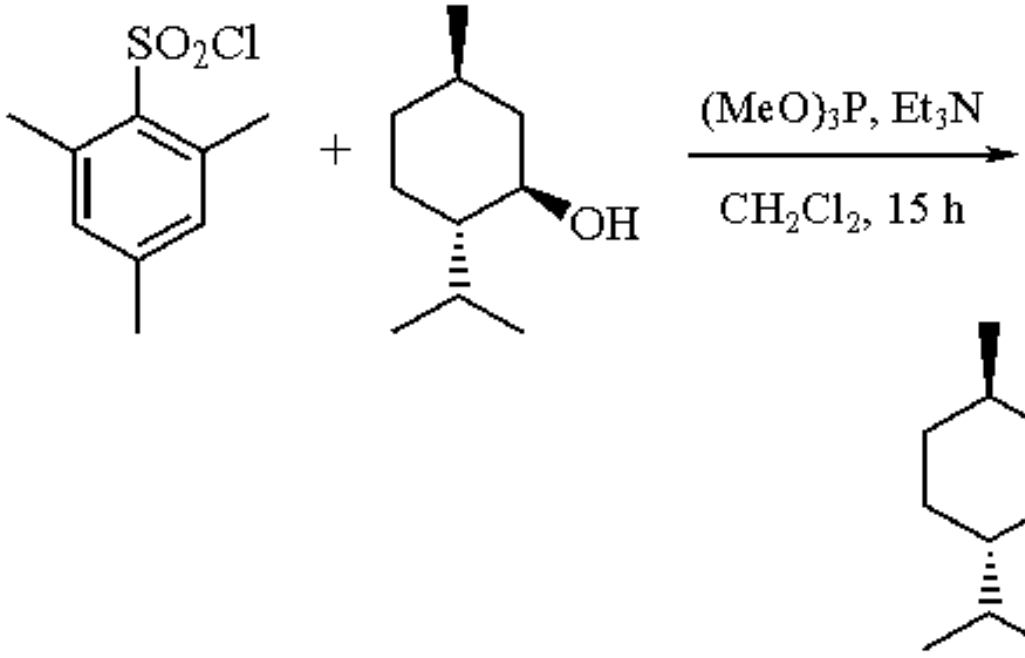

(8)

Sulfonylalkyne Synthesis.

Sulfonylalkynes have been synthesized (eq 9) and subsequently reacted with *N*-(1-alkynyl)anilines to give 2-anilino-5-sulfinylfurans.[23]

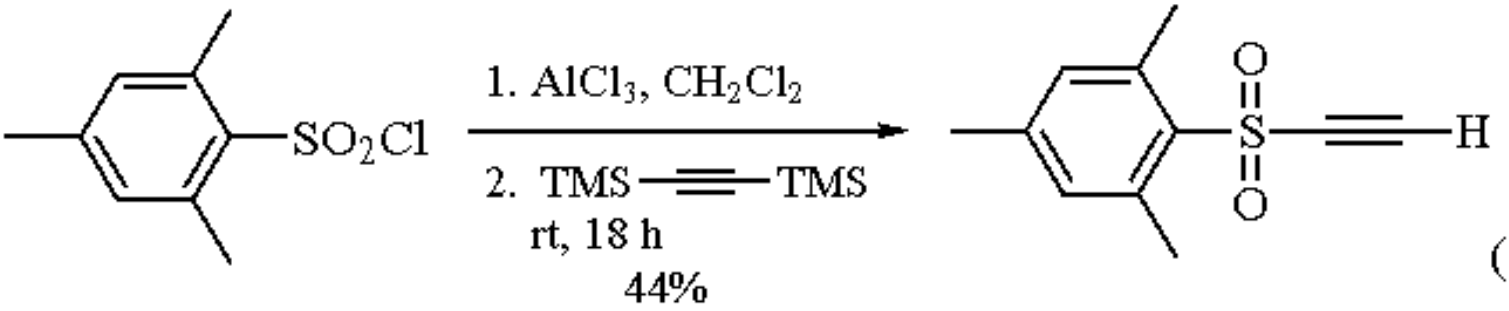

(9)

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Mesitylenesulfonylhydrazide

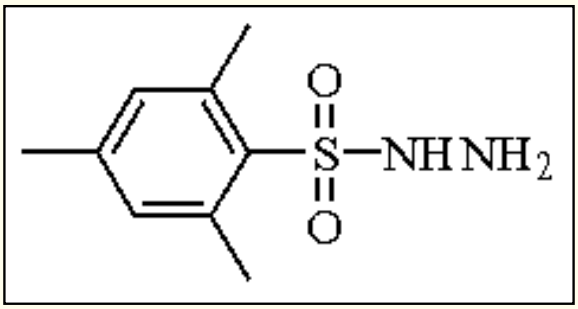

[16182-15-3] · $C_9H_{14}N_2O_2S$ · Mesitylenesulfonylhydrazide · (MW 214.32)

(used to form diazene;[1] condenses with ketones and aldehydes to form hydrazones that can be used as a source of reactive intermediates such as diazoalkanes, carbenes, carbenium ions, and alkyllithiums;[7,8] a good reagent for the Eschenmoser fragmentation[4])

Alternate Names: MSH; 2,4,6-trimethylbenzenesulfonylhydrazide.

Physical Data: mp 105 °C (dec).

Solubility: sol ether, THF, benzene, dichloromethane, chloroform, ethanol; insol water, hydrocarbons.

Form Supplied in: solid; widely available.

Analysis of Reagent Purity: IR, NMR.

Handling, Storage, and Precautions: is stable for many months below 0 °C and should be stored in a freezer. It is a toxic, potentially flammable solid which should be handled with gloves in a fume hood under an inert atmosphere.

Alkene Reduction/Allylic Diazene Rearrangement.

Mesitylenesulfonylhydrazide in refluxing methanol is a convenient source of diazene (diimide). It has intermediate reactivity, decomposing 16 times faster than ***p-Toluenesulfonylhydrazide*** (tosylhydrazide) and 24 times slower than ***2,4,6-Triisopropylbenzenesulfonylhydrazide*** (trisylhydrazide) under base-catalyzed conditions.[1] An analogous use of MSH is in allylic diazene rearrangements.[2] Eq 1 illustrates a recent example whereby an allylic alcohol is ionized with a Lewis acid and the resulting allyl cation trapped with MSH to give the diazene, which stereospecifically yields the rearranged product.[3]

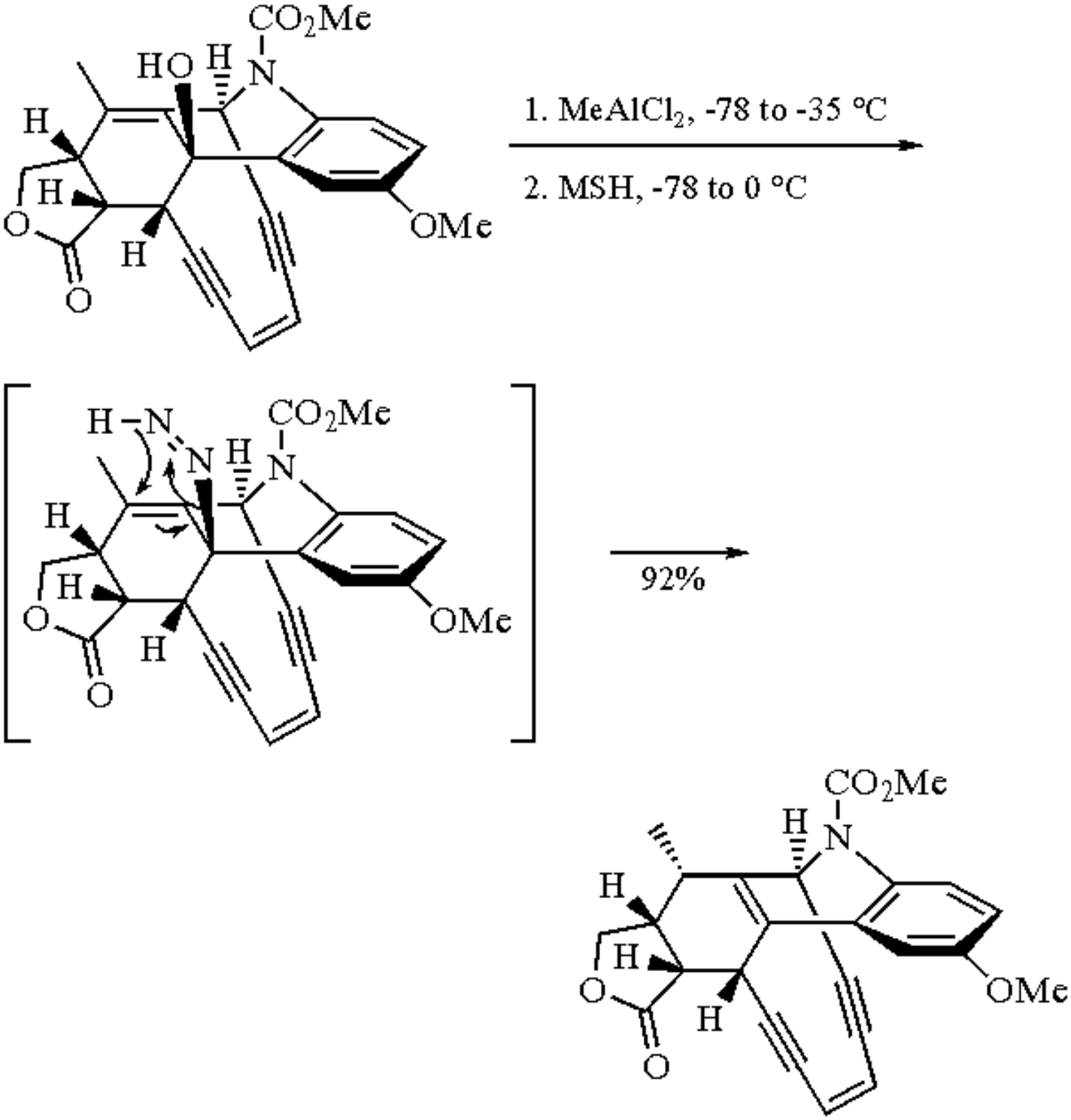

Eschenmoser Fragmentation.

MSH condenses with ketones to form hydrazones, which participate in the Eschenmoser fragmentation. Eq 2 shows the mild fragmentation of two epoxy ketones to form 1-cyclononyn-4-one and 1-cyclodecyn-4-one in 1:1 CH_2Cl_2-AcOH at rt; compounds not accessible using the less reactive *p*-toluenesulfonylhydrazide.[4]

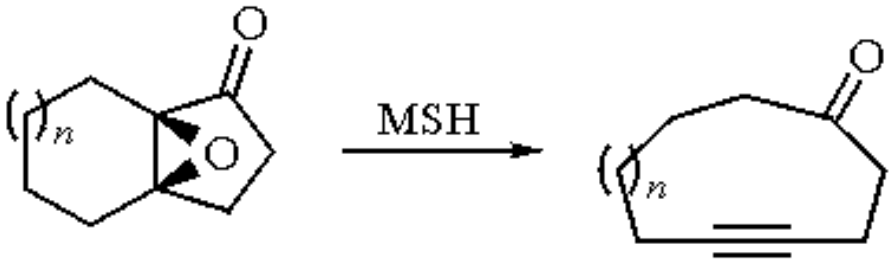

(2)

$n = 1$, 43%; $n = 2$, 69%

Miscellaneous.

MSH is oxidized by ***Benzeneseleninic Acid*** to give selenosulfonates in excellent yield and which themselves have diverse synthetic utility.[5,6] The few examples that employ mesitylenesulfonylhydrazones in the aprotic Bamford-Stevens reaction show that triisopropylbenzenesulfonylhydrazones are superior.[7,8] Hydrazones of esters (hydrazimidates) have been prepared using MSH but their properties have not been investigated.[9]

Related Reagents.

2,4-Dinitrobenzenesulfonylhydrazide; ***p-Toluenesulfonylhydrazide***; ***2,4,6-Triisopropylbenzenesulfonylhydrazide***.

---

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Mesitylsulfonylimidazole

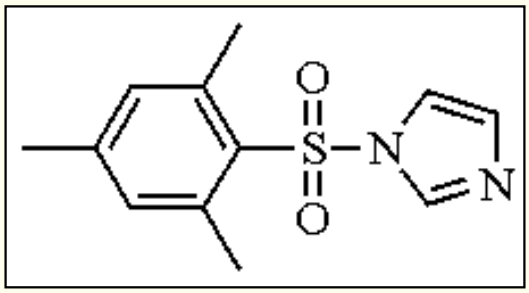

[54230-59-0] · $C_{12}H_{14}N_2O_2S$ · Mesitylsulfonylimidazole · (MW 250.35)

(condensing agent for oligonucleotide synthesis[1])

Alternate Name: MSI.

Physical Data: mp 97-99 °C.

Form Supplied in: solid; widely available from commercial sources.

Preparative Method: readily prepared by the reaction of equimolar ratios of ***Mesitylenesulfonyl Chloride***, ***Imidazole***, and ***Triethylamine*** in a chloroform solution (eq 1).

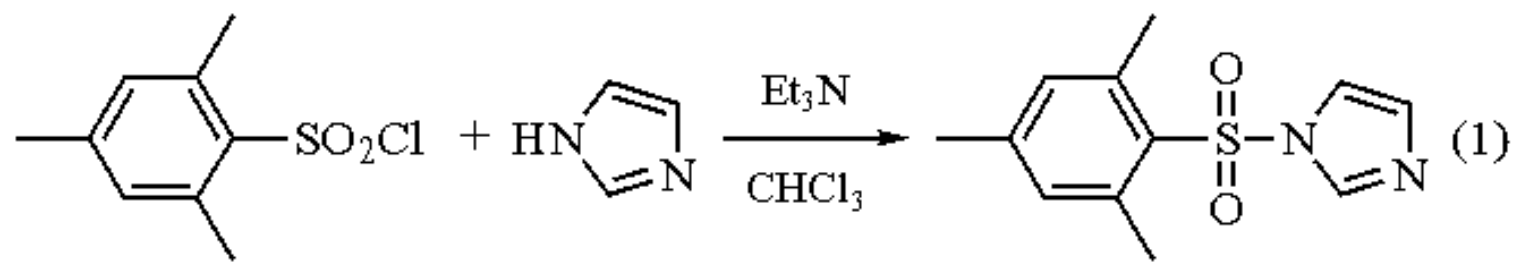

Oligonucleotide Synthesis.

MSI[1] was reported as a condensing agent for oligonucleotide synthesis by activation of phosphomonoester groups of nucleotides (eq 2).[2] Very few reports of the use of this reagent have appeared in literature. Reactions with MSI are reported to be very slow, but acid-sensitive functional groups are unaffected by these reaction conditions.[3]

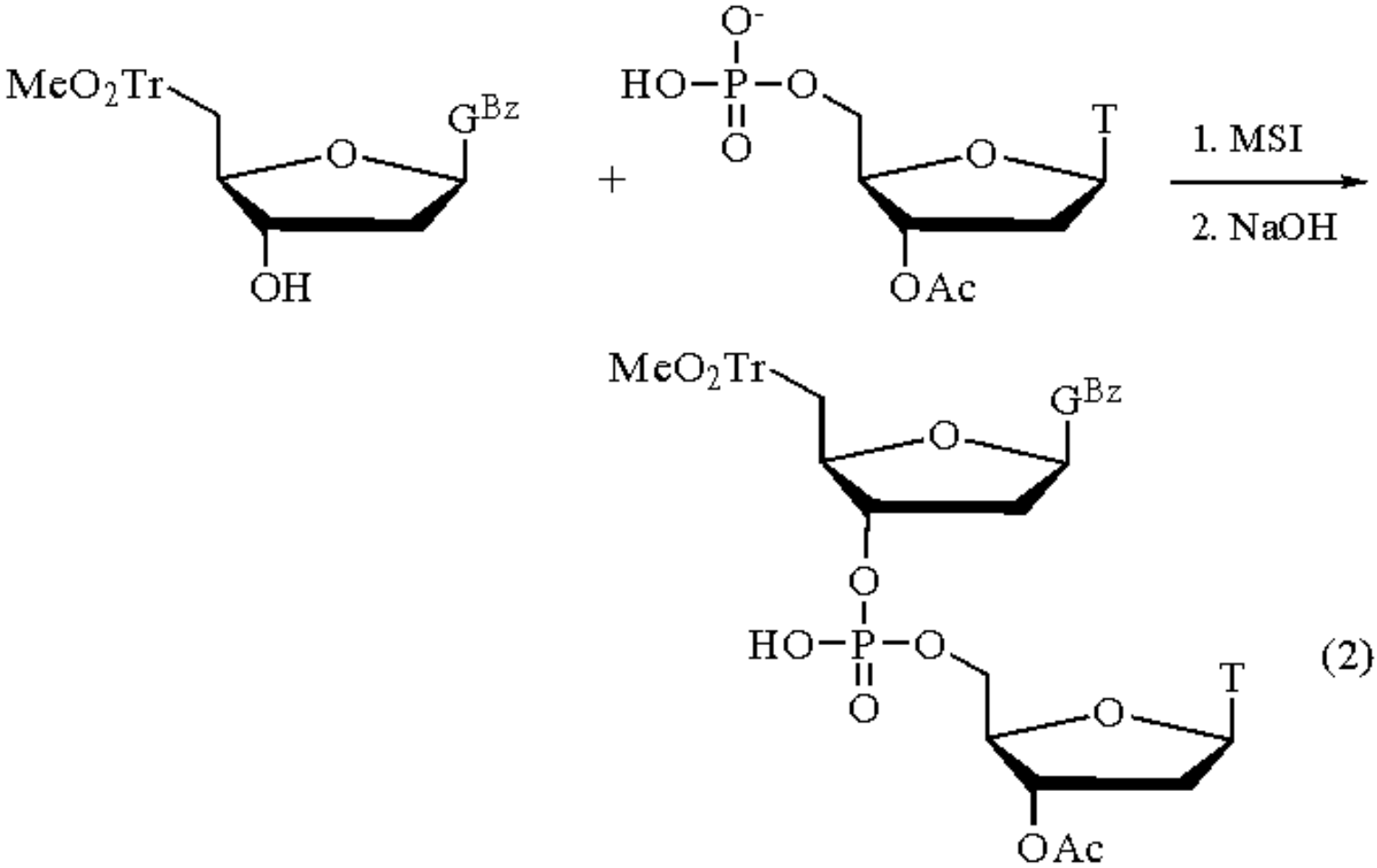

(2)

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Mesitylsulfonyl-1*H*-1,2,4-triazole

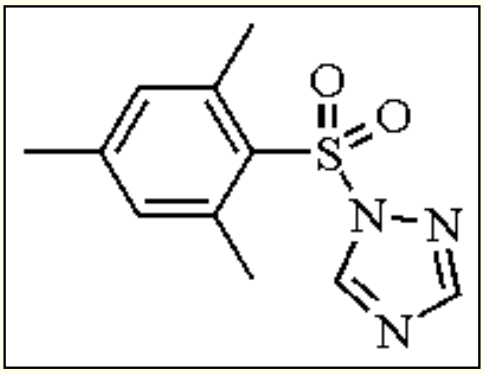

[54230-59-0] · $C_{11}H_{13}N_3O_2S$ · Mesitylsulfonyl-1*H*-1,2,4-triazole · (MW 251.34)

(reagent for phosphate activation[1] and nucleotide condensation[2])

Alternate Name: MST.

Physical Data: mp 135 °C.

Form Supplied in: solid; widely available from commercial sources.

Preparative Method: readily prepared by the reaction of equimolar ratios of ***Mesitylenesulfonyl Chloride***, ***1,2,4-Triazole***, and ***Triethylamine*** in a chloroform solution (eq 1).[3]

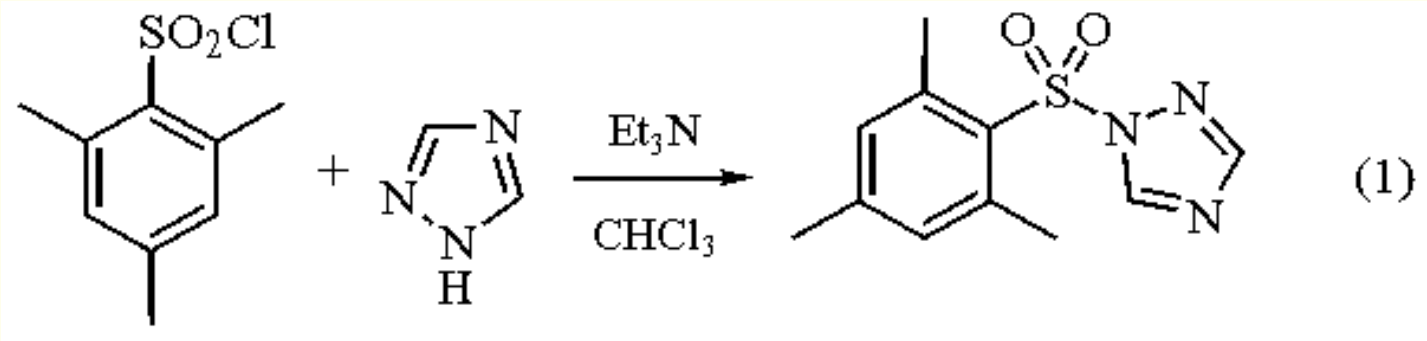

Purification: recrystallization from benzene.

Phosphate Activator.

MST was shown to be an effective catalyst for the phosphorylation of a 5´-protected mononucleoside.[1] MST was stirred with *p*-chlorophenyl phosphorodichloridate and triethylamine and the resulting agent was used directly for the

phosphorylation of 5´-protected nucleosides in 70-85% yields.

Oligonucleotide Synthesis.

As originally reported, the triester approach to the formation of oligonucleotides involved using triisopropylbenzenesulfonyl chloride (TPS) as a condensing agent for a 5´-3´ internucleotide condensation. Since that time, many modifications of this procedure have been reported, including (i) using a stepwise phosphorylation then condensation procedure,[2] (ii) synthesizing the oligonucleotide in the 3´-5´ rather than the 5´-3´ direction,[2] (iii) varying the protecting groups used in these transformations, and (iv) changing the condensing agent. MST is one of the more recently reported condensing agents for the synthesis of oligonucleotides through the formation of 3´,5´-internucleotide bonds via the triester approach. The initial report of the use of MST was in the synthesis of a fully protected dinucleotide (eq 2).[3]

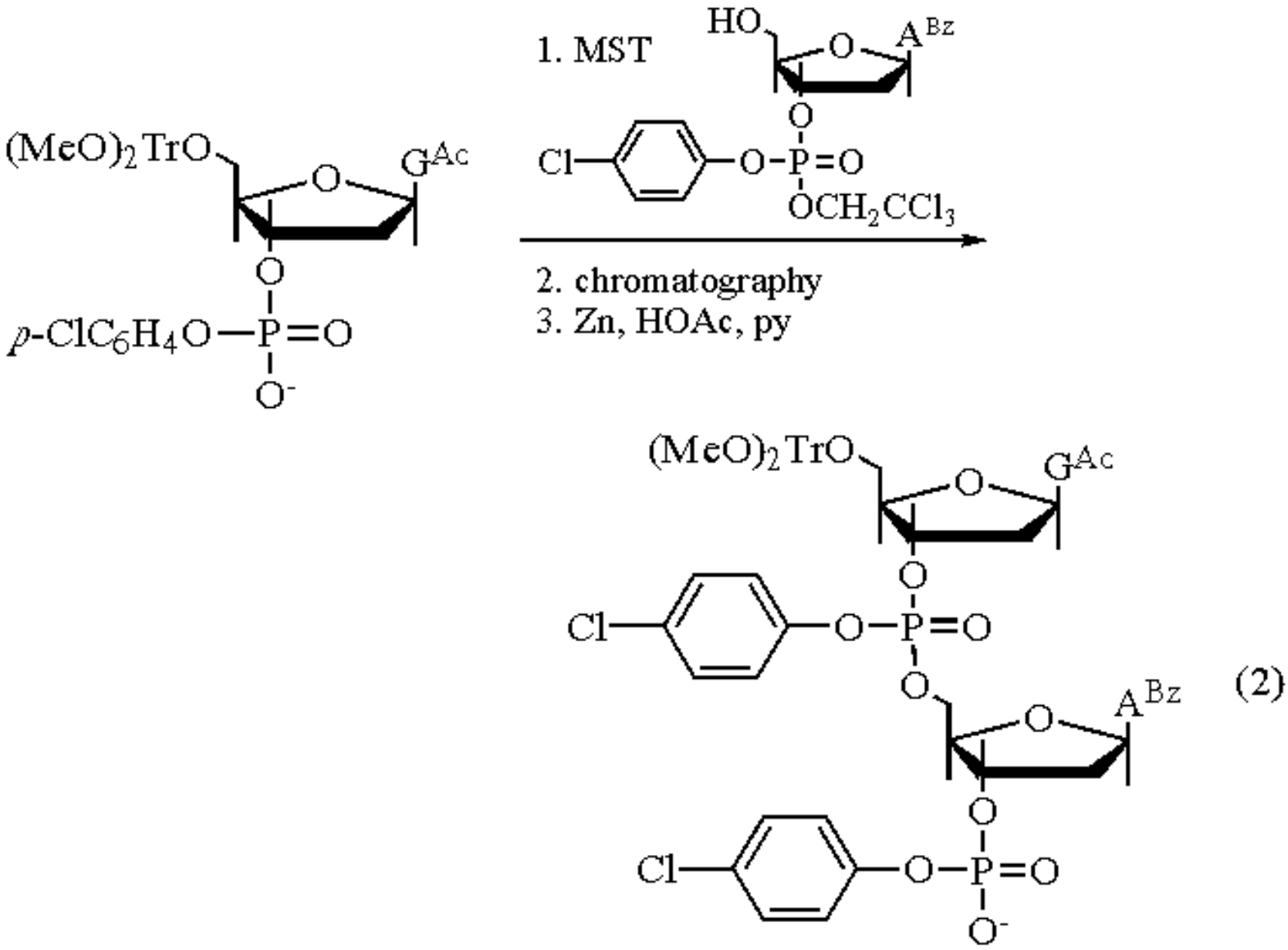

A follow-up full paper by the same authors extended this methodology to the synthesis of hexanucleotides by an iterative phosphorylation and condensation sequence.[1] This paper also kinetically compared this reagent to some of the previously used condensing agents. It was reported that although the reaction using MST was significantly slower than that using TPS, the reaction mixture was much cleaner and the yields were much higher. This was especially true for

synthesis of nucleotides that contained purine units, which were formed only in low yields when TPS was employed as the condensing agent, perhaps due to the liberation of HCl from the reagent. MST was also employed as the condensing reagent in the synthesis of 3´,5´-bisphosphorylated oligonucleotides.[4]

Oligoribonucleotide Synthesis.

Subsequent work showed that this reagent was useful in the synthesis of the less stable oligoribonucleotides as well as deoxyribonucleotides.[5] In the same iterative manner as described above for deoxyribonucleotide synthesis, the tetrameric ribonucleotide GpApGpC was formed (eq 3). Yields were reported to be significantly improved over previously described methods that employed TPS as the condensing agent, especially in the coupling of purine residues. Note again that MST can also be used in the phosphorylation step of the condensation sequence. MST was also used as a condensing agent for the synthesis of 2´(3´)-*O*-aminoacyl triribonucleoside diphosphates.[6]

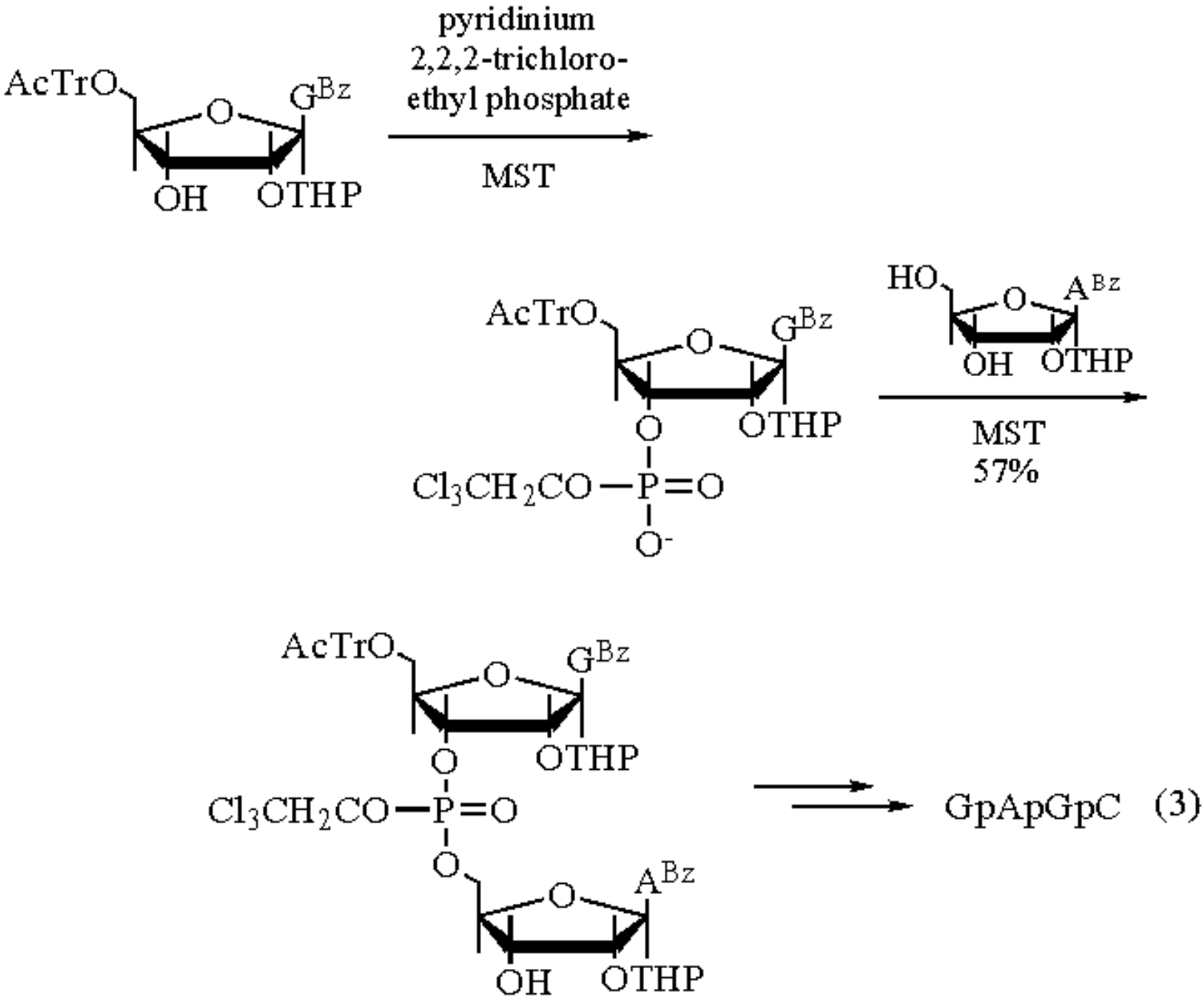

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Mesityllithium[1,2]

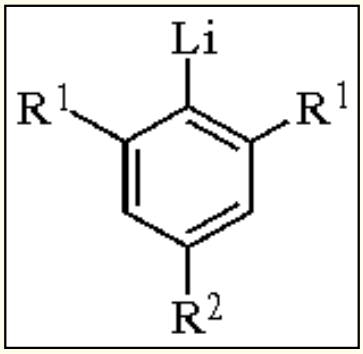

(**1**; $R^1 = R^2 = Me$)

[5806-59-7] · $C_9H_{11}Li$ · Mesityllithium · (MW 126.14) (**2**; $R^1 = R^2 =$ *i*-Pr)

[74226-59-8] · $C_{15}H_{23}Li$ · 2,4,6-Triisopropylphenyllithium · (MW 210.32) (**3**; $R^1 = R^2 =$ *t*-Bu)

[35383-91-6] · $C_{18}H_{29}Li$ · 2,4,6-Tri-*t*-butylphenyllithium · (MW 252.41) (**4**; $R^1 = R^2 =$ *t*-$BuCH_2$)

[76804-36-9] · $C_{21}H_{35}Li$ · 2,4,6-Trineopentylphenyllithium · (MW 294.50) (**5**; $R^1 = R^2 = CF_3$)

[444-40-6] · $C_9H_2F_9Li$ · 2,4,6-Tris(trifluoromethyl)phenyllithium · (MW 288.05) (**6**; $R^1 = R^2 = (SiMe_3)_2CH$)

[125444-10-2] · $C_{27}H_{59}LiSi_6$ · 2,4,6-Tris[bis(trimethylsilyl)methyl]phenyllithium · (MW 559.34) (**7**; R^1 = Me, R^2 = *t*-Bu)

[126062-41-7] · $C_{12}H_{17}Li$ · 4-*t*-Butyl-2,6-dimethylphenyllithium · (MW 168.23) (**8**; R^1 = Et, R^2 = *t*-Bu)

[149266-65-9] · $C_{14}H_{21}Li$ · 4-*t*-Butyl-2,6-diethylphenyllithium · (MW 196.29) (**9**; $R^1 = R^2$ = Me, .Et_2O)

[119088-34-5] · $C_{13}H_{21}LiO$ · Mesityllithium · (MW 200.28) (**10**; $R^1 = R^2 =$ *i*-Pr, .Et_2O)

[107742-58-5] · $C_{19}H_{33}LiO$ · Mesityllithium · (MW 284.46) (**11**; $R^1 = R^2 =$ *t*-Bu, .3THF)

[149764-17-0] · $C_{30}H_{53}LiO_3$ · Mesityllithium · (MW 468.77) (**12**; $R^1 = R^2$ = Et, .Et_2O)

[107742-59-6] · $C_{16}H_{22}LiO$ · Mesityllithium · (MW 237.32) (**13**; $R^1 = R^2$ = Ph, .2Et_2O)

[133777-60-3] · $C_{32}H_{37}LiO_2$ · Mesityllithium · (MW 460.63)

(used for the generation of other amine-free organolithium compounds; derivatives are also synthetic building

blocks for the preparation of compounds containing low-coordinate main Group element functional groups which are otherwise not stable, i.e. steric protection)

Alternate Name: 2,4,6-trimethylphenyllithium.

Preparative Methods: the corresponding bromobenzene derivative is treated with 2 equiv ***t-Butyllithium***[3] in THF solution,[4,5] a method which leads to a 1:1 mixture of the desired Li derivatives (**1**)-(**8**) and ***Lithium Bromide*** (no alkyl halide is present under these conditions; eq 1).

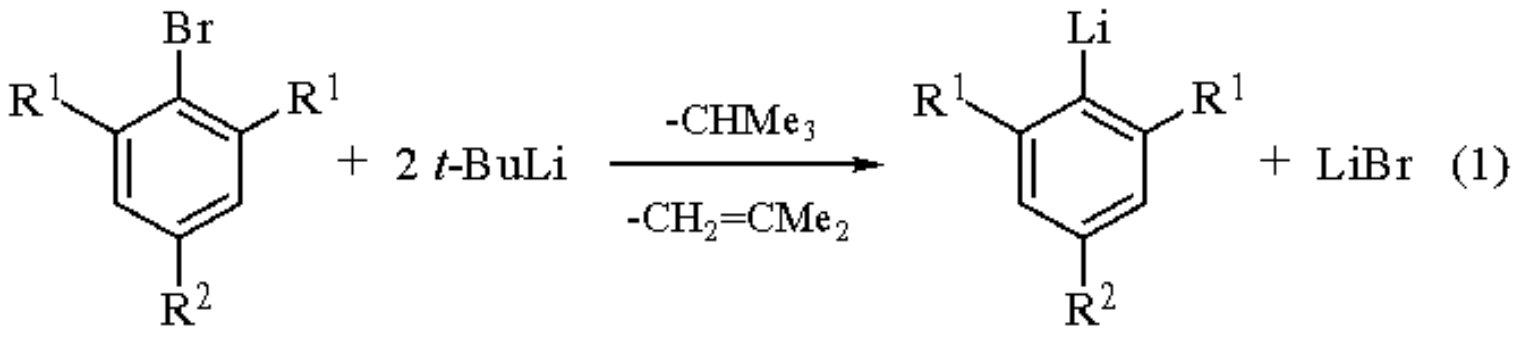

According to X-ray structure determinations and molecular weight measurements in solution, the highly hindered organolithium compounds in the series (**1**)-(**13**) are monomeric,[6,7] i.e. not aggregated as are most other Li derivatives.

Handling, Storage, and Precautions: solutions of (**1**)-(**8**) may be kept under Ar or N_2 in a refrigerator; normally they are used right away; with (**1**), (**2**), and (**4**), a transmetalation from the nuclear to a benzylic position would lead to thermodynamically more stable Li compounds (such rearrangements[8] are catalyzed by tertiary amines, for instance ***N,N,N´,N´-Tetramethylethylenediamine***).

Use of *o,o´*-Disubstituted Compounds as Bases.

Two examples are shown in eqs 2 and 3.[3,4] The 1:1 acylation of Li enolates shown in the first reaction gives best yields of diketones such as (**14**) at -75 °C when the enolate solutions are amine-free (see ***Methyl 4-Nitrobutanoate*** and ***Methyl 3-Nitropropanoate***). The enolate formation from benzyl methyl ketone produces the thermodynamically less stable isomer (**15**) preferentially over the more stable one (**16**).[4,9]

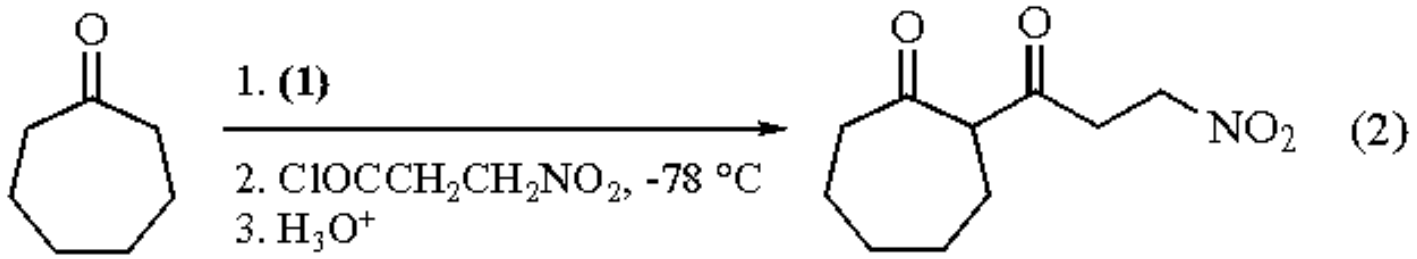

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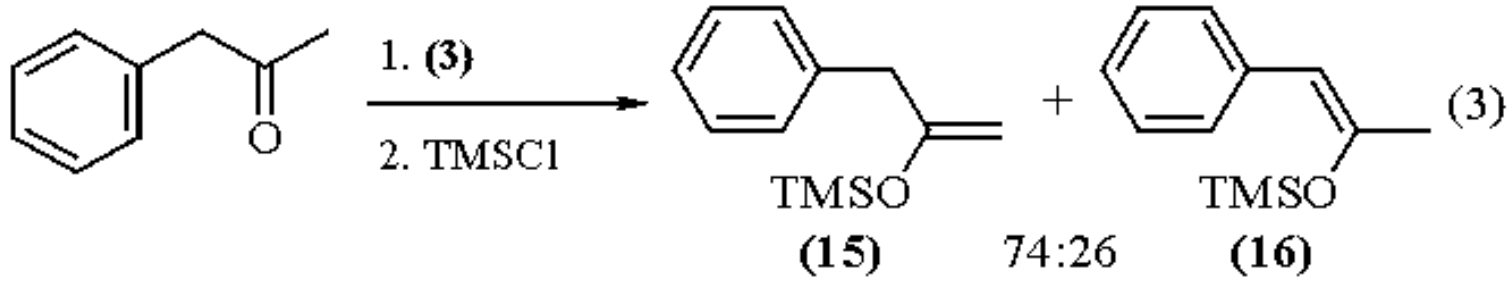

Preparation of Low-Coordinate Main Group Element Derivatives.

Due to the steric hindrance, especially in the 2,4,6-tri-*t*-butyl aryl compounds (**3**) and (**11**), called supermesityllithium, it is possible to prepare derivatives of types of compounds which are otherwise not stable because they would be too reactive to be isolated. Three examples are the selenoaldehyde (**17**),[10] the dibora-allene anion derivative (**18**),[11] and the diphosphene (**19**).[12] A literature search reveals that this technique of steric protection was used all over the Periodic Table, including transition metals (consider also the principle of sterically protected but electronically effective functional groups,[13] and compare also the stabilization of tetrahedrane by *t*-butyl substitution[14]).

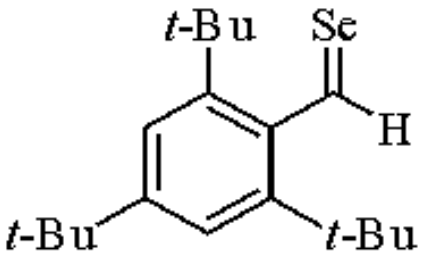

(17)

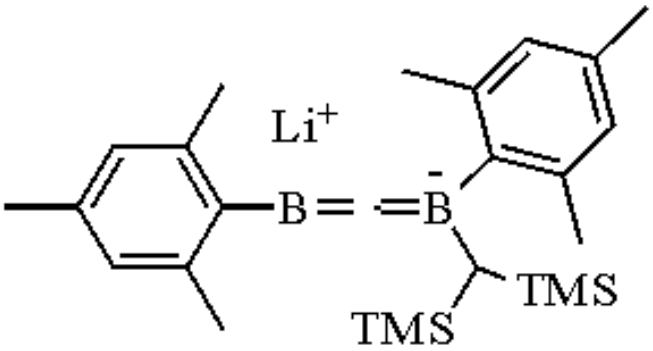

(18)

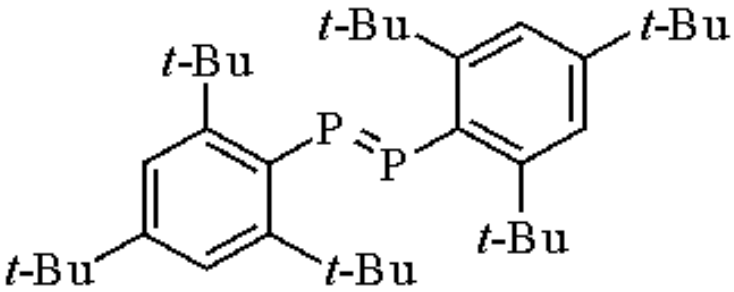

(19)

Related Reagents.

Lithium Diisopropylamide; ***Lithium 2,2,6,6-Tetramethylpiperidide***; ***Phenyllithium***.

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Mesityloxytris(dimethylamino)phosphonium Azide

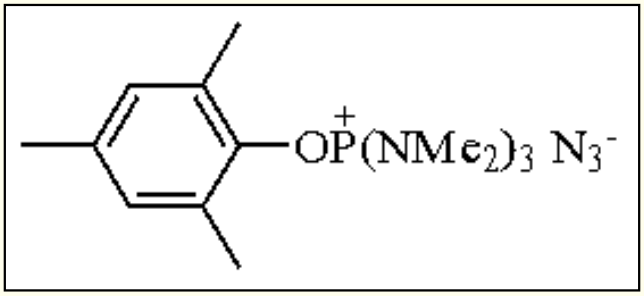

[73014-63-8] · $C_{15}H_{29}N_6OP$ · Mesityloxytris(dimethylamino)phosphonium Azide · (MW 340.47)

(organic soluble source of azide ion[1])

Physical Data: mp 110-112 °C.

Solubility: sol most organic solvents.

Form Supplied in: not commercially available from common sources.

Preparative Method: readily prepared in a 68% yield from 2,4,6-trimethylphenol by treatment with ***Hexamethylphosphorous Triamide*** then ***Sodium Azide*** (eq 1).[1]

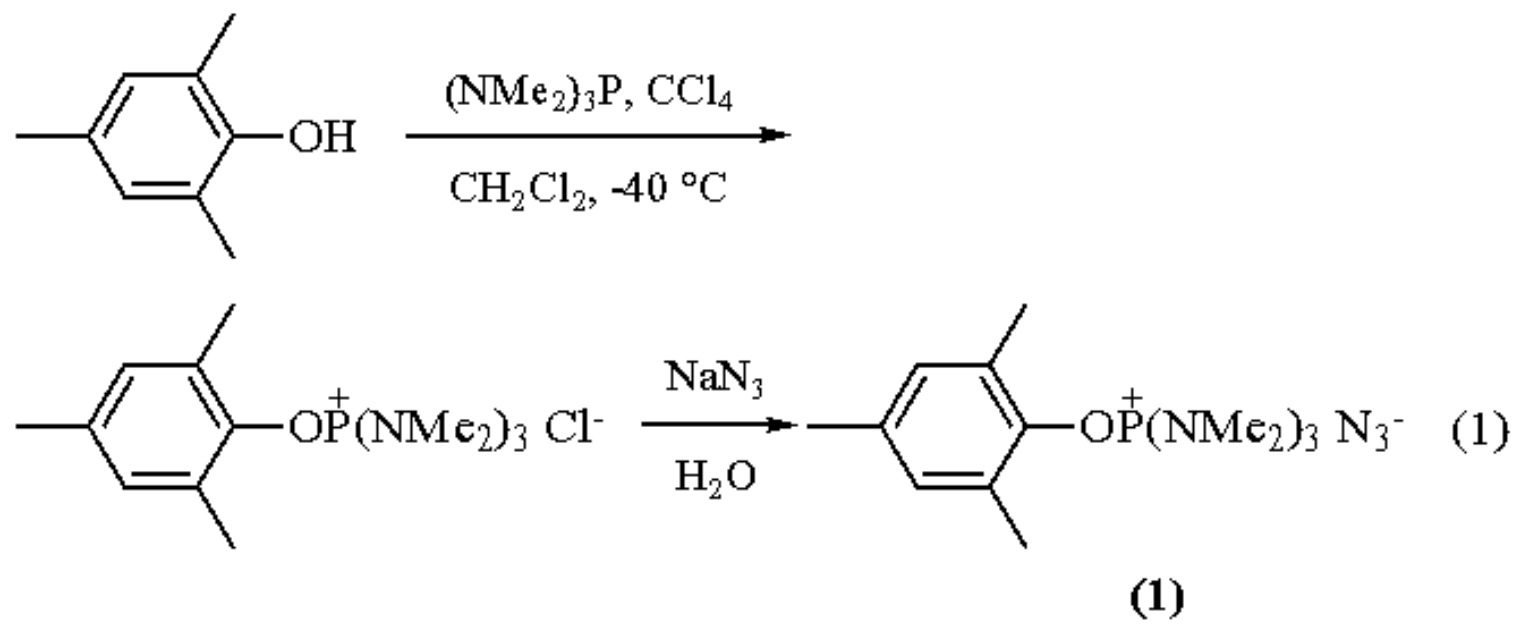

Purification: precipitation from an acetone solution by the addition of diethyl ether.

Mesityloxytris(dimethylamino)phosphonium azide is an organic soluble form of azide that is reported to be a better source of azide than tetrabutylammonium azide. It has been used for the preparation of glycosyl azides (eq 2).[1] The anomeric alcohol is first activated through formation of the phosphonium chloride by treatment with carbon tetrachloride and $(NMe_2)_3P$. The phosphonium salt is then reacted with the phosphonium azide, forming the glycosyl azide and regenerating $(NMe_2)_3P$.

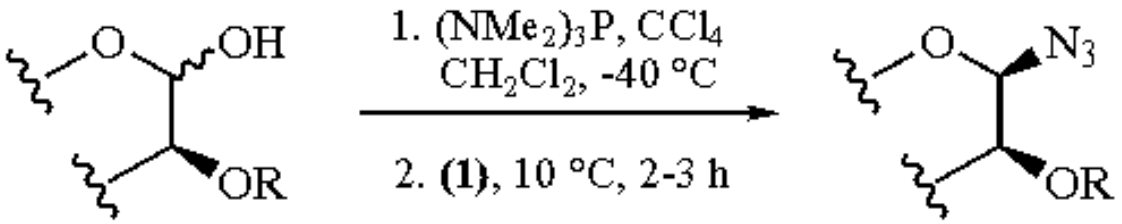

(2)

The intermediate phosphonium chlorides are formed with a *trans* configuration relative to the C-2 substituent and the substitution generally occurs with inversion of configuration to give a *cis*-azide. Reported yields are good, mostly in the 65-80% range. Most common carbohydrate protecting groups appear to be stable to these conditions, including acetals, trityl (eq 3), benzyl (eq 4), and *t*-butyldiphenylsilyl. The resulting glycosyl azides are used in the synthesis of triazole nucleosides,[2] and purine[3] or pyrimidine[4] nucleosides.

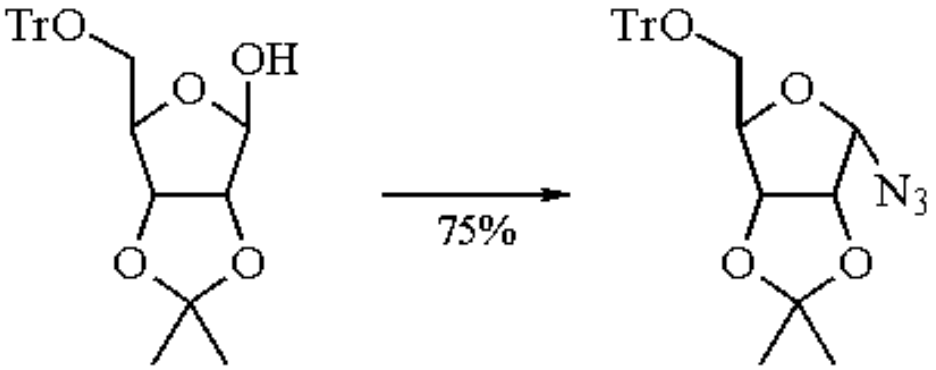

(3)

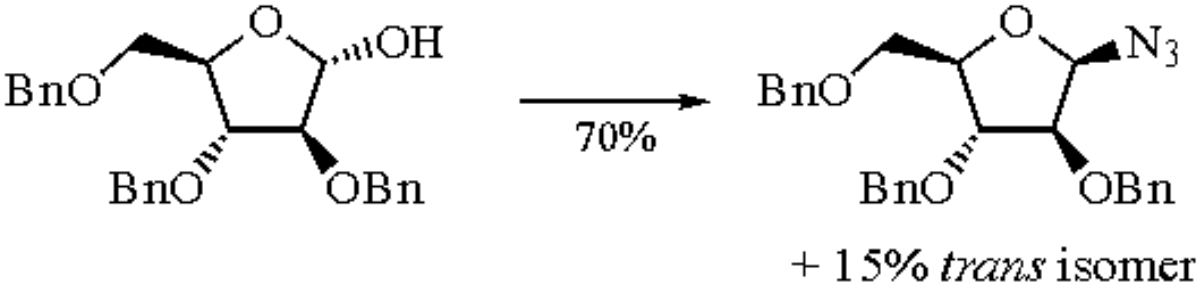

(4)

Several advantages of this method over previously reported methods are described. The major advantage is that the use of toxic silver azide is eliminated. The reagent can be prepared from readily available starting materials and is soluble in organic solvents. The phosphonium azide is crystalline and nonhygroscopic. The reaction is fast and performed at low temperatures and the resulting glycosyl azide is readily separated from the water-soluble byproducts. The major disadvantage of this method is that $(NMe_2)_3P$ must be used. A later reported method which employs ***Azidotrimethylsilane*** and a Lewis acid catalyst has been reported to be a better method to carry out this transformation.[5]

1. Chretien, F.; Castro, B.; Gross, B. *S* **1979**, 937.
2. Chretien, F.; Gross, B. *JHC* **1982**, *19*, 263.
3. Chretien, F.; Gross, B. *T* **1982**, *38*, 103.
4. Ralph, R. K.; Shaw, G. *JCS* **1956**, 1877.
5. Logue, M. W.; Han, B. Y. *Carbohydr. Res.* **1983**, *121*, 287.

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O-(Mesitylsulfonyl)hydroxylamine[1]

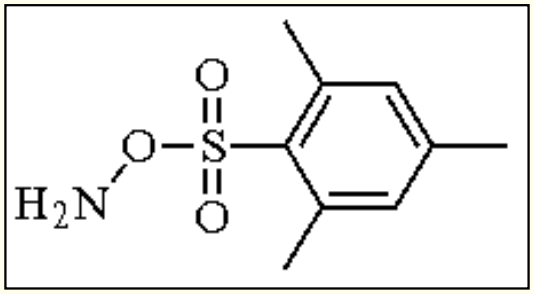

[36016-40-7] · $C_9H_{13}NO_3S$ · *O*-(Mesitylsulfonyl)hydroxylamine · (MW 215.2)

(reagent for electrophilic aminations, NH_2 transfer to nucleophiles)

Physical Data: mp 93-94 °C.[1]

Solubility: very sol diethyl ether, chloroform, dichloromethane, benzene, ethanol, THF; insol water and petroleum ether.

Analysis of Reagent Purity: IR (KCl) ν(cm^{-1}) 3340, 3250, 1600, 1350, 1190, 1180.[1]

Preparative Methods: to a solution of 89 g (330 mmol) *O*-(mesitylsulfonyl)acetohydroxamate (**1**) in dioxane is added with stirring 30 mL perchloric acid (70%) at 0 °C within 10 min, and then stirred for another 10 min. After about 20 mL of the acid has been added, the reaction mixture becomes pasty. The crude reaction mixture is poured into ice-water to give a white solid of *O*-(mesitylsulfonyl)hydroxylamine (**2**) (eq 1) which is collected, washed with cold water (500 mL), then with cold petroleum ether (300 mL), and dried by maintaining suction for about 1 h; yield 55-65 g (77-92%).[1]

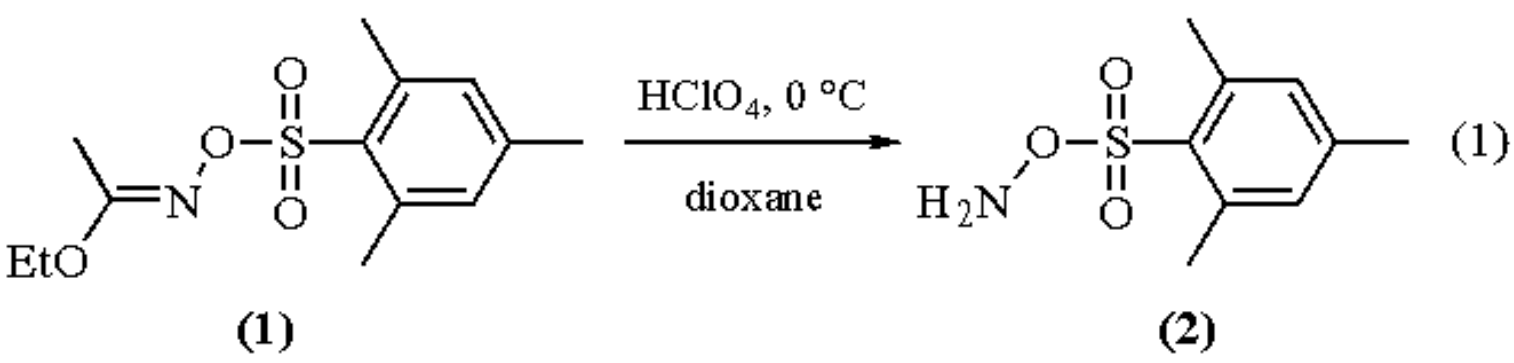

The product should be stored in a refrigerator below 0 °C. Iodometric titration indicates that (**2**) thus prepared contains 20-30% water. It can be used for most applications. A further purification can be achieved by dissolution of a small amount in diethyl ether at room temperature and precipitation with petroleum ether.

Handling, Storage, and Precautions: **caution**: *O*-(mesitylsulfonyl)hydroxylamine (**2**) must be handled with care. A first report about a rapid decomposition when standing at room temperature appeared in 1977.[2] After an

explosion of (**2**) during storage below 0 °C,[3] as suggested above,[1] it is strongly recommended that (**2**) be prepared immediately prior to use, and that it not be stored.[3]

Reactions with Heteroaromatic Amines.

N-Amine salts of heteroaromatic amines have received wide attention as synthetic intermediates for heterocyclic compounds.[4] The use of (**2**) in place of, e.g. ***Hydroxylamine-O-sulfonic Acid***, has many advantages. The amination procedure is outlined in (eq 2) and the results for some representative heteroaromatic systems are summarized in Table 1.

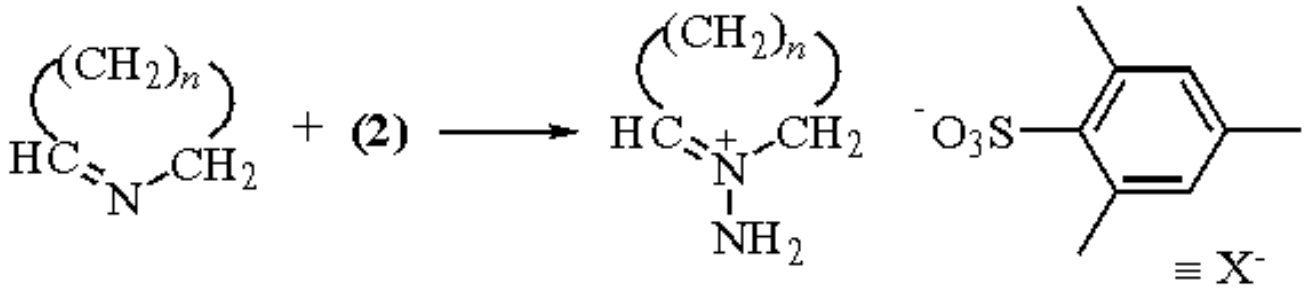

(2)

Table 1 *N*-Amine Salts[a] Formed from Heteroaromatic Amines and (**2**) According to Eq 2

Compound		Yield (%)
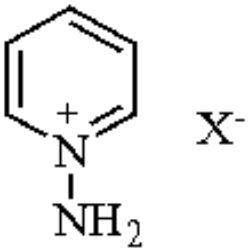	**(3)**	80[5]
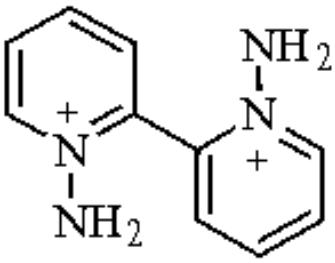	**(4)**	42[6]
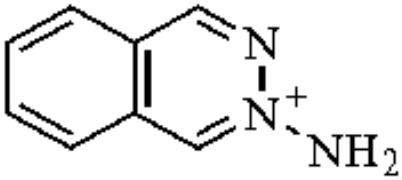	**(5)**	53[7]

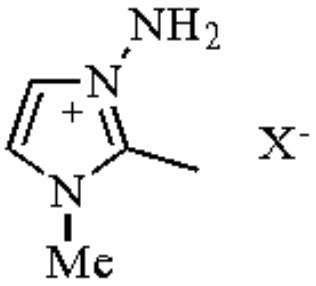	(6)	54[8]
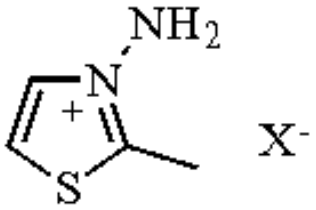	(7)	81[9]
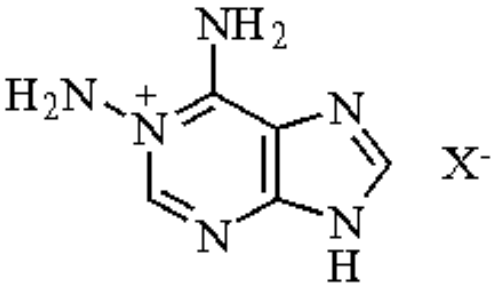	(8)	65[10]

[a] X^- = mesitylsulfonate.

Typical Procedure for *N*-Amination.

To an ice-cold solution of the amine (e.g. 1.00 mmol ***Pyridine***) in dichloromethane (2 mL) is added dropwise a solution of (**2**) (1.00 mmol) in dichloromethane (2 mL). The reaction mixture is allowed to stand at 20 °C for 10 min. After addition of diethyl ether, the precipitated crystals are collected and recrystallized from methanol/ethyl acetate to give the *N*-aminopyridinium mesitylsulfonate (**3**); 235 mg yield (80%), mp 125-126 °C.[1]

Reactions with Tertiary Amines.

Reagent (**2**) aminates a variety of tertiary amines, including alkaloids, under very mild conditions to give the corresponding 1,1,1-trisubstituted hydrazonium salts in high yields.[11] Some typical examples are listed in Table 2.

Table 2 Reactions of **(2)** with Tertiary Amines[11]

	Compound	Yield (%)
$Bu_3\overset{+}{N}-NH_2$ X^-	**(9)**	87
$Ph-\overset{+}{N}(Me)_2-NH_2$ X^-	**(10)**	89
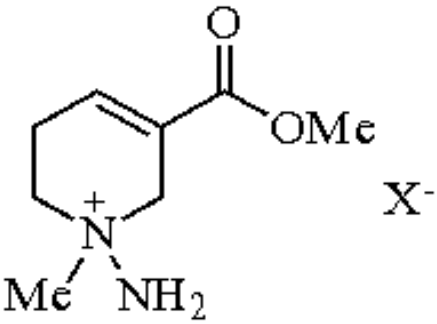	**(11)**	77
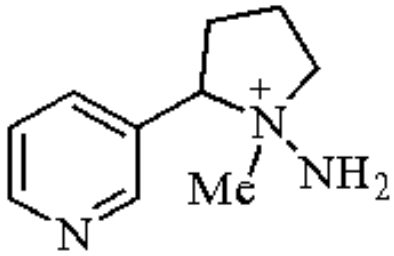	**(12)**	54

Reactions with Secondary Amines.

The formation of 1,1-disubstituted hydrazines with (**2**) occurs in lower yield than with hydroxylamine-*O*-sulfonic acid or ***Chloramine***; another useful reagent is ***O-Mesitoylhydroxylamine*** (**13**),[1,12] which gives (**14**) in 58% yield.

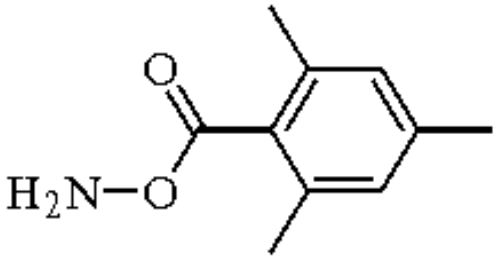

(13)

$(PhCH_2)_2N\text{-}NH_2$

(14)

More interesting is the reaction between (**2**) and compounds of the type (**15**), which leads (probably via **16-18**) to benzodiazepine derivatives such as (**19**) (eq 3).[13]

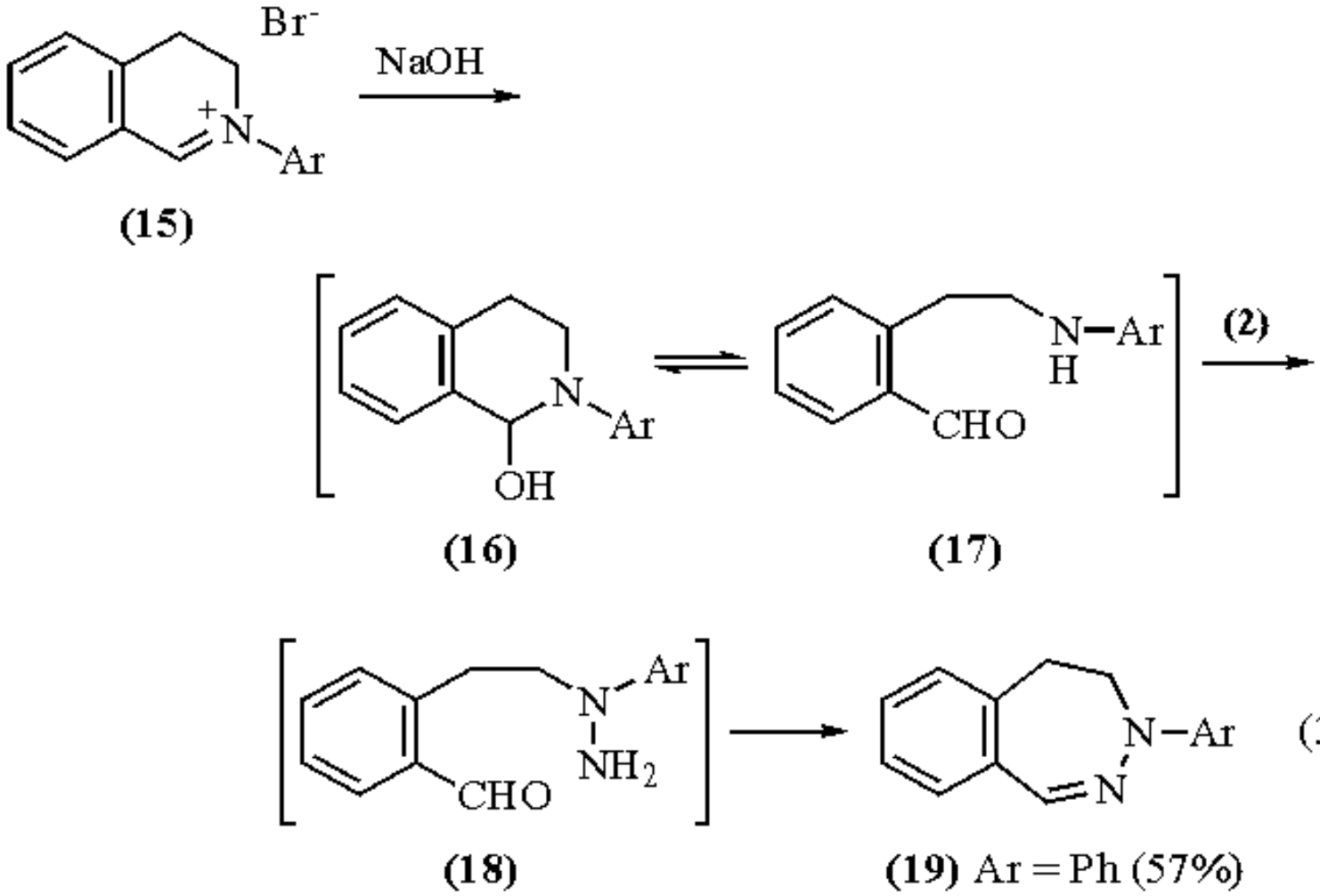

Reactions with the Anionic Nitrogen of Amides, Imides, and Pyrroles.

Reagent (**2**) is not a successful aminating reagent for these anionic species, with *O*-mesitoylhydroxylamine (**13**) being the more effective. Two examples, derived from their sodium salt, are (**20**) and (**21**).[14,15]

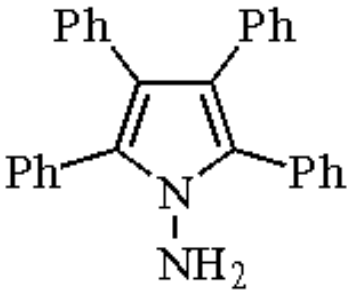

(20) 37%

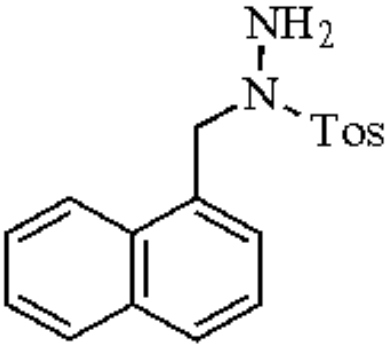

(21) 43%

Reactions with Sulfides.

The reactions of sulfides with (**2**) provide the easiest and most efficient access to *S*-amine mesitylsulfonates (**22**) (eq 4). A few examples from a long list are collected in Table 3.[16]

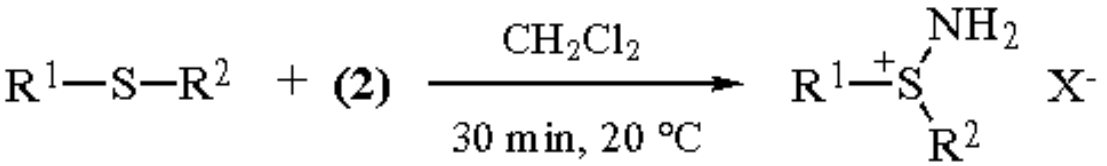

(4)

(22)

Table 3 Reactions of (2) with Sulfides

(22)	Yield (%)
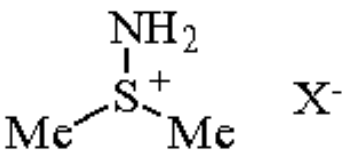	66
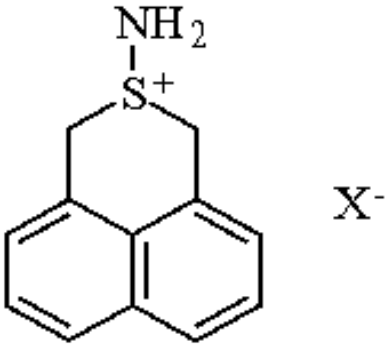	90
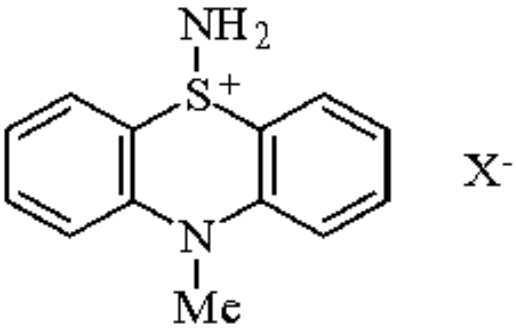	84

With allyl sulfides, consecutive reactions of the *S*-amine mesitylsulfonates (**23**) lead, probably via the intermediate sulfilimines (**24**), to allylamines (**25**) (eq 5).[1]

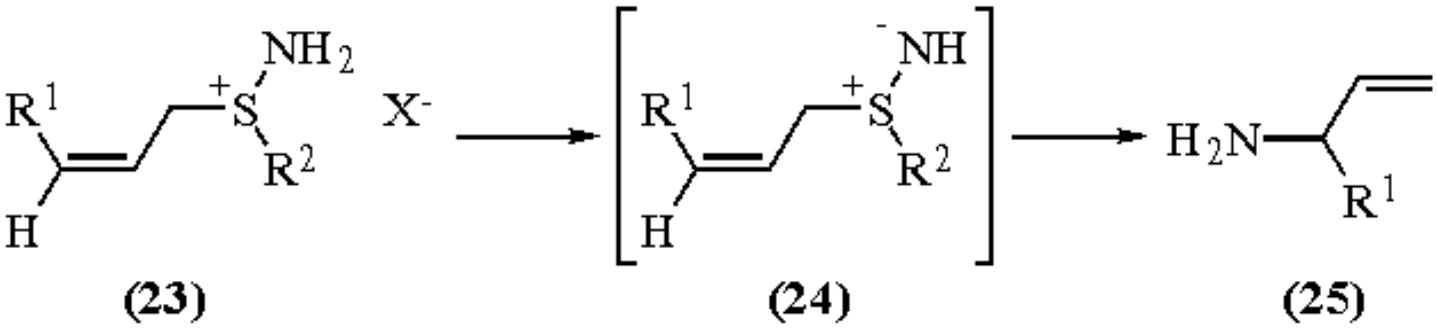

(5)

Reactions with Sulfoxides.

The synthetically very important sulfoximines (**28**) are easily prepared from sulfoxides (**26**) and (**2**) via the *S*-aminosulfoxonium mesitylsulfonates (**27**) (eq 6). Some pertinent examples for the formation of (**27**) are given in Table 4.

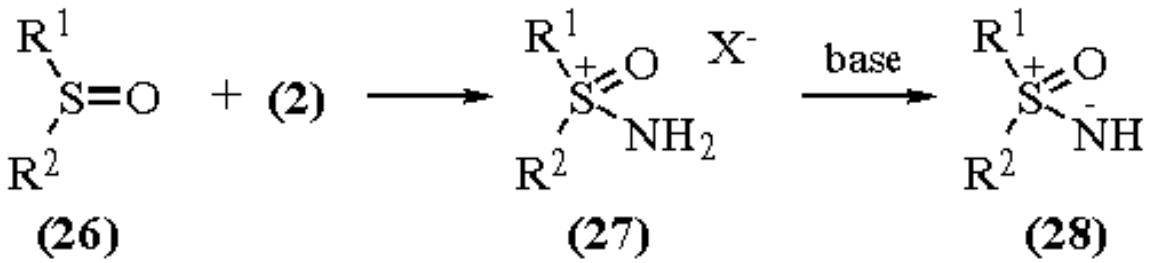

(6)

Table 4 Reactions of **(2)** with Sulfoxides

Compound		Yield (%)
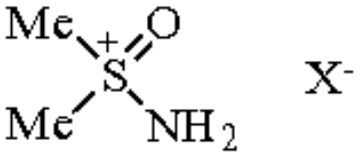	**(29)**	72[17]
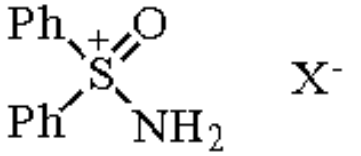	**(30)**	65[17]
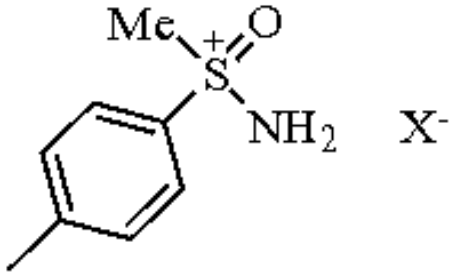	**(31)**	80[18]
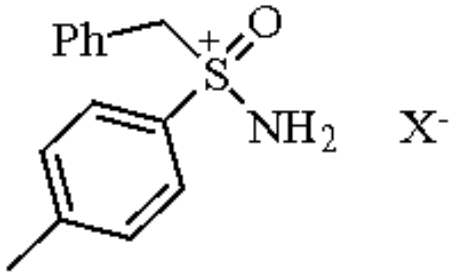	**(32)**	60[18]

Reactions with *S,S*-Acetals.

S,S-Acetals are readily dethioacetalized by (**2**). This is thus a method to cleave *S,S*-acetals from α,β-unsaturated ketones, ketones, and aldehydes (eq 7 and Table 5).[19]

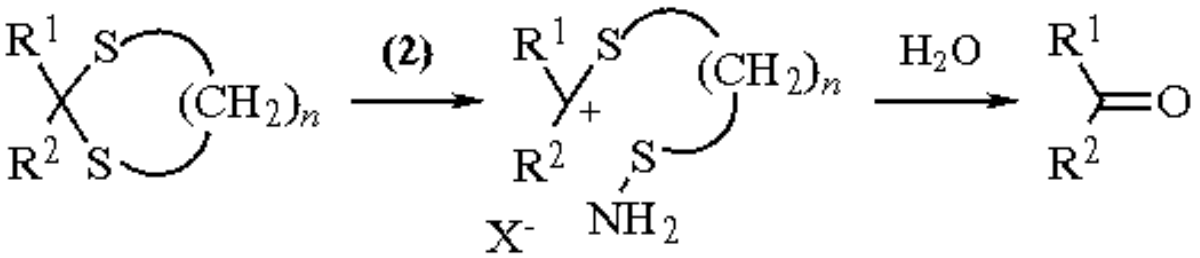

(7)

Table 5 Reactions of *S,S*-Acetals with (**2**) (eq 7)

R^1	R^2	*n*	Carbonyl compound (%)
Ph	H	3	74
PhCH=CH	H	3	72
Ph	Ph	2	85

The oxidation at sulfur with (**2**) is also achieved in the case of disulfides, thioketones, and thiols.[1]

Reactions with Phosphines.

Not surprisingly, (**2**) also aminates phosphines to give *P*-aminophosphonium salts such as (**33**) in very good yields (eq 8).[1] Other electrophilic H_2N transfer reagents aminate phosphines in a similar fashion.[1]

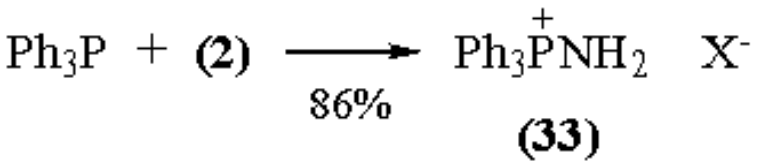

(8)

Reactions with Carbanions.

The amination of carbanions with (**2**) has also been investigated (eq 9).[20] The α-amino diethyl phosphonoacetate (**34**) was formed in moderate yields. Most probably, the basic anion deprotonated (**2**) at least in part, which should lead to fast decomposition of the resulting nitrenoid. In a similar fashion, aminomalonitrile tosylate (**35**) has been formed via a simple

procedure (eq 10).[3]

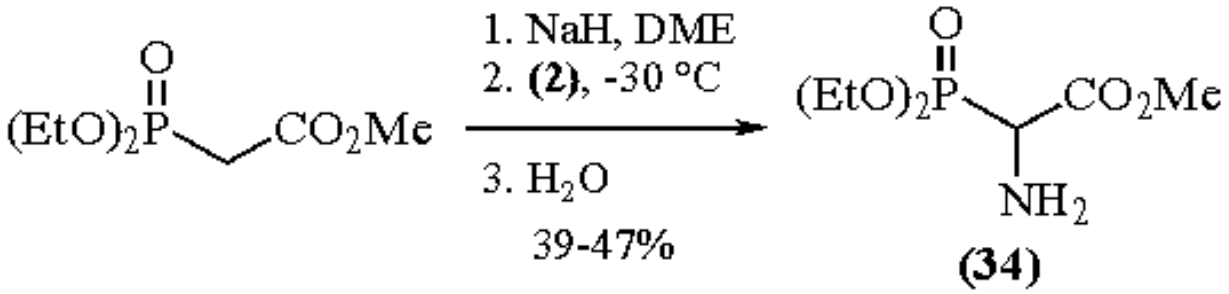

(9)

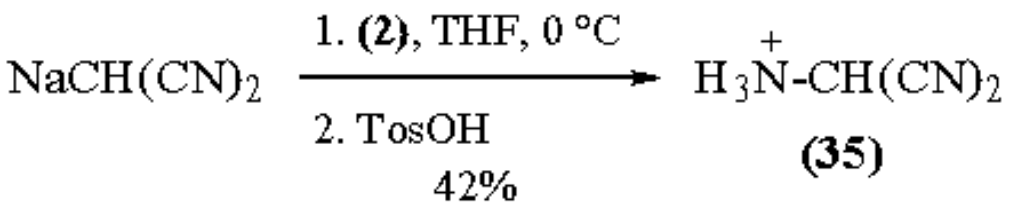

(10)

Amination of the enolate precursor to give 2-*exo*-amino-6-*endo*-(methylthio)-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**36**) in 38% yield has been described.[21]

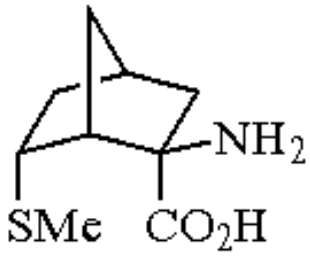

(36)

Since early observations of electrophilic aminations of organoboranes with hydroxylamine-*O*-sulfonic acid or chloramine,[22] it is not surprising that the reaction of R_3B with (**2**) similarly gives primary amines, albeit under milder conditions. Some amines formed via di- or trialkylboranes are (**37**)-(**39**), shown with the corresponding alkenes (Scheme 1).[23]

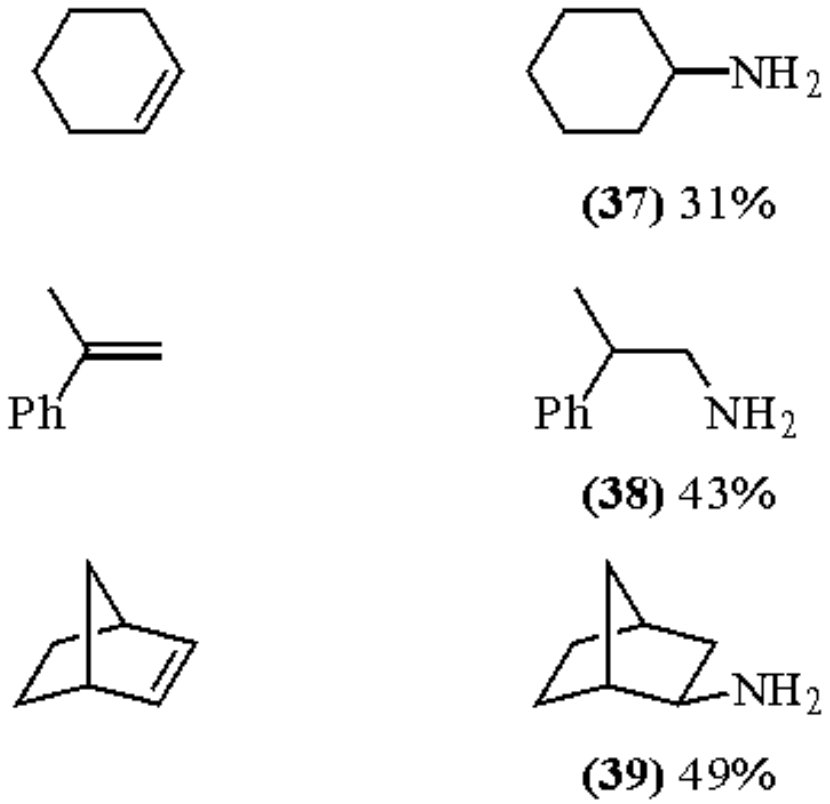

Scheme 1

There exists a variety of aminating reagents for carbanions which are much better than (**2**). An excellent review on this topic has been written[20c] (see also ***O-(Diphenylphosphinyl)hydroxylamine***).

Reactions with Electrophiles.

Reagent (**2**) also reacts with electrophiles, although this chemistry is of minor importance. Thus reaction of (**2**) with ketones (**40**) leads to the corresponding oximes (**41**), which are intermediates for the Beckmann and Neber rearrangements (eq 11).[24,25]

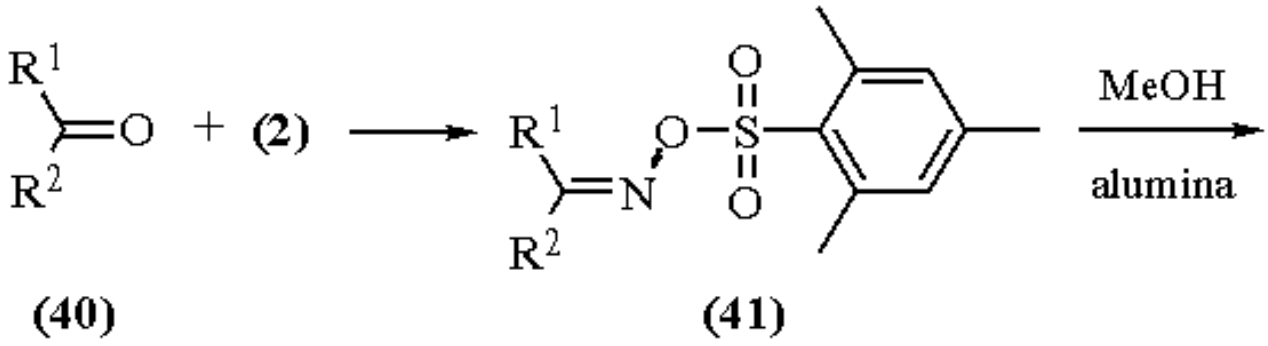

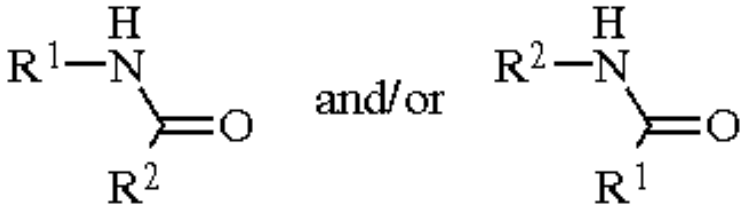

(11)

With Schiff bases derived from aliphatic aldehydes (**42**) (aldimines), (**2**) forms diaziridines (**43**) (eq 12).[1,26]

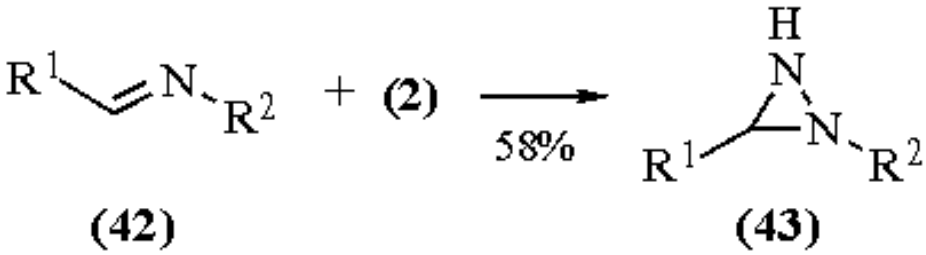

(12)

$R^1 = C_6H_{13}$; $R^2 = Cy$

If R^1 is a phenyl group as in (**44**), phenylhydrazones are formed instead (eq 13).[27]

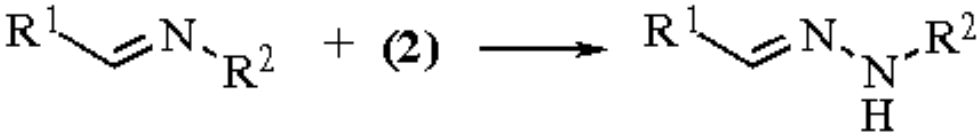

(13)

(44)

$R^1 = Ph$; $R^2 = t\text{-}Bu$

Finally, it has been reported that (**2**) also reacts with strongly electrophilic alkenes like (**45**) to give (**46**), which after treatment with base affords 1*H*-aziridines such as (**47**) (eq 14).[28]

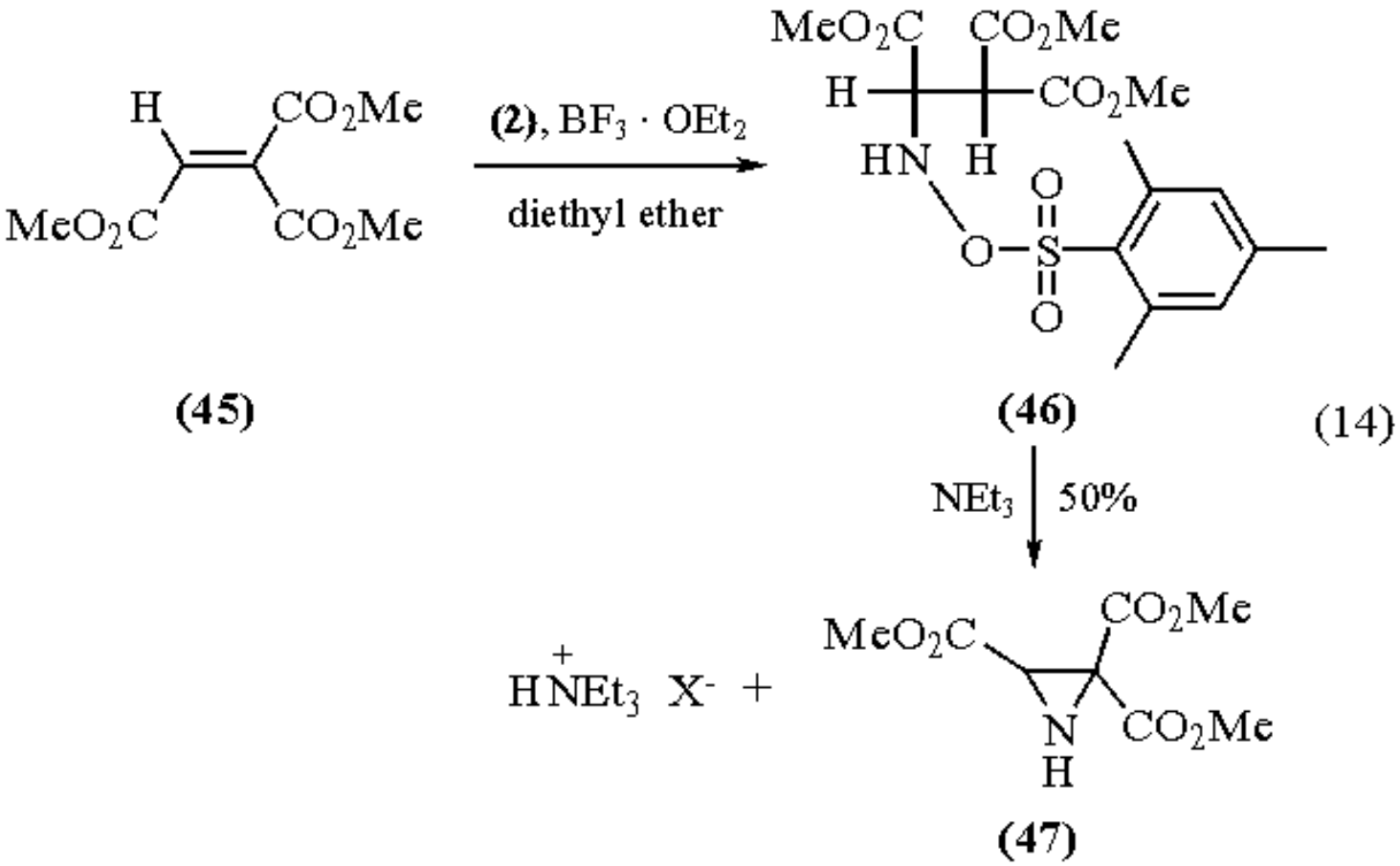

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18. Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *JOC* **1974**, *39*, 2458.
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27. Tamura, Y.; Hayashi, H.; Nishimura, Y.; Ikeda, M. *JHC* **1975**, *12*, 225.
28. Métra, P.; Hamelin, J. *CC* **1980**, 1038.

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Methacrolein

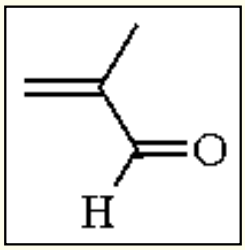

[78-85-3] · C_4H_6O · Methacrolein · (MW 70.10)

(used in cycloaddition reactions, aldol reactions; undergoes both 1,2- and 1,4-additions)

Alternate Name: 2-methylpropenal.

Physical Data: mp -81 °C; bp 69 °C; vapor pressure 121 mmHg at 20 °C; *d* 0.837 g cm^{-3}.

Solubility: miscible with water, alcohol, ether.

Form Supplied in: colorless liquid; widely available. *Drying:* fractional distillation (freshly distilled methacrolein turns cloudy within 1 or 2 h at rt; this can be prevented by the addition of 1% hydroquinone).[1]

Handling, Storage, and Precautions: methacrolein is extremely flammable, and a severe irritant and lachrymator. Use in a fume hood.

Diels-Alder Reactions.

Methacrolein (**1**) has been widely used in Diels-Alder reactions, where it most commonly functions as the dienophile[2] (eq 1); X = Me, CO_2Me, OMe;[2a] O_2CNMe_2;[2b] CH_2CO_2Me[2c]).

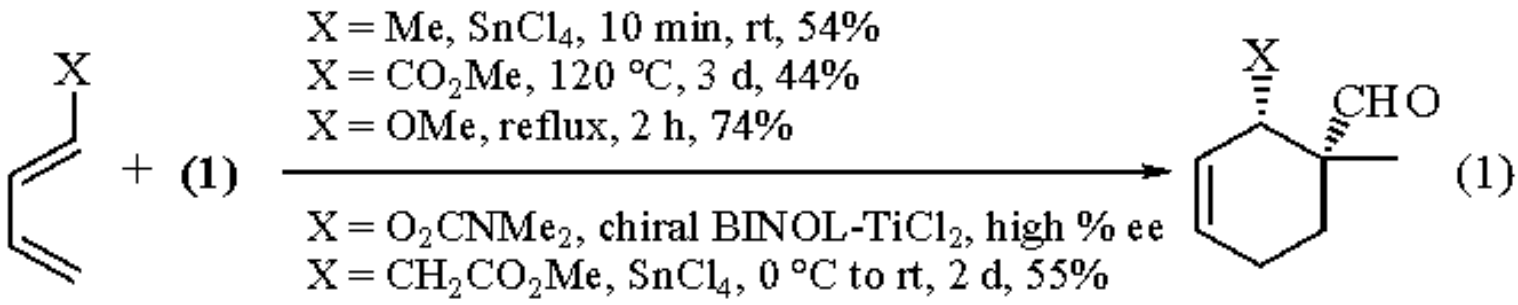

Methacrolein also undergoes a Diels-Alder reaction with itself to produce a dimer (eq 2).[1]

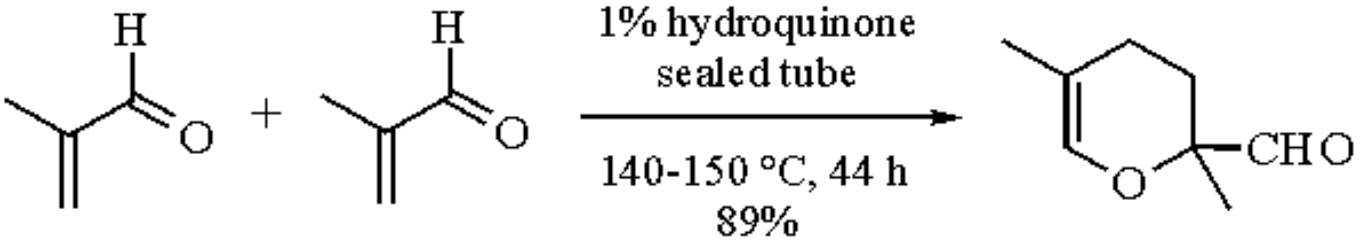

(2)

When treated with electron-rich alkenes, generally in the presence of a Lewis acid, methacrolein undergoes a hetero-Diels-Alder reaction (eq 3).[3]

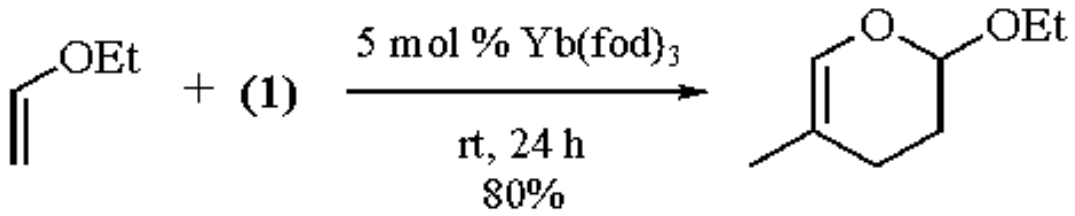

(3)

There are numerous examples in which chiral Lewis acid catalysts have been used to obtain enantioselective [4 + 2] cycloadditions.[4] A few of these are listed in Table 1 as applied to the reaction of methacrolein with cyclopentadiene (eq 4).[5]

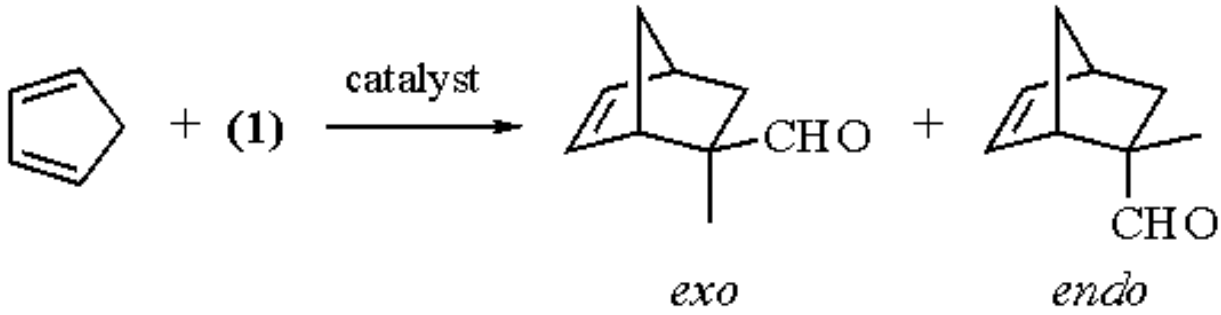

(4)

Table 1 Examples of Chiral Lewis Acid Catalysts (eq 4)

Catalyst[a]	*exo*:*endo*	ee (%)	Yield (*exo* + *endo*) (%)
A[5a]	49:1	98	100
B[5b]	99:1	97	84
C[5c]	8:1	96	85
D[5d]	37:1	90	85

[a] Prepared from (A) 3,3¢bis(2-phenyl)-4-phenanthrol and Et_2AlCl, (B) 1-methyl-2-(*S*)-(diphenylhydroxylmethyl)pyrrolidine and BBr_3, (C) 2,6-dimethoxybenzoyltartaric acid and BH_3, (D) (*S*)-1,1¢bi-2-naphthol and $H_2BBr{\cdot}SMe_2$.

Nucleophilic 1,2-Additions.

The reactions of methacrolein with Grignard reagents (eq 5),[6a] organozincs (eq 6),[7] alkyllithiums,[8] and lithium,[9] tin,[10] and boron[11] enolates yield, selectively, the products from 1,2-addition. These allylic alcohols are useful intermediates for a number of transformations, including formation of allyl vinyl ethers which then undergo Claisen rearrangements (eq 5).[6,8a,12]

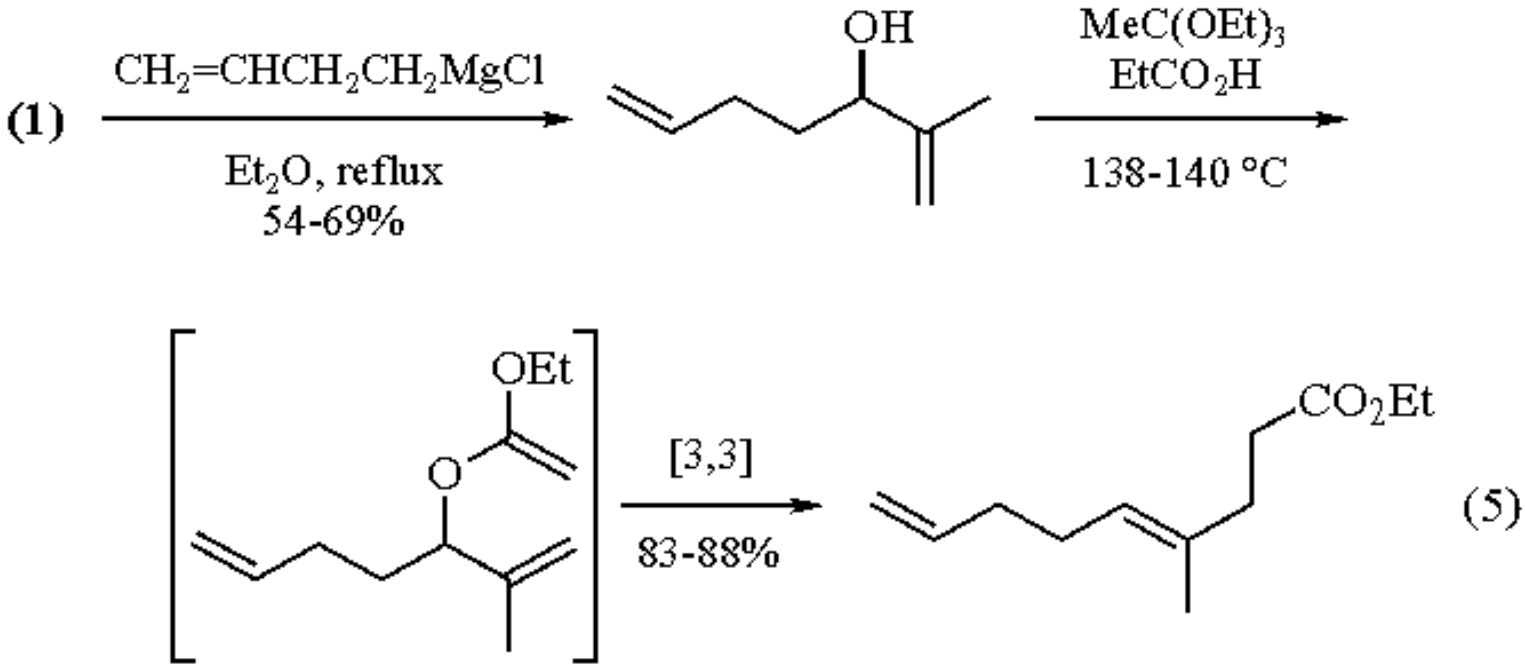

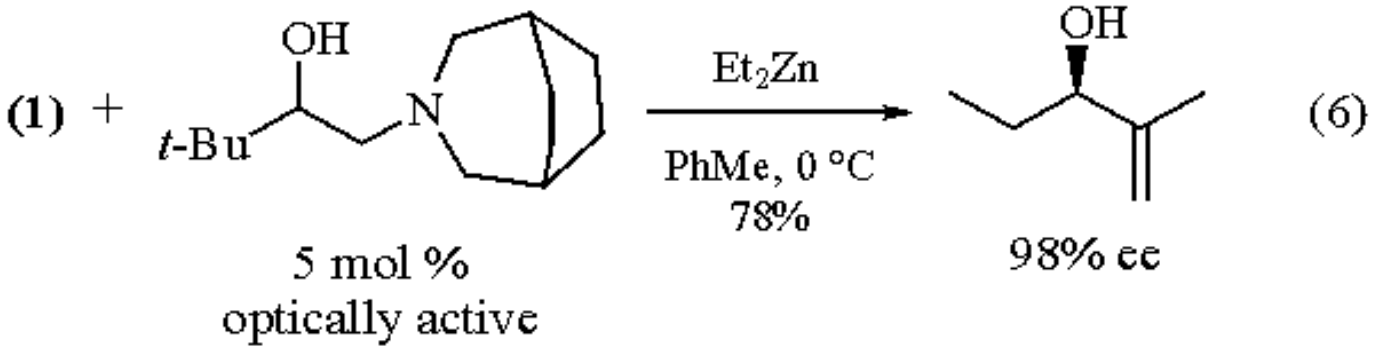

Reaction of methacrolein with lithium enolates of hindered aryl esters yields selectively the *threo* aldol products (eq 7).[9c]

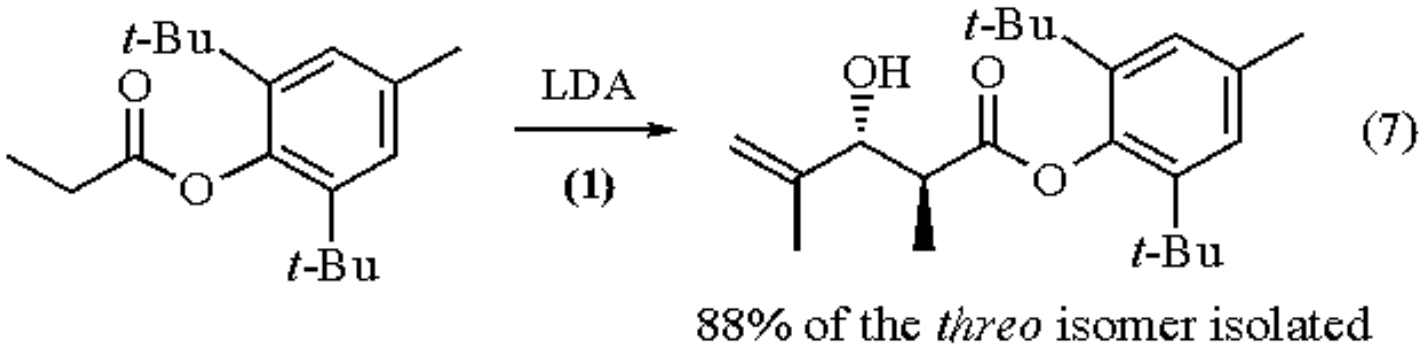

The reaction of the boron enolate of a chiral imide with methacrolein allows for the selective synthesis of *syn* aldol products (eq 8), which can be elaborated into α-amino acids.[11f]

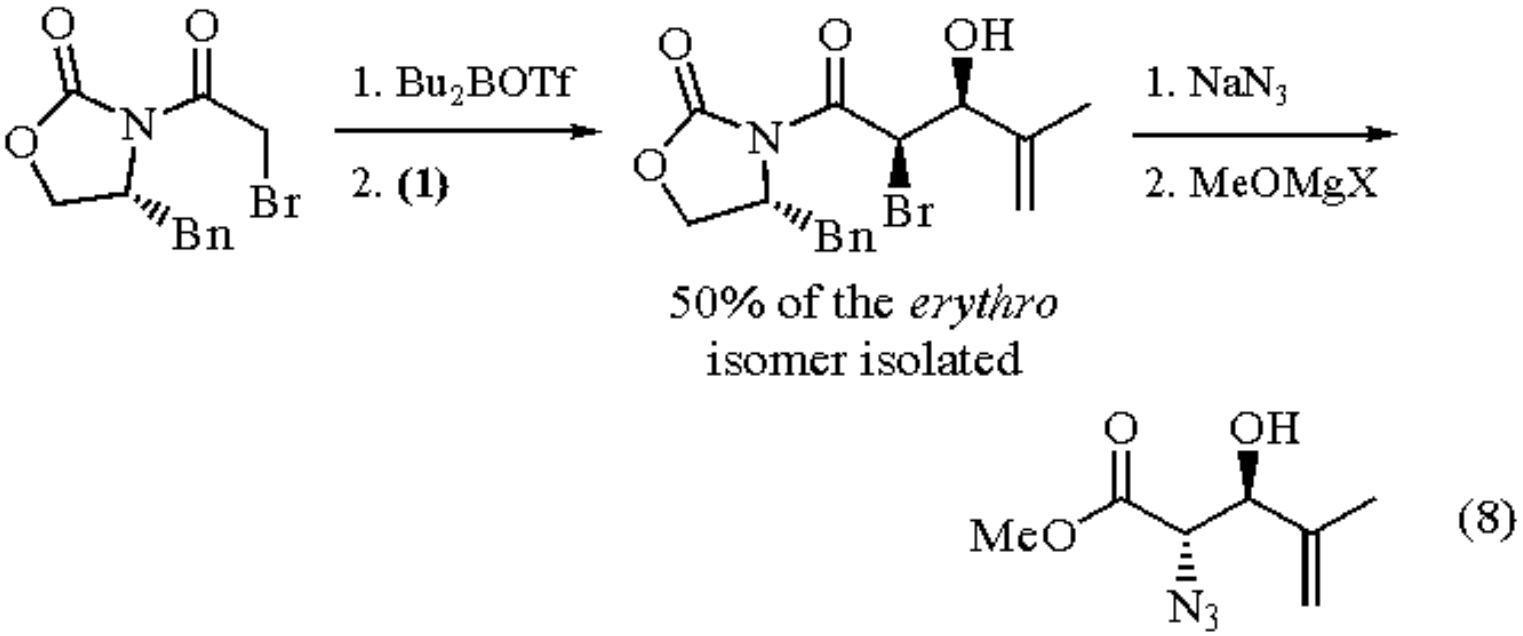

A useful extension of the Evans methodology allows the selective preparation of either the *anti* aldol or the *syn* aldol products from the same substrate by simply changing the reaction conditions (eq 9).[11c]

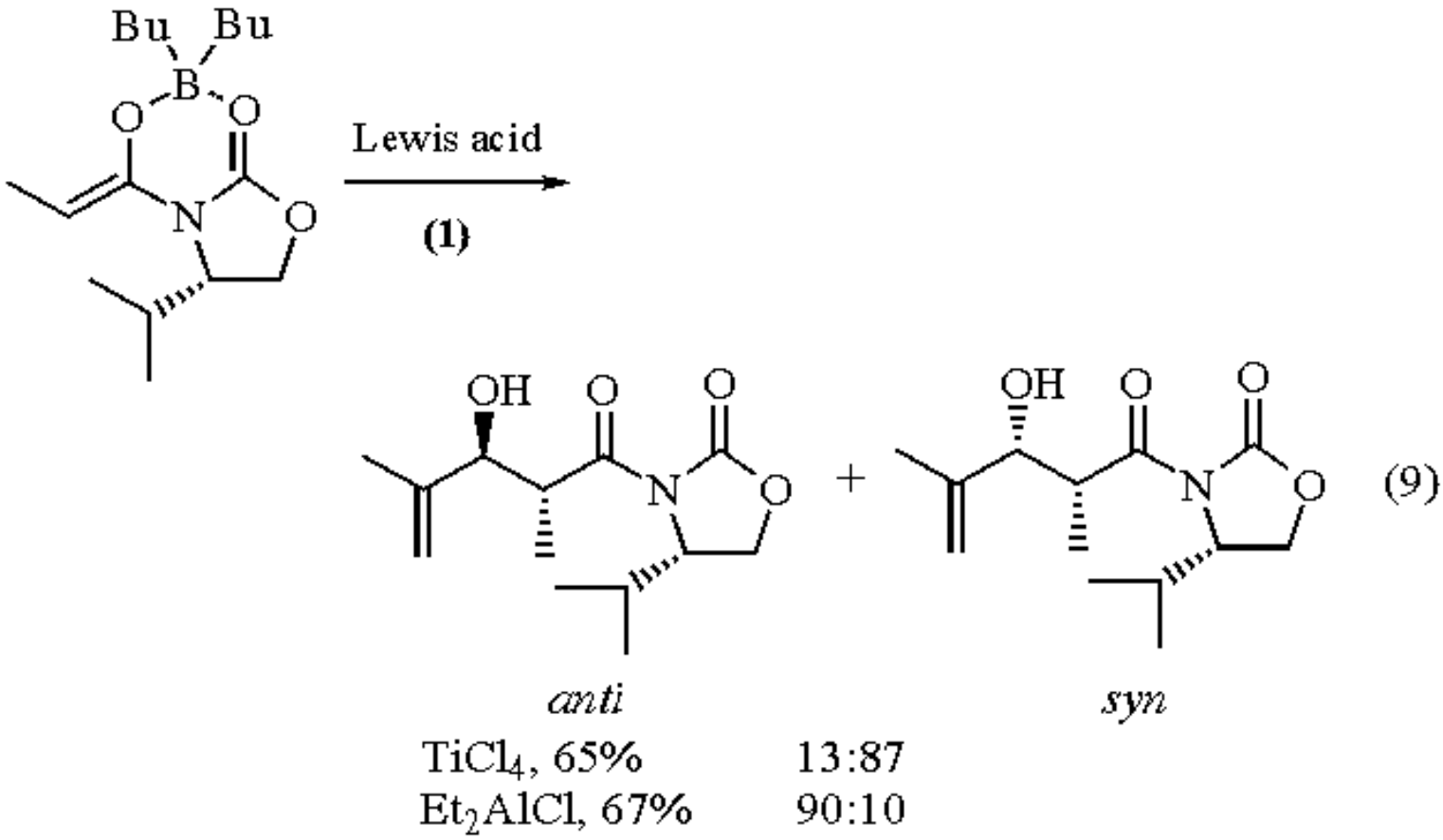

Other 1,2-additions to methacrolein lead to the formation of acetals (eq 10),[13] imines (eq 11),[14] cyano ethers (eq 12),[15a] cyano esters (eq 13),[15b] and acyl silanes (eq 14).[16]

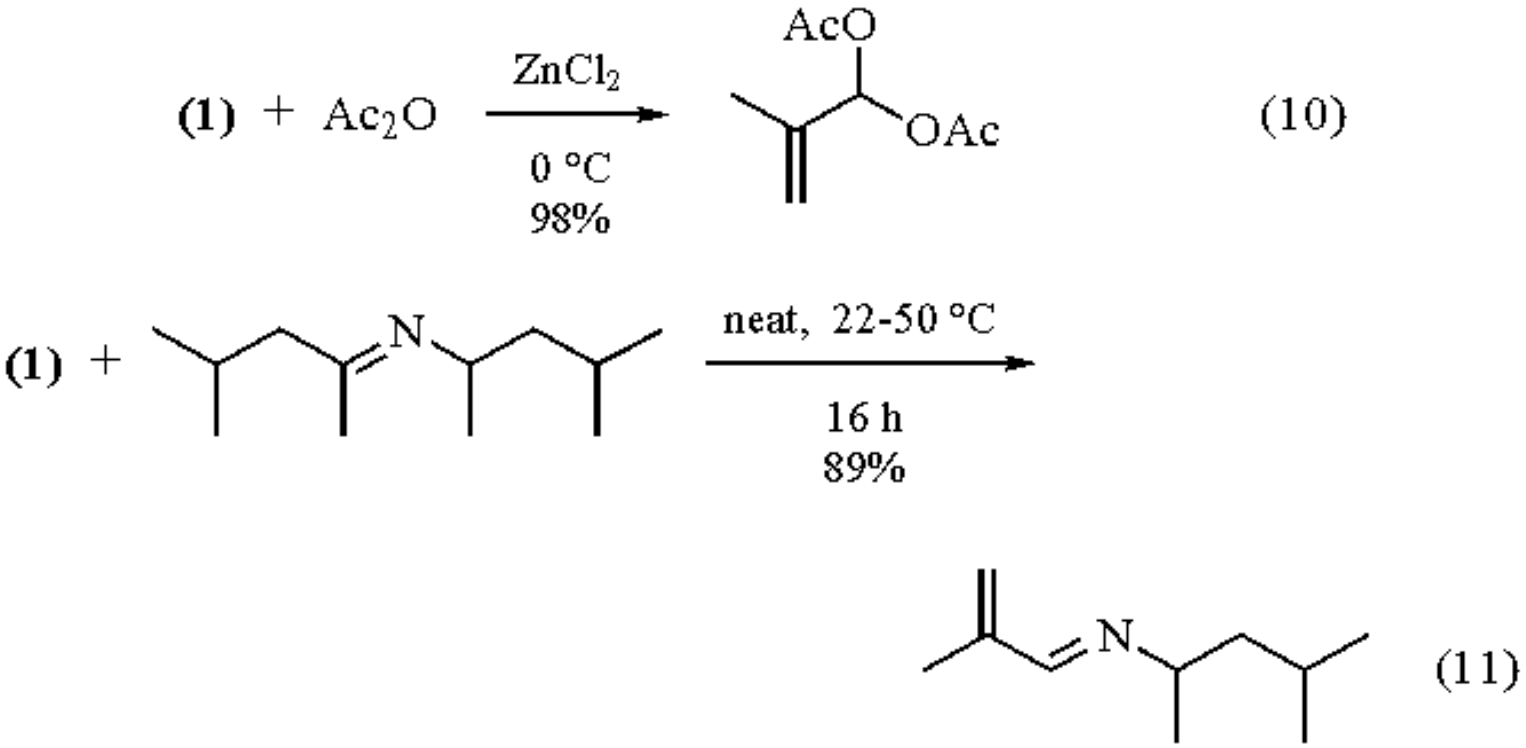

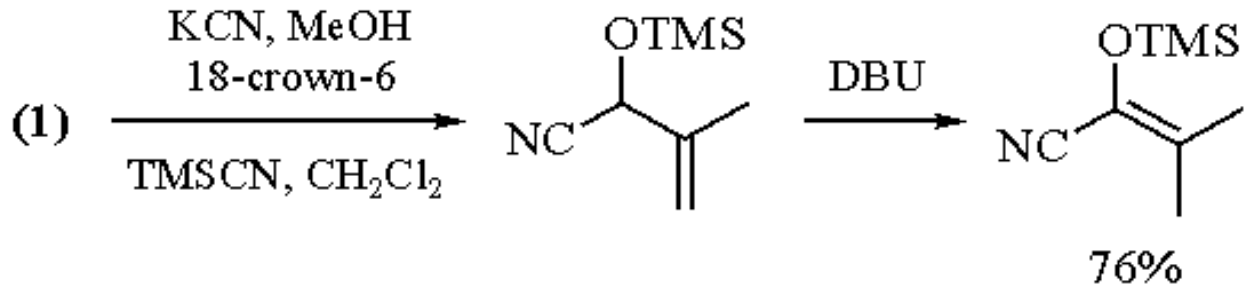

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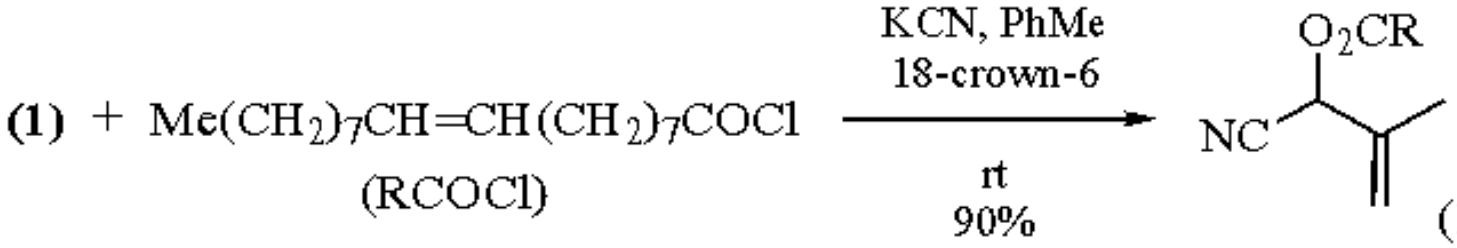

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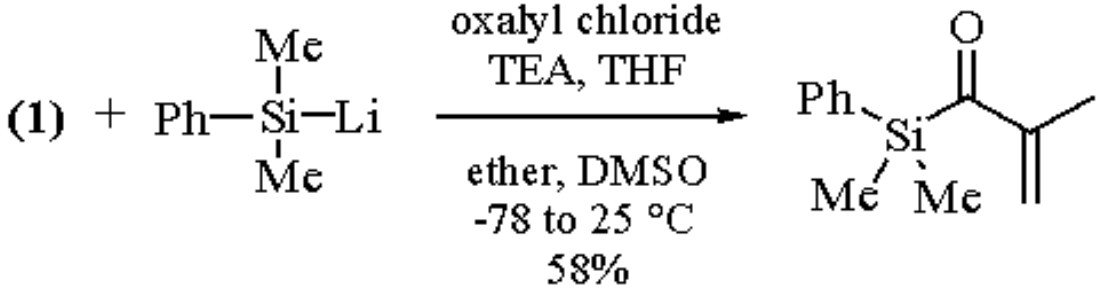

(14)

Nucleophilic 1,4-Additions.

Nucleophilic 1,4-addition of amines,[17] thiols,[18] and phosphorus reagents[19] to methacrolein leads to a wide variety of products in high yield (eqs 15-19).

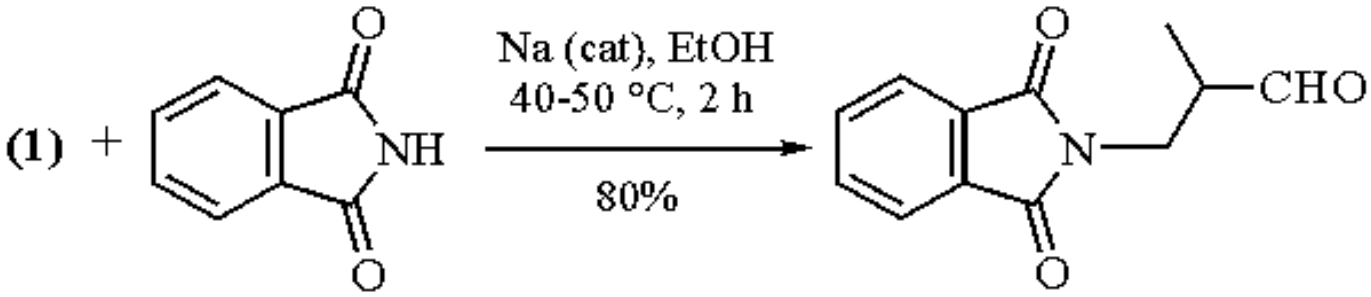

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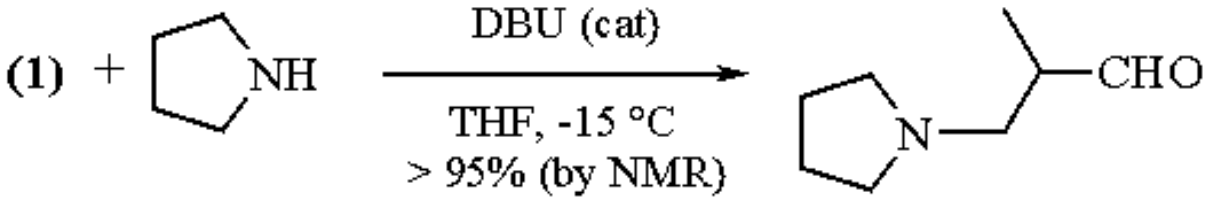

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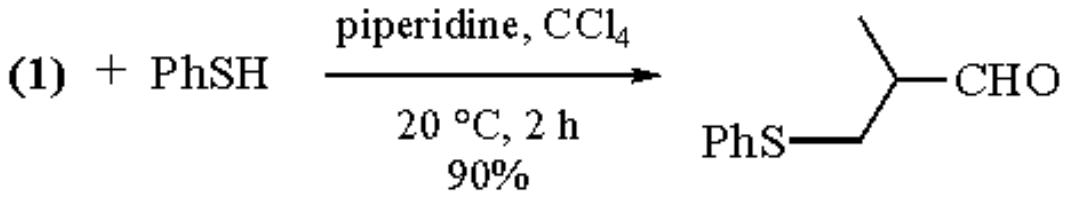

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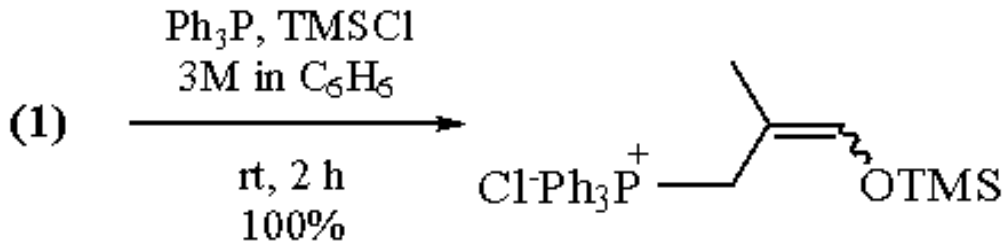

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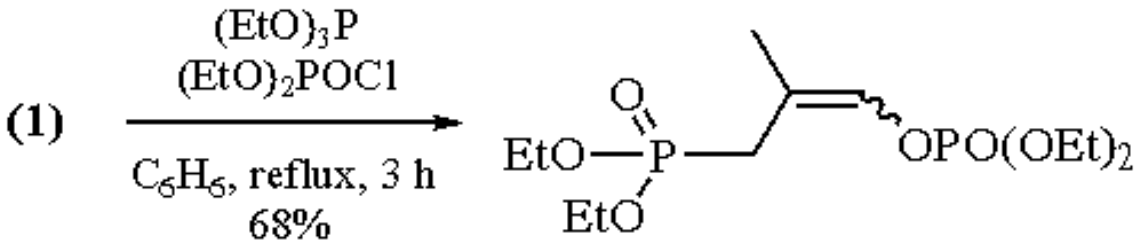

(19)

The 1,4-addition of alkaline ***Hydrogen Peroxide***, with careful control of the pH, occurs in good yield to give α-methylglycidaldehyde.[20] The 1,4-addition of alcohols to methacrolein is less successful (however, a synthetically useful example is shown in eq 20).[21]

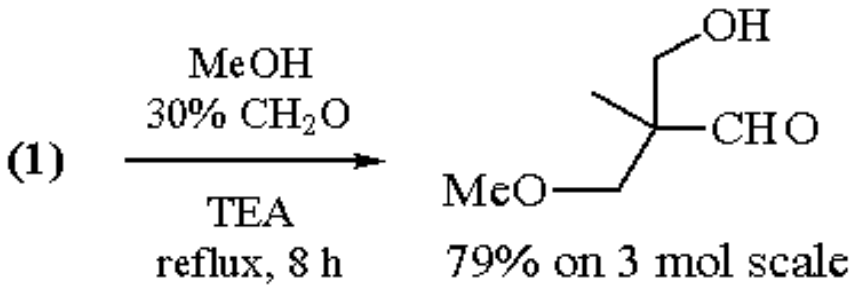

(20)

Unlike α,β-unsaturated ketones, α,β-unsaturated aldehydes such as methacrolein give poor yields of 1,4-addition products with carbon nucleophiles due to the preference for 1,2-addition to the carbonyl. Two important exceptions are the reactions with trialkylboranes (eq 21),[22] and the copper-catalyzed addition of Grignard reagents (eq 22).[23] Significantly, the latter procedure has been greatly improved by the addition of ***Chlorotrimethylsilane*** and ***Hexamethylphosphoric Triamide***.[23]

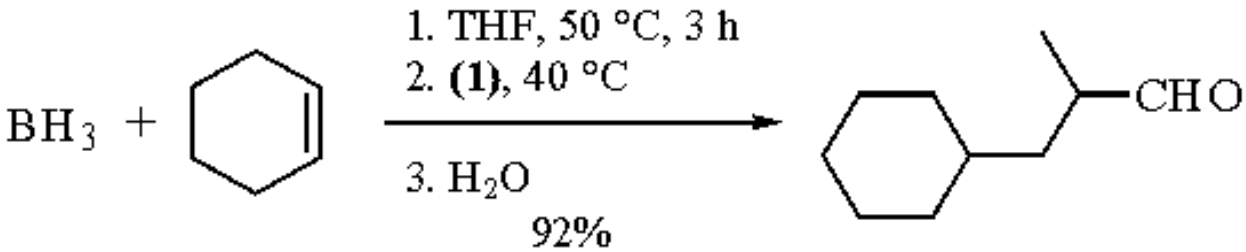

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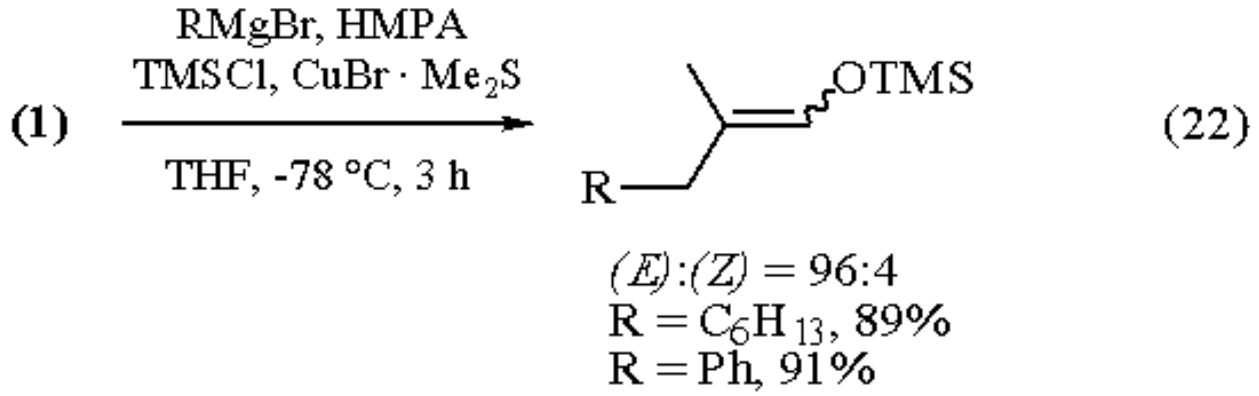

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α-Methacrolein *N*-*t*-Butylimine

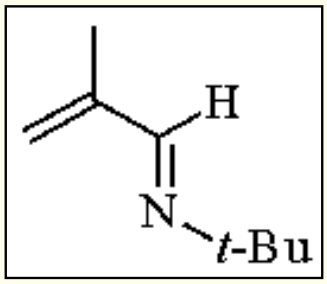

(*s-cis*)

[81569-06-4] · $C_8H_{15}N$ · α-Methacrolein *N*-*t*-Butylimine · (MW 125.24) (structure unspecified)

[90554-32-8]

(α,β-unsaturated aldimine or 1-aza-1,3-diene; useful building block for heterocyclic synthesis as a heterodiene or a functionalized imine and alkene[1-4])

Physical Data: bp 28-30 °C/10 mmHg.

Solubility: sol most organic solvents such as ether, alcohol, carbon tetrachloride, chloroform, dichloromethane, benzene, hexane.

Form Supplied in: colorless liquid.[1]

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H, *t*-Bu), 1.93 (s, 3H, Me), 5.28 (m, 1H, =C*H*H), 5.50 (m, 1H, =CH*H*), 7.84 (s, 1H, N=CH).[1,6]

Preparative Methods: by dehydrohalogenation of α-haloaldimines, which are prepared by halogenation of the corresponding aldimine with *N*-halosuccinimide (eq 1).[5,6] Alternatively, prepared by condensation of *N*-*t*-butylmethanimine and 1-piperidino-1-propene (eq 2).[1,2] Preparation of this type of γ-unsubstituted azadiene by direct condensation of an α,β-unsaturated aldehyde with an amine usually suffers from low yields due to side reactions.[7,8]

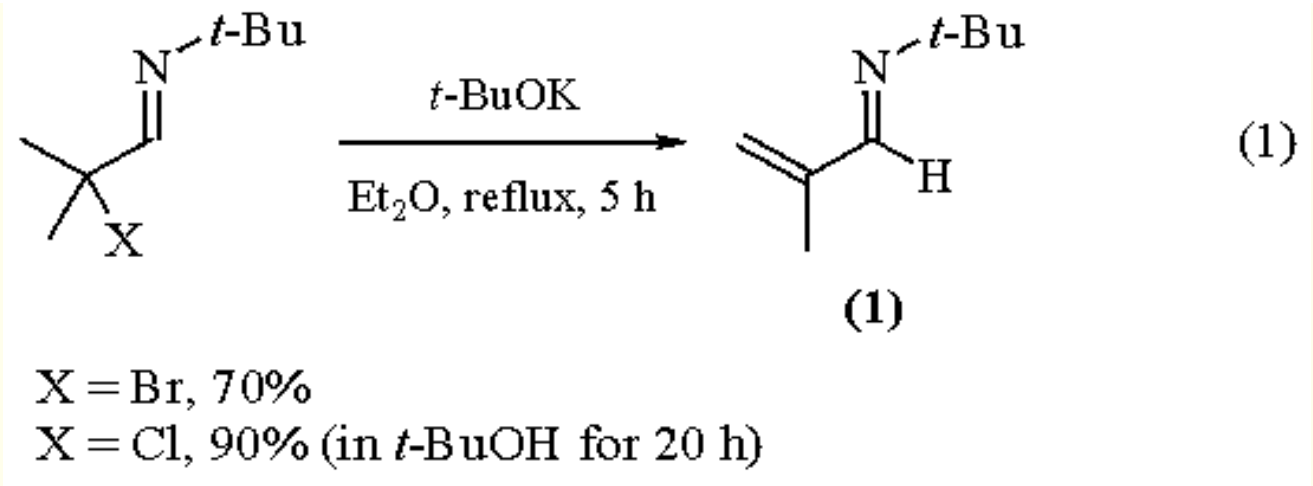

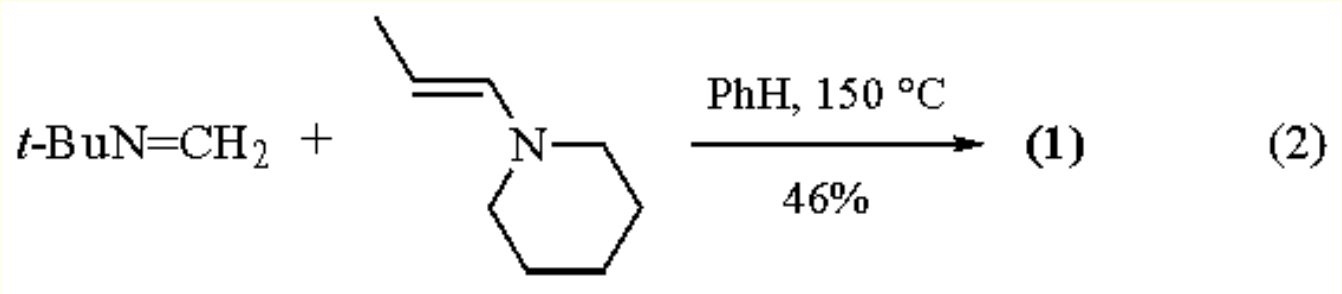

Handling, Storage, and Precautions: hygroscopic and should be handled in a dry atmosphere. It neither hydrolyzes in the absence of acid nor polymerizes upon heating and can be stored in a refrigerator for many months. Use in a fume hood.

Introduction.

α-Methacrolein *N*-*t*-butylimine (**1**) is known to be a heterodiene with considerable stability and versatile utility in organic synthesis as an electron-deficient alkene and an alkenyl imine, as well as an azadiene which has no substituent on the terminal carbon and the *s*-*cis* structure favorable for 1,4-cycloaddition leading to nitrogen-containing heterocycles. Another feature of the compound is the *t*-butyl group that often eliminates upon thermal or acidic treatment.

Polymerization.

While polymerization of imine (**1**) is not reported, analogous *N*-alkylmethacroleinimines such as *N*-cyclohexyl-3-methyl-1-aza-1,3-butadiene are known to polymerize by anionic catalysts but not by cationic or radical initiators. The polymerization proceeds through double bond addition and reactivity of this type with aldimines is less than that of methyl methacrylate.[8]

Oxidation.

Although oxidation of imine (**1**) itself is not reported, conversion of its analogs to alkenyloxaziridines with ***m***-

Chloroperbenzoic Acid occurs readily (eq 3).[3] Reaction of (**1**) with singlet oxygen does not proceed, while γ-substituted analogs are oxidized to 1,2-dioxolanes (eq 4).[9,10]

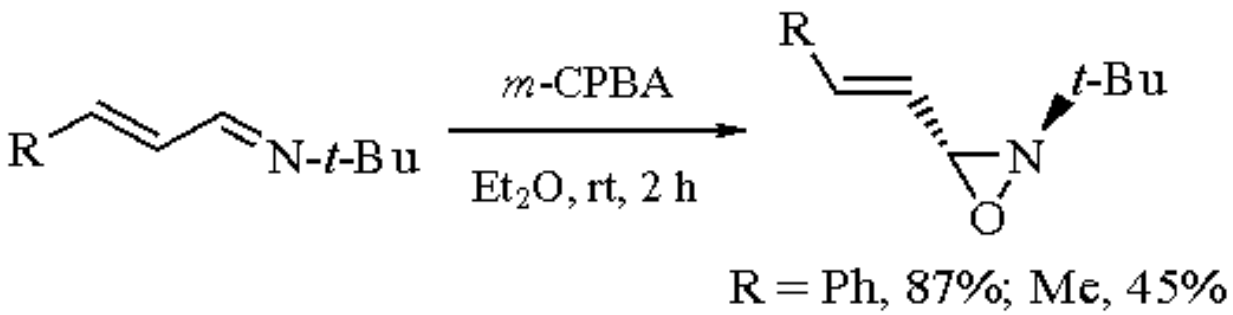

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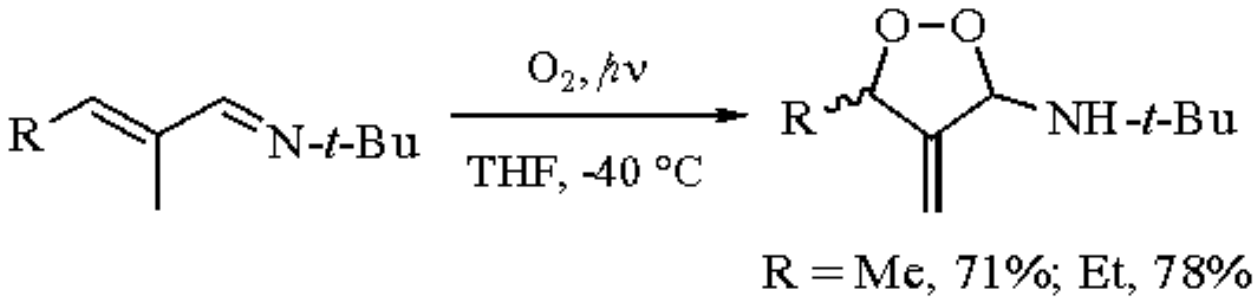

(4)

Reduction.

Selective reduction of *N*-alkylazadienes including imine (**1**) is a facile method for synthesis of secondary allylic amines (eq 5).[5]

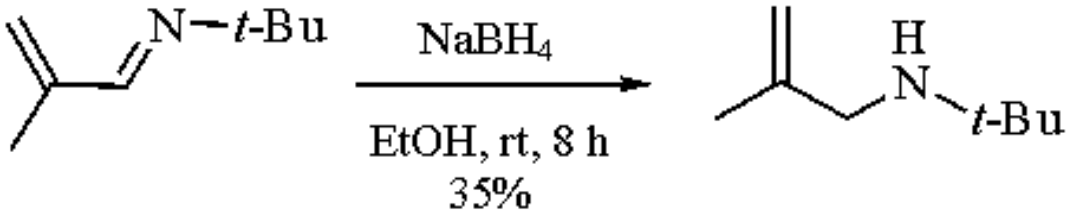

(5)

Cycloaddition Leading to Heterocycles.

Methacrolein imines and their analogs react with various 1,3-dipoles, enophiles, and dienophiles to give four-, five-, and six-membered heterocyclic compounds; some representative examples are given below.

1,2-Cycloaddition of 1-Aza-1,3-dienes.

β-Alkenyl-β-lactams are synthesized by addition of ketenes across the C=N bond (eq 6). Formation of five-membered heterocycles from analogs via nitrilium ylide dipolar cycloaddition to the C=N or C=C bond (eqs 7 and 8) is reported.[3]

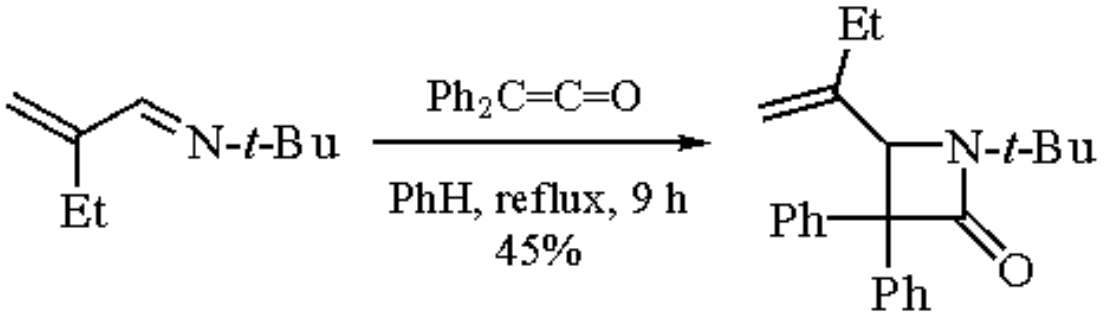

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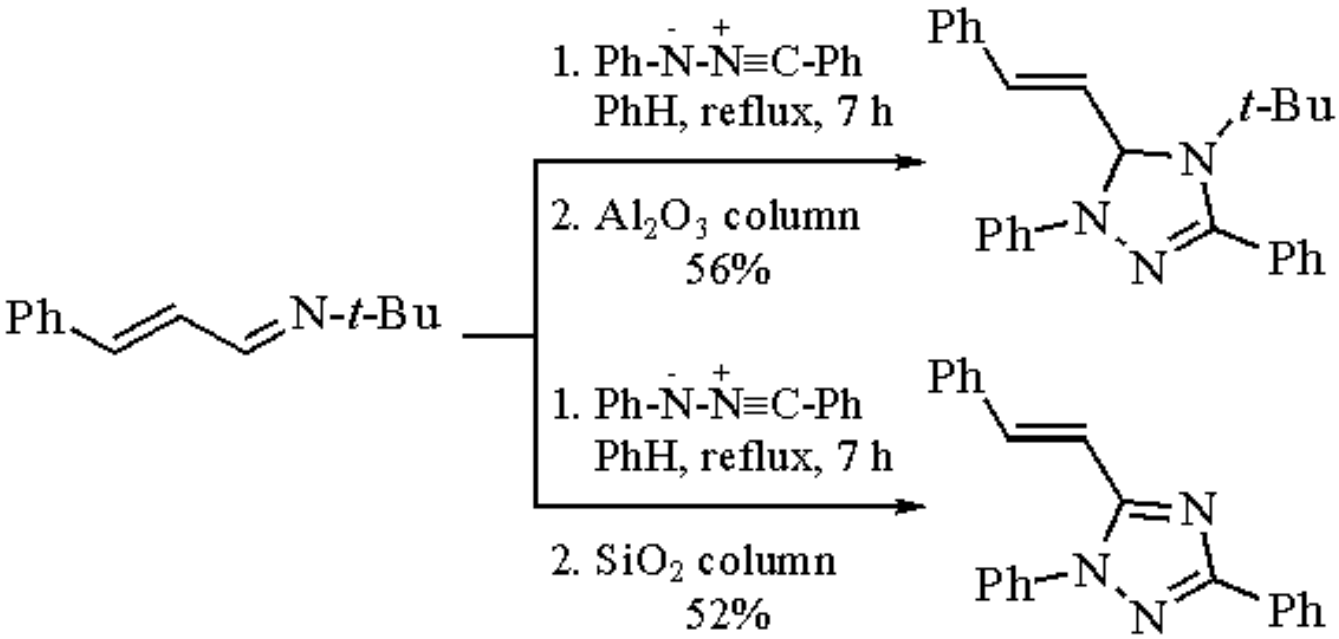

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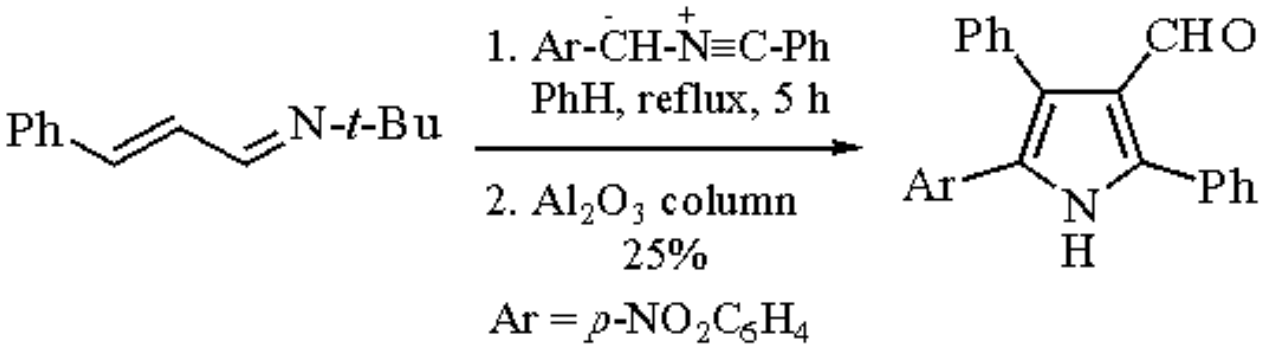

(8)

1,4-Cycloaddition of 1-Aza-1,3-dienes.

Formation of 3,5-disubstituted pyridines via [4 + 2] cycloaddition/cycloelimination of enamines to 1-aza-1,3-butadiene intermediates including (**1**) is known (eq 9).[1,2] This process is an inverse electron demand Diels-Alder reaction and can be performed with the isolated 1-azadienes to give various unsymmetrical 3,5-disubstituted pyridines (eq 10).[1,2]

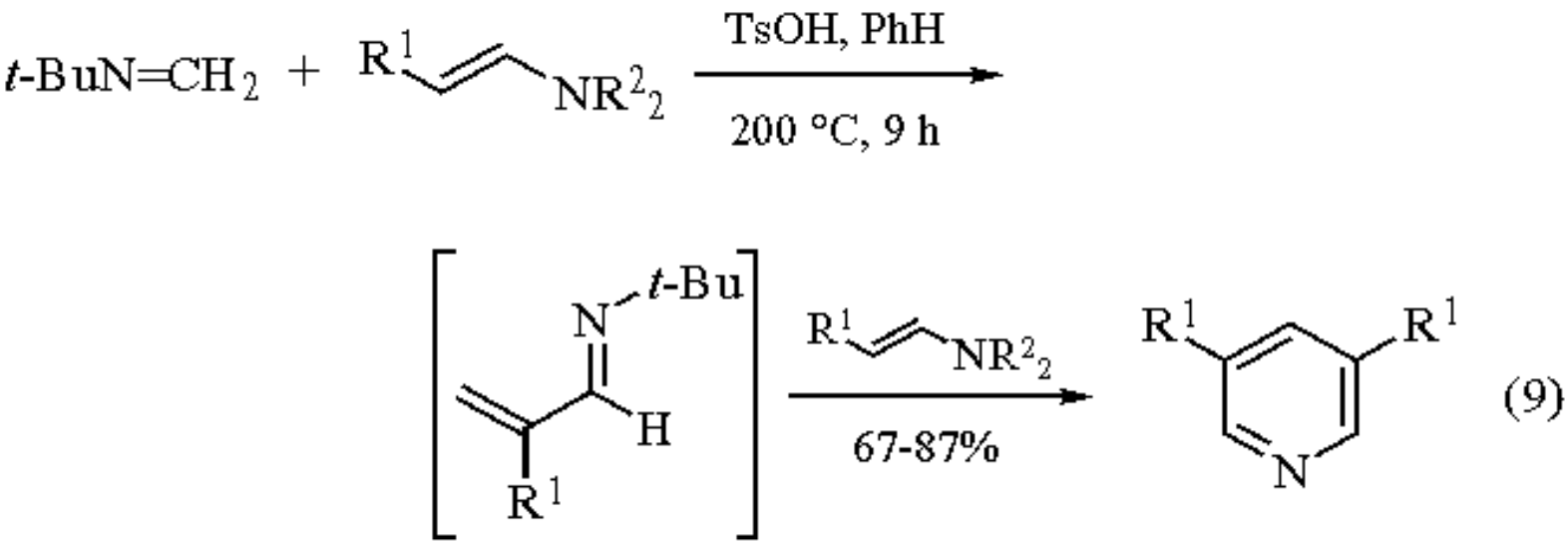

R^1 = Me, Et, *i*-Pr, Cy, Ph, SPh; $NR^2{}_2$ = piperidino, morpholino, etc.

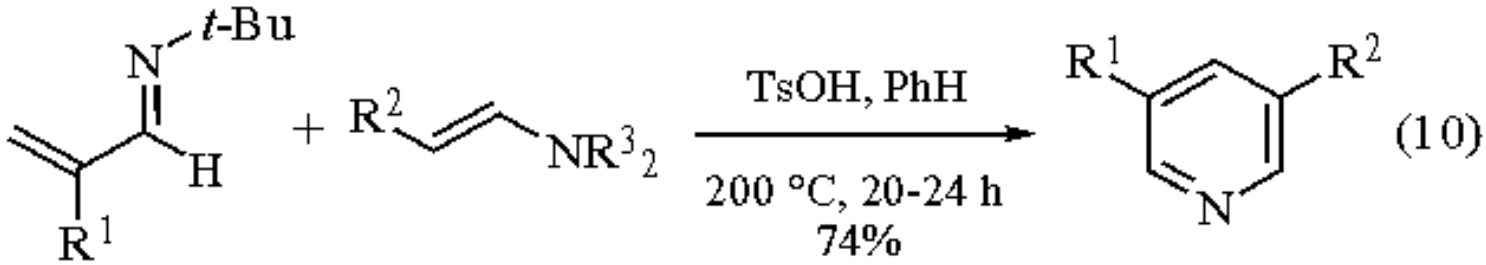

R^1 = Et, *i*-Pr
R^2 = Me, Et, *i*-Pr, Ph, EtOCO, piperidino, PhO, PhS, $PhSO_2$
$NR^3{}_2$ = piperidino, morpholino, etc.

Dihydropyridones (δ-lactams) are also prepared by Michael addition of ester enolates and subsequent cyclization (eq 11).[4]

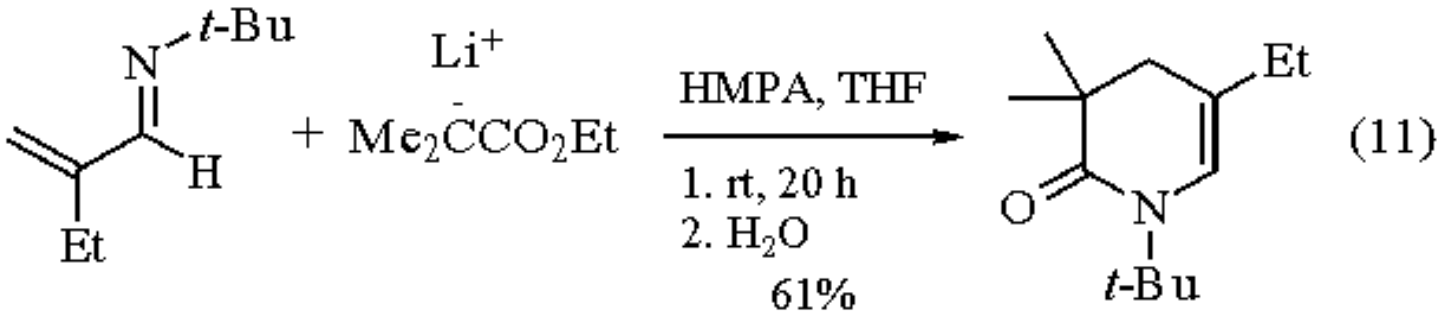

Related Reagents.

Acrolein; ***3-Ethoxyacrolein***; ***Methacrolein Dimethylhydrazone***; ***Propionaldehyde t-Butylimine***.

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Methacrolein Dimethylhydrazone

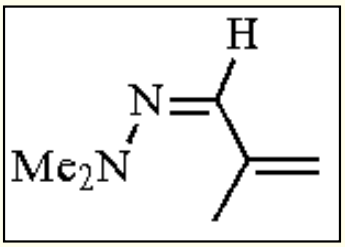

[66064-57-1] · $C_6H_{12}N_2$ · Methacrolein Dimethylhydrazone · (MW 112.174)

(electron-rich 1-azadiene reacting with electron-poor alkenes to yield Diels-Alder adducts[1-5])

Physical Data: bp 40-42 °C/20 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: conveniently prepared either by the direct treatment of ***N,N-Dimethylhydrazine*** with ***Methacrolein*** or by a Hoffmann cleavage of the pyrazolinium iodide also obtained from methacrolein (eq 1).[1-5] These methods have been successfully applied to the preparation of various α,β-unsaturated hydrazones (Table 1).

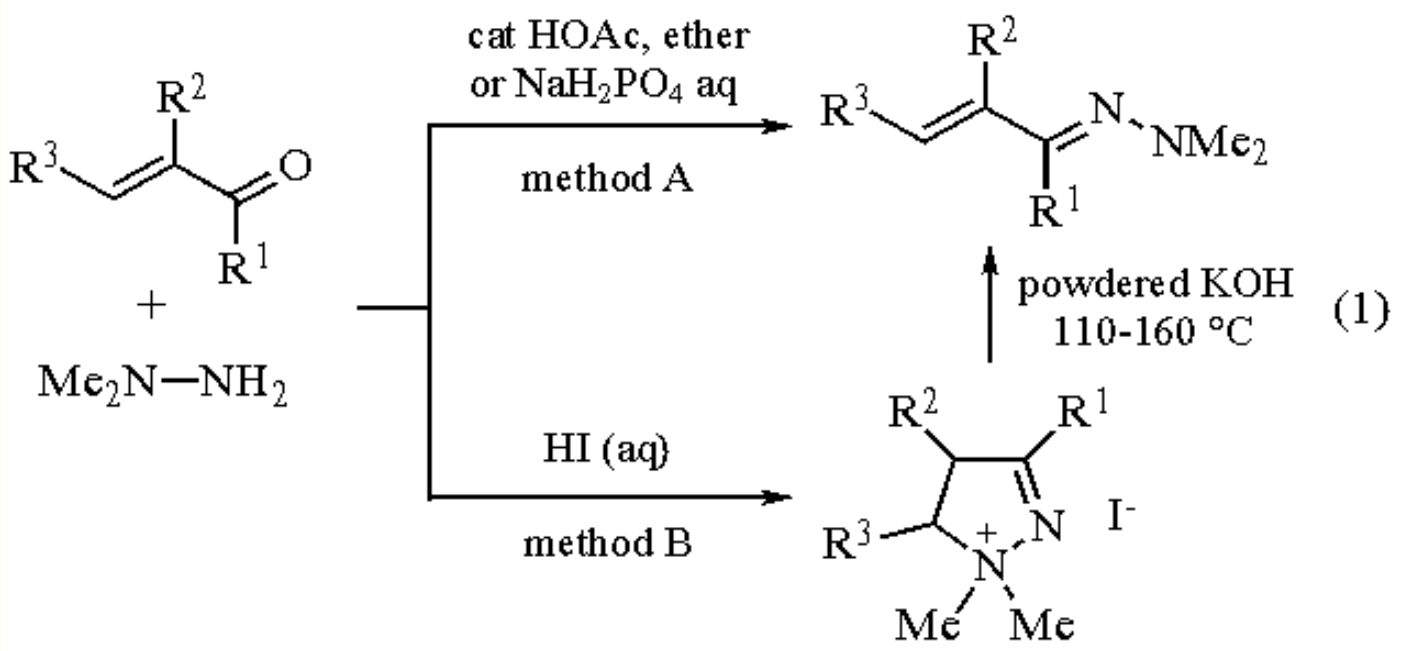

Table 1 Synthesis of a,b-Unsaturated Hydrazones

R^1	R^2	R^3	Yield (method A) (%)	Yield (method B) (%)
H	Me	H	96	50
H	H	H	20	
H	H	Me	98	
H	H	Ph	88	
H	Et	H	85	56
Me	H	H	10	71
Me	Me	H		21

Handling, Storage, and Precautions: the compound darkens when kept at rt; however, it can be kept for long periods in the refrigerator without decomposition.

Diels-Alder Reactions.

Methacrolein dimethylhydrazone reacts as an electron-rich diene in Diels-Alder reactions with alkenes bearing electron-withdrawing groups (eqs 2 and 3).[1,5]

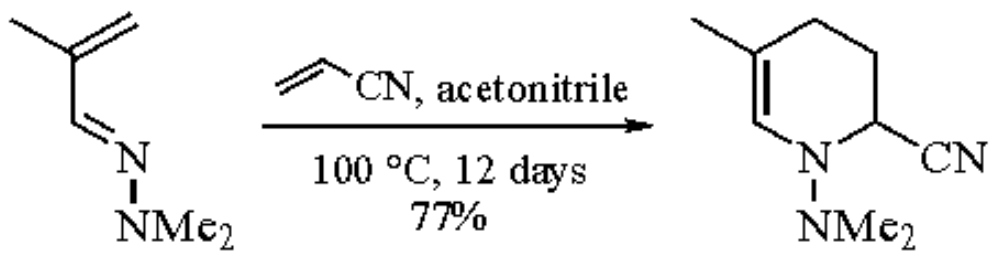

(2)

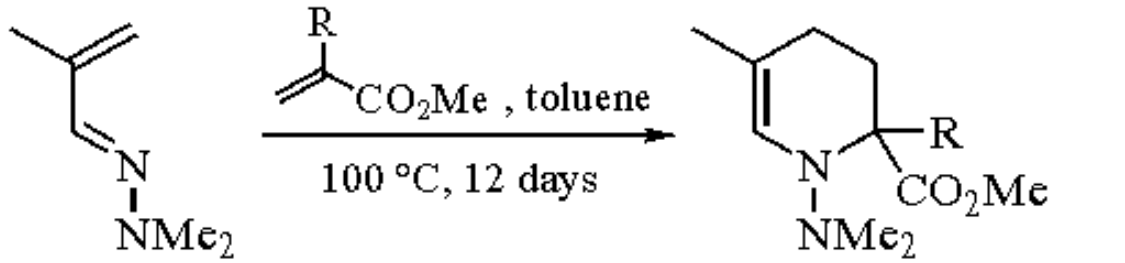

(3)

R = H (68%), Me (33%)

The diene is moderately reactive and best results are obtained with more reactive dienophiles (eqs 4 and 5).[1,6,7]

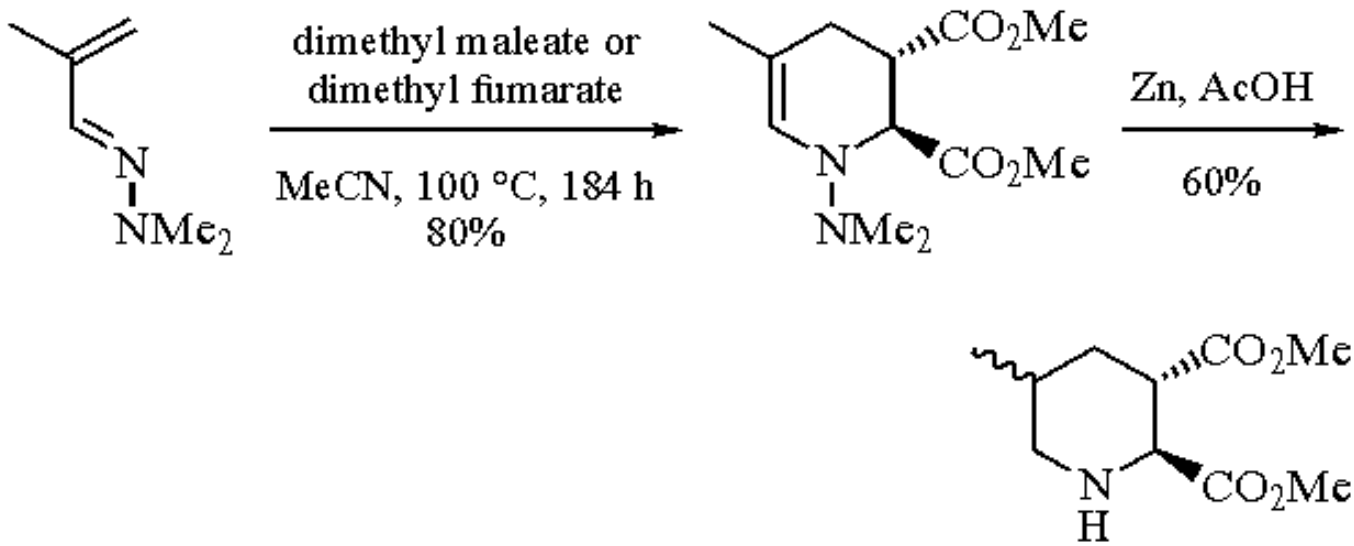

(4)

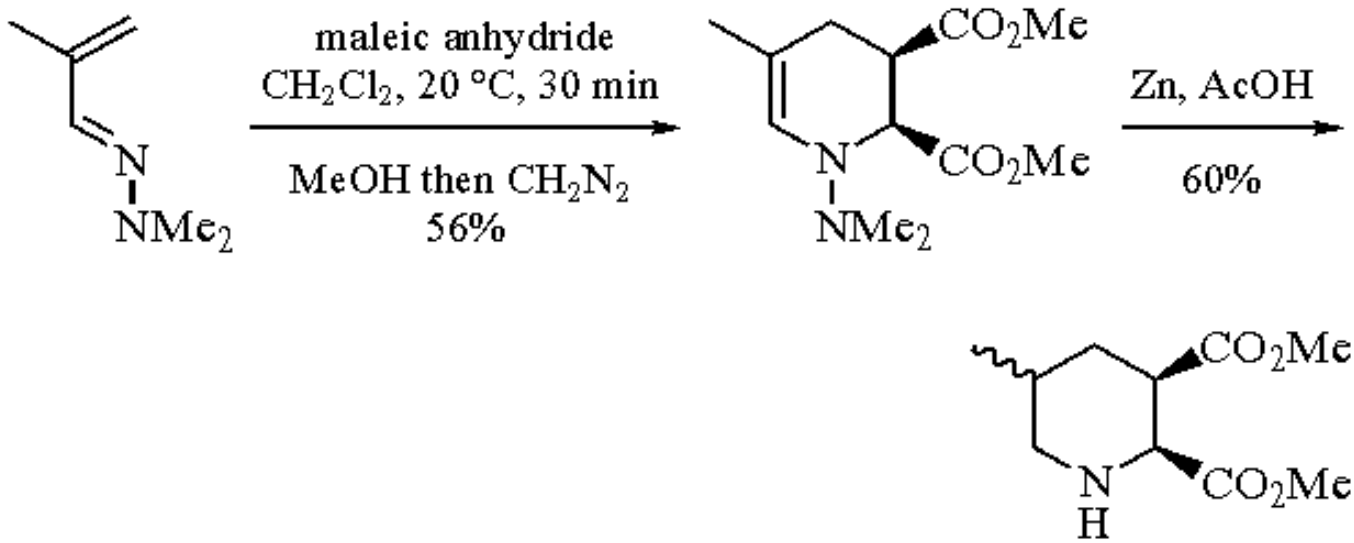

(5)

Dimethyl maleate was isomerized to the more stable dimethyl fumarate under these conditions and, therefore, both dienophiles yielded the *trans* adducts. Reductive cleavage of the N-N bond was readily effected by ***Zinc-Acetic Acid*** to yield substituted piperidines.

Pyridines could not be obtained by reacting α,β-unsaturated hydrazones with alkynic dienophiles.[6] However, they were readily obtained by reaction of methacrolein dimethylhydrazone with alkenic dienophiles bearing a nucleofugal group (eq 6)[3] or with an allenic dienophile (eq 7).[5]

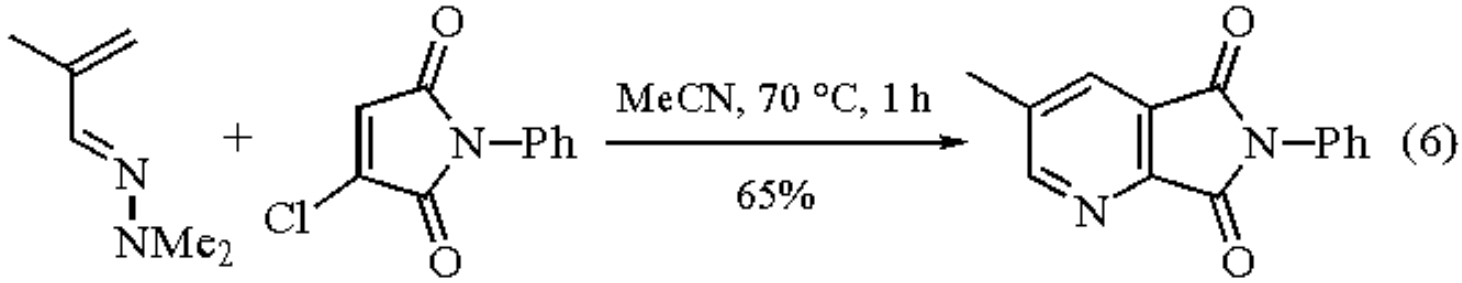

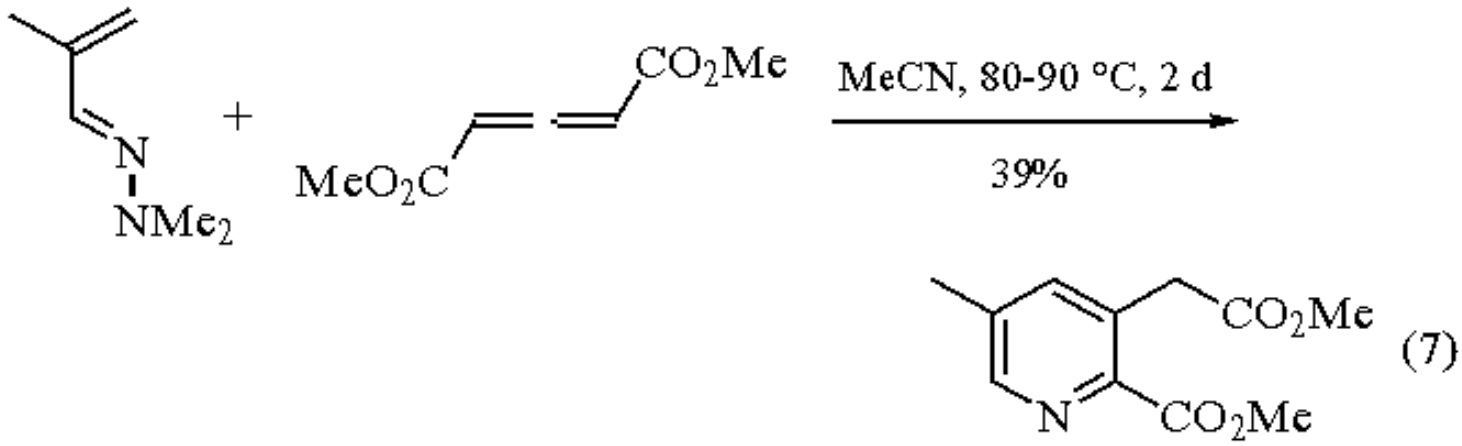

Methacrolein dimethylhydrazone and related 1-azadienes have been extensively used for the preparation of aza- and diazaanthraquinone derivatives.[1,8] The cycloaddition reaction is highly regioselective (eqs 8 and 9).

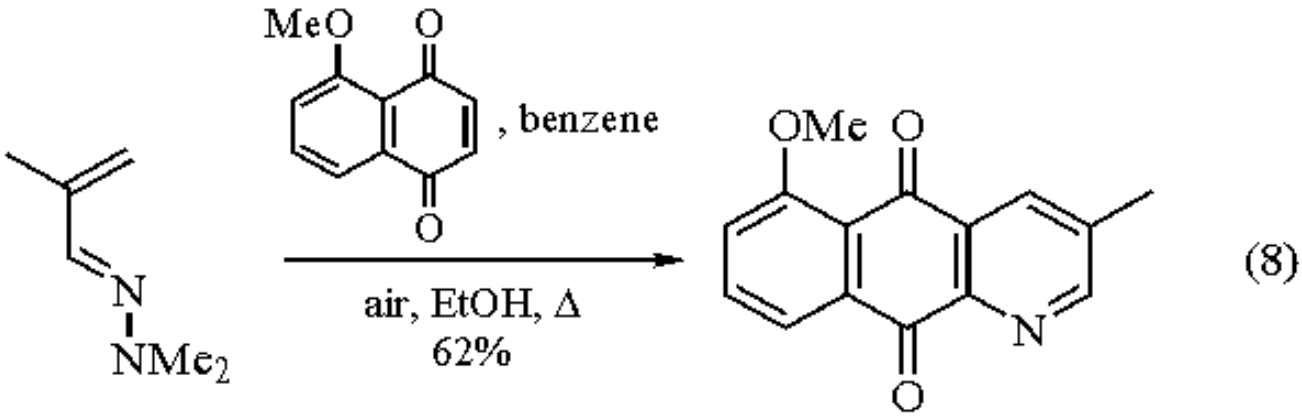

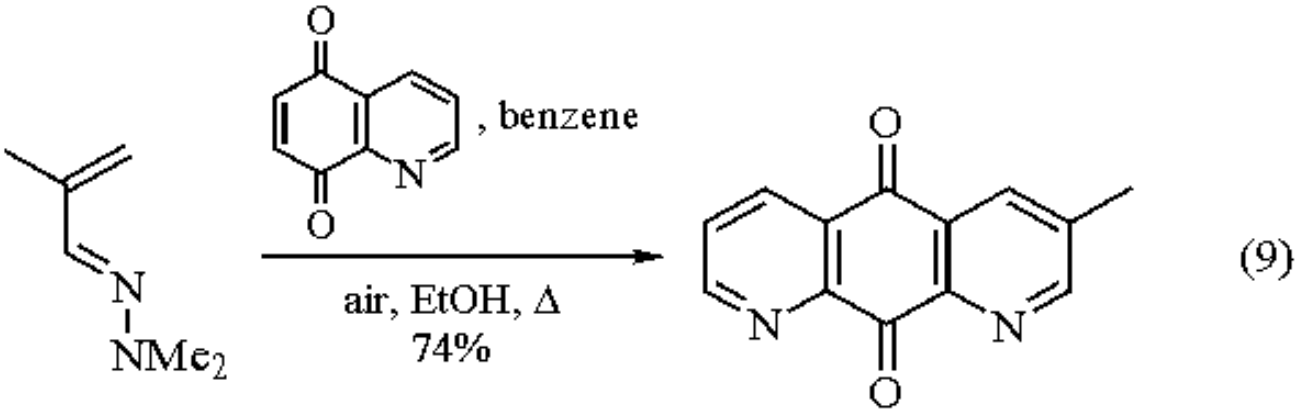

Only few examples of intramolecular cycloadditions involving α,β-unsaturated hydrazones have been described.[9]

Asymmetric Cycloadditions.

Only one example of a reaction of methacrolein dimethylhydrazone with a chiral dienophile has been reported (eq 10).[10]

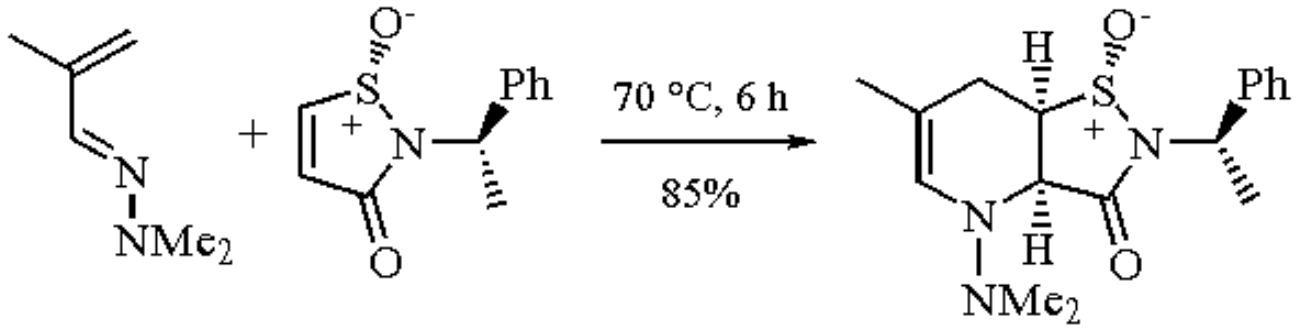

(10)

Also it has been recently shown that the replacement of the dimethylamino group by a chiral pyrrolidine gives a 1-azadiene which cycloadds to cyclic dienophiles with high facial selectivities (eq 11).[11] However, this diene did not react with dimethyl fumarate or acrylic derivatives.

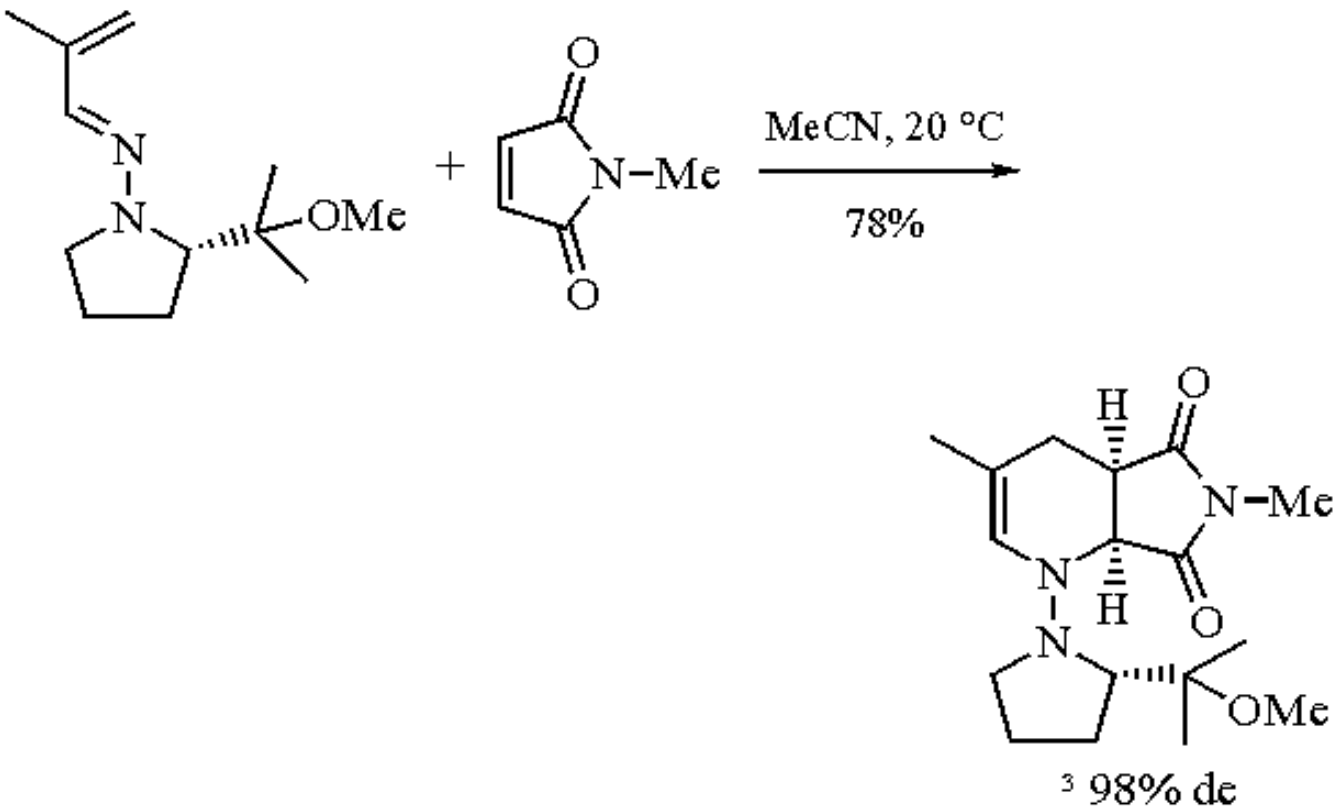

(11)

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Methallyl Bromide

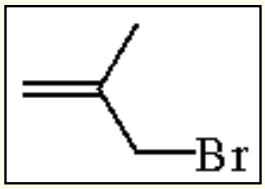

[1458-98-6] · C_4H_7Br · Methallyl Bromide · (MW 135.01)

(alkylating agent attacking C, N, O, and S nucleophiles, often with enantiomeric or diastereomeric selectivity; alkyl-metal reagents provide α-(methallyl) alcohols with various carbonyl systems; provides derivatives leading to polymers and to other reagents)

Alternate Name: 3-bromo-2-methylpropene.

Physical Data: bp 94-95 °C; *d* 1.313 g cm^{-3}.

Solubility: organic solvents; sparingly sol water.

Form Supplied in: yellow to brown liquid.

Purification: wash with water and aq. $NaHCO_3$ until washings are not acidic. Dry ($MgSO_4$) and fractionally distill.

Handling, Storage, and Precautions: toxic irritant liquid; protect from light in brown glass. Use in a fume hood.

Methallyl derivatives are prepared by halide ion exchange of ***Methallyl Chloride*** (eq 1);[1] LiN_3 gives the azide[2] and KCNO provides tris(methallyl) isocyanurate through cyclic trimerization of the ROCN product.[3] Methallyl chloride undergoes conventional alkylation reactions with amines, alkoxides, etc.[4] (see ***Allyl Bromide***).

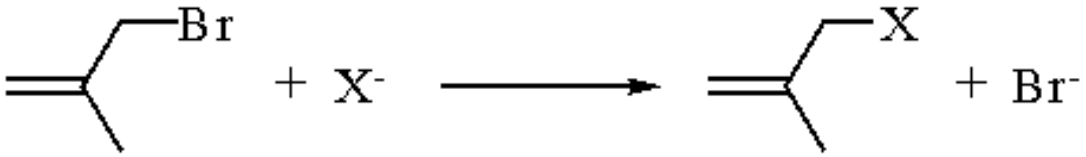

(1)

Barbier-type reactions occur (eq 2); octanal gives $RCH(OH)CH_2C(Me)=CH_2$ (R = heptyl) in the presence of Sb, and α,β-unsaturated aldehydes give only 1,2-addition.[5] Indium behaves similarly.[6] Mn in EtOAc or THF with ***Zinc Chloride*** (catalytic amount) gives homoallylic alcohols with both R^1CHO and R^1COR^2,[7] and the analogous Zn-

induced reaction in DMF is also successful.[8] The reaction with either R^1CHO or R^1COR^2 may be performed electrochemically, using a Cd-modified anode and reversing the polarity of the cell regularly.[9]

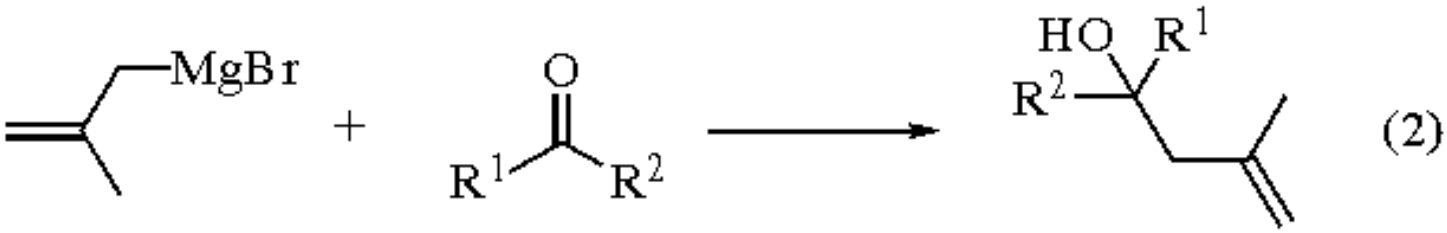

(2)

An interesting extension of the reductive alkylation reaction involves the use of the complex between ***Tin(II) Chloride*** and the disodio derivative of (+)-diethyl tartarate, which, when treated sequentially with methallyl bromide and then with R^1CHO, gives $CH_2{=}C(Me)CH_2CH(OH)R^1$ in good yield and with substantial ee (16-65%).[10] ***Samarium(II) Iodide*** promotes the alkylation of octanoyl chloride in THF. No ketones can be isolated from the reaction, which yields only the tertiary alcohol $R_2C(C_7H_{15})OH$ (R = methallyl).[11]

Lithiated species have been generally used as nucleophiles towards methallyl bromide. ***Lithium Diisopropylamide*** in THF-PhH at 0 °C deprotonates isobutyronitrile, which then methallylates in good yield.[12] The corresponding reactions of the phenylsulfonylbutenolide (**1**) (eq 3)[13] and of imidothioesters[14] proceed regioselectively.

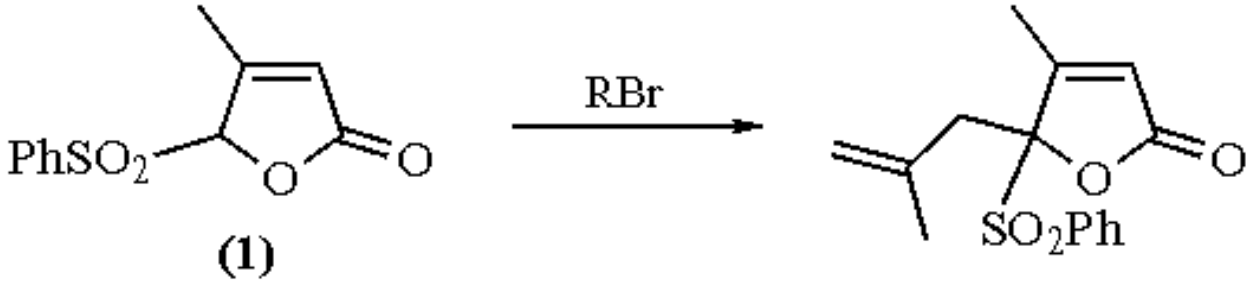

(1)

(3)

2-Cyclohexenone reacts with methallyl bromide (RBr) and $LiC(SPh)_3$ in THF-NMP to give 2-methallyl-3-[tris(phenylthio)methyl]cyclohexanone (**2**) regiospecifically (eq 4). Treatment of (**2**) with ***Silver(I) Trifluoromethanesulfonate*** in THF provides 5-phenylthio-7-methyl-1-tetralone (**3**).[15] The diastereoselective allylation of a camphor imine by methallyl bromide has also been reported.[16]

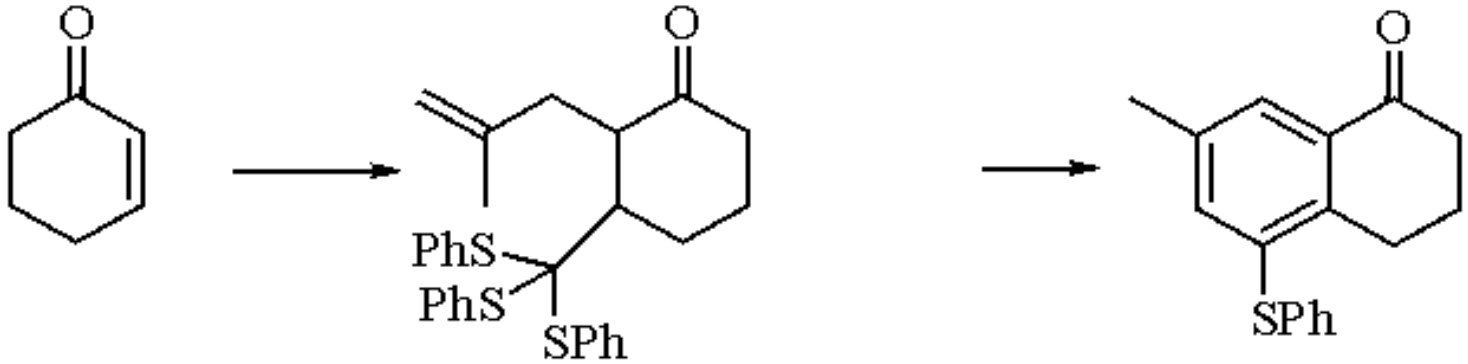

(2)

(3)

(4)

Addition reactions also occur, and are exemplified by the reaction with $CHBr_3$ and NaOH in the presence of a phase-

transfer catalyst. Either addition of CBr_3^- or of **:**CBr_2 can be achieved specifically;[17] the similar addition of **:**CCl_2 has also been reported.[18] Pd-catalyzed ethoxycarbonylation of methallyl bromide (NaOEt-Na_2PdCl_4-$[(Ph_2P)_2CH_2]_2$ at rt) is also readily achieved.[19]

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Methallyl Chloride

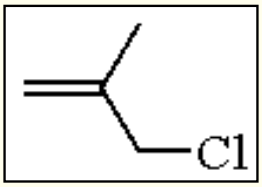

[563-47-3] · C_4H_7Cl · Methallyl Chloride · (MW 90.56)

(four-carbon alkylating agent and isobutyl halide equivalent;[1] acetone carbenium ion equivalent and annulating agent;[2] a nucleophile after conversion to an organometallic[3])

Alternate Name: 3-chloro-2-methylpropene.

Physical Data: bp 71.5-72.5 °C; *d* 0.9165 g cm^{-3}.

Form Supplied in: colorless liquid of 97-98% purity; 90% technical grade is also available (*d* 0.93 g mL^{-1}).

Purification: may be distilled from P_2O_5 prior to use.

Handling, Storage, and Precautions: lachrymator; irritating to mucous membranes and a CANCER SUSPECT AGENT. Use in a fume hood.

Electrophilic Alkylation.

As an electrophile, methallyl chloride undergoes nucleophilic displacement by a variety of substrates including Grignard reagents,[6] carbanions,[7] enolates,[8] carbonyl compounds,[9] alkynes,[10] alcohols,[11] phenols,[12] amines,[13,14] amides,[15] organoboranes,[16] and cyanide[17] to give the four-carbon alkylated product. The individual reagents, methallyl chloride, bromide, and iodide, should be considered as having unique reactivity profiles. For example, ***Methallyl Bromide*** is best suited for low temperature reactions (i.e. <-40 °C) with enolates.[18] Under these conditions the chloride is too unreactive, whereas ***Methallyl Iodide*** leads to mixtures of non- and dialkylated products.

When alkylation is followed by hydrogenation, the net result is addition of an isobutyl group, analogous to alkylation with an isobutyl halide.[1] Under standard catalytic hydrogenation conditions, isomerization to the more highly substituted alkene can also occur (eq 1).[19] Hydrogenation over Wilkinson's catalyst (***Chlorotris(triphenylphosphine)rhodium(I)***) avoids isomerization and affords the saturated product.

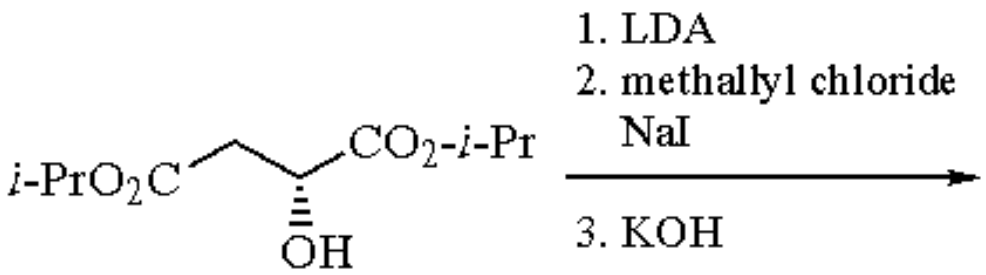

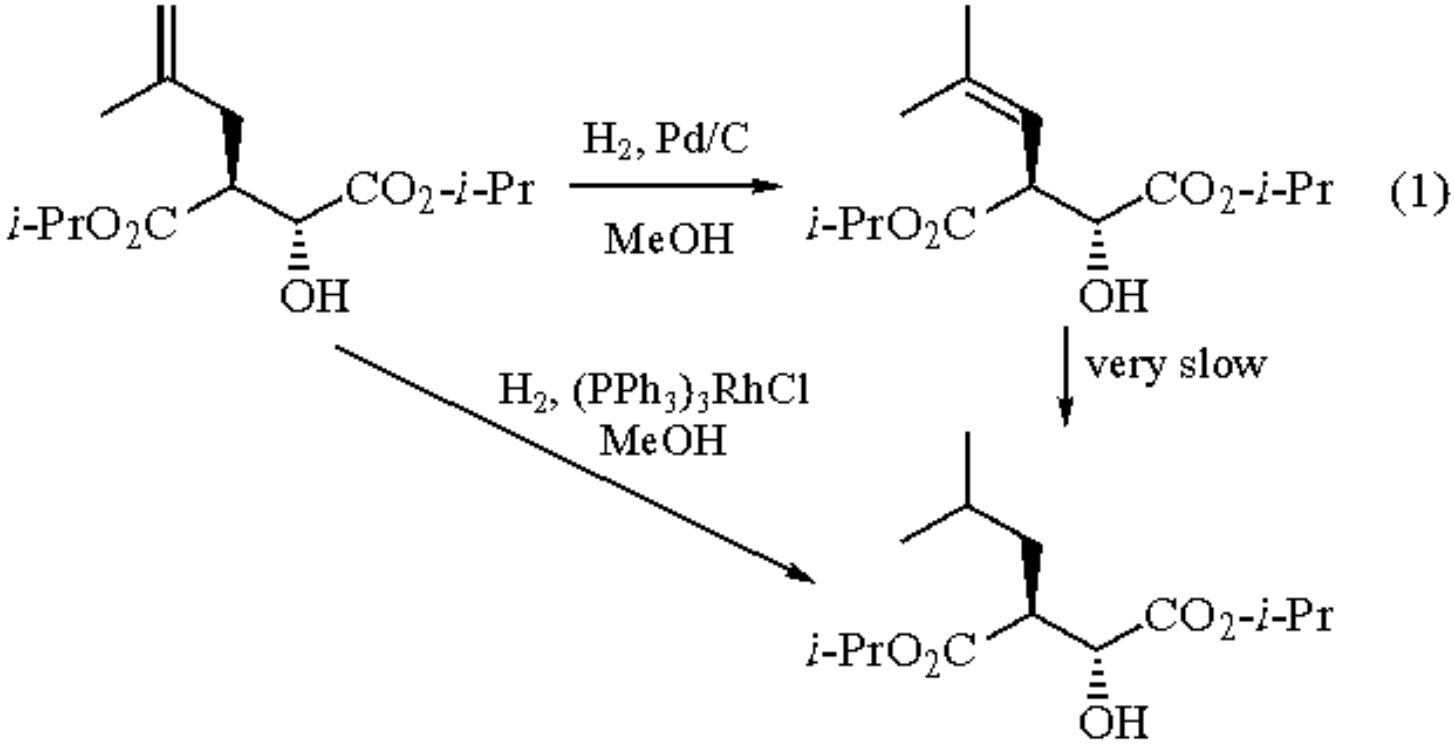

Under acid-catalyzed conditions, methallyl chloride can be used for the Friedel-Crafts alkylation of benzene to give 1´-chloro-*t*-butylbenzene.[20]

Annulation Reactions.

When the alkylation with methallyl iodide is coupled with an ozonolysis, the net effect is an alkylation with acetone.[21] More often, alkylation is followed by ozonolysis and a base-catalyzed annulation process to generate a cyclopentenone (eq 2).[2,22]

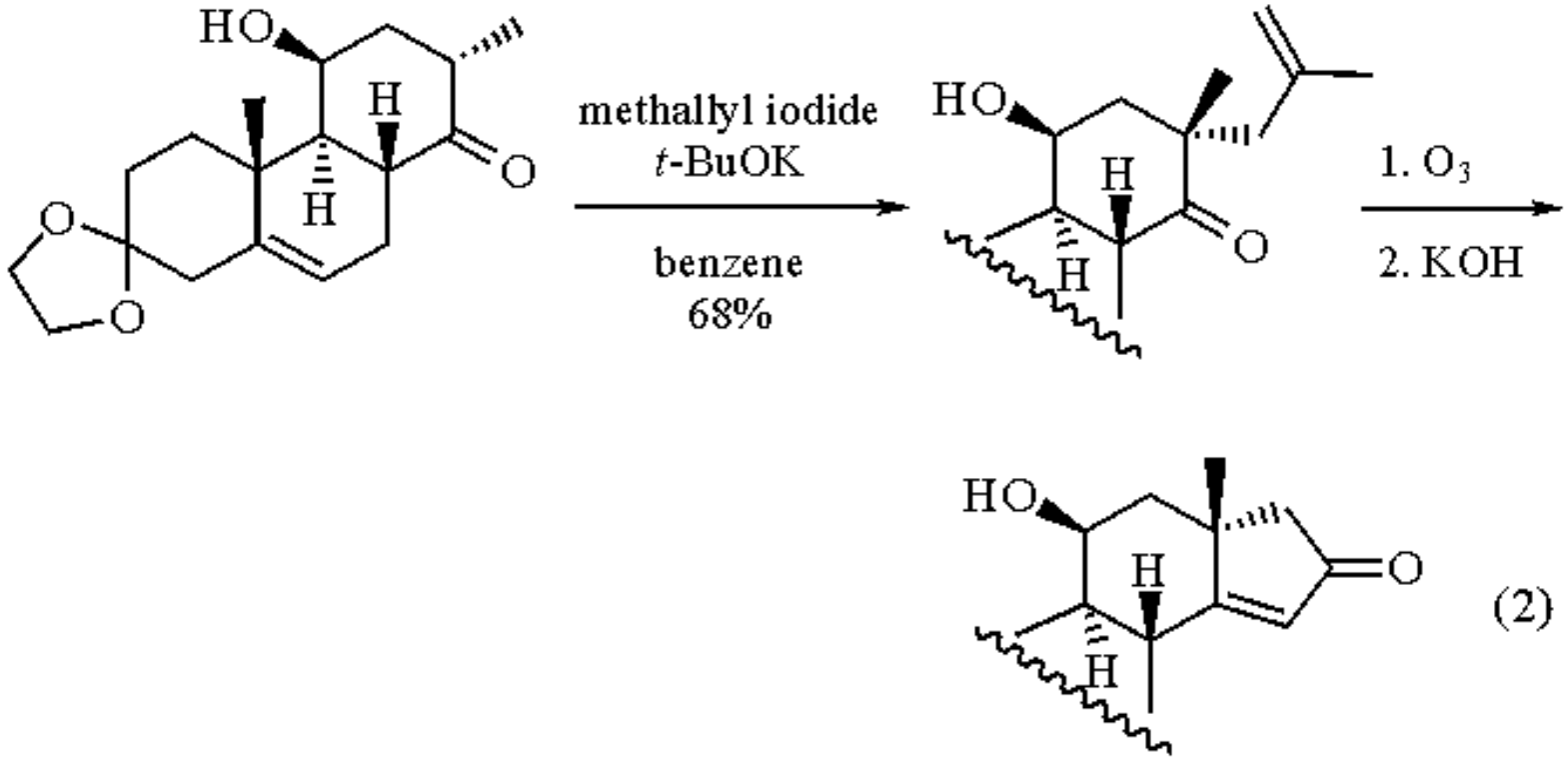

While ***2-Methoxyallyl Bromide*** offers an alternative to methallyl halides for both the acetonylation of anions and cyclopentenyl annulations, the instability of the reagent requires preparation prior to use. Methallyl chloride and bromide have the distinct advantage of being stable, commercially available compounds. Similarly, ***Isopropenyl Acetate*** is a comparable three carbon-annulating agent, but modest overall yields typically follow its use (see also ***Propargyl Chloride***).

With a dicarboxylic acid ester, methallylation and cyclization may be carried out in such a way so as to generate a cyclohexenone system (eq 3).[23]

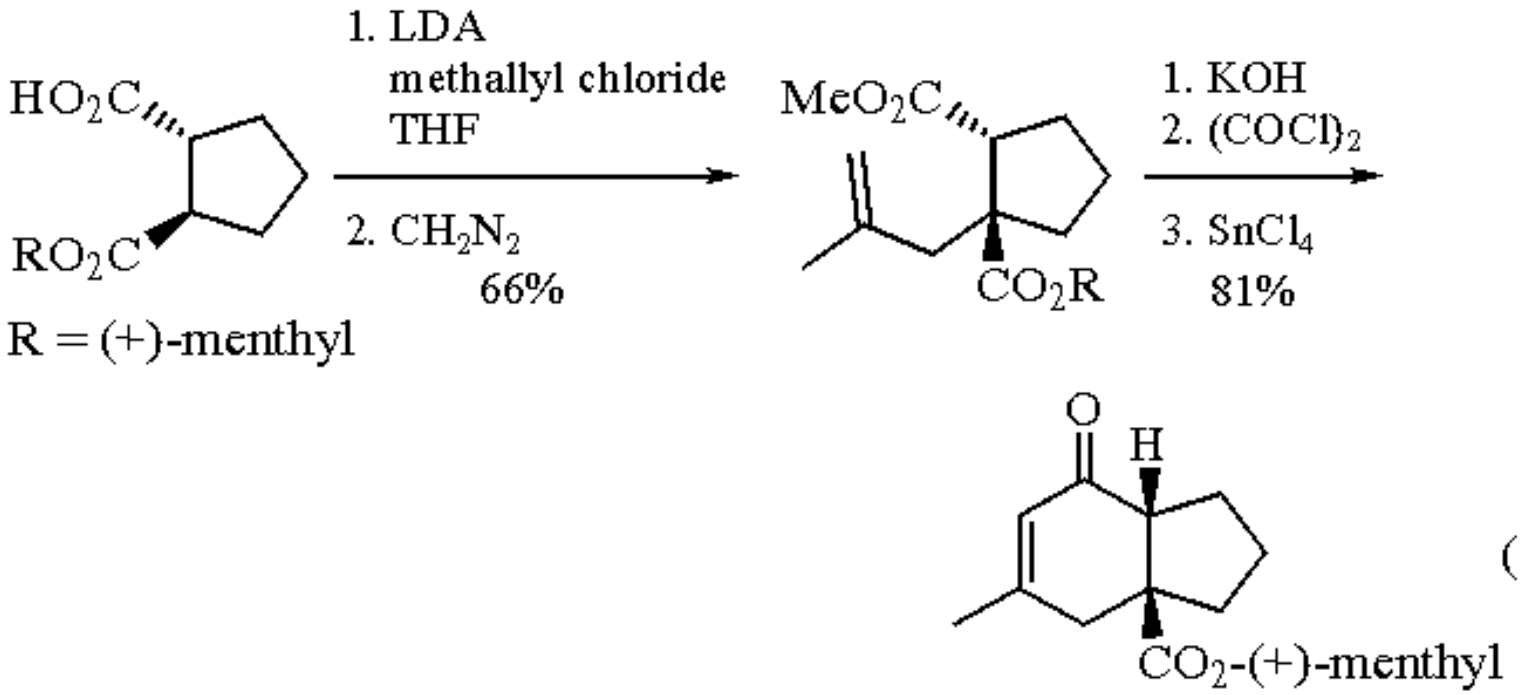

Methallyl chloride, after conversion to the Grignard reagent, has also been used for the benzoannulation of 2-hydroxymethylene ketones (eq 4).[24]

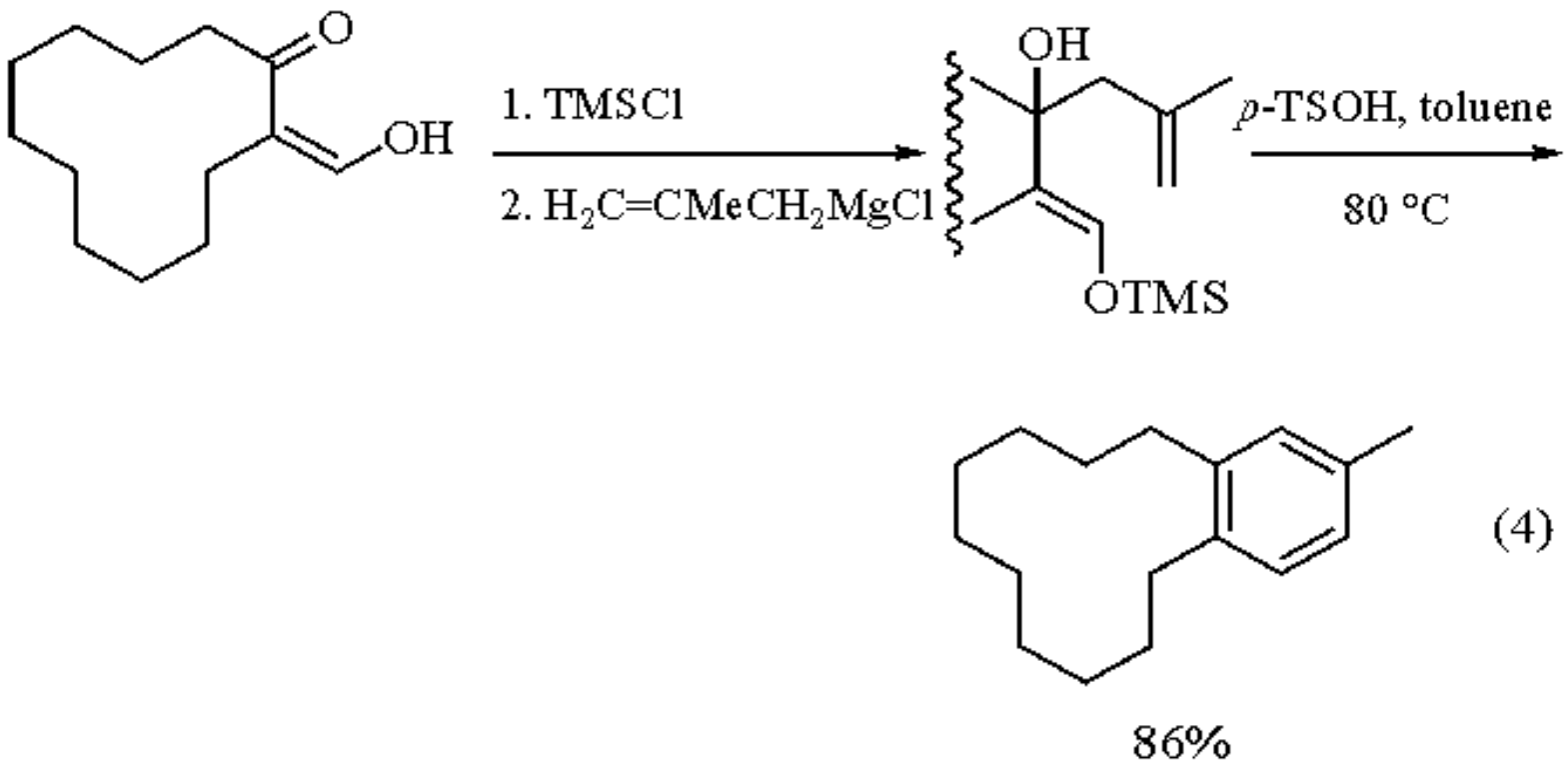

(4)

Sigmatropic Rearrangements.

Because of the allylic functionality, alkylation with methallyl halides often provides intermediates which are ideally constructed to undergo intramolecular rearrangement. Phenols may be efficiently alkylated with methallyl chloride in DMF to give the corresponding isopropenyl ether.[12] Under thermal conditions, Claisen rearrangement of the ether provides the *o*-methallylphenol in high yield. When the reaction of an enolate with methallyl chloride gives mixtures of both *C*- and *O*-alkylated products, the Claisen rearrangement has been employed to afford solely the *C*-alkylated product.[22a] Similarly, the thio-Claisen rearrangement has been used to effect α-methallylation of a dithioester.[25] This method has been further extended to include asymmetric induction in the thio-Claisen rearrangement of both dithioesters[26] and thioamides.[27] Alkylation on the oxygen of a chiral allylic alcohol allows for a [2,3]-sigmatropic Wittig rearrangement with this asymmetric induction (eq 5).[11a]

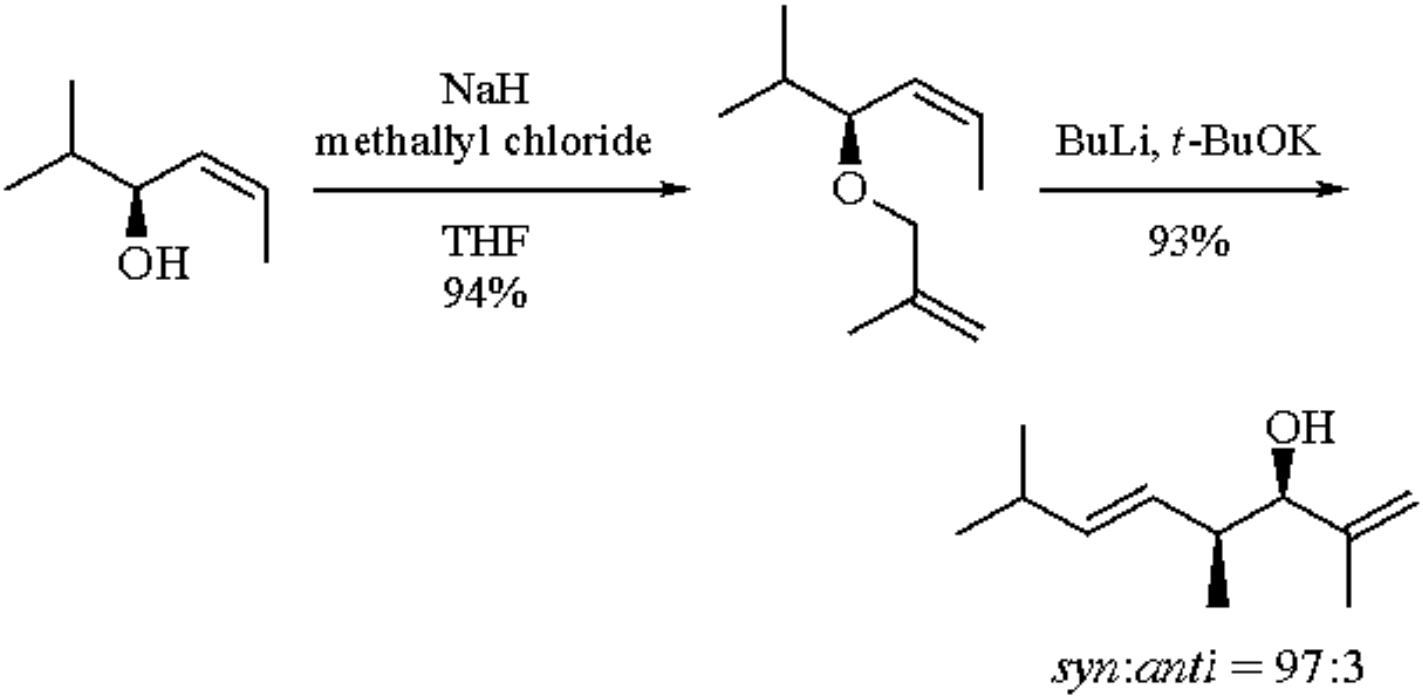

(5)

In the case of a chiral oxathianone, effective alkylation on sulfur requires use of the highly reactive methallyl triflate.[5] Through the intermediacy of the ylide, [2,3]-sigmatropic rearrangement affords a diastereomeric mixture of substituted oxathianones (eq 6). By contrast, direct *C*-alkylation could be expected to be essentially nonselective, giving rise to a nearly equal mixture of diastereomers.

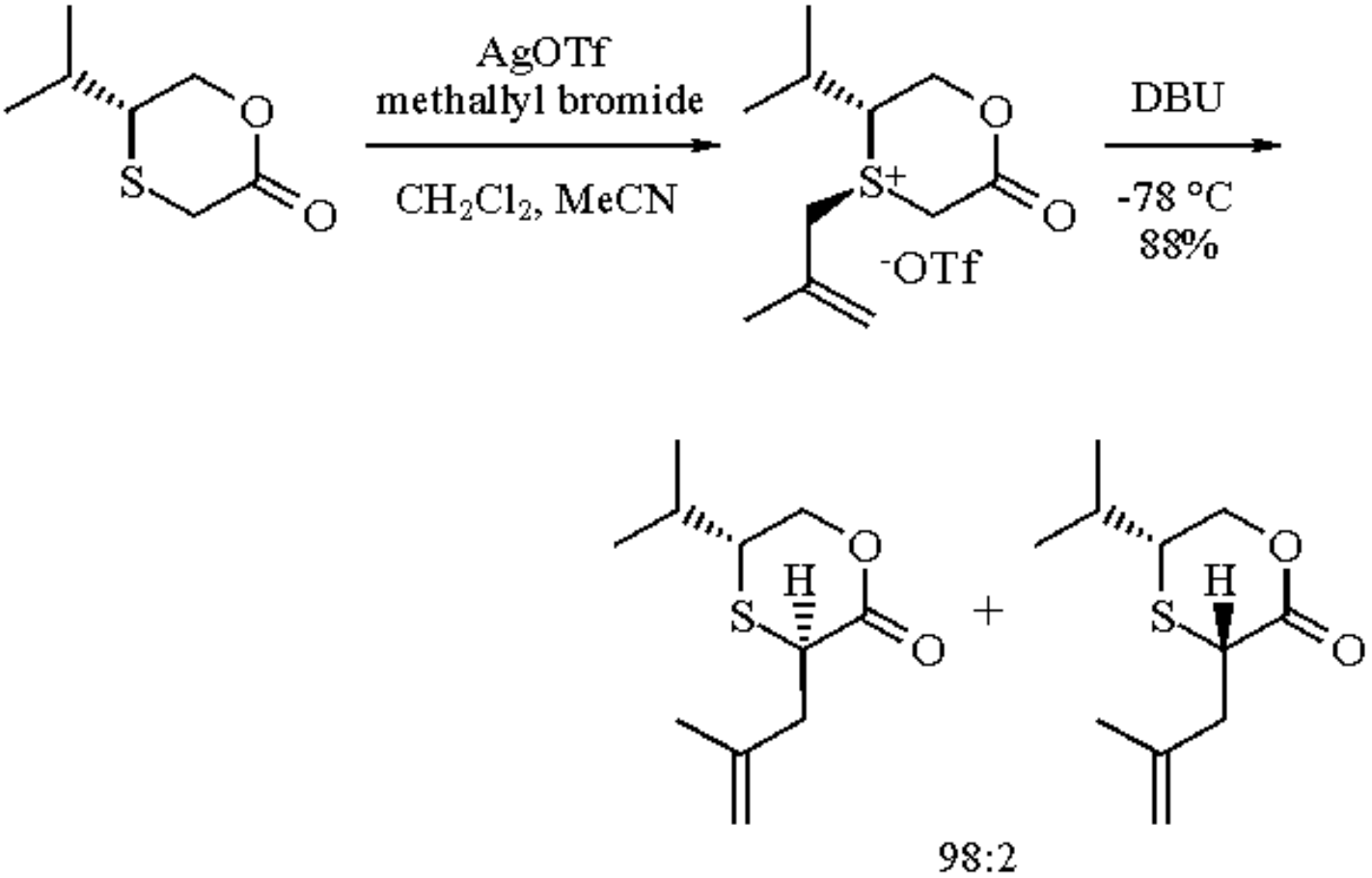

(6)

The methallyl group has also seen utility in a diastereoselective intramolecular ene cyclization, whereby Lewis acid catalysis provides a moderate yield of the indolizidine (eq 7).[14]

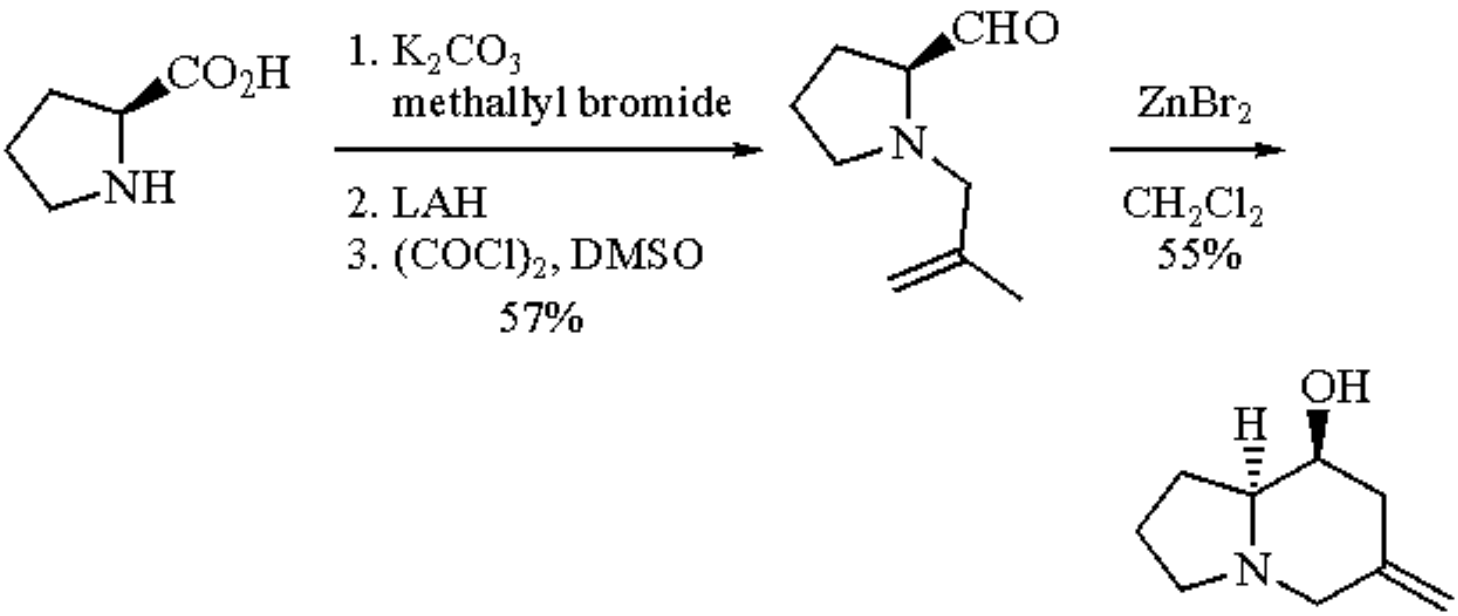

(7)

Nucleophilic Reactions.

As a halide, methallyl chloride can be converted to a wide variety of organometallic species for subsequent use as a nucleophile. This includes the methallyl organometallics of magnesium,[3,28] cerium,[29] lithium,[30] manganese,[31] mercury,[32] tin,[33] and zinc.[34] The π-(2-methallyl)nickel bromide complex has found utility in the reaction with various electrophiles.[35] Because of the nonbasic nature of the reagent, this is the preferred method of preparation for compounds such as methallylbenzene (eq 8),[4] where the nonconjugated product is desired. An alternate approach, the reaction of a methallyl halide with phenylmagnesium bromide, is complicated by both double bond isomerization and rearrangement.

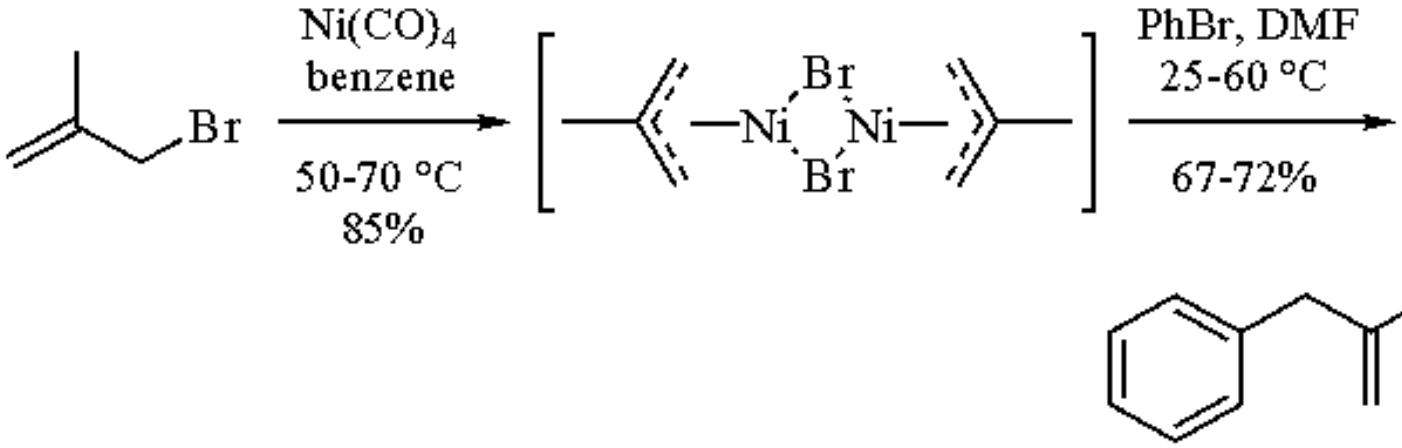

(8)

Finally, the α-halomethallyllithium species can be generated in situ via the ***Lithium Diisopropylamide*** deprotonation of methallyl chloride.[36] The resulting allyl carbanion undergoes exclusive α-alkylation with primary bromides (secondary bromides give unacceptable yields) to give alkylated products which retain both the chloride and the double bond functionality (eq 9).

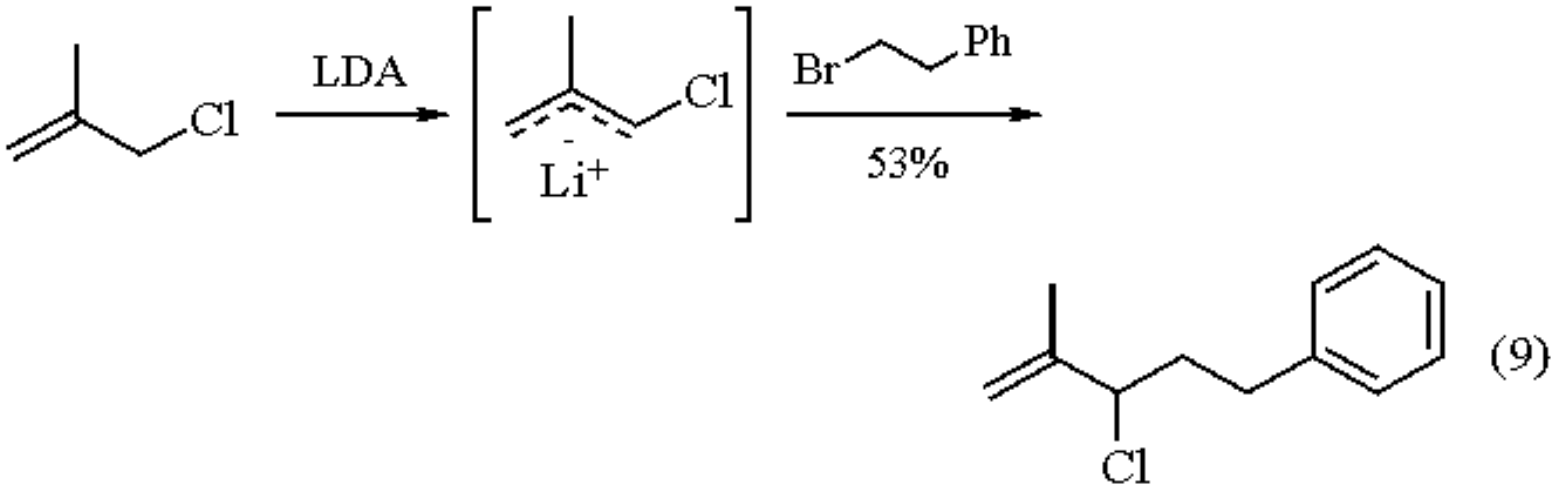

The above lithiated intermediate also reacts with ***Diethylaluminum Chloride*** to give a γ-chloromethallylaluminum species.[37] This in turn reacts stereoselectively with aldehydes to provide *cis*-substituted epoxides, via an intermediate *syn*-chlorohydrin.

---

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Methallyl Iodide

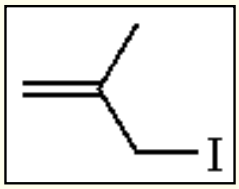

[3756-30-7] · C_4H_7I · Methallyl Iodide · (MW 182.01)

(unstable but reactive alkylating agent attacking C, N, and S nucleophiles; the products are susceptible to addition reactions, especially electrophilically, across C=C systems)

Physical Data: golden-yellow liquid; bp 116-118 °C (dec), 37-40 °C/29 mmHg, 25-30 °C/3-5 mmHg.

Solubility: misc most organic solvents; sparingly misc aqueous media.

Preparative Methods: prepared from ***Methallyl Chloride*** by reaction with ***Sodium Iodide*** in acetone, MEK, or DMF.

Purification: wash with aq. $Na_2S_2O_3$; dry, and distill under reduced pressure.[1a]

Handling, Storage, and Precautions: sensitive to light and heat; prepare as required; decomposes appreciably after a few hours. Use in a fume hood.

The major reported use of methallyl iodide is as an allylating agent when its reactivity outweighs its sensitivity to light and heat.[1] The expected chemical reactions are those of the other methylallyl halides and, by extension, those of allyl halides. *N*-Alkylation occurs with iodo lactams[2] and with indoles.[3] *N*,*O*-Diacetylhydroxylamine is also *N*-methallylated when ***Potassium Carbonate*** is added to a solution of it and methallyl iodide in DMF; the methallyl iodide is preformed from the chloride and NaI in DMF (rt, 3 h; 91% conversion to the iodide).[4] Li derivatives of silylated acrylate esters (deprotonated by ***Methyllithium***) are specifically attacked on C by substituted allyl iodides.[5] 2-Cyclohexenone derivatives[6,7] give 6-(methallyl) derivatives via the corresponding carbanion (eq 1).

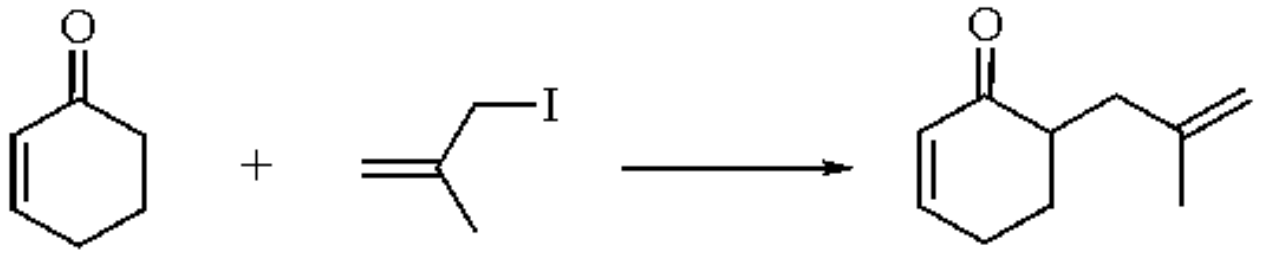

(1)

The crystalline Na enolate salts of 2,4-pentanedione derivatives similarly undergo specific (meth)allylation at C-3

using aprotic solvents such as DMSO.[8] The carbanion derived (LDA-THF-HMPA, -75 °C) from methyl crotonate apparently undergoes α-attack with an allylic shift (eq 2).[9]

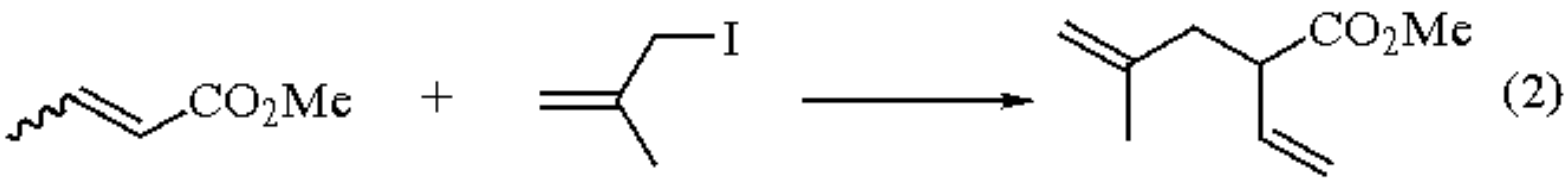

Stereoselective attack occurs with chiral half-esters of methylmalonic acid, using ***Lithium Diisopropylamide*** (2 mole) and RI (R = allyl, methallyl).[10] Similarly, the glycine enolate synthon (**1**) has been used to provide α-(methallyl)glycine in a remarkably stereoselective process.[11]

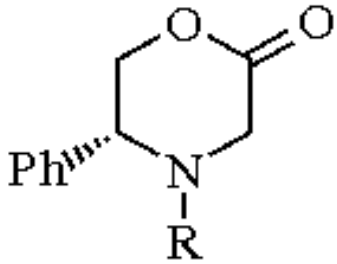

(1) R = CO_2-*t*-Bu, CO_2Bn

Friedel-Crafts alkylation of benzene and other simple arenes may be brought about with Lewis acids (e.g. ***Aluminum Chloride***, ***Boron Trifluoride***) but (meth)allyl iodide with Cl_3CCO_2Ag (20 °C; 2 h) attacks benzofuran at both the 2- and 3-positions, though benzothiophene is allylated only at C-2.[12]

Related Reagents.

Allyl Bromide; ***Allyl Chloride***; ***Allyl Iodide***; ***Methallyl Bromide***; ***Methallyl Chloride***.

---

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Methallyllithium

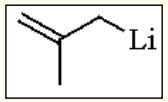

[61777-16-0] · C_4H_7Li · Methallyllithium · (MW 62.05)

(methallylating agent in substitutions and additions; used to attach methallyl groups to other metals and nonmetals)

Alternate Name: 3-lithio-2-methylpropene.

Physical Data: colorless crystals;[1] ^1H, ^{13}C, and ^6Li NMR spectra have been reported on solutions.[2]

Solubility: sol ethers; sparingly sol hydrocarbons.[1]

Preparative Methods: TMEDA complex by metalating ***Isobutene*** with ***n-Butyllithium/N,N,N´,N´-Tetramethylethylenediamine***;[3] by metalating isobutene with butyllithium/***Potassium t-Butoxide***, and then reacting the methallylpotassium with ***Lithium Bromide*** in ether;[4] from methallyltin compounds by exchange with ***Phenyllithium*** or butyllithium.[1]

Form Supplied in: prepared in situ and used directly.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas to exclude oxygen and moisture.

Reactions.

Resonance-stabilized Li reagents such as methallyllithium are stronger nucleophiles but weaker bases than alkyllithium reagents, permitting displacement of halides from alkyl halides in Wurtz-type couplings (eq 1).[3] Additions to aldehydes and ketones,[3a] epoxides, and ***Carbon Dioxide*** also go well.[4] Methallyllithium has been used as a source of methallyl groups attached to boron[5] (useful in the synthesis of chiral homoallylic alcohols as shown in eq 2) and transition metals.[6] On heating, methallyllithium disproportionates, giving off isobutene and providing a source of dilithiotrimethylmethane (eq 3).[7]

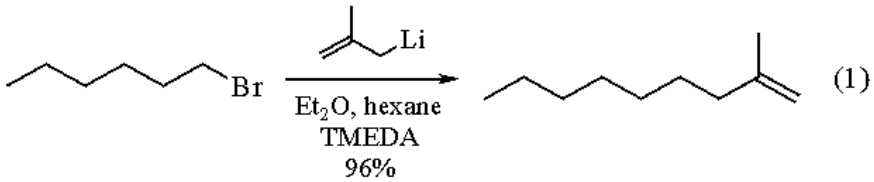

(1)

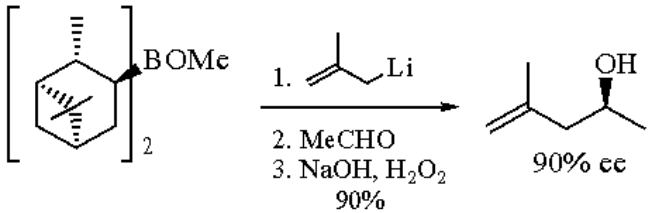

(2)

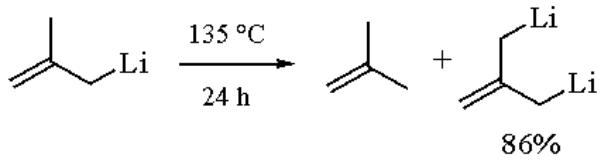

(3)

Related Reagents.

Table 1 lists some useful methallyllithium derivatives.[3b,7-22] See also ***Allyllithium*** and ***Allylmagnesium Bromide***.

Table 1 Methallyllithium Derivatives

Structure	Name	Formula	Ref.
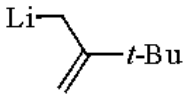	Allyllithium, 2-*t*-butyl-	$C_7H_{13}Li$	8
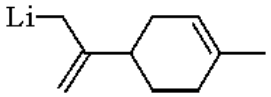	Allyllithium, 2-(4-methyl-3-cyclohexenyl)-	$C_{10}H_{15}Li$	9
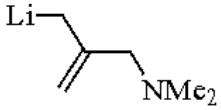	Allyllithium, 2-(dimethylamino)-	$C_6H_{12}NLi$	10
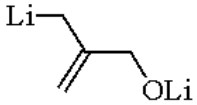	Lithium, 3-lithiomethyl-2-propen-1-oxide	$C_4H_6OLi_2$	11
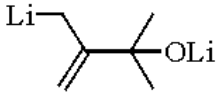	Lithium 2,2-dimethyl-3-lithiomethyl-2-propen-1-oxide	$C_6H_{10}OLi_2$	12
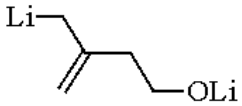	Lithium 4-lithiomethyl-4-buten-1-oxide	$C_5H_8OLi_2$	13
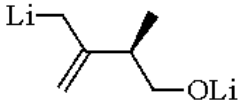	Lithium 3-methyl-4-lithiomethyl-4-buten-1-oxide	$C_6H_{10}OLi_2$	14
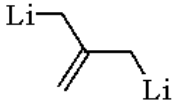	Allyllithium, 2-lithiomethyl-	$C_4H_6Li_2$	3b, 7, 15

Methallyllithium

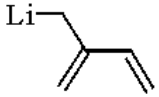	Allyllithium, 2-vinyl	C_5H_7Li	16
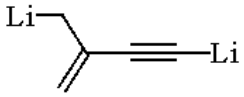	Allyllithium, 2-lithioethynyl-	$C_5H_4Li_2$	17
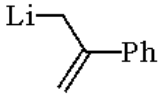	Allyllithium, 2-phenyl-	C_9H_9Li	18
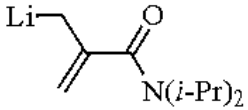	Allyllithium, 2-(diisopropylaminocarbonyl)-	$C_{10}H_{18}NOLi$	19
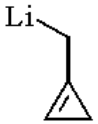	Cyclopropene, 1-lithiomethyl-	C_4H_5Li	20
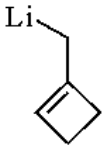	Cyclobutene, 1-lithiomethyl-	C_5H_7Li	21
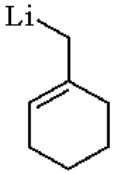	Cyclohexene, 1-lithiomethyl-	$C_7H_{11}Li$	22

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Methallylmagnesium Chloride[1]

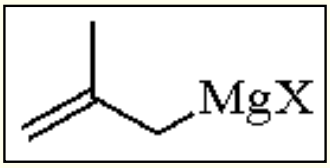

(X = Cl)

[5674-01-1] · C_4H_7ClMg · Methallylmagnesium Chloride · (MW 114.87) (X = Br)

[33324-92-4] · C_4H_7BrMg · Methallylmagnesium Bromide · (MW 159.32)

(structural unit in organic synthesis; reagent for aromatic annulation and for propenyl ketone synthesis; acetone enolate equivalent)

Alternate Name: 2-methyl-2-propenylmagnesium chloride.

Solubility: sol ether, THF.

Analysis of Reagent Purity: contains 2,5-dimethyl-1,5-hexadiene, the symmetrical dimer. The amount of dimer present depends upon the method of preparation.

Handling, Storage, and Precautions: air- and moisture-sensitive and is best stored at -20 °C under argon.

Grignard Synthesis.

The preparation of allylic and benzylic organomagnesium halides often takes place irreproducibly or in poor yield due to competing dimerization of the reactive halide. The most common solution to the general problem is to use excess magnesium.[1a] Alternatively, a more reactive form of the metal can be utilized. ***Magnesium*** turnings can be activated by treatment with ***Iodine*** or ***1,2-Dibromoethane***.[1b] A highly reactive form of magnesium can be prepared by reducing anhydrous magnesium chloride with ***Lithium*** in THF, using naphthalene as an electron carrier.[2] The metallic powder which results (Rieke magnesium) can be converted to Grignard reagents in high yield by addition of an alkyl halide. Metallic magnesium can also be evaporated and co-condensed with THF at low temperature in a metal-atom reactor.[3] This leads to the formation of a reactive magnesium slurry which is also very effective for the Grignard synthesis.[4] When magnesium powder is irradiated in an ultrasonic bath in the presence of anthracene in THF, a magnesium complex of anthracene is formed which is in equilibrium with free anthracene and a reactive form of magnesium metal. Slow addition of halides at -65 °C led to the Grignard reagents.[5] A disadvantage of this method is the requirement that the reaction product(s) be separated from anthracene.

Preactivation of magnesium turnings by mechanical stirring in the absence of solvent for 2 d under dry nitrogen in a Schlenk tube constitutes a simple method for the clean synthesis of diverse allylic and benzylic Grignard reagents.[6] Fragmentation of the metal surface to form microcrystalline particles effectively increases the surface area of the metal. Yields of (**1**)-(**5**) were high in all cases. The simplicity of this method, the absence of alkali metal salts or anthracene in the final product, and especially the high yields recommend its use.

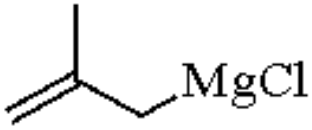

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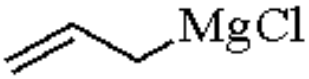

(2) 95%

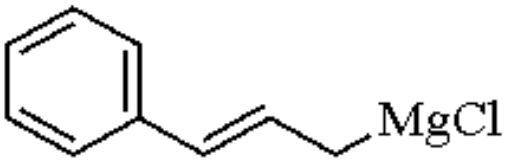

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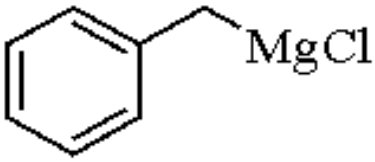

(4) 100%

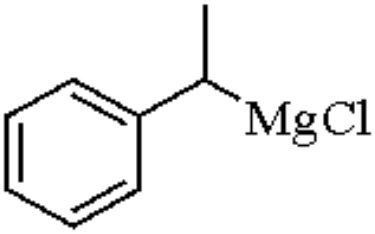

(5) 95%

Propenyl Ketone Synthesis.[7]

Addition of excess methallylmagnesium chloride to an ester leads to the tertiary alcohol (eq 1). Exposure of the alcohol to ***Potassium Hydride*** in HMPA at 40 °C results in cleavage of one allylic C-C bond with loss of methallyl anion, and irreversible proton transfer to form the ketone enolate. Workup with aq NH_4Cl produces the unsaturated ketone as a mixture of α,β- and β,γ-isomers. This is an unconventional but effective method for converting esters to ketones.

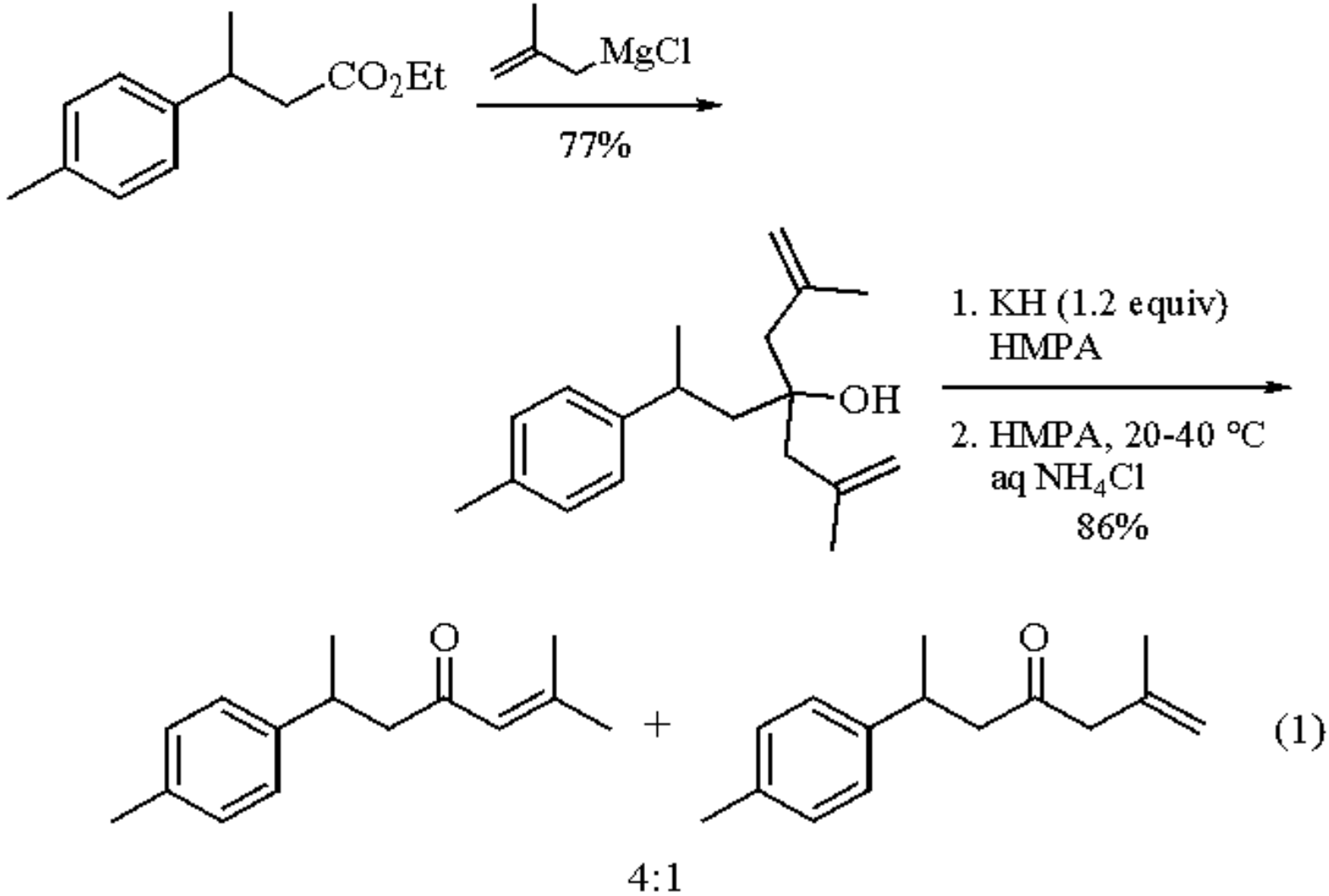

Aromatic Annulation.

Nucleophilic addition of methallylmagnesium chloride to the α-oxoketene dithioacetal derived from menthone (eq 2) forms a tertiary allylic alcohol.[8] Exposure of this material to ***Boron Trifluoride Etherate*** in nitromethane initiates a series of reactions which results in the annulation of an aromatic ring. Similar chemistry has been reported for vinylogous silyl esters.[9] An advantage of this approach to aromatic ring synthesis is the control over the alkyl substitution pattern. A methyl, or other cation-stabilizing group, in the Grignard reagent is essential for high yields of annulated products.[10]

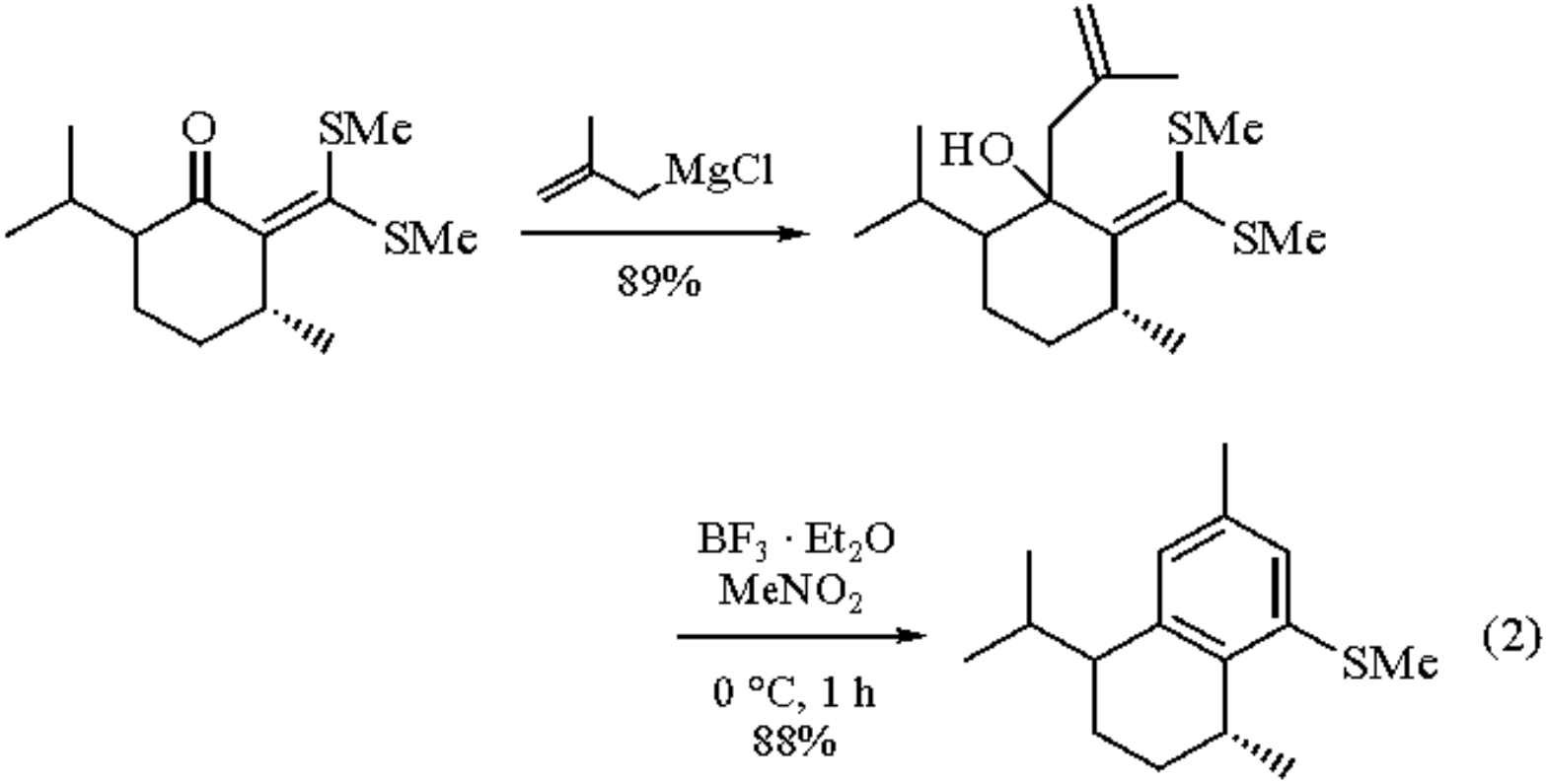

Acetone Enolate Equivalent.

Methallylmagnesium chloride serves as a convenient masked form of acetone enolate. Oxidative cleavage of the methylene group unmasks the carbonyl group.[11]

Related Reagents.

Allylic barium halides offer certain advantages over the corresponding Grignard reagents. For example (eq 3), reduction of BaI_2 with lithium biphenylide in THF, followed by addition at -78 °C of a slight deficiency of 1-chloro-2-methyl-2-butene, produces an organobarium chloride which was treated with cyclohexanone.[12] Workup leads to the tertiary alcohol in 92% yield with excellent selectivity.

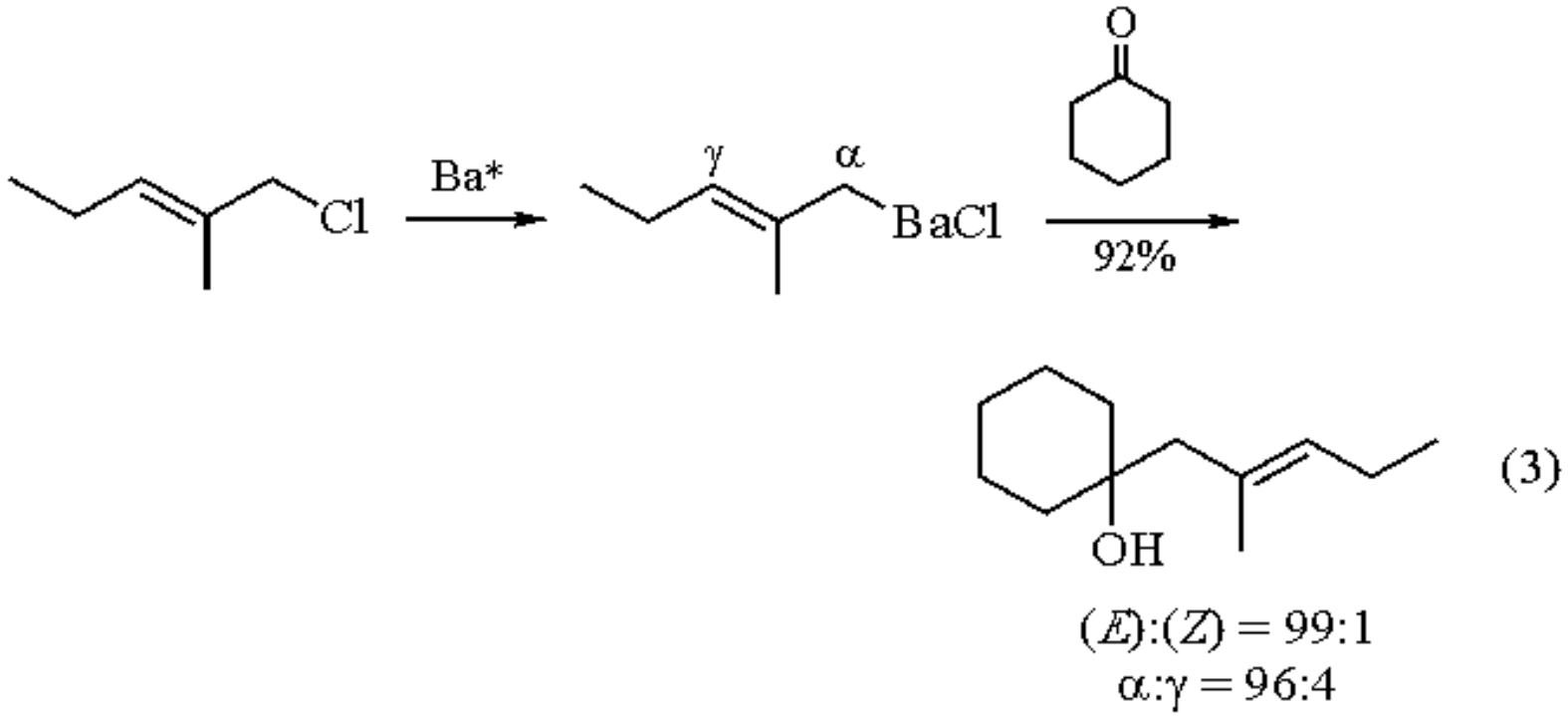

See also ***Methallyllithium***.

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Methaneselenol[1]

MeSeH

[6486-05-1] · CH_4Se · Methaneselenol · (MW 95.01)

(powerful nucleophilic species able to produce methaneselenolates and methyl selenides including functionalized ones; methaneselenol and methaneselenolates are valuable reducing agents)

Physical Data: bp 25.5 °C.[1a]

Solubility: sol most organic solvents.

Form Supplied in: sealed ampoule.

Analysis of Reagent Purity: as stable, benzene-soluble MeSe-DNP selenides using Sanger's reagent (1-fluoro-2,4-dinitrobenzene, FDNB) in DMF.[2,3] The molecular ion of MeSe-DNP is prominent in the spectra (*m/e* 262, with selenium fragments at 247 (-Me) and 169 (-$2NO_2$); a peak corresponding to the loss of MeSe is not observed).[3] TLC plate (including its visualization)[2,3] and HPLC[2] of MeSe-DNP are described.

Handling, Storage, and Precautions: volatile, bad smelling compound; use only in a fume hood. Store in cold room. Destroy by slow addition to a cold aqueous solution of NaOCl in the presence of an organic solvent. Clean the vessel with aqueous solution of NaOCl.

General Considerations.

Methaneselenol is a volatile, bad smelling liquid usually prepared by reduction of dimethyl diselenide (prepared from elemental selenium, aqueous KOH and potassium bisulfite) with ***Hypophosphorous Acid*** (H_3PO_2) or by acid hydrolysis of methaneselenolates (eq 1).[4,5] Methaneselenolates are prepared from ***Methyllithium*** or methylmagnesium iodide and elemental ***Selenium***[6] or from methaneselenol and bases (such as K_2CO_3,[7] NEt_3, pyridine,[4] KOH, or NaH) or more conveniently by reduction of dimethyl diselenide with ***Sodium Borohydride***[8,9] or with metal hydrides (eqs 1 and 2).[10] The synthesis of a series of methylseleno derivatives of Group 14 has been achieved[6] from methaneselenol with Group 14 amines or halides or on reaction of the latter compounds with methylselenolithium, methylselenomagnesium iodide, lithium tetra(methylseleno)aluminate, or methylseleno(trimethyl)silane.

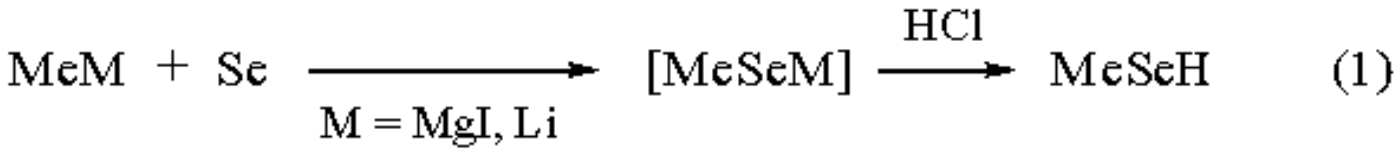

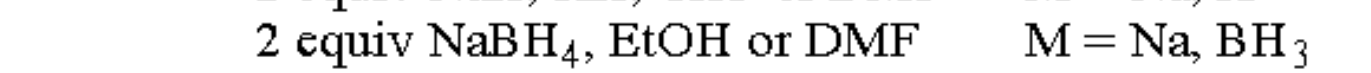

Methaneselenol and the corresponding metal selenolates are powerful nucleophiles and in some cases act as reducing agents. Although methaneselenol is easily oxidized by oxygen present in air to dimethyl diselenide, the reaction is best achieved using ***Hydrogen Peroxide*** (stoichiometric),[11] methaneseleninic acid,[11] or ***Sodium Perborate***, (eq 3).[12] Use of an excess of hydrogen peroxide leads to methaneseleninic acid or methaneperseleninic acid, depending upon the amount of reagent used.[11,13]

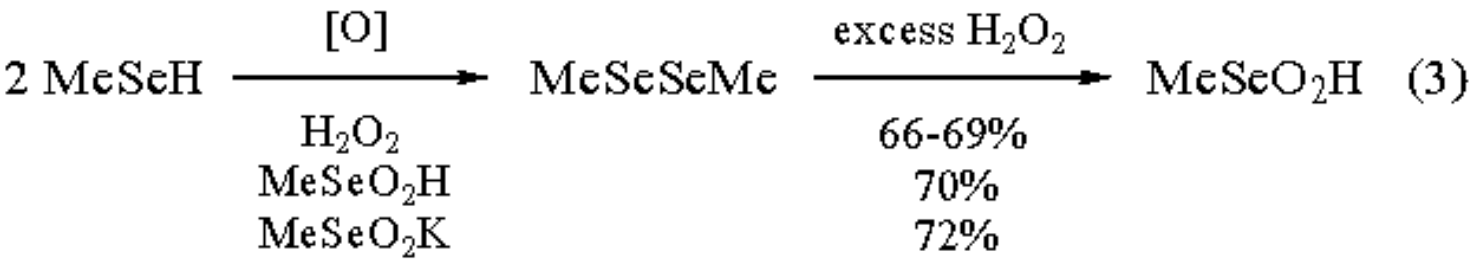

Reactions of Methaneselenol.

Methaneselenol reacts with alcohols in the presence of an acid catalyst to form methyl selenides (eq 4).[14,15] The reaction, which is best achieved in the presence of ***Zinc Chloride***, only occurs with those alcohols which can form an intermediate carbenium ion, such as tertiary alcohols,[16] *s*-allyl and *t*-allyl alcohols,[15-18] and benzyl alcohols.[14,16] This reaction is used to form *t*-alkyl methyl selenides which cannot be prepared efficiently from methaneselenolates and alkyl halides. Methaneselenol reacts with ethylene oxide to produce 2-methylselenoethanol.[19]

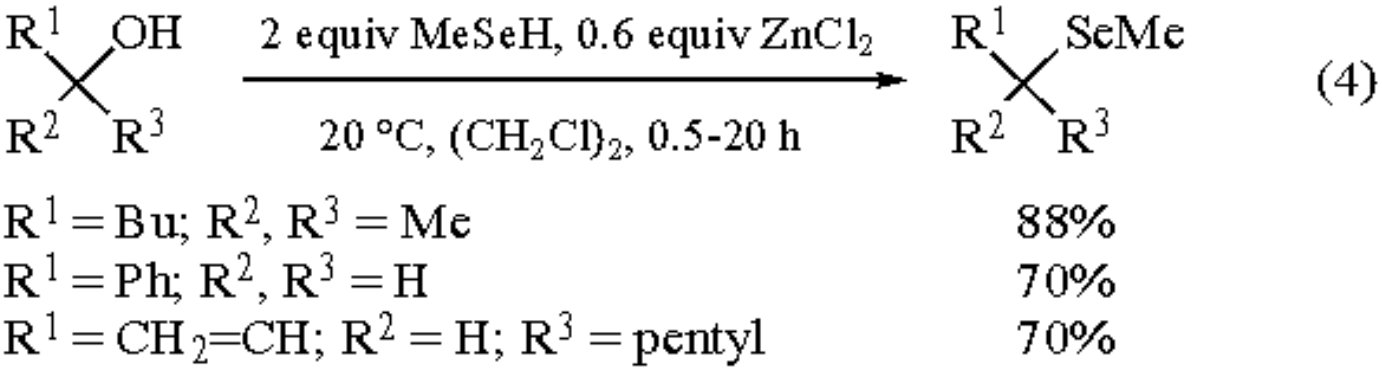

Methaneselenol (1 equiv) and ***Hydrobromic Acid*** or ***Hydrochloric Acid*** also react with aldehydes to form α-haloalkyl

selenides (45-54% yields) and small amounts (20%) of selenoacetals.[20] The synthesis of the latter, which proved to be particularly valuable starting materials for the synthesis of α-selenoalkyllithiums,[21-23] is achieved by reaction of methaneselenol (2 equiv) with aldehydes or ketones in the presence of an acid catalyst (eq 5).[24] Best results are usually obtained using zinc chloride (0.5 equiv), although ***Titanium(IV) Chloride*** (0.3 equiv) is best used for aromatic or hindered carbonyl compounds (eq 5).[24] Reduction leading to methyl selenides occurs from aromatic ketones and with ketones when the reaction is carried out with an excess of zinc chloride for a long time (eq 5).[24,25] The reaction has been successfully used for the synthesis of a large variety of selenoacetals,[16,21,23,24,26-35] including those derived from (a) cyclanones (4-7 membered), β-chloropropanal (HCl, 20 °C, 65% yield), which proved to be a valuable precursor of 1,1-bis(methylseleno)cyclopropane,[31] and (b) unsaturated carbonyl compounds which afford, besides the expected unsaturated selenoacetals, products resulting from 1,4-addition.[36] Straight-chain enals and enones mainly lead to selenoacetals,[36] whereas cyclic enones produce 1,3-bis(methylseleno)propenes.[36] Modification of this method allows the direct synthesis of 2-methylseleno-2-phenylthiopropane from propanal, methaneselenol, benzenethiol (1 equiv each), and zinc chloride and of 1-methoxy-1-methylselenodecane from decanal, methaneselenol (1 equiv each), methanol, and ***Boron Trifluoride Etherate*** in THF.[37]

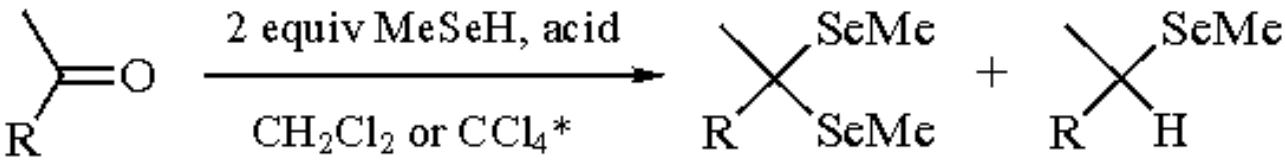

R = C_9H_{17}	0.5 equiv $ZnCl_2$, 20 °C, 3 h	91%	0%
	5 equiv $ZnCl_2$, 20 °C, 16 h	0%	91%
R = Ph	0.5 equiv $ZnCl_2$, 20 °C, 3 h	68%	26%
	1 equiv $TiCl_4$-NEt_3*, 20 °C, 3 h	72%	0%

Acetals also produce selenoacetals under closely related conditions. Best results are obtained with $BF_3.OEt_2$ as catalyst on straight-chain derivatives (eq 6)[37] and with $ZnCl_2$ on 1-ethoxy-1-trimethylsilyloxycyclopropane (eq 7 60% yield).[38] Extension of this reaction to orthoesters leads to selenoorthoesters (eq 8).[39]

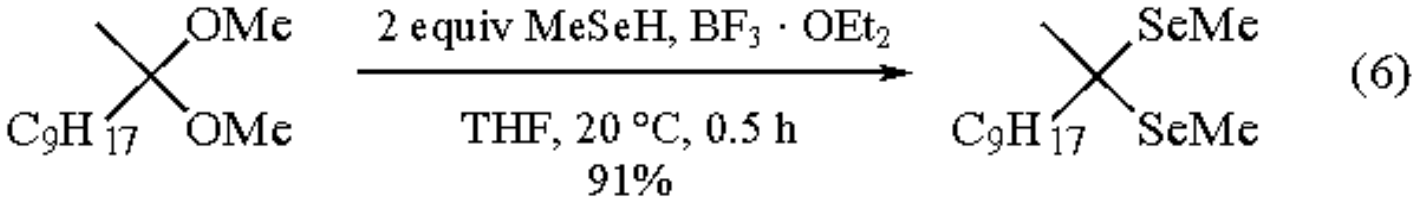

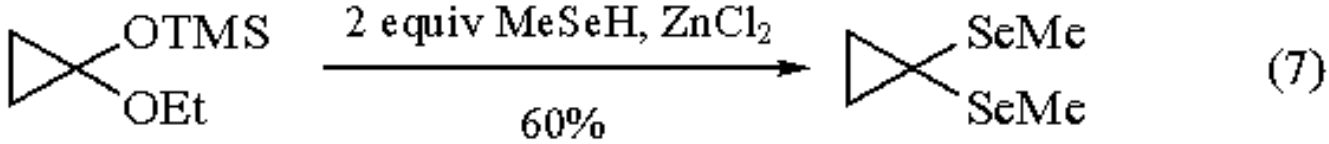

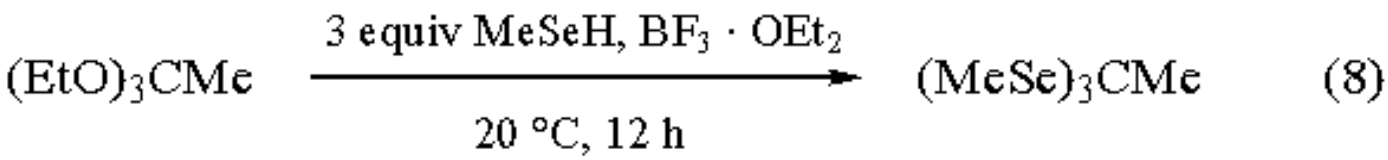

Reactions of Methaneselenolates.

Methaneselenolates are excellent nucleophiles which react with a large variety of organic halides and usually provide the corresponding methyl selenides (eq 9).[1a,1b,10,40,41] However, primary benzyl halides, especially iodides bearing a nitro group on the aromatic ring, suffer significant reduction to the corresponding arylalkane.[42] Potassium or sodium methaneselenolates react with (a) α,α-dihalomethanes which leads to 1,1-bis(methylseleno)methane (MeSeK, CH_2I_2 or CH_2Br_2, EtOH, 20 °C, 76%[30] or CH_2Cl_2, phase-transfer catalysis, MeSeNa, $Et_4N^+Cl^-$, DMF, 93%),[43] (b) aromatic halides bearing an electron-withdrawing group on the aromatic ring such as 4,6-dibromoisophthalaldehyde (DMF, 20 °C, 12 h, 74%)[7] and ethyl 2-chloronicotinate (EtOH, reflux, 1 h, 88%)[44] to furnish 4,6-dimethylselenoisophthalaldehyde and ethyl 2-methylselenonicotinate, respectively (eq 10). β-Halo- and β-selenoalkyl halides do not produce the corresponding selenides but instead lead to alkenes (eq 11).[45] This reduction reaction is stereospecific with *vic*-dibromides and occurs by a formal antiperiplanar elimination reaction.

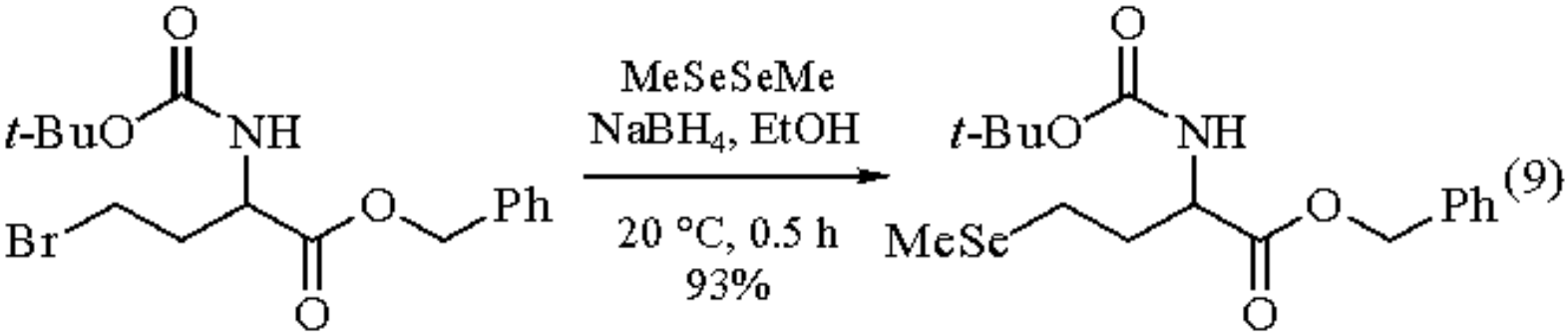

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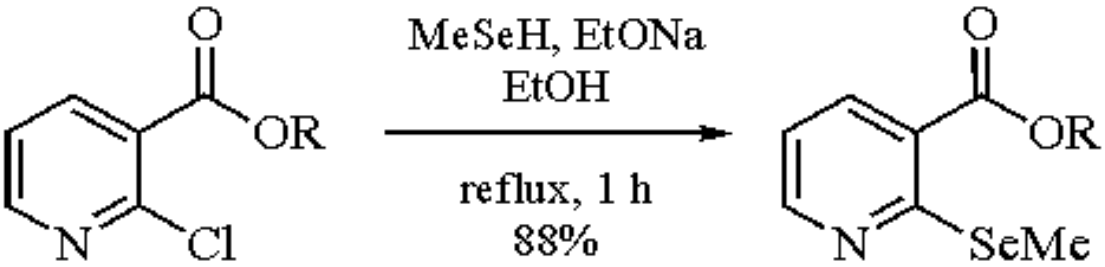

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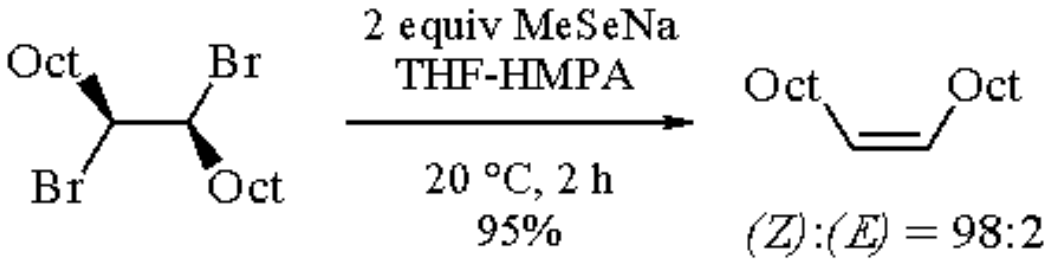

(11)

Methaneselenolates react with epoxides[8,9] and diethyl cyclopropane-1,1-dicarboxylate[46] to produce β-hydroxyalkyl methyl selenides and γ-methylselenobutyrates, respectively (eq 12). In HMPA or DMF they deprotect[47,48] aryl methyl ethers, sulfides, and selenides, producing the corresponding phenolates, arylthiolates, and arylselenolates (eq 13).

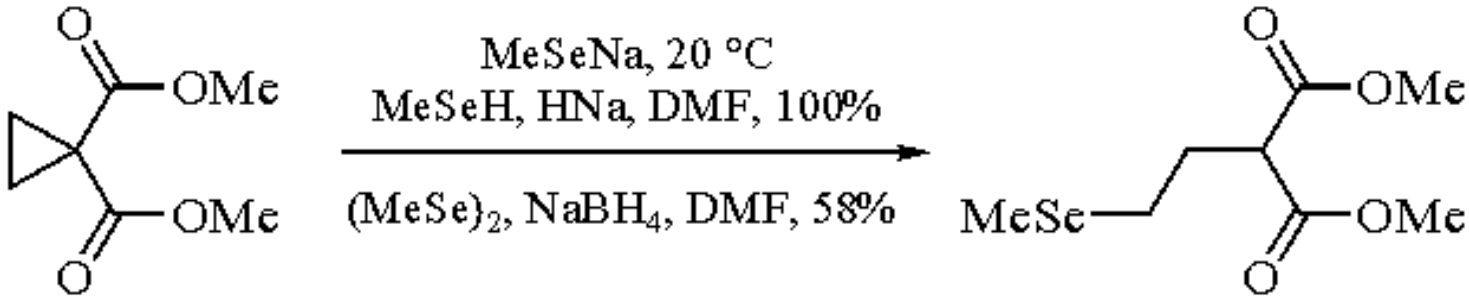

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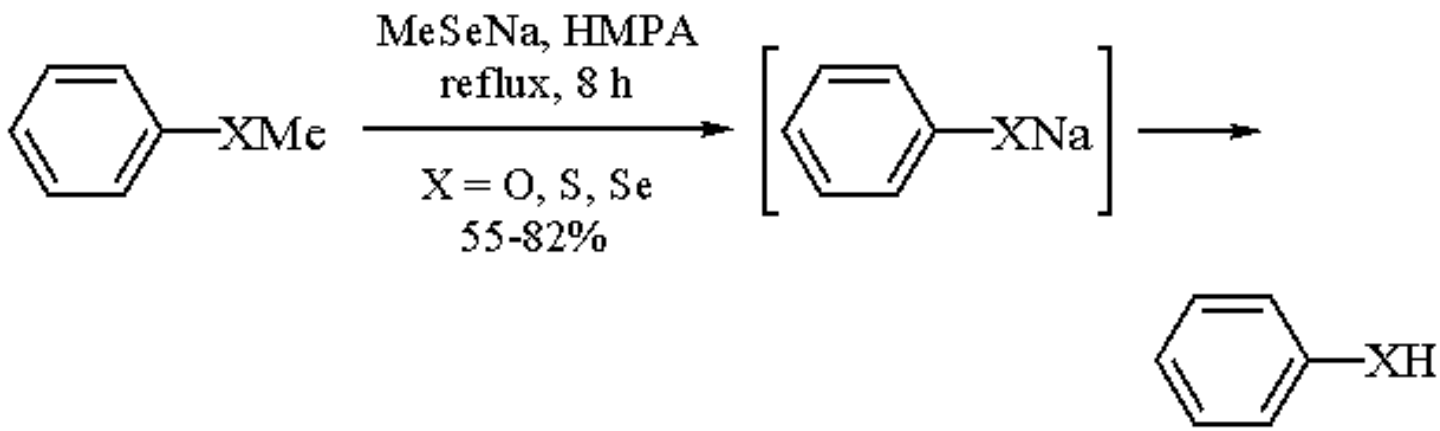

(13)

Methaneselenol, in the presence of pyridine, selectively adds to α,β-unsaturated aldehydes and ketones[49] and reacts with acid chlorides to produce the corresponding methylselenoesters.[4] If the reaction is performed in the presence of ***Chlorotrimethylsilane***, the intermediate enolates are trapped and γ-methylseleno-1-silyloxyalkenes are isolated.[50]

Methaneselenol or its sodium salt react with imidates or chloroimidates, respectively, and produce selenoimidates in poor (15%) to moderate (40-50%) yields.[51] Finally, Beckmann rearrangement of oxime *O*-sulfonates with simultaneous nucleophilic trapping of the imino carbocation intermediate by aluminum selenolate provides a new and highly efficient route to imino selenoethers (eq 14).[52]

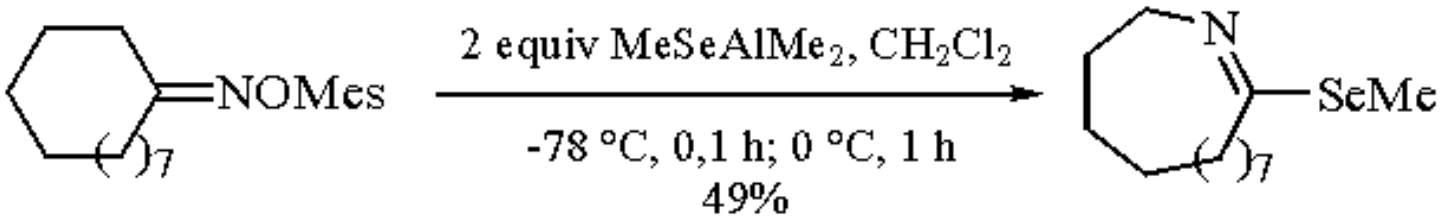

(14)

Related Reagents.

Benzeneselenol; ***Methanethiol***; ***Phenyl Trimethylsilyl Selenide***.

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Methanesulfenyl Chloride[1]

MeSCl

[5813-48-9] · CH_3ClS · Methanesulfenyl Chloride · (MW 82.56)

(reacts as a pseudohalogen;[1] reacts with carbanions and enolates to add the thiomethyl group α to the carbonyl;[2,3] adds across the double bonds of alkenes and allenes;[4,5] adds across triple bond of alkynes[6,7])

Physical Data: bp 27-28 °C/53-60 mmHg.

Solubility: sol ether, THF, dichloromethane, chloroform, carbon tetrachloride, dimethoxyethane.

Preparative Methods: by treatment of ***Dimethyl Disulfide*** at -15 °C with ***Sulfuryl Chloride***, or by treatment of ***Methanethiol*** with ***Chlorine*** gas in CCl_4 at -15 °C.[1] The latter procedure may be considered a variation of the former since it involves the intermediate formation of the disulfide. The reagent is not commercially available.

Purification: can be used crude from the above preparations. If purification is necessary it must be distilled at low temperature, under vacuum, due to its instability.

Handling, Storage, and Precautions: undergoes decomposition within 1-2 d even when kept in a refrigerator; lasts less than 1 month when stored at -78 °C.

Reaction with Nucleophilic Heteroatoms.

Methanesulfenyl chloride reacts with most N nucleophiles in a manner which can be considered as a direct substitution. Reaction with amines has recently found a use in the preparation of 7-methoxycephalosporins (eq 1).[8]

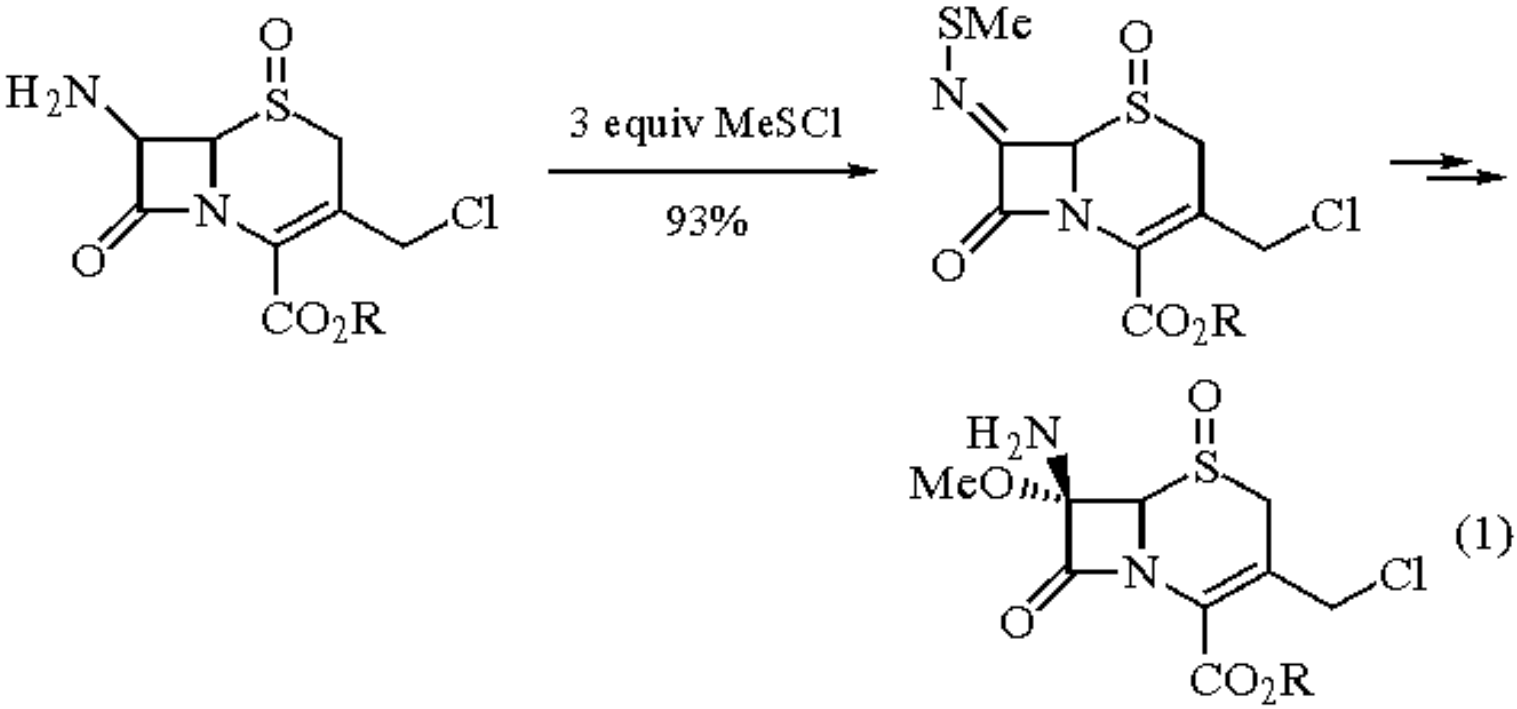

Methanesulfenyl chloride reacts similarly with thiols and other sulfur nucleophiles to give disulfides.[9] The reaction with alcohols gives complex mixtures of products and is not generally useful.[10] Alkoxides, however, react with methanesulfenyl chloride to give methanesulfenate esters when 1 equiv or less of methanesulfenyl chloride is employed (eq 2); methylsulfinate esters are formed when a 0.5 M excess of methanesulfenyl chloride is used (eq 3).[10]

$$\mathrm{MeSCl} + \mathrm{LiOC_5H_{11}} \xrightarrow[\text{-20 to -60 °C, 35-74\%}]{\text{THF or } Et_2O} \mathrm{MeSOC_5H_{11}} + \mathrm{LiCl} \quad (2)$$

$$3\ \mathrm{MeSCl} + 2\ \mathrm{LiOR} \xrightarrow[\text{-20 to -60 °C, 35-84\%}]{\text{THF or } Et_2O} \mathrm{Me(O)S(OR)} + \mathrm{MeSSMe} + \mathrm{RCl} + 2\ \mathrm{LiCl} \quad (3)$$

Reaction with Carbanions.

Methanesulfenyl chloride has also been used to thiomethylate carbanions, forming thiomethyl ethers (eq 4).[2]

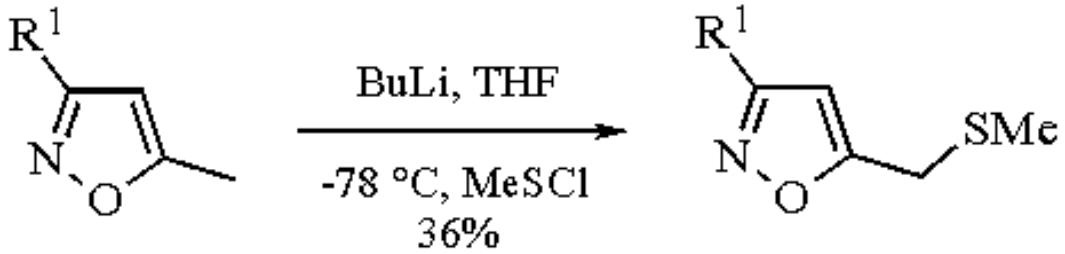

(4)

Reaction with Alkenes, Allenes, and Alkynes.

Methanesulfenyl chloride adds to alkenes to give *anti* adducts with high stereoselectivity and proceeds through a thiiranium ion intermediate.[1,4] For additions to unsymmetrically substituted alkenes the ratio of regioisomers is governed by the steric requirements of the alkene substituents, and to an extent the nature of the solvent used, but gives predominantly anti-Markovnikov addition with alkyl substituted alkenes (Table 1).[4,6] In general, methanesulfenyl chloride tends to give a higher ratio of anti-Markovnikov adducts than do arenesulfenyl chlorides.[11]

Table 1 Effect of Sulfenyl Chloride Used and Alkene Substituent upon Product Ratio in the Addition of Sulfenyl Chlorides to Alkenes

System	Markovnikov (%)	anti-Markovnikov (%)
MeSCl + $MeCH{=}CH_2$	18	82
PhSCl + $MeCH{=}CH_2$	32	68
MeSCl + $Me_2CHCH{=}CH_2$	6	94
PhSCl + $Me_2CHCH{=}CH_2$	13	87
MeSCl + $Me_2C{=}CH_2$	20	80
MeC(O)SCl + $Me_2C{=}CH_2$	68	32

Reaction with allenes is similar with addition generally occuring at the least substituted double bond.[5]

The reaction of methanesulfenyl chloride with alkynes is similar to that with alkenes.[1] The addition is stereospecifically *anti* and goes through a thiirenium ion intermediate to give predominantly anti-Markovnikov products.[6,7]

The high regio- and stereoselectivity characteristic of the addition of methanesulfenyl chloride, and sulfenyl halides in general, to alkenes, allenes, alkynes, and other π-nucleophiles make this reaction very useful. This is especially so when the substrate contains an internal nucleophilic center capable of competing with chloride ion for attack of the thiiranium or thiirenium ion intermediate, such as in sulfenolactonization (eq 5),[12] or when there is additional functionality present which

may participate (eq 6).[13] In eq 6 the methanesulfenyl chloride initially adds to the allene to give a thiiranium ion which is then attacked by the isolated double bond.

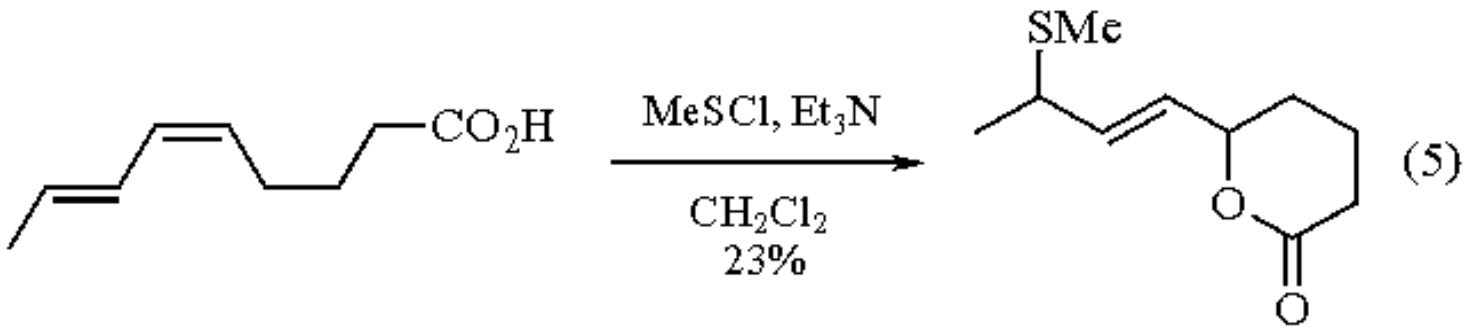

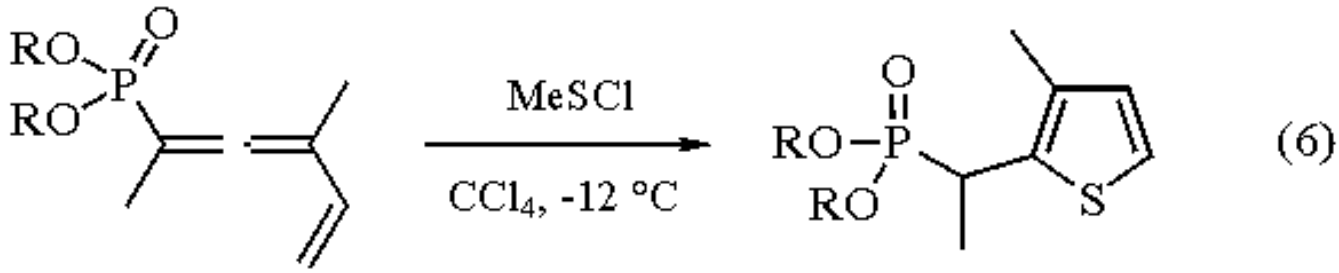

Reaction with Enols and Enolates.

Methanesulfenyl chloride reacts with enols and enolates to give α-sulfenylated carbonyls (eq 7).[3,14,15]

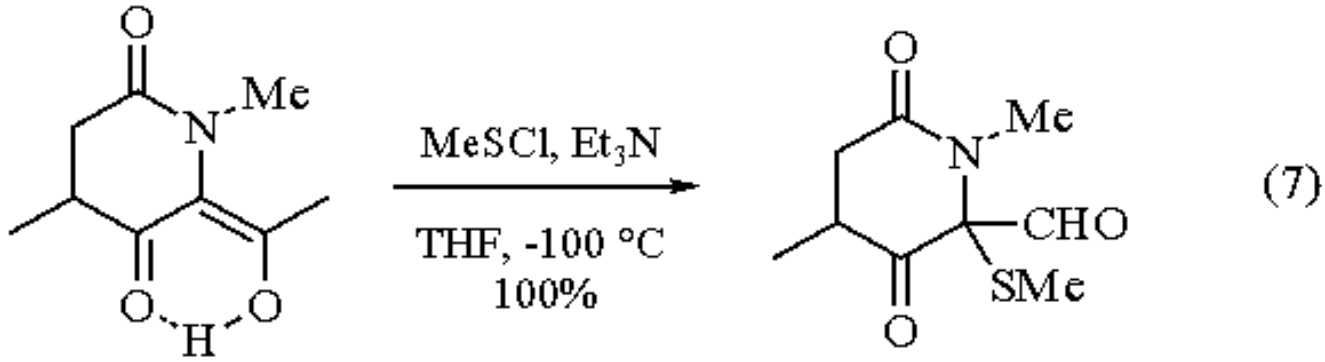

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Methanesulfonic Acid

$MeSO_3H$

[75-75-2] · CH_4O_3S · Methanesulfonic Acid · (MW 96.12)

(cyclocondensation reagent; precursor for methanesulfonyl chloride and anhydride; catalyst for polymerization, alkylation, and esterification reactions)

Alternate Name: MsOH.

Physical Data: mp 20 °C; bp 167 °C/10 mmHg, 122 °C/1 mmHg; *d* 1.481 g cm^{-3}; *n*D20 1.3210.

Solubility: sol water, ethanol, ether; insol hexane; very sparingly sol benzene, toluene.

Form Supplied in: technical quality is 95% pure containing 2% water.

Analysis of Reagent Purity: ^{17}O NMR.[1]

Preparative Method: by oxidation of ***Dimethyl Sulfide*** with ***Dimethyl Sulfoxide*** in the presence of water and a catalytic amount of ***Hydrogen Bromide***.[17]

Purification: stir with P_2O_5 (20 g for 500 mL of the acid) at 100 °C for 0.5 h and then distill under vacuum.

Handling, Storage, and Precautions: irritant and highly corrosive liquid; should be stored in glass containers. Use in a fume hood.

Cyclization Reactions.

MsOH is a weaker acid than ***Trifluoromethanesulfonic Acid*** and hence only few reports exist on the use of pure MsOH in cyclocondensation reactions.[2] MsOH in dichloromethane effects a symmetry allowed cyclization of the precursor diene to afford 1,2,3,4-tetramethyl-5-(trifluoromethyl)cyclopentadiene, which is used as a ligand in organometallic chemistry (eq 1).[3]

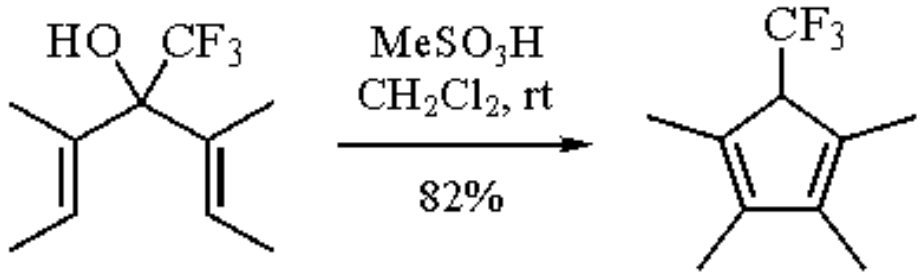

(1)

A 1:10 solution by weight of ***Phosphorus(V) Oxide*** in MsOH[4] is a convenient alternative to ***Polyphosphoric Acid*** for cyclization reactions. For example, the classical preparation of cyclopentenones via intramolecular acylation of alkenoic acids or their lactones (eq 2) and Beckmann rearrangement using polyphosphoric acid (eq 3) give comparable yields when performed with MsOH/P_2O_5.[4]

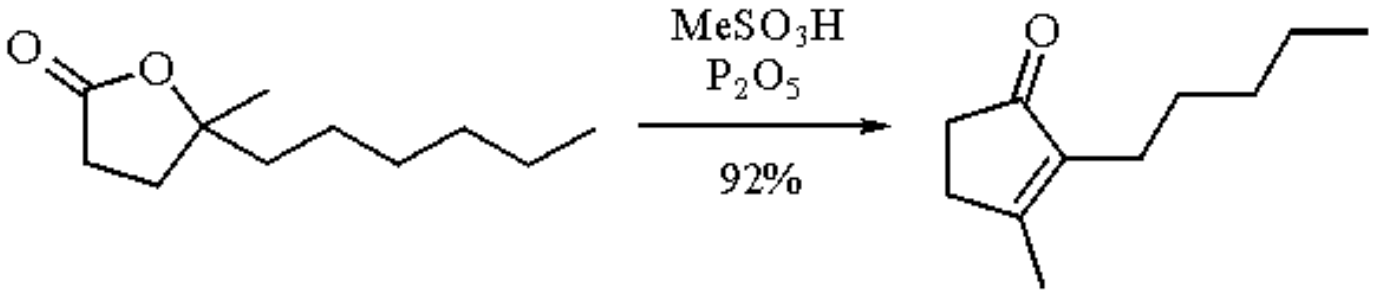

(2)

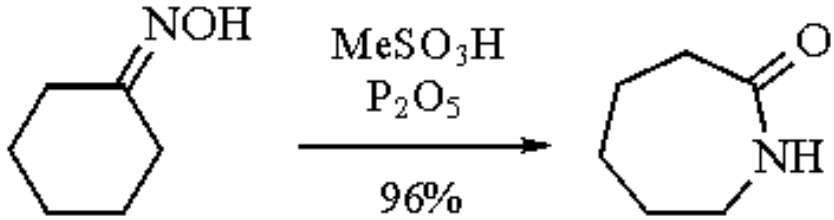

(3)

MsOH in conjunction with P_2O_5 has been used in the rearrangement of 2-vinylcyclobutanones to spiro and fused cyclopentenones (eqs 4 and 5).[5]

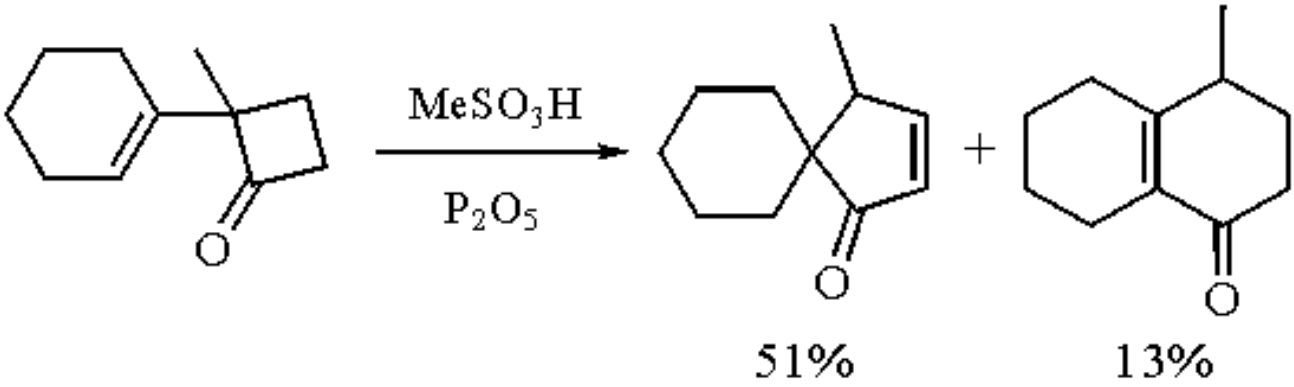

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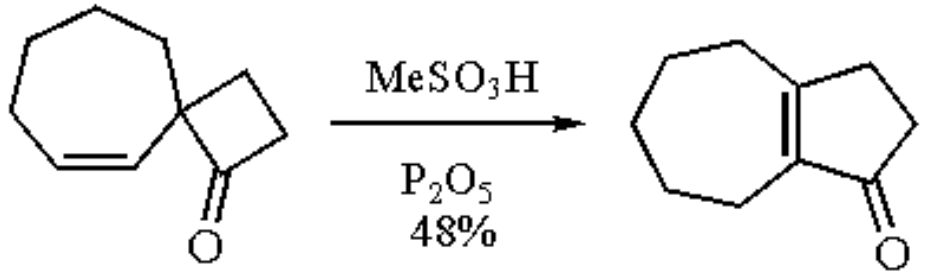

(5)

3-Unsubstituted indoles are formed regioselectively by treatment of precursor hydrazones with MsOH/P_2O_5.[6] In the example given in eq 6,[6] only 2-3% of the undesired 3-isomer is formed. Because decomposition sometimes occurs, it is advisable to dilute the reagent with a suitable polar, nonbasic solvent like sulfolane or dichloromethane.

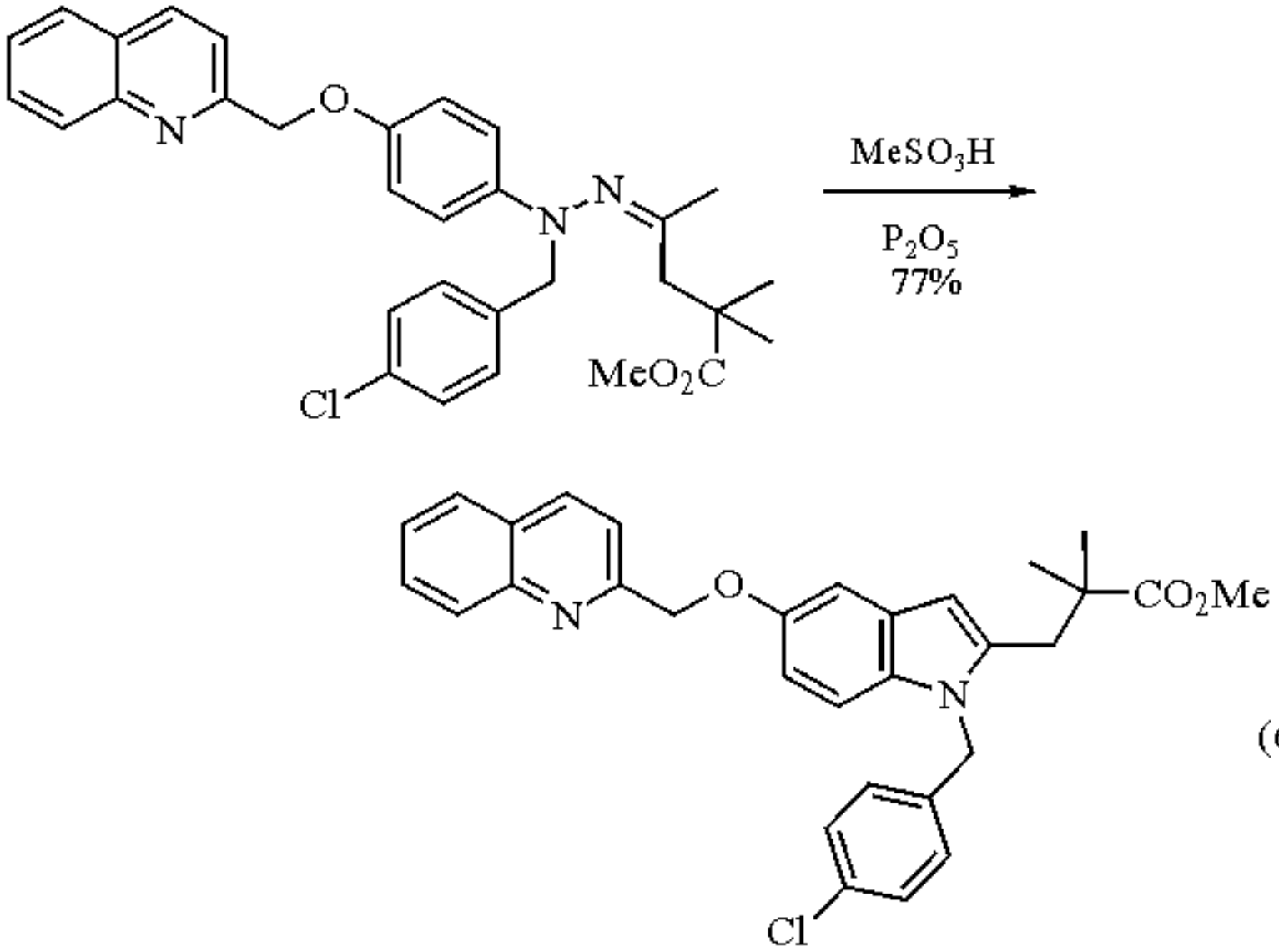

(6)

MsOH itself is a better cyclizing agent than an admixture with P_2O_5 for the cyclization of 3-arylpropanoic and 4-arylbutanoic acids to 1-indanones (eq 7) and 1-tetralones (eq 8).[7]

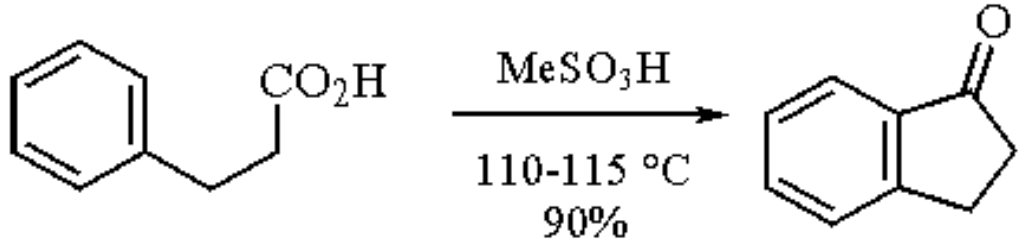

(7)

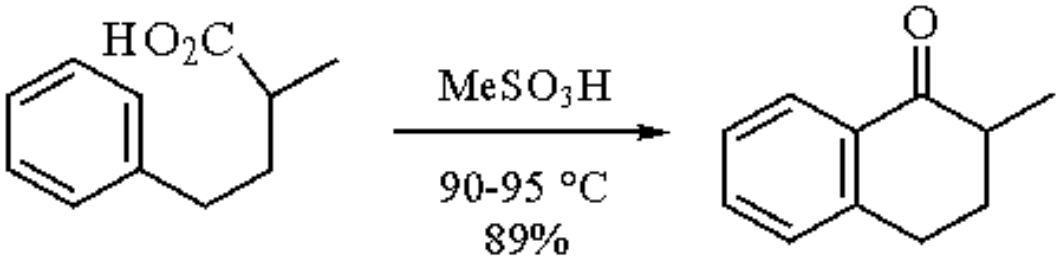

(8)

Cyclization with neat MsOH is also observed in the formation of cyclopentenones from 2-vinylcyclobutanones (eq 9).[5]

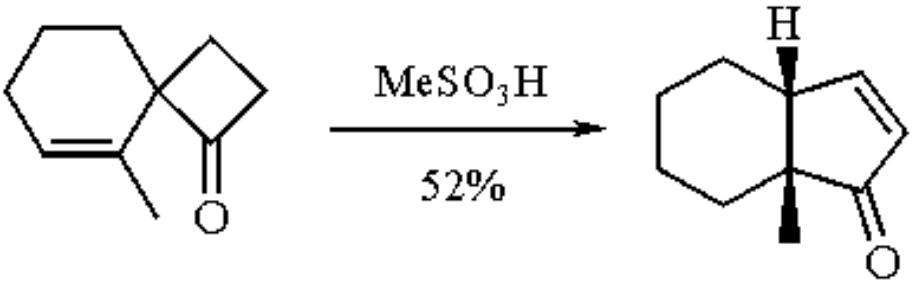

(9)

MsOH has also been employed successfully in cyclocondensation reactions in the field of heterocycles (eq 10).[8,18] Thus the hexahydroimidazo[1,2-*a*]pyrimidine-5,7-dione shown in eq 10 gives the corresponding cyclized product in 81% yield.[8]

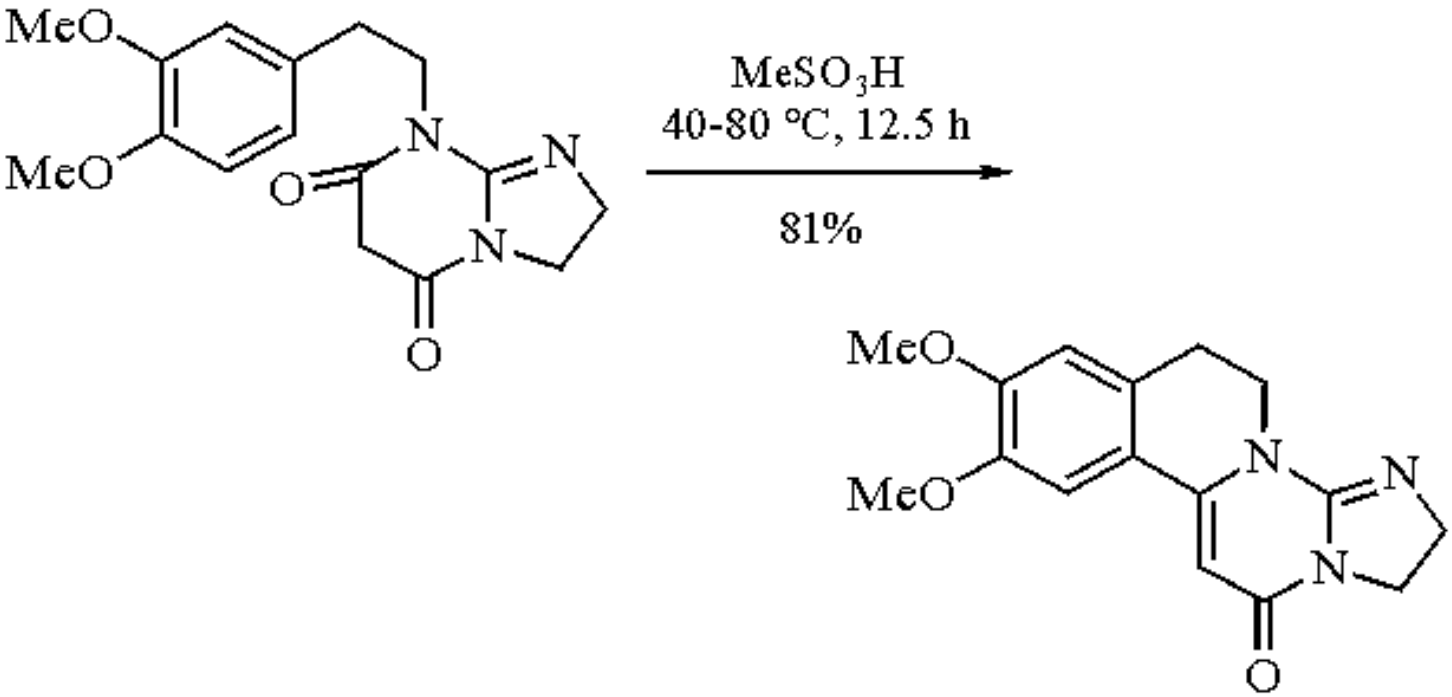

(10)

Other Applications.

MsOH is superior to ***Sulfuric Acid*** as the solvent and catalyst for the conversion of benzoic acid to ***Perbenzoic Acid*** (eq 11).[9]

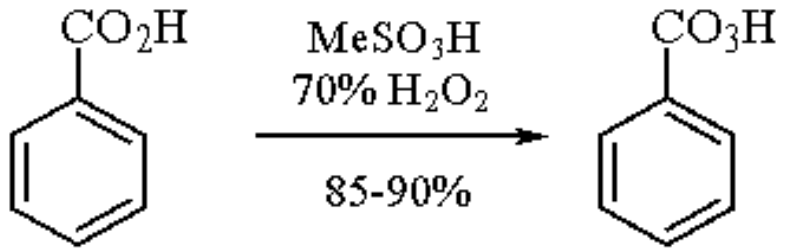

(11)

MsOH in the presence of methionine is the reagent of choice and an excellent substitute for ***Boron Tribromide*** for *O*-demethylation of opioid derivatives (eq 12).[10] Among the other reagents tested, only TfOH is as effective as MsOH/methionine.

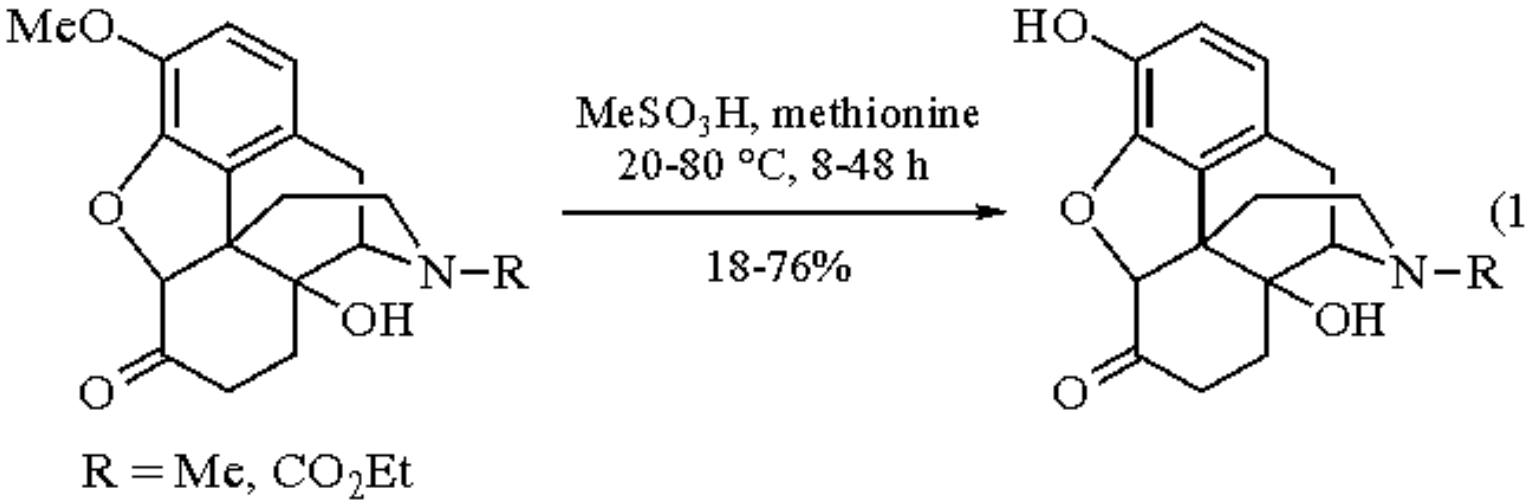

(12)

Schmidt rearrangement of optically active cyclic β-keto esters with retention of configuration is effectively carried out with MsOH in the presence of ***Sodium Azide*** (eq 13).[11]

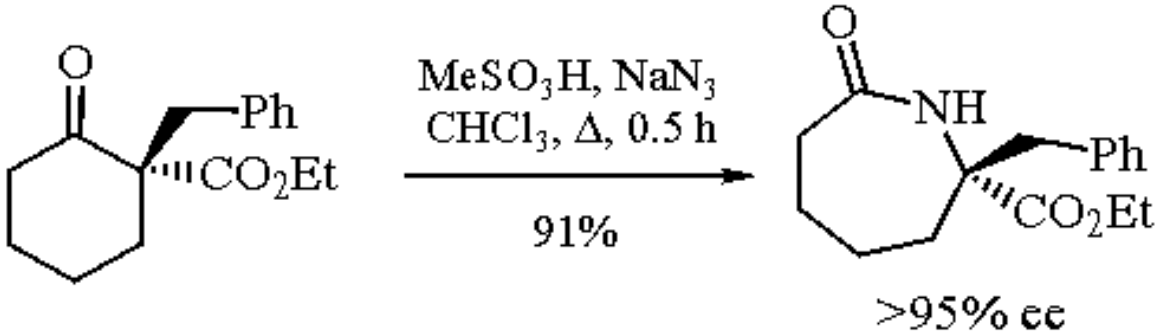

(13)

Attempted acid-induced cyclization with MsOH of an intermediate diazo ketone involved in the synthesis of tricyclo[5.2.1.0^{4,10}]decane-2,5,8-trione affords the corresponding methylsulfonyloxy derivative via the protonated

diazonium salt (eq 14).[12]

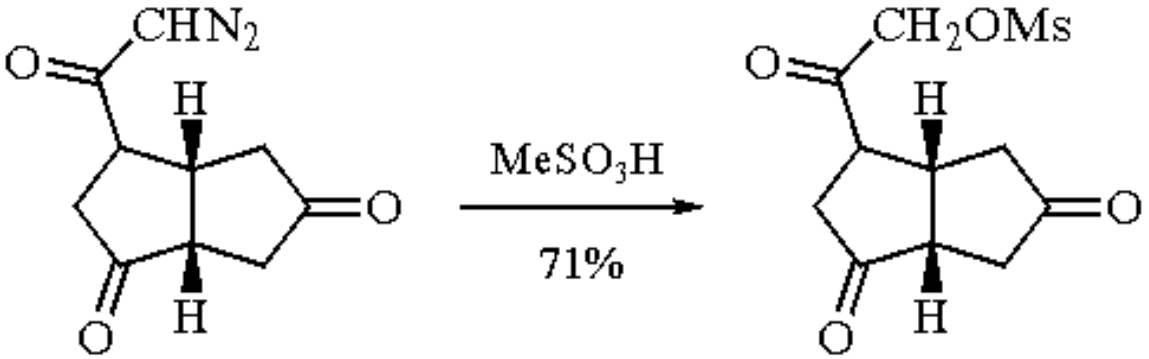

(14)

MsOH is a useful reagent for the condensation of 2-(hydroxymethylene)cyclohexanone with sulfonamides in the presence of molecular sieves to afford products in the *cis-u* diastereoisomeric forms and with >90% stereoselectivity (eq 15).[13]

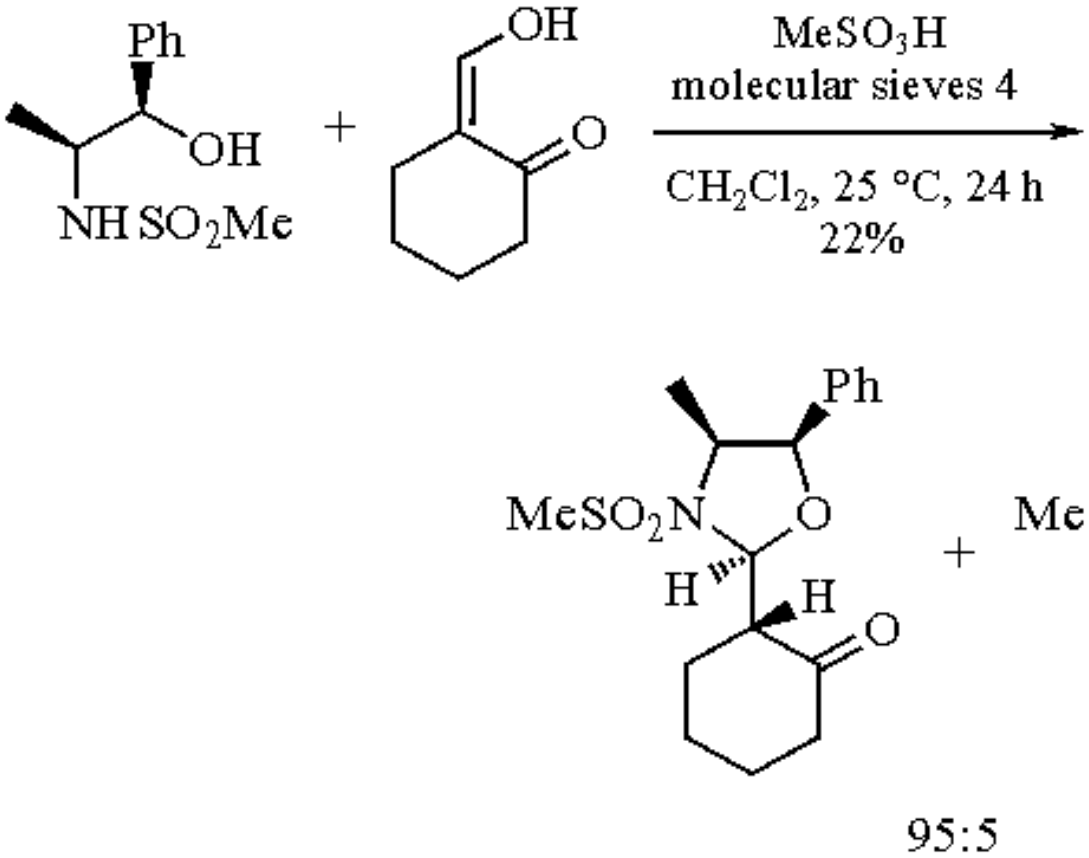

(15)

The reaction of trimethylphosphine-borane with MsOH in dichloromethane gives the methanesulfonate derivative of the borane (eq 16).[14] This compound can be condensed with diphenylphosphine-borane in the presence of ***Sodium Hydride*** to give the corresponding dimer. By repeating the sequences of mesylation and condensation, a tetramer containing a linear P-B bond has been synthesized.[14]

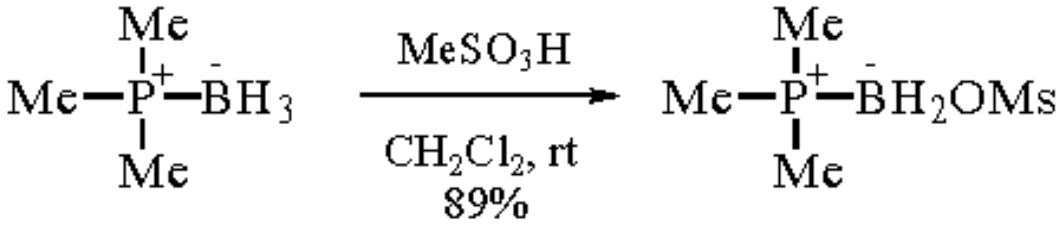

(16)

MsOH has also been used to deblock the benzyl protecting group[15] and to carry out the acidic hydrolysis of esters.[16]

Related Reagents.

Phosphorus(V) Oxide-Methanesulfonic Acid; ***Polyphosphoric Acid***; ***Trifluoroacetic Acid***; ***Trifluoromethanesulfonic Acid***.

---

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Methanesulfonic Anhydride

$(MeSO_2)_2O$

[7143-01-3] · $C_2H_6O_5S_2$ · Methanesulfonic Anhydride · (MW 174.22)

(preparation of sulfonates[1-3])

Physical Data: mp 69-70 °C; bp 125 °C/4 mmHg.

Solubility: sol organic solvents.

Form Supplied in: off-white powder; widely available.

Purification: can be recrystallized from diethyl ether.

Handling, Storage, and Precautions: corrosive; moisture sensitive. Store in a cool, dry place.

Sulfonate Formation.

The preparation of an alkyl methanesulfonate from an alcohol can be achieved by treatment of an alcohol with methanesulfonic anhydride in the presence of ***Pyridine*** or ***2,4,6-Collidine*** (eq 1).[1] The use of methanesulfonic anhydride rather than ***Methanesulfonyl Chloride*** eliminates the formation of small amounts of alkyl chlorides which occurs when methanesulfonyl chloride is used. Methanesulfonic anhydride, however, does not work very well for the formation of mesylates of unsaturated alcohols. Glycosyl mesylates (eq 2)[2,3] and 11-*O*-methylsulfonylerythromycins[4] have been synthesized using methanesulfonic anhydride.

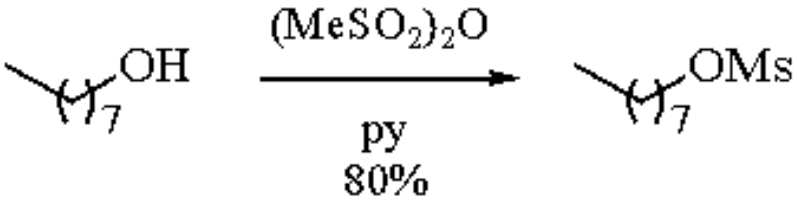

(1)

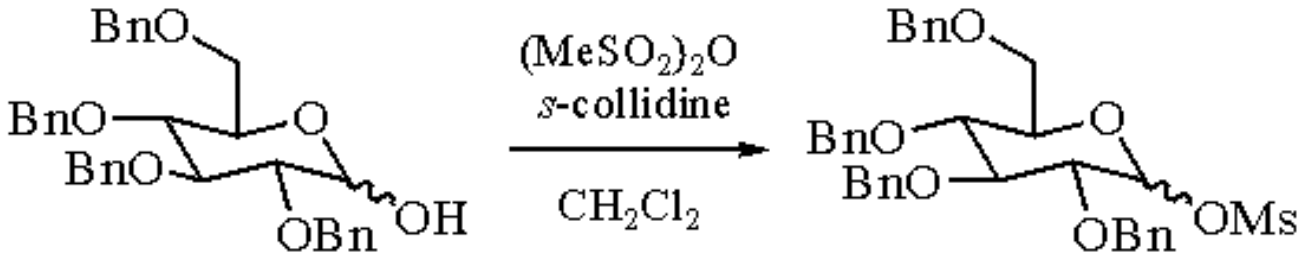

(2)

Glycosyl mesylates can be converted to glycosides by treatment with alcohols, and have also been used as intermediates in the synthesis of oxyglycals. Preparation of methyl ethers by solvolysis of mesylates in methanol has been reported.[5] Treatment of glycidols with methanesulfonic anhydride yields the epoxy mesylate which can then be treated with ***Tellurium*** to produce the allyl alcohol (eq 3).[6]

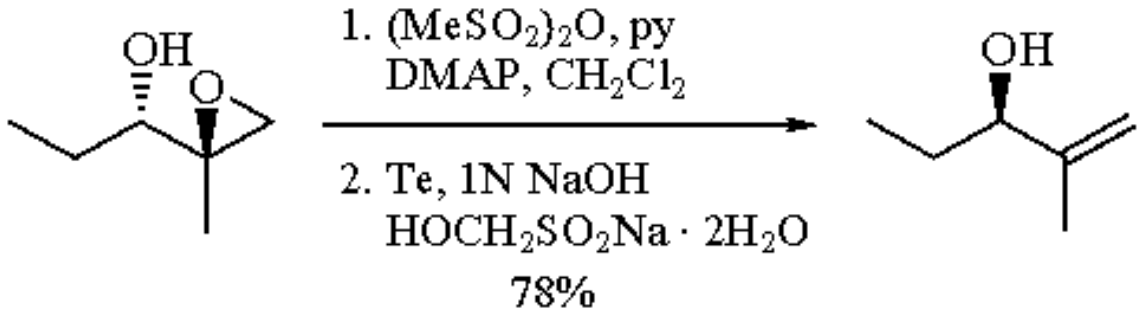

(3)

Sulfonamide Formation.

Treatment of amines with methanesulfonic anhydride in acetonitrile yields the methanesulfonamide (eq 4).[7] Sulfonamides are versatile protecting groups for the amino group, displaying good stability to both acidic and basic conditions. The sulfonamide group can be cleaved by ***Lithium Aluminum Hydride*** or dissolving metal reductions. Methanesulfonamides are also present in some biologically active molecules.

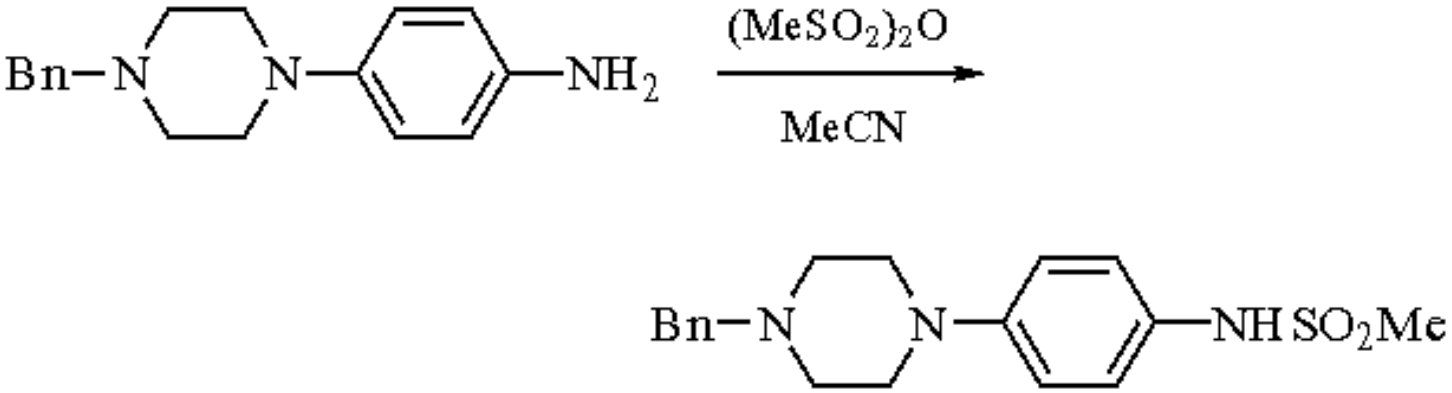

(4)

Sulfone Formation.

Friedel-Crafts methylsulfonation of benzene or substituted benzenes can be achieved via treatment with methanesulfonic anhydride in the presence of a Lewis acid catalyst (eqs 5 and 6).[8,9] Unlike methanesulfonyl chloride, which sulfonates only activated benzenes, treatment of deactivated benzenes with methanesulfonic anhydride produces the desired sulfones in good yields.[8,10] Diaryl sulfones can be formed using methanesulfonic anhydride and ***Sulfuric***

Acid (eq 7).[11]

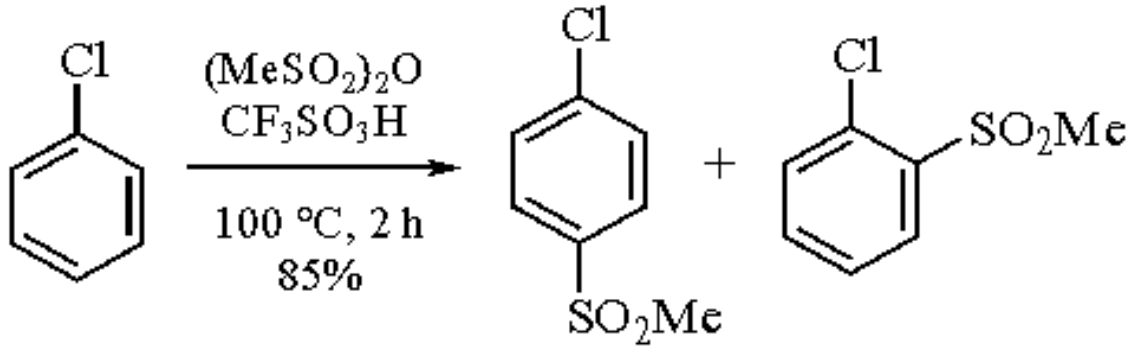

(5)

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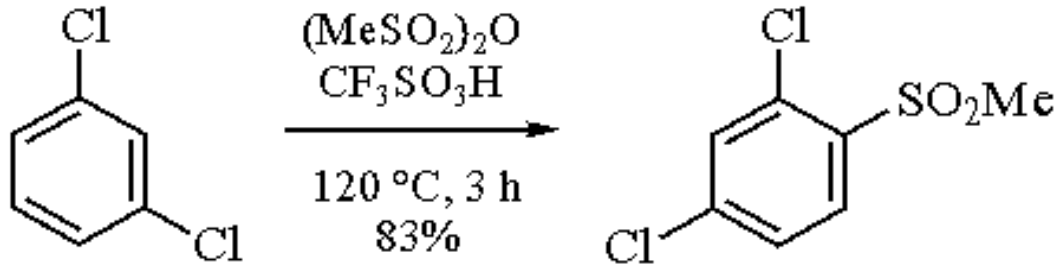

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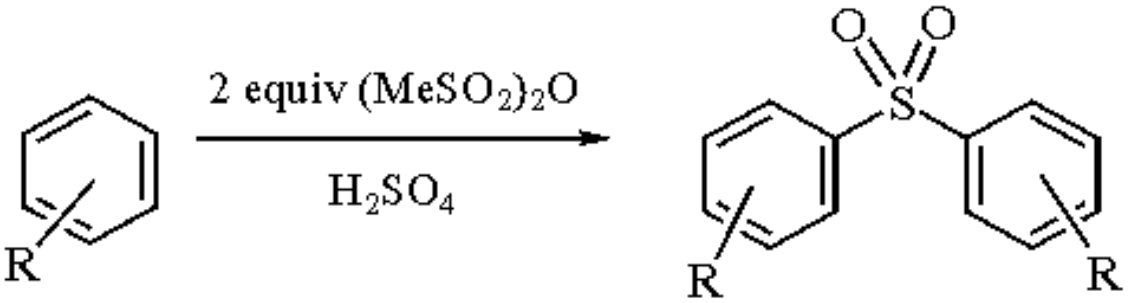

(7)

R = H, Et, Me, OEt, OMe

Oxidation of Alcohols.

Primary and secondary alcohols can be oxidized to aldehydes and ketones in good yields via treatment with methanesulfonic anhydride and ***Dimethyl Sulfoxide*** in HMPA (eqs 8 and 9). Dichloromethane can be substituted as the solvent, but the use of HMPA leads to cleaner products. Methanesulfonic anhydride works especially well for the conversion of primary alcohols to aldehydes.[12] Benzylic aldehydes can also be formed using this method.

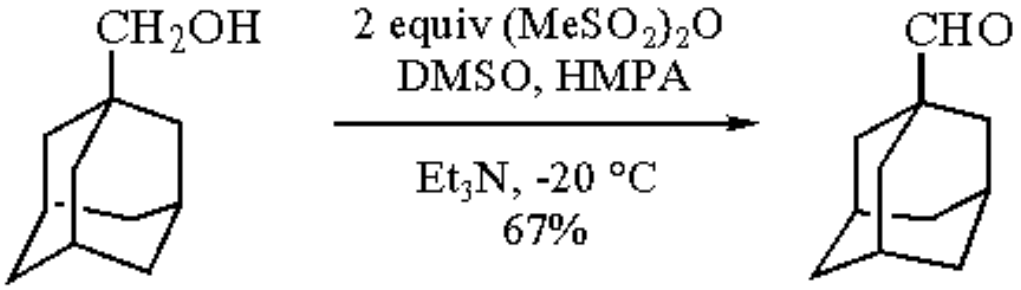

(8)

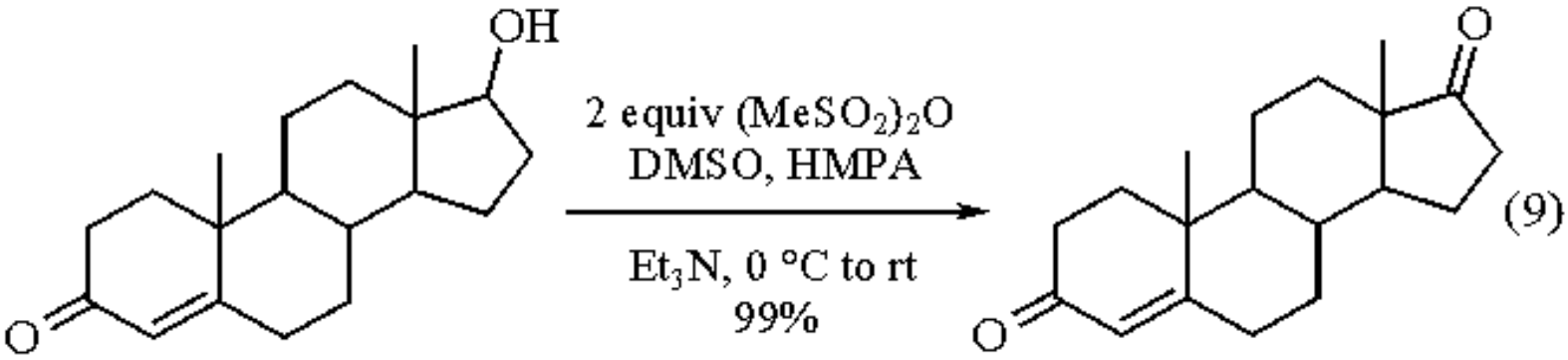

Related Reagents.

Acetic Anhydride; ***Benzoyl Chloride***; ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***; ***Methanesulfonyl Chloride***; ***p-Toluenesulfonyl Chloride***; ***Trifluoroacetic Anhydride***.

---

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Methanesulfonyl Azide

$MeSO_2N_3$

[1516-70-7] · $CH_3N_3O_2S$ · Methanesulfonyl Azide · (MW 121.14)

(diazo transfer reagent for activated methylene,[1] methine,[1,2] and methyl[3] groups; functionalization of double and triple bonds)

Alternate Name: mesyl azide.

Physical Data: mp 18-20 °C; bp 44-45 °C/1 mmHg; *n*20D 1.4675; *d*204 1.4361 g cm^{-3}.

Solubility: sol Et_2O, MeOH, MeCN; sparingly sol 95% EtOH, cold H_2O.

Form Supplied in: low-melting white solid or clear, colorless oil.

Analysis of Reagent Purity: IR, NMR, refractive index.

Preparative Methods: reaction of ***Methanesulfonyl Chloride*** with ***Sodium Azide*** in MeOH(EtOH)/H_2O[1,3] or acetone[2] (55-61 or 96% yields, respectively). By substituting acetone for methanol, the formation of $MeSO_2OMe$ is avoided and the reagent is obtained in >95% purity.[2]

Purification: crystallization from ether in dry-ice/acetone or from 95% EtOH at -75 °C; distillation in vacuo.

Handling, Storage, and Precautions: should be stored in the cold and the dark. Explosive when heated above 130 °C. No experimentalists have reported any difficulty handling MsN_3, but proper caution should be used, as with all azide reagents. Use in a fume hood.

Diazo Transfer Reagent.

Methanesulfonyl azide (MsN_3) is claimed to be a superior reagent[1,2] for diazo transfer reactions.[4] It is useful for both of the main strategies for accomplishing this process: (a) direct transfer of the diazo function to activated methylene groups; and (b) transfer to the methine position of α-acyl carbonyl substrates with a subsequent cleavage of the acyl group.

Direct transfer with MsN_3 has been reported for alkyl-,[1a] aryl-,[5a] and alkynyl-substituted (eq 1)[6] 3-keto esters, *N*,*N*-

disubstituted acetoacetamides,[5b] derivatives of malonic acid,[7] and 2,4-pyrrolidinediones,[8] and for alkynyl-substituted phenylsulfonyl acetates,[6] to give corresponding diazo dicarbonyl or diazo carbonylsulfonyl compounds in high yields. The process is usually realized with ***Triethylamine*** as the base,[4] or in the presence of sodium acetate.[5a]

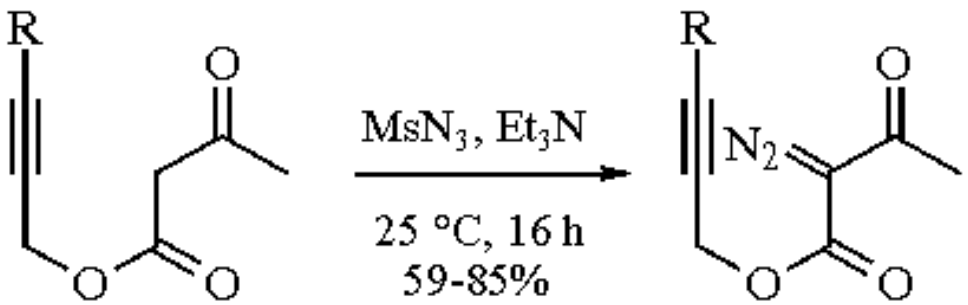

(1)

R = H, Me, Ph, TMS, etc.

A very rare diazo transfer onto a methyl group is shown in eq 2.[3] Reaction of oxime ethers with 1 equiv of ***n-Butyllithium*** followed by addition of MsN_3 to the enolate affords pure 2-diazo oxime ethers.

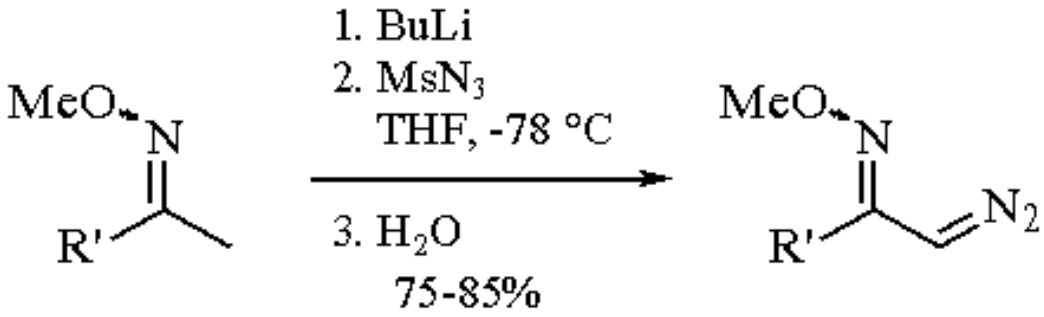

(2)

R' = Me, Ar

The deformylation and deacetylation strategy using MsN_3 is an efficient route to numerous saturated,[1,5] alkynyl-substituted,[6] and chiral 2-diazo esters[5,9] and 2-diazo ketones.[2,6] Substituting trifluoroacetylation of lithium enolates for the usual Claisen formylation step[4] can be used to prepare unsaturated cyclic and acyclic 2-diazo ketones via α-trifluoroacetyl ketones (eq 3).[2]

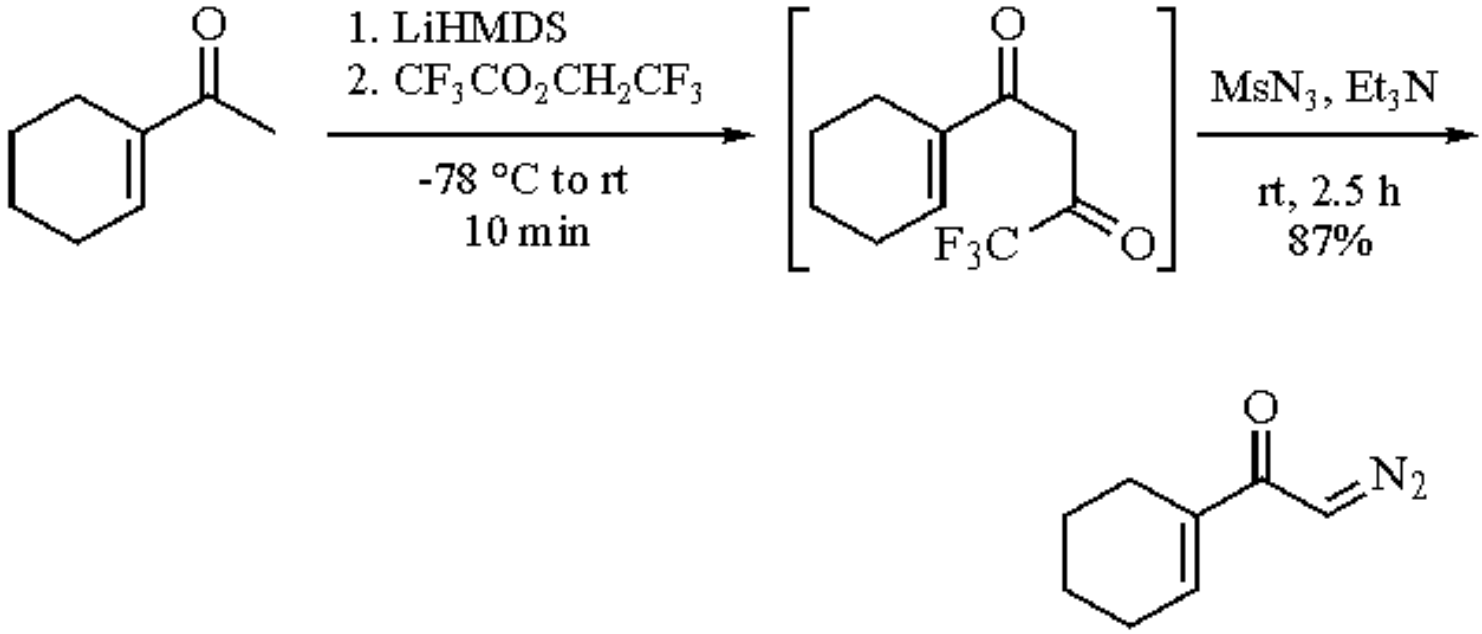

(3)

Significant regioselectivity can be achieved in this process when ***Lithium Diisopropylamide*** or ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LTMP) is employed for generation of the enolate from 2-octanone (eq 4).[2]

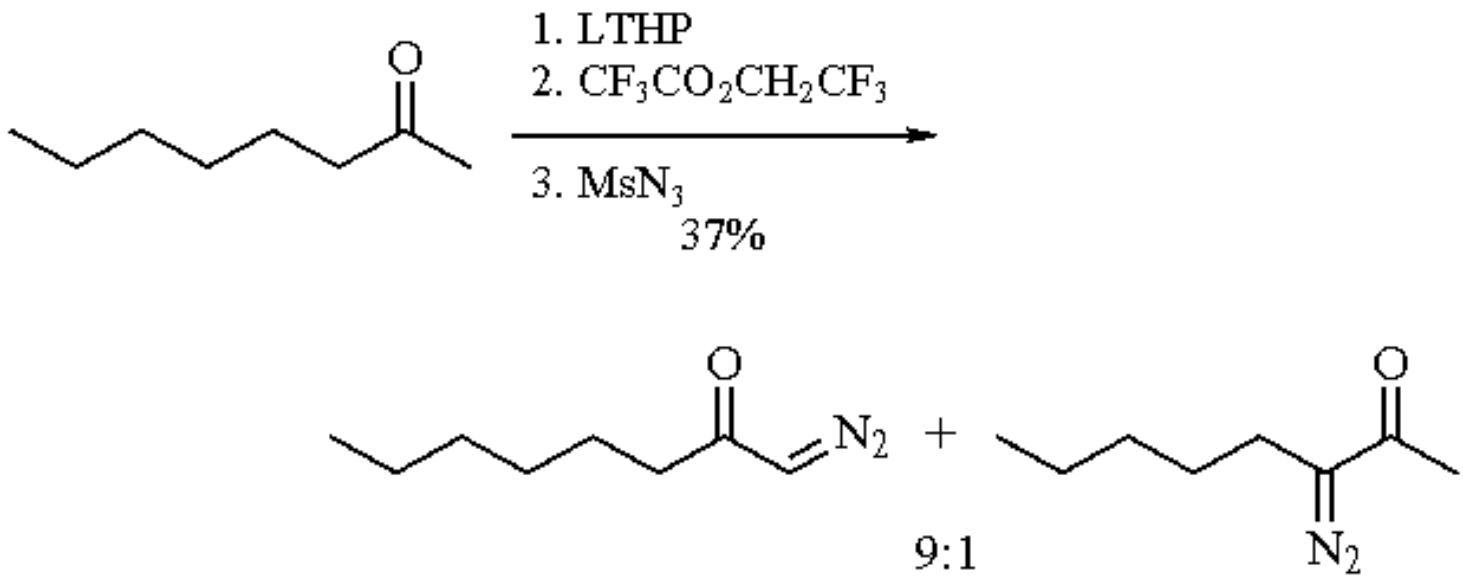

(4)

1,3-Dipole.

Cycloaddition reactions of MsN_3 with activated triple bonds of alkoxyalkynes[10] and alkynylamines[11] give rise to substituted 1,2,3-triazoles (>85%)[11c] or their open-chain diazo isomers (54-96%). The particularly nucleophilic double bonds of 5-alkylidenedihydrotetrazoles react with mesyl azide to produce stable zwitterions or iminotetrazines, after elimination of N_2 and a 1,2-shift of a nitrogen atom in a postulated intermediate triazoline (eq 5).[12]

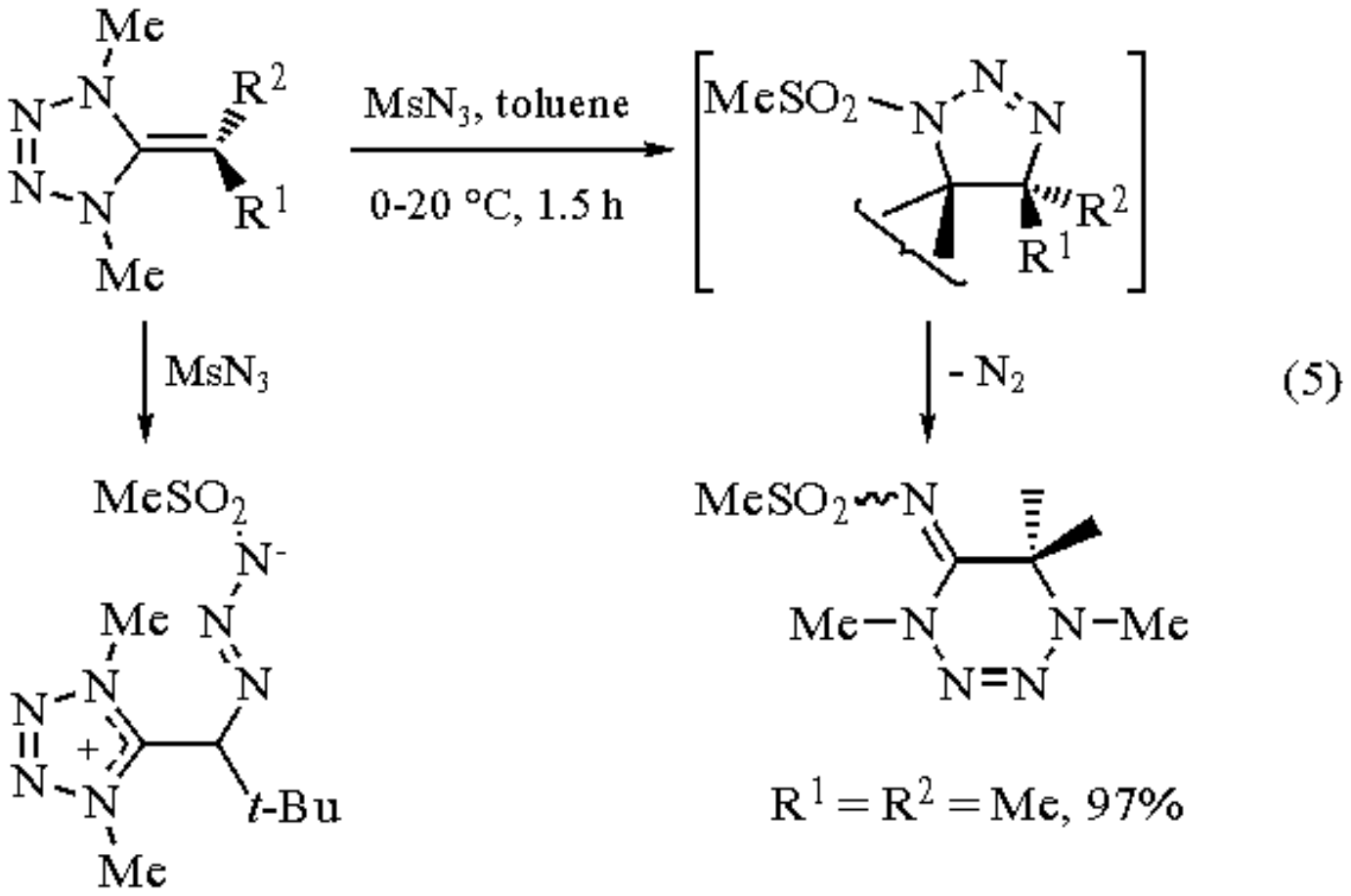

Regioselective formation of α-piperidone imines,[13] α-imino ethers,[14] and aziridines[15] occurs almost quantitatively in MsN_3 cycloadditions with the nucleophilic double bonds of tetrahydro- and dihydropyridines, vinyl ethers, and diazanorbornadiene. A tendency towards α-imino ether formation decreases in the order N_3SO_2Me > N_3CO_2Me > N_3Ph.[14] Isolation of tetracyclic azetidines from cycloaddition reactions of MsN_3 with 7-substituted norbornadienes has also been reported.[16]

Imination Agent and Nitrene Radical Precursor.

The imination of ***Triphenylphosphine***[17] and other trivalent phosphorus compounds[18] (Staudinger reaction[19]) with MsN_3 gives iminophosphoranes in good yields (eq 6).[18a] A related triphenylarsine imine, $Ph_3As{=}NSO_2Me$, is formed by Cu-catalyzed decomposition of MsN_3 at 110 °C in the presence of ***Triphenylarsine*** (74% yield).[20]

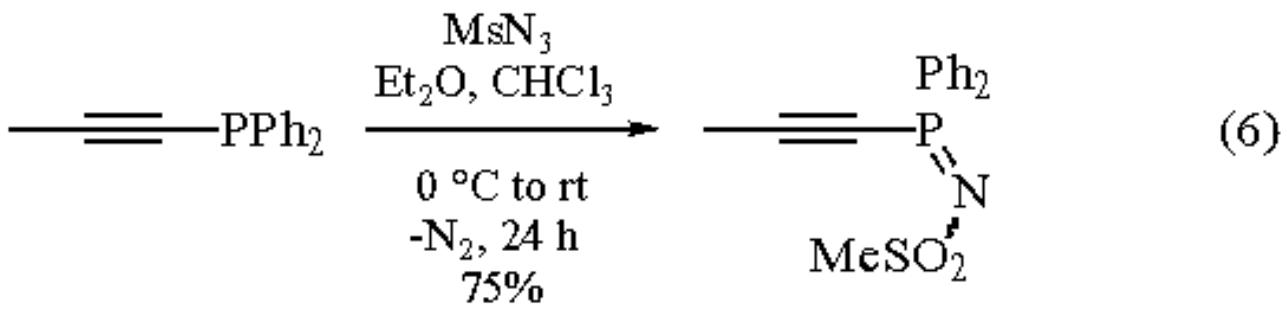

Efficient reduction of mesyl azide to the sulfonamide by hydrogen abstraction from the surrounding medium occurs on

photolysis in isopropyl alcohol[21] and a few other solvents.[22] However, methanesulfonylnitrene and the species generated by the photolysis or thermolysis of MsN_3 in hydrocarbons, aromatic, and other substrates are usually relatively unselective reagents.[23]

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Methanesulfonyl Chloride

$MeSO_2Cl$

[124-63-0] · CH_3ClO_2S · Methanesulfonyl Chloride · (MW 114.56)

(synthesis of methanesulfonates;[1] generation of sulfene)

Alternate Name: mesyl chloride.

Physical Data: bp 60 °C/21 mmHg; *d* 1.480 g cm^{-3}.

Solubility: insol water; sol alcohol, ether.

Form Supplied in: liquid of 98% or 99+% purity.

Handling, Storage, and Precautions: highly toxic; corrosive; lachrymator; moisture sensitive; store in a cool dry place.

Methanesulfonates.

The most common use of methanesulfonyl chloride is for the synthesis of sulfonate esters from alcohols. This can be readily accomplished by treatment of an alcohol with mesyl chloride in the presence of a base (usually ***Triethylamine*** or ***Pyridine***).[1] The methanesulfonates formed are functional equivalents of halides. As such they are frequently employed as intermediates for reactions such as displacements, eliminations, reductions,[2] and rearrangements.[3] Selective mesylation of a vicinal diol is a common method of preparation of epoxides.[4] Alkynyl mesylates can be used for the synthesis of trimethylsilyl allenes.[5] Oxime mesylates undergo a Beckmann rearrangement upon treatment with a Lewis acid.[6] Aromatic mesylates have been used as substrates for nucleophilic aromatic substitution.[7] Mesylates are more reactive than tosylates toward nucleophilic substitution, but less reactive toward solvolysis.

Protection of Alcohols.

In addition to being used as a halide equivalent, methanesulfonates have also been used as protecting groups for alcohols and phenols. The use of methanesulfonate as a protecting group for alcohols is mainly limited to carbohydrate synthesis due to the lability of the methanesulfonate group toward nucleophilic attack. The sulfonate ester is stable to acidic conditions and can be cleaved by ***Sodium Amalgam***.[8]

Protection of Amines.

Amines also react with mesyl chloride to form the corresponding sulfonamide. The sulfonamide group is one of the most stable nitrogen-protecting groups, with good stability to both acidic and basic conditions. The sulfonamide can be cleaved back to the amine by ***Lithium Aluminum Hydride*** or dissolving metal reductions.[9] In addition to treatment of amines with mesyl chloride, other reports for the preparation of sulfonamides include a Reissert-type reaction of mesyl chloride with phthalazine[10] and addition of mesyl chloride to lactim ethers (eq 1).[11]

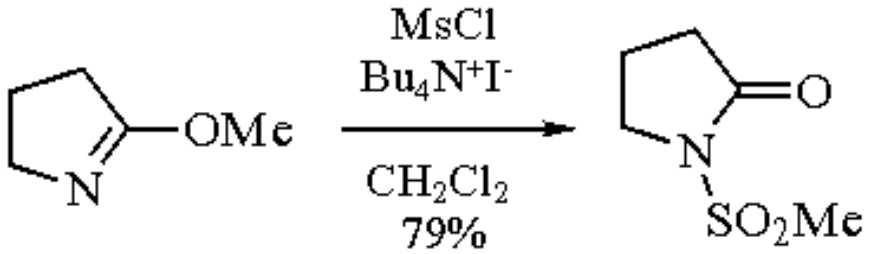

(1)

Chlorination.

Methanesulfonyl chloride can effect the direct chlorination of various substrates. The most notable of these reactions is the selective chlorination of the C-6 primary hydroxy group of carbohydrates (eq 2).[12] Under these conditions, 2-furyl alcohol (eq 3)[13] and guanine *N*-oxide (eq 4)[14] can also be chlorinated directly.

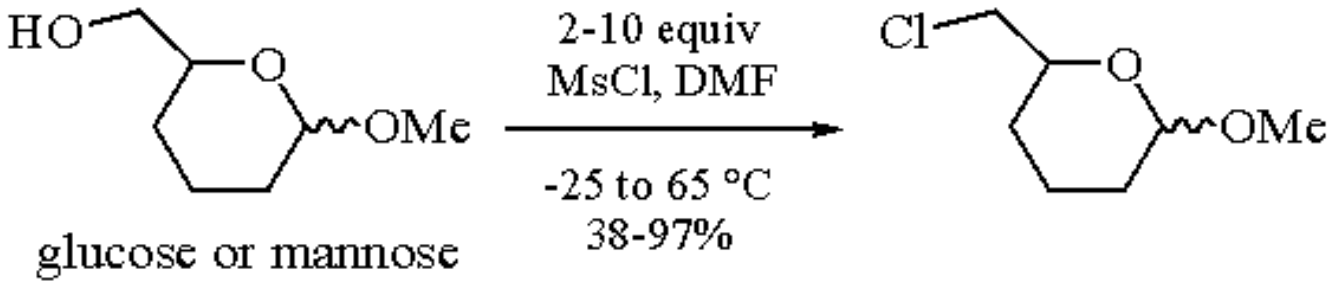

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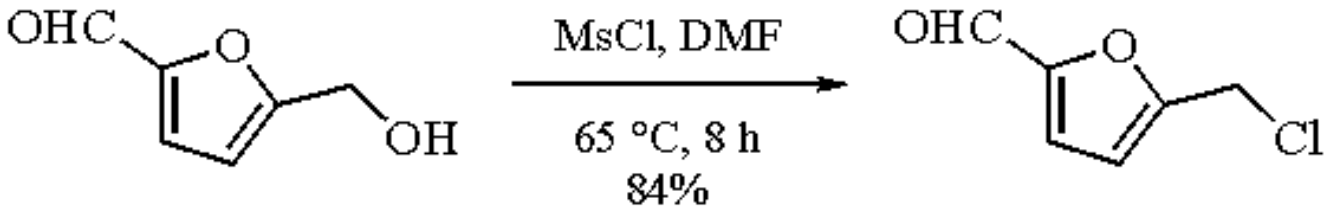

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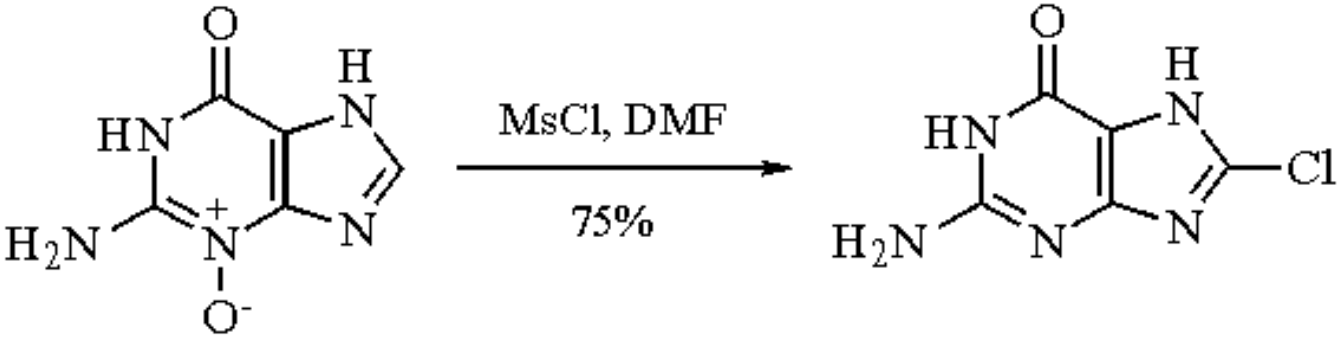

(4)

Meyers developed a procedure for the direct conversion of allylic alcohols to allylic chlorides that is general for a variety of terpenes (eq 5).[15] Primary alcohols give yields in the 85% range. A single example of a secondary alcohol produced the chloride in 50% yield. Certain allylic alcohols also undergo stereospecific chlorination under the conditions normally employed for mesylate formation (eq 6).[16]

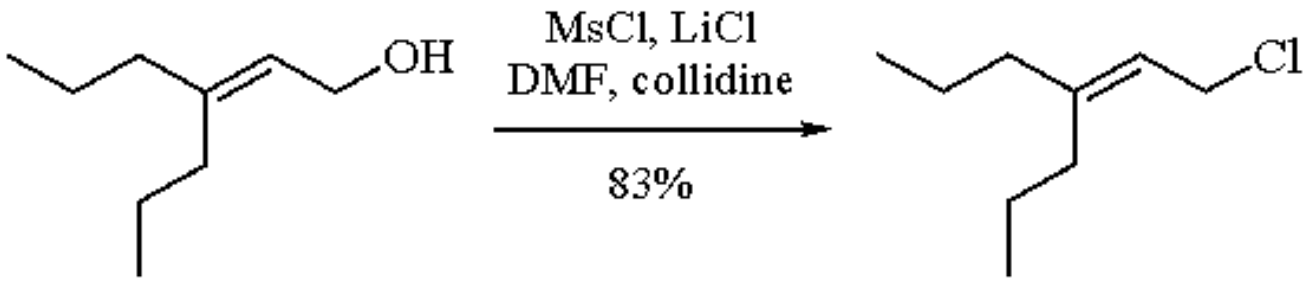

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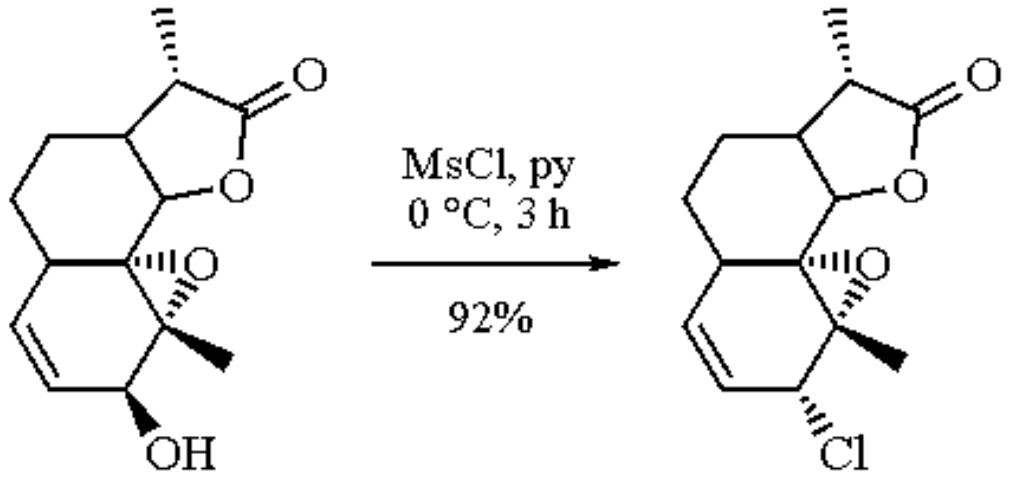

(6)

Under Lewis acid catalysis, mesyl chloride reacts with unactivated benzenes to produce the aromatic chloride and only trace amounts of the corresponding sulfone (eq 7).[17] Mesylates have also been used as intermediates for the transformation of alcohols into halides.

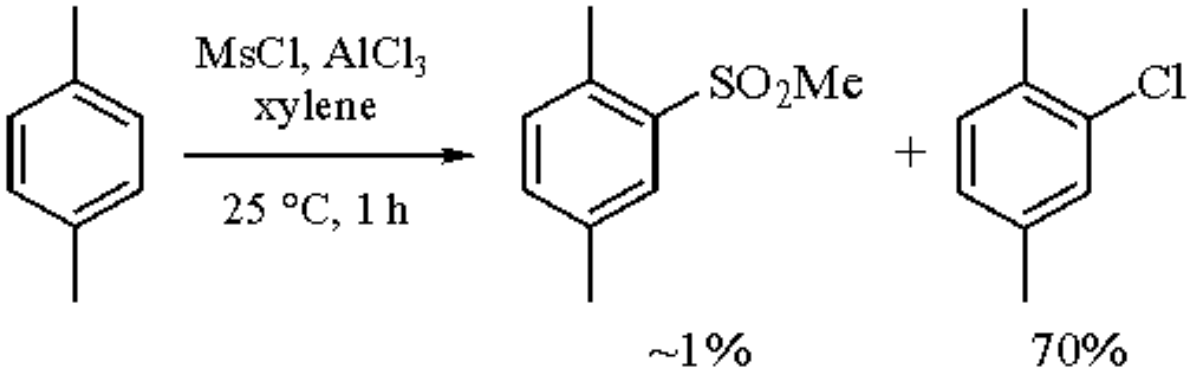

(7)

Interconversion of Carboxylic Acid Derivatives.

Methanesulfonyl chloride is employed in the activation of carboxylic acids for the preparation of anhydrides (eq 8),[18] nitriles (eq 9),[19] amides (eq 10), and esters (eq 11).[20]

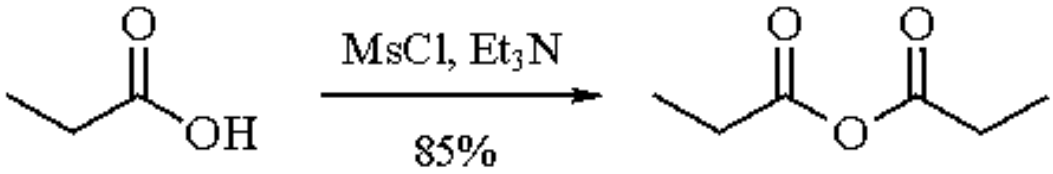

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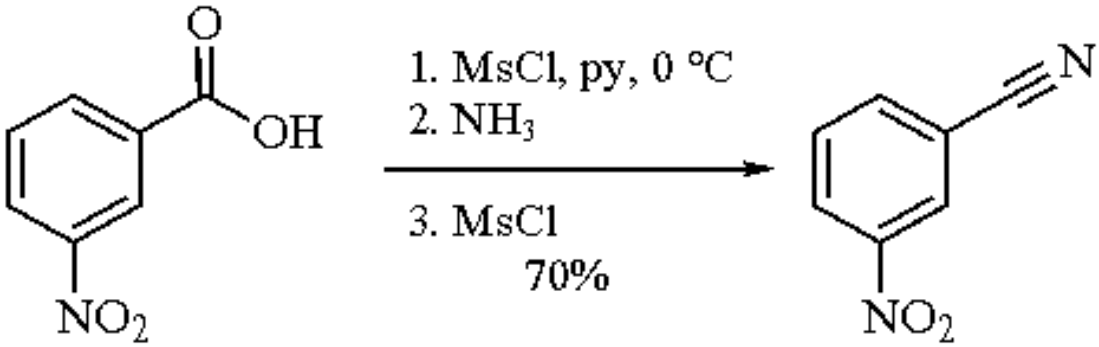

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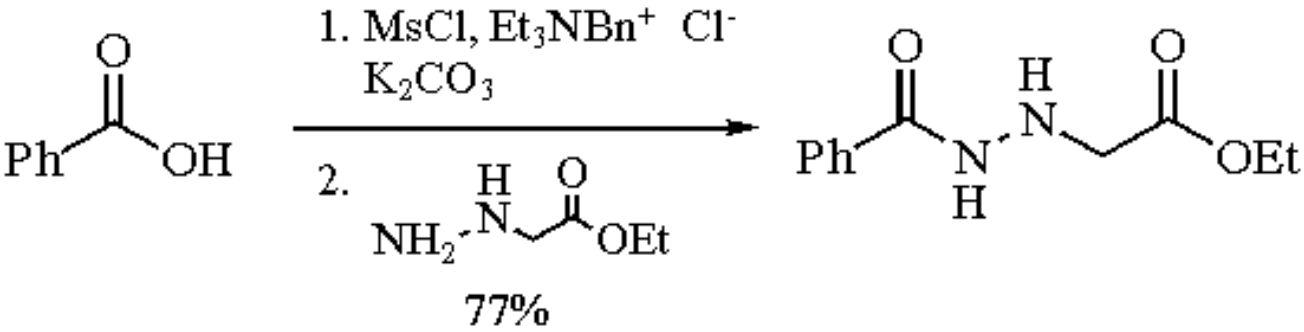

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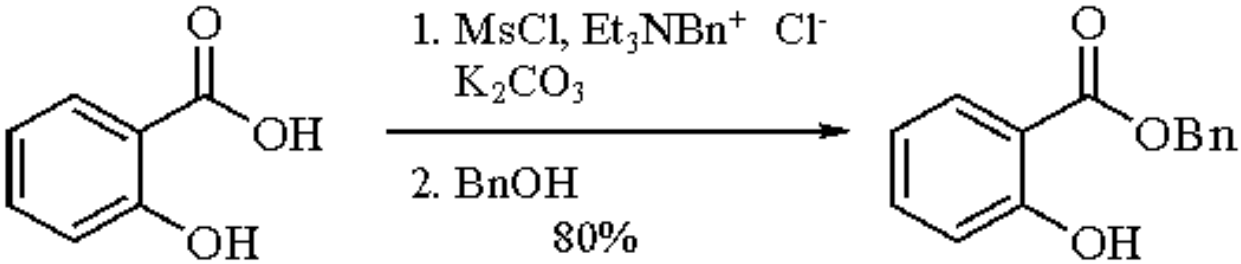

(11)

Eliminations.

Alkene formation by elimination can also be achieved with mesyl chloride. This is general for a variety of substrates. Peterson reported the elimination of β-hydroxy silanes to give predominantly *trans*-alkenes upon treatment with mesyl chloride (eq 12).[21] In a similar manner, β-hydroxy phenylselenates can also be eliminated (eq 13).[22]

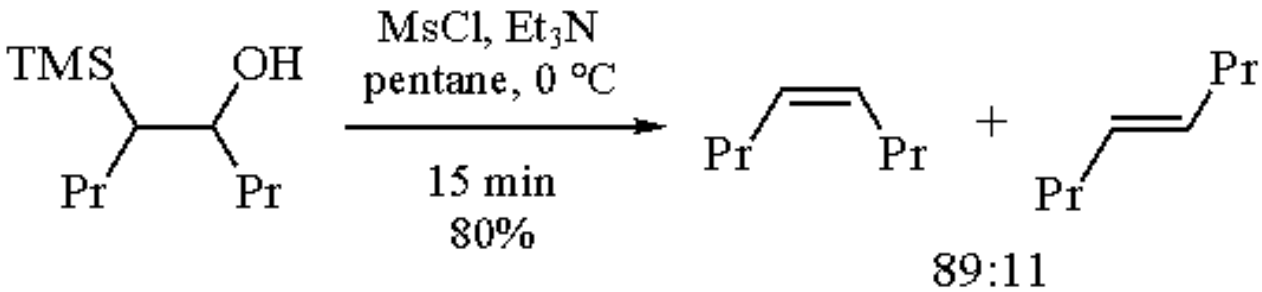

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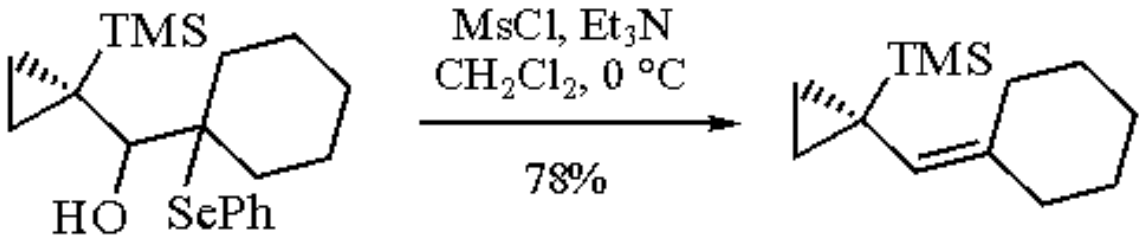

(13)

Corey reported a mild elimination of iodohydrins by activation with mesyl chloride (eq 14).[23] The major advantage of this method over traditional methods is that the use of a strong reducing agent (***Zinc*** or ***Tin(II) Chloride***) is avoided.

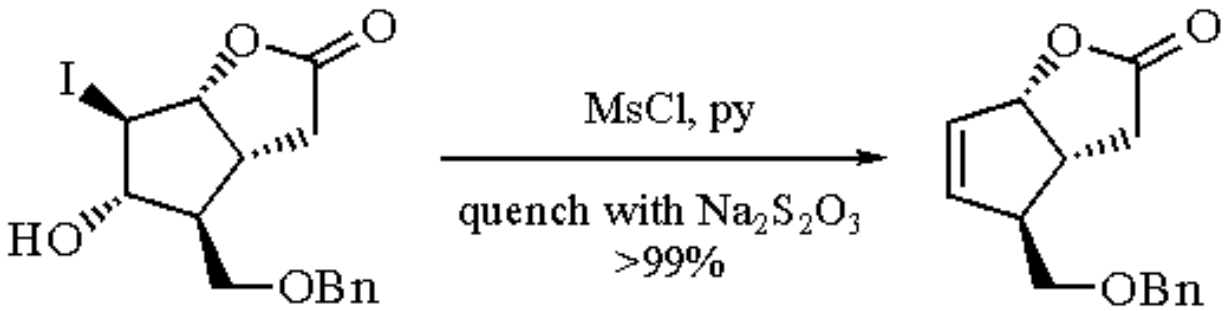

(14)

The direct elimination of tertiary alcohols by treatment with mesyl chloride has also been reported.[24] A variety of acid sensitive functional groups including silyl ethers and acetals are stable to these reaction conditions (eq 15). Mixtures of *cis* and *trans* and internal and terminal alkenes are formed in all cases where possible (eq 16).

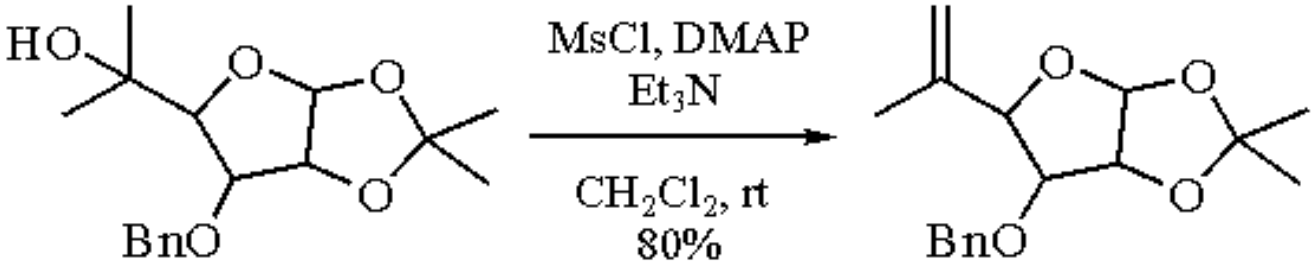

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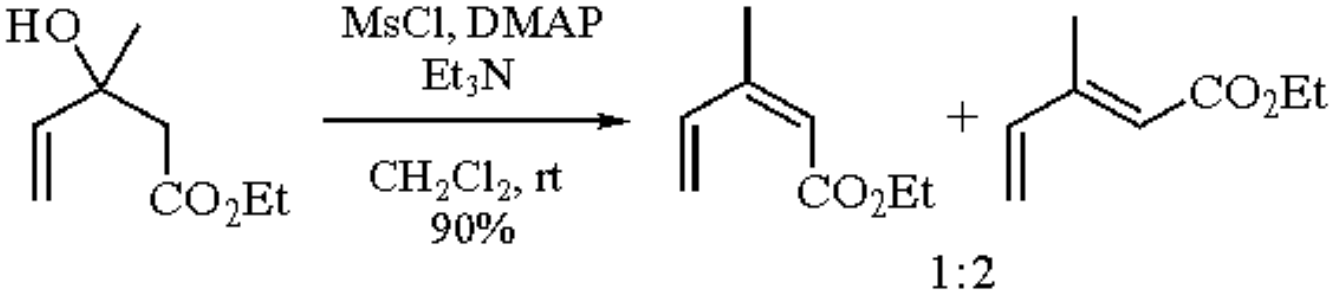

(16)

The synthesis of α-methylene lactones[25] and ketones[26] via the elimination of a mesylate has also been reported (eqs 17 and 18). In these cases, the pyridine or triethylamine is sufficiently basic to induce elimination under standard mesylate forming conditions.

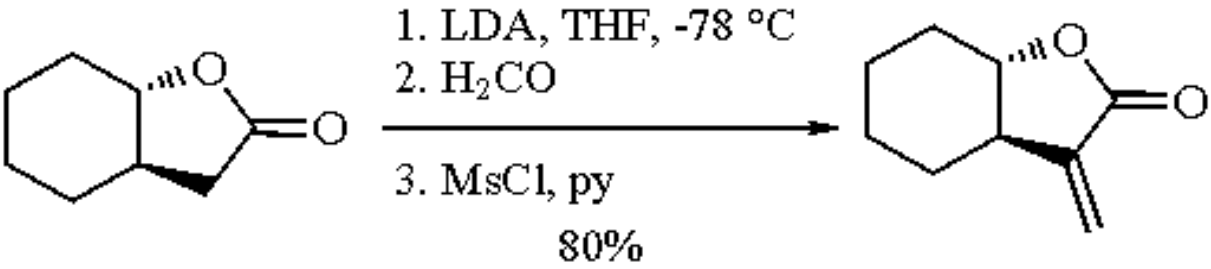

(17)

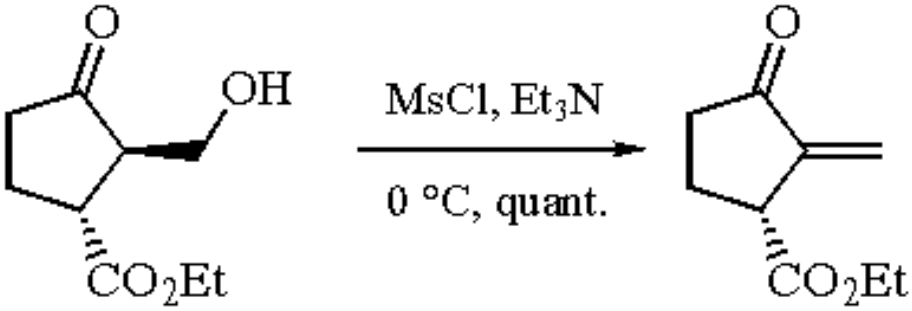

(18)

Heterocycles.

Sulfene, generated by the treatment of methanesulfonyl chloride with base, undergoes [2 + 2], [3 + 2], and [4 + 2] cycloadditions to produce four-, five-, and six-membered heterocycles, respectively. Alkynyl amines[27] and enamines[28] both undergo [2 + 2] cycloadditions with sulfene to produce four-membered cyclic sulfones (eqs 19 and 20).

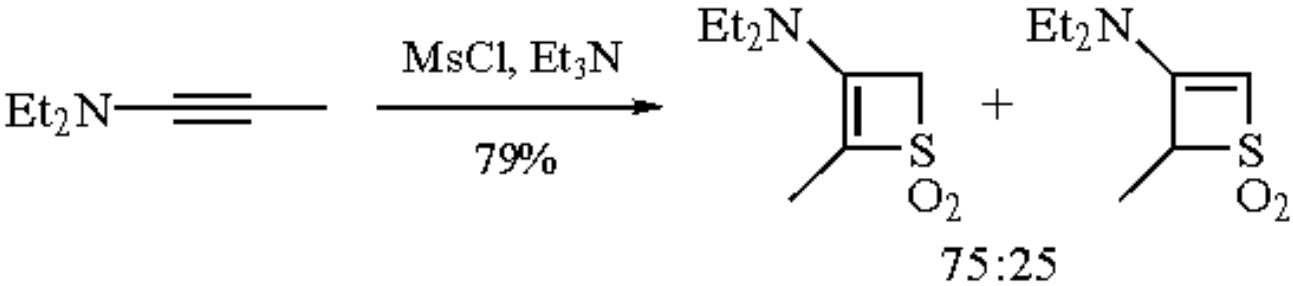

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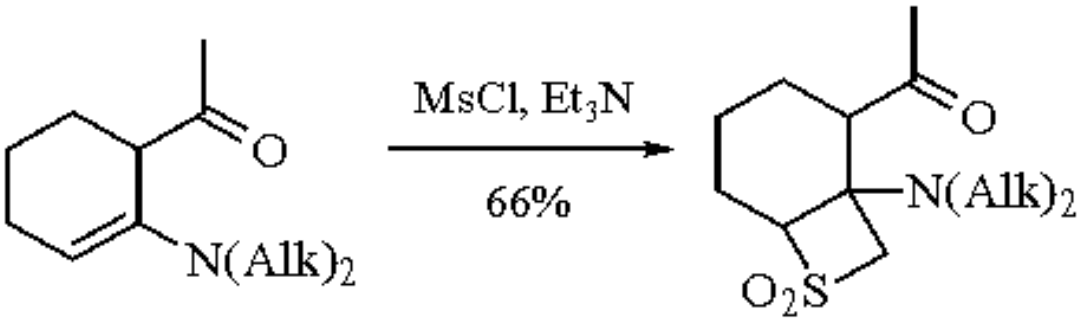

(20)

Five-membered sultones can be formed by reaction of α-hydroxy ketones with sulfene (eq 21).[29] Sulfene adds in a [4 + 2] manner across azadienes (eq 22)[30] and enones (eq 23).[31]

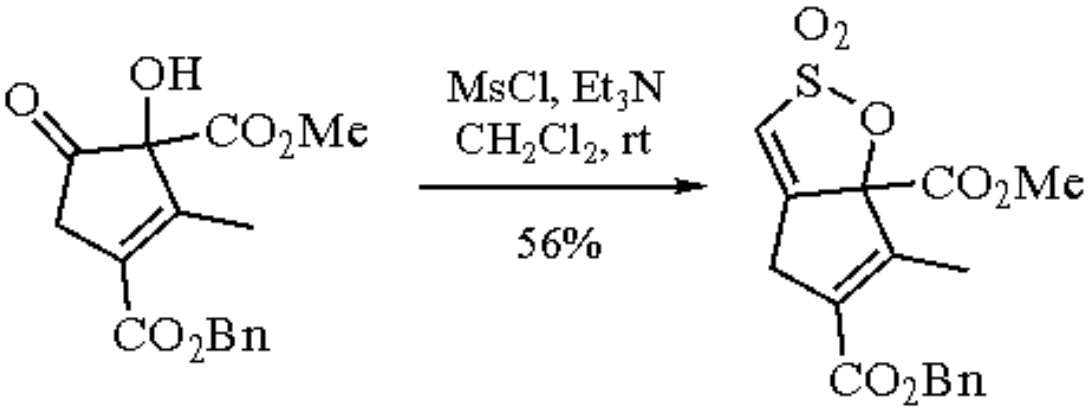

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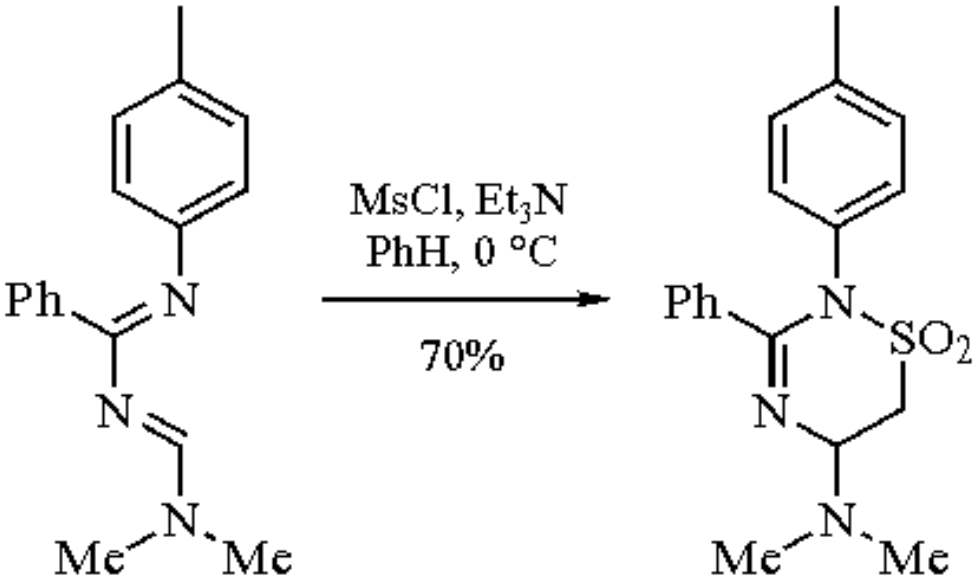

(22)

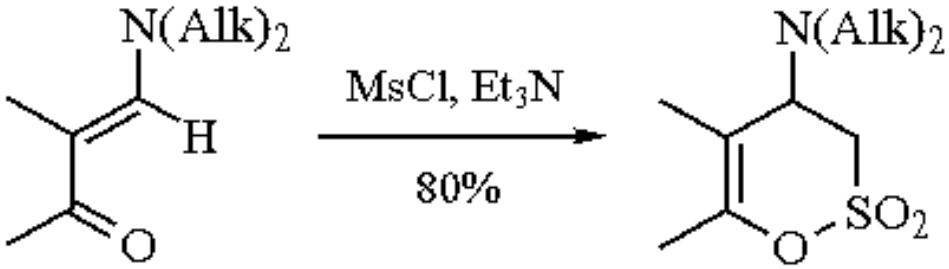

(23)

Addition Across Alkenes and Alkynes.

In the presence of a catalyst (usually ***Copper*** or ruthenium), methanesulfonyl chloride adds across alkenes and alkynes to produce β-chloro sulfones.[32] The stereochemistry of the product of addition across phenylacetylene depends on the reaction conditions used. In the absence of an added hydrochloride salt, the *cis* addition product predominates (eq 24), whereas the *trans* product is favored when the salt is added (eq 25).

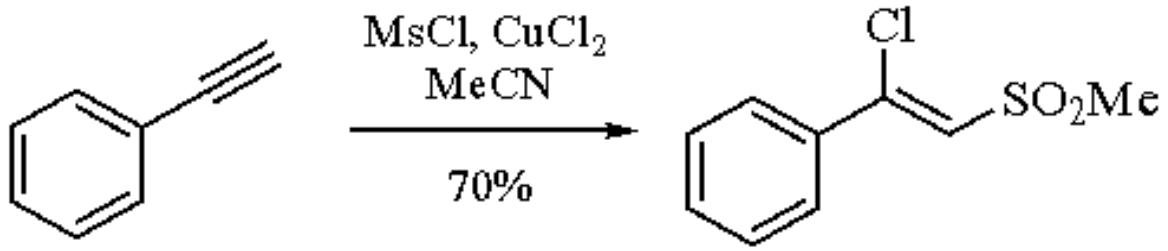

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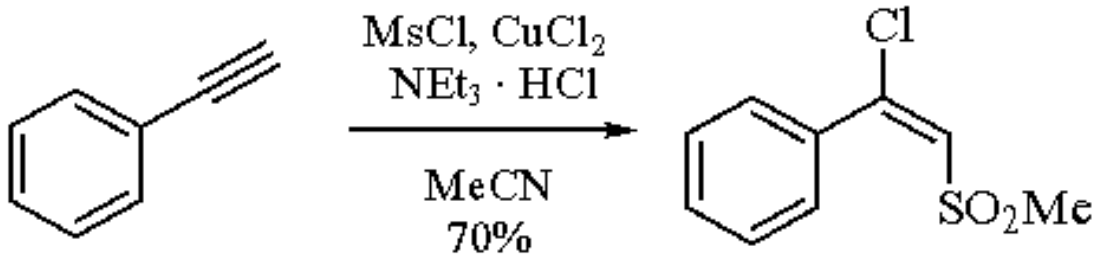

(25)

TMS-substituted alkenes and alkynes are especially useful in these reactions (eqs 26 and 27).[33] Using this methodology, allylic sulfones can be prepared (eq 28). Kamigata reported only minor success in inducing chirality into this reaction by the use of optically active ruthenium catalysts (eq 29).[34]

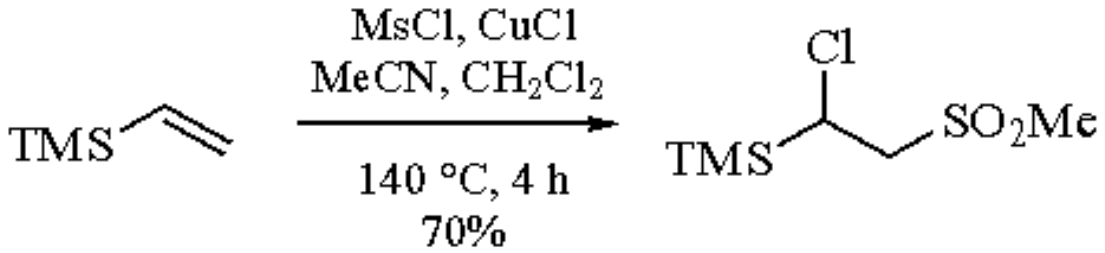

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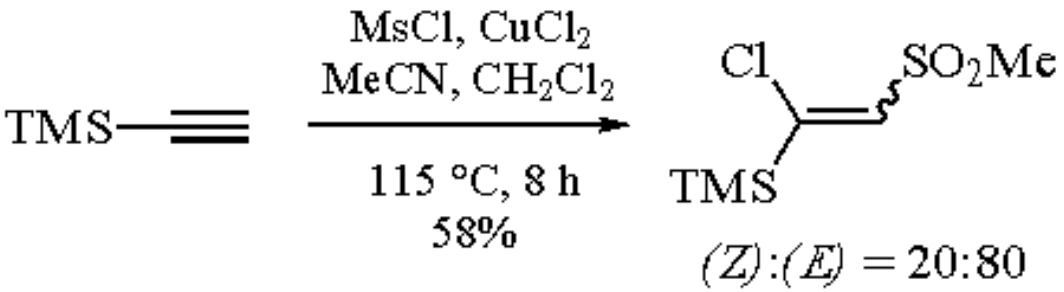

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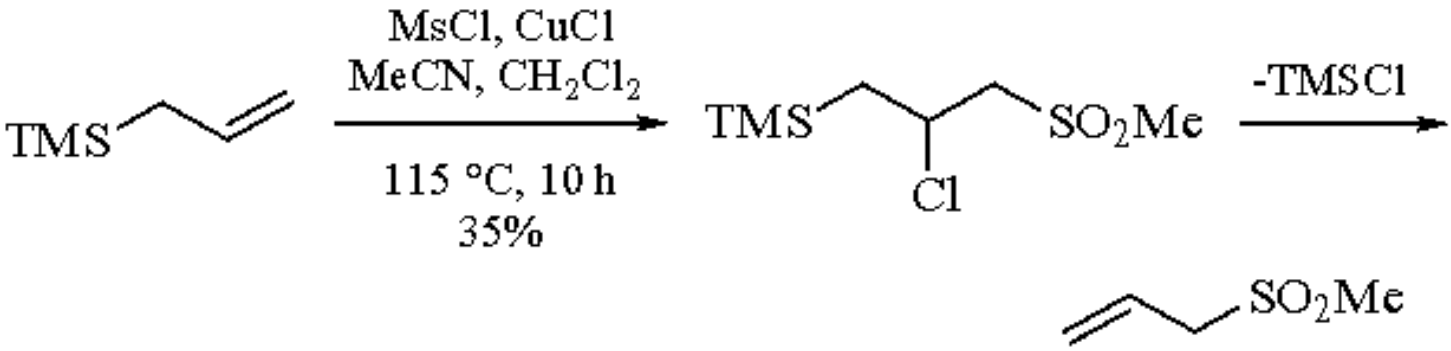

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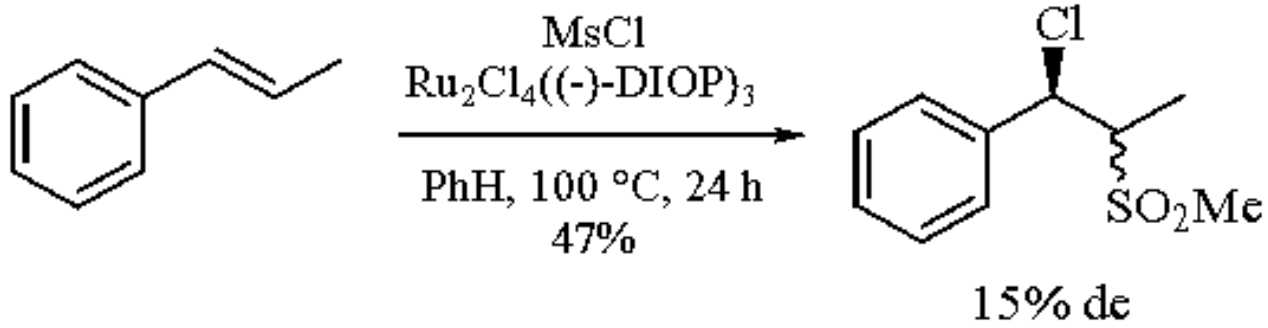

(29)

Synthesis of Vinyl and Allyl Sulfones.

In addition to the methods presented above, vinyl and allyl sulfones have been prepared by the palladium-catalyzed cross coupling of vinyl- and allylstannanes with sulfonyl chlorides (eq 30).[35]

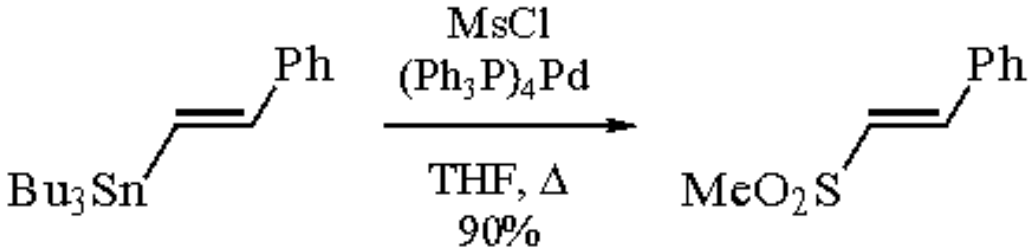

(30)

Acyliminium Cyclizations.

Formation of acyliminium ions by treatment of α-hydroxy amides with methanesulfonyl chloride is a mild way of effecting acyliminium ion cyclizations. Under these conditions, allylstannanes (eq 31)[36] and cyclic vinyl sulfides (eq 32)[37] undergo addition to the iminium ion generated. The allylstannane cyclizes with a high degree of *endo* selectivity.

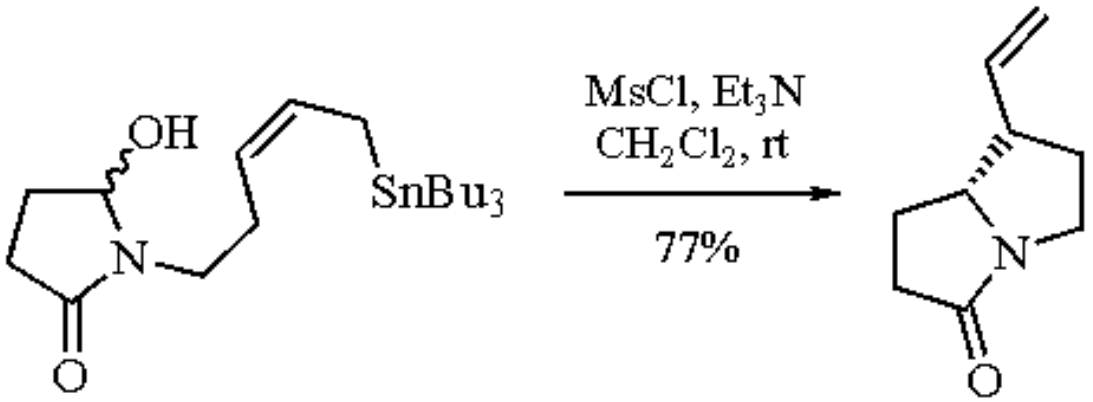

(31)

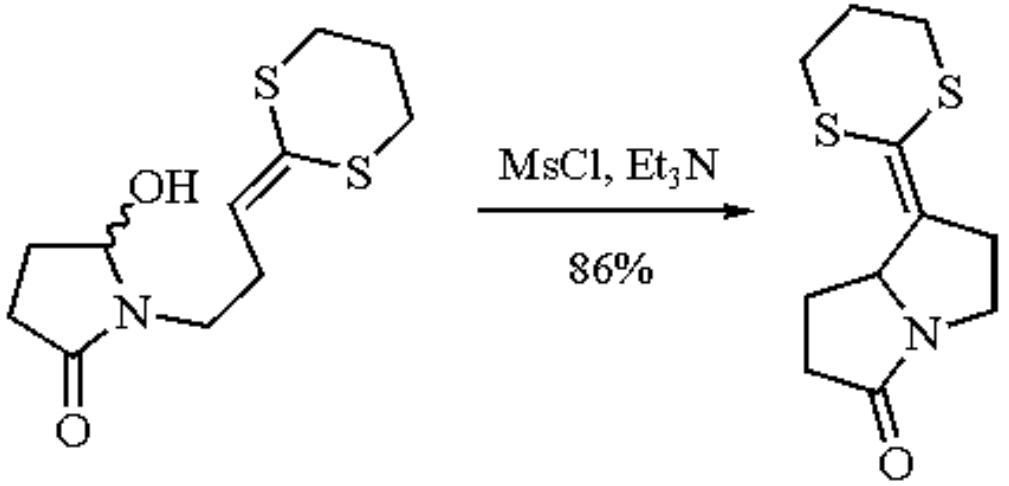

(32)

Lactone Inversion.

Lansbury demonstrated the use of mesyl chloride for lactone inversion in his synthesis of aromatin (eq 33).[38] This method is superior to the classical methods since the problems of racemization and relactonization are overcome.

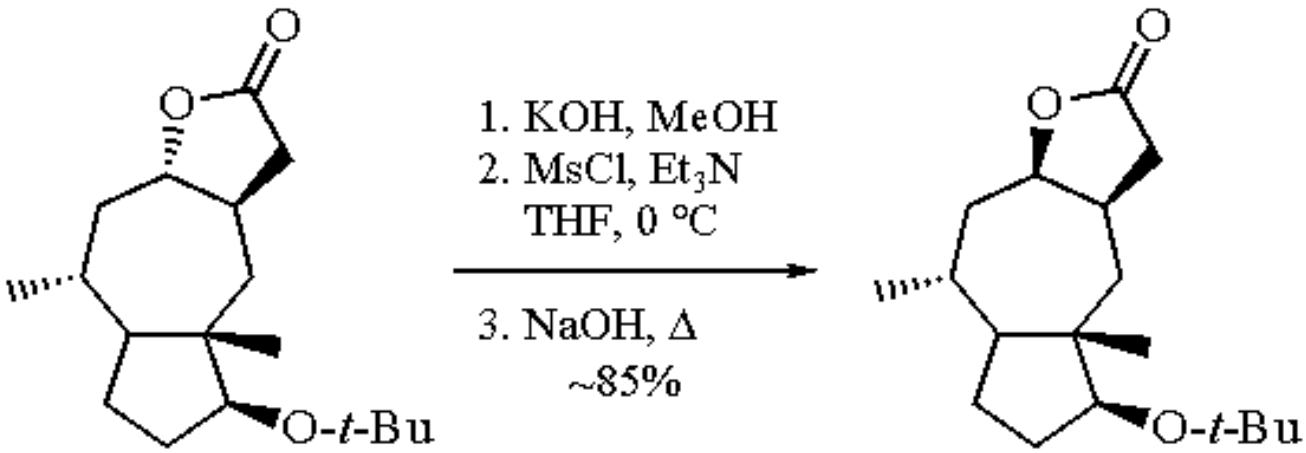

(33)

Rearrangement of Thioacetals to Aldehydes.

Sato et al. reported the rearrangement of α-hydroxy thioacetals to α-sulfenyl aldehydes (eq 34).[39] The thioacetals are prepared by the addition of the anion of methoxy(phenylthio)methane to aldehydes and ketones. This reaction is general for alkyl, allyl, and aromatic carbonyl compounds.

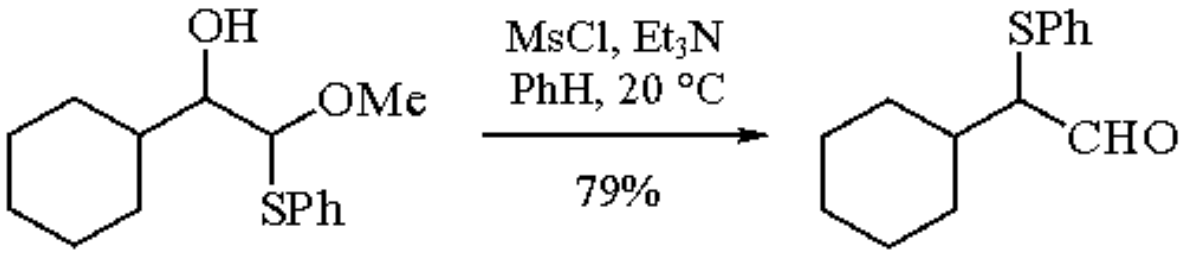

(34)

Related Reagents.

Methanesulfonyl Chloride-Dimethylaminopyridine.

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Methanesulfonyl Chloride-Dimethylaminopyridine

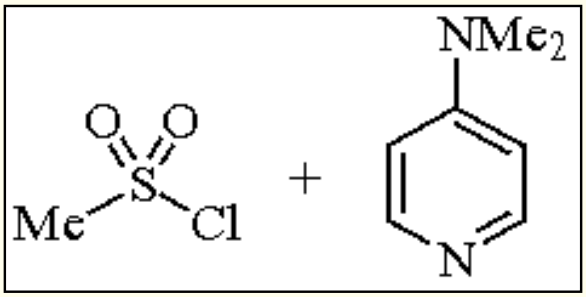

(MsCl)

[124-63-0] · CH_3ClO_2S · Methanesulfonyl Chloride-Dimethylaminopyridine · (MW 114.56) (DMAP)

[1122-58-3] · $C_7H_{10}N_2$ · Methanesulfonyl Chloride-Dimethylaminopyridine · (MW 122.19)

(conversion of alcohols to alkenes[1])

Alternate Name: Furukawa's reagent.

Physical Data: see ***Methanesulfonyl Chloride*** and ***4-Dimethylaminopyridine***.

Preparative Method: MsCl (2.5 equiv), DMAP (1.25 equiv), H_2O (1 equiv), and CH_2Cl_2 are stirred at rt for 2-3 d.

Handling, Storage, and Precautions: effective even after 6 months; for handling the components, see ***Methanesulfonyl Chloride*** and ***4-Dimethylaminopyridine***.

Conversion of Alcohols to Alkenes.

Furukawa and co-workers found that treatment of alcohols with MsCl/DMAP/H_2O/CH_2Cl_2 (Furukawa's reagent) produces the dehydrated products in good yields (eq 1).[1] In the absence of water, the dehydrated products can still be formed, but in very poor yield. Some examples of secondary alcohols undergoing this elimination have also been reported (eq 2).[2]

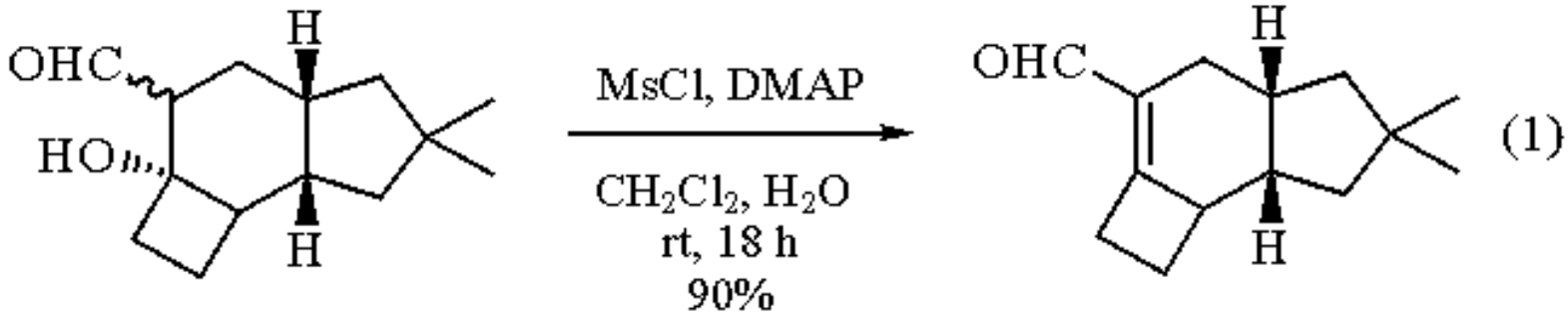

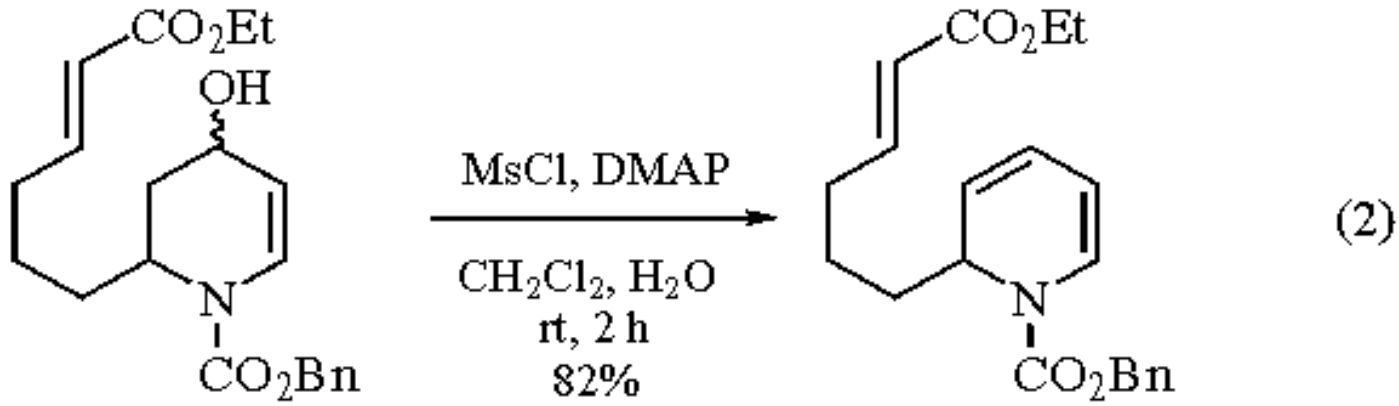

Yodav and co-workers reported that treatment of a variety of tertiary alcohols with methanesulfonyl chloride in the presence of DMAP and ***Triethylamine*** produces the dehydrated products (eq 3).[3] Acid-sensitive functionalities are not affected by the reaction conditions.

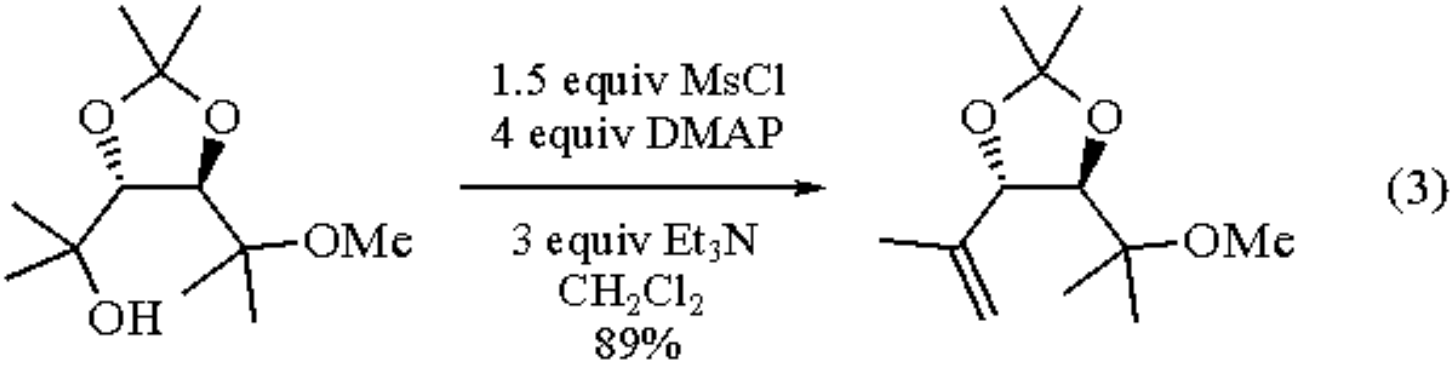

Mixtures of internal and terminal and *cis*- and *trans*-alkenes are formed in all cases. The reaction can be run at rt or below. For compounds with acid-sensitive groups, this method offers advantages over the use of other reagents used to effect this transformation.

Mesylate Formation.

Treatment of a secondary alcohol with methanesulfonyl chloride in the presence of DMAP yields the corresponding mesylate in good yield (eq 4).[4]

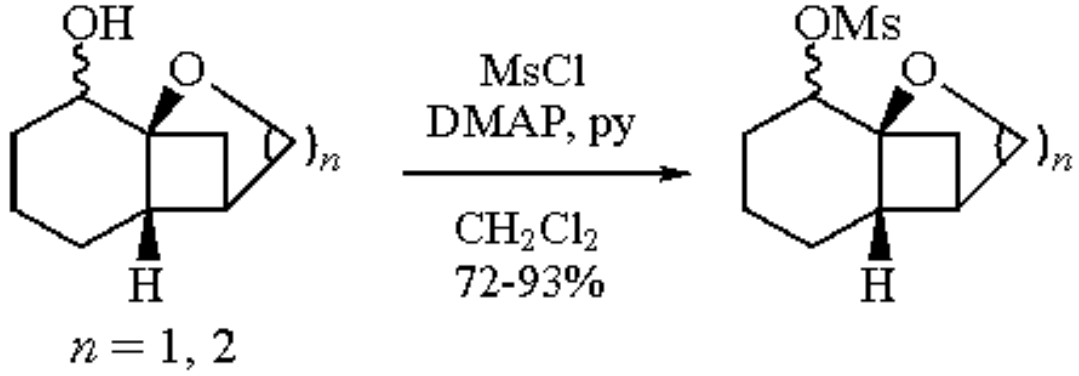

(4)

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Methanethiol

MeSH

[74-93-1] · CH_4S · Methanethiol · (MW 48.12)

(conjugate base is utilized in nucleophilic aliphatic[1] and aromatic substitution;[2] addition to alkenes,[3] alkynes,[3] and as a Michael donor;[3c] formation of *S,S*-acetals for carbonyl protection,[4] umpolung reagent formation,[5] and thionium ion generation;[6] formation of *O,S*-acetals by protecting group interconversion;[7] formation of glycosylation substrates,[8] thioesters,[9] and thiocarbamates[10])

Physical Data: mp -123 °C; bp 6 °C; *d* 0.8665 g cm^{-3} (4 °C).

Solubility: sol water at 20 °C (23.30 g L^{-1}); very sol ethyl alcohol, ether.

Form Supplied in: gas; lecture bottle; widely available.

Handling, Storage, and Precautions: flammable, corrosive gas with a pungent odor. It is imperative that methanethiol be used in a well-ventilated hood. Exposure can be minimized by slow distillation from the storage container into the reaction vessel[11] and/or trapping the boil-off in a solution containing a strong oxidizing agent (e.g. $KMnO_4$[12]).

Nucleophilic Substitutions.

Reaction of methanethiolate (MeS^-), prepared from the reaction of MeSH with base, with primary and secondary alkyl halides or sulfonates provides methyl alkyl sulfides in good to excellent yields. As with alkoxide nucleophiles, primary substrates are most useful, secondary substrates provide lower yield, and elimination predominates with tertiary substrates. Displacement of appropriate primary chlorides provides sulfinyl sulfides (eq 1),[13] secondary tosylates can afford methylthio derivatives of proline (eq 2),[14] and S_N2' addition to substituted cyclopentenes results in stereospecific *anti* addition (eq 3).[15]

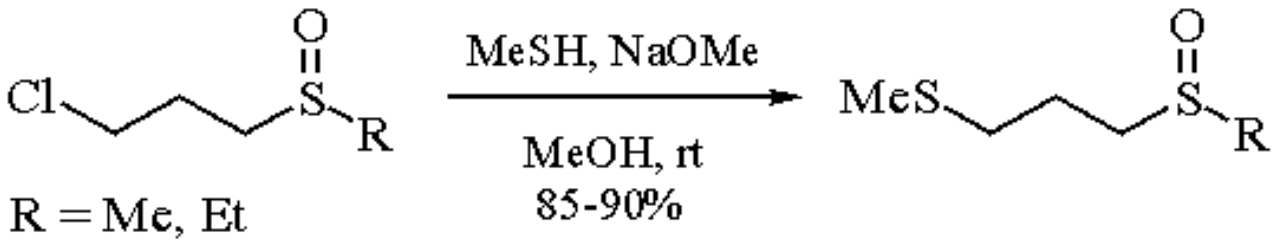

(1)

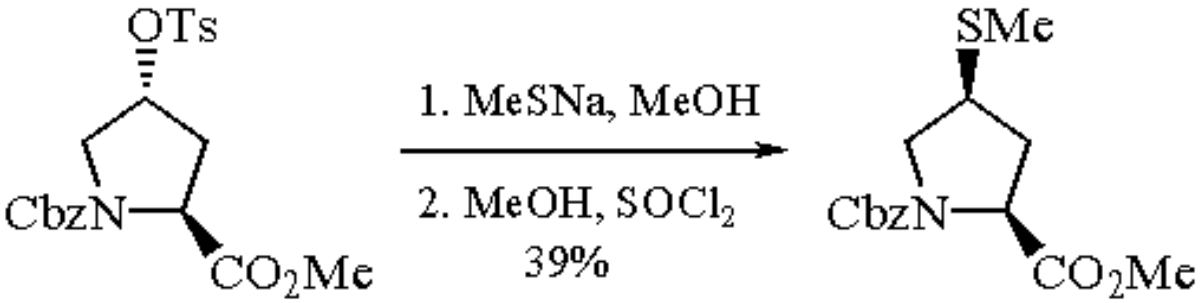

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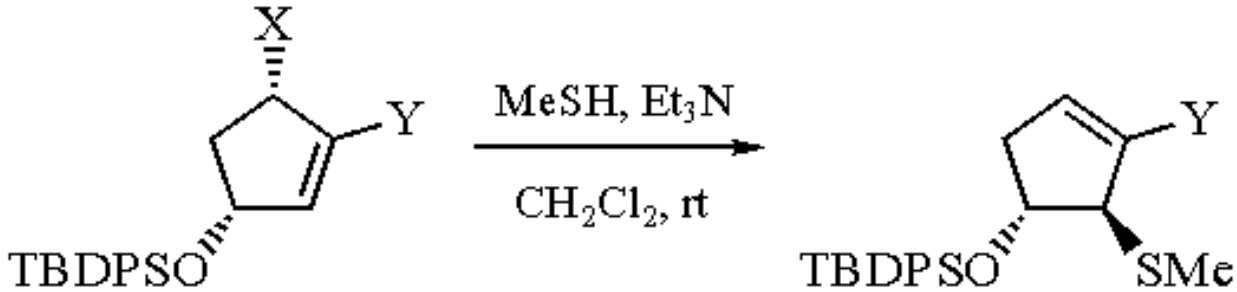

(3)

$X = OSO_2Me$	$Y = CO_2Me$	76%
$X = NMe_3BF_4$	$Y = CO_2Me$	91%
$X = OSO_2Me$	$Y = SO_2Ph$	73%
$X = NMe_3BF_4$	$Y = SO_2Ph$	52%

Epoxides undergo nucleophilic cleavage to provide β-hydroxy sulfides. Epichlorohydrin reacts with methanethiolate to provide an important intermediate for the generation of 1,3-bis(methylthio)allyllithium (eq 4),[11] α,β-epoxy ketones yield α-thiomethyl enones,[16] and 4-methyloxetanone provides β-(methylthio)butyric acid (eq 5).[17] Nucleophilic aromatic substitution of activated aryl halides is well documented[2] and even unactivated aryl halides react with methanethiolate in HMPA to give substituted arenes (eq 6),[18] with other alkanethiolates demonstrating this reactivity in various aprotic solvents (DMA,[19] DMF,[20] and polyglymes[21]).

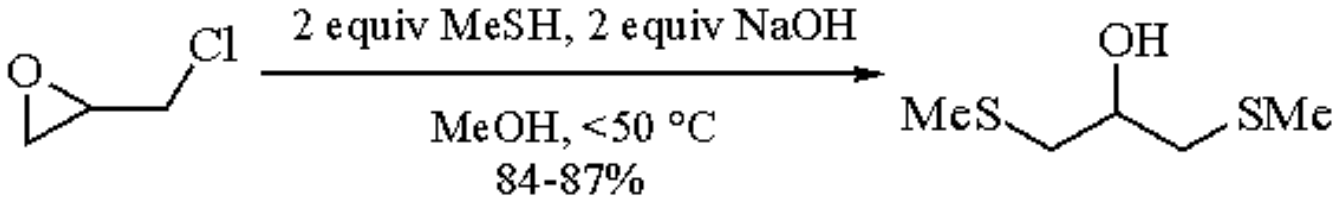

(4)

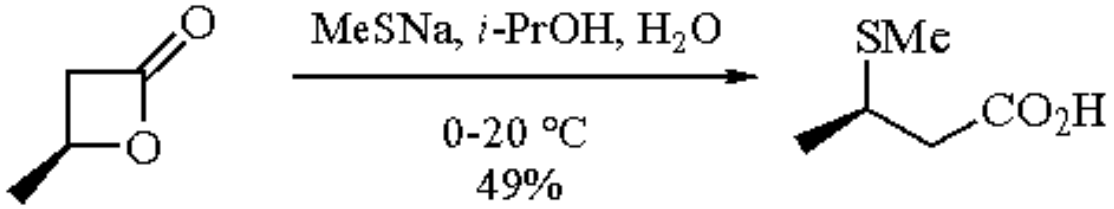

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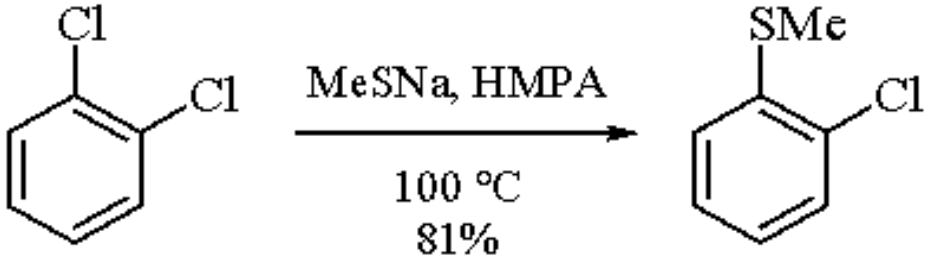

(6)

Additions to Carbon-Carbon Multiple Bonds.

Electrophilic and radical addition of methanethiol and nucleophilic addition of methanethiolate to carbon-carbon multiple bonds is well documented.[3] Recent examples include the radical addition to α-allylglycine derivatives to provide trifunctional amino acids,[22] the stereospecific nucleophilic addition of potassium methanethiolate to alkyl alkynyl sulfides (eq 7),[23] under phase-transfer catalysis, and addition to propargyl sulfone.[24] Methanethiolate undergoes Michael addition to alkenes conjugated to electron-withdrawing substituents.[3c] When Michael addition is followed by protonation at low temperatures, high diastereoselectivity is obtained with nitro alkenes (eq 8).[25]

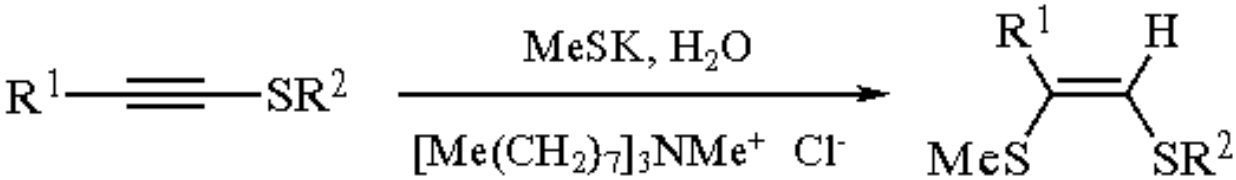

(7)

$R^1 = Me$, $R^2 = Et$	86%
$R^1 = Et$, $R^2 = Me$	88%

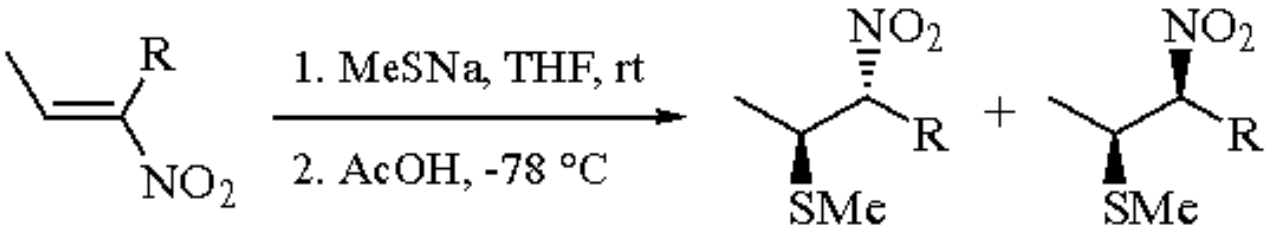

(8)

R = Me	64%	90:10
R = Ph	82%	95:5

Formation of *S,S*- and *O,S*-Acetals.

Thioacetals are generally regarded as robust protecting groups for carbonyl compounds. Reactions of aldehydes, ketones, or acetals with MeSH and catalytic Brønsted or Lewis acid provides dimethyl dithioacetals, generally in good to excellent yield.[4] For labile substrates, ***Titanium(IV) Chloride*** at low temperature has proven successful (eq 9).[12a] Acetal exchange occurs readily with MeSH in the presence of ***Bromodimethylborane*** to give *O,S*-acetals, allowing conversion of MEM and MOM ethers into (methylthio)methyl (MTM) ethers (eq 10).[7] Formation of methyl thioglycosides (eq 11)[8] with the methanethiol analog methyl trimethylsilyl sulfide ($MeSSiMe_3$) provides the 1,2-*trans*-

thioglycoside stereospecifically.

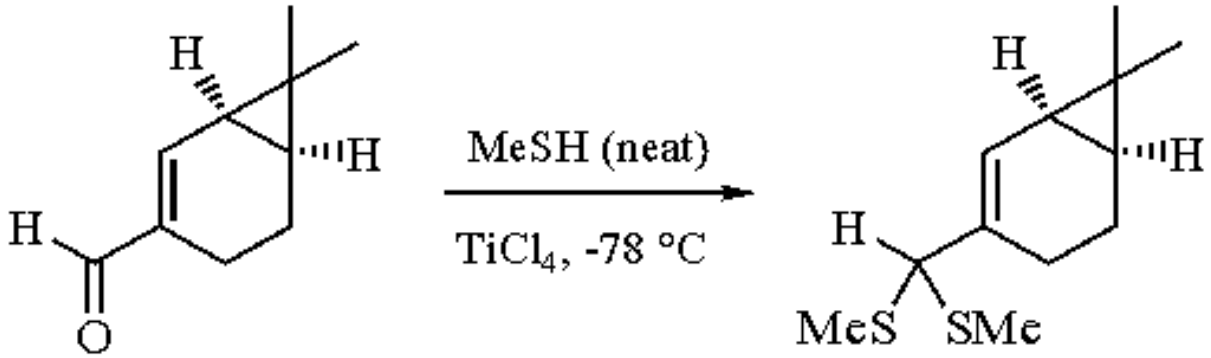

(9)

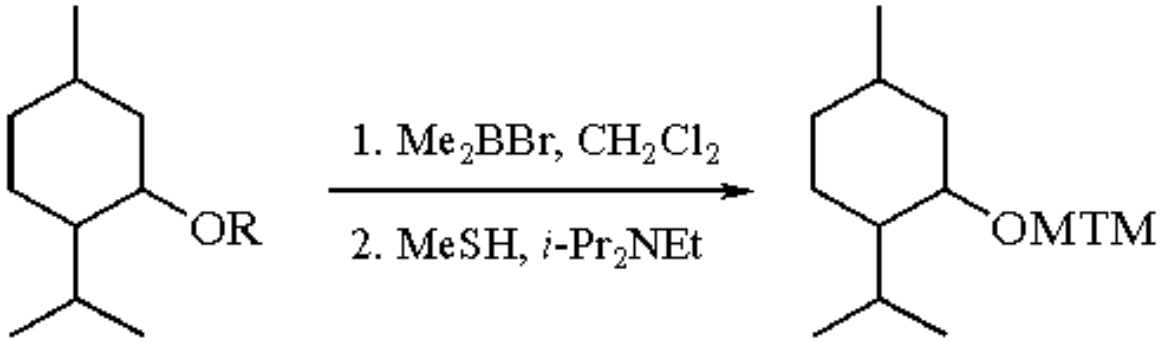

(10)

R = MOM 91%
R = MEM 89%

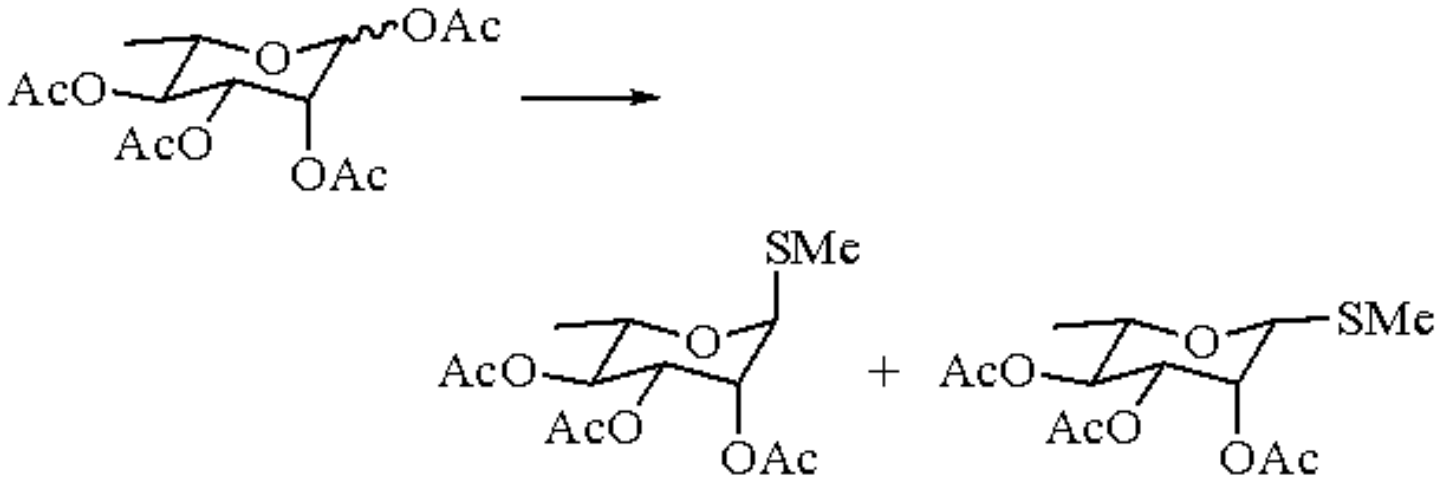

(11)

MeSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0-15 °C	7:1	86%
MeSTMS, $BF_3 \cdot Et_2O$, CH_2Cl_2, 25 °C, 36 h	100:0	66%

The utility of these thioacetals includes desulfurization with ***Raney Nickel*** to give methylene or methyl compounds[26] and the well documented[5] use as acyl anion equivalents or umpolung reagents upon deprotonation. Dimethyl dithioacetals provide intermediate thionium ions upon treatment with ***Dimethyl(methylthio)sulfonium Tetrafluoroborate*** (DMTSF); these undergo inter- and intramolecular additions with allylstannanes,[27] silyl enol

ethers,[6,28] vinylsilanes,[6] and indoles (eq 12).[29] Methyl *S*-glycosides undergo stereospecific glycosylation under the influence of nitrosyl tetrafluoroborate.[8]

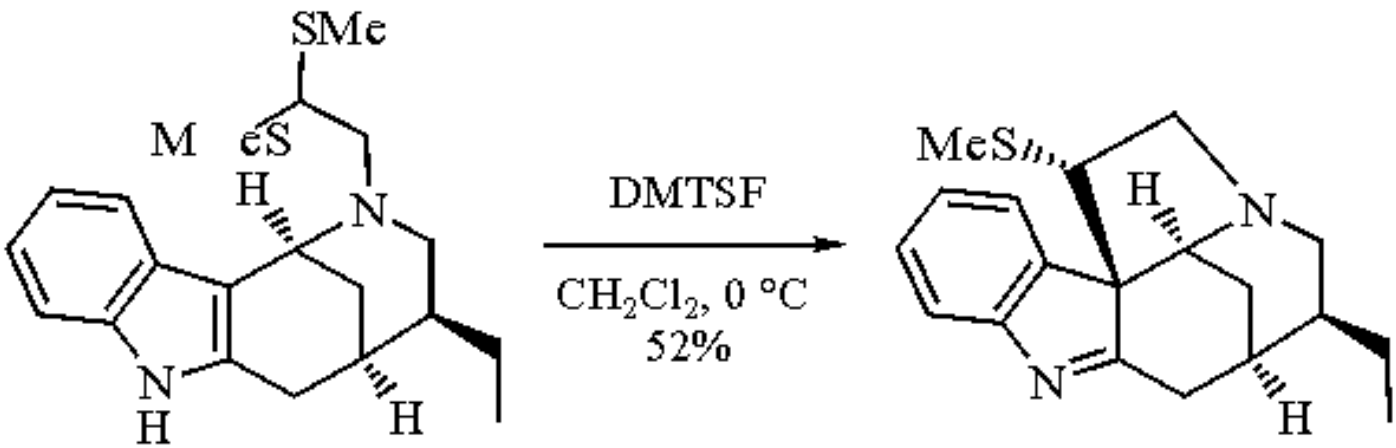

(12)

Other Applications.

Methanethiol reacts with derivatized carboxylic acids and isocyanates to provide thioesters[9] and thiocarbamates,[10] respectively. Lithium methanethiolate cleaves hindered methyl esters to the corresponding acids[30] and, under forcing conditions, methyl phenyl ethers to phenols. Pyrrolizidinediones have been reduced with ***Sodium Borohydride*** in EtOH to give the corresponding ethoxy lactams. Exchange with MeSH under acidic conditions then provides the lactam thioether (eq 13).[31] Reduction of analogous pyrrolizidinediones in the presence of MeSH provides the corresponding lactam thioethers directly (eq 14).[32]

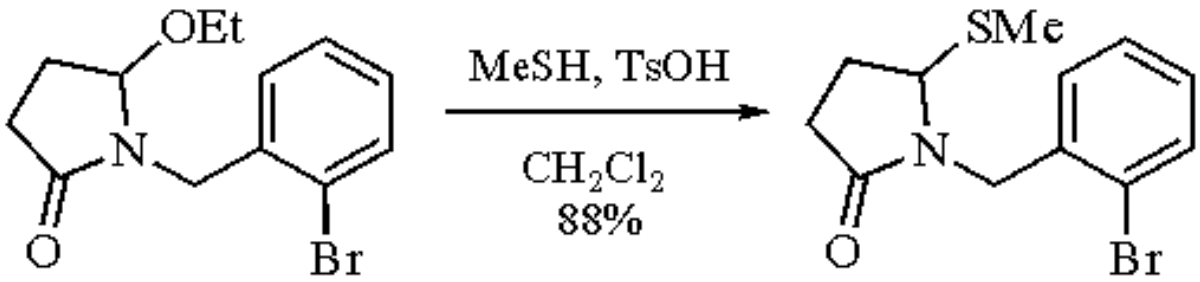

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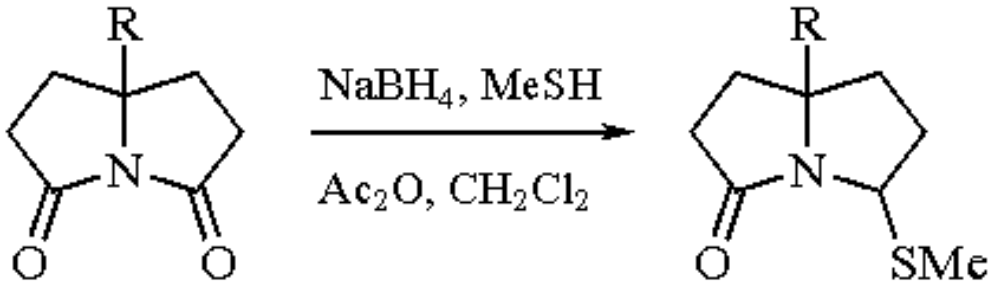

(14)

R = H, 44%; Me, 54%; $CH_2CH_2CO_2Me$, 20%

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Methanesulfonamide

$MeSO_2NH_2$

[3144-09-0] · CH_5NO_2S · Methanesulfonamide · (MW 95.14)

(methanesulfonamide-derived reagents are used in the synthesis of porphyrins[1] and in Mitsunobu reactions;[2] methanesulfonamide itself is useful in the synthesis of nitriles,[4] *N*-sulfonyloxaziridines,[5] macrocycles,[6] site-directed antagonists,[7,8] and as a catalyst turnover reagent in osmium-catalyzed asymmetric dihydroxylations[9,10])

Physical Data: mp 91-92 °C.

Form Supplied in: white crystalline solid; widely available.

Handling, Storage, and Precautions: should be stored in a cool dry place. It is an irritant and should be handled carefully. Use in a fume hood.

Methanesulfonamide-Derived Reagents.

N-(2-Methylthio-1-*p*-toluenesufonyl)methanesulfonamide, derived from methanesulfonamide, methylthioacetaldehyde dimethyl acetal and *p*-toluenesulfenic acid, has been used as a key intermediate in the synthesis of symmetrically substituted porphyrins (eq 1).[1]

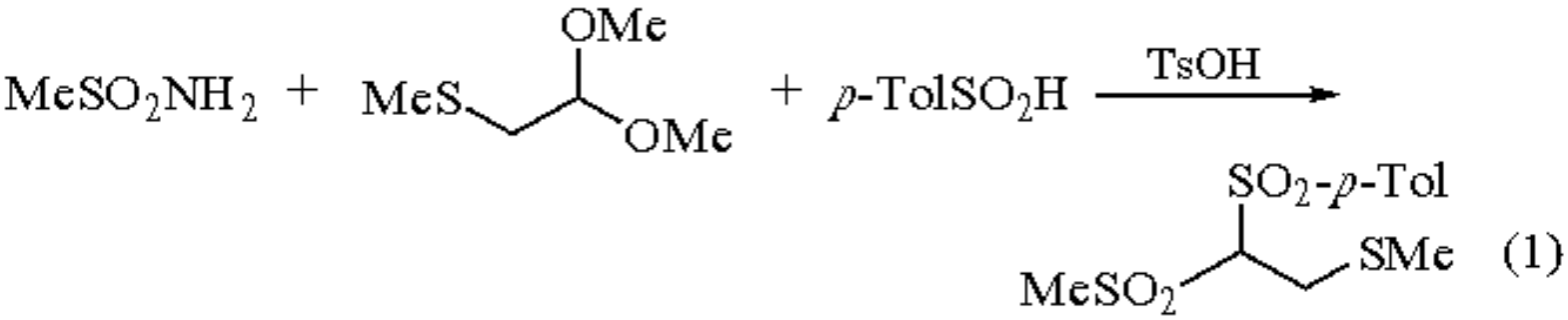

t-Butyl ((2-(trimethylsilyl)ethyl)sulfonyl)carbamate (**3**), a reagent for use in the Mitsunobu reaction, has been prepared from methanesulfonamide (eq 2).[2] Treatment of methanesulfonamide with ***n-Butyllithium*** in THF, followed by acylation with ***t-Butyl Azidoformate*** in the presence of ***Sodium Hydride*** and ***N,N,N´,N´-Tetramethylethylenediamine***, gave sulfonamide (**1**). Treatment of (**1**) with 2 equiv of ***Lithium Diisopropylamide*** gave the dianion (**2**). Addition of ***(Iodomethyl)trimethylsilane*** to (**2**) gave (**3**). An alternate route to (**3**) involves deprotonation of the known sulfonamide (**4**)[3] with ***Methyllithium***, followed by acylation with *t*-butyl azidoformate in the presence of sodium hydride (eq 3). The

use of this reagent in Mitsunobu reactions has been well demonstrated.[2]

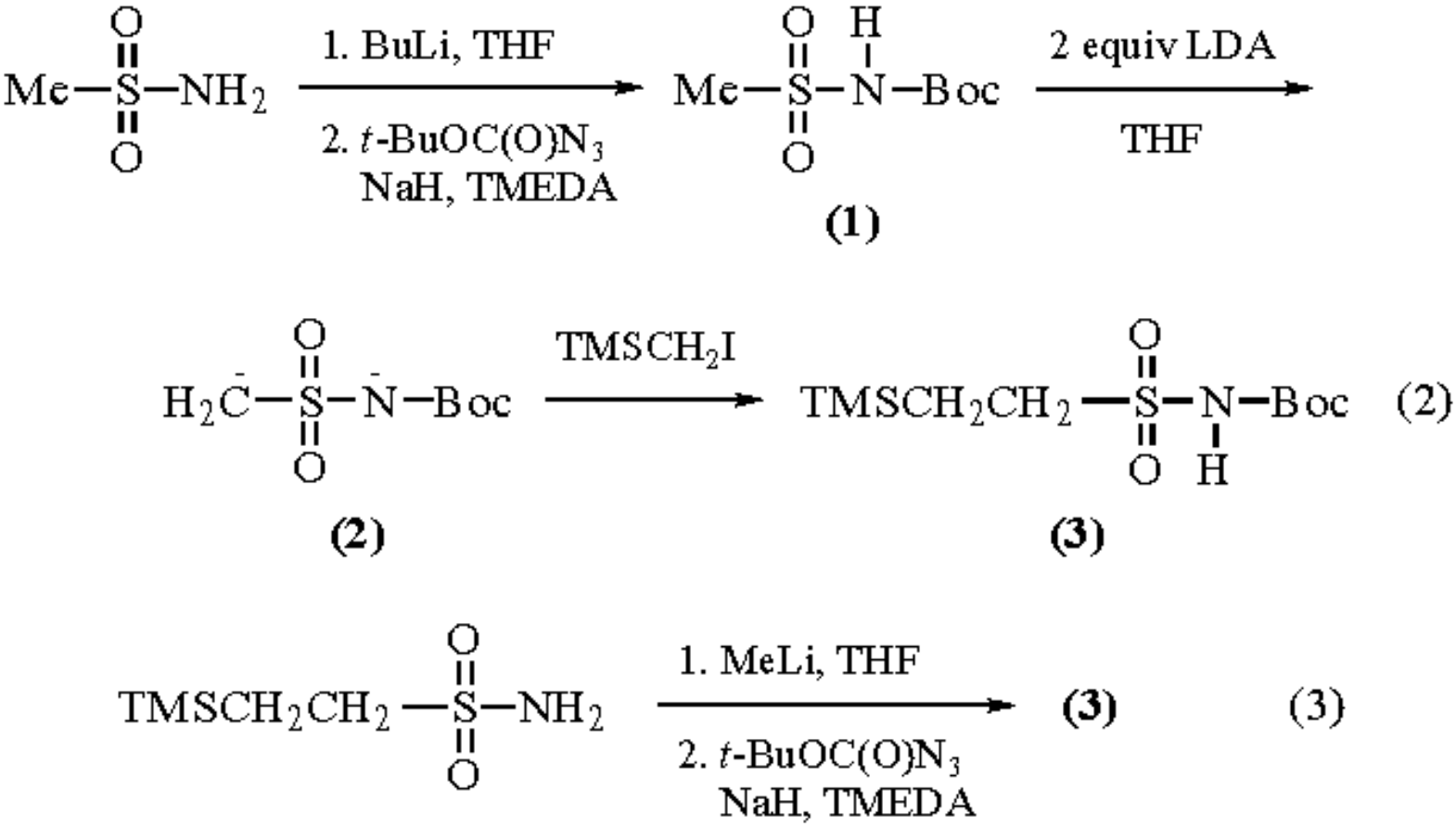

Use in Synthetic Transformations.

The classical procedure for conversion of carboxylic acids to the corresponding nitriles through amides is simplified by the use of methanesulfonamide as the nitrogen source.[4] A variety of chlorobenzonitrile isomers and homologs, which are otherwise difficult to prepare, are made accessible through this route (eq 4).

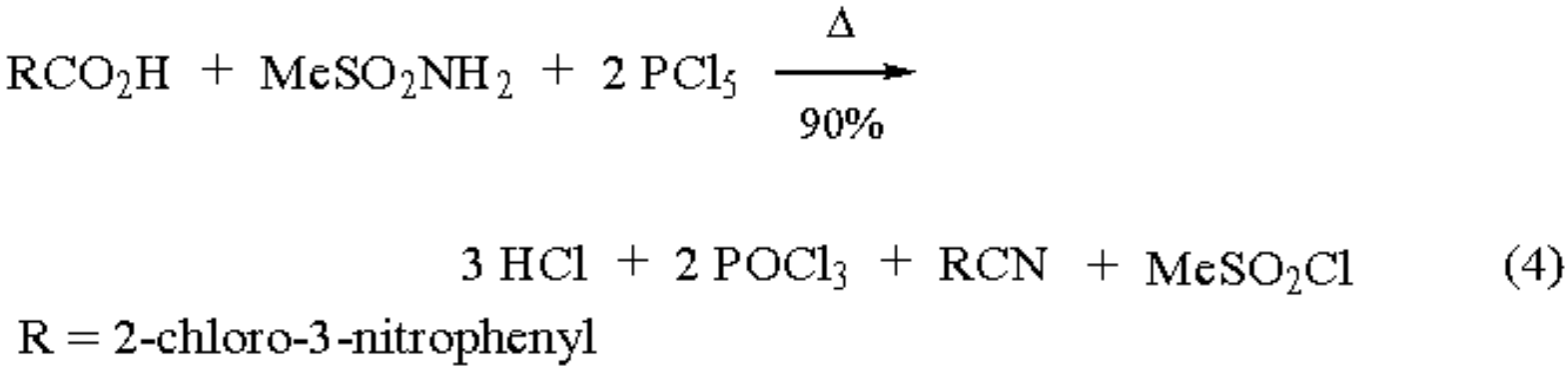

N-Sulfonyloxaziridines are gaining importance as potential neutral chiral oxidants. *N*-Methanesulfonylimines, the precursors for the synthesis of *N*-sulfonyloxaziridines, are conveniently prepared by the reaction of methanesulfonamide with aromatic aldehydes (eq 5).[5]

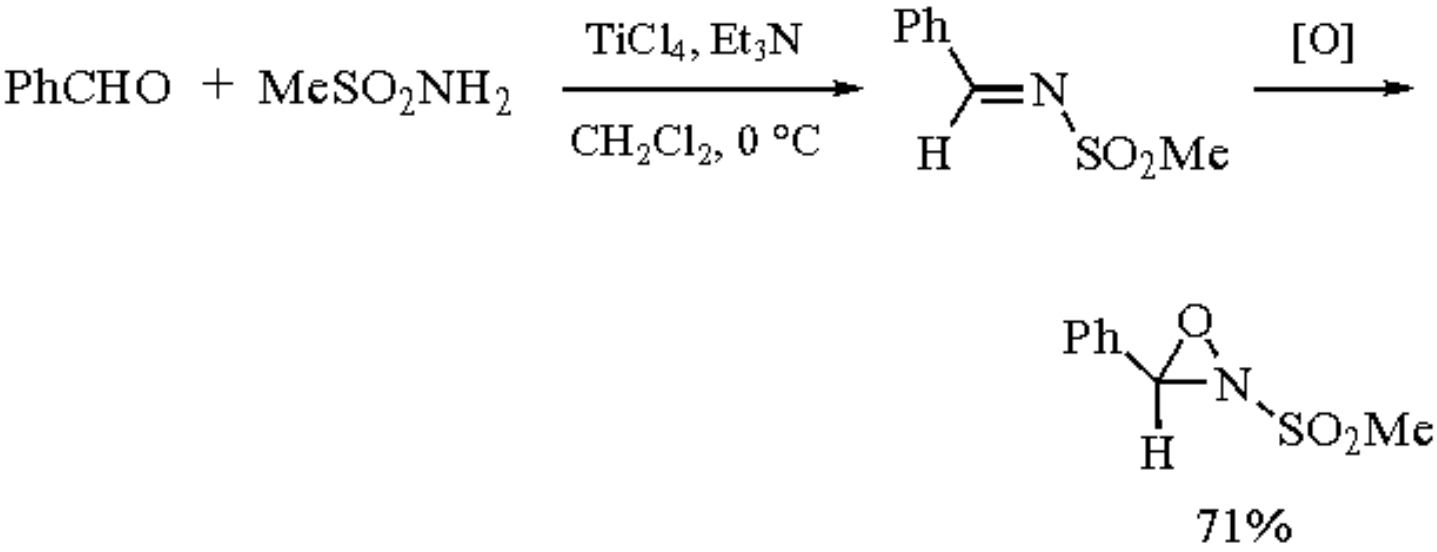

(5)

Methanesulfonamide has been used as a locking fragment in the template synthesis of the azacyclam family of macrocycles. Methanesulfonamide in the presence of ***Formaldehyde***, ***Triethylamine***, and Cu^{II} effectively closes the open-chain tetramine 1,9-diamino-3,7-diazanonane to give (3-methanesulfonyl-1,3,5,8,12-pentaazacyclotetradecane)dinitratocopper(II) as a crystalline solid (eq 6).[6]

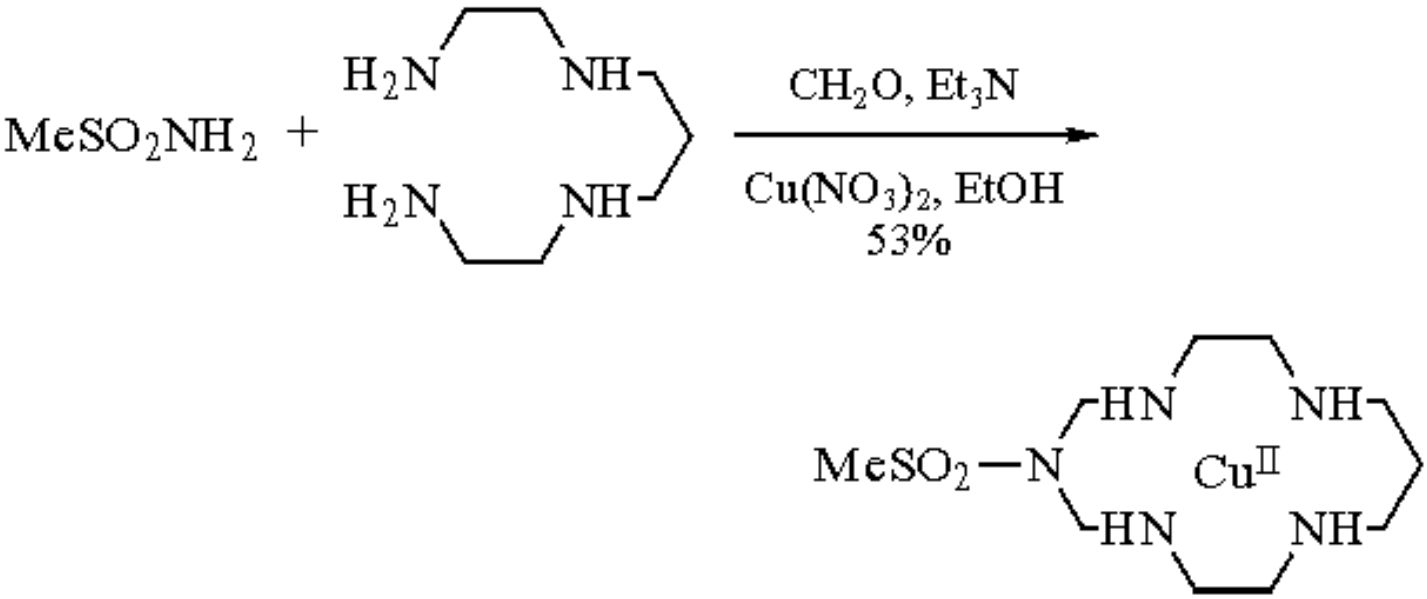

(6)

Methanesulfonamide reacts with 6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid to give the corresponding *N*-methylsulfonyl derivative, which is a well-characterized antagonist at the glycine site of the NMDA receptor and AMPA receptor (eq 7).[7]

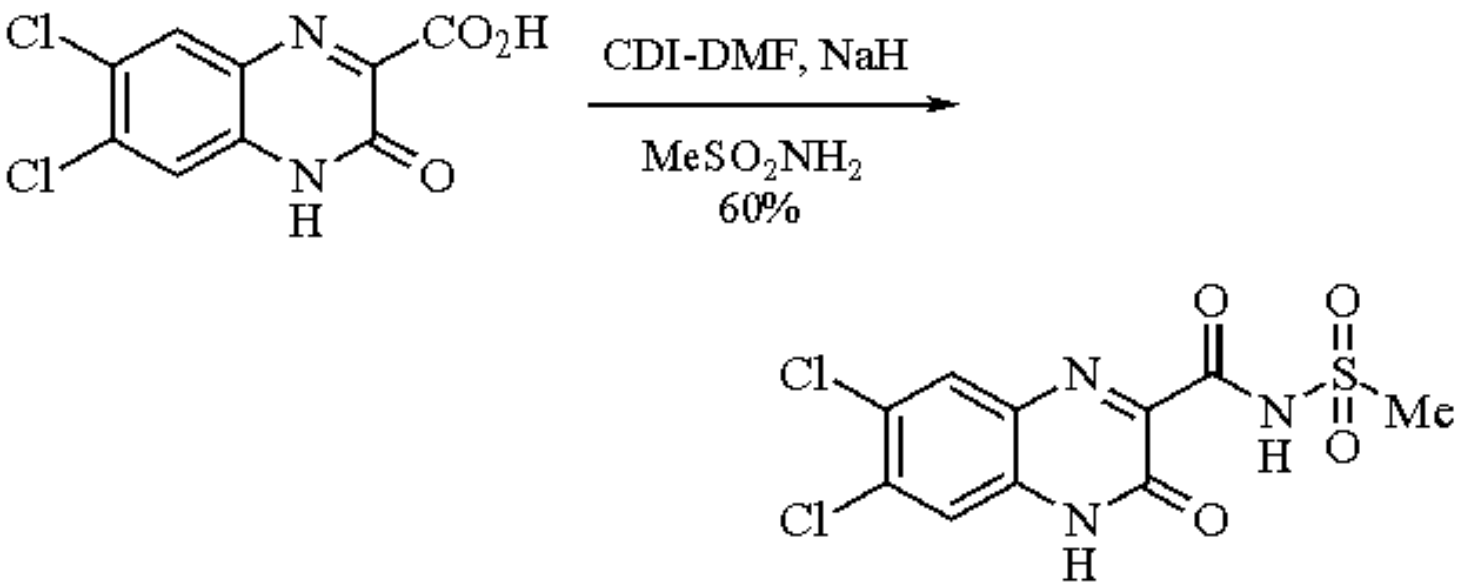

(7)

A highly potent histamine H_2 receptor antagonist has been prepared by reaction of methanesulfonamide with the corresponding imidate (eq 8).[8]

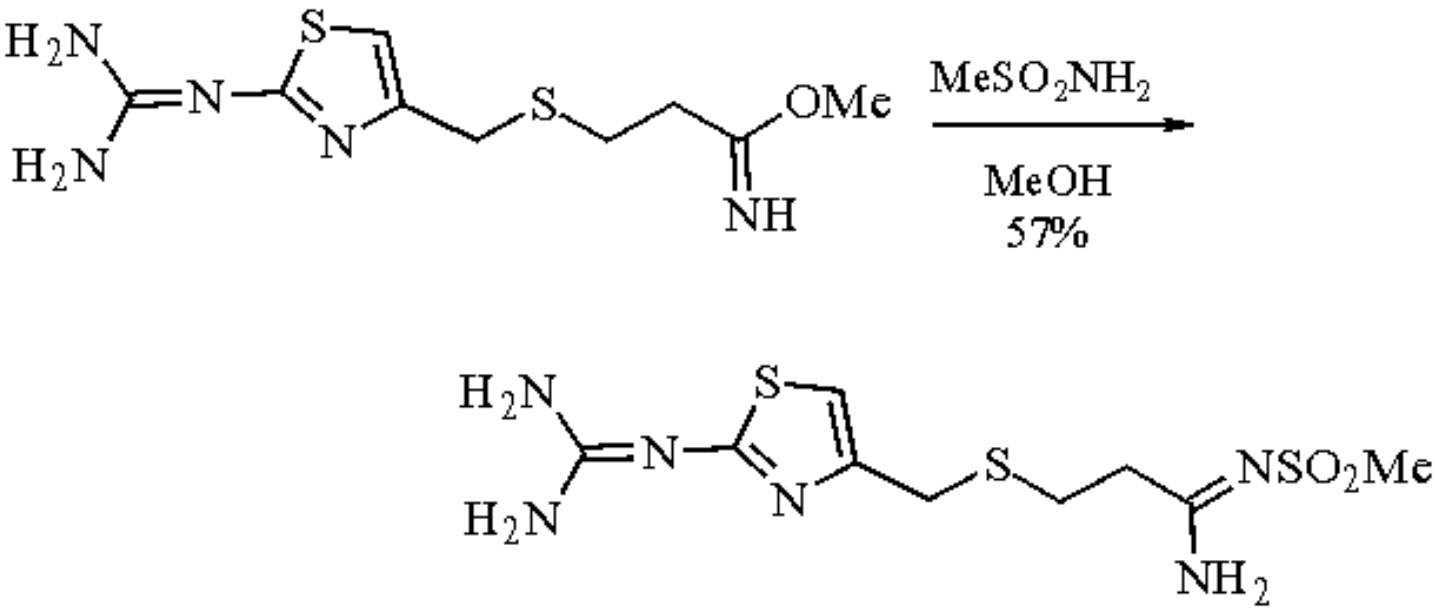

(8)

Use as a Catalyst Turnover Reagent.

In the case of osmium-catalyzed asymmetric dihydroxylation of nonterminal trisubstituted alkenes, 1,2-disubstituted alkenes,[9] and α,β- and β,γ-unsaturated amides,[10] where the hydrolysis of the osmate ester is turnover limiting, the presence of methanesulfonamide leads to shorter reaction times (eq 9).

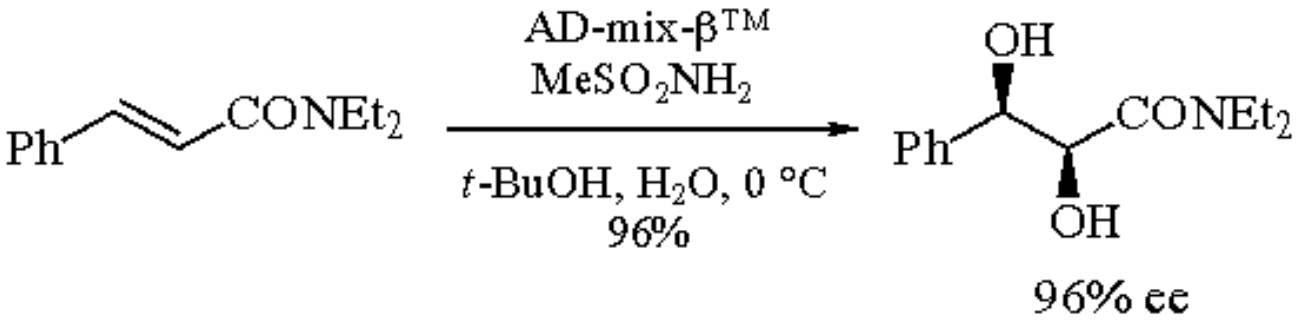

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Methoxyacetonitrile

$MeOCH_2CN$

[1738-36-9] · C_3H_5NO · Methoxyacetonitrile · (MW 71.09)

(a protected formaldehyde equivalent that undergoes metalation and addition to various electrophiles and that intercepts various nucleophiles at the cyano group)

Physical Data: bp 49 °C/60 mmHg,[1] 111 °C/624 mmHg,[2] 120-121 °C/759 mmHg;[3] *d* 0.956 g cm^{-3}.

Solubility: sol ethyl ether, chloroform, acetone, most common organic solvents.

Form Supplied in: liquid. *Drying:* distillation from phosphorus pentoxide.

Preparative Method: from ***Formaldehyde***, ***Sodium Cyanide***, and ***Dimethyl Sulfate***.[4]

Handling, Storage, and Precautions: an organic cyanide; should be handled with due care in a fume hood.

Metalation.

The deprotonation of methoxyacetonitrile with various bases (e.g. ***n-Butyllithium***, ***Lithium Diisopropylamide***, ***Sodium Hydride***) produces the corresponding nitrile-stabilized anion. Self-condensation of lithiomethoxyacetonitrile *[69521-26-2]* occurs in some cases.[5]

Additions to Carbonyl Electrophiles.

The addition of the nitrile-stabilized anion of methoxyacetonitrile to aldehydes and ketones gives β-hydroxy-α-methoxy nitriles (eq 1)[6] or α-methoxyacrylonitriles (eq 2)[6,7] depending on the reaction conditions. In the latter case the α-methoxyacrylonitriles are protected acyl cyanides, and demethylation using benzyl thiol in the presence of an amine provides acetamides (eq 2).[6] Bromination[5,8] of methoxyacetonitrile and an Arbuzov reaction provides 2-(diethoxyphosphono)-2-methoxyacetonitrile,[5] a useful reagent for the conversion of carbonyl compounds to α-methoxyacrylonitriles (Horner-Emmons-Wittig reaction) that complements the direct condensation of methoxyacetonitrile with carbonyl compounds (eq 2). The addition of methoxyacetonitrile to a putative iminium salt, derived from isopropoxy- or *t*-butoxybis(dimethylamino)methane, provides an avenue to β-dimethylamino-α-methoxyacrylonitriles.[9,10]

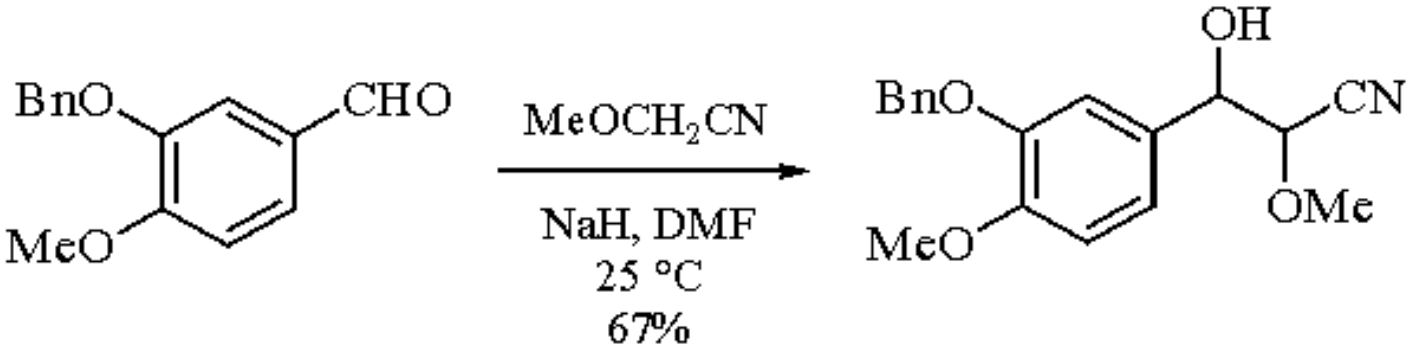

(1)

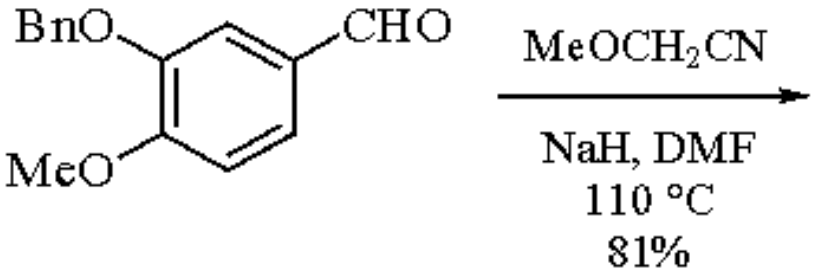

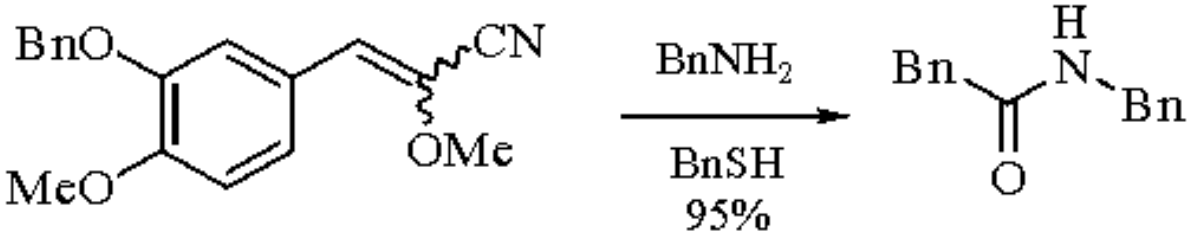

(2)

Additions to the Cyano Group.

The nucleophilic addition of Grignard[11-16] or organolithium reagents[17] as well as the acid-catalyzed addition (Hoesch reaction) of activated arenes[18] to the cyano group of methoxyacetonitrile leads to α-methoxy ketones. These products are useful intermediates for the synthesis of heterocycles (e.g. coumarins,[18] flavanones,[18-22] quinolinones,[14] pyrazoles[12]) or the synthesis of carbocycles.[15] Nucleophilic additions to methoxyacetonitrile followed by an intramolecular *N*-alkylation provides a one-step construction of 3,4-dihydroquinolines, albeit in modest yield.[23] The sequential addition of a Grignard reagent and an organolithium reagent to methoxyacetonitrile permits the addition of two alkyl groups to afford β-methoxy primary amines $MeOCH_2CR_2NH_2$, having an adjoining quaternary carbon.[24]

Other Reactions.

The acid-catalyzed addition of alcohols with methoxyacetonitrile (Pinner reaction) produces α-methoxy orthoesters[25,26] and the cyano group of methoxyacetonitrile intercepts carbocations (Ritter reaction) leading to decalins[27] or heterocycles.[28,29] A cobalt-catalyzed cycloaddition of methoxyacetonitrile to α,o-diynes leads to tetrahydroisoquinolines[30] and a [3 + 2] cycloaddition of the anion of ***p-Tolylthiomethyl Isocyanide*** to methoxyacetonitrile provides a substituted imidazole.[31]

Related Reagents.

Acetonitrile; ***N,N-Diethylaminoacetonitrile***; ***Lithioacetonitrile***; ***p-Tolylthiomethyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***.

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Methoxyacetyl Chloride

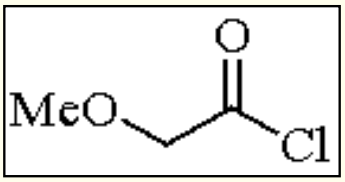

[38870-89-2] · $C_3H_5ClO_2$ · Methoxyacetyl Chloride · (MW 108.53)

(acylating reagent;[1] precursor to methoxyketene;[4] in combination with Lewis acids is a reagent for aromatic chloromethylation[12])

Physical Data: bp 112-113 °C; *n*D20 1.4190; *d* 1.87 g cm^{-3}.

Solubility: miscible with most nonprotic organic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: reacts readily with water, alcohols, and other protic solvents. Stable to storage at rt for long periods if kept moisture-free in closed bottles.

Acylation: Generation of Methoxyketene.

Methoxyacetyl chloride has been used for the preparation of esters and amides by reaction with alcohols and amines.[1,2] Schotten-Baumann conditions or tertiary amine catalysis (eq 1)[3] gives excellent yields. Use of ***Triethylamine***, most commonly at rt, results in smooth generation of methoxyketene, [2 + 2] cycloaddition of which with both cyclic and acyclic imines (eq 2)[4] gives stereopure β-lactams in good to excellent yield.[5-8]

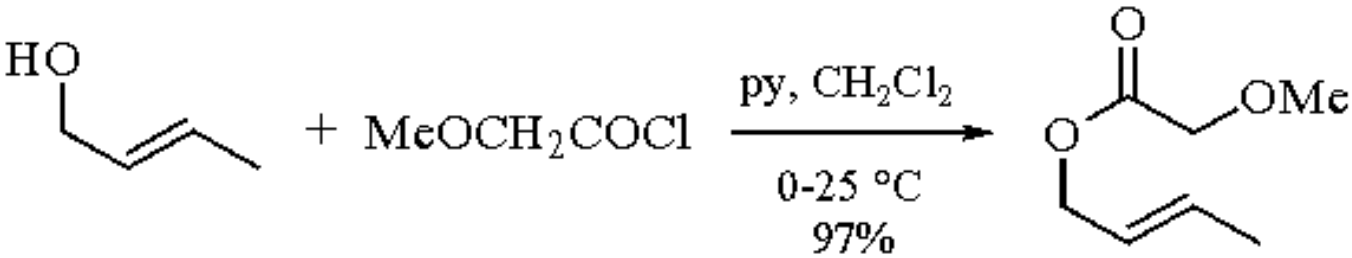

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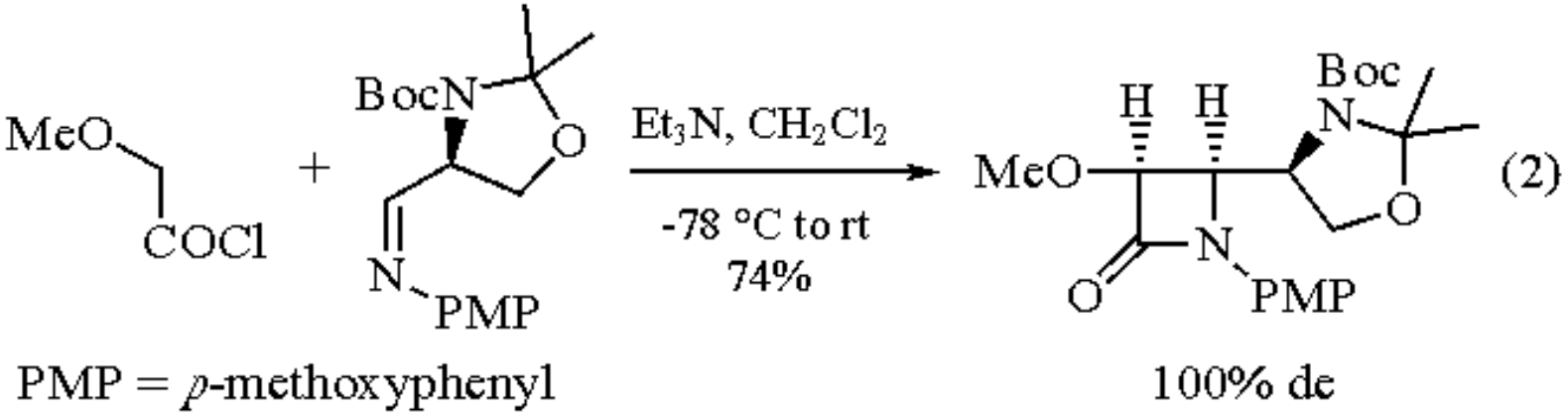

Aromatic Chloromethylation.

Although commercially available in bulk quantities, methoxyacetyl chloride can also be readily prepared in excellent yield by simple reaction of methoxyacetic acid with ***Thionyl Chloride***.[9] It is important, however, that the reagent be prepared and distilled fairly rapidly, and that it not be exposed for prolonged periods to acids as, like other alkoxyacetic acids, it undergoes decarbonylative decomposition to produce chloromethyl methyl ether. Both protic and Lewis acids catalyze the decarbonylation, and the procedure has been recommended as a convenient means of generating ***Chloromethyl Methyl Ether*** free of ***Bis(chloromethyl) Ether*** (eq 3).[9-11]

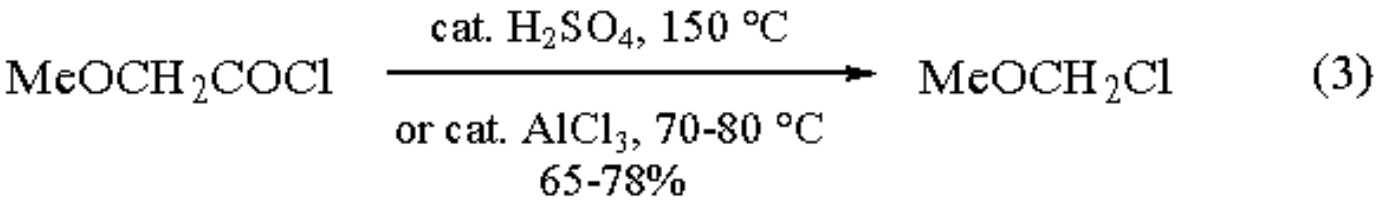

Aluminum Chloride-catalyzed decarbonylation is relatively slow at 0-5 °C in nitromethane, and it has been suggested that $MeO^{+}{=}CH_2\ AlCl_4^{-}$ is formed under these conditions. When the reaction is carried out in the presence of certain types of aromatic substrates, smooth chloromethylation is observed (eq 4).[12,13] The procedure is especially useful for anisoles which contain a powerful electron-withdrawing substituent in the *ortho* or *para* position (eqs 5 and 6). With aromatic substrates highly activated to electrophilic substitution, use of the same conditions leads either to formation of diarylmethanes (eq 7) or to polymerization.

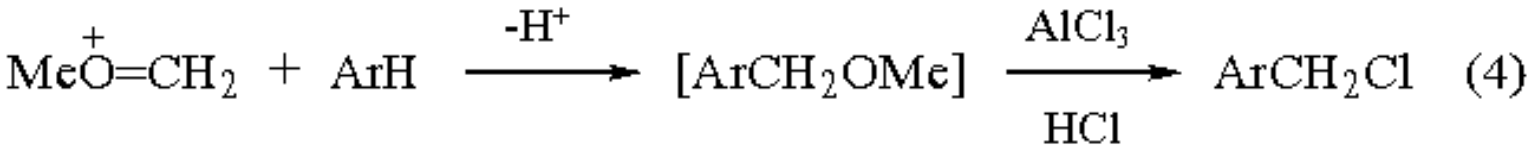

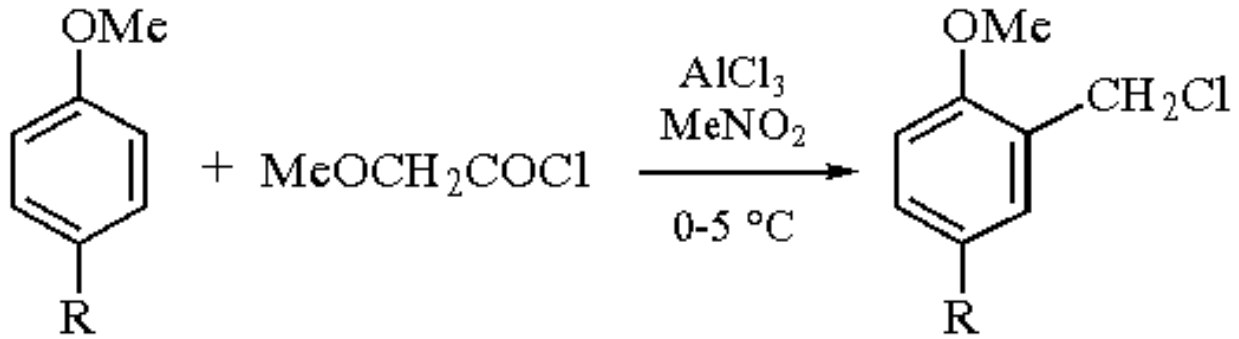

(5)

R = CHO, 70%; COMe, 99%
CN, 90%; NO_2, 89%

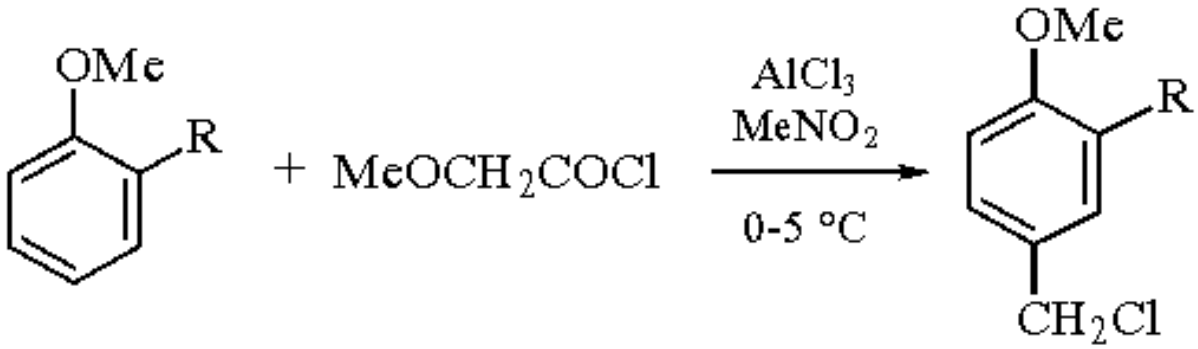

(6)

R = CHO, 90%; COMe, 50%

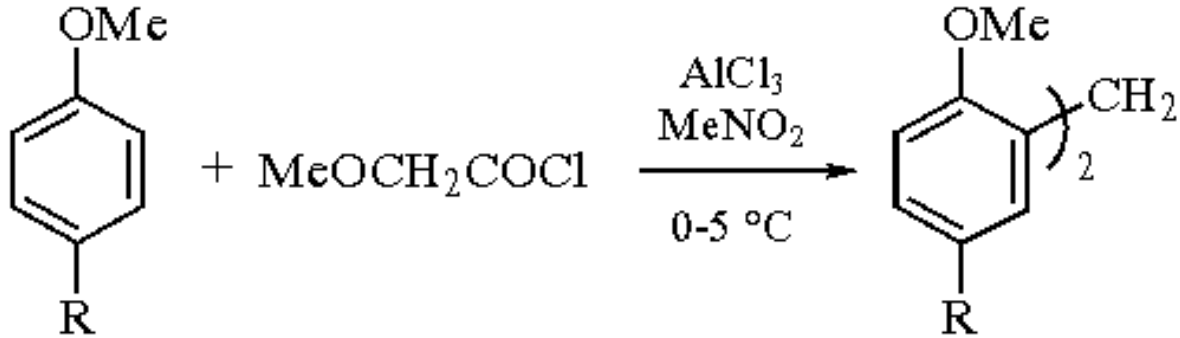

(7)

Related Reagents.

Chloromethyl Methyl Ether.

---

1. Reese, C. B.; Stewart, J. C. M. *TL* **1968**, 4273.
2. Bowden, B. F.; Picker, K.; Ritchie, E.; Taylor, W. C. *AJC* **1975**, *28*, 2681.
3. Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *JOC* **1983**, *48*, 5221.
4. Palomo, C.; Cossio, F. P.; Cuevas, C. *TL* **1991**, *32*, 3109.
5. Bose, A. K.; Fahey, J. L.; Manhas, M. S. *JHC* **1973**, *10*, 791.
6. Bose, A. K.; Manhas, M. S.; Chib, J. S.; Chawla, H. P. S. *JOC* **1974**, *39*, 2877.

7. Foxton, M. W.; Mearman, R. C.; Newall, C. E.; Ward, P. *TL* **1981**, *22*, 2497.
8. Nagao, Y.; Kumagai, T.; Takao, S.; Abe, T.; Ochiai, M.; Inoue, Y.; Taga, T.; Fujita, E. *JOC* **1986**, *51*, 4737.
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10. Jones, M. *S* **1984**, 727.
11. Basavaiah, D.; Dharma Rao, P.; Gowriswari, V. V. L. *SC* **1988**, *18*, 1411.
12. McKillop, A.; Madjdabadi, F. A.; Long, D. A. *TL* **1983**, *24*, 1933.
13. Abassi, F.; Hodge, P.; Khoshdel, E. *Polym. Commun.* **1988**, *29*, 368.

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1-Methoxyallenyllithium[1]

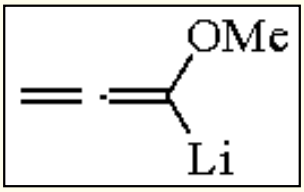

[61186-66-1] · C_4H_5LiO · 1-Methoxyallenyllithium · (MW 76.03)

(acryloyl carbanion equivalent; reagent for the synthesis of α,β-unsaturated carbonyl compounds, methoxybutadienes, acylsilanes, methoxycyclopropanes; reagent for annulation of 2-furanones, methoxyfurans, methylenecyclopentanones, and hydroxyquinones)

Alternate Name: (1-methoxy-1,2-propadienyl)lithium.

Physical Data: parent allene: bp 51.5-52.5 °C/760 mmHg;[2] n_D^{20} 1.4264;[2] ^{1}H NMR ($CDCl_3$) δ 6.77 (t, *J* = 5.9 Hz, 1 H), 5.48 (d, *J* = 5.9 Hz, 2 H), 3.42 (s, 3 H).[3]

Preparative Methods: methoxyallene[2,4] is easily prepared from ***Propargyl Alcohol*** by conversion to the methyl ether with aqueous ***Sodium Hydroxide*** and ***Dimethyl Sulfate*** followed by treatment with finely powdered ***Potassium t-Butoxide*** for 2-3 h at 70 °C. The overall yield of methoxyallene, following vacuum distillation, is 82% (eq 1).[5] Use of a heating mantle should be avoided; uneven heating during the isomerization or the distillation leads to polymerization of the sensitive allene. The allene can be stored over K_2CO_3 at -20 °C for several weeks without appreciable decomposition. Abstraction of the α-hydrogen atom from methoxyallene takes place rapidly on treatment with ***n-Butyllithium*** in ether at -30 °C.[6]

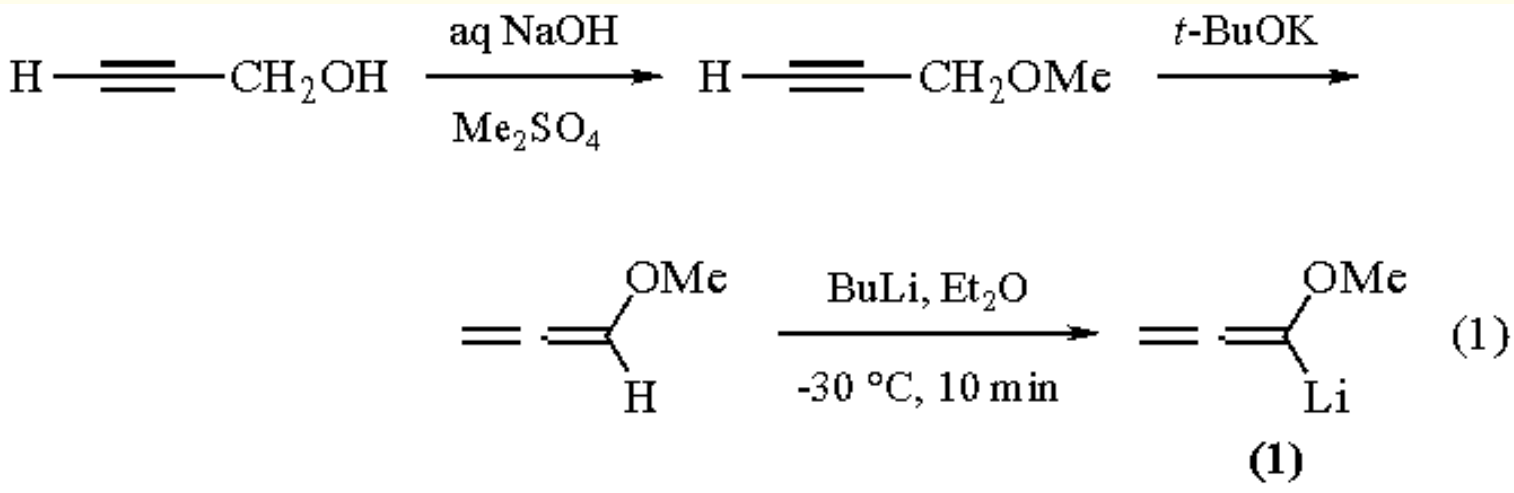

Handling, Storage, and Precautions: the parent allene is best stored at -20 °C, or below, over anhydrous K_2CO_3. Hydrolysis or polymerization take place in the presence of acid.

Introduction.

1-Methoxyallenyllithium (**1**) is a reactive nucleophile which functions as an acryloyl anion equivalent in its reactions with electrophiles.

Carbonyl Addition Reactions.[3]

Addition of (**1**) to cyclohexanone and hydrolysis of the methyl enol ether gives the hydroxy enone in 92% yield (eq 2).[6] The addition of (**1**) to chiral aldehydes shows good *anti* selectivity (eq 3).[7] The stereochemical preference for addition has been rationalized according to the Felkin-Anh model. Exposure of the major adduct to catalytic potassium *t*-butoxide leads to the 2,5-dihydrofuran derivative, which can be hydrolyzed to the furanone. Considerable attention has been focused on this unusual transformation.[8] The cyclohexenone adduct of (**1**) undergoes base-catalyzed conversion to the methoxydihydrofuran in what is formally a rare 5-*endo*-digonal cyclization (eq 4). It is noteworthy that no [1,3]- or [3,3]-sigmatropic rearrangements take place, even though these are not obviously precluded by geometrical constraints.[8]

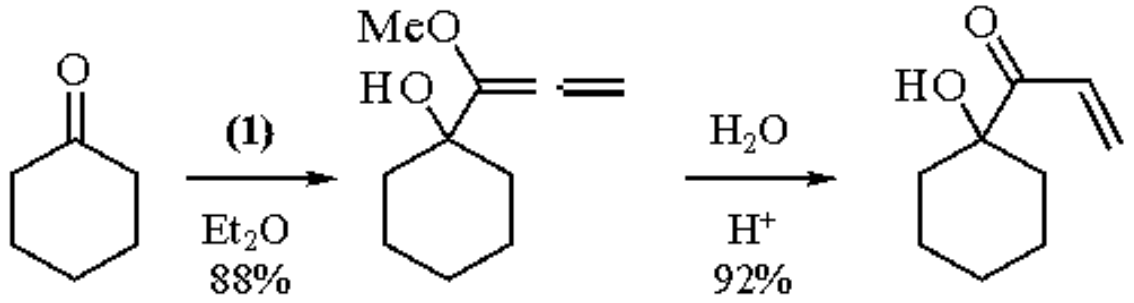

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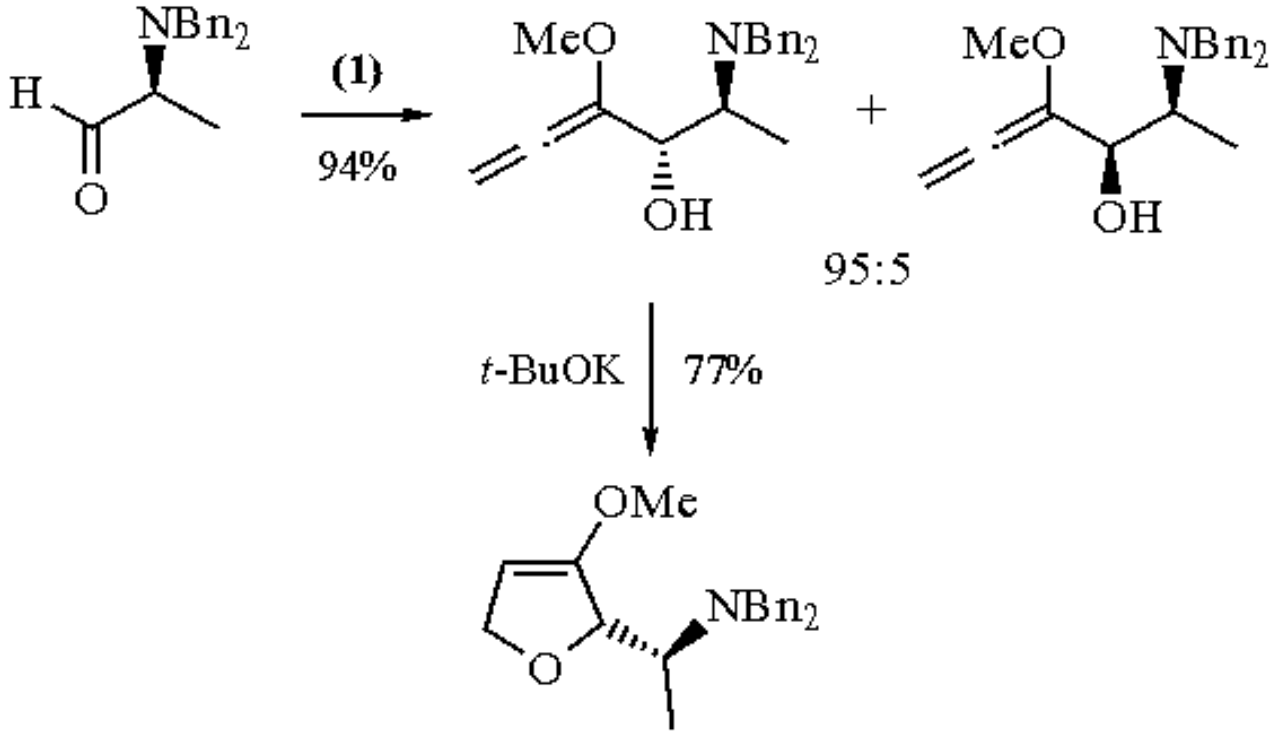

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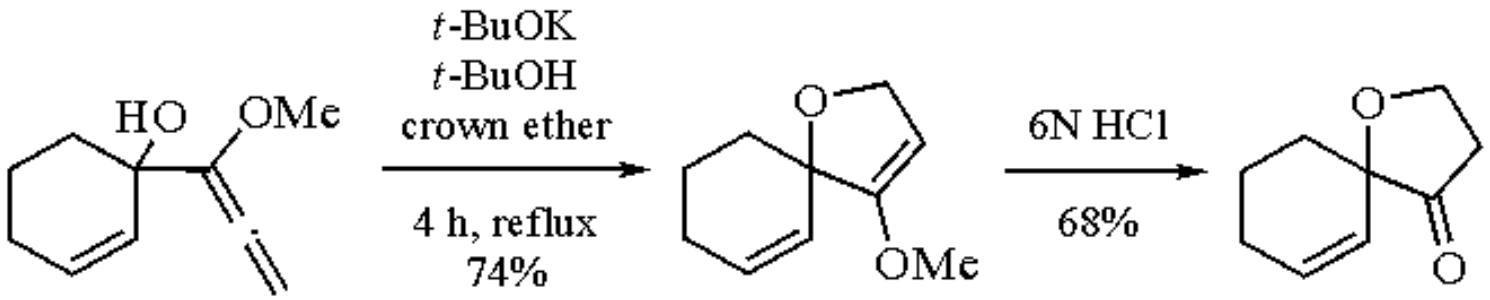

(4)

Chelation controlled addition of (**1**) to carbonyl compounds is also known. Cleavage of the amine protecting group in the proline-derived ketone (**2**) results in a labile amino ketone (eq 5).[9] Addition of (**1**) to this ketone leads to a single product which is converted to the bicyclic methyl enol ether (**3**) by exposure to slightly less than 1 equiv of dry ***p-Toluenesulfonic Acid*** in acetonitrile at 23 °C.

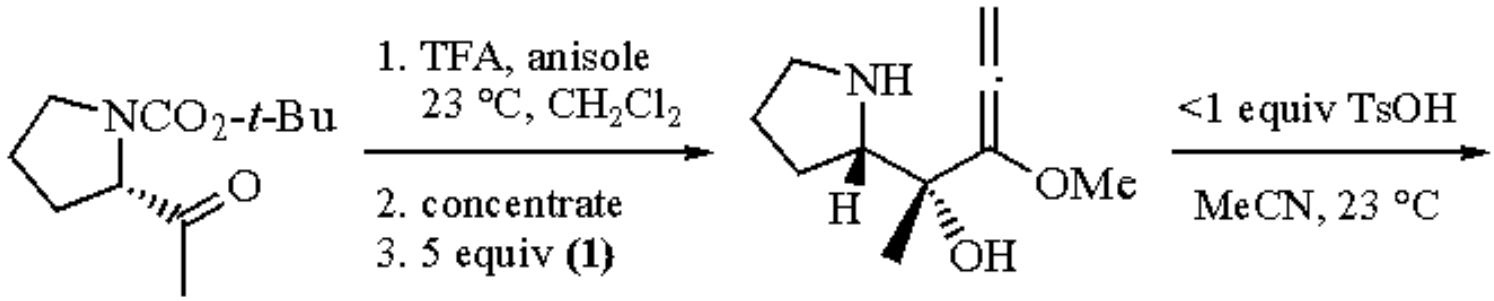

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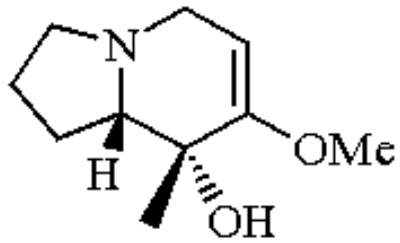

(5)

(3)
35-40% overall

Addition of (**1**) to 3-chloro-2-butanone (eq 6), followed by brief exposure of the product to ***Potassium Hydroxide***, leads to an epoxy allene.[10] Rearrangement to 3-methoxy-2,4,5-trimethylfuran is accomplished by treatment with base. The mechanism is postulated to proceed by initial abstraction of a vinyl hydrogen with epoxide ring opening, leading to an intermediate enynol which undergoes base-catalyzed cyclization to the furan.

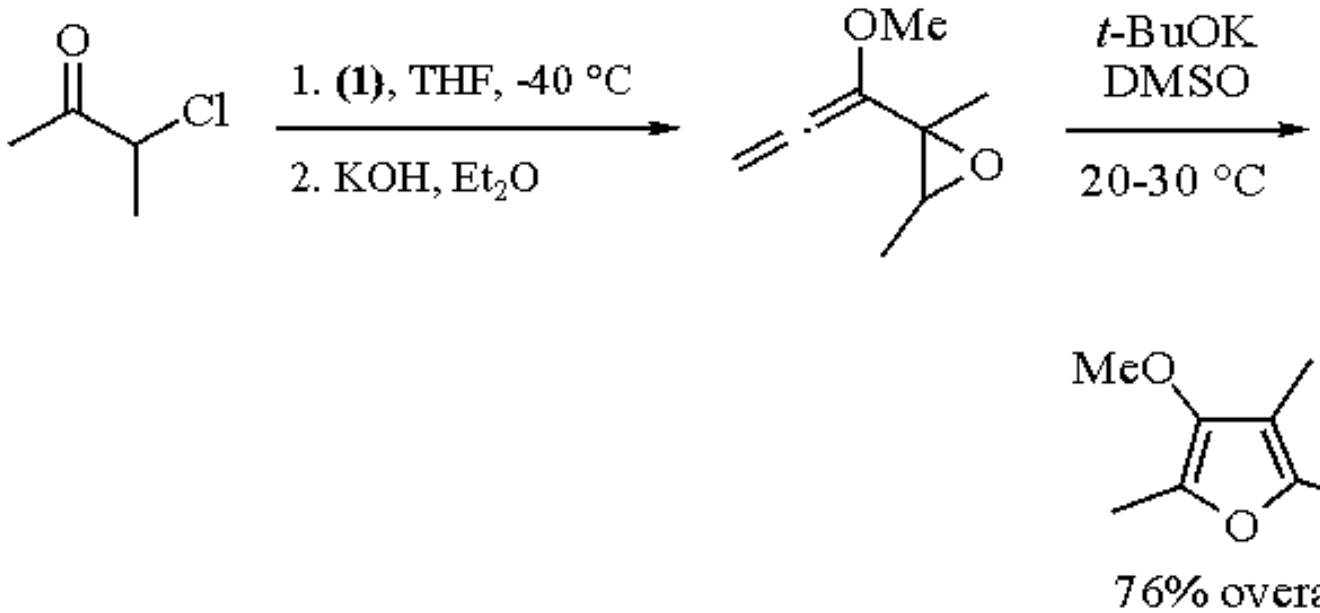

(6)

Additions to Alkyl Halides.

A convergent synthesis of α,β-unsaturated ketones makes use of (**1**) (eq 7).[11] Alkylation of (**1**) with a primary alkyl halide at C-1 is followed by deprotonation of the allene product at C-3 with *n*-butyllithium.[2] Quenching of the 1-methoxy-3-lithioallene with a second alkyl halide and hydrolysis of the product forms enones in excellent overall yield. The 1-methoxy-3-lithioallene can be intercepted by a variety of electrophiles (eq 8).[12] This work demonstrates the utility of (**1**) both as an α- and as a γ-acyl anion equivalent. The kinetic preference for the exclusive formation of the (*Z*)-keto ester (eq 8) is noteworthy, and is the result of stereoelectronic control during the protonation step.

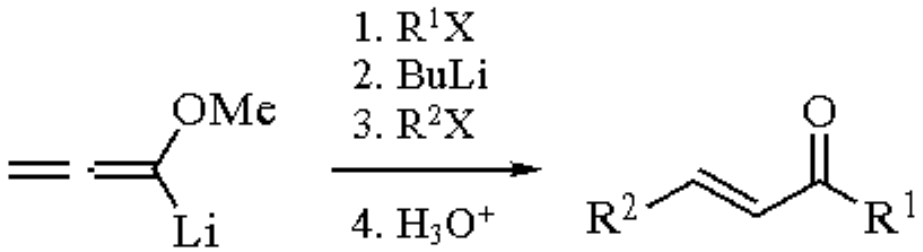

(7)

R^1	R^2	Yield (%)
Bu	Et	91
Bu	Me	86
Et	C_5H_{11}	66
Me	Bu	89

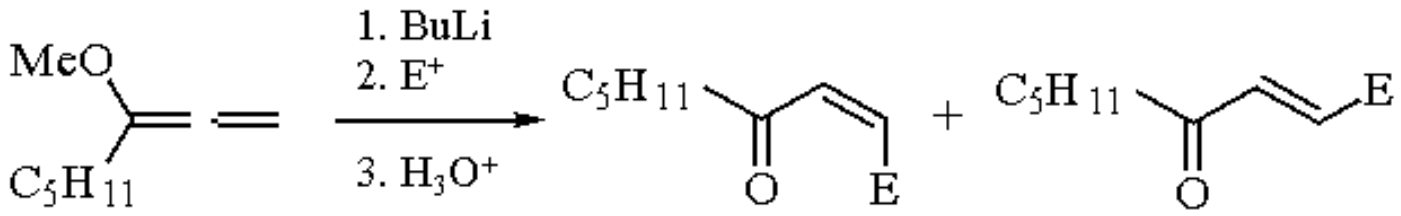

(8)

E^+	E	Yield (%)	(*Z*):(*E*)
Me_2S_2	SMe	60	19:81
TMSCl	TMS	60	63:37
CO_2; MeI	CO_2Me	65	100:0

The products of alkylation of (**1**) with alkyl halides can be rearranged to methoxy dienes (eq 9). Exposure of the adducts to ***Pyridinium p-Toluenesulfonate*** at rt produces 1-substituted 2-methoxybutadienes in moderate yield with good selectivity for the (*E*) isomer.[13]

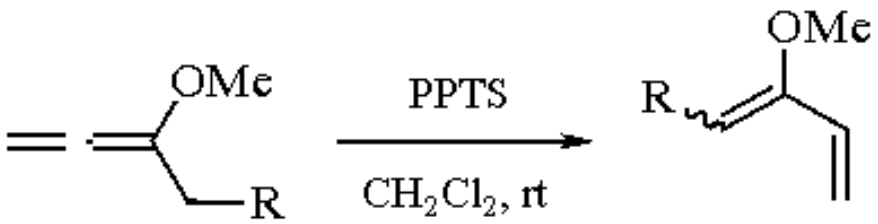

(9)

R	Yield (%)	(*E*):(*Z*)
Pr	47	5:1
$PhCH_2$	39	100:1
Ph	49	16:1
$BrCH_2CH_2$	41	6:1

More highly substituted methoxybutadienes are also accessible through (**1**). The adducts of (**1**) with carbonyl compounds (eq 10) are converted to the methanesulfinate ester derivatives.[14] Copper-catalyzed Grignard addition takes place selectively at the sp-hybridized carbon of the allene with displacement of methanesulfinate to produce 2-alkyl- or 2-aryl-3-methoxy-1,3-dienes in 70-95% overall yield (eq 10). Enol ether hydrolysis gives enones. Homocuprates are unsatisfactory in this instance because they attack the sulfur atom preferentially.

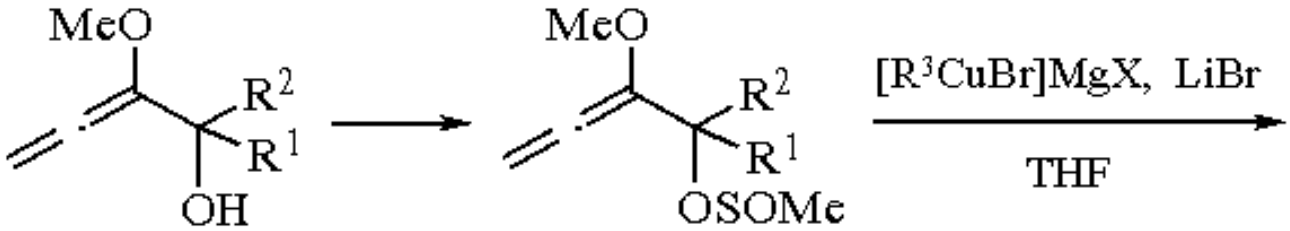

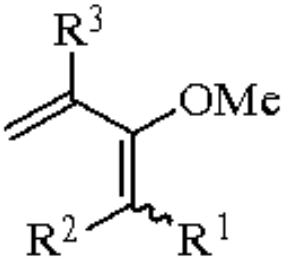

70-95% (10)

The alkylation products of (**1**) are useful for the synthesis of dioxaspiro compounds. For example, the allene (**4**), which is available in quantitative yield from (**1**), can be deprotonated with ***t-Butyllithium***, and the γ-anion trapped with ***Ethylene Oxide*** in 88% yield (eq 11).[15] Silyl protecting group cleavage, followed by mild, acid-catalyzed intramolecular acetalization, leads to a mixture of diastereoisomeric dioxaspiro compounds. Where additional control elements are present in the rings, the reaction can be biased toward a single product.[16]

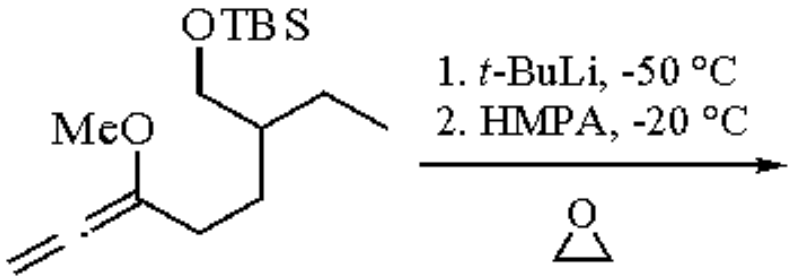

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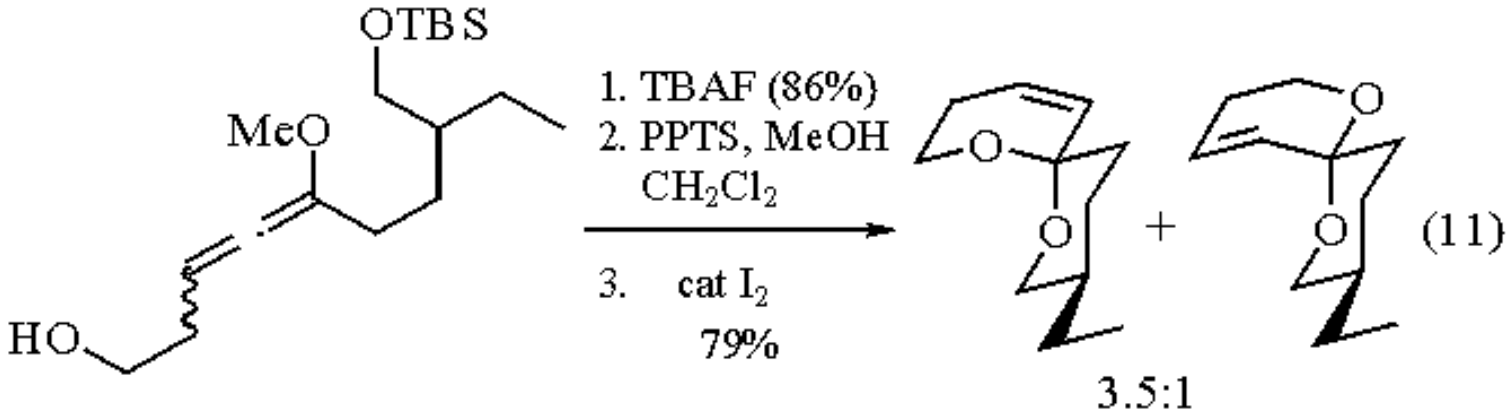

(11)

The trapping of (**1**) by heteroatomic electrophiles to give (**5**) has been described.[6,17-19]

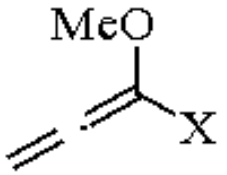

(5)

X =			
	TMS	(TMSCl)	50%
	$SnMe_3$	(Me_3SnCl)	61%
	SMe	(Me_2S_2)	75%
	I	(I_2)	95%

Reaction with Trialkylboranes.

An unusual synthesis of methoxycyclopropanes which proceeds from (**1**) has been disclosed (eq 12).[20] Exposure of the 9-BBN (see ***9-Borabicyclo[3.3.1]nonane***) adduct of 1-methylcyclohexene to a small excess of (**1**), followed by acidification and oxidative workup, leads to the methoxycyclopropane in high yield. The mechanism presumably involves acid-catalyzed rearrangement of a lithium borate salt, accompanied by allylic migration of boron. This is supported by the observation that use of deuterioacetic acid results in the formation of a methoxycyclopropane product in which one methylene group of the three-membered ring is fully deuterated.

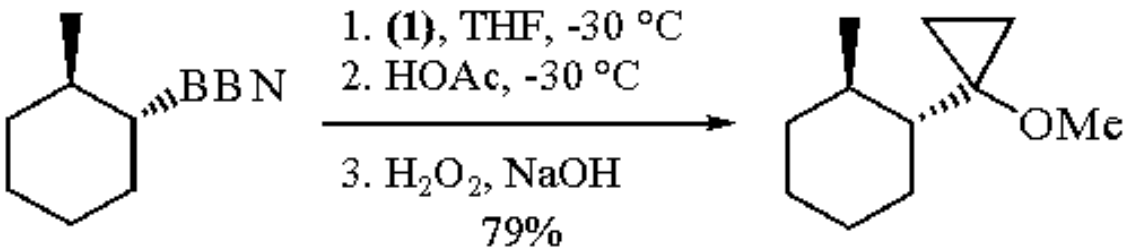

(12)

Related 1-Alkoxyallenyllithiums and Reactions.

1-(1-Ethoxyethoxy)allenyllithium (**6**)[2] has been used to convert an aldehyde into an α,β-alkynic ketone (eq 13).[21] Aldehyde addition and quenching of the alkoxide with ***Chlorotrimethylsilane***, followed by treatment with *n*-butyllithium, leads to trimethylsilyl oxide elimination and generation of the ketone enol ether. The allenyllithium (**6**) has also been used for the preparation of acylsilanes.[22] Trapping with ***t-Butyldimethylchlorosilane*** leads to the allenylsilane which upon hydrolysis gives the silyl enone, and upon treatment with peroxy acid gives 1-*t*-butyldimethylsilyl-1,2-propanedione, presumably through an allene oxide intermediate (eq 14).

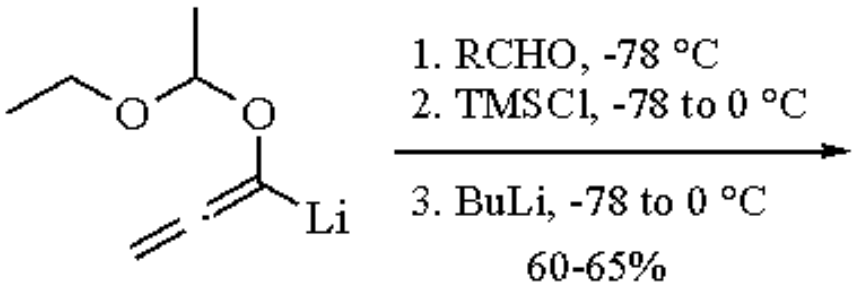

(6)

(13)

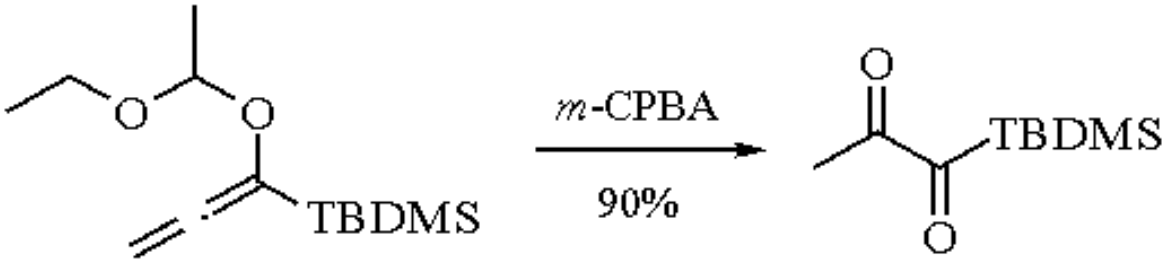

(14)

1-(Methoxymethoxy)allenyllithium (**7**) has been used in a cationic cyclopentannulation reaction.[23] Addition of (**7**) to 3-methyl-2-buten-1-one produces a tertiary alcohol which cyclizes to a five-membered ring upon treatment with ***Trifluoroacetic Anhydride*** and 2,6-***2,6-Lutidine*** (eq 15) in a process reminiscent of the Nazarov reaction. The success of the cyclization reaction requires that the oxygen substituent on the allene be capable of departing as a stable cation.[24]

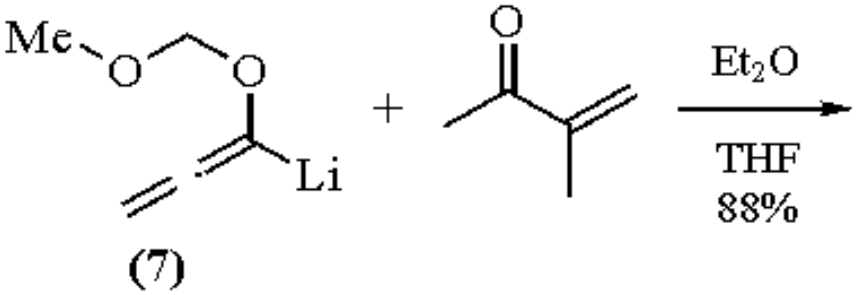

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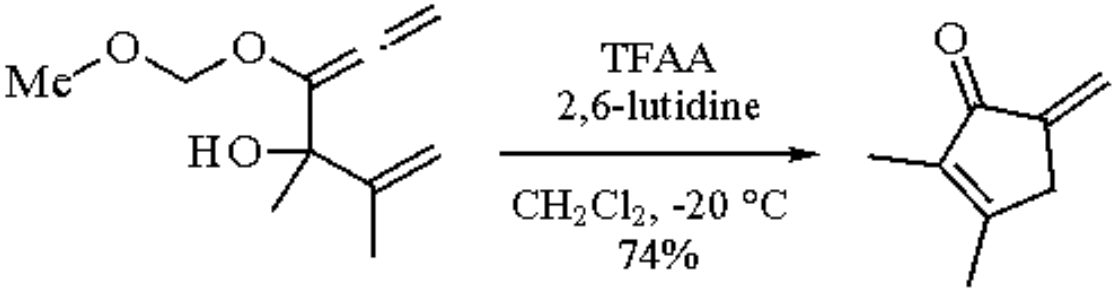

(15)

Addition of (**7**) to the vinylogous silyl ester (**8**), followed by treatment of the product with fluoride, produces a tertiary allenic alcohol (eq 16). Epoxidation with buffered peroxy acid produces an epoxy keto aldehyde, presumably from intramolecular trapping of an oxyallyl zwitterion. Methanolic KOH leads to a hydroxy quinone which is *O*-methylated with ***Diazomethane***.[25] Treatment of the adduct of (**7**) and (**8**) with ***Boron Trifluoride Etherate*** in dichloromethane leads to the cyclopentannulation product (eq 17).[26]

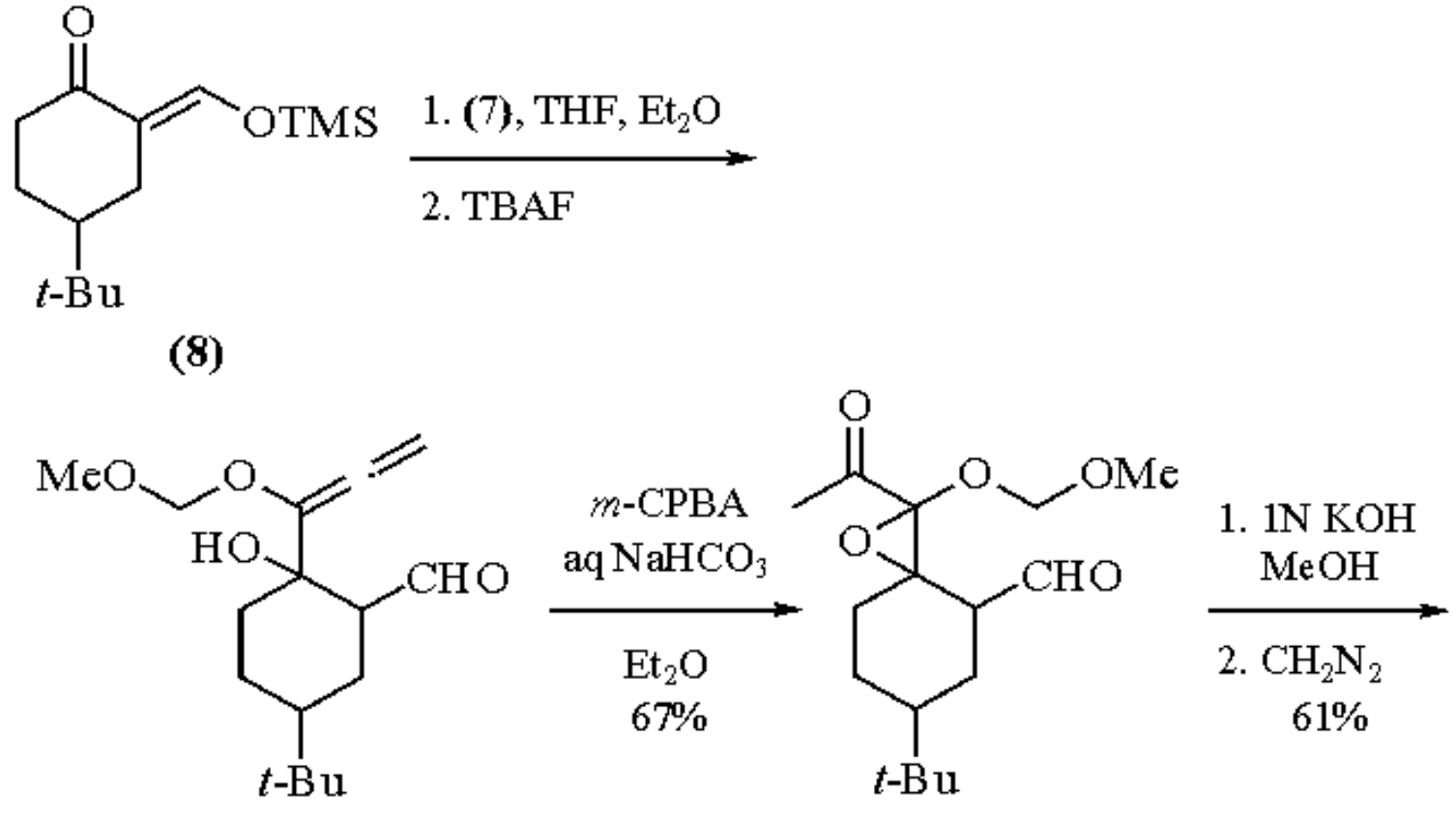

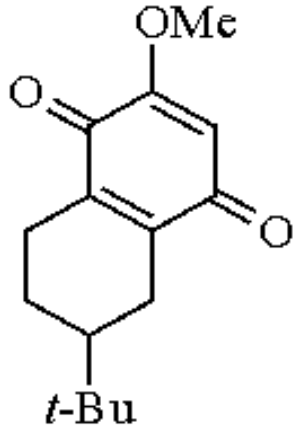

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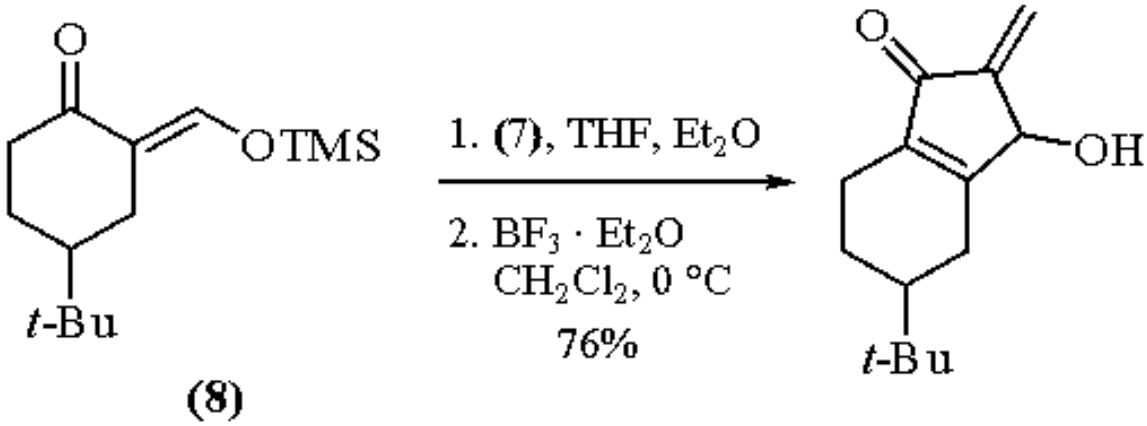

(17)

Related Anions.

Trialkylsilyloxyallenes can be prepared from 2,2-dimethyl-4-methylene-1,3-dioxolane (eq 18).[27] Deprotonation with 2 equiv ***s-Butyllithium*** leads to the allylic carbanion which fragments to the lithium alkoxide of 1,2-propadien-1-ol. Quenching with ***t-Butyldiphenylchlorosilane*** leads to the siloxyallene in high overall yield. Allene deprotonation takes place under the same conditions as for (**1**).

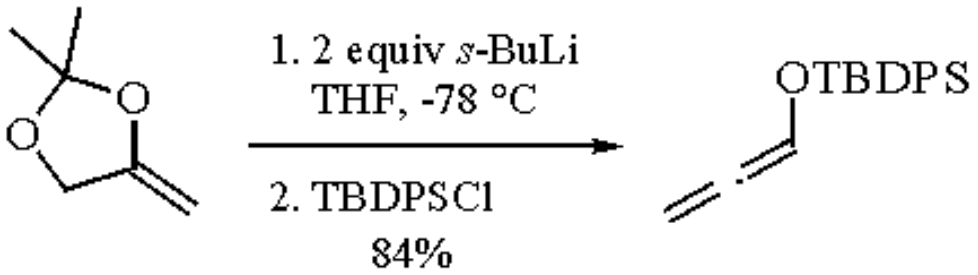

(18)

The allenyllithium (**10**) is prepared selectively in 80% yield, along with 5-6% of (**9**), by γ-deprotonation of *t*-butoxyallene with sterically encumbered lithium dicyclohexylamide.[11] Deprotonation of 1-phenylthioprop-1-yne with *n*-butyllithium/TMEDA at -78 °C leads to thiophenoxyallenyllithium (**11**).[28] Anion (**12**) bears asymmetry on the ether sidechain. Modest levels of asymmetric induction are found in the addition reactions of (**12**) with ketones.[29] 1-Methoxy-1,2,3-butatrienyllithium (**13**) is prepared by treating 1,4-dimethoxy-2-butyne with 2 equiv *n*-butyllithium at -78 °C and warming to -45 °C.[30] This reagent has been used for a synthesis of enynes. The related lithioallenes (**14**)-(**16**)[24] and the copper derivative (**17**)[31] have also been described.

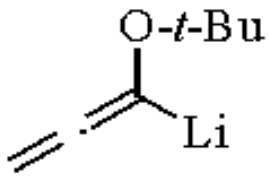

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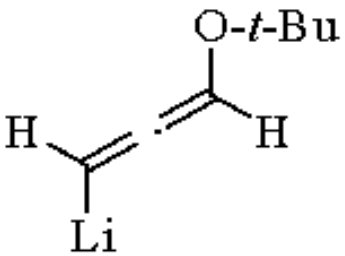

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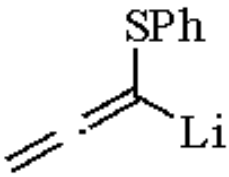

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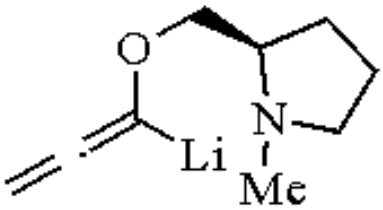

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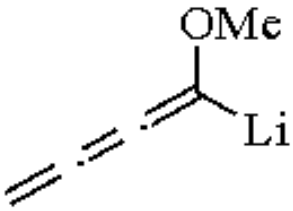

(13)

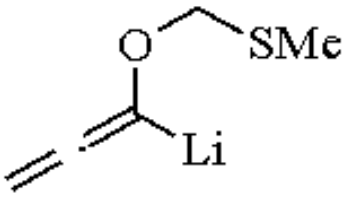

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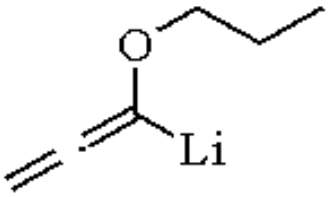

(15)

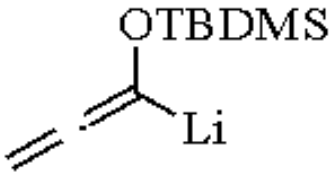

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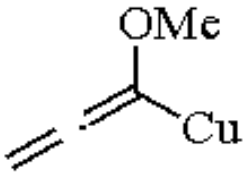

(17)

Related Reagents.

Allenyllithium; ***1-Trimethylsilyl-1-methoxyallene***.

---

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2-Methoxyallyl Bromide

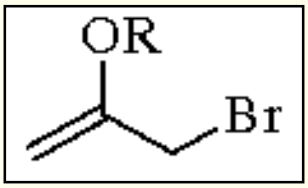

(R = Me)

[26562-24-3] · C_4H_7BrO · 2-Methoxyallyl Bromide · (MW 151.01) (R = Et)

[26562-26-5] · C_5H_9BrO · 2-Ethoxyallyl Bromide · (MW 165.04)

(three-carbon electrophile in alkylations;[1] three-carbon component in arene cycloadditions;[2] bromoacetone equivalent;[1] cyclopentenone annulation reagent;[3] acetone equivalent in nucleophilic additions[4])

Alternate Names: 3-bromo-2-methoxy-1-propene; 1-(bromomethyl)vinyl methyl ether.

Physical Data: a mixture of 2-methoxyallyl bromide, 1-bromo-2-methoxypropene, and 1-bromo-2,2-dimethoxypropane in a ratio of 65:21:14 has bp 134-137 °C; *d* 1.16 g cm^{-3}.[4] A mixture of 2-ethoxyallyl bromide and 1-bromo-2-ethoxypropene in a ratio of approx 3:1 has bp 53-55 °C/26 mmHg.[5]

Solubility: sol common organic solvents (i.e. diethyl ether, THF).

Analysis of Reagent Purity: gas chromatography using Carbowax 20M (or comparable) stationary phase.[1,6]

Preparative Methods: Greenwood and Hoffman reported that treatment of ***2-Methoxypropene*** with ***N-Bromosuccinimide*** in CCl_4 at 55-65 °C provides a CCl_4 solution of 2-methoxyallyl bromide and 1-bromo-2-methoxypropene in an approx 3:1 ratio.[6] Alternatively, Jacobson's modification of existing pyrolytic procedures, pyrolysis of 1-bromo-2,2-dimethoxypropane in the presence of diisopropylethylammonium tosylate, results in a 65:21:14 ratio of 2-methoxyallyl bromide, 1-bromo-2-methoxypropene, and 1-bromo-2,2-dimethoxypropane with high mass recovery (85-90%).[1] In both cases the product mixtures are utilized in subsequent reactions. Polymerization limits the latter procedure to a scale of 30 g or less. 2-Ethoxyallyl bromide has been synthesized by pyrolysis of 1-bromo-2,2-diethoxypropane.[5] The mixture, a 3:1 ratio of 2-ethoxyallyl bromide and 1-bromo-2-ethoxypropene, is obtained in approx. 50% overall yield.

Purification: purification is performed by distillation. Synthetic procedures provide the reagent as a mixture containing 60-70% of 2-methoxyallyl bromide.[4-6] The remainder consists of 1-bromo-2-methoxypropene and/or 1-bromo-2,2-dimethoxypropane, depending on the method of synthesis.

Handling, Storage, and Precautions: neat 2-methoxyallyl bromide is unstable at rt and sensitive to moisture.[6] Mixtures obtained from the thermal cracking of 1-bromo-2,2-dimethoxypropane have been stored for extended periods at -20 °C.[1] Alternatively, a 50% solution in CCl_4 may be stored over Na_2CO_3 at rt in the dark.[6] *Caution*: this is an alkylation reagent; proper protective equipment should be worn and its use restricted to a fume hood.

Alkylations.

2-Methoxyallyl bromide (**1**) has been utilized as a three-carbon electrophile (bromoacetone equivalent) with carbanions derived from enamines,[1,7] esters,[1] nitriles,[1,8] ketones,[1,3] sulfones,[10,11] β-keto esters,[1] and substituted malonates (eq 1).[1] Dianions of carboxylic acids have been alkylated at the α-position[1] and, in the case of α,β-unsaturated acids, at the γ-position in the presence of $CuBr.SMe_2$ (see ***Copper(I) Bromide***).[12] Additional nucleophiles have included Grignard reagents,[13] copper enolates derived from conjugate additions,[14,15] alcohols (eq 2),[16] and lithiated aromatics (2-aryl-5-methyl-1,3,4-oxadiazoles and 4,5-diphenyl-2-methyl-1,3 oxazole) (eq 3).[17,18] The enol is more easily hydrolyzed to the ketone than other electrophilic acetone synthons (see ***2,3-Dichloropropene*** and ***Propargyl Chloride***).[1] Alternatively, the enol functionality has been retained in the synthesis of 1,3-dienes.[11,16]

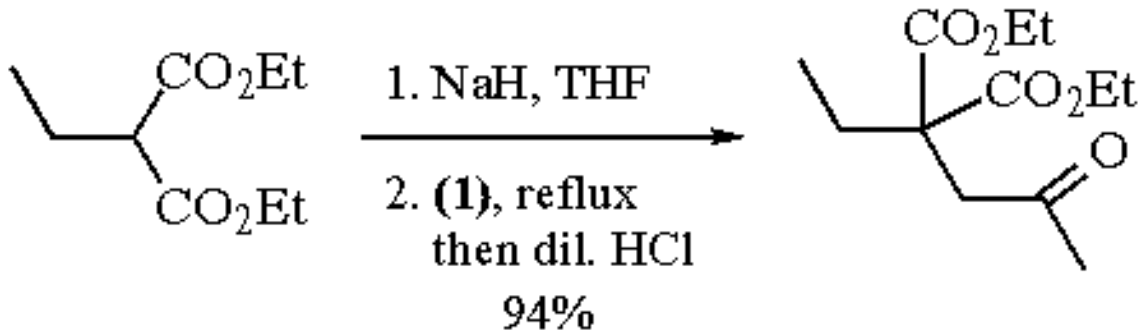

(1)

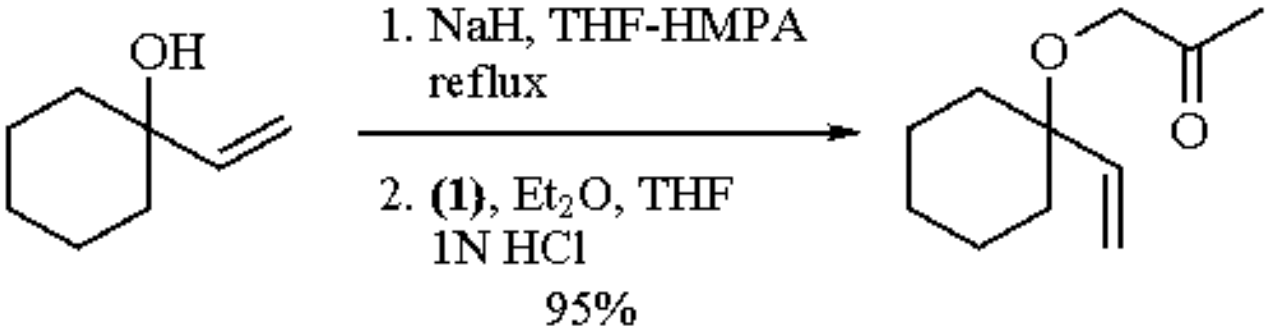

(2)

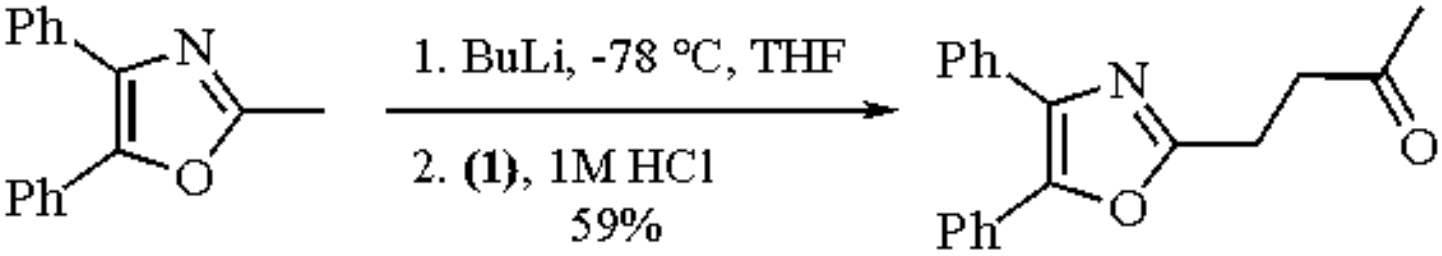

(3)

Cyclopentenone Annulation.

Alkylation of ketones with (**1**), followed by hydrolysis, results in 1,4-diketones which provide a cyclopentenone upon base-induced cyclization. This methodology has been utilized for the de novo synthesis of substituted cyclopentenones and the annulation of cyclopentenones on to existing cyclic systems (eq 4).[1,3,9]

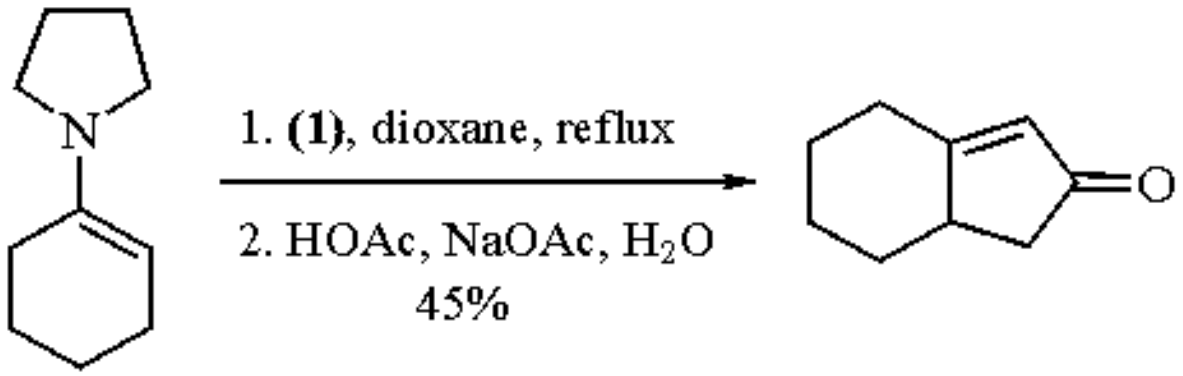

(4)

[4 + 3] Cycloaddition.

In the presence of ***Silver(I) Trifluoroacetate*** and ***Sodium Carbonate***, furan and (**1**) undergo a [4 + 3] cycloaddition, presumably via a 2-methoxyallyl cation, to give 8-oxabicyclo[3.2.1]oct-6-en-3-one after an acidic workup (eq 5).[2,19] Other dienes also react in this manner, albeit in low yields.[20,21]

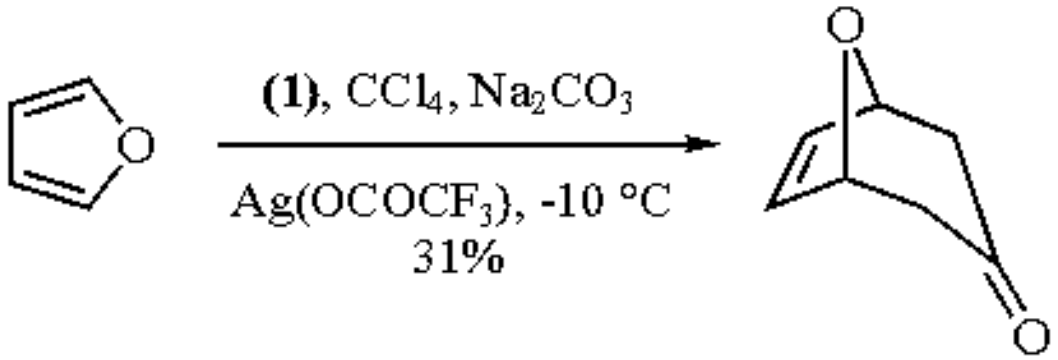

(5)

Nucleophilic Addition.

π-(2-Methoxyallyl)nickel bromide, prepared from (**1**) and ***Tetracarbonylnickel***, reacts with aryl, alkyl, and vinyl halides, aldehydes, and ketones to give acetone addition products after mild acid hydrolysis (eq 6).[4]

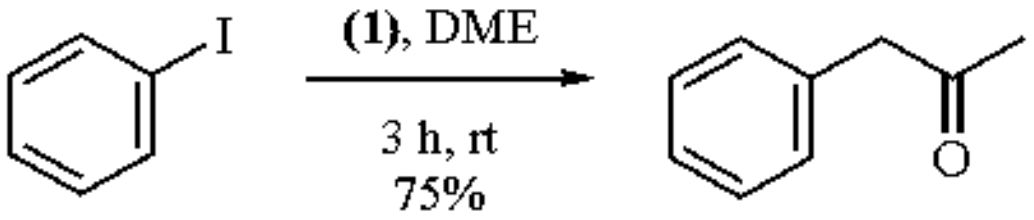

(6)

Related Reagents.

Bromoacetone; ***3-Chloro-2-trimethylsilyloxy-1-propene***; ***2,3-Dichloropropene***; ***Methallyl Bromide***; ***Propargyl Chloride***.

---

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1-Methoxyallyllithium

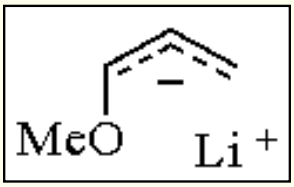

[53356-78-8] · C_4H_7LiO · 1-Methoxyallyllithium · (MW 78.05)

(reagent used for three-carbon homologation as a homoenolate anion equivalent)

Preparative Methods: the lithio anions of alkyl allyl ethers can generally be prepared by deprotonation with ***s-Butyllithium*** in THF at -65 °C or in ether or pentane with added ***N,N,N´,N´-Tetramethylethylenediamine*** in less than 30 min. ***n-Butyllithium*** can also be used as the base in THF with added TMEDA at -78 °C for 7 h.[1]

Handling, Storage, and Precautions: this and similar 1-alkoxyallyllithium reagents are stable for at least 1 day at -75 °C. At -50 °C there is at least 40% conversion to Wittig rearrangement products after 4 h and >81% conversion after 24 h. After 2 h at -25 °C, there is >89% rearrangement.[2]

General Considerations.

The impetus in the development of the title compound (**1**) was the desire for a convenient homoenolate anion equivalent. The first studies of the generation and reactivity of (**1**) brought out the major problem associated with its use: ambiguity in the site of its reactivity with electrophiles. Studies began almost immediately to find alternative reagents which exhibited predictable, controlled α vs. γ reactivity with electrophiles. This section will be concerned not only with (**1**), but with allied nucleophilic 3-alkoxy-1-propenyl reagents. Reagents of this genre have been covered in small sections of several larger reviews.[3]

1-Alkoxyallyllithiums.

The parent substance (**1**) was reported in 1974[4] along with brief studies of the reactivity of other alkyl allyl ethers. Mixtures of α and γ adducts were obtained in all reactions of the lithio anion regardless of the identity of R^1 (eq 1). The only reasonable (and often repeated) generalities arising from this study are that reaction with alkyl halides takes place predominantly at the γ-position while reaction with aldehydes and ketones occurs at the α-position. Even so, there are many exceptions, and perhaps the most accurate statement one may make regarding the reactivity of 1-alkoxyallyllithiums is that the site of reaction is dependent in a complex way on the identities of the cation, electrophile, solvent system, temperature, and the presence of additives.[5] In the case of reaction at the γ-site, *cis* isomers (**4**γ and **5**γ) are formed exclusively. This observation has prompted many workers to assume the structure of (**1**) to be the internally chelated species (**6**), whether or not a σ-bonded structure is called for in this and related cases. Attempts at rationalizing the observed selectivities have been few and are inadvisable in any case when dealing with mixtures where either the

transition state energy differences in a kinetic process or the product energy differences in a thermodynamic process are, for the most part, less than 1 kcal mol^{-1}. Regioselectivity control with the lithio anions and simple alkyl groups for R^1 appears to be problematic at this point. It was found by Evans in the original study that treatment of the anion (**3**) (R^1 = Me) with 1 equiv of ***Zinc Chloride*** or ***Cadmium Chloride***[6] favors α-alkylation (**5**α) with carbonyl compounds. Yamamoto also realized good regiochemical control in the reaction of 1-isopropoxyallyllithium and 1-(methoxymethoxy)allyllithium with carbonyl compounds by forming aluminum ate complexes with ***Triethylaluminum*** prior to addition of the electrophile resulting in exclusively α-adducts (**5**α).[7] A noteworthy aspect of the reactivity of these reagents is the aldehyde vs. ketone selectivity shown in eq 2.

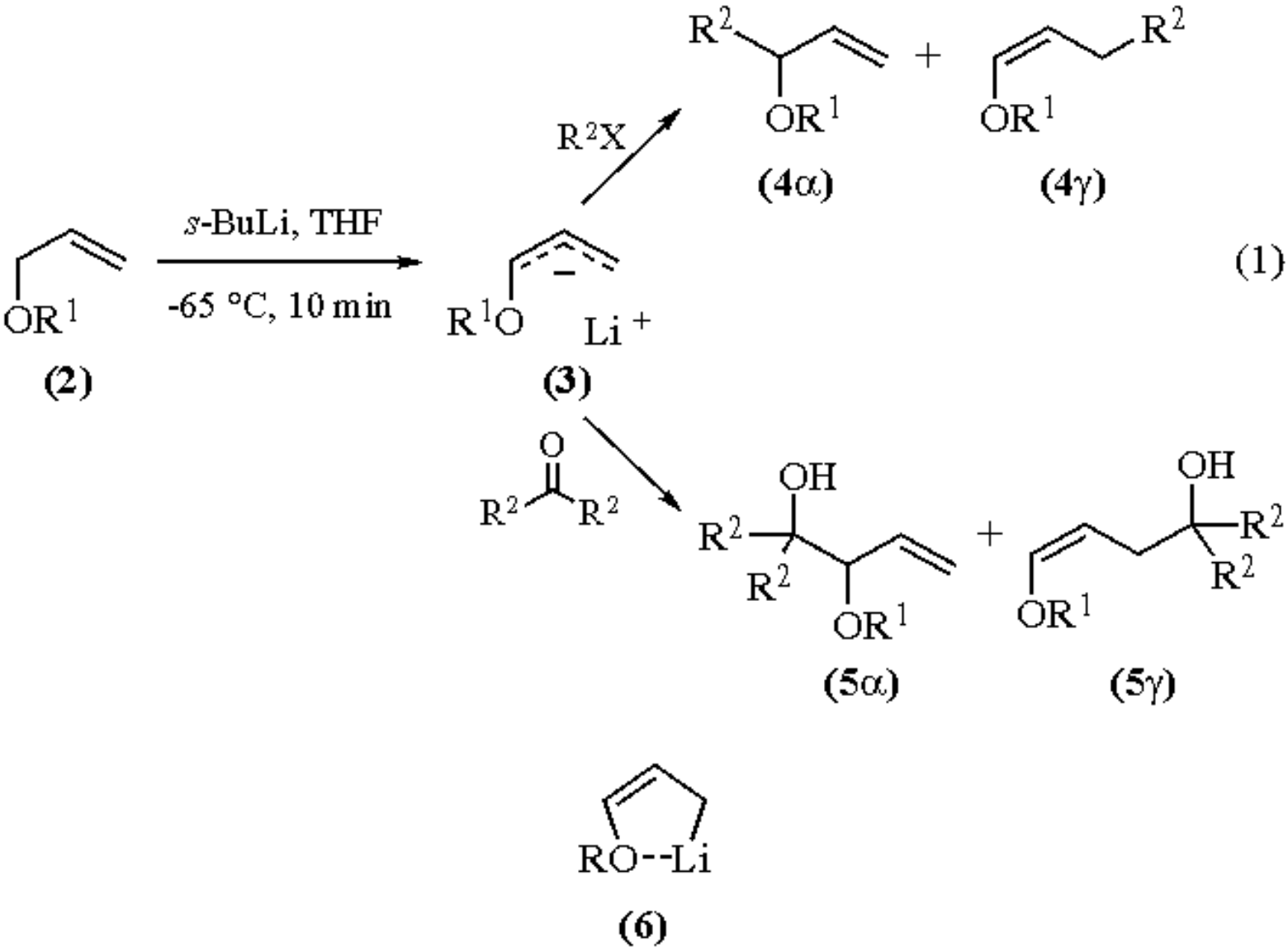

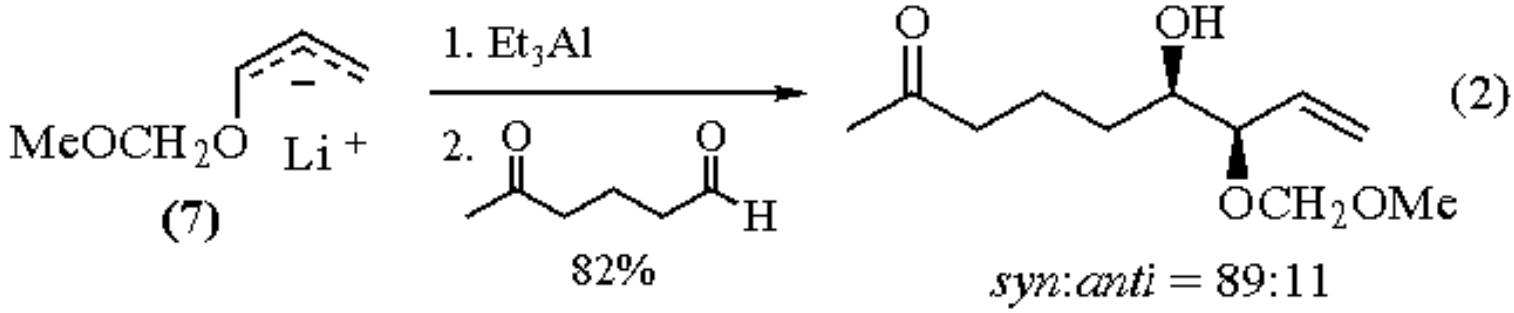

A report by Still[8] describes the generation and reactivity of the silyloxy anions (**9**), which also show the trend of predominant, but not exclusive, reaction at the γ-position with alkyl halides (**4**γ). A subsequent report by Still describes the trend of predominant, but not exclusive, reaction at the α-position with carbonyl compounds (**5**α).[9] However, when R^1 = trimethylsilyl and 5% ***Hexamethylphosphoric Triamide*** is included in the reaction mixture, exclusive α-addition to aldehydes and ketones is observed (eq 3).

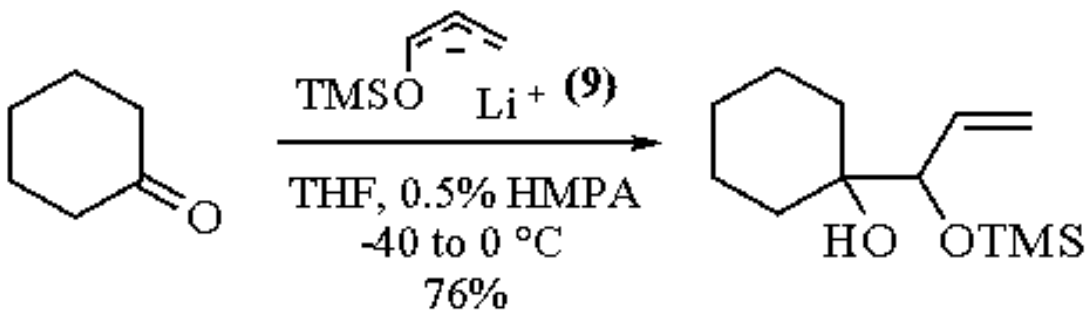

(3)

Generation of 1-Silyloxyallyllithiums via Brook Rearrangement.

1-Silyloxyallyllithiums as a class can also be formed in situ via Brook rearrangement (eq 4). The intermediate lithioalkoxide (**11**) is generated either by addition of vinyllithiums (see ***Vinyllithium***) to silyl ketones (**10**)[10] or by deprotonation of silyl carbinols (**13**) by *n*-BuLi.[11] Carbon to oxygen silyl group migration allows entry to the 1-silyloxyallyllithium reagents which can be trapped in situ with alkyl halides, resulting in the γ-alkylation products (**14**) in good yield. However, this technology has not been applied to the parent allyl systems (**10** or **13**) (R = H).

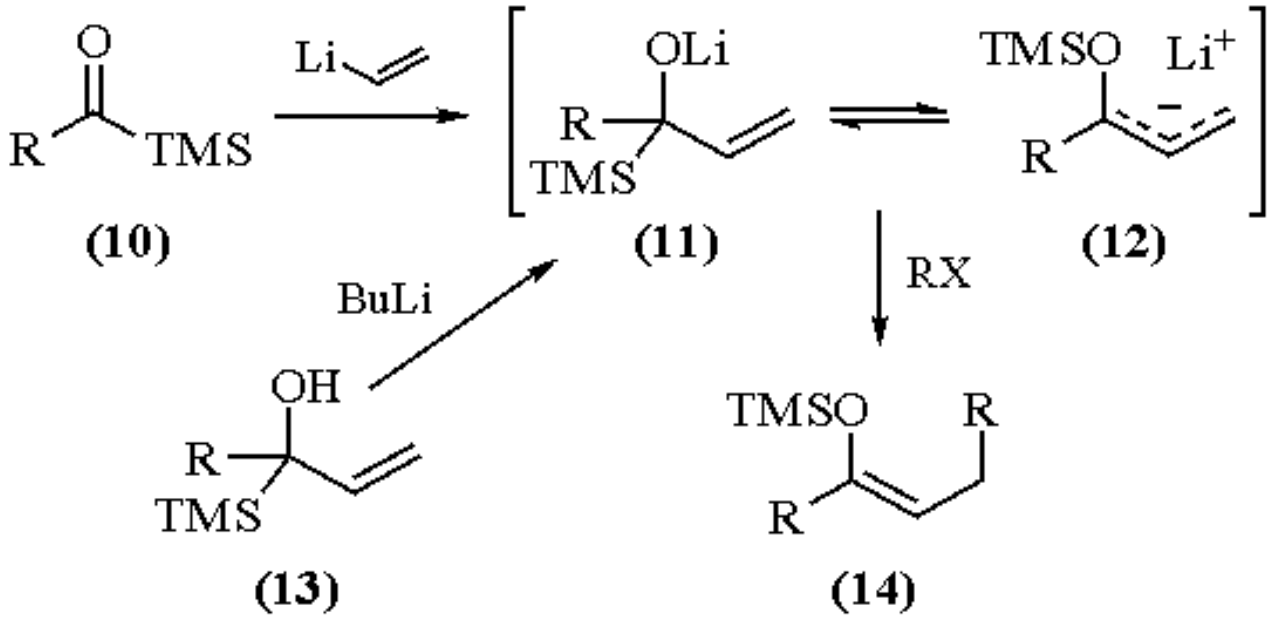

(4)

Lithiated Allyloxybenzimidazoles.

These derivatives have been found by Mukaiyama to be easily deprotonated and to undergo reaction with alkyl halides and aldehydes to give products of predominantly α-alkylation (**15** -> **16** or **17**) (eq 5).[12] Because the 2-benzimidazolyl

group can act as a good leaving group, this process can be exploited as a method to produce *cis*- and *trans*-vinyloxiranes (eqs 6 and 7).[13] When the addition is mediated by Et_3Al, the *syn*-products (**21**) are predominant and these lead to the *cis*-isomers (**22**).[14]

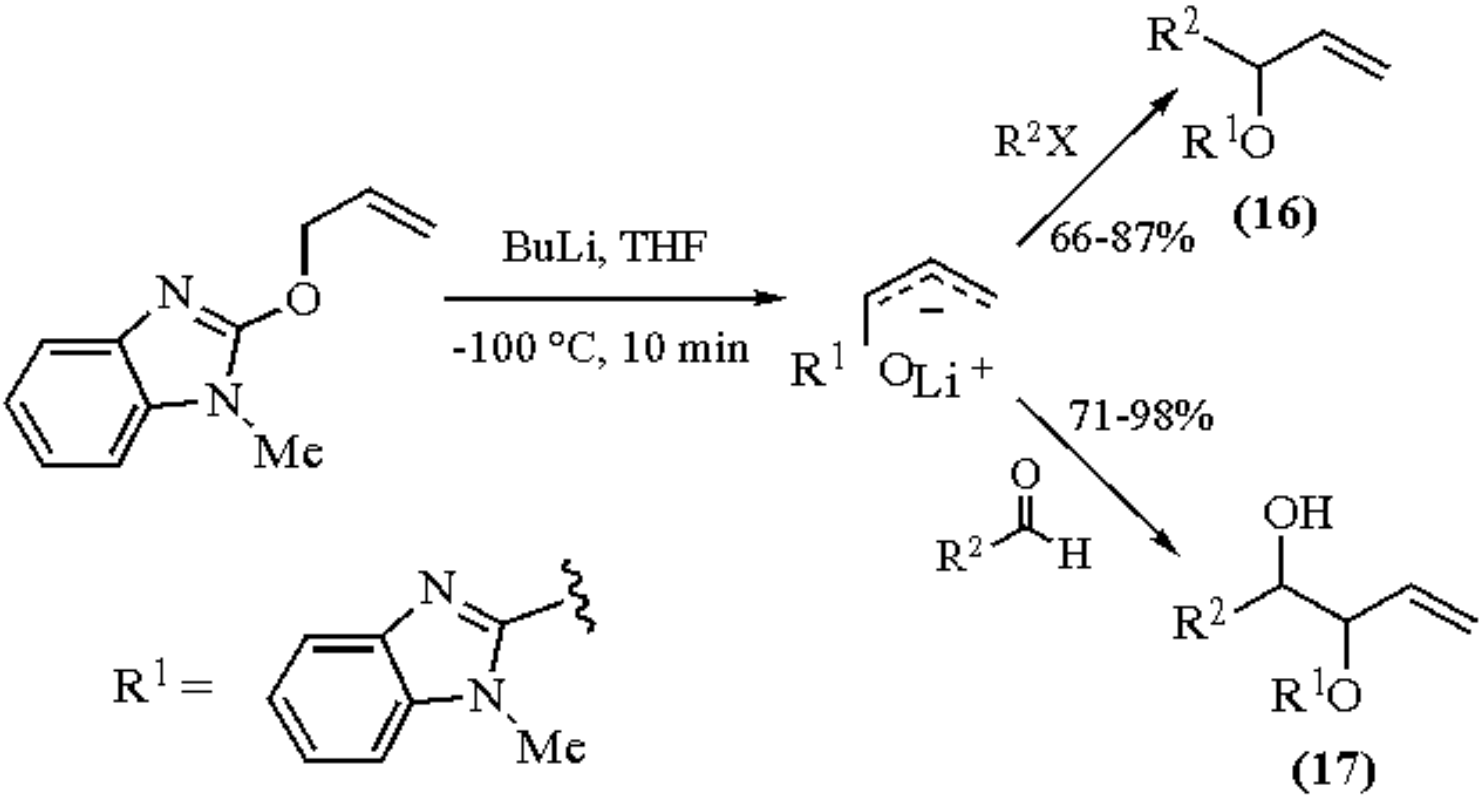

(5)

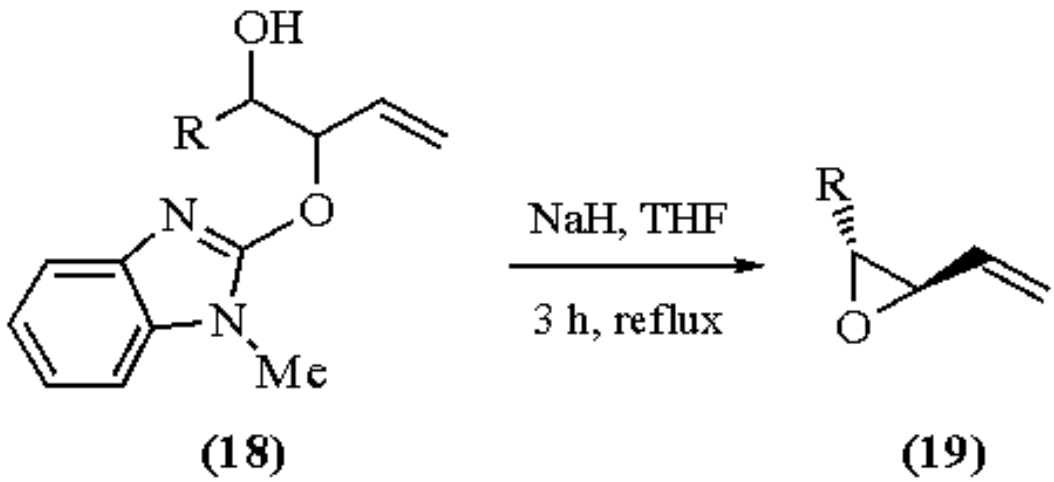

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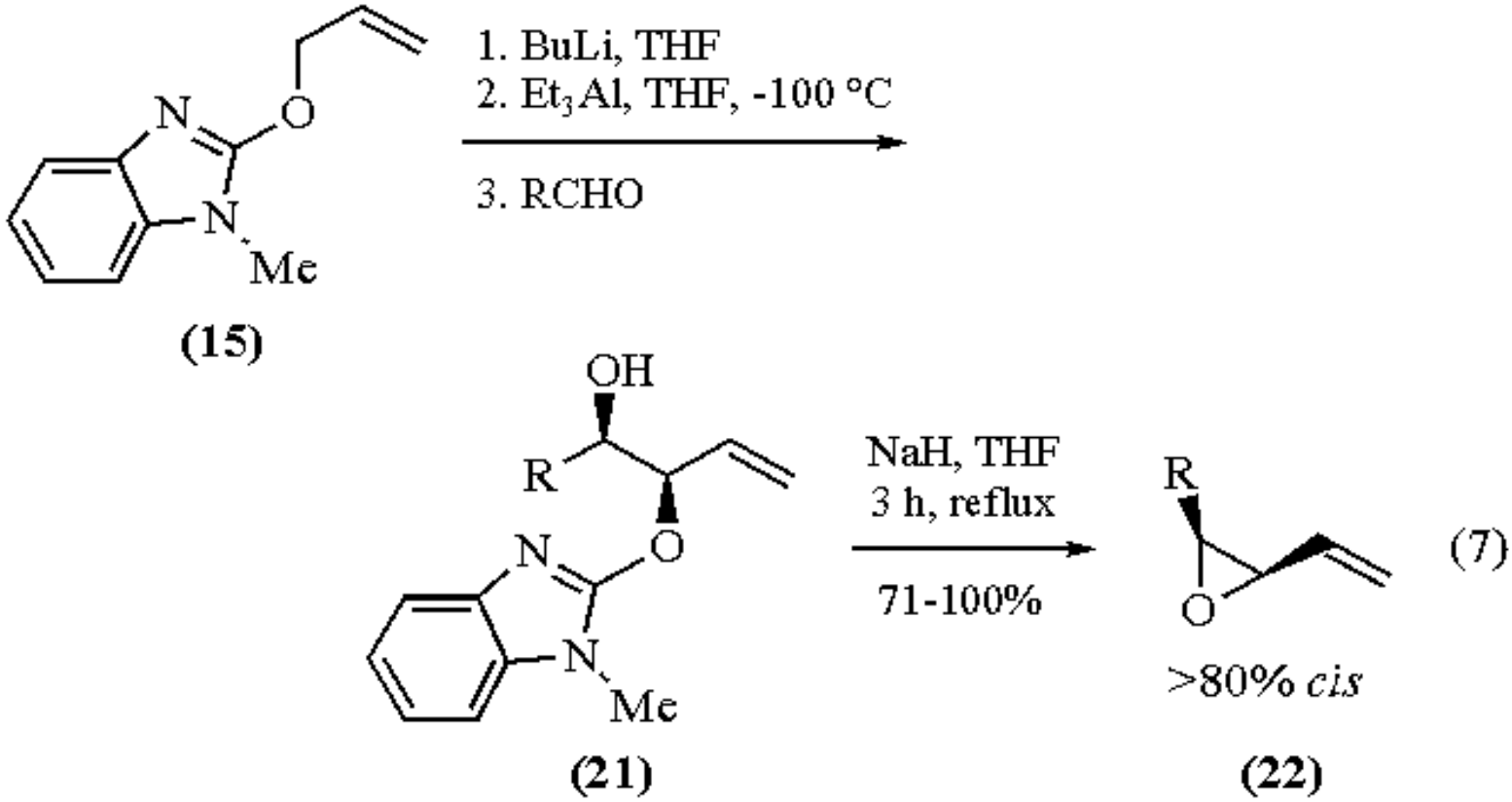

Lithiated Allylic Carbamates.

A significant advance in developing regiocontrolled γ-reactivity of 1-alkoxyallylcarbanions has been made by Hoppe.[15] The lithio derivatives of (**23**) and (**24**) undergo predominantly γ-alkylation when treated with alkyl halides[16] or aldehydes,[17] respectively, realizing a long sought goal of developing a homoenolate equivalent in the 1-alkoxyallyllithium system. Hydrolysis of the aldol adducts (**25**) leads to δ-hydroxy carbonyl compounds as lactols (**26**) or lactol ethers (eq 8). More importantly, deprotonation of substituted derivatives of (**23**) and (**24**) also proceeds well, opening up a family of homoenolate equivalents. Using this methodology, a synthesis of protected 4-oxoalkanoates has been developed (**27** -> **29**) which proceeds in moderate yield and with excellent γ-selectivity (eq 9).[18]

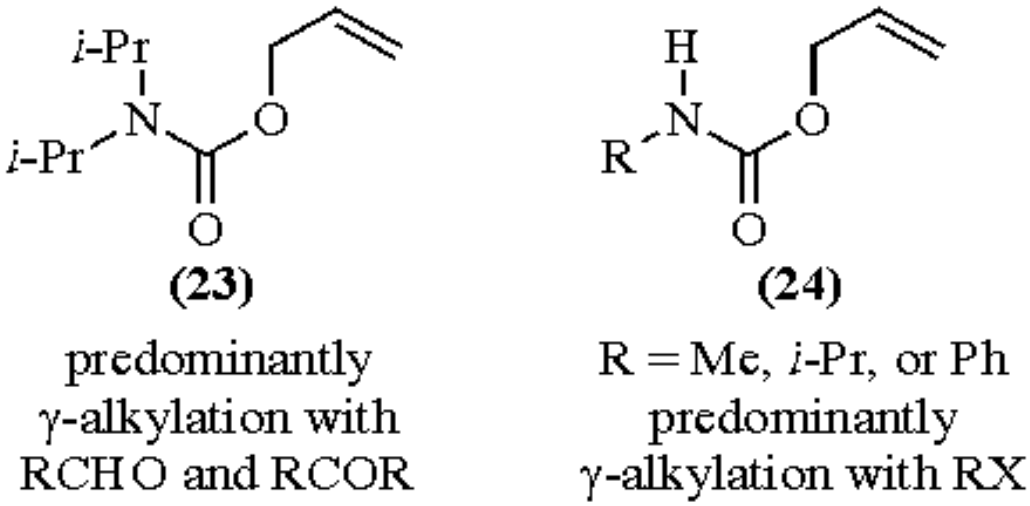

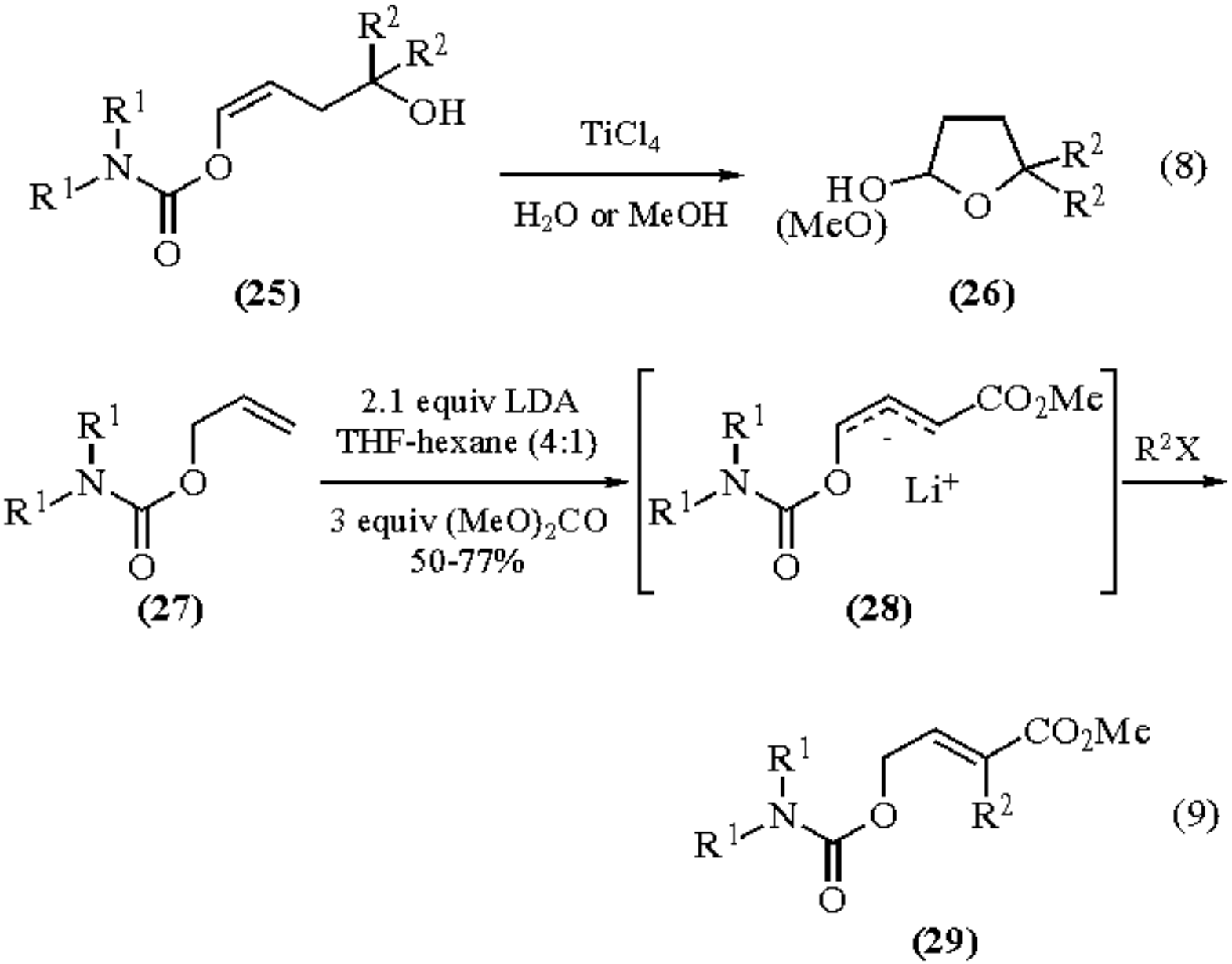

Diastereoselectivity in Additions to Aldehydes with γ-Alkoxyallylboronates.

1-Methoxyallyllithium may be converted to an intermediate γ-alkoxyallylboronate (**30**) by treatment with $(RO)_2B$-X (eq 10). This species undergoes highly regio- and diastereoselective additions to aldehydes to generate *syn*- and *anti*-1,2-diols.[19] A family of reagents (**31** and **32**) were prepared[20] and examined for their diastereoselectivity in reactions with aldehydes. The *cis*-isomers (**31**) give rise to predominantly the *syn*-products (**33**) (eq 11) while the *trans*-isomers (**32**) produce predominantly *anti*-products (**34**) (eq 12). A related study agrees with these results in the case of *cis*-γ-alkoxyallylboronates[21] and these reagents have seen use in target molecule synthesis.[22]

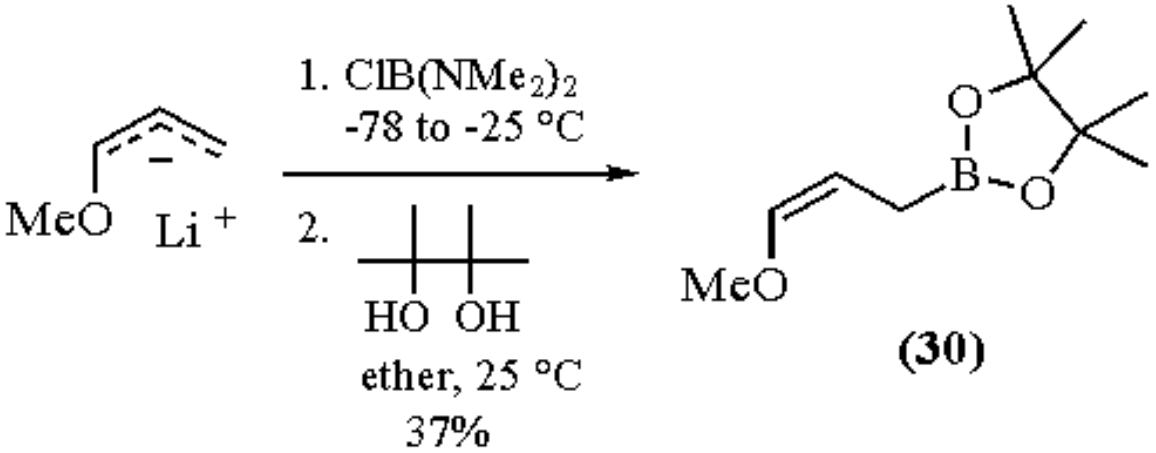

(10)

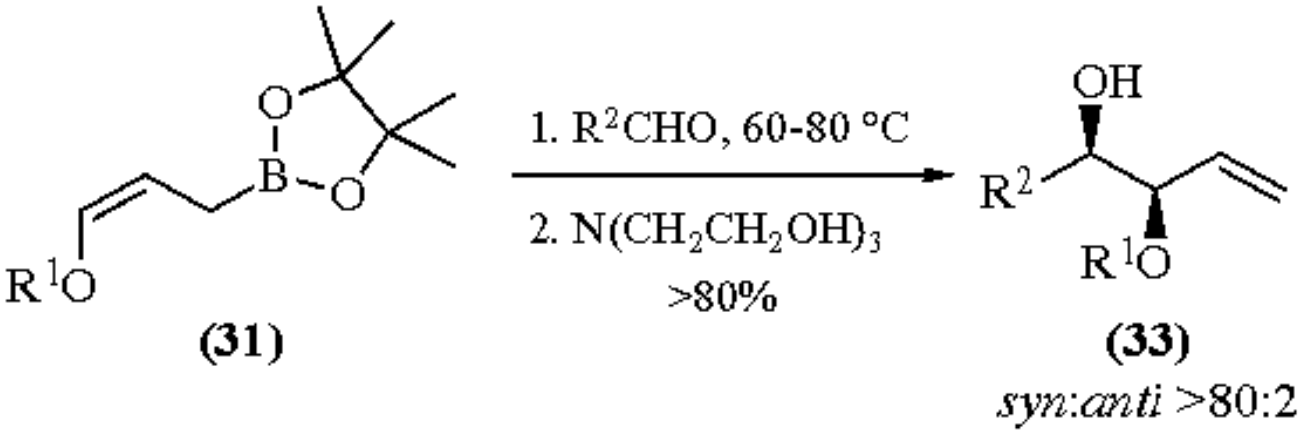

(11)

$R^1 = Me, CH_2OMe, CH_2CH_2TMS, CMe_2OMe$
$R^2 = Me, Et, i\text{-}Pr, Ph$

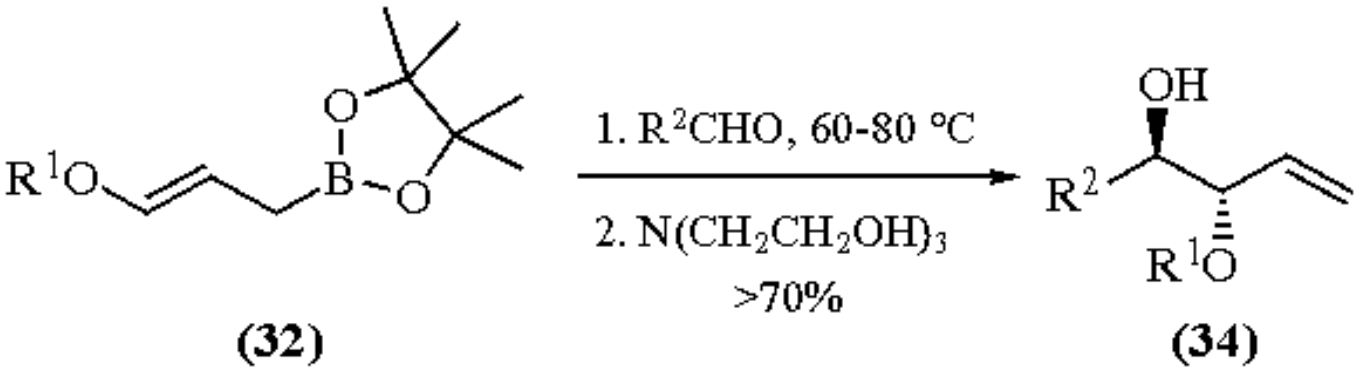

(12)

$R^1 = Me, CH_2CH_2TMS$
$R^2 = Me, Et, i\text{-}Pr, Ph$

Brown later extended this methodology, developing an enantioselective method for constructing *syn*-1,2-diols.[23] The boranes (**36**) and (**39**) are prepared from 1-methoxyallyllithium as exemplified in (**1**) -> (**36**) (eq 13). These enantiocomplementary reagents regio- and enantioselectively transfer a three-carbon unit to aldehydes, giving the enantiomeric diol precursors (**38**) (eq 13) and (**40**) (eq 14) in good yield with excellent enantioselectivity.

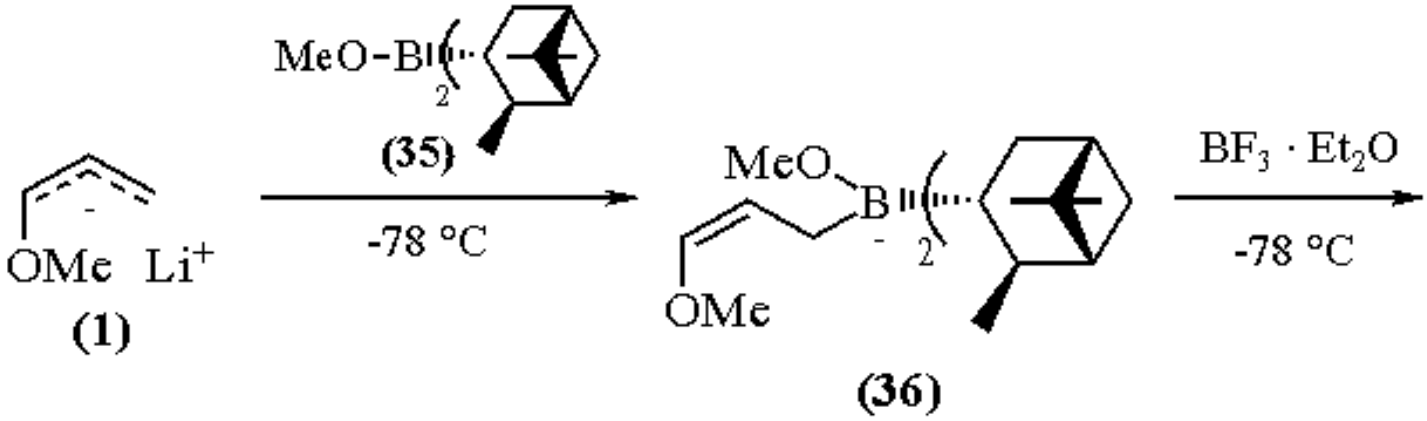

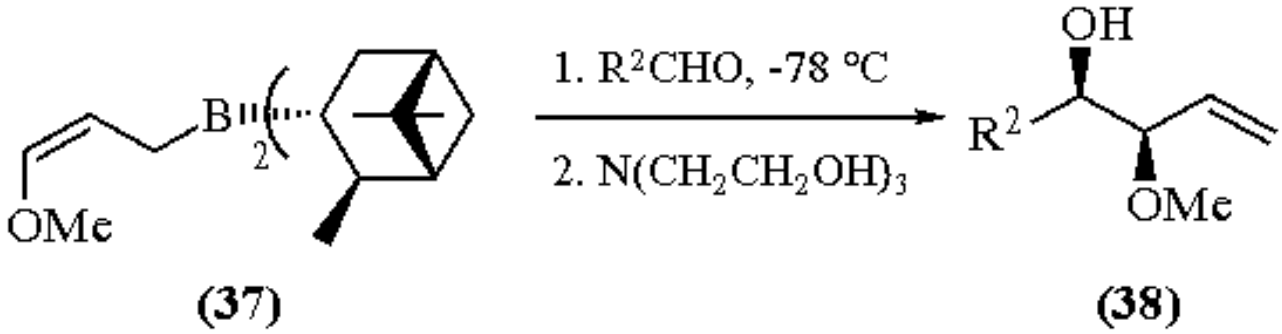

(13)

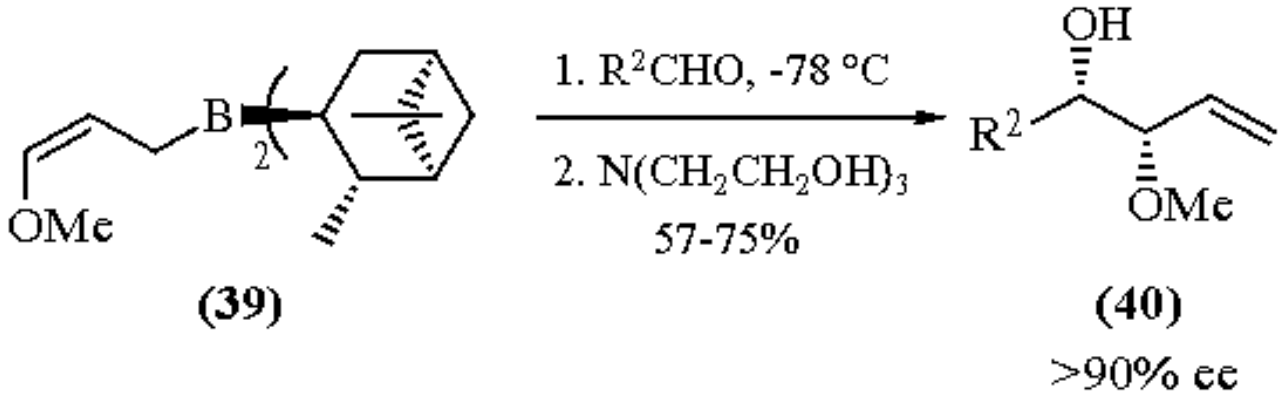

(14)

The stannane (**41**), also prepared from (**1**) shows diastereoselectivity similar to (**31**) in its Lewis acid-promoted reactions with aldehydes (eq 15).[24] Transformations analogous to the (**1**) to (**38**) conversion can be performed on systems having considerable complexity (**42**).[25]

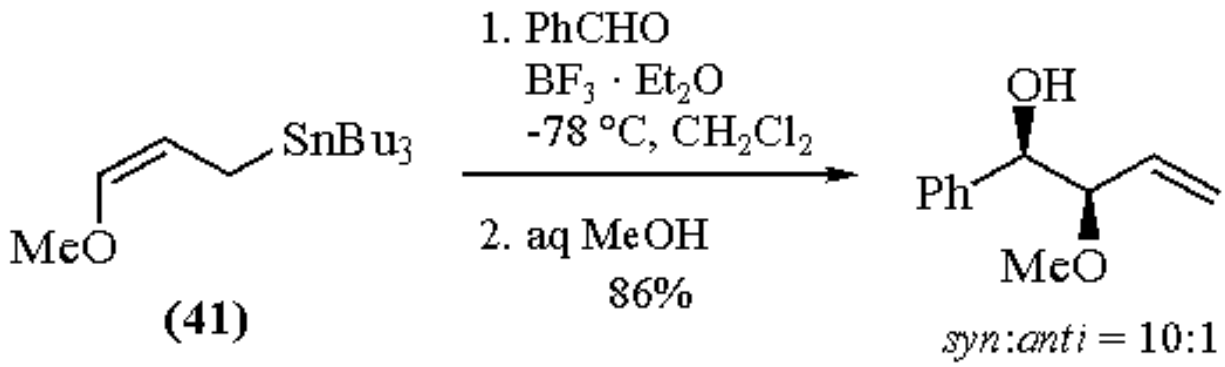

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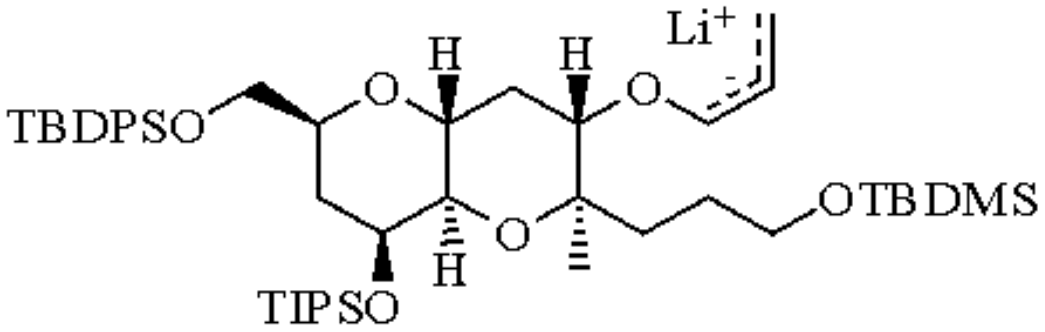

(42)

Arene Ring Annulation.

The zinc ate complex of 1-methoxyallyllithium has been used in a method for the annulation of catechol rings onto cyclic ketones.[26] Reaction of the α-hydroxymethylene ketone (**43**) with the zinc reagent gives the enal (**44**). Without purification, this is oxidized to the methyl ketone (**45**) which is cyclized and aromatized with base to the catechol monomethyl ether (**46**) in good overall yield (eq 16).

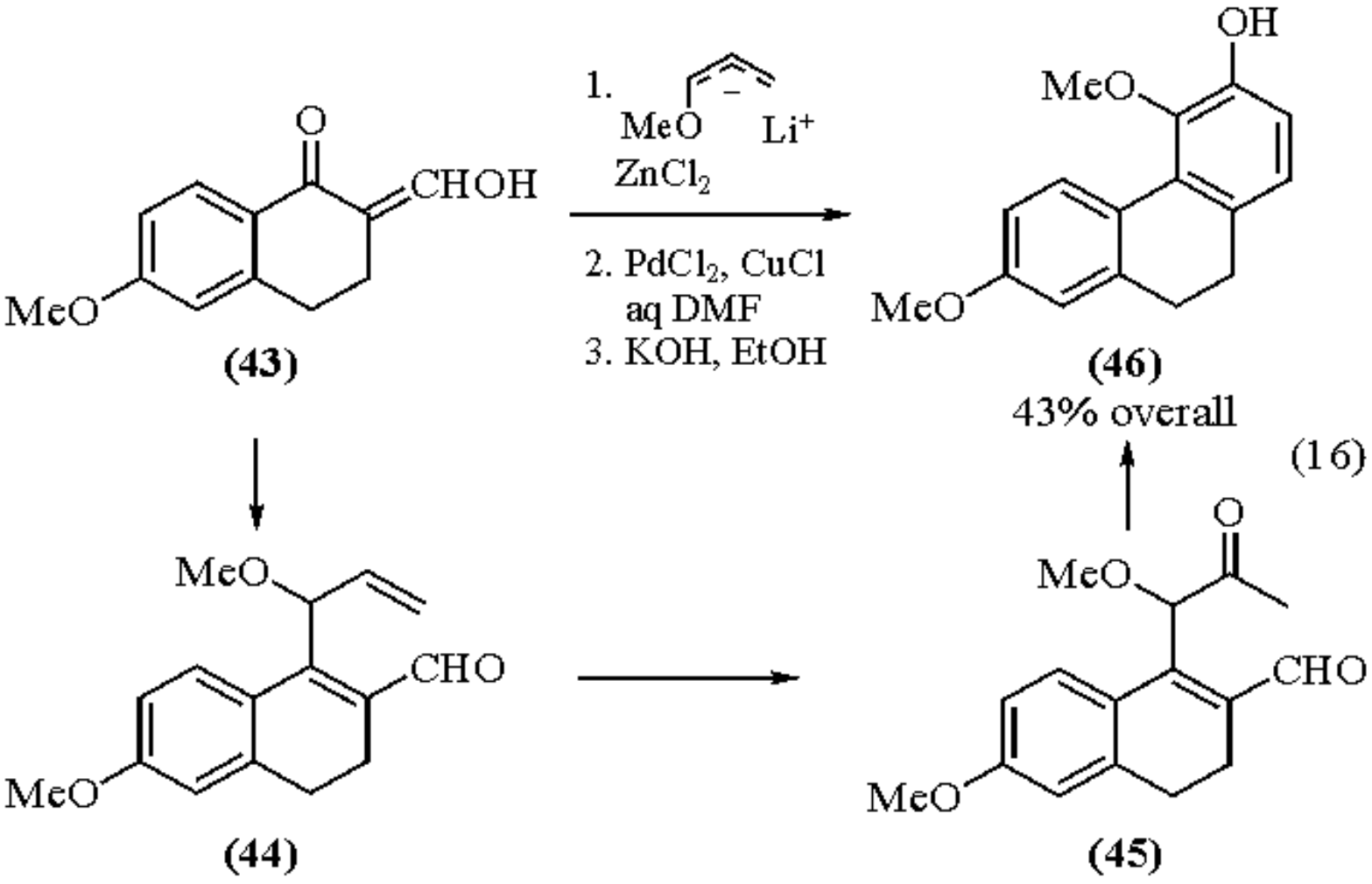

γ-Keto Aldehyde Synthesis.

Trialkylsilyloxyallyllithiums can be generated and treated with trialkylchlorosilanes to trap the Brook rearrangement product (**49**) as the bis-silanes (**50**) in good yield. These substances can be treated with acyl chlorides in the presence of ***Titanium(IV) Chloride*** to provide γ-keto aldehydes (**51**) after a hydrolytic workup (eq 17).[27]

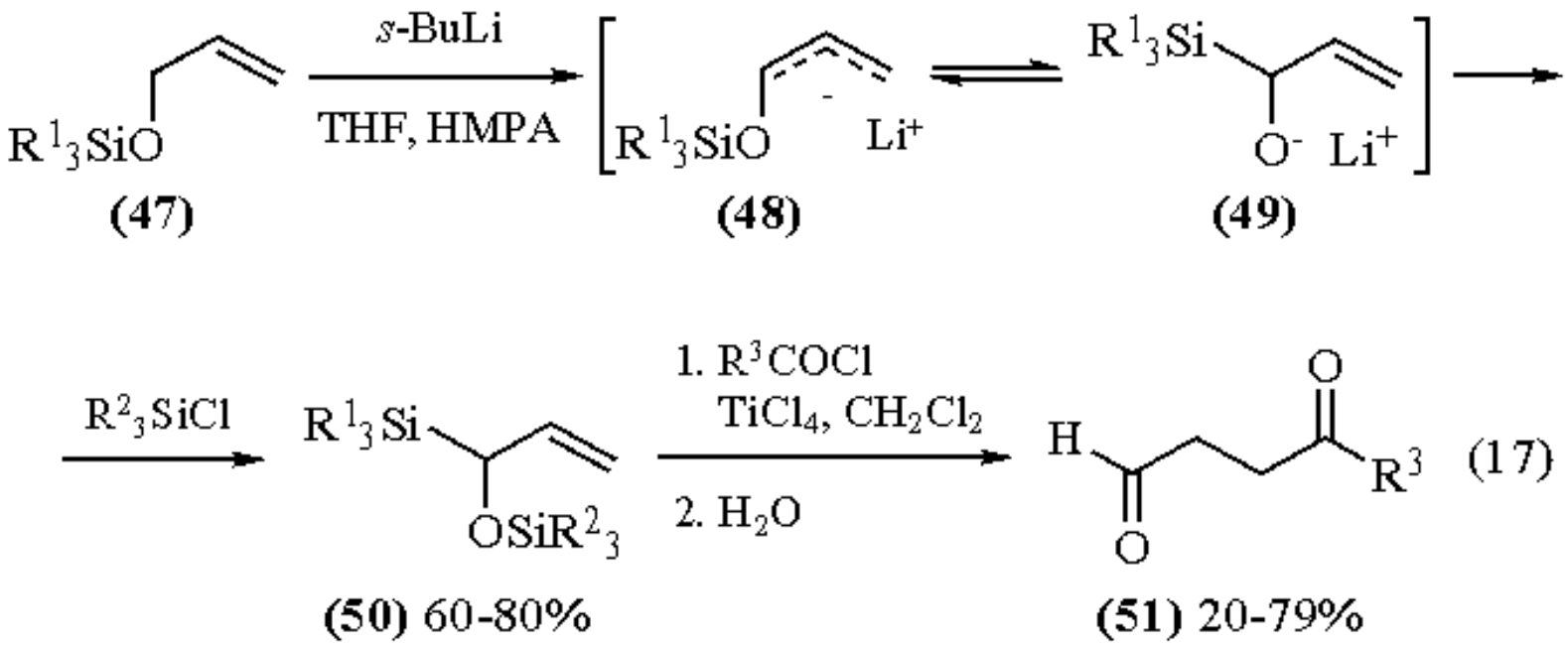

Related Reagents.

Allyllithium; ***t-Butoxymethyllithium***; ***(E)-1-(N,N-Diisopropylcarbamoyloxy)crotyllithium***.

---

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p-Methoxybenzaldehyde

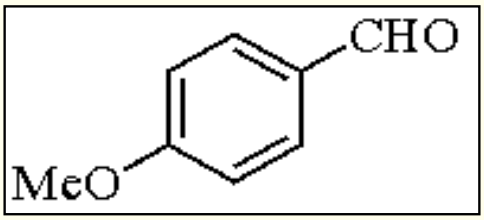

[123-11-5] · $C_8H_8O_2$ · *p*-Methoxybenzaldehyde · (MW 136.16)

(protection of diols as the versatile *p*-methoxybenzylidene acetal; protection of dithiols,[1] amines, hydroxy amines,[2] and diamines[3])

Alternate Name: *p*-anisaldehyde.

Physical Data: bp 248 °C; *d* 1.119 g cm^{-3}.

Form Supplied in: clear liquid; widely available.

Protection of Diols.

p-Methoxybenzylidene acetals are easily prepared from diols by reaction of the aldehyde in the presence of an acid catalyst such as ***Hydrogen Chloride***[4,5] or ***Zinc Chloride***.[6] They can also be prepared from the diol and *p*-$MeOC_6H_4CH_2OMe$ by oxidation with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** (CH_2Cl_2, rt, 30 min, 49-82% yield)[7] or by acid-catalyzed acetal exchange with *p*-$MeOC_6H_4CH(OMe)_2$.[8] The *p*-methoxybenzylidene acetal can be prepared by DDQ oxidation of a *p*-methoxybenzyl group that has a neighboring hydroxy function.[9] This methodology has been used to advantage in a number of syntheses.[10-12] Reaction of an epoxide with *p*-methoxybenzaldehyde in the presence of ***Tin(IV) Chloride*** results in the formation of the acetal without prior conversion to the diol (eq 1).[13]

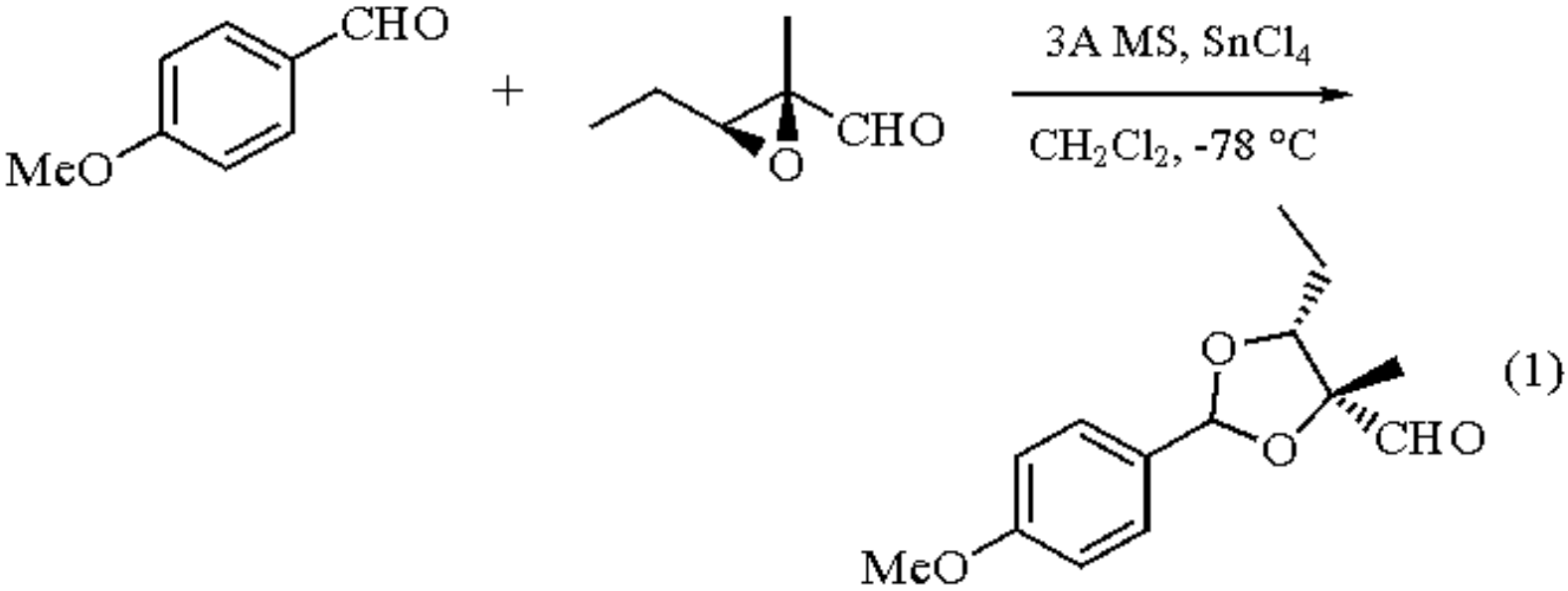

The advantages of the *p*-methoxybenzylidene acetal are that acid-catalyzed hydrolysis (80% AcOH, 25 °C, 10 h, 100% yield) is 10 times faster than that of the benzylidene group;[5] it is cleaved oxidatively with ***Cerium(IV) Ammonium Nitrate*** (MeCN, H_2O)[14] and it is relatively stable to Na/NH_3.[15]

As with the benzylidene group, a variety of methods have been developed to effect cleavage of one of the two C-O bonds in this acetal. Cleavage with ***Diisobutylaluminum Hydride***[10,16,17] has proven to be quite selective and is controlled by both electronic and steric factors. Oxidative cleavage with DDQ[7] results in the formation of a mixture of the two possible monobenzoates. In the carbohydrate field, selective cleavage to give either the more- or less-substituted derivative is possible with the proper choice of reagents (eq 2).[4,14,18,19] Use of $LiAlH_4/AlCl_3$,[12] $BH_3.NMe_3/AlCl_3$,[4] BH_3.THF, heat,[20] or $NaBH_3CN$/TMSCl/MeCN[11] results in cleavage at the less-hindered side of the acetal, whereas $NaBH_3CN$/HCl,[4] or $NaBH_3CN$/TFA/DMF[11] result in formation of an MPM ether at the less-hindered alcohol.

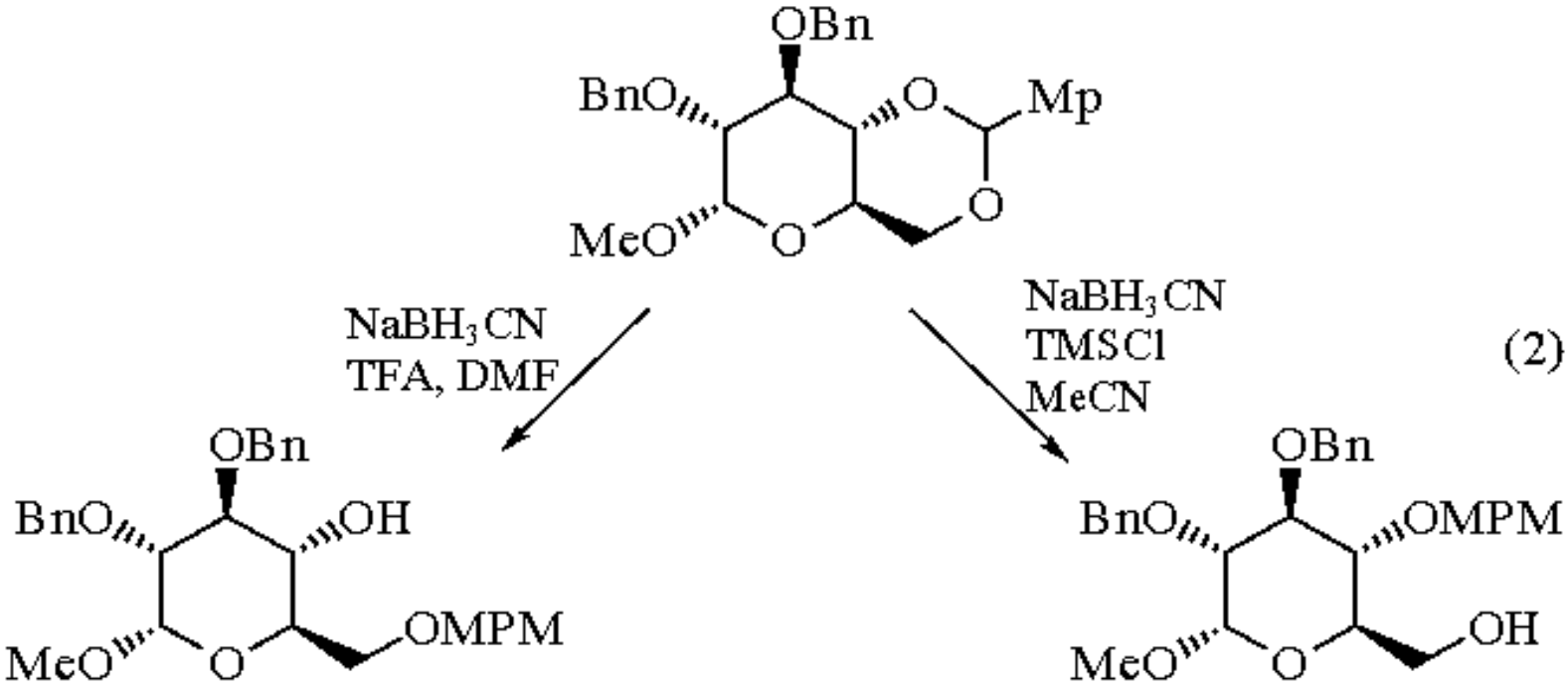

Protection of Amines.

p-Methoxybenzaldehyde has been used to protect an amine as the MPM derivative by reductive amination with ***Sodium Borohydride***.[21] It is also used to prepare imine derivatives of glucosamines which are used in glycoside couplings.[22]

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p-Methoxybenzyl Chloride[1]

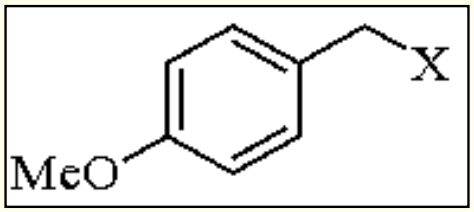

(X = Cl)

[824-98-6] · C_8H_9ClO · *p*-Methoxybenzyl Chloride · (MW 156.62) (X = Br)

[2746-25-0] · C_8H_9BrO · *p*-Methoxybenzyl Bromide · (MW 201.07)

(protection of alcohols,[3] thiols,[42] phenols,[29] amides,[55] amines,[50] and carboxylic acids[31])

Alternate Name: MPMCl.

Physical Data: X = Cl: bp 117-118 °C/14 mmHg; *d* 1.155 g cm^{-3}.

Solubility: sol all organic solvents.

Form Supplied in: the chloride is commercially available. The bromide is not commercially available and is prepared immediately before use because of its instability.[2]

Preparative Methods: to prepare the bromide, an ether solution of the alcohol is stirred with concd HBr, the phases are separated, and the organic phase is washed with saturated aq. NaBr, dried over K_2CO_3, and concentrated.

Handling, Storage, and Precautions: the chloride is stored over K_2CO_3 to stabilize it; the bromide is stored in the freezer to prevent polymerization, which occurs within a few days at rt.[2]

Protection of Alcohols.

The inherent stability of the MPM ether, coupled with a large repertoire of methods for its removal under mild conditions that do not normally effect other functional groups, makes it a particularly effective derivative for the protection of alcohols. The most common method for its introduction is by the Williamson ether synthesis. A number of bases can be used to generate the alkoxide, but ***Sodium Hydride***[3] in DMF (eq 1) or THF[4] (eq 2) is the most common. Other bases such as ***n-Butyllithium***,[5] ***Potassium Methylsulfinylmethylide*** (dimsylpotassium)[6] (eq 3), and

Sodium Hydroxide under phase-transfer conditions[7] are also used. From these results, it is clear that protection can be achieved without interference from Payne rearrangement, and considerable selectivity can be obtained. In the ribose case, selectivity is probably achieved because of the increased acidity of the 2´-hydroxy group. The additive ***Tetra-n-butylammonium Iodide***[8] is used for in situ preparation of the highly reactive *p*-methoxybenzyl iodide, thus improving the protection of very hindered alcohols. Selective monoprotection of diols is readily occasioned with *O*-stannylene acetals.[9]

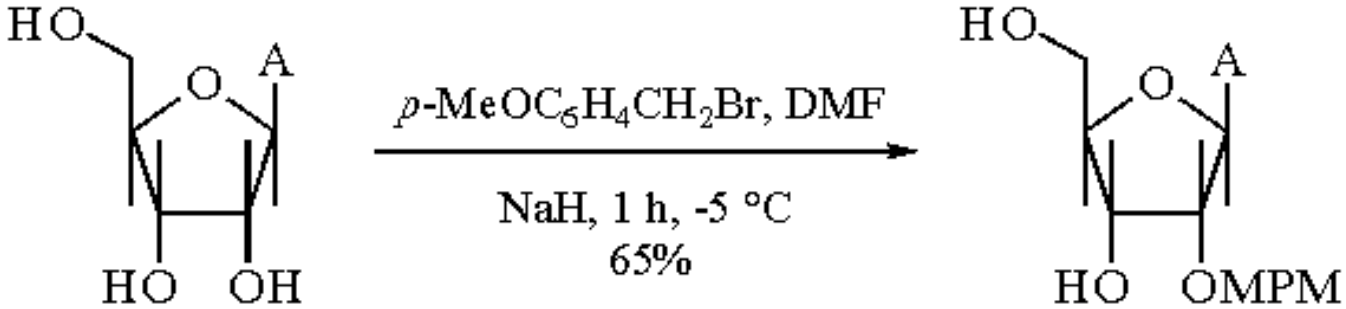

(1)

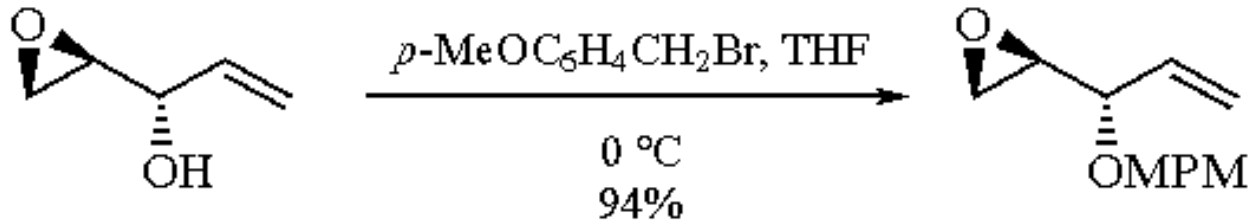

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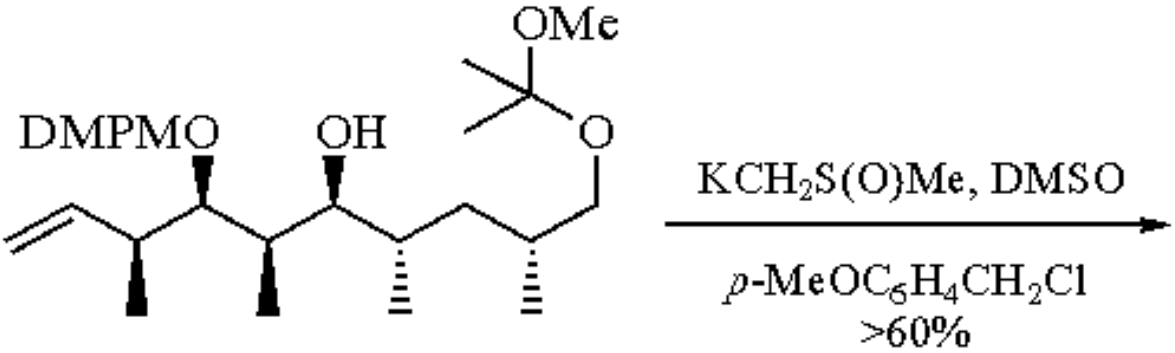

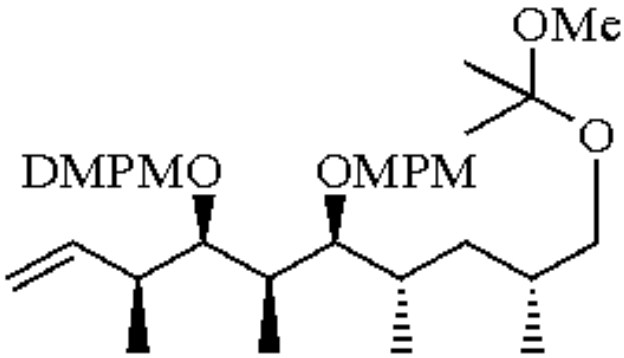

(3)

Cleavage of the MPM group is usually achieved oxidatively with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone***.[10-12] When DDQ is used, overoxidation of the alcohol occasionally occurs,[13,14] but for the most part this is not a problem. In general, selective cleavage of the MPM group is achieved in molecules containing benzyl groups, but more forcing conditions will result in benzyl cleavage.[15] ***Cerium(IV) Ammonium Nitrate***,[16] trityl tetrafluoroborate,[17] photolysis,[18]

electrolytic oxidation,[19] dimethylboron bromide,[20] ***Boron Trichloride***,[21] ***Iodotrimethylsilane***,[22] ***Tin(II) Chloride***/***Chlorotrimethylsilane***/anisole,[23] hydrogenolysis,[24] and ozonolysis[25] have also been used to cleave this derivative. Selectivity for the *O*-MPM is achieved over an amide MPM derivative with DDQ.[26]

In the presence of neighboring hydroxyl groups, the DDQ oxidation of MPM ethers leads to cyclic acetals, thus affording a level of selectivity which may not be possible to achieve otherwise.[27] In a synthesis of erythronolide (eq 4), the critical oxidative cyclization had to be performed with freshly recrystallized DDQ supported on molecular sieves in order to prevent acid-catalyzed isomerization of the acetal from its initial kinetic disposition to the more thermodynamically favorable orientation.[28]

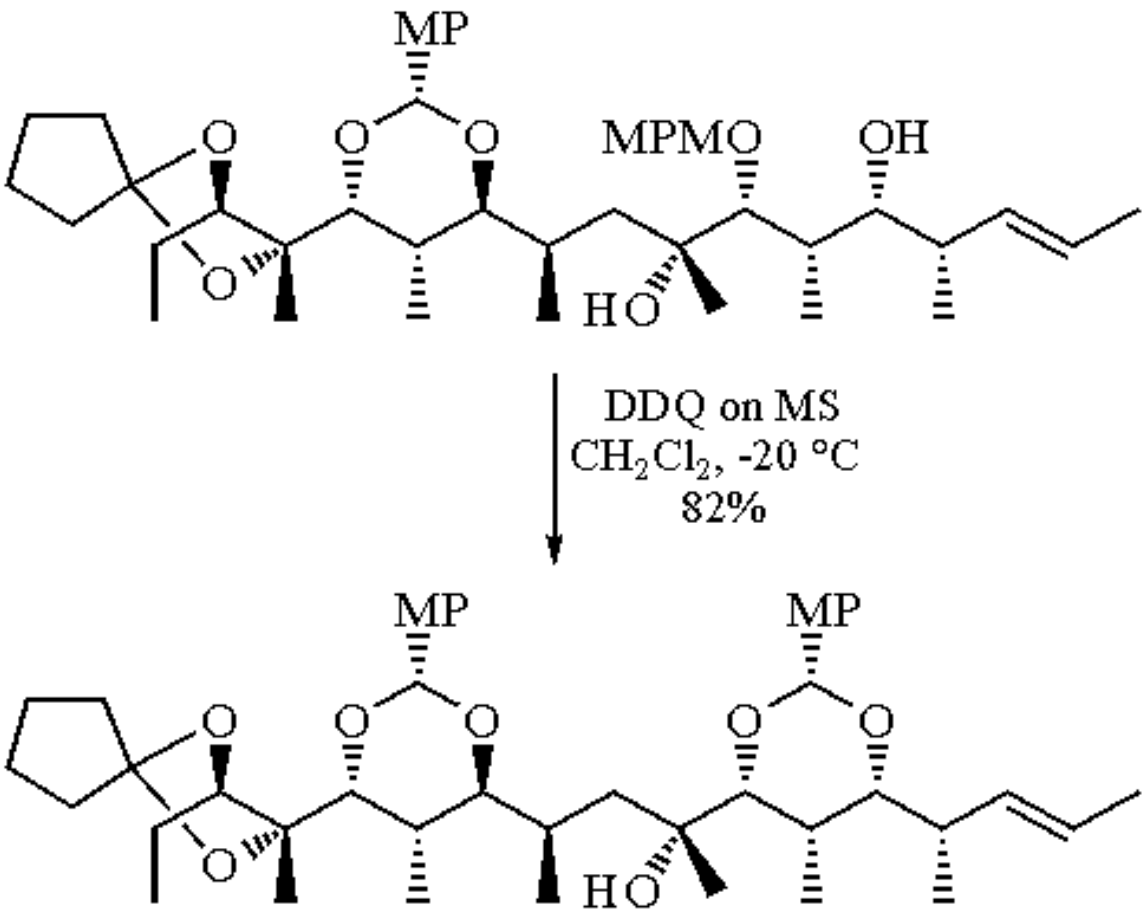

(4)

Protection of Phenols.

Protection of phenols is achieved using *p*-methoxybenzyl chloride ($Bu_4N^+I^-$, K_2CO_3) in acetone,[29] or the benzyl bromide (*i*-Pr_2NEt) in CH_2Cl_2.[30] Deprotection is occasioned with ***Trifluoroacetic Acid***[29] or ***10-Camphorsulfonic Acid***/$Me_2C(OMe)_2$.[30]

Protection of Carboxylic Acids.

p-Methoxybenzyl esters have been prepared from the Ag^I salt of amino acids and the benzyl halide (Et_3N, $CHCl_3$, 25 °C, 24 h, 60% yield),[31] and from cephalosporin precursors and the benzyl alcohol [$Me_2NCH(OCH_2$-*t*-$Bu)_2$, CH_2Cl_2, 90% yield],[32] and from the benzyl halide ($NaHCO_3$, DMF).[33] They are also prepared by activation of the acid with

isopropenyl oxychloroformate ($MeOC_6H_4CH_2OH$, DMAP, 0 °C, CH_2Cl_2, 91%).[34] They are cleaved by acidic hydrolysis (CF_3CO_2H/PhOMe, 25 °C, 3 min, 98% yield;[35] HCO_2H, 22 °C, 1 h, 81% yield),[31] by heating with phenol,[36] by treatment with $AlCl_3$ (anisole, CH_2Cl_2 or $MeNO_2$, -50 °C; $NaHCO_3$, -50 °C, 73-95% yield),[37,38] or by $CF_3CO_2H/B(OTf)_3$.[39]

Protection of Thiols.

The protection of thiols as *S*-*p*-methoxybenzyl thioethers is occasioned with MPMCl and a base such as NH_3,[40] KOH (MeOH),[41] and NaH (THF, 60 °C, 1 h).[42] The reduction of disulfides with ***Lithium Aluminum Hydride*** affords an intermediate thiolate that can be trapped with MPMCl to give the thioether.[43] The cleavage of *S*-*p*-methoxybenzyl thioethers is effected with $Hg(OAc)_2/CF_3CO_2H$ (0 °C, 10-30 min), $Hg(OCOCF_3)_2$/aq AcOH (20 °C, 2-3 h, followed by H_2S or $HSCH_2CH_2OH$, 100% yield),[44,45] $Hg(OCOCF_3)_2/CF_3CO_2H$/anisole,[46] CF_3CO_2H/reflux,[40] anhydrous HF/anisole (25 °C, 1 h, quant),[47] $(4\text{-}BrC_6H_4)_3NH^+ SbCl_6^-$ (75%),[48] HCO_2H (5 °C, 30 min, 45%).[42] During the synthesis of peptides which contain 4-methoxybenzyl-protected cysteine residues, sulfoxide formation may occur (eq 5). These sulfoxides, when treated with HF/anisole, form thiophenyl ethers that cannot be deprotected; therefore the peptides should be subjected to a reduction step prior to deprotection.[49]

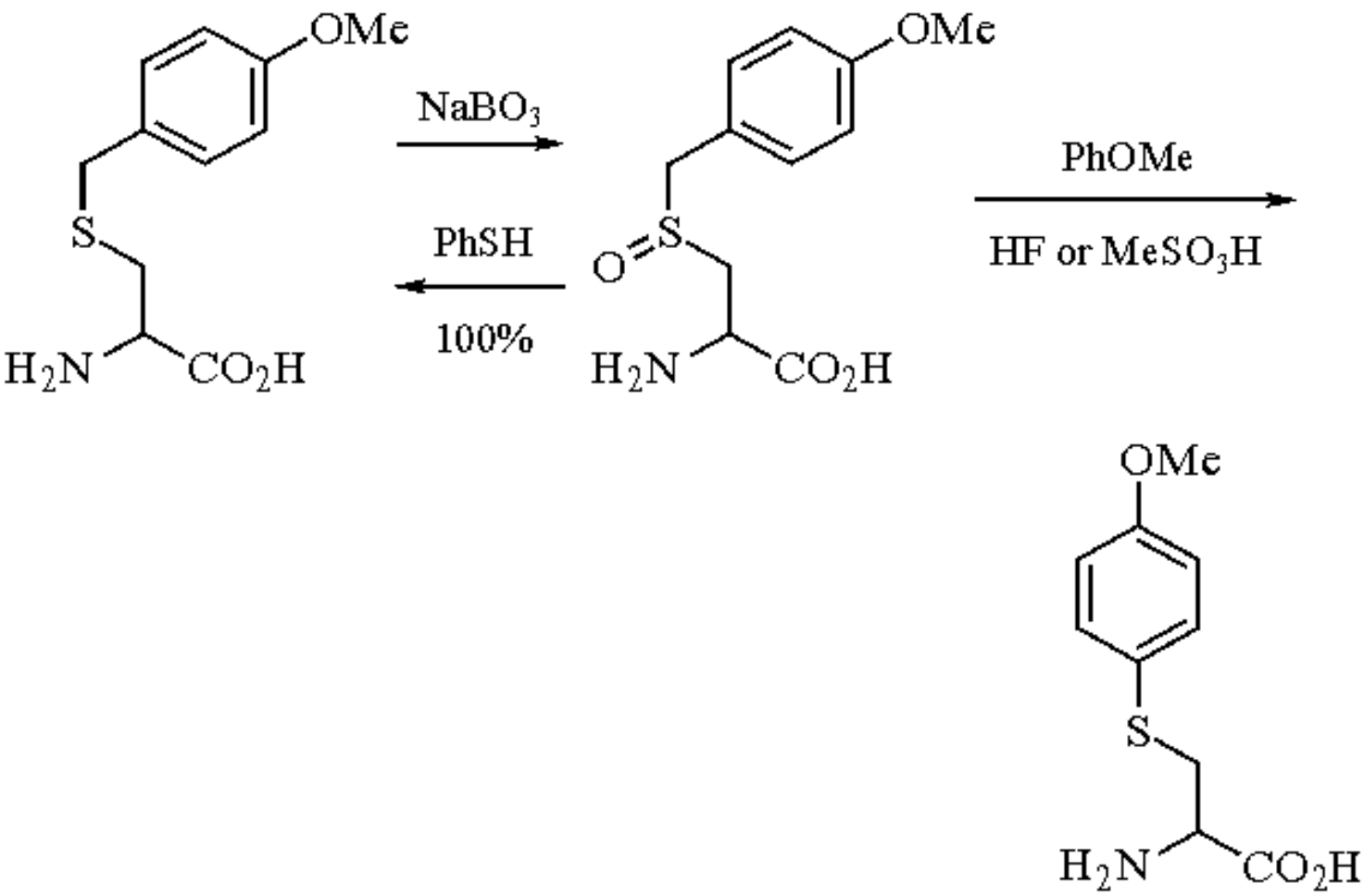

(5)

Protection of Amines.

The use of the MPM group to protect amines has not seen many applications, but a few examples are available in the literature. The MPM group can be introduced on an aromatic amine with MPMBr (DMF, KI, K_2CO_3, 92%),[50] or by reductive amination (anisaldehyde, PhH, H_2O; $NaBH_4$, MeOH, 92%),[51] but for the most part the MPM group acts as a carrier for the nitrogen to be introduced into a molecule. MPM amines can be cleaved by hydrogenolysis,[52] oxidation to the imine followed by hydrolysis,[53] or acylation with MeCHClOCOCl (CH_2Cl_2, -7 °C, 5 min; MeOH, reflux, 89%).[54]

Protection of the Amide Nitrogen.

Of the few methods for protection of the amide NH, the MPM group has found success where other methods have not been entirely successful.[55] The group can be introduced using methods similar to those used for alcohols: MPMCl/NaH/DMF,[56] MPMBr/NaH,[55] MPMCl (DBU, MeCN, 60 °C, 5 h, 92%),[57] MPMCl/Ag_2O.[58]

The most common method for removal of the amide MPM group is by oxidation with DDQ[59] or CAN.[60] With CAN, the benzoyl imide is sometimes a byproduct of the reaction (eq 6), but this is easily cleaved by hydrolysis.[61] The amide MPM group is also cleaved by solvolysis in TFA[51] or $AlCl_3$/anisole.[62] Metalation with ***t-Butyllithium*** followed by reaction with oxygen (62%) has been used successfully (eq 7).[63]

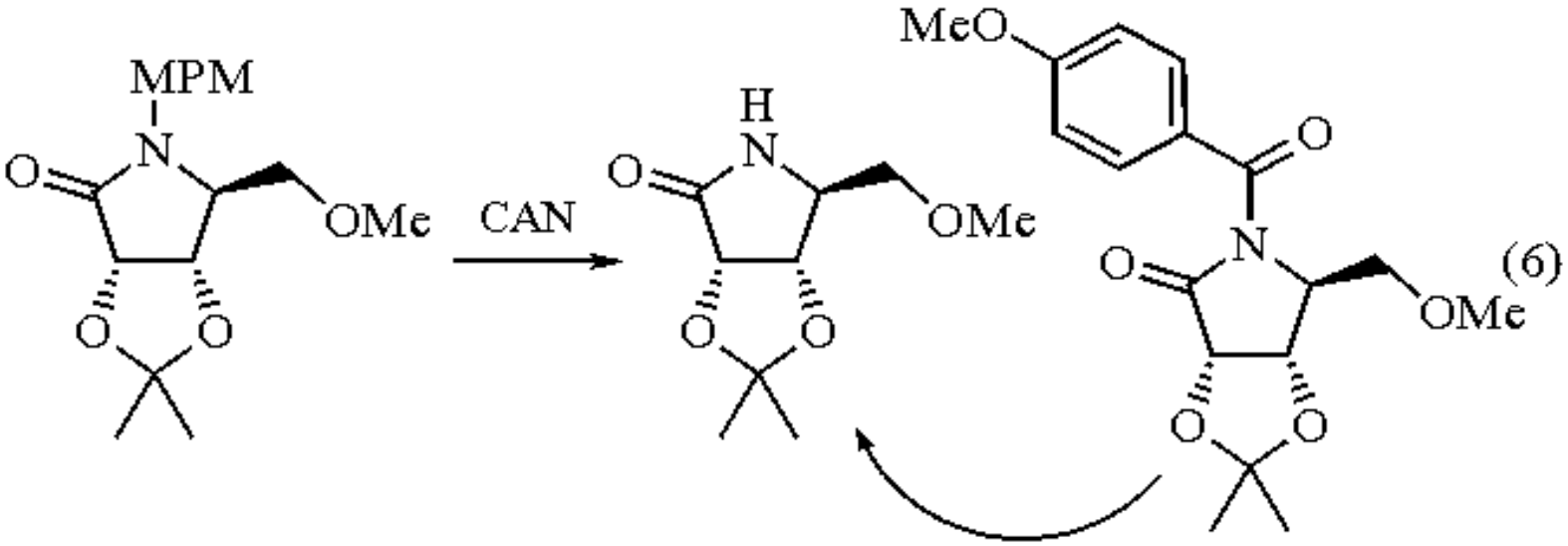

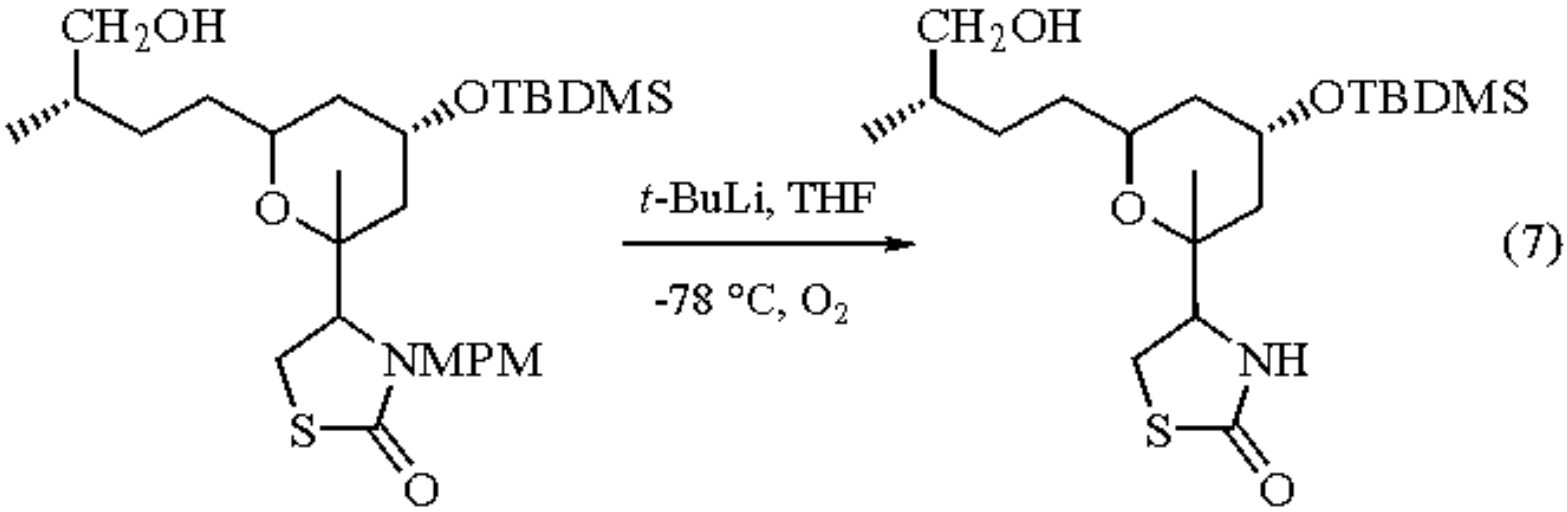

Protection of Phosphates.

There is one example where the MPM group is used for phosphate protection. It is cleaved with 48% aq HF/MeCN/H_2O (eq 8).[64]

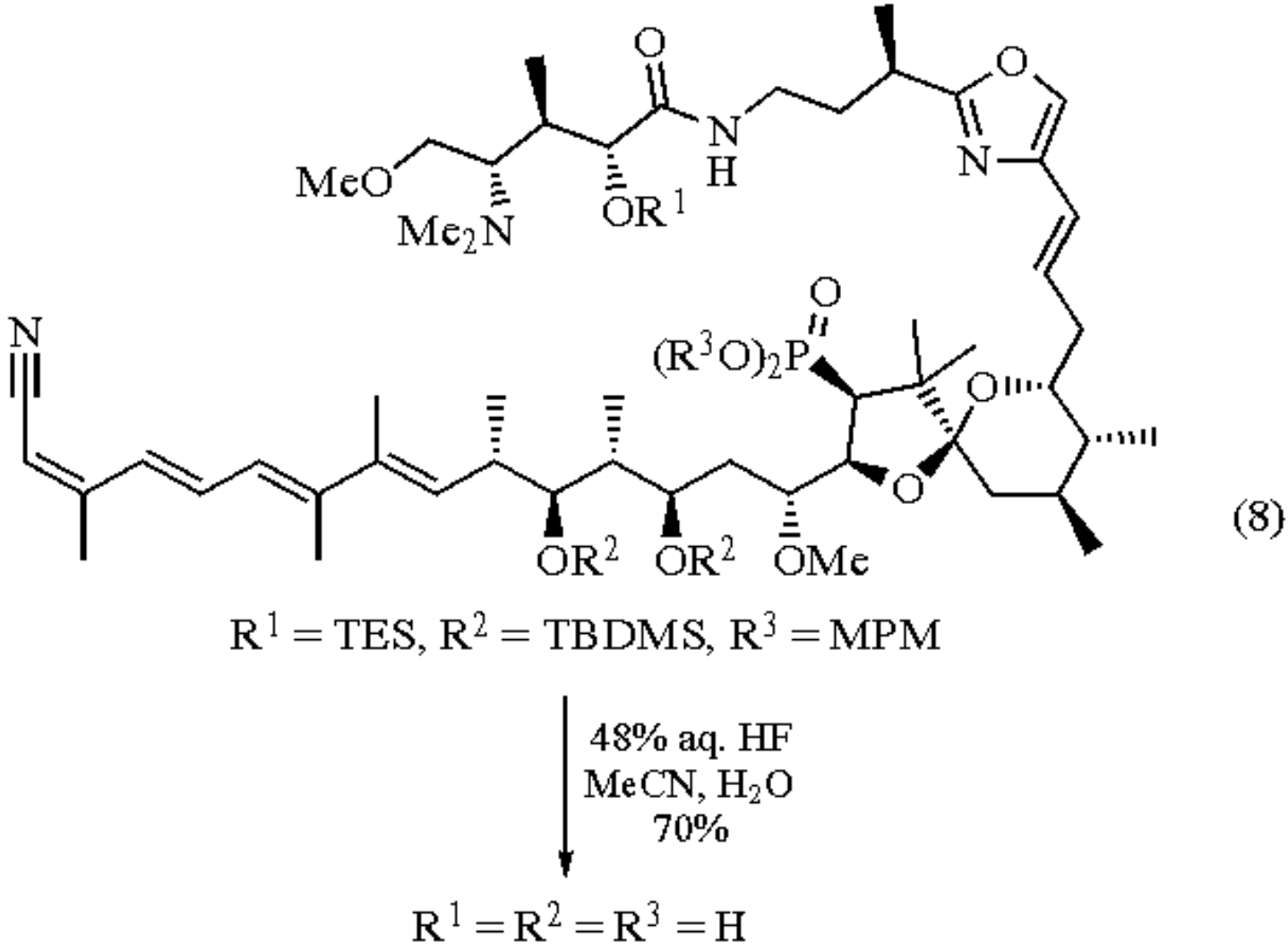

Related Reagents.

Benzyl Bromide; ***Benzyl Chloride***; ***Benzyl Iodide***; ***3,4-Dimethoxybenzyl Bromide***; ***(p-Methoxybenzyloxy)methyl Chloride***; ***4-Methoxybenzyl 2,2,2-Trichloroacetimidate***.

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(*p*-Methoxybenzyloxy)methyl Chloride[1]

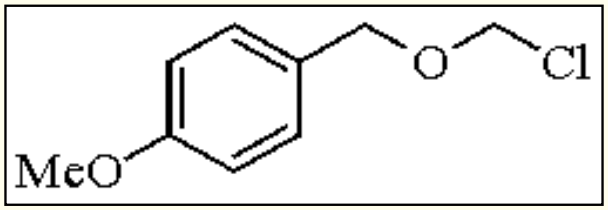

[88023-78-3] · $C_9H_{11}ClO_2$ · (*p*-Methoxybenzyloxy)methyl Chloride · (MW 186.65)

(protection of alcohols;[1] one-carbon synthon[4])

Alternate Name: PMBM-Cl; 4-methoxybenzyl chloromethyl ether.

Physical Data: bp 66-67 °C/0.01 mmHg.

Preparative Method: easily prepared from the MTM ether of *p*-methoxybenzyl alcohol by treatment with ***Sulfuryl Chloride*** in CH_2Cl_2 at -78 °C followed by solvent evaporation and distillation.

Handling, Storage, and Precautions: decomposes upon storage[1] but can be stored in the freezer for at least 3 days.[2]

Alcohol Protection.

The PMBM group was developed as an alcohol protecting group for protection of the allylic alcohol in the indole (**1**) when other groups were found not to be suitable. The PMBM group is readily introduced (PMBM-Cl, ***Diisopropylethylamine***, CH_2Cl_2, rt, 5-30 h) on to a variety of structural types, as illustrated in Table 1. PMBM-Cl has also been used to trap alkoxides directly (eq 1).[3]

Table 1 Protection of Alcohols

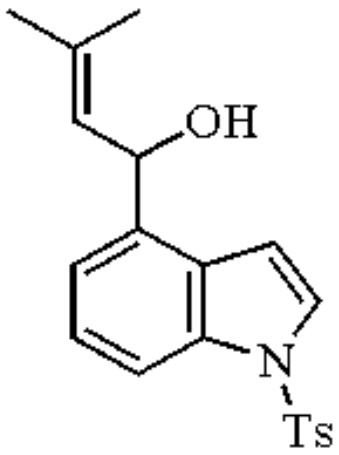	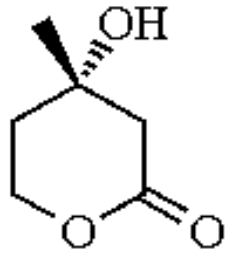
(1) Protection 100% Deprotection 65%[a]	Protection 84% Deprotection 89%
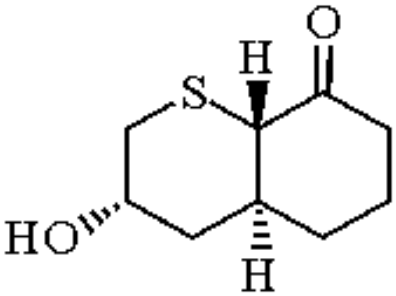	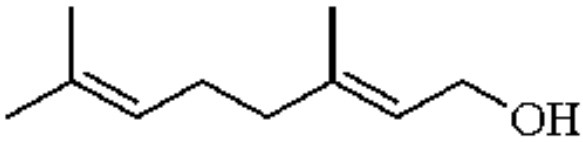
Protection 78% Deprotection 88%	Protection 95% Deprotection 63% + 21% geranial

[a] Only the rearranged tertiary alcohol was isolated.

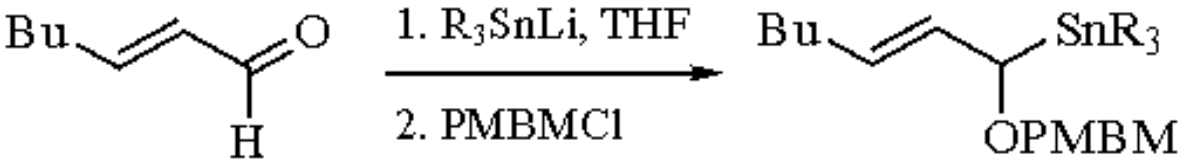

(1)

Deprotection is accomplished oxidatively with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone***, but conditions used for the deprotection of the *p*-methoxybenzyl group may also be suitable. It may also be cleaved by a simple hydrolysis with 3:1 THF/6 M HCl at 50 °C.

One-Carbon Synthon.

The preparation of 4-methoxybenzyloxymethyllithium from PMBM-Cl proceeds smoothly and is used in a reaction with crotonaldehyde to form a differentially protected diol derivative (eq 2).[4]

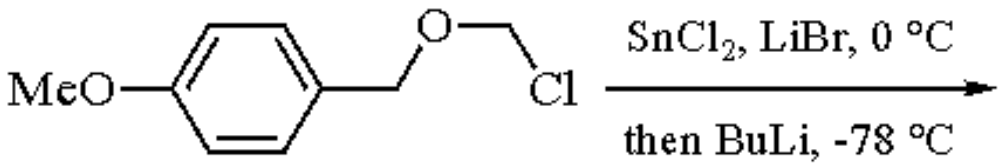

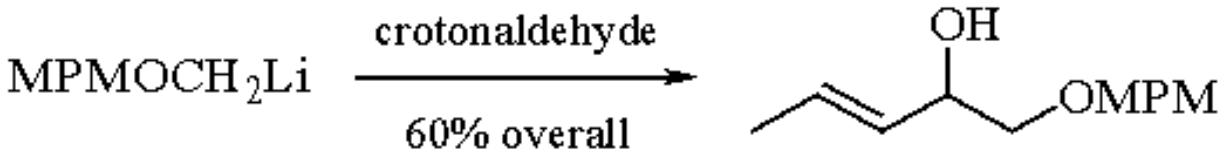

(2)

Related Reagents.

p-Methoxybenzyl Chloride; ***4-Methoxybenzyl 2,2,2-Trichloroacetimidate***.

---

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4-Methoxybenzyl 2,2,2-Trichloroacetimidate[1]

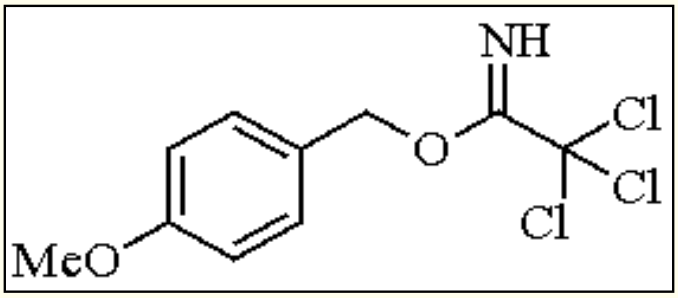

[89238-99-3] · $C_{10}H_{10}Cl_3NO_2$ · 4-Methoxybenzyl 2,2,2-Trichloroacetimidate · (MW 282.56)

(reagent for the protection of alcohols under mildly acid conditions)

Physical Data: bp 135-137 °C; *d* 1.361 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear liquid.

4-Methoxybenzyl 2,2,2-trichloroacetimidate is used to protect alcohols as the *p*-methoxybenzyl ether. It was first used in oligoribonucleotide synthesis[2] and the utility and generality of the method was extended by Yonemitsu.[3] The main advantage of using this reagent is that it provides an alternative to the Williamson ether synthesis, which is commonly used to introduce this protective group under basic conditions. Since this reagent is used to install the group under acidic conditions, it provides a method to protect base-sensitive alcohols. Protic acids such as ***Trifluoromethanesulfonic Acid***, ***10-Camphorsulfonic Acid***,[5] and ***p-Toluenesulfonic Acid***[6] generally give excellent yields of product. ***Boron Trifluoride Etherate***[7] and ***Triphenylmethyl Perchlorate*** are also effective catalysts. The preferred solvents are ether and CH_2Cl_2, but hydrocarbon cosolvents have been used.[2,7,8] Tertiary, secondary, and primary alcohols are protected with equal efficiency, but the question of selectivity has not been addressed. The reagent can be used to install the *p*-methoxybenzyl ether group in the presence of a variety of other protective groups, the most notable of which is the the *t*-butyl group considering the strong acids used as catalysts.[4] Table 1 shows some of the structural types that have been protected with this reagent. Many of these examples serve to illustrate cases where basic conditions could not be used to achieve protection. For a discussion of the deprotection of the MPM group, see ***p-Methoxybenzyl Chloride***.

Table 1 Protection of Alcohols

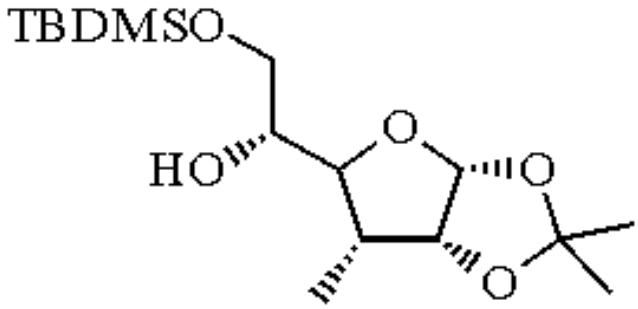

$TrClO_4$, Et_2O, 82%

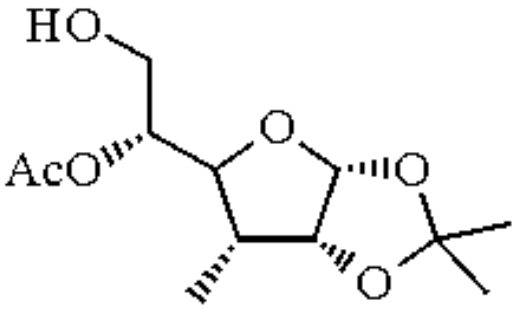

$TrClO_4$, Et_2O, 85%

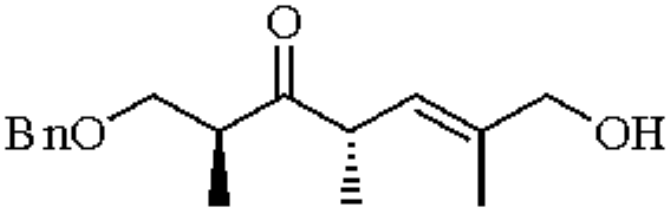

$TrClO_4$, Et_2O, 73%

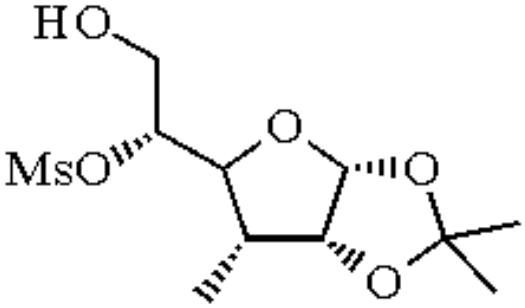

$TrClO_4$, Et_2O, 91%

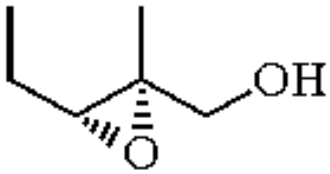

TfOH, Et_2O, 82%

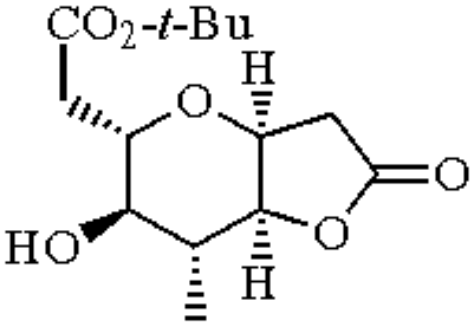

TfOH, Et_2O, >80%

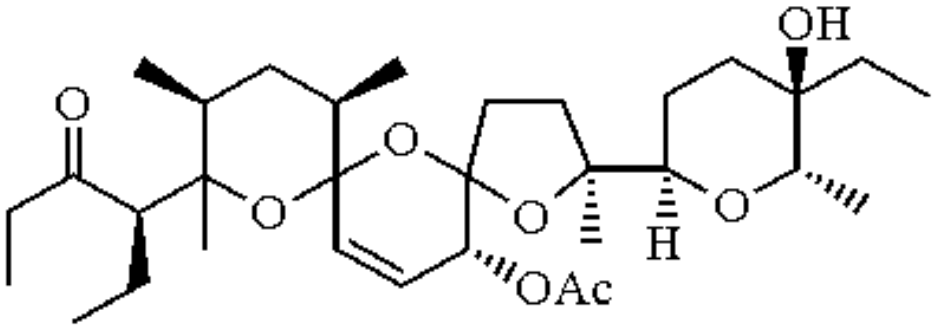

TfOH, Et_2O, 71%

Related Reagents.

Benzyl Bromide; ***Benzyl Chloride***; ***Benzyl Iodide***; ***3,4-Dimethoxybenzyl Bromide***; ***p-Methoxybenzyl Chloride***; ***(p-Methoxybenzyloxy)methyl Chloride***.

---

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1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene[1]

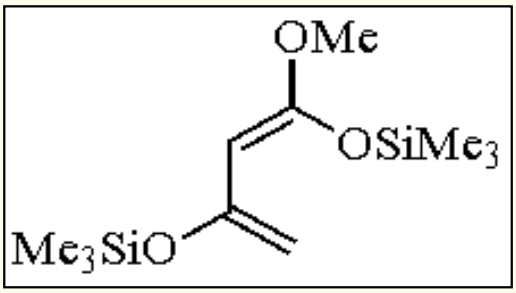

[67609-52-3] · $C_{11}H_{24}O_3Si_2$ · 1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene · (MW 260.53) (*E*)

[74590-73-1] (*Z*)

[81114-98-9]

(reactive diene for the Diels-Alder reaction;[1,2] acetoacetic ester dianion equivalent that reacts with various electrophiles[3])

Physical Data: bp 56-58 °C/2.0 mmHg.[2]

Solubility: insol H_2O; sol most organic solvents.

Preparative Methods: from methyl acetoacetate according to the scheme shown in eq 1.[2,3] A detailed experimental procedure is described by Chan et al.[3c] It is critical that the reaction temperature for the metalation step be less than -23 °C. Under these conditions, essentially pure diene is obtained, but at rt the reaction gives a 3:1 mixture of the diene and *C*-silylated products derived by rearrangement. The stereochemistry of the diene was first proposed to be (*E*),[3a] but later was shown to be (*Z*) by precise NMR studies.[4]

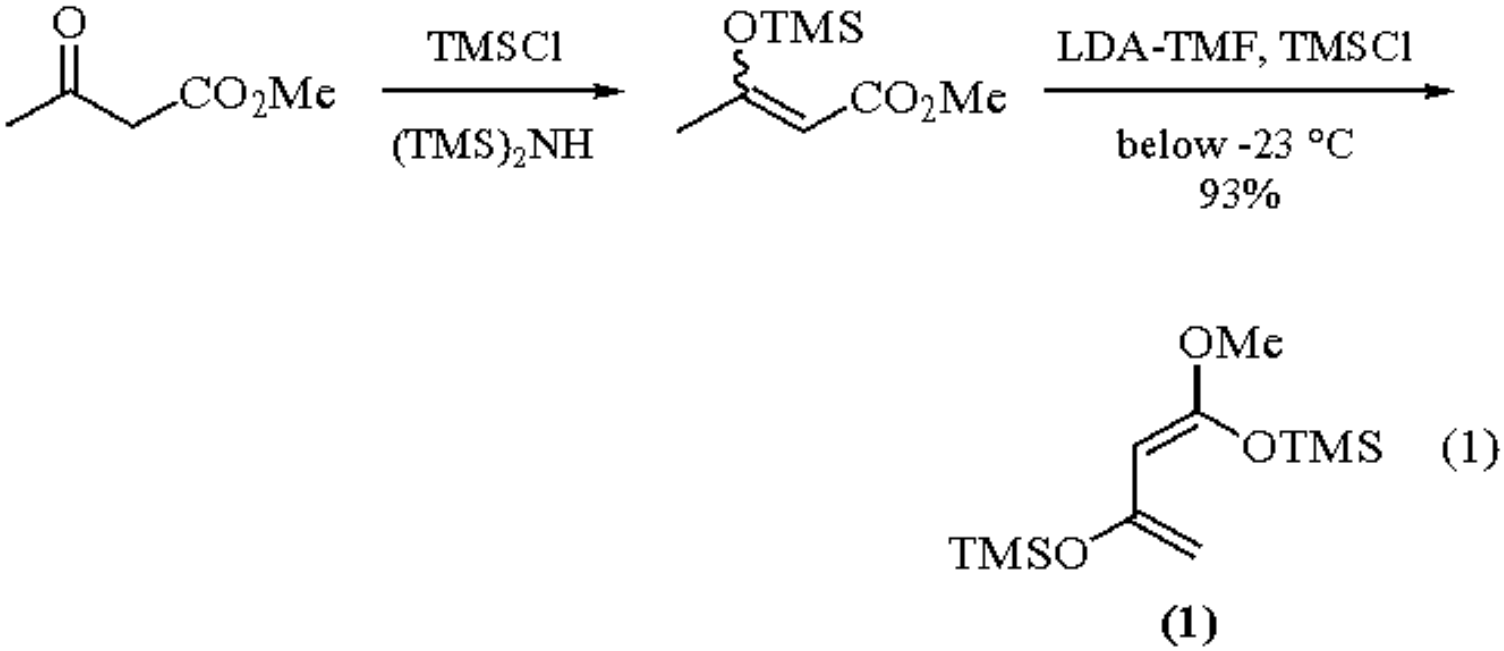

Handling, Storage, and Precautions: although this diene is purified safely by distillation below 80 °C,[2,5] *O*- to *C*-migration of a silyloxy group is observed at elevated temperatures (see eq 2).[3,5] Crude diene may be used directly without further purification and it can be kept in a stoppered container in a freezer for several weeks without appreciable decomposition. It is slowly hydrolyzed when exposed to air and moisture.[3c]

Thermal Rearrangement.

On being heated at 120 °C for 1 h, the diene (**1**) and related analogs rearrange to give *C*-silyl-(*E*)-α,β-unsaturated esters (eq 2).[5] Flash vacuum pyrolysis of the diene at 680 °C gives an allene ester via concomitant elimination of methyl trimethylsilyl ether (eq 3).[6]

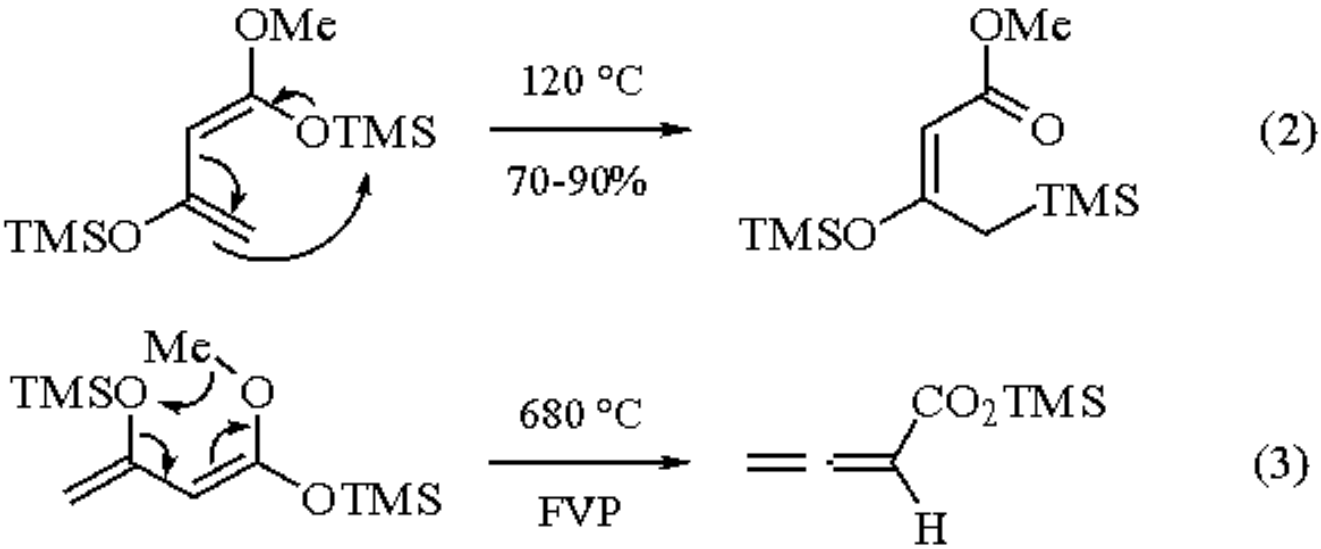

Diels-Alder Reactions.

The diene reacts with ***Dimethyl Acetylenedicarboxylate*** in toluene at reflux to give aromatic products (eq 4). Elimination of methanol predominates over loss of trimethylsilanol.[2] Reaction with allenedicarboxylate gives similar products (eq 5).[7]

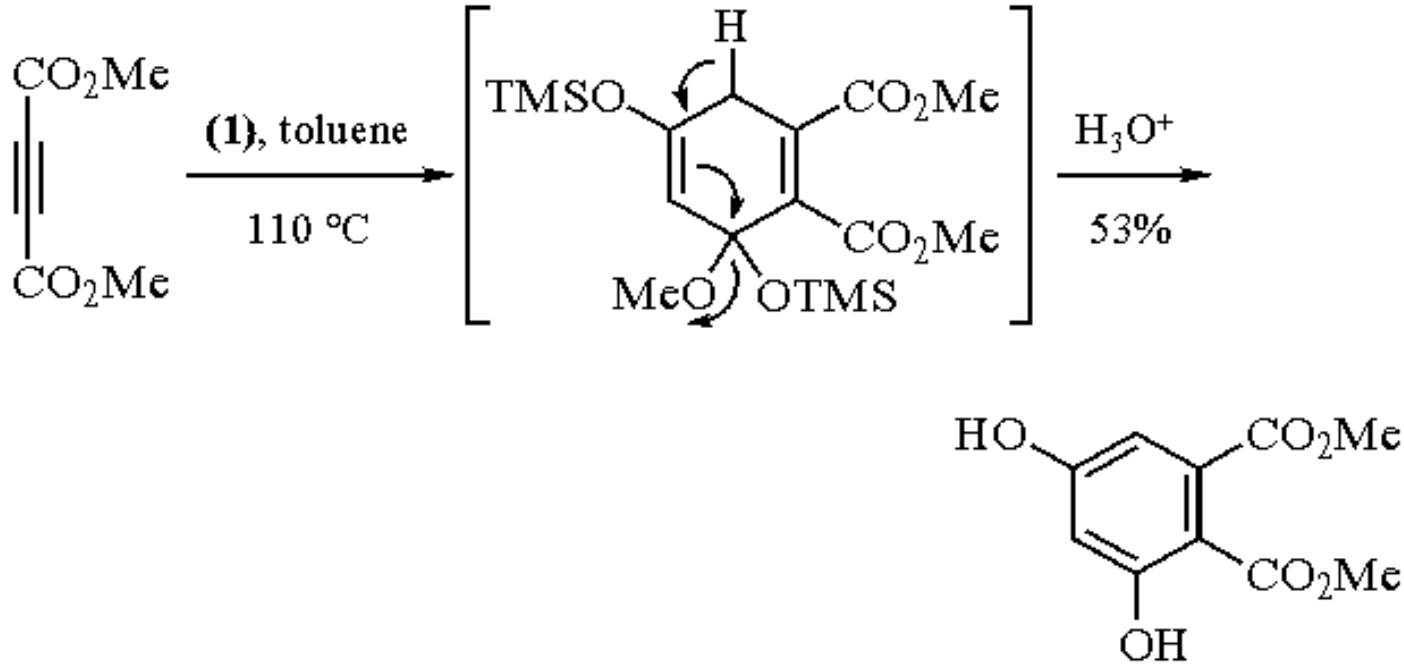

(4)

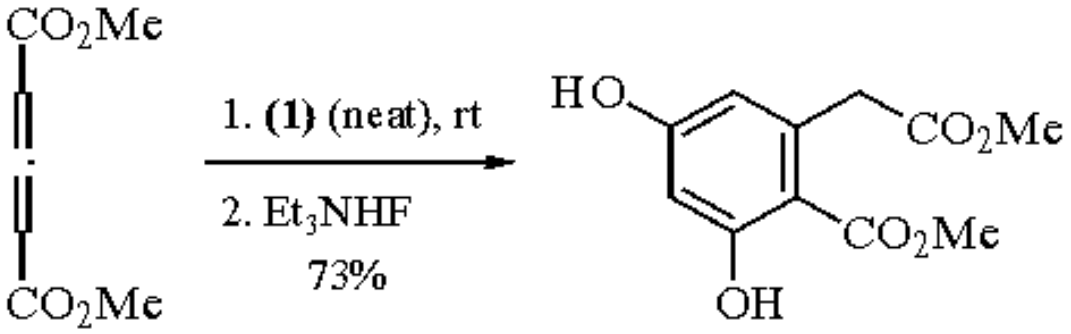

(5)

The most widely used dienophiles with (**1**) are quinones, such as benzoquinones,[4,8] naphthoquinones,[9-11] and anthraquinones,[12] with or without halogen-substituents at the α-position. In general, the reaction proceeds very smoothly at rt or below to give adducts in moderate yields (50-70%). With monohalogenated quinones the reaction is rapid and the initial Diels-Alder adducts usually lose HCl to give quinone derivatives directly (eq 6).[9] In the particular case of 2,6-dichlorobenzoquinone, the initial double Diels-Alder adduct was isolated as a crystalline product. X-ray crystallographic analysis of this intermediate established that the stereochemical course of the cycloaddition is via the *cis-endo* mode (eq 7).[4] In reactions with *vic*-dihalogenated quinones, however, only substitution of halide by an acetoacetate residue occurs and no cycloadducts are obtained.[13]

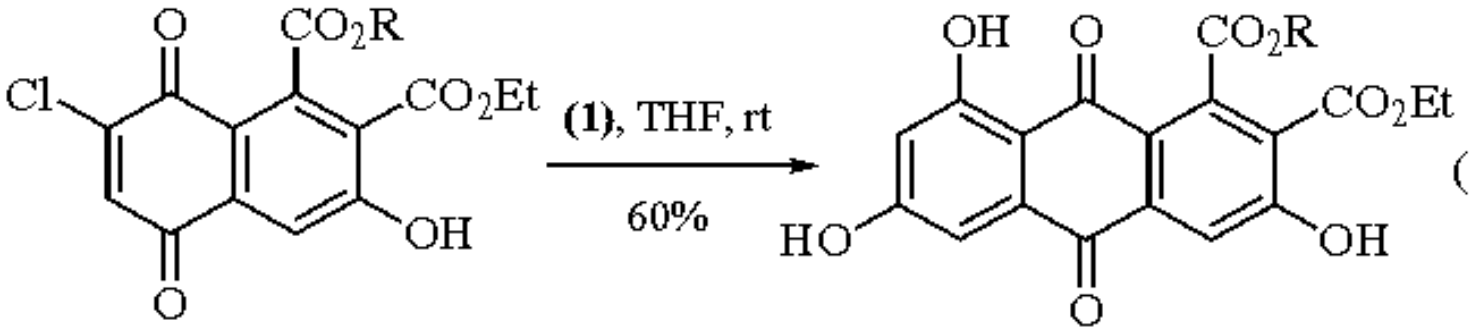

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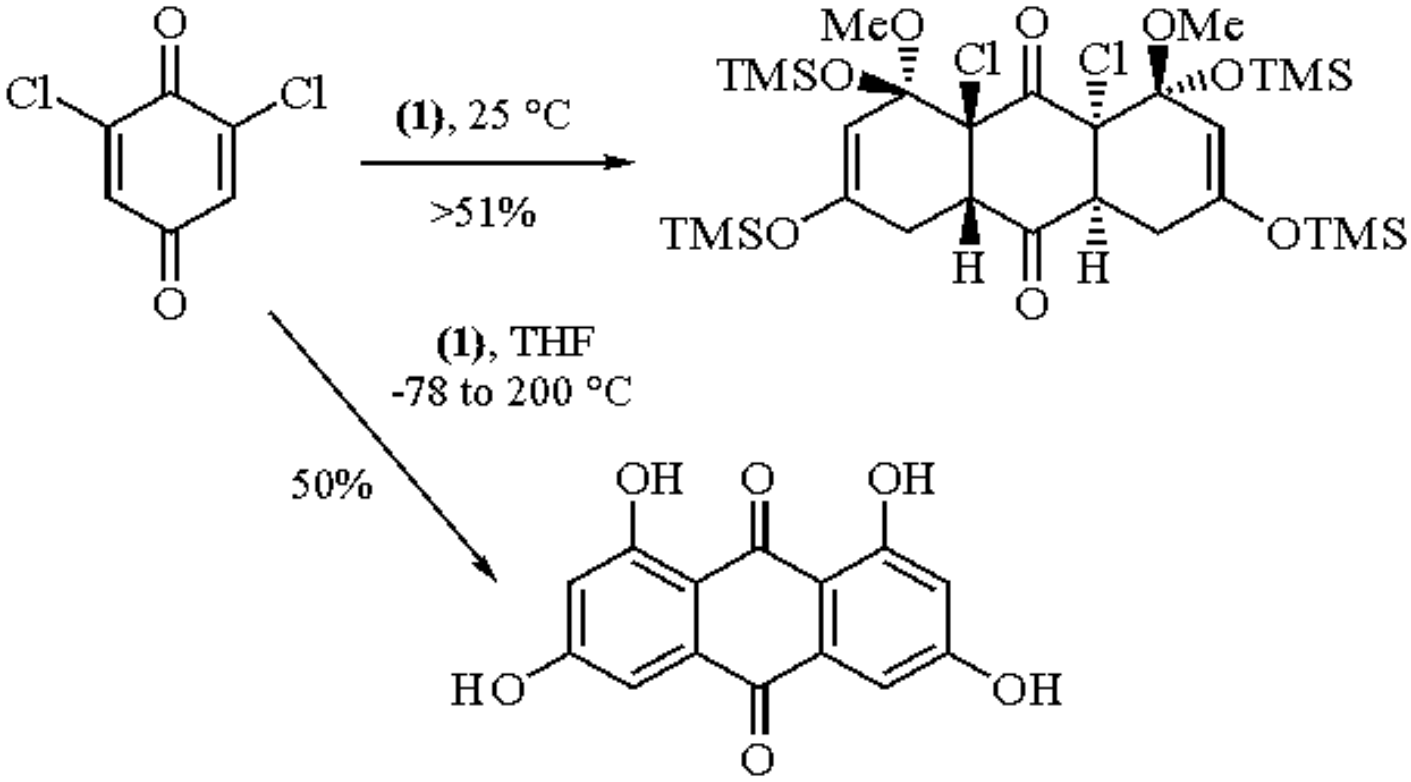

(7)

These methodologies have been applied to the syntheses of quinoid substances with fused aromatic systems, such as (±)-averufin (eq 7),[8] (±)-2-hydroxyaklavinone (eq 8),[10] and naphthopyran antibiotics.[13] Reaction with a sulfonamide dienophile gives adducts which are converted to potential anti-inflammatory drugs, oxicams (eq 9).[14]

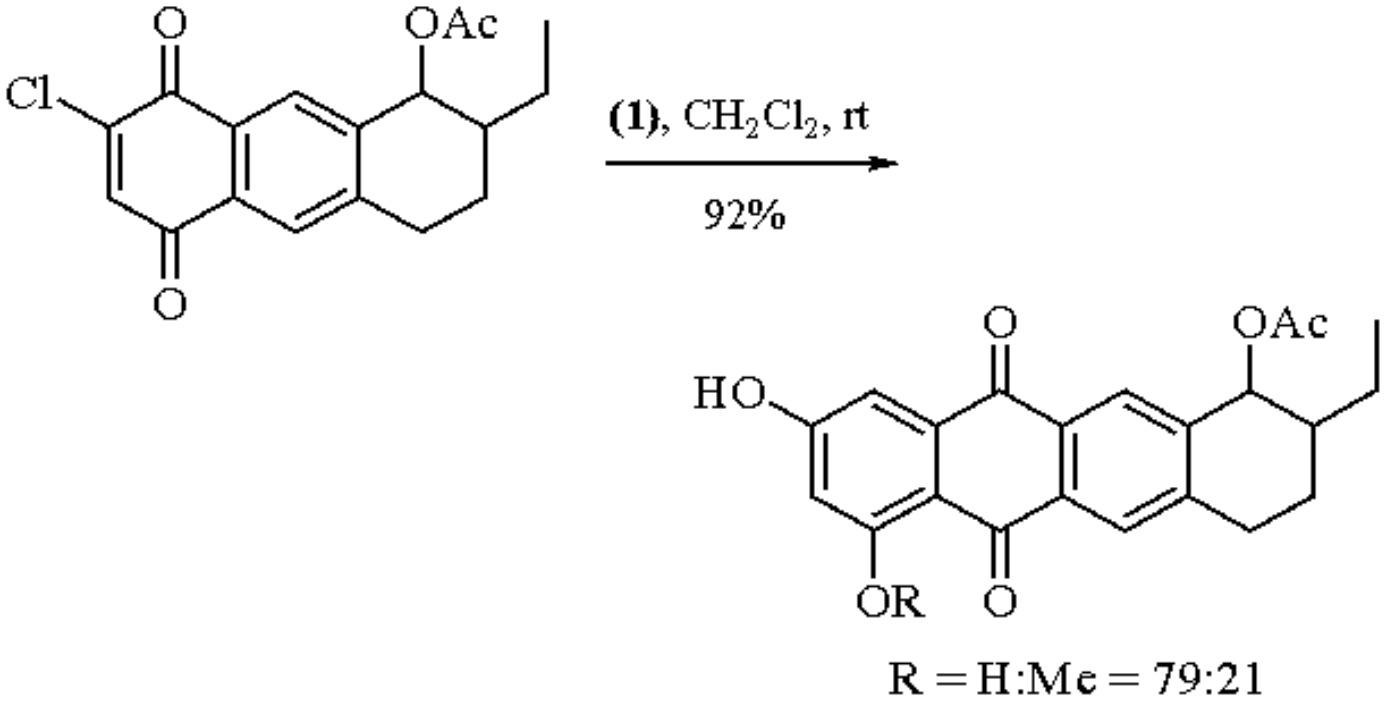

(8)

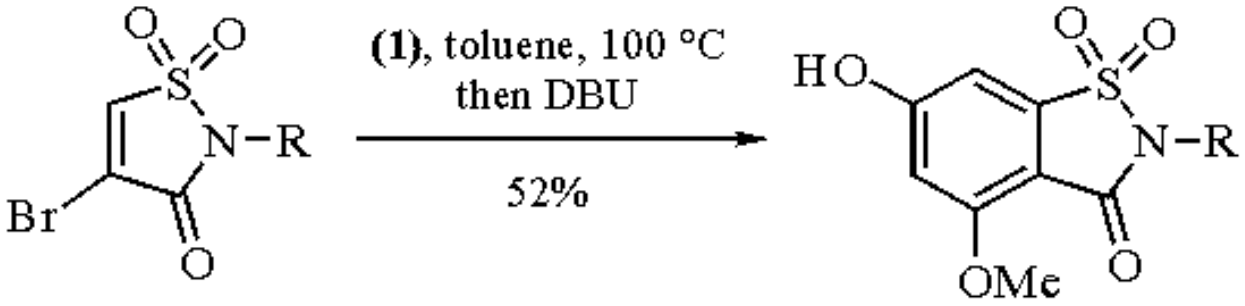

(9)

Reactions with Electrophiles.

The diene reacts as a masked acetoacetate dianion with various electrophiles such as halogens,[3] carbonyls,[3,15-17] acetals,[18-20] acyl halides,[3] and imines.[21] These reactions give 4-substituted acetoacetates and their derivatives exclusively, and are promoted by Lewis acids such as ***Titanium(IV) Chloride***, ***Trimethylsilyl Trifluoromethanesulfonate***, ***Tin(II) Chloride***, etc. (eq 10).

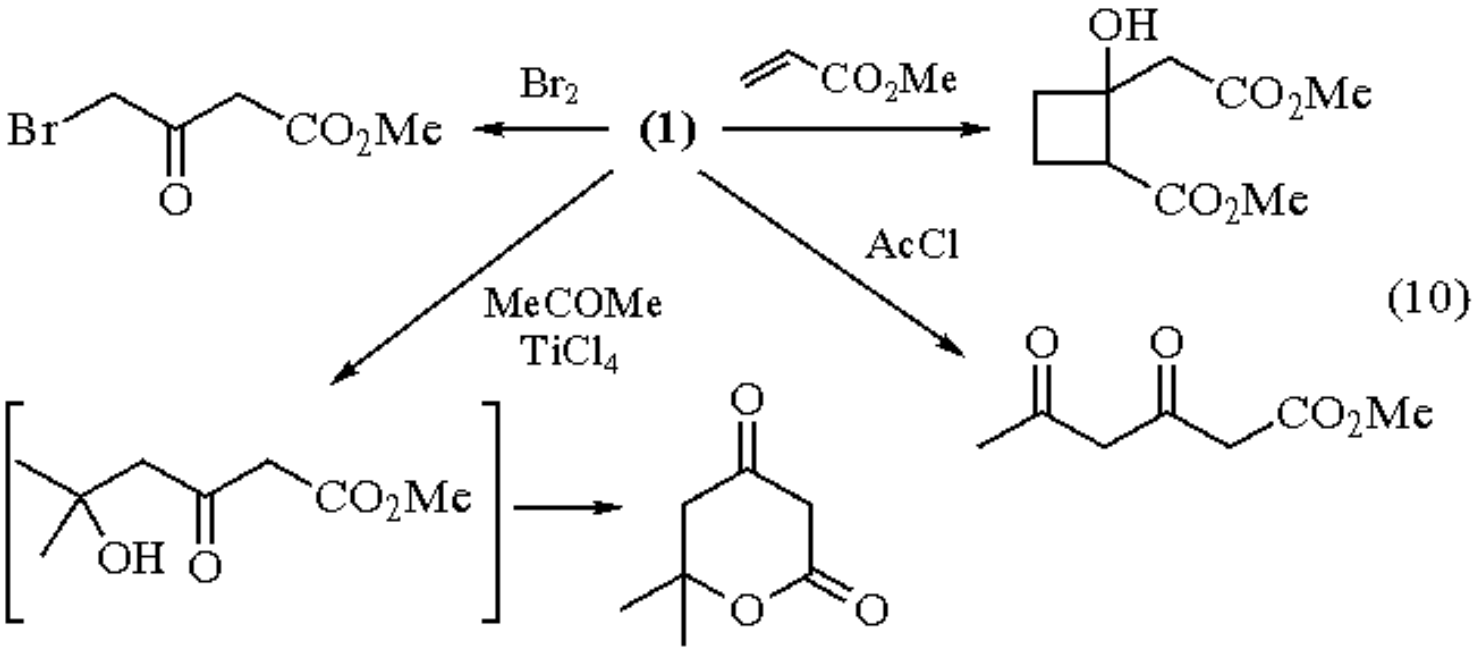

(10)

These reactions have been applied to the synthesis of sclerin,[3] (±)-Δ^1-tetrahydrocannabinol (eq 11),[18] (-)-pestalotin (eq 12),[15] sperabilins,[17] (+)-dihydrocompactin,[16] and (+)-mevinolin analogs.[20] In the case of pestalotin synthesis, highly diastereoselective condensation is executed by the addition of the diene to a solution of $TiCl_4$ and 2-benzyloxyhexanal (*syn*:*anti* = 99:1). Addition of $TiCl_4$ to a mixture of the diene and the aldehyde, however, gives a mixture of diastereomers (*syn*:*anti* = 54:46).

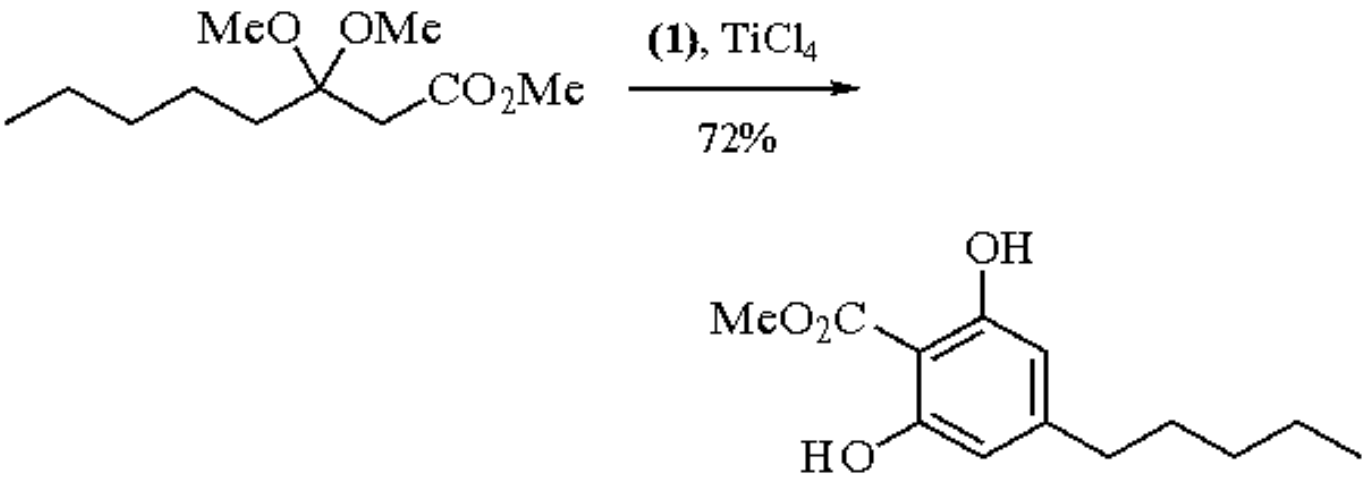

(11)

1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene

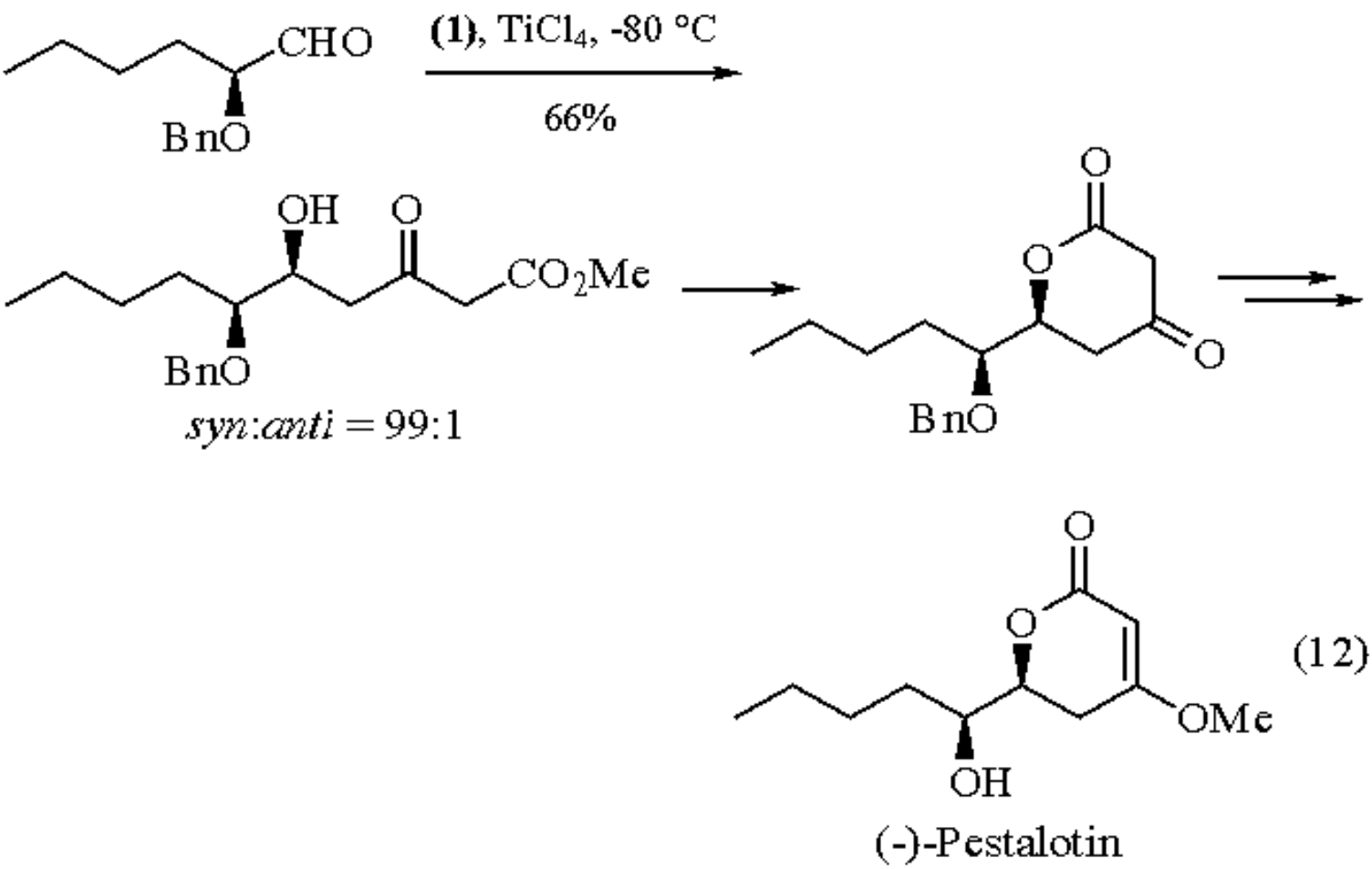

(12)

A synthesis of substituted dihydrofurans involves treatment of (**1**) with ***Tetra-n-butylammonium Fluoride*** to give the ester enolate, which reacts with a cyclohexadiene-Co complex (eq 13).[22]

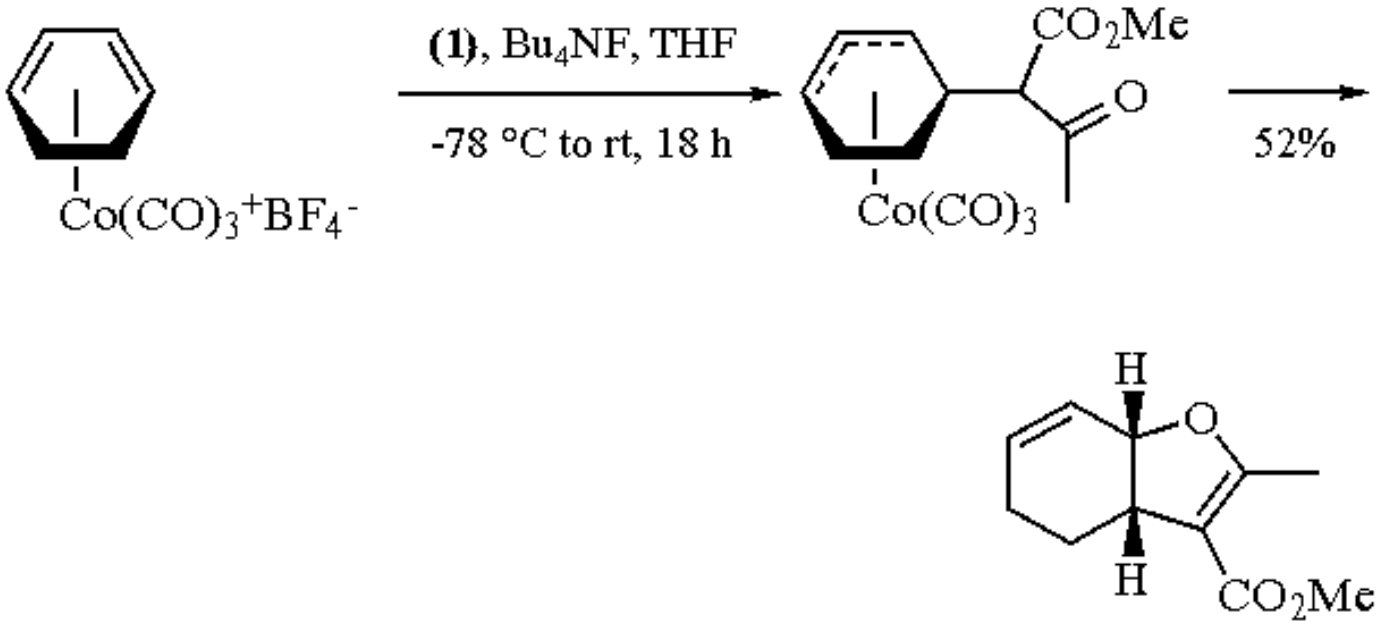

(13)

Other Annulation Reactions.

Reactions with 1,2-,[23] 1,3- (eq 14),[24] 1,4-, and 1,5-dicarbonyl compounds or their derivatives (eq 15)[25] give annulation

products with five- to eight-membered rings via double aldol-type cyclocondensations.

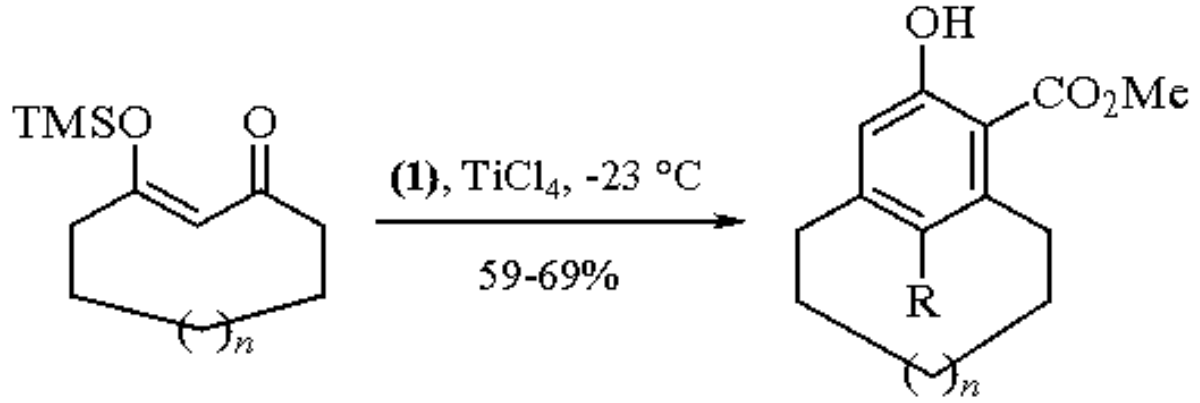

(14)

$n = 7, 10$; R = Me, H, or Bn

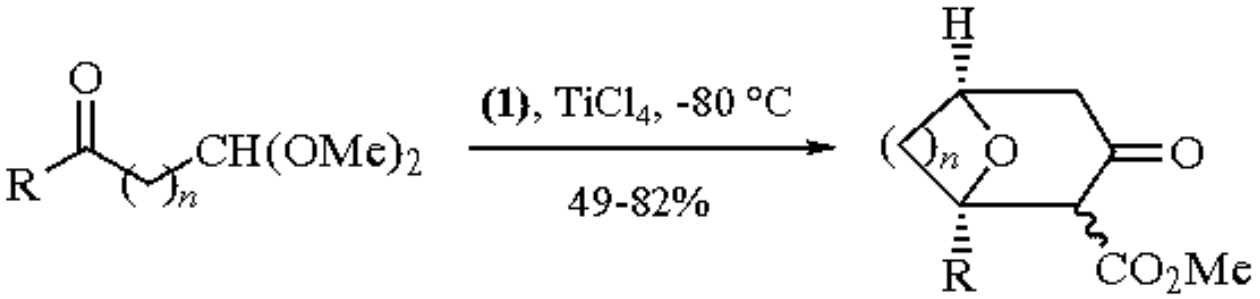

(15)

$n = 2, 3$; R = Me, Ph, *t*-Bu

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2-Methoxy-1,3-butadiene

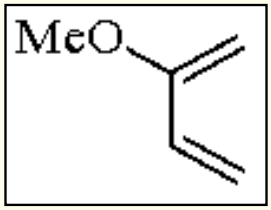

[3588-30-5] · C_5H_8O · 2-Methoxy-1,3-butadiene · (MW 84.13)

(2π or 4π partner in cycloaddition reactions;[1] regioselective cyclopropanation substrate;[16] dihydrofuran precursor;[18] δ-hydroxy ketone synthon)

Physical Data: bp 75 °C; *d* 0.827 g cm^{-3}.

Solubility: sol alcohol, ether, benzene, acetone.

Form Supplied in: colorless liquid; not commercially available, but its precursor, 1,3,3-trimethoxybutane, can be purchased.

Preparative Method: by slow addition of the acetal precursor to a preheated mixture (150 °C) of acetal and $KHSO_4$ (1:1 w/w), and collection of the diene-containing distillate in a flask cooled to -78 °C. The distillate is poured into water, the organic and aqueous layers are separated, and the organic layer is dried with 4 Å molecular sieves. The resulting mixture is fractionally distilled in the presence of hydroquinone to afford the diene in modest yield.[5]

Handling, Storage, and Precautions: classified as a flammable liquid; reported to be toxic.

Reactivity.

2-Methoxy-1,3-butadiene (**1**) is a multifaceted diene that has seen application both as a masked cyclohexanone precursor in Diels-Alder cycloadditions and as an allylic vinylic ether. Polarization of the diene by the methoxy group dictates the regioselectivity of the reactions of (**1**);[1] the dipole moment has been calculated using the Halverstadt-Kumler method.[2] The regioselectivity observed is consistent with predictions obtained from frontier molecular orbital (FMO) theory using terminal and secondary orbital calculations,[3] and by Hehre's reactive surface mapping technique.[1,4]

Cycloaddition Reactions.

2-Methoxy-1,3-butadiene (**1**) is commonly used as a 4π component in $[_{\pi}4_s + _{\pi}2_s]$ cycloadditions to prepare masked

cyclohexanone (cyclohexanone methyl enol ether) systems. (**1**) reacts readily with a variety of dienophiles to afford predominately the *para*-isomer (eq 1). The *para*/*meta* ratio of isomers is highly dependent upon the dienophile. Glyoxylate esters (eq 2),[6] nitroso compounds (eq 3),[7] and bicyclic dienophiles[8] often afford regioisomeric mixtures, while quinones,[9] acrylic acid derivatives,[10] and cycloalkenes[11] afford exclusively the *para*-isomer. The observed predominance for the *para*-isomer has allowed this reagent to be used in key steps for the synthesis of several natural products,[12] most notably the anthracyclinone antibiotics (eq 4).[13]

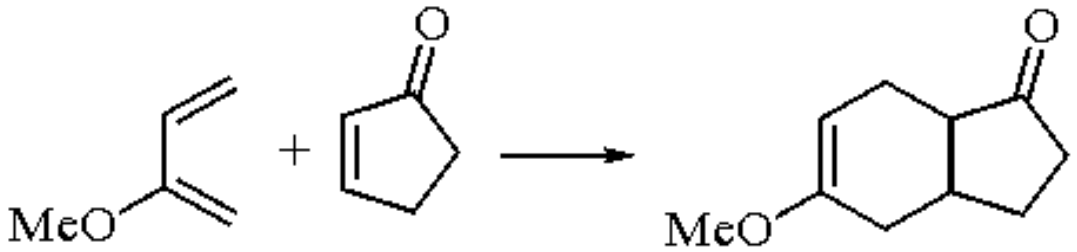

(1)

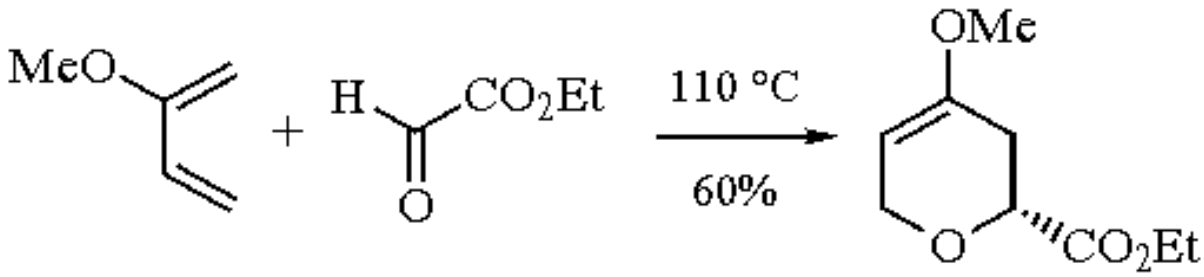

(2)

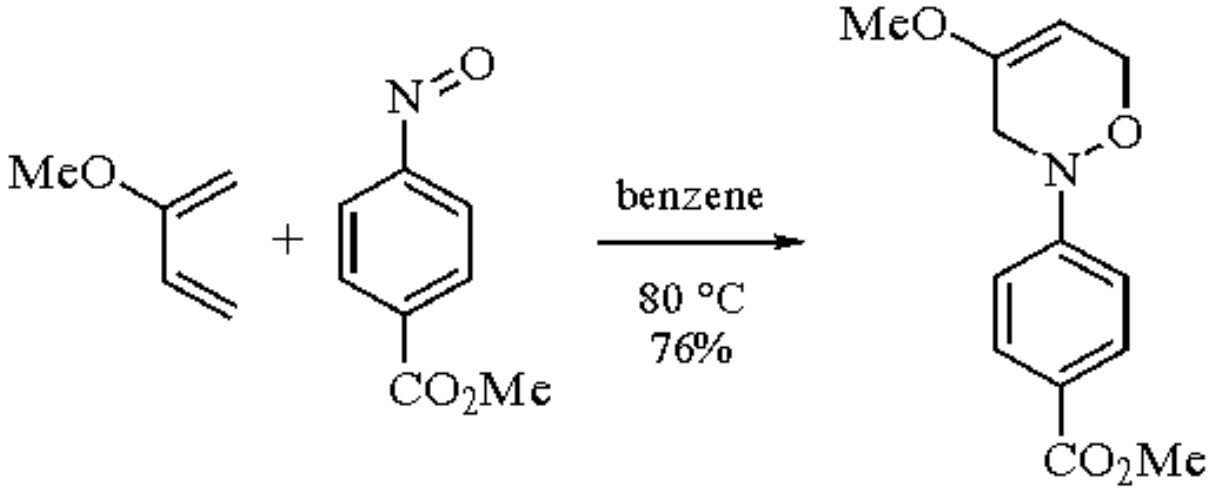

(3)

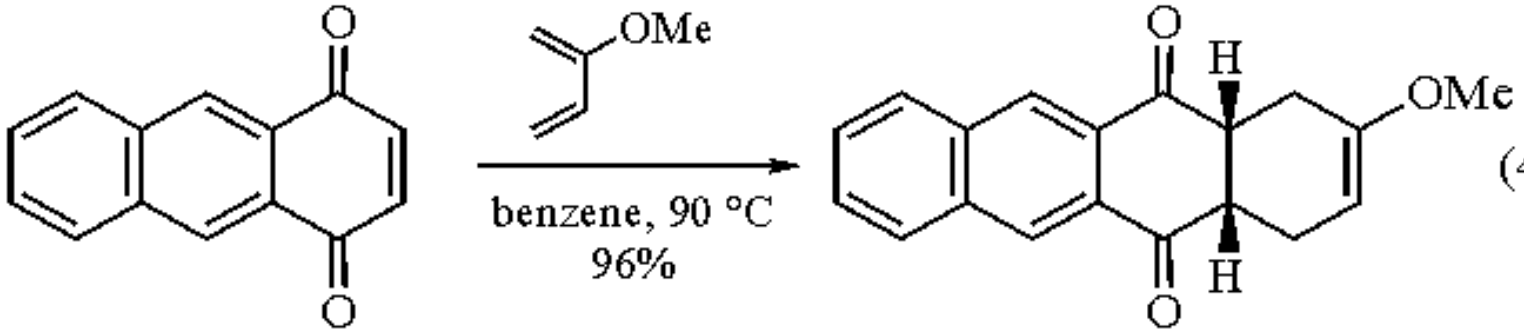

(4)

In cycloaddition reactions with Fischer-type carbenes (eq 5) and other dienophiles, 2-methoxy-1,3-butadiene can be

exposed to extreme temperatures (219 °C, sealed tube) without significant decomposition.[12] However, (**1**) rapidly decomposes when exposed to Lewis acids (eq 6).[14] Depending upon the dienophile and temperature, (**1**) also can act the 2π component in [4 + 2] cycloadditions. Cycloaddition of (**1**) with electron-deficient 5-methoxycarbonyl-2-pyranones (eq 7) at 25 °C affords the expected tetrahydrocoumarin, resulting from participation of (**1**) as the 4π reaction partner; warming the reaction mixture to 114 °C provides the 2-oxabicyclo[2.2.2]oct-5-en-3-one system, where the vinyl ether double bond reacts as the 2π component in this inverse electron-demand Diels-Alder reaction.[15]

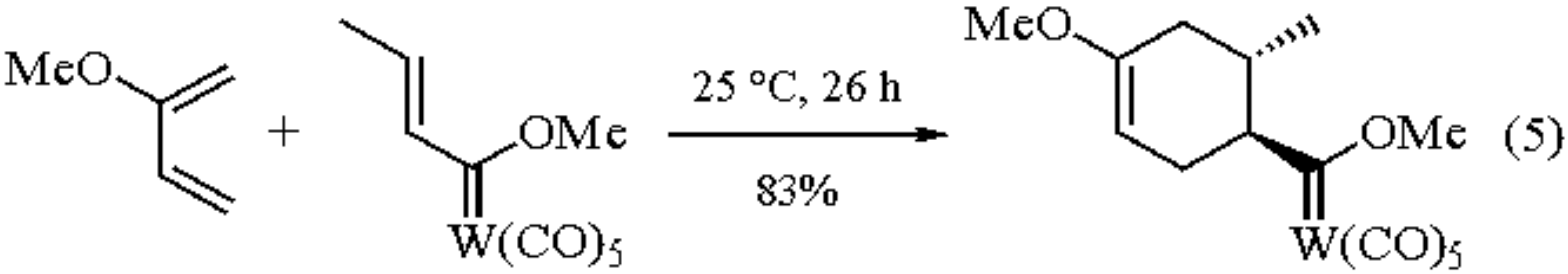

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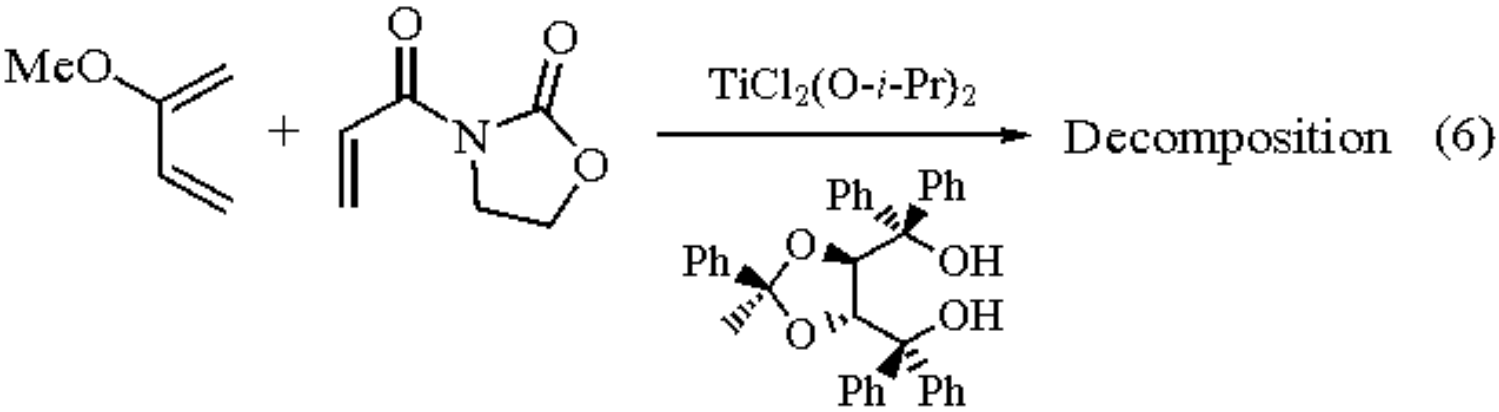

Decomposition (6)

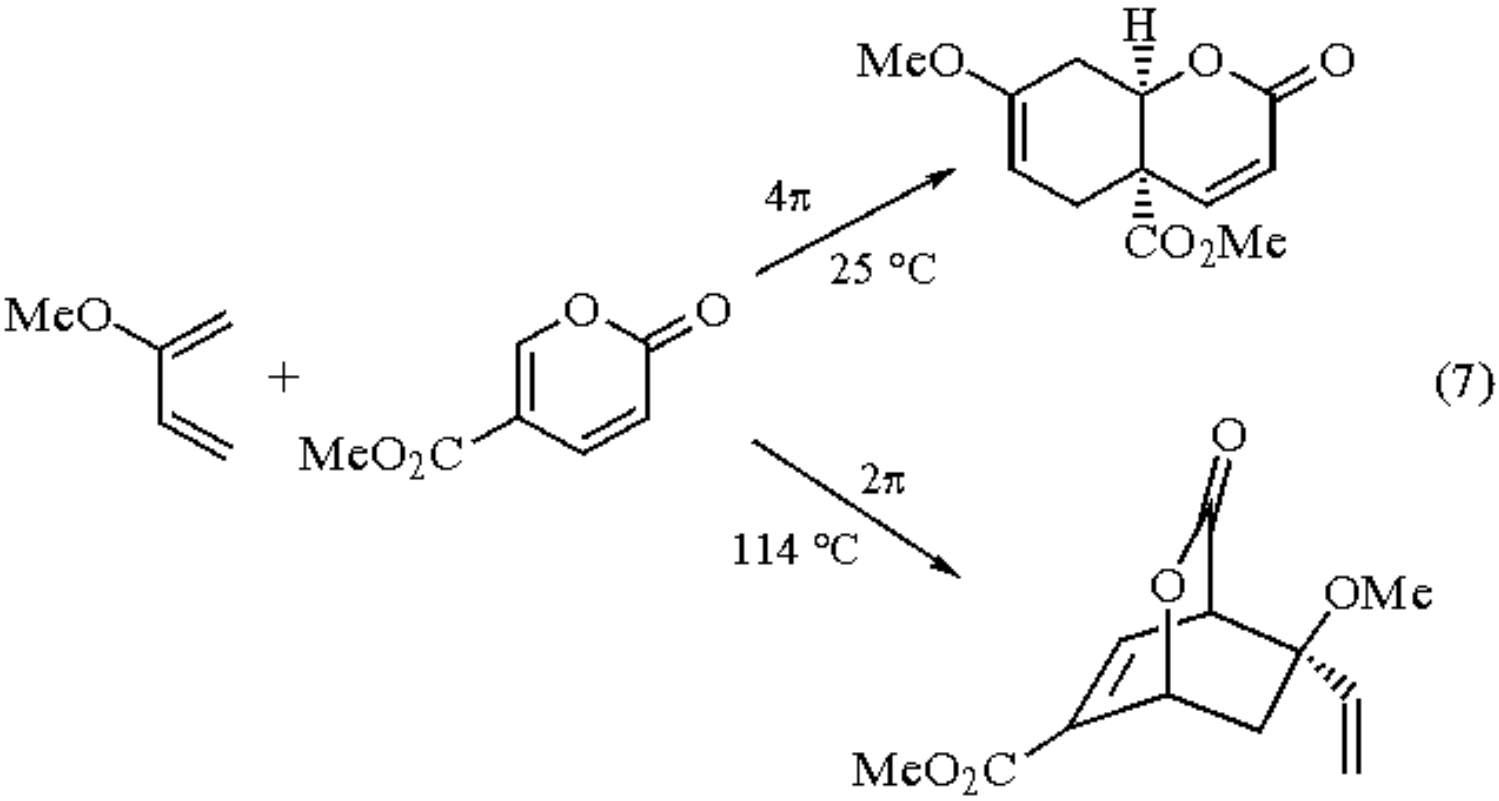

(7)

(**1**) is also highly chemoselective with respect to the dienophile. In the synthesis of daunomycinone analogs, cycloaddition between (**1**) and an anthracene bisquinone affords the cycloadduct where the diene adds across the more electron-deficient tetrasubstituted double bond, rather than the more accessible, but less reactive, disubstituted double bond (eq 8).

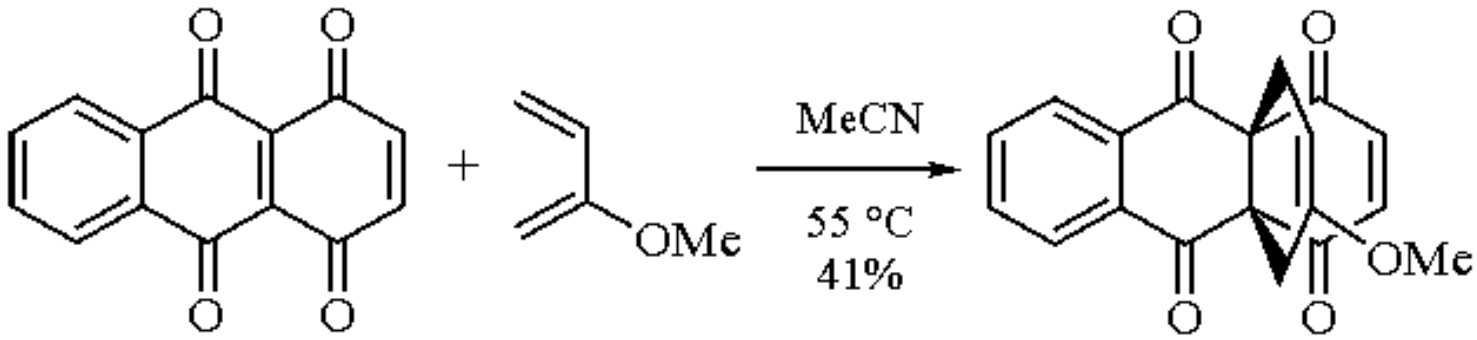

(8)

Miscellaneous Reactions.

Predictable regioselectivity in the reactions of 2-methoxy-1,3-butadiene makes it an ideal cyclopropanation substrate. Reaction of (**1**) with the metallocarbenoid generated from ***Ethyl Diazoacetate*** occurs exclusively at the electron-rich 1,2-double bond to afford a 0.8 *trans*/*cis* isomeric mixture regardless of the cyclopropanation catalyst (eq 9).[16] The best cyclopropanation catalyst is ***Dirhodium(II) Tetraacetate***.

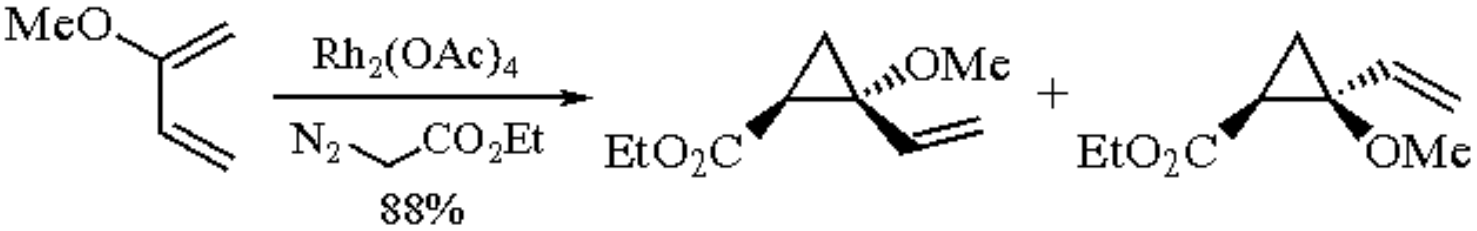

(9)

Transition metal-mediated transformation of these vinylcyclopropanes has been reported. Conversion of vinylcyclopropanes to dihydrofuran systems occurs with ***Copper Bronze*** (eq 10), whereas treatment with Pd^{II} and/or Rh^{I} or Rh^{II} affords ethyl 4-methoxy-2,4-hexadienoate (eq 11).[17] The same vinylcyclopropane has been transformed to a dihydrofuran via an oxepin intermediate under acidic conditions in the presence of rhodium tetraacetate (eq 12).[18]

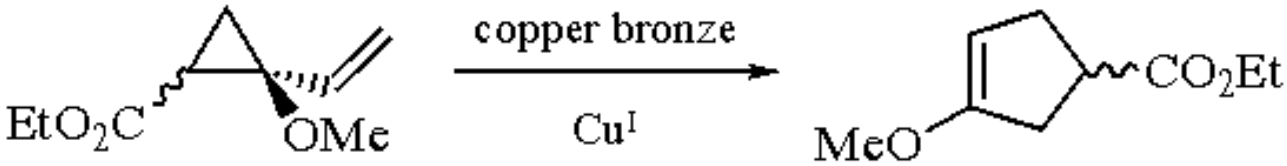

(10)

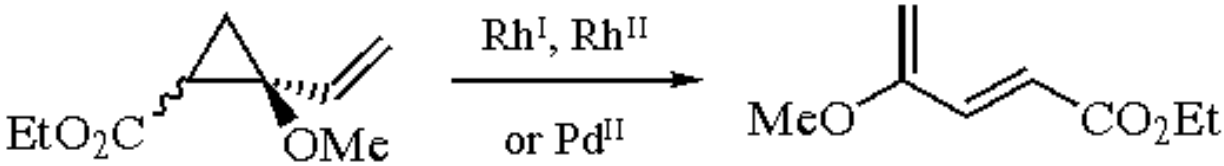

(11)

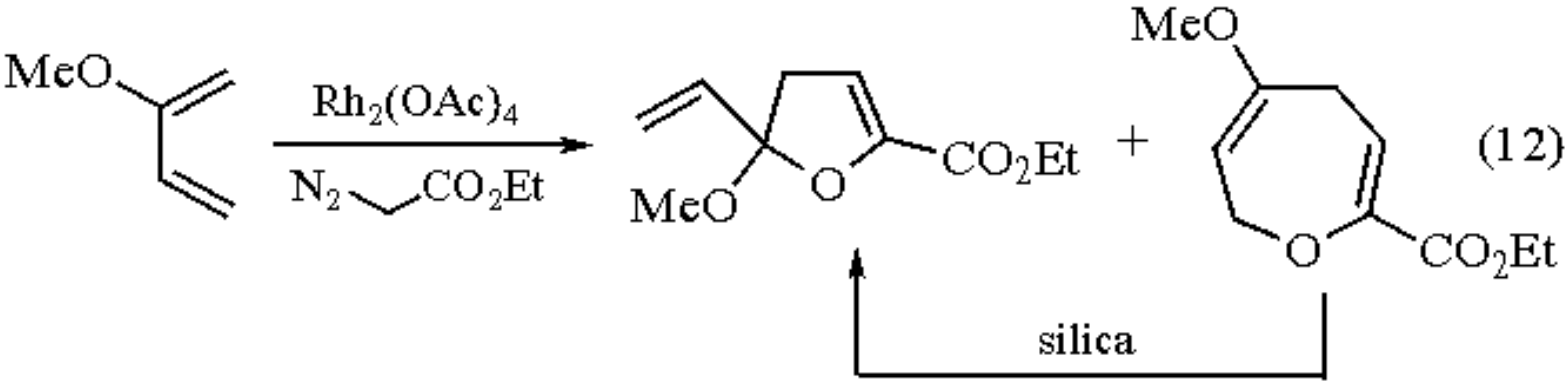

δ-Hydroxy ketone systems have been prepared using (**1**). Alkylation of 2-methoxy-1,3-butadiene at the 4-position with an α-alkoxy iron carbene affords 6-ethoxy-6-phenylhex-3-en-2-one after acidic hydrolysis (eq 13).[19] Electroreductive coupling of (**1**) with acetone followed by acid hydrolysis of the enol ether affords 6-hydroxy-6-methyl-2-heptanone in 78% yield (eq 14).[20]

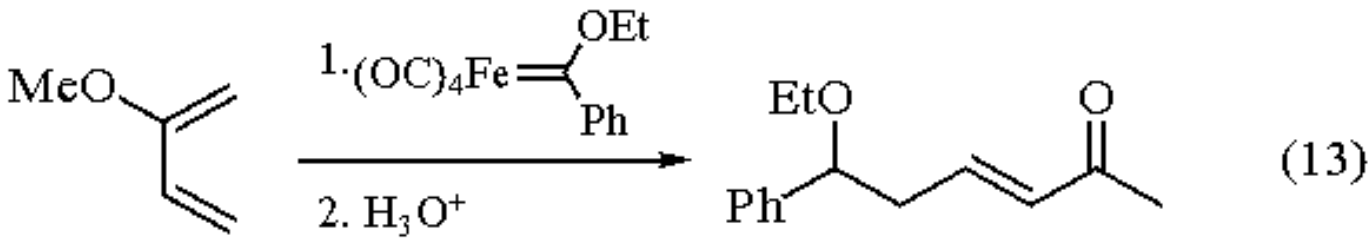

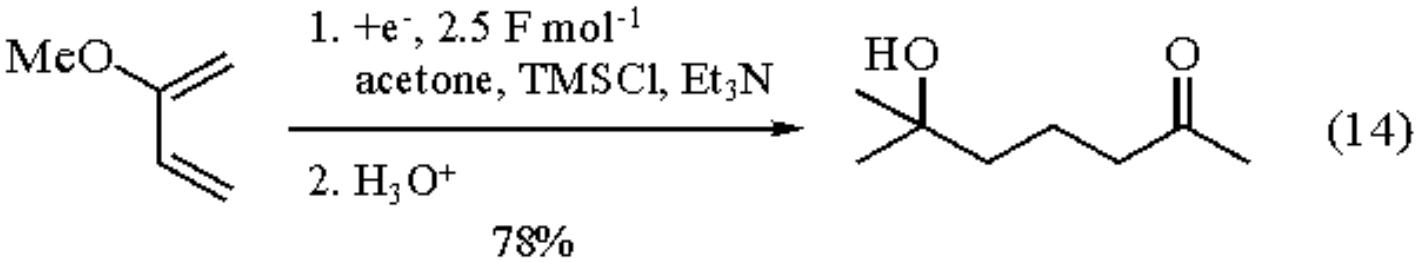

The vinyl ether portion of (**1**) permits the rapid formation of unsymmetrical allylic acetals that can be converted via Claisen rearrangement to chroman systems in a one-pot reaction sequence (eq 15).[21]

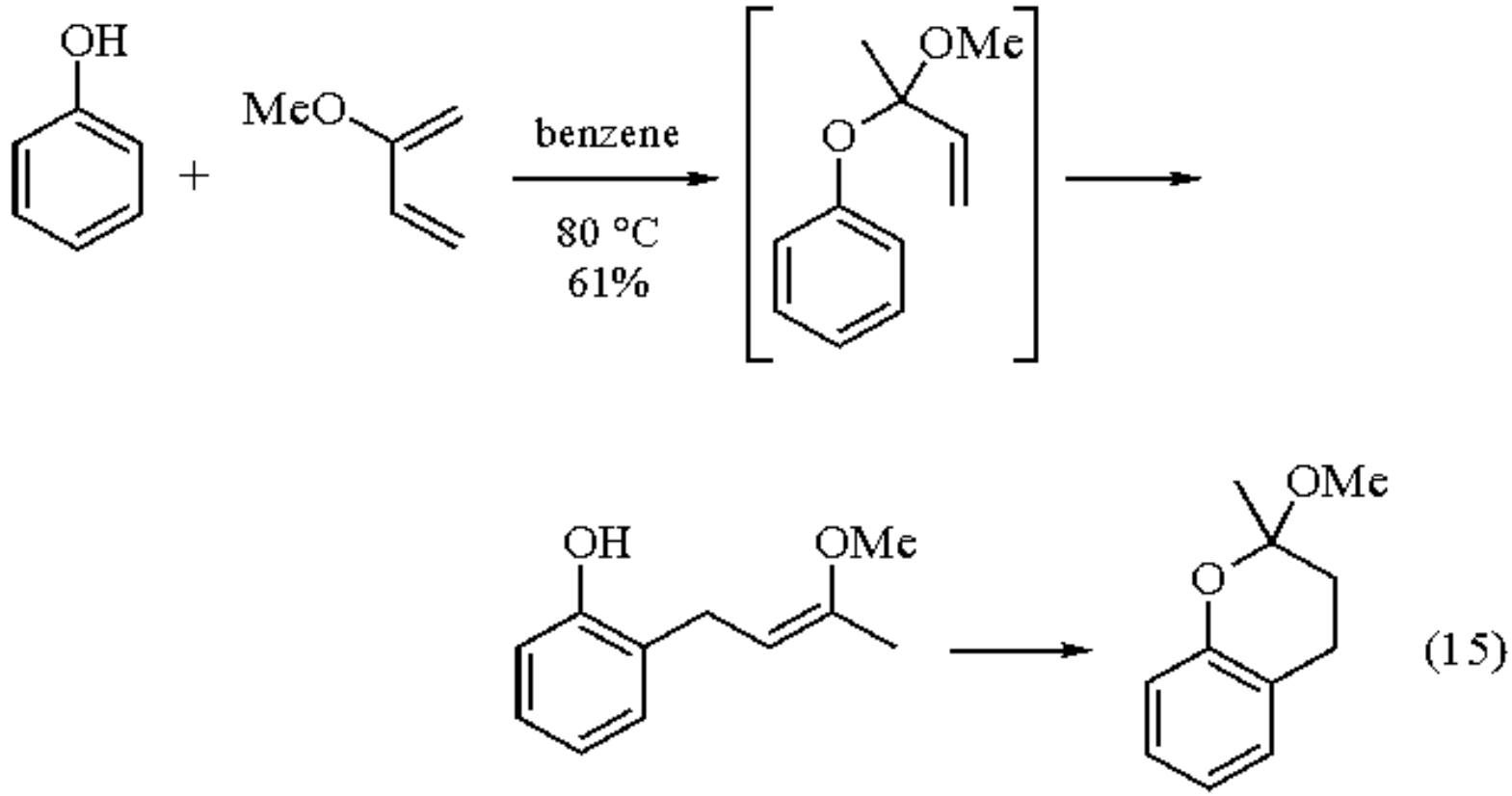

(15)

Related Reagents.

1-Acetoxy-1,3-butadiene.

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1-Methoxy-3-buten-2-one

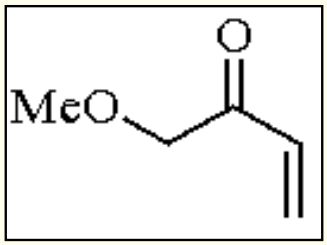

[43042-58-6] · $C_5H_8O_2$ · 1-Methoxy-3-buten-2-one · (MW 100.13)

(methyl vinyl ketone equivalent used in Robinson annulation,[1] and Diels-Alder,[2] [2 + 2],[3] and Michael addition[4] reactions)

Alternate Name: methoxymethyl vinyl ketone.

Physical Data: bp 52 °C/30 mmHg.

Solubility: sol dichloromethane, methanol, ethanol, diethyl ether.

Form Supplied in: generated in situ from 1,4-dimethoxy-2-butanone,[5] which is in turn synthesized from 2-butyne-1,4-diol (widely available).

Analysis of Reagent Purity: ^{1}H NMR[1a] [($CDCl_3$, δ 3.43 (s, 3H, Me); 4.25 (s, 2H, CH_2); 5.83 (dd, 1H, *J* = 1.7, 10 Hz, 4-H); 6.32 (dd, 1H, *J* = 1.7, 18 Hz, 4-H); 6.49 (dd, 1H, *J* = 10, 18 Hz, 3-H)] and GC.

Preparative Methods: the precursor, 1,4-dimethoxy-2-butanone, is prepared[5] by dimethylation of 2-butyne-1,4-diol, followed by oxidation with red ***Mercury(II) Oxide***. In situ generation is possible either by acid-induced elimination using ***p-Toluenesulfonic Acid***,[1a] base-induced elimination using ethanolic ***Potassium Hydroxide***,[1b] or pyrolysis in the presence of sodium benzoate.[6]

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: the colorless liquid is best used immediately upon generation. This toxic reagent should be handled in a fume hood.

Robinson Annulation.

This reagent was introduced by Wenkert[1b] in 1967 as a Robinson annulation component (***Methyl Vinyl Ketone*** equivalent) which produces cyclohexenones bearing an oxygen substituent at the 4-position of the newly constructed

six-membered ring. The α-oxygenation provides flexibility in the elaboration of cyclic frameworks, as seen in the synthesis of the decalone derivative (-)-valeranone (eq 1),[1b] as well as in the synthesis of the spirocyclic (-)-acorenone via an alkylative 1,2-carbonyl transposition (eq 2).[1c,d]

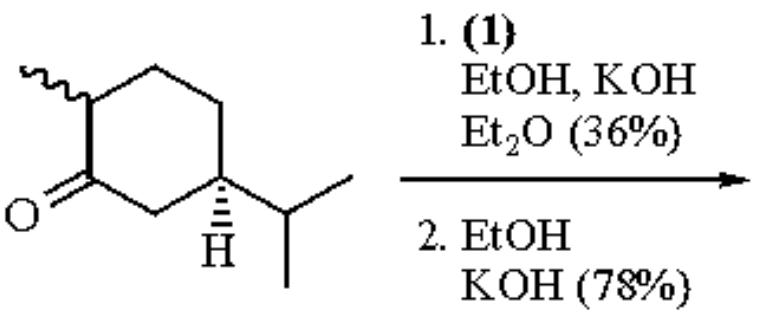

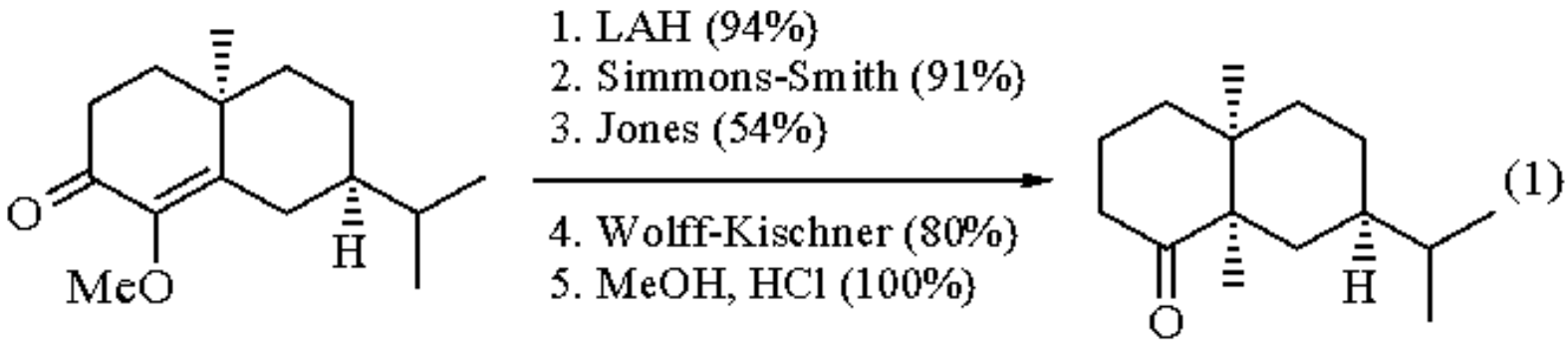

(1)

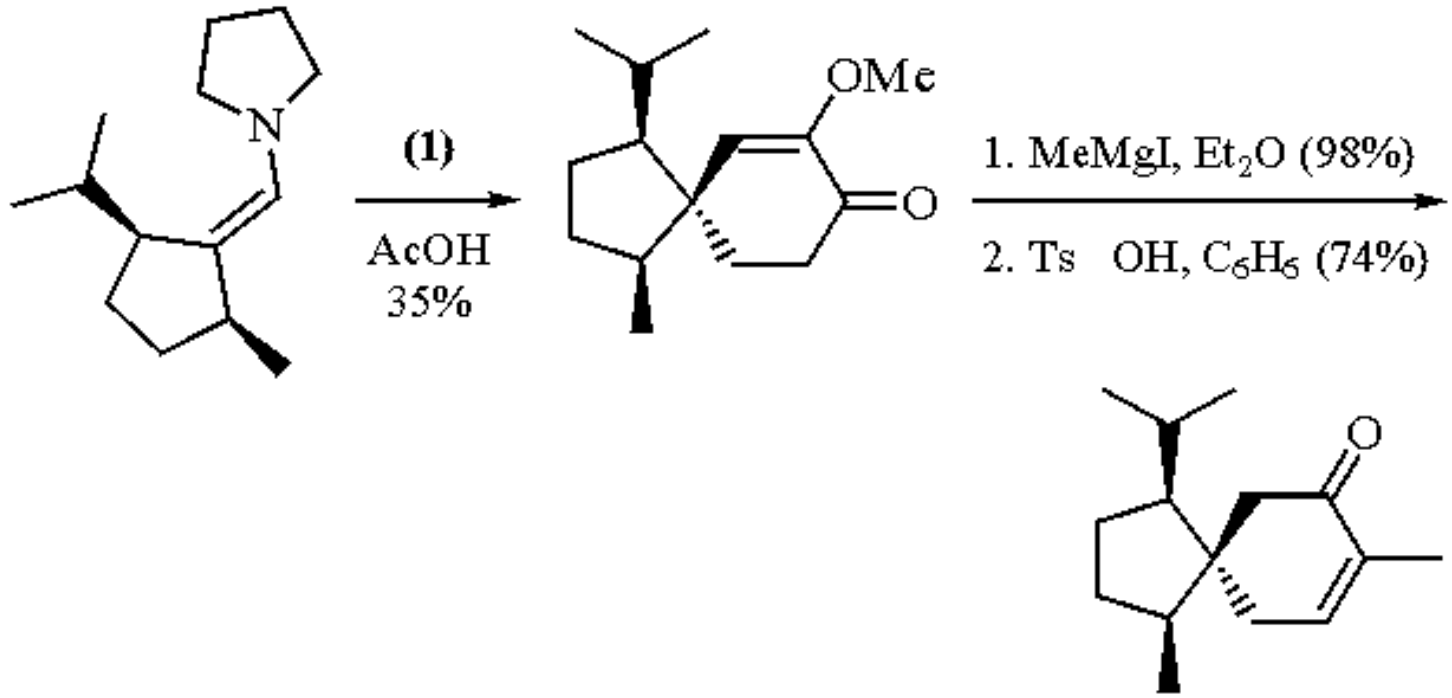

(2)

Diels-Alder Chemistry.

The use of (**1**) as a dienophile in Diels-Alder reactions provides a route for the construction of useful synthetic building

blocks such as isopiperitenone derivatives (eq 3)[2a] and, after ozonolysis and treatment with *N*-aminophthalimide, 2-methoxypyrrole derivatives (eq 4).[2b]

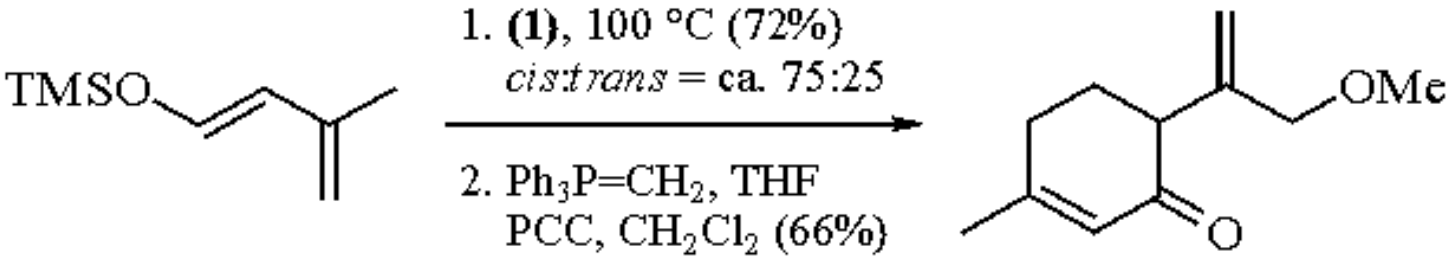

(3)

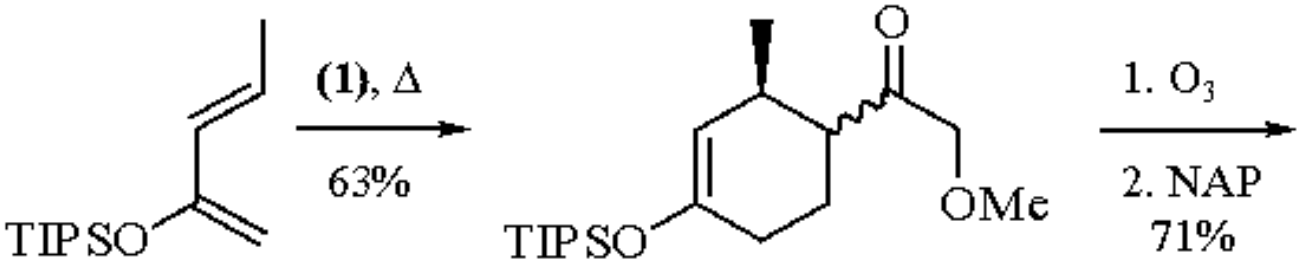

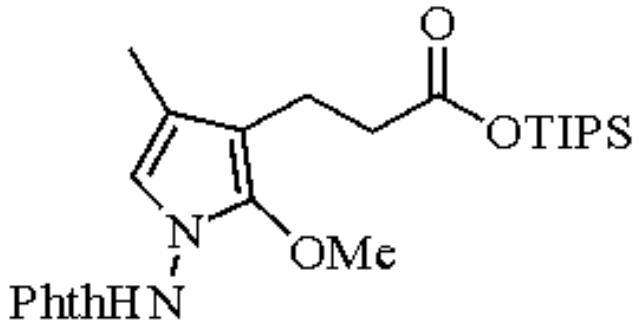

(4)

[2 + 2] Cycloadditions.

Another facet of this reagent's utility involves Lewis acid-catalyzed [2 + 2] cycloaddition,[3] allowing for the construction of functionalized cyclobutane rings (eq 5).

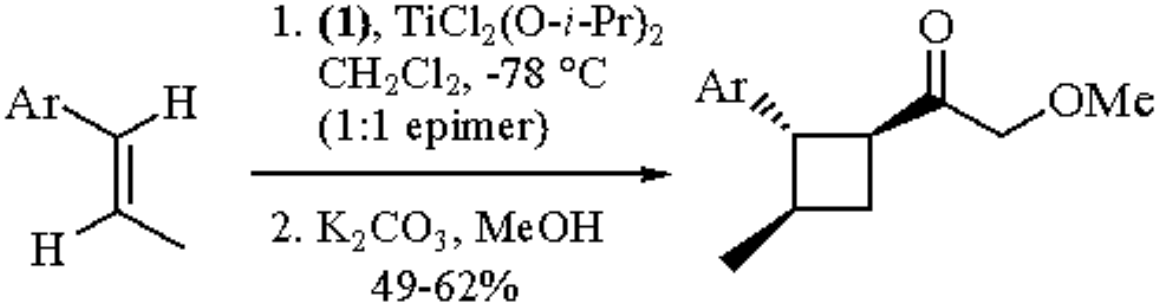

(5)

Michael Additions.

In addition to annulations, this reagent functions as a Michael acceptor for nucleophiles. Somei et al.[4] have shown that

a tricyclic heterocycle can be generated via Heck coupling of (**1**) to the iodoindole (**2**) followed by a Michael addition involving the nitronate anion (eq 6).

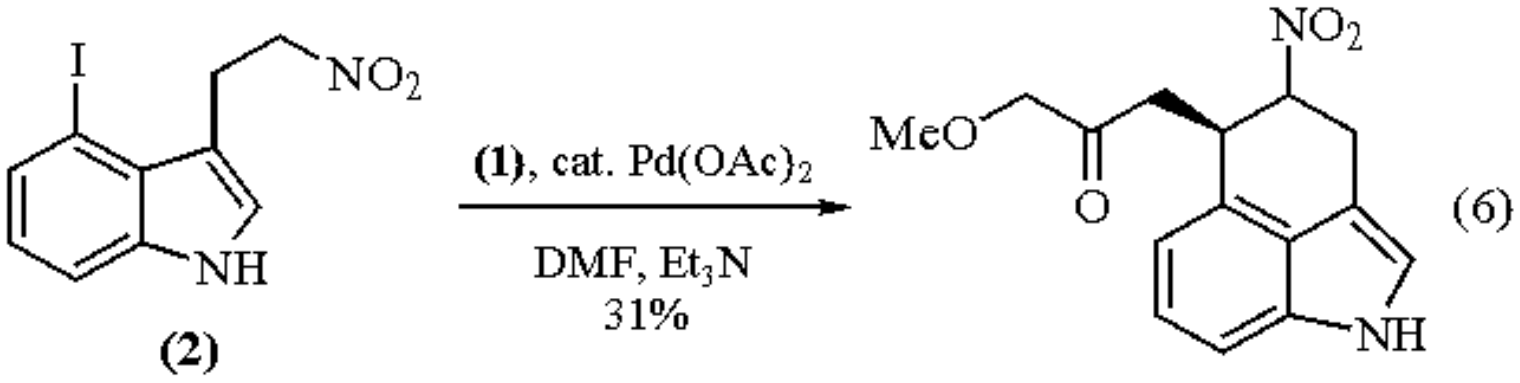

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4-Methoxy-3-buten-2-one[1]

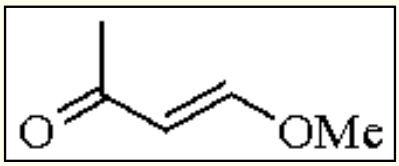

[51731-17-0] · $C_5H_8O_2$ · 4-Methoxy-3-buten-2-one · (MW 100.13)

(versatile four-carbon synthon; precursor to the Danishefsky diene;[2] Diels-Alder dienophile;[3] dipolarophile;[4] electrophilic four-carbon synthon subject to conjugate addition at C-4 followed by elimination of the methoxide anion;[5] its enolate is a nucleophilic four-carbon building block[6])

Physical Data: bp 200 °C/760 mmHg, bp 61-63 °C/12 mmHg; d_4^{20} 0.997 g cm^{-3}; n_D^{20} 1.469.

Solubility: sol THF, ether, acetonitrile, benzene

Form Supplied in: liquid, over 97% (GC) pure; commercially available in 10 or 50 mL units.

Analysis of Reagent Purity: GC analysis appears best; also IR;[7a] UV (cyclohexane) λ_{max} 237 nm (ε 13450);[7b] ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H), 3.70 (s, 3H), 5.55 (d, 1H, *J* = 13.0 Hz), and 7.53 (d, 1H, *J* = 13.0 Hz);[6a,7c,d] ^{13}C NMR ($CDCl_3$) δ 27.5, 57.6, 107.0. 163.6, 196.6.[7e,f]

Handling, Storage, and Precautions: may be harmful by inhalation, ingestion, or skin absorption; may cause skin and eye irritation; in addition to standard safety practice, mechanical exhaust is required.[8] Do not breathe vapor. Store in refrigerator under nitrogen or argon.

Introduction.

4-Methoxy-3-buten-2-one may be regarded as a vinylogous homolog of methyl acetate and has three functional groups and one acidic site. Each of these shows characteristic reactivity.

Danishefsky Diene and Analogs.

4-Methoxy-3-buten-2-one is a valuable starting compound for the preparation of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, the Danishefsky diene (eq 1), and its equivalent.[2] These dienes undergo Diels-Alder cycloaddition or cyclocondensation reactions with a variety of dienophiles (see ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***).[2,9] A couple of slightly modified procedures for the preparation of the Danishefsky diene have also been reported.[10]

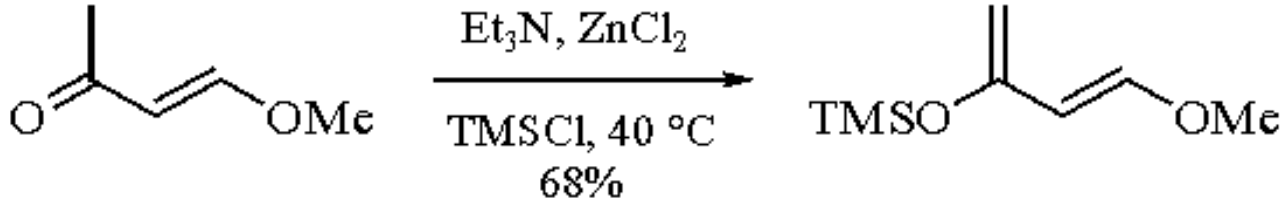

(1)

Diels-Alder Dienophile and Dipolarophile.

Only a handful of examples of cycloaddition reactions involving the C=C bond of this reagent have been reported. While no reaction can be observed in the absence of a catalyst, this C=C bond undergoes a Diels-Alder reaction with cyclopentadiene in the presence of the Lewis acid ***Tin(IV) Chloride***, providing the adduct with an *endo*/*exo* ratio of 15:1 (eq 2).[3] In general, the cycloadducts are unstable due to their propensity for the elimination of methanol.

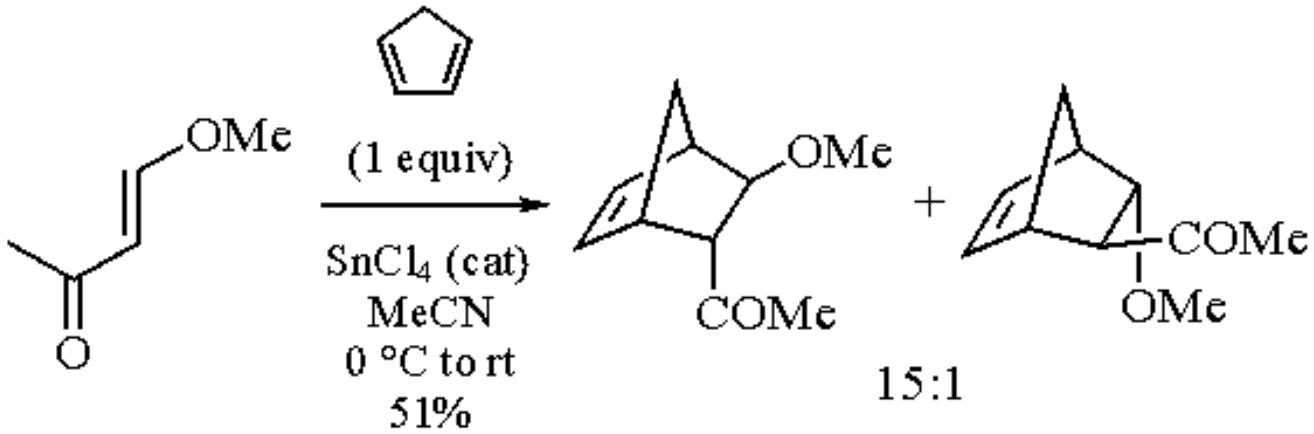

(2)

The [2 + 3] cycloaddition reaction involving the C=C bond is also reported. Thus treatment of this reagent with 2-[(trimethylsilyl)methyl]-3-(trimethylsilyl)-2-propenyl carboxylates in the presence of a catalytic amount of ***Tetrakis(triphenylphosphine)palladium(0)*** provides the cyclopentane product in a highly regioselective manner (eq 3).[11] This captodative enone also undergoes an efficient, highly regioselective [2 + 3] dipolar cycloaddition reaction with acetonitrile oxide to give (after the elimination of methanol) 4-acetyl-3-methylisoxazole (eq 4).[4] Interestingly, a reversal in regioselectivity is observed for the corresponding reaction with 3-buten-1-one whereby the major product upon subsequent oxidation is 5-acetyl-3-methylisoxazole.[4] The 1-diazo derivative of 4-methoxy-3-buten-2-one is a versatile four-carbon building unit used for the efficient annulation of highly substituted aromatic rings (eq 5).[12] The diazo ketone first undergoes photochemical Wolff rearrangement to the vinylketene, which subsequently reacts with alkoxy alkynes in a [2 + 2] cycloaddition mode; the resulting cyclobutenones proceed through a sequence of electrocyclic ring cleavage and closure, and finally aromatization through tautomerization. The product shown in eq 5 has been converted to the host defense stimulant maesanin in 67% yield by oxidation with O_2 and ***Tetra-n-butylammonium Fluoride***.[12]

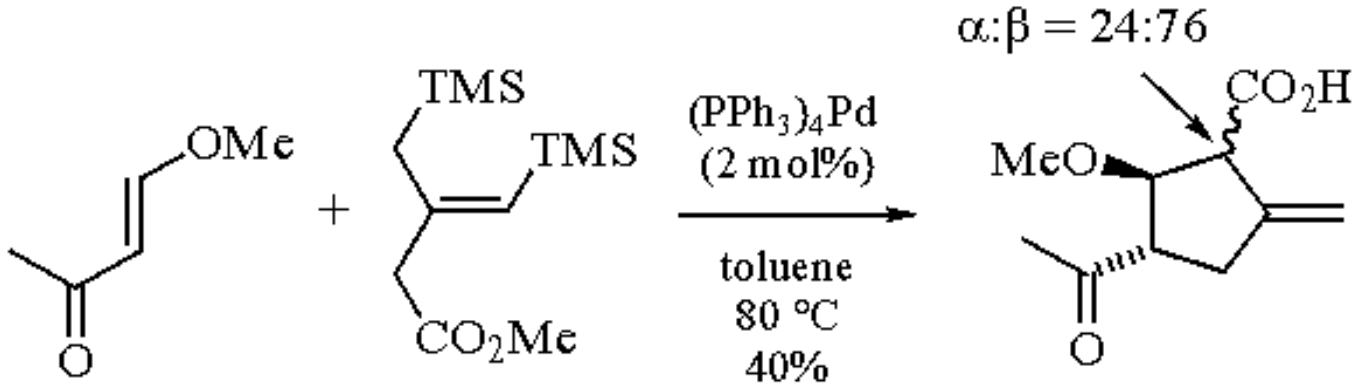
α:β = 24:76
OMe
O
TMS
TMS
CO2Me
(PPh3)4Pd
(2 mol%)
toluene
80 °C
40%
CO2H
MeO
O

(3)

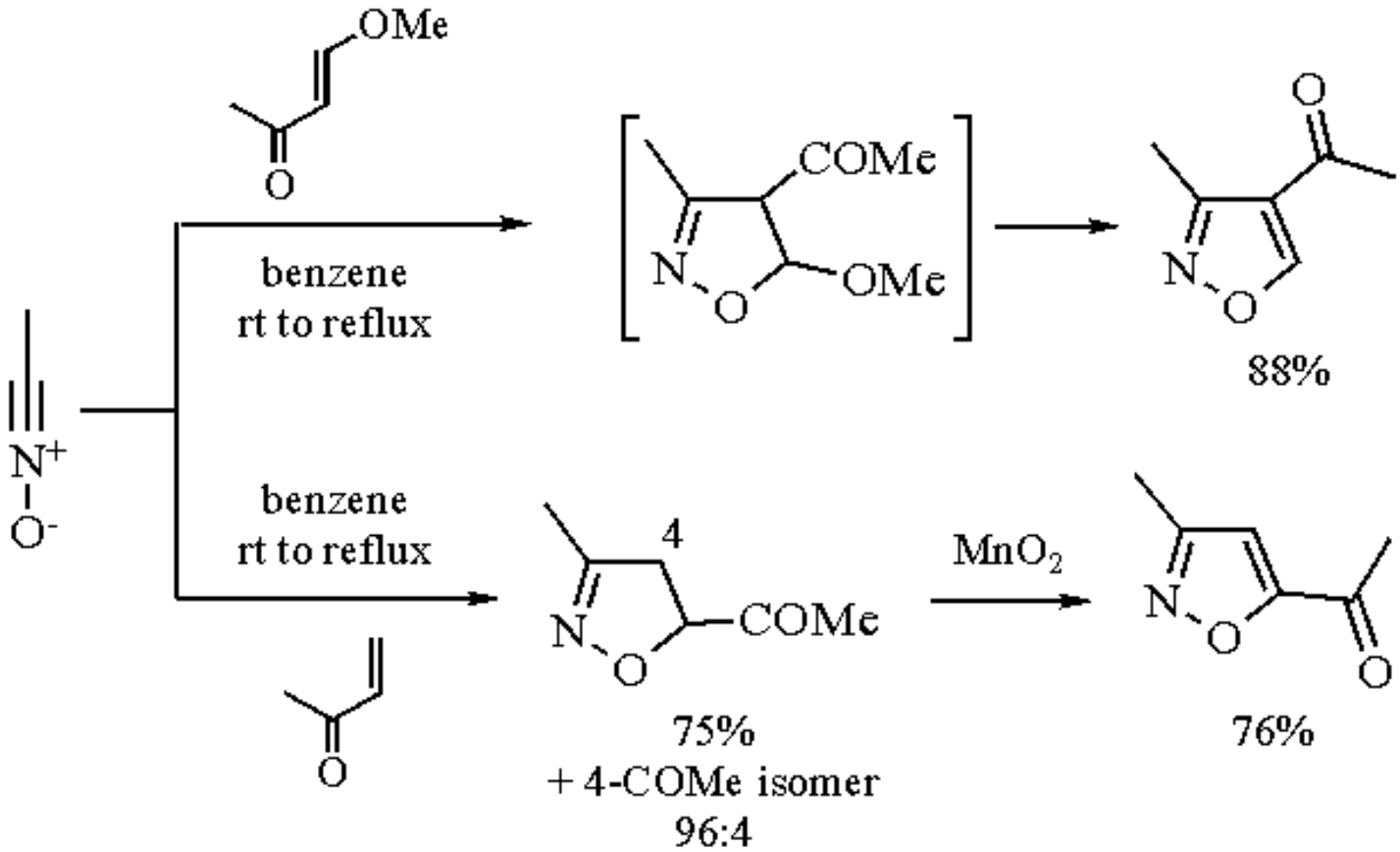
OMe
O
benzene
rt to reflux
COMe
OMe
N
O
O
88%
N+
O-
benzene
rt to reflux
4
COMe
MnO2
O
75%
+ 4-COMe isomer
96:4
76%

(4)

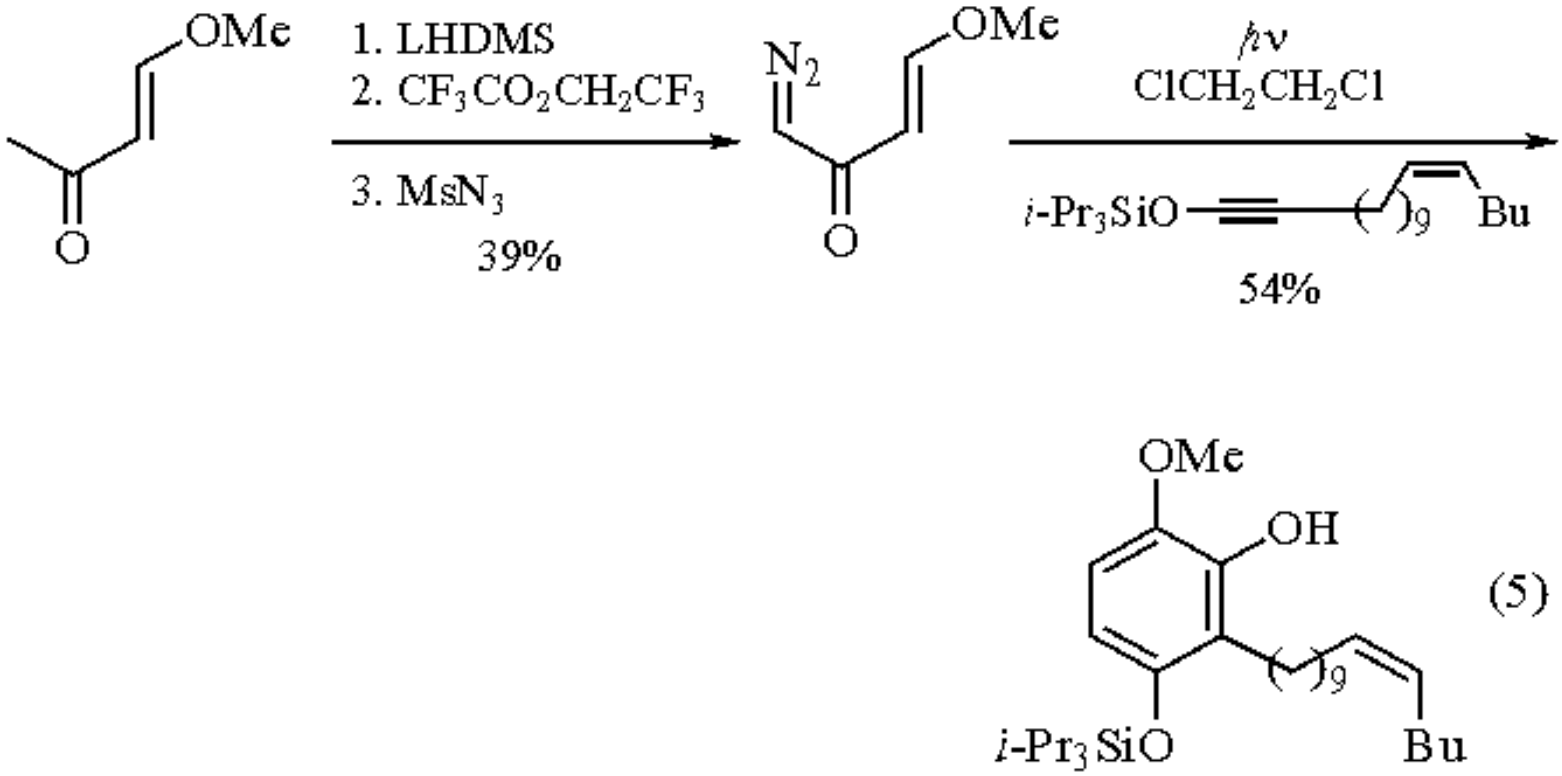

(5)

Synthesis of β-Substituted Enones through a Conjugate Addition/Elimination Sequence.

A number of nucleophiles have been added to C-4 of 4-methoxy-3-buten-2-one; the resulting adducts rapidly eliminate methanol in the reaction medium, providing a variety of β-substituted enones as shown in eq 6.[5b] A recent example includes the use of lithiated diethyl prop-2-enylphosphonate as a nucleophile.[13]

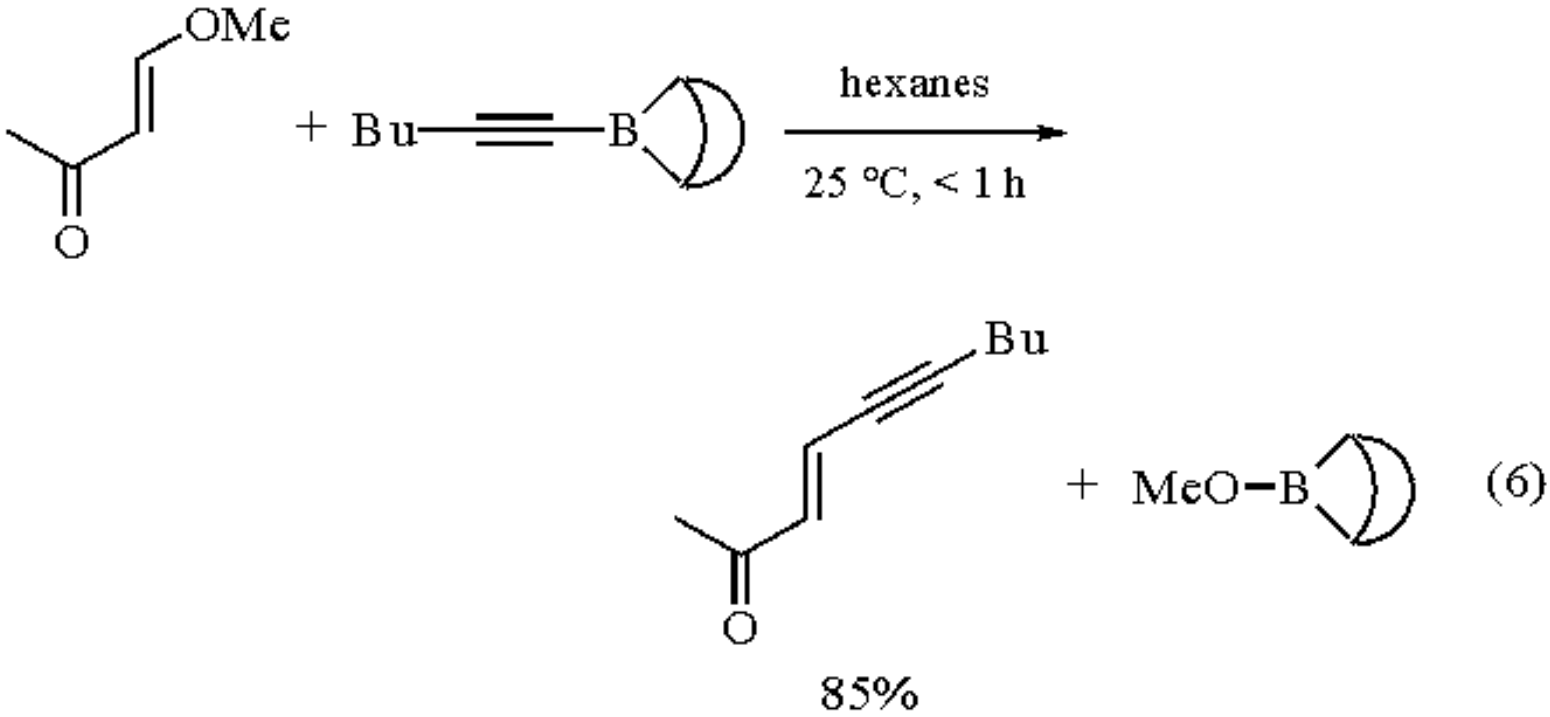

(6)

Addition Reactions of the Enolate Derivative.

The addition of the lithium enolate of 4-methoxy-3-buten-2-one to acid chlorides followed by acid treatment of the resulting enol provides γ-pyrones in good to excellent yields (eq 7).[6a] A similar, yet direct formation of γ-pyrones has been reported which uses 2.2 equiv of the potassium enolate of 4-methoxy-3-buten-2-one for the reaction with acid chlorides followed by aqueous workup (eq 8).[6b] In a similar vein, the lithium enolate of this reagent adds to a Boc-protected α-amino aldehyde (eq 9). The formation of the major stereoisomer (indicated in eq 9) of the 88:12 mixture (53% combined yield) is consistent with the prediction on the basis of the Felkin-Anh transition state conformation of the aldehyde.[14]

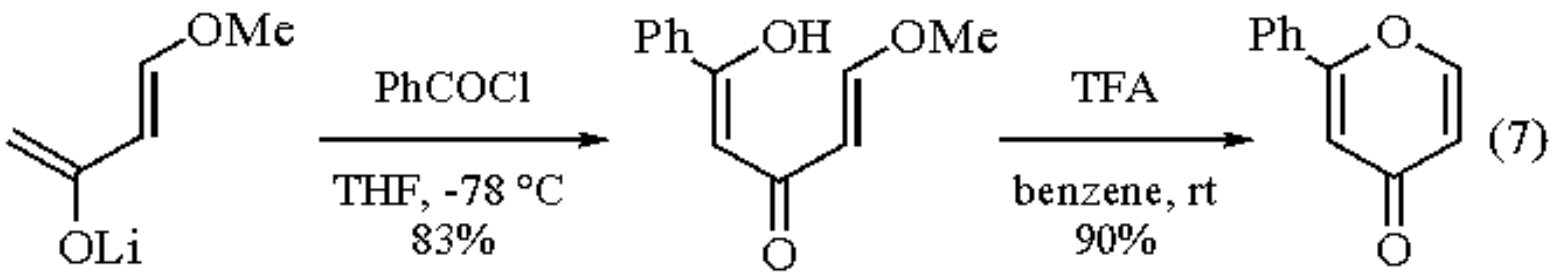

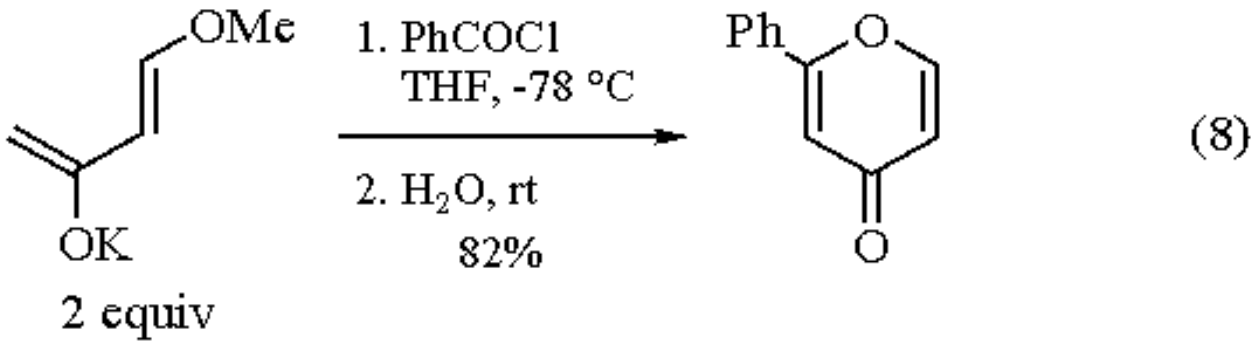

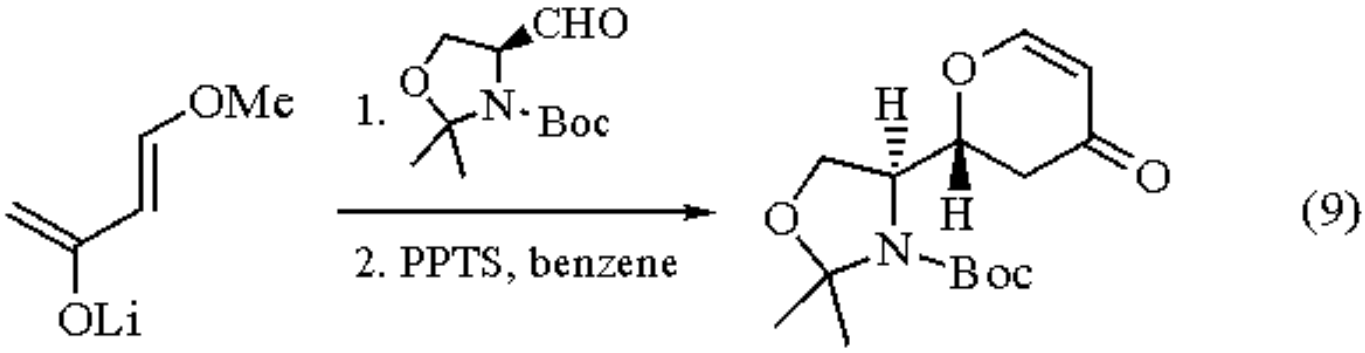

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(*Z*)-1-Methoxy-1-buten-3-yne[1]

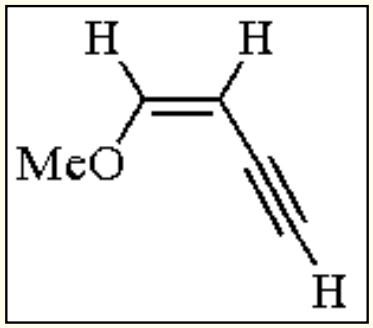

[3685-19-0] · C_5H_6O · (*Z*)-1-Methoxy-1-buten-3-yne · (MW 82.11)

(convenient building block for synthesis of spiroacetals, dialkynes, enones, and dienes)

Physical Data: bp 52 °C/28 mmHg.

Solubility: slightly sol H_2O; sol standard organic solvents.

Form Supplied in: 50 wt % solution in methanol-water.

Purification: can be obtained anhydrous by saturation of the solution of 1-methoxy-1-buten-3-yne in methanol-water with solid NaCl followed by extraction with ether and distillation under reduced pressure (52 °C/28 mmHg).

Handling, Storage, and Precautions: store under nitrogen.

(*Z*)-1-Methoxy-1-buten-3-yne is readily deprotonated by ***n-Butyllithium*** in THF. The resulting anion reacts with alkyl halides, carbonyl compounds, and trialkylchlorosilanes. The anion of 1-methoxy-1-buten-3-yne has been used in a direct synthesis of spiroacetals (eq 1).[2] When (*Z*)-1-methoxy-1-buten-3-yne is treated with 2 equiv of *n*-butyllithium, the monoanion of 1,3-butadiyne is formed (eq 2).[3] If 3 equiv of *n*-butyllithium are used, the dianion of 1,3-butadiyne is generated. (*Z*)-1-Methoxy-1-buten-3-yne also serves as a convenient precursor to α,β;γ,δ-unsaturated aldehydes by a sequence involving addition of its anion to an aldehyde followed by reduction of the resulting acetylenic alcohol using ***Lithium Aluminum Hydride*** and acid-mediated hydrolysis (eq 3).[4]

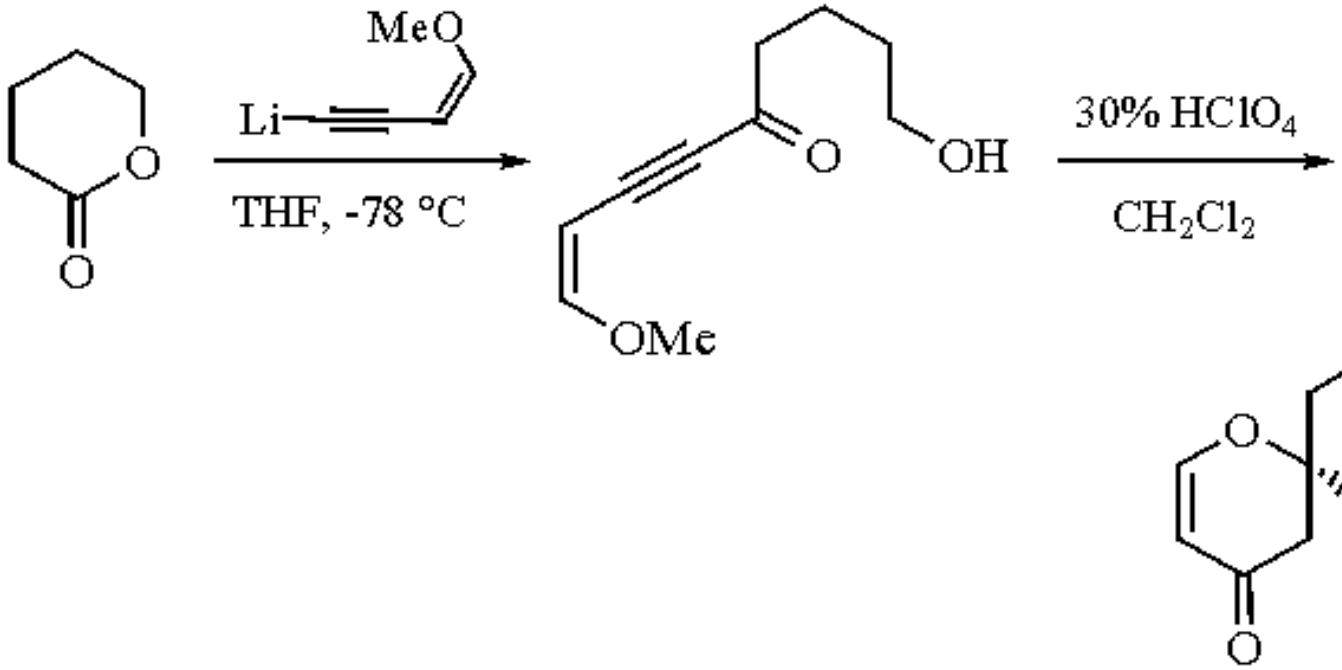

(1)

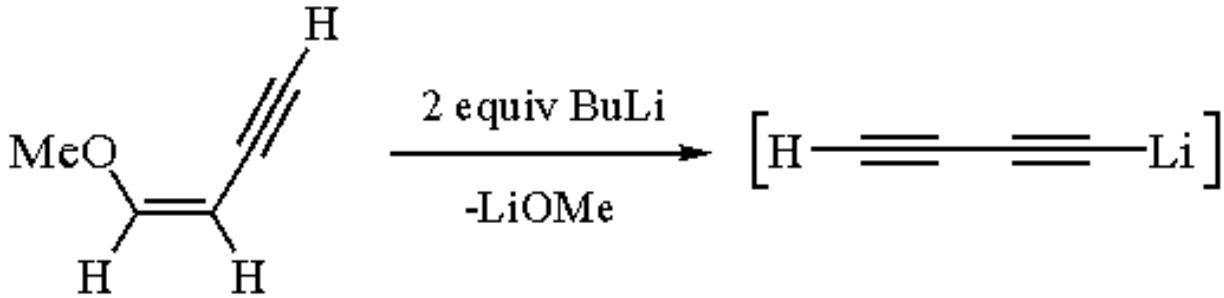

(2)

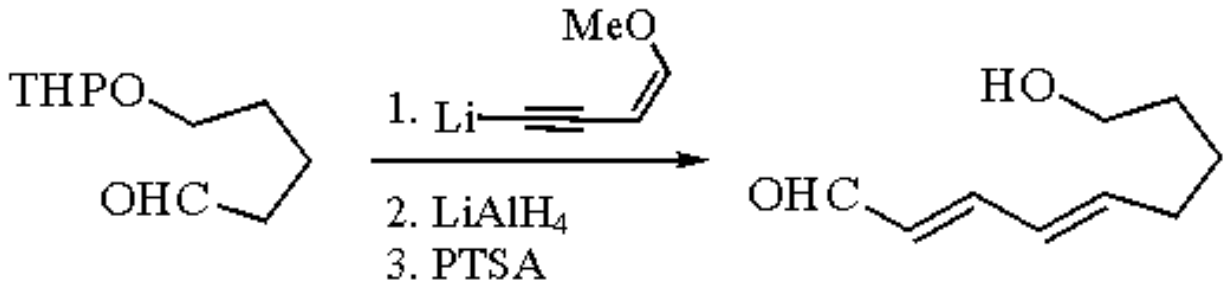

(3)

1-Methoxy-1-buten-3-yne can be alkylated and treated with dialkylboranes to form vinylboranes (eq 4).[5] The regiochemistry of the hydroboration reaction appears to be directed by the methoxy group. The vinylborane can be oxidized to provide a β-methoxy enone. The hydrozirconation of 1-methoxy-1-buten-3-yne proceeds regioselectively to form a diene which reacts with *N*-(phenylselenyl)phthalimide to afford 1-phenylselenyl-4-methoxy-1,3-butadiene in good yield.[6] 1-Methoxy-1-buten-3-yne also reacts with cyclopropyl carbene chromium complexes to form cyclopentenones.[7] (*Z*)-1-Methoxy-1-buten-3-yne can also be converted into a copper salt which reacts with aryl iodides, acid chlorides, and alkyl halides.[8]

(Z)-1-Methoxy-1-buten-3-yne

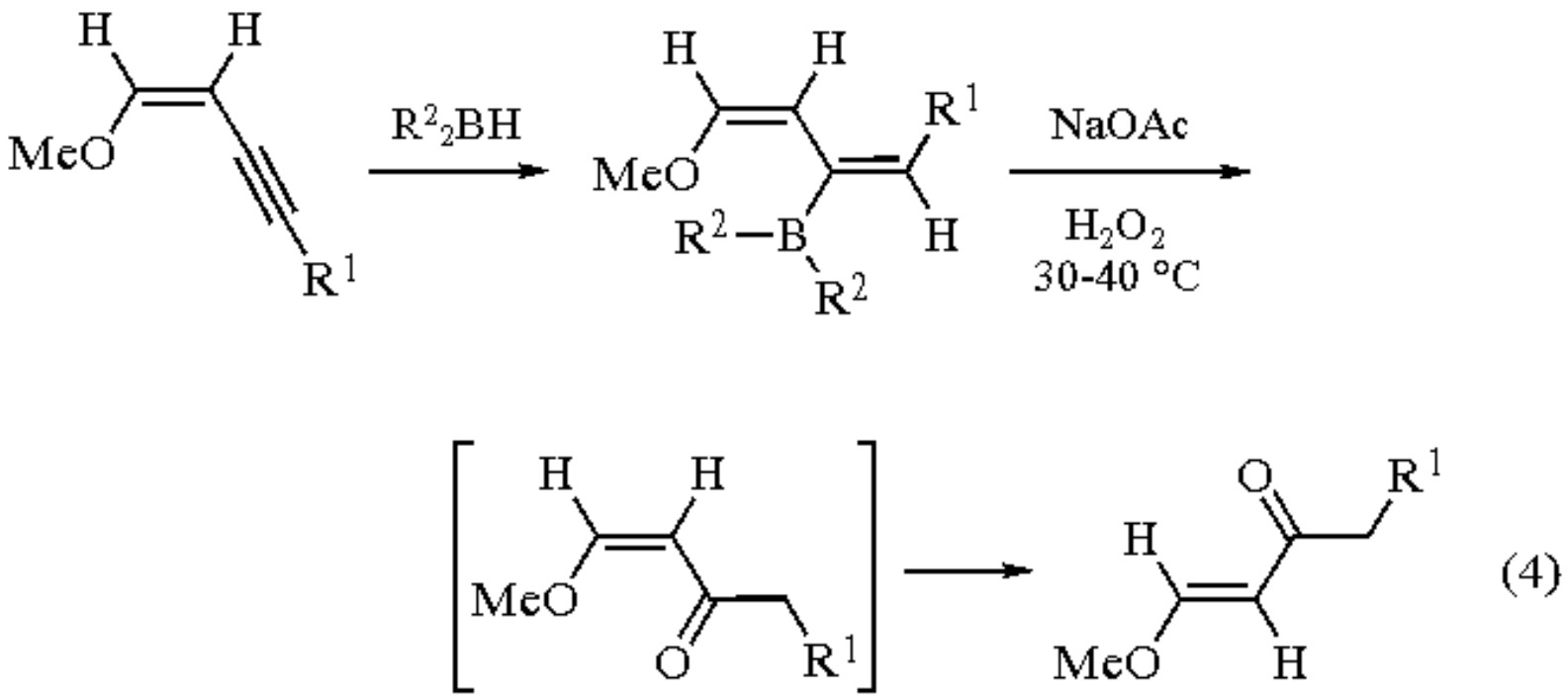

R^2 = cyclohexyl, 1,2-dimethylpropyl

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2-Methoxycarbonylbenzoyl Chloride[1]

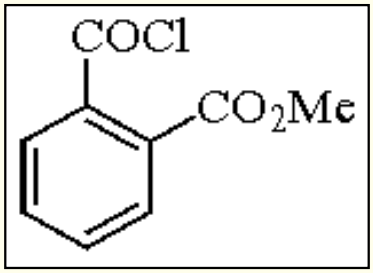

[4397-55-1] · $C_9H_7ClO_3$ · 2-Methoxycarbonylbenzoyl Chloride · (MW 198.61)

(*N*-phthaloylation of α-amino acids; preparation of isocoumarins)

Physical Data: mp 48-52 °C; bp 107-110 °C/0.1 mmHg; fp >110 °C.

Solubility: sol most organic solvents.

Form Supplied in: pale yellow oil.[1]

Preparative Method: heat *o*-methoxycarbonylbenzoic acid (methyl hydrogen phthalate) with ***Thionyl Chloride*** for 1 h on a steam bath (eq 1).[1]

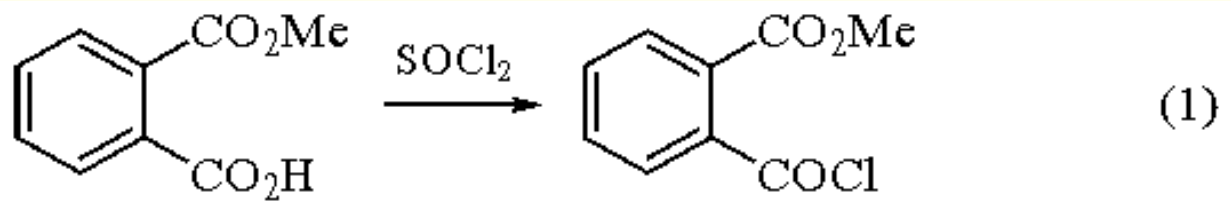

Handling, Storage, and Precautions: corrosive and moisture sensitive; reacts with protic solvents; use in a fume hood; do not breathe vapors and avoid contact with skin, eyes, and clothing; causes burns and irritation of the respiratory system; lachrymator; use immediately after preparation.

Phthaloyl Amino Acids.

2-Methoxycarbonylbenzoyl chloride is used in the *N*-phthaloylation of α-amino acids.[2] *N*-Phthaloyl-α-amino acids may be obtained by heating mixtures of phthalic anhydride[3] and the appropriate α-amino acids. In a number of cases, racemization occurs and the experimental conditions are too drastic for the preparation of *N*-phthaloyl-α-amino acids containing additional functional groups. In addition, when α-amino acid esters are used, 2,5-diketopiperazines may result as the major product. On the other hand, the reagent reacts with α-amino acid esters at 0 °C (2 h) in THF or 1,4-dioxane in the presence of Et_3N to give *N*-phthaloyl-α-amino acid esters[2] in high yields (90-85%) and without racemization (eq 2). Under these

mild conditions the formation of 2,5-diketopiperazines and anhydrides is also suppressed. The reagent forms an intermediate *N*-(*o*-methoxycarbonylbenzoyl)amino acid ester with the amino acid ester (eq 2), which eliminates MeOH to gave the *N*-phthaloyl-α-amino acid ester. The corresponding *N*-phthaloyl-α-amino acids are obtained by selective removal of the ester group (i.e. Me, Et, Bn, *t*-Bu). The preferred ester is benzyl, since this group is easily removed by hydrogenolysis without racemization; the yields for (**1**) are consistently high (Tables 1 and 2).[4,5]

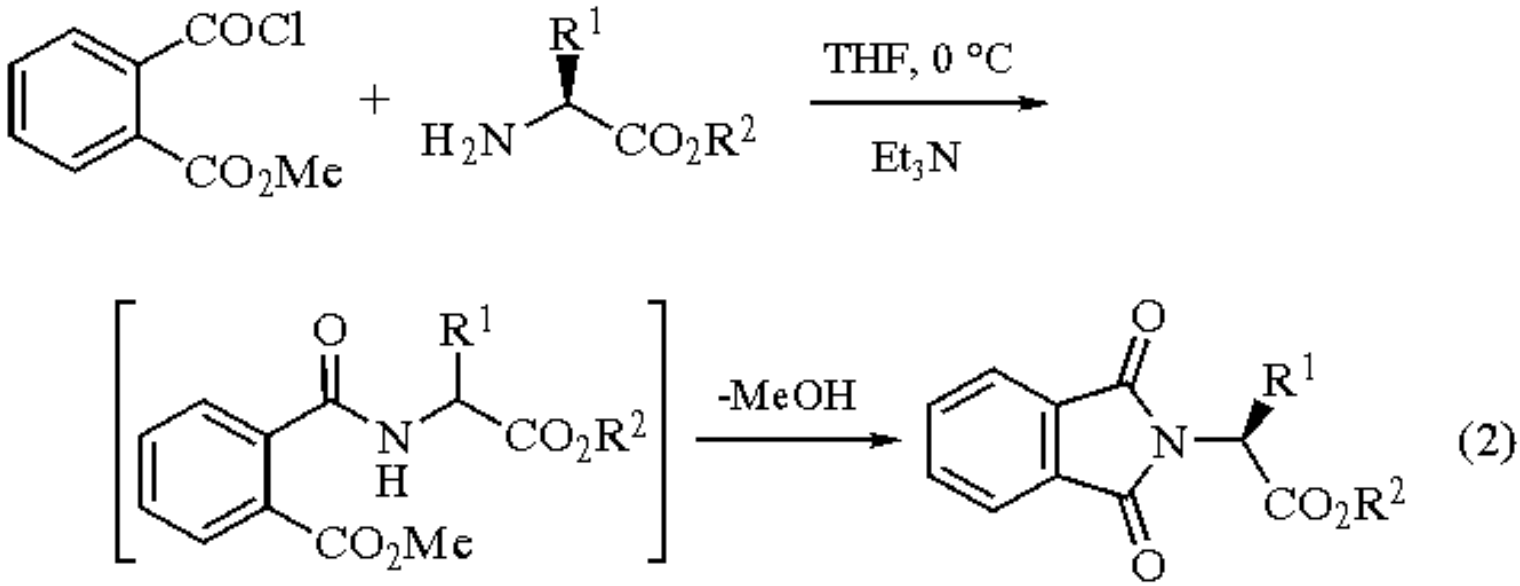

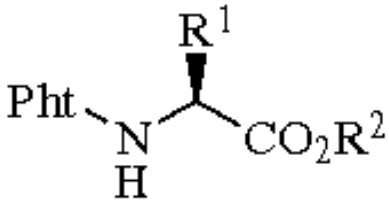

(1)

Table 1 *N*-Phthaloyl-a-amino Acid Esters Prepared According to eq 2

R^1	R^2	Yield (%)
H	Et	85
H	CH_2Ph	89
H	*t*-Bu	96
i-Bu	Et	73
i-Bu	CH_2Ph	88
$MeSCH_2CH_2$	Me	90
$H_2NCOCH_2CH_2$	4-$NO_2C_6H_4CH_2$	95
H_2NCOCH_2	4-$NO_2C_6H_4CH_2$	98

Table 2 *N*-Phthaloyl-a-Amino Acid Benzyl Esters Prepared According to eq 2, Followed by Hydrogenolysis

Amino acid	*N*-Phthaloyl amino acid ester (%)	*N*-Phthaloyl amino acid (%)	Mp (°C)
Ala	92	83	151 152
L-Ala	95	83	147 148
L-Asn	98	80	210 211
L-Asp	95	88	225 227
L-Cys(Nim-Bn)	85	85	169 170
L-Glu	97	92	163 164
Gly	90	83	194 195
L-His(Nim-Bn)	80	73	162 (dec)
L-Ile	87	82	121 124
L-Leu	99	96	122 123
L-Lys	96	93	80 88
Met	99	85	211 214
L-Phe	95	88	186 187
L-Ser	96	89	136 138
L-Thr	99	67	144 145
L-Trp	90	81	202 205
L-Tyr	96	93	173 174
L-Val	99	89	118 119

Isocoumarins.

Some isochroman-1,4-diones (R = H, OMe) were prepared in good yield using *o*-methoxycarbonylbenzoyl chloride and appropriate diazoethyl ketones.[6-8] They were reduced with ***Sodium Borohydride*** to the related 4-hydroxy-3-methyl-3,4-dihydroisocoumarins (eq 3)

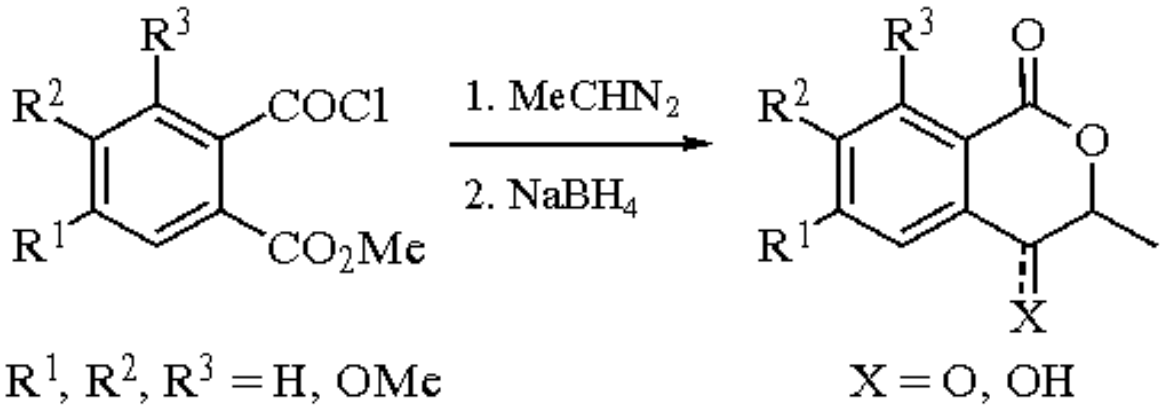

(3)

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Methoxycarbonylmethanesulfonyl Chloride

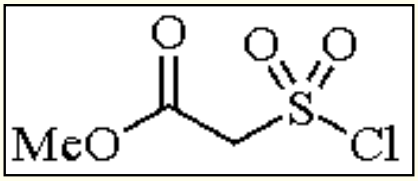

[56146-83-9] · $C_3H_5ClO_4S$ · Methoxycarbonylmethanesulfonyl Chloride · (MW 172.60)

(synthesis of sultam analogs of β-lactams;[3] synthesis of biologically active sulfonamides[4-6])

Physical Data: bp 98 °C/8 mm Hg; *d* 1.505 g cm^{-3}; fp >110 °C.

Solubility: sol C_6H_6, CH_2Cl_2, Et_2O.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: reagent purity may be determined by standard analytical techniques.

Preparative Methods: from chlorosulfonylacetyl chloride by reaction with 1 equiv of methanol;[1] may also be prepared by chlorination of sodium methoxycarbonylmethanesulfonate with ***Phosphorus(V) Chloride***[2] or by direct chlorination of methyl thioglycolate.[3]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: moisture sensitive; causes burns.

Synthesis of β-Sultams.[3]

Formation of the β-sultam (eq 1) proceeds via addition of methoxycarbonylmethanesulfonyl chloride to a solution of the desired imine (1 equiv) and a tertiary amine base (1.5 equiv) at -78 °C. Best results are obtained using THF as the solvent and ***Pyridine*** as the base. Yields are moderate to high. In general, the yields are higher when the R^1 substituent is aryl rather than alkyl.

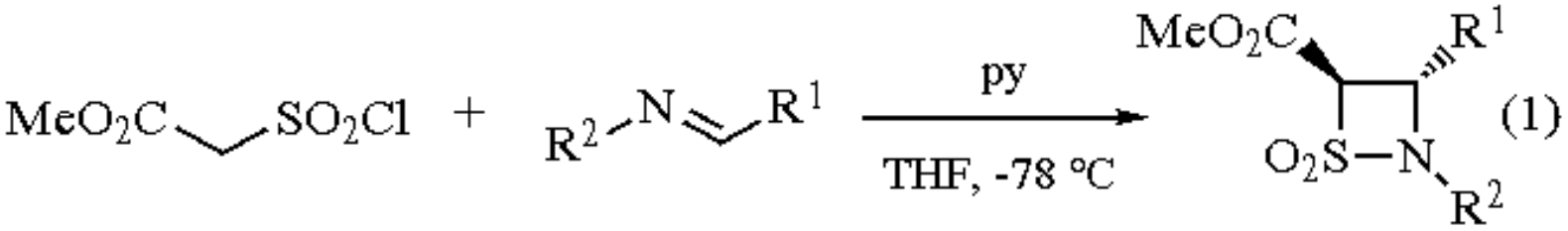

Synthesis of Sulfonamides.[4-6]

Sulfonamides are formed in moderate to good yields by the reaction of methoxycarbonylmethanesulfonyl chloride with the desired amine in the presence of ***Triethylamine*** (eq 2). This reaction is usually carried out using arylamines, but can be extended to peptidic amines.[6]

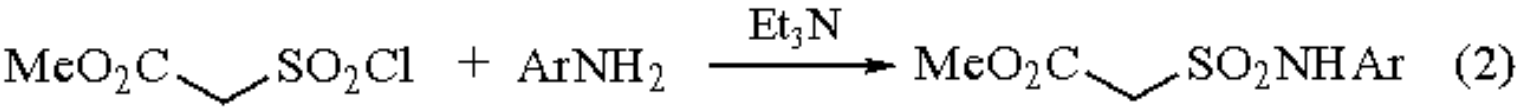

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(Methoxycarbonylmethylene)triphenylphosphorane[1]

$Ph_3P{=}CHCO_2Me$

[2605-67-6] · $C_{21}H_{19}O_2P$ · (Methoxycarbonylmethylene)triphenylphosphorane · (MW 334.37)

(stabilized phosphorane reagent useful for Wittig alkenation reactions to give methyl acrylate esters on reactions with carbonyl compounds[1] and ozonides;[2] formation of heterocyclic rings[3])

Alternate Name: methyl (triphenylphosphoranylidene)acetate.

Physical Data: mp 169-171 °C.

Solubility: sol $CHCl_3$ (26 g 100 mL^{-1}); slightly sol EtOH (2.7 g 100 mL^{-1}), THF (3.8 g 100 mL^{-1}); insol water (<0.5 g 100 mL^{-1}).

Form Supplied in: white crystalline powder; commercially available.

Preparative Methods: readily prepared by mild base treatment of (methoxycarbonylmethyl)triphenylphosphonium bromide (pK_a 8.8) (eq 1).[4,5]

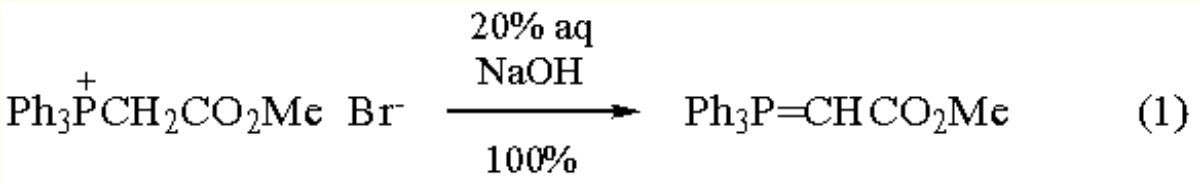

Handling, Storage, and Precautions: storage at 5 °C in a tightly sealed bottle is recommended for prolonged periods. The compound decomposes to triphenylphosphine oxide in MeOH-water 1:1 ($t_{1/2}$ ca. 1.5 h) and in weakly basic aqueous solution (0.5 mM NaOH in MeOH-water 1:1) ($t_{1/2}$ ca. 1 h).

Weakly Basic Phosphorus Ylide.

(Methoxycarbonylmethylene)triphenylphosphorane is slightly less stable than the corresponding ethyl ester, but is widely used in a similar manner for Wittig alkenations and other reactions (see ***(Ethoxycarbonylmethylene)triphenylphosphorane***). As with the ethyl ester, this reagent exists in solution as a 3:1 mixture of *cis*/*trans* ylide/enolates (eq 2).[4,6] X-ray structure determination shows the *cis* form to have a short P-C bond and considerable C-C double bond character.[7] There is increasing exchange of the two forms at higher temperatures, and also in the presence of trace amounts of a proton source such as water.[6] Wittig reactions with the reagent work best as the exchange rate increases, due to the presence of greater amounts of the reactive ylide tautomer, so that it can be counterproductive to be overly scrupulous in drying these reactions.[6]

(Methoxycarbonylmethylene)triphenylphosphorane

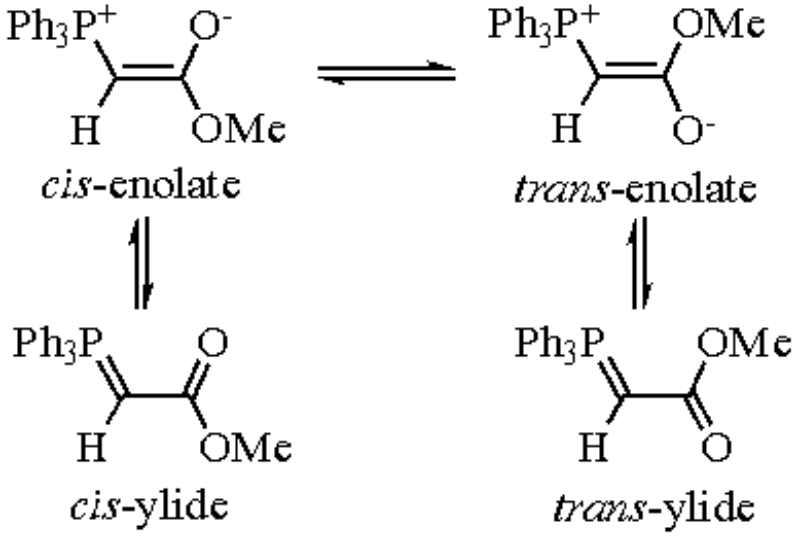

(2)

Wittig Alkenation Reactions.

Among the many examples of the use of this reagent in synthesis,[1] only a few will be highlighted here. Typical reactions with aldehydes produce primarily the (*E*)-alkene, as in the condensation with PhCHO to give methyl cinnamates (eq 3).[8] Although Wittig reaction intermediates have not been observed by spectroscopic means,[9] it is expected that such reactions proceed through a four-membered oxaphosphetane prior to formation of products. The stereocontrol can be altered by the choice of solvent, temperature, and other factors.[1]

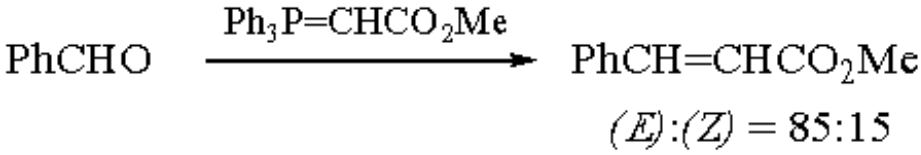

(3)

Treatment of $MeC(O)CF_3$ with $Ph_3P{=}CHCO_2Me$ results in formation of largely the (*E*) product (*E*:*Z* = 95:5), whereas condensation with the related Horner-Wadsworth-Emmons (HWE) reagent $(MeO)_2P(O)CHCO_2Me^-Na^+$ is not particularly stereoselective.[10] Larger amounts of the (*Z*)-isomer are often observed in reactions with aldehydes bearing adjacent hydroxy or alkoxy groups, such as those derived from carbohydrates.[1a] For example, reaction of a galactose-derived aldehyde with the phosphorane gives mainly the (*Z*)-alkene (eq 4); many other related systems have been examined.[11] The reactions of α-hydroxy carbonyl compounds are faster than those in which the hydroxy groups are protected.[12]

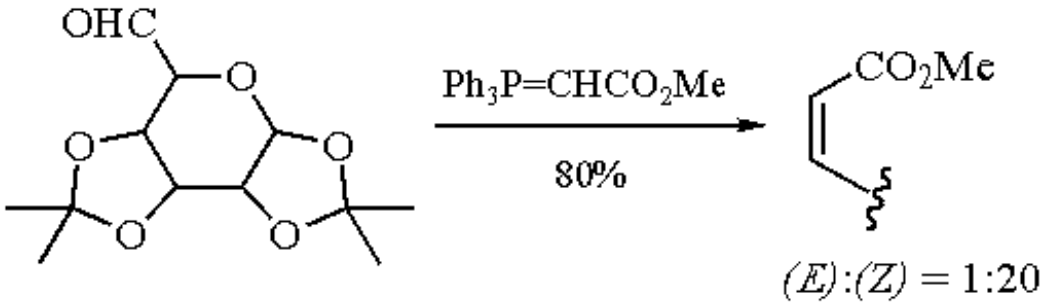

(4)

In cases where reactions are sluggish, such as those involving hindered carbonyls, the use of $Bu_3P{=}CHCO_2Me$ can prove advantageous.[1,12] In addition, this reagent often reacts with higher levels of (*E*) stereocontrol.[1,13]

Wittig/Michael reactions on the anomeric hemiacetals of sugars can lead directly to a *C*-glycoside structure. For example, an arabinose derivative was condensed with the phosphorane to give an anomeric mixture of *C*-glycosides (eq 5).[14] When this reaction is carried out using $Ph_3P{=}CHCO_2$-*t*-Bu, a 2:3 mixture of (*E*):(*Z*) noncyclized alkene isomers is observed.[15]

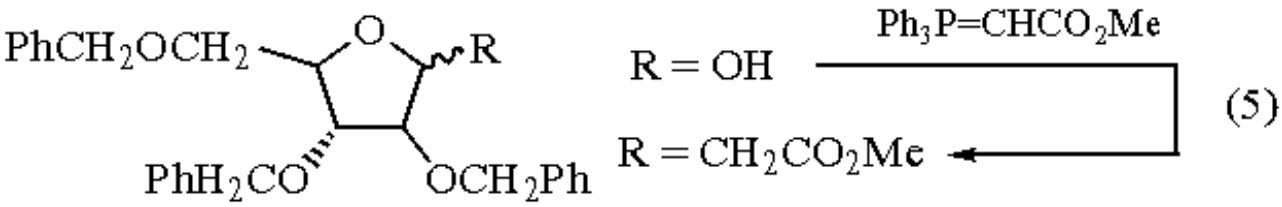

Imides react with the phosphorane to produce *N*-vinyl amides.[16] Thioimides react in a thio-Wittig reaction, albeit in low yields (eq 6).[17] The (*Z*)-isomer converts to the (*E*)-isomer upon a silica gel chromatography.

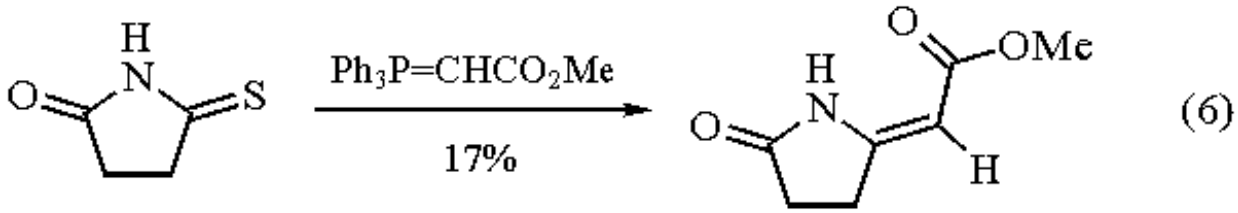

The phosphorane reacts with anhydrides to give enol lactones.[16] With highly substituted anhydrides the condensation occurs at the least hindered carbonyl; however, other factors come into play with only moderate steric hindrance. For example, 2-methyl- and 2-phenylsuccinic anhydrides suffer considerable attack at the 1-carbonyl.[16,18] This effect is particularly pronounced in the case of 2-methoxysuccinic anhydride, in which case complexation of the oxygen is thought to direct the phosphorane to the 1-carbonyl (eq 7).[18]

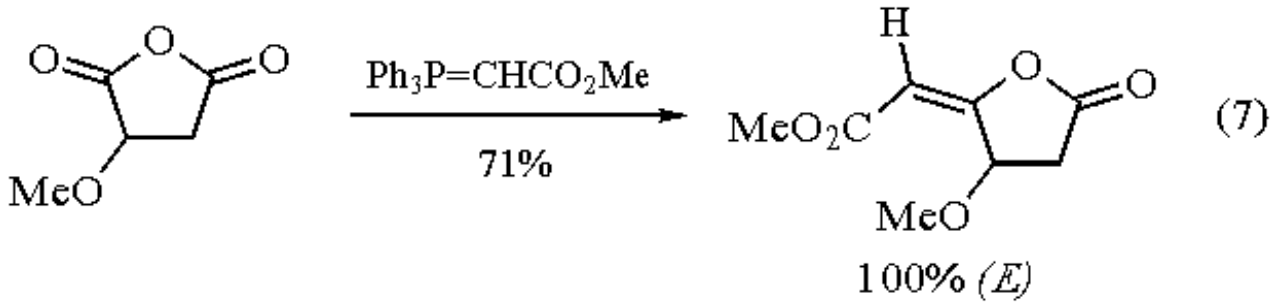

Alkenations of Ozonides.

Ozonides react directly with the phosphorane in the preparation of *trans*-acrylate esters (eq 8).[2] The sequence can be applied to a one-pot homologation of alkenes to (*E*)-acrylate esters.[2] Trapping experiments have shown that it is the ozonide itself, and not opened species such as a carbonyl ylide, which is the reactive partner.[2b]

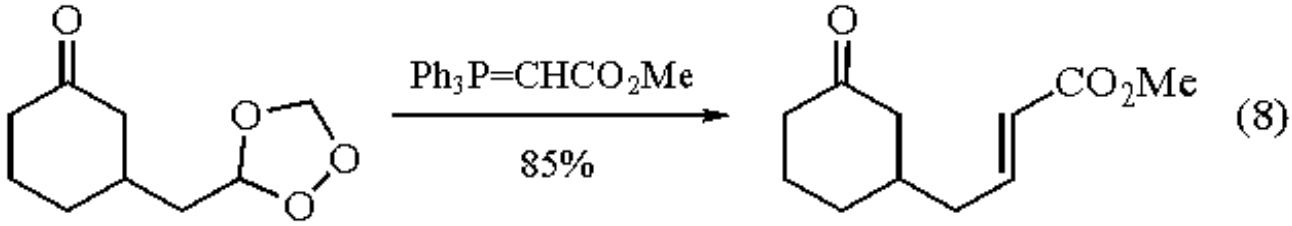

Heterocyclic Ring Formation.

Several different ring systems can be prepared using stabilized phosphoranes, as they have both ylide and ester reactive sites (see ***(Ethoxycarbonylmethylene)triphenylphosphorane***). One example specifically involving (methoxycarbonylmethyl)triphenylphosphorane is the preparation of 2-chromenes from *o*-acyloxybenzyl bromide (eq 9).[3] In this condensation the ylide is first benzylated with the benzyl halide functionality, followed by intramolecular Wittig reaction with the *o*-acetoxy group.

(Methoxycarbonylmethylene)triphenylphosphorane

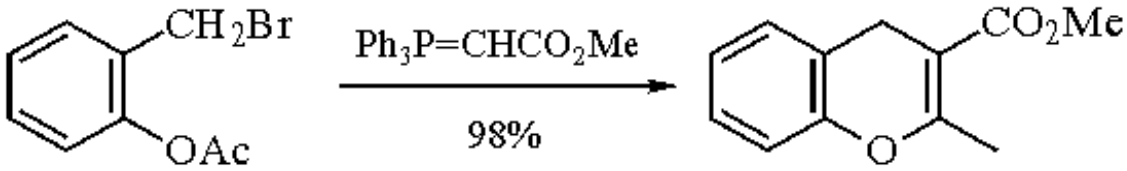

(9)

Condensation with benzoquinones involves initial Wittig reaction, followed by Michael addition of a second phosphorane. Elimination of triphenylphosphine and cyclization of the ester affords coumarin derivatives (eqs 10 and 11).[19]

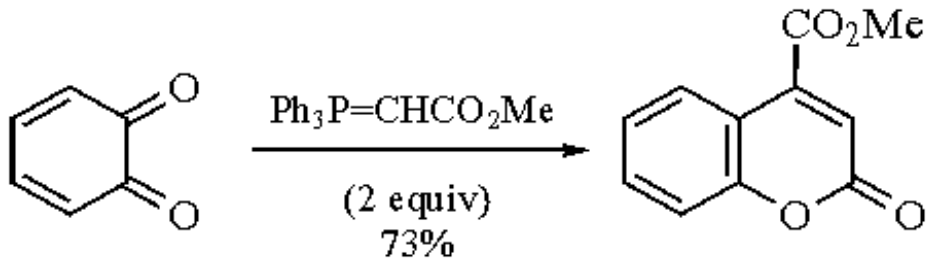

(10)

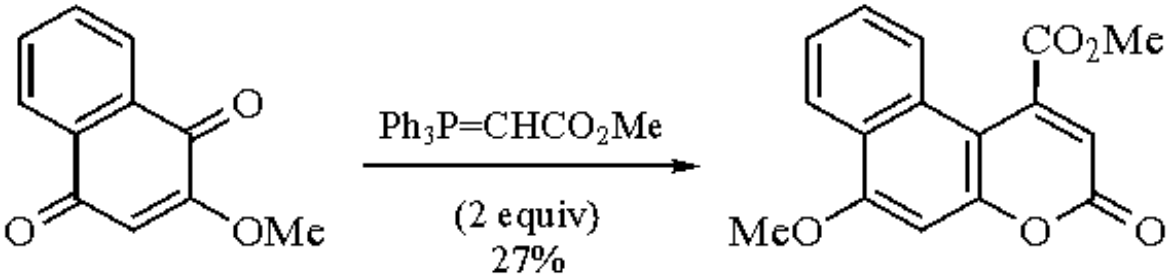

(11)

Alkylation.

The reagent is sufficiently nucleophilic to be alkylated with reactive electrophiles to produce phosphorus reagents often suitable for further reactions.[1] Hydrolysis of the triphenylphosphorus and ester moieties after alkylation affords the corresponding carboxylic acids (eq 12).[19]

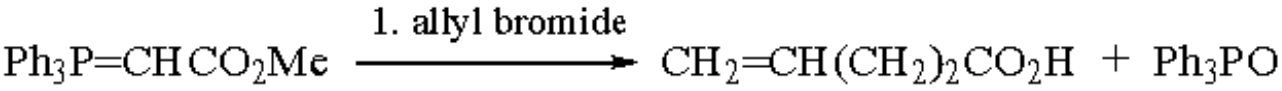

(12)

Alternatively, alkylation of the phosphorane with an α-halo ketone is followed immediately by elimination of triphenylphosphine to give an α,β-unsaturated γ-keto ester.[20] This reaction has been used in the synthesis of isocardenolides (eq 13).[21]

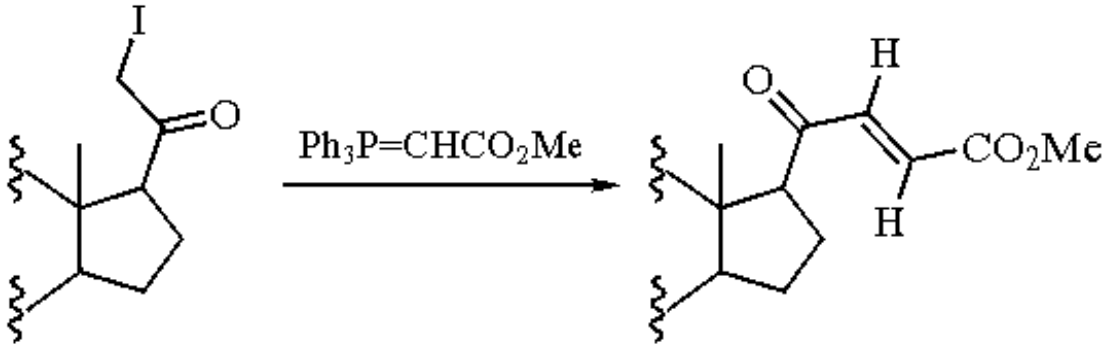

(13)

(Methoxycarbonylmethylene)triphenylphosphorane

The ylide can be halogenated[22] or sulfenylated[23] to prepare more complex ylides, which can then undergo Wittig reactions to yield vinyl halides or vinyl sulfides, respectively. Treatment of the phosphorane with a strong base in the absence of an added electrophile, followed by addition of ***Chlorotrimethylstannane***, leads to $Ph_3P{=}C{=}C{=}O$,[24] which is a useful reagent for the construction of certain heterocyclic rings.[25]

---

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The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, USA

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p-Methoxycarbonylperbenzoic Acid

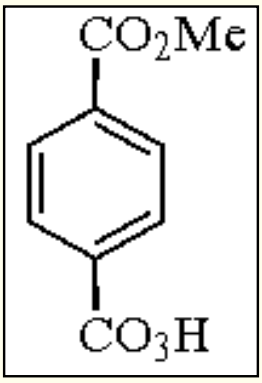

[28276-78-0] · $C_9H_8O_5$ · *p*-Methoxycarbonylperbenzoic Acid · (MW 196.17)

(electrophilic reagent which delivers oxygen to alkenes[1])

Alternate Name: PMCPBA.

Physical Data: white crystalline solid; dec. 125 °C.

Solubility: sol ether, dioxane, CH_2Cl_2, $CHCl_3$; slightly sol benzene; insol cyclohexane, CCl_4.

Analysis of Reagent Purity: iodometric titration.

Preparative Methods: a mixture of aldehyde (**1**) (98% pure, 2 g) and CCl_4 (50 mL) is stirred under oxygen in a glass reactor at 25 °C and irradiated with a 2 kW high-pressure mercury lamp until about 95% of the theoretical amount of oxygen is absorbed (0.5 h) (eq 1). The product, which separates as a white crystalline powder, is collected and dried (yield 2.0 g, 84%; peroxy acid content 90%); this material can be used for general oxidation reactions.[1]

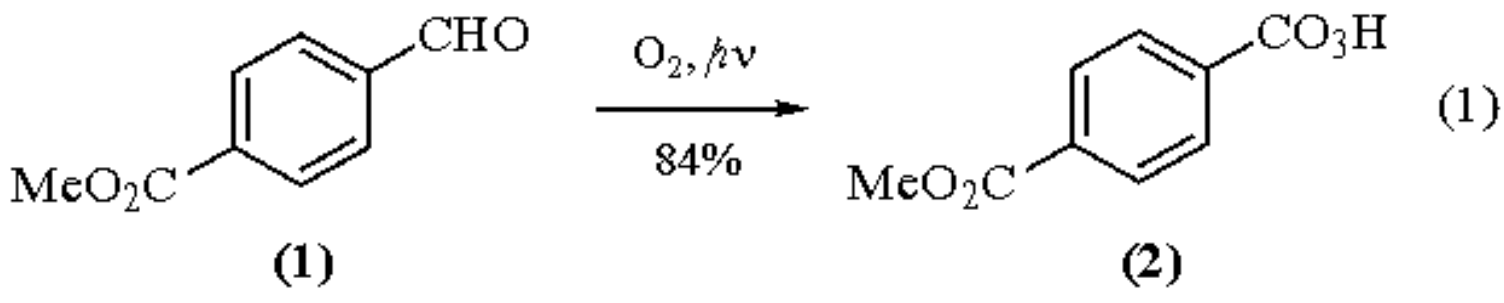

Purification: recrystallization from methanol.

Handling, Storage, and Precautions: the peroxy acid (**2**) is as stable as ***m-Chloroperbenzoic Acid*** and

shows less than 5% decomposition after storage at 10 °C for 1 year. (**2**) irritates nasal membranes and causes sneezing. Since the reagent is a peroxide and potentially explosive, care is required in carrying out reactions with it. During workup, check for peroxides before solvent removal. This reagent should be handled in a fume hood.

Epoxidation of Alkenes.

A number of alkenes have been epoxidized using the peroxy acid (**2**); the yields of epoxides obtained are comparable to the yields obtained using ***Perbenzoic Acid***. The following is a representative procedure. To a stirred mixture of peroxy acid (**2**) (6.112 g, 0.03 mol) and 200 mL of $CHCl_3$ maintained below 20 °C, is added dropwise a solution of cyclohexene (**3**) (2.544 g, 0.03 mol) in 20 mL of $CHCl_3$. The reaction mixture is stirred at 20 °C for 12 h. The precipitate of *p*-methoxycarbonylbenzoic acid (4.650 g) is removed by filtration. The filtrate is washed with aq Na_2CO_3 solution, aq $NaHSO_3$, and brine and then dried. The residue obtained after solvent removal is distilled under reduced pressure to furnish the epoxide (**4**) (yield 90%) (eq 2).[1]

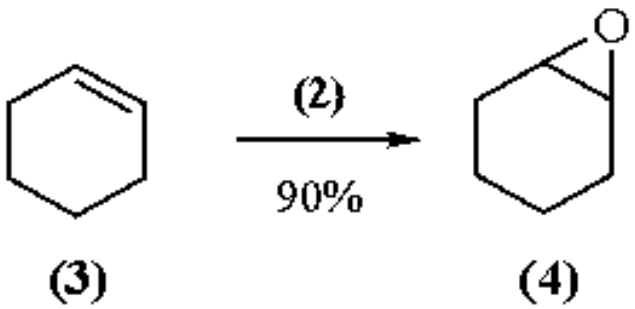

(2)

The epoxidation of the triene (**5**) with the peroxy acid (**2**) is regio- and stereoselective, furnishing almost exclusively the epoxide (**6**) (eq 3).[2] Epoxidation of the triene (**5**) with MoO_5.2HMPA furnishes a 5:1 mixture of epoxides (**6**) and (**7**); epoxidation of (**5**) with ***Hydrogen Peroxide-Peracetic Acid*** furnishes a 2:1 mixture of epoxides (**6**) and (**7**).

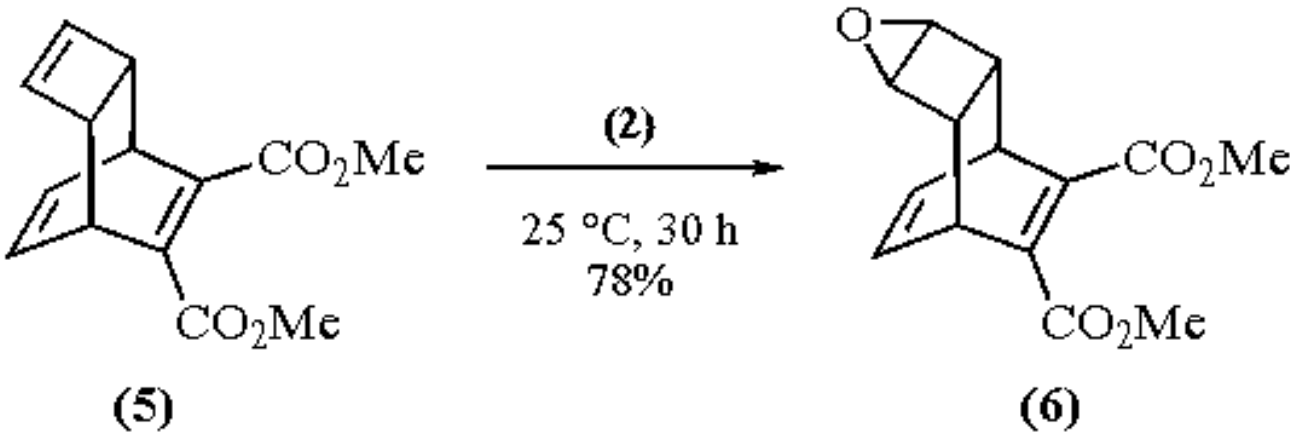

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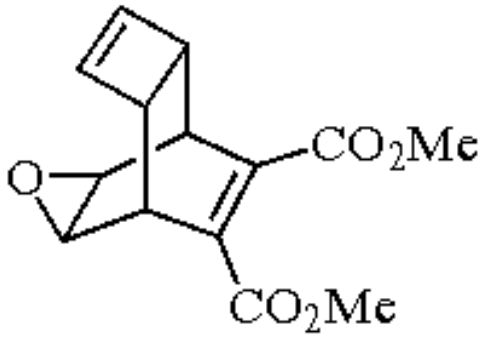

(7)

Epoxidation of cholesteryl acetate (**8**) in CH_2Cl_2 furnishes a mixture of α- and β-epoxides in 65:35 ratio. The influence of solvents on the stereochemistry of epoxidation of (**8**) has been examined. The highest amount of β-epoxide (58%) is obtained when CCl_4 (in which the reagent is insoluble) is used as solvent; the highest amount of α-epoxide (76%) is obtained when *t*-butanol is used as solvent.[3]

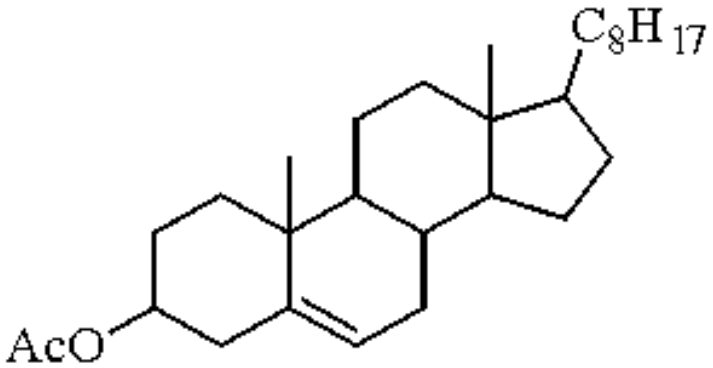

(8)

Baeyer-Villiger Reaction.

Ketones undergo oxygen insertion reaction when reacted with the peroxy acid (**2**) (eq 4).[1] The yields obtained are comparable with perbenzoic acid oxidations.

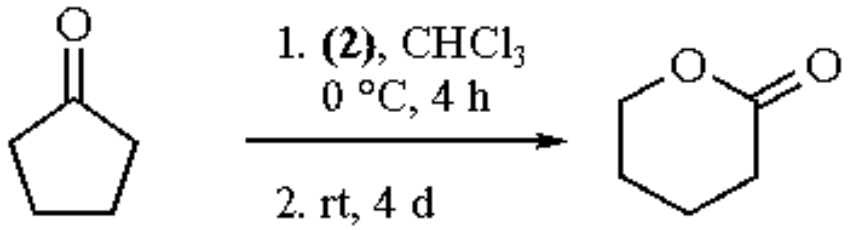

(4)

(9) **(10)**

Oxidation of N-Heterocycles.

The oxidation of N-heterocycles to *N*-oxides proceeds smoothly when they are treated with a suspension of (**2**) in $CHCl_3$. The oxidation of pyridine, 3,4-dimethylpyridine, and 2-methylquinoline has been carried out employing both *m*-CPBA and acid (**2**); reagent (**2**) is as effective as *m*-CPBA.[4]

In the epoxidation of alkenes which are moderately or highly reactive, the yields obtained with (**2**) are comparable with the yields obtained using *m*-CPBA or $MeCO_3H$. However, *m*-CPBA and $MeCO_3H$ are available commercially; (**2**) is not available commercially but can be prepared easily in a short time and has a long shelf life.

---

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Methoxycarbonylsulfamoyl Chloride[1]

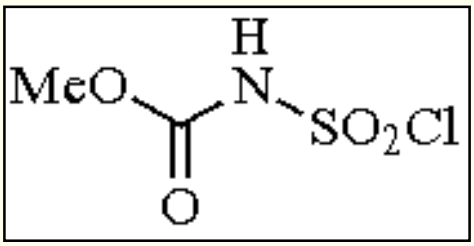

[36914-92-8] · $C_2H_4ClNO_4S$ · Methoxycarbonylsulfamoyl Chloride · (MW 173.59)

(precursor for the Burgess reagent;[1] regent for heterocyclic cycloaddition[6])

Physical Data: mp 70-74 °C.

Solubility: sol benzene, cyclohexane, THF, MeCN.

Form Supplied in: white crystalline solid.

Preparative Method: readily prepared in high yield from the reaction of ***Chlorosulfonyl Isocyanate*** and anhydrous methanol.[1]

Handling, Storage, and Precautions: is moisture sensitive and should be stored in a dark bottle, protected from light. Violent decomposition has been observed when the product is stored in a clear-glass container or when advertently exposed to sunlight.

Formation of the Inner Salt of the Burgess Reagent.

The reaction of anhydrous ***Triethylamine*** with methoxycarbonylsulfamoyl chloride (**1**) in benzene produces the inner salt of ***(Methoxycarbonylsulfamoyl)triethylammonium Hydroxide*** (the Burgess reagent) (eq 1).[1] The Burgess reagent has been used in the formation of urethanes from primary alcohols; the urethanes are converted to primary amines upon hydrolysis.[1,2] The Burgess reagent has commonly been used in stereospecific *cis* elimination of secondary and tertiary alcohols to provide alkenes,[2,3] and in the synthesis of vinyltributyltin compounds.[4]

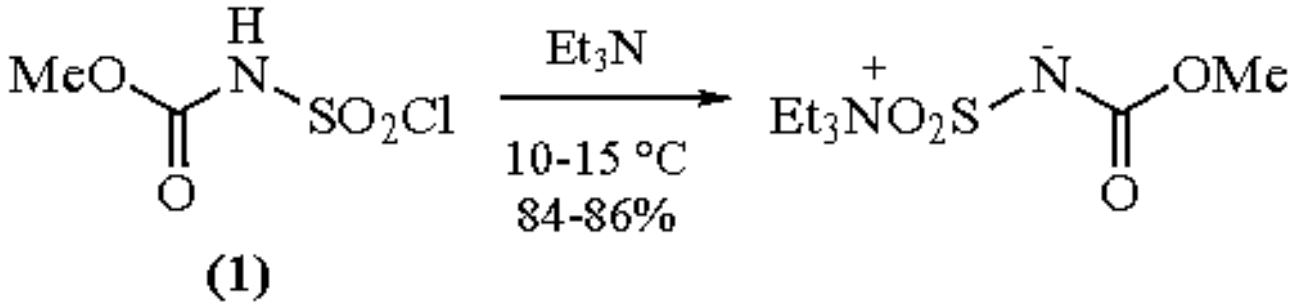

Cycloaddition Reactions.

Deprotonation of reagent (**1**) with ***Sodium Hydride*** provides the salt form of reagent (**1**), which undergoes cycloaddition with various alkenes. Decomposition of the salt form at 30 °C in THF yields the solvent complex of methyl *N*-sulfonylurethane, whereas reaction of the salt with acetonitrile, or other nitrile compounds, provides substituted 1,3,4,5-oxathiazines (eq 2). Both species are prone to cycloaddition reactions with alkenes (eq 2); however, the advantage of the latter species is the possibility of using higher reaction temperatures, thus enabling the formation of cycloadducts from otherwise unreactive alkenes.[5,6] The stereospecificity of the cycloaddition reaction has been investigated with a model substrate, *trans*-styrene-β-*d*, in both THF and acetonitrile. In both cases, cycloadducts (**4**) and (**5**) are formed in a ratio of 1:3 in 72% overall yield;[5] therefore, both [2 + 2] and [2 + 4] cycloadducts are formed with complete stereospecificity.

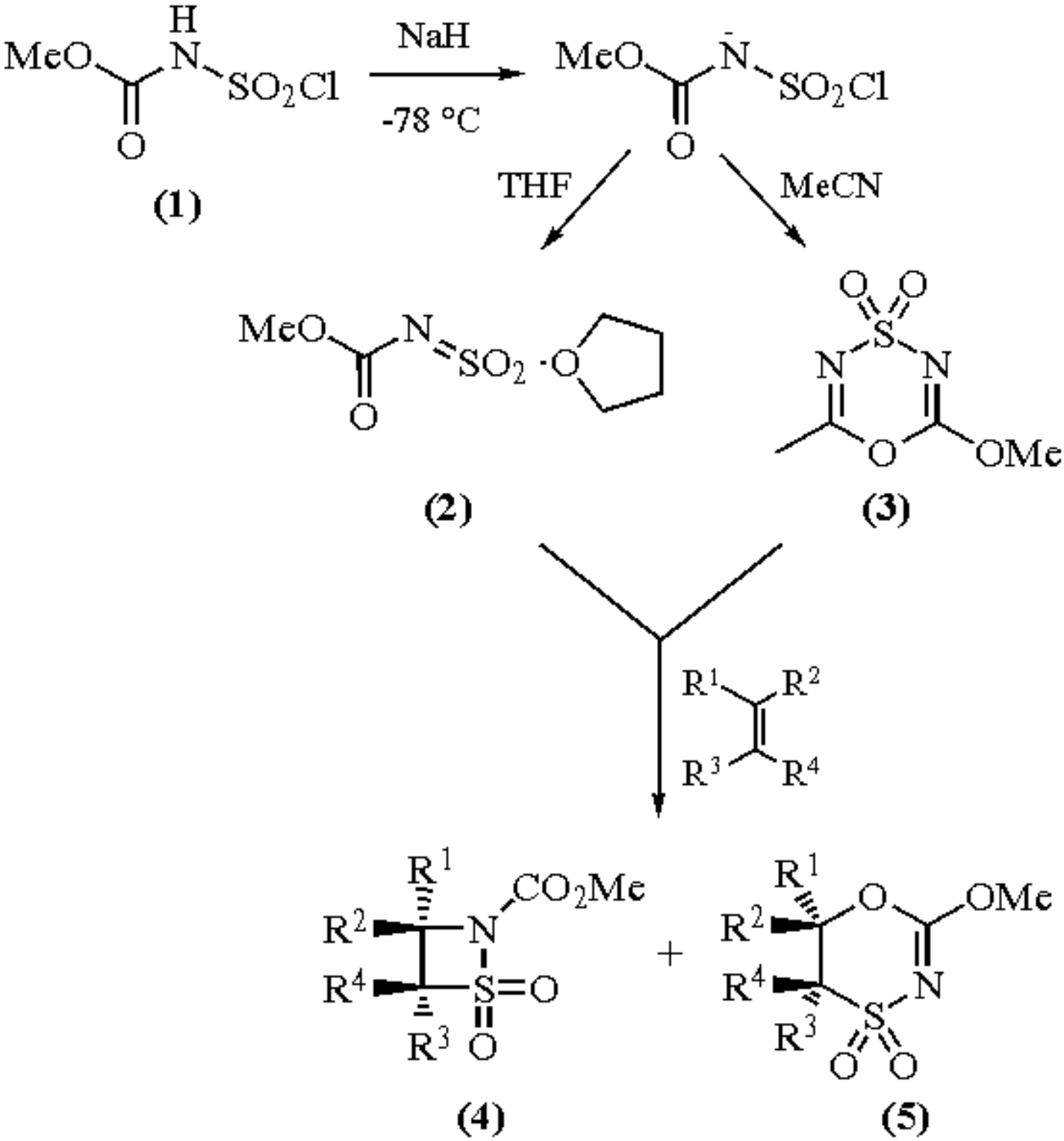

(2)

Intermediates (**2**) and (**3**) react with ynamines to form heterocycles (eq 3).[7] As with the cycloaddition reactions with alkenes, the nature of the product is dependent on whether species (**2**) or (**3**) is allowed to react with the ynamine.

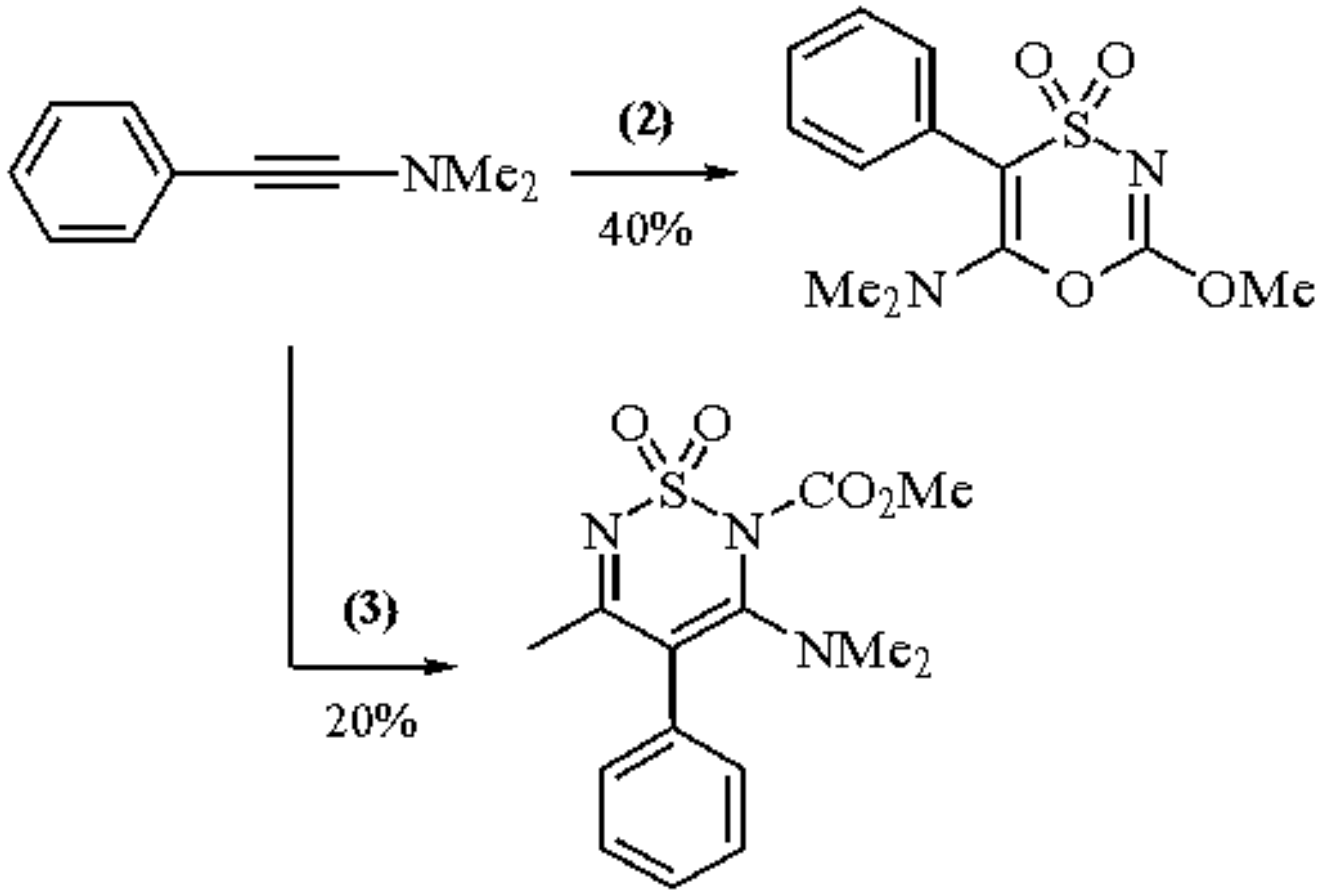

(3)

Metal-assisted cycloadditions with intermediate (**2**) have been reported (eq 4).[8] These reactions are dominated by the metal functioning as an electron-donor center.

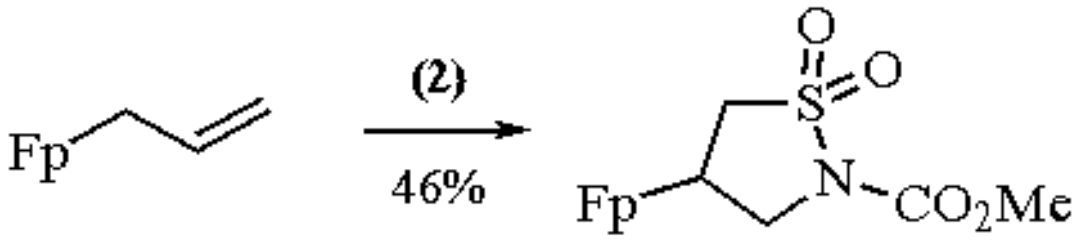

(4)

$Fp = \eta^5\text{-}C_5H_5Fe(CO)_2$

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5. Burgess, E. M.; Williams, W. M. *JACS* **1972**, *94*, 4386.
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(Methoxycarbonylsulfamoyl)triethylammonium Hydroxide[1]

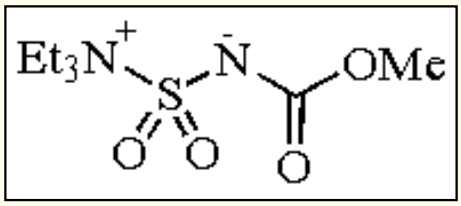

[29684-56-8] · $C_8H_{18}N_2O_4S$ · (Methoxycarbonylsulfamoyl)triethylammonium Hydroxide · (MW 238.35)

(dehydration agent[1])

Alternate Name: Burgess reagent.

Physical Data: mp 76-79 °C.

Solubility: sol benzene, toluene, THF, triglyme, acetonitrile.

Form Supplied in: colorless solid.

Preparative Method: although the Burgess reagent is commercially available, it can be easily synthesized in two steps:[1a] the reaction of anhydrous methanol with ***Chlorosulfonyl Isocyanate*** followed by the addition of ***Triethylamine*** affords the reagent in good yield.

Handling, Storage, and Precautions: moisture sensitive; the use of anhydrous solvent and atmosphere in reactions with this reagent is recommended.

Formation of Carbamates.

The reaction of primary alcohols with the Burgess reagent (**1**) produces alkyl *N*-methoxycarbonylsulfamate salts, which decompose on thermolysis via an S_N2 (or S_Ni) mechanism to give methyl urethanes (eqs 1 and 2).[1a,b] The products are isolated in good yields. Hydrolysis of the carbamate produces primary amines. Transformations of alcohols to amines are often multistep syntheses; therefore this reaction provides a distinct advantage over the existing methodology for such substitution reactions.

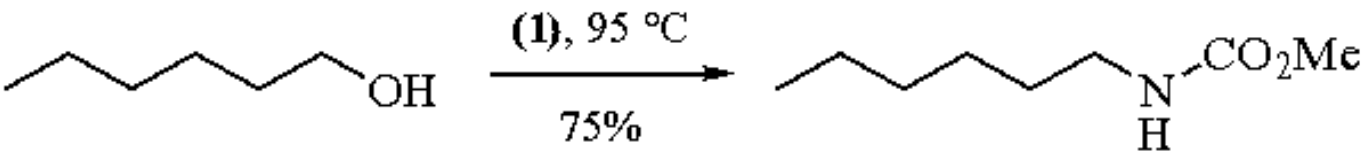

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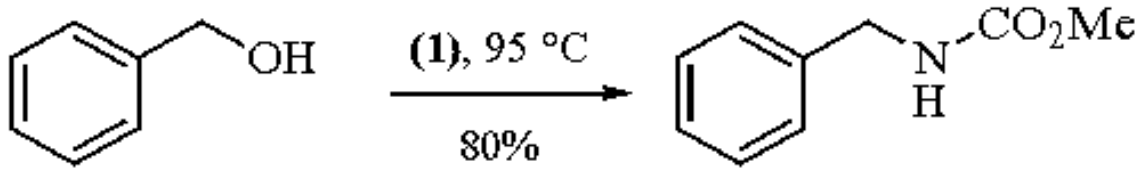

(2)

It was noted that when this reaction was applied to allylic alcohols, either elimination (see below) or an S_Ni' rearrangement ensued.[1c] The fate of this reaction can be determined by the experimental conditions employed. Whereas the reaction in triglyme gave good yields of dienes (eq 3), thermal decomposition of the *N*-methoxycarbonylsulfamate intermediate at 80 °C as a solid provided >90% of the allylurethane product (eq 4).

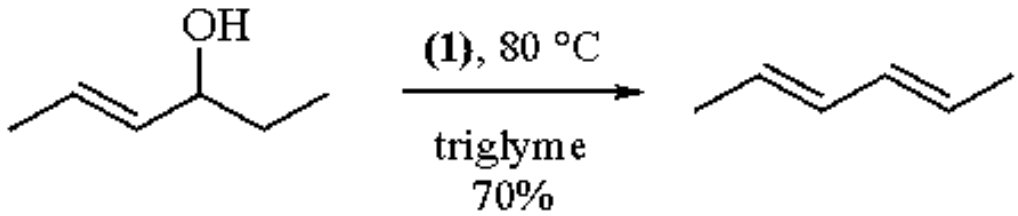

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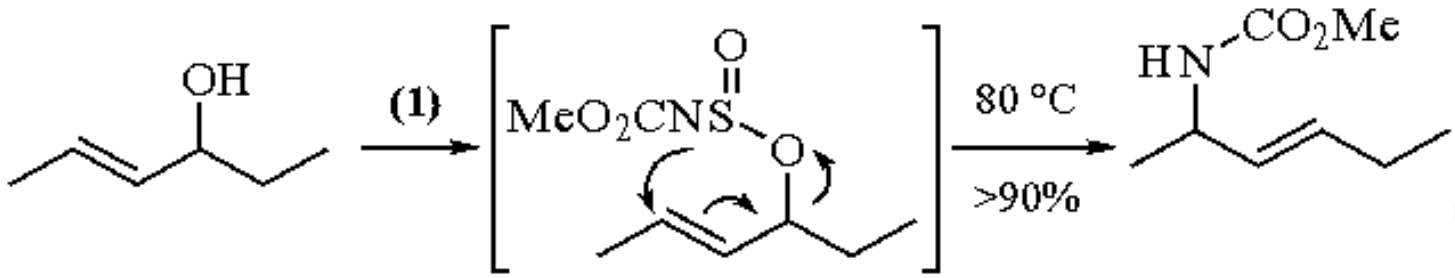

(4)

Formation of Alkenes.

The products of the reaction of the Burgess reagent with secondary and tertiary alcohols decompose smoothly at temperatures between 30 and 80 °C in a variety of solvents to give alkenes.[1] The stereochemical course of the reaction was established to be stereospecific *cis* elimination. This reaction minimizes the type of rearrangement products that are typical for carbonium ion-mediated elimination reactions. For example, the reaction of the Burgess reagent with 3,3-methyl-2-butanol gave three products in the ratios given in eq 5.[1a] The last two alkenes were generated as a consequence of the Wagner-Meerwein rearrangement, whereas the first product formed by direct β-proton removal. The choice of solvent did not affect the product ratios significantly. Usually, competition between the Wagner-Meerwein rearrangement and β-proton abstraction lies entirely in the direction of the former, which is not seen when the Burgess reagent is used.

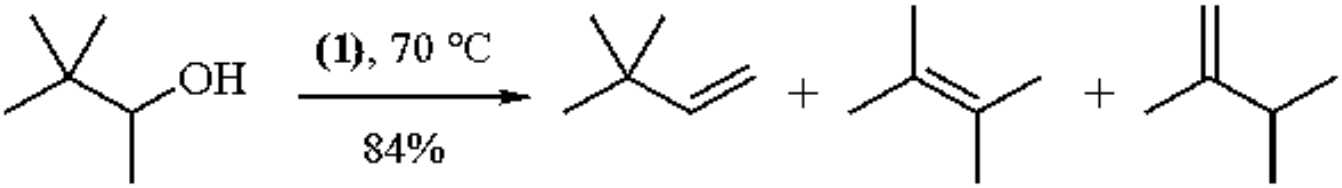

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1:3:1.5

The reaction of the Burgess reagent with 2-*endo*-methylbicyclo[2.2.1]heptan-2-ol afforded a mixture of the two cycloalkenes shown in eq 6.[1a] The ratio of the products was unexpectedly 1:1, an observation which was attributed to the

steric effects of the *endo* C-5 hydrogen, whereby the rate of proton abstraction at C-3 would be attenuated. No rearrangement products were reported. The reaction in eq 7 proceeded to give the sole product shown; no evidence for the formation of 2-cyclopropylidenepropane was found on grounds that the β-cyclopropyl hydrogen is sterically encumbered and unavailable for elimination.[1a] The reaction in eq 8 afforded a product mixture favoring the (*Z*)-isomer.[2] The selectivity is somewhat less in the case of acid-catalyzed dehydration of the same compound. It is noteworthy that similar CS_2-mediated dehydrations in the presence of base require pyrolysis at temperatures exceeding 200 °C.[2] Some related applications for the Burgess reagent are shown in eqs 9 and 10.[3,4] Dehydration of eq 9 with ***Acetic Anhydride*** in the presence of ***Pyridine*** at 70 °C gave only 56% of the desired product.

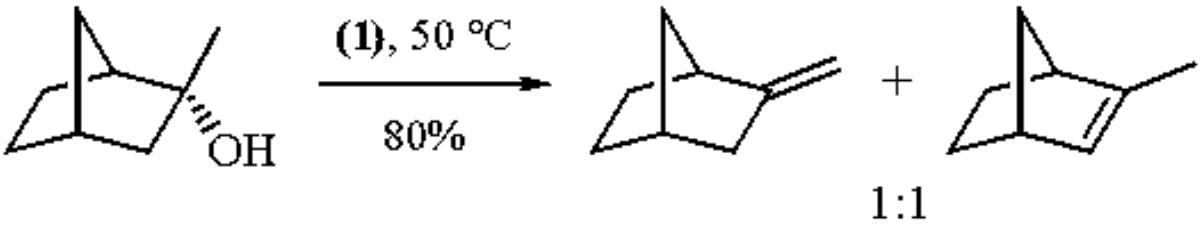

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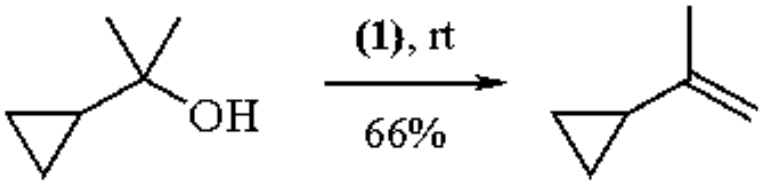

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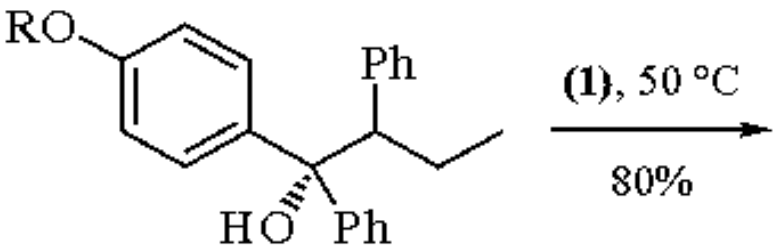

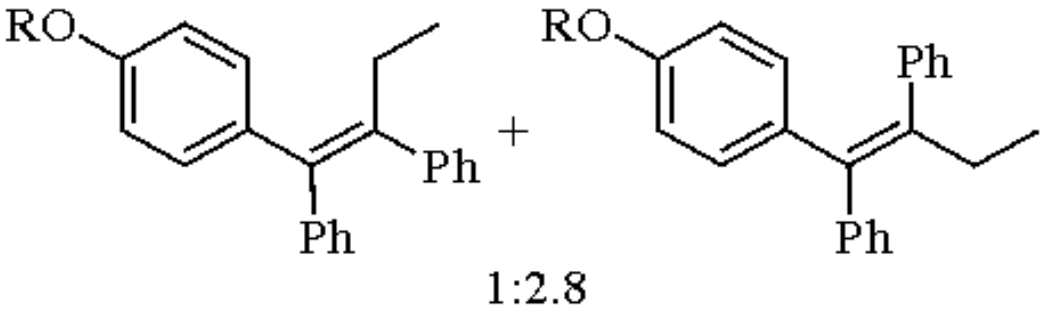

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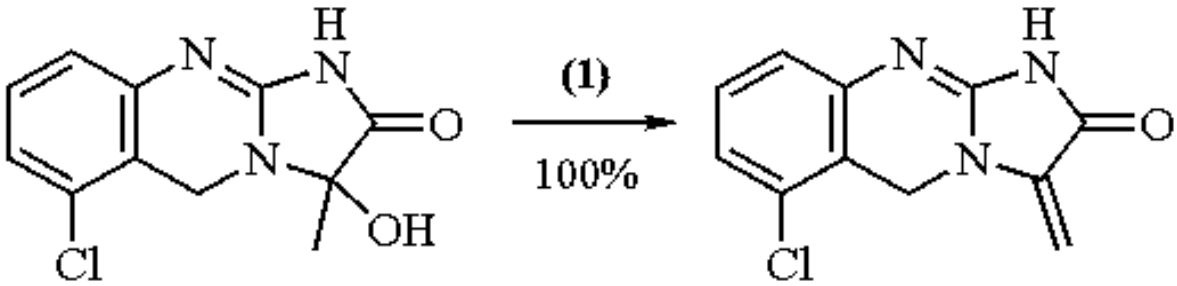

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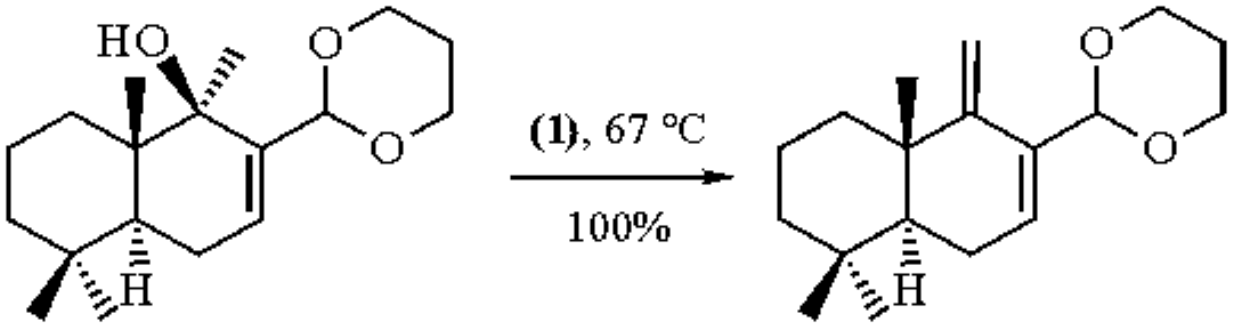

(10)

The requirement for a *cis* elimination chemistry was discussed earlier; however, there are a few exceptional reaction outcomes reported in steroid chemistry.[5] The results depicted in eqs 11 and 12 were unanticipated since the 11α-hydroxyl and 9β-hydrogen (eq 11) are *trans*-diaxial, as are the 3α-hydroxyl and 4β-hydrogen in eq 12. These results are rationalized by an intramolecular 1,2-hydrogen transfer. For example, it was suggested for eq 11 that a C-11 cation is formed first, which subsequently undergoes an intramolecular hydrogen transfer from C-9 to C-11. The resultant C-9 carbocation was postulated to be quenched by the loss of a hydrogen from C-11 and the formation of the Δ^9-double bond.[5]

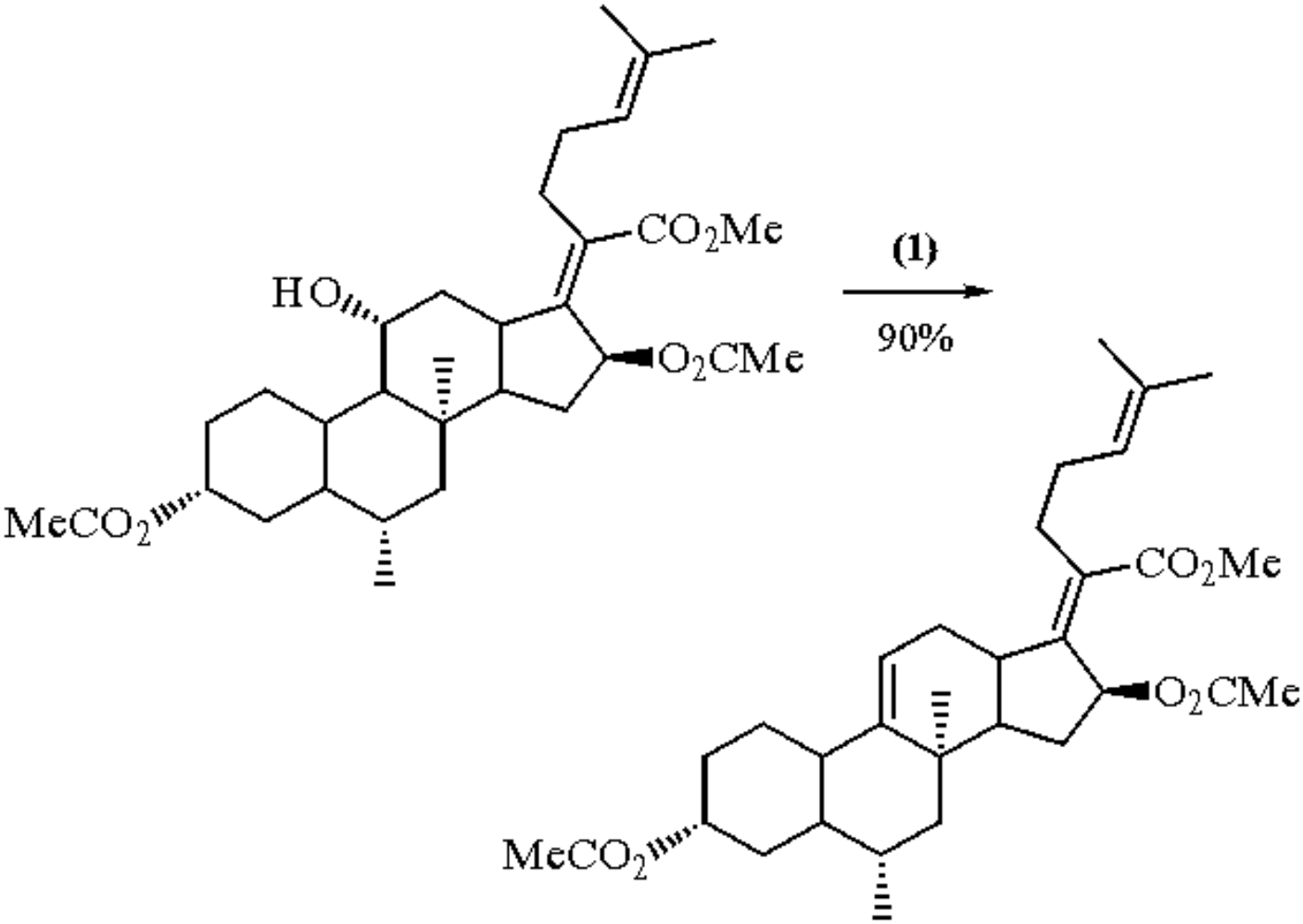

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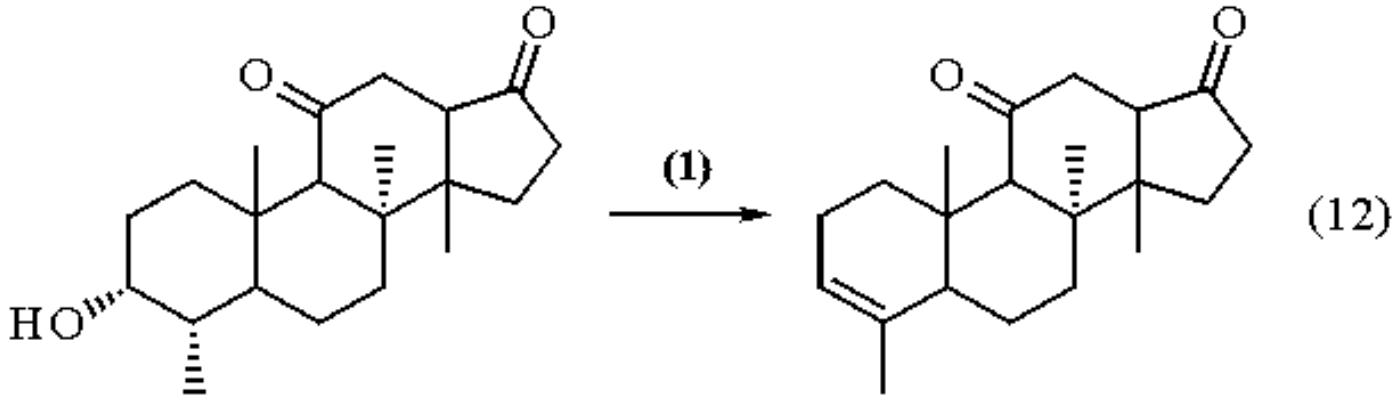

Formation of Dienones and Furanones.

Furanones are formed typically by treatment of α-hydroxy enones with acid; the reaction is presumed to proceed via an acid-labile dienone, although no direct evidence for the existence of such an intermediate has been demonstrated. It has been shown that α-hydroxy enones undergo dehydration in the presence of the Burgess reagent to give isolable dienones, which are cyclized to give the corresponding furanones in a separate acid-catalyzed step (eq 13).[6]

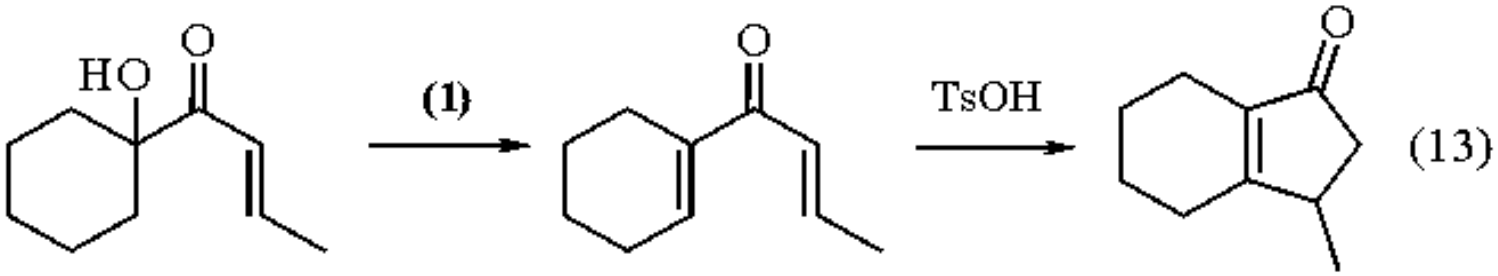

Formation of Vinyltributyltin Compounds and Tributyltin Isocyanate.

The use of the Burgess reagent in the facile formation of vinyltributyltin compounds has been reported.[7] This type of molecule is otherwise typically synthesized under drastic flash pyrolytic conditions. Reaction of the butyltin Grignard reagent with ketones results in tertiary alcohols, which in the presence of the Burgess reagent furnish the vinytributyltin products (eq 14).

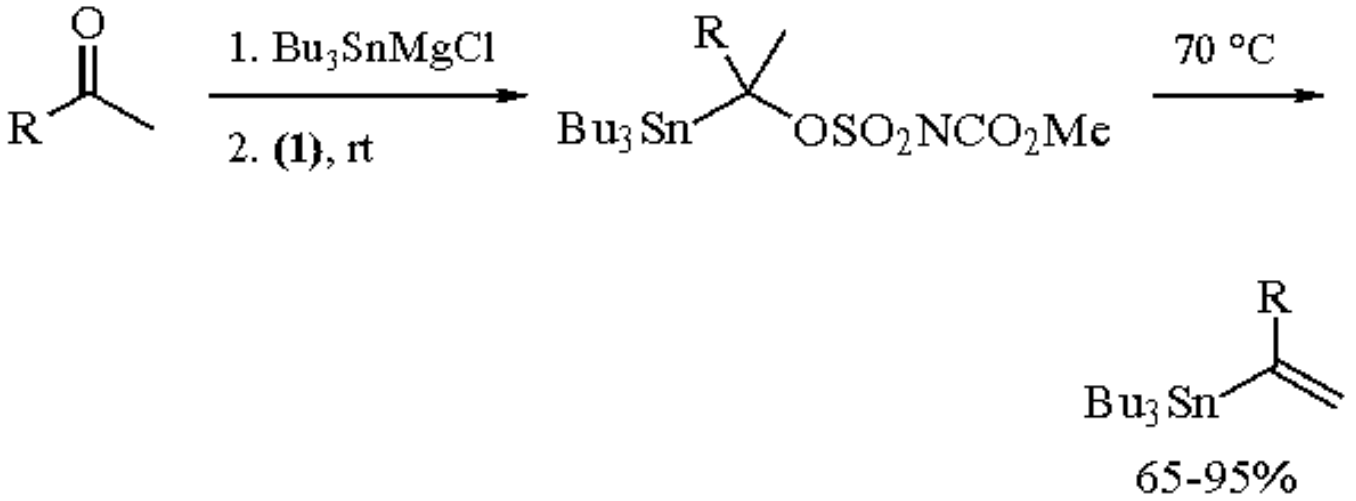

(14)

It was discovered that a side reaction during the vinyltributyltin formation, was the production of tributyltin isocyanate.[8] The formation of tributyltin isocyanate could account for the major portion of the product mixture when cyclic ketones are used, an observation which was attributed to the thermal instability of the intermediary organotin alcohols. These reagents decompose at elevated temperatures to the corresponding ketone and tributyltin hydride, which react with (**1**) to give rise to the isocyanate (eq 15). Correspondingly, it has been shown that tin hydride reduction of (**1**) gives tributyltin isocyanate in quantitative yield (eq 16).

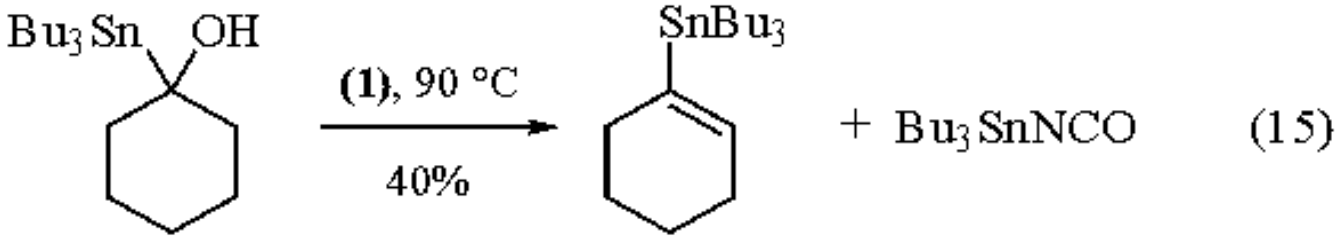

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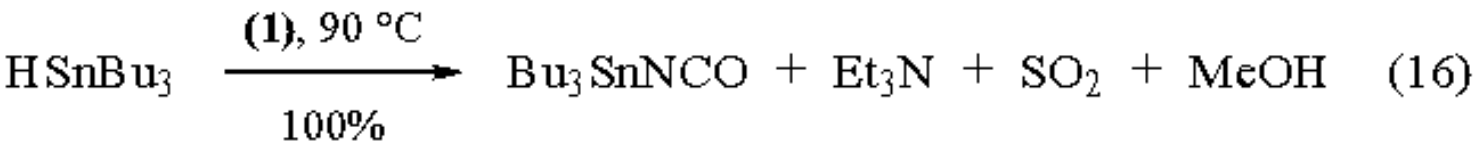

(16)

Formation of Nitriles.

Dehydration of the primary amide function by the Burgess reagent takes place under mild conditions (eqs 17 and 18), and there is often no need for protection of many functionalities in more complex molecules; the reagent has been shown to tolerate alcohols, esters epoxides, ketones, carbamates, and secondary amides.[9] Excellent chemoselectivity is observed in this reaction, which takes place at room temperature.

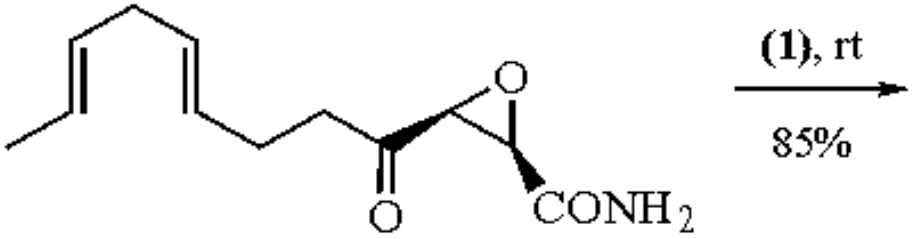

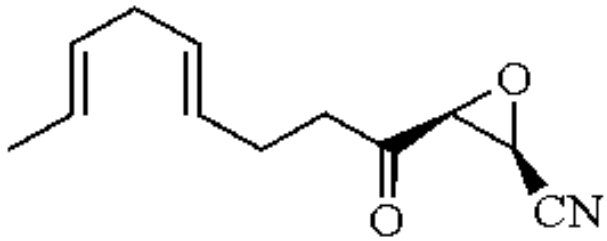

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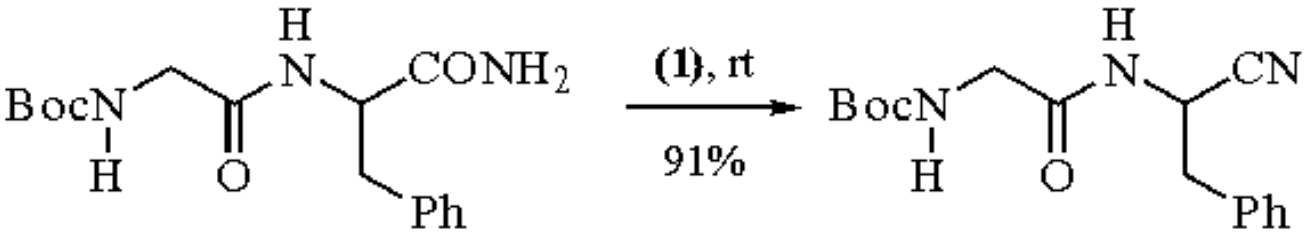

(18)

Electrophilic Addition.

The ethyl analog of (**1**), (ethoxycarbonylsulfamoyl)triethylammonium hydroxide (**2**), has also been reported.[10] Compound (**2**) has been shown to undergo electrophilic addition to alkenes in average to good yields (eqs 19 and 20).

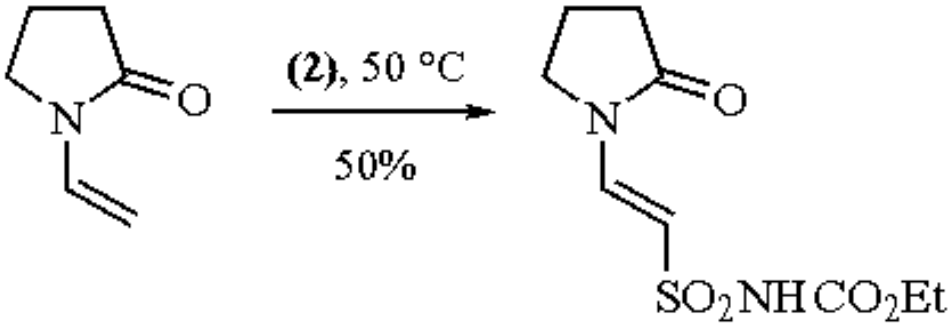

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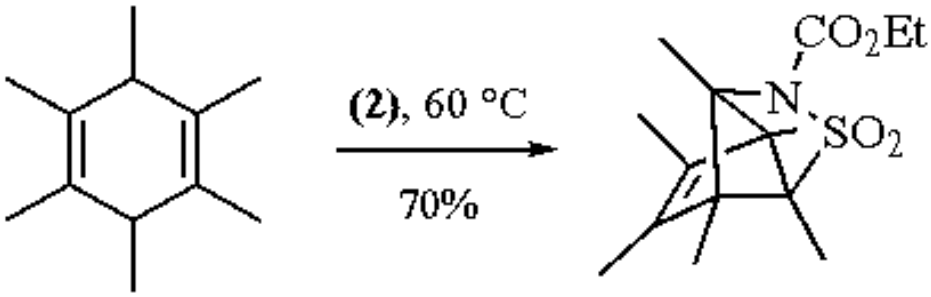

(20)

1. (a) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *JOC* **1973**, *38*, 26. (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A.; Williams, W. M. *OSC* **1988**, *6*, 788. (c) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *JACS* **1970**, *92*, 5224.
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4-Methoxycarbonylthiolan-3-one

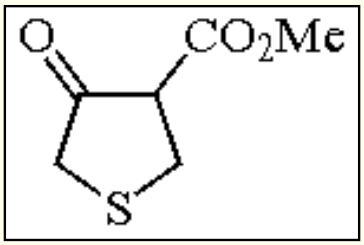

[2689-68-1] · $C_6H_8O_3S$ · 4-Methoxycarbonylthiolan-3-one · (MW 160.21)

(building block for polynuclear heterocyclic compounds;[1,9] precursor of substituted thiophenes;[10-12] synthetic equivalent of α-acrylate anion[13,14])

Alternate Name: methyl 4-oxothiolane-3-carboxylate.

Physical Data: mp 37-38 °C;[15-17] bp 128.5 °C/20 mmHg,[15] 116-117 °C/9 mmHg,[18] 109 °C/4 mmHg;[15] IR (KBr[16] or CCl_4[17]), ^{1}H NMR,[16,17] MS,[17] and a study of the keto-enol equilibrium[18] have been reported.

Preparative Methods: prepared by Dieckmann reaction of the Michael adduct of methyl thioglycolate and ***Methyl Acrylate***. Careful choice of the reaction conditions (MeONa, toluene, 80-120 °C) and a suitable workup procedure are recommended in order to control the direction of the cyclization which, in principle, can produce both 3-oxo-2-carboxylate and 4-oxo-3-carboxylate isomers.[15-17,19] A more sophisticated method to accomplish a direction-controlled Dieckmann cyclization leading to exclusive formation of the target compound as the ethyl ester *[78647-31-1]* requires the less common ethoxycarbonylethyl thioethoxycarbonylmethyl sulfide as the starting material.[20]

α-Acrylate Anion Equivalent.

Alkylation of 4-methoxycarbonylthiolan-3-one (**1**) with a variety of alkyl halides in the presence of ***Potassium Carbonate*** provides *C*-alkylated products in excellent yields. Their treatment with aqueous ***Sodium Hydroxide*** affords α-substituted acrylate esters through tandem Dieckmann-Michael retrograde reactions (eq 1).[13] This strategy has been successfully applied to the formal synthesis of integerrinecic acid.[14]

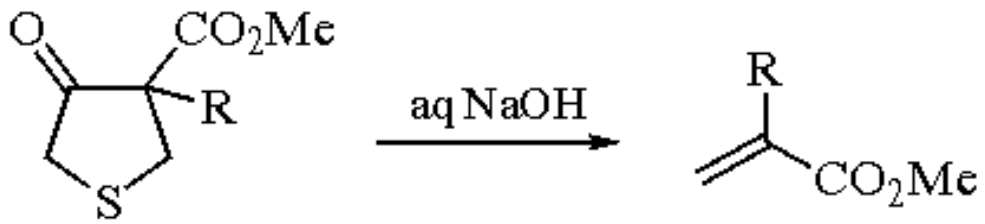

(1)

Building Block for Polynuclear Heterocyclic Compounds.

Aniline can chemoselectively react with both the ester and ketone carbonyl groups of (**1**) affording an enamine or an amide, respectively, depending on the experimental conditions used (eq 2).[21]

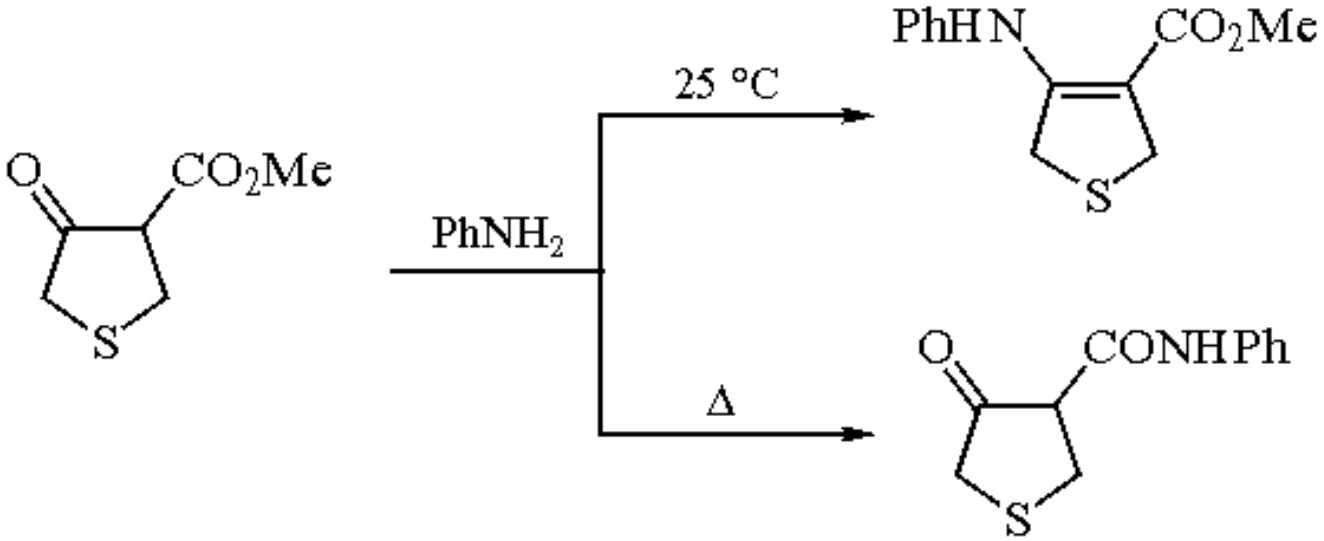

One of the most common synthetic approaches to the construction of heterocyclic compounds involves the reaction of β-keto esters with bifunctional nucleophiles. Thus a variety of reactions of (**1**) with different bifunctional heteronucleophiles, including hydrazine,[1] substituted aminotriazoles,[2] 2-aminopyridines,[3] *o*-phenylenediamines,[5-7] and *o*-aminothiophenol,[8] lead to polynuclear condensed thieno compounds (e.g. **2**-**8**) of potential medicinal interest featuring the pyrazolone, pyrimidinone, benzodiazepine, and benzothiazepine nuclei. Cannabinoid analogs can be prepared through cyclization of the condensation products of (**1**) with bifunctional oxygenated nucleophiles such as substituted resorcinols.[9]

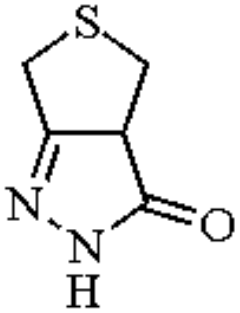

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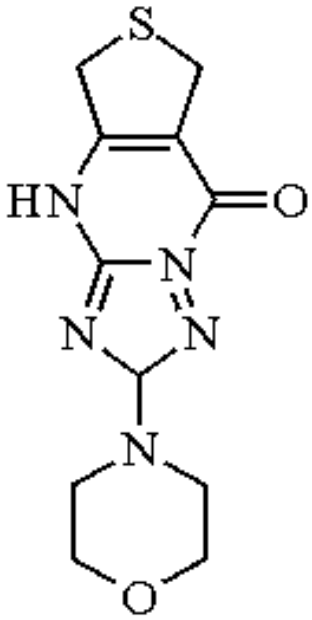

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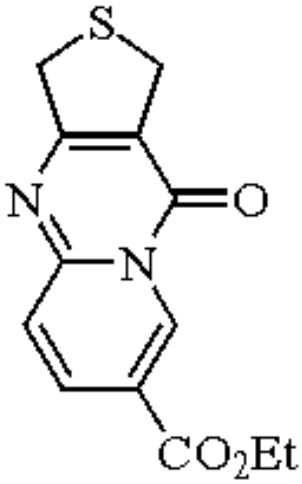

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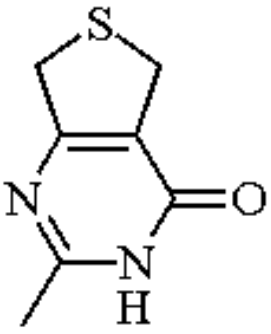

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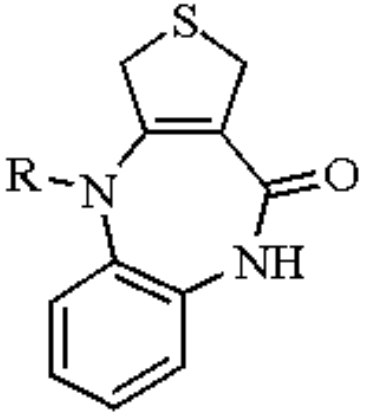

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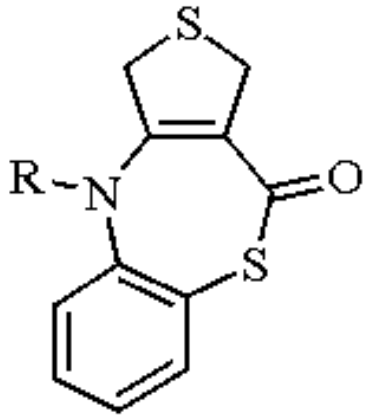

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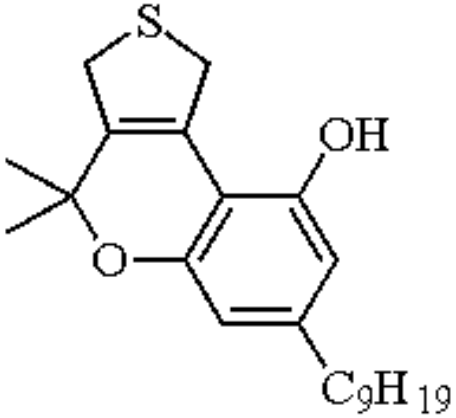

(8)

Methyl (2*R*,3*S*)-2-Methyl-3-hydroxybutanoate.[22]

This useful chiral building block, which is not easy to obtain with high optical purity by reduction of the corresponding open chain β-keto ester, can be conveniently prepared by diastereo- and enantioselective ***Baker's Yeast*** reduction of (**1**), followed by ***Raney Nickel*** promoted desulfurization (eq 3).

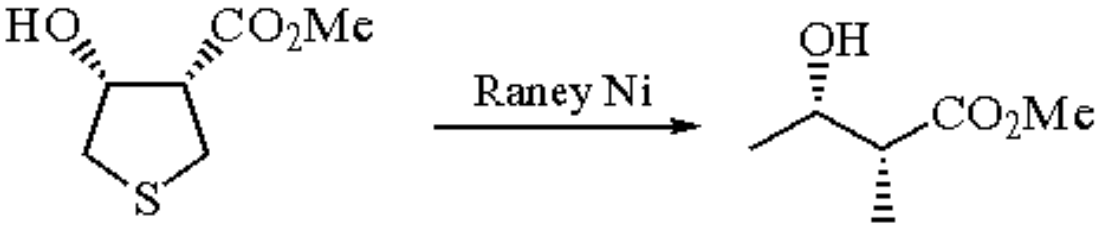

(3)

Ring Expansion.

The *C*-alkylated products of (**1**) with diiodomethane[23] and chloromethyl phenyl selenide[24] undergo radical-promoted ring expansion on treatment with ***Tri-n-butylstannane*** to give the expanded γ-keto ester in 64% yield (eq 4).

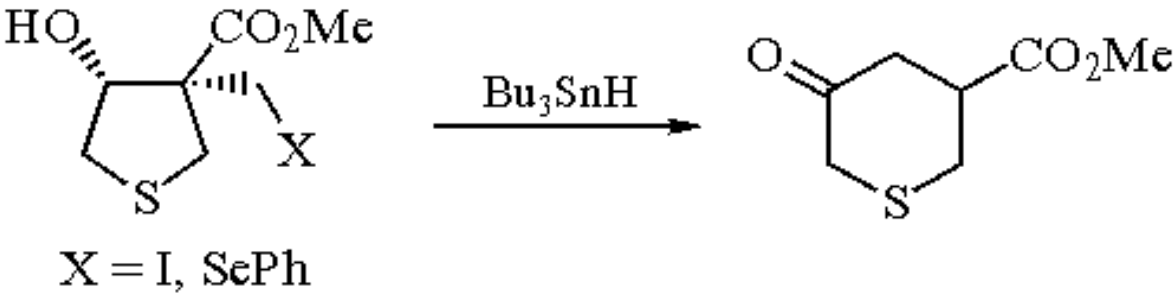

(4)

Related Reagents.

4-Cyanothiolan-3-one; ***Ethyl Acetoacetate***; ***Ethyl Acrylate***; ***Methyl 3-(Dimethylamino)propionate***; ***Methyl 3-Hydroxypropionate***.

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4. Tomé, A. C.; O'Neill, P. M.; Storr, R. C.; Cavaleiro, J. A. S. *SL* **1993**, 397.
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9. Razdan, R. K.; Terris, B. Z.; Handrick, G. R.; Dalzell, H. C.; Pars, H. G.; Howes, J. F.; Plotnikoff, N.; Dodge, P.; Dren, A.; Kyncl, J.; Shoer, L.; Thompson, W. R. *JMC* **1976**, *19*, 549.
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18. Duus, F. *T* **1981**, *37*, 2633.
19. Hromatka, O.; Binder, D.; Eichinger, K. *M* **1973**, *104*, 1348.
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22. Hoffmann, R. W.; Helbig, W.; Ladner, W. *TL* **1982**, *23*, 3479.
23. Dowd, P.; Choi, S.-C. *TL* **1989**, *30*, 6129.
24. Dowd, P.; Choi, S.-C. *T* **1991**, *47*, 4847.

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B-Methoxydiisopinocampheylborane[1]

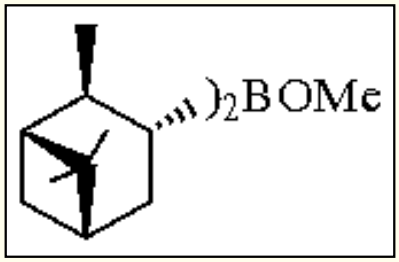

(+)

[85134-98-1] · $C_{21}H_{37}BO$ · *B*-Methoxydiisopinocampheylborane · (MW 316.39) (-)

[99438-28-5]

(intermediate for the synthesis of *B*-allyl- and *B*-crotyldiisopinocampheylboranes;[2] reacts with potassium hydride to form an asymmetric reducing agent[3])

Physical Data: mp >110 °C.

Form Supplied in: white solid; commercially available; typical impurities include the disproportionation products $IpcB(OMe)_2$ and $B(OMe)_3$.

Analysis of Reagent Purity: ^{11}B NMR (δ +52).

Preparative Methods: prepared in two steps from either (+)- or (-)-α-pinene (eq 1).

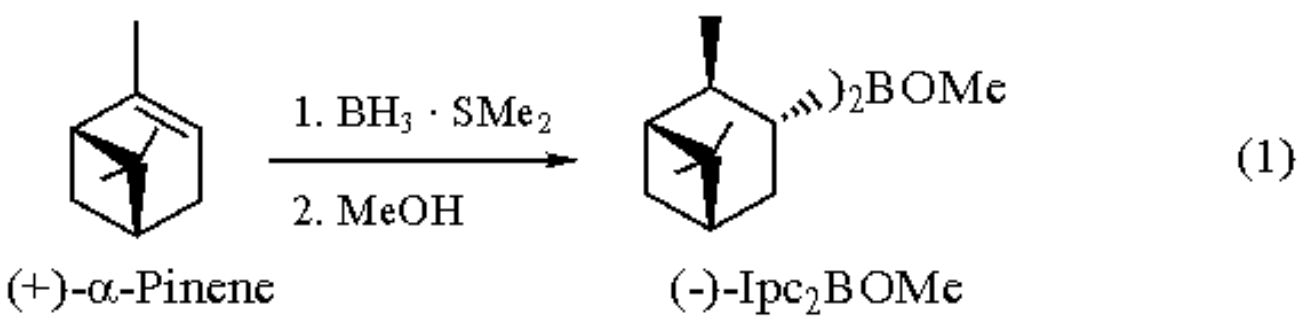

Preparation of *B*-Allyldiisopinocampheylborane and Related Reagents.

Addition of allylic Grignard or potassium reagents to *B*-methoxydiisopinocampheylborane (Ipc_2BOMe) provides the

corresponding allylic boranes (eqs 2 and 3).[2] Note that (-)-Ipc_2BOMe, derived from (+)-α-pinene, produces (+)-Ipc_2BAll and Ipc_2BCrt reagents, and (+)-Ipc_2BOMe gives the corresponding (-)-allylic boranes. These allyl and crotyl boranes condense with aldehydes to provide secondary homoallylic alcohols with high levels of enantioselection (see also ***B-Allyldiisopinocampheylborane*** and ***B-Crotyldiisopinocampheylborane***).

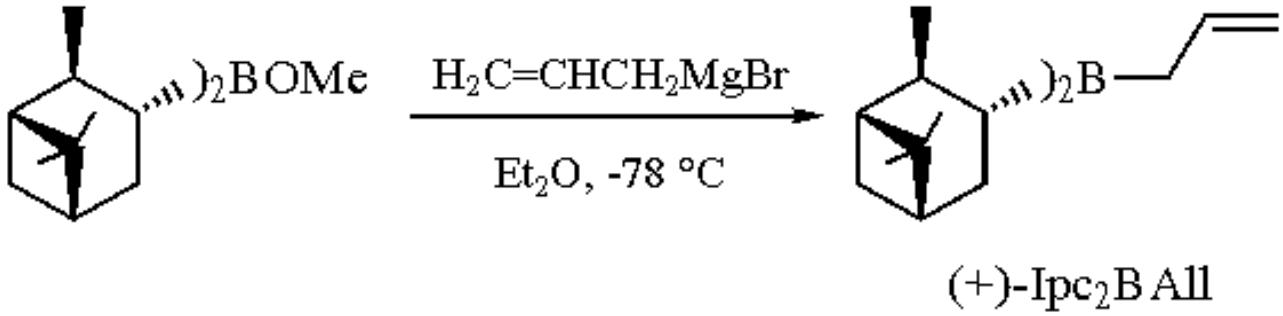

(2)

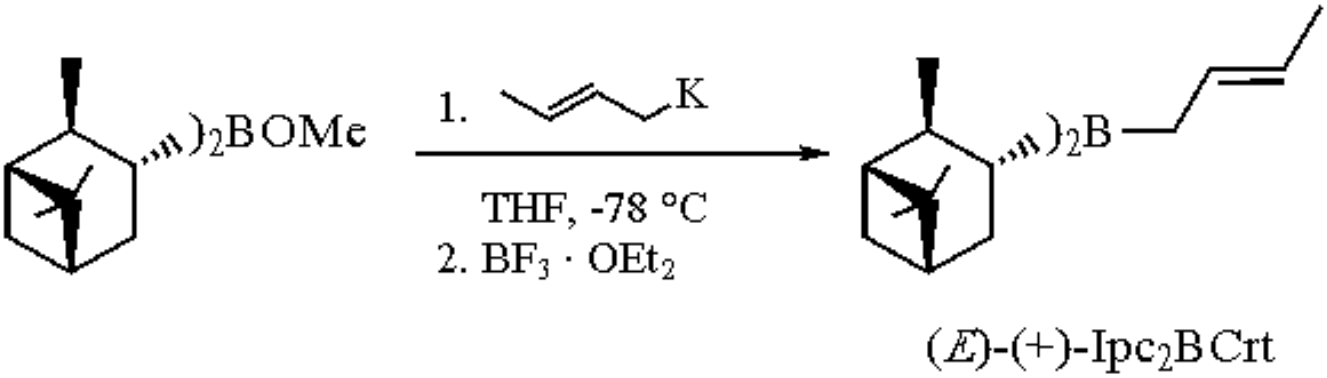

(3)

Acetylide Coupling.

B-Methoxydiisopinocampheylborane reacts with ***Lithium (Trimethylsilyl)acetylide*** to provide, after iodine-promoted rearrangement and desilylation, α-chiral monosubstituted alkynes in excellent yield (eq 4).[4]

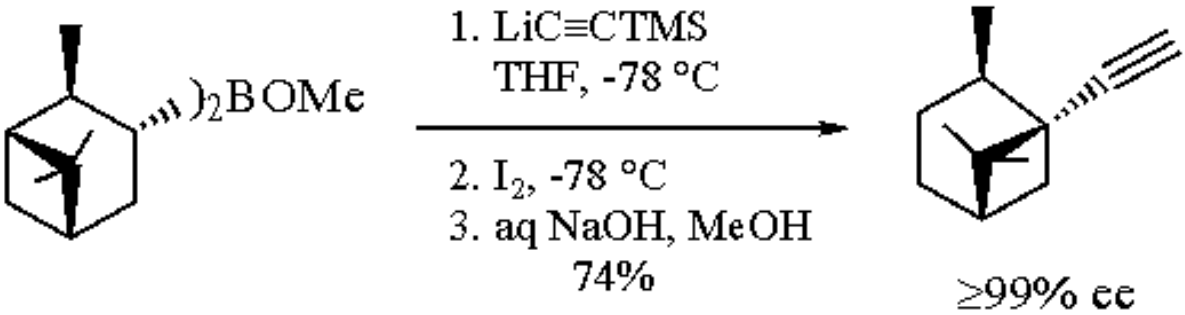

(4)

B-Methoxydiisopinocampheylborohydrides.

Treatment of Ipc_2BOMe with an excess of ***Potassium Hydride*** produces the corresponding potassium *B*-methoxydiisopinocampheylborohydride.[3] The reduction of ketones with this reagent proceeds in high yield but with modest enantioselection (eq 5).

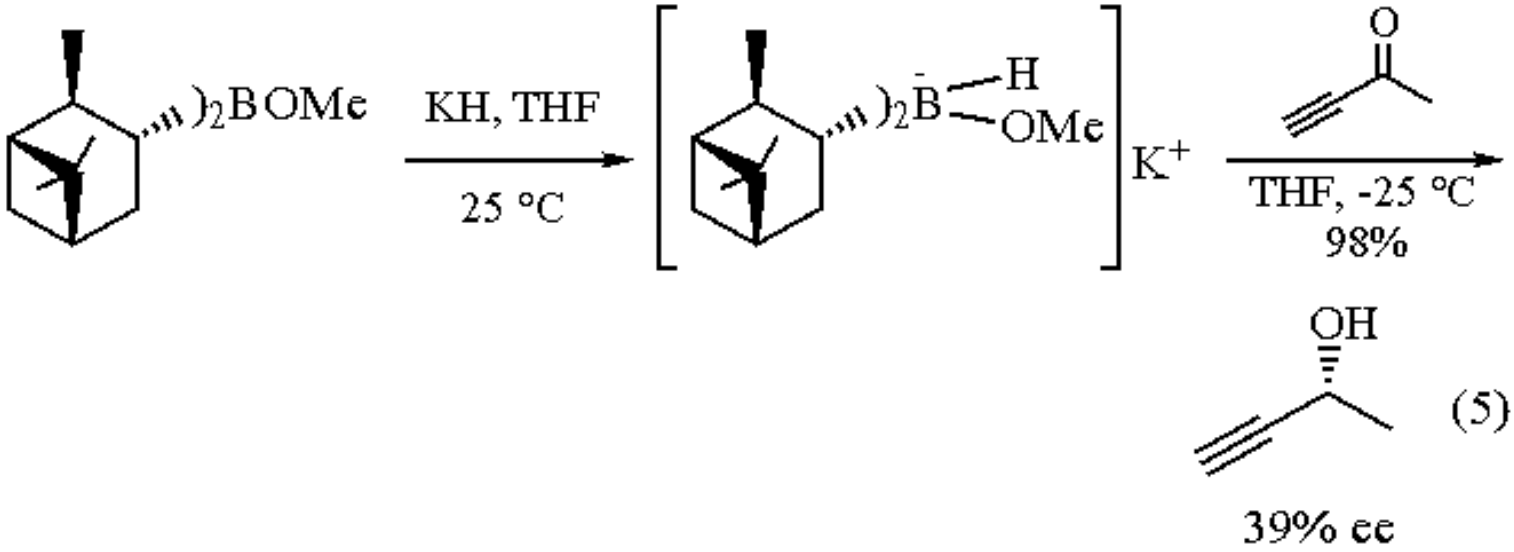

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(Methoxydimethylsilyl)(trimethylsilyl)methane

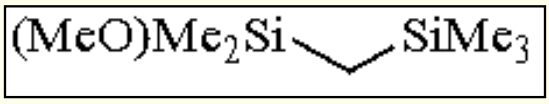

[5180-98-8] · $C_7H_{20}OSi_2$ · (Methoxydimethylsilyl)(trimethylsilyl)methane · (MW 176.45)

(Peterson alkenation reagent; synthesis of vinyl silanes from aldehydes and ketones[1])

Physical Data: bp 150-152 °C,[2] 54-58 °C/20 mmHg.[3]

Solubility: sol common organic solvents (THF, Et_2O, CH_2Cl_2, pentane, etc.)

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3 H), 0.10 (s, 6 H), 0.02 (s, 9 H), -0.14 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 49.94, 4.14, 1.13, 0.03.[3]

Preparative Methods: prepared in 75% yield by treatment of $MeOSiMe_3$ with ***t-Butyllithium*** in pentane at -78 °C to ambient temperature followed by addition of ***Chlorotrimethylsilane*** at 0 °C.[2] Alternatively, the reagent is prepared in 34% yield by treatment of ***Trimethylsilylmethylmagnesium Chloride*** with ***Dichlorodimethylsilane*** followed by LiOMe in THF.[3]

Handling, Storage, and Precautions: use in a well-ventilated fume hood. Contact with the eyes and skin should be avoided.

Peterson Alkenation Reactions.[4]

The synthesis of vinylsilanes via alkenation reactions of [bis(trimethylsilyl)methyl]lithium is restricted to nonenolizable aldehydes and ketones.[5] However, [(methoxydimethylsilyl)(trimethylsilyl)methyl]lithium (**1**), generated from the title reagent by treatment with ***t-Butyllithium*** in pentane at rt, undergoes Peterson alkenation with aldehydes and ketones to give vinylsilanes in good yield (eq 1). Interestingly, the methoxydimethylsilyl unit is preferentially eliminated from the β-hydroxydisilane intermediate. Alkenation reactions of (**1**) with aldehydes and unsymmetrical ketones are only moderately stereoselective (eqs 2 and 3).

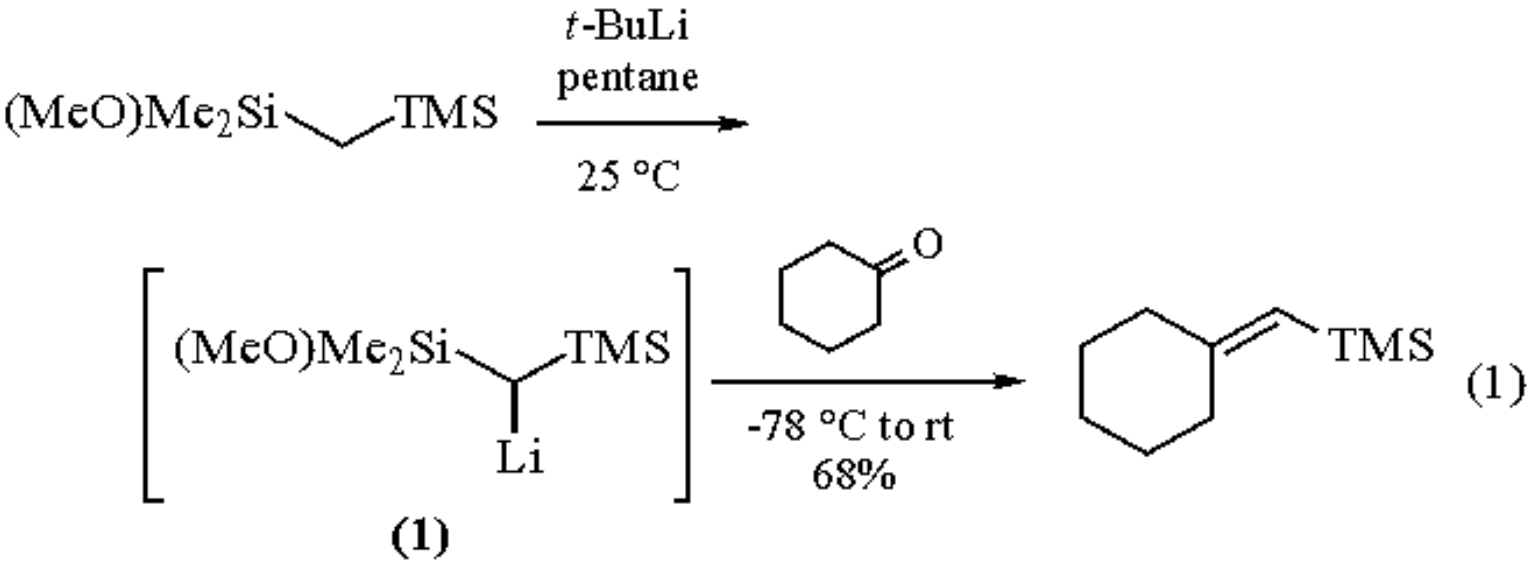

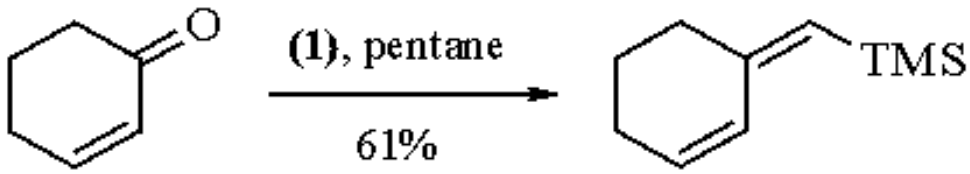

(2)

(*E*):(*Z*) = 2:1

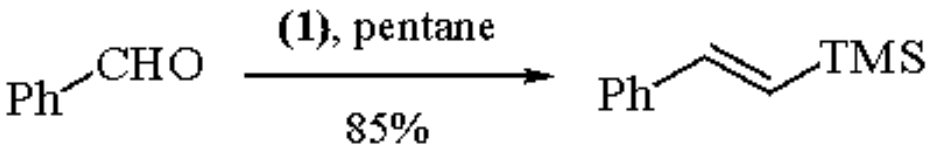

(3)

(*E*):(*Z*) = 3:1

Avery and co-workers have applied this methodology to the synthesis of vinylsilane intermediates utilized in syntheses of artemisinin analogs (eqs 4 and 5).[6] The low efficiency of these Peterson alkenation reactions (31-50%) suggests that the relatively hindered carbonyl groups undergo competitive deprotonation by the anion (**1**).

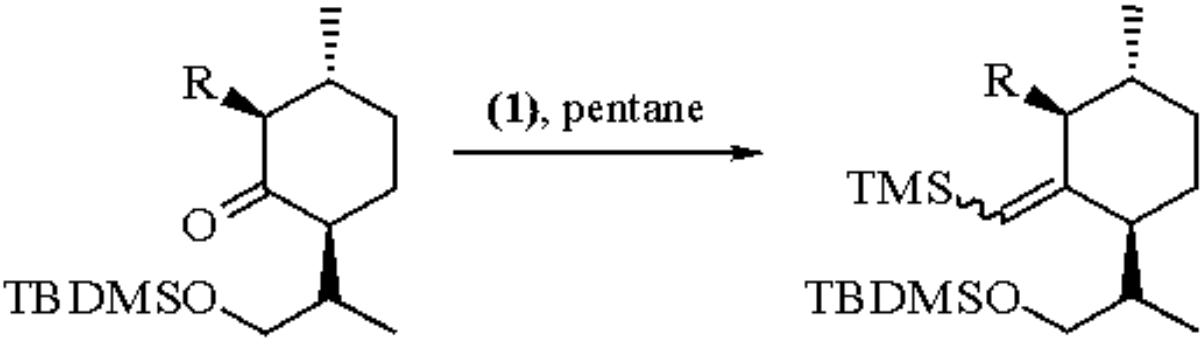

(4)

R = H, 39%
R = Me, 31%

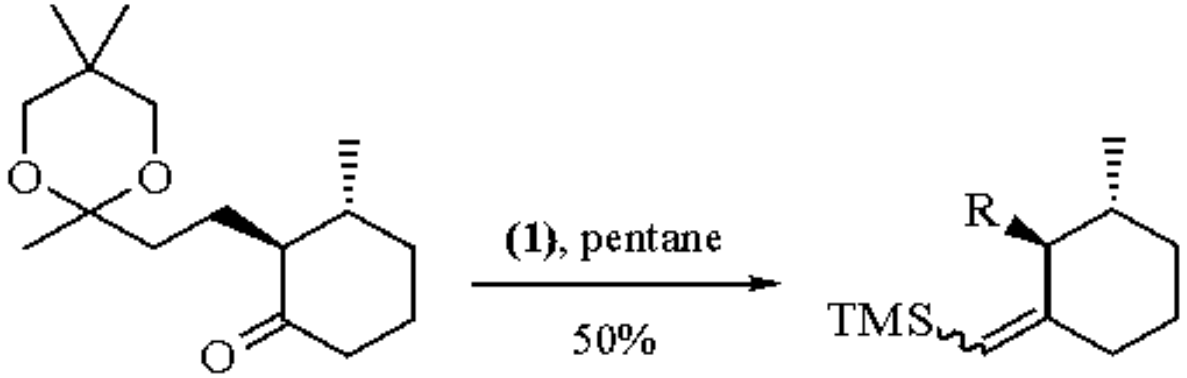

(5)

Related Reagents.

Bis(trimethylsilyl)methane; ***Tris(trimethylsilyl)methane***.

---

1. Bates, T. F.; Thomas, R. D. *JOC* **1989**, *54*, 1784.
2. Bates, T. F.; Thomas, R. D. *JOM* **1989**, *359*, 285.
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2-Methoxy-1,3-dioxolane

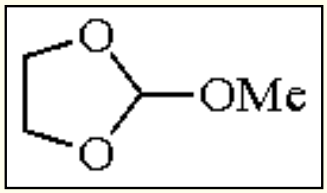

[19693-75-5] · $C_4H_8O_3$ · 2-Methoxy-1,3-dioxolane · (MW 104.12)

(mild acetalization agent;[1] protected formyl group synthon[5])

Physical Data: bp 129 °C; *d* 1.092 g cm^{-3}.

Solubility: sol alcohol, acetone, THF, CH_2Cl_2.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: GC, NMR spectroscopy.

Handling, Storage, and Precautions: moisture sensitive, flammable liquid. Incompatible with oxidizing agents and strong acids.

Mild Acetalization Agent.

A principal advantage of 2-methoxy-1,3-dioxolane for carbonyl protection is the mild reaction conditions (25 °C to reflux, 2-24 h, usually in CH_2Cl_2, or neat, with catalytic ***p-Toluenesulfonic Acid***) used. Efficient trans-acetalization occurs with aldehydes or ketones, especially with acid-labile substrates or when other methods fail (eqs 1-4).[1-4]

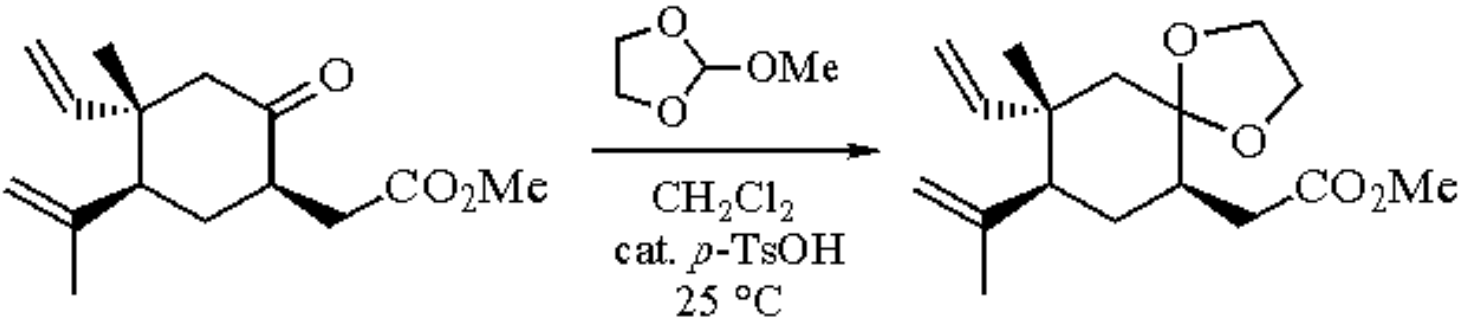

(1)

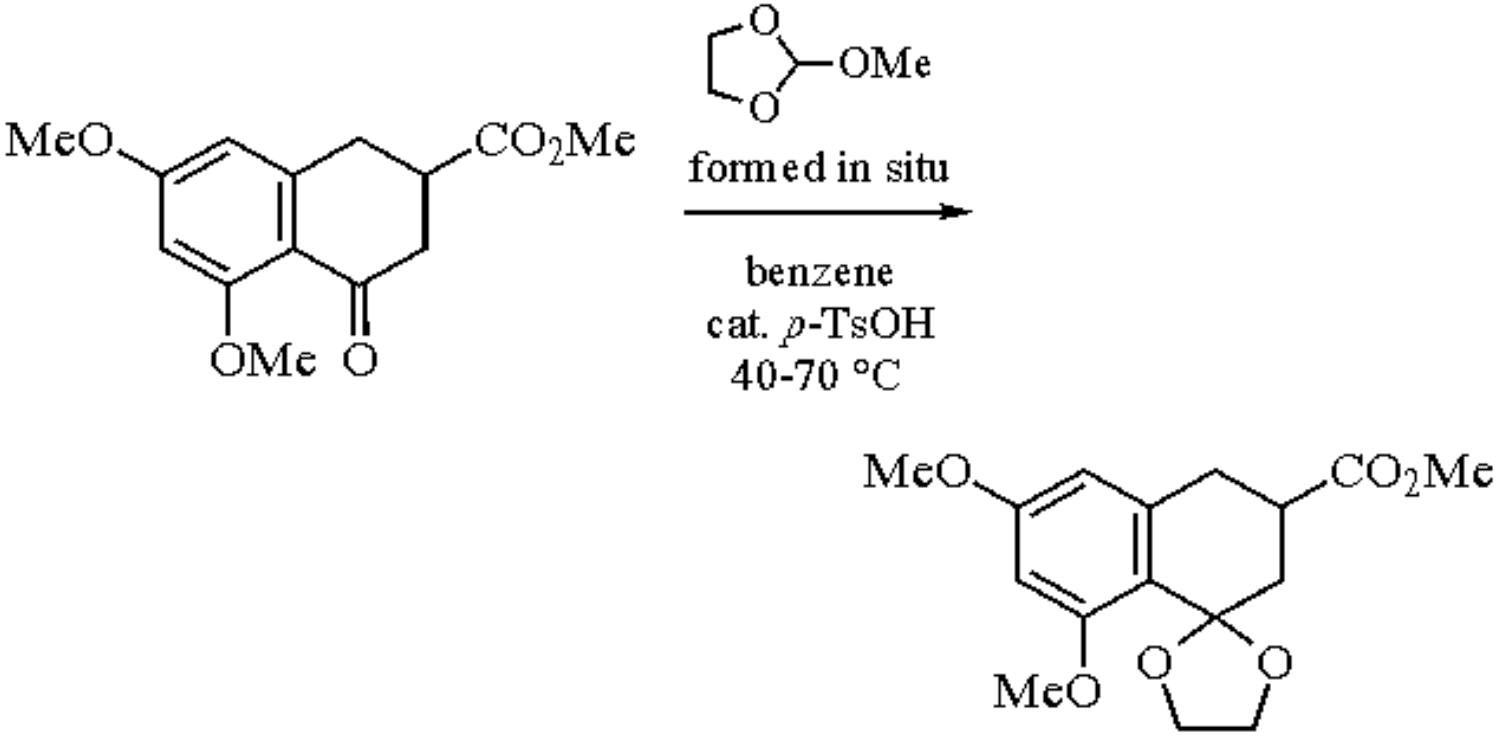

(2)

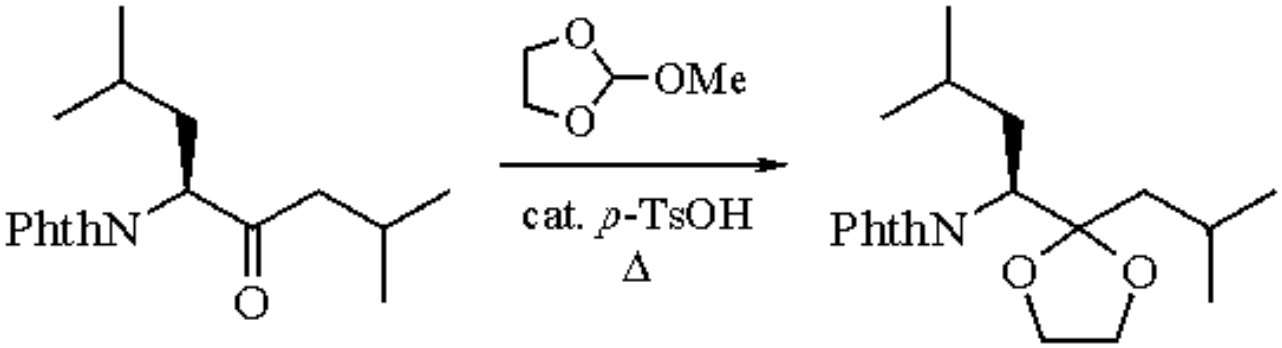

(3)

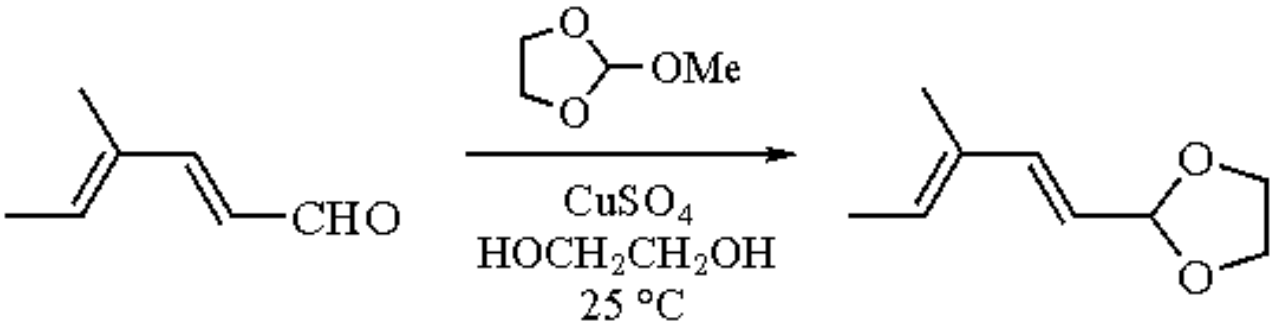

(4)

Protected Formyl Group Synthetic Equivalent.

The reagent can be used for the introduction of a base-stable protected formyl substituent on carbonyl compounds. With silyl enol ethers (eq 5),[5] morpholino enamines,[6] or titanium enolates (eq 6),[7] 2-methoxy-1,3-dioxolane gives regiospecifically protected dicarbonyl compounds.

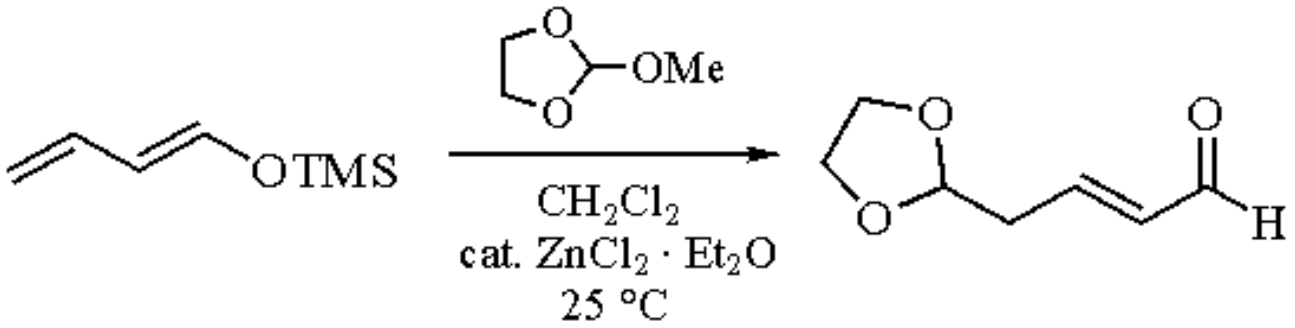

(5)

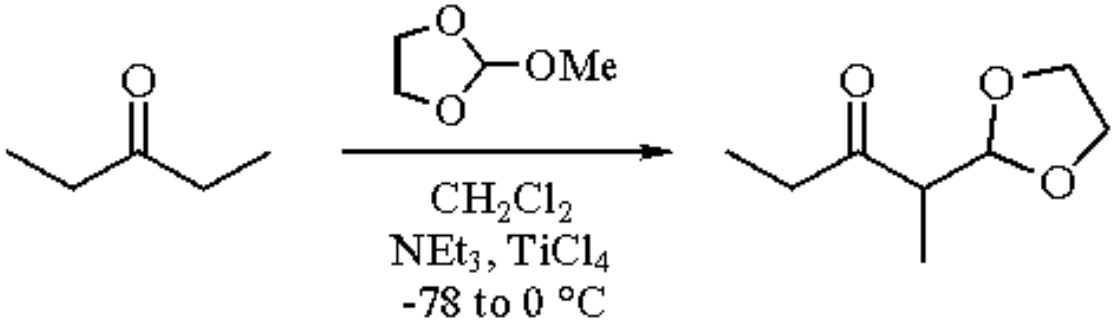

(6)

This reagent can also be used as a protected formyl synthetic equivalent when reacted with aryl Grignard reagents (eq 7)[8] and allylsilanes (eq 8)[9] to afford acetals.

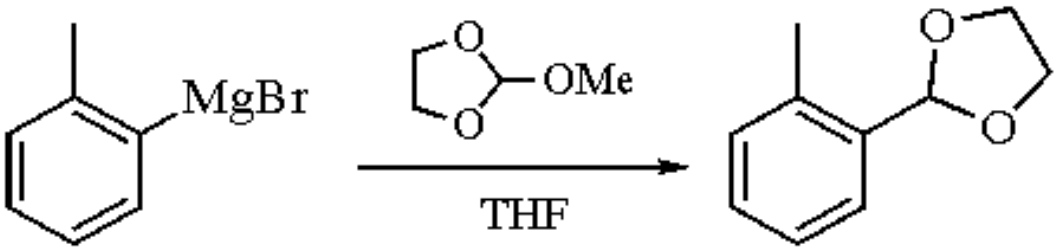

(7)

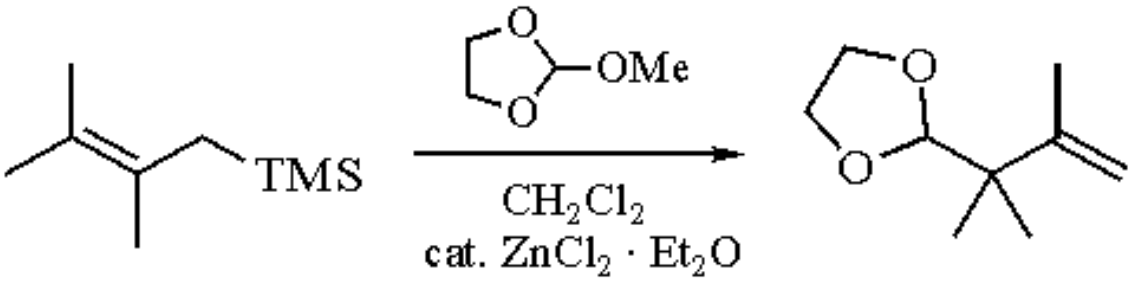

(8)

Related Reagents.

2-Butanone Ethylene Acetal; ***Ethylene Glycol***.

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1. Friedrich, D.; Bohlmann, F. *T* **1988**, *44*, 1369.
2. Glatz, B.; Helmchen, G.; Muxfeldt, H.; Porcher, H.; Prewo, R.; Senn, J.; Stezowski, J. J.; Stojda, R. J.; White, D. R. *JACS* **1979**, *101*, 2171.

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8. Tanimoto, S.; Shimojo, S.; Oda, R. *Yuki Gosiei Kagaku Kyokai Shi* **1968**, *26*, 435 (*CA* **1968**, *69*, 77 137g).
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2-Methoxyethoxymethyl Chloride[1]

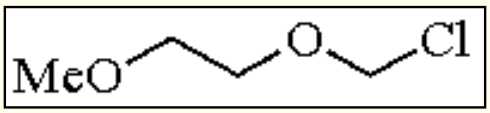

[3970-21-6] · $C_4H_9ClO_2$ · 2-Methoxyethoxymethyl Chloride · (MW 124.58)

(protection of alcohols,[2] phenols,[15] and carboxylic acids;[20] functionalized one-carbon synthon[23])

Alternate Name: MEMCl.

Physical Data: bp 50-52 °C/13 mmHg; *d* 1.094 g cm^{-3}.

Handling, Storage, and Precautions: moisture sensitive; a lachrymator and possible carcinogen.

Protection of Alcohols.

The 2-methoxyethylmethyl (MEM) group was developed as a protective group that can be introduced with the ease of the methoxymethyl (MOM) group but can be cleaved under milder conditions, thus affording another level of selectivity in deprotection.[2] The most common method for its introduction is occasioned with MEMCl and ***Diisopropylethylamine*** (CH_2Cl_2, 25 °C, 3 h, quant.). Introduction of the MEM group is also faster than the formation of the related MOM derivative, which may be the result of anchimeric assistance. Alternatively the salt, $MEMNEt_3^+ Cl^-$ (MeCN, reflux, 30 min, >90% yield) may be used for its introduction, but this procedure has not seen extensive use. An alkoxide prepared from ***Sodium Hydride*** or ***Potassium Hydride***, when treated with MEMCl (THF or DME, 0 °C, 10-60 min, >95% yield), affords the MEM ether. The reaction of tributyltin ethers in the presence of ***Cesium Fluoride***, DMF, and MEMCl has also been used to prepare MEM ethers, but this method is primarily used as part of a scheme for the interconversion of protective groups.[3] For example, the reaction of THP ethers with $Bu_3SnSMe/BF_3.Et_2O$ gives the corresponding tin ethers. Since the MEM group is of low steric demand, little selectivity is expected when protecting two similar alcohols, but electronic effects can be used to advantage to achieve modest selectivity (eq 1).[4]

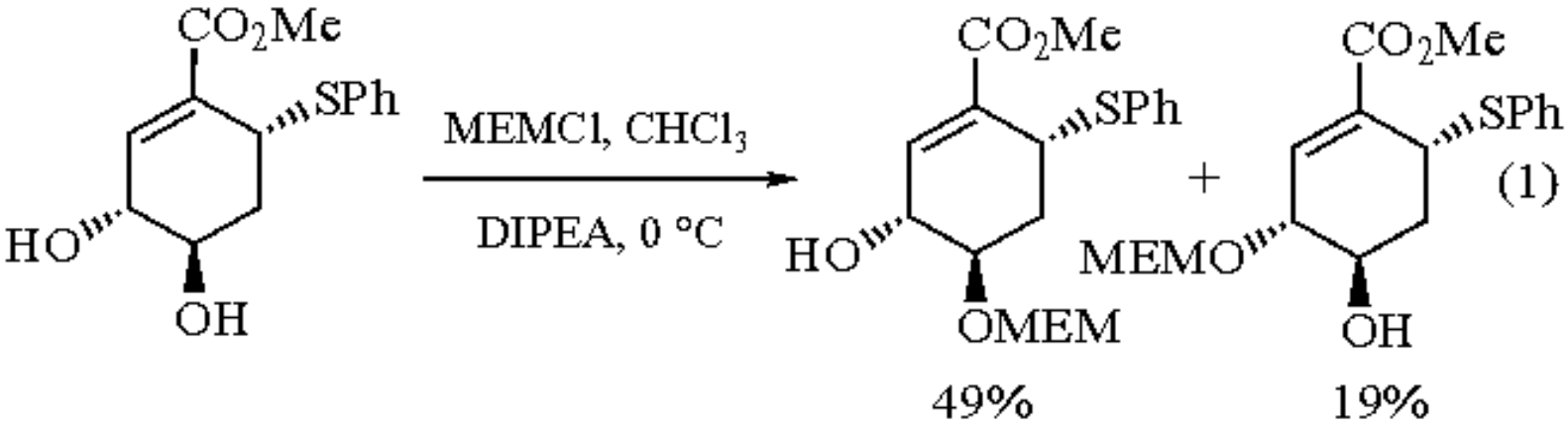

The original method devised to effect deprotection is to treat the MEM derivative with ***Zinc Bromide*** (CH_2Cl_2, 25 °C, 2-10 h, 90% yield)[1] or ***Titanium(IV) Chloride*** (CH_2Cl_2, 0 °C, 20 min, 95% yield)[1] to form a chelate, which upon further reaction reconstitutes the alcohol. Since then a number of other cleavage methods have been developed which rely on the fact that the MEM group can be viewed as an acetal or ether. Reagents such as ***Bromodimethylborane*** (CH_2Cl_2, -78 °C, $NaHCO_3$, H_2O, 87-95% yield),[5] Ph_2BBr (CH_2Cl_2, -78 °C, 71% yield),[6] (-SCH_2CH_2S-)BBr,[7] (*i*-$PrS)_2BBr$ (DMAP, K_2CO_3, H_2O),[8] and 2-bromo-1,3,2-benzodioxaborole[9] cleave ethers like BBr_3. Me_2BBr cleaves MTM and MOM ethers and acetals, but (*i*-$PrS)_2BBr$ converts the MEM group to the *i*-$PrSCH_2$- ether which can be cleaved using the same conditions used to cleave the MTM ether. The cyclic thio derivative appears to be sterically sensitive (eq 2). It does not cleave benzyl, allyl, methyl, THP, TBDMS, and TBDPS ethers, whereas the related oxygen analog (2-bromo-1,3,2-benzodioxaborole) is a much more powerful reagent and cleaves the following groups in the order: MOMOR &AApprox; MEMOR > *t*-Boc > Cbz > *t*-BuOR > BnOR > allylOR > *t*-BuO_2CR &AApprox; secondary alkylOR > BnO_2CR > primary alkylOR >> alkylO_2CR. The *t*-butyldimethylsilyl group is stable to this reagent.

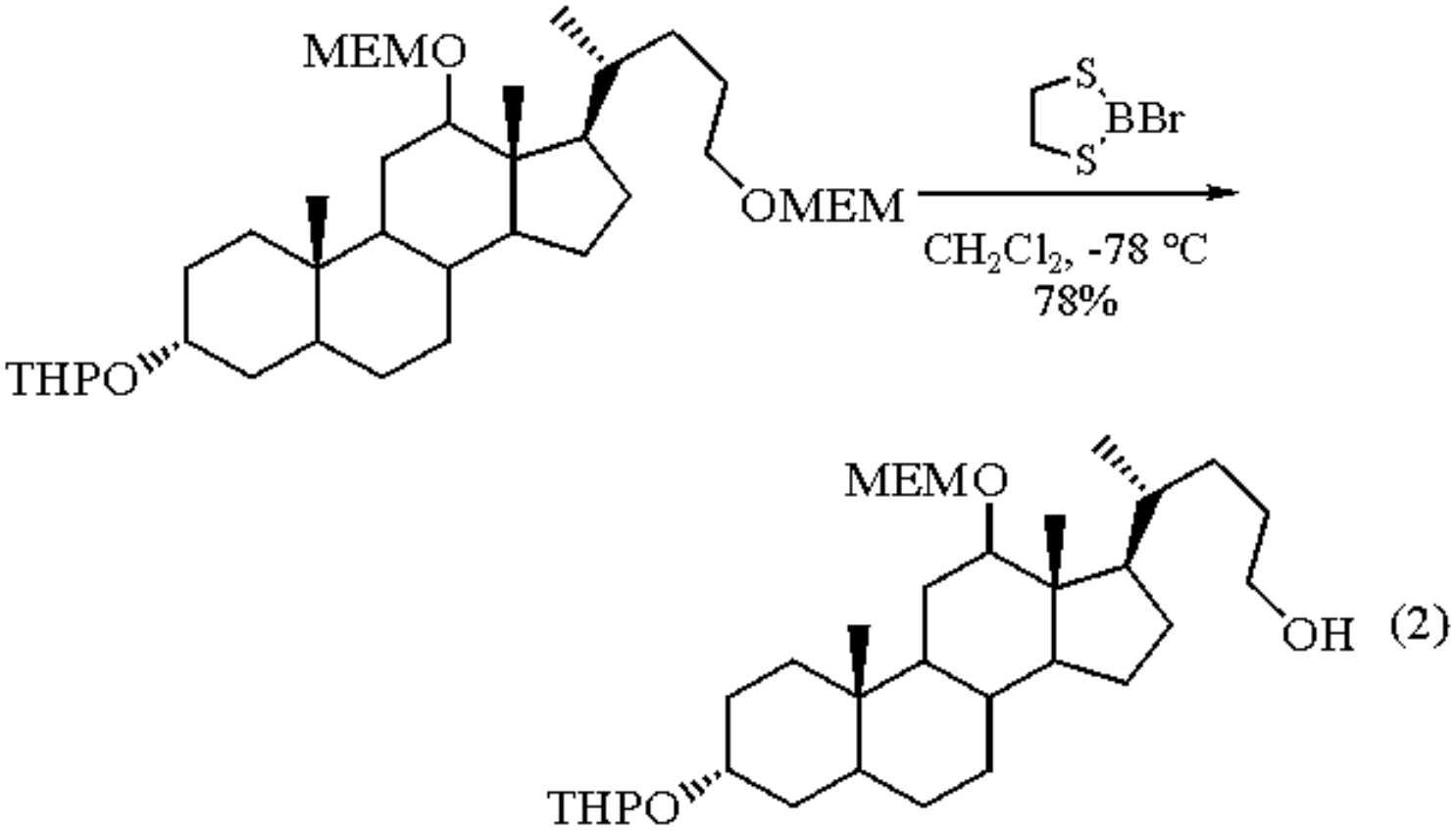

(2)

Protic acids such as ***Pyridinium p-Toluenesulfonate*** (*t*-BuOH, or 2-butanone, heat, 80-99% yield)[10] and ***Tetrafluoroboric Acid*** (CH_2Cl_2, 0 °C, 3 h, 50-60% yield)[11] can also be used to cleave the MEM ethers. The former also cleaves the MOM ether and has the advantage that it cleanly cleaves allylic ethers which can not be cleaved by Corey's original procedure. The MEM group is reasonably stable to CF_3CO_2H/CH_2Cl_2 (1:1), which is used to cleave Boc groups, and to 0.2 N HCl, but it is not stable to 2.0 N HCl or HBr-AcOH.[12] ***Iodotrimethylsilane*** has long been known as a powerful reagent for the cleavage of ethers, esters, carbamates, etc., and thus it is no surprise that it will cleave the MEM ether as well. It does tend to form iodides when cleaving allylic and benzylic ethers, but this is somewhat suppressed when the reagent is prepared in situ (Me_3SiCl, NaI, MeCN, -20 °C, 79%).[13] In a synthesis of tirandamycin, deprotection of a MEM ether was unsuccessful using conventional methods and an entirely new method was developed which oxidizes the methylene (*n*-BuLi, THF; then $Hg(OAc)_2$, H_2O, THF, 81% yield) (eq 3).[14]

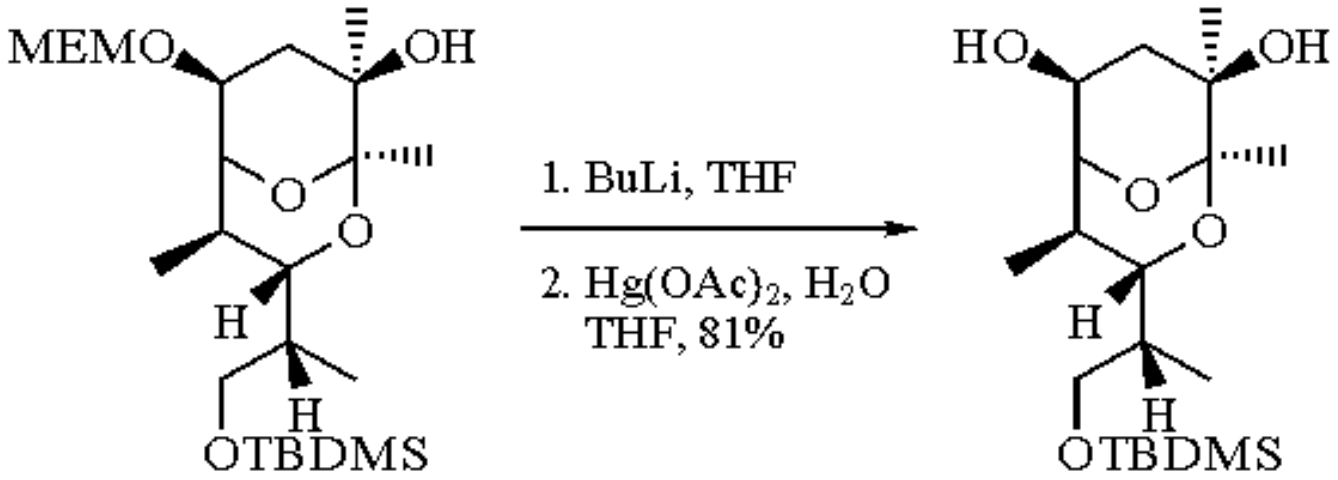

(3)

Protection of Phenols.

Methoxyethoxymethyl chloride can also be used to protect phenols. The conditions for its introduction are similar to those used for alcohols (NaH, THF, 0 °C; $MeOCH_2CH_2OCH_2Cl$, 0 °C -> 25 °C, 2 h, 75% yield).[15,16] In contrast to the alcohol derivatives, phenolic MEM ethers can be cleaved with ***Trifluoroacetic Acid*** (CH_2Cl_2, 23 °C, 1 h, 74% yield).[17] 1 M HCl (THF, 5 h, 60 °C)[18] and HBr/EtOH[19] will also effect cleavage. In general, the cleavage conditions used for alcohols are also effective with the phenolic derivatives. During an examination of the asymmetric reduction of an acetophenone derivative with ***(+)-B-Chlorodiisopinocampheylborane***, it was found that a phenolic MEM ether was slowly cleaved (eq 4).[16]

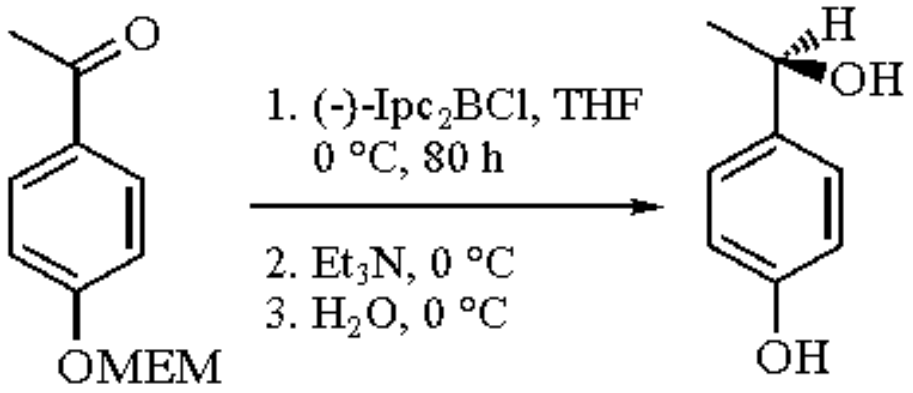

(4)

Protection of Acids.

Carboxylic acids are converted to MEM esters using conditions similar to those used for alcohol protection (MEMCl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C, 2 h).[20] Deprotection of this ester is effected with 3 M HCl (THF, 40 °C, 12 h) or with $ZnBr_2$[21] or $MgBr_2$.[22]

Miscellaneous Uses.

Outside of the protective group arena, MEMCl has been used to alkylate enolates[23] and aryllithium reagents in the presence of Ph_2TlBr.[24] MEM ethers have also proven to be a good one-carbon source for the preparation of isochromans (eq 5)[25] and other oxygen heterocycles (eq 6).[26]

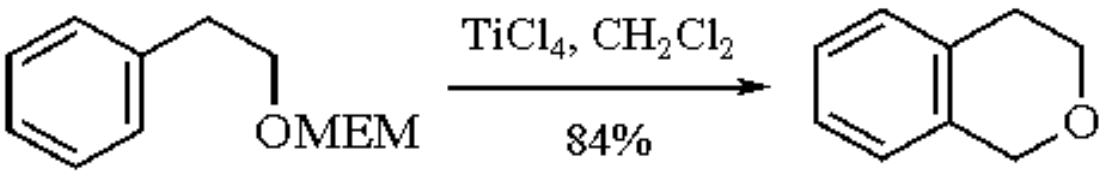

(5)

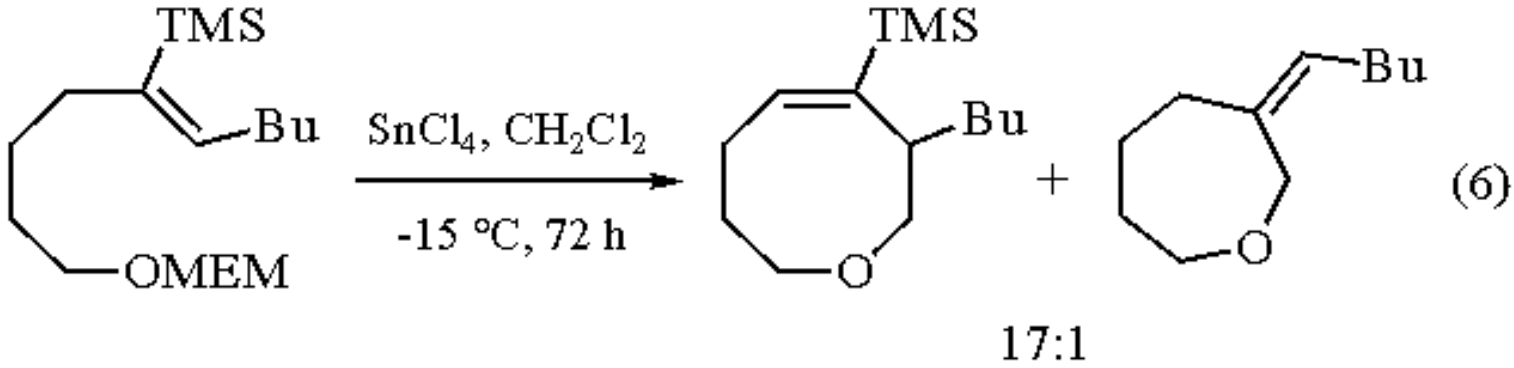

Guaiacolmethyl chloride (GUMCl) (**1**) is a reagent similar to MEMCl, but it produces derivatives that are somewhat more acid sensitive. In fact the GUM group can be removed in the presence of a MEM group. It is a more sterically demanding reagent, and thus it is possible to introduce this group selectively onto a primary alcohol in the presence of a secondary alcohol. Because of its similarity to a *p*-methoxyphenyl group, it should be possible to remove it oxidatively. Cleavage is effected with $ZnBr_2$ in CH_2Cl_2 just as with the MEM group.[27]

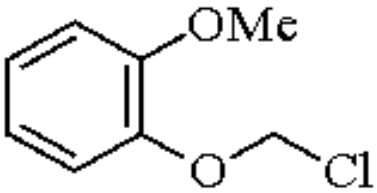

(1)

Related Reagents.

Chloromethyl Methyl Ether.

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3-Methoxyisoprene[1]

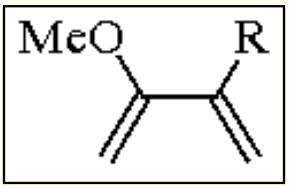

(R = Me)

[25408-63-3] · $C_6H_{10}O$ · 3-Methoxyisoprene · (MW 98.16) (R = Et)

[17466-15-8] · $C_7H_{12}O$ · 3-Ethoxyisoprene · (MW 112.19)

(used as an equivalent of isopropenyl methyl ketone in iterative Claisen rearrangements and as a diene in the Diels-Alder reaction)

Alternate Name: 2-methoxy-3-methyl-1,3-butadiene.

Physical Data: R = Me: bp 93-95 °C. R = Et: bp 113-114 °C.

Preparative Method: R = Me: from 2-methyl-3-butyn-2-ol by successive dehydration, addition of methanol, and elimination of methanol.[1]

Iterative Claisen Rearrangements.

The methoxy group of 3-methoxyisoprene exchanges with secondary allylic alcohols under acid catalysis and the resultant intermediate undergoes Claisen rearrangement.[2] This technique has been applied in an iterative synthesis of squalene (**1**) (eq 1).[1a,3] The rearrangement provides cleanly an (*E*)-alkene and a terminal isopropenyl ketone which, upon reduction, affords an allylic alcohol that is ready for a second rearrangement. Each 3-methoxyisoprene is translated into an isoprene unit in the final product. A similar, alternative, approach to squalene employs isopropenyl methyl ketone dimethyl acetal (2,2-dimethoxy-3-methyl-3-butene) (**2**), which is readily available from isopropenyl methyl ketone.[4]

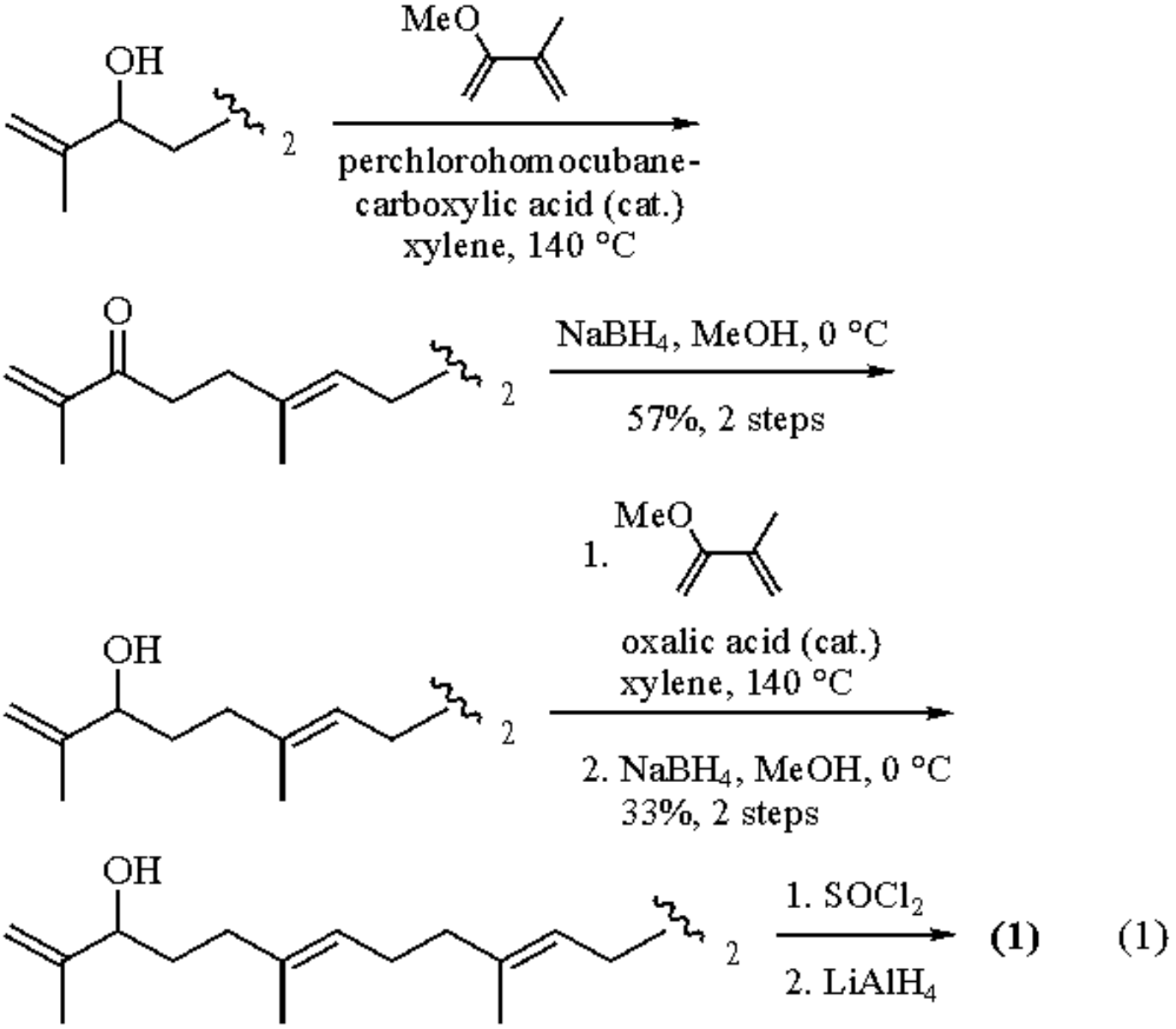

(1)

Reagent (**2**), followed by methyl vinyl ketone diethyl acetal (3,3-diethoxy-1-butene) (**3**), and, again, reagent (**2**) have been applied successively in an iterative extension of methallyl alcohol in refluxing toluene with 2,4-dinitrophenol as a catalyst (eq 2).[4] Two iterations of methyl 2-hydroxy-3-butenoate with 2-methoxy-3-ethyl-1,3-butadiene[1] or 3,3-dimethoxy-2-ethyl-1-butene[4] play a critical role in the synthesis of the C_{18} *Cecropia* juvenile hormone.

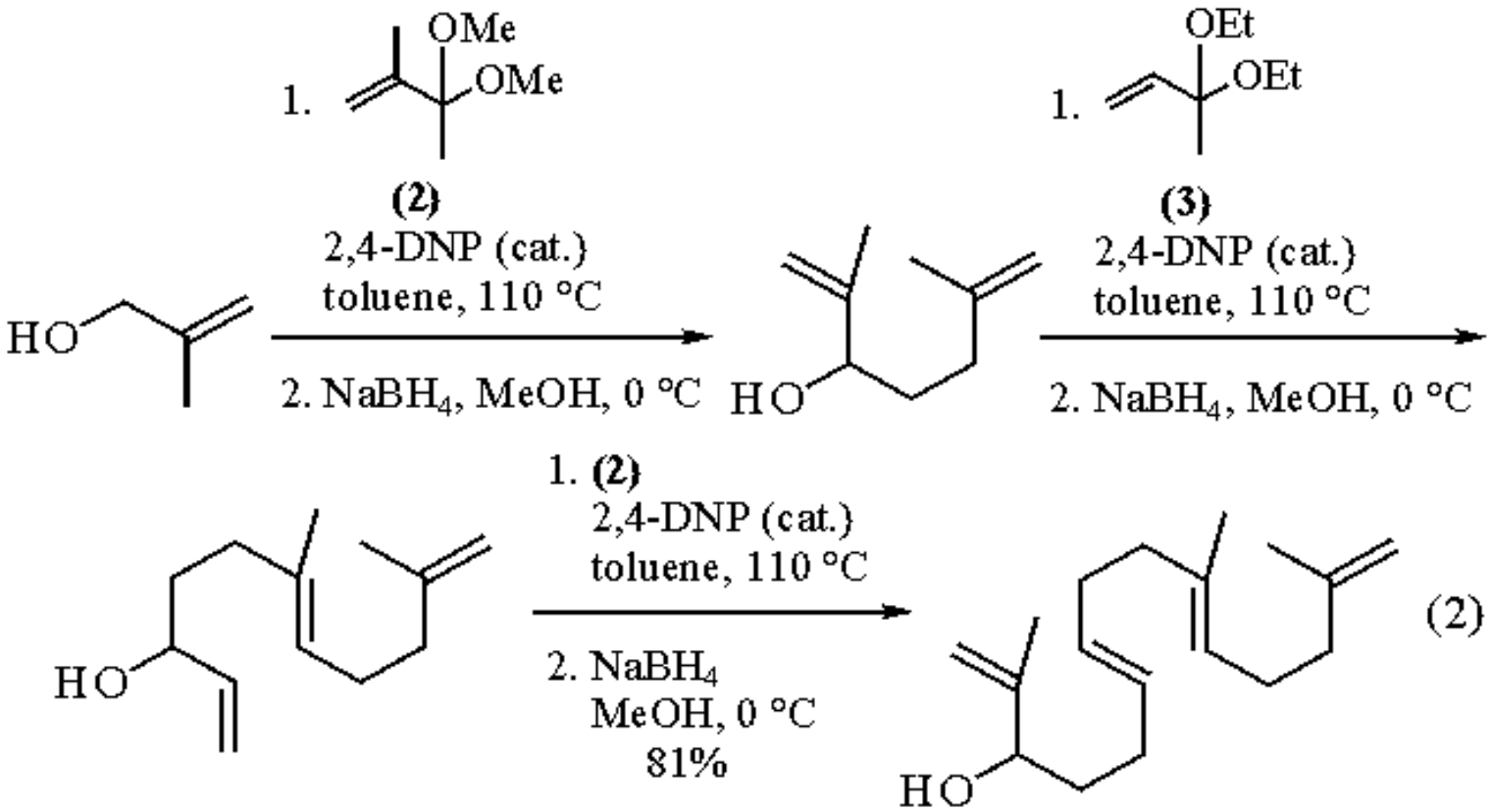

Enolic β-diketones react with 2-methoxy-1,3-butadiene (eq 3)[5] and methacrolein diethyl acetal (3,3-diethoxy-2-methyl-1-propene) (eq 4)[6] to give products that are believed to arise from exchange of the enol form of the diketone with the alkoxy residue of the reagent followed by sigmatropic rearrangement (see also ***2-Methoxy-1,3-butadiene*** and ***3,3-Diethoxy-1-propene***). An alternative mechanism holds that the enol adds in an S_N2' fashion to the oxonium ion. Hydrolysis of the enol ethers gives carbonyl compounds. The overall process is the equivalent of a neutral Michael addition of the diketone to the unsaturated aldehydes from which the reagents were derived.

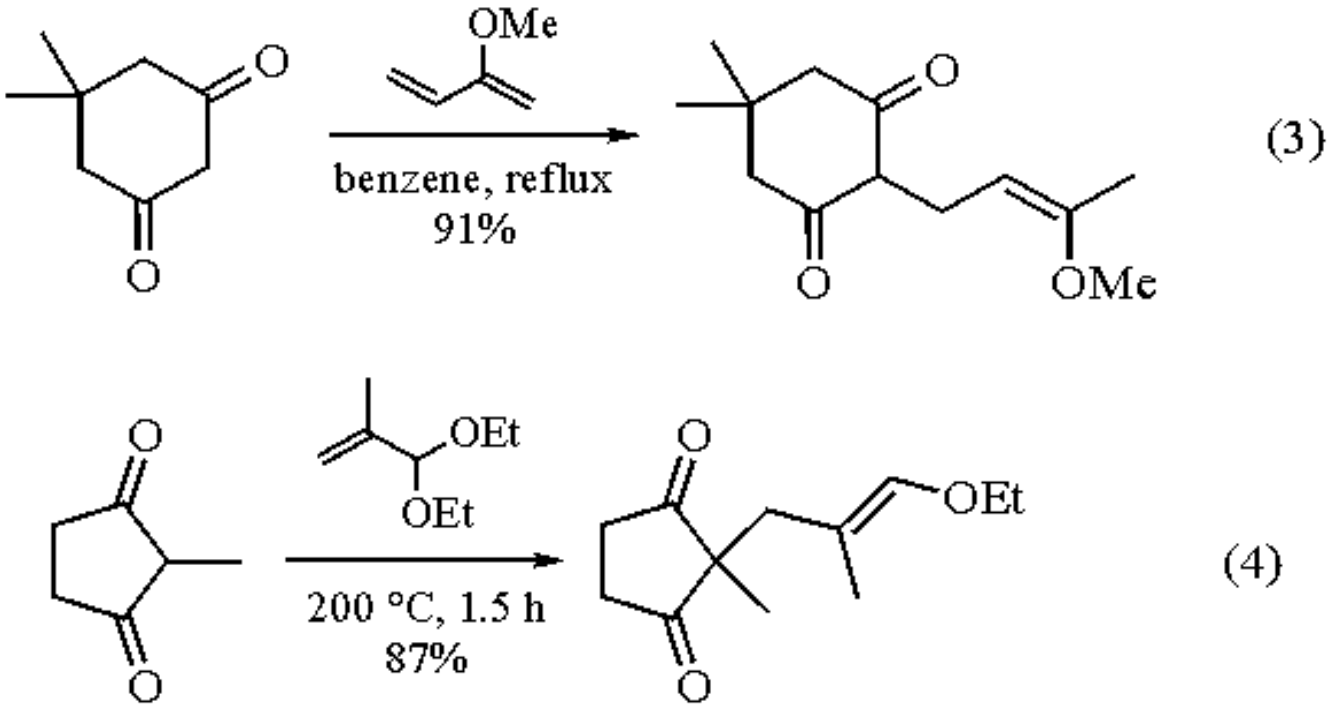

Diels-Alder Reaction.

3-Methoxyisoprene reacts regioselectively with methyl coumalate in a thermal Diels-Alder reaction. Hydrolysis of the enol ether affords an α-methylcyclohexanone (eq 5).[7]

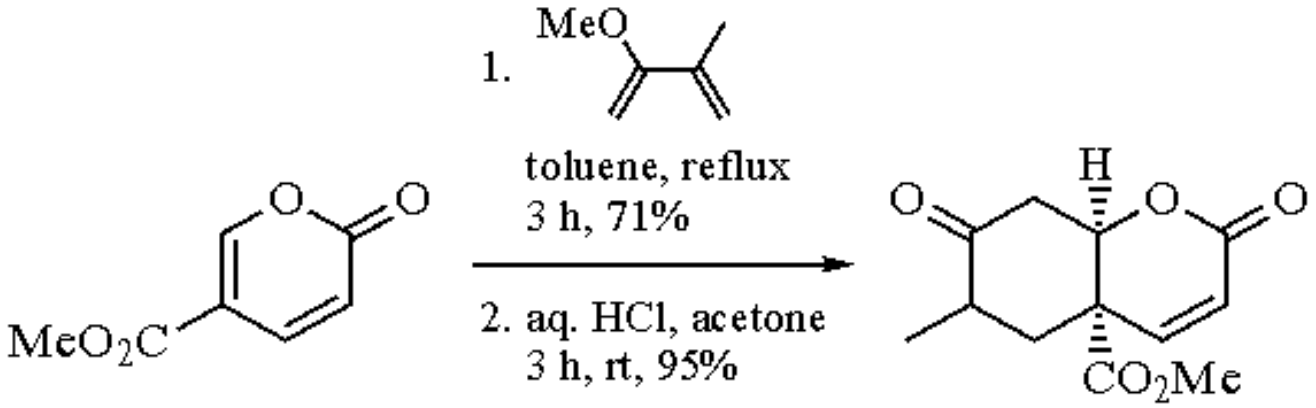

(5)

Related Reagents.

1,3-Butadiene; ***3,3-Diethoxy-1-propene***; ***1-Ethoxy-1-propene***; ***Ethyl Vinyl Ether***; ***Isoprene***; ***2-Methoxy-1,3-butadiene***; ***2-Methoxypropene***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***Methyl Vinyl Ketone***; ***2-Trimethylsilyloxy-1,3-butadiene***.

---

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N-Methoxy-*N*-methylacetamide[1]

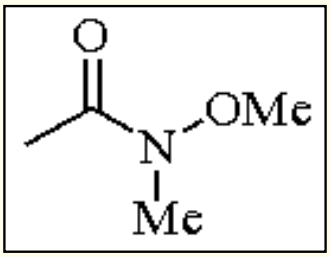

[78191-00-1] · $C_4H_9NO_2$ · *N*-Methoxy-*N*-methylacetamide · (MW 103.14)

(acetylation of carbon nucleophiles; formation and transient protection of ketones; C-nucleophile in enolate anion condensations; preparation of aldehydes)

Physical Data: bp 40-44 °C/20 mmHg.[2]

Solubility: sol ether and other organic solvents.

Analysis of Reagent Purity: ^{1}H NMR δ 2.12, 3.18, 3.70; ^{13}C NMR δ 19.58, 31.98, 60.86, 171.59; IR (neat) 2950, 1670, 1410, 1380 cm^{-1}.[2]

Preparative Method: reaction of ***Acetyl Chloride*** with commercially available ***N,O-Dimethylhydroxylamine*** hydrochloride in pyridine, followed by distillation at reduced pressure (65%).[2]

Handling, Storage, and Precautions: the compound is stable but should be protected from moisture; use in a fume hood.

General Considerations.

The title compound (**1**) and its analogs are versatile reagents for the acetylation of organolithium and magnesium reagents to form methyl ketones.[3] Lithium reagents have been reported to be superior to magnesium.[4] The reactions are carried out in ethereal solvents at 0 or -78 °C. Coordination stabilizes the resulting tetrahedral adduct. Thus further reaction to form tertiary carbinols is generally not observed.[5] The methyl ketone is generated by workup under mild acidic conditions (eq 1). Many examples have been reported. Higher homologs of the title compound have frequently been employed in acylation reactions and generally give favorable results. *N*-Methoxy-*N*-methylamides are sufficiently more reactive than the corresponding methyl esters that attack on difunctional starting materials occurs exclusively at the amide (eq 2).[6,7]

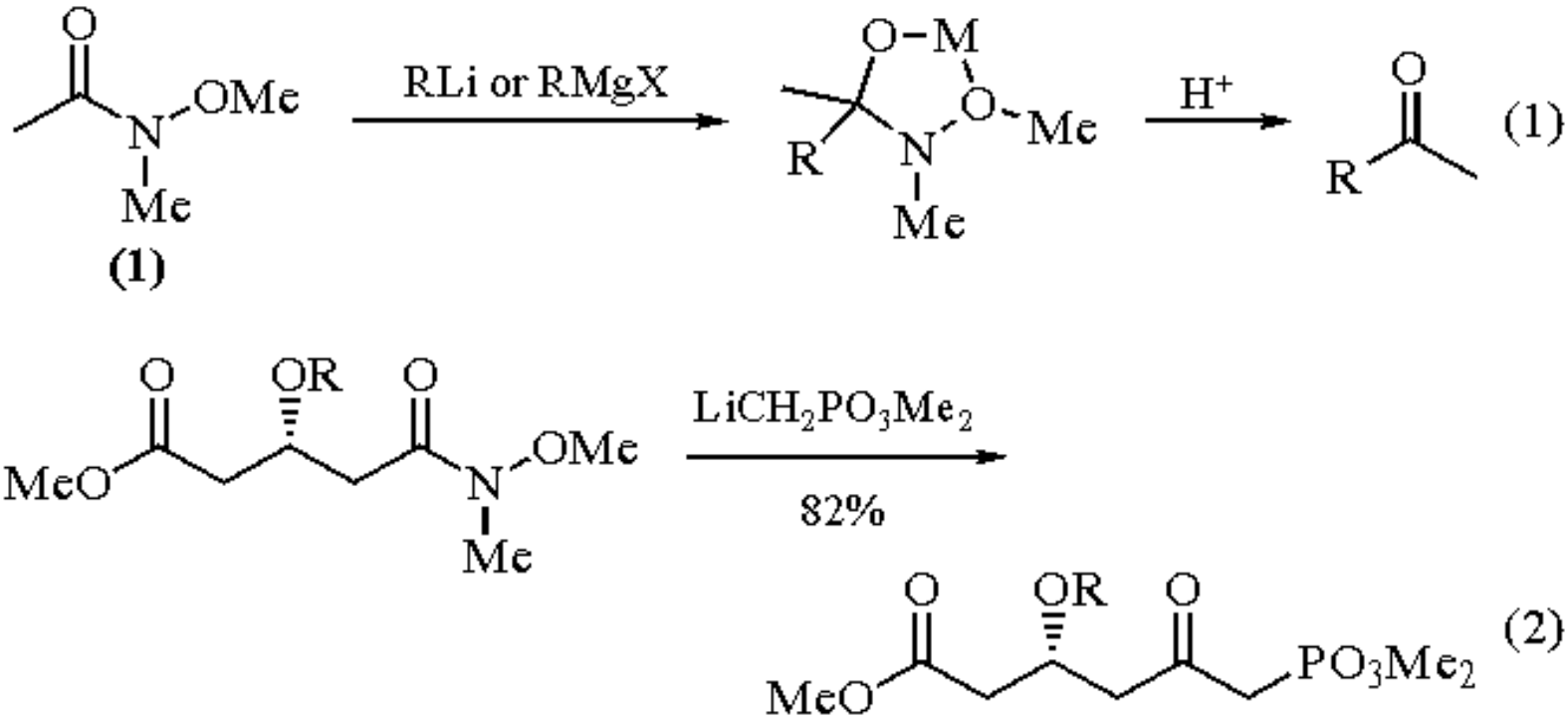

The tetrahedral complex has been used to mask the resulting ketone during subsequent transformations.[8] The complex has also been used to facilitate an intramolecular Diels-Alder condensation by providing conformational constraints.[9]

Compound (**1**) is an excellent reagent for acetylation of strongly nucleophilic enolate anions (eq 3).[2] It is less prone to enolate formation than ethyl acetate and uses a stoichiometric quantity of the nucleophile rather than 2 equiv commonly required in Claisen-type condensations. With less nucleophilic enolate anions, good results have been claimed in some cases[10] and poor results in others.[2,11] Tandem reaction of a bis(*N*-methoxy-*N*-methylamide) has been used in a biomimetic synthesis of pretetramide.[12]

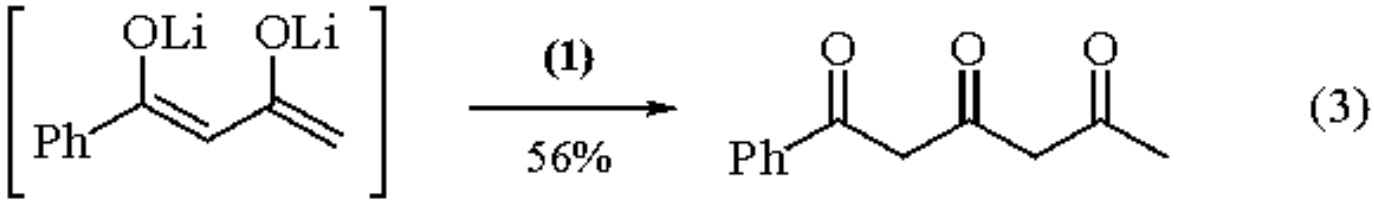

The lithium salt (**2**) of the enolate anion of (**1**) can be prepared by treatment of (**1**) with ***Lithium Diisopropylamide***. The corresponding zinc reagent (**3**) can be prepared from the bromoacetamide and powdered zinc.[13] These reagents will condense with carbonyl compounds and the adducts can subsequently be used as acylating agents.

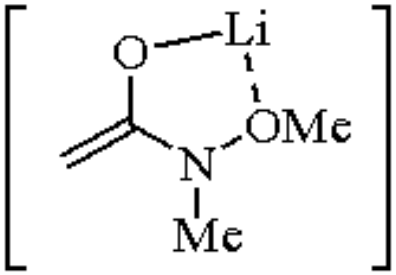

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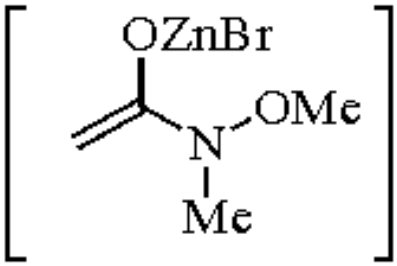

(3)

N-Methoxy-*N*-methylamides undergo reduction to aldehydes with ***Lithium Aluminum Hydride***, ***Diisobutylaluminum Hydride***, and other hydride reagents.[3] *i*-Bu_2AlH is more selective than $LiAlH_4$ for stopping at the aldehyde.

Related Reagents.

Acetic Anhydride; ***Acetyl Chloride***; ***Acetyl Cyanide***; ***Acetyl Methanesulfonate***; ***Acetyl p-Toluenesulfonate***; ***N,O-Dimethylhydroxylamine***; ***Imidazole***.

---

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(Methoxymethyl)bis(trimethylsilyl)amine

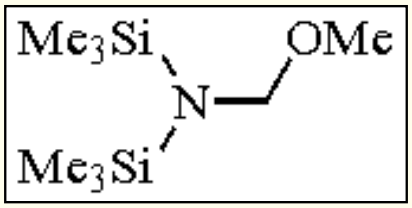

[88211-44-3] · $C_8H_{23}NOSi_2$ · (Methoxymethyl)bis(trimethylsilyl)amine · (MW 205.50)

(electrophilic *N*,*N*-bis(trimethylsilyl)aminomethylating agent for a variety of molecules; after desilylation, the overall transformation achieves primary aminomethylation[1,2])

Physical Data: bp 94-95 °C/83 mmHg; *d* 0.873 g cm^{-3}; *n*20D 1.431-1.434.

Solubility: sol organic solvents such as hexane, dichloromethane, ether, alcohol; stable in neutral or basic solvents; unstable in protic solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: ^{1}H NMR δ ($CDCl_3$): 0.14 (18H, s, 2 × $(CH_3)_3Si$), 3.17 (3H, s CH_3O), 4.82 (2H, s, CH_2); ^{13}C NMR δ ($CDCl_3$): 1.90 (q), 53.4 (q), 80.9 (t).

Handling, Storage, and Precautions: fairly stable at rt; for long storage, keep at 0-10 °C in the absence of moisture.

General Considerations.

This reagent, conveniently prepared[3,4b] by the reaction of ***Lithium Hexamethyldisilazide*** or ***Sodium Hexamethyldisilazide*** with ***Chloromethyl Methyl Ether*** in THF, is utilized for introduction of a primary aminomethyl unit into a variety of molecules by a two-step procedure involving *N*,*N*-bis(trimethylsilyl)aminomethylation followed by solvolytic removal of the trimethylsilyl groups. The reagent can be regarded as a synthetic equivalent for $^+CH_2NH_2$, and it functions as a reagent for achieving Mannich-type transformations[5] which are rarely possible to afford primary amines. The reagent reacts successfully with Grignard and organolithium compounds,[3] ketene silyl (or bissilyl) acetals,[4] silyl sulfides, and silyl phosphites.[6] While the *N*,*N*-bis(trimethylsilyl)aminomethylated products themselves are useful as *N*-protected primary amines,[7] they are easily desilylated to the corresponding primary aminomethyl compounds in protic media.

Primary Aminomethylation of Organometallic

Compounds.[3]

Grignard compounds react with the reagent in equimolar proportions to produce aminomethylated products in the *N*-silyl-protected form. Alkyl, allyl, and aryl Grignard reagents react smoothly in Et_2O at rt usually in high yield, whereas alkynyl Grignard reagents react under reflux in THF. Alkyllithium compounds and aryllithium compounds (prepared in situ by lithiation of arenes with *n*-BuLi) do not react with the reagent unless an equimolar amount of anhydrous ***Magnesium Bromide*** (best prepared from 1,2-dibromoethane and Mg in Et_2O) or $MgCl_2$ is present. Organoaluminum compounds derived from allyl and propargyl bromides have also been shown to undergo *N*,*N*-bis(trimethylsilyl)aminomethylation with this reagent (eqs 1-6).[8]

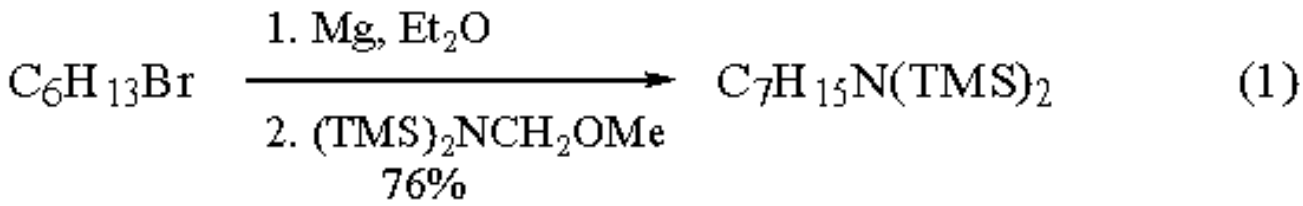

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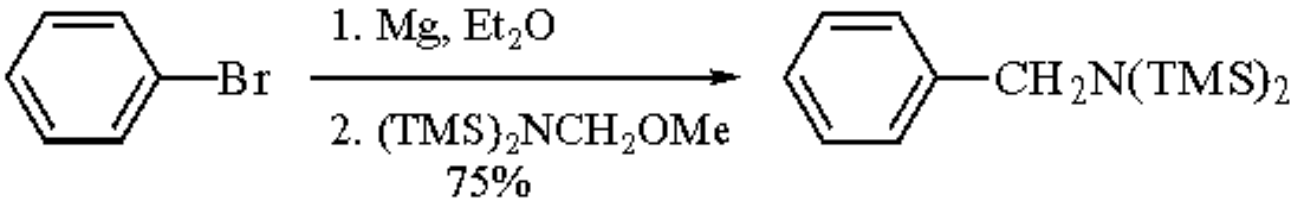

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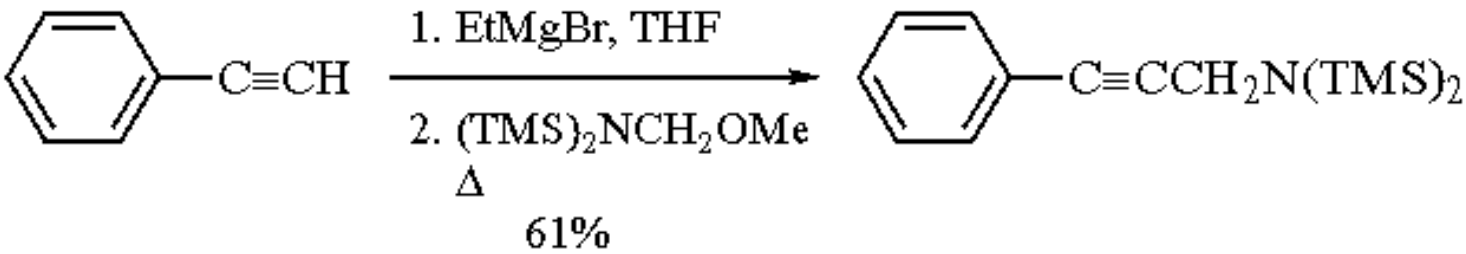

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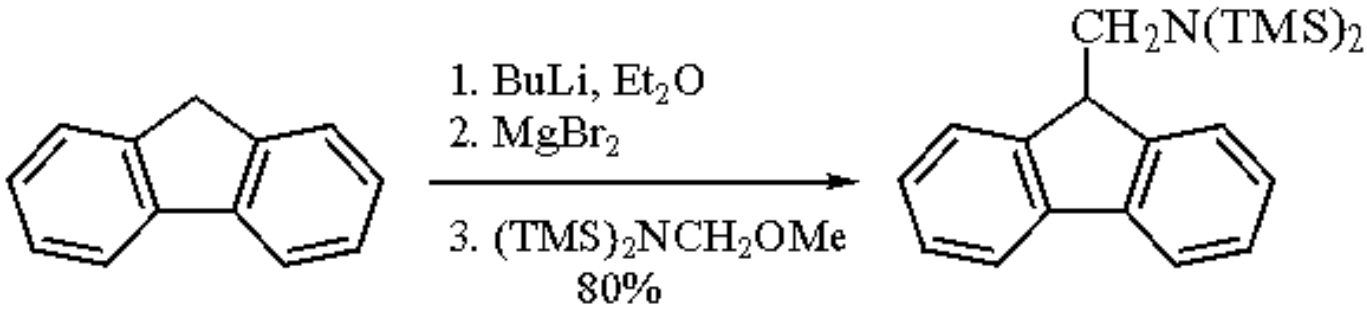

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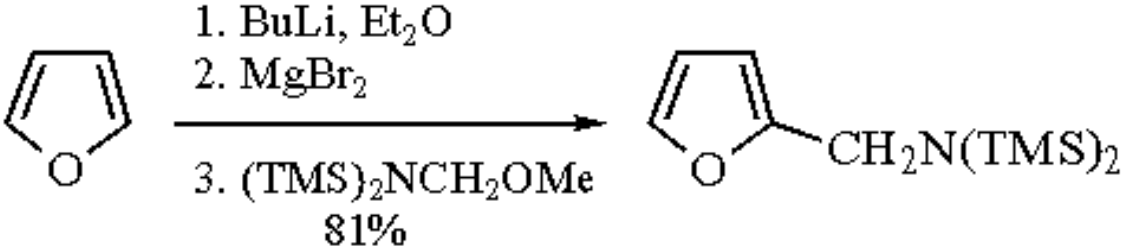

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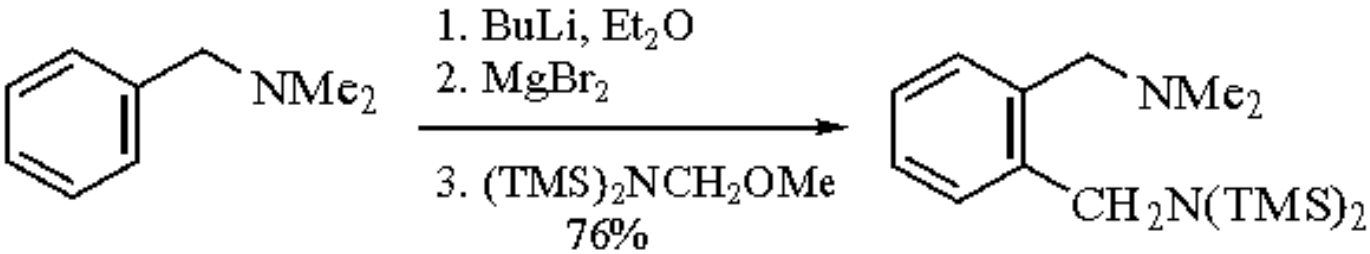

(6)

Solvolytic removal of the *N*-trimethylsilyl groups in the products leads to the corresponding primary amines and is easily accomplished in refluxing MeOH or EtOH in the presence of a catalytic amount of acid such as TsOH or HCl. Silica gel is also capable of catalyzing the solvolysis.

Primary Aminomethylation of Carboxylic Acids and Esters.[4]

The reaction of ketene silyl acetals with the reagent followed by desilylation provides a general method for α-aminomethylation of carboxylic acids and esters. Ketene silyl acetals and bissilyl acetals, prepared from carboxylic esters and acids, respectively, by treatment with ***Lithium Diisopropylamide*** (LDA) and ***Chlorotrimethylsilane***, react smoothly with the reagent in CH_2Cl_2 at rt in the presence of a catalytic amount (0.01 mol equiv) of ***Trimethylsilyl Trifluoromethanesulfonate*** to afford *N*,*N*-bis(trimethylsilyl)-β-aminocarboxylic esters, generally in high yields. The triflate-catalyzed reaction involves electrophilic attack of $[(Me_3Si)_2N{=}CH_2]^+TfO^-$ with release of Me_3SiOMe (eqs 7-9).

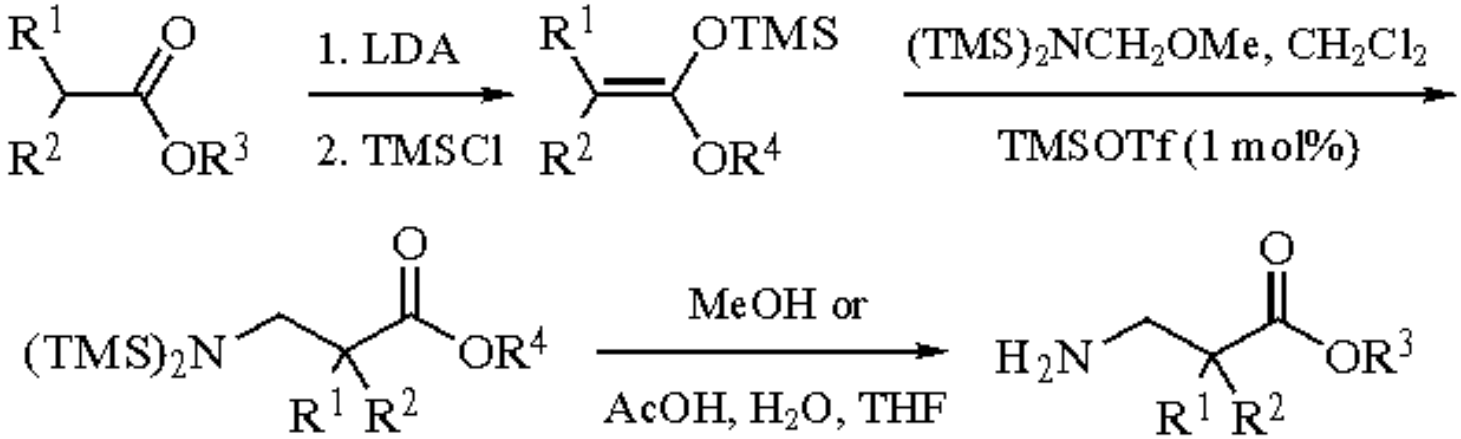

(7)

$R^1, R^2 = H$ or alkyl, $R^3 = $ alkyl or H, $R^4 = $ alkyl or TMS

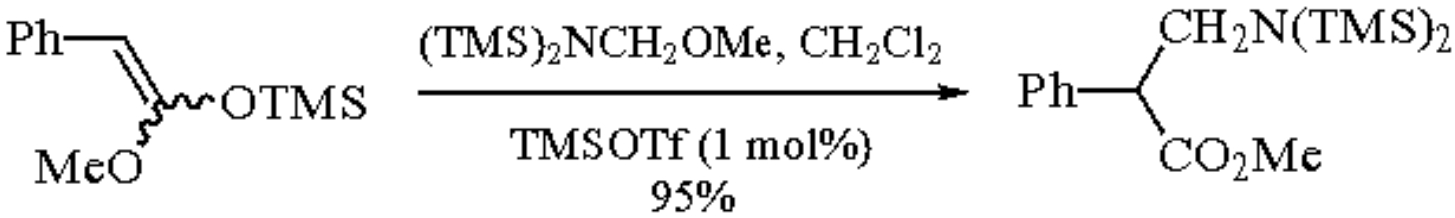

(8)

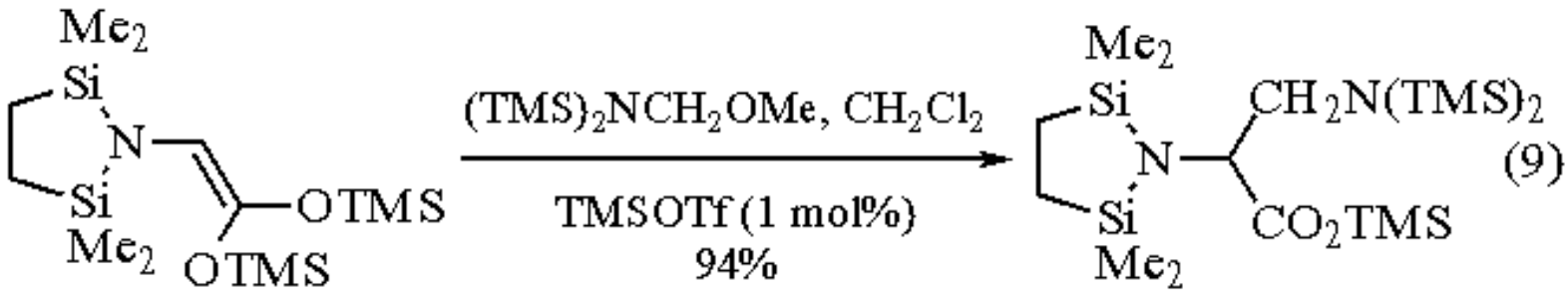

The alkyl and trimethylsilyl esters of *N*,*N*-bis(trimethylsilyl)-β-aminocarboxylic acids are desilylated to the corresponding β-amino acids by treatment with catalytic amounts of acid in aqueous solvents. Selective removal of the *N*-trimethylsilyl groups of the alkyl esters can be performed with AcOH-aq. THF to give the corresponding β-amino acid esters.

N,N-Bis(trimethylsilyl)aminomethylation of Heteroatoms.[6]

Electrophilic introduction of a *N*,*N*-bis(trimethylsilyl)aminomethyl group with this reagent is possible at sulfur and phosphorus atoms by using silyl sulfides and silyl phosphites. The reaction of the reagent with phenyl- or alkylthiotrimethylsilanes and trimethylsilyl dithiocarbamates smoothly proceeds on heating at 60 °C in the presence of ***Zinc Bromide*** (0.05 mol equiv) to give *N*,*N*-bis(trimethylsilyl)aminomethylated sulfur compounds. $PhSCH_2N(SiMe_3)_2$ behaves similarly to the title reagent and is especially effective for *N*,*N*-bis(trimethylsilyl)aminomethylation of cuprate complexes.[2]

The reaction of the reagent with trimethylsilyl phosphite proceeds well at 60 °C in the presence of ***Tin(II) Chloride*** (0.05 mol equiv) to give *N*,*N*-bis(trimethylsilyl)aminomethylphosphonates in good yields (eqs 10-12).

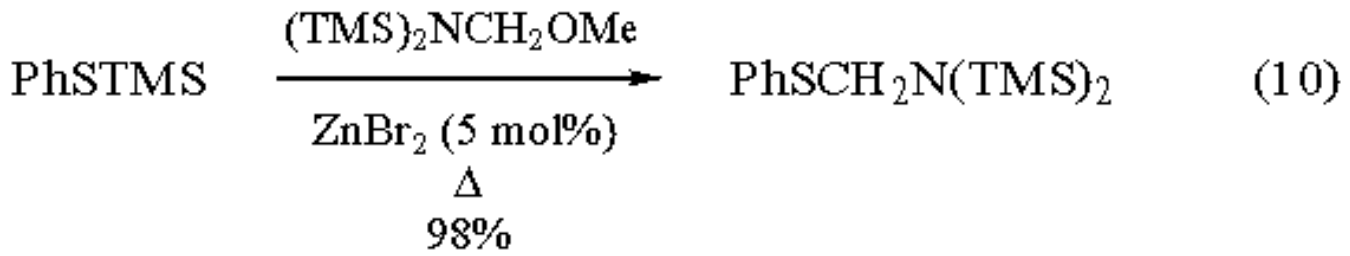

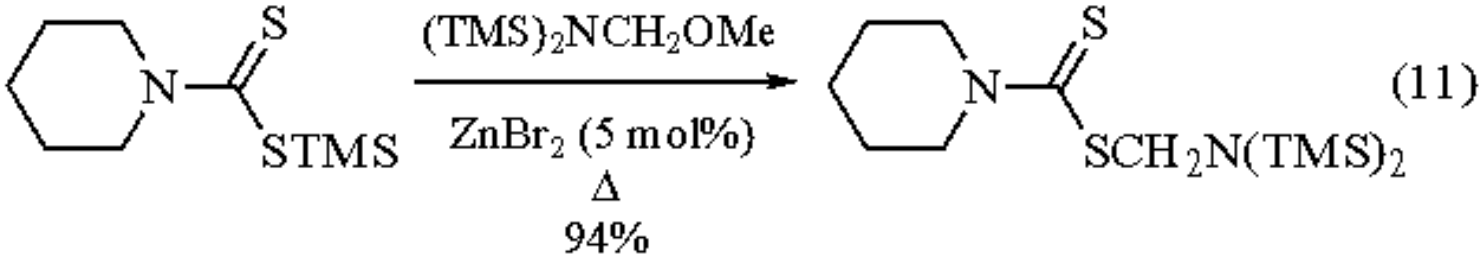

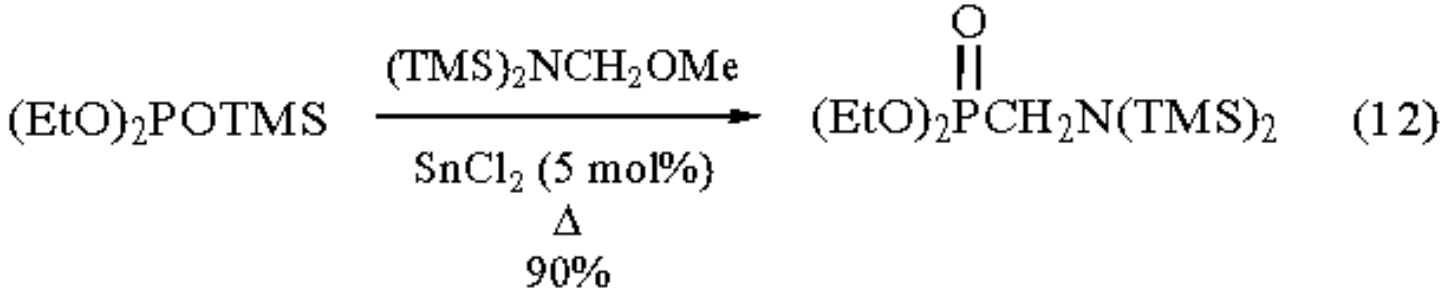

N,*N*-Bis(trimethylsilyl)aminomethylphosphonates are desilylated to give aminomethylphosphonates, whereas *N*,*N*-bis(trimethylsilyl)aminomethylated sulfur compounds are not convertible to primary aminomethyl sulfides because of their instability.

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(3-Methoxy-3-methyl-1-butynyl)copper(I)[1]

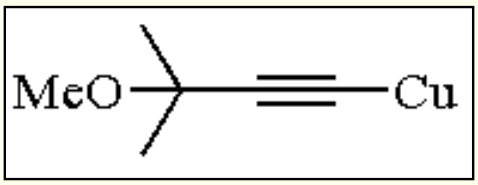

[66769-63-9] · C_6H_9CuO · (3-Methoxy-3-methyl-1-butynyl)copper(I) · (MW 160.70)

(nontransferable ligand used in cuprate preparation for selective ligand transfer to electrophiles[2])

Physical Data: red solid.

Solubility: sol THF; moderately sol ether (0.1 M at 0 °C); insol hexane, H_2O.

Preparative Methods: lithiation of 3-methoxy-3-methyl-1-butyne followed by addition of ***Copper(I) Iodide***. Usually prepared and used in situ. Copper(I) acetylides can be stored under water, then dried in the air.

Handling, Storage, and Precautions: copper(I) acetylides are reported to be explosive when dry. Prepared reagent should be used within a few days for best results. Use in a fume hood.

Mixed Organocuprates.

Since their introduction by Corey in 1972,[3] mixed organocuprates of composition [RC&tbond;CCuR^t]Li have received widespread use for their ability (when R^t is sp^2- or sp^3-bound to Cu) to effect selective transfer of R^t to suitable electrophiles.[2] Of the range of organocuprates which have been investigated for use as nontransferable[4] or dummy ligands, cuprates derived from 3-methoxy-3-methyl-1-butynylcopper are among the most attractive (see also ***3,3-Dimethyl-1-butynylcopper(I)***, ***1-Hexynylcopper(I)***, and ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***). This stems from a combination of their high solubility in traditional solvents for coupling reactions (ether, THF), and the economy of using an inexpensive alkynic precursor.[2] Treatment of the alkyne with the requisite organolithium species yields synthetically useful lithium organocuprate derivatives (eq 1).

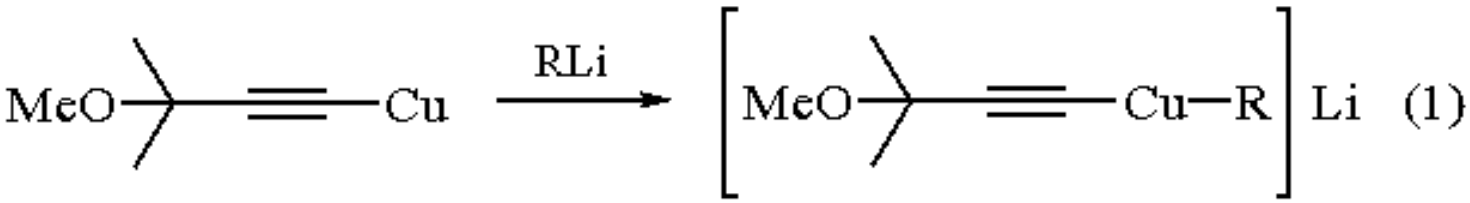

Mixed Alkyl Cuprates.

Mixed alkyl cuprates will selectively alkylate alkyl halides in moderate yield (eq 2).[2] Higher yields have been reported for alkyl transfer by converting the cuprate into a lithium dialkylcuprate, which transfers one alkyl group.[5] Alkyl delivery to cycloalkenones (eq 3)[2] and epoxides[6] is efficient, and near-quantitative yields are obtained using a variety of alkyl donors.

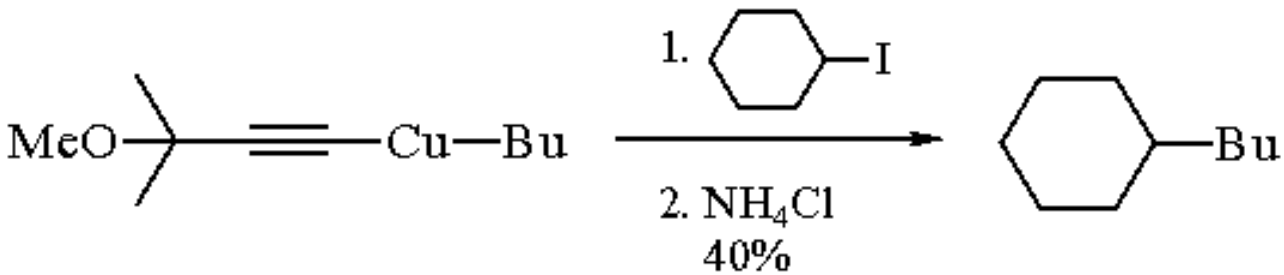

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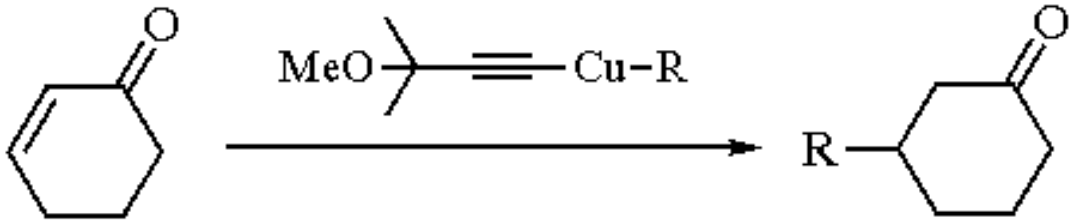

(3)

R = Bu, 100%; R = *i*-Pr, 95%
R = *t*-Bu, 95%

Mixed Alkenyl and Aryl Cuprates.

Delivery of alkenyl and aryl groups is probably the most versatile and celebrated application of mixed cuprates containing this dummy ligand. A variety of excellent examples demonstrate the high degree of efficiency of the process;[7-11] the heavily substituted nature of many of the combining species is a testimony to the tolerance of such mixed cuprates. The 3-methoxy-3-methyl-1-butynyl ligand was found to be clearly superior to a phenylthio dummy ligand in a variety of vinylcopper species.[10] S_N2' addition sequences are also possible, giving highly functionalized products (eq 4).[12] Asymmetric induction (up to 92% ee) has been reported for the conjugate addition of the mixed lithiocuprate derived from the anion of methyl norephedrine acetone imine to cycloalkenones.[13,14]

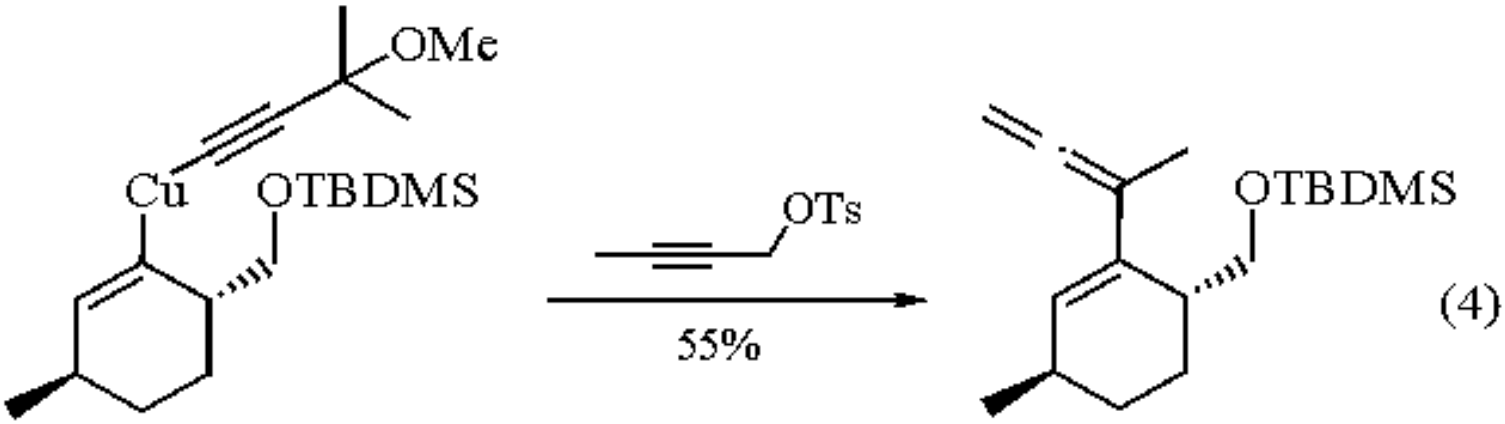

Trimethylstannylcopper Reagents.

Treatment of ***Trimethylstannyllithium*** with 3-methoxy-3-methyl-1-butynylcopper results in formation of the corresponding trimethylstannylcopper species (eq 5).[15] Such reagents are, as predicted, able to chemoselectively transfer the nondummy ligand to an electrophile. Thus, addition of a stannylcopper species to alkynes results in formation of (*E*)-alkenes (eq 5) with very high selectivity.

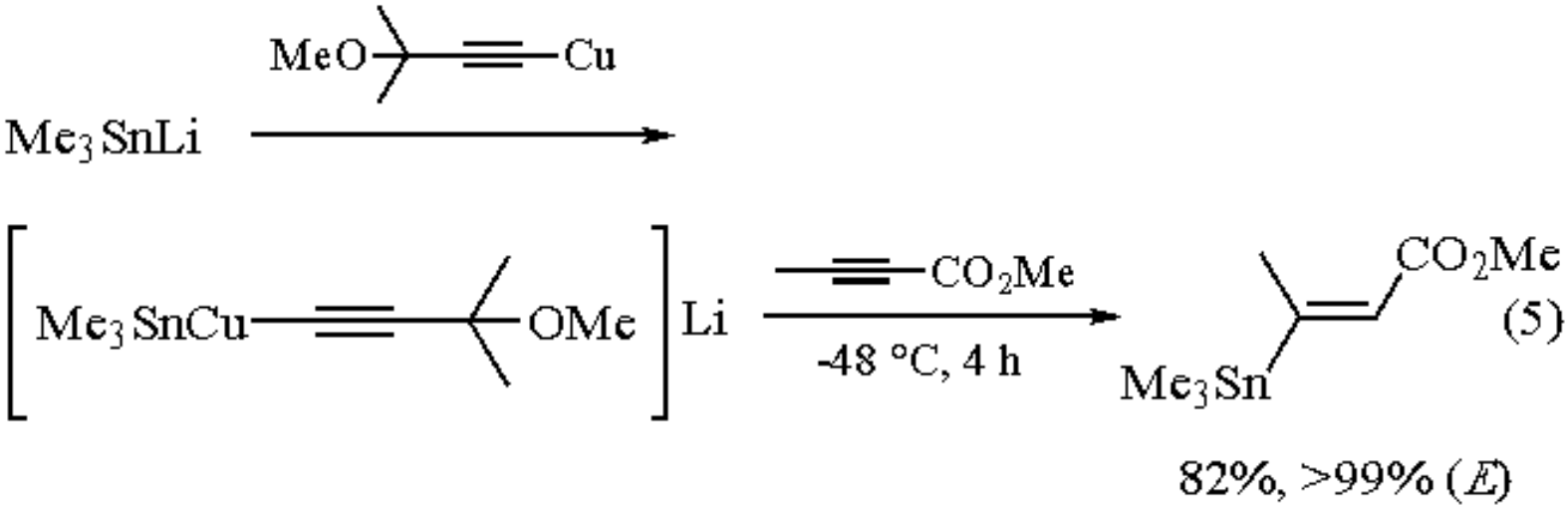

Related Reagents.

For lithium dialkylcuprates, see ***Lithium Dimethylcuprate***; for phenylthio mixed cuprates, see e.g. ***Lithium Methyl(phenylthio)cuprate*** and ***Phenylthiocopper(I)***. Also see ***Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate***, ***Lithium (1-Pentynyl)(2-tri-n-butylstannylvinyl)cuprate***, ***Lithium Phenylthio(trimethylstannyl)cuprate***, ***Tri-n-butylstannylcopper***, and ***Trimethylstannylcopper-Dimethyl Sulfide***.

---

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5-(Methoxymethyl)-1,3-cyclopentadiene

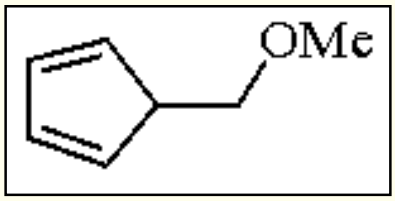

[39872-54-3] · $C_7H_{10}O$ · 5-(Methoxymethyl)-1,3-cyclopentadiene · (MW 110.17)

(Diels-Alder cycloaddition diene, particularly useful in prostaglandin synthesis)

Solubility: sol most organic solvents.

Preparative Methods: prepared via the alkylation of freshly sublimed ***Thallium(I) Cyclopentadienide*** with ***Chloromethyl Methyl Ether*** in ether (-20 °C) according to the method of Corey and co-workers.[1,2] Thallium(I) cyclopentadienide is prepared via the reaction of cyclopentadiene with thallium(I) sulfate and aqueous potassium hydroxide (eq 1).[2-4] **Caution**: thallium and its salts are known to be highly toxic.[5] Other 5-alkyl-substituted 1,3-cyclopentadienes (e.g. 5-(benzyloxymethyl)-1,3-cyclopentadiene[2,6]) are prepared similarly.

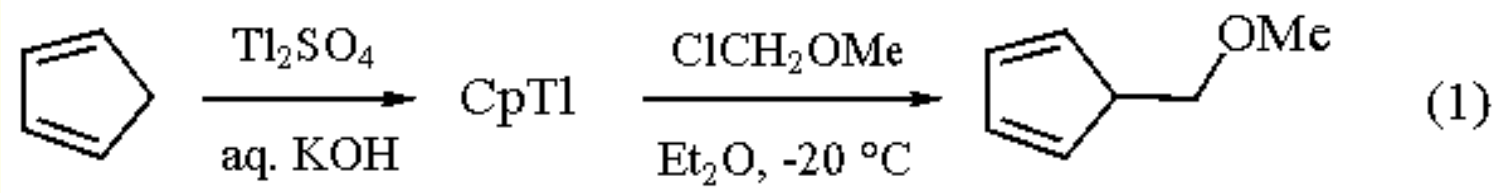

Handling, Storage, and Precautions: 5-alkyl-substituted 1,3-cyclopentadienes undergo facile double bond migration;[7,8] as such, 5-(methoxymethyl)-1,3-cyclopentadiene is typically prepared fresh and used without isolation.

General Considerations.

The reactions of 5-(methoxymethyl)-1,3-cyclopentadiene with Diels-Alder cycloaddition ketene equivalents[9] have been widely studied due to their pivotal role in the classic Corey approach to the synthesis of prostaglandins. The cycloadducts are converted to the norbornenone which undergoes Baeyer-Villiger oxidation and subsequent rearrangement to the key lactone precursor to prostaglandins (eq 2).[10]

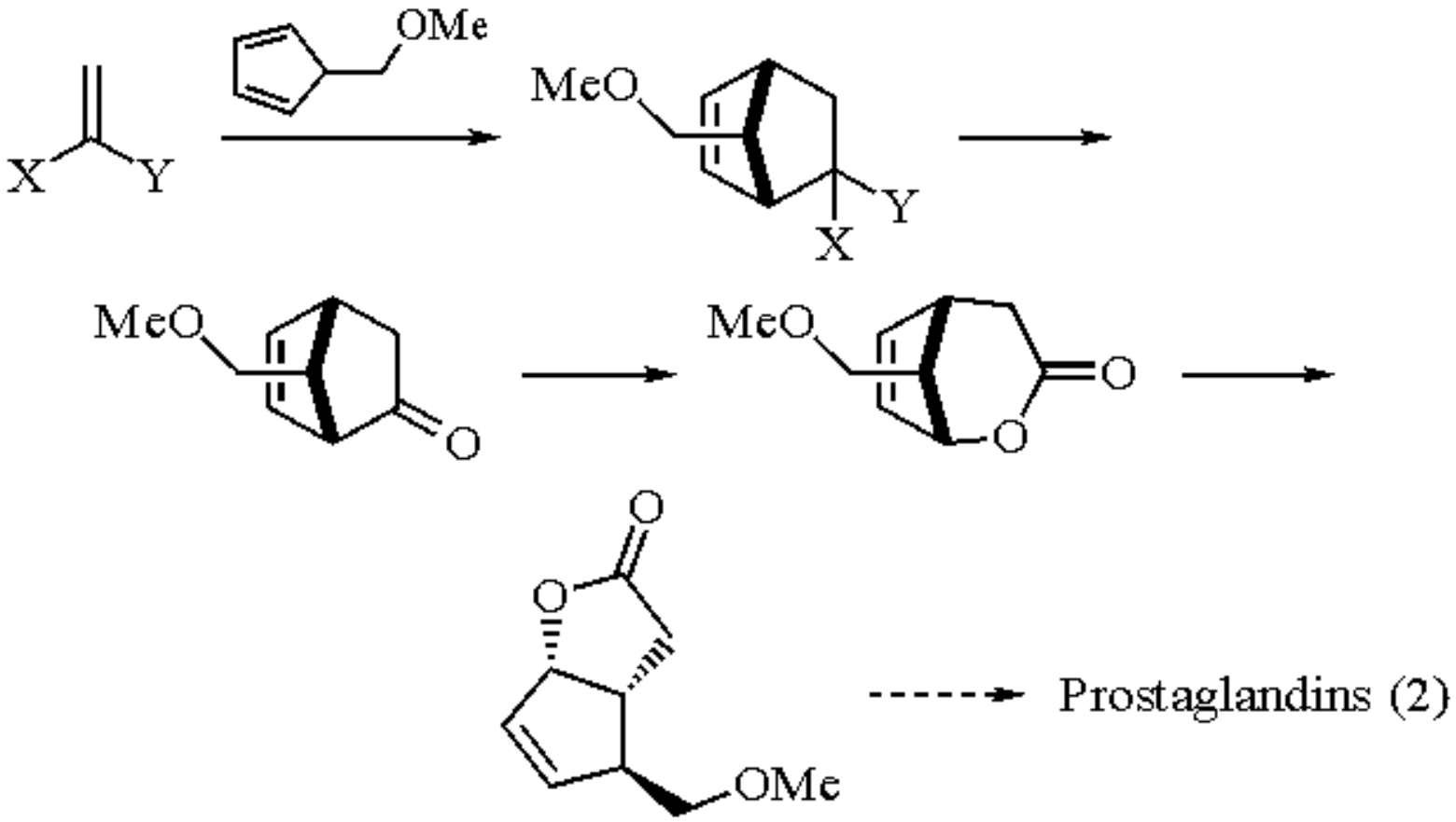

The reaction of 5-(methoxymethyl)-1,3-cyclopentadiene with ***2-Chloroacrylonitrile*** catalyzed by dry ***Copper(II) Tetrafluoroborate*** (0.3 equiv, 0 °C, 18 h) is reported to yield cycloadduct in 80-90% yield.[1] Aqueous $Cu(BF_4)_2$ apparently leads to facile isomerization of 5-(methoxymethyl)-1,3-cyclopentadiene and the use of aq $Cu(BF_4)_2$ catalysis leads to formation of the cycloadduct derived from 1-(methoxymethyl)-1,3-cyclopentadiene.[11] The reaction of 5-(methoxymethyl)-1,3-cyclopentadiene with 2-chloroacryloyl chloride in ether (0 °C, 18 h), without added Lewis acid catalyst, affords a mixture of diastereomeric cycloadducts.[12] Treatment of the cycloadduct with ***Sodium Azide*** (dimethoxyethane, 25 °C (1.5 h), then reflux (2 h)), followed by hydrolysis in 35% aq HOAc (55-60 °C) affords the 7-*syn*-methoxymethyl-2-norbornen-5-one (eq 3). The yield of norbornenone is 82% based on the amounts of thallium(I) cyclopentadienide and chloromethyl methyl ether used.

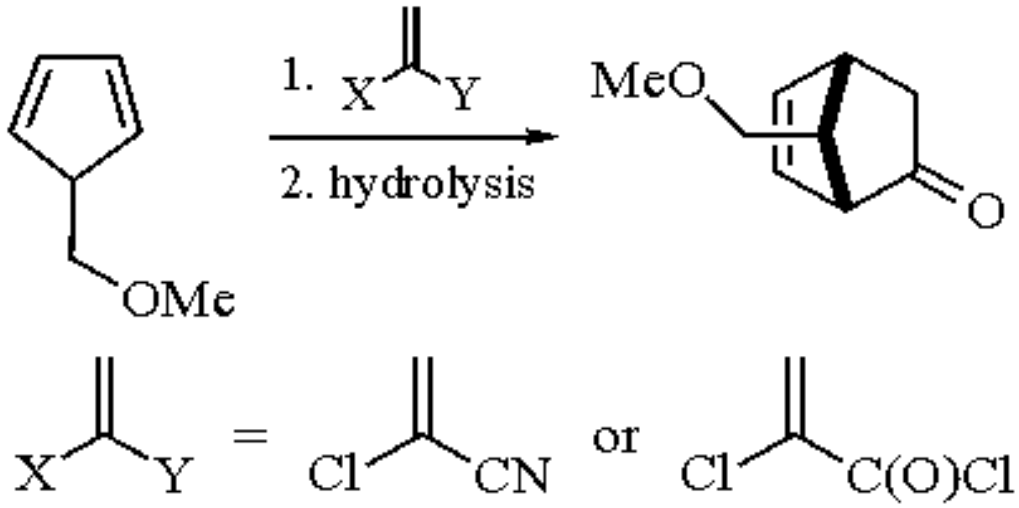

(3)

Treatment of 5-(methoxymethyl)-1,3-cyclopentadiene with ***Nitroethylene*** at -15 °C (or lower) affords a 9:1 mixture of cycloadducts in good yield (eq 4).[13,14] The minor cycloadduct arises from apparent isomerization to 1-(methoxymethyl)-1,3-cyclopentadiene. Acrylic acid has also been used as a dienophile in the reaction with 5-(methoxymethyl)-1,3-cyclopentadiene.[15]

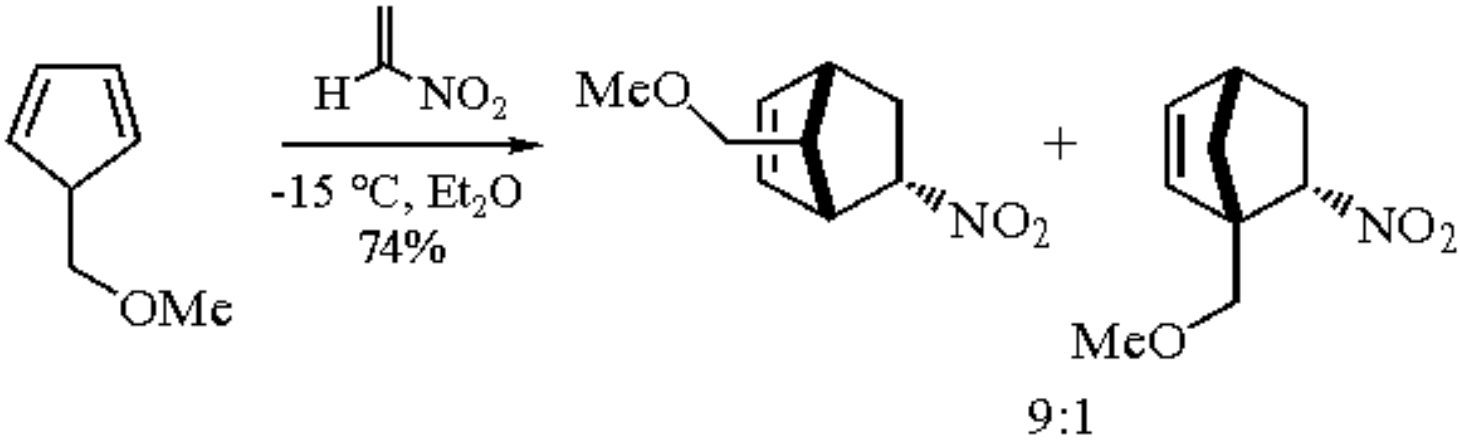

(4)

Kanematsu and co-workers[16] reported the formation of a novel class of photoresponsive crown ethers via the [4 + 2] cycloaddition of 5-(methoxymethyl)-1,3-cyclopentadiene with a crowned *p*-benzoquinone followed by photochemical [2 + 2] cycloaddition. 5-(Methoxymethyl)-1,3-cyclopentadiene undergoes regio- and stereoselective cycloaddition with the benzoquinone under Lewis acid catalysis (***Boron Trifluoride Etherate***, -20 °C, CH_2Cl_2, 93%). The resulting cage compound undergoes quantitative thermal ring opening (110 °C, 3 h) and clean photochemical reclosure (eq 5).

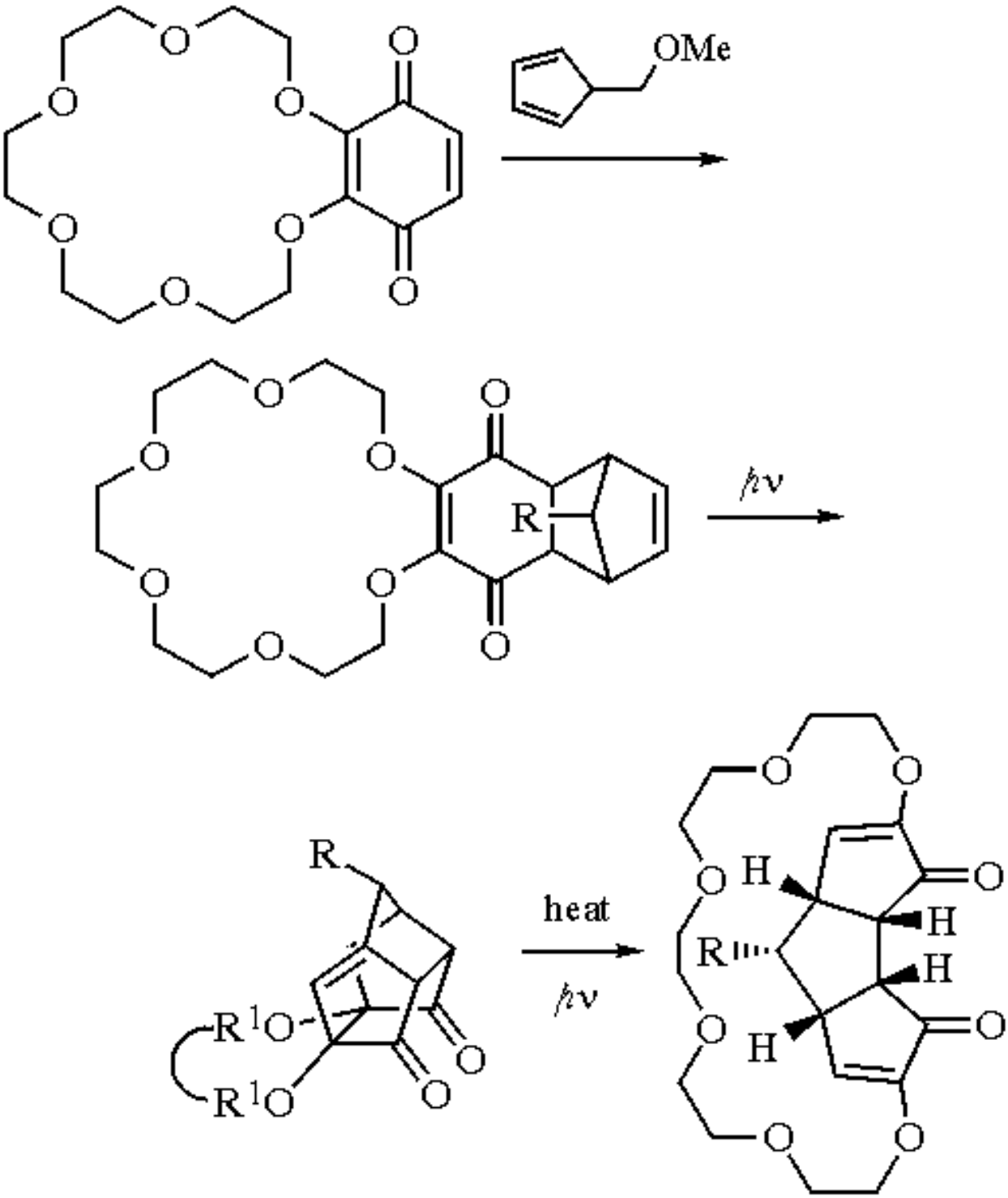

(5)

5-Alkyl-substituted 1,3-cyclopentadienes undergo facile double bond migration.[7] For example, thermolysis of 5-(methoxymethyl)-1,3-cyclopentadiene via flash vacuum pyrolysis (FVP; 220 °C) affords a 1:1.5 equilibrium mixture of the 1- and 2-(methoxymethyl)-1,3-cyclopentadienes (eq 6).[8]

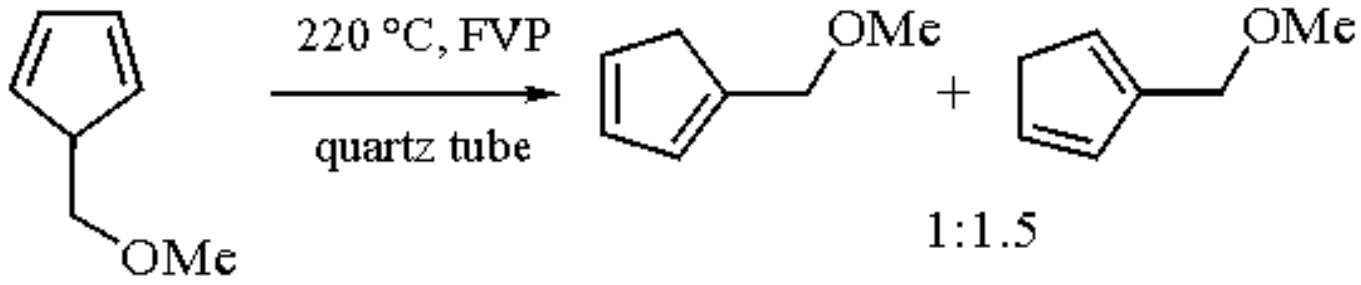

(6)

Related Reagents.

5-Bromo-1,3-cyclopentadiene; ***Cyclopentadiene***; ***5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene***.

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Methoxymethyl(diphenyl)phosphine Oxide[1]

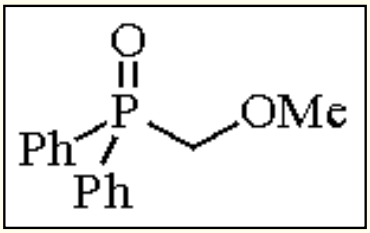

[4455-77-0] · $C_{14}H_{15}O_2P$ · Methoxymethyl(diphenyl)phosphine Oxide · (MW 246.26)

(Horner-Wittig reagent for the preparation of methoxyvinyl ethers and hence homologous aldehydes;[2] the anion has greater stability and nucleophilicity than the analogous phosphonium ylide)

Physical Data: mp 114-116 °C; bp 138-139 °C/0.1 mmHg.

Solubility: sol THF, DME, CH_2Cl_2; insol H_2O.

Form Supplied in: white solid; commercially available.

Handling, Storage, and Precautions: commercial material (97-98%) is satisfactory as received. The toxicological properties of the reagent are unknown.

General Considerations.

Methoxymethyl(diphenyl)phosphine oxide has been widely[3] used in the Horner-Wittig reaction converting both aldehydes and ketones, including enolizable ones, into methoxyvinyl ethers (and hence to higher aldehydes) (eq 1). The reagent is available commercially or by routes A (90%),[2] B (89%),[4] or C (25%).[5] Its anion, generated from ***Lithium Diisopropylamide*** in THF, is more stable than the corresponding phosphonium ylide (Ph_3+P--CHOMe) and readily adds to the carbonyl substrate giving good yields of isolable β-hydroxyphosphine oxides. Alkene formation does not usually occur spontaneously (for exceptions, see eqs 4 and 6) because the lithium counterion binds strongly to the oxygen of the initial adduct, preventing attack by oxygen on phosphorus. In the case where R^1 &neq; R^2 the diastereoisomeric alcohols can often be separated by fractional crystallization or chromatographically. Completion of the Horner-Wittig reaction is achieved by treating the adducts with ***Sodium Hydride*** (or ***Potassium Hydride***) at ambient temperature. This elimination is stereospecifically *syn*, with each diastereomer giving a single geometric isomer. The methoxyvinyl ether(s) are readily separated from the phosphinate byproduct. Mild acid hydrolysis furnishes the homologous aldehyde.

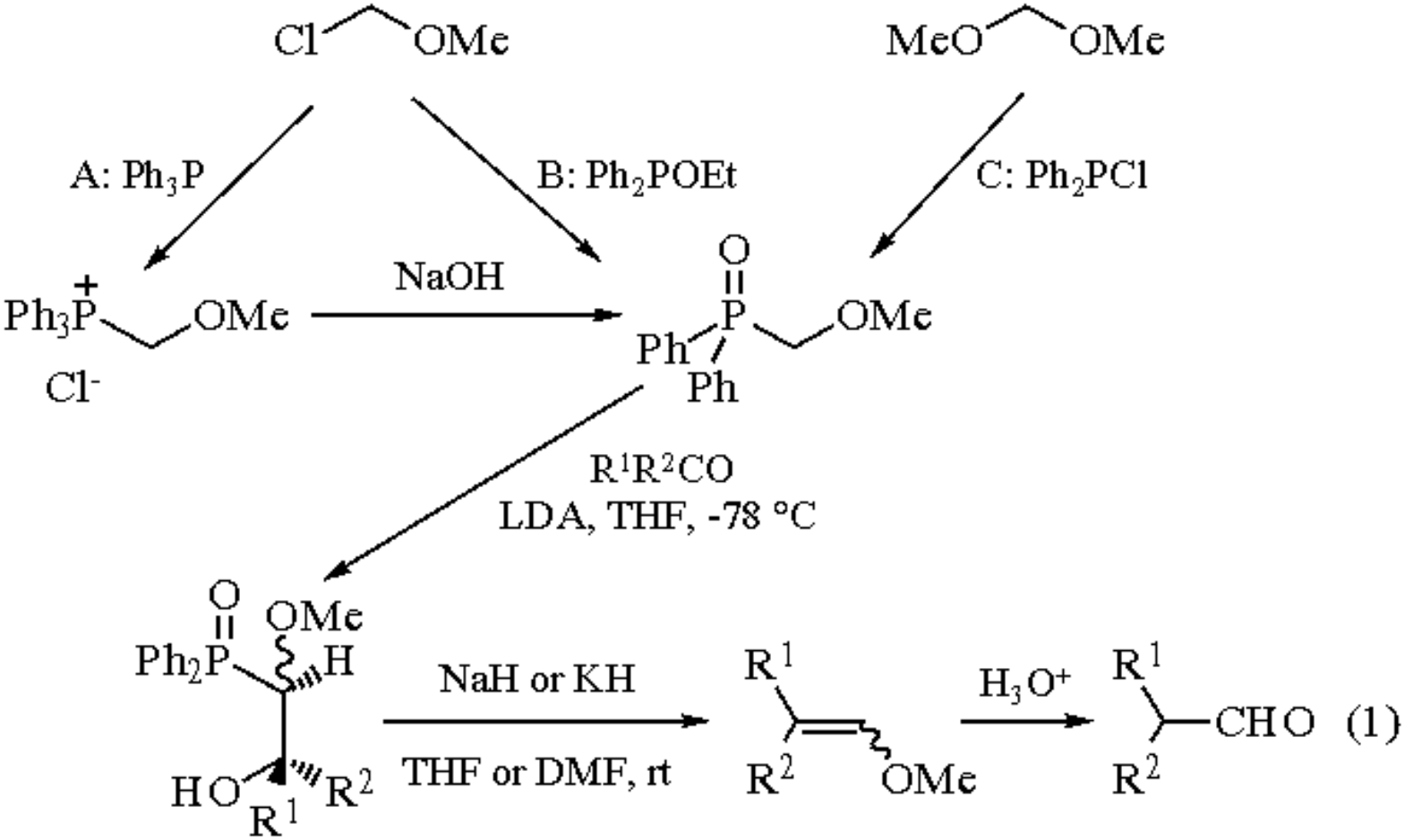

The more nucleophilic and sterically less demanding nature of the $Ph_2P(O)CH_2OMe$ anion is illustrated by the examples in eqs 2-4.[6,7] In each case the ketone was inert towards the analogous phosphonium ylide. Diastereoselective attack of the anion on the 2-acylindole (**1**)[8] leads to single vinyl ether (**2**) (eq 4).

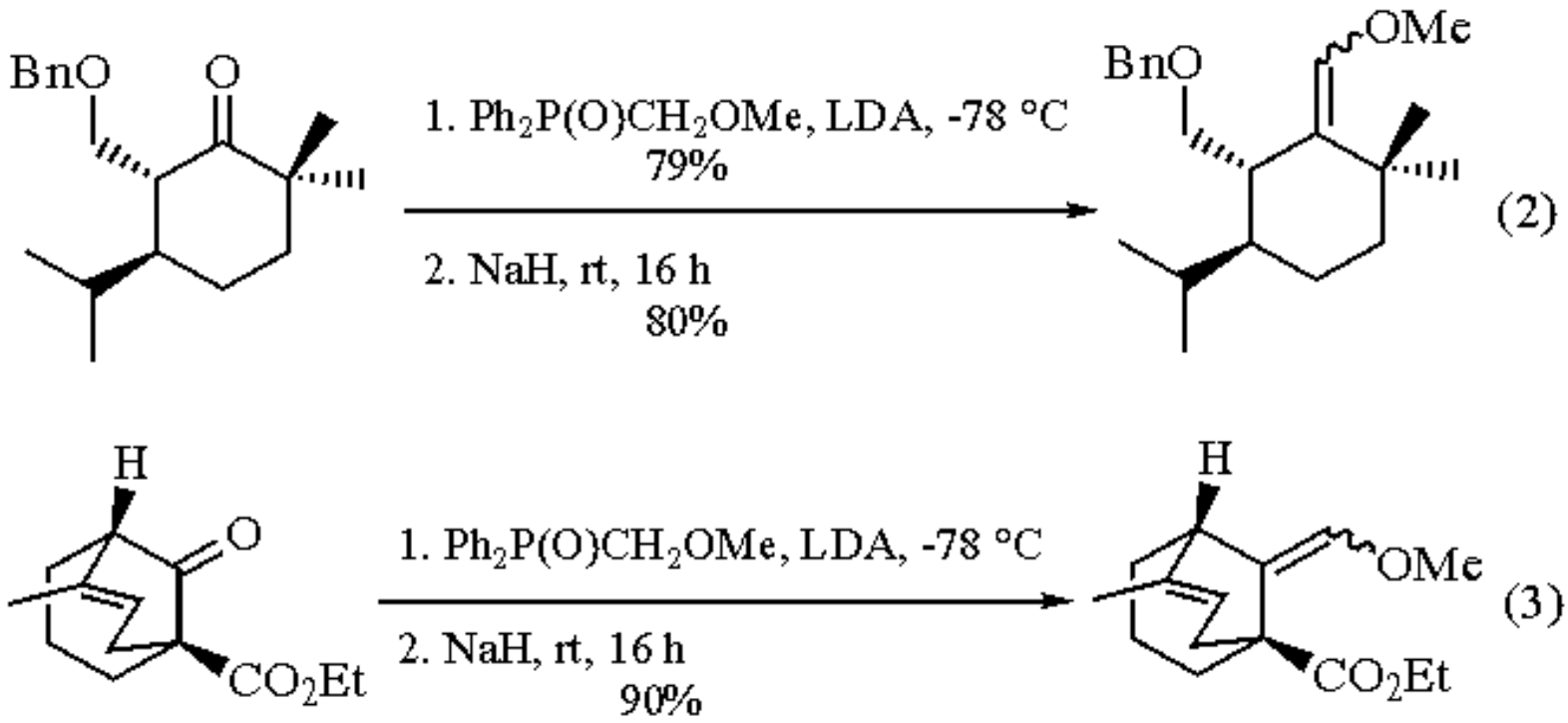

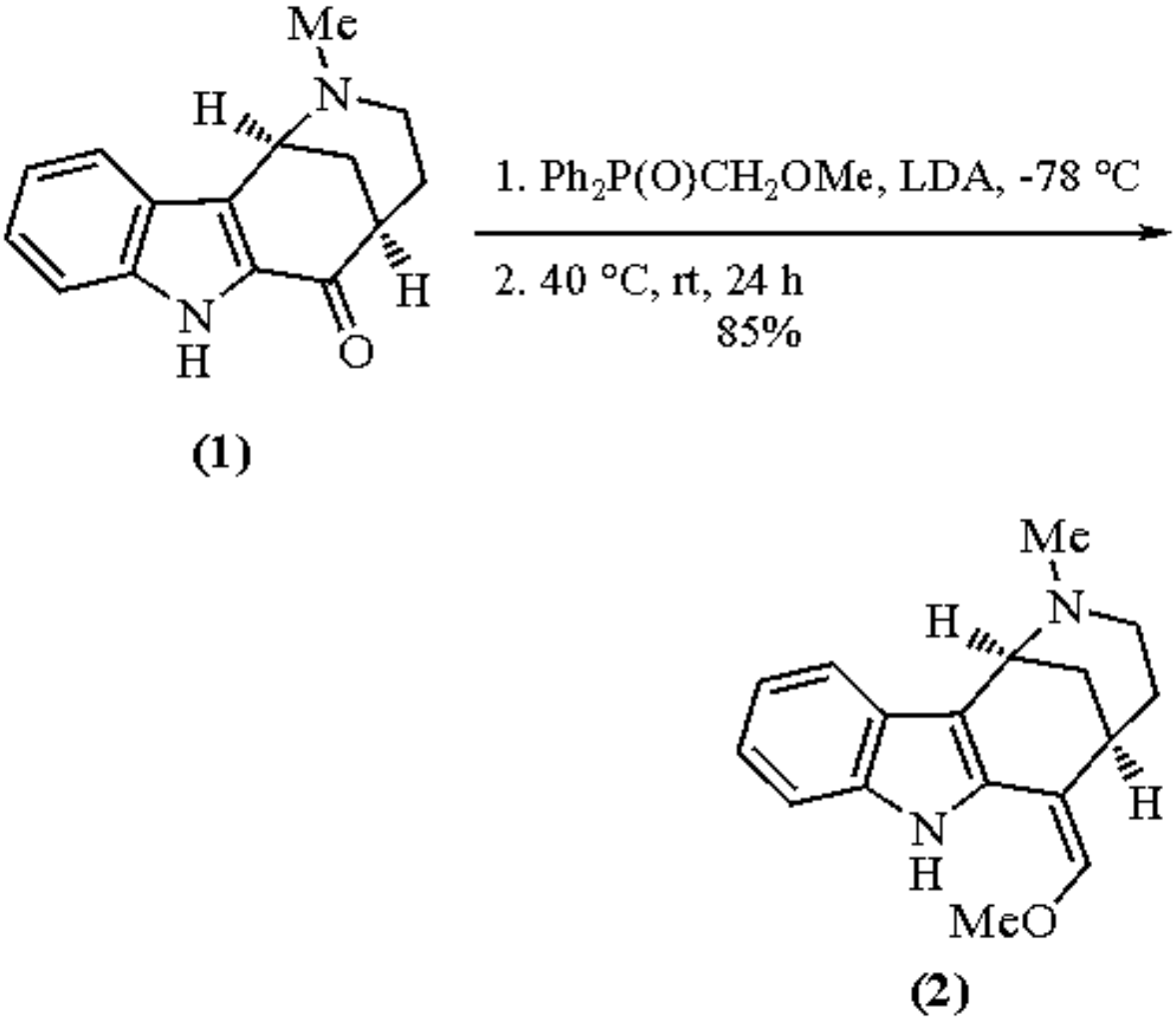

(4)

With enones, the anion undergoes 1,2-addition to afford 1-methoxy-1,3-dienes (eqs 5-7).[9,10] The phosphonium ylide, in contrast (eq 7), underwent 1,4-addition with the bicyclic ketone (**3**) to furnish the fused methoxycyclopropane (**4**).[11]

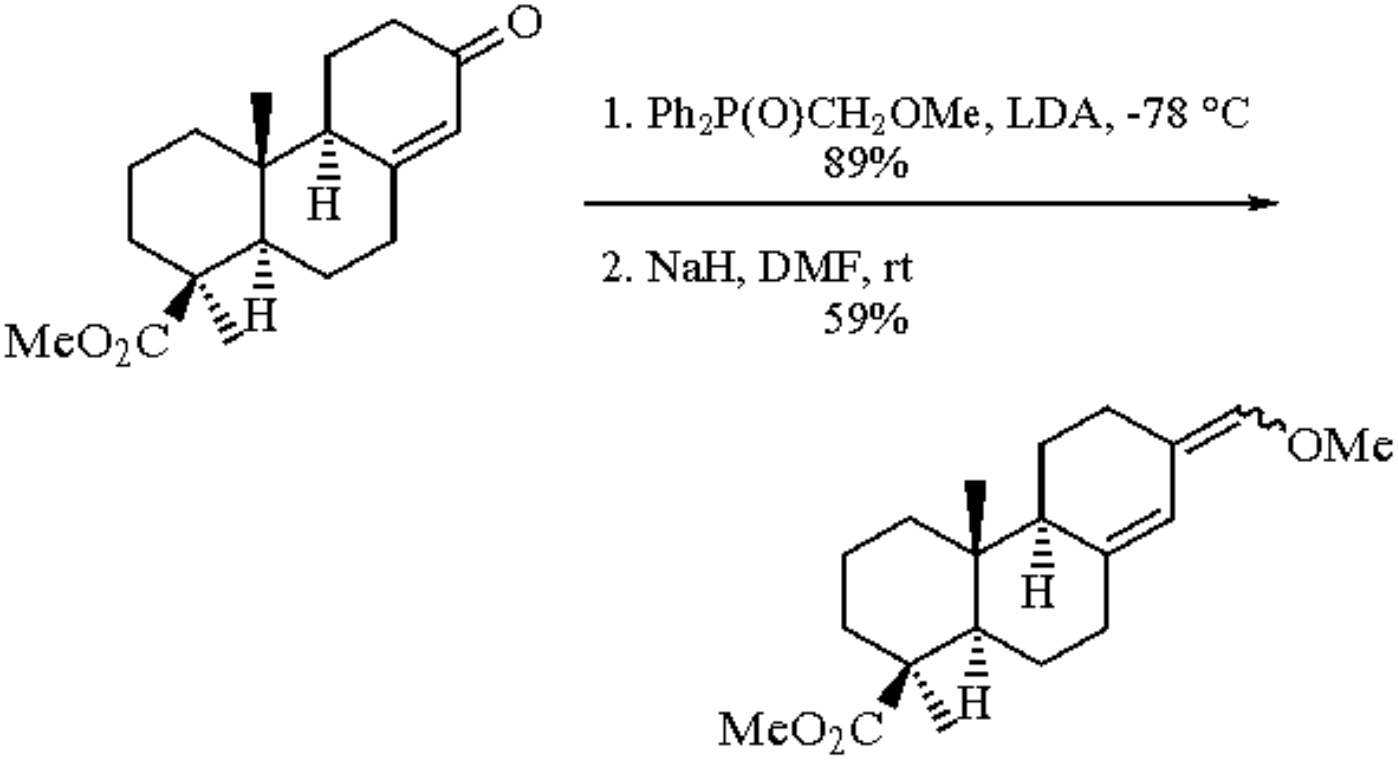
O
H
H
MeO2C
1. Ph2P(O)CH2OMe, LDA, -78 °C
89%
2. NaH, DMF, rt
59%
OMe
H
H
MeO2C

(5)

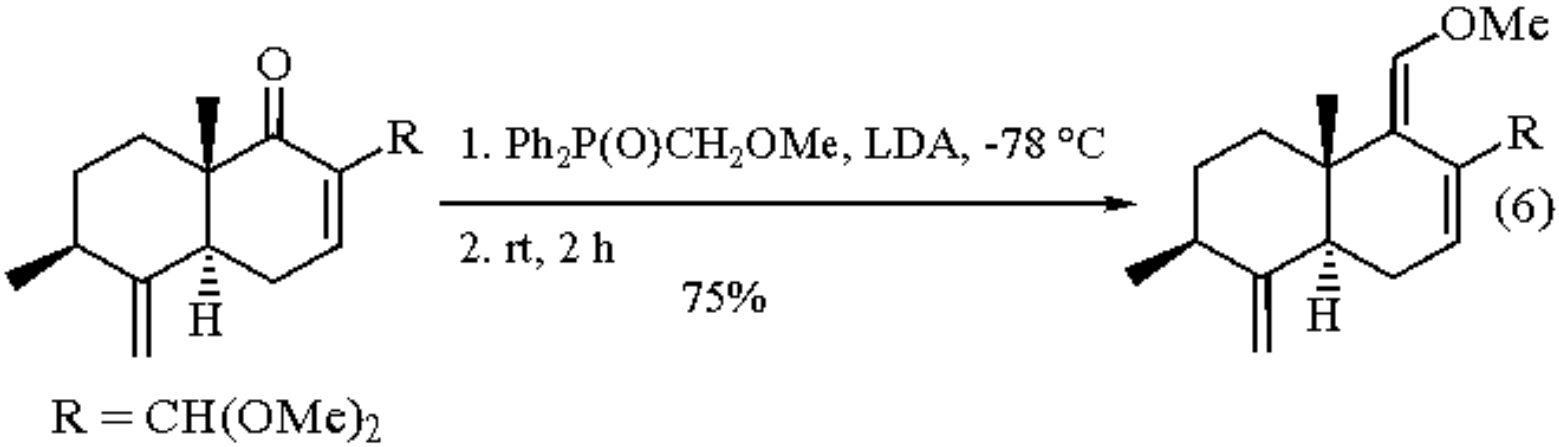
O
R
H
1. Ph2P(O)CH2OMe, LDA, -78 °C
2. rt, 2 h
75%
OMe
R
H
R = CH(OMe)2

(6)

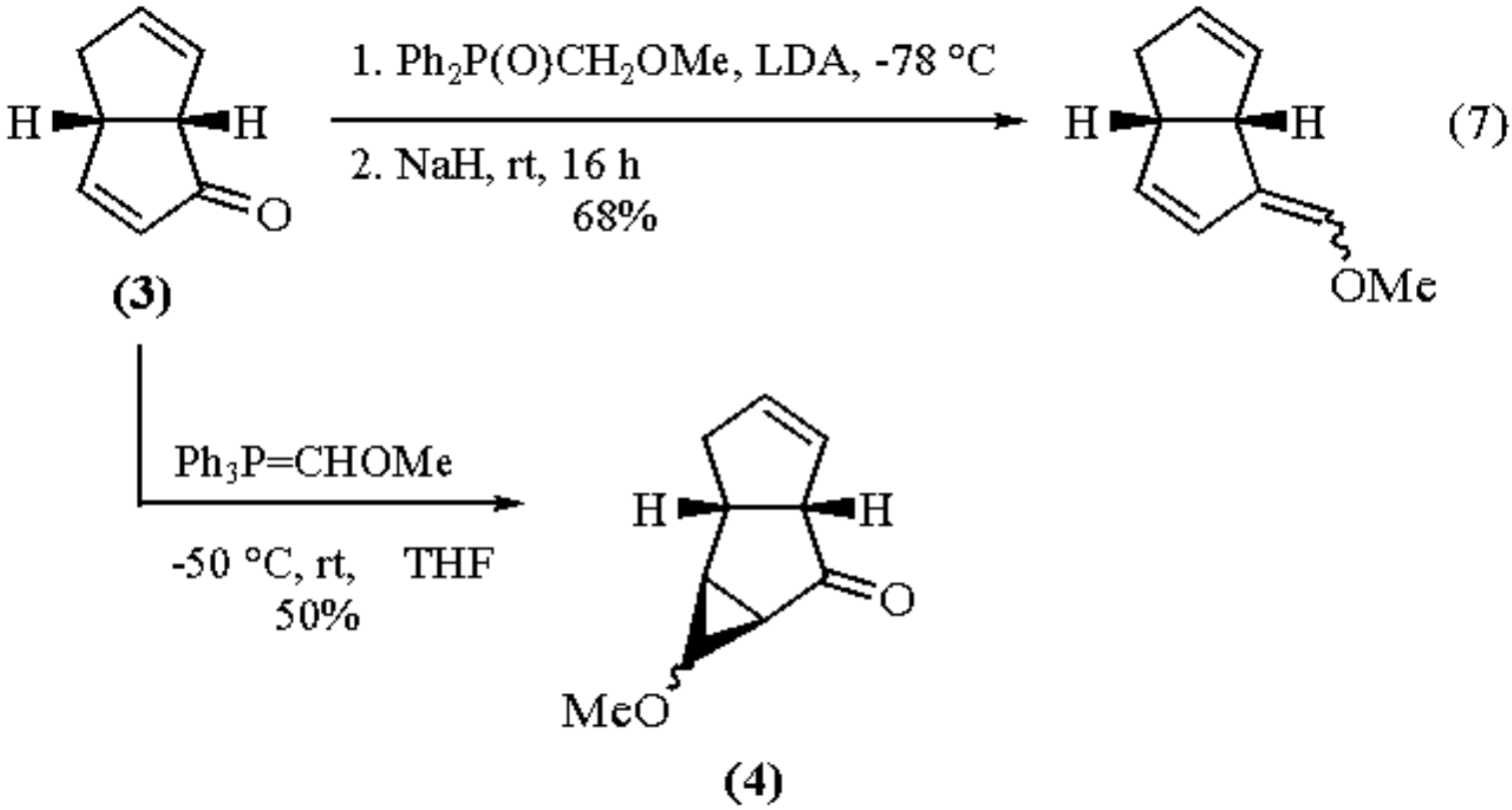

Isolation of a single β-hydroxyphosphine oxide is exemplified in eq 8.[12] The (*RS*,*SR*) adduct (**5**), which crystallized preferentially, was required to prepare (*E*,*E*)-1-methoxy-4-trimethylsilyl-1,3-butadiene, a Diels-Alder substrate.

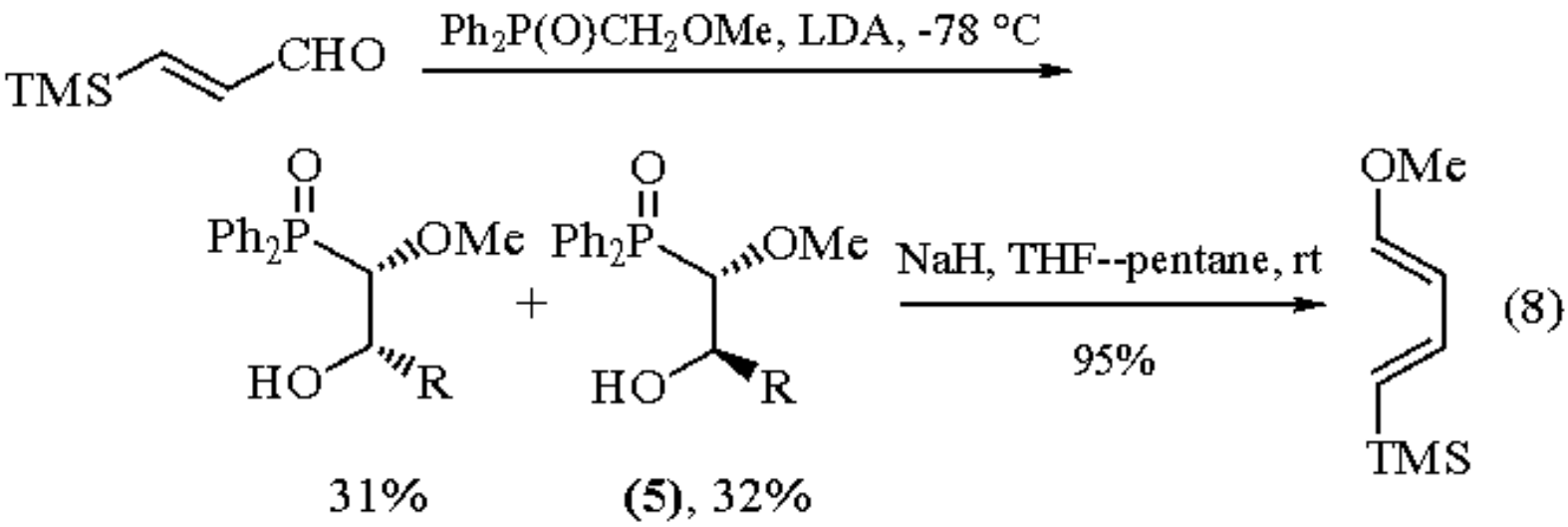

Lactones[13] also react with the phosphonate anion, thus providing an alternative stratagem to obtain vinyl ether (**6**) (eq 9).

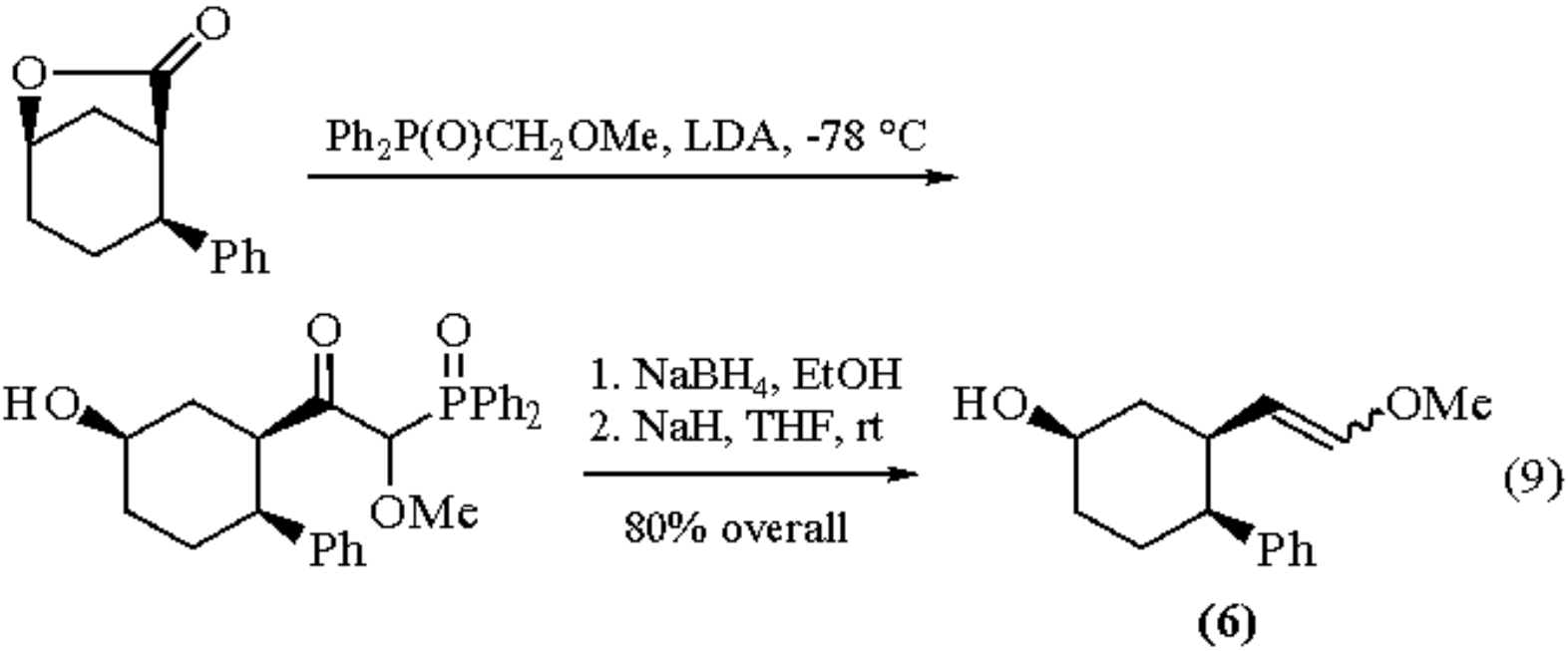

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3-(Methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene[1]

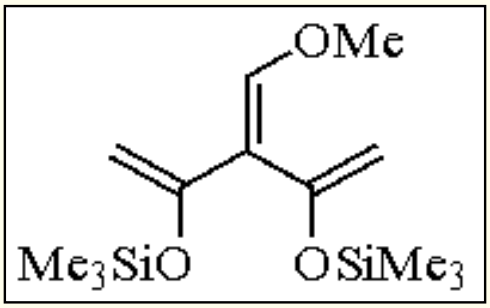

[90330-49-7] · $C_{13}H_{26}O_3Si_2$ · 3-(Methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene · (MW 286.57)

(a reagent for reiterative Diels-Alder reactions[1])

Physical Data: colorless liquid; bp 72 °C/1.8 mmHg;[3a] IR, ^{1}H NMR, ^{13}C NMR, and MS spectra.[3a]

Solubility: very sol most organic solvents; decomposition occurs in protic solvents.

Preparative Method: by the bissilylation of 3-(methoxymethylene)-2,4-pentanedione[2] using ***Chlorotrimethylsilane***, dry ***Zinc Chloride***, and ***Triethylamine***.[3]

Purification: vacuum distillation.

Handling, Storage, and Precautions: stored safely for a few weeks in a refrigerator under nitrogen atmosphere; hydrolytic conditions should be avoided for reactions and handling.

General Considerations.

3-(Methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene (**1**) is a reactive cross-conjugated triene and can be effectively utilized in sequential Diels-Alder reactions, which are called diene-transmissive Diels-Alder reactions,[1] producing a variety of hydrobenzene and -naphthalene ring systems bearing many functional groups.

Phenol Synthesis.

3-(Methoxymethylene)-2,4-bis(trimethylsilyloxy)-1,4-pentadiene (**1**) smoothly reacts, at rt, with alkynes activated by

electron-withdrawing substituents. The 1:1 cycloadducts with unsymmetrical dienophiles are formed with high regioselectivity, and they undergo spontaneous elimination of methyl trimethylsilyl ether to give *o*-hydroxyacetophenone derivatives in moderate yields (eq 1).[3a]

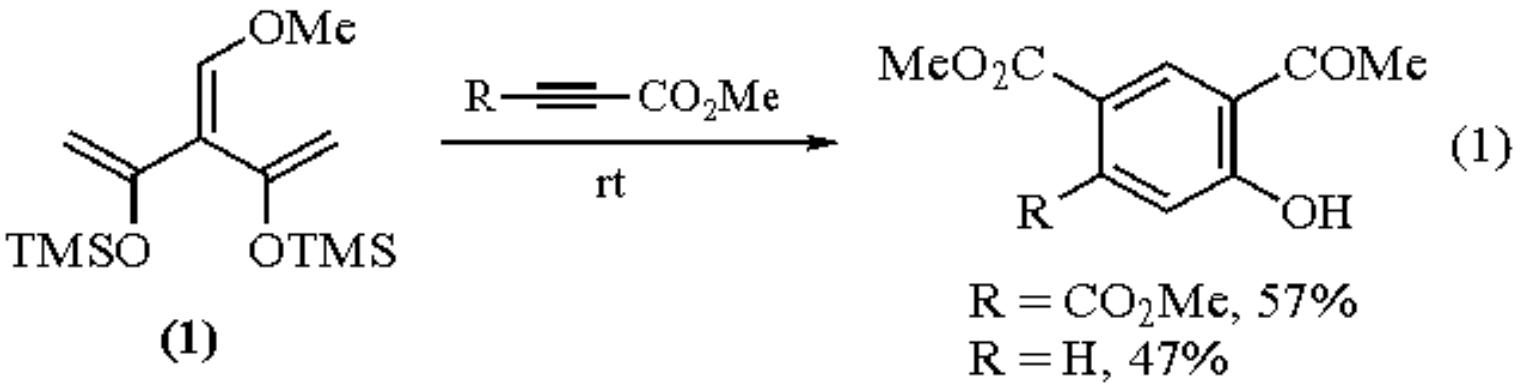

Cyclohexenone Synthesis.

On the other hand, the reactions of (**1**) with electron-deficient alkenes require heating under reflux in benzene to produce either 3-cyclohexen-1-ones (the 1:1 cycloadducts) or tetrahydronaphthalen-1-ones (the 1:2 cycloadducts), depending upon the molar amounts of the dienophiles used or the reaction temperatures applied (eq 2).[3] When unsymmetrically substituted alkenes are employed (2 equiv), both the initial and second stages of the ring-forming processes are exclusively regioselective.[4]

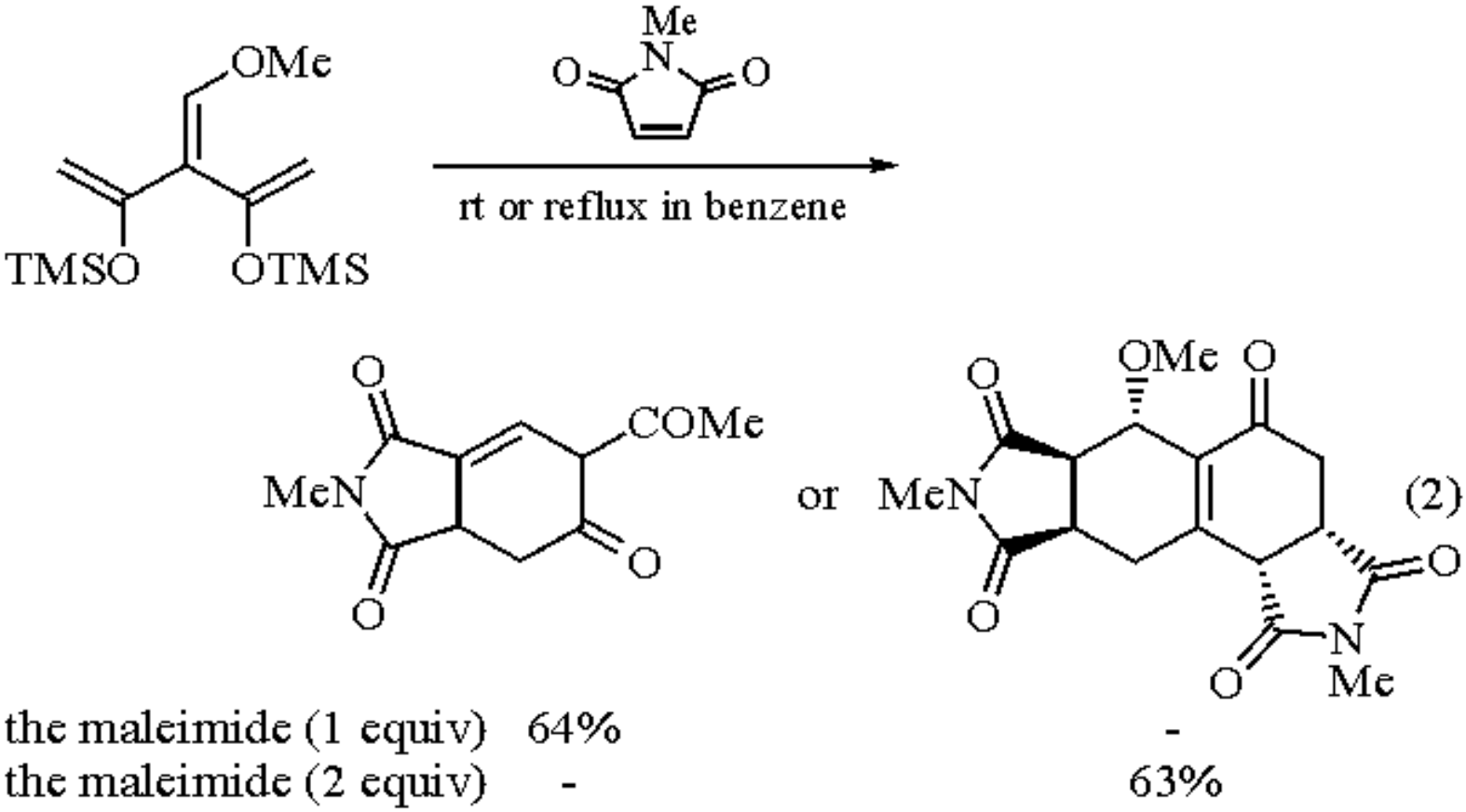

Fused Phenol Synthesis.

Diels-Alder reactions of (**1**) with alkene dienophiles at rt form 1:1 cycloadducts selectively. A second ring-forming reaction can then be performed by using a variety of dienophiles. Especially, the cross reactions with alkynic dienophiles are useful, providing a convenient entry to highly functionalized tetrahydronaphthalen-1-ol derivatives (eq 3).[5]

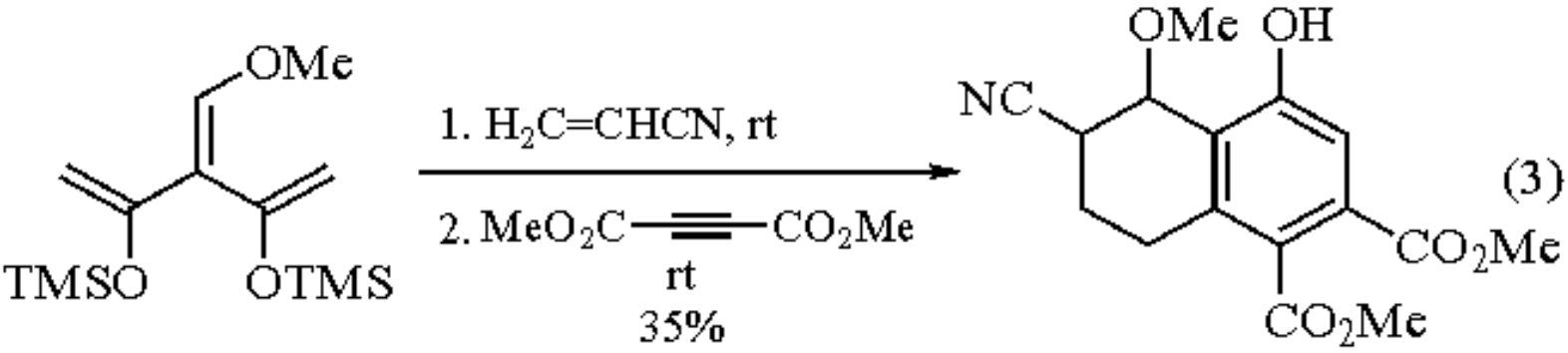

Derivatives and Synthetic Equivalents.

Cross-conjugated trienes (**2**) bearing various substituents at the central double bond are accessible by applications of the synthetic procedures mentioned above.[6]

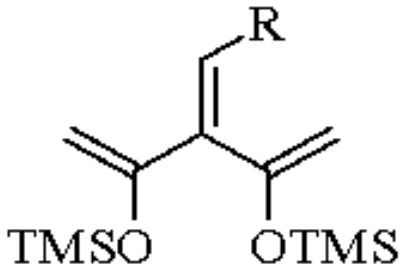

(2)

R = alkyl, alkenyl, aryl, hetaryl

Ring formation using two different dienophiles can also be performed with synthetic equivalents of cross-conjugated trienes.[7-10] The Grignard reagent of 2-chloro-1,3-butadiene (see ***1,3-Butadienyl-1-magnesium Chloride***) reacts with ketones to produce diene alcohols which serve as a versatile synthetic equivalent of cross-conjugated trienes.[7,8] A typical sequence of reactions involves initial Diels-Alder reaction of 1-(1-methylene-2-propenyl)-1-cyclopentanol with ***Dimethyl Acetylenedicarboxylate*** (DMAD), dehydration of the resulting 1,4-hexadiene with molecular sieves 5A, and a second Diels-Alder reaction with DMAD to give dihydrobenz[*e*]indenetetracarboxylate after dehydrogenative aromatization with ***Chloranil*** (eq 4).[8]

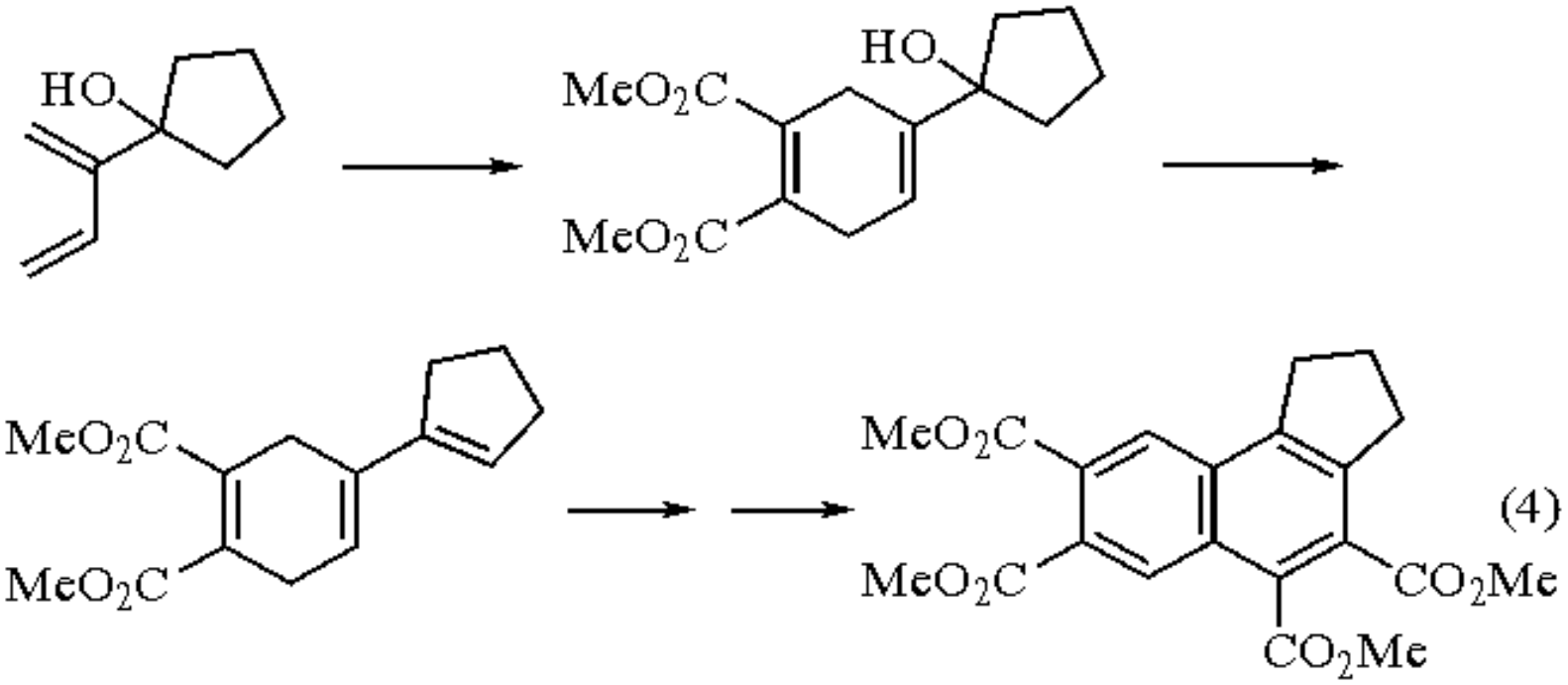

Related Reagents.

1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene; ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***; ***2-Trimethylsilyloxy-1,3-butadiene***.

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Methoxymethylenetriphenylphosphorane

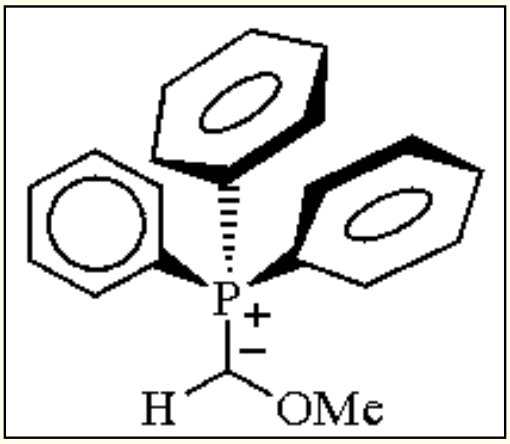

[20763-19-3] · $C_{20}H_{19}OP$ · Methoxymethylenetriphenylphosphorane · (MW 306.36)

(Wittig reagent for carbonyl homologation; vinyl ether synthesis[1-8])

Physical Data: deep red in solution; unstable at 25 °C.[1-3]

Solubility: sol organic solvents; decomposes in protic solvents, aldehydes, and ketones.[1]

Analysis of Reagent Purity: unstable at 25 °C, decomposing completely in <24 h producing PPh_3 (70%; ^{31}P NMR δ -5.1 ppm) and other unidentified species.[2] The ylide gives a ^{31}P NMR signal at δ 7.9 ppm (-90 °C) which is shifted upfield to 5.8 ppm ($^2J_{P\text{-}H}$ = 48 Hz; $^3J_{P\text{-}H}$ = 12 Hz) at ambient temperatures.

Preparative Methods: by the deprotonation of methoxymethyl(triphenyl)phosphonium chloride (from ***Triphenylphosphine*/*Chloromethyl Methyl Ether***)[4a,b] with a number of bases (alkyllithiums, alkoxides, dimsylsodium, amides).[4-8]

Handling, Storage, and Precautions: should be generated in situ at low temperature (e.g. -90 °C) under a nitrogen atmosphere and used immediately.

Vinyl Ether Homologs from Carbonyl Compounds.

The Wittig alkenation of carbonyl compounds has evolved to occupy a preeminent position in the hierarchy of carbon-carbon bond-forming reactions.[1] With α-alkoxy substitution, Wittig reagents convert carbonyl derivatives into their vinyl ether homologs, and methoxymethyltriphenylphosphorane (**1**) has enjoyed widespread use in this regard since its generation in 1958 by Levine (eq 1).[4a] In a more extensive study of α-substituted Wittig reagents (e.g. Ph_3PCHX, X = OH, Cl, OMe, SMe, and OAr), it was determined that ***Phenyllithium*** is superior to ***n-Butyllithium*** for the

deprotonation of the phosphonium salt and that X = OC_6H_4Me-*p* gives better yields of vinyl ether products than (**1**) in several cases.[4b,c] Moreover, the thermal instability of (**1**) has resulted in the reagent being commonly used in stoichiometric excess (2-4 equiv).[2-8]

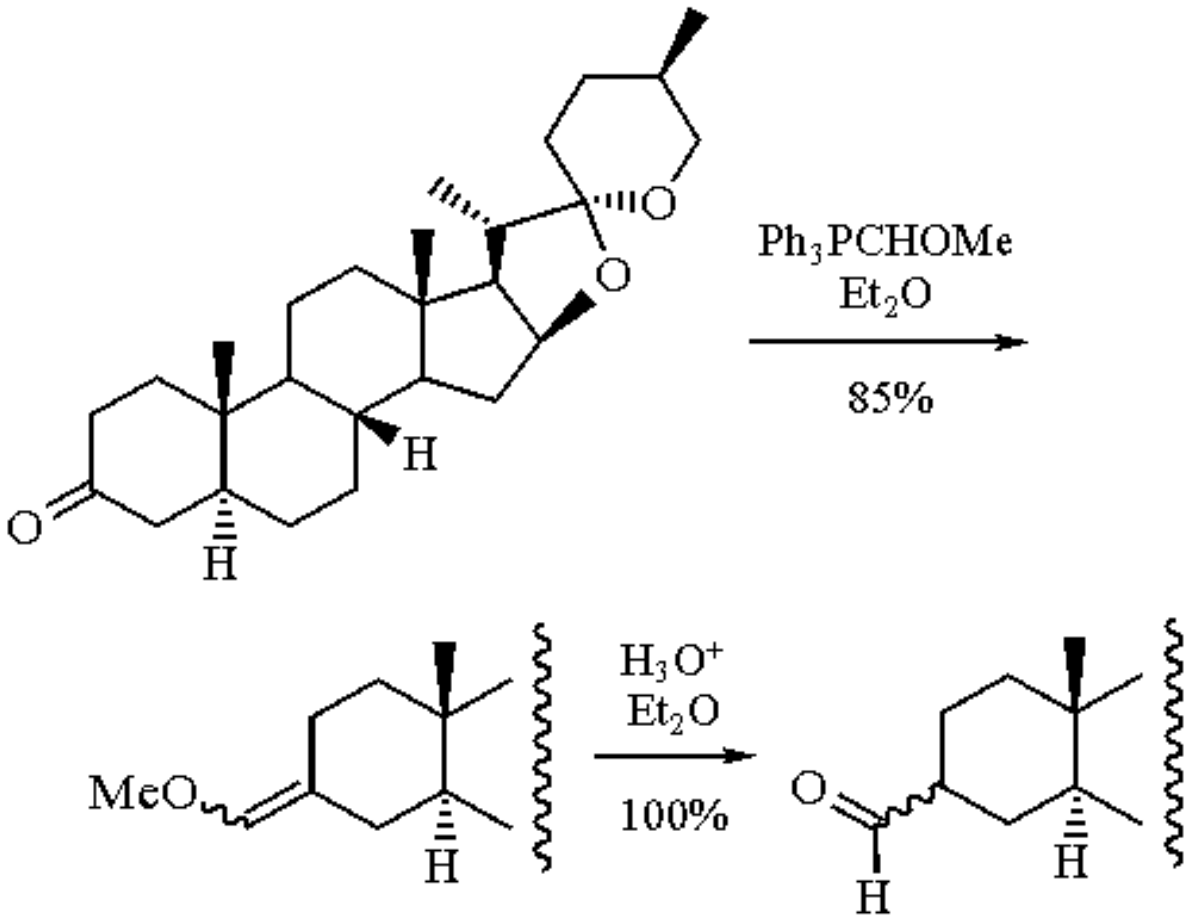

While butylidene products have been observed on numerous occasions when *n*-BuLi has been used to generate (**1**),[4b,o,s] this base continues to be used for its preparation. Recently, it was discovered that *n*-BuLi, but not ***t-Butyllithium***, displaces PhLi from $(Ph_3PCH_2OMe)Cl$, ultimately producing $Ph_2(MeOCH_2)PCHPr$, which accounts for the observed butylidene products when employing this base.[2] Therefore, either PhLi[4a,b] or *t*-BuLi[4s] is superior to *n*-BuLi for the generation of (**1**). Alternatively, amide bases (e.g. ***Lithium Diisopropylamide***),[6] alkoxides (e.g. ***Potassium t-Butoxide***)[7] and ***Sodium Methylsulfinylmethylide***[8] are effective bases for the preparation of (**1**). As an example, (**1**) prepared from the *t*-BuKO method has been used for the effective conversion of conjugated enones to 1,3-dienyl ethers which function as useful Diels-Alder substrates (eq 2).[7d]

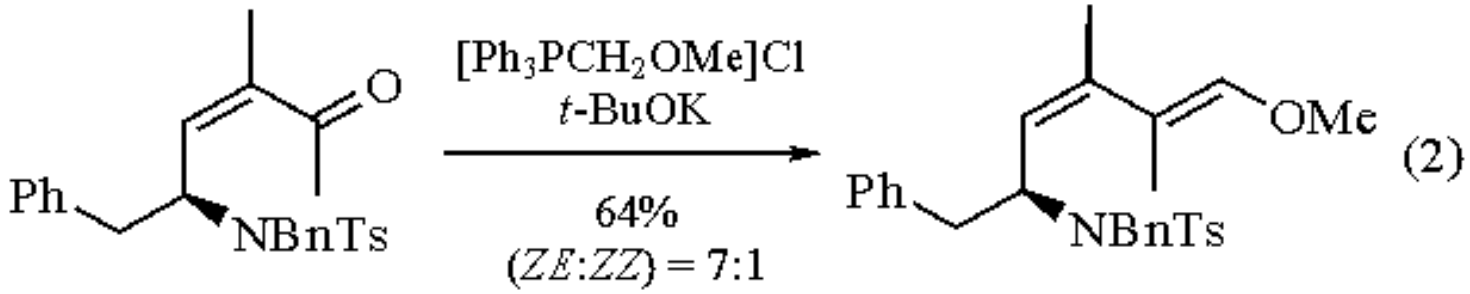

Insufficient comparative data exist for a definitive judgement on the best method to generate (**1**). However, the fact

that (**1**) decomposes at 25 °C suggests that its generation and reaction with carbonyl substrates should be conducted at low temperatures (i.e. -70 to -90 °C). A survey of representative procedures suggests that *t*-BuLi, which can be used to generate (**1**) at -90 °C, may eliminate the need for using a large excess of (**1**) because this method avoids its exposure to higher temperatures which result in its partial decomposition.[2] Moreover, even relatively hindered ketones are converted to the corresponding oxaphosphetanes at this temperature. Aliphatic carbonyl derivatives are likely to form these intermediates irreversibly, whereas their conjugated counterparts may well undergo complete or partial equilibration, ultimately giving rise to (*E*)-alkenes as the major vinyl ether products.[1a] With slow warming to 25 °C, the decomposition of the intermediate oxaphosphetane produces the corresponding vinyl ether very cleanly, at least in the systems examined (eq 3).[2] The excellent yields which have been achieved for many substrates add support to this generality.

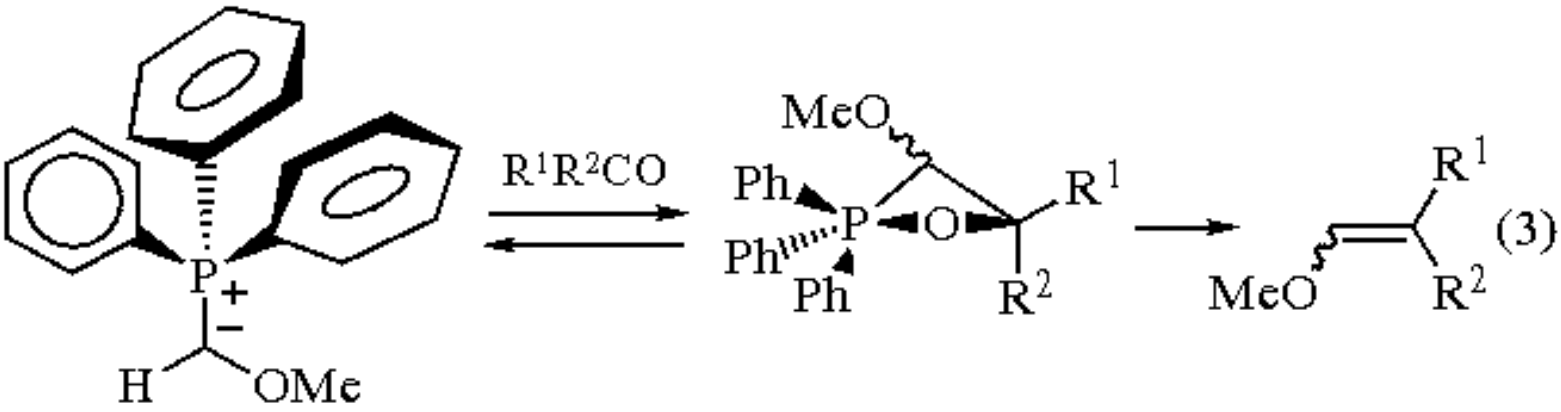

Both aldehydes and ketones undergo reaction with (**1**), leading to vinyl ethers. While the product stereochemistry is not always reported, sufficient data are currently available for representative systems to indicate that unsymmetrical carbonyl compounds normally lead to (*Z*/*E*) product mixtures under Li^+-catalyzed conditions. A recent study employing the Levine-Wittig-Schlosser method (PhLi, Et_2O) provides useful stereochemical information for aromatic aldehydes which give roughly equal amounts of both *cis* and *trans* vinyl ethers under these conditions (e.g. PhCHO, 40:60; *p*-$MeOC_6H_4CHO$, 54:46; *o*-$CF_3C_6H_4CHO$, 45:55).[5g] With aliphatic derivatives, as mentioned above, kinetic control is operative and the process is more (*Z*) selective, as can be observed below for octanal[5g] and pentanoyltrimethylsilane[2] where the silyl group reverses the stereochemical relationship of the alkyl group with respect to the methoxy group in the vinyl ether products (**2**) and (**3**).

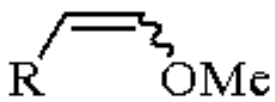

(2)
R = C_7H_{15} (54:46)

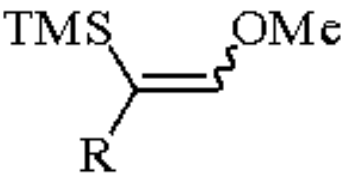

(3)
R = Bu (79:21)

Numerous synthetic applications have been found for (**1**) and several representative examples are shown in (**4**)-(**7**), which include the base and solvent employed for the generation of (**1**) as well as the yield and isomeric (*Z*/*E*) distribution of the vinyl ether products derived from their carbonyl precursors.[4d,4s,7c,7e]

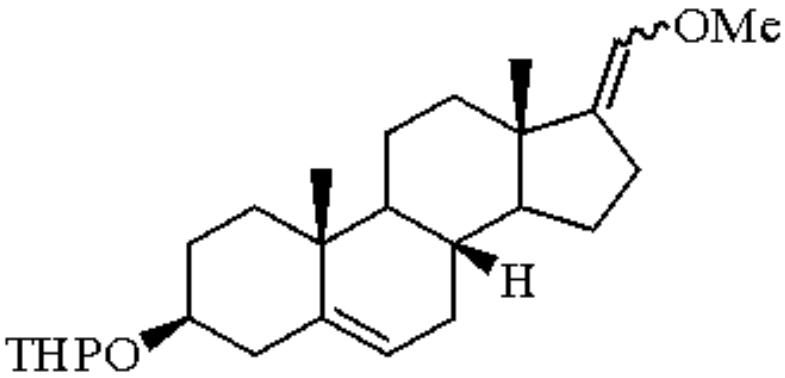

(4)
$KOCMe_2Et$, PhMe
100% (1:4)

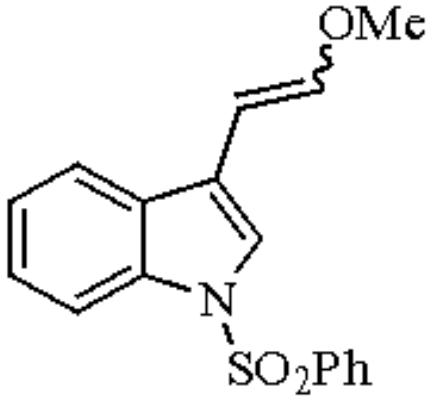

(5)
BuLi, THF
80% (1:3)

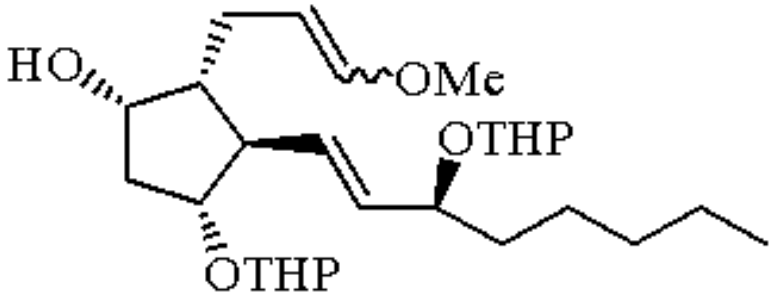

(6)
t-BuOK, THF
87% (1:2)

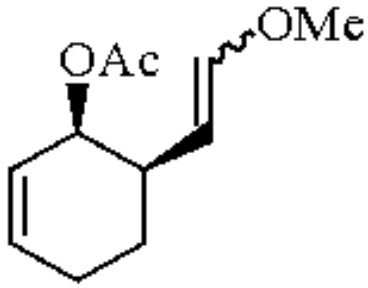

(7)
t-BuLi, THF
88% (2:3)

It can be noted from the above that the (*E*) isomer is isolated as the major product in each case, a result which may be attributable to oxaphosphetane equilibration either through its formation (i.e. highly conjugated systems) or through the participation of proximate functionality (e.g. alkoxy).[1a] In certain cases, these substrate features can result in a highly (*E*)-selective process, e.g. (**8**) and (**9**).[6g]

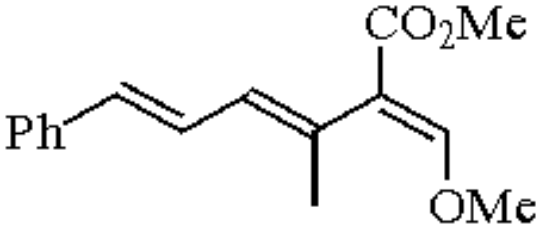

(8)

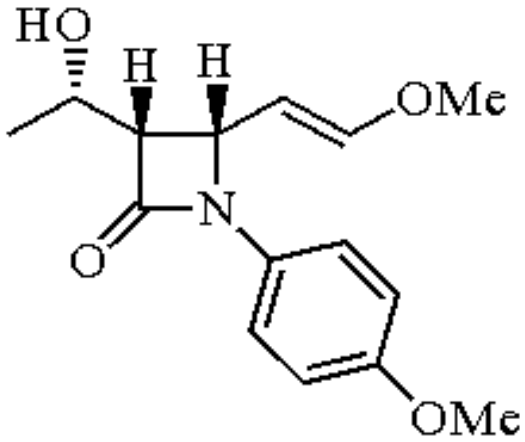

(9)

Homologation of Carbonyl Compounds.

The vast majority of the synthetic applications of (**1**) involve the homologation of carbonyl compounds. Often the intermediate vinyl ether is converted directly to the aldehyde (or acetal) which itself is a required intermediate for the total synthesis of a target molecule which can be a natural product (e.g. (+)-pleuromutilin (eq 4))[6e] or compounds of theoretical interest, such as 2a,8a,8b,8c-tetrahydropentaleno[6,1,2-*aji*]azulene (eq 5).[4p] The intermediate vinyl ethers can also be oxidized to provide α,β-unsaturated aldehydes as an important extension of the methodology (eq 6).[5i]

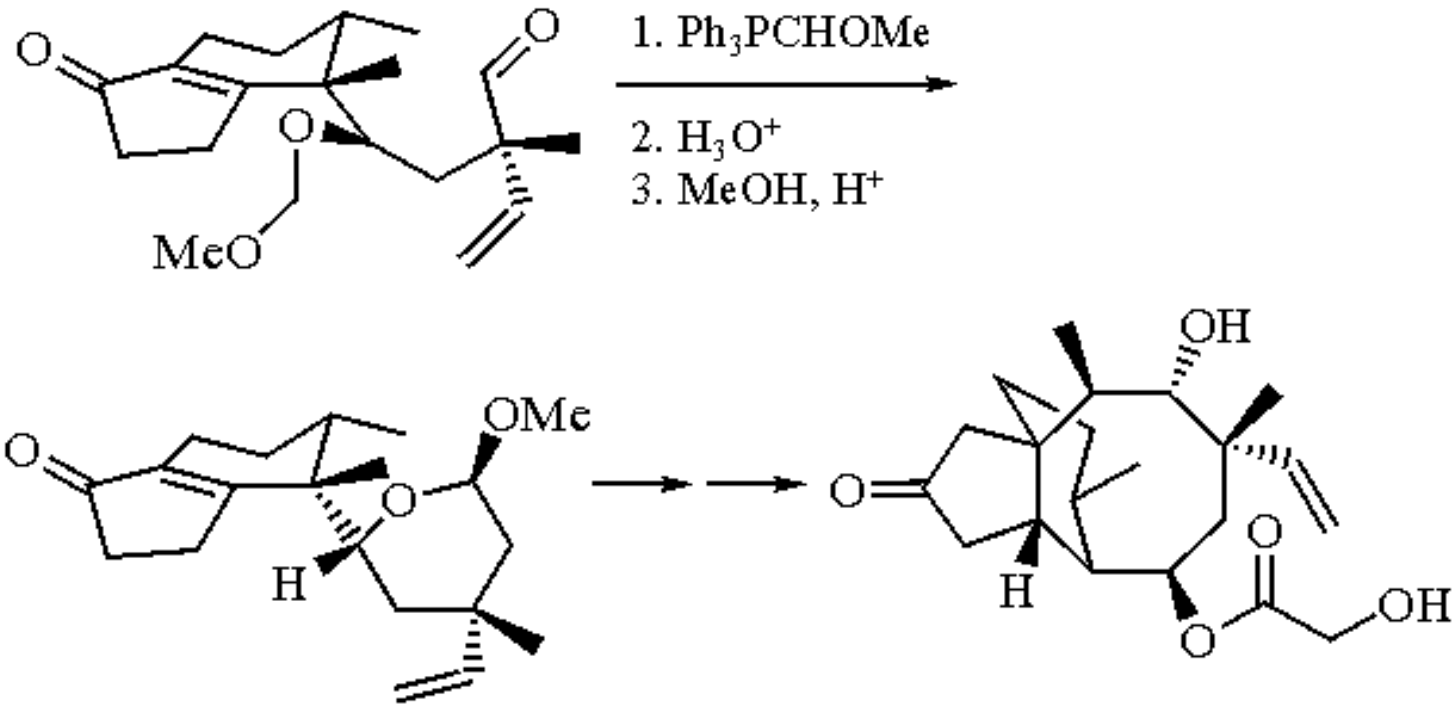

(4)

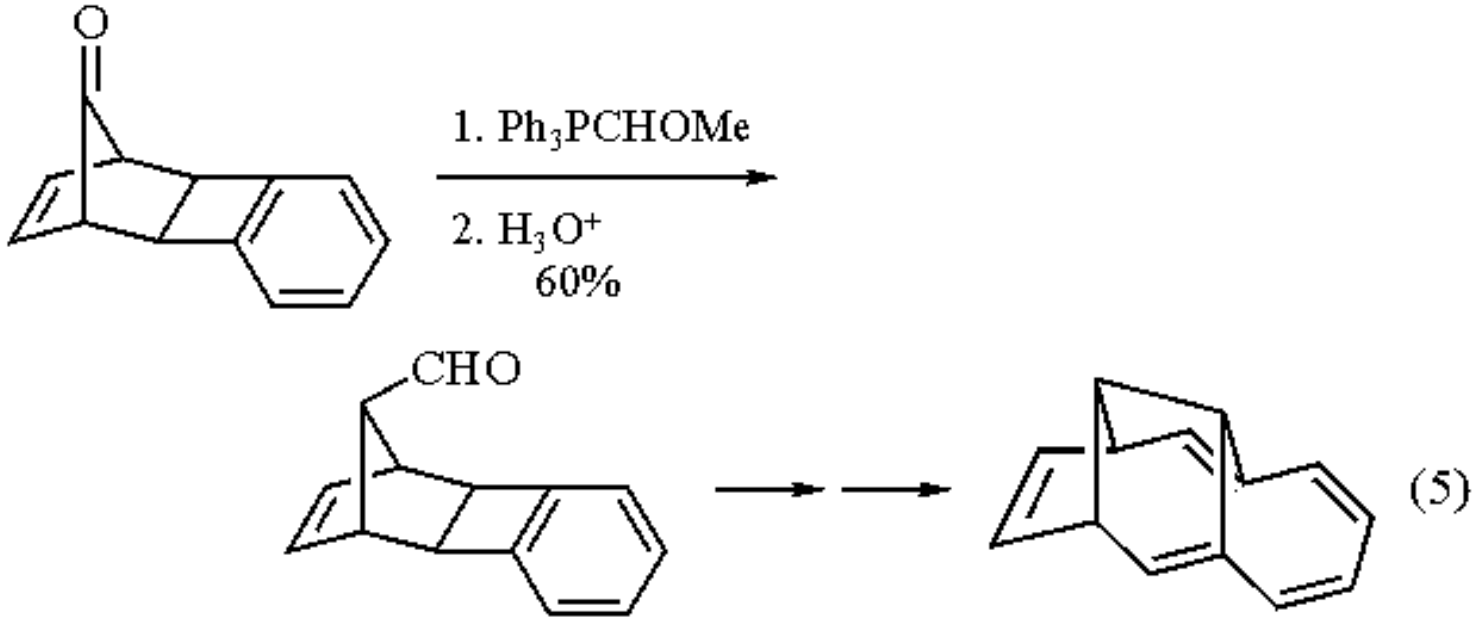

(5)

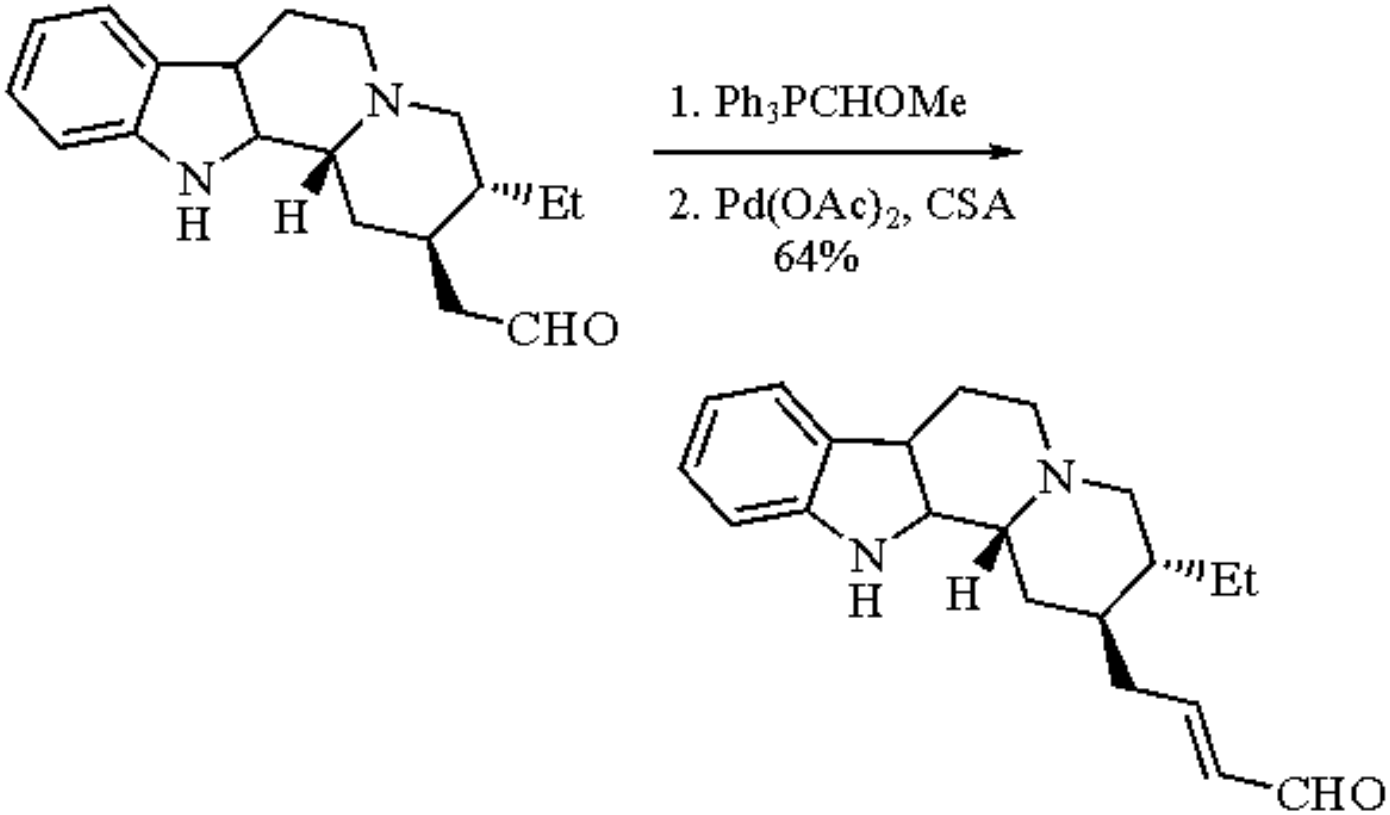

(6)

The hydrolysis of the vinyl ethers normally occurs smoothly with dilute aqueous acid at 25 °C, mild conditions which make these derivatives especially attractive precursors to the desired aldehydes, particularly in systems where the aldehyde must be generated selectively in the presence of other protected carbonyl functionalities (eq 7).[5f] For certain applications, other alkoxymethylene ylides (Ph_3PCHOR, R = $(CH_2)_2SiMe_3$,[7d] THP,[5j] or $Ph_2P(O)CHLi(OMe)$,[5k] or $Ph_2PCHLi(OMe)$)[9] provide alternative or superior choices to (**1**) for the alkenation process or other subsequent conversions. However, (**1**) is a proven reagent for the effective homologation of aldehydes, both saturated and unsaturated, as well as their ketone counterparts.

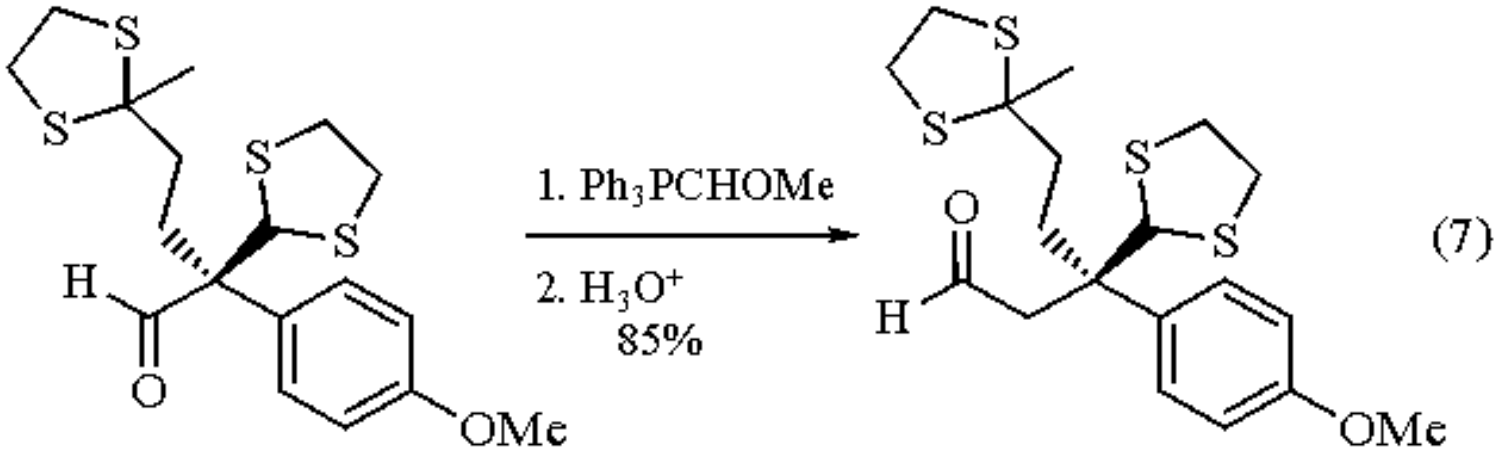

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(4*S*,5*S*)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline[1]

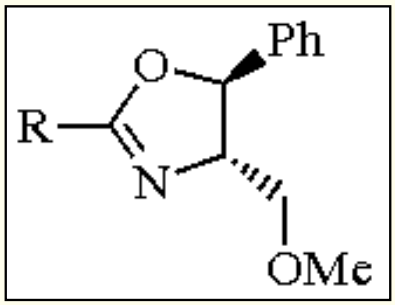

(**1**; R = Me)

[52075-14-6] · $C_{12}H_{15}NO_2$ · (4*S*,5*S*)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline · (MW 205.28) (**2**; R = Et)

[51594-37-7] · $C_{13}H_{17}NO_2$ · (4*S*,5*S*)-4-Methoxymethyl-2-ethyl-5-phenyl-2-oxazoline · (MW 219.31) (**3**; R = $ClCH_2$)

[54623-66-4] · $C_{12}H_{14}ClNO_2$ · (4*S*,5*S*)-4-Methoxymethyl-2-chloromethyl-5-phenyl-2-oxazoline · (MW 239.72)

(enantiopure carboxylic ester derivatives for synthesis of enantiomerically pure or enriched 2- and 3-substituted alkanoic acids, γ-butyrolactones, valerolactones, and benzovalerolactones by α-lithiation and asymmetric alkylations)

Physical Data: (**1**): bp 85-87 °C/0.20 mmHg; [α]$CHCl_3$D -118°. (**2**): bp 91-93 °C/0.25 mmHg; [α]$CHCl_3$D -84.2°. (**3**): [α]$CHCl_3$D -84.1°.

Preparative Methods: (**1**) and (**2**): cyclocondensation of commercially available (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol with the appropriate orthoester, followed by methylation of the free hydroxy group (eq 1).[2a]

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline

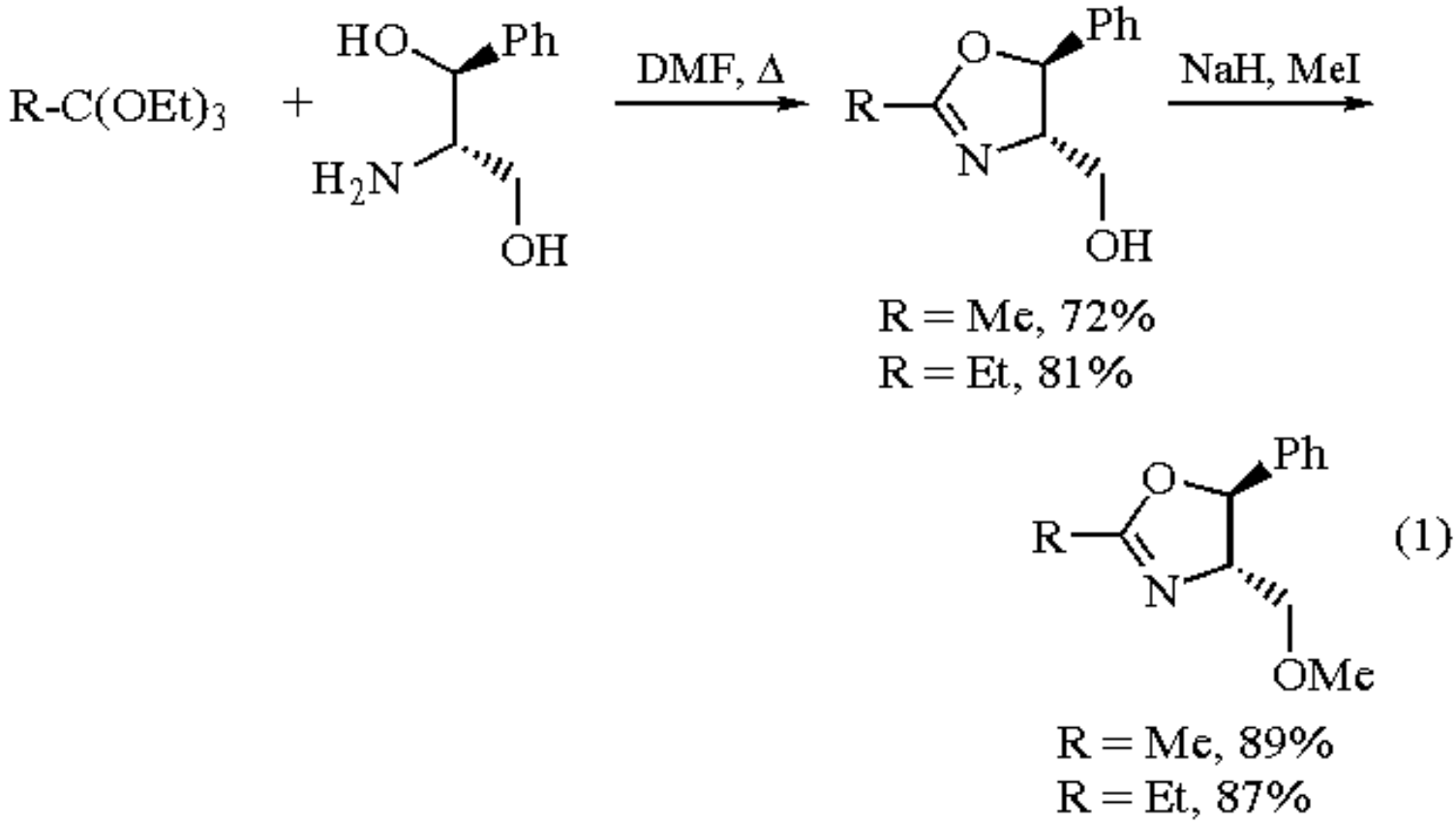

Handling, Storage, and Precautions: no special precautions.

Asymmetric Alkylations.

The asymmetric synthesis of 2-alkanoic acids can be accomplished be treatment of the lithio salt of the 2-ethyl-2-oxazoline with alkyl halides followed by acidic hydrolysis of the oxazoline (eq 2).[2]

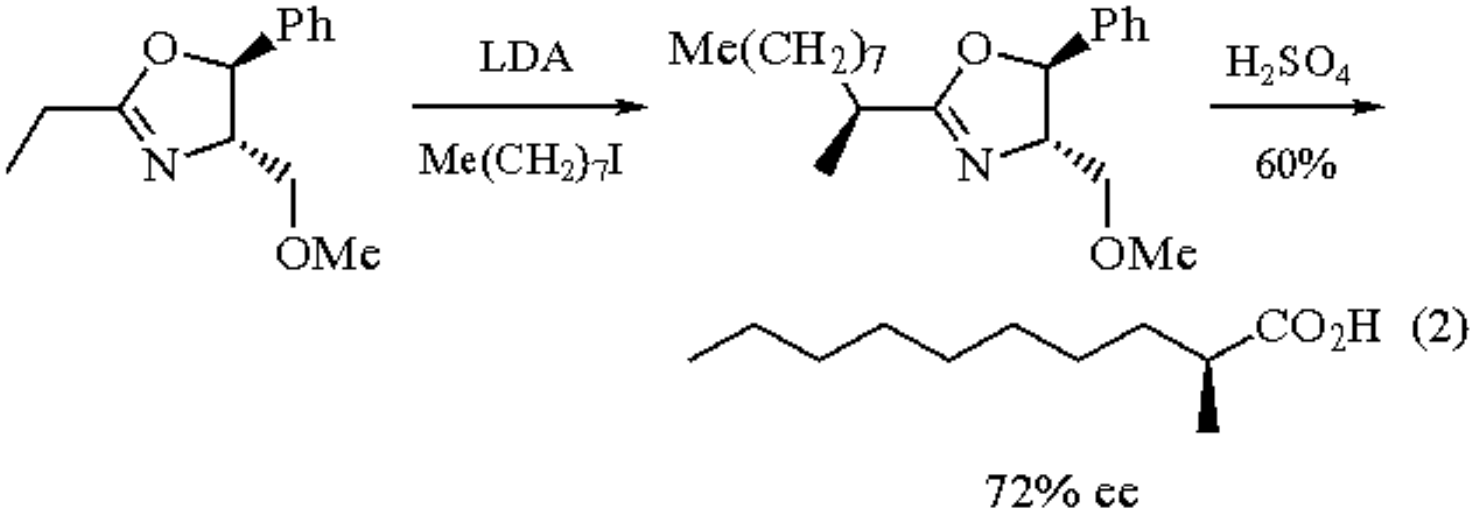

Alkylation of the 2-methyl-2-oxazoline (base/electrophile) results in homologated 2-oxazolines. A second alkylation sequence proceeds with asymmetric induction and results in the formation of highly substituted chiral 2-alkyl alkanoic

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline

acids. Use of ethylene oxide as the electrophile in this process allows for the formation of chiral α-substituted γ-butyrolactones and α-substituted γ-valerolactones with good stereoselectivity (60-80% ee; eq 3).[3]

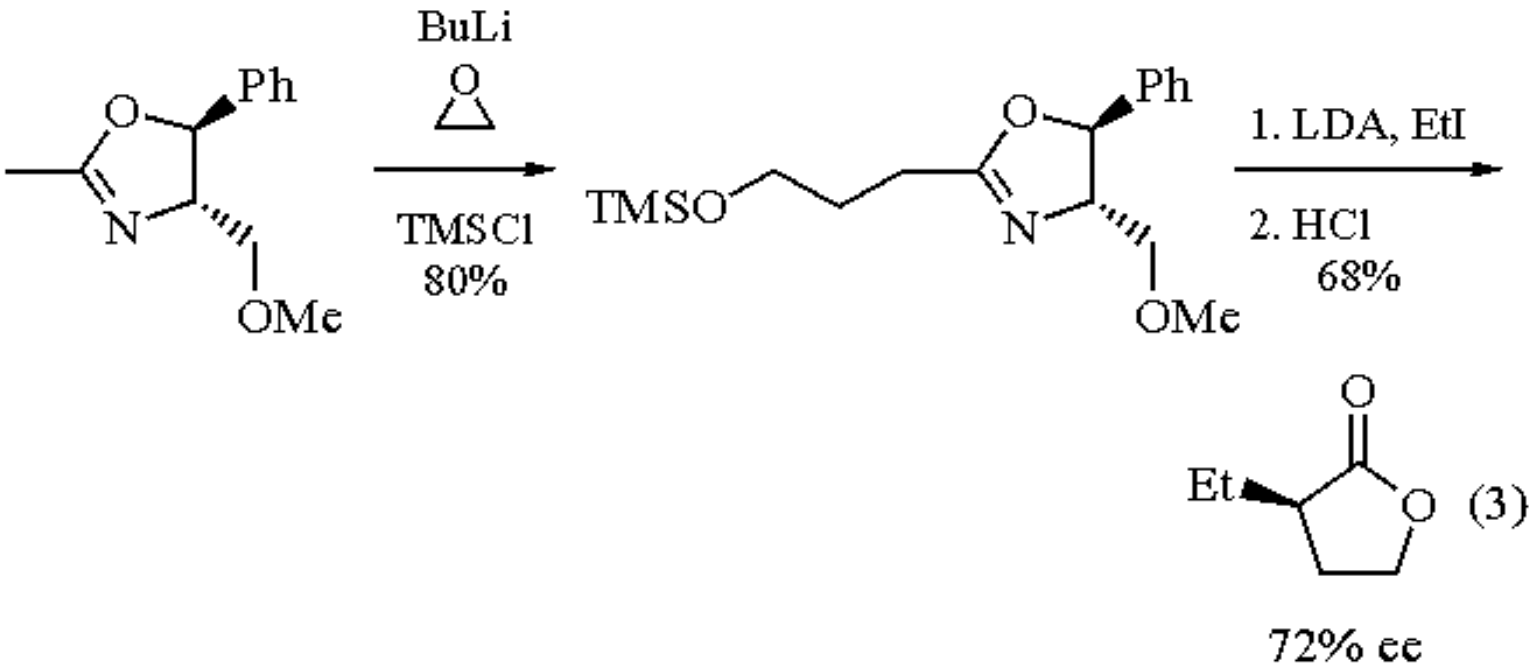

Conjugate Additions to 2-Vinyloxazolines.

The 2-methyl-2-oxazoline can be converted into a phosphonate for Horner-Emmons alkenations. A variety of (*E*)-alkenes containing the chiral oxazoline auxiliary (α,β-unsaturated oxazolines) can be synthesized in high yields (80-93%) as the sole geometric isomer (eq 4).[4] Conjugate addition of alkyllithium reagents to these Michael acceptors affords, after oxazoline hydrolysis, the 3-substituted alkanoic acids (or corresponding alcohol) with a high level of stereoselectivity (91-99% ee; eq 4).[4]

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline

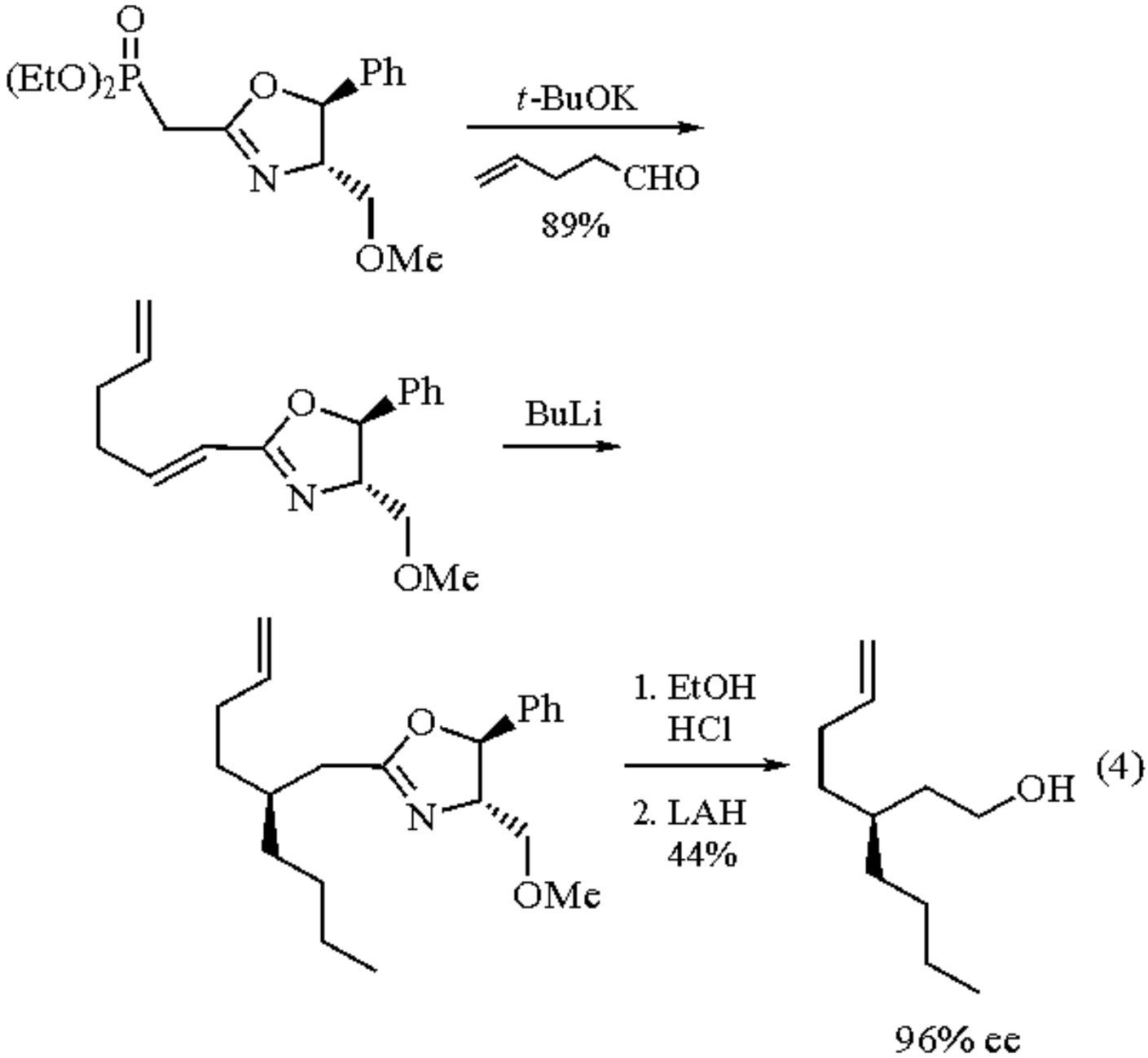

Use of appropriately substituted chiral α,β-unsaturated oxazolines allows access to 3-substituted δ-valerolactones and 4-substituted 2-chromanones with high stereoselectivity (95-98%; eq 5).[4a-c]

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline

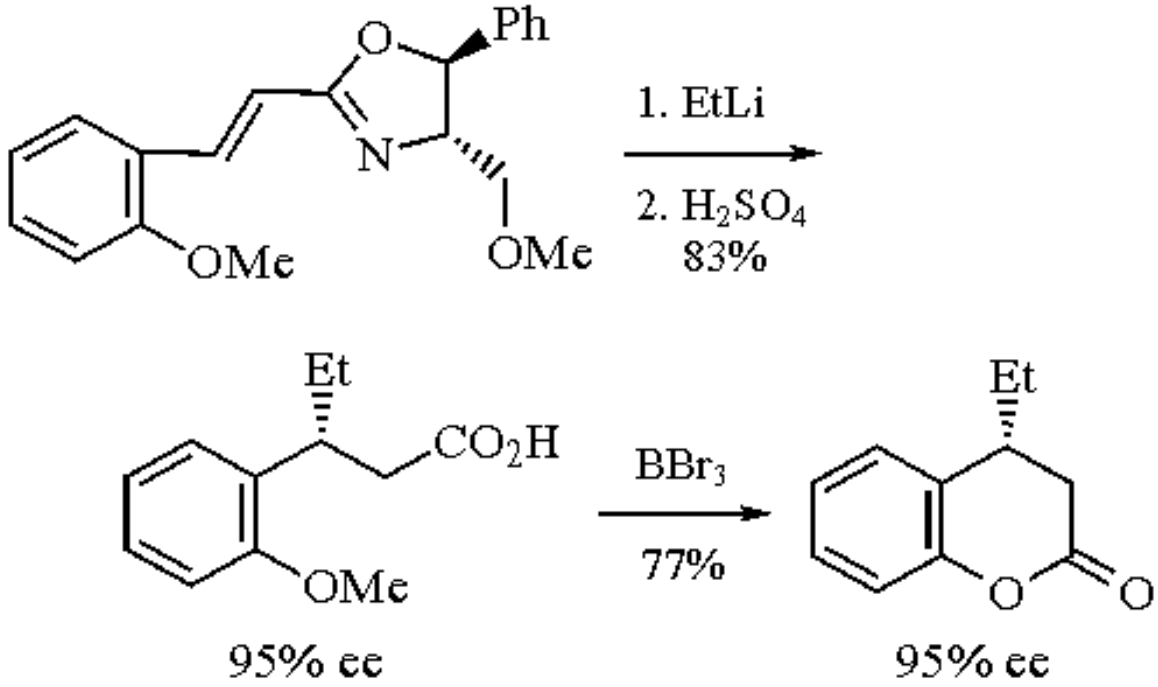

(5)

Asymmetric Aldol Additions.

2-Ethyl-2-oxazoline takes part in aldol condensations as its boron azaenolate. The *erythro* selectivity for this protocol is excellent (95:5 to 98:2) but the enantioselectivity is only moderate (29-71% ee; eq 6).[5]

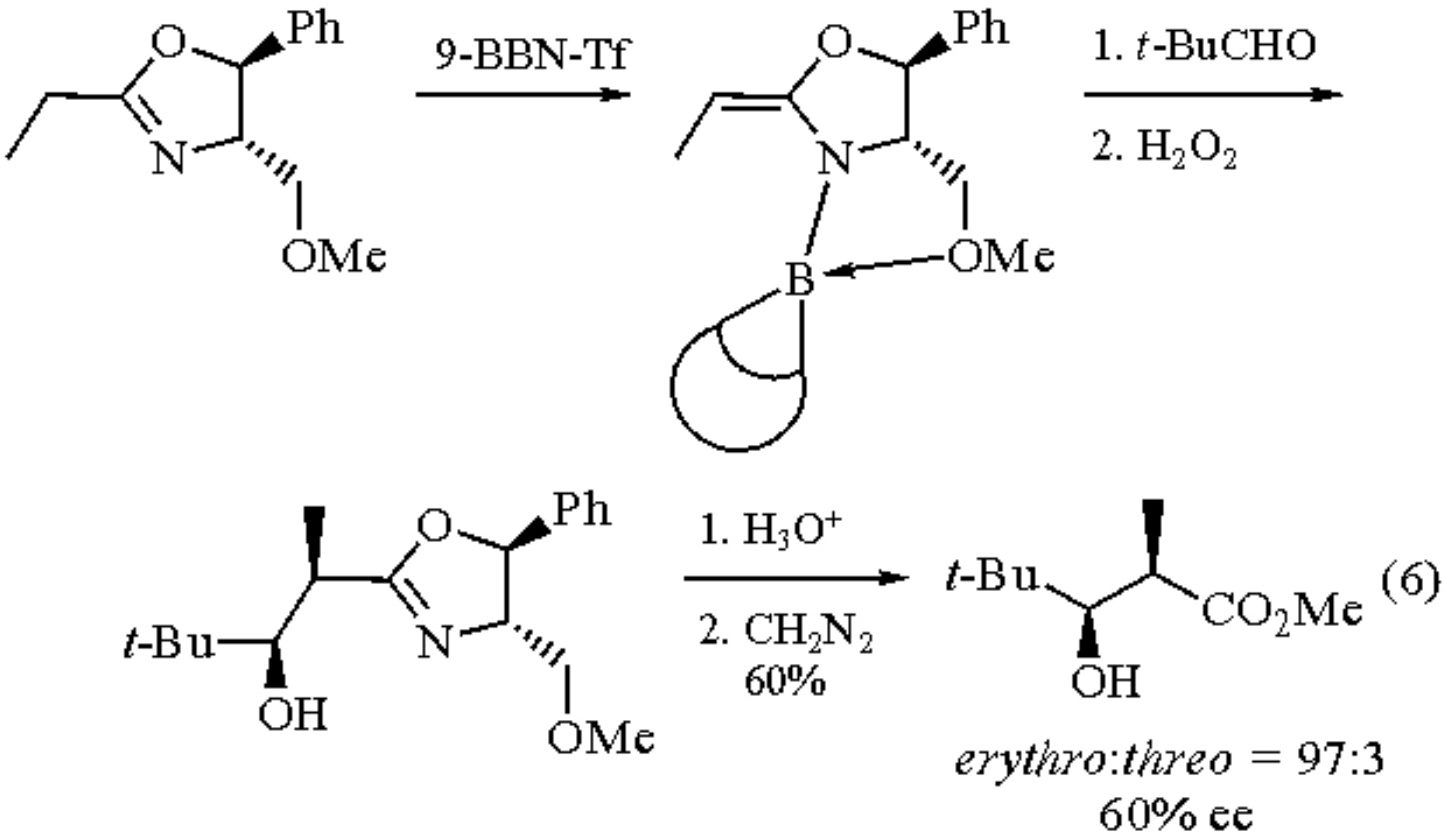

(6)

Enantioenriched α-Chloro Carboxylic Acids.

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline

Reaction of (1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol with the ethyl imidate of chloroacetonitrile gives (-)-2-chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline (eq 7).[6]

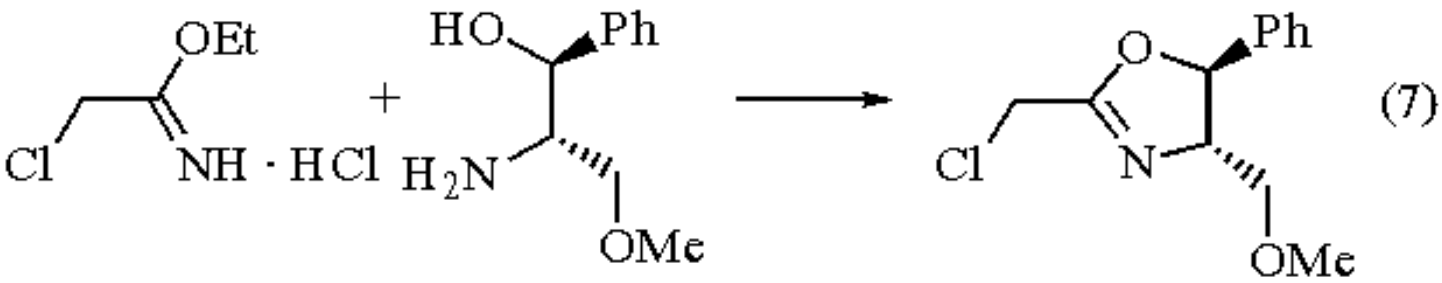

Alkylation of this oxazoline is accomplished by metalation with ***Lithium Diisopropylamide*** followed by adding a premixed solution of the electrophile and 2 equiv of HMPA (eq 8). Hydrolysis of the oxazoline moiety affords the enantioenriched 2-chloroalkanoic acids, albeit with low optical purity.[6]

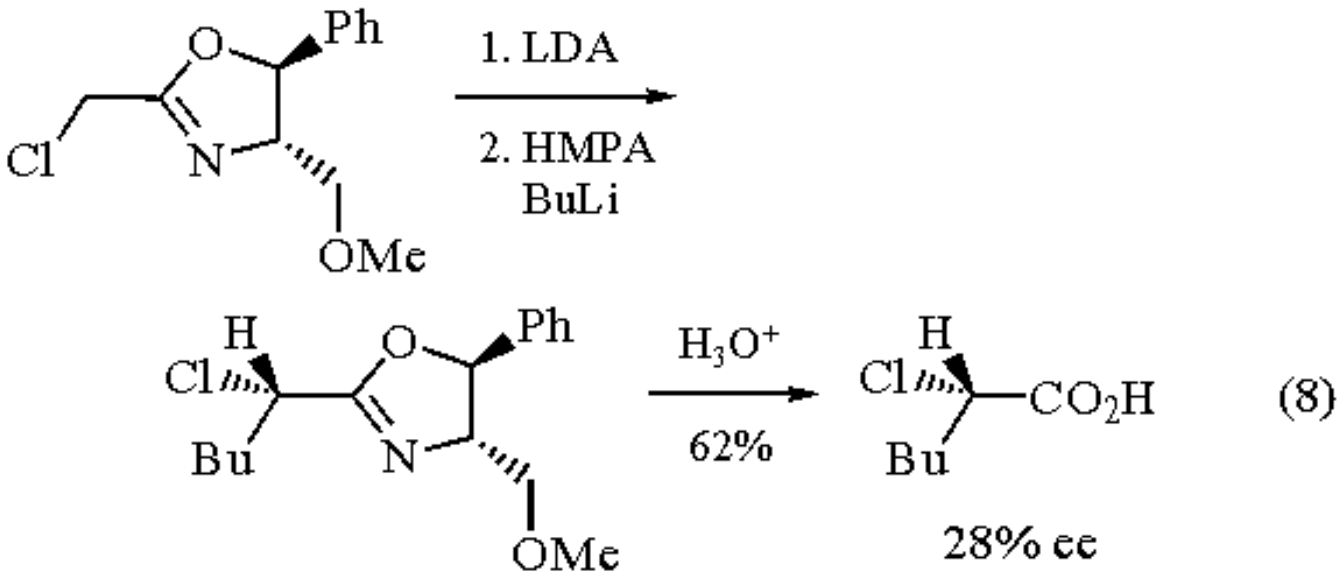

Related Reagents.

(R)-(+)-t-Butyl 2-(p-Tolylsulfinyl)propionate; ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***(R,R)-2,5-Dimethylborolane***; ***2-(o-Methoxyphenyl)-4,4-dimethyl-2-oxazoline***; ***(S)-4-Benzyl-2-oxazolidinone***; ***3-Propionylthiazolidine-2-thione***; ***2,4,4-Trimethyl-2-oxazoline***.

---

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2-Methoxy-6-methyl-1,4,3,5-oxathiadiazine 4,4-Dioxide

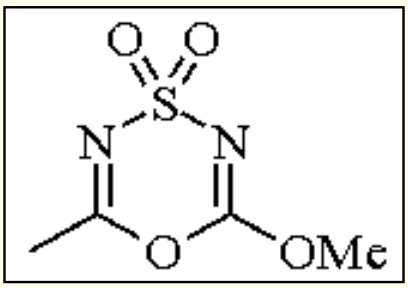

[40028-33-9] · $C_4H_6N_2O_4S$ · 2-Methoxy-6-methyl-1,4,3,5-oxathiadiazine 4,4-Dioxide · (MW 178.19)

(reagent for in situ generation of methyl *N*-sulfonylurethane; provides lower concentrations and higher reaction temperatures than direct formation)

Physical Data: mp 102-103 °C.

Preparative Method: reaction of ***Methoxycarbonylsulfamoyl Chloride*** with ***Sodium Hydride*** in acetonitrile[1] leads to the title reagent (**1**).

General Considerations.

Methyl *N*-sulfonylurethane (**2**) has demonstrated a high degree of electrophilic reactivity in cycloadditions with a variety of alkenes to provide 2-methoxycarbonyl-1,2-thiazetidines (**3**) and 2,3-dihydro-6-methoxy-1,4,5-oxathiazines (**4**) (eq 1).[2] Additions to alkynes proceed to give exclusively the 1,4,3-oxathiazine (**5**) (eq 2).

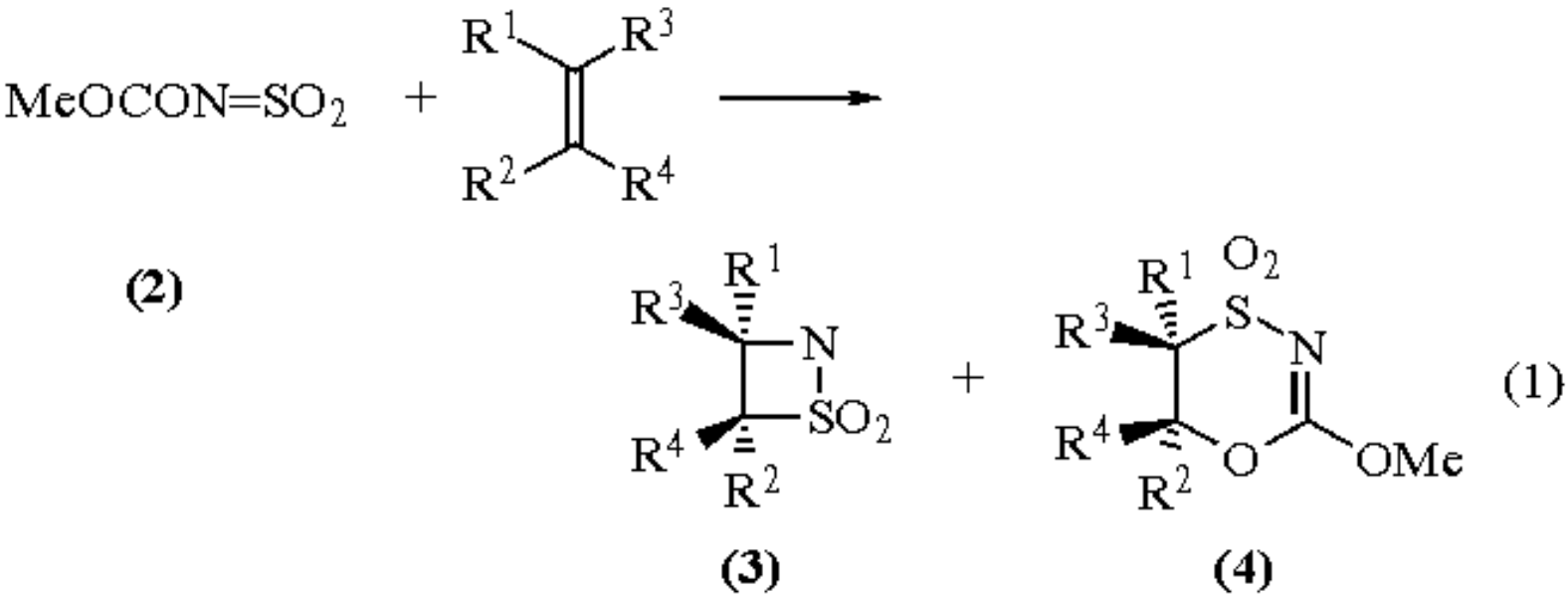

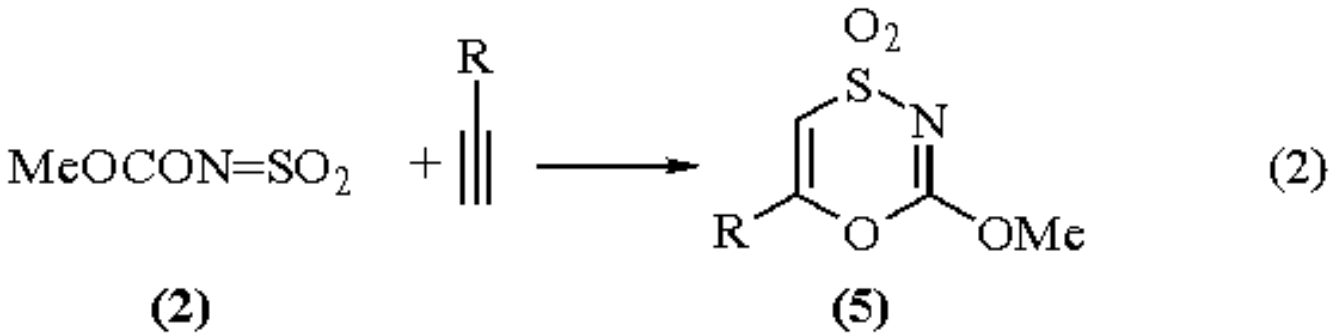

This unstable reagent has been prepared by two methods. First, by direct dehalogenation of methoxycarbonylsulfamoyl chloride using sodium hydride.[2] The second involves the in situ fragmentation of the title reagent (**1**).[3] This reagent apparently undergoes a thermal [2 + 4] cycloreversion above 30 °C. Reaction of (**1**) with a variety of alkenes provides identical products to those reported with (**2**). This second method has the advantage that longer reaction times and higher temperatures are possible. Cycloadducts were obtained from otherwise unreactive alkenes such as *cis*-stilbene and cyclooctatetraene, employing this method.

The two methods give differing results, however, in the addition to ynamines (**6**).[4] In this case the low-temperature generation provided the expected product (**7**), while the cycloreversion method led to the new product (**8**) (eqs 3 and 4).

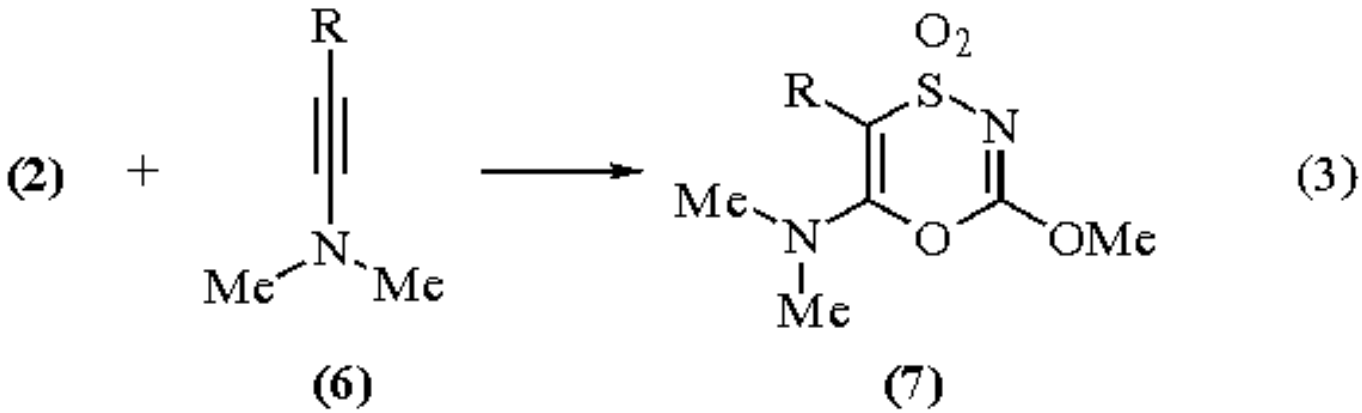

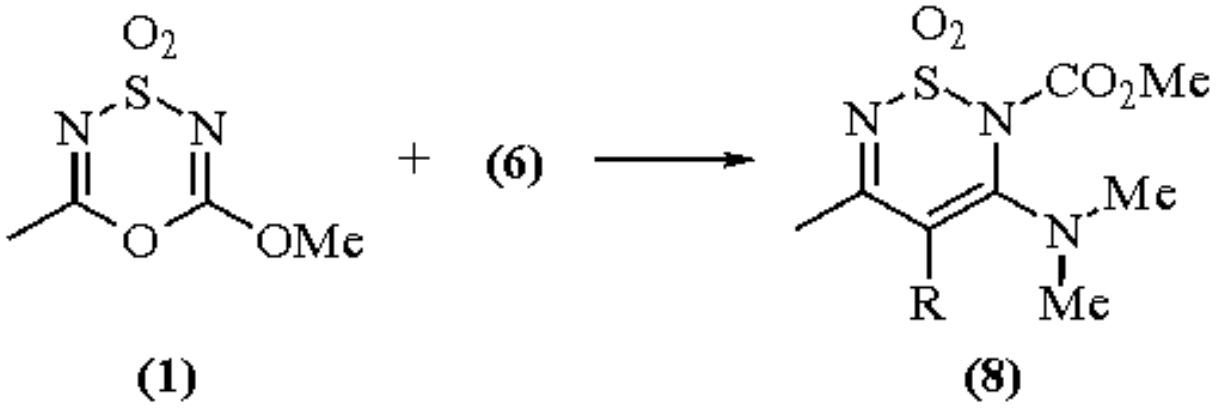

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(*S*)-2-Methoxymethylpyrrolidine[1]

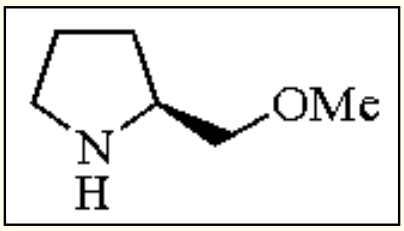

[63126-47-6] · $C_6H_{13}NO$ · (*S*)-2-Methoxymethylpyrrolidine · (MW 115.20)

(chiral auxiliary; asymmetric syntheses with SMP enamines[2] and SMP amides;[3] asymmetric Birch reductions;[4] asymmetric Diels-Alder reactions[5])

Alternate Name: SMP.

Physical Data: bp 75 °C/40 mmHg; *d* 0.930 g cm^{-3}; n_D^{20} 1.4467; α_D^{20} -3 to -4° (neat).

Solubility: sol H_2O, ether, dichloromethane.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: store at 0-4 °C under an argon atmosphere.

General Considerations.

Since the pioneering times of the mid-1970s, (*S*)-2-methoxymethylpyrrolidine has been one of the most generally useful chiral auxiliaries in asymmetric synthesis, with a very broad range of applications. As a proline derivative, it generally shows high stereoselectivities due to the rigidity of the five-membered ring and the ability to coordinate metal fragments[6,7] (see also ***(S)-1-Amino-2-methoxymethylpyrrolidine***, SAMP).

Lithiated SMP formamides and thioformamides have been used as acylanion equivalents (d^1 synthons) in the synthesis of enantiomerically pure α-hydroxy ketones and vicinal diols.[7] Metalated SMP aminonitriles have been used in nucleophilic acylation reactions to give α-hydroxy ketones.[8]

SMP enamines have a very broad range of applications as d^2 synthons. Cyclohexanone SMP enamine can be used for efficient Michael additions to nitroalkenes, Knoevenagel acceptors,[2a,b] and to a nitroallylic ester in a [3 + 3] carbocyclization[2c] with excellent stereoselectivities (eq 1). The synthesis of γ-oxo-α-amino acids using SMP enamines has been developed (eq 2).[2d]

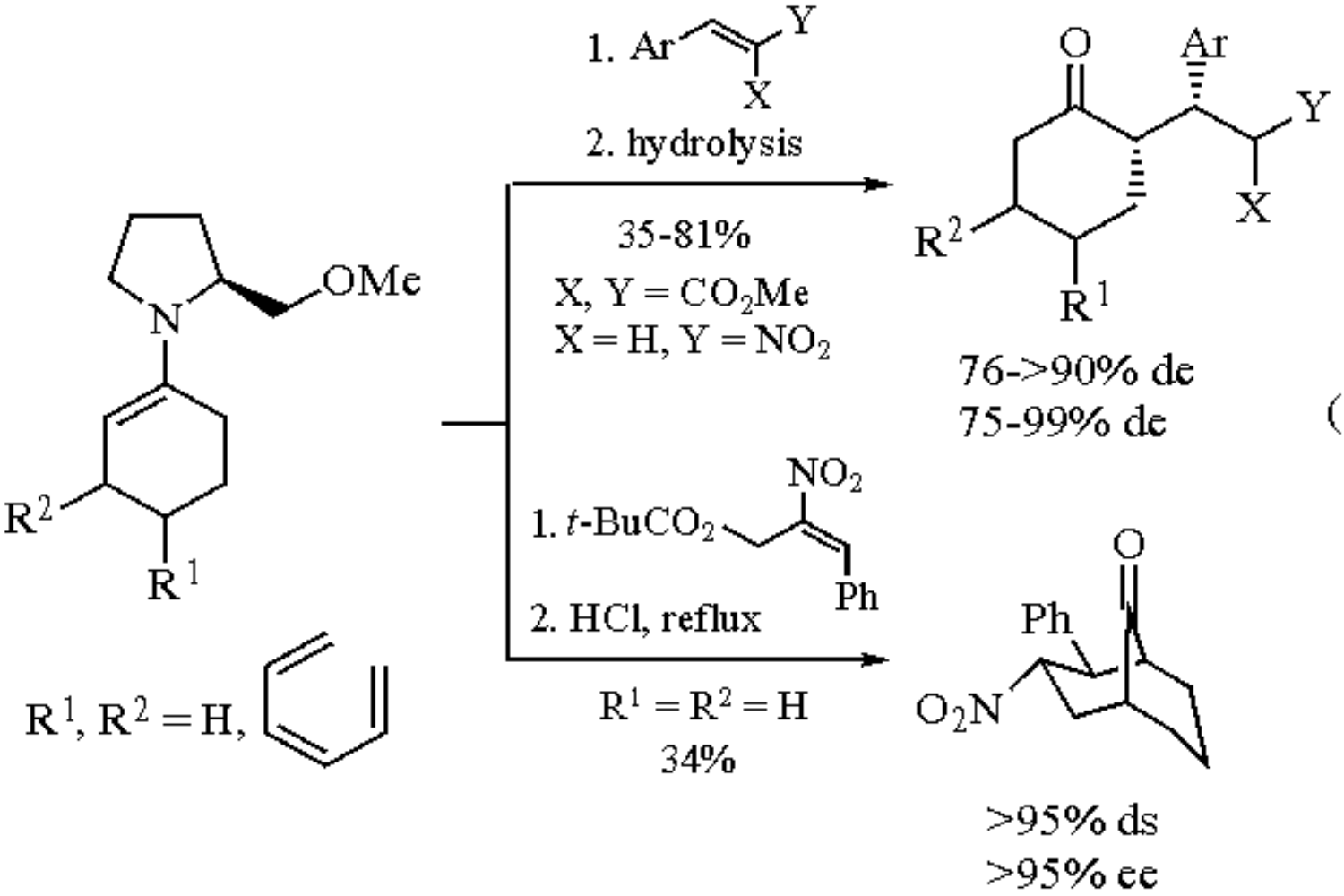
1. Ar Y X
2. hydrolysis
35-81%
X, Y = CO2Me
X = H, Y = NO2
76->90% de
75-99% de
OMe
N
R2
R1
R1, R2 = H,
1. t-BuCO2 NO2 Ph
2. HCl, reflux
R1 = R2 = H
34%
O2N
Ph
>95% ds
>95% ee

(1)

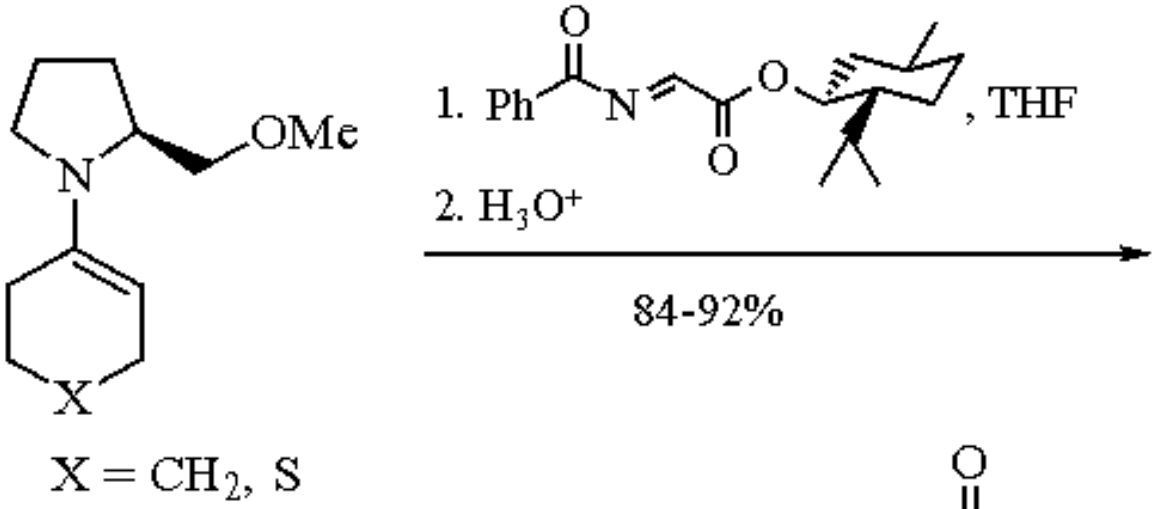

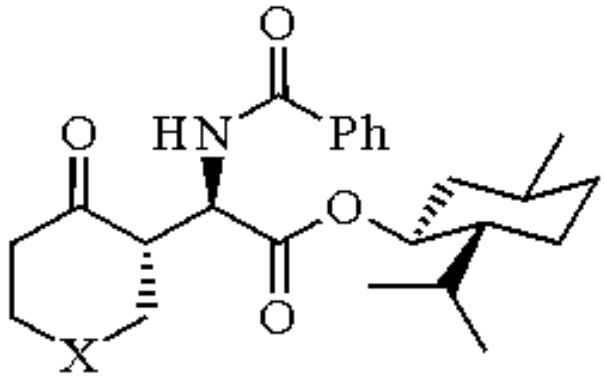

(2)

≥ 98% de/ee

SMP amide enolates have been employed by several research groups. Alkylation of SMP amide enolates gives α-substituted acids (eq 3).[3a,b] Excellent yields and stereoselectivities are observed in the Birch reduction of aromatic SMP amides with subsequent alkylation (eq 4).[4]

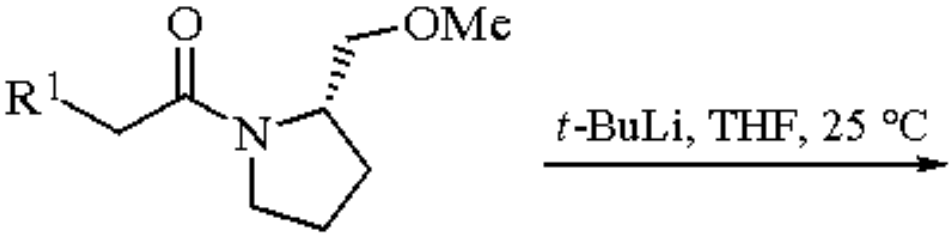

R^1 = alkyl; R^2 = alkyl, allyl, benzyl

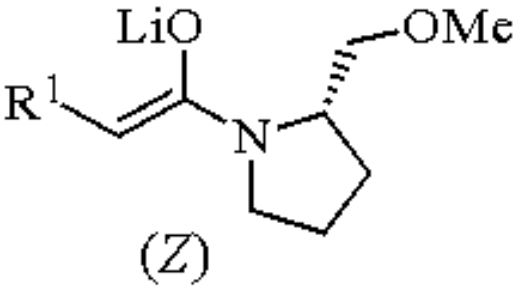

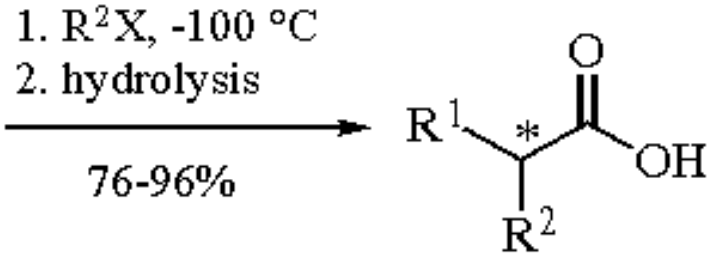

(3)

52-94% ee

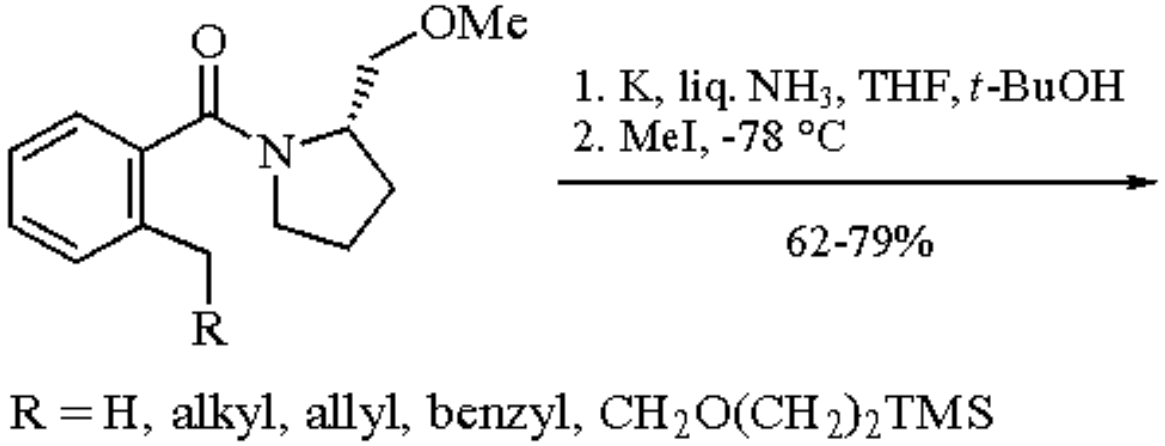

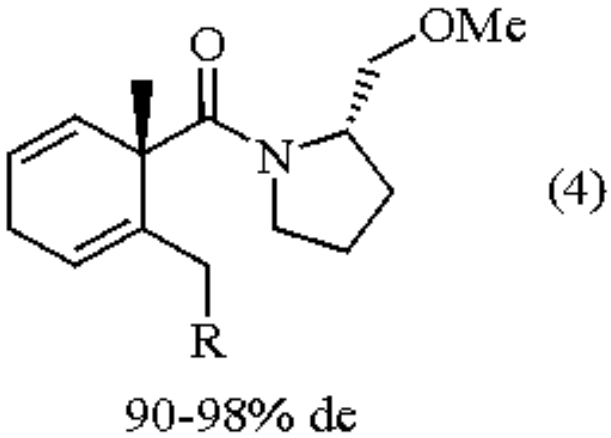

(4)

SMP amides have been used in vanadium(II)-promoted pinacol cross-coupling[3c,d] and in asymmetric oxidations with chiral oxaziridines.[3e] The diastereoselective addition of thiocarboxylic acids to 1-(2-methylacryloyl) SMP amides[3f] and the stereocontrolled addition of various organometallics to α-keto SMP amides[3g] have been studied.

Metalated SMP allylamines or enamines have been used as the first chiral homoenolate equivalents (d^3 synthons; eq 5).[9]

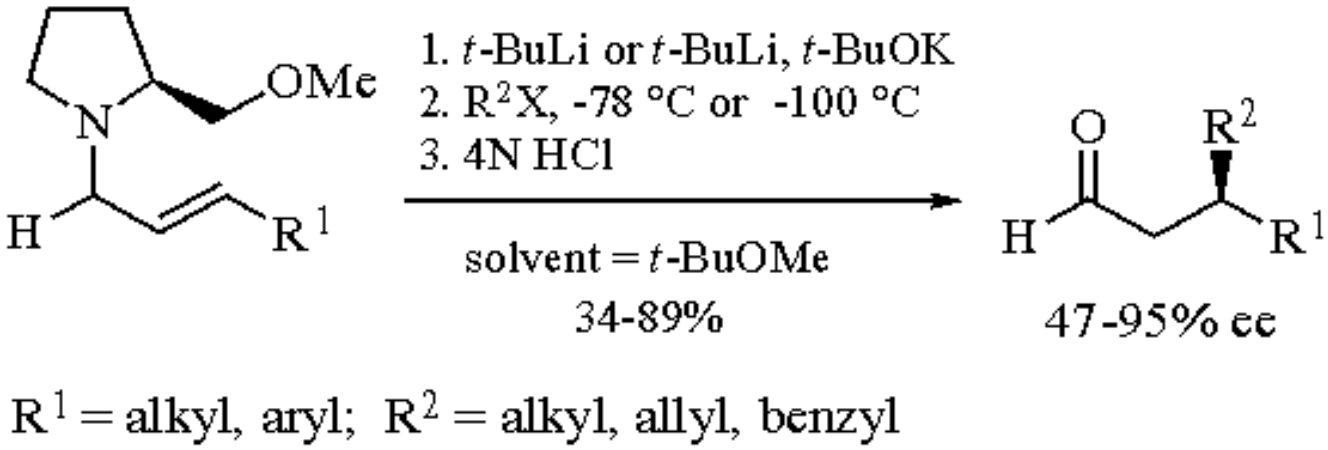

(5)

SMP is a useful chiral auxiliary in various cycloaddition reactions. Chiral 2-amino-1,3-dienes have been used in the Diels-Alder reaction with 2-aryl-1-nitroethylenes,[5a,b] and 5-aryl-2-methyl-substituted 4-nitrocyclohexanones were

obtained in excellent enantiomeric purities (ee = 95-99%) and diastereoselectivities (ds = 75-95%; eq 6). The photo-Diels-Alder reaction of SMP acrylonitrile with 1-acetylnaphthalene has been carried out.[5b] After hydrolysis of the adduct, the 1,4-diketone was obtained in excellent enantiomeric purity (ee &egt; 97%; eq 7).

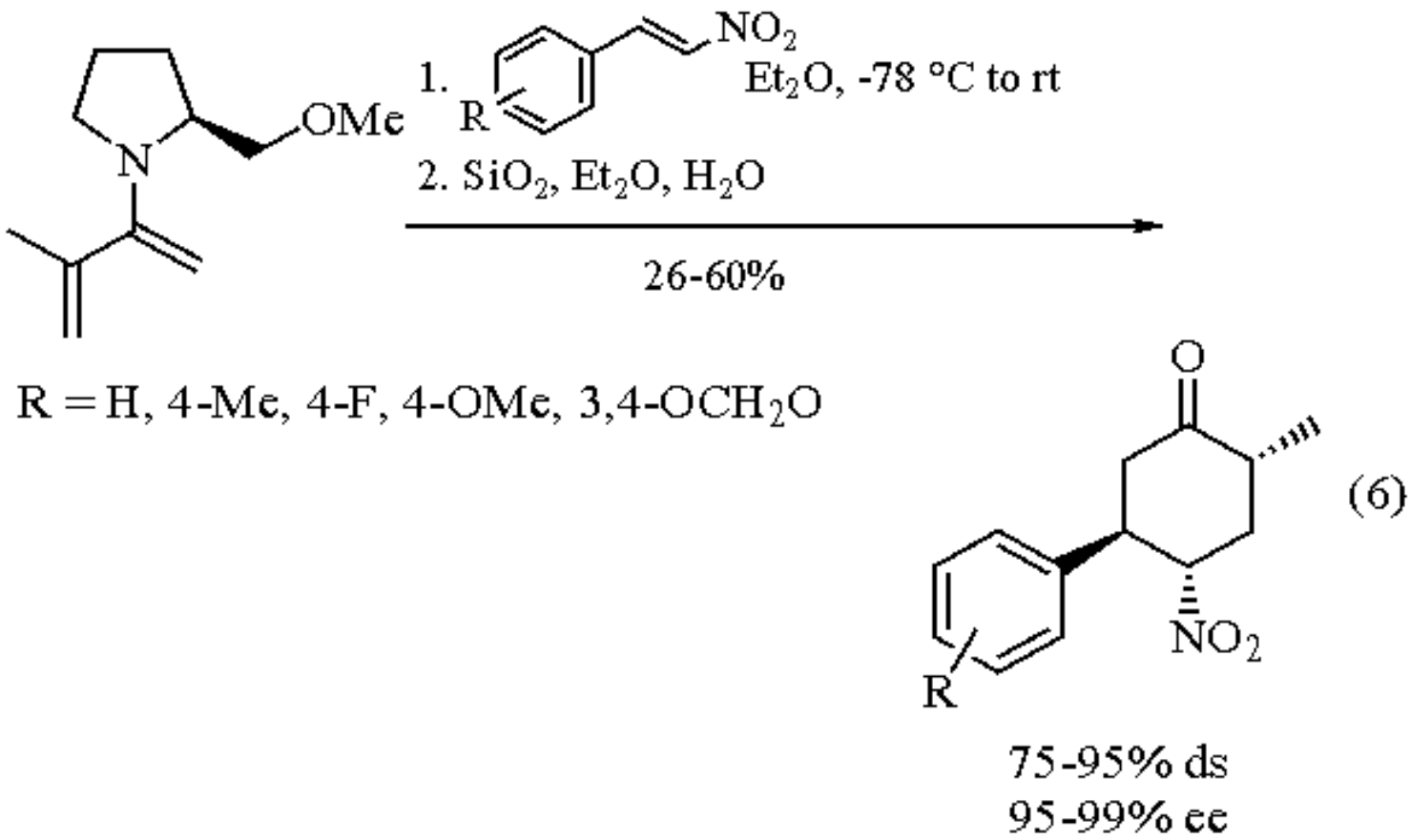

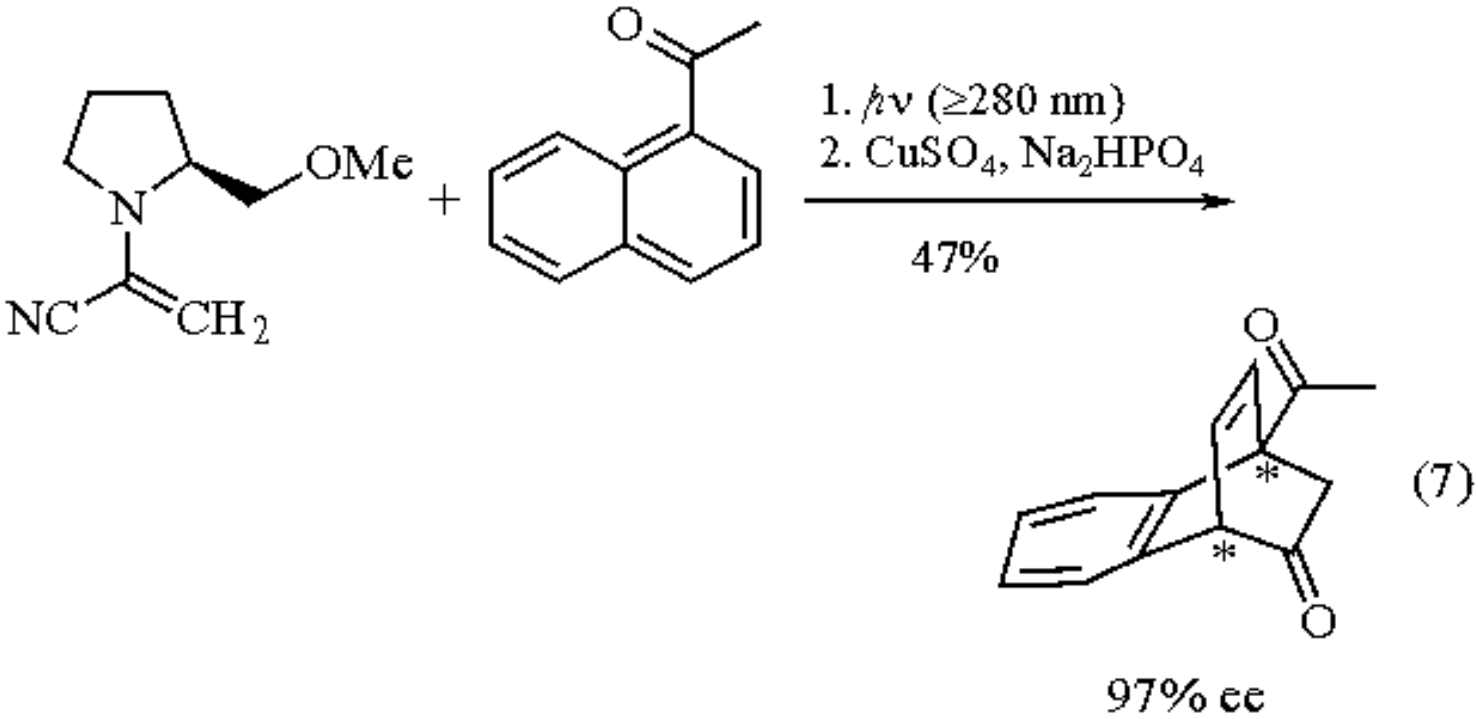

Stereoselective Diels-Alder reactions have been performed variously, using chirally modified sulfines as

dienophiles,[5c] chiral ynamines,[5d] SMP enamines,[5e] SMP acrylamides,[5f] and the in situ preparation of SMP *N*-acylnitroso dienophiles.[9g,h,i] The [2 + 2] cycloaddition reactions of chiral keteniminium salts obtained from SMP amides with alkenes have been studied.[10]

Various metalated chiral organosilicon compounds bearing the SMP moiety have been alkylated to synthesize chiral alcohols.[11] Excellent regio- and stereoselectivities have been observed in the alkylation of chiral silylpropargyl anions (eq 8).[11f]

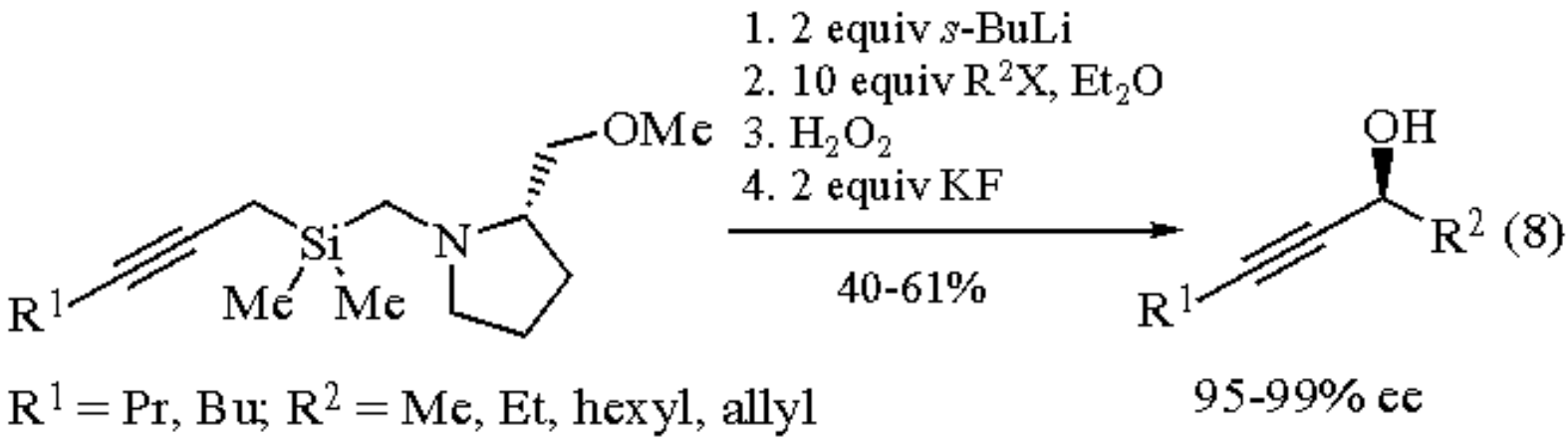

(8)

The elegant application of SMP as a chiral leaving group has been studied,[13] using chiral nitroalkenes in the reaction with zinc enolates.[12] The coupling products were obtained in very good yields and enantiomeric purities (eq 9). SMP methyl-2-cycloalken-1-ones undergo conjugate addition with lithium diorganocuprates followed by elimination of the chiral auxiliary to form optically active cycloalkanones (eq 10).

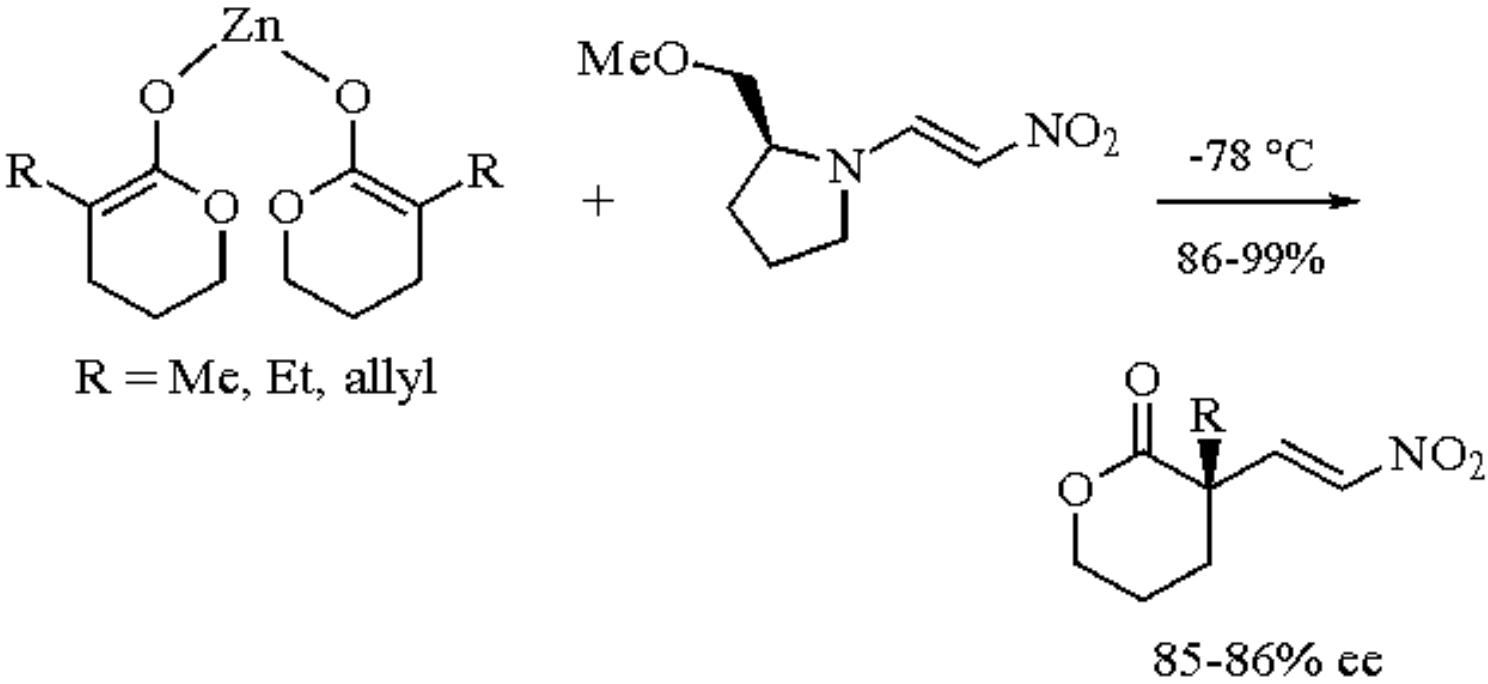

(9)

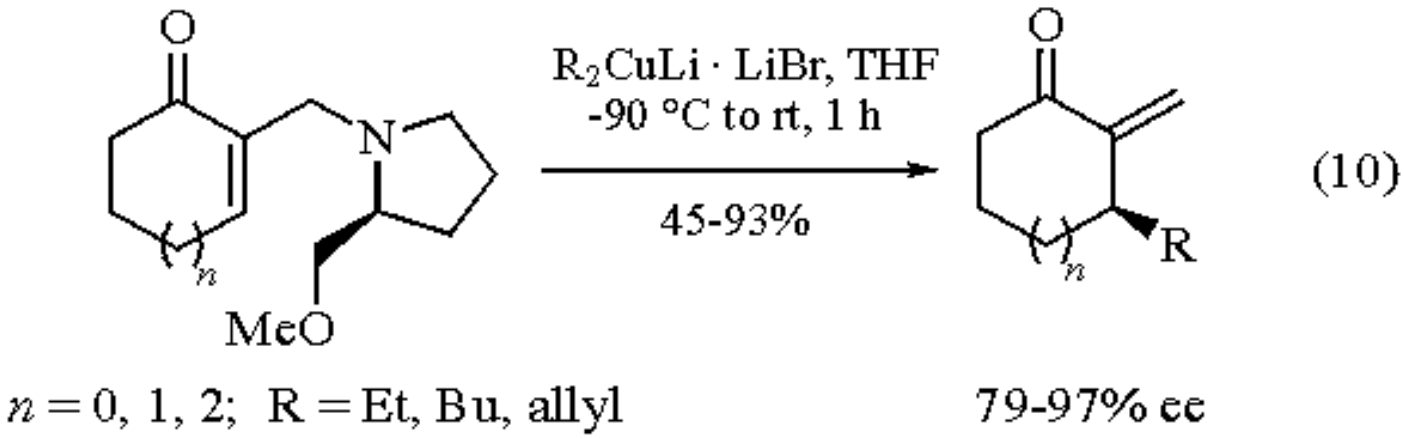

Various other applications are conjugate addition,[14] the ultrasound-promoted perfluoralkylation of SMP enamines,[15] the enantioselective fluorodehydroxylation of SMP 1-yl-sulfur trifluoride,[16] asymmetric telomerization of butadiene,[17] the chiral modification of ruthenium clusters,[18] and the application of SMP amide bases.[19]

Related Reagents.

(S)-1-Amino-2-methoxymethylpyrrolidine.

---

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(Methoxymethyl)trimethylsilane[1]

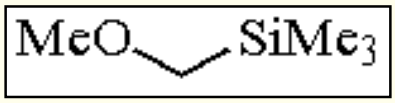

[147-14-4] · $C_5H_{14}OSi$ · (Methoxymethyl)trimethylsilane · (MW 118.28)

(Peterson alkenation reagent;[1] synthesis of enol ethers;[2] one-carbon homologation of ketones to aldehydes;[2] synthetic equivalent of lithiomethyl methyl ether[2])

Physical Data: bp 83 °C/760 mmHg;[2b] *d* 0.758 g cm^{-3}.[3]

Solubility: sol common solvents (THF, Et_2O, CH_2Cl_2, etc.).

Form Supplied in: colorless liquid, 98% purity.

Analysis of Reagent Purity: ^1H NMR: (CCl_4) δ 3.4 (s, 3 H), 3.1 (s, 2 H), 0.2 (s, 9 H).[2b]

Preparative Methods: prepared in 75% yield by the reaction of ***(Chloromethyl)trimethylsilane*** and ***Sodium Methoxide*** in dry methanol at reflux.[3]

Handling, Storage, and Precautions: the reagent is flammable and an irritant. It should be used in a well ventilated fume hood. Contact with the eyes and skin should be avoided.

Carbonyl Addition Reactions.[2]

Treatment of the title reagent with ***s-Butyllithium*** (1.4 M in cyclohexane) in THF at -78 °C to -25 °C provides a solution of methoxy(trimethylsilyl)methyllithium (**1**) that reacts with aldehydes and ketones to give the carbonyl adducts that are isolated in 55-89% yield (eq 1). Elimination of lithium trimethylsilanolate (Me_3SiOLi) does not occur under these conditions.

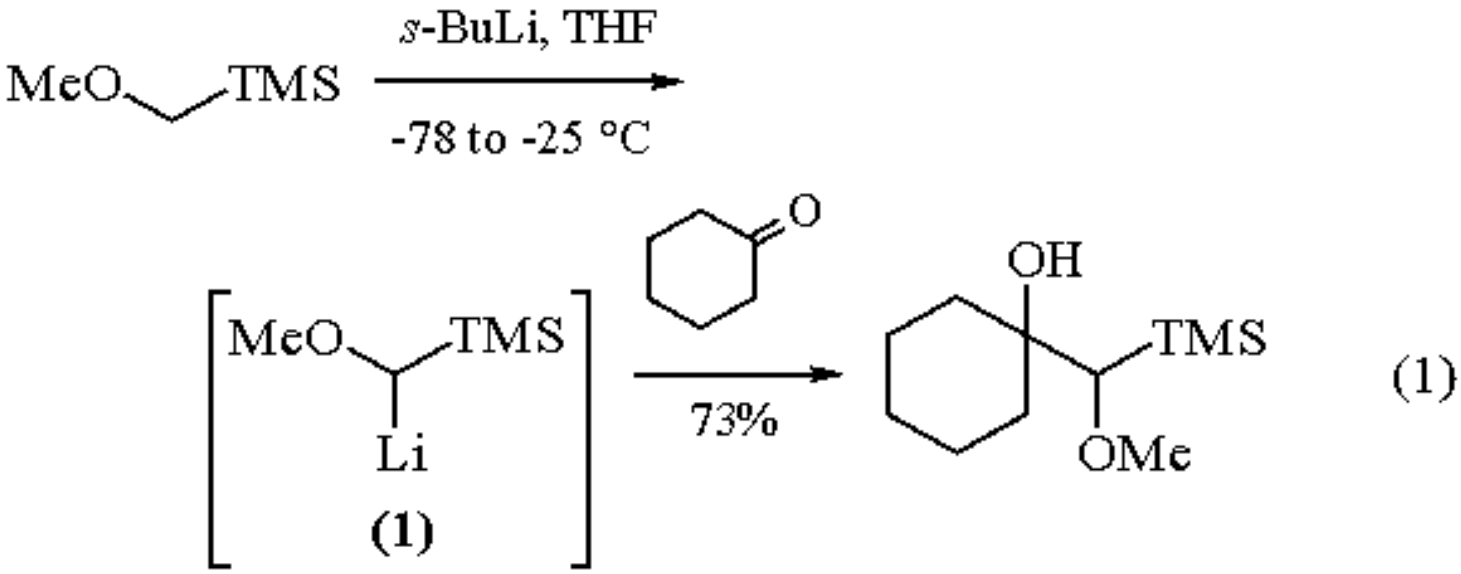

Peterson Alkenation.[2]

Treatment of the (β-hydroxy-α-methoxyalkyl)trimethylsilane adducts with ***Potassium Hydride*** in THF at 60 °C results in elimination of potassium trimethylsilanolate to give enol ethers in 70-87% yield (eq 2). Alternatively, when the 1:1 carbonyl adducts are treated with 90% ***Formic Acid*** at ambient temperature, they undergo elimination and hydrolysis to give the one-carbon homologated aldehydes (eq 3). This procedure fails with acid-sensitive aldehydes, such as 1-prenylacetaldehyde.[2b]

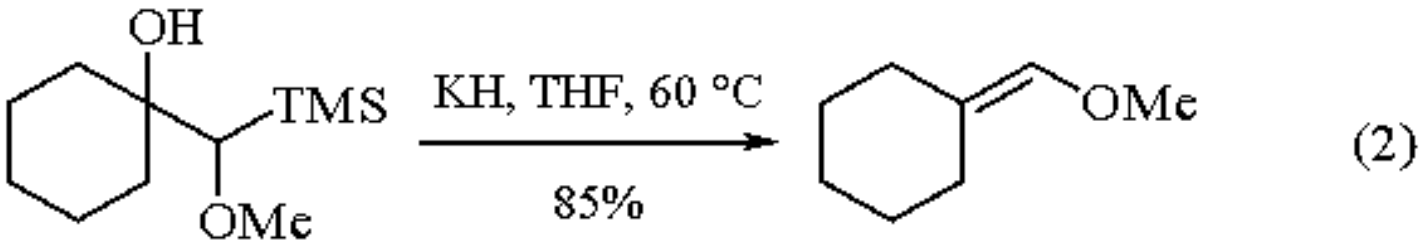

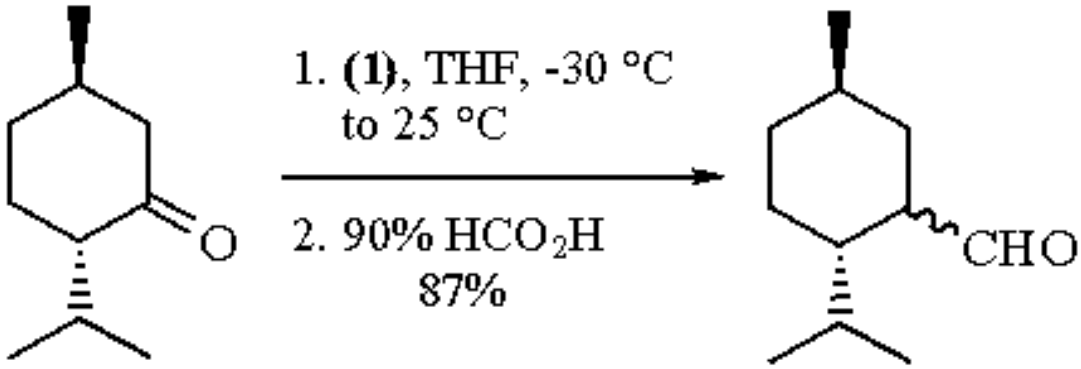

Kende utilized this methodology for the conversion of (**2**) to (**3**) during the total synthesis of (±)-warburganal and (±)-isotadeonal (eq 4).[4] The ketone function of (**2**) is quite hindered and failed to give satisfactory results in reactions with methylenetriphenylphosphorane, α-methoxymethylphosphonate, and tosylmethyl isocyanide.

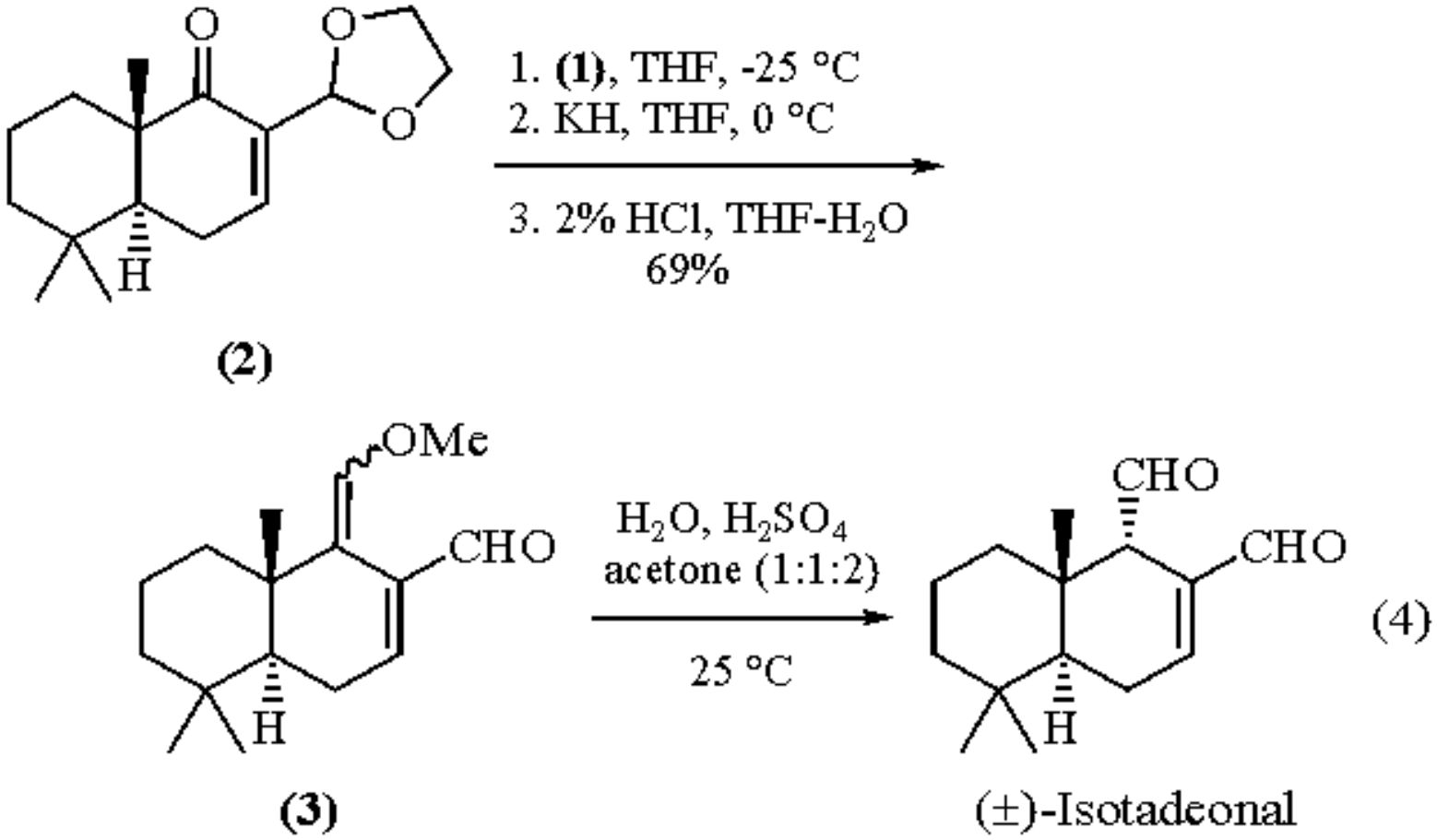

Other Conversions.

Treatment of the carbonyl adducts of (**1**) with dry ***Cesium Fluoride*** in DMSO at 80 °C results in protodesilylation without elimination of the β-hydroxy group (eq 5). Alternatively, oxidation of the carbonyl adducts with ***Pyridinium Chlorochromate*** provides α-methoxy-α-trimethylsilyl ketones, which desilylate when chromatographed on silica gel to give α-methoxy ketones (eq 6). Carbanion (**1**) thus functions as a synthetic equivalent of $MeOCH_2Li$ for carbonyl addition reactions.

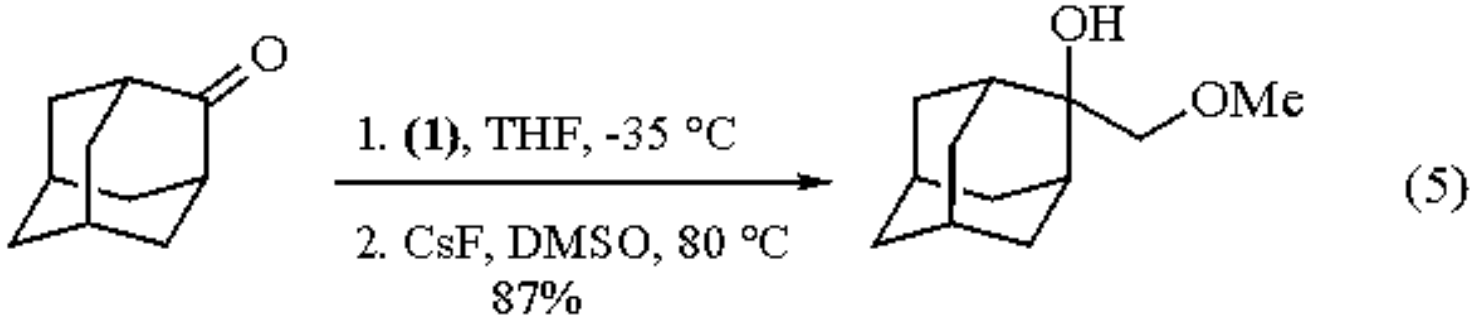

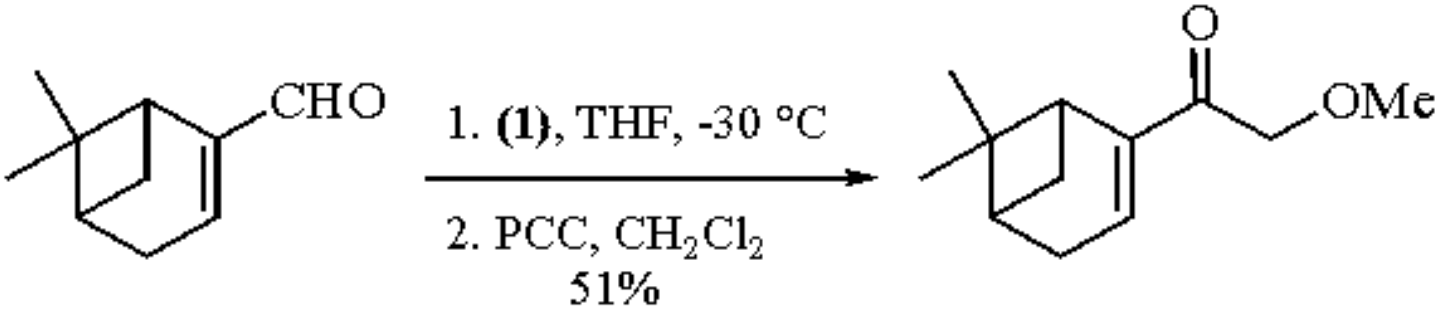

(6)

Related Reagents.

Methoxymethyl(diphenyl)phosphine Oxide; ***Methoxymethylenetriphenylphosphorane***; ***p-Tolylsulfonylmethyl Isocyanide***.

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1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene

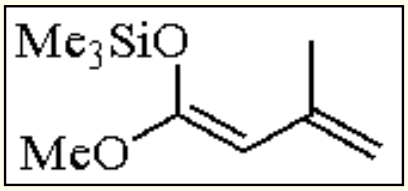

[73311-51-0] · $C_9H_{18}O_2Si$ · 1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene · (MW 186.36) (*E*)

[76927-59-8] (*Z*)

[76915-33-8]

(diene in Diels-Alder reactions; nucleophile; alkene substrate)

Physical Data: bp 40 °C/0.3 mmHg.

Analysis of Reagent Purity: for the thermodynamically favored isomer of the diene: ^{1}H NMR (C_6D_6, 270 MHz) δ 4.90 (br, d, *J* = 2.7 Hz, 1 H), 4.65 (m, *J* = 1.4, 2.7 Hz, 1 H), 4.23 (s, 1 H), 3.15 (s, 3 H), 2.00 (dd, *J* = 0.7, 1.4 Hz, 3 H), 0.14 (s, 9 H); ^{13}C NMR (15 MHz, C_6D_6, off-resonance decoupled) δ 159.4 (s), 141.9 (s), 110.2 (t), 83.7 (d), 56.5 (q), 25.6 (q), 2.2 (q); IR (hexane) 1660 cm^{-1}. The only difference between the ^{1}H NMR (C_6D_6) spectra of the two diene isomers are the CH_3O resonances, which appear at δ 3.15 and 3.12.

Preparative Method: silyl enolization of methyl 3-methyl-2-butenoate gives a 1:1 mixture of (*Z*) and (*E*) isomers.[1]

Purification: distillation at 65 °C/1 mm Hg or heating the mixture to 115 °C for 40 min causes isomerization to the thermodynamically favored isomer.

Handling, Storage, and Precautions: silyl migration occurs at 117 °C.[1a,2] Use in a fume hood.

Diels-Alder Reactions.

This diene has been used extensively in carbo-Diels-Alder reactions with a wide variety of quinones,[3] a trisubstituted alkene,[4] a β-phenylsulfinylnitroalkene,[5] and a tetrachlorocyclopropane (to prepare a troponoid).[6] Dienophiles that

have been used with the diene in hetero-Diels-Alder reactions include an orthoquinone (eq 1),[3g] thioaldehydes (eq 2),[7] and imine-$TiCl_4$ complexes.[8]

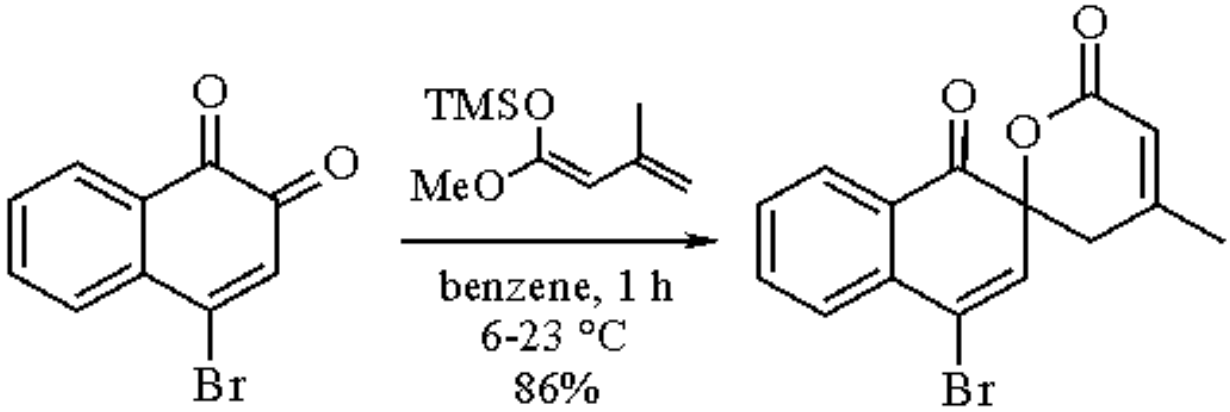

(1)

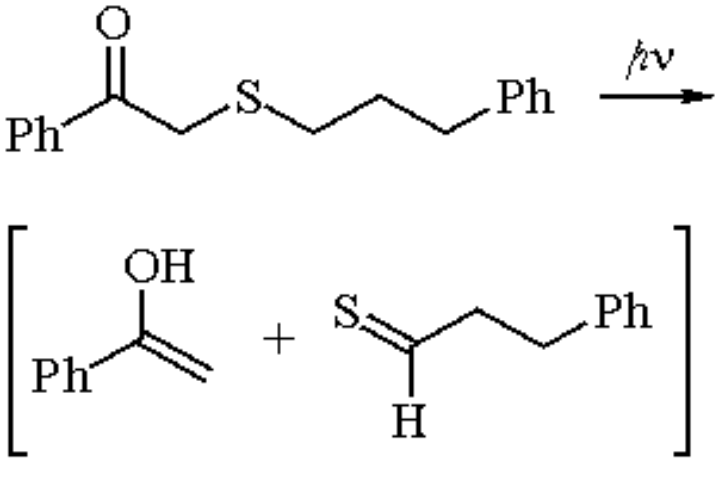

(2)

Alkylations.

With one exception,[9] the 3-methyl substituent of this diene appears to encourage predominantly γ- over α-attack in reactions with electrophiles such as 1,3-dithienium tetrafluoroborate (eq 3),[10] PCl_3 or $AsCl_3$,[11] the PhSCl adduct of dihydropyran,[12] and PhSCl (eq 4).[1d] The use of *i*-Pr or *t*-Bu ester analogs of this diene and/or bulky electrophiles further enhances γ selectivity.[13]

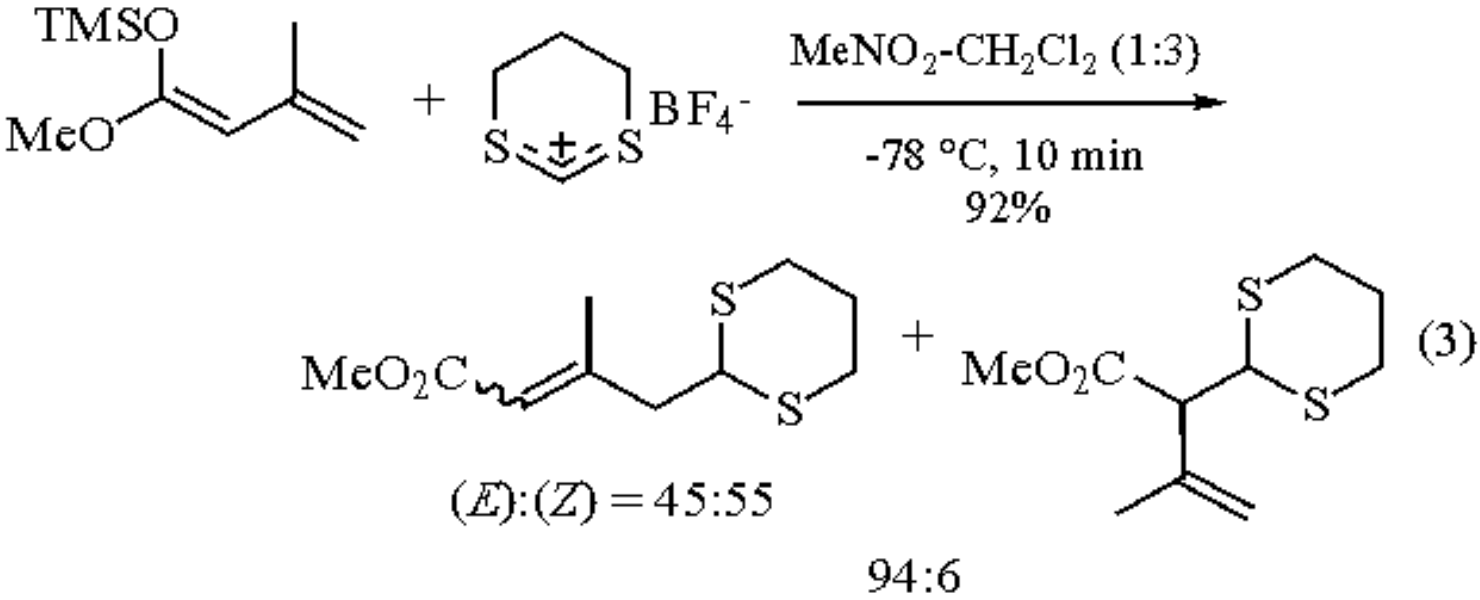

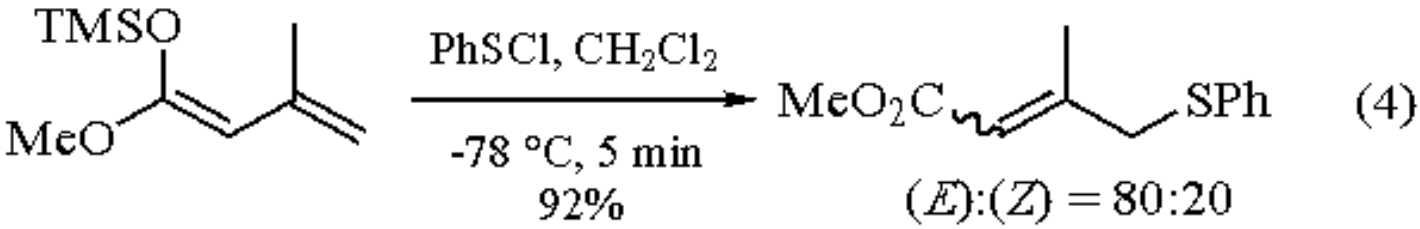

Chrysanthemic acid derivatives undergo ***Titanium(IV) Chloride***-catalyzed reactions with the diene (eq 5).[14] Homo coupling of the diene to give unsaturated esters has also been reported under $TiCl_4$-catalyzed conditions (eq 6).[15]

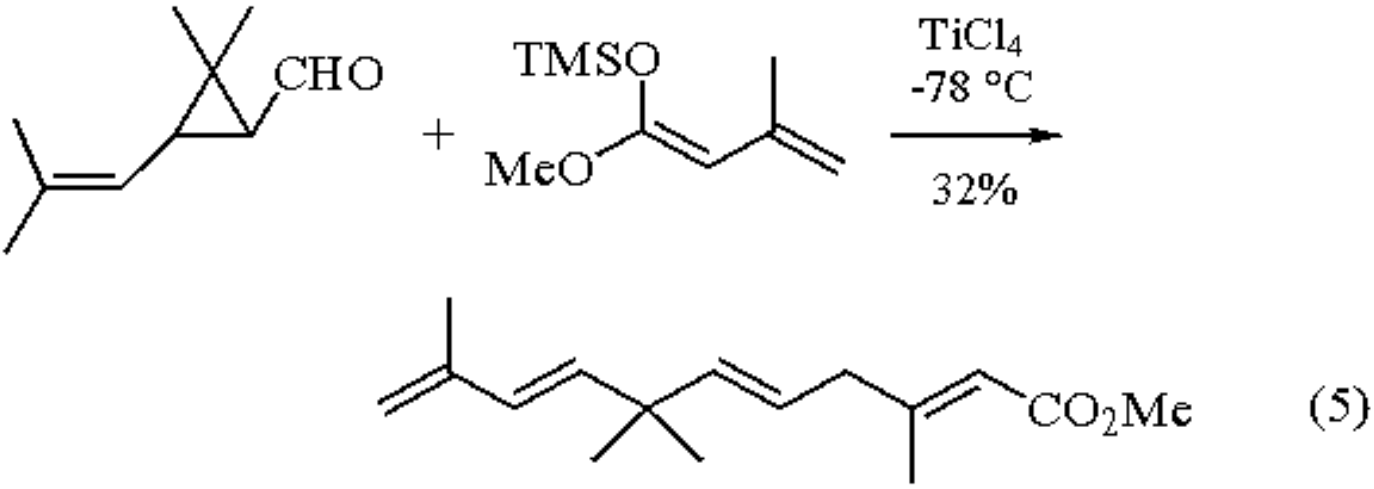

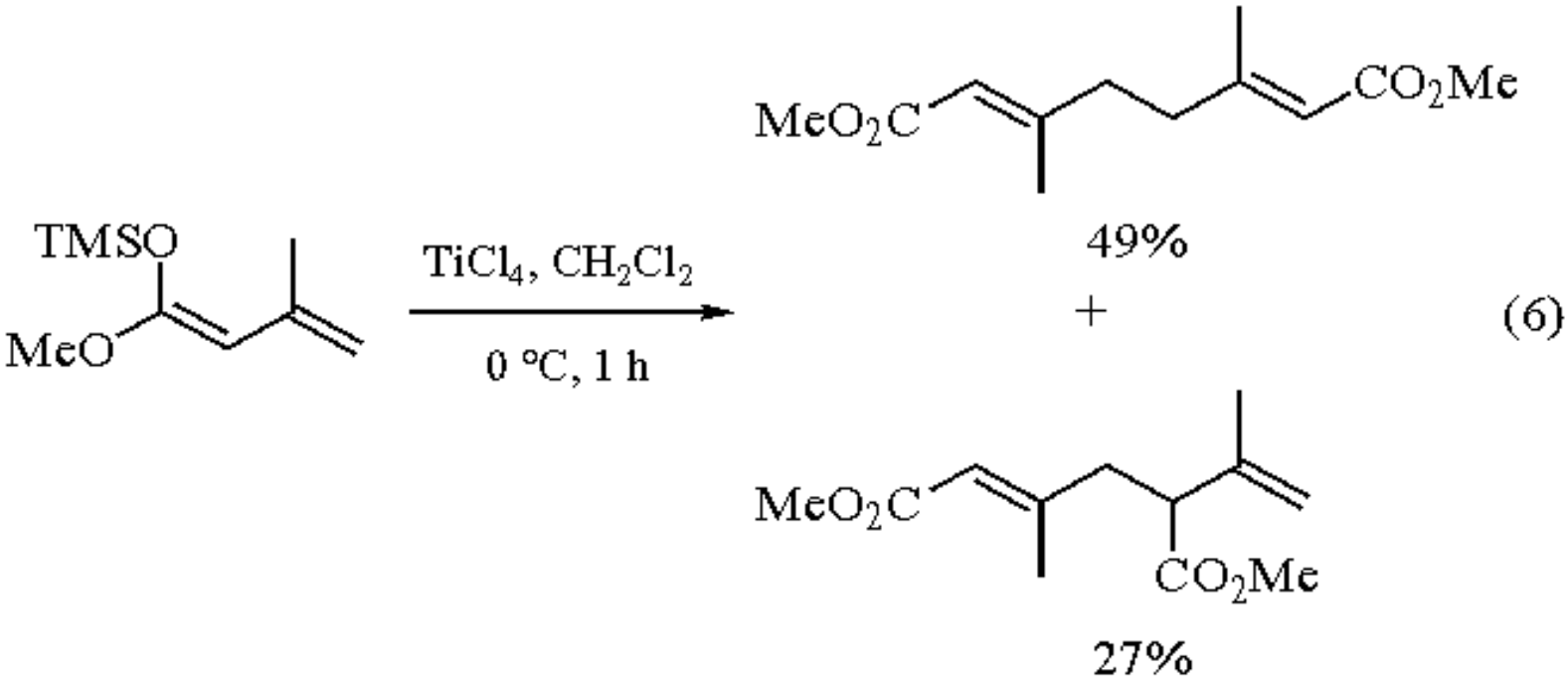

(6)

Amination.

Addition of 3-acetoxyaminoquinazolinone to the diene occurs at both double bonds to give a mixture of intermediate aziridines which then ring open (eq 7).[16]

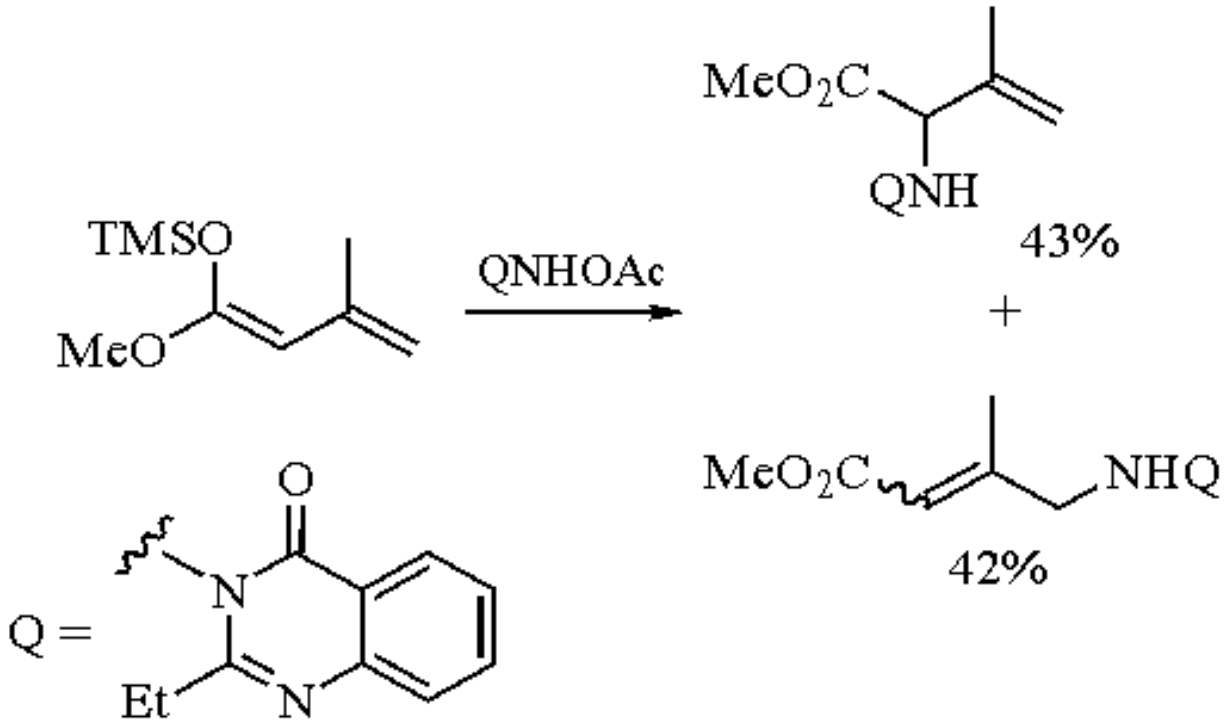

(7)

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(*E,Z*)-1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene

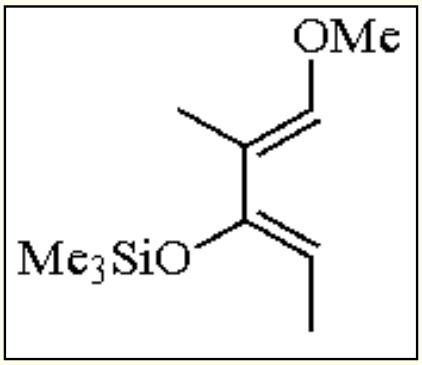

[72486-93-2] · $C_{10}H_{20}O_2Si$ · 1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene · (MW 200.39)

(highly functionalized diene used for a variety of [4 + 2] reactions including Diels-Alder and hetero-Diels-Alder reactions)

Physical Data: bp 83-85 °C/22 mmHg.

Preparative Method: prepared in multigram quantities as a colorless or slightly yellow liquid from 3-pentanone and ethyl formate via a three-step procedure (ca. 40% overall yield).[1]

Handling, Storage, and Precautions: easily hydrolyzed but may be stored indefinitely under anhydrous conditions at 0 °C.

General Considerations.

(*E,Z*)-1-Methoxy-2-methyl-3-(trimethylsilyloxy)-1,3-pentadiene (**1**) and its parent compound, Danishefsky's diene (***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***), have been used extensively for the synthesis of both carbocycles and heterocycles via formal [4 + 2] reactions. A wide variety of dienophiles show reactivity with (**1**).[2]

Early investigations into the reactivity of (**1**) in the Diels-Alder reaction showed that both alkenes and alkynes functioned well as dienophiles.[3] These observations facilitated the synthesis of a variety of highly substituted carbocycles. For example, the thermal cycloaddition of (**1**) with either ***Methacrolein*** or ***Dimethyl Acetylenedicarboxylate*** in refluxing benzene afforded the expected cycloadducts (eqs 1 and 2). The silyl enol ethers were hydrolyzed with subsequent loss of methanol to furnish 2,4,4,6-tetrasubstituted cyclohexeneone (**2**) and pentasubstituted benzene derivative (**3**).[3]

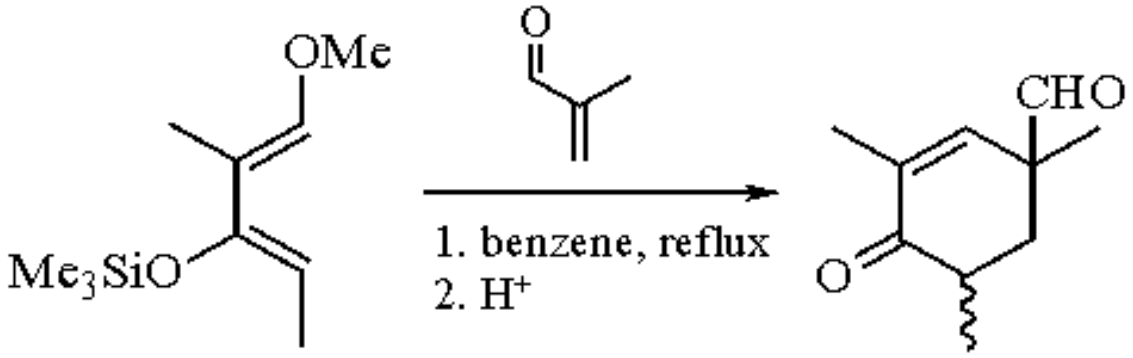

(1)

(1) (2)

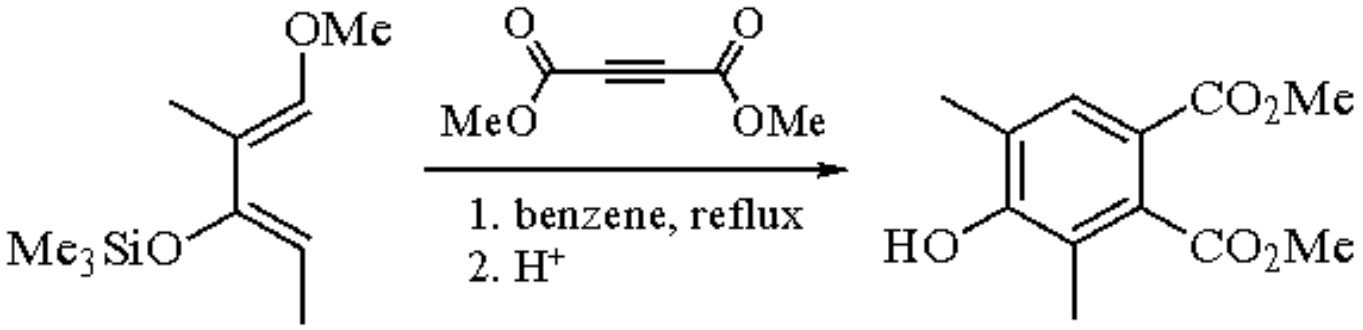

(2)

(1) (3)

The highly electron-rich nature of diene (**1**) enables it to participate in cyclocondensation reactions with dienophiles of relatively low reactivity, such as aldimines and aldehydes. The condensation of (**1**) with imines has seen only limited application in synthesis.[4] In contrast, diene (**1**) has been used extensively in the Lewis acid-catalyzed diene aldehyde cyclocondensation (LADAC) reaction for the synthesis of 5,6-dihydro-4-pyrones (eq 3).[5] This reaction can be regarded as occurring either through a [4 + 2] cycloaddition or via a Mukaiyama aldol process. It is often the case that both types of products (e.g. **4** and **6**) are observed in a single experiment. Acid-promoted elimination or cyclization affords the pyrones (**8**) and (**9**). Levels of simple diastereoselection for the cyclocondensation are often as great as 10:1 and are highly dependent on choice of Lewis acid and solvent, polar solvents (e.g. CH_2Cl_2, MeCN) affording *trans*-substituted pyrones and nonpolar solvents (e.g. toluene) leading to the *cis* isomers.[6]

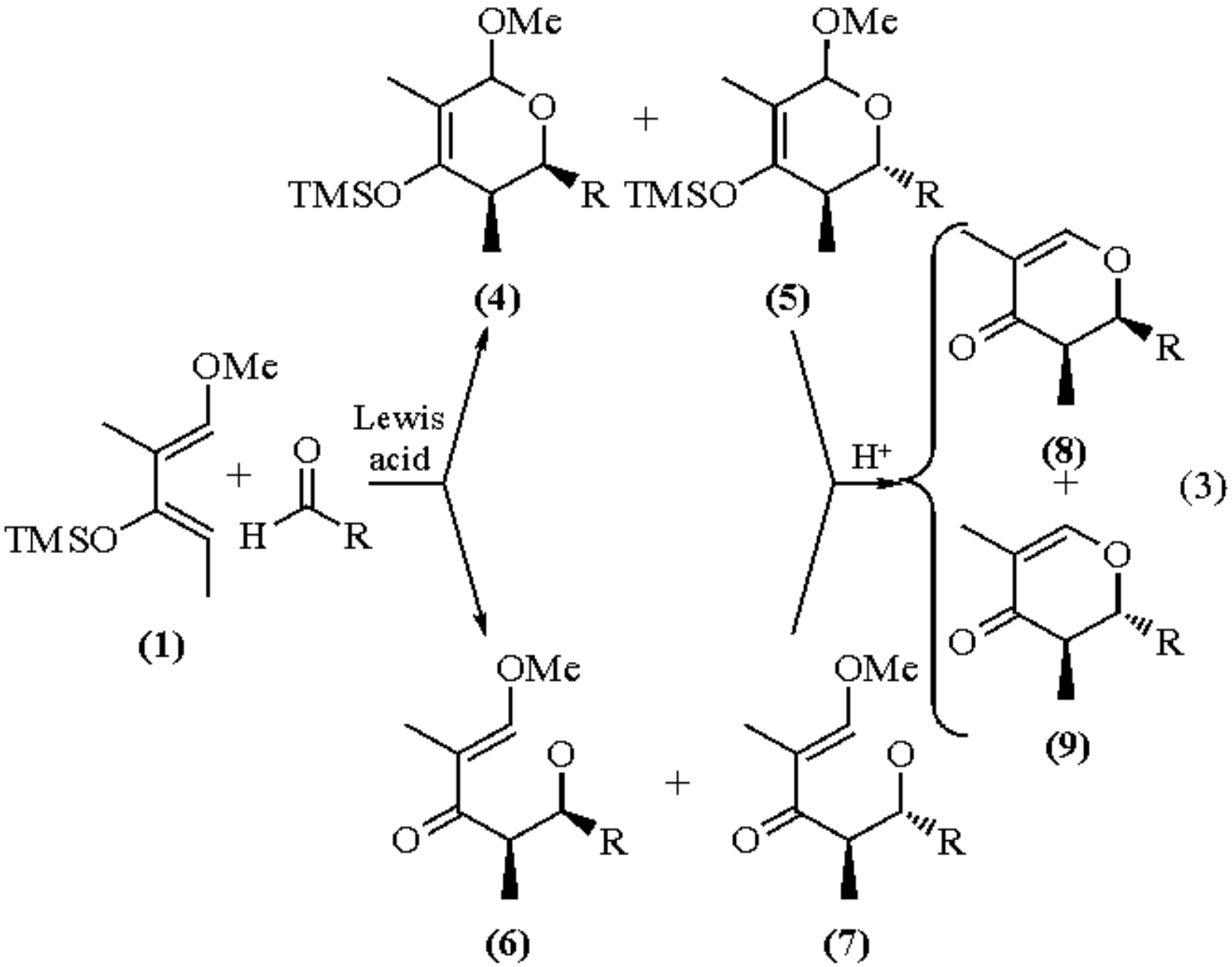

Cyclocondensation of (**1**) with aldehydes possessing chirality often shows excellent diastereofacial selectivity.[5a] Aldehydes bearing alkyl substitution at the α-position typically manifest diastereofacial selection consistent with the rules advanced by Cram and Felkin.[7] Chelation control (cyclic Cram model) can also be achieved using aldehydes having α- or β-alkoxy or -thioalkyl substitution. For example, the ***Magnesium Bromide***-catalyzed condensation of (**1**) with (*S*)-2-benzyloxypropanal (**10**) provides a single diastereomer having a *cis* relationship between the pyrone substituents and diastereofacial selectivity corresponding to chelation controlled addition to the aldehyde (eq 4).[8]

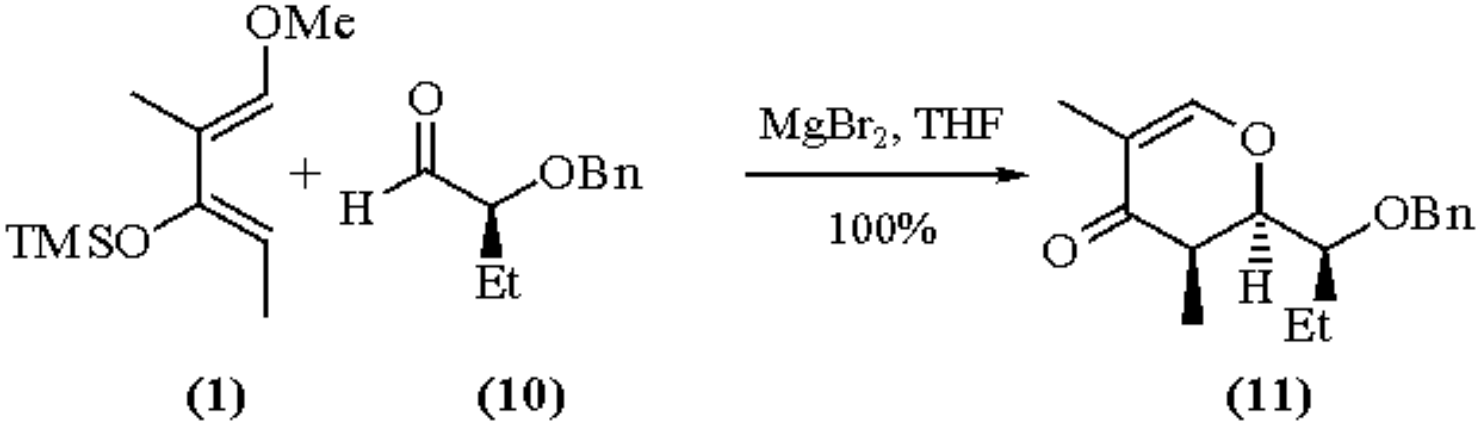

(4)

Recently, under the aegis of chiral catalysts, (**1**) has been shown to participate in the diene-aldehyde cyclocondensation reaction with several aldehydes to afford cycloadducts of very high enantiomeric excess. Several Lewis acid catalysts have been employed, including $Eu(hfc)_3$,[9] (*R*)-(+)-3,3´-bis(triphenylsilyl)binaphthol/$AlMe_3$,[10] and bis(3-acylcamphorato)oxovanadium(IV).[11] The enantiomeric excesses observed in these reactions are somewhat variable, ranging from 40 to >98% ee. However, many examples show high efficiency and enantioselectivity. Yamamoto has recently demonstrated that tartrate-based chiral catalysts (**12**) promote the efficient (84% yield) cyclocondensation of (**1**) with furfural to afford pyrone (**13**) with excellent diastereo- and enantioselectivity (eq 5).[12] Use of the enantiomeric catalyst leads to the enantiomer of (**13**) with comparable selectivity.

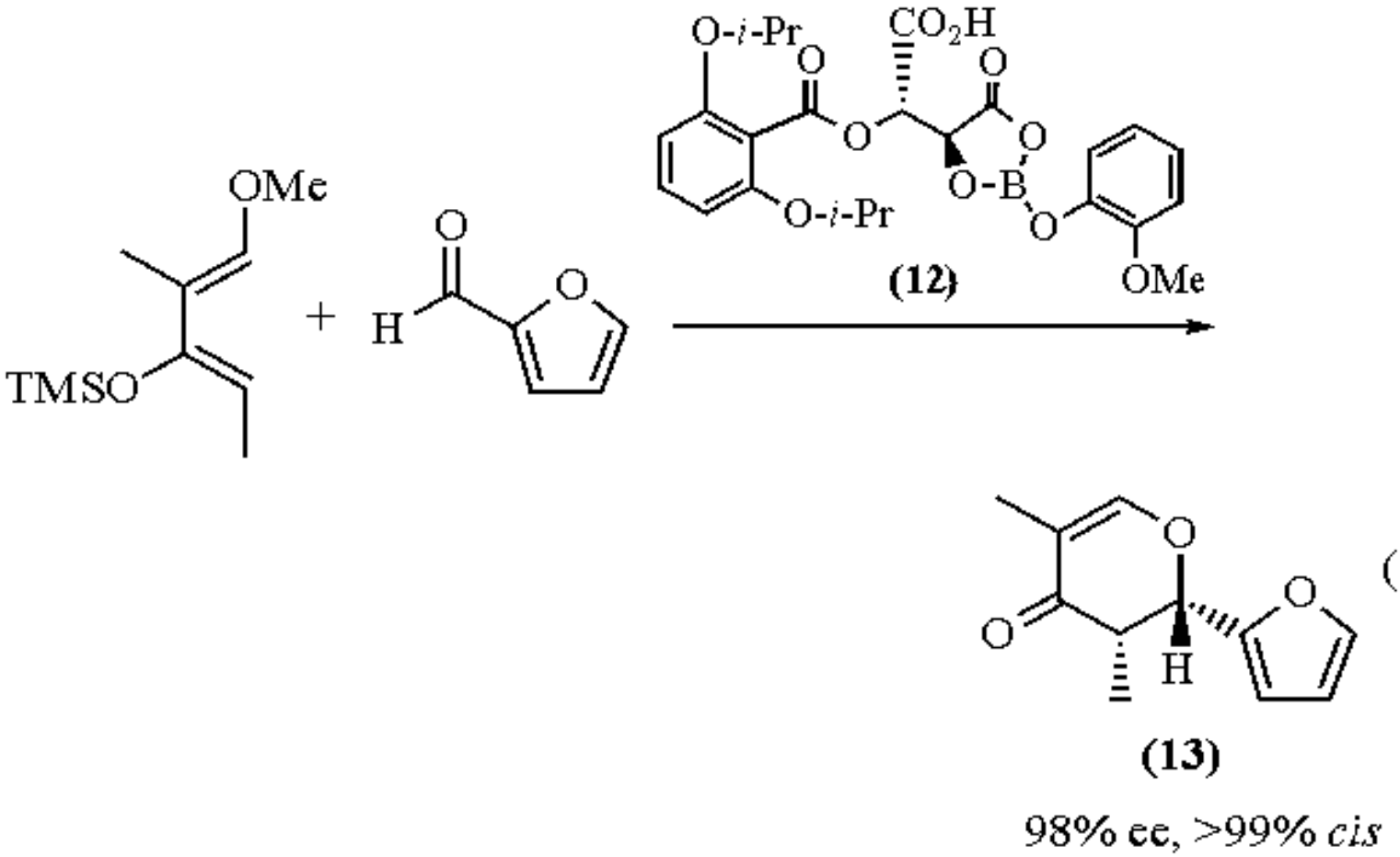

(5)

The capacity for (**1**) to participate in diastereo- and enantioselective reactions has resulted in its being used in several syntheses of important natural products, including zincophorin,[13] rifamycin,[14] the Prelog-Djerassi lactone,[5a] and

rapamycin.[15]

Related Reagents.

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene.

---

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2. The use of this and similar dienes in synthesis has been reviewed: (a) Danishefsky, S. J. *ACR* **1981**, *14*, 400. (b) Danishefsky, S. J. *Aldrichim. Acta* **1986**, *19*, 59.
3. Danishefsky, S.; Yan, C.-F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M., Jr.; Fritsch, N.; Clardy, J. *JACS* **1979**, *101*, 7001.
4. Danishefsky, S.; Langer, M. E.; Vogel, C. *TL* **1985**, *26*, 5983.
5. (a) Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *JACS* **1985**, *107*, 1246. (b) Danishefsky, S.; Chao, K. H.; Schulte, G. *JOC* **1985**, *50*, 4650.
6. A wide variety of Lewis acids have been employed to catalyze this process, including Boron Trifluoride Etherate, Titanium(IV) Chloride, Magnesium Bromide, and Zinc Chloride.
7. (a) Cram, D. J.; Kopecky, K. R. *JACS* **1959**, *81*, 2748. (b) Chirest, M.; Felkin, H.; Prudent, N. *TL* **1968**, 2199.
8. (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Raimondi, L. *JOC* **1992**, *57*, 3605. (b) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *JACS* **1985**, *107*, 1256.
9. (a) Bednarski, M.; Danishefsky, S. *JACS* **1983**, *105*, 3716. (b) Bednarski, M.; Maring, C.; Danishefsky, S. *TL* **1983**, *24*, 3451.
10. Maruoka, K.; Yamamoto, H. *JACS* **1989**, *111*, 789. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *JACS* **1988**, *110*, 310.
11. Togni, A. *OM* **1990**, *9*, 3106.
12. Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *JOC* **1992**, *57*, 1951.
13. Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *JACS* **1988**, *110*, 4368.
14. Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *JACS* **1987**, *109*, 862.
15. Chen, S. H.; Horvath, R. F.; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *JOC* **1991**, *56*, 5834.

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1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene[1]

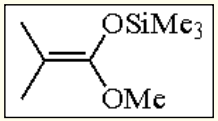

[31469-15-5] · $C_8H_{18}O_2Si$ · 1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene · (MW 174.35)

(functional equivalent of enolate of methyl isobutyrate; ester enolate surrogate in electrophilic reactions including alkylation,[2] aldol reaction,[3-5] Michael reaction,[5a,6-8] initiator for group transfer polymerization of acrylates,[9] nitroarylation,[10] oxidation,[11] dimerization,[12] and cycloadditions[13-15])

Alternate Name: dimethylketene methyl trimethylsilyl acetal.

Physical Data: bp 35 °C/15 mmHg; *d* 0.858 g cm^{-3}.

Solubility: freely sol organic solvents.

Form Supplied in: clear colorless liquid; 95% pure.

Analysis of Reagent Purity: GC and NMR; likely impurities are methyl isobutyrate and hexamethyldisiloxane.

Handling, Storage, and Precautions: irritant; flammable; moisture sensitive; use in a fume hood.

General Considerations.

Ketene alkyl silyl acetals are functional equivalents of enolates of esters that can be readily prepared and stored. The title compound is a prototypical ketene silyl acetal (KSA) that can been prepared by either of the two most commonly employed methods: (a) deprotonation of the α-hydrogen of an ester followed by silylation (eq 1),[16] and (b) metal-catalyzed hydrosilylation of α,β-unsaturated esters (eq 2).[17]

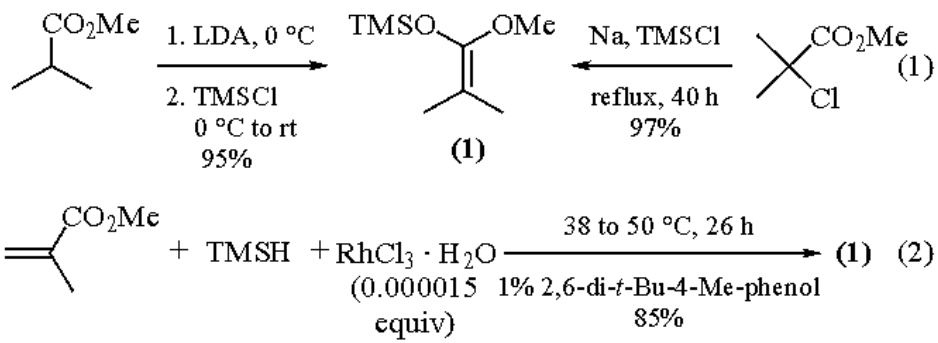

Most of the reactions of KSAs are characterized by the highly nucleophilic nature of this class of compounds. Under many reaction conditions they also serve as silylating agents, often facilitating product formation via the trapping of an unstable intermediate.[10]

Electrophilic Reactions.

Alkylation.

Ketene silyl acetals readily undergo Lewis acid-mediated alkylation (eq 3) with alkylating agents that form stable carbenium ions (tertiary, benzylic, allylic, those carrying an α-oxygen, sulfur, or nitrogen).[2] The reaction can be extended to primary

alkylation by use of α-chloroalkyl phenyl sulfides which are valuable intermediates for not only alkylation but also alkylidenation.[18] Examples of electrophiles (see Table 1) include alkyl glycosides,[19] *N*-alkylhexahydro-1,3,5-triazine,[20] α-acetoxy[21] or α-sulfonyl amides,[22] cationic η^5-dienyliron complexes,[23] electron-deficient pyridines,[24] and elemental fluorine.[25] Addition to dimethyl acetals[5] give products which are protected aldol (eq 4) derivatives. Dibutyltin ditriflate can be used to activate acetals selectively in these type of reactions.[26]

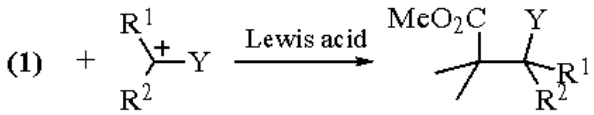

(Y = cation-stabilizing group)

Table 1 Prototypical Reactions of Ketene Alkyl Silyl Acetals

Electrophile	Reaction conditions	Product	Yield (%)
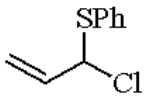	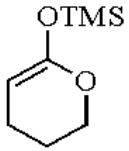 , 0.02 equiv $ZnBr_2$, CH_2Cl_2, 20 h, rt	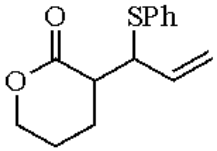	76
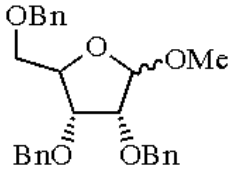	**(1)**, $ZnCl_2$, TMSBr, CH_2Cl_2, rt	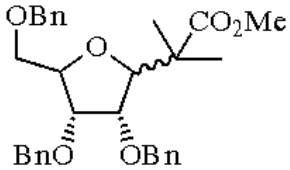	63 α:β = 5:1
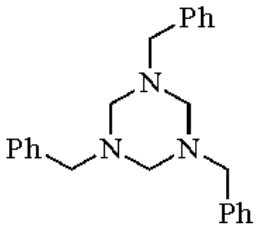	**(1)**, 0.01 equiv CF_3SO_3H, CH_2Cl_2, rt, 3 h	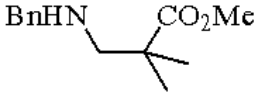	83
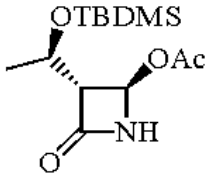	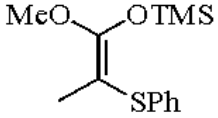 , 0.1 equiv ZnI_2, 1 h, MeCN, rt	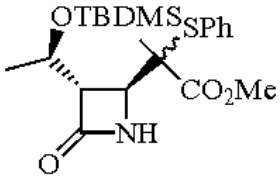	95
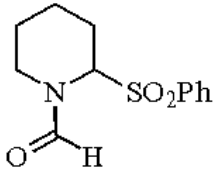	**(1)**, $AlCl_3$, -78 °C to rt, CH_2Cl_2, 30 min	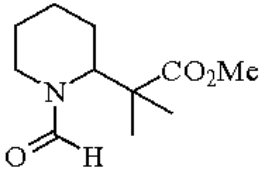	89

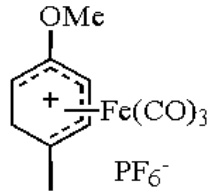	1. **(1)**, CH_2Cl_2, MeCN, Δ; 2. Me_3NO, PhH, 55 °C	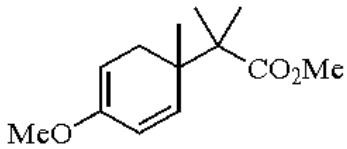	-
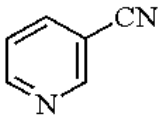	**(1)**, Fe montmorillonite, CH_2Cl_2, rt, 2 h	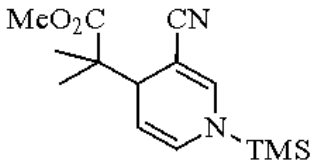	94
5% F_2/N_2	**(1)**, Cl_3CF, -78 °C	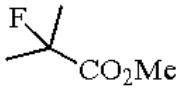	76

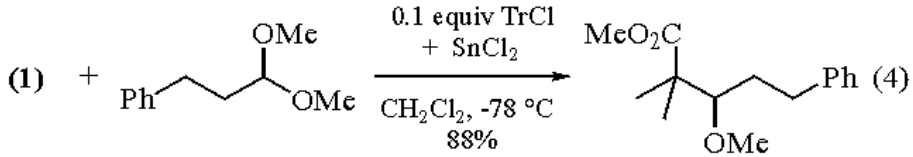

(4)

Aldol Reactions: Addition to Aldehydes and Imines.

Since its discovery, the Mukaiyama aldol reaction[27] has attracted considerable attention and several improvements in reaction conditions have been reported. Most useful catalysts for this reaction appear to be recently reported lanthanide triflates (eq 5),[3] ***Bis(cyclopentadienyl)titanium Bis(trifluoromethanesulfonate)***, or $Cp_2Zr(OTf)_2$.THF,[28] The metallocene salt also catalyzes additions to ketones (eq 6). This reaction can also be carried out under essentially neutral conditions by warming (70 °C) a stoichiometric mixture of the aldehyde and the KSA in acetonitrile (eq 7).[8,29] When an optically active aldehyde is used, a slightly better stereochemical control is noticed under catalysis of ***Zinc Iodide***.[29]

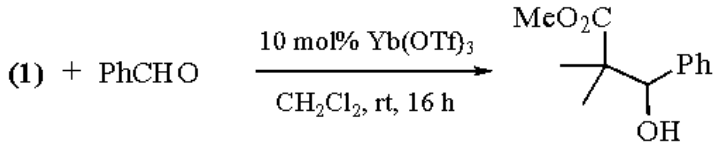

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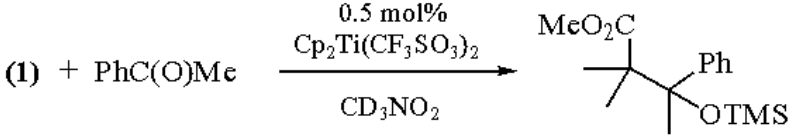

(6)

1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene

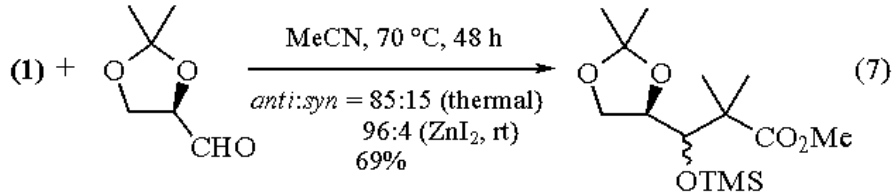

In the presence of an amino acid-derived boronate (e.g. **2**)[30] or a diamine-tin(II), complex,[31] as Lewis acids, optically active aldol products are obtained in good yields (eq 8). In the addition of KSAs to iminies, a diphosphonium ditriflate[32] (eq 9) or an acidic montmorillonite clay[33] has been claimed to give better results than the originally reported Lewis acids (***Titanium(IV) Chloride***[34] and ***Trimethylsilyl Trifluoromethanesulfonate***[35]). The products of this reaction are valuable intermediates for the synthesis of β-lactams.[36] Two excellent reviews covering this area have recently appeared.[4,37]

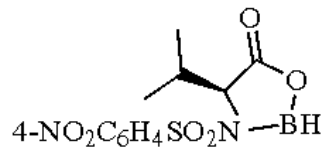

(2)

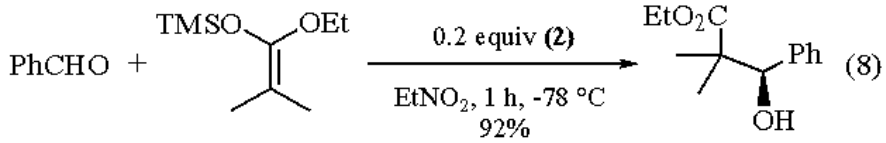

90% ee

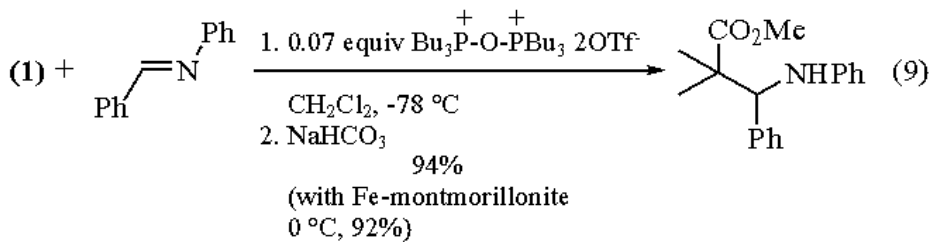

Mukaiyama-Michael Reactions.

1,4-Addition of ketene alkyl silyl acetals to α,β-unsaturated carbonyl compounds (eq 10) is promoted by a variety of Lewis acids[38] (for example, $TiCl_4$, $Ti(OR)_4$, $SnCl_4$, trityl perchlorate, lanthanide salts, Al-montmorillonite clay), or Lewis bases such as fluoride ion (eq 11),[7] or quaternary ammonium carboxylates.[39] Lanthanide salts are particularly effective catalysts,[40] and in the case of ***Ytterbium(III) Trifluoromethanesulfonate***, the catalyst can be recovered (eq 10).[38]

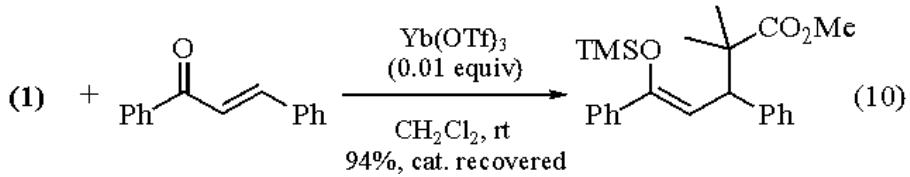

1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene

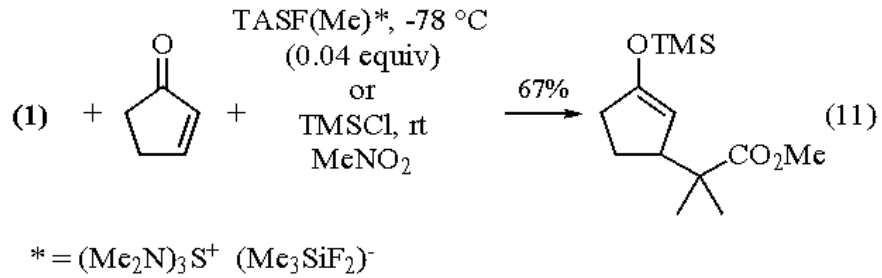

This reaction can also be carried out thermally,[7,8] under neutral conditions. The thermal reaction is the most convenient when the conjugate adduct is to be trapped as the regiochemically pure silyl enolate. In the case of the disubstituted KSAs such as the title compound, this addition reaction is sluggish, and may require electrophilic catalysis (eq 11) (TMSCl,[7] 5.0 M $LiClO_4/Et_2O$[41]) or high pressure.[42] Sequential Michael additions to α,β-unsaturated esters lead to polymers (group transfer polymerization) whose molecular weight and end group functionality can be controlled (eq 12).[9] Mechanistic studies indicate an associative intramolecular silicon transfer process via (**2**), with concomitant C-C bond formation during the polymer growth. Other Michael-type reactions include additions to acetylenecarboxylic esters (eq 13),[15,43] and nitroalkenes (eq 14).[44] Stereochemical[45] and mechanistic (electron transfer?)[46] studies on the Mukaiyama-Michael reaction have been reported and ways of improving the diastereoselectivity have been prescribed.[6]

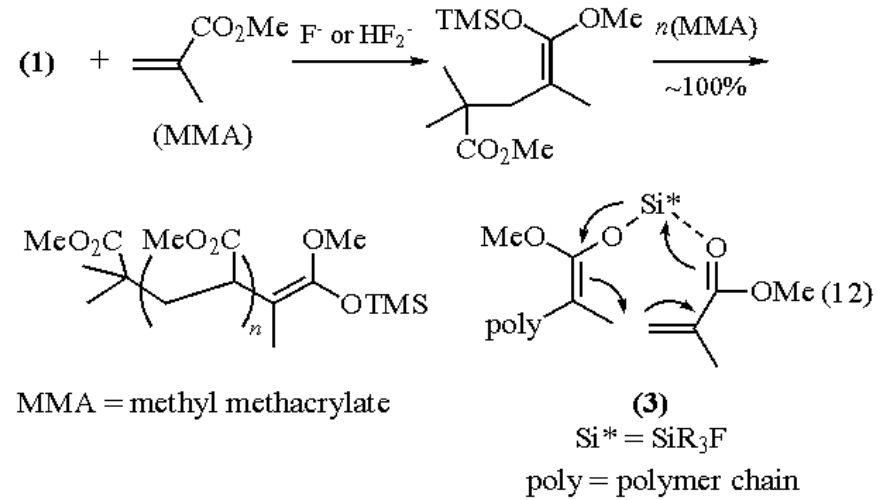

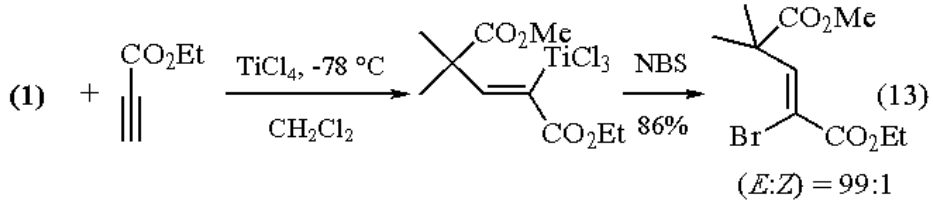

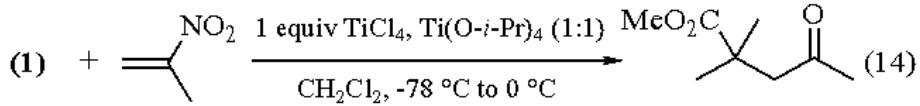

Nitroarylation.

In the presence of stoichiometric amounts of ***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate***, (**1**) undergoes addition to aromatic nitro compounds to give dihydroaromatic nitro intermediates (eq 15), which are easily oxidized to α-nitroaryl carbonyl compounds by ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** or ***Bromine***.[10] These compounds are potentially useful for the synthesis of oxindoles and aryl acetic acids.

1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene

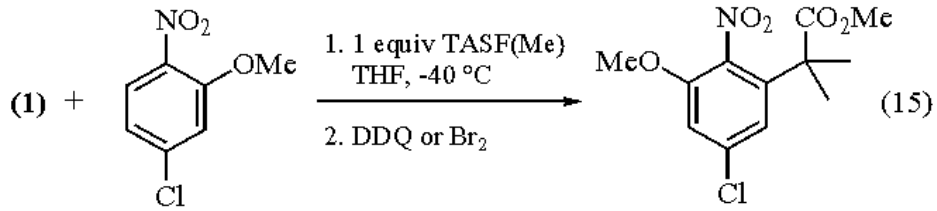

Oxidation of Ketene Silyl Acetals.

Singlet oxygen oxidizes KSAs resulting in a cleavage of C-C bonds (eq 16),[47] the reaction presumably proceeding through a silyl peroxide intermediate. ***Lead(IV) Acetate***[11] and ***m-Chloroperbenzoic Acid***[48] oxidize KSAs to α-acetoxy (or hydroxy) carboxylic acid derivatives. Oxidative dimerization of ketene silyl acetals by $TiCl_4$ (eq 17)[12] can be understood in terms of single-electron transfer to the Lewis acids.[49]

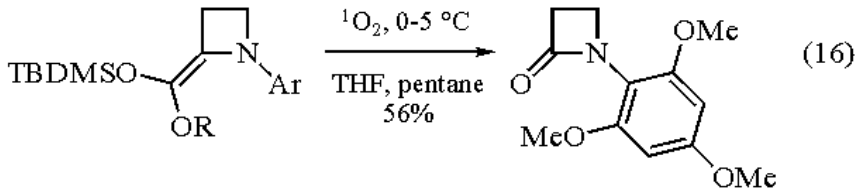

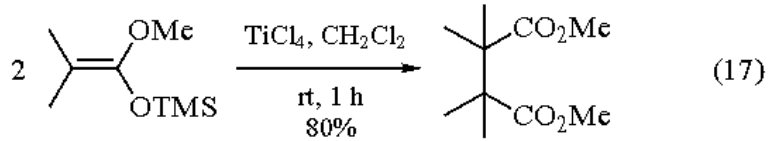

Cycloaddition Reactions of Ketene Silyl Acetals.

In the presence of ***Zirconium(IV) Chloride***, KSA adds to ethyl propiolate in a [2 + 2] fashion (eq 18).[15] Other cycloaddition reactions include cycloaddition to imines (eq 19),[13] addition of ***Ethyl Azidoformate***,[14] chlorovinylcarbene,[50] and (ethoxycarbonyl)nitrene.[51] Synthesis of β-lactams from KSAs and imines have attracted considerable attention and the subject has been reviewed recently.[4,37] Cyclopropanation of KSAs with Et_2Zn/CH_2I_2 to provide cyclopropanone acetals is also known (eq 20).[52]

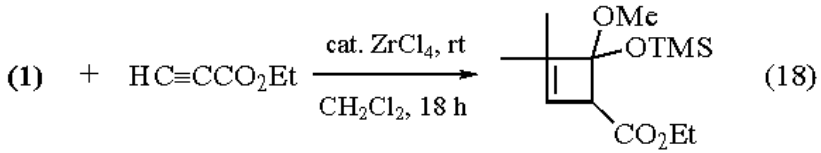

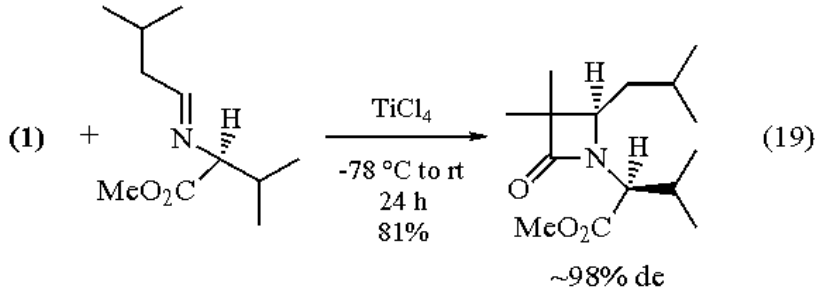

1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene

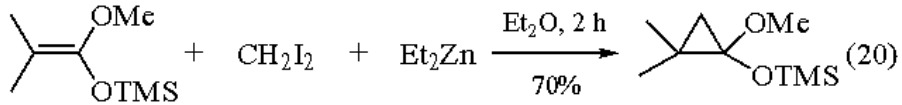

Related Reagents.

t-Butyl α-Lithioisobutyrate; ***Dilithioacetate***; ***Ethyl Lithioacetate***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Tris(trimethylsilyloxy)ethylene***.

---

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2-(*o*-Methoxyphenyl)-4,4-dimethyl-2-oxazoline[1,2]

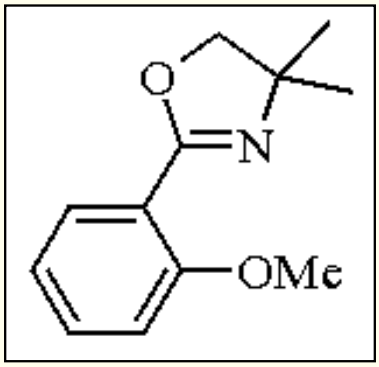

[57598-33-1] · $C_{12}H_{15}NO_2$ · 2-(*o*-Methoxyphenyl)-4,4-dimethyl-2-oxazoline · (MW 205.28)

(electrophilic arylation of Grignard reagents, lithium reagents, and lithium amides by methoxy displacement; synthesis of *o*-substituted benzoic acids, *o*,*o*´-biphenyls, and *o*-aminobenzoates[3,4])

Alternate Name: 2-(2´-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole.

Preparative Method: prepared from *o*-anisic acid and 2-amino-2-methyl-1-propanol in two steps.[3,4]

Handling, Storage, and Precautions: no special precautions are warranted.

General Considerations.

The title reagent, upon treatment with Grignard and organolithium reagents, undergoes displacement of the methoxy group (2-oxazolines are quite resistant to nucleophilic attack; Table 1).[4,5]

Table 1 Nucleophilic Displacement of the Title Reagent

Nucleophile	Product	Yield (%)
BuMgBr	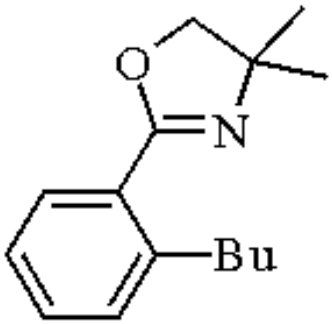	85
PhMgBr	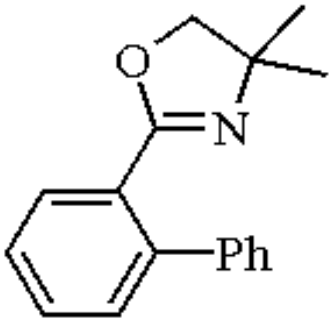	95

Many nucleophiles have been used for this methoxy displacement reaction, and a wide array of substitution on the aryl group of the oxazoline is also tolerated. Thus, this method allows facile preparation of unsymmetrical biphenyls as their *ortho* carboxylic acids and esters, after hydrolysis of the oxazoline (eqs 1-3).[6-8]

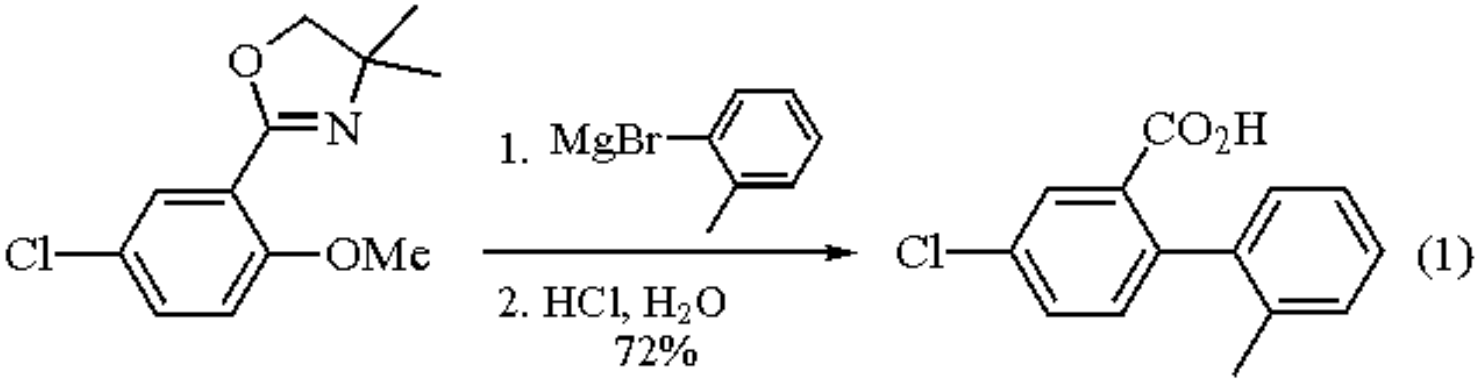

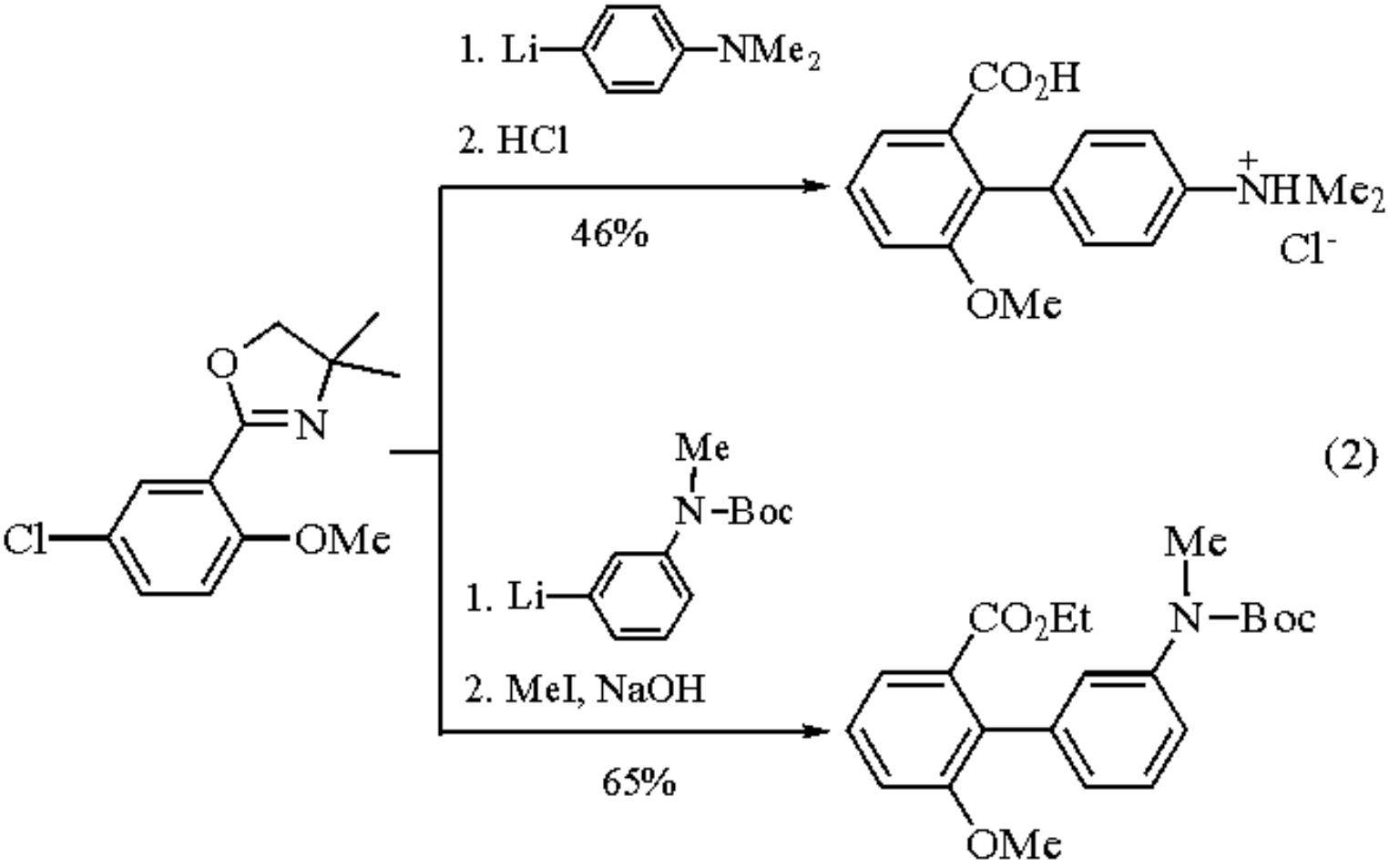
1. Li
NMe2
2. HCl
46%
CO2H
NHMe2
Cl-
OMe
O
N
Cl
OMe
Me
N-Boc
1. Li
2. MeI, NaOH
65%
CO2Et
Me
N-Boc
OMe

(2)

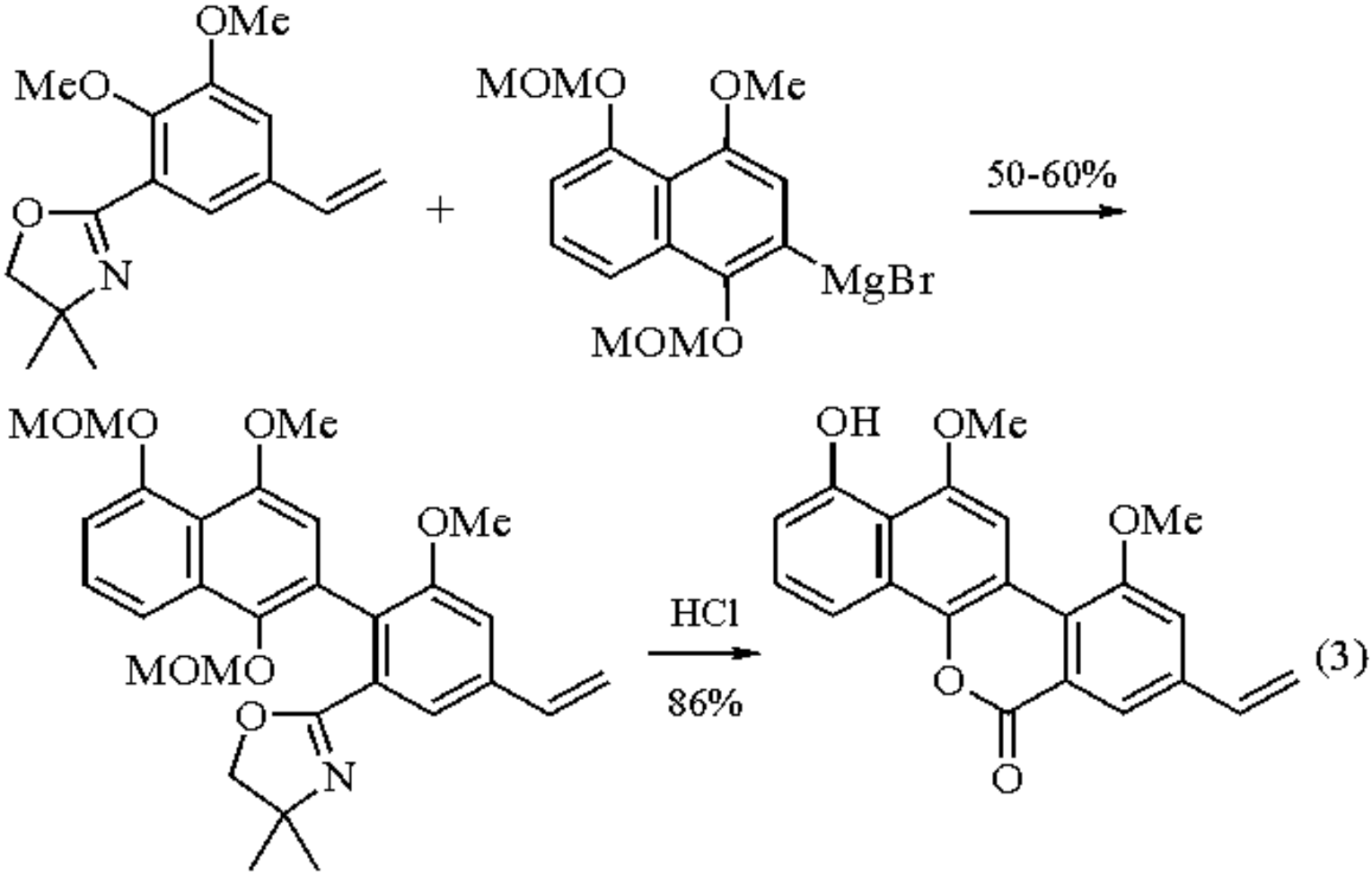

Moreover, the oxazoline can be directly converted to a variety of other functional groups, including ketones, alcohols, aldehydes, and nitriles.[1,2] Similar arylations occur by nucleophilic aromatic substitution of 2-(*o*-fluoroaryl)[9-11] and 2-(*o*-aminonaphthyl)oxazolines with Grignard and organolithium reagents. An extension of this methodology incorporates the lithio salts of primary and secondary amines as nucleophiles[12,13] (eq 4).

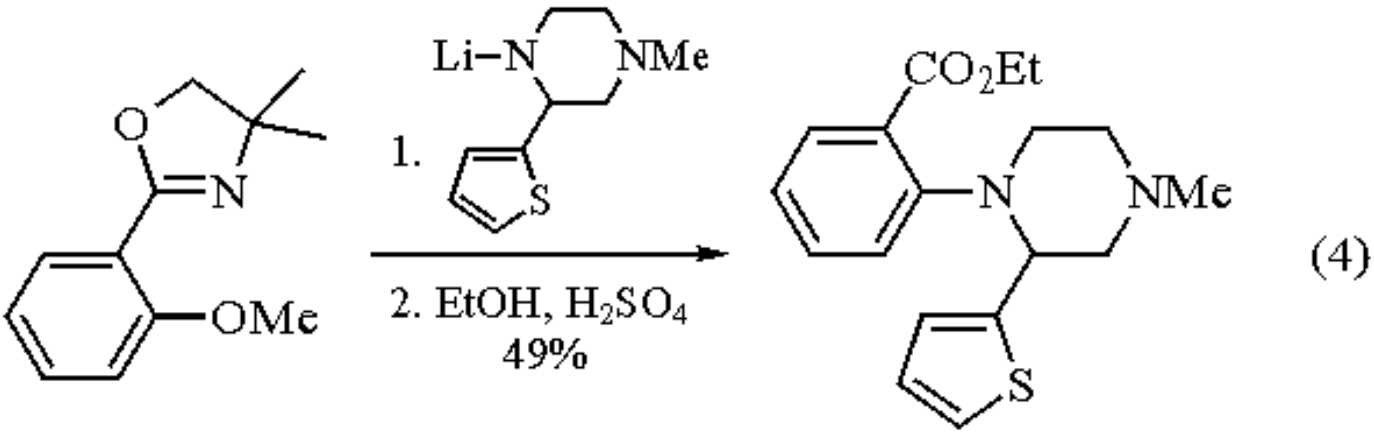

2-(*o*-Methoxyaryl)oxazolines derived from amino alcohols other than 2-amino-2-methyl-1-propanol can also participate in the above described methodology. For example, *o*-anisic acid and ethanolamine combine to form the corresponding oxazoline (75%), and on treatment with a Grignard reagent, the *o*-alkylated aryl oxazoline is obtained (eq 5).[14]

2-(o-Methoxyphenyl)-4,4-dimethyl-2-oxazoline

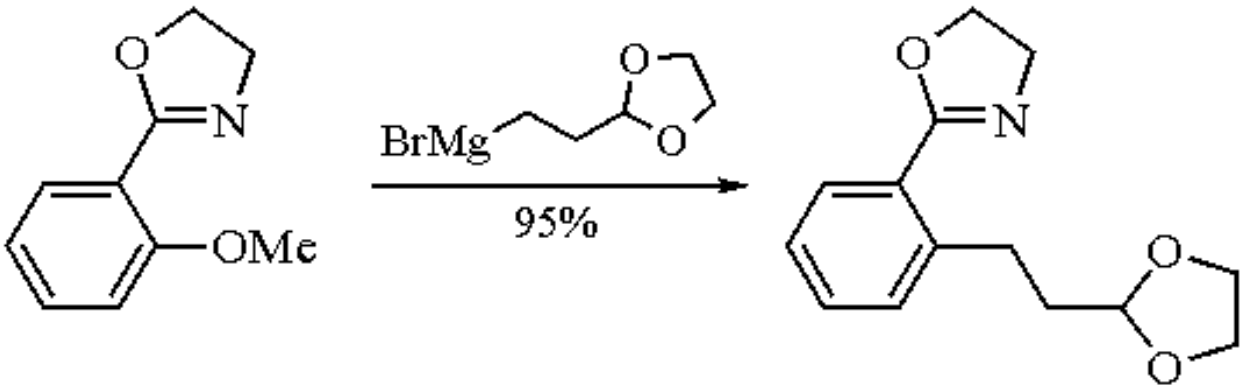

(5)

Optically active biphenyls and binaphthyls can be prepared by using the appropriately substituted chiral oxazoline precursors (eqs 6 and 7).[15-18]

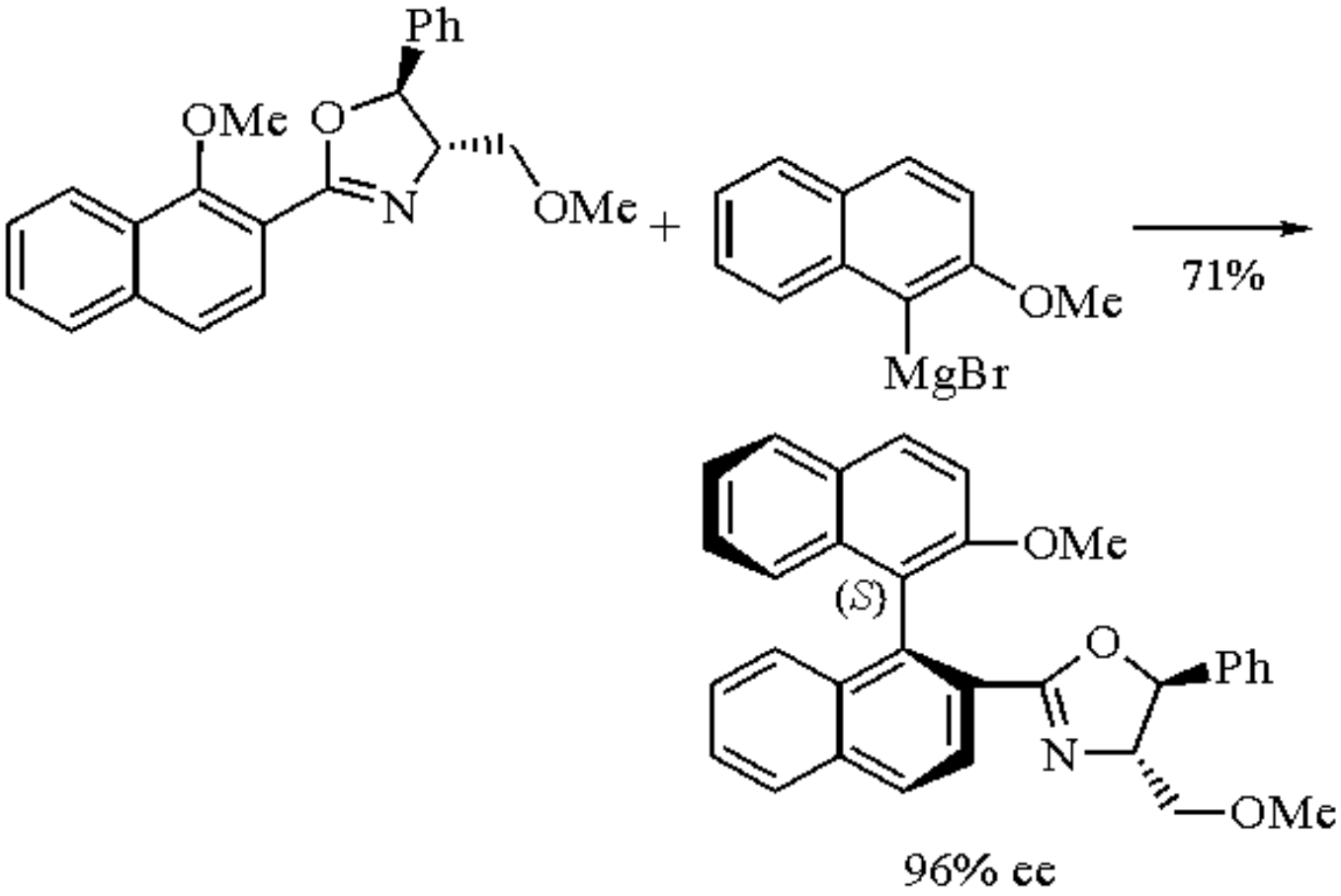

(6)

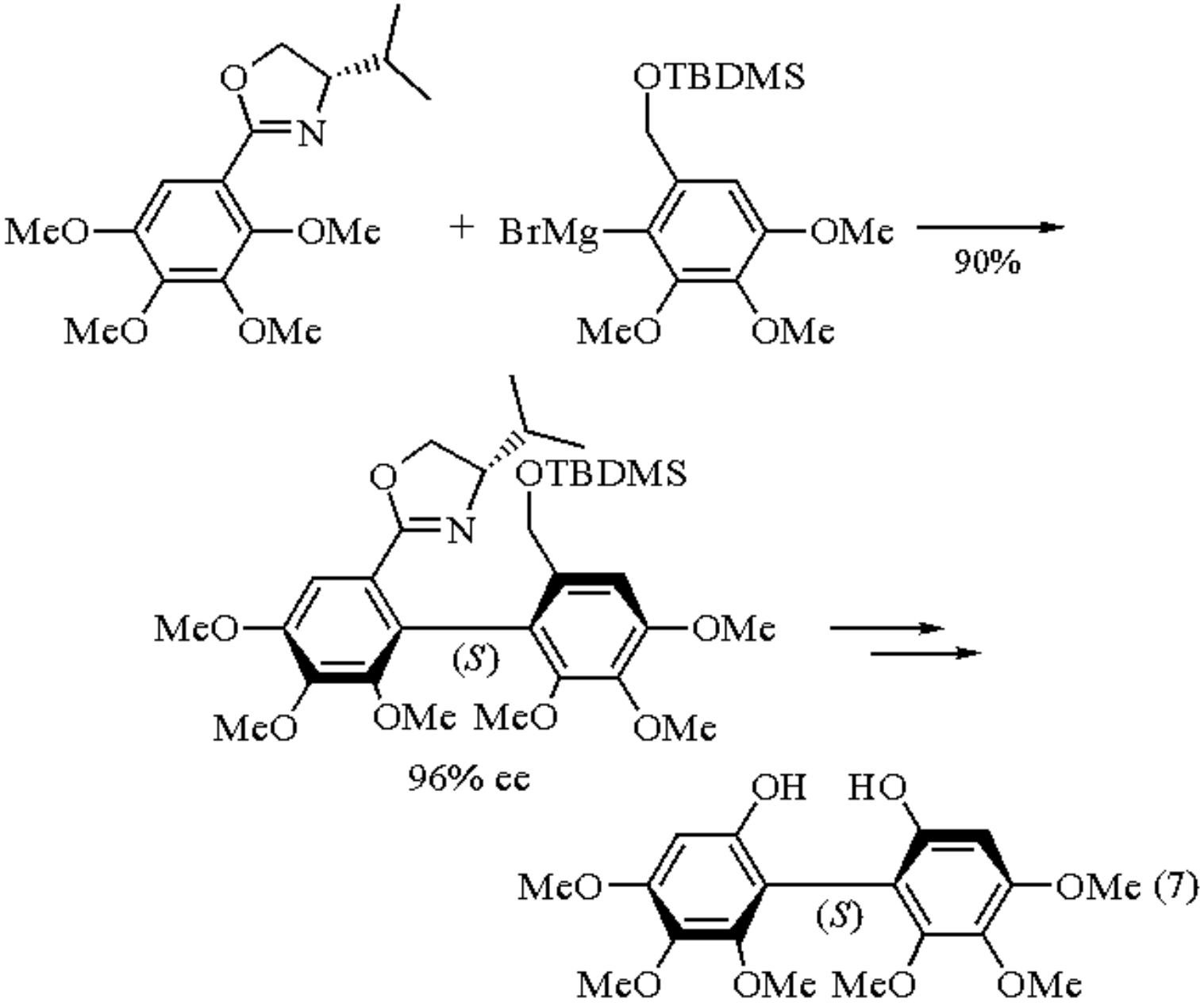

The same process is applicable to methoxy displacement from enantiomerically pure 2-(*o*-methoxyaryl)oxazolines. Optically active biphenyls can be rapidly accessed in this manner.[19] For example, an enantiomerically pure (*S*)-valinol-derived oxazoline reacts with Grignard reagents to form C_2-symmetric biaryls after further elaboration (eq 7).[20]

A similar transformation of *o*-methoxybenzaldehydes to *o*-substituted benzaldehydes has been accomplished by conversion of the benzaldehyde to *N*-(2,4-dimethyl-3-pentyl)imine, which is resistant to nucleophilic attack at the C=N bond.[21] Similar methodology has been utilized to prepare enantiomerically enriched binaphthyls.[22] Likewise, bulky esters *ortho* to a methoxy group can be substituted for the oxazoline group in the above mentioned protocol, thus affording biaryls[23] and binaphthyls.[24] In addition, *ortho*-substituted fluoroaryl oxazoles undergo nucleophilic aromatic substitution reactions.[25]

Related Reagents.

(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline; ***2,4,4-Trimethyl-2-oxazoline***.

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20. Meyers, A. I.; Meier, A.; Rawson, D. J. *TL* **1992**, *33*, 853.
21. Flippin, L. A.; Carter, D. S.; Dubree, N. J. P. *TL* **1993**, *34*, 3255.
22. Shindo, M.; Koga, K.; Tomioka, K. *JACS* **1992**, *114*, 8732.
23. Hattori, T.; Suzuki, T.; Miyano, S. *CC* **1991**, 1375.
24. Hotta, H.; Suzuki, T.; Miyano, S. *CL* **1990**, 143.
25. Cram, D. J.; Bryant, J. A.; Doxsee, K. M. *CL* **1987**, 19.

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7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone

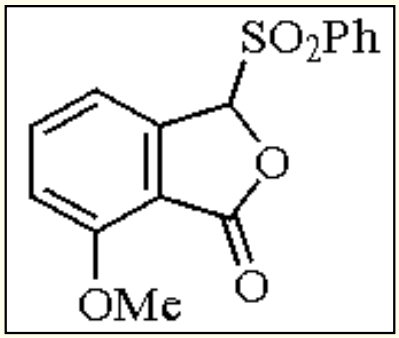

[65131-09-1] · $C_{15}H_{12}O_5S$ · 7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone · (MW 304.34)

(regioselective synthesis of 1,4-dihydroxy-2,3-disubstituted naphthalenes)

Physical Data: colorless solid; mp 176-177 °C.

Solubility: partially sol THF; sol acetone.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.10 (s, 1H), 7.04 (d, *J* = 8 Hz, 1H), 7.40-7.92 (m, 7H).

Preparative Methods: ethyl 2-methoxy-6-methylbenzoate is oxidized via the dibromide to the corresponding 3-hydroxyisobenzofuranone, which is subsequently treated with thiophenol and catalytic acid. Oxidation to the sulfone is accomplished with either ***m-Chloroperbenzoic Acid*** or ***Hydrogen Peroxide***.[1a] An alternative one-step method utilizing the requisite phthaldehydic acid has also been described.[2]

Handling, Storage, and Precautions: apparently stable at rt and requires no special handling or precautions.

Aromatic Annulation.

7-Methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**1**) can be deprotonated at -78 °C with either ***Lithium Diisopropylamide*** or ***Lithium t-Butoxide*** to form a soluble yellow anion which can be utilized as an effective nucleophile in the Michael reaction. The initial anionic adduct cyclizes with concomitant elimination of benzenesulfinic acid to yield a 1,4-dihydroxynaphthalene which is unambiguously disubstituted at the 2- and 3-positions (eq 1).[1b]

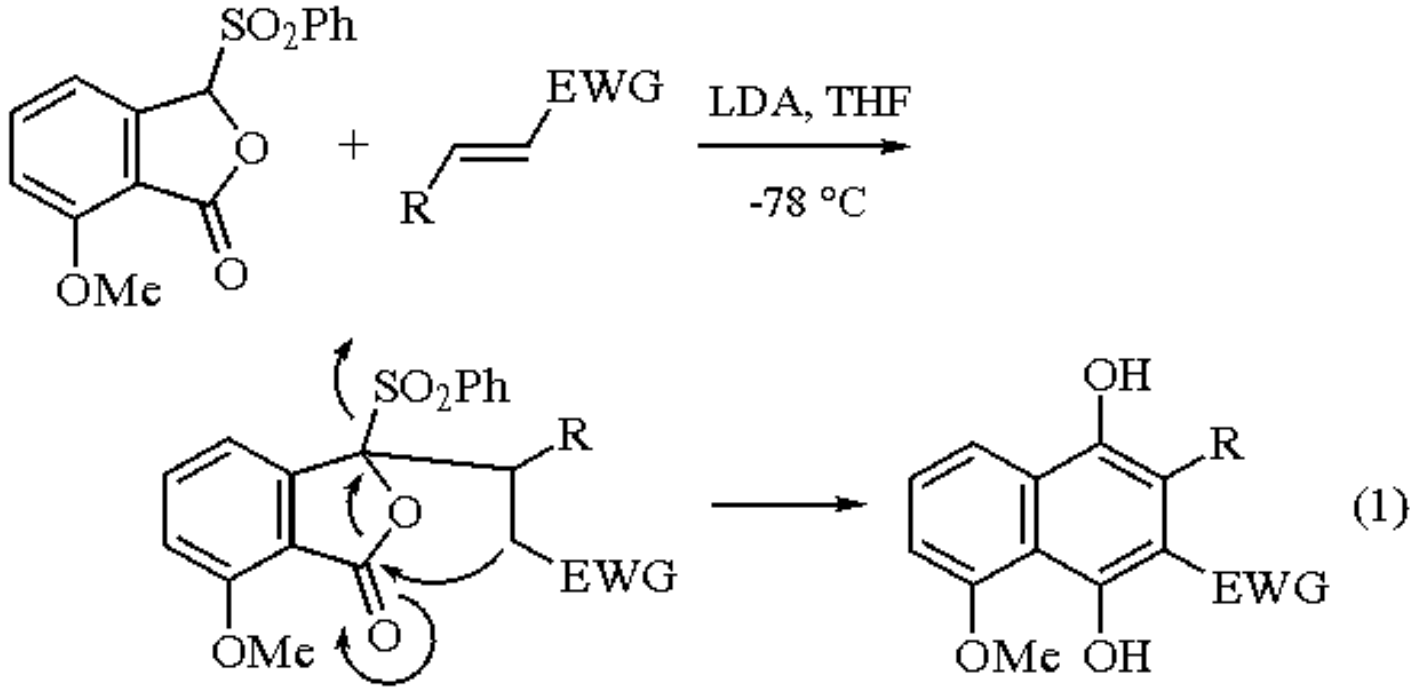

The 1,4-dihydroxynaphthalene products are susceptible to air oxidation and are frequently protected as the 1,4-dimethoxy derivatives. Alternatively, they may be intentionally oxidized to the naphthoquinones. A variety of acyclic and cyclic Michael acceptors participate in this reaction and yields are generally good. A few representative examples are seen in Table 1.[1b,3]

Table 1 Examples of Michael Acceptors which React with **(1)**

Michael acceptor	Yield (%)
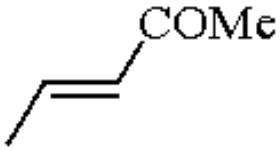	68
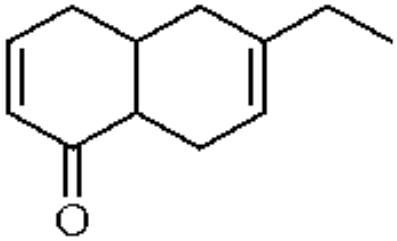	91
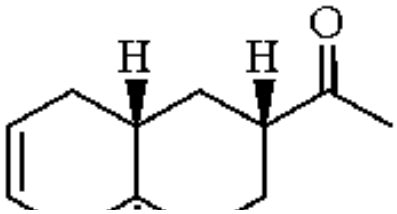	93

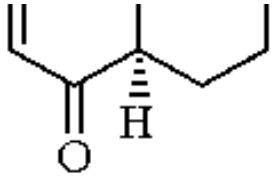

93

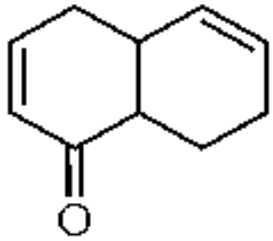

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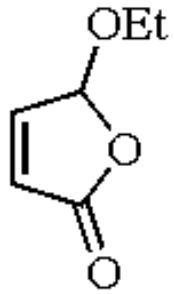

74

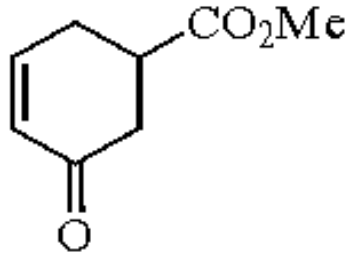

85

In fact, (**1**) represents a group of reagents (**2**)-(**6**) all having the 3-(phenylsulfonyl)isobenzofuranone moiety and all capable of the aromatic annulation reaction previously discussed.[1b,4-6]

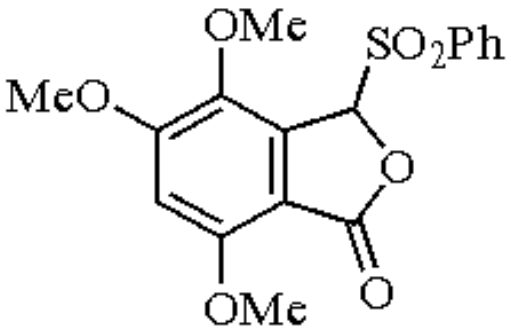

(2)

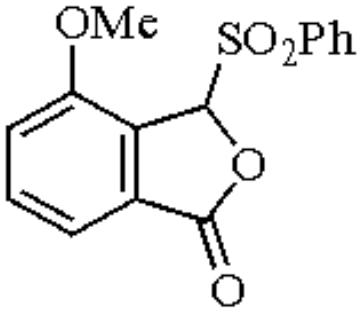

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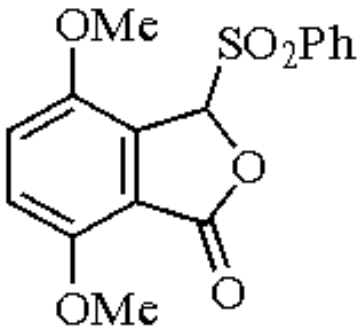

(4)

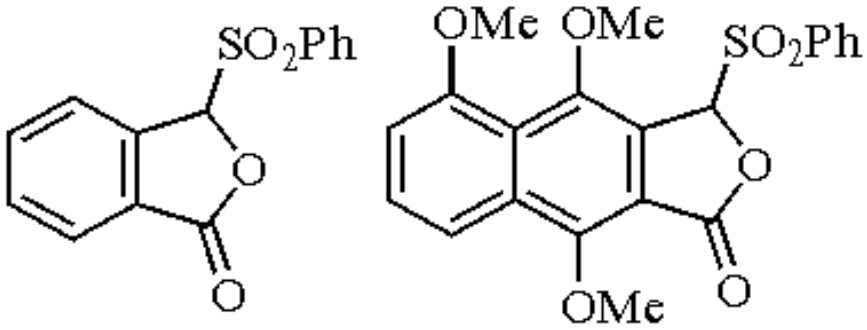

(5) (6)

Under conditions similar to those described above, these compounds have been frequently utilized as building blocks for the synthesis of a wide range of molecules in the anthracyclinone family.

Alternative Reagents.

3-Cyanoisobenzofuranones have also been synthesized and shown to be useful in identical aromatic annulation reactions (eq 2).[7] Moreover, in several direct comparisons of 3-cyano vs. 3-phenylsulfonyl, the cyano version generally provides higher yields of the desired product.[8] Nevertheless, on a large scale the liability of cyanide waste streams could be an important negative factor.

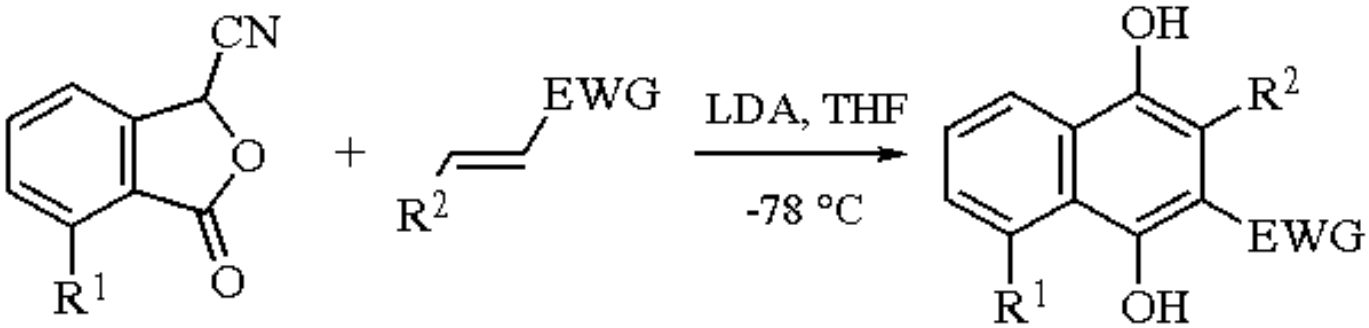

(2)

Related Reagents.

Similar aromatic annulations have been reported with a number of conceptually related reagents,[1b,9] the common thread of these methods being regioselective installation of substituents in the 2- and 3-positions of the newly formed naphthalene.

---

1. (a) Hauser, F. M.; Rhee, R. P. *JOC* **1980**, *45*, 3061. (b) Hauser, F. M.; Rhee, R. P. *JOC* **1978**, *43*, 178.
2. Kadiyala, V. S. N.; Murty, R. P.; Dutta, K.; Mal, D. *SC* **1990**, *20*, 1705.
3. (a) Hauser, F. M.; Prasanna, S. *T* **1984**, *40*, 4711. (b) Hauser, F. M.; Mal, D. *JACS* **1983**, *105*, 5688. (c) Hauser, F. M.; Prasanna, S.; Combs, D. W. *JOC* **1983**, *48*, 1328. (d) Hauser, F. M.; Prasanna, S. *JACS* **1981**, *103*, 6378. (e) Hauser, F. M.; Prasanna, S. *JOC* **1982**, *47*, 383.
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JOC **1983**, *48*, 3439.
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9. (a) Dodsworth, D. J.; Calcagno, M.-P.; Ehrmann, E. U.; Devadas, B.; Sammes, P. G. *JCS(P1)* **1981**, 2120. (b) Dodd, J. H.; Weinreb, S. M. *TL* **1979**, 3593. (c) Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *TL* **1978**, 2213.

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2-Methoxy-3-phenylthio-1,3-butadiene

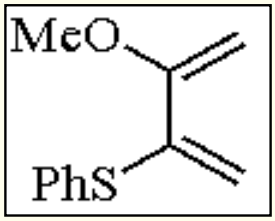

[60603-16-9] · $C_{11}H_{12}OS$ · 2-Methoxy-3-phenylthio-1,3-butadiene · (MW 192.30)

(Diels-Alder diene)

Solubility: sol most organic solvents.

Preparative Methods: the cyclobutene precursors (e.g. **1**) to the reagent and related dienes are available from cyclobutanone in three steps (eq 1).[1] The ring opening of the cyclobutenes to form the title reagent (**2**) and related dienes may be accomplished by flash vacuum pyrolysis (eq 2), or is often carried out in situ in the presence of a dieneophile. Due to the instability of the dienes, they should be formed as needed from the precursor cyclobutenes.

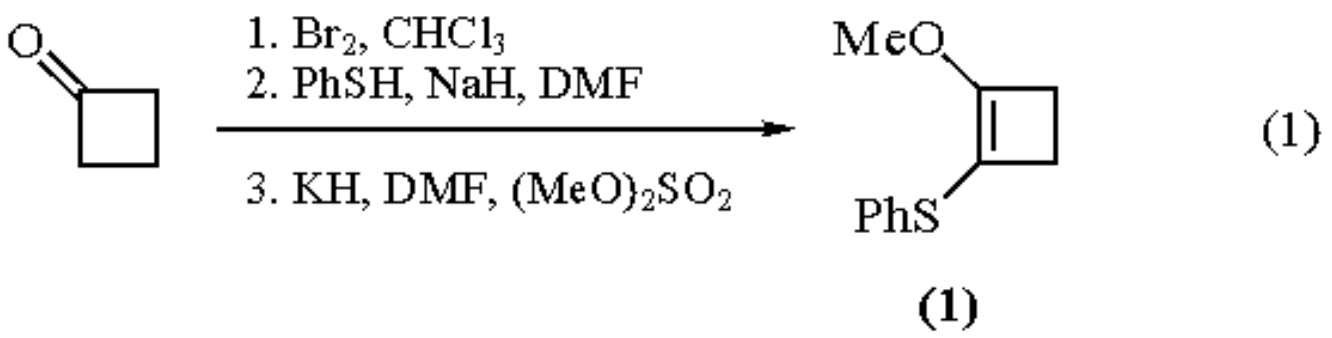

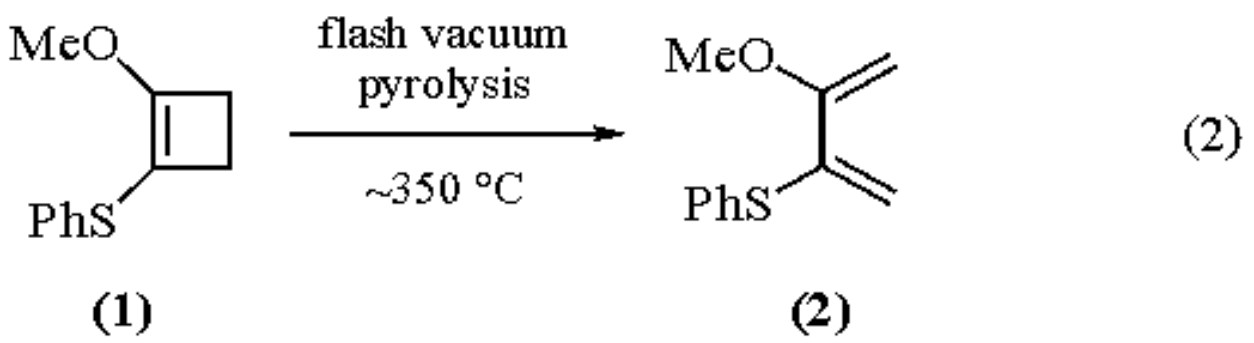

Handling, Storage, and Precautions: the dienes should be both formed and used in the presence of a radical inhibitor such as BHT.

General Considerations.

2-Alkoxy(acyloxy)-3-arylthiobuta-1,3-dienes such as (**2**) are highly reactive and versatile in Diels-Alder reactions.[2] The Diels-Alder regiochemistry is usually controlled by the sulfur (eq 3), but the competition between dominance by the sulfur or oxygen depends on the substitution on the heteroatoms, the presence of Lewis acids, and the choice of dienophile. For example, the 2-acetoxy-3-*p*-anisylthiobutadiene (**3**) displays an increased tendency for sulfur dominance, especially in the presence of Lewis acids (eq 4). With an electron-withdrawing 2´-pyrimidyl group on the sulfur, the oxygen becomes dominant (eq 5).

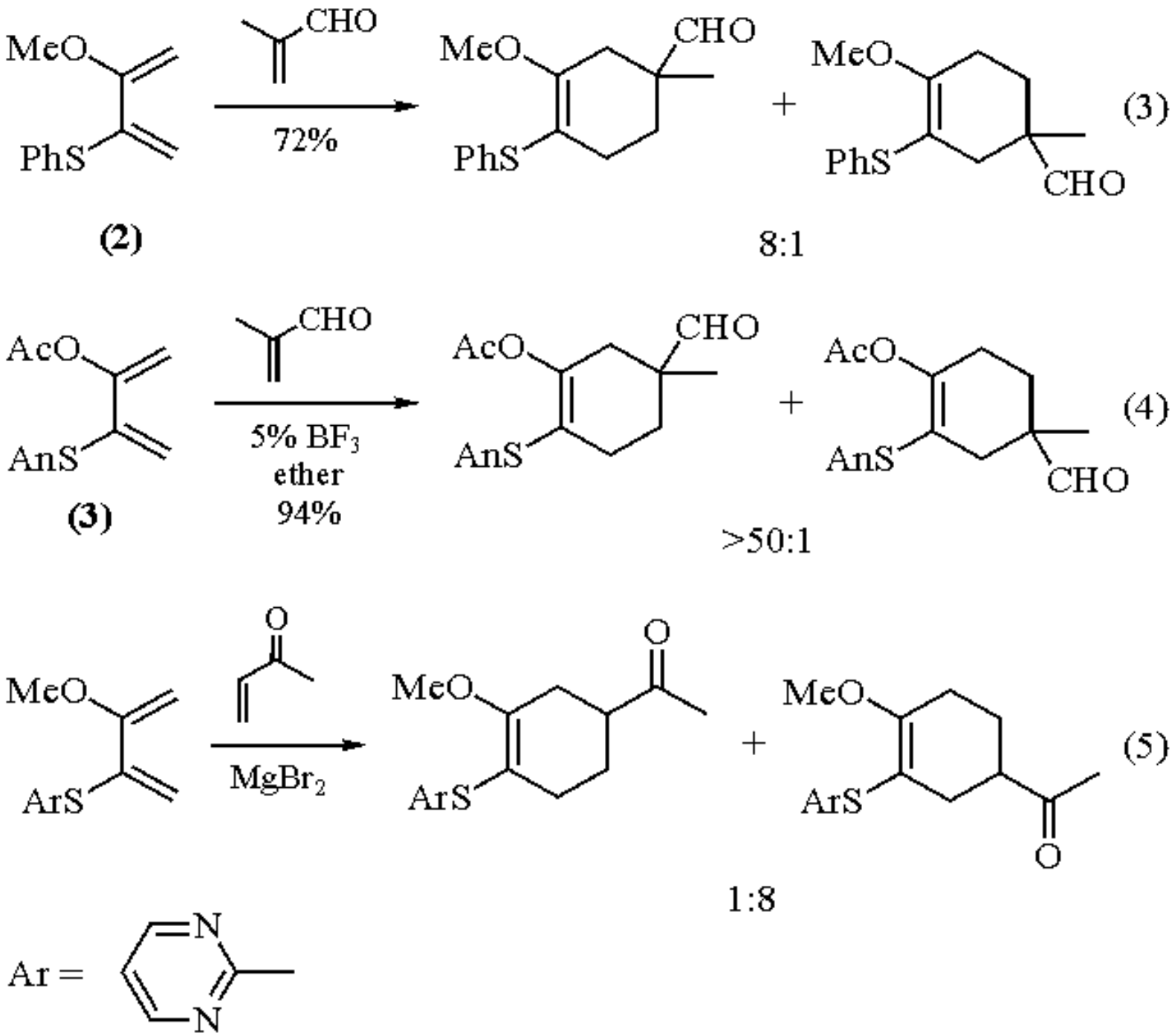

When the sulfur dominates the regiochemistry, these dienes provide entries into 1,3-disubstituted cyclohexanes after

hydrolysis and desulfurization, reversing the normal orientation of Diels-Alder reactions. The more readily available and stable 1-phenylthio derivatives should be considered as alternatives for this purpose (see ***2-Methoxy-1-phenylthio-1,3-butadiene***). The phenylthio group is also useful for directing alkylations of the ketone obtained on hydrolysis of the Diels-Alder adducts (eq 6).

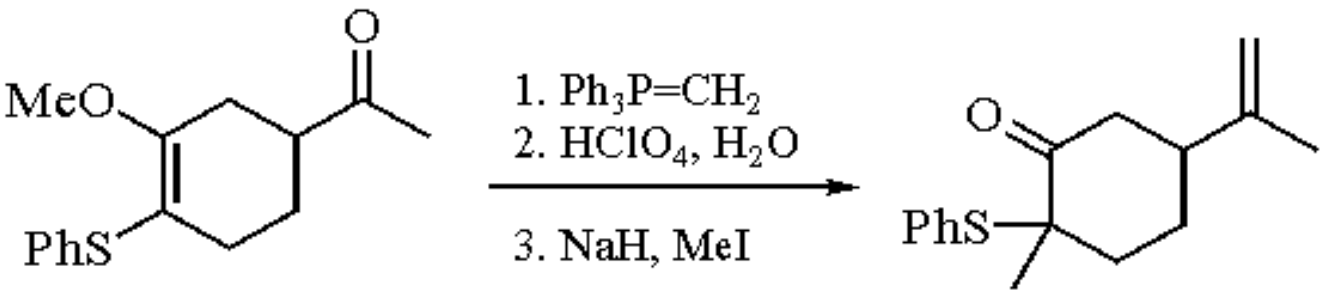

(6)

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1. Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *JACS* **1980**, *102*, 3548.
2. Trost, B. M.; Bridges, A. J. *JACS* **1976**, *98*, 5017. Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *JACS* **1980**, *102*, 3554.

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2-Methoxy-1-phenylthio-1,3-butadiene

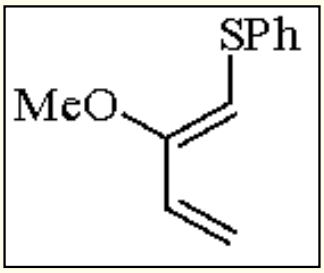

[65415-13-6] · $C_{11}H_{12}OS$ · 2-Methoxy-1-phenylthio-1,3-butadiene · (MW 192.30) (*E*)

[67315-81-5] (*Z*)

[60466-66-2]

(Diels-Alder diene[3])

Physical Data: bp 85-95 °C/0.005 mmHg.[1]

Solubility: sol most organic solvents.

Preparative Methods: the pure (*Z*) reagent is available in two steps from ***Bis(phenylthio)methane*** and ***Acrolein*** by an *Organic Syntheses* procedure (eq 1).[1] Related dienes may be prepared either similarly or by *O*-methylation of enolates derived from sulfenylated enones.[2]

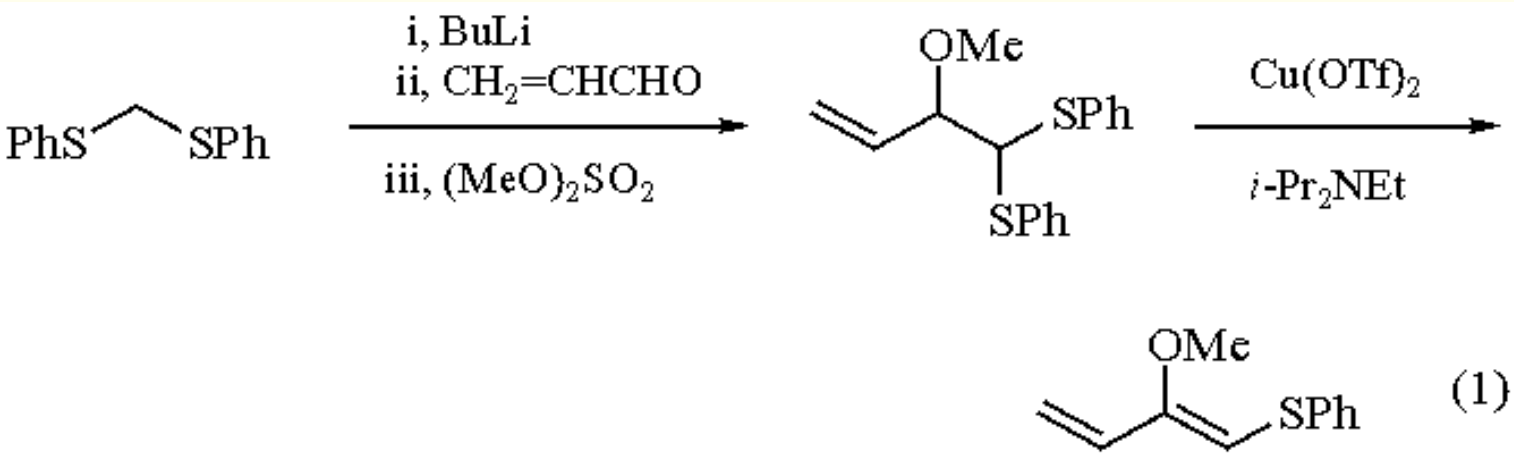

Handling, Storage, and Precautions: the (*Z*) reagent should be stored in a freezer in the presence of a radical inhibitor to avoid isomerization.[1]

General Discussion.

2-Alkoxy-1-phenylthio-substituted dienes are highly useful in Diels-Alder reactions due to their ready availability,[1,2] good reactivity, high selectivity,[3] and the many useful transformations of the product cyclohexenyl sulfides.[3,4] As shown in eq 2, the phenylthio group generally controls the regiochemistry. The Lewis acid-catalyzed reactions with enones seem particularly effective.[3] Hetero Diels-Alder reactions with diacylimines (eq 3) are also highly regioselective.[5] A nice example of the possible product transformations is the conversion in eq 4 with utilization of the Diels-Alder stereochemistry via a 2,3-sigmatropic rearrangement.[3]

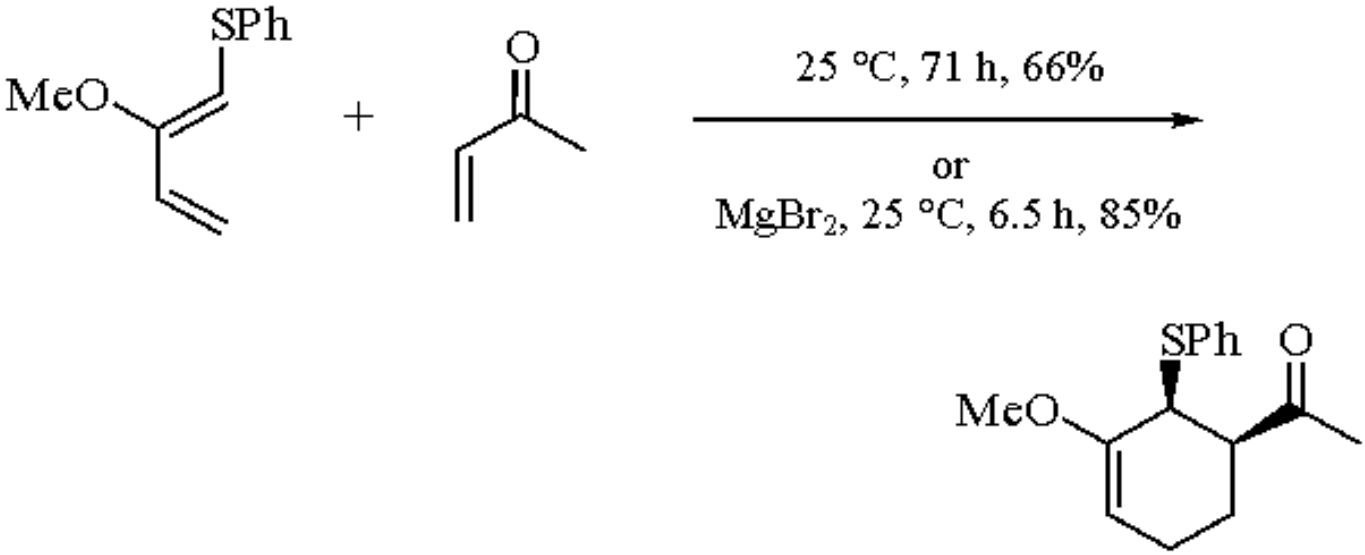

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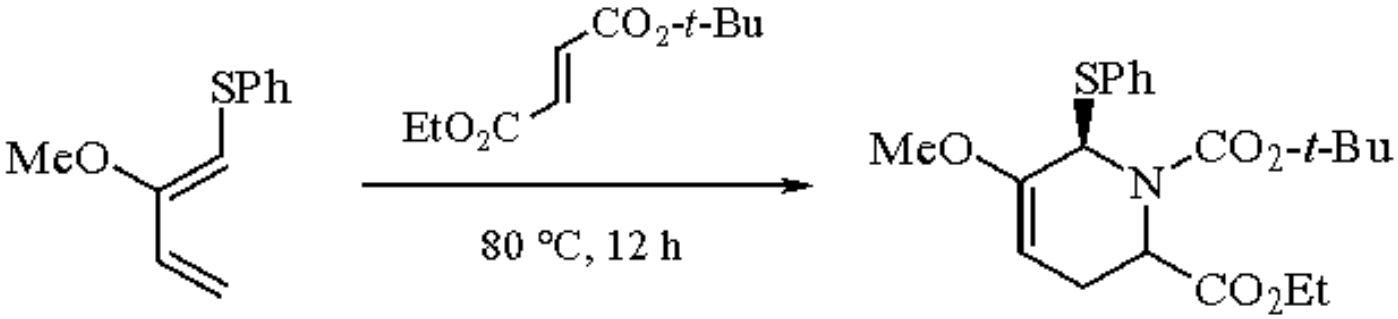

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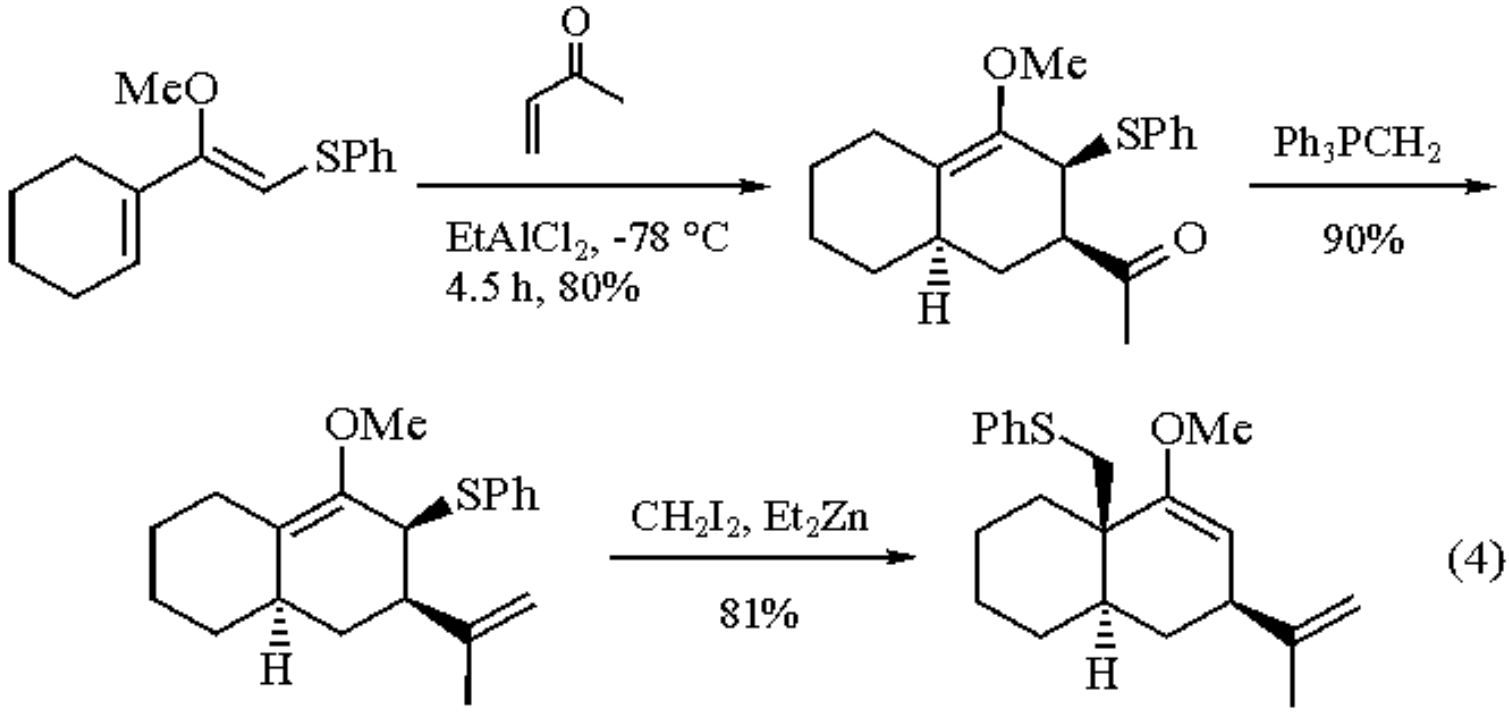

(4)

The Diels-Alder reactions of 2-methoxy-1-phenylthiobutadiene with ***Acrylonitrile*** (eq 5) served as a key example in arguments supporting a large influence of secondary orbital interactions on the regiochemistry of Diels-Alder reactions, because the regioselectivity is significantly higher for the *endo* products.[6] This argument has been compromised in recent years by a continuing lack of ab initio support for the Woodward-Hoffmann-type secondary orbital interaction.[7]

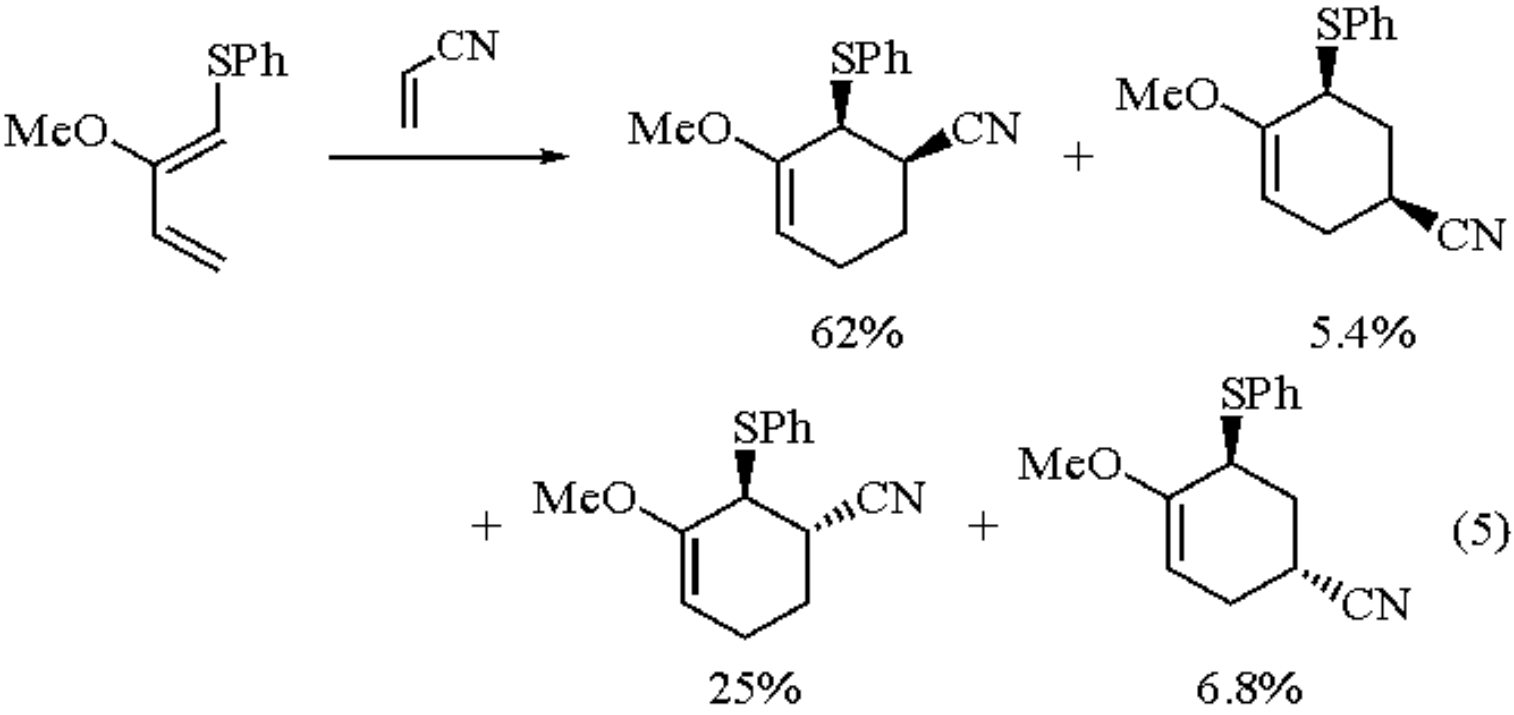

(5)

Related Reagents.

1-Acetoxy-1,3-butadiene; ***2-Methoxy-3-phenylthio-1,3-butadiene***; ***1-Trimethylsilyloxy-1,3-butadiene***; ***2-Trimethylsilyloxy-1,3-butadiene***.

1. (a) Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R. *OS* **1980**, *59*, 202. (b) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *JOC* **1976**, *41*, 3218.
2. Cohen, T.; Kosarych, Z. *TL* **1980**, *21*, 3955.
3. Cohen, T.; Kosarych, Z. *JOC* **1982**, *47*, 4005.
4. (a) Kozikowski, A. P.; Huie, E.; Springer, J. P. *JACS* **1982**, *104*, 2059. (b) Kozikowski, A. P.; Sugiyama, K.; Springer, J. P. *JOC* **1981**, *46*, 2426. (c) Evans, D. A.; Bryan, C. A.; Sims, C. L. *JACS* **1972**, *94*, 2891.
5. Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *TL* **1981**, *22*, 4607.
6. (a) Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *JOC* **1978**, *43*, 4052. (b) Alston, P. V.; Ottenbrite, R. M.; Cohen, T. *JOC* **1978**, *43*, 1864. (c) Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M.; Cohen, T. *JOC* **1983**, *48*, 5051.
7. Singleton, D. A. *JACS* **1992**, *114*, 6563, and references therein.

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Methoxy(phenylthio)methane[1]

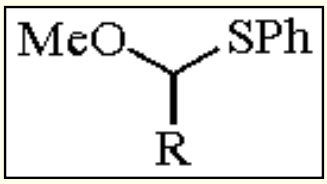

(R = H)

[13865-50-4] · $C_8H_{10}OS$ · Methoxy(phenylthio)methane · (MW 154.25) (R = Li)

[95540-81-1] · C_8H_9LiOS · Methoxy(phenylthio)methyllithium · (MW 160.18)

(carbonyl anion equivalent useful for homologation and ring expansion)

Physical Data: bp 113-114 °C/18 mmHg; *d* 1.047 g cm^{-3}.

Form Supplied in: neat liquid; commercially available.

Preparative Methods: via the base-catalyzed condensation of ***Thiophenol*** and ***Chloromethyl Methyl Ether***[2] or via the ***Boron Trifluoride Etherate***-catalyzed condensation of thiophenol and ***Dimethoxymethane***.[3]

Handling, Storage, and Precautions: store under inert gas to avoid air oxidation of the sulfide. Hydrolysis of the reagent releases thiophenol (stench!) which is known to be toxic. Use in a fume hood.

One-Carbon Homologations.

Methoxy(phenylthio)methane is a convenient one-carbon homologation reagent (also see ***1,3-Dithiane*** and ***Methoxy(phenylthio)trimethylsilylmethane***) with distinct differences from similar reagents derived from dithioacetals. Since the reagent possesses two different functional groups (methoxy and phenylthio), chemoselective manipulation of either functional group can be performed, resulting in an extremely versatile reagent. Methoxy(phenylthio)methane undergoes a facile deprotonation at the central carbon upon treatment with ***Lithium Diisopropylamide*** or ***n-Butyllithium*** at -78 °C in THF. The resultant anion reacts with a variety of electrophiles such as alkyl halides, aldehydes, ketones, and epoxides (eq 1).[4] The thioacetal products thus formed can be chemically manipulated to afford a variety of homologated products.

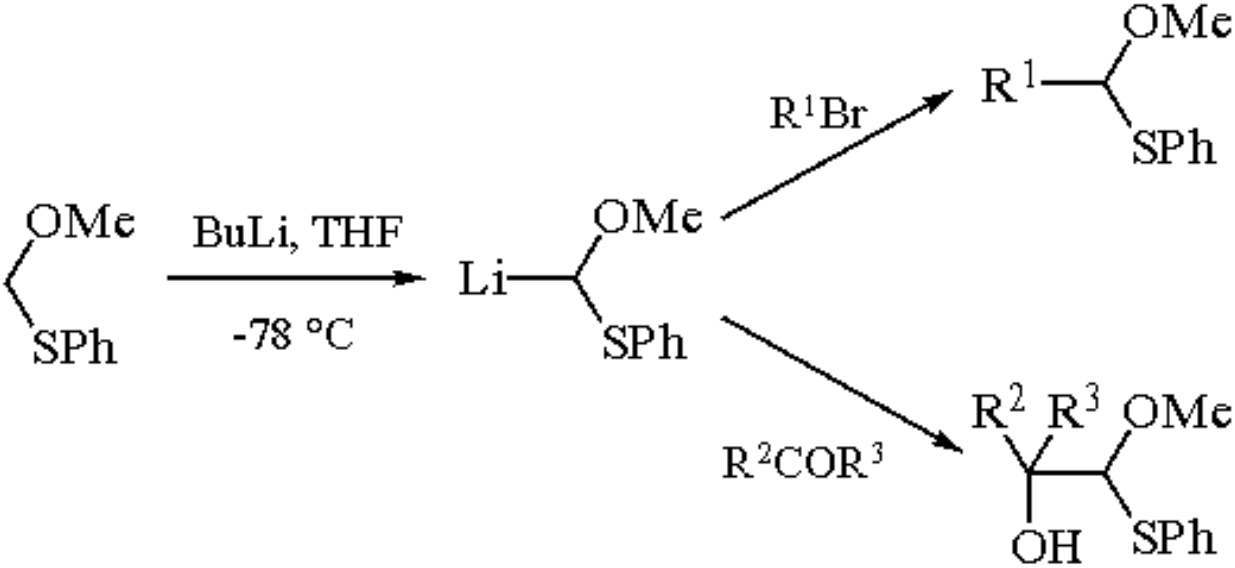

(1)

For example, treatment with ***p-Toluenesulfonic Acid*** in methanol affords dimethoxyacetals which can be further hydrolyzed to aldehydes (eq 2).[4] Aldehydes are also available in one step by oxidation of the sulfide to the sulfoxide with ***m-Chloroperbenzoic Acid*** and hydrolytic workup (eq 2).[4] Vinyl ethers are produced via a thermal elimination of benzenesulfenic acid (eq 3).[4] Alternately, the anion formed from the addition of methoxy(phenylthio)methyllithium to aldehydes can be treated with ***Carbon Disulfide*** and ***Iodomethane*** to form a xanthate which when treated with ***Tri-n-butylstannane*** effects a radical reductive elimination to form (*Z*)- and (*E*)-enol ethers (eq 4).[5]

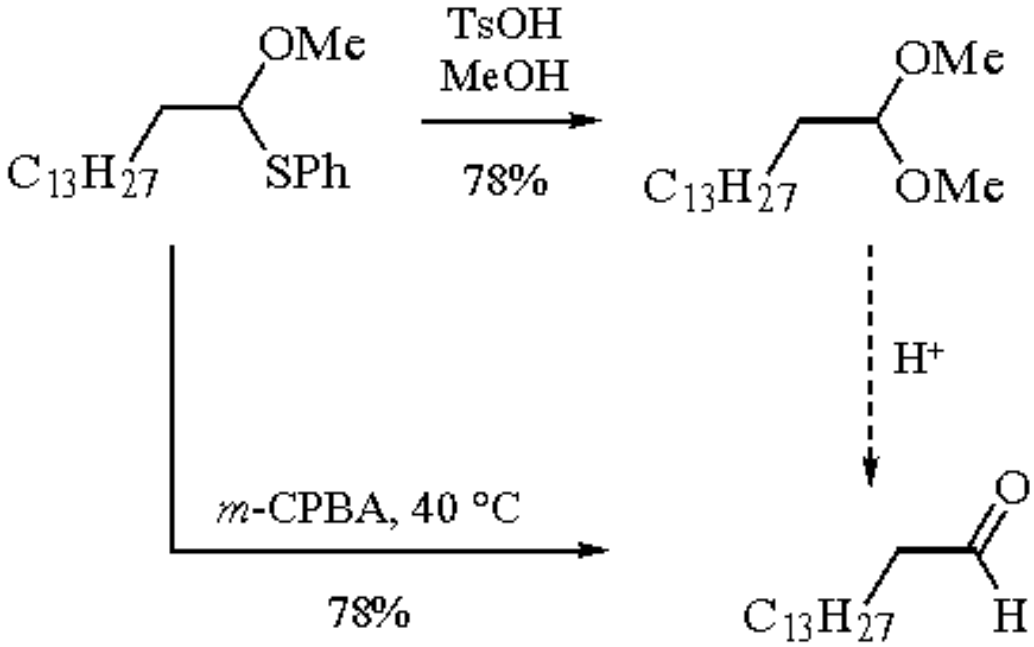

(2)

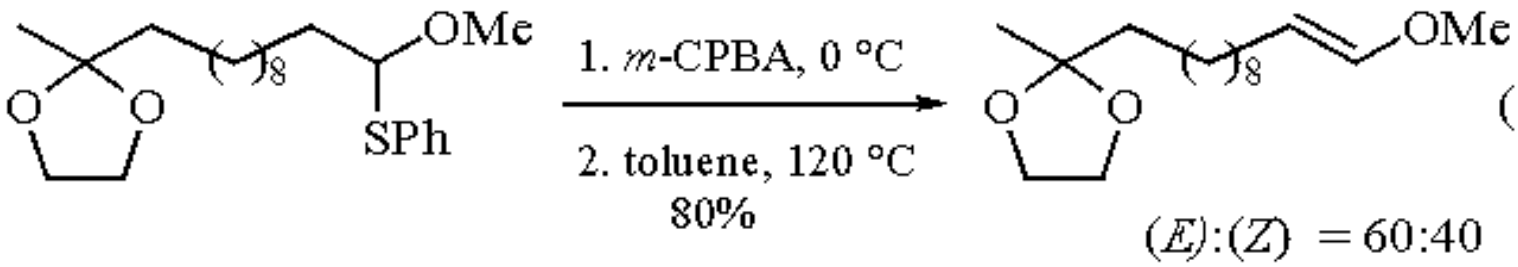

(3)

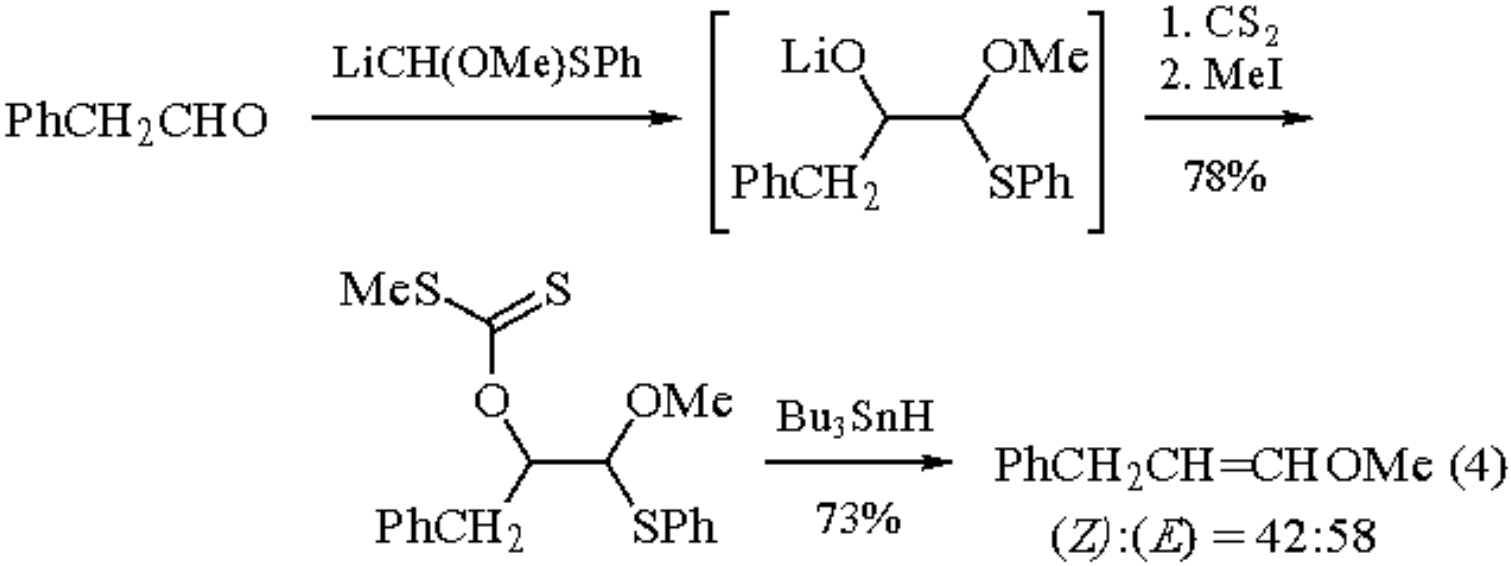

In addition, carboxylic acids are accessible from the homologated thioacetals via Jones oxidation (eq 5).[4] Conjugate addition of methoxy(phenylthio)methyllithium to a vinyl sulfone, followed by Jones oxidation and elimination of benzenesulfenic acid, afforded a dienoic acid (eq 6).[6] A novel approach to α-phenylthioaldehydes, which involves a phenylthio migration, results from treating the adducts of methoxy(phenylthio)methyllithium and ketones with ***Thionyl Chloride*** in ***Pyridine*** (eq 7)[7] or by treating the corresponding aldehyde adducts with ***Methanesulfonyl Chloride*** and ***Triethylamine***.[8] α-Phenylthioaldehydes thus obtained can be homologated further or converted to benzo[*b*]thiophenes.[9]

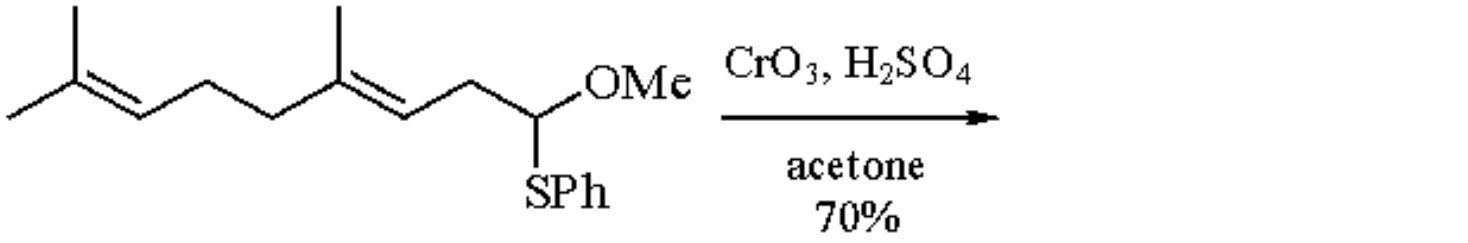

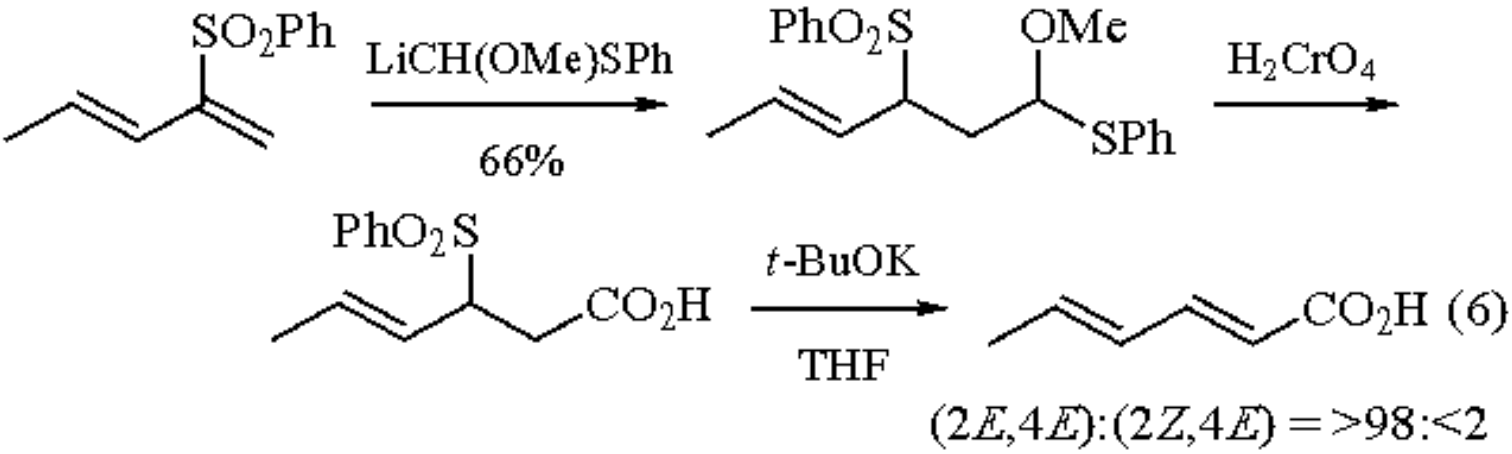

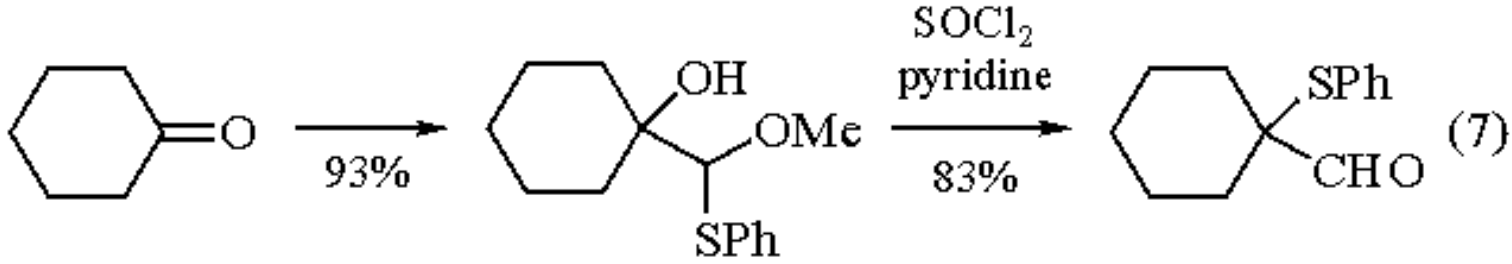

Alkylboronic esters available via the hydroboration of alkenes with dihaloboranes followed by alcoholysis can be homologated by reacting them with methoxy(phenylthio)methyllithium and treating the resulting ate complex with ***Mercury(II) Chloride*** followed by ***Hydrogen Peroxide*** (eq 8).[10] The use of an optically pure boronic ester affords optically pure aldehydes.[11]

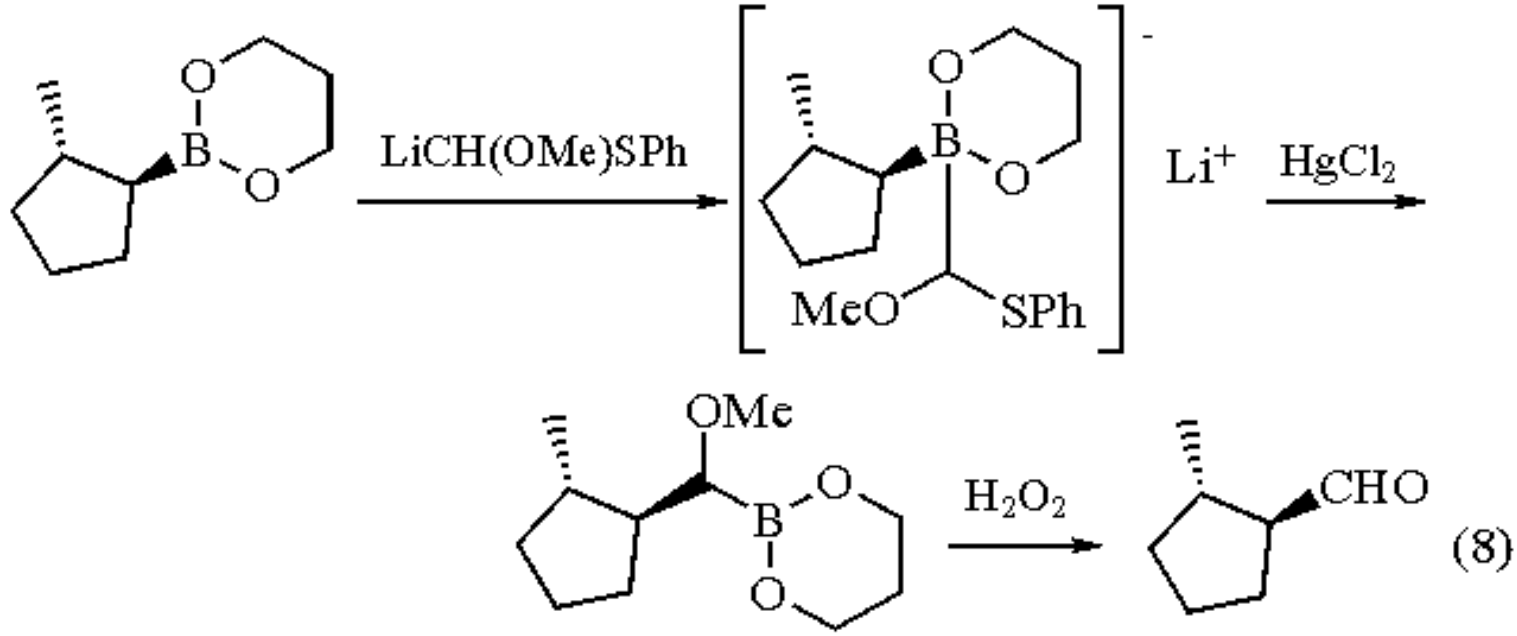

Homologation via Operations on Thioacetals.

Four-carbon 1,3- and 1,4-dicarbonyl homologated compounds are accessible via subsequent manipulation of the adducts resulting from the condensation of methoxy(phenylthio)methyllithium with aldehydes. For example, reaction of the acylated adducts with enol silyl ethers under Lewis acid catalysis results in carbon-carbon bond formation and 1,2-migration of the phenylthio moiety. Such α-methoxy-γ-phenylthio ketones were converted into 1,3-dicarbonyl or 1,4-dicarbonyl compounds (Scheme 1).[12] Alternately, the α-phenylthioaldehydes can be converted into 1,4-dicarbonyl compounds (Scheme 1).

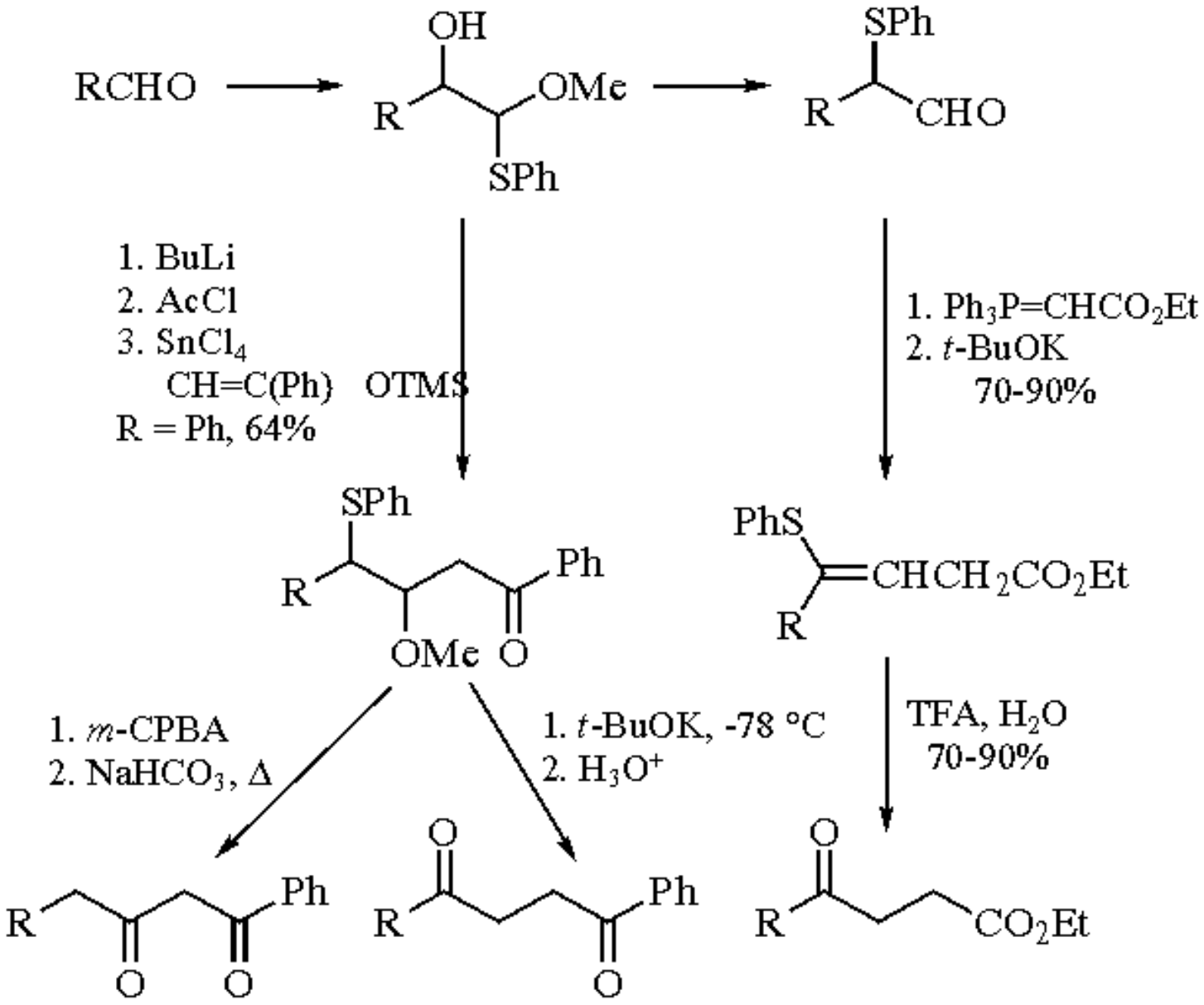

Scheme 1

The use of the thioacetal products as electrophiles in Lewis acid-promoted reactions of allyl- and propargylstannanes allows access to three-carbon homologated methyl ethers or phenyl sulfides (eq 9). Employment of ***Boron Trifluoride Etherate*** as the Lewis acid results in the selective cleavage of the phenylthio group to provide ether products. Similarly, the use of ***Titanium(IV) Chloride*** results in cleavage of the methoxy group and formation of phenyl thiosulfide products. These reactions partially compensate for the inability of monoalkylated *O,S*-acetals to undergo dialkylation. Apparently, substitution of one of the alkylthio groups for methoxy sufficiently decreases the stability of an α-carbanion such that it cannot be formed, thus precluding its alkylation (in contrast, dithioacetals can be dialkylated).

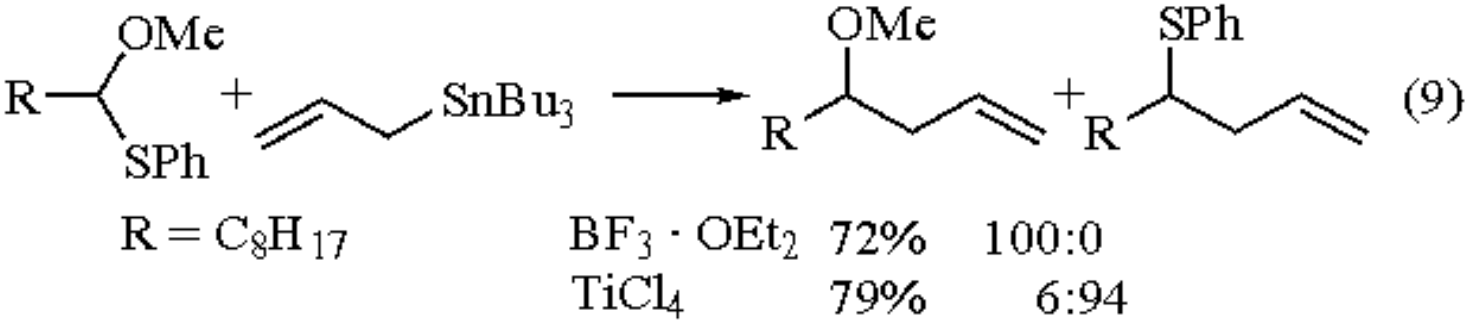

Ring Expansions.

Trost first demonstrated the advantages of methoxy(phenylthio)methane over ***Bis(phenylthio)methane*** as an acyl anion equivalent in a synthesis of α-methylene-δ-lactones via the ring expansion of γ-butyrolactones (eq 10).[2a] Use of the *O*,*S*-acetal reagent avoided problems encountered with enolization. Methoxy(phenylthio)methane has also been utilized for the ring expansion of nonenolizable 2-*n*-butylthiomethylene cyclohexanones to 3-formyl-2-cyclohepten-1-ones (eq 11).[13]

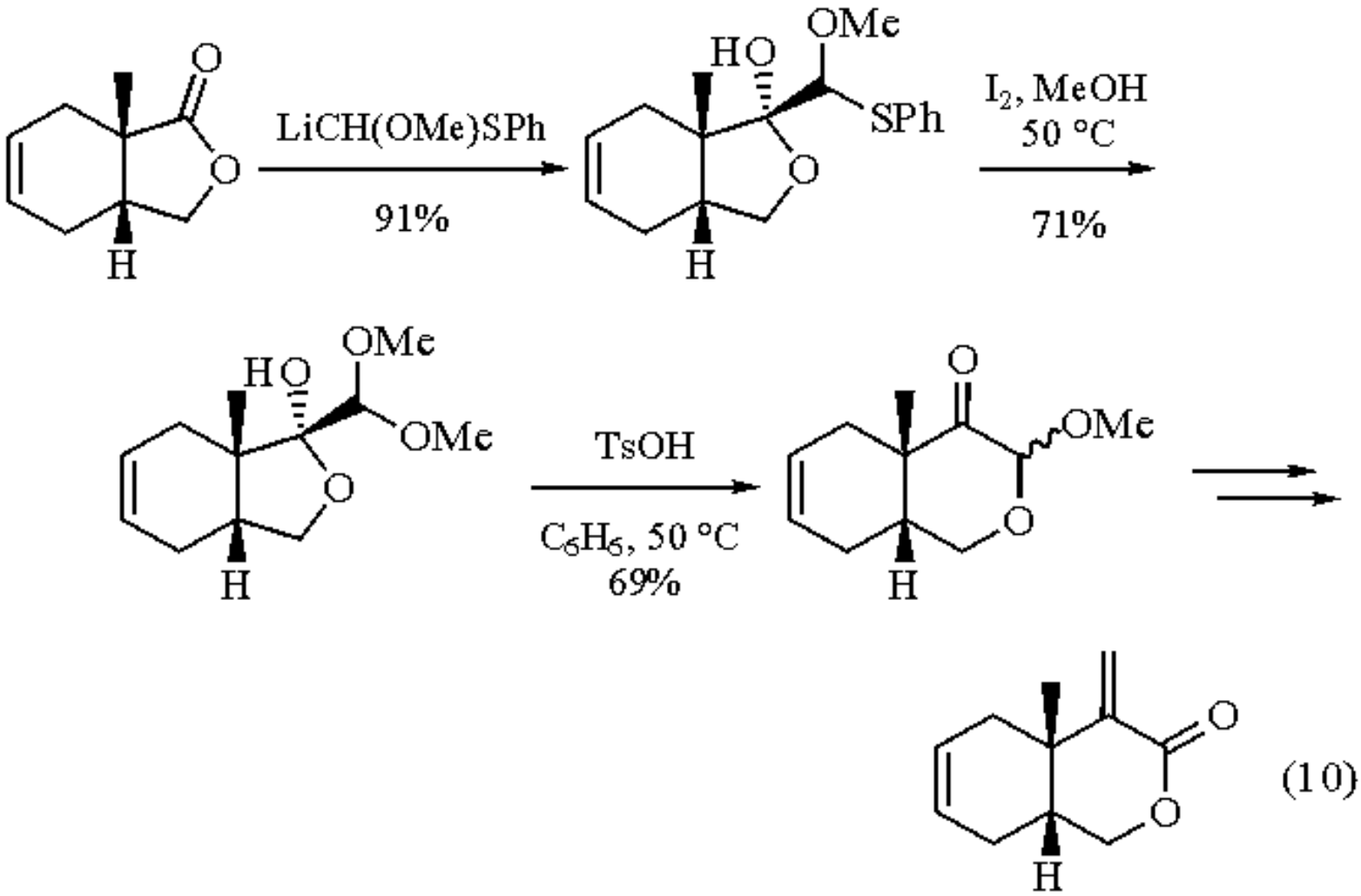

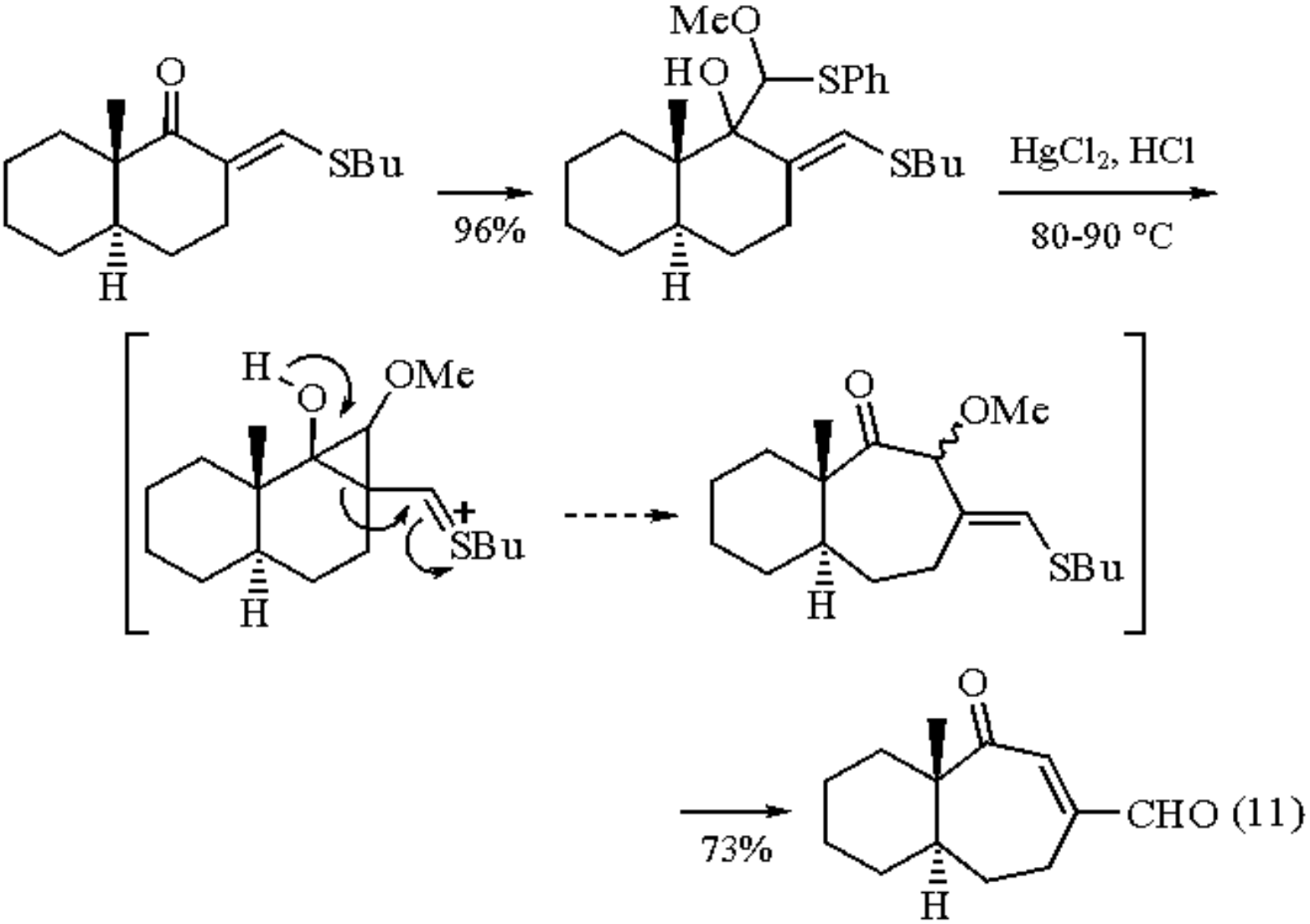

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Donna L. Romero

Methoxy(phenylthio)trimethylsilylmethane

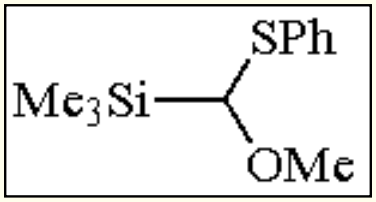

[88738-21-0] · $C_{11}H_{18}OSSi$ · Methoxy(phenylthio)trimethylsilylmethane · (MW 226.45)

(convenient homologation reagent for carbonyl compounds and alkyl halides; acyl anion equivalent)

Physical Data: bp 120-122 °C/10 mmHg.

Solubility: sol ether, THF, dioxane, methanol, ethanol, benzene, hexane.

Form Supplied in: colorless liquid.

Preparative Method: from methoxy(phenylthio)methyllithium (see ***Methoxy(phenylthio)methane***) with ***Chlorotrimethylsilane***.[1]

Homologation of Carbonyl Compounds.

Methoxy(phenylthio)trimethylsilylmethyllithium (**1**), an acyl anion equivalent, is generated by treating methoxy(phenylthio)trimethylsilylmethane with ***n-Butyllithium*** at -80 °C in THF. This anion adds to carbonyl compounds in 1,2-fashion, providing ketene *O,S*-acetals via Peterson alkenation (eq 1).[1a] The ketene *O,S*-acetals thus obtained are converted to methyl esters by methanolysis in the presence of ***Hydrogen Chloride*** and ***Mercury(II) Chloride***. This procedure was applied to the synthesis of (±)-β-eudesmol (eq 2).[1a]

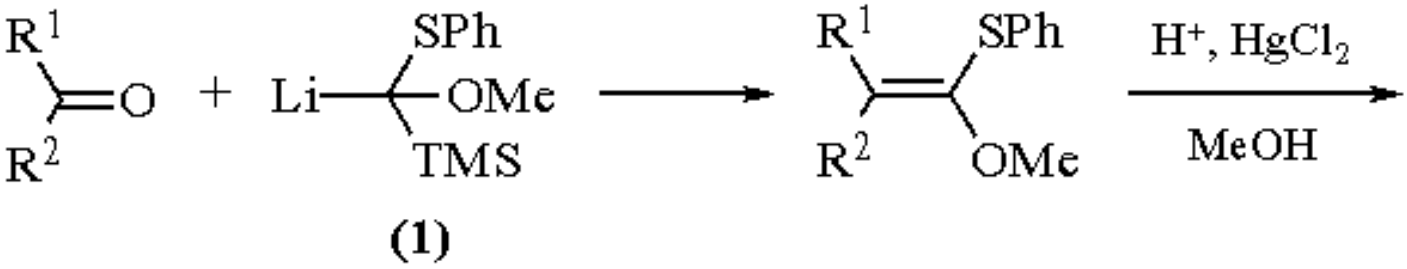

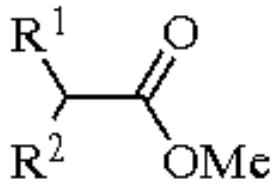

(1)

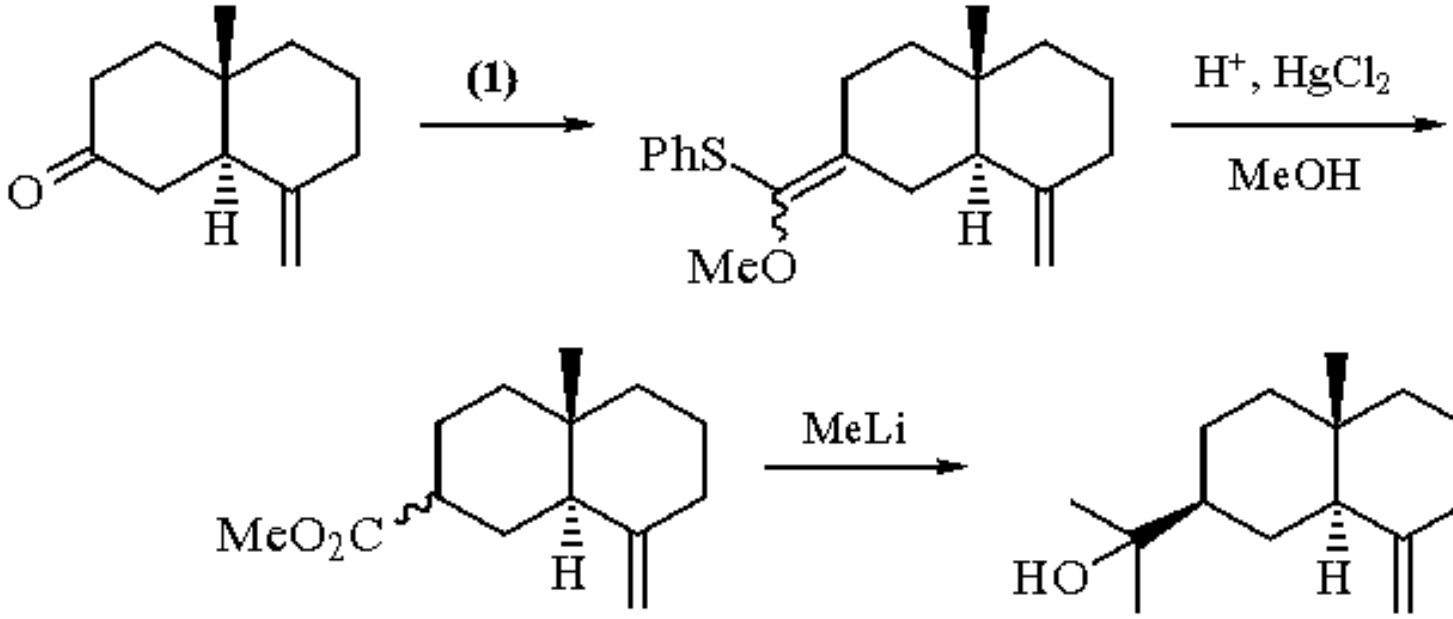

(2)

(±)-β-eudesmol

Cleavage of the ketene *O*,*S*-acetals under neutral or mildly basic conditions can be executed by using ***Iodotrimethylsilane*** to give the phenyl thioester or the ketene *O*-silyl,*S*-acetal (eqs 3 and 4).[2] In addition, amides can be prepared by sequential treatment of ketene *O*,*S*-acetals with lithium thiomethoxide in HMPA followed by addition of an amine (eq 5).[2]

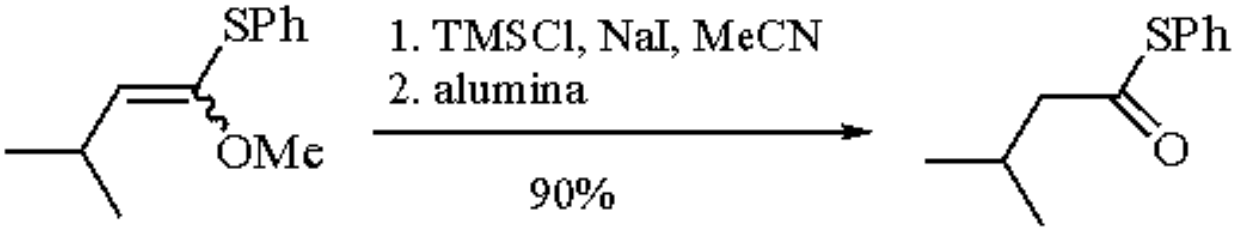

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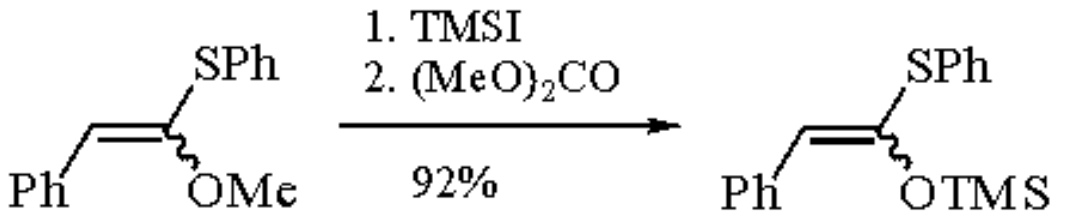

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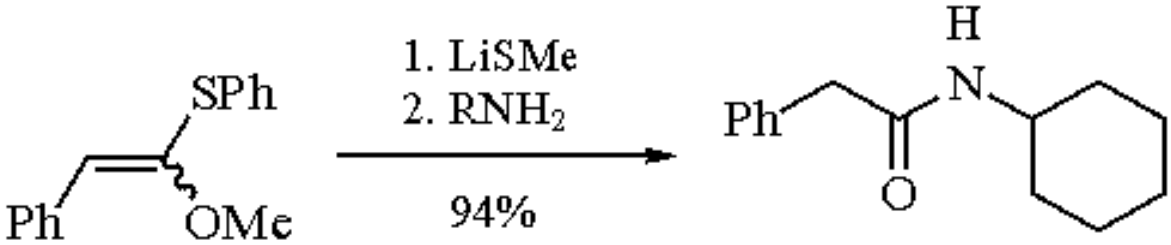

(5)

The reaction of anion (**1**) with cyclic α,β-unsaturated ketones provides 1,4-addition products in the presence of HMPA (eqs 6 and 7).[3] The resulting enolate can be trapped with various alkyl halides to give α- and β-disubstituted cyclic ketones with the *trans* configuration. This protocol was successfully applied to syntheses of sarkomycin and prostaglandin.[4]

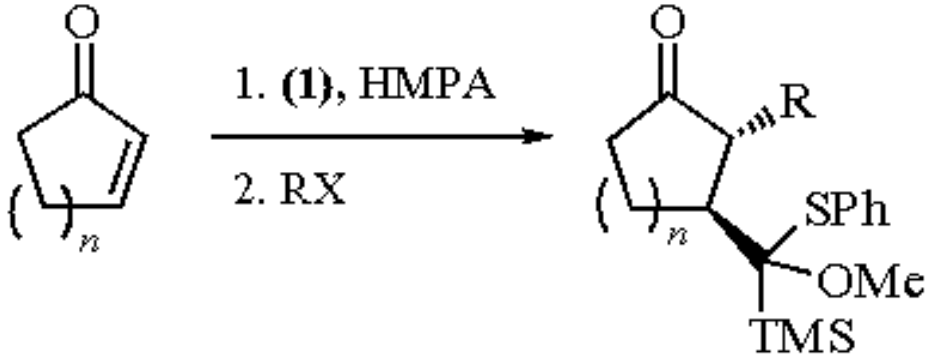

(6)

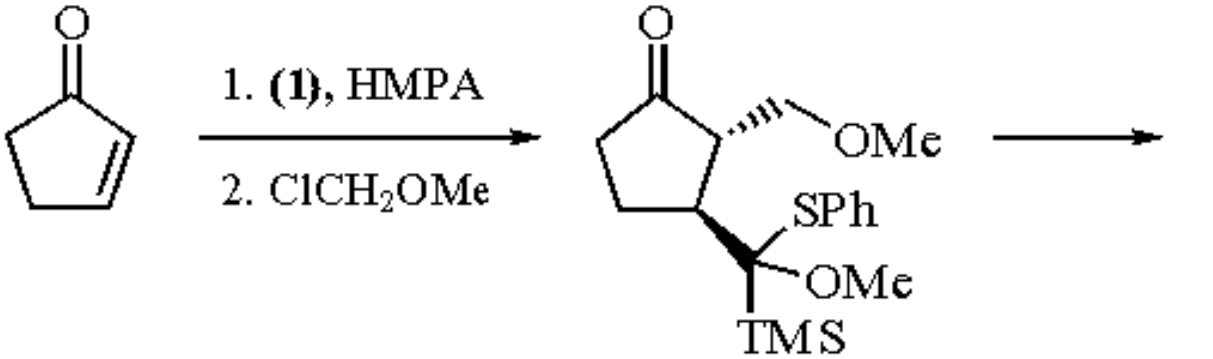

(7)

Homologation of Alkyl Halides.

Carbanion (**1**) serves as an acylsilane anion equivalent in reactions with alkyl halides. The alkylation proceeds smoothly at -40 °C in the presence of HMPA to provide *O,S*-acetals which are easily transformed into acylsilanes via oxidation with ***Sodium Periodate*** in wet dioxane (eq 8).[5] Acetalization of acylsilanes gives α-trimethylsilyl acetals, which are orthoester synthetic equivalents (eq 9).[6] The synthesis of isocarbacyclin was achieved by using this procedure.

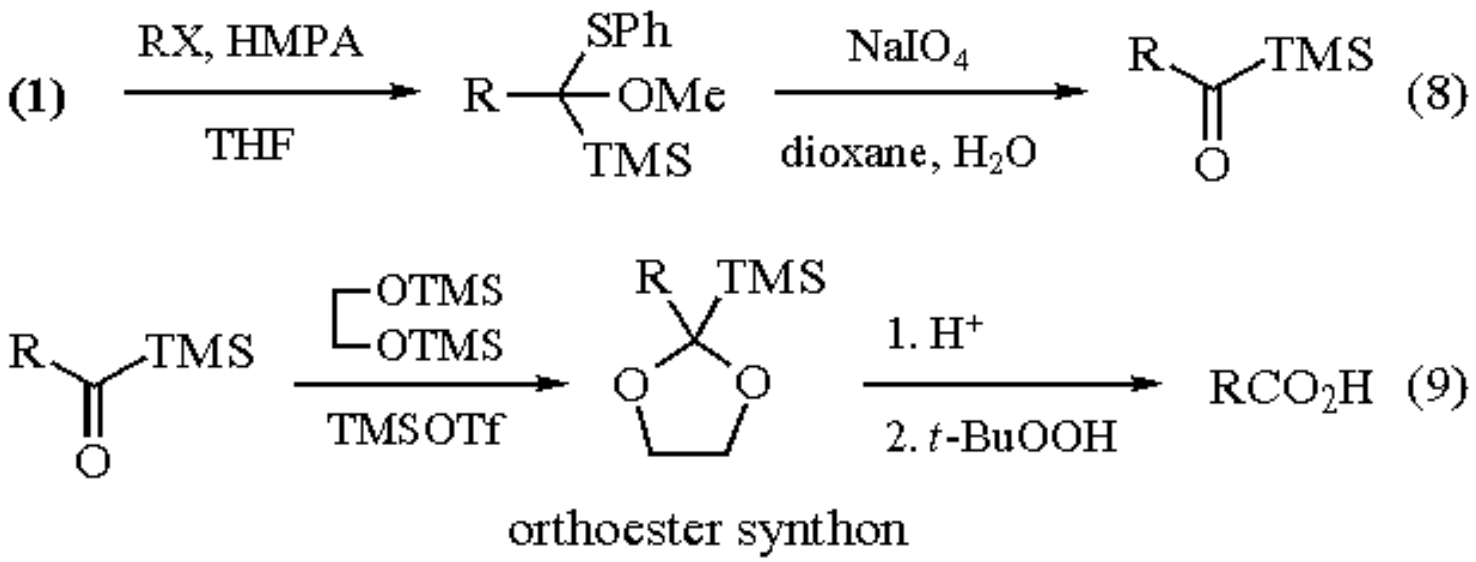

In another synthetic application, the alkylation products of (**1**) undergo facile thermal elimination of methanol to afford (*Z*)-1-phenylthio-1-trimethylsilylalkenes in good yields with high stereoselectivity (eq 10).[7] The elimination is facilitated by oxygen and is further accelerated by the addition of ***Triethylborane***, which implies the involvement of a radical pathway. The resulting (*Z*)-1-phenylthio-1-trimethylsilylalkenes are transformed into (*E*)-vinylsilanes by reductive cleavage of the thiophenyl group with ***Lithium Naphthalenide*** (eq 11).[7]

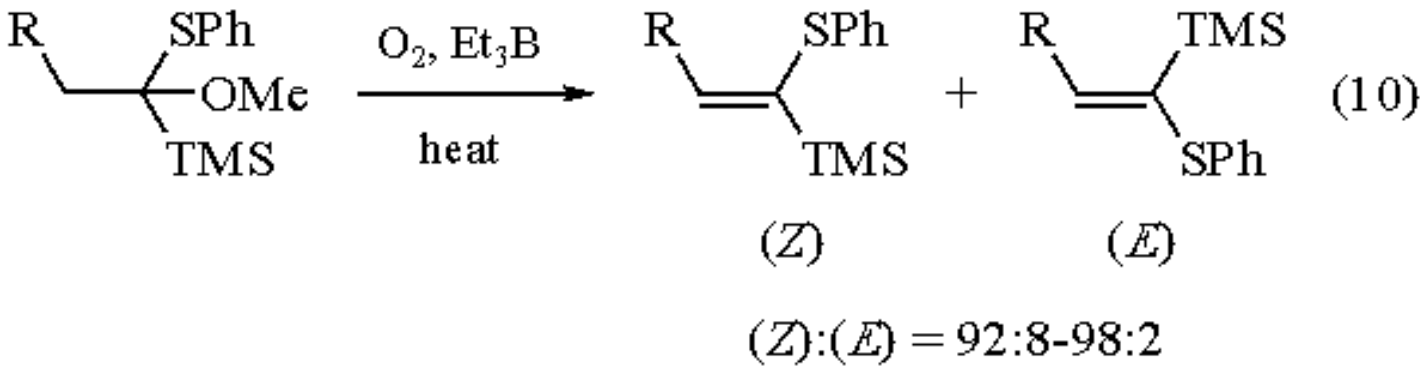

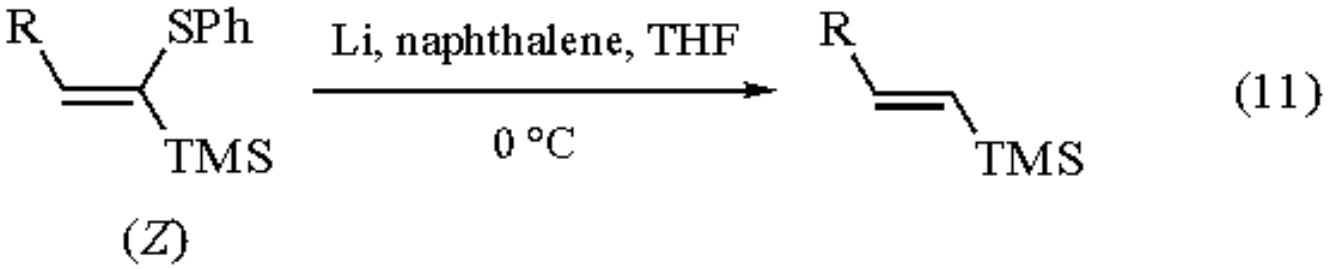

Homologation of Arenes and Alk-1-enes.

Methoxy(phenylthio)trimethylsilylmethane undergoes Friedel-Crafts reaction with arenes in the presence of Lewis acids such as ***Titanium(IV) Chloride*** and ***Tin(IV) Chloride*** to afford (aryl(phenylthio)methyl)trimethylsilanes (eq 12).[8] This reagent also reacts with terminal alkenes in the presence of $SnCl_4$ to give ene products (eq 13).[8]

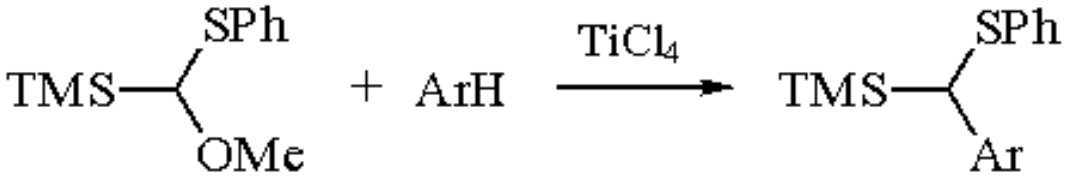

(12)

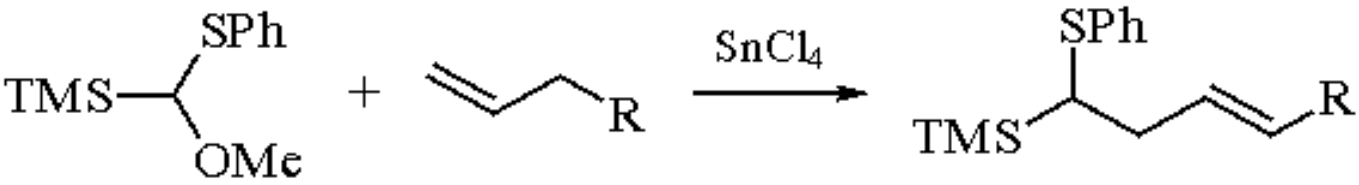

(13)

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1-Methoxy-1,2-propadiene

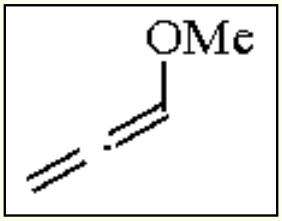

[13169-00-1] · C_4H_6O · 1-Methoxy-1,2-propadiene · (MW 70.10)

(undergoes lithiation and reaction with electrophiles at C-1,[1] hetero-Diels-Alder[2] and dipolar[3] cycloadditions, and transition metal-catalyzed,[4,5] radical,[6] and electrophilic[7] addition reactions)

Alternate Name: methoxyallene.

Physical Data: bp 51-52 °C.

Solubility: sol THF, ether, pentane, hexane, CH_2Cl_2, $CHCl_3$, DMSO.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$) δ 6.77 (1H, t, *J* = 5.9 Hz), 5.48 (2H, d, *J* = 5.9 Hz), 3.42 (3H, s).

Preparative Methods: not commercially available, but can be prepared[1] on a tens-of-grams scale by the base-catalyzed isomerization of 1-methoxy-2-propyne (methyl propargyl ether) (eq 1). Related 1-alkoxy-1,2-propadiene ethers can be prepared similarly. A convenient version of this preparation has been reported.[8]

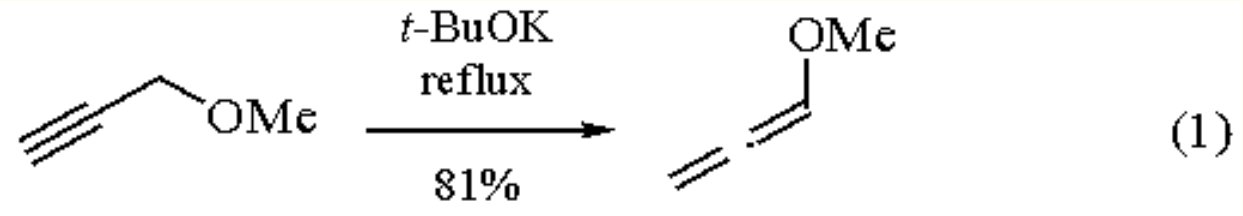

Purification: by distillation.

Metalation.

Many applications of 1-methoxy-1,2-propadiene require that it be converted to lithiated,[1,9-11] magnesiated,[12] zincated,[13] or cuprated[14] derivatives. Some of the conditions reported for effecting metalations at C-1 are summarized

in eq 2.

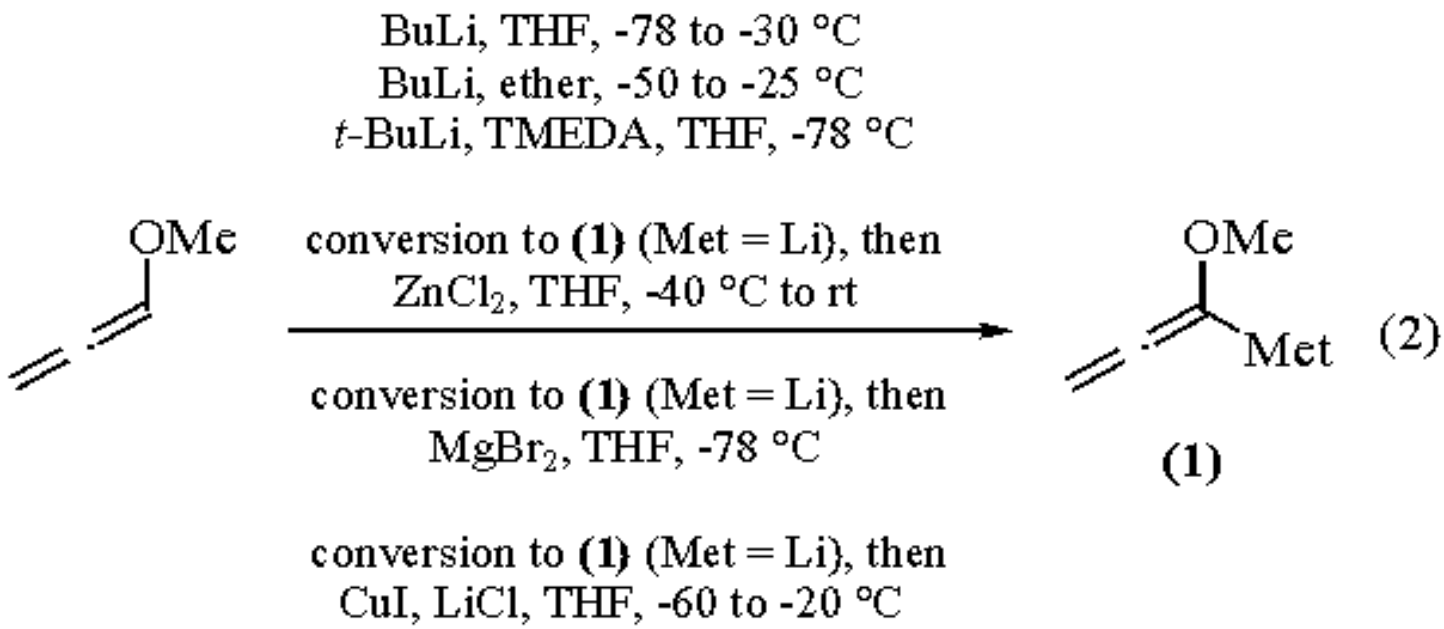

Owing to the steric requirement of the *t*-Bu substituent, lithiation can be directed with considerable selectivity to C-3 in 1-*t*-butoxy-1,2-propadiene (eq 3).[15,16] A minor amount of lithiation at C-1 occurs in this procedure. Related metalated intermediates of some significance in synthesis include (**3**)[16-20] and (**4**).[19]

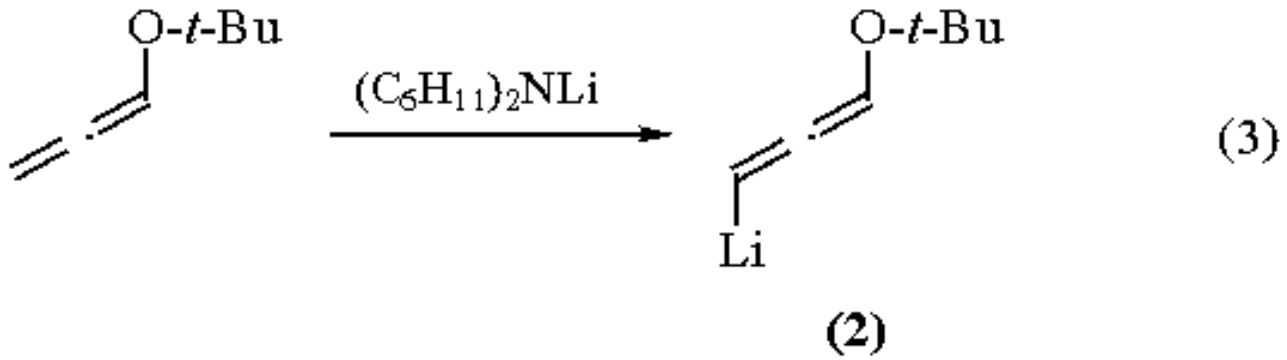

Reaction of Electrophiles with Metalated Derivatives.

Through the intervention of metalated derivatives of the type described in the previous section, 1-methoxy-1,2-

propadiene and related allene ethers function as synthesis equivalents for the conventionally unavailable acryloyl acyl (**5**) and β-acryloyl (**6**) anions, and acryloyl dianion (**7**). These equivalencies depend on the electrophilic modification of derivatives like (**1**), (**2**),[15,16] and (**3**)[16-20] (eqs 4-6).

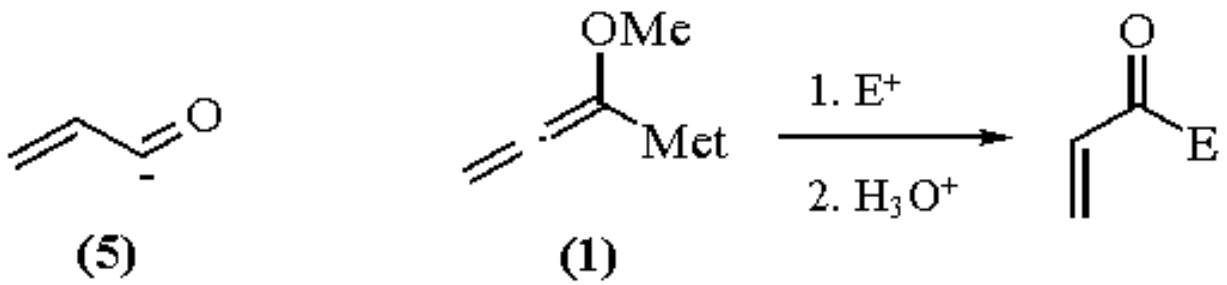

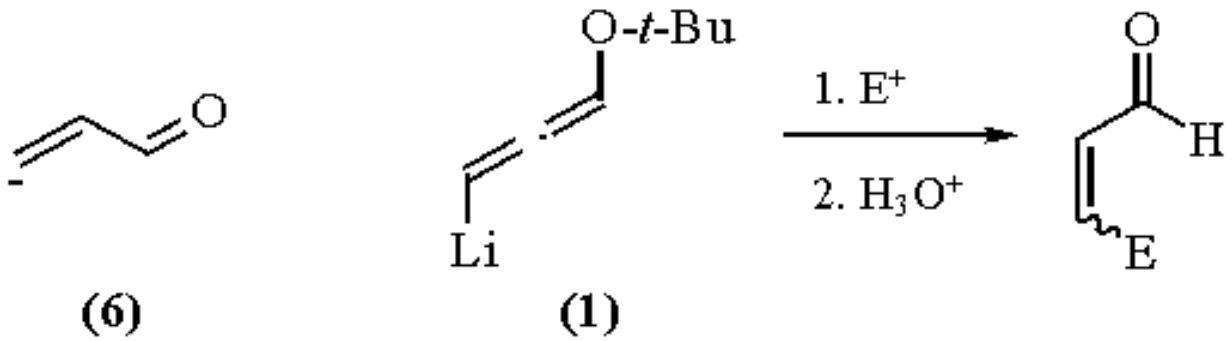

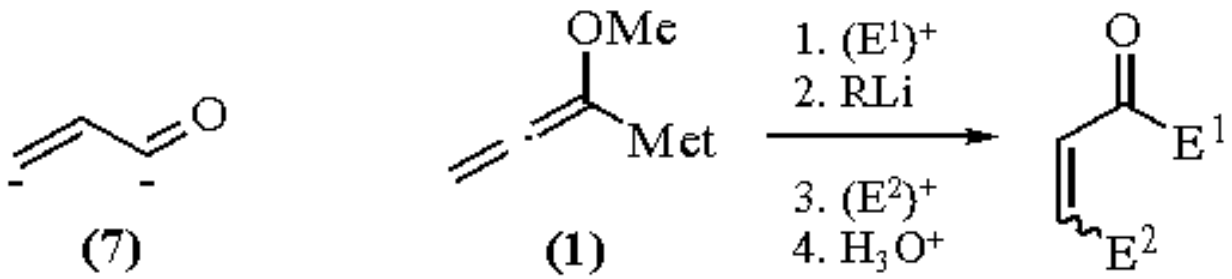

Examples of the capture of (**1**) (Met = Li) by relatively simple electrophiles[16,21-23] include those in eqs 7-10.[9,17,18,20,24-30] These invariably involve electrophilic attack at C-1 rather than C-3 in this potentially ambident nucleophile. (**1**) also engages in transition metal-mediated processes that elaborate the C-1 position (eqs 11 and 12).[11,31,32]

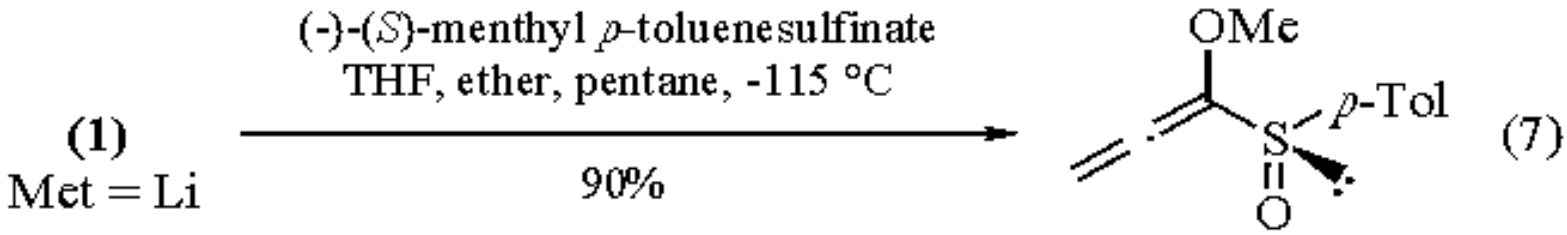

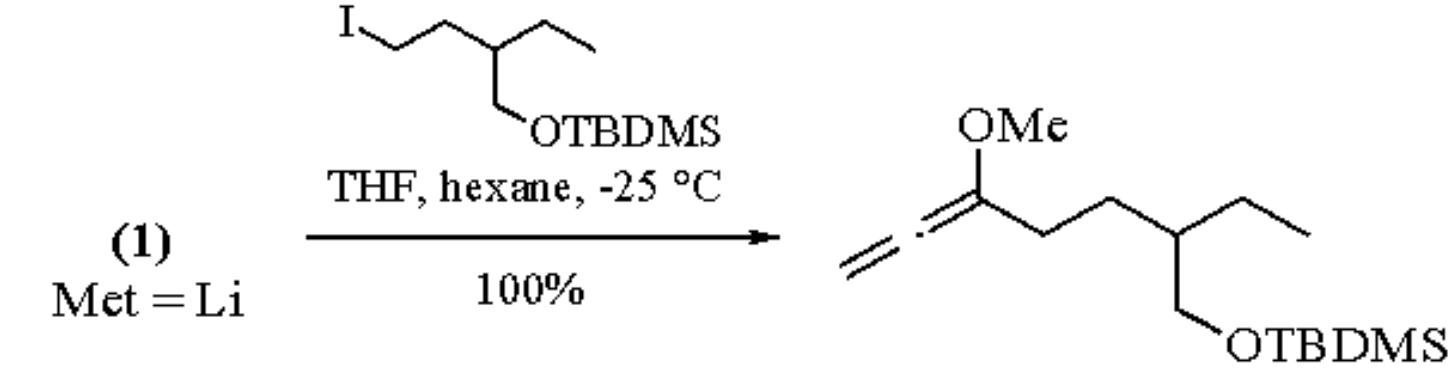
I
OTBDMS
THF, hexane, -25 °C
100%
(1)
Met = Li
OMe
OTBDMS

(8)

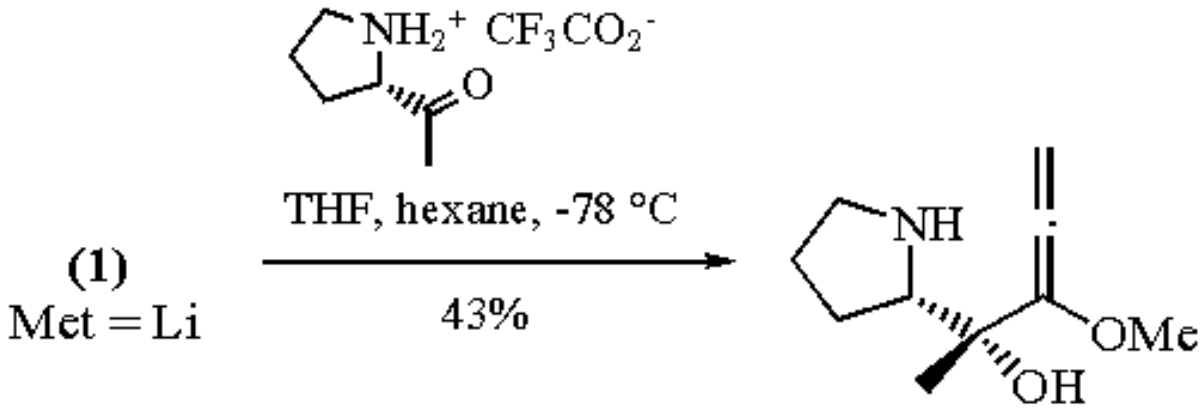
NH2+ CF3CO2-
O
THF, hexane, -78 °C
43%
(1)
Met = Li
NH
OMe
OH

(9)

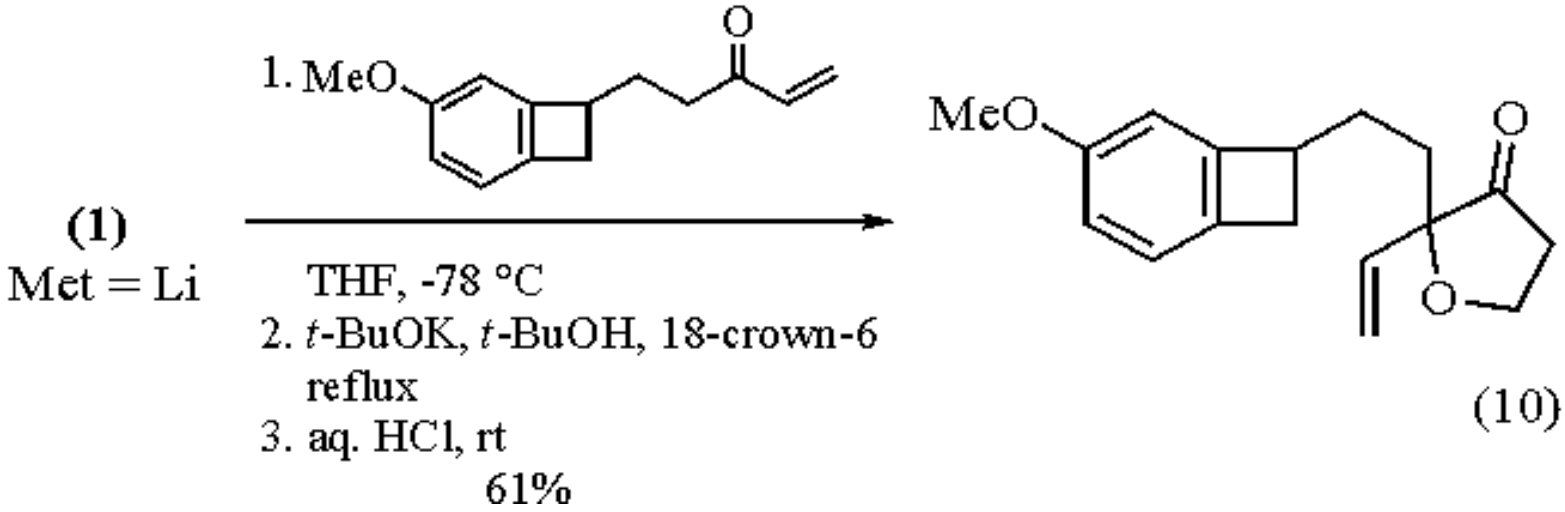
1. MeO
O
(1)
Met = Li
THF, -78 °C
2. t-BuOK, t-BuOH, 18-crown-6
reflux
3. aq. HCl, rt
61%
MeO
O
O

(10)

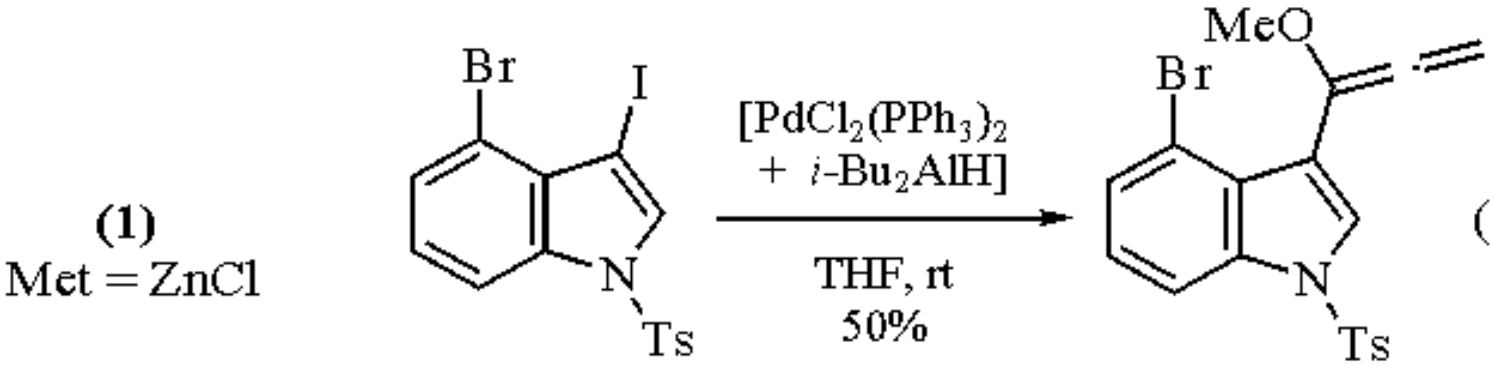
(1)
Met = ZnCl
Br
I
N
Ts
[PdCl2(PPh3)2
+ i-Bu2AlH]
THF, rt
50%
MeO
Br
N
Ts

(11)

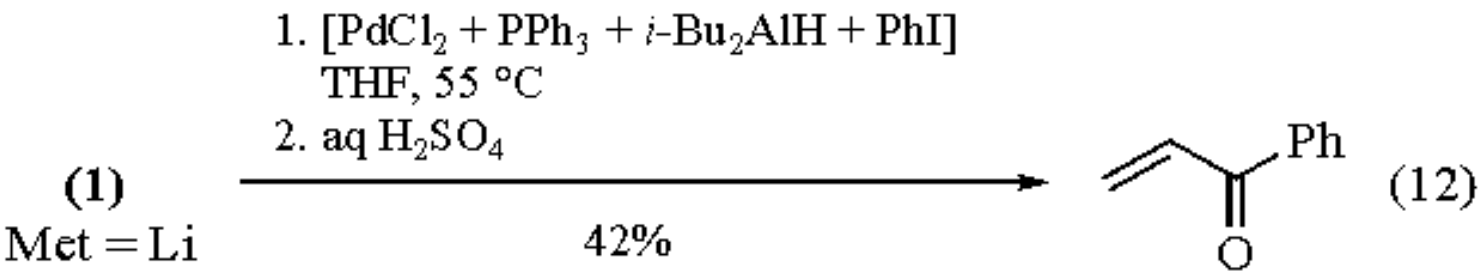

Hetero-Diels-Alder Cycloadditions.

The literature contains several examples of hetero-Diels-Alder reactions involving 1-methoxy-1,2-propadiene wherein inversion of the conventional electronic roles of the 4π and 2π components occurs. Reactions of this reagent with vinyl nitroso compounds,[33,34] unsaturated aldehydes and ketones,[35-37] and unsaturated sulfonimines[2,38] (eq 13) have been reported. The *endo* selectivity witnessed in the sulfonimine reactions is to be contrasted with an example of *exo* selectivity involving a vinyl nitroso coreactant.[33] The oxygenated double bond of the reagent is invariably attacked, and is intermediate in its reactivity relative to ethyl vinyl ether (more reactive) and trimethylsilyl vinyl ether (less reactive).[39]

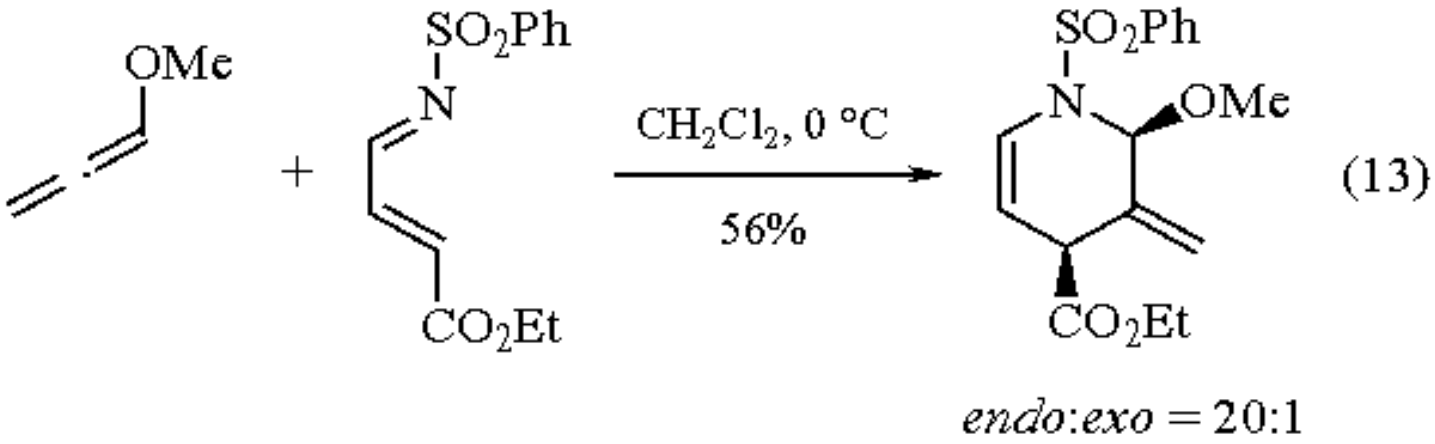

Dipolar Cycloadditions.

This reagent likewise is reactive toward appropriate 4π components in dipolar cycloadditions. Examples involving nitrile imines,[40] nitrile oxides,[41] and diazo compounds[3] (eq 14) have been reported. The characteristic regioselectivity in this cycloaddition class differs from that described above.

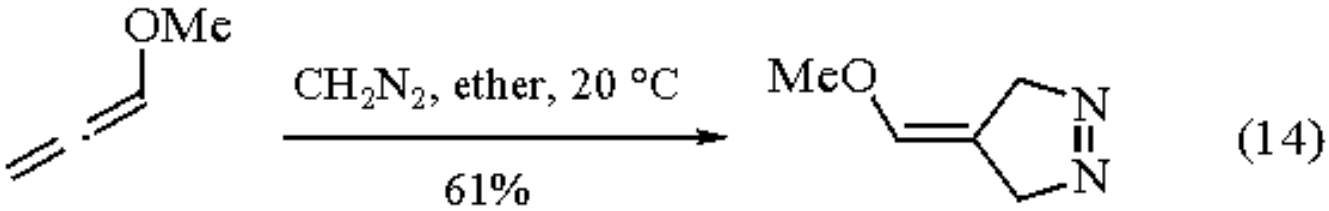

Copper-Mediated Additions of Organometallic Reagents.

A mixture of this reagent and a catalytic amount of a copper(I) halide effects the propargylation of Grignard reagents, a process that involves a formal S_N2' displacement of the methoxy group (eq 15).[4,42,43] However, when the stoichiometric ratio of the copper(I) halide to the Grignard reagent (RMgX) is increased, simple addition products of the type $RCH_2CH{=}CHOMe$ are delivered after aqueous workup.[44] In the latter cases, larger R groups lead to increased proportions of the (*E*)-enol ether products.

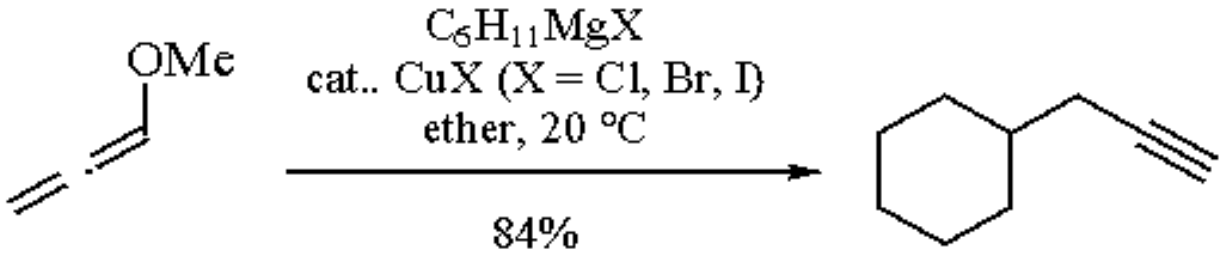

(15)

An unusual copper-mediated addition process has been devised whereby two methylene groups derived from ***Iodomethylzinc Iodide*** are added across the 1,2-double bond of 1-methoxy-1,2-propadiene to give an organometallic intermediate that can be trapped by aldehydes and ketones (eq 16).[14]

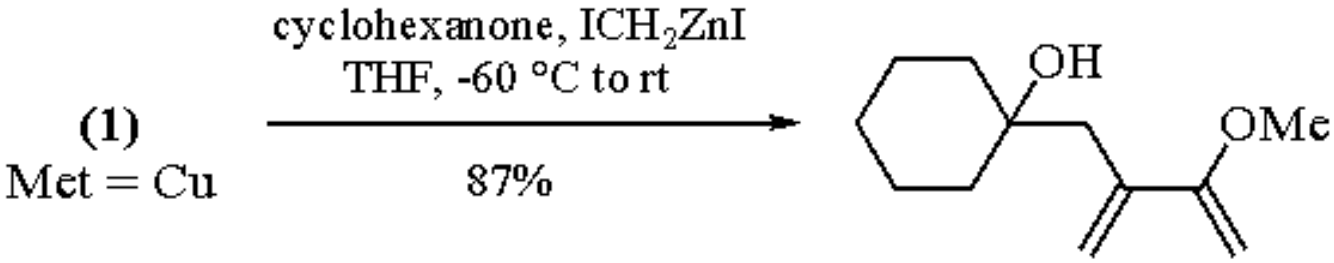

(16)

Other Transition Metal-Mediated Additions.

Palladium and molybdenum catalyze the addition of tin, silicon, and germanium reagents of the type $R^1{}_6Sn_2$,[45,46] $R^1{}_3SiSnR^2{}_3$,[45,47] $R^1{}_3GeSnR^2{}_3$,[48] and $R^1{}_3SnH$[47,49] to 1-methoxy-1,2-propadiene. The addition reagent, the metal, and the size of the R^1 and R^2 groups all play roles in determining the regio- and stereoselectivity of these reactions (eqs 17 and 18).[45,47] For example, the regioselectivity shown in eq 17 for attack at the nonoxygenated double bond is reversed in an example involving *n*-$Bu_3SnGeMe_3$.[48] The stereo- and regioselectivity in eq 18 are much superior to those of the radical addition that produces the same materials (see below).

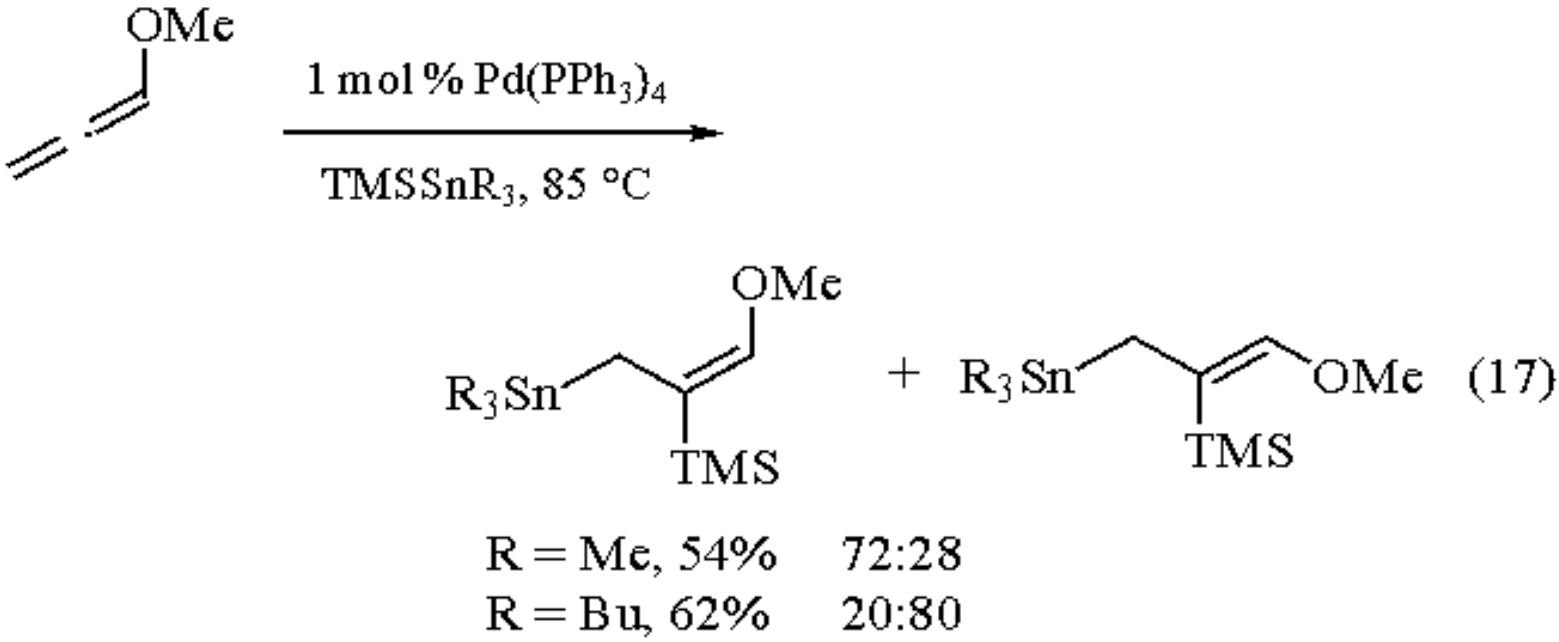

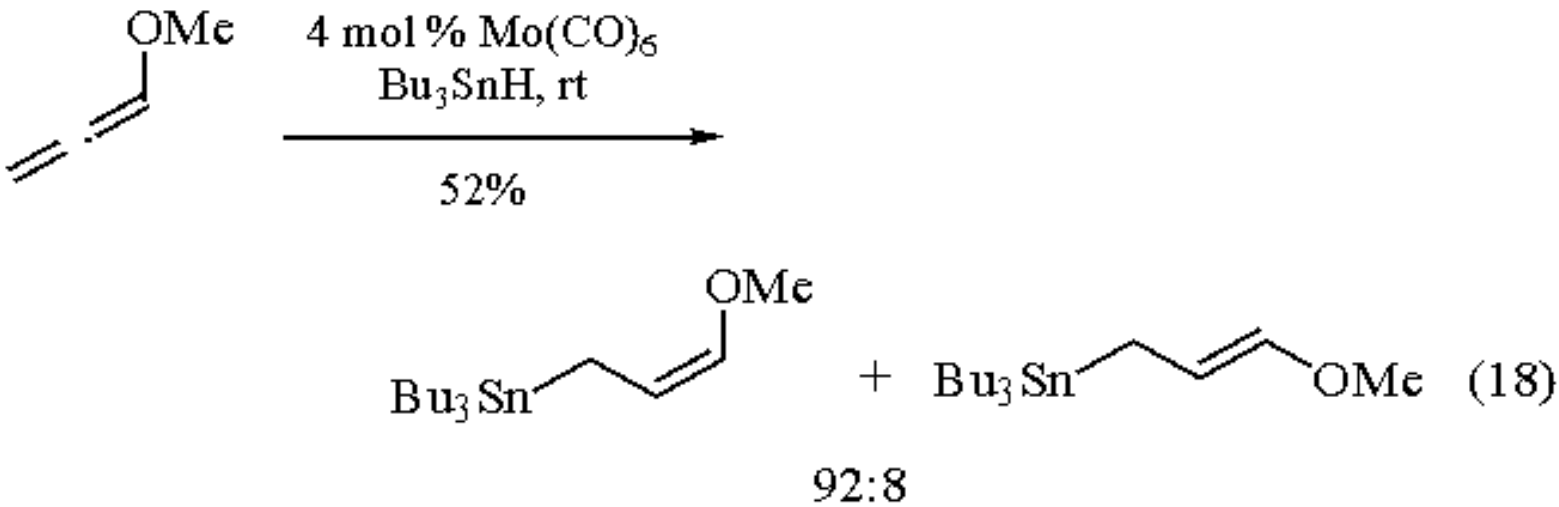

Transition metal-mediated transformations that involve 1-methoxy-1,2-propadiene in the creation of new carbon-carbon bonds, but which are difficult to classify, have been reported.[50,51] However, a few examples that occur by way of palladium (eq 19)[5] and iron catalysis[52,53] appear to be related.

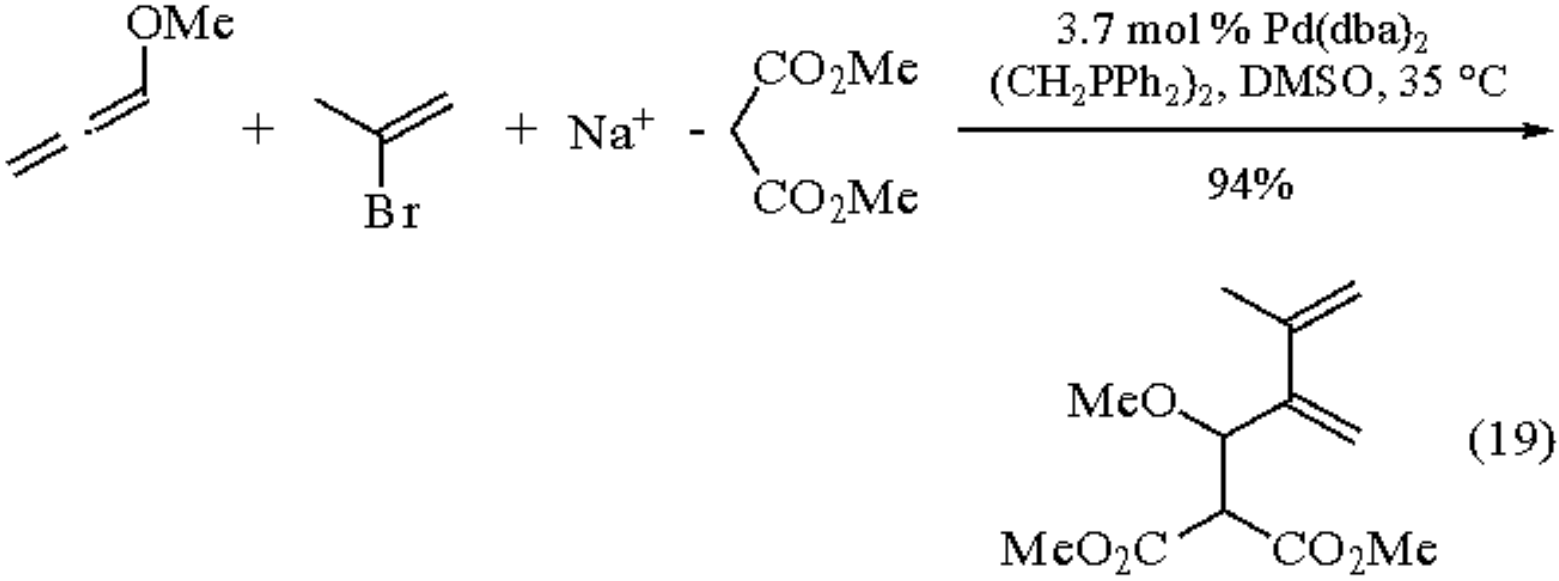

(19)

Radical Additions.

Tri-n-butylstannane adds nonselectively in radical fashion to 1-methoxy-1,2-propadiene to give, among other products, a low yield of the enol ethers that arise from attachment of the tin to C-3.[47] In contrast, both ***Diphenylphosphine***[54] and ***Thiophenol*** (eq 20; product ratio reflects equilibrium mixture of geometrical isomers)[6] add selectively to the central C-2 carbon, a reflection of the intermediacy of allylic radicals.

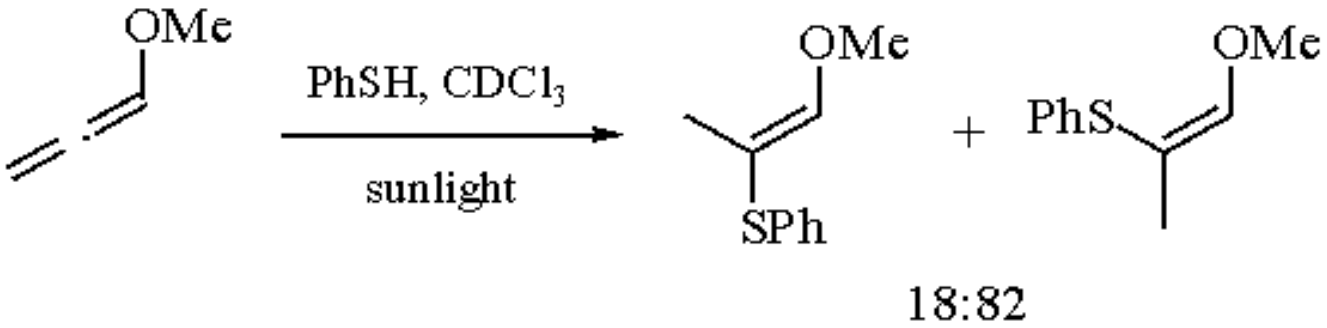

(20)

Electrophilic Additions.

The π-electron-rich character of this reagent conferred by its alkoxy group makes it highly reactive in processes initiated by the addition of an electrophile. Interesting examples include eqs 21 and 22,[7,55] wherein it can be seen that the nucleophilic reaction partner can attach itself either to C-1 or to C-3. A number of additional applications of this reaction type require 1-methoxy-1,2-propadiene to provide a mixed acetal when exposed to an appropriate nucleophile in the presence of an electrophilic initiator.[56]

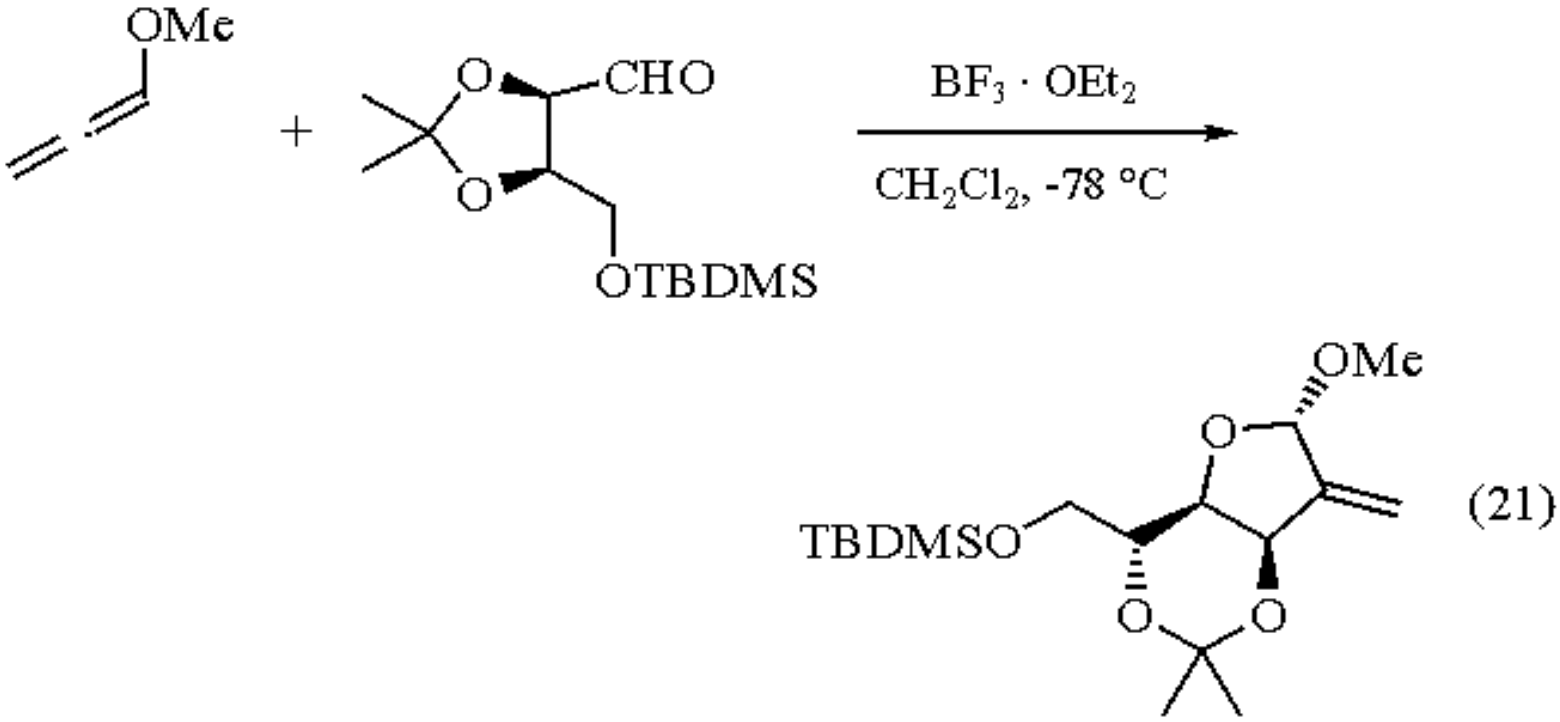

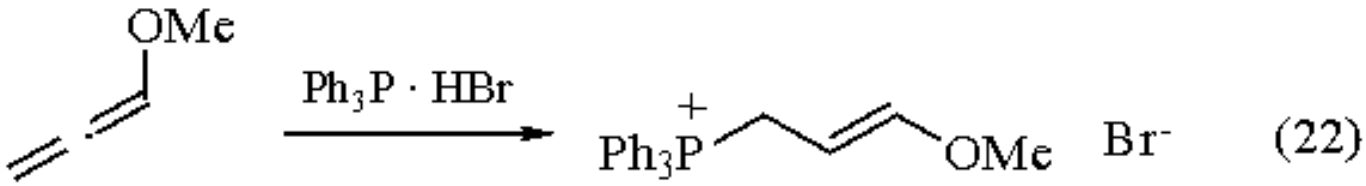

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Charles Swindell

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2-Methoxypropene[1]

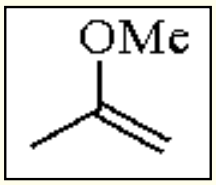

[116-11-0] · C_4H_8O · 2-Methoxypropene · (MW 72.12)

(electron-rich alkene used in the monoprotection of aliphatic,[2] allylic,[3] and propargylic[4] alcohols, often followed by Claisen[3b -e] or other[2a,4c] rearrangements; protection of peroxides,[5] cyanohydrins,[6] α-hydroxy ketones,[2b] and phenols;[7] condensation with amines;[8] protection of 1,2-[9,10] and 1,3-diols,[10,11] sometimes followed by Prins[9f,g] rearrangements; protection of 1,2-dithiols[10a] and α-hydroxy carbamates;[12] participant in pericyclic reactions;[13] formation of 2-methoxyallyl halides[14] and substituted furans[4b])

Alternate Names: 2-MP; isopropenyl methyl ether.

Physical Data: bp 34-36 °C; *n*20D 1.3820; *d* 0.753 g cm^{-3}; flash point -29 °C.

Form Supplied in: colorless liquid; commercially available.

Preparative Method: prepared in high yield from ***Succinic Anhydride***, ***2,2-Dimethoxypropane***, benzoic acid, and ***Pyridine***.[15]

Handling, Storage, and Precautions: flammable liquid; light-sensitive; should be refrigerated.

Monoprotection of Alcohols.

2-Methoxypropene is used as a protective group for aliphatic,[2,11d] allylic,[3] and propargylic[4] alcohols, masking them as their mixed acetals (eq 1). Deprotection can be accomplished by stirring in MeOH over ion exchange resin,[4a] by reaction in methanol with catalytic ***Acetyl Chloride***,[11d] by ***Potassium Carbonate*** in methanol,[2c] or by 20% ***Acetic Acid***.[3a] A general advantage of this acetal, which undergoes hydrolysis at approximately 10^3 times the rate of THP,[2d,3a] is that it does not confer an additional diastereomeric center to the protected substrate. Access to allyl vinyl ethers for subsequent Claisen rearrangements[3b-e] is illustrated in eq 2.

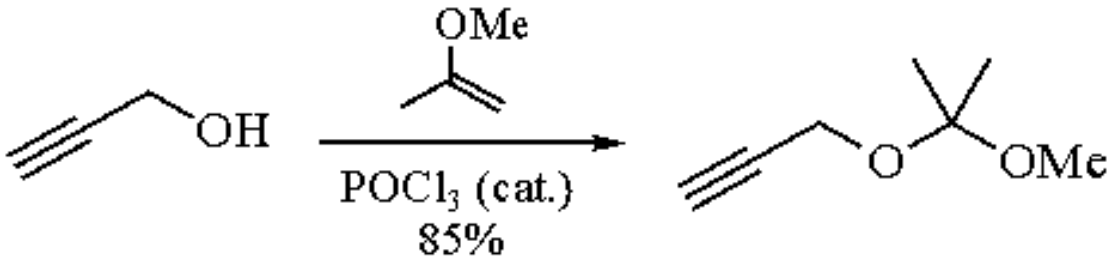

(1)

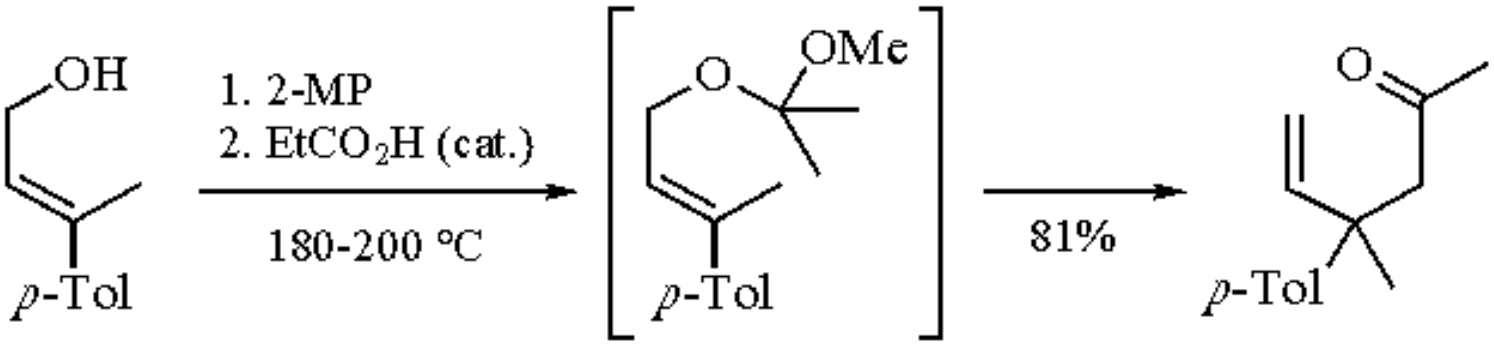

(2)

A useful entry into β-keto allenes is provided by the reaction of 2-MP with tertiary propargylic alcohols.[4c] Base-catalyzed rearrangement of the allenes affords conjugated dienones (eq 3).

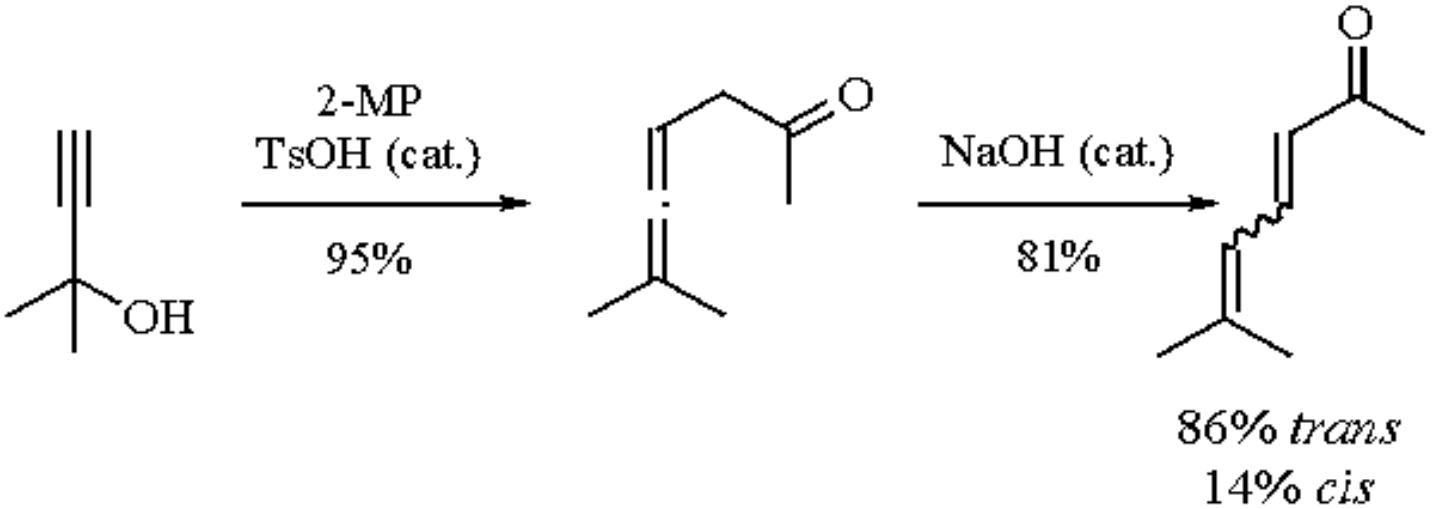

(3)

Stable allylic peroxyacetals have been prepared by reacting 2-MP with hydroperoxides (eq 4).[5] Organomercury functionality is tolerated in this reaction.[5b] Cyanohydrins,[6] α-hydroxy ketones,[2b] and phenols[7] are similarly protected.

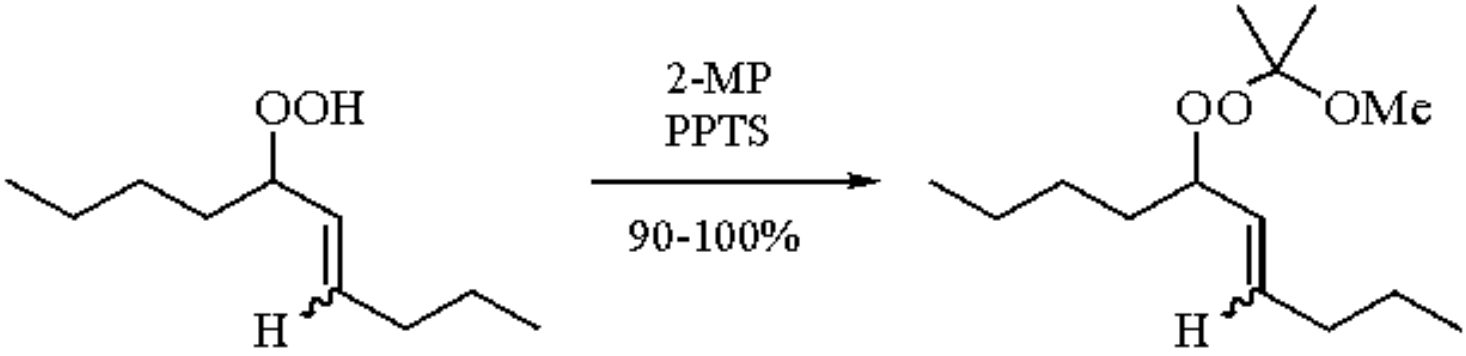

(4)

Condensation with Amines.

Imine formation with loss of methanol occurs under acidic conditions, as illustrated in eq 5.[8]

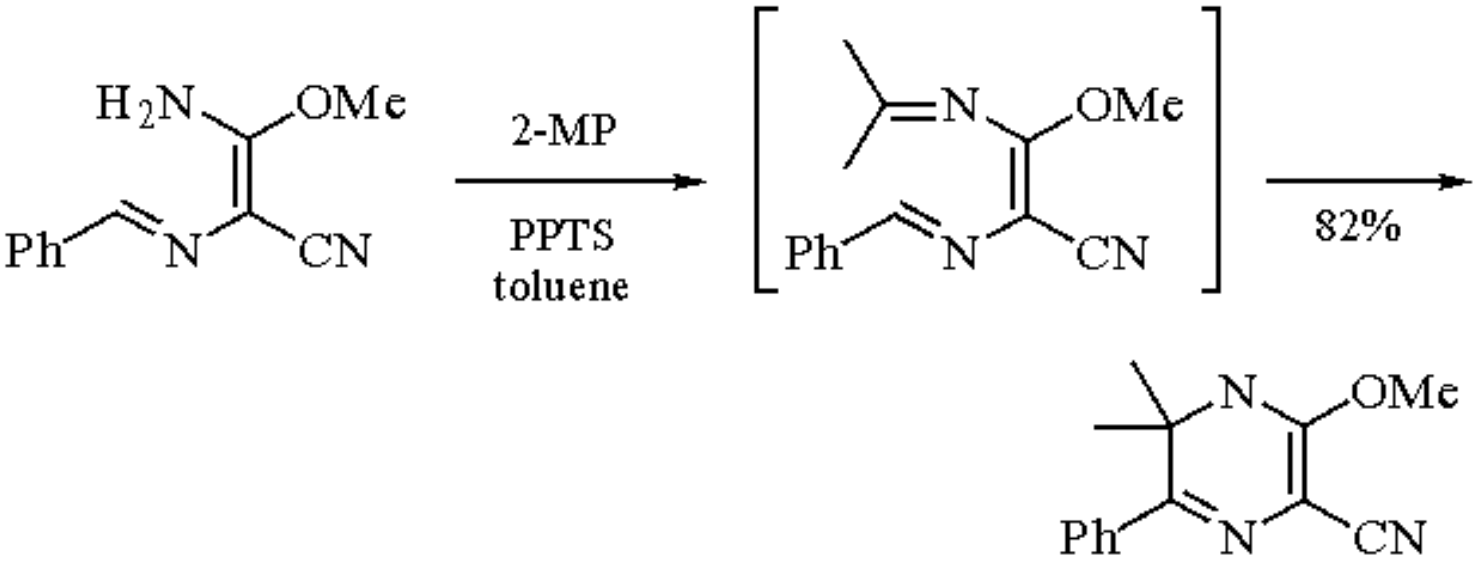

(5)

Protection of 1,2- and 1,3-Diols and 1,3-Dithiols.

When another hydroxy group is in close proximity to the initially protected alcohol functionality, acetonide formation occurs.[9-11] The kinetic product is preferentially formed.[10b,c,11c] As anomeric hydroxy groups do not usually[11] participate, this reagent provides complementary selectivity to the more traditional acid/acetone acetonation protocol. Control of the amount of 2-MP can result in varying degrees of protection (eq 6).[10b]

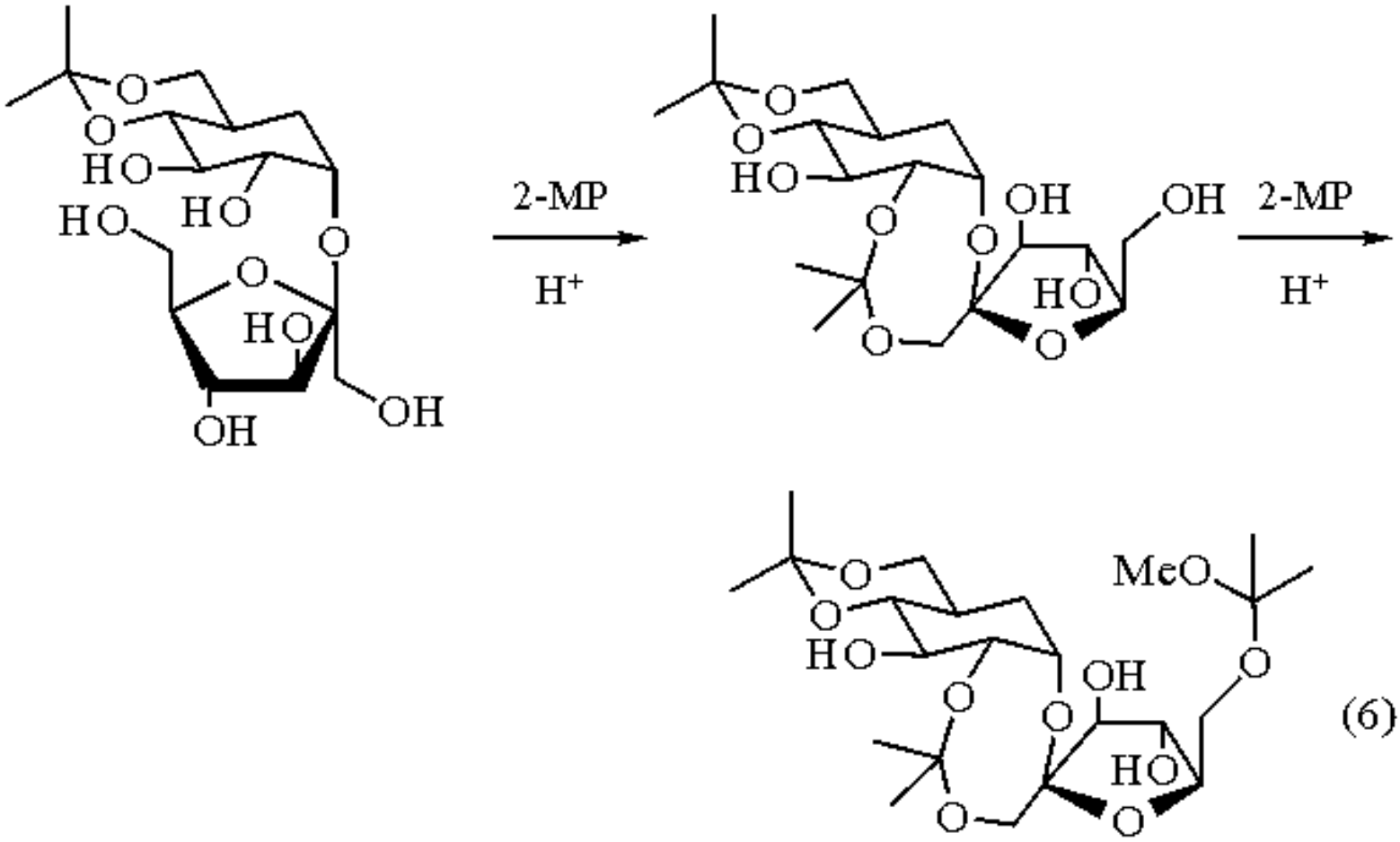

(6)

Acetonide formation using ***n-Butyltrichlorostannane*** with 2-MP[10a] is quite general for 1,2- and 1,3-diols, as well as for 1,3-dithiols. Monoacetonide formation occurs with 1,2,3- and 1,2,4-triols. Yields of the acetonides (e.g. **1**-**5**) show improvement over conventional procedures.[10a]

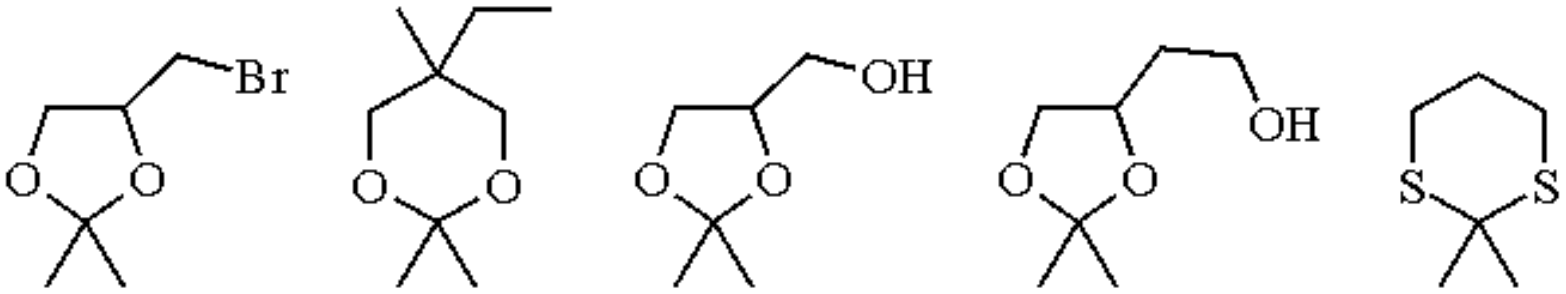

(1) 83% **(2)** 94% **(3)** 77% **(4)** 82% **(5)** 98%

Protection of α-Hydroxy Carbamates.

Aminal formation from α-hydroxy carbamates also occurs using 2-MP, as illustrated in eq 7.[12]

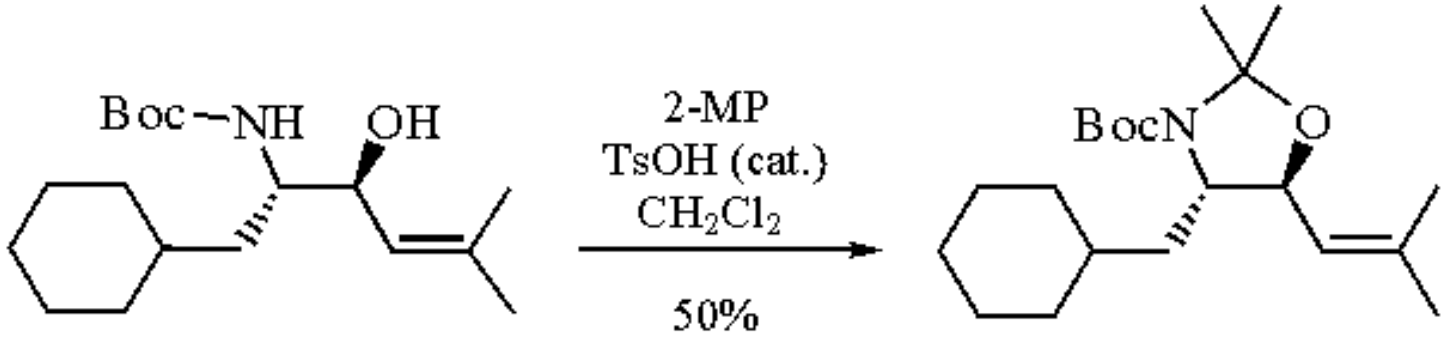

(7)

Participation in Pericyclic Reactions.

2-MP is an active participant in pericyclic reactions. A few examples include a substitution-dependent ene reaction with an alkynyl Fischer carbene complex (eq 8),[13c] a [2 + 3] reaction with 2-amino-1,4-naphthoquinone (eq 9),[13f] a solvent-dependent photochemical cycloaddition with *o*-naphthoquinones,[13j] and reaction with 2-nitro-1,3-dienes to provide α,β-unsaturated 1,4-diones (eq 10).[13g]

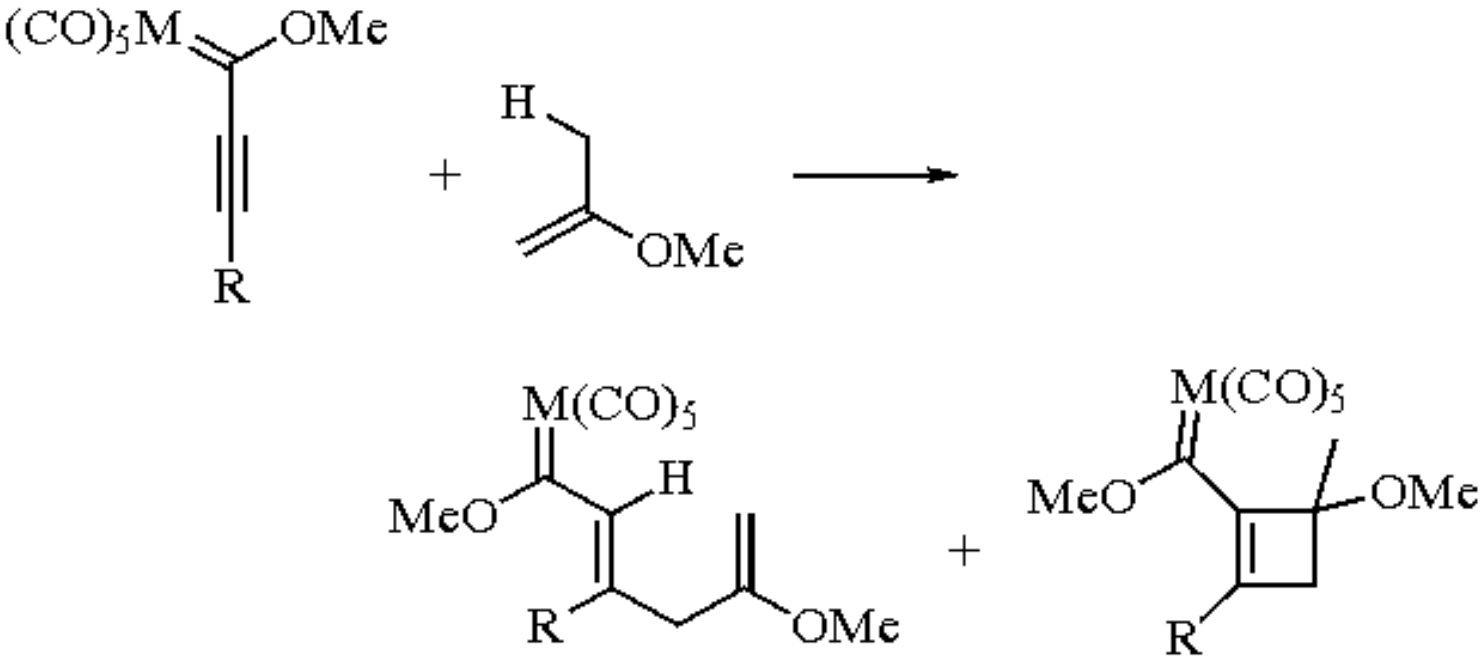

(8)

M = W, Cr	R = TMS	30%	<2%
	R = Me	<2%	63%

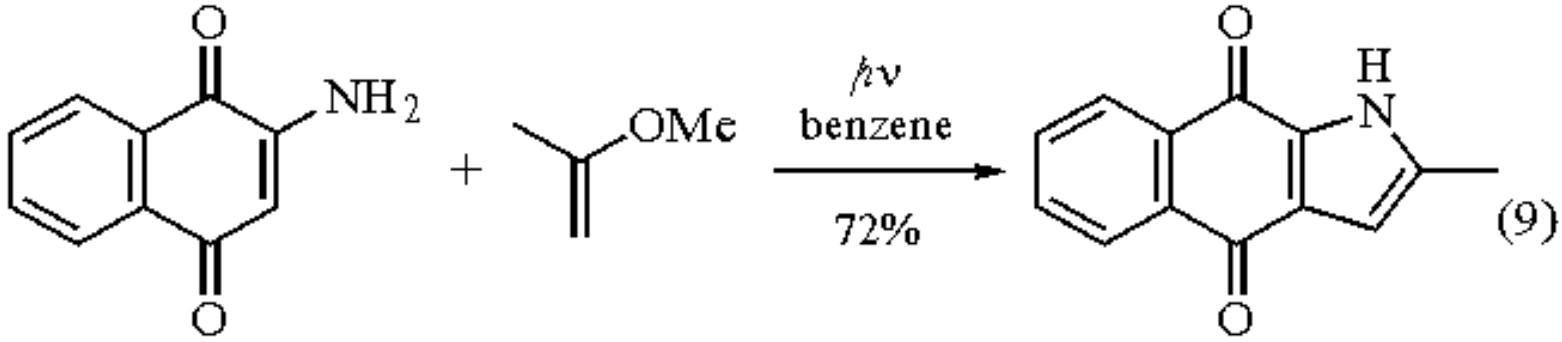

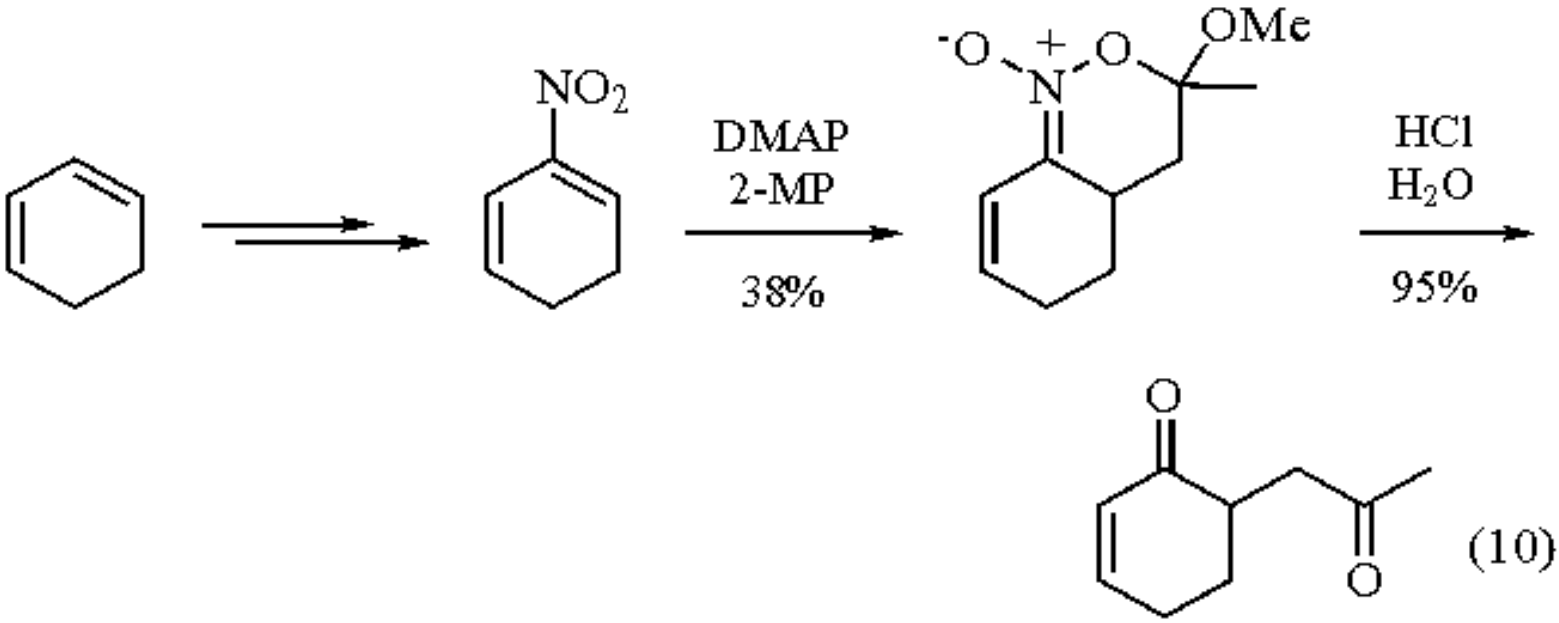

Reaction with *N*-Halosuccinimides.

2-Methoxyallyl and -vinyl halides are formed by reaction of 2-MP with *N*-halosuccinimides.[14] Also, treatment of propargylic alcohols with 2-MP and ***N-Bromosuccinimide*** results in the formation of bromo acetals, which are subsequently cyclized to furans in good yield (eq 11).[4b]

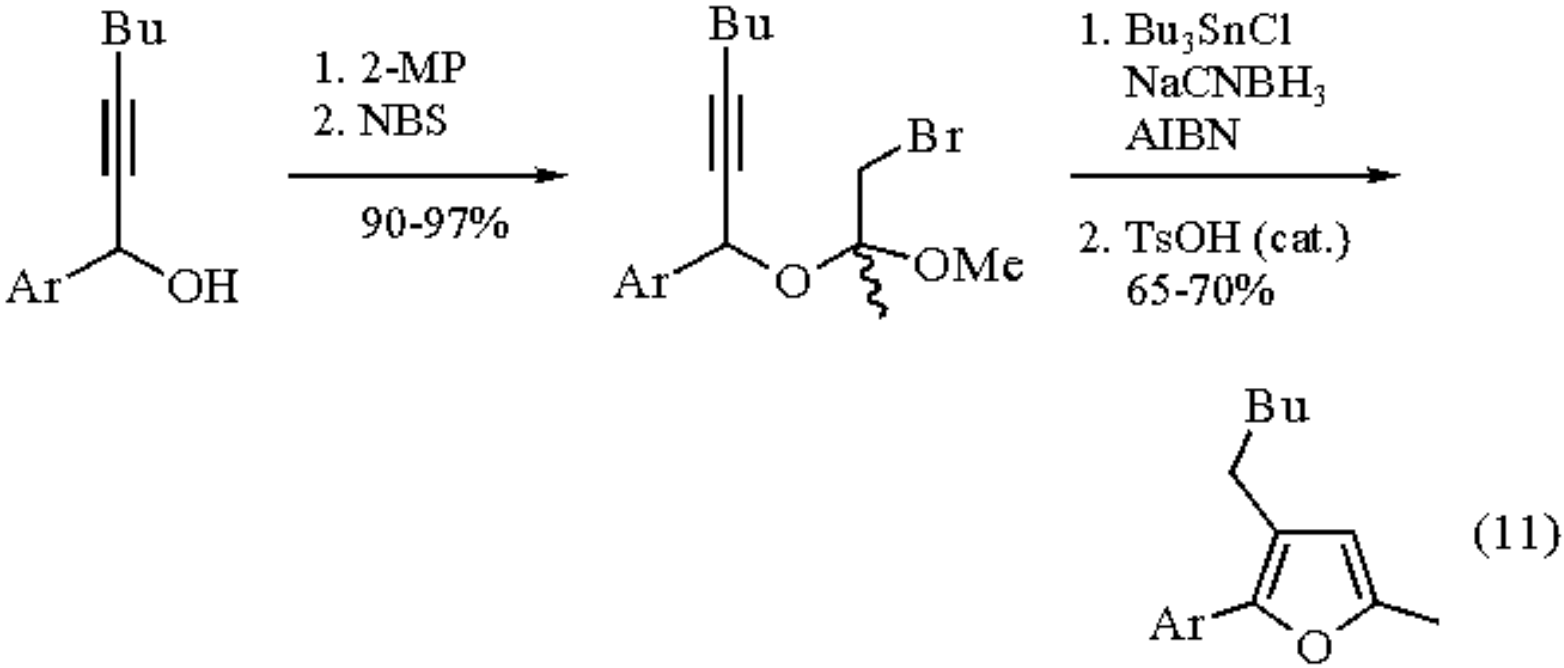

Related Reagents.

2,2-Dimethoxypropane.

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1. *FF* **1969**, *2*, 230; **1975**, *5*, 360; **1981**, *9*, 304; **1984**, *11*, 329; **1986**, *12*, 291.
2. (a) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *TL* **1991**, *32*, 4015. (b) Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *T* **1990**, *46*, 1757. (c) Tietze, L. F.; Lögers, M. *LA* **1990**, 261. (d) Reese, C. B.; Saffhill, R.; Sulston, J. E. *JACS* **1967**, *89*, 3366.
3. (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *JACS* **1972**, *94*, 7827. (b) Srikrishna, A.; Krishnan, K.; Vankateswarlu, S. *CC* **1993**, 143. (c) Srikrishna, A.; Krishnan, K. *IJC(B)* **1990**, *29B*, 879. (d) Gajewski, J. J.; Gee, K. R.; Jurayj, J. *JOC* **1990**, *55*, 1813. (e) Saucy, G.; Marbet, R. *HCA* **1967**, *50*, 2091.
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8. Freeman, F.; Kim, D. S. H. L. *JOC* **1992**, *57*, 550.
9. (a) Kozikowski, A. P.; Ognyanov, V. I.; Fauq, A. H.; Nahorski, S. R.; Wilcox, R. A. *JACS* **1993**, *115*, 4429. (b) van der Klein, P. A. M.; Filemon, W.; Boons, G. J. P. H.; Veeneman, G. H.; van der Marel, G. A.; van Boom, J. H. *T* **1992**, *48*, 4649. (c) Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1991**, *219*, 115. (d) Shing, T. K. M.; Tang, Y. *T* **1991**, *47*, 4571. (e) Fujisawa, T.; Takemura, I.; Ukaji, Y. *TL* **1990**, *31*, 5479. (f) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *JACS* **1991**, *113*, 5354. (g) Brown, M. J.; Harrison, T.; Herrington, P. M.; Hopkins, M. H.; Hutchinson, K. D.; Mishra, P.; Overman, L. E. *JACS* **1991**, *113*, 5365.
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11. (a) Guanti, G.; Banfi, L.; Narisano, E.; Thea, S. *SL* **1992**, 311. (b) Srikrishna, A.; Krishnan, K.; Yelamaggad, C.

V. *T* **1992**, *48*, 9725. (c) Jung, M. E.; Clevenger, G. L. *TL* **1991**, *32*, 6089. (d) Thomé, M. A.; Giudicelli, M. B.; Picq, D.; Anker, D. *J. Carbohydr. Chem.* **1991**, *10*, 923.
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15. Newman, M. S.; Vander Zwan, M. C. *JOC* **1973**, *38*, 2910.

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(*S*)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid

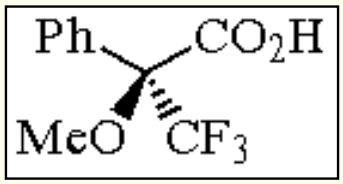

[17257-71-5] · $C_{10}H_9F_3O_3$ · (*S*)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid · (MW 234.19)

(determination of enantiomeric purity and absolute configuration of alcohols and amines[1])

Alternate Name: MTPA.

Physical Data: bp 115-117 °C/1.5 mmHg; $[\alpha]_D$ -71.8° (*c* 3.28, MeOH); *d* 1.344 g cm^{-3}.

Solubility: readily sol hexane, ether, THF, CH_2Cl_2, benzene.

Form Supplied in: both enantiomers are commercially available and generally possess similar applications.

Preparative Methods: both enantiomers are available by resolution of the racemic acid with α-phenylethylamine.[1] Other procedures have been described.[2]

Analysis of Reagent Purity: the enantiomeric purity of the reagent can be evaluated by capillary GC analysis of its methyl ester on a chiral stationary phase,[3] HPLC analysis of the corresponding 1-(α-naphthyl)ethylamide,[2] or by $LiAlH_4$ reduction to the corresponding alcohol, which is analyzed by chiral GC.[4]

Handling, Storage, and Precautions: very stable; commercial samples remain useful after extended periods of time.

Determination of the Enantiomeric Purity of Alcohols, Amines, and Other Compounds by Derivatization.

The enantiomeric purity of a variety of chiral amines and alcohols can be assayed by reaction with chiral MTPA, followed by determination of the diastereomeric purity of the resulting amide or ester.[1] This is usually done by chromatographic (HPLC, GC, TLC, etc.) or spectroscopic methods (^1H NMR, ^{19}F NMR, etc.). Either type of

experiment may provide the desired information and in fact they are often used in combination. MTPA is frequently converted to the corresponding acid chloride (MTPA-Cl) by refluxing in ***Thionyl Chloride***. After distillation, MTPA-Cl is treated with the desired amine or alcohol.[1] An improved procedure for the microscale preparation of MTPA-Cl with ***Oxalyl Chloride***, which does not require distillation of the MTPA-Cl prior to reaction with the alcohol/amine, has been described.[5] Alternatively, MTPA reacts directly with amines and alcohols in the presence of condensing agents such as ***1,3-Dicyclohexylcarbodiimide***[6] or 2-chloro-1-methylpyridinium chloride.[7] Inherent in the successful use of these procedures is the need to ensure complete derivatization of the alcohol/amine, so that the diastereomeric purity of the derivative is truly reflective of the enantiomeric purity of the alcohol/amine under scrutiny.[8]

Alcohols.

When using the ^{1}H NMR spectra of MTPA esters to determine the enantiomeric purity of alcohols, the MTPA methoxy peaks tend to be most useful. This technique can be sensitive enough to detect as little as 1% of the minor alcohol enantiomer. The enantiomeric purity of chiral alcohols (**1**)[9] and (**2**)[10] has been determined this way. The enantiomeric purity of primary alcohols (**3**)[11] and (**4**),[12,13] in which the asymmetric center is not the carbinol carbon, has also been determined by ^{1}H NMR analysis of their MTPA esters. A slight variation of this methodology is the use of shift reagents like $Eu(fod)_3$ to increase the chemical shift separation between diastereotopic MeO peaks; this procedure has been used in the analysis of alcohols (**5**)[14] and (**6**).[15]

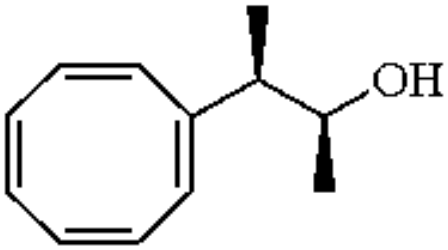

(1)

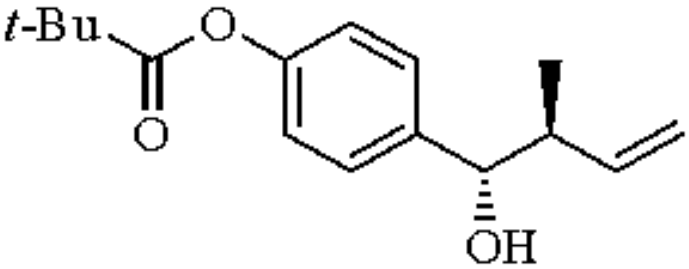

(2)

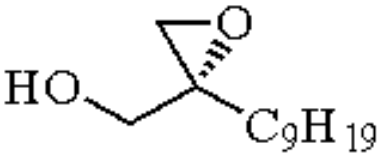

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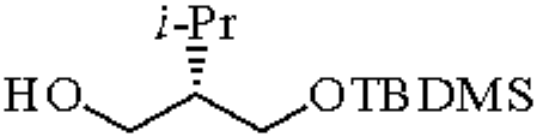

(4)

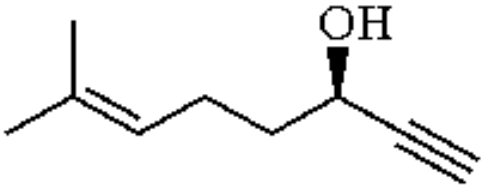

(5)

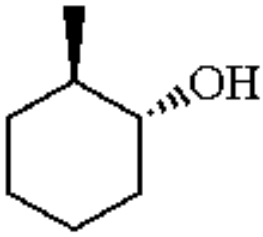

(6)

^{19}F NMR is also extremely useful in the analysis of MTPA esters, and is often used in combination with ^{1}H NMR.[1] The CF_3 peak(s) is easy to observe, being unencumbered by unrelated peaks. Enantiomeric analysis of primary alcohols, e.g. (**7**),[16,17] as well as secondary alcohols (**8**)[18] and (**9**)[19] has been performed utilizing this method. ^{19}F NMR analysis of MTPA esters in the presence of shift reagents has also been utilized to increase the separation between diastereomeric ^{19}F peaks.[15]

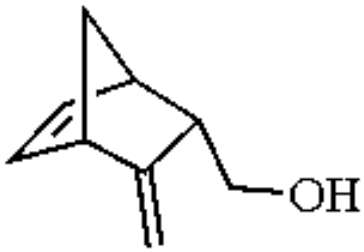

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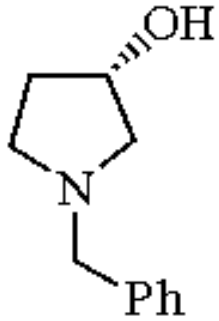

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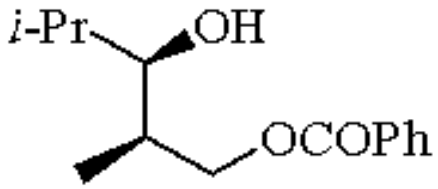

(9)

^{13}C NMR analysis of MTPA esters has not received much attention, but some examples have been described, e.g. the MTPA ester of (**10**).[20]

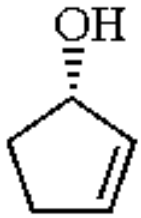

(10)

Almost every available chromatographic technique has been utilized in the analysis of MTPA esters. For example, capillary GLC was used to evaluate the diastereomeric composition of the MTPA esters of chiral alcohols (**5**),[14] (**11**),[21] and (**12**).[22] HPLC is routinely used, for analytical as well as preparative purposes (see below).

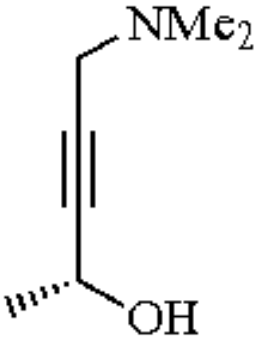

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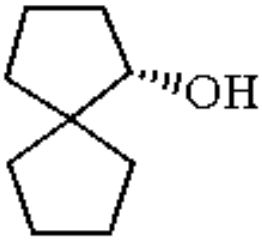

(12)

Amines.

In a manner similar to alcohols, the enantiomeric purity of primary and secondary amines can be assayed by ^{1}H NMR analysis of their MTPA amides.[1] The technique has been particularly useful for amino acid derivatives,[23] e.g. (**13**),[24] (**14**),[25] and (**15**).[26]

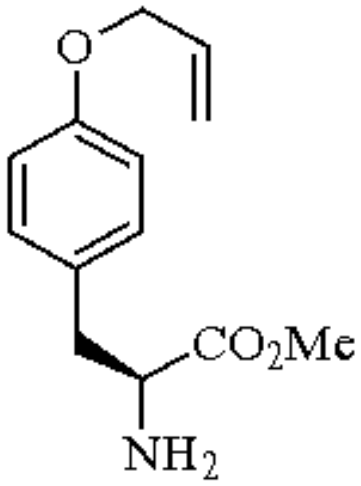

(13)

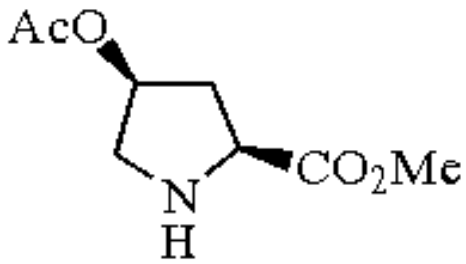

(14)

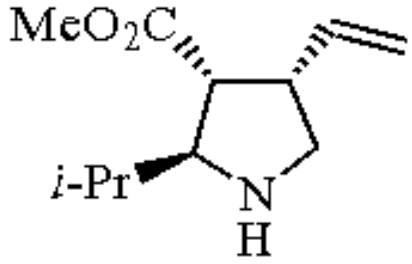

(15)

^{19}F NMR spectroscopy is extremely sensitive in the stereochemical evaluation of MTPA amides of a wide range of amino acids (as low as 0.05% of the minor isomer detectable).[27,28] HPLC analysis of diastereomeric MTPA amides may provide valuable analytical information on the enantiomeric composition of chiral primary and secondary amines.[29]

Other Compounds.

In theory, any chiral compound with a reactive functional group can be derivatized with (*S*)- or (*R*)-MTPA in order to assess its enantiomeric purity. An example is the derivatization of cyclic carbamates, followed by ^{1}H NMR analysis (eq 1).[30] Similarly, axially chiral biaryls bearing amine or alcohol substituents, e.g. (**16**) and (**17**), have been analyzed via the corresponding MPTA derivatives.[31]

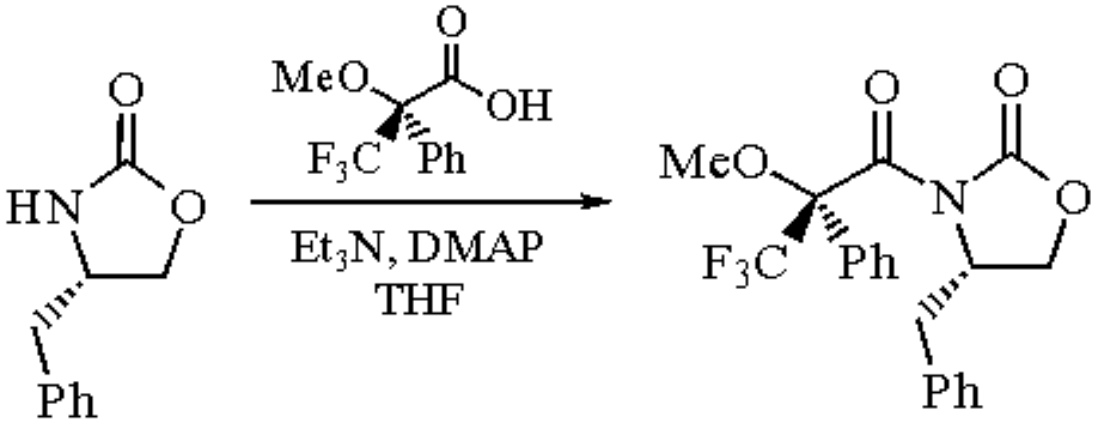

(1)

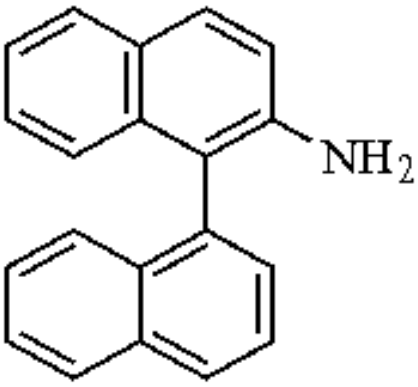

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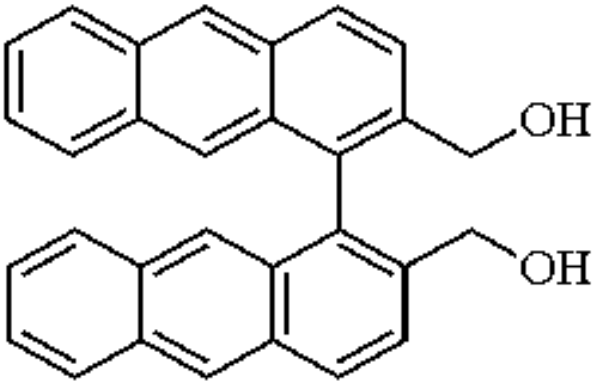

(17)

Noncovalent MTPA Derivatives.

The enantiomeric purity of some chiral amines can be determined by ^{1}H NMR with (*S*)- or (*R*)-MTPA as a chiral solvating agent.[32,33] The method is particularly useful for chiral tertiary amines that are not amenable to conversion into MTPA amides, e.g. (**18**) and (**19**),[34] although it has been utilized for primary and secondary amines as well, e.g. (**20**).[35]

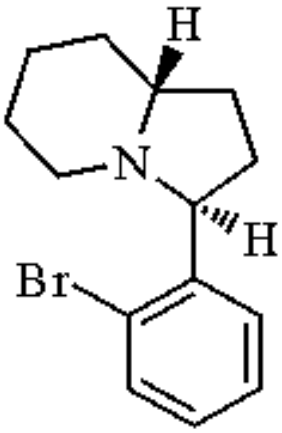

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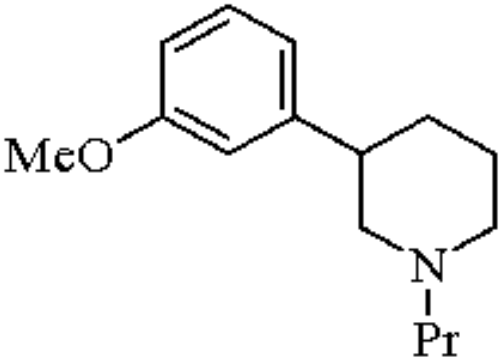

(19)

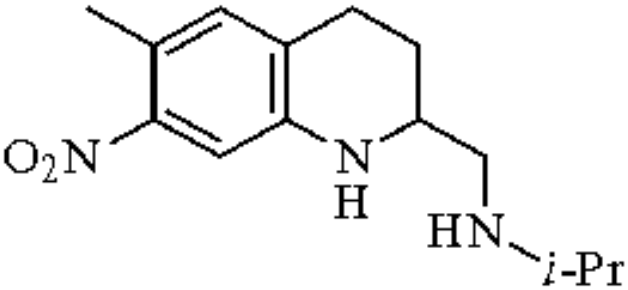

(20)

Determination of Absolute Configuration in Alcohols and Amines.

The configuration of chiral alcohols and amines (where the heteroatom is attached to the stereocenter) has been correlated with the ^{19}F chemical shifts of their MTPA derivatives.[36] The model is not fully predictive, although the exceptions can often be rationalized. However, ^{1}H NMR spectroscopy of MTPA esters and amides has been more widely used in the assignment of configuration to chiral alcohols and amines.[37] Analysis of the chemical shifts of the MTPA methoxy peaks, in the presence of shift reagents, allows the correct stereochemical analysis of a series of bicyclic alcohols, such as (**6**).[15] The ^{1}H NMR shifts of the hydrogens directly attached to the carbinol carbons in MTPA esters have also been used to establish the configuration of chiral acyclic secondary alcohols.[38] Other peaks in

the MTPA derivatives have been used in the stereochemical elucidation of a series of alcohol natural products.[39] Although less commonly used, ^{13}C NMR spectroscopy of MTPA derivatives has been used in the stereochemical study of a large group of chiral alcohols.[40] The stereochemistry of amino acids has also been amenable to study by ^{1}H NMR spectroscopy of their MTPA derivatives.[23,41]

Preparative Uses of MTPA Derivatives.

Resolution of racemic compounds on a preparative scale is always a challenging endeavor. Conversion of the enantiomeric mixture into a mixture of diastereomers, each with unique physical properties, makes it possible to separate the components by a variety of physical methods, such as fractional recrystallization, distillation, or chromatography. One of the earliest uses of MTPA was the resolution of racemic alcohols via the separation of diastereomeric MTPA esters by preparative gas-liquid chromatography, followed by alcohol regeneration with ***Lithium Aluminum Hydride*** (eq 2).[1] More frequently, diastereomeric MTPA esters have been separated by high performance liquid chromatography (HPLC), followed by alcohol regeneration either by ester hydrolysis (eq 3)[42] or reduction (eq 4).[43]

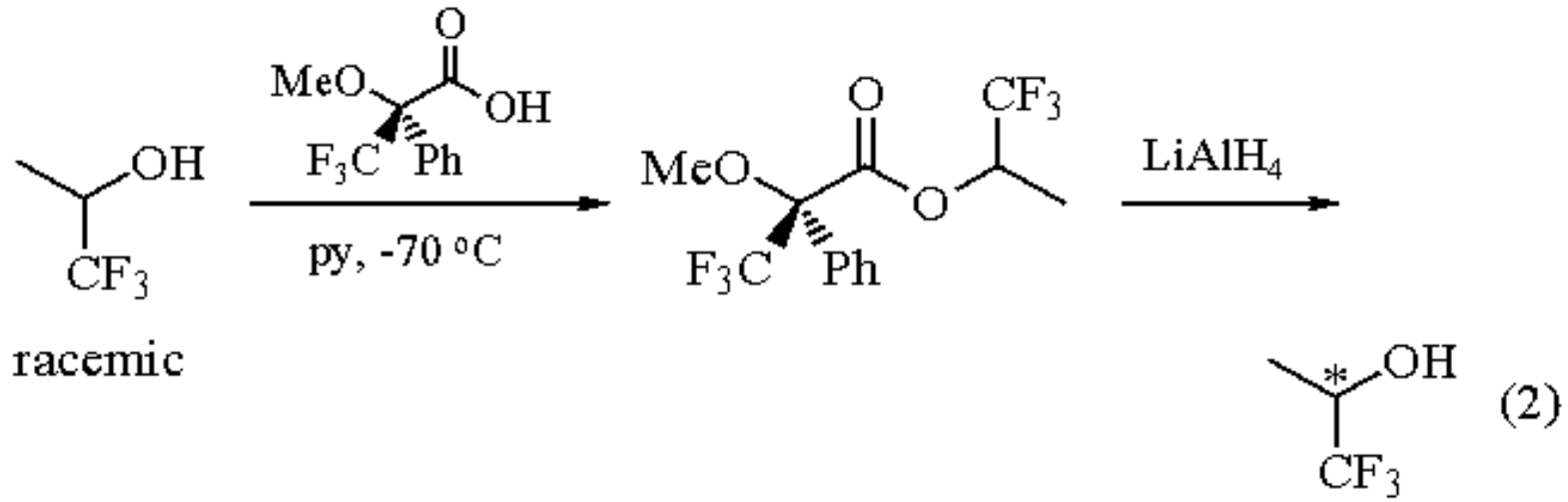

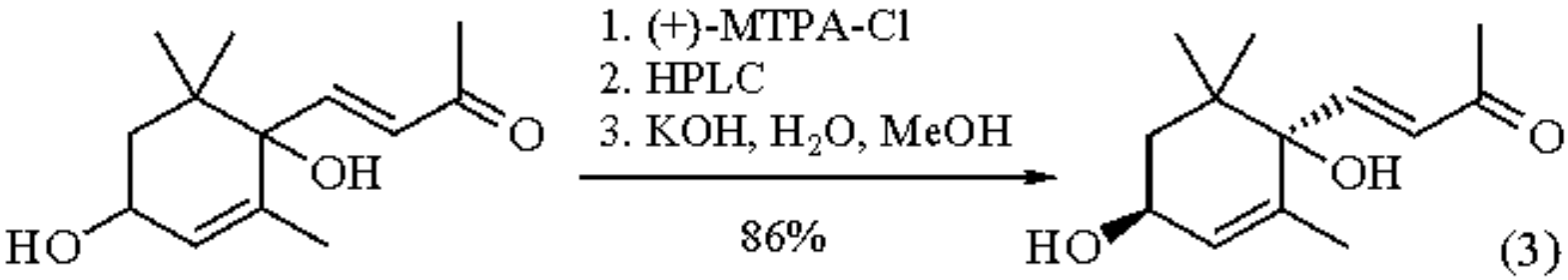

(S)-(-)-alpha-Methoxy-alpha-(trifluoromethyl)phenylacetic Acid

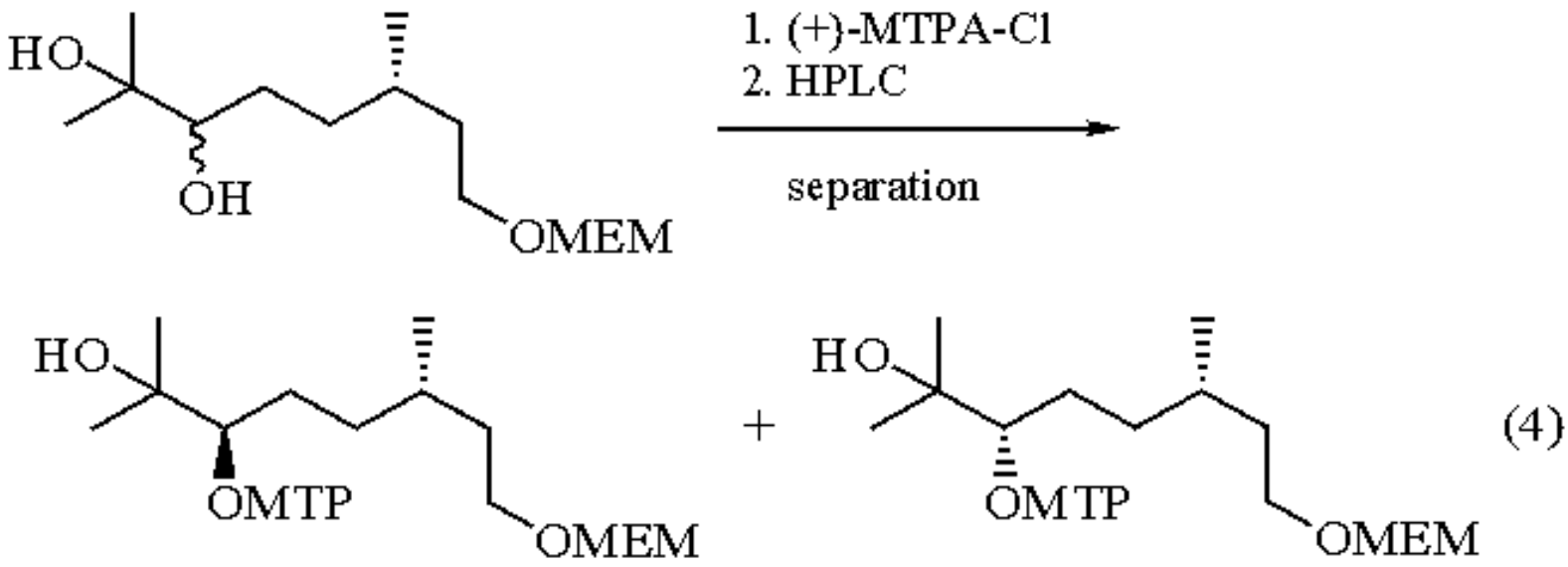

This procedure is useful even when the carbinol carbon is not the asymmetric center of the molecule (eq 5).[44]

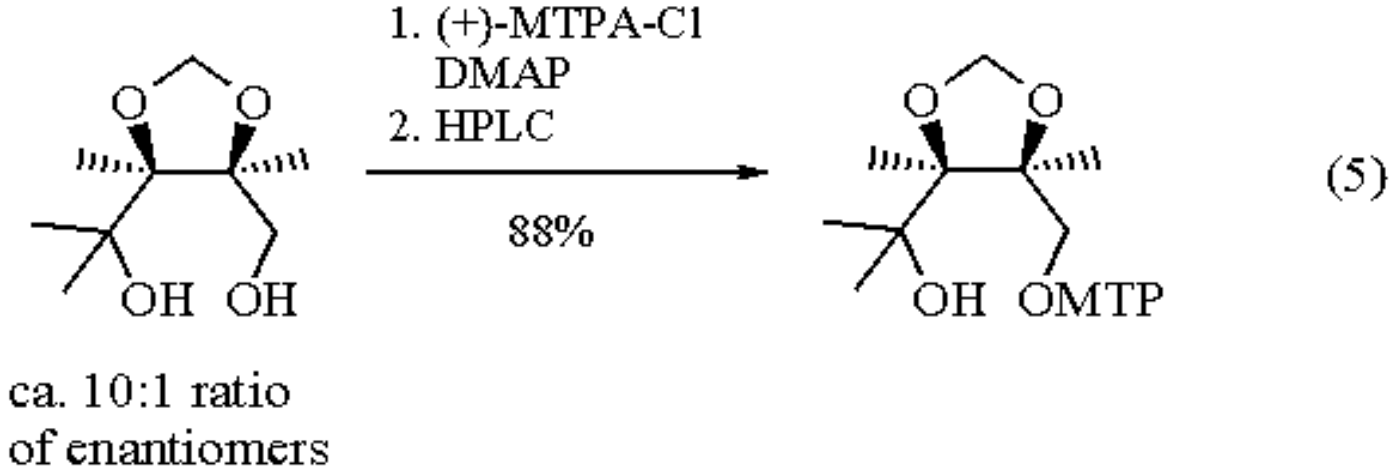

Far fewer examples of diastereomeric ester separations by fractional recrystallization have been described. However, this procedure is extremely practical for the resolution of a series of bromohydrins (eq 6).[45]

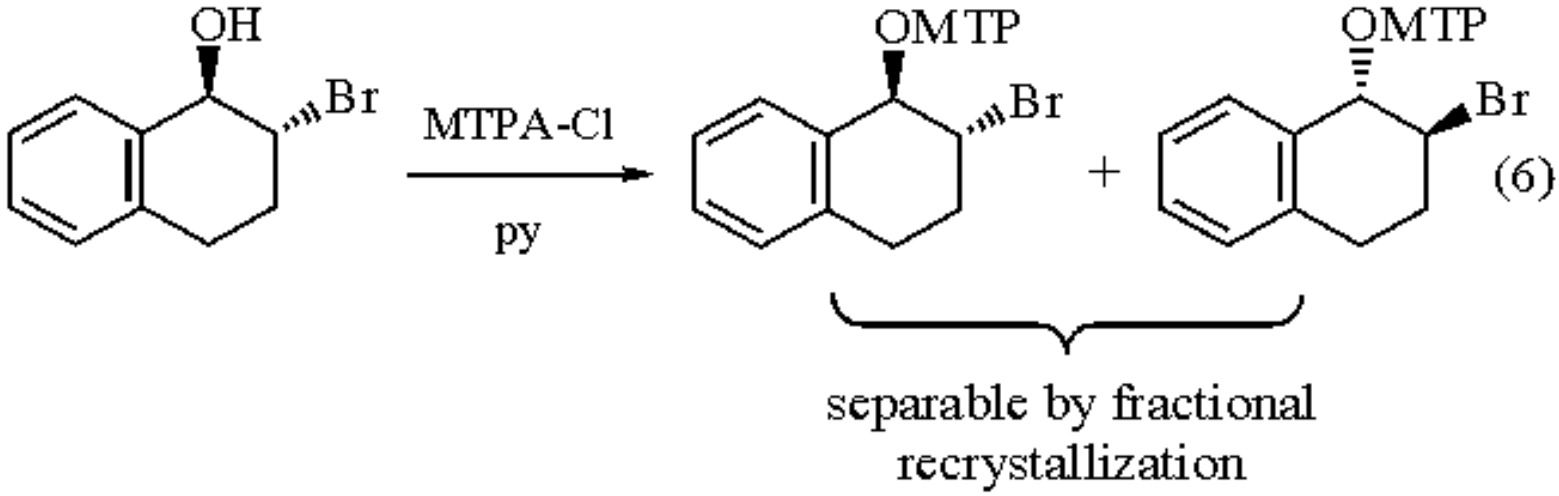

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Juan C. Jaen

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene[1]

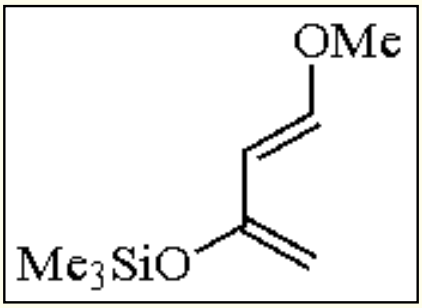

[59414-23-2] · $C_8H_{16}O_2Si$ · 1-Methoxy-3-trimethylsilyloxy-1,3-butadiene · (MW 172.33) (*E*)

[54125-02-9]

(highly reactive diene for Diels-Alder reactions[1a,b] and hetero-Diels-Alder reactions[1c])

Alternate Name: Danishefsky's diene.

Physical Data: bp 68-69 °C/14 mmHg; *n*20D 1.4540; *d* 0.885 g cm^{-3}.

Solubility: insol H_2O; sol most organic solvents.

Form Supplied in: colorless neat liquid; may contain 3-5% of 4-methoxy-3-buten-2-one. This level of purity is sufficient for most preparative purposes.

Analysis of Reagent Purity: checked easily by its ^1H NMR spectrum.[2,4]

Preparative Methods: the diene was originally prepared from ***4-Methoxy-3-buten-2-one*** with ***Chlorotrimethylsilane-Triethylamine-Zinc Chloride*** in benzene as shown below (68% yield, eq 1).[2a] A detailed experimental procedure for preparative scale work is described by Danishevsky et al. (45-50%).[3] TMSCl-***Sodium Iodide*** in acetonitrile is also a mild procedure for the preparation of this reagent (60%).[4] At the present time, the most efficient method is to use TMSCl-***Lithium Bromide***-Et_3N in THF (91%).[5]

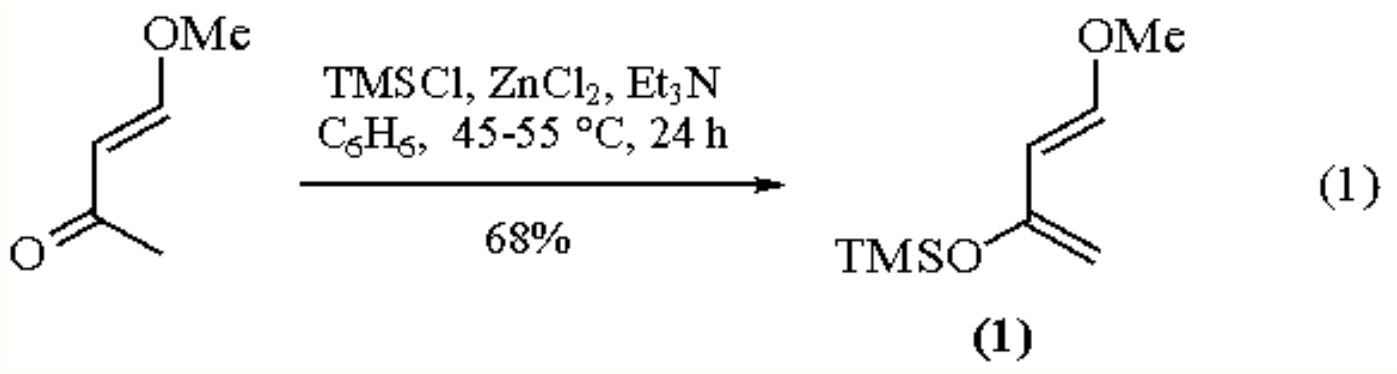

Handling, Storage, and Precautions: this diene can be kept in a stoppered container without appreciable decomposition, but it is extremely moisture sensitive.

Diels-Alder Reactions.

General Aspects.

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (**1**) is one of the most reactive species for use in the Diels-Alder reaction and was the first example of a multioxygenated polar 1,3-diene for preparative use. More recently, analogous siloxy dienes with two or more oxygen functions have been prepared and their reactivities have been studied widely.[1a,b] The extremely high reactivity of this diene is illustrated by its reaction with ***Maleic Anhydride***, in which instantaneous exothermic reaction leads to the formation of the adduct via *cis-endo* addition. The stereochemical course of the reaction is unambiguously determined by the isolation of the initial adduct before acidic workup (eq 2).[2,3]

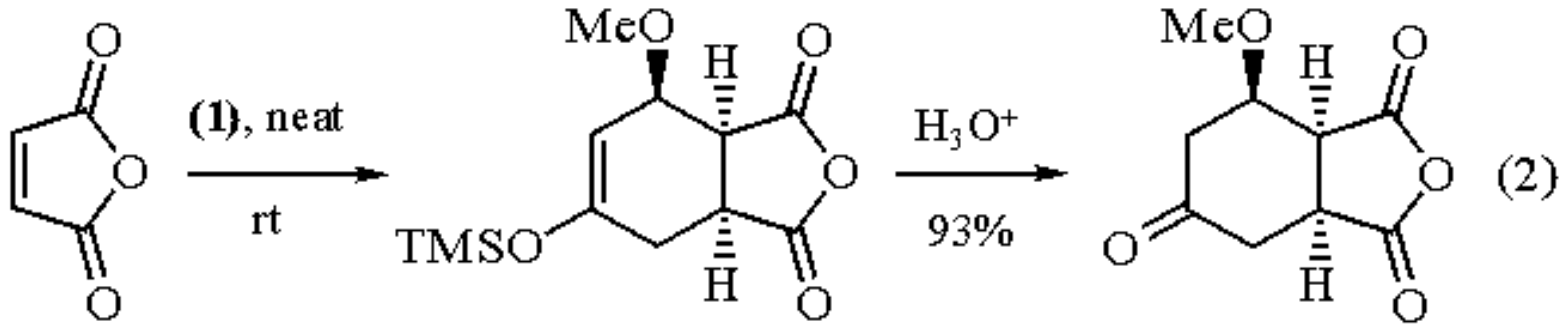

The utility of this diene for the preparation of functionalized aromatic systems is demonstrated by the facile conversion of ***Dimethyl Acetylenedicarboxylate*** to a hydroxyphthalate (eq 3) and ***1,4-Benzoquinone*** to an oxygenated naphthalene (eq 4).[2]

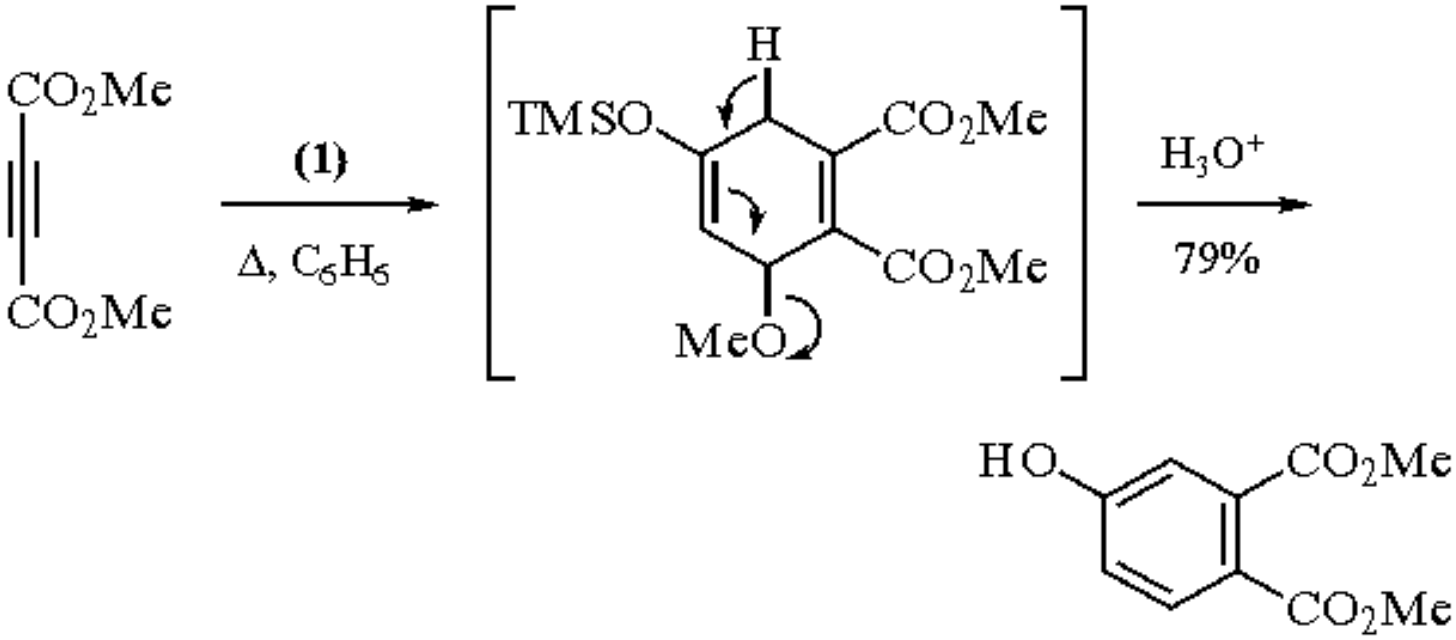

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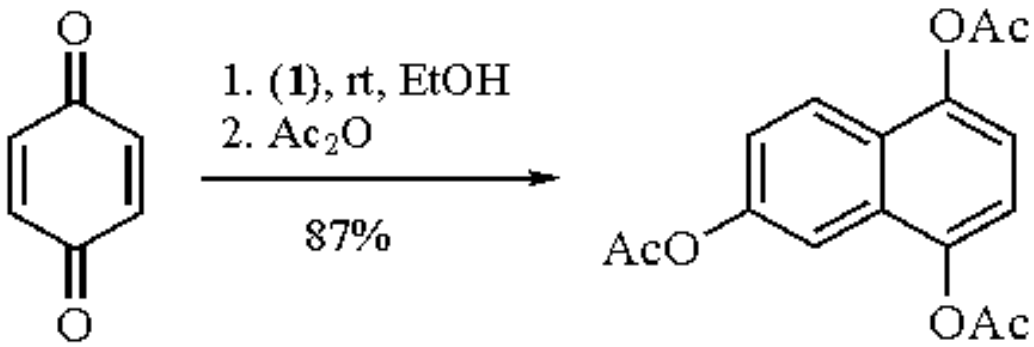

(4)

The second pathway leads to alicyclic compounds. In most cases, α,β-unsaturated cyclohexenones are produced. For example, treatment with a reactive dienophile such as ***Methacrolein*** or ***Methyl Acrylate*** gives the desired system (eqs 5 and 6).[2,6] The important feature is that only one regioisomer is obtained by high orientational specificity of electron-donating substituents at the 1,3-positions of the diene.

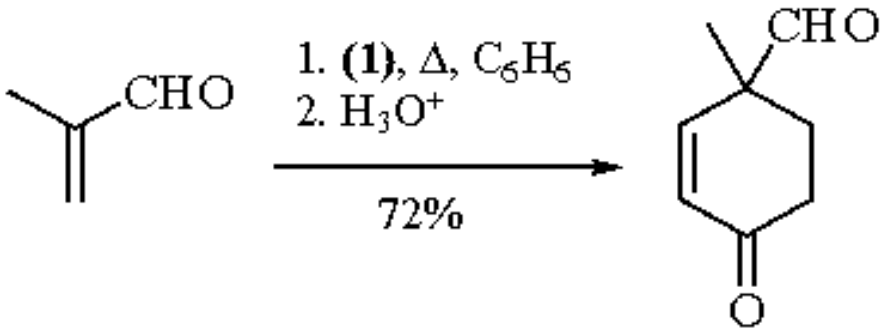

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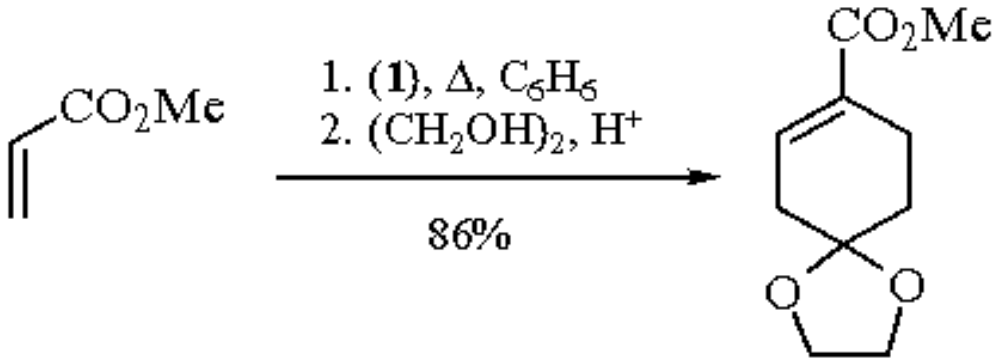

(6)

The remarkable reactivity of this siloxy diene is exemplified by successful reaction with poor dienophiles such as methyl 1-cyclohexenecarboxylate, which does not give Diels-Alder adducts with ordinary dienes like butadiene. It requires more severe conditions, but the reaction gives a Δ^1-*cis*-3-octalone system in good yield (eq 7); this is not very easy to access via other methods. Several other examples show the generality of this process.[6]

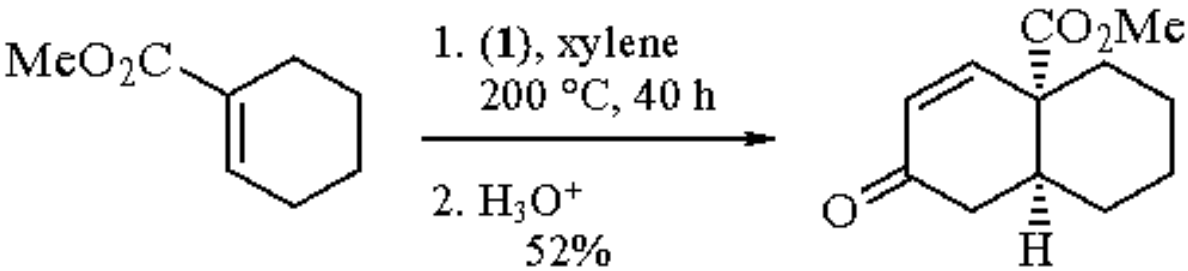

(7)

The excellent reactivity and regio- and stereoselectivity of this diene have been demonstrated, and there have been enormous numbers of publications on applications to the synthesis of various types of carbocyclic systems.

Condensed Aromatic Compounds.

Completely opposite regioselectivity is seen when juglone (eq 8) and its methyl ether (eq 9) are reacted with this diene. Directing effects, with or without chelation by the hydroxy or methoxy group, clearly explain the selectivity.[7] The more polar carbonyl group, marked with an asterisk, controls the regiochemistry.

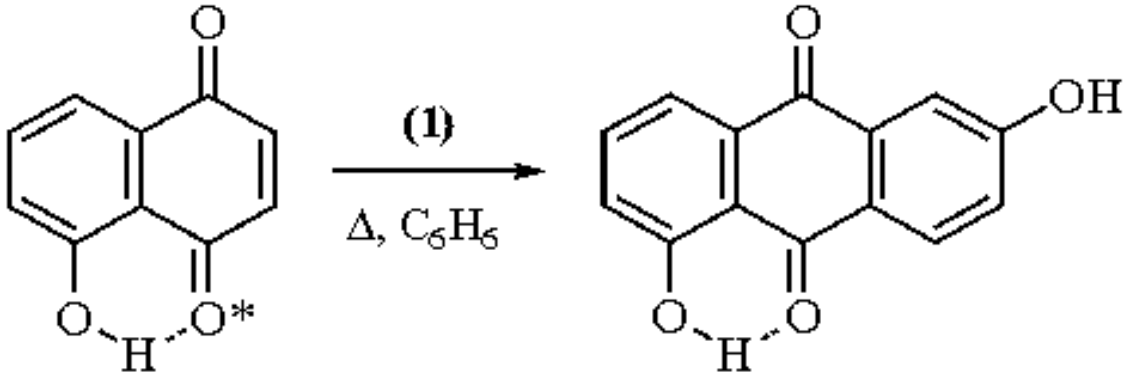

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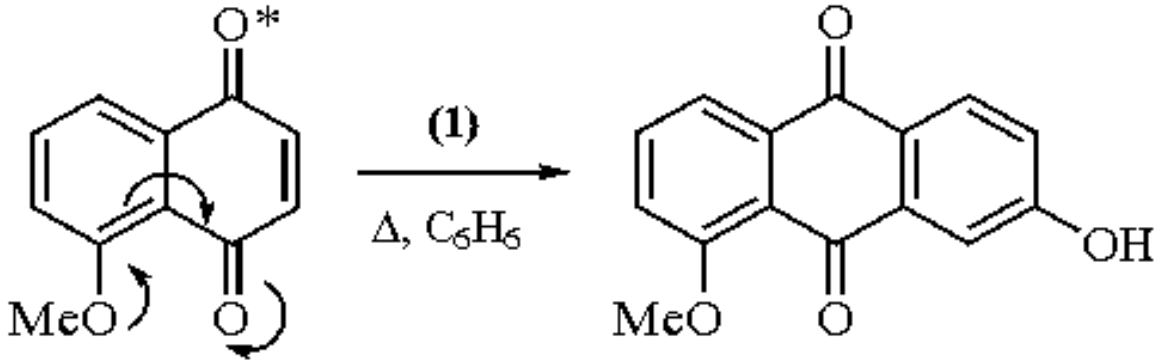

(9)

Similar regioselectivity is observed with 2,3-dichloro-5-hydroxy-1,4-naphthoquinone (eq 10),[8] 6,8-dimethoxy-1,4-naphthoquinone,[9] and anthraquinone derivatives.[10,11] These methodologies have been widely applied to the synthesis of alizarin analogs,[8] daumnomycinone,[12] and related anthracyclinones and their derivatives.[10,11,13]

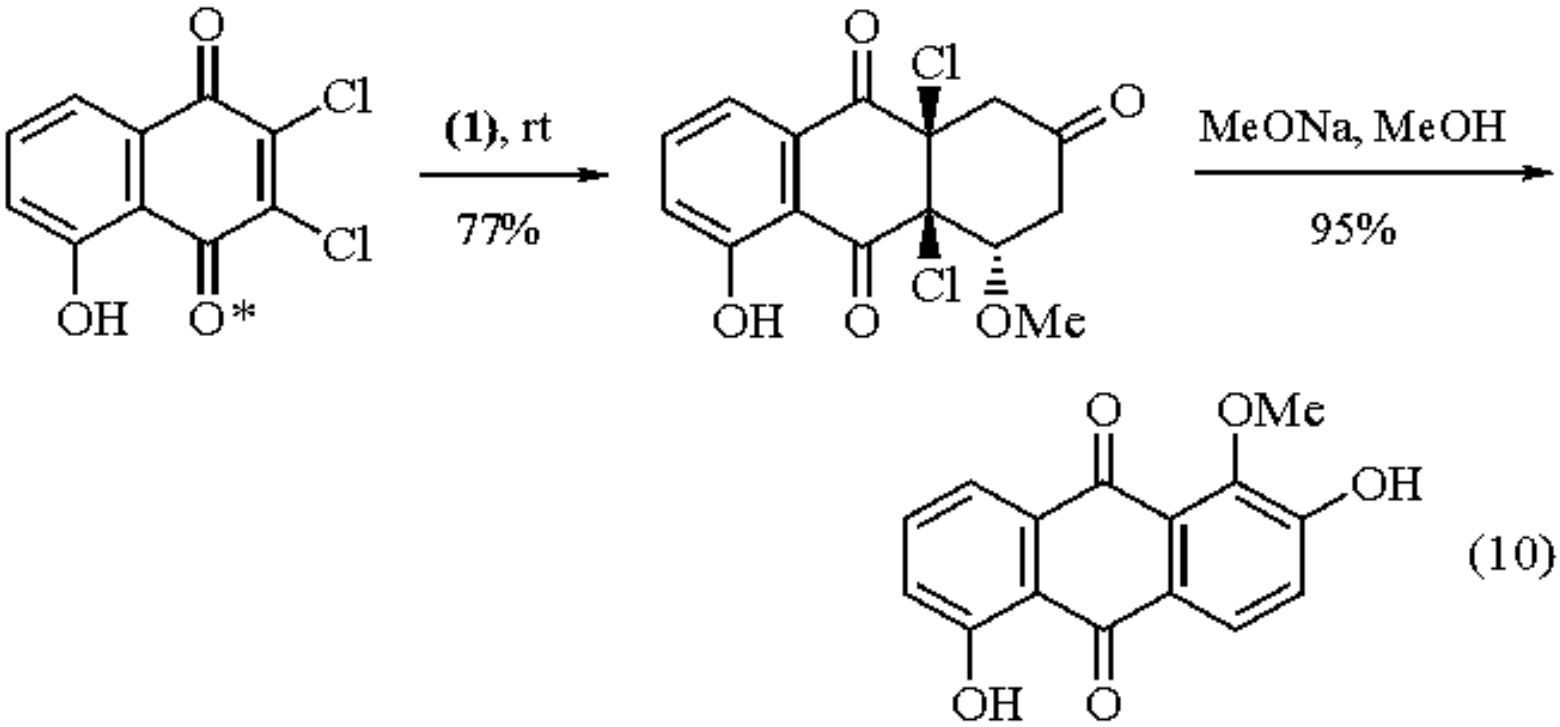

(10)

Alkyl or alkoxy quinones[14] also give single isomers regioselectively (eq 11), while a chloroquinone[15] gives the opposite type of adduct as the sole product (eq 12).

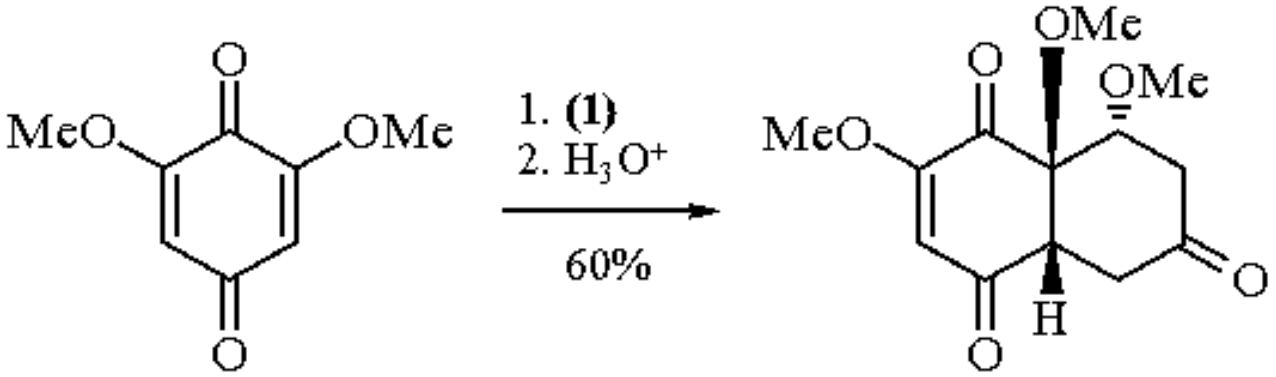

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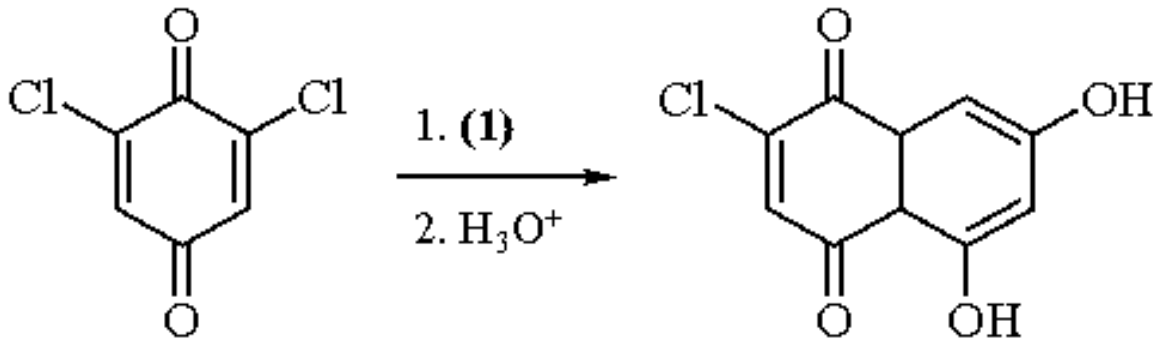

(12)

Stereospecific cycloaddition from the less hindered side of an epoxyanthraquinone derivative gives a single adduct, which has been converted to a daunomycinone analog (eq 13).[16]

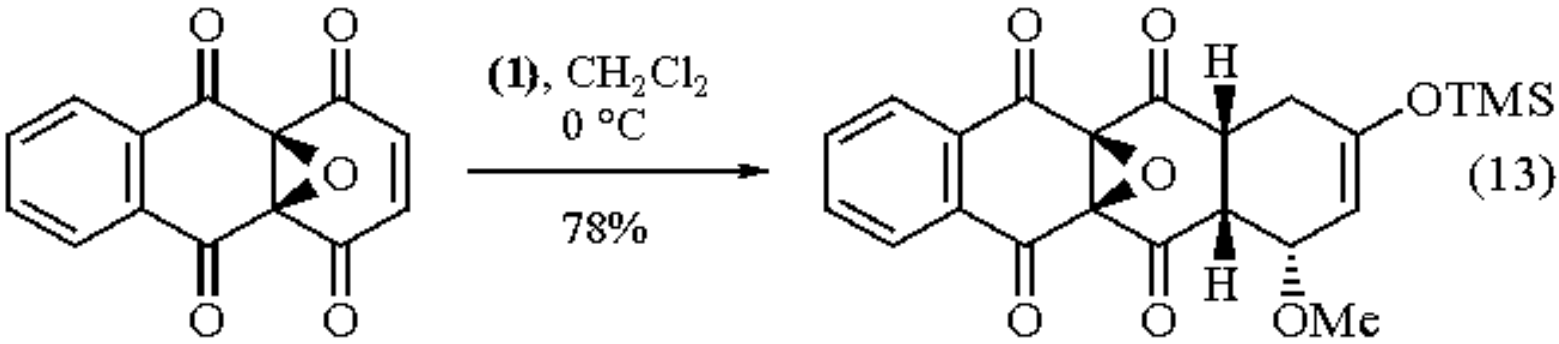

(13)

Reaction with an unsymmetrically substituted spiro-ene-dione dienophile also gives primarily the adduct from attack at the less hindered face (eq 14); the product is convertible to the fredericamycin A skeleton.[17]

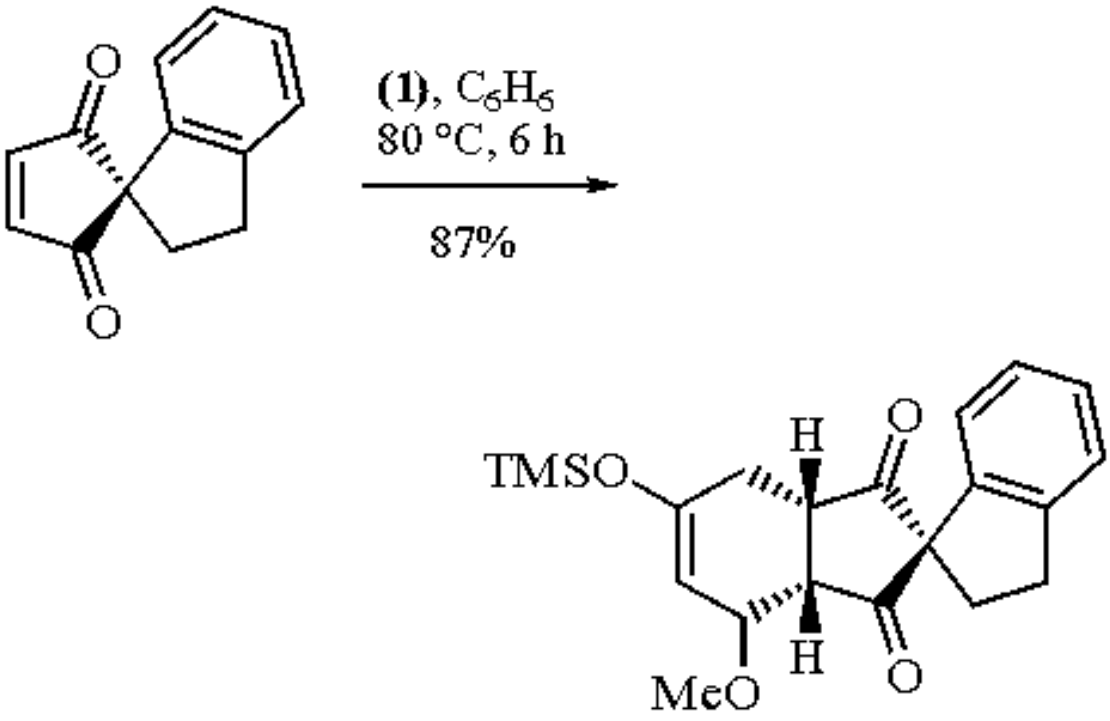

+ β-isomer (14)

6:1

Cyclohexenones and Analogs.

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene

As described earlier, α,β-unsaturated aldehydes and ketones are good dienophiles and the resulting polyfunctional cyclohexenones have been used for the synthesis of ajugarin I (eq 15)[18] and damscones.[19] The diene can even react with (trifluoromethyl)ethylenes to give the adducts regioselectively.[20]

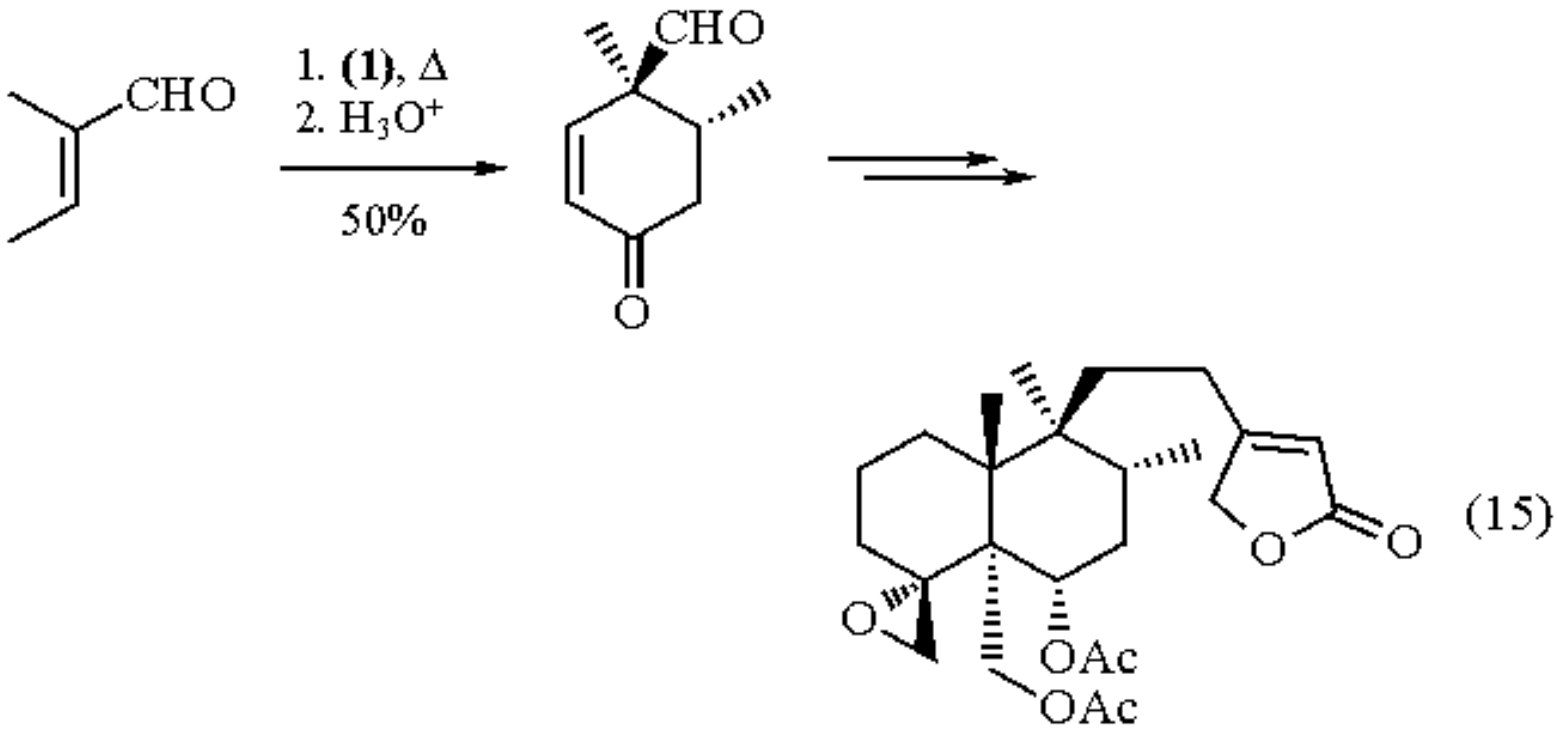

(15)

Ajugarin I

Doubly activated dienophiles such as methylenemalonates,[21] alkylidenemalononitriles[22] and 2-trifluoromethylacrylates[23] easily react with the diene to give enones and dienones (eq 16), from which the cannabinoid skeleton[22] and trifluororetinal have been synthesized.[23]

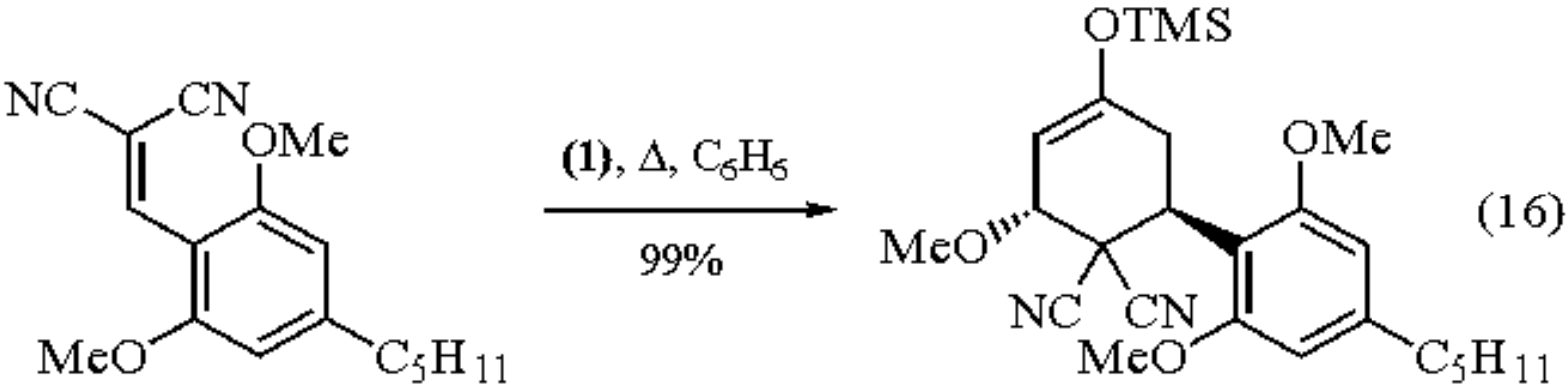

(16)

Dienones are directly obtained using dienophiles with additional functionality such as sulfoxide (eq 17)[24-26] or acetate.[27] The process has been applied to the synthesis of prephenate,[24,27] pretyrosines,[25] and tazettine.[26]

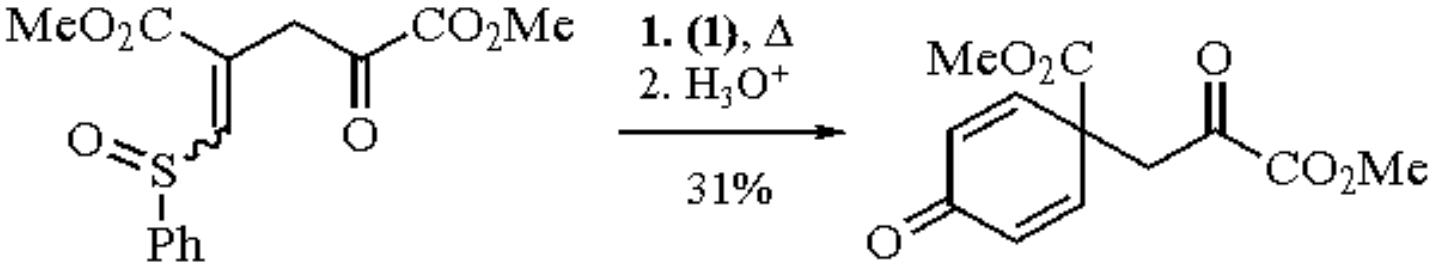

(17)

Vinyl sulfones are useful dienophiles for the preparation of monocyclic cyclohexenones[28,29] or phenols.[30] Reactions with nitro alkenes give precursors for cyclic nitro alkenes[31] and amino alcohols.[32]

Fused Alicyclic Ring Systems.

As discussed earlier, even cyclohexenones or cyclohexene esters are useful dienophiles and various types of adducts with fused ring systems have been synthesized from these reaction partners. For example, methyl 1,4-cyclohexadienecarboxylate gives the *cis*-hexalin system, which is employed for the synthesis of vernolepin (eq 18).[33]

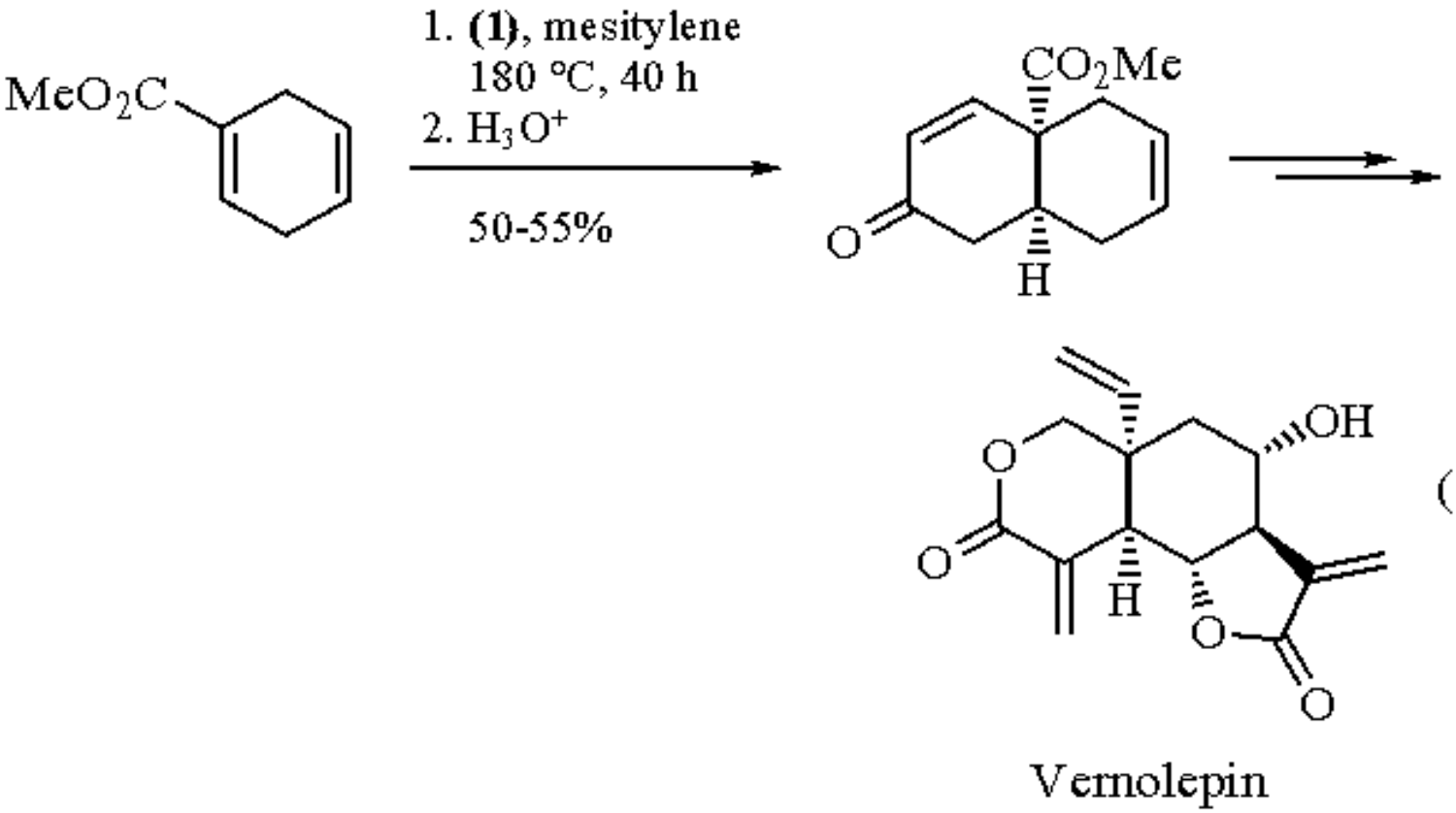

(18)

This general procedure for the construction of *cis*-fused decalin or extended systems has been applied to the synthesis of pentalenolactone,[34] both racemic and natural quassinoids, picrasin B, quassin (eq 19),[35] the compactin skeleton,[36] and (±)-halipanicine.[37]

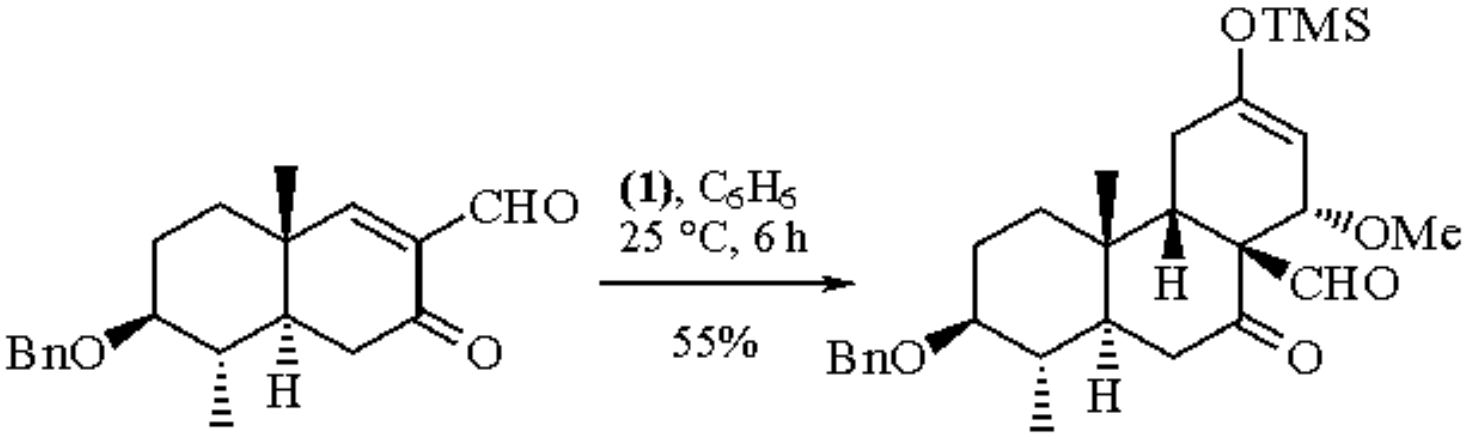

(19)

Reactions with cyclopentene dienophiles give *cis*-fused hydrindenones.[38,39] In the case of 3-alkoxycarbonylcyclopentadienone, the alkoxycarbonyl group is the principal substituent for controlling the orientation of the cycloaddition (eq 20).[40] With the ene-dione of fused cyclopentanes, single regioisomers are produced because the carbonyl group (asterisk) is oriented out of the plane of the other conjugated enone (eq 21).[41] Using an activated dioxopyrroline as the dienophile, the spirocyclic system of the Erythrina alkaloid skeleton is constructed and the synthesis of Erythrina alkaloids has been achieved (eq 22).[42]

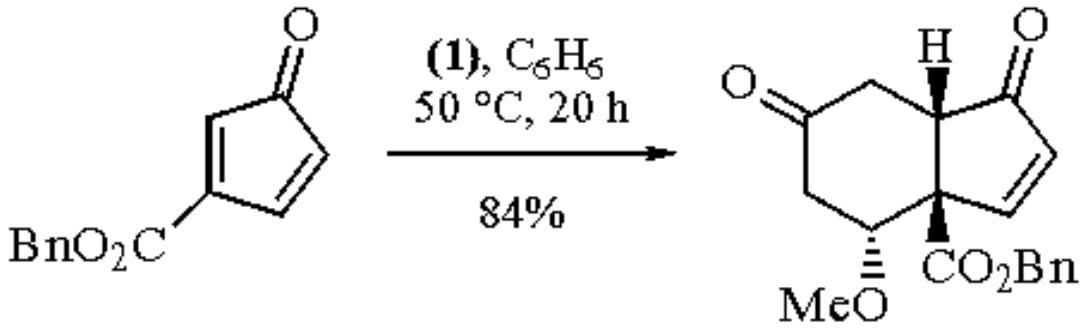

(20)

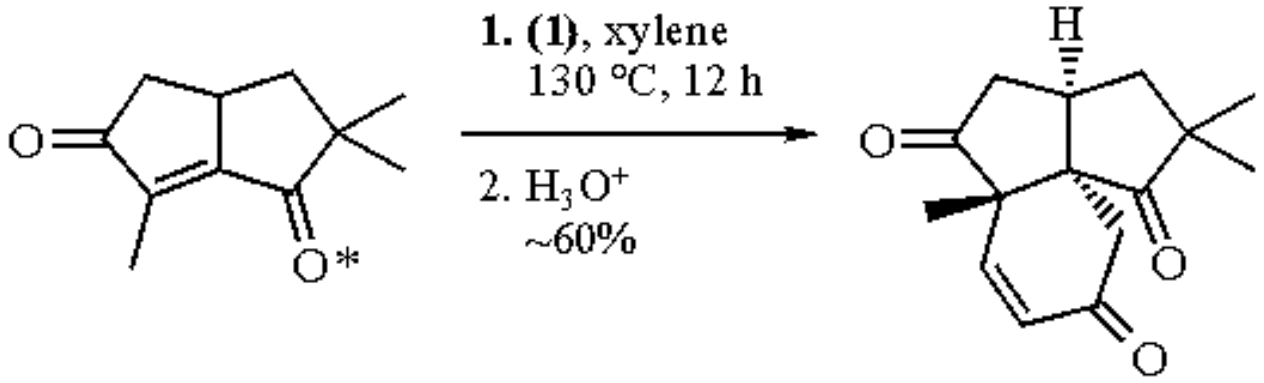

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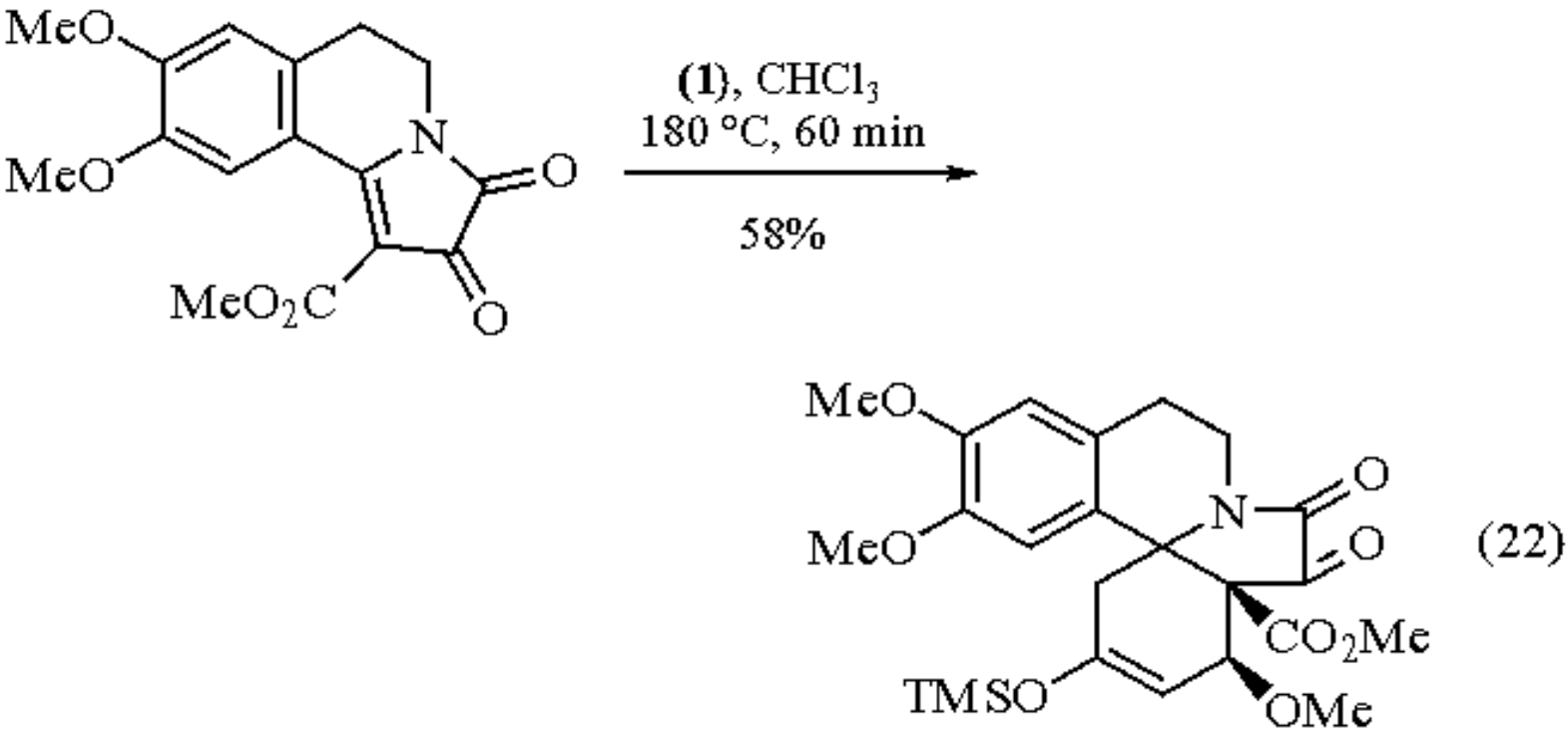

(22)

Cycloaddition with 1-acetylcyclobutene gives a bicyclic adduct, which is transformed to a cyclooctadienone (eq 23).[43] Exceptional stereoselectivity is also observed with bridged enones and a strained enone is a very reactive dienophile, giving the *exo* adduct exclusively in excellent yield (eq 24).[44]

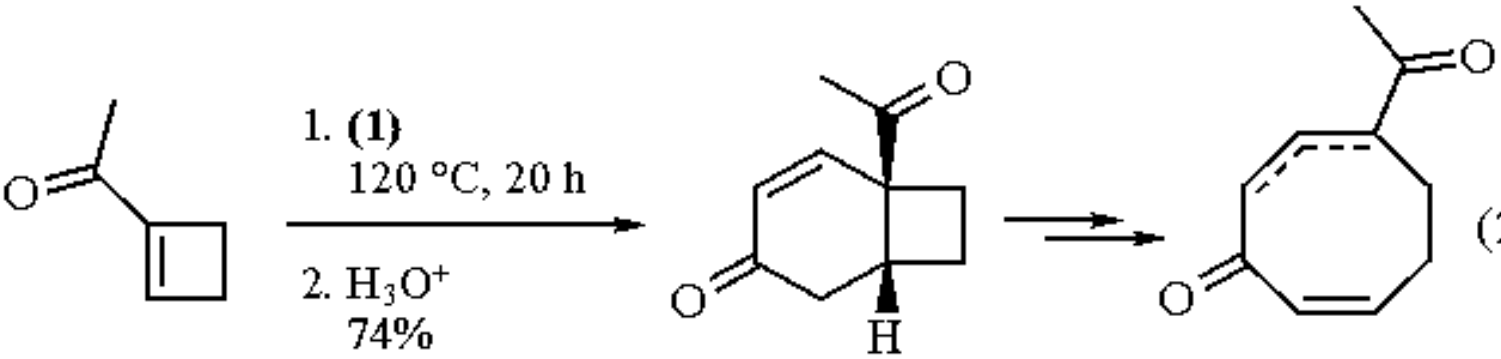

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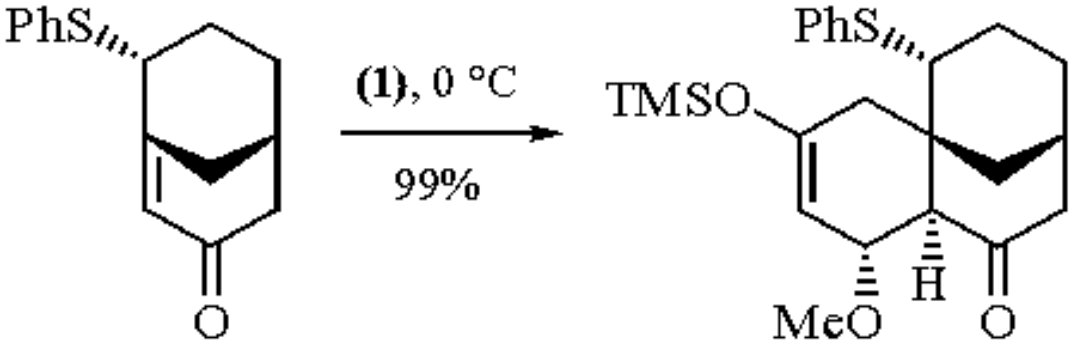

(24)

Lactones are poor dienophiles under normal conditions, but, using high pressure, they smoothly afford the corresponding *endo* adducts (eq 25).[45]

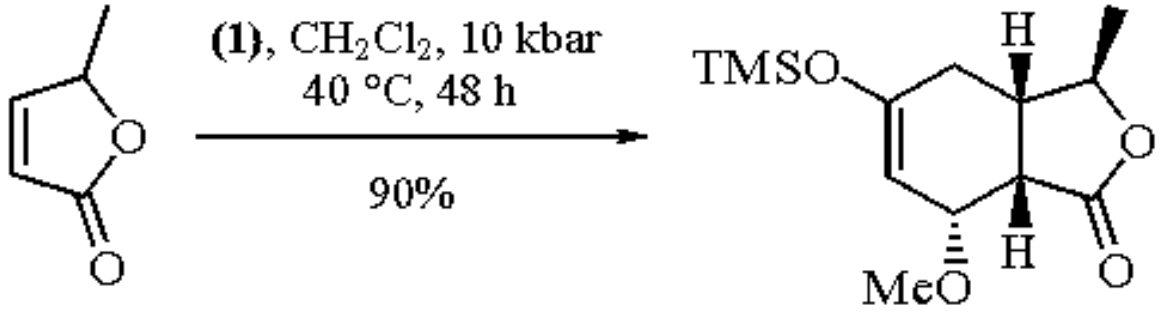

(25)

On the other hand, γ-lactams (eq 26) and δ-lactams (eq 27) are much better dienophiles and give hydroisoindolines[46] and hydroisoquinoline-type manzamine skeletons.[47] Even 2,4-bis(methoxycarbonyl)furan reacts with this diene to give fused heterocycles (eq 28).[48]

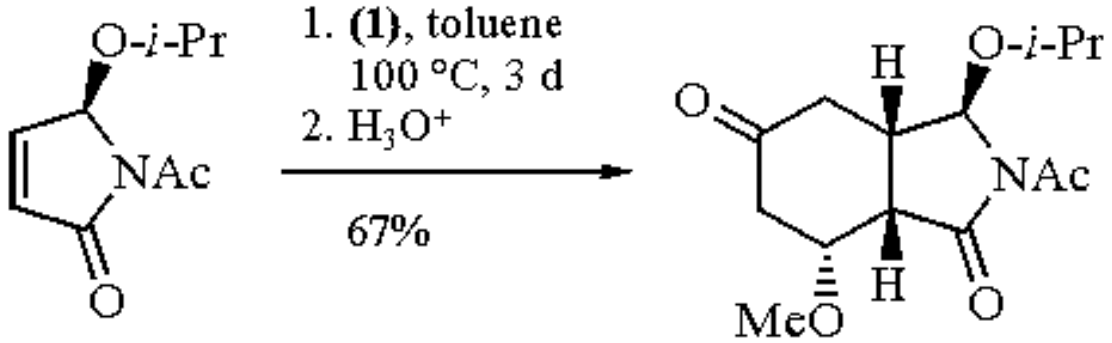

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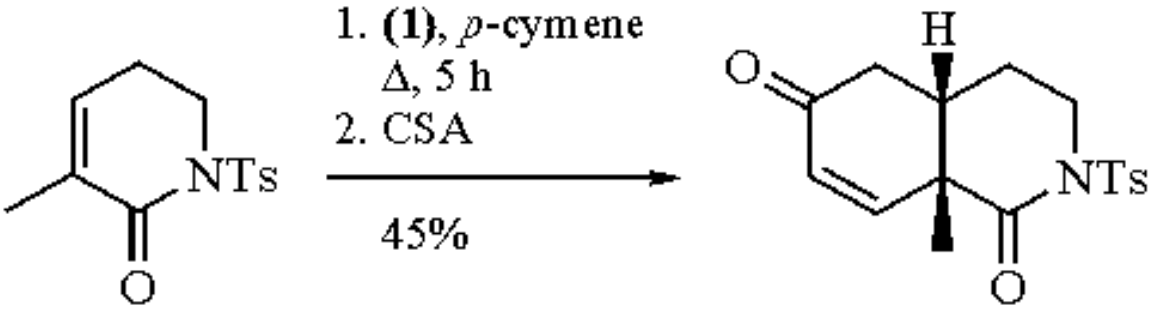

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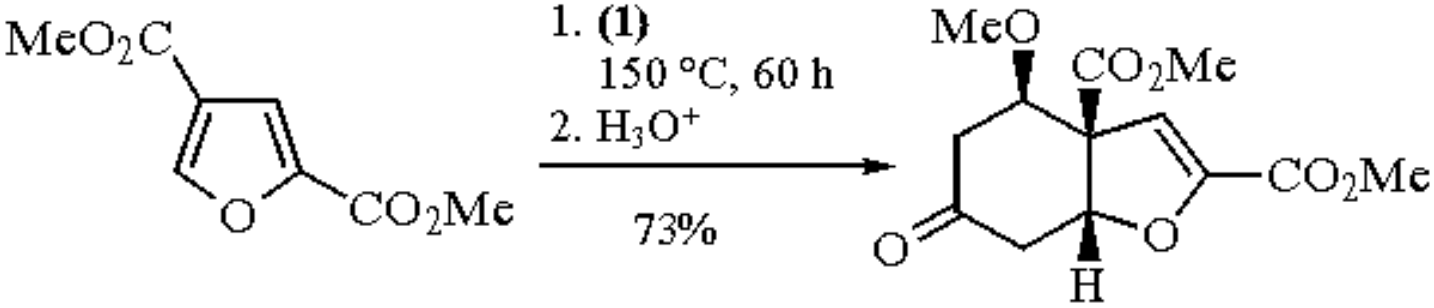

(28)

Miscellaneous.

Danishefsky's diene reacts with strong electrophiles such as 2-methylene-1,3-cyclopentanedione to give Michael-type adducts at low temperature, but, on heating, it gives the usual cycloadduct (eq 29).[49]

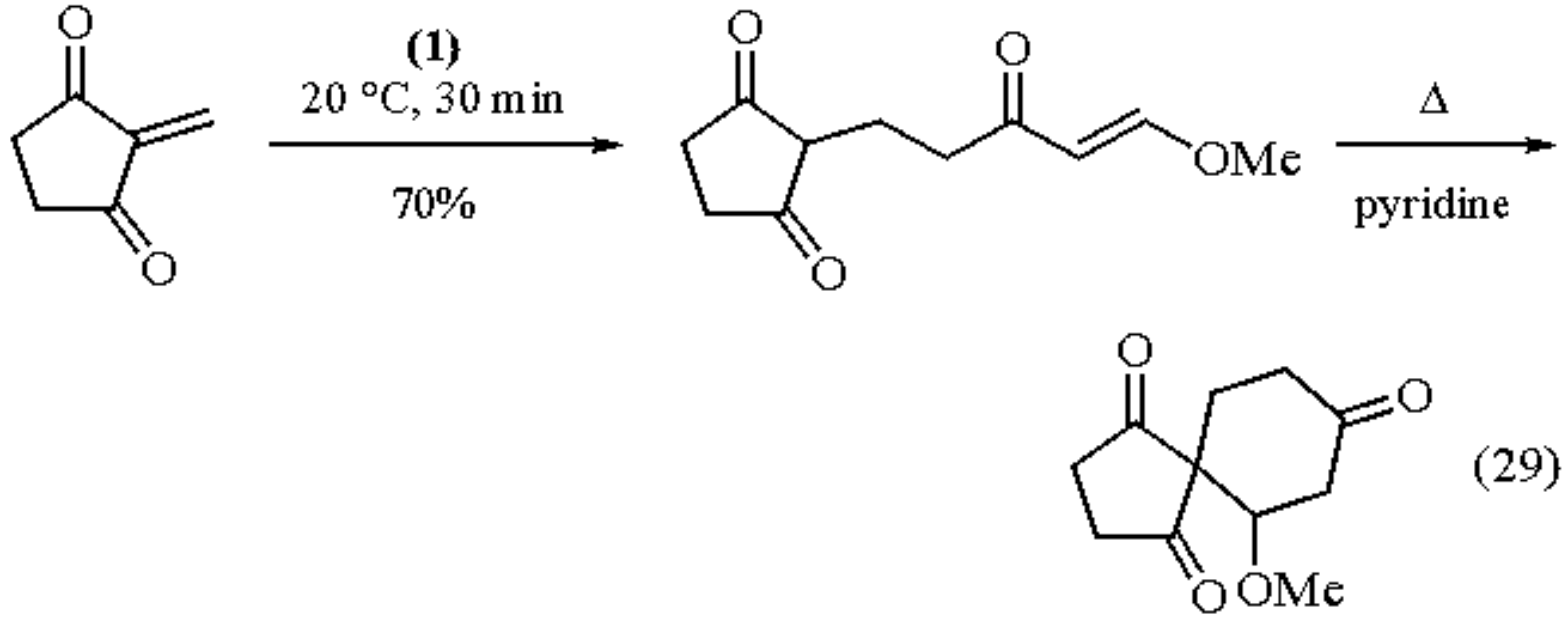

(29)

The electron-rich enol ether moiety of the diene reacts with carbenes preferentially to give cyclopropane analogs, which afford hydroguaiazulene derivatives via Cope rearrangement (eq 30).[50]

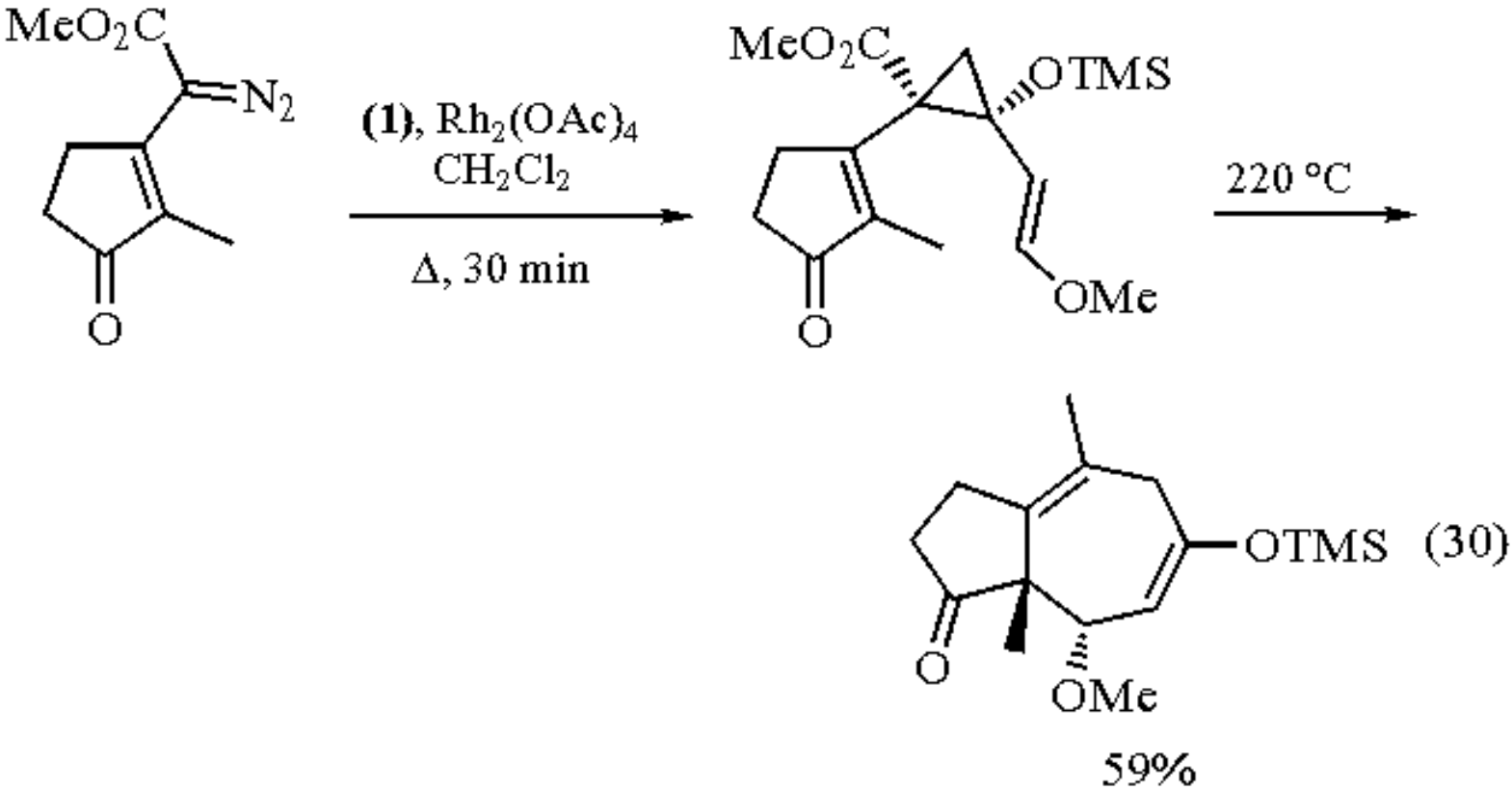

(30)

Strained alkenes are useful dienophiles and tetrachlorocyclopropene reacts with the diene at ambient temperature to give substituted tropones and tropolones via bicycloheptenes (eq 31).[51] Polyhalocyclobutenes give benzocyclobutenones in good yield on a preparative scale (eq 32).[52]

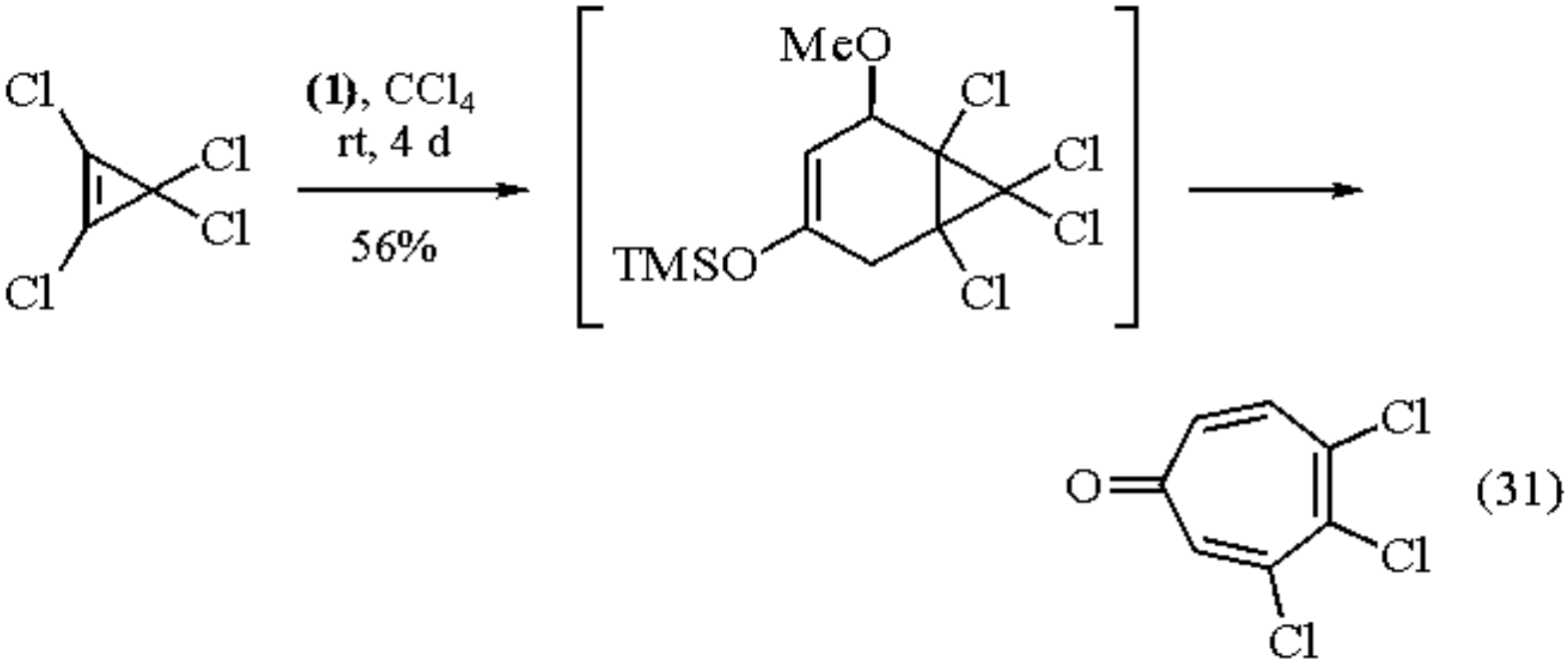

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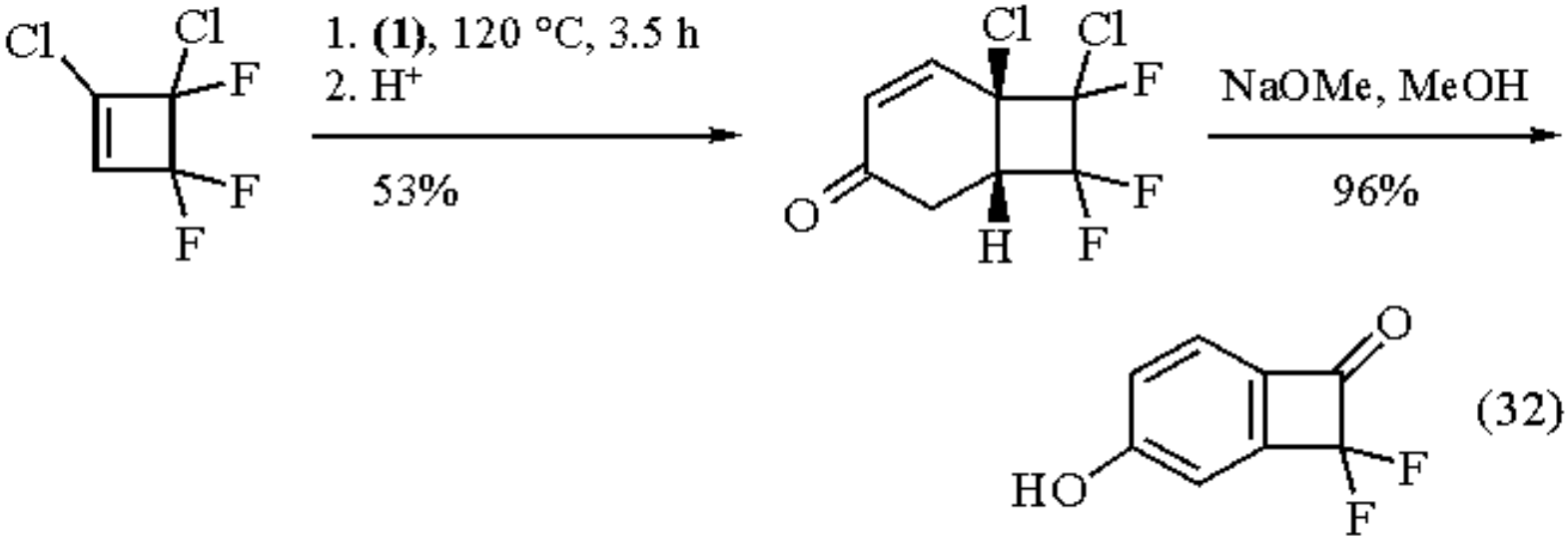

(32)

Hetero-Diels-Alder Reactions.

General Aspects.

Activated hetero-alkenes such as carbonyls and imines with electron-withdrawing substituents react with the diene under pyrolytic conditions to give dihydropyrones (eq 33)[53-55] and dihydropyridones, respectively (eq 34).[54,56,57] In these cases, however, reactions are limited only to special hetero-alkenes.

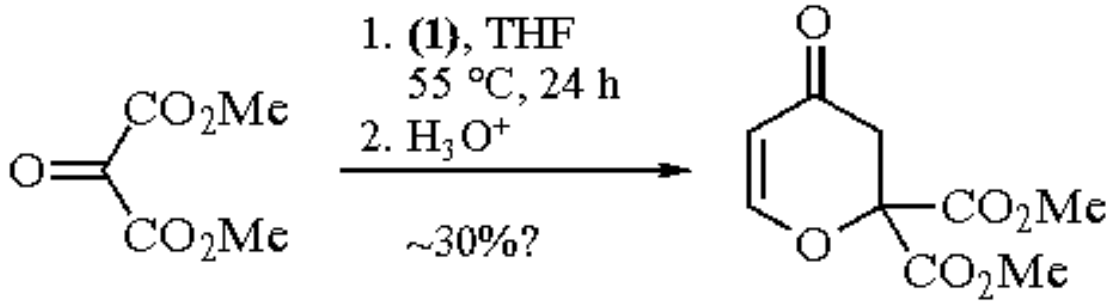

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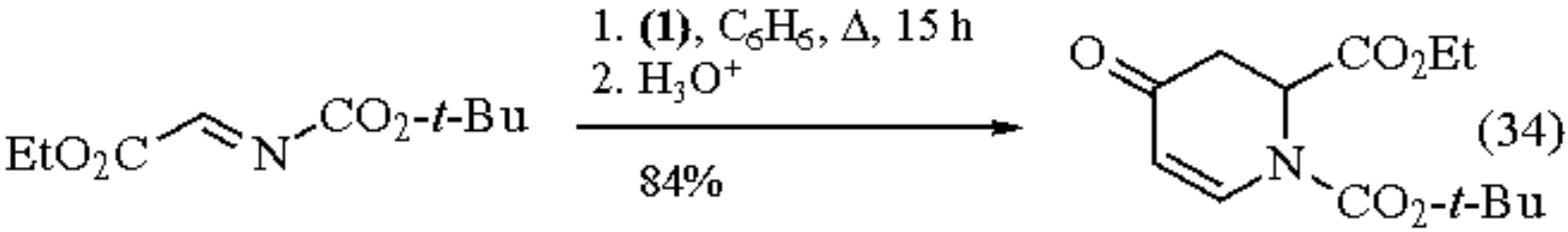

(34)

A major generalization of this heterocycle synthesis has been achieved by the reaction of hetero-alkenes with the diene in the presence of Lewis acid catalysts. In these cases, even hetero-alkenes without activating groups can react under mild conditions to give the corresponding heterocycles (eqs 35 and 36).[58,59]

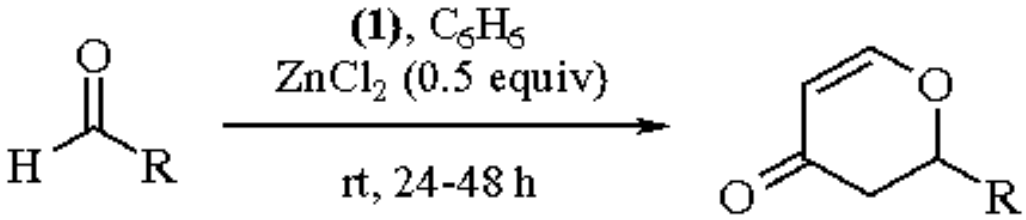

(35)

R	Yield (%)
$PhCH_2OCH_2$	87
Ph	65
Et	48
$CbzNHCH_2$	80

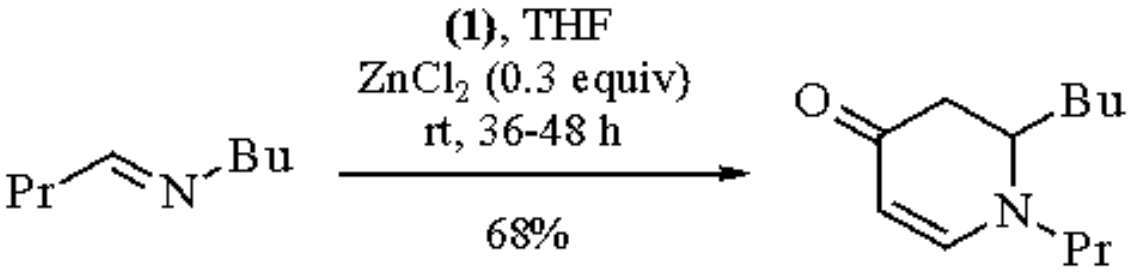

(36)

The most common catalyst is ***Zinc Chloride***, but $ZnBr_2$, $MgCl_2$, $MgBr_2$, BF_3 etherate, $TiCl_4$, and alkylaluminum chlorides are also useful. In some cases, even the lanthanide reagent $Eu(fod)_3$ can catalyze the cycloaddition to give

cyclic acetals,[60] and partial asymmetric induction is observed using $Eu(hfc)_3$ as a catalyst (eq 37).[61]

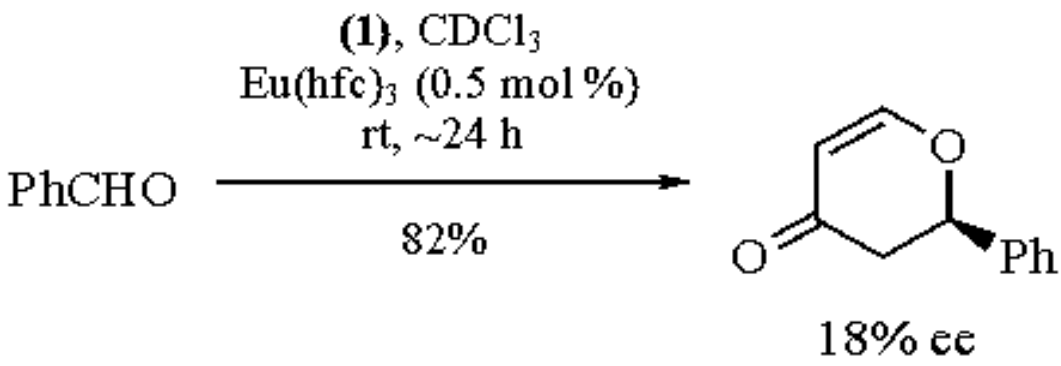

(37)

A mechanistic survey has revealed that this hetero-Diels-Alder reaction proceeds mainly via a pericyclic pathway with *endo* addition, but an aldol-type stepwise process is also followed and the ratio varies with the Lewis acid used.[62]

Oxygen Heterocycles.

Hetero-Diels-Alder reactions of chiral aldehydes give substituted dihydropyrones with high diastereoselectivity and Cram products are formed exclusively or predominantly. In the case of α-alkoxy or α-amino aldehydes, excellent selectivities are achieved (eqs 38-40).[63,64] The diastereoselectivity of the reaction with a protected serine-aldehyde is influenced by the amount of Lewis acid employed (eq 41).[65] Because of this high stereoselectivity and since the resulting multifunctionalized pyrone derivatives can be converted to various oxygen heterocycles, a number of natural products, especially carbohydrates and analogs, have been synthesized by this method. The following are representative examples: spiroacetals (*Mus musculus* pheromone[64a] and avermectins[66]); hexoses (fucose and daunosamine[67]); unusual sugars (tunicaminyluracil,[68] octosyl acid A,[69] and galantinic acid[70]); *C*-glycosides (papulacandins[71]).

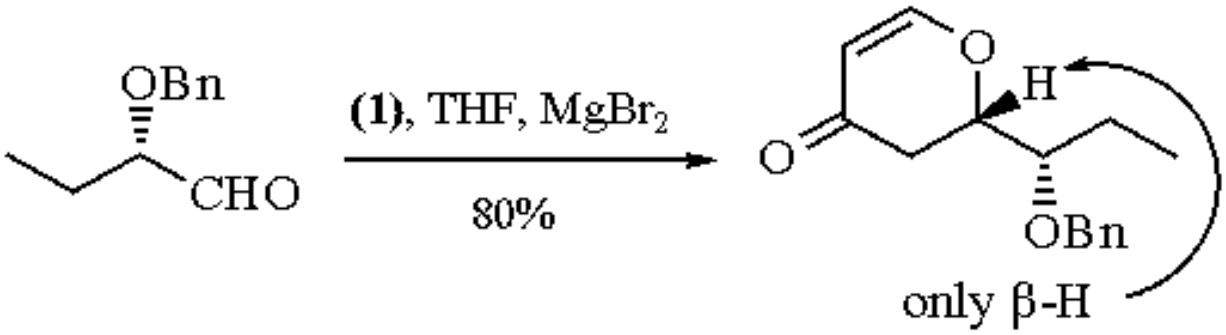

(38)

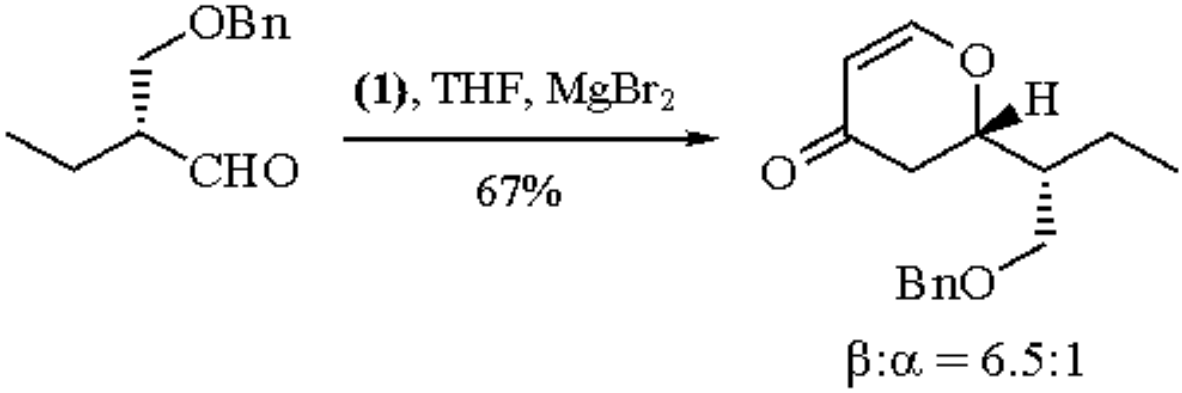

(39)

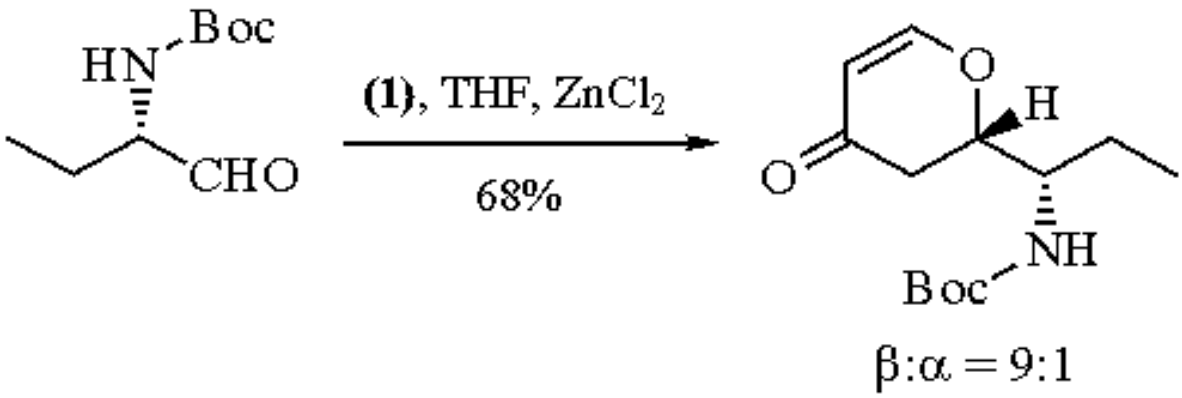

(40)

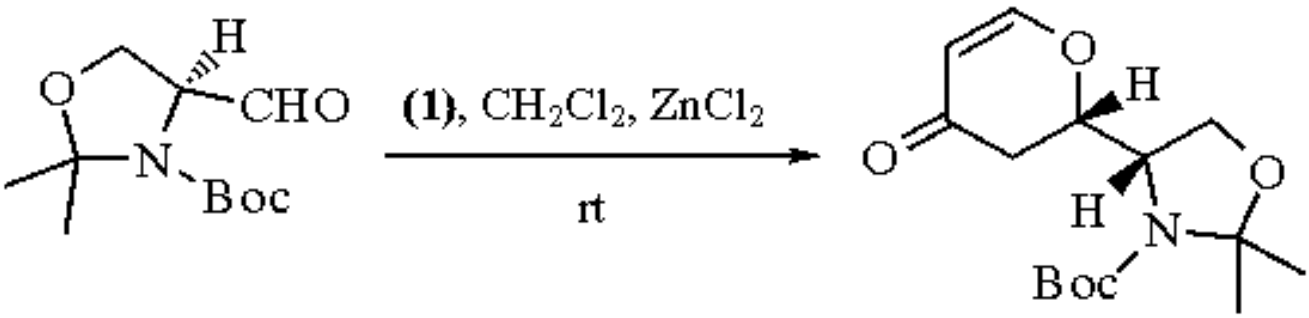

(41)

Amount of catalyst	Ratio (β:α)	Yield (%)
2 mol %	1:1.3	94
7	18:1	89
70	60:1	57
5 (in THF)		0

Even remote chiral centers afford rather high diastereoselectivity, giving the desired isomers as major products; these are convertible to mevinolin and pravastatin (eq 42).[72]

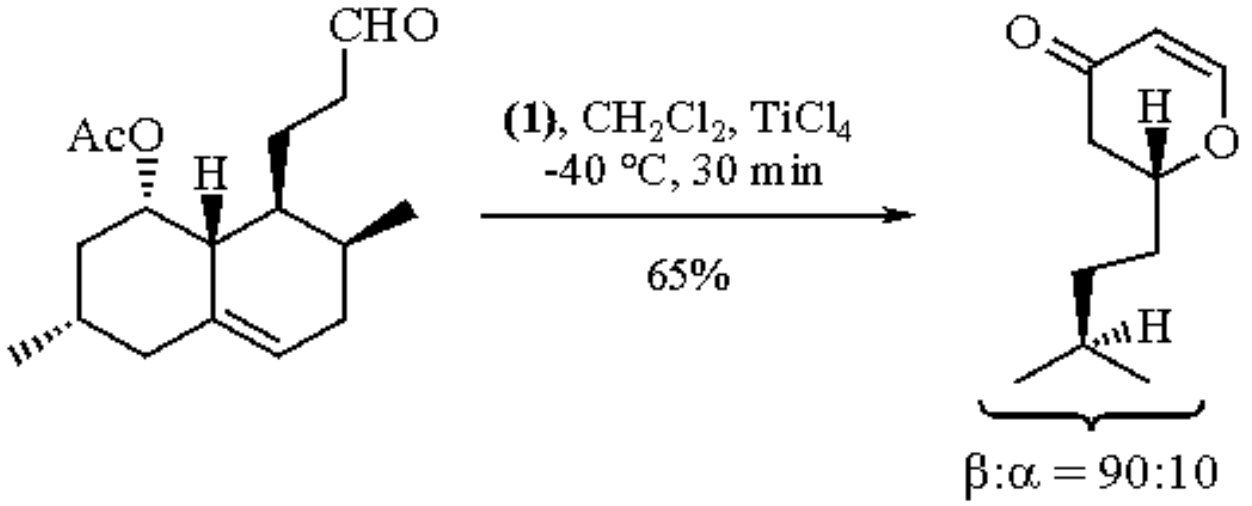

(42)

Nitrogen and Sulfur Heterocycles.

As mentioned earlier, dihydropyridones and arylquinolizinones are readily prepared (eq 43).[73] Reaction with triazolediones without a catalyst gives pyridazine derivatives.[74] The diene reacts with in situ formed thioaldehydes without a catalyst to give thiopyranones (eq 44).[75]

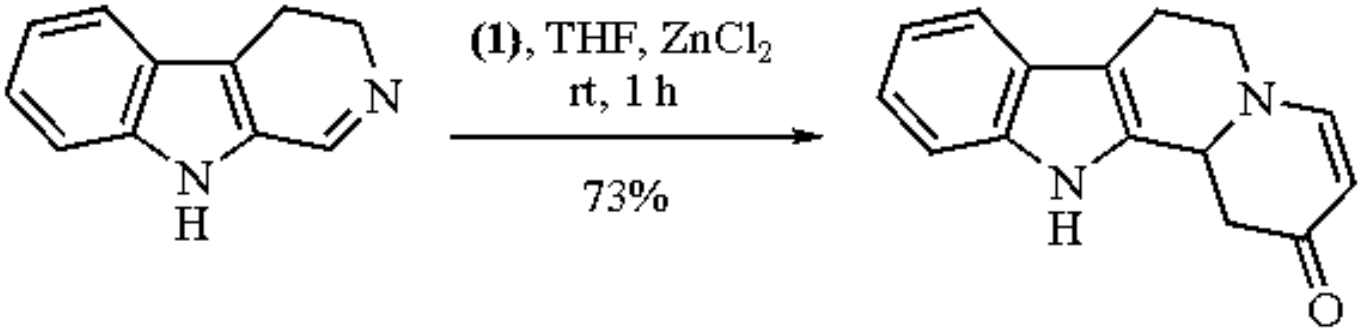

(43)

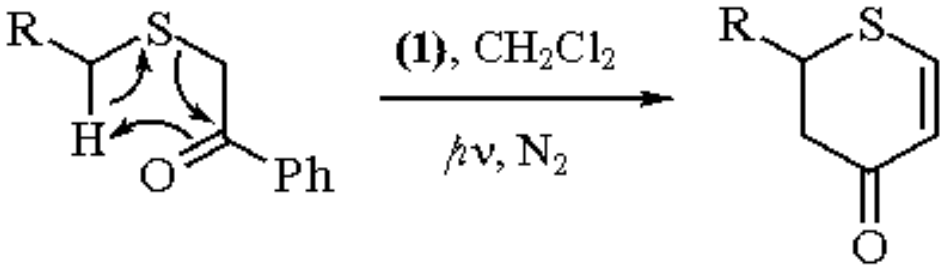

(44)

R = $PhCH_2CH_2$	84%
R = $PhSeCH_2CH_2$	73%
R = Ph	74%

Miscellaneous.

Extremely polar hetero-alkenes react smoothly with the diene to give heterocycles. For example, reaction with

nitrosobenzene at 0 °C gives substituted oxazinones (eq 45).[76] Phosphabenzenes are prepared by the reaction with chlorophosphorus ylides formed in situ (eq 46).[77] Arsabenzene is formed using the arsine ylide.[78] Reaction with singlet oxygen yields cyclic peroxides.[79]

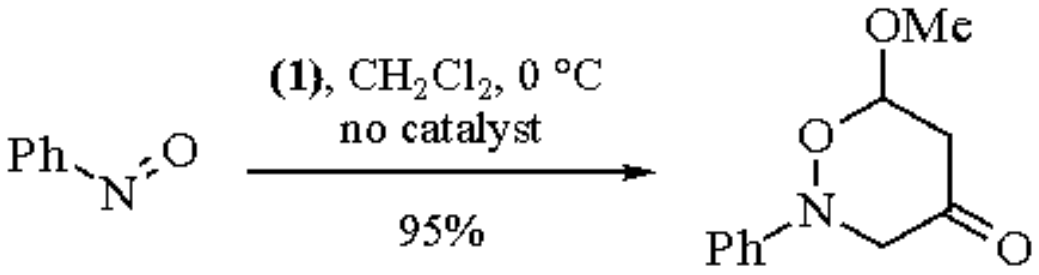

(45)

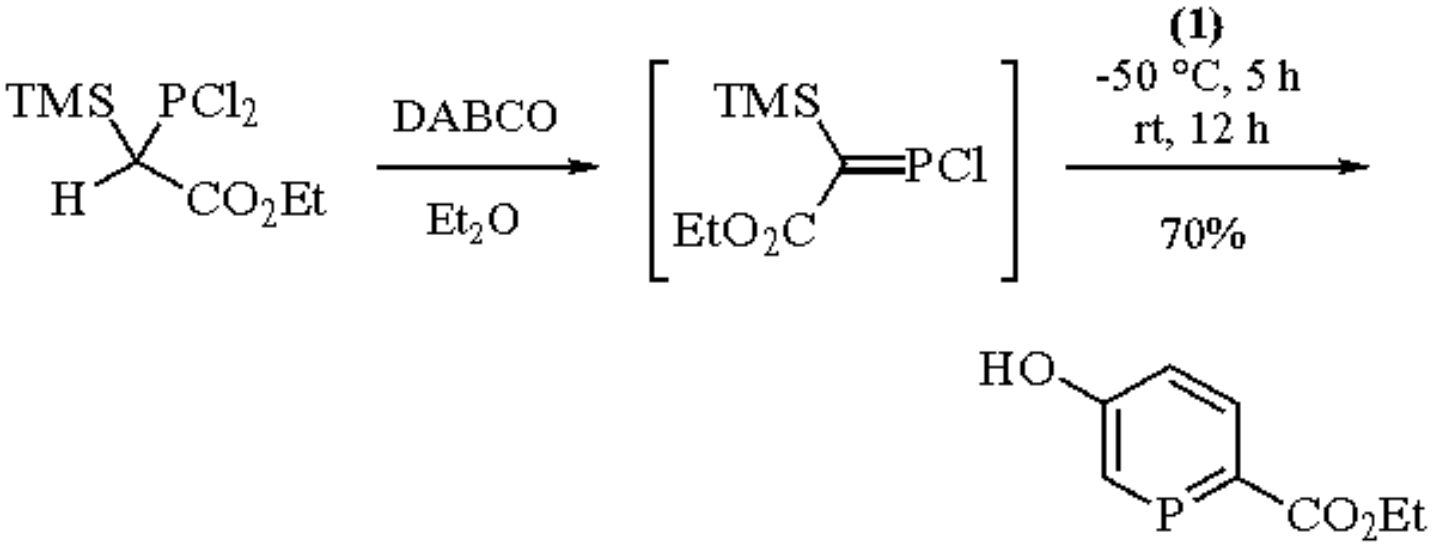

(46)

Asymmetric Synthesis.

Asymmetric Diels-Alder reactions with dienophiles containing a chiral auxiliary usually give adducts with high diastereoselectivity. For example, reaction with a nitro alkene having a chiral sulfoxide gives the hydrindenone with 95% ee after elimination of the sulfoxide.[80] In the case of 5-(-)-menthyloxy-5*H*-furanone, the reaction gives two diastereomers via both *endo* and *exo* attack, but diastereofacial selectivity is exclusive (eq 47).[81] Reaction with *O*-β-D-glucosyljuglone gives a single adduct (eq 48); this is a versatile precursor for optically active anthracyclinones.[82]

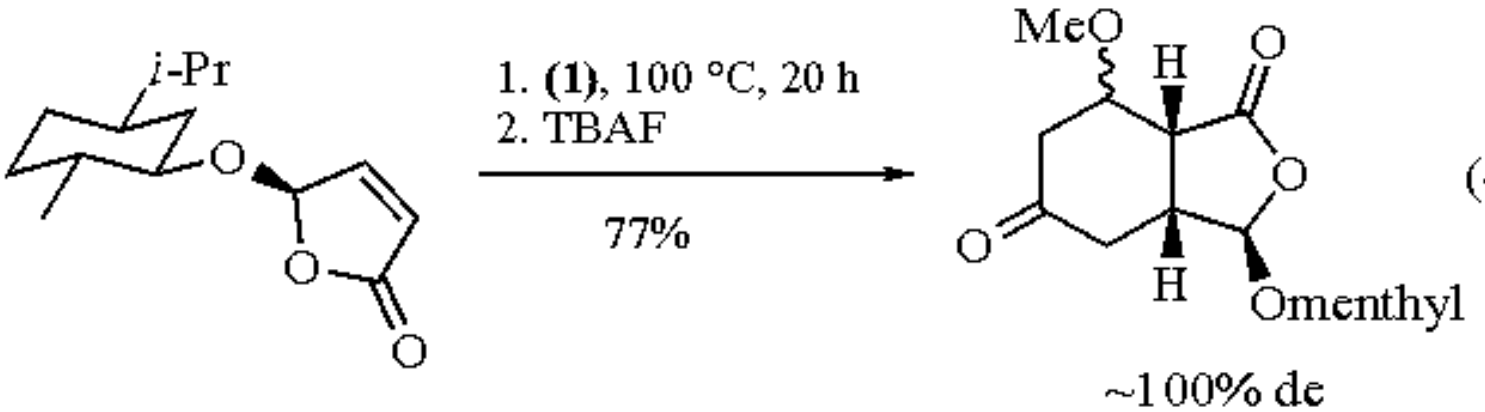

(47)

1-Methoxy-3-trimethylsilyloxy-1,3-butadiene

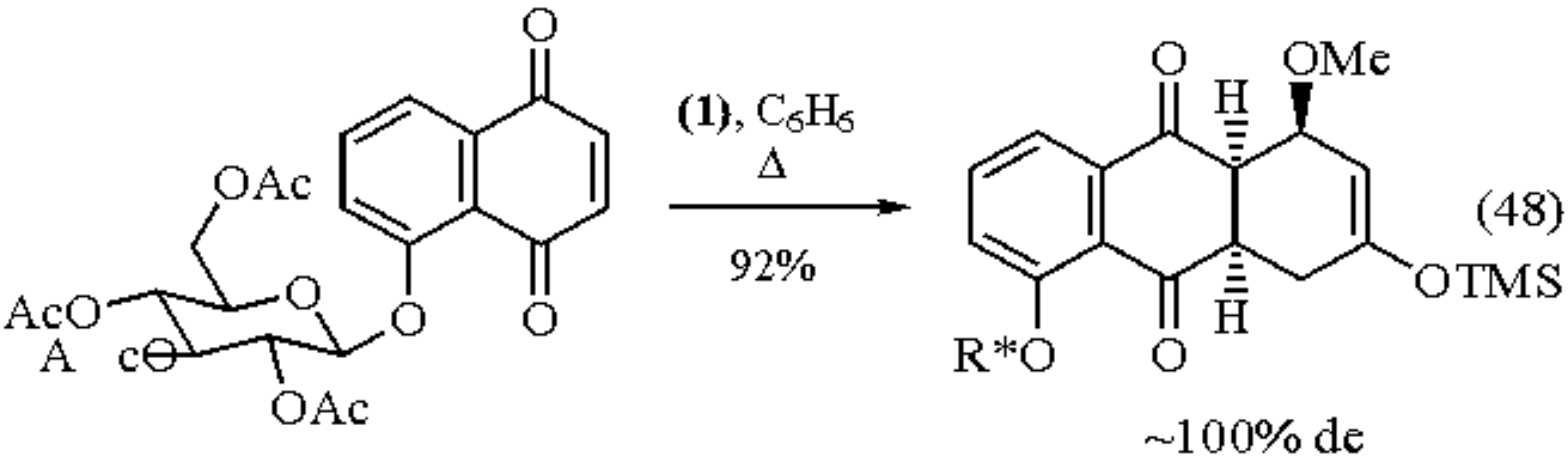

(48)

In the hetero-Diels-Alder reaction, the imine derived from D-galactosylamine gives the (*S*)-adduct preferentially, from which (*S*)-anabasin is obtained.[83] Imines of optically active amino acids give substituted pyridones with high diastereoselectivity (eq 49).[84]

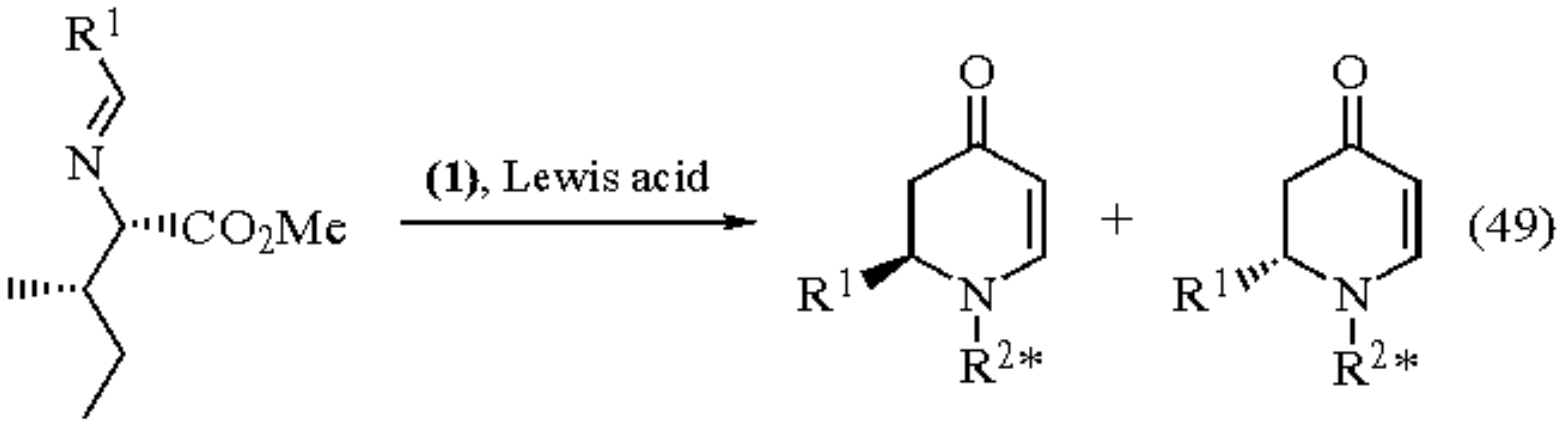

(49)

R^1	LA, Sol	Temp (°C)	Ratio	Yield
Pr	$ZnCl_2$, THF	0	15:85	11%
i-Pr	Et_2AlCl, CH_2Cl_2	-78 to -20	97: 3	45%
i-Pr	$MeAlCl_2$, CH_2Cl_2	-78 to -20	93: 7	50%
$EtOCO(CH_2)_2$	Et_2AlCl, CH_2Cl_2	-78 to -20	93: 7	50%

Catalytic asymmetric hetero-Diels-Alder reactions using chiral acyloxyboranes[85] or oxazaborolidines[86] give substituted hydropyranones and hydropyridones with ca. 70-95% ee (eqs 50 and 51).

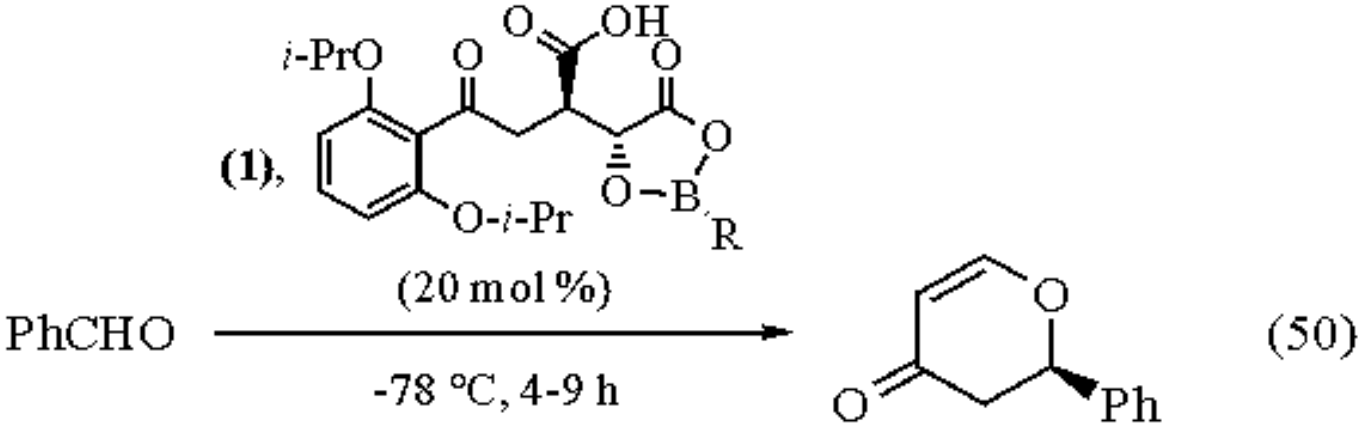

R	ee	Yield
o-$MeOC_6H_4$	79%	80%
1,3,5-$Me_3C_6H_2$	95%	47%

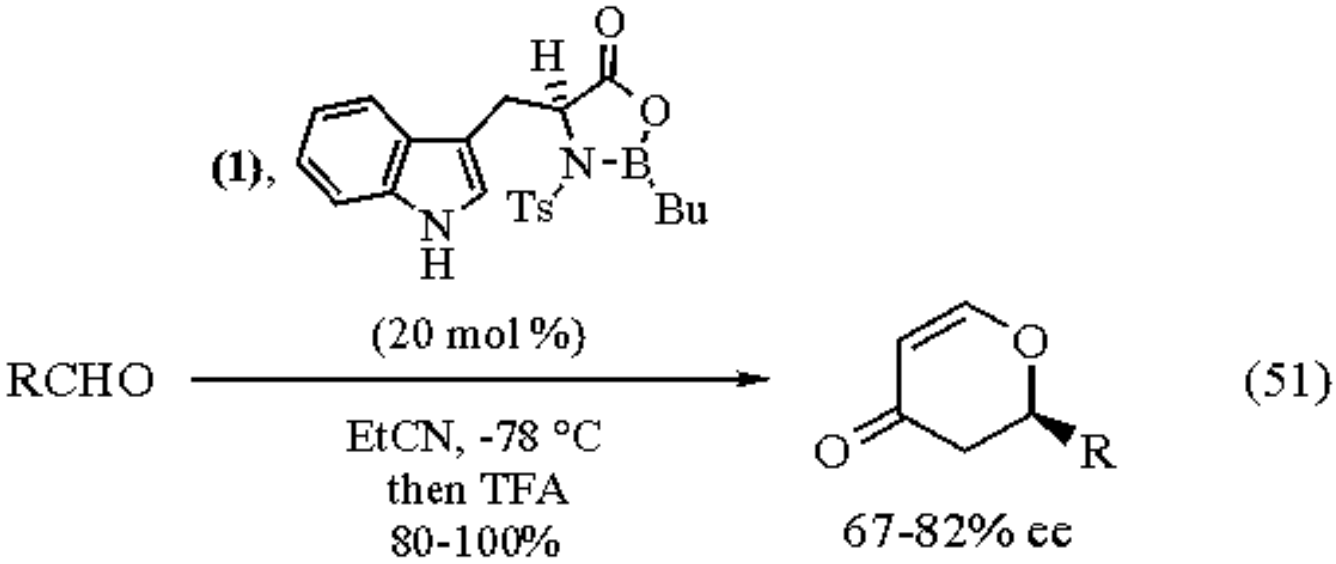

Related Reagents.

1-Acetoxy-1,3-butadiene; ***2-Methoxy-1-phenylthio-1,3-butadiene***; ***1-Trimethylsilyloxy-1,3-butadiene***; ***2-Trimethylsilyloxy-1,3-butadiene***.

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1-Methoxy-1-(trimethylsilyloxy)propene[1]

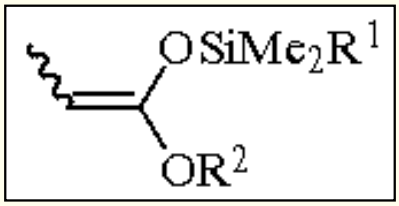

(**1**; R^1 = Me, R^2 = Me)

[34880-70-1] · $C_7H_{16}O_2Si$ · 1-Methoxy-1-(trimethylsilyloxy)propene · (MW 160.32) (*E*)-(**1**)

[72658-09-4] (*Z*)-(**1**)

[72658-03-8] (**2**; R^1 = *t*-Bu, R^2 = Et)

[83165-77-9] · $C_{11}H_{24}O_2Si$ · 1-Ethoxy-1-(*t*-butyldimethylsilyloxy)propene · (MW 216.44) (*E*)-(**2**)

[89043-55-0] (*Z*)-(**2**)

[73967-98-3]

(reactive nucleophile in Mukaiyama-type aldol reactions[2,3] with aldehydes,[15-29] imines,[30] acetals,[36] dialkoxycarbenium ions,[40] and orthoesters;[41] Michael-type additions to α,β-unsaturated carbonyl compounds;[42-46] substitution reactions with allylic alcohols and esters;[56] acylations;[53] aminations;[54] hydroxylations;[55] and pericyclic reactions;[59] silylating agent[67])

Alternate Name: methylketene methyl trimethylsilyl acetal.

Physical Data: (*Z*)-(**1**): bp 57 °C/18 mmHg; ^{1}H NMR data have been reported.[11] (*Z*)- and (*E*)-(**2**): ^{1}H and ^{13}C NMR data have been reported.[8b]

Solubility: highly sol organic solvents.

Preparative Methods: since the first preparation of a ketene trialkylsilyl acetal by Petrov in 1959 by the reaction of triethylsilane and methyl acrylate,[4] several alternative pathways have been explored.[5] Ainsworth and co-workers prepared 1-methoxy-1-(trimethylsilyloxy)propene in 90% yield by deprotonation of methyl propionate with ***Lithium Diisopropylamide*** at -78 °C followed by addition of ***Chlorotrimethylsilane***.[6] Reaction of the lithium enolate of methyl acetate with TMS-Cl provides 65% *O*-silylated and 35% *C*-silylated products (eq 1).[7] Substitution on the alcohol portion of the ester favors *C*-silylation while substitution on the α-carbon favors *O*-silylation. An increase in the steric bulk of the silylating agent (e.g. use of ***t-Butyldimethylchlorosilane***) results in significantly more *O*-silylation.

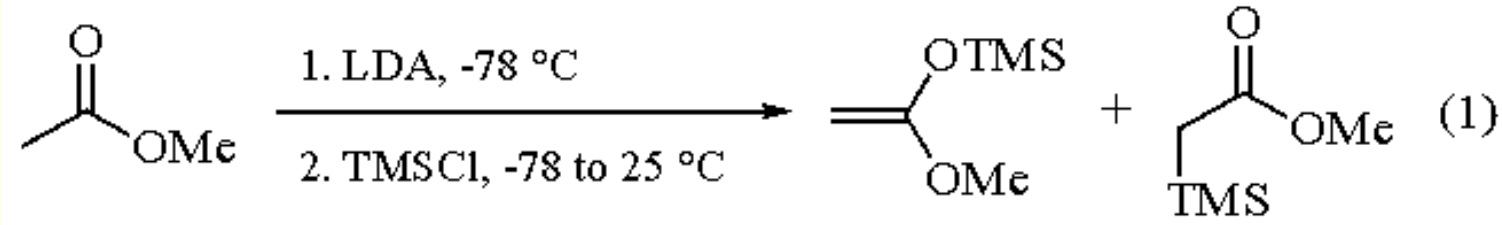

Silyl ketene acetal geometry is controlled by the selective formation of the (*E*)- and (*Z*)-ester enolate. Deprotonation of methyl propionate with LDA in THF at -78 °C gives, upon silylation, a 6:94 ratio of the thermodynamic (*Z*) and kinetic (*E*) silyl ketene acetals (eq 2).[8] As noted by Ireland and co-workers, a change in the reaction solvent results in a reversal in selectivity. In a THF-23% HMPA mixture, the silyl ketene acetals are isolated in a 84:16 ratio. In THF-45% DMPU ratios of up to 98:2 are obtained. With bulkier amide bases and in the absence of dipolar additives, a (*Z*):(*E*) ratio of 5:95 is observed.[9,10]

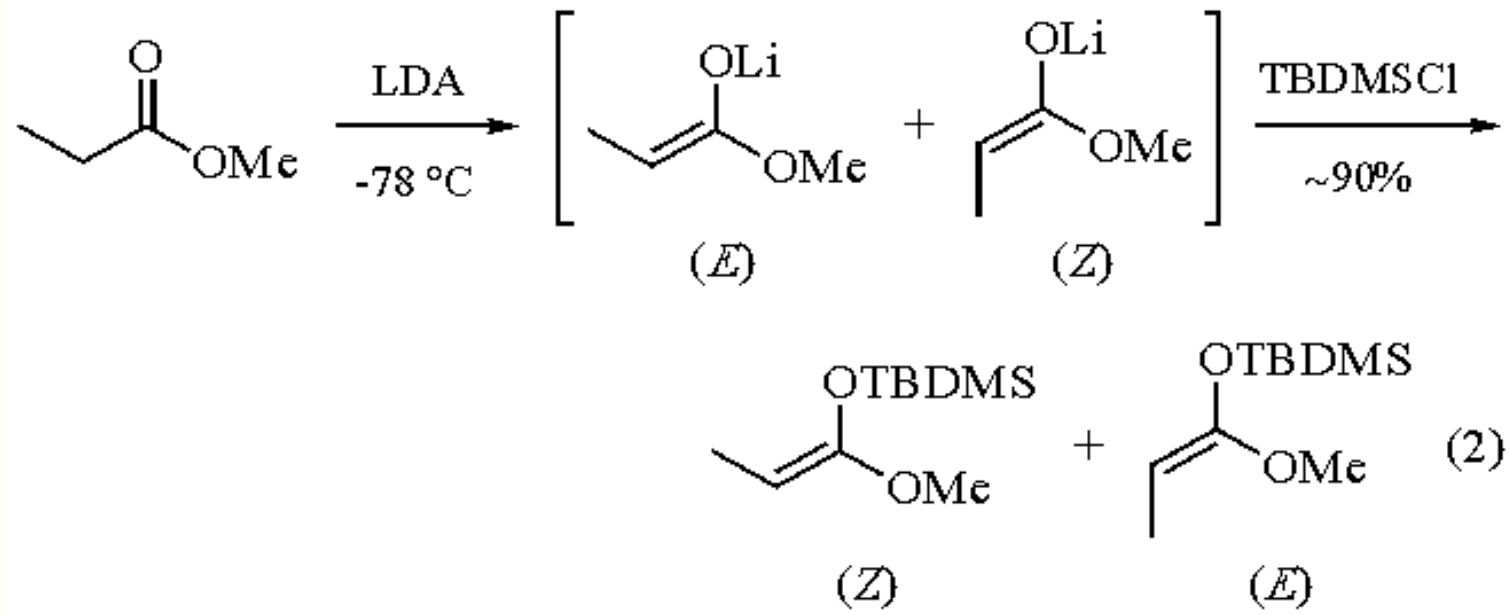

THF	(*Z*):(*E*) = 6:94
THF, 23% HMPA	(*Z*):(*E*) = 84:16
THF, 45% DMPU	(*Z*):(*E*) = >95: 5

Treatment of alkyl carboxylates with trialkylsilyl triflates in the presence of ***Triethylamine*** yields the thermodynamically more stable (*Z*)-ketene acetals at rt; however, a mixture of *O*- and *C*-silylated products is generally obtained.[11] The (*Z*)-isomers are also prepared by the reaction of triethylsilyl perchlorates with aliphatic esters.[12] The action of zinc powder on α-bromo esters in the presence of TMS-Cl and TMEDA-Et_3N leads mainly to (*E*)-ketene acetals, while the reaction of trialkylsilanes on alkyl acrylates catalyzed by Wilkinson's reagent (***Chlorotris(triphenylphosphine)rhodium(I)***) gives the corresponding (*Z*)-isomers (*Z*:*E* >98:2).[13]

Handling, Storage, and Precautions: easily hydrolyzed and oxidized by exposure to air. Storage is possible in sealed tubes at rt. Use in a fume hood.

Alkylation.

The α-*t*-alkylation of silyl ketene acetals was reported by Reetz and Schwellnus.[14]

Additions to Aldehydes, Imines, and Oximes.

Silyl ketene acetals add to aldehydes[2,3,19] in the presence of a Lewis acid ($TiCl_4$, BF_3, $SnCl_4$, $TrClO_4$, cationic iron complexes,[15] HgI_2,[16] lanthanides,[17] and clay montmorillonite).[18] High diastereofacial selectivity in Lewis acid-mediated additions of methylketene acetals to aldehydes was reported by Heathcock and Flippin.[20 -24] The scope of this reaction was further extended by the introduction of camphor and *N*-methylephedrine derived chiral silyl ketene acetals.[25-28] The asymmetric variant of the Mukaiyama reaction also provides an efficient *anti*-selective chiral propionate equivalent (eqs 3 and 4). Reetz and Fox used a catalytic amount of ***Lithium Perchlorate*** suspended in CH_2Cl_2 for Mukaiyama aldol reactions of aldehydes with a silyl ketene acetal.[29]

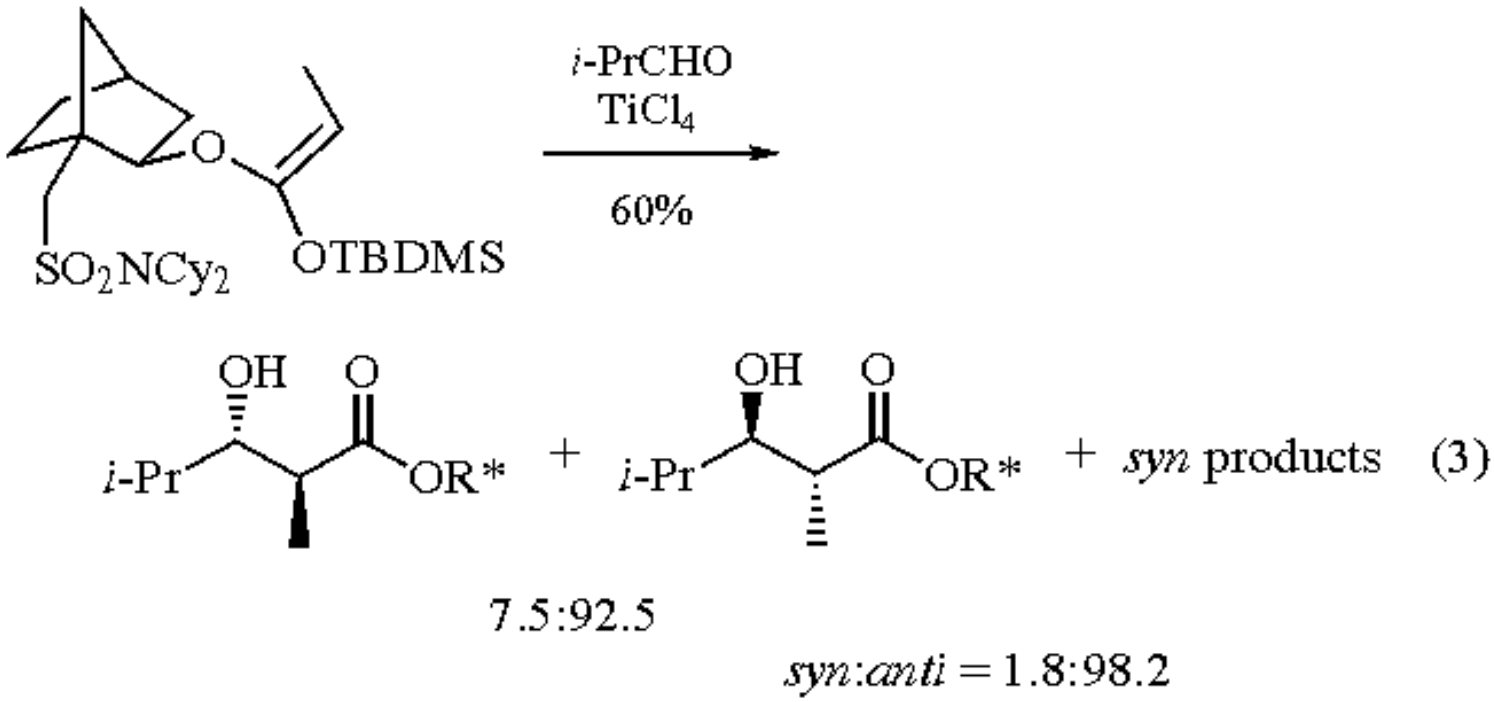

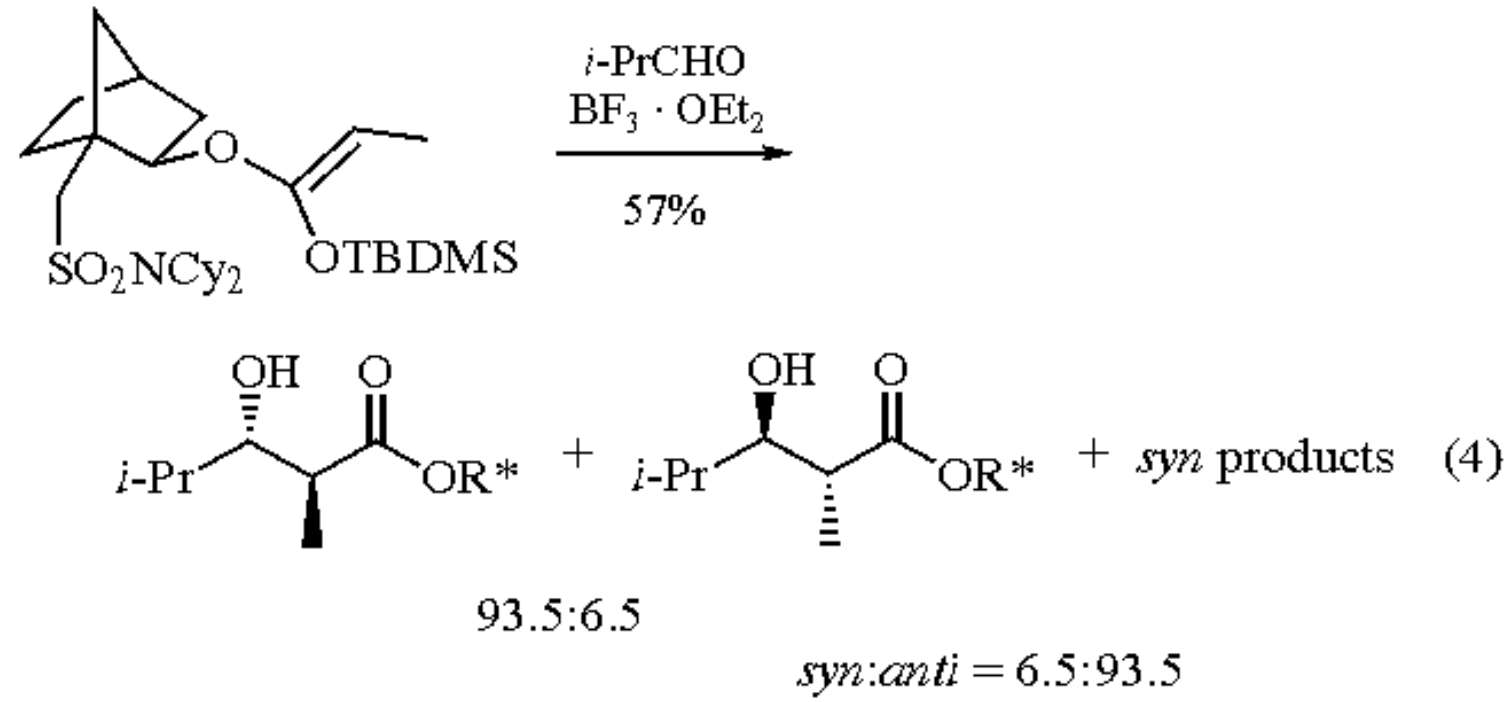

High diastereoselectivities have been achieved in the Lewis acid-mediated addition of silyl ketene acetals to imines (eq 5).[30,31] In related applications, additions of *O*-silylated ketene acetals to β-lactams were used in the synthesis of carbapenem antibiotics.[32-34] Sekiya and co-workers have demonstrated that silyl ketene acetals add to *O*-benzyl oxime ethers in the presence of catalytic amounts of ***Trimethylsilyl Trifluoromethanesulfonate*** to afford β-benzyloxy amino esters.[35]

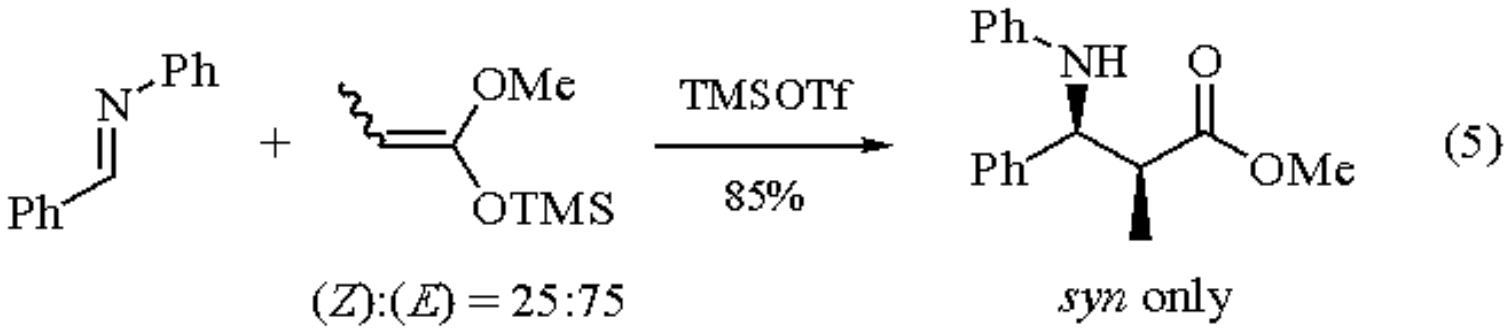

Additions to Acetals, Dialkoxycarbenium Ions, and Orthoesters.

Much attention has focused on the use of methylketene derivatives for the opening of chiral acetals.[36] Trimethylsilyl triflate-catalyzed addition of (*E*)-methylketene methyl trimethylsilyl acetal to benzaldehyde dimethyl acetal gives *syn*- and *anti*-esters in a 50:50 ratio, whereas the (*Z*)-silyl ketene acetal results in a 55:45 ratio (eq 6).[37]

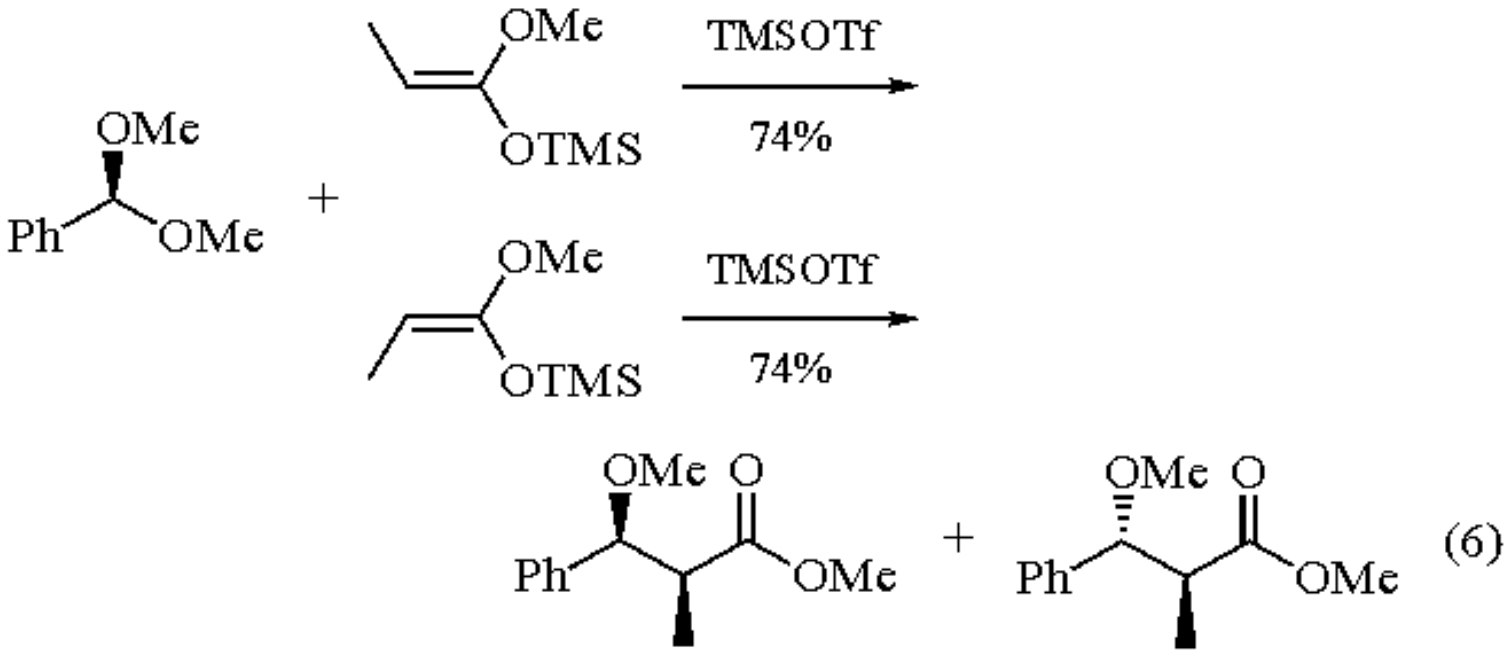

syn:*anti* = 50:50

syn:*anti* = 55:45

A chain-extended trimethylsilyl ketene acetal was used by Johnson et al. in combination with ***Titanium(IV) Chloride*** for a stereoselective acetal opening in the preparation of enantiomerically pure mevinolin analogs (eq 7).[38,39]

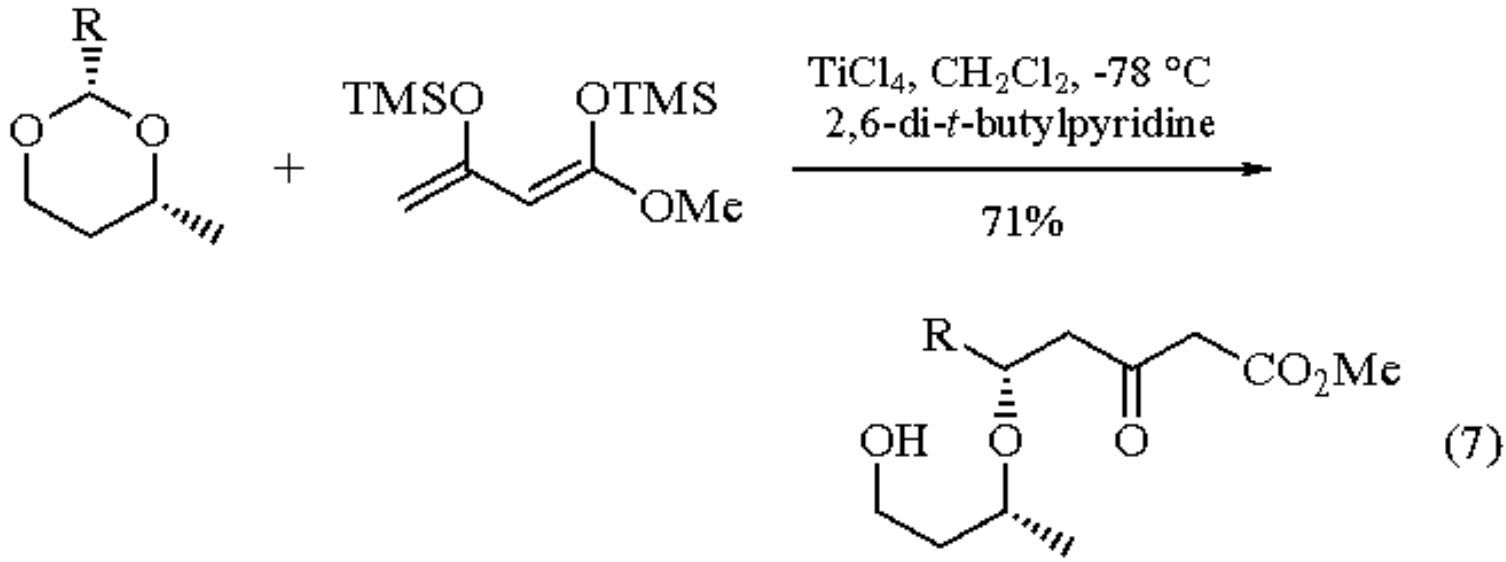

1,3-Dioxolan-2-ylium cations react with silyl ketene acetals to give β-keto esters, selectively monoprotected at the ketone carbonyl (eq 8).[40]

1-Methoxy-1-(trimethylsilyloxy)propene

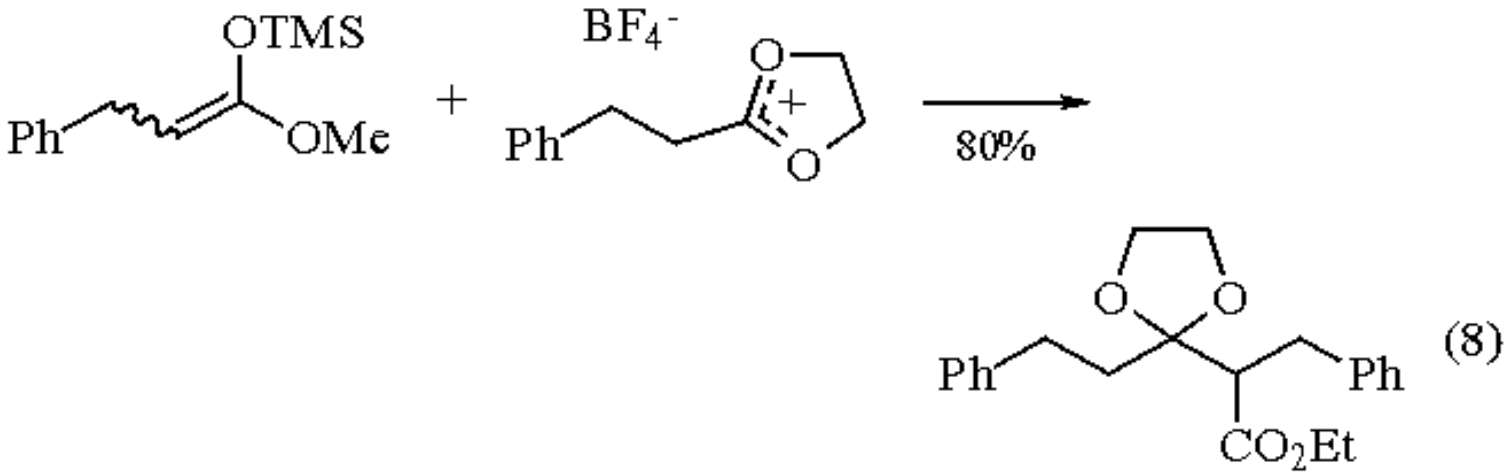

The reaction of an enolic orthoester with silyl ketene acetals results in the regiospecific formation of diketo ester monoacetals.[41]

Additions to α,β-Unsaturated Carbonyl Compounds.

The $TiCl_4$-catalyzed addition of silyl ketene acetals to α,β-unsaturated enones is often superior to enolate addition protocols, especially for the preparation of β-quarternary centers.[42,43] Danishefsky and co-workers reported an interesting tandem Michael-aldol sequence (eq 9).[44] Acetonitrile or high pressure are often sufficient to promote additions in the absence of a Lewis acid.[45,46] In a related process, aromatic heterocycles can be prepared by addition of silyl ketene acetals to nitrobenzenes.[47]

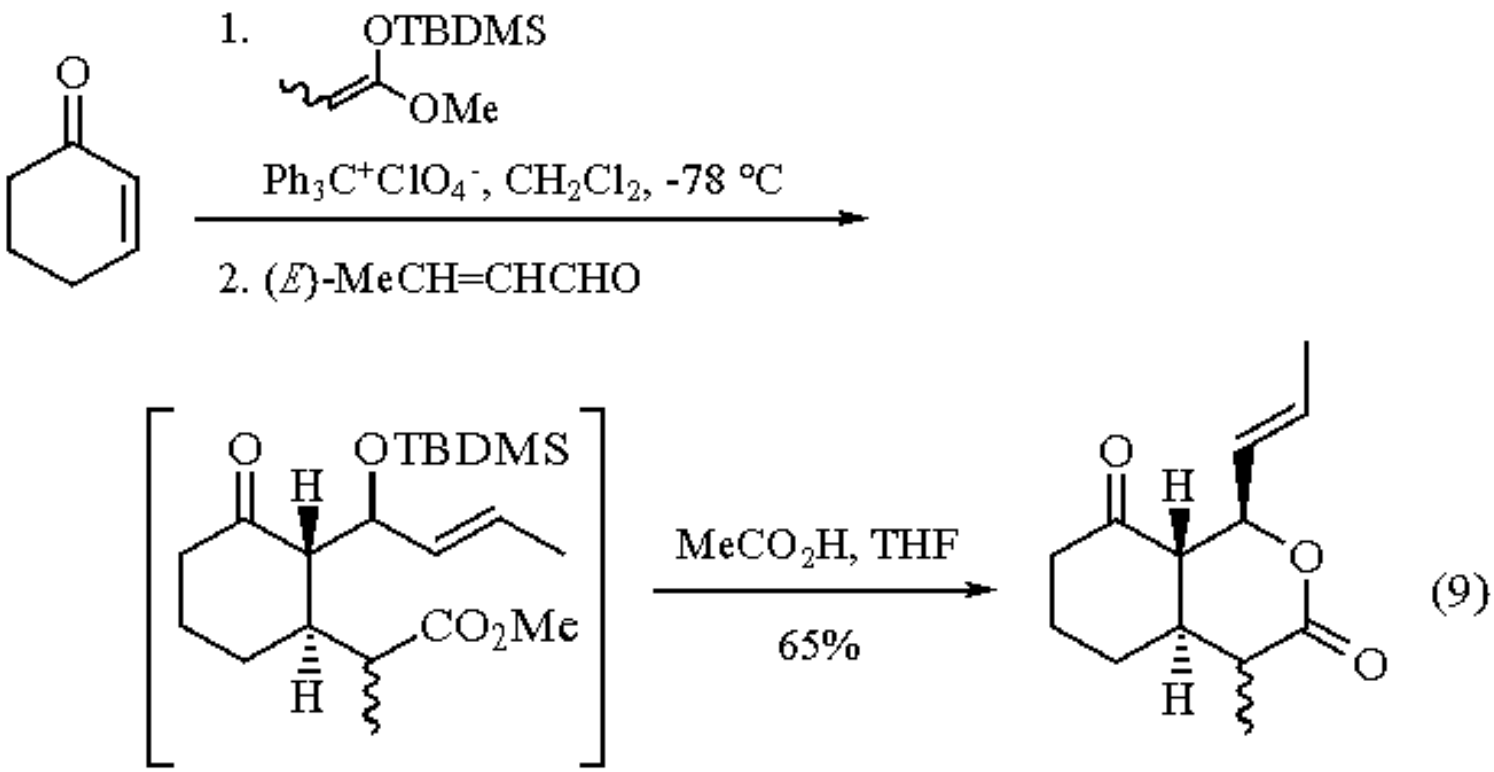

Alkylations with Allylic Alcohols and Esters.

Pearson and Schkeryantz[48] used a lithium perchlorate-promoted substitution of a tertiary alcohol with ketene silyl acetals for the preparation of a key intermediate in the synthesis of (±)-γ-lycorane.[49,50] Grieco and co-workers have also used cyclopropyl alcohols in substitution reactions of this type.[51] Pd^0-catalyzed coupling of allyl acetates and ketene silyl acetals leads to cyclopropane derivatives via alkylation of the central carbon (C-2) of the allyl group.[52]

Acylation, Amination, and Hydroxylation.

Acylation of silyl ketene acetals with acid chlorides occurs regioselectively and results in β-keto esters after acid hydrolysis.[53] α-Amino acid esters are prepared by amination of silyl ketene acetals with 3-acetoxyaminoquinazolin-4(3*H*)-ones followed by N-N bond cleavage.[54] Silyl ketene acetals may be epoxidized by peroxyacids and subsequently cleaved with fluoride ion to reveal the α-hydroxy esters.[55] Related sequences involve $^1O_2$,[56] and ***Lead(IV) Acetate***,[57] as well as camphor-derived auxiliaries.[58]

Claisen Rearrangements.

Silyl ketene acetals of allyl esters undergo rapid Claisen rearrangements,[8b,59] at or above rt to give γ,δ-unsaturated carboxylic acid derivatives (eq 10).[60]

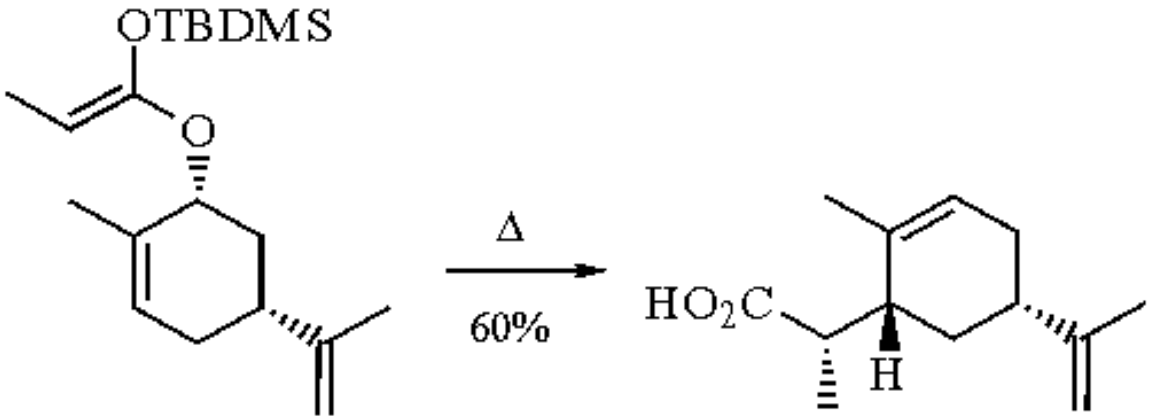

(10)

Reactions with Sulfur-Containing Electrophiles.

Paterson has developed an alkylation of geminal phenylthio chlorides with silyl enol ethers as a general method to prepare 1,5 dicarbonyl compounds (eq 11).[61] Alkylation of the silyl enol ether gives a homoallylic sulfide. Ozonolysis of the alkene with concomitant sulfur oxidation produces an unstable sulfoxide which is thermally extruded to give a mixture of alkene isomers.

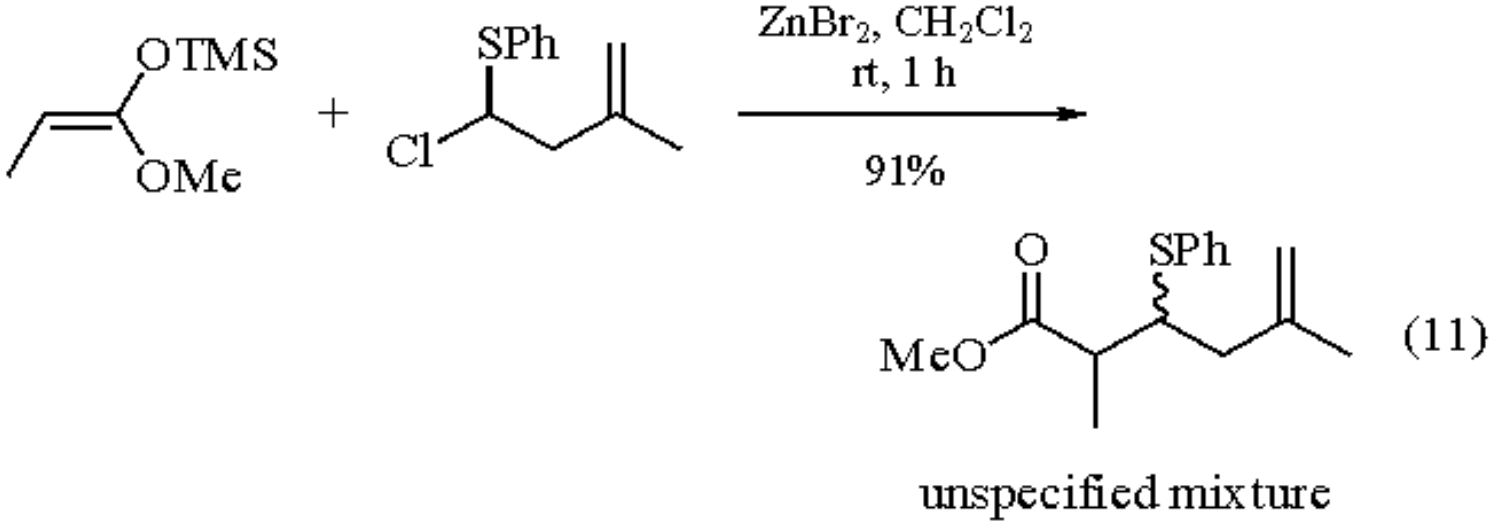

The ketene acetal has also been reported to react with dithianyl cations. Treatment of 1,3-dithian-2-ylium tetrafluoroborate with the silyl enol ether results in a β-dithio ester which can subsequently be hydrolyzed to a β-keto ester (eq 12).[62]

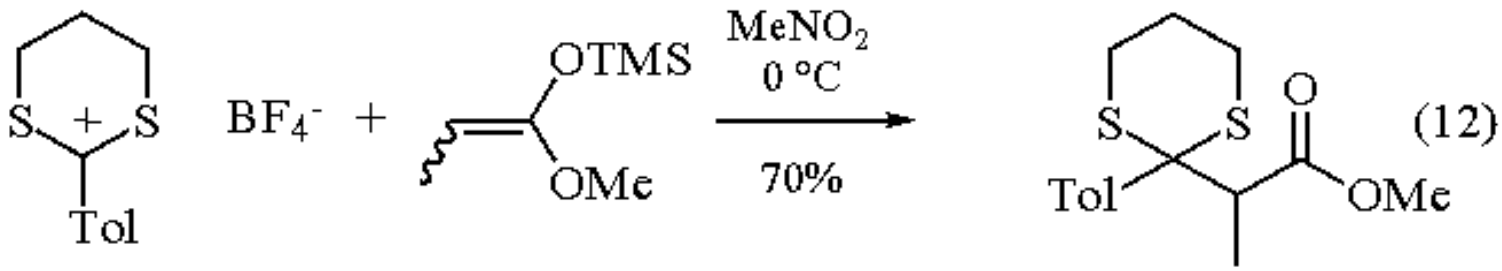

Cycloadditions and Photochemistry.

Silyl ketene acetals undergo inverse electron demand hetero-Diels-Alder reactions with enones.[63] Photochemically induced Diels-Alder and [2 + 2] cycloadditions of silyl ketene acetals with dienes have been reported by Schuster and co-workers.[64] Cyclopropanes with vicinal donor and acceptor ligands will heterolytically cleave to form zwitterionic intermediates. In the presence of the ketene silyl acetal, a [3 + 2] cycloaddition reaction can occur with the zwitterionic intermediate to form highly substituted cyclopentenones (eq 13).[65]

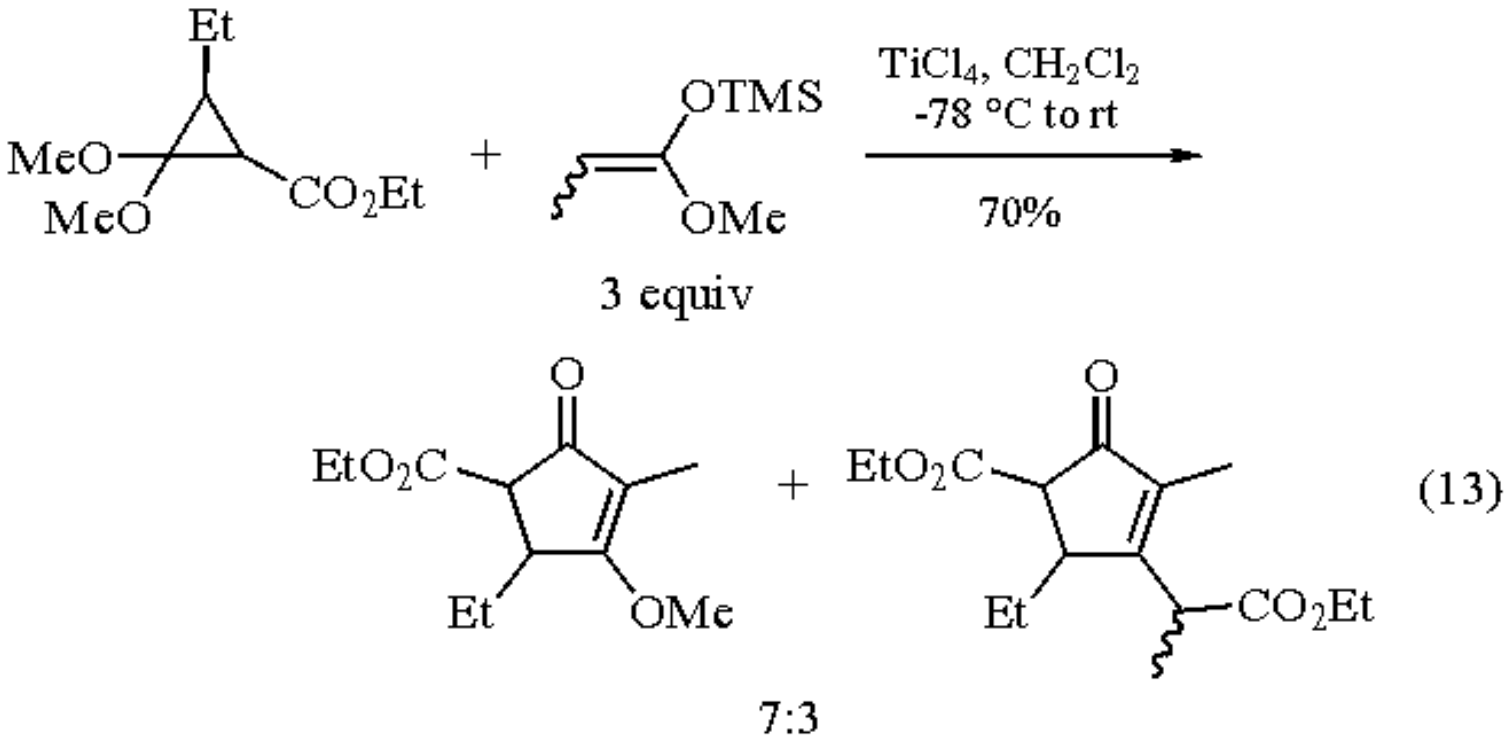

Reactions with Nitrenes.

N-Protected α-amino esters are produced by the reaction of (ethoxycarbonyl)nitrene with methylketene ethyl trimethylsilyl acetal.[66]

Use as a Silylating Agent.

1-Methoxy-1-(trimethylsilyloxy)propene has been used as a mild silylating agent for phenols, alcohols, carboxylic acids, thiols, and amides.[67]

Related Reagents.

Ketene Bis(trimethylsilyl) Acetal; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***Ketene Diethyl Acetal***; ***1-Methoxy-3-methyl-1-trimethylsilyloxy-1,3-butadiene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Methylketene Bis(trimethylsilyl) Acetal***; ***Methylketene Dimethyl Acetal***; ***Tris(trimethylsilyloxy)ethylene***.

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1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene[1]

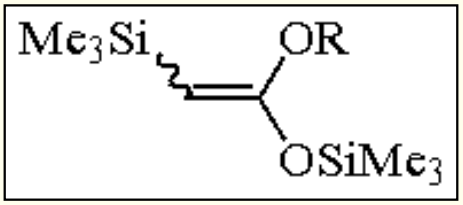

(**1**; R = Me)

[32583-40-7] · $C_9H_{22}O_2Si_2$ · 1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene · (MW 218.49) (*E*)-(**1**)

[35003-73-7] (*Z*)-(**1**)

[35003-74-8] (**2**; R = Et)

[65946-56-7] · $C_{10}H_{24}O_2Si_2$ · 1-Ethoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene · (MW 232.52)

(two-carbon nucleophile toward aldehydes[2] and α,β-unsaturated ketones[3] with the assistance of Lewis acids; in combination with $TiCl_4$, a reagent for (*Z*)-selective alkenation of aldehydes[2])

Alternate Name: *O*-methyl-*C*,*O*-bis(trimethylsilyl)ketene acetal.

Physical Data: (**1**) bp 40-41 °C/0.5 mmHg; *d* 0.852 g cm^{-3}. (*E*)-(**1**) bp 86-87 °C/45 mmHg. (*Z*)-(**1**) bp 80-81 °C/25 mmHg. (**2**) bp 55-60 °C/0.3 mmHg.

Solubility: sol most aprotic solvents; reacts readily with H_2O and protic solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: measurement of the ^1H NMR spectrum is the most reliable way to evaluate the purity and isomer ratio; ^1H NMR, δ (CCl_4, 60 MHz), (*E*): 0.00 ($CSiMe_3$), 0.27 ($OSiMe_3$), 3.00 (CH), 3.54 (OMe); (*Z*): 0.00 ($CSiMe_3$), 0.18 ($OSiMe_3$), 2.87 (CH), 3.55 (OMe). ^{13}C NMR, δ ($CDCl_3$, 25 MHz), (*E*): -0.30 (=$CSiMe_3$), 0.04 ($OSiMe_3$), 53.79 (OMe), 72.61 (=CH), 161.45 (=C); (*Z*): 0.04 (=$CSiMe_3$), 0.38 ($OSiMe_3$), 54.96 (OMe), 63.78 (=CH), 164.57 (=C).

Preparative Methods: to a THF solution (260 mL) of ***Lithium Diisopropylamide*** (LDA), generated from ***n-Butyllithium*** (0.218 mol) and ***Diisopropylamine*** (22.4 g, 0.222 mol), is added methyl (trimethylsilyl)acetate (23.0 g, 0.517 mol) at -78 °C. After being stirred for 3.5 h at -78 °C, the reaction mixture is quenched with an excess of ***Chlorotrimethylsilane*** (28.3 g, 0.260 mol) at the same temperature. The mixture is stirred for 1.5 h at rt and concentrated under reduced pressure. Distillation of the residual liquid yields 27.8 g (81%

E:*Z* &AApprox; 3:1) of the title reagent as a colorless liquid. The pure (*E*)-form is prepared by distillation of the mixture obtained immediately after quenching of the ester enolate anion formed by the use of ***Lithium Hexamethyldisilazide*** instead of LDA.[4] The pure (*Z*)-form is prepared by isomerization of the (*E*)-form in a CH_2Cl_2 solution containing an equimolar amount of ***Bromotrimethylsilane*** and a catalytic amount of $HgBr_2$.[5]

Handling, Storage, and Precautions: the pure liquid and solutions must be stored in the absence of moisture. The sample sealed in an ampule under Ar can be stored for more than a year without decomposition; however, gradual isomerization from the (*E*)-form to the (*Z*)-form is observed on the storage.

Two-Carbon Homologation.

This reagent, like most *O*-silyl-ketene acetals,[6-8] becomes a powerful nucleophile in the presence of ***Titanium(IV) Chloride***[2,3] or other types of accelerators. The trimethylsilyl group on the α-carbon atom plays an important role as a control factor in stereodifferentiation in aldol reactions. Essentially, *syn* selectivity is observed in the reaction with aldehydes (eq 1) despite small variations in the geometry of the starting ketene acetal. The nucelophilic species generated by the addition of $TiCl_4$ is also highly reactive as a Michael donor toward α,β-unsaturated ketones. The *C*-trimethylsilyl group remaining in the products is readily replaced by H after protodesilylation under mild conditions.[3,9] As a consequence, this reagent has remarkable advantages as an equivalent of the methyl trimethylsilylacetate anion or the dimethyl malonate anion in the reactions with aldehydes, ketones, and α,β-unsaturated ketones. It has been utilized for introducing the β-side chain in the synthesis of (±)-methyl jasmonate[3,10] (eq 2) and (±)-methyl dihydrojasmonate.[3]

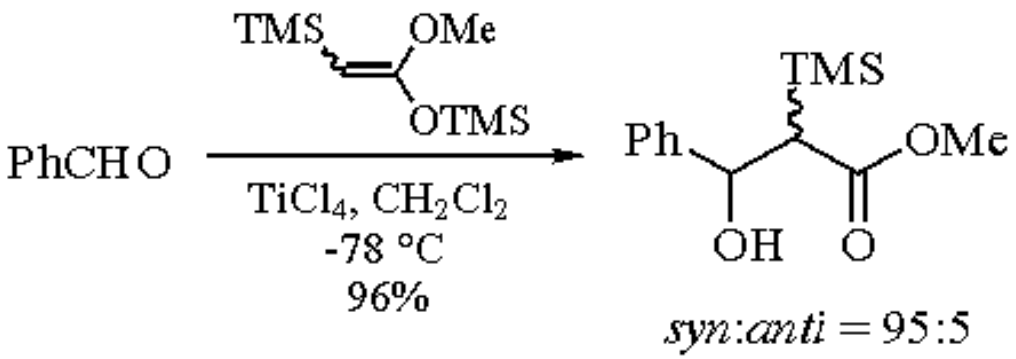

(1)

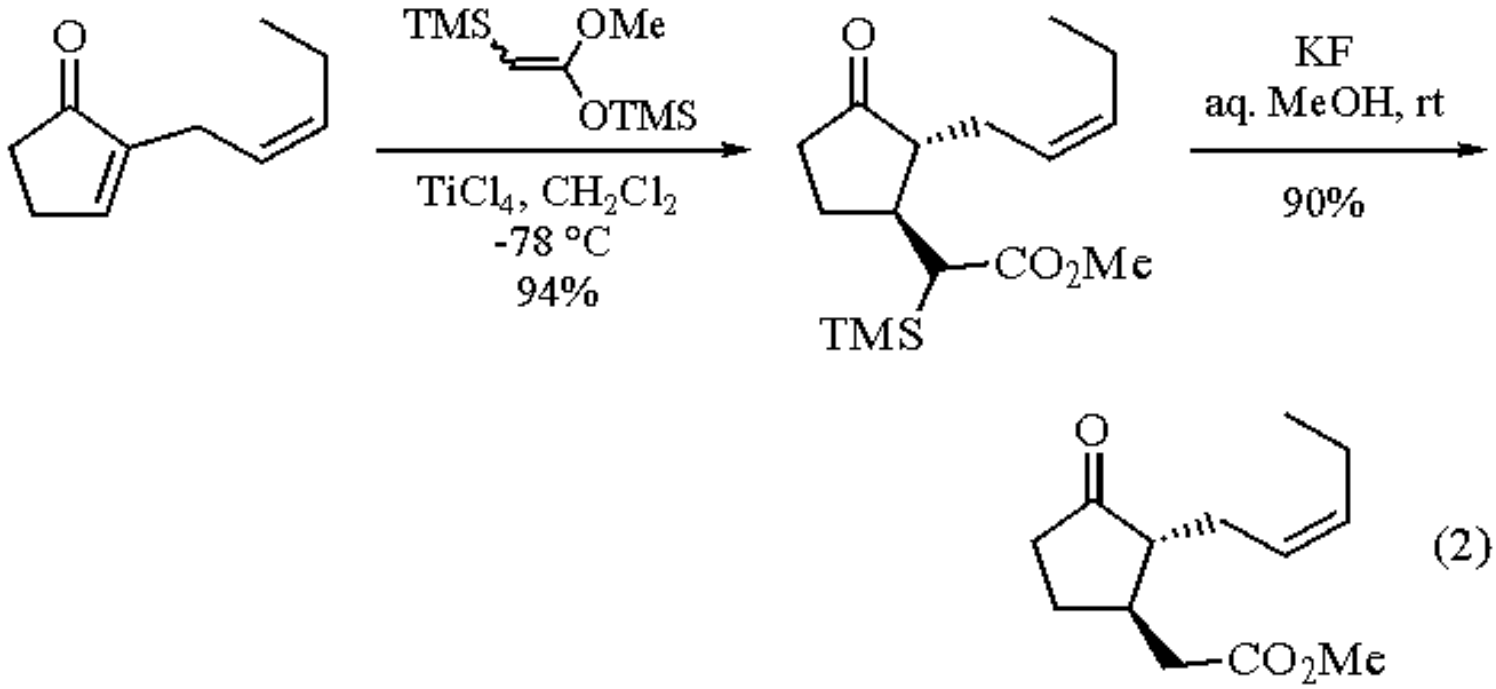

(2)

The resulting *C*-trimethylsilyl group in the Michael-type adducts is capable of participating in the Peterson-type alkenation.[11] For example, the *O*-ethyl analog of the title reagent has been used for the synthesis of α-methylene δ-lactones from α,β-unsaturated ketones (eq 3).[12] Intermolecular coupling has also been accomplished by the reaction of silyl ketene acetals with 1-adamantyl bromide,[13] $GeCl_4$,[14] PCl_3,[15] or $AsCl_3$.[16]

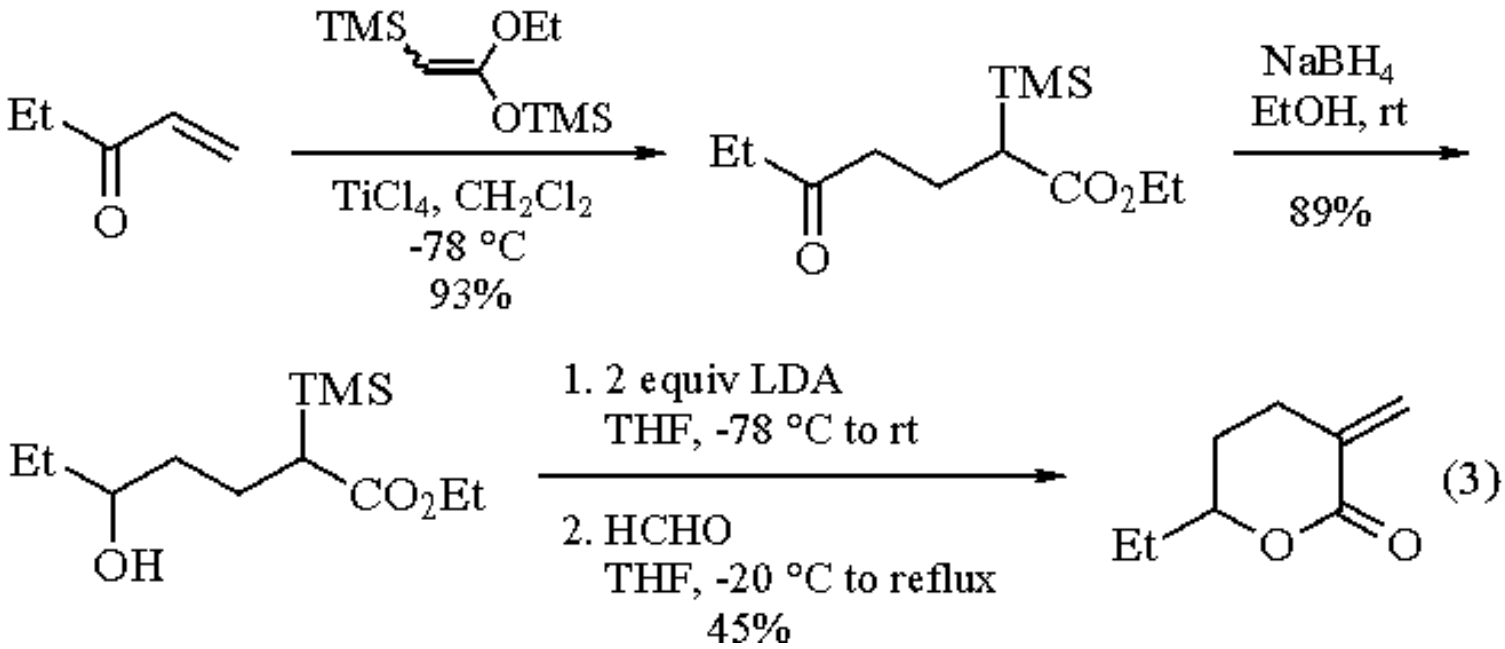

(3)

Carbonyl Alkenations.

The title ketene acetal is an efficient C_2 condensation unit toward aldehydes and gives methyl 2-alkenoates in a one-pot operation with the assistance of Lewis acids.[2] The high (*Z*) selectivity of the $TiCl_4$-induced reactions contrasts with the results of analogous condensations using the ethyl trimethylsilylacetate anion[11] or Wittig-Horner-type reagents.[17] That this transformation is the overall result of two steps, aldol-type addition and Peterson-type β-elimination, has been confirmed

by the isolation of aldol adducts under kinetic conditions. Reaction of the isolated *syn* isomer with $TiCl_4$ or $BF_3.Et_2O$ leads specifically to (*Z*)-methyl 2-alkenoates (eq 4). On the other hand, the *anti*-isomers give (*E*)-alkenes (eq 5). The predominant formation of (*Z*)-methyl 2-alkenoate is attained by the *syn*-selective aldol-type coupling under acidic conditions. High (*Z*) selectivity has been realized by use of (*Z*)-ketene acetals or modified Lewis acids (eq 6 and Table 1).[2,18]

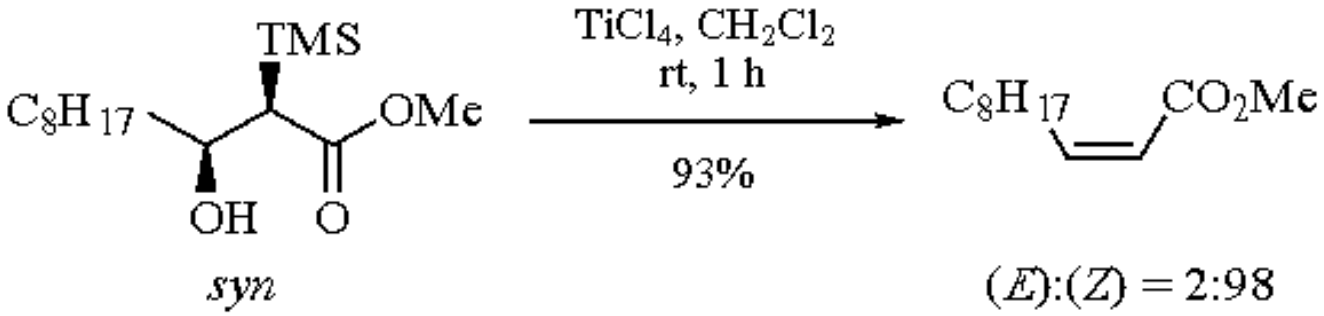

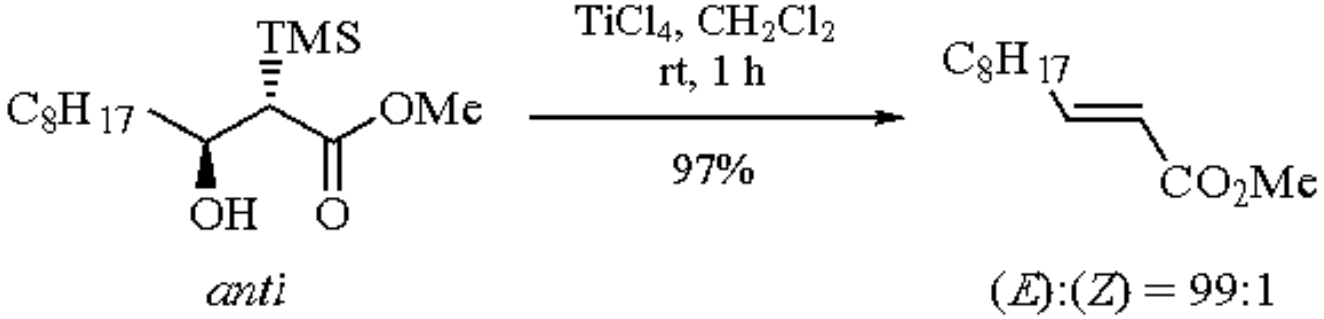

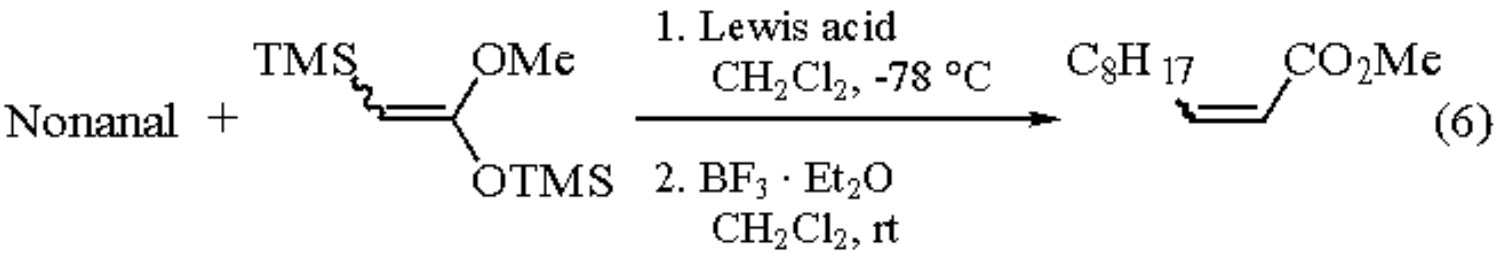

Table 1 Effect of the Geometry of Ketene Acetal and Lewis Acid in the Alkenation of Nonanal

Geometry of ketene acetal	Lewis acid	Product	
		Yield (%)	(*E*:*Z*)
(*Z*)	$TiCl_4$	90	5:95
(*Z*)	$TiCl_3$(O-*i*-Pr)	89	4:96
(*E*)	$TiCl_3$(O-*i*-Pr)	99	17:83
(*E*:*Z*) » 3:1	$TiCl_4$	91	14:86
(*E*:*Z*) » 3:1	$TiCl_2(O\text{-}i\text{-}Pr)_2$	89	12:88
(*E*:*Z*) » 3:1	$TiCl_3$(O-*i*-Pr)	88	7:93

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl Trimethylsilylacetate***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***Methylketene Bis(trimethylsilyl) Acetal***; ***Methylketene Dimethyl Acetal***; ***Tetramethoxyethylene***; ***Tris(trimethylsilyloxy)ethylene***.

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18. Matsuda, I., unpublished results.

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1-Methoxyvinyllithium[1]

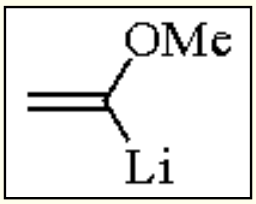

[42722-80-5] · C_3H_5LiO · 1-Methoxyvinyllithium · (MW 64.02)

(acetyl anion equivalent; umpoled synthon; precursor to vinyl ethers)

Alternate Name: MVL.

Physical Data: white powder.

Solubility: sol THF, diethyl ether; insol alkanes; decomposes violently in protic solvents.

Analysis of Reagent Purity: the reagent reacts rapidly and quantitatively with chlorosilanes such as ***Chlorotrimethylsilane*** (TMSCl). To an aliquot of MVL solution at -78 °C, TMSCl (&egt;1 equiv) and *n*-decane standards are added. The yield of MVL is determined by GC analysis.

Preparative Methods: an ~1 M solution is prepared by the dropwise addition of ***t-Butyllithium*** (2 M) in pentane to a solution of methyl vinyl ether (2 M) in THF at ca. -78 °C, followed by slow warming (3 h) to 0 °C.[2] The pure solid is prepared from the reaction of ***n-Butyllithium*** in hexanes (ca. 2 M) with tetrakis(α-methoxyvinyl)tin (ca. 0.5 M) in pentane at 0 °C.[3] The precipitated lithium reagent is washed several times under an inert atmosphere with dry pentane to remove the tin impurities. The reagent can be isolated (>95%) or dissolved in ethereal solvents for subsequent reactions.

Handling, Storage, and Precautions: solid MVL is extremely dangerous, reacting explosively with atmospheric oxygen. Solutions of MVL can be pyrophoric and contact with atmosphere and moisture must be avoided. Individuals should thoroughly familiarize themselves with the special handling techniques required for such reagents prior to use.[4]

Nucleophilic Acylation and α-Alkoxyvinyllithium Reagents.

α-Methoxyvinyllithium is a very useful acetyl anion equivalent[1] because it readily adds to a variety of electrophiles, and the resulting vinyl ether adducts are readily hydrolyzed to the acetyl derivatives under dilute acid conditions,

normally in <1 h at 25 °C. In addition to methyl vinyl ether (MVE) and ***Ethyl Vinyl Ether*** (EVE), other vinyl ethers such as 1-propenyl, 1,3-dienyl, allenyl, and β-styryl ethers, but not β,β-disubstituted vinyl ethers, can also be α-lithiated.[1,5] However, even under optimal conditions the deprotonations of MVE and EVE also produce minor amounts of dilithioacetylene (1-2%). Fortunately, tetrakis(α-methoxyvinyl)tin is formed free of alkynic impurities with a nominal excess of MVL because lithium acetylides are efficiently displaced from tin.[3] Now available commercially, this tin reagent provides unsolvated MVL as a pure solid reagent from its reaction with *n*-butyllithium in hexanes through a simple transmetalation procedure. For research applications, MVL generated by this Sn/Li exchange method is superior to the reagent generated by the deprotonation of MVE both with respect to efficiency and product isolation (eq 1). The corresponding process for the preparation of ***1-Ethoxyvinyllithium*** (EVL) is less efficient because of its greater solubility in pentane compared to MVL.[6]

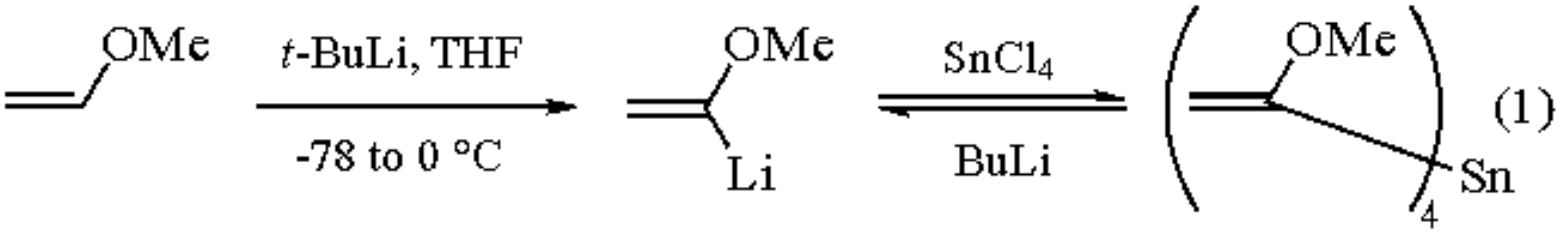

(1)

Addition to Carbon Electrophiles.

MVL readily adds to aldehydes and ketones to give excellent yields of the corresponding α-methoxyvinyl carbinols.[5a,7] Even ketones prone to enolization (e.g. phenylacetone, cyclopentanone) undergo smooth addition with high diastereofacial selectivity (e.g. eq 2).[7k] Moreover, 1,2-addition is observed with α,β-unsaturated aldehydes and ketones. The reagent undergoes double addition to esters to produce 3-hydroxy-2,4-pentanediones, which serve as highly useful precursors to 2-pyrazolin-4-ones (eq 3).[8]

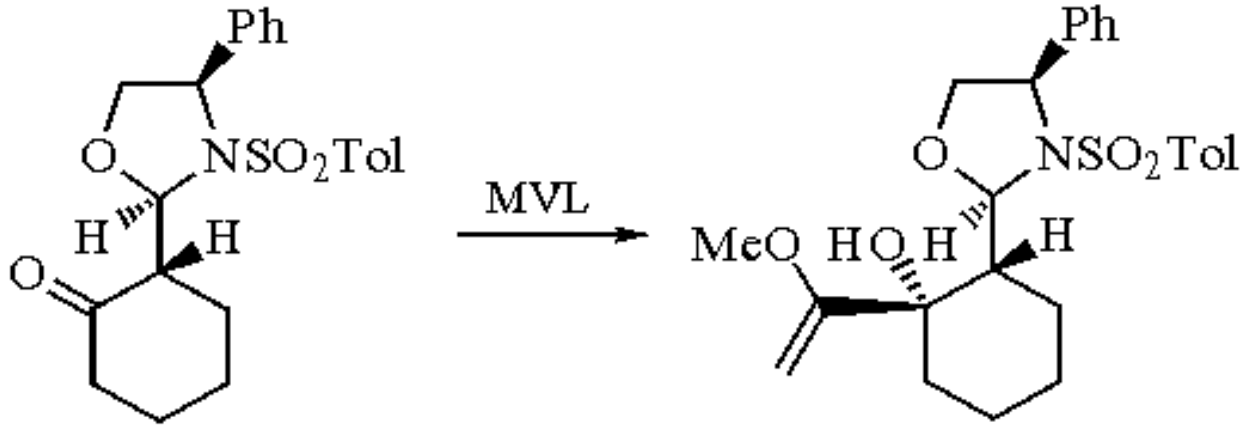

(2)

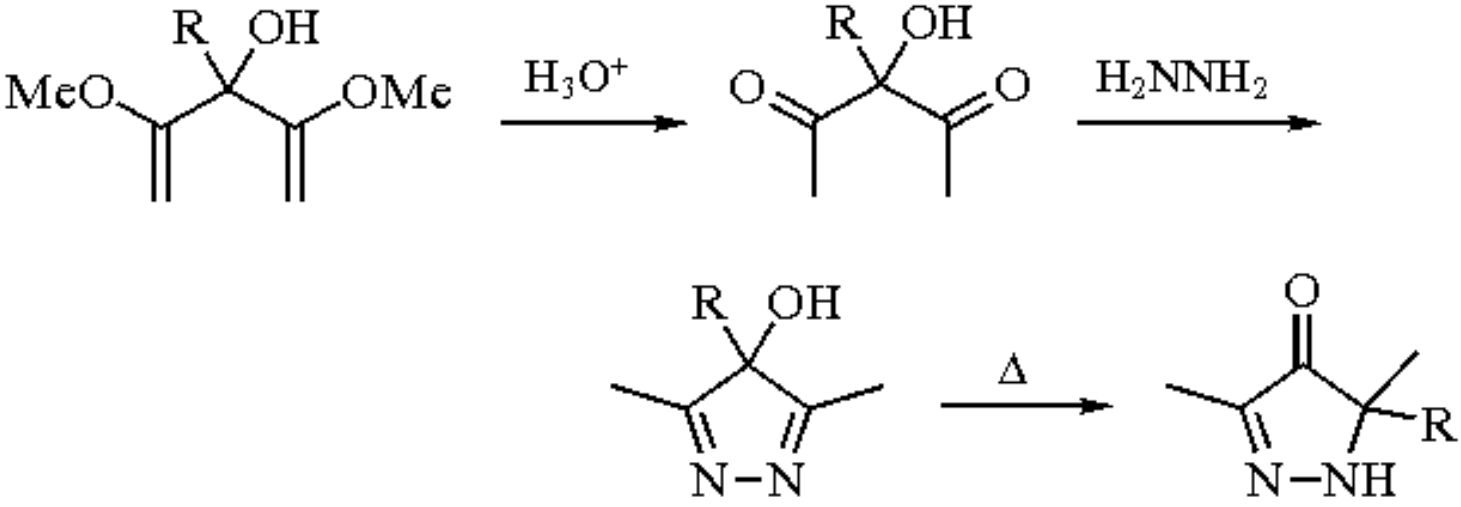

(3)

Benzonitrile undergoes mainly monoaddition leading to α-diketones. MVL also adds to the carbonyl carbon of ***Phenacyl Bromide***, producing an α-methoxyvinyl epoxide which is hydrolyzed to an acetylated vicinal diol (eq 4). In some cases (e.g. γ,γ-dimethylallyl bromide and 1-iodooctane), alkylation can be achieved, but ***Benzyl Bromide*** gives only 1,2-diphenylethane.[5a]

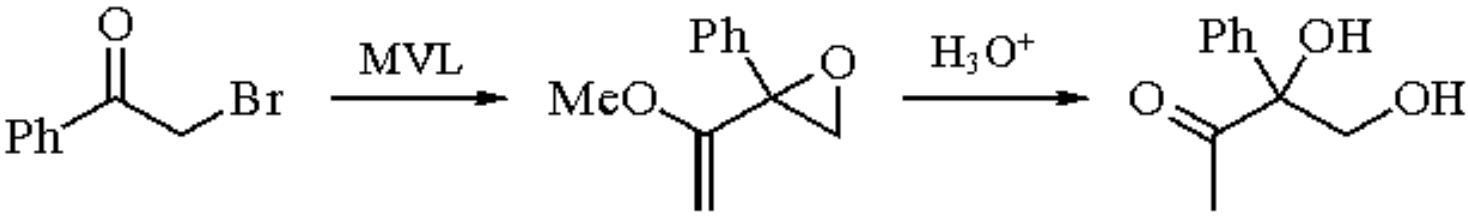

(4)

Organocuprates from MVL.

The preparation of the α-methoxyvinylcuprate reagent $LiCu[C(OMe)=CH_2]_2$ was first accomplished through the deprotonation of MVE followed by treatment with purified ***Copper(I) Iodide*** and added ***Dimethyl Sulfide*** as a complexing agent (see ***Lithium Bis(1-methoxyvinyl)cuprate***).[9] The analogous α-ethoxyvinylcuprate is prepared similarly (see ***Lithium Bis(1-ethoxyvinyl)cuprate***). Both reagents undergo conjugate addition to α,β-unsaturated ketones, the process being less effective with β,β-disubstituted substrates (eq 5).[10] The corresponding unsaturated aldehydes undergo 1,2-addition. Moreover, these reagents efficiently vinylate allylic and benzylic halides, but neither primary nor secondary bromides nor epoxycyclohexane produce satisfactory results. From the transmetalation procedure the higher order organocuprate $Li_2Cu(CN)[C(OMe)=CH_2]_2$ is easily prepared from MVL and ***Copper(I) Cyanide*** in THF and this also undergoes allylation, providing 2-methoxy-1,4-pentadiene (eq 6), a useful intermediate for the preparation of either *exo*-brevicomin or frontalin in optically active form.[11]

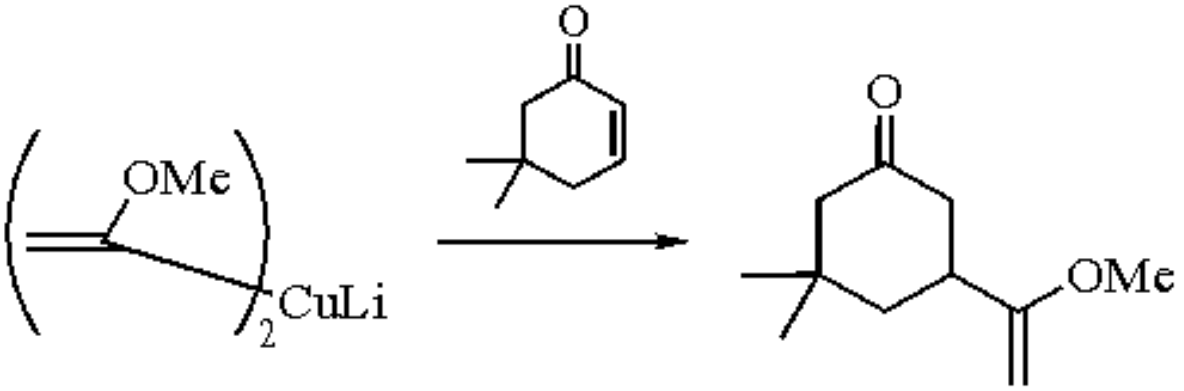

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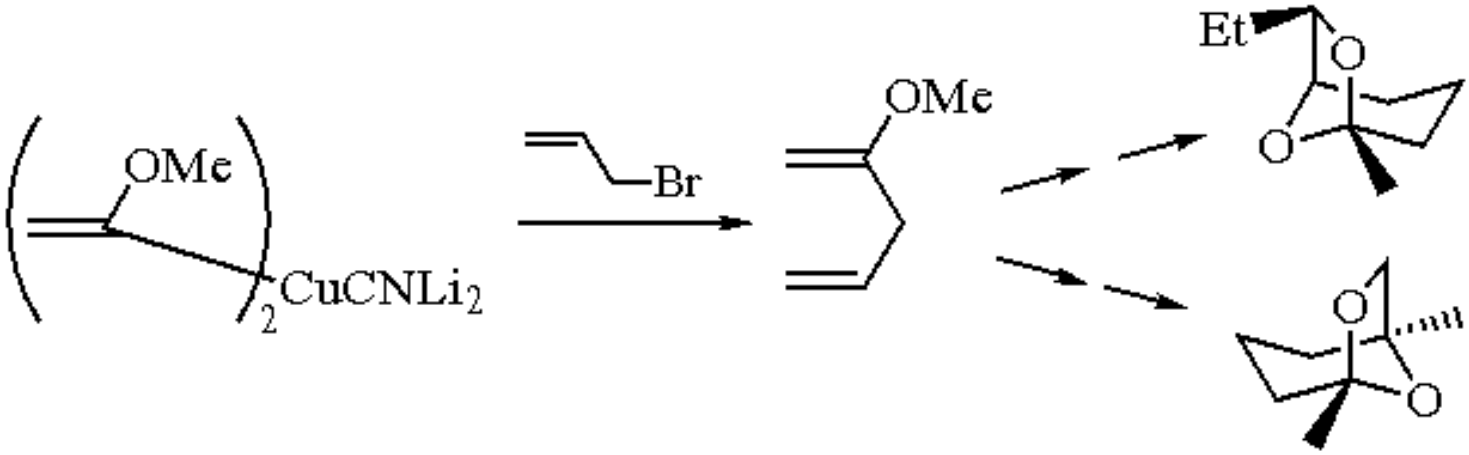

(6)

α-Methoxyvinyl Derivatives of Group 14 Metalloids.

With the correct stoichiometry, the preparation of α-methoxyvinylsilanes, -germanes, and -stannanes from MVL and the metalloidal halide is a particularly efficient process (eq 7).[12] From one to four α-methoxyvinyl groups can be introduced, with no limitations being encountered over a wide range of metalloidal substituents. However, an excess of the halometalloid with respect to MVL can result in the hydrolysis of the α-methoxyvinyl moiety. Moreover, with ***Chlorotrimethylstannane***, an excess of MVL can also displace methyl groups from tin. While the deprotonation methodology gives excellent results under the proper conditions, the Sn/Li exchange route is superior for small scale reactions. The tin derivatives provide a simple access to MVL and also undergo smooth Stille coupling to produce α-methoxy enones.[12] Mechanistic studies have demonstrated that the protonation of the vinyl ether moiety is rate-limiting with the rate increasing in the order: H < Si < Ge < Sn < C for a series of α-substituted α-methoxyvinyl compounds.[13] Acetyl (e.g. **1**) and even polyacetyl derivatives (e.g. **2**) can also be prepared, but in the case of silanes, bulky substituents (e.g. *i*-Pr) are required to prevent product decomposition.[14]

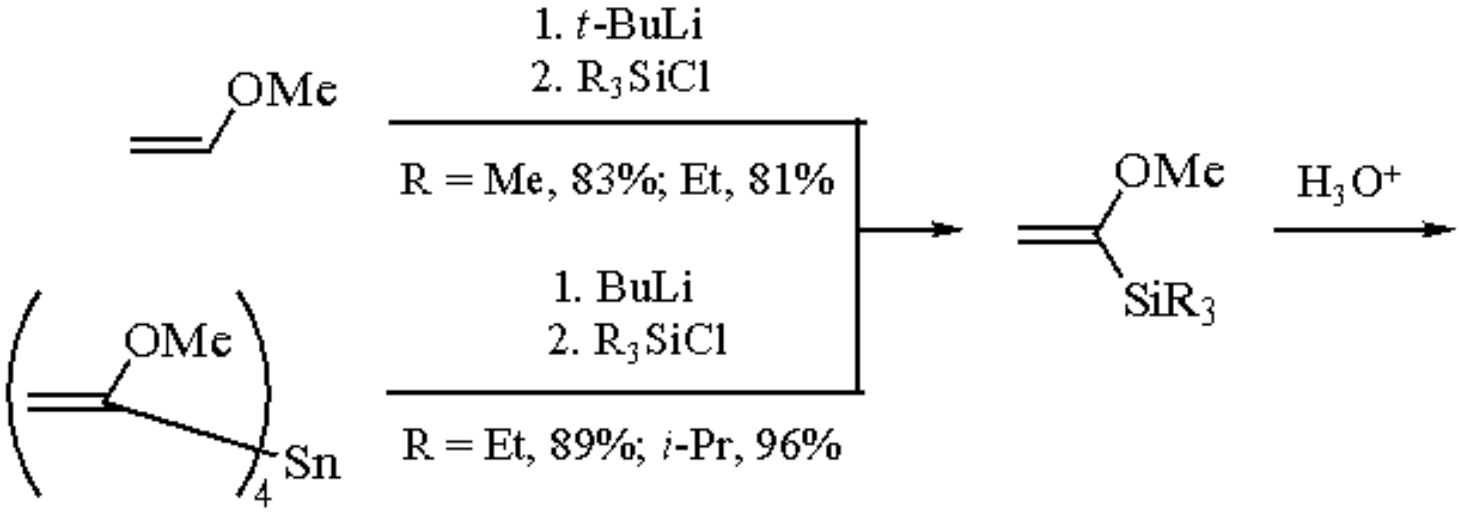

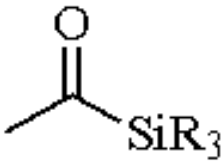

(7)

R = Me, 83%; Et, 93%; *i*-Pr, 93%

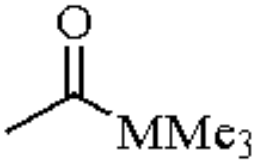

M = Ge, 71%; Sn, 47%

(1)

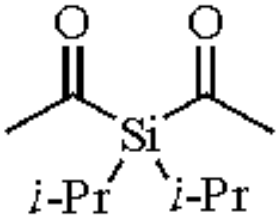

90%

(2)

Markovnikov Vinylboranes.

Early studies on the reaction of MVL (generated by deprotonation) implicated the intermediacy of internal (Markovnikov) vinylboranes.[15] More recently, trialkylboranes have been found to undergo the clean addition of MVL (from Sn/Li exchange) to produce the organoborate complex which reacts efficiently with Me_3SiCl to give the corresponding Markovnikov vinylboranes which are isolable in high yields (70-90%) (eq 8).[16] Suzuki-Miyaura coupling of these boranes to alkenyl bromides occurs with complete retention of configuration, resulting in the efficient construction of stereodefined 1,3-dienes.[17] Styrenes and enynes are similarly prepared.

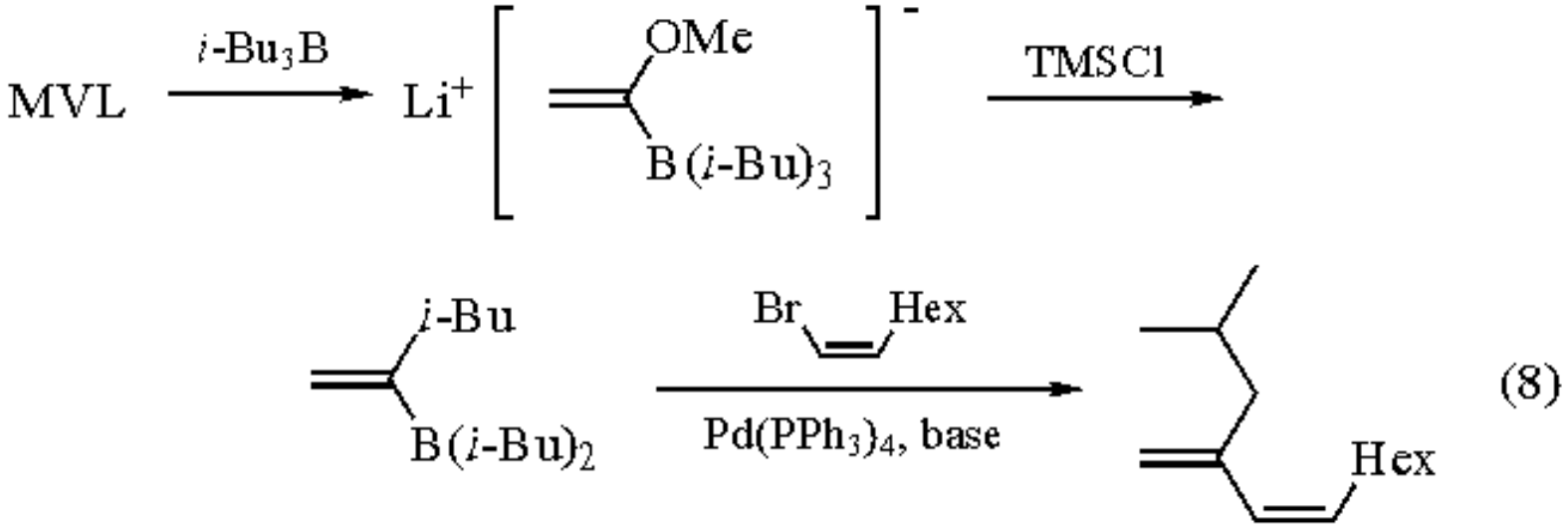

N,*N*-Diethyl vinylcarbamate can also be smoothly α-metalated,[18] but the organoborates derived from these reagents undergo rearrangment through a thermal rather than TMSCl-induced process.[19]

Related Reagents.

1,2-Dimethoxyvinyllithium; ***1-Ethoxyvinyllithium***.

---

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Methyl Acrylate

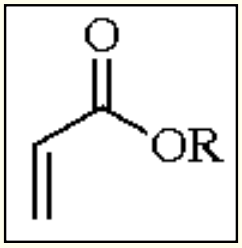

(**1**; R = Me)

[96-33-3] · $C_4H_6O_2$ · Methyl Acrylate · (MW 86.10) (**2**; R = Et)

[140-88-5] · $C_5H_8O_2$ · Ethyl Acrylate · (MW 100.13) (**3**; R = *n*-Bu)

[141-32-2] · $C_7H_{12}O_2$ · Butyl Acrylate · (MW 128.19) (**4**; R = *t*-Bu)

[1663-39-4] · $C_7H_{12}O_2$ · *t*-Butyl Acrylate · (MW 128.19)

(electrophile in conjugate addition reactions; dienophile or dipolarophile in cycloaddition reactions; acceptor in radical addition reactions; used in ene reactions)

Alternate Name: methyl propenoate.

Physical Data: (**1**) mp -75 °C; bp 80 °C. (**2**) mp -71 °C; bp 99 °C. (**3**) bp 145 °C. (**4**) bp 61-63 °C/60 mmHg.

Solubility: sol most organic solvents; slightly sol water.

Purification: wash repeatedly with aqueous NaOH to remove inhibitors, wash with H_2O, dry over $CaCl_2$, and distill under reduced pressure.

Handling, Storage, and Precautions: store at 0 °C in the dark (material will polymerize if exposed to light). Inhibited with up to 200 ppm hydroquinone monomethyl ether. Lachrymator and potential vesicant. Use in a fume hood. The ethyl ester (**2**) is a cancer suspect agent.

Conjugate Additions.

Acrylic acid esters have been used as Michael acceptors for a variety of nucleophiles. A typical example using an

amino alcohol is shown in eq 1.[1] This example illustrates chemoselectivity (amine over alcohol) and demonstrates that primary amines can undergo multiple additions.[2] This reaction has been performed with anilines,[3] imines,[4] guanidines,[5] hydrazones,[6] xanthines,[7] and pyrrolopyrimidines.[8] Other heteroatomic nucleophiles have also been used, including alcohols,[9] thiols,[10] halides,[11] and phosphorus reagents.[12]

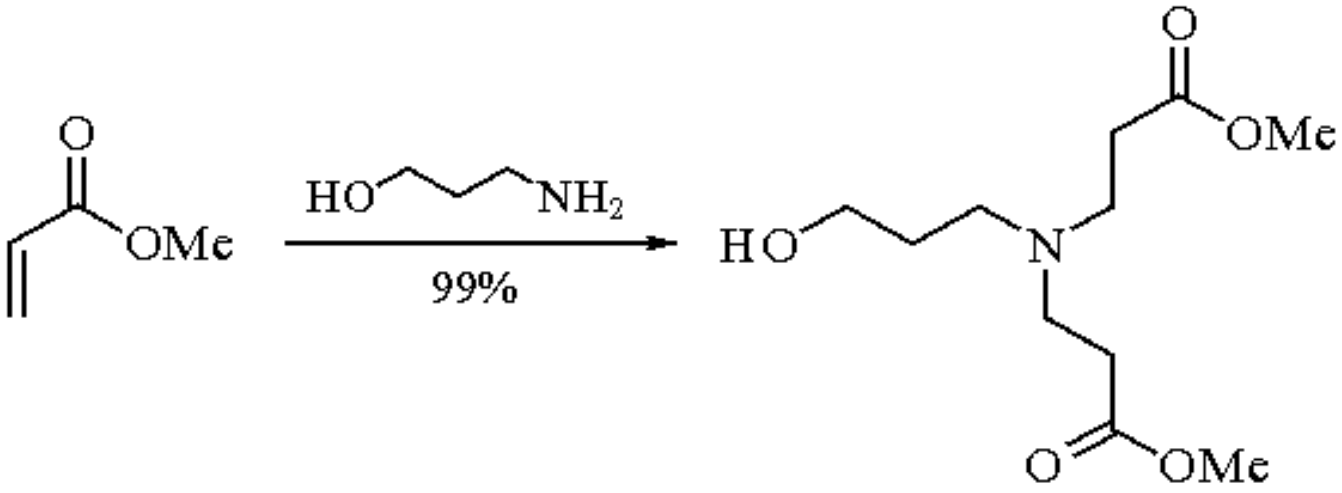

(1)

A variety of carbon nucleophiles have also been used with acrylates in conjugate additions. An example using an enamine is shown in eq 2.[13,14] This reaction has been extended to the synthesis of optically active esters through the use of chiral amines (eq 3).[15,16]

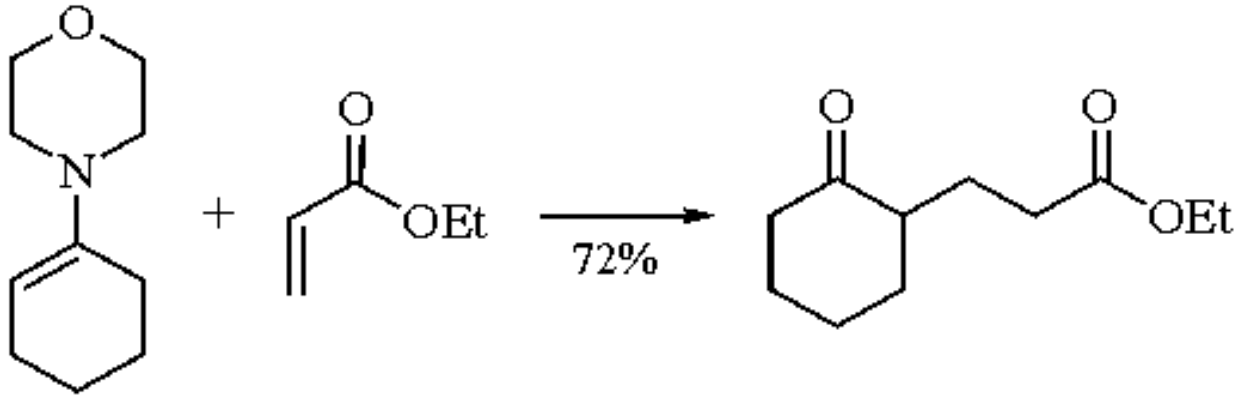

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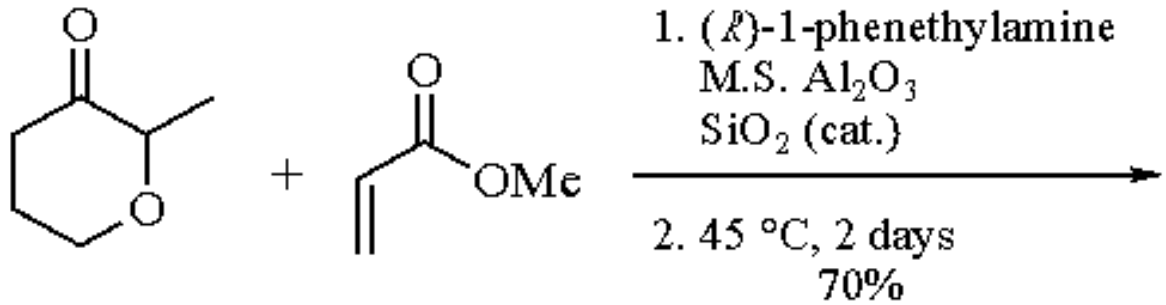

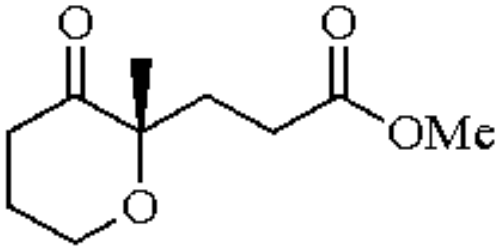

(3)

94% ee

Stabilized azaallyl anions have also been used in asymmetric conjugate additions with methyl acrylate, as shown in eq 4.[17,18] Other stabilized anions used in this reaction include hydrazones,[19] malonates,[20] α-cyano anions,[21] ester enolates,[22] α-nitro anions,[23] α-sulfonyl anions,[24] phosphorus ylides,[25] and organozinc reagents.[26]

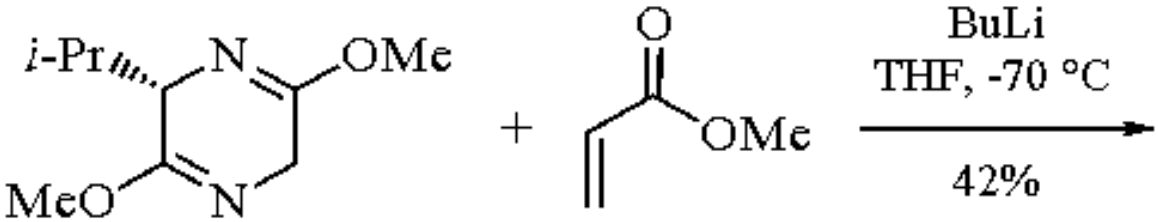

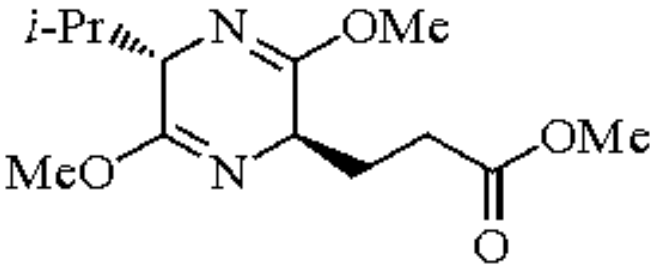

(4)

98% de

Enolates formed upon Michael addition of nucleophiles to acrylates have been trapped with a variety of electrophiles. An example of an intermolecular trapping with an aldehyde is shown in eq 5.[27,28] Other traps have included ketones,[29] *N*-tosyl imines,[30] and Michael acceptors.[31]

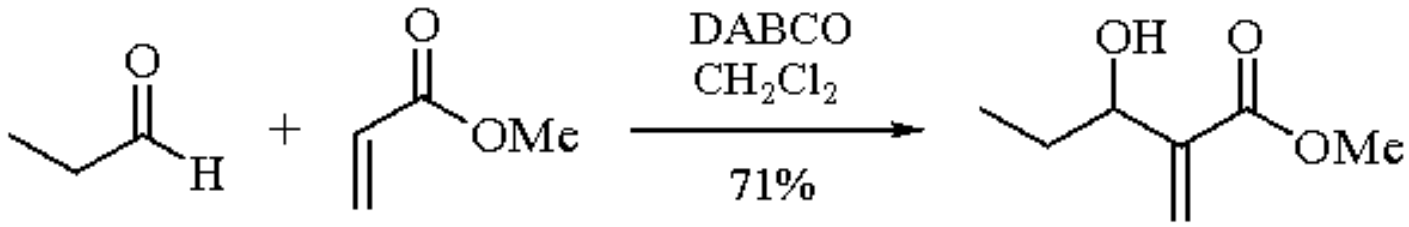

(5)

Intramolecular variants of these reactions are also well known. For example, eq 6 shows an intramolecular trapping with an enone to produce a bicyclic ring system.[32] Both chiral enolates[33] and chiral acrylates[34] have been used in this reaction. Other intramolecular traps have included esters[35] and ketones.[36]

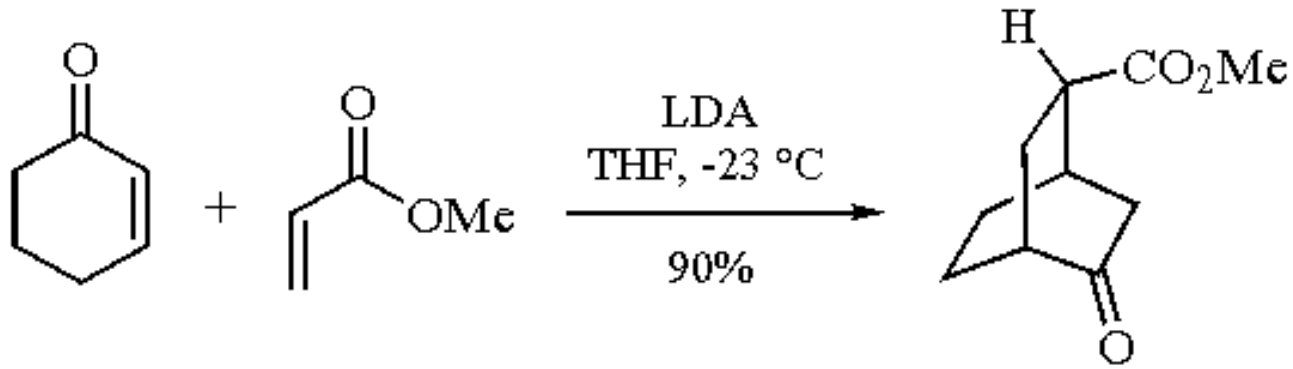

(6)

Cycloaddition Reactions.

Acrylates are commonly used as dienophiles in Diels-Alder reactions. *Endo* products predominate when stereochemistry is involved. A simple example is shown in eq 7.[32b,37]

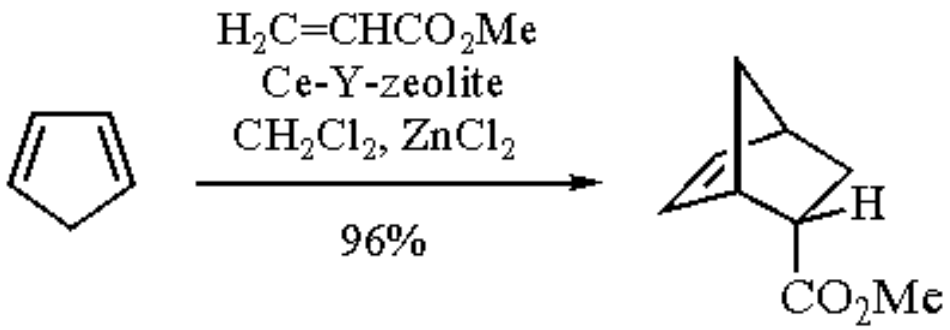

(7)

A wide variety of attempts at asymmetric induction have been reported for this reaction. Chiral acrylate esters have been used in the cycloaddition process (eq 8),[38,39] as well as chiral catalysts.[40]

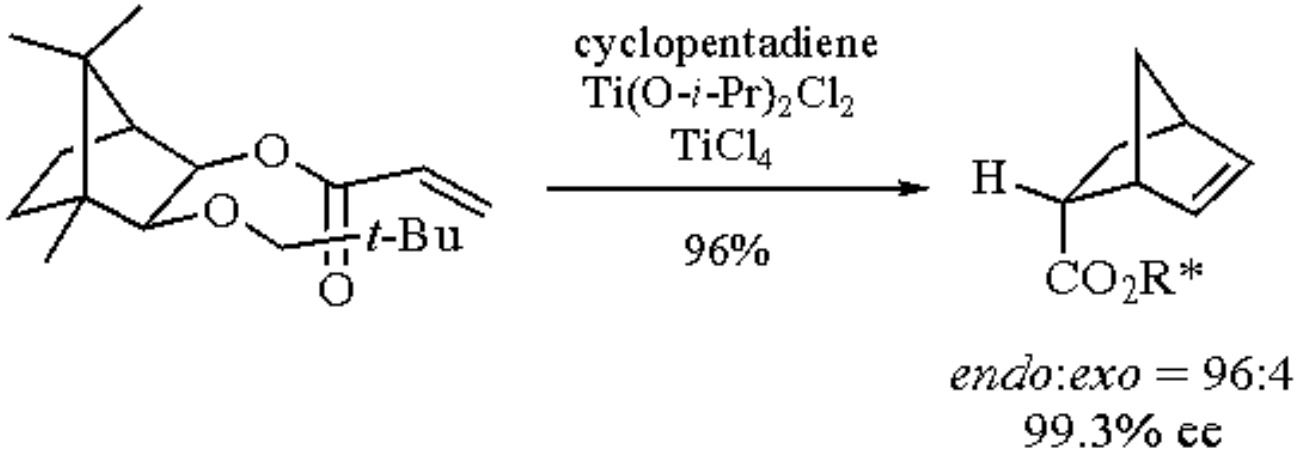

(8)

Acrylates have further utility as dipolarophiles and have been used to trap nitrile oxides (eq 9),[41] nitrones,[42] azomethine ylides,[43] and azomethine imines.[44] They have also been used in hetero Diels-Alder reactions[45] and [2 + 2] cycloadditions.[46]

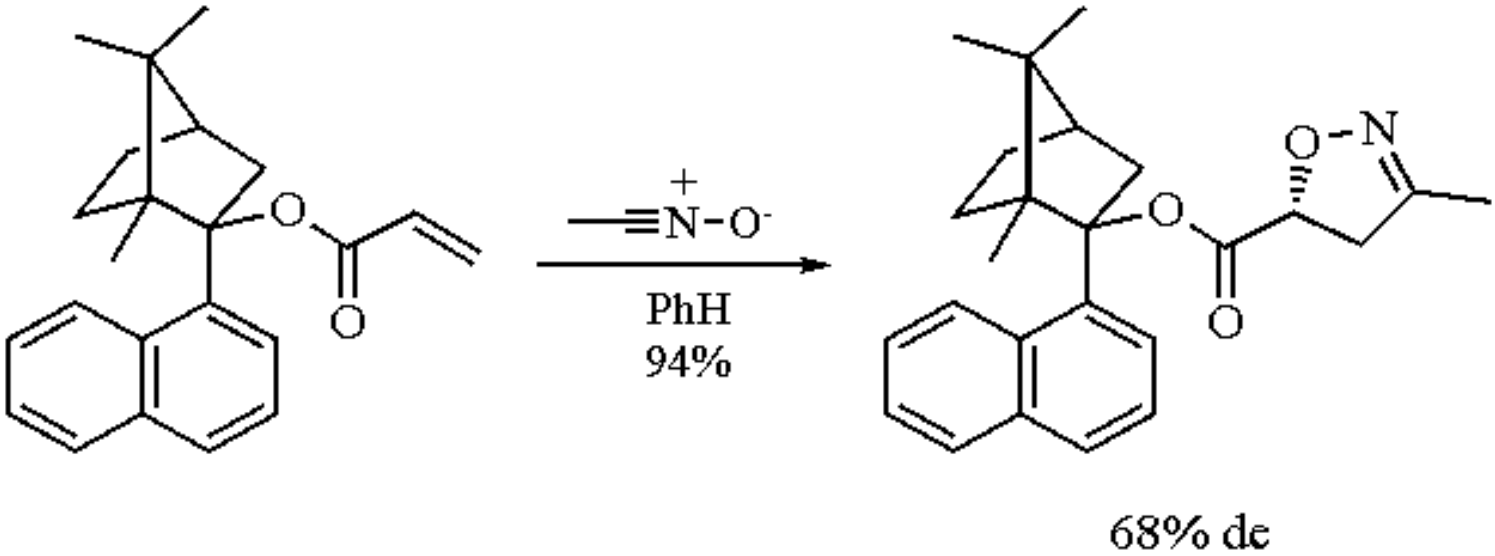

(9)

Radical Trap.

Acrylates have been used as traps for alkyl radicals in radical chain processes.[47] A variety of radical precursors may be used and intramolecular cyclization often precedes intermolecular trapping. Frequently, it is necessary to use a large excess of the acrylate to enhance trapping. The example in eq 10 shows the reaction of cyclohexyl iodide with methyl acrylate in the presence of ***Tris(trimethylsilyl)silane***.[48]

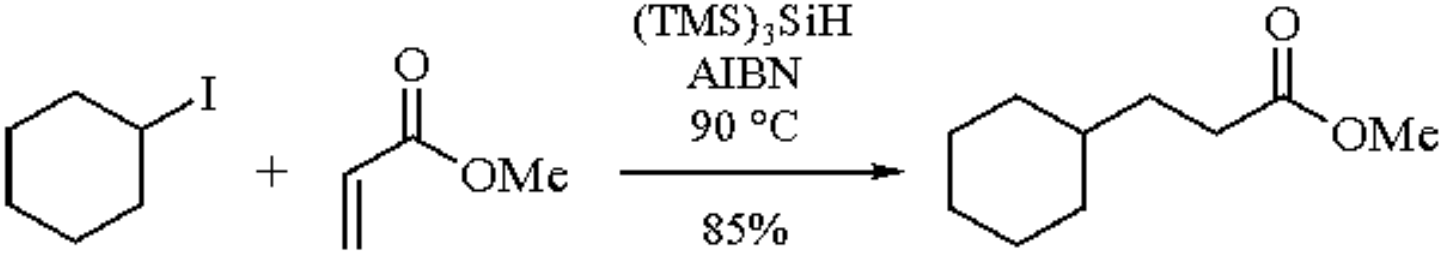

(10)

Curran has developed atom transfer cycloaddition as a means of forming new rings and maintaining high levels of functionality in the final products (eq 11).[49] Acyl radicals have also been trapped by acrylates to produce 1,4-dicarbonyl compounds.[50] Ketones reduced with ***Samarium(II) Iodide*** have been trapped with ethyl acrylate to give the corresponding lactones (eq 12).[51]

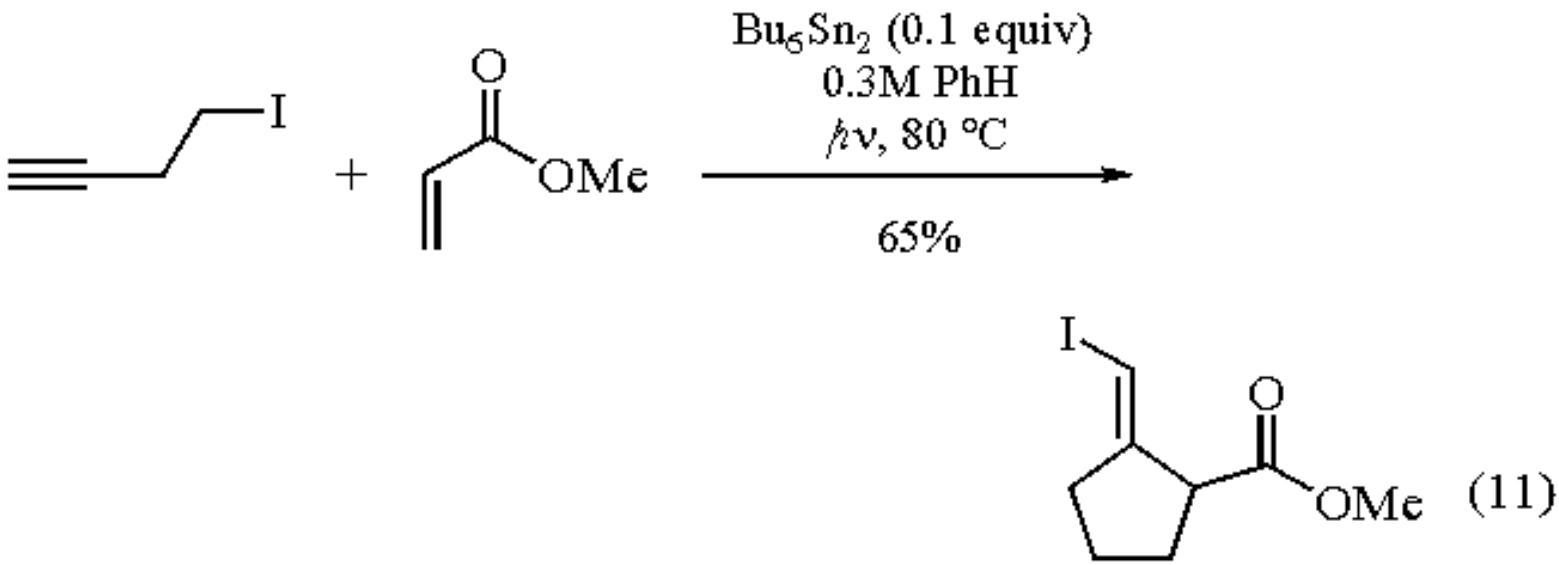

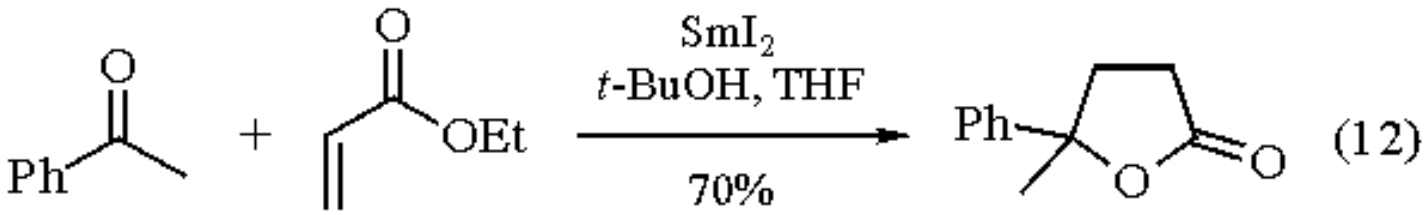

Arylations and Vinylations.

Aryl and vinyl halides and triflates have been coupled to acrylates in the presence of palladium catalysts to produce the corresponding unsaturated esters. This method is very versatile and stereospecific when substituted vinyl halides are used. Coupling reactions with an aryl bromide,[52] a vinyl triflate,[53] and a vinyl halide[54] are shown in eqs 13-15.

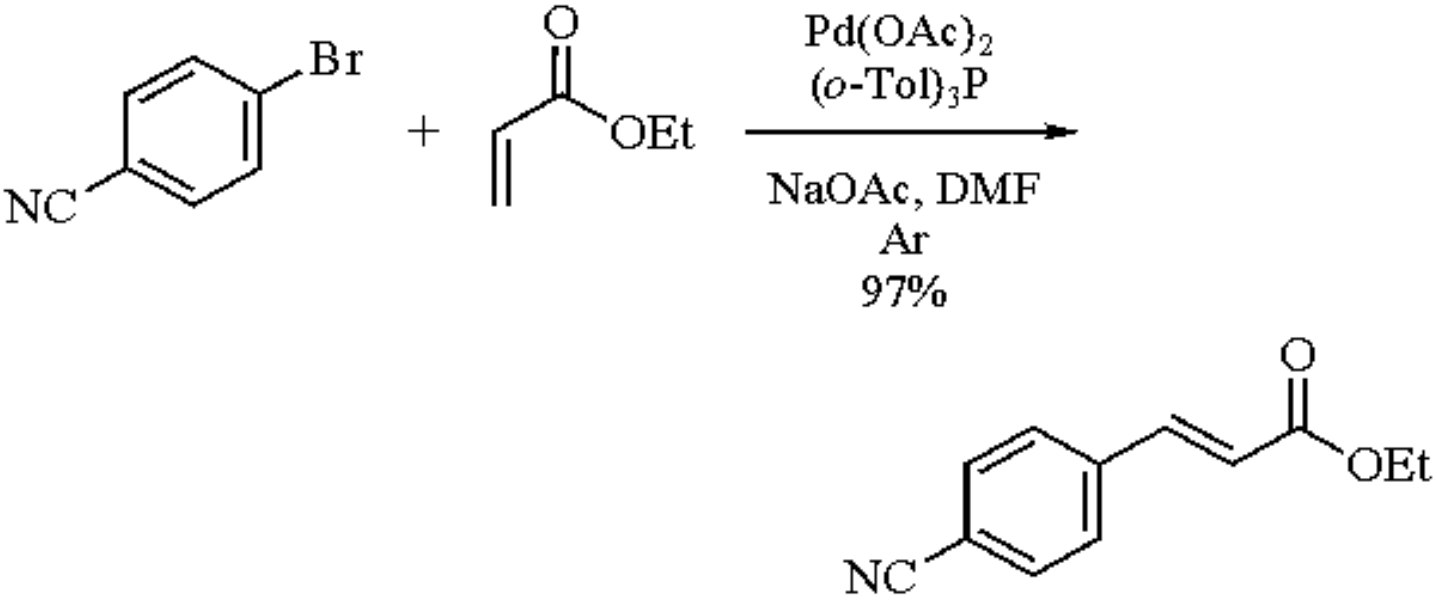

(13)

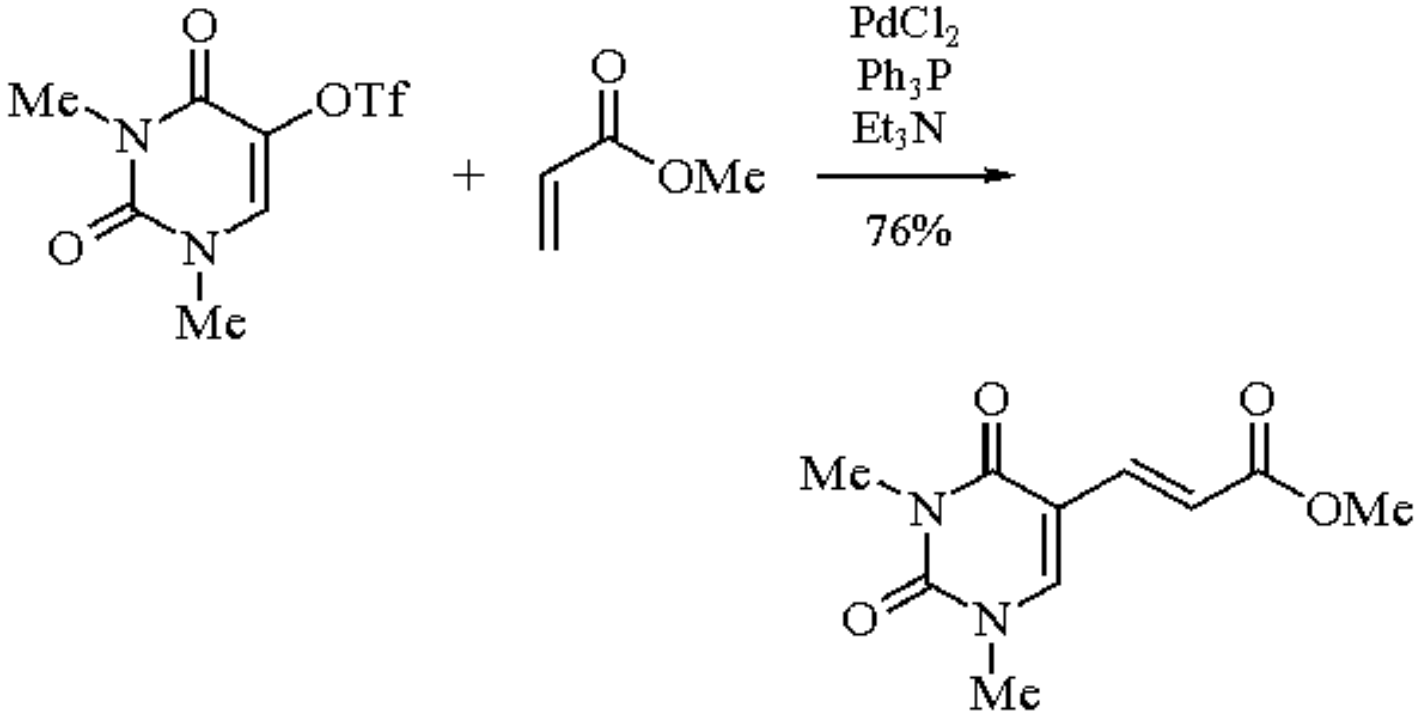

(14)

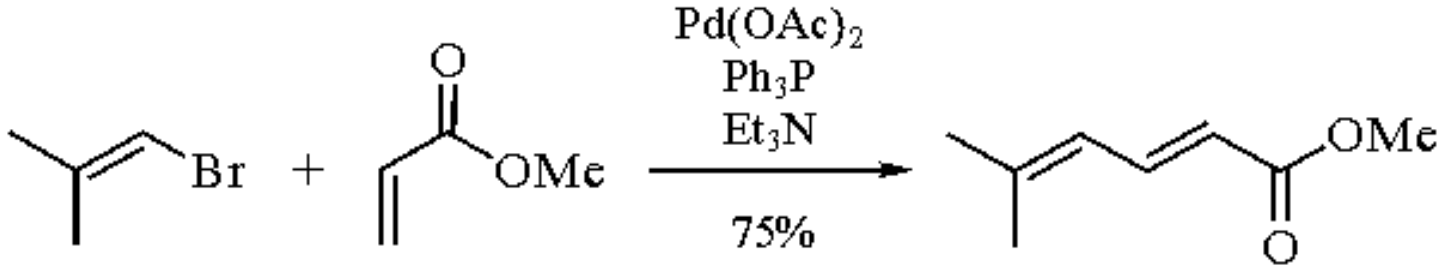

(15)

Acrylates have also been oxidatively coupled to indoles and furans using palladium salts (eq 16). These reactions appear to proceed via π-complexation to the heterocyclic double bond, conversion to the σ-complex, addition to the acrylate, and subsequent reductive elimination of the palladium species.[55,56]

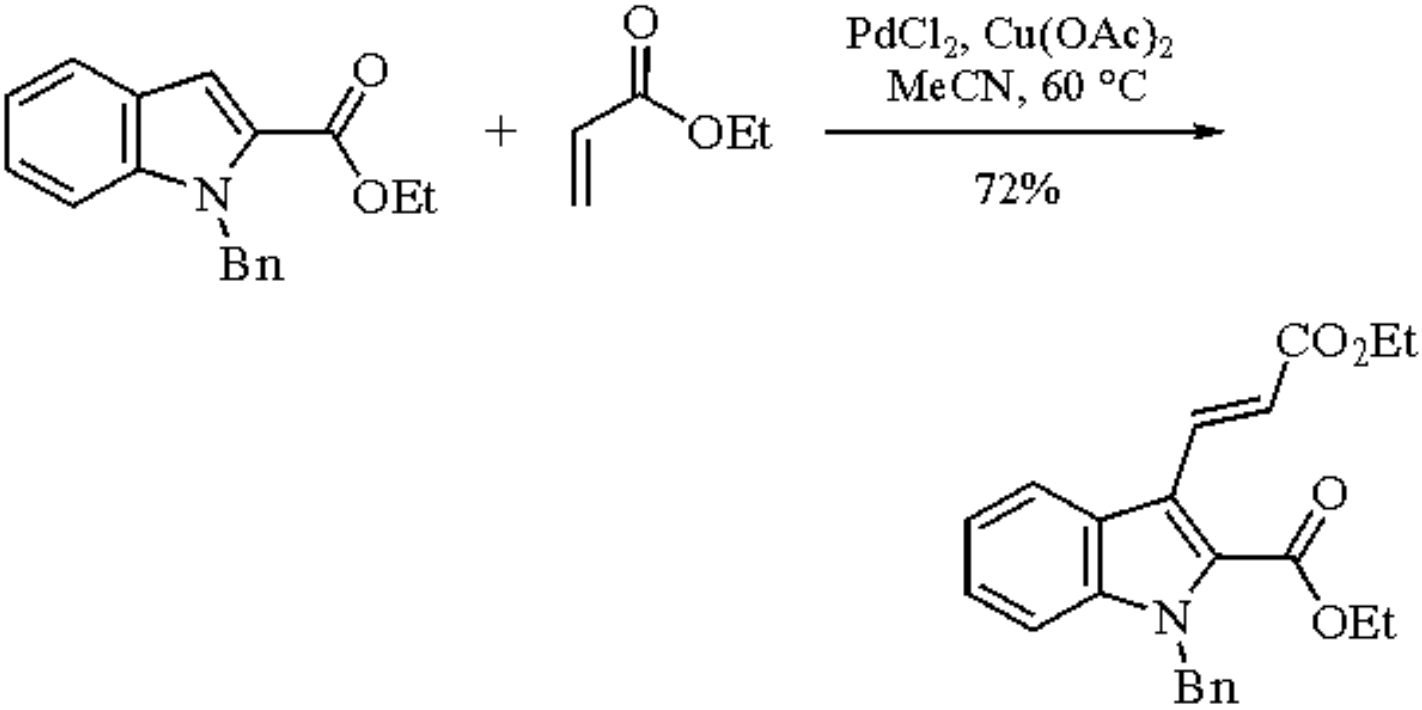

(16)

An interesting extension of this palladium chemistry, shown in eq 17, involves the vinylation of an imino iodide.[57] Under the same conditions, the corresponding imino chlorides are recovered unchanged.

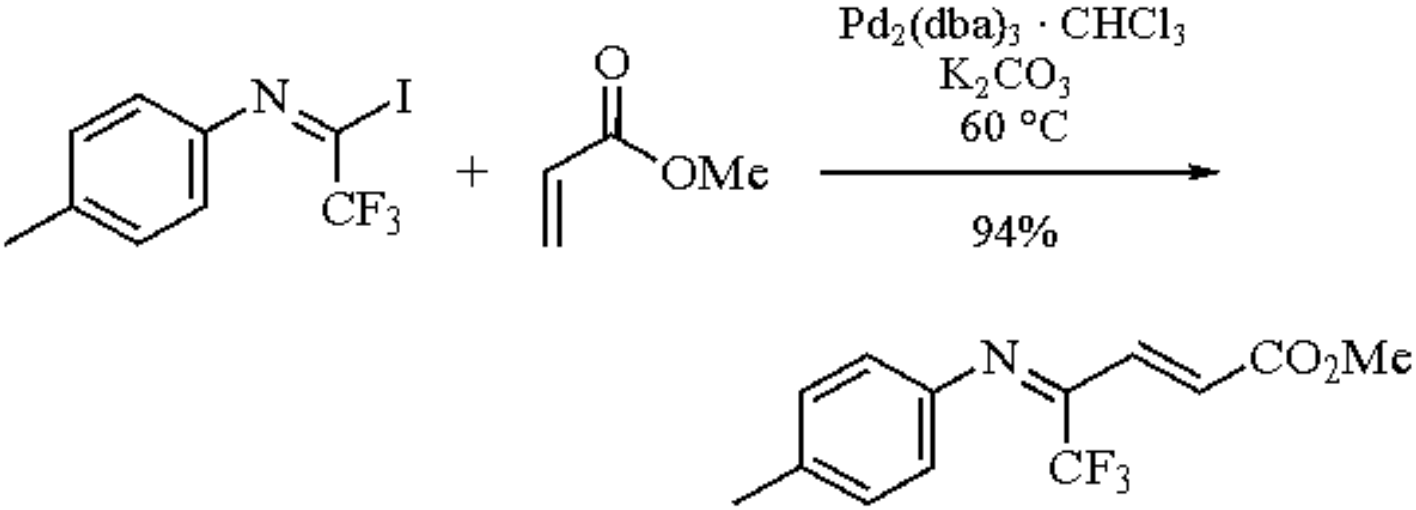

(17)

Ene Reactions.

Acrylates have been used in Lewis acid catalyzed ene reactions. Methyl acrylate reacts with (-)-β-pinene (eq 18) at rt with catalysis by ***Aluminum Chloride***.[58] This reaction can be stereoselective and may proceed better if a salt mixture is present.[59]

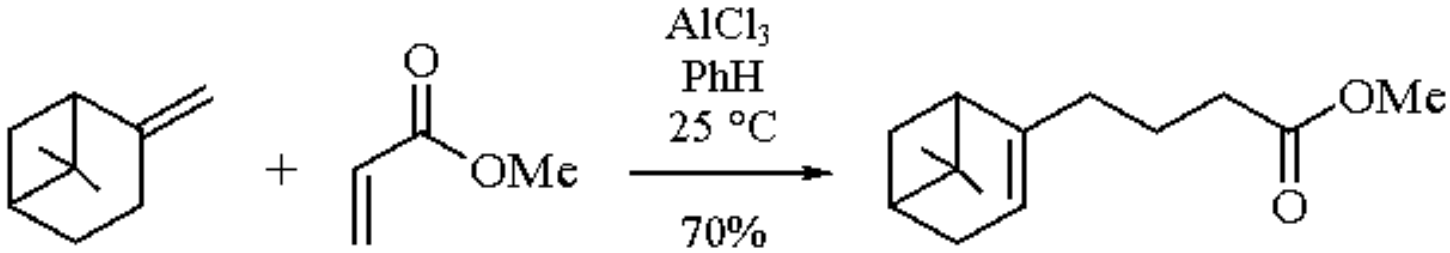

(18)

Transesterifications.

The transesterification of acrylates is best carried out using ***p-Toluenesulfonic Acid*** in the presence of hydroquinone as an inhibitor of polymerization. A representative example is shown in eq 19.[60]

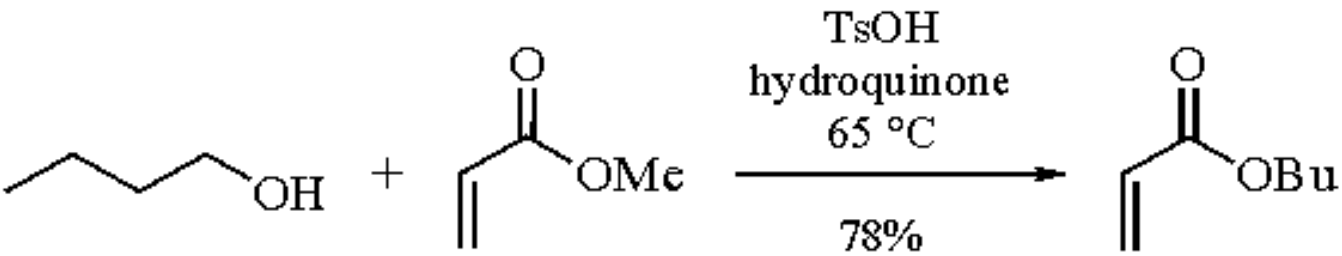

(19)

Related Reagents.

Ethyl Acrylate.

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Methylaluminum Bis(4-bromo-2,6-di-*t*-butylphenoxide)

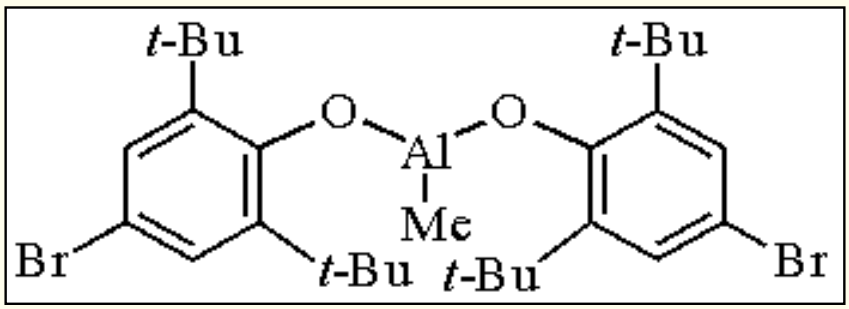

[118495-99-1] · $C_{29}H_{43}AlBr_2O_2$ · Methylaluminum Bis(4-bromo-2,6-di-*t*-butylphenoxide) · (MW 610.50)

(designer Lewis acid for Claisen rearrangements;[1-4] epoxide rearrangements;[5-7] intramolecular ene reactions;[8-10] α-primary alkylation of ketones;[11] oxetanone synthesis[12])

Alternate Name: MABR.

Solubility: sol toluene, CH_2Cl_2.

Form Supplied in: prepared from commercially available reagents and used in situ.

Preparative Method: prepared by reaction of a 1-2 M hexane solution of ***Trimethylaluminum*** with 4-bromo-2,6-di-*t*-butylphenol (2 equiv) in CH_2Cl_2 or toluene at 25 °C for 1 h.[1]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Claisen Rearrangement.

The modified organoaluminum reagent methylaluminum bis(4-bromo-2,6-di-*t*-butylphenoxide) was developed as a bulky Lewis acid for effecting the stereoselective Claisen rearrangement of allylic vinyl ethers.[1] Thus reaction of 1-isobutyl-2-propenyl vinyl ether with MABR in CH_2Cl_2 at -78 °C affords (*Z*)-7-methyl-4-octenal with high stereoselectivity (*E*/*Z* = 7:93). This selectivity is opposite to that observed in ordinary thermal and Lewis acid-induced rearrangements (eq 1). The Claisen rearrangement of the optically active substrate with MABR reveals a chairlike transition-state conformation with the isobutyl substituent axial in order to relieve a severe 1,2-steric interaction between the isobutyl and very bulky MABR ligands.[2]

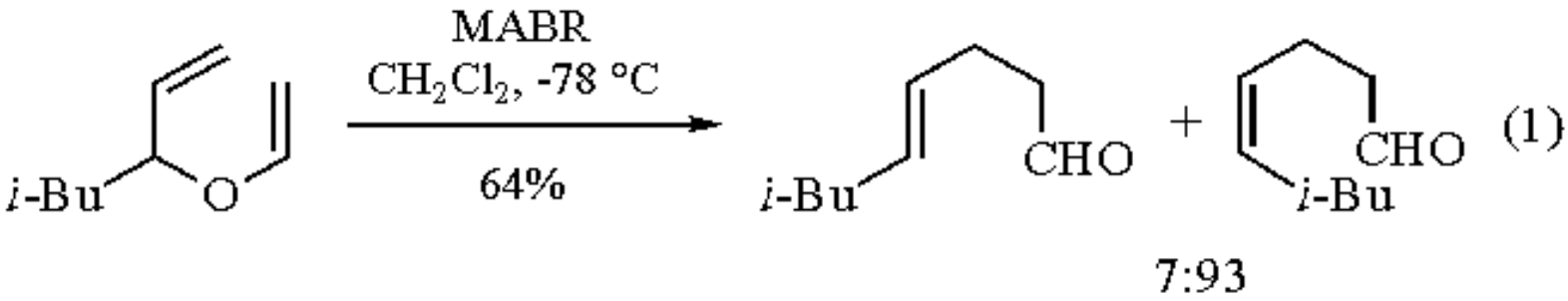

Such unusual behavior is also observed in the MABR-promoted Claisen rearrangement of bisallylic vinyl ethers and allylic phenyl ethers (eq 2).[3,4]

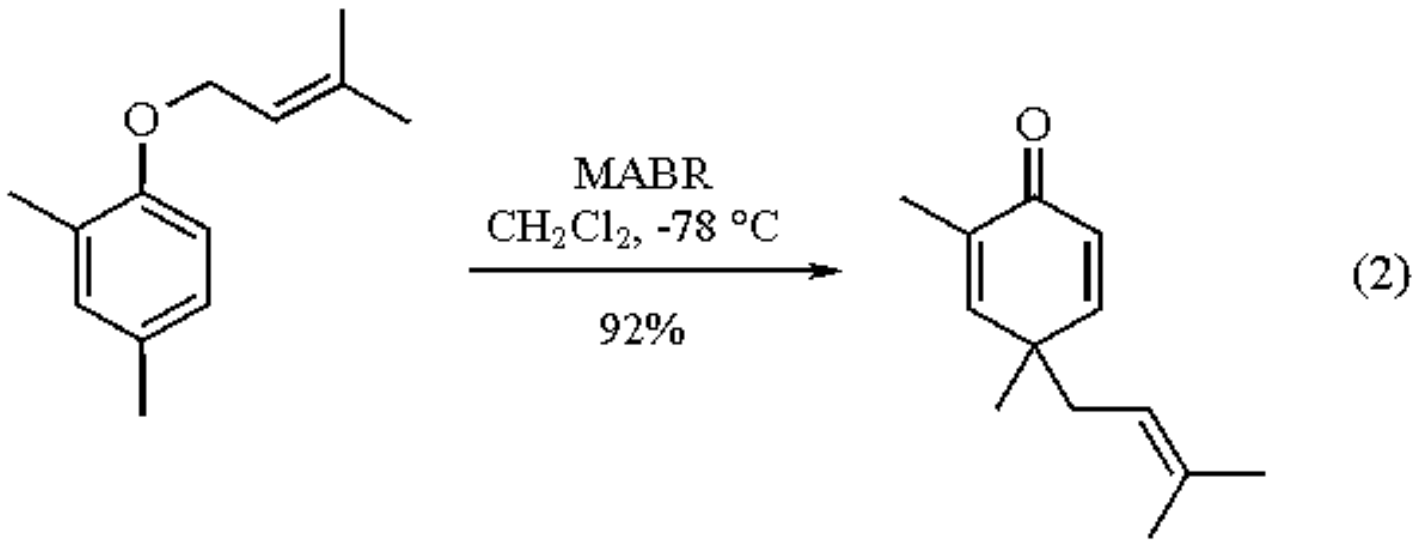

Epoxide Rearrangements.

A new, stereocontrolled rearrangement of epoxy silyl ethers to β-siloxy aldehydes has been effected using MABR as a catalyst under mild conditions. Used in combination with the Sharpless asymmetric epoxidation of allylic alcohols, this rearrangement represents a new approach to the synthesis of various optically active β-hydroxy aldehydes, useful intermediates in natural product synthesis (eq 3).[5] MABR has also been used to transform a variety of simple epoxides to carbonyl compounds with high efficiency and selectivity.

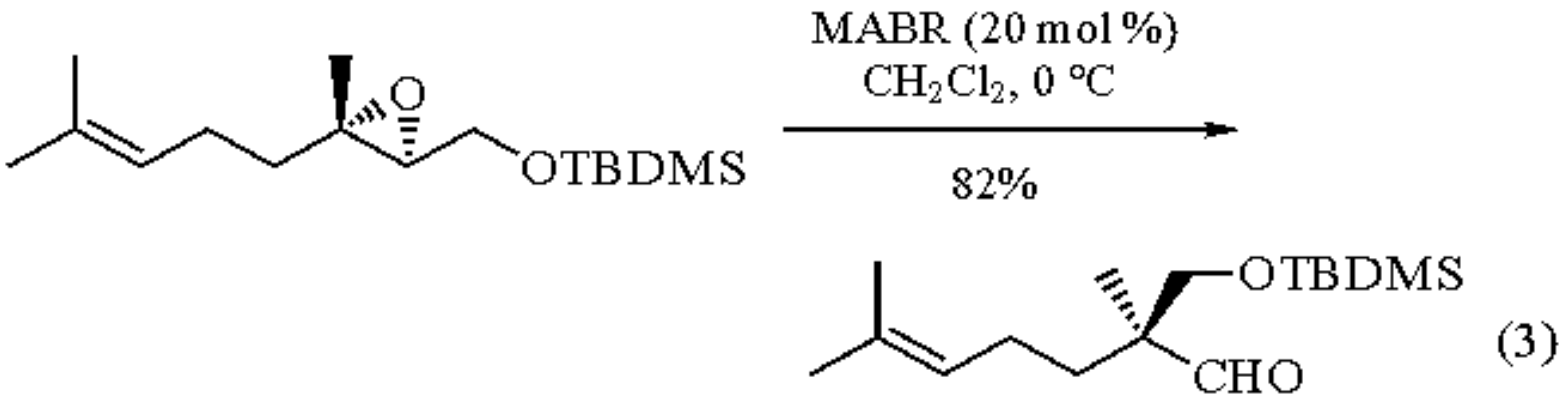

This approach enables the practical asymmetric synthesis of both *erythro* and *threo* aldols based on the MABR-promoted selective rearrangement of optically active *threo* and *erythro* epoxy silyl ethers (eq 4).[6] The migratory aptitude of alkyl substituents in the Lewis acid-promoted epoxide rearrangement has been investigated with the MABR reagent.[7]

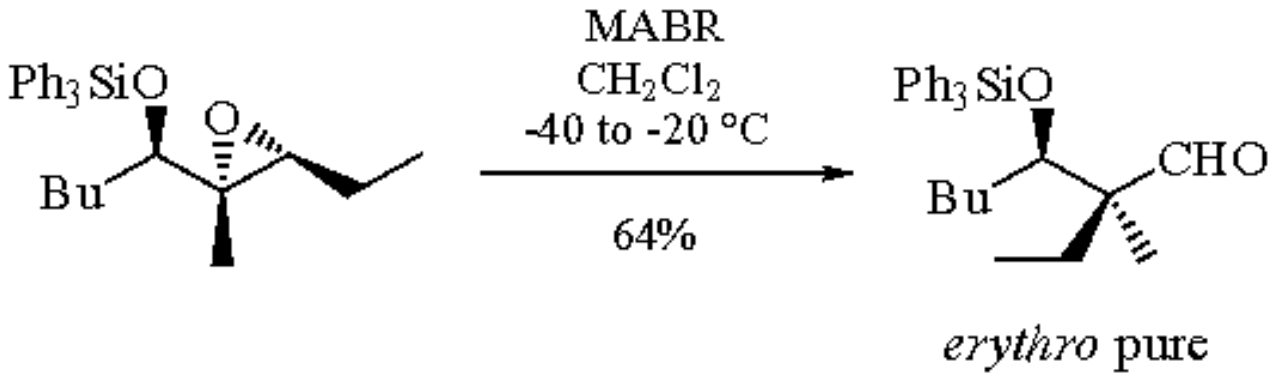

(4)

Intramolecular Ene Reactions.

The intramolecular ene reaction of α-substituted δ,ε-unsaturated aldehydes has been executed with high *trans* selectivity, not observed with ordinary Lewis acids (eq 5).[8] This method has been used for the asymmetric synthesis of the cyclohexyl fragment of FK-506.[9] Since MABR is also the reagent of choice for epoxide rearrangements, this approach has been directly applied to the cyclization of alkenic epoxides (eq 6).[10]

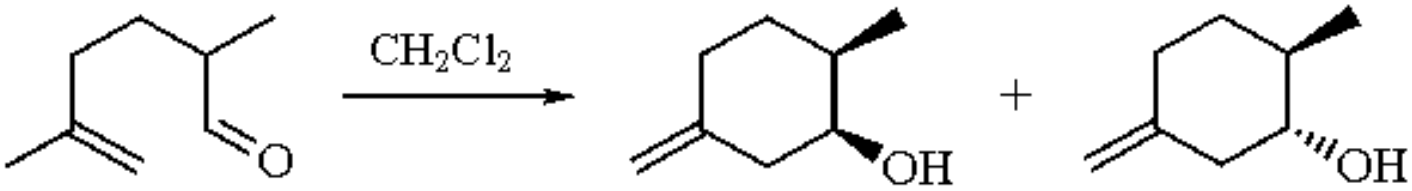

(5)

Me_2AlCl	65%	9: 1
$BF_3 \cdot OEt_2$	58%	19: 1
MABR	85%	1:32

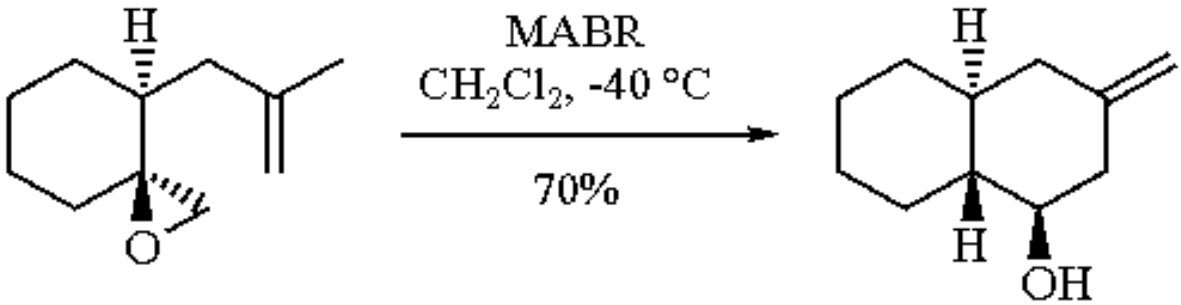

(6)

α-Primary Alkylation of Ketones.

α-Primary alkylation of carbonyl compounds via the corresponding enol silyl ethers with primary alkyl triflates has been realized in the presence of MABR under mild conditions (eq 7).[11] Here, only monoalkylation products are obtained.

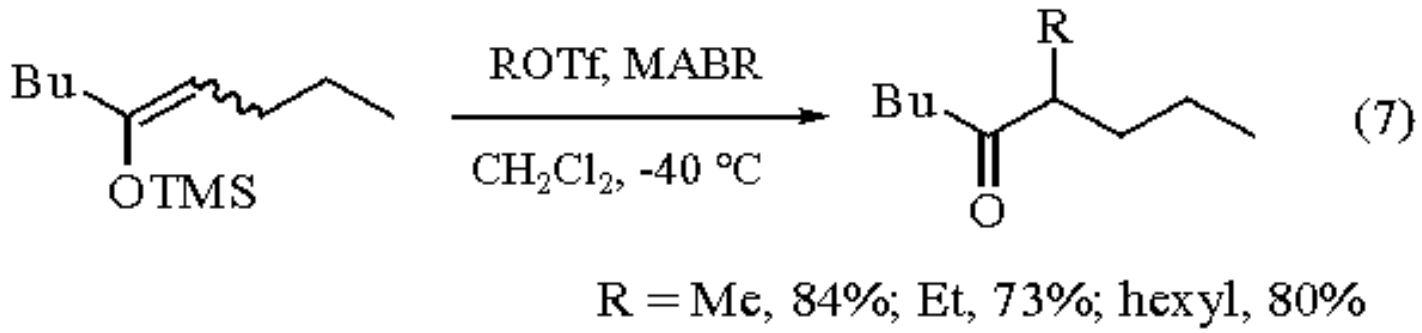

Oxetanone Synthesis.

Reaction of ***Trimethylsilylketene*** and aldehydes with MABR affords *cis*-2-oxetanones with high selectivity (eq 8).[12] In the case of aromatic and α,β-unsaturated aldehydes, (*Z*)-2-alkenoic acids are directly obtained via the ring opening of the intermediary *cis*-2-oxetanones (eq 9).

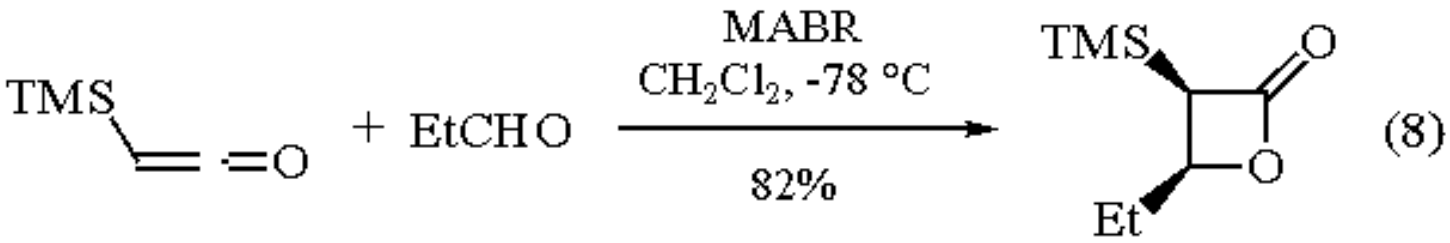

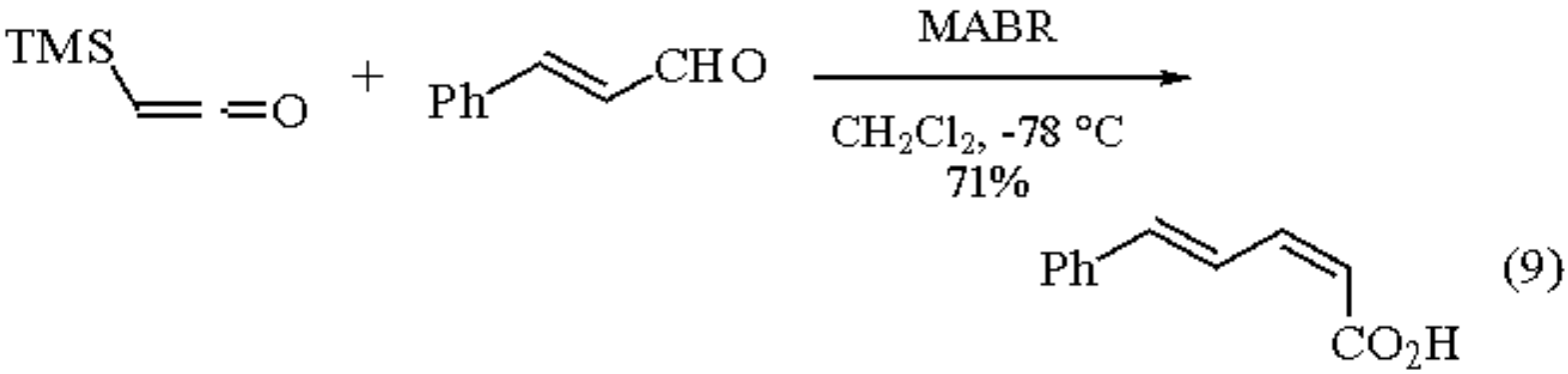

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Keiji Maruoka & Hisashi Yamamoto

Nagoya University, Japan

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Methylaluminum Bis(2,6-di-*t*-butyl-4-methylphenoxide)

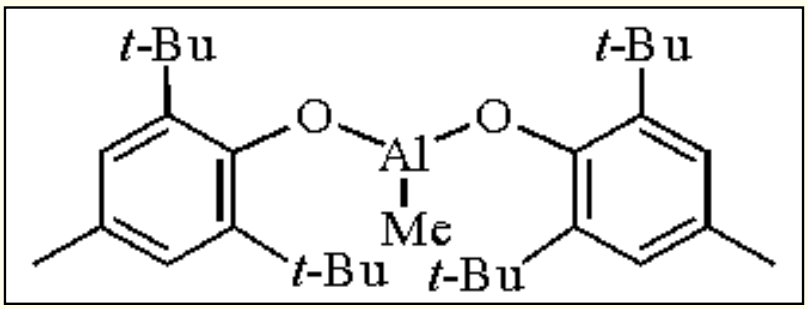

[65260-44-8] · $C_{31}H_{49}AlO_2$ · Methylaluminum Bis(2,6-di-*t*-butyl-4-methylphenoxide) · (MW 480.78)

(designer Lewis acid for amphiphilic alkylation,[1,4,5] amphiphilic reduction,[6] conjugate addition,[7-10] discrimination of two different substrates (ethers and ketones),[12-14] strereocontrolled cycloadditions,[15-17] and polymerization[18])

Alternate Name: MAD.

Physical Data: a crystal structure of a MAD-benzophenone complex has been reported.[3]

Solubility: sol CH_2Cl_2, toluene, hexane.

Form Supplied in: prepared from commercially available reagents and used in situ.

Preparative Method: prepared by reaction of a 1-2 M hexane solution of ***Trimethylaluminum*** with 2 equiv of 2,6-di-*t*-butyl-4-methylphenol in toluene or CH_2Cl_2 at rt for 1 h.[1,2]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Amphiphilic Alkylation.

The exceptionally bulky, oxygenophilic organoaluminum reagent methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) has been developed for the stereoselective activation of carbonyl groups. Combination of MAD with Grignard reagents or organolithium reagents generates the amphiphilic alkylation systems, where substituted cyclohexanones and cyclopentanones afford equatorial alcohols with high stereoselectivity (eqs 1-3).[1] The X-ray

crystallographic determination of a benzophenone-MAD complex shows that the ketone coordinates such that the aluminum is in the nodal plane of the C=O π-bond.[3]

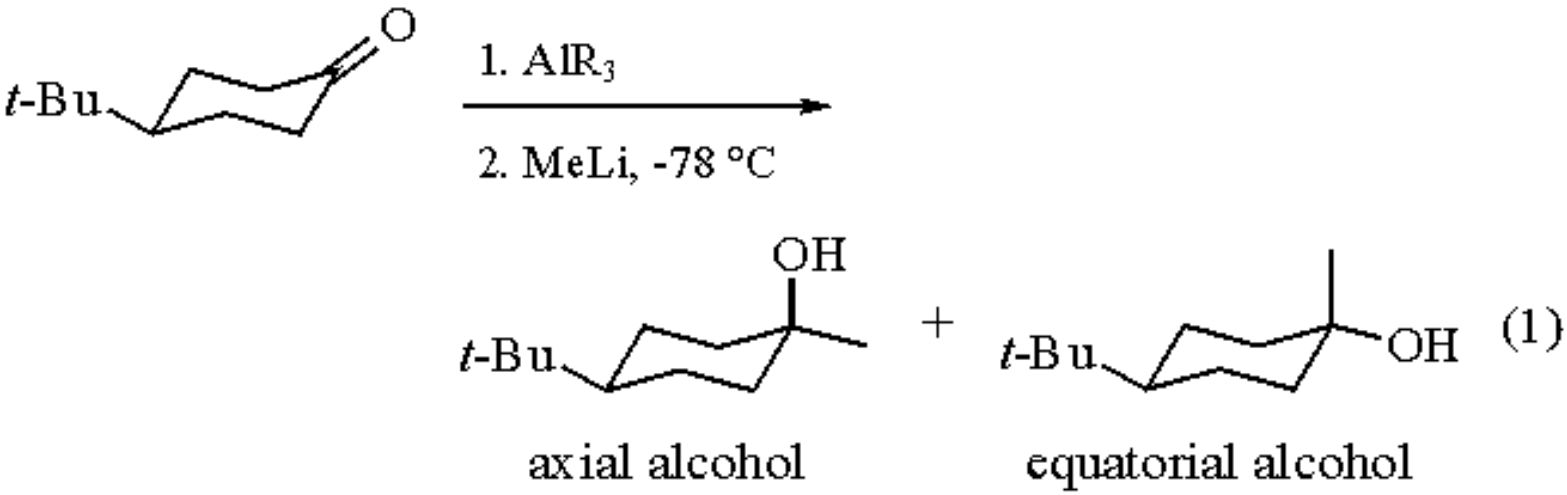

Al reagent	none		79:21
	Me_3Al		76:24
	i-Bu_3Al		64:36
	Me_2AlOPh		72:28
	MAD	84%	1:99

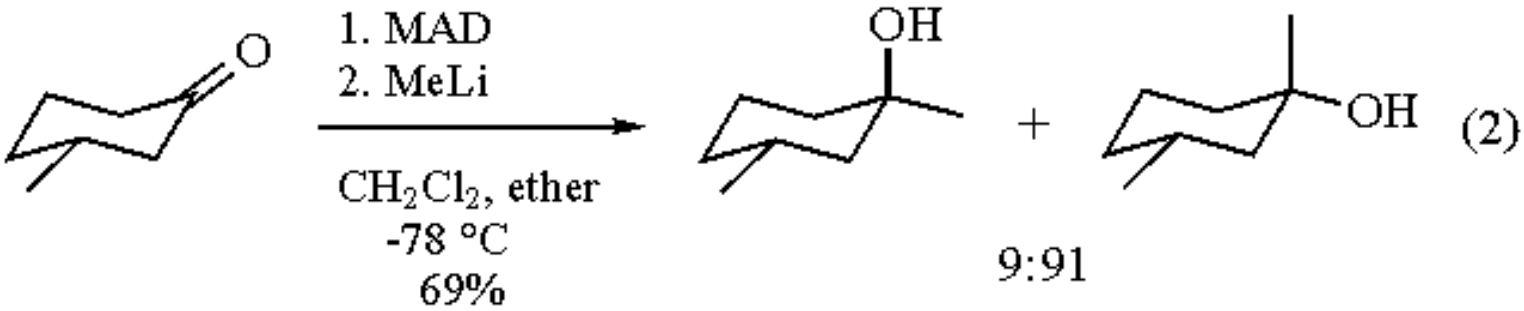

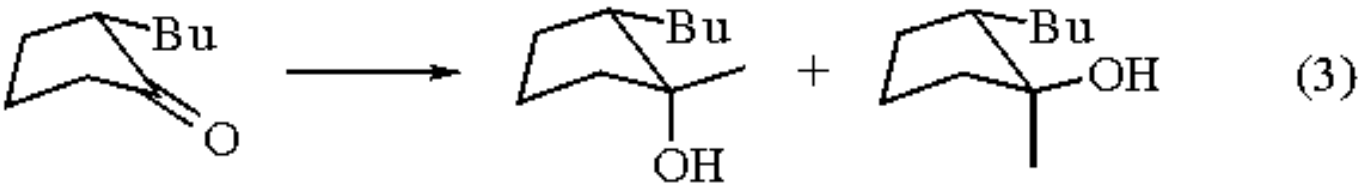

MeLi	77%	75:25
MAD, MeLi	82%	1:99

This methodology has been used in the final step of the stereocontrolled synthesis of a defense substance of the termite *Nastitermes princeps*, a secotrinervitane diterpene. Whereas ***Methyllithium*** adds exclusively to the β-face of the ketone to furnish the α-alcohol as the sole isolable product, attack of methyllithium occurs preferably at the α-face of the carbonyl in the amphiphilic alkylation system using MAD/MeLi to give the desired substance as a major

product (eq 4).[4]

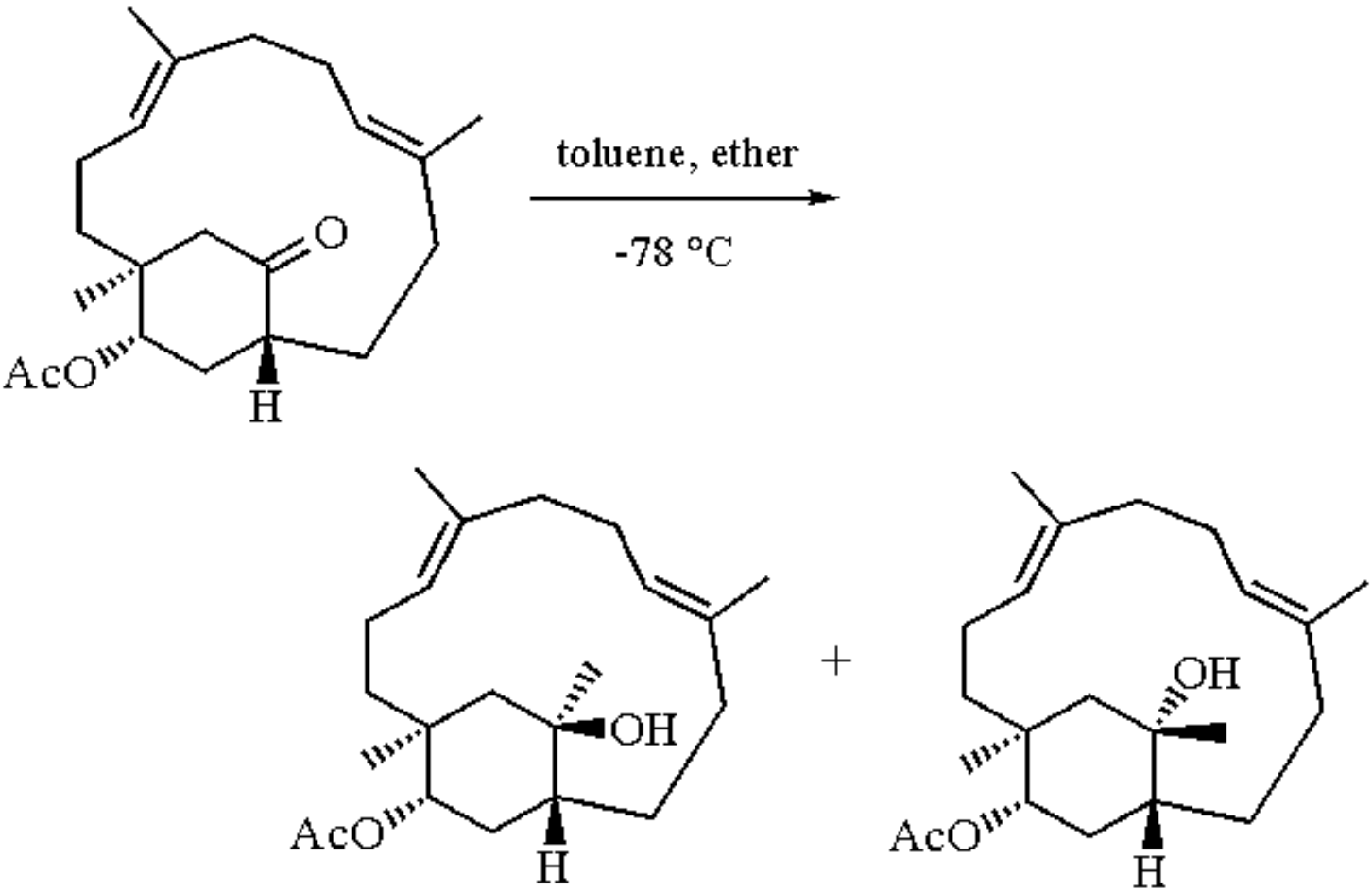

(4)

MeLi	91%	0:100
MAD, MeLi	30%	75:25

Alkylation of α-substituted aldehydes with the MAD/RMgX system provides *anti*-alcohols preferentially (eq 5).[1] This amphiphilic system allows the chemoselective carbonyl alkylation and reduction of aldehydes in the presence of ketones (eq 6).[5]

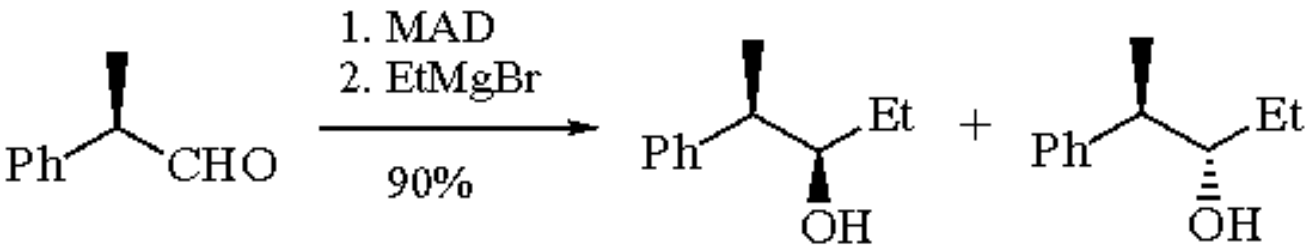

(5)

25:75

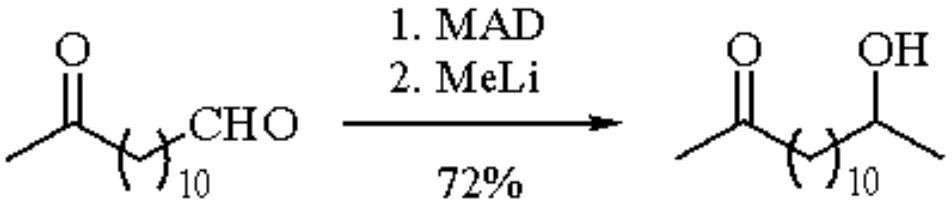

(6)

Amphiphilic Reduction.

In contrast to the facile MAD-mediated alkylation of cyclic ketones with primary organolithiums or Grignard reagents, both alkylation and reduction take place with *s*-alkylmagnesium halides. When a bulky nucleophile such as *t*-BuMgCl is employed for the amphiphilic reaction system, substituted cyclohexanones afford equatorial alcohols exclusively as reduction products with high selectivity (eq 7).[6]

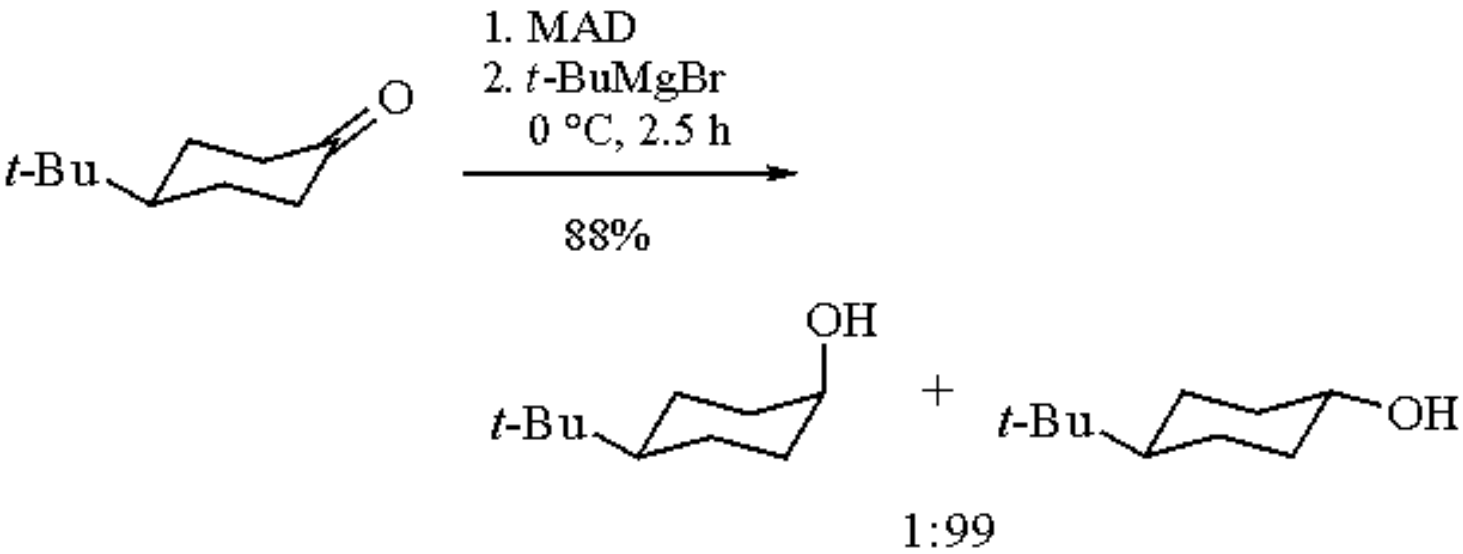

(7)

Conjugate Addition.

The MAD/RLi system can also be used for conjugate alkylation and reduction of α,β-unsaturated ketones with organolithiums and ***Lithium n-Butyl(diisobutyl)aluminum Hydride***, respectively (eqs 8 and 9).[7,8] This method is particularly effective for the conjugate alkylation and reduction of quinone monoacetals and their derivatives (eqs 10 and 11).[9,10]

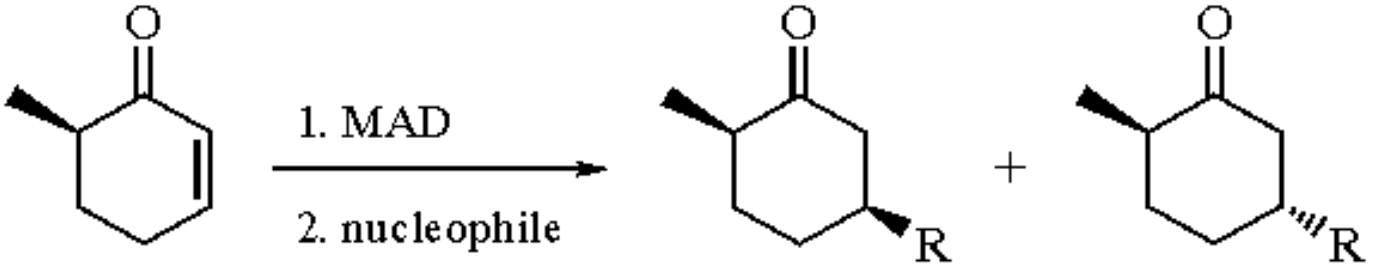

(8)

MeLi	68%	29:71
BuLi	59%	17:83
PhLi	71%	33:67
$H_2C{=}C(O\text{-}t\text{-}Bu)OLi$	87%	10:90

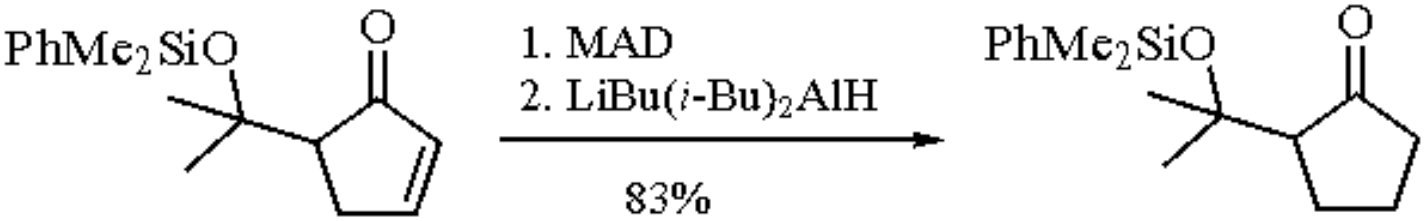

(9)

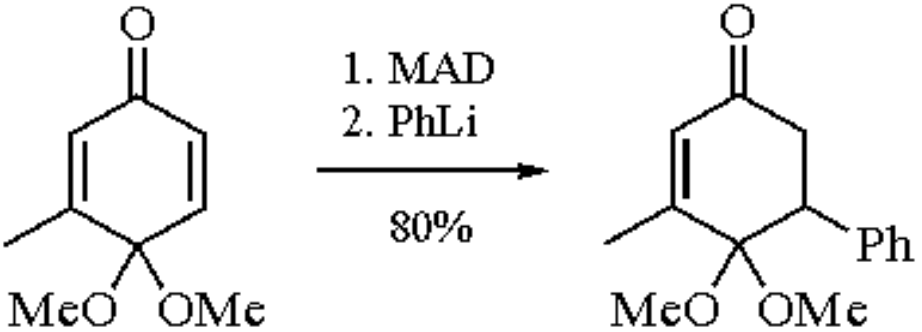

(10)

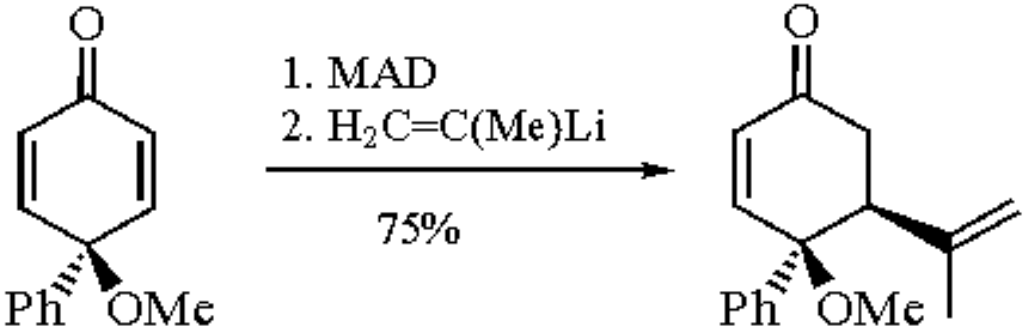

(11)

Discrimination of Two Different Oxygen-Containing Substrates.

MAD can be used as a Lewis acidic receptor for the discrimination of two different oxygen-containing substrates based on selective Lewis acid-base complex formation.[11] Indeed, in an equimolar mixture of methyl and ethyl ether

substrates, MAD coordinates to the methyl ether exclusively (eq 12). This chemistry has been applied to a new type of coordination chromatography using polymeric, bulky organoaluminum compounds as a stationary phase that allows a surprisingly clean separation of structurally similar methyl ethers from ethyl ethers.[12,13]

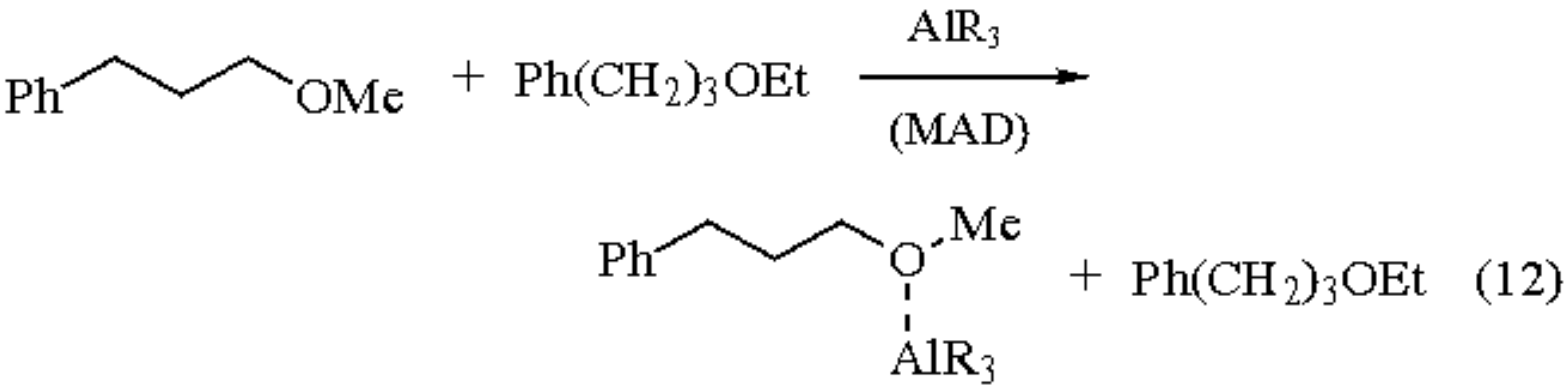

Selective reduction of sterically more hindered ketones has been effected with the MAD/***Diisobutylaluminum Hydride*** system by selective complexation of the less hindered ketones with MAD and subsequent attack of *i*-Bu_2AlH at the free, more hindered ketones (eq 13).[14]

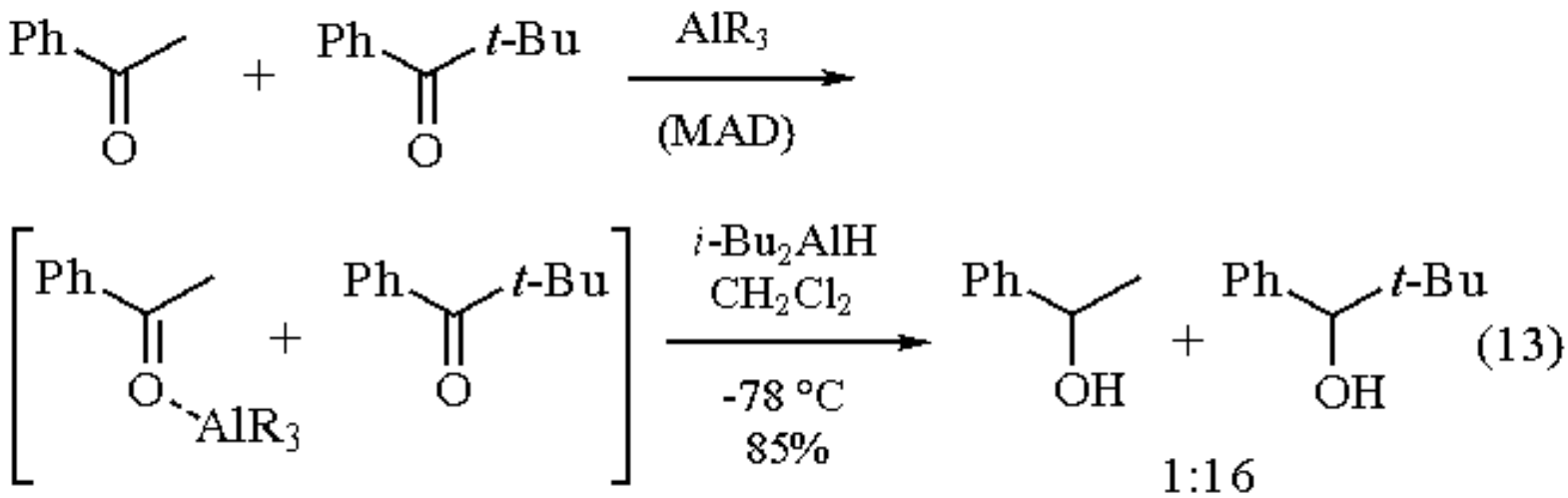

The selective binding behavior of Lewis acidic MAD for two different ester groups allows the regio- and stereocontrolled Diels-Alder reaction of unsymmetrical fumarates (eq 14).[15]

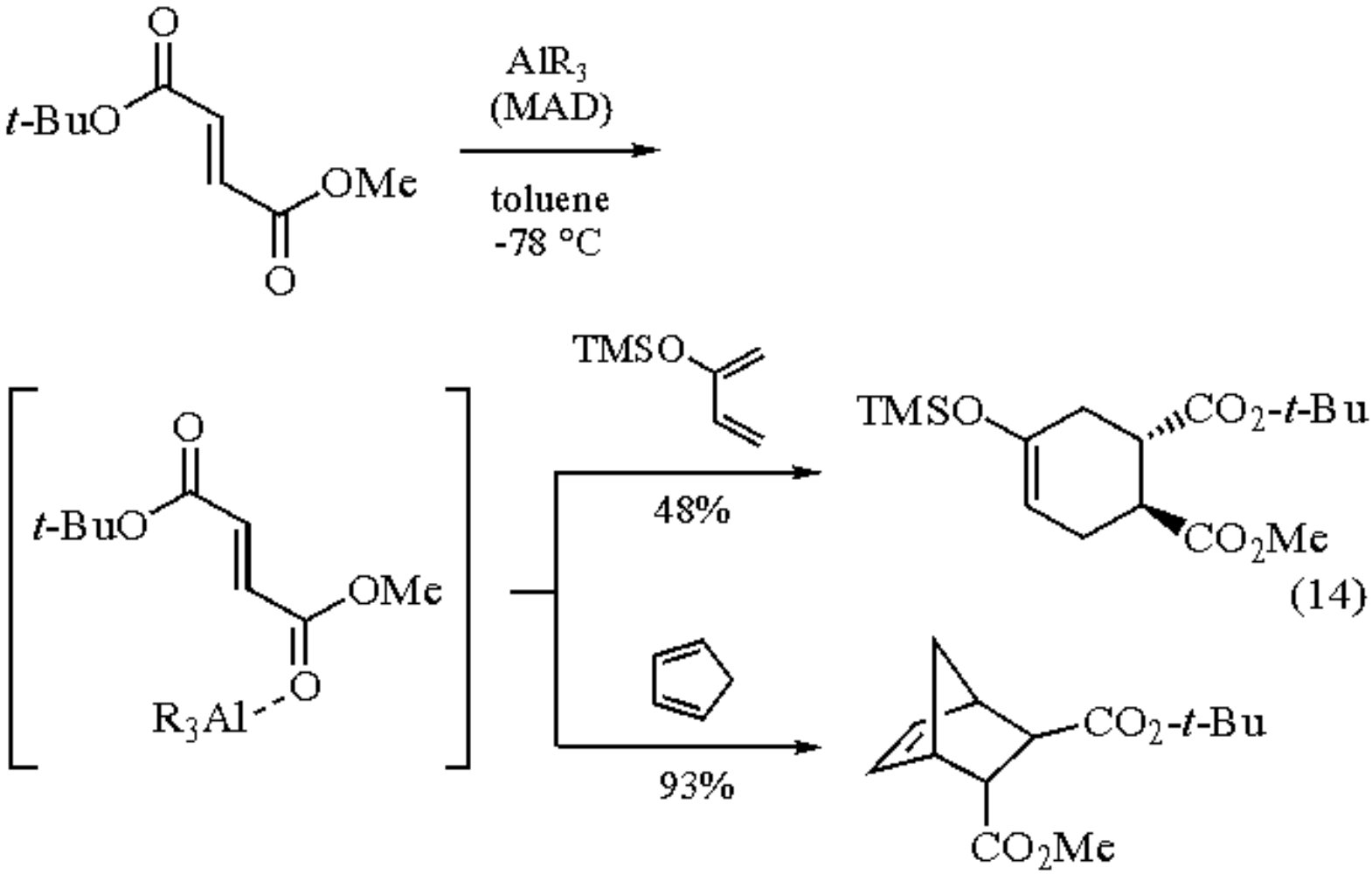

(14)

Cycloadditions.

The steric effects of MAD on stereoselectivity in the Diels-Alder reactions of cyclic dienes and α,β-unsaturated aldehydes has been studied (eq 15).[16] MAD promotes very mild and highly stereocontrolled [2 + 4] cycloaddition between a pyrone sulfone and an enantiomerically pure vinyl ether. After 12 h at -45 °C in 4:1 toluene/CH_2Cl_2 with 0.5 equiv of MAD and 2.5 equiv of the vinyl ether, cycloadducts are isolated in 93% yield as a 98:2 ratio of the *endo* diastereomers (eq 16).[17]

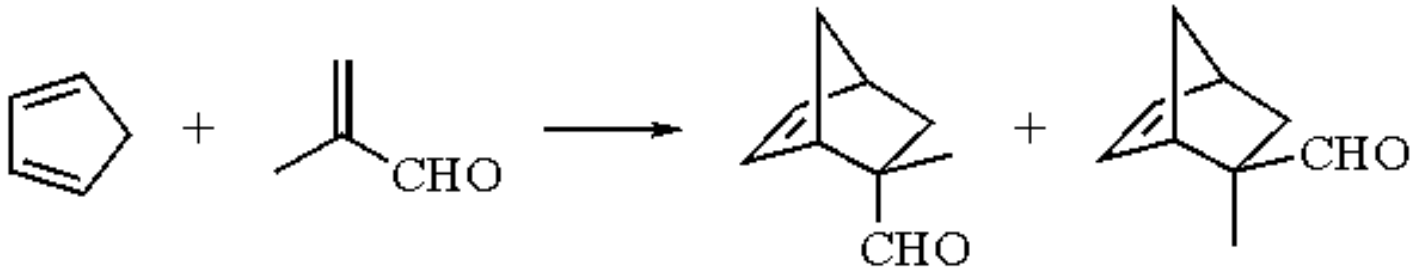

(15)

heat		1:5
Me_3Al	64%	1:15
MAD	76%	1:48

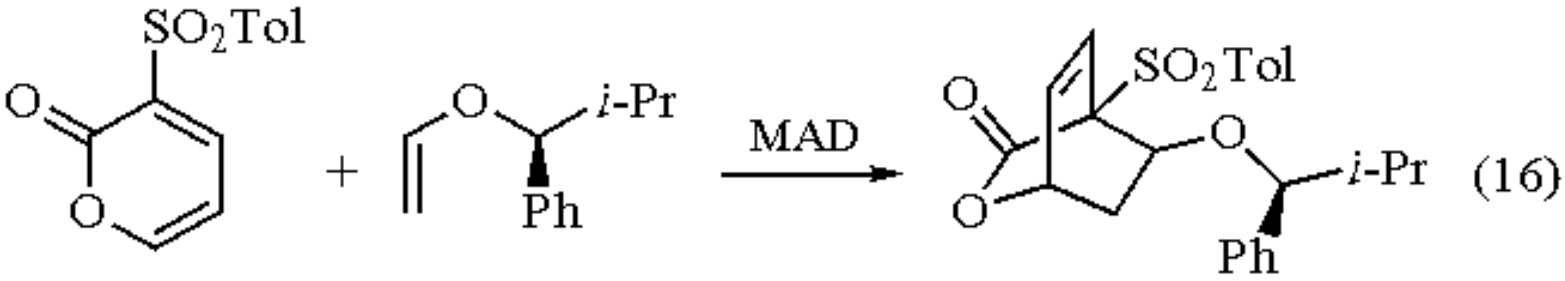

Polymerization.

A novel, Lewis acid-induced Michael addition of an enolate complex to an α,β-unsaturated ester has been developed, where the unfavorable reaction between the nucleophile and Lewis acid is sterically suppressed.[18] For example, the addition polymerization of methyl methacrylate (MMA) via an enolate complex of aluminum tetraphenylporphyrin (**1**) as the nucleophilic growing species has been effected in the presence of MAD, producing polymer molecules cleanly with a narrow molecular weight distribution (eq 17).

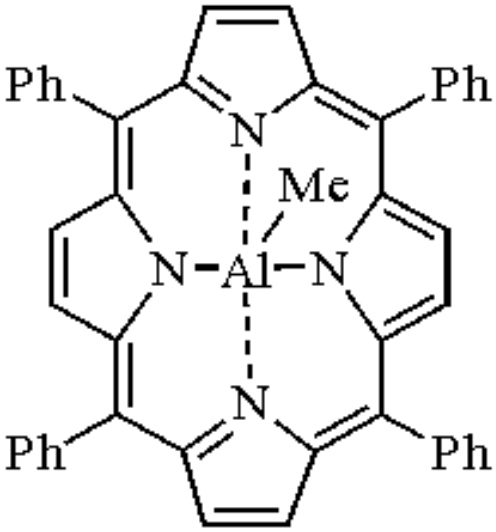

(1) (TPP)AlMe

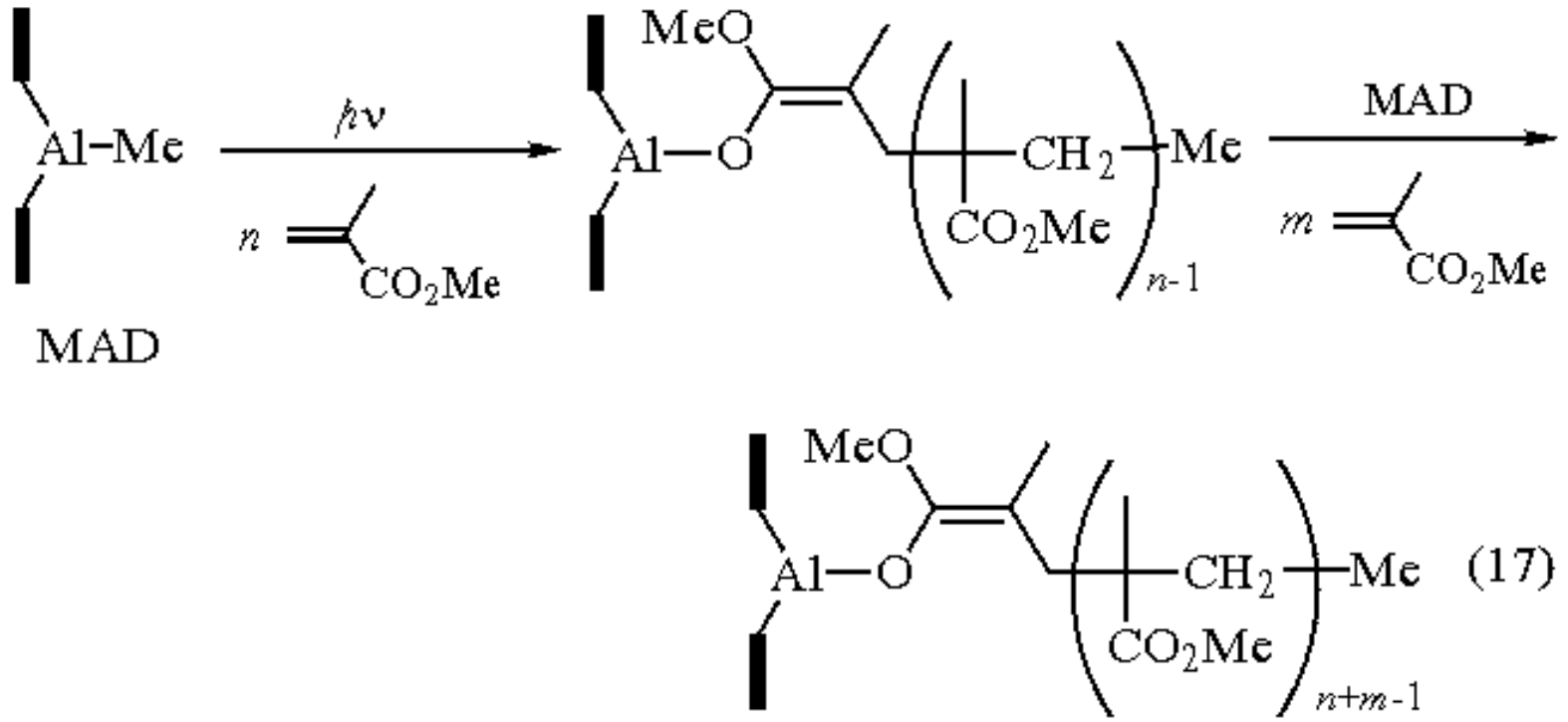

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18. (a) Kuroki, M.; Watanabe, T.; Aida, T.; Inoue, S. *JACS* **1991**, *113*, 5903. (b) Adachi, T.; Sugimoto, H.; Aida, T.; Inoue, S. *Macromolecules* **1992**, *25*, 2280. (c) Adachi, T.; Sugimoto, H.; Aida, T.; Inoue, S. *Macromolecules* **1993**, *26*, 1238.

Methylaluminum Bis(2,6-di-*t*-butylphenoxide)

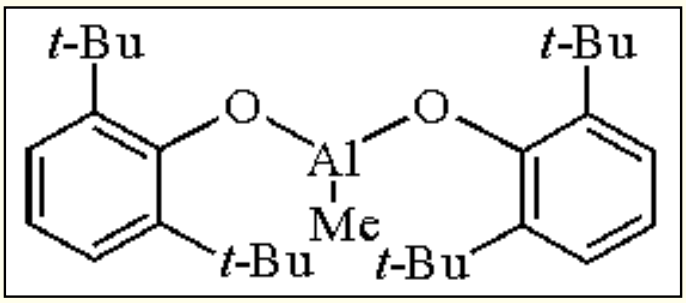

[128353-30-0] · $C_{29}H_{45}AlO_2$ · Methylaluminum Bis(2,6-di-*t*-butylphenoxide) · (MW 452.72)

(designer Lewis acid for amphiphilic alkylation and conjugate addition)

Solubility: sol CH_2Cl_2, toluene, hexane.

Form Supplied in: prepared from commercially available reagents and used in situ.

Preparative Method: prepared by reaction of a 1-2 M hexane solution of ***Trimethylaluminum*** with 2 equiv of 2,6-di-*t*-butylphenol in toluene or CH_2Cl_2 at rt for 1 h in a similar manner to that described in the preparation of MAD or MAT.[1]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Amphiphilic Alkylation.

The exceptionally bulky, oxygenophilic organoaluminum reagent methylaluminum bis(2,6-di-*t*-butylphenoxide), like ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD) and ***Methylaluminum Bis(2,4,6-tri-t-butylphenoxide)*** (MAT), has been used for stereoselective activation of carbonyl groups. Combination of this modified organoaluminum compound, as a bulky Lewis acid, with Grignard reagents or organolithium reagents generates the amphiphilic alkylation system, in which substituted cyclohexanones afford equatorial alcohols with high selectivity (eq 1).[2] This approach is quite useful in the stereoselective alkylation of steroidal ketones. Thus reaction of cholestan-3-one with ***Methyllithium*** gives predominantly 3β-methylcholestan-3α-ol (axial alcohol), whereas the amphiphilic methylation of the ketone gives 3α-methylcholestan-3β-ol (equatorial alcohol) exclusively (eq 2).[1,2]

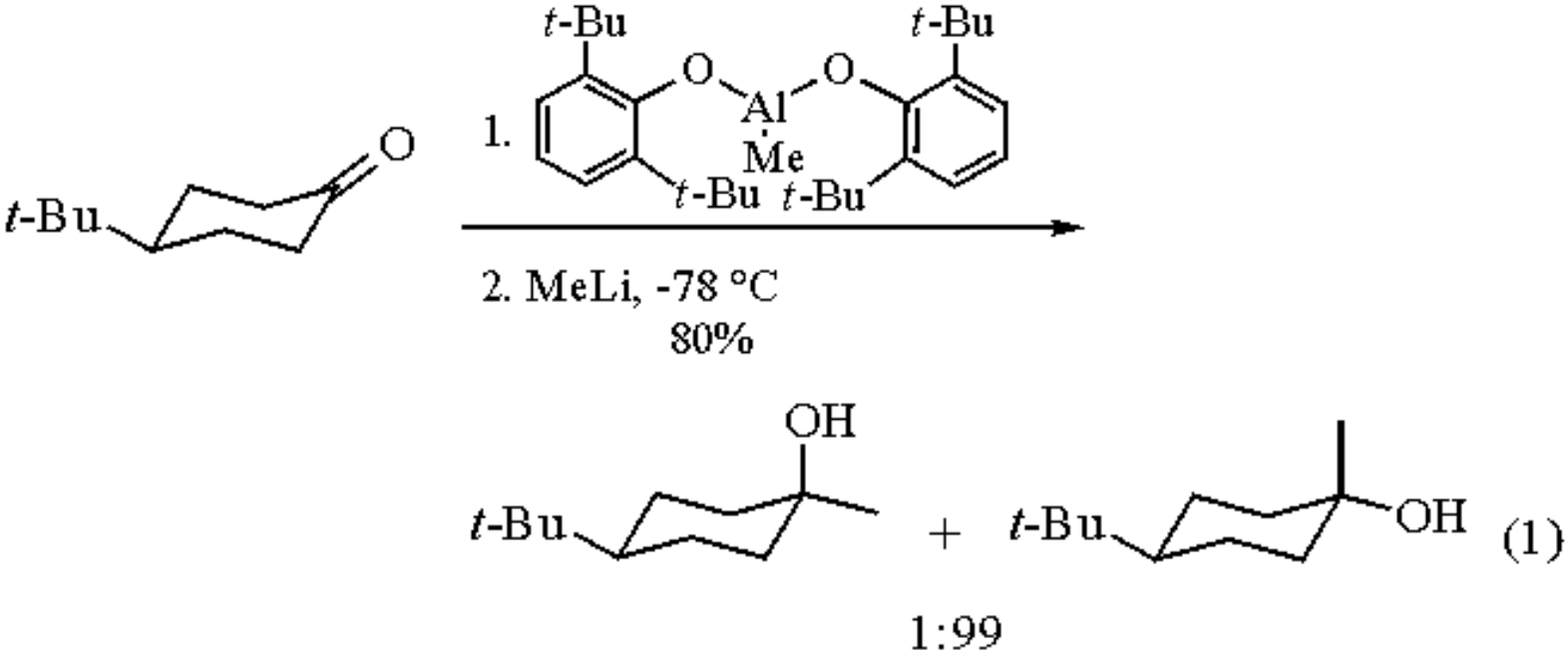
t-Bu
t-Bu
O
O
Al
Me
t-Bu t-Bu
1.
O
t-Bu
2. MeLi, -78 °C
80%
OH
t-Bu
+
t-Bu
OH
(1)
1:99

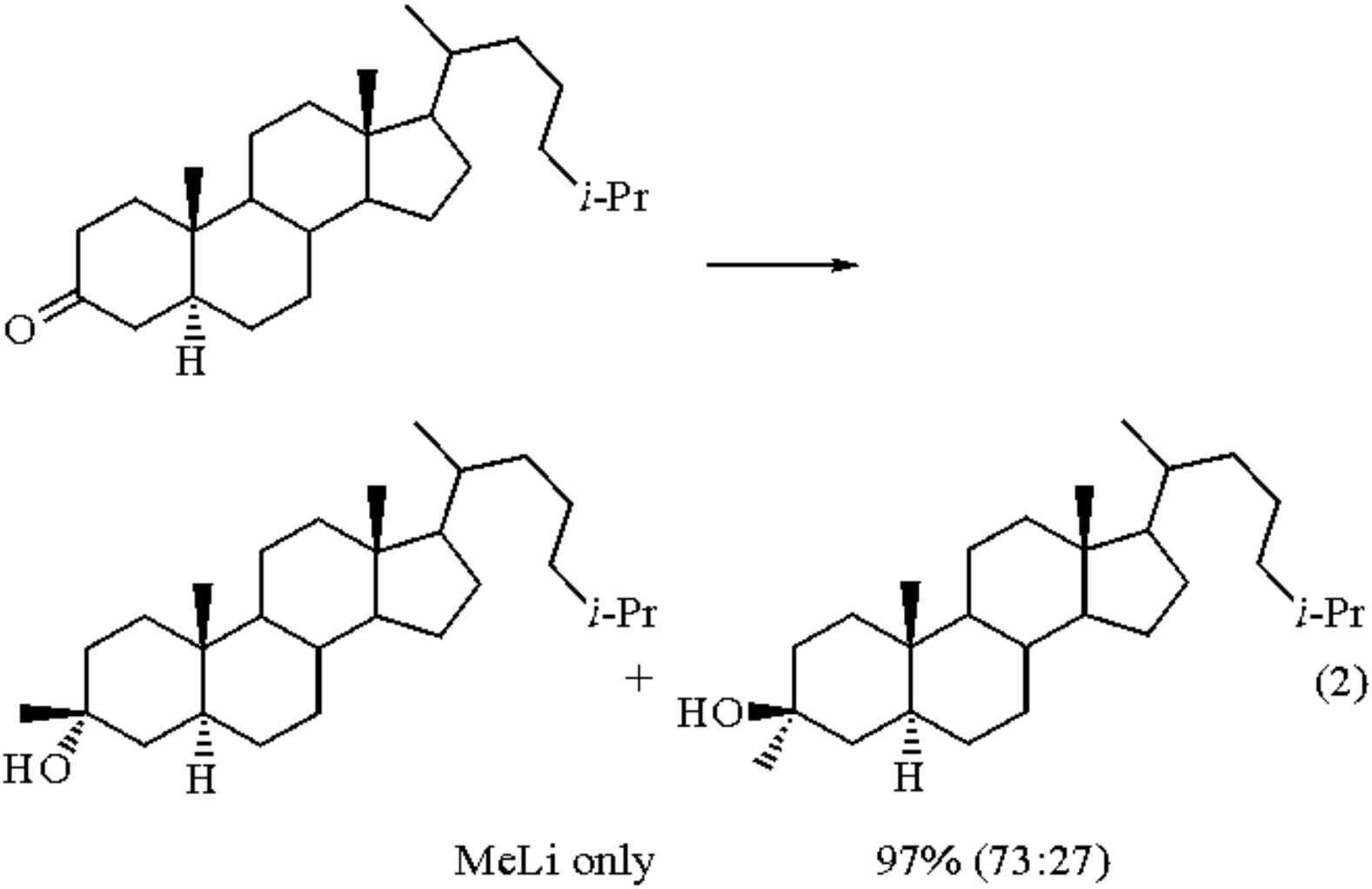
i-Pr
O
H
i-Pr
HO
H
+
i-Pr
HO
H
(2)
MeLi only
97% (73:27)

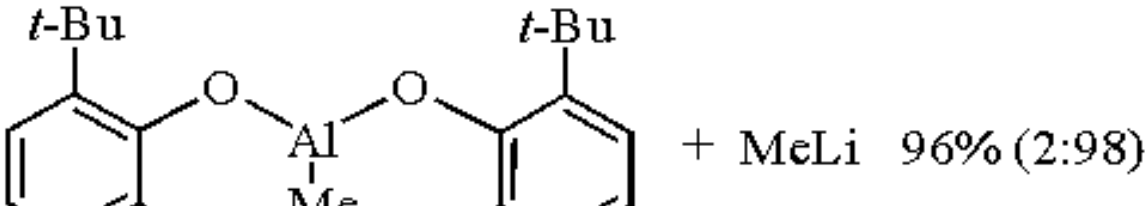
t-Bu
t-Bu
O
O
Al
+ MeLi 96% (2:98)

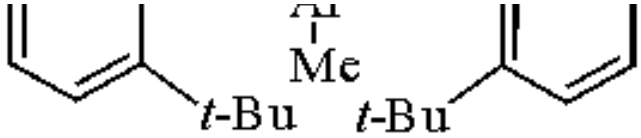

+ MeLi 96% (2:98)

The amphiphilic alkylation of α-substituted aldehydes using the title aluminum reagent and Grignard reagents affords *anti*-alcohols preferentially (eq 3), as also observed with MAD/RMgX or MAT/RMgX.[2]

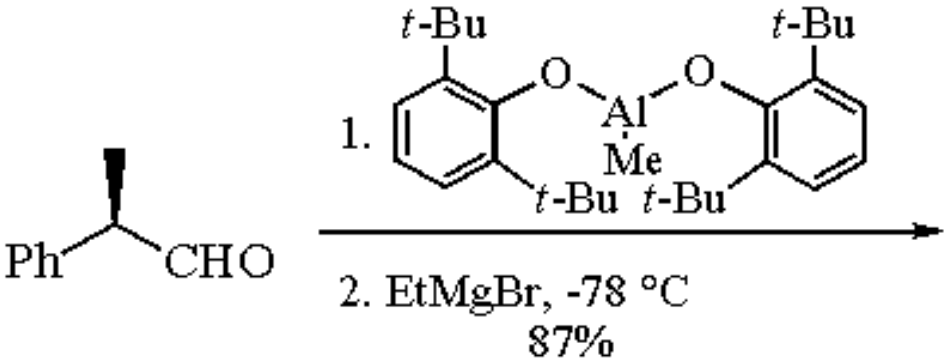

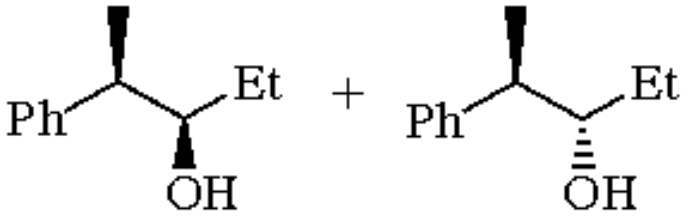

(3)

28:72

Conjugate Addition.

The title reagent has also been used for conjugate alkylation and reduction of α,β-unsaturated ketones with organolithiums and ***Lithium n-Butyl(diisobutyl)aluminum Hydride***, respectively (eqs 4 and 5).[3] The 1,4 vs. 1,2 selectivity is not much different from that observed with MAD or MAT.[4]

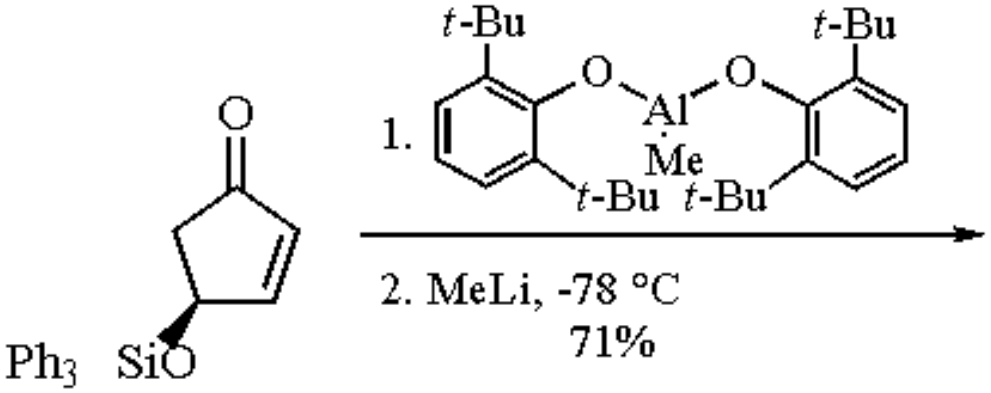

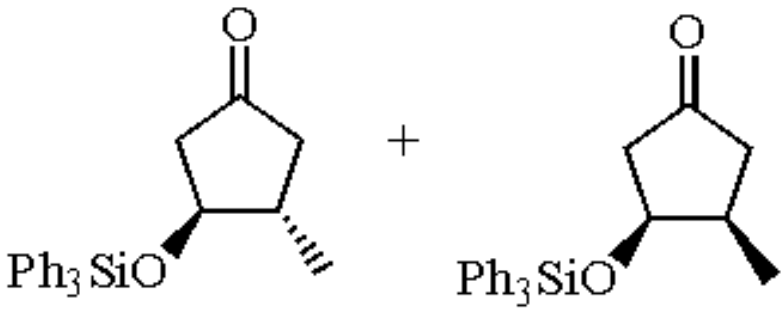

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60:40

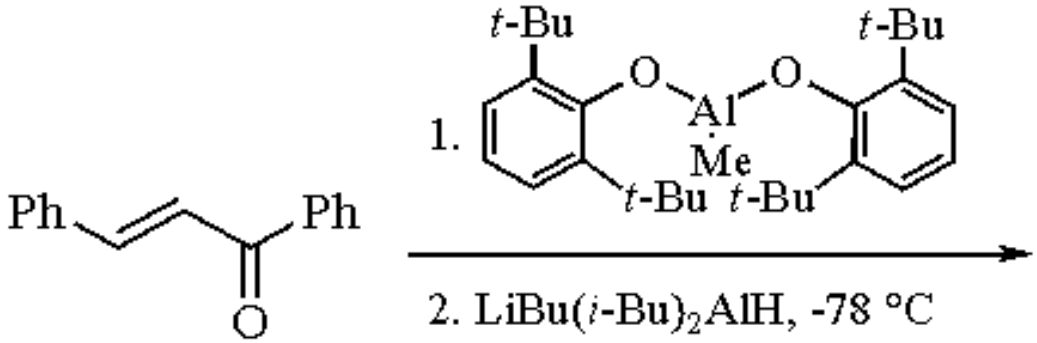

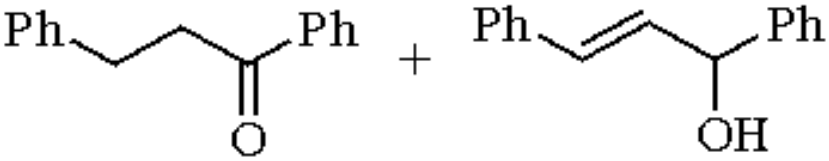

(5)

58% 25%

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1. (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *JACS* **1985**, *107*, 4573. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *JACS* **1988**, *110*, 3588.
2. Itoh, T.; Maruoka, K.; Yamamoto, H., unpublished results.
3. Nonoshita, K.; Maruoka, K.; Yamamoto, H., unpublished results.
4. (a) Maruoka, K.; Nonoshita, K.; Yamamoto, H. *TL* **1987**, *28*, 5723. (b) Nonoshita, K.; Maruoka, K.; Yamamoto, H. *BCJ* **1988**, *61*, 2241.

Methylaluminum Bis(2,6-diphenylphenoxide)

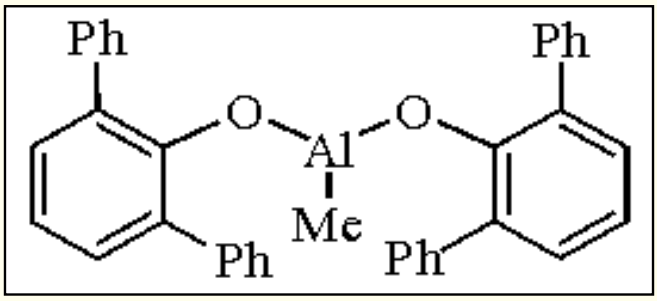

[118496-00-7] · $C_{37}H_{29}AlO_2$ · Methylaluminum Bis(2,6-diphenylphenoxide) · (MW 532.64)

(designer Lewis acid for Claisen rearrangements,[1,3] aza-Cope rearrangements,[4] cycloadditions,[5] epoxide rearrangement,[6] stabilization of reactive aldehydes,[7] and aldehyde recognition[8,9])

Alternate Name: MAPH.

Solubility: sol toluene, CH_2Cl_2.

Form Supplied in: prepared from commercially available reagents and used in situ.

Preparative Method: treatment of 2,6-diphenylphenol (2 equiv) in dry CH_2Cl_2 with a 1 M hexane solution of ***Trimethylaluminum*** at 25 °C for 1 h.[1]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Claisen Rearrangement.

The modified organoaluminum reagent MAPH was developed for effecting the stereoselective Claisen rearrangement of allylic vinyl ethers.[1] Thus reaction of 1-isobutyl-2-propenyl vinyl ether with MAPH in toluene at -20 °C affords, after reduction of the Claisen products with ***Sodium Borohydride***, (*E*)-7-methyl-4-octen-1-ol with high stereoselectivity (eq 1), superior to that observed in the thermal rearrangement (*E*/*Z* ratio = 92:8). The Claisen rearrangement of the optically active substrate with MAPH reveals a chairlike transition-state, with the isobutyl substituent equatorial.[2]

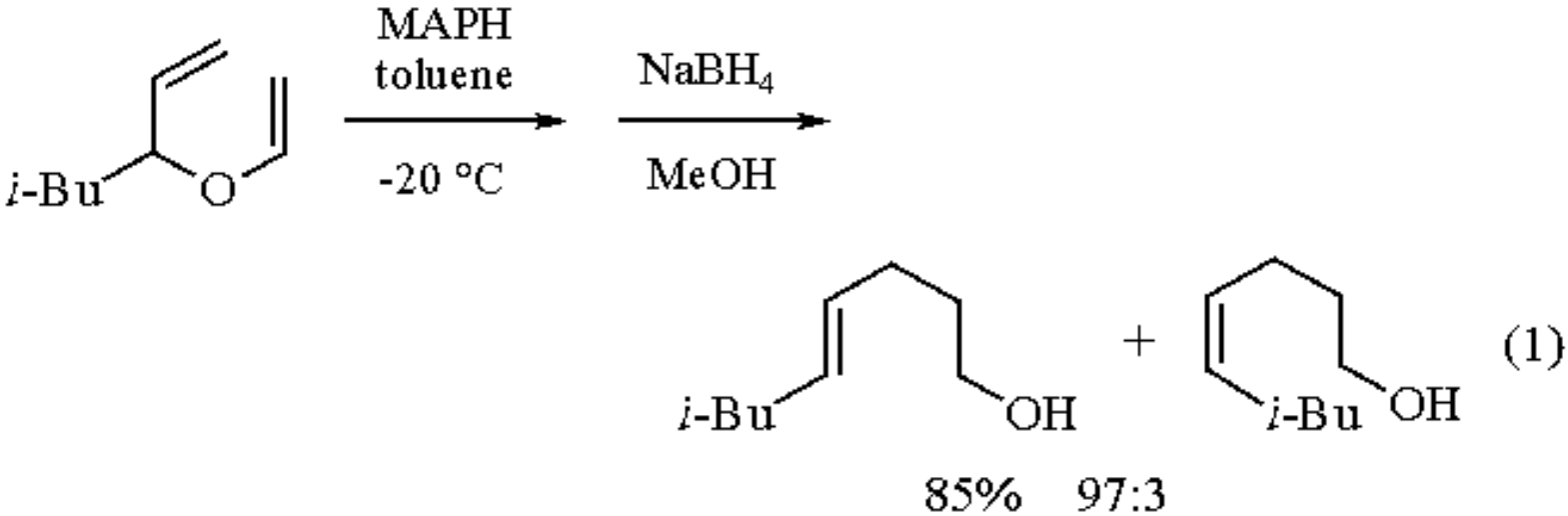

The organoaluminum-promoted Claisen rearrangement of bisallylic vinyl ethers exhibits unprecedented regiochemical control not observed in the thermal Claisen rearrangement (eq 2).[3]

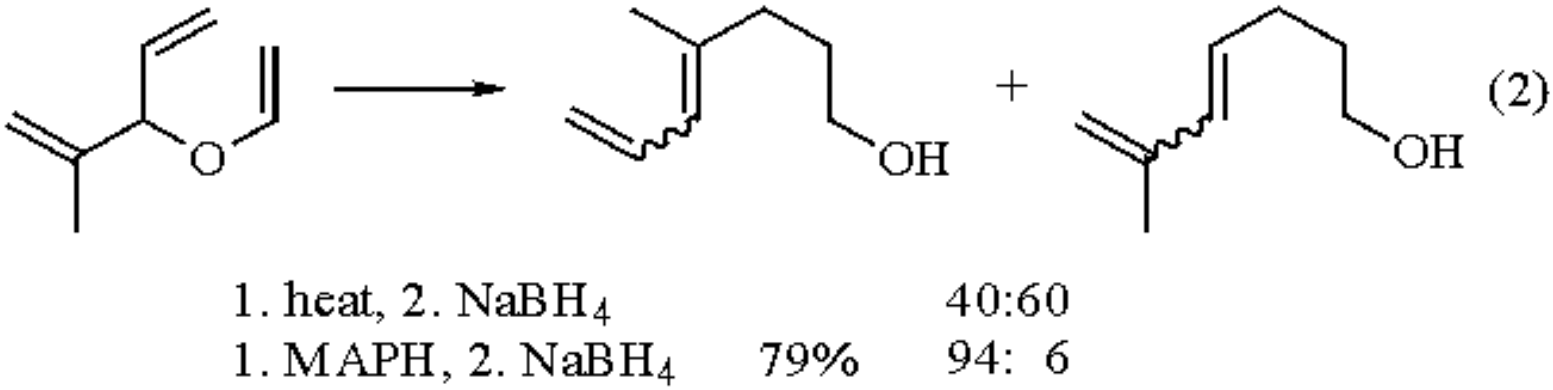

Aza-Cope Rearrangement.

The advantage of MAPH over other Lewis acids is exemplified by the Lewis-acid promoted 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamine substrates.[4] Here, MAPH shows highest diastereoselectivity in the C-C bond forming process (eq 3).

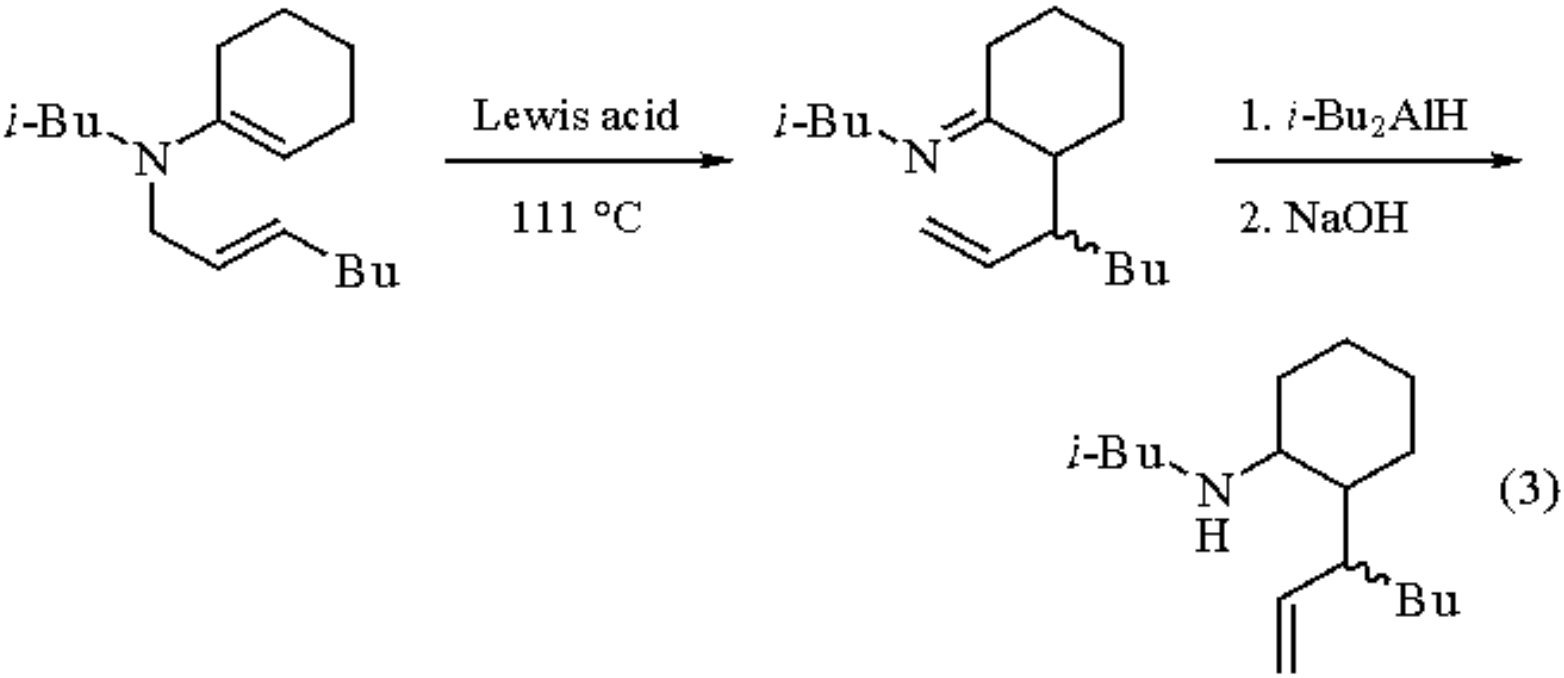

$TiCl_4$	72%	55:45
Me_3Al	94%	67:33
MAPH	73%	77:23

Tandem [4 + 2]/[3 + 2] Cycloaddition.

The [4 + 2] cycloaddition of a nitro alkene with a chiral (+)-camphor vinyl ether, promoted by MAPH, followed in tandem by a [3 + 2] cycloaddition of the intermediate nitronate with an intramolecularly tethered electron-deficient alkene, allows for the construction of five stereogenic centers with excellent stereoselectivity. The stereochemistry is opposite to that formed with a titanium reagent (eq 4).[5]

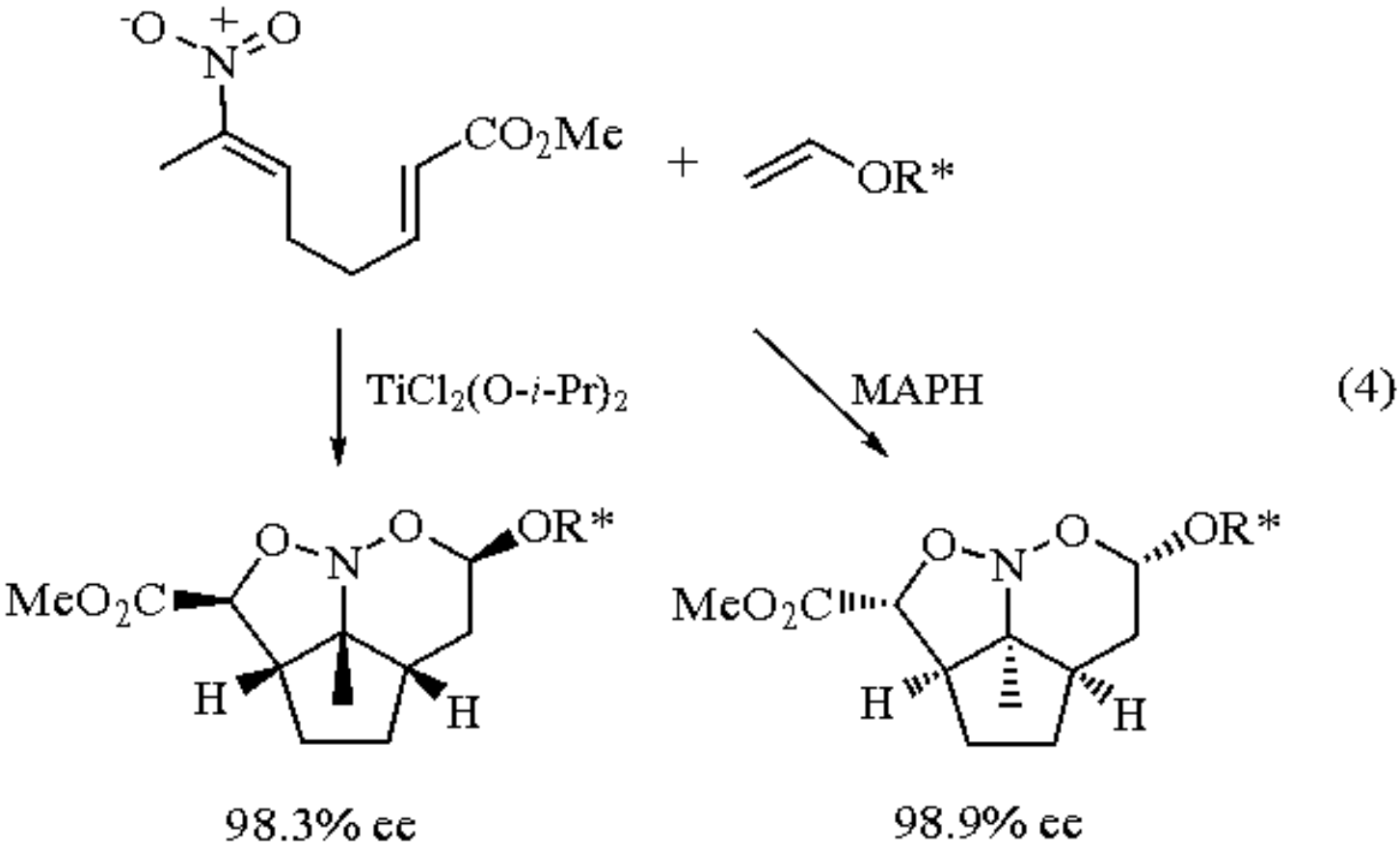

Catalytic Rearrangement of Epoxides.

MAPH mixed with silanized silica gel can be utilized as a stationary phase for immobilized organoaluminum columns. These can be used as a workup-free reactor for the catalytic rearrangement of various epoxides to carbonyl compounds.[6]

Stabilization of Reactive Aldehydes.

Reactive aldehydes such as formaldehyde and α-chloro aldehydes can be successfully generated by treatment of readily available trioxane and α-chloroacetaldehyde trimers, respectively, with MAPH and stabilized as their 1:1 coordination complexes with MAPH. The resulting CH_2=O.MAPH complex reacts with a variety of alkenes to furnish ene reaction products with excellent regio- and stereoselectivities (eq 5).[7] In addition, these complexes can be used as stable sources of formaldehyde and α-chloroacetaldehyde, respectively, for use in nucleophilic addition reactions with various carbanions (organometallics, enolates, etc.) (eq 6).[8]

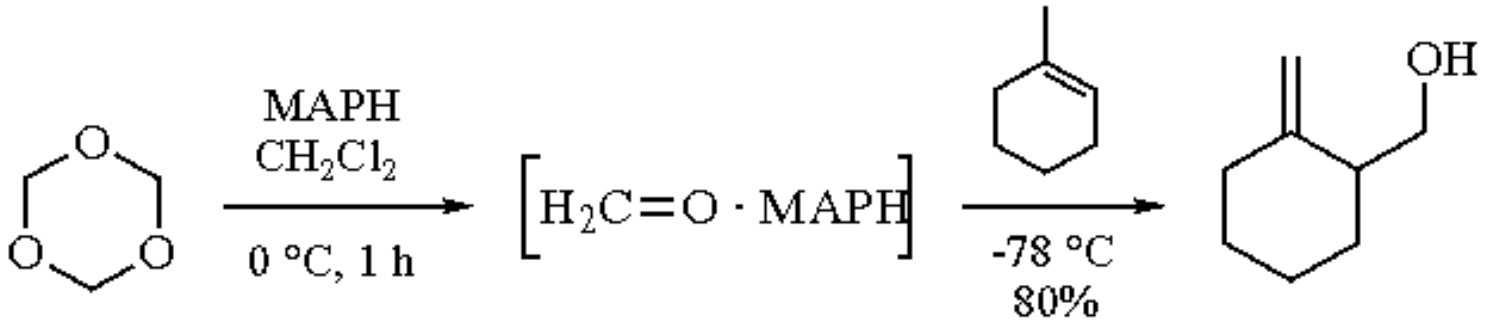

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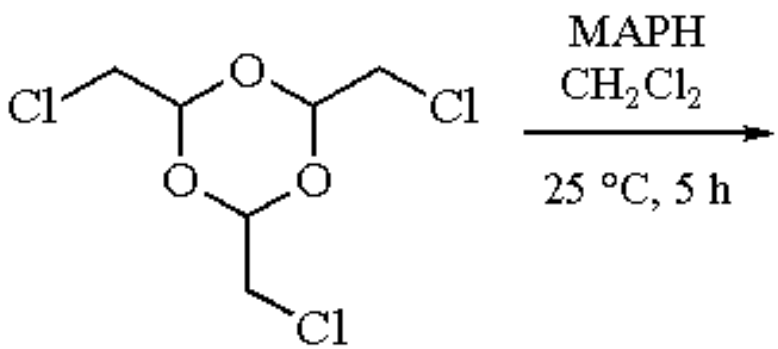

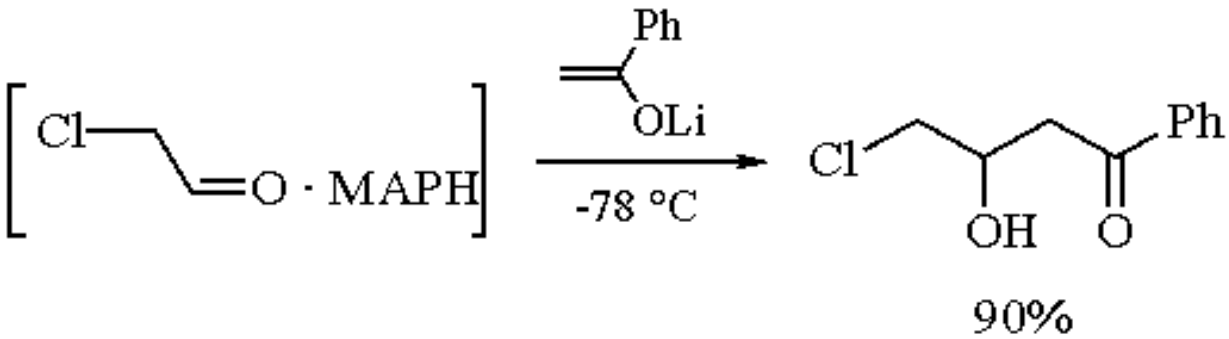

(6)

Chemoselective Functionalization.

The high recognition and stabilization ability of MAPH enables the chemoselective alkylation of sterically more hindered aldehydes using alkyllithiums as the nucleophile (eq 7).[9]

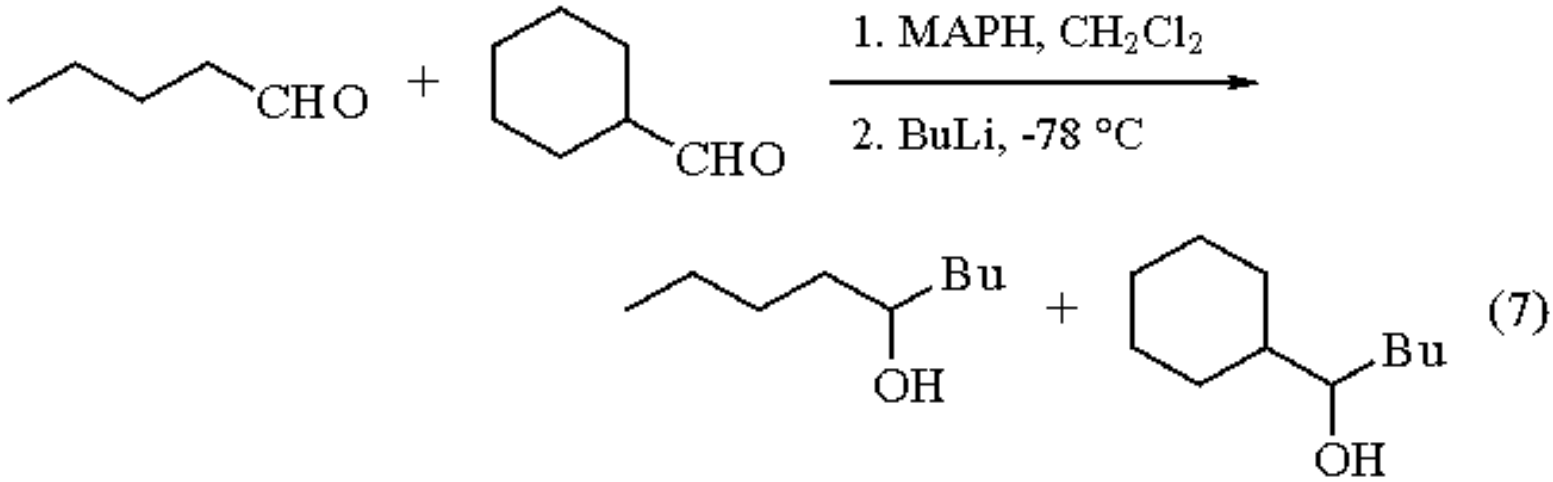

MAPH (1 equiv), BuLi (1 equiv)	76%	1: 6.5
MAPH (2 equiv), BuLi (1 equiv)	45%	1:14

---

1. (a) Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *JACS* **1988**, *110*, 7922. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *JACS* **1990**, *112*, 316.
2. Nonoshita, K.; Maruoka, K.; Yamamoto, H. *BCJ* **1992**, *65*, 541.
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5. (a) Denmark, S. E.; Schnute, M. E. *JOC* **1991**, *56*, 6738. (b) Denmark, S. E.; Senanayake, C. B. W. *JOC* **1993**, *58*, 1853. (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *JOC* **1993**, *58*, 1859.
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7. (a) Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H. *JACS* **1990**, *112*, 7422.
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Methylaluminum Bis(2,4,6-tri-*t*-butylphenoxide)

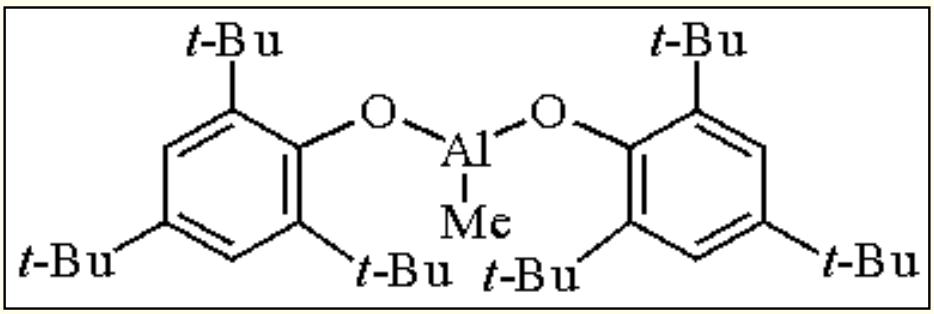

[65260-46-0] · $C_{37}H_{61}AlO_2$ · Methylaluminum Bis(2,4,6-tri-*t*-butylphenoxide) · (MW 564.96)

(designer Lewis acid for amphiphilic alkylation,[1] conjugate addition,[2,3] and polymerization[4])

Alternate Name: MAT.

Solubility: sol CH_2Cl_2, toluene.

Form Supplied in: prepared from commercially available reagents.

Preparative Method: prepared by reaction of a 1-2 M hexane solution of ***Trimethylaluminum*** with 2 equiv of 2,4,6-tri-*t*-butylphenol in CH_2Cl_2 at rt for 1 h.[1]

Handling, Storage, and Precautions: the dry solid and solutions are highly flammable and must be handled in the absence of oxygen and moisture. The solution should be used as prepared for best results. Use in a fume hood.

Amphiphilic Alkylation.

The exceptionally bulky, oxygenophilic organoaluminum reagent MAT, like ***Methylaluminum Bis(2,6-di-t-butyl-4-methylphenoxide)*** (MAD), has been used for stereoselective activation of carbonyl groups. In combination with Grignard reagents or organolithium reagents, amphiphilic alkylation of substituted cyclohexanones affords equatorial alcohols almost exclusively. The equatorial selectivity is generally superior to that observed with MAD/RMgX or MAD/RLi systems (eqs 1 and 2).[1]

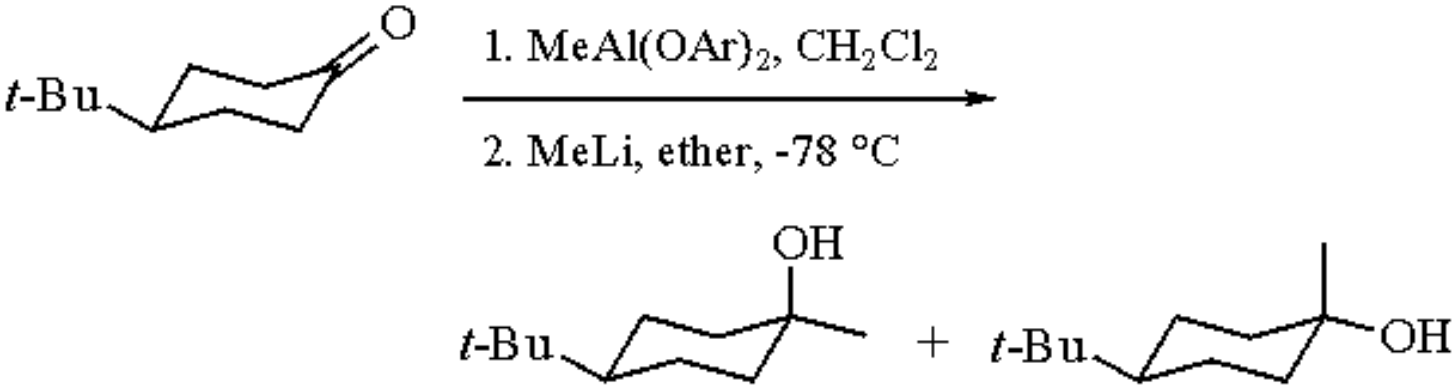

MAD, MeLi	84%	1 :99
MAT, MeLi	92%	0.5:99.5

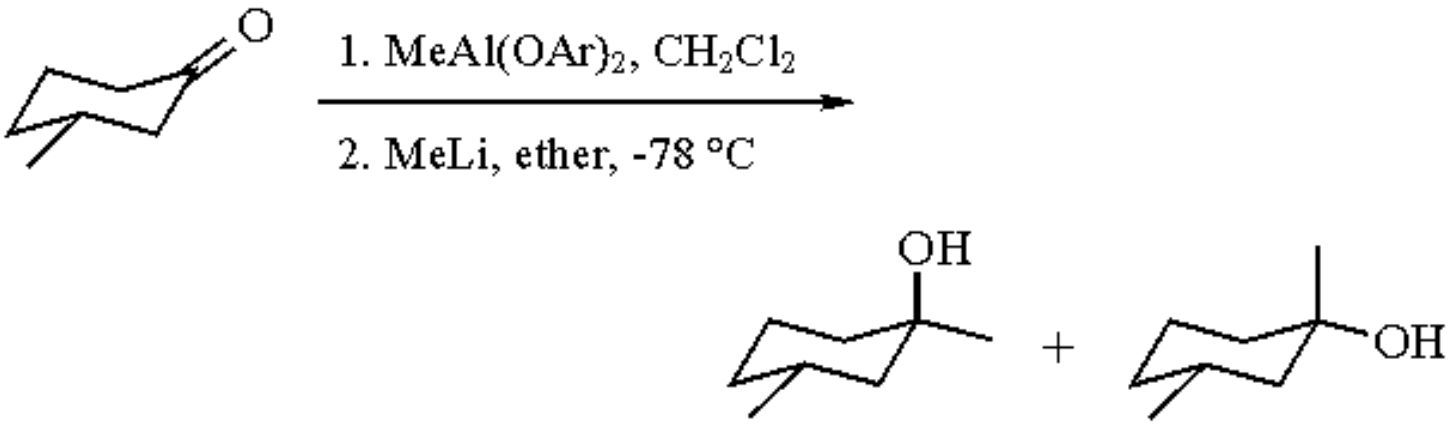

MAD, MeLi	69%	9:91
MAT, MeLi	95%	3:97

This approach is useful in the stereoselective alkylation of steroidal ketones. Thus the amphiphilic alkylation of cholestan-3-one with MAT/MeLi gives 3α-methylcholestan-3β-ol (equatorial alcohol) almost exclusively with only trace amounts of 3β-methylcholestan-3α-ol (axial alcohol) (eq 3).[1]

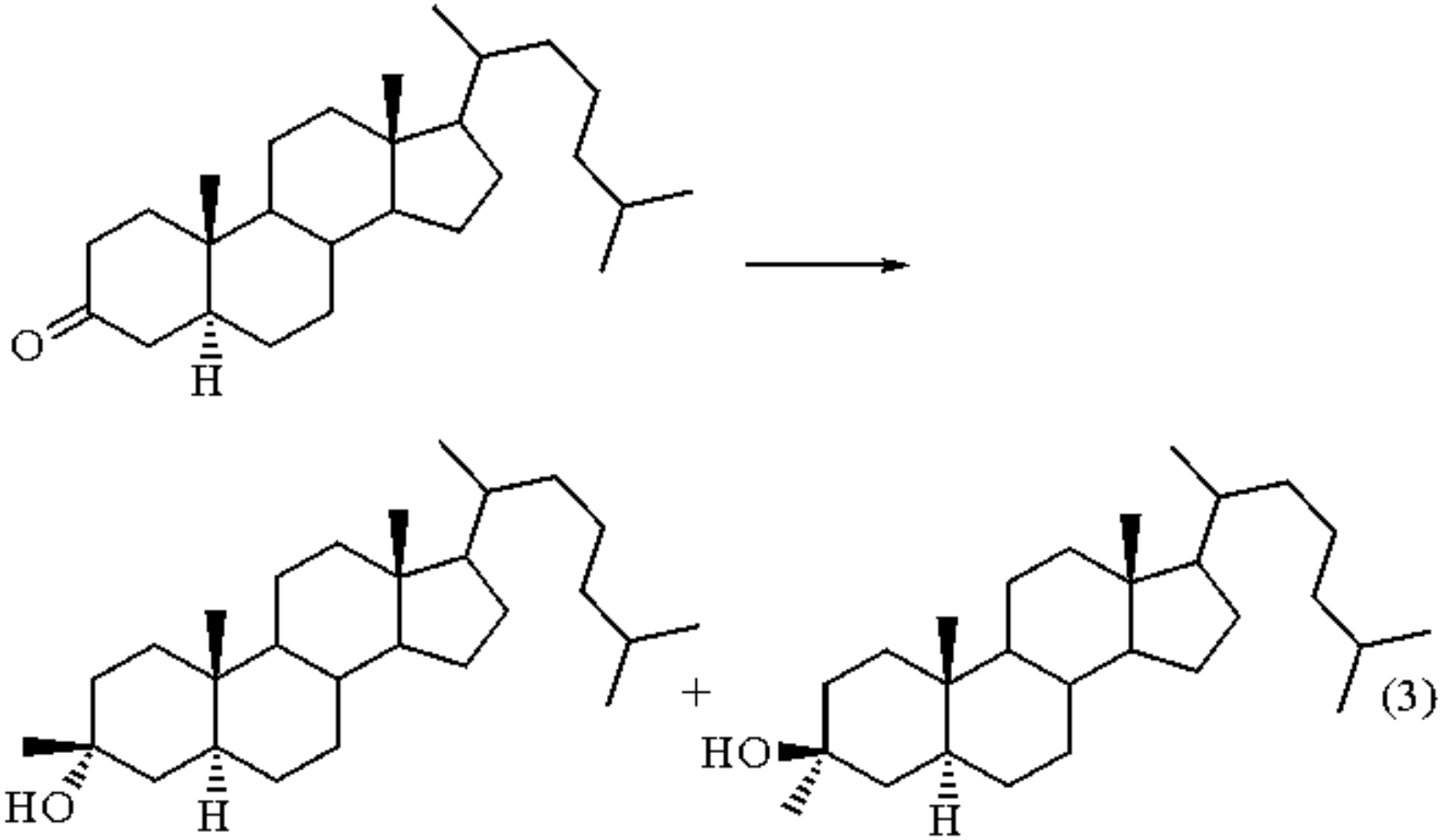

MAD, MeLi	98%	2:98
MAT, MeLi	99%	1:99

A similar trend is observed in the amphiphilic alkylation of α-substituted aldehydes with MAT/RMgX, giving *anti*-alcohols preferentially (eq 4).

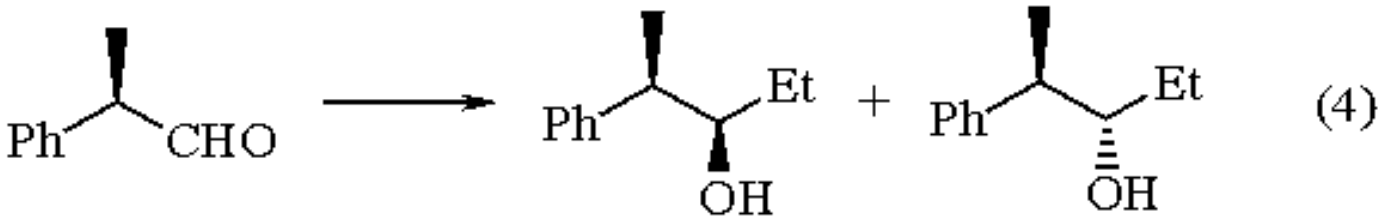

MAD, EtMgBr	90%	25:75
MAT, EtMgBr	90%	13:87

Conjugate Addition.

The MAT/RLi system can also be used for conjugate addition of organolithiums to α,β-unsaturated ketones. MAT gives comparable results to MAD in 1,4-selectivity (eq 5).[2] However, the conjugate reduction of α,β-unsaturated

ketones with MAT/***Lithium n-Butyl(diisobutyl)aluminum Hydride*** gives generally less satisfactory results (eq 6).[3]

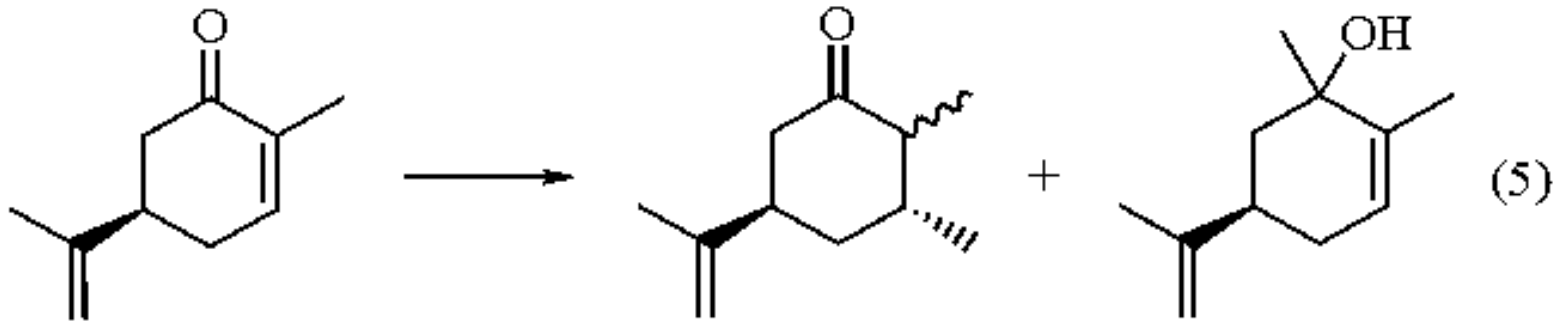

MAD, MeLi	65%	16%
MAT, MeLi	63%	31%

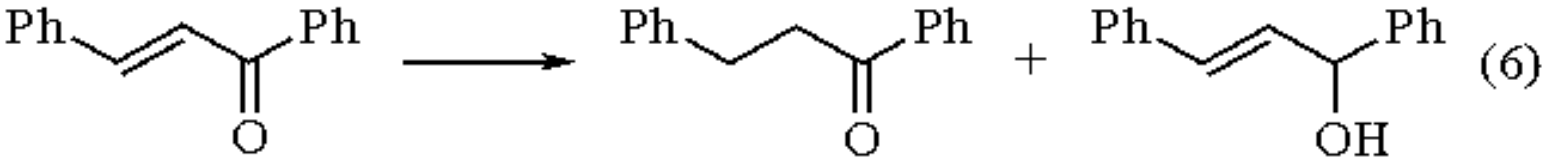

MAD, LiBu(i-Bu)$_2$AlH	60%	28%
MAT, LiBu(i-Bu)$_2$AlH	37%	61%

Polymerization.

The addition polymerization of methyl methacrylate (MMA) via an enolate complex of aluminum tetraphenylporphyrin as the nucleophilic growing species has been effected in the presence of MAT and the related Lewis acid MAD.[4]

---

1. (a) Maruoka, K.; Itoh, T.; Yamamoto, H. *JACS* **1985**, *107*, 4573. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *JACS* **1988**, *110*, 3588.
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Methylaluminum Dichloride[1]

$MeAlCl_2$

[917-65-7] · CH_3AlCl_2 · Methylaluminum Dichloride · (MW 112.92)

(strong Lewis acid that can also act as a proton scavenger; reacts with HX to give methane and $AlCl_2X$)

Alternate Name: dichloro(methyl)aluminum.

Physical Data: mp 72.7 °C; bp 94-95 °C/100 mmHg.

Solubility: sol most organic solvents; stable in alkanes or arenes.

Form Supplied in: commercially available as solutions in hexane or toluene.

Analysis of Reagent Purity: solutions are reasonably stable but may be titrated before use by one of the standard methods.[1b]

Handling, Storage, and Precautions: must be transferred under inert gas (Ar or N_2) to exclude oxygen and water. Use in a fume hood.

Introduction.

The general properties of alkylaluminum halides as Lewis acids are discussed in the entry for ***Ethylaluminum Dichloride***. $MeAlCl_2$ is used less frequently than $EtAlCl_2$, since $EtAlCl_2$ is much cheaper and comparable results are usually obtained. In some cases, use of $MeAlCl_2$ is preferable, since the methyl group of $MeAlCl_2$ is less nucleophilic than the ethyl group of $EtAlCl_2$ and $EtAlCl_2$ can transfer a hydride.

Catalysis of Diels-Alder Reactions.

$MeAlCl_2$ has been used as a catalyst for Diels-Alder[2-4] and retro-Diels-Alder reactions.[5] $MeAlCl_2$ is the catalyst of choice for intramolecular Diels-Alder reactions of furans (eq 1) due to the ease of handling and reaction workup.[2]

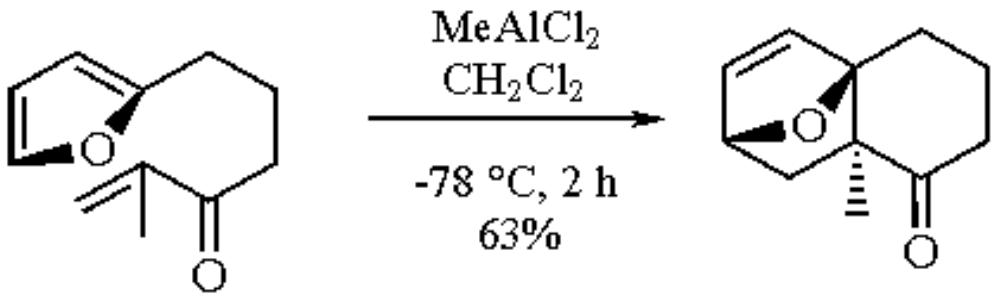

(1)

Catalysis of Ene Reactions.

$MeAlCl_2$ has been used as a catalyst for ene reactions of trifluoroacetaldehyde[6] and for intramolecular ene reactions of trifluoromethyl ketones (eq 2).[7] Use of $EtAlCl_2$ leads to the ene adduct in lower yield accompanied by 25% of the saturated analog resulting from hydride delivery to the zwitterion.

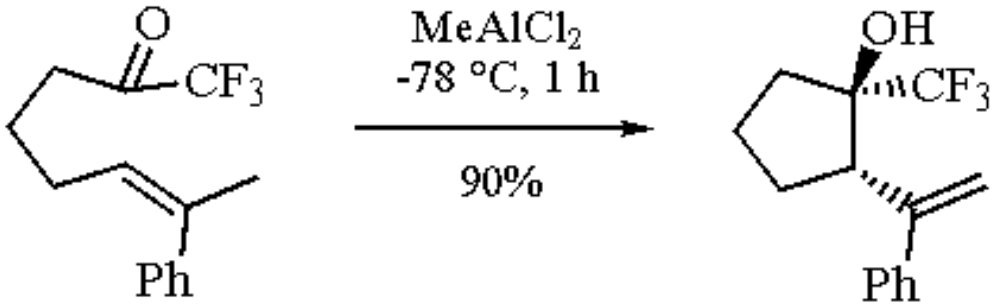

(2)

Generation of Electrophilic Cations.

1:2 Aldehyde- or ketone-$MeAlCl_2$ complexes add intramolecularly to alkenes to give zwitterions that undergo 1,2-hydride and alkyl shifts to regenerate a ketone (eqs 3 and 4).[8-11] $EtAlCl_2$ can transfer a hydride to the zwitterion to give the reduced product (eq 3).[8]

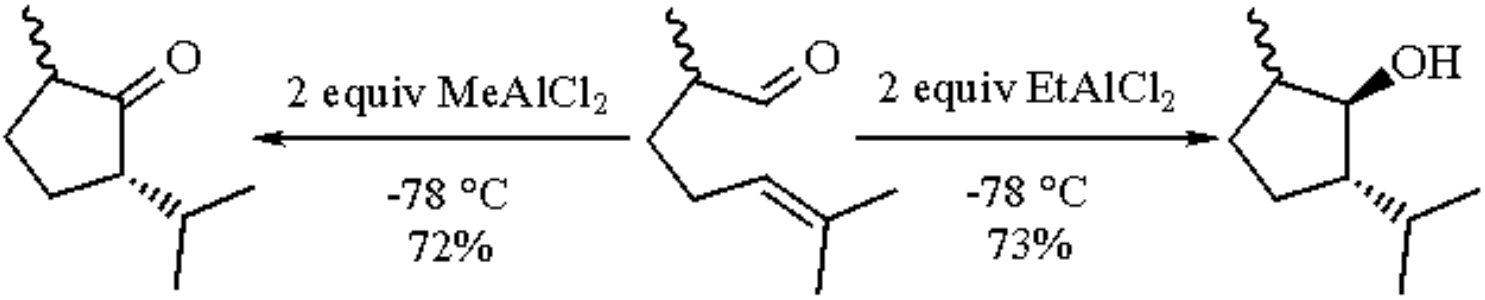

(3)

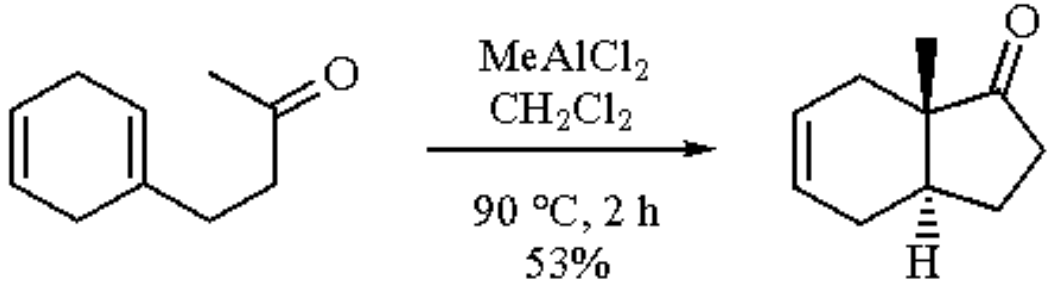

(4)

$MeAlCl_2$ has been used as the catalyst for epoxide-initiated cation-alkene cyclizations.[12] A tertiary alcohol has been converted to a hydrazide by reaction with $MeAlCl_2$ in the presence of ***Mesitylenesulfonylhydrazide***.[13] α-Trimethylsilyl enones can be prepared by isomerization of 1-(trimethylsilyl)-2-propynyl trimethylsilyl ethers with $MeAlCl_2$.[14]

Nucleophilic Additions.

$MeAlCl_2$ has occasionally been used to introduce a methyl group. γ-Lactones react with $MeAlCl_2$ to give carboxylic acids with a methyl group at the γ-position.[15] The reagent prepared from $MeAlCl_2$ and ***Dichlorobis(cyclopentadienyl)titanium*** adds to trimethylsilylalkynes in a *syn* fashion.[16] Optimal stereoselectivity is obtained using $MeAlCl_2$ to transfer a methyl group to a formyl amide (eq 5).[17]

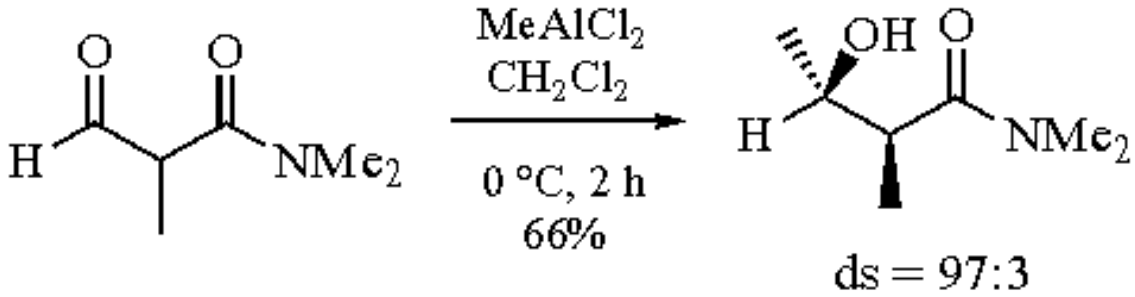

(5)

Related Reagents.

Diethylaluminum Chloride; ***Dimethylaluminum Chloride***; ***Ethylaluminum Dichloride***.

---

1. (a) For reviews, see ref. 1 in Ethylaluminum Dichloride. (b) *Aluminum Alkyls*; Stauffer Chemical Co.: Westport, CT, 1976.
2. (a) Rogers, C.; Keay, B. A. *TL* **1991**, *32*, 6477. (b) Rogers, C.; Keay, B. A. *CJC* **1992**, *70*, 2929.
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Barry B. Snider

Brandeis University, Waltham, MA, USA

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2-(Methylamino)thiophenol

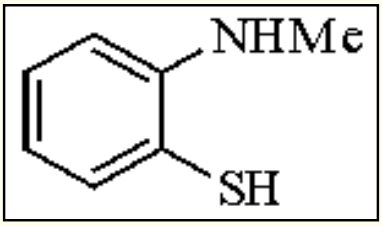

[21749-63-3] · C_7H_9NS · 2-(Methylamino)thiophenol · (MW 139.24)

(template for assisting ring closure of cyclic ketones;[1] protecting group for ketones and aldehydes[2])

Physical Data: mp 65 °C; bp 126 °C/18 mmHg.

Solubility: sol ethanol, chloroform.

Form Supplied in: solid; commercially available.

Preparative Methods: reduction of ***2-Methylbenzothiazole*** with ***Lithium Aluminum Hydride***,[3] hydrolysis of *N*-methylbenzothiazolone,[4] or reduction of the disulfide with ***Sodium Borohydride***.[1]

Purification: vacuum distillation.

Handling, Storage, and Precautions: store away from air to avoid dimerization.

Template for Ketone Synthesis.

2-(Methylamino)thiophenol (**1**) has been used to assist in the formation of bonds to carbonyl carbons, leading to cyclic[1,5-7] and acyclic ketones,[5] as well as to β,γ-unsaturated esters and ketones.[7] Amido sulfides can be formed by treatment of (**1**) with an alkyl bromide followed by an acid chloride. Deprotonation with ***Lithium Diisopropylamide*** leads to acyl transfer (eq 1). Reductive desulfurization then liberates the new ketone. Enolizable amides will undergo acyl transfer only after oxidation of the thioether to a sulfoxide or sulfone.[1]

2-(Methylamino)thiophenol

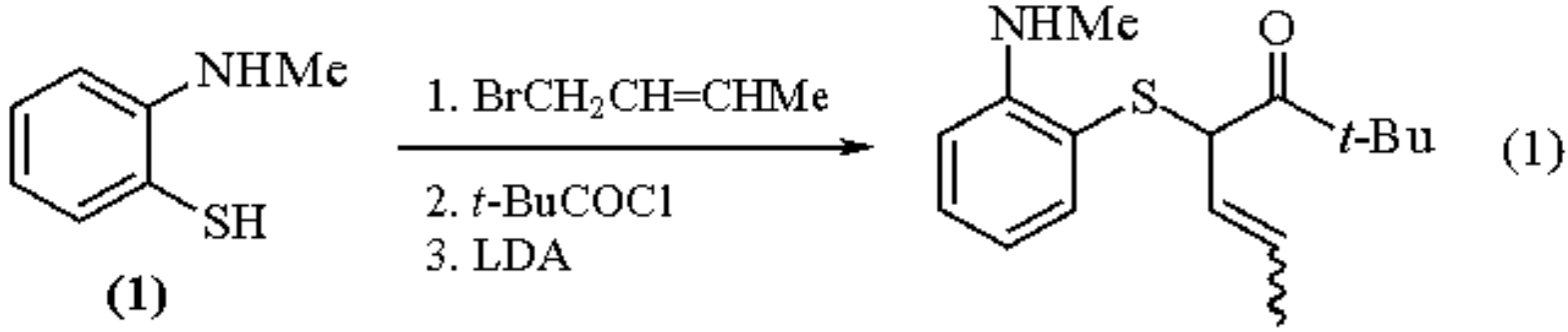

Benzothiazine and Benzothiazoline Synthesis.

A variety of heterocycles have been prepared starting from (**1**). Treatment of (**1**) with bromo esters leads to the formation of 2-substituted 2*H*-1,4-benzothiazin-3-ones (eq 2).[8] Alkylation of (**1**) with dibromopyridazine-3,6-dione provides access to 10-methyl-2,3-dihydropyridazino[4,5-*b*][1,4]benzothiazine-1,4-diones.[9]

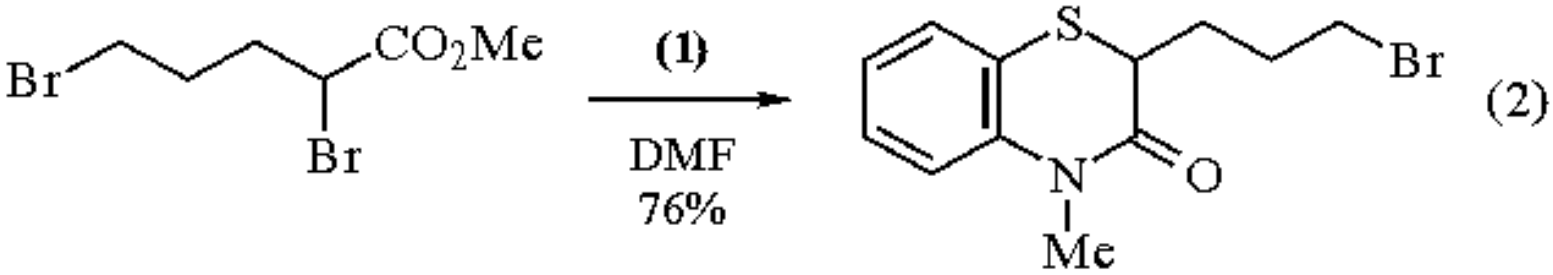

Condensation of (**1**) with aldehydes or ketones results in benzothiazolines, which can be used as protecting groups for aldehyde and ketone carbonyl groups.[2] The benzothiazoline moiety is highly resistant to attack by acids, bases, and reducing agents. The reaction is selective for aldehydes over ketones (eq 3), conjugated ketones over nonconjugated ketones, and ketones over acids and esters. The selectivity for conjugated over nonconjugated ketones is superior to that of acetalization or thioacetalization. Hydrolysis to regenerate the aldehyde proceeds in good yield with mild oxidants ($AgNO_3$, NCS, $HgCl_2$, others) or with FSO_3Me.

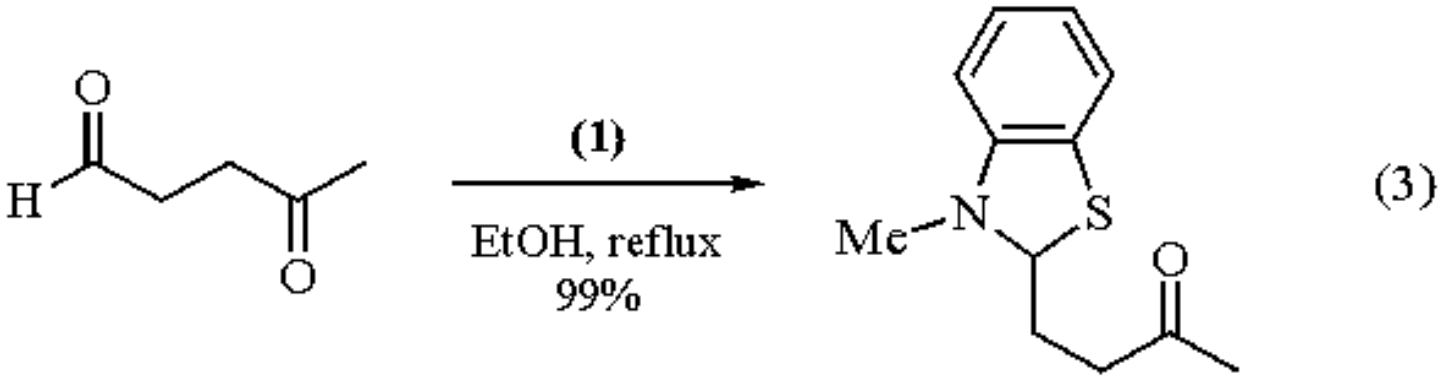

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N-Methylanilinium Trifluoroacetate

$Ph{+}NH_2Me\ CF_3CO_2^-$

[29885-95-8] · $C_9H_{10}F_3NO_2$ · *N*-Methylanilinium Trifluoroacetate · (MW 221.20)

(α-methylenating agent for ketones;[1] activates internucleotide coupling[2])

Alternate Name: N-MATA.

Physical Data: mp 66.5 °C.

Solubility: insol pentane; sol THF; very sol MeCN.

Form Supplied in: crystalline white salt.

Analysis of Reagent Purity: elemental analysis.

Preparative Method: prepared from commercial grade ***Trifluoroacetic Acid*** and *N*-methylaniline (1:1) in dry Et_2O under a nitrogen atmosphere with cooling in an ice-bath.[1c]

Purification: by sublimation and drying in a desiccator under vacuum at rt.

Handling, Storage, and Precautions: nonhygroscopic; not deliquescent; can be weighed in the air and stored for months under an inert atmosphere.

Methylene Transfer Reagent.

Ketones of various types form α-methylene ketones by direct methylene transfer from formaldehyde in the presence of N-MATA (eq 1).[1,3,4]

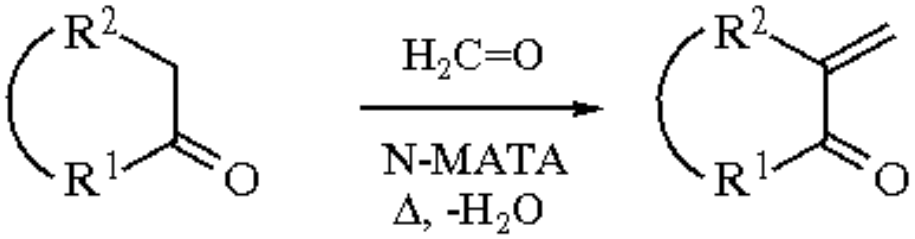

(1)

Both paraformaldehyde and trioxane can be used as the source of formaldehyde, but, with the latter, low yields of methylene ketones are sometimes obtained.[3] With cyclohexanone, cyclopentanone, or aldehydes, preformation of the iminium intermediate [CH_2=+NMePh] is recommended from paraformaldehyde and N-MATA prior to addition of the carbonyl compound.[1c] Saturated[1] and unsaturated,[1b] cyclic,[1a,c,3] and acyclic,[1b,4] as well as methyl ketones,[1b,4] can be successfully used in the process (eqs 2 and 3).[1a,4]

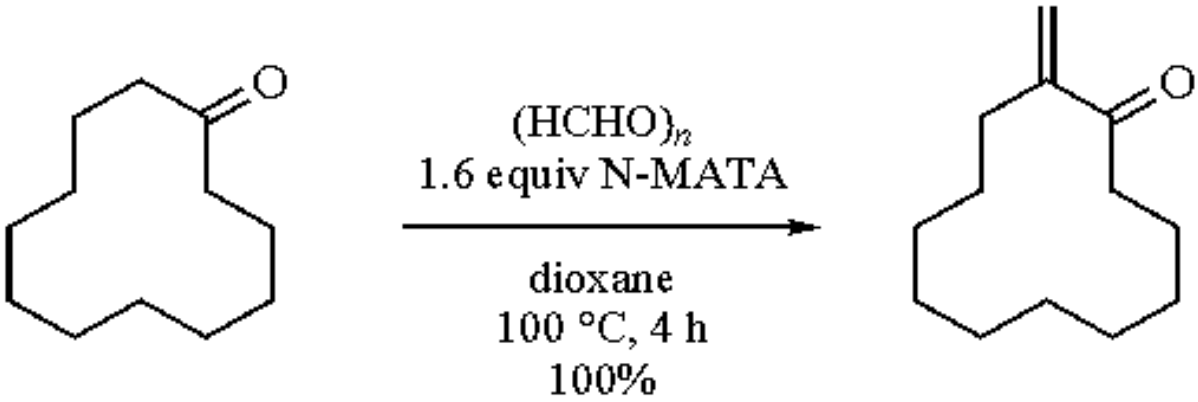

(2)

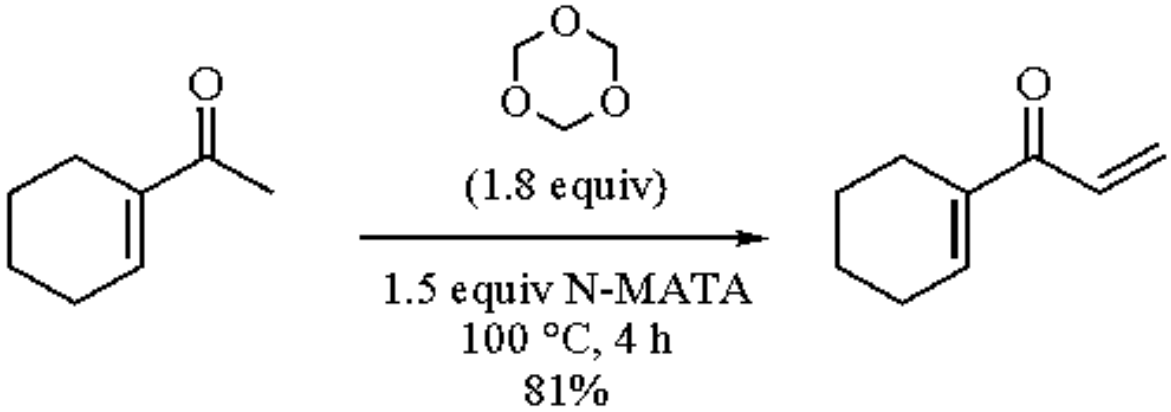

(3)

Linear methyl ketones react at both the α- and α´-positions to give a mixture of regioisomeric methylene ketones (eq 4),[1b] as well as some divinyl ketone as a side product.

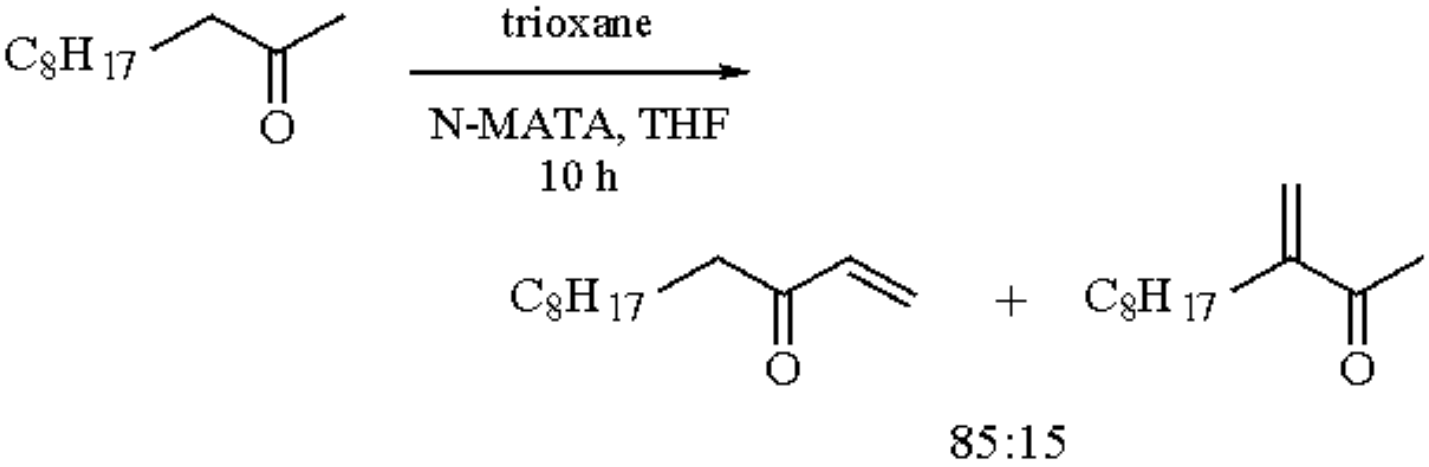

(4)

The reaction is not applicable to γ- or δ-lactones, or strained cyclic ketones such as norcamphor or cyclobutanone.[1a,c]

Activating Agent in Internucleotide Coupling.

Deoxynucleoside methyl- and phenylphosphoramidites[2] and also phosphorothioamidites[5] are effectively activated by N-MATA for condensation with other suitably protected nucleosides to give deoxydinucleoside phosphates (eq 5).[2] Phosphorodithioates[5] or oligonucleotides (over 95%) have also been prepared in this manner using a polymer silica gel support.[2]

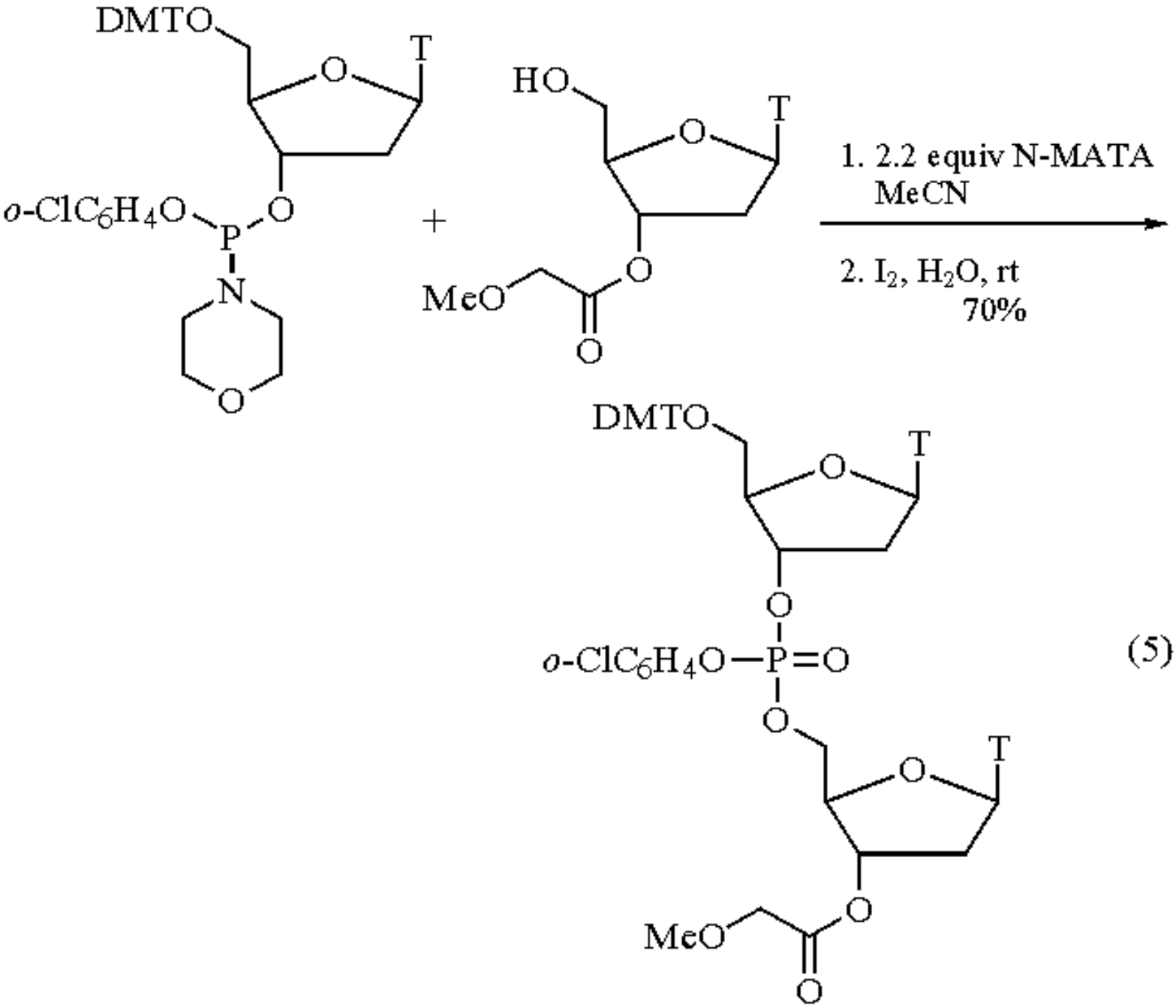

(5)

DMT = di-*p*-anisylphenylmethyl, T = 1-thiminyl

In the synthesis of deoxydinucleoside phosphorodithiolates, however, N-MATA causes excessive detritylation and the most satisfactory activator in this process is pyridinium tetrafluoroborate.[5]

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Methyl Benzenesulfinate[1]

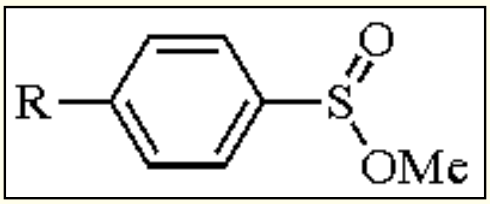

(**1**; R = H)

[670-98-4] · $C_7H_8O_2S$ · Methyl Benzenesulfinate · (MW 156.22) (*R*)-(**1**)

[111698-33-0] (*S*)-(**1**)

[112425-42-0] (±)-(**1**)

[114376-00-0] (**2**; R = Me)

[672-78-6] · $C_8H_{10}O_2S$ · Methyl *p*-Toluenesulfinate · (MW 170.25) (*R*)-(**2**)

[64396-66-3] (*S*)-(**2**)

[59203-01-9] (±)-(**2**)

[59153-37-6] (-)-(**2**)

[69979-69-7] (+)-(**2**)

[69979-70-0]

(synthesis of sulfinyl compounds;[2] preparation of menthyl arenesulfinates[3])

Physical Data: (**1**) bp 76-78 °C/0.45 mmHg; *n*25D 1.5436; *d* 1.1948 g cm^{-3}. (**2**) bp 129-130 °C/14 mmHg; *n*25D 1.5405; *d* 1.1498 g cm^{-3}.

Solubility: (both compounds) sol alcohol, Et_2O, benzene; insol H_2O.

Preparative Methods: prepared by oxidation of ***Diphenyl Disulfide*** (or *p*-tolyl disulfide) with ***Lead(IV) Acetate*** in MeOH,[4a] or by reaction of ***Benzenesulfinyl Chloride*** (or *p*-toluenesulfinyl chloride) with MeOH.[4b]

Analysis of Reagent Purity: (**1**) NMR,[5a] IR,[5b] UV.[5b] (**2**) NMR,[5a] IR,[5c] UV.[5d]

Handling, Storage, and Precautions: these compounds are reported to produce extreme and prolonged burning sensations on contact with the skin.

Preparation of Sulfinyl Compounds.

Methyl arenesulfinates react with compounds containing activated methylene groups, such as ketones[6] and sulfones,[7] in the presence of ***Sodium Hydride*** in DME or Et_2O to form α-arylsulfinyl compounds; arylsulfinyl chlorides react similarly (see ***Benzenesulfinyl Chloride***). These sulfinyl-activated compounds are useful synthetic intermediates since they can undergo further reaction;[8] the sulfinyl group can then be removed by reductive cleavage with agents such as ***Aluminum Amalgam***, Li(Hg), or ***Raney Nickel***.[9] Alternatively, the sulfoxide group may be removed via β-hydrogen elimination either by thermolysis (ca. 80 °C) (eq 1),[10,11] or by treatment with base (e.g. RO^-, CO_3^{2-}) with concomitant formation of a double bond.[11] Because of the mildness of the procedure, this is one of the better methods for the conversion of ketones, aldehydes, and esters into their α,β-unsaturated derivatives.[12]

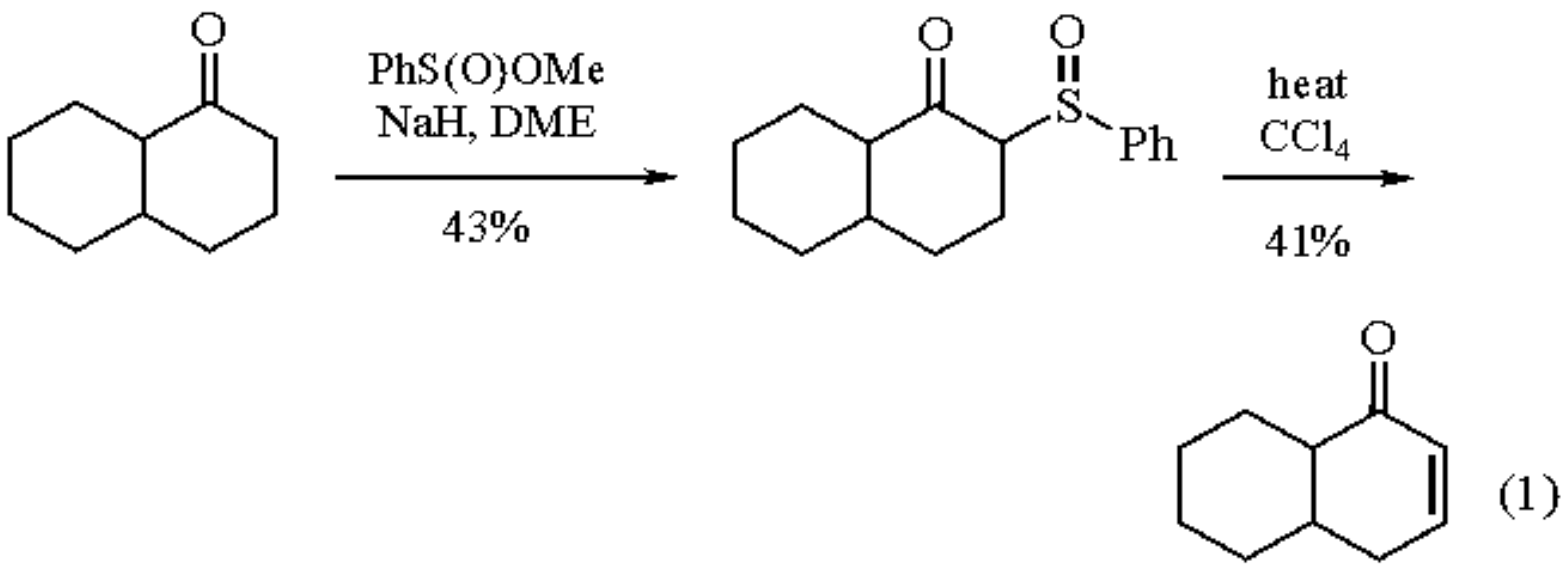

(1)

Sulfinylation of a series of lactams by methyl benzenesulfinate is superior to sulfenylation with diphenyl disulfide followed by oxidation; substantial bissulfenylation occurs using the latter procedure.[13]

Methyl benzenesulfinate has been used to prepare unsaturated sulfoxides via reaction with functionalized unsaturated Grignard reagents,[14] and by reaction with phosphonates to form α-phosphoryl sulfoxides that, in turn, form vinyl sulfoxides by Horner-Emmons reactions with aldehydes and ketones.[15] These unsaturated sulfinyl compounds undergo a variety of synthetically useful reactions such as cycloadditions,[16] Michael additions,[17] and various rearrangements.[18,19]

p-Tolylsulfinylmethyl phenyl sulfone, available from methyl *p*-toluenesulfinate and ***Methyl Phenyl Sulfone***, reacts with aldehydes and some ketones to form vinyl sulfoxides; these sulfoxides afford γ-hydroxy-α,β-unsaturated sulfones after alkene isomerization and rearrangement (eq 2).[7]

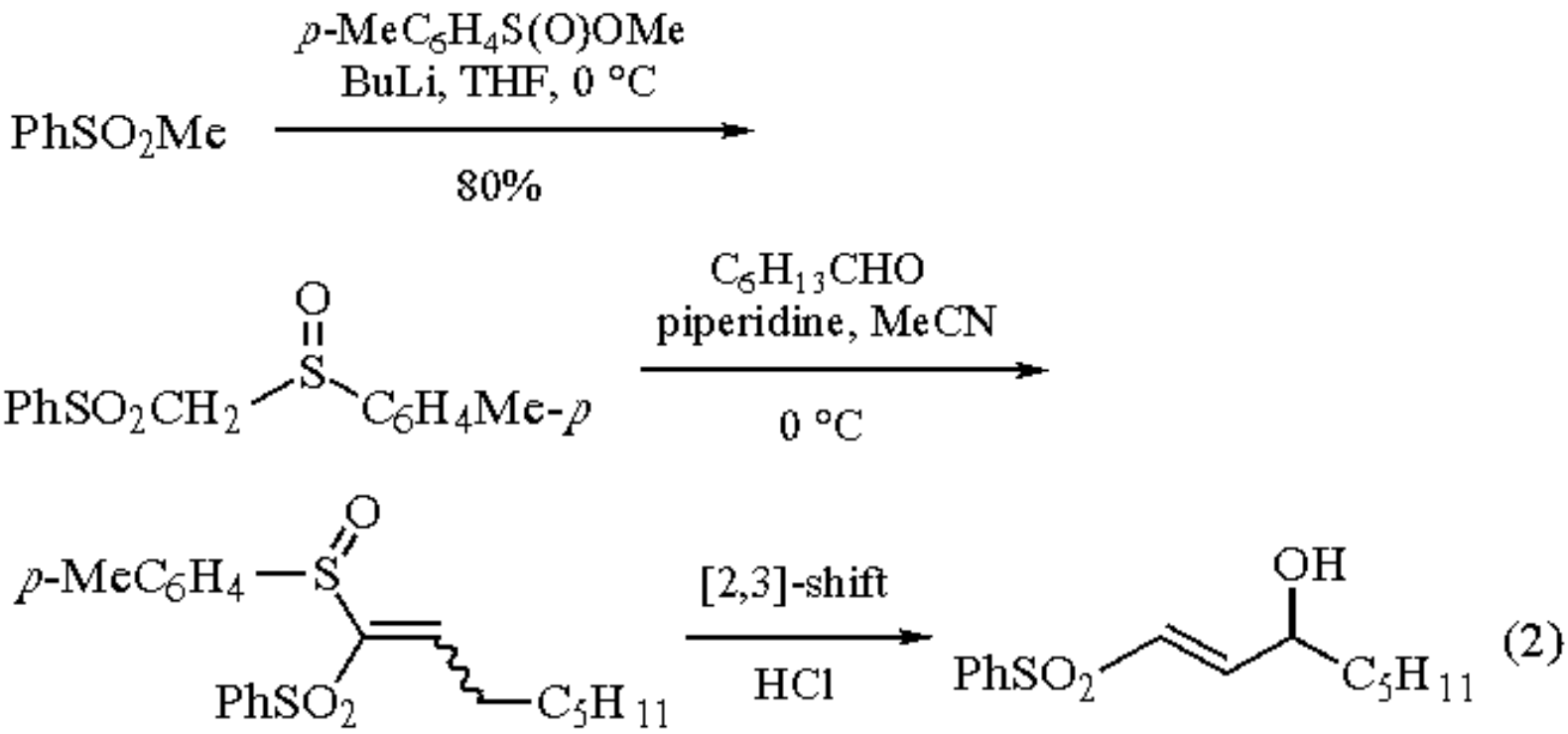

Asymmetric Synthesis.

Although chiral sulfoxides have been prepared in high yield and enantiomeric purity via reaction of optically active *p*-$MeC_6H_4S(O)OMe$ with silyl enol ethers,[20] a more common procedure has been through reaction of a Grignard reagent or metalated substrate with menthyl *p*-toluenesulfinate (MenTs).[3] Methyl *p*-toluenesulfinate has been used to prepare menthyl *p*-toluenesulfinates,[21] which are very useful chiral sulfinyl-transfer reagents; the resulting chiral sulfoxides have been used widely in asymmetric synthesis[22] (see ***Benzenesulfinyl Chloride*** and ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***). For example, MenTs has been used to generate β-hydroxy carboxylic esters in high optical yields (eq 3).[23]

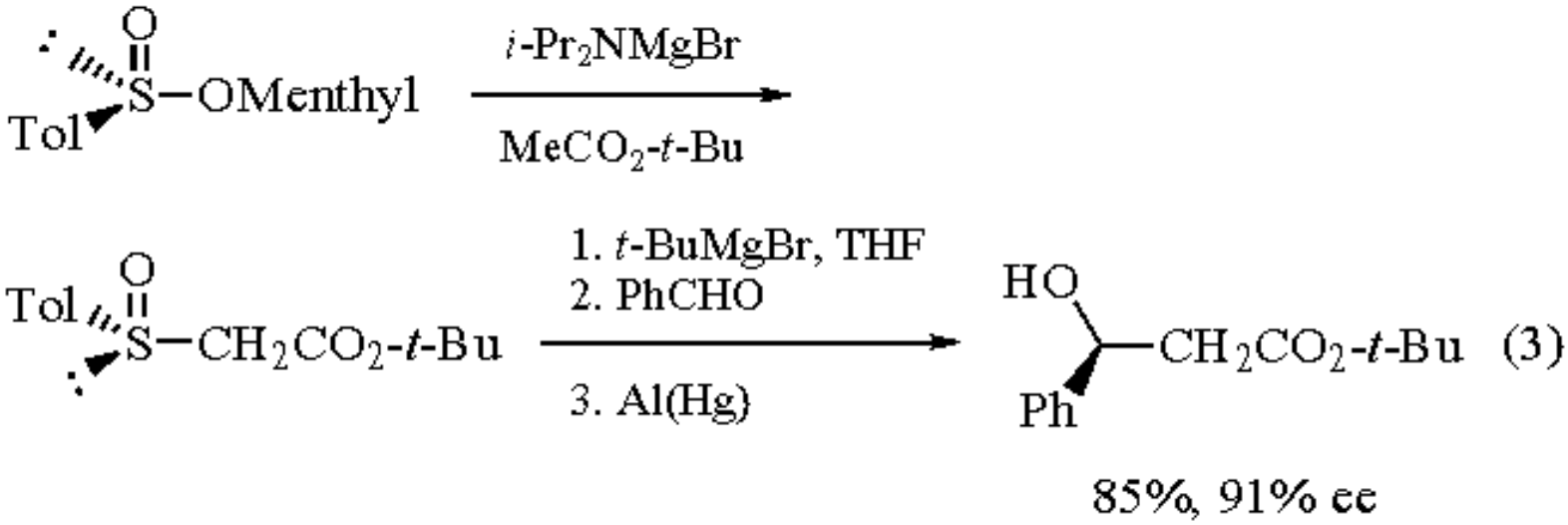

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2-Methylbenzothiazole[1]

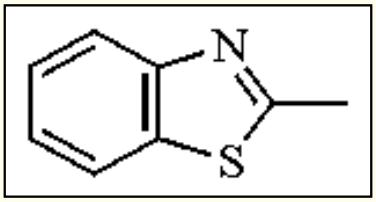

[120-75-2] · C_8H_7NS · 2-Methylbenzothiazole · (MW 149.23)

(the α-lithio derivative represents a masked enolate;[2] the α-trimethylsilyl derivative is used for Peterson alkenations[3])

Physical Data: mp 14 °C; bp 238 °C/765 mmHg; bp 151 °C/15 mmHg; *d* 1.1763 g cm^{-3}; n_D 1.6092.

Solubility: insol H_2O; sol ethanol; very sol diethyl ether, THF.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^1H and ^{13}C NMR spectra.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: should be freshly distilled before use for best results. Toxic by inhalation, in contact with skin, and if swallowed. Use in a fume hood.

Introduction.

2-Methylbenzothiazole (**1**) has been used[4] in base- and acid-mediated condensations with aldehydes to give products which normally undergo dehydration in situ to give alkenes (**2**) (eq 1).

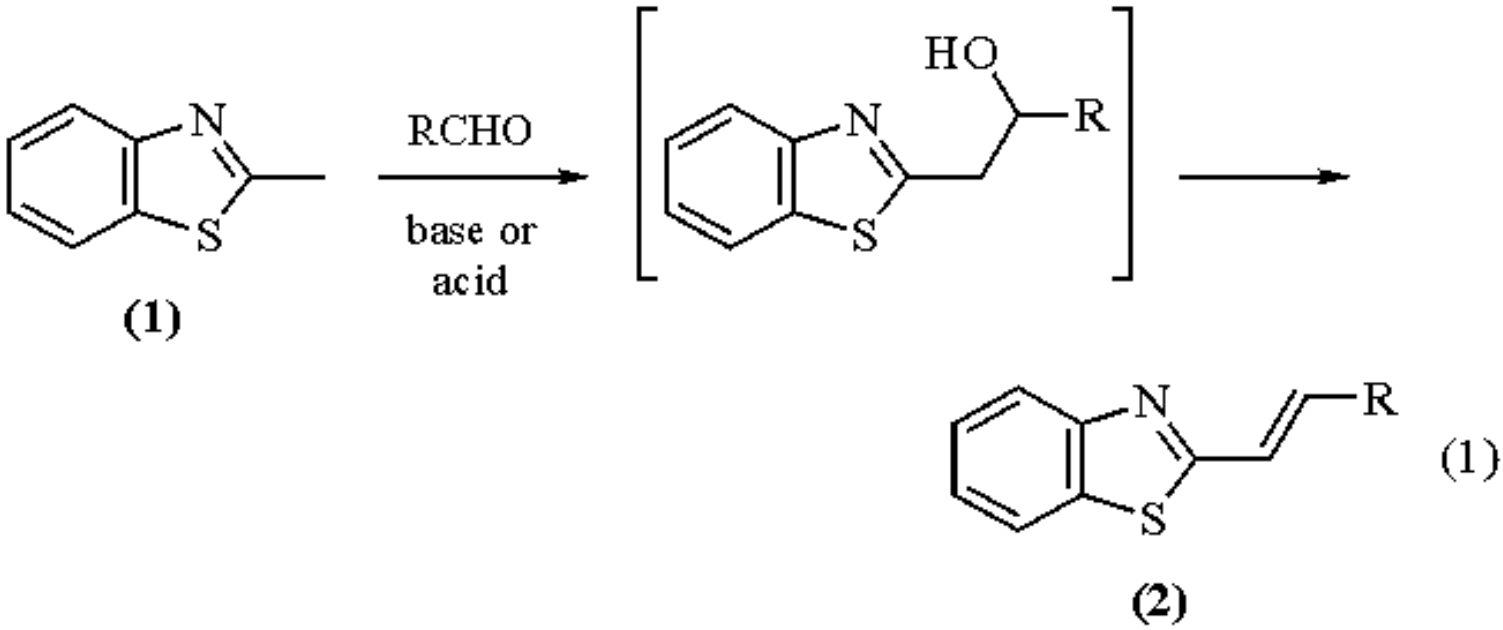

α-Lithio-2-methylbenzothiazole.[1]

This reagent is readily available by lithiation of 2-methylbenzothiazole (**1**) with ***n-Butyllithium*** at -78 °C (eq 2),[1,3] which gives rise to a yellow precipitate (indicating the formation of the organometallic compound) when diethyl ether is used as a solvent or to a clear light-brown solution in THF or 1,2-dimethoxyethane.

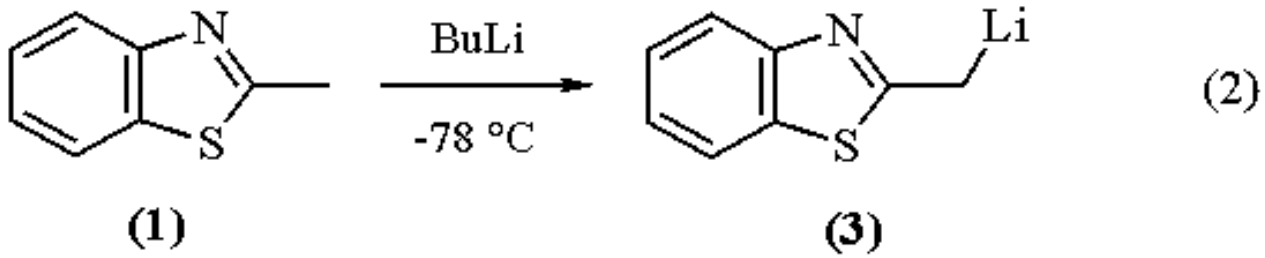

α-Lithio-2-methylbenzothiazole (**3**) reacts with various electrophiles such as aldehydes and ketones[2] to afford 2-(2-hydroxyalkyl)benzothiazoles in high yields (eq 3).

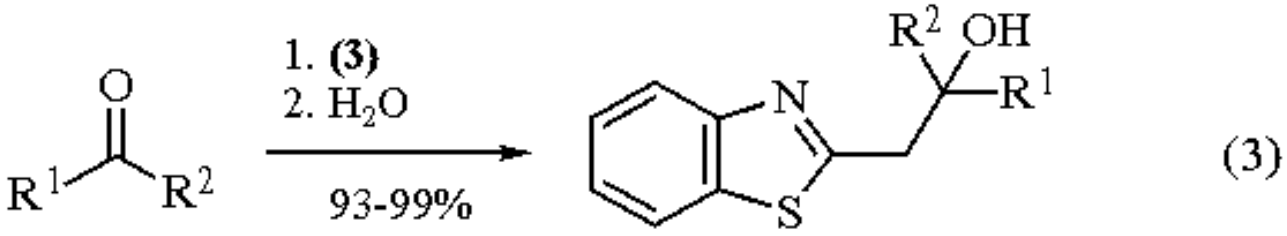

Chikashita et al.[2] have demonstrated the synthetic equivalence of (**3**) to a masked enolate anion through the liberation of the aldehyde by cleavage of the ***Benzothiazole*** ring (eq 4).

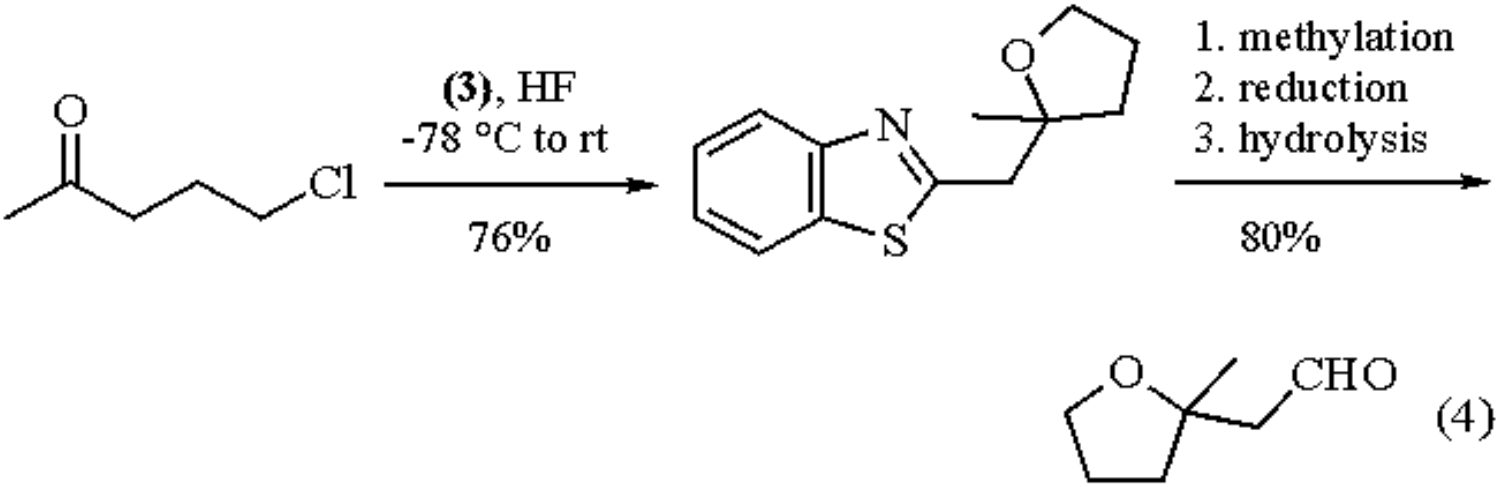

More recently, Lochon et al.[5] have reported the reaction of (**3**) with other electrophiles such as esters (eq 5) and nitriles (eq 6). When the same reaction is carried out with acyl chlorides, bisacylated compounds are obtained (eq 7).

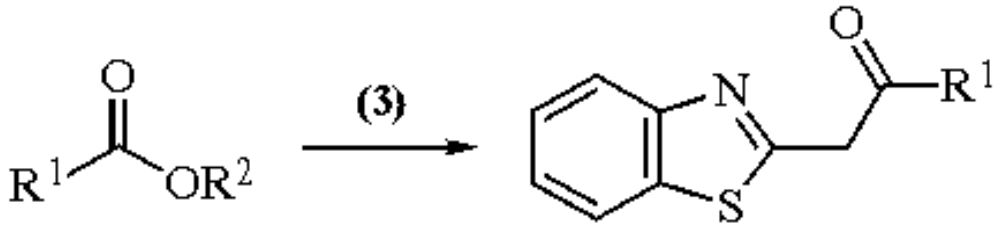

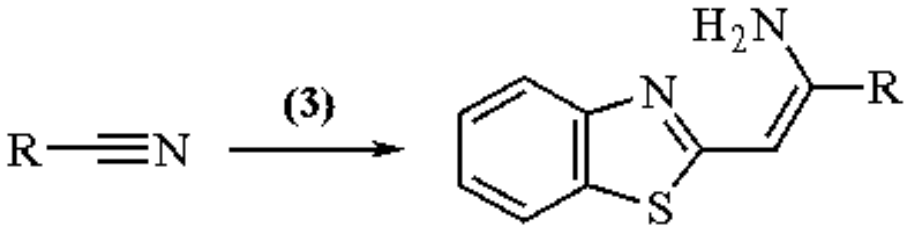

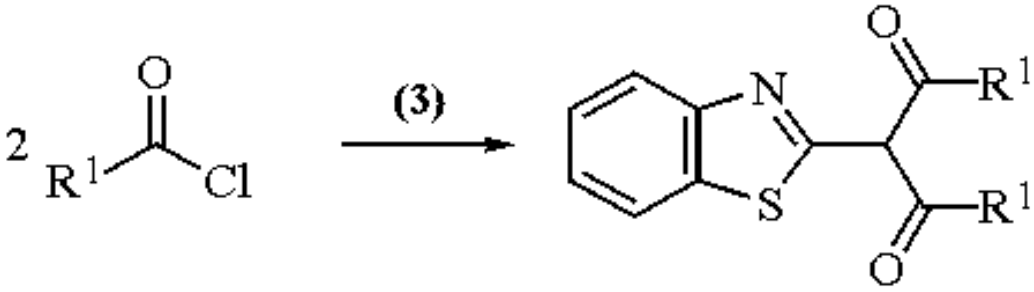

2-(Trimethylsilylmethyl)benzothiazole.

α-Lithio-2-methylbenzothiazole (**3**) is quantitatively silylated with ***Chlorotrimethylsilane*** to give reagent (**4**), which can be further metalated and condensed with carbonyl compounds to give the corresponding alkenes (eq 8).[3] This two-carbon homologation sequence corresponds to a Peterson alkenation, i.e. it is an alternative to the Wittig and Horner-Emmons reactions.[6] Endocyclic analogs such as 2-(1-cyclohexenyl)- and 2-(1-cyclopentenyl)benzothiazoles are accessible via addition of 2-lithiobenzothiazole (see ***Benzothiazole***) to corresponding cyclic ketones and subsequent dehydration.[3]

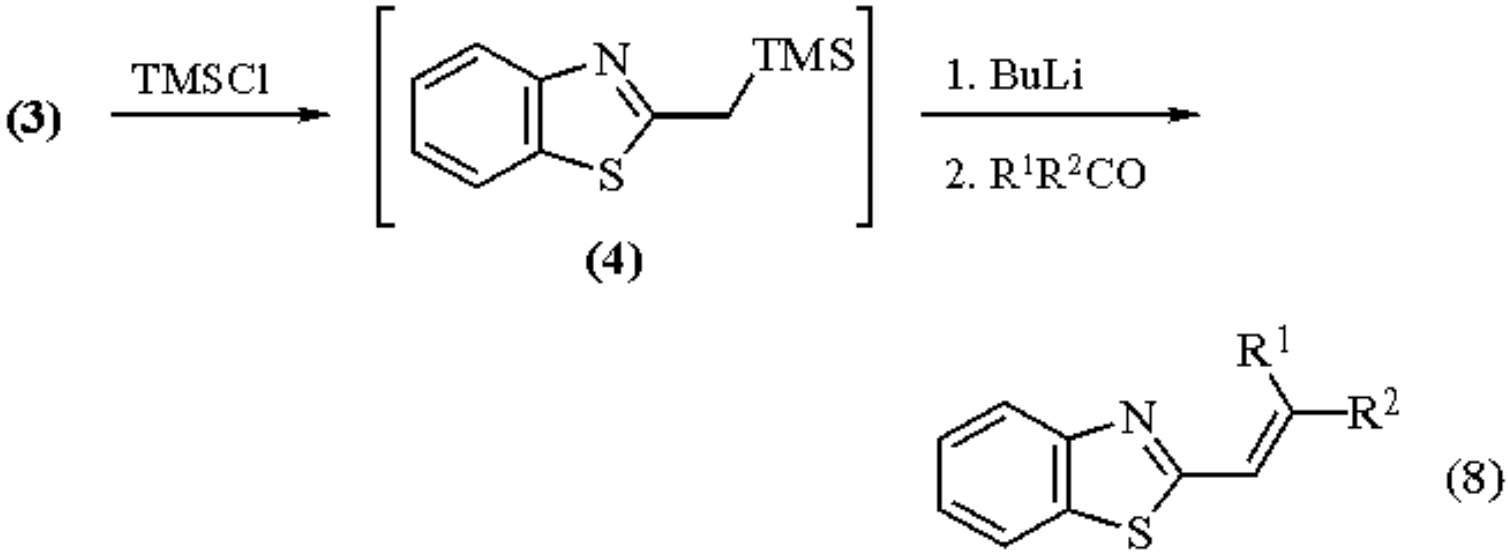

The vinylbenzothiazole (**5**), derived from cyclohexanone through (**4**), undergoes efficient conjugate addition reactions with a variety of alkyllithium reagents (alkyl, vinyl, phenyl, and allyl) as well as with acetone and acetaldehyde *N*,*N*-dimethylhydrazone anions.[7a] The resulting adduct carbanions may be protonated (MeOH) or alkylated in situ with methyl, allyl, and propargyl halides. The double bond of (**5**) can be hydrogenated (H_2, Pd/C, EtOH) smoothly without catalyst poisoning. Conversion of the benzothiazole moiety to the formyl group is accomplished by *N*-methylation ($MeOSO_2F$, CH_2Cl_2), reduction ($NaBH_4$, EtOH), and hydrolysis ($AgNO_3$, aq. MeCN, pH 7). Aldol cyclization of the liberated aldehyde onto the α- or β-acetonyl substituents provide effective methods for fused and spiro annulation of cyclohexenone or cyclopentenone rings (e.g. eq 9).[7b]

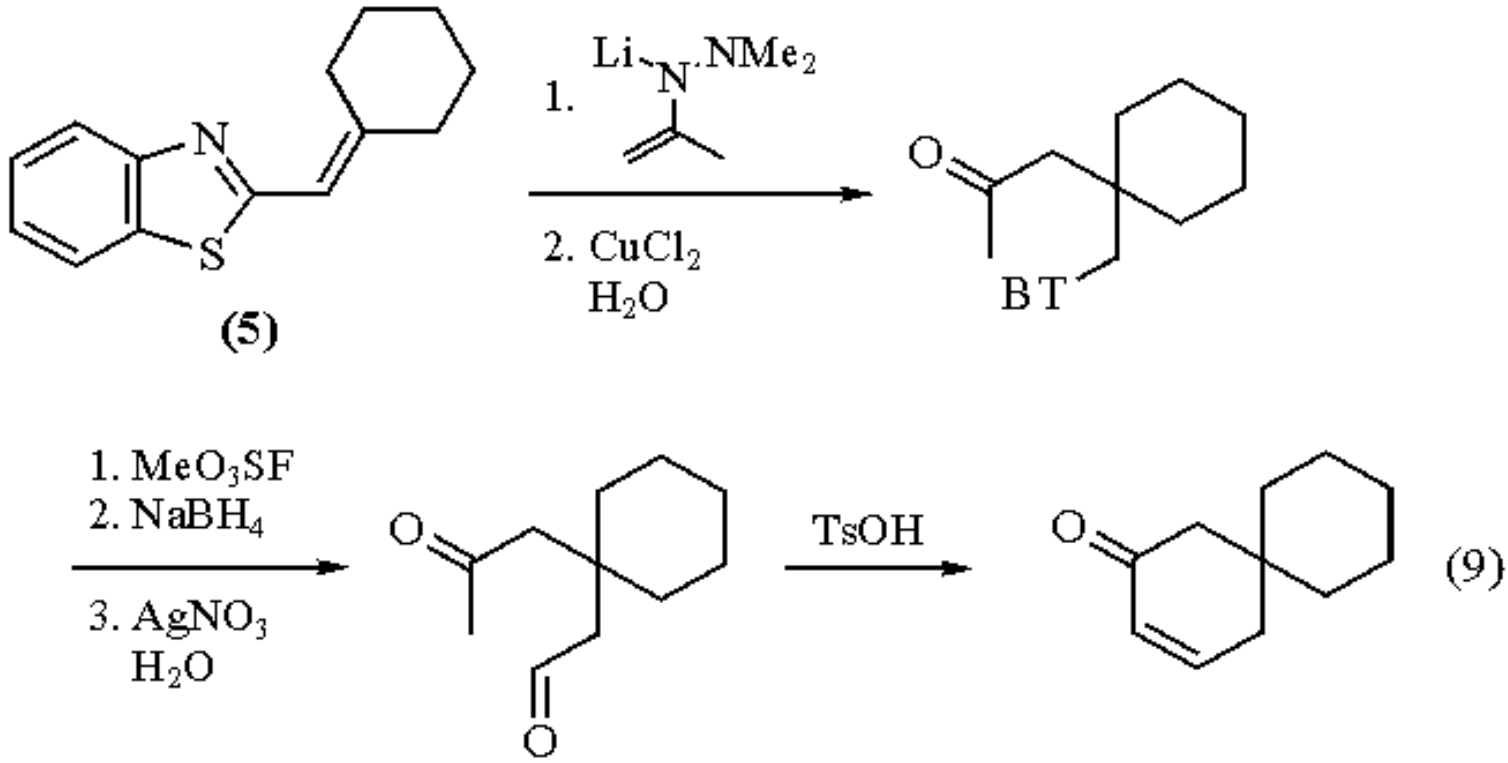

Other 2-Alkylbenzothiazoles.

Florio et al.[8] have reported the metalation of 2-alkylbenzothiazoles (2-ethyl, 2-propyl, and 2-phenyl) to give the corresponding α-lithioalkylbenzothiazoles which undergo aldol condensations with carbonyl compounds (eq 10).

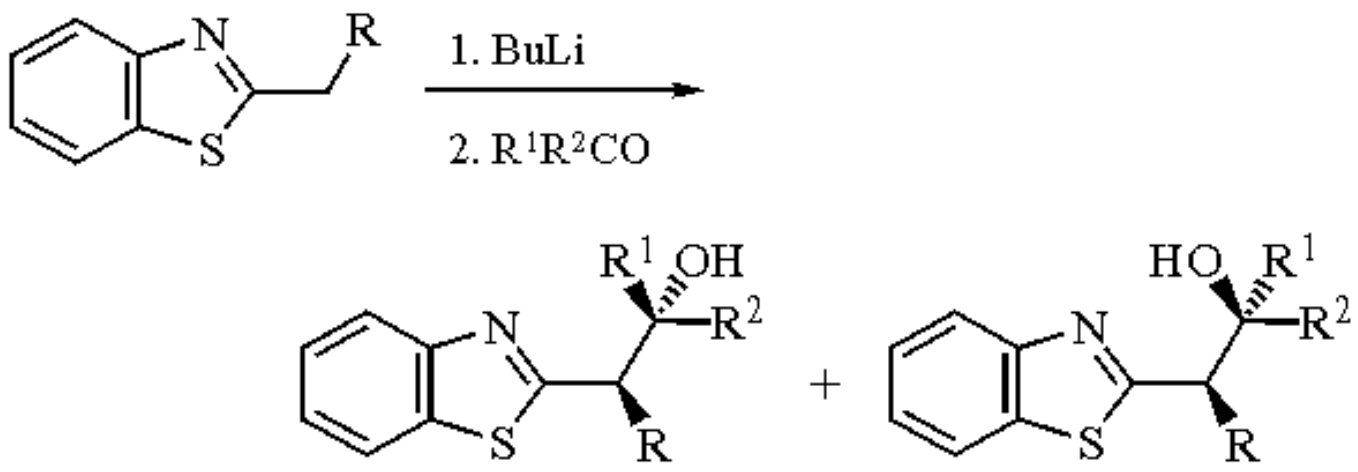

(10)

More recently,[9] the Darzens reaction between the lithio derivative of 2-chloromethylbenzothiazole (**6**) and carbonyl compounds to furnish epoxides has been described (eq 11).

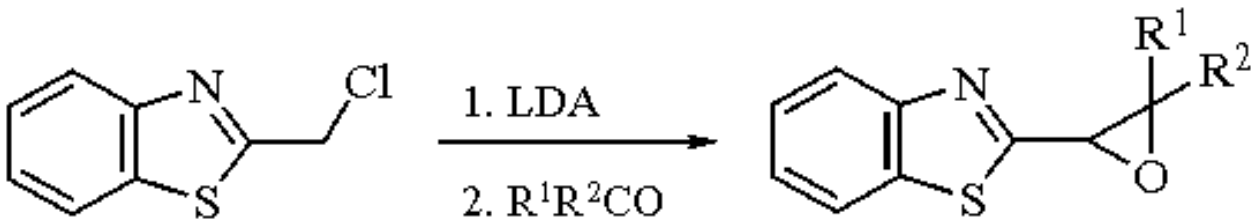

(11)

(6)

Related Reagents.

Benzothiazole; ***2-Methyl-2-thiazoline***; ***5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4H)-oxazine***; ***2,4,4-Trimethyl-2-oxazoline***; ***2-(Trimethylsilyl)thiazole***.

---

1. For an extensive study on the metalation of 2-methylbenzothiazole with several reagents, see: Costa, M. V.; Lochon, P. *JOM* **1985**, *293*, 265.
2. Chikashita, H.; Ikegami, S.; Okumura, T.; Itoh, K. *S* **1986**, 375.
3. Corey, E. J.; Boger, D. L. *TL* **1978**, 5.
4. Dryanska, V.; Ivanov, C. *S* **1976**, 37.
5. Costa, M. V.; Brembilla, A.; Roizard, D.; Lochon, P. *JHC* **1991**, *28*, 1541.
6. Knott, E. B. *JCS* **1965**, 3793.
7. (a) Corey, E. J.; Boger, D. L. *TL* **1978**, 9. (b) Corey, E. J.; Boger, D. L. *TL* **1978**, 13.
8. (a) Epifani, E.; Florio, S.; Ingrosso, G. *TL* **1987**, *28*, 6385. (b) Epifani, E.; Florio, S.; Ingrosso, G. *T* **1987**, *43*, 1937.
9. Florio, S.; Troisi, L. *TL* **1992**, *33*, 7953.

Alessandro Dondoni

(*S*)-α-Methylbenzylamine

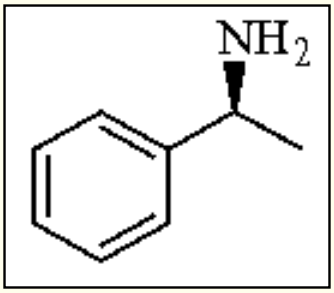

[2627-86-3] · $C_8H_{11}N$ · (*S*)-α-Methylbenzylamine · (MW 121.20)

(resolving agent for carboxylic acids;[7-11] determination of enantiomeric purity of carboxylic acids;[16,17] stereospecific reactions of carbonyl compounds;[18] reductive amination of carbonyl compounds[29,30])

Physical Data: bp 187 °C; *d* 0.940 g cm^{-3}; $[\alpha]_D$ -39° (neat).

Solubility: readily sol all organic solvents.

Form Supplied in: both enantiomers are commercially available.

Analysis of Reagent Purity: the enantiomeric purity of the reagent can be assessed by NMR analysis of the corresponding Mosher's amide.[4] Chiral complexing reagents (such as 1,1´-binaphthyl-2,2´-diylphosphoric acid) have also been used in the direct NMR analysis of the reagent.[5,6]

Preparative Methods: racemic α-methylbenzylamine has been resolved utilizing chiral acids such as tartaric acid[1] and (*S*)-(-)-carbamalactic acid,[2] among others. Several stereospecific syntheses have been reported.[3]

Handling, Storage, and Precautions: stable at rt for extended periods of time when stored under nitrogen.

Resolving Reagent for Carboxylic Acids and Other Types of Compounds.

A large number of carboxylic acids have been resolved via their diastereomeric salts with (*S*)- or (*R*)-α-methylbenzylamine (**1**). The ready availability of both enantiomers of (**1**) guarantees access to both enantiomers of the desired acid. Compounds (**2**)-(**6**) are representative examples of acids obtained in high enantiomeric purity.[7-11] Alternatively, racemic carboxylic acids have been resolved by covalent derivatization with (**1**) and separation of the

resulting diastereomeric amides by physical means such as chromatography (eq 1)[12] or fractional crystallization (eq 2).[13]

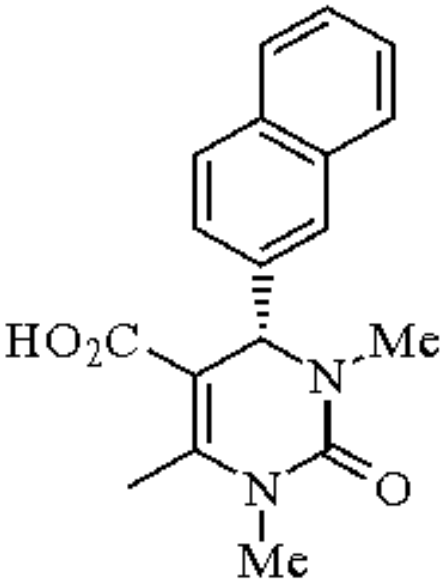

(2)

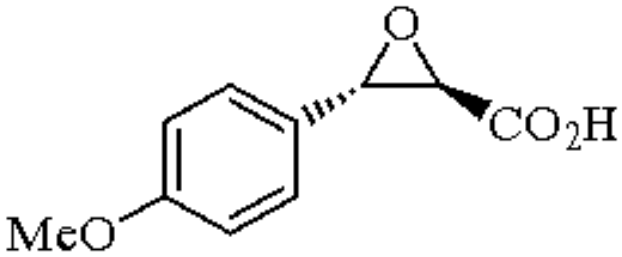

(3)

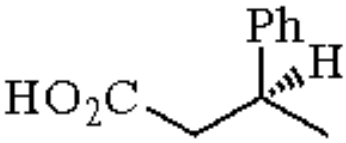

(4)

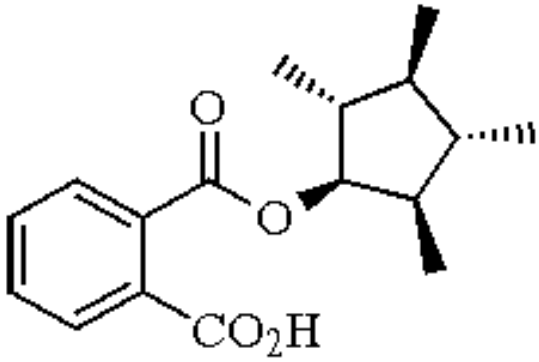

(5)

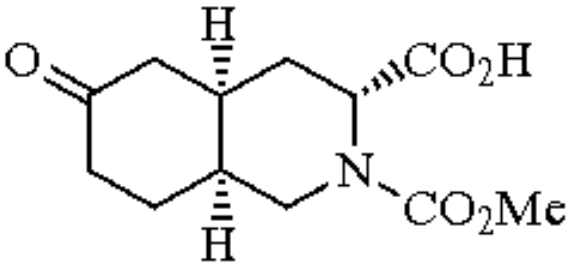

(6)

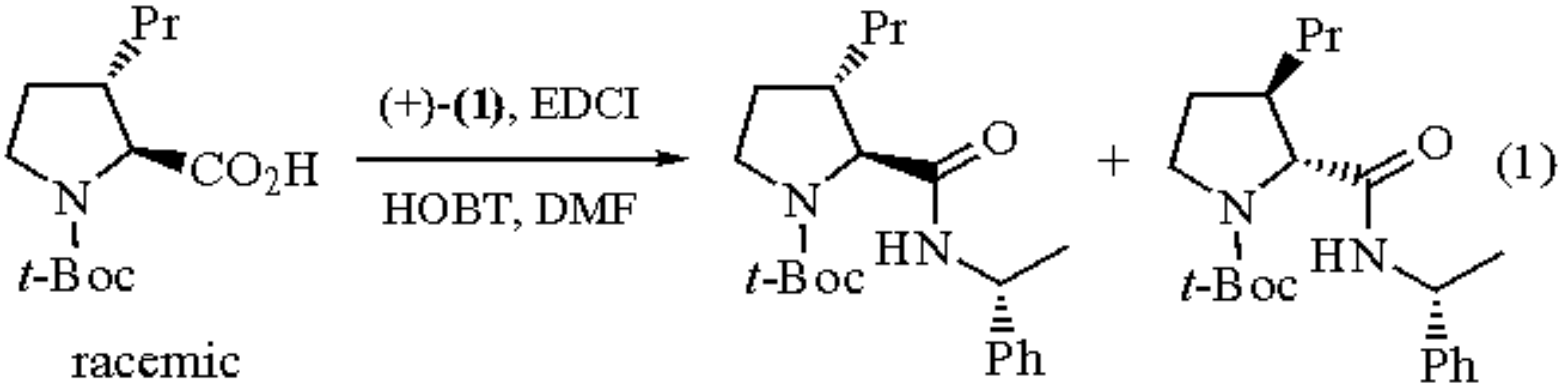

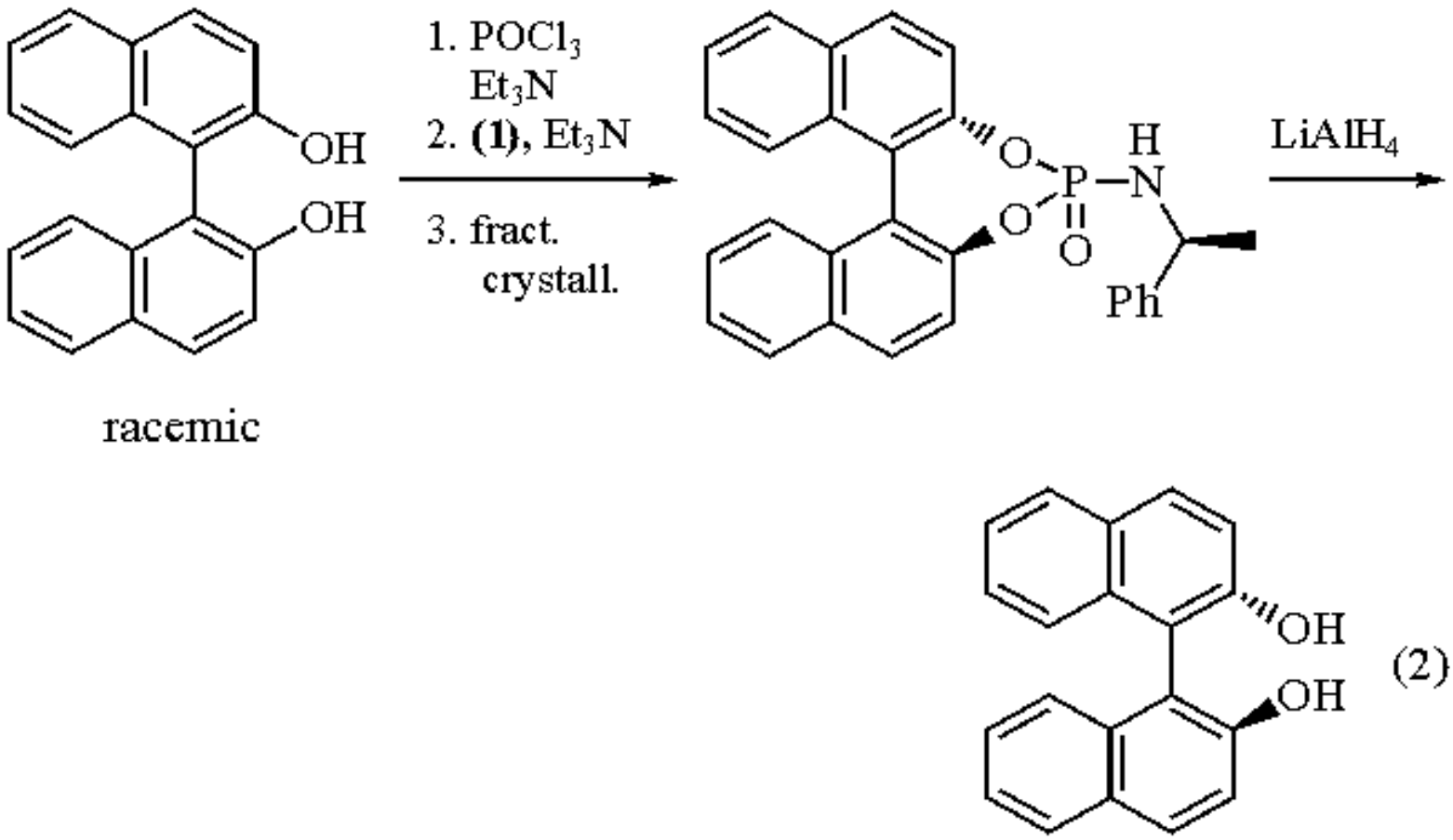

(2)

Racemic compounds other than carboxylic acids have also been resolved by reaction with enantiomerically pure (**1**) and separation of the corresponding diastereomeric mixtures by physical methods. For example, reaction of a racemic β-substituted γ-butyrolactone with (**1**) yields a mixture of hydroxy amides, which can be separated by fractional recrystallization and chromatography (eq 3).[14] Amide hydrolysis regenerates the chiral hydroxy acids, which spontaneously cyclize to produce the chiral lactones.

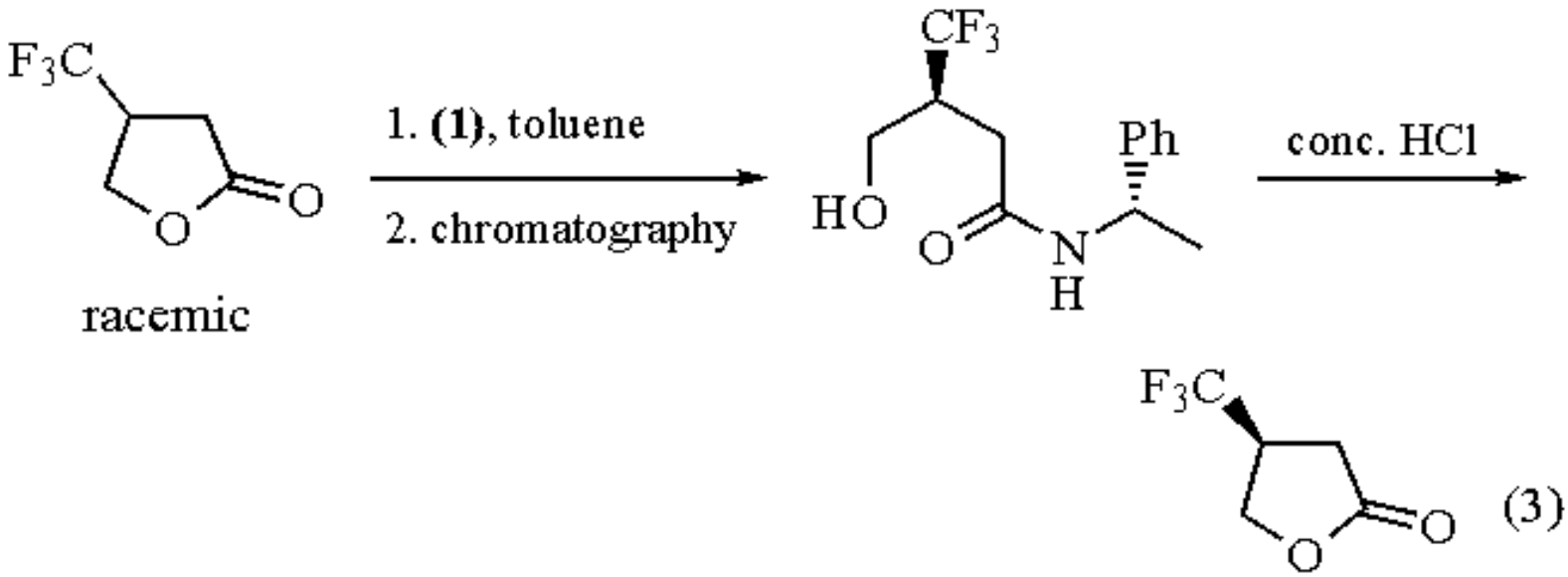

(3)

The displacement of a variety of leaving groups by (**1**) produces diastereomeric mixtures of amines, which can be separated into diastereomerically pure secondary amines and, following reductive removal of the α-methylbenzyl

group, serve as a source of chiral primary amines (eq 4).[15]

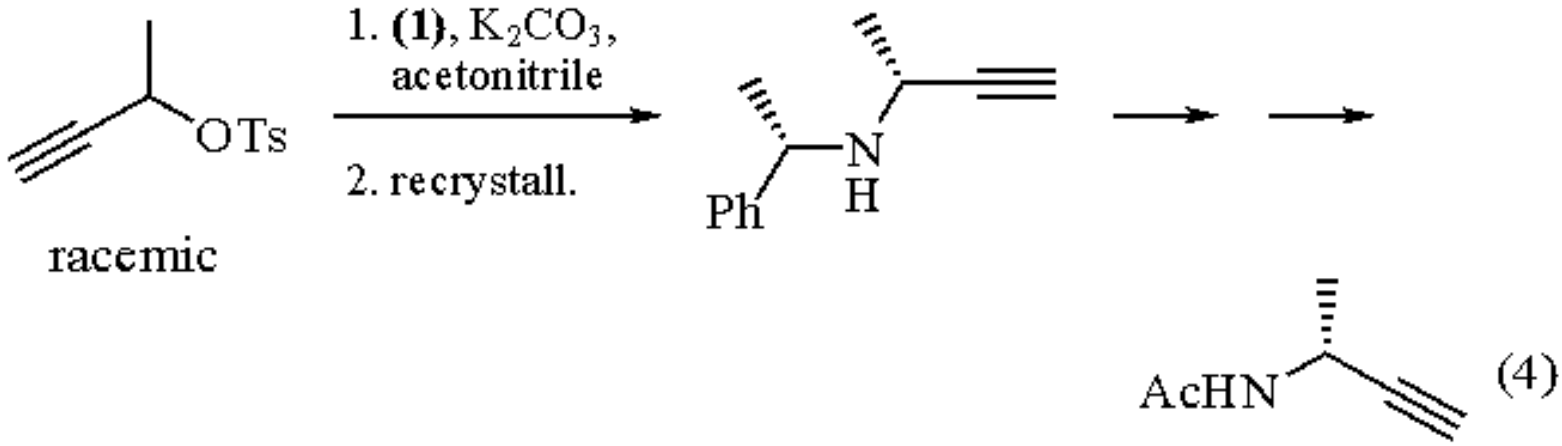

Reagent for the Determination of Enantiomeric Purity of Carboxylic Acids.

Amine (**1**) is frequently used as a derivatizing reagent for determining the enantiomeric purity of carboxylic acids by HPLC, with limits of detection often as low as 1%. Most commonly used coupling methods include use of dehydrating agents such as ***1,3-Dicyclohexylcarbodiimide*** (eq 5)[16] and the mixed anhydride method (eq 6).[17]

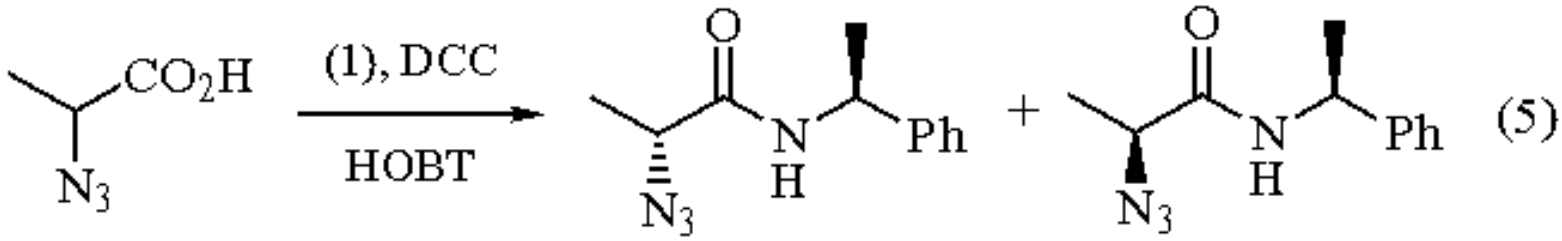

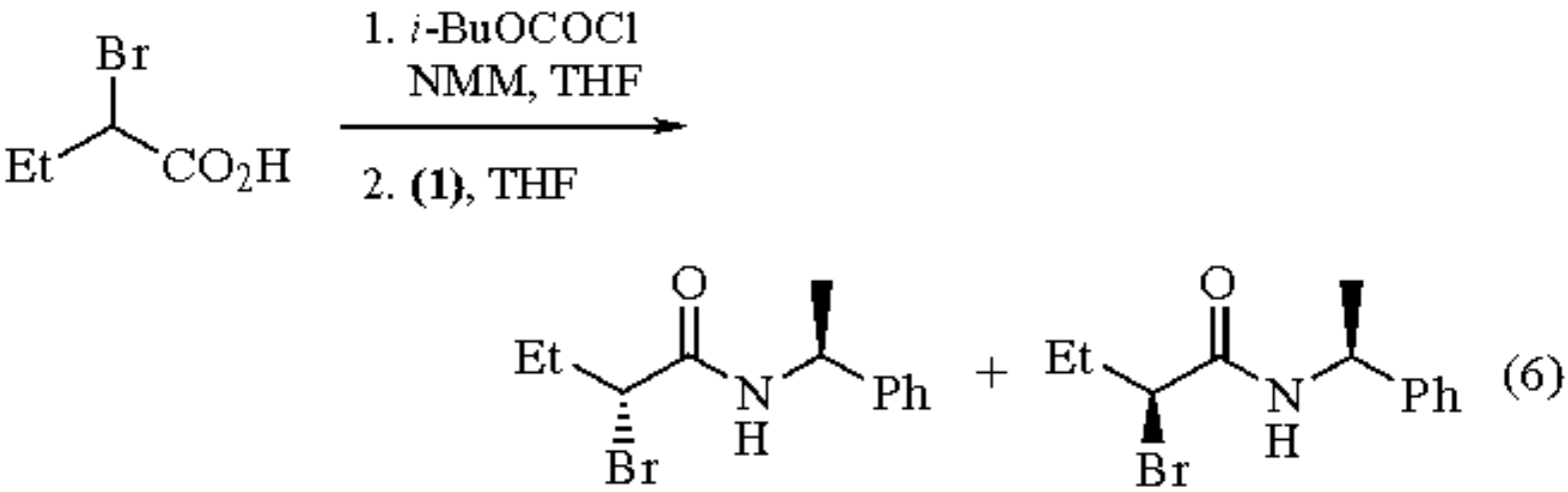

Stereospecific Reactions of Carbonyl Compounds.

One of the most frequent uses of both enantiomers of reagent (**1**) is in promoting the stereospecific reaction of

carbonyl compounds via the corresponding chiral imines. The transfer of chirality from (**1**) to the newly formed bonds is generally most effective in cyclization reactions. Some examples are the Lewis acid-catalyzed cyclization of o-unsaturated aldehyde imines to produce amines of high enantiomeric purity (eq 7),[18] the enantioselective synthesis of γ,δ-unsaturated aldehydes via the aza-Claisen rearrangement of derivatives of (**1**) (eq 8),[19] and the asymmetric Lewis acid-catalyzed aza-Diels-Alder reaction of aldehyde imines with electron-rich dienes (eq 9).[20]

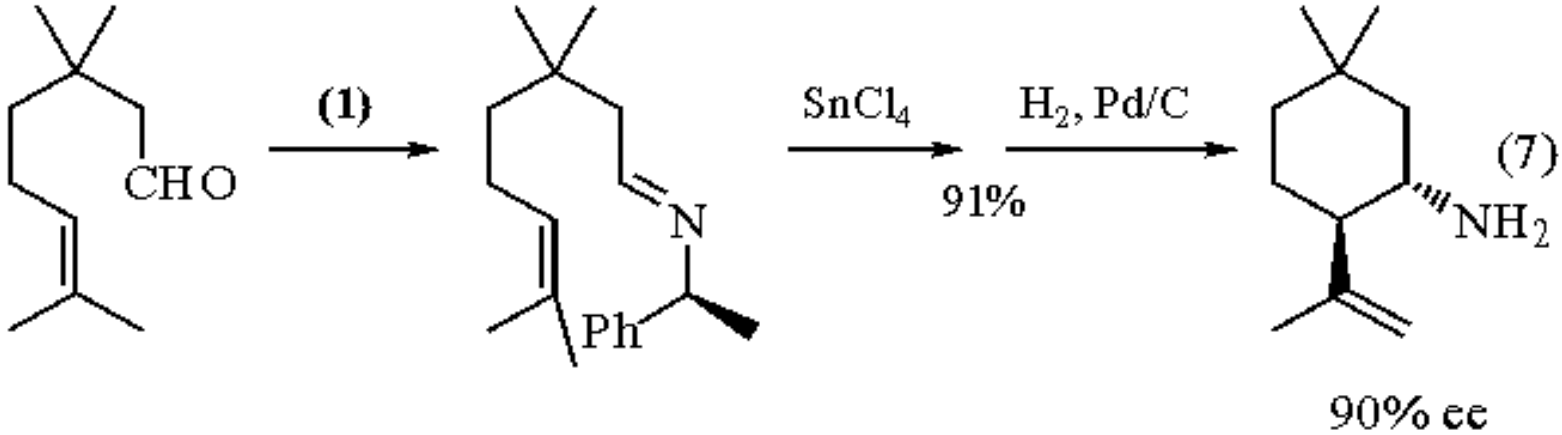

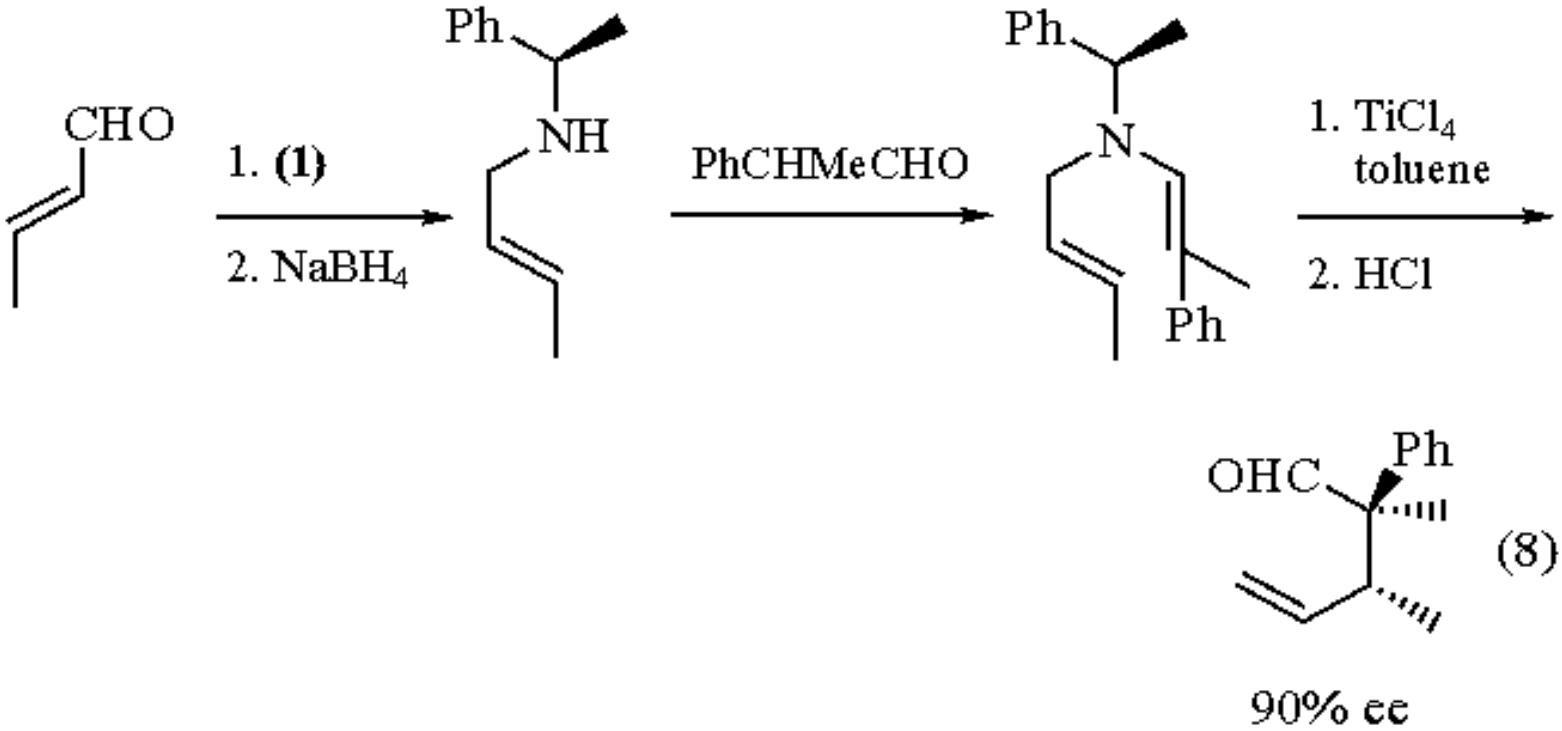

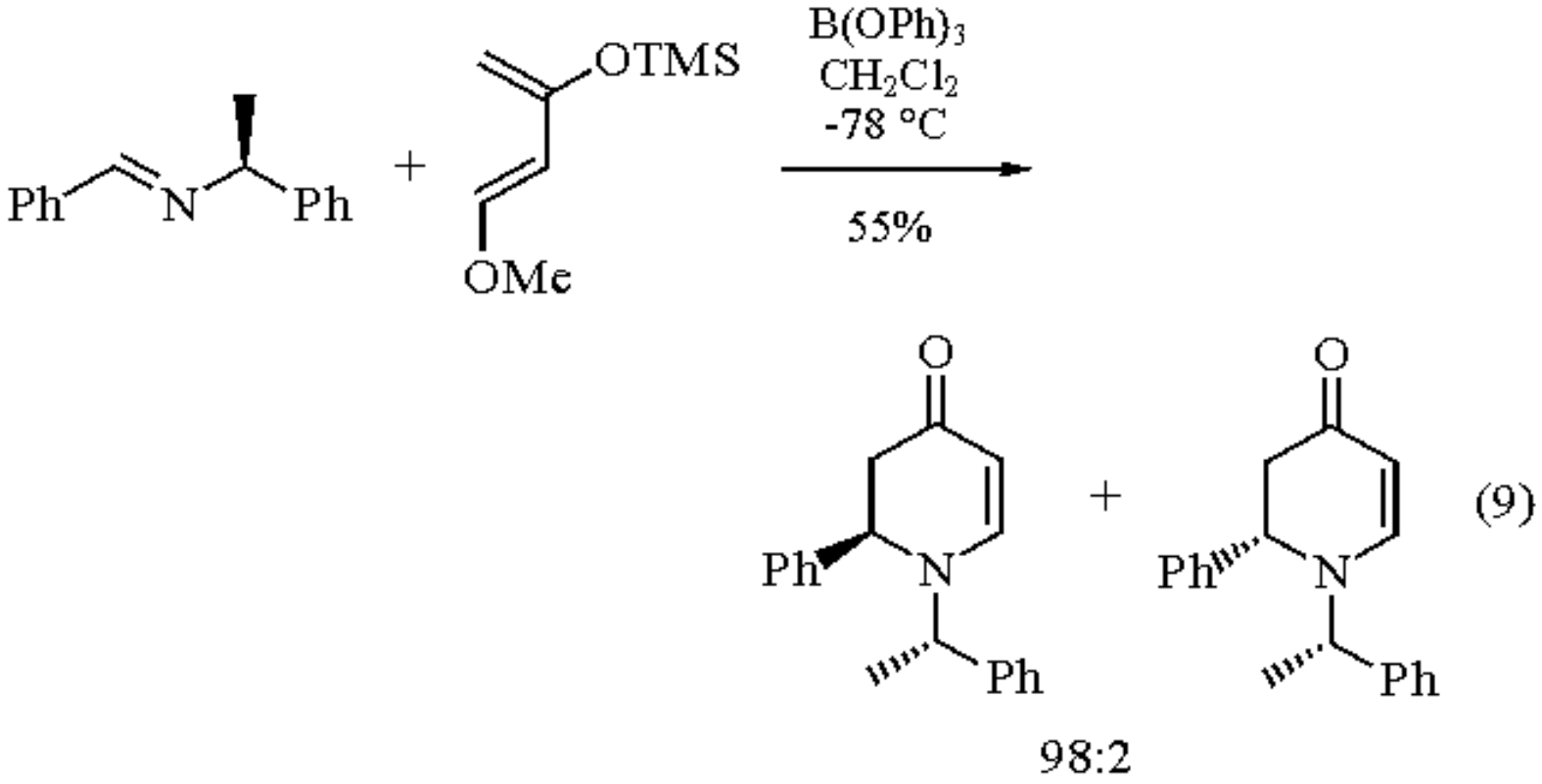

Enantiomerically pure disubstituted β-lactams are also available by cyclization of acyclic intermediates containing (**1**) as a chiral appendage, which is later removed by catalytic hydrogenation (eq 10).[21]

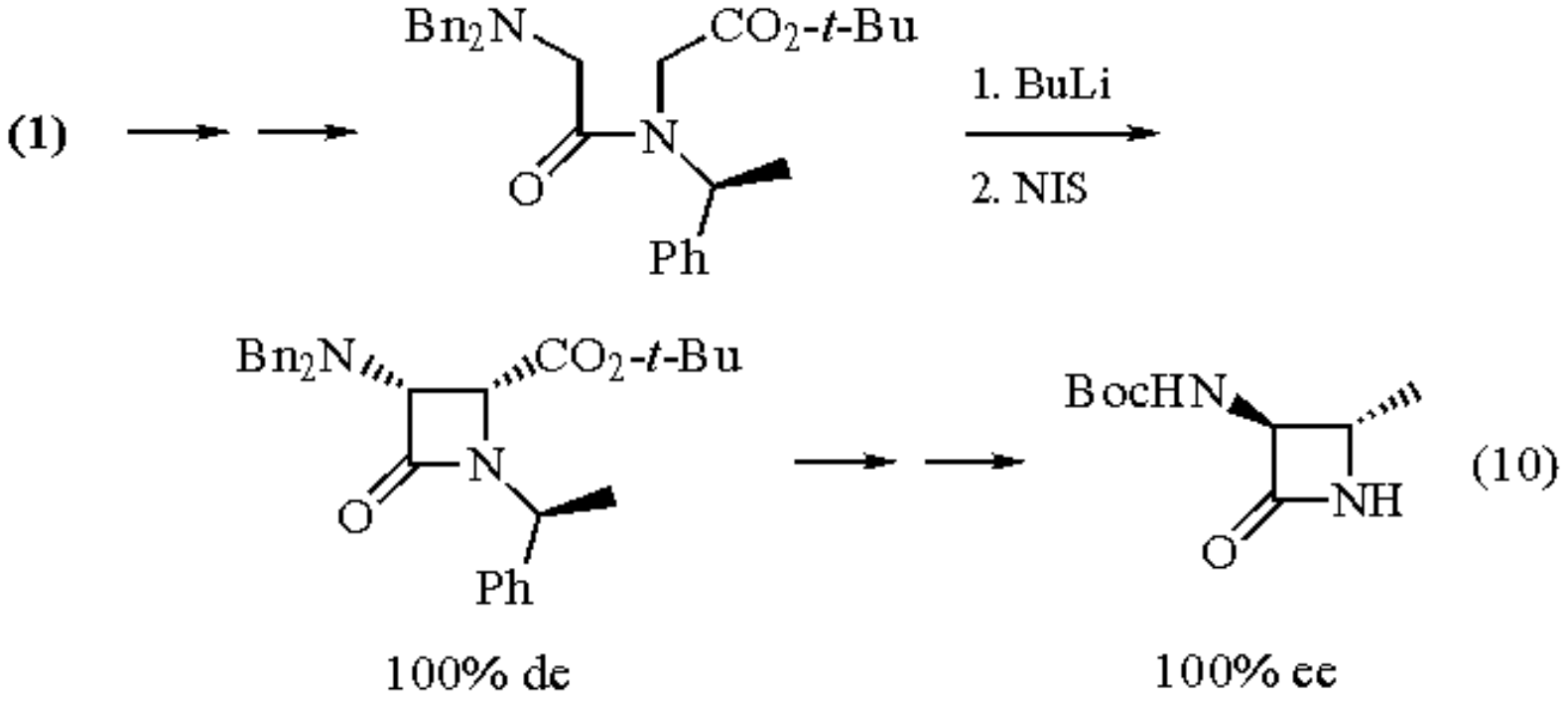

Examples of highly stereoselective acyclic reactions include the Zr-mediated coupling of aldehydes with imines of (**1**) to produce chiral amino alcohol derivatives (eq 11),[22] and the addition of cyanide to aldimines of (**1**) to yield intermediates that can be elaborated into enantiomerically pure α-amino acids (eq 12).[23]

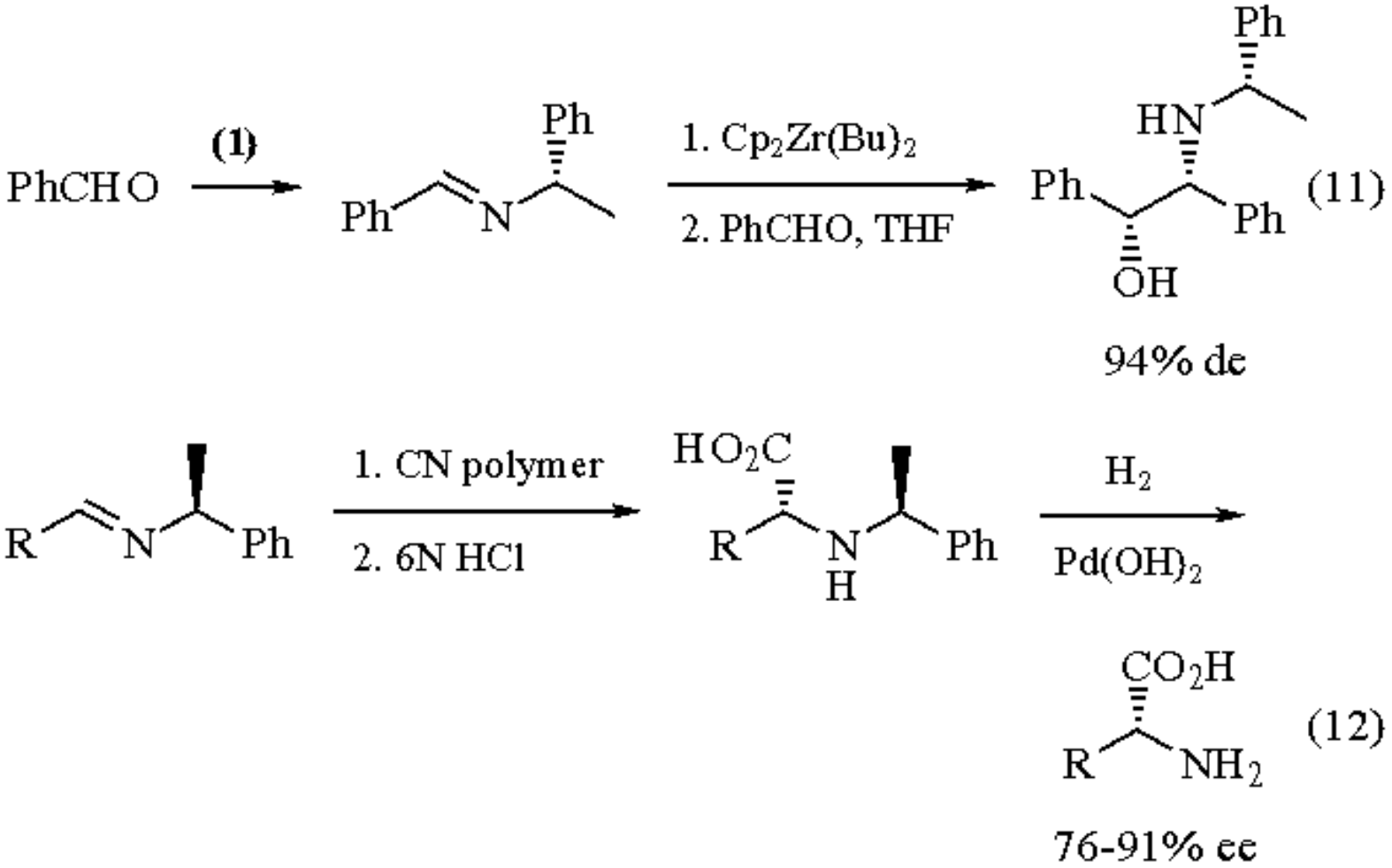

Another frequent use of (**1**) and its enantiomer is the stereospecific conjugate addition of carbonyl compounds to α,β-unsaturated systems. Most published examples contain chiral imine derivatives of cyclic ketones, which add to α,β-unsaturated esters and ketones in a highly stereoselective manner (eqs 13 and 14).[24,25] When the ketone is not symmetrically substituted, reaction usually occurs at the most substituted α-position, including those cases where the ketone is α-substituted by oxygen (eq 15).[26] High stereoselectivity can also be achieved when the Michael acceptor is other than an unsaturated ketone or ester, such as a vinyl sulfone (eq 16).[27] Intramolecular variations of this transformation have also been described (eq 17).[28]

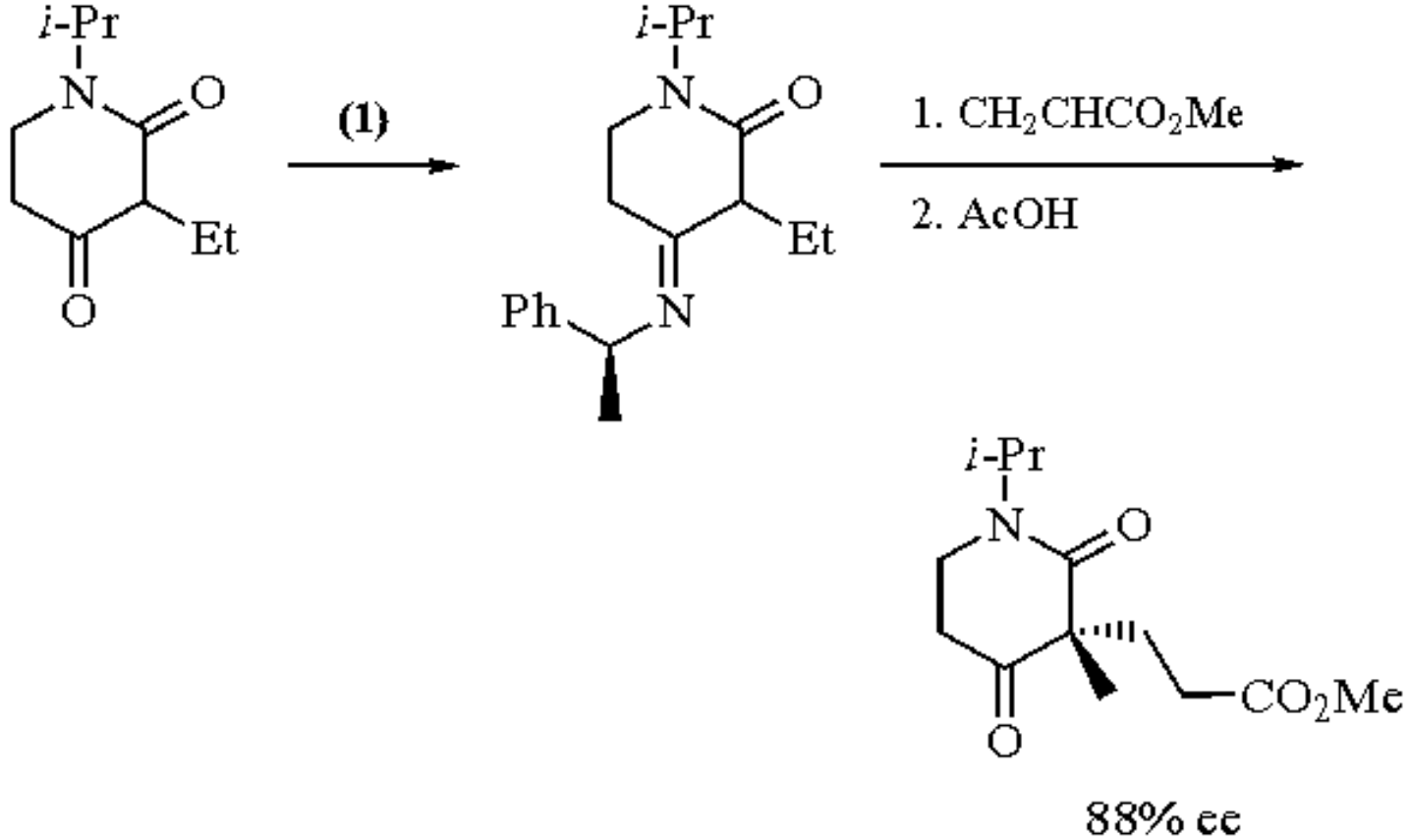
i-Pr
N
O
Et
O
(1)
i-Pr
N
O
Et
Ph
N
1. CH2CHCO2Me
2. AcOH
i-Pr
N
O
CO2Me
O
88% ee

(13)

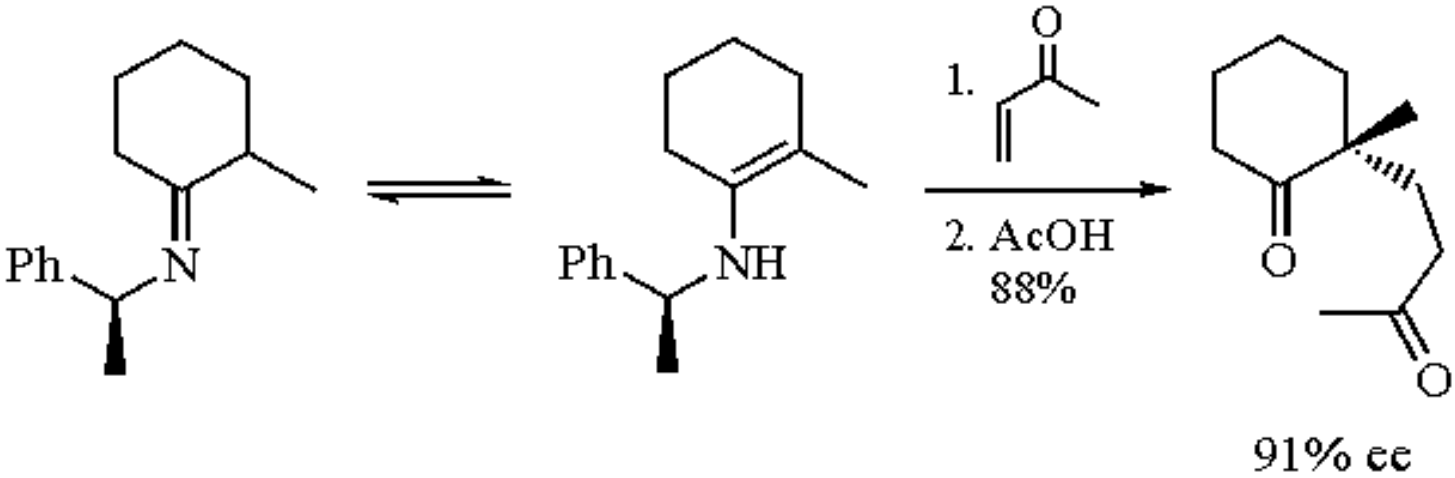
Ph
N
Ph
NH
1.
O
2. AcOH
88%
O
O
91% ee

(14)

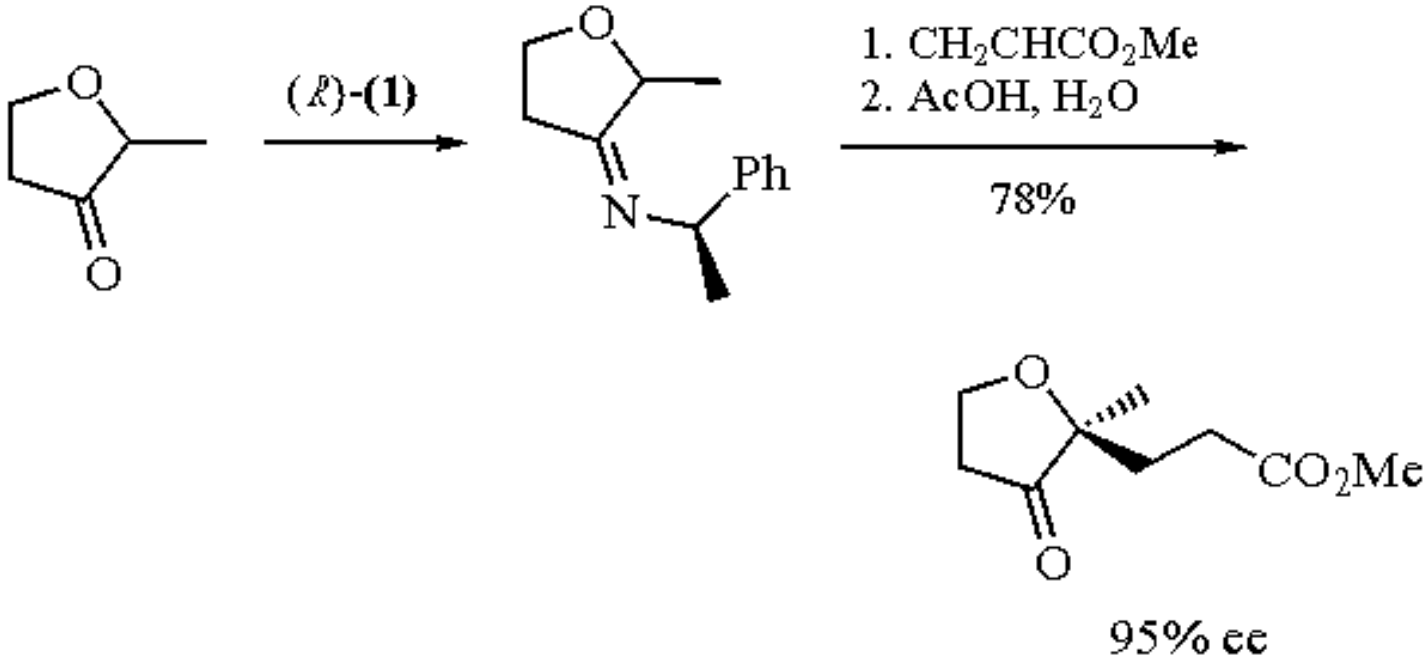
(R)-(1)
1. CH2CHCO2Me
2. AcOH, H2O
78%
Ph
N
O
CO2Me
95% ee

(15)

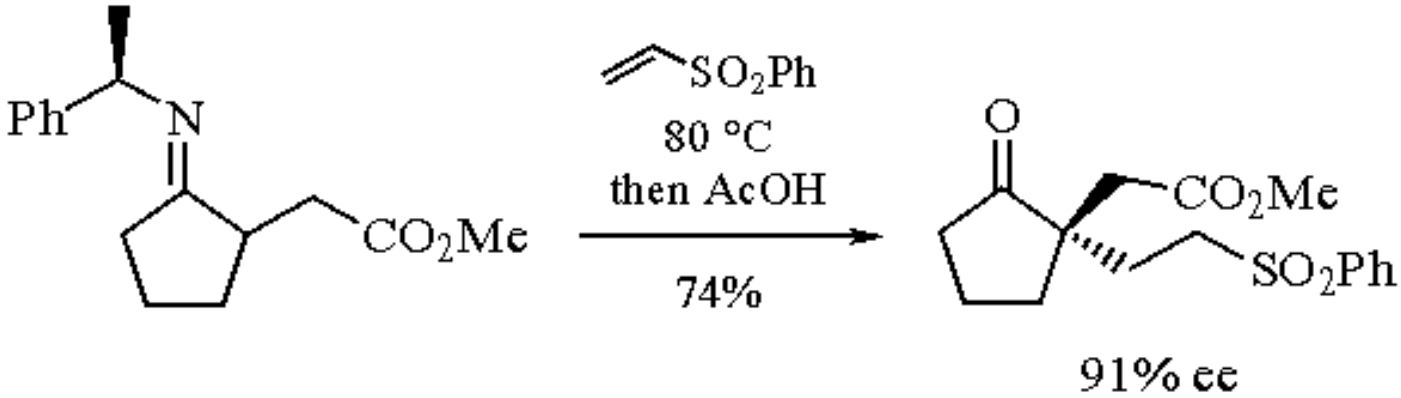
Ph
N
CO2Me
SO2Ph
80 °C
then AcOH
74%
CO2Me
SO2Ph
91% ee

(16)

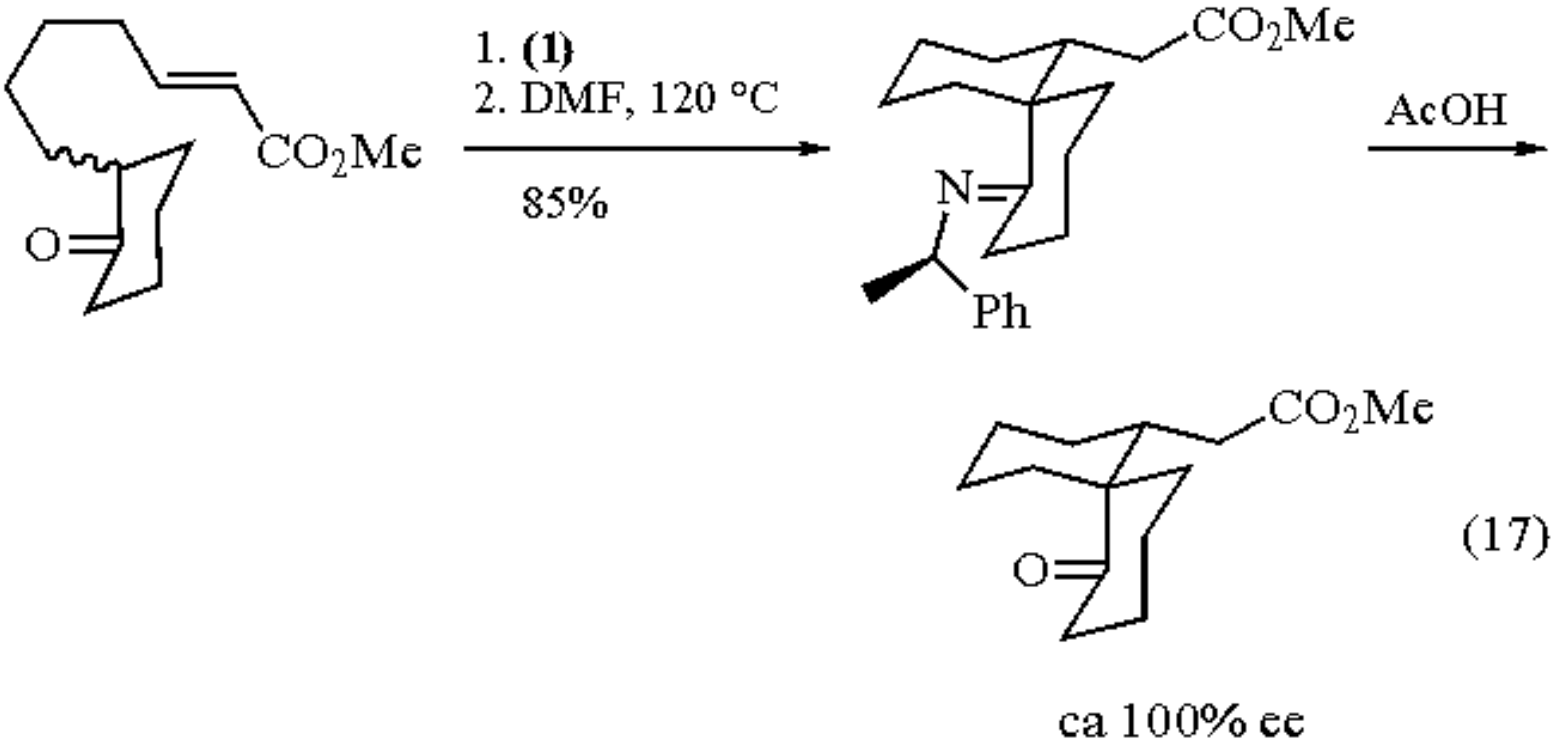
CO2Me
1. (1)
2. DMF, 120 °C
85%
N
Ph
AcOH
CO2Me
ca 100% ee

(17)

Stereospecific Reductive Amination of Carbonyl Compounds.

Catalytic or chemical reduction of chiral imines derived from (**1**) often proceeds with high diastereoselectivity. Reductive removal of the α-methylbenzyl group yields chiral primary amines (eqs 18 and 19).[29,30]

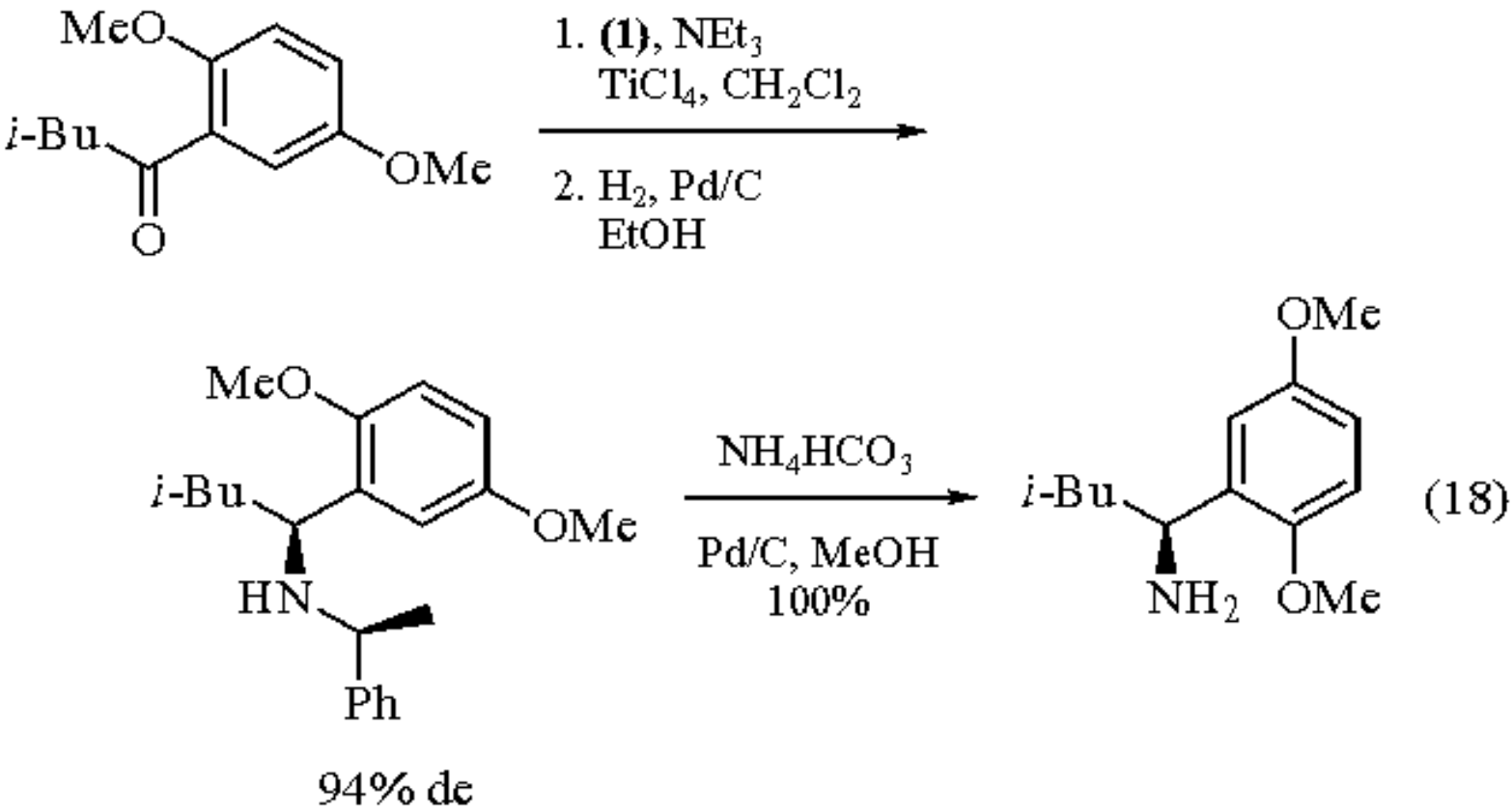

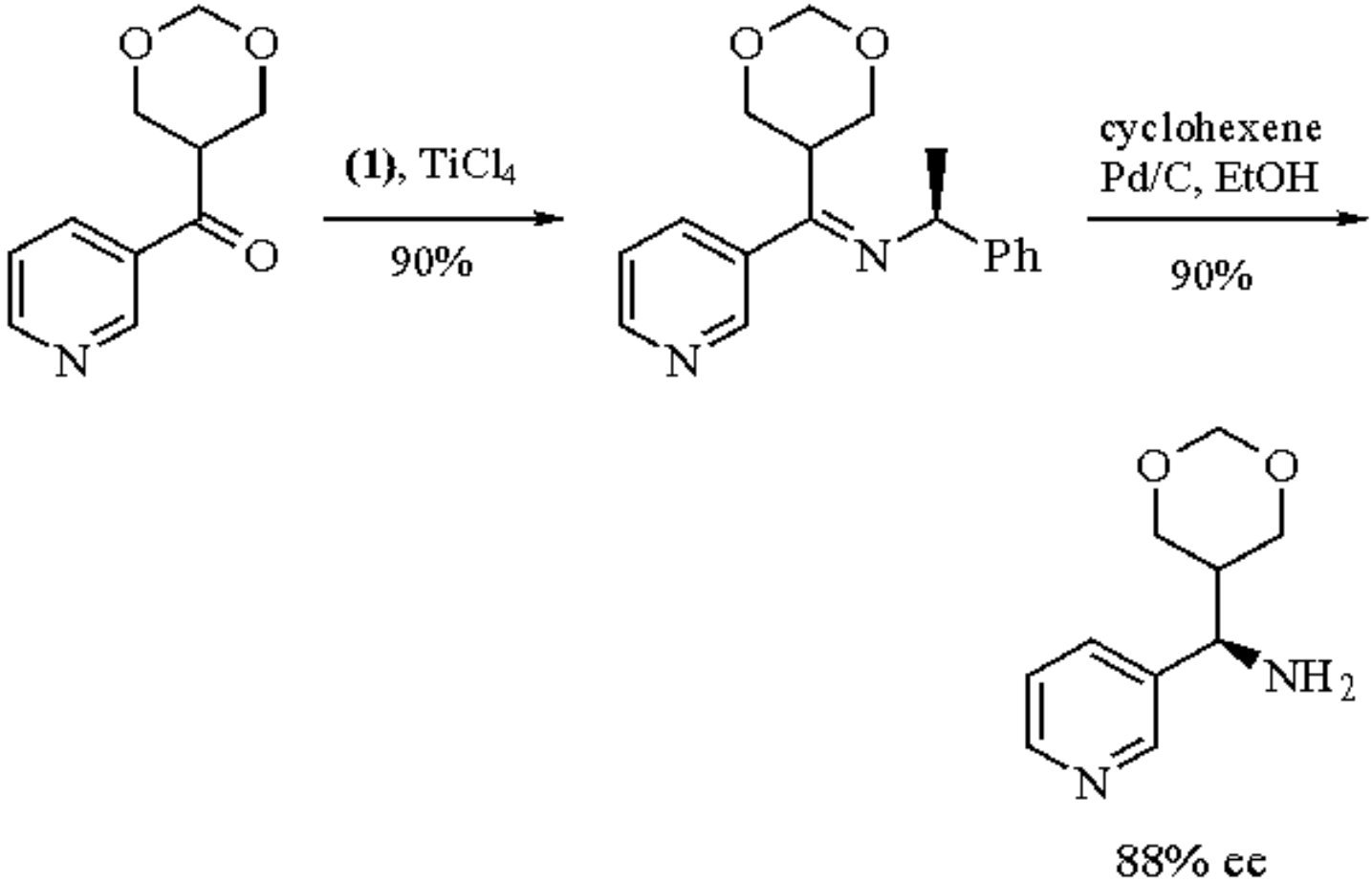

(19)

Removable Chiral Appendage.

Even in reactions that proceed with moderate stereoselectivity, incorporation of a chiral moiety such as (**1**) frequently provides an opportunity to easily separate diastereomeric products. For example, the introduction of (**1**) into an imidazolone structure allows the easy separation of diastereomers by chromatography. Reductive removal of the chiral appendage and imidazolone hydrolysis provides a synthesis of optically pure α-amino acids (eq 20).[31] In another example, even though the conjugate addition of (**1**) to methyl crotonate proceeds with low stereoselectivity, the diastereomeric conjugates are easily separated by chromatography and elaborated to provide optically active β-amino esters (eq 21).[32] Similarly, cycloaddition of the aldimine of (**1**) with a substituted ketene produces a mixture of β-lactams, which can be separated by chromatography as a source of optically active β-lactams (eq 22).[33]

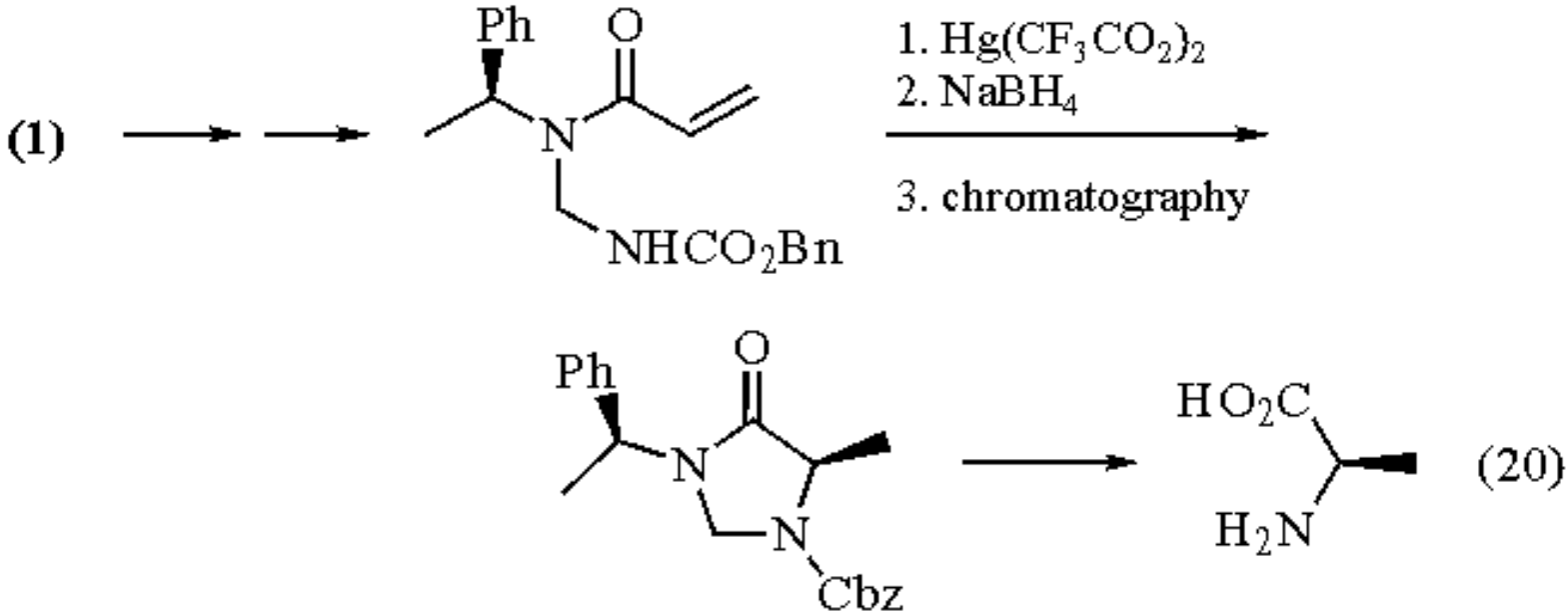
(1)
Ph
O
N
NHCO2Bn
1. Hg(CF3CO2)2
2. NaBH4
3. chromatography
Ph
O
N
N
Cbz
HO2C
H2N
(20)

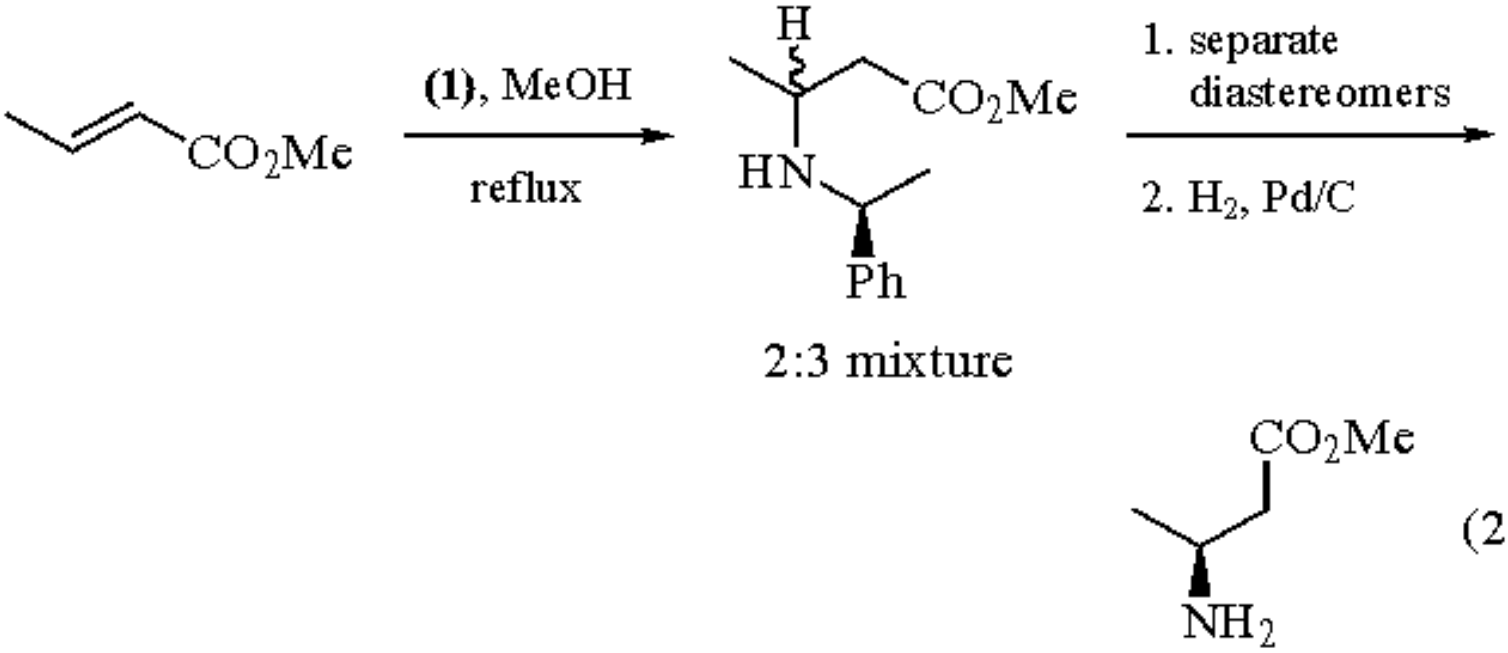
CO2Me
(1), MeOH
reflux
H
CO2Me
HN
Ph
2:3 mixture
1. separate diastereomers
2. H2, Pd/C
CO2Me
NH2
(21)

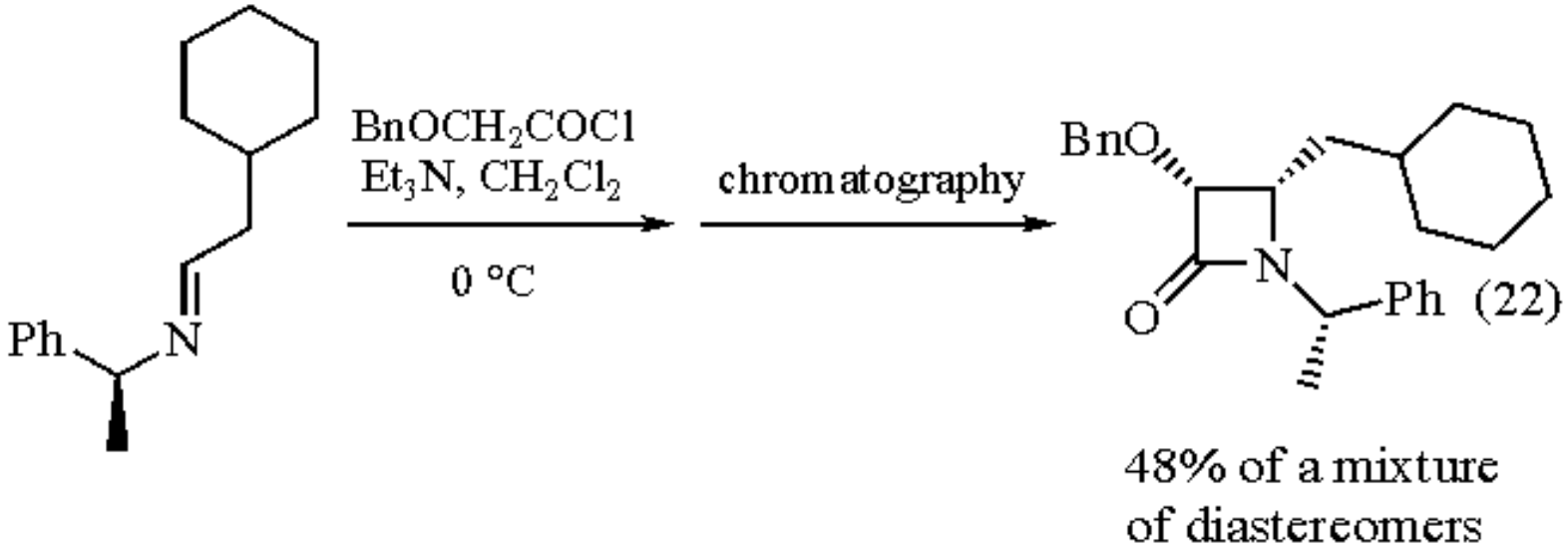

Miscellaneous Uses.

Substituted derivatives of (**1**), e.g. (**7**), react with α,β-unsaturated carbonyl systems in a highly stereoselective manner to produce chiral β-aminocarbonyl compounds.[34] The lithium amides of a different type of substituted derivatives, e.g. (**8**), have been used to deprotonate symmetrical ketones, usually cyclic, in a highly stereoselective manner.[35]

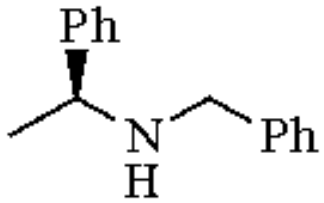

(7)

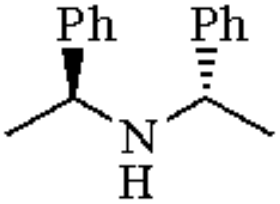

(8)

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2. Brown, E.; Viot, F.; Le Floc'h, Y. *TL* **1985**, *26*, 4451.
3. (a) Wu, M.-J.; Pridgen, L. N. *JOC* **1991**, *56*, 1340. (b) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *JOC* **1991**, *56*, 4.
4. Dale, J. A.; Dull, D. L.; Mosher, H. S. *JOC* **1969**, *34*, 2543.
5. Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *JOC* **1989**, *54*, 5826.
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Methyl *N*-Benzylidenealaninate

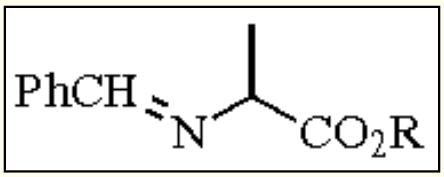

D-(**1**; R = Me)

[112674-72-3] · $C_{11}H_{13}NO_2$ · Methyl *N*-Benzylidenealaninate · (MW 191.25) L-(**1**)

[40216-71-5] DL-(**2**; R = Et)

[60930-36-1] · $C_{12}H_{15}NO_2$ · Ethyl *N*-Benzylidenealaninate · (MW 205.28) L-(**2**)

[60855-77-8] L-(**3**; R = *t*-Bu)

[78688-64-9] · $C_{14}H_{19}NO_2$ · *t*-Butyl *N*-Benzylidenealaninate · (MW 233.34) L-(**4**; R = $PhCH_2$)

[81852-01-9] · $C_{17}H_{17}NO_2$ · Benzyl *N*-Benzylidenealaninate · (MW 267.35)

(metalation generates azadienolate anions which undergo α-alkylation and cycloaddition with electron-deficient alkenes and alkynes; alkylation and hydrolysis gives α-alkyl-α-methyl amino acids; cycloaddition affords 3-pyrroline- and pyrrolidine-2-carboxylates; ketenes and 2-(ethoxycarbonyl)allylzinc bromide add to the imine to form β-lactams and α-methylene-γ-lactams, respectively)

Physical Data: L-(**1**) bp 84 °C/0.04 mmHg. L-(**2**) bp 100 °C/0.3 mmHg.

Preparative Methods: prepared by condensation of benzaldehyde with the alkyl alaninate ester hydrochloride[1,2] in the presence or absence of dehydrating agents (molecular sieves or Na_2SO_4).[36,41] For example, a solution of triethylamine (30.3 g, 0.3 mol) in CH_2Cl_2 is added slowly to a suspension of alanine methyl ester hydrochloride (41.8 g, 0.3 mol) and freshly distilled benzaldehyde (31.8 g, 0.3 mol) in CH_2Cl_2 cooled to 0 °C. The reaction mixture is stirred overnight at rt. The product is isolated and distilled under reduced pressure to give 46 g (80%) of the imine.

Handling, Storage, and Precautions: although stable at rt, the compound is normally stored under argon at 0 °C.

α-Alkylation: Synthesis of α-Methyl α-Amino Acids.

Benzaldimine esters of alanine are versatile alanine anion synthons. The protected alaninates can be deprotonated with a variety of bases (typically ***Lithium Diisopropylamide***, ***Lithium Hexamethyldisilazide***, or ***Potassium t-Butoxide*** in THF at -

78 °C, or ***Potassium Carbonate*** or ***Potassium Hydroxide*** at rt in the presence of PTC) (eq 1). The anion reacts regiospecifically with alkyl halides (low enantiometric excess of ~16-50% is obtained with asymmetric PTC),[16] carbonyl derivatives, or Michael acceptors to yield, after deprotection, α-methyl α-amino acid analogs. Numerous examples of this methodology have been reported (Table 1). The adducts can be either purified by distillation in vacuo or directly hydrolyzed in acidic medium to the corresponding free amino acid analogs.

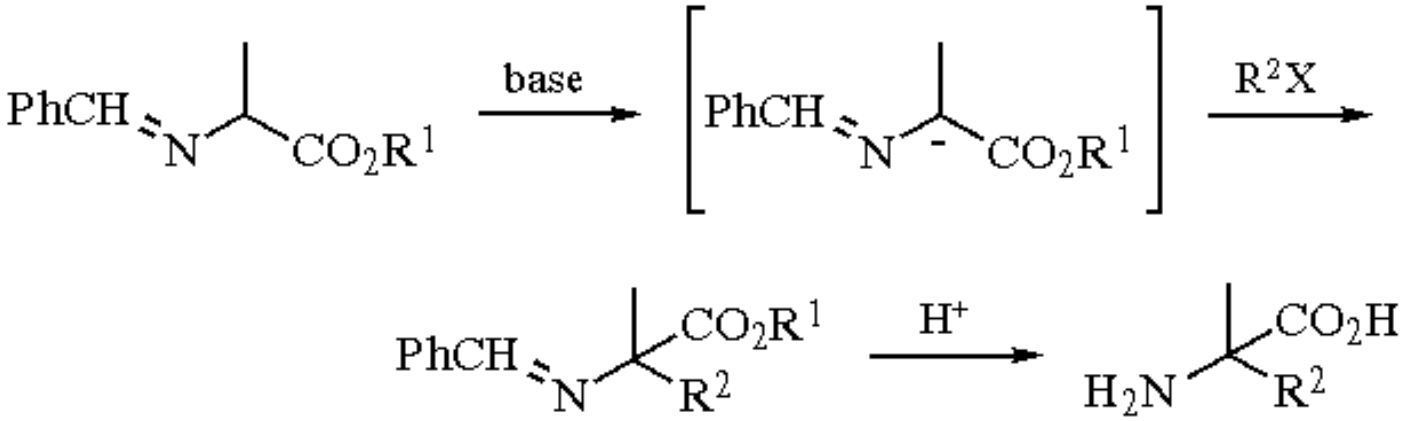

(1)

Table 1 a-Methyl a-Amino Acids Synthesized According to eq 1

Side chain	Type of base[a]	Yield (%)
Alkyl[5,16,40]	A	>80
Benzyl[5,16,40]	A, B	>80
Allyl[5,16,40]	A, B	>80
Cyanomethyl[5]	A	>80
Methoxymethyl[5]	A	>80
Methoxymethylphenyl[40]	B	90
Methylthiomethyl[5]	A	>80
Phthalimidoalkyl[5]	A	>80
Halomethyl[6,17,41]	A, B	>80
Haloalkyl[13]	A	>65
Hydroxymethyl[3]	A	~27
Arylsulfonylvinyl[7]	A	57
Heterocyclylmethyl[8,12,16]	A	>80
Carboxyalkyl[9,11,26,40]	A, B	>80
Cyanoalkyl[10,26,40]	B	92

Cyanoalkyl[10,20,40]	B	92
Phosphoalkyl[12]	A	
Benzylselenomethyl[14]	A	~65
Aryl[15]	B	~45

[a] Key to bases used: A = LDA, LHMDS, NaH, or KH; B = PTC with KOH, K_2CO_3, or Ar_3BiCO_3

γ-Alkylation.

An abnormal alkylation in the γ-position is observed with hindered α-bromo esters (eq 2).

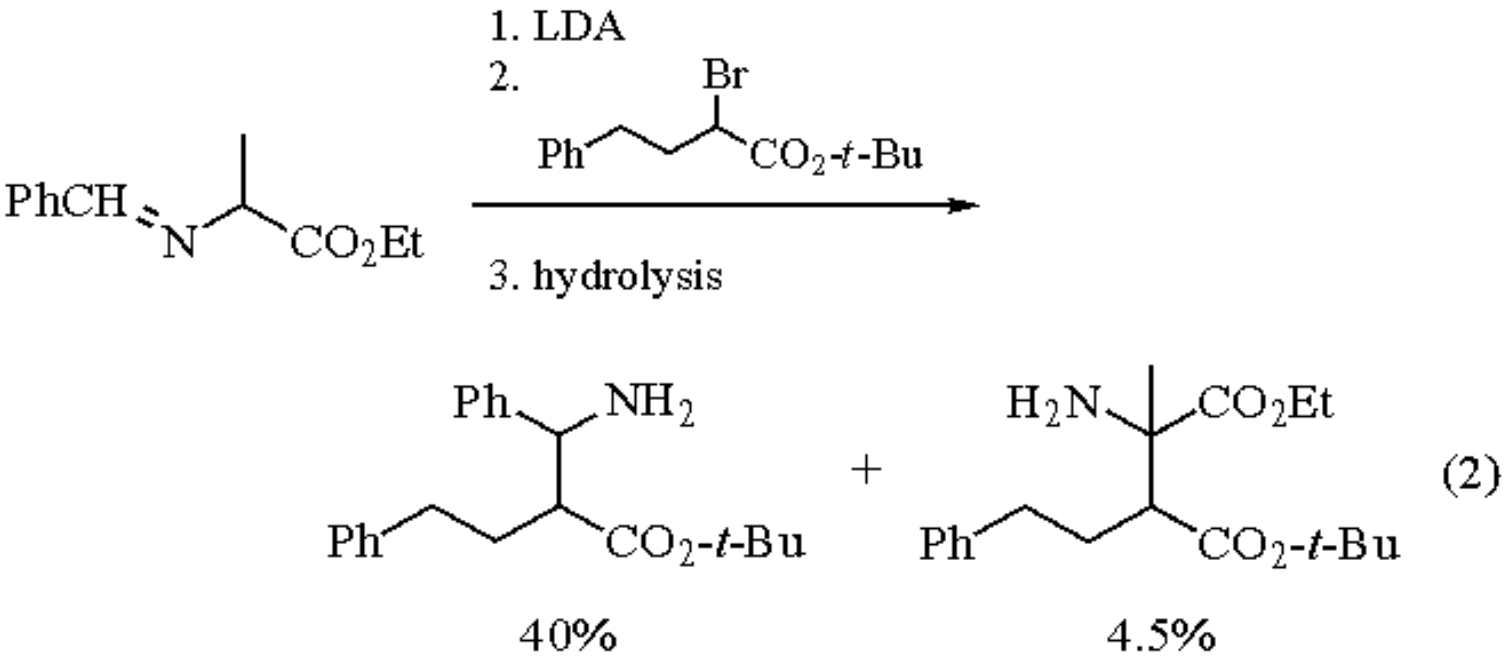

Preparation of 3-Pyrrolines and Pyrrolidines.

N-Benzylidenealaninate anions react with alkenes and alkynes bearing electron-withdrawing groups to give [2 + 3] adducts. The reaction proceeds in good yield through a Michael addition of the α-anion followed by cyclization on the imine to give the 3-pyrroline and pyrrolidine derivatives (eq 3).

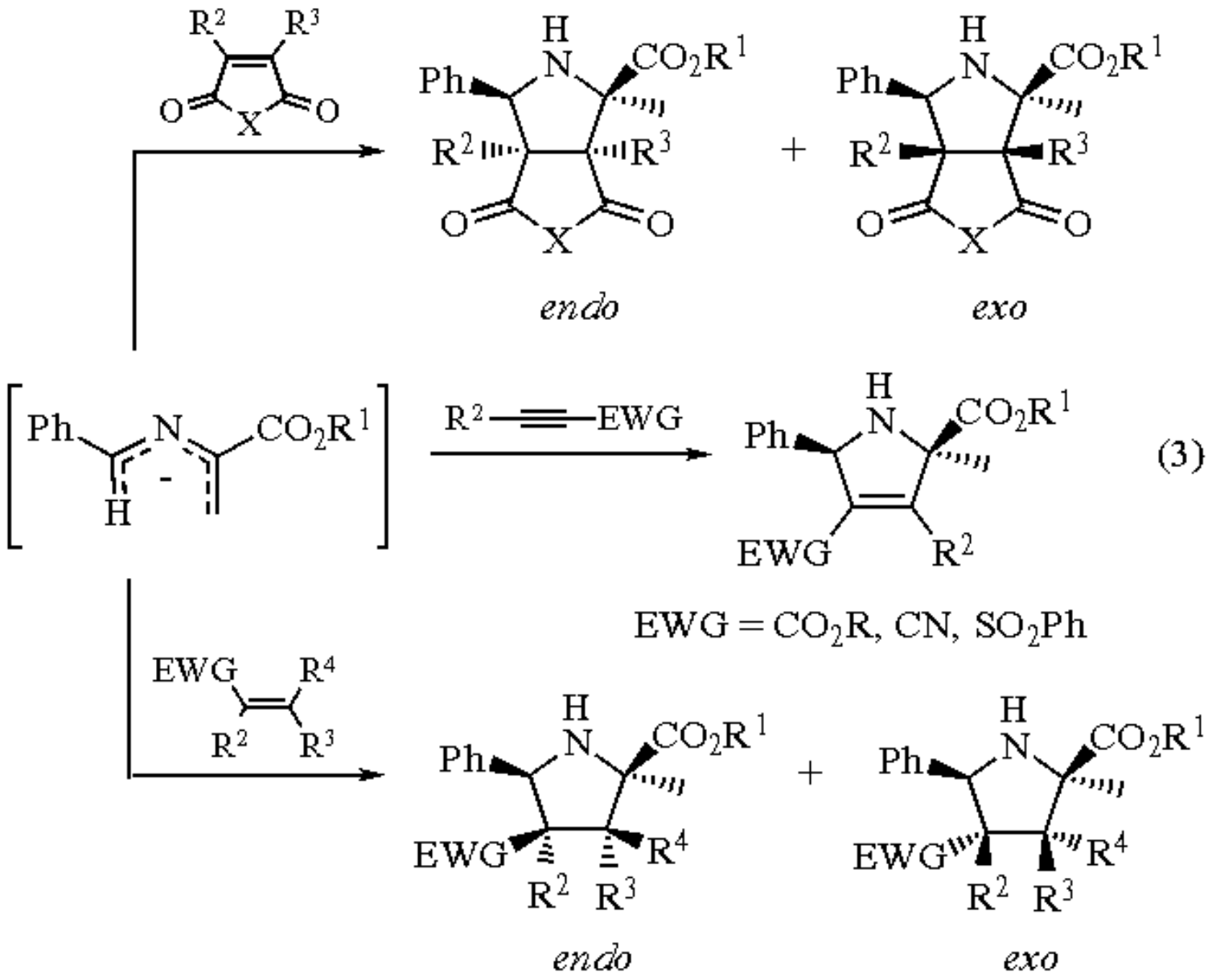

Generally, the addition is carried out in refluxing toluene or xylene[2-5,18-22,31] and the 5-*endo-trig* cyclization adducts[26] are formed; the *endo* product is usually the major isomer. The *endo*:*exo* ratio varies from 2.3:1 to 6.9:1 for the monocyclic products. Only the *endo* isomer is observed for the bicyclic pyrrolidines.[22] The use of more polar solvents (acetonitrile, THF, CH_2Cl_2)[24,25,29] with nitrogen bases (***Triethylamine***, ***1,8-Diazabicyclo[5.4.0]undec-7-ene***)[25] and metal ions (Ag, Li, Zn, Mg)[16,23-25,29,33] increases the rate of the reaction and also the amount of *endo* adduct, which in some cases is the sole isomer formed.[24,29,33] The use of stronger bases (***Sodium Hydride***,[30] benzyltrimethylammonium methoxide[26]) yields mixtures of *endo* and *exo* adducts. Phenyl vinyl sulfone in DMSO containing NEt_3-LiOAc[28] gives a 3:10 mixture of *endo* and *exo* adducts. The Ti^{IV} salts (***Chlorotitanium Triisopropoxide***, ***Dichlorotitanium Diisopropoxide***)[27,32] of methyl *N*-benzylidenealaninate anions give a γ-cycloaddition adduct with methyl acrylate (eq 4).

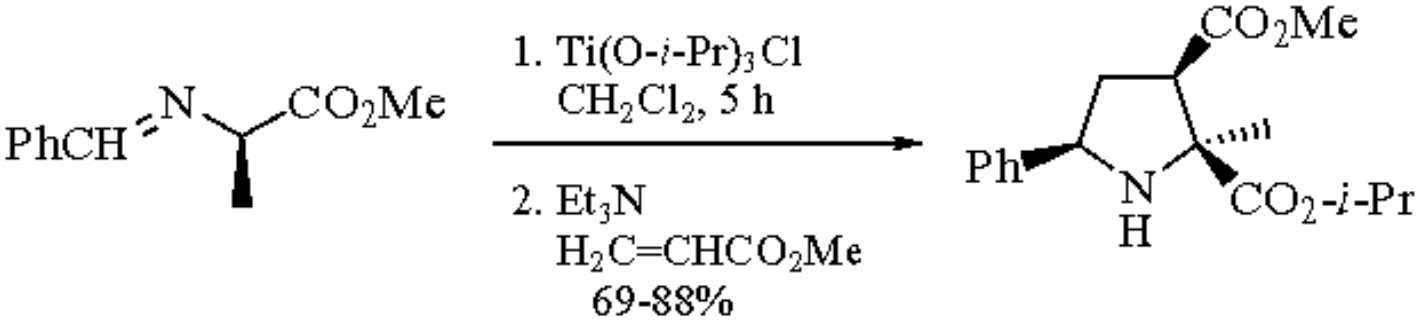

(4)

Preparation of 3-Substituted 4-Phenyl-2-azetidinones (β-Lactams).

N-Benzylidenealaninates react with ketenes (generated in situ by treatment of the corresponding acid chloride with triethylamine) to give diastereoisomeric mixtures of *cis*-β-lactams (eq 5).[34-37]

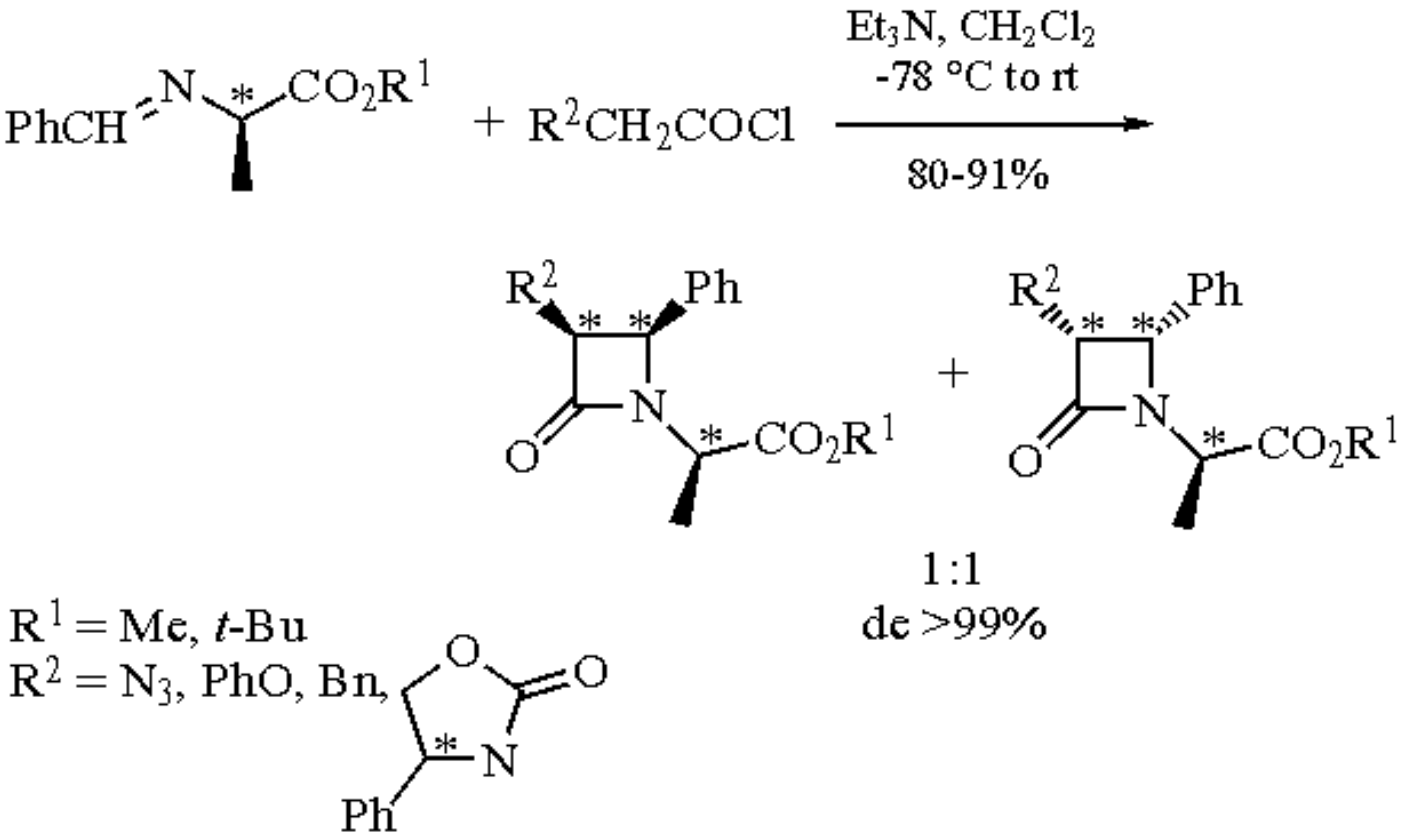

(5)

Preparation of γ-Lactams.[38]

Addition of an excess of organozinc reagents derived from 2-(bromomethyl)acrylates to racemic *N*-benzylidenealaninate gives the corresponding α-methylene-γ-lactams as racemic mixtures. If the pure (*R*) or (*S*) isomer of the imine is used, only one enantiomer (*RR*) or (*SS*) of the α-methylene-γ-lactam is obtained with ee >95% (eq 6).

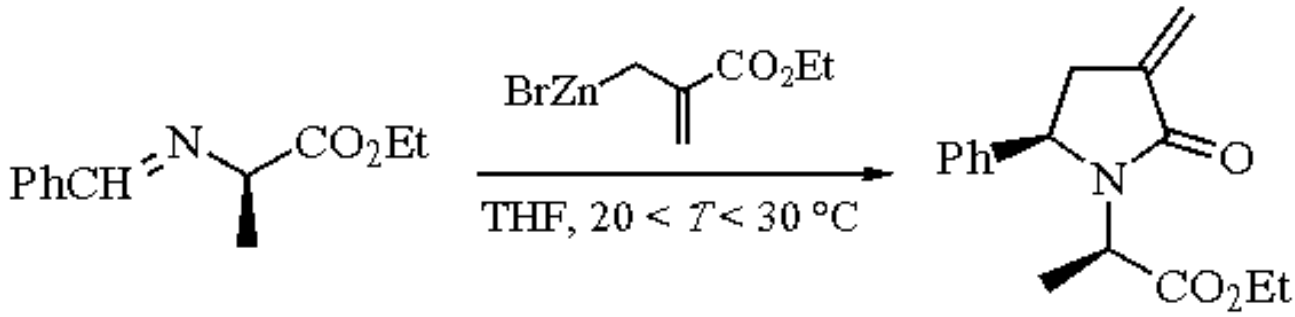

(6)

N-Oxidation: Synthesis of Oxaziridines and Nitrones.[39]

N-Oxidation of the imine by ***Monoperoxyphthalic Acid*** affords oxaziridines, which rearrange to nitrones by acid catalysis (eq 7).

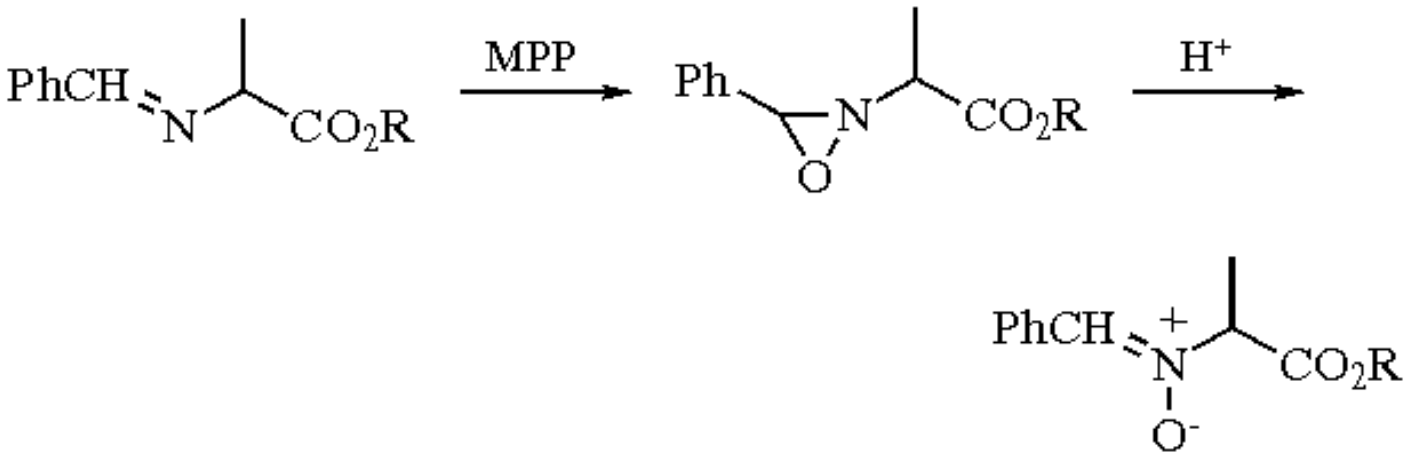

(7)

Related Reagents.

Benzophenone Imine; ***1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone***; ***Diethyl Acetamidomalonate***; ***Ethyl N-Benzylideneglycinate***; ***Ethyl N-(Diphenylmethylene)-2-acetoxyglycinate***; ***Ethyl N-(Diphenylmethylene)glycinate***; ***Ethyl N-Benzylideneglycinate***; ***Methyl α-Phenylglycinate***.

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Methylbis(methylthio)sulfonium Hexachloroantimonate[1]

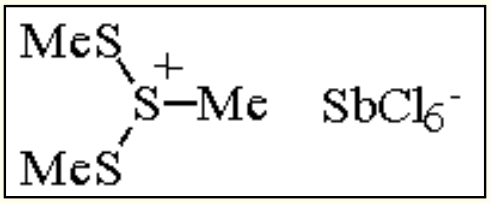

[56648-69-2] · $C_3H_9Cl_6S_3Sb$ · Methylbis(methylthio)sulfonium Hexachloroantimonate · (MW 475.78)

(methylthiolating agent for several functional groups;[1] can induce cyclization of functionalized alkenes and alkynes[1])

Physical Data: mp 123-125 °C (dec).

Solubility: sol CH_2Cl_2, SO_2; reacts with H_2O, protic solvents, acetone, and other enolizable carbonyl derivatives.

Analysis of Reagent Purity: ^{1}H NMR spectrum at -50 °C in CD_2Cl_2 of the pure compound shows two signals at δ 3.6 and 3.0 with an intensity ratio 1:2.[2] At higher temperature in this solvent, as well as in other solvents (SO_2,[3] CD_3CN[4]), a single coalescence line is observed. This behavior is due to trace amounts of dimethyl disulfide impurities.[3]

Preparative Methods: to an ice cooled solution of ***Antimony(V) Chloride*** (7.85 mmol) in anhydrous CH_2Cl_2 (5 mL), a solution of ***Methanesulfenyl Chloride*** (7.85 mmol) and ***Dimethyl Disulfide*** (7.85 mmol) in CH_2Cl_2 (10 mL) is added dropwise. The product partially precipitates from the solution. Addition of *n*-pentane causes complete precipitation of the hexachloroantimonate salt. The product (95% yield) is isolated by filtration in a dry box and can be used without any further purification.[3] Alternatively, to a well-stirred solution of dimethyl disulfide (0.1 mol) in dry CH_2Cl_2 (50 mL) is dropped at 0 °C a solution of $SbCl_5$ (0.1 mol) in dry CH_2Cl_2 (50 mL). After completion of the addition the salt starts crystallizing as yellowish needles. Addition of dry Et_2O completes the precipitation of the product (92% yield).[4]

Purification: crystallization by solution in dry CH_2Cl_2 and addition of dry *n*-pentane or Et_2O.

Handling, Storage, and Precautions: stable for some months if stored in the refrigerator; sensitive to moisture, protic solvents, and enolizable carbonyl compounds.

Functional Group Methylthiolation.

The main feature of methylbis(methylthio)sulfonium hexachloroantimonate ($Me_3S_3SbCl_6$) is the easy transfer of a methylsulfenylium ion to a variety of functional groups more nucleophilic than the sulfur of dimethyl disulfide. The low nucleophilicity of the disulfide and of the hexachloroantimonate ion allows the isolation, or the characterization, of positively charged reaction products.

The methylthiolation of dialkyl or cyclic sulfides with $Me_3S_3SbCl_6$ proceeds smoothly at 0 °C in CH_2Cl_2 and gives methylthiosulfonium salts in good yields (60-80%).[5] Methylthiosulfonium salts can also be prepared by methylation of disulfides with trimethyloxonium salts.[6] However, the latter method cannot be applied to the synthesis of methylthiosulfonium salts derived from cyclic sulfides (eq 1). The reaction of $Me_3S_3SbCl_6$ with diphenyl sulfide gives an almost equimolar mixture of 4-methylthiodiphenyl sulfide and 4,4´-bis(methylthio)diphenyl sulfide (eq 2).[2] Other examples of methylthiolation of aromatic substrates have been reported.[7]

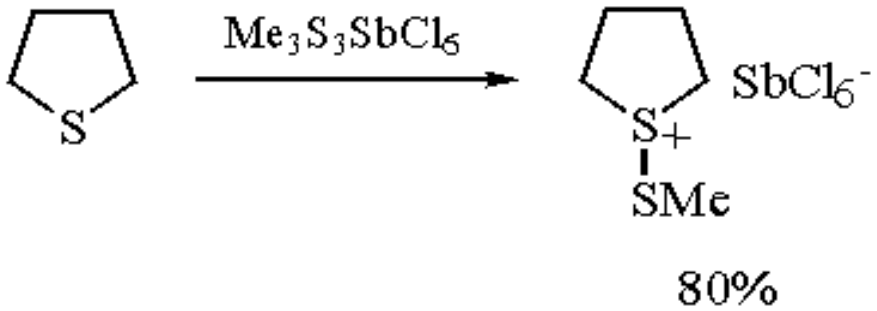

(1)

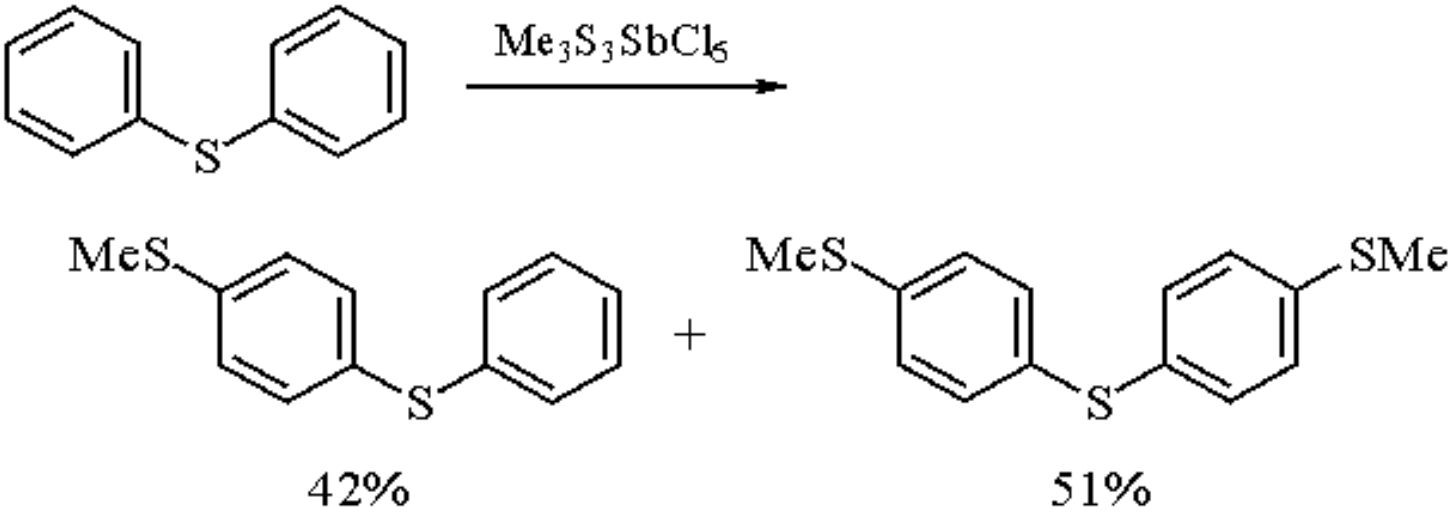

(2)

The reaction of $Me_3S_3SbCl_6$ with alkenes[8-12] and alkynes[13-16] gives thiiranium and thiirenium ions respectively. Depending on the structure of the unsaturated derivatives and reaction conditions, the three-membered ring sulfonium ions can be spectroscopically characterized or isolated as stable hexachloroantimonate salts. Some examples are shown in eqs 3-6. It is important to note the formation of only *trans,trans*-1-methylthiiranium salts from (*Z*)-alkenes[8,10,11] (eq 3) and the rearrangement of *cis,trans*-1-methyl-2,3-di-*t*-butylthiiranium ion to a thietanium ion (eq 4).[10,11] Dialkylacetylenes give thiirenium ions which are stable at low temperature in SO_2 solution. The presence of bulky alkyl residues makes these ions stable enough to be isolated at rt as hexachloroantimonate salts (eq 5).[14,16] Arylalkylacetylenes undergo addition of the Me_3S_3 residue to the triple bond (eq 6).[17] The characteristic reactivity of

thiiranium and thiirenium ions implies attack at ring carbons by nucleophiles with ring opening.[1] Nucleophiles also attack the sulfonium sulfur;[1] however, this reaction is masked sometimes by its reversibility.

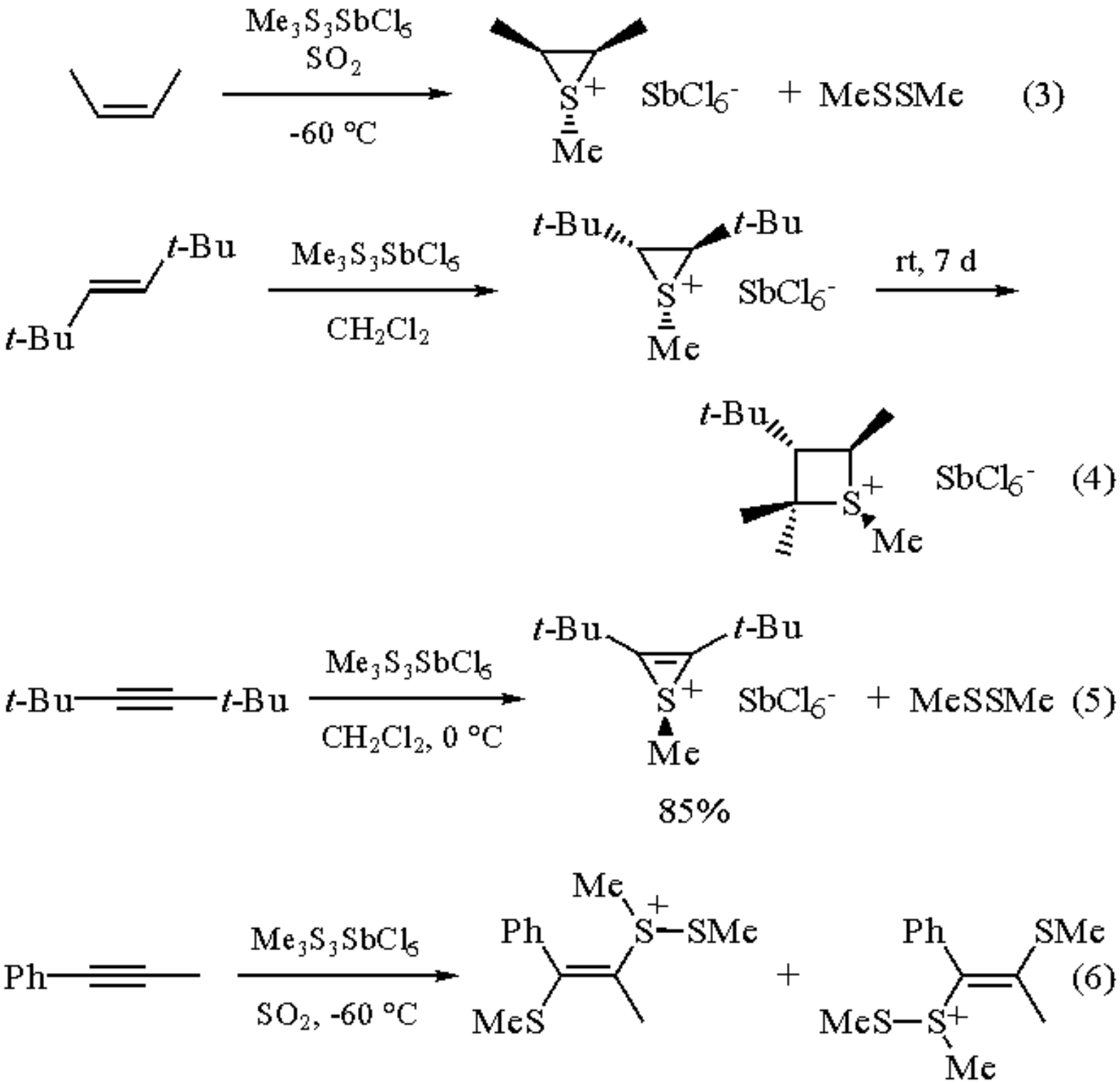

Cyclofunctionalization of Alkenes and Alkynes.

The nucleophilic ring opening of thiiranium and thiirenium ions has been exploited for the synthesis of functionalized heterocycles using $Me_3S_3SbCl_6$ and suitably substituted alkenes and alkynes (eqs 7-13).[7,18-23]

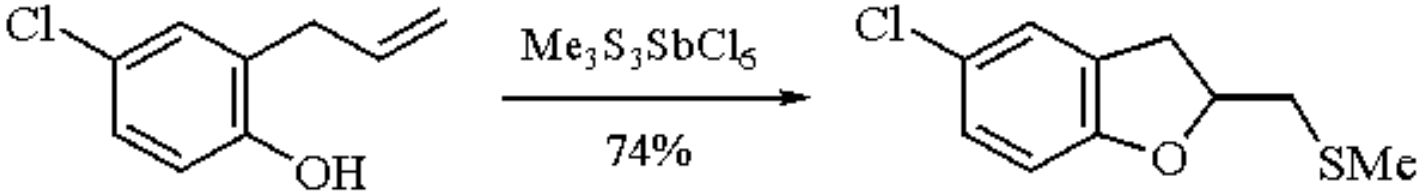

(7)

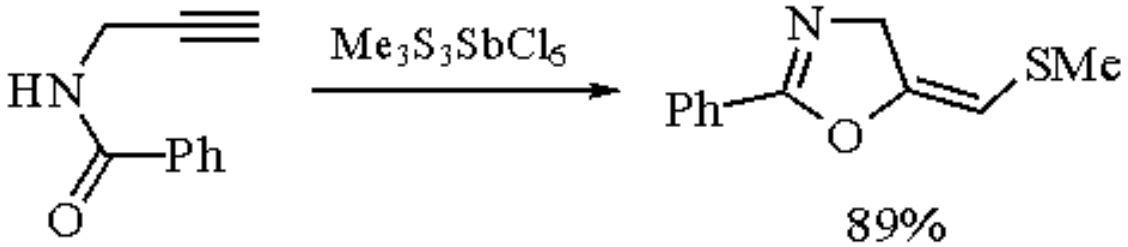

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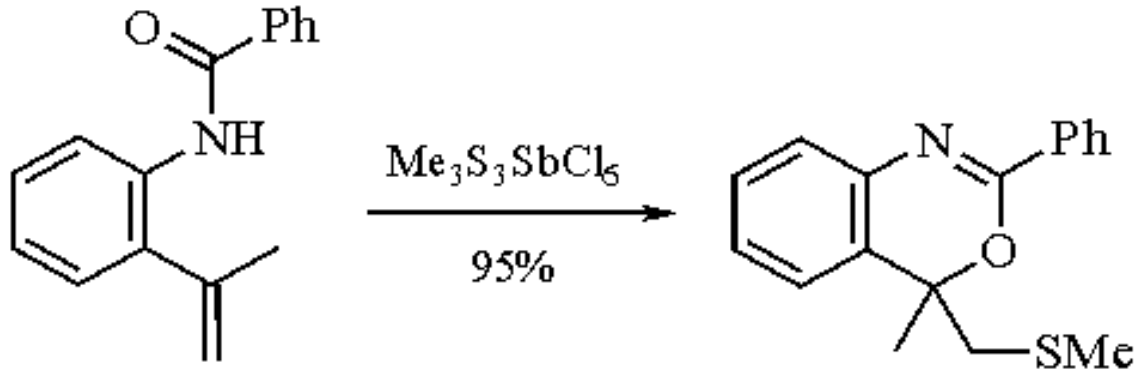

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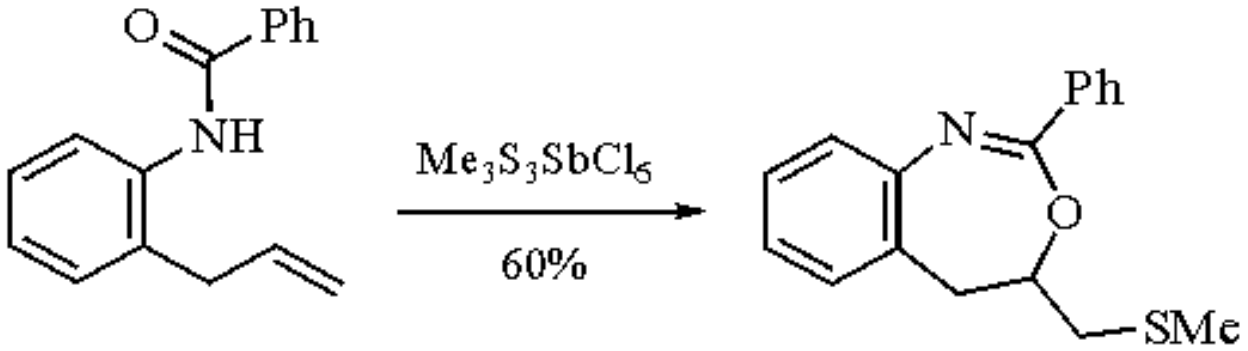

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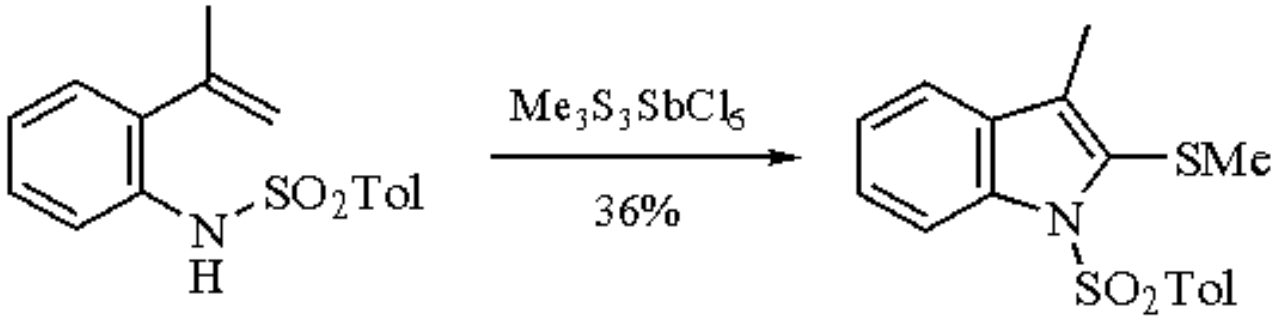

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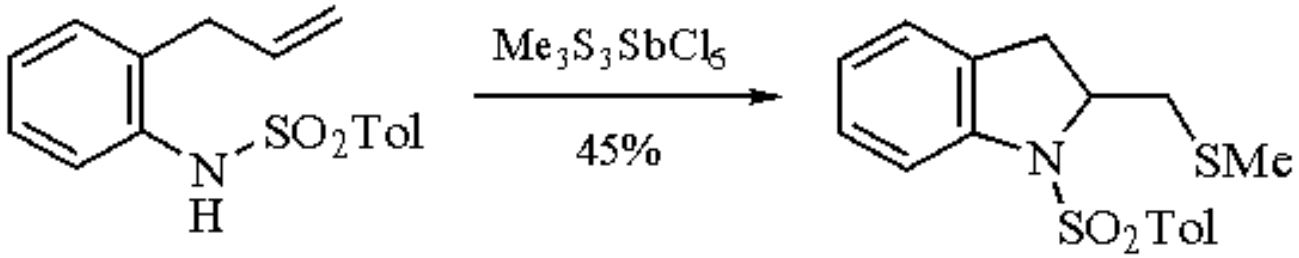

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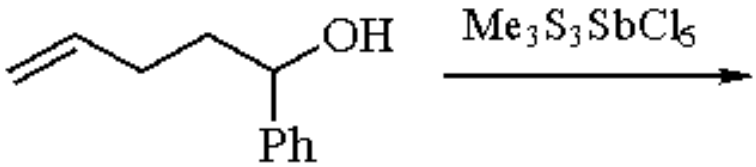

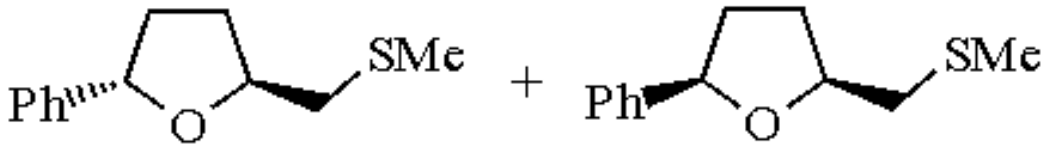

(13)

41% 41%

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Giuseppe Capozzi, Stefano Menichetti, & Cristina Nativi

Università di Firenze, Italy

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Methyl Bis(2,2,2-trifluoroethoxy)phosphinylacetate

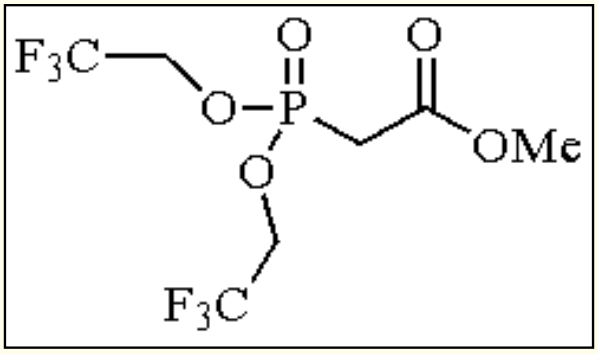

[88738-78-7] · $C_7H_9F_6O_5P$ · Methyl Bis(2,2,2-trifluoroethoxy)phosphinylacetate · (MW 318.13)

(Horner-Emmons reagent for the production of α,β-unsaturated esters with (*Z*) selectivity)

Alternate Name: bis(2,2,2-trifluoroethyl) (methyoxycarbonylmethyl)phosphonate

Physical Data: d 1.504 g cm^{-3}.

Solubility: sol THF, DME, CH_2Cl_2.

Form Supplied in: oil; widely available.

Preparative Methods: prepared by reaction of methyl dichlorophosphonoacetate with trifluoroethanol in benzene.

Purification: silica gel chromatography.

Handling, Storage, and Precautions: irritant.

Modified Wittig Reagent.

The Horner-Emmons reaction carried out by reacting methyl bis(trifluoroethoxy)phosphinylacetate with an aldehyde in the presence of a strongly dissociated base system yields α,β-unsaturated esters with a strong preference for the (*Z*) geometry. The reaction is not overly sensitive to the type of aldehyde used. Examples are shown in eqs 1-3.[1,2]

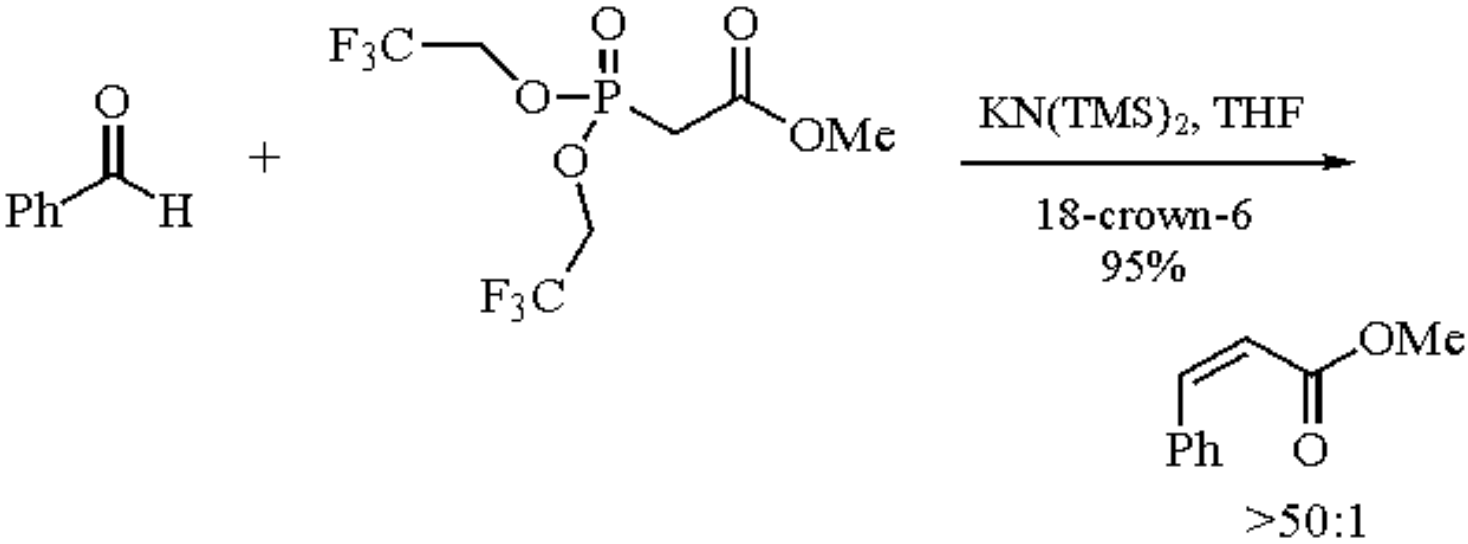

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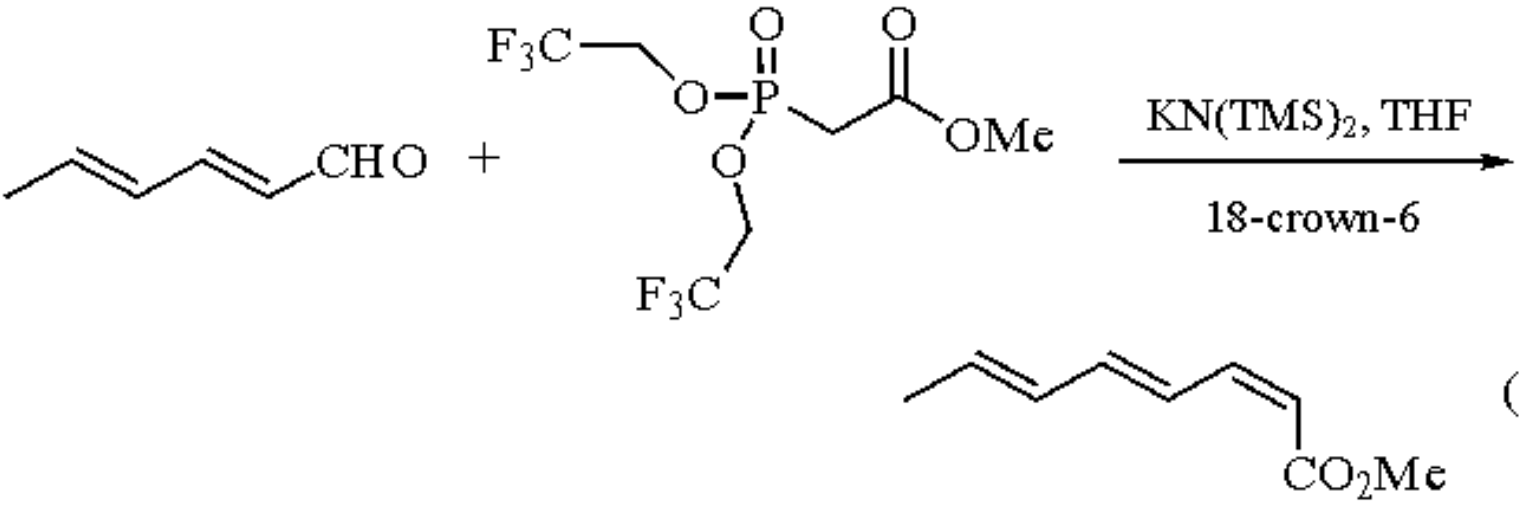

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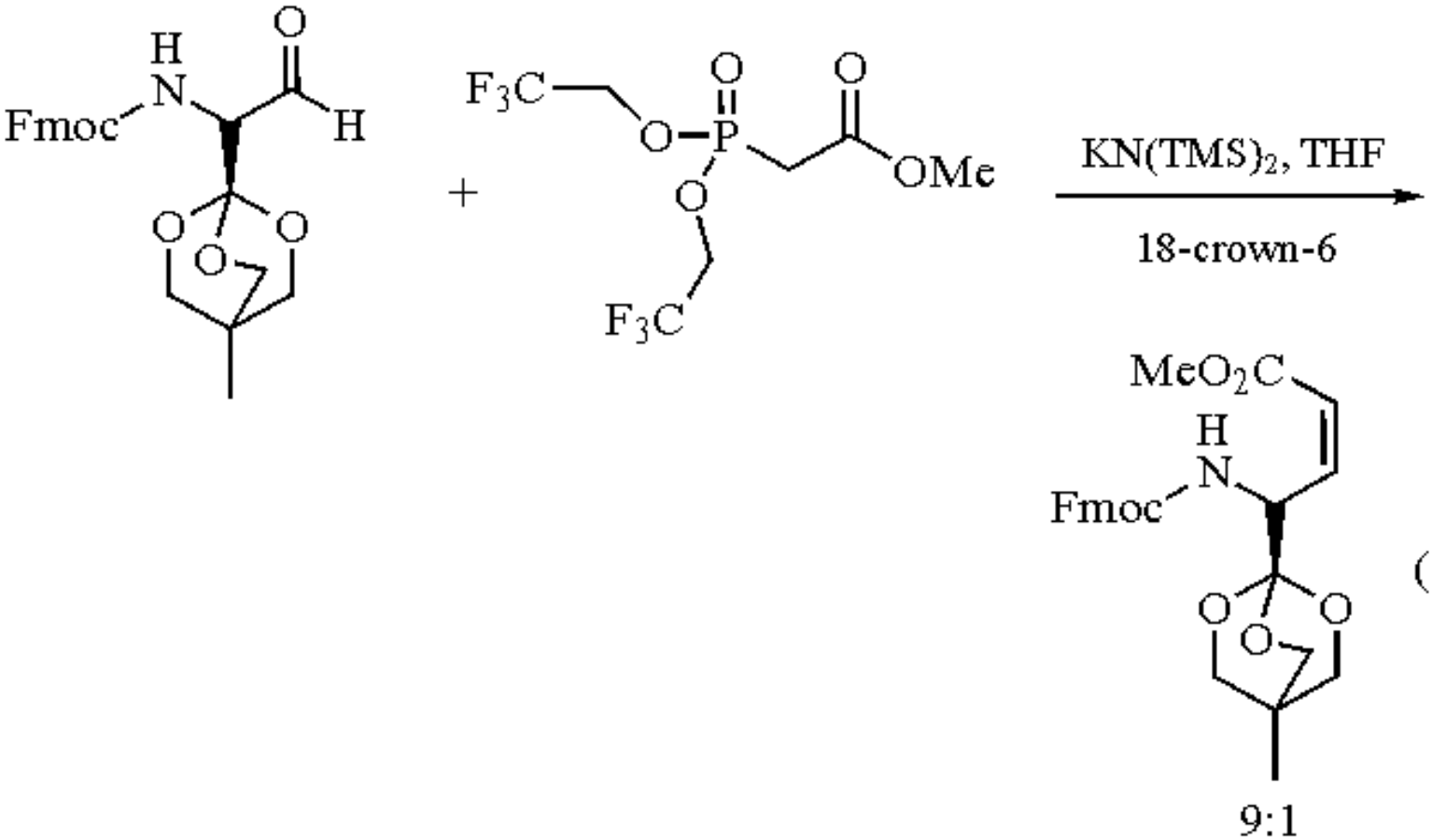

(3)

The strongly dissociated base system is necessary to maximize the (*Z*) selectivity of the alkenation reaction (see eq 4).[1,3]

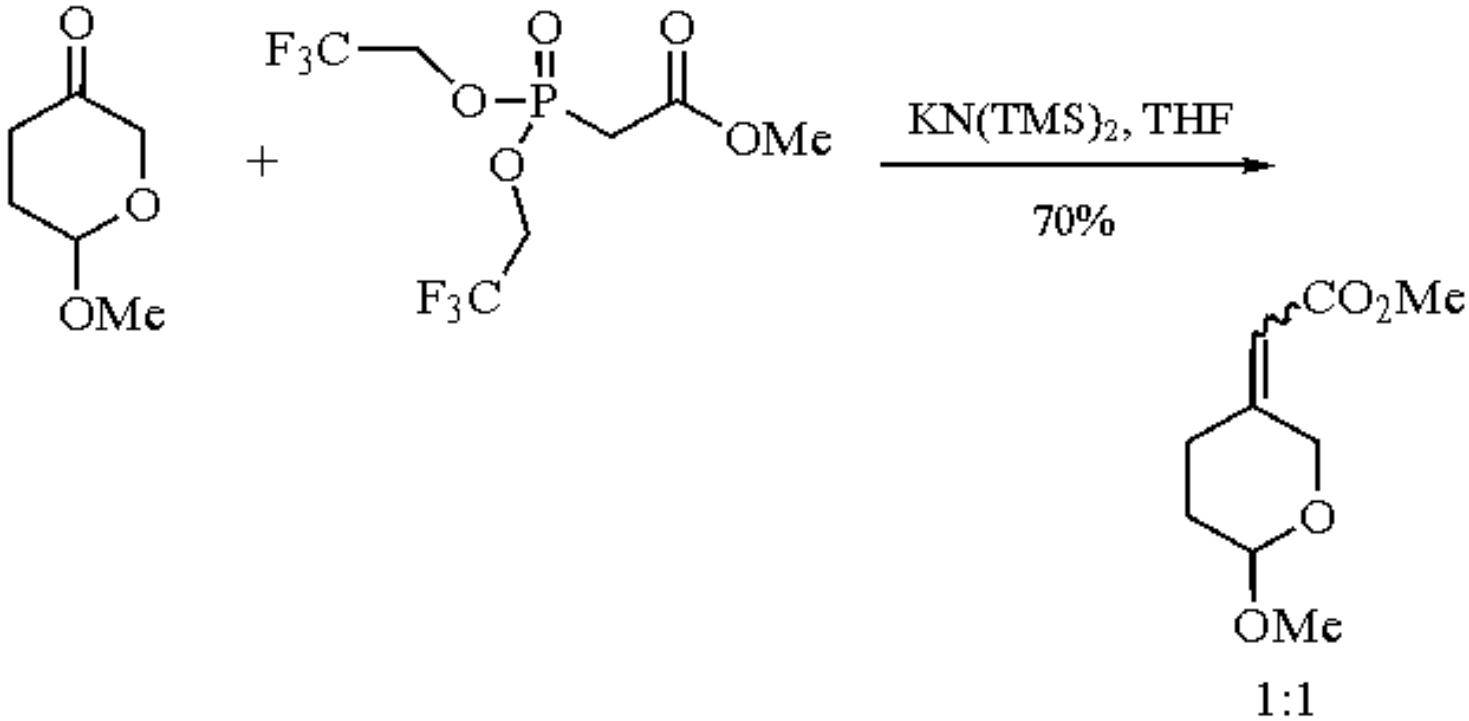

(4)

In general, the reagent is slow to react with ketones, especially aryl ketones, providing little or no reaction (eq 5).[4] The majority of references to this reagent involve aldehydes as the coupling partner.[5]

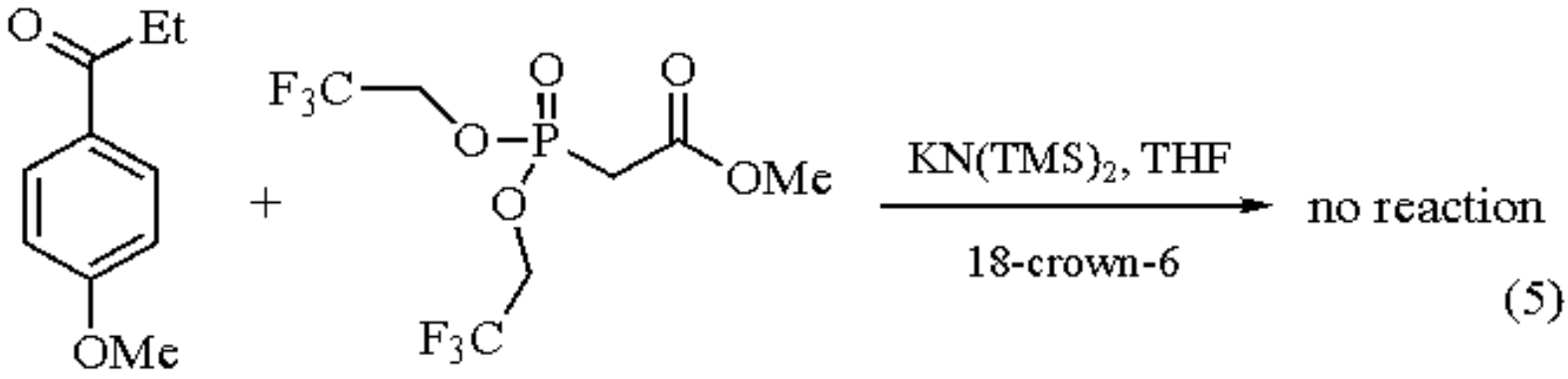

Other Uses.

The anion of methyl bis(trifluoroethoxy)phosphinylacetate can undergo an S_N2 reaction with suitable electrophiles to make a more complex trisubstituted modified Wittig reagent, which can undergo alkenation reactions.[6]

---

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Brad DeHoff

Syntex Technology Center, Boulder, CO, USA

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N-Methyl-*N,O*-bis(trimethylsilyl)hydroxylamine

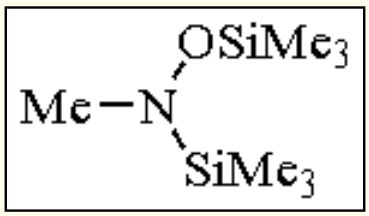

[22737-33-3] · $C_7H_{21}NOSi_2$ · *N*-Methyl-*N,O*-bis(trimethylsilyl)hydroxylamine · (MW 191.47)

(bis-trimethylsilylated *N*-methylhydroxylamine;[1-3] can convert aldehydes and ketones to *N*-methyl nitrones with regio- and chemoselectivity;[3] source of methylnitrene by pyrolysis;[4,5] source of the trimethylsilyl(methyl)aminyl radical by photolysis[6])

Physical Data: bp 40-41 °C/10 mmHg;[2,7,8] *n*20D 1.4146.[2]

Solubility: sol benzene, toluene, CH_2Cl_2, $CHCl_3$.[2]

Form Supplied in: colorless liquid;[2,8,9] commercially available.

Preparative Method: obtained in 52% yield by reaction of ***N-Methylhydroxylamine*** with ***Chlorotrimethylsilane*** (2.0 equiv) and ***Triethylamine*** (3.3 equiv) in ether at 25 °C.[1,2]

Handling, Storage, and Precautions: hydrolyzes readily upon exposure to moisture; stored without decomposition for several months in a sealed bottle at -10 to -15 °C;[2] relatively thermally stable, having $t_{1/2}$ of 46.5 h at 140 °C;[4] dec at 180-190 °C.[10]

N-Methyl Nitrone Formation.

Aldehydes or ketones react with a stoichiometric amount of $Me_3SiN(Me)OSiMe_3$ (**1**) in benzene at 50 °C for 24 h to give *N*-methyl nitrones in good to excellent yields (eq 1).[1] For deactivated carbonyl compounds, such as *p*-nitrobenzaldehyde, *p*-(dimethylamino)benzaldehyde, and 2-furaldehyde, addition of ***Trimethylsilyl Trifluoromethanesulfonate*** (0.03-0.04 equiv) as a catalyst is necessary for the formation of *N*-methyl nitrones; otherwise accumulation of hemiaminal intermediates (**2**) occurs. Sequential intra- and intermolecular [3 + 2] cycloadditions can be carried out in situ for substrates containing a C=C or a C=N double bond (eqs 2 and 3).

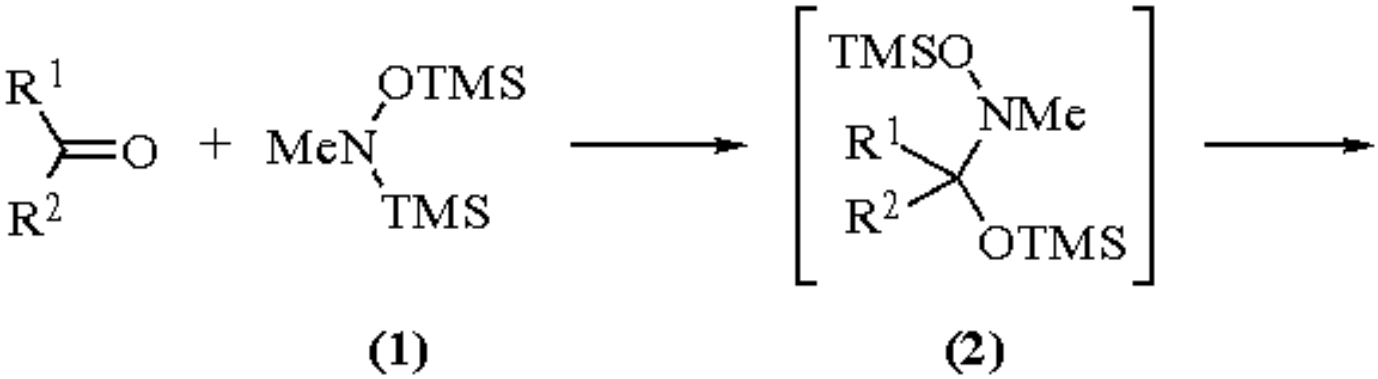

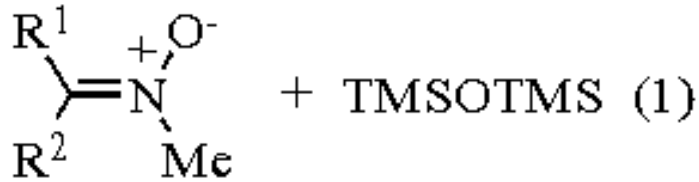

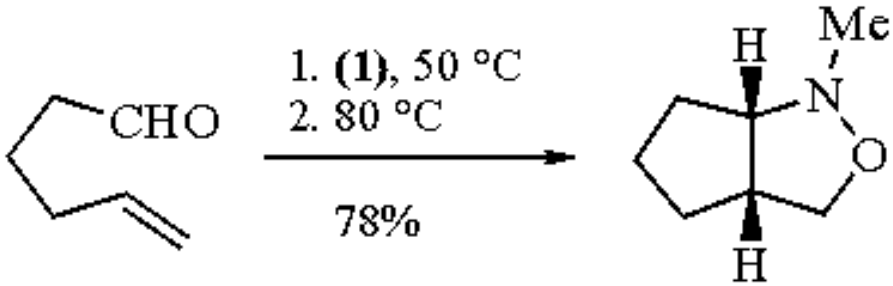

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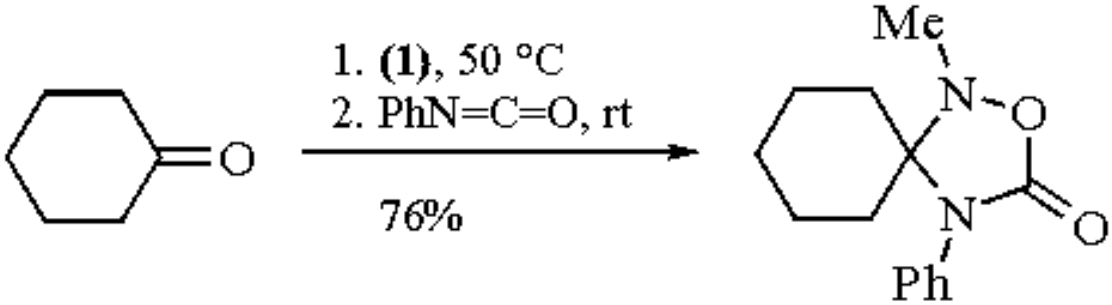

(3)

Regio- and Chemoselective Nitrone Formation.

The trimethylsilyl cationic (Me_3Si^+) moiety in $Me_3SiN(Me)OSiMe_3$ serves as a bulky proton,[11] which enables this reagent to react selectively with carbonyl groups having different steric environments. For example, regioselective nitrone formation occurs exclusively at the C-3, instead of the sterically more crowded C-20, carbonyl group in 5α-pregnane-3,20-dione in benzene at reflux (eq 4). Also, $Me_3SiN(Me)OSiMe_3$ preferentially reacts with trimethylacetaldehyde in the presence of acetone to afford the corresponding nitrone. The selectivity offered by $Me_3SiN(Me)OSiMe_3$ is higher than that offered by MeNHOH.HCl (14:1 versus 6:1). $Me_3SiN(Me)OSiMe_3$ reacts preferentially with aldehyde functionality in the presence of chlorides. This is evidenced by the reaction of $Me_3SiN(Me)OSiMe_3$ with 5-chloropentanal (1.0 equiv) in CH_2Cl_2 at reflux to give a nitrone in 79% yield without any substitution product being formed.

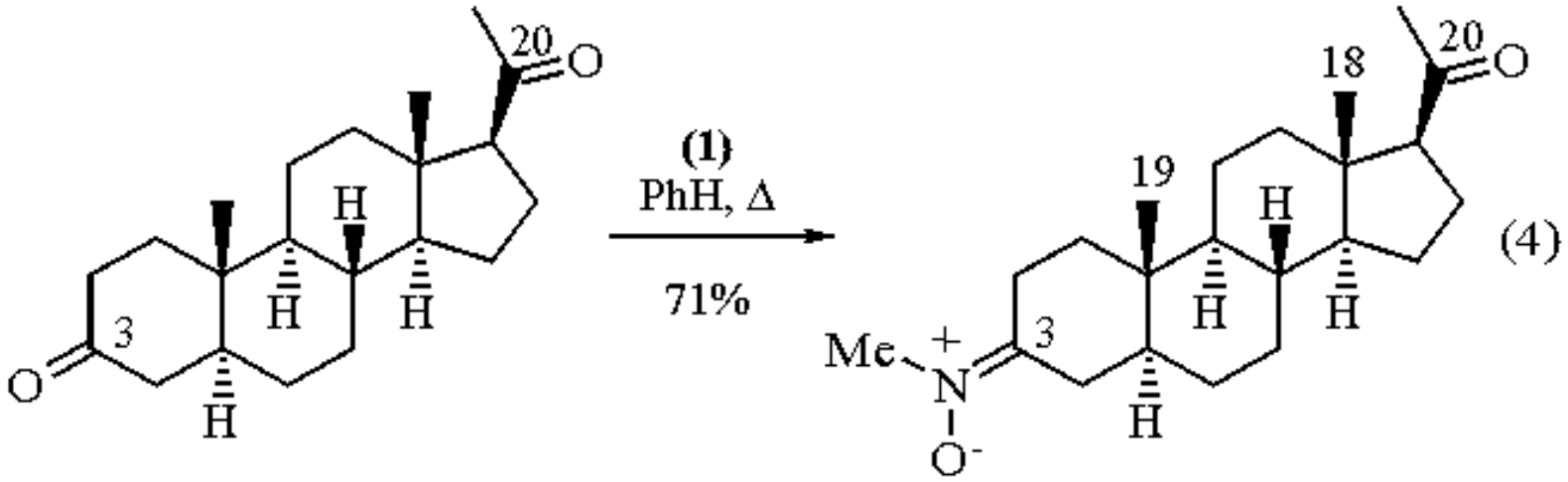

Protection of the Carbonyl Group.

For carbonyl compounds containing a second reducible functionality, selective reduction of the latter can be accomplished by protection of the carbonyl group in its hemiaminal form by use of $Me_3SiN(Me)OSiMe_3$. An example is shown in eq 5, in which 4-cyanobenzaldehyde is first treated with 1.3 equiv of $Me_3SiN(Me)OSiMe_3$ to give a hemiaminal intermediate. In situ, 1.2 equiv of a reducing agent are added to afford terephthalaldehyde in 80-93% yields after acidic workup. The applicable reducing agents include $NaBH_4$, Super-Hydride, L-Selectride, K-Selectride, LS-Selectride, BH_3.THF, 9-BBN, DIBAL, Red-Al, and Bu_3SnH.[2] This method provides a way to carry out protection-reduction-deprotection in one flask.

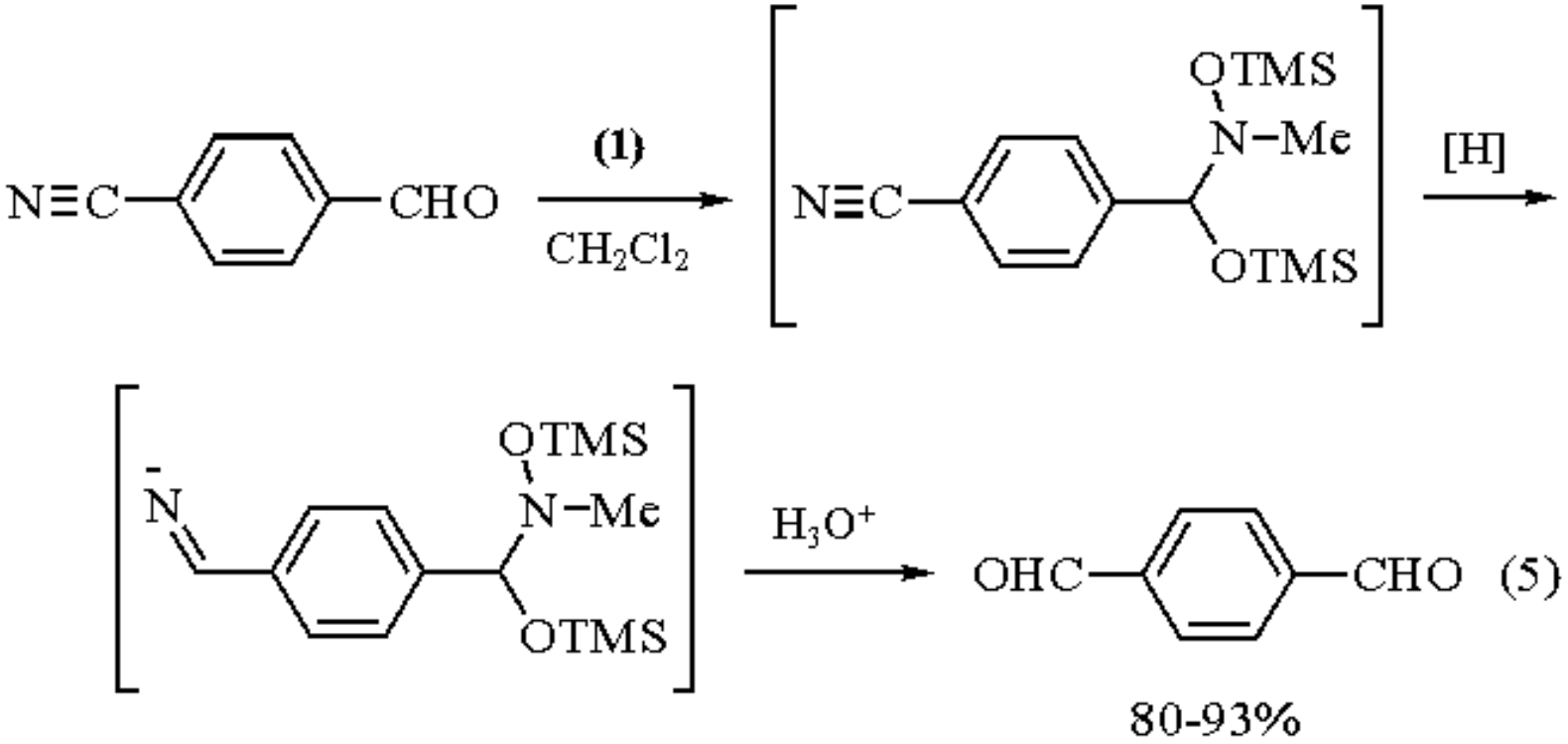

Methylnitrene Formation.

Pyrolysis of $Me_3SiN(Me)OSiMe_3$ at 150 °C gives methylnitrene (Me&NNuml;**:**) through α-deoxysilylation.[4,5] The nitrene intermediate can be trapped by $(MeO)_2MeSiH$ to give the insertion product $(MeO)_2MeSiNHMe$.

Silylalkylaminyl Radical Formation.

Irradiation of $Me_3SiN(Me)OSiMe_3$ with 260-340 nm UV light gives the trimethylsilyl(methyl)aminyl radical (Me(Me_3Si)N&bdot;).[6] This radical is more reactive than the Me_2N&bdot; radical and can be trapped by use of trialkyl phosphites to afford phosphoranyl radicals, such as &bdot;$P(OEt)_3N(Me)SiMe_3$.

---

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10-Methyl-10-bora-9-oxabicyclo[3.3.2]decane

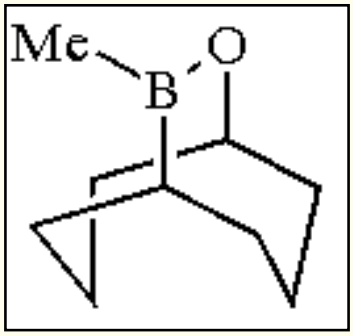

[99966-26-4] · $C_9H_{17}BO$ · 10-Methyl-10-bora-9-oxabicyclo[3.3.2]decane · (MW 152.07)

(air-stable methylating agent via Suzuki-Miyaura coupling[1])

Physical Data: bp 50 °C/3 mmHg.[1,2]

Solubility: sol organic solvents; insol water.[2]

Analysis of Reagent Purity: can be isolated in pure form and analyzed efficiently by GC or standard spectroscopic techniques (e.g. ^{11}B NMR ($CDCl_3$) δ 54.7 ppm).[2]

Preparative Methods: a one-pot sequence (57%) from *B*-MeO-9-BBN by reaction with MeLi in Et_2O at -78 °C, followed by ***Trimethylamine N-Oxide*** (TMANO) (1 equiv) in CH_2Cl_2 at 0 °C.[1] Alternatively, the intermediate *B*-Me-9-BBN can be isolated and oxidized with TMANO in $CHCl_3$ at 0 °C to afford the reagent (81%).[2]

Handling, Storage, and Precautions: indefinitely stable at 25 °C when stored under a nitrogen atmosphere; it can also be handled in the open atmosphere for brief periods of time without significant decomposition. Its preparation involves the handling of dangerously pyrophoric or flammable reagents (i.e. *B*-Me-9-BBN, *B*-MeO-9-BBN, MeLi). Individuals should thoroughly familiarize themselves with the special handling techniques required for such reagents prior to their use.[3]

Methylation via Suzuki-Miyaura Coupling.

The highly efficient oxidation of *B*-alkyl-9-BBN derivatives with TMANO leads to the exclusive formation of 10-alkyl-10-bora-9-oxabicyclo[3.3.2]decanes which are remarkably resistant to further oxidation compared to other borinate esters (eq 1).[2] This feature provides alkylboranes which are particularly convenient to handle while still undergoing useful carbon-carbon bond-forming reactions such as Pd-catalyzed cross coupling with alkenyl, alkynyl, and aryl bromides under basic conditions. The process occurs with retention of configuration in the case of the vinyl bromides, and *gem*-dibromides are efficiently dimethylated (eq 2).[1]

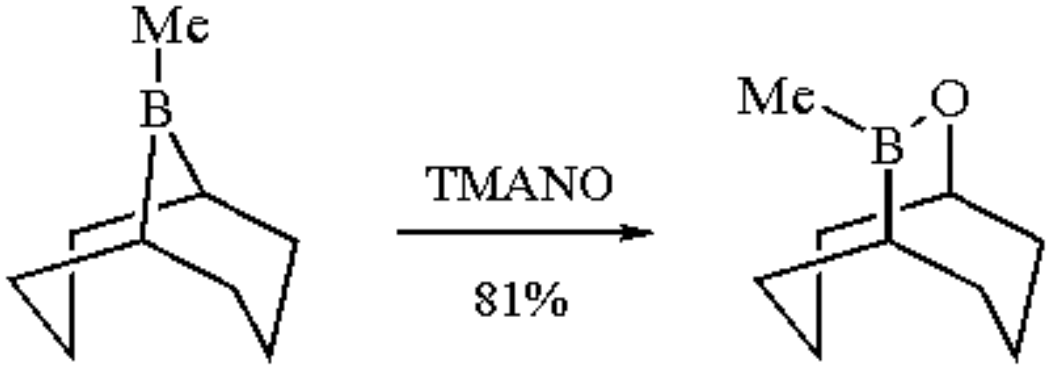

(1)

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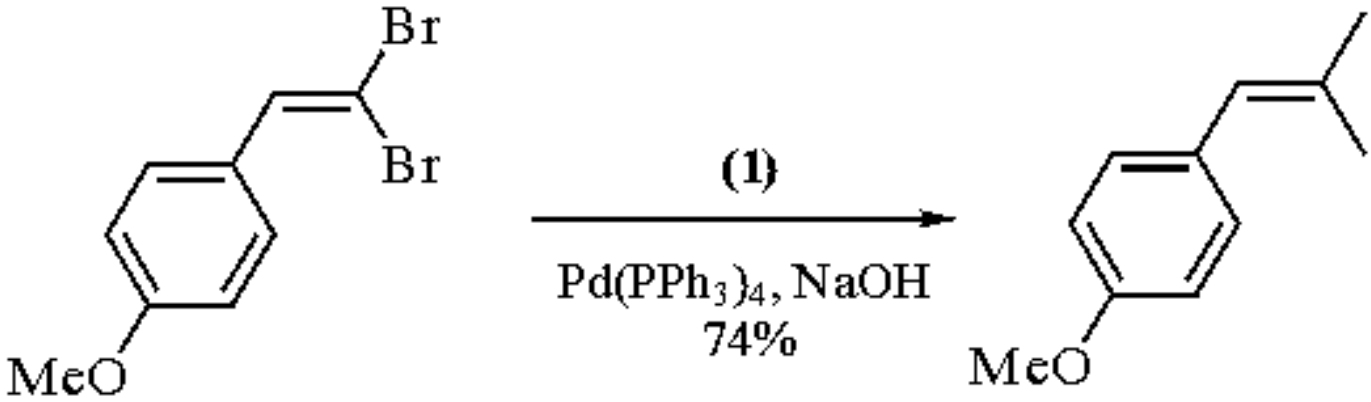

(2)

Related Reagents.

Tetramethylstannane.

---

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Midland, M. M.; Levy, A. B.; Kramer, G. W. *Organic Synthesis via Boranes*; Wiley: New York, 1975.

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Methyl Bromoacetate

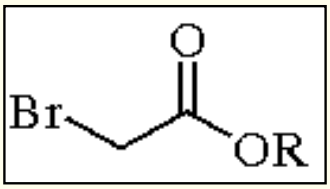

(**1**; R = Me)

[96-32-2] · $C_3H_5BrO_2$ · Methyl Bromoacetate · (MW 152.98) (**2**; R = Et)

[105-36-2] · $C_4H_7BrO_2$ · Ethyl Bromoacetate · (MW 167.01)

(forms a variety of enolates; the bromine atom is readily substituted by nucleophiles; undergoes carbonyl substitution reactions)

Physical Data: (**1**) bp 51-52 °C/15 mmHg; *d* 1.616 g cm^{-3}; *n*20D 1.4580. (**2**) bp 58-59 °C/15 mmHg; *d* 1.506 g cm^{-3}; *n*20D 1.4489.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; widely available.

Purification: vacuum distillation; decomposes upon distillation at atmospheric pressure.

Handling, Storage, and Precautions: corrosive lachrymator, irritating to eyes and respiratory system; should be used only in a chemical fume hood.

Formation of Enolates.

The reagent reacts with zinc metal to produce a zinc enolate (**3**) (eq 1) which is usually trapped in situ by aldehydes or ketones to produce β-hydroxy esters (the Reformatsky reaction).[1] Similar redox reactions to form enolates occur with a variety of metals.[1a]

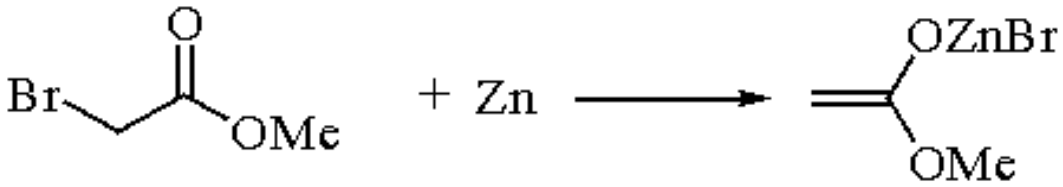

(1)

(3)

Proton removal with alkoxide bases forms α-bromo ester enolates (**4**) (eq 2), which are trapped in situ by aldehydes or ketones to produce glycidic esters (the Darzens condensation).[2] The use of ***Lithium Dicyclohexylamide*** gives excellent yields.[3] Enolates analogous to (**4**) (M = Li) are produced with ***Lithium Hexamethyldisilazide***.[4]

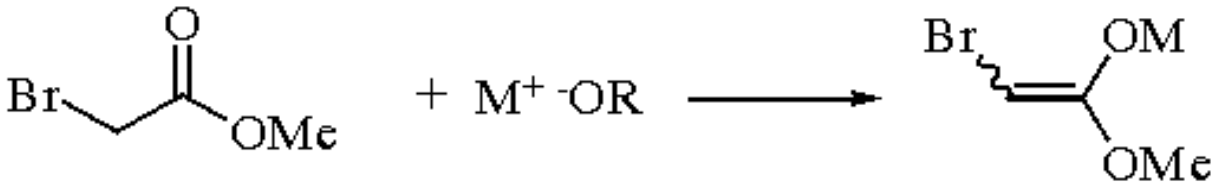

(2)

(4)

Nucleophilic Substitution.

The bromine in methyl bromoacetate is readily substituted by nucleophiles. Substitution with ***Triphenylphosphine***[5] or with trialkyl phosphites[6] produces reagents used for Wittig alkenation reactions. Similar alkenation reagents are obtained with ***Tri-n-butylstibine*** (eq 3),[7] ***Dibutyl Telluride*** (eq 4),[8] and tributylarsine.[9] A wide variety of carbon nucleophiles are alkylated by methyl bromoacetate including ketone[10] and ester enolates,[11] metallo imines,[12] hydrazones,[13] oximes,[14] and metal π-allyls.[15]

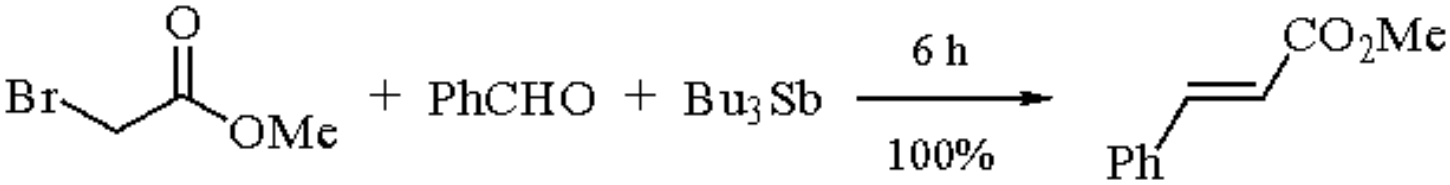

(3)

79% (*E*)

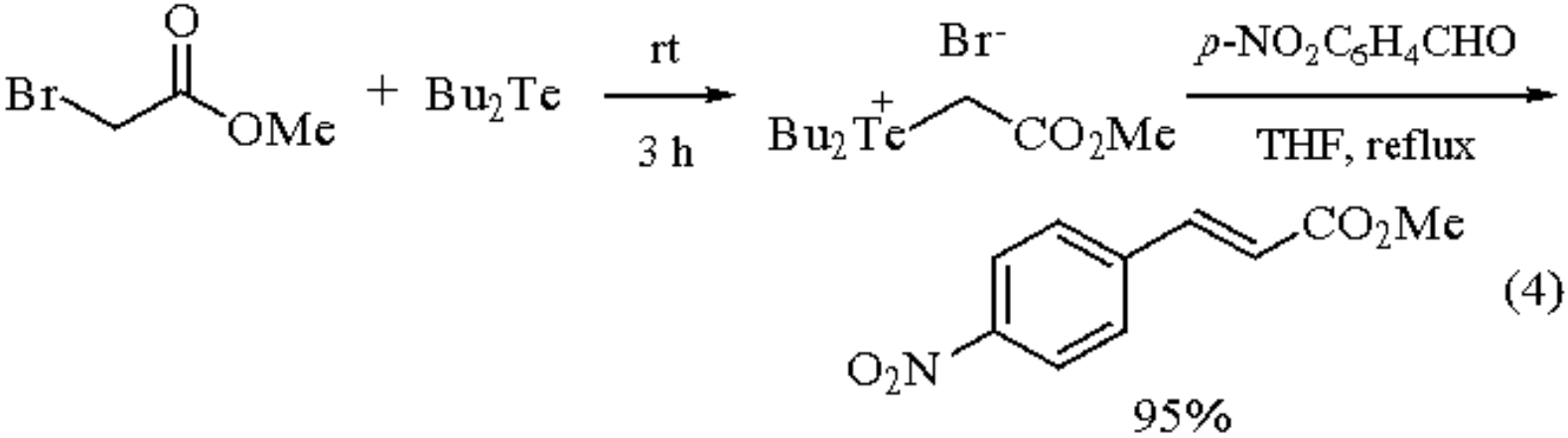

(4)

Carbonyl Substitution.

Reaction of methyl bromoacetate with lithium perfluoroalkyls gives good yields of ketones (eq 5), presumably as a result of the stability of the intermediate hemiacetal anion (**5**).[16] Transesterification of methyl bromoacetate can be achieved efficiently with a distannoxane catalyst (eq 6).[17]

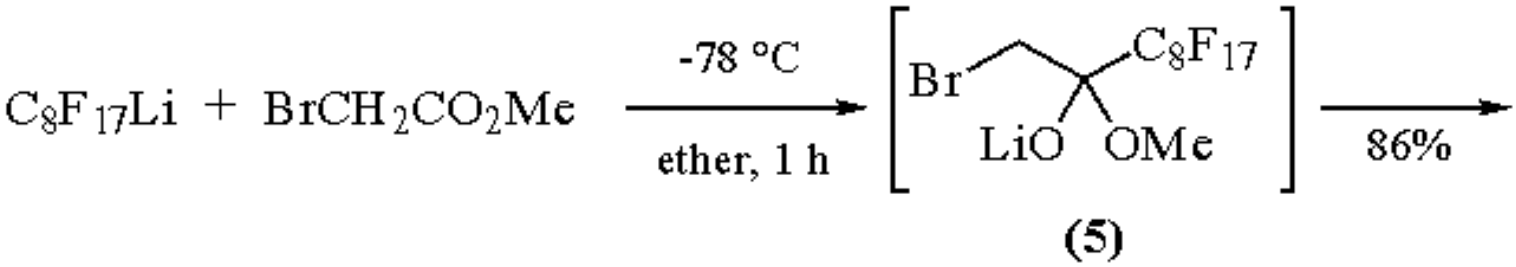

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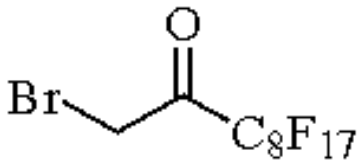

(5)

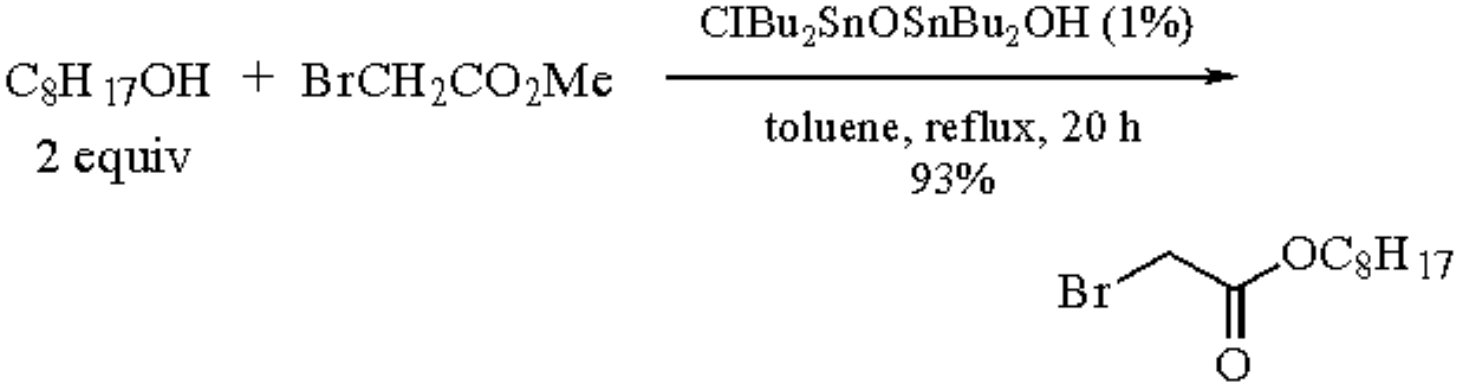

(6)

Related Reagents.

Chloroacetonitrile; ***Methyl Chloroacetate***.

1. (a) Rathke, M. W.; Weipert, P. *COS* **1991**, *2*, 277. (b) Rathke, M. W. *OR* **1975**, *22*, 423.
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Methyl 2-Bromo-*N*-(*t*-butoxycarbonyl)glycinate

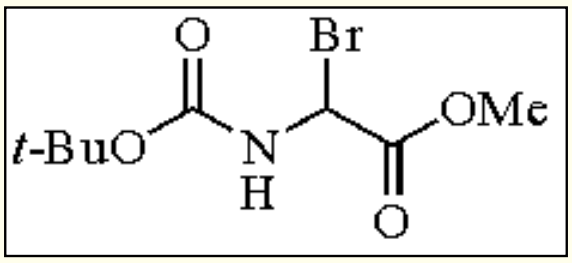

[135924-45-7] · $C_8H_{14}BrNO_4$ · Methyl 2-Bromo-*N*-(*t*-butoxycarbonyl)glycinate · (MW 268.13)

(reagent for amino acid synthesis)

Solubility: sol THF, CH_2Cl_2.

Form Supplied in: oil.[1]

Preparative Method: ***N-Bromosuccinimide*** bromination of methyl *N*-Boc-glycinate.[2]

Handling, Storage, and Precautions: can be stored at -20 °C for several months. It has to be protected from moisture to avoid hydrolysis. Use in a fume hood.

Reactions under Basic and Neutral Conditions.

Methyl 2-bromo-*N*-(*t*-butoxycarbonyl)glycinate (**1**), is a building block for α-amino acid synthesis.[3] A variety of analogs with different *N*-acyl and ester groups have been obtained in the same manner. The replacement of the bromine with nucleophiles allows the incorporation of side chains at the α-carbon of glycine. Thus with phosphites, α-phosphonyl esters[2,4,5] are accessible, which are converted to (*Z*)-dehydroamino acid derivatives by means of the Horner-Wadsworth-Emmons reaction (eq 1).[6]

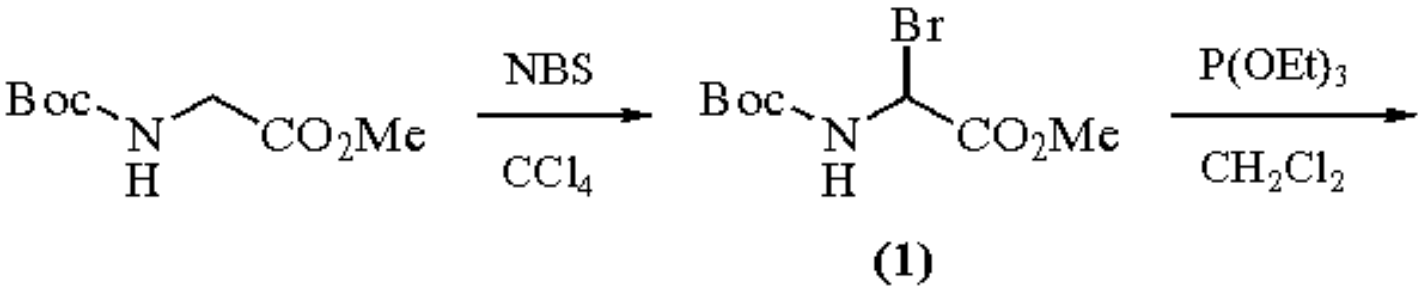

(1)

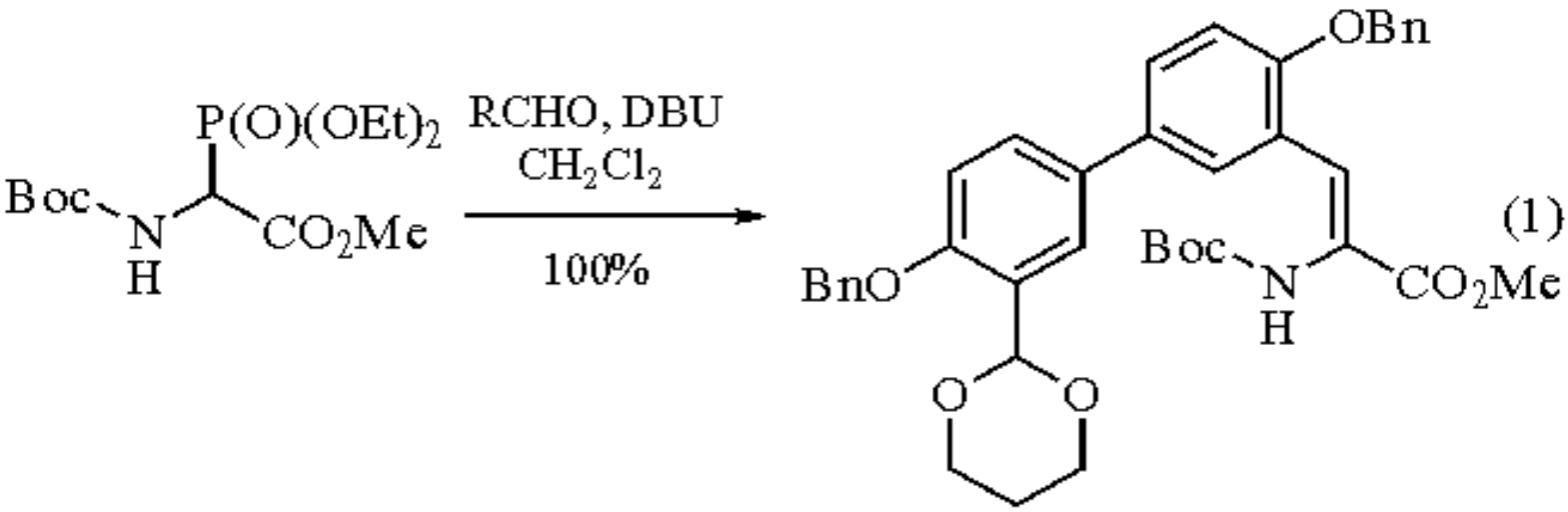

(*E*):(*Z*) = 5:95

When reagent (**1**) is treated with tertiary amines an *N*-acylimino acetate intermediate is formed which smoothly adds organometallic reagents,[7,8] β-dicarbonyl compounds,[7] silyl enol ethers,[7] and other *C*-nucleophiles[9] to the C=N group. In the case of cyclic enamines[10] the addition can be achieved with remarkably high stereoselectivity (eq 2).

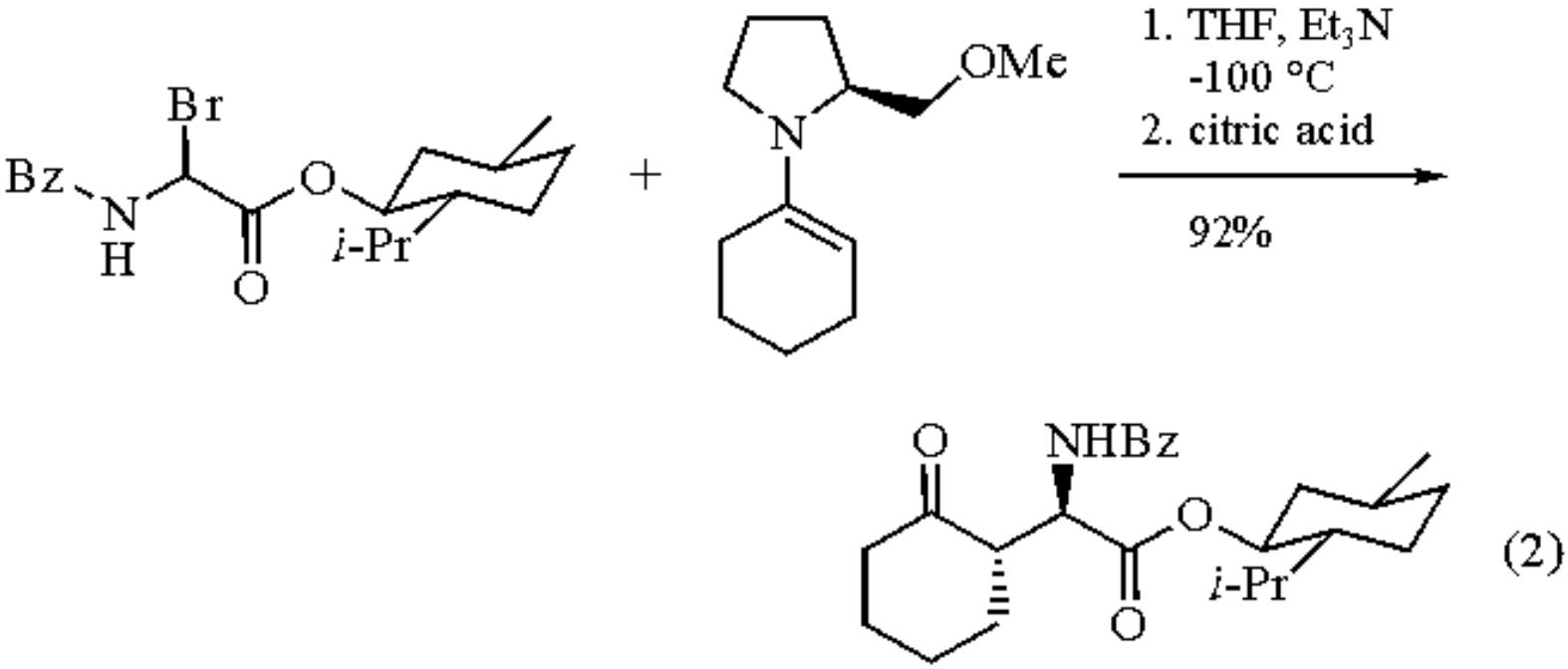

>98% de

As illustrated in eq 3, the use of an 8-phenylmenthyl ester enables the diastereoselective addition of Grignard reagents.[11] The difficulties in hydrolyzing the sterically hindered ester can be circumvented by the use of Oppolzer's auxiliary (eq 4).[12] In this case the free amino acid is easily accessible by treatment of the product with ***Boron Tribromide***.

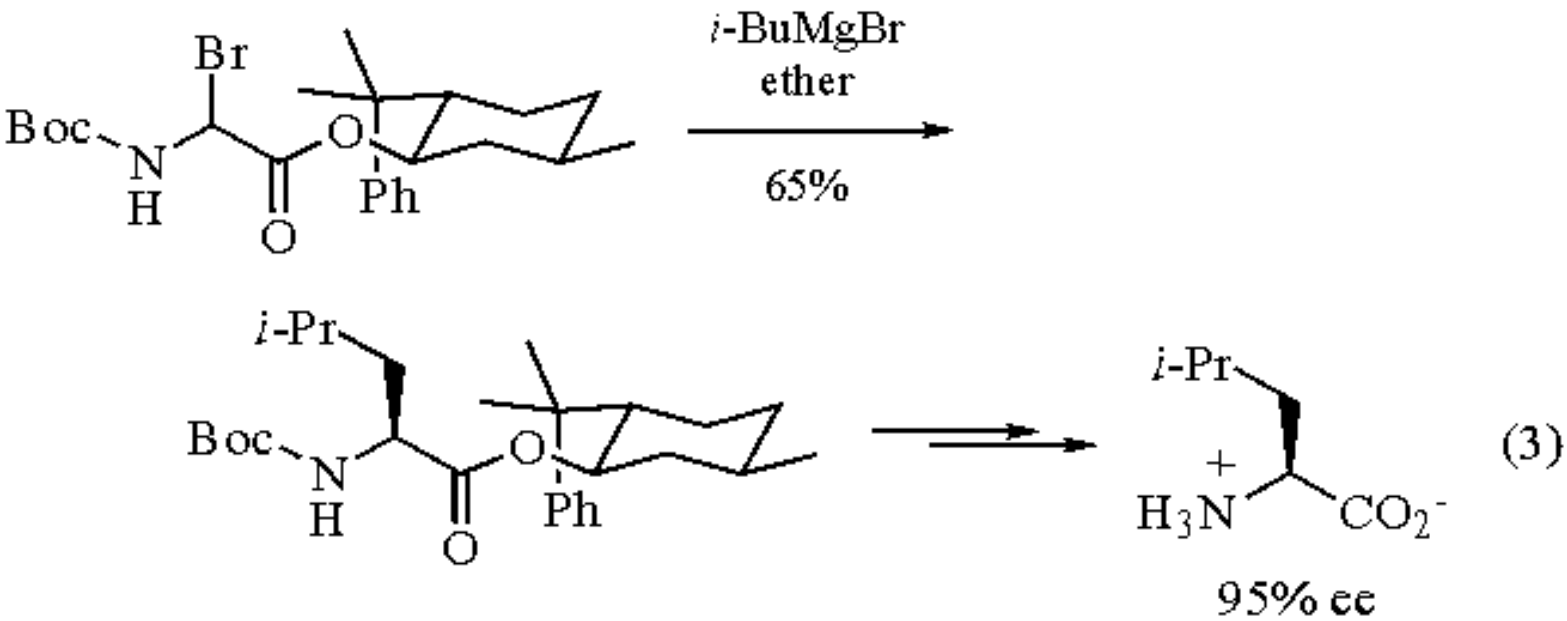

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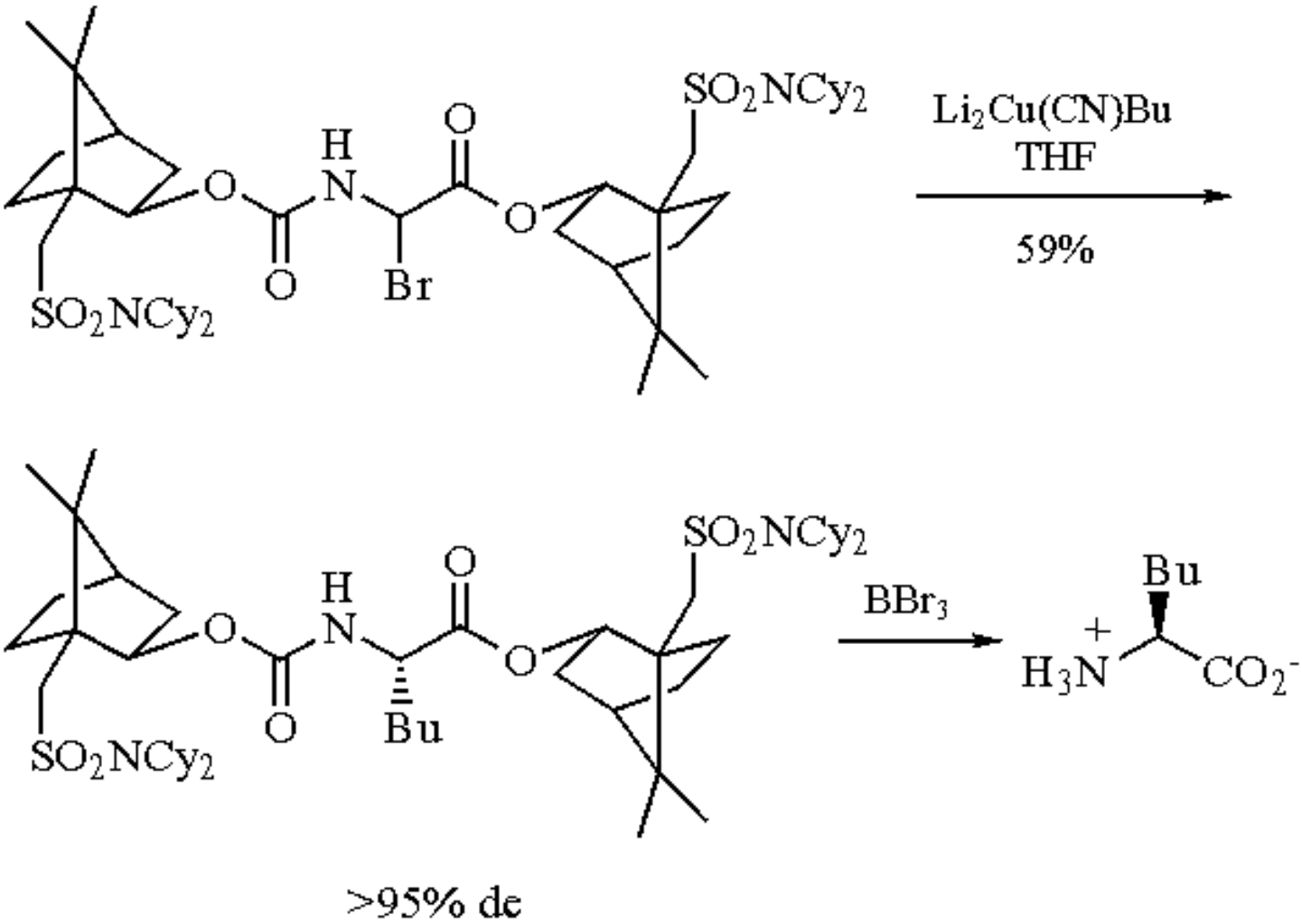

(4)

Alternatively, enantiopure amino acids can be obtained by enzymatic resolution of the racemic products.[7,13] Thus treatment of 2-acetylamino-4-oxo-4-phenylbutyric acid with hog renal acylase provides the pure L-amino acid in high overall yield (eq 5).[7]

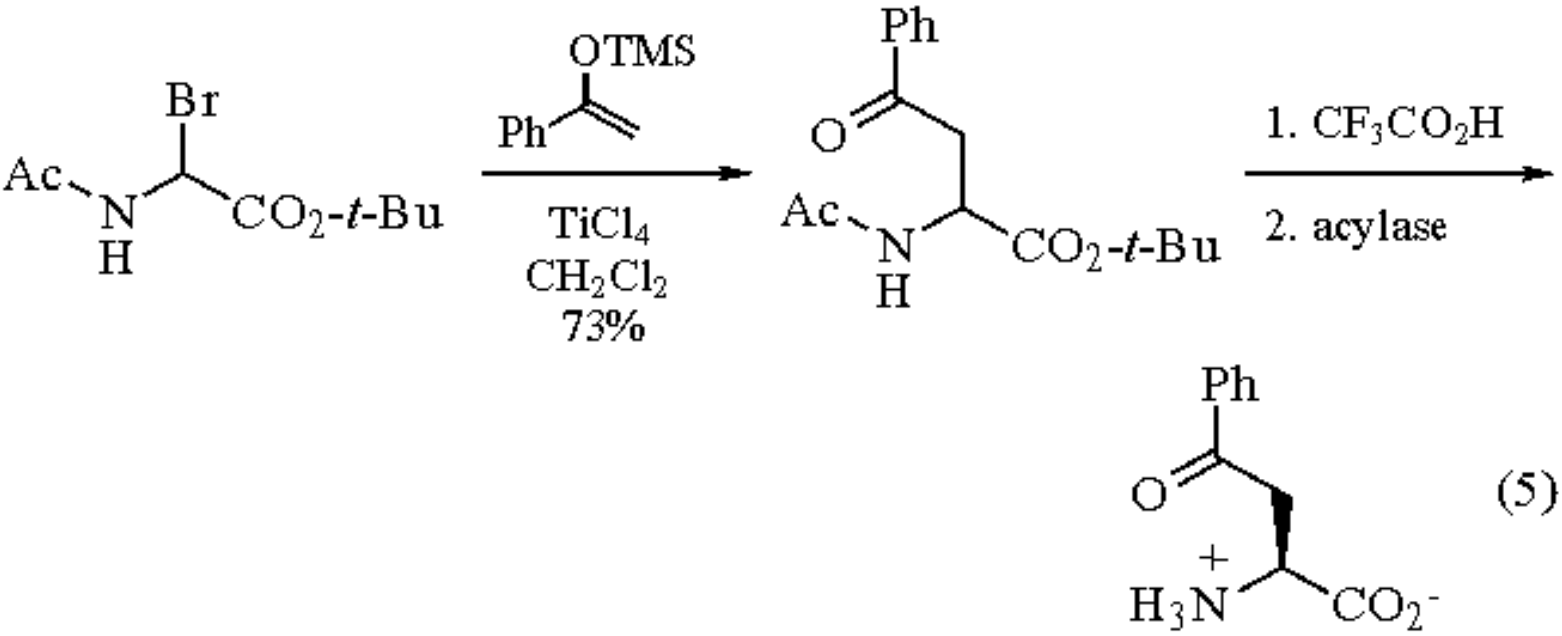

(5)

Reactions under Acidic Conditions.

2-Methoxy- and 2-haloglycinate esters with acid-stable urethane protecting groups can be used for acid-catalyzed amidoalkylations[14] of arenes,[15] vinylsilanes,[16] allylsilanes,[8b,17] and silyl enol ethers.[18] The glycine reagents can be obtained from glyoxylic acid hydrate by condensation with an *O*-alkylcarbamate followed by appropriate transformation of the resulting α-hydroxyglycine derivative. Electrochemical oxidation offers an alternative approach to these compounds.[19] Upon treatment of the α-methoxyglycine reagents with Lewis acids, highly electrophilic *N*-acyliminium intermediates are formed.[20] The scope of this method is illustrated by the stereoselective amidoalkylation of anisole (eq 6)[21] and the Sakurai-type addition of allylsilanes (eq 7).[17]

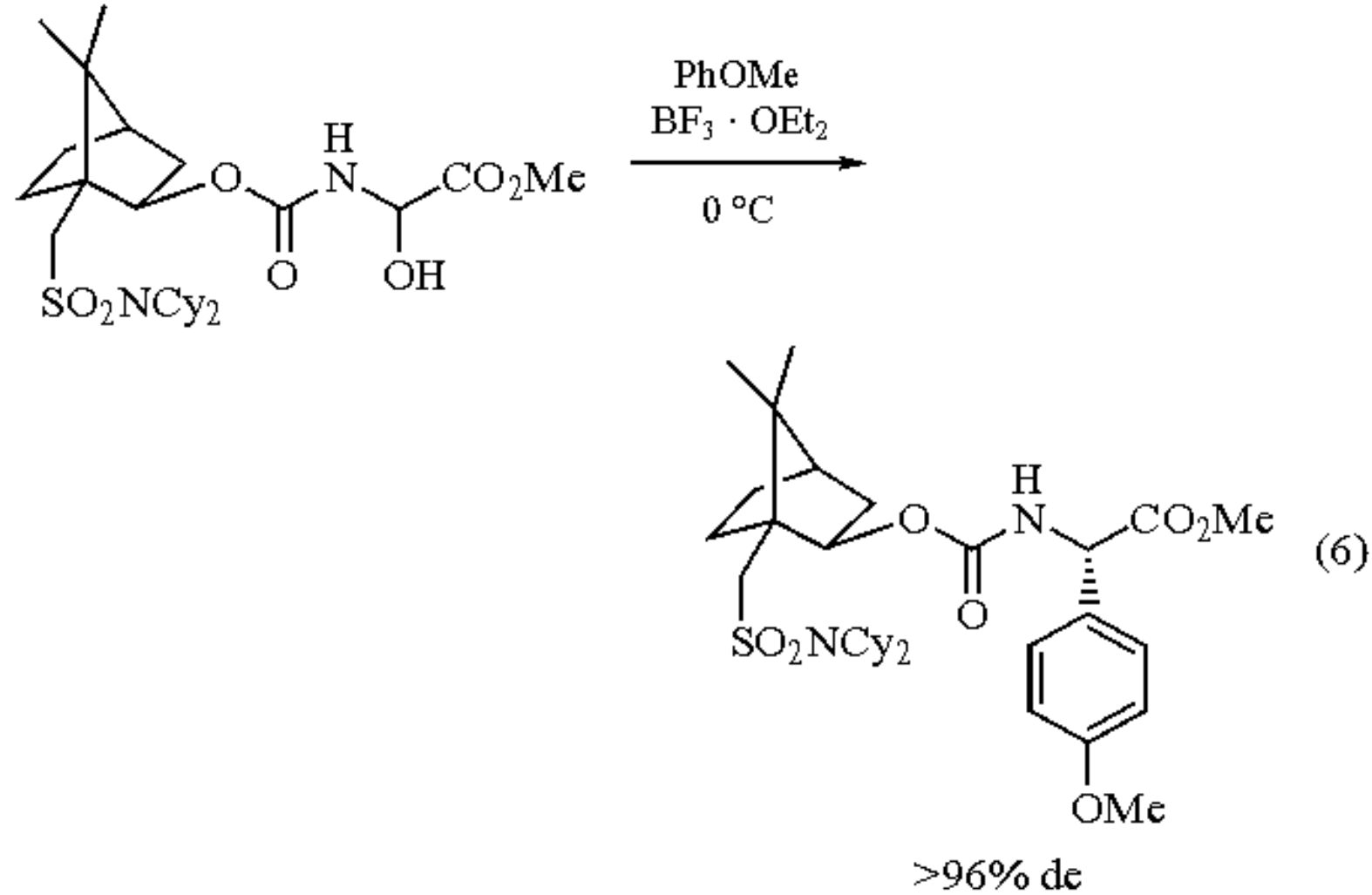

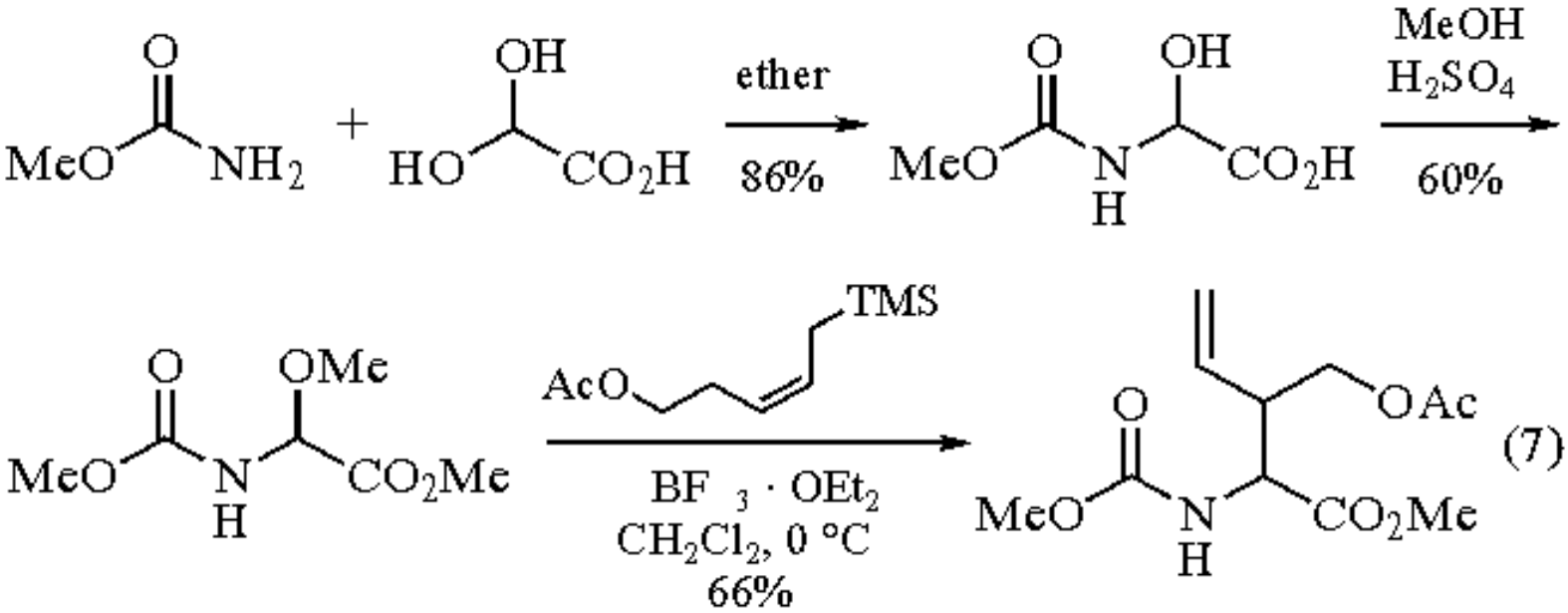

Radical Reactions.

Treatment of the α-bromo compounds with stannanes in the presence of ***Azobisisobutyronitrile*** induces radical

reactions which lead to the formation of 2-deuteroglycine,[22] 2-allylglycine, and 2-propargylglycine derivatives.[22b,23] Again the reaction with an 8-phenylmenthyl ester proceeds with excellent diastereoselectivity (eq 8).[24]

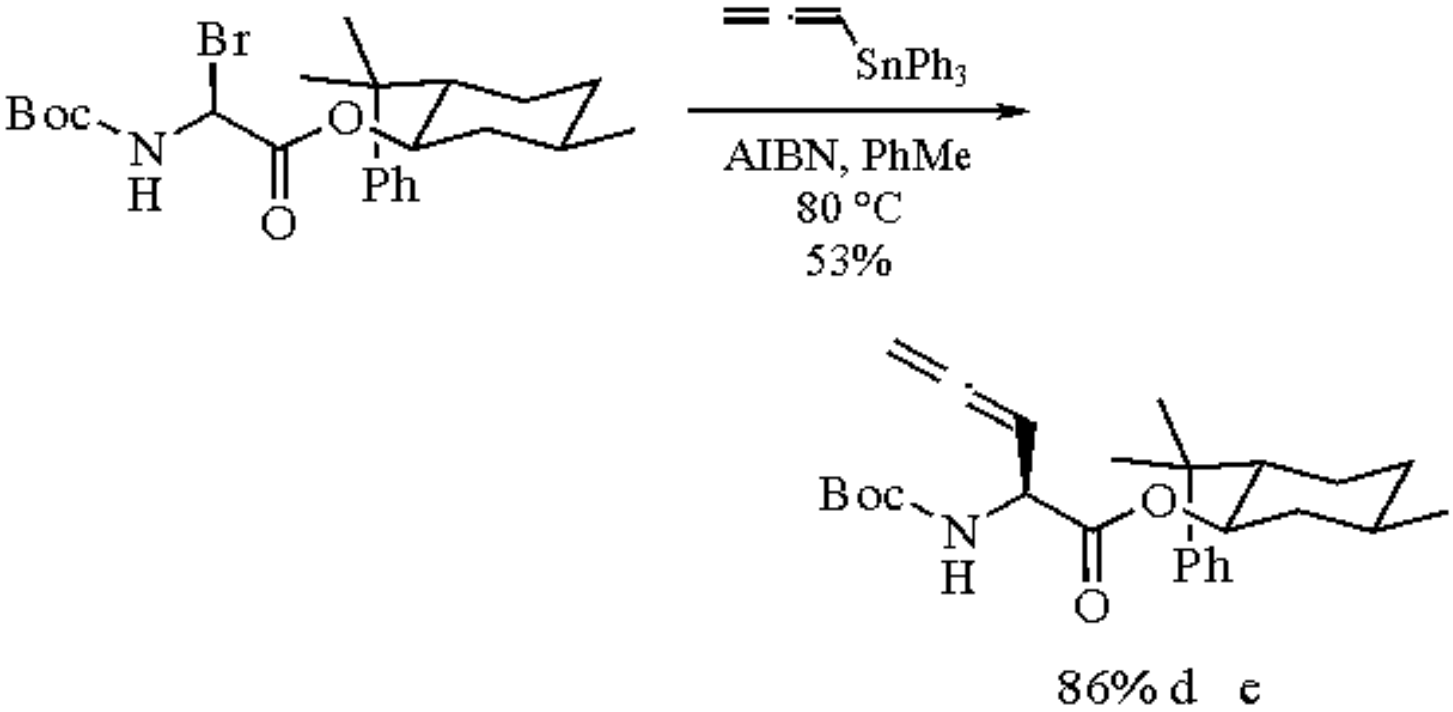

(8)

The reactions of 2-bromoglycinates with nucleophiles and radicals have recently been extended to peptide derivatives[1,25] and the synthesis of α,α-disubstituted α-amino acids.[17b,26]

Related Reagents.

10-Dicyclohexylsulfonamidoisoborneol; ***Ethyl N-Benzylideneglycinate***; ***Ethyl N-(Diphenylmethylene)-2-acetoxyglycinate***; ***Ethyl N-Benzylideneglycinate***; ***Glyoxylic Acid***; ***Methyl Glyoxylate***; ***(-)-8-Phenylmenthol***.

---

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Methyl 4-Bromocrotonate

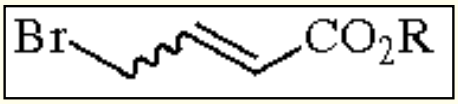

(**1**; R = Me)

[1117-71-1] · $C_5H_7BrO_2$ · Methyl 4-Bromocrotonate · (MW 179.02) (*E*)-(**1**)

[6000-00-6] (*Z*)-(**1**)

[56699-18-4] (**2**; R = Et)

[6065-32-3] · $C_6H_9BrO_2$ · Ethyl 4-Bromocrotonate · (MW 193.05) (*E*)-(**2**)

[37746-78-4] (*Z*)-(**2**)

[119011-89-1]

(precursor for Reformatsky reagents;[1-9] alkylating agent;[22-41] 1,4-addition electrophile[42-45])

Alternate Names: methyl 4-bromo-2-butenoate; methyl γ-bromocrotonate.

Physical Data: (**1**) bp 83-85 °C/13 mmHg; *d* 1.4900 g cm^{-3} (19 °C); *n*20D 1.50210. (**2**) bp 99.0-99.5 °C/17 mmHg; *d* 1.3990 g cm^{-3} (23 °C); *n*23D 1.49050.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid as a mixture of (*E*) and (*Z*) isomers. The methyl ester is available commercially.

Analysis of Reagent Purity: NMR, GC.

Preparative Methods: ethyl or methyl crotonate is treated with ***N-Bromosuccinimide***/CCl_4 and ***Dibenzoyl Peroxide***.[18b]

Handling, Storage, and Precautions: handle under nitrogen and in a fume hood. Store refrigerated and tightly closed. **Caution**: harmful material: allergenic, corrosive, lachrymator, and irritant.

Reformatsky and Other Anionic Reactions.

Methyl and ethyl 4-bromocrotonate have been used extensively as Reformatsky reagents. The reaction has been investigated with regard to the issue of alkylative regioselectivity of the allylic organometallic species toward simple aldehydes and ketones (eq 1).[2-8] In general, it is observed that by using ZnCu(HOAc) in ethyl ether, only α-addition occurs, and when Zn (dry) in THF or cyclohexane is used, γ-addition is favored.[3,6,8,9] Yields range between 90-95%.[6] Additional investigations lead to the development of conditions which furnish either the α-1,2 (**3**) (ZnCu(HOAc), Et_2O, 3 min) or the γ-1,4 (**6**) (Zn, THF, 4 h) adducts of α,β-enones.[8] The structure of the electrophile may affect the stereochemical outcome of the reaction as well.[10,11]

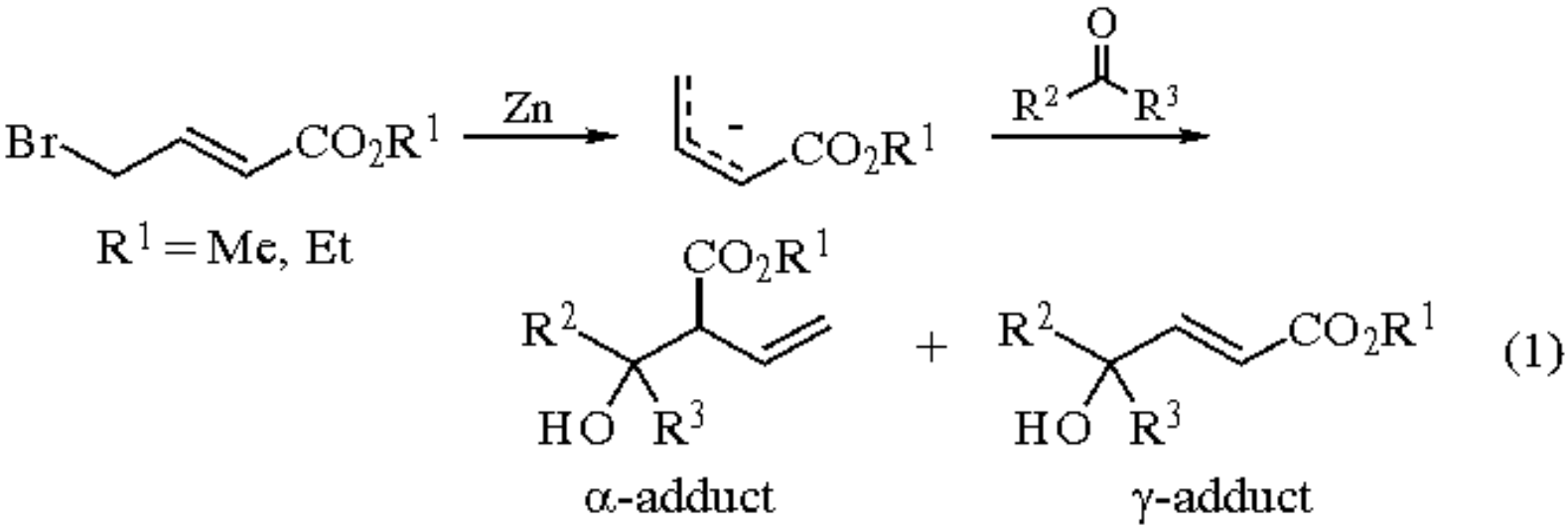

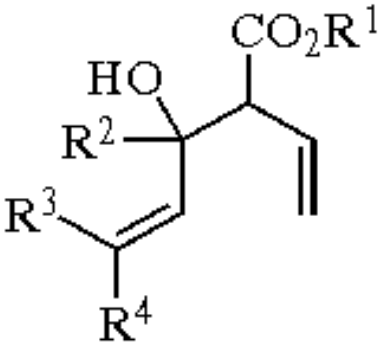

(3) α-1,2

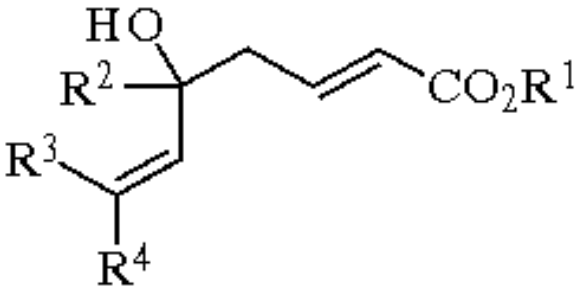

(4) γ-1,2

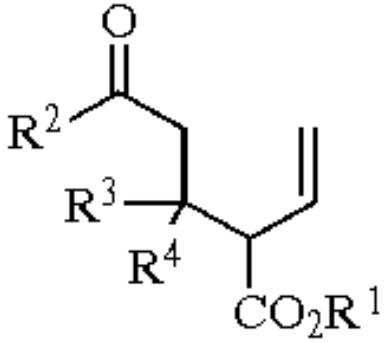

(5) α-1,4

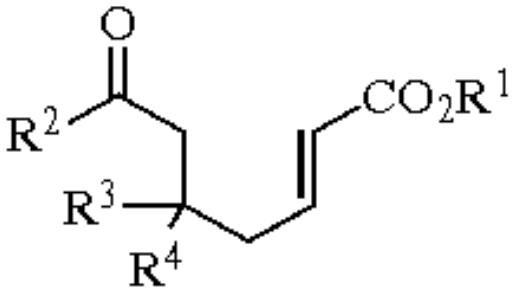

(6) γ-1,4

Other variations in the formation of the organo-Zn compound include the addition of ***Diethylaluminum Chloride***,[12] ***Silver***,[13] ***Boron Trifluoride Etherate***,[14] and ***Dichlorobis(cyclopentadienyl)titanium***.[15] In all cases, the α- or γ-regioselectivity of addition can be controlled, and yields range between 44-99%.

Zn has been replaced by other metallic reagents in the formation of the allylic carbanion. These include ***Cerium/Mercury(II) Chloride***[16] and $Bu_3SnAlEt_2$.[17] The reagents derived from these sources produce α-adducts in 51 and 74% yields, respectively, when treated with methyl 4-bromocrotonate and benzaldehyde, but the conjugated product is isolated from the cerium-mediated reaction. Electrolysis of methyl 4-bromocrotonate and treatment with α,β-unsaturated esters afford exclusively the α-adduct (in a Michael type addition) in 39% yield.[18] When mixtures of an imonium salt and methyl 4-bromocrotonate are subjected to electroreduction, Reformatsky-type products are obtained, in which only the γ-adducts form (93% yield).[19] The same results are obtained when the Reformatsky reaction is performed with Zn and imonium salts in acetonitrile (90% yield).[20]

When treated with the hindered base potassium 2,6-di-*t*-butylphenoxide, ethyl 4-bromocrotonate yields the α-bromo anion, which, in the presence of trialkylboranes, results in alkyl transfer and (upon workup) deconjugation of the alkene in 72-89% yields.[21]

Bromide Replacement.

Many examples of the direct replacement of the bromide from ethyl or methyl 4-bromocrotonate have been reported. Thus the 4-bromocrotonate esters undergo substitution at C-4 with aryltributylstannanes (catalyzed by palladium, 71-91% yield),[22] arenetricarbonylchromium anions (58% yield),[23] organomanganese derivatives of 3-sulfolenes (82% yield),[24] diphenylamine or *N*-methylaniline (catalyzed by copper(II) perchlorate and copper metal, 76-94% yield),[25] thiols under basic conditions (71% yield),[26a] and a variety of alcohols with ***Potassium Carbonate*** (83-87% yield).[26b]

Displacement of the bromide in methyl 4-bromocrotonate with allylic inversion (i.e. at C-2) can be achieved with organocopper reagents in 49-61% yields.[27] Mixtures of direct and allylic displacements (27:73, 91% yield) were obtained when alkylzirconium derivatives were used in the presence of ***Copper(I) Cyanide*** as catalyst.[28]

Triethyl phosphite reacts with methyl 4-bromocrotonate via C-4 alkylation. The resulting phosphonate, after deprotonation, serves as a typical Wadsworth-Emmons reagent (with aldehydes), furnishing the extended dienes in 84% yield (initial γ-addition).[29a] Triphenylarsine reacted with ethyl 4-bromocrotonate to yield, under basic conditions, an ylide which displayed Wittig-like reactivity toward ketones and aldehydes (45-95% yields).[29b]

The presence of the α,β-unsaturated ester moiety in ethyl and methyl 4-bromocrotonates makes them attractive as bifunctional electrophiles. In these cases, a cyclization follows the direct alkylation. Thus carbocyclic compounds have been obtained by palladium-catalyzed cyclizations[30] or [4 + 2] cycloadditions.[31] Indoles, isoquinolines, and other nitrogen heterocycles can be formed by palladium-catalyzed cyclizations,[32] oxidative electrocyclizations,[33] [4 + 2] cycloadditions,[34] or Michael additions.[35] Oxygen heterocycles are formed by radical cyclizations,[36] intramolecular 1,4-condensations,[37] palladium-catalyzed cyclizations,[38] [4 + 2] cycloadditions,[34] or Claisen rearrangements.[39] Sulfur heterocycles were formed through a variety of intramolecular cyclizations, all following initial sulfur alkylation at C-4.[40] Morpholines were prepared by intramolecular 1,4-cycloadditions.[41]

1,4-Additions and Subsequent Cyclopropane Formation.

When nucleophiles such as lithium alkylthiolates,[42] lithium ester enolates,[43] sulfur-containing carbanions,[44] or cross-conjugated lithium enolates[45] react with ethyl or methyl 4-bromocrotonate in a conjugate fashion, a ring closure by attack of the resulting enolate on C-4 follows to form the corresponding cyclopropanes. In some cases the direct substitution of the bromide is a competitive reaction.[42,43a]

Related Reagents.

Methyl 2-Bromocrotonate.

---

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Methyl 2-Bromocrotonate

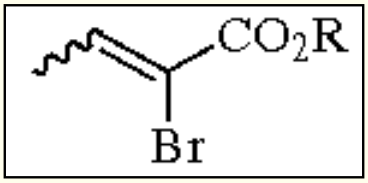

(**1**; R = Me)

[17642-18-1] · $C_5H_7BrO_2$ · Methyl 2-Bromocrotonate · (MW 179.02) (*E*)-(**1**)

[36297-23-1] (*Z*)-(**1**)

[22966-48-9] (**2**; R = Et)

[59065-89-3] · $C_6H_9BrO_2$ · Ethyl 2-Bromocrotonate · (MW 193.05) (*E*)-(**2**)

[51263-38-8] (*Z*)-(**2**)

[51263-39-9]

(vinyl cyclopropanation/oxiranation reagent;[1,2] bisannulating agent[3a])

Alternate Names: methyl 2-bromo-2-butenoate; methyl α-bromocrotonate.

Physical Data: (**1**) bp 61 °C/9 mmHg; *d* 1.5064 g cm^{-3} (17 °C); *n*17D 1.48700. (**2**) bp 69-70 °C/12 mmHg; *d* 1.3952 g cm^{-3} (18.4 °C); *n*18D 1.47660.

Solubility: sol most organic solvents.

Form Supplied in: light yellow liquid as a mixture of (*E*) and (*Z*) isomers. The methyl ester is available commercially.

Analysis of Reagent Purity: NMR, GC.

Preparative Methods: ethyl or methyl crotonate is treated with Br_2/CCl_4 or Br_2/AcOH followed by dehydrobromination with quinoline[2] or DBU.[1]

Handling, Storage, and Precautions: handle under nitrogen in a fume hood; these reagents are moisture sensitive. Store refrigerated and in brown bottles to avoid polymerization. Caution: lachrymator and irritant; may be harmful.

Vinylcyclopropanation/Oxiranation Reagents.

The lithium dienolate of ethyl 2-bromocrotonate, formed upon low temperature addition to ***Lithium Diisopropylamide***, was reacted with enones to yield vinylcyclopropanes as *endo* and *exo* isomer mixtures (eq 1).[1,4] The *endo*/*exo* ratio was variable, and independent of the (*E*/*Z*) ratio of the starting ethyl bromocrotonate.

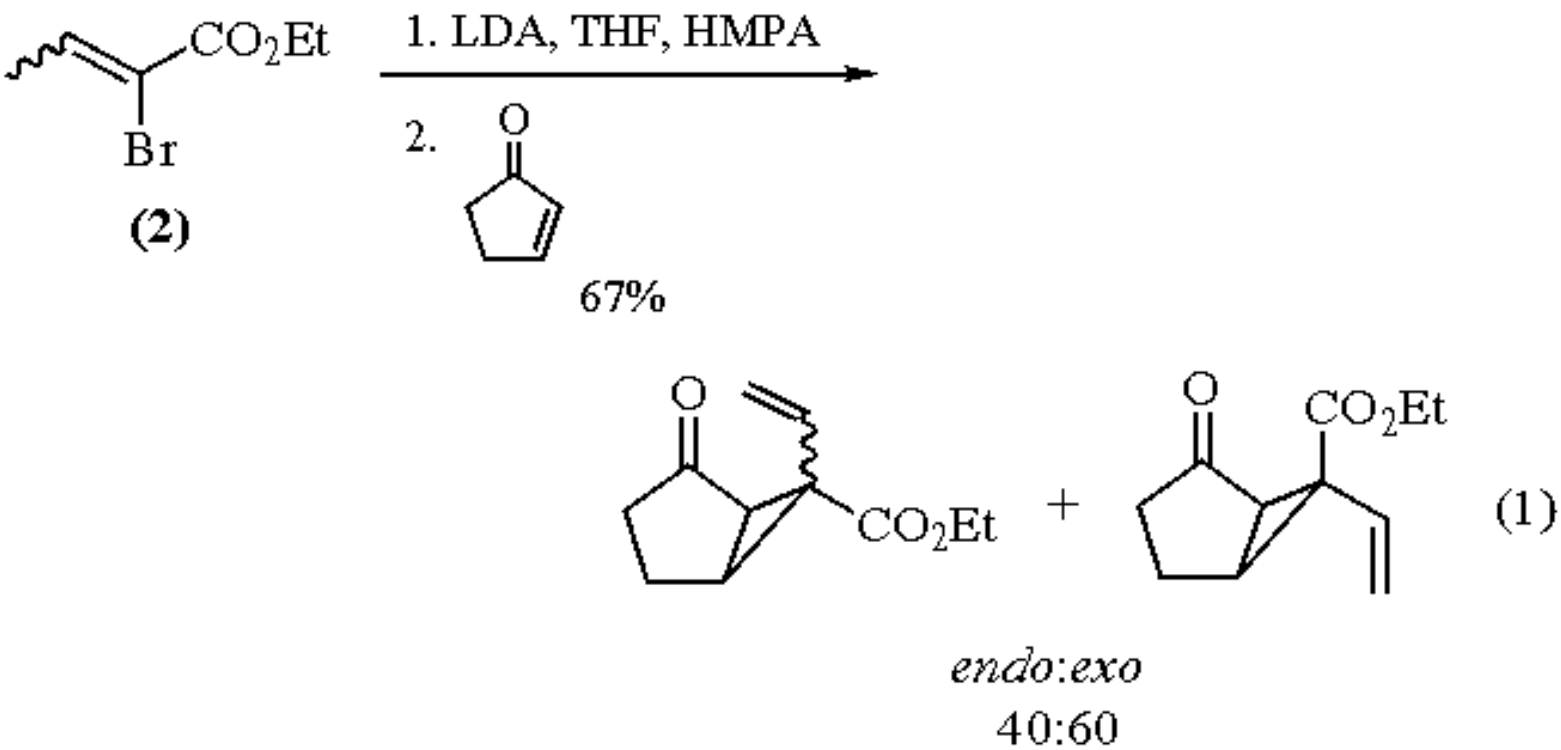

Yields of isolated products varied from 30 to 90%, depending on the enone. Thermal rearrangement of these vinylcyclopropanes afforded cyclopentene annulated systems (eq 2).[1,4,5]

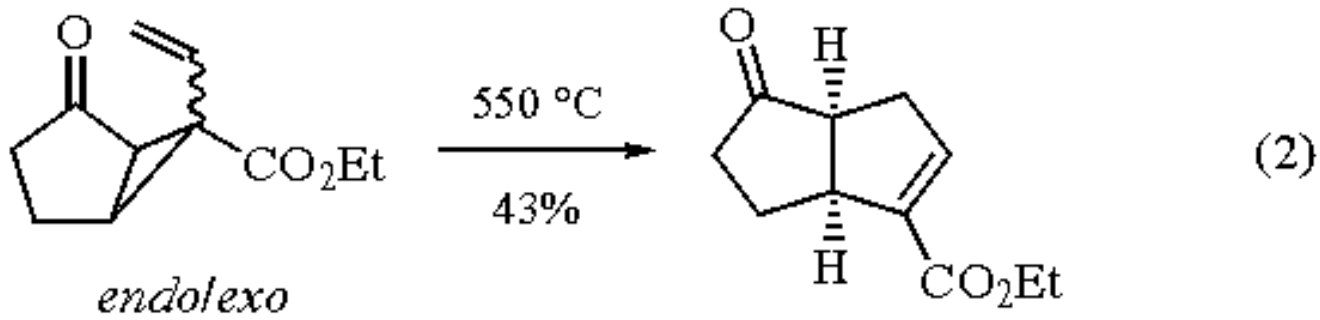

This method was successfully applied to the synthesis of a number of natural products, including pentalenene (**3**)[6] (nonlinear sesquiterpene) and retigeranic acid (**4**)[1,7] (sesterterpene).

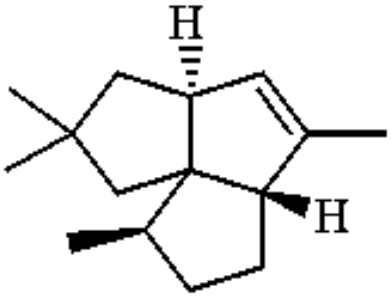

(3) Pentalenene

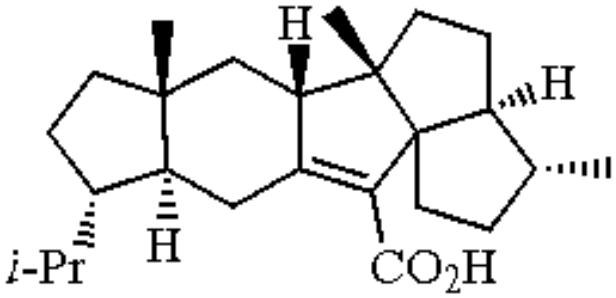

(4) Retigeranic acid

Reaction of the lithium dienolate of ethyl 2-bromocrotonate, with aldehydes as the electrophiles, furnished vinyloxiranes[2] in yields ranging from 47 to 70%. Only one stereoisomer (*anti*) was formed (eq 3). Aldehydes were, in general, more reactive than ketones. The vinyloxiranes were subjected to pyrolysis to afford the corresponding dihydrofurans in 7-95% yield (eq 3).[2] This method was applied to the synthesis of the natural product ipomeamarone (**5**).[8]

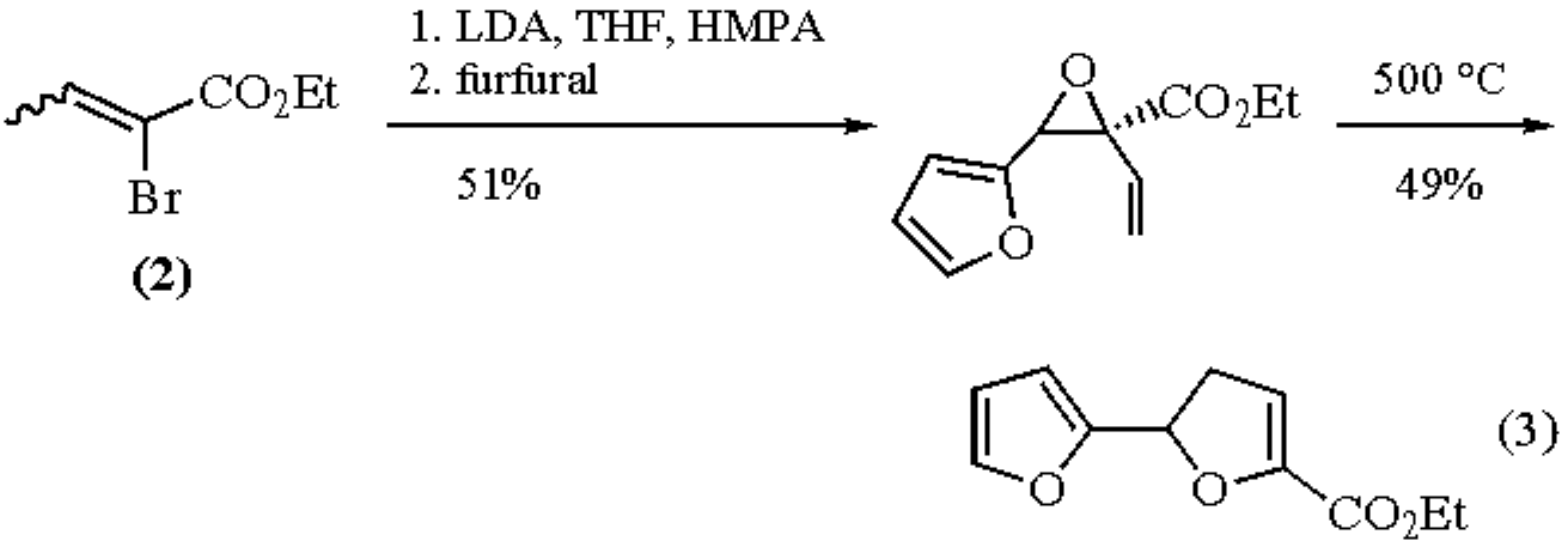

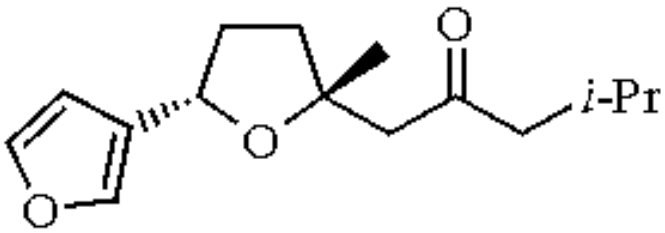

(5) Ipomeamarone

Bisannulation Reactions.[9]

Addition of a cross-conjugated dienolate to methyl 2-bromocrotonate resulted in double Michael addition, followed by alkylation. In the case of 2-cyclohexenone, the formation of the tricyclic system shown in eq 4 was accomplished in a one-step synthesis.[3] Yields ranged between 25 and 55%.

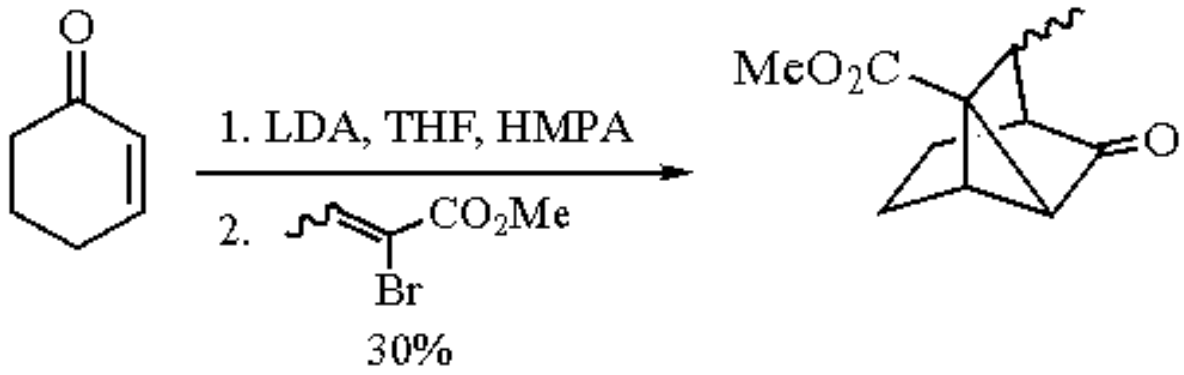

(4)

Natural products ishwarane (**6**)[10] and helminthosporal (**7**)[11] were prepared using this methodology.

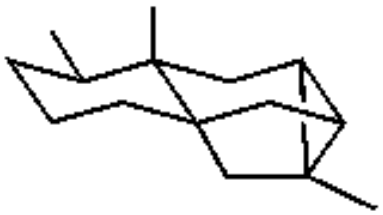

(6) Ishwarane

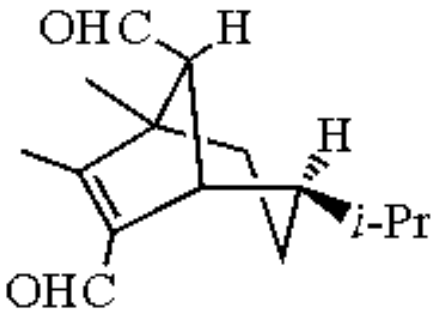

(7) Helminthosporal

Use of acetylcyclohexenes as the enone component furnished the tricycle shown in eq 5.[12] Yields varied between 20 and 61%.

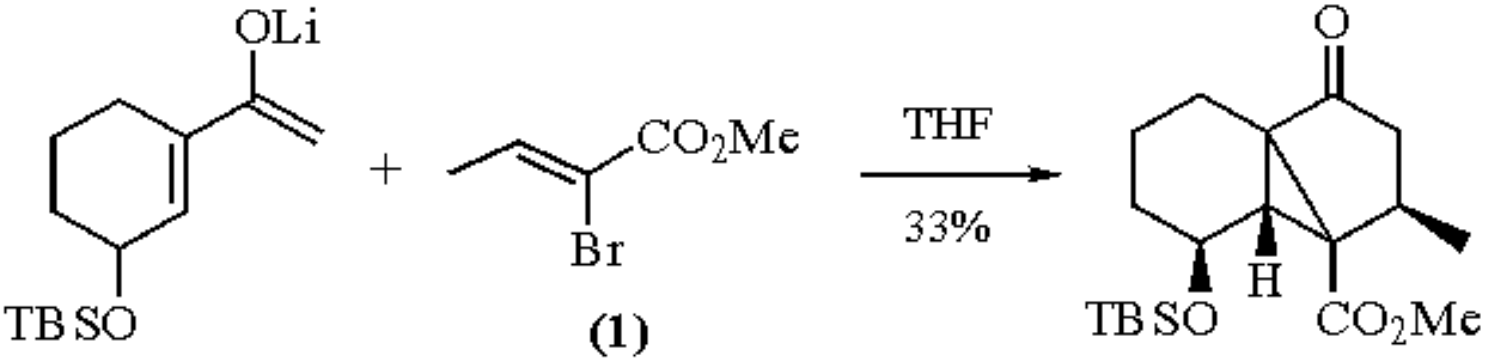

(5)

Substitution of Bromine.

Methyl 2-bromocrotonate is a substrate for halogen-metal exchange with ***Lithium Dimethylcuprate***; organocopper reagent (**8**) is the product.[13]

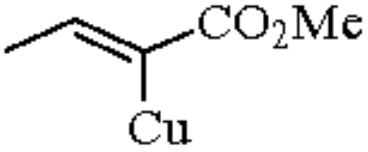

(8)

Reaction of methyl 2-bromocrotonate with ethanethiol produces the 2-ethylthiocrotonate (**9**).[14] When (**9**) is subjected to the bisannulation protocol of eq 4, the reaction stops at the point of the double Michael addition (eq 6).[15] The sulfide product lends itself to further modification (oxidation/elimination).

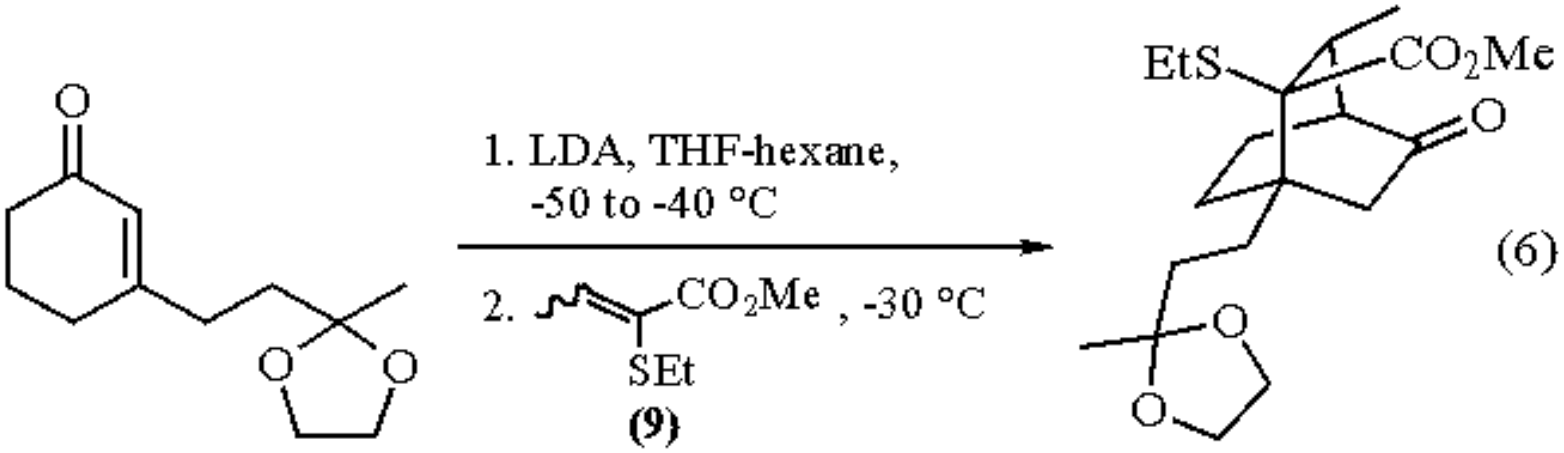

(9)

74%

Related Reagents.

Methyl 4-Bromocrotonate.

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Methyl (*Z*)-(2)-(Bromomethyl)-2-butenoate

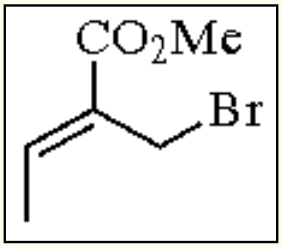

[60941-07-3] · $C_6H_9BrO_2$ · Methyl (*Z*)-(2)-(Bromomethyl)-2-butenoate · (MW 193.05)

(synthon for α-methylene-γ-butyrolactones[1,2] and allylic and vinylic substitution products[3])

Alternate Name: methyl β´-bromotiglate.

Physical Data: bp 68 °C/3 mmHg.[2]

Preparative Methods: allylic bromination of methyl 3-hydroxy-2-methylenebutanoate[4] with ***N-Bromosuccinimide/Dimethyl Sulfoxide***[5] or ***Hydrogen Bromide/Sulfuric Acid***.[2]

Synthesis of α-Methylene-γ-Butyrolactones.

Dreiding was the first to demonstrate that treatment of the title reagent (**1**) and cyclohexanone with zinc in THF gave a 78% yield of the spirocyclohexane α-methylene-γ-butyrolactone (eq 1).[1] When Reformatsky conditions were applied to (**1**) and 2-methylpropanal, a diastereomeric mixture of the *exo*-methylene lactones was obtained (eq 2).[6] In contrast, allylic chromium complexes of the reagent react with aliphatic and aromatic aldehydes to give α-methylene-γ-butyrolactones diastereoselectively in good yields (eq 3).[2] The title reagent (**1**) and an aluminum/tin reagent gave a 54% yield of the uncyclized product which could be cyclized to the lactone in a separate step (eq 4).[2]

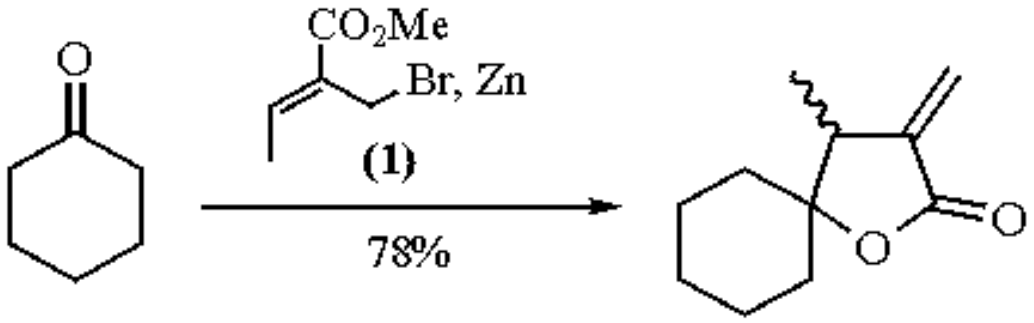

(1)

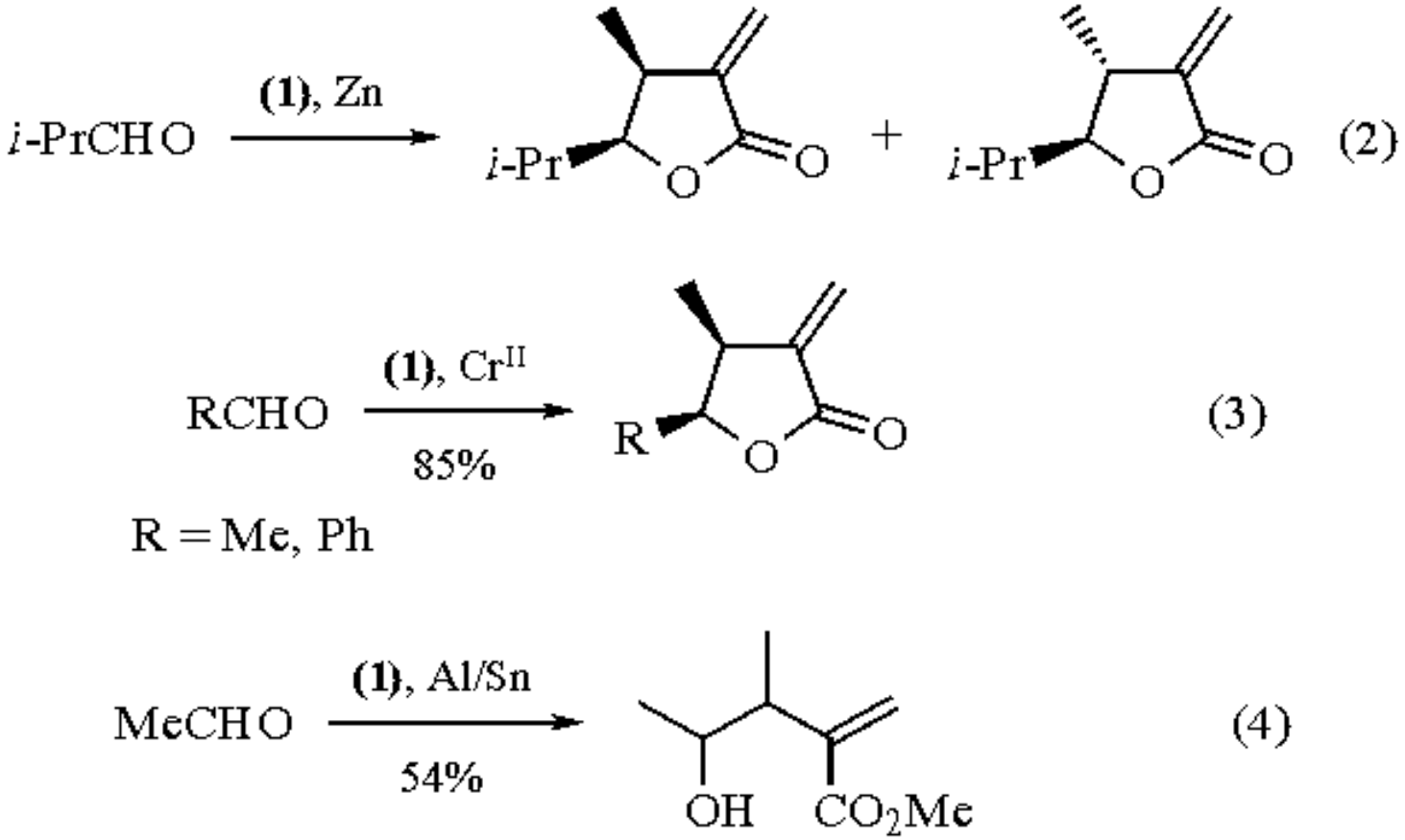

Nucleophilic Displacements.

Both allylic and vinylic products are obtained from the nucleophilic displacement of bromide from the reagent (eq 5).[3] The product distribution is dependent on the nature of the base and nucleophile and in most cases both substitution routes are observed. Attack at the allylic carbon of the reagent (to give **2**) is favored by increasing the steric bulk of the nucleophile and using ***Sodium Ethoxide*** in ethanol as base. For example, when R is hydrogen (eq 5) a 4:1 ratio of normal (**2**) to rearranged (**3**) product is obtained using sodium ethoxide in ethanol. This is reversed to give a 1:4 ratio of (**2**) to (**3**) when ***Sodium Hydride*** in THF is the base-solvent system. When R is benzyl, only allylic product (**2**) is obtained with NaOEt/EtOH and the product distribution of (**2**) to (**3**) is 4:1 with sodium hydride as base.

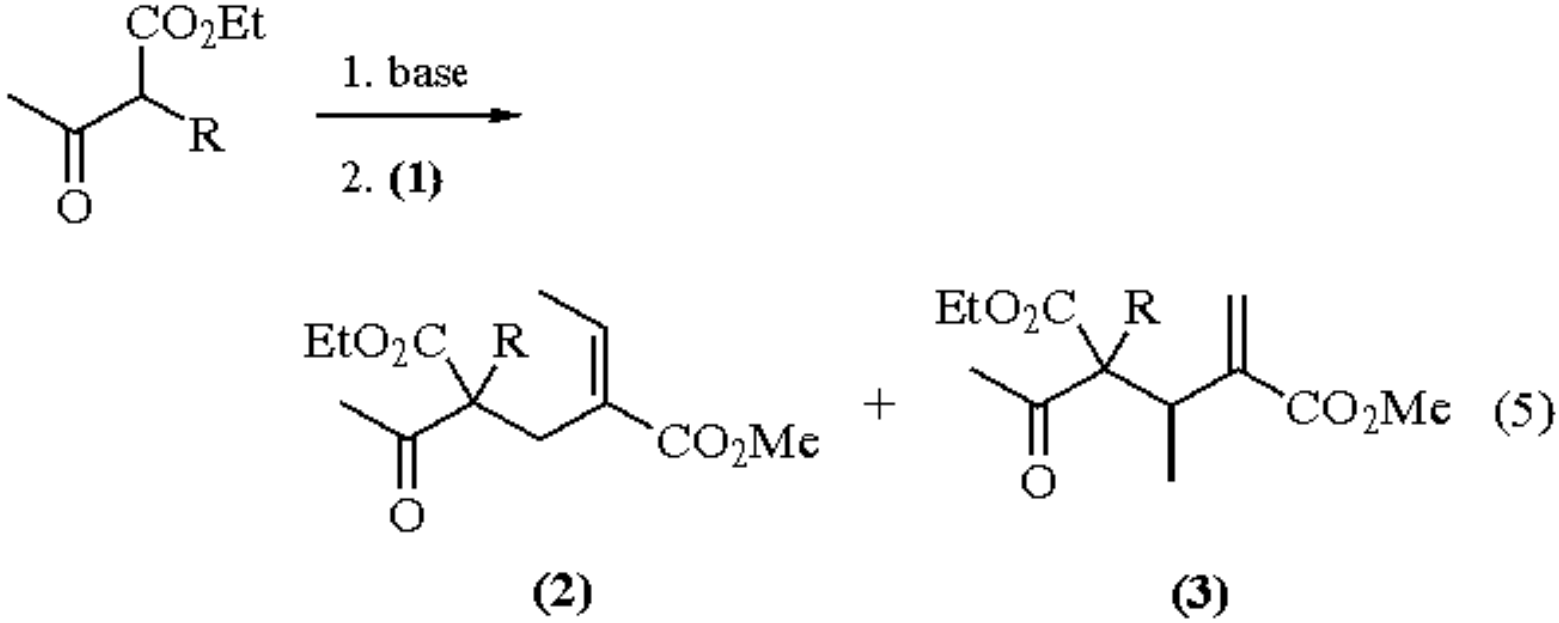

Natural Product Synthesis.

Zinc-mediated coupling of methyl β´-bromotiglate has been used in the synthesis of necic acid and related compounds.[7] Thus addition of (**1**) to zinc in DMSO gave an 85% yield of the dimer (**4**) (eq 6). In contrast, treatment of (**1**) with ***Magnesium*** in THF gave a mixture of (**4**), (**5**), and (**6**) in a ratio of 11:7:1 (eq 6). Mikanecic acid-type structures can be obtained by treating the reagent with ***Potassium t-Butoxide*** (eq 7).[5] Recently, the reagent has been used as a synthon in the synthesis of kijanolide.[8]

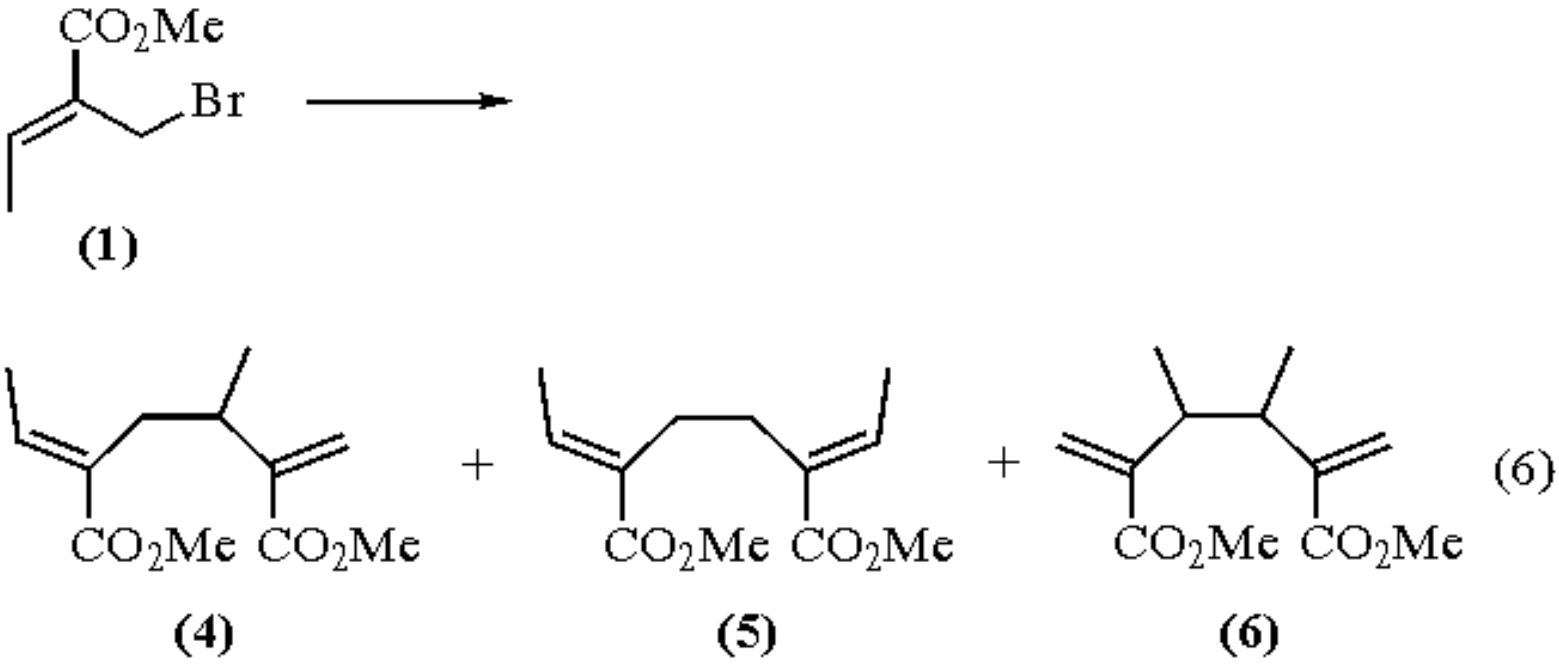

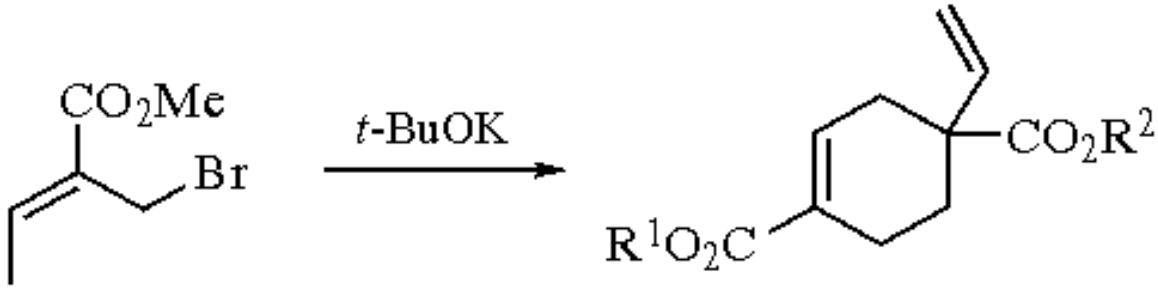

(1) (7)

$R^1 = R^2 = H$, 33%
$R^1 = H$, $R^2 = Et$, 20%
$R^1 = R^2 = Et$, 15%

Related Reagents.

Ethyl 2-(Bromomethyl)acrylate.

---

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Methyl 2,3-Butadienoate[1]

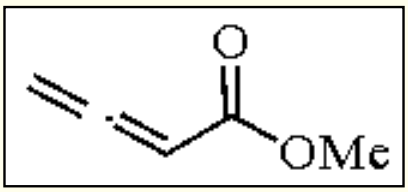

[18913-35-4] · $C_5H_6O_2$ · Methyl 2,3-Butadienoate · (MW 98.11)

(reactive electrophilic reagents for nucleophilic addition,[2] Michael addition,[3,4] [2 + 2],[5,6] [2 + 3],[7,8] and [2 + 4][9,10] cycloadditions, and hetero-Cope rearrangements[4])

Physical Data: bp 40 °C/14 mmHg.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: IR (film): 1965/1940, 1725 cm^{-1}; ^1H NMR (CCl_4): 5.65-5.35 (H-C(2)), 5.25-5.00 (2H-C(4)), 3.68 ppm (OMe).

Preparative Methods: most conveniently obtained via a Wittig reaction of $[E(R)CHPPh_3]^+X^-$ or $E(R)C{=}PPh_3$ and RR´CHCOCl (R, R´ = H, alkyl) in the presence of ***Triethylamine*** in CH_2Cl_2.[1] Alternatively, the Wittig reaction can be performed with the corresponding ketenes.[11]

Purification: rapid distillation under reduced pressure in a short-path distillation apparatus or column chromatography on Alox N with hexane/Et_2O (9:1). Hydroquinone may be added for distillation.

Handling, Storage, and Precautions: can undergo polymerization and so should be stored in the presence of hydroquinone. For best results, it should be freshly distilled. Use in a fume hood.

Preparation of Substituted 2,3-Butadienoates.

The method described above also works with α,β-unsaturated acid chlorides to yield 4-vinyl substituted 2,3-butadienoates[12] and may likewise be applied as a ring closure procedure for the synthesis of endocyclic allenelactones.[10] Alternative methods for the synthesis of 2,3-butadienoates and analogs include the Pd^0-catalyzed carbonylation of propargylic carbonates[13] and halides.[14] In the presence of acrylates instead of CO, vinyl analogs of allenic esters are obtained.[15] 2-Substituted 2,3-butadienoates are available from the Wittig reaction of corresponding

phosphoranes or phosphonates with ketenes[11,16,17] or by the oxidative degradation of 3,4-substituted pyrazol-3(2*H*)-ones with Tl^{III} salts[9,18] or ***(Diacetoxyiodo)benzene***.[19] 2-Phenyl-substituted 2,3-butadienoates have been prepared by a combined photolysis of trimethoxy-(1-methoxycarbonylbenzylidene)phosphorane and cyclohexanones in benzene.[20] Dimethyl 2,3-pentadienedioate can be prepared in three steps from diethyl acetone-1,3-dicarboxylate.[21]

Addition of Nucleophiles.

Nucleophiles add to 2,3-butadienoates and their analogs at the C-3 position.[22-24] The addition of primary or secondary amines leads to the formation of β-amino acrylates,[2a,3,25,26] which, on hydrolysis, yield β-keto esters (eq 1).[3] In a similar manner, β-azido crotonates can be synthesized which are photolytically transformed into 2*H*-azirine-3-carboxylates.[27] ***Triphenylphosphine*** adds to 2,3-butadienoates under acid catalysis to yield the corresponding phosphonium salts which, on treatment with MeONa/MeOH, form (*E*)-4-methoxy-2-butenoates (eq 2).[28,29] The methylation of ethyl 2,3-butadienoate at C-3 with ***Lithium Dimethylcuprate*** at -90 °C was utilized in the synthesis of lavandulol.[30]

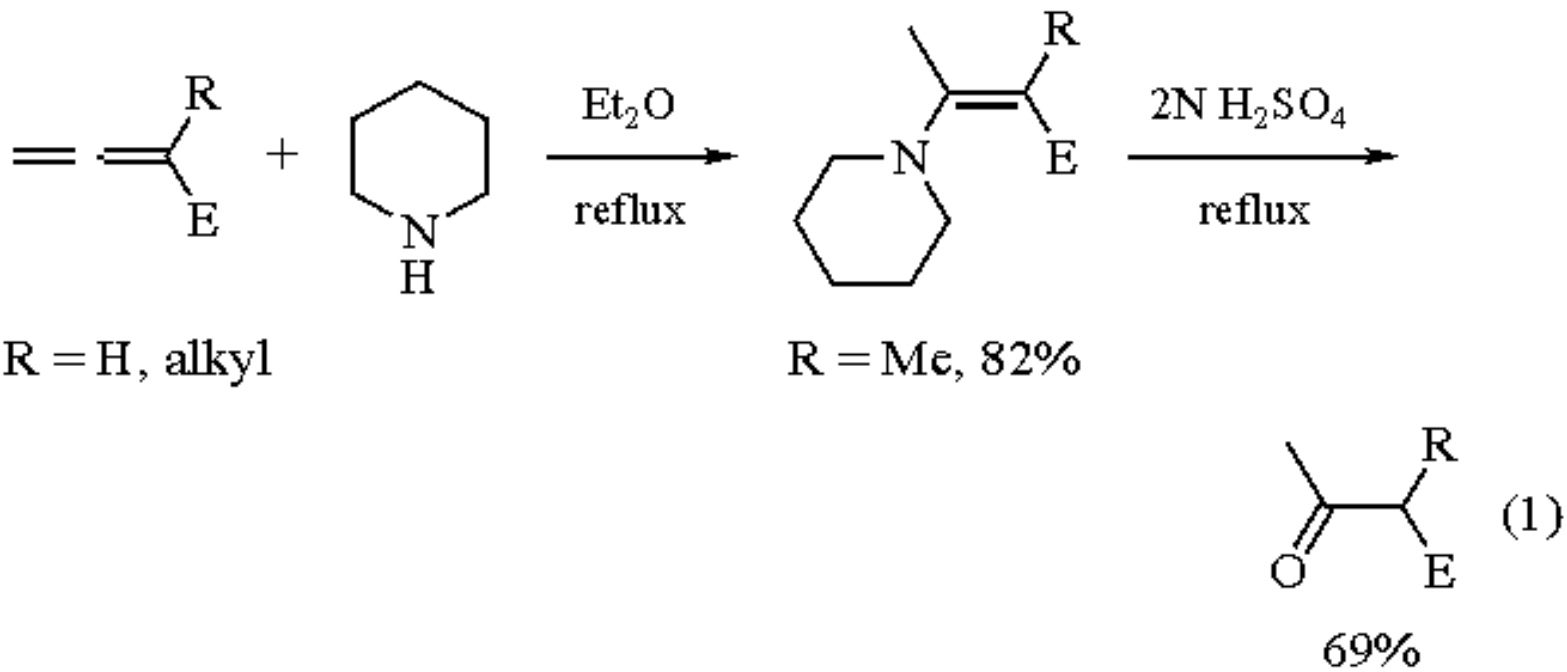

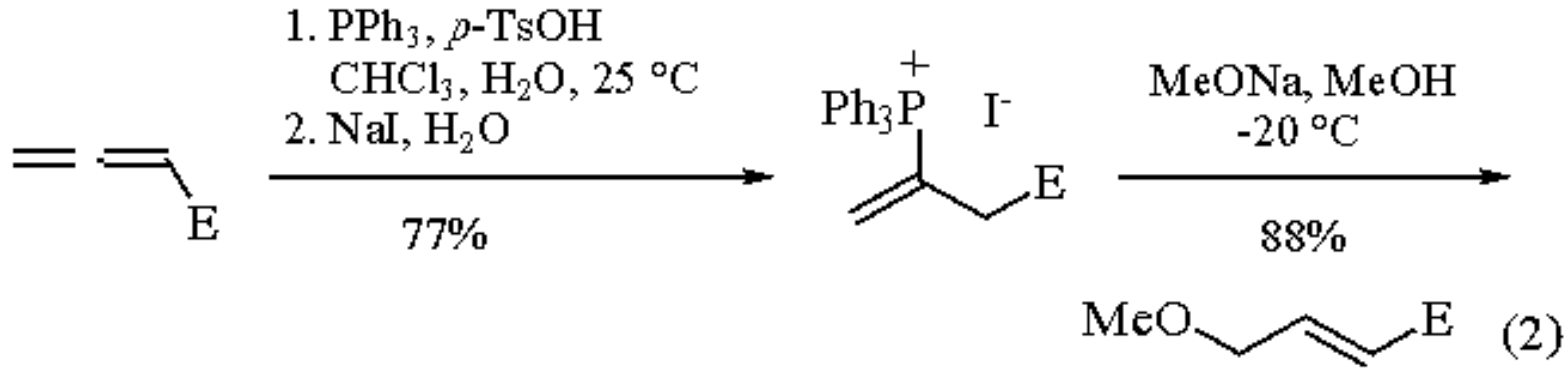

Grignard reagents add in the same way to allenecarboxylic acids.[31] Blechert showed that ethyl 2,3-butadienoate reacts with the Li salt of *N*-acetyl-*N*-phenylhydroxylamines to yield, via a hetero-Cope rearrangement, ethyl 4-(2-

acetamidophenyl)-3-oxo-butanoates which undergo indolization upon treatment with ***Formic Acid*** (eq 3).[4]

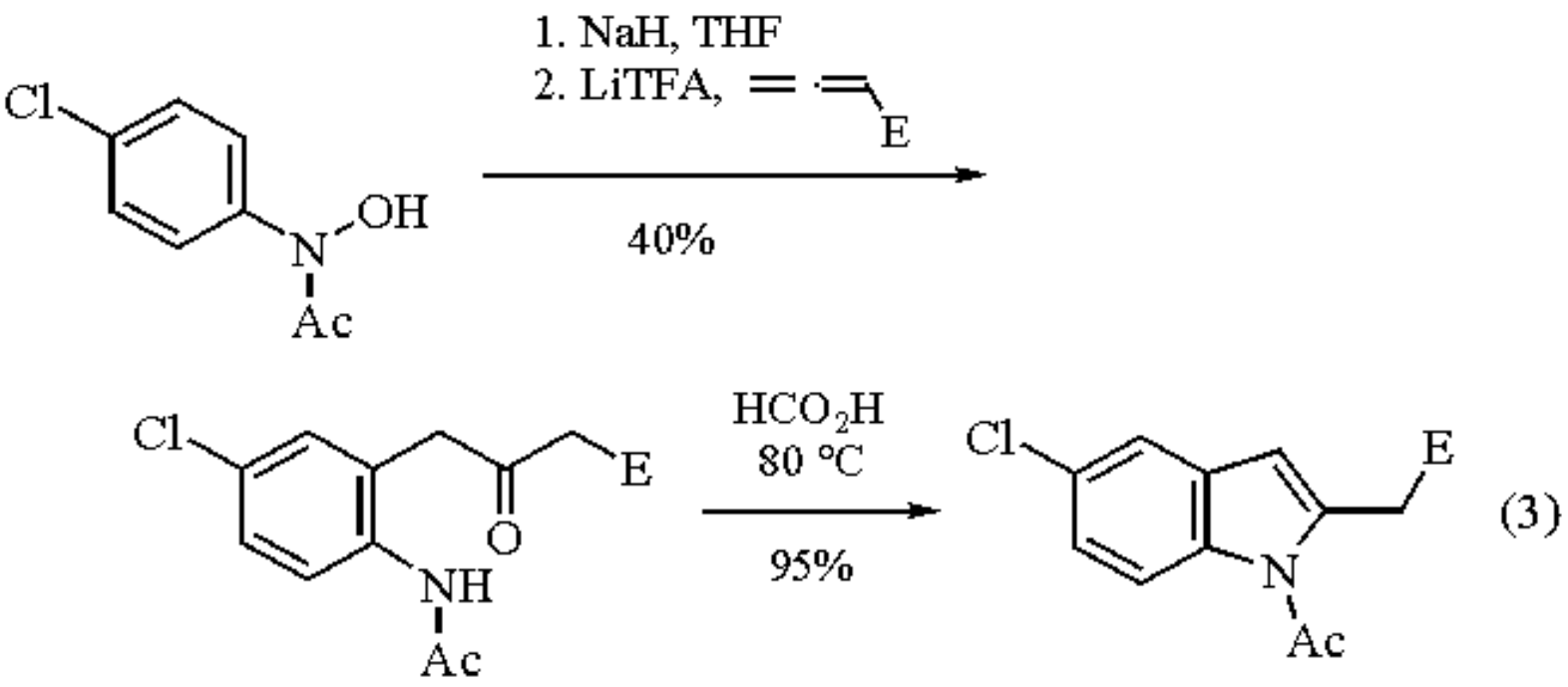

Cycloadditions.

[2 + 2] Cycloadditions of 2,3-butadienoates with simple alkenes, promoted by ***Ethylaluminum Dichloride***[5] or ***Aluminum Chloride***,[6] take place at the C(3)=C(4) double bond without loss of the stereochemical integrity of the alkenes and lead to the formation of the corresponding cyclobutylideneacetates (eq 4). Conjugated imines seem to add to ethyl 2,3-hexadienoate in a similar manner when heated to reflux in benzene.[32] The azetidines which are formed primarily rearrange to yield 2-cyclohexenones after hydrolysis.

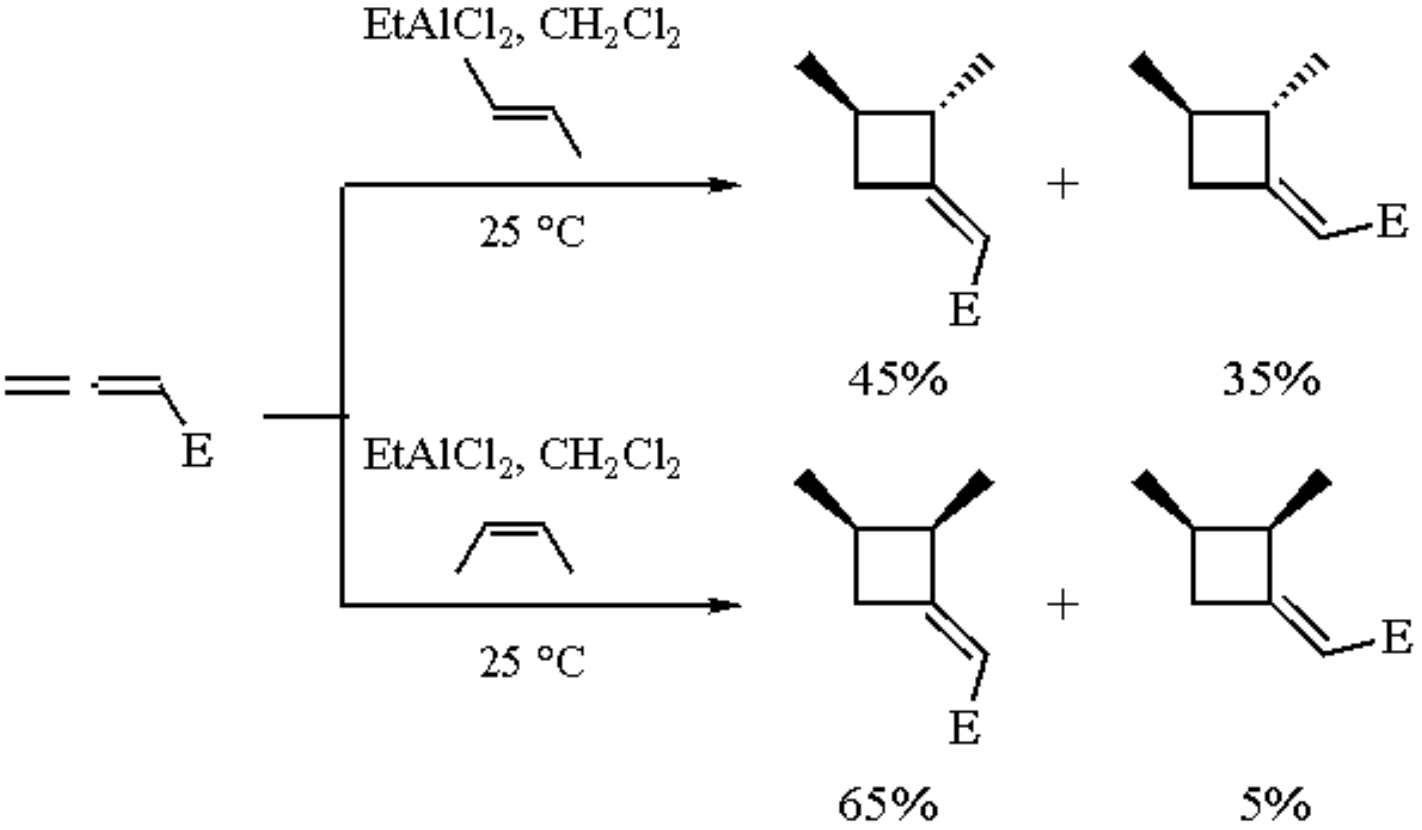

(4)

[2 + 3] Cycloadditions of 2,3-butadienoates and analogs have been investigated with nitrilium betaines (nitrile ylides,[7,33] nitrile imines,[34] nitrile oxides[34]), diazonium betaines (diazoalkanes,[35] azides[34]), and nitrones.[8,36] All 1,3-dipolar cycloadditions occur at the C(2)=C(3) double bond, but often regioisomers are formed. The cycloadducts may isomerize (spontaneously or with base catalysis) to yield the corresponding heteroaromatics (eq 5). Nitrones react smoothly with methyl 2,3-butadienoate and its 2-methyl derivative to yield regioselectively 5-methyleneisoxazolidines which, on heating, may undergo a 1,3-H shift or a skeletal rearrangement to the corresponding 3-pyrrolidones (eq 6).[8,37]

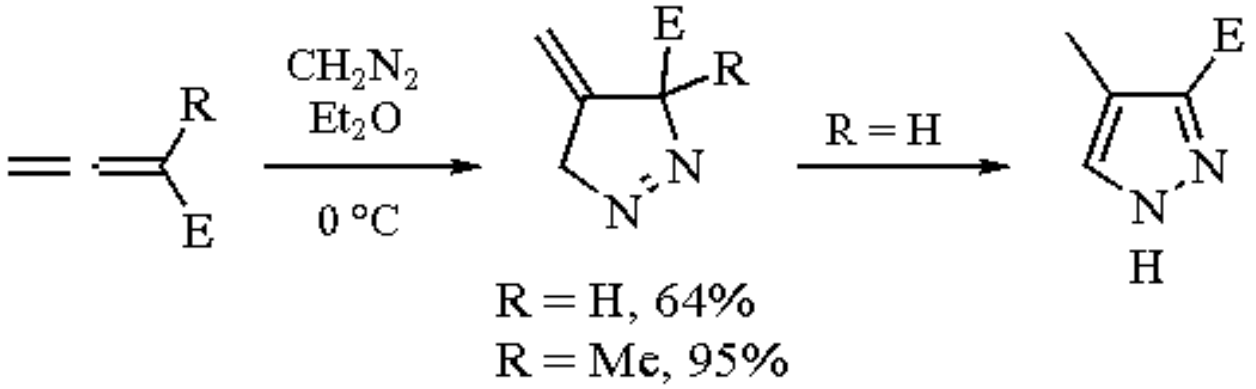

(5)

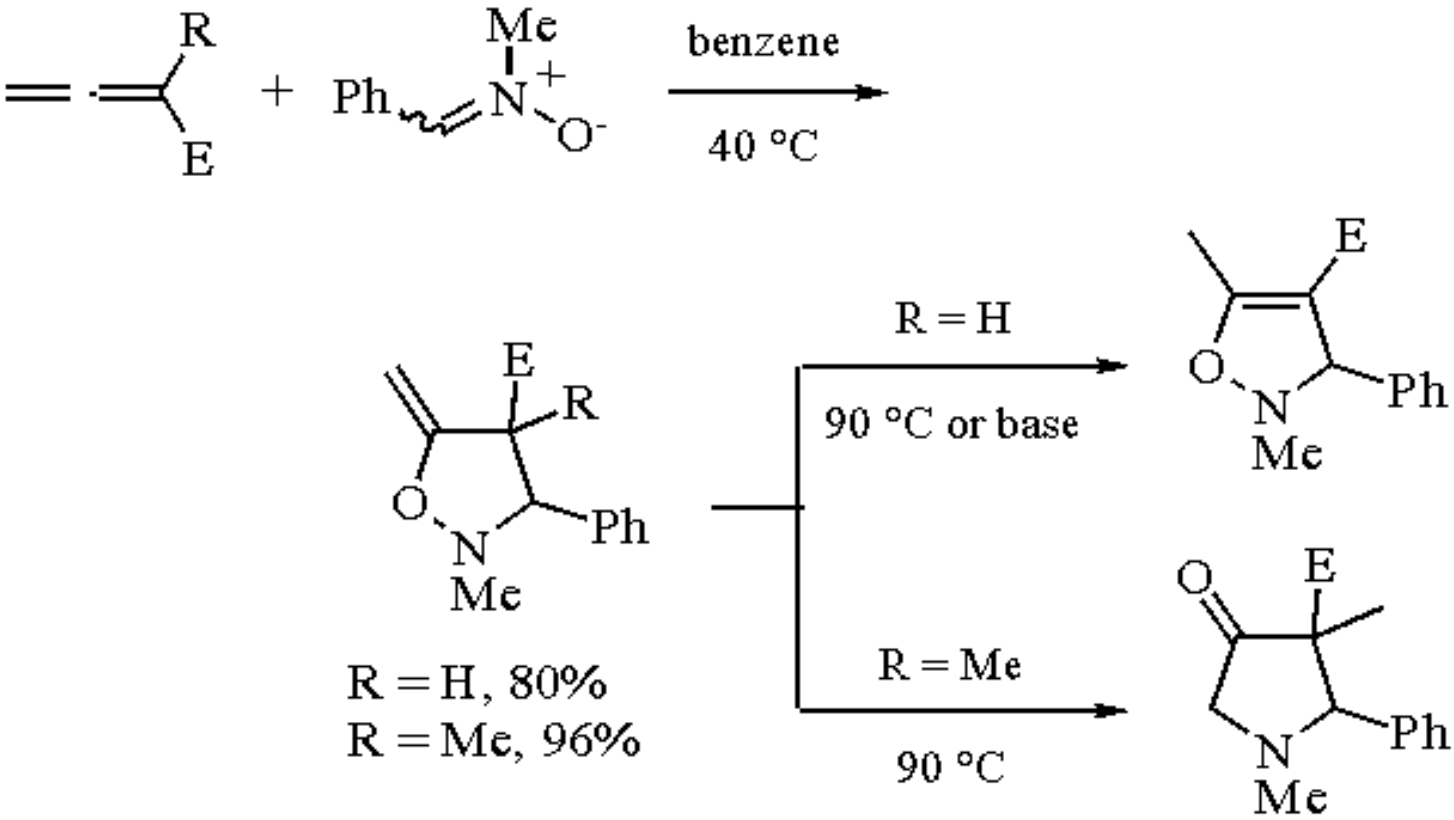

(6)

[4 + 2] Cycloadditions with allenecarboxylates as dienophiles have also been studied.[9,22,23] Thermal reaction with cyclopentadiene leads to the formation of *endo*- and *exo*-3-methylenebicyclo[2.2.1]hept-5-ene-2-carboxylates in a ratio of ca. 2:1.[9] The addition of $AlCl_3$[9] or $M(fod)_3$ (M = Eu, Pr)[38,39] allows the cycloaddition to be carried out at lower temperatures and with higher *endo*/*exo* ratios. The cycloaddition with furan as diene can also be catalyzed by $M(fod)_3$ and leads also to a predominance of the *endo* product.[40] Synthetically valuable [4 + 2] cycloadditions of 2,3-butadienoates and analogs with ***1,1-Dimethoxy-3-trimethylsilyloxy-1,3-butadiene*** have been performed by Gerlach and co-workers[10] and applied to the synthesis of (+)-(*R*)-lasiodiplodin (eq 7).

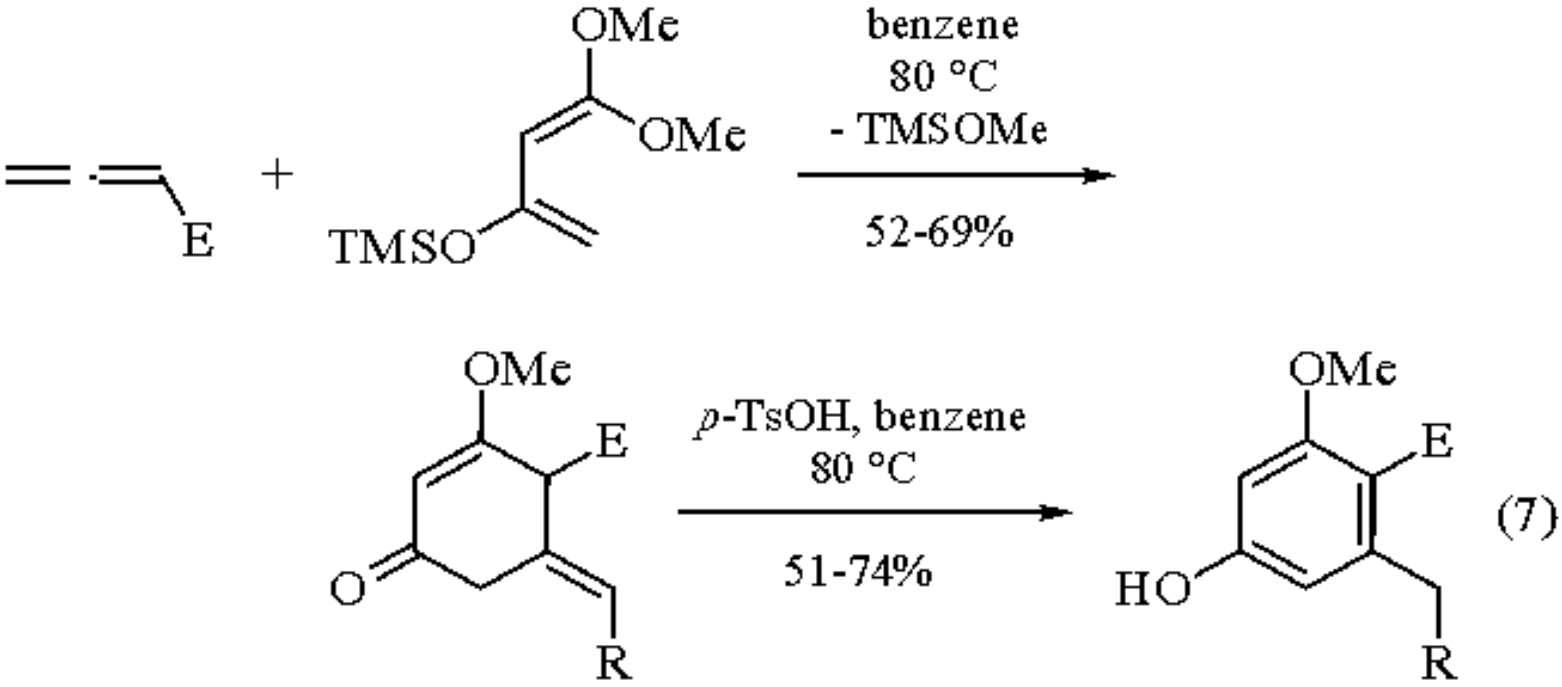

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3-Methyl-3-buten-1-ynylcopper(I)[1]

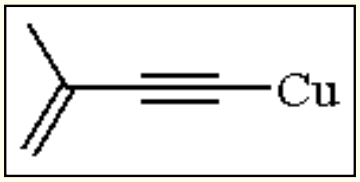

[56964-06-8] · C_5H_5Cu · 3-Methyl-3-buten-1-ynylcopper(I) · (MW 128.65)

(coupling agent for introduction of the isopropenyl group;[2] nucleophilic species which effects decarbonylative ring contraction of bicyclic lactones[3])

Alternate Name: copper(I) isoprenylacetylide.

Physical Data: bright yellow solid; mp 120-200 °C (dec);[2] IR (KBr) 3095, 3003, 2970, 2921, 1932, 1603, 1440, 1428, 1380, 1363, 1255, 895, 878, 709, 552, 525 cm^{-1}.[4]

Solubility: sol pyridine, DMF, ethanol; insol water.

Preparative Method: ***Hydroxylamine*** hydrochloride reduction of ***Copper(II) Sulfate*** in aq ammonium hydroxide followed by addition of isopropenylacetylene in ethanol.[2] *Drying:* solid dried under P_2O_5 in vacuo.

Handling, Storage, and Precautions: all solid copper(I) acetylides are potentially explosive. Use in a fume hood.

Coupling Reactions.

Organocuprates such as isopropenylcopper alkynes couple to a variety of electrophiles (see also ***1-Hexynylcopper(I)***, ***1-Pentynylcopper(I)***, ***Phenylethynylcopper(I)***). The couplings, typically performed on aryl and vinyl iodides and bromides, give rise to substituted alkynes, which in one report included products of the dienyne class (eq 1).[5]

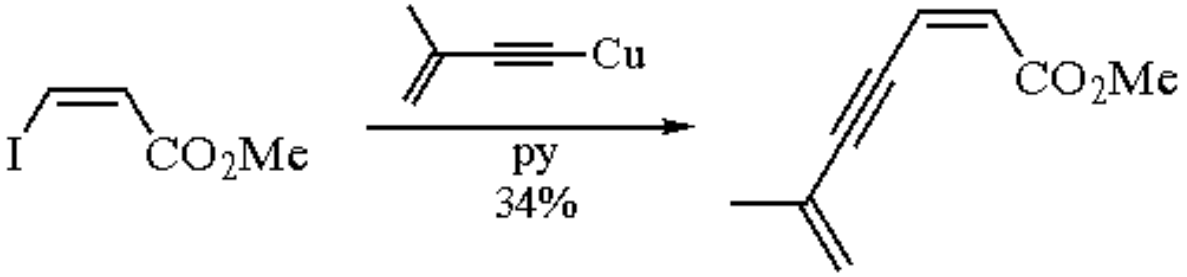

(1)

Coupling onto aryl iodides is one of the more studied reactions, due to its importance in the synthesis of natural product systems. A representative example is seen in the synthesis of frustulosin, a tetrasubstituted aromatic natural product (eq 2).[6]

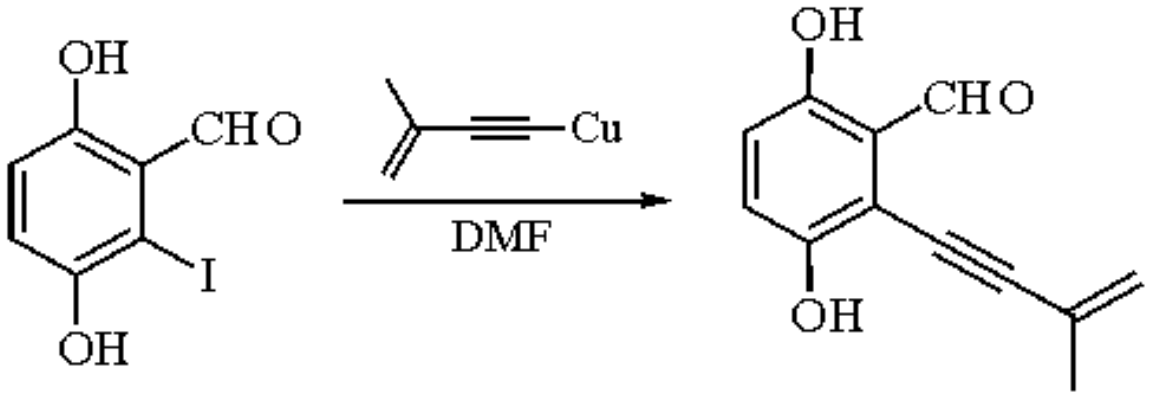

(2)

Isolation of the disubstituted alkynic product is often not possible where an *o*-hydroxy group is present. Instead, concomitant cyclization to yield benzofuran-type structures usually ensues under the reaction conditions.[7] Numerous examples have been documented.[2,8-10] Often, heavily functionalized molecules do not pose any problem to the sequence, yielding complex heterocycles (eq 3).[11]

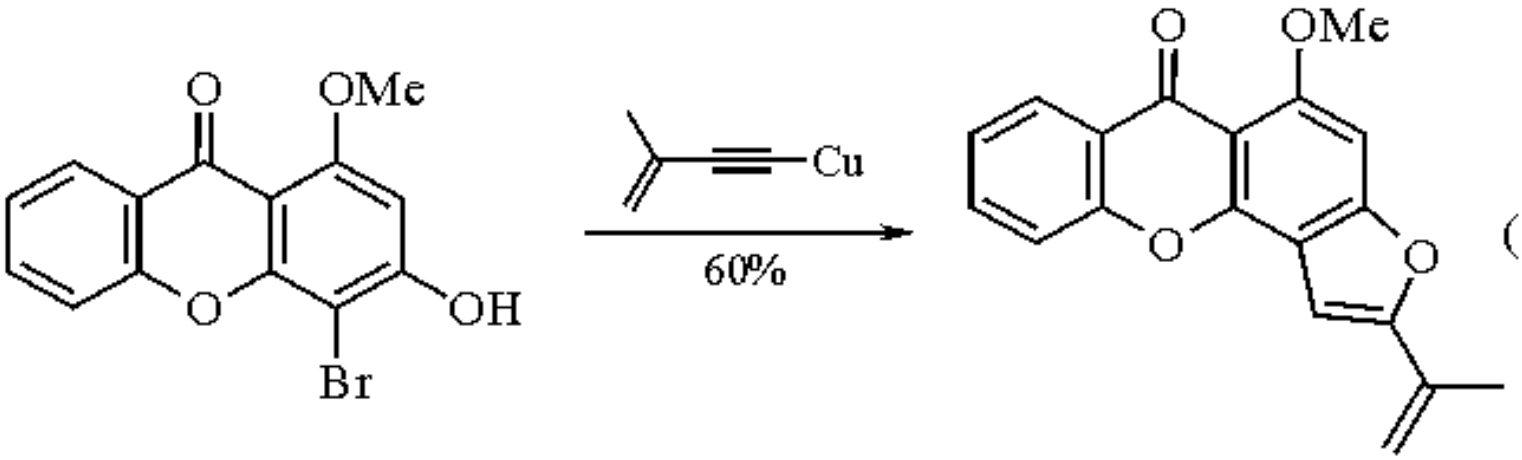

(3)

The requirement for an *o*-hydroxy group is not strict, as phenolic derivatives such as acetates[12,13] and even methyl ethers[14] have been shown to yield the corresponding cyclized benzofurans under the harsh reaction conditions, which typically involve thermolysis either in refluxing pyridine or quinoline.[12-14] Thus thermolysis of an *o*-iodo diacetate in pyridine yields a benzofuran (eq 4), an intermediate which was used in the synthesis of the dibenzofuranoid *Cannabis* constituents cannabifuran and dehydrocannabifuran.[15]

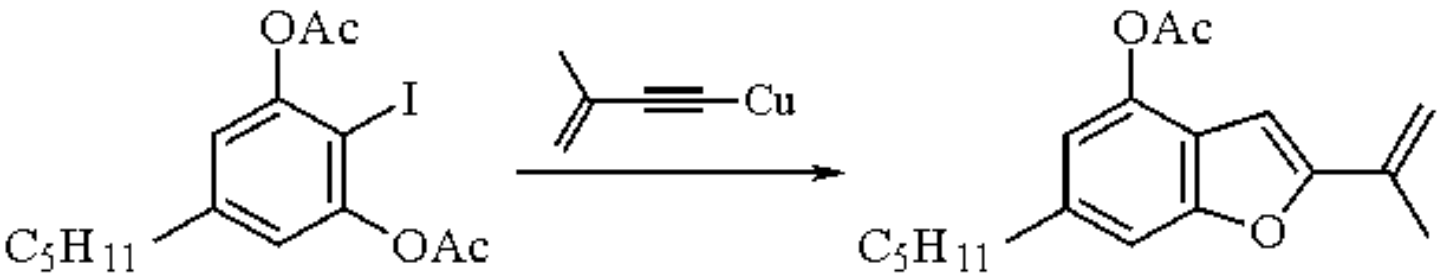

(4)

Nucleophilic Displacements.

Copper isopropenylacetylide can behave as a simple nucleophile under certain circumstances, effecting decarbonylative ring contractions (eq 5).[3]

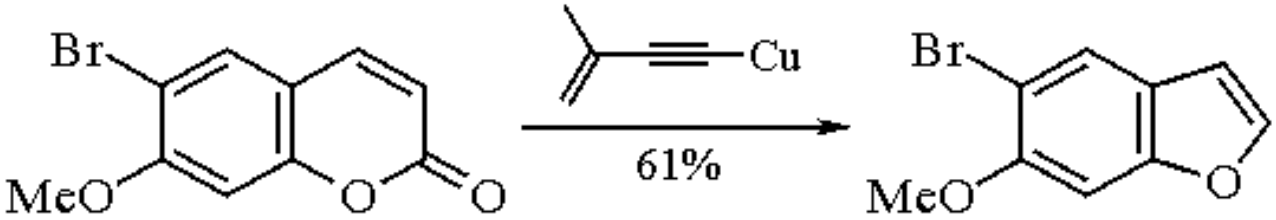

(5)

The benzofuran product would presumably not be accessible via the traditional tolane cyclization route due to competing reactions at the bromo site.[9]

---

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3-Methyl-2-butenylmagnesium Chloride[1]

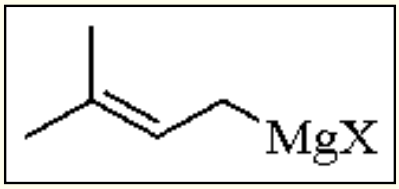

(X = Cl)

[32916-51-1] · C_5H_9ClMg · 3-Methyl-2-butenylmagnesium Chloride · (MW 128.90) (X = Br)

[63847-45-0] · C_5H_9BrMg · 3-Methyl-2-butenylmagnesium Bromide · (MW 173.35)

(terpene synthesis)

Alternate Names: chloro(3-methyl-2-butenyl)magnesium; prenylmagnesium chloride.

Physical Data: ^{13}C NMR solution data have been reported.[2]

Solubility: sol ether, THF.

Purification: solutions should be titrated before use by one of the standard methods.

Preparative Methods: prepared in situ under an inert atmosphere from prenyl chloride and an excess of magnesium in ether[3] or in THF.[4]

Handling, Storage, and Precautions: is air- and moisture-sensitive and is best stored at -20 °C under argon.

Grignard Synthesis.

The reagent is prepared by slow addition at 5 °C of 1.0 equiv of prenyl chloride in THF to 1.2 equiv of ***Magnesium*** turnings in the same solvent (350 ml per mol of the chloride). The reaction is initiated at 25 °C. The yield is estimated to be 90%.[4] The reagent appears to be a σ-bonded structure with the metal attached to the primary carbon. The internal isomer (metal bonded to the tertiary carbon) is present in low concentration. Structural changes to the reagent immediately prior to the reaction cannot be ruled out.[2]

Prenylation of Allylic Functional Groups.[5-7]

The copper(I)-catalyzed addition of prenylmagnesium chloride (**1**) to allylic chlorides leads in good yield and in high selectivity to the product of γ-attack (eq 1).[5]

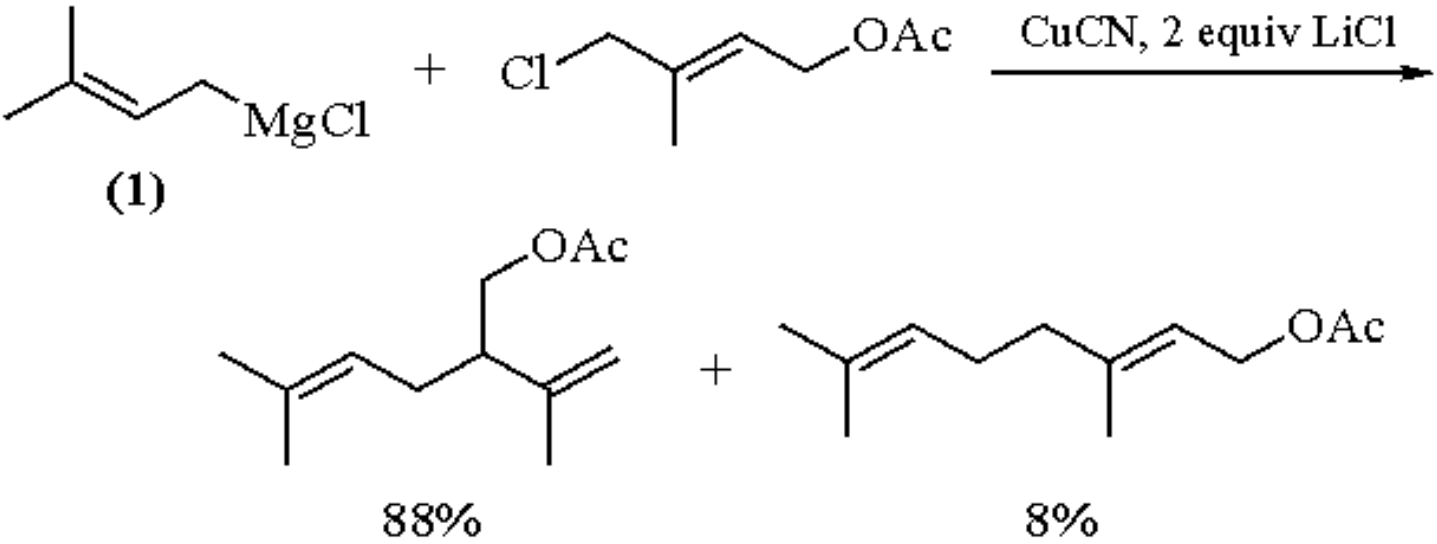

(1)

Similar reactivity is observed for the copper(I)-catalyzed displacement of allylic phosphonates by (**1**) (eq 2).[6]

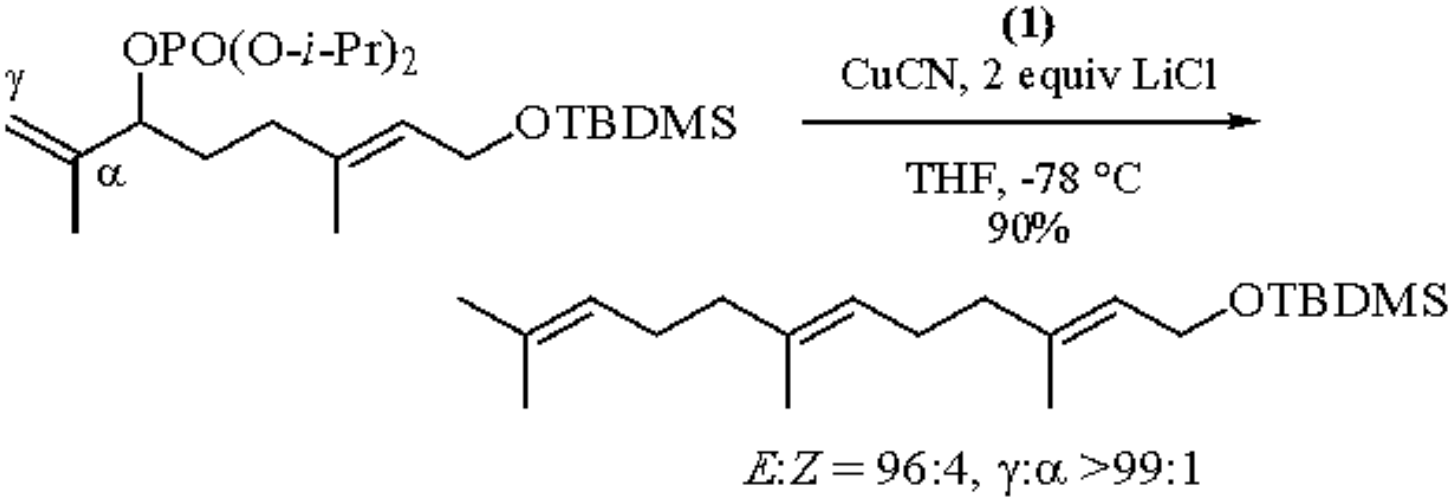

(2)

In the absence of copper(I), S_N2 displacement of allylic phosphonates by (**1**) takes place at the tertiary carbon of the nucleophile (eq 3). Bidentate complexation of two of the phosphate oxygen atoms with the metal is postulated to take place.[7]

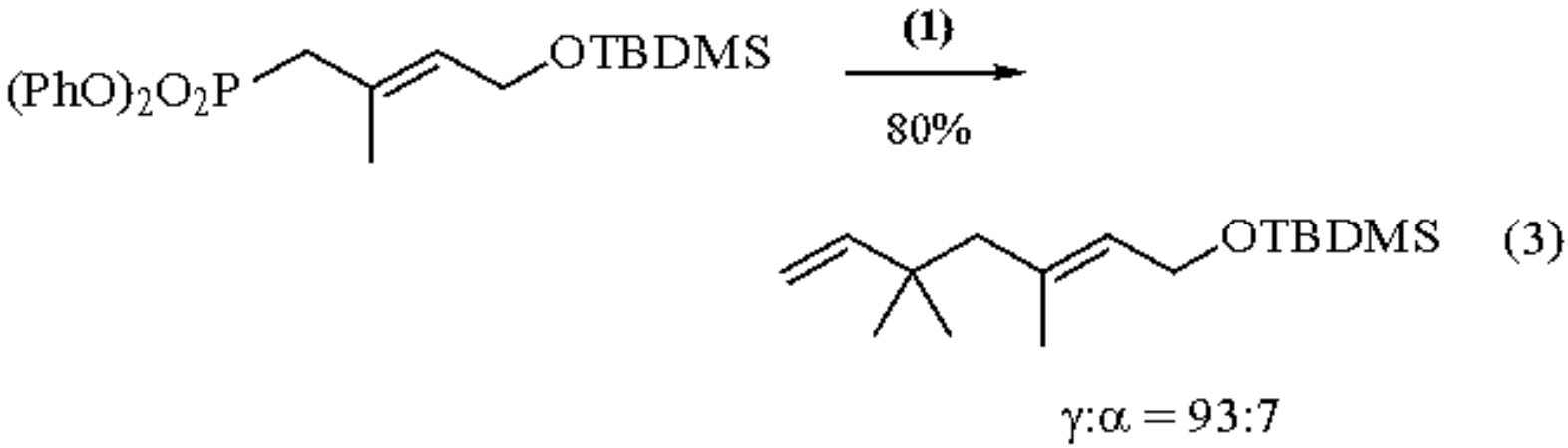

Addition Reactions.

Addition of (**1**) to aldehydes[8] and ketones[9] also takes place at the tertiary carbon with excellent selectivity. The trend is reversed in acylsilanes, particularly those with bulky isopropyl groups on silicon.[8,10] This tendency is reinforced by substituting (**1**) for prenylzinc bromide. In general, the copper(I)-catalyzed addition reactions of (**1**) occur at the primary carbon. For example, the copper(I)-catalyzed ring opening of ***Epichlorohydrin*** by (**1**) takes place at the primary carbon of the nucleophile.[11]

The addition of (**1**) to 3,3-dimethylcyclopropene, followed by trapping of the intermediate cyclopropyl organometal by ***Carbon Dioxide***, constitutes an effective approach to chrysanthemic acid analogs.[12] The ***Dichlorobis(cyclopentadienyl)titanium***-catalyzed addition of (**1**) to ***Isoprene*** also takes place at the tertiary carbon, and is regioselective with respect to both nucleophile and isoprene. Trapping of the intermediate organometal with carbon dioxide produces carboxylic acid (**2**) in excellent yield (eq 4).[13]

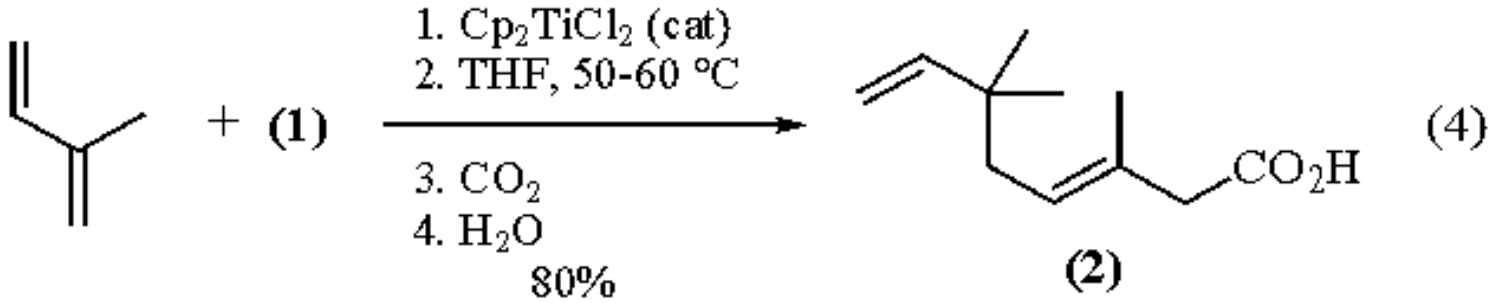

Related Reagents.

Allylmagnesium Bromide; ***Crotylmagnesium Bromide***; ***Methallylmagnesium Chloride***.

---

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2-(3-Methylbutoxy)-1,3-benzodithiolane[1]

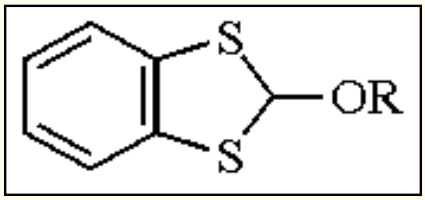

(**1**; R = $CH_2CH_2CHMe_2$)

[55315-56-5] · $C_{12}H_{16}OS_2$ · 2-(Methoxyethoxyethoxy)-1,3-benzodithiolane · (MW 240.42) (**2**; R = *n*-C_3H_7)

[55315-54-3] · $C_{10}H_{12}OS_2$ · 2-Propoxy-1,3-benzodithiolane · (MW 212.36) (**3**; R = *n*-C_4H_9)

[55315-55-4] · $C_{11}H_{14}OS_2$ · 2-Butoxy-1,3-benzodithiolane · (MW 226.39) (**4**; R = $CH_2CH_2OCH_2CH_2OMe$)

[131549-15-0] · $C_{12}H_{16}O_3S_2$ · 2-(3-Methylbutoxy)-1,3-benzodithiolane · (MW 272.42)

(reagent for synthesis of 2-substituted 1,3-benzodithiolanes by substitution of the 2-alkoxy group by various carbon and hetero nucleophiles; 2-lithio-1,3-benzodithiolanes are useful for nucleophilic acylation)

Physical Data: (**1**) pale yellow oil; bp 120-125 °C/0.1 mmHg. (**2**) bp 104-106 °C/0.1 mmHg. (**3**) bp 116-118 °C/0.1 mmHg. (**4**) bp 152-156 °C/0.5 mmHg.

Preparative Methods: prepared[1] by adding dropwise 0.1 L of a solution of ***Anthranilic Acid*** (3 M in dioxane) to a gently refluxing solution of ***Isopentyl Nitrite*** (0.36 M), 3-methylbutanol (0.60 M) and ***Carbon Disulfide*** (0.15 L) in 1,2-dichloroethane (0.8 L). Diazotization of anthranilic acid with isopentyl nitrite generates, beside 1 equiv of 3-methylbutanol, reactive benzyne, which reacts with excess S=C=S to give 1,3-benzodithiole-2-carbene. Reaction of this carbene with 3-methylbutanol, as described by Nakayama,[1] gives 2-(3-methylbutoxy)-1,3-benzodithiolane (**1**) in about 50% yield. This method has been extended to prepare 2-(propoxy)-1,3-benzodithiolanes (**2**) and 2-(butoxy)-1,3-benzodithiolanes (**3**), but the yields are poor. Similarly, when a mixture of freshly prepared diazonium-2-carboxylate (from anthranilic acid, 25.7 g),[3] 2-(2-methoxyethoxy)ethanol (32 mL), CS_2 (63 mL), and CH_2Cl_2 (1.125 L) is allowed to reflux (1.5 h), about 25% yield of 2-[(2-methoxyethoxy)ethoxy]-1,3-benzothiole (**4**) can be obtained readily.[2]

Handling, Storage, and Precautions: dithiolane (**1**) is a stable and easy to handle material at ambient temperature. Thermally, it is unstable, undergoing substantial decomposition during distillation to give mainly 2,2´-bi(1,3-benzodithiolylidene).[4a] Use in a fume hood.

Introduction.

2-(3-Methylbutoxy)-1,3-benzodithiolane (**1**) and other related dithio orthoesters, upon treatment with acetic acid at rt, undergo smooth ionization to generate in situ the resonance-stabilized carbocation intermediate 1,3-benzodithiolium ion (**5**).[4b] Indeed, the propensity to form this 10π-electron aromatic system (i.e. **5**) is so great that treatment of (**1**) with either 42% ***Tetrafluoroboric Acid***[5] or trityl fluoroborate,[6] can be employed to obtain 1,3-benzodithiolium fluoroborate in yields in excess of 95%. Thus (**1**) has become a convenient precursor for the 1,3-benzodithiolium ion (**5**) (eq 1).

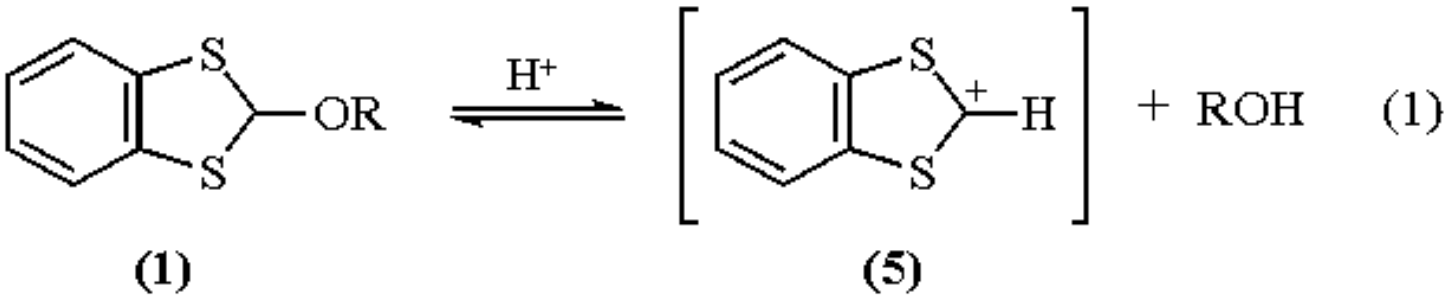

Reactions with Nucleophilic Reagents.

Dithiolane (**1**) reacts with nucleophiles, such as *N*,*N*-dialkylarylamines,[4b] polymethoxybenzene,[4b] aliphatic and aromatic thiols,[7a] activated methylene compounds,[7b] indole and pyrrole,[7c] and Grignard reagents, (64-89%)[7d-f] in a predictable manner to give a variety of 2-substituted 1,3-benzodithioles. While (**1**) is unreactive towards phenylethynylmagnesium bromide, the dithio orthoester (**4**) having a chelating group gave the 2-phenylethynyl-1,3-benzodithiole in 55% yield.[2]

1,3-Benzodithiolane Anions as Nucleophilic Acylation Reagents.[7f,8]

The 2-alkyl-1,3-benzodithiolanes are readily lithiated with ***n-Butyllithium*** in THF at -30 °C and the resulting anions may be alkylated with alkyl halides to give 2,2-dialkyl-1,3-benzodithiolanes.[8] This procedure for nucleophilic acylation is completed by hydrolysis to liberate the dialkyl ketones.

Alternatively, the intermediate anion may be efficiently coupled to branched organoboranes, producing hindered ketones or tertiary alcohols by one or two boron-carbon alkyl migrations, as shown in eq 2.[7f]

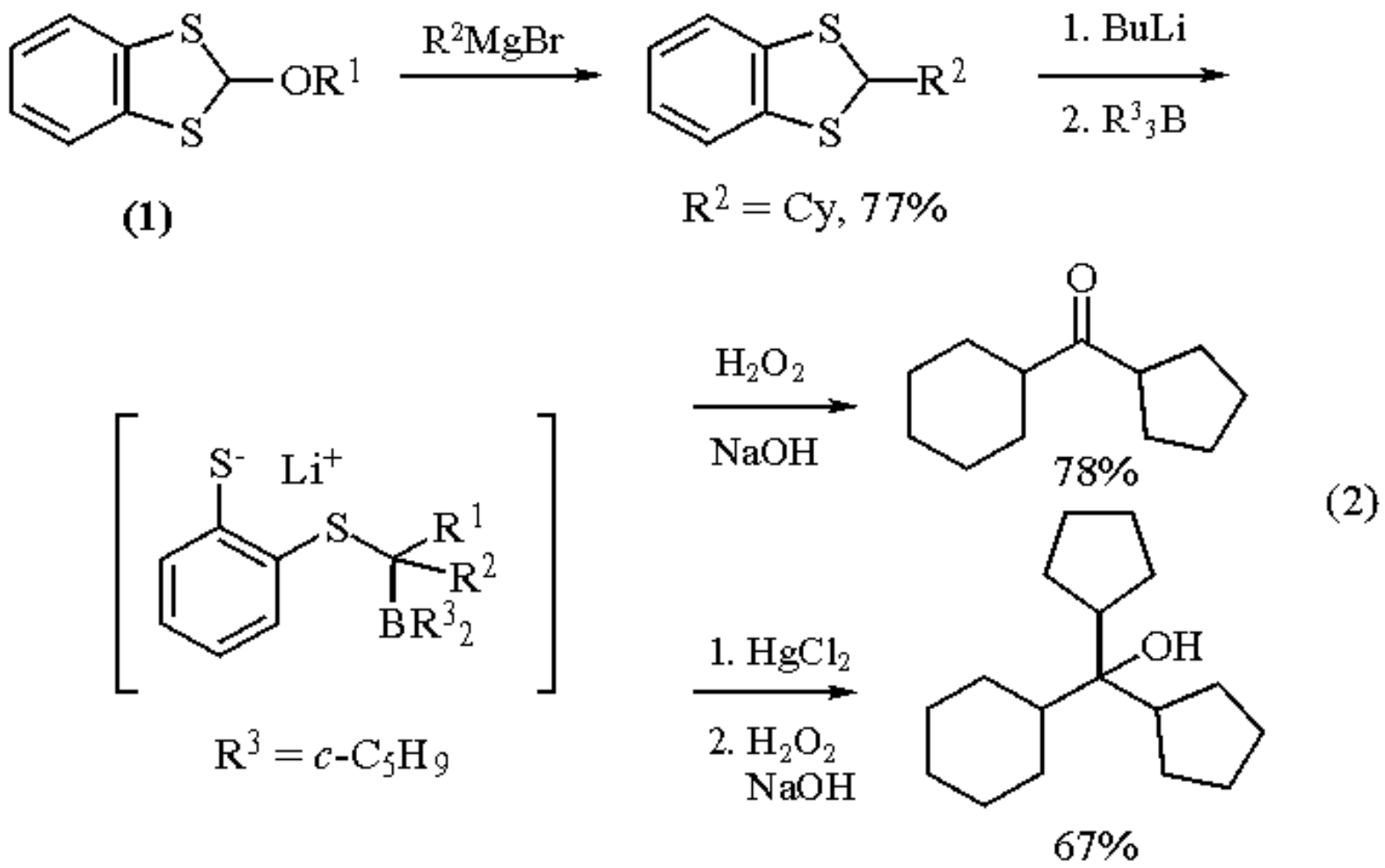

Reaction with Aqueous Chlorine.

Treatment of (**1**) with aqueous chlorine at or around 0-5 °C gives a highly useful compound, 1,2-benzenedisulfonyl dichloride,[9] in 90-95% yield.

Related Reagents.

1,3-Benzodithiol-1-ium Tetrafluoroborate; ***1,3-Dithiane***; ***2-Lithio-1,3-dithiane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***.

---

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(*R*)-Methyl 2-*t*-Butyl-3(2*H*)-oxazolecarboxylate

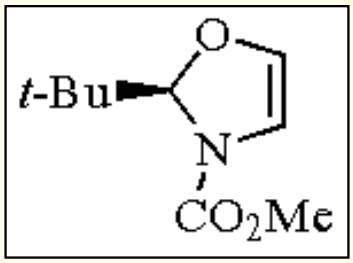

[104173-34-4] · $C_9H_{15}NO_3$ · (*R*)-Methyl 2-*t*-Butyl-3(2*H*)-oxazolecarboxylate · (MW 185.25)

(chiral oxazoline with highly reactive double bond;[1-3] chiral derivative of α-hydroxy- or α-aminoacetaldehyde; reactions with acylating reagents,[1a,2] with carbenes,[1a,3] and with electron-poor alkenes;[1a,3] cycloadditions;[1a,3] building block for the synthesis of amino alcohols and aminohydroxy carboxylic acid derivatives[1-3])

Physical Data: bp 70 °C/0.02 mmHg; [α]rtD = +434° (*c* 1, $CHCl_3$).

Solubility: sol all common nonprotic organic solvents.

Preparative Method: the acetal from serine methyl ester and pivaladehyde is *N*-methoxycarbonylated and saponified to give the *cis*-half ester (**2**) (61% yield). Oxidative decarboxylation by electrolysis in AcOH (1:3 by weight) in the presence of 5% Et_3N affords (**3**) (87%), which upon heating with NH_4Br in toluene yields the title oxazoline (**1**) (75% after distillation in vacuo) (eq 1).[4]

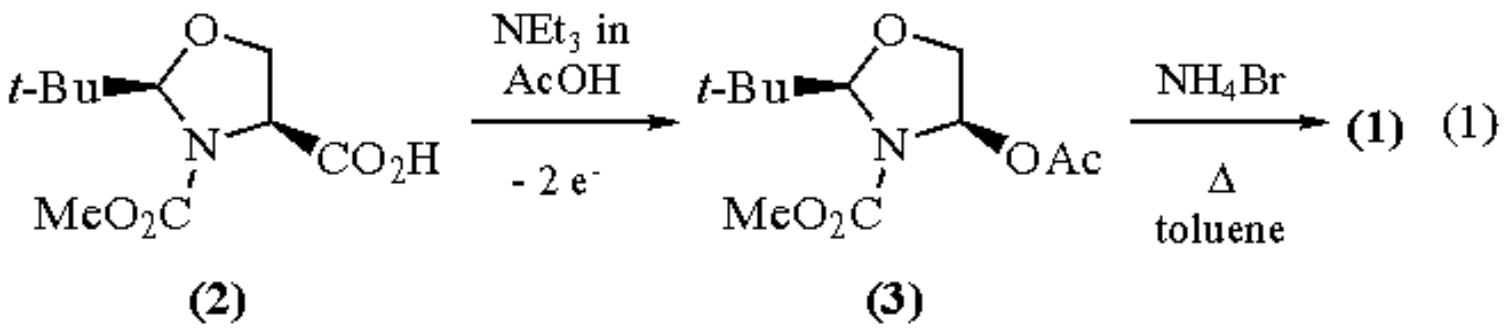

Handling, Storage, and Precautions: stable over many months in a freezer under inert atmosphere (N_2 or Ar). Use in a fume hood.

Reactions with Electrophiles at C-4.

(R)-Methyl 2-t-Butyl-3(2H)-oxazolecarboxylate

The oxazoline (**1**) can be metalated on the double bond carbon atom next to the ester group, and the resulting Li derivative coupled with electrophiles (eq 2).[2]

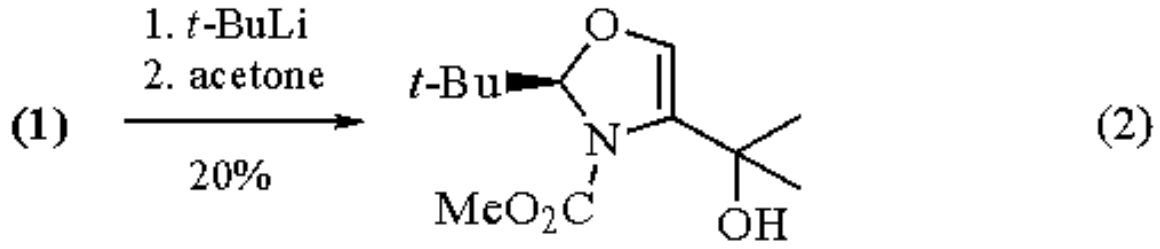

Direct Reactions with Electrophiles at C-5.

Vilsmeier and Friedel-Crafts reactions lead to 5-acyl derivatives (eq 3),[2] which can be further elaborated[3] as indicated in eq 4; a single enantiopure diastereoisomer of the anhydride (**4**) is formed. Seebach and co-workers[3] erroneously assigned (**4**) as arising from an *exo* rather than the *endo* addition.

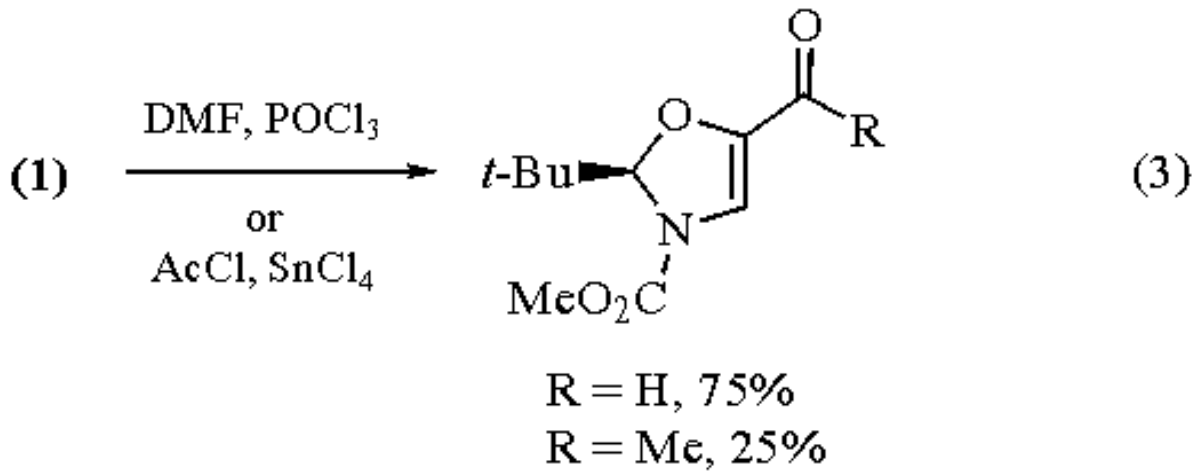

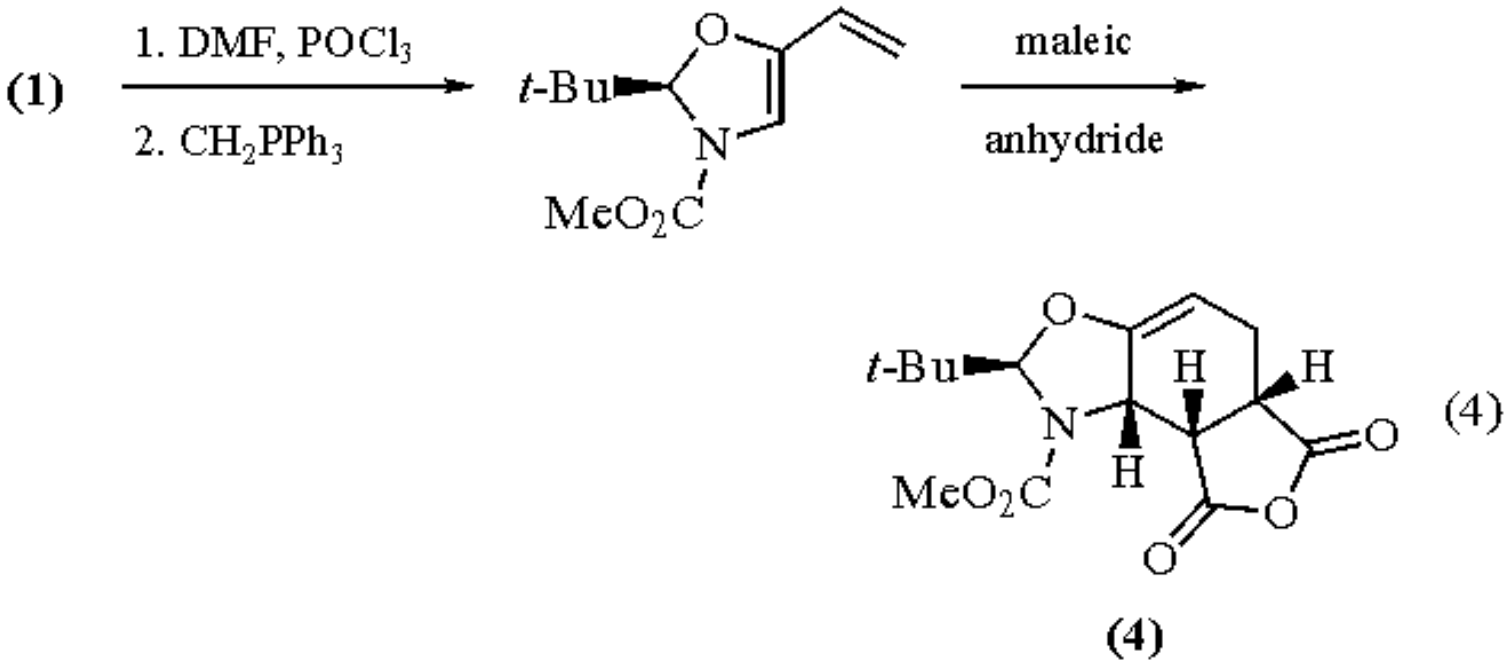

Cycloadditions.[3]

[2 + 1], [2 + 2], and [4 + 2] cycloadditions with electrophilic reactants such as carbenes (eq 5), tetracyanoethylene (eq 6), and α-keto-β,γ-unsaturated nitriles[5] (eq 7) lead to interesting products which are all enantiopure; see, for instance, the 5-amino-6-hydroxy-2-keto acid (**5**).

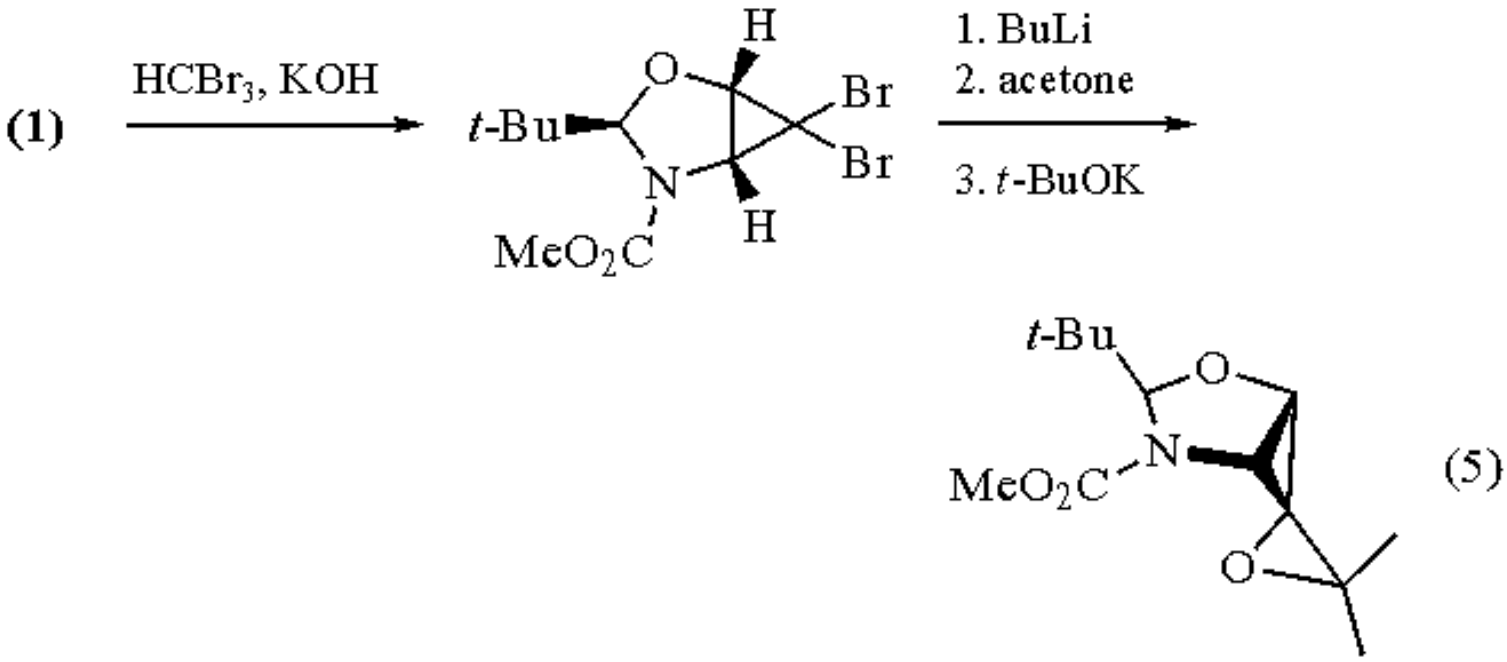

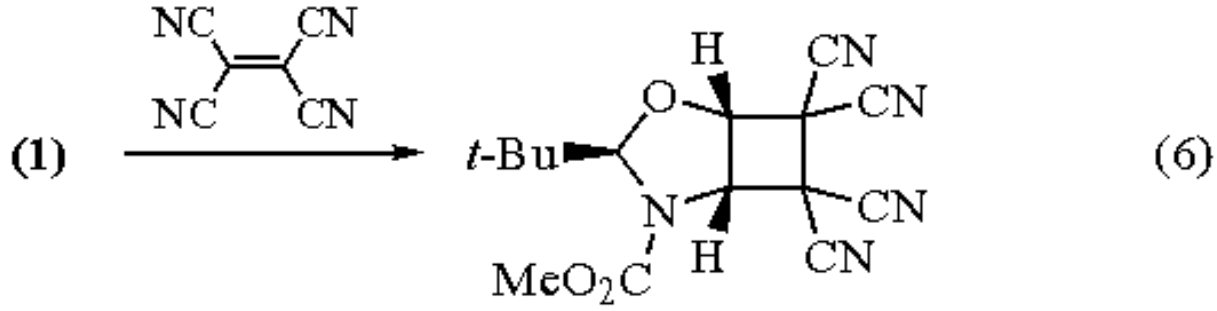

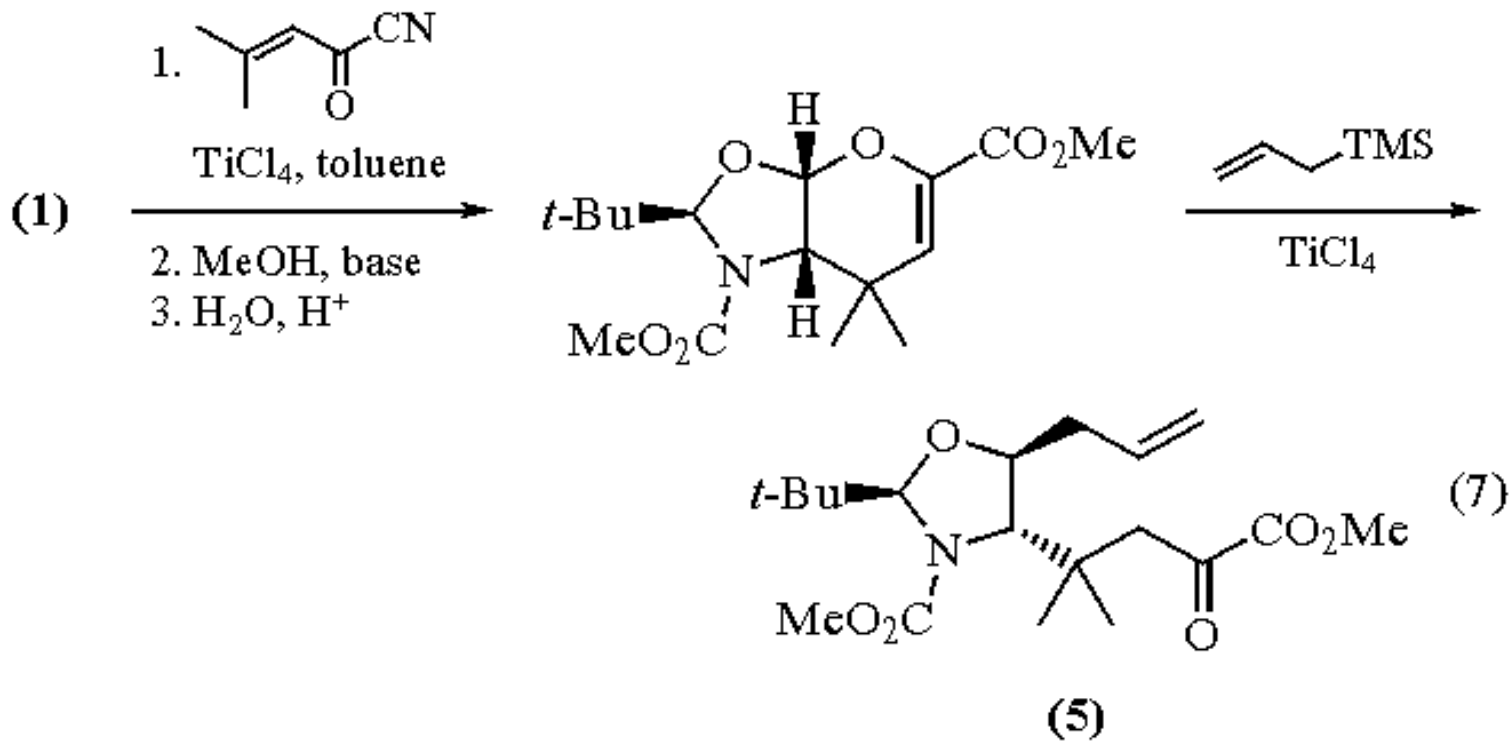

Other 2,3-Dihydrooxazoles and -thiazoles from α-Amino Acids.

Table 1 shows oxazolines and thiazolines also prepared from amino acids (serine, threonine, or cysteine), with or without decarboxylation; common to all of them is the conversion of the original stereogenic center to a trigonal center, and chirality due to a *t*-butyl-substituted acetal carbon in the ring (see Table 1).[1-4,6,7] The structure and reactivity of such acetals has been discussed.[8,9]

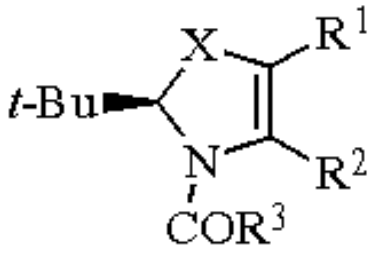

(6)

Table 1 2,3-Dihydrooxazoles and -thiazoles (**6**) from a-Amino Acids

X	R^1	R^2	R^3	Amino acid
O	H	H	OMe	Serine[1 4]
O	Me	H	OMe	Threonine[1 4]
O	H	CO_2Me	OMe	Serine[1a,2]
O	Me	CO_2Me	OMe	Threonine[1a,2]
O	Me	Me	OMe	Threonine[2]
S	H	H	OCH_2Ph	Cysteine[6]
S	H	CO_2Me	OCH_2Ph	Cysteine[6,7]
S	H	CO_2Me	OMe	Cysteine[7]
SO	H	H	OCH_2Ph	Cysteine[6,7]
SO_2	H	H	OCH_2Ph	Cysteine[7]

Related Reactions.

The photochemistry (Paterno-Büchi reactions) of the achiral oxazoline (**7**) has been studied.[10] The analogous urethane (**8**), which is chiral by attachment of an apocamphanoyl group, shows an intriguing stereoselectivity pattern in its reaction with electrophiles.[11] For another case of an oxidative decarboxylation as a key step in the application of the SRSC (self-regeneration of stereogenic centers) principle, see the preparation of the dihydropyrimidone (**9**) from aspartic acid.[12]

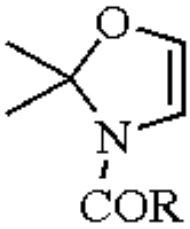

(7)

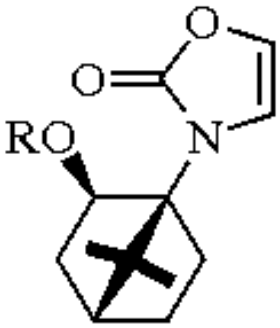

(8)

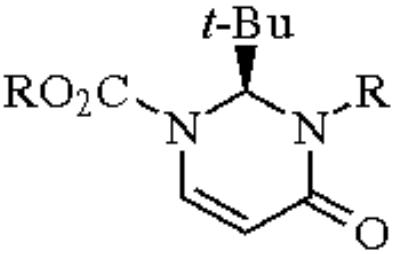

(9)

Related Reagents.

1-Benzoyl-2-t-butyl-3,5-dimethyl-4-imidazolidinone; ***(2S,4S)-3-Benzoyl-2-t-butyl-4-methyl-1,3-oxazolidin-5-one***; ***N-t-Butoxycarbonyl-N-methylaminomethyllithium***; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one***.

---

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2-Methylbut-3-yn-2-ol[1]

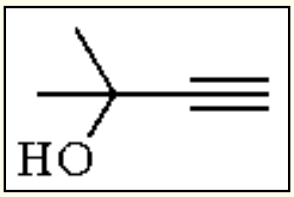

[115-19-5] · C_5H_8O · 2-Methylbut-3-yn-2-ol · (MW 84.13)

(monoprotected alkyne;[1] undergoes Claisen rearrangements to conjugated dienoates and dienones)

Physical Data: mp 2.6 °C; bp 104 °C; *d* 0.868 g cm^{-3}.

Solubility: miscible with H_2O, alcohols, benzene, EtOAc, petroleum ethers.

Form Supplied in: colorless liquid; widely available. *Drying:* removal of residual water by azeotropic distillation (bp 90.7 °C, 28.4% H_2O).[1b]

Monoprotected Alkyne.

2-Methylbut-3-yn-2-ol (MB) has been used extensively as an alkyne equivalent in the preparation of arylalkynes and unsymmetrical diarylalkynes; acetylene itself leads to mixtures. These products are used mainly in the polymer or liquid crystal field. MB is a cheap alternative to ***Trimethylsilylacetylene***,[2] in the presence of which it may be selectively cleaved.[3] After palladium-catalyzed coupling of MB with an aromatic halide, the terminal alkyne function can be unmasked by heating in the presence of base; removal of acetone by distillation drives the reaction to completion (eq 1). One-pot procedures have been developed.[4] The methodology has been used on a wide range of aromatic[5] and heteroaromatic[6] halides (reactivity I > Br > Cl) as well as vinyl halides[7] and triflates.[8] Yields are good (normally 60-80% for the two steps) and most functionalities are compatible (aldehydes must be protected)[5] with the reaction conditions. When the coupling takes place *ortho* to a hydroxy or an amino group, benzofurans[9] and indoles[10] can result.

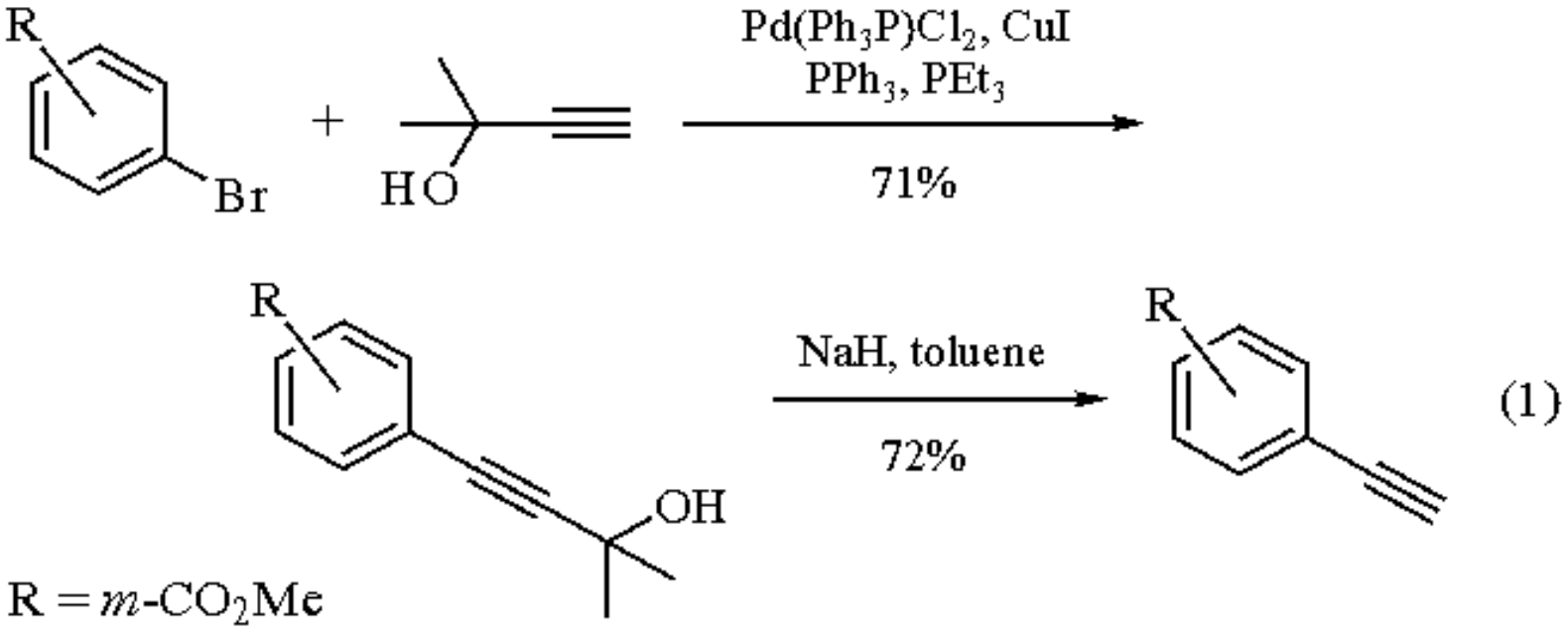

Oxidative Coupling with Alkynes.

Treatment of MB with ***Copper(I) Chloride*** in the presence of oxygen followed by heating the product with NaOH in xylene gives 1,3-butadiyne (diacetylene) in 80% yield.[11] Nonsymmetrical 1,3-diynes are produced from the coupling of MB with haloalkynes in the presence of Cu^{I} salts (Cadiot-Chodkiewicz coupling). Acetone can of course be removed as mentioned to allow further manipulation (eq 2).[12]

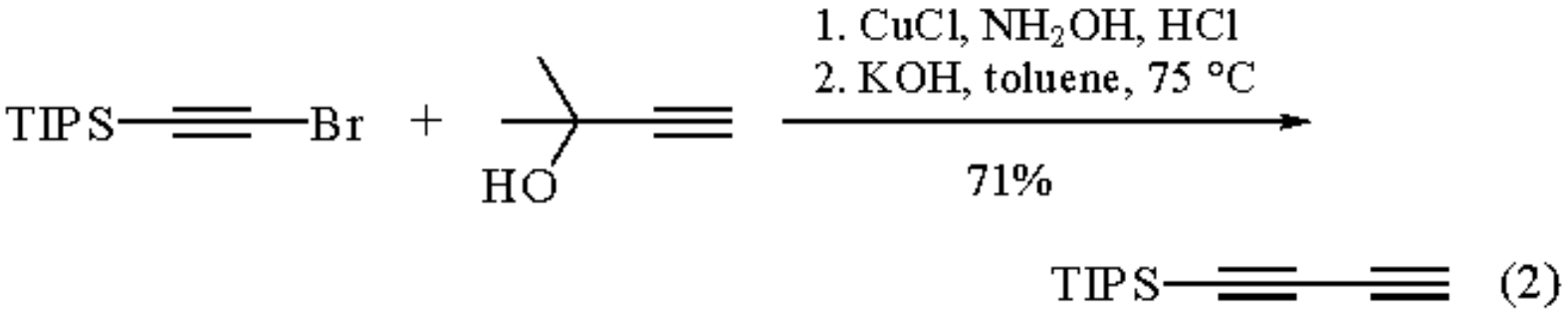

Claisen Rearrangements and Isomerizations.

Reaction of 2-methylbut-3-yn-2-ol with orthoesters gives, after Claisen rearrangement and isomerization of the allenes thus formed, 5-methyl hexa-2,4-dienoates,[13] useful in the preparation of alkyl chrysanthemates.[14] Similarily, reaction with enol ethers gives 6-methyl-3,5-dien-2-ones with *trans* selectivity (eq 3).[15] Isomerization (Meyer-Schuster rearrangement) of 2-methylbut-3-yn-2-ol in the presence of a titanium/copper-based catalyst gives 3-methyl-2-butenal in good yield (83%) (eq 4).[16] Partial hydrogenation gives 2-methylbut-3-en-2-ol.[17] Both of these compounds are of use in the synthesis of vitamin K-type products.[18]

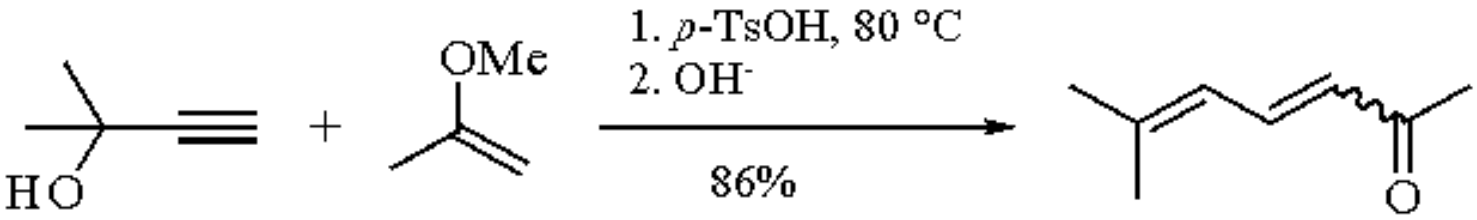

(3)

cis:*trans* = 14:86

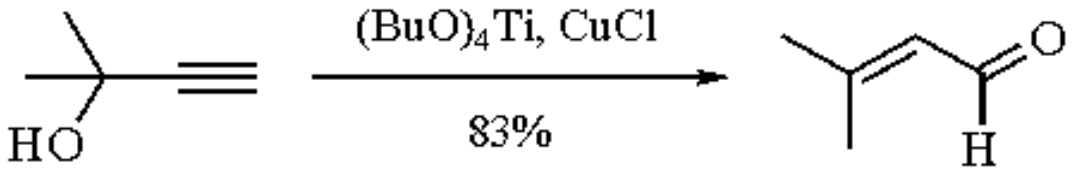

(4)

Chromene Preparation.

3-Chloro-3-methyl-1-butyne[19] (prepared with MB/HCl/$CuCl_2$, yield 69%) is the reagent of choice for the preparation of the chromene system in potassium-channel blockers such as cromakalim (eq 5).[20]

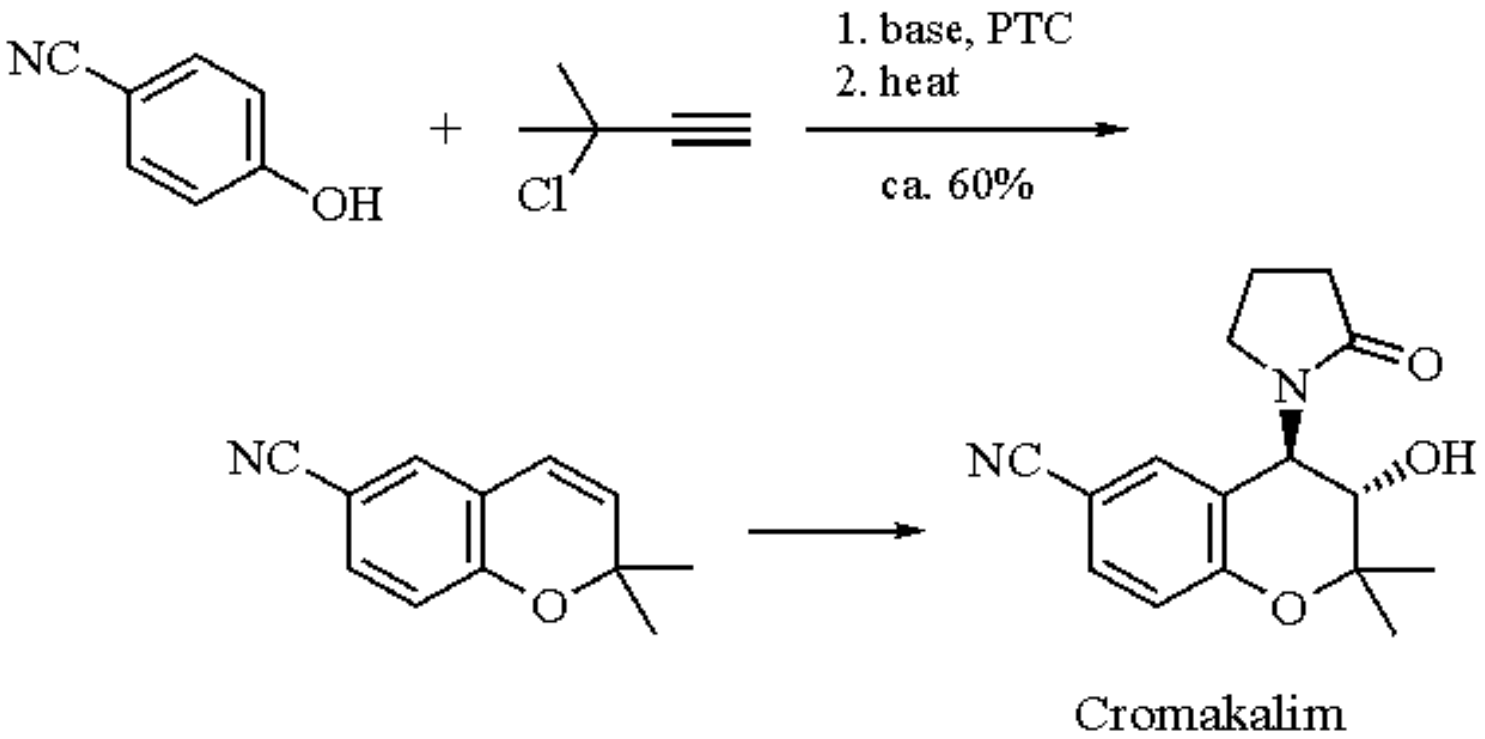

(5)

Related Reagents.

Acetylene; ***(Trimethylsilyl)ethynylcopper(I)***; ***Dilithium Acetylide***; ***Ethynyldimethylaluminum***; ***Dipotassium Acetylide***; ***Ethynylmagnesium Bromide***; ***Lithium Acetylide***; ***Lithium (Trimethylsilyl)acetylide***; ***Trimethylsilylacetylene***.

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Methyl Chloroacetate

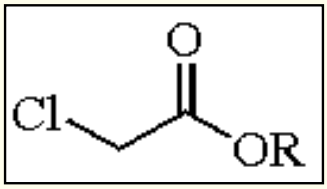

(**1**; R = Me)

[96-34-4] · $C_3H_5ClO_2$ · Methyl Chloroacetate · (MW 108.53) (**2**; R = Et)

[105-39-5] · $C_4H_7ClO_2$ · Ethyl Chloroacetate · (MW 122.56)

(alkylating agent;[1] undergoes Michael[2,3] and Darzens[4] condensations; effects two-carbon homologation of alkenes;[5] widely used in heterocyclic synthesis)

Physical Data: (**1**) mp -33 °C; bp 130-132 °C; *d* 1.238 g cm^{-3}.[6] (**2**) mp -26 °C; bp 144-146 °C; *d* 1.1498 g cm^{-3}.[6]

Solubility: insol water; sol alcohol, ether.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: store in a cool dry place. Toxic, corrosive lachrymator. Avoid contact and inhalation. Use in a fume hood.

Alkylation.

Methyl chloroacetate has been widely used as an alkylating agent for sulfur,[1,7-9] nitrogen,[1,10,11] and oxygen[1,12,13] nucleophiles under standard conditions. Reaction with phosphide anions affords o-phosphinocarboxylic acids.[14] Malonates are alkylated to form the 1,1,1-trialkoxycarbonyl derivatives,[15] which are easily monodecarboxylated and may function as masked 1,1-diesters in a synthetic sequence. *C*-Alkylation of ketones is accomplished by their reaction with Grignard reagents in HMPA to form magnesium enolates which are readily and selectively *C*-alkylated with methyl chloroacetate.[16]

Michael Reaction.

Reaction of α-halo esters, such as methyl chloroacetate, with α,β-unsaturated esters in the presence of base furnishes

cyclopropane derivatives (eq 1).

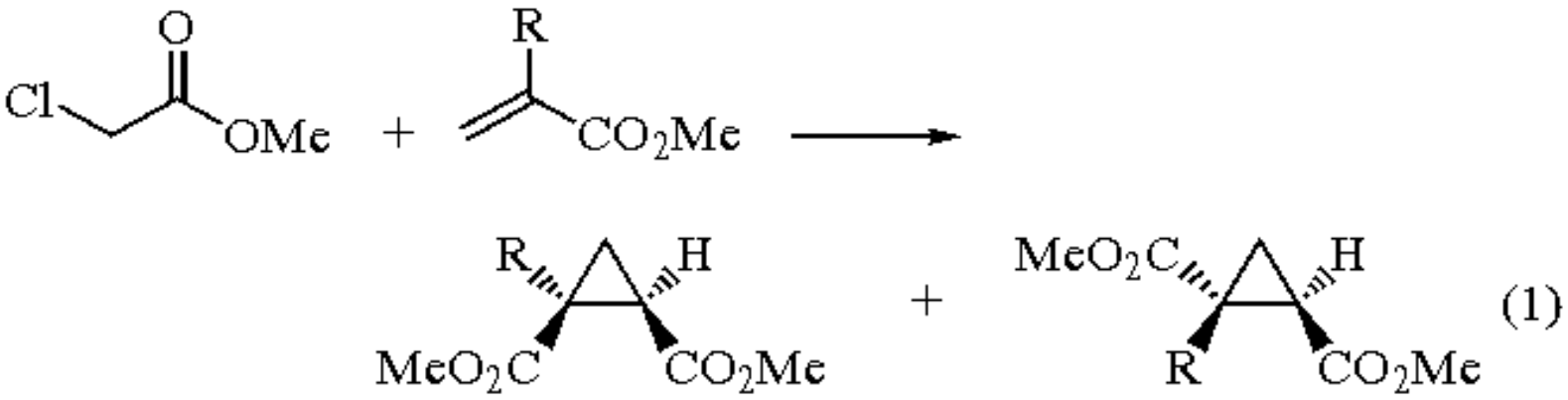

The effects of leaving group, base catalyst, and solvent polarity and solvating ability on the ratio of *cis*:*trans* isomer formation have been investigated.[2,3]

Darzens Condensation.

Methyl chloroacetate reacts with aldehydes and ketones in the presence of base to afford glycidic esters (eq 2).[4]

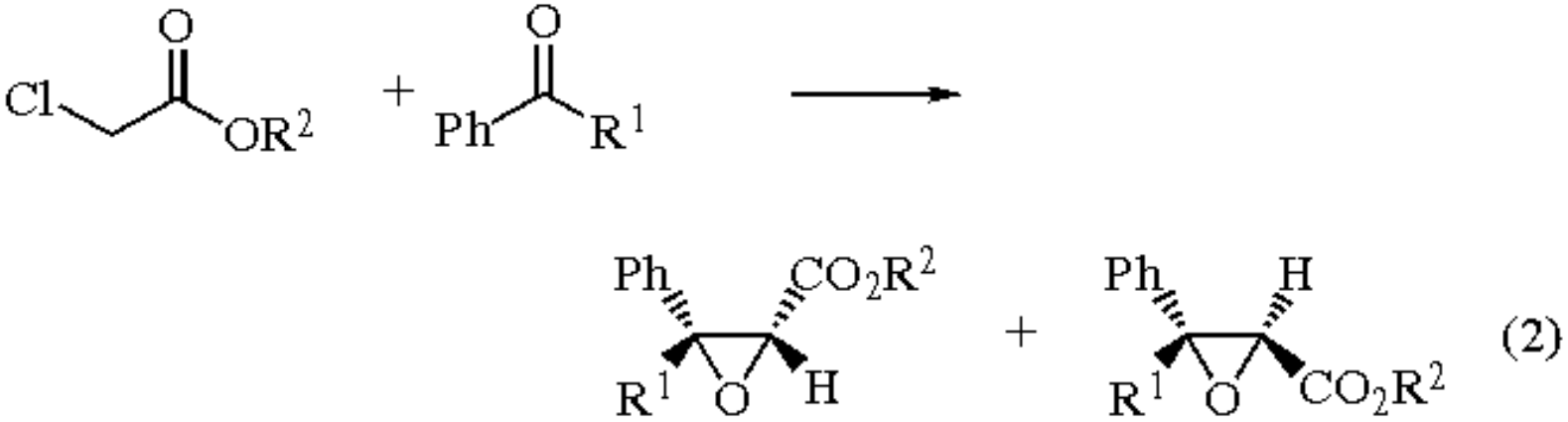

Subsequent hydrolysis to the corresponding glycidic acids and decomposition furnishes aldehydes or ketones, efficiently accomplishing one-carbon homologation. Mechanistic studies have investigated the effects of various esters (R^2)[17] and reaction temperature[18] on *cis*:*trans* isomer ratios obtained. In homologation sequences, dianions of α-halocarboxylic acids have often been employed to circumvent premature epoxide cleavage during ester hydrolysis.[19] A procedure involving reaction of ethyl chloroacetate with benzalaniline broadens the scope of the Darzens synthesis to include preparation of aziridine esters (eq 3).[20] The *trans*-aziridine is formed preferentially.

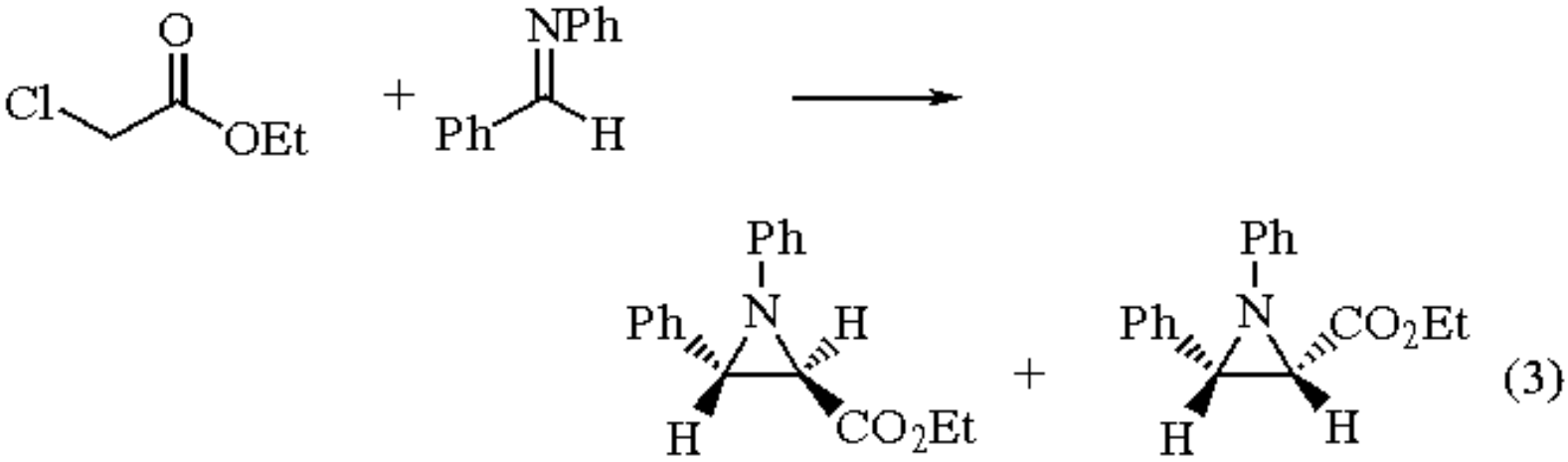

Two-Carbon Alkene Homologation.

Methyl chloroacetate adds to alkenes and dienes under redox catalysis by ***Copper(I) Chloride*** in the presence of 2,2´-bipyridyl or 1,10-phenanthroline, affording α-chloro esters or unsaturated esters.[21] Alkenes which have been converted to the corresponding trialkylboranes react with ethyl chloroacetate to effect two-carbon homologation of the alkene and furnish the corresponding esters (eq 4).[5] The reaction is widely applicable and yields are generally high. Reactions with ethyl bromoacetate proceed at a slightly faster rate, with somewhat higher yields.

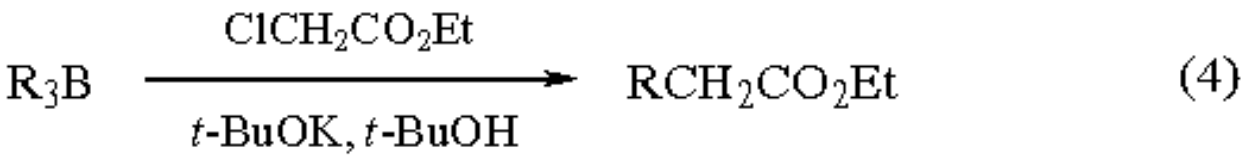

Heterocycles.

A wide variety of heterocycles has been synthesized employing ethyl or methyl chloroacetate. Among the precursor nucleophiles, thiourea, salicylonitriles, mercaptobenzaldehydes, and cyanopyridinethiones furnish triazines,[22] benzofurans,[23] benzothiophenes,[24] and thienopyridines,[25] respectively.

Related Reagents.

Chloroacetonitrile; ***Iodoacetonitrile***; ***Methyl Bromoacetate***; ***Methyl Dichloroacetate***.

---

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Methyl Chloroformate

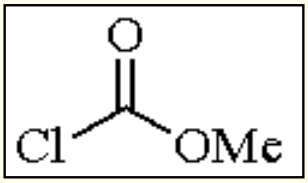

[79-22-1] · $C_2H_3ClO_2$ · Methyl Chloroformate · (MW 94.50)

(protecting agent for many functional groups;[1-16] activates N-heteroaromatic rings and carboxylic acids toward nucleophilic attack;[17-26] methoxycarbonylating agent for organometallic reagents and enolates[27-39])

Alternate Name: MCF.

Physical Data: bp 70-72 °C; *d* (20 °C) 1.223 g cm^{-3}; *n*20D 1.3870.

Solubility: slightly sol water with slow decomposition; miscible with alcohols, benzene, chloroform, ether, etc.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: flammable liquid; vesicant; its vapors are highly toxic, lachrymatory, and strongly irritating to the eyes. It should be handled with caution in a fume hood using protective gloves.

Functional Group Protection.

The protection of alcohols[1] and phenols[2] as their methyl carbonates can be achieved using methyl chloroformate under basic conditions (eq 1). Primary and secondary alkylamines are readily protected as their methyl carbamates using MCF, typically in the presence of Et_3N,[3,4] Na_2CO_3,[5] K_2CO_3,[6] or $NaHCO_3$.[7] Selective *N*-protection of amino alcohols can be achieved under these conditions (eq 2).[5]

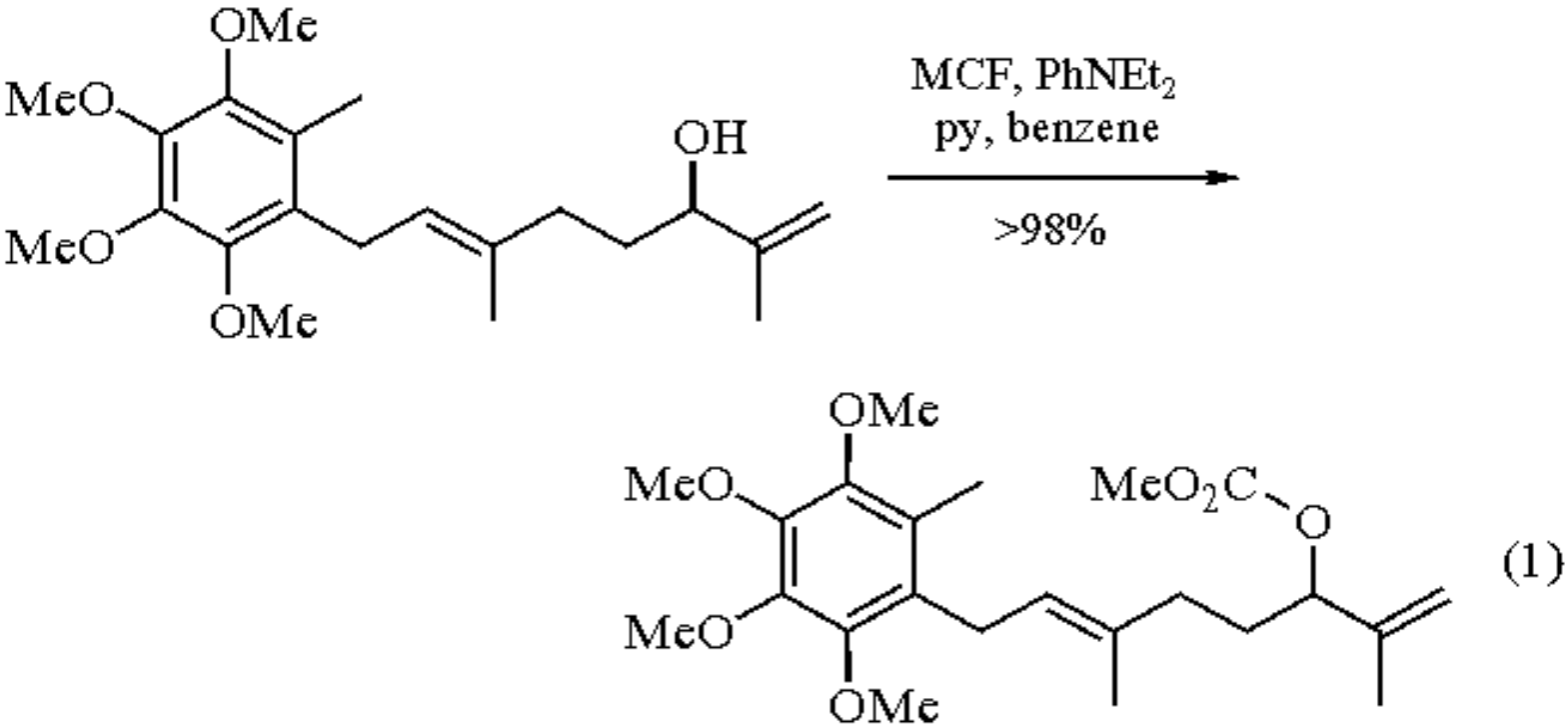

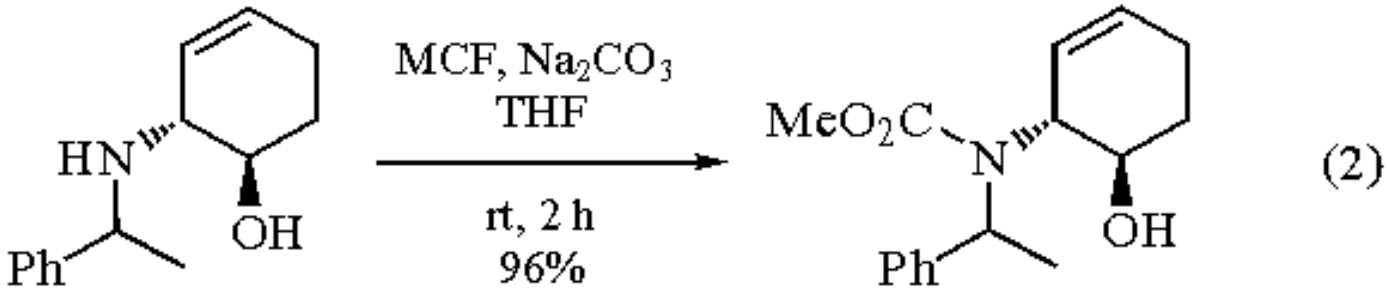

Methyl carbonates are more resistant to basic hydrolysis than simple esters; however, both alcohol-[1c] and phenol-derived[2] methyl carbonates can be selectively hydrolyzed under mildly basic conditions in the presence of a methyl carbamate derivative, allowing for the overall selective *N*-protection of amino alcohols and amino phenols (eq 3).

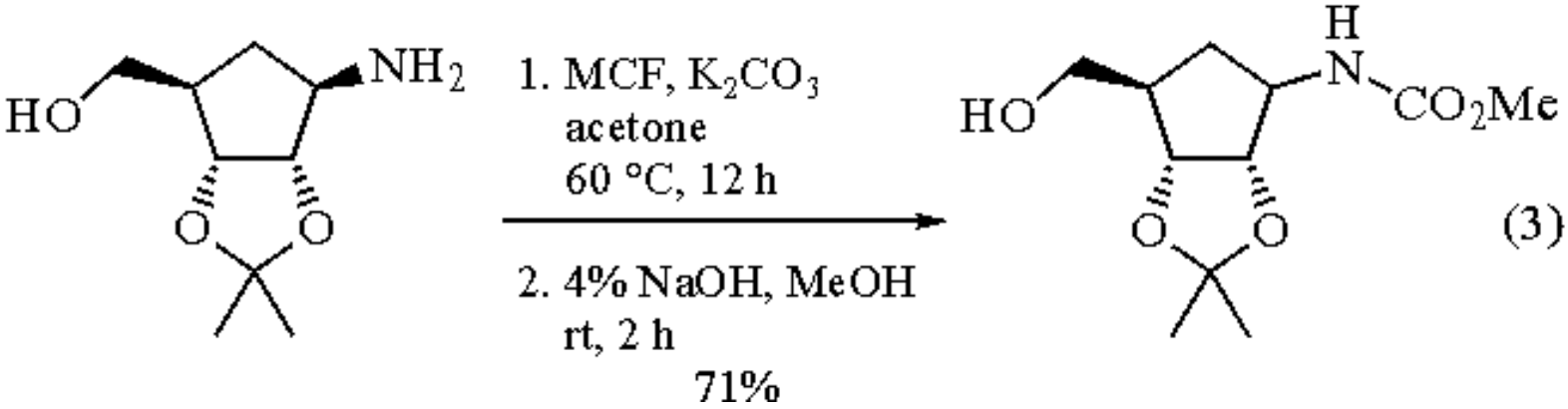

MCF is also useful for the *N*-protection of α-amino acids (Schotten-Baumann conditions),[8] primary arylamines (using pyridine as base),[1b,9] amides (using ***Triethylamine/4-Dimethylaminopyridine*** as base),[10] and pyrrole and indole ring nitrogens (using NaH or KH as base).[11] *N*-Silylpyrroles can be converted to the corresponding methyl carbamates under milder conditions than are required for the direct *N*-protection of pyrroles.[12] *ortho*-Phenylenediamines are

readily converted to the corresponding benzimidazole-2-carbamates using MCF in the presence of $MeSCH(NH_2)=NH$.[13] The forcing conditions that are often required for removal of a methyl carbamate protecting group (e.g. ***Hydrazine***, KOH,[14] or aq $Ba(OH)_2$)[15] have limited the utility of this *N*-protecting group when compared with other carbamates; although milder *N*-deprotection conditions have been reported (***Iodotrimethylsilane***, $CHCl_3$, 50 °C; then MeOH),[16] this chemistry has not seen widespread use. ***Lithium Aluminum Hydride*** reduction of methyl carbamates affords the corresponding *N*-methylamines,[3,4] providing an attractive method for the overall *N*-methylation of primary and secondary amines (eq 4).

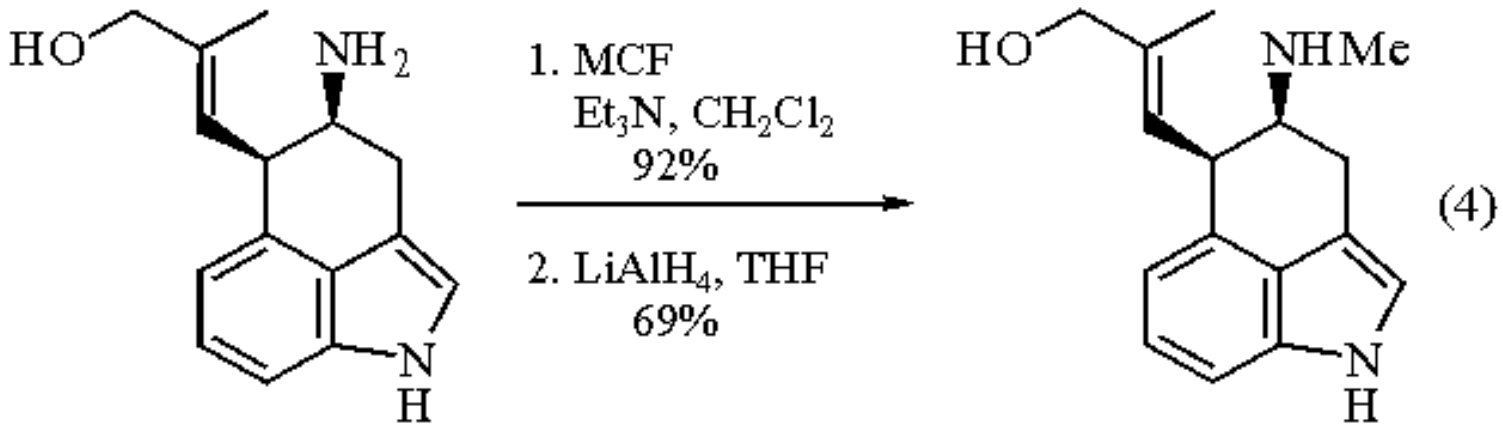

(4)

Activation of N-Heteroaromatic Rings Toward Nucleophilic Attack.

Pyridine, quinoline, and isoquinoline rings are activated by MCF toward in situ nucleophilic attack, leading to the formation of 1,2- and/or 1,4-dihydropyridines, -quinolines, or -isoquinolines. The addition of alkyl Grignard reagents proceeds with variable and often poor regioselectivity.[17] However, alkenyl- and alkynyl-Grignard reagents (eq 5),[17b] unhindered allylic[18] and allenylic[19] stannanes, cyanide ion,[20] and ***Sodium Borohydride*** (in MeOH at -70 °C[21]) all add with high 1,2-selectivity. Highly 1,4-selective addition reactions are observed using alkylcopper reagents (eq 6),[17a,22] dialkylcuprates,[17b,23] silyl enol ethers,[22] and benzylic stannanes.[24] The 1,4-addition of aryllithium reagents,[25] and methyllithium and methylmagnesium bromide,[26] to chiral 3-oxazolinylpyridines proceeds with high regio- and diastereofacial selectivity (eq 7). Removal of the chiral auxiliary affords chiral 4-substituted dihydropyridines in high ee.

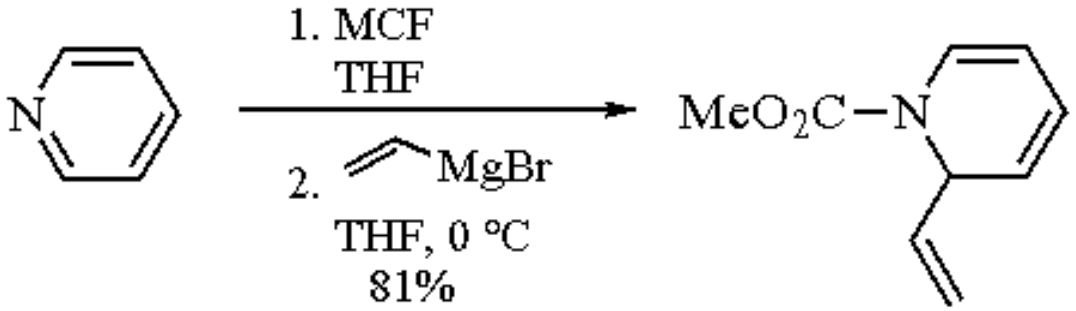

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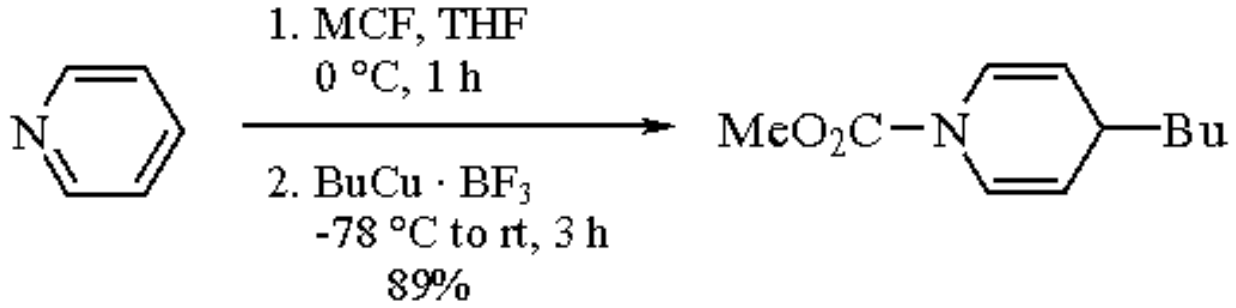

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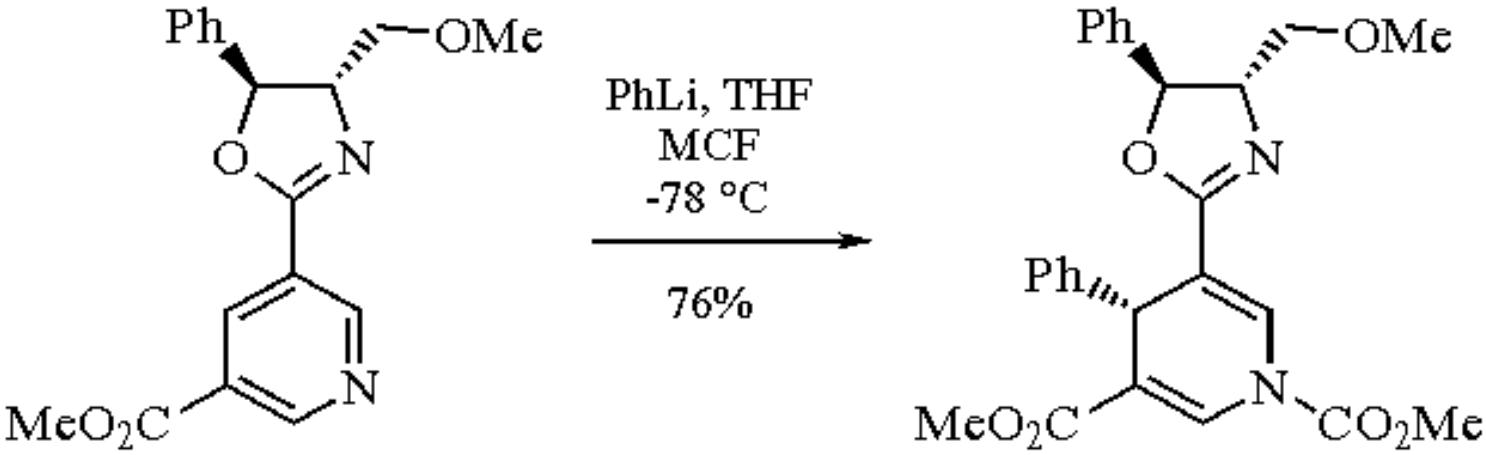

(7)

89:11 diastereoselectivity

Methoxycarbonylation of Organometallic Reagents and Enolates.

Deprotonation of terminal alkynes (typically using *n*-BuLi,[27] LDA,[28] or EtMgBr[29]), followed by trapping the resulting alkynyllithium or -Grignard reagent with MCF, offers an excellent route to methyl alkynoates (eq 8) (see ***2,2,2-Trichloroethyl Chloroformate*** if subsequent cleavage to the carboxylic acid is desired). A related approach to methyl alkynoates proceeds via homologation of an aldehyde to the corresponding α,α-dibromoalkene. Dehydrobromination and halogen-metal exchange followed by trapping the resultant alkynyllithium with MCF provides the methyl alkynoate in high overall yield (eq 9).[30] Aryllithium[31] and alkenylaluminium[32] species are also effectively methoxycarbonylated by MCF, but the trapping of simple primary alkyllithiums with MCF appears to be of little synthetic utility.[33] The in situ trapping of a simple phosphonium ylide with MCF followed by deprotonation provides a convenient synthetic approach to α-methoxycarbonylphosphonium ylides (eq 10).[34]

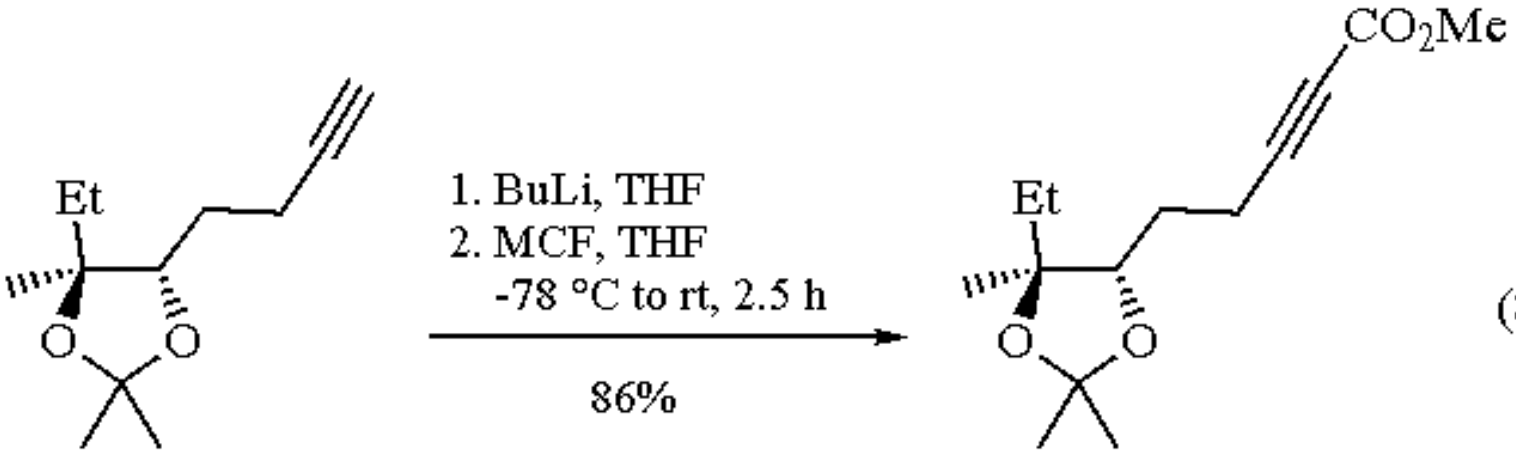

(8)

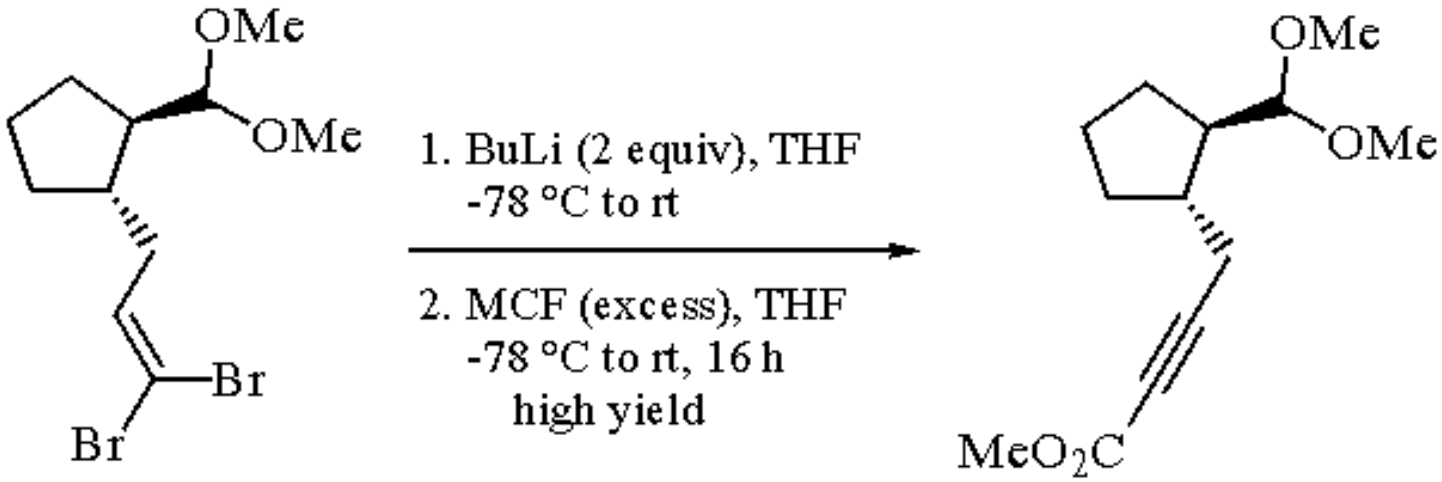

(9)

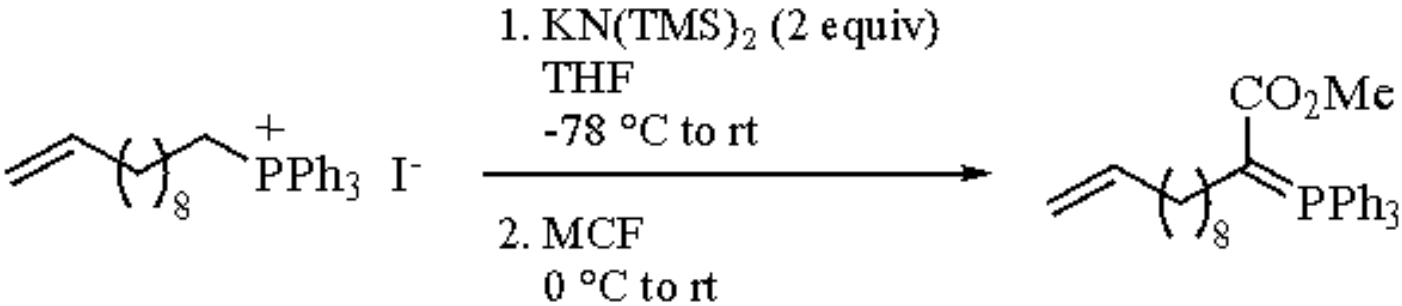

(10)

The *C*-methoxycarbonylation of lithium ester[35] and amide[36] enolates can be effectively accomplished using MCF. Addition of *n*-BuLi to a chiral 1-oxazolinylnaphthalene followed by trapping the resulting azaenolate with MCF affords the *C*-acylation product with high diastereoselectivity (eq 11).[37] In contrast, reaction of copper[38] and potassium[39] ketone enolates with MCF typically results in *O*-acylation to afford the corresponding enol carbonates (eq 12). The weak nucleophilicity of enol carbonates (they are stable to peroxy acids and ***Ozone***)[38a] makes them useful masked enolate equivalents.

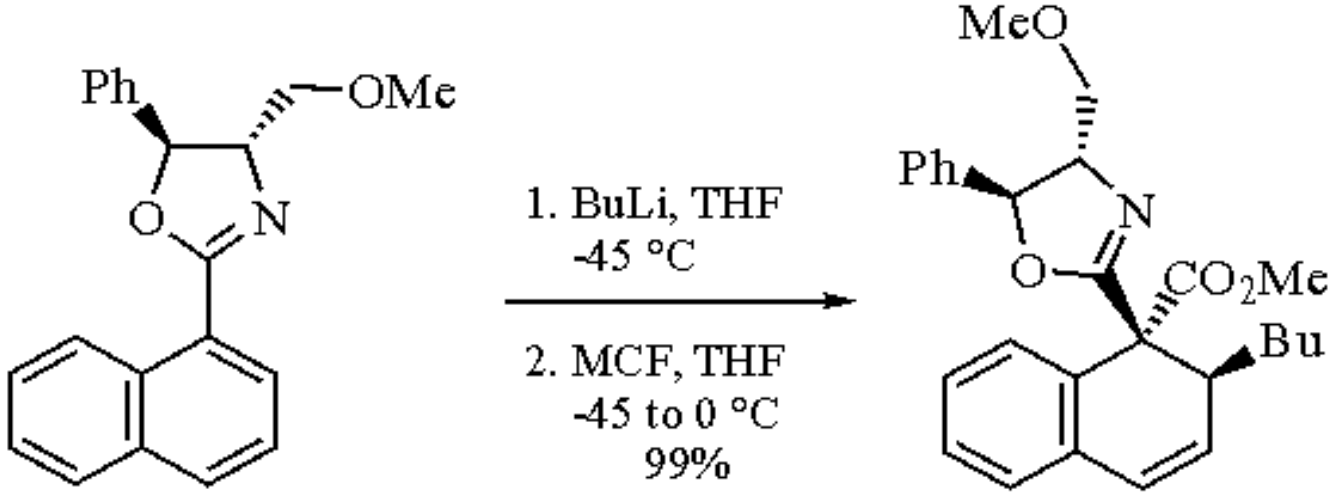

(11)

97:3 diastereoselectivity

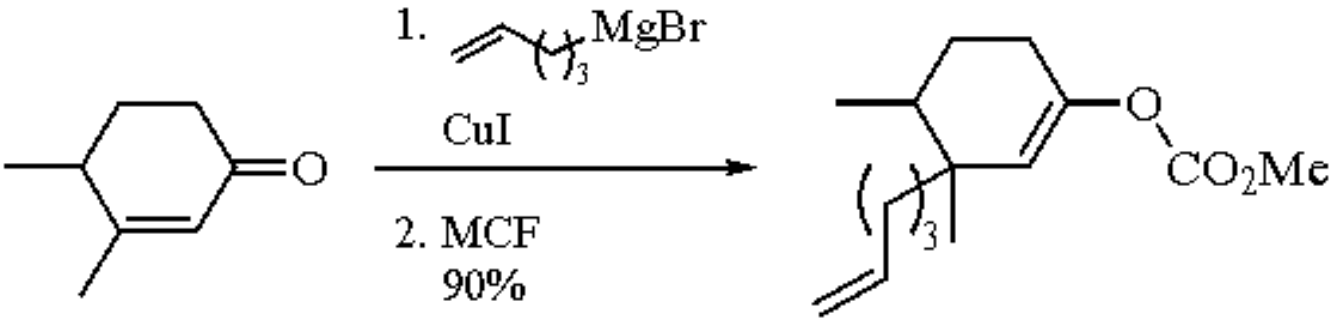

(12)

Activation of Carboxylic Acids as Mixed Anhydrides.

Activation of *N*-(alkoxycarbonyl)-α-amino acids as mixed anhydrides using MCF/*N*-methylpiperidine in CH_2Cl_2 minimizes urethane byproduct formation and racemization during peptide bond formation.[40] Reaction of these mixed anhydrides with ***N,O-Dimethylhydroxylamine*** followed by $LiAlH_4$ reduction provides an attractive route to the corresponding *N*-(alkoxycarbonyl)-α-amino aldehydes (eq 13).[41] Attempts to generate mixed anhydrides from *N*-acyl-α-amino acids using MCF result in cyclization to the corresponding 5(4*H*)-oxazolones.[42,43]

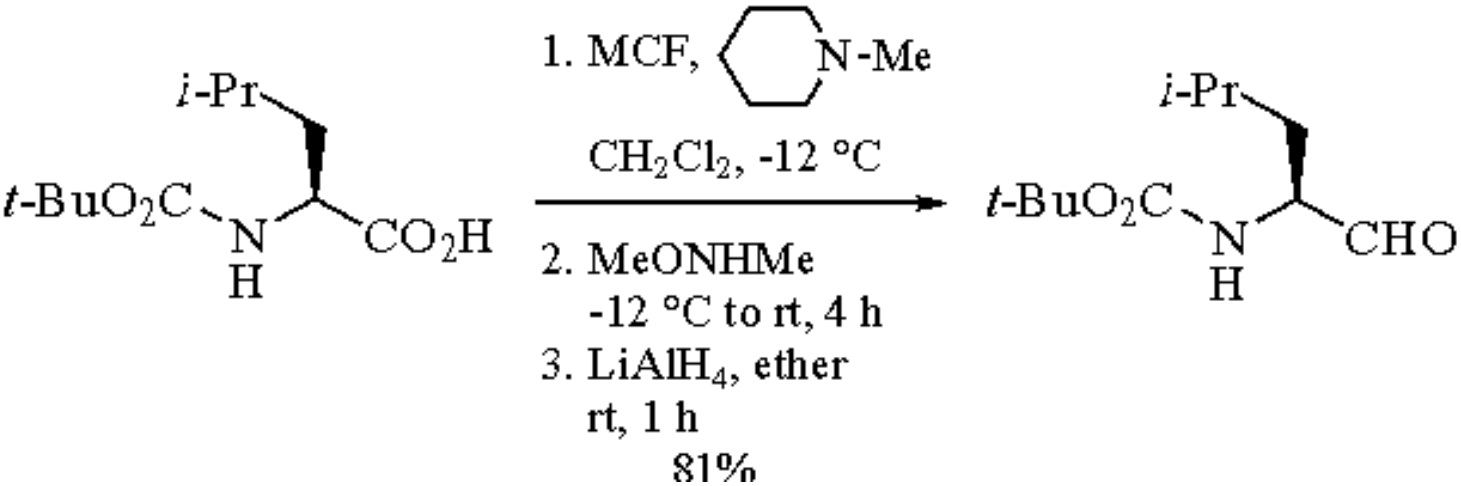

(13)

α-Diazo ketones may be conveniently prepared by reaction of a mixed anhydride with ***Diazomethane***; the mixed anhydrides are typically prepared either by treatment of the parent carboxylic acid with MCF/***Triethylamine***[44] or by treatment of the corresponding methyl ester with potassium silyloxide and then MCF.[45] Attack by amines[46] or *N*-silylamines[47] on such mixed anhydrides provides a useful approach to amide synthesis (eq 14), while acyl azides are prepared in excellent yield by reaction of the mixed anhydride with ***Sodium Azide***.[48]

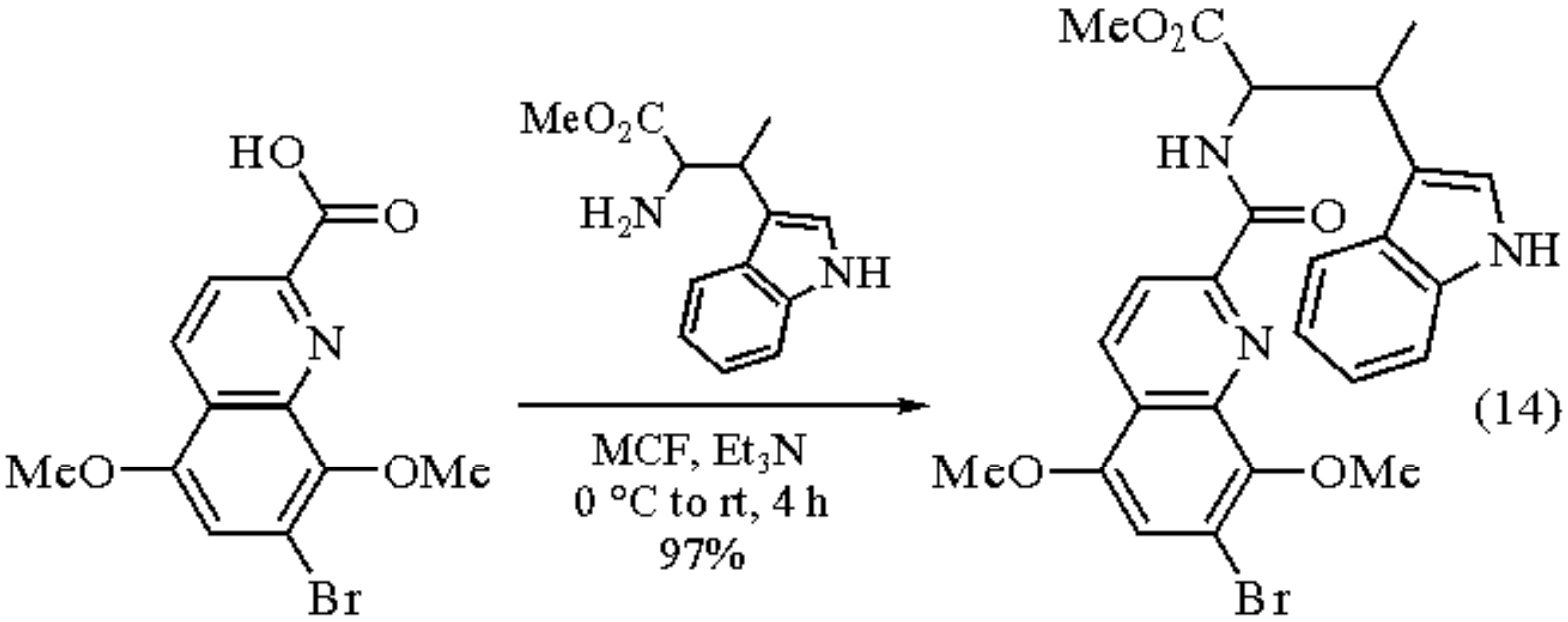

(14)

While the mixed anhydrides derived from the reaction of carboxylic acids with methyl chloroformate using Et_3N as base are relatively stable, the addition of catalytic amounts of ***4-Dimethylaminopyridine*** or *N*-methylmorpholine results in facile conversion to the corresponding methyl esters under very mild reaction conditions that are compatible with sensitive functionality.[49]

Related Reagents.

Benzyl Chloroformate; ***2,2,2-Trichloroethyl Chloroformate***.

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Methyl Chlorooxalate

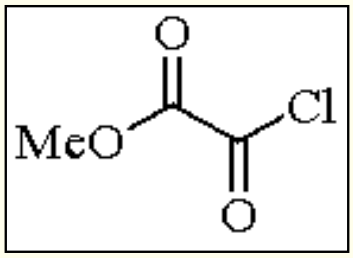

[5781-53-3] · $C_3H_3ClO_3$ · Methyl Chlorooxalate · (MW 122.51)

(acylating agent;[1] heterocycle synthesis;[2] deoxygenation intermediate;[3] chiral α-hydroxy ketones[4])

Alternate Names: MCO; methyl oxalyl chloride.

Physical Data: bp 118-120 °C; *d* 1.332 g cm^{-3}.

Form Supplied in: liquid; commercially available.

Preparative Methods: originally prepared from methyl oxalate and phosphorus pentachloride,[5] a simpler procedure involves treatment of crystalline potassium methyl oxalate with thionyl chloride and isolation of the product by distillation.[6]

Handling, Storage, and Precautions: corrosive liquid; lachrymator. Use in a fume hood.

Oxalyl Transfer.

Much of the chemistry of methyl chlorooxalate (MCO) is simply that of an acylating agent and parallels that of standard acid chlorides. Thus, in addition to acylating a variety of alcohols, this reagent has also been reported to acylate naphthols,[1] indoles,[7] and oxazoles.[8] An interesting acylation of a 1-deoxy-1-diazo fructose derivative (**1**) with MCO provided the product (**2**) in 65% yield (eq 1).[9] Attempts to use simpler acid chlorides (acetyl or benzoyl) for this chain elongation were not successful.

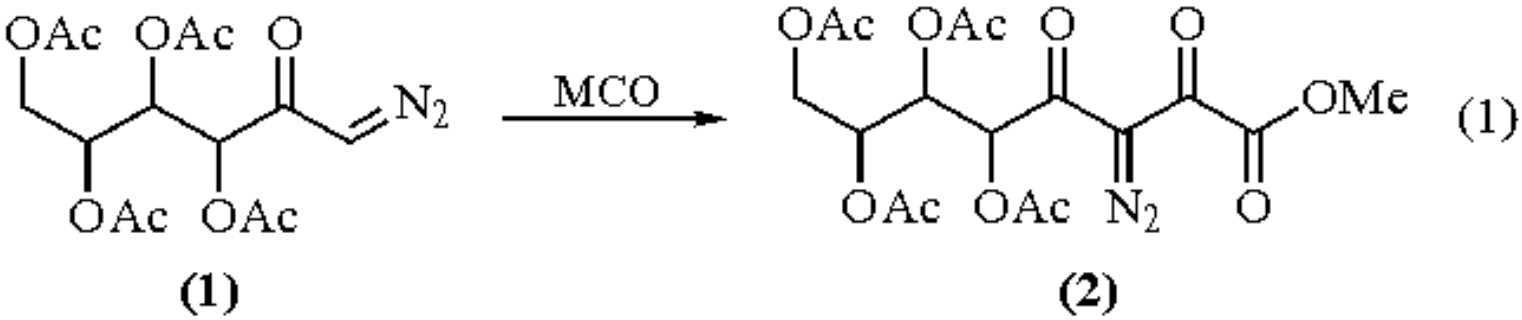

Heterocycle Synthesis.

Methyl chlorooxalate can be used to prepare a number of carboxy-substituted ring systems. For example, treatment of (**3**) with MCO in pyridine gave the isoflavone (**4**) in 66% yield (eq 2).[2] Another interesting use of this reagent in an intramolecular cyclization is the reported construction of penems and carbapenems.[10] Treatment of either (**5a**) or (**5b**) with ***Triethyl Phosphite*** provides the cyclized products (**6a**) and (**6b**) in 83% and 92% yields, respectively (eq 3). This reaction is thought to proceed by generation of a carbene intermediate. MCO has also been used for the construction of indole systems.[11]

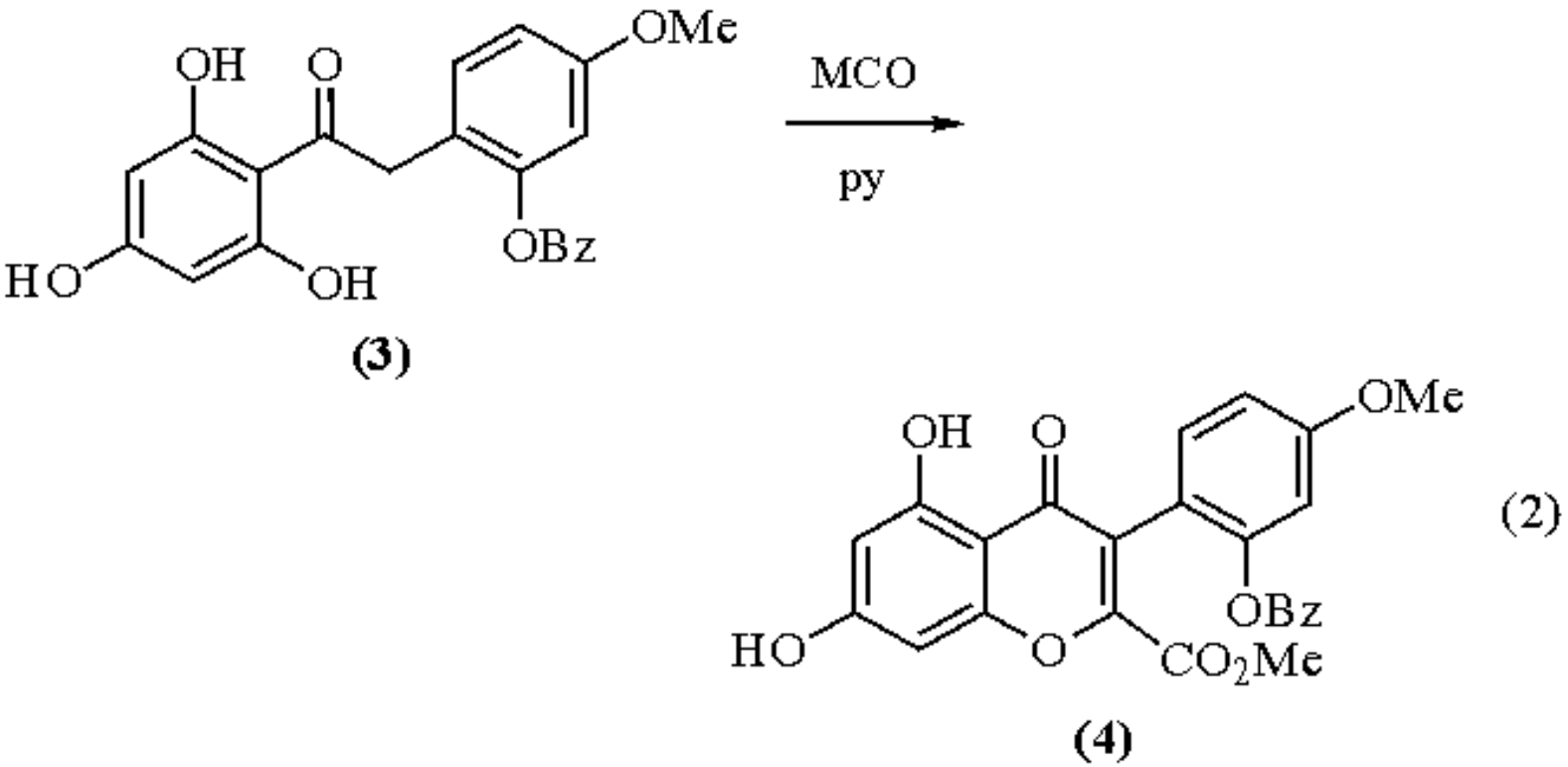

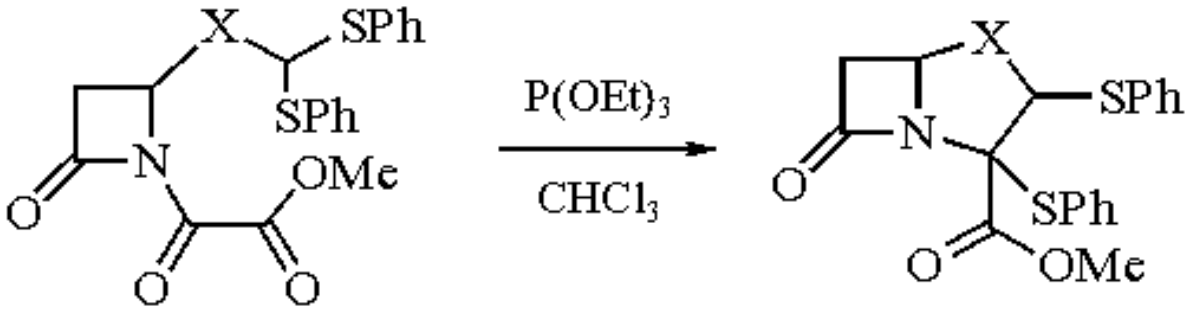

(3)

(5a) X = CH_2
(5b) X = S

(6a) 83%
(6b) 92%

Deoxygenation of Alcohols.

Methyl chlorooxalate has found use in the deoxygenation of tertiary and secondary alcohols.[3] A number of gibberellic acid derivatives were acylated with this reagent under mild conditions without the use of base. The resulting methyl oxalyl esters were treated with ***Tri-n-butylstannane*** and 2,2´-azo-2-methylpropionitrile in refluxing toluene to provide the deoxygenated products in good yield (eq 4).

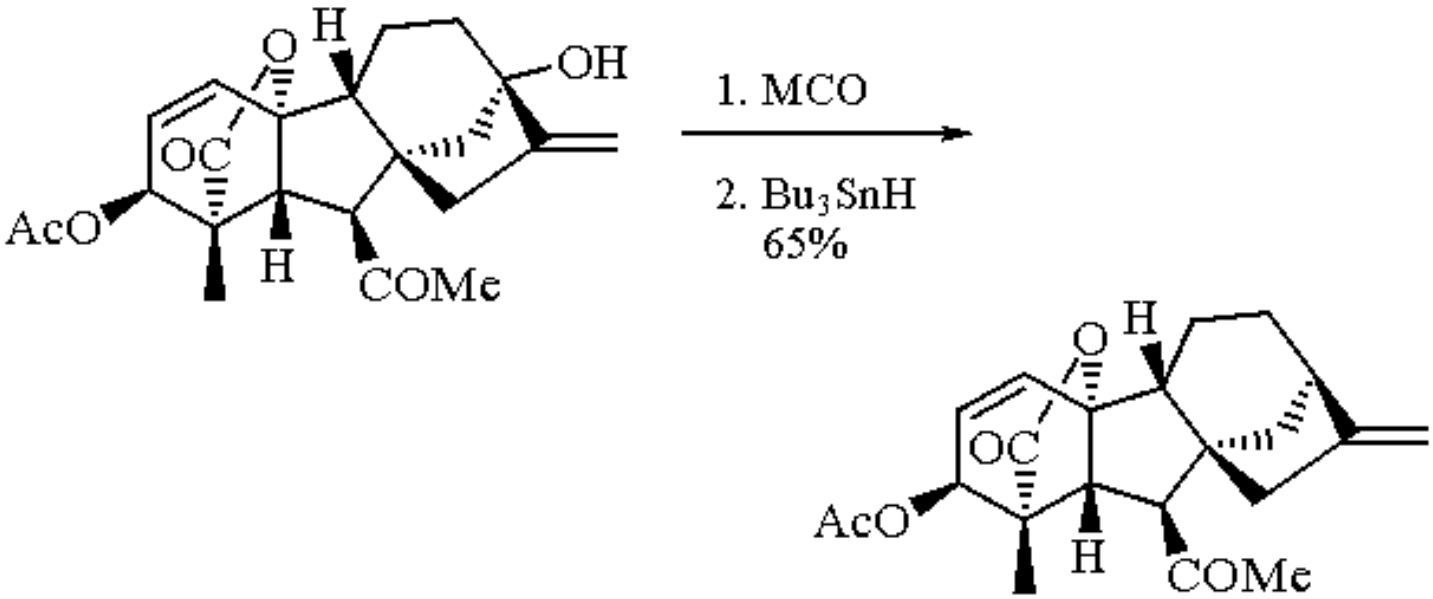

(4)

Finally, an interesting application of this reagent for the preparation of chiral α-hydroxy ketones has recently been reported.[4]

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Methyl α-Chloro-α-phenylthioacetate

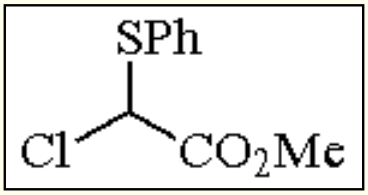

[85920-99-6] · $C_9H_9ClO_2S$ · Methyl α-Chloro-α-phenylthioacetate · (MW 216.70)

(an a^2 carbon electrophile for the introduction of methoxycarbonylmethyl and methoxycarbonylmethylidene groups by Lewis acid-catalyzed reaction with silyl enol ethers followed by a reductive or oxidative step)

Physical Data: bp 105-107 °C/18 mmHg.[1]

Solubility: freely sol CH_2Cl_2.

Analysis of Reagent Purity: δ ($CDCl_3$) 7.47 (5H, m), 5.57 (1H, s), and 3.77 (3H, s).

Preparative Methods: by chlorination of methyl phenylthioacetate using ***Sulfuryl Chloride***[2] or ***N-Chlorosuccinimide*** (NCS):[3,4] methyl phenylthioacetate (16.8 g) is stirred with powdered NCS (13.3 g) in CCl_4 at rt for 10 h, the mixture filtered, the filtrate evaporated, and the residue distilled using a short Vigreux column.[1]

Handling, Storage, and Precautions: generally prepared shortly before use. It is stable in the absence of water, and should be kept in a stoppered flask or sealed ampule if it is not used immediately. It is an alkylating agent, and should therefore be kept in a well-ventilated hood, with skin and eyes protected while handling it.

Methyl α-chloro-α-phenylthioacetate (**2**) reacts with silyl enol ethers (**1**) in the presence of Lewis acids, typically ***Zinc Bromide*** in catalytic quantities[3,4] or ***Titanium(IV) Chloride*** in stoichiometric quantities,[4] to give the 1,4-dicarbonyl products (**3**) (eq 1). The reaction is regiospecific (eqs 2 and 3),[4] and γ-selective with the silyl dienol ether (**4**) (eq 4).[3]

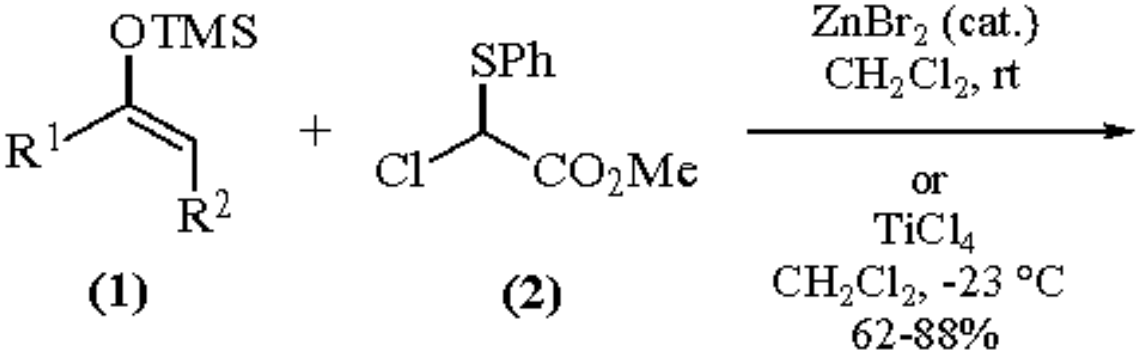

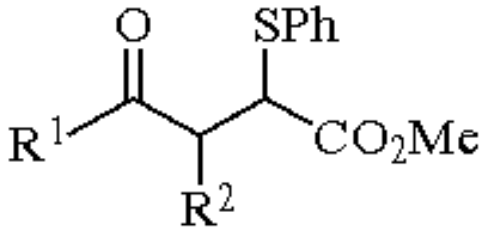

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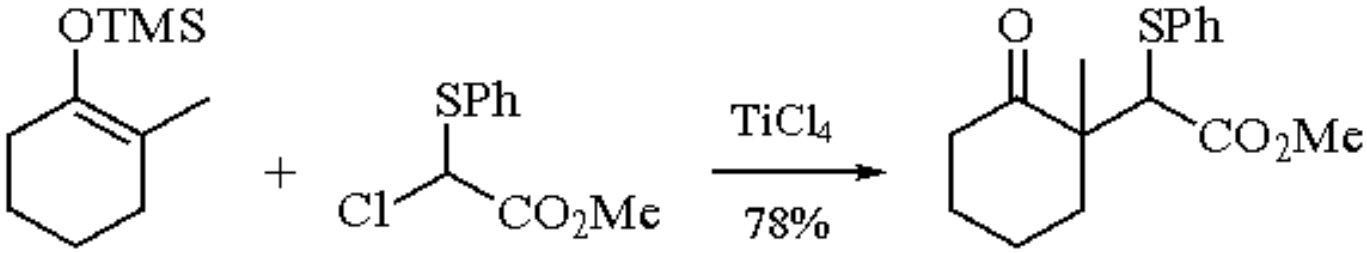

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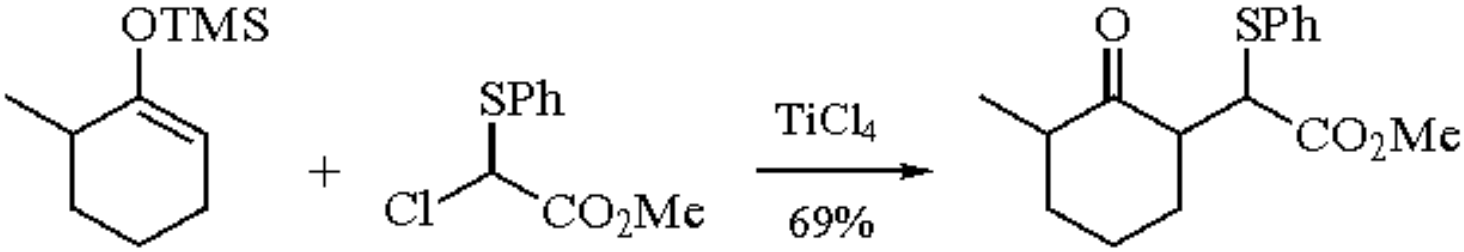

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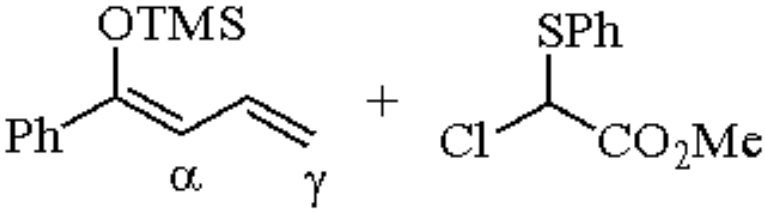

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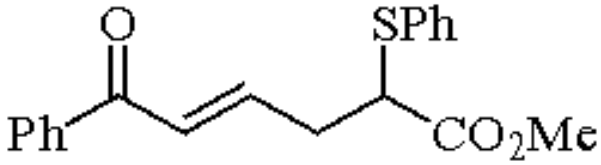

(4)

The $ZnBr_2$ reactions typically take 0.5-2 h at rt in CH_2Cl_2, and are carried out by adding the anhydrous salt to a 1:1

mixture of silyl enol ether and the chloride (**1**). The $TiCl_4$ reactions are carried out similarly, and typically take 2 h at -23 °C.

The products (**3**) can be desulfurized with ***Raney Nickel*** to give overall the products (**5**) of methoxycarbonylmethylation (eq 5).[3,4] They can also be oxidized using ***Sodium Periodate*** to give the corresponding sulfoxides, which undergo rapid cycloelimination when there is an appropriately placed hydrogen atom to give overall the products (**6**) of methoxycarbonylmethylidenation (eq 6).[3,4]

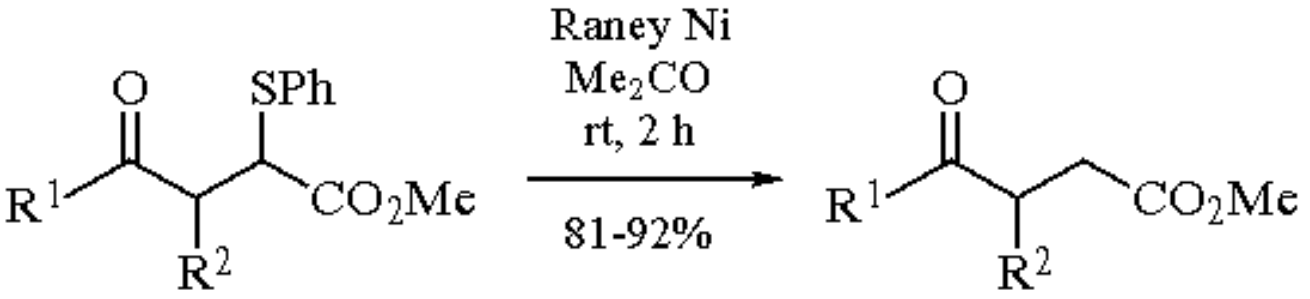

(5)

(3) (5)

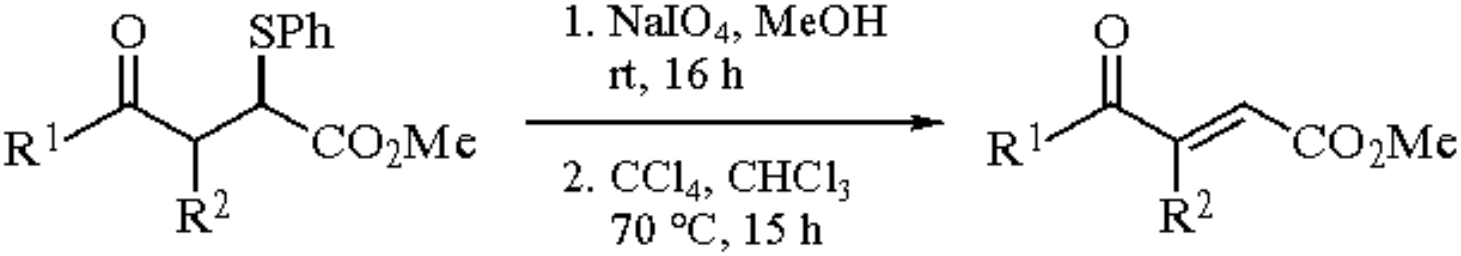

(6)

(3) (6)

The homolog methyl 2-chloro-2-phenylthiopropanoate (**7**) can be used in similar reactions (eqs 7-9), but the oxidative desulfurization takes place towards the methyl group, giving the α-methylene ester (**8**) when R^2 is not hydrogen (eq 9).[4]

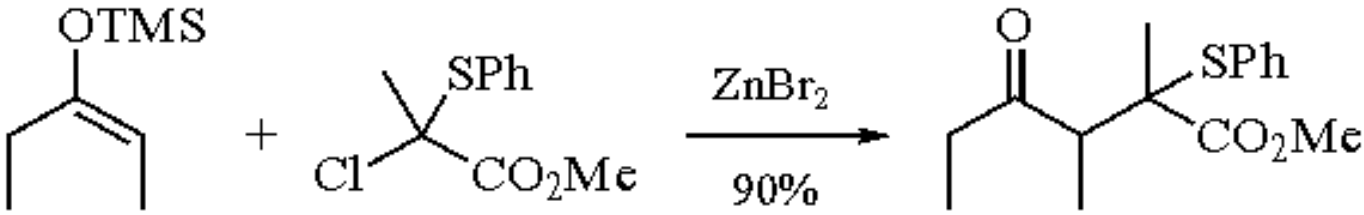

(7)

(7)

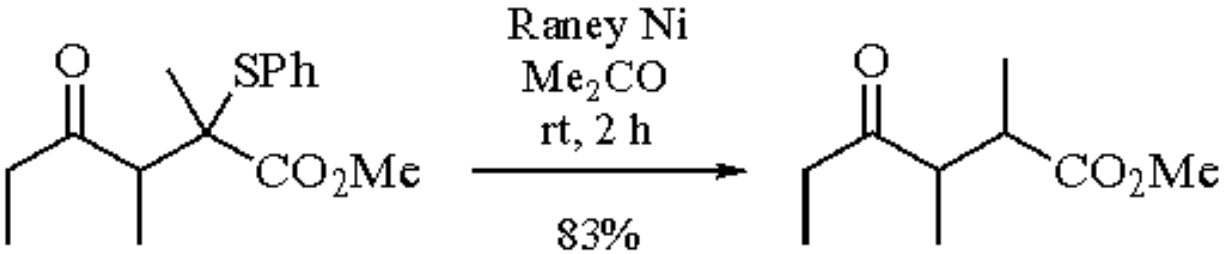

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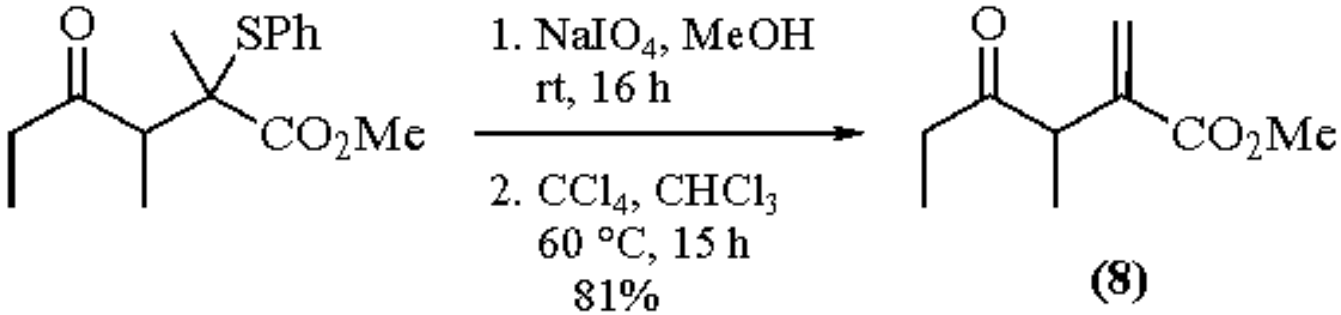

(9)

(8)

The corresponding Lewis acid-catalyzed reaction of silyl enol ethers with α-chloro-α-phenylthioketones gives furans.[5]

Related Reagents.

Chloromethyl Phenyl Sulfide.

---

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Ian Fleming

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Methylcopper[1]

MeCu

[1184-53-8] · CH_3Cu · Methylcopper · (MW 78.59)

(nucleophilic reagent for substitution reactions;[1b] selective for conjugate additions;[1c,d,2] adds to triple bonds[3])

Physical Data: oligomeric yellow solid;[4] stable at -10 °C, mp 20 °C (dec to ethane), explodes at 30-35 °C.[30]

Solubility: slightly sol ether, THF; sol dimethyl sulfide (DMS), tributylphosphine.

Preparative Methods: methylcopper and other alkylcopper species are most commonly prepared from equimolar amounts of alkyllithium or Grignard reagent and purified copper(I) halide in ether or THF.[3a,c,5-10] The byproduct halide salts, which can influence reagent activity, are easily removed by washing the precipitated alkylcopper with fresh solvent.[7,10] Alkylcoppers can be prepared from alkyl halides and highly active zero-valent copper.[11]

Handling, Storage, and Precautions: alkylcoppers are generally not long lived at temperatures above 0 °C. They are more thermally stable and more reactive when used in dimethyl sulfide.[12] Methylcopper may decompose explosively when dry.[30] Use in a fume hood.

Nucleophilic Substitutions.

Acyl chlorides are converted to the corresponding methyl ketones on treatment with methylcopper.[12,13] Ring opening of heterocycles, involving S_N2 processes, occurs with epoxides,[11,12,14] β-lactones,[15] and cyclic acetals.[16] In the latter case, mandelic acid-derived 1,3-dioxolan-4-ones react with Grignard-derived alkylcoppers to deliver protected chiral secondary alcohols in good yield and 54-94% diastereomeric excess (eq 1).

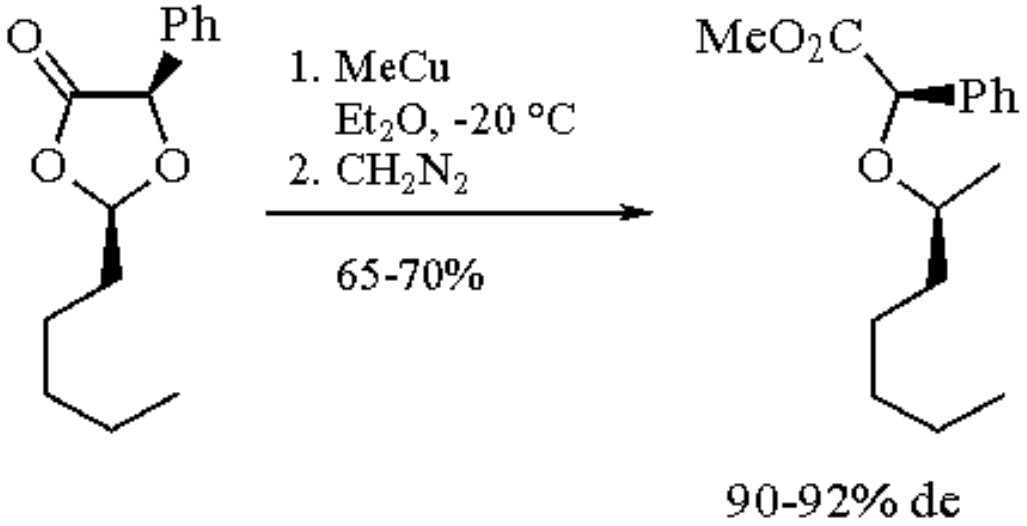

(1)

Primary alkylcoppers surpass many organometallic reagents in their selectivity for S_N2' substitution. Allyl halides,[17] allyl ethers,[9] propargyl sulfonates,[18] and propargyl halides[8] (eqs 2 and 3) all suffer predominately S_N2' attack.

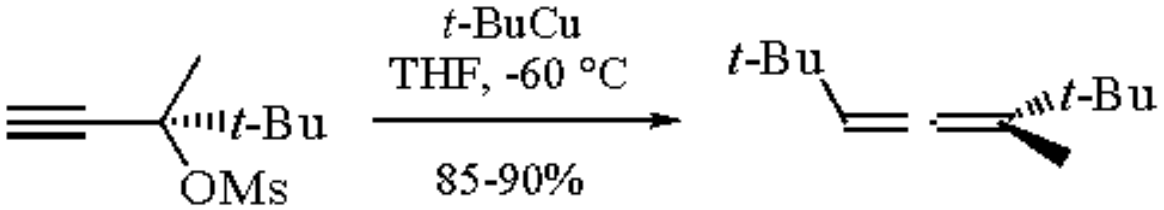

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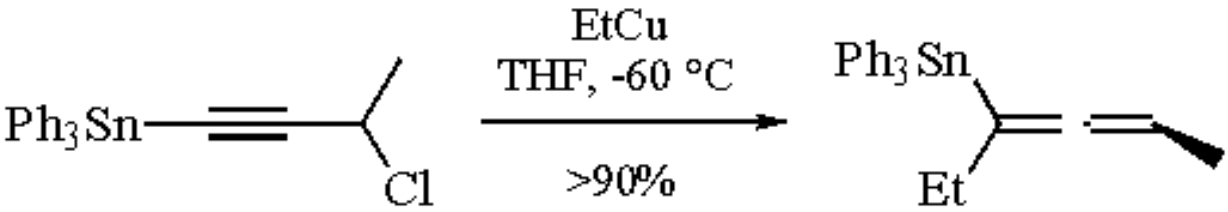

(3)

Conjugate Additions.

As with cuprate reagents, alkylcoppers undergo conjugate addition to electron-poor alkenes and alkynes. Substrates include nitroalkenes,[7] alkenylsulfones,[19] alkynoates,[20] cyanoalkynes,[21] and alkynic sulfoxides[5,22] and sulfones.[22a,23] With the alkynes, the reaction gives exclusively the product of *cis* addition across the triple bond.

The addition of alkylcopper to alkenones, alkenals, and alkenoates is accelerated by ***Chlorotrimethylsilane*** or ***Iodotrimethylsilane***, the adducts being isolable as the silyl enol ethers.[10,24,25] Chemoselectivity (1,4- vs. 1,2-addition) is also enhanced by these silanes. The enhanced rates enable the use of both alkyl groups of dialkylcuprate reagents (eq 4).[24] Enhanced rate and chemoselectivity are likewise fostered by the use of stoichiometric or greater quantities of DMS[12] or trialkylphosphines.[20a,26]

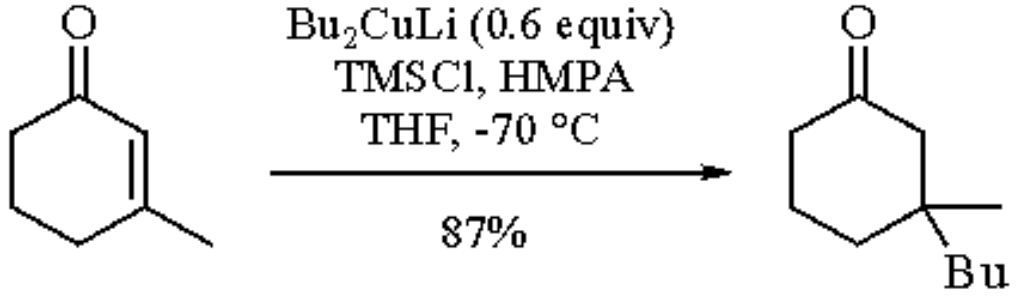

(4)

The diastereoselectivities of conjugate additions of alkylcoppers to γ-alkoxyalkenoates[27] and optically active alkenylsulfoximines[28] have also been investigated. The sulfoximine adducts can be converted to optically active 3-alkylcarboxylic acids.

Additions to Alkynes.

Alkylcopper species add to terminal alkynes stereospecifically (*syn*) and with good regioselectivity to generate alkenylcopper species; subsequent addition of an electrophile provides the di- or trisubstituted alkene. The copper atom usually attaches to the 1-position in the addition step (eqs 5 and 6),[9,29] but this can be influenced by directing groups and choice of solvent.[3a]

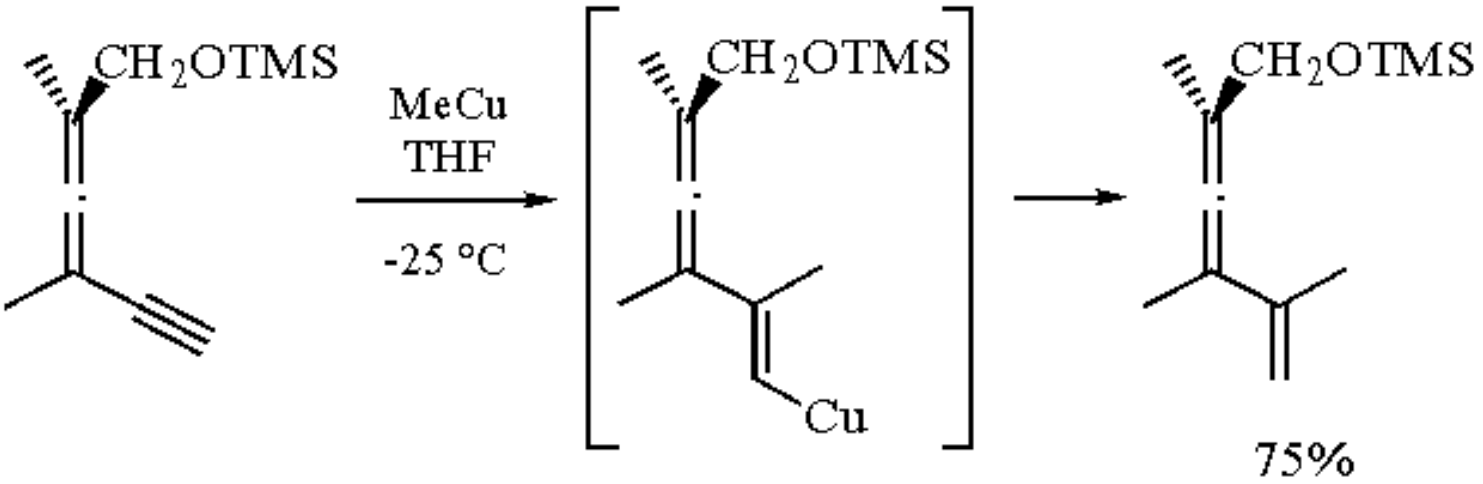

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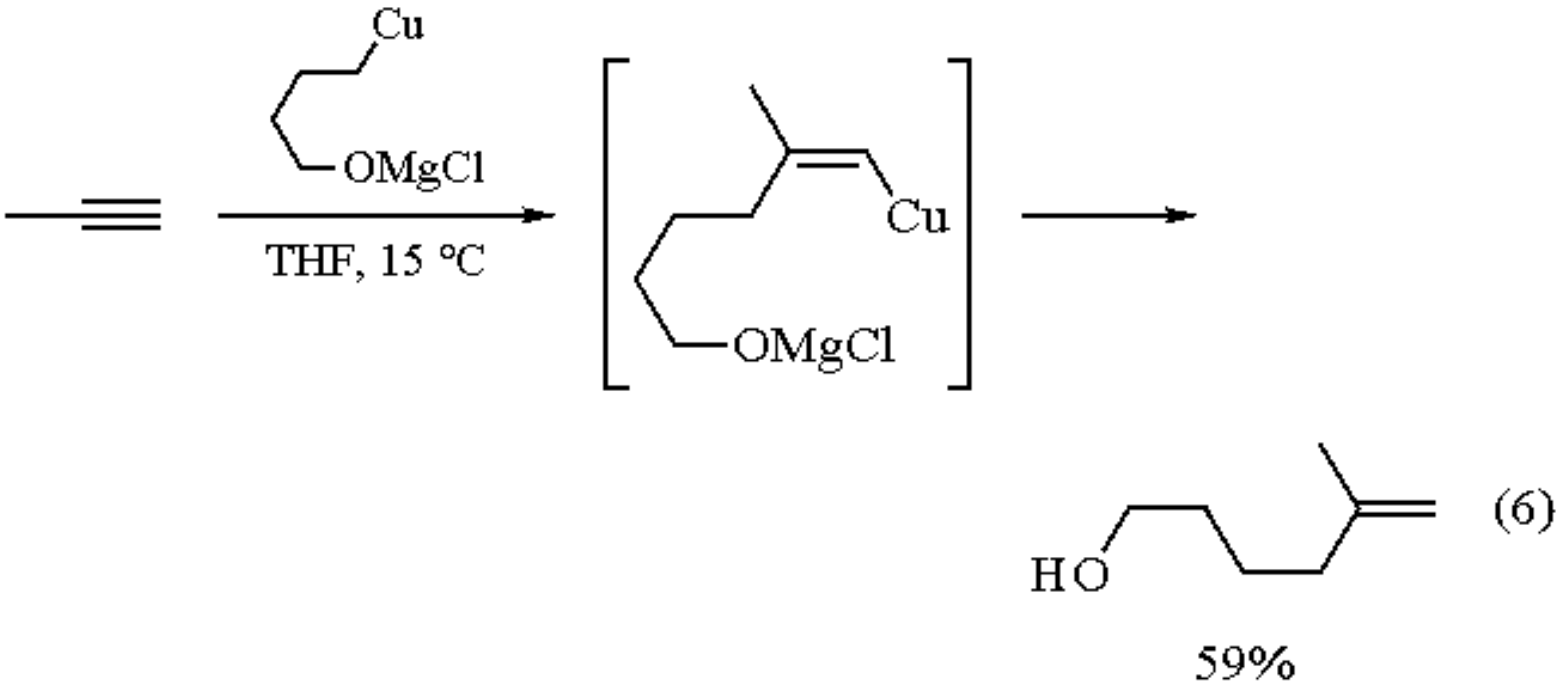

Related Reagents.

n-Butylmagnesium Bromide-Methylcopper(I); ***Lithium Dimethylcuprate***; ***Methylcopper-Boron Trifluoride Etherate***; ***Methylcopper-Tributylphosphine***; ***Phenylcopper***; ***Phenylcopper-Boron Trifluoride Etherate***; ***Trifluoromethylcopper(I)***; ***Vinylmagnesium Bromide-Methylcopper***.

---

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Methylcopper-Boron Trifluoride Etherate[1]

$MeCu/BF_3.OEt_2$

(MeCu)

[1184-53-8] · CH_3Cu · Methylcopper-Boron Trifluoride Etherate · (MW 78.59) ($BF_3.OEt_2$)

[109-63-7] · $C_4H_{10}BF_3O$ · Methylcopper-Boron Trifluoride Etherate · (MW 141.95)

(selective nucleophilic reagent for conjugate additions[2] and substitution reactions[1])

Preparative Method: prepared by the addition of ***Boron Trifluoride Etherate*** to a suspension of ***Methylcopper*** in Et_2O or THF at -75 °C.[2]

Handling, Storage, and Precautions: see entries for ***Boron Trifluoride Etherate*** and ***Methylcopper***. Use in a fume hood.

Conjugate Additions.

The combination of an alkylcopper with boron trifluoride produces a nucleophilic reagent which is more reactive than the alkylcopper alone and which can exhibit regioselectivity on a par with organocuprate reagents. For example, in each of two syntheses of the sesquiterpene modhephene, RCu/BF_3 was used to establish a quaternary center by conjugate addition to a 3-alkyl-2-cyclopentenone moiety (eq 1).[3,4] Alkenoates and alkenoic acids are also suitable substrates.[2,5] In the development of methodology for asymmetric synthesis, the alkylcopper/BF_3 combination was found to be effective in preparing β-substituted carboxylic acids.[6] High enantiomeric excesses (94-98%) were obtained by the use of a camphorsulfonamide auxiliary (eq 2).[6a]

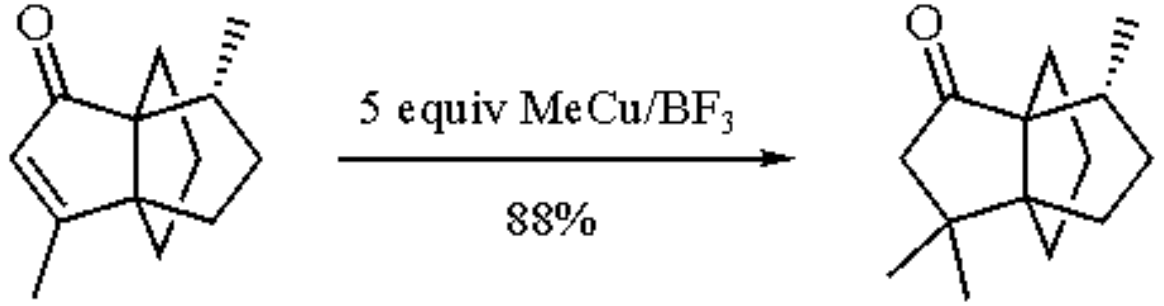

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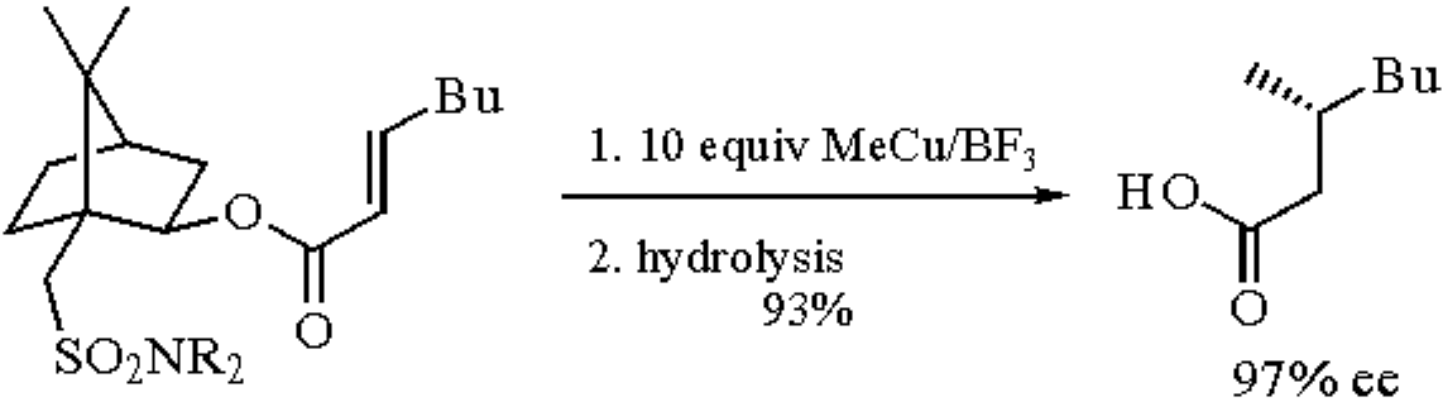

(2)

Enhancements of rate and regioselectivity in conjugate additions have also been observed with the combinations of alkylcopper/halosilane[7] and alkylcopper/***Aluminum Chloride***.[8]

Nucleophilic Substitutions.

Acetals are converted to the corresponding monosubstitution products on treatment with alkylcopper/BF_3.[9,10] Similarly, orthoformates give acetals in high yield.[9] Chiral cyclic acetals undergo this monosubstitution reaction stereoselectively (eq 3), although cuprates with BF_3 were found to give better results.[10]

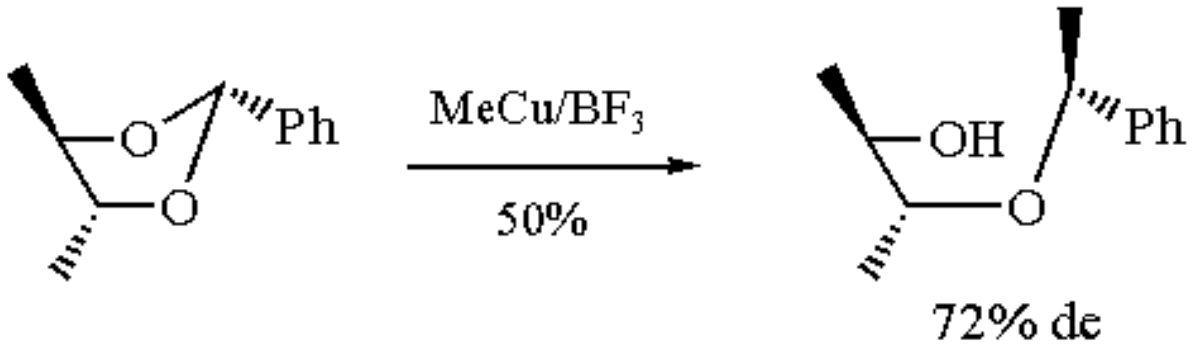

(3)

Allylic halides, ethers, esters, and alcohols suffer regioselective γ-attack by alkylcopper/BF_3.[11] Propargyl chloride and acetate afford 1,2-heptadiene. The stereoselectivity of these substitutions has been less rigorously examined, but appears to be less dramatic than the regioselectivity. The regioselectivity of attack on γ-acetoxy-α,β-enoates by alkylcopper/$AlCl_3$ has also been documented.[12]

Related Reagents.

Methallyllithium; ***Phenylcopper-Boron Trifluoride Etherate***.

---

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Methylcopper-Tributylphosphine[1]

$MeCu.PBu_3$

[24743-95-1] · $C_{13}H_{30}CuP$ · Methylcopper-Tributylphosphine · (MW 280.95)

(reagent for 1,4-addition of methyl group;[2] methylation of aryl iodides;[3] ring opening of β-propiolactones[4])

Alternate Name: methyl(tributylphosphine)copper.

Physical Data: mp 57-60 °C; dec above 90 °C.

Preparative Methods: prepared from ***Methyllithium*** or methylmagnesium halides and ***Copper(I) Iodide-Tributylphosphine*** complex.

Handling, Storage, and Precautions: sensitive to air and moisture. Hydrolysis produces methane, which can be an explosion hazard. Handle in a fume hood.

Introduction.

House and co-workers first described the reactions of methylcopper stabilized by tributylphosphine in the 1960s.[5] Yamamoto and co-workers[6] carried out a comprehensive study of the formation and stability of phosphine complexes of alkylcopper species. MeCu-tributylphosphine was prepared from copper(II) acetoacetate and dimethylethoxyaluminum. The complex was isolated (mp 57-60 °C) and shown to be light- and air-sensitive. Thermal decomposition[6b] occurred between 90 and 130 °C with the evolution of methane (61%) and ethane (39%); ethane was presumed to arise by hydrogen abstraction from the phosphine ligands. Since ethylene was not observed, the possibility of α-elimination was excluded.

Enone Additions.

1,4-Addition of MeCu-tributylphosphine to pent-3-en-2-one in the presence of ***Lithium Iodide*** provided 4-methylpentan-2-one in 99% yield. Subsequent studies[2] compared the reactivity of ***Methylcopper***, MeCu-tributylphosphine, and MeCu-trimethyl phosphite in 1,4-additions to 5-methylcyclohex-2-enone.

Methylcopper alone was unreactive, providing less than 1% of the 1,4-addition product. MeCu-tributylphosphine gave a 34% yield, while the MeCu-trimethyl phosphite reagent resulted in a 90% yield of *trans*-3,5-dimethylcyclohexanone (eq 1). Both of the phosphine complexes were generated in situ and required that lithium iodide be present in the reaction mixture for 1,4-addition to occur. Noyori and co-workers[7] reinvestigated the 1,4-addition of tributylphosphine-stabilized organocopper reagents and determined that the best results were obtained when 2 equiv of tributylphosphine were added to the organocopper reagent. MeCu-tributylphosphine proved to be the least reactive of the alkyl copper species investigated. For example, MeCu-tributylphosphine provided the 1,4-addition product from cyclopentenone in 73% yield, while reaction with the corresponding butyl copper reagent resulted in a 93% yield of 3-butylcyclopentane.

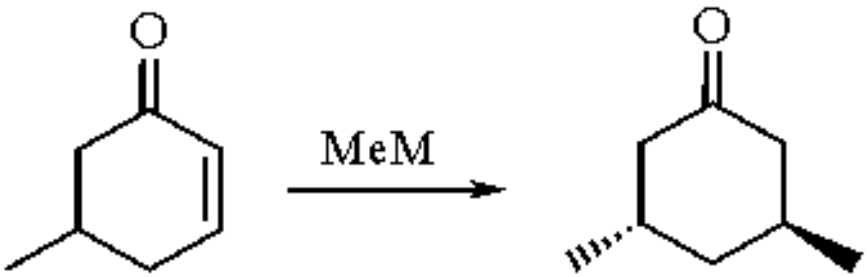

(1)

$MeCu \cdot PBu_3$	34%
$MeCu \cdot P(OMe)_3$	90%
MeCu	0%

The reactivity of MeCu-tributylphosphine has also been directly compared with that of ***Methylcopper-Boron Trifluoride Etherate***.[8] In reaction with acetylcyclohexene, MeCu-tributylphosphine provided the 1,4-addition product in 55% yield, while the MeCu-boron trifluoride complex gave the same product in 68% yield (eq 2). Only a trace of the 1,2-addition product was noted in each reaction. Interestingly, the addition of boron trifluoride to preformed MeCu-tributylphosphine did not result in improved yields of the 1,4-adduct.

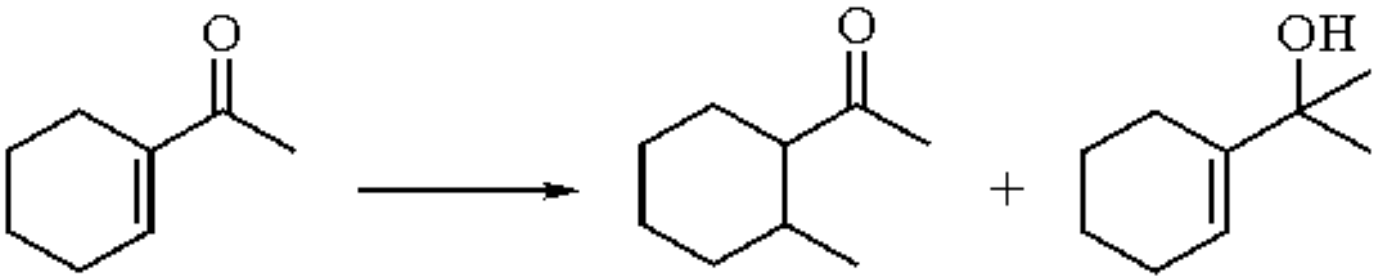

(2)

$MeCu \cdot PBu_3$	55%	1%
$MeCu \cdot BF_3$	68%	2%
$MeCu \cdot PBu_3 \cdot BF_3$	39%	2%

These results are in contrast to the observations by Oppolzer and co-workers[9] in the asymmetric 1,4-addition

of MeCu-tributylphosphine to (-)-8-phenylmenthol crotonate esters (eq 3). In this study, MeCu-tributylphosphine resulted in much better yields of the 1,4-adduct and improved enantioselectivity when compared to MeCu-boron trifluoride. However, the combination of MeCu-tributylphosphine and boron trifluoride proved to be the reagent mixture of choice for asymmetric conjugate addition to a camphor-derived neopentyl ether chiral auxiliary. The asymmetric synthesis of (*S*)-citronellic acid was achieved using this method in 92% ee (eq 4).[9] Similar results were obtained with a dicyclohexylsulfonamide chiral auxiliary, providing the methyl addition product in >94% ee (eq 5).[10] This methodology can be applied to the synthesis of deoxypolypropionate derivatives in excellent optical purity.[11]

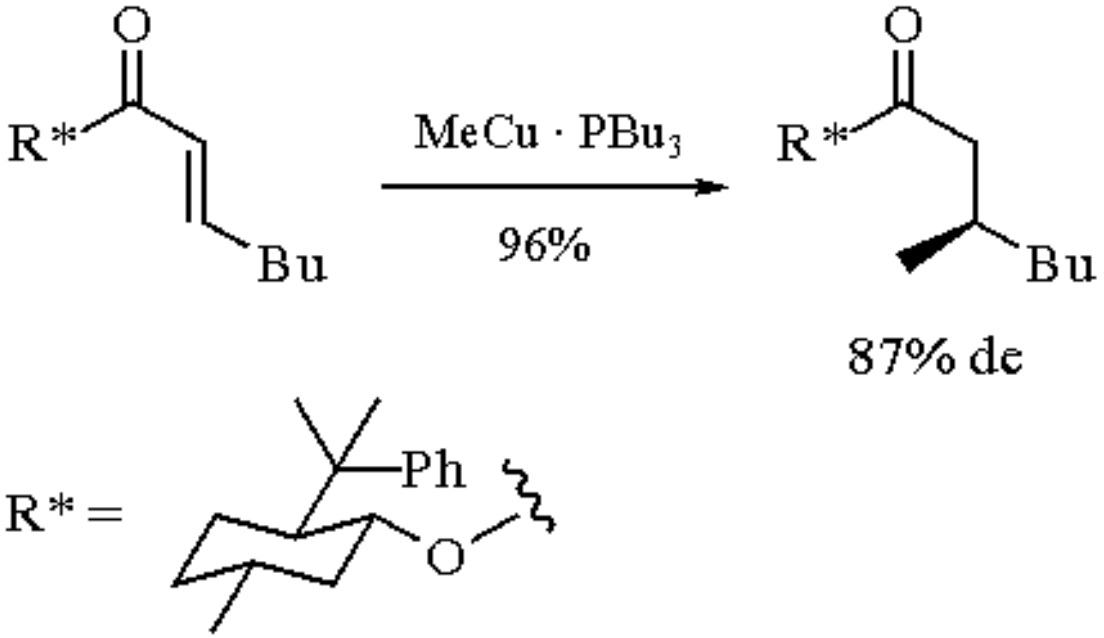

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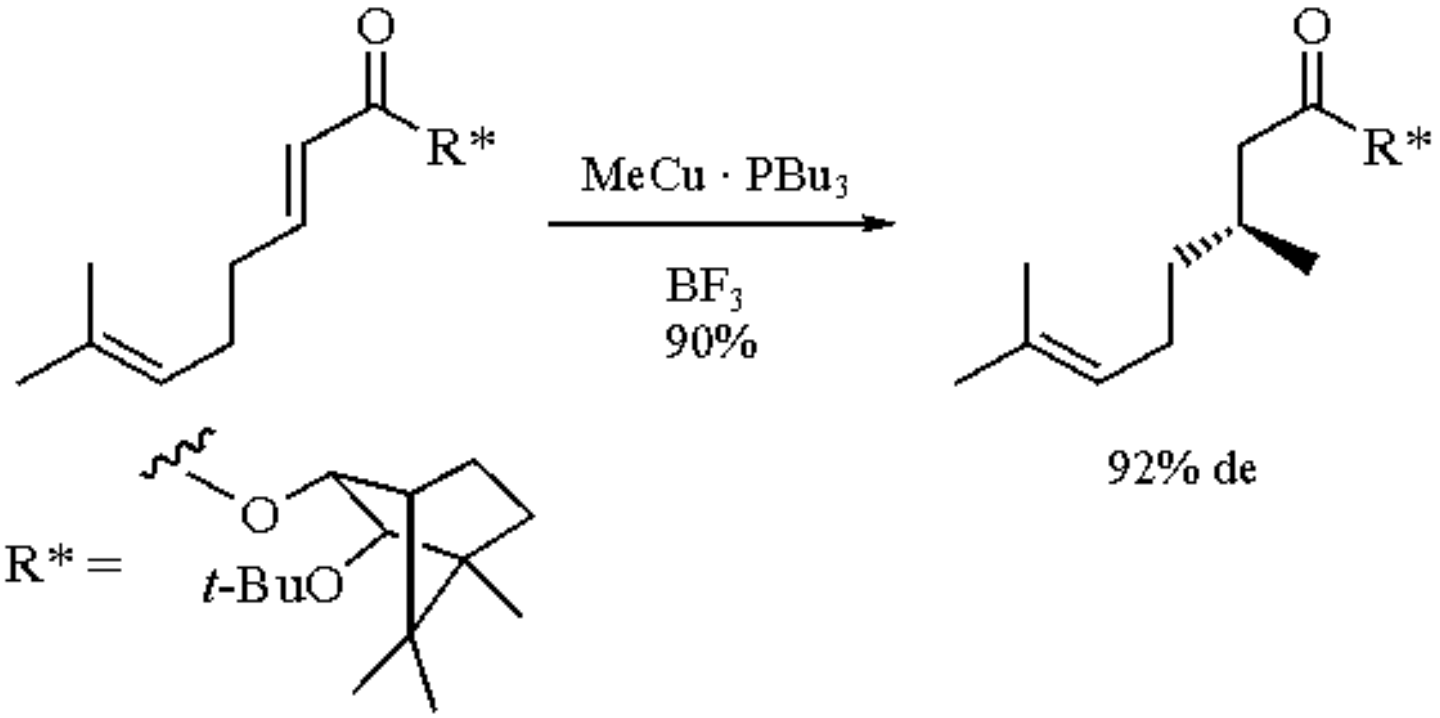

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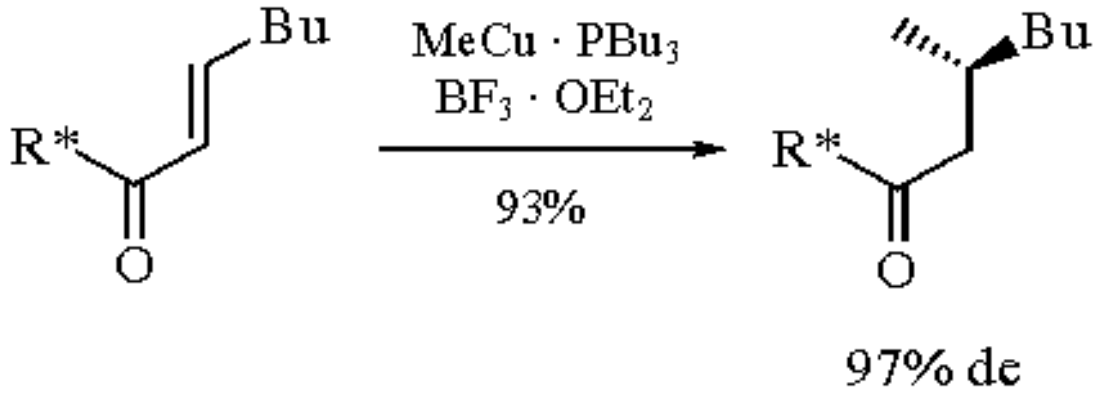

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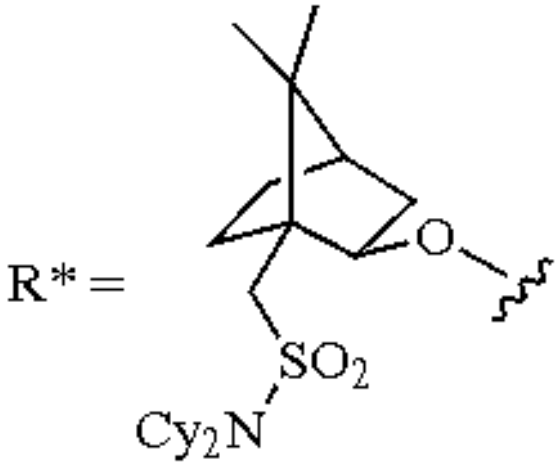

Displacement Reactions.

MeCu-tributylphosphine can also be used in coupling and displacement reactions. Reaction with 1-iodonaphthalene provided the methylated derivative in good yield.[3] Regioselective ring opening of β-propiolactones occurs cleanly with the tributylphosphine-stabilized copper reagent (eq 6).[4] MeCu-tributylphosphine also gave somewhat better results than ***Lithium Dimethylcuprate*** in the S_N2' displacement of optically active allenic bromides to form optically active alkynes (eq 7).[12]

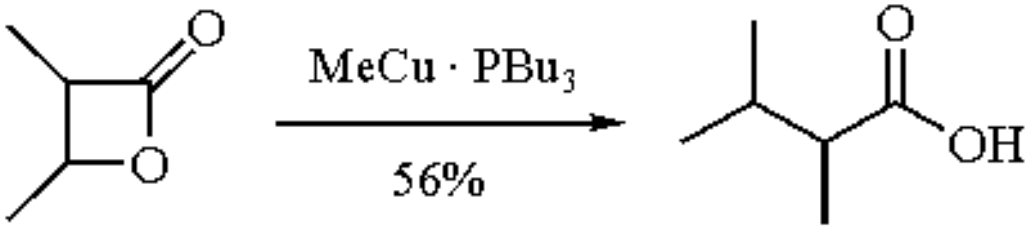

(6)

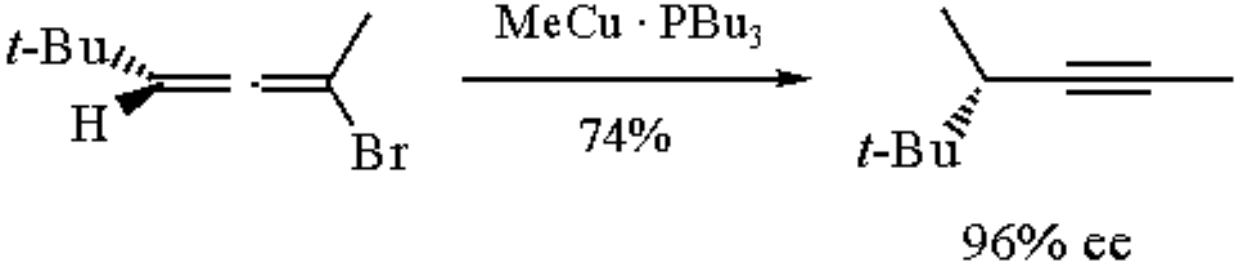

(7)

Related Reagents.

Copper(I) Iodide-Tributylphosphine; ***Lithium Dimethylcuprate***; ***Methylcopper***; ***Methylcopper-Boron Trifluoride Etherate***; ***Tri-n-butylphosphine***.

---

1. (a) Posner, G. H. *OR* **1972**, *19*, 1. (b) Posner, G. H. *OR* **1975**, *22*, 253. (c) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (d) Normant, J. F. *S* **1972**, 63. (e) Yamamoto, Y. *AG(E)* **1986**, *25*, 947. (f) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980.
2. House, H. O.; Fischer, W. F., Jr., *JOC* **1968**, *33*, 949.
3. Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashpe, R. W.; House, H. O. *JACS* **1969**, *91*, 4871.
4. Kawashima, M.; Sato, T.; Fujisawa, T. *T* **1989**, *45*, 403.
5. House, H. O.; Respess, W. L.; Whitesides, G. M. *JOC* **1966**, *31*, 3128.
6. (a) Miyashita, A.; Yamamoto, A. *BCJ* **1977**, *50*, 1102. (b) Miyashita, A.; Yamamoto, T.; Yamamoto, A. *BCJ* **1977**, *50*, 1109.
7. (a) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *TL* **1980**, *21*, 1247. (b) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. *Isr. J. Chem.* **1984**, *24*, 118.
8. Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *JOC* **1982**, *47*, 119.
9. Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Loher, H. *TL* **1983**, *24*, 4971.
10. Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *HCA* **1985**, *68*, 212.
11. Oppolzer, W.; Moretti, R.; Bernardinelli, G. *TL* **1986**, *27*, 4713.
12. Corey, E. J.; Boaz, N. W. *TL* **1984**, *25*, 3059.

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Methyl Cyanodithioformate

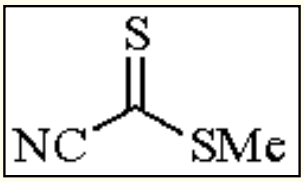

[17008-22-9] · $C_3H_3NS_2$ · Methyl Cyanodithioformate · (MW 117.21)

(electron-deficient thiocarbonyl compound; readily undergoes Diels-Alder and ene reactions with dienes and alkenes, respectively; reacts readily with amines)

Physical Data: deep purple; bp 50-60 °C/1 mmHg.

Preparative Method: addition of ***Sodium Cyanide*** to ***Carbon Disulfide*** in DMF affords sodium cyanodithioformate, which is converted to the unsolvated tetraethylammonium cyanodithioformate by treatment with tetraethylammonium bromide in ethanol. Reaction of the tetraethylammonium salt with excess ***Iodomethane*** in acetonitrile for 1 min provides methyl cyanodithioformate in 65% yield.[1]

Handling, Storage, and Precautions: dimerizes on standing and in the presence of nucleophiles. It should be prepared immediately before use.

Methyl cyanodithioformate (**1**) is an electron-deficient thiocarbonyl compound[2] that reacts readily with dienes to give dihydrothiopyran Diels-Alder adducts.[3-5] The regiochemistry of these cycloadditions is opposite to that observed with electron-deficient carbonyl compounds. Reaction of 1-methoxy-1,3-butadiene with (**1**) at 0 °C for 1 h affords mainly dihydrothiopyran (**2**) in which the cyano group has added *endo*. Reaction of (**2**) with ***Osmium Tetroxide*** affords the carbohydrate analog (**3**) (eq 1).[3d]

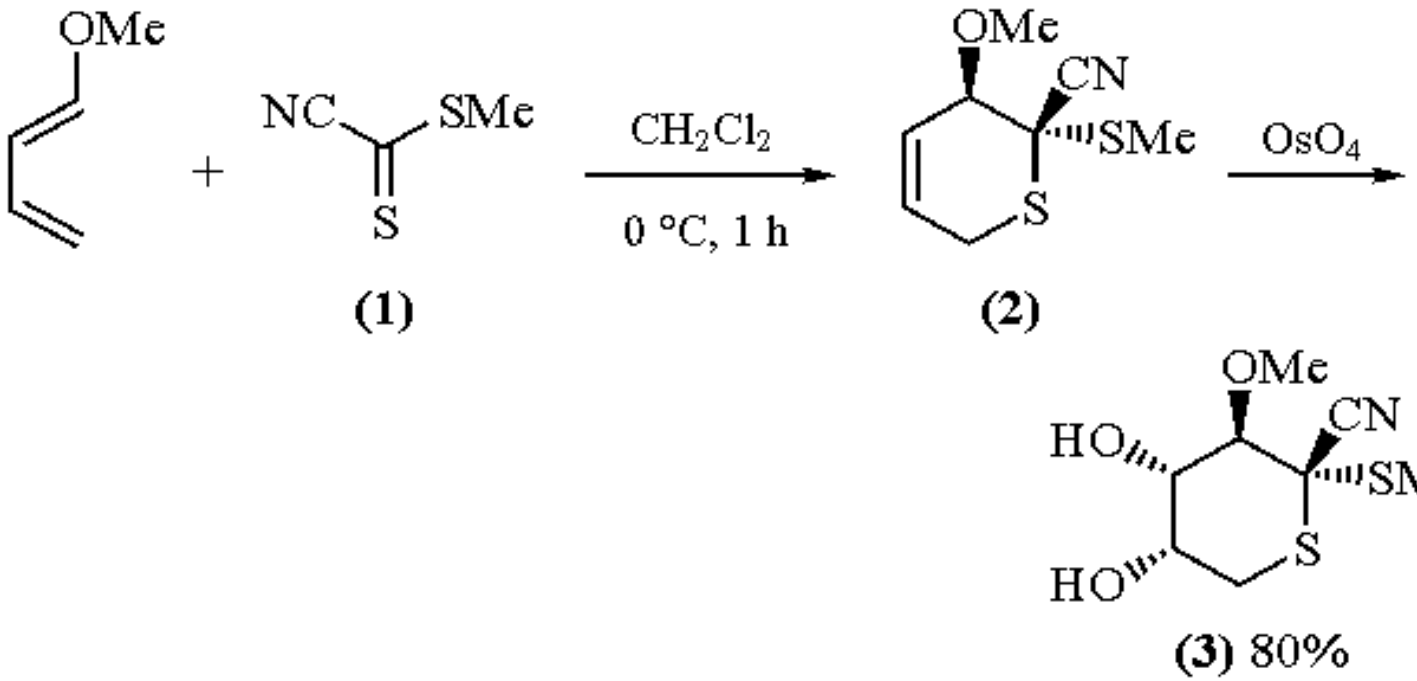

(1)

Methyl cyanodithioformate undergoes ene reactions with excess alkene in toluene at 100-110 °C for 5-72 h, affording allylic sulfide ene adducts in 45-83% yield.[6] A carbon-sulfur, rather than carbon-carbon, bond is formed in the ene reaction, as shown for β-pinene in eq 2. Treatment of the adduct (**4**) with ***Lithium Diisopropylamide*** or ***n-Butyllithium*** in THF/HMPA generates an anion that undergoes a [2,3]-sigmatropic rearrangement to give (**5**) after trapping with MeI. Reduction of (**5**) with deactivated W-4 ***Raney Nickel*** affords nitrile (**6**). This sequence provides a procedure for the insertion of a functionalized carbon into an allylic carbon-hydrogen bond.

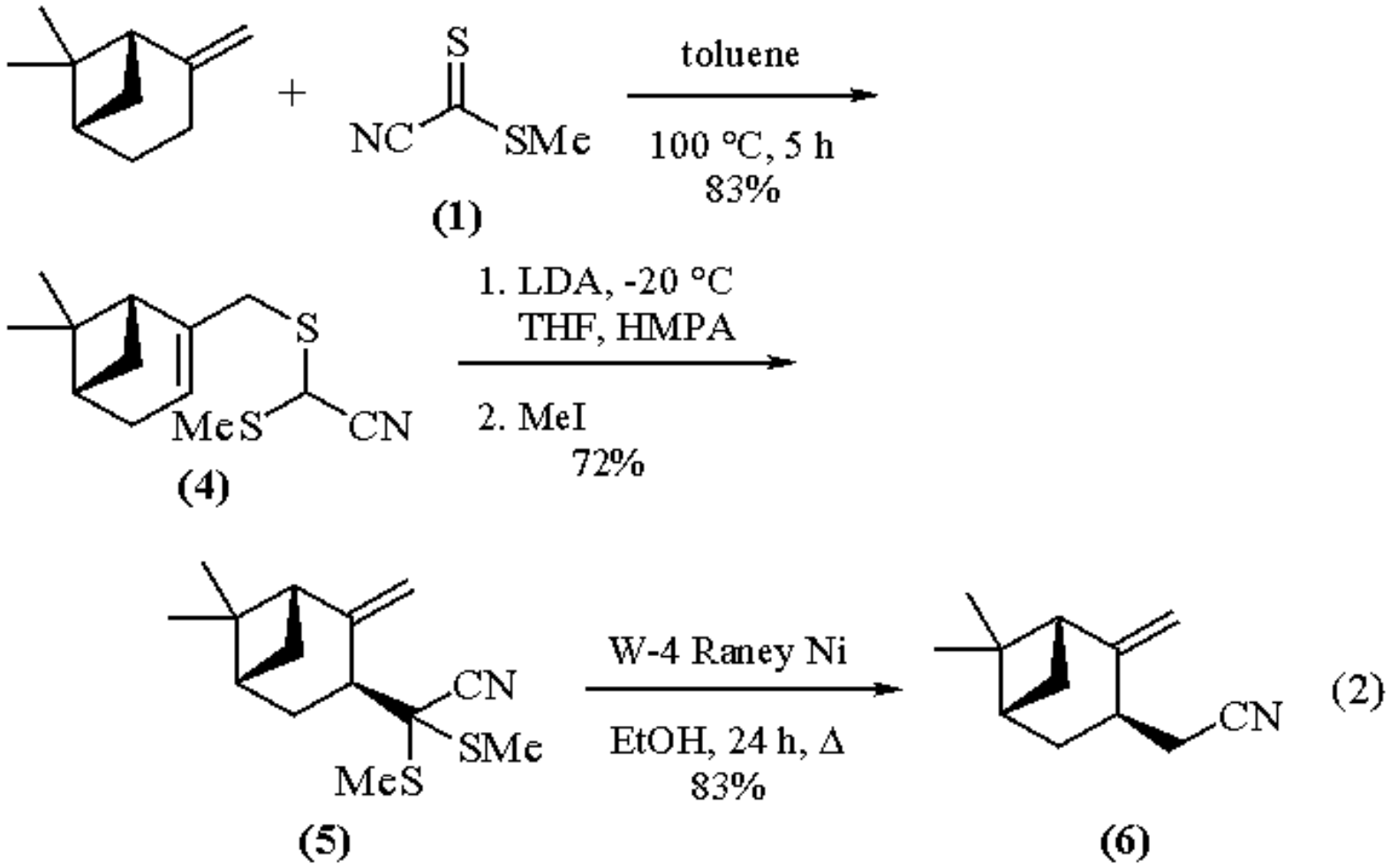

Methyl cyanodithioformate undergoes condensation reactions with amines[7] and dipolar cycloadditions followed by extensive rearrangements with triazolium imide 1,3-dipoles.[8]

---

1. Simmons, H. E.; Blomstrom, D. C.; Vest, R. D. *JACS* **1962**, *84*, 4756.
2. Metzner, P. *S* **1992**, 1185.
3. (a) Vyas, D. M.; Hay, G. W. *CC* **1971**, 1411. (b) Vyas, D. M.; Hay, G. W. *JCS(P1)* **1975**, 180. (c) Vyas, D. M.; Hay, G. W. *CJC* **1971**, *49*, 3755. (d) Vyas, D. M.; Hay, G. W. *CJC* **1975**, *53*, 1362.
4. Friedrich, J. D. *JOC* **1987**, *52*, 2442.
5. Hoederath, W.; Hartke, K. *AP* **1984**, *317*, 938.
6. Snider, B. B.; Hrib, N. J.; Füzesi, L. *JACS* **1976**, *98*, 7115.
7. de Diego, C.; Gómez, E.; Avendaño, C. *H* **1985**, *23*, 649.
8. Butler, R. N.; O'Shea, P. D.; Cunningham, D.; McArdle, P. *JCS(P1)* **1989**, 371.

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Methyl Cyanoformate[1]

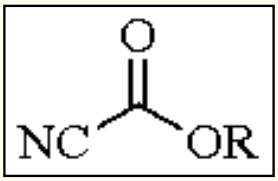

(**1**; R = Me)

[17640-15-2] · $C_3H_3NO_2$ · Methyl Cyanoformate · (MW 85.07) (**2**; R = Et)

[623-49-4] · $C_4H_5NO_2$ · Ethyl Cyanoformate · (MW 99.10) (**3**; R = $PhCH_2$)

[5532-86-5] · $C_9H_7NO_2$ · Benzyl Cyanoformate · (MW 161.17)

(agent for the regioselective methoxycarbonylation of carbanions;[1,2] reacts with organocadmium reagents to form α-keto esters;[3] may function as a dienophile,[4] dipolarophile,[5] or radical cyanating agent[6])

Physical Data: (**1**) mp 26 °C; bp 100-101 °C; *d* 1.072 g cm^{-3}. (**2**) bp 115-116 °C; *d* 1.003 g cm^{-3}. (**3**) bp 66-67 °C/0.6 mmHg; *d* 1.105 g cm^{-3}.

Solubility: sol all common organic solvents; dec by H_2O, alcohols, amines.

Form Supplied in: colorless liquid; methyl cyanoformate, as well as the ethyl and benzyl analogs, is available commercially.

Preparative Methods: small quantities of cyanoformate esters (up to 30 g) may be conveniently prepared from alkyl chloroformates by procedures employing phase-transfer catalysis with either ***18-Crown-6***[7] or ***Tetra-n-butylammonium Bromide***,[8] but several workers have found the products to be unsatisfactory when prepared on a larger scale.

Handling, Storage, and Precautions: store over 4Å molecular sieves; highly toxic; flammable; use in a fume hood.

Regioselective Methoxycarbonylation of Ketones.

Methyl cyanoformate gives generally excellent results in the regiocontrolled synthesis of β-keto esters by the *C*-acylation of preformed lithium enolates (eq 1)[1,2] and is normally superior to the more traditional acylating agents such as acyl halides, anhydrides,[9] and CO_2,[10] partly because these reagents afford variable amounts of *O*-acylated

products.[11] The enolates may be generated in a variety of ways, including direct enolization of ketones with suitable bases (eq 2),[2] liberation from silyl enol ethers and acetates (eq 3),[12] conjugate additions of cuprates to α,β-unsaturated ketones[13] (eq 4),[14] or by the reduction of enones by lithium in liquid ammonia (eq 5).[1,12]

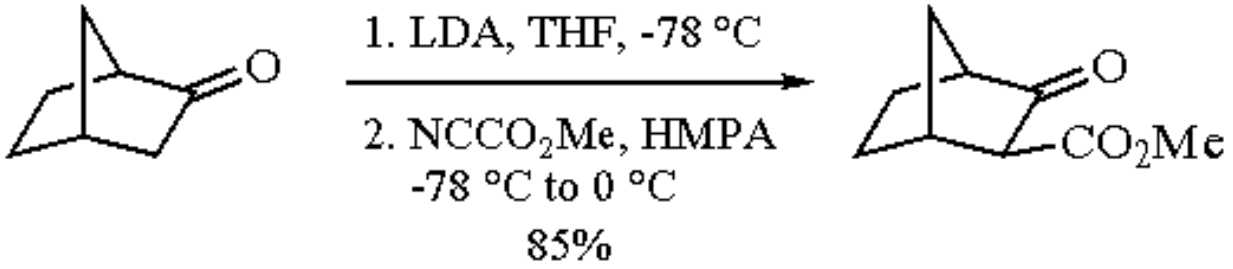

(1)

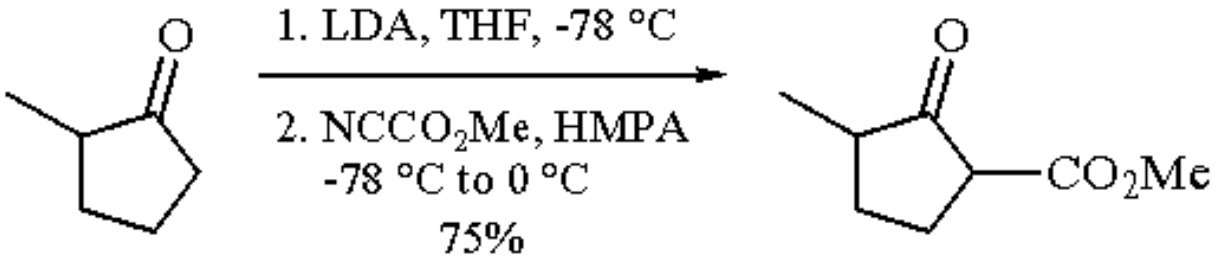

(2)

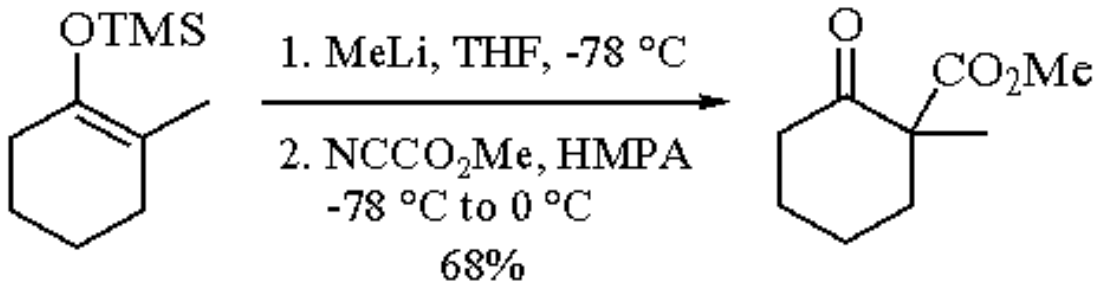

(3)

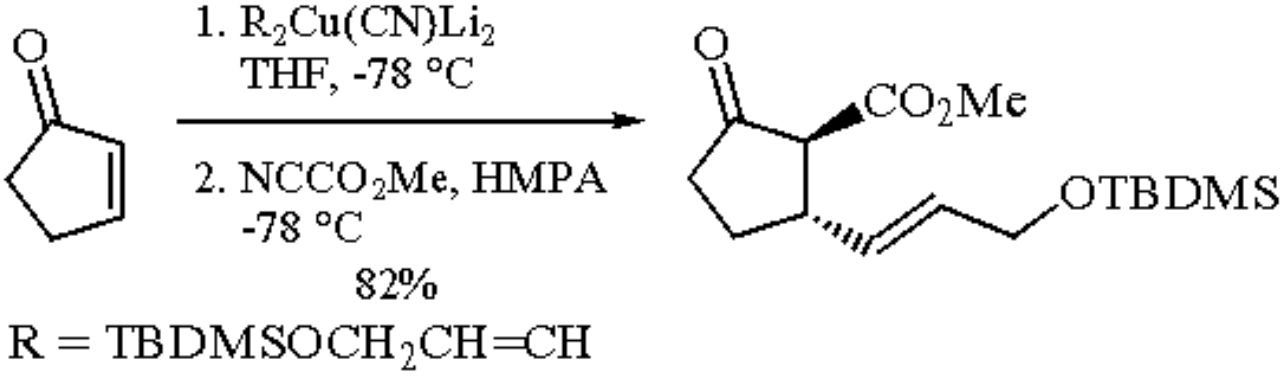

(4)

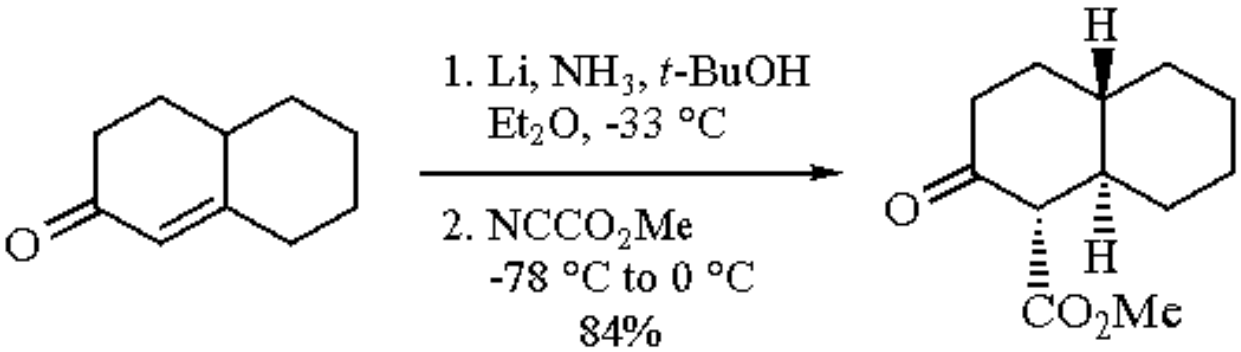

(5)

Lithium enolates derived from sterically unencumbered cyclohexanones undergo preferential axial acylation (eq 6), whereas equatorial acylation is favored with $\Delta^{1(9)}$-2-octalones (eq 7),[12] even in the absence of an alkyl substituent at C-10.[15]

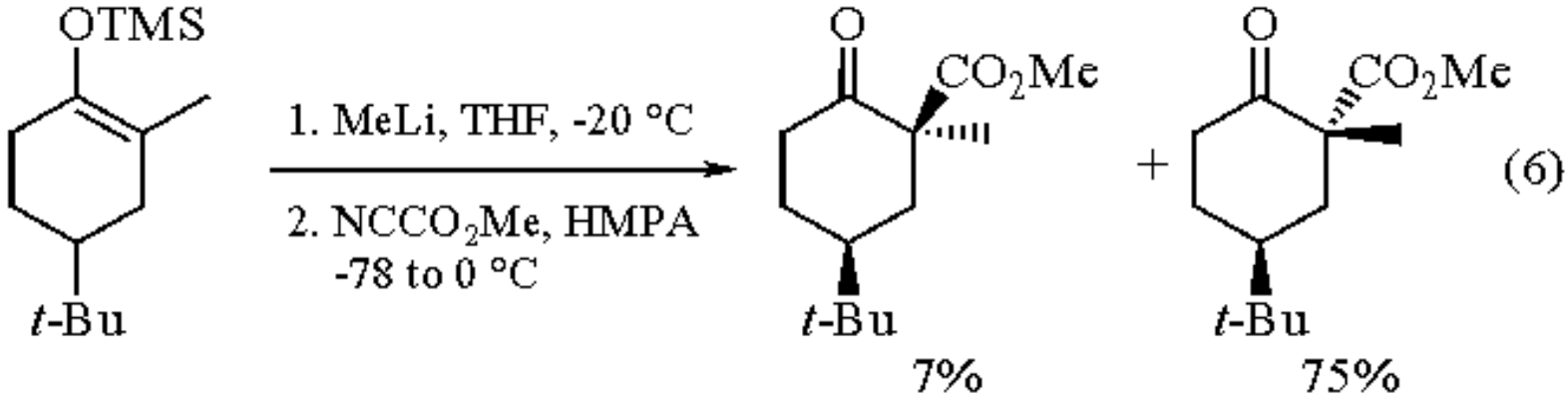

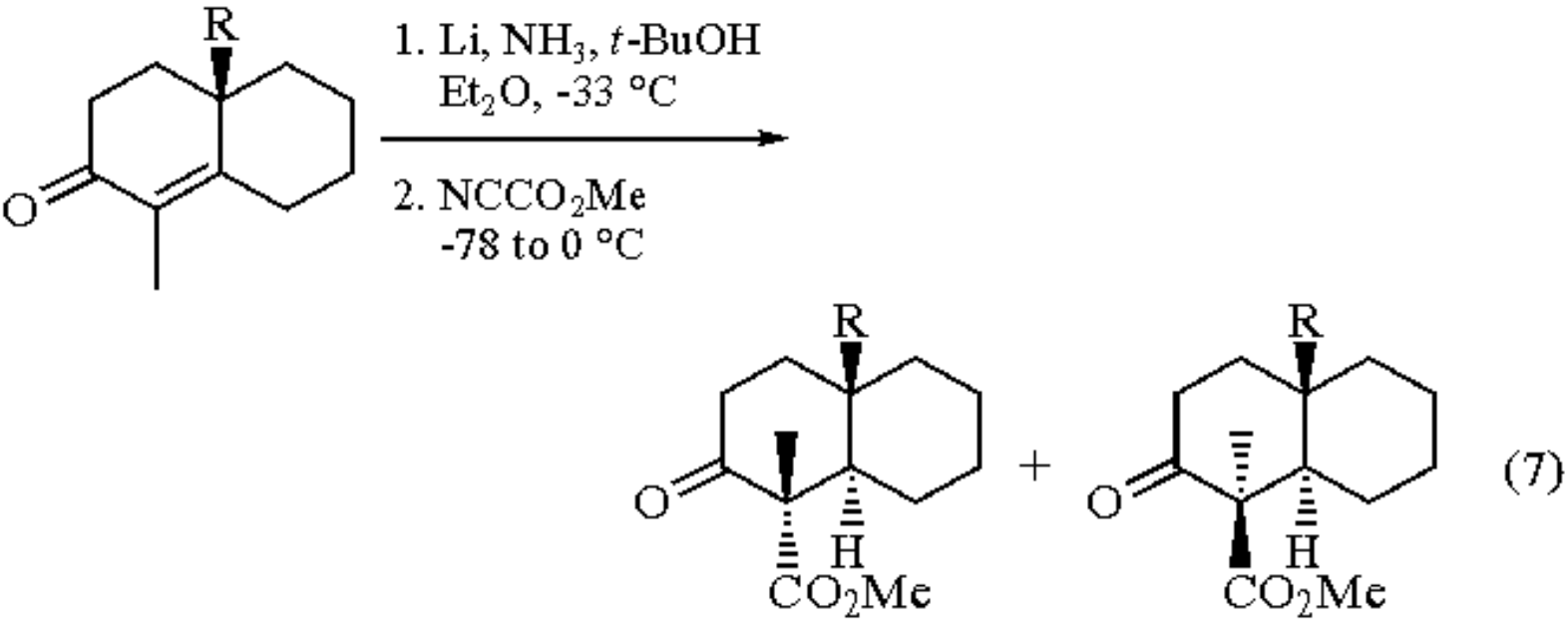

R = H	53%	14%
R = Me	78%	0%

For compounds in which the β-carbon of the enolate is sterically hindered, treatment with methyl cyanoformate may result in variable degrees of *O*-acylation, although this problem may be ameliorated by the use of diethyl ether as the solvent. In several cases a switch from predominantly *O*-acylation in THF to predominant *C*-acylation in diethyl ether has been observed (eqs 8-10).[12]

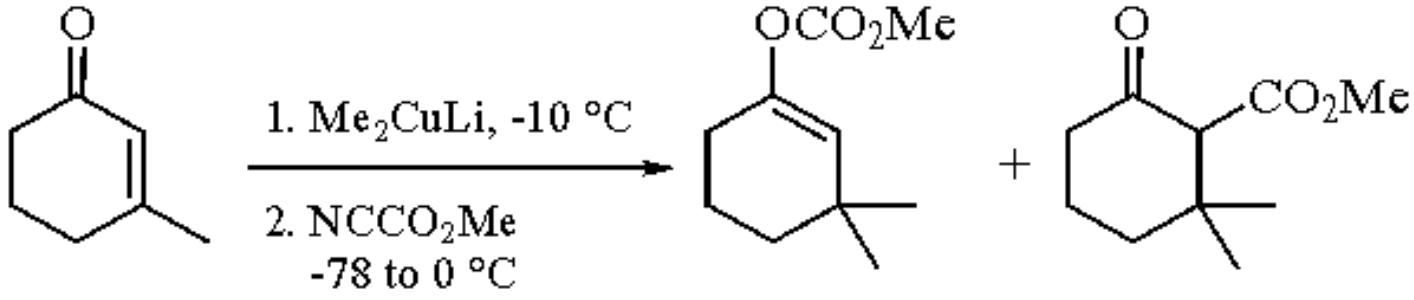

(8)

solvent: THF	87%	0%
solvent: Et_2O	6%	78%

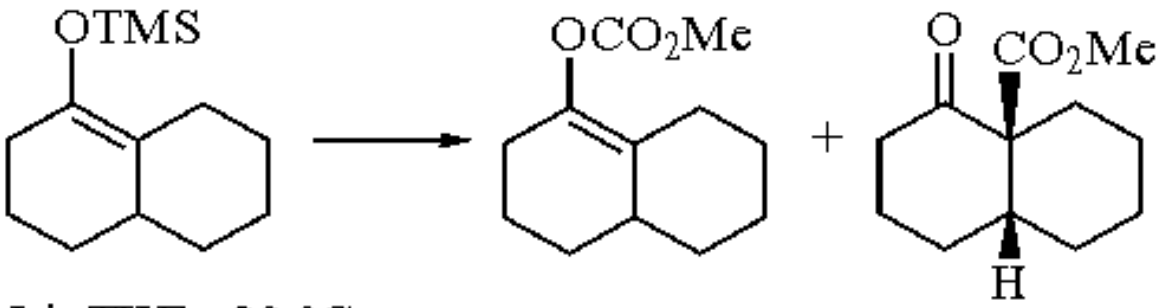

(9)

MeLi, THF, -20 °C $NCCO_2Me$, -78 to 0 °C	78%	0%
BuLi, Et_2O, -10 °C $NCCO_2Me$, -78 to 0 °C	9%	68%

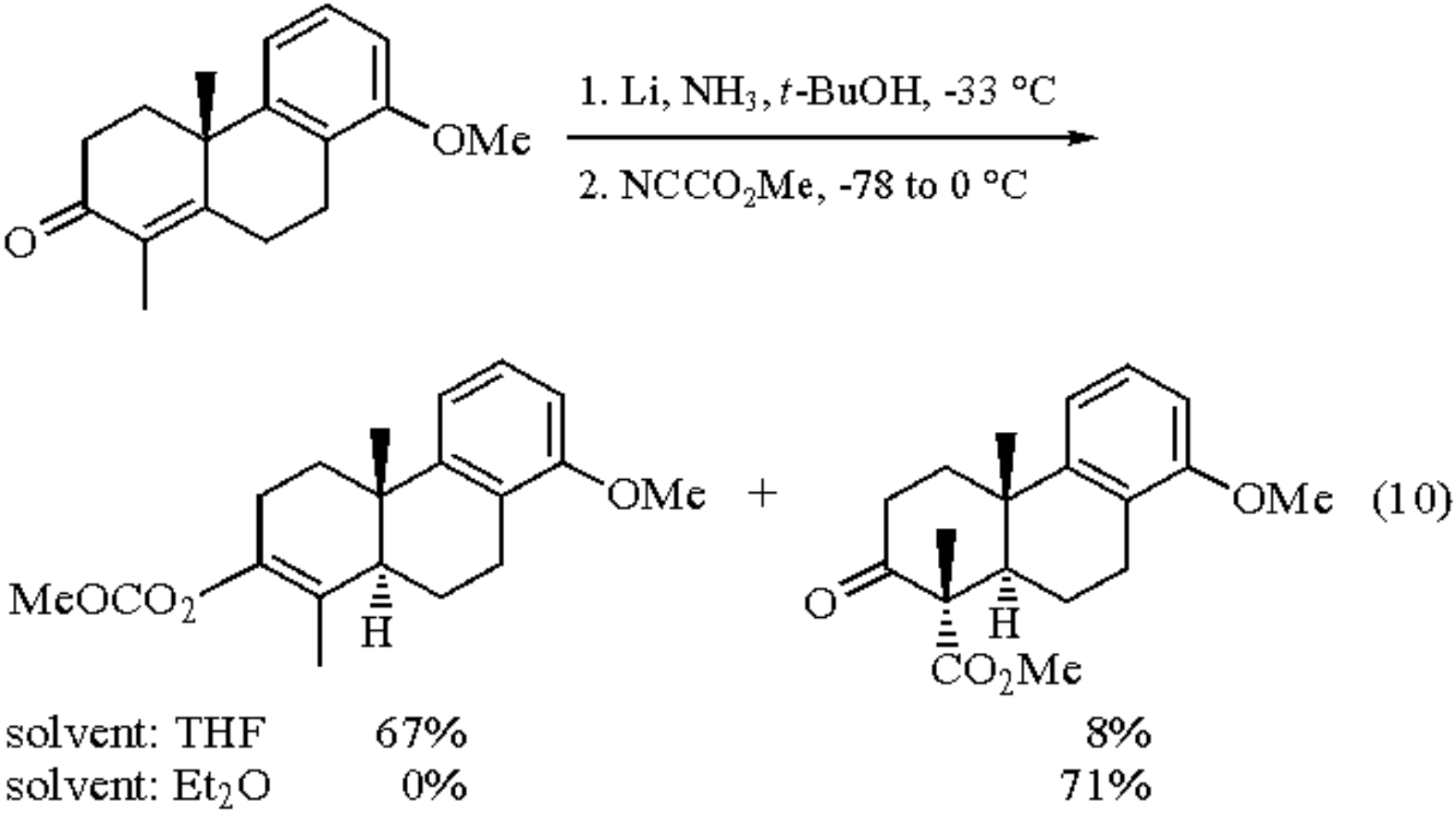

A comparative study of lithium, sodium, and potassium enolates indicated that the lithium derivatives reacted most satisfactorily.[2] There may be substrates for which the thermodynamic enolates are required, however, and the sodium and potassium enolates may therefore be selected. Good results have been reported with these intermediates (eqs 11 and 12), although the latter afford significant amounts of *O*-acylated products.[16,17] Quite apart from the issue of regioselectivity, the cyanoformate-based procedure is exceptionally reliable and makes it possible to prepare β-keto esters from ketones under especially mild conditions. It is not only the method of choice with sensitive substrates,[16] but it will often ensure superior results with more robust compounds as well.

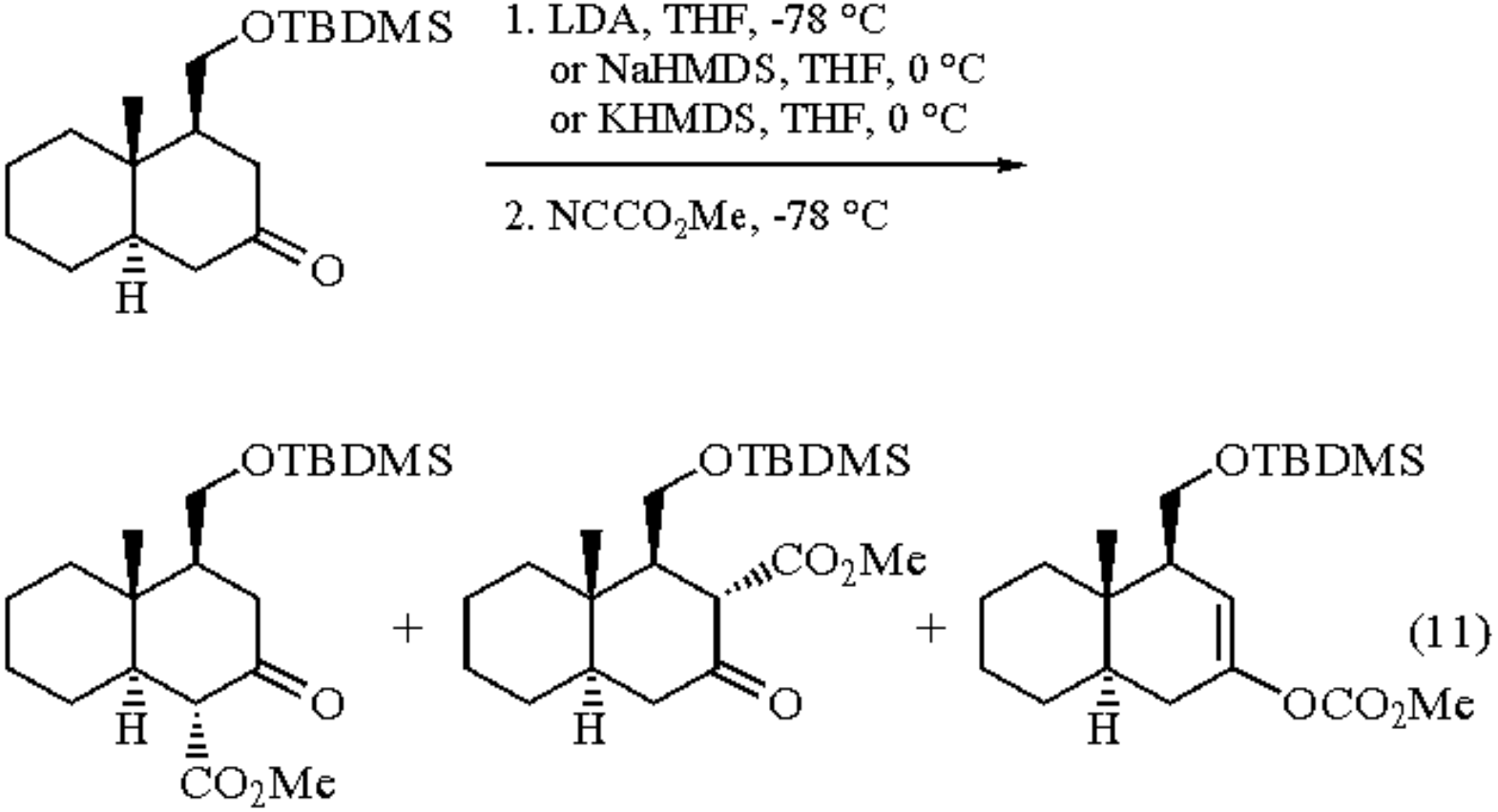

LDA	4:1:0
NaHMDS	1:7:0
KHMDS	0:1:1.5

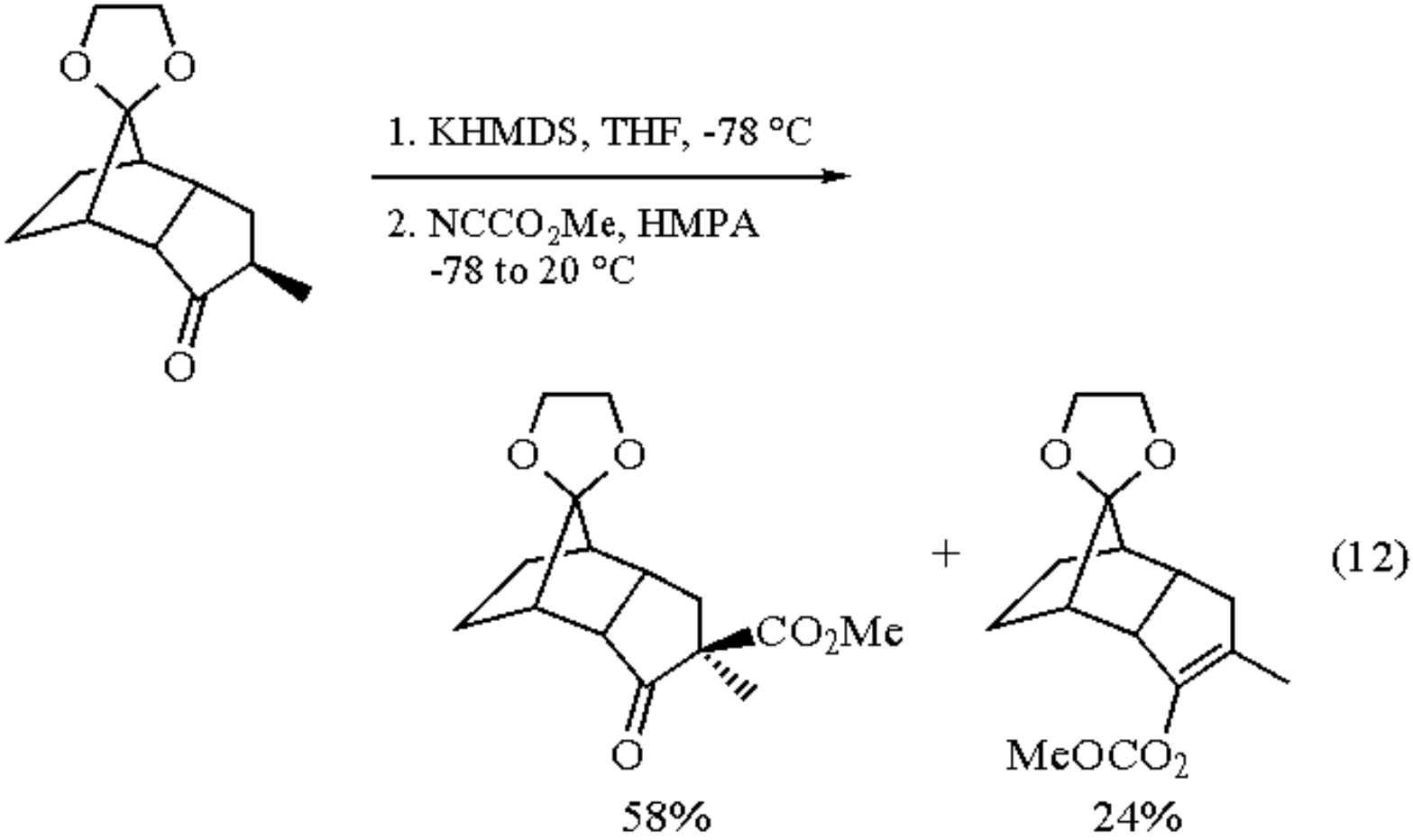

(12)

Methoxycarbonylation of Miscellaneous Carbon Acids.

The title reagent has also been applied to the methoxycarbonylation of esters (eq 13),[18] lactones (eq 14),[19] phosphonates (eq 15),[20] imines (eq 16),[21] and the *N*-acylation of lactams (eq 17).[22]

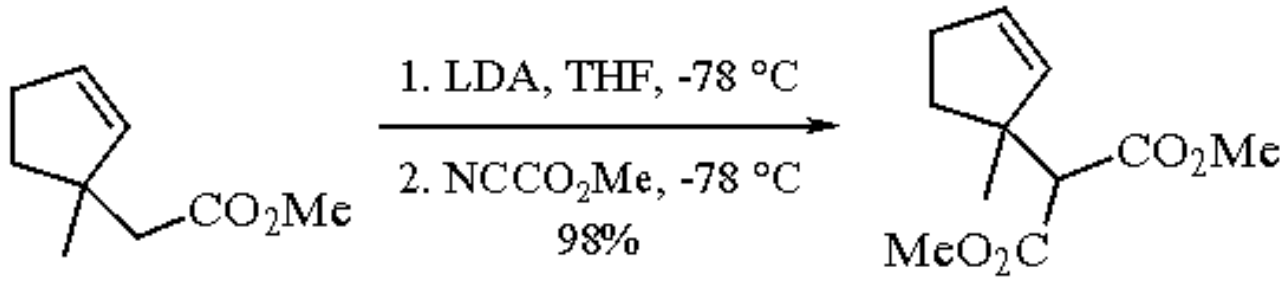

(13)

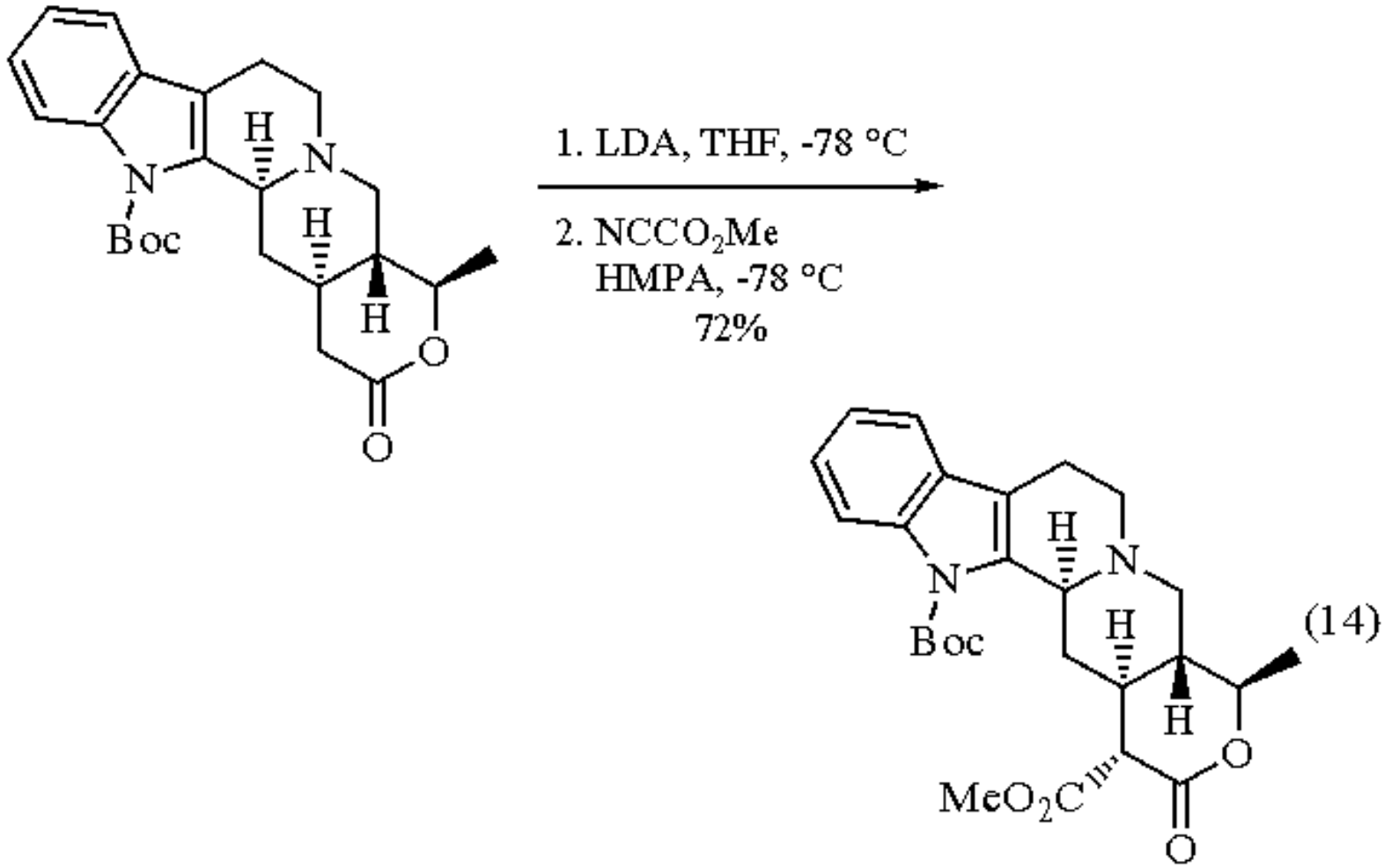
1. LDA, THF, -78 °C
2. NCCO2Me
HMPA, -78 °C
72%
Boc
MeO2C
(14)

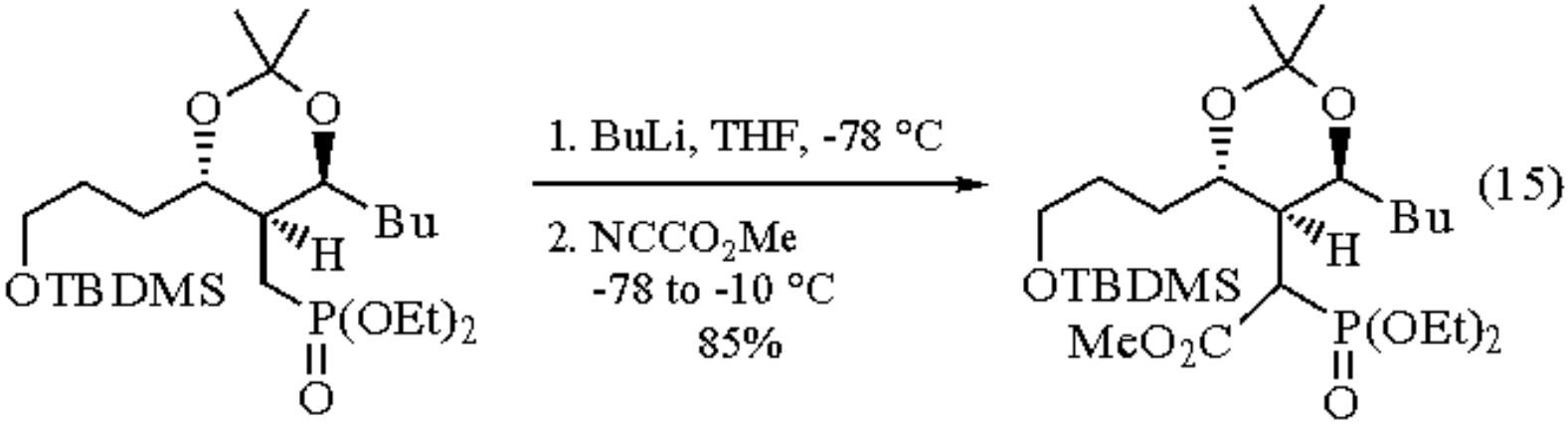
1. BuLi, THF, -78 °C
2. NCCO2Me
-78 to -10 °C
85%
OTBDMS
Bu
P(OEt)2
MeO2C
(15)

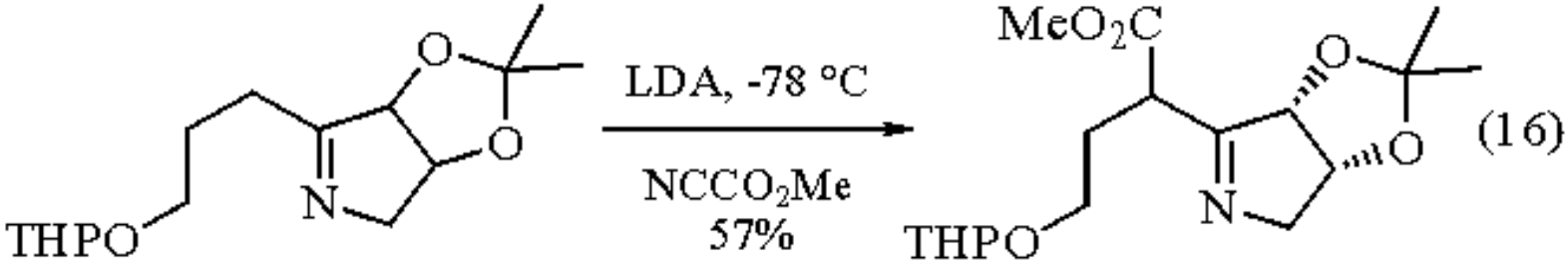
LDA, -78 °C
NCCO2Me
57%
THPO
MeO2C
(16)

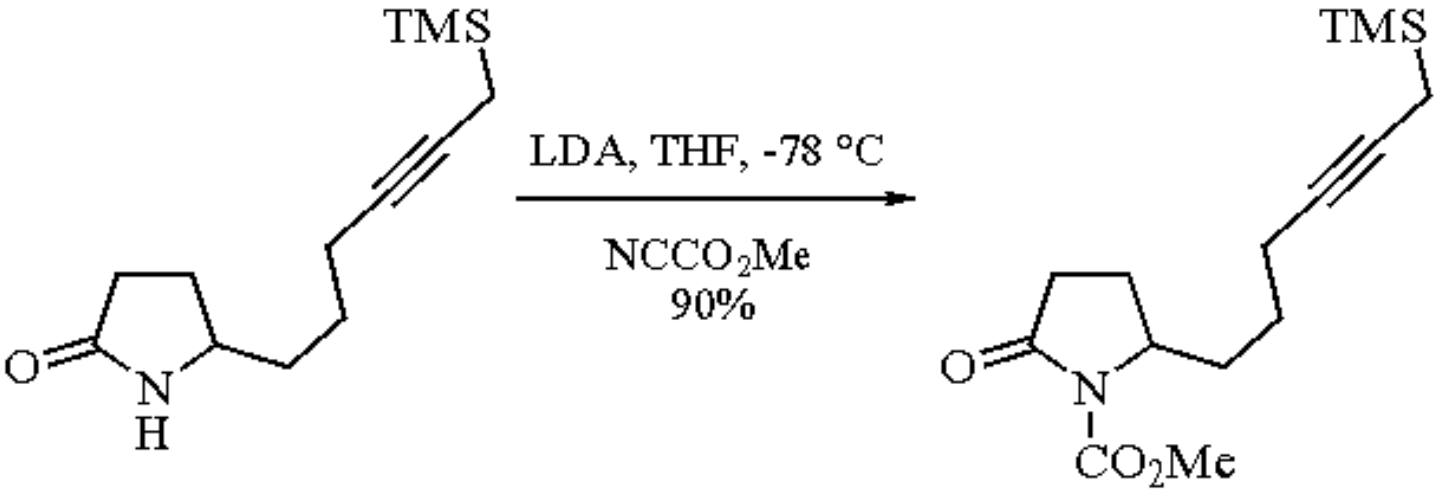

(17)

Higher Alkyl Cyanoformates.

A range of other alkyl cyanoformates has been successfully utilized for the acylation of enolate anions, including ethyl,[23] allyl,[24] benzyl,[25] and *p*-methoxybenzyl,[26] but not *t*-butyl cyanoformate, which appears to be insufficiently reactive. Enantiomerically enriched cyanoformates derived from (+)-menthol, (-)-borneol, and the Oppolzer alcohol were reported to furnish good chemical yields, but the level of enantioselectivity was disappointingly low (eq 18).[27]

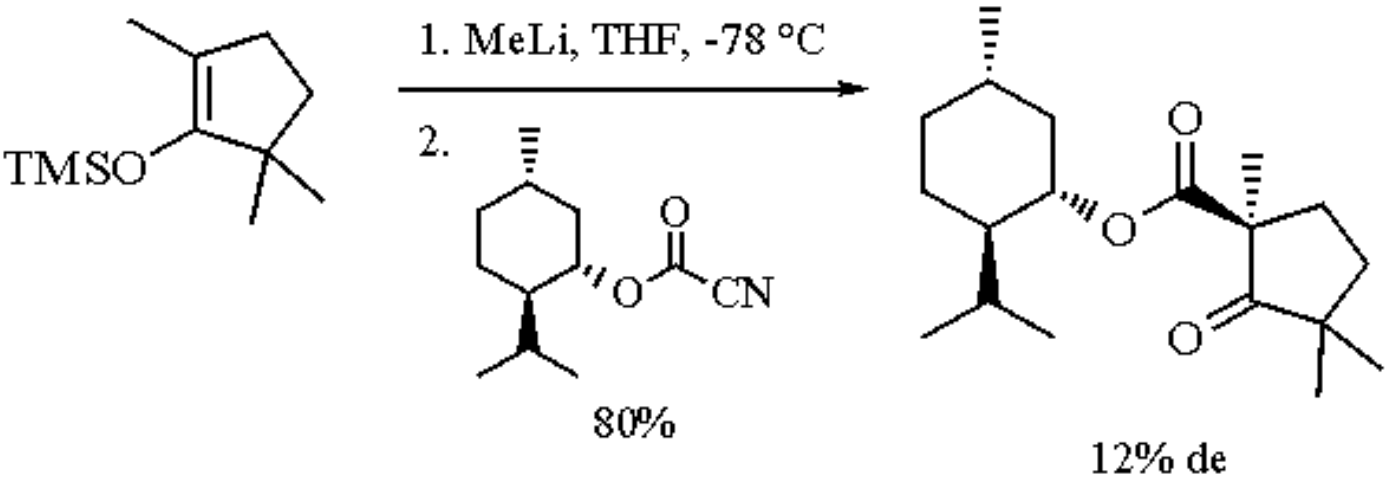

(18)

Additions to the Nitrile Group.

Ethyl cyanoformate reacts with organocadmium reagents to afford α-keto esters (eq 19),[3] and with malonate esters, β-keto esters, and other active methylene compounds to give α-aminoacrylates (eq 20).[28] Both processes require catalysis with Lewis acids, of which ***Zinc Chloride*** has proven to be the most effective.

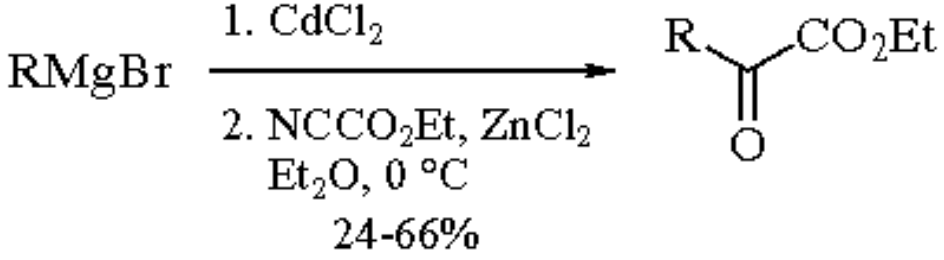

(19)

R = Ph, *i*-Pr, *s*-Bu, cyclohexyl, cyclopentyl

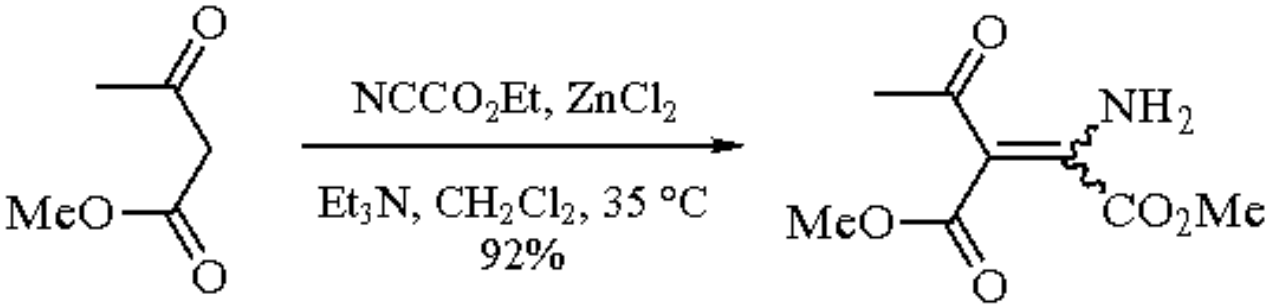

(20)

Cycloadditions.

Methyl and ethyl cyanoformate have been reported to undergo [4 + 2] cycloadditions, e.g. with cyclopentadienones[4] and 2-alkyl-1-ethoxybuta-1,3-dienes to form pyridines (eq 21),[29] and with cyclobutadienes to form Dewar pyridines (eq 22).[30] Ethyl cyanoformate is also an effective dipolarophile, undergoing 1,3-dipolar addition to azides (eq 23)[31] and cyclic carbonyl ylides (eq 24).[5]

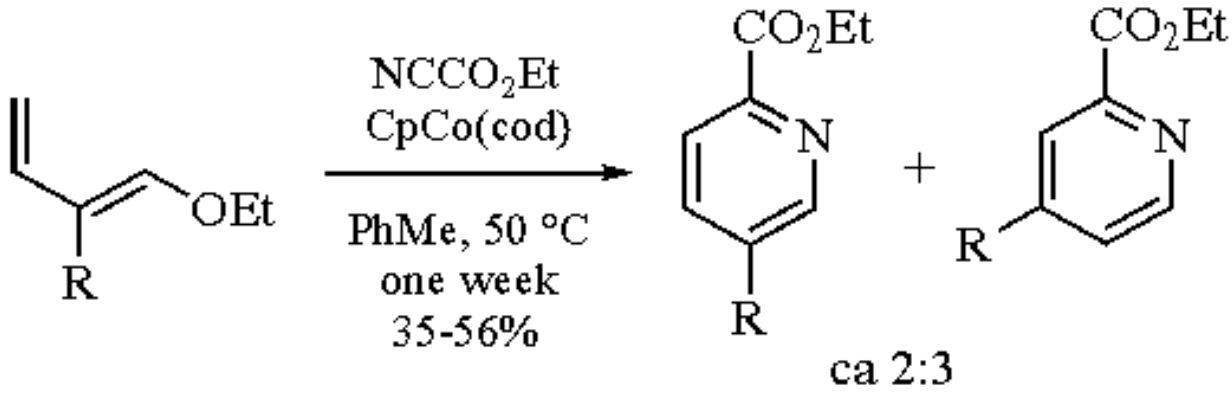

(21)

R = Me, Et, Pr, *i*-Pr, Bu, C_5H_{11}

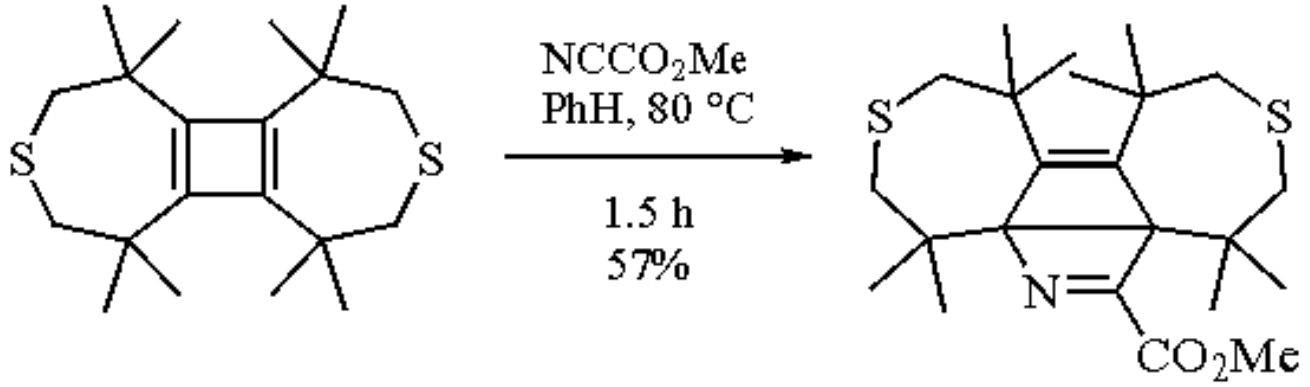

(22)

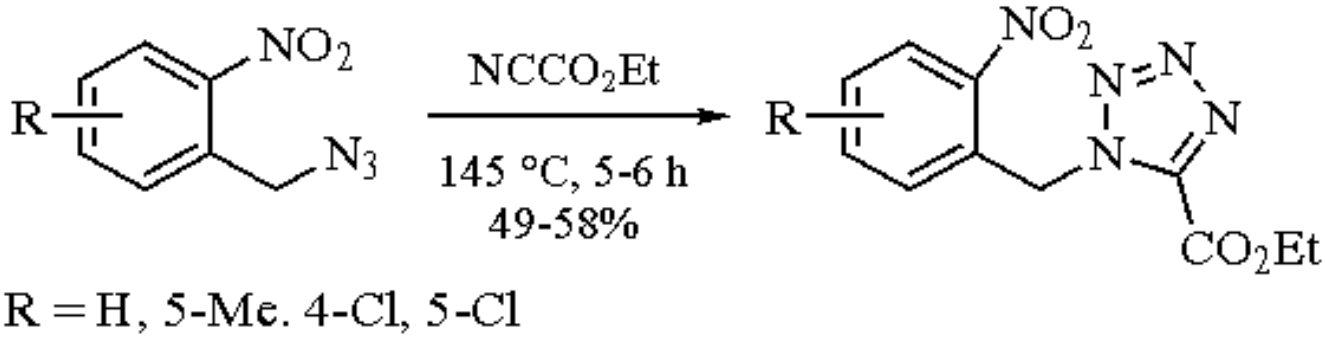

(23)

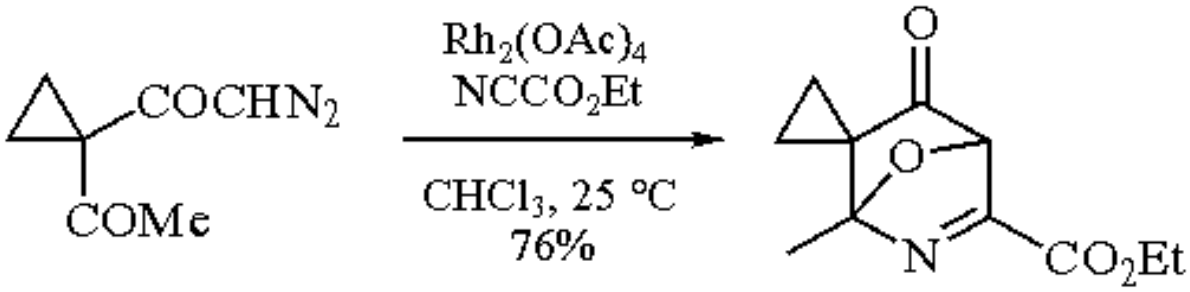

(24)

Radical Cyanation.

The peroxide-initiated radical cyanation of cyclohexane and 2,3-dimethylbutane with methyl cyanoformate has been carried out in 72% and 77% yield, respectively.[6]

Related Reactions.

β-Keto ester formation from ketones may be achieved directly with dialkyl carbonates[32] and dialkyl dicarbonates,[33] or indirectly with dialkyl oxalates,[34] methyl magnesium carbonate,[35] and ethyl diethoxyphosphinyl formate.[36] Regiocontrol is problematical, however, and is more reliably effected by trapping enolates with carbon dioxide,[10] carbon disulfide,[37] or carbon oxysulfide[38] followed by methylation. In the latter cases, the dithio and thiol esters are converted into the parent carboxy esters by mercury(II)-catalyzed hydrolysis. The chemistry of acyl cyanides, but excluding cyanoformates, has been the subject of several reviews.[39]

Related Reagents.

Acetyl Cyanide; ***Carbon Dioxide***; ***Carbon Oxysulfide***; ***N,N´-Carbonyldiimidazole***; ***Diethyl Carbonate***; ***Methyl Chloroformate***; ***Methyl Magnesium Carbonate***.

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(*R*)-4-Methylcyclohexylidenemethylcopper

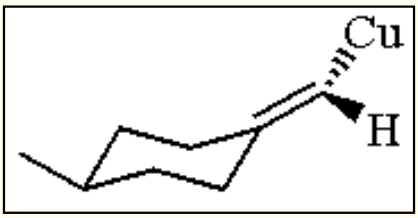

[60164-96-7] · $C_8H_{13}Cu$ · (*R*)-4-Methylcyclohexylidenemethylcopper · (MW 172.76)

(optically active vinylcopper reagent;[1] useful in stereospecific synthesis of axially dissymmetric dienes and alkenes[1,2])

Solubility: dark black suspensions of the reagent (0.26 M) have been prepared in THF-pentane.[1,2]

Preparative Methods: (-)-(*R*)-(4-methylcyclohexylidene)methyl bromide[3,4] in THF is treated with ***s-Butyllithium*** in pentane at -75 °C to give a solution of (*R*)-4-methylcyclohexylidenemethyllithium. Addition of 1 equiv of ***Copper(I) Iodide*** to this mixture, followed by stirring at -35 °C for 30 min, gives a dark black suspension of (*R*)-4-methylcyclohexylidenemethylcopper (eq 1).[2] (*S*)-4-Methylcyclohexylidenemethylcopper may be prepared from (+)-(*S*)-(4-methylcyclohexylidene)methyl bromide[3,4] using a similar procedure.[1,2]

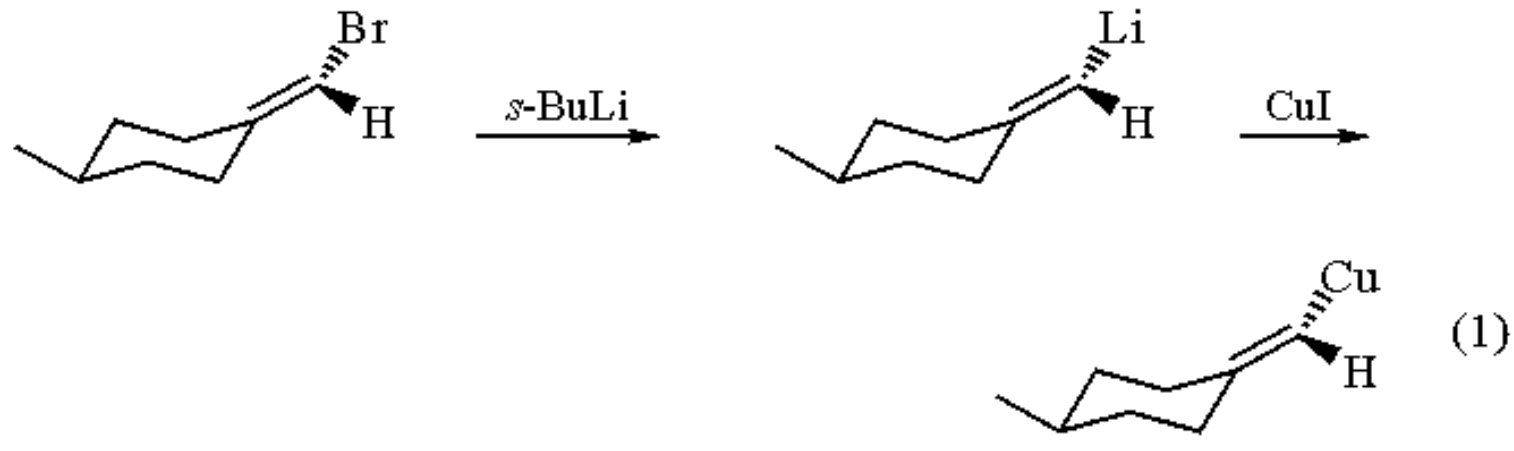

Handling, Storage, and Precautions: the reagent is prepared under inert gas atmosphere at temperatures of -35 °C or below. Upon heating to rt, or exposure to oxygen, the reagent decomposes with formation of bis(4-methylcyclohexylidene)ethane. Use in a fume hood.

Oxidative Coupling: Synthesis of Optically Active Dienes of Biaxial Dissymmetry.

Alkenylcopper reagents undergo thermal or oxidative coupling to give 1,3-dienes with retention of configuration at the

alkenic bond.[5] Passage of a stream of oxygen through a solution of (*R*)-4-methylcyclohexylidenemethyl-copper affords (*aR*,*aR*)-bis(4-methylcyclohexylidene)ethane in 30% yield (eq 2).[1,2] The dissymmetry of the latter compound results from the combination of two chiral alkenic axes which are oriented in a planar transoid conformation. The chiroptical properties of this and closely related planar acyclic 1,3-dienes have been reported.[2,6] Additional members of this novel class of optically active dienes could be synthesized by oxidative coupling of analogous chiral vinylcopper reagents.

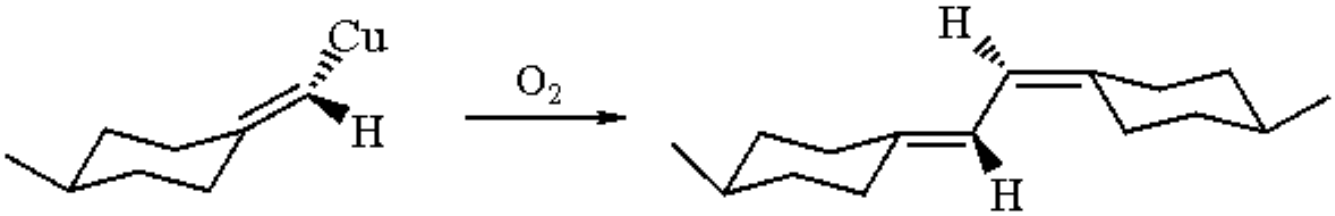

(2)

Alkylation: Formation of Optically Active 4-Methylcyclohexylidenealkanes.

Alkenylcopper reagents can be alkylated by treatment with alkyl halides and other electrophiles.[7] Reaction of (*S*)-4-methylcyclohexylidenemethylcopper (enantiomer of the title reagent) with ***Iodomethane*** gives (+)-(*S*)-4-(methylcyclohexylidene)ethane with 98% retention of configuration (eq 3).[1,2] Alkylation of (*R*)-4-methylcyclohexylidenemethylcopper with methyl iodide and other alkyl halides is expected to show similar stereospecificity.

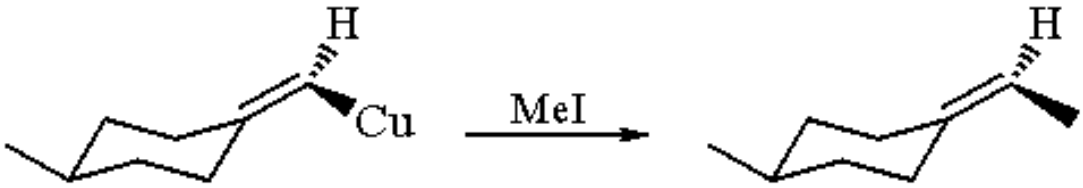

(3)

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2-Methyl-1,3-cyclopentanedione[1]

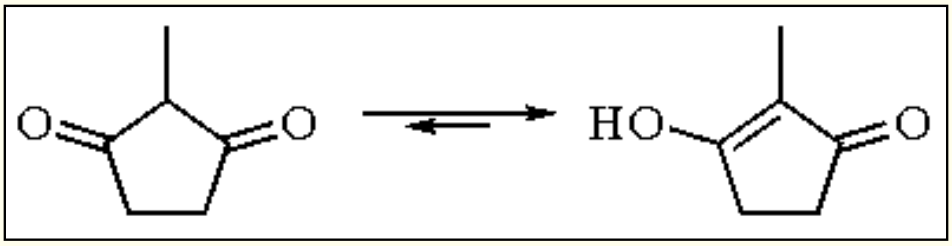

[765-69-5] · $C_6H_8O_2$ · 2-Methyl-1,3-cyclopentanedione · (MW 112.14)

(building block for the total synthesis of 19-norsteroids[2] and many other naturally occurring cyclopentanoids;[1] precursor for 2,2-, 2,4-, and 2,5-dialkylated cyclopentanediones[1])

Alternate Name: MCPD.

Physical Data: mp 214-216 °C.

Solubility: sparingly sol cold H_2O, MeOH, EtOH; insol cold Et_2O, benzene, toluene; sol boiling H_2O.

Form Supplied in: colorless solid; commercially available.

Preparative Methods: $AlCl_3$-promoted acylation of succinic acid with propanoyl chloride in nitromethane[3] or cyclization of 4-oxohexanoic acid[4] or its esters.[5]

Handling, Storage, and Precautions: the pure reagent is a stable compound, which is reputed to be of low toxicity.

Introduction.

2-Methyl-1,3-cyclopentanedione (**1a**) is completely enolized and therefore has the structure of 3-hydroxy-2-methyl-2-cyclopenten-1-one (**1b**).[6]

Reactions with Nucleophiles at the Carbonyl Group.

With alcohols in the presence of acidic catalysts (**1**) forms 3-alkoxy-2-methyl-2-cyclopenten-1-ones (enol ethers).[7] With primary or secondary amines the corresponding 3-amino-2-methyl-2-cyclopenten-1-ones (enamino ketones) are obtained.[8] These derivatives of (**1**) afford 2,3-dialkylated 2-cyclopenten-1-ones in reactions with organolithium or Grignard reagents (eq 1).[1]

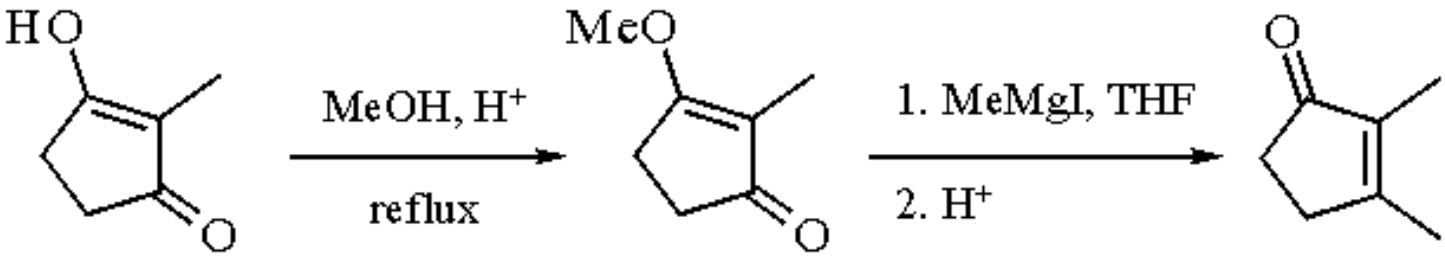

(1)

Reactions with Electrophiles at C-2.

Diketone (**1**) reacts with the tertiary allyl alcohol (**2**) to give the secosteroid (**3**), which represents a key intermediate in the estrone synthesis of Torgov (eq 2).[9]

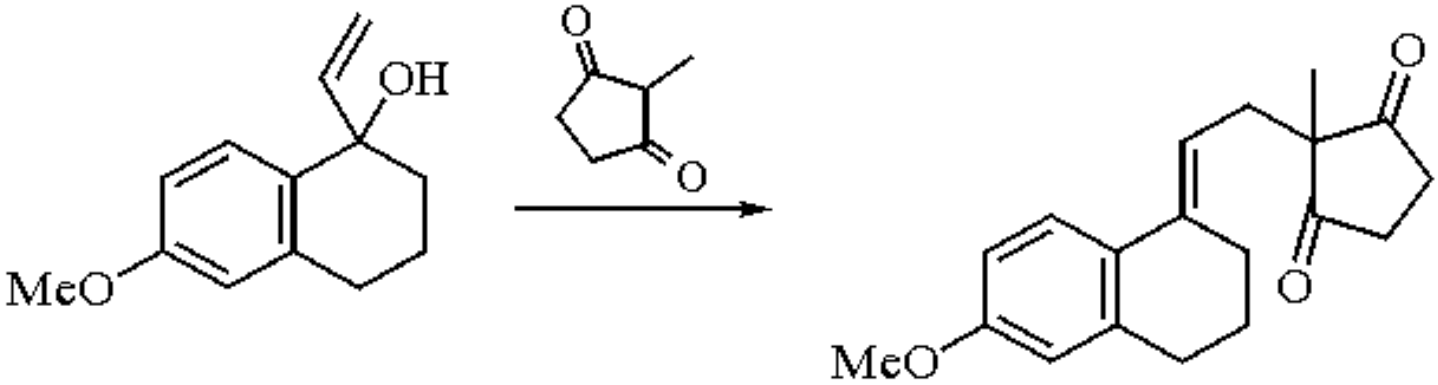

(2)

(2) **(3)**

Diketone (**1**) adds in a Michael reaction to α,β-unsaturated carbonyl compounds, acrylonitrile, nitroalkenes, and Mannich bases, forming 2,2-disubstituted 1,3-cyclopentanediones.[1,10] The thus available triketone (**4**) affords the (*S*)-diketone (**5**) in a highly enantioselective aldol condensation catalyzed by (*S*)-proline (eq 3).[11,12]

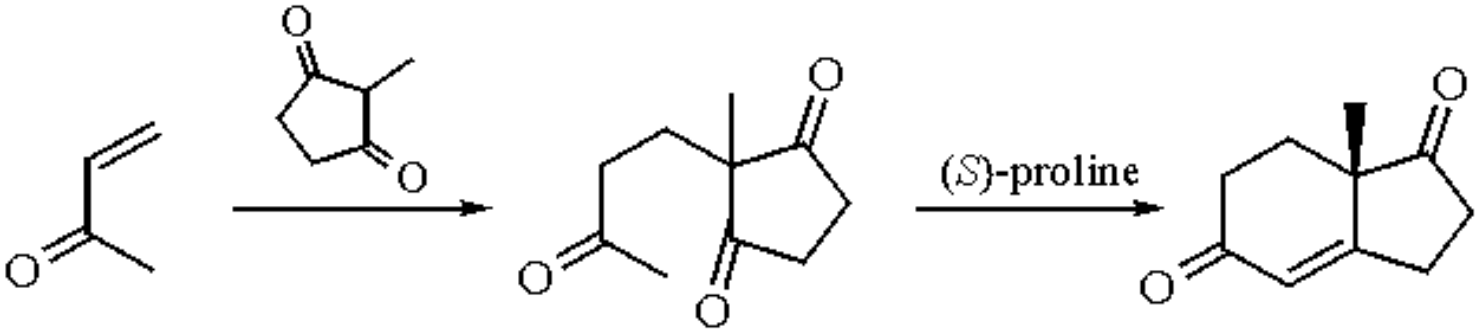

(3)

(4) **(5)**

The palladium(0)-catalyzed reaction of allyl acetate with (**1**) affords exclusively the 2-allylated compound (eq 4),[13] whereas allyl, propargyl, and benzyl halides, as well as alkyl bromoacetates, react with the potassium or sodium salt of (**1**) to form mixtures of *C*- and *O*-alkylated products. In water as solvent the *C*-alkylation is favored; in DMF or DMSO the *O*-alkylation predominates.[14] 2,2-Disubstituted 1,3-cyclopentanediones are easily cleaved by aqueous sodium hydroxide in a retro aldol reaction to 5-substituted 4-oxoalkanoic acids (eq 4).[15]

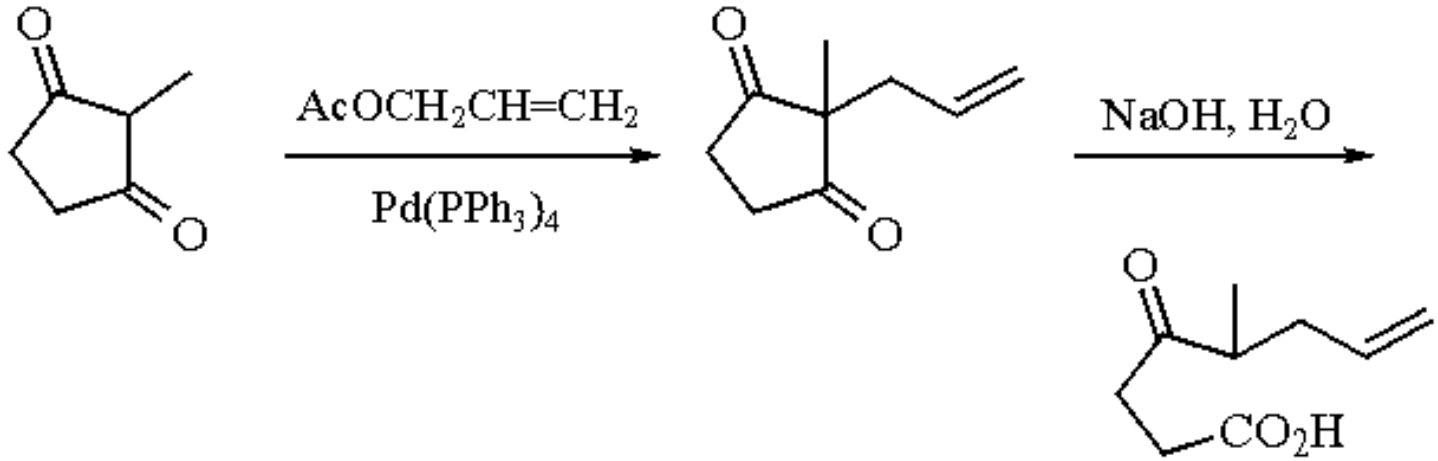

(4)

Reactions with Electrophiles at the Enolic Hydroxy Group.

The enolic hydroxy group of (**1**) is substituted by chloro, sulfonyloxy, diethoxyphosphinyloxy, or trimethylsilyloxy groups by reaction with ***Oxalyl Chloride***, sulfonyl chlorides, ***Diethyl Phosphorochloridate***, and ***Hexamethyldisilazane***, respectively.[1] The β-substituted enones obtained serve as intermediates for many further reactions (eq 5).[1]

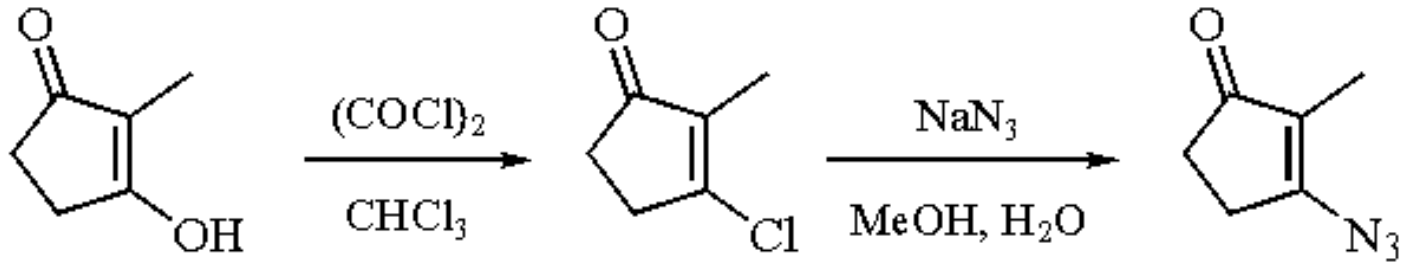

(5)

Reactions with Electrophiles at C-4 and C-5.

Enol ethers and enamines of (**1**) are versatile intermediates for further functionalization. ***Lithium Diisopropylamide*** deprotonates these compounds at C-5,[16,17] whereas ***Lithium Hexamethyldisilazide*** removes a proton at C-4.[17-19] The monoanions thus obtained can be selectively alkylated in the corresponding positions (eq 6). By repeating the deprotonation and subsequent alkylation, 2,4,5-trialkylated 1,3-cyclopentanedione derivatives are available.[18]

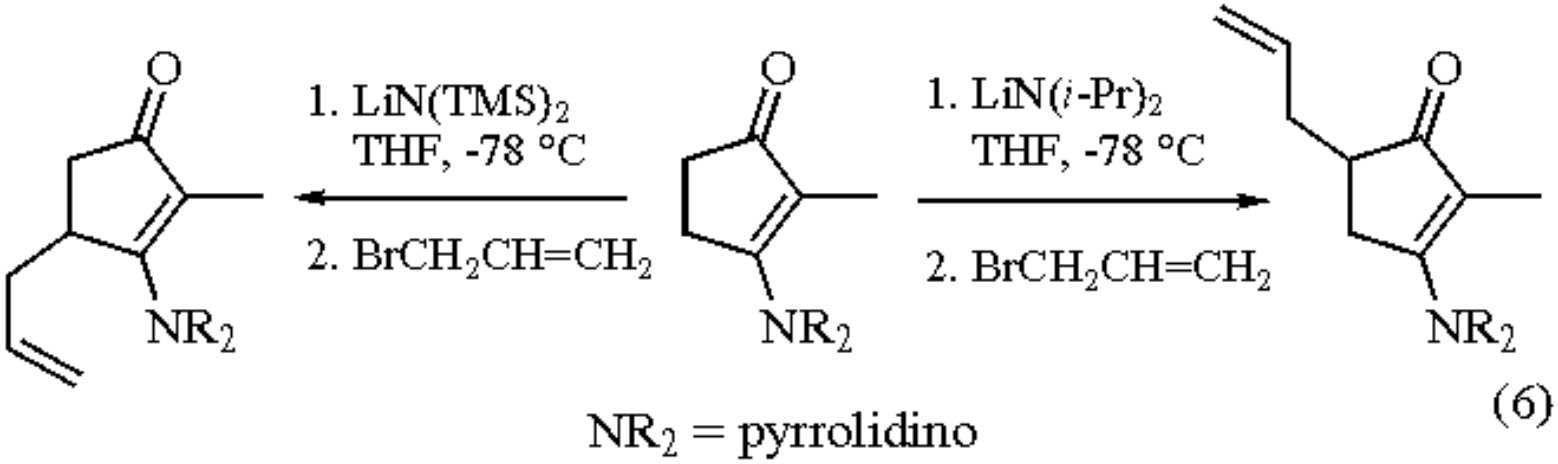

The reactions reported here for (**1**) are typical also for its higher alkyl homologs.

Related Reagents.

1,3-Cyclohexanedione; ***1,3-Cyclopentanedione***.

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Methyl Diazoacetate[1]

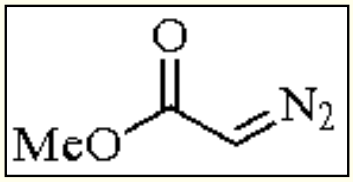

[6832-16-2] · $C_3H_4N_2O_2$ · Methyl Diazoacetate · (MW 100.09)

(cyclopropanation of alkenes;[2,3] cyclopropenation of alkynes;[4] addition to aromatic substrates;[5,6] insertion into polar X-H bonds;[7] condensation with carbonyls;[8] 1,3-dipolar cycloaddition with enamines[9] and alkynes,[10] yielding substituted pyrazolines and pyrazoles)

Physical Data: bp 39-43 °C/10 mmHg.

Solubility: sol diethyl ether, dichloromethane, chloroform, benzene.

Preparative Method: from methyl glycinate hydrochloride and sodium nitrite upon treatment with a 5% solution of sulfuric acid.[11]

Handling, Storage, and Precautions: extreme caution should be exercised in handling methyl diazoacetate since it is thermally unstable and has been found to detonate if heated rapidly or overheated (do not expose to temperatures >50 °C), emitting toxic fumes of NO_x. Diazo esters are also toxic and should be handled in a well-ventilated fume hood.

Cyclopropanation.

Under catalytic conditions, methyl diazoacetate readily forms an ester carbenoid which adds to a variety of alkenes, yielding cyclopropyl esters. ***Dirhodium(II) Tetraacetate*** effectively catalyzes the addition of methyl diazoacetate to *cis*-2-octene.[2] Substituted conjugated dienes can be selectively cyclopropanated with methyl diazoacetate.[12] The observed regio- and stereoselectivity is determined by the choice of catalyst and the electronic characteristics of the diene. The enantioselective cyclopropanation of an alkene with methyl diazoacetate can be achieved with the use of a chiral catalyst.[13] Methyl diazoacetate reacts under copper catalysis with the trimethylsilyl enol ether of cyclopentanone to give a silyloxycyclopropane. Treatment with a fluoride source yields a 1,4-keto ester (eq 1).[14,15]

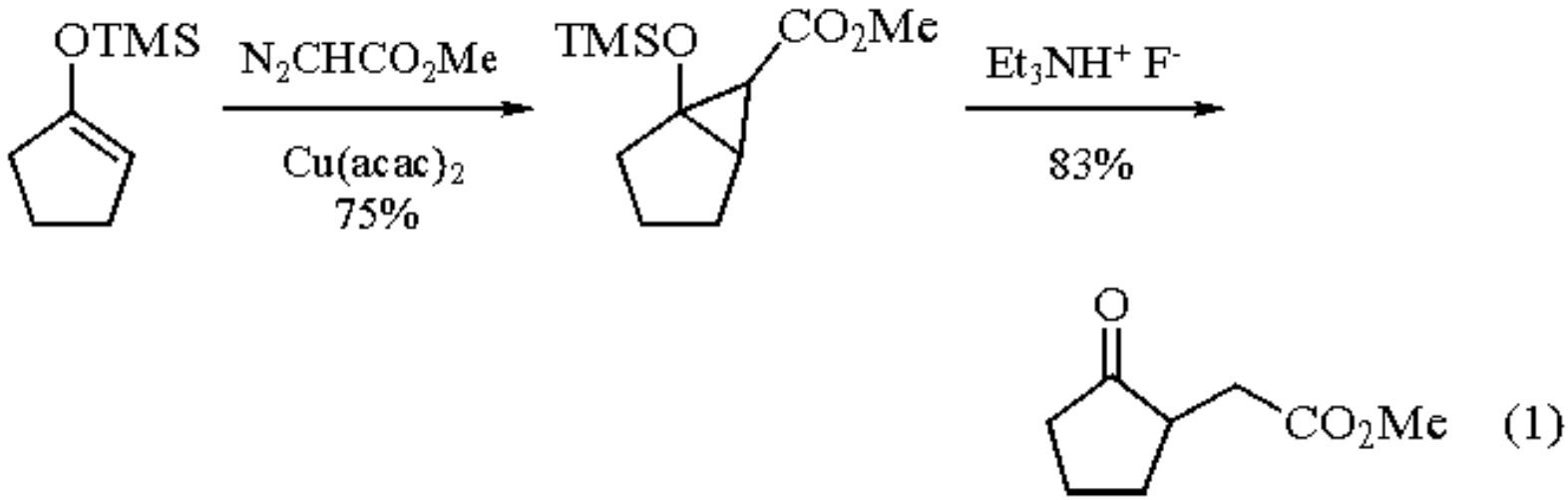

2-(Trimethylsilyloxy)buta-1,3-diene can be cyclopropanated in a regioselective manner with methyl diazoacetate and ***Copper(II) Acetylacetonate***. Subsequent nucleophilic addition of methanol yields methyl 6-methoxy-4-oxohexanoate in excellent yield (eq 2).[16]

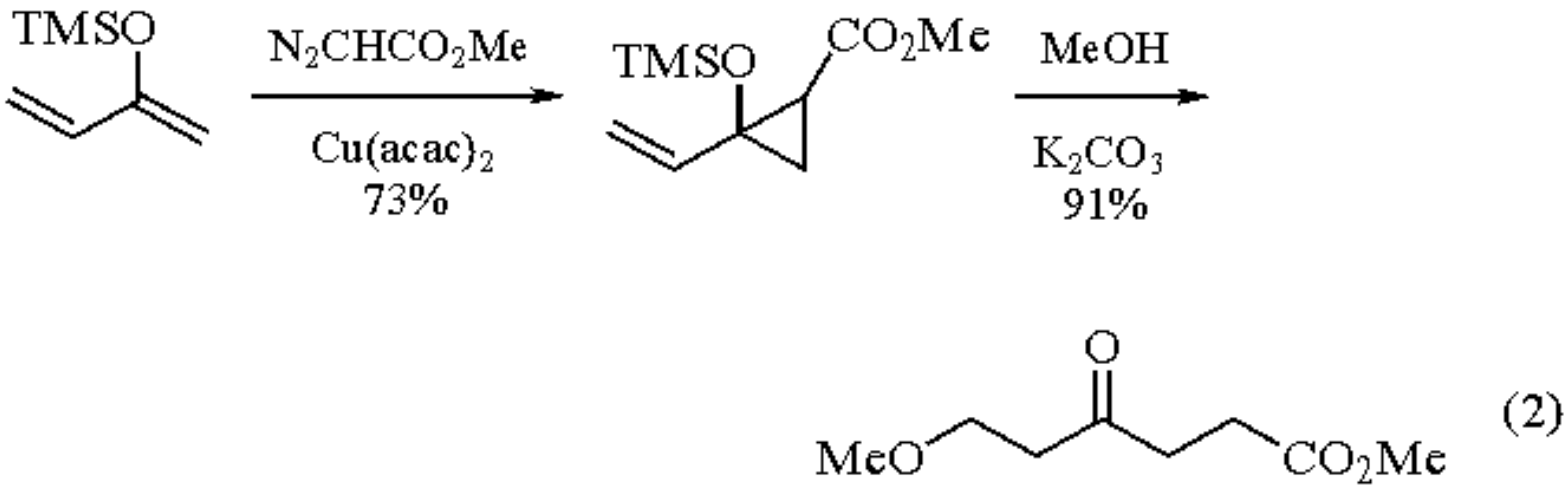

A number of 6- or 7-functionalized 4-oxoalkanoates can be prepared utilizing this protocol with a variety of Michael adducts. Methyl diazoacetate addition to ***Allyltrimethylsilane*** followed by treatment with ***Tetra-n-butylammonium Fluoride*** yields methyl 4-pentenoate (eq 3).[17] Cyclopropyl boronates[18] and cyclopropyl amines[19] can also be prepared from methyl diazoacetate under catalytic conditions.

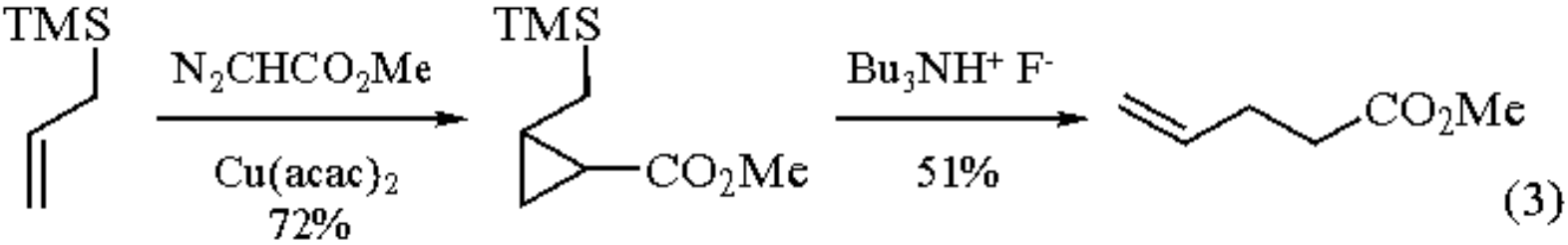

The addition of the methyl diazoacetate-derived carbene to benzene gives rise to methyl cyclohepta-2,4,6-triene-1-carboxylate with a high degree of selectivity (eq 4).[5] The rhodium-catalyzed addition to substituted phenyls yields an isomeric mixture of products. In addition to substituted phenyls, methyl diazoacetate can add to various aromatic hetrocycles.[6]

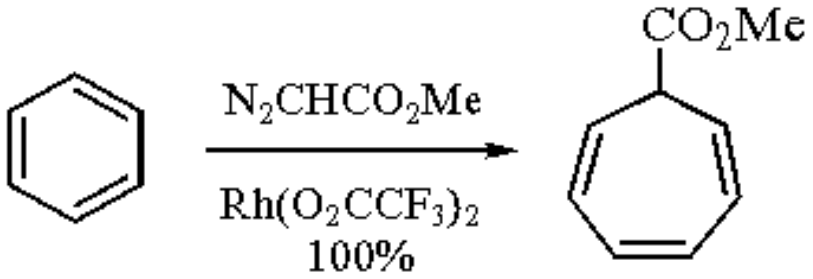

(4)

Cyclopropenation.

Cyclopropenyl esters are formed by the addition of methyl diazoacetate to various alkynes using $Rh(OAc)_2$ as the catalyst.[20] This cyclopropenation protocol is incompatible with alkynic alcohols (eq 5).[4] The catalyzed insertion of methyl diazoacetate into the O-H bond successfully competes with cyclopropene formation. High enantioselectivity can be achieved in a cyclopropenation with the use of a chiral dirhodium(II) carboxylate.[21]

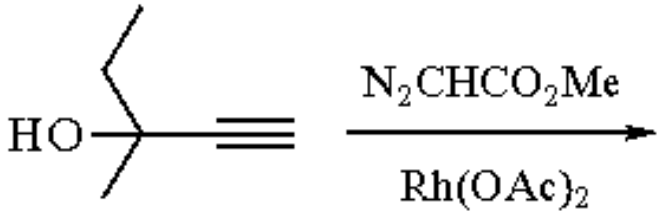

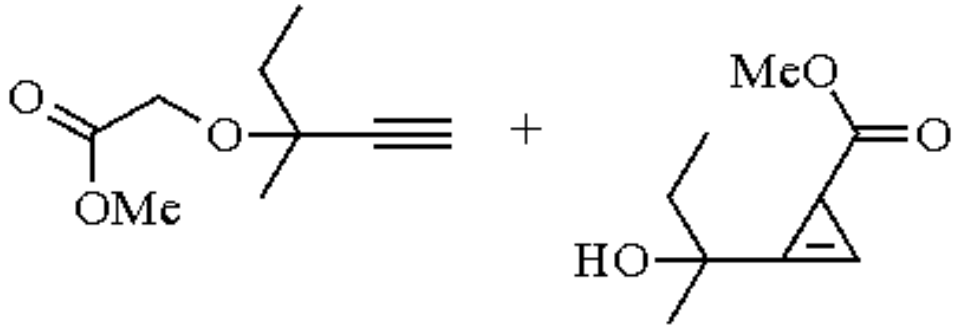

37% 36%

(5)

Insertion.

The insertion of methyl diazoacetate into the X-H bond (where X = S or O) is catalyzed efficiently with rhodium carboxylates.[7,22] The catalyzed insertion into allyl alcohol yields an α-alkoxy ester (eq 6).[23] Mild selectivity can be achieved over a competitive cyclopropanation with an appropriate catalyst.

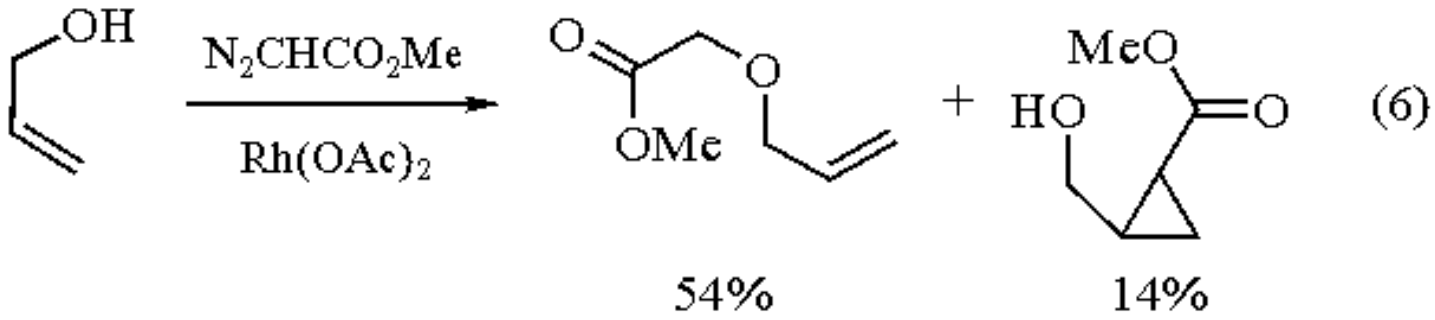

Condensation.

Lewis acid-catalyzed addition of methyl diazoacetate to an aldehyde provides a convenient method for the preparation of a 1,3-dicarbonyl. Treatment of 2,3-*O*-isopropylidene-D-glyceraldehyde with methyl diazoacetate yielded methyl (4*R*)-4,5-*O*-isopropylidene-3-keto-4,5-dihydroxypentanoate in good yield (eq 7).[24]

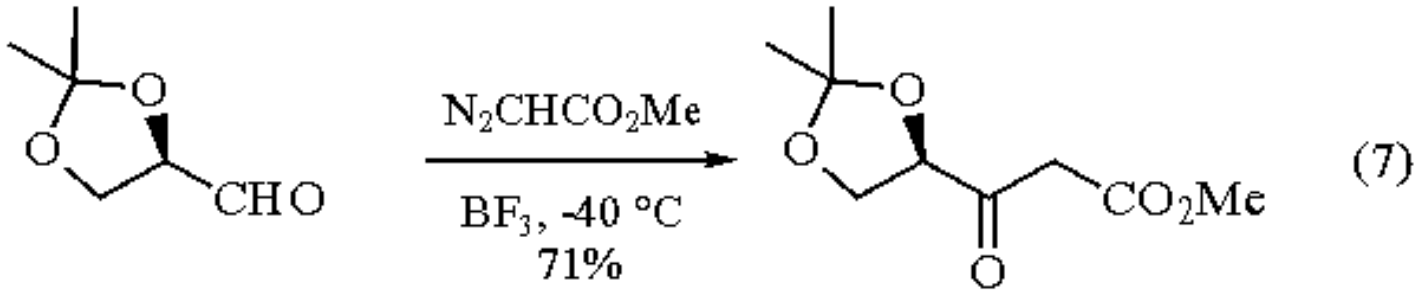

1,3-Dipolar Cycloaddition.

The uncatalyzed 1,3-dipolar cycloaddition of methyl diazoacetate with a suitable dipolarophile yields a substituted pyrazoline or pyrazole.[9,10,25] *N*-(1-Cyclohexenyl)pyrrolidine reacts with methyl diazoacetate, yielding a pyrazoline which eliminates pyrrolidine to give a pyrazole in excellent yield (eq 8).

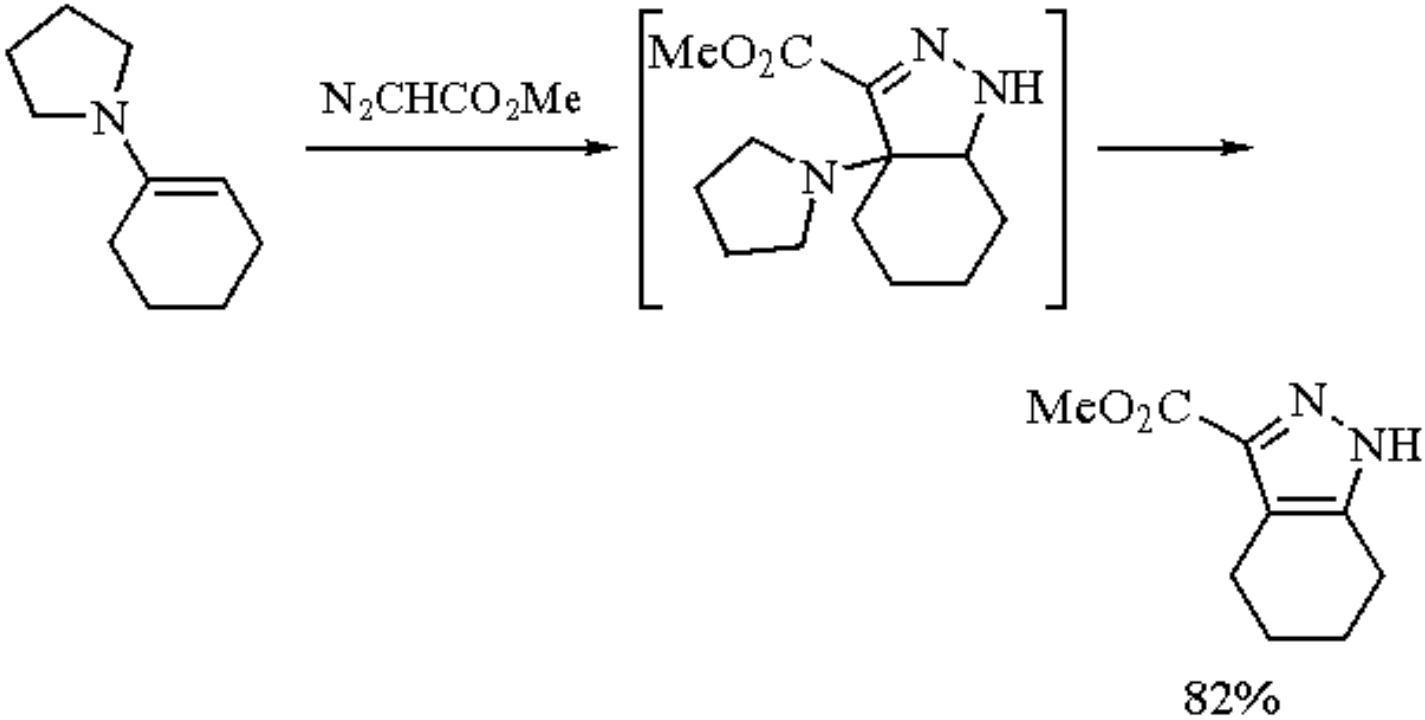

(8)

Related Reagents.

Diazoacetaldehyde; ***Diazoacetone***; ***Dimethyl Diazomalonate***; ***Ethyl Diazoacetate***.

---

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O-Methyldibenzofuranium Tetrafluoroborate[1]

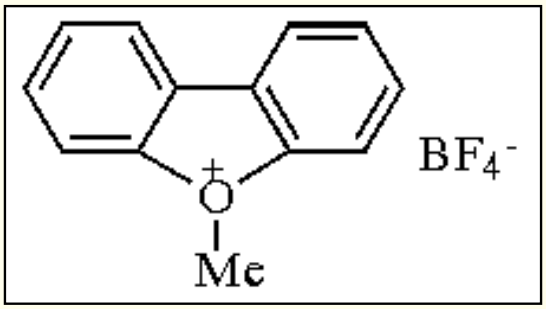

[36883-49-5] · $C_{13}H_{11}BF_4O$ · *O*-Methyldibenzofuranium Tetrafluoroborate · (MW 270.05)

(methylating agent, more powerful than trimethyloxonium salts[1,2])

Solubility: sol dichloromethane; insol benzene.

Preparative Methods: obtained as an unstable off-white solid by heating dry 2-methoxybiphenyl-2´-yldiazonium tetrafluoroborate in anhydrous benzene.[2,3] The diazonium precursor is conveniently prepared.[3] For synthetic applications the reagent is generated in situ by refluxing a solution (or suspension) of the dry diazonium tetrafluoroborate in anhydrous CH_2Cl_2 in the presence of a suitable substrate.[2,3]

Handling, Storage, and Precautions: the anhydrous diazonium precursor is unstable; it should be stored in vacuo over phosphoric anhydride at rt for a maximum of 2-3 days. Although information on hazardous properties is lacking, skin and eye contact with solutions of the methylating reagent or with the diazonium precursor should strictly be avoided (see also ***Triethyloxonium Tetrafluoroborate***). Use in a fume hood.

Introduction.

O-Methyldibenzofuranium tetrafluoroborate (**1**) has not yet been established as a widely employed reagent, although its methylating power has been reported to exceed that of trimethyloxonium salts or methyl fluorosulfonate.[2,3] The rare use of (**1**) may be due to two disadvantages of its use: the multistep synthesis of its precursor and the fact that methyl transfer from (**1**) to suitable substrates is coupled with the formation of dibenzofuran, which has to be separated from the methylation product. Alkylations with the readily available trimethyloxonium salts do not require extra separation, since only volatile dimethyl ether is formed as a byproduct.

Functional Group Alkylations.

The advantage of the in situ preparation of (**1**) is clearly demonstrated by the methylation of pyridine: when (**1**) is generated from its diazonium precursor (eq 1) in the presence of pyridine, *N*-methylpyridinium tetrafluoroborate is formed in essentially quantitative yield (eq 2).[3] Addition of pyridine to the preformed tetrafluoroborate (**1**) or to the analogous 2,4,6-trinitrobenzenesulfonate (**2**) gives lower yields (28% or 44%, respectively) of the pyridinium salt.[3] The reagent (**1**) is also capable of methylating halogenated pyridine derivatives (eqs 2 and 3).[2,3] When using trialkyloxonium salts the corresponding alkylations occur only to a small extent (<15%).[3] In the following sequences the reagent is indicated as $MeDIB^+BF_4^-$ (**1**), although methylations are performed via the in situ procedure using the diazonium precursor; in all reactions, dibenzofuran is the common byproduct.

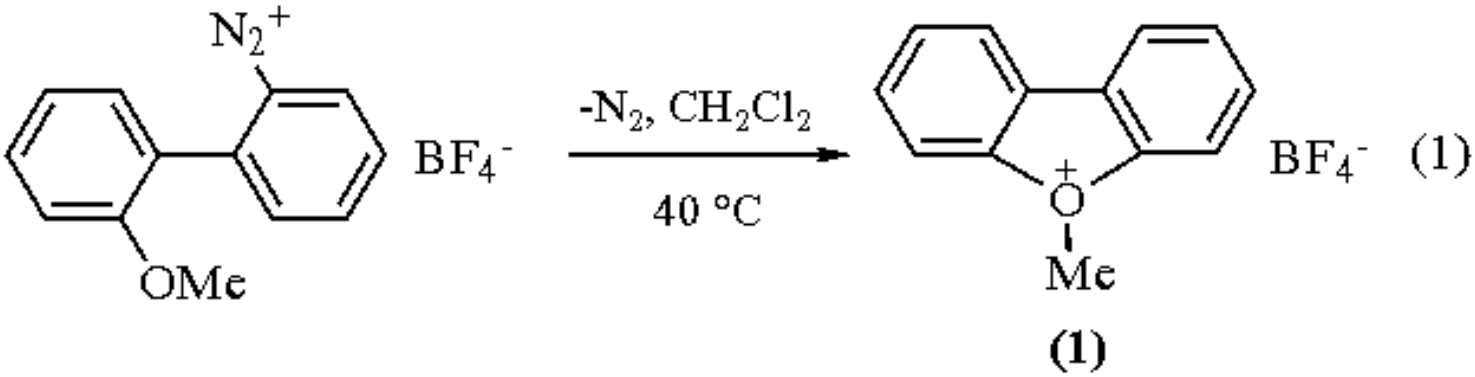

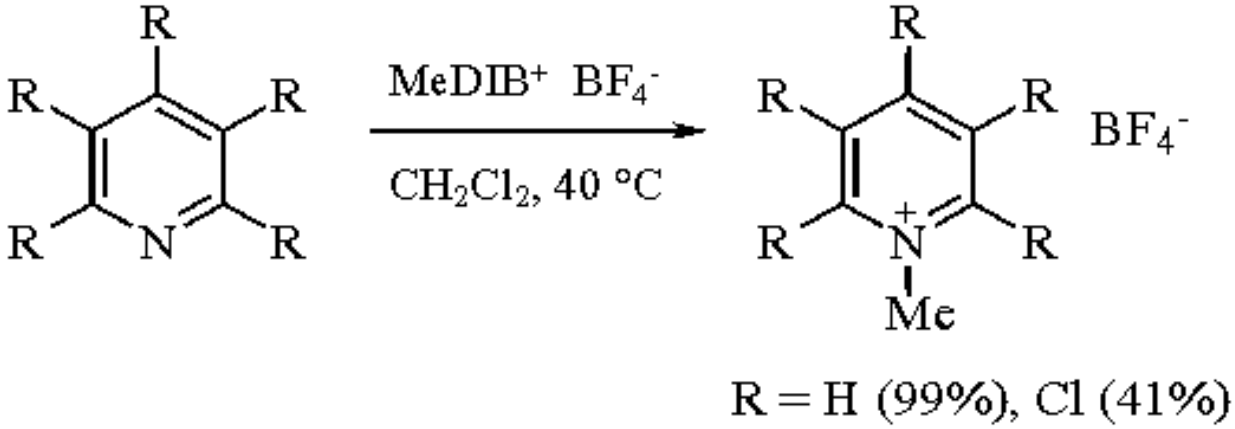

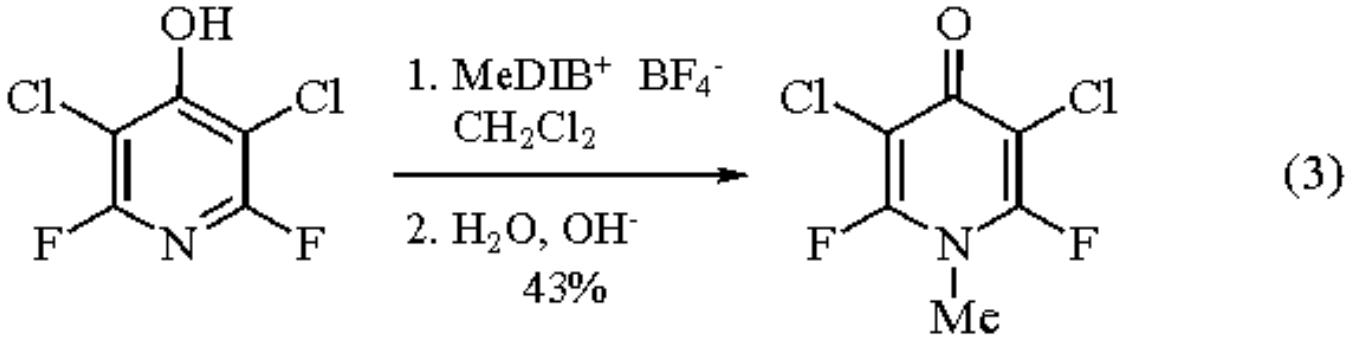

Reaction of (**1**) with *N*,*N*-dimethyl-1-naphthylamine results in the formation of the quaternary ammonium salt.[2,3] Similar to methylation with trimethyloxonium tetrafluoroborate, benzonitrile reacts with (**1**) to yield *N*-methylbenzonitrilium tetrafluoroborate, which may be hydrolyzed to *N*-methylbenzamide (eq 4).[3]

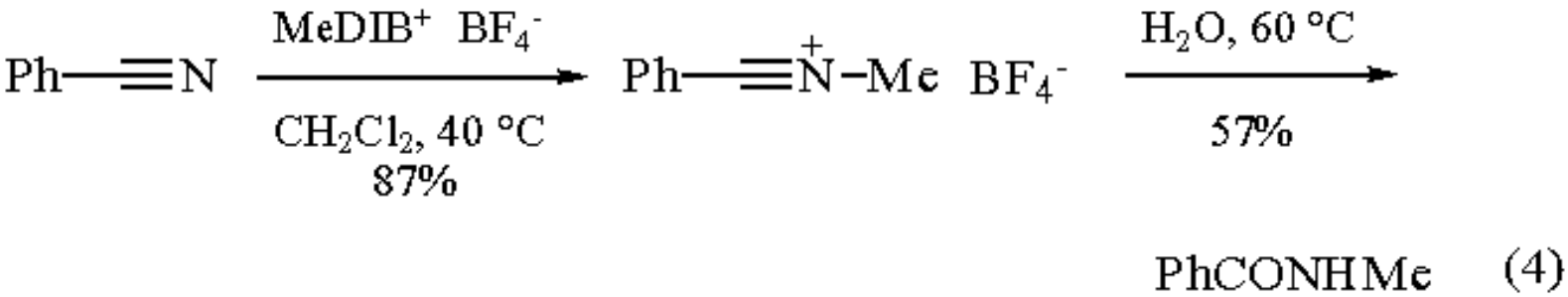

O-Methylations via (**1**) have been reported to occur with tetrahydrofuran, α-pyridone, or dimethyl sulfoxide (eq 5) to give high yields of *O*-methyltetrahydrofuranium salt,[2] 2-methoxypyridine,[2,3] and methoxydimethylsulfonium tetrafluoroborate,[2,3] respectively. Methylation of benzo[*b*]thiophene via (**1**) results in the formation of *S*-methylbenzo[*b*]thiophenium tetrafluoroborate (eq 6).[3]

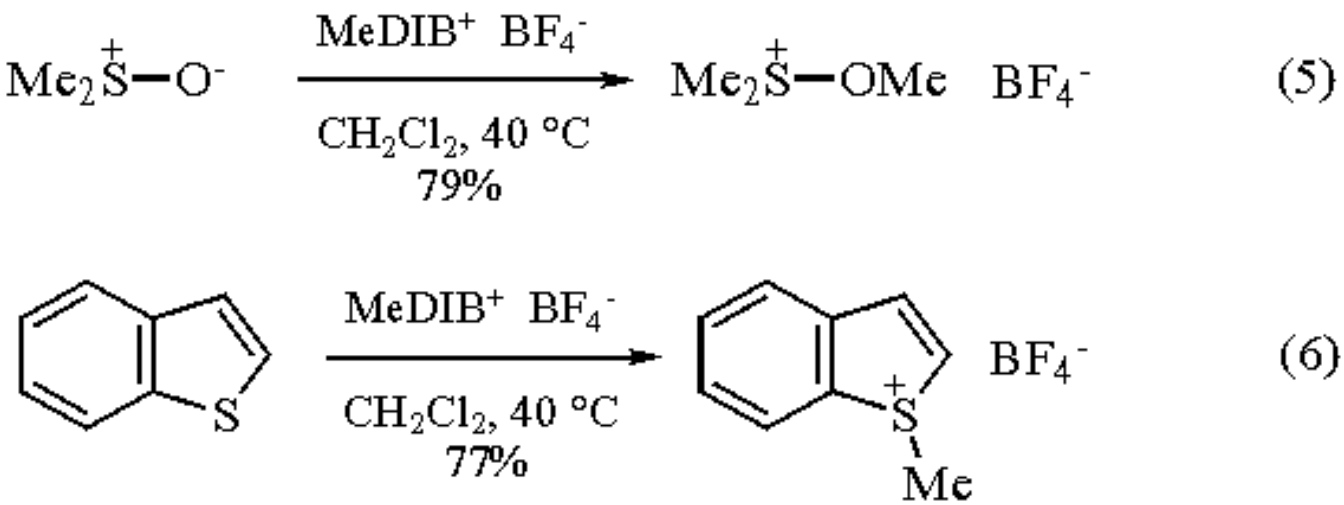

O-Methylation of anisole has not been achieved using either trimethyloxonium tetrafluoroborate or methyl fluorosulfonate.[2,3] However, methyl transfer to anisole oxygen has been shown to proceed when *O*-trideuteriomethyldibenzofuranium tetrafluoroborate is generated in situ from its appropriate diazonium precursor in the presence of anisole. After aqueous workup a mixture of trideuteriomethoxybenzene, unlabeled anisole, and benzofuran is obtained.[3]

Hydride Acceptor Agent.

Hydride transfer to the methyl group of (**1**) formed in situ has been reported to occur in the reaction with cycloheptratriene, to give tropylium tetrafluoroborate (eq 7),[3] or with triphenylmethane, to yield triphenylcarbenium tetrafluoroborate (21%).[3]

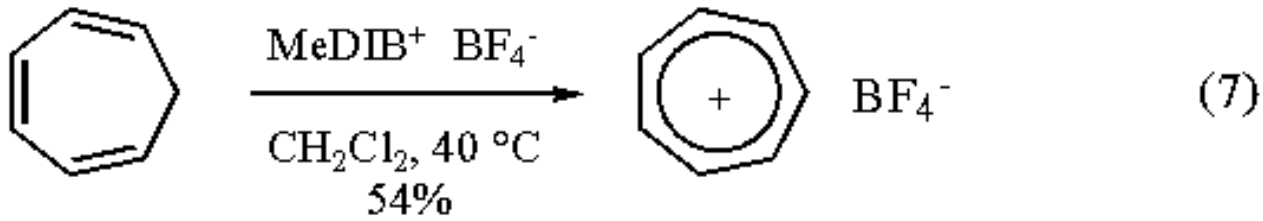

Related Reagents.

Dimethoxycarbenium Tetrafluoroborate; ***Dimethyliodonium Hexafluoroantimonate***; ***Methyl Fluoride-Antimony(V) Fluoride***; ***Methyl Trifluoromethanesulfonate***; ***Triethyloxonium Tetrafluoroborate***.

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Philipps-Universität Marburg, Germany

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N-Methyl-*N,N´*-di-*t*-butylcarbodiimidium Tetrafluoroborate

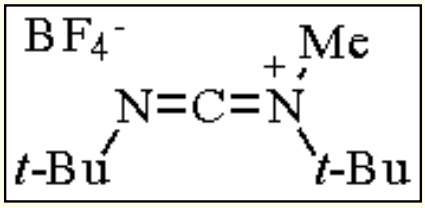

[39509-34-7] · $C_{10}H_{21}BF_4N_2$ · *N*-Methyl-*N,N´*-di-*t*-butylcarbodiimidium Tetrafluoroborate · (MW 256.14)

(dehydrative coupling)

Physical Data: mp 85-86 °C.

Form Supplied in: colorless hygroscopic crystals.

Preparative Method: N,N-di-*t*-butylcarbodiimide (1 equiv) is added dropwise to 1 equiv of ***Trimethyloxonium Tetrafluoroborate*** at 0 °C and stirred for 6 h before warming to rt and stirring for an additional 18 h. Isolation under fairly anhydrous conditions gives the diimidium salt in 62% yield.[1]

Dehydrative Coupling.

The reagent has been used in dehydrative coupling processes.[2] For example, diols (**1**) may be dehydratively cyclized to ethers by 1.0 equiv of the diimidium salt (**2**) and slightly more than 1 equiv of ***Triethylamine*** (eq 1) to give the corresponding cyclic ether and the urea (**3**). Yields vary and examples of ring sizes larger than seven members formed in the process have not been reported.

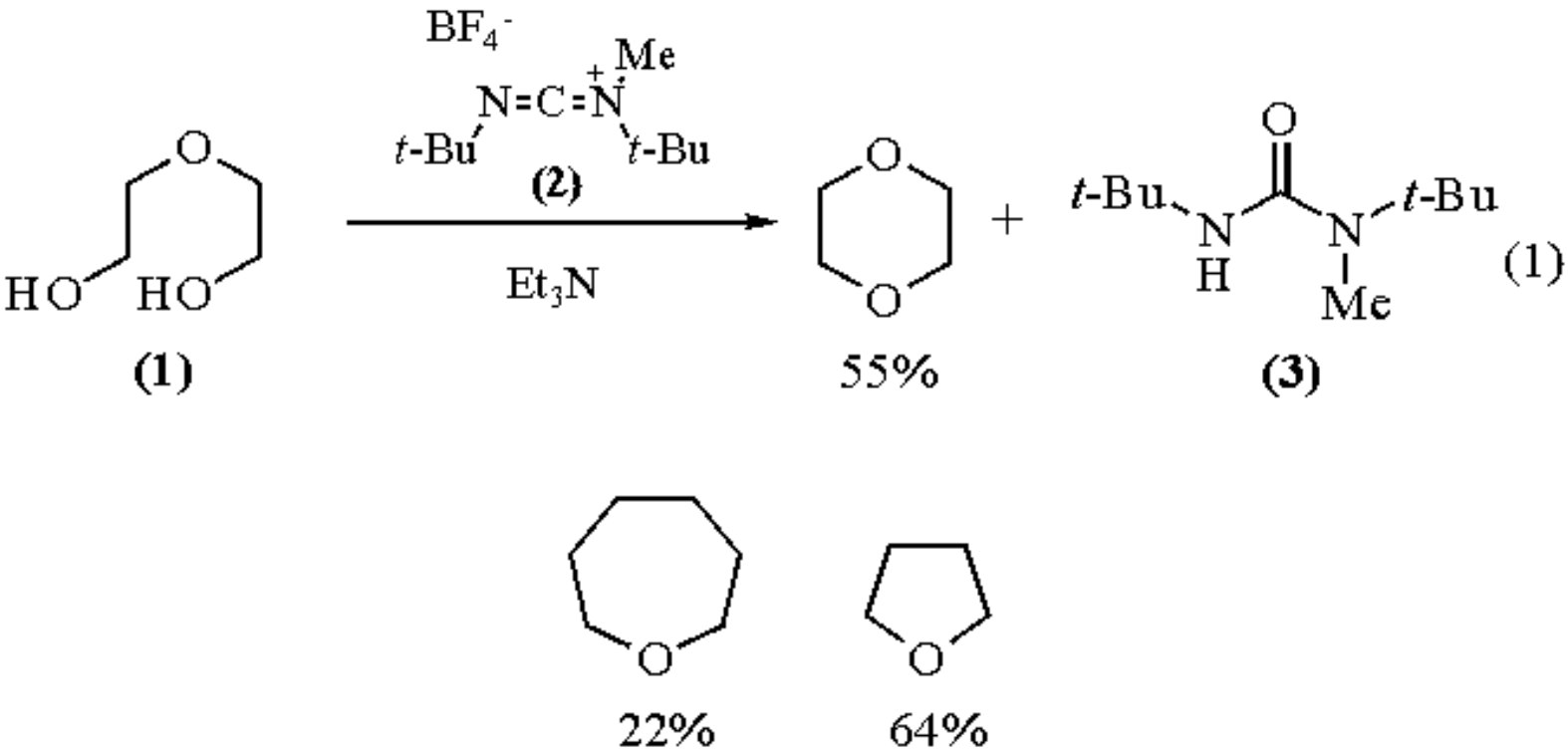

Appropriately protected amino acids have been coupled to dipeptides (eq 2). There is no apparent reason to favor this reagent over others in this process.

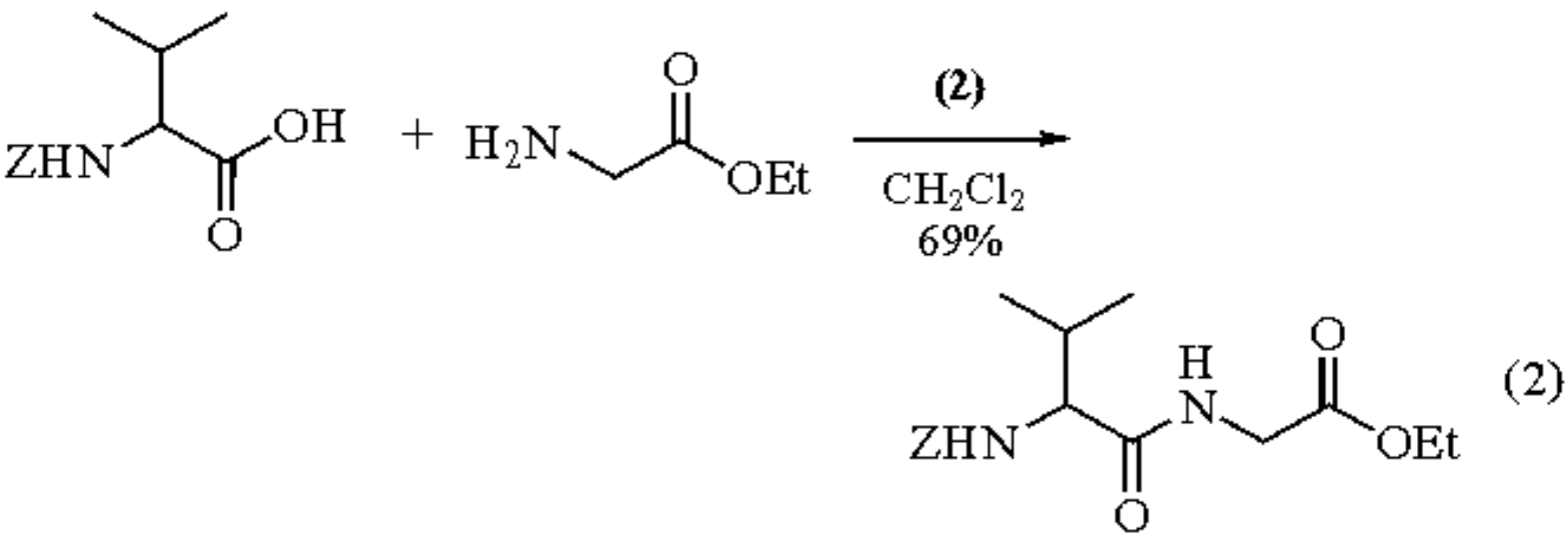

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Methyl Dichloroacetate

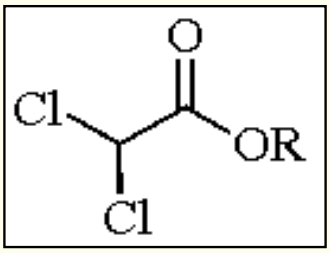

(**1**; R = Me)

[116-54-1] · $C_3H_4Cl_2O_2$ · Methyl Dichloroacetate · (MW 142.97) (**2**; R = Et)

[535-15-9] · $C_4H_6Cl_2O_2$ · Ethyl Dichloroacetate · (MW 157.00) (**3**; R = *i*-Pr)

[25006-60-4] · $C_5H_8Cl_2O_2$ · Isopropyl Dichloroacetate · (MW 171.03)

(synthesis of α-chloroglycidic esters[1] and/or 3-chloro 2-keto ester isomers[1,2] (Darzens reaction); 2,2-dichloro esters (alkylation);[3] 1,2-dialkoxycarbonylchlorocyclopropanes (Michael reaction);[4] precursor[5] for Reformatsky reagents; precursor for 1,1-dithioalkyl (or aryl) acetates[6])

Physical Data: (**1**) bp 143 °C; *d* 1.3774 g cm^{-3}. (**2**) bp 157 °C; *d* 1.2827 g cm^{-3}. (**3**) bp 164-165 °C; *d* 1.2053 g cm^{-3}.

Solubility: sol ether, acetone, alcohol, THF, chloroform.

Handling, Storage, and Precautions: lacrymatory; handle in a well-ventilated fume hood. The reagents are quite stable at rt under neutral conditions.

Introduction.

Dichloracetic esters have a very acidic α-proton which allows, after deprotonation with the appropriate bases, Darzens reaction with carbonyl compounds and imines, alkylation, and Michael reactions followed by cyclization with acrylic esters.

Synthesis of α-Chloroglycidic Esters, β-Chloro α-Keto Esters, and 2,2-Dichloro Esters.

One of the most important applications of dichloro acetates has been found in the synthesis of α-chloroglycidic esters[1] and their β-chloro α-keto ester isomers via the Darzens reaction in the presence of potassium or sodium alcoholates in alcohols.[7] When applied to aromatic aldehydes in aprotic media this reaction gives α-chloropyruvates.[2] The reaction also applies to various carbonyl compounds, such as carbohydrates[8] and steroids.[9] The same reaction was developed from the corresponding 2-dichloromethyl-4,4-dimethyl-2-oxazolidine (eq 1).[10]

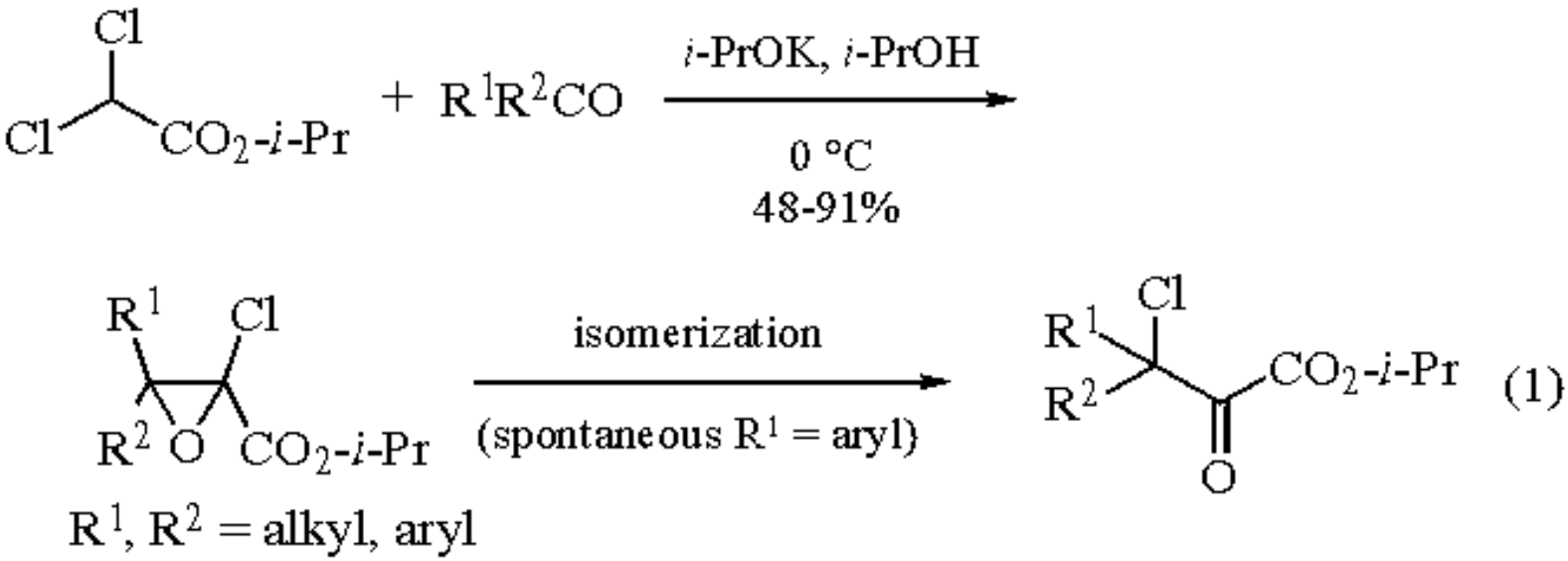

In the presence of imines this reaction gave analogous 1-chloro-1-alkoxycarbonylaziridines (eq 2).[11]

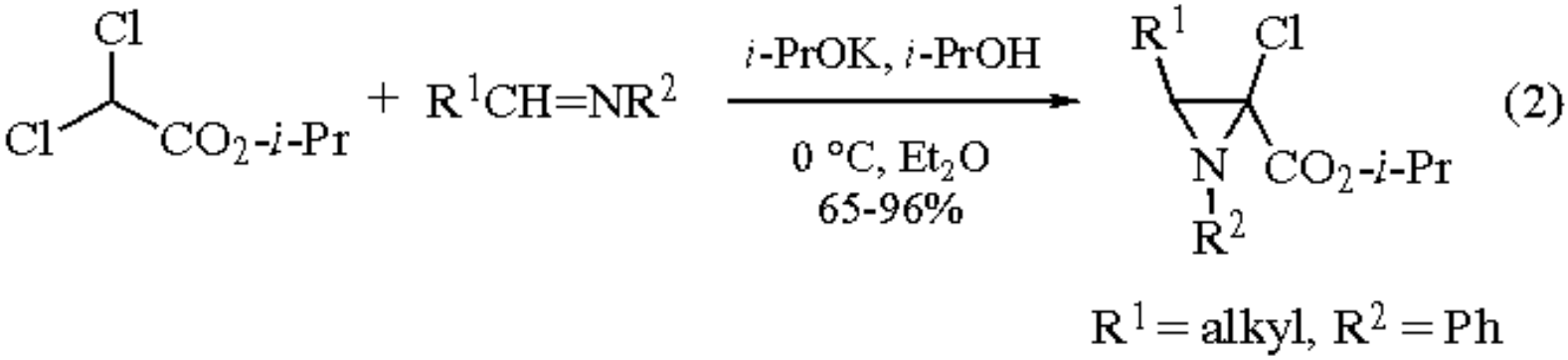

Tandem Darzens-hydrolysis reactions have been used for the synthesis of natural 3-hydroxy 2-keto esters,[12] while tandem Darzens-isomerization-dehalogenation gave rise to α-keto esters (eq 3).[8]

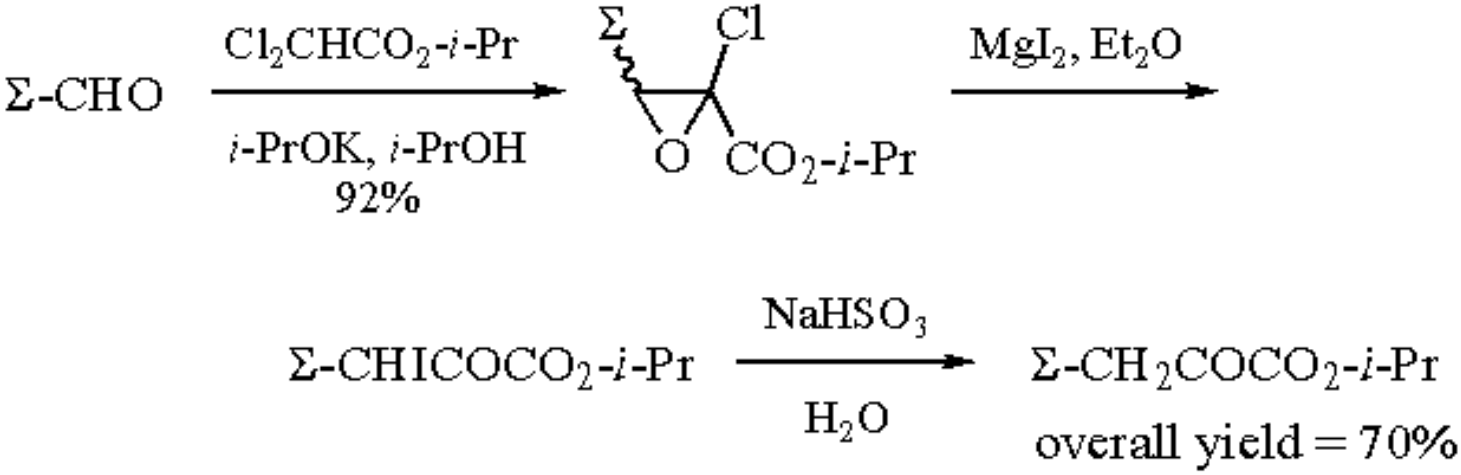

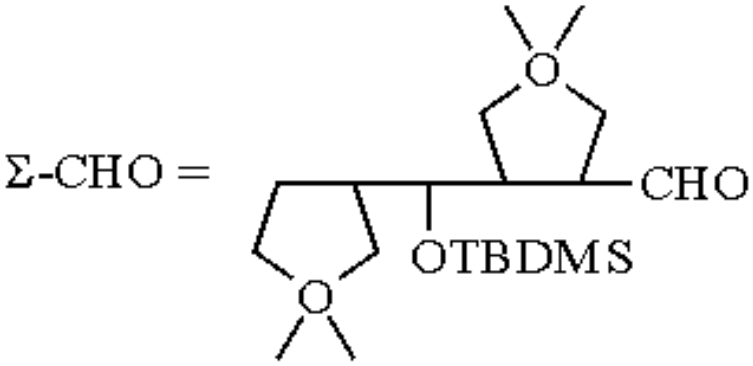

Lithium dichloroenolates have been prepared by deprotonation of dichloracetates with ***Lithium Diethylamide***,[3] ***Lithium Diisopropylamide***,[13] ***Lithium Dicyclohexylamide***,[14] or ***n-Butyllithium***.[15] Coupling of these anions with carbonyl compounds afforded 3-hydroxy-2,2-dichloroesters[3,15] or α-chloroglycidic esters[15] at rt, while 2,2-dichloroalkanoates have been prepared by alkylation of bromoalkanes in the presence of HMPA (eq 4).[3,13,16]

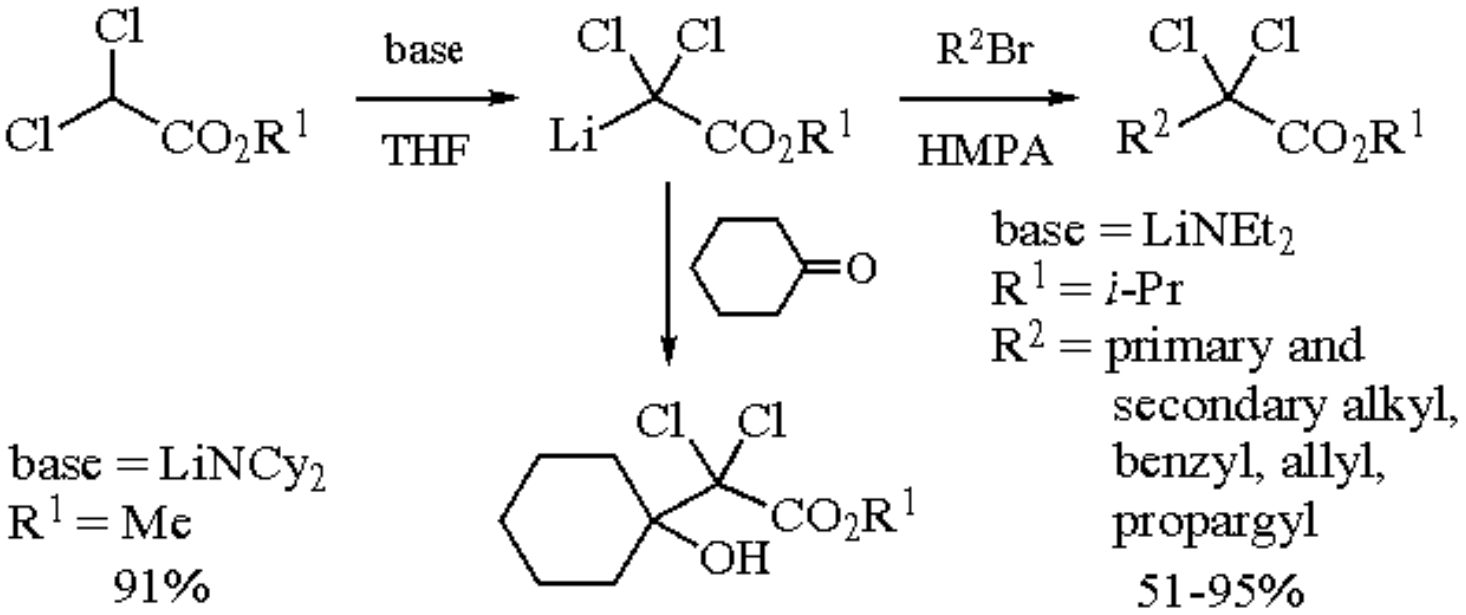

However, vicarious substitution of nitroarenes by dichloroacetate potassium enolates (***Potassium t-Butoxide*** in DMF) only gave the corresponding α-chlorobenzyl esters via addition of enolates and subsequent hydrochloric acid elimination (eq 5).[17]

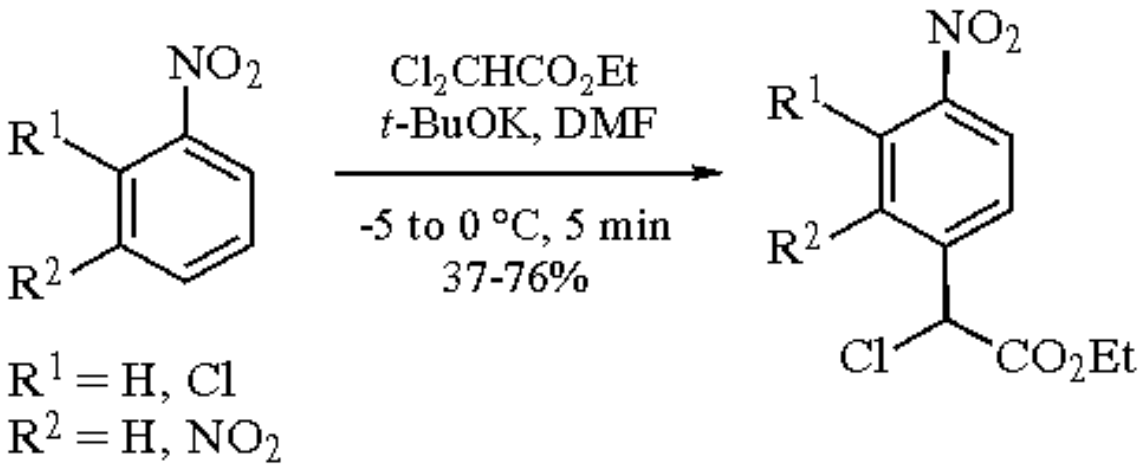

(5)

Preparation of 1,2-Dialkoxycarbonyl-1-chlorocyclopropanes.

Dichloroenolates from dichloroacetates have been involved in a tandem Michael-cyclization reaction with acrylic esters in the presence of lithium hydride,[18] electrogenerated bases,[19] or under mildly basic phase-transfer conditions[20] (eq 6).

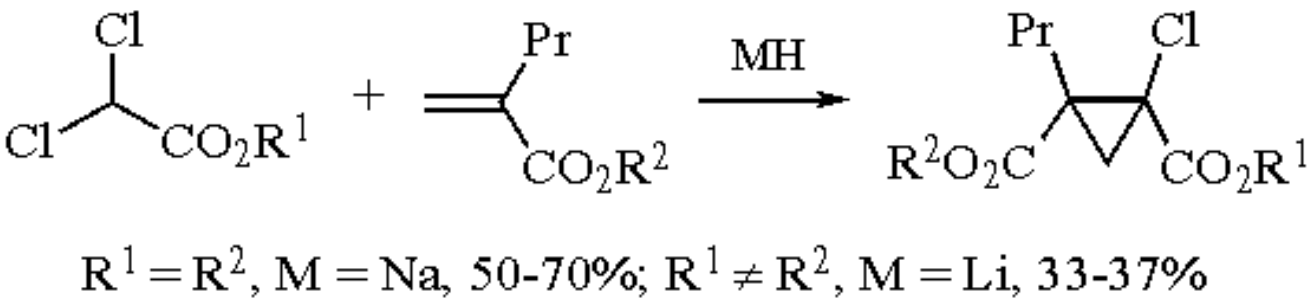

(6)

Chlorine abstraction by metals (Zn/Ag)[21] or under electrocatalysis[22] with a zinc sacrificial anode in the presence of a nickel complex led to the formation of the intermediate Reformatsky reagents MCHCl-CO_2R and allowed preparations of 3-hydroxy-2-chloroalkanoates or glycidic esters on coupling with carbonyl compounds (eq 7).

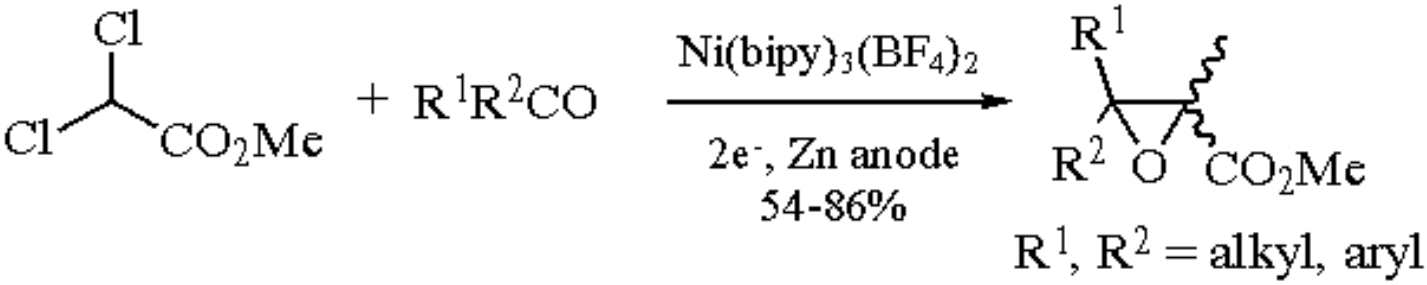

(7)

The corresponding copper carbenoids, obtained intermediately by reaction of copper in DMSO, gave mixtures of fumarates and maleates.[23]

Selective Synthesis of 2,4-Dichloroalkanoates and 2,2-

Dichloroalkanoates.

Addition of dichloroacetates to 1-alkenes by a radical pathway can lead to the formation of both 2,4-dichloroalkanoates and 2,2-dichloroalkanoates, depending on reaction conditions.[24] When performed in the presence of 0.7 mol % dichlorotris(triphenylphosphine)ruthenium(II)[25] or copper(I) chloride-1,10 phenanthroline complexes,[26] 2,4-dichloroalkanoates are formed exclusively, while 2,2-dichloroalkanoates are formed preferentially in the presence of peroxides (eq 8).[27] The mechanism of this reaction has been fully investigated.[25,28] Butadiene can also be used as a substrate.[29]

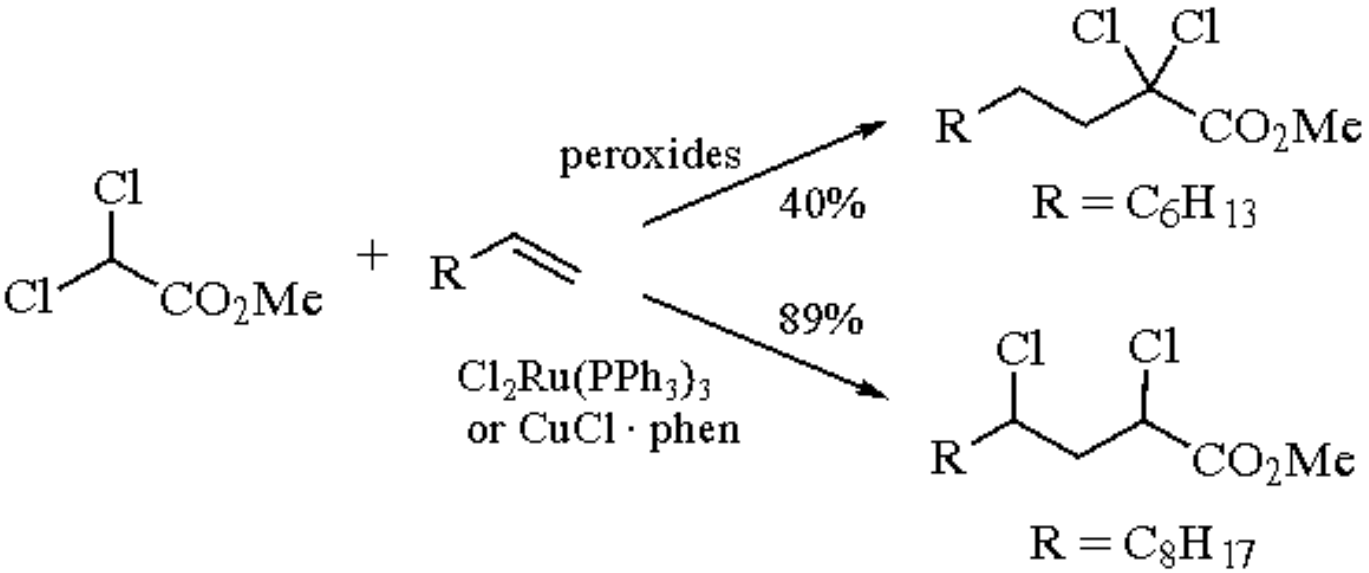

(8)

Miscellaneous.

Dialkyl-[6] and diarylthioacetates[6,30] can be easily prepared by substitution of dichloroacetates by thiolates. Reaction with ***Phosphorus(III) Chloride*** occurs in the presence of ***Triethylamine*** and leads to the formation of the corresponding dichlorophosphines.[31]

Related Reagents.

Dichloroacetonitrile; ***Methyl Chloroacetate***.

---

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Philippe Coutrot & Claude Grison

Nancy University, France

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Methyl Dichlorofluoroacetate

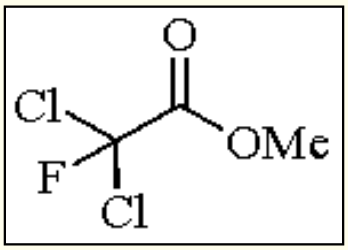

[431-44-77] · $C_3H_3Cl_2FO_2$ · Methyl Dichlorofluoroacetate · (MW 160.96)

(Reformatsky-type reactions with aldehydes to give 2-fluoroenoates)

Physical Data: bp 82-85 °C/0.5 mmHg.

Solubility: usually used in polar solvents (acetone)

Analysis of Reagent Purity: satisfactory microanalytical data reported.[1]

Preparative Method: prepared in 65% yield by reaction of methyl trichloroacetate and ***Antimony(III) Chloride*** in the presence of ***Bromine***.[1,2]

The methyl ester of dichlorofluoroacetic acid is a useful reagent in Reformatsky-type reaction with aldehydes (eq 1).[2] This procedure allows preparation of 2-fluoroenoates (**1**) in synthetically useful yields; (*Z*)-isomers are formed in high preponderance (&egt;93% (*Z*)-isomer obtained). In the absence of molecular sieves the reaction does not occur.

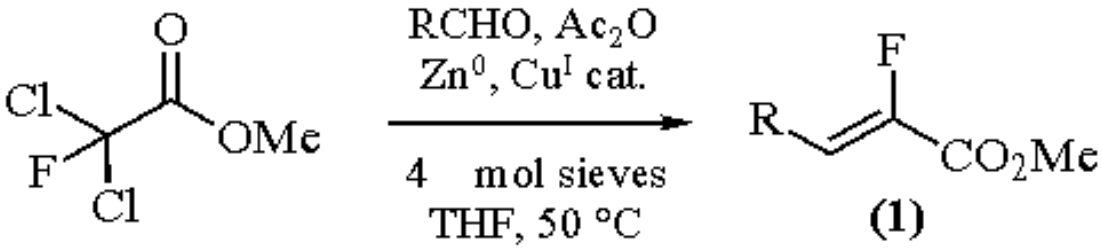

(1)

The use of anhydride sources as an alternative to the simple acetyl anhydride employed in eq 1 has been reported as an improvement to this method (Table 1 and eq 2).[3] The same report describes several reactions in which the previously claimed high selectivity for the (*Z*)-isomer in the alkenation reaction is not observed; up to 40% (*E*)-alkene is obtained.

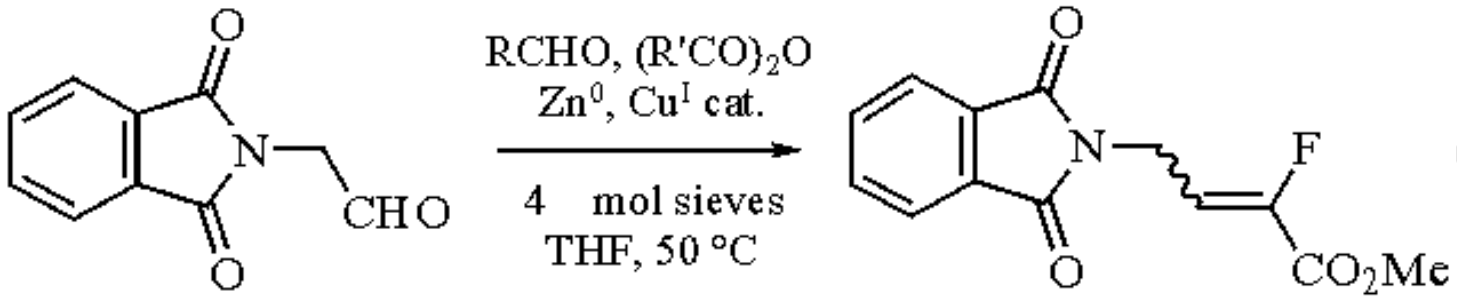

(2)

Table 1 Alkene Geometry in 2-Fluoroenoates (**2**)

R	Yield (%)	(*Z*):(*E*) ratio
Me	53	75:25
CF_3	42	60:40

1. Gryszkiewicz-Tochimowski, E.; Sporzynski, A.; Wnuk, J. *RTC* **1947**, *66*, 419.
2. Ishihara, T.; Kuroboshi, M. *CL* **1987**, 1145.
3. Allmendinger, T. *T* **1991**, *47*, 4905.

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N-Methyl-*N,N´*-dicyclohexylcarbodiimidium Iodide

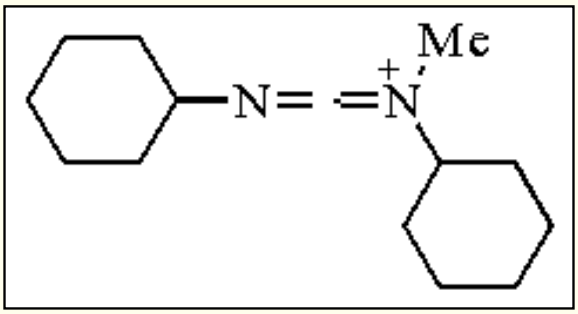

[36049-77-1] · $C_{14}H_{25}IN_2$ · *N*-Methyl-*N,N´*-dicyclohexylcarbodiimidium Iodide · (MW 348.31)

(conversion of alcohols to iodides)

Physical Data: colorless hygroscopic crystals; mp 111-113 °C.

Preparative Method: ***1,3-Dicyclohexylcarbodiimide*** (42 g, 0.204 mol) was dissolved in a large excess of ***Iodomethane*** (90 mL, 1.45 mol) and stirred at 70 °C for 3 days under a nitrogen atmosphere. The excess MeI was removed by distillation under reduced pressure and the residue was dissolved in dry toluene (150 mL) at 40 °C. The resulting crystalline mass was filtered off under an inert atmosphere and the crystals were washed with cold, dry toluene until colorless. The product was dried under vacuum (0.1 mmHg) at rt to provide 35 g (75%) of colorless crystals.

Handling, Storage, and Precautions: the compound should be stored under an inert atmosphere at refrigerator temperatures, where it is reputed to be stable for several months.

Conversion of Alcohols to Iodides.

First reported in 1972, the sole reported use of *N*-methyl-*N,N´*-dicyclohexylcarbodiimidium idodide (**1**) is in the conversion of alcohols to iodides. The original article[1] contains the first description of the preparation in bulk of a carbodiimidium salt and describes its use in the preparation of some primary and secondary iodides. In three of the examples, inversion of configuration was exclusive, (**2**) -> (**4**), hinting at a mechanism such as that shown in eq 1. The reagent was said to be good for the preparation of very hindered secondary iodides, but the yields are generally low (eqs 2 and 3). The reagent is, however, quite successful in preparing iodides from alcohols in multifunctional compounds (**6**),[2] (**7**),[3] and (**8**).[4]

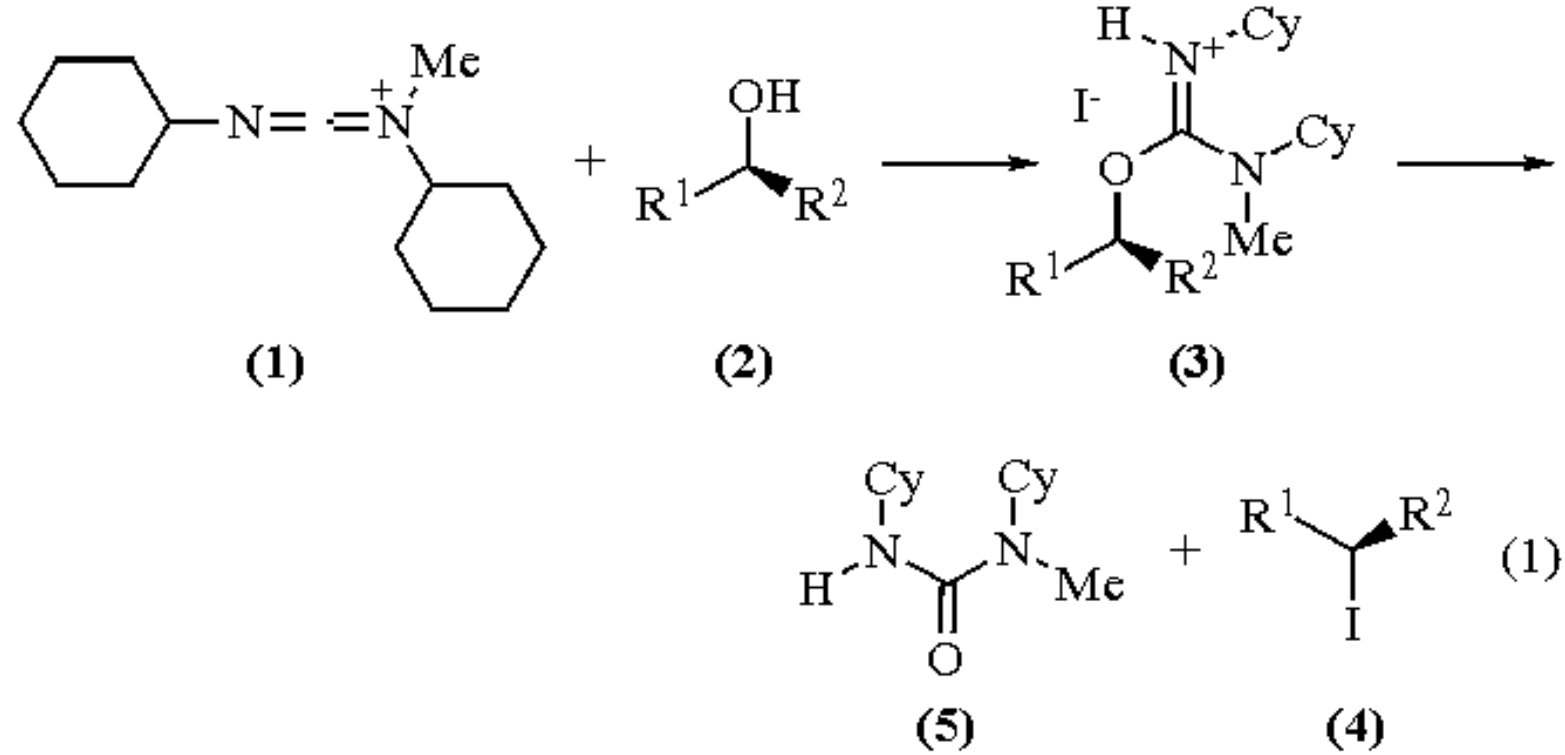
Me
N
OH
R1
R2
H
Cy
I-
O
Me
(1)
(2)
(3)
Cy
H
Me
O
(5)
(4)
(1)

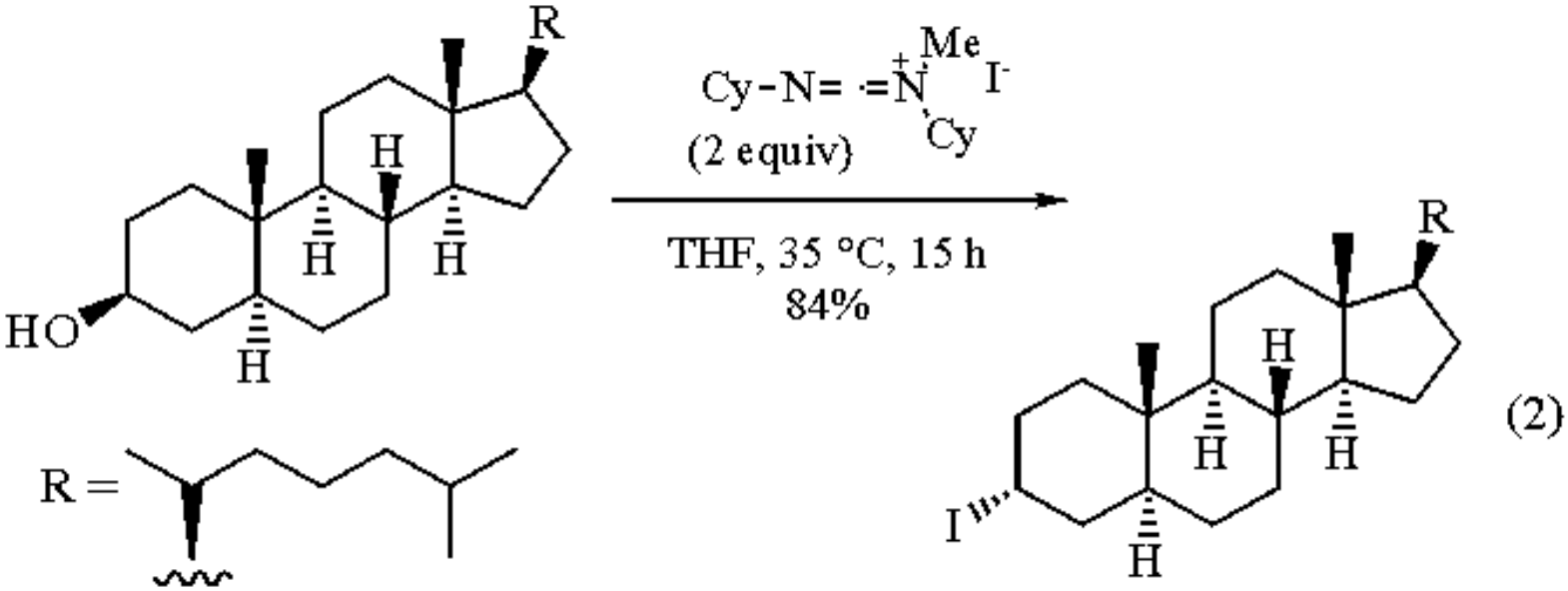
R
H
HO
Cy-N=
Me
I-
Cy
(2 equiv)
THF, 35 °C, 15 h
84%
R =
I
(2)

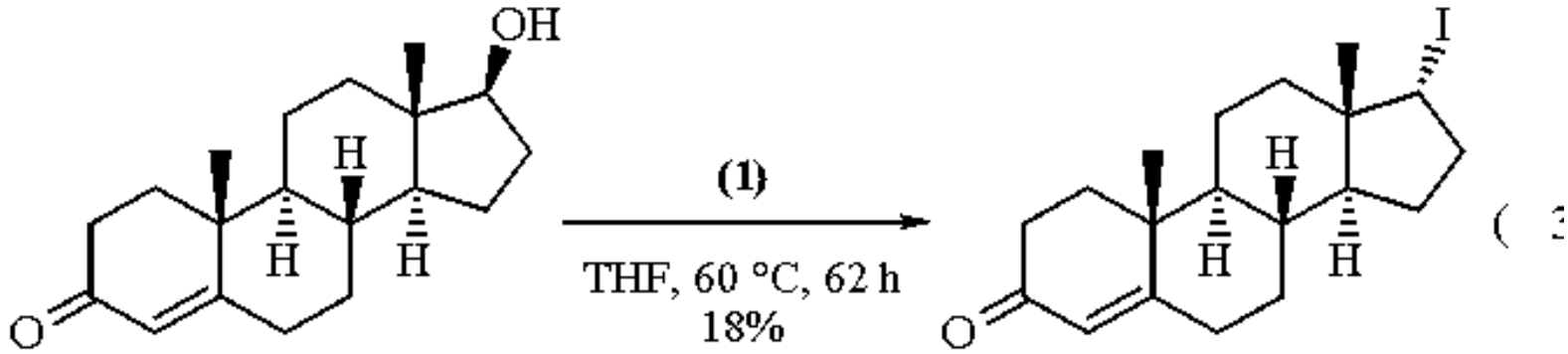
OH
H
O
(1)
THF, 60 °C, 62 h
18%
I

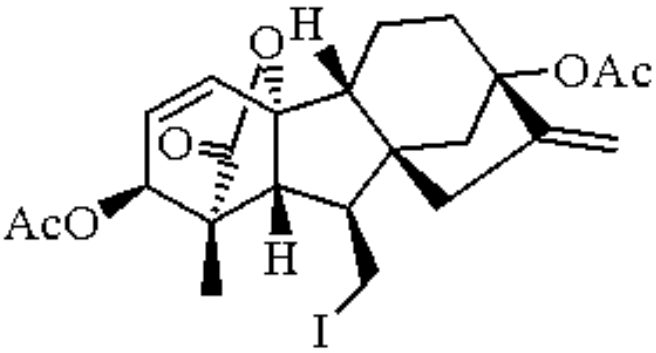

(6) 54%

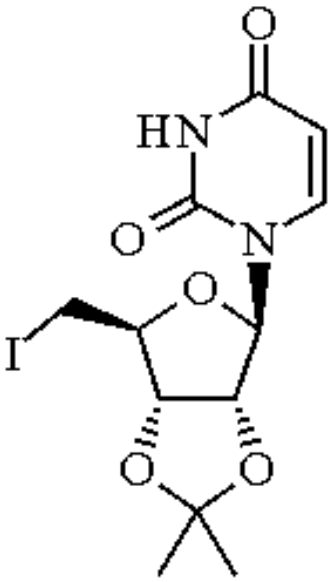

(7) 25%

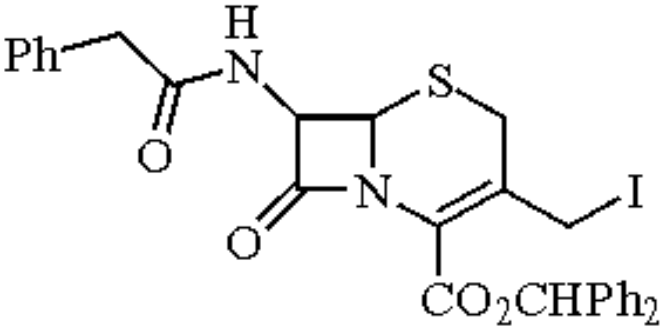

(8)

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4. Scartazzini, R.; Bickel, H. *CA* **1974**, *80*, 95 974j.

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Methyl Diethylamidosulfite[1]

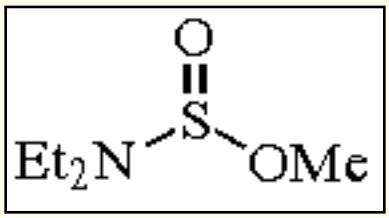

[21954-69-8] · $C_5H_{13}NO_2S$ · Methyl Diethylamidosulfite · (MW 151.26)

(conversion of carboxylic acids to *N*,*N*-diethylamides[2])

Physical Data: bp 73-74 °C/10 mmHg.

Solubility: sol diethyl ether.

Form Supplied in: clear oil.

Analysis of Reagent Purity: titration with iodine.

Preparative Method: reaction of diethylamine and chlorosulfurous acid in diethyl ether.[1,2]

Purification: vacuum distillation.[2]

Handling, Storage, and Precautions: prolonged heating at atmospheric pressure causes decomposition with evolution of sulfur dioxide.

This reagent reacts with primary and secondary carboxylic acids in the presence of pyridine to give *N*,*N*-diethylamides (eq 1). The reaction is typically run at rt and requires a long reaction time (several days). In general, tertiary acids and α-amino carboxylic acids do not react.[2,3]

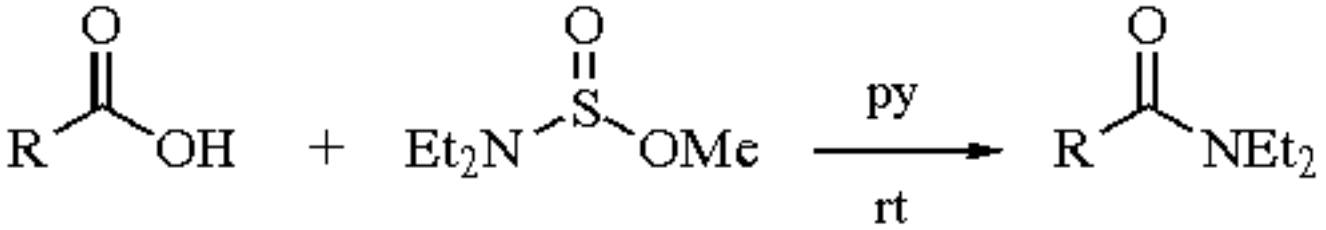

(1)

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1. (a) Zinner, G. *CB* **1958**, *91*, 966. (b) Voss, M.; Blanke, E. *LA* **1931**, *485*, 258.
2. Takei, H.; Shimizu, H.; Hizo, M.; Mukaiyama, T. *BCJ* **1968**, *41*, 1925.
3. Becker, H. G. O.; Funk, K. F. *JPR* **1961**, *14*, 55.

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Methyl Diformylacetate

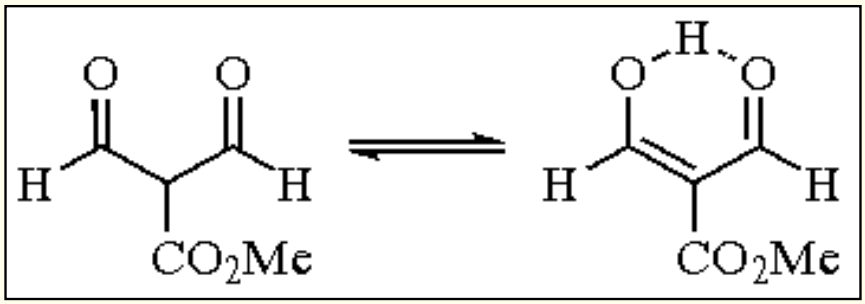

(dione)

[50427-65-1] · $C_5H_6O_4$ · Methyl Diformylacetate · (MW 130.11) (enol)

[39947-70-1]

([2 + 2] cycloaddition[1] (de Mayo reaction);[2] [4 + 2]cycloaddition (hetero-Diels-Alder reaction with inverse electron demand);[3] transformation to enamino aldehydes and their photochemical and thermal cycloadditions;[4] Wittig reaction[5])

Physical Data: bp 54-55 °C/3.5 mmHg.

Solubility: slightly sol water; sol aqueous alkali and diethyl ether.

Form Supplied in: colorless liquid.

Preparative Methods: by Panizzi's formylation procedure[6] of commercially available methyl 3,3-dimethoxypropanoate[7] with methyl formate,[1i] by diformylation of potassium monomethyl malonate with dimethyl formamide and phosphorus oxychloride followed by decarboxylation, and by ozonolysis of dimethyl 2,5-cyclohexadiene-1,4-dicarboxylate.[8]

Purification: fractional vacuum distillation.

Handling, Storage, and Precautions: stable for at least 6 months if stored at -20 °C; it is a highly acidic compound. Use in a fume hood.

Methyl diformylacetate (**1**) undergoes photochemical [2 + 2] cycloadditions ([2 + 2] photoannulation) with alkenes. Thus irradiation of (**1**) and the alkene (**2**) leads primarily to the *cis*-fused cyclobutane derivative (**3**), which by retro-aldol cleavage to a 1,5-dialdehyde and cyclization gives the hemiacetal (**4**). Treatment of (**4**) with methanol in the presence of IR-120 cation exchange resin yields the methyl acetal (**5**) (eq 1), which was converted into the iridoid-

glucoside loganin.[1i,j] In a similar way, methyl diformylacetate has been used for the synthesis of hydroxyloganin, secologanin derivatives, and sarracenin.[1a-g]

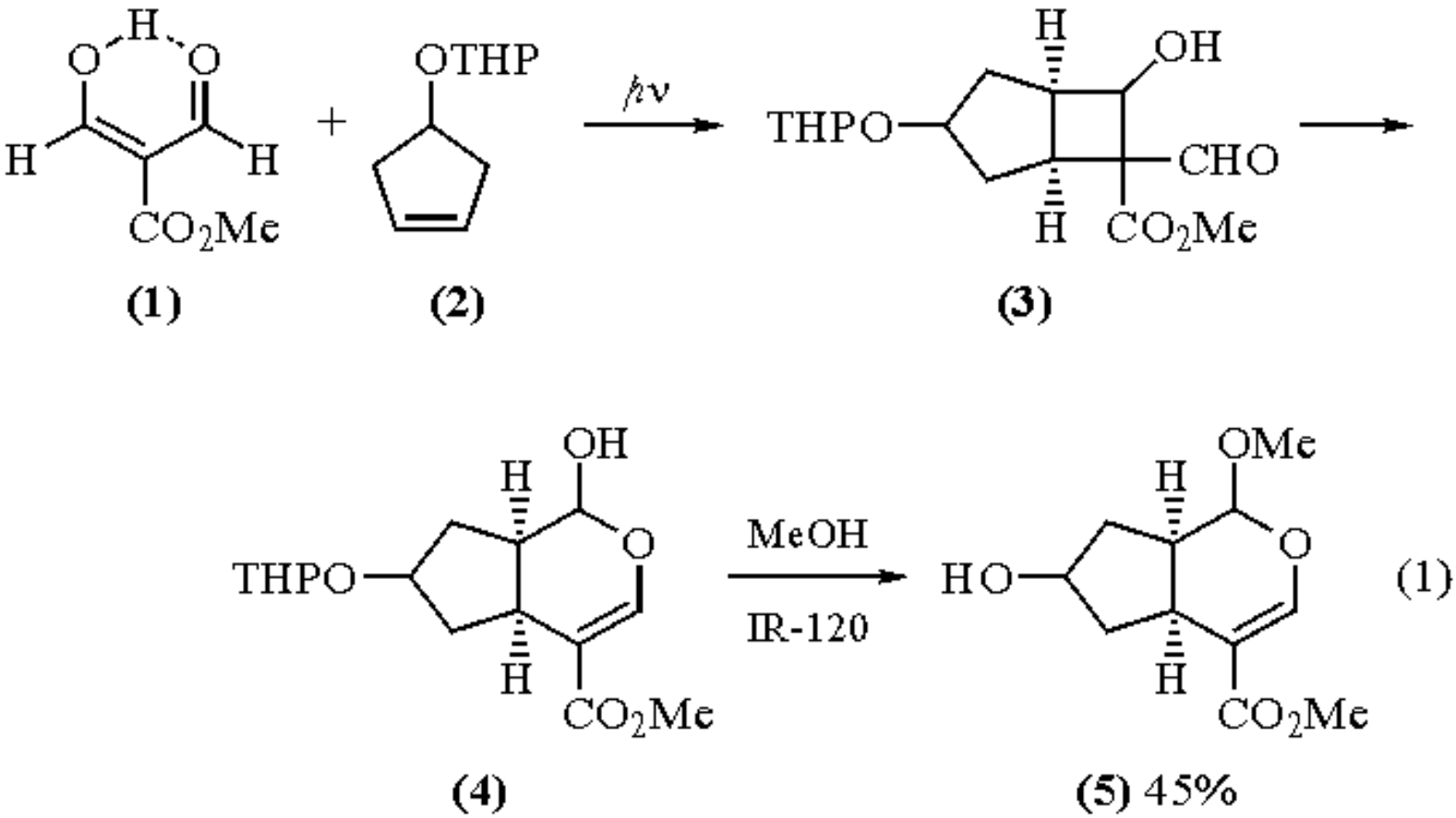

In the photoaddition of methyl diformylacetate with ***Isobutene*** the two possible regioisomeric dihydropyrans (**6**) and (**7**) were formed in the ratio 2.5:1 (eq 2).[1c]

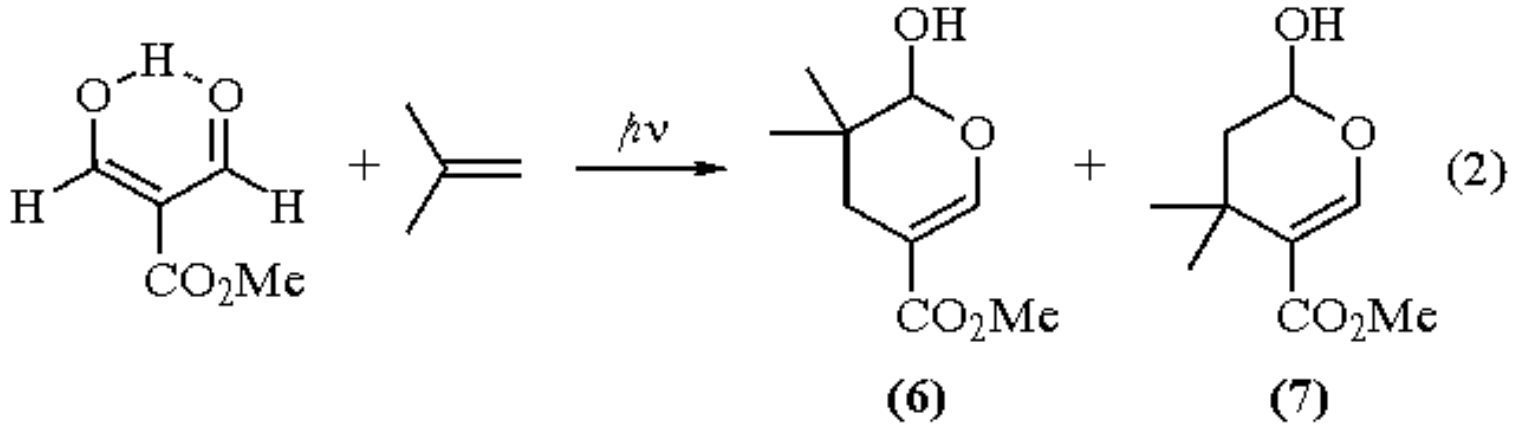

Methyl diformylacetate can also be employed as heterodiene in [4 + 2] cycloaddition with reactive dienophiles like enol ethers to give dihydropyrans. Thus the hetero-Diels-Alder reaction with inverse electron demand of (**1**) and 1-methoxycyclopentene at 20 °C for 200 h leads to the diastereomers (**8**) and (**9**) in the ratio 3:1 with 82% yields (eq 3).[3a] Methyl *O*-acyldiformylacetates are more reactive in the cycloadditions and the diastereomeric ratio is almost inverted. The use of chiral *O*-acyl derivatives allows an asymmetric induction.[3a] Triformylmethane may be used in a similar way.[3b]

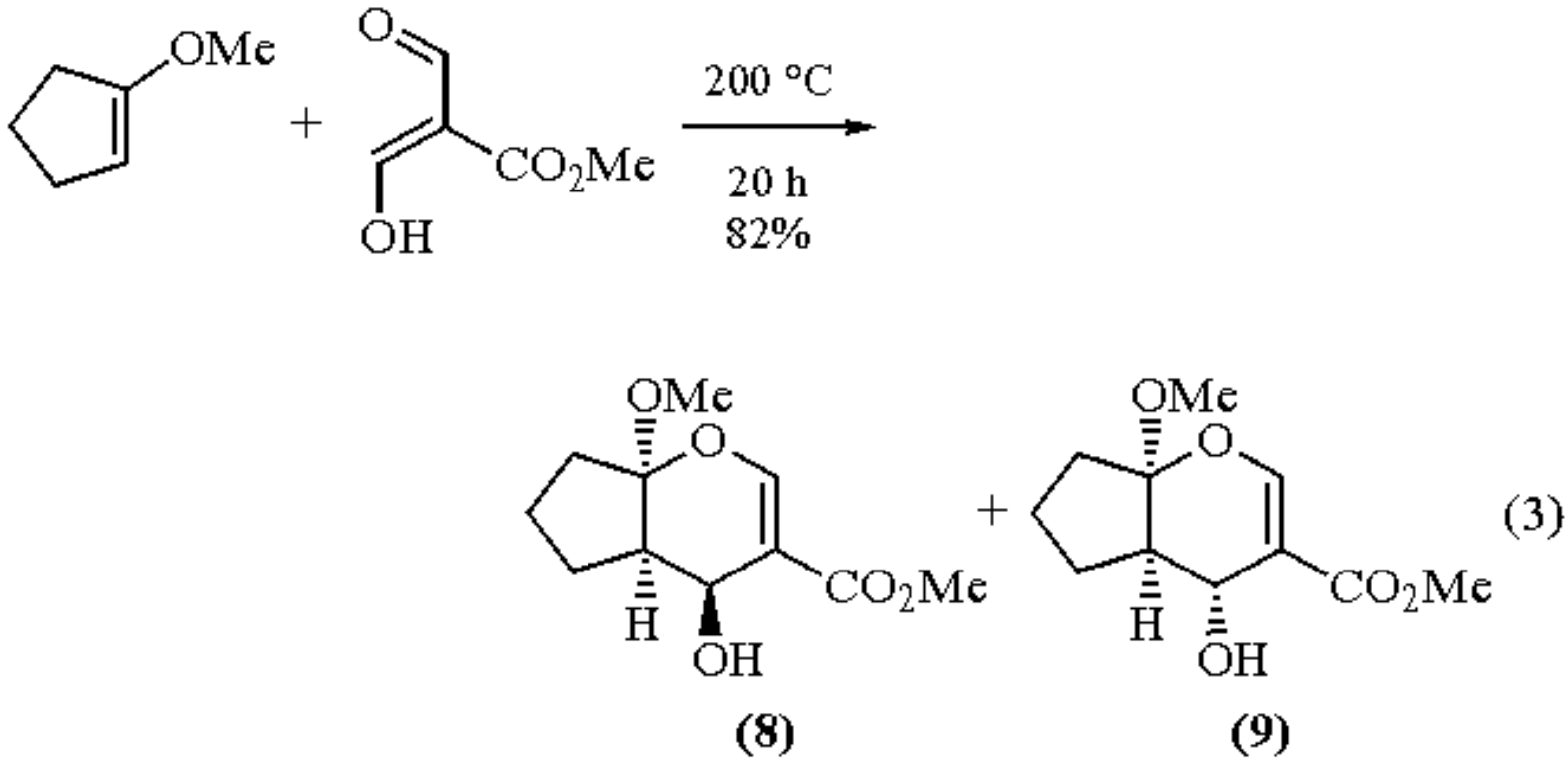

Enamino aldehydes (**8**) were prepared by condensation of methyl diformylacetate with amines in the presence of a drying agent such as flame-dried Na_2SO_4 (eq 4).[4a] The [2 + 2] photoannulation of (**8**) with alkenes gives 2-hydroxytetrahydropyridines, which easily undergo elimination of water on treatment with an acid to afford 1,4-dihydropyridines. The reaction is highly selective; thus with electron-donating alkenes only 3-substituted 2-hydroxytetrahydropyridines are obtained (eq 5), and with electron-accepting alkenes only 4-substituted 2-hydroxytetrahydropyridines are obtained (eq 6).[4]

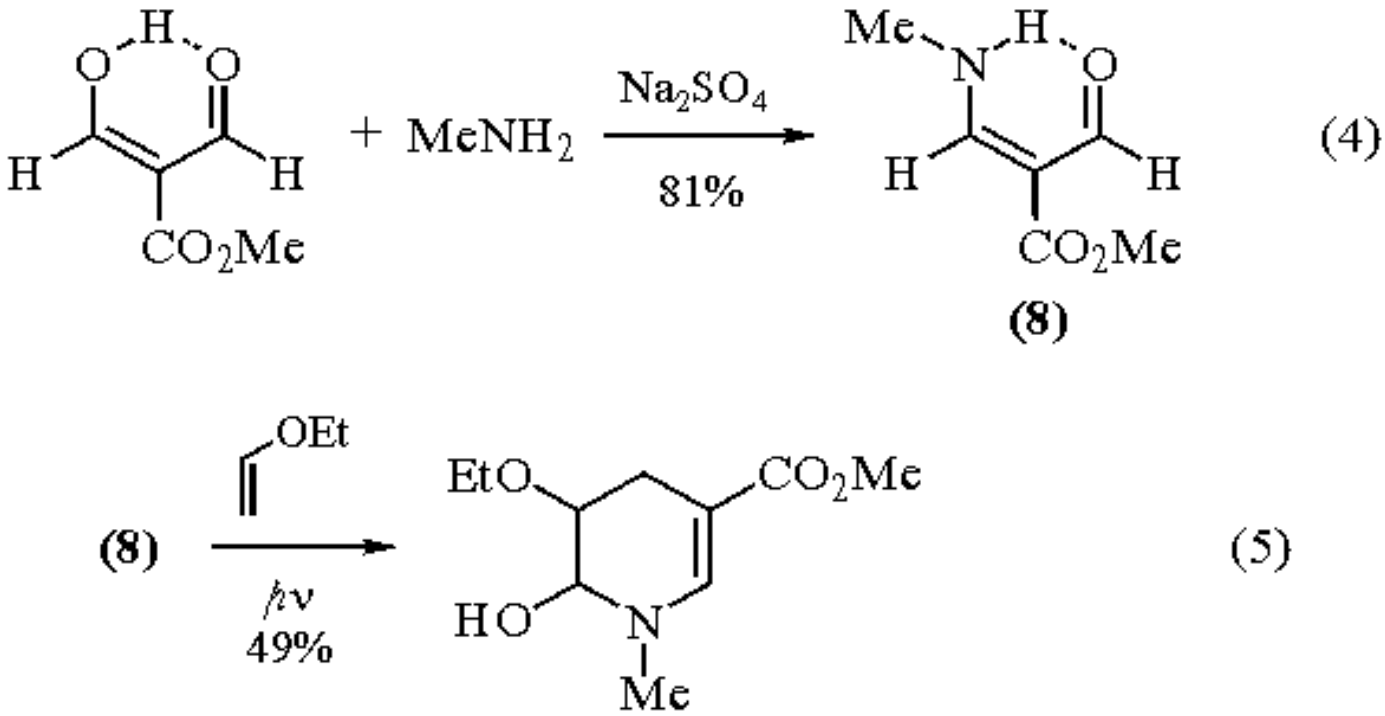

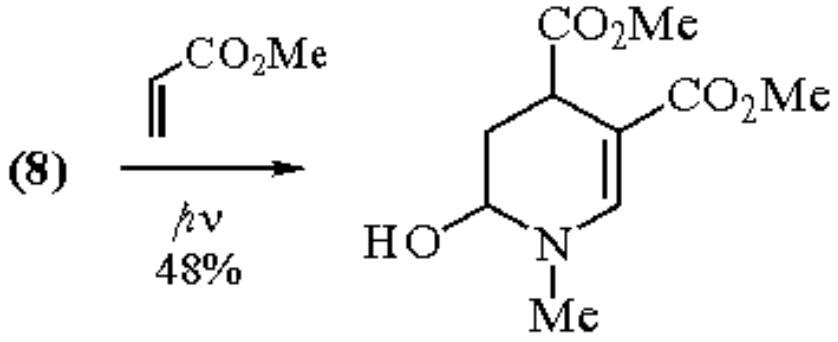

(6)

In a sequential transformation,[9] which consists of a [2 + 2] photoannulation of an enamino aldehyde, obtained from (**1**), and an intramolecular C-C bond formation of the intermediate iminium salt, benzo[*a*]quinolizidines, quinolizidines, and pyrido[1,2-*a*]azepines can be synthesized.[4a,f]

N-Acyl-enamino aldehydes from (**1**) react with enol ethers in a hetero-Diels-Alder reaction with inverse electron demand to give 4-aminodihydropyrans with the skeleton of branched amino sugars of the garosamine type.[4c]

Methyl diformylacetate[5b] and its acetylated form[5a] were also used as carbonyl compounds for a Wittig reaction, with moderate yields.

Related Reagents.

3-Ethoxyacrolein; ***Ethyl 3,3-Diethoxypropanoate***; ***Ethyl 3-Ethoxyacrylate***; ***Ethyl Hydroxymethyleneacetate, Sodium Salt***; ***Malondialdehyde***.

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1. (a) Tietze, L. F.; Glüsenkamp, K. H.; Nakane, M.; Hutchinson, C. R. *AG* **1982**, *94*, 81. (b) Baldwin, S. W.; Crimmins, M. T. *JACS* **1982**, *104*, 1132. (c) Baldwin, S. W.; Crimmins, M. T.; Cheek, V. I. *S* **1978**, 210. (d) Hutchinson, C. R.; Mattes, K. C.; Nakane, M.; Partridge, J. J.; Uskoković, M. R. *HCA* **1978**, *61*, 1221. (e) Kinast, G.; Tietze, L. F. *CB* **1976**, *109*, 3626. (f) Tietze, L. F. *JACS* **1974**, *96*, 946. (g) Tietze, L. F. *CB* **1974**, *107*, 2499. (h) Partridge, J. J.; Chadha, N. K.; Uskoković, M. R. *JACS* **1973**, *95*, 532. (i) Büchi, G.; Carlson, J. A.; Powell Jr., J. E.; Tietze, L. F. *JACS* **1973**, *95*, 540. (j) Büchi, G.; Carlson, J. A.; Powell Jr., J. E.; Tietze, L. F. *JACS* **1970**, *92*, 2165.
2. De Mayo, P. *ACR* **1971**, *4*, 41.
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4. (a) Tietze, L. F.; Wünsch, J. R.; Noltemeyer, M. *T* **1992**, *48*, 2081. (b) Tietze, L. F.; Bergmann, A.; Brüggemann, K. *S* **1986**, 190. (c) Tietze, L. F.; Voss, E.; Harms, K.; Sheldrick, G. M. *TL* **1985**, *26*, 5273. (d) Tietze, L. F.; Bergmann, A.; Brüggemann, K. *TL* **1983**, *24*, 3579. (e) Tietze, L. F.; Brüggemann, K. *AG* **1982**, *94*, 550. (f) Tietze, L. F.; Brüggemann, K. *AG* **1979**, *91*, 575.
5. (a) Ramage, R.; MacLeod, A. M. *T* **1986**, *42*, 3251. (b) Ramage, R.; MacLeod, A. M. *CC* **1984**, 1008.
6. Panizzi, L. *G* **1946**, *76*, 56.
7. Methyl 3,3-dimethoxypropanoate can also be prepared by acylation of methyl vinyl ether followed by methanolysis in the presence of potassium carbonate: Tietze, L. F.; Meier, H.; Voss, E. *S* **1988**, 274.
8. (a) Hutchinson, C. R.; Nakane, M.; Gollman, H.; Knutson, P. L. *OS* **1986**, *64*, 144. (b) Nakane, M.; Gollman, H.; Hutchinson, C. R.; Knutson, P. L. *JOC* **1980**, *45*, 2536.

Methyl Dilithioacetoacetate

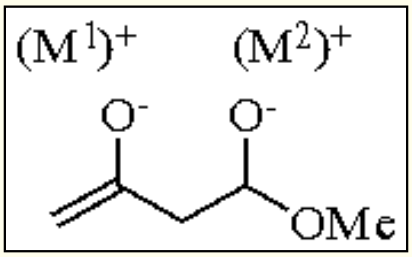

[30568-00-4] ($M^1 = M^2 = Li^+$)

[53437-05-1] · $C_5H_6Li_2O_3$ · Methyl Dilithioacetoacetate · (MW 127.99) ($M^1 = Li^+$, $M^2 = Na^+$)

[64670-05-9] · $C_5H_6LiNaO_3$ · Methyl Lithiosodioacetoacetate · (MW 144.04)

(four-carbon chain, all four carbons of which can be reacted regioselectively; versatile starting material in synthesis of complex molecules; undergoes γ-alkylation and γ-acylation)

Solubility: sol THF, ether, dimethoxyethane, and HMPA; slightly sol hydrocarbon solvents.

Form Supplied in: generated in situ.

Analysis of Reagent Purity: NMR spectroscopy or mass spectrometry of D_2O quench.[1]

Preparative Methods: dianion (**1**) is prepared in a dry solvent, usually THF or diethyl ether, by adding the β-keto ester to 1.1 equiv of ***Sodium Hydride***, which has been washed free of mineral oil, and then adding 1.05 equiv of ***n-Butyllithium*** at 0 °C (eq 1).[1] It may also be prepared by treating the β-keto ester with 2.0 equiv of ***Lithium Diisopropylamide*** or ***Lithium 2,2,6,6-Tetramethylpiperidide*** at 0 °C.[1] These methods may be used to generated the dianions of a wide range of β-keto esters. The dianion (**1**) may be quenched with D_2O and the degree of dianion formation determined by integration of the ^1H NMR methyl peak at δ 2.2 relative to the ester signal or by mass spectrometry.[1] Occasionally it is necessary to add HMPA to dissolve the dianions of more substituted β-keto esters.

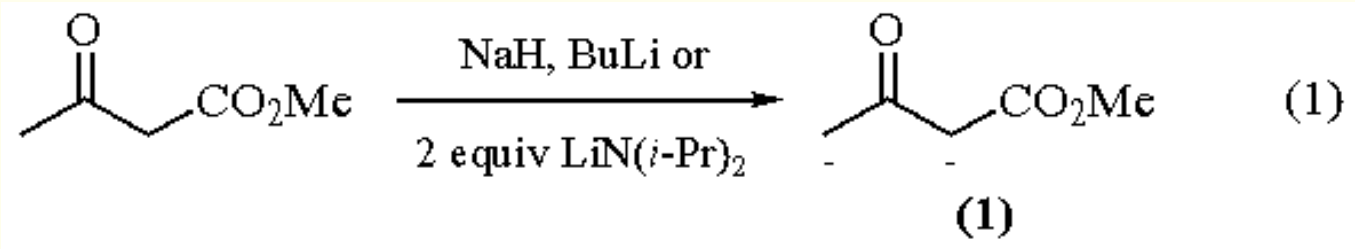

Handling, Storage, and Precautions: generated in solution; stable for hours at 0 °C; reacts with moisture and oxygen.

Introduction.

Acetoacetate esters provide a four-carbon chain to homologate simpler molecules. The utility of this homologation is that all four carbons subsequently can be reacted regioselectively. Thus the acetoacetate unit is one of the most versatile starting materials available in the synthesis of complex natural and unnatural products.

Alkylation of Methyl Acetoacetate Dianion.

The dianion (**1**) reacts with primary and secondary halides and sulfonates to give the γ-alkylated products (**2**) in good yield (eq 2 and Table 1). Halides are the most common alkylating agents. However, sulfonates will also react. The triflate is effective in the case of hindered alkylating agents.[7] Primary halides react without difficulty. Secondary halides are less reactive and some do not react under these conditions. Tertiary halides do not undergo alkylation. The reaction is compatible with a number of other functional groups and protecting groups. It is not necessary to protect alcohol groups, provided excess dianion is used. Following monoalkylation of (**1**), addition of a second equiv of base will regenerate a dianion which can be alkylated a second time (eq 3).[57] Highest yields in this one-pot bisalkylation required the addition of ***N,N´-Dimethylpropyleneurea***.[57] Other esters of acetoacetate, such as ethyl, *t*-butyl, and 2-trimethylsilylethyl, have also been used in these reactions.

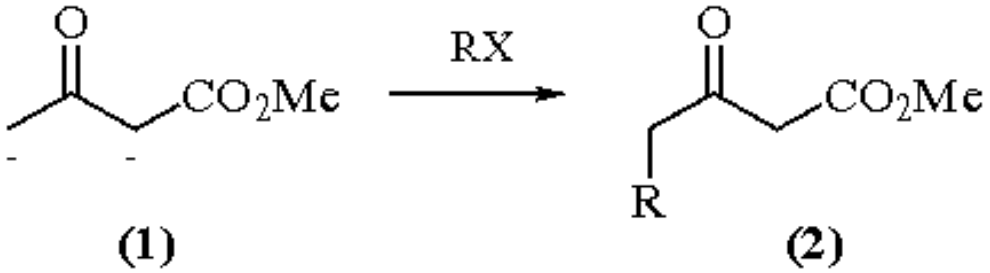

(2)

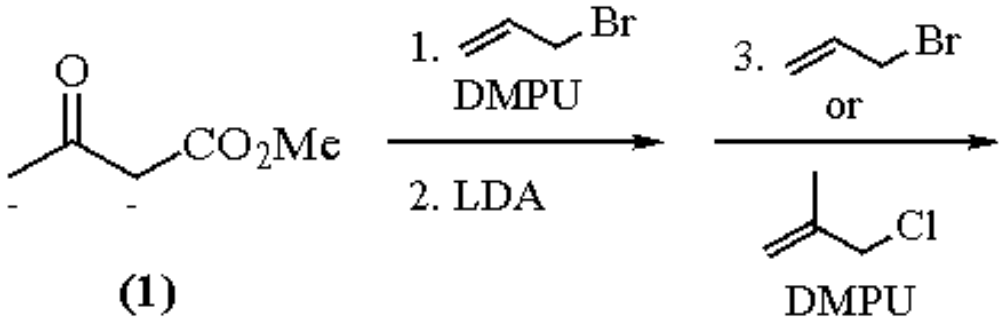

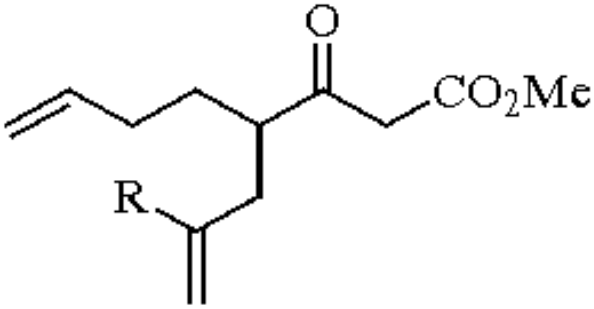

(3)

R = H, Me
57-58%

Table 1 Alkylation of Acetoacetate Dianions with Halides, Sulfonates, and Epoxides (eqs 2, 3, and 5)

Alkylating agent	Yield (%)	Ref.
Alkyl halides	50-90	1-26, 54, 56
Alkyl sulfonates	30-90	4b, 7, 53
Allylic halides	40-100	1, 5-7, 9, 14, 27-46
Alkynyl halides	85-90	25, 47, 48
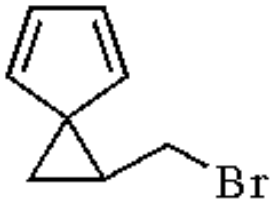	43	49
Benzylic halides	40-85	1, 18, 50-52
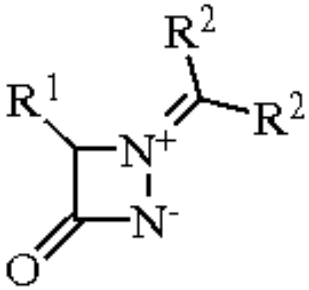	30-50	55
Epoxides	50-90	16, 59-61

A recent example which exemplifies the complex carbon skeletons which can be assembled from acetoacetate dianions is taken from the synthesis of latrunculin A (eq 4).[58] The dianion of the β-keto ester (**3**) reacts with the phosphonium salt (**4**) which is generated in situ. The resulting phosphorane is treated with an aldehyde to give the diene β-keto ester (**5**), all in one pot. The next higher vinylog of (**4**) yields (*E*,*E*,*Z*)-trienes in the same reaction.[58c]

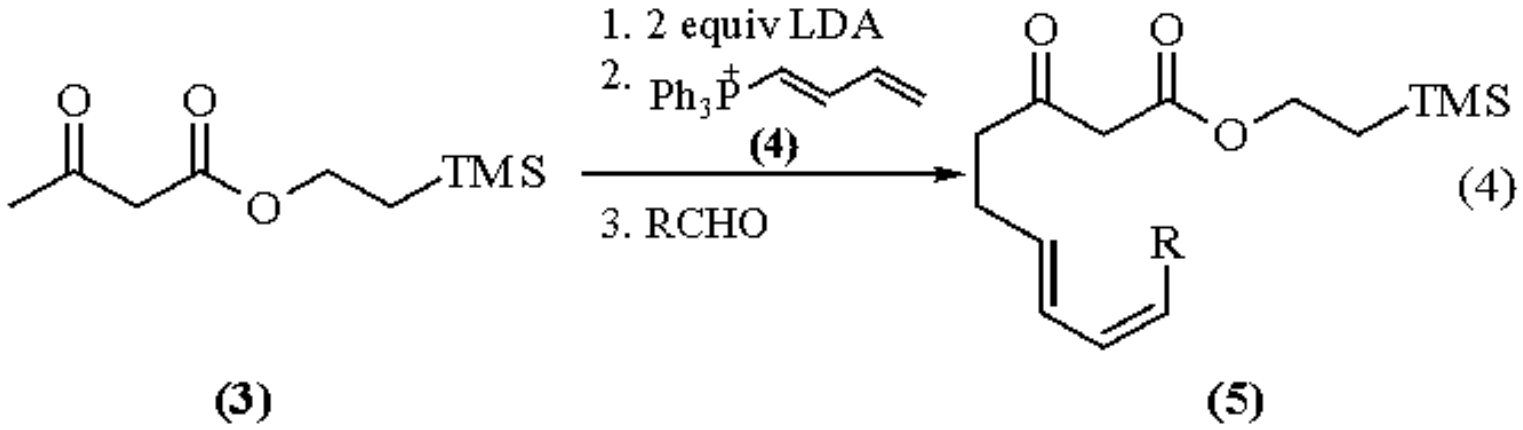

Epoxides react with (**1**) to give alcohols (Table 1). In the case of simple epoxides the initially formed alcohols often could not be isolated, because they underwent cyclization to tetrahydrofuranylidene-2-acetates (**6**) (eq 5).[16] In the case of more complex epoxides the alcohols usually could be isolated in good yield and in most cases the opening of the epoxide ring was regioselective.[68-70]

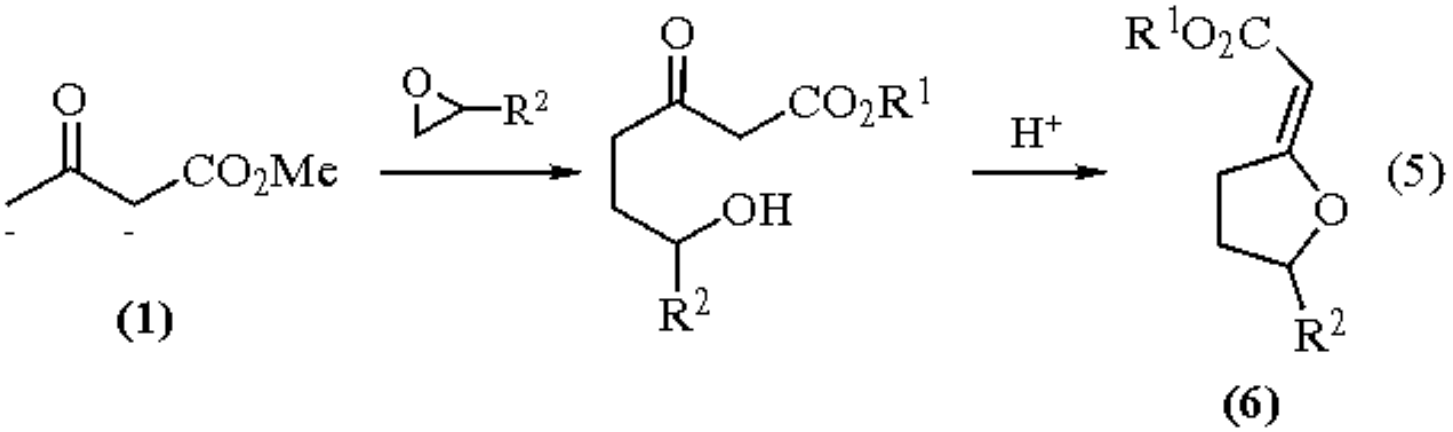

The dianion of methyl acetoacetate reacts with other simple electrophiles including benzenesulfenyl halides,[62] alkyl nitrates,[63] chlorophosphates,[64] and carbon dioxide.[65] Often the reaction is very clean, leading to the γ-substituted product.

The dianion (**1**) undergoes aldol condensations with a variety of aldehydes (Table 2). The resulting δ-hydroxy-β-keto esters (**7**) can be cyclized to the β-keto-δ-lactones, oxidized or dehydrated (eq 6). The stereoselectivity in the addition to chiral aldehydes is low, although it can be improved with the addition of Lewis acids.[77] In the case of α,β-unsaturated aldehydes and ketones, only 1,2-addition is observed.

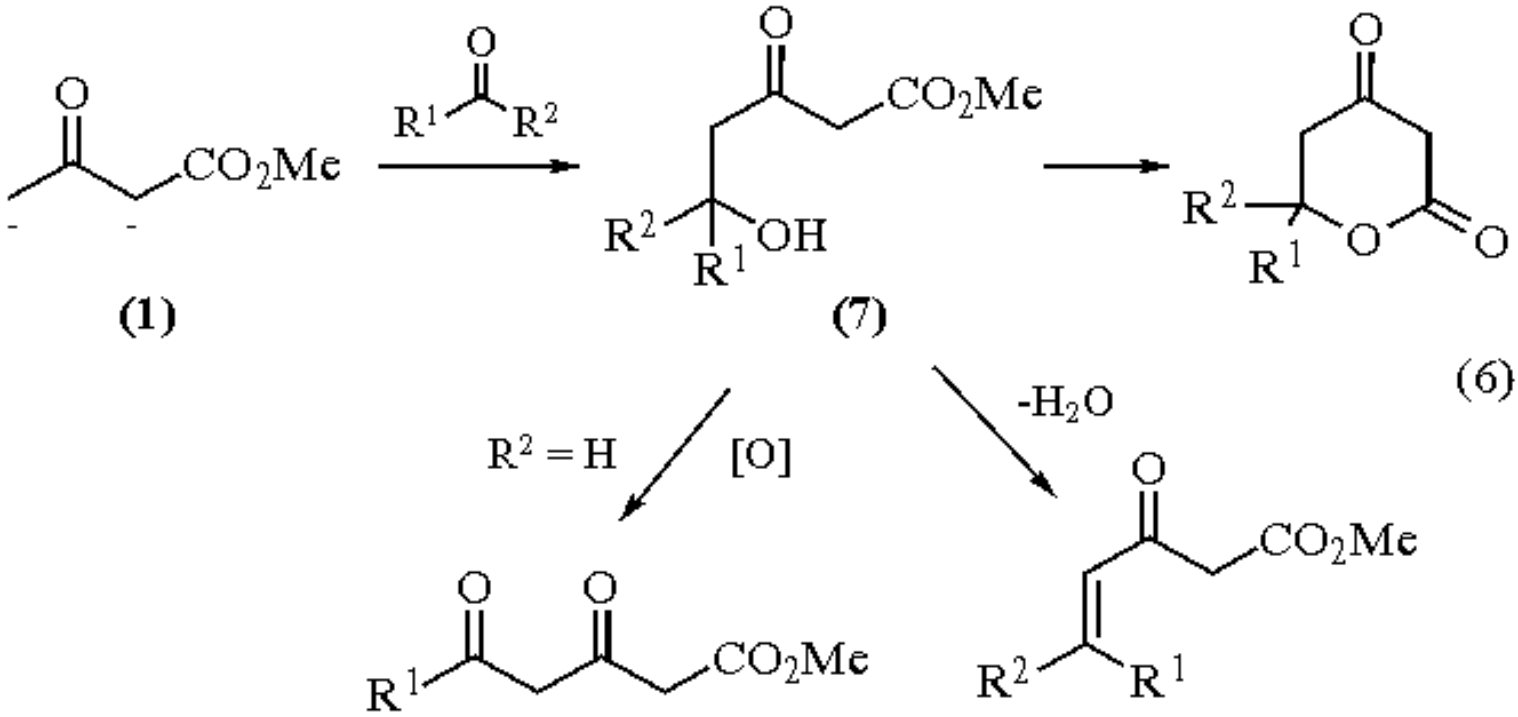

Table 2 Aldol Condensations of Acetoacetate Dianions with Aldehydes and Ketones (eq 6)

R^1COR^2	Yield (%)	Ref.
Aliphatic aldehydes	25-90	66-69, 71-77
Aromatic aldehydes	70-95	67, 68, 70
Conjugated aldehydes[a]	50-100	50, 68, 78-85
Aliphatic ketones	25-70	67, 68, 86, 87
Conjugated ketones[a]	60-85	67, 88, 89
Aromatic ketones	60-95	67, 90
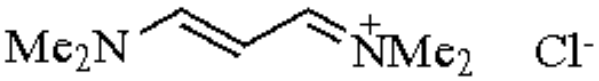	17	91

[a] Yield of 1,2-addition product.

Dianion (**1**) can be acylated. A limited amount of work has been carried out using nitriles as the acylating agent and the product was found to be the enamino β-keto ester (**8**) (eq 7).[92]

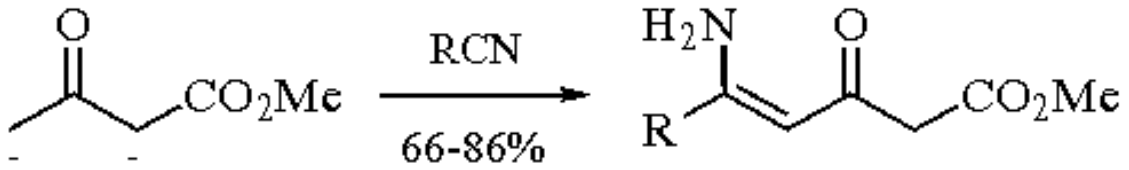

(7)

(1) **(8)** R = Me, Ph

A much larger range of ester derivatives have been condensed with dianion (**1**) (Table 3). Because the monoanion of the initial product (**9**) is more acidic than the monoanion (**10**) of acetoacetate, the starting dianion (**1**) is quenched as the reaction proceeds. Initially this problem was overcome by adding an extra equiv of base during the reaction.[92] However, the problem does limit the yield of (**9**) (eq 8). Now an excess of dianion (**1**) is usually used to optimize the yield of acylated product (**9**). It was also found that addition of ***Boron Trifluoride Etherate*** improves the yield of (**9**).[93] Addition of TMEDA also leads to increased yields in these acylations.[94]

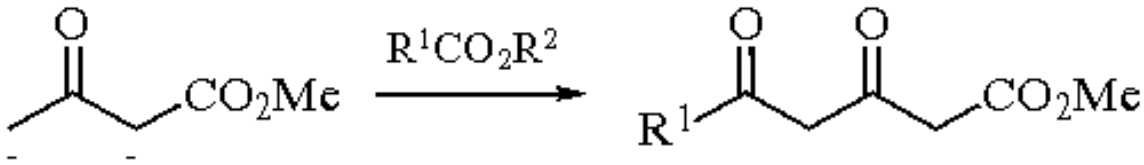

(8)

(1) **(9)**

Table 3 Acylation Reactions of Acetoacetate Dianions (eqs 8-10)

Acylating reagent	Yield (%)	Ref.
Aliphatic esters	45-80	92, 93, 96c
Aromatic esters	40-85	92-94
Lactones	40	95-96d
Diesters	30-95	100-102
Amides	60-85	93
Bisamides	45-70	93
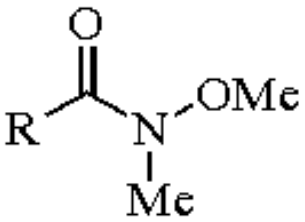	40-90	96b, 103

The acylated products have been used in the synthesis of many polyketide aromatic natural products.[96] For example, condensation of (**1**) with the monoanion (**10**) of methyl acetoacetate yields the triketo ester (**11**), which can be cyclized to the orsellinate (**12**) (eq 9).[92,97] The conversion of (**1**) to (**12**) can be carried out in one pot by refluxing the solution of the

dianion (**1**) and the monoanion (**10**) (eq 9).[98,99] These condensations could be applied to dicarboxylic acid derivatives to yield polyketo diesters which readily cyclized (eq 10).[96,101] Acylations with amides in the presence of $BF_3.Et_2O$ led to improved yields of the triketo esters (**11**).[93] This was further refined with the use of *N*-methoxy-*N*-methylamides as acylating agents.[96b,103]

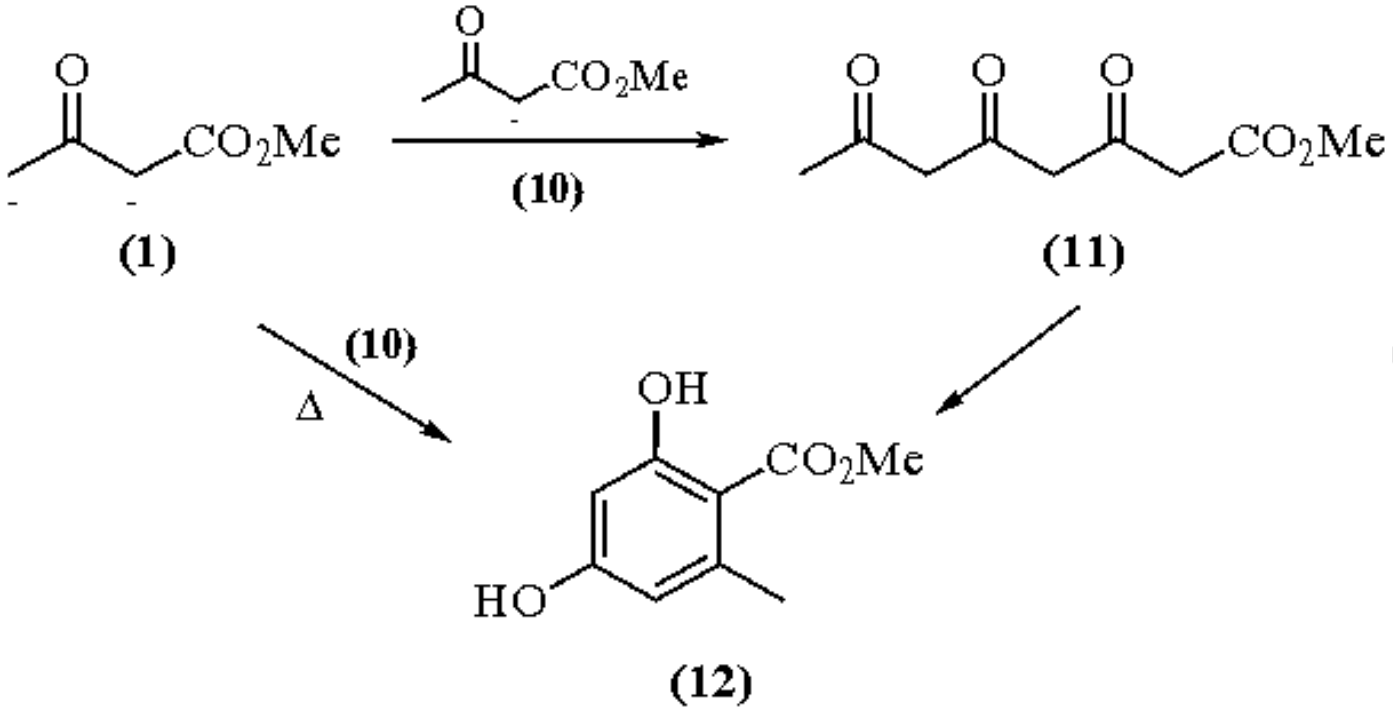

(9)

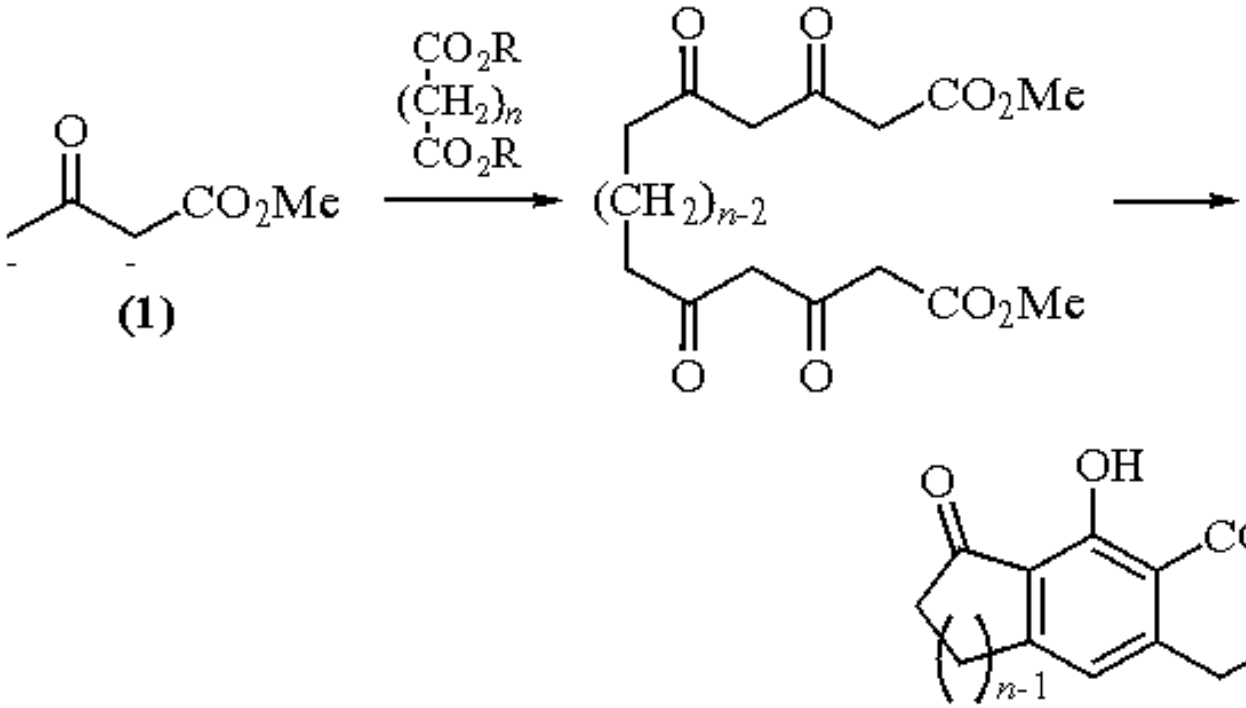

(10)

Dianion (**1**) undergoes 1,4-addition to certain Michael acceptors such as α,β-unsaturated thioamides,[104] α,β-unsaturated sulfoxides,[105] and α,β-unsaturated sulfones.[106]

Dianion (**1**) has proven to be so useful that several synthetic equivalents to it have been developed and these are listed in Table 4. Most of these reagents are generated under the strongly basic conditions that (**1**) is formed under. However, the

bistrimethylsilyl ether (**13**) reacts with alkylating and acylating reagents in the presence of Lewis acids and provides a very useful complement to (**1**).

Table 4 Synthetic Equivalents to the Acetoacetate Dianion

Synthetic equivalent	Reaction	Ref.
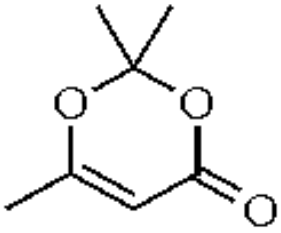	Aldol	107
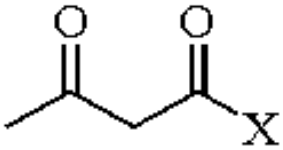 X = NMe_2, S-*t*-Bu	Alkylation, aldol, acylation	108, 109
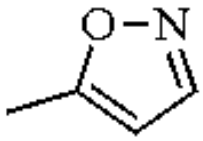	Alkylation, aldol, acylation	110
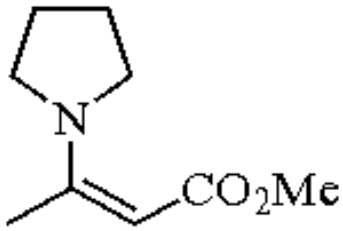	Alkylation	111
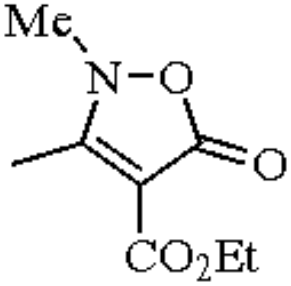	Alkylation	112
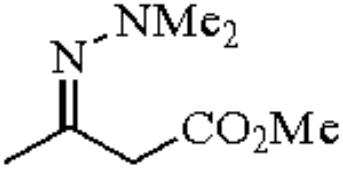	Aldol	113

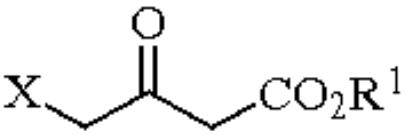	Wittig	114-116
$X = PO(OR_2)_2$, $P(O)Ph_2$		
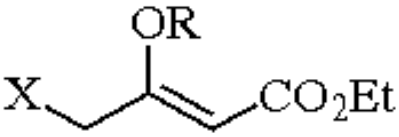	Wittig	117, 118
$X = PO(OMe)_2$, PPh_3^+		
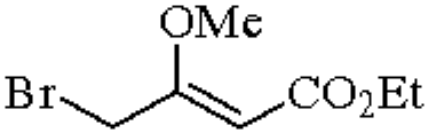	Reformatsky	119
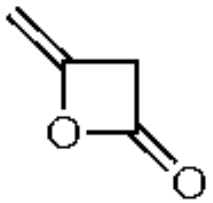	Alkylation	121
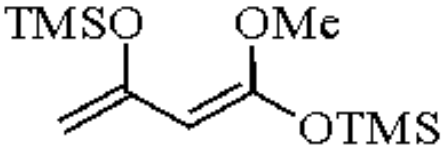 **(13)**	Alkylation, aldol, acylation	120

Related Reagents.

Acetoacetic Acid; ***Acetone***; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***Diketene***; ***Dimethyl 1,3-Acetonedicarboxylate***; ***Ethyl Acetoacetate***; ***Ethyl 4-Chloroacetoacetate***; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***1-Methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene***; ***N-Methoxy-N-methylacetamide***; ***2,4-Pentanedione***; ***Trimethylsilylacetone***; ***2,2,6-Trimethyl-4H-1,3-dioxin-4-one***.

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1. (a) Weiler, L. *JACS* **1970**, *92*, 6702; (b) Huckin, S. N.; Weiler, L. *JACS* **1974**, *96*, 1082.
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4. (a) Sum, P. E.; Weiler, L. *CJC* **1979**, *57*, 1475; (b) Alderdice, M.; Spino, C.; Weiler, L. *CJC* **1993**, *71*, 1955.
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Methyl 3-(Dimethylamino)propionate[1]

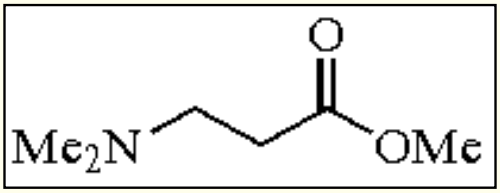

[3853-06-3] · $C_6H_{13}NO_2$ · Methyl 3-(Dimethylamino)propionate · (MW 131.20)

(masked acrylate synthetic equivalent; for preparation of α-methylene esters, acids, and lactones[2])

Physical Data: bp 56 °C/15 mmHg.

Solubility: sol all common solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: ^{1}H and ^{13}C NMR; GC.

Preparative Method: reaction of ***Methyl Acrylate*** with dimethylamine in ether at 0-25 °C.[3]

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: routine laboratory techniques; exhibits typical tendency of amines to undergo slow oxidation in the air. Use in a fume hood.

Preparation of 2-Substituted Acrylate Derivatives.

Methyl 3-(dimethylamino)propionate undergoes straightforward enolate formation upon treatment with ***Lithium Diisopropylamide***. The resulting enolate undergoes high yield reactions with a number of alkylating agents. A representative reaction sequence is shown using a cyclic allylic halide (eq 1). The alkylation product is converted to the quaternary ammonium salt using ***Iodomethane*** followed by ***1,5-Diazabicyclo[4.3.0]non-5-ene***-induced elimination to give the 2-substituted acrylate derivative. Among the possible further reactions are iodo lactonization of the free acid and then either ***1,8-Diazabicyclo[5.4.0]undec-7-ene***-induced dehydroiodination or ***Tri-n-butylstannane***-promoted reductive deiodination.

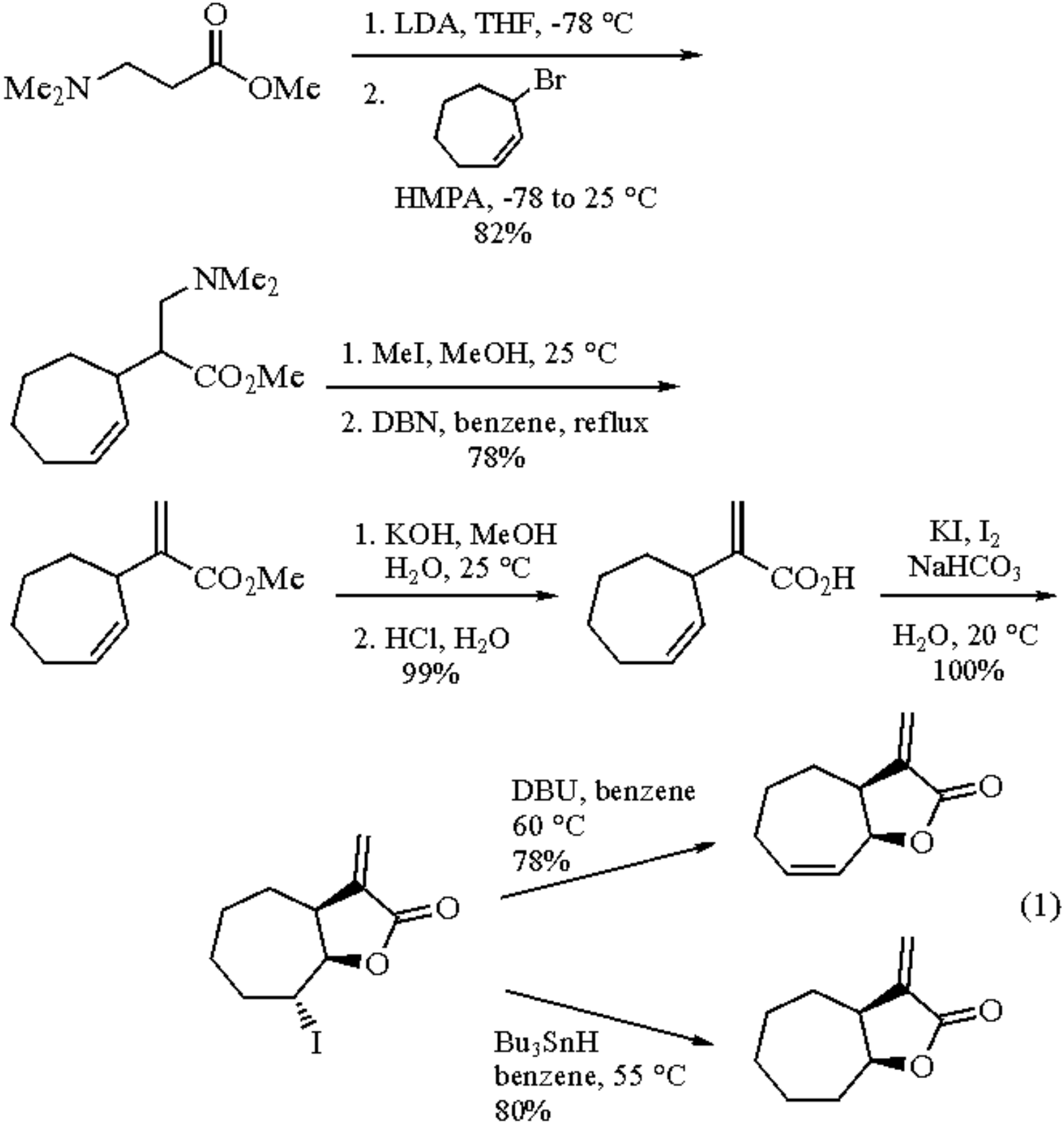

Alternative Reagents.

The primary motivation for the development of this reagent and a large number of related methods was the common natural occurrence of α-methylene lactones. Literally thousands of these compounds are known, and several of them

possess antitumor activity.[1] The other methods are too numerous to describe here,[1] but a recent modification of the present method employs imines in place of alkyl halides in the reaction of the enolate; the ultimate products are α-alkylidene-β-lactam derivatives.[4]

Related Reagents.

Ethyl Acrylate; ***Formaldehyde***; ***Methyl 3-Hydroxypropionate***.

---

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Methyl (4*R*,5*R*)-(*E*)-3-(1,3-Dimethyl-4,5-diphenyl-2-imidazolidinyl)propenoate

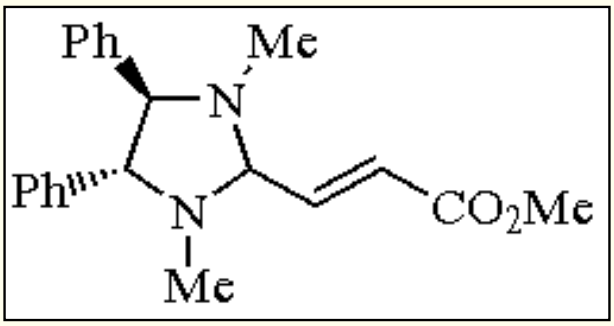

[135212-29-2] · $C_{21}H_{24}N_2O_2$ · Methyl (4*R*,5*R*)-(*E*)-3-(1,3-Dimethyl-4,5-diphenyl-2-imidazolidinyl)propenoate · (MW 336.47)

(a chiral synthetic equivalent of methyl (*E*)-4-oxo-2-butenoate)

Physical Data: colorless needles (MeOH); mp 109-110 °C; [α]23D +45.0° (*c* 0.6, $CHCl_3$);[1] IR, ^{1}H NMR, ^{13}C NMR, MS spectral data, and X-ray structural data are also available.[1]

Solubility: very sol dichloromethane, chloroform, ethyl acetate, acetone; sol methanol, ethanol; hardly sol hexane.

Analysis of Reagent Purity: chiral HPLC.[1]

Preparative Methods: both the (4*R*,5*R*) and (4*S*,5*S*) compounds are readily available by condensation of optically active 1,2-bis(methylamino)-1,2-diphenylethanes[2] with methyl (*E*)-4-oxo-2-butenoate.[3]

Pyrrolidine Synthesis.

The lithium (*Z*)-enolate of methyl *N*-benzylideneglycinate undergoes a cycloaddition rapidly at -78 °C with methyl (4*R*,5*R*)-(*E*)-3-(1,3-dimethyl-4,5-diphenyl-2-imidazolidinyl)propenoate (**1**) to give pyrrolidine-2,4-dicarboxylate in quantitative yield and as a single stereoisomer (eq 1).[1] Removal of the chiral auxiliary from the cycloadduct can be readily performed by treatment with conc ***Sulfuric Acid*** in MeOH at rt to produce the optically pure pyrrolidine-2,4-dicarboxylate bearing an acetal substituent at the 3-position.

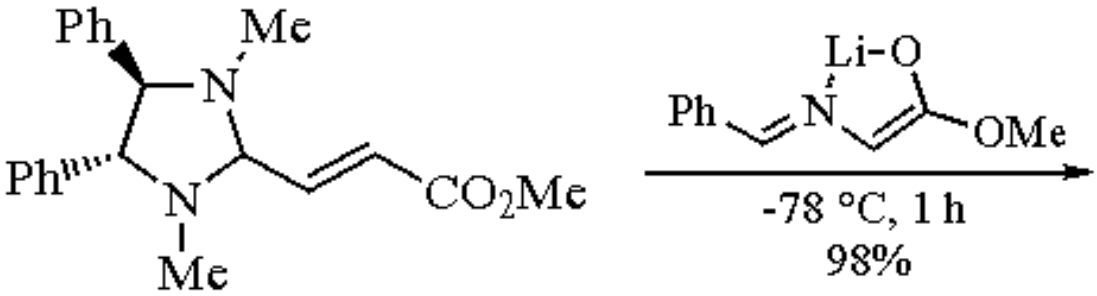

(1)

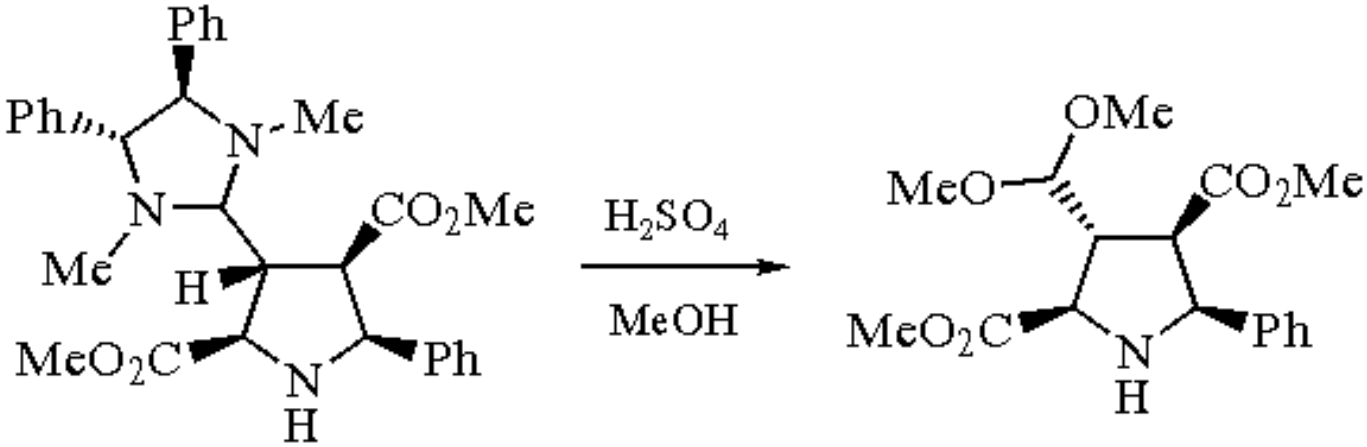

(1)

Asymmetric Nitrile Oxide Cycloadditions.

Although the dipolar cycloadditions of nitrile oxides with (**1**) are poor both in reactivity and regioselectivity, regioisomeric isoxazolines are obtained as single diastereomers (eq 2).[4] Removal of the chiral auxiliary can again be performed by an acetal exchange reaction under reflux in MeOH in the presence of H_2SO_4.

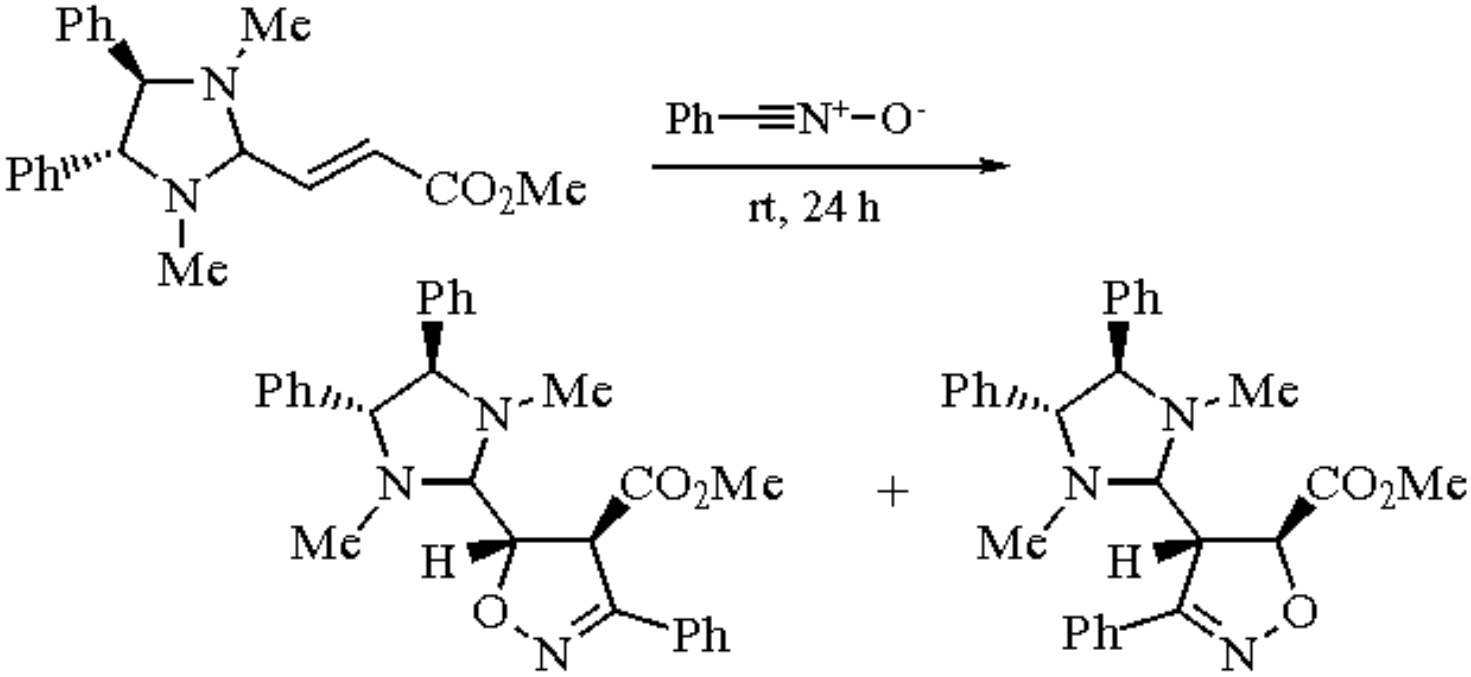

34% 16%

(2)

Related α,β-Unsaturated Esters.

Similar α,β-unsaturated esters bearing a heterocyclic chiral auxiliary of α-amino acid origin at the β-position are known and have been utilized in asymmetric synthesis. Effective asymmetric conjugate additions of cuprates to (**2**),[5] (**3**),[6] and (**5**),[7] epoxidations of (**3**),[8] and dipolar cycloadditions of (**2**)[9] have been reported. Although oxazolidine (**4**)[10] is only obtained as an 86:14 equilibrating mixture of stereoisomers, reactions with the lithium (*Z*)-enolate of methyl *N*-benzylideneglycinate (see ***Ethyl N-Benzylideneglycinate***) are exclusively diastereoselective.

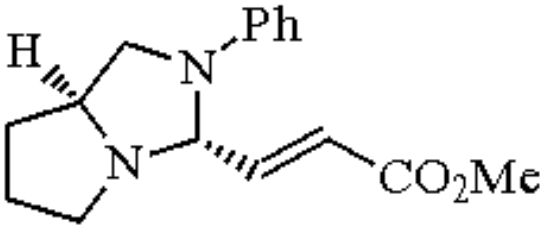

(2)

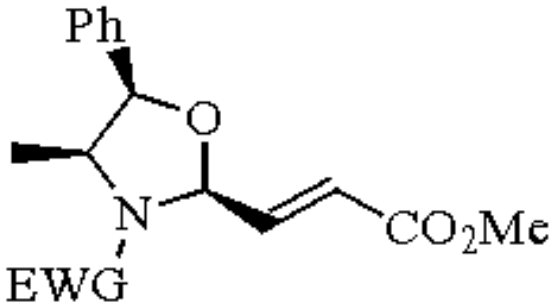

(3) EWG = BnOCO, *p*-Ts

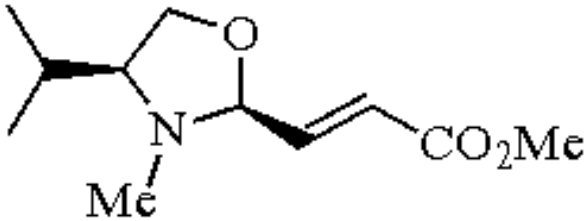

(4)

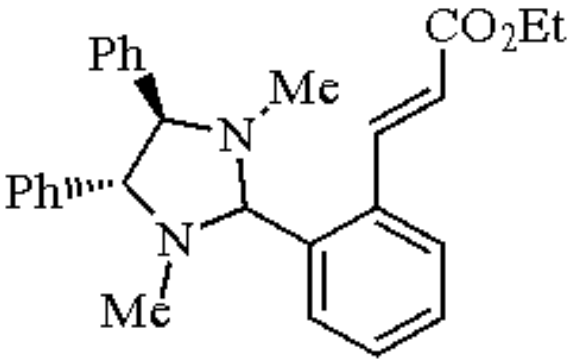

(5)

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Methyldiphenylchlorosilane

$MePh_2SiCl$

[144-79-6] · $C_{13}H_{13}ClSi$ · Methyldiphenylchlorosilane · (MW 232.80)

(protecting group for alcohols; reacts with carboxylic acids and sulfoximes; C-silylates lithium ester enolates)

Physical Data: bp 295 °C/760 mmHg; *d* 1.128 g cm^{-3}; *n*20D 1.5742.

Form Supplied in: clear or transparent, pale yellow liquid.

Analysis of Reagent Purity: gas chromatography on a nonpolar column such as SE-30.

Solubility: sol most organic solvents; reacts with protic solvents such as alcohols, acids, amines, water.

Purification: vacuum distillation is preferred method.

Handling, Storage, and Precautions: chlorosilanes react with water and even moisture in the air to generate HCl and siloxanes, care should be taken to minimize contact with air. Use in a fume hood.

Protecting Group for Alcohols.

The reaction of methyldiphenylchlorosilane with alcohols in the presence of imidazole provides the methyldiphenylsilyl-protected alcohol. The protection of primary, secondary, and tertiary alcohols proceeds with high yields. The methyldiphenylsilyl-protected alcohols are intermediate in stability between those of the trimethylsilyl- and *t*-butyldimethylsilyl-protected ones.[1] It has been shown that, in general, the phenyl-substituted silyl groups are more readily removed by base, where electronic factors are more important, than the trialkylsilyl protecting groups. On the other hand, with acid hydrolysis steric factors play a more significant role and the phenyl-substituted silyl groups are more stable than the trimethylsilyl group, but less stable than the more sterically hindered triethylsilyl and other trialkylsilyl groups.[2] The methyldiphenylsilyl ethers can be oxidized by the chromium reagents ***Dipyridine Chromium(VI) Oxide***, ***Pyridinium Chlorochromate***, and ***Pyridinium Dichromate*** (eq 1). [1]

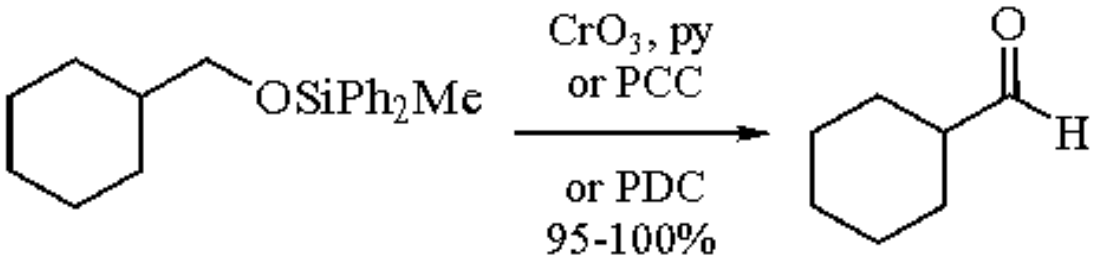

(1)

A primary alcohol was readily methyldiphenylsilylated by the reaction of methyldiphenylchlorosilane in the presence of an amine. In eq 2 the amine is also the reagent being silylated.[3]

$$MePh_2SiCl + 2\,HOCH_2CH_2NR_2 \longrightarrow MePh_2SiOCH_2CH_2NR_2 + HOCH_2CH_2NR_2 \cdot HCl \quad (2)$$

$$R = Me\ (99\%),\ Et\ (95\%)$$

The methyldiphenylsilyl esters of carboxylic acids can be prepared by the reaction of the chlorosilane with the acid in the presence of ***Triethylamine*** or with the potassium salt of the acid (eqs 3 and 4).[4]

$$MePh_2SiCl + RCO_2H \xrightarrow{Et_3N} RCO_2SiPh_2Me + Et_3N \cdot HCl \quad (3)$$

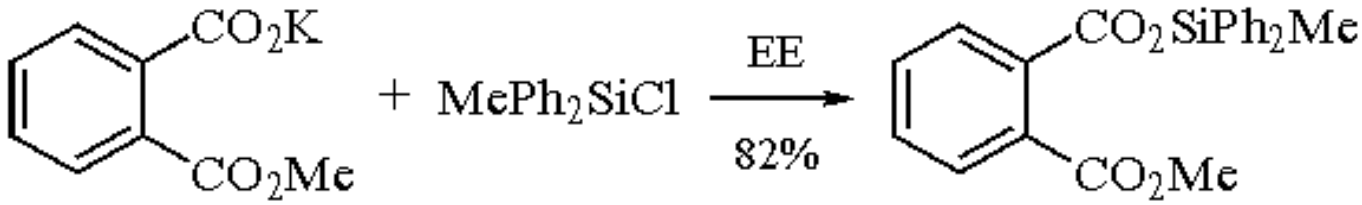

(4)

Sulfoximes can be silylated with methyldiphenylchlorosilane. The resulting methyldiphenylsilylated sulfoximes can be deprotonated at the methyl group and the anion condensed with aldehydes. The diastereospecificity is greater with the methyldiphenylsilyl group than with the *t*-butyldimethylsilyl group (eqs 5 and 6).[5]

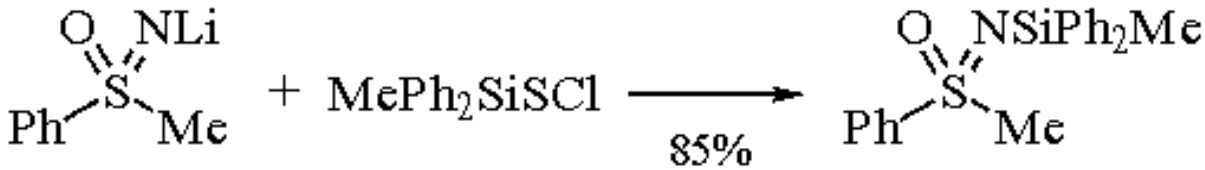

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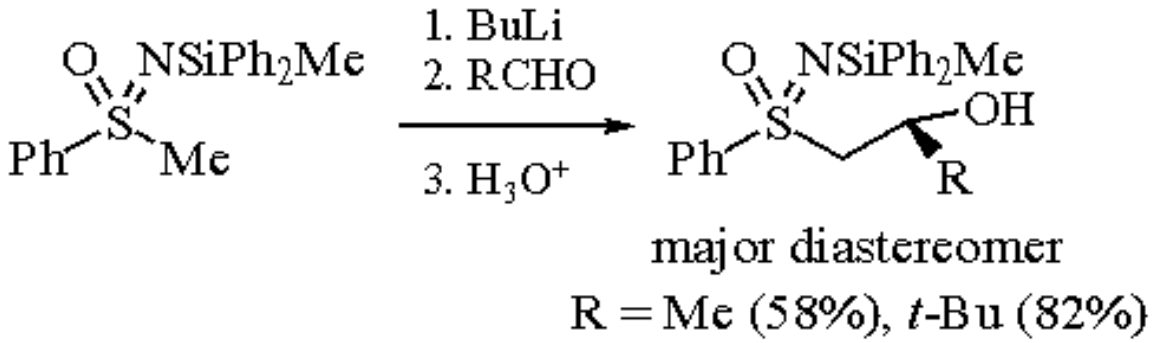

(6)

C-Silylation of Lithium Ester Enolates.

A very useful asset of methyldiphenylchlorosilane is its ability to directly provide α-(methyldiphenylsilyl) esters (eq 7).[6] These α-(methyldiphenylsilyl) esters have themselves proved to be precursors to alkenes, ketones, α-(methyldiphenylsilyl) ketones, and enol silyl ethers and have been used in the synthesis of some natural products.[6b] An elegant use of the methyldiphenylsilyl group in synthesis (eq 8) is that reported by Villanueva and Prieto,[7] who methyldiphenylsilylated the protected ethyl 4-oxolevulinate to give the α-silyl ester (**1**). This was then treated with 3-phenylpropylmagnesium bromide to give ketone (**2**), a reaction made possible by the presence of the bulky methyldiphenylsilyl group. This ketone was then regioselectively deprotonated on the side opposite to the methyldiphenylsilyl group and the resulting enolate trimethylsilylated to give enol silyl ether (**3**), which was subjected to an intramol ecular Mukaiyama reaction to give cyclopentanone (**4**). Deprotonation and reaction with ***Formaldehyde*** produces a methylenomycin B derivative, (**5**).

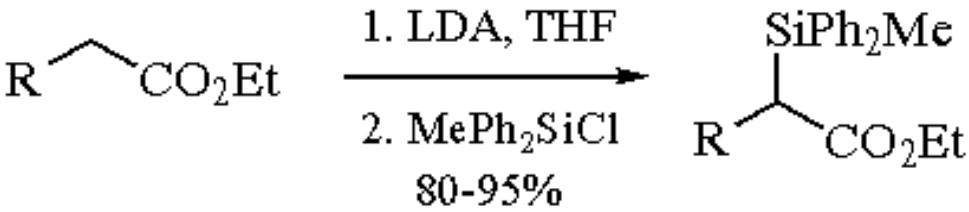

(7)

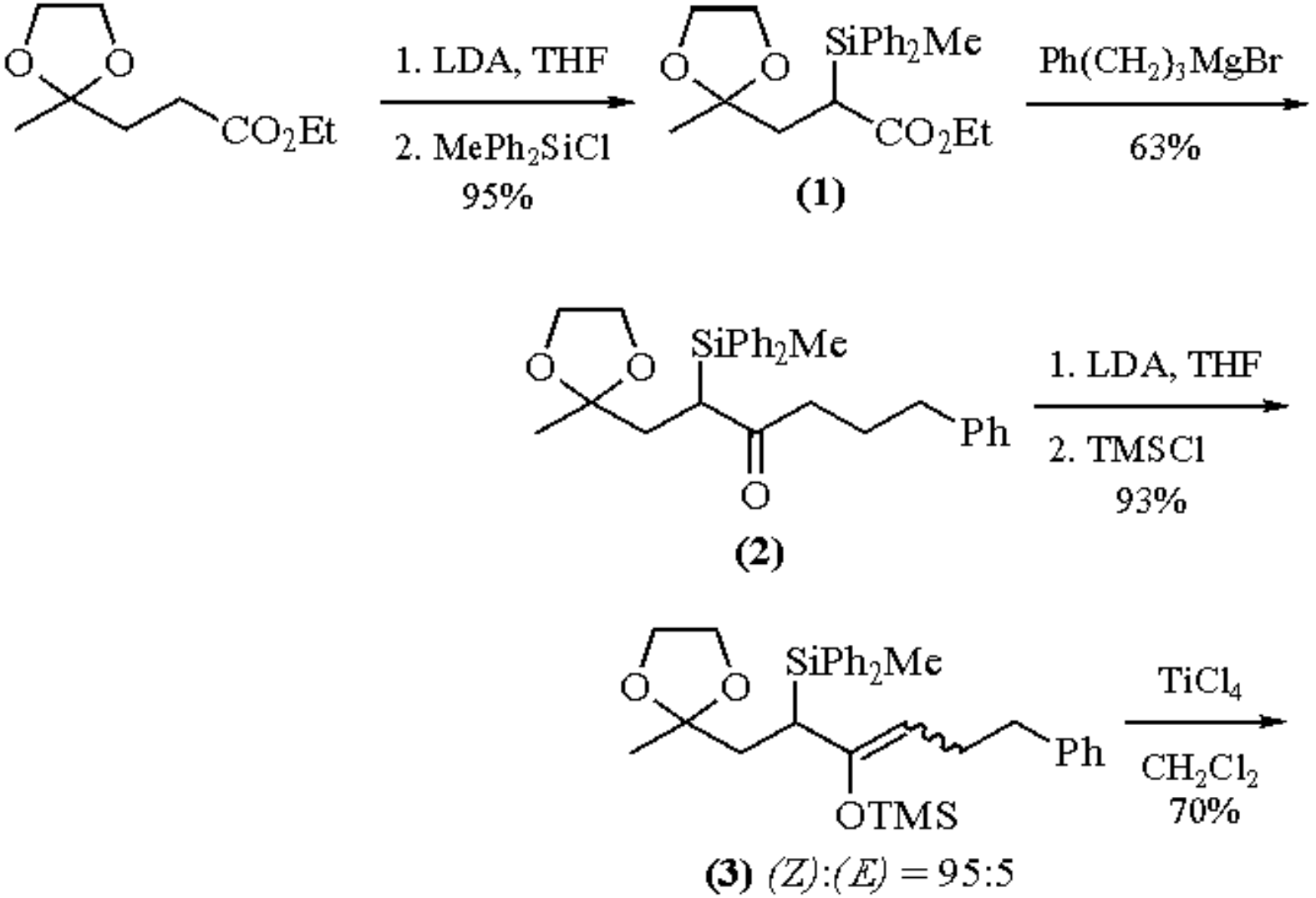

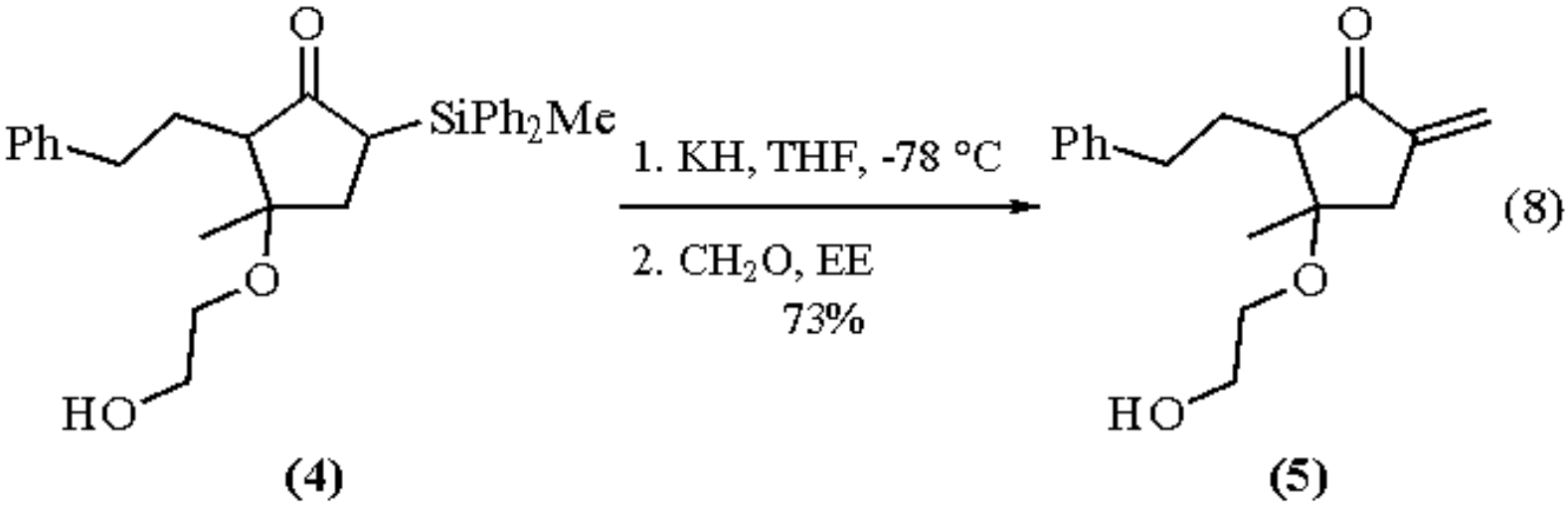

(8)

Other Methyldiphenylsilylations.

Methyldiphenylchlorosilane was used to form 6-silyluracils and uridines.[8] The yields were better than those obtained with ***Chlorotrimethylsilane*** (eq 9). The methyldiphenylsilylation of the lithium anion of 3-triethylsilyloxy-1,4-pentadiene occurs to place the methyldiphenylsilyl group on the 1-position, providing, after deprotection, the β-

methyldiphenylsilyl ketone (**6**) (eq 10).[9]

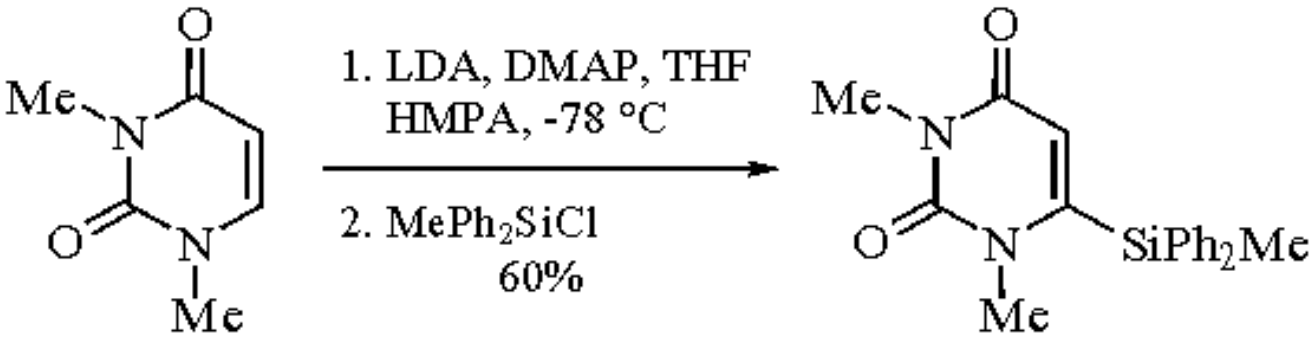

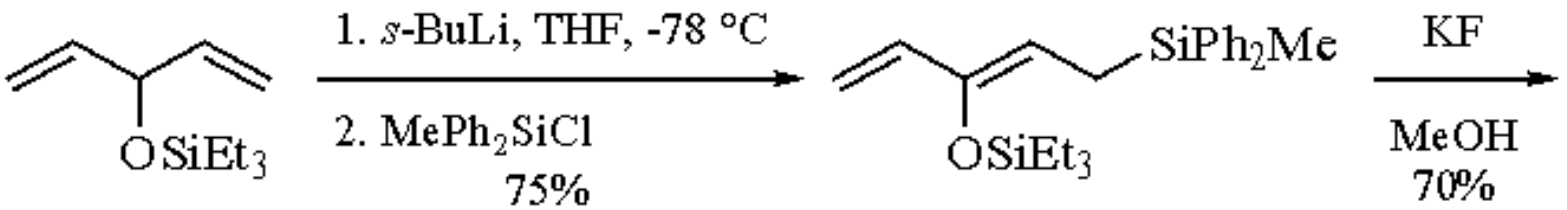

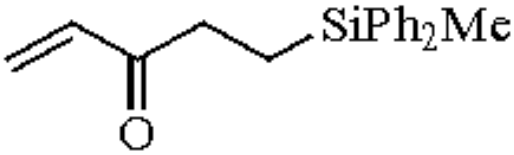

(10)

(6)

Related Reagents.

t-Butyldimethylchlorosilane; ***t-Butyldiphenylchlorosilane***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***.

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Gerald L. Larson

2,2´-Methylenebis(1,3,2-dioxaborinane), Lithium Complex[1]

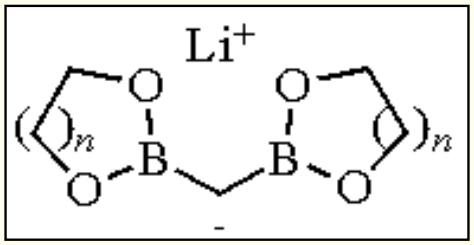

(**1**; *n* = 2)

[63035-39-2] · $C_7H_{13}B_2LiO_4$ · 2,2´-Methylenebis(1,3,2-dioxaborinane), Lithium Complex · (MW 189.76)
(**2**; *n* = 1)

[57404-82-7] · $C_5H_9B_2LiO_4$ · 2,2´-Methylenebis(1,3,2-dioxaborolane), Lithium Complex · (MW 161.70)

(converts aldehydes to (*E*)-alkenylboronic esters,[1,2] which can be converted to the homologous aldehyde[3] or coupled with alkenyl halides;[4] converts primary alkyl halides to 1,1-alkylidenebis(boronic esters)[2])

Physical Data: air-sensitive solid; precipitates from THF at 0 °C. The immediate precursor, 2,2´-methylenebis(1,3,2-dioxaborinane), crystallizes from 4:1 Et_2O/pentane, mp 42-43 °C, ^1H NMR δ 0.13 (s, BCH_2B).

Preparative Methods: methylenebis(boronic acid) tetramethyl ester is prepared by addition of a mixture of $(MeO)_2BCl$ and CH_2Cl_2 to Li dispersion in THF vigorously stirred at -40 to -30 °C,[1a,5] then transesterified with 1,3-propanediol.[2] The lithium complex is formed by treatment with ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LiTMP) and TMEDA in THF.[2]

Handling, Storage, and Precautions: 2,2´-methylenebis(1,3,2-dioxaborinane) can be transferred and weighed in air, but should be stored under an inert atmosphere. The lithium complex is generated as needed and must be protected from moisture and oxygen.

Reagent Preparation.

Dimethoxyboron chloride is prepared by mixing ***Trimethyl Borate*** with ***Boron Trichloride*** below 0 °C, then mixed with dichloromethane and added to a vigorously stirred suspension of lithium metal dispersion in THF kept at an internal temperature between -40 and -30 °C by manipulating the rate of addition and the position of the -78 °C cooling bath.[1a,5] It is essential that the stirring be very vigorous, that there be some excess of $(MeO)_2BCl$ and CH_2Cl_2 over the

amount of Li, and that large amounts of unreacted $(MeO)_2BCl/CH_2Cl_2$ not be allowed to accumulate before the exothermic reaction sets in. The lithium salts are filtered with the aid of celite in a large Büchner funnel under a blanket of argon (*CAUTION*: some pyrophoric lithium metal may remain). The filtrate is given an initial rapid distillation, and the distillate is redistilled to separate the $CH_2[B(OMe)_2]_2$ (**3**), bp 48-52 °C 15 mmHg (35%). Treatment of (**3**) with 1,3-propanediol and crystallization from 4:1 Et_2O/pentane yields 2,2´-methylenebis(1,3,2-dioxaborinane) (**4**), mp 42-43 °C (78%). The lithium complex of 2,2´-methylenebis(1,3,2-dioxaborinane) (**1**) precipitates on treatment of (**4**) with LiTMP and TMEDA in THF (eq 1).[2] For some purposes, (**1**) can be used as a slurry, but for reaction with aldehydes the yields are much improved if (**1**) is filtered in a Schlenk apparatus first.[2]

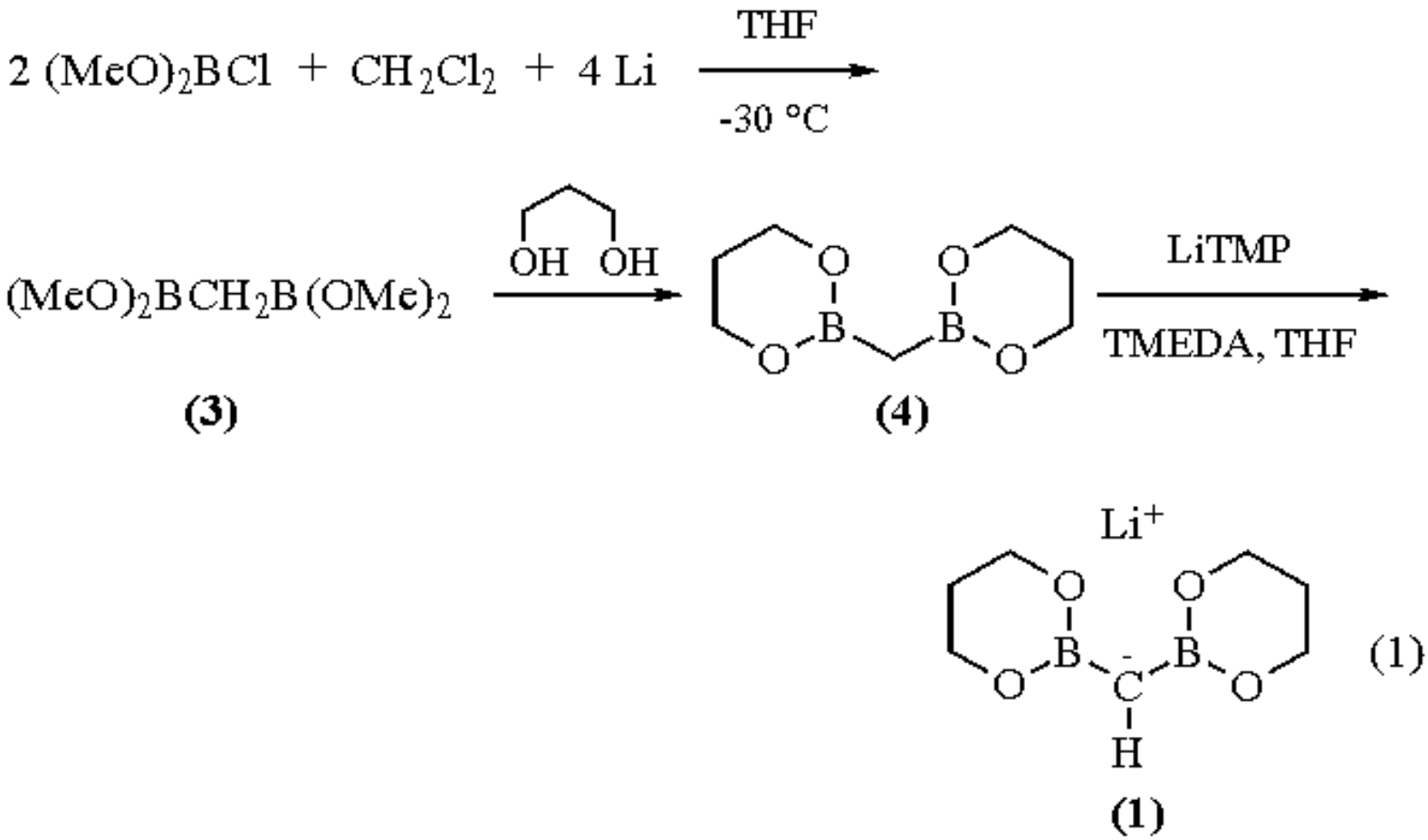

Substitution of $CHCl_3$ for CH_2Cl_2 in the above procedure provides $HC[B(OMe)_2]_3$,[1a,5] which with ethylene glycol yields 2,2´,2´´-methanetris(1,3,2-dioxaborolane) (**5**), which with BuLi forms the lithium complex of 2,2´-methylenebis(1,3,2-dioxaborolane) (**2**) (eq 2).[6] Yields of $HC[B(OMe)_2]_3$ varied more than those of (**3**),[2] and the deprotonation of (**4**) is generally more practical even though the lithiation of (**2**) is cleaner, and use of (**2**) does not require the Schlenk filtration.

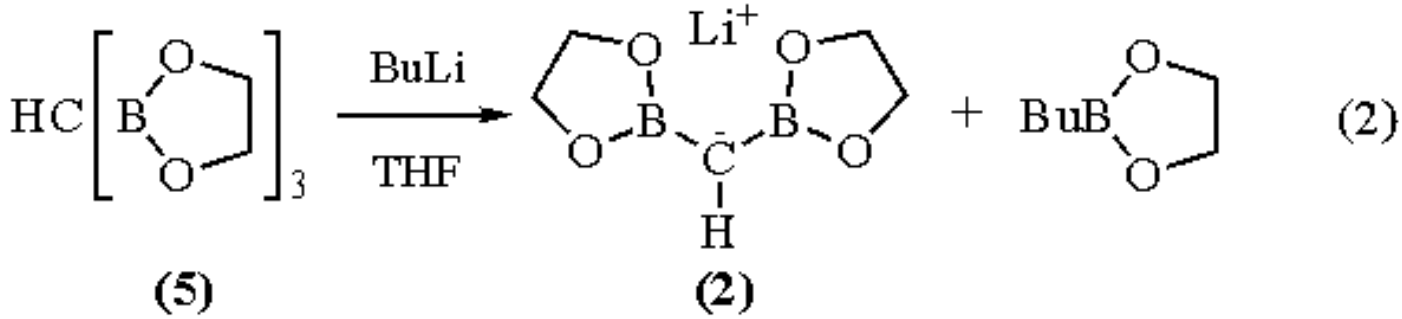

Alkenylboronic Esters.

A key step in the palytoxin synthesis was reaction of (**1**) with a structurally complicated aldehyde to form the corresponding (*E*)-1-alkenylboronic ester (eq 3), (*E*):(*Z*) ratio 8:1.[4] The usual route to (*E*)-1-alkenylboronic esters, hydroboration of an alkyne with catecholborane,[7] could not be used in this case because of interference by a remote urethane substituent.

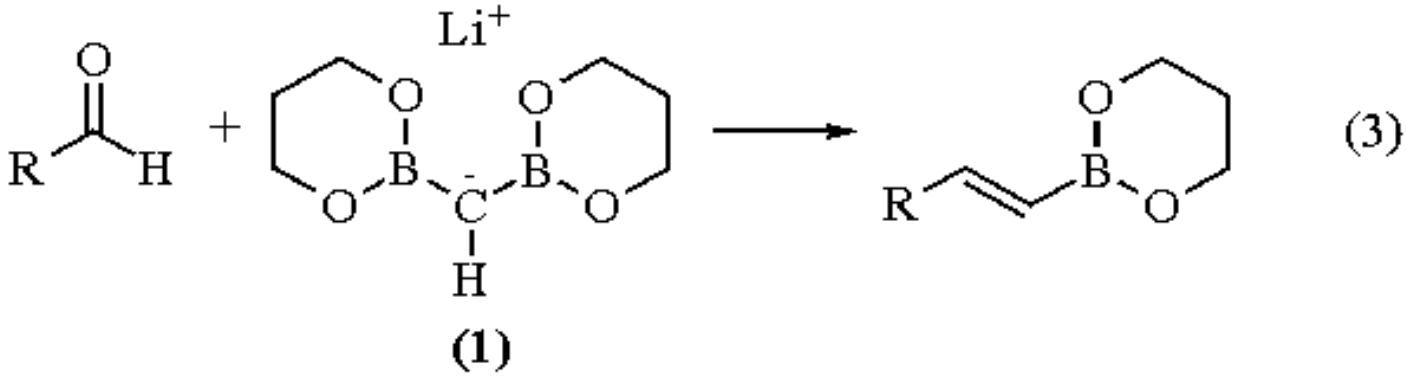

The model reactions for the foregoing chemistry were previous work done with (**2**), which yielded a series of (*E*)-1-alkenylboronic esters in ~10:1 (*E*):(*Z*) ratio.[6]

Carbonyl Homologation.

Reaction of (**2**) with aldehydes followed by in situ oxidation with ***Hydrogen Peroxide*** buffered with $NaHCO_3$ or, preferably, ***Sodium Perborate*** yields the homologous aldehydes (eq 4).[3]

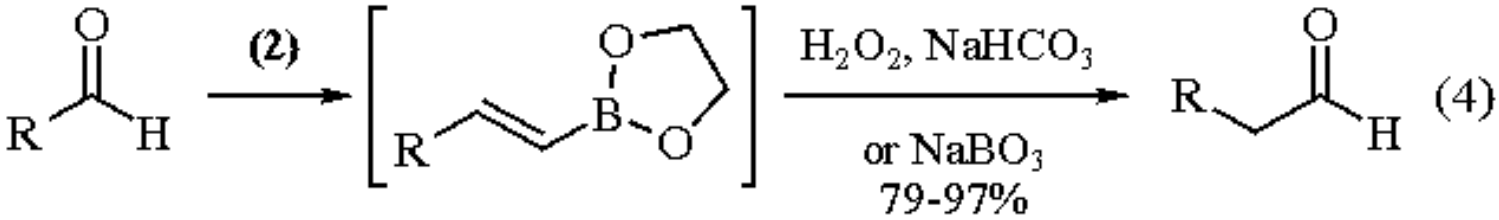

$R = Me(CH_2)_n$, $n = 3, 4, 7$; $R = Ph$; $R = H_2C{=}CH(CH_2)_3$

Ketones $R_2C{=}O$ were similarly converted to $R_2CH\text{-}CHO$ (65-81%). The use of (**1**) for this purpose has been shown to

give equivalent results in the one example tested, heptanal to octanal, but only if the (**1**) is collected by filtration in a Schlenk apparatus before reaction with the aldehyde.[3]

Alkylation and Acylation of (1).

Primary alkyl bromides or iodides alkylate (**1**), and the resulting 1,1-diboronic esters (**6**) can be deprotonated and alkylated a second time (eq 5).[2] In general, a better route to (**6**) is provided by dihydroboration of an alkyne with $HBCl_2$,[8] provided there is no interfering functionality or chain branching in R^1.

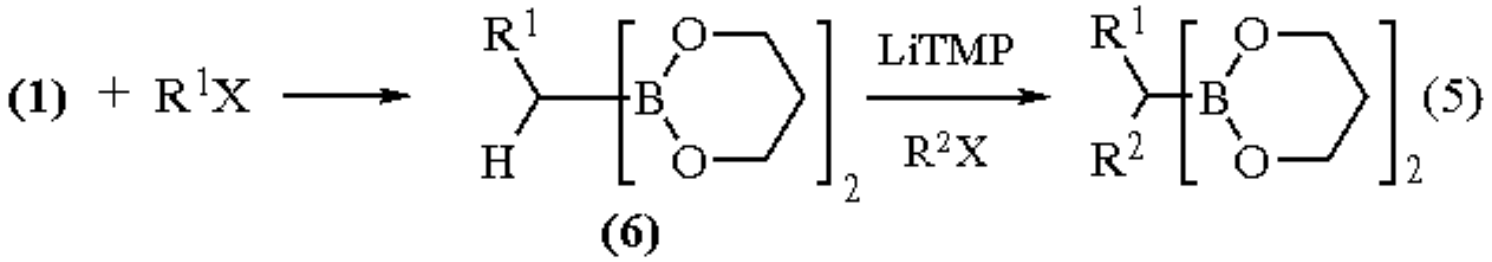

Reaction of (**1**) or the anion from (**6**) with carboxylic esters yields ketones (eq 6).[2] The recent ready availability of $RCH_2CH(BCl_2)_2$ and hence (**6**) via hydroboration[8] makes this route potentially useful.

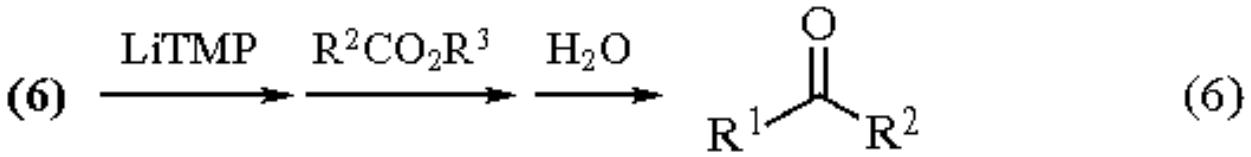

Related Reagents.

Other boronic esters that can be deprotonated and undergo reactions analogous to those of (**1**) include $Me_3SiCH_2BO_2C_2Me_4$[9] and $PhSCH_2BO_2C_2Me_4$.[10]

---

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Methylenecyclobutane

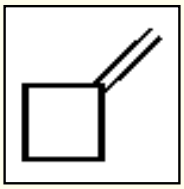

[1120-56-5] · C_5H_8 · Methylenecyclobutane · (MW 68.13)

(synthesis of 1-methylcyclobutene, cyclobutanone, and cyclopentanone)

Physical Data: bp 42 °C; *n*20D 1.4210.

Form Supplied in: usually available in ampules because of volatility.

Preparative Methods: may be prepared in 70% yield by ***Zinc*** reduction of pentaerythritol tetrabromide.[1] Typical impurities in samples prepared by this method are 2-methyl-1-butene and spirocyclopropane. An alternative synthesis is available via methylenation of ***Cyclobutanone***.[2]

Purification: NMR spectroscopy is the best method for determination of purity unless a GC equipped for determination of quite volatile materials is readily available.

Handling, Storage, and Precautions: use in a fume hood.

Methylenecyclobutane is used to prepare 1-methylcyclobutene by base-catalyzed double bond isomerization.[3] A useful allyllithium reagent may be prepared from methylenecyclobutane via ***n-Butyllithium/N,N,N´,N´-Tetramethylethylenediamine*** mediated metalation (eq 1).[4,5] Reaction of the cyclobutenylmethyllithium anion with electrophiles gives mixtures of regioisomeric products. In some cases the major cyclobutene products may be thermolyzed to give 2-substituted 1,3-butadienes.[4,5]

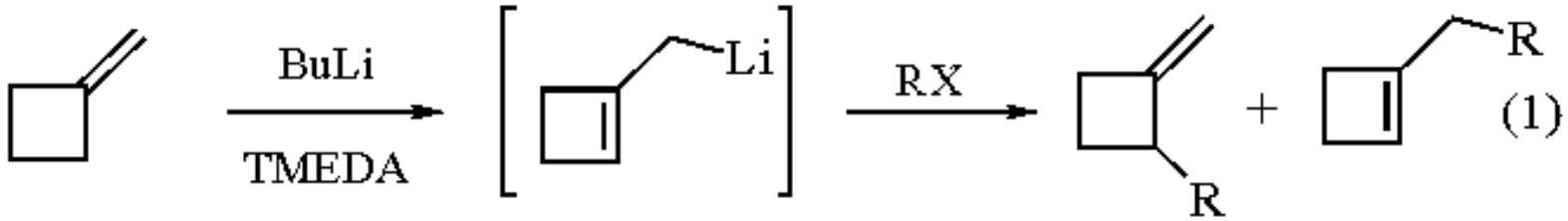

Methylenecyclobutane has also been used to prepare cyclobutanone[2] by ozonolysis (eq 2) and cyclopentanone[6] by ring expansion (eq 3).

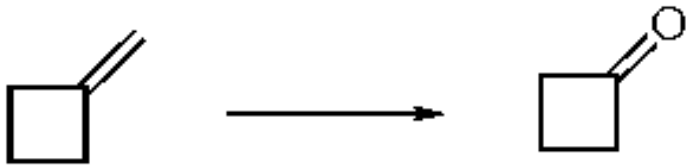

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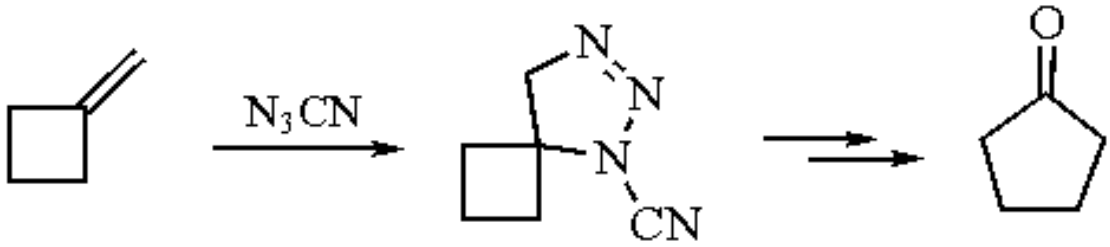

(3)

Related Reagents.

Cyclobutanone; ***Methylenecyclopropane***; ***Squaric Acid***; ***Tricarbonyl(cyclobutadiene)iron***.

---

1. Roberts, J. D.; Sauer, C. W. *JACS* **1949**, *71*, 3925.
2. Fitjer, L.; Quabeck, U. *S* **1987**, 299.
3. Shabtai, J.; Gil-Av, E. *JOC* **1963**, *28*, 2893.
4. Wilson, S. R.; Phillips, L. R. *TL* **1975**, 3047.
5. Wilson, S. R.; Phillips, L. R.; Natalie, Jr., K. J. *JACS* **1979**, *101*, 3340.
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Methylenecyclopropane[1]

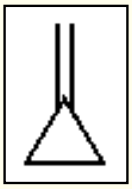

[6142-73-0] · C_4H_6 · Methylenecyclopropane · (MW 54.10)

(four-carbon building block useful for thermal, photochemical, and transition metal-mediated cycloadditions;[1] epoxidation and rearrangement yields cyclobutanone;[2] can be metalated[3] or transformed to 2,4-dilithio-1-butene[4])

Physical Data: bp 11 °C; *d* 0.85 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid.

Preparative Method: readily prepared by treatment of 3-chloro-2-methyl-1-propene with sodium *t*-butoxide (eq 1).[2]

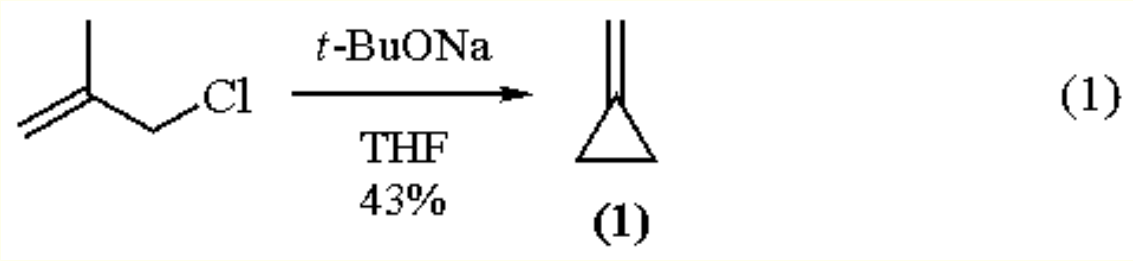

Cycloaddition.

Methylenecyclopropane (**1**) reacts as a dienophile in the Diels-Alder reaction (eq 2)[5] and undergoes photochemical [2 + 2] cycloadditions with both electron-rich and electron-poor alkenes (eq 3).[6] Neat thermolysis of (**1**) yields a mixture of [2 + 2] dimers (eq 4).[7]

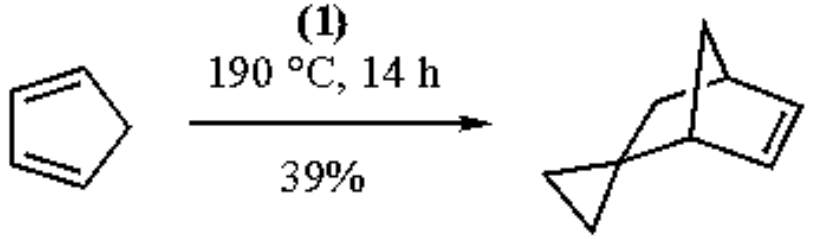

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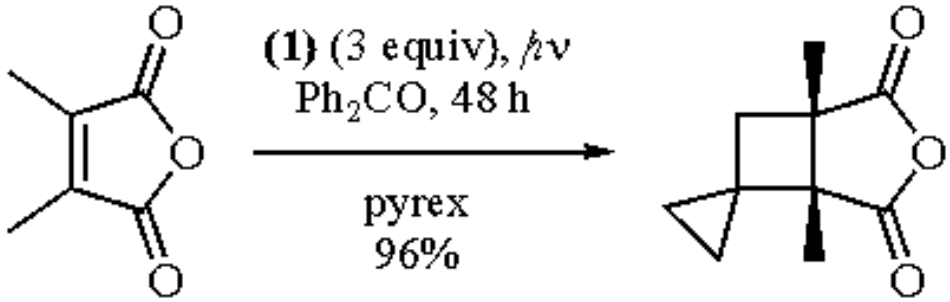

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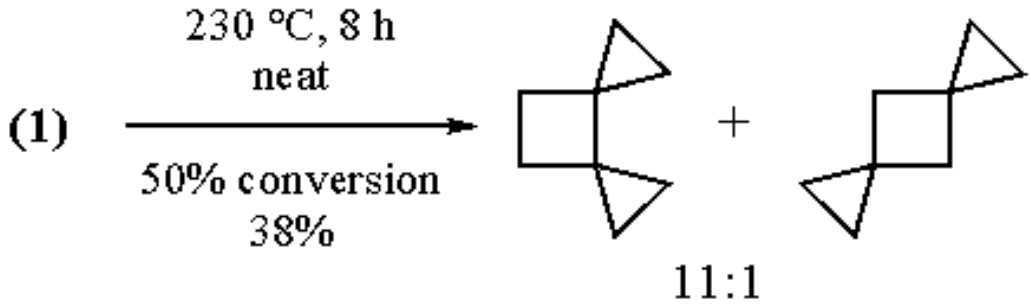

(4)

Dipolar cycloadditions proceed smoothly and regioselectively between (**1**) and ***Diazomethane***,[8] ***Phenyl Azide***,[8] and nitrones (eq 5).[9] The major nitrone cycloadducts such as (**2**) thermally rearrange to give 4-oxopiperidines (eq 6).[9]

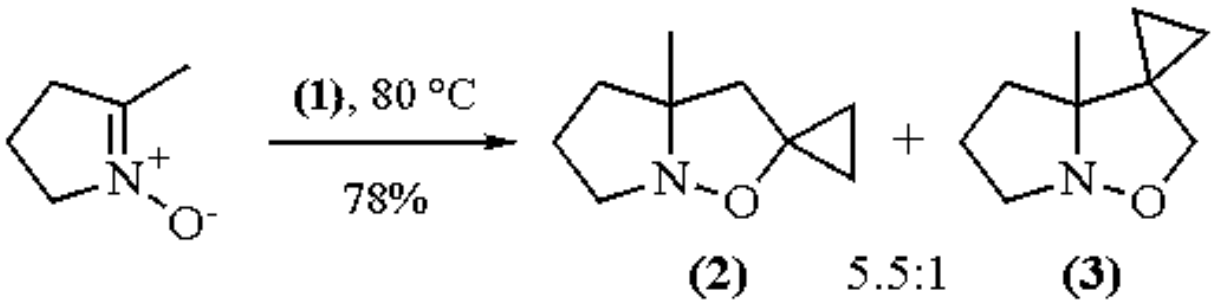

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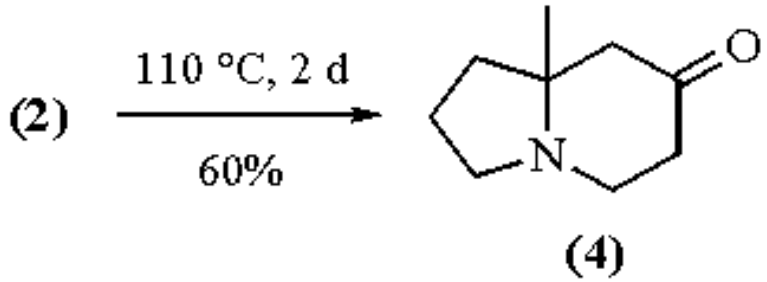

(6)

Transition metal-mediated chemistry of (**1**) can involve several intermediate forms (**5**)-(**7**) (eq 7). Reactions involving

Mo, Fe, Co, Rh, Ni, Pd, and Pt have been reported.[1]

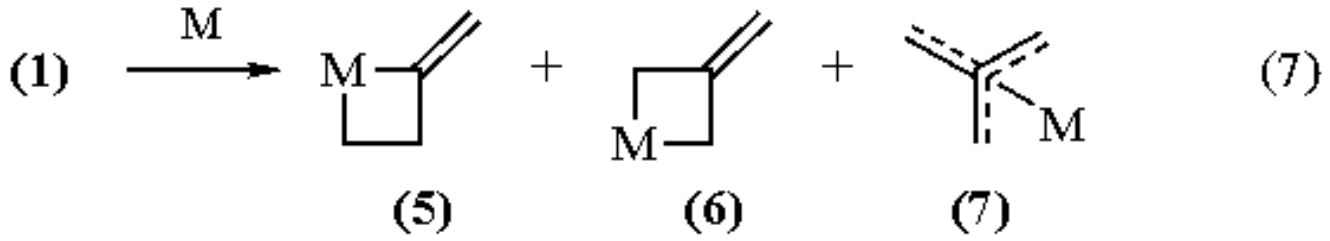

Palladium-catalyzed dimerization of methylenecyclopropane gives a high yield of (**8**) (eq 8)[11a] (compare with eq 4).

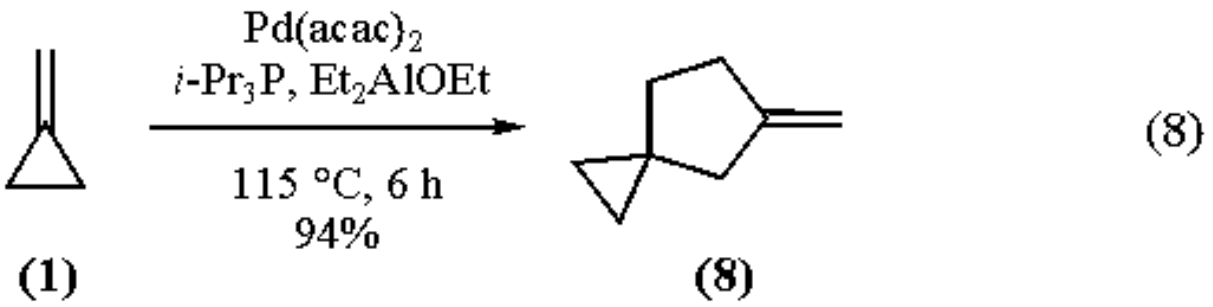

Cycloadditions with 1-trimethylsilyl-1-alkynes[10] and with α,β-unsaturated aldehydes, ketones, esters, nitriles, and sulfones have been extensively studied[11] and representative results are shown in eq 9. Metal-catalyzed [2 + 2] reactions of (**1**) have also been reported.[12]

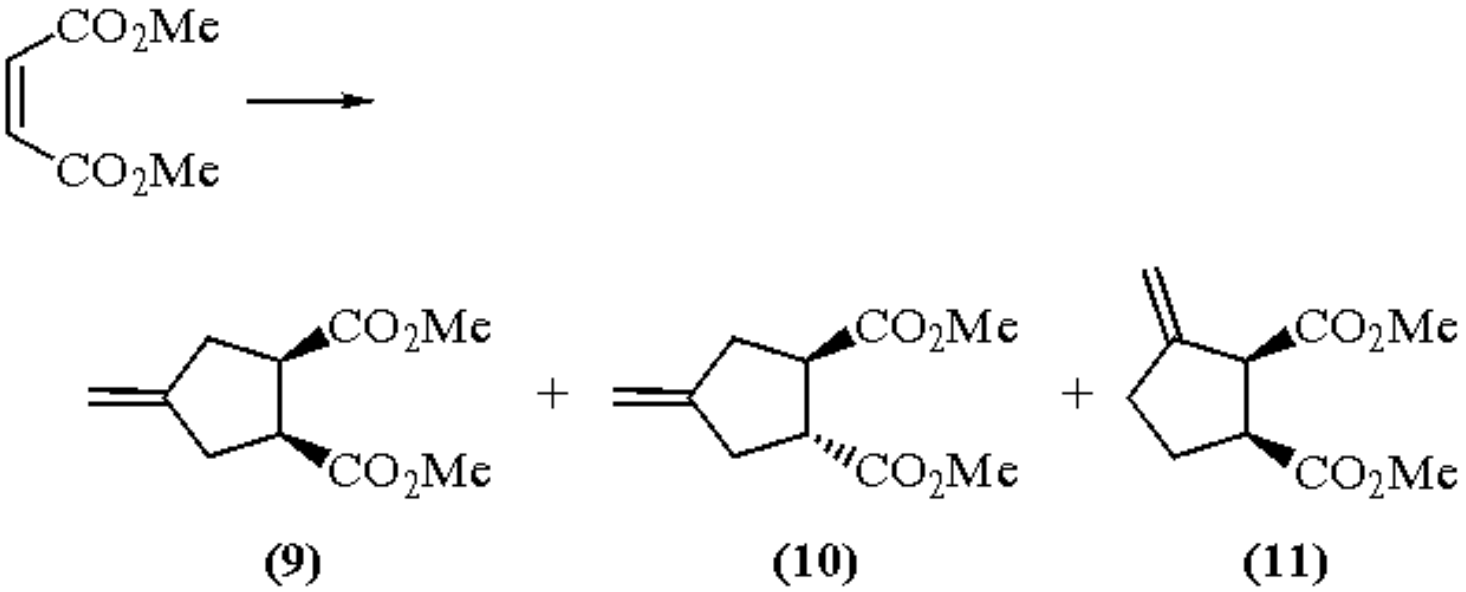

(9)

Conditions	(8)	(9):(10):(11)	Yield
$Pd(acac)_2$ *i*-Pr_3P	19%	2:3:-	67%
$Ni(cod)_2$ $(ArO)_3P$	-	1:3:-	42%
$Ni(C_2H_3CN)_2$	-	3:2:45	20%

Other Chemistry.

Under carefully optimized conditions, (**1**) can be condensed with ***Carbon Dioxide*** to give butenolide (**12**) in good yield (eq 10).[13]

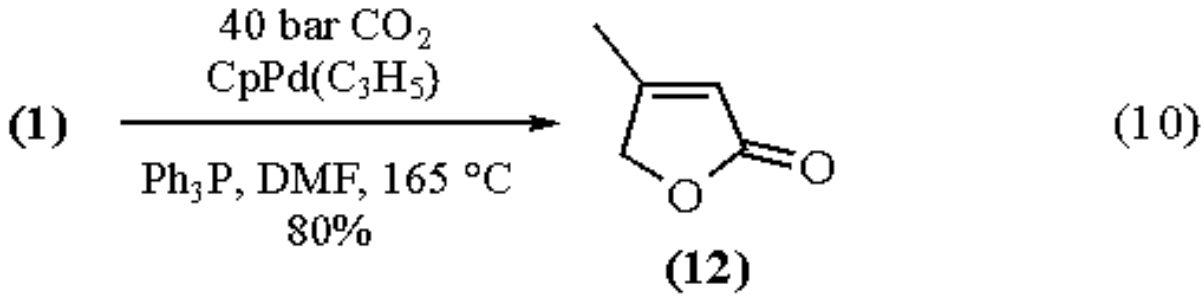

(10)

Epoxidation of (**1**) yields the isolable oxaspiropentane, which exothermically rearranges to cyclobutanone (**13**) with catalytic ***Lithium Iodide*** (64% overall) (eq 11).[2]

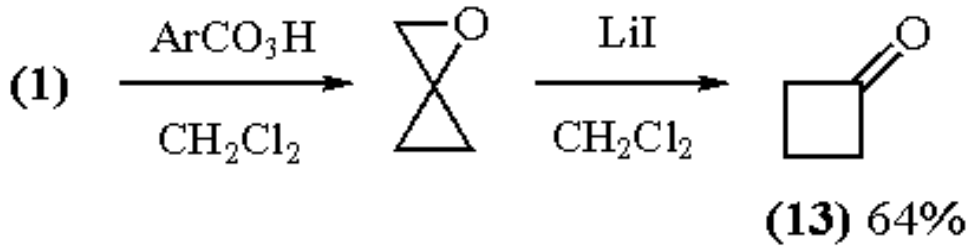

(11)

Deprotonation of (**1**) occurs at C-2, yielding an allylic anion.[3] This ambident nucleophile reacts exclusively at the ring position to yield 2-substituted methylenecyclopropanes (eq 12).

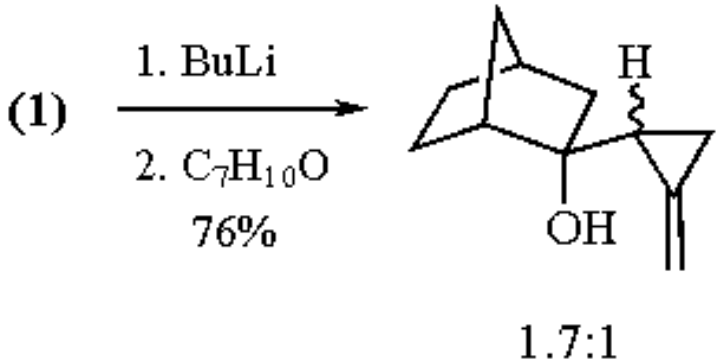

(12)

Treatment of (**1**) with ***Lithium*** in ether yields a stable solution of dilithiobutene (**14**) (70-75%) (eq 13).[4]

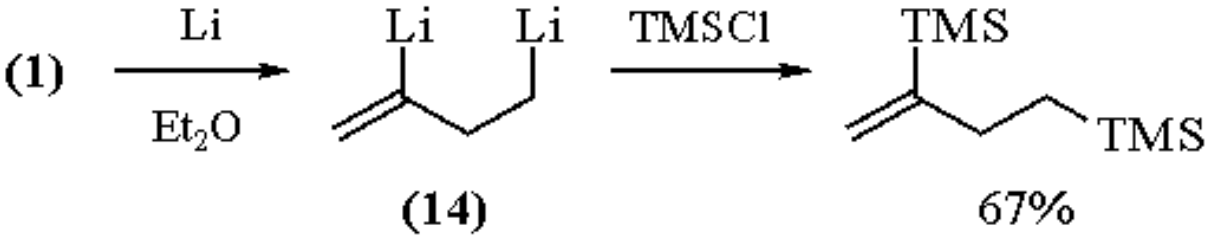

(13)

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1. Reviews: Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. Chan, D. M. T. *COS* **5**, 271. Ohta, T.; Takaya, H. *COS* **5**, 1185. Trost, B. M. *AG(E)* **1986**, *25*, 1.
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9. Brandi, A.; Dürüst, Y.; Cordero, F. M.; De Sarlo, F. *JOC* **1992**, *57*, 5666.
10. Binger, P.; Lü, Q.-H.; Wedemann, P. *AG(E)* **1985**, *24*, 316.
11. (a) Binger, P.; Schuchardt, U. *AG(E)* **1977**, *16*, 249-250. (b) Noyori, R.; Kumagai, Y.; Umeda, I.; Takaya, H. *JACS* **1972**, *94*, 4018. (c) Binger, P.; Wedemann, P. *TL* **1985**, *26*, 1045.
12. Noyori, R.; Ishigami, T.; Hayashi, N.; Takaya, H. *JACS* **1973**, *95*, 1674.

Methylenetriphenylphosphorane[1]

$Ph_3P{=}CH_2$

[3487-44-3] · $C_{19}H_{17}P$ · Methylenetriphenylphosphorane · (MW 276.33)

(methylenating agent for aldehydes and ketones;[1] can convert lactols into hydroxy alkenes;[2] can form a lithio derivative;[3] can be transformed into a β-ketophosphorus ylide[4-6])

Physical Data: mp 96 °C; yellow crystals turning white in air.

Solubility: sol ether, THF, DME, benzene, toluene, DMSO; water and protic solvents destroy the reagent completely.

Form Supplied in: not available commercially; prepared as a solution immediately prior to use.

Analysis of Reagent Purity: ylide concentration can be calibrated by color end-point titration of an aliquot with PhCHO in ether or $PhCO_2H$ in THF at -20 °C under N_2.

Preparative Methods: usually prepared by treatment of a suspension of ***Methyltriphenylphosphonium Bromide*** (or iodide) in an appropriate solvent with a strong base. Butyllithium, dimsylsodium, *t*-BuOK, and sodamide are commonly used. Typically, a suspension of dry methyltriphenylphosphonium bromide in dry ether or THF is treated with ***n-Butyllithium*** at 0 °C under N_2 and the resulting solution is stirred at rt for 1 h. A yellow to deep orange color indicates the ylide formation. The dimsylsodium (***Sodium Methylsulfinylmethylide***) procedure[7] requires heating a suspension of NaH in dry DMSO at 75-80 °C for 1 h followed by ice-cooling prior to the addition of phosphonium bromide. A salt-free ylide is usually prepared using ***Sodium Amide*** in liquid ammonia[8] or in refluxing THF.[9]

Handling, Storage, and Precautions: should always be handled under N_2 or Ar. The ylide should be used as prepared for best results.

Methylenation of Aldehydes and Ketones.

The most versatile utility of $Ph_3P{=}CH_2$ is Wittig methylenation[10] of aldehydes and ketones.[1,10] Under salt-free conditions, 1,2-oxaphosphetanes have been observed as the only intermediate in the methylenation of aldehydes and ketones.[8] Even in cases where a lithium base is used, the classically favored betaine intermediate could not be observed. Decomposition of 1,2-oxaphosphetanes upon warming then provides terminal alkenes from aldehydes and 1,1-disubstituted alkenes from ketones. Hydroxy aldehydes[11a] and ketones[11b] can be directly converted to hydroxy

alkenes when excess reagent is employed (eqs 1 and 2). Often one-carbon homologation of an alcohol can be achieved through a sequence of oxidation, Wittig methylenation, and hydroboration (eq 3).[12]

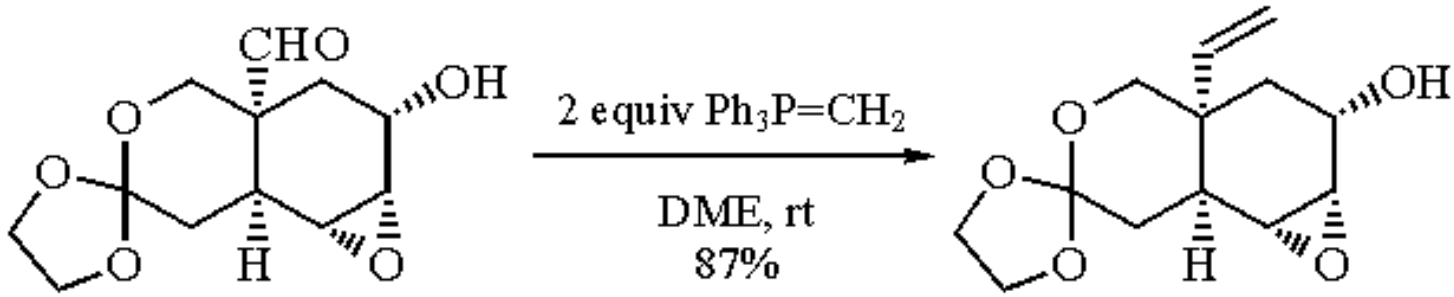

(1)

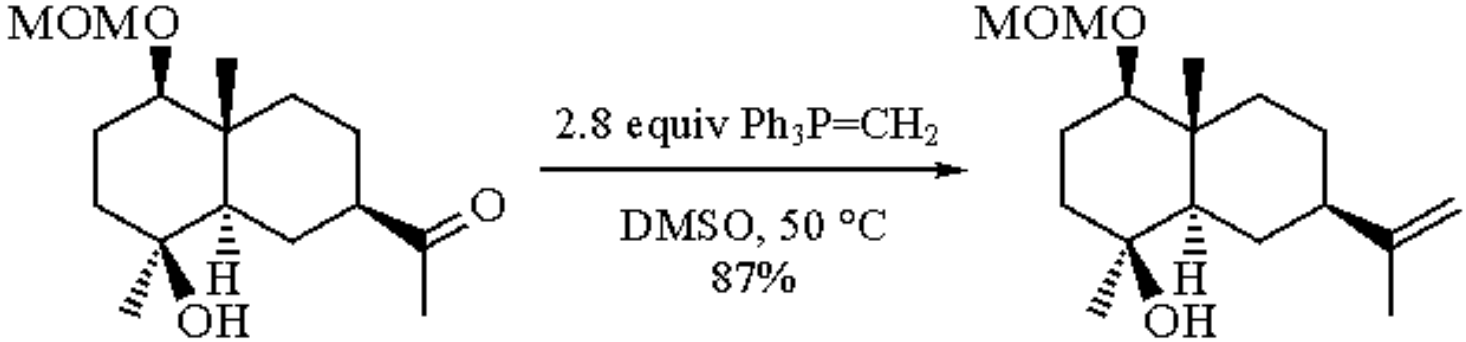

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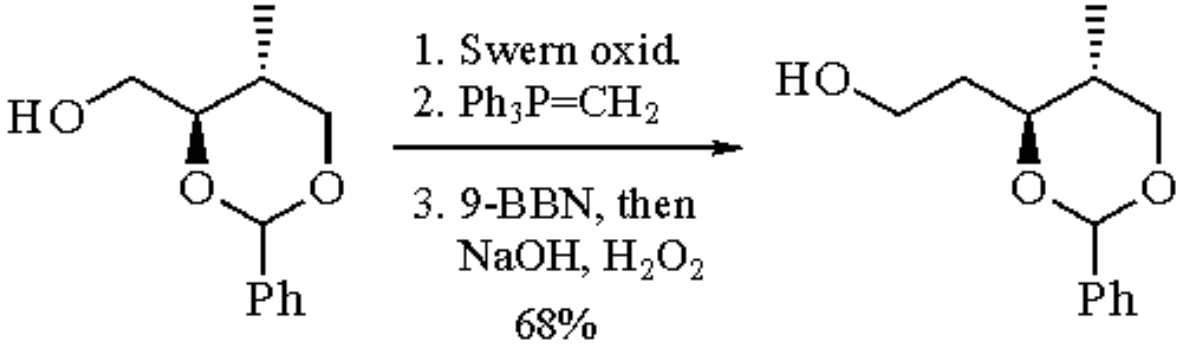

(3)

Vinyl cyclopropanes[13a] and cyclobutanes[13b] are conveniently prepared from corresponding cyclopropyl and cyclobutyl carbonyl compounds. Likewise, vinyl epoxides[14] and aziridines[15] can be prepared (eqs 4 and 5). α,β-Unsaturated aldehydes and ketones are readily converted to 1,3-dienes (eqs 6 and 7).[16]

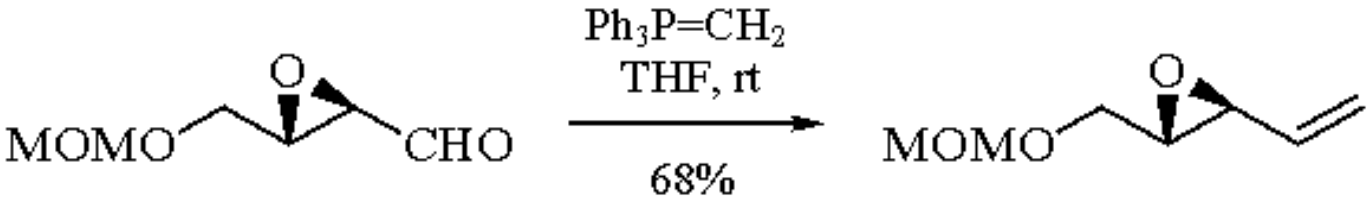

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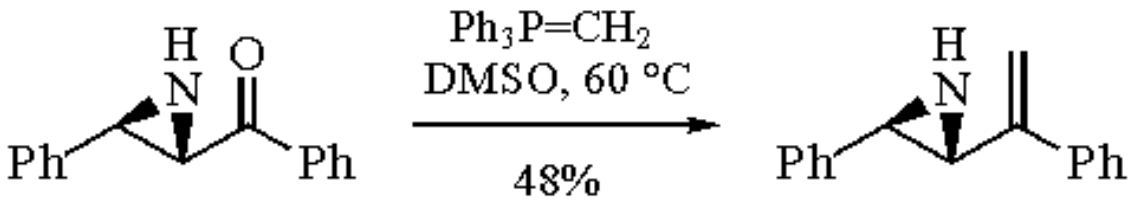

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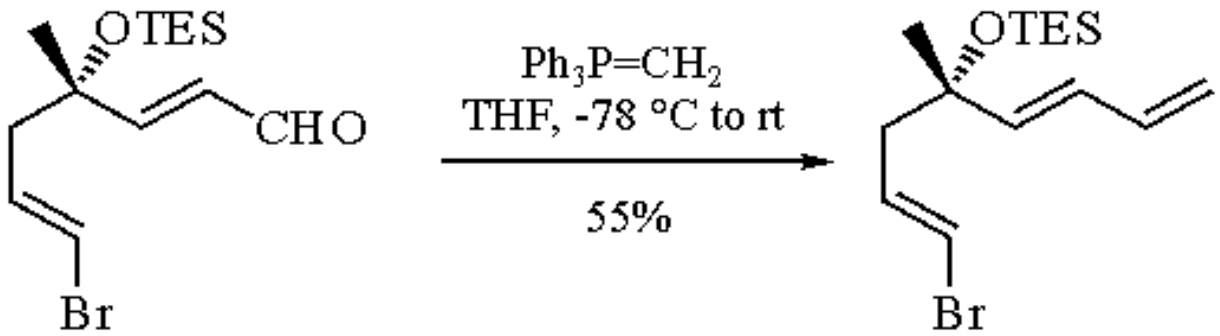

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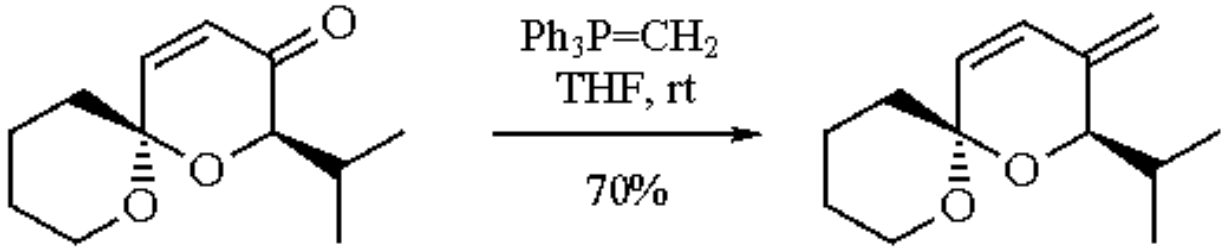

(7)

Substituted 1,3-dienes can be prepared by the treatment of corresponding enals and enones with $Ph_3P{=}CH_2$. Some examples include dienyl iodide,[17a] silyldiene,[17b] and dienyltin[17c] (eqs 8-10). Under carefully controlled reaction conditions, dienol ethers and sulfides are obtained from vinylogous formates and thioesters, respectively (eqs 11 and 12).[18] The 1,3-dienes prepared this way are often used as Diels-Alder dienes.

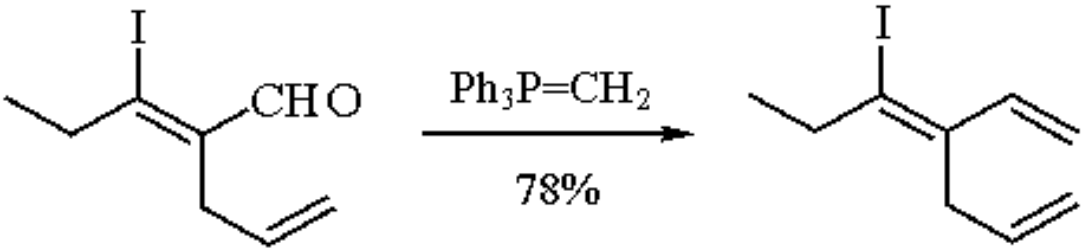

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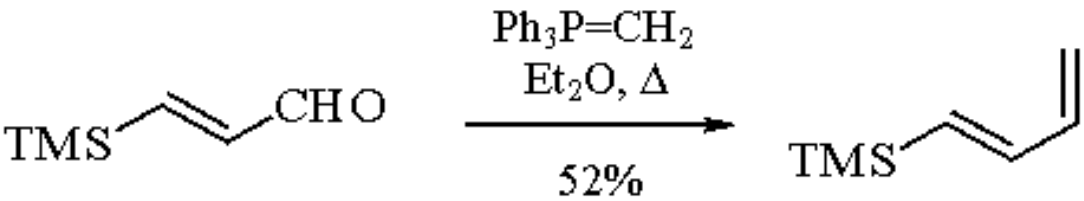

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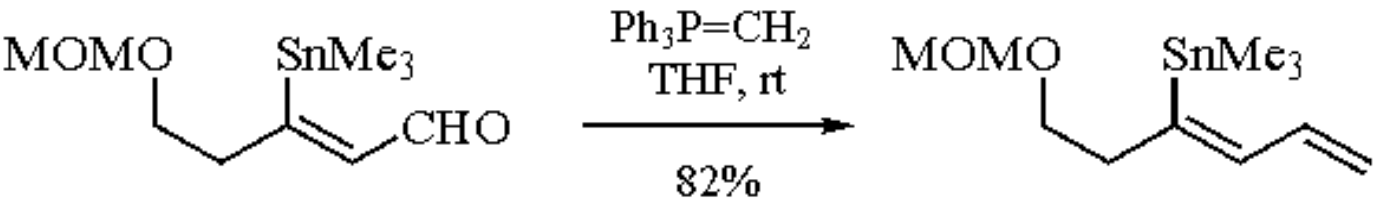

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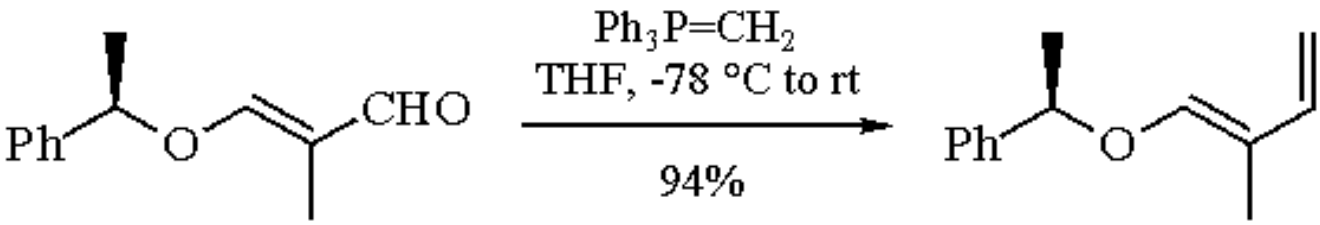

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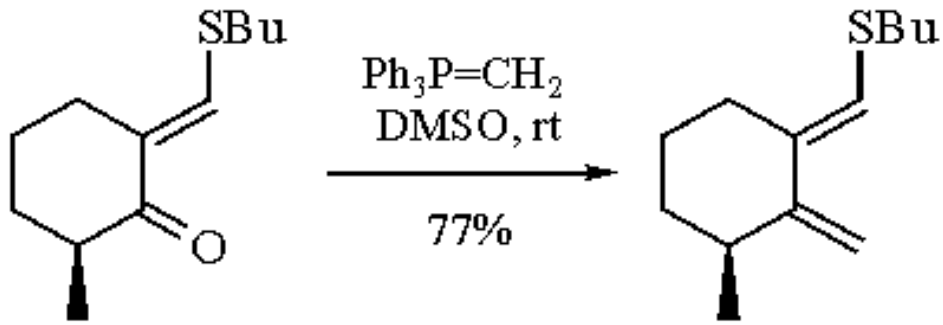

(12)

α-Thioalkoxy aldehydes give rise to allylic sulfides in reaction with $Ph_3P{=}CH_2$.[19] Wittig methylenation can also be effected even in the presence of unusual functional groups such as a phosphonate ester,[20] *O*-silyl oxime,[21] peracetal,[22] and ketene dithioacetal[23] (eqs 13-16).

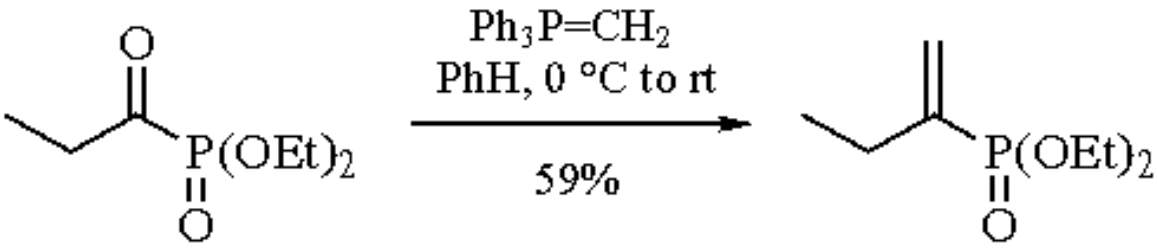

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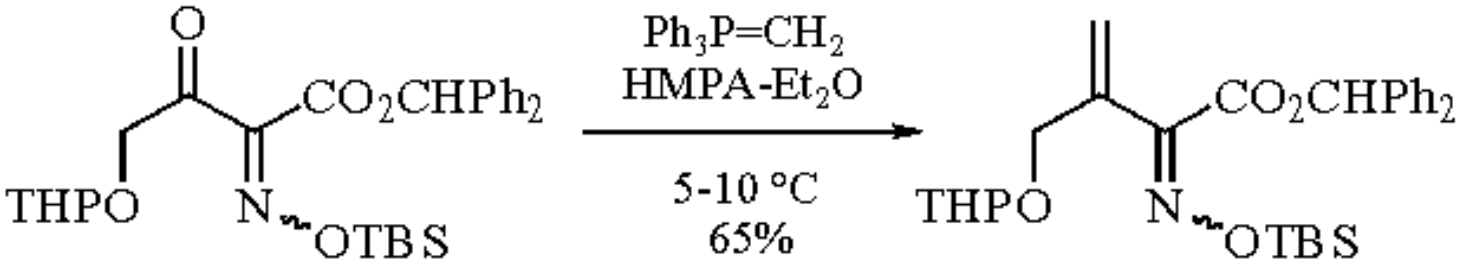

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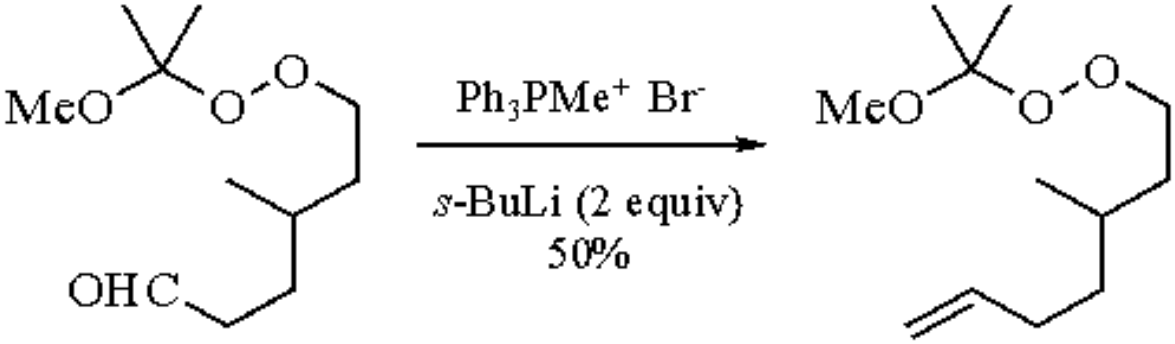

(15)

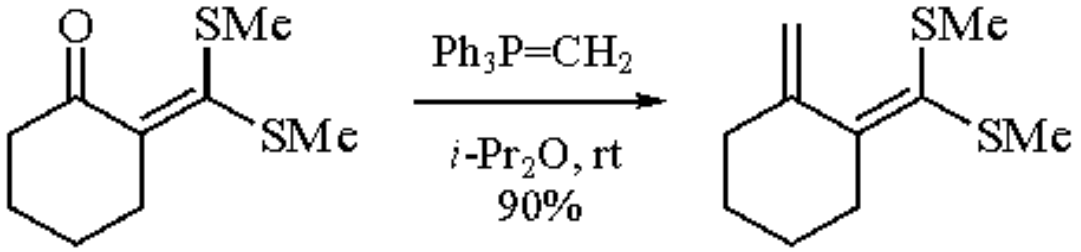

(16)

However, sterically hindered and enolizable ketones are not readily methylenated with $Ph_3P{=}CH_2$.[24] Methylenation of a sterically hindered ketone generally requires a substantial excess of the reagent at elevated temperature and a minimum amount of solvent, as demonstrated in a modhephene synthesis (eq 17).[24a] In this particular example, it was necessary to add the ketone to a preheated (92 °C) solution of a sevenfold excess of $Ph_3P{=}CH_2$ in toluene. One practical modification used to increase the yield of methylenation of enolizable ketones is the repeated additions of stoichiometric amounts of water and the reagent.[24b] Cyclooctanone was therefore methylenated in ether in 89% yield (44%, otherwise) after five cycles of additions (eq 18).

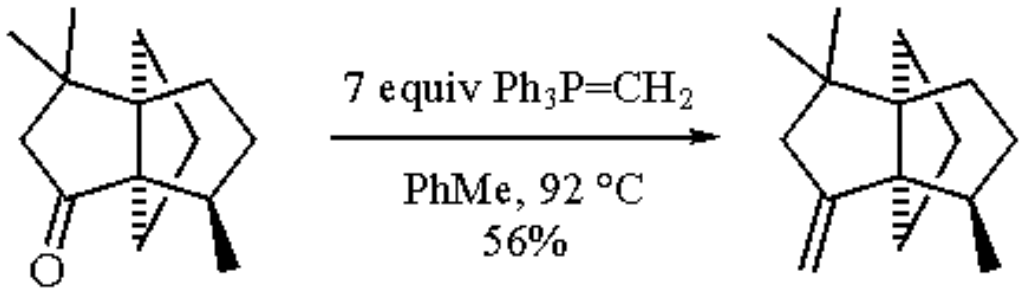

(17)

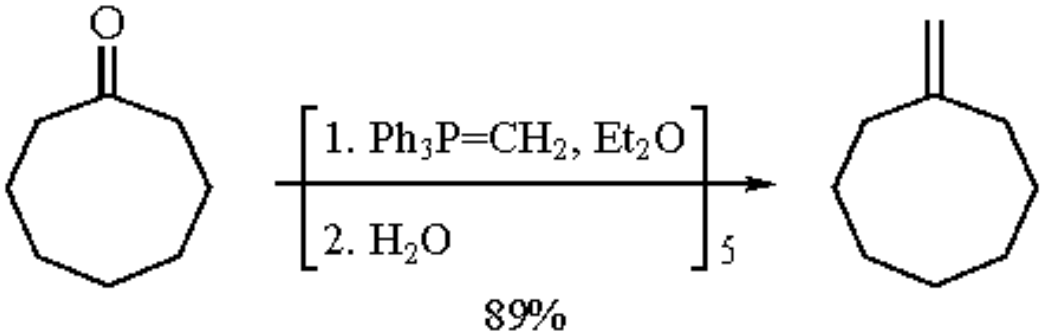

(18)

Other problems commonly observed in Wittig methylenation are β-elimination,[25a,b] retro-aldol,[25c,d] and α-ketol rearrangement,[25e] all of which are caused by the basic nature of $Ph_3P{=}CH_2$ (eqs 19-21).

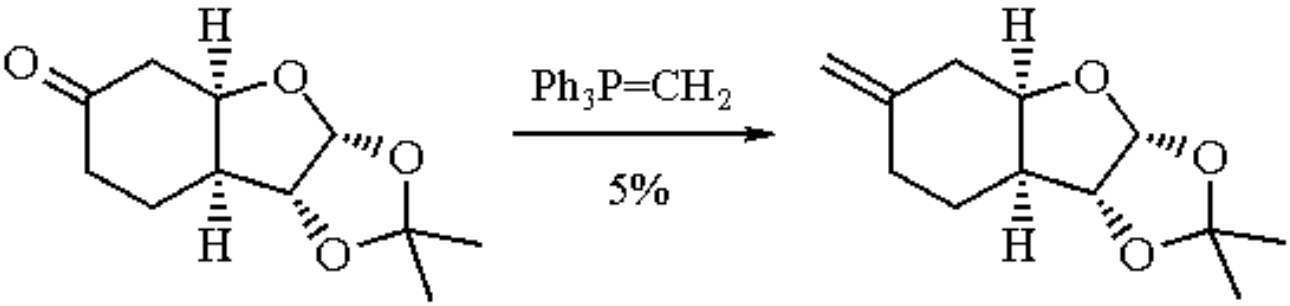

(19)

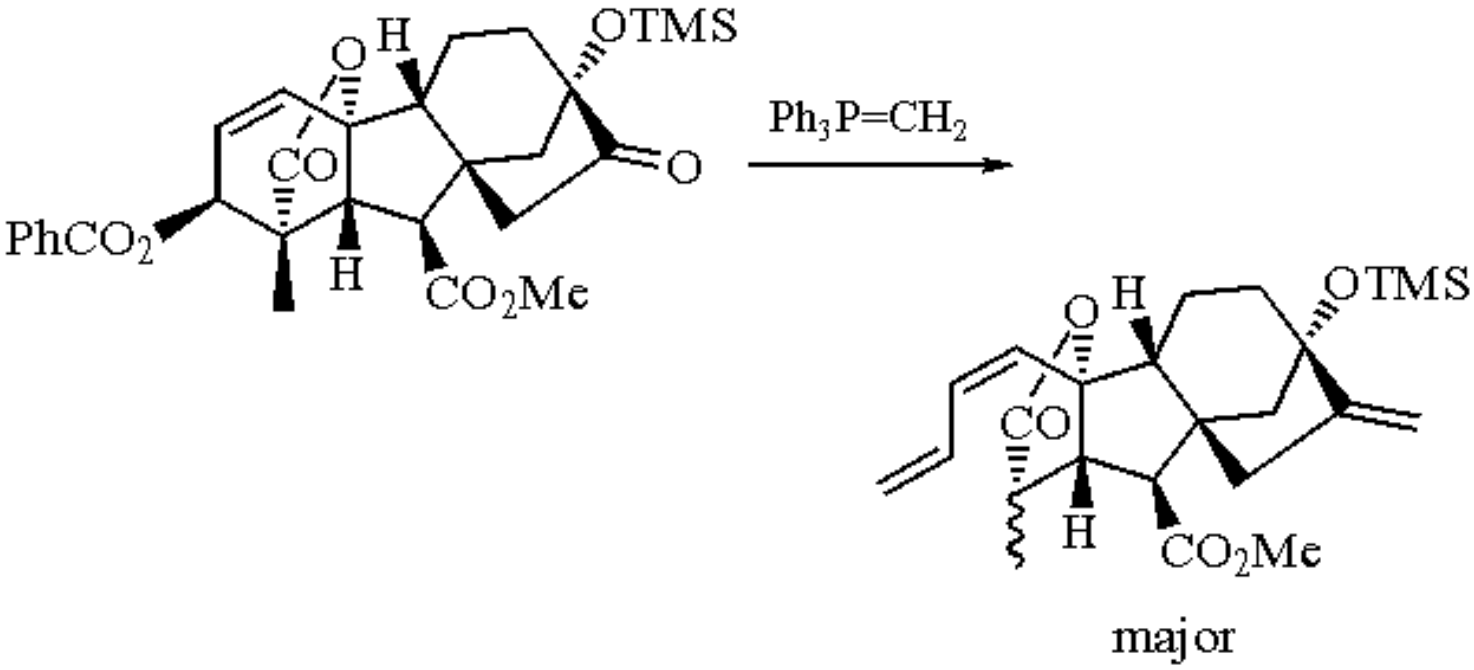

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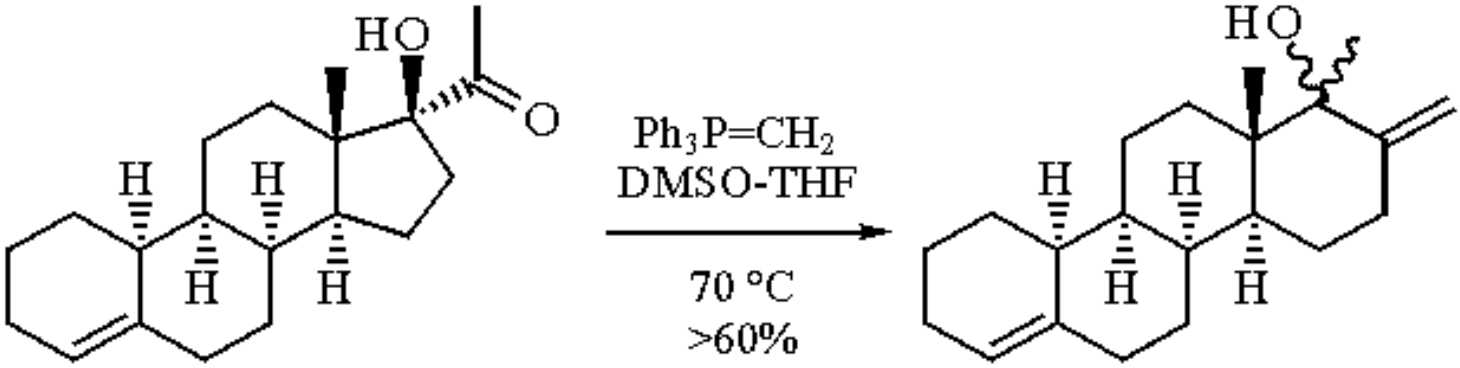

(21)

Methylenation of Lactols and Carbinollactams.

Lactols readily undergo methylenation with excess $Ph_3P{=}CH_2$ to give hydroxy terminal alkenes (eqs 22 and 23).[2] γ-Lactones,[26] as well as δ-lactones,[27] can be converted to acyclic alkenic products via reductive methylenation (eq 24). α-Substituted lactols are sometimes disposed to a rapid equilibration with the more stable conformers through their acyclic tautomers, giving rise to the epimerized product (eq 25).[26e] o-Carbinollactams also undergo methylenation to give corresponding alkenic amides (eq 26).[28]

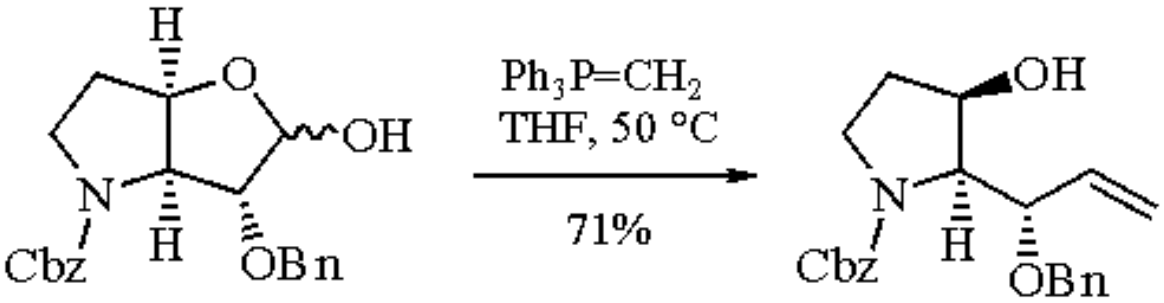

(22)

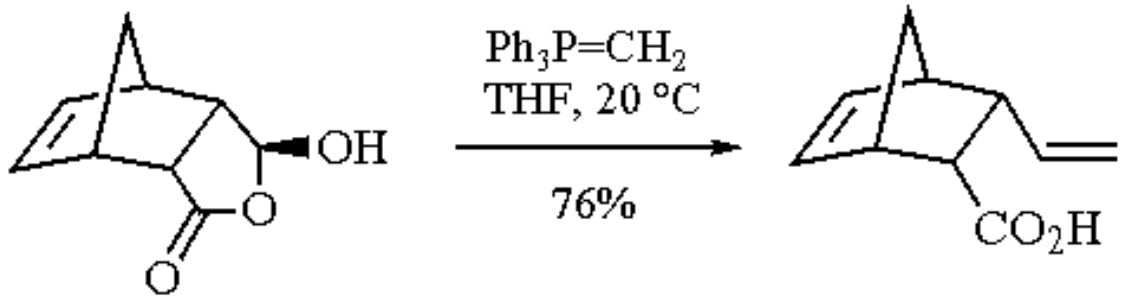

(23)

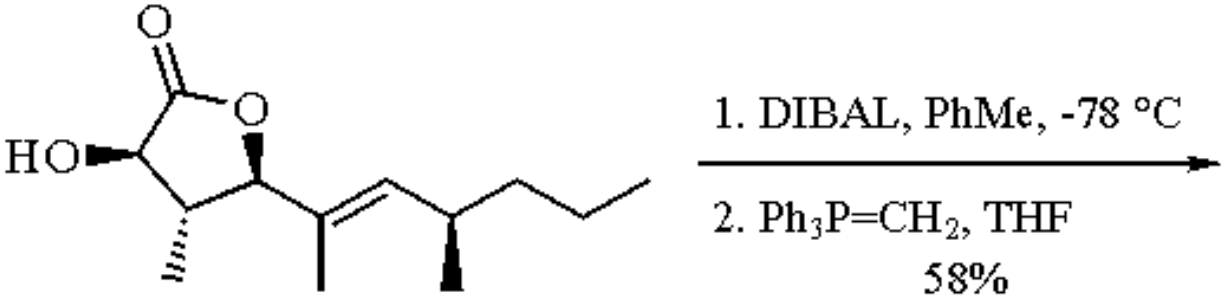

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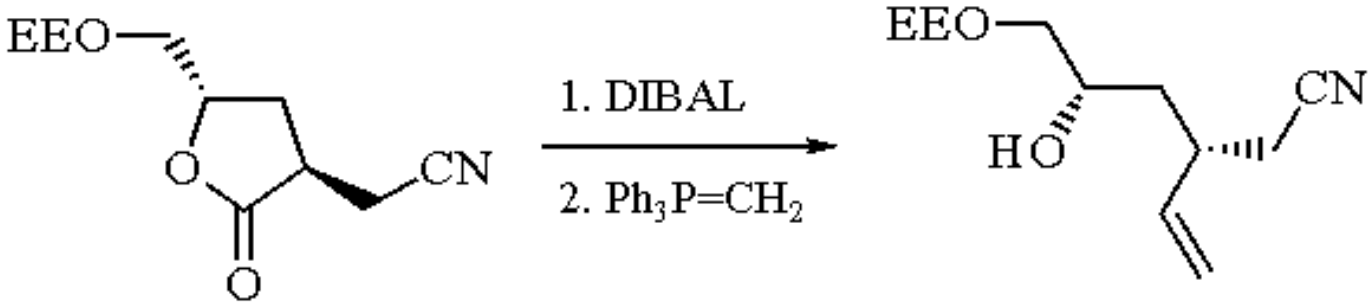

(25)

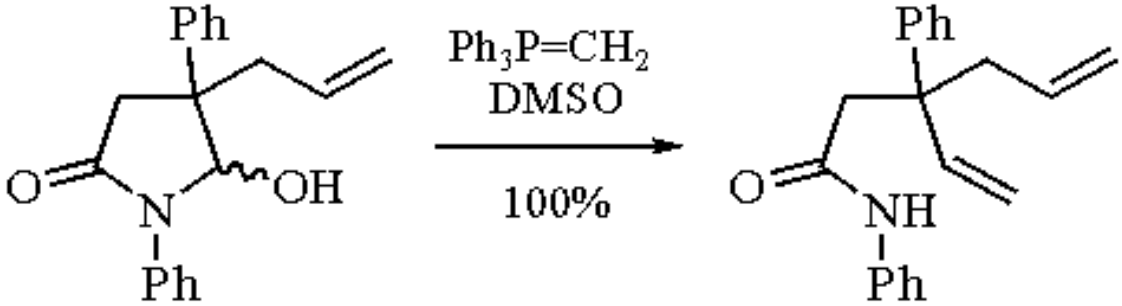

(26)

Reaction with Esters and Carbonyl Equivalents.

$Ph_3P{=}CH_2$ can react with esters to give either acetylated or isopropenyl compounds, depending on the nature of the

ester and the reaction conditions.[29] Aromatic esters usually give rise to isopropenyl compounds, while aliphatic esters result in a mixture of both (eqs 27 and 28).[29a] Polar aprotic solvents and salt-free conditions favor the formation of isopropenyl compounds.[29b] This method has been used recently in the synthesis of the unnatural enantiomer of rothrockene (eq 29).[30]

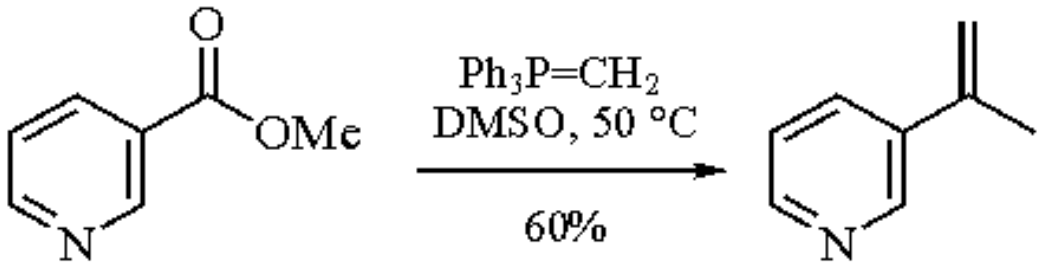

(27)

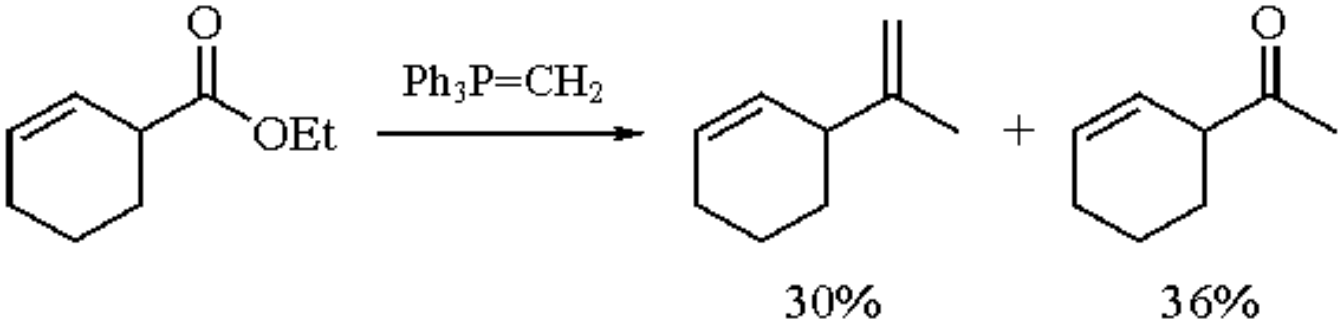

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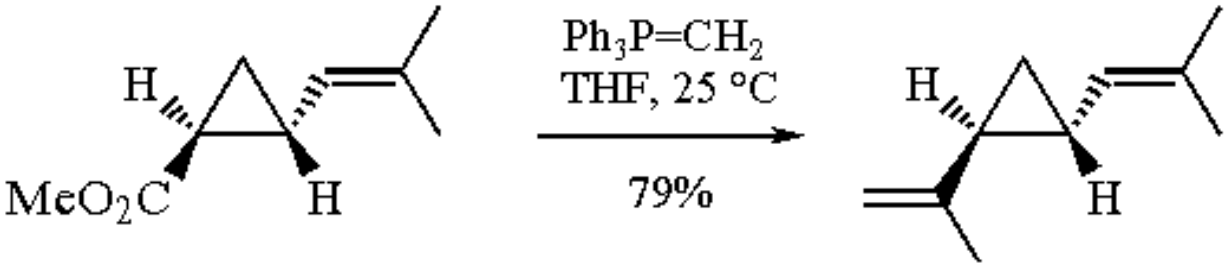

(29)

Carbonyl equivalents such as mixed acetals[31] and β-acyloxy enol esters[32] also react with $Ph_3P{=}CH_2$ to provide corresponding alkenic products (eqs 30 and 31).

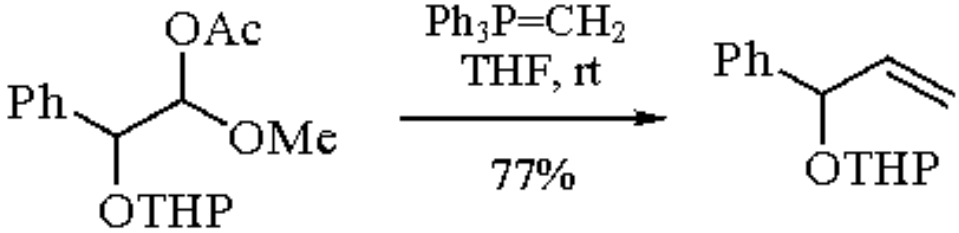

(30)

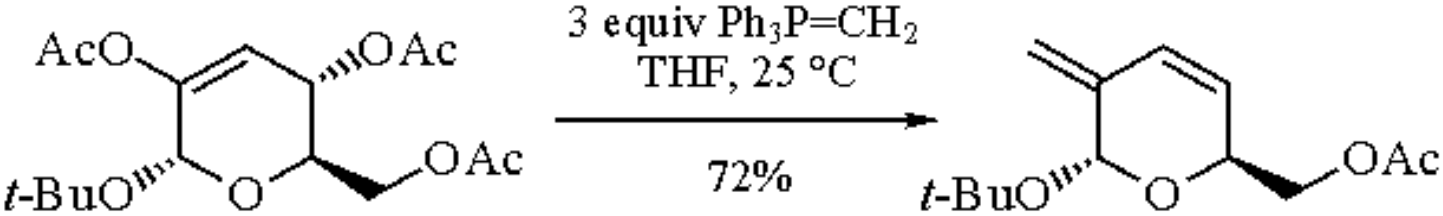

(31)

Formation of Allylic and Homoallylic Alcohols via Oxido Ylides.

$Ph_3P{=}CH_2$ can be activated by lithiation with ***t-Butyllithium*** (or ***s-Butyllithium***) in ether.[3] α-Lithiomethylenetriphenylphosphorane ($Ph_3P{=}CHLi$) thus formed reacts with a hindered ketone, which is unaffected by $Ph_3P{=}CH_2$, to give a methylenated compound. Reaction of $Ph_3P{=}CHLi$ with 2 equiv of aldehyde results in formation of a *trans*-allylic alcohol via a β-oxido ylide (eq 32). $Ph_3P{=}CHLi$ also reacts with an epoxide to give a γ-oxido ylide which in turn couples with an aldehyde to provide a *trans*-homoallylic alcohol (eq 33). β-Oxido ylides are also formed in a SCOOPY reaction[33a] in which a mixture of *cis*- and *trans*-allylic alcohols is usually obtained (eq 34).[33b]

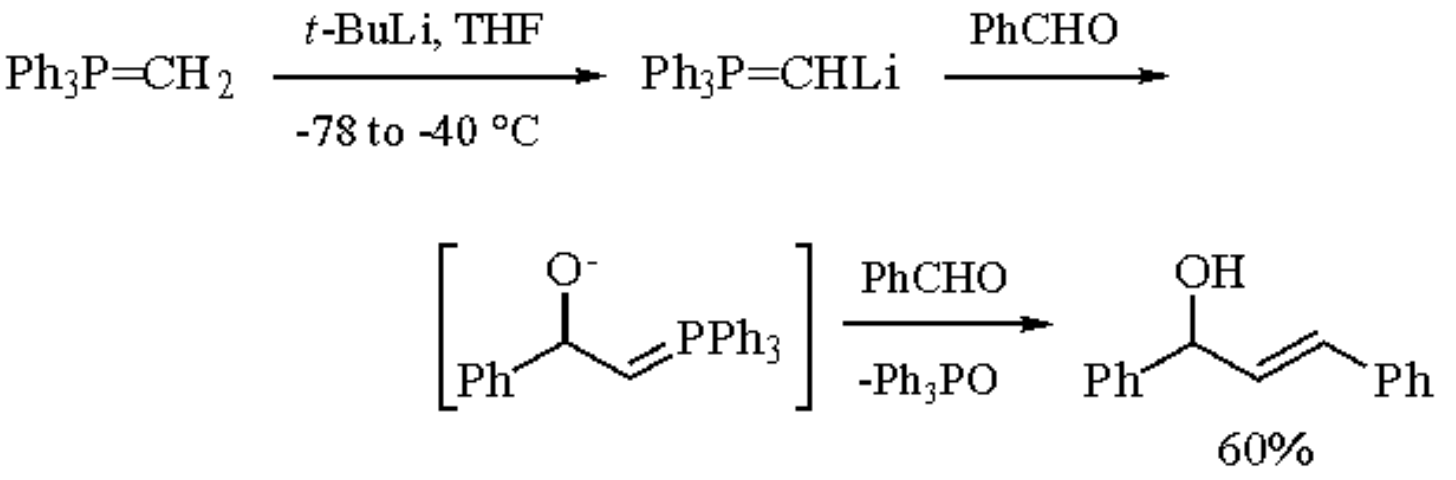

(32)

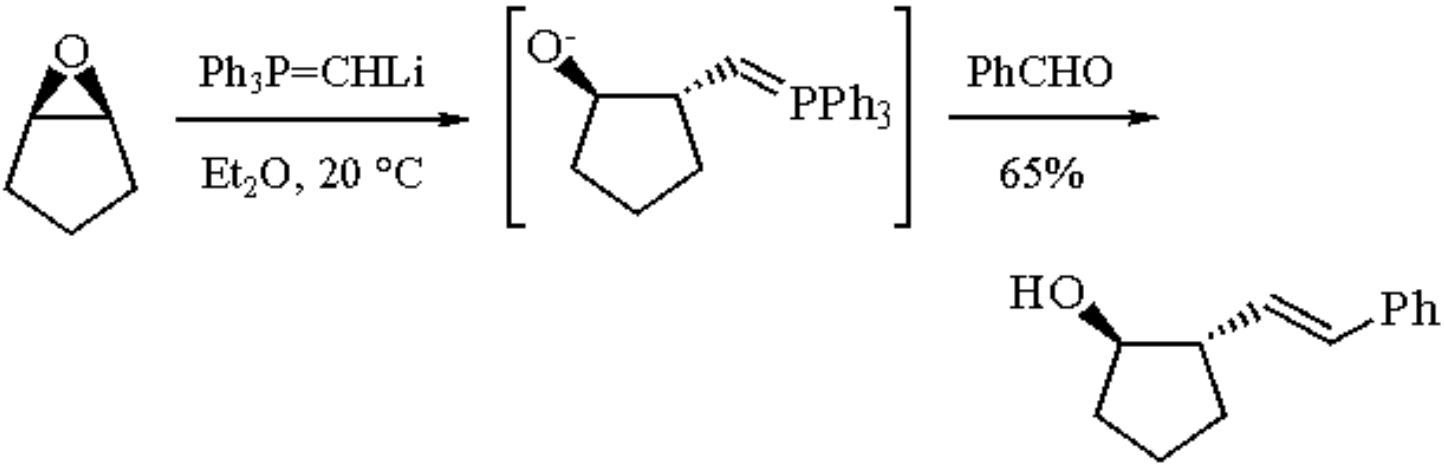

(33)

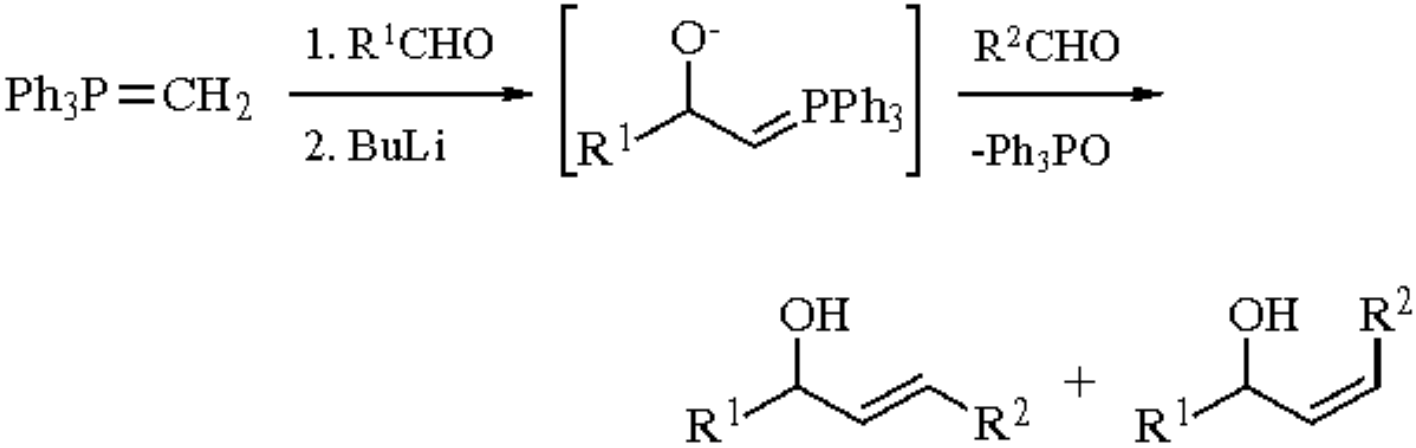

(34)

Formation of Extended Phosphorus Ylides.

Various phosphorus ylides can be produced by reaction of $Ph_3P{=}CH_2$ with electrophiles. β-Ketophosphorus ylides are prepared by acylation of $Ph_3P{=}CH_2$ with an ester,[4] thioester,[5] acid chloride,[6] acylimidazole,[34] or even with a 5(4*H*)-oxazolone[35] (eqs 35-39). β-Thiocarbonylphosphorus ylides can be prepared in a similar manner.[36]

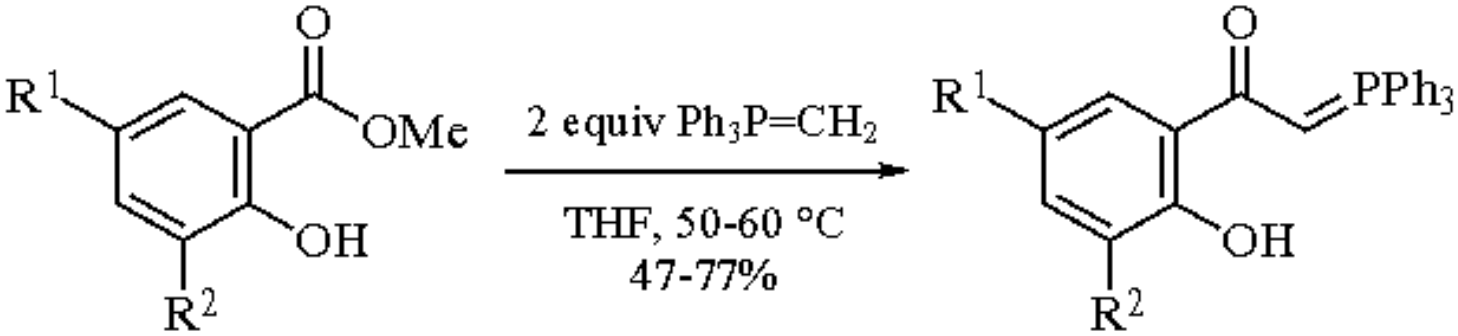

(35)

$R^1 = H, OMe$
$R^2 = H, Me, Pr, allyl$

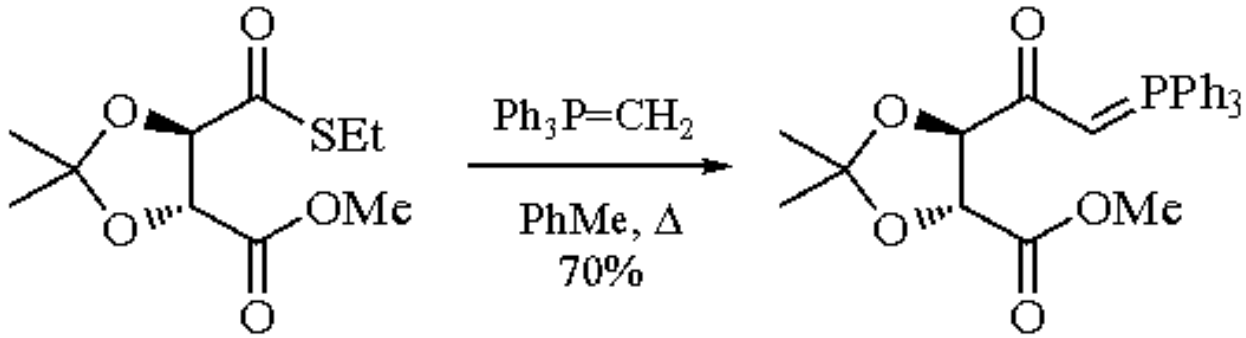

(36)

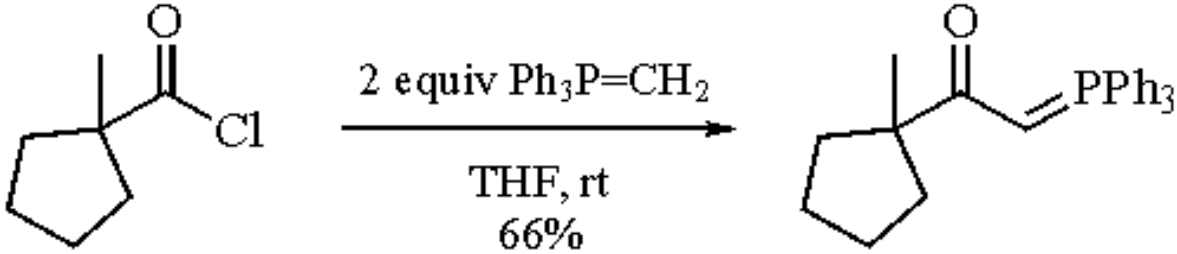

(37)

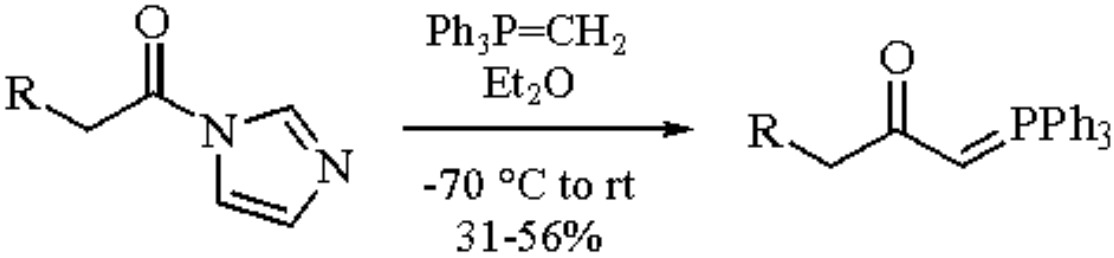

(38)

$R = CyCH_2CH_2$, C_7H_{15}, $MeOCH_2CH_2CH_2$

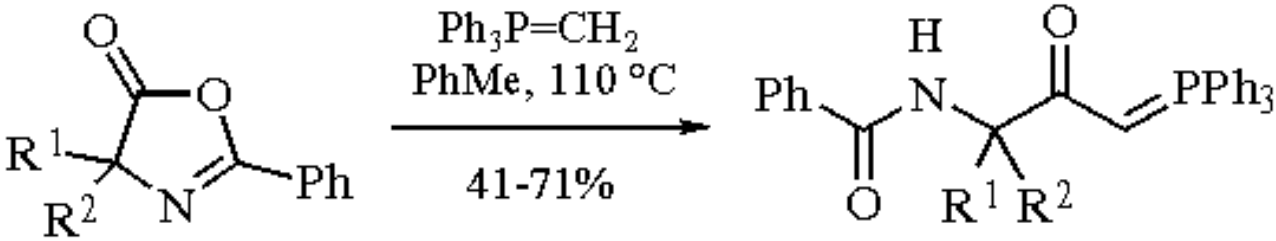

(39)

$R^1 = R^2 = Ph$
$R^1 = Me$, $R^2 = Ph$

On the other hand, alkylation of $Ph_3P{=}CH_2$ with alkyl halides provides novel phosphonium salts which in turn can yield ylides upon treatment with a base (eq 40).[37] Likewise, four- through seven-membered cyclic phosphorus ylides can be prepared by alkylation of corresponding alkyl dihalides with $Ph_3P{=}CH_2$ followed by deprotonation (eq 41).[38] Alkylation can also be effected with 1-alkylbenzotriazole,[39a] epoxide,[39b,c] or lactone.[39d] In the latter case, lactones may undergo either alkylation or acylation depending upon the reaction conditions used.[39d,e]

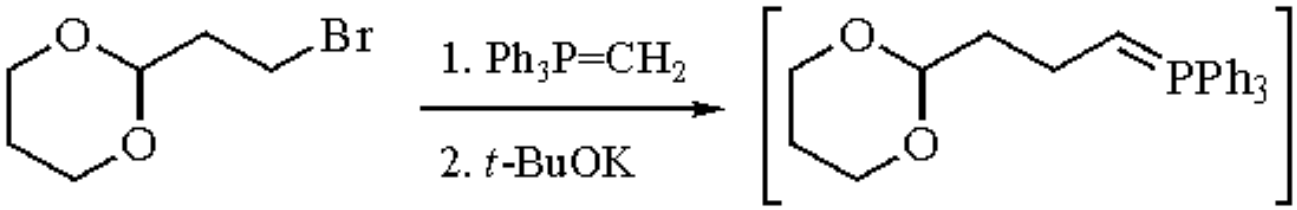

(40)

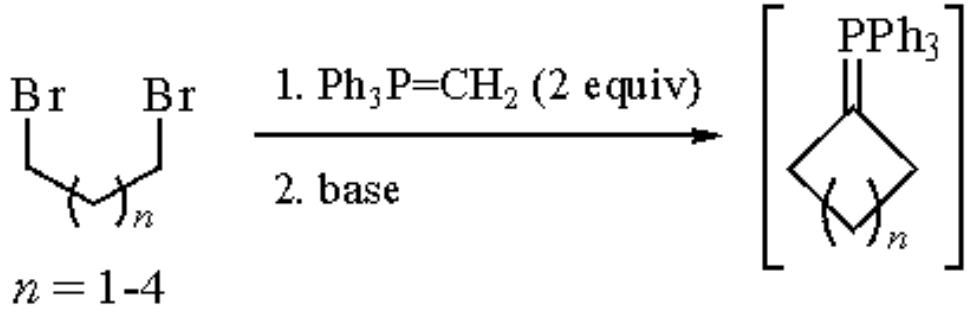

(41)

Other electrophiles which can be reacted with $Ph_3P{=}CH_2$ include a disulfide,[40] sulfonyl halide,[41] halosilane,[42] selenenyl halide,[43] and cyanate[44] to yield various ylides after treatment with a base. Transylidation[45] of phosphonium salts with $Ph_3P{=}CH_2$ provides yet another entry to extended ylides (eq 42).[46] Phosphacumulene ylides have been prepared via double transylidation with $Ph_3P{=}CH_2$ (eq 43).[47] Allylidenephosphoranes are also formed from the reaction of $Ph_3P{=}CH_2$ with dialkylaluminum alkylidenamides (eq 44).[48]

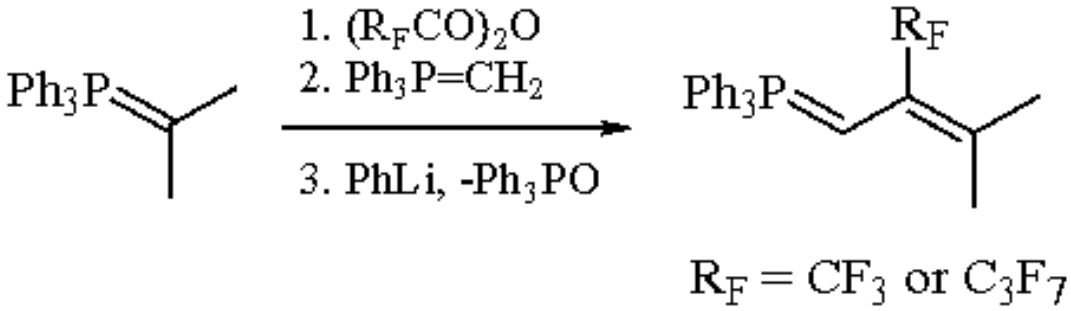

(42)

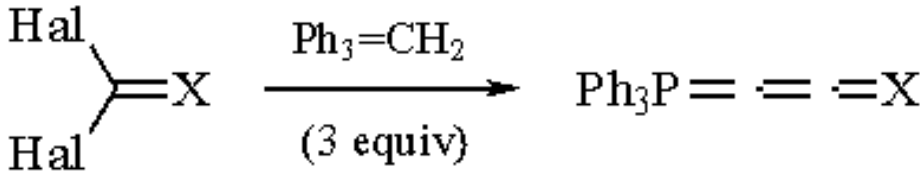

(43)

$X = CR^1R^2$, NR, S; Hal = Cl, Br

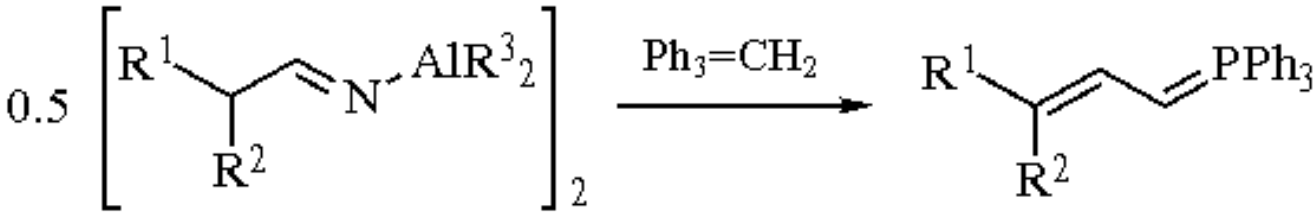

(44)

R^1, R^2 = H or alkyl; R^3 = alkyl

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(1*R*,2*S*)-*N*-Methylephedrine[1]

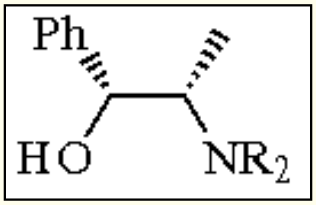

(**1**; R = Me)

[552-79-4] · $C_{11}H_{17}NO$ · (1*R*,2*S*)-*N*-Methylephedrine · (MW 179.29) (**2**; R = *n*-Bu)

[115651-77-9] · $C_{17}H_{29}NO$ · (1*R*,2*S*)-*N*,*N*-Dibutylnorephedrine · (MW 263.47) (**3**; R = CH_2=$CHCH_2$-)

[150296-38-1] · $C_{15}H_{21}NO$ · (1*R*,2*S*)-*N*,*N*-Diallylnorephedrine · (MW 231.37) (**4**; R = $Ph(CH_2)_4$)

[132284-82-3] · $C_{29}H_{37}NO$ · (1*R*,2*S*)-*N*,*N*-Bis(4-phenylbutyl)norephedrine · (MW 415.67) (**5**; R = -$(CH_2)_5$-)

[133576-76-8] · $C_{14}H_{21}NO$ · (1*R*,2*S*)-*N*-Piperidinonorephedrine · (MW 219.36)

(chiral ligand for the enantioselective reduction of ketones with lithium aluminum hydride; chiral auxiliary for the diastereoselective aldol condensation; chiral catalyst for the enantioselective Darzens reaction; chiral catalyst for the enantioselective alkylation of aldehydes with dialkylzincs; chiral catalyst for the enantioselective conjugate addition of dialkylzincs to enones; chiral catalyst for the enantioselective alkylation of imines with dialkylzincs; chiral catalyst for the enantioselective Michael addition of nitromethane to α,β-unsaturated ketones)

Alternate Name: [*R*-(*R**,*S**)]-α-[1-(dimethylamino)ethyl]benzenemethanol.

Physical Data: (**1**) mp 86-88 °C; [α]21D -29.2° (*c* 5, MeOH). (**2**) bp 170 °C/2 mmHg; [α]25D + 24.4° (c 2, hexane).

Solubility: sol many organic solvents.

Form Supplied in: (**1**) colorless crystals; (**2**) colorless oil; (**1**) and (**2**) are commercially available.

Enantioselective Reduction of Ketones with Lithium Aluminum Hydride-*N*-Methylephedrine.

Aryl alkyl ketones and α-alkynic ketones are reduced enantioselectively by a chiral complex of ***Lithium Aluminum***

Hydride, *N*-methylephedrine (**1**), and 3,5-dimethylphenol (molar ratio, 1:1:2) to afford optically active alcohols with 75-90% ee (eq 1).[2]

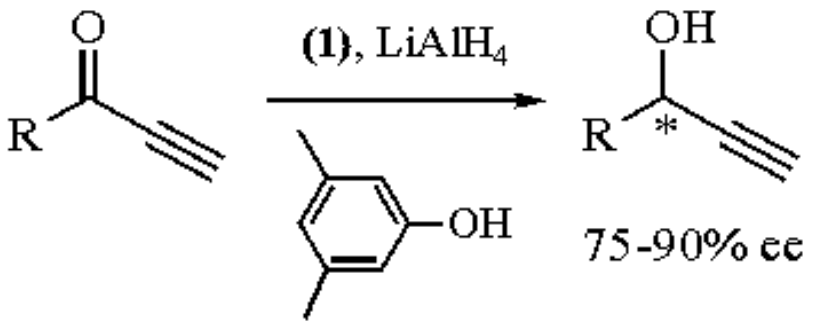

(1)

The optically active alkynyl alcohols are converted into the corresponding optically active 4-alkyl-γ-butyrolactones[3] and 4-alkylbutenolides.[4]

A chiral complex of (**1**), $LiAlH_4$, and *N*-ethylaniline (molar ratio, 1:1:2) reduces aryl alkyl ketones to optically active alcohols in high ee.[5] α,β-Unsaturated ketones are reduced enantioselectively to afford optically active (*S*)-allylic alcohols with 80-98% ee. An intermediate in an anthracyclinone synthesis is prepared in 92% ee by the enantioselective reduction of a cyclic α,β-unsaturated ketone (eq 2).[6]

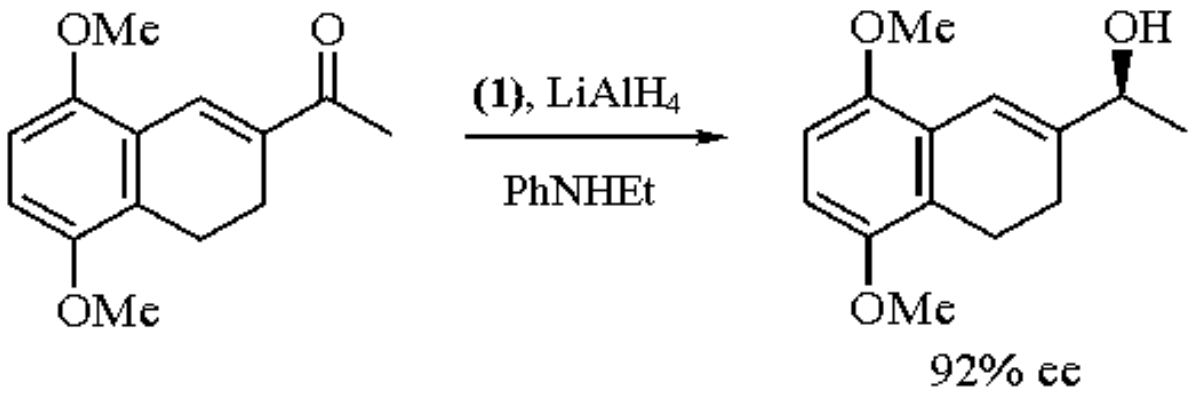

(2)

A chiral complex of (**1**), $LiAlH_4$, and 2-ethylaminopyridine (molar ratio, 1:1:2), prepared in refluxing ether for 3 h, reduces cyclic ketones to (*R*)-alcohols in 75-96% ee.[7] Advantages of the enantioselective reduction of ketones with $LiAlH_4$ modified with (**1**) and additives are the ready availability of (**1**) in either enantiomeric form and easy removal of (**1**) from the reaction mixture by washing with dilute acid.

anti-Selective Aldol Condensation and Related Reactions.

Silyl ketene acetals react with aldehydes in the presence of ***Titanium(IV) Chloride*** to give β-hydroxy esters.[8] The silyl ketene acetal derived from (1*R*,2*S*)-(**1**)-*O*-propionate reacts with benzaldehyde in the presence of $TiCl_4$ and ***Triphenylphosphine*** to afford the *anti*-α-methyl-β-hydroxy ester in 94% de (eq 3).[9]

(1R,2S)-N-Methylephedrine

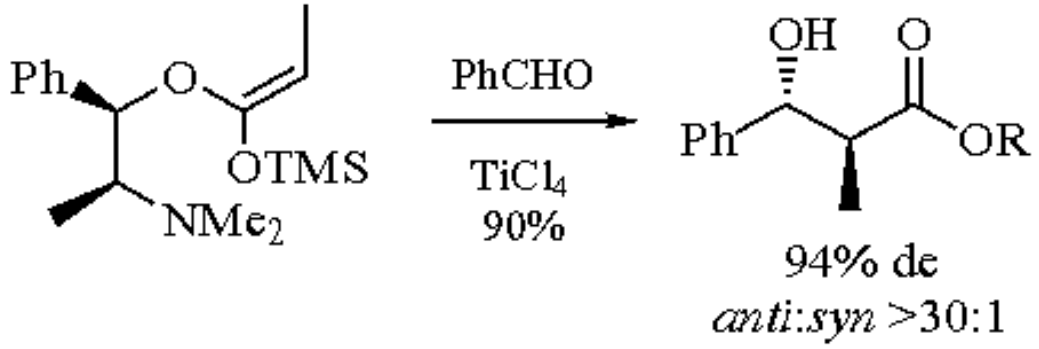

(3)

When the same silyl ketene acetal is reacted with benzylideneaniline in the presence of $TiCl_4$, the *anti*-β-amino ester is obtained (*anti*/*syn* > 10/1). Cyclization of the β-amino ester affords the *trans*-β-lactam in 95% ee (eq 4).[10]

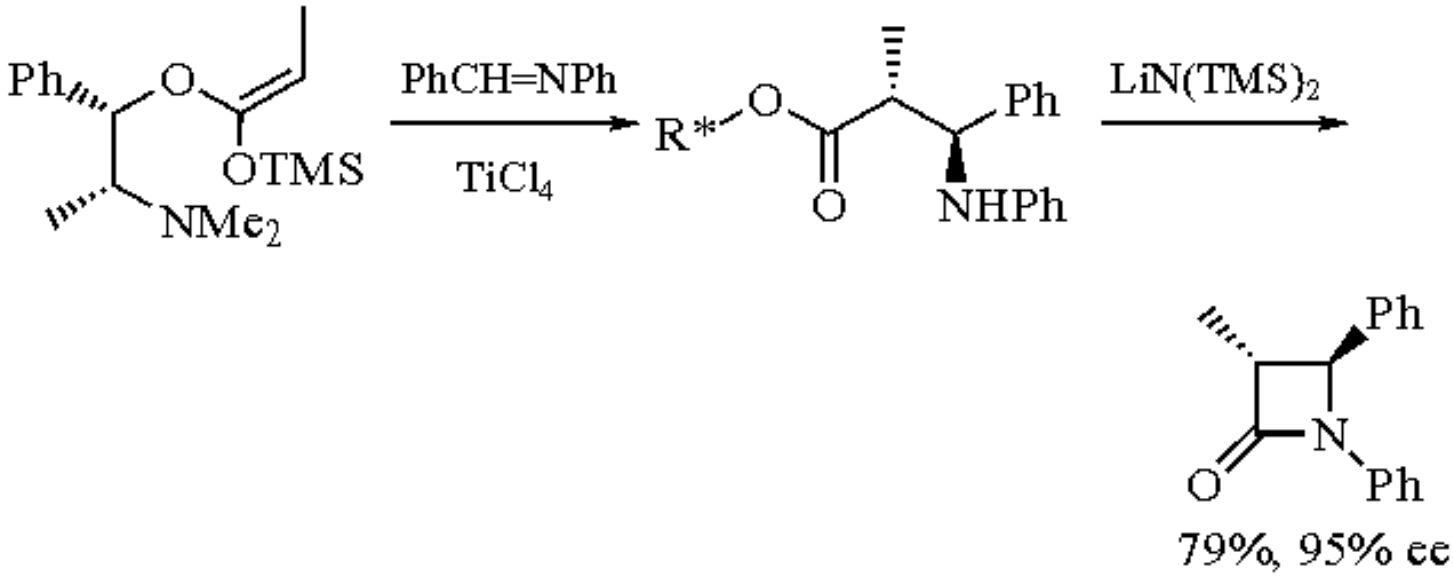

(4)

The reaction of this silyl ketene acetal with ***Di-t-butyl Azodicarboxylate*** in the presence of $TiCl_4$ affords the adduct in 45-70% yield with ca. 90% de. The subsequent treatment of the adduct with ***Trifluoroacetic Acid*** and ***Lithium Hydroxide*** affords (*R*)-α-hydrazo acids (eq 5).[11]

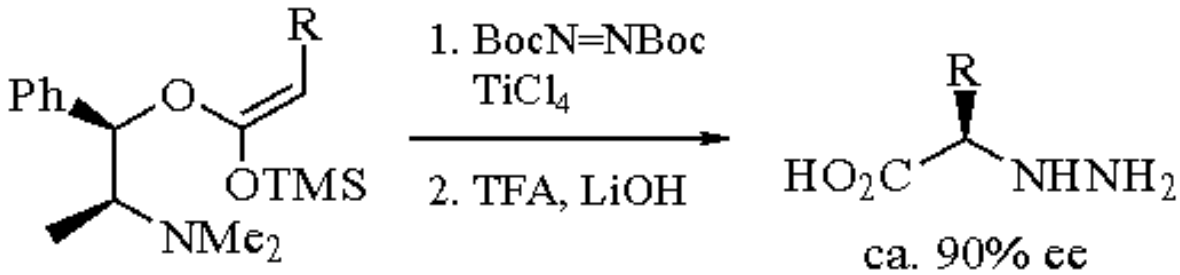

(5)

Enantioselective Butylation of Carbonyl Compounds with Lithium Tetra-*n*-butylaluminate Modified with (1).

The reaction between lithium tetra-*n*-butylaluminate and (**1**) forms the chiral lithium alkoxytri-*n*-butylaluminate. This chiral ate complex reduces carbonyl compounds to form secondary and tertiary alcohols in 8-31% ee (eq 6).[12]

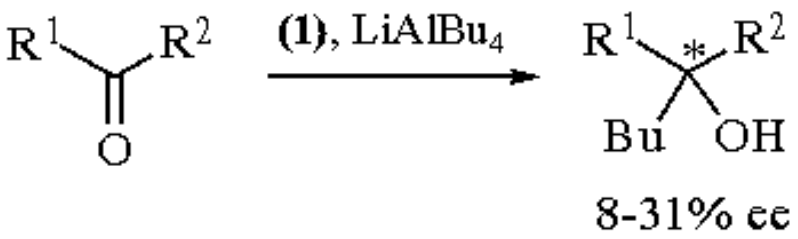

(6)

Enantioselective Darzens Reaction.

An enantioselective Darzens reaction between ethyl methyl ketone and chloromethyl *p*-tolyl sulfone in the presence of a chiral ammonium salt derived from (**1**) and chloromethylpolystyrene affords an optically active α,β-epoxy sulfone in 23% ee.[13]

Catalytic Enantioselective Alkylation of Aldehydes with Dialkylzincs.[1]

The chiral *N*,*N*-dialkylnorephedrines, analogs of (**1**), are highly efficient catalysts for the enantioselective addition of dialkylzincs to aliphatic and aromatic aldehydes.[14,15] Optically active aliphatic and aromatic secondary alcohols with high ee are obtained using *N*,*N*-dialkylnorephedrines (4-6 mol%) as chiral catalyst precursors. When (1*S*,2*R*)-*N*,*N*-dialkylnorephedrine is used as a chiral catalyst precursor, prochiral aldehydes are attacked at the *si* face to afford (*S*)-alcohols (when the priority order is $R^1 > R^2$) (eq 7).

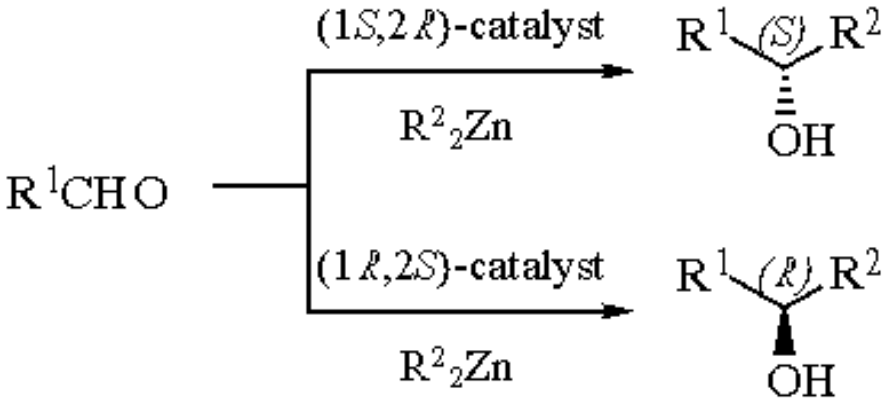

(7)

N-Alkyl substituents on the (1*S*,2*R*)-*N*,*N*-di-*n*-alkylnorephedrines have a significant effect on the enantioselectivity of the addition of diethylzinc to aldehydes (3-methylbutanal). As shown in Table 1, the optical purity of the product [(*S*)-5-methylhexane-3-ol] increases as the chain length of the *N*-*n*-alkyl substituent increases and reaches a peak of 93% ee at a chain length of four carbons (Table 1, entry 4). Thus, among *N*,*N*-di-*n*-alkylnorephedrines examined, (1*S*,2*R*)-*N*,*N*-di-*n*-butylnorephedrine (DBNE) (**2**) is the best chiral catalyst precursor.[14,15]

Table 1 Effect of *N*-Alkyl Substituents of (1*S*,2*R*)-*N*,*N*-Dialkylnorephedrine as Chiral Ligand for the Addition of Diethylzinc to 3-Methylbutanal to Yield (*S*)-5-Methylhexan-3-ol

Entry	*N*-Alkyl substituent	Yield (%)	ee (%)
1	Me (**1**)	53	53
2	Et	95	83
3	*n*-Pr	90	87
4	*n*-Bu (DBNE) (**2**)	92	93
5	*n*-C_5H_{11}	91	85
6	*n*-C_6H_{13}	85	83
7	*n*-C_7H_{15}	80	79
8	*n*-C_8H_{17}	53	76
9	$(CH_2)_5$ (**5**)	81	70

As shown in Table 2 (eq 7), the advantages of *N*,*N*-di-*n*-alkylnorephedrines (most typically DBNE) over other chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes are as follows:

- 1)DBNE is highly enantioselective for the alkylation of *aliphatic* aldehydes (Table 2, entries 5-11) as well as for the alkylation of *aromatic* aldehydes (Table 2, entries 1-4). Most of other types of chiral catalysts are effective only for the alkylation of *aromatic* aldehydes. Thus, various types of optically active *aliphatic* alcohols are first synthesized using DBNE (Table 2, entries 5-11). (It should be noted that the structures of aliphatic alcohols synthesized by asymmetric reduction of ketones or by asymmetric hydroboration of alkenes have been somewhat limited.)
- 2)The structures of dialkylzincs catalyzed by *N*,*N*-di-*n*-alkylnorephedrines (most typically DBNE) are not limited to *primary* ones. Diisopropylzinc (with a *secondary* alkyl substituent) adds to benzaldehyde in the presence of a catalytic amount of DBNE to afford the corresponding alcohol with high ee (entry 4).[15] The reaction of diisopropylzinc in the presence of other types of catalysts may result in the reduction of aldehydes.
- 3)*N*,*N*-Di-*n*-alkylnorephedrines are readily synthesized in a one-pot reaction between norephedrine and alkyl iodide in the presence of potassium carbonate.[14,15] (DBNE is commercially available.)
- 4)Either enantiomer of the *N*,*N*-di-*n*-alkylnorephedrines are available. Therefore by using the appropriate enantiomer of *N*,*N*-di-*n*-alkylnorephedrine as a chiral catalyst precursor, the optically active alcohol of the desired configuration with the same ee can be synthesized (entries 8 and 9).

Table 2 Enantioselective Addition of Dialkylzincs to Aldehydes using Norephedrine-Derived Chiral Catalyst (eq 7)

Entry	R^1	R^2	Catalyst (6 mol %)	Yield (%)	ee (%)	Config.
1	Ph	Et	(1*S*,2*ℓ*)-DBNE	100	90	(*S*)
2	2-MeOC_6H_4	Et	(1*S*,2*ℓ*)-DBNE	100	94	(*S*)
3	Ph	Et	(1*S*,2*ℓ*)-DBNE	94	95	(*S*)
4	Ph	*i*-Pr	(1*S*,2*ℓ*)-DBNE	73	91	(*S*)
5	Me_2CHCH_2	Et	(1*S*,2*ℓ*)-DBNE	92	93	
6	$n\text{-}C_6H_{13}$	Me	(1*S*,2*ℓ*)-DBNE	70	90	(*S*)
7	$n\text{-}C_6H_{13}$	*n*-Pr	(1*S*,2*ℓ*)-DBNE	100	90	
8	$n\text{-}C_8H_{17}$	Et	(1*S*,2*ℓ*)-DBNE	95	87	(*S*)
9	$n\text{-}C_8H_{17}$	Et	(1*ℓ*,2*S*)-DBNE	99	87	(*ℓ*)
10	$n\text{-}C_8H_{17}$	Et	(1*S*,2*ℓ*)-(**6**)	87	>95	(*S*)
11	$n\text{-}C_8H_7$	Et	(1*S*,2*ℓ*)-(**3**)	61	88	(*S*)
12	$4\text{-}CF_3C_6H_4$	Et	(1*S*,2*ℓ*)-DBNE	92	91	(*S*)
13	$4\text{-}FC_6H_4$	Et	(1*S*,2*ℓ*)-DBNE	83	93	
14	PhCDO	Et	(1*S*,2*ℓ*)-DBNE	92	94	(*S*)
15	$Me(CH_2)_5CDO$	Et	(1*S*,2*ℓ*)-DBNE	79	84	(*S*)

Optically active fluorine-containing alcohols (91-93% ee) (entries 12 and 13)[16] and deuterio alcohols (84-94% ee) (entries 14 and 15)[17] are synthesized, respectively, by the enantioselective alkylation of fluorine-containing aldehyde and deuterio aldehyde using DBNE.

(1*S*,2*R*)-1-phenyl-2-(1-pyrrolidinyl)propan-1-ol (**6**) (entry 10) and (1*S*,2*R*)-*N*,*N*-diallylnorephedrine (**3**) (entry 11) are also highly enantioselective catalyst precursors.[15]

Enantioselective Addition of Various Organozinc Reagents to Aldehydes.

(1R,2S)-N-Methylephedrine

Catalytic enantioselective addition of dialkynylzinc reagents to aldehydes using (1*S*,2*R*)-DBNE (20 mol %) affords optically active (*R*)-alkynyl alcohols with 43% ee in 99% yield.[18] When an alkylalkynylzinc is used with (1*S*,2*R*)-DBNE (5 mol %), an alkynyl alcohol with 40% ee is obtained.[18] When 2-phenylzinc bromide is reacted with an aldehyde in the presence of 1 equiv of the lithium salt of (1*R*,2*S*)-(**1**), the corresponding alkynyl alcohol is obtained in 88% ee (eq 8).[19]

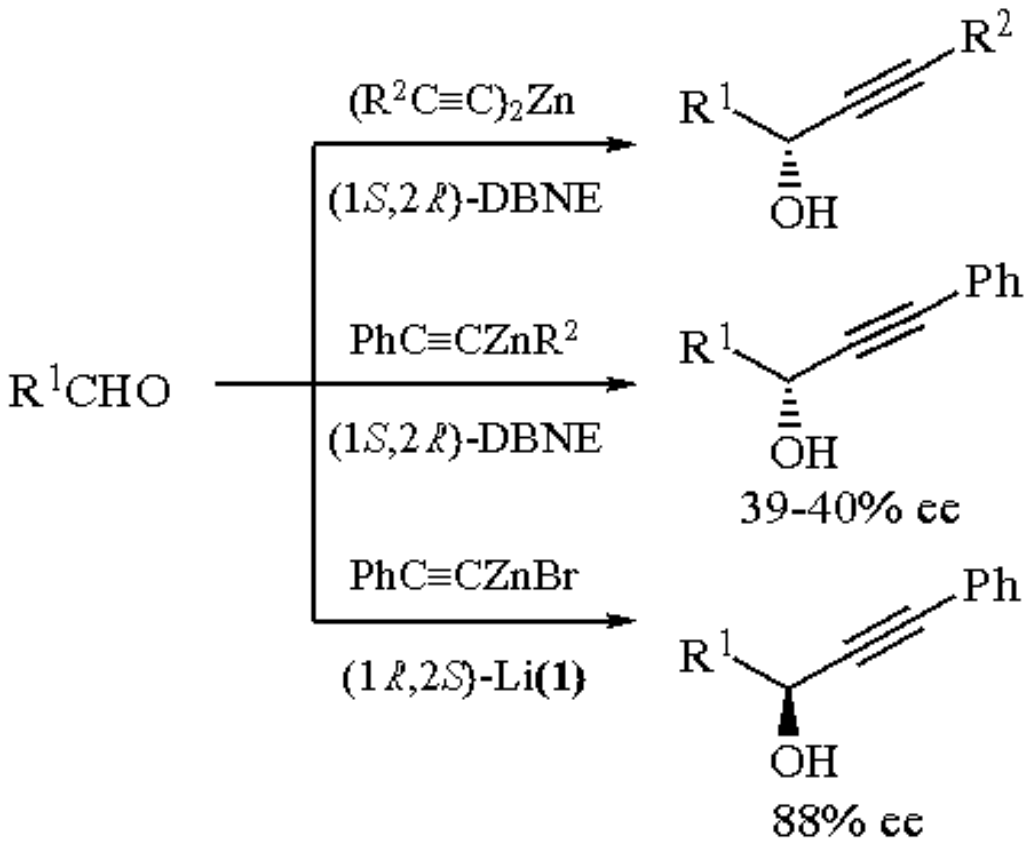

(8)

Alkenylzinc bromides add to aldehydes to afford optically active allyl alcohols with 88% ee in 80% yield using a stoichiometric amount of the lithium salt of (1*S*,2*R*)-(**1**) (eq 9).[20]

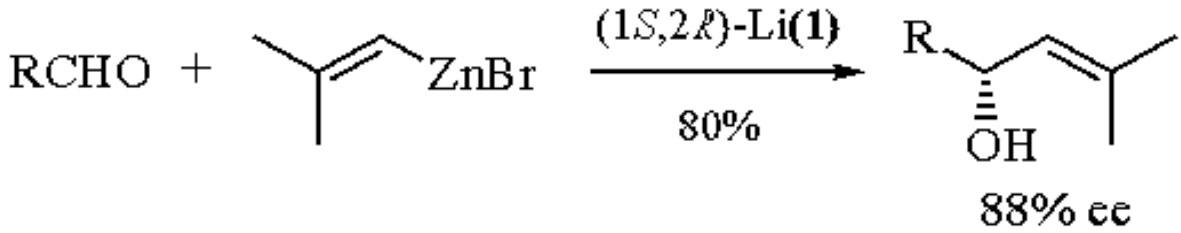

(9)

A mixture of phenyl Grignard and zinc halide adds to aldehydes in the presence of a stoichiometric amount of (1*R*,2*S*)-DBNE to afford optically active phenyl alcohols with 82% ee in 90% yield (eq 10).[21]

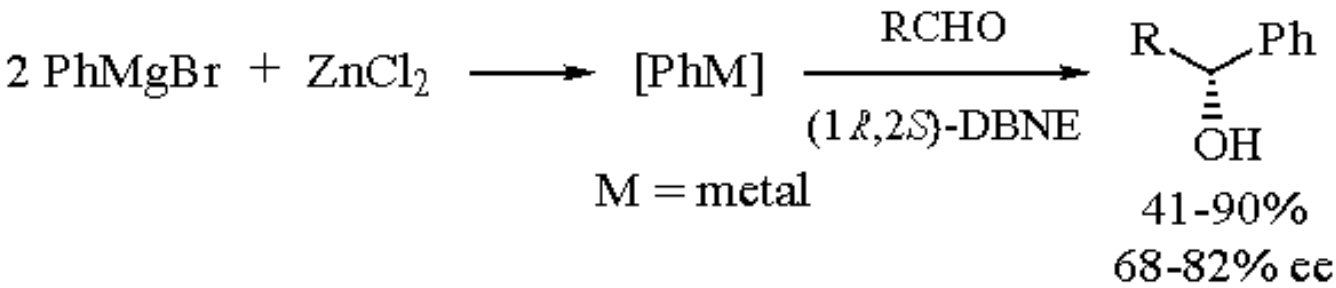

(10)

(1R,2S)-N-Methylephedrine

Difurylzinc adds to aldehydes in the presence of a stoichiometric amount of the lithium salt of (1*S*,2*R*)-*N*,*N*-bis(4-phenylbutyl)norephedrine (**4**) to afford optically active furylalcohols with 73% ee in 58% yield (eq 11).[22a]

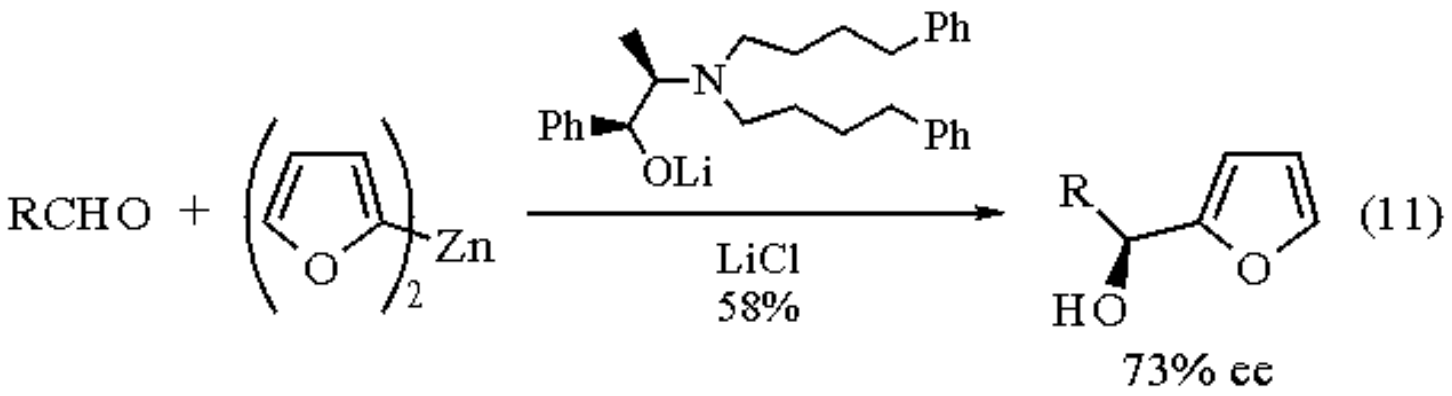

Enantioselective addition of a Reformatsky reagent to aldehydes[22b] and ketones[22c] in the presence of DBNE or *N*,*N*-diallylnorephedrine (**3**) affords the corresponding β-hydroxy esters in up to 75% ee (eq 12).

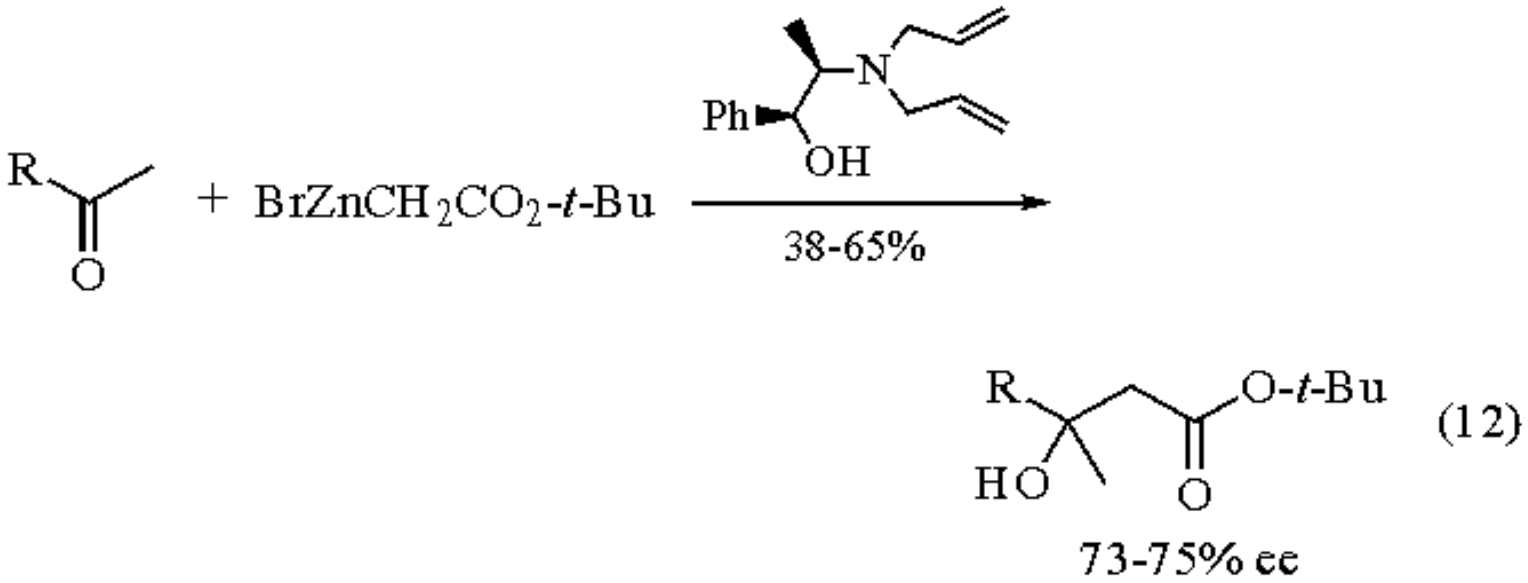

Enantioselective Addition of Dialkylzincs to Aldehydes with Functional Groups.

Enantioselective and chemoselective addition of dialkylzincs to formyl esters using (1*S*,2*R*)-DBNE as a catalyst affords optically active hydroxy esters. The subsequent hydrolysis of the esters afford the corresponding optically active alkyl substituted lactones with up to 95% ee (eq 13).[23]

(1R,2S)-N-Methylephedrine

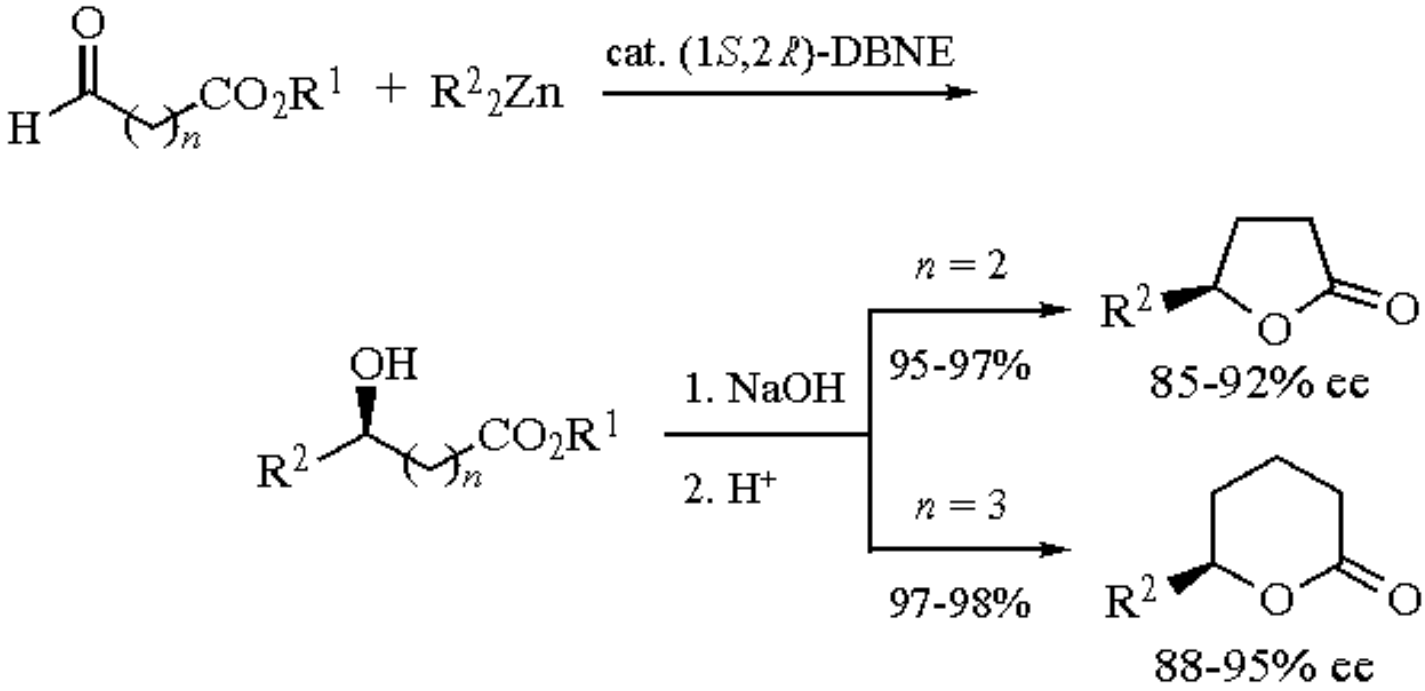

(13)

Enantio- and chemoselective addition of diethylzinc to keto aldehydes using DBNE as a chiral ligand affords optically active hydroxy ketones with 91% ee in 84% yield (eq 14).[24] This reaction cannot be realized by Grignard reagents or alkyllithium reagents because of the strong reactivity towards both aldehydes and ketones.

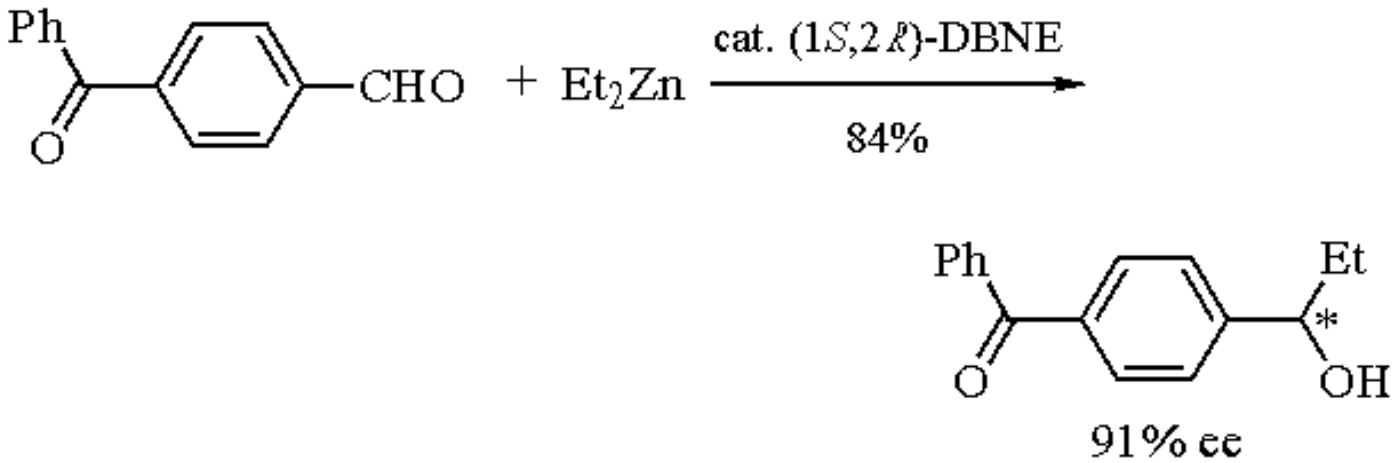

(14)

Enantioselective addition of dialkylzinc to furyl aldehydes using DBNE as a chiral catalyst affords optically active furyl alcohols in up to 94% ee (eqs 15 and 16).[25]

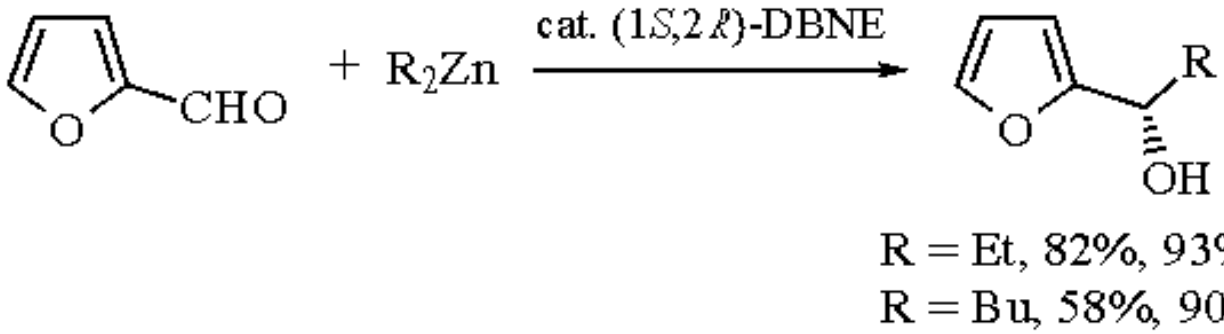

(15)

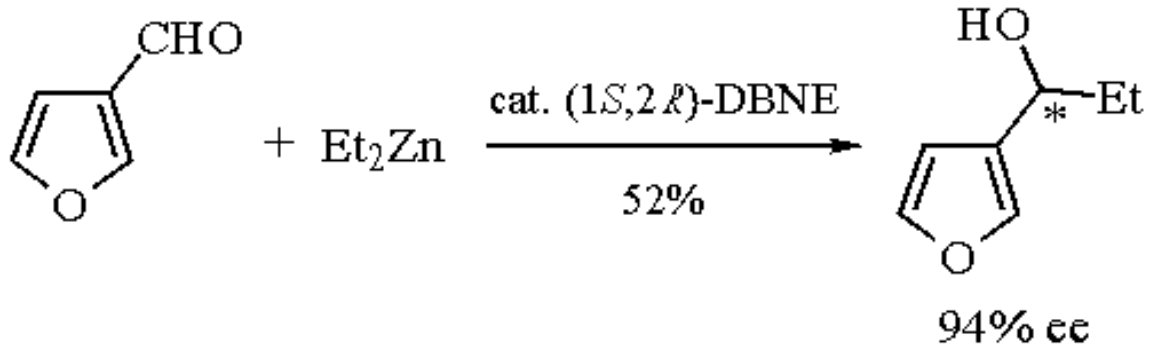

(16)

Enantioselective additions of dialkylzincs to 4-(diethoxymethyl)benzaldehyde,[26] 3-pyridinecarbaldehyde,[27] terephthalyl aldehyde,[28] and 2-bromobenzaldehyde[29] using DBNE as a chiral catalyst afford, after appropriate treatment, optically active hydroxy aldehydes,[26] pyridyl alcohols (eq 17),[27] diols (eq 18),[28] and 3-alkylphthalides (eq 19),[29] respectively, with high ee.

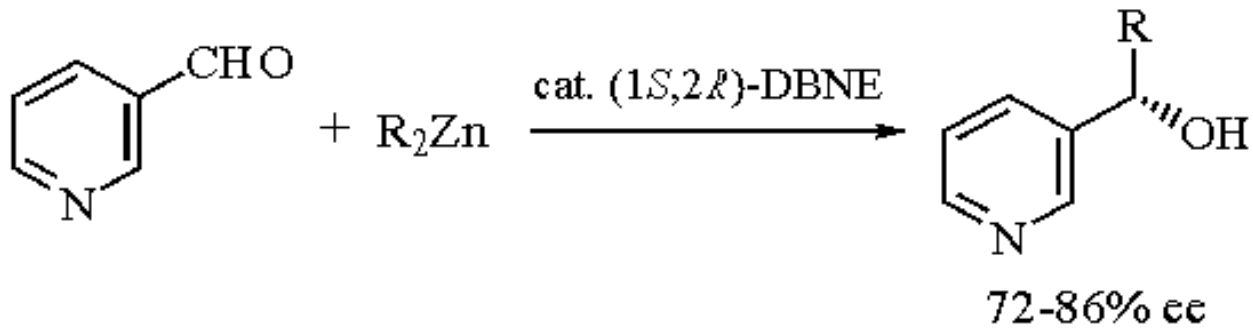

(17)

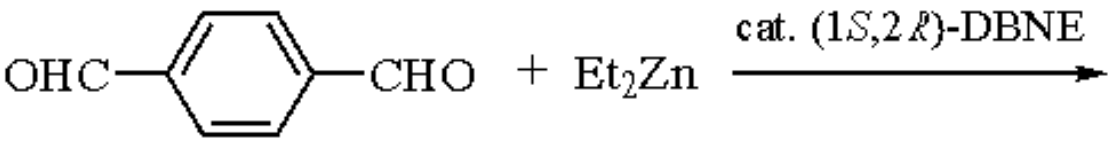

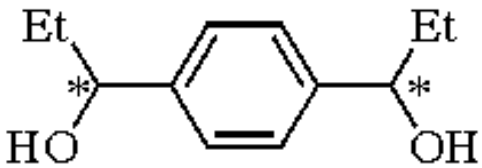

(18)

100% ee

(1R,2S)-N-Methylephedrine

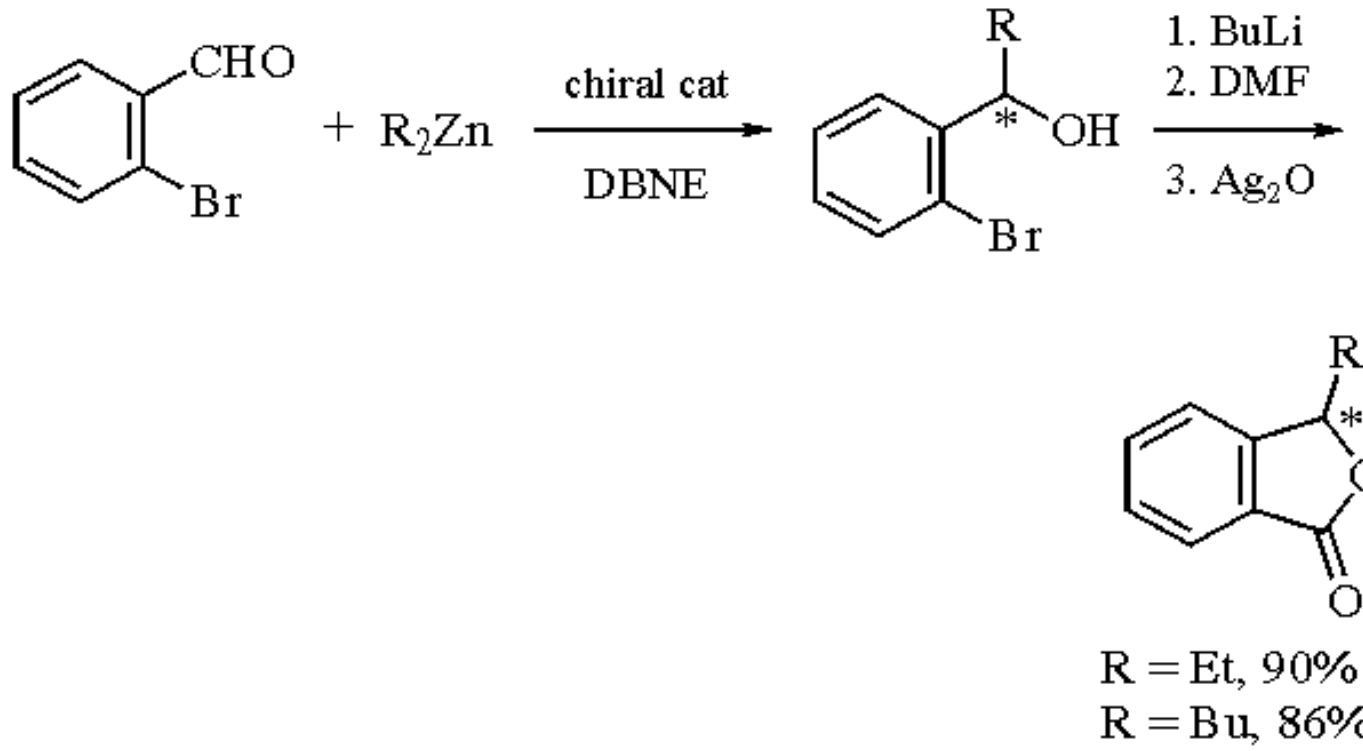

A highly functionalized chiral aldehyde when treated with Et_2Zn using (1*R*,2*S*)-DBNE as a chiral catalyst affords the optically active alcohol with 82% de in 98% yield (eq 20).[30] The alcohol has been further elaborated into (+)-lepicidin.

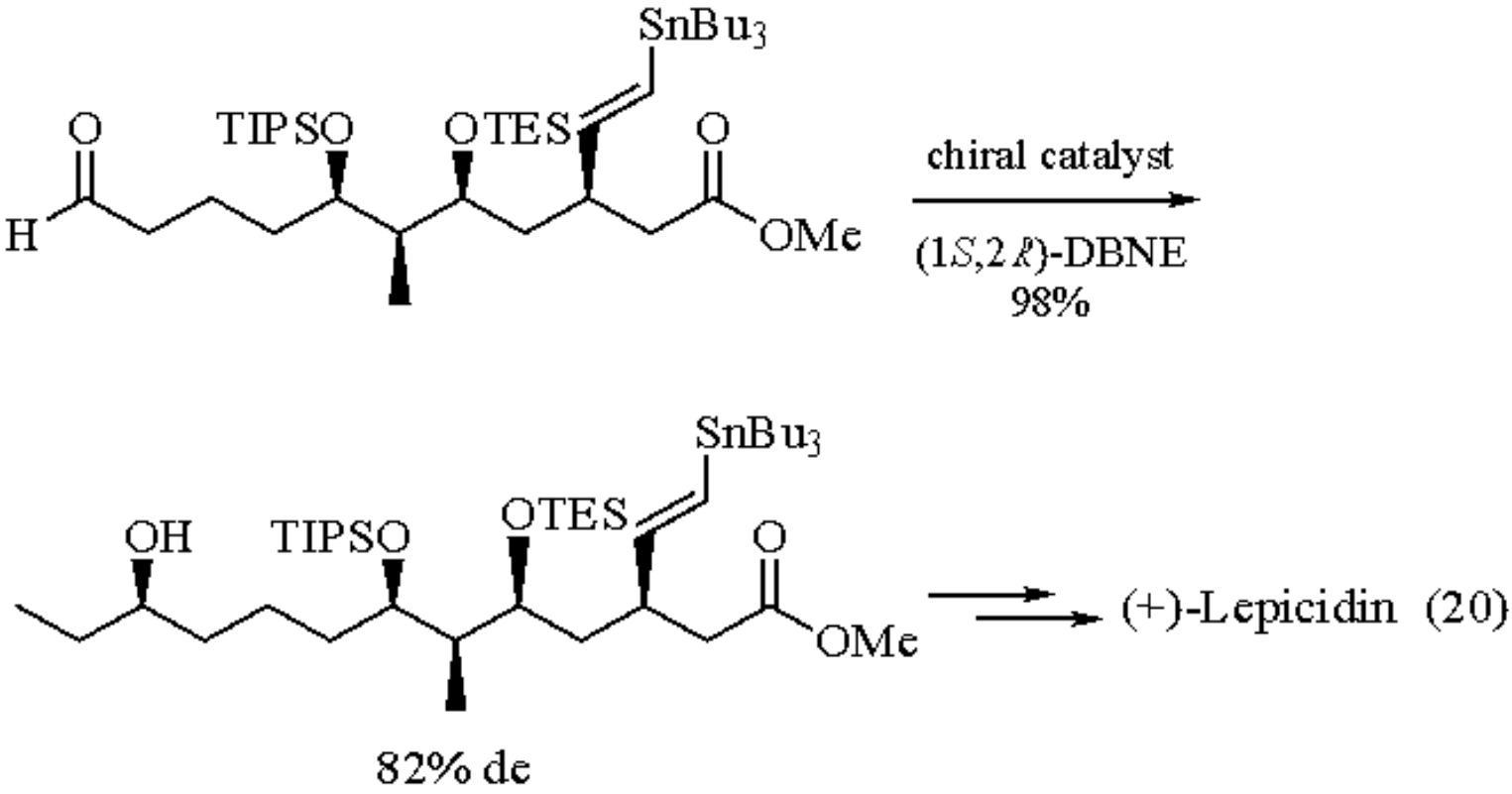

Stereoselective Addition of Dialkylzincs to Chiral Aldehydes.

Stereoselective addition of dibutylzinc to racemic 2-phenylpropanal using (1*S*,2*R*)-DBNE as a chiral catalyst affords

optically active alcohols (84% ee, 92% ee) as a result of the *si* face attack of the aldehyde regardless of its configuration (eq 21).[31]

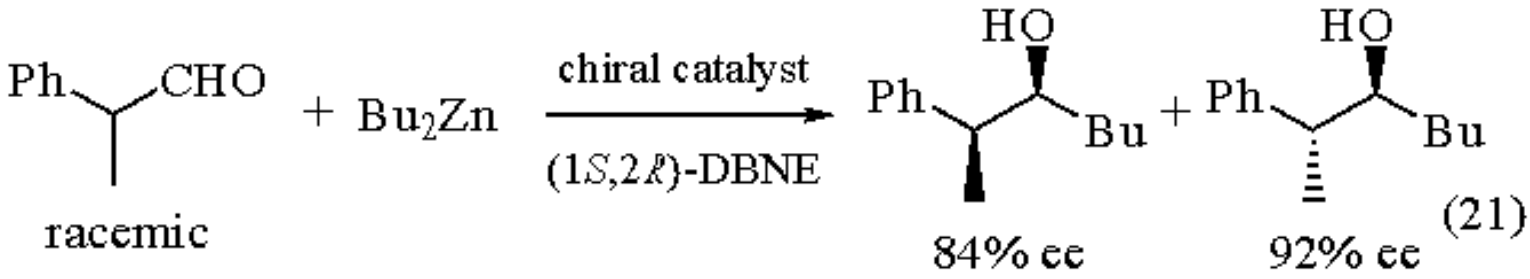

By changing the configuration of the chiral catalyst precursor (DBNE), stereoselective synthesis of optically active *syn* (78% de) and *anti* (91% de) 1,3-diols has been reported in the addition of diethylzinc to optically active β-alkoxyaldehyde (eq 22).[32] The method has an advantage over the R_2Zn-$TiCl_4$ method,[33] which is only *anti* selective.

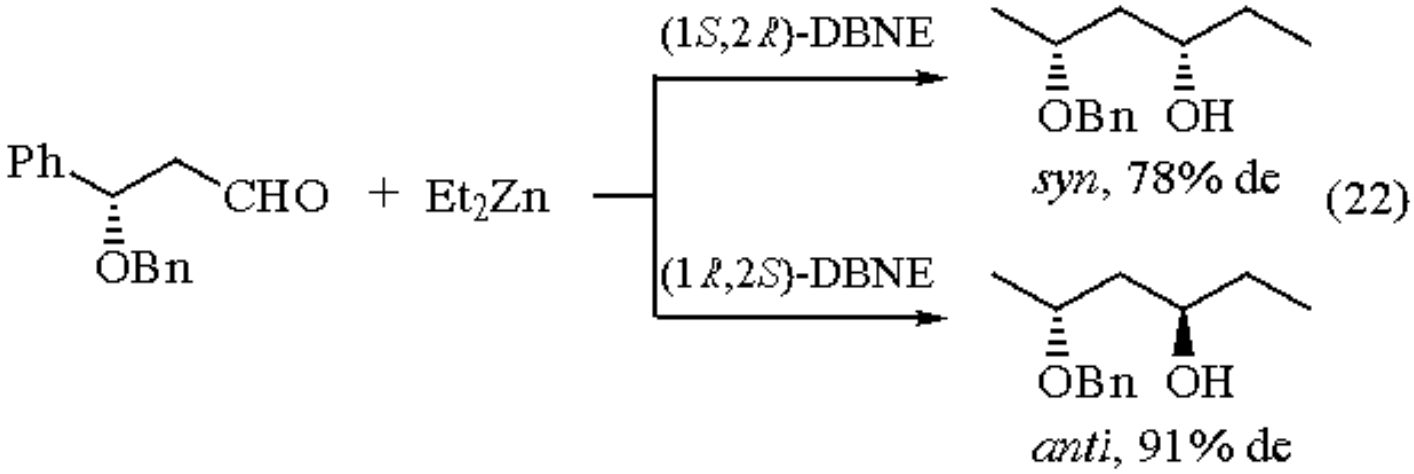

Catalytic Enantioselective Conjugate Addition of Dialkylzincs to Enones.

A chiral nickel complex modified with DBNE and an achiral ligand such as 2,2´-bipyridyl in acetonitrile/toluene is an highly enantioselective catalyst for the addition of dialkylzincs to enones.[34] β-Substituted ketones with up to 90% ee are obtained (eq 23).[34c] The method is the first highly enantioselective catalytic conjugate addition of an organometallic reagent to an enone.

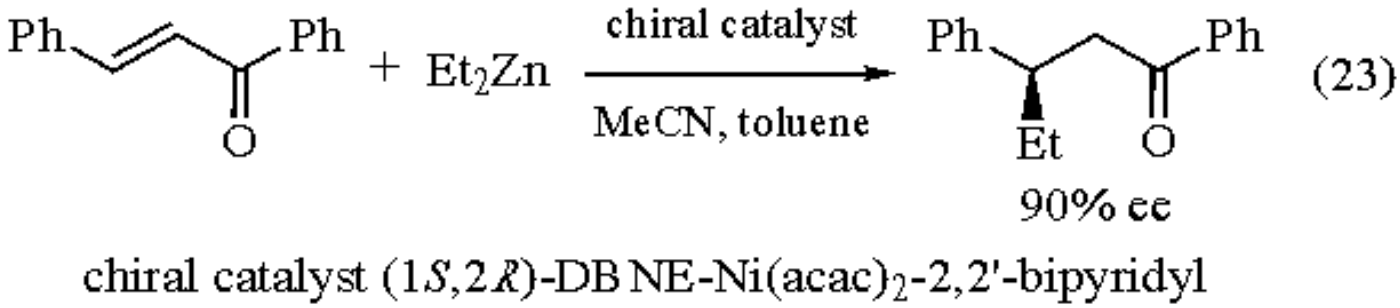

In addition, a chiral amino alcohol [1-phenyl-2-(1-piperidinyl)propan-1-ol] mediates the reaction without using any nickel

(1R,2S)-N-Methylephedrine

compound to afford the adduct in 94% ee (eq 24).[34d]

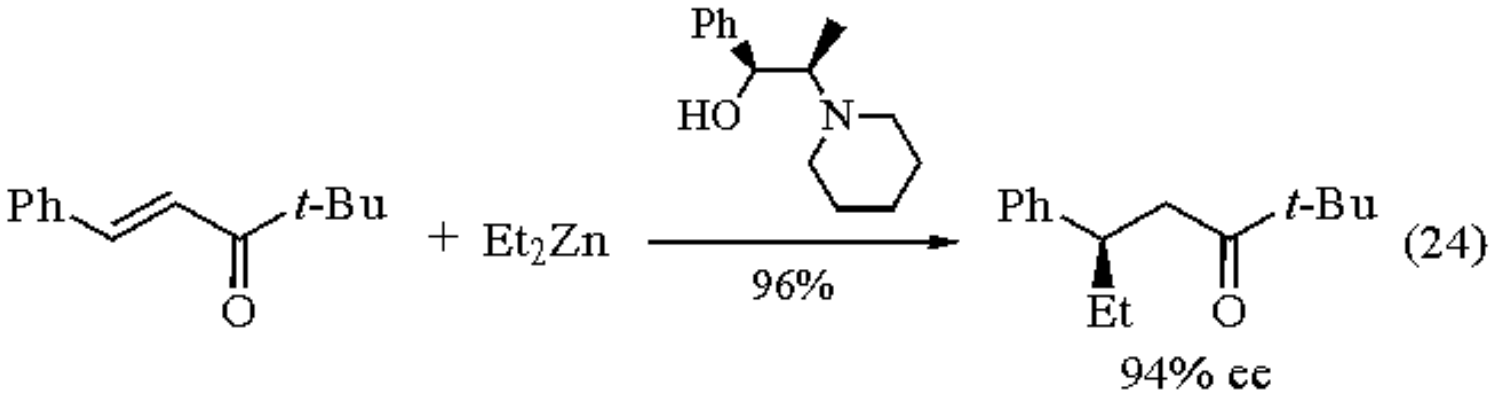

Enantioselective Addition of Dialkylzincs to Imines.

Enantioselective addition of dialkylzincs to *N*-diphenylphosphinoylimines in the presence of DBNE or its analog affords optically active phosphoramides. Subsequent hydrolysis affords optically active amines in up to 91% ee (eq 25).[35] When the amount of DBNE is catalytic (10 mol %), the enantioselectivity is 75% ee. One of the advantages of this method over the alkyllithium method[36] is the use of a lesser amount of chiral ligand.

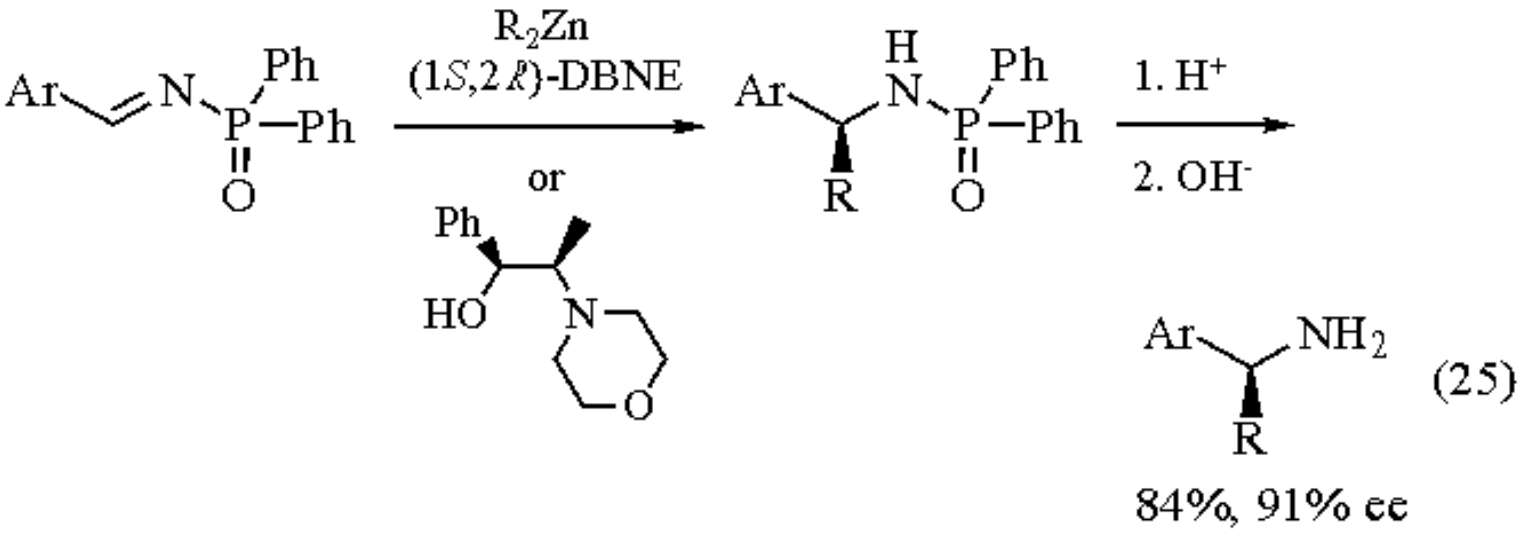

Diethylzinc also adds to *N*-(amidobenzyl)benzotriazoles (masked *N*-acylimines) in the presence of DBNE to afford an optically active amide with 76% ee (eq 26).[37]

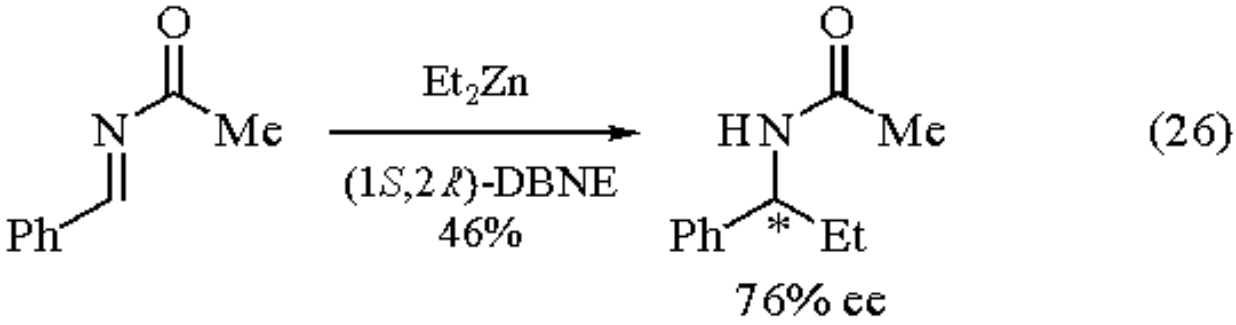

Asymmetric Michael Addition of Nitromethane to Enone.

N-Methylephedrinium fluoride catalyzes the Michael addition of nitromethane to chalcone to afford the adduct with 23% ee in 50% yield (eq 27).[38]

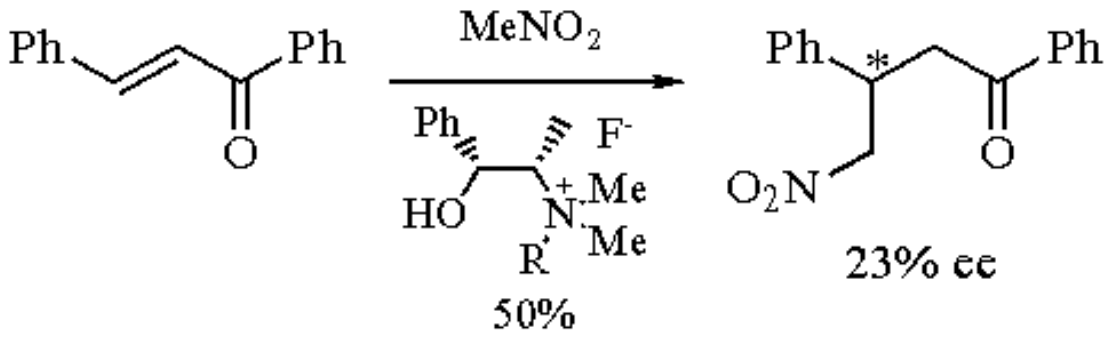

(27)

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Methyl Fluoride-Antimony(V) Fluoride[1]

MeF/SbF_5

(MeF)

[593-53-3] · CH_3F · Methyl Fluoride-Antimony(V) Fluoride · (MW 34.04) (SbF_5)

[7783-70-2] · F_5Sb · Methyl Fluoride-Antimony(V) Fluoride · (MW 216.75)

(reactive methylating agent;[1] Friedel-Crafts type electrophilic methylations; preparation of onium salts)

Physical Data: MeF: bp -78.2 °C; SbF_5: bp 149.5 °C.

Form Supplied in: MeF: gas; SbF_5: viscous liquid. Both are commercially available.

Preparative Methods: prepared by mixing equimolar amounts of freshly distilled MeF and ***Antimony(V) Fluoride*** in SO_2F_2 solution at low temperature.[2] The reagent can also be prepared in situ in the reaction flask.

Handling, Storage, and Precautions: corrosive, moisture sensitive, and potentially carcinogenic. Thus, caution should be exercised accordingly. Use in a fume hood.

Introduction.

Methyl fluoride/antimony(V) fluoride is the most reactive methylating agent reported.[1] It methylates almost all organic bases, including hydrocarbons. The structure of MeF/SbF_5 has been extensively studied.[2-4] MeF and SbF_5 form a strong donor-acceptor complex in SO_2F_2 solution, but not a free methyl cation, which is too reactive to exist in the condensed state. When more nucleophilic solvents such as SO_2 and SO_2ClF are used, *O*-methylation products, Me+O=SO and Me+O=SOClF are, respectively, formed. These systems in their own right are highly effective methylating agents.

Friedel-Crafts Methylation and Related Reactions.

Aromatic compounds are readily alkylated with MeF/SbF_5 in high yields (eq 1).[2d] In the case of toluene, a mixture of isomers was obtained with *ortho*:*meta*:*para* ratio of 54:18:28. Even highly deactivated perfluoronaphthalene is reported to react with MeF/SbF_5 to form 1- and 2-methylheptafluoronaphthalene (2:1) in 40-50% yields (eq 2).[5]

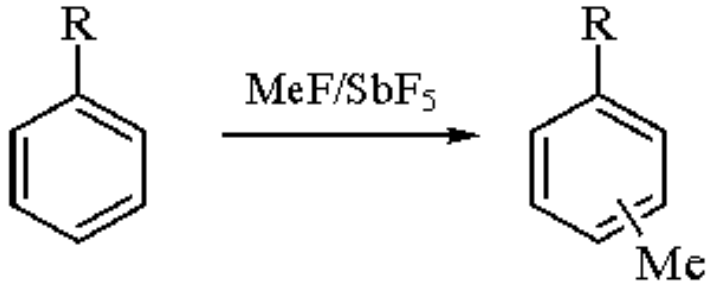

(1)

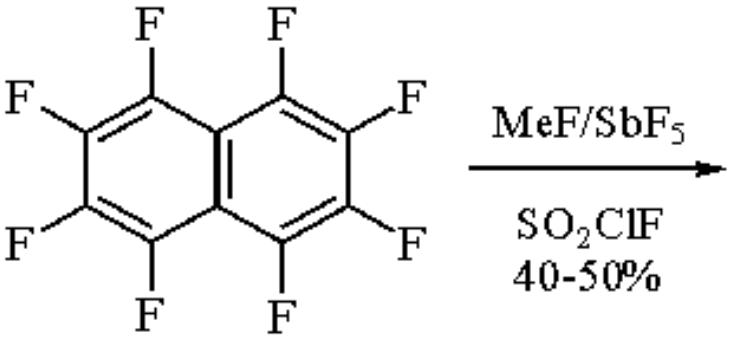

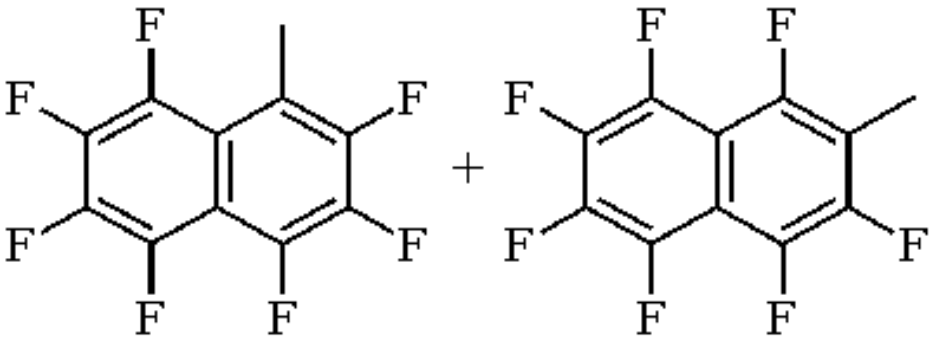

(2)

Methyl fluoride/antimony(V) fluoride can add the methyl group to double bonds of alkenes to form carbenium ions (eq 3).[2c] The reagent also reacts with CO to form the acetylium ion. Hydrolysis of the ion yields acetic acid.[2c] In the presence of excess MeF, self-condensation to the *t*-butyl cation takes place via initial formation of ethyl fluoride through σ-C-H bond insertion (eq 4).[2c]

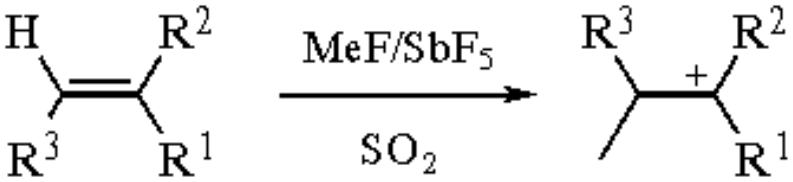

(3)

(4)

Methylation of Heteroatoms.

Methyl fluoride/antimony(V) fluoride has been widely used for methylation of heteroatoms. Various nitrogen-

containing compounds have been studied, including cyanogen halides,[6a] nitriles (eq 5),[6a,6b] sulfur difluoride imides,[6c] sulfur trifluoride imides and derivatives,[6d] and fluorinated imines (eq 6).[6e] In most cases, stable methylation salts are isolated. For example, the sulfur(VI) dication $[(Me_2N)_2SF_2]^{2+}$ is prepared upon treating NSF_2NMe_2 with MeF/SbF_5 in SO_2 solution (eq 7).[6f]

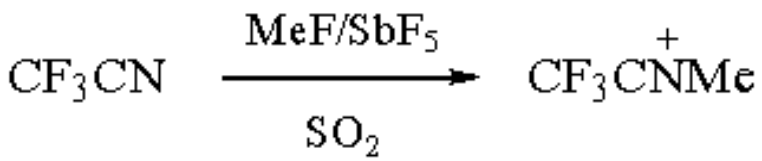

(5)

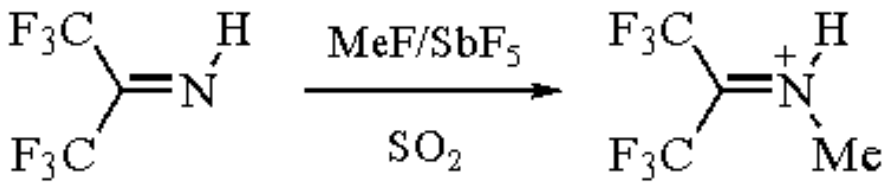

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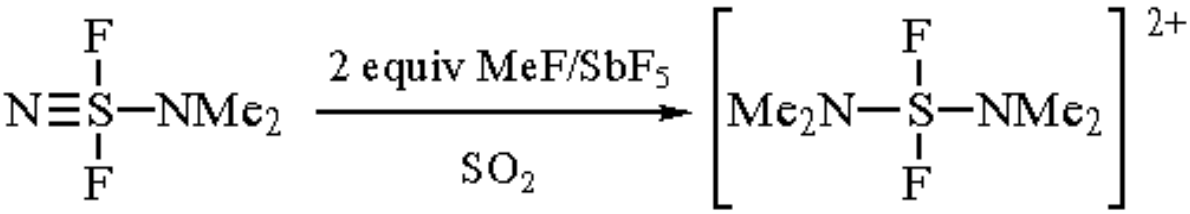

(7)

As mentioned, MeF/SbF_5 is able to *O*-methylate SO_2. Similarly, methylated oxonium ions are obtained from ethers (eq 8), sulfoxides, nitrates, and ketones.[2a,2c,7] It is reported that even weak nucleophiles, such as sulfones, were successfully alkylated with MeF/SbF_5 (eq 9).[7] At higher temperature, MeF/SbF_5 reacts with ***Copper(I) Oxide*** to form dimethyl ether (eq 10);[8a] in the presence of CO the reaction produces methyl acetate.[8b]

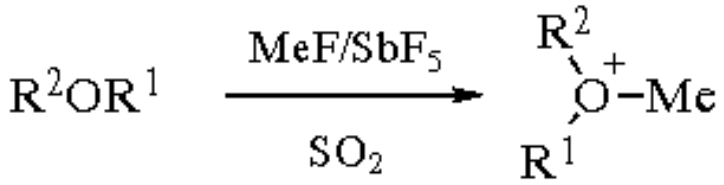

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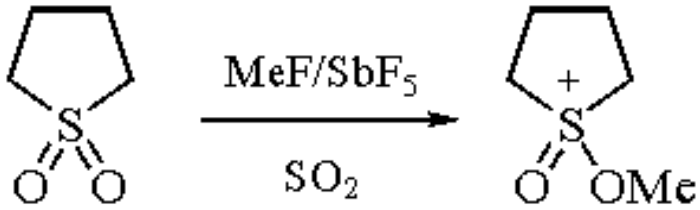

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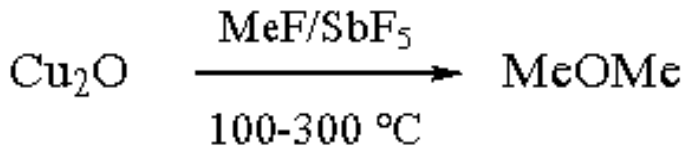

(10)

Sulfur-containing compounds are similarly alkylated with MeF/SbF_5. Sulfonium salts were prepared from starting

materials such as sulfides (eq 11)[2d,9a,9b] and thiophosphoryl halides (eq 12).[9c,9d]

$$(CF_3)_2S \xrightarrow[SO_2]{MeF/SbF_5} (CF_3)_2\overset{+}{S}Me \qquad (11)$$

$$X^1{}_2X^2PS \xrightarrow[SO_2]{MeF/SbF_5} X^1{}_2X^2P\overset{+}{S}Me \qquad (12)$$

$$X^1 = Br, Cl;\ X^2 = Br, Cl, F$$

Treatment of alkyl halides (with the exception of fluorides) with MeF/SbF_5 leads to formation of alkyl(methyl)halonium ions.[2c] A series of cyclopropyl- as well as vinylhalonium ions have also been prepared (eq 13).[10] The preparation of the methyl(trifluoromethyl)iodonium ion is interesting since CF_3 is a strongly electron-withdrawing group (eq 14).[11] Reaction between Br_2 and MeF/SbF_5 generates the dimethylbromonium ion. In contrast, the polycationic species $(MeI_2)_n{}^{n+}(SbF_6{}^-)_6$ are obtained upon the treatment of MeF/SbF_5 with I_2 (eq 15).[12]

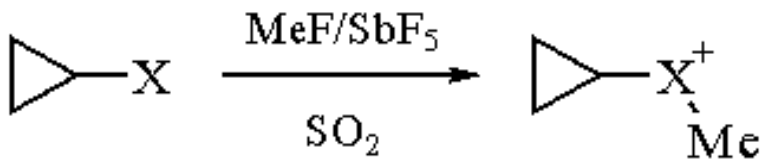

(13)

$$X = Cl, Br, I$$

$$CF_3I \xrightarrow[SO_2]{MeF/SbF_5} CF_3\overset{+}{I}Me \qquad (14)$$

$$I_2 \xrightarrow[SO_2]{MeF/SbF_5} (MeI_2)_n{}^{n+} \qquad (15)$$

Related Reagents.

Dimethyliodonium Hexafluoroantimonate; ***O-Methyldibenzofuranium Tetrafluoroborate***; ***Methyl Trifluoromethanesulfonate***; ***Trimethyloxonium Tetrafluoroborate***.

---

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N-Methylformanilide

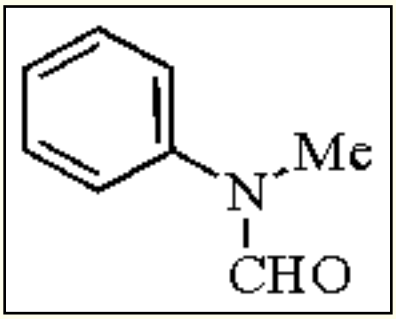

[93-61-8] · C_8H_9NO · *N*-Methylformanilide · (MW 135.18)

(formylating reagent for certain organometallics;[1] used in combination with $POCl_3$ for Vilsmeier-Haack reactions[2] and heterocycle syntheses[3,4])

Alternate Name: *N*-methyl-*N*-phenylformamide.

Physical Data: mp 8-13 °C; bp 243-244 °C; *d* 1.095 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: IR, NMR.

Handling, Storage, and Precautions: irritant, toxic.

General Discussion.

N-Methylformanilide (**1**) has been used for formylating organolithium and Grignard reagents (eq 1).[1]

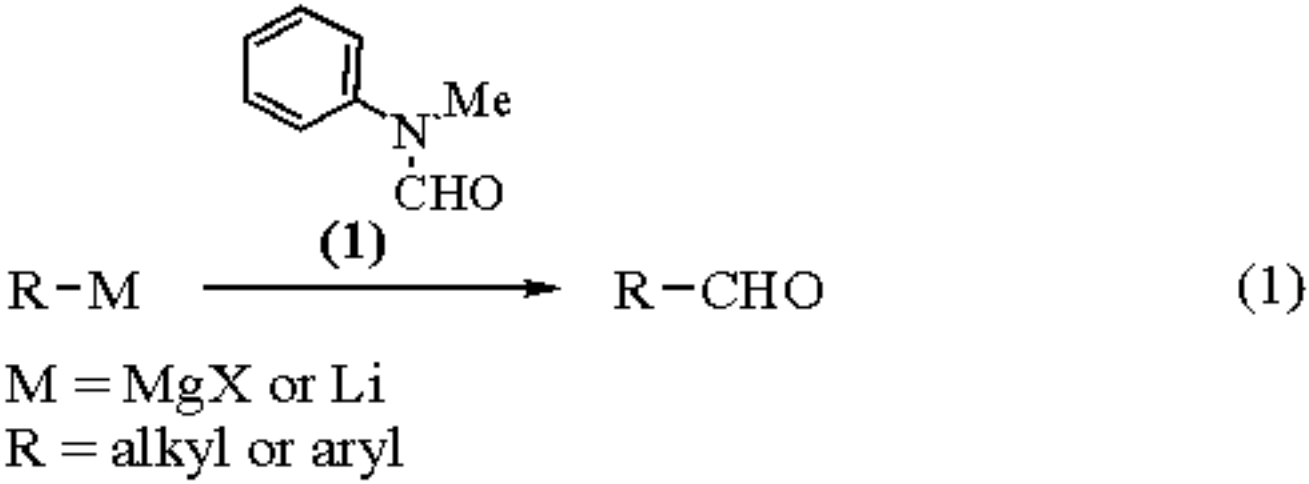

Alternatively, formylation can be achieved under Vilsmeier-Haack reaction conditions.[2] In this manner, aromatic compounds such as (**2**) can be formylated by treatment with the chloromethylene ammonium salt generated from reagent (**1**) (eq 2).

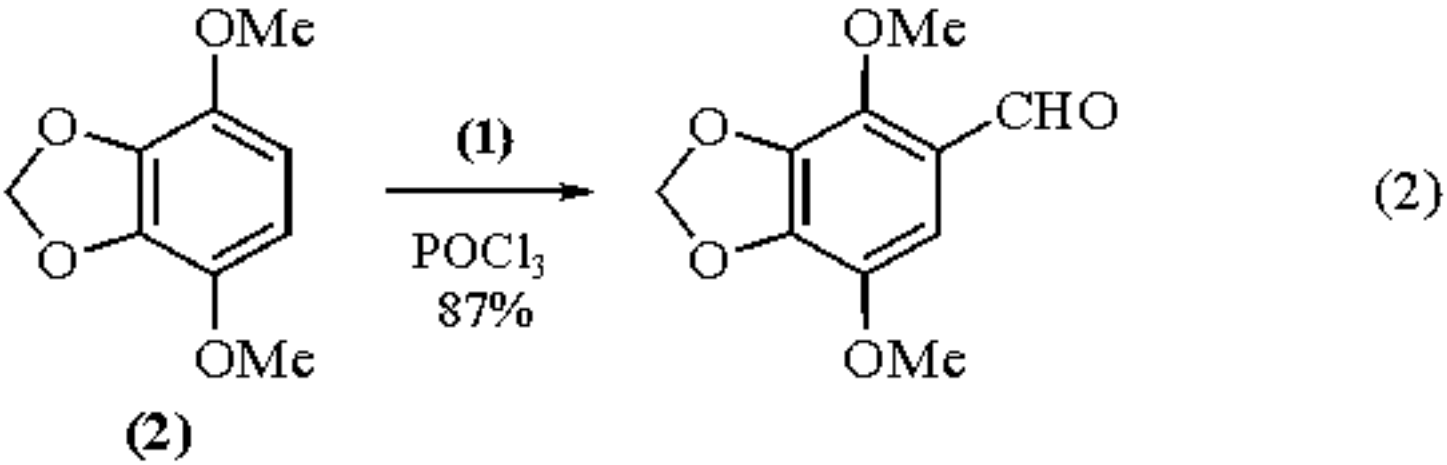

1,3-Cyclohexanediones and vinyl acetates undergo some interesting transformations on reaction with (**1**) in the presence of ***Phosphorus Oxychloride*** (eqs 3 and 4).[3] A wide variety of vinyl compounds other than vinyl acetate have been successfully utilized in this reaction (eq 4).[3b]

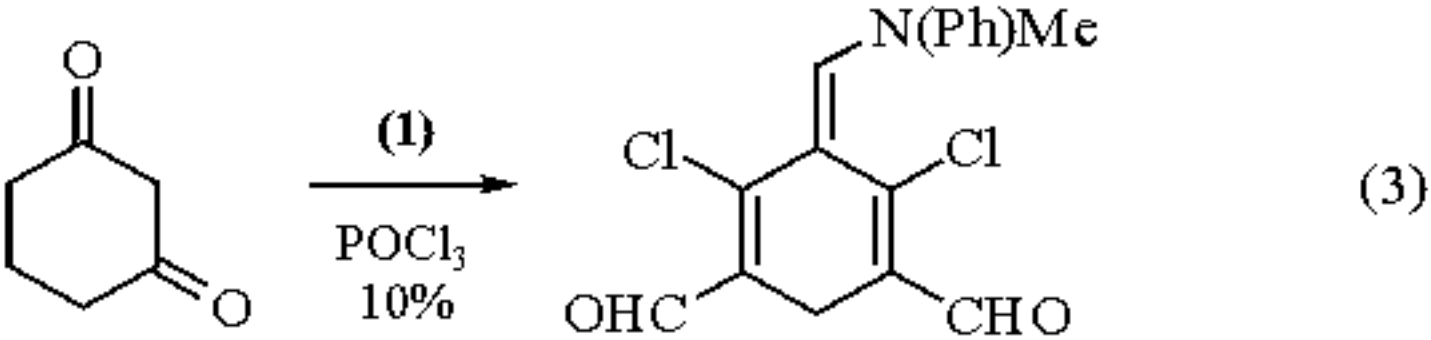

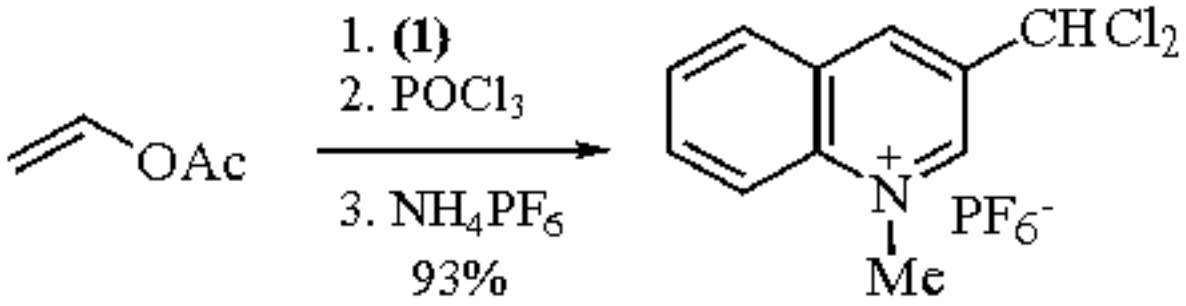

(4)

1,3,5-Triazines (**3**) can be obtained by condensing cyanoamidines with (**1**) and phosphorus oxychloride (eq 5).[4] Enaminals can be afforded by the reaction of (**1**) with a vinyl ether and ***Oxalyl Chloride***.[5]

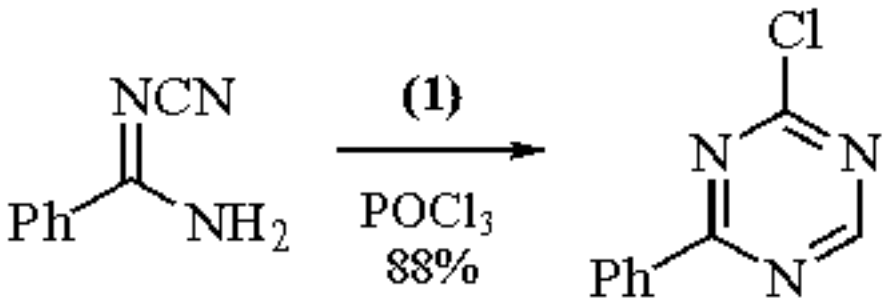

(5)

(3)

A convenient synthesis of both symmetrical and unsymmetrical 1,5-diketones (**4**) has been achieved (eq 6).[6]

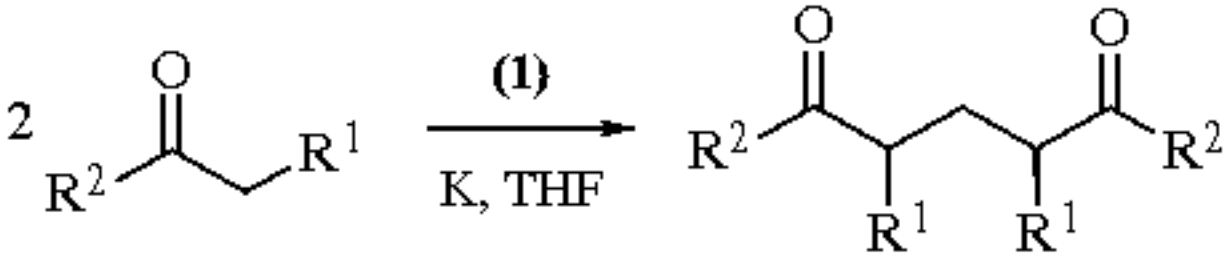

(6)

(4)

N-Acylamino-2-azaallene salts are the products of reaction of (**1**) with nitrilium salts.[7] Enamines can be easily made by reacting metal carbene complexes with (**1**).[8] Reduction of (**1**) to *N*,*N*-dimethylaniline can be effected using bis(2-bromoethylselenium dibromide) and sodium borohydride.[9]

Related Reagents.

N,N-Dimethylformamide; ***N-Formylpiperidine***; ***N-Methyl-N-phenyl(chloromethylene)ammonium Phosphorochloridate***; ***N-Methyl-N-(2-pyridyl)formamide***.

1. (a) Talley, J. J.; Evans, I. A. *JOC* **1984**, *49*, 5267. (b) Azzena, U.; Melloni, G.; Piroddi, A. M.; Azara, E.; Contini, S.; Fenude, E. *JOC* **1992**, *57*, 3101. (c) Jacob, P. III; Shulgin, A. T. *JMC* **1983**, *26*, 746. (d) Amaratunga, W.; Frechet, J. M. J. *TL* **1983**, *24*, 1143.
2. (a) Yamamura, K.; Miyake, H.; Murata, I. *JOC* **1986**, *51*, 251. (b) Rizzacasa, M. A.; Sargent, M. V. *JCS(P1)* **1987**, 2017. (c) Deschamps, E.; Mathey, F. *JOC* **1990**, *55*, 2494.
3. (a) Katritzky, A. R.; Marson, C. M.; Palenik, G.; Koziol, A. E.; Luce, H.; Karelson, M.; Chen, B. C.; Brey, W. *T* **1988**, *44*, 3209. (b) Meth-Cohn, O. *TL* **1985**, *26*, 1901. (c) Meth-Cohn, O. *S* **1986**, 76.
4. Harris, R. L. N. *AJC* **1981**, *34*, 623.
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7. Jochims, J. C.; Glocker, M. O. *CB* **1990**, *123*, 1537.
8. (a) Soderberg, B. C.; Hegedus, L. S. *JOC* **1991**, *56*, 2209. (b) Aumann, R.; Hinterding, P. *CB* **1990**, *123*, 611.
9. Akabori, S.; Takanohashi, Y. *CL* **1990**, 251.

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Methyl Formate

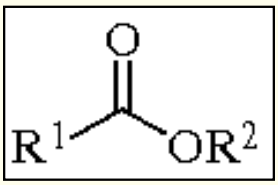

(**1**; R^1 = H, R^2 = Me)

[107-31-3] · $C_2H_4O_2$ · Methyl Formate · (MW 60.06) (**2**; R^1 = H, R^2 = Et)

[109-94-4] · $C_3H_6O_2$ · Ethyl Formate · (MW 74.09) (**3**; R^1 = H, R^2 = Pr)

[110-74-7] · $C_4H_8O_2$ · Propyl Formate · (MW 88.12) (**4**; R^1 = H, R^2 = Bu)

[592-84-7] · $C_5H_{10}O_2$ · Butyl Formate · (MW 102.15) (**5**; R^1 = H, R^2 = *t*-Bu)

[762-75-4] · $C_5H_{10}O_2$ · *t*-Butyl Formate · (MW 102.15) (**6**; R^1 = D, R^2 = Me)

[23731-38-6] · $C_2H_3DO_2$ · Methyl Formate · (MW 61.06)

(formylating agent for carbonyl compounds;[1-3] electrophile for organometallic agents[4])

Physical Data: (**1**) bp 34 °C; *d* 0.974 g cm^{-3}. (**2**) bp 52-54; *d* 0.917 g cm^{-3}. (**3**) bp 80-81 °C; *d* 0.904 g cm^{-3}. (**4**) bp 106-107 °C; *d* 0.892 g cm^{-3}. (**5**) bp 82-83 °C; *d* 0.872 g cm^{-3}. (**6**) bp 32.1 °C; *d* 0.990 g cm^{-3}.

Solubility: partially sol water; miscible with alcohol, ether.

Form Supplied in: liquid; widely available in 97-99% purity.

Handling, Storage, and Precautions: most formates are colorless, flammable, irritant, and moisture-sensitive liquids. Inhalation of methyl formate vapor produces nasal and conjunctional irritation, retching, narcosis, death from pulmonary effects. Ethyl formate is irritating to skin, mucous membranes, and, in high concentrations, narcotic. Use in a fume hood.

Among all the formates listed, methyl and ethyl formate are the most widely used agents in organic synthesis. These formates are mainly used as a formylating agent for carbonyl compounds. As shown in eq 1, cyclohexanone (**7**) is converted into the enolate (**8**) in the presence of either ***Sodium Ethoxide*** or ***Sodium Hydride*** and condensed with ethyl formate to give 2-hydroxymethylene cyclohexanone (**9**) or its tautomer, 2-formylcyclohexanone (**10**).[1i]

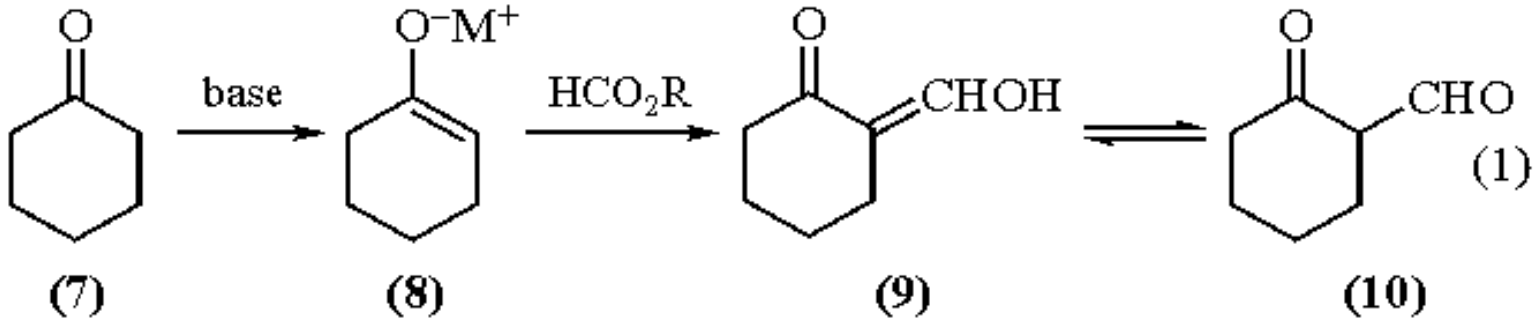

To generate enolate (**8**) from the carbonyl compounds, sodium alkoxide[1] or sodium hydride (or ***Potassium Hydride***)[2] is generally used. Examples for using ***Potassium t-Butoxide*** are also reported.[3] The solvent can be either benzene, toluene, ether, dimethoxyethane, or THF. **Caution**: gas evolution has been cited in the formylation of cyclopentanone with ethyl formate in a solution of potassium *t*-butoxide in THF.[3] Among the carbonyl compounds, ketones are the most commonly used substrates for the formylation. A few examples for formylating lactones[5] and esters[6] are also reported.

A classic example of the synthetic utility is illustrated (eq 2) in the formylation of a cyclic ketone to block one α-position (**11** to **12** to **13a-c**) and alkylating the α´-position (**13a-c** to **14a-c**). The blocking group is then removed (**14a-c** to **15** to **16**).[1b,1c,1g]

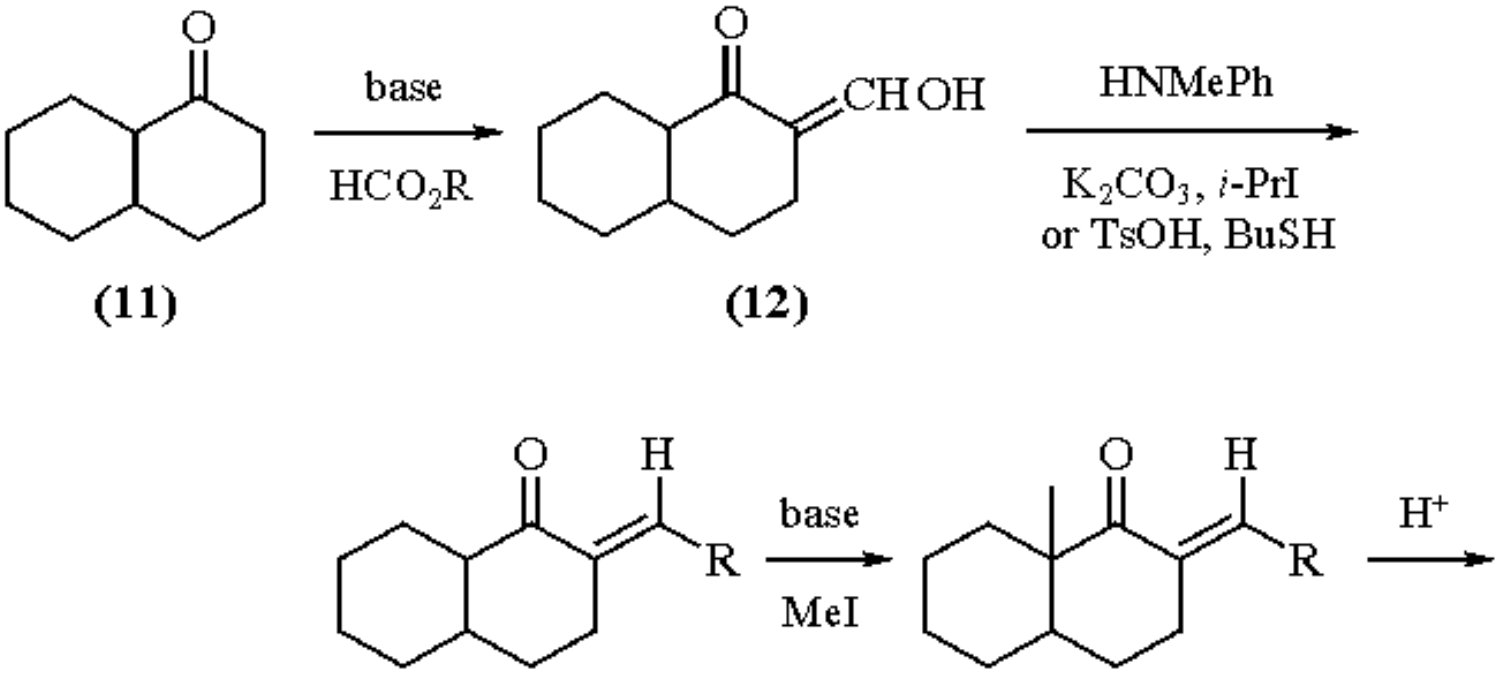

(13a) R = NMePh
71% from **(11)**
(13b) R = O-*i*-Pr
93% from **(11)**
(13c) R = SBu
64% from **(11)**

(14a) R = NMePh
(14b) R = O-*i*-Pr
(14c) R = SBu

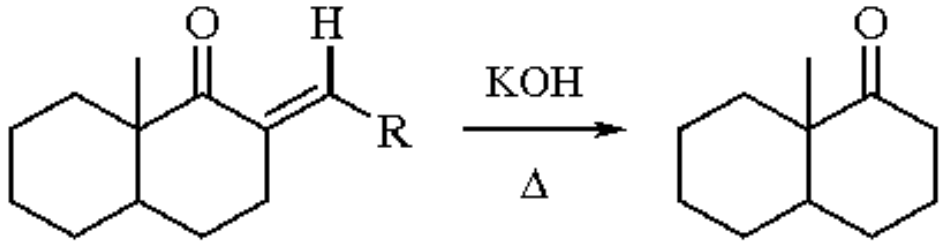

(2)

(15) R = OH or SH

(16) 68% from **(13a)**
43% from **(13b)**
66% from **(13c)**

Organometallic agents are combined with the formates to give alcohols or aldehydes.[4] For example, treatment of an ethereal solution of 5-pentenylmagnesium bromide with methyl formate at 0 °C gives undeca-1,10-dien-6-ol in 86% yield (eq 3).[4c]

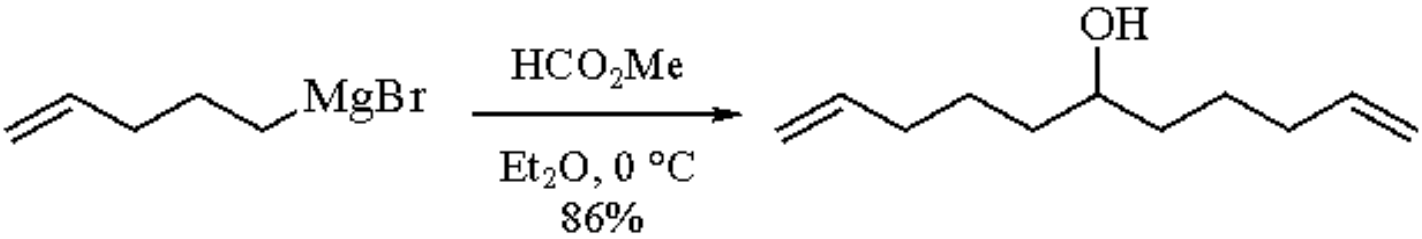

(3)

The carbanion generated from the deprotonation of *O,S*-acetal (**17**) reacts with ethyl formate at -80 °C to give the aldehyde (**18**) in 89% yield (eq 4).[4d]

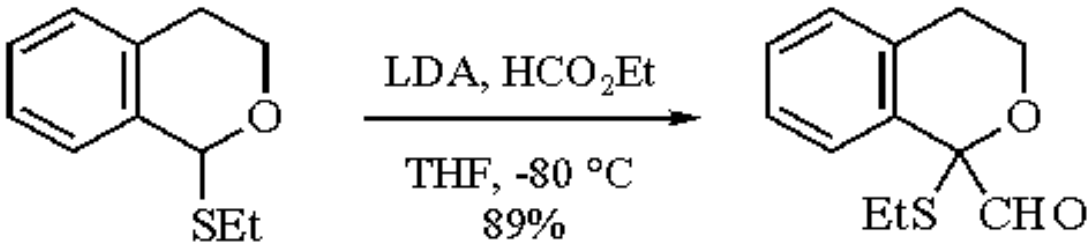

(4)

(17) **(18)**

The formates are also reported to react in the following unusual transformations. Nitrobenzene is reacted with the formates, catalyzed by $PdCl_2(PPh_3)_2$, together with Bu_3PO/KBr under carbon monoxide atmosphere, to give *N*-phenylcarbamates in 29-63% yield (eq 5).[7]

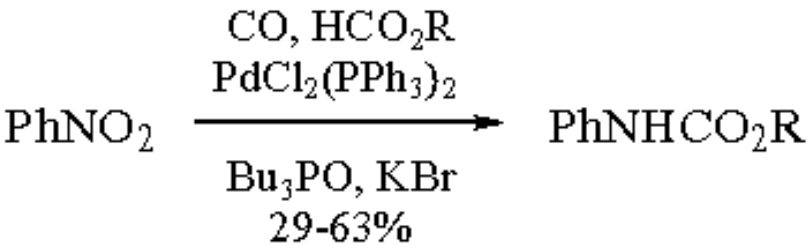

(5)

Benzylic, aryl, and alkyl halides react with the formates under carbon monoxide atmosphere, in the presence of $(RhLCl)_2$ (L = 1,5-hexadiene), KI, and, optionally, $Pd(PPh_3)_4$, to give the corresponding carboxylate esters in 20-94% yield (eq 6).[8]

$$R^1X \xrightarrow[\text{(L = 1,5-hexadiene)}\ \text{20-94\%}]{CO,\ HCO_2R,\ KI,\ (RhLCl)_2} R^1CO_2R^2 \qquad (6)$$

The formates add regioselectively to alkenes or alkynes, such as *p*-methylstyrene, catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)*** and ***1,4-Bis(diphenylphosphino)butane*** under carbon monoxide atmosphere, to give the linear isomer and the branched isomer (6.5:1 ratio) in 67% yield (eq 7).[9]

$$p\text{-}MeC_6H_4CH{=}CH_2 \xrightarrow[(Ph_2P)_2(CH_2)_4,\ \text{toluene, 150 °C},\ \text{67\%}]{CO,\ HCO_2Bu,\ Pd(PPh_3)_4}$$

$$p\text{-}MeC_6H_4(CH_2)_2CO_2Bu + p\text{-}MeC_6H_4CH(CO_2Bu)Me \qquad (7)$$

6.5:1

---

1. (a) Prelog, V.; Geyer, U. *HCA* **1945**, *28*, 1677. (b) Birch, A. J.; Robinson, R. *JCS* **1944**, 501. (c) Johnson, W. S.; Posvic, H. *JACS* **1947**, *69*, 1361. (d) Johnson, W. S.; Petersen, J. W.; Gutsche, C. D. *JACS* **1947**, *69*, 2942. (e) Wilds, A. L.; Shunk, C. H. *JACS* **1950**, *72*, 2388. (f) Frank, R. L.; Varland, R. H. *OSC* **1955**, *3*, 829. (g) Ireland, R. E.; Marshall, J. A. *CI(L)* **1960**, 1534; *JOC* **1962**, *27*, 1615, 1620. (h) Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Neumann, H. C.; Christiansen, R. G.; Clarke, R. L.; Ackerman, J. H.; Page, D. F.; Dean, J. W.; Dickinson, W. B.; Carabateas, C. *JACS* **1961**, *83*, 1478. (i) Ainsworth, C. *OSC* **1963**, *4*, 536. (j) Schenone, P.; Bignardi, G.; Morasso, S. *JHC* **1972**, *9*, 1341. (k) Boatman, S.; Harris, T. M.; Hauser, C. R. *OSC* **1973**, *5*, 187.
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5. (a) Rakhit, S.; Gut, M. *JOC* **1964**, *29*, 229, 859. (b) Harmon, A. D.; Hutchinson, C. R. *TL* **1973**, 1293. (c) Yamada, K.; Kato, M.; Hirata, Y. *TL* **1973**, 2745. (d) Murray, A. W.; Reid, R. G. *CC* **1984**, 132. (e) Lehmann, J.; Neugebauer, M.; Marquardt, N. *AP* **1990**, *323*, 117.
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7. Lin, I. J. B.; Chang, C. S. *J. Mol. Catal.* **1992**, *73*, 167.
8. Buchan, C.; Hamel, N.; Woell, J. B.; Alper, H. *CC* **1986**, 167.
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Methyl Glyoxylate

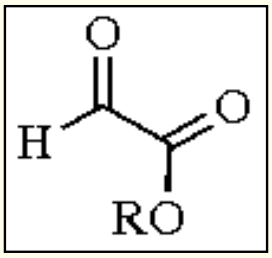

(**1**; R = Me)

[922-68-9] · $C_3H_4O_3$ · Methyl Glyoxylate · (MW 88.07) (**2**; R = Et)

[924-44-7] · $C_4H_6O_3$ · Ethyl Glyoxylate · (MW 102.10) (**3**; R = *n*-Bu)

[6295-06-3] · $C_6H_{10}O_3$ · Butyl Glyoxylate · (MW 130.16) (**4**; R = $PhCH_2$)

[52709-42-9] · $C_9H_8O_3$ · Benzyl Glyoxylate · (MW 164.17) (**5**; R = *i*-Pr)

[924-53-8] · $C_5H_8O_3$ · Isopropyl Glyoxylate · (MW 116.13) (**6**; R = phenylmenthyl)

[129444-92-4] · $C_{18}H_{24}O_3$ · 8-Phenylmenthyl Glyoxylate · (MW 288.42)

(two-carbon synthon utilized in electrocyclic processes (Diels-Alder reaction[1], ene reactions[2]), various condensations (Mannich,[3] aldol,[4] Wittig,[5] Prins,[6] acyloin[7]), carbinolamine formation,[8] and Friedel-Crafts reactions[9])

Alternate Name: methyl oxoacetate.

Physical Data: (**1**) bp 45-50 °C/29 mmHg. (**2**) bp 49 °C/35 mmHg. (**3**) mp 46-48 °C; bp 55 °C/14 mmHg. (**4**) bp 130-132 °C/25 mmHg. (**5**) bp 34-36 °C/18 mmHg. (**6**) bp 135-140 °C/0.3 mmHg.

Solubility: sol most organic solvents, e.g. ether, CH_2Cl_2, THF, acetone, etc. (**1**) sol H_2O (as monohydrate).

Form Supplied in: prepare fresh before use for optimum results. *Drying:* distill from P_2O_5.[10b]

Preparative Methods: efficient methods include oxidative cleavage of tartrate diesters, ozonolysis of maleate/fumarate derivatives, exchange reaction between appropriate dialkoxyacetate and glyoxylic acid, and NaOAc-catalyzed elimination of nitrite ion from nitrate esters.[10]

Purification: distillation of methyl glyoxylate monohydrate through a 10-cm Vigreux column.

Handling, Storage, and Precautions: store under N_2 in a refrigerator due to their tendency to form a monohydrate and/or polymerize.

Ene Reactions.

Thermal ene reactions of glyoxylate esters with alkenes (cyclohexene, 1-alkenes, β-pinene and isobutene) occur at 150 °C, whereas the Lewis acid ($AlCl_3$, $SnCl_4$, $FeCl_3$) catalyzed ene reactions proceed at a lower temperature (25-45 °C).[11] The *endo*/*exo* selectivity of the thermal and ***Iron(III) Chloride***-catalyzed ene reactions of methyl glyoxylate with *cis*- and *trans*-2-butene, cyclohexene, 2-methyl-2-butene and 1-methylcyclohexene has been well studied. With *cis*-2-butene at 200 °C, a 7.4:1 mixture of *endo*/*exo* adducts is obtained. Similar reaction with *trans*-2-butene produced a 1:0.57 mixture of *endo*/*exo* adducts (eq 1). With cyclohexene and $FeCl_3$ catalyst, a 4.4:1 mixture of *endo*/*exo* adduct is obtained.[12] Extensive *cis*-*trans* isomerization of the double bond in the substrate under the reaction conditions, as well as contamination of halogen adducts in the products, point to a stepwise cationic mechanism for the Lewis acid-catalyzed glyoxylate-ene reactions.[13]

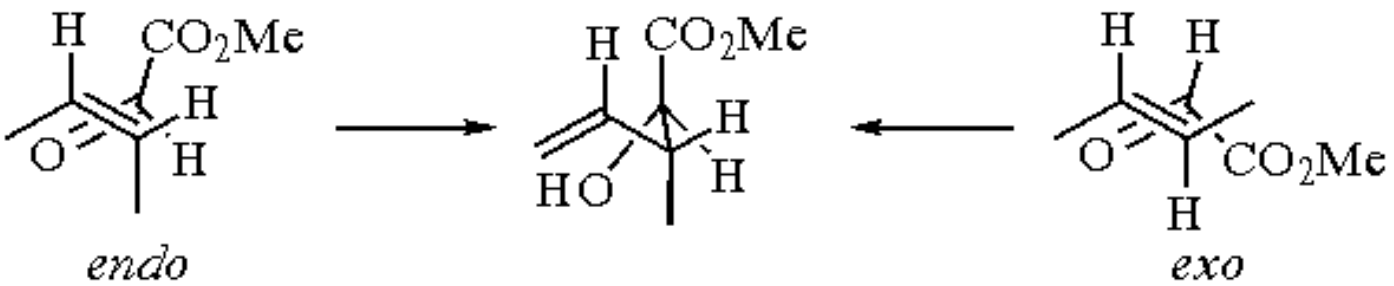

(1)

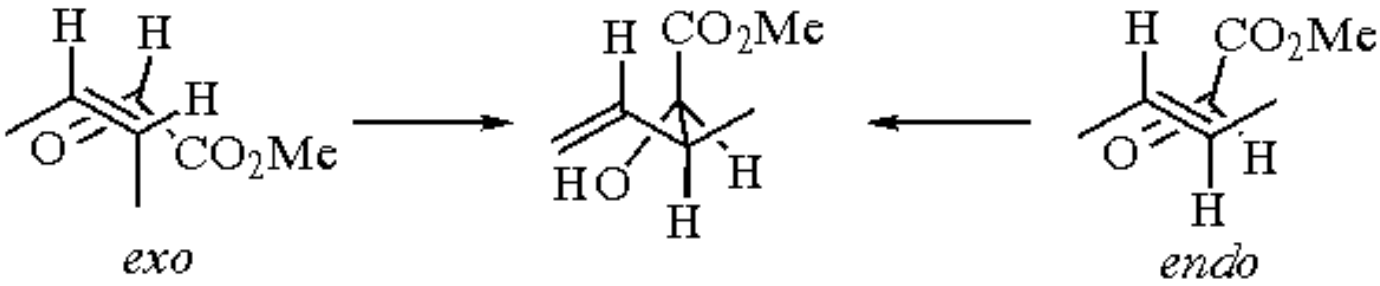

The reaction course of vinylsilane with glyoxylate, on the other hand, depends on the geometry of the vinylsilane and the Lewis acid employed.[14] ***Tin(IV) Chloride***-catalyzed reaction of *trans*-vinylsilane produces the ene adduct; that of the *cis*-vinylsilane produces both the ene adduct and a silicon substitution product. When ***Titanium(IV) Chloride*** was substituted for $SnCl_4$, the *cis* isomer underwent substitution to the exclusion of ene reaction (eq 2).

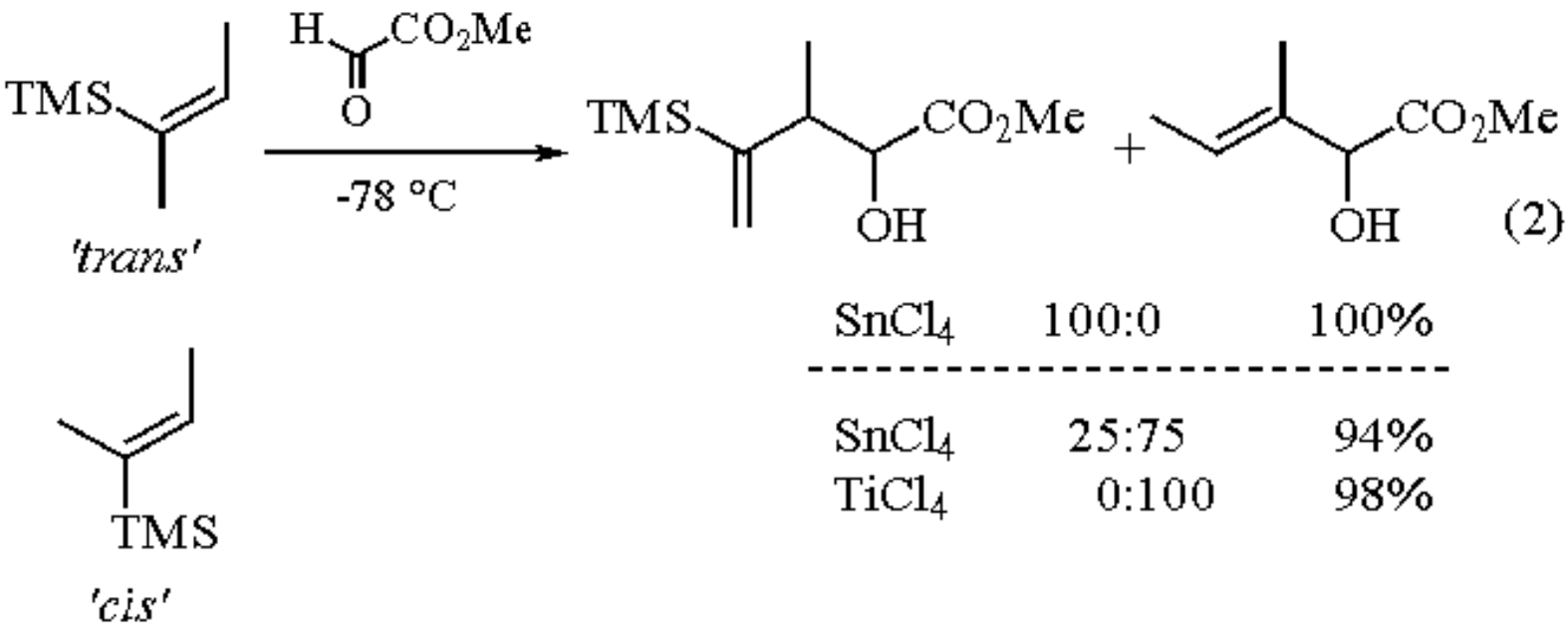

When the alkene bears a silyl substituent, the glyoxylate-ene reaction produces only a single regioisomer, the vinylsilane (eq 3).[15] Allylic ethers with a wide range of protecting groups also produce single regioisomers via glyoxylate-ene reactions (eq 4).[16] Excellent stereo- and regiocontrol are obtained with a 1,2-unsymmetrically disubstituted allylic component, producing exclusively the *anti* ester, which serves as a synthetic precursor for oxetanocin A (eq 5).[17]

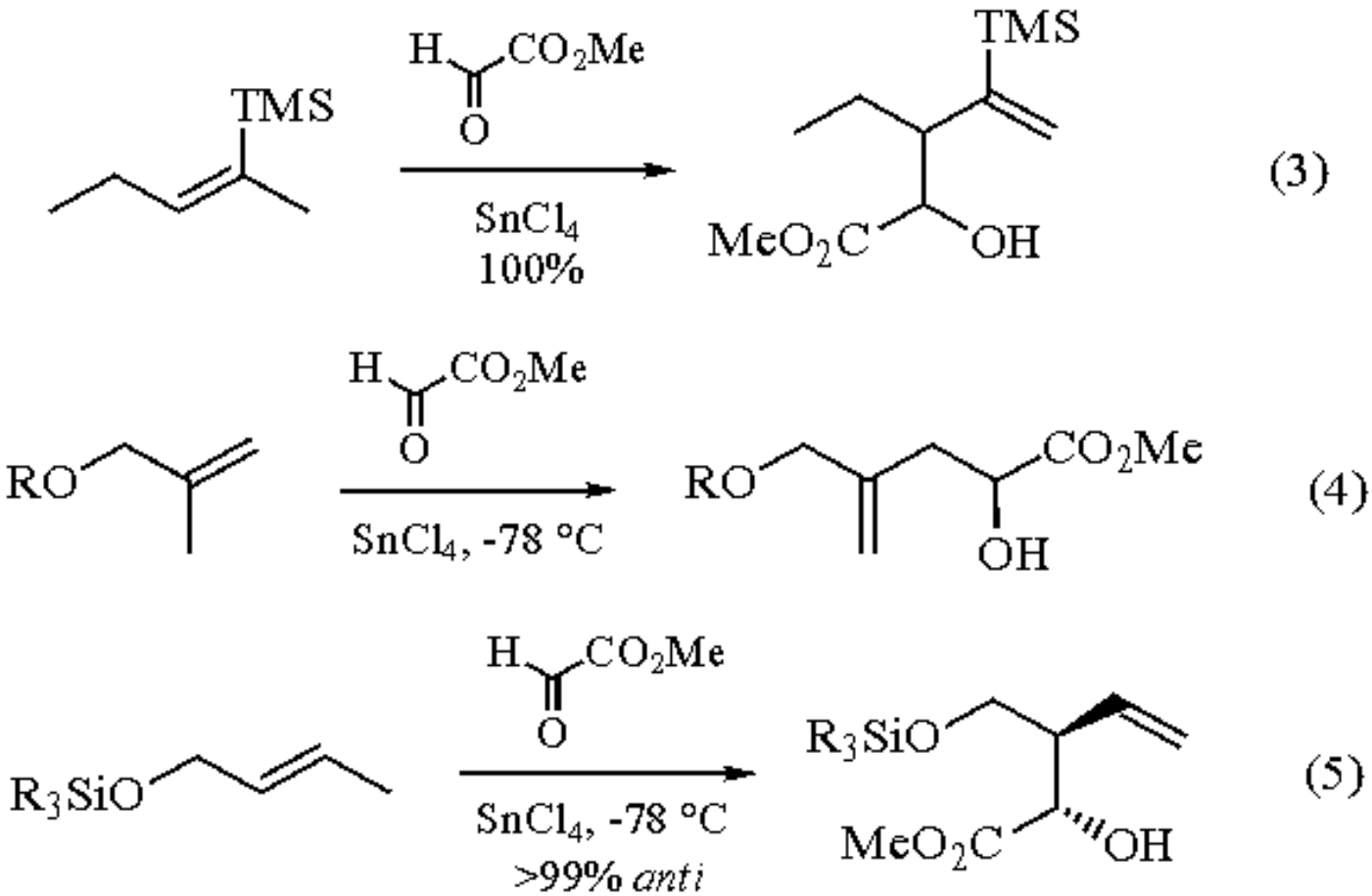

By appropriate choice of the Lewis acid, the glyoxylate-ene reactions have been shown to proceed with a high level of

either *syn* or *anti* diastereoselection, irrespective of the ene geometry (eq 6).[18b] The regio- and stereoselective glyoxylate-ene reactions have been exploited in the syntheses of brassinosteroids,[18b] avenaciolide,[18] tetrahydrofuranyl units of polyether antibiotics (eq 7),[19] and highly functionalized unsaturated amino acids (eq 8).[20]

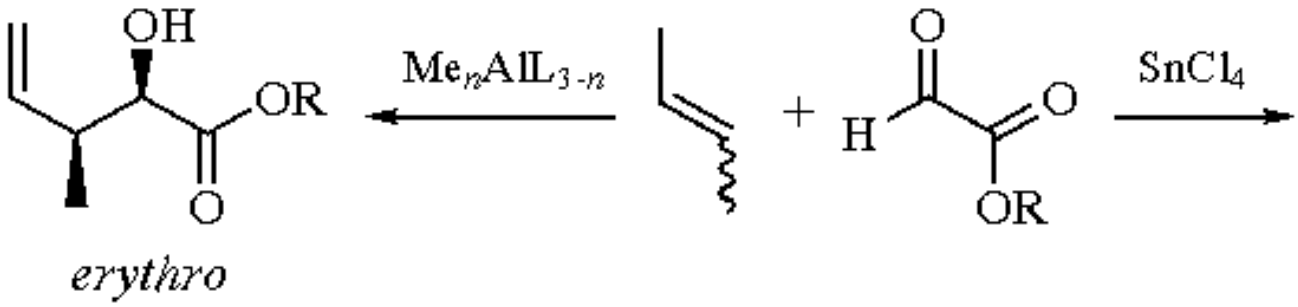

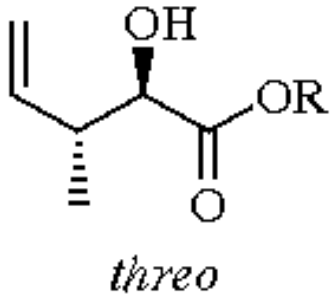

(6)

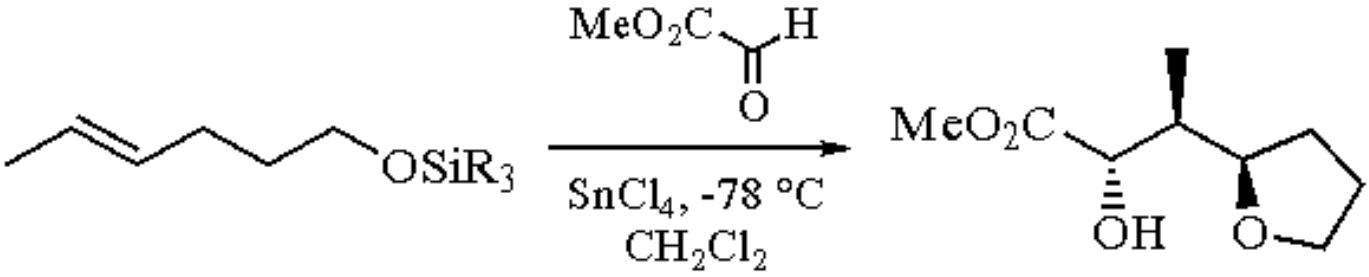

(7)

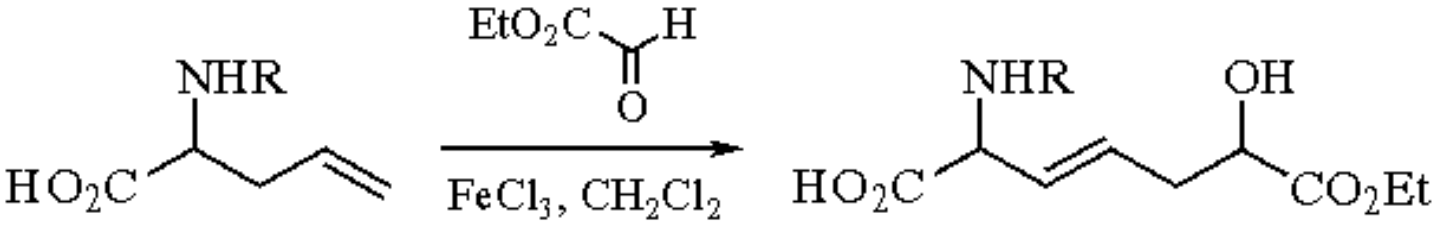

(8)

A high level of asymmetric induction (>99%) can be obtained in the glyoxylate-ene reaction with chiral glyoxylate esters derived from cyclohexyl-based chiral auxiliaries (eq 9).[21]

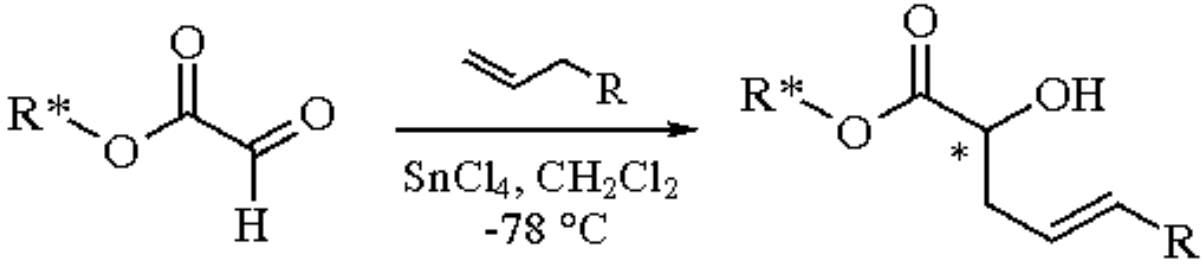

(9)

R* = 8-phenylmenthyl,
trans-2-phenylcyclohexyl

>99% de

A chiral titanium complex prepared in situ from $(i\text{-PrO})_2TiX_2$ (X = Cl or Br) and (*R*)- or (*S*)-binaphthol in the presence of molecular sieves (MS 4Å) has been shown to be a catalyst for an efficient asymmetric glyoxylate-ene reaction (eq 10).[22] The catalytic glyoxylate-ene reaction has been extended to vinyl sulfides, providing a high level of enantioface selection (>99% ee) along with high *anti* diastereoselectivity (eq 11).[23]

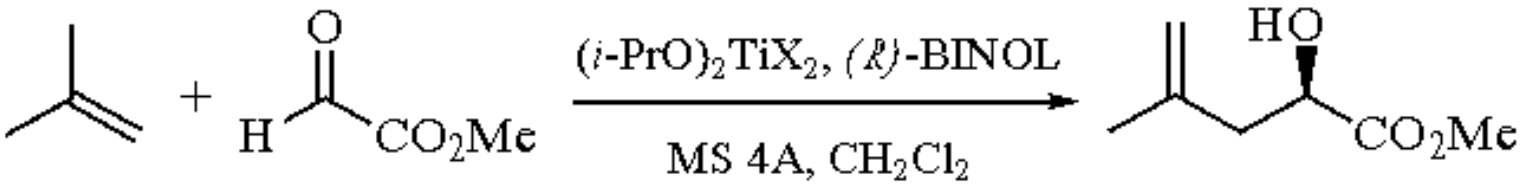

(10)

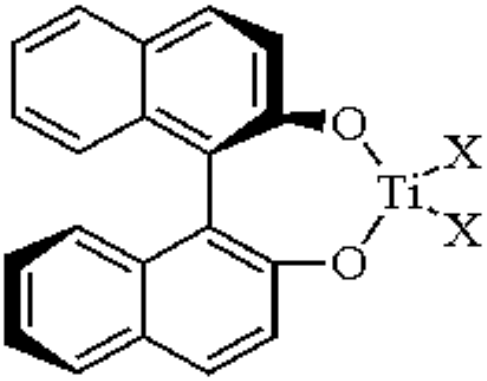

X = Cl (10 mol%) 95% ee, 72% yield (8 h)
(1 mol%) 93% ee, 78% yield (8 h)
X = Br (10 mol%) 94% ee, 87% yield (3 h)

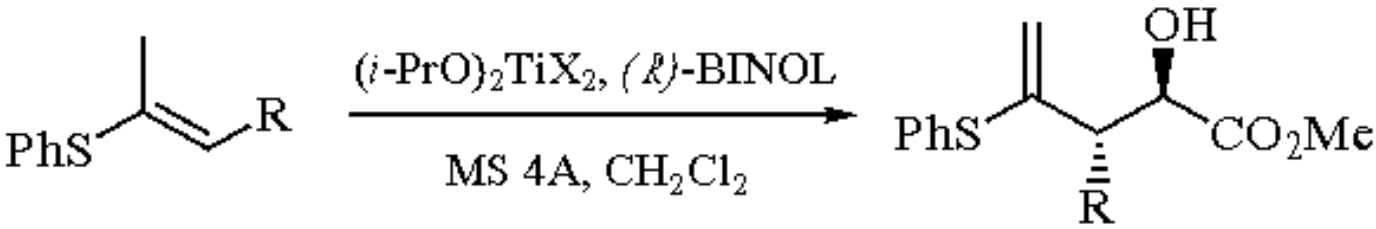

(11)

anti, >99% ee

The catalytic ene technology has been utilized in the asymmetric synthesis of functionalized carbocyclic building blocks,[24] a 1α,25-$(OH)_2$-vitamin D_3 synthon,[25] as well as in asymmetric desymmetrization of prochiral bis-allylic silyl ethers (eq 12).[26]

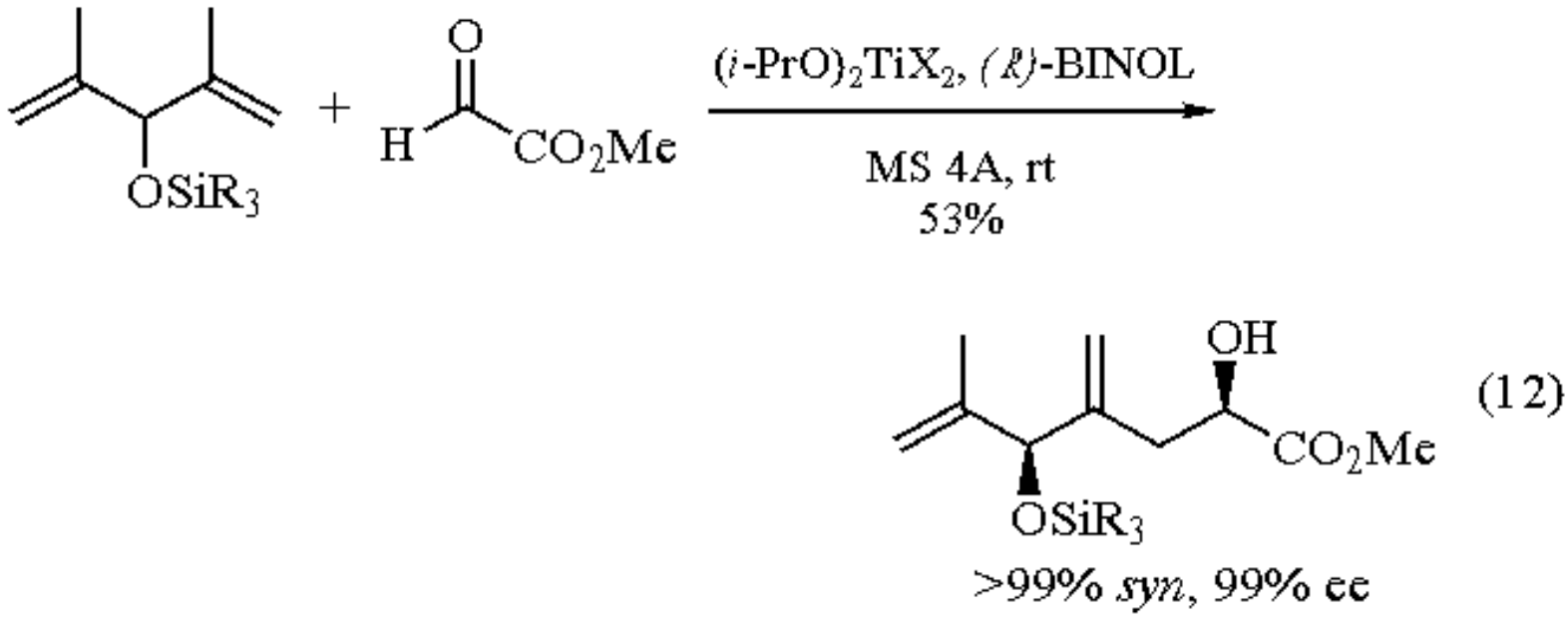

(12)

In asymmetric ene reactions of racemic allylic as well as homoallylic ethers, the chiral BINOL-titanium catalyst discriminates between the two enantiomeric substrates sufficiently to provide efficient kinetic resolution.[16a,2c] Also, the chiral titanium complex derived from partially resolved BINOL is found to exhibit a remarkable level of asymmetric amplification, wherein the enantiomeric excess of the product significantly exceeds that of the chiral mediator employed.[27]

Cycloaddition Reactions.

[4 + 2] Cycloadditions of various alkoxy-1,3-butadiene derivatives with alkyl glyoxylates, under thermal as well as Lewis acid-catalyzed conditions, afford the corresponding dihydropyran derivatives, which are important intermediates in the total synthesis of monosaccharides and δ-lactones (eq 13).[28] These cycloadditions are facilitated by high pressure and microwave radiation.[29]

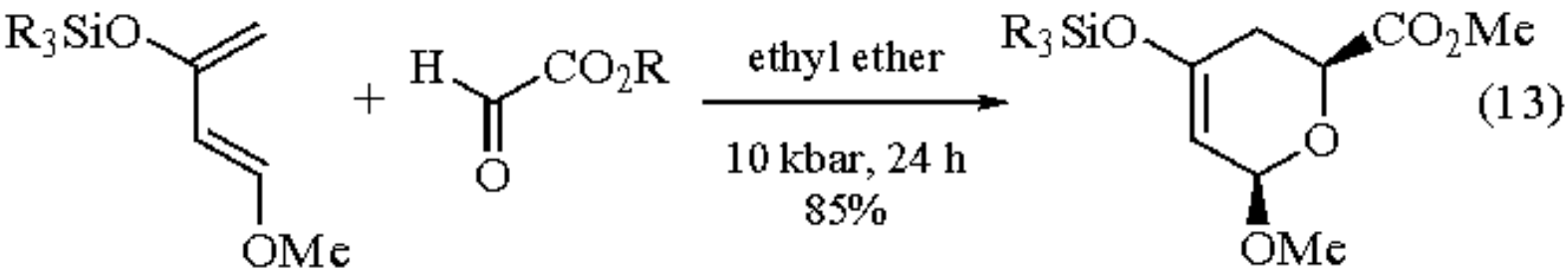

(13)

The chiral BINOL-titanium complex (eq 10) is also an effective catalyst for the hetero Diels-Alder reaction between methyl glyoxylate and 1-methoxy-1,3-butadiene, providing the *cis* adduct in 96% ee (eq 14). Similar cycloaddition of methyl glyoxylate and 1-methoxy-1,3-pentadiene simultaneously produces three stereogenic centers with high selectivity (eq 15).[30]

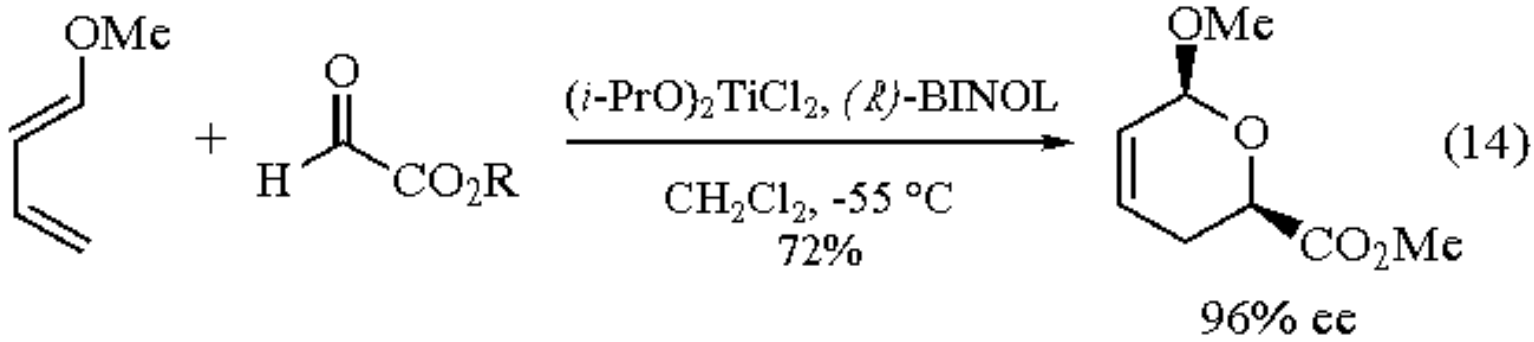

(14)

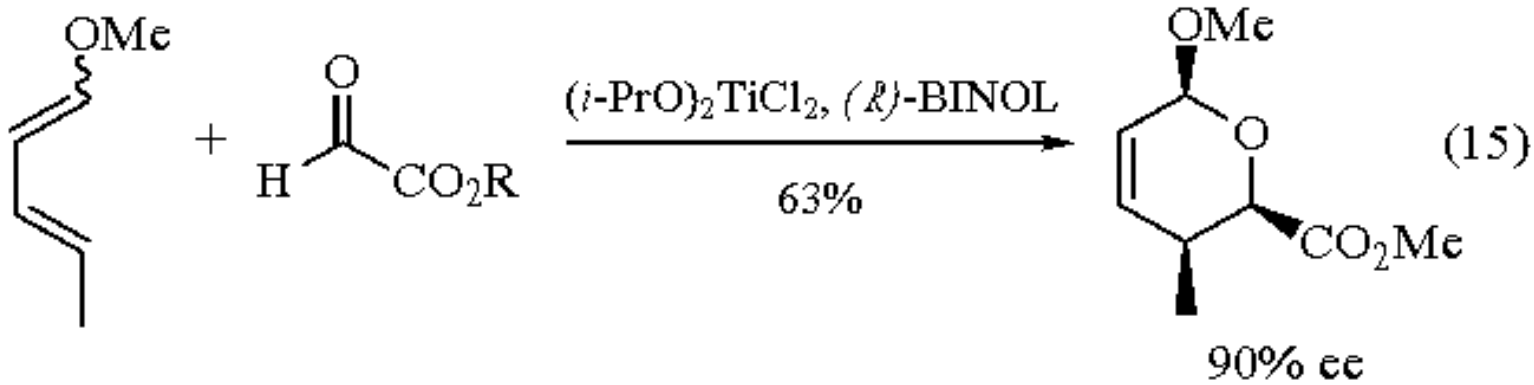

(15)

Organometallic Addition.

The reaction of 2-butenylstannanes with glyoxylate esters is *syn* selective, whereas the *anti* isomer is preferentially produced via the corresponding 9-BBN derivative. The selectivity increases with increasing steric bulk of the ester group (eq 16).[31]

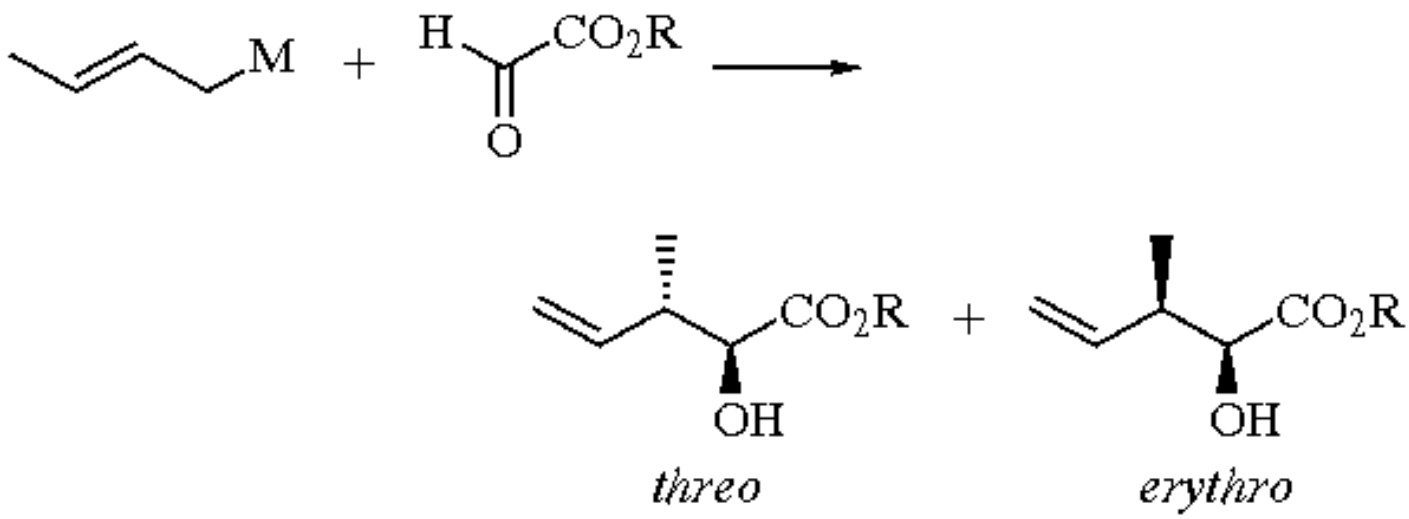

(16)

M = $SnBu_3$	R = Me	25:75
	R = *i*-Pr	10:90
M = 9-BBN	R = Me	25:75
	R = *i*-Pr	10:90

Asymmetric addition of various organometallic reagents (M = Mg, Zn, Sn) to chiral 8-phenylmenthyl glyoxylate produces the corresponding α-hydroxy esters in high (>99%) enantiomeric excesses.[32]

Aromatic Substitution.

Ortho-hydroxyalkylation of phenols (via complexes of metal phenolates) with chiral glyoxylates produces the corresponding *ortho*-hydroxymandelic ester in high diastereomeric purity (eq 17).[33]

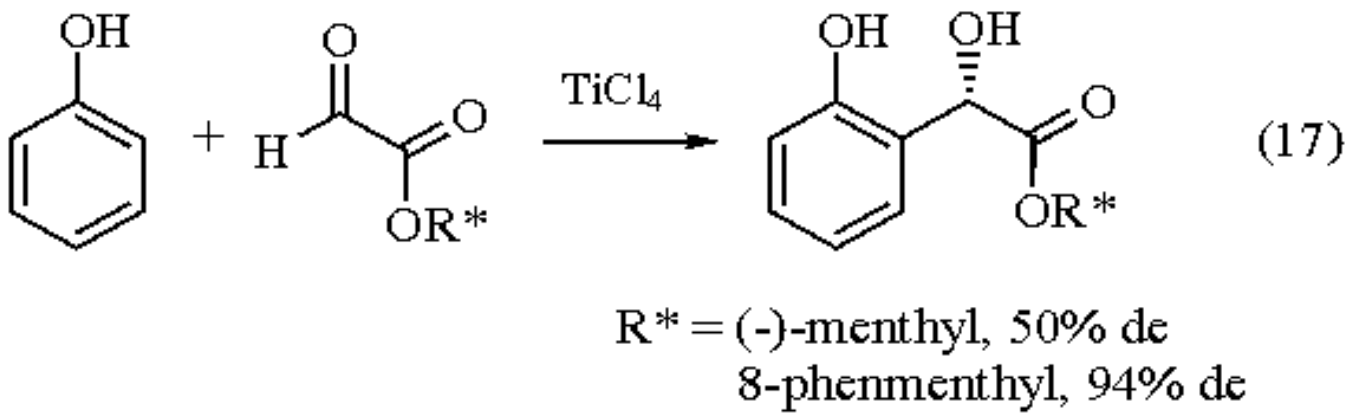

Glyoxylate as Nucleophile.

The two-carbon acyl anion equivalent derived from a glyoxylate ester acetal has been utilized for the preparation of novel heterocyclic α-oxoacetic acid esters (eq 18).[34]

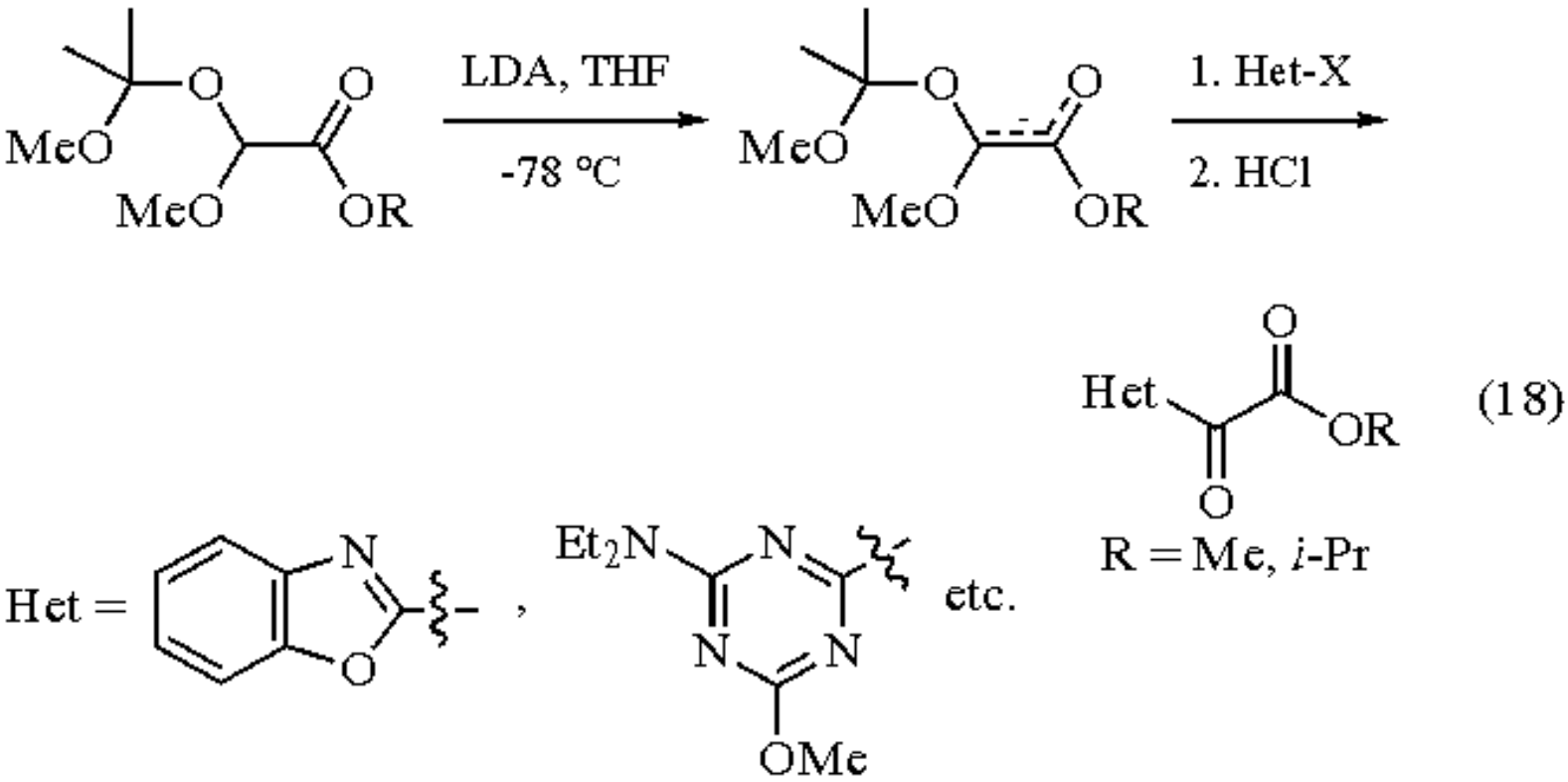

Cross Coupling.

Reductive cross-coupling reactions of glyoxylate esters with carbonyl compounds in the presence of low-valent titanium compounds produce the corresponding α,β-dihydroxy carboxylates (eq 19).[35]

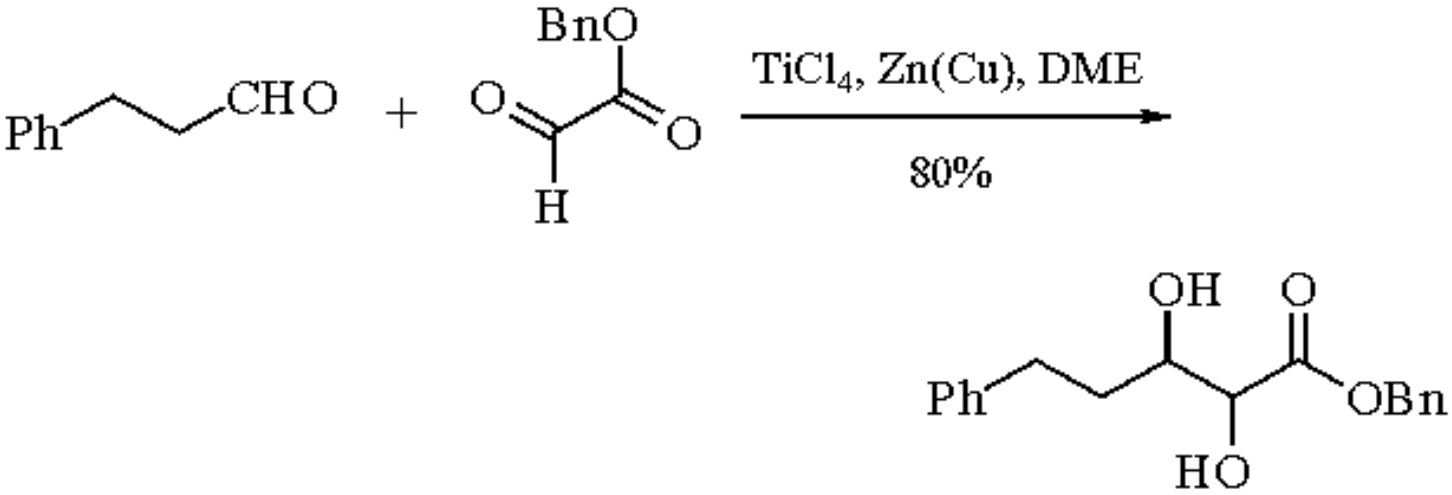

(19)

The glyoxylate esters have been utilized as valuable synthetic intermediates in the syntheses of actinolbin,[36] oxacyclic carbocyclic esters,[37] tetrahydro-4*H*-furoazepines,[38] and (±)-naphthyridinomycin.[39] A chiral synthesis of Pravastatin®, an important HMG-CoA reductase inhibitor, utilizes desymmetrization of 1-methyl-4-methylenecyclohexane by a catalytic asymmetric ene reaction, which provides the initial asymmetric framework (eq 20).[26b]

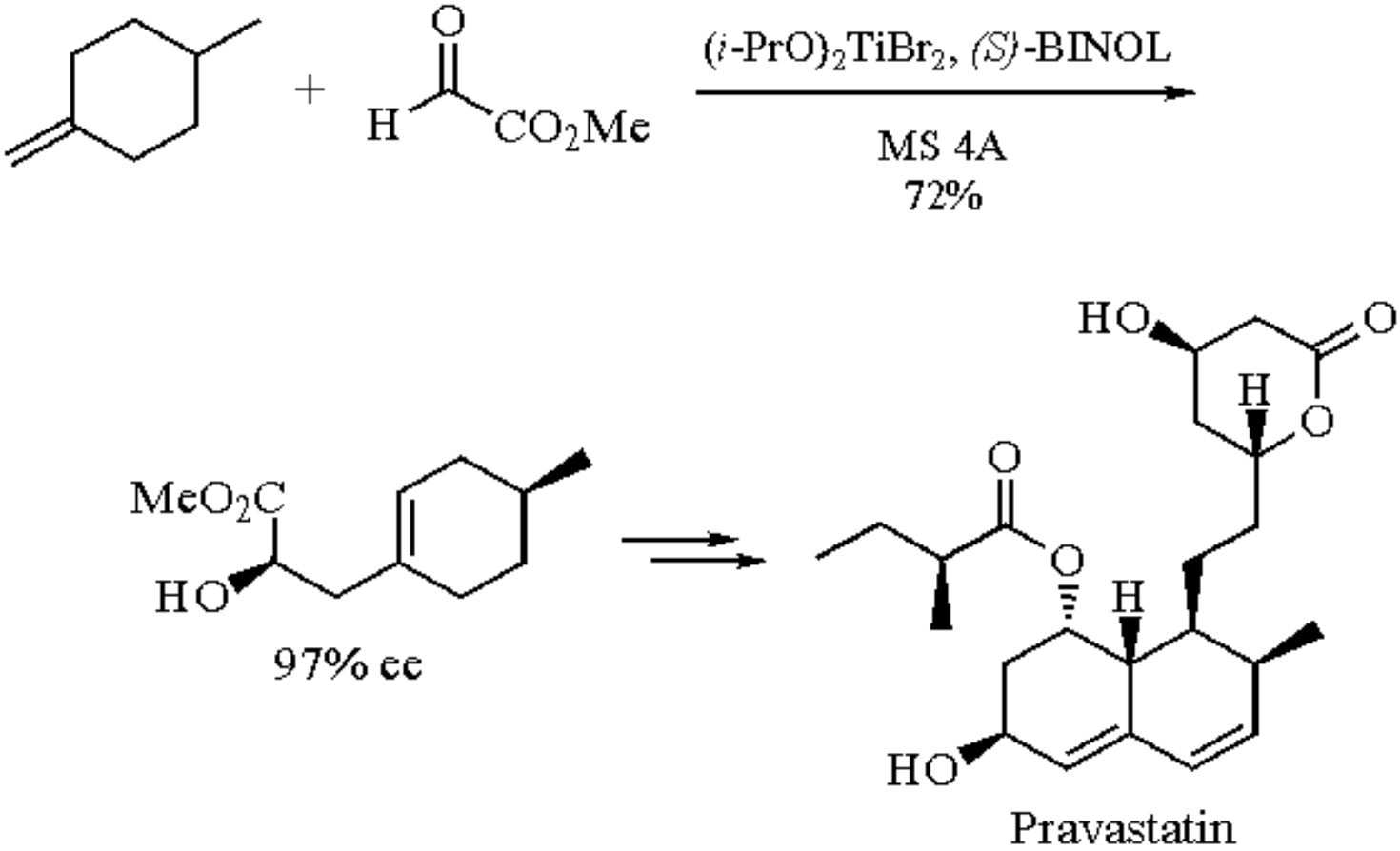

(20)

α-Imino esters derived from glyoxylate esters are valuable synthetic intermediates and act as enophiles[40] and/or dienophiles[41] to produce nonproteinogenic α-amino acids,[42] β-lactams,[43] an anti-Bredt lactam,[44] β,γ-alkynylglycine derivatives,[45] and proline analogs.[46]

Related Reagents.

Glyoxal Diethyl Acetal; ***Ethyl Diethoxyacetate***; ***Glyoxal***; ***Glyoxylic Acid***; ***Glyoxylic Acid Diethyl Dithioacetal***; ***8-Phenylmenthyl Glyoxylate***; ***Tin(IV) Chloride***; ***Titanium(IV) Chloride***.

---

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Methyl Hydrazinocarboxylate

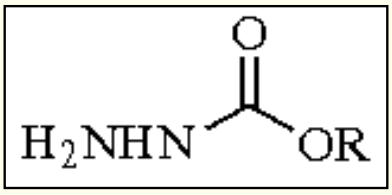

(**1**; R = Me)

[6294-89-9] · $C_2H_6N_2O_2$ · Methyl Hydrazinocarboxylate · (MW 90.10) (**2**; R = Et)

[4114-31-2] · $C_3H_8N_2O_2$ · Ethyl Hydrazinocarboxylate · (MW 104.13) (**3**; R = *t*-Bu)

[870-46-2] · $C_5H_{12}N_2O_2$ · *t*-Butyl Hydrazinocarboxylate · (MW 132.19)

(used for conversion of ketones to nitriles, dehydrohalogenation of α-bromo ketones, and formation of azidoformates)

Alternate Name: methyl carbazate.

Physical Data: (**1**) mp 70-73 °C; bp 108 °C/12 mmHg. (**2**) mp 44-47 °C; bp 110 °C/22 mmHg. (**3**) mp 39-42 °C; bp 65 °C/0.03 mmHg.

Ketones to Nitriles.

Methyl and ethyl carbazate are used as derivatizing reagents for aldehydes and ketones.[1] The methyl derivative is employed in the conversion of ketones to nitriles through the base-catalyzed decomposition of the intermediate diazene (eq 1).[2] The procedure also works well for α-substituted ketones. If the diazene decomposition is conducted in aprotic medium (DME) in the presence of stoichiometric base (LiOMe), the resultant nitrile anion can be alkylated.

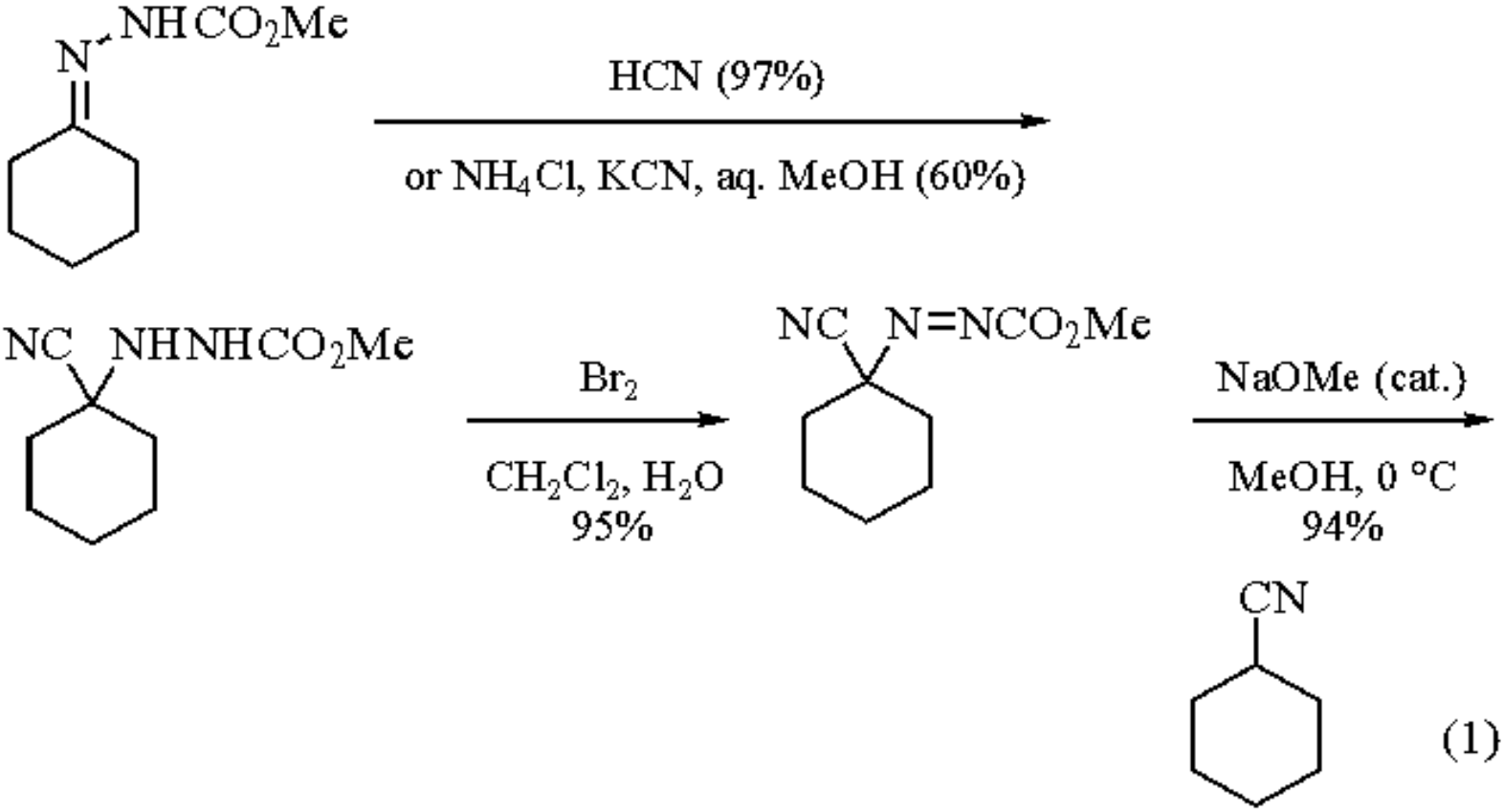

Dehydrohalogenation.

Ethyl carbazate is employed in the Kendall-Mattox dehydrohalogenation of α-bromo ketones (eq 2).[3]

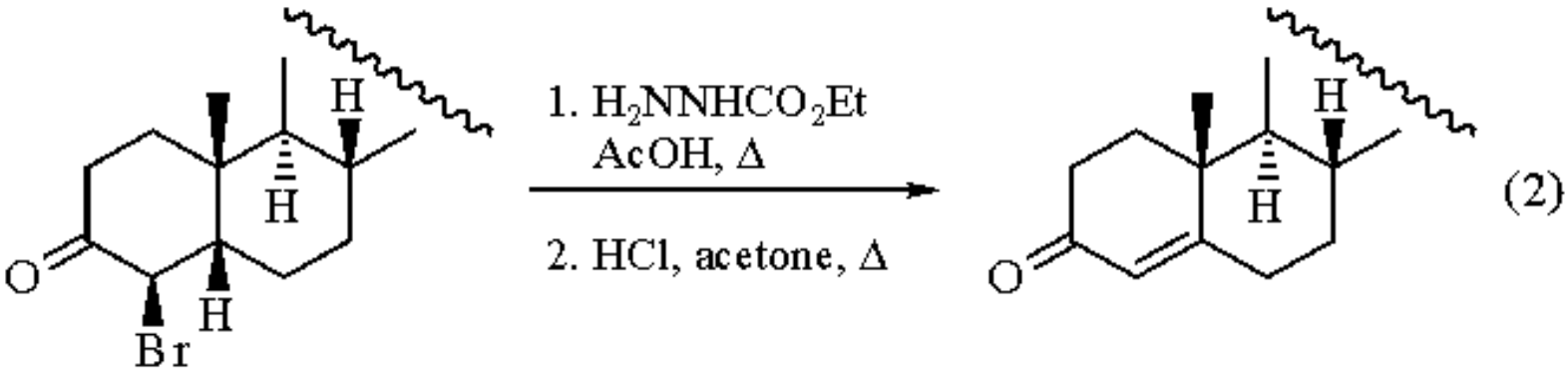

t-Butyl Azidoformate.

Nitrosation converts *t*-butyl carbazate into ***t-Butyl Azidoformate***, a reagent for the protection of amines as their Boc derivatives.[4]

Related Reagents.

2,4-Dinitrophenylhydrazine; ***Hydrazine***; ***Semicarbazide***; ***p-Toluenesulfonylhydrazide***; ***p-Tolylsulfonylmethyl***

Isocyanide; ***2,4,6-Triisopropylbenzenesulfonylhydrazide***; ***Trimethylaminoacetohydrazide Chloride***.

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N-Methylhydroxylamine

MeNHOH

[593-77-1] · CH_5NO · *N*-Methylhydroxylamine · (MW 47.07) (.HCl)

[4229-44-1] · CH_6ClNO · *N*-Methylhydroxylamine Hydrochloride · (MW 83.53)

(ambident nucleophile; reagent for the preparation of *N*-methyl nitrones from aldehydes and ketones, of *N*-methylhydroxamic acids from carboxylic acids and related functional groups, and of heterocyclic compounds)

Physical Data: mp 38.5 °C; bp 115 °C, 60-63 °C/20 mmHg;*n*20D 1.4164. HCl salt: mp 88-90 °C.

Solubility: very sol H_2O, methanol, ethanol; sparingly sol diethyl ether. HCl salt: sol H_2O, ethanol.

Form Supplied in: widely available as the HCl salt, a clear-to-white solid (hygroscopic).

Preparative Methods: usually prepared in solution form by treatment of the HCl salt with a suitable base; used directly upon preparation as it gradually decomposes upon standing.

Handling, Storage, and Precautions: the HCl salt is a possible irritant; avoid skin and eye contact, avoid inhaling particles. The salt is hygroscopic and must be protected from moisture during storage.

Formation and Reactions of Nitrones.

The condensation of *N*-methylhydroxylamine with aldehydes and ketones leads readily to the formation of *N*-methyl nitrones. In some cases, such as *N*-methyl-*C*-phenyl nitrone, the condensation product can be isolated and characterized prior to subsequent reactions; the more usual practice, however, is the in situ generation of nitrones as a prelude to subsequent cycloaddition reactions,[1] the most common of the

reactions of nitrones. *N*-Methyl nitrones have been shown to undergo cycloadditions with mono-, di-, and trisubstituted alkenes as well as mono- and disubstituted alkynes. Consistent with FMO theory, *N*-methyl-*C*-phenyl nitrone gives 5-substituted isoxazolidines with monosubstituted alkenes such as 1-hexene and styrene; however, strongly electron-withdrawing substituents alter the cycloaddition regiochemistry.[2] Methyl acrylate and phenyl vinyl sulfone give mixtures of cycloadducts, while nitroethylene gives only the 4-substituted isoxazolidine.

Intramolecular cycloadditions of *N*-methyl nitrones (eq 1) have been extensively studied since the 1960s.[3] The influence of a number of factors (e.g. length of chain connecting alkene and nitrone, type of atoms in the connecting chain, presence of chiral centers, alkene geometry) on the regiochemistry and stereochemistry have been reported.[1] Fused polycyclic ring systems are often obtained, while in selected cases bridged cycloadducts are found. In one case a reverse Cope elimination reaction has been observed in competion with *N*-methyl nitrone formation and cycloaddition.[4] There are a number of examples of natural product total synthesis, including (+)-chanoclavine I,[5] (-)-bisabolol,[6] and hirsutene,[7] in which intramolecular *N*-methyl nitrone cycloadditions have been utilized.

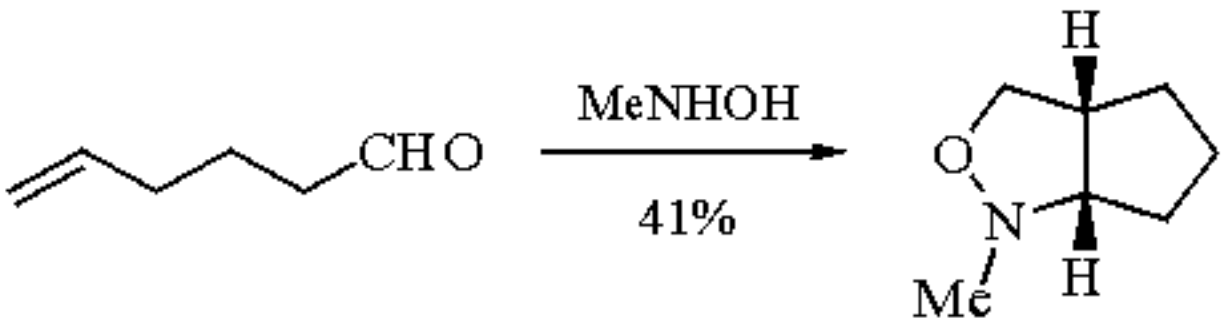

(1)

In addition to [3 + 2] cycloaddition reactions, *N*-methyl nitrones can also be used as precursors to vinylnitrosonium cations for [4 + 2] cycloadditions.[8]

Additional reagents derived from *N*-methylhydroxylamine are described in the literature for the preparation of nitrones. These include *N*-methylhydroxylamine-*O*-sulfonic acid,[9] which has been shown to react with imines to afford nitrones, and *N*-methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine,[10] which allows formation and cycloaddition of nitrones under nonbasic, aprotic conditions.

Other Reactions.

Carboxylic acids and related functional groups are readily converted to *N*-methylhydroxamic acids through *N*-acylation (eq 2).[11]

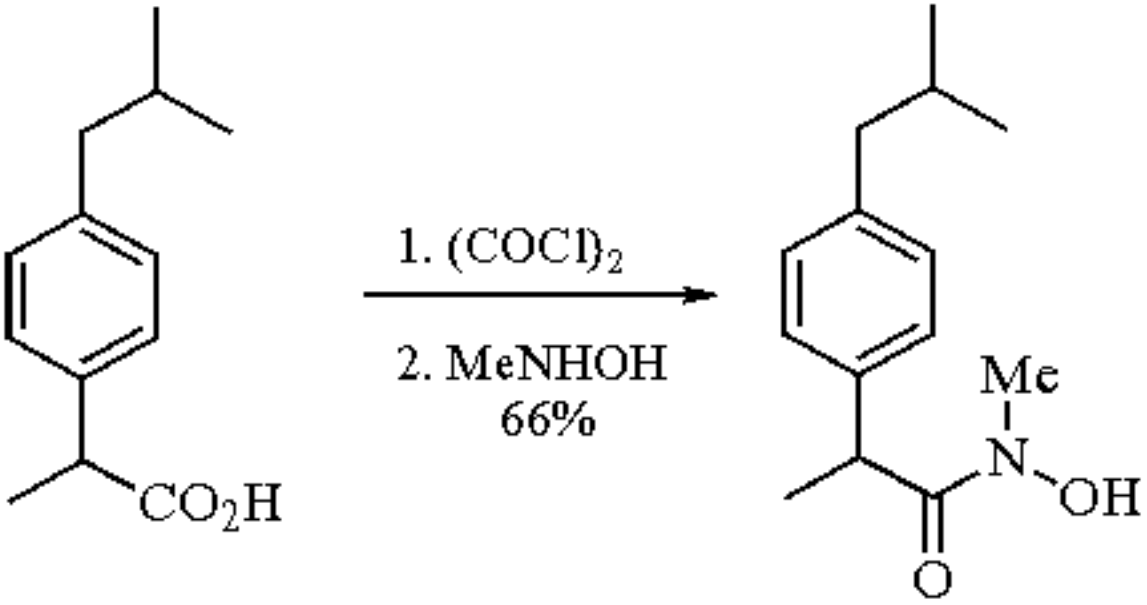

(2)

If *N*-methylhydroxylammonium chloride is acylated under nonbasic conditions, however, *O*-alkanoylhydroxylamines are obtained as the *O*-acylation product.[12] α,β-Unsaturated compounds readily undergo conjugate addition, giving β-amino-*N*-hydroxy-*N*-methylcarboxylate esters which cyclize in the presence of base to isoxazolidin-5-ones (eq 3).[13] Unsaturated sugar lactones also give isoxazolidin-5-ones,[14] while sugar enolones give the simple conjugate addition product.[15] Interestingly, when *N*-methylhydroxylamine is slowly generated in the presence of both aqueous formaldehyde and an unsaturated carbonyl compound, the preferred reaction is formation of *N*-methyl nitrone followed by cycloaddition to the unsaturated carbonyl compound (eq 4).[16] Isoxazolidin-5-ones are also readily prepared by the Reformatsky reaction of purified nitrones, such as *N*-methyl-*C*-phenyl nitrone, with α-bromo esters in the presence of zinc.[17]

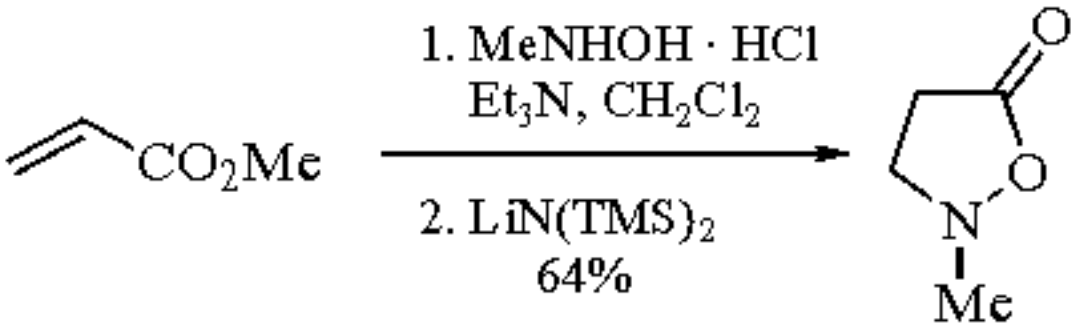

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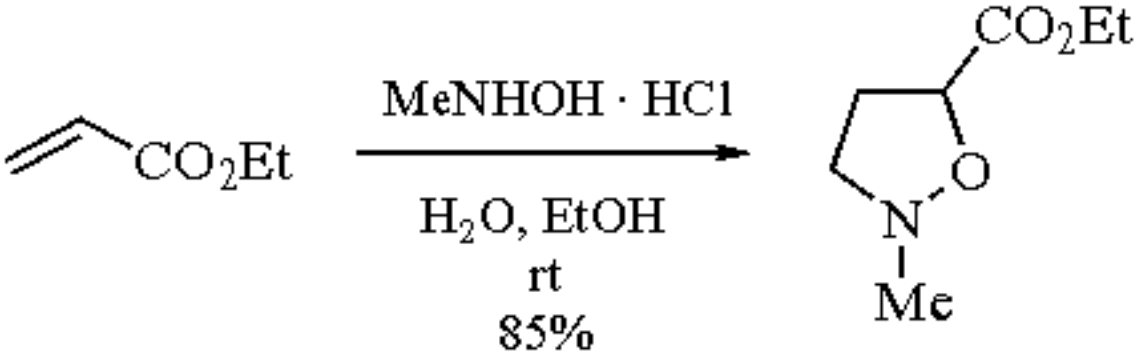

(4)

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O-Methylhydroxylamine

$MeONH_2$

[67-62-9] · CH_5NO · *O*-Methylhydroxylamine · (MW 47.07)

(for electrophilic amination;[1] for conversion of aldehydes and ketones to methoxyimines)

Alternate Name: methoxyamine.

Physical Data: mp -86.4 °C; bp 48.1 °C; pK_b 9.40.

Solubility: miscible with water, alcohol, ether, hexane.

Form Supplied in: white HCl salt (mp 149 °C).

Analysis of Reagent Purity: IR[2] and ^{1}H NMR.[3]

Preparative Methods: from methylation of adduct of sodium nitrite and sodium metabisulfite,[4] or fractional distillation from the HCl salt in sodium hexyloxide/hexanol.[5]

Handling, Storage, and Precautions: a highly mobile and poisonous clear colorless liquid and should be refrigerated. Methoxyamine is a severe irritant. Use in a fume hood.

Introduction of the Methoxyimino Function.

The methoxyimino (*O*-methyl oxime ether) group is easily introduced by treating ketones or aldehydes with the HCl salt of methoxyamine. The methoxyimino function is a convenient and often most effective way of protecting ketones or aldehydes during alkaline transformations.[6] For example, the ring of the dioxabicyclooctane (**1**) was opened with methoxyamine.HCl to afford the 6-methoxyiminooxepane (**2**) (eq 1).[7] Attempts to trap the intermediate ketones as the dithioacetal led to intractable product mixtures. After acetylating the 3-hydroxy group, the desired oxepan-6-one was recovered in 73% yield by treating the methoxyimine in acetone with 2 N HCl at rt for 3 h.

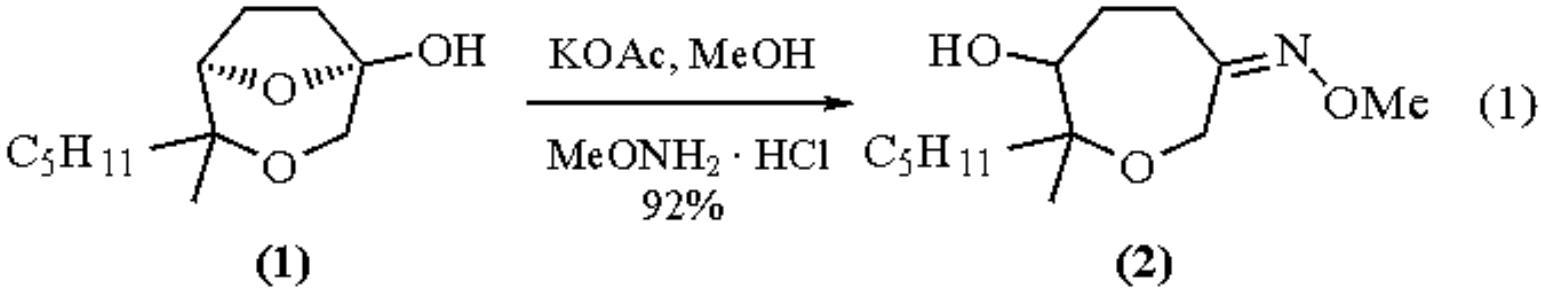

α,β-Unsaturated methoxyimines are readily prepared by treating the corresponding ketones or aldehydes with methoxyamine.HCl.[8] Except in cases of α,β-unsaturated aldehydes or highly reactive α,β-unsaturated ketones, the free base of methoxyamine undergoes 1,4-addition regioselectively (see below).

As a NH_2^+ Synthon.

Lithium salts of strongly basic carbanions can be stoichiometrically converted to the corresponding primary amines by treating with 2 equiv of methyllithium-methoxyamine (eq 2).[9]

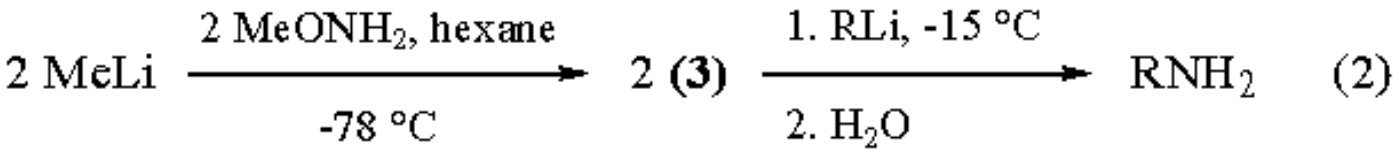

To prepare the methyllithium-methoxyamine adduct (**3**), a hexane solution of methoxyamine is added dropwise to an ether solution of ***Methyllithium*** at -78 °C. Then, to obtain the primary amine, an organolithium is added, the reaction mixture is allowed to warm to -15 °C for 2 h, and then quenched with water. Examples of primary amines prepared via eq 2 are provided in Table 1.

Table 1 Aminations of Organolithiums with 2 Equiv Methyllithium-Methoxyamine (Eq 2)

RLi	Yield RNH_2 (%)[a, b]
MeLi	80
EtLi	78
BuLi	71
s-BuLi	71
t-BuLi	80[c]
BnLi	97
PhLi	90
o-$MeOC_6H_4Li$	96
m-$MeOC_6H_4Li$	73
p-$MeOC_6H_4Li$	28

m-$MeOC_6H_4Li$	73
p-$MeOC_6H_4Li$	28
p-MeC_6H_4Li	93
m-ClC_6H_4Li	46
$H_2C{=}CHCH_2Li$	78
$Me_2C{=}CHCH_2Li$	21[d]
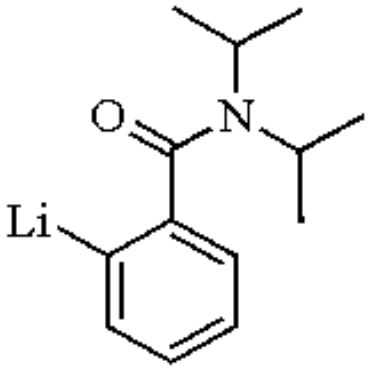	14[d, e]
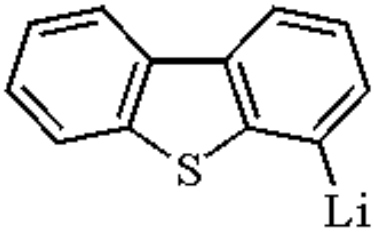	55[e]

[a] Based on moles RLi. [b] Isolated as amide. [c] Required 1 h reflux. [d] Based on moles RLi precursor. [e] Isolated as amine.

Lithium α-lithiophenylacetate, 2-lithiocyclohexanone, 2-lithiothiophene, 2-lithiofuran, or 3-lithiopyridine could not be aminated via eq 2.

The best yields of primary amines from (**3**) are obtained with organolithium compounds.[10] While organozinc, magnesium, and copper compounds are aminated with (**3**), the yields are generally low.

As a $^{-}NH^{+}$ Synthon.

Since the nitrogen of methoxyamine functions both as a nucleophilic and electrophilic center, methoxyamine can be used to prepare secondary amines and nitrogen heterocycles. The methoxyamine (**4**) was prepared by converting acetophenone to the methoxyimine with methoxyamine.HCl in methanol/pyridine at reflux overnight, followed by reduction with ***Borane-Pyridine*** complex and HCl in methanol at -10 °C to 10 °C for 10 min (eq 3).[11]

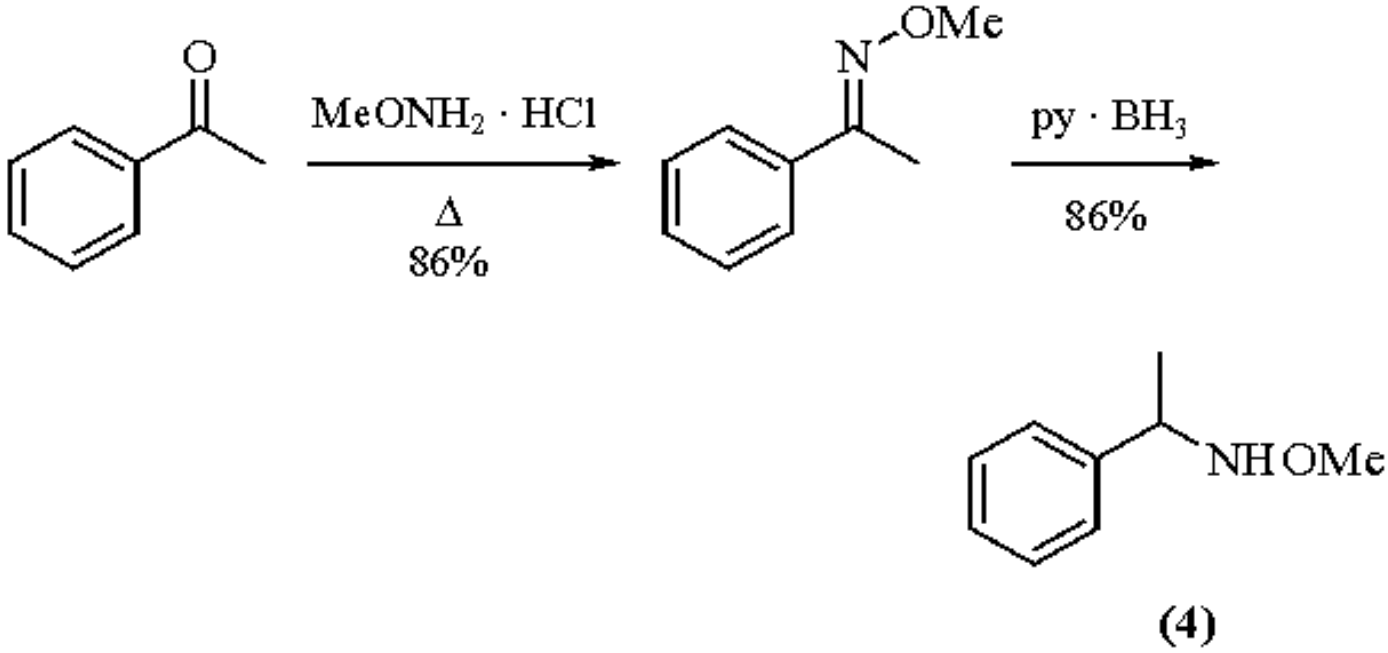

(3)

It was found that treating (**4**) with methyllithium followed by ***n-Butyllithium*** afforded the secondary amine (**5**) (eq 4).

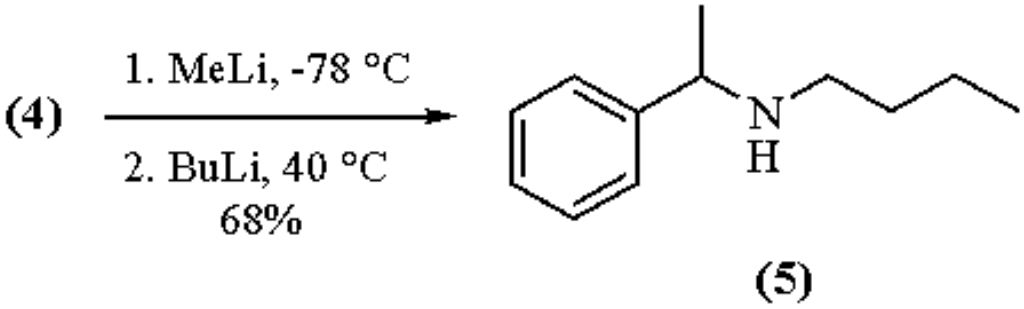

(4)

The electrophilic aminations of carbanions with *N*-monosubstituted methoxyamines are executed as with methoxyamine (see above). However, only 1 equiv of the methyllithium adduct is required. Furthermore, because the amination reaction occurs by a S_N2 displacement,[5] it must be conducted at higher temperatures when the nitrogen of the *N*-monosubstituted methoxyamine is sterically hindered.[10] Other examples of secondary amines prepared by the above approach have been published.[10,11]

Intramolecular electrophilic amination of the *N*-substituted methoxyamines (**6**) provides the corresponding nitrogen heterocycles (**7**) (eq 5).[10,11]

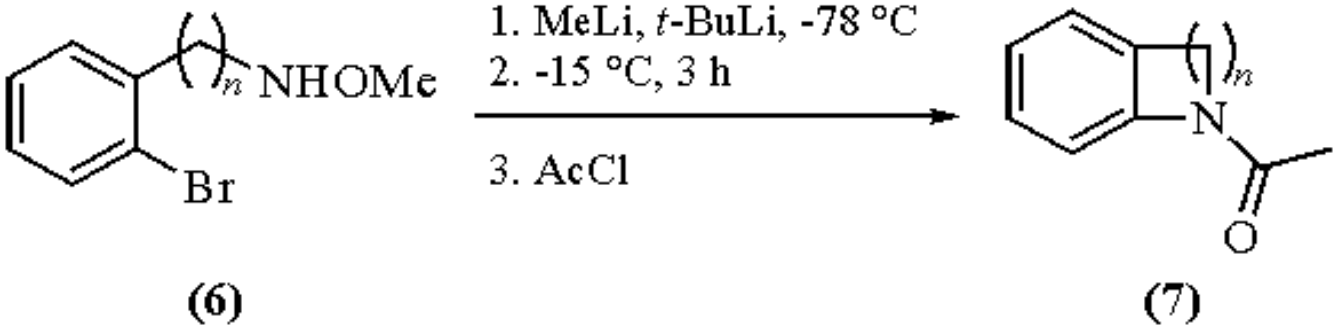

(5)

The methoxyamines (**6**) were prepared by reductive amination of the corresponding aldehydes with methoxyamine and pyridine-borane complex (see above). Then they were treated with methyllithium in the presence of ***t-Butyllithium***, to effect halogen-metal exchange,[12] and, after warming to -15 °C for 3 h, the nitrogen heterocycles (**7**) were isolated as the *N*-acetyl derivatives. The yields of (**7**), based on the starting aldehyde, when n = 1, or its progenitor, when n = 2, 3, and 4, were 16, 15, 25, and 9%, respectively.

Treating α,β-unsaturated ketones with the free base of methoxyamine at rt results in 1,4-addition.[8] Treating the resulting β-methoxyamino ketones (**8**) with 2 equiv of ***Sodium Methoxide*** yields the *trans*-ketoaziridines (**9**) stereoselectively (eq 6).[8,13,14]

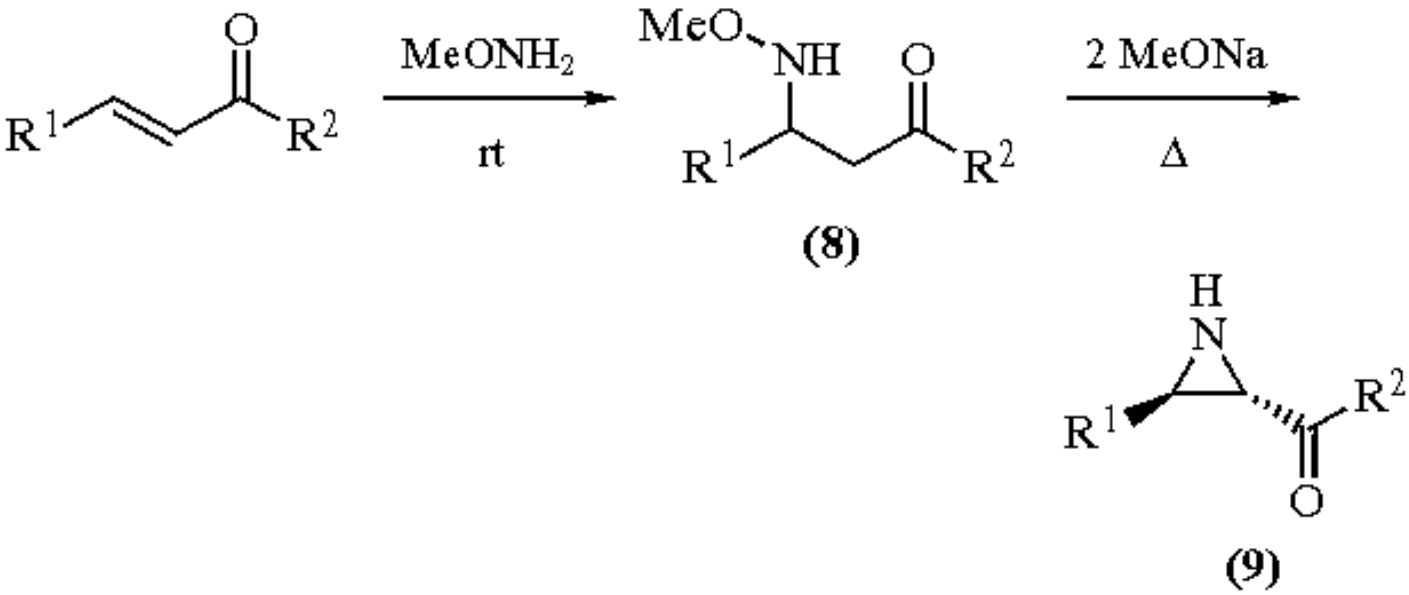

(6)

Alternatively, the *trans*-ketoaziridines are obtained directly by treating the α,β-unsaturated ketones with methoxyamine in the presence of alkoxide. The yields of (**9**), when R^1 = phenyl and R^2 = 4-methoxyphenyl or 4-methylphenyl, were 46 and 61%, respectively.

The keto ester (**10**) and methoxyamine.HCl react to afford the methoxyimine (**11**).[15] Radical cyclization of (**11**) with ***Tri-n-butylstannane*** and ***Azobisisobutyronitrile*** (AIBN) affords the indan (**12**) (eq 7).

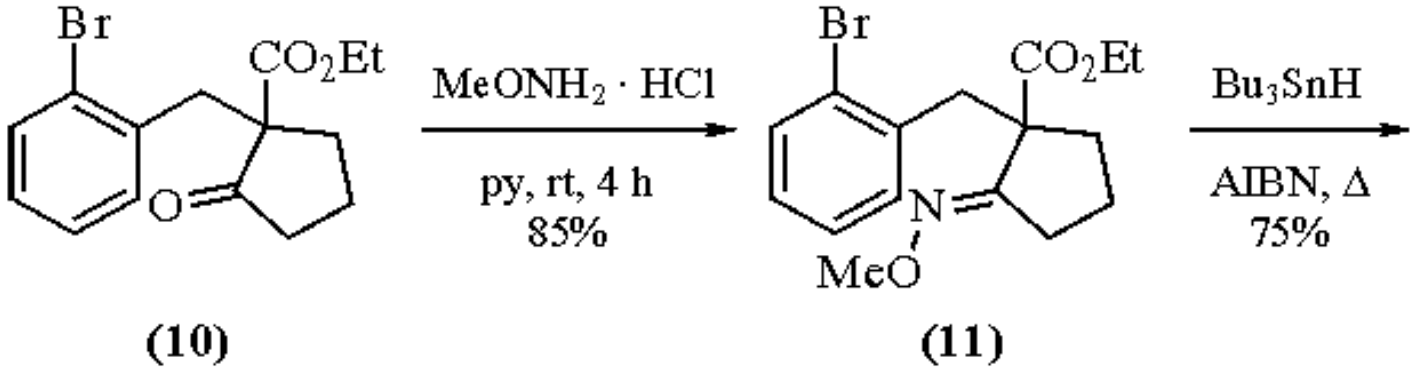

(10) **(11)**

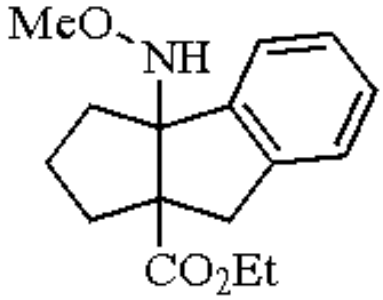

(12) (7)

It was found that (**12**) could be rearranged to the quinoline (**13**) with ***Lithium Aluminum Hydride*** (LAH) (eq 8).[16]

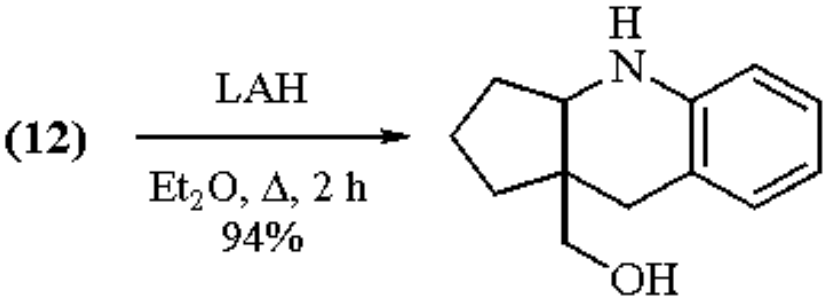

(12) **(13)** (8)

Kostyanovsky and co-workers treated the *N*-tosylate (**14**) with methoxyamine and obtained the diaziridine (**15**) (eq 9).[17]

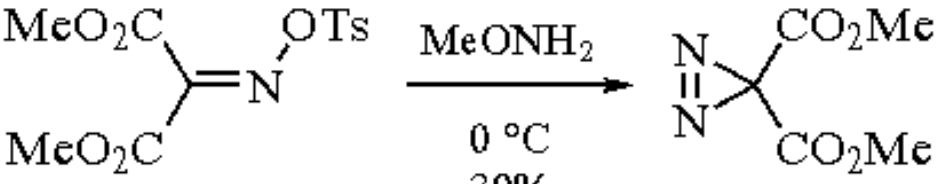

(14) **(15)** (9)

As a $^{-}NH^{-}$ Synthon.

The N-O linkage can be reductively cleaved under mild conditions.[18] Consequently, the *N*-methoxy group should function as an activating/protecting group when preparing disubstituted nitrogen compounds with methoxyamine. This strategy was elegantly demonstrated in the synthesis of β-lactam precursors of monobactam antibiotics.[19] L-Serine (**16**) was treated sequentially with ***Di-t-butyl Dicarbonate*** (Boc_2O) and methoxyamine.HCl, in one pot, to afford the Boc-protected hydroxamate (**17**) (eq 10).

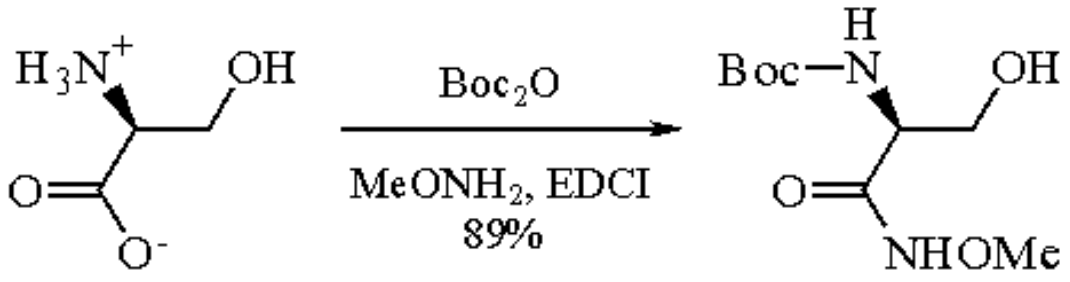

(10)

(16) **(17)**

The condensation to (**17**), which occurred in 30 min at rt, was mediated by ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride*** (EDCI). The mesylate (**18**), prepared by treating (**17**) with ***Methanesulfonyl Chloride***, was easily cyclized to the 1-methoxyazetidinone (**19**) (eq 11).

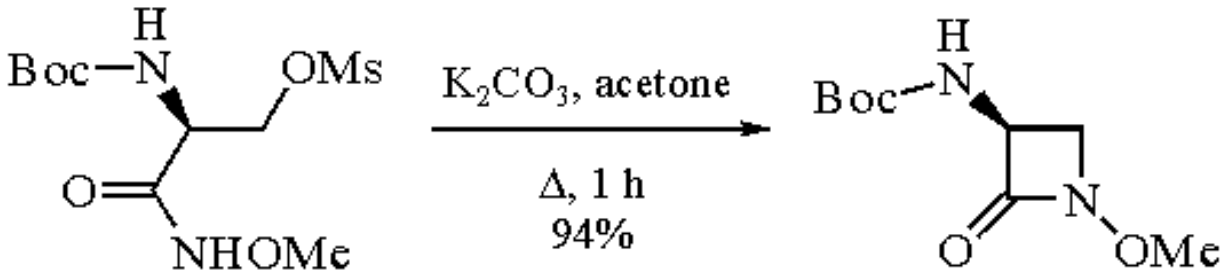

(11)

(18) **(19)**

Reductive cleavage of the *N*-methoxy group of (**19**) afforded the β-lactam (**20**) (eq 12).

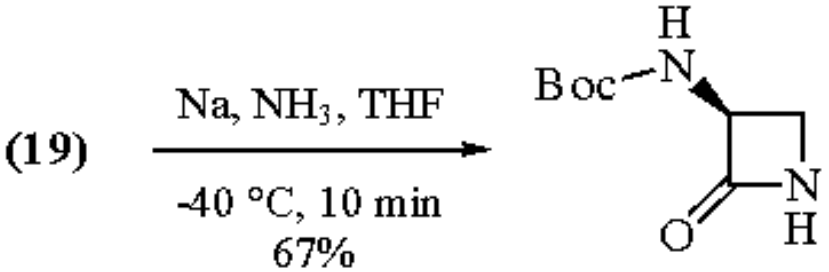

(12)

(20)

L-Threonine and L-allo-threonine were also converted to the respective β-lactams in comparable yields using the above sequence. The conversion of amino acid to β-lactam proceeded stereospecifically in all cases.

Anti-Bredt β-lactams are also prepared using the above strategy.[20] However, the hydroxamate was cyclized under Mitsunobu conditions.[21] Thus treatment of the hydroxamate (**21**) with ***Triphenylphosphine*** and ***Diethyl Azodicarboxylate***

(DEAD) generated the 1-methoxyazetidinone (**22**) (eq 13).

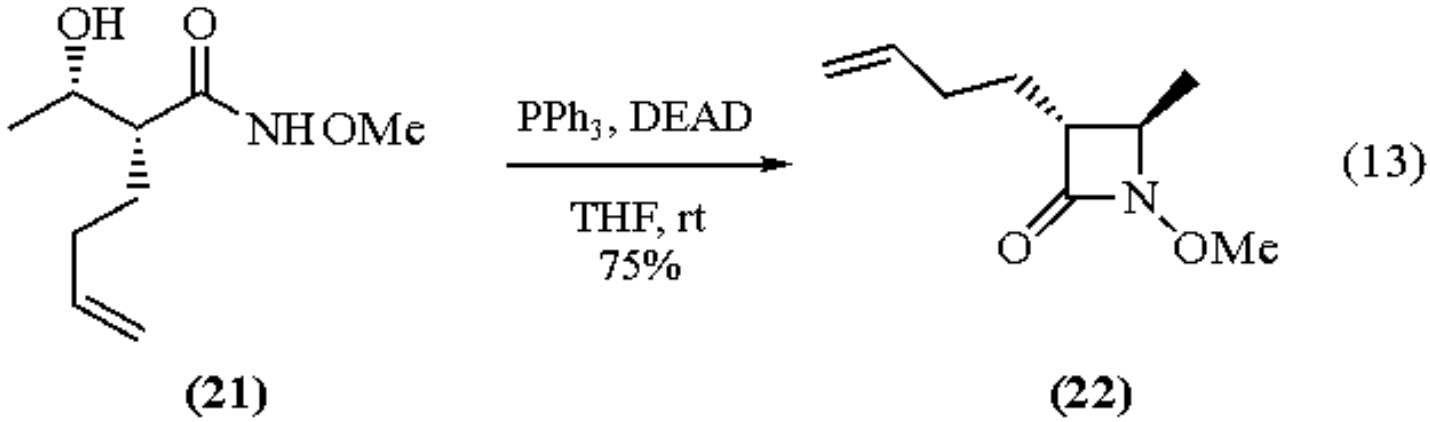

The primary amide versions do not cyclize to the β-lactams by either of the above methods. This is due to competing proton transfers. An alkoxy or acyloxy substituent on the amide nitrogen lowers the pK_a of the amide enough that cyclization becomes competitive.[22] The methoxy substituent appears to be particularly advantageous due to the ease with which it is reductively cleaved.[19]

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Bruce J. Kokko

James River Corporation, Neenah, WI, USA

Methyl 3-Hydroxypropionate

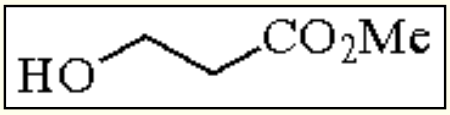

[6149-41-3] · $C_4H_8O_3$ · Methyl 3-Hydroxypropionate · (MW 104.12)

(preparation of α-substituted acrylate and hydracrylate derivatives;[1] photochemical conjugate additions;[2] protection of the carboxy group[3])

Alternate Names: methyl 3-hydroxypropanoate; methyl hydracrylate.

Physical Data: bp 71-73 °C/9 mmHg.[4]

Analysis of Reagent Purity: ^{1}H NMR and MS.[5]

Preparative Methods: two methods have been published: reaction of β-***Propiolactone*** with ***Sodium Methoxide*** in MeOH (17-36%),[5,6] or treatment of 3-hydroxypropionitrile with HCl in aqueous MeOH (68%).[4] The latter method appears to be more desirable based upon yield of product and the high cost and toxicity of β-propiolactone.

Preparation of α-Substituted Acrylate and Hydracrylate Derivatives.

Methyl 3-hydroxypropionate (**1**) is a useful reagent for the preparation of α-substituted acrylate and hydracrylate derivatives. Reaction of the dianion arising from (**1**) with a variety of electrophiles is shown in eq 1.[1] The alkylated products can be dehydrated under acidic (***Phosphoric Acid***) or basic (***p-Toluenesulfonyl Chloride***, ***Pyridine***) conditions (eq 2).[7] An interesting example of this method is shown in eq 3.[8] Treatment of the dianion of (**1**) with an aldehyde gives an intermediate diol. The less hindered hydroxy group is then eliminated in two steps by reaction with TsCl, followed by treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.

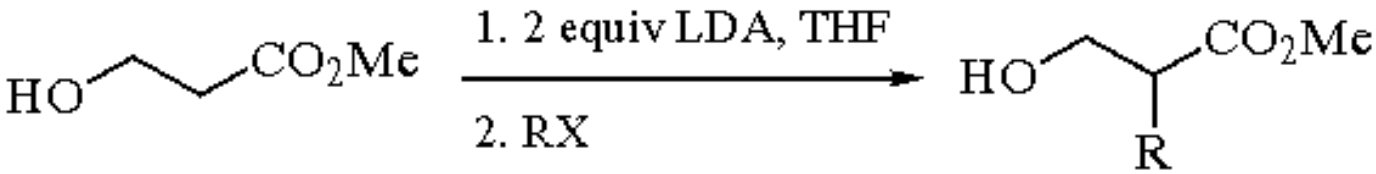

(1)

RX	R	Yield (%)
MeI	Me	94
i-PrI	*i*-Pr	89
MOMCl	$MeOCH_2$	95
$(MeS)_2$	MeS	88

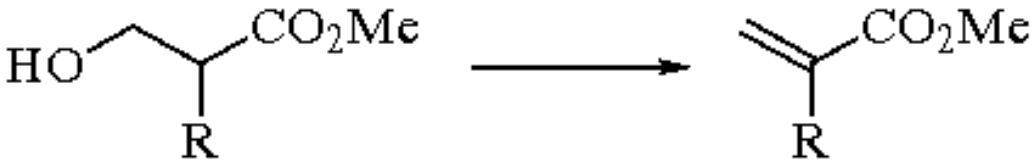

(2)

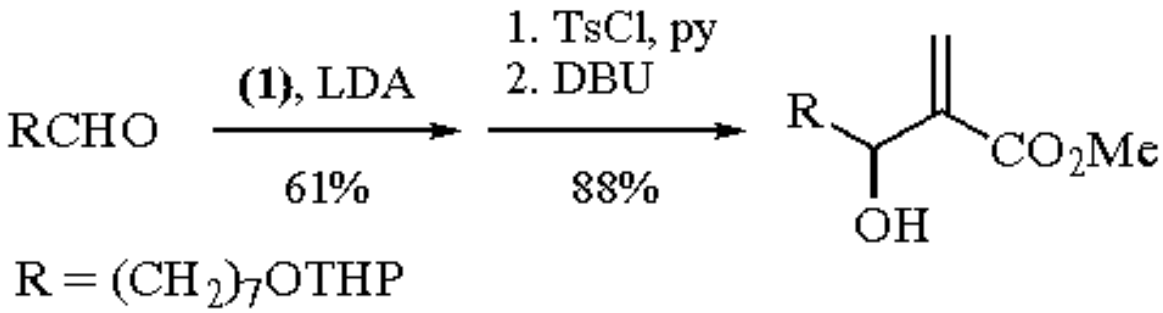

(3)

Photochemical Conjugate Addition.

A photochemically induced conjugate addition reaction has been observed between (**1**) and a conjugated enone in the presence of benzophenone (eq 4).[2] If the hydroxy group in the product is protected as a THP acetal (***3,4-Dihydro-2H-pyran***, ***p-Toluenesulfonic Acid***) prior to isolation, the yield increases to 71%.

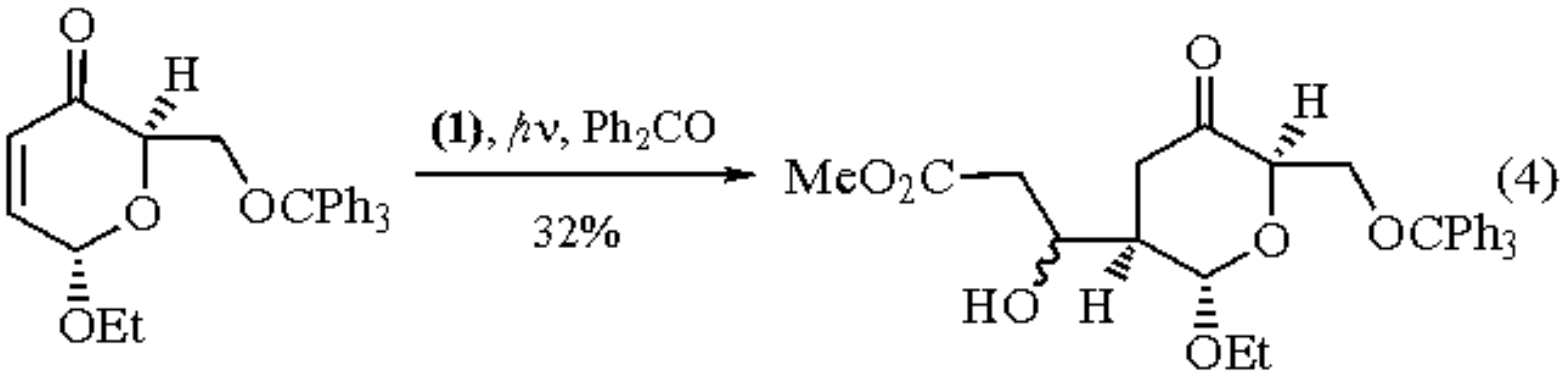

(4)

Protection for the Carboxy Group.

The 2-methoxycarbonylethyl esters derived from (**1**) have been used as protecting groups for the carboxy functionality.[3] Beginning with the carboxylic acid, mixed anhydride formation followed by esterification with (**1**) in the presence of ***4-Dimethylaminopyridine*** gives the protected ester (eq 5). Deprotection occurs upon treatment with DBU in acetonitrile (eq 6).

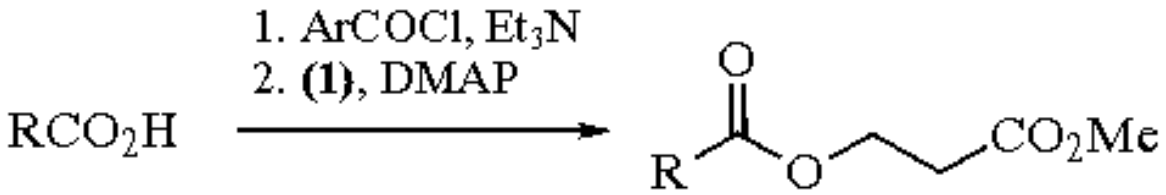

(5)

Ar = 2,4,6-trichlorophenyl

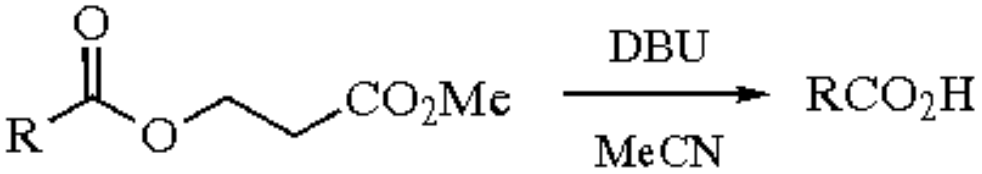

(6)

Related Reagents.

Ethyl Acrylate; ***Ethyl 3-Hydroxybutanoate***; ***Methyl 3-(Dimethylamino)propionate***; β-***Propiolactone***.

---

1. Herrmann, J. L.; Schlessinger, R. H. *TL* **1973**, 2429.
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Methyl Hypofluorite

MeOF

[36336-08-0] · CH_3FO · Methyl Hypofluorite · (MW 50.04)

(used for adding the elements of MeO and F across double bonds,[1] for electrophilic methoxylation α to carbonyls,[2] and as a tool for introducing the short lived ^{11}C isotope for positron emission tomography (PET)[3])

Physical Data: mp -142 °C; bp -33 °C (by extrapolation); ^{19}F NMR +120 ppm ($^3J_{HF}$ = 45 Hz); ^1H NMR 4.51 ppm ($^3J_{HF}$ = 45 Hz).

Handling, Storage, and Precautions: MeOF is an unstable substance and for all practical purposes has to be prepared in situ in solution and used soon after its formation. **Neat solid and liquid MeOF can be unpredictably explosive at temperatures above** -78 °C. The concentration of the reagent is determined iodometrically (MeOF + 2KI + H_2O -> I_2 + KF + MeOH + KOH). As with all hypofluorites, it may be toxic and should be treated accordingly. Use in a fume hood.

Addition to Alkenes.

Although MeOF has been a subject for several theoretical studies,[4] it was synthesized only recently by passing relatively concentrated fluorine through methanol in the presence of acetonitrile.[1] Unlike other hypofluorites such as ***Trifluoromethyl Hypofluorite*** or ***Acetyl Hypofluorite*** the fluorine in MeOF is nucleophilic, leaving the rest of the molecule (MeO) to act as a strong electrophile. This formally constitutes the previously unknown methoxylium ion. This is evident from the addition of MeOF to unsymmetrical alkenes such as styrene, which produces exclusively 1-fluoro-1-phenyl-2-methoxyethane (eq 1).[1]

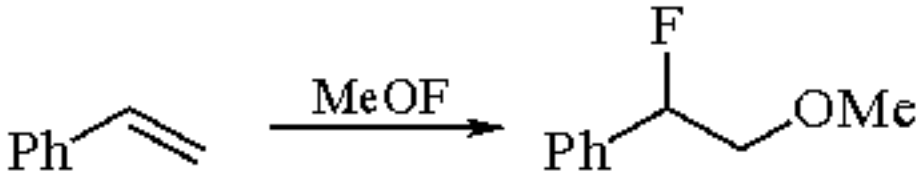

(1)

Methoxylation of Ketones.

This unique electrophilic system was used to methoxylate ketones in their α-position in a fast and direct mode. It was found that the methoxylation is best when performed on methyl enol ethers.[2] Since this reaction takes only a few seconds, and since it is relatively easy to make $^{11}CH_3OH$ (half life of the positron emitting ^{11}C isotope is about 20 min), this method adds a new route (to the very few existing ones) for incorporating this isotope into organic molecules for PET studies (eq 2).[3]

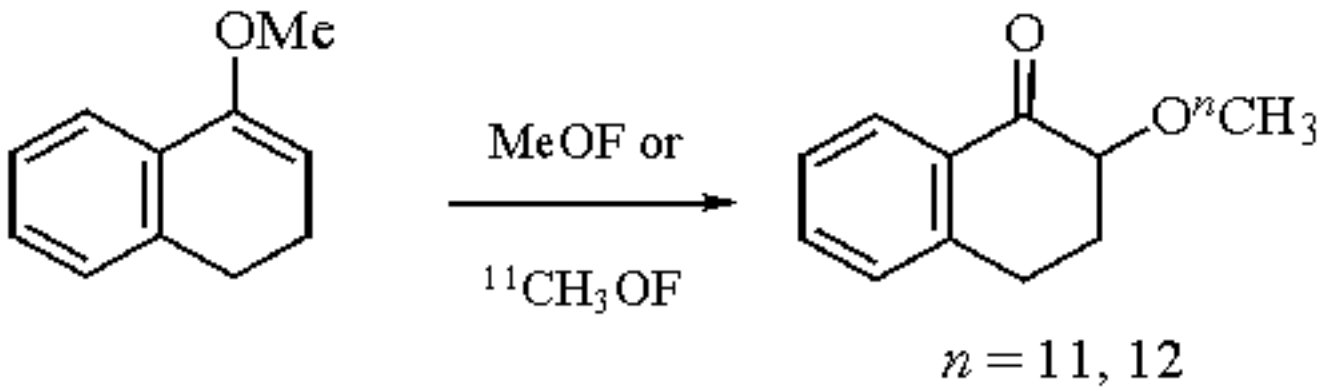

(2)

It should be noted that addition of the elements of MeO and F can also be achieved when electrophilic fluorination reagents such as CF_3OF,[5] $FClO_3$,[6] or $CsSO_4F$[7] are reacted with alkenes in the presence of MeOH (eq 3). The same is true when XeF_2/MeOH is employed, although in this case the intermediate MeOXeF was suggested (eq 4).[8] In some of these reactions the fluorine acts as an electrophile, but in others most of the regioselectivity is lost.

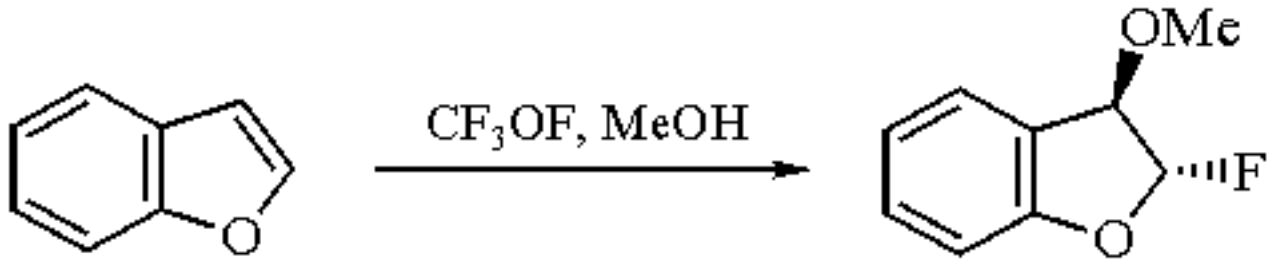

(3)

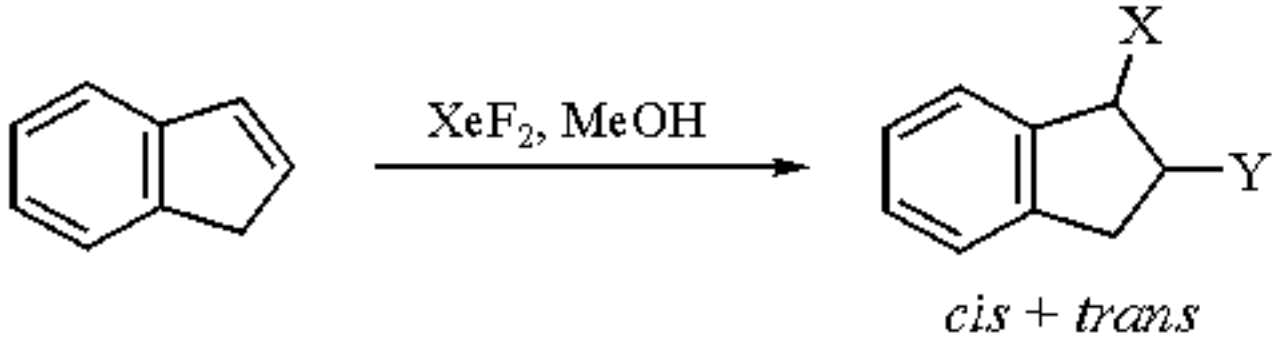

(4)

X = OMe, Y = F; X = F, Y = OMe

Related Reagents.

Hypofluorous Acid.

---

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4. See for example: Lee, I.; Cho, J. K.; Song, C. H. *JCS(F2)* **1988**, *84*, 1177.
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Shlomo Rozen

Tel Aviv University, Israel

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N-Methylimidazole

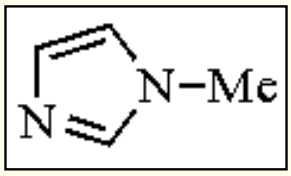

[616-47-7] · $C_4H_6N_2$ · *N*-Methylimidazole · (MW 82.12)

(phosphorylation; acylation)

Physical Data: bp 195-197 °C; *d* 1.031 g cm^{-3}.

Solubility: usually used in THF, Et_2O.

Form Supplied in: redistilled liquid (99+%); packed under nitrogen.

Analysis of Reagent Purity: the reagent may be analyzed using standard techniques.

Purification: dried with sodium metal and then distilled.

Handling, Storage, and Precautions: store at 0 °C under dry argon. The compound is harmful in contact with skin and if swallowed, and causes burns.

Introduction.

N-Methylimidazole is used for phosphorylation and acylation. It can be lithiated at the 2-position by treating with ***n-Butyllithium*** at -78 °C in THF or diethyl ether. The Grignard reagent can also be prepared by exchange with ***Ethylmagnesium Bromide*** at the 2-position.[1]

Phosphorylation.

Alcohols may be phosphorylated in good yield by the reaction of phosphorous acid, mercury(II) chloride and *N*-methylimidazole (eq 1). An intermediate salt (**1**) is formed. This method has been used to prepare nucleoside 5´-phosphates in yields of 60-70%.[2] Similarly, amines may be phosphorylated by reaction with ***Phosphorus Oxychloride*** and *N*-methylimidazole (eq 2).[3]

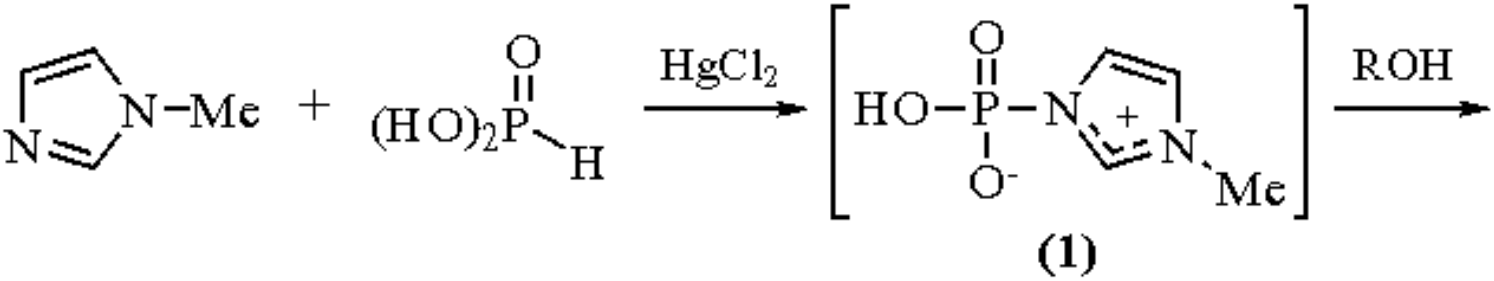

(1)

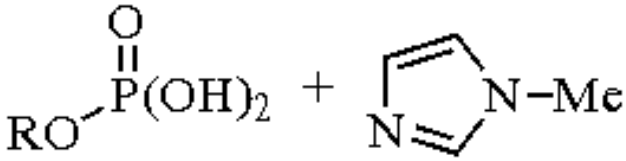

(1)

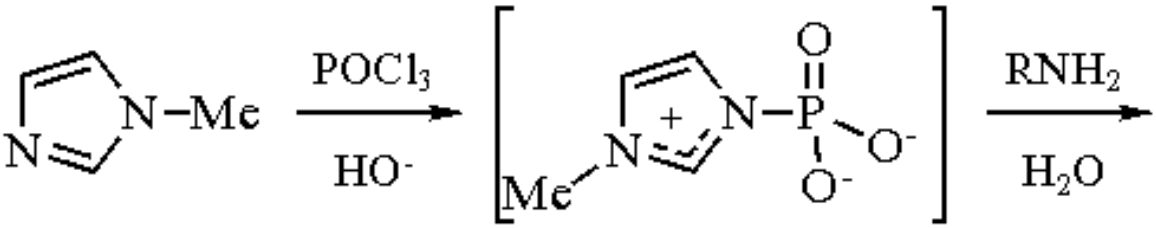

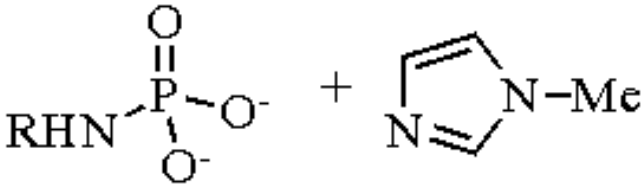

(2)

Acylation.

N-Methylimidazole reacts with acid chlorides and chloroformates to give *N*-acylimidazolium salts. These can then be used as effective acylating agents, for example of amines, in aqueous solution (eq 3).[4]

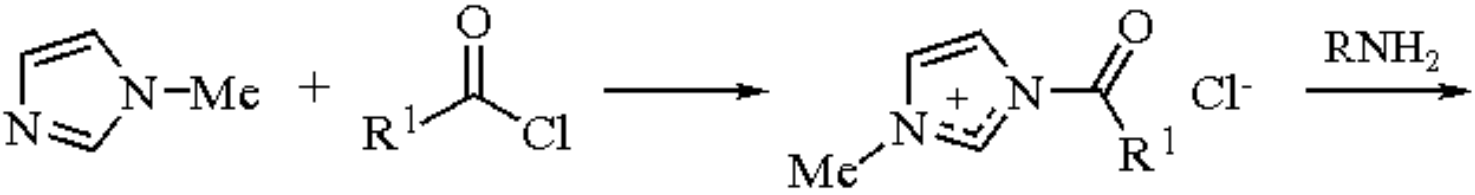

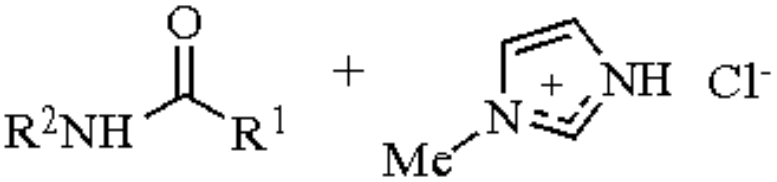

(3)

N-Methylimidazole has been used as an effective catalyst of acylation by ***Acetic Anhydride***. It has a catalytic activity about 4×10^2 greater than pyridine (eq 4).[5]

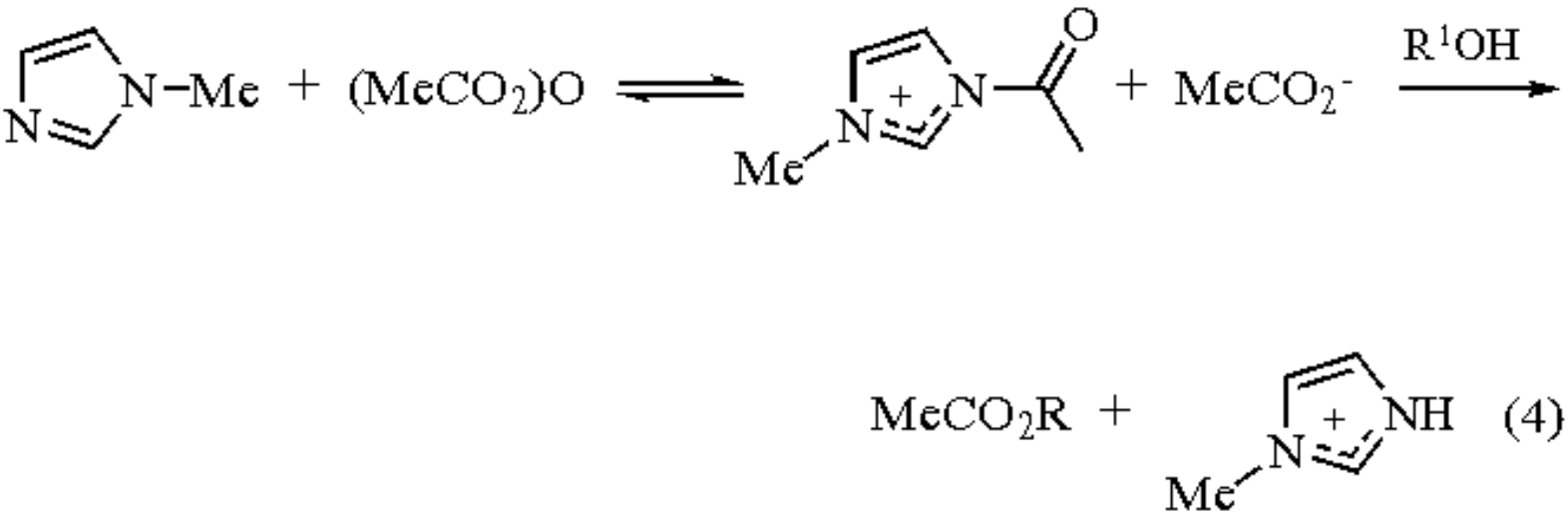

(4)

Reactions of 2-Lithio-1-methylimidazole.

2-Lithio-1-methylimidazole reacts with ketones at -78 °C in 65-96% yield to give 2-(1-hydroxyalkyl)-1-methylimidazoles. These can be dehydrated with hot acetic anhydride to give 2-vinyl-1-methylimidazoles in 73-85% yield (eq 5).[6]

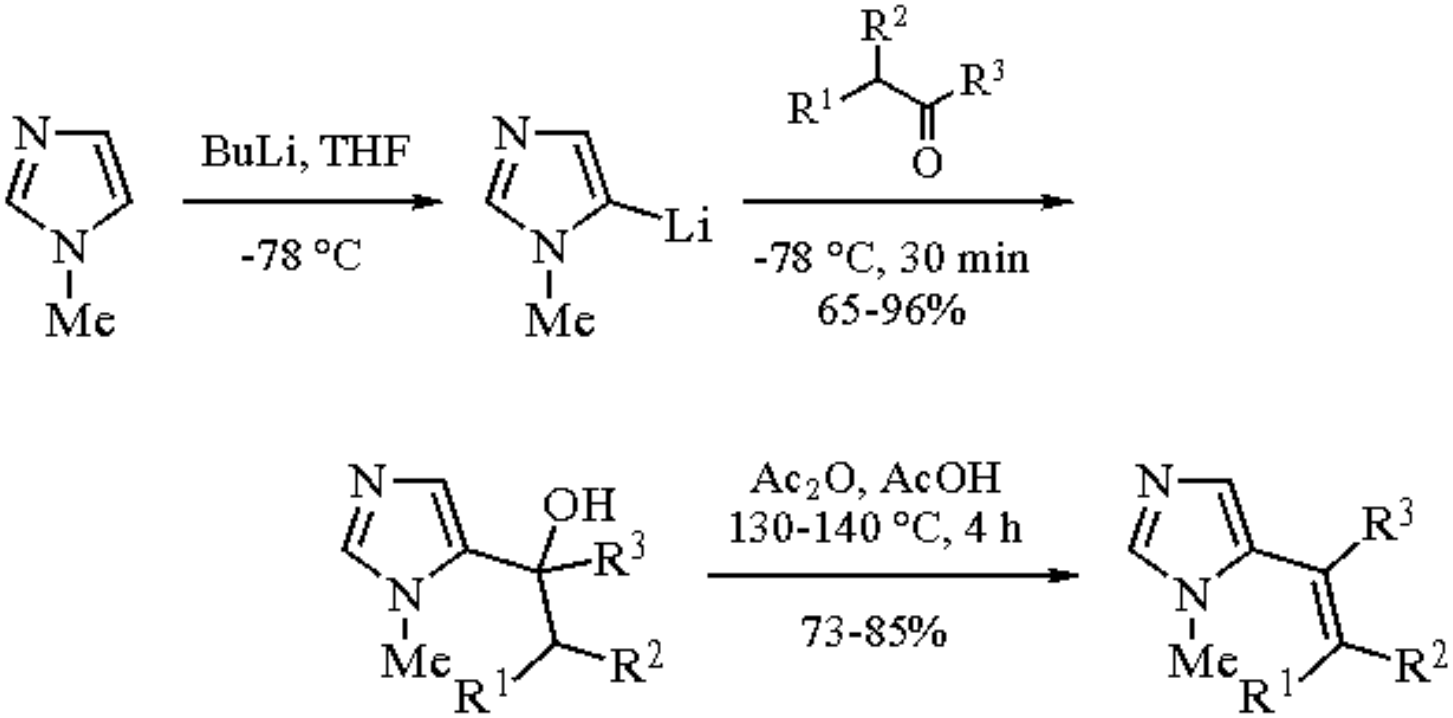

(5)

2-Lithio-1-methylimidazole reacts with alkyl or aryl nitriles to give 2-acyl-1-methylimidazoles (acid anhydrides, acid chlorides and amides give poor, nonreproducible yields of the ketones). These then yield 1-methylimidazolethylenes via a Wittig reaction. Vinylimidazoles are reported to be potentially useful as monomers in the synthesis of heterocyclic polymers (eq 6).[7]

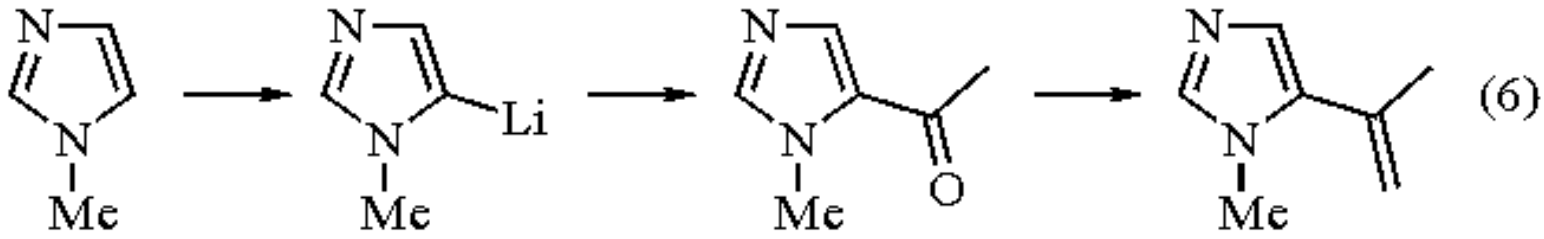

2-Imidazolylsilanes may be synthesized by reacting ***Chlorotrimethylsilane*** with 2-lithio-1-methylimidazole and subsequent transsilylation (eq 7).[8]

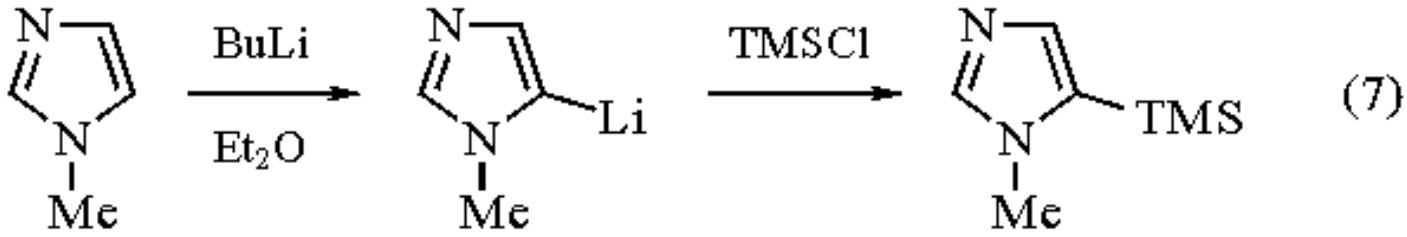

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8. Jutzi, P.; Jakriss, W. *CB* **1969**, *106*, 2815.

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Methyl Isocyanate[1]

MeN=C=O

[624-83-9] · C_2H_3NO · Methyl Isocyanate · (MW 57.06)

(carbamoylates NH, OH, SH, and active CH compounds; converts epoxides to 1,2-amino alcohols via 2-oxazolidinones; undergoes [2 + *x*] cycloadditions to give rise to heterocycles; transforms aldoximes to nitriles[2] and nitroalkanes to nitrile oxides[3])

Alternate Name: MIC.

Physical Data: mp -17 °C; bp 39 °C; *d* 0.96 g cm^{-3}.

Solubility: sol chlorinated, aromatic, ethereal solvents; reacts violently with H_2O, basic, and protic solvents.

Form Supplied in: colorless liquid; no longer widely available. Usually prepared industrially in situ as needed.

Handling, Storage, and Precautions: **Warning: Highly toxic! Lachrymator! Irritant! Extremely flammable!** Use only in a fume hood. Wear protective gloves and preferably a NIOSH-approved respirator. All transfers and reactions should be carried out under anhydrous conditions. Store in a cool dry place, taking care to avoid contamination with protic, basic, or organometallic materials, as these may induce (exothermic) polymerization. Toxicity data for methyl isocyanate are available.[1]

N-Methylcarbamoylation.

The *N*-methylcarbamate (urethane) and *N*-methylurea moieties are common targets in organic synthesis, due to their function as pharmacophores in a stunning variety of compounds of pharmaceutical and agricultural interest. A typical method for their introduction makes use of the propensity of methyl isocyanate to add active hydrogen-bearing atoms (in either neutral or ionized form) to the central carbon atom.[4] Reaction with alkyl-[5] and arylamines,[6,7] sulfonamides,[8] and guanidines[9] proceeds to give the ureas, often with high regioselectivity.[6,7,10] Ring nitrogen atoms of heterocycles that bear a hydrogen (e.g. pyrazoles[10]) may also be carbamoylated under conditions mild enough even to avoid rupture of aziridines.[11] Both alcohols[12-14] and aryl hydroxys[15] react readily with MIC, yielding the carbamates. Reaction of secondary alcohols is typically slow and incomplete, unless catalysts (usually basic) are used.[16] A novel rearrangement of carbamate derivatives of hydroxamic acids affords *N*-methyl amino acids (eq 1).[17]

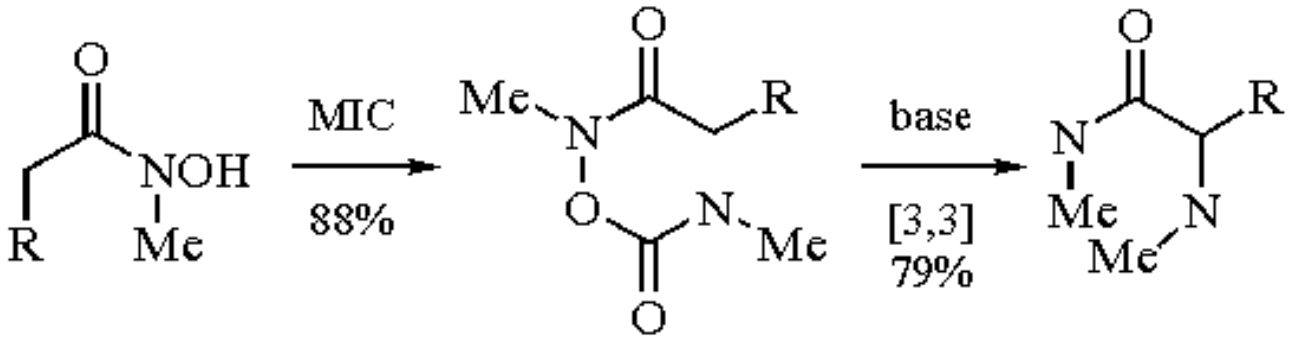

(1)

Thiols and thiocarbonyls that may be enolized react similarly;[18] a protocol for the protection of peptidic SH groups as *N*-methylthiocarbamates has recently been developed.[19] Malonates,[20] cyanoacetates,[20] and dithianes[21] may be cleanly mono-*N*-methylcarbamoylated upon treatment with MIC.

Conversion of Oxiranes to 2-Oxazolidinones and 1,2-Amino Alcohols.

This transformation is very similar to that of simple epoxides to 2-oxazolidinones induced by ***p-Toluenesulfonyl Isocyanate***. However, due to the lower reactivity of MIC, it is most often carried out in two or more steps via the epoxycarbamate derived from α-hydroxy epoxides (eq 2)[12,22] or α-hydroxy esters.[13] Hydrolysis of the 2-oxazolidinone yields the 1,2-amino alcohol.

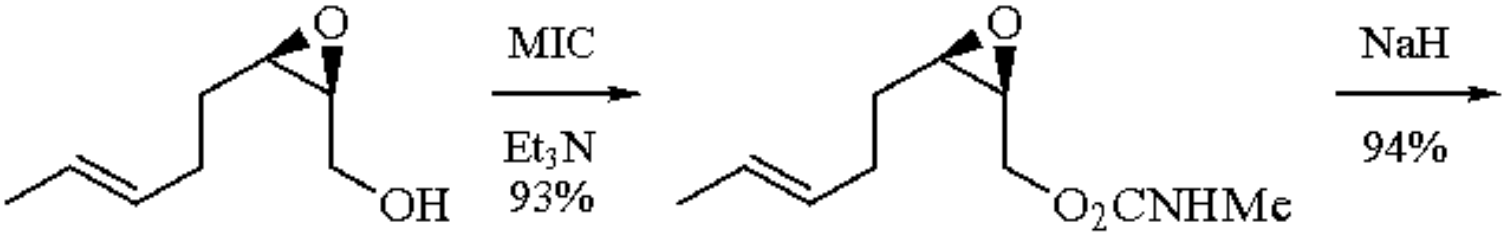

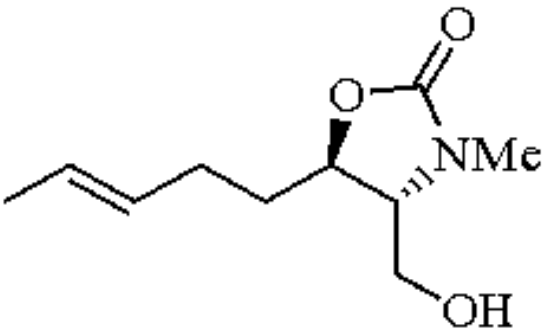

(2)

Heterocycle Synthesis via Tandem Electrophilic-Nucleophilic Ring Closure.

The electrophilicity of the central carbon atom and latent nucleophilicity of the nitrogen atom endow MIC with the potential to form adducts with any other atomic array that exhibits a similar donor-acceptor character. Thus, a huge variety of heterocyclic products may be prepared with MIC (eq 3), and this list is not exhaustive.

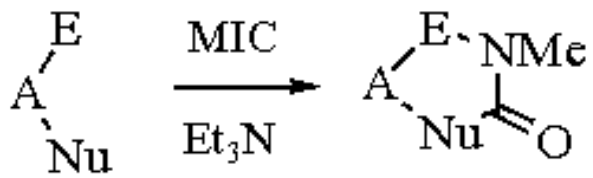

(3)

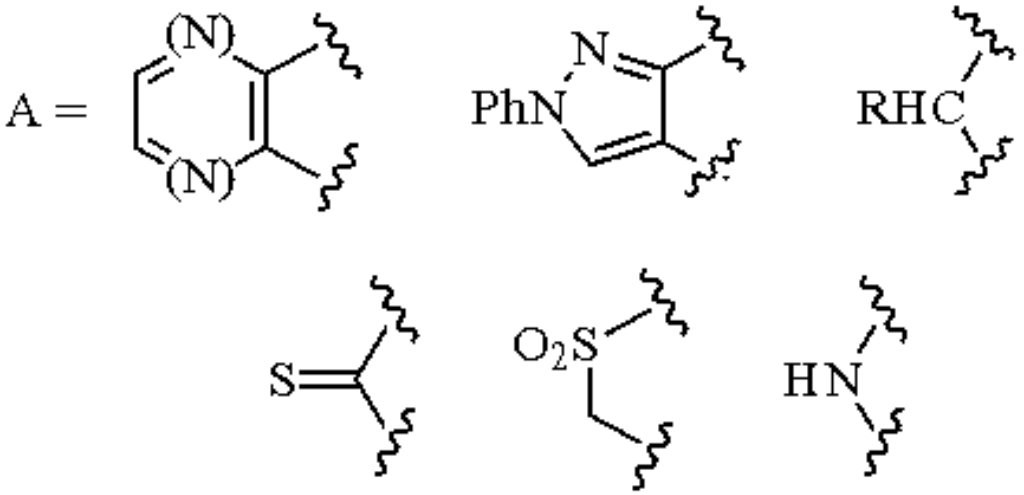

Nu = NH, NR, OH; E = CN, C=O, C=N, Michael acceptor

Reaction with ynamines gives [2 + 2] adducts of single regiochemistry.[23] Azomethine ylides derived from aziridines afford 4-imidazolinones by [2 + 3] cycloaddition highly regioselectively.[24] Other [2 + 3] adducts are 1,2,4-triazol-5-ones (from hydrazides),[25] imidazolin-5-imin-2-one-4-thiones (from cyanothioamides),[26] 1,2,4-triazolin-5-ones (from hydrazones),[27] and 2-oxazolones (from ketols).[28] Some examples of [2 + 4] adducts are 1,3-benzoxazines (from hydroxychalcones),[29] 1,2,4-oxathiazine *S*,*S*-dioxides (from alkynylsulfonamides),[30] pteridineimines (from aminocyanodiazines),[31] pyrazolopyrimidinones (from aminocyanopyrazoles),[32] 1,2,4-thiadiazin-3-one *S*,*S*-dioxides (from β-ketosulfonamides),[33] triazinones (from 1,3-diazadienes),[34] and 1,3-oxazine-2,4-diones (from 1,3-dioxan-4-ones).[35] While most of these annulations are triggered or completed by base catalysis, a thermal reaction has also appeared in the literature (eq 4).[35]

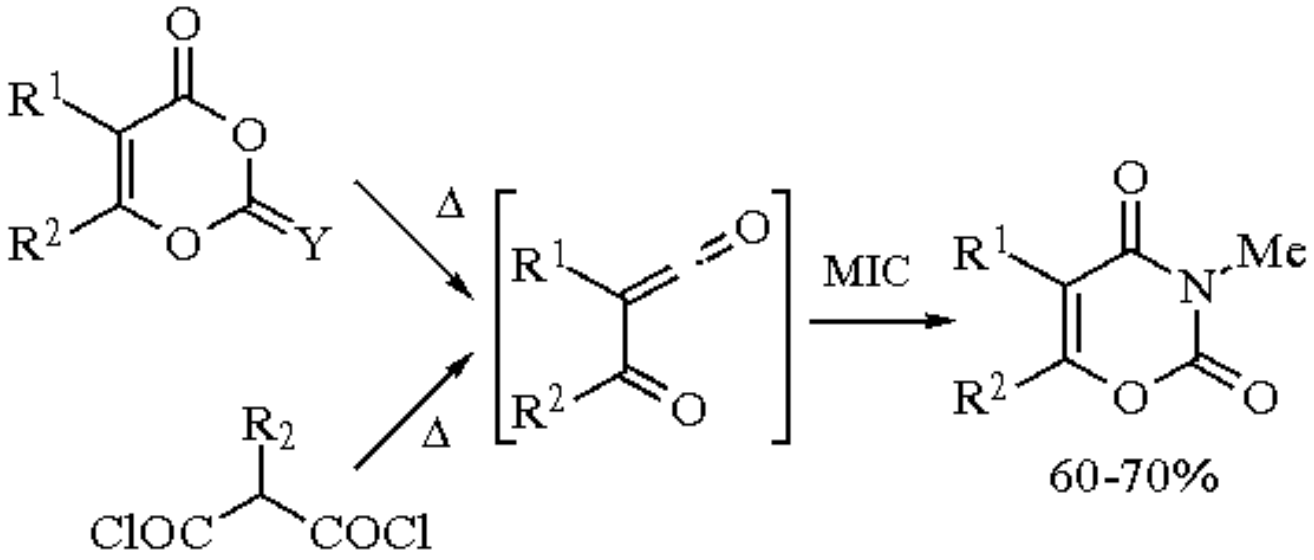

(4)

$Y = Me_2, (CH_2)_5$; $R^1 = CO_2R$, alkyl, H; R^2 = alkyl, H

Azaphosphoranes (from azides and phosphines) are easily converted to carbodiimides with MIC,[36] and these also show a propensity for condensation with a variety of nucleophiles. An interesting strategy for [5 + 1] annulation utilizes intramolecular addition of the nucleophile (eq 5).[37] Note that the NH group reacts with MIC before the azaphosphorane does.[38]

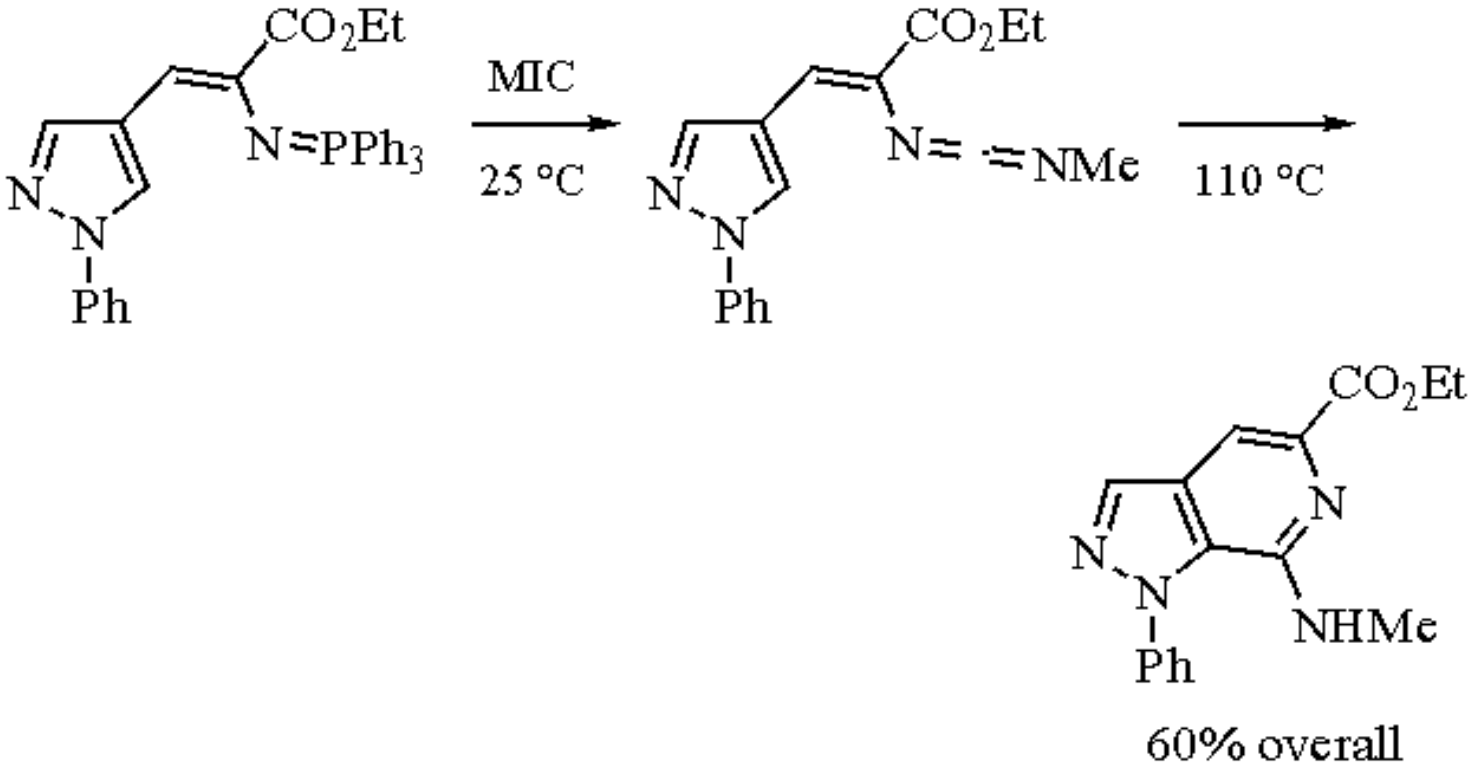

(5)

A number of unsaturated hydrocarbons react with MIC via the intermediacy of nickelacycles. Allenes give, after hydrolysis, 1:1 adducts with MIC (α-methyleneamides),[39] as does styrene (*N*-methyldihydrocinnamide).[40] Alkynes afford 2:1 adducts (2-pyridones) with MIC and this reaction is catalytic in nickel complex,[41] unlike the styrene and allene reactions, which are stoichiometric in nickel.

Functional Group Interchanges.

Aldoximes are converted to nitriles in high yield upon treatment with MIC.[2] In a very closely related reaction, alkyl nitro compounds yield nitrile oxides when subjected to reaction with MIC.[3] These dipolar species are easily trapped intramolecularly, and this protocol provides an alternative to harsher reagents. Both functional group interchanges are dehydrations that exploit the high reactivity of MIC with H_2O.

Related Reagents.

Phenyl Isocyanate; ***p-Toluenesulfonyl Isocyanate***.

---

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Methyl Isocyanide

R-+N&tbond;C-

(**1**; R = Me)

[593-75-9] · C_2H_3N · Methyl Isocyanide · (MW 41.06) (**2**; R = *n*-Bu)

[2769-64-4] · C_5H_9N · Butyl Isocyanide · (MW 83.15) (**3**; R = Cy)

[931-53-3] · $C_7H_{11}N$ · Cyclohexyl Isocyanide · (MW 109.19)

(reactive amphiphilic reagents for 1,1-additions to form heterocyclic *N*-*t*-butylimines, iminoyl halides, α-hydroxy amides, α,β-enals, α-acylamino amides via Passerini reactions, and polymethylene imines; oxidative additions to isocyanates and isothiocyanates[1,2])

Physical Data: (**1**) bp 60 °C; *d* 0.75 g cm^{-3}. (**2**) bp 123-124 °C; *d* 0.79 g cm^{-3}. (**3**) bp 173-176 °C, 56-58 °C/11 mmHg; *d* 0.88 g cm^{-3}.

Solubility: sol most organic solvents, e.g. methanol, ethanol, ether, toluene, dichloromethane.

Form Supplied in: pure liquids; methyl isocyanide is not commercially available; *n*-butyl and cyclohexyl isocyanides are commercially available.

Analysis of Reagent Purity: by GC.

Preparative Methods: the preparation of methyl isocyanide is well established.[3]

Handling, Storage, and Precautions: should be freshly distilled before use; foul smelling liquid; should be stored and used in a fume hood. Contaminated equipment should be washed with 5% methanolic sulfuric acid.

Heterocyclic Imines.[2]

[4 + 1] Cycloadditions of dimethyl tetrathiooxalate with alkyl isocyanides afford 2-imino-1,3-dithiolines under simple reaction conditions in good yields (eq 1).[4] Iminodioxolidine derivatives are available in good yields from cyanoketimines (eq 2).[5]

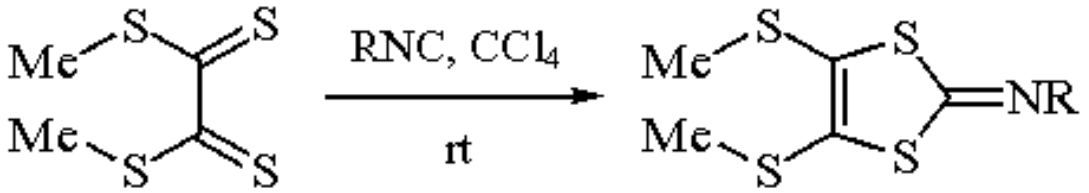

(1)

R = Me (81%), Bu (90%), Cy (83%)

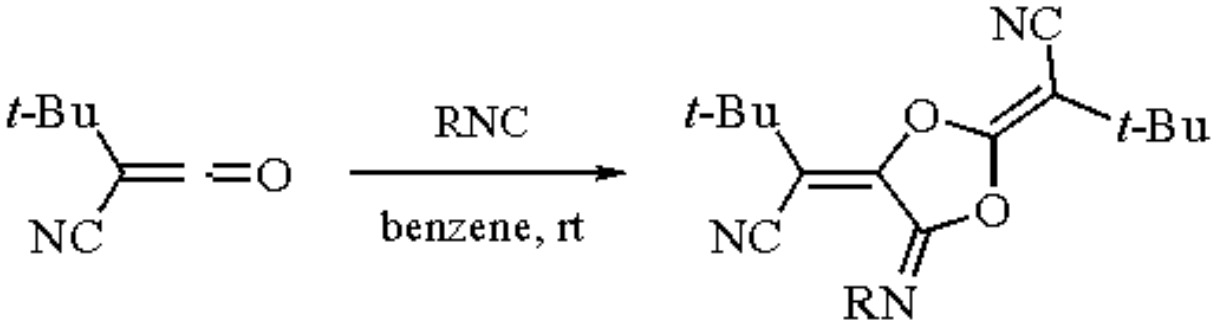

(2)

R = Bu (70%), *t*-Bu (97%), Cy (82%)

Iminoyl Halides via 1,1-Additions.

Chlorination of cyclohexyl isocyanide (**3**) in THF containing $HgCl_2$ incorporates the solvent in a ring-opening reaction (eq 3).[6] Pivaloyl chloride reacts with methyl isocyanide (**1**) to give an α-keto iminoyl chloride (eq 4).[7] *N*-Alkyl perfluoroalkylimidoyl iodides are easily accessible by copper-catalyzed condensation of iodo perfluoroalkanes and alkyl isocyanides in excellent yields. The products can be reduced by ***Sodium Borohydride*** to the corresponding secondary amines (eq 5).[8]

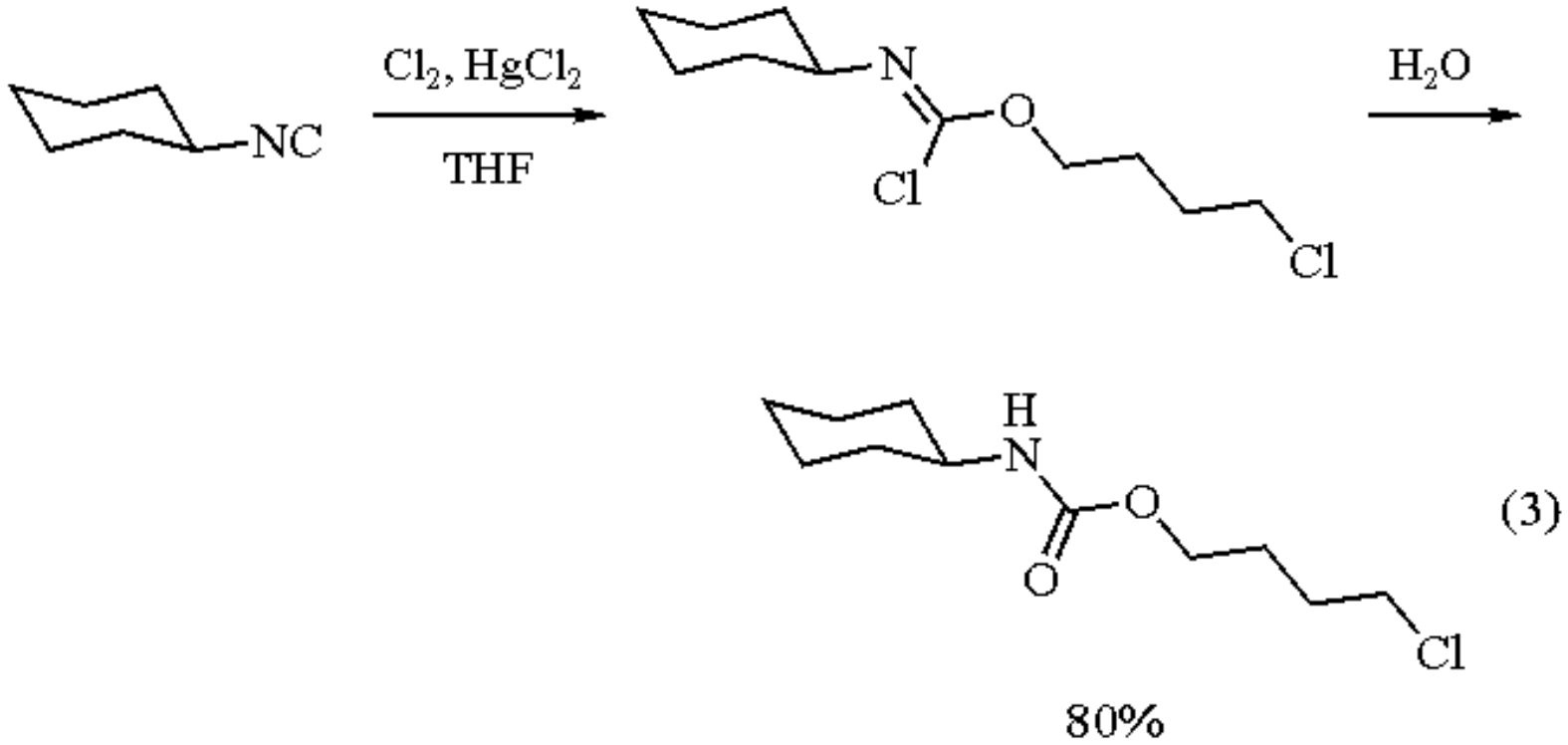

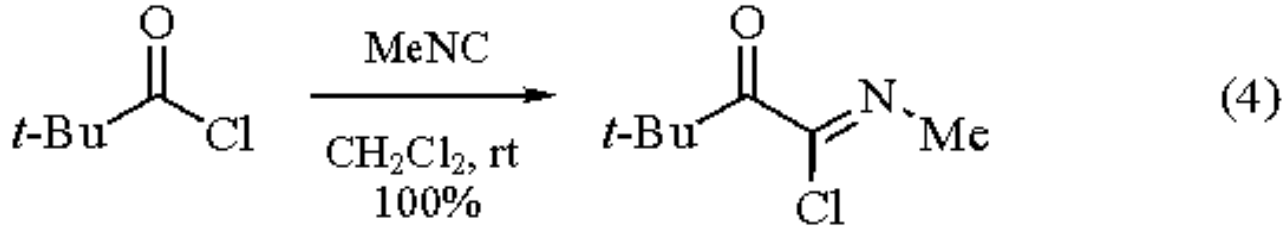

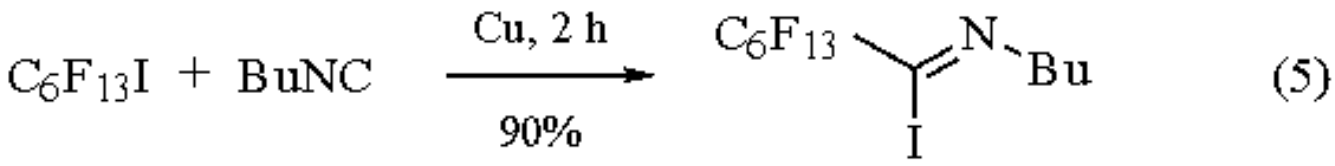

The Ugi four-component reaction between aldehydes, methyl isocyanide, and ammonium trifluoroacetate affords α-amino *N*-methylamides (eq 6).[9] Nocardicine, a monocyclic β-lactam antibiotic, is synthesized in one step together with the β-lactam by an Ugi reaction (eq 7).[10]

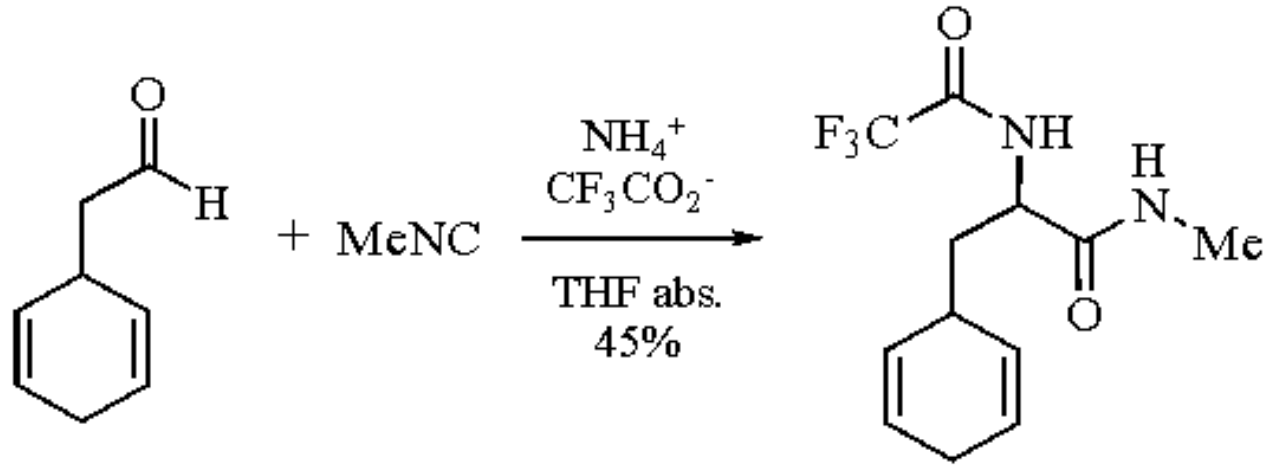

(6)

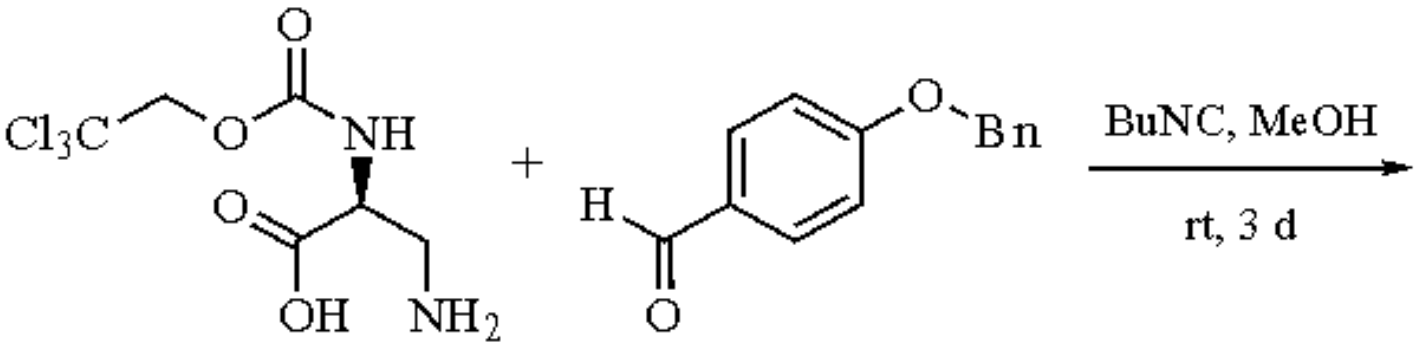

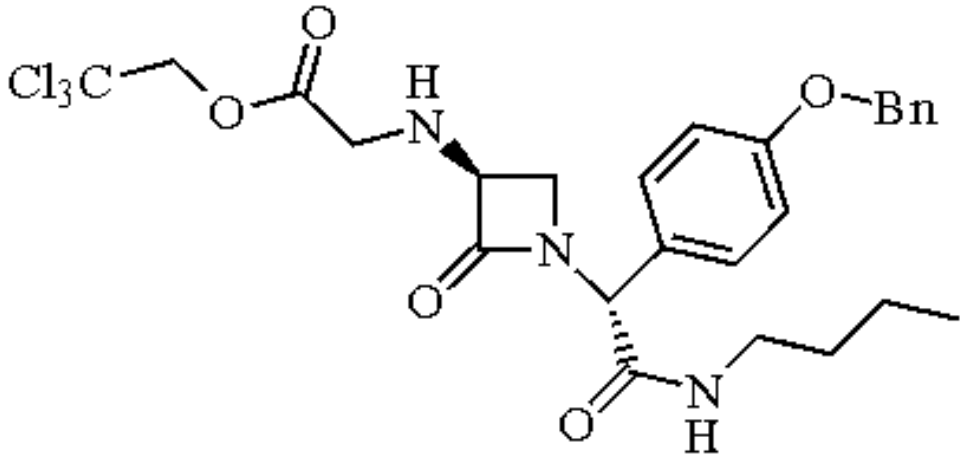

(7)

68% diastereomers

Other Applications.

α,β-Unsaturated aldehydes are available in a one-pot reaction, zirconium catalyzed, with *n*-butyl isocyanide (**2**) and alkynes (eq 8).[11]

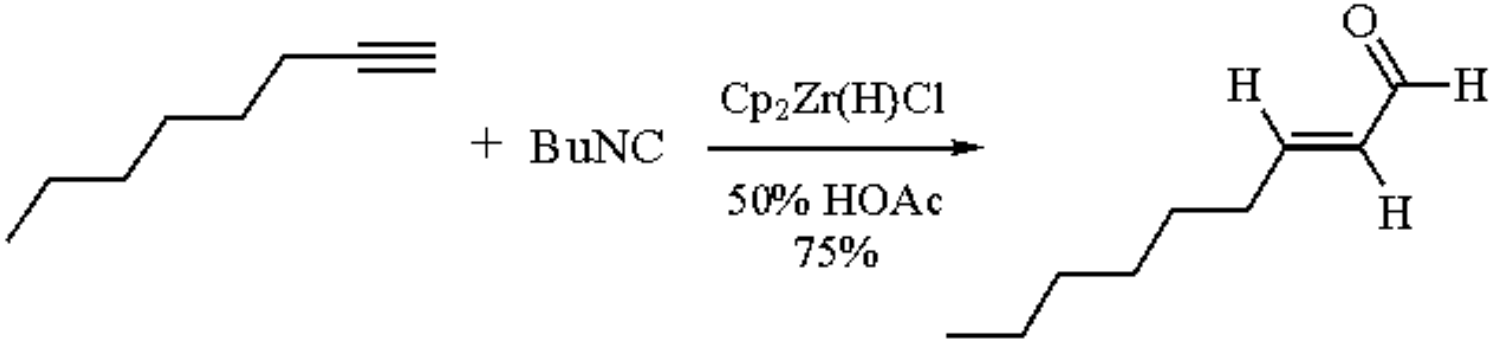

(8)

The reaction of methyl isocyanide with ***Titanium(IV) Chloride*** in CH_2Cl_2 affords an iminoyltitanium reagent which undergoes 1,2-addition to aldehydes and ketones. Hydrolysis of the adduct gives the homologous α-hydroxy-*N*-methylamide (eq 9).[12]

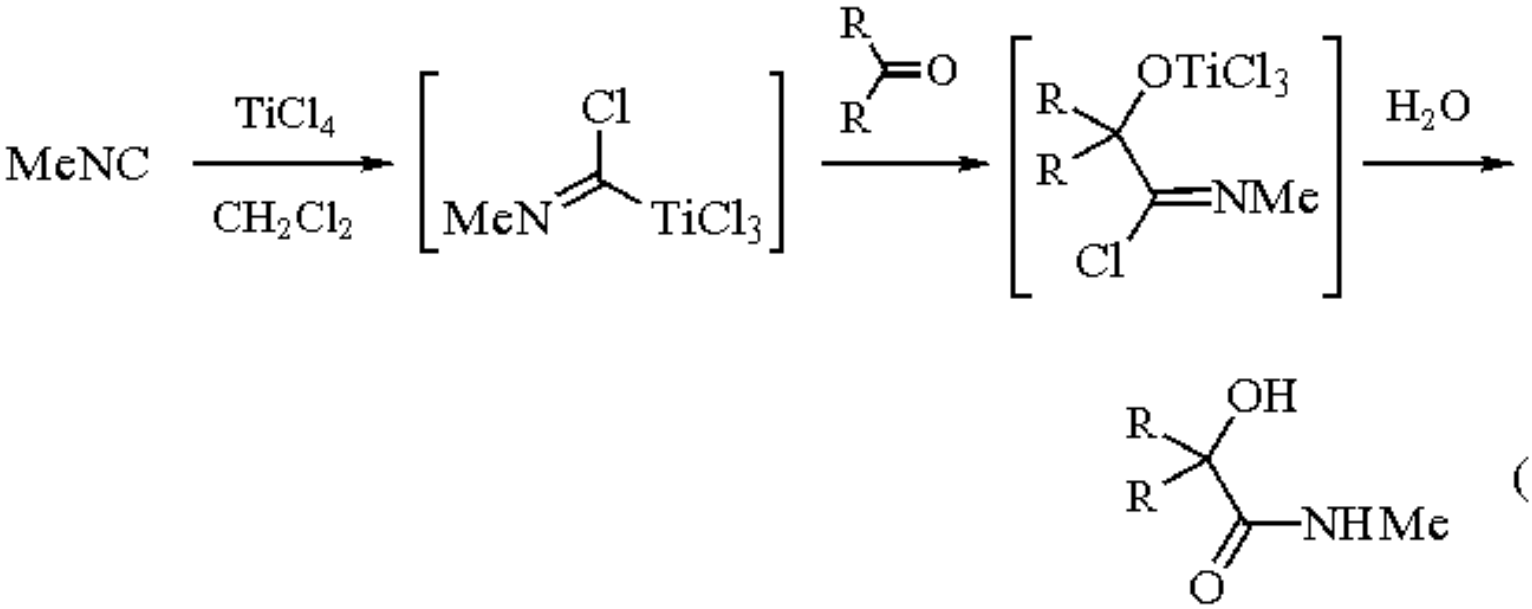

(9)

Isocyanides undergo formal [1 + 4] cycloaddition to cisoid α,β-enones in the presence of ***Diethylaluminum Chloride*** or ***Ethylaluminum Dichloride*** to give *N*-alkyl imines of β,γ-butenolides (eq 10).[13] The imines can be solvolyzed to γ-keto esters or hydrogenated and hydrolyzed to γ-butyrolactones.

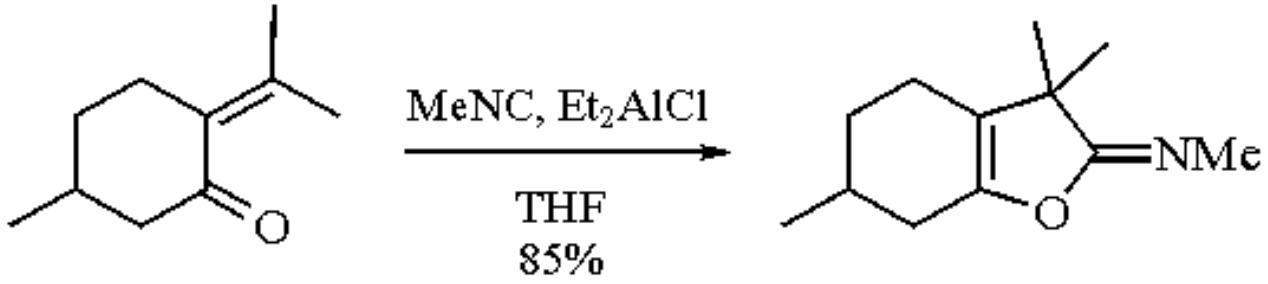

(10)

Oxidative addition of oxygen, sulfur, and selenium to alkyl isocyanides affords isocyanates,[14] isothiocyanates (eq 11),[15] and, isoselenocyanates,[16] respectively.

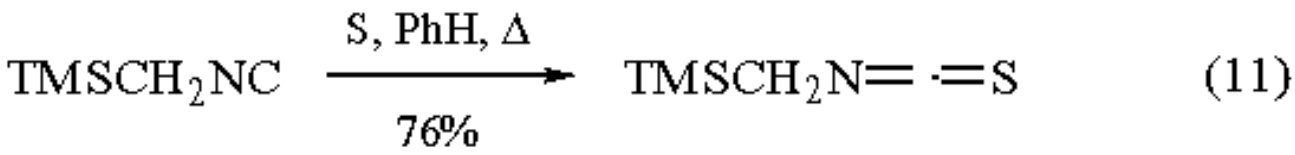

Polymerization of isocyanides with Ni^{II} catalysis leads to helical polymethyleneimine (*M* > 30 000 for *n*-butyl isocyanide, 75%).[17]

Related Reagents.

t-Butyl Isocyanide; ***Cyclohexyl Isocyanide***; ***Ethyl Isocyanoacetate***; ***Phenyl Isocyanide***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***.

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Methyl Isothiocyanate[1]

MeN=C=S

[556-61-6] · C_2H_3NS · Methyl Isothiocyanate · (MW 73.13)

(thiocarbamoylates NH, OH, SH, and organometallic compounds; used for preparation of a variety of heterocycles; derivatizes amino acids and peptides)

Alternate Name: MITC.

Physical Data: mp 31 °C; bp 117 °C; *d* 1.07 g cm^{-3}.

Solubility: sol chlorinated, aromatic, hydrocarbon, ethereal solvents; reacts violently with H_2O, basic and protic solvents.

Form Supplied in: white to pale orange solid; commercially available.

Handling, Storage, and Precautions: **Warning: Toxic! Lachrymator! Irritant! Extremely flammable!** Use only in a fume hood. Wear protective gloves and preferably a NIOSH-approved respirator. All transfers and reactions should be carried out under anhydrous conditions. Store in a cool dry place, taking care to avoid contamination with protic, basic, or organometallic materials, as these may induce (exothermic) polymerization.

N-Methylthiocarbamoylation.

Methyl isothiocyanate often differs from ***Methyl Isocyanate*** in reactivity, due to its lower overall electrophilicity and the high nucleophilicity of the S atom.[2] Thus, while reaction of oxiranes with methyl isocyanate has often been reported, the same is not true for MITC, and requires a catalyst.[3] Alkyl, aryl, primary, and secondary amines require no catalyst for serviceable reaction rates, and yield *N*,*N*´-disubstituted thioureas, which often display useful biological activity.[4] Alcohols react slowly with MITC (days);[5] the use of alkanolate salts increases the rate markedly.[6] The nucleophilicity of the S atom in alkenylthiocarbamates may be attenuated to allow the preparation of 1,2-amino alcohols (from the oxazolidinones, see eq 1).[6]

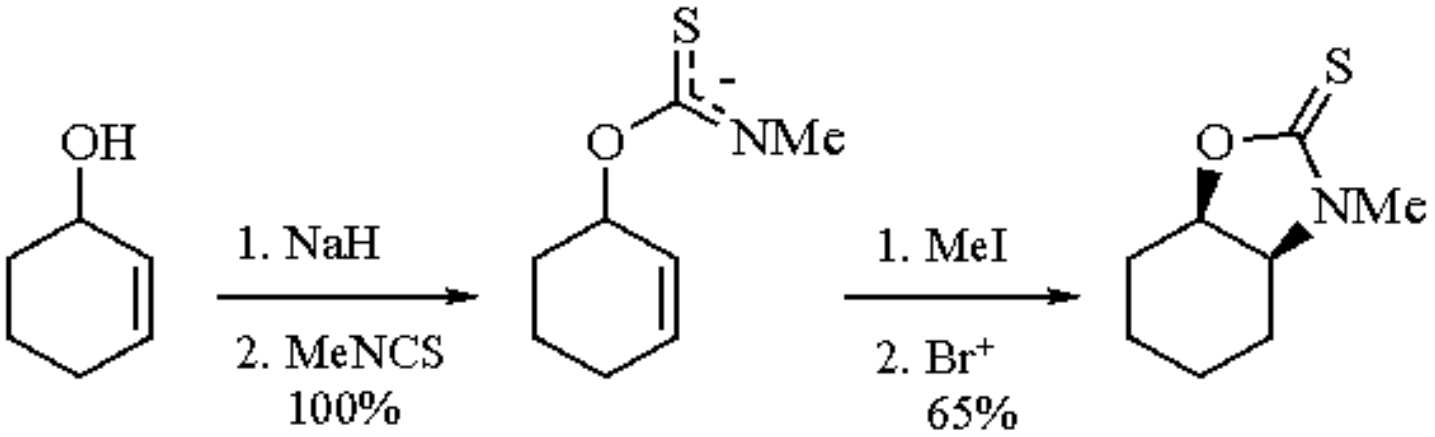

(1)

Thiols react sluggishly (days, weeks), but often completely with MITC.[7] Use of catalytic silylated thiol greatly increases the rate.[8] Organometallic compounds[9] and enolates[10] react with MITC to provide *C*-thiocarbamoylated products, usually with high yields. Electron-rich aromatics will undergo extremely *para*-selective Friedel-Crafts acylation with MITC in high yield.[11]

Heterocycle Synthesis.

Although not used as widely for heterocycle preparation as is methyl isocyanate, MITC provides access to a considerable variety of products. Hydrazino ketones, amino ketones, and aminoimidazoles afford (triazolo)imidazole derivatives.[12] Amidines give triazines,[13] amidrazones yield thiadiazoles,[14] and diazomethane derivatives afford thiotriazoles.[15] Hydroxychalcones provide 1,3-benzoxazine-2-thiones[16] and arylpropynamides yield thiazolidin-4-ones[17] upon treatment with MITC. Finally, cyanothioamides and enolizable ketones give 1,3-thiazoles[18] and pyrimidinedithiones,[19] respectively (see eq 2).

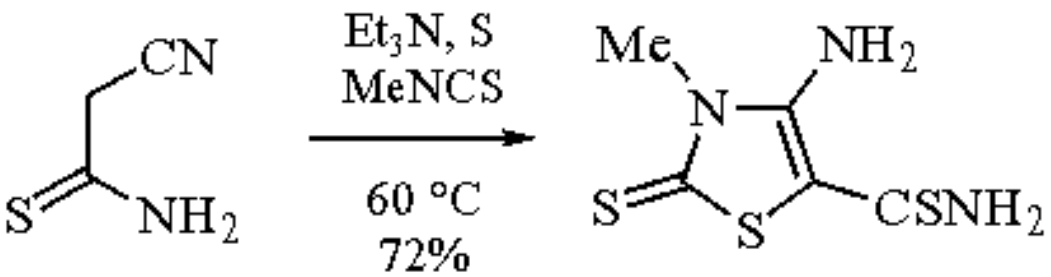

(2)

Phenyl isothiocyanate is generally interchangeable with MITC in the above reactions, but it seems uniquely able to undergo a Diels-Alder type reaction with 2-azadienes (see eq 3).[20]

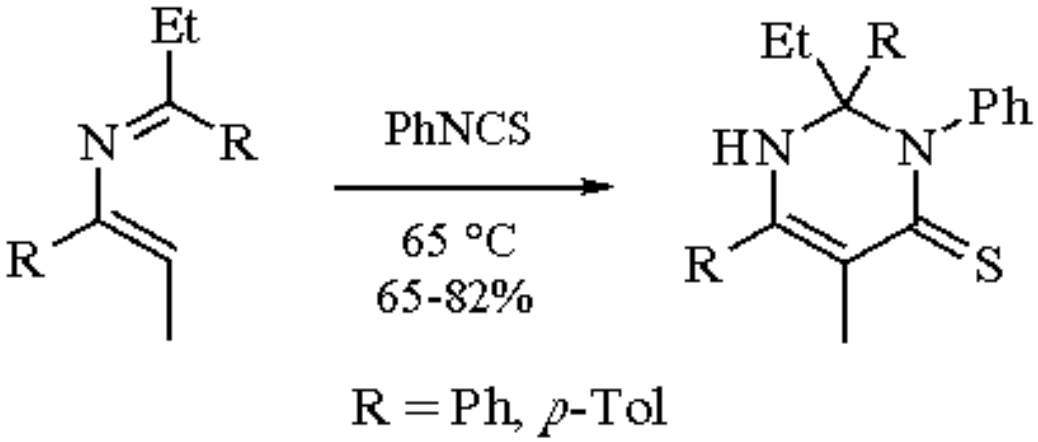

(3)

Amino Acid and Peptide Derivatization.

MITC converts nearly all amino acids into 2-thioxo-4-oxoimidazolidines. These derivatives are readily differentiated by TLC, GC, and circular dichroism analyses, which is of use for protein analysis.[21] Peptides may be modified for enhancement of activity and/or augmentation of bioavailability by reaction of side chain NH, OH, or SH groups with MITC.[22]

Related Reagents.

Methyl Isocyanate; ***Phenyl Isocyanate***.

---

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S-Methylisothiosemicarbazide[1]

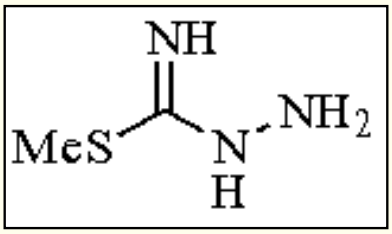

[44387-06-6] · $C_2H_7N_3S$ · *S*-Methylisothiosemicarbazide · (MW 105.19)

(synthesis of substituted 1,2,4-triazines,[1] tetrazoles,[2] and guanylhydrazones[3])

Alternate Names: methyl hydrazinecarboximido thioate; *S*-methylisothiocarbohydrazide; *S*-methylisothiosemicarbazone.

Physical Data: mp 140 °C (HI salt);[2] mp 144-146 °C (TsOH salt).[4]

Preparative Methods: HI salt:[2] prepared by refluxing thiosemicarbazide and methyl iodide in absolute ethanol for 45 min. Crystallized upon cooling the reaction mixture to give 90% yield. Recrystallized from absolute ethanol. TsOH salt:[4] prepared by refluxing a mixture of 0.5 mol of thiosemicarbazide and 0.5 mol of methyl *p*-toluenesulfonate in 500 mL of methanol for 18 h. After reducing the volume to 250 mL in vacuo, the mixture was treated with 500 mL of ether to give 135 g of *S*-methylisothiosemicarbazide tosylate.

Handling, Storage, and Precautions: use in a fume hood.

S-Methylisothiosemicarbazide readily reacts with α-dicarbonyl compounds to afford the 3-methylthio derivatives of 1,2,4-triazines.[1] α-Keto aldehydes exclusively gave the expected 5-substituted 3-methylthio-1,2,4-triazines (eq 1).[1] Diethyl oxomalonate produces two isomers, depending on reaction conditions.[4] In acetic acid at reflux, the reaction product was 3-methylthio-5-oxo-6-ethoxycarbonyl-4,5-dihydro-1,2,4-triazine. When the free *S*-methylisothiosemicarbazide was used in aqueous solution, in addition to the above product, a less polar isomer was formed in 3:2 ratio (eq 2).[5] The condensation with an indole anhydride was reported to give only one product (eq 3).[6] 3-Amino-1,2,4-triazine 4-oxide was formed in modest yield when the HBr salt of *S*-methylisothiosemicarbazide was heated with an α-diketone monooxime under mild acidic conditions (eq 4).[7]

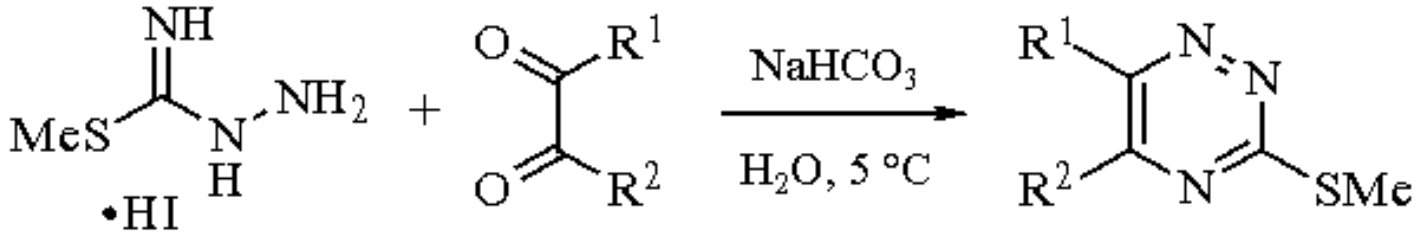

(1)

R^1	R^2	Yield (%)
H	Me	64
Me	Me	86
H	Ph	81
Ph	Ph	88

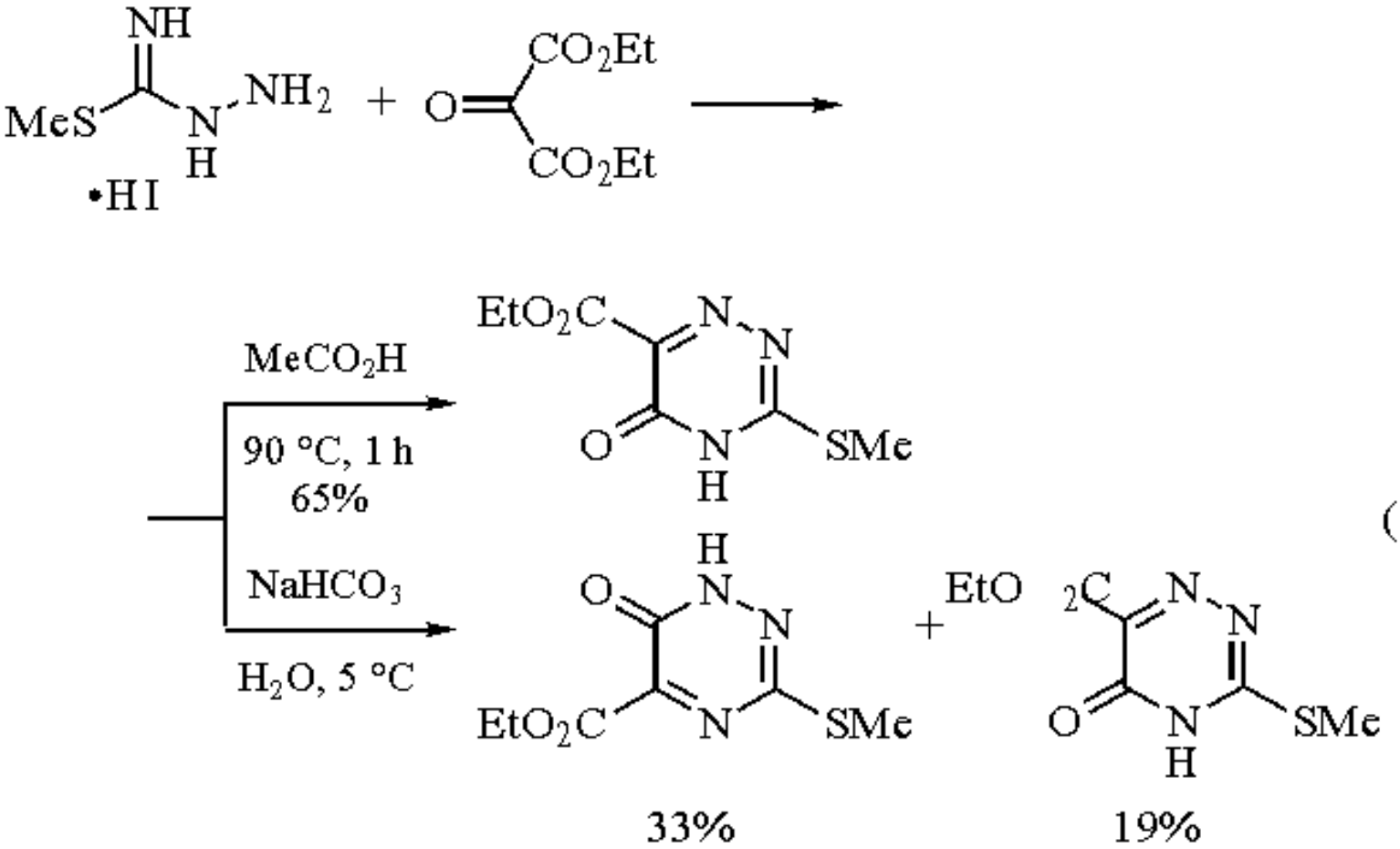

(2)

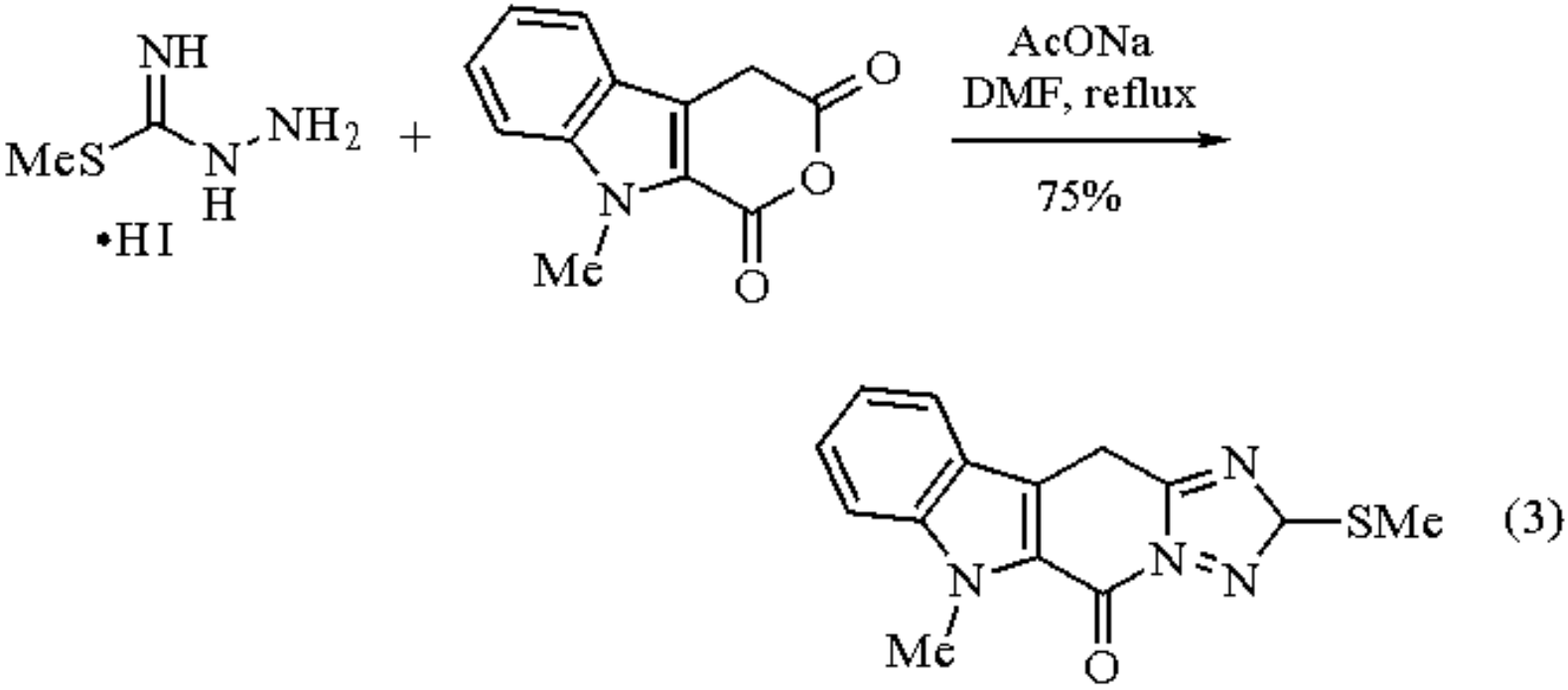

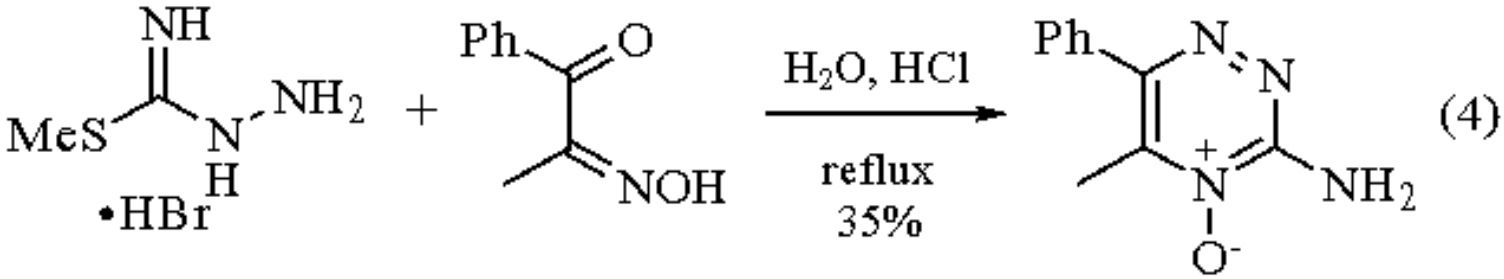

Formation of methylthiotetrazole was achieved by using the HCl salt of *S*-methylisothiosemicarbazide and potassium nitrite (eq 5).[2] Isothiocyanates also react with *S*-methylisothiosemicarbazide to give an intermediate which upon heating yielded substituted triazoles (eq 6),[8] but when the intermediate was heated in the presence of hydrochloric acid it afforded substituted thiadiazoles (eq 7).[8] Substituted guanylhydrazones can be easily prepared by condensation with aldehydes followed by aminolysis (eq 8).[3]

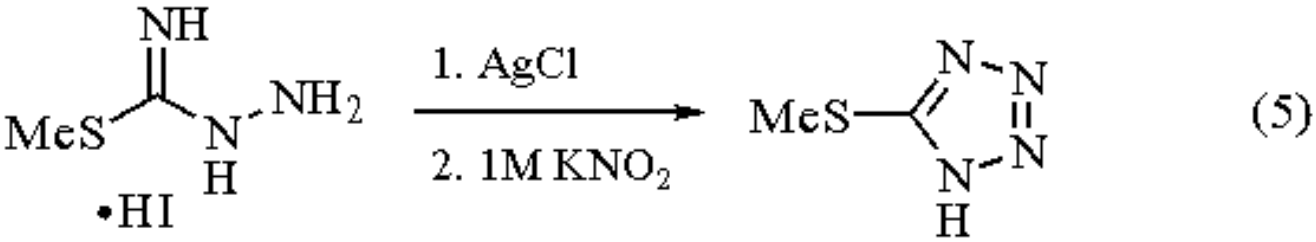

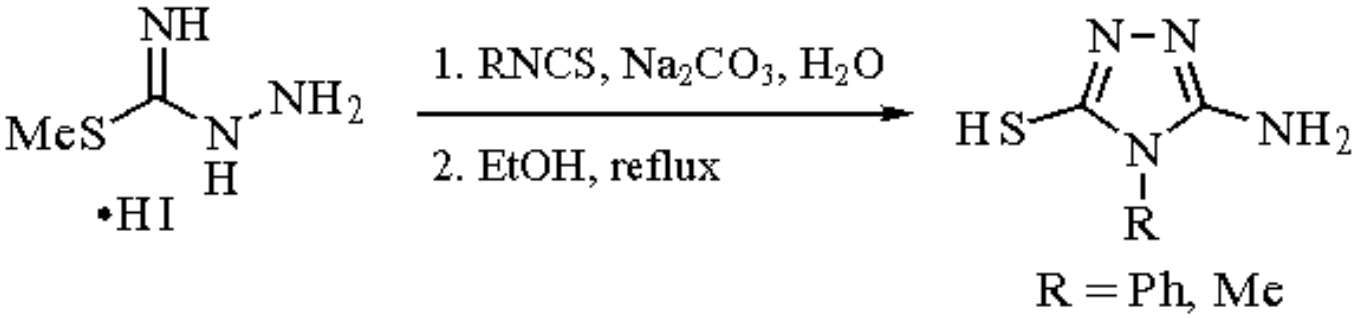

(6)

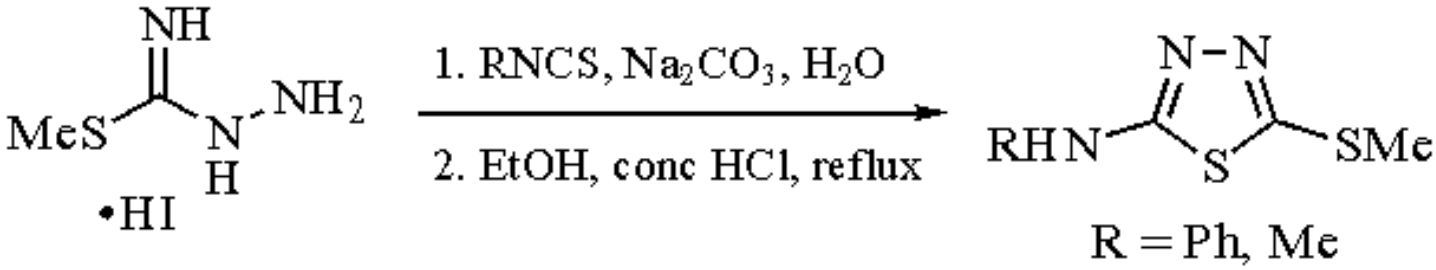

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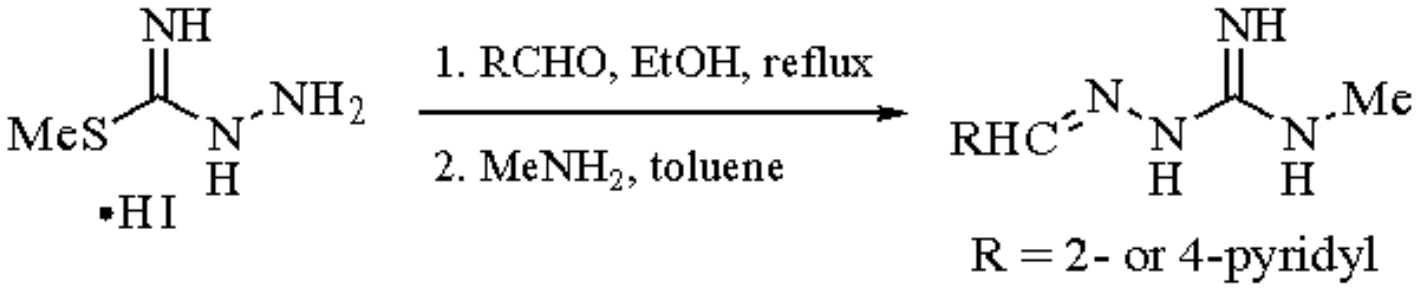

(8)

Related Reagents.

N,N-Dimethyldithiocarbamoylacetonitrile; ***Dimethylthiocarbamoyl Chloride***; ***Hydrazine***; ***Methyl Glyoxylate***; ***Semicarbazide***; ***Sodium Trithiocarbonate***; ***1,1´-Thiocarbonyldiimidazole***.

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S-Methylisothiourea

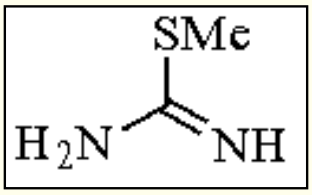

[2986-19-8] · $C_2H_6N_2S$ · *S*-Methylisothiourea · (MW 90.17)

(synthesis of heterocycles;[1] guanylation reagent;[2] source of methanethiol[3])

Physical Data: free base not isolated; sulfate salt mp 240-241 °C.

Solubility: salts sol water, methanol, ethanol.

Form Supplied in: commercially available as 2-methyl-2-thiopseudourea sulfate *[867-44-7]* (MW 278.37).

Preparative Methods: both *S*-methylisothiourea sulfate[4] and *S*-ethylisothiourea hydrobromide[5] can be readily synthesized.

Handling, Storage, and Precautions: salts are toxic; when heated to decomposition, salts emit toxic fumes of SO_x and NO_x. *S*-Ethylisothiourea hydrogen sulfate reacts with Cl_2 to produce nitrogen trichloride (***Trichloramine***), a dangerous explosive.[6] Use in a fume hood.

Heterocycle Synthesis.

One of the most widely used syntheses of pyrimidines involves condensation of *S*-methylisothiourea with various 1,3-bis electrophilic compounds including β-dialdehydes, β-keto aldehydes, β-diketones, β-aldehydo esters, β-keto esters, malonic esters, β-alkoxy-α,β-unsaturated malonates, cyanoacetates, and malonitriles.[1b,7] The ease of formation of six-membered rings is evidenced in the reaction of ethyl 4-bromoacetoacetate with *S*-methylisothiourea which led only to the pyrimidine, albeit in low yield,[8a] whereas base-catalyzed condensation of phenacyl bromide with *S*-benzylisothiourea afforded only the expected 2-benzylthio-4-phenylimidazole (eq 1).[8b]

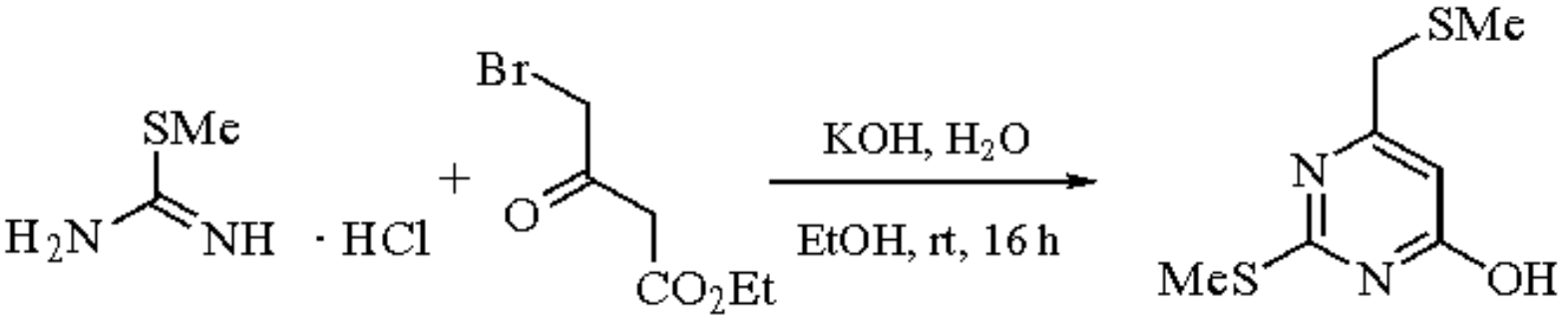

(1)

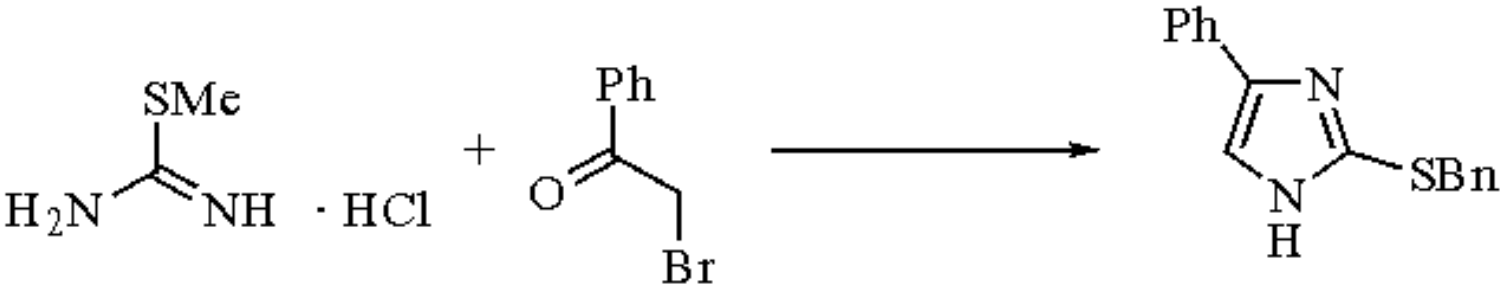

Synthesis of 2-substituted 5-acylpyrimidines is achieved using *S*-methylisothiourea hydroiodide and ethoxymethylene-β-diketones, with unsymmetrical 1,3-diketones yielding regioisomeric pyrimidines (eq 2).[9] Triformylmethane reacts with *S*-methylisothiourea to give 2-methylmercapto-5-formylpyrimidine in 33% yield,[10] whereas use of a 2-iminovinamidinium salt yields this compound quantitatively.[11] With equimolar amounts of triacetylmethane and *S*-methylisothiourea, the expected pyrimidine was not formed.[12] Instead, a triazine was isolated which was postulated to arise from condensation of 2 equiv of the isothiourea with the triketone via a biguanidine intermediate (eq 3).

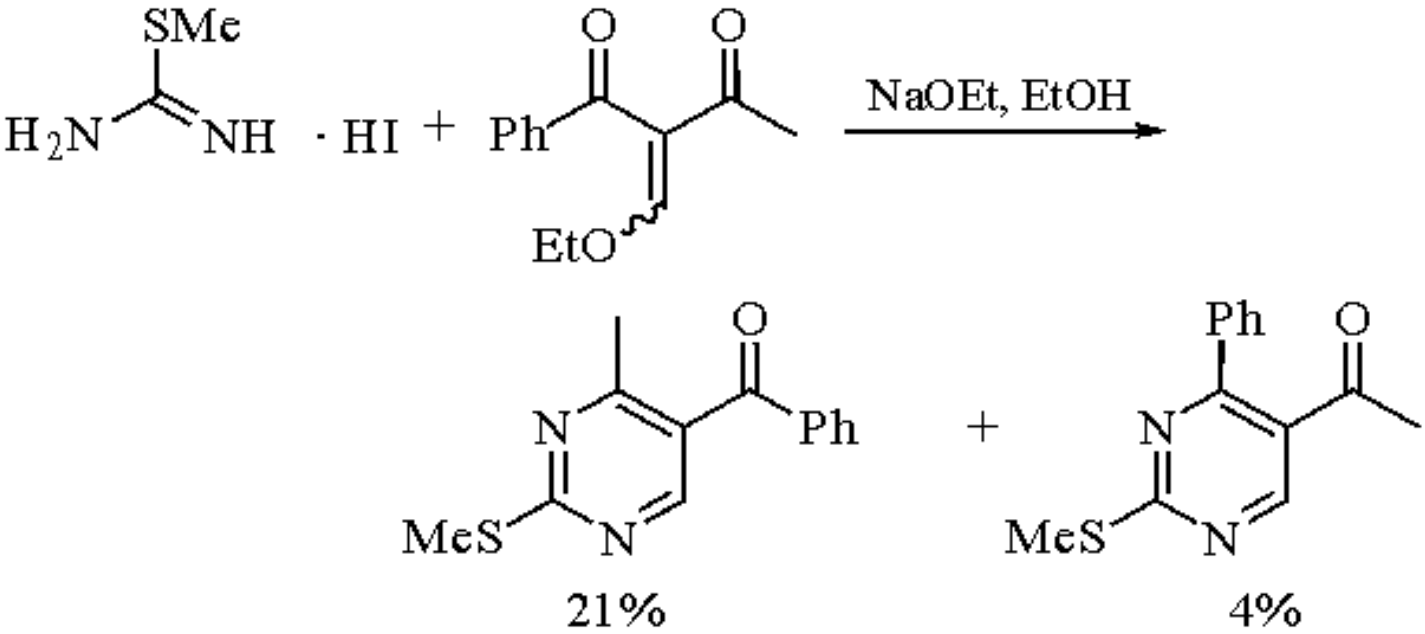

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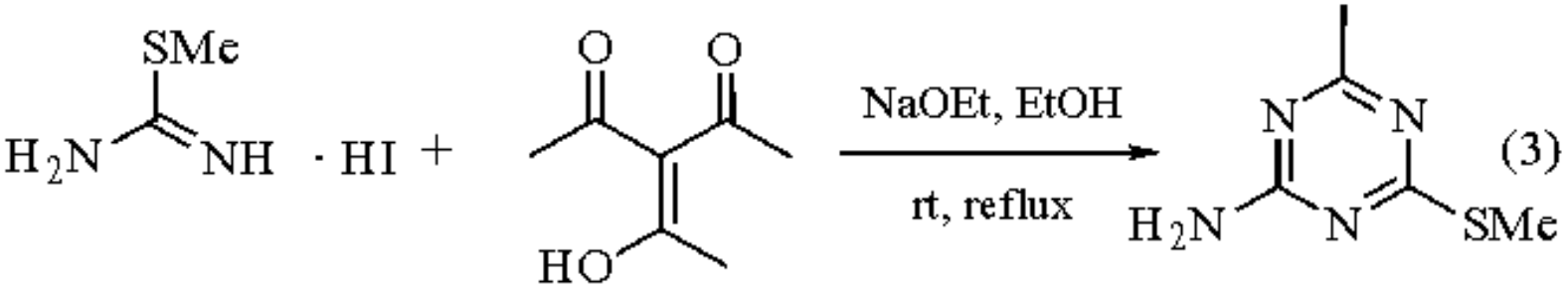

Triarylpyrylium salts react with *S*-methylisothiourea to yield 2-methylmercapto-4,6-diarylpyrimidines.[13] A convenient synthesis of *trans*-5,6-diphenyl-5,6-dihydrouracils involves condensation of *S*-methylisothiourea with diphenylcyclopropenone followed by hydrolysis. Although both *cis* and *trans* isomers were detected in the crude reaction mixture, prolonged reaction times in the basic medium afforded only the thermodynamic product.[14]

A new synthesis of 1,3,5-triazines involves ring opening of 2-aroylimino-1,3-thiazetidines with *S*-methylisothiourea, cyclodehydration, and subsequent loss of thioformaldehyde (eq 4).[15]

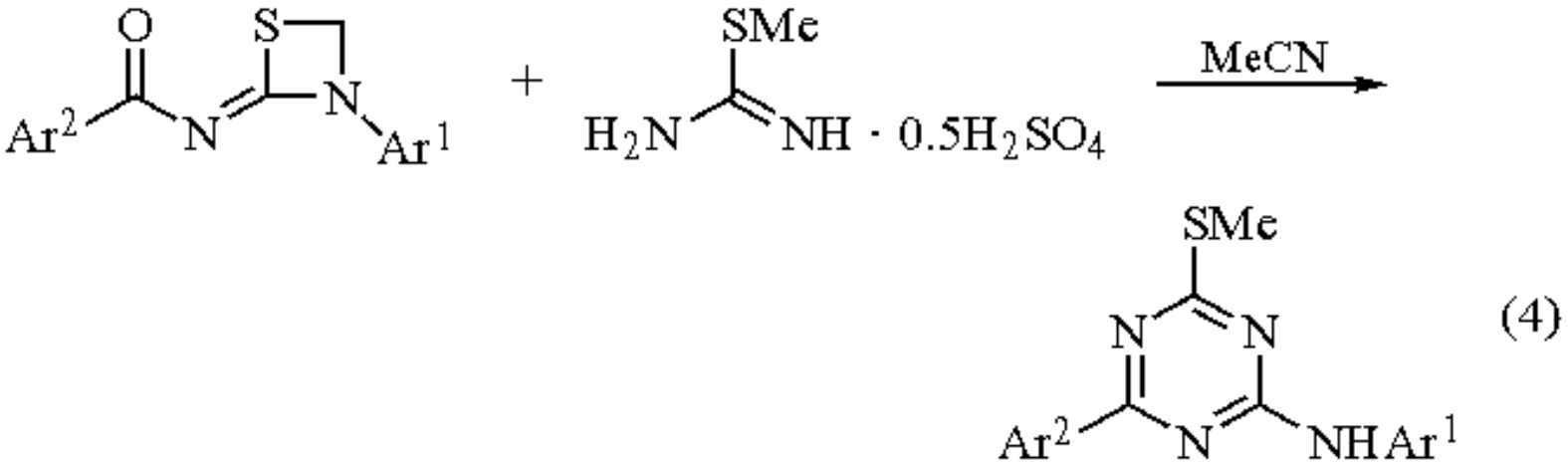

A series of 5,6-dihydro-3-methylthio-4*H*-1,2,4-thiadiazine 1,1-dioxides have been prepared from *S*-methylisothiourea and 2-chloroethanesulfonyl chloride derivatives.[16] Reaction of an alkyl chloroformate with *S*-methylisothiourea gives either the mono- or di-*N*-alkoxycarbonyl derivative,[17] while reaction with chloromethanesulfonyl chloride affords the corresponding sulfonamide,[18] all useful intermediates for synthesis of a variety of heterocycles.

Guanylation Reagent.

The Rathke synthesis of guanidines using *S*-methylisothiourea is one of the oldest and most common methods available.[2] Selective reactions of primary vs. secondary amines with this reagent are possible,[19] while selectivity between primary amines and anilines has also been described.[20] Nitration of *S*-methylisothiourea gives the mono-*N*-nitro derivative in high yield, a useful reagent for direct preparation of *N*-nitro-protected guanidines, as well as in solid-phase peptide synthesis (SPPS).[21] N^G-Methyl-L-arginine has been prepared using *S*-methylisothiourea.[22] A series of *N*,*N*,*N*′-trialkylguanidines have been prepared from *N*-monoalkyl-*S*-methylisothioureas and secondary amines.[23] 1*H*-Pyrazole-1-carboxamidine hydrochloride has been reported as an alternative guanylating agent to *O*-methylisourea, *S*-methylisothiourea, or commercially available 1-guanyl-3,5-dimethylpyrazole nitrate for use in SPPS.[24] None of these reagents was sufficiently reactive for generalized use in SPPS, although 1-guanyl-3,5-dimethylpyrazole is superior to *S*-methylisothiourea for synthesis of some guanidines.[25]

Direct introduction of di-Boc-protected guanidine moieties during the total synthesis of racemic 15-deoxyspergualin[26] and caracasanamide[27] was achieved with *N*,*N*´-bis(*t*-butoxycarbonyl)-*S*-methylisothiourea, itself readily prepared from *S*-methylisothiourea and ***Di-t-butyl Dicarbonate***. Analogously, *N*,*N*´-bis(benzyloxycarbonyl)-*S*-methylisothiourea, available from *S*-methylisothiourea and ***Benzyl Chloroformate***, has been used in the synthesis of both L- and D-*C*-α-methylarginine.[28] Guanylation of the tridentate copper complexes of *erythro*- and *threo*-2-hydroxy-L-ornithine with *S*-methylisothiourea gave the (3*S*)- and (3*R*)-L-arginines in good yield. *O*-Methylisourea tosylate was not as efficient in this conversion.[29]

Source of Methanethiol.

A mild method for generating methanethiol involves warming an aqueous solution of *S*-methylisothiourea sulfate with 5N NaOH and trapping the liberated thiol as the sodium salt with sodium ethoxide.[3]

Related Reagents.

Acetoxime O-(2,4,6-trimethylphenyl)sulfonate; ***Cyanogen Bromide***; ***Diphenyl Cyanocarbonimidate***; ***Formamidine Acetate***; ***Guanidine***; ***O-Methylisourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

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O-Methylisourea[1]

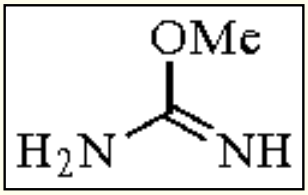

[2440-60-0] · $C_2H_6N_2O$ · *O*-Methylisourea · (MW 74.10)

(synthesis of heterocycles;[2] guanylation reagent;[3] selective alkylating agent[4])

Physical Data: mp 44-45 °C; bp 82 °C/9 mmHg; pK_a 9.9 (25 °C).

Solubility: free base readily sol most organic solvents. Salts sol water, methanol, ethanol.

Form Supplied in: commercially available as *O*-methylisourea hydrogen sulfate *[29427-58-5]* (MW 172.16) or *O*-methylisourea sulfate *[52328-05-9]* (MW 246.24).

Preparative Methods: O-methylisourea hydrochloride is prepared in 69-80% yield by adding 1.15 equiv HCl(g) with ice cooling to cyanamide dissolved in excess anhydrous methanol. The free base is obtained from the salt using powdered KOH in a water-ether mixture or with sodium methoxide in methanol.[5] The monoacetate salt can be prepared from the free base with 1 equiv of HOAc.[6] *Drying:* vacuum desiccator over P_2O_5.

Handling, Storage, and Precautions: salts are hygroscopic and should be stored in a desiccator even for brief periods. Heating *O*-methylisourea to decomposition can liberate toxic fumes of NO_x. Use in a fume hood.

Heterocycle Synthesis.

O-Methylisourea has been used to prepare a variety of substituted pyrimidines by condensation with β-diketones.[7] Interestingly, if the condensation is conducted at rt with 30% aqueous K_2CO_3, the 2-methoxy analogs are isolated in good yield (eq 1), whereas reactions performed in refluxing ethanol afforded the 2-hydroxy derivatives directly (eq 2). An attractive synthesis of uracils, which obviates problems encountered using thiourea or an alkylisothiourea, involves condensation of *O*-methylisourea with a β-keto ester in aqueous ethanol. The resulting 2-methoxy-6-alkyl- or 2-methoxy-5,6-dialkyl-4(3*H*)-pyrimidinone is smoothly hydrolyzed to the corresponding uracil with dilute acid.[8]

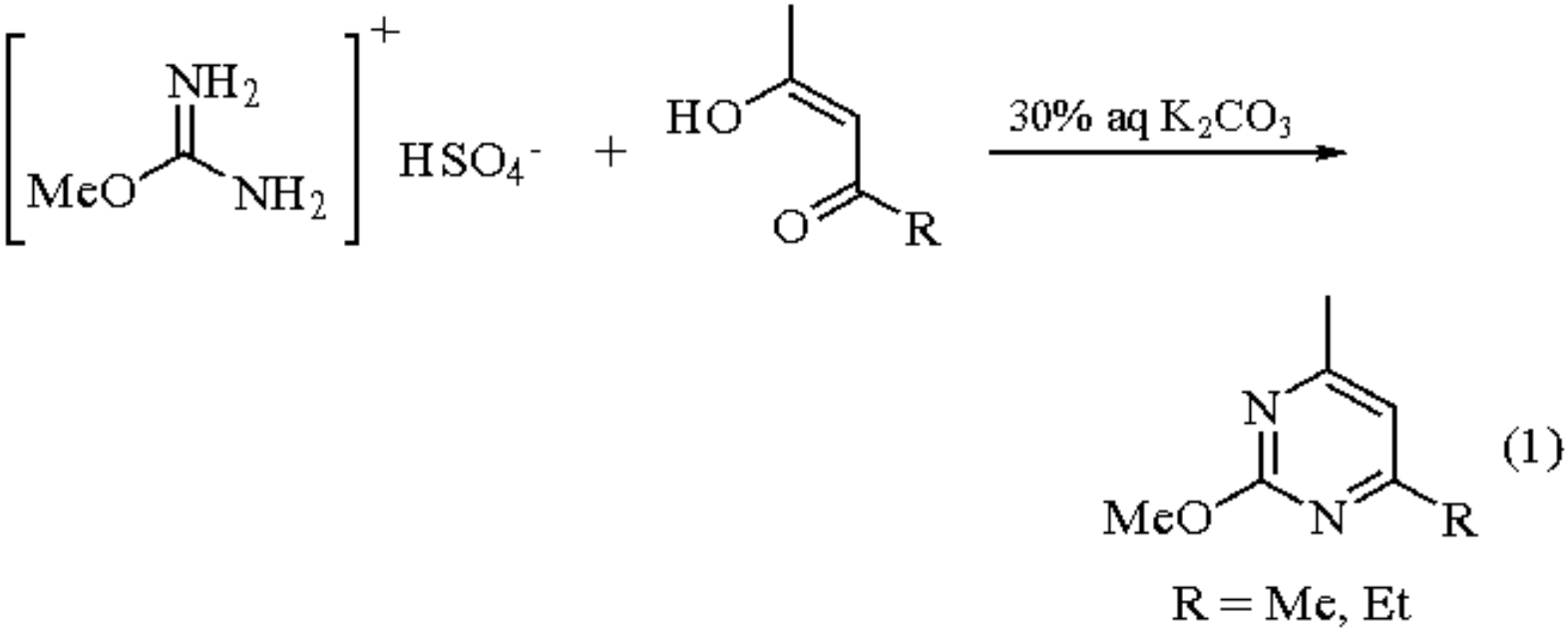

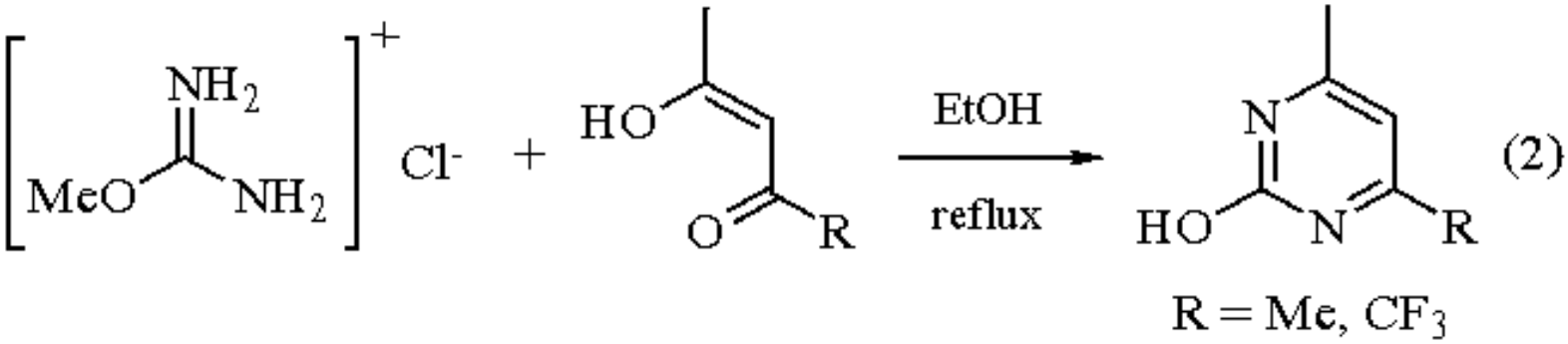

Conjugate addition of *O*-methylisourea hydrogen sulfate to a preformed α-alkylidene-β-keto ester, subsequent cyclization, and acid hydrolysis affords 1,2,3,4-tetrahydro-6-methyl-2-oxo-5-pyrimidinecarboxylic acid esters, thus providing an attractive alternative to the Biginelli condensation (eq 3).[9a] Mixtures of both 1,4- and 1,2-dihydropyrimidines are obtained. Substitution of an alkylisothiourea affords the 2-thioxo derivatives after hydrolysis.[9b] Selective functionalization of the pyrimidine N-3 nitrogen with a variety of electrophiles, an otherwise difficult transformation, is possible using the 1,4-dihydropyrimidine.[9c]

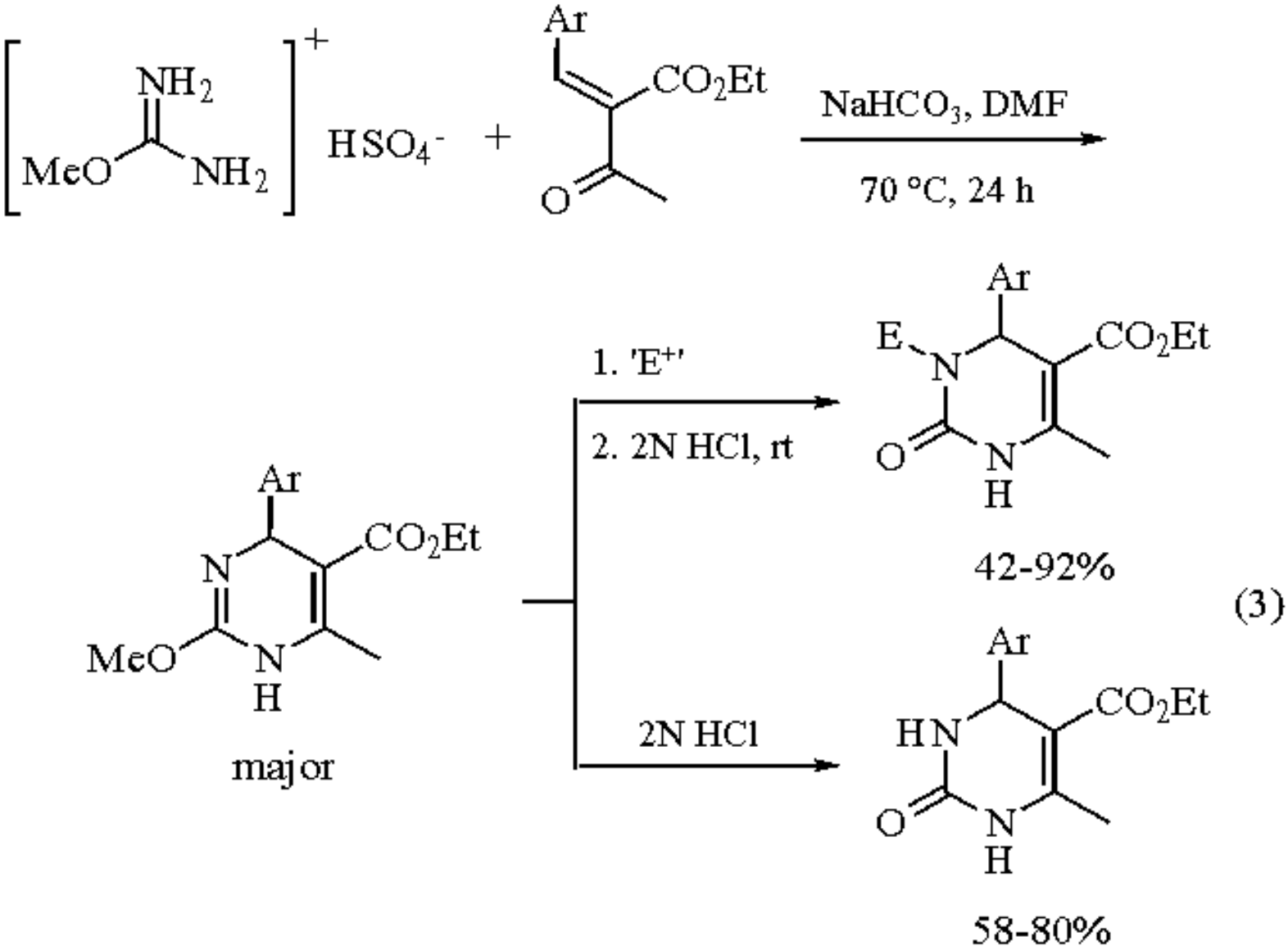

(3)

A general synthesis of 2-substituted 5-formylpyrimidines from 2-iminovinamidinium salts and a variety of amidines including *O*-methylisourea has been described.[10] Cyclization of an unsaturated β-keto ester with *O*-methylisourea afforded a 1,4-dihydropyrimidine ester which was smoothly converted to the acyl portion of the bicyclic guanidine alkaloids crambine A and crambine B. Attempts to incorporate the guanidine moiety directly using guanidine itself were uniformly unsuccessful.[11] Oxidation of *O*-methylisourea *p*-toluenesulfonate[12] in a Graham reaction[13] generated bromomethoxydiazirine, a precursor to fluoromethoxycarbene.[14] Reaction of *O*-ethylisourea with ***Methyl Chloroformate*** followed by *o*-phenylenediamine produced 2-aminobenzimidazoles protected as the methylurethane.[15]

Guanylation Reagent.

Guanylation of primary and secondary aliphatic amines has been accomplished in good to excellent yields using *O*-methylisourea sulfate.[16] Diamines yield the analogous bis-guanidines, while amino alcohols produce hydroxy guanidines. Reaction of ornithine[17] and lysine[18] containing peptides with *O*-methylisourea sulfate at pH 10-11 smoothly generates the arginine and homoarginine analogs without guanylation of the *N*-terminus.[19] Incorporation of C-13 labels into homoarginine-containing derivatives of cytochrome *c* was accomplished using ^{13}C-labeled *O*-

methylisourea.[20]

Alkylating Agent.

Methylation of the SH group of mercaptoethanol can be achieved using *O*-methylisourea at pH 8.5. Functionalized side chains of simple amino acids such as arginine, aspartic acid, histidine, methionine, glutamine, and serine do not react under these conditions, although some guanylation of the N-terminal amino group was observed.[4] Selective methylation of the cysteine residues, with subsequent inactivation of papain, has been reported based on these observations.[21] When *O*-methylisourea was heated with 2 equiv KI, methyl iodide was obtained in excellent yield.[22]

Related Reagents.

Aminoiminomethanesulfonic Acid; ***Cyanogen Bromide***; ***Diphenyl Cyanocarbonimidate***; ***Formamidine Acetate***; ***Guanidine***; ***S-Methylisothiourea***; ***1H-Pyrazole-1-carboxamidine Hydrochloride***.

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Methylketene Bis(trimethylsilyl) Acetal

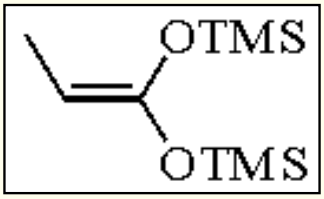

[31469-22-4] · $C_9H_{22}O_2Si_2$ · Methylketene Bis(trimethylsilyl) Acetal · (MW 218.44)

(reactive nucleophile in Mukaiyama-type aldol reactions;[1,2] additions to imines[7] and enones;[8] alkylations with α-halo sulfides;[9] α-hydroxylations[10])

Alternate Name: 1,1-bis(trimethylsilyloxy)propene.

Physical Data: bp 63-68 °C/12 mmHg.

Solubility: highly sol organic solvents.

Preparative Methods: ketene bis(trialkylsilyl) acetals are prepared by silylation of lithium trialkylsilyl carboxylates or treatment of the dianions of carboxylic acids with ***Chlorotrimethylsilane*** at -78 °C (eq 1).[3] Alternatively, silyl carboxylates are silylated by trialkylsilyl triflates in the presence of ***Triethylamine***.[4]

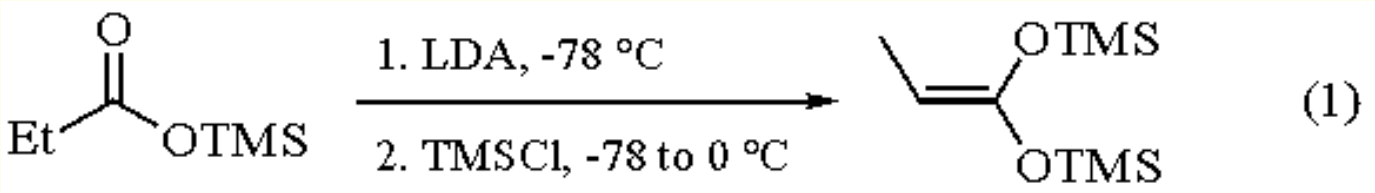

Handling, Storage, and Precautions: easily hydrolyzed and oxidized by exposure to air. Storage possible in sealed tubes at rt.

Additions to Aldehydes.

Dubois and co-workers examined the stereochemistry of the Lewis acid-catalyzed Mukaiyama aldol condensation of ketene bis(trimethylsilyl) acetals.[5] Mainly the *anti*-hydroxy acid is obtained from methylketene bis(trimethylsilyl) acetal, benzaldehyde, and ***Titanium(IV) Chloride*** (eq 2). With increasing size of the alkyl substituent on the ketene, the *syn* isomer predominates. Fluoride anion also serves as a catalyst, providing predominantly *syn* product (eq 2).[6]

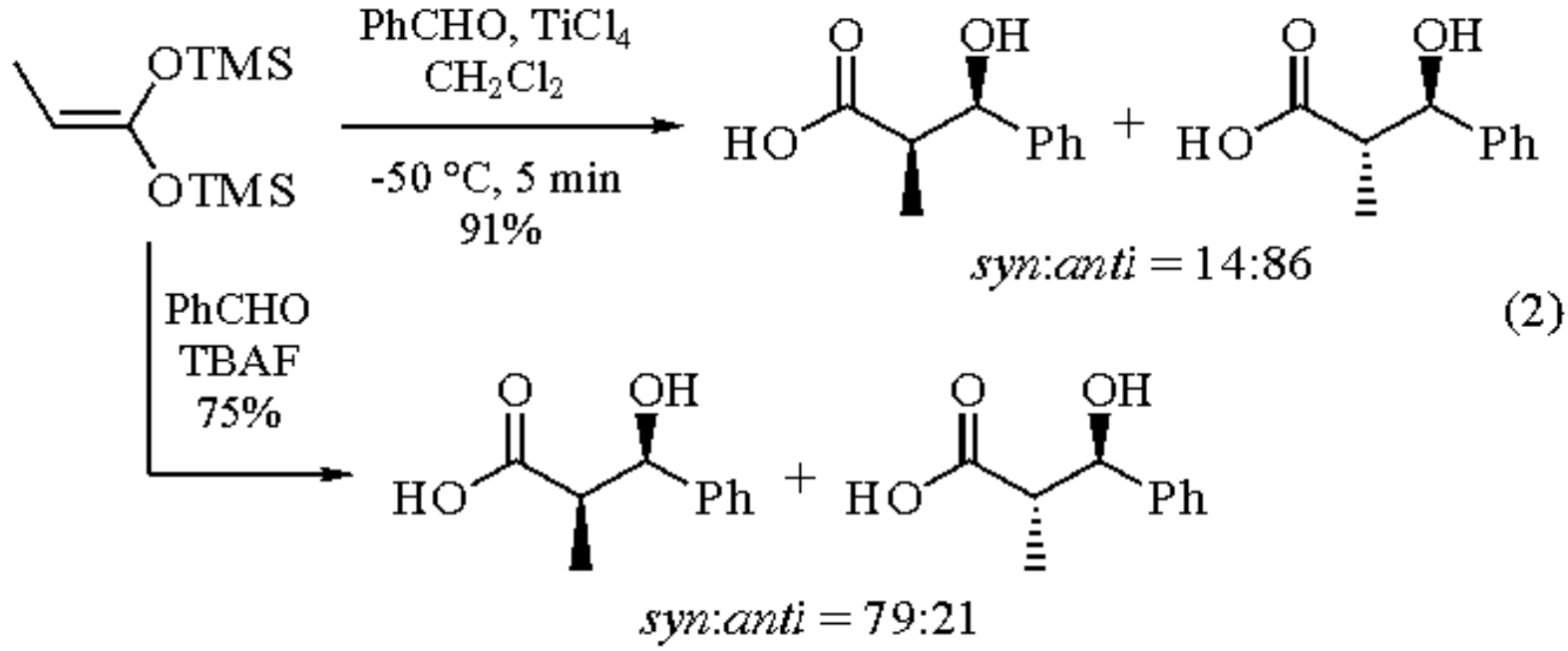

Additions to Imines.

A diastereoselective synthesis of β-amino esters by $TiCl_4$-mediated reaction of *N*-tosylaldimines with ketene bis(trimethylsilyl) acetals was realized (eq 3).[7]

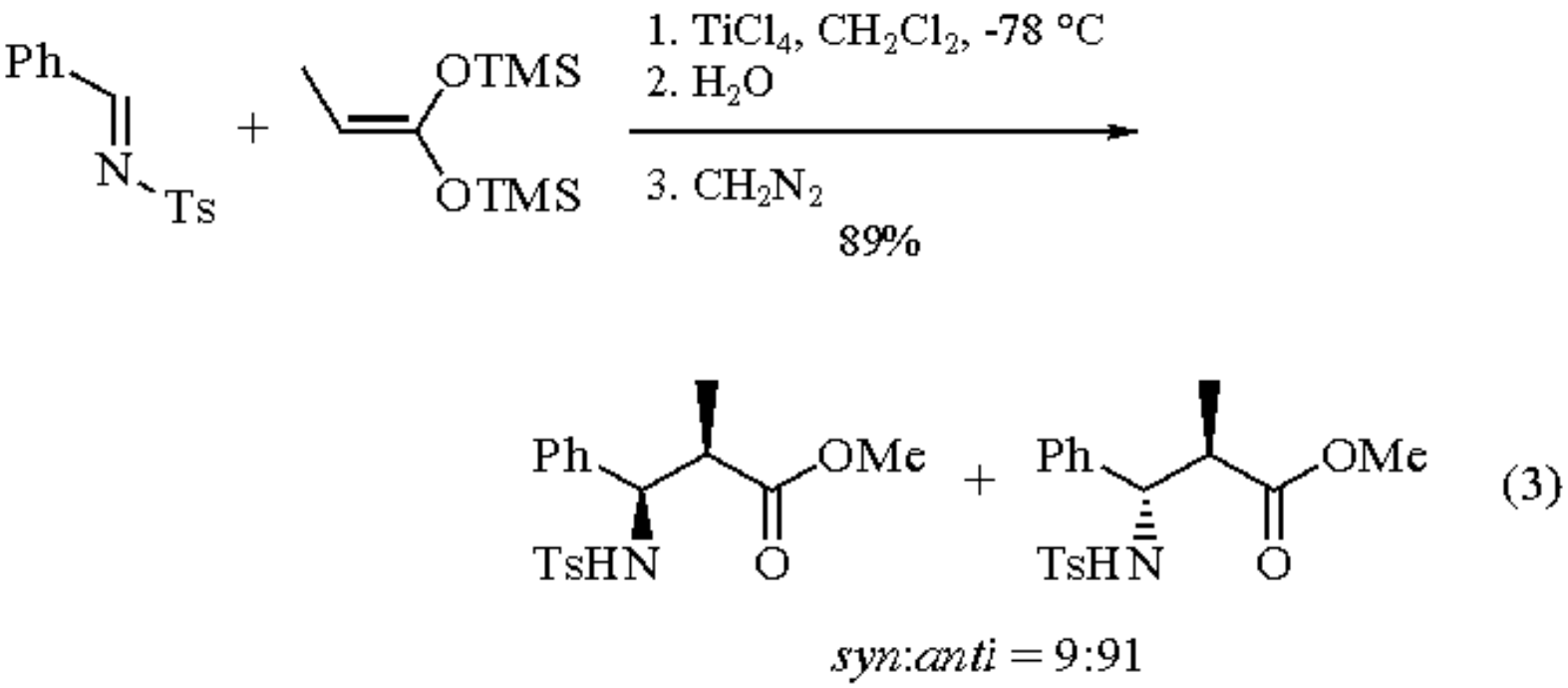

Alkylation by α-Halo Sulfides.

The ***Zinc Bromide***-catalyzed phenylthioalkylation of methylketene bis(trimethylsilyl) acetal with α-chloro sulfides provides phenylthiolactones which can be converted to α,β-unsaturated γ- and δ-lactones (eq 4).[9]

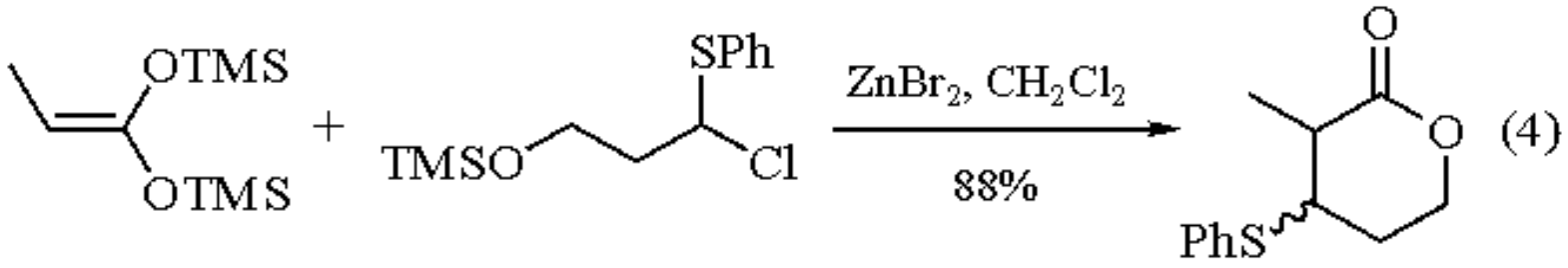

Additions to α,β-Unsaturated Carbonyl Compounds.

The regio- and stereoselectivity of $TiCl_4$-catalyzed 1,2- and 1,4-additions of ketene bis(trimethylsilyl) acetals to α,β-unsaturated enones and enals were investigated by Bellassoued and Mladenova.[8]

Hydroxylations.

Treatment with peroxy acids in hexane followed by acidic workup allows isolation of α-hydroxy acids in good yields.[10] Bissilyl ketene acetals devoid of β-protons undergo a clean sigmatropic ene reaction with $^1O_2$ to generate the α-silylperoxy silyl ester quantitatively (eq 5).[11]

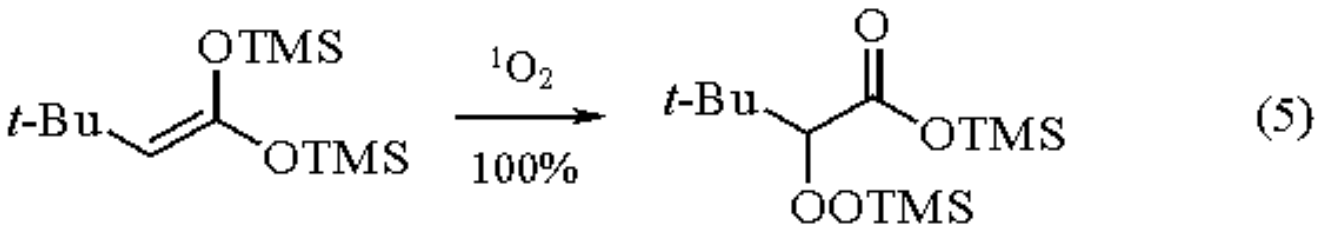

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene Diethyl Acetal***; ***1-Methoxy-2-methyl-1-(trimethylsilyloxy)propene***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Methylketene Dimethyl Acetal***; ***Tetramethoxyethylene***; ***Tris(trimethylsilyloxy)ethylene***.

---

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Methylketene Dimethyl Acetal[1]

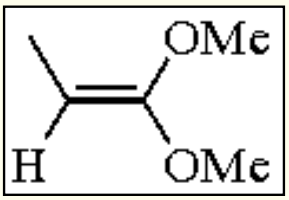

[5434-53-6] · $C_5H_{10}O_2$ · Methylketene Dimethyl Acetal · (MW 102.15)

(electron-rich alkene which can act as propionyl carbocation equivalent in reactions with electrophiles; undergoes [2 + 2] cycloadditions with electron-deficient alkenes, aldehydes, and imines; also participates in inverse Diels-Alder reactions and 1,3-dipolar cycloadditions)

Alternate Name: 1,1-dimethoxypropene.

Physical Data: bp 99 °C.

Preparative Methods: best method is from acrolein dimethyl acetal by isomerization of the double bond with potassium amide.[2] The method is also applicable for other dialkoxy analogs.

Handling, Storage, and Precautions: sensitive to moisture, especially in the presence of traces of acids. It can be stored for longer time in dry base-rinsed vessels under nitrogen.

General Reactivity.

Dimethoxypropene belongs to the class of the ketene acetals. These compounds react as strong electron-rich alkenes due to the electron-donating ability of the two alkoxy groups.

Over the years, the chemistry of the ketene acetals has been reviewed several times.[1a,c,d] Electronically symmetrical ketene acetals sometimes show different chemistry than the electronically asymmetrical ketene acetals like the 1,1-dialkoxyethylenes. In cycloadditions, the former give mostly stable cycloadducts, whereas the latter give unstable cycloadducts or products derived from dipolar intermediates. In this respect, dimethoxypropene shows an intermediate behavior.[3] Since the mid-1970s, much attention has also been paid to the alkyl trialkylsilylketene acetals. In reactions with electron-poor double bonds these compounds often yield acyclic products, whereas the dialkylketene acetals yield cycloadducts.[1c] 1,1-Dimethoxypropene has been more extensively studied since the mid-1980s due to its easy availability and because it can act as propionyl carbocation equivalent.

Acids, alcohols, and thiols react rapidly with ketene acetals, but these reactions have not been explored for synthetic purposes. The main application of 1,1-dimethoxypropene lies in the field of cycloaddition reactions.

Carbenes.

Ethyl Diazoacetate reacts with 1,1-dimethoxypropene in the presence of ***Copper(II) Acetylacetonate*** to give ethyl 2,2-dimethoxy-3-methylcyclopropane-1-carboxylate, which can be methanolized in situ to ethyl 4,4,4-trimethoxy-3-methylbutanoate (eq 1).[4]

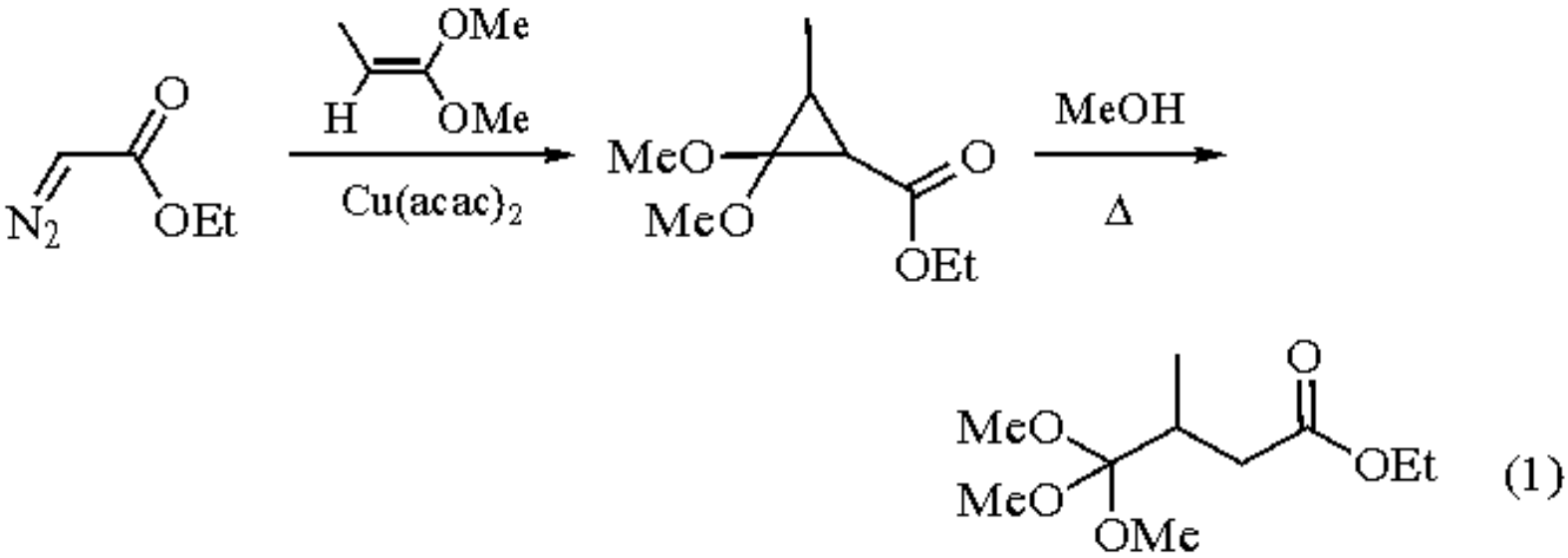

The analogous reaction with diazo ketones which was investigated for 1,1-diethoxypropene yields 2,2-diethoxy-3-methyldihydrofurans (eq 2).[5]

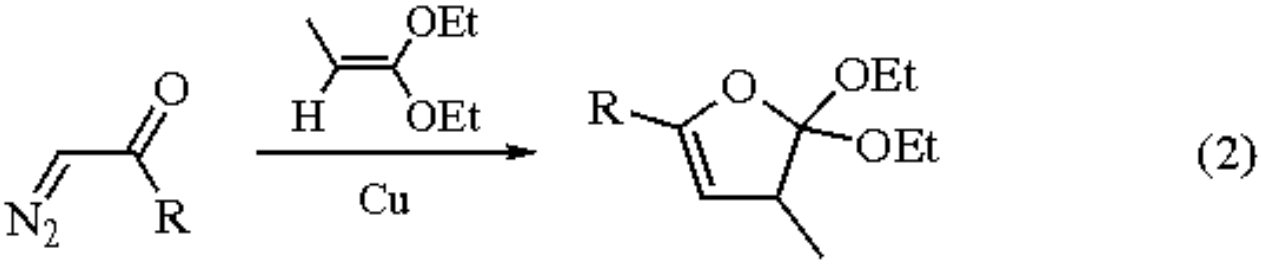

Cyclobutanes.

Electron-deficient alkenes undergo polar [2 + 2] cycloadditions with 1,1-dimethoxypropene (eq 3).[6]

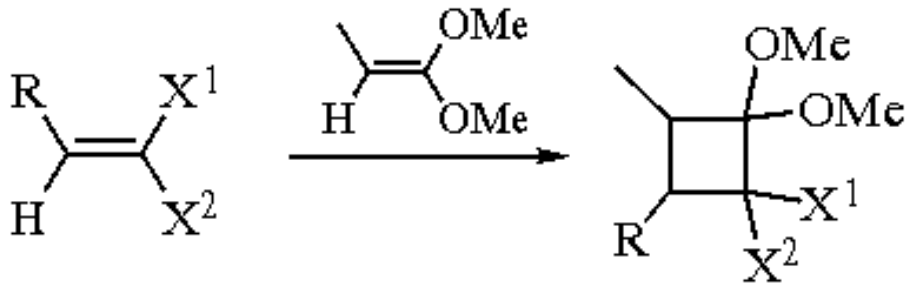

(3)

R = H, alkyl, phenyl

X^1 and/or X^2 = electron withdrawing substituent

The resulting cyclobutanes can be further hydrolyzed into cyclobutanones[7] or γ-funtionalized esters.

Oxetanes.

Carbonyl compounds having electron-withdrawing substituents add to 1,1-dimethoxypropene to give 2,2-dimethoxy-3-methyloxetanes. In the presence of Lewis acids the cycloaddition can be performed with normal aldehydes.[2]

This cycloaddition can also be achieved under high pressure without Lewis acids. The combination of Lewis acids and high pressure extends the scope of the reaction to include ketones.[8] The reaction has very high regioselectivity. Furthermore the *cis*/*trans* stereoselectivity is controlled by the reaction conditions.[9] Interestingly, the photochemical cycloaddition gives mainly the products with the reverse regiochemistry.[10,11] As reactive orthoesters, the oxetanes are easily hydrolyzed to β-hydroxy esters or methanolyzed to β-hydroxy orthoesters (eq 4).[12]

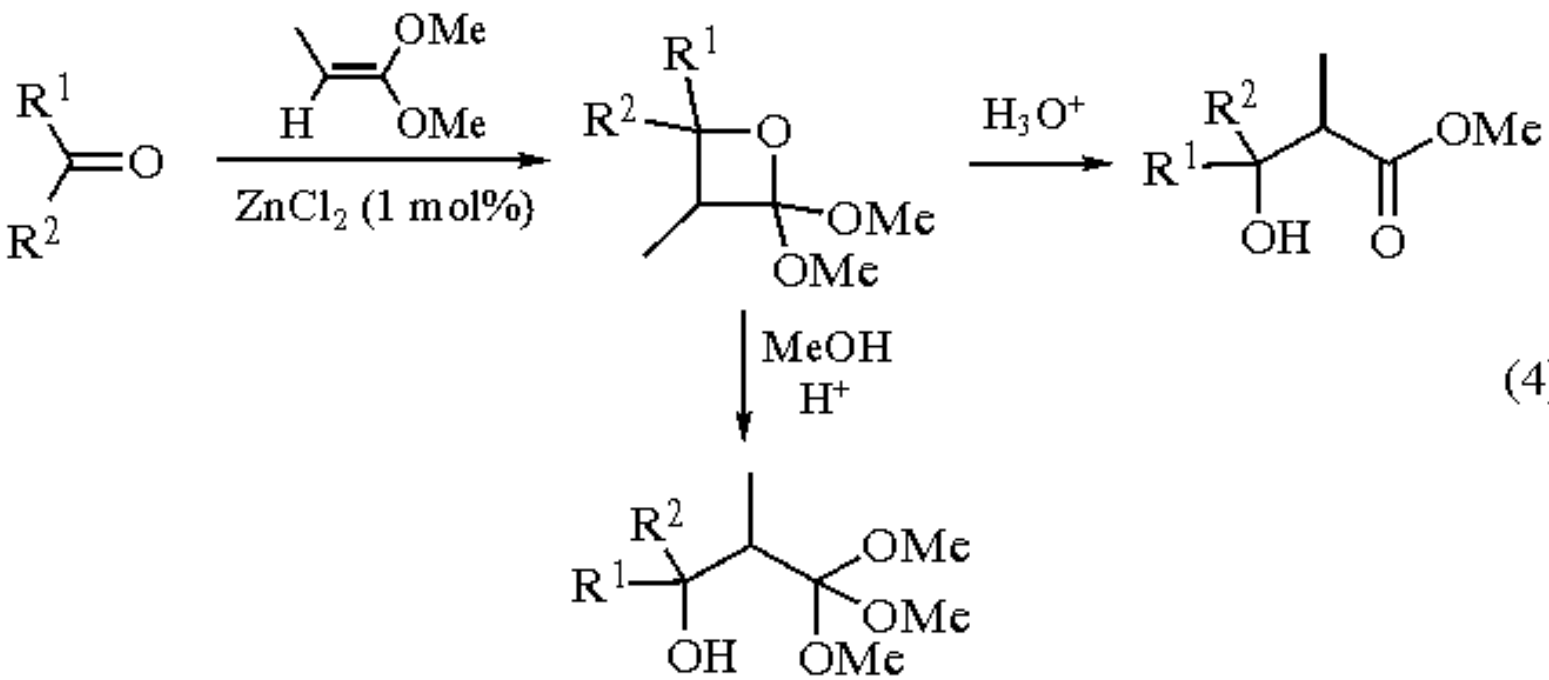

(4)

Oxetanes obtained in this way from α- or β-oxy-functionalized aldehydes or ketones are interesting precursors for the synthesis of 3-methyl-4-hydroxy-γ- or δ-lactones (eq 5).[13,14]

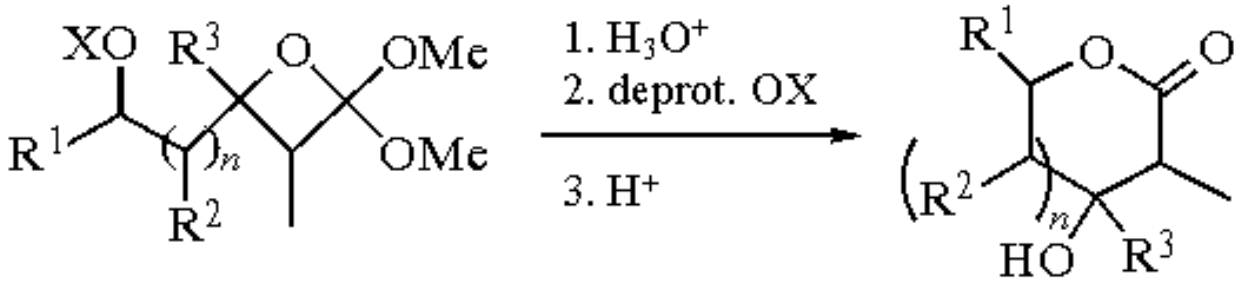

(5)

The oxetanes from α,β-epoxy aldehydes have been further converted into 4-hydroxy-5-hydroxymethyl-3-methyltetrahydrofuran-2-ones (eq 6).[15]

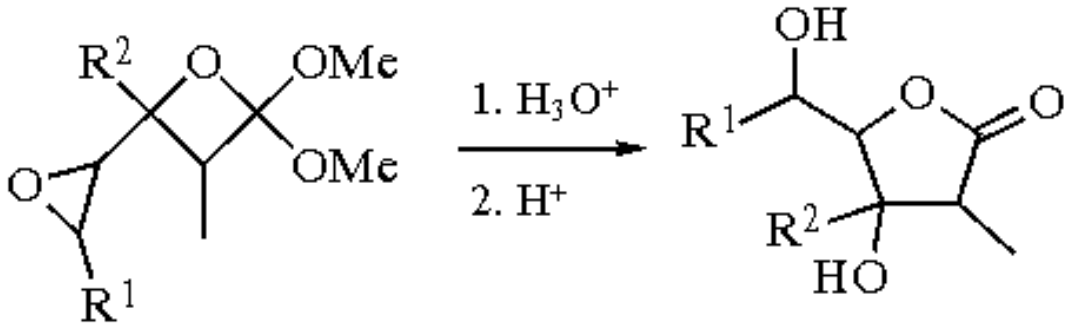

(6)

Cycloaddition reactions of α-diketones with 1,1-dimethoxypropene afford mono- and bis-oxetanes which can be further converted to bis-γ-lactones (eq 7).[16]

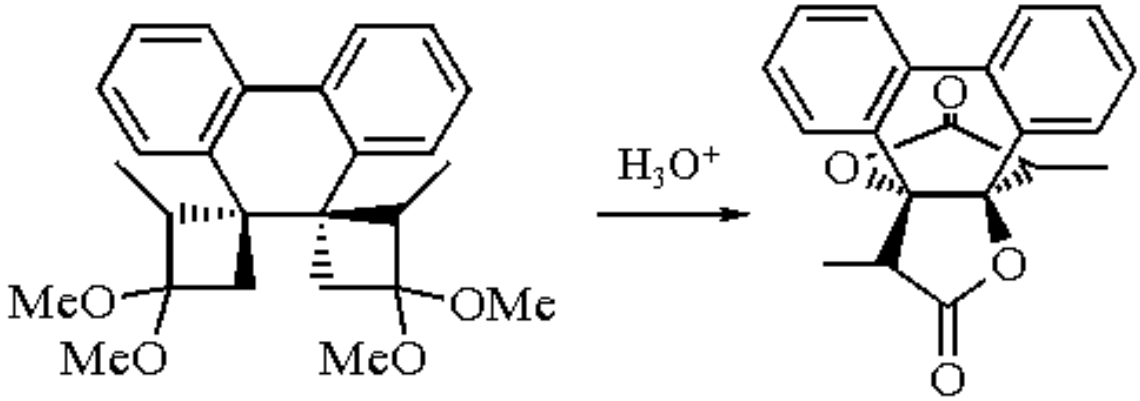

(7)

α,β-Unsaturated aldehydes undergo cycloadditions to the kinetically favored oxetanes at low temperatures in the presence of Lewis acids, whereas above rt the thermodynamically more stable 2,2-dimethoxydihydropyrans are formed (eq 8). Cyclobutanes are the main products under high pressure without Lewis acid catalyst.[17]

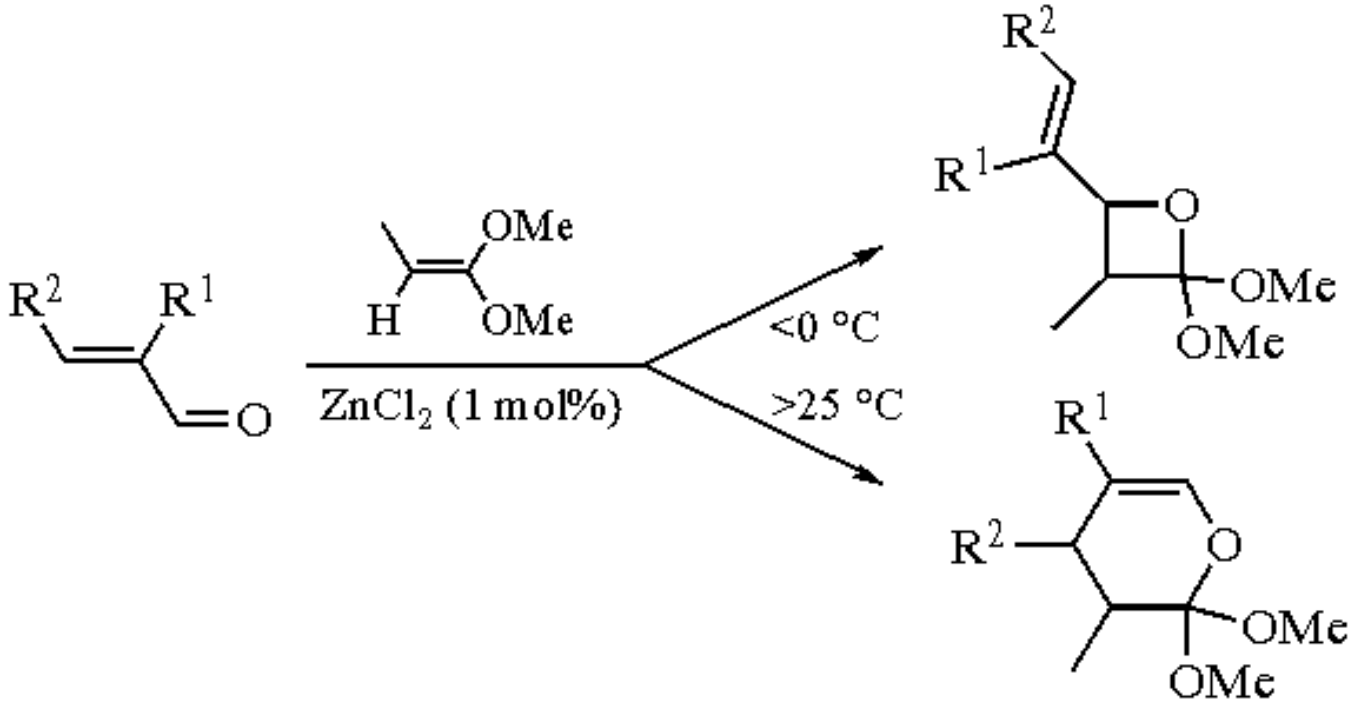

(8)

Azetidines.

Electron-deficient imines undergo [2 + 2] cycloaddition with 1,1-dimethoxypropene to give 2,2-dimethoxy-3-methylazetidines. The scope of the reaction can be extended to weakly activated imines by application of high pressure (eq 9).[18]

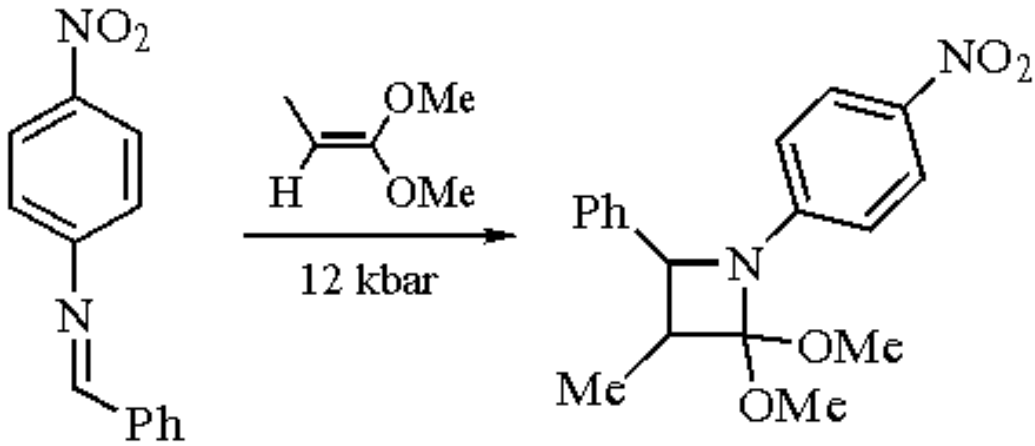

(9)

p-Chlorophenyl isocyanate affords the β-lactam 1-*p*-chlorophenyl-4,4-dimethoxy-3-methylazetidin-2-one.[19]

Benzonitrile adds photochemically to 1,1-dimethoxypropene. The cycloadduct is not stable and it reacts further by ring opening to 1,1-dimethoxy-2-aza-3-phenylpenta-1,3-diene (eq 10).[20]

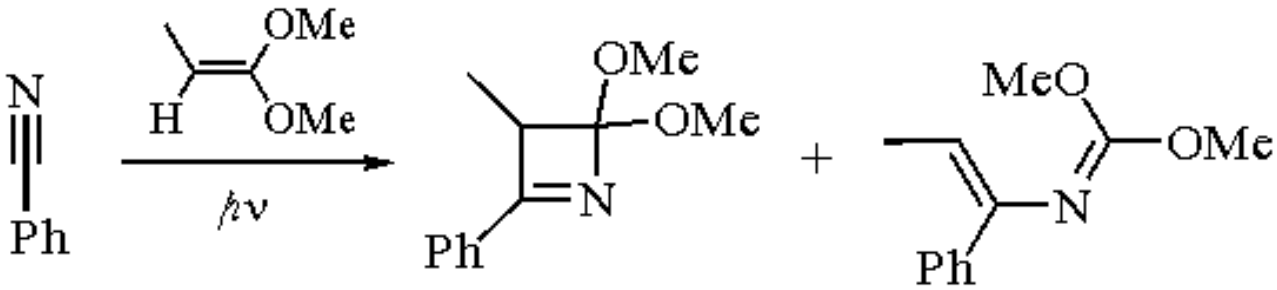

(10)

Diels-Alder Reactions.

Apart from cycloadditions with α,β-unsaturated carbonyl compounds, inverse electron-demand Diels-Alder reactions of 1,1-dimethoxypropene with electron-poor alkenes have been infrequently investigated. Only 1,1-dicyanobutadienes having a preferred cisoid conformation give Diels-Alder adducts. Transoid 1,1-dicyanobutadienes yield [2 + 2] cycloadducts. Interestingly, 5-nitropyrimidine reacts with 1,1-dimethoxypropene via an unstable Diels-Alder adduct to give 2-hydroxy-3-methyl-5-nitropyridine (eq 11).[21]

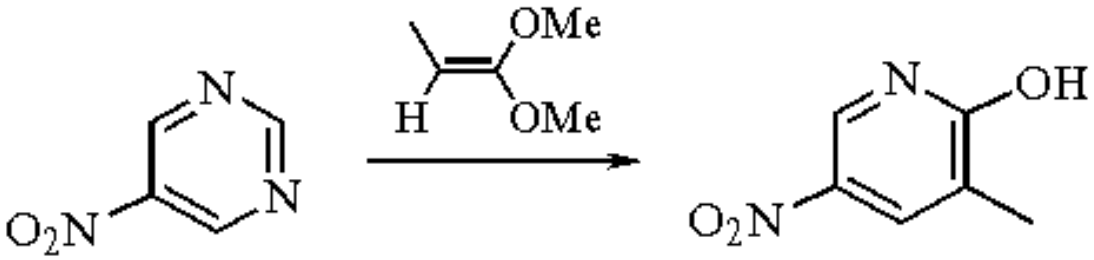

(11)

1,3-Dipolar Cycloadditions.

Most of the 1,3-dipolar cycloadditions have been studied with 1,1-dialkoxyethylenes. ***Ethyl Azidoformate*** and 1,1-dimethoxypropene form a triazoline cycloadduct at -15 °C, whereas at 35 °C ethyl *N*-(1,2-dimethoxypropylidene)carbamate is obtained.[1b,d] Three-membered ring compounds which can open up to 1,3-dipolar intermediates react with 1,1-dimethoxypropene to form five-membered cycloadducts, e.g. 2,2-dimethoxy-3-methyltetrahydrofurans from epoxides (eq 12) and 1,1-dimethoxy-2,2-dicyano-5-methylcyclopentanes from 1,1-dicyanocyclopropanes.[1c]

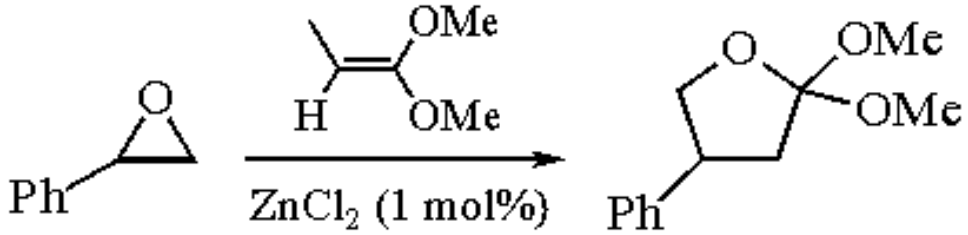

(12)

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***Ketene Diethyl Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Tetramethoxyethylene***; ***Tris(trimethylsilyloxy)ethylene***.

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Methyl Lithiodithioacetate[1]

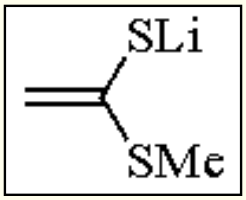

[82452-67-3] · $C_3H_5LiS_2$ · Methyl Lithiodithioacetate · (MW 112.16)

(enolate equivalent, capable of reacting as a carbon or sulfur nucleophile)

Preparative Methods: colorless solutions of the reagent are prepared by addition of ***Lithium Diisopropylamide*** to an ether or THF solution of methyl dithioacetate at -78 °C; reaction is complete in minutes.

Handling, Storage, and Precautions: solutions in THF are stable for at least 24 h at 20 °C.[2] Solutions of the closely related ethyl lithiodithioacetate are reported to decompose rapidly above 0 °C.[3]

Reaction as a Carbon Nucleophile.

Methyl lithiodithioacetate gives aldol products with simple aldehydes.[4] Selective conjugate addition is observed with enones (eq 1).[5] The unexpected *syn* selectivity in the reaction arises from internal proton transfer to produce (**1**). Similar reactions conducted in the presence of ***Chlorotitanium Triisopropoxide*** (4 equiv) give exclusively the 1,2-addition product (eq 2).[6] A variety of transformations possible for the products obtained from reactions with carbonyl compounds is described in a review article.[1]

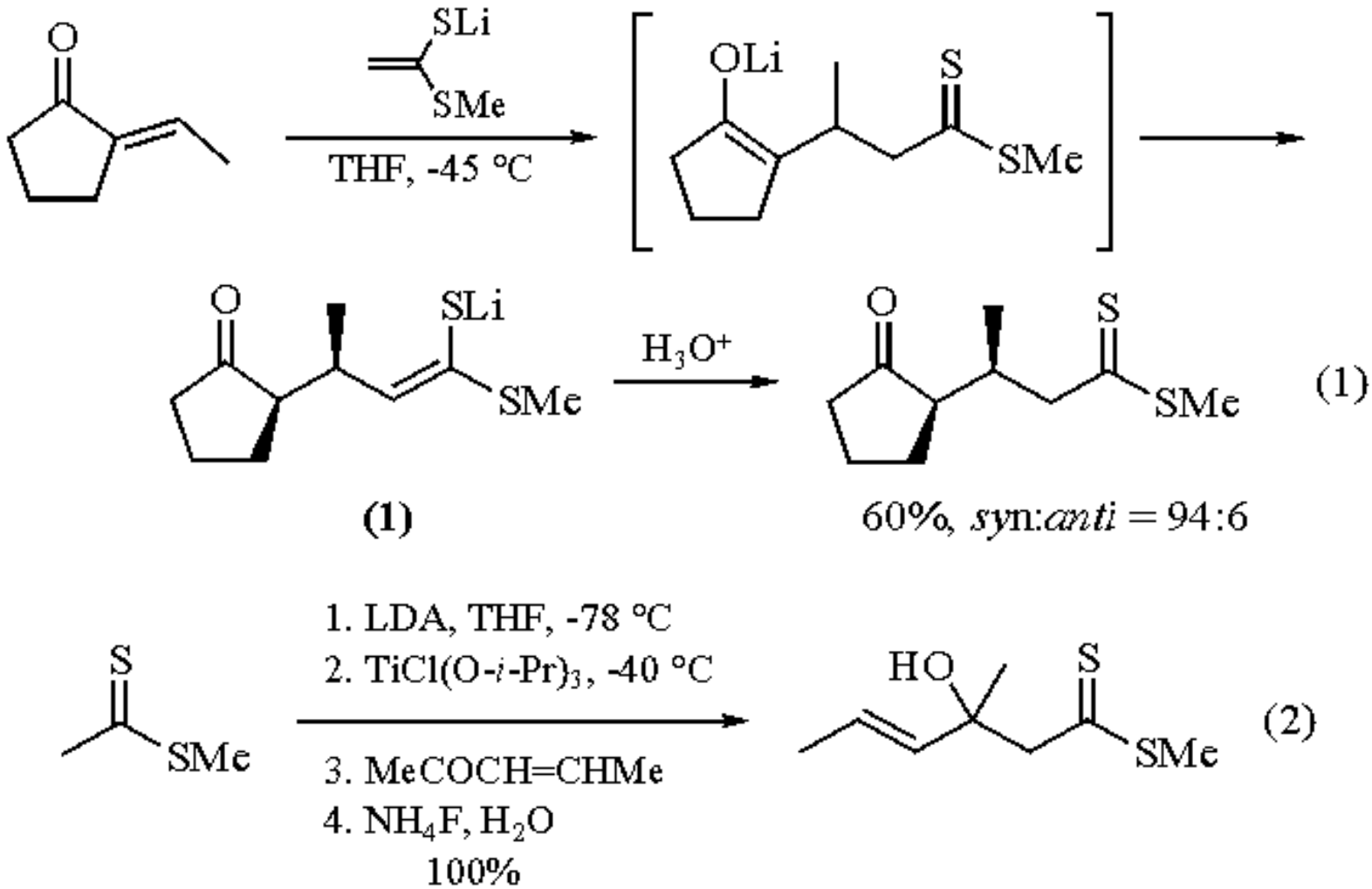

Reaction as a Sulfur Nucleophile.

Methyl lithiodithioacetate reacts exclusively as a sulfur nucleophile with a variety of alkyl halides,[7] epoxides,[8] and with ***Chlorotrimethylsilane***.[9] Presumably, *C*-allylation products can be obtained by the thio-Claisen rearrangement, examined in detail with aldol products derived from methyl lithiodithioacetate.[4]

Related Reagents.

t-Butyl α-Lithioisobutyrate; ***Dilithioacetate***; ***Ethyl Bromozincacetate***; ***Ethyl Lithioacetate***.

---

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Methyllithium

MeLi

[917-54-4] · CH_3Li · Methyllithium · (MW 21.98)

(methylating agent for several functional groups; cleaves protecting groups; synthesis of other methyl organometallics, i.e. of Cu, Ga, Ti, Mg, Si, Ir, B; can function as a base; reduces transition metals)

Physical Data: unsolvated solid is pyrophoric; densities listed below.

Solubility: insol hydrocarbon solvents; moderately sol ethereal solvents; reacts exothermically with water and protic solvents to generate methane.

Form Supplied in: commonly available as >1.4 M in diethyl ether, *d* >0.732 g mL^{-1}; >1.5 M in diethyl ether (with ~1.0 equiv of LiBr), *d* >0.852 g mL^{-1}. New formulations are >1 M in THF/cumene with 0.08 M Me_2Mg,[1] *d* 0.86 g mL^{-1}; 70 wt % solid[2] complexed with 22 wt % diethyl ether, 6% LiCl, and ~1% LiOH.

Analysis of Reagent Purity: titration of 0.5 N *s*-butanol in toluene (10 mL) with methyllithium via tared syringe at 15 °C using 2,2´-biquinoline as an indicator.

Handling, Storage, and Precautions: methyllithium in diethyl ether is pyrophoric in absence of LiBr, according to US Dept of Transportation regulations (49 CFR 173, Appendix E), while all other available formulations (solution and solid) are nonpyrophoric. Store in a cool, dry place in a tightly sealed container under an inert atmosphere.

Introduction.

Most preparations involve use of diethyl ether[3] or THF[1] from which solvated solids[4,5] may be isolated. Unsolvated methyllithium[1,6] preparations would allow systematic investigation of solvent[7] and halide[8] effects. Aggregation and crystal studies have been reported.[9]

Addition Reactions.

Methyllithium can have different stereoselectivity compared to methyl Grignards in 1,2-additions to cyclic carbohydrates,[10] heterocycles,[11] and acyclic[12] substrates. The origin of the high diastereoselectivity in nucleophilic addition to ketones (eq 1) is based on chelation control.[13a] Stereoselectivity can also be affected by prior complexation of the carbonyl compound with aluminum and other Lewis acids.[13b]

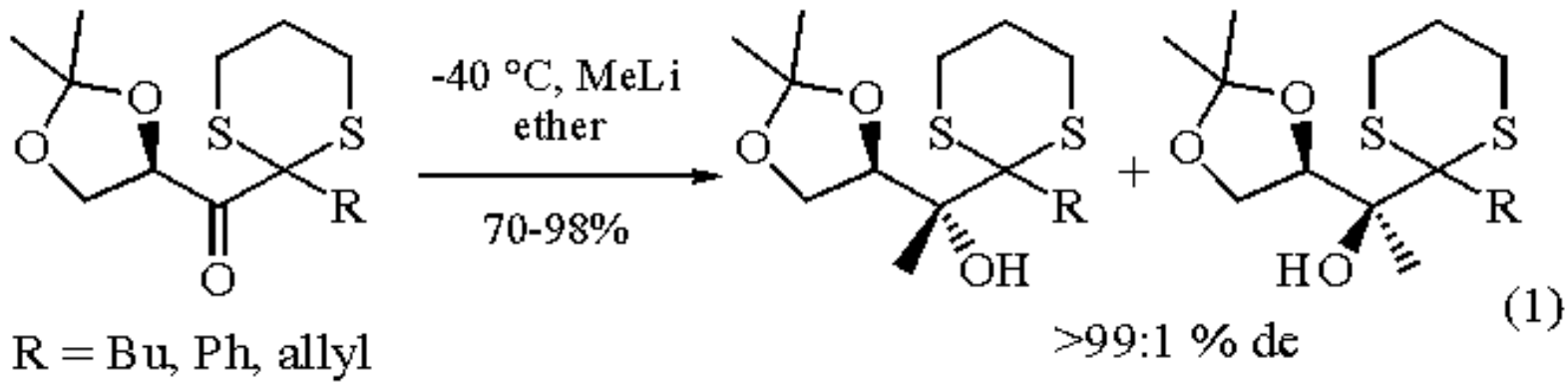

Conversion of organolithiums to organometallics of titanium,[14] cerium,[15] and zinc[16] has lead to improved chemo- and stereoselectivity. For instance, conversion of MeLi to a chiral titanate prior to 1,2-addition to benzaldehyde resulted in 91% ee (eq 2).[14a]

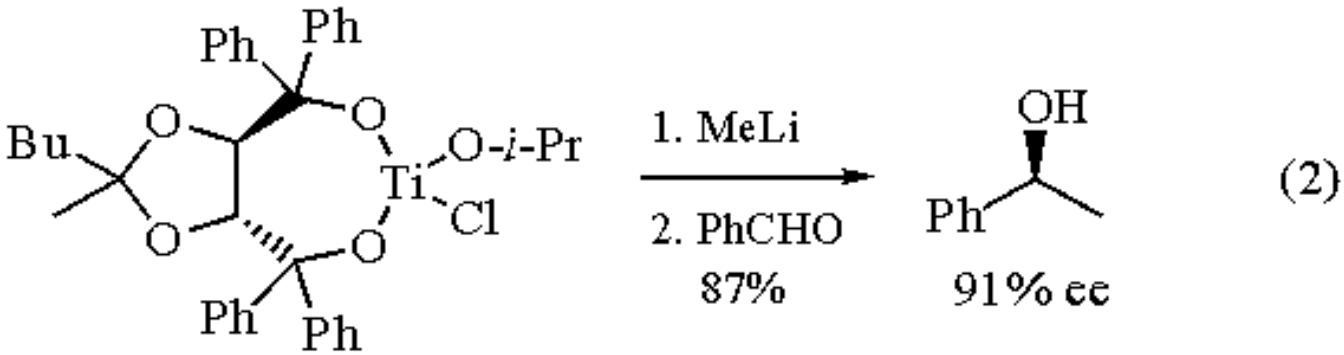

Methyl ketones can be prepared from acids[17] and esters, usually with greater success by subsequent treatment with ***Chlorotrimethylsilane***.[18,19] Methyllithium is a convenient deacylating agent for alkoxycarboxyl- and benzoyl-protected secondary hydrazides.[20] Addition of methyllithium with ***Lithium Bromide*** to silyl ketone (**1**) gave silyl enol ethers (**2**) with high stereochemical purity when warmed to 0 °C (eq 3).[21]

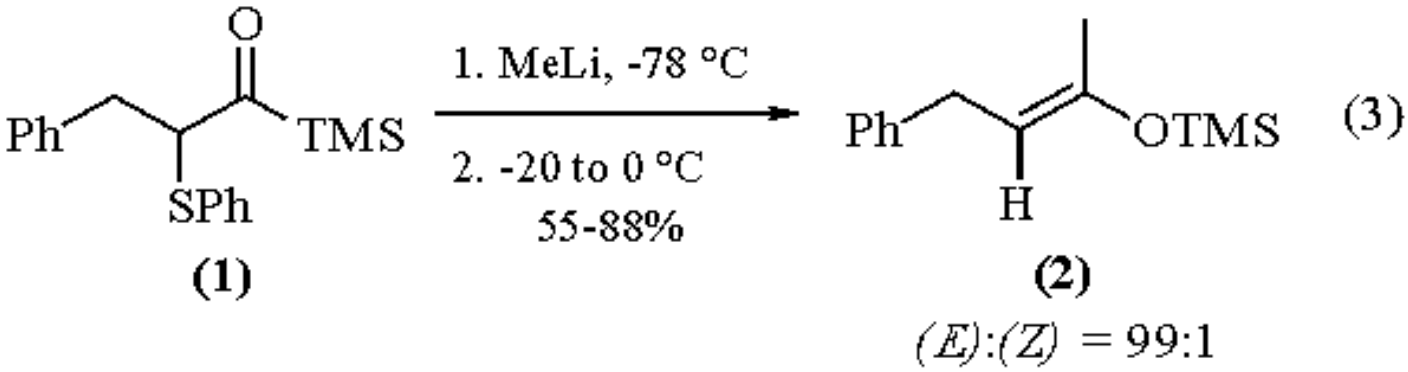

Similarly, almost quantitative yields of 2,2-difluoroenol silyl ethers were obtained from a perfluoroacylsilane.[22] Enolates, free of amine, can be prepared by cleavage of silyl enol ethers[23] and enol trifluoromethanesulfinates with methyllithium.[24]

Of 1,2-additions to carbon-nitrogen multiple bonds, nitriles, imines, and oxazolidine are the most useful substrates. For

instance, addition of methyllithium in cumene/THF to protected cyanohydrins gave excellent yield of methyl steroidal ketones after hydrolysis.[25] Addition of aryl heterocycles, such as tetrazines[26] and pyrazines,[27] are problematic.

Conjugate addition is routinely achieved by prior transformation to the corresponding cuprate[28,29] or even aluminate.[30] In absence of any co-metals, methyllithium will undergo 1,4-addition to naphthalimines[31] in the presence of ***Hexamethylphosphoric Triamide*** (eq 4). Without HMPA, methyllithium undergoes 1,2-additions to naphthalimines[31] and oxazolidines.[32]

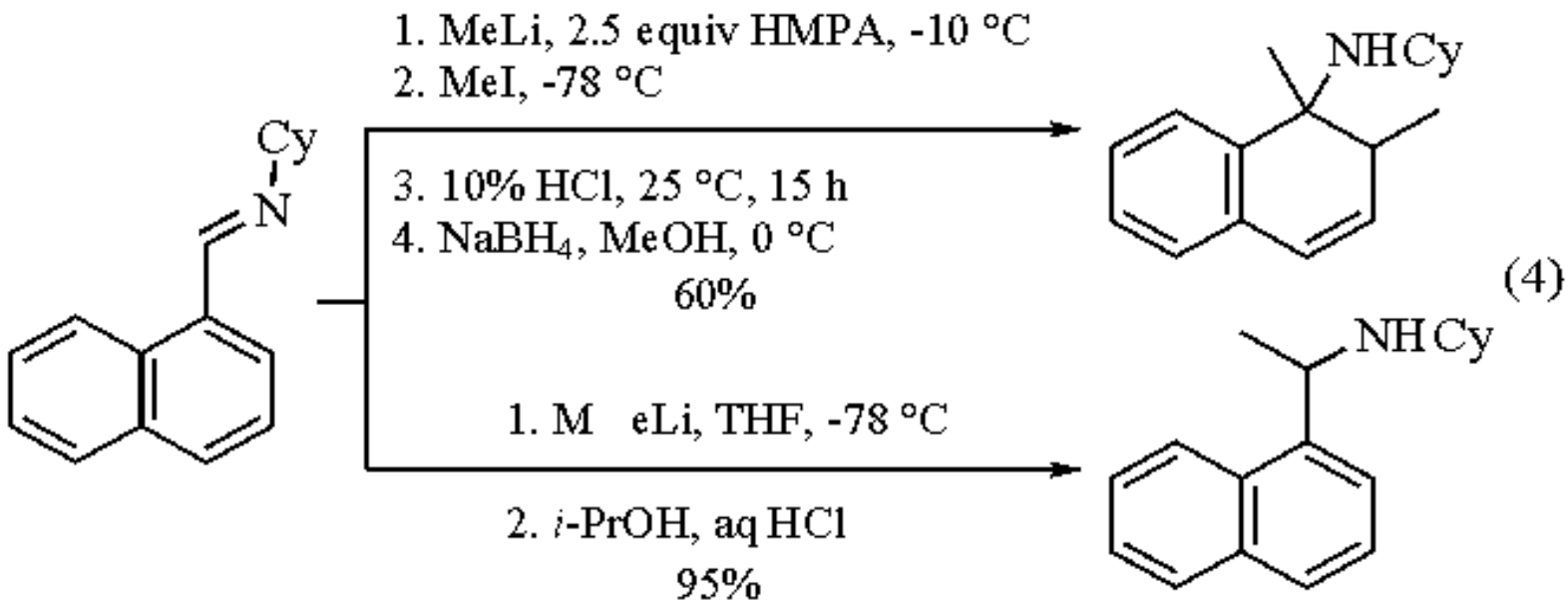

(4)

Secondary allylic alcohols, 3-substituted with SO_2Ph and $SiMe_3$, will undergo conjugate addition to give only the *syn*-adduct.[33] Asymmetric addition to sulfines in the presence of chiral ligands had only modest stereoselectivity.[34]

Miscellaneous Reactions.

Methyllithium was the base of choice for the metalation of *o*-allylbenzamide, which cyclizes to a naphthol derivative (eq 5).[35]

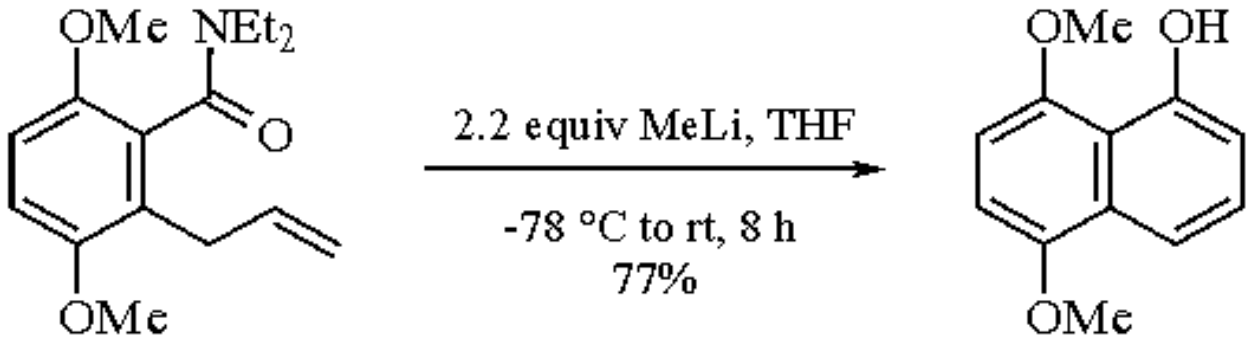

(5)

Rearrangement of *gem*-dibromides of cyclopropyl derivatives with methyllithium leads to mixtures of allenes[36a] and monobromide derivatives.[36] Substituted epoxides,[37] silacyclopentane,[38] and cyclotriphosphazene[39] can be ring opened. The transmetalation of trimethylstannyl compounds to form vinyl-, allenyl-, and propargyllithium reagents is usually best done with methyllithium.[40] Zero-valence Pd for coupling alkenyl halides and organolithiums can be prepared from

Palladium(II) Chloride and methyllithium.[41] Even preparation and utility of transition metal-activated organic compounds of molybdenum[42a] and tungsten[42b] are reported.

Related Reagents.

Dilithium Trimethylcuprate; ***Dichlorodimethyltitanium***; ***Lithium Cyano(methyl)cuprate***; ***Lithium Dimethylcuprate***; ***Methylcopper***; ***Methylmagnesium Bromide***; ***Methyltitanium Triisopropoxide***; ***Lithium Trimethylzincate***.

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Methylmagnesium Bromide[1]

MeMgX

(X = Br)

[75-16-1] · CH_3BrMg · Methylmagnesium Bromide · (MW 119.25) (X = Cl)

[676-58-4] · CH_3ClMg · Methylmagnesium Chloride · (MW 74.80) (X = I)

[917-64-6] · CH_3IMg · Methylmagnesium Iodide · (MW 166.25)

(adds to many unsaturated functional groups; methyl can displace halide and like groups; can function as a strong base and a Lewis acid)[1b-f]

Physical Data: NMR, IR, kinetic, and calorimetric observations indicate that MeMgBr in Et_2O and THF, and MeMgCl in Et_2O, actually are mixtures of MeMgX, Me_2Mg, and MgX_2.[2] MeMgBr is essentially monomeric in THF, but it and MeMgI are associated significantly in Et_2O except at low concentrations.[3] Solids isolated include $MeMgBr(THF)_3$,[4] shown by X-ray diffraction to have five-coordinate Mg, and (low-melting) $MeMgX(Et_2O)_2$ (X = Br or I).[5] Complete removal of Et_2O leaves a mixture of Me_2Mg and MgX_2 (X = Cl or Br).[6]

Solubility: MeMgBr and MeMgI sol Et_2O; MeMgCl and MeMgBr sol THF. MgI_2 precipitates when MeMgI is prepared in THF, leaving mainly Me_2Mg in solution; some $MgCl_2$ generally precipitates when MeMgCl is prepared in Et_2O, particularly if the solution stands for several days. All are insoluble in hydrocarbons.

Form Supplied in: solutions of MeMgCl in THF, MeMgBr and MeMgI in Et_2O and Bu_2O, and MeMgBr in toluene/THF are commercially available.

Analysis of Reagent Purity: a small excess is used ordinarily to ensure that sufficient reagent is present, but concentration should be determined when exact stoichiometry is important.[7] R-Mg is conveniently determined by hydrolysis of an aliquot followed by addition of excess acid and back-titration with base.[8] Since this procedure does not distinguish R-Mg from HO-Mg and RO-Mg formed from reaction of the Grignard reagent with water and oxygen, respectively, a direct titration[9] more specific for R-Mg or a double titration procedure[10] should be used when such exposure is suspected. A qualitative color test is convenient for detecting the presence of Grignard reagent.[11]

Preparative Methods: [1c,e,12,13] in spite of their commercial availability, solutions of MeMgCl,[14,15] MeMgBr,[14,16] and MeMgI[17] are often prepared from reaction of a methyl halide and Mg, usually in Et_2O or THF.

Handling, Storage, and Precautions: Grignard reagents react readily with oxygen, water, and carbon dioxide. Reactants and apparatus used in their preparations and reactions should be dry throughout preparation, storage, and use; Grignard reagent solutions should be maintained under nitrogen or argon, though the vapor of a volatile solvent (especially Et_2O) provides some protection for short periods of time. Methyl Grignard reagents do not significantly attack Et_2O or THF at normal reaction temperatures.

Structure.[1a,c]

The structure of a Grignard reagent, an important influence on reactions, is more elaborate than implied by the formula RMgX. In solution, a Grignard reagent is a mixture (Schlenk equilibrium) of RMgX, R_2Mg, and MgX_2, the composition varying with solvent and X. Mg is most commonly four-coordinate in solids but may have even higher coordination;[18] all evidence indicates similar coordination in solutions. The additional bonds to Mg result from some combination of association by bridging of the X atom (or R group) between two Mg atoms and coordination by donor molecules (usually solvent). Coordination by donor groups of substrates can play an important role in reactions.

Workup Procedures.[13]

Workup of a Grignard reaction requires adding a proton source and removing magnesium salts. This is done conveniently by adding an aqueous HCl or H_2SO_4 solution and separating the organic and aqueous layers. When products cannot tolerate acids, however, a saturated aqueous ammonium chloride solution is generally used, either a large volume[19] sufficient to dissolve all magnesium salts or, alternatively, just enough[15] to completely precipitate the magnesium salts, leaving a nearly anhydrous solution of the product.

Representative Applications.[1b-f]

A Grignard reagent is used in an extraordinary variety of reactions, the majority leading to attachment of its organic group to an electrophilic carbon atom of the substrate. Most common are additions to carbonyl groups (eq 1),[20] nitriles, and imines (eq 2),[21] and displacements of halide and like leaving groups. Although generally less reactive than organolithium compounds, Grignard reagents are often used for convenience, because of a different reactivity pattern, or to minimize competing reactions. MeMgX and MeLi, for example, sometimes exhibit quite different regioselectivities (eq 1) and stereoselectivities (eq 2). The key step in the synthesis of chiral $O{=}CHCH(Me)NH_2$ (eq 2) also illustrates the common practice in Grignard reagent additions of using a disposable group whose coordination or steric effects impart stereoselectivity.

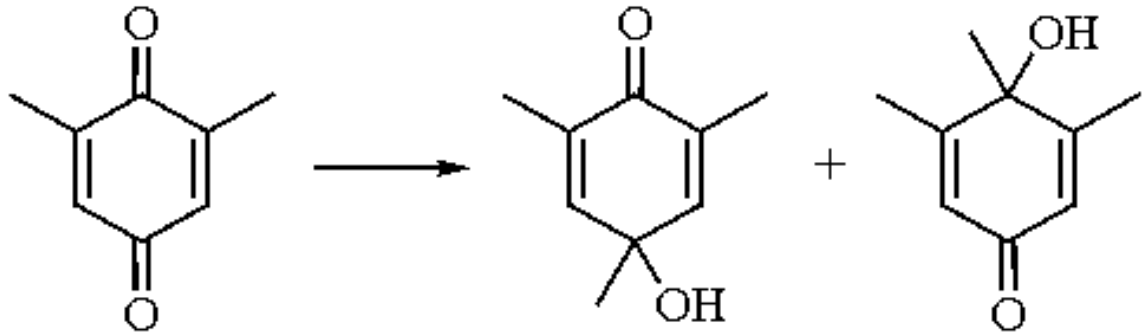

(1)

MeMgBr, THF, -78 °C	60%	-
MeLi, TMEDA, THF, -107 °C	9%	87%

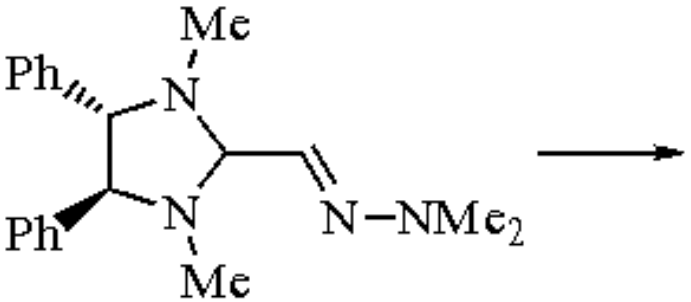

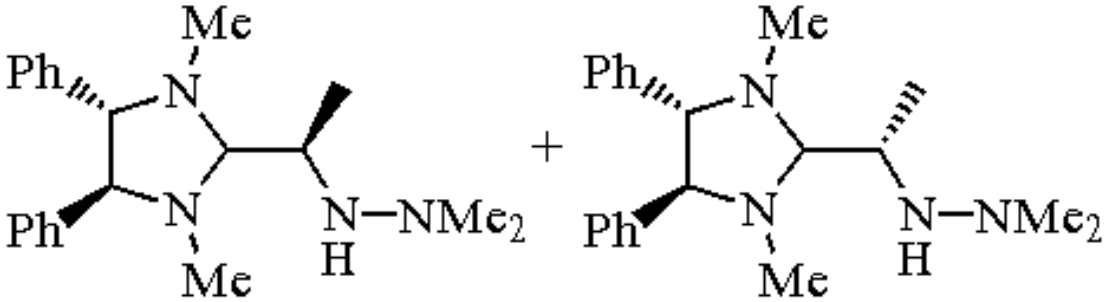

(2)

MeMgBr, Et_2O, reflux, 24 h	80:20
MeMgBr, toluene, 20 °C, 1 h	94:6
MeLi, Et_2O, -78 °C to rt	2:98

Grignard reagents are strong bases and Lewis acids, a problem in many reactions but of use in others. MeMgX, for example, extracts a proton from most N-H and O-H bonds and from particularly acidic C-H bonds. Volumetric measurement of the methane evolved from reaction with a compound of MeMgI was once a significant procedure (Zerewitinoff determination) for quantitative determination of its active hydrogens.[22] MeMgX still is used as a base, for example in forming magnesium amides (eq 3)[23] and enolates. Cleavage of aryl-alkyl ethers (eq 4)[24] is a displacement that must require the Lewis acid properties of the Grignard reagent. Me_2Mg is sometimes used in place of MeMgX to minimize reactions, such as isomerization of oxiranes to aldehydes or ketones,[25] that involve Lewis acidity but not displacement.

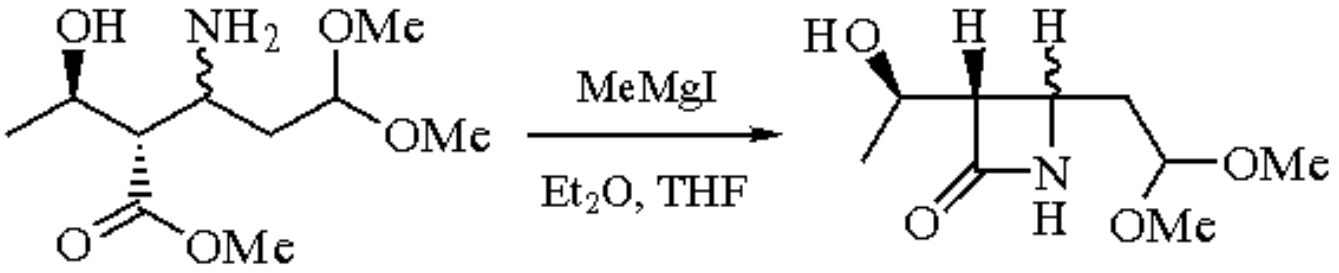

(3)

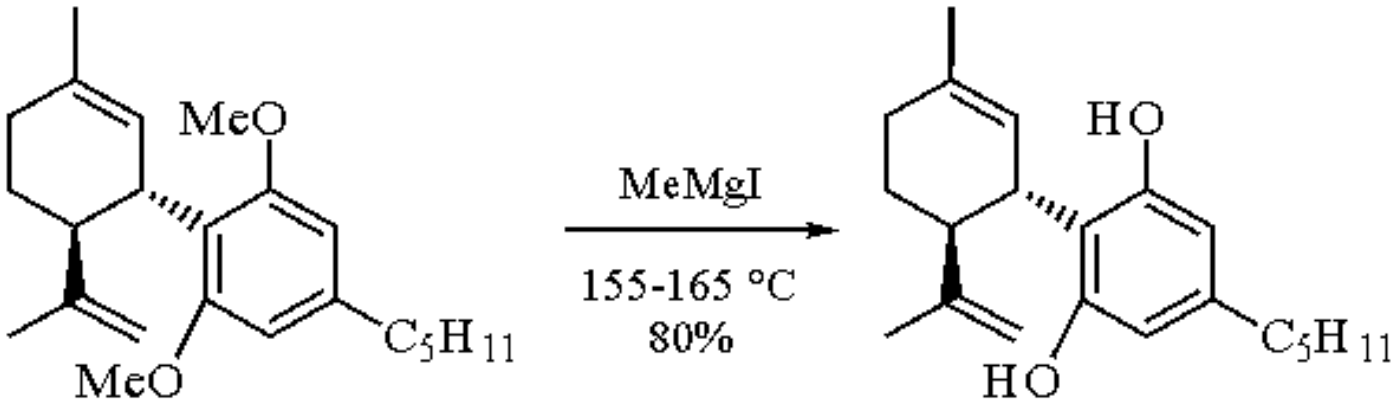

(4)

Strongly coordinating solvents tend to reduce reactivity in additions to unsaturated functions but to increase reactivity in reactions with alkyl halides and as bases. The greater rate and stereoselectivity of an addition (eq 2) in toluene than in Et_2O illustrate the importance of solvent.

Transition metal impurities, often introduced in the Mg used to prepare a Grignard reagent, can lead to unwanted products,[26] and where this is a problem particularly pure Mg should be used. Catalytic or stoichiometric amounts of transition metal compounds, of course, often are added deliberately to Grignard reagents.[27] Examples are copper compounds[28] to promote 1,4-additions to α,β-unsaturated carbonyl compounds (one variant of organocuprate chemistry) and nickel compounds[29] to promote substitution of aryl and vinyl halides.

Related Reagents.

Methylcopper; ***Methylcopper-Boron Trifluoride Etherate***; ***Methylcopper-Tributylphosphine***; ***Methyllithium***; ***Methyltitanium Trichloride***.

---

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Methyl Magnesium Carbonate[1]

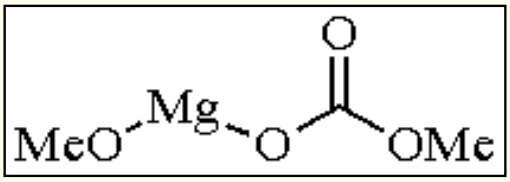

[4861-79-4] · $C_3H_6MgO_4$ · Methyl Magnesium Carbonate · (MW 130.40)

(agent for the α-carboxylation of nitroalkanes, ketones, lactones, hydantoins, and phenols[1])

Alternate Name: MMC.

Preparative Methods: prepared in situ by saturating a solution (2 M) of ***Magnesium Methoxide*** in DMF with ***Carbon Dioxide***.[3] It is assumed to have the formula $MeOMgOCO_2Me.(CO_2)_n$ where *n* varies with temperature and solvent.[2]

Carboxylation of Nitroalkanes and Ketones.

Stiles and Finkbeiner discovered that methyl magnesium carbonate readily carboxylated nitroalkanes at the α-position (eq 1).[2] They concluded that the reaction proceeds to give a magnesium chelate which confers stability on the products (eq 2).[4] The procedure has recently been used to prepare isotopically labelled α-oxoglutaric acid from [^{13}C]nitromethane.[5]

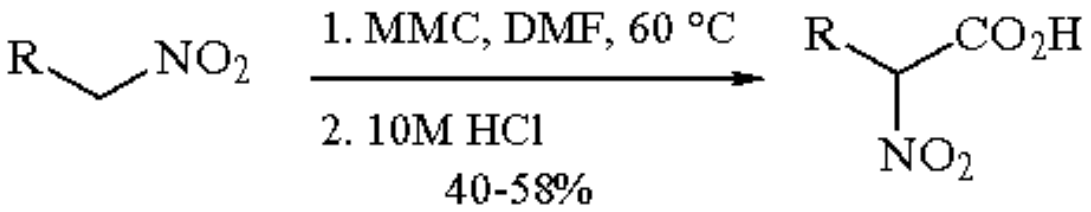

(1)

R = H, Me, Et, Pr, Bu, *i*-Pr, pentyl, Bn

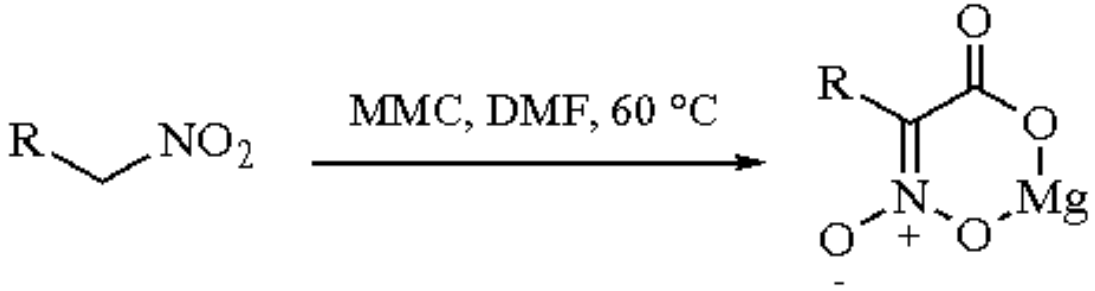

(2)

MMC has also been used to carboxylate ketones (eqs 3 and 4), although quite vigorous conditions (100-130 °C) are required.[6] The process is considered to be reversible and results in the carboxy group occupying the less hindered location. It is thus highly selective for carboxylation at the terminal methyl group of 2-alkanones.[7] Carboxylation at a methine site has not been observed. β-Tetralones, which might have been expected to undergo carboxylation at the more acidic C-1 position, afford the C-3 isomers (eq 5) since the *peri* interaction between the aromatic ring and a carboxy group at C-1 would be destabilizing.[8]

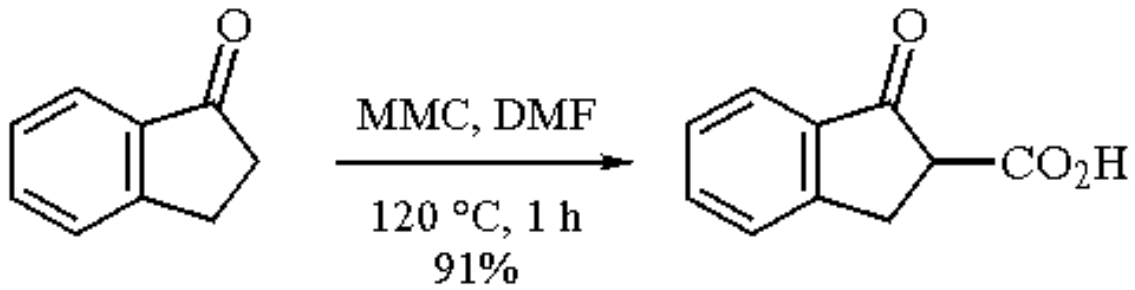

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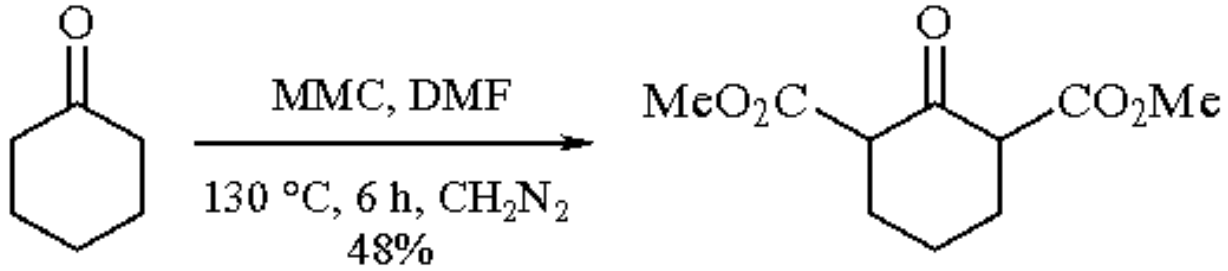

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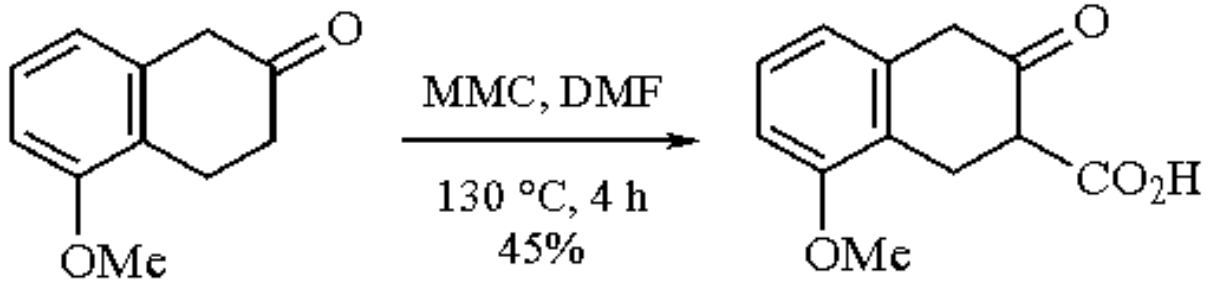

(5)

The carboxylation of hydrindenones with MMC (eq 6) was observed to take a very different course[9,10] from that experienced with the equivalent octalone (eq 7)[9] and with cholest-4-en-3-one (eq 8).[11] The difference was attributed to a preference for heteroannular dienolate formation in the hydrindene substrate, relative to the decalin systems. Carboxylation of a ketone, used as an intermediate in the synthesis of quassins, failed when a neighboring acetoxy group underwent hydrolysis. When the interfering hydroxy was protected as a TBDMS or THP ether, however, an excellent yield of the desired product was obtained (eq 9).[12]

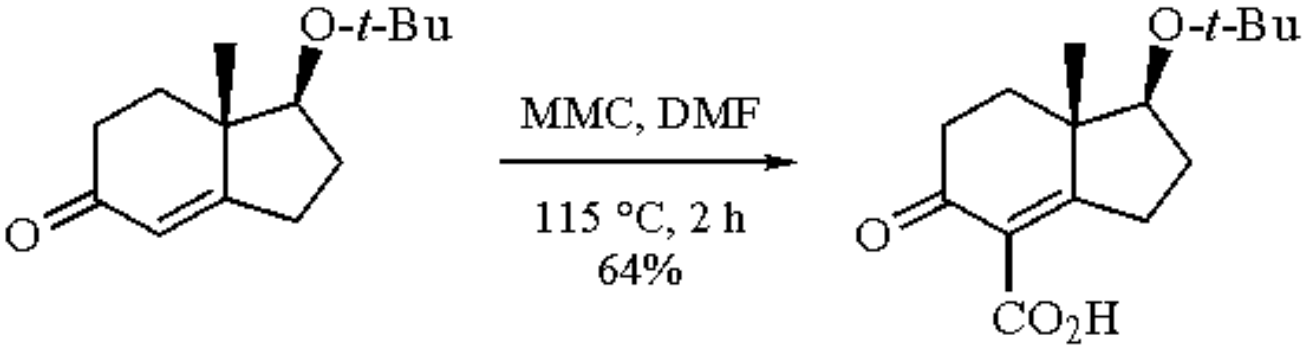
O-t-Bu
MMC, DMF
115 °C, 2 h
64%
O-t-Bu
O
CO2H

(6)

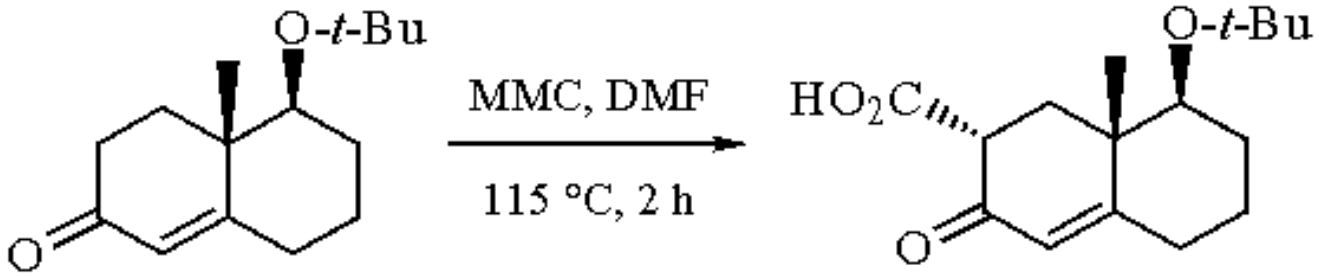
O-t-Bu
MMC, DMF
115 °C, 2 h
HO2C
O-t-Bu
O

(7)

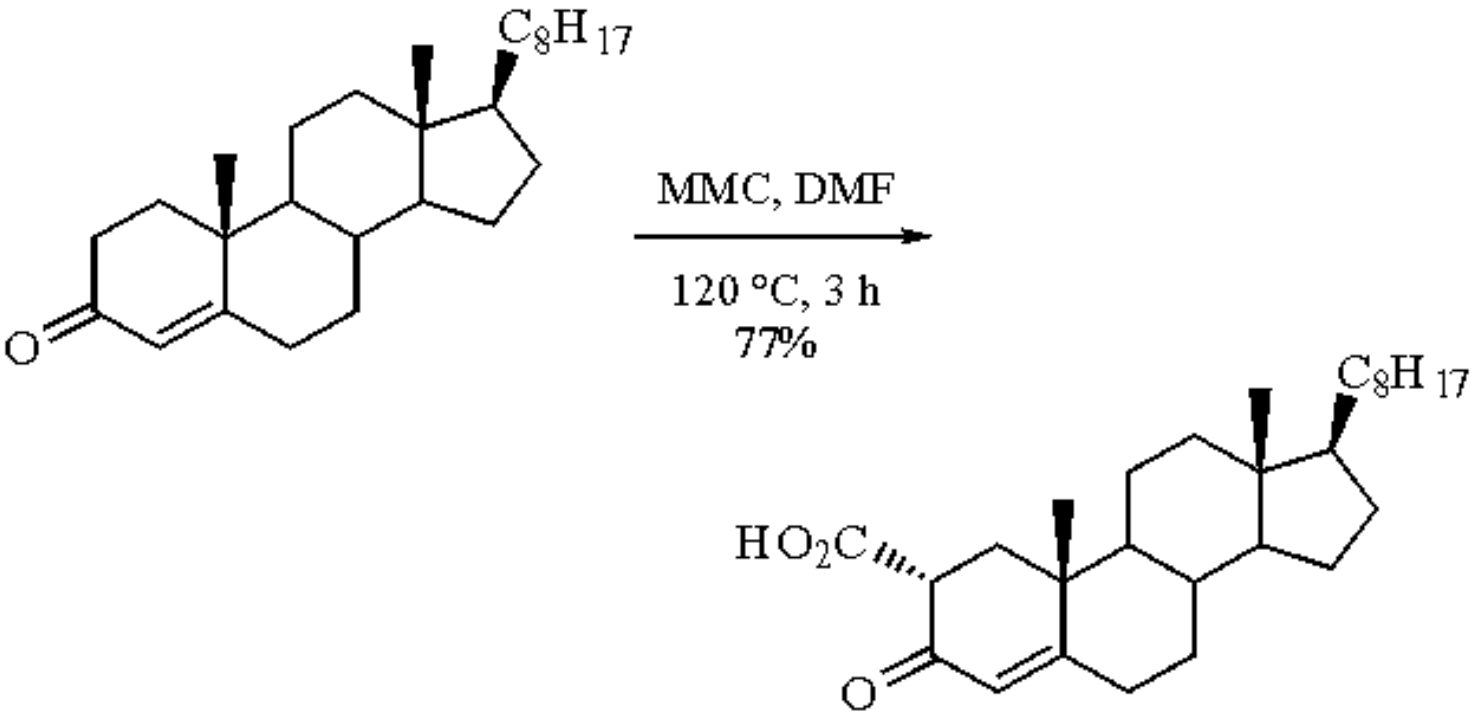
C8H17
MMC, DMF
120 °C, 3 h
77%
C8H17
HO2C
O

(8)

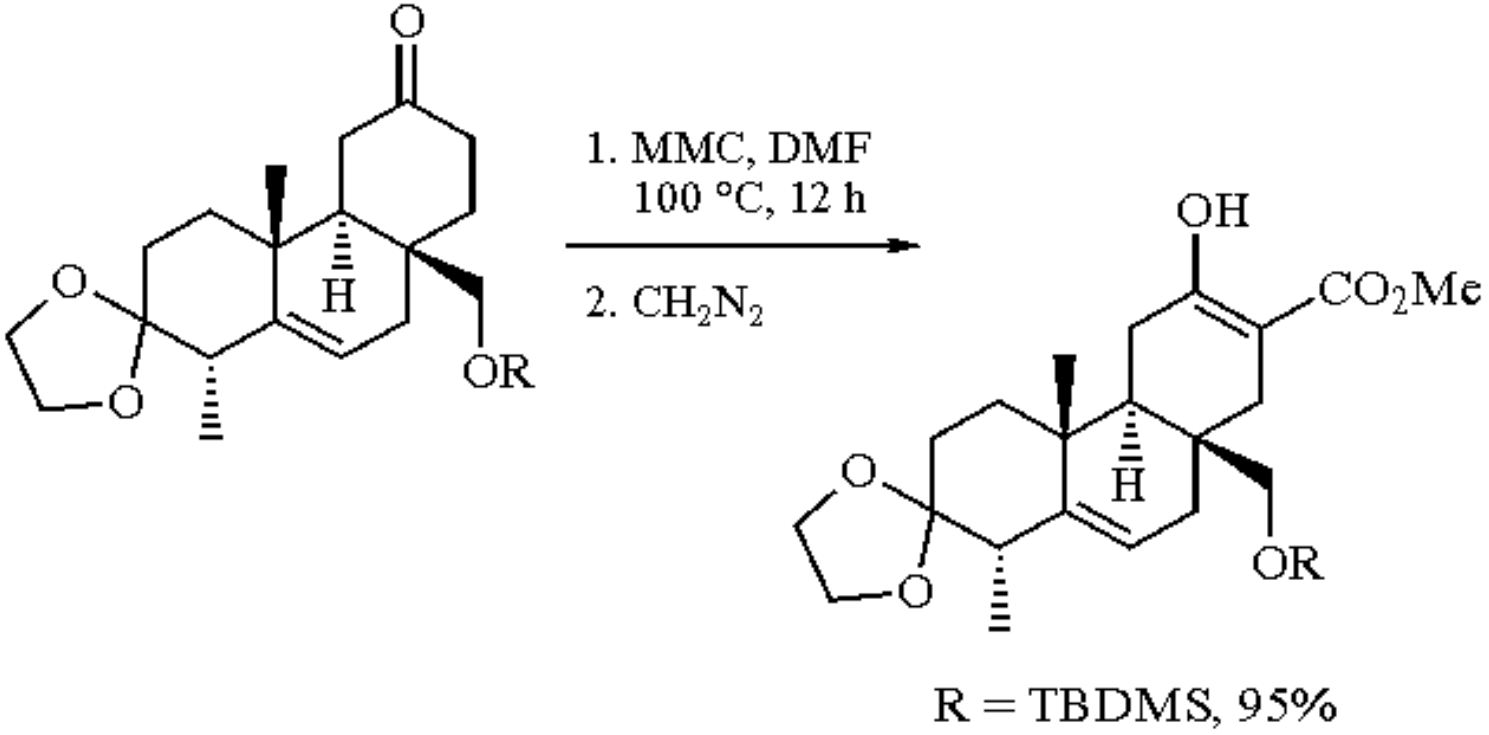

(9)

Carboxylation and α-Methylenation of Lactones.

Lactones are readily carboxylated with MMC and the higher stability of the products, relative to those from ketones, ensures generally excellent yields (eq 10).[13] The carboxylic acid products may be used in a particularly efficaceous preparation of α-methylene lactones with formaldehyde (eq 11)[14] or Eschenmoser's salt (eq 12).[15]

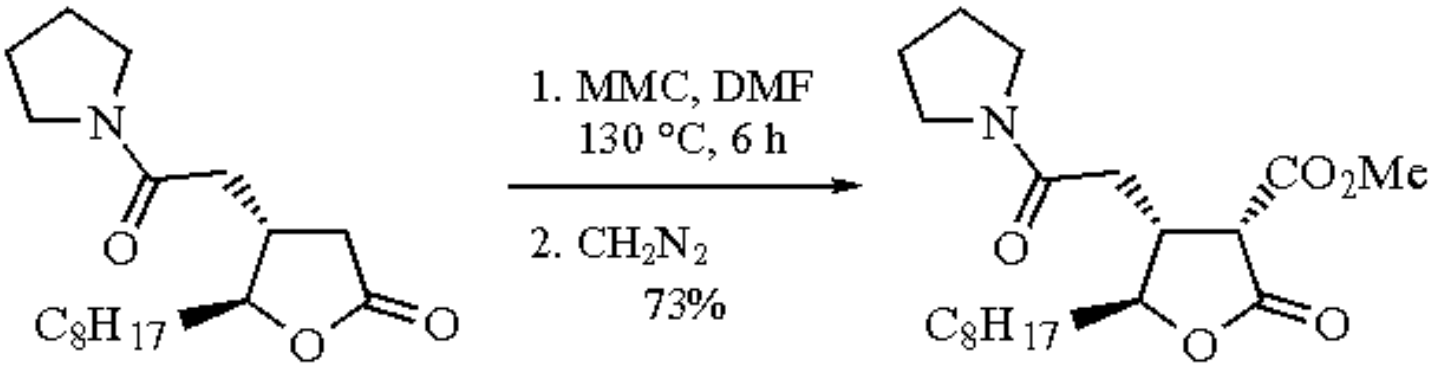

(10)

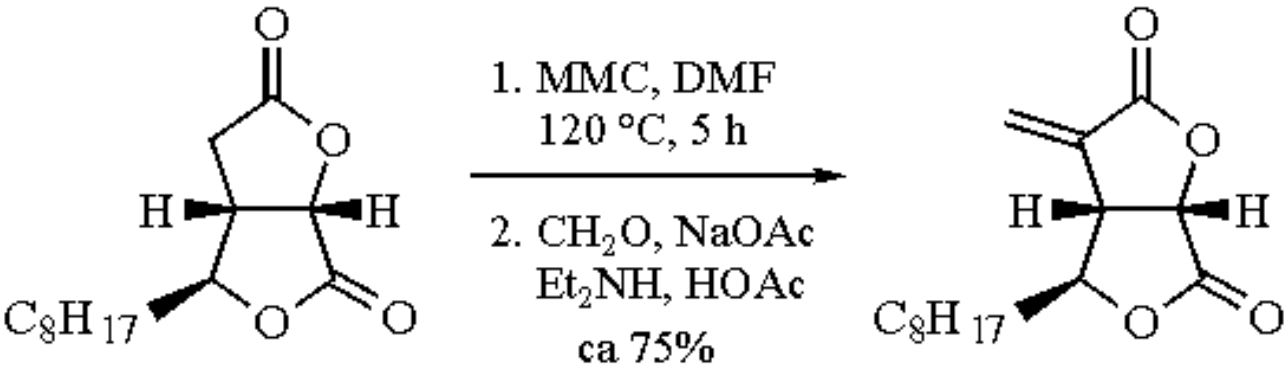

(11)

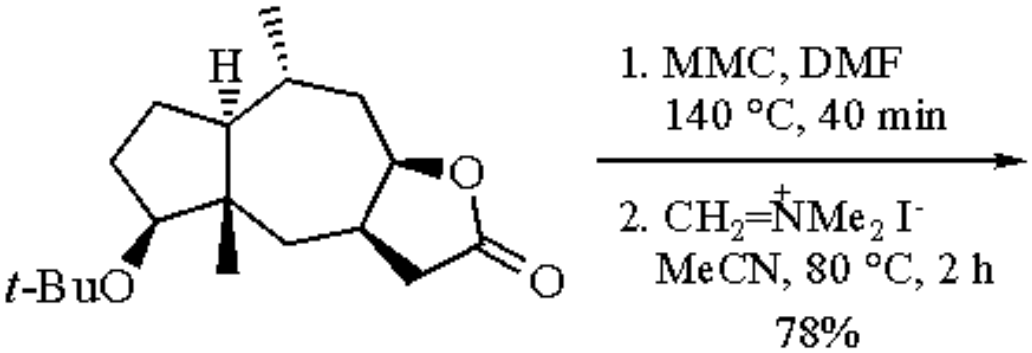

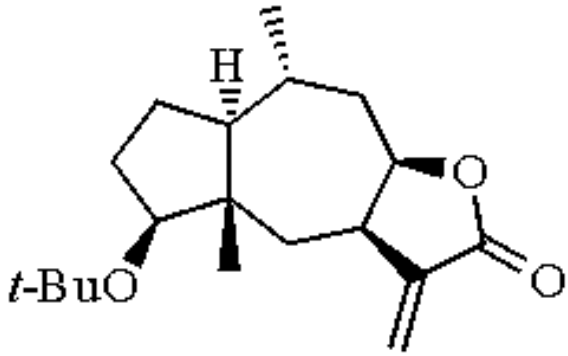

(12)

During the synthesis of protolichesterinic acid, the carboxylation failed on a lactone substrate bearing a methoxycarbonyl substituent, but the reaction proceeded satisfactorily with the parent acid (eq 13).[16]

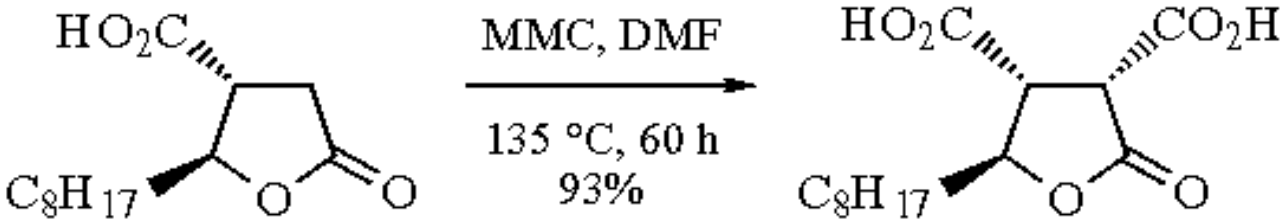

(13)

Miscellaneous Carboxylations.

Hydantoins are readily carboxylated with MMC (eq 14) and the products may be alkylated in situ (eq 15).[17] The carboxylation of resorcinols has been reported, including a phenolic intermediate in the synthesis of cannabinoids (eq 16).[18]

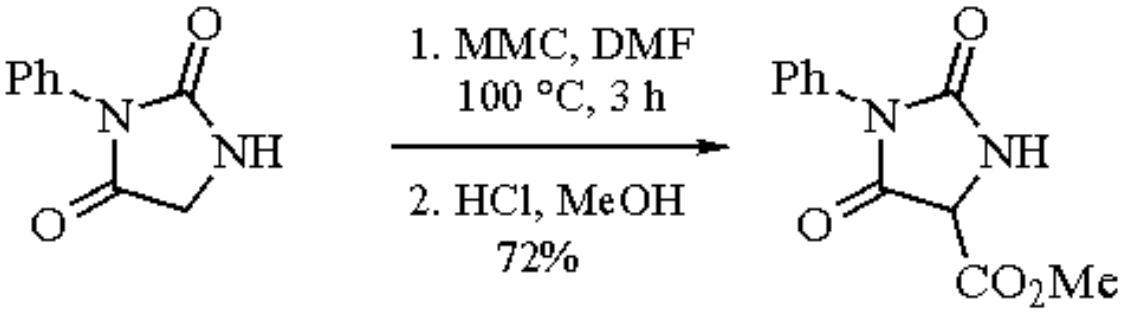

(14)

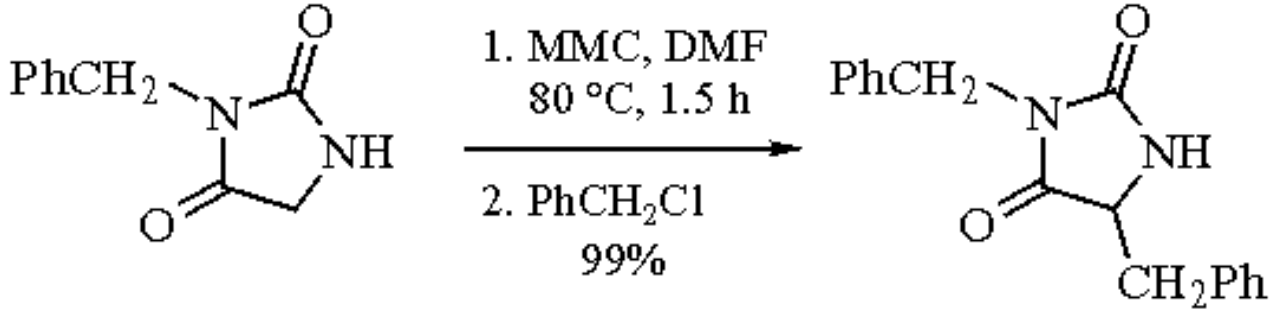

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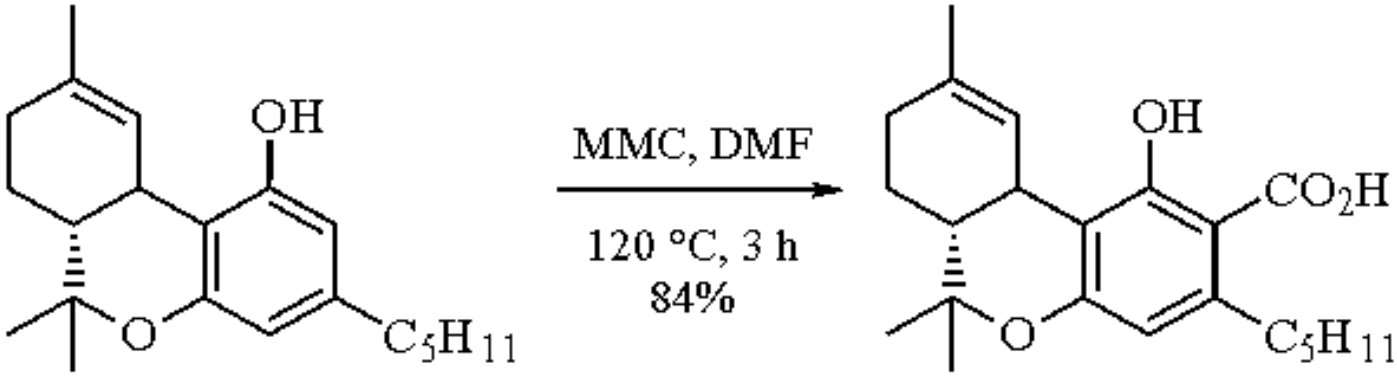

(16)

Related Reactions.

Modest yields have been obtained from the carboxylation of ketones with a 2:1 complex of potassium phenoxide and CO_2,[19] and with the complexes (**1**),[20] (**2**),[21] (**3**),[22] and (**4**).[23] However, the ureide complexes (**5**)[24] afforded significantly improved yields, as does a mixture of ***Triethylamine*** with ***Magnesium Iodide*** (prepared in situ from $MgCl_2$ and NaI) in acetonitrile.[25] This last magnesium carbamate differs from the others in allowing carboxylation at methine positions, as in dimethylcyclohexanone (65% yield) and isobutyrophenone (90% yield).

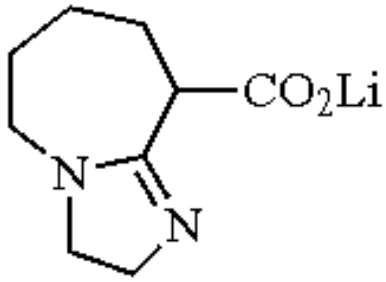

(1)

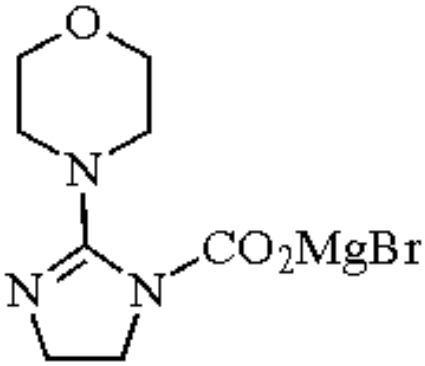

(2)

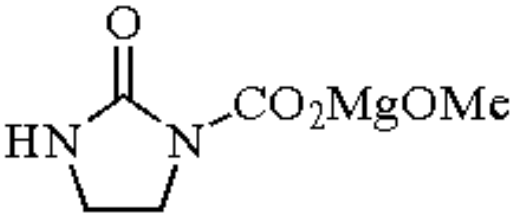

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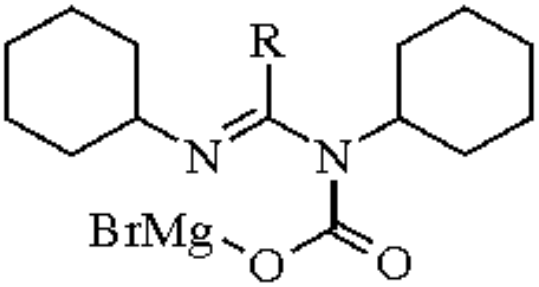

(4) R = Ph, Bu

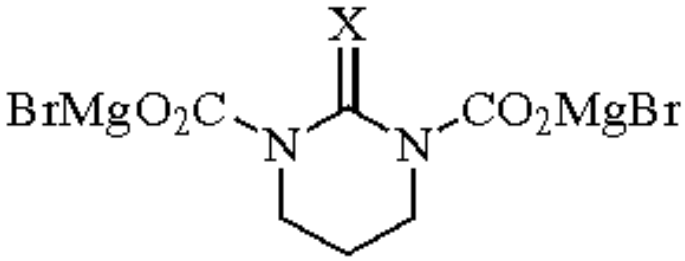

(5) X = O, S

Related Reagents.

Carbon Dioxide; ***Carbon Oxysulfide***; ***N,N´-Carbonyldiimidazole***; ***Diethyl Carbonate***; ***Methyl Chloroformate***; ***Methyl Cyanoformate***.

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Methylmagnesium *N*-Cyclohexylisopropylamide[1]

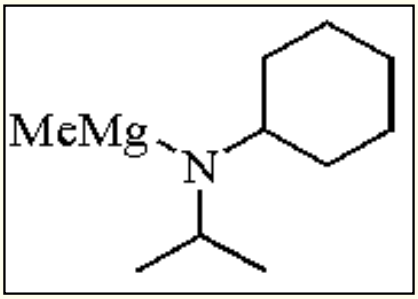

[102276-92-6] · $C_{10}H_{21}MgN$ · Methylmagnesium *N*-Cyclohexylisopropylamide · (MW 179.63)

(isomerization of epoxides to allylic alcohols[1])

Alternate Name: MMA.

Solubility: sol toluene.

Form Supplied in: prepared and used in situ.

Preparative Methods: prepared by adding ***n-Butyllithium*** (1 equiv) to a 0 °C solution of *N*-cyclohexylisopropylamine in anhydrous toluene (0.85 M). After 15 min, ***Methylmagnesium Bromide*** (1 equiv, 3 M in Et_2O) is introduced dropwise. Stirring is continued for another 30-45 min, during which time a white precipitate develops.[1a]

Handling, Storage, and Precautions: moisture sensitive; prepared and used in situ.

Isomerization of Epoxides to Allylic Alcohols.[1]

The isomerization of epoxides to allylic alcohols (eq 1) is a common and preparatively useful functional group interchange.[2] Methylmagnesium *N*-cyclohexylisopropylamide is an efficient reagent for the isomerization of epoxides to allylic alcohols. Although the nature of the reagent and its state of aggregation are unknown, the formation of allylic alcohols from epoxides is assumed to proceed by a β-elimination pathway by analogy with related systems.[2]

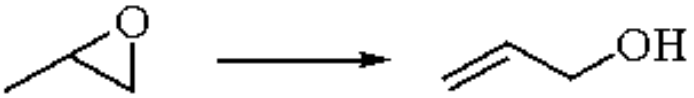

(1)

The epoxide in toluene is added to a 3-4 fold excess of MMA (final MMA concentration 0.55 M) at 0 °C and the mixture is

maintained under the conditions summarized in Table 1. Proton abstraction from a methyl group is greatly preferred over that from a methylene in acyclic[3] (entry 1) and cyclic (entry 2) systems. However, in some cases such as a 1,1-disubstituted epoxide (entry 3) and a simple cyclic epoxide (entry 5), nucleophilic addition of methyl from MMA is the major result. In contrast, the more sterically biased pyranoside[4] in entry 4 isomerizes exclusively to the allylic alcohol. It is noteworthy that, unlike lithium amides,[5] MMA converts 5,6-epoxycyclooctene (entry 6) to 2,5-cyclooctadien-1-ol without significant ketone or conjugate diene formation. Exposure of 14,15-epoxyicosatrienoic acid (**1**) (entry 7) to MMA affords 15-hydroxyicosatetraenoic acid (15-HETE; **2**). The yield of 15-HETE decreases dramatically if THF or toluene/HMPA (2:1) is the solvent.[6,7] Abstraction of an allylic proton in a related bis-epoxide (**3**) (entry 8) also leads to a conjugated (*E*,*Z*)-dienol (**4**).

Table 1 Reaction of Epoxides with MMA

Entry	Epoxide	Conditions	Product	Yield (%)
1	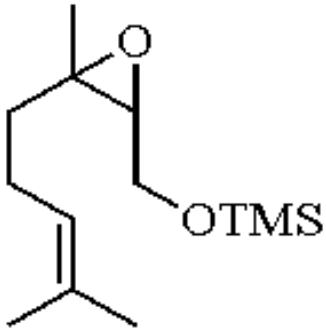	0 °C, 75 h	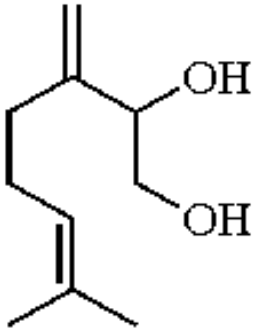	96
2	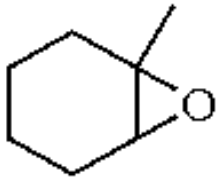	0 °C, 20 h	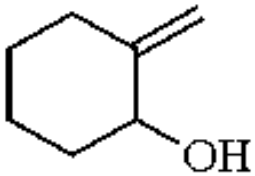	85
3	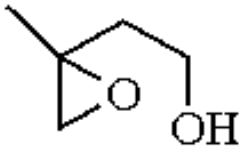	0 °C, 7 h	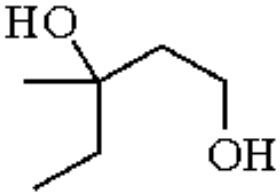	50
4	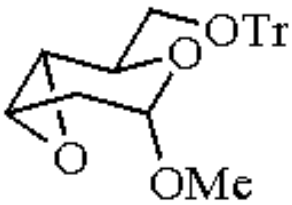	0 °C, 1.5 h	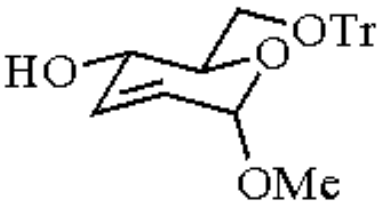	94
5	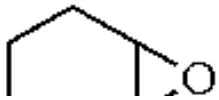	24 °C, 16 h	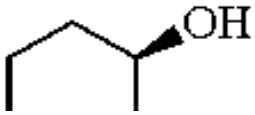	42

5		24 °C, 16 h	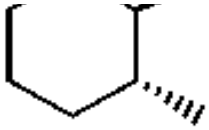	42
6	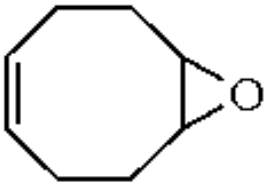	24 °C, 13 h	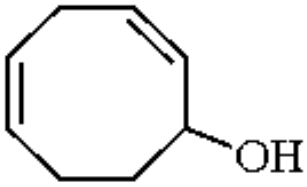	43
7	**(1)**	0 °C, 3 h	**(2)**	51
8	**(3)**	0 °C, 1.5 h	**(4)**	37
9	**(5)**	24 °C, 20 h	**(6)**	45
			(7)	45

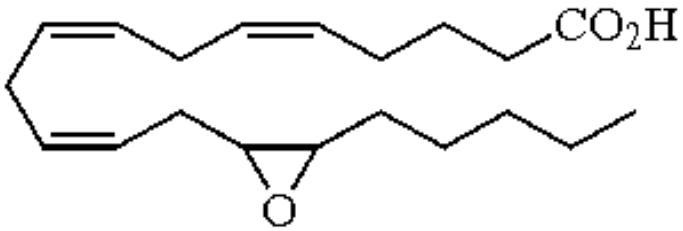

(1)

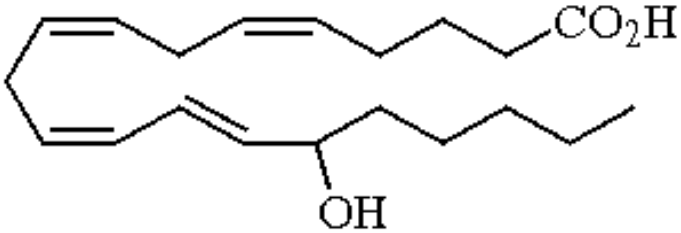

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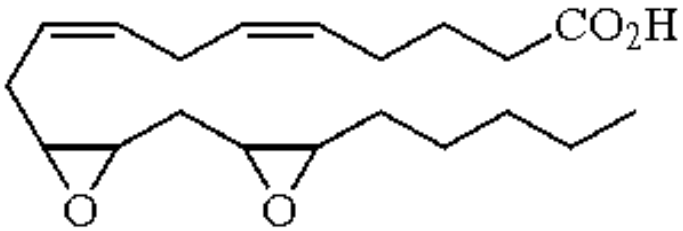

(3)

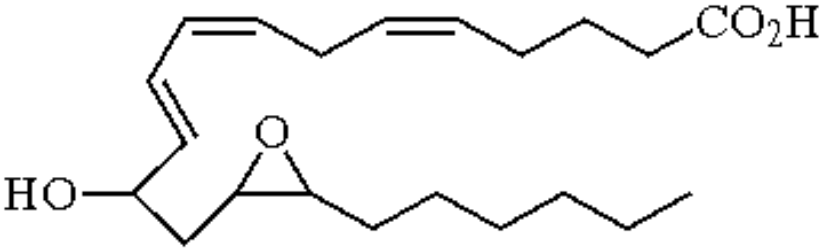

(4)

The epoxide (**5**) of oleic acid displays intermediate reactivity with respect to isomerization or nucleophilic addition. Treatment with MMA furnishes approximately equal amounts of allylic alcohols (**6**) and methyl addition product (**7**) (entry 9). The ethylmagnesium and isopropylmagnesium analogs of MMA behave similarly. On the other hand, phenylmagnesium *N*-cyclohexylisopropylamide gives rise to only allylic alcohol (**6**), albeit in low yield (~20%).

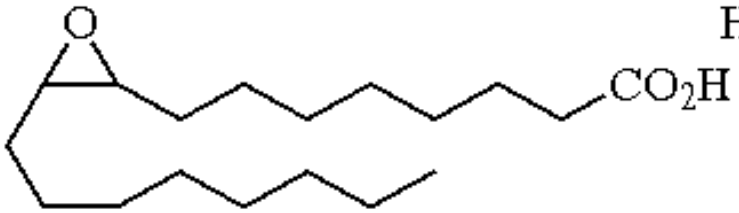

(5)

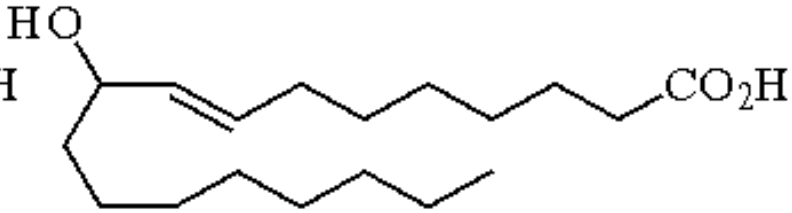

(6)

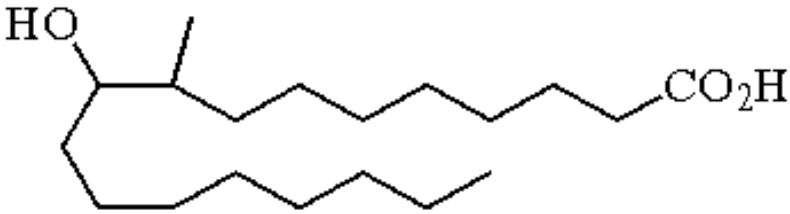

(7)

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Methylmagnesium Iodide-Copper(I) Chloride[1]

MeMgI-CuCl

(MeMgI)

[917-64-6] · CH_3IMg · Methylmagnesium Iodide-Copper(I) Chloride · (MW 166.25) (CuCl)

[7758-89-6] · ClCu · Methylmagnesium Iodide-Copper(I) Chloride · (MW 99.00)

(methyl group transfer in 1,4- and 1,6-conjugate additions to unsaturated carbonyl compounds; coupling with acid chlorides gives methyl ketones)

Physical Data: see entries for ***Methylmagnesium Bromide*** and ***Copper(I) Chloride***.

Preparative Methods: generated in situ by using varying, often catalytic, amounts of purified and dried CuCl.

Handling, Storage, and Precautions: air- and moisture-sensitive. Use in a fume hood.

Conjugate Additions.

While the reaction of methylmagnesium iodide with α,β-unsaturated carbonyl compounds usually produces a mixture of 1,2- and 1,4-adducts, a selective 1,4-addition is observed in the presence of copper(I) chloride in most cases. Many successful conjugate additions to acyclic[2] or cyclic[3-5] enones (including steroidal ketones[6]) as well as to enoate esters[7] have been reported (eqs 1-3). A similar transformation of phenylpropiolic acid gives 3-phenyl-2-butenoic acid.[8]

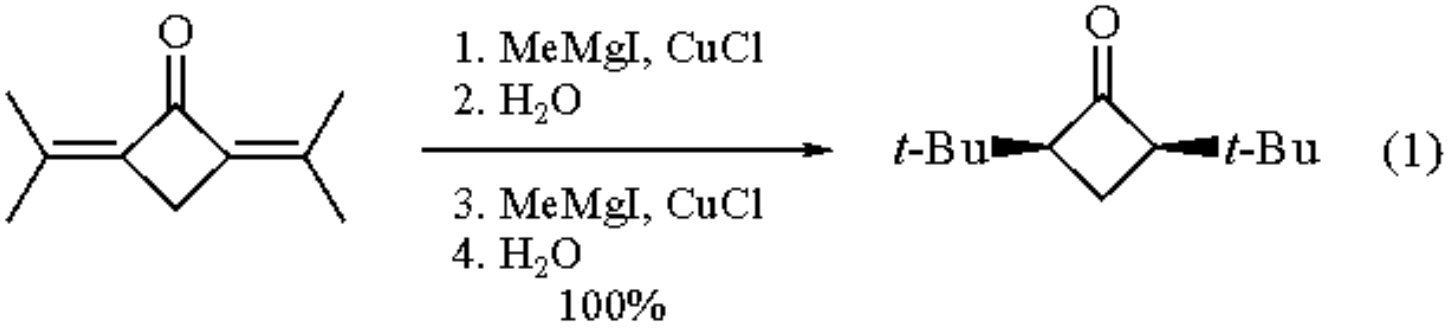

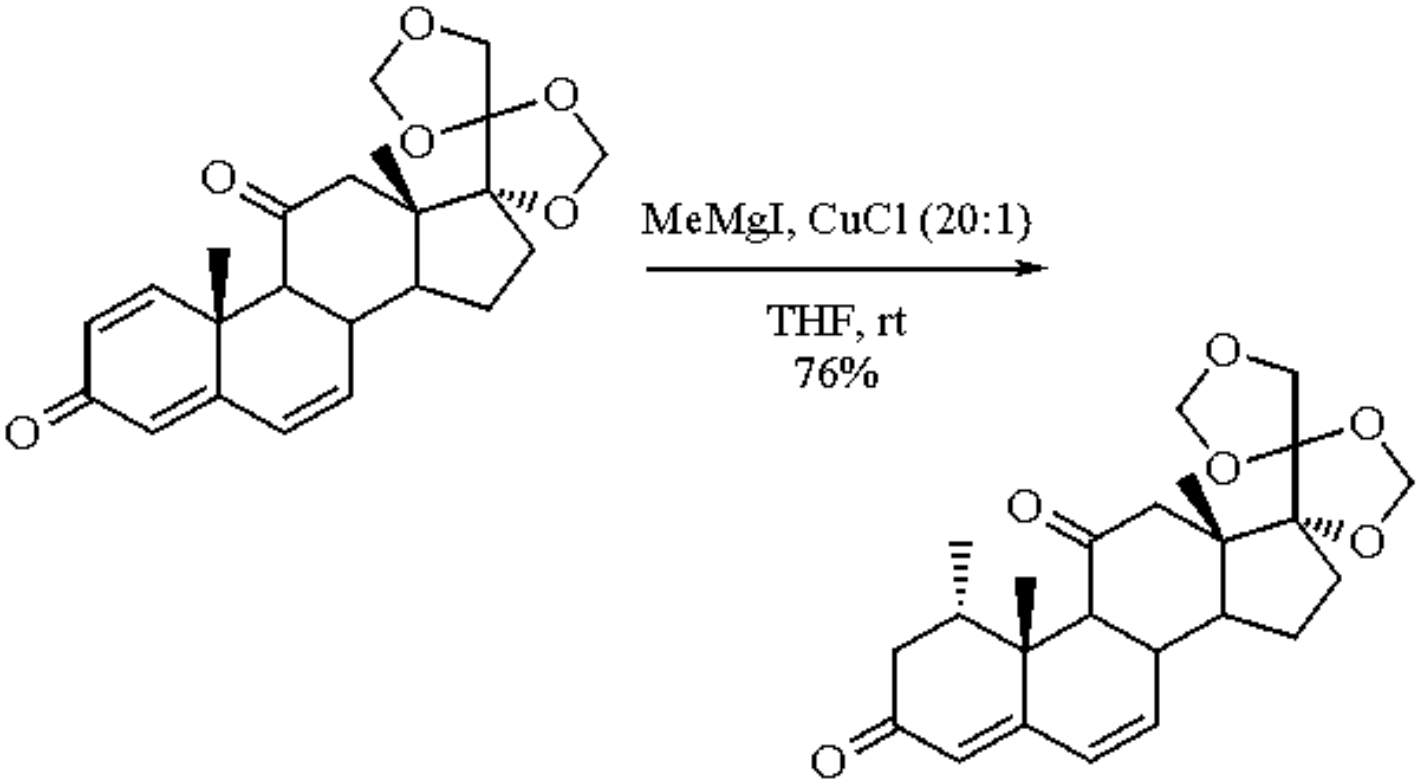

(2)

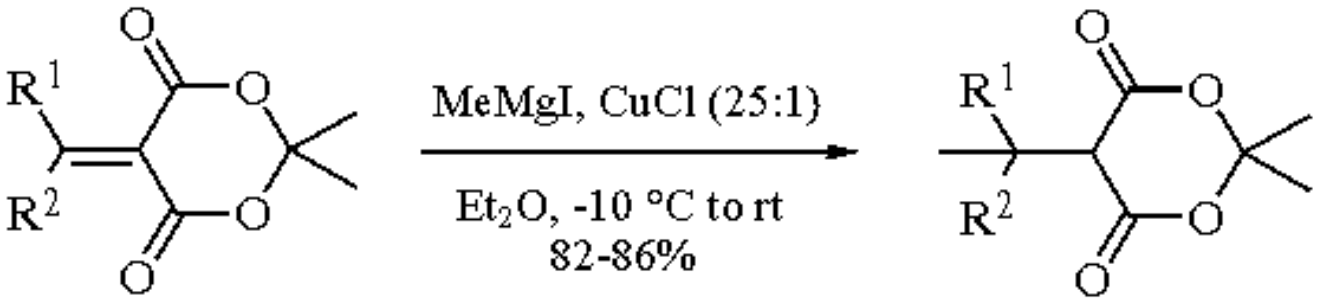

(3)

A conjugate 1,6-addition is possible (eq 4).[9]

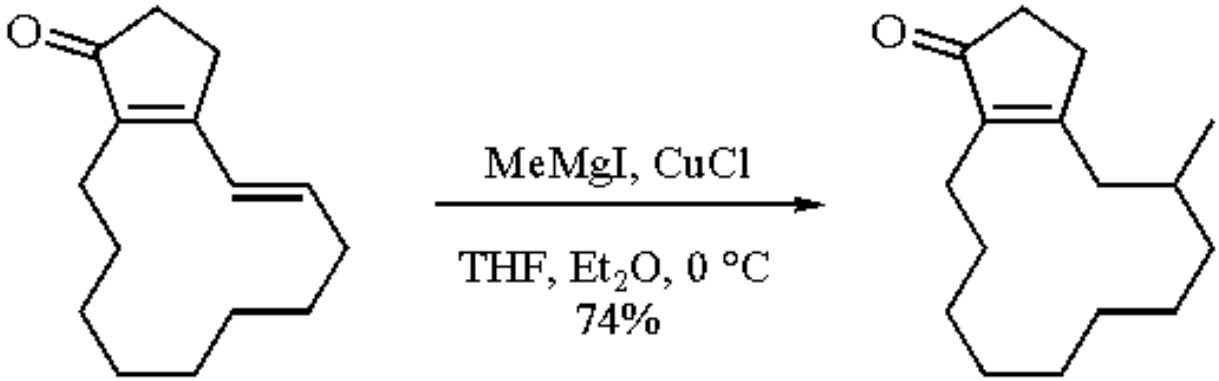

(4)

Addition to cyclic enones usually proceeds stereoselectively (eqs 1 and 2). Being irreversible, the reaction is governed by kinetic control. The stereochemical outcome can be predicted in most cases on the basis of transfer of the methyl group from the reagent perpendicular to the alkenic bond and from the least hindered side of the substrate.[3c,6e]

Steric hindrance may result in low yield of the addition product. Reduction of the alkenic bond[7c] or 1,2-addition to the

carbonyl group[6a] have been observed as major reaction pathways for sterically hindered substrates.

Synthesis of Methyl Ketones.

Treatment of acid chlorides, including highly sterically hindered derivatives, with MeMgI in the presence of CuCl gives methyl ketones in excellent yields.[10]

Related Reagents.

Ethylmagnesium Bromide-Copper(I) Iodide; ***1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Bromide-Copper(I) Iodide***.

---

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Methyl Methanethiosulfonate[1]

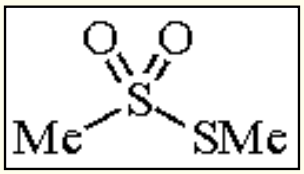

[2949-92-0] · $C_2H_6O_2S_2$ · Methyl Methanethiosulfonate · (MW 126.22)

(methylsulfenylating agent with many applications;[2] reagent for the rapid and selective modification of the essential SH groups of enzymes. The MeS-protecting group is easily removed under mild conditions[3])

Alternate Name: S-methyl thiomethanesulfonate.

Physical Data: bp 69-71 °C/0.4 mmHg; *d* 1.227 g cm^{-3}; *n* 1.5130.

Form Supplied in: colorless oil; widely available.

Handling, Storage, and Precautions: stench; irritant. Use in a fume hood.

Introduction.

Methyl methanethiosulfonate is a versatile reagent mainly used to form sulfenylated intermediates used en route to the synthesis of various interesting compounds. It is a much more reactive and effective sulfenylating agent than ***Dimethyl Disulfide*** or MeSCl.[4] $MeSSO_2Me$ (and its reaction products) has little odor, which makes it considerably more agreeable to work with than MeSSMe. The MeS group transferred via deprotonation of the substrate's acidic proton with a base, followed by electrophilic substitution, can serve as a protecting group,[5] an activating group for carbanion formation, or as a masked ketone or aldehyde. It can serve as a handle for subsequent transformation to various functionalities (e.g. alkene, ketone, and alkyl group) via oxidation or reduction.

Preparation of 2-(Methylthio)alkanoic Acids and Esters and 3-Methylthio-2-alkanones.

2-(Methylthio)alkanoic acids and esters are synthesized by successive treatment of substituted malonic esters with ***Sodium Ethoxide*** and $MeSSO_2Me$, followed by alkaline hydrolysis which causes concurrent decarboxylation (eq 1).[6]

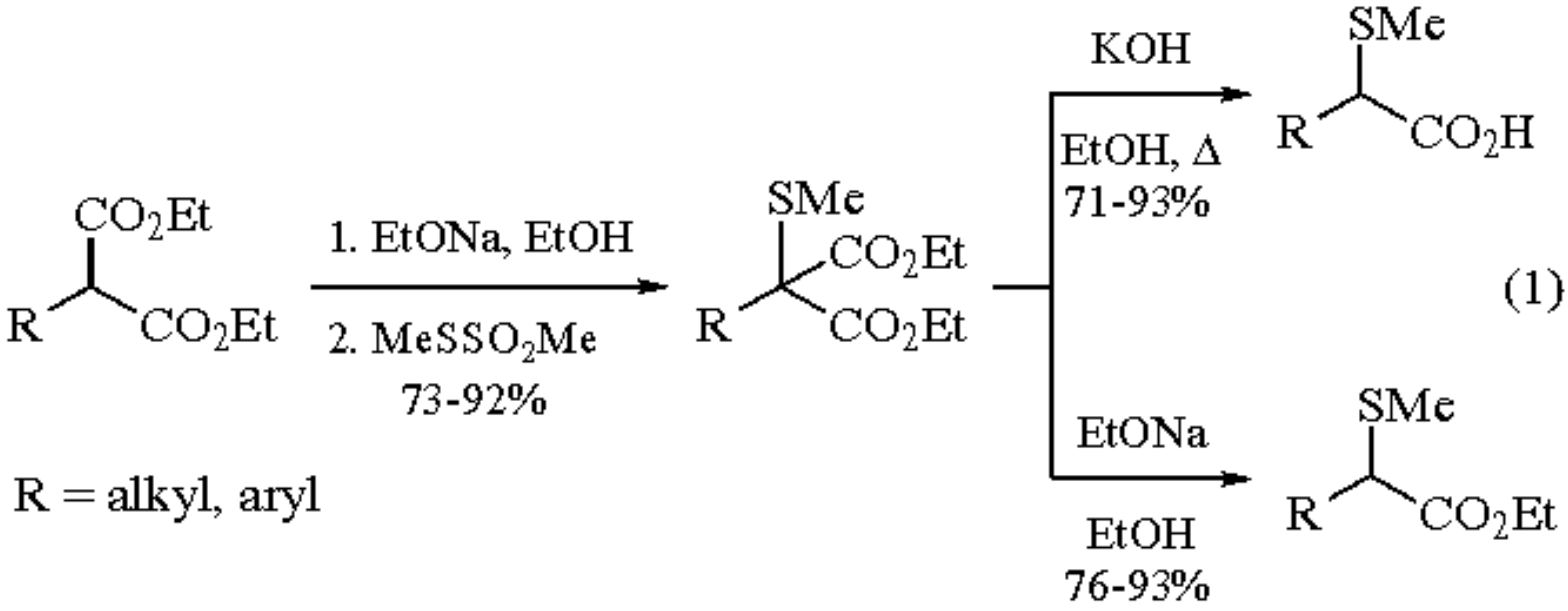

More conveniently, 2-(methylthio)alkanoic esters are prepared from 2-acetylalkanoates (eq 2).[7] MeSSMe cannot replace $MeSSO_2Me$ as the sulfenylating agent in this transformation. Advantages of these methods over others such as sulfenylation of an alkanoic acid and its ester or alkylation of (methylthio)acetic acid are (1) simplicity of the procedure; (2) efficiency and convenience of using inexpensive base (EtONa) and EtOH as solvent with high product yields; and (3) no bissulfenylation. Moreover, the latter method allows direct α-sulfenylation of 2-acetylalkanoates which also contain an additional keto group, without its protection (eq 2).

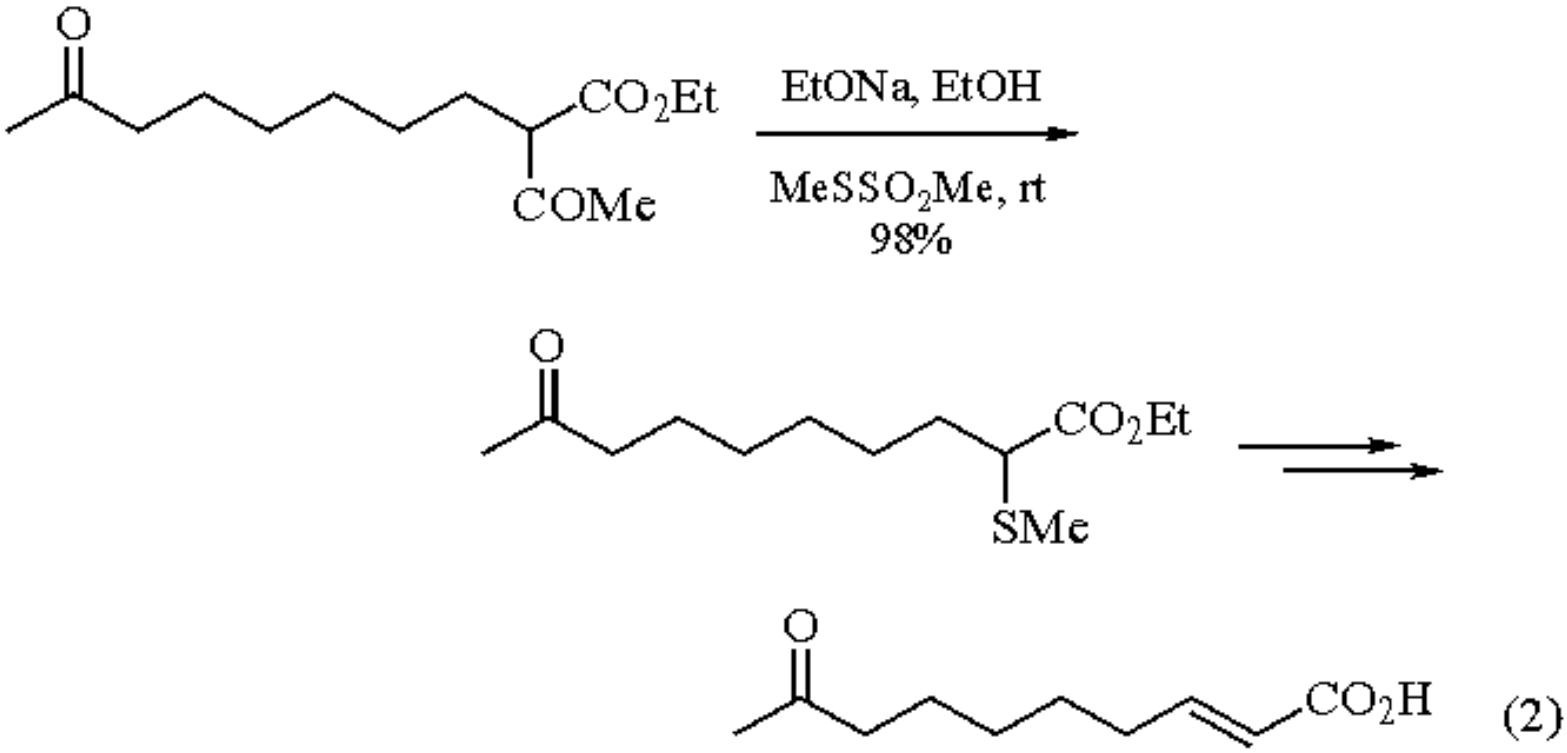

This contrasts to thiomethylation of methyl 9-oxodecanoate with MeSSMe and lithium cyclohexyl(isopropyl)amide, as reported by Trost.[8] In spite of various reaction conditions employed, Trost's procedure gives less than 30% yield of 2-methylthio-9-oxodecanoate, accompanied by bissulfenylation when the 9-oxo group is not protected. Moreover, toxic HMPA is required to obtain 86% of the sulfenylated ester even when the 9-oxo group is protected. The transformation

described in eqs 1 and 2 works with $PhSSO_2Ph$ as well.

Similarly, 3-methylthio-2-alkanones are prepared by the reaction of a 3-alkyl-2,4-pentanedione with 1 mol equiv (important) of $MeSSO_2Me$ in the presence of EtONa in EtOH at rt or ***Potassium Carbonate*** in acetone at reflux followed by addition of MeOH and reflux. An advantage of using weaker base K_2CO_3 in this reaction is that no bissulfenylation takes place even when excess sulfenylating agent is used. The method was applied to an efficient synthesis of pseudoionone (eq 3).[9]

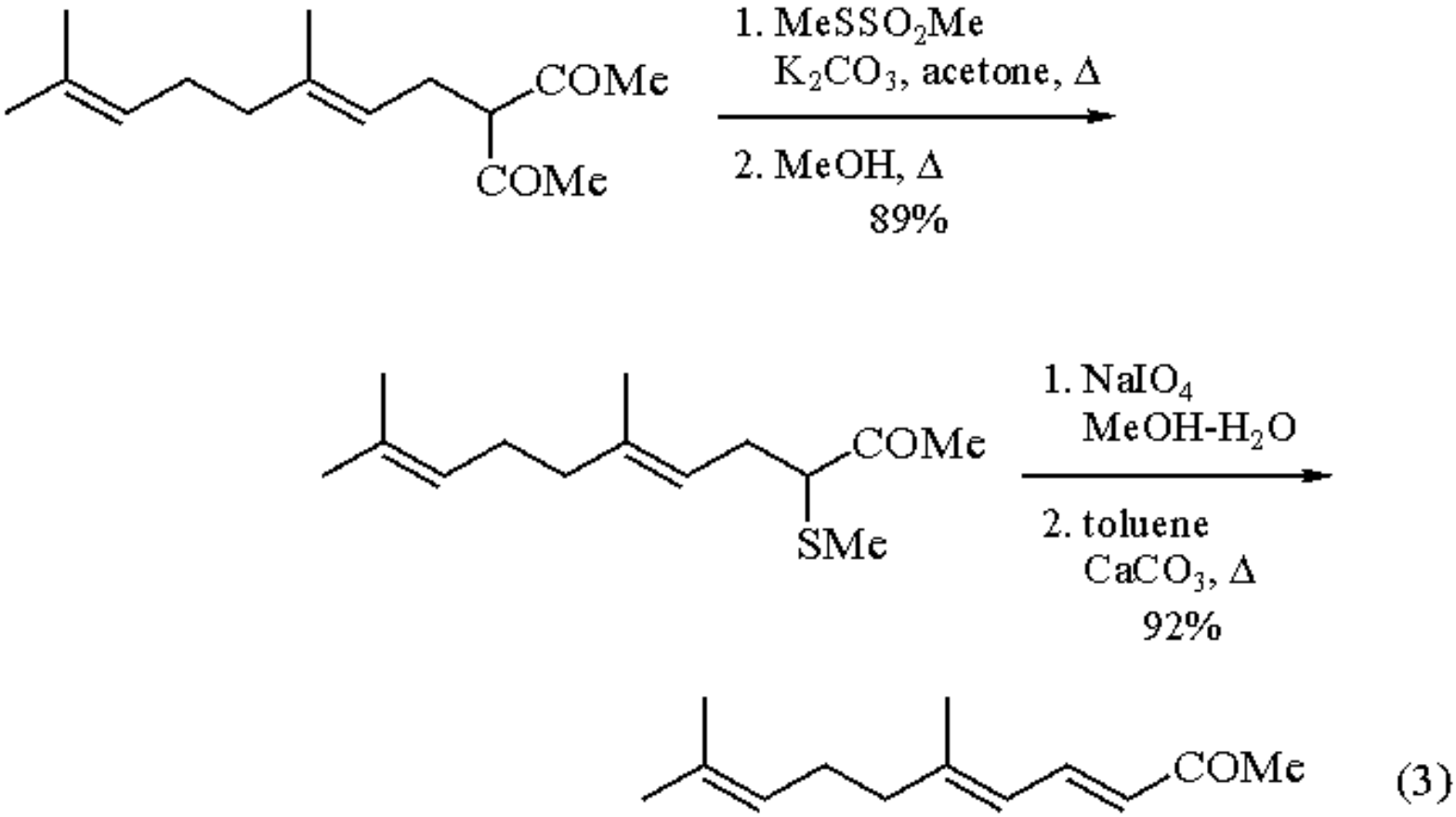

Diethyl 1-Methylthio-1(*Z*),3-butadienephosphonate.

An efficient synthesis of diethyl 1-methylthio-1(*Z*),3-butadienephosphonate from ***Diethyl Methylthiomethylphosphonate*** is carried out in four steps without contamination with the (*E*) geometric isomer (eq 4).[10] The methylthiobutadienephosphonate reacts smoothly with enamines. It also undergoes 1,4-addition with dialkylcuprates to yield exclusively (*E*)-alkenes. The resultant allylic phosphonates from these additions can be employed for the synthesis of 2-methylthio-substituted butadienes.

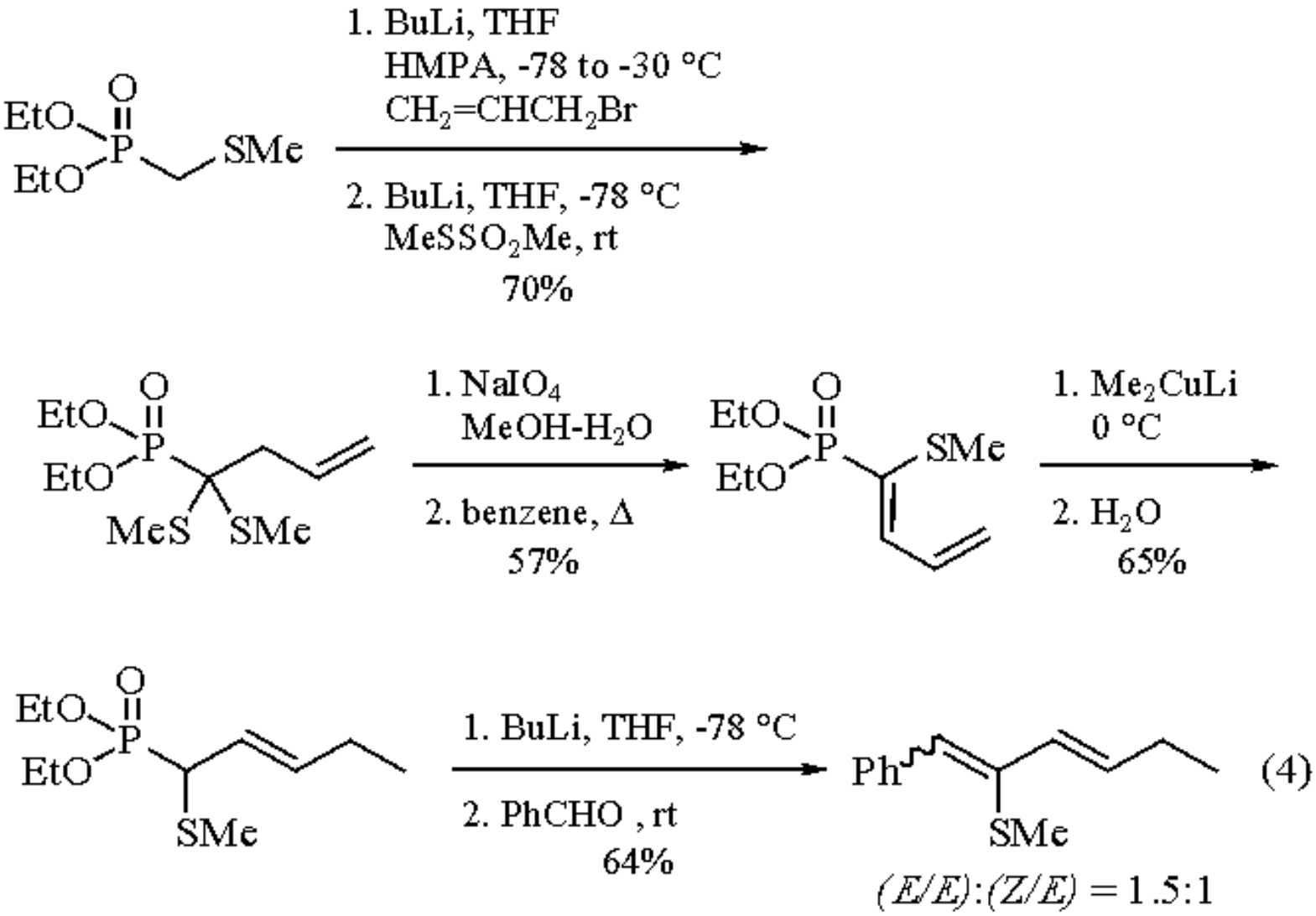

One-Pot Procedure for α-Methylthio β-Keto and Enamine Phosphonates.

α-Methylthio β-keto and enamine phosphonates are prepared from diethyl methylphosphonate by a one-pot procedure using a nitrile as an acyl cation equivalent, followed by treatment with $MeSSO_2Me$ as an electrophile (eq 5).[11]

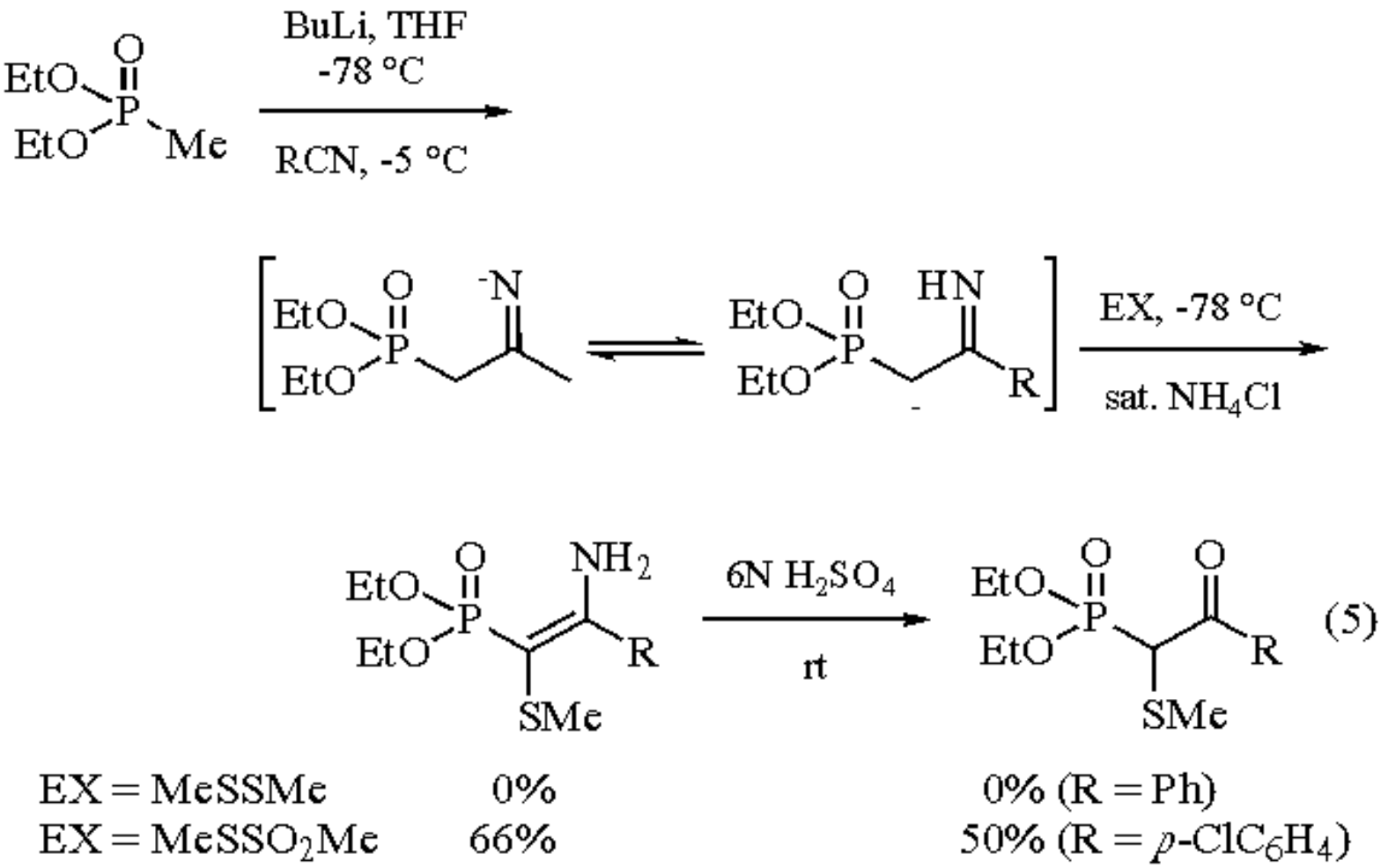

MeSSMe does not undergo this transformation due to the low reactivity of the anion toward the electrophilic sulfur moiety; however, the reaction proceeds smoothly with PhSSPh, PhSCl, and PhSeBr. Interestingly, $PhSO_2Cl$ affords α-chloro substituted phosphonates but no α-sulfonylated products.

γ-Oxocrotonate Derivatives through Bis(methylsulfenylation).

An efficient sequence of reactions to transform an alkoxycarbonylmethyl group to γ-oxocrotonate via bis(methylsulfenylation) is described in a synthesis of brefeldin-A (eq 6).[12]

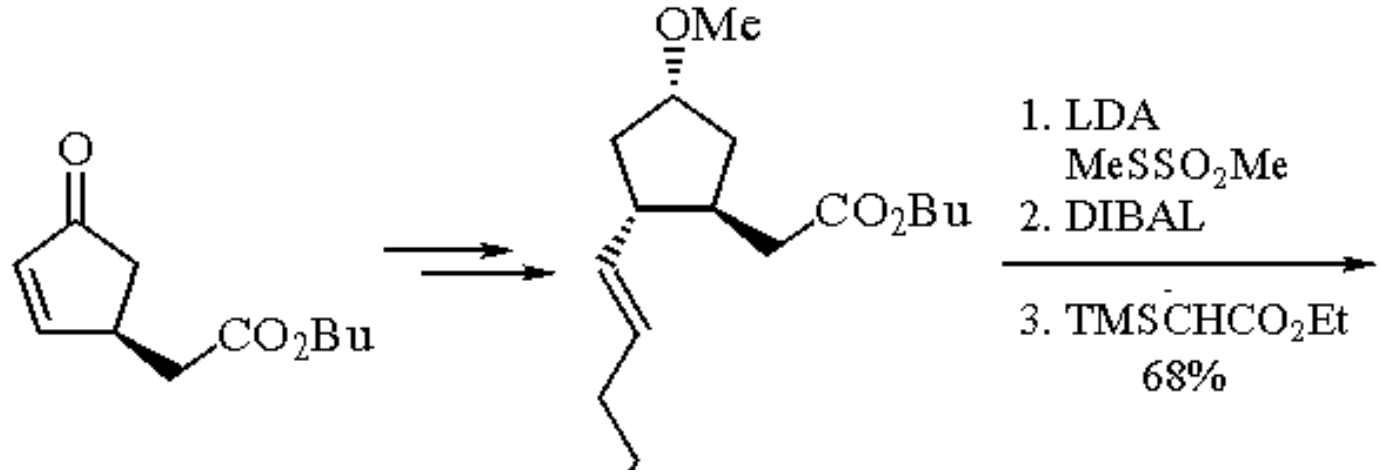

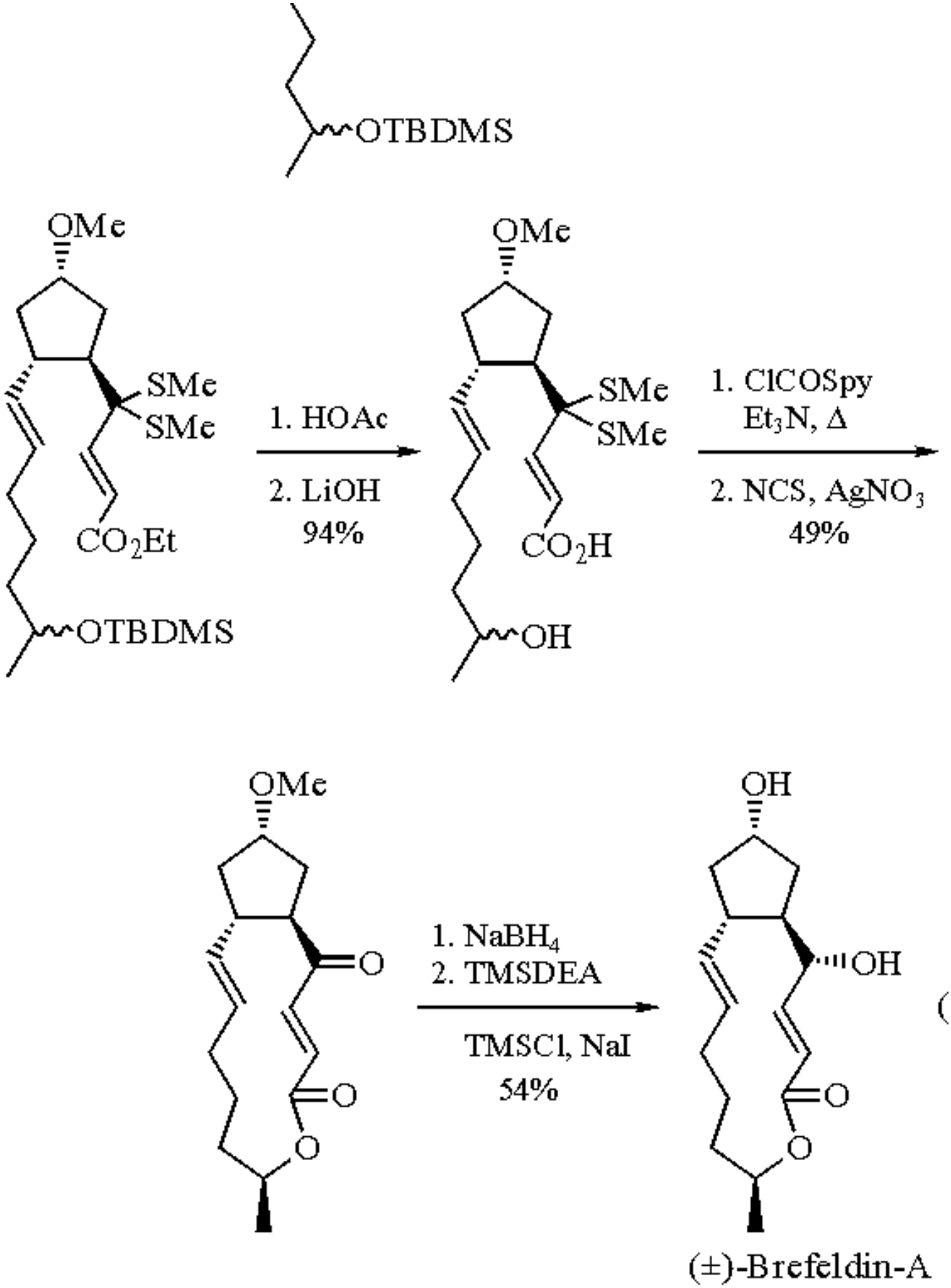

(6)

It is important that the methoxycarbonylmethyl group is treated twice with 1 equiv of ***Lithium Diisopropylamide*** and $MeSSO_2Me$ each to effect a one-pot bis(methylsulfenylation). Two equiv of both LDA and $MeSSO_2Me$ cannot be present at the outset of the reaction since destruction of the reagent(s) occurs faster than the introduction of the second

MeS group.[13] It is also noteworthy that a direct, one-step hydrolysis of the thioacetal group in the homologated ester to give ultimately the required γ-oxocrotonate is possible only with the dimethyl thioacetal but not with the diphenyl equivalent.[8]

Dithioacetal Formation.

Dithioacetals are prepared from activated methylene compounds with $MeSSO_2Me$ absorbed on ***Potassium Fluoride-Alumina*** (eq 7). Microwave irradiation without solvent provides a powerful activation for this preparation. MeSCl gives only poor yields and MeSSMe does not react under these conditions.[14]

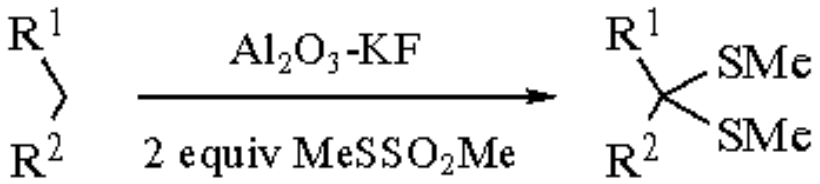

(7)

$R^1 = CO_2Et$; $R^2 = CO_2Et$, CN, Ph, MeCO (70-94%)
$R^1 = CO_2Et$; $R^2 = PO(OEt)_2$ (21%)
$R^1 = PO(OEt)_2$; $R^2 = PO(OEt)_2$ (95%)

Stereoselective Methylsulfenylation of Enones and Alkenes.

An α-oxoketene dithioacetal containing two different alkylthio substituents was prepared stereoselectively from a β-alkylthio-α,β-enone via treatment with LDA and $MeSSO_2Me$ in THF-HMPA (eq 8).[15] Use of MeSCl in this reaction yields a 1:1 mixture of the stereoisomers, possibly due to isomerization of the double bond geometry by the chloride ion formed in the reaction (eq 9). The reaction of the α-oxoketene dithioacetal with organocuprate reagents proceeds stereospecifically (eq 10), in that the alkylthio substituent *syn* to the ketone carbonyl is replaced by the cuprate ligand in all cases studied.

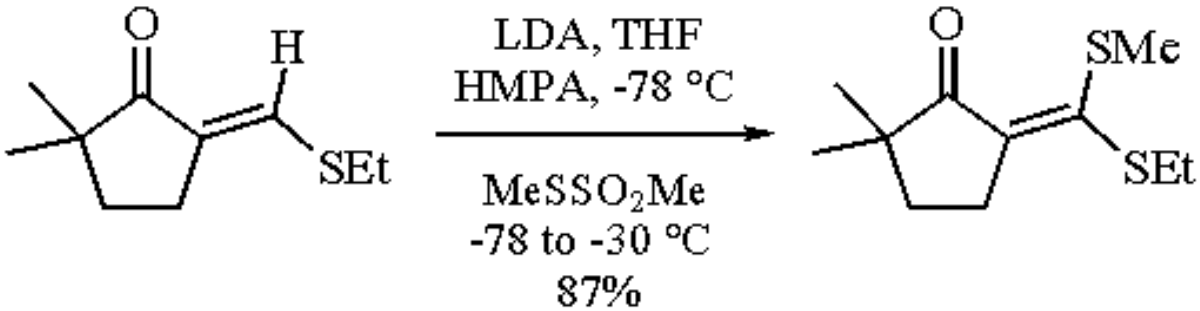

(8)

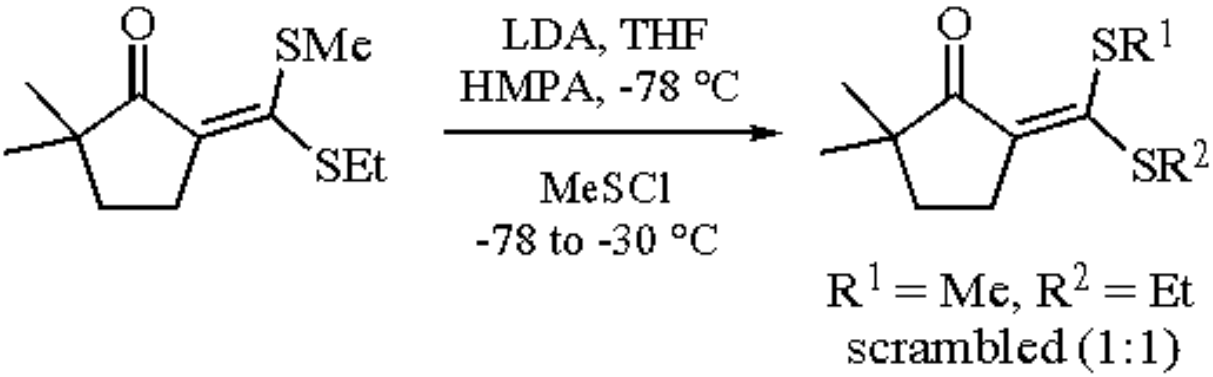

(9)

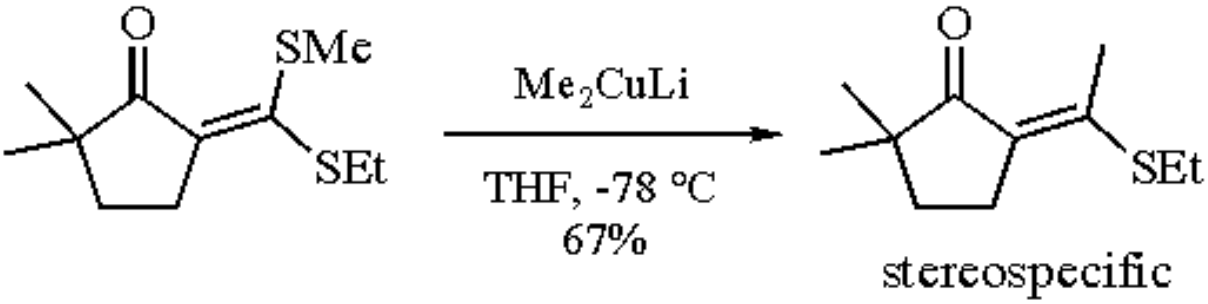

(10)

1-(Methylthio)-substituted cyclopropenes are easily prepared by electrophilic substitution of the protected monolithiated 3,3-dimethylcyclopropenes. Upon heating or under photolysis, the substituted cyclopropenes rearrange to allenes via possible mechanisms described in eq 11. Both the substituted cyclopropenes and rearranged products provide an interesting combination of functionalities, which make them potentially useful building blocks in organic synthesis.[16]

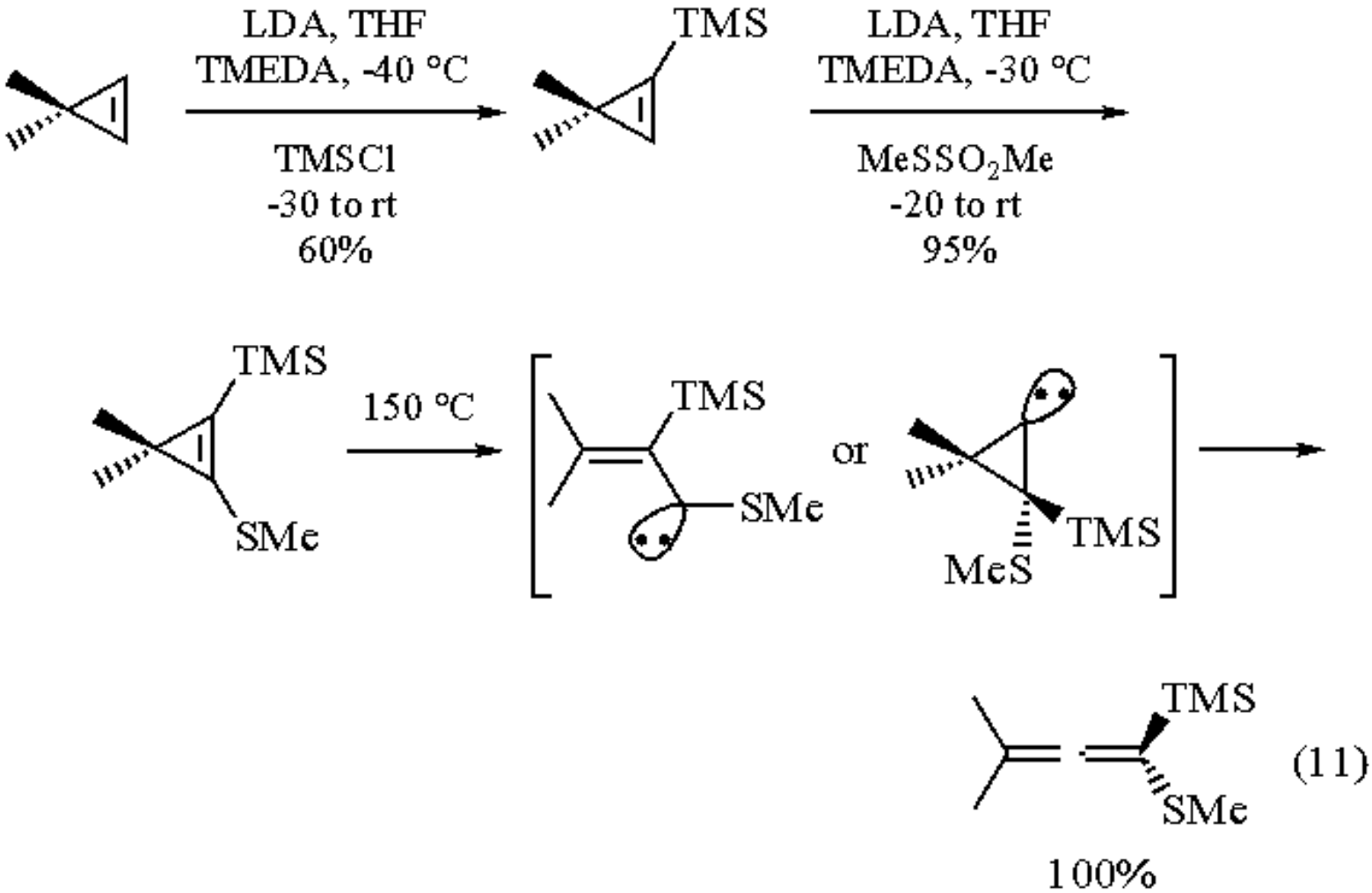

Unsymmetrical Disulfides.

Unsymmetrical aryl and alkyl disulfides are prepared from silyl sulfides and $MeSSO_2Me$ in $CHCl_3$ at 60 °C.[17] Methyl 2- and 4-pyridyl disulfide are prepared conveniently from 2- and 4-thiopyridone and $MeSSO_2Me$ in the presence of NaOH in H_2O in excellent yields.[18]

Related Reagents.

Dimethyl Disulfide; ***Methylsulfenyl Trifluoromethanesulfonate***; ***Methyl p-Toluenethiosulfonate***.

---

1. Trost, B. M. *CRV* **1978**, *78*, 363.
2. Laszlo, P.; Mathy, A. *JOC* **1984**, *49*, 2281.
3. (a) Smith, D. J.; Maggio, E. T.; Kenyon, G. L. *B* **1975**, *14*, 766. (b) Welches, W. R.; Baldwin, T. O. *B* **1981**, *20*, 512.
4. (a) Scholz, D. *S* **1983**, 944 (methylsulfenylation of cyclic ketones). (b) Wladislaw, B.; Marzorati, L.; Ebeling, G. *PS* **1990**, *48*, 163 (methylsulfenylation of *o*-, *m*-, *p*-substituted benzylsulfones). See also Ref. 14.
5. Shah, N. V.; Cama, L. D. *H* **1987**, *25*, 221 (MeS group is used for protection of the azetidinone NH; the protected *N*-SMe is acid stable).

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12. (a) Le Drian, C.; Greene, A. E. *JACS* **1982**, *104*, 5473. (b) Greene, A. E.; Le Drian, C.; Crabbé, P. *JOC* **1980**, *45*, 2713.
13. In contrast to bis(phenylsulfenylation). See (a) Ref. 8; also (b) Trost, B. M.; Massiot, G. S. *JACS* **1977**, *99*, 4405; (c) Trost, B. M.; Mao, M. K. T. *TL* **1980**, *21*, 3523.
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15. Dieter, R. K.; Silks, III, L. A.; Fishpaugh, J. R.; Kastner, M. E. *JACS* **1985**, *107*, 4679.
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18. Kitson, T. M.; Loomes, K. M. *Anal. Biochem.* **1985**, *146*, 429.

Kumiko Takeuchi

Eli Lilly and Company, Indianapolis, IN, USA

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Methyl 5-Methoxy-3-oxopentanoate

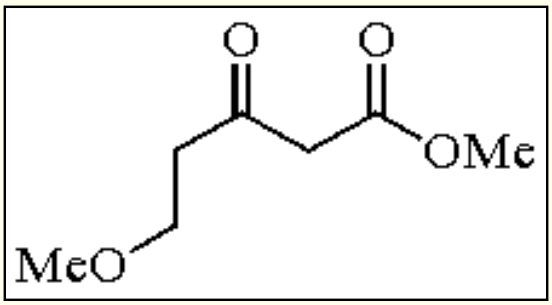

[62462-05-9] · $C_7H_{12}O_4$ · Methyl 5-Methoxy-3-oxopentanoate · (MW 160.19)

(precursor to the annulating agent, Nazarov's reagent;[1] can function as an annulating agent under acidic reaction conditions[2])

Physical Data: bp 75-76 °C/0.5 mmHg.

Analysis of Reagent Purity: IR, NMR.[3]

Preparative Methods: see below.

General Discussion.

Methyl 5-methoxy-3-oxopentanoate was first synthesized by Nazarov[1] and co-workers in 1953 utilizing the Hunsdiecker cleavage. Several modern methods have been reported for preparation of this compound. Heathcock[2] and co-workers based their synthesis of the ethyl 5-ethoxy analog on a reaction developed by Ireland.[4] The magnesium enolate of ethyl hydrogen malonate is reacted with β-ethoxypropionyl chloride followed by decarboxylation (eq 1). The title compound was also prepared in this manner.[5]

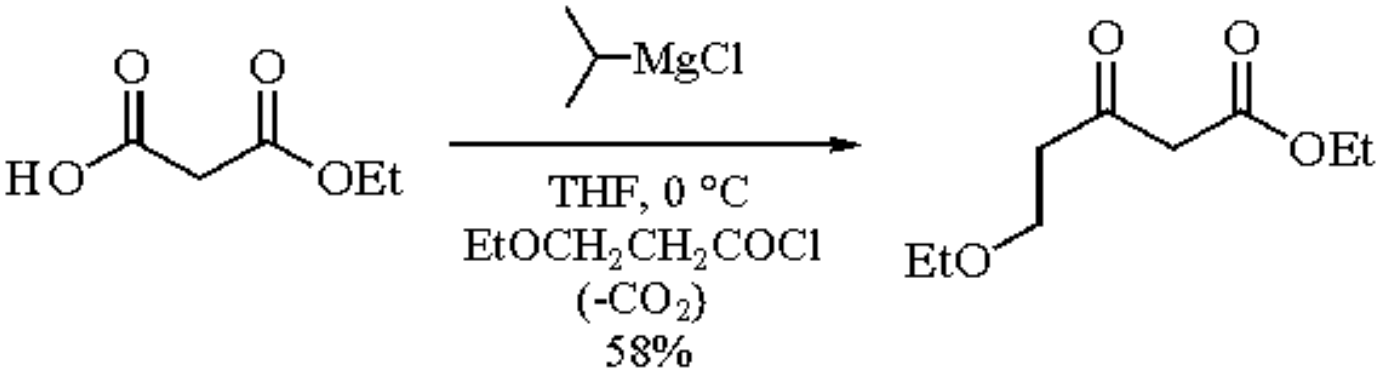

(1)

Trost[6] prepared methyl 5-phenylthio-3-oxopentanoate by alkylation of the dianion of methyl acetoacetate (eq 2). In this case, iodomethyl phenyl sulfide must be prepared from thioanisole and sulfuryl chloride. The resulting ***Chloromethyl Phenyl Sulfide*** is then treated with ***Sodium Iodide*** in acetone.

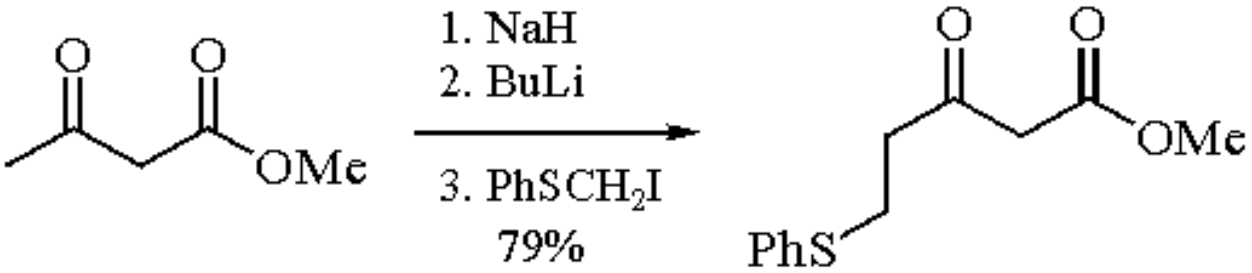

(2)

Methyl 5-methoxy-3-oxopentanoate has also been prepared using ***Chloromethyl Methyl Ether*** (R^2 = H) as the alkylating agent (eq 3).[7] Compounds with R^1 = R^2 = alkyl groups were reported also.

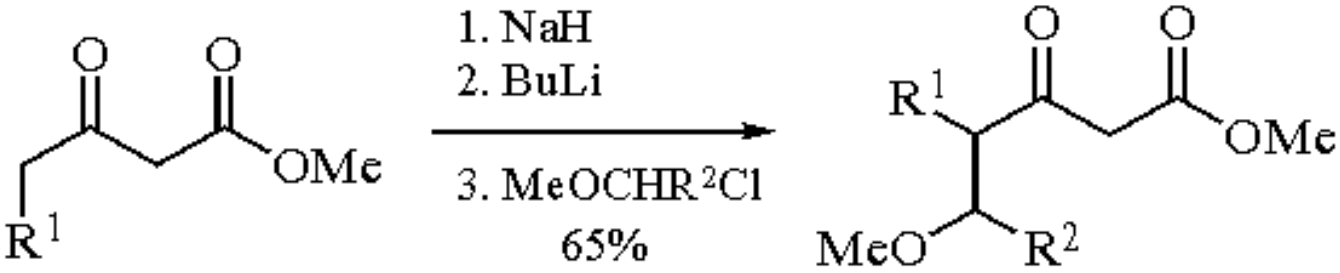

(3)

An alternative preparation of methyl 5-methoxy-3-oxopentanoate involves a Friedel-Crafts reaction,[3] as shown in eqs 4 and 5.

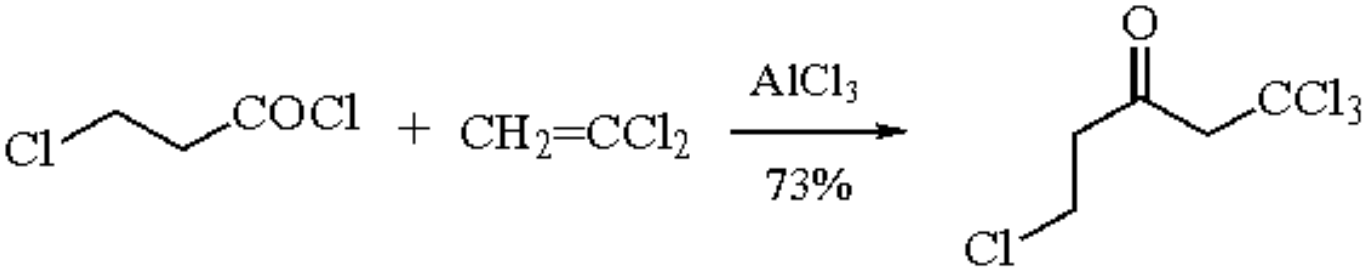

(4)

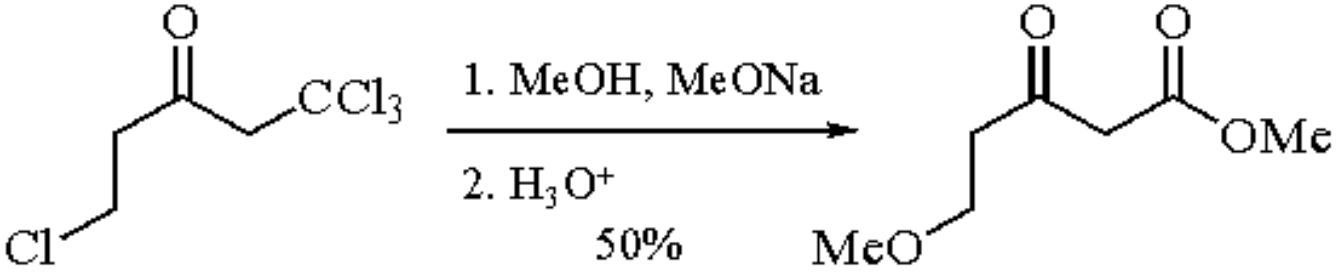

(5)

A novel Wittig-type reaction[8] has also been used to prepare 5-alkoxy-3-oxopentanoate esters (eq 6). The advantage here is the flexibility of the alkoxy and ester groups.

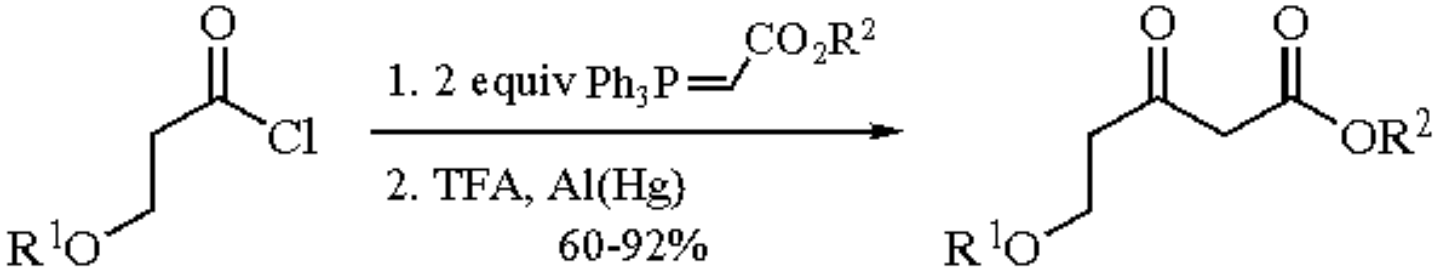

Methyl 5-methoxy-3-oxopentanoate has been used in two principal areas. The first is to prepare and isolate ***Methyl 3-Oxo-4-pentenoate*** (Nazarov's reagent),[2] a now well-known annulating agent. Methanol is eliminated under acidic conditions to give the Michael acceptor (eq 7). The methanol elimination is sometimes difficult and isolation of Nazarov's reagent can be problematic due to rapid polymerization.

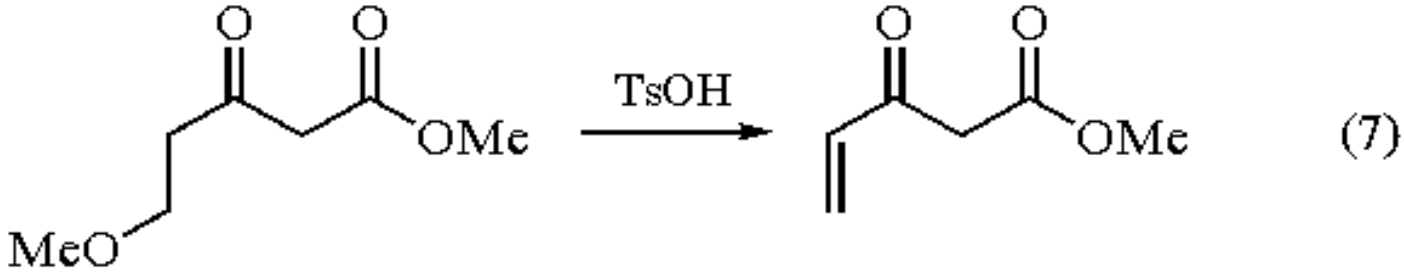

In the 5-thiophenoxy compound (eq 2), elimination and isolation are reported to be facile processes (eq 8).[6]

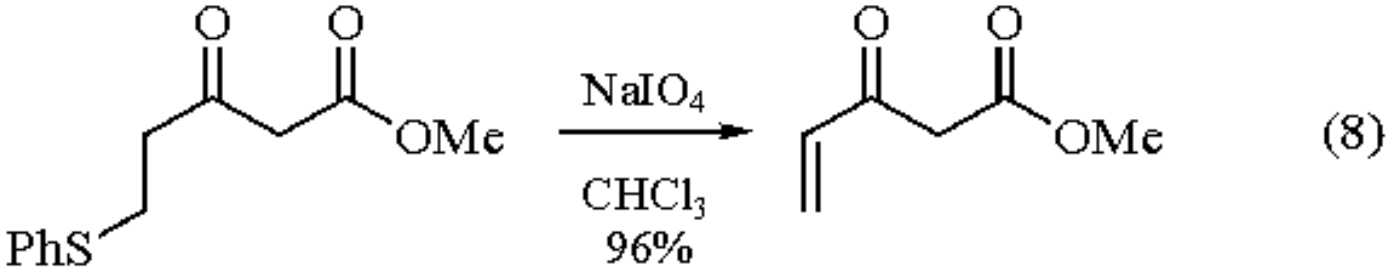

Heathcock[2] circumvented the isolation difficulties of Nazarov's reagent by reaction of ethyl 5-ethoxy-3-oxopentanoate under acid catalysis in the presence of the nucleophile. Nazarov's reagent is generated in situ and the annulation occurs smoothly (eq 9). Several groups have utilized this method in synthesis.[5]

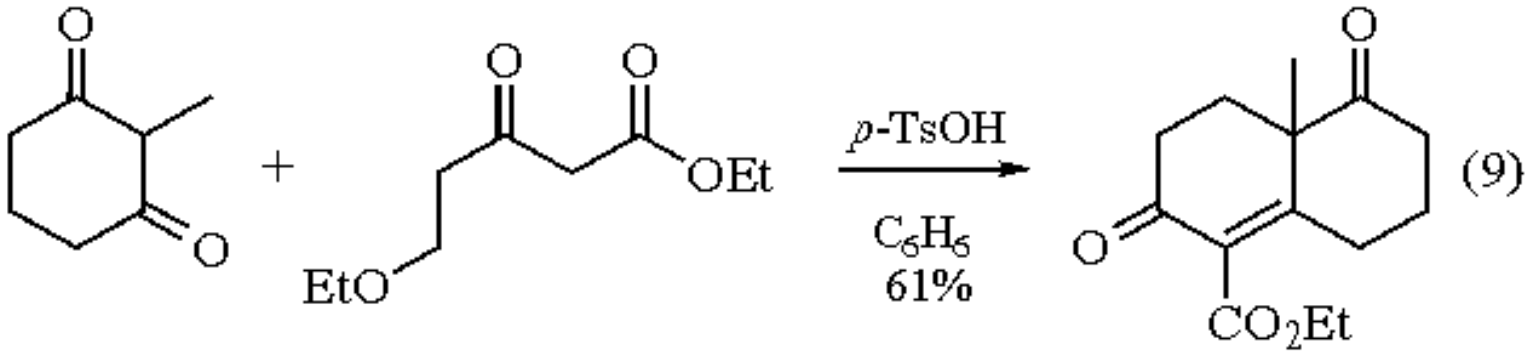

Related Reagents.

t-Butyl (E)-3-Oxo-4-hexenoate; ***Chloromethyl Phenyl Sulfide***; ***1,3-Cyclohexanedione***; ***Ethyl Acetoacetate***; ***Methyl 6-Oxo-1-cyclohexenecarboxylate***; ***Methyl 3-Oxo-4-pentenoate***; ***Methyl Vinyl Ketone***.

---

1. Nazarov, I. N.; Zav'yalov, S. I. *ZOB* **1953**, *23*, 1703. Akhrem, A. A.; Chernov, Yu. G. *ZOR* **1987**, *23*, 288.
2. Ellis, J. E.; Dutcher, J. S.; Heathcock, C. H. *SC* **1974**, *4*, 71.
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Methyl(methylene)oxonium Hexafluoroantimonate

$MeOCH_2^+SbF_6^-$

[41581-97-9] · $C_2H_5F_6OSb$ · Methyl(methylene)oxonium Hexafluoroantimonate · (MW 280.82)

(methoxymethylating agent; methylating agent; cationic polymerization initiator)

Preparative Methods: can be prepared either by treating ***Methoxyacetyl Chloride*** with anhydrous hexafluoroantimonic acid (see ***Hydrogen Fluoride-Antimony(V) Fluoride***) in SO_2, or by combining ***Chloromethyl Methyl Ether*** with the acid in methylene chloride.[1] In both cases, the pure $MeOCH_2^+SbF_6^-$ was obtained by washing the crude products with dry Freon 113.

Handling, Storage, and Precautions: is corrosive and moisture sensitive. It should be stored in a Teflon or Nalgene bottle under anhydrous conditions.

General Discussion.

The methyl(methylene)oxonium ion ($MeOCH_2^+$) is one of the few stable primary carbenium ions and has been a subject of many experimental and theoretical studies.[5-7] The experimental investigation of the carbenium ion has been carried out both in liquid[5] and gas phases.[6] The hexafluoroantimonate salt is a stable crystalline compound and is capable of electrophilic addition to carbon-carbon double bonds.[8] When methyl geranylate was combined with $MeOCH_2^+SbF_6^-$, cyclization occurred. Both epimers of the cyclization product were obtained in almost equal molar ratio (eq 1). However, when the substrate was changed to geranylacetone, one of the epimers was produced as a predominant product (eq 2). The low stereoselectivity in the case of methyl geranylate at the epimeric site is due to the decreased electron density of the α,β-unsaturated methyl carboxylic ester double bond in the molecule.

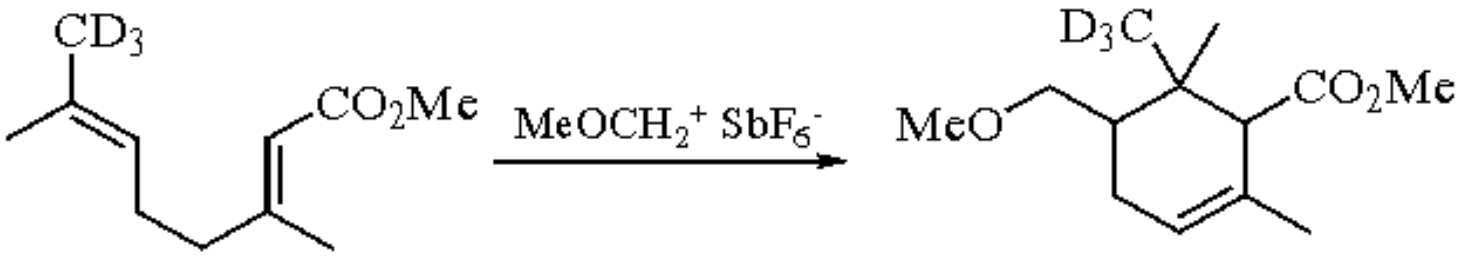

(1)

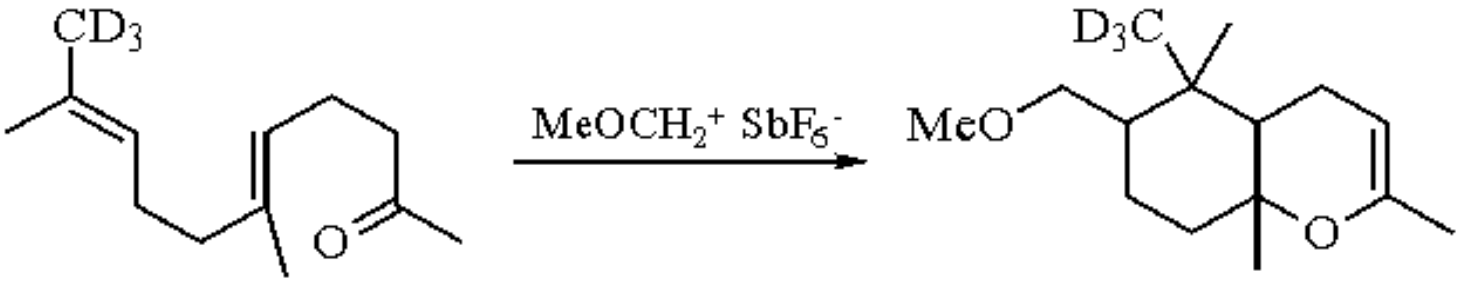

(2)

Due to the ambident nature of methyl(methylene)oxonium ion, $MeOCH_2^+SbF_6^-$ is also capable of methylation of nucleophiles through displacement of formaldehyde. This was shown in the reaction of $MeOCH_2^+SbF_6^-$ with benzene (eq 3).[1] Toluene was obtained in high yield in the reaction.

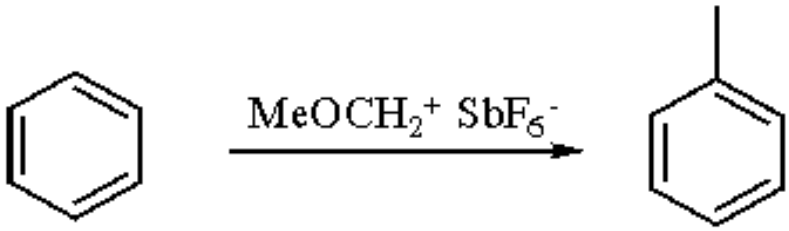

(3)

It was reported that $MeOCH_2^+SbF_6^-$ can also initiate cationic polymerization.[9]

Methoxycarbenium salts with other counterions such as ClO_4^-,[2] BF_4^-,[3] and $SbCl_6^-$ [4] are also known and have been used in organic synthesis.

Related Reagents.

Chloromethyl Methyl Ether.

---

1. Olah, G. A.; Svoboda, J. J. *S* **1973**, 52.
2. Jaacks, V.; Frank, H.; Grunberger, E.; Kern, W. *Makromol. Chem.* **1968**, *115*, 290.
3. (a) Roitburd, G. V.; Smit, W. A.; Semenovsky, A. V.; Shchegolev, A. A.; Kucherov, V. F.; Chizhov, O. S.; Kadentsev, V. I. *TL* **1972**, 4935. (b) Smit, V. A.; Roitburd, G. V.; Semenovskii, A. V.; Kucherov, V. F.; Chizhov, O. S.; Kadentsev, V. I. *IZV* **1971**, 2356.
4. Komarov, B. A.; Rozenberg, B. A.; Enikolopyan, N. S. *IZV* **1974**, 1874.
5. (a) Olah, G. A.; Bollinger, J. M. *JACS* **1967**, *89*, 2993. (b) White, A. M.; Olah, G. A. *JACS* **1969**, *91*, 2943.
6. For example, see: (a) Okada, S.; Abe, Y.; Taniguchi, S.; Yamabe, S. *JACS* **1987**, *109*, 295. (b) Kim, J. K.; Bonicamp, J.; Caserio, M. C. *JOC* **1981**, *46*, 4236.
7. For example, see: (a) Farcasiu, D.; O'Donnell, J. J.; Wiberg, K. B.; Matturro, M. *CC* **1979**, 1124. (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *JACS* **1992**, *114*, 850.
8. Mustafaeva, M. T.; Kuzovkin, V. A.; Smit, V. A.; Semenovskii, A. V.; Kucherov, V. F. *DOK* **1973**, *208*, 1103.
9. Rozenberg, B. A. In *Cationic Polym. Relat. Processes, Proc. Int. Symp., 6th*; Goethals, E. J., Ed.; Academic: London, 1984 (*CA* **1984**, *101*, 211 777a).

Methyl *O*-Methyllactate[1]

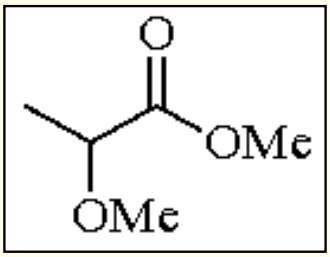

[17639-76-8] · $C_5H_{10}O_3$ · Methyl *O*-Methyllactate · (MW 118.15)

(lithium enolate used in the stereoselective synthesis of 2-methoxy-3-hydroxypropionate derivatives[3])

Physical Data: bp 130-131 °C.

Preparative Methods: by esterification of the known *O*-methyllactic acid.[2,3a]

The (*Z*)-lithium enolate (**2**), derived from reaction of methyl *O*-methyllactate (**1**) with ***Lithium Diisopropylamide***, reacts with aldehydes to form (**3**) (*l* isomer) in preference to (**4**) (*u* isomer) (eq 1).[3] The stereoselectivity is approximately 3:1 in reactions with straight-chain and aromatic aldehydes. Stereospecificity is achieved in reactions with aldehydes with branching at the α-carbon. Other ethers (e.g. benzyl or MEM) derived from methyl lactate exhibit the same trend in stereoselectivity, although the magnitude is lower.[3] Stereoselectivity in favor of compounds of *u* relative stereochemistry, illustrated in (**4**), is obtained in reactions using the benzyl ether derivative of a hindered ester (e.g. **5**).[3] The stereoselectivity in aldol reactions of (**2**) has been used to set the relative stereochemistry at C-3 and C-4 in a synthesis of L-cladinose (**6**).[4]

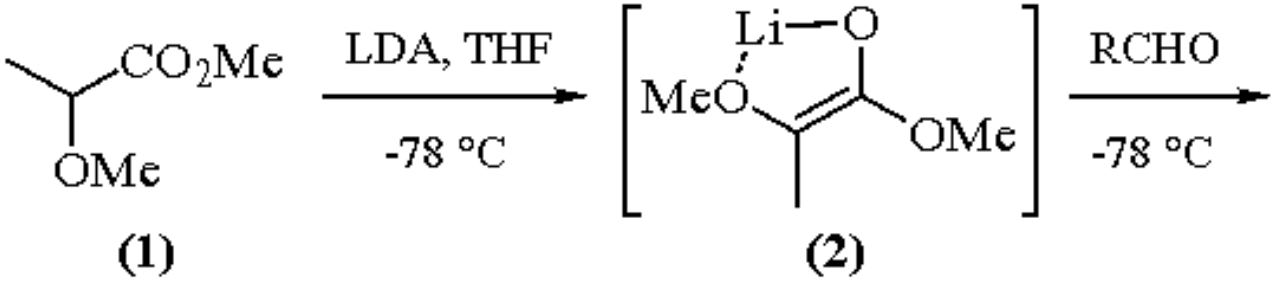

(1) (2)

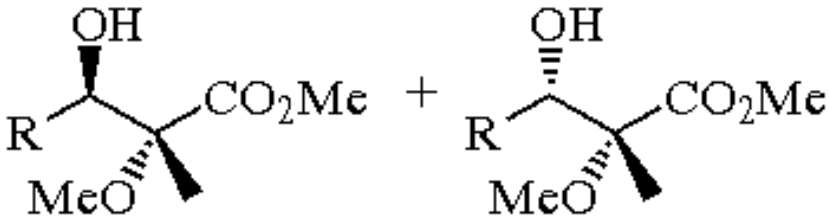

(1)

(3) (4)

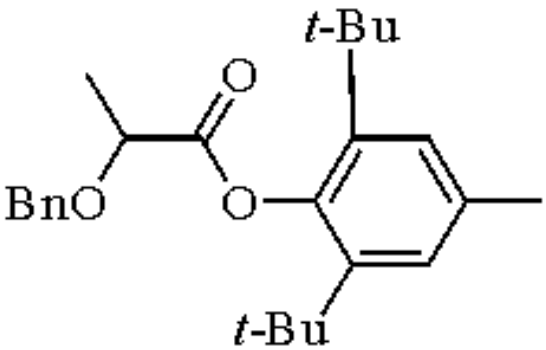

(5)

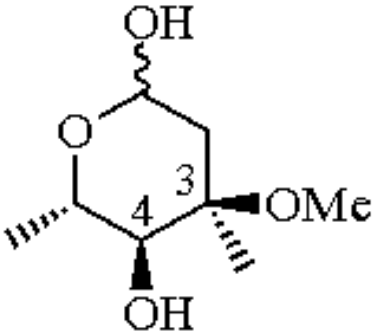

(6)

Related Reagents.

(R,R)-2-t-Butyl-5-methyl-1,3-dioxolan-4-one; ***Ethyl Lithioacetate***; ***Ethyl Mandelate***; ***Phenoxyacetic Acid***; ***Tris(trimethylsilyloxy)ethylene***.

---

1. (a) Heathcock, C. H. *Modern Synthetic Methods* Scheffold, R. Ed.; VCH: Weinheim, 1992. (b) Heathcock, C. H. *COS* **1991**, *2*, Chapter 1.6. (c) Heathcock, C. H. *Asymmetric Synthesis*; Academic: New York, 1984; Vol. 3.
2. (a) Oki, M.; Hirota, M. *BCJ* **1963**, *36*, 290. (b) Petrov, A. A.; Gantseva, B. V.; Kiseleva, O. A. *ZOB* **1953**, *23*, 737.
3. (a) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Marki, H.-P.; Montgomery, S. H. *JACS* **1984**, *106*, 8161. (b) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *JACS* **1981**, *103*, 4972.
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Methyl 2-Methylthioacrylate

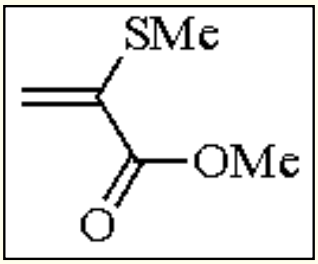

[43228-10-0] · $C_5H_8O_2S$ · Methyl 2-Methylthioacrylate · (MW 132.20)

(versatile and reactive Michael acceptor[2-5])

Physical Data: bp 78 °C/12 mmHg.

Solubility: sol Et_2O, THF, EtOH, and most organic solvents.

Analysis of Reagent Purity: IR, NMR, GLC.

Preparative Methods: prepared either by the reaction of methyl 2-chloroacrylate[1a] or methyl 2-bromoacrylate[1b] with ***Methanethiol*** in the presence of ***Triethylamine*** and ***N,N-Dimethylformamide***. It is also obtained[1c] quantitatively by chlorination of methyl 2-alkylthiopropionates (alkyl = Me/Et) with ***Sulfuryl Chloride*** at 0 °C followed by dehydrochlorination using refluxing chloroform. For preparation of alkyl 2-alkylsulfonylacrylates and its uses, see Gipstein.[8]

Handling, Storage, and Precautions: since the reagent is an acrylate, it should be stored under N_2 in the refrigerator and should be inhibited with ionol or 100 ppm of hydroquinone monomethyl ether. Use in a fume hood.

1,4-Dicarbonyl Compounds.

Lithium enolates derived from esters,[2a] lactones,[2a] and thioacetal monosulfoxide[2b] undergo smooth Michael addition in high yield. These adducts on hydrolysis give the corresponding carbonyl analogs (eqs 1-3). Enamines[2a] give high yields of Michael adducts (eq 4).

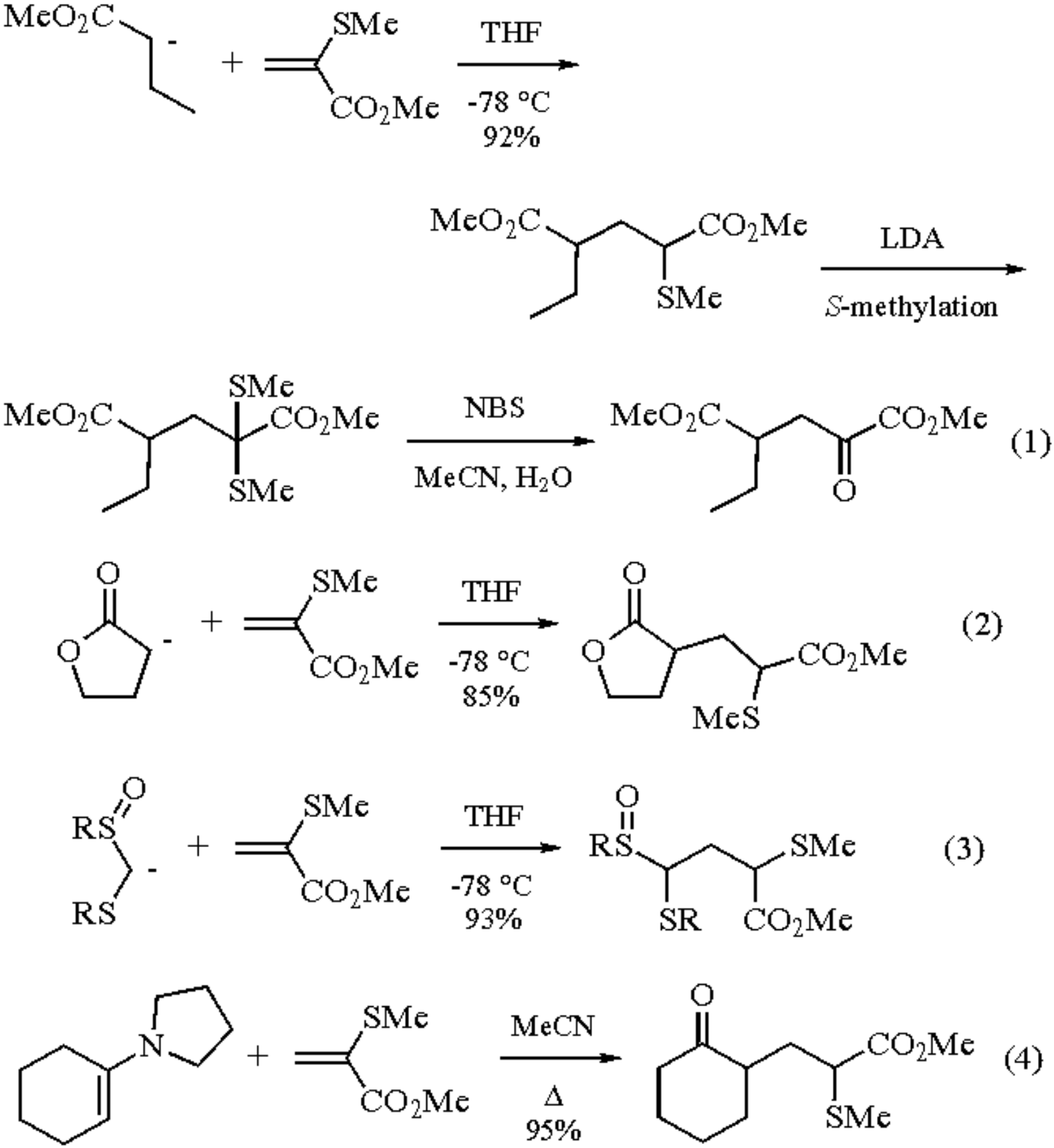

Synthesis of (±)-Vincamine.[3]

The lithium enolate of a lactam undergoes Michael addition to methyl 2-methylthioacrylate at -78 °C, furnishing 98%

yield of the adduct (eq 5) which was later converted to (±)-vincamine alkaloid. A similar Michael addition was used in the synthesis of α-kainic acid (eq 6).[4]

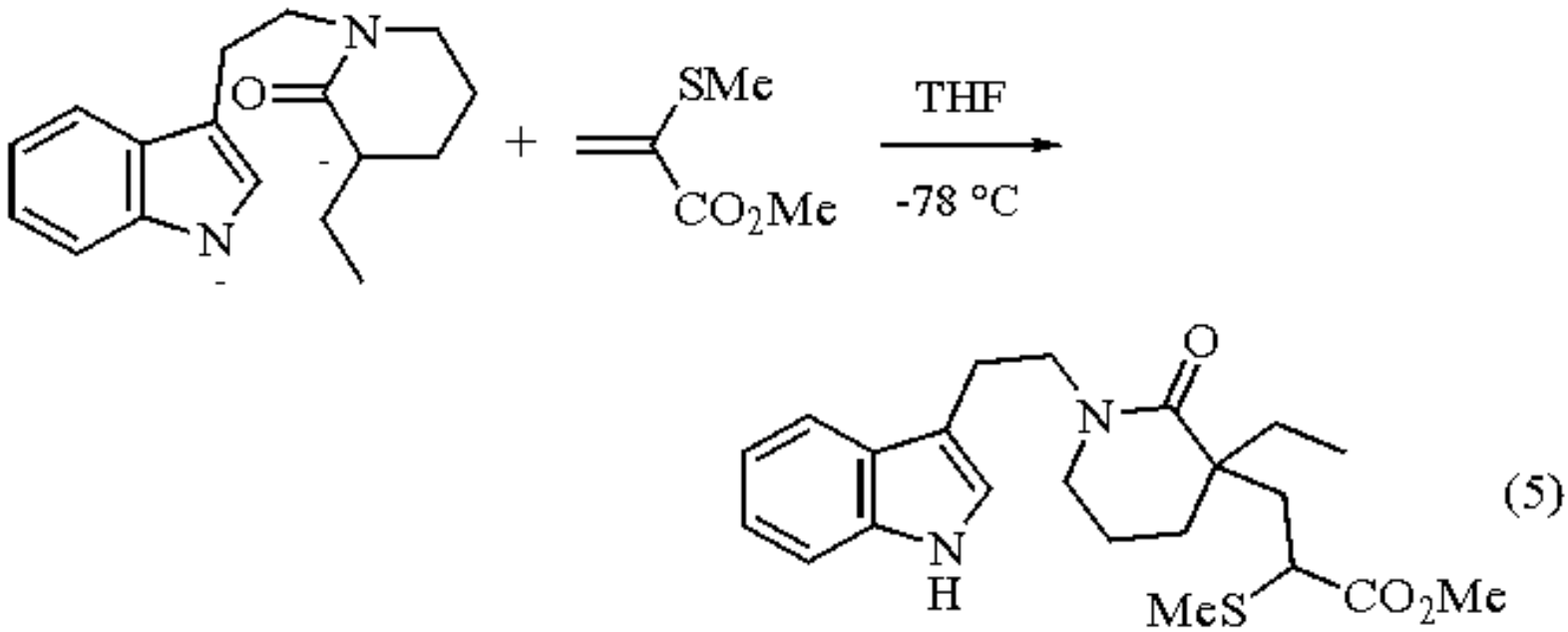

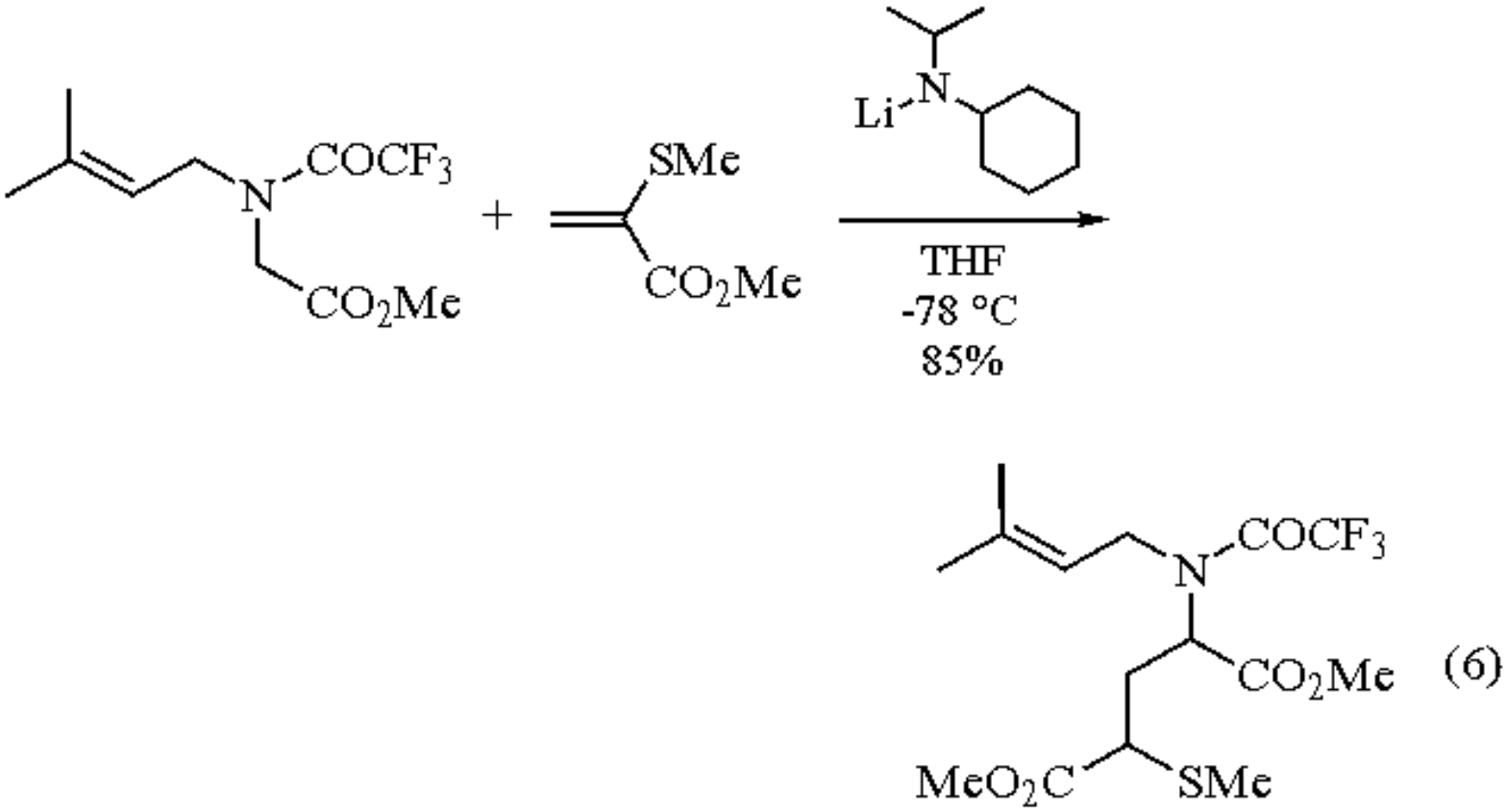

Diels-Alder Substrate.

The reagent undergoes a facile, ***Aluminum Chloride***-catalyzed Diels-Alder[5a] reaction with ***Isoprene***, ***Cyclopentadiene***, and cyclohexadiene and gives [4 + 2] addition products (eqs 7 and 8). If the reaction is carried out under thermal

conditions, mixtures of *endo* and *exo* adducts are formed. These adducts are converted to ketones using ***N-Chlorosuccinimide***/*t*-butanol.

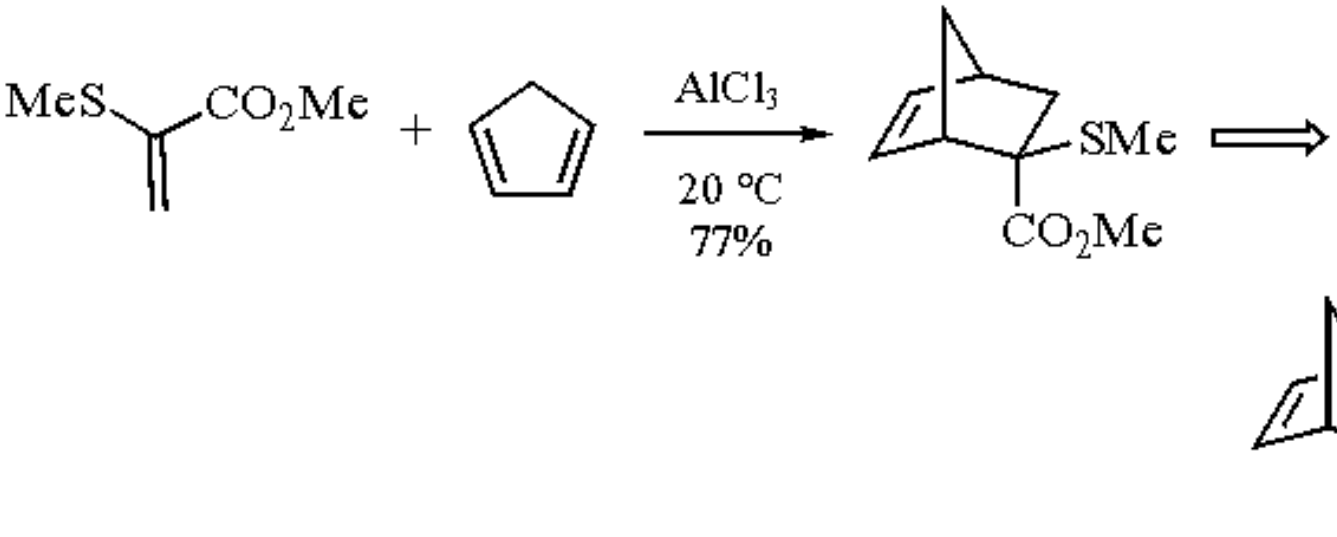

(7)

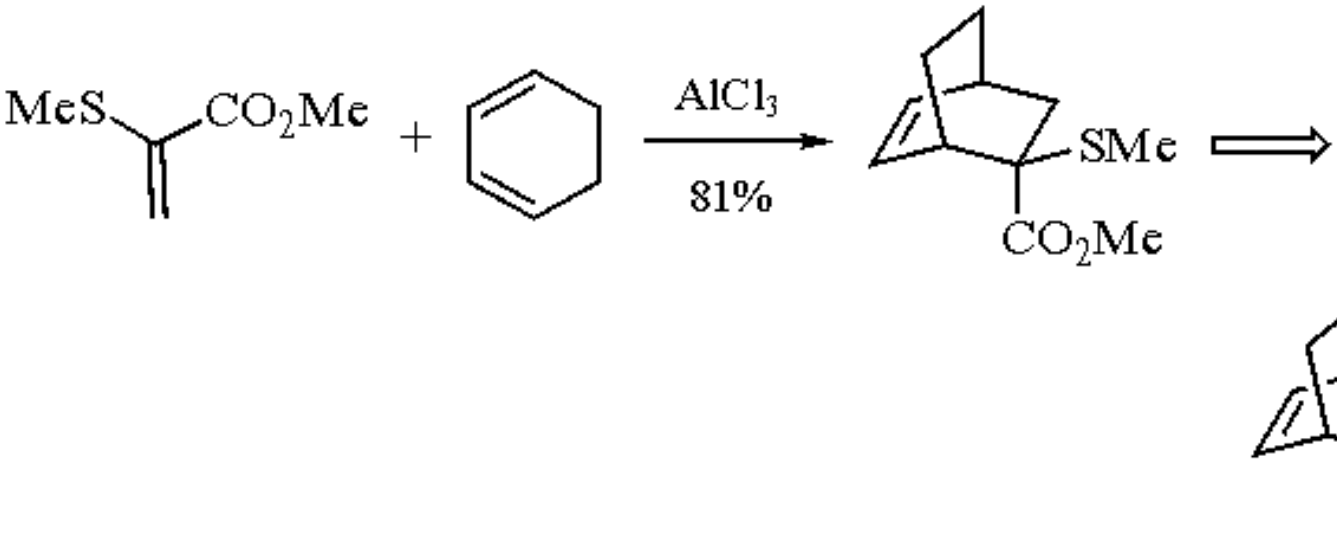

(8)

This further demonstrates that methyl 2-methylthioacrylate can be regarded as a ketene[5b] equivalent. With electron-poor dienes such as 3-aryl-1,2,4,5-tetrazine,[6] it gives regioselectively only one of two possible [4 + 2] cycloadducts (eq 9).

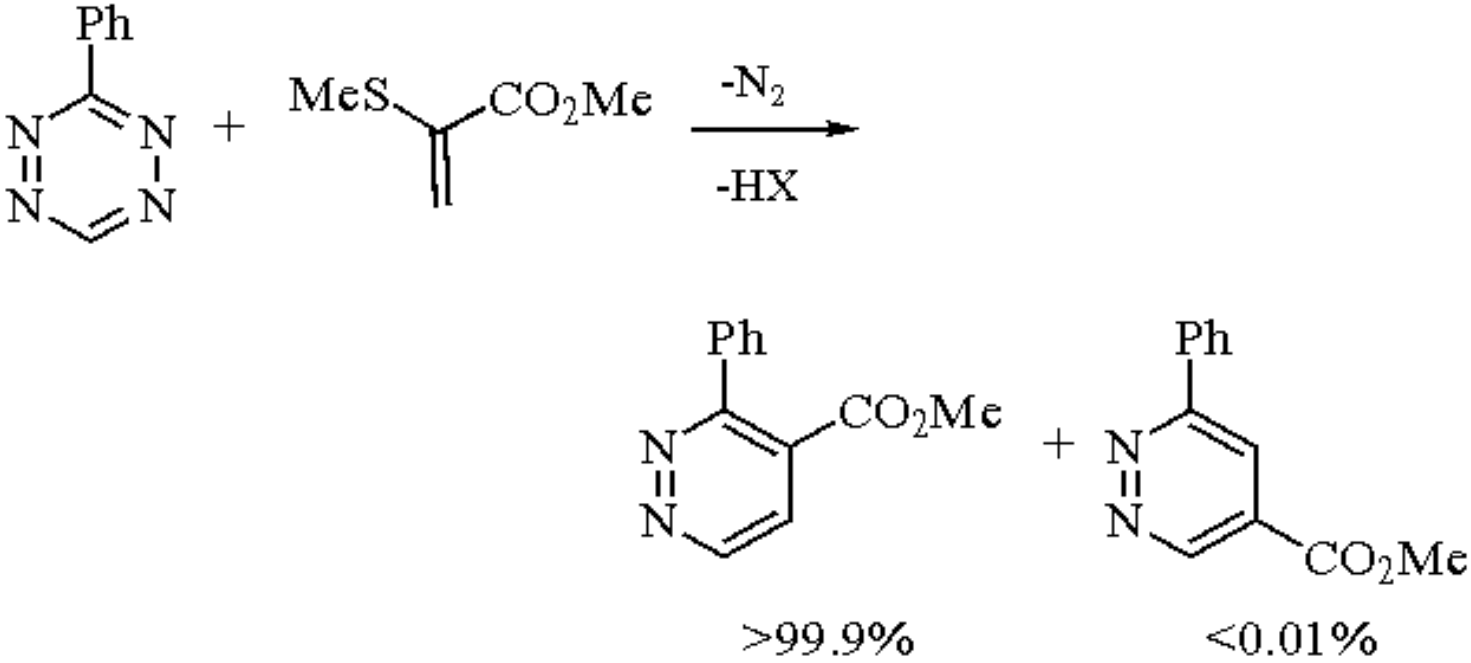

(9)

Use of this reagent in the acid-catalyzed ene reaction[7] does not give any ene product; instead, it rearranges to *trans*-β-(methylthio)acrylate (eq 10).

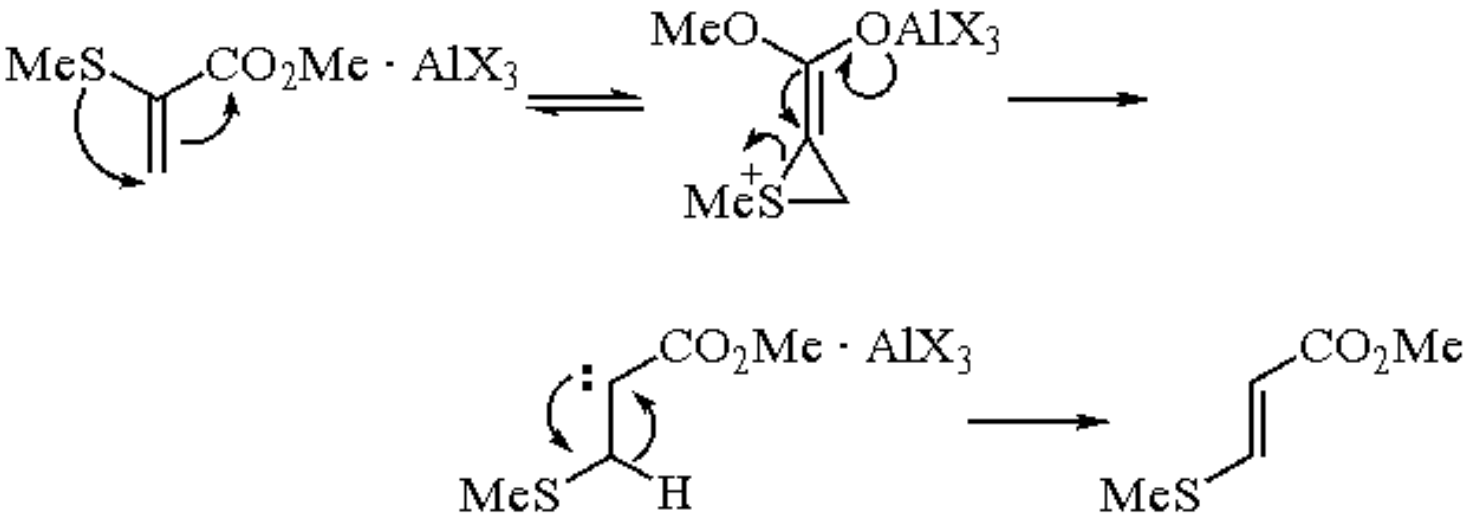

(10)

Related Reagents.

Methyl 2-Trimethylsilylacrylate; ***Trimethyl 2-Phosphonoacrylate***.

---

1. (a) Gundermann, K.-D.; Thomas, R. *CB* **1958**, *91*, 1330 (*CA* **1958**, *52*, 19 930b). (b) Boucher, J.-L.; Stella, L. *T* **1988**, *44*, 3595. (c) Iriuchijima, S.; Tanokuchi, K.; Tadokoro, K.; Tsuchihashi, G. *ABC* **1976**, *40*, 1031.
2. (a) Cregge, R. J.; Herrmann, J. L.; Schlessinger, R. H. *TL* **1973**, 2603. (b) Herrmann, J. L.; Richman, J. E.; Schlessinger, R. H. *TL* **1973**, 3271.
3. Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *JACS* **1979**, *101*, 1540.

4. Oppolzer, W.; Andres, H. *HCA* **1979**, *62*, 2282.
5. (a) Stella, L.; Boucher, J.-L. *TL* **1982**, *23*, 953. (b) Boucher, J.-L.; Stella, L. *T* **1988**, *44*, 3607.
6. Meier, A.; Sauer, J. *TL* **1990**, *31*, 6855.
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8. Gipstein, E.; Willson, C. G.; Sachdev, H. S. *JOC* **1980**, *45*, 1486.

Anubhav P. S. Narula

International Flavors & Fragrances, Union Beach, NJ, USA

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N-Methylmorpholine *N*-Oxide[1]

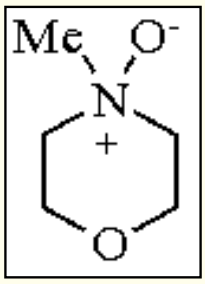

[7529-22-8] · $C_5H_{11}NO_2$ · *N*-Methylmorpholine *N*-Oxide · (MW 117.17)

(used as a co-oxidant with OsO_4[2] and ruthenates;[3] acts a mild oxidizing agent[4])

Alternate Name: NMO.

Physical Data: mp 75-76 °C (as monohydrate)

Solubility: sol water, acetone, alcohol, ether.

Form Supplied in: colorless deliquescent crystals; available commercially.

Purification: crystallize from ethanol.

Handling, Storage, and Precautions: refrigerate; hygroscopic; irritant; handle in a fume hood using gloves; avoid skin contact and inhalation; in case of contact, rinse immediately with water.

Co-oxidation Reagent.

N-Methylmorpholine *N*-oxide is commonly used as a mild co-oxidant. The stoichiometric use of ***Osmium Tetroxide*** to *cis*-dihydroxylate alkenes is avoided by using NMO as a reoxidant (eq 1).[1,2,5] This reagent is preferred over other *cis*-dihydroxylation reagents such as ***Potassium Permanganate***, ***Iodine-Silver Acetate***, or ***Osmium Tetroxide*** in the presence of barium perchlorate or ***Hydrogen Peroxide***, since these reagents give poor yields, require cumbersome workups, or are prohibitively expensive for large-scale glycolization reactions.[2,5] See also ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***.

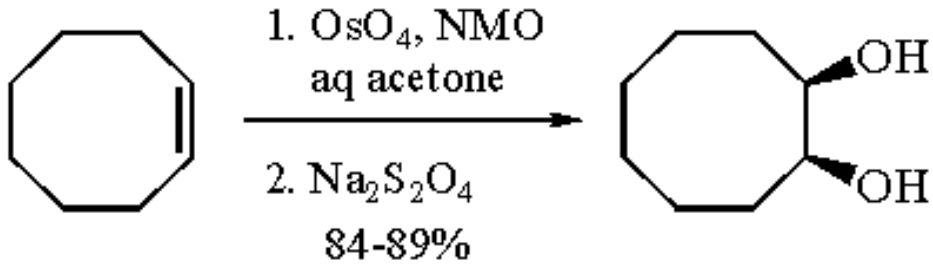

(1)

Oxidation of allylic alcohols using NMO/OsO_4 occurs with high stereoselectivity. The relative stereochemistry of the incoming hydroxy group is *erythro* to the hydroxy, alkoxy, or methyl group in the allylic position of the product (eq 2).[6] Similar results are obtained using this procedure to oxidize higher-carbon sugars containing allylic alcohols.[7]

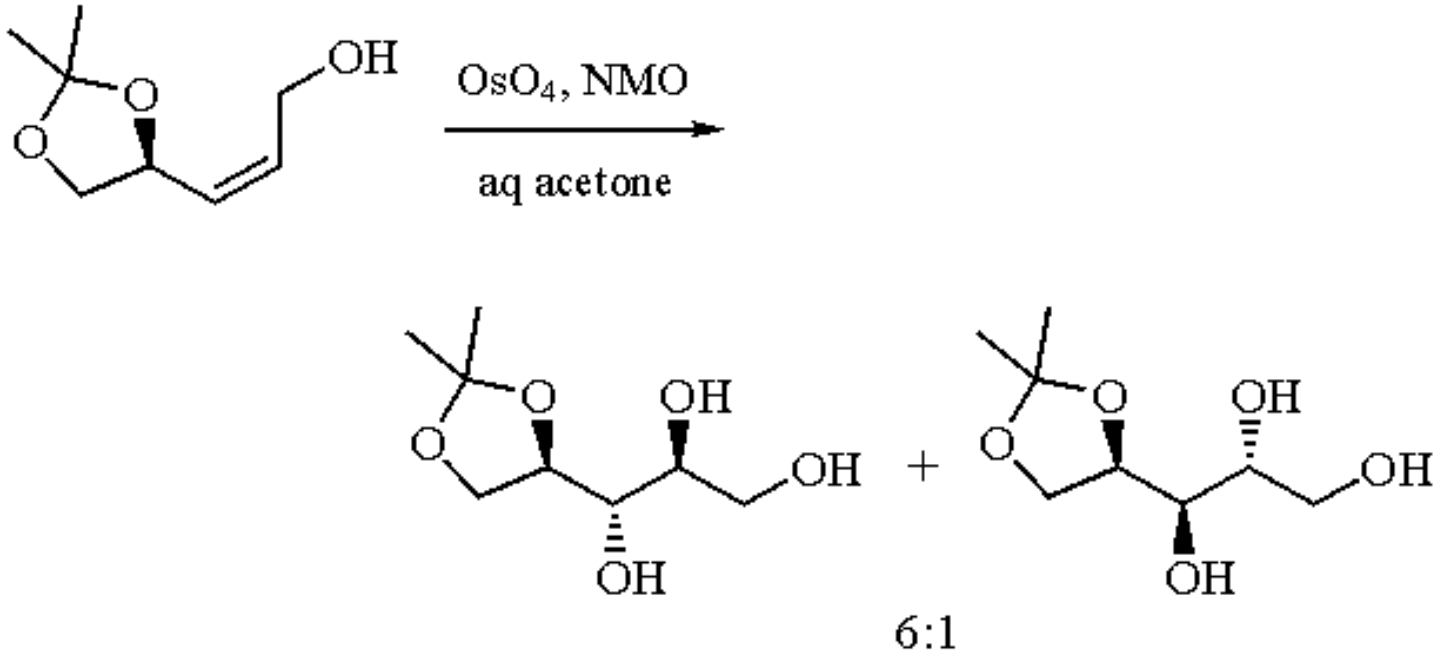

(2)

Asymmetric dihydroxylation is accomplished by using NMO in the presence of OsO_4 and dihydroquinidine *p*-chlorobenzoate (eq 3).[8] This procedure works well for a variety of alkenes but gives the best results for those alkenes with aromatic directing groups. The method is insensitive to scale, moisture, and can be run with very low concentrations of OsO_4.

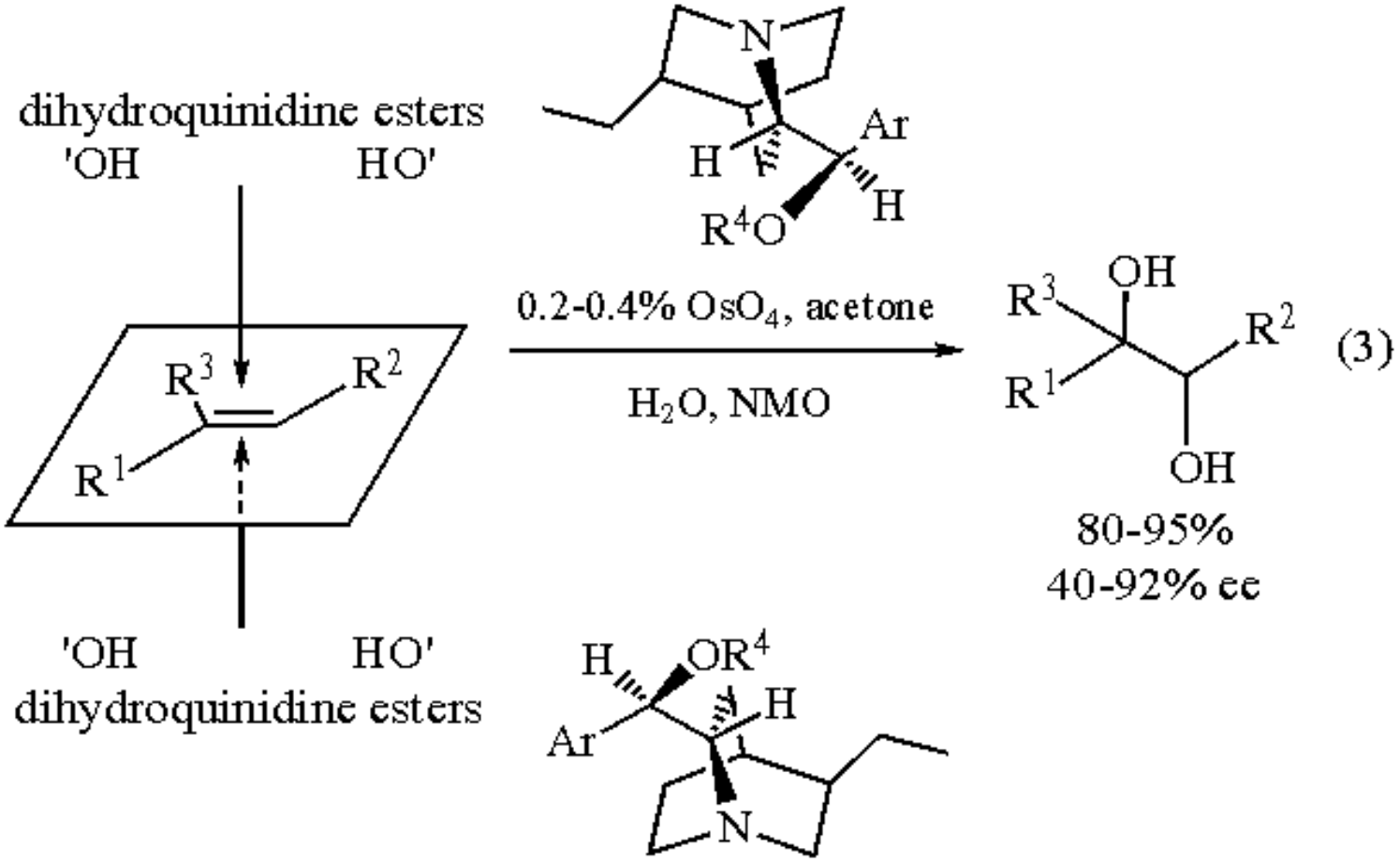

A kinetic study using ***Trimethylamine N-Oxide*** in place of NMO as a reoxidant has been reported.[9] Crystallographic analysis of an isolated intermediate using NMO (eq 4) has provided mechanistic evidence for osmate ester intermediates in tertiary amine *N*-oxide oxidation systems.[1,10]

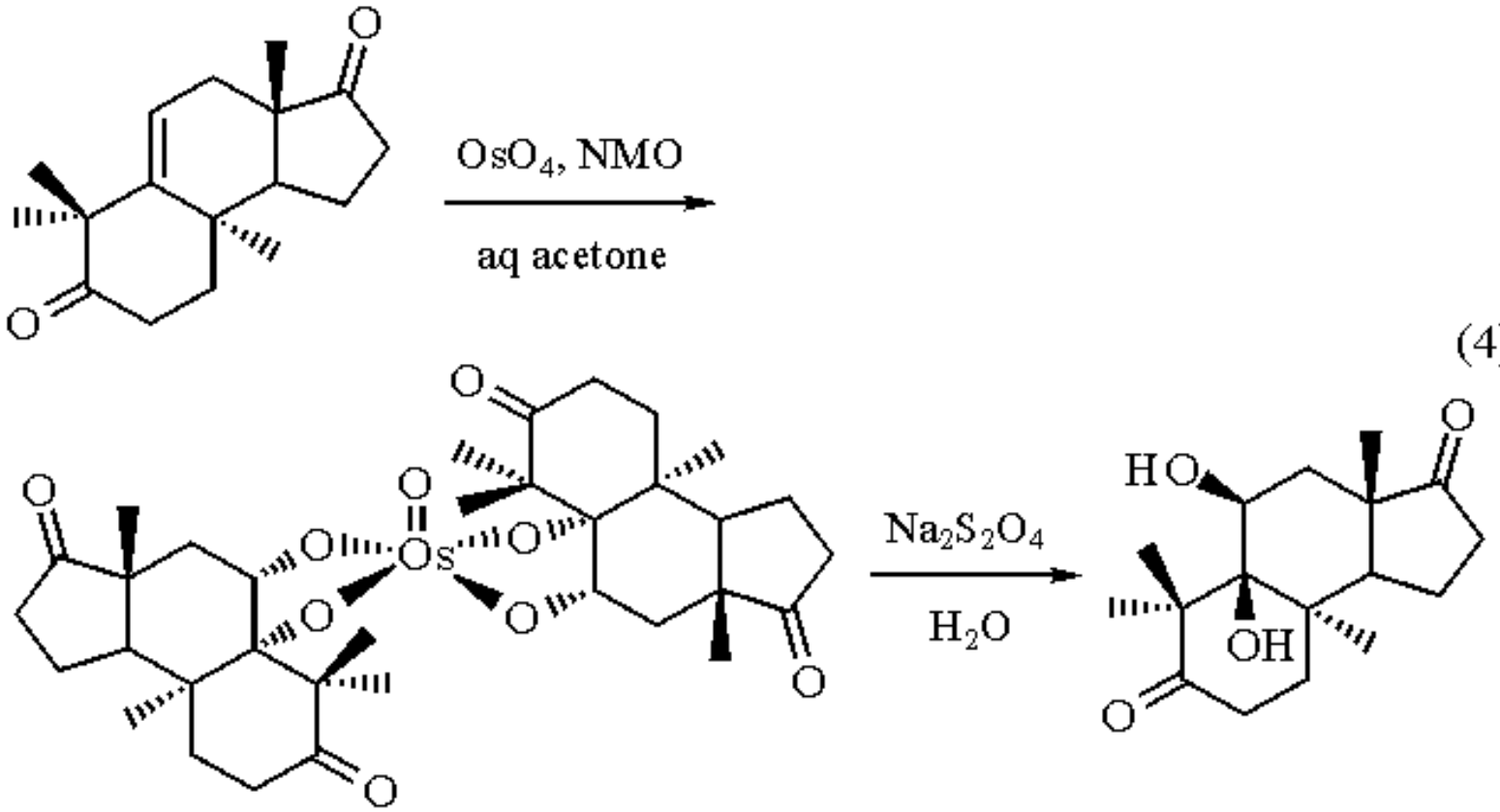

(4)

Intermediate *cis*-diols generated by NMO/OsO_4 oxidation can be cleaved to give the corresponding dialdehydes by periodate oxidation (eq 5).[11]

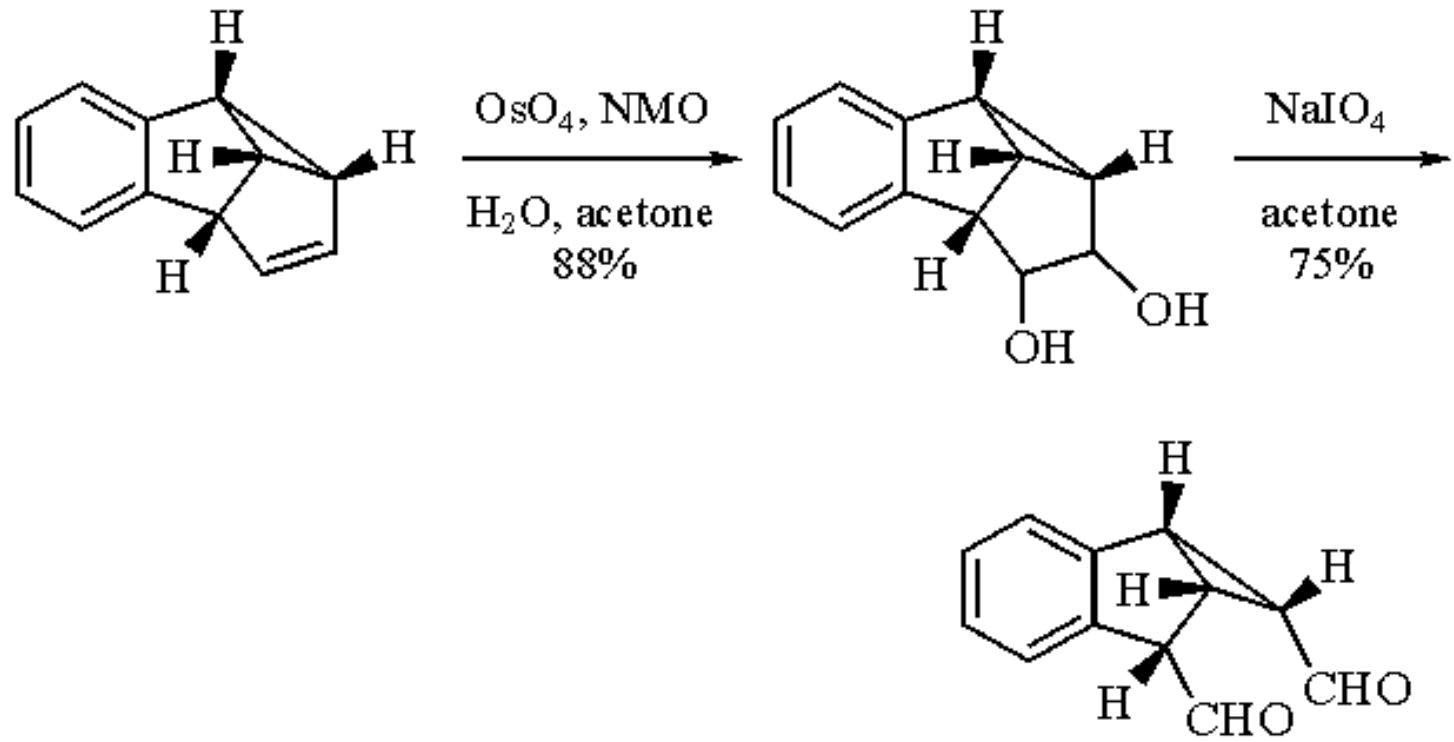

(5)

α-Hydroxyaldehydes and their tautomeric hydroxymethyl ketones can be conveniently prepared using NMO/OsO_4 or $KMnO_4$ to *cis*-hydroxylate enol phosphonates (eq 6).[12] The oxidation step is accomplished in high yields and the

overall synthesis requires only three steps from a ketone.

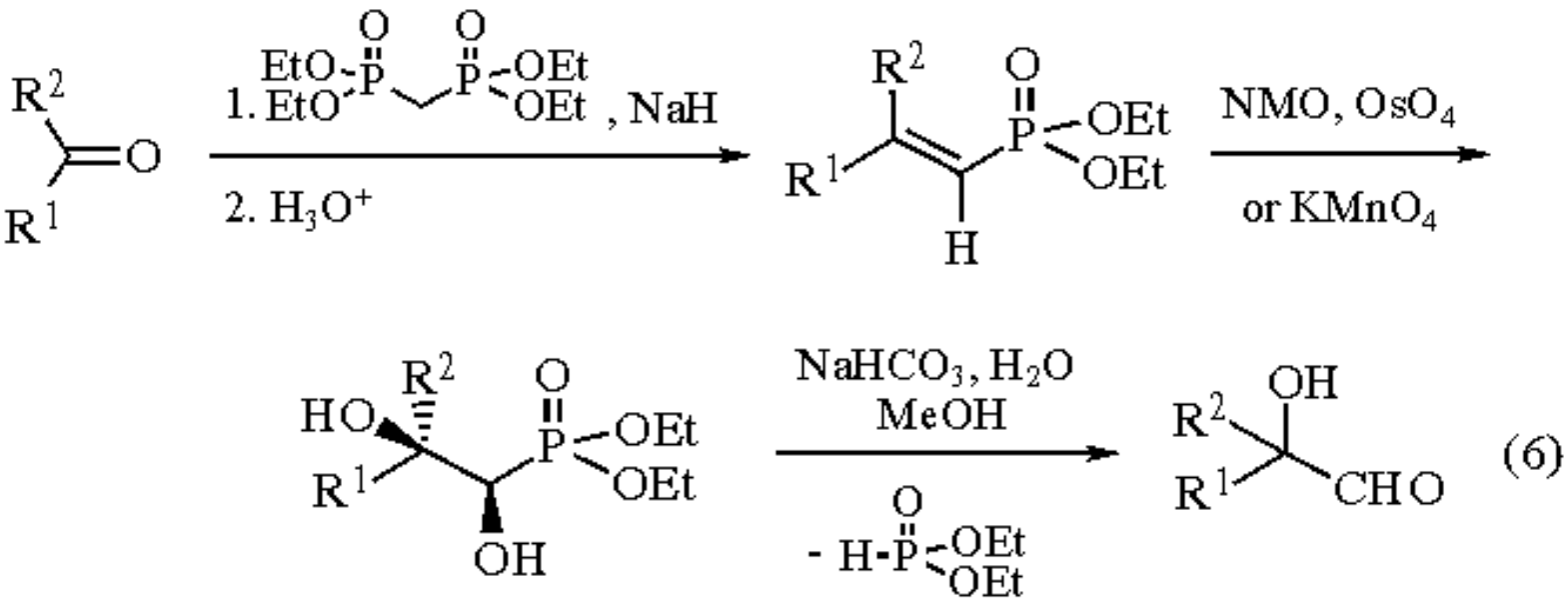

The NMO/OsO_4 oxidation system efficiently oxidizes terminal alkenes. However, this reagent may be replaced in some cases by ***Potassium Ferricyanide***/OsO_4 to give comparable yields of the corresponding 1,2-diol (eq 7).[13]

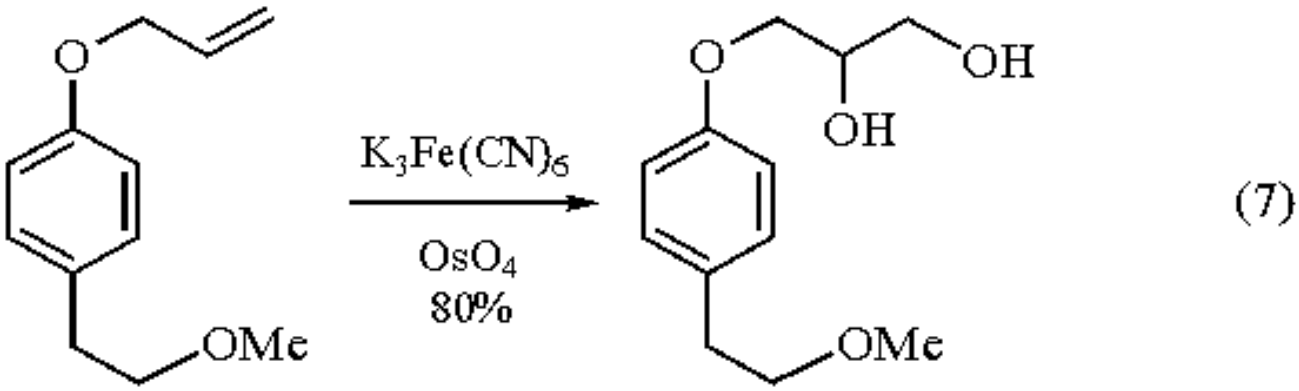

Besides OsO_4, other oxidants can be used catalytically in the presence of NMO. For example, epoxides are left intact when oxidizing a primary alcohol with NMO in the presence of catalytic ***Tetra-n-propylammonium Perruthenate*** (TPAP) (eq 8) and when oxidizing a secondary alcohol using catalytic tetra-*n*-butylammonium perruthenate (TBAP) (eq 9).[3] This reagent will also oxidize 1,4- and 1,5-primary/secondary diols to lactones.[14]

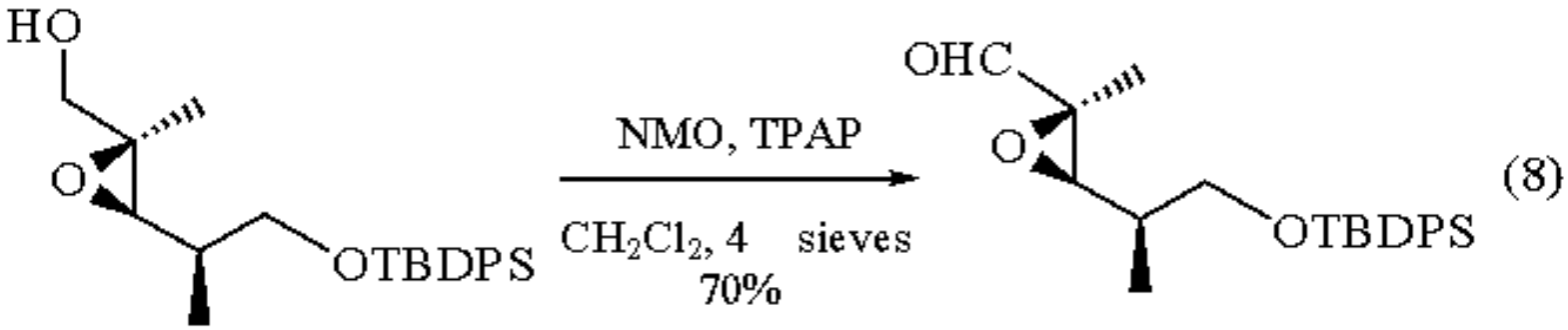

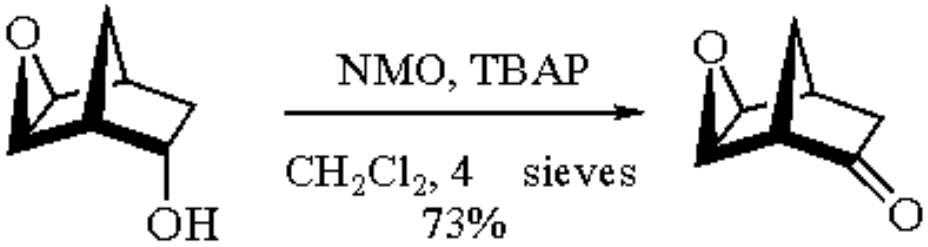

(9)

NMO along with a catalytic amount of $RuCl_2(PPh_3)_3$ will oxidize alcohols to aldehydes and ketones; $RuCl_2(PPh_3)_3$/NMO efficiently oxidizes (+)-carveol to (+)-carvone in 94% yield at rt after 2 h.[15] This reagent system will also oxidize sulfides and phosphines to their respective oxides.[16]

Mild Oxidant.

Activated halides can efficiently be converted to aldehydes or ketones under mild conditions using NMO. For example, cinnamyl bromide is converted to cinnamaldehyde by stirring the activated halide with NMO in acetonitrile.[4] This reagent will oxidize a halide in the presence of a double bond (eq 10).

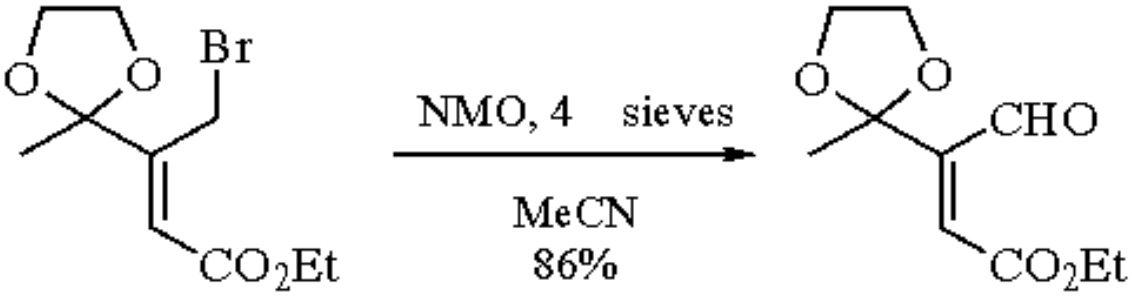

(10)

NMO can also be used as a reoxidant in the Pauson-Khand reaction for the synthesis of cyclopentenones.[17] This reaction typically is run at elevated temperatures (60-110 °C) or with ultrasound at 45 °C. Milder conditions are used with NMO, thus allowing for higher stereoselectivity in cycloadditions involving dicobalt hexacarbonyl complexes of alkynes (eq 11).

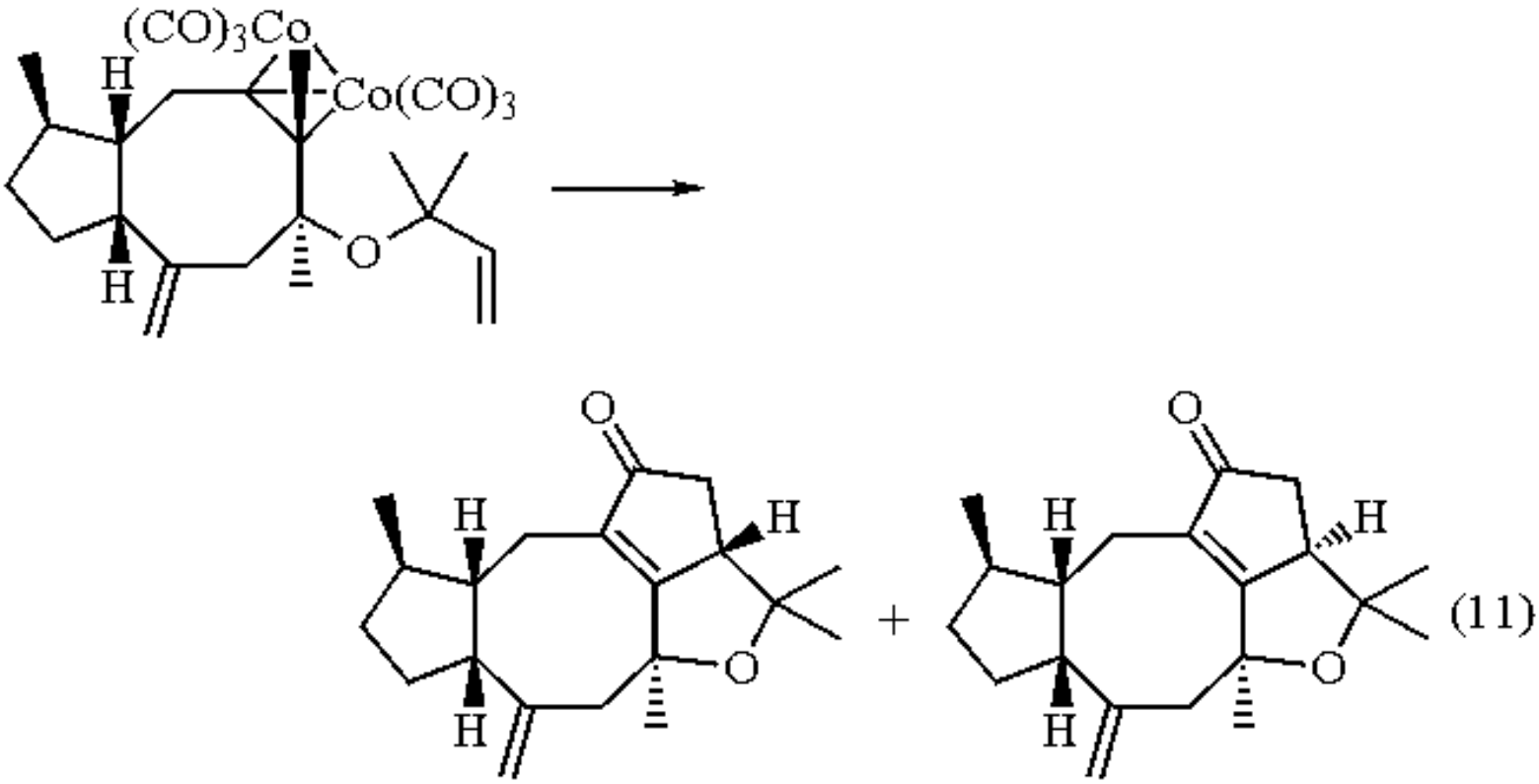

Conditions	Yield (%)	Stereoselectivity
NMO, CH_2Cl_2, rt	68	11:1
MeCN, 82 °C	75	4:1
MeCN,))))), 45 °C	45	3:1

Peptide synthesis can be performed using NMO as a mild oxidizing agent in the presence of the peptide hydrochloride, ***Diphenyl Diselenide*** and ***Tri-n-butylphosphine*** at 60 °C.[18] The phosphine and selenide act as a reductant and oxidant respectively. NMO inhibits the formation of byproducts by oxidizing selenophenol produced in the reaction mixture (eq 12) (see also ***Trimethylamine N-Oxide***).

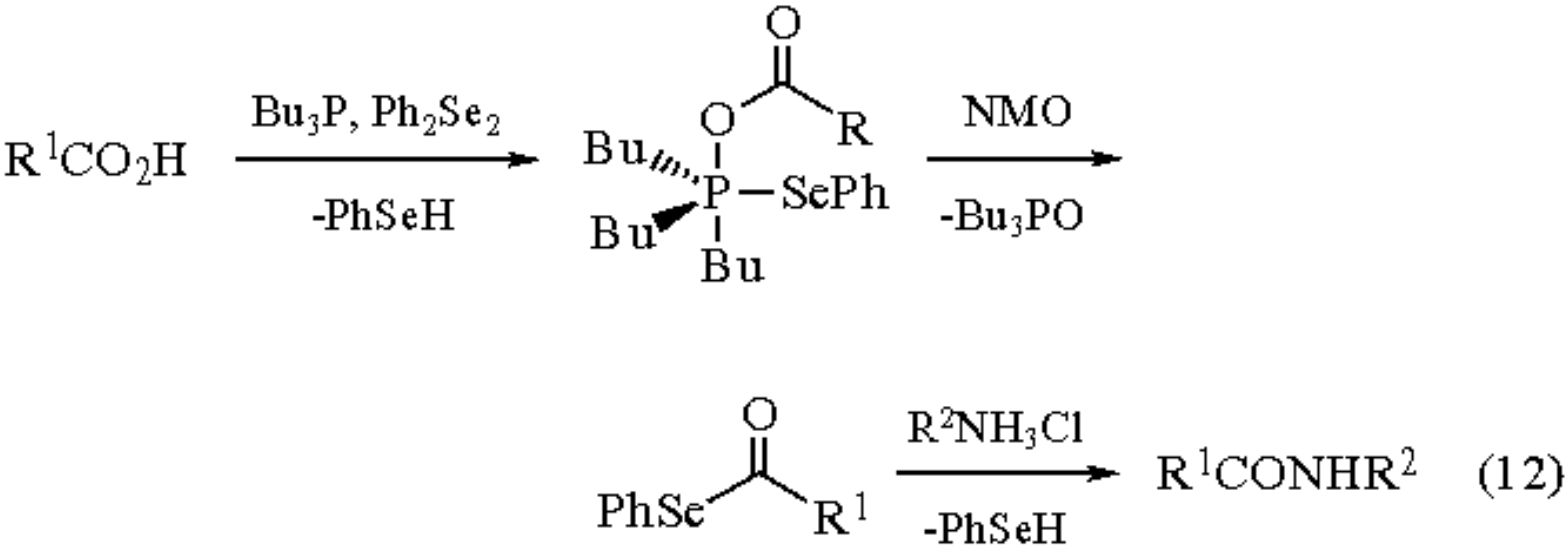

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Methyl 3-Nitroacrylate

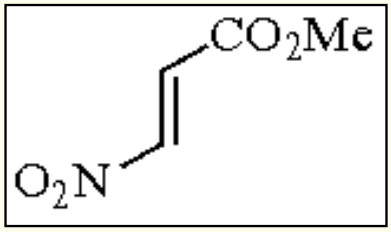

[4749-37-5] · $C_4H_5NO_4$ · Methyl 3-Nitroacrylate · (MW 131.10) (*E*)

[52745-92-3] (*E*)-ethyl ester

[5941-50-4] · $C_5H_7NO_4$ · Ethyl 3-Nitroacrylate · (MW 145.13)

(Diels-Alder dienophile;[4] Michael acceptor[13])

Physical Data: bp 73 °C/10 mmHg; mp 38 °C.[1]

Preparative Methods: by reaction of ***Methyl Acrylate*** with either nitryl chloride[1] or N_2O_4/iodine (see ***Nitrogen Dioxide*** and ***Iodine***),[2] followed by elimination with sodium acetate (eq 1). An *Organic Synthesis* preparation of the corresponding ethyl ester using N_2O_4/iodine has been reported.[3]

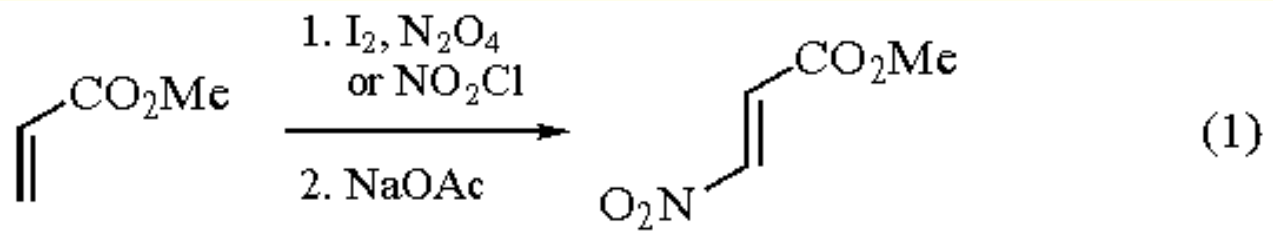

Purification: can be crystallized from methanol-water or vacuum distilled.[1] However, significant losses were reported on vacuum distillation of the ethyl ester, which was best crystallized from pentane at -15 to 0 °C.[3]

Handling, Storage, and Precautions: lachrymatory solid; best stored in a refrigerator.

Diels-Alder Reactions.

Methyl 3-nitroacrylate is a very electron-deficient and highly reactive dienophile with electron-rich or unactivated dienes in Diels-Alder reactions (e.g. eq 2).[4-7] The nitro group is readily eliminated from the adducts, making the reagent a useful ***Methyl Propiolate*** equivalent for Diels-Alder reactions (eq 3).[4]

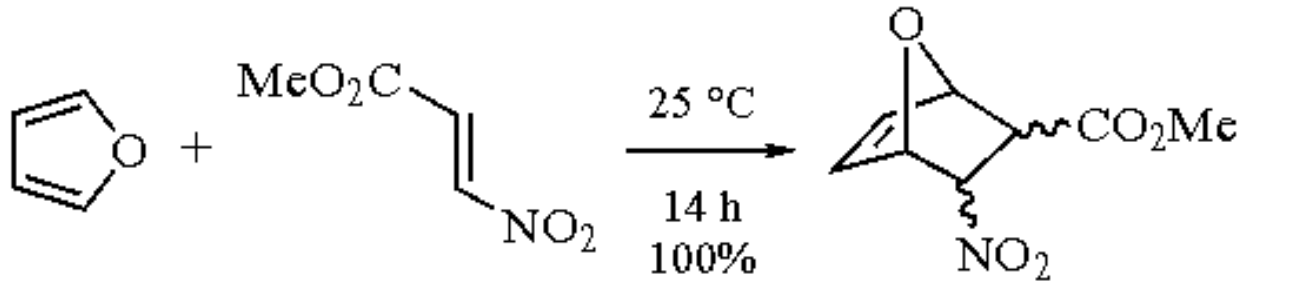

(2)

2:1 mixture of isomers

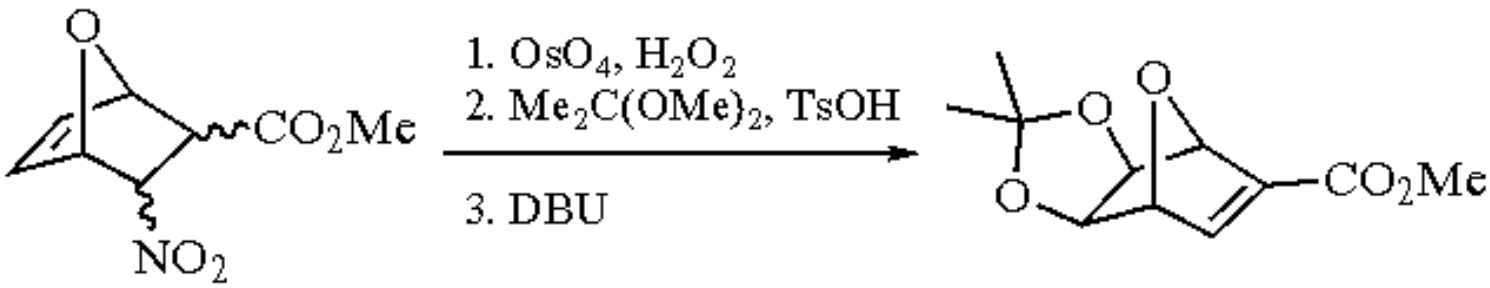

(3)

A most useful aspect of these reactions is that the nitro group controls the regioselectivity. Thus the regioselectivity after elimination is reversed from that preferred in reactions of methyl propiolate, affording *meta* disubstituted final products instead of the usual *ortho*/*para* (eq 4).[5] This regioselectivity has been used to advantage in the Diels-Alder-based synthesis of isogabaculine.[8]

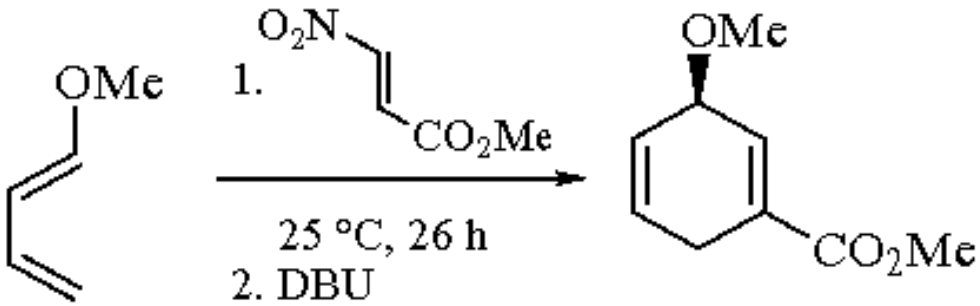

(4)

The Diels-Alder adducts can also be reduced to the amine, as in an approach to the synthesis of gelsemine (eq 5).[9] The adduct with furan (eq 2) has seen particular use in synthesis of various *C*-nucleosides[4,10] and (+)-compactin.[11]

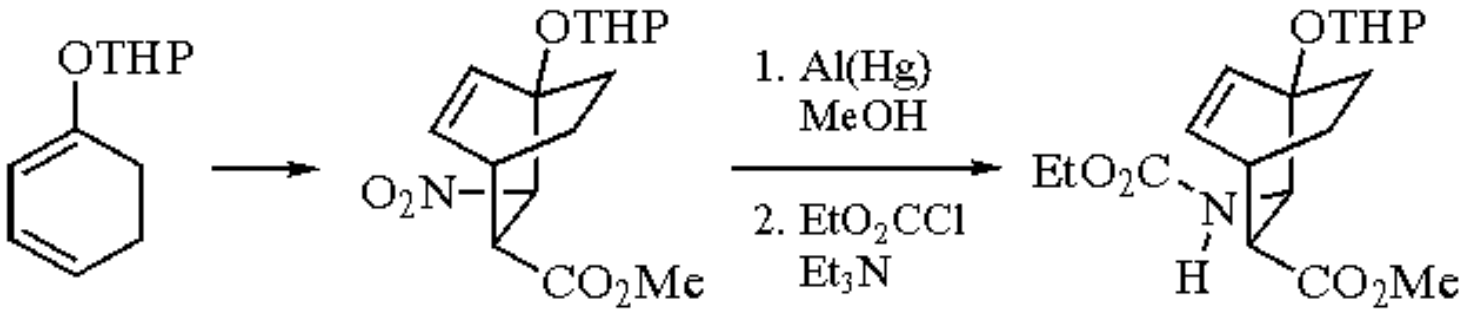

(5)

43% + 39% *exo*

Very low *endo* stereoselectivity has generally been observed in the reactions of methyl 3-nitroacrylate. The high regioselectivity of the Diels-Alder reactions does not also necessarily apply to 1,3-dipolar cycloadditions; reactions with nitrones afforded all four possible adducts with very low selectivity.[12]

Michael Additions.

Methyl nitroacrylate is also a powerful Michael acceptor. The nitro group dictates the regiochemistry of the addition of nucleophiles. This allows the equivalent of Michael additions α in methyl propiolate. McMurry takes advantage of this in his α-methylenelactone synthesis (eq 6).[13]

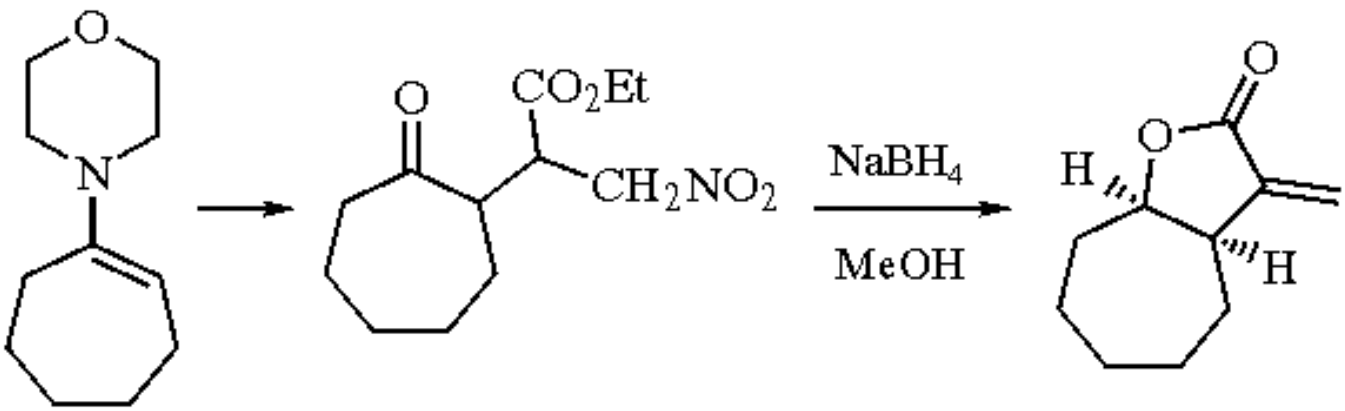

(6)

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Methyl 4-Nitrobutanoate[1]

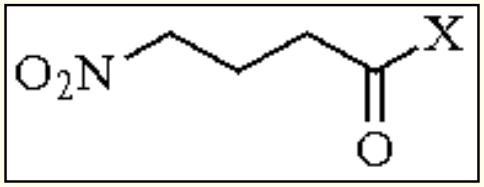

(**1**; X = OMe)

[13013-02-0] · $C_5H_9NO_4$ · Methyl 4-Nitrobutanoate · (MW 147.15) (**2**; X = OH)

[16488-43-0] · $C_4H_7NO_4$ · 4-Nitrobutanoic Acid · (MW 133.12) (**3**; X = OEt)

[2832-16-8] · $C_6H_{11}NO_4$ · Ethyl 4-Nitrobutanoate · (MW 161.18) (**4**; X = Cl)

[75938-95-3] · $C_4H_6ClNO_3$ · 4-Nitrobutanoyl Chloride · (MW 151.56)

(bifunctional C_4 synthetic building blocks with d^4 reactivity; preparation of functionalized carbo-[2,3] and heterocyclic[4] compounds; undergoes nitroaldol,[5] Michael addition, and ketone acylation reactions[6]; the α-NO_2 position has also been acylated;[7] the mononitrile oxide can be trapped by alkene and alkyne groups to give isoxazoline and isoxazole derivatives[8,9])

Physical Data: (**1**) bp 106-110 °C/9 mmHg. (**2**) bp 120 °C/0.04 mmHg. (**3**) bp 97-98 °C/1 mmHg. (**4**) bp 70 °C/0.03 mmHg.

Solubility: sol most common organic solvents.

Form Supplied in: the methyl ester (**1**) is commercially available.

Preparative Methods: the esters (**1**) and (**3**) are prepared by Michael addition of ***Nitromethane*** to the corresponding acrylates[10] (higher primary and secondary nitroalkanes can be added likewise); (**2**) is obtained by acid-catalyzed hydrolysis of the ester; the acid chloride (**4**) is prepared from the acid (**2**) and ***Thionyl Chloride***.[6]

Handling, Storage, and Precautions: as for the 3-nitropropanoic acid derivatives (see ***Methyl 3-Nitropropanoate***).

Ring Forming Reactions of 4-Nitrobutanoic Acid Derivatives.

The nucleophilic reactivity of the α-NO_2 position in the esters (**1**) and (**3**) or the electrophilicity of the acid chloride carbonyl group in (**4**) may be used to form the first bond of a new ring. In the second step, an intramolecular acylation or Henry reaction leads to ring formation.

Thus a Mannich-type variation of the nitroaldol addition of (**3**) to aromatic aldehydes produces a *trans*-substituted aryl-nitro-valerolactam, the nitro group of which can be reduced to give the lactam (**5**), a 4,5-diamino acid derivative (eq 1).[4]

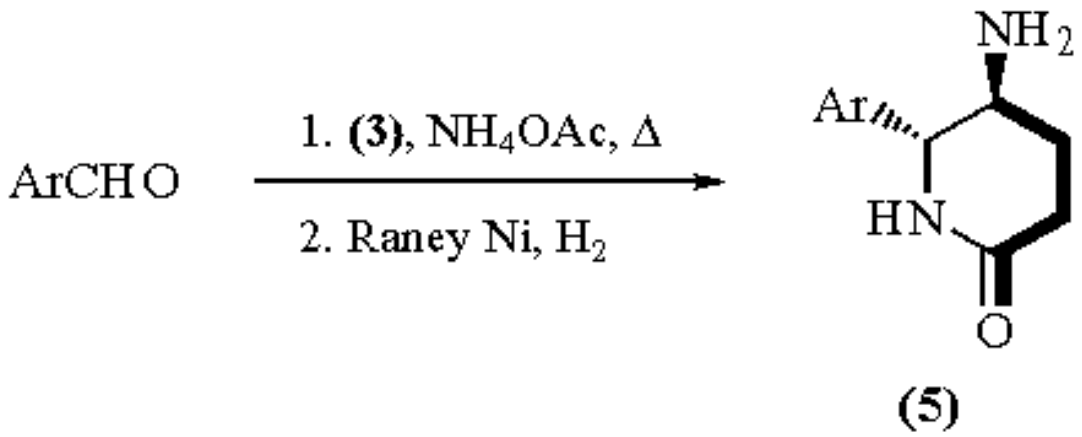

(1)

Michael addition of the ethyl ester (**3**) to enones to afford (**6**) and Dieckmann condensation produces nitro diketones (**7**) with a bicyclo[4.3.0]nonane, -[4.4.0]decane, or -[5.4.0]undecane skeleton in ca. 20% overall yield (eq 2).[3]

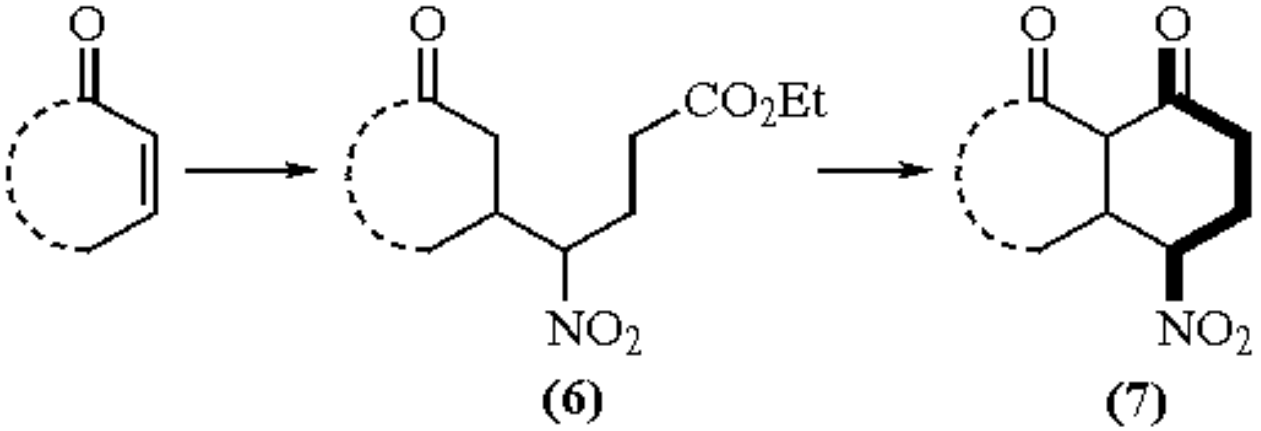

(2)

Ketone lithium enolate acylation with the acid chloride (**4**) under conditions as specified in the article ***Methyl 3-Nitropropanoate*** furnishes 6-nitro 1,3-diketones (**8**), as demonstrated with numerous examples (yields 40-85%).[6,11] Those products of type (**8**) containing no ring or a six- or a twelve-membered ring, but not the cyclopentanone, -heptanone, and -octanone derivatives, undergo cyclization ($NaHCO_3$)/THF/H_2O) to give hydroxy-nitro ketones such as (**9**) and (**10**).[2] The 8-methyl-substituted decalin (**9**), isolated as a single diastereoisomer in 50% yield, reacts with ***Methyltitanium Triisopropoxide*** to give the nitrodiol (**11**) containing five stereogenic

centers also as a single diastereoisomer.[12,13] Acetalization and ***Raney Nickel*** catalyzed hydrogenation of the nitro group of (**9**) (R = H) lead to the amino alcohol (**12**) (77% overall), the oxalate salt of which undergoes Tieffeneau-Demjanov rearrangement upon treatment with $NaNO_2/H_2O$; after acetal cleavage, the *trans*-fused bicyclic diketone (**13**) is isolated in 80% yield.

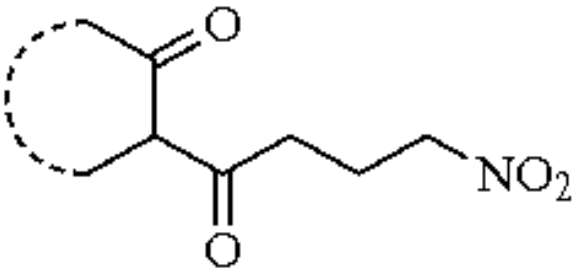

(8)

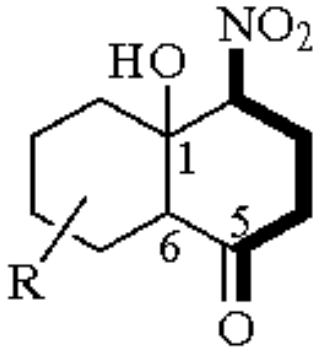

(9)

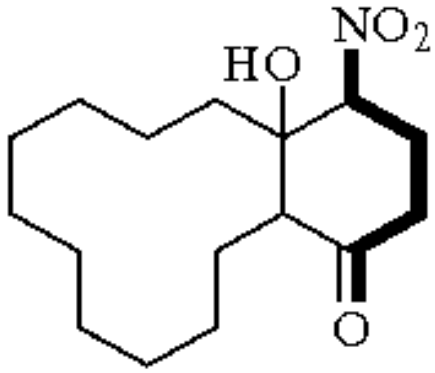

(10)

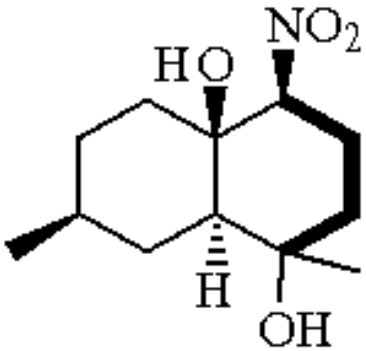

(11)

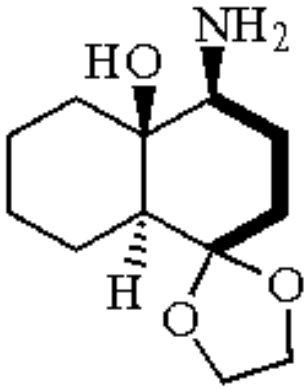

(12)

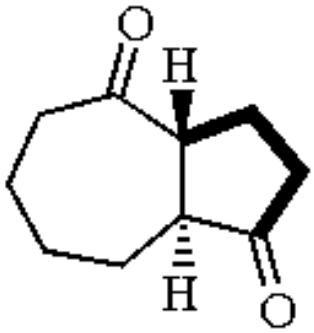

(13)

The 1,2-, 1,4-, and 1,6-distances between functional groups in the products (**5**)-(**13**) show that 4-nitrobutanoic acid is a reagent with reactivity umpolung (d^1),[14] which is itself prepared by a reaction involving reactivity umpolung (d^1 reactivity when nitromethane is added to acrylate).

---

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9. Reactions not involving C-C bond formation such as (a) CH_2NO_2 -> CHO, (b) CH_2NO_2 -> CH=NOH, (c) CH_2NO_2 -> CN, and (d) CH_2NO_2 -> CSNHOH can only be alluded to here: (a) Simoneau, B.; Brassard, P. *T* **1988**, *44*, 1015. (b) Kende, A. S.; Mendoza, J. S. *TL* **1991**, *32*, 1699. (c) Wehrli, P. A.; Schaer, P. *JOC* **1977**, *42*, 3956. (d) Hwu, J. R.; Tsay, S.-C. *T* **1990**, *46*, 7413.
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11. The same nitro diketones (**8**) can also be prepared by Michael addition of doubly deprotonated 1,3-diketones to nitroethylene: Ehrig, V.; Seebach, D. *CB* **1975**, *108*, 1961 (*CA* **1975**, *83*, 96 645b).
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1-Methyl-3-nitro-1-nitrosoguanidine

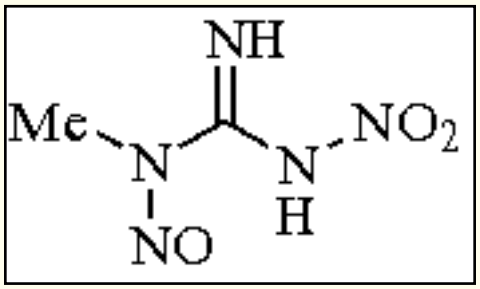

[70-25-7] · $C_2H_5N_5O_3$ · 1-Methyl-3-nitro-1-nitrosoguanidine · (MW 147.12)

(precursor to diazomethane[1])

Alternate Names: MNNG; *N*-methyl-*N´*-nitro-*N*-nitrosoguanidine.

Physical Data: mp 118 °C (dec).

Solubility: sol alcohol, chloroform, acetone.

Form Supplied in: orange-yellow powder; commercially available.

Handling, Storage, and Precautions: shelf life of several years (somewhat longer than that of ***N-Methyl-N-nitroso-p-toluenesulfonamide***); store in brown bottle, refrigerated; severe irritant, carcinogen, potent mutagen;[2] contact may lead to sensitization, so contact by all routes must be avoided; handle in a fume hood.

General Discussion.

This reagent reacts to generate ***Diazomethane*** upon treatment with aqueous sodium hydroxide at rt. For the generation of small quantities of diazomethane (e.g. less than 1 mmol), this compound is probably the reagent of choice. A convenient apparatus (Figure 1) has been reported by Fales et al;[3,4] the following procedure is representative.

1 mmol (133 mg) of the reagent is placed in the inside tube through its screw-cap opening along with 0.5 mL of water to dissipate any heat generated. 3 mL of ether is placed in the outside tube and the two parts

are assembled with a butyl O-ring and held with a pinch-type clamp. The lower part is immersed in an ice bath and about 0.6 mL of 5 N sodium hydroxide is injected through the silicone rubber septum via a syringe with a narrow-gauge (No. 22) needle to prevent leakage around the shank.[1,3] Diazomethane is collected in ether.

The alkali injection must be dropwise and very slow to control the volume of gas produced. At least 45 min are required for acceptable yields (over 50%). Solvents other than ether can be used for the collection of diazomethane. It is generally desirable to dissolve the substrate for reaction with diazomethane in the solvent in the outer tube prior to the generation, so that the reagent is consumed as it is produced.

---

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2. A large number of papers have also reported biological use of this reagent as mutagen and carcinogen. For example: (a) Druckrey, H.; Preussmann, R.; Ivankovic, S.; Schmahl, D. *Z. Krebsforsch.* **1967**, *69*, 103. (b) Sugimura, T.; Fujimura S.; Baba, T. *Cancer Res.* **1970**, *30*, 455. (c) Fujimura, S.; Kogure, K.; Oboshi, S.; Sugimura, T. *Cancer Res.* **1970**, *30*, 1444. (d) Takayama, S.; Kuwabara, N.; Azama, Y.; Sugimura, T. *J. Natl. Cancer Inst.* **1971**, *46*, 973. (e) McCann, J.; Choi, E.; Yamasaki, E.; Ames, B. N. *PNA* **1975**, *72*, 5135.
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Methyl 3-Nitropropanoate[1]

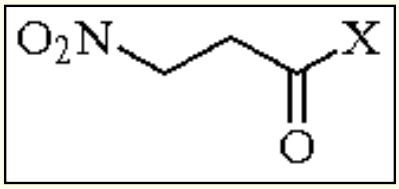

(**1**; X = OMe)

[20497-95-4] · $C_4H_7NO_4$ · Methyl 3-Nitropropanoate · (MW 133.12) (**2**; X = OH)

[504-88-1] · $C_3H_5NO_4$ · 3-Nitropropanoic Acid · (MW 119.09) (**3**; X = OEt)

[3590-37-2] · $C_5H_9NO_4$ · Ethyl 3-Nitropropanoate · (MW 147.15) (**4**; X = Cl)

[51834-15-2] · $C_3H_4ClNO_3$ · 3-Nitropropanoyl Chloride · (MW 137.53)

(nitroaldol additions,[2,3] condensation[4] reactions, and Michael additions[5] involving the NO_2-substituted carbon; the α-carbonyl carbon in dilithionitronate enolates of the esters undergoes alkylations,[6-9] double alkylations,[6,8] and aldol[6,8] and Michael additions;[6,8] elimination of HNO_2 from the products gives α,β-unsaturated esters with substituents in either the β-[2,3a,5b] or the α-position,[8,9] thus making the reagent a synthetic equivalent of acrylate anions with d^3 or d^2 reactivity;[8,10] precursor to nitrile oxide for [3 + 2] cycloadditions;[11] 3-nitropropanoyl chloride can be used for enolate acylation[12-15] and five-membered ring annulation[14])

Physical Data: (**1**) bp 63 °C/0.5 mmHg. (**2**) mp 65-68 °C. (**3**) bp 146 °C/760 mmHg. (**4**) bp 123 °C/10 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: the acid (**2**) and its esters (**1**) and (**3**) are prepared from the corresponding 3-halopropanoic acid derivatives with nitrite. (**2**) is a commercial product and can be esterified[8] and converted to the acid chloride (**4**)[15,18] and anhydride[15] by conventional methods.

Handling, Storage, and Precautions: the acid (**2**) is a natural, toxic metabolite of aspartic acid in plants[16] and in fungi.[17] The nitropropanoic acid derivatives should be handled with caution, as should all nitro compounds of low molecular weight. They are stable when stored in dark bottles in a refrigerator. Acid chloride (**4**) should be stored with exclusion of air and moisture.

Reactions of the Esters (1) and (3) at C-3.

Although the 3-nitropropanoate esters readily undergo HNO_2 elimination to acrylates, it is possible to carry out typical nitronate transformations such as the Henry reaction and the Michael addition to enones. The resulting chain-elongated β-nitro esters (**5**) can then be subjected to β-elimination, so that the carbon skeleton of the compound introduced as an electrophile has been elongated by a β-acrylate unit (eq 1).

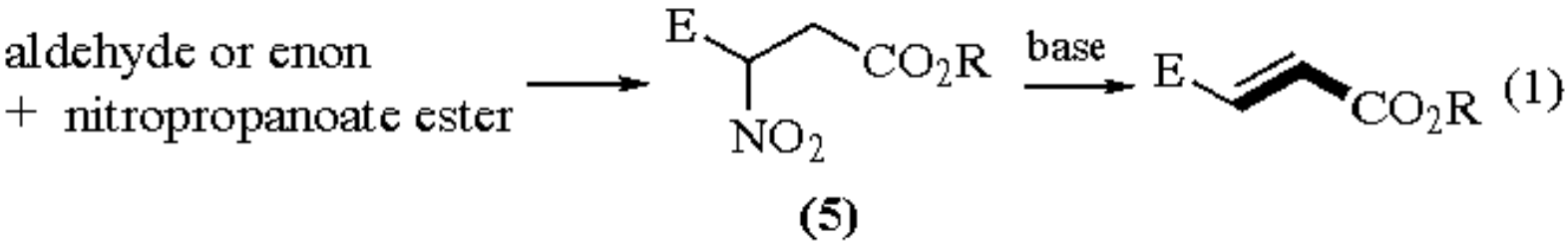

Alternatively, the original adducts can be converted without loss of the nitrogen functionality; for example, reduction of NO_2 to NH_2 leads to β-amino acid derivatives. Thus, nitropropanoate esters (**1**) and (**3**) have been used for the synthesis of amino sugars, e.g. (**6**),[3b,3c] of macrolides such as brefeldin,[2b] of macrodiolides such as pyrenophorin via the intermediate (**7**),[2a] and of bicyclo[3.3.0]octane-2,8-dione (**9**) (by Michael addition of (**3**) with cyclopentenone, HNO_2 elimination to (**8**), hydrogenation, and Dieckmann condensation) (eq 2).[5b]

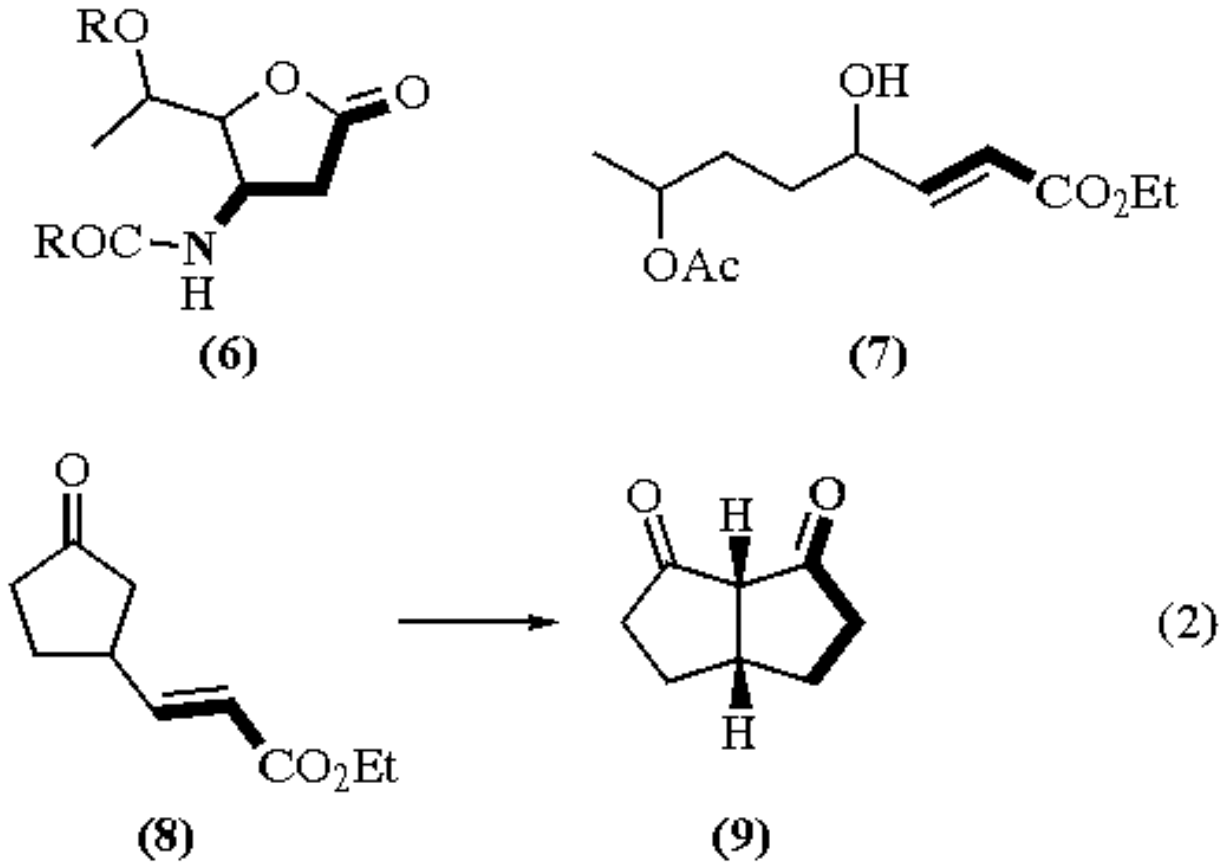

Reactions of the Esters (1) and (3) at C-2.

Double deprotonation of 3-nitropropanoate esters to nitronate enolates (**10**) enables alkylation (by alkyl halides and enones) and hydroxyalkylation (by aldehydes and ketones) at the 2-position, to give α-substituted acrylates (**11**) (eq 3).[8,9]

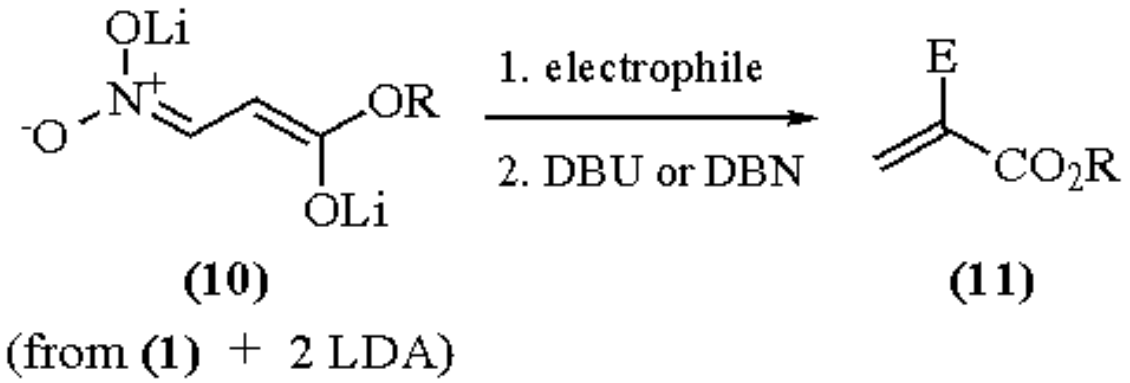

The reaction with alkyl iodides and bromides to give monoalkylated products (**12**) is so efficient that an in situ double alkylation is possible; for instance, a 71% yield of (**13**) (R^1 = Me, R^2 = Bn) is obtained.[8] Addition to aldehydes to give (**14**) (R^2 = H) gives better yields (50-85%) than addition to ketones (<30%). The products (**15**) and (**16**) of HNO_2 elimination are formed in high yields when Eiter bases[19] are employed. The overall yield for the preparation of (**15**) (R = $CH_2CH{=}CH_2$) from methyl 3-nitropropanoate (**1**) and allyl bromide is 64%, and that for the preparation of the hydroxy methylene ester (**16**) (R = C_5H_{11}) from (**1**) and hexanal is 71%.

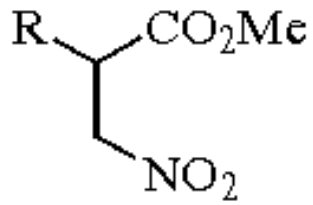

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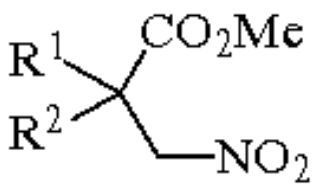

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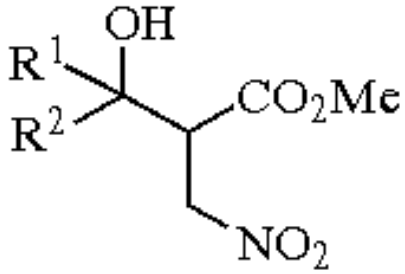

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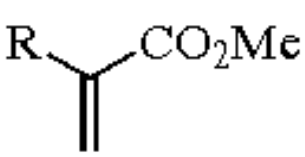

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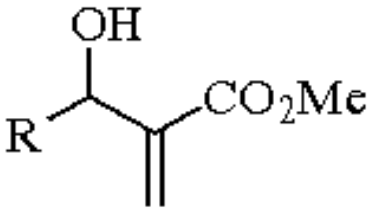

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Lithium Enolate Acylation and Five-Membered Ring Annulation.

Direct 1:1 acylation of amine-free solutions of ketone lithium enolates by addition to a 3-nitropropanoyl chloride (**4**) solution in THF (both cooled to temperatures between -78 and -100 °C) gives 5-nitro 1,3-diketones (**17**) in yields of 40-

80% (eq 4). The enolates may be derived from open-chain ketones such as diethyl ketone, or from cyclic ketones with, for instance, six-, seven-, eight-, and twelve-membered rings.[12-15]

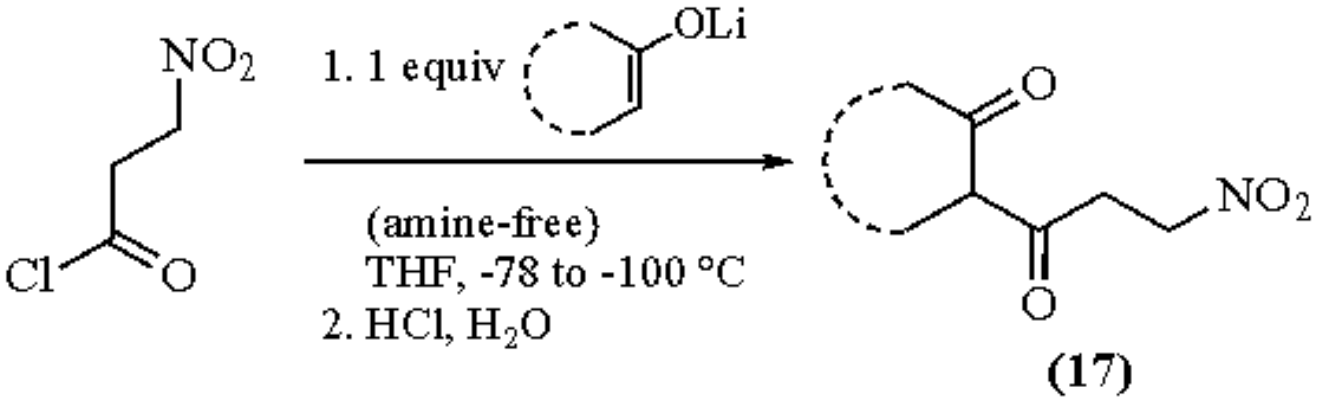

(4)

Meerwein acylation of ketones with the anhydride of 3-nitropropanoic acid/BF_3 is also feasible.[15,20] The products of type (**17**) undergo nitroaldol cyclization with formation of a hydroxynitrocyclopentanone ring which, depending upon the particular structure and upon the conditions used, may lose HNO_2 to give a hydroxycyclopentenone derivative. Examples are the annulation products (**18**) (mp 155-156 °C) and (**19**) (mp 68-70 °C) of cyclododecanone and cycloheptanone. The hydroxy enone with a tertiary hydroxy group may rearrange to the isomer with a secondary hydroxy group, e.g. (**20**) obtained from cyclohexanone. Pure products (as single diastereoisomers, where applicable) can be isolated in yields of 15-90%.[14]

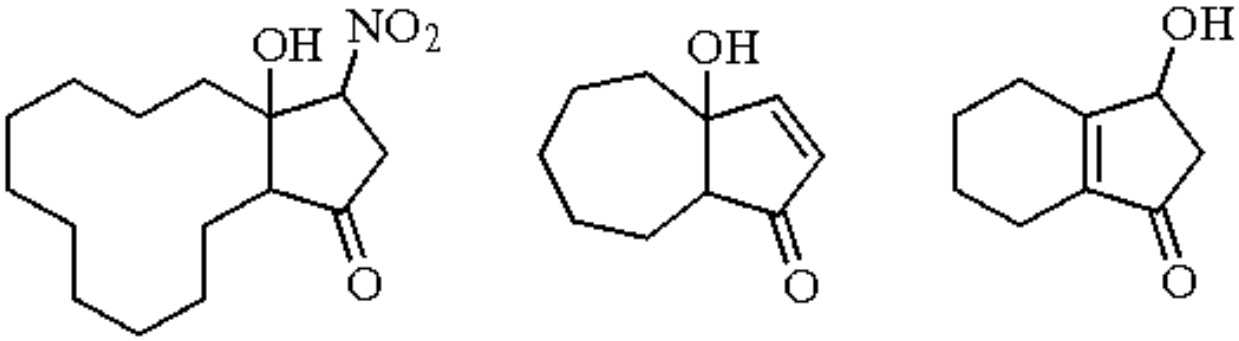

(18) (19) (20)

Related Reagents.

Lithium α-Lithiomethanenitronate; ***O,O-Dilithio-1-nitropropene***; ***Methyl 4-Nitrobutanoate***; ***Nitroethane***; ***Nitromethane***.

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N-Methyl-*N*-nitrosoacetamide[1]

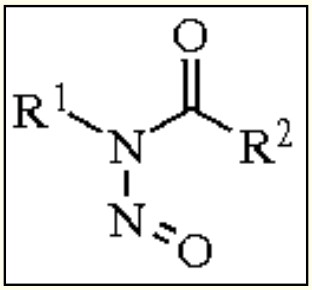

(**1**; R^1 = Me, R^2 = Me)

[7417-67-6] · $C_3H_6N_2O_2$ · *N*-Methyl-*N*-nitrosoacetamide · (MW 102.11) (**2**; R^1 = Me, R^2 = Pr)

[16395-81-6] · $C_5H_{10}N_2O_2$ · *N*-Methyl-*N*-nitrosobutyramide · (MW 130.17) (**3**; R^1 = Bu, R^2 = Me)

[14300-06-2] · $C_6H_{12}N_2O_2$ · *N*-Butyl-*N*-nitrosoacetamide · (MW 144.20) (**4**; R^1 = Bu, R^2 = Et)

[99389-05-6] · $C_7H_{14}N_2O_2$ · *N*-Butyl-*N*-nitrosopropionamide · (MW 158.23)

(alkylating agent;[2] source of diazomethane;[3] useful as activated acylating agent;[4] precursor to esters and alkenes[1a,5,6])

Physical Data: (**1**) bp 115-116 °C/760 mmHg. (**2**) bp 59-60 °C/14 mmHg. (**3**) bp 35-37 °C/0.1 mmHg. (**4**) bp 63-65 °C/6 mmHg.

Solubility: sol benzene, Et_2O, $CHCl_3$, acetone.

Preparative Methods: nitrosation of *N*-alkyl amides with ***Sodium Nitrite***/acid mixtures, ***Nitrosyl Chloride***, or ***Nitrogen Dioxide***.[10] *N*-Deprotonation of the amide with ***n-Butyllithium*** or ***Sodium Hydride***, followed by treatment with nitrosonium salts[11] or ***Nitrogen Dioxide***,[12] is a second approach that is particularly useful in the preparation of thermally labile nitrosoamides.

Handling, Storage, and Precautions: the stability of *N*-nitrosoamides is dependent largely on steric factors.[1a,7] For *N*-nitrosoacetamides, RN(NO)COMe, compounds with a primary *N*-alkyl group are stable for weeks at 25 °C if kept dry; decomposition occurs at approx 75 °C. Compounds with secondary *N*-alkyl groups decompose at 25 °C ($t_{1/2}$ about 0.5 h). Compounds with tertiary alkyl groups must be synthesized and utilized at low temperatures. Alkyl substitution on the acyl group leads to increases in decomposition rates similar to those for the alkyl group. *N*-Nitrosoamides are decomposed by acids and bases. Nitrosoamides bearing small alkyl groups possess potent mutagenic[8] and carcinogenic[9] (local and systemic) activity. Use in a fume hood and take reasonable precautions.

Alkylation Reactions.

N-Alkyl-*N*-nitrosoamides (**1**) are thermolabile compounds which undergo first-order decay[7] to yield, via diazotate esters (**5**), diazonium carboxylate ion pairs (**6**) as reaction intermediates (eq 1).[13] If the alkyl group is allylic, secondary, or tertiary, highly active nitrogen-separated ion pairs (**7**) are formed;[13a] the carbocations can subsequently undergo the usual types of reactions: nucleophilic capture by solvent or counterion, proton elimination, and skeletal rearrangement (eq 2).

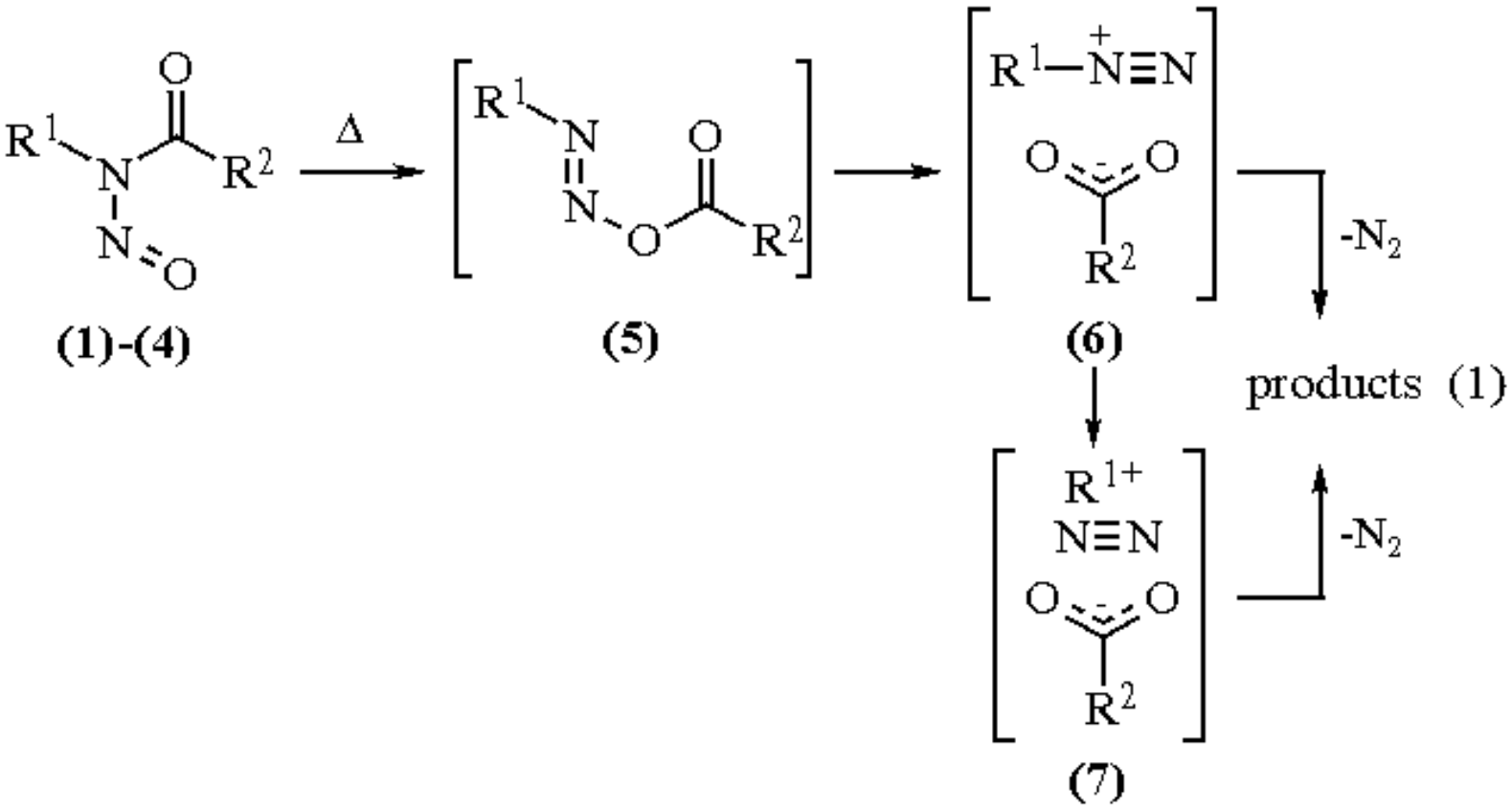

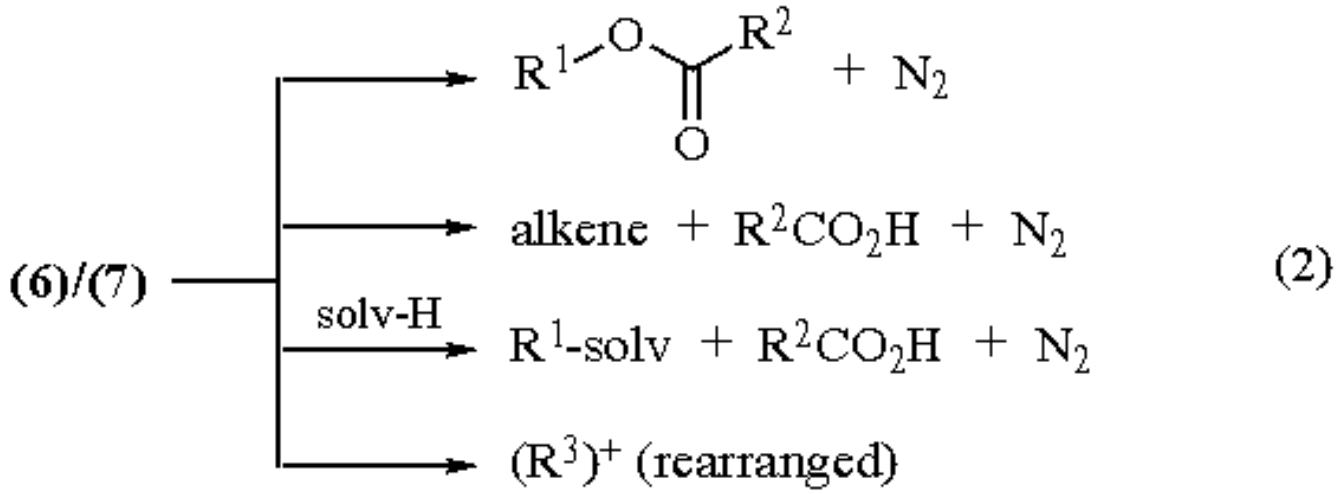

Analogs of the nitrosoamides are known, and the counterions can be derived from a range of acids (carboxylic,

carbonic, carbamic, sulfonic, etc.). In nonreactive solvents, ion pair combination to give the corresponding ester can be the major reaction (eq 2); the esters are usually formed with retention of configuration. Further, a nitrosoamide labeled in the carbonyl group with ^{18}O decomposes to yield ester with a preponderance of ^{18}O in the carbonyl group.[13a] If the solvent (and the carbocation) are sufficiently reactive, solvent capture becomes the major reaction.[2b,13a] For example, the decomposition of *N*-benzyl-*N*-nitrosotrifluoromethanesulfonamide (**8**) in benzene ($t_{1/2}$ &AApprox; 10-20 min) at 30 °C yields ~60% diphenylmethane,[2b] and decomposition in acetonitrile yields the nitrilium salt.[2b] The nitrosoamide decomposition, thus, can produce a series of alkylating agents of differing activity: carbocations, nitrilium salts (and related products from relatively unreactive solvents), and alkyl sulfonate esters. The nitrosoamide decomposition is a method for the production of highly reactive alkylating agents under mild conditions in nonpolar solvents and in the absence of electrophilic agents;[2b] it lends itself especially to transformations of isotopically labeled amines and chiral amines.

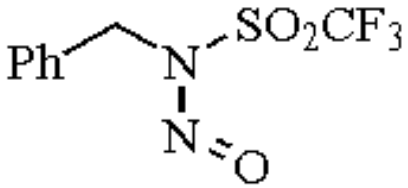

(8)

Acylation Reactions.

N-Nitrosation of amides markedly activates the amide group to cleavage by nucleophiles. For example, thiolate ions react at rt with nitrosoamides to afford *S*-alkyl and *S*-aryl thioesters in good yields (eq 3);[3a] byproducts arising from *N*- to *S*-*trans*-nitrosations are rarely formed.[3a]

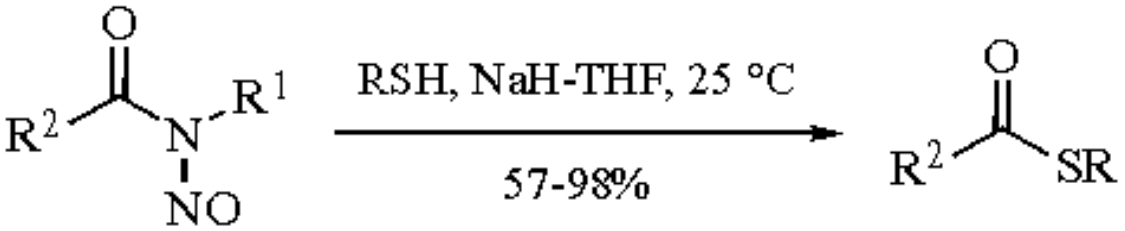

(3)

Amides of general formula R^1CONHR^1 can be nitrosated and the resulting nitrosoamides converted into R^1CONH_2, R^1CONHR^2, or $R^1CONR^2R^3$ by reaction with ammonia or an amine.[14] The overall two-step reaction is almost quantitative.[14] By this approach, *N*-alkyl amides are formed without the competitive *O*- and *C*-alkylations that may occur in the direct alkylation of amides. Analogous reactions with aromatic amines are less successful.[14] In another application, racemic carboxylic acids have been converted into diastereomeric amides; separation of the diastereomers by chromatography and subsequent deamination via the nitrosoamide route, followed by ester hydrolysis, affords essentially the pure chiral carboxylic acids.[15]

N-Nitrosoamides react with alkoxide-alcohol mixtures to yield diazoalkanes corresponding to the amine moiety of the amide (eq 4).[24] This approach is widely used to synthesize this very useful class of alkylating agents (see ***Diazomethane***).

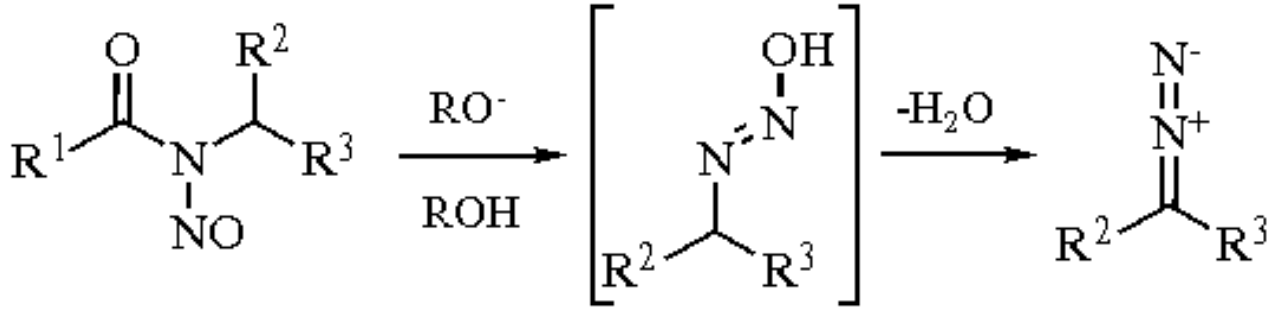

(4)

Acylation and Alkylation Reactions.

The generation of highly reactive carbocations from *N*-nitrosoamides lends itself to the active-site mapping and inhibition of enzymes.[4b,c] In these studies, R^1 and R^2 are recognized by the binding site of the enzyme, and the carbocation formed alkylates nucleophilic centers in the active site such as amide linkages and amino acid side chains.[4b]

Miscellaneous Reactions.

The acyl groups of nitrosoamides are readily reduced to primary alcohols (50-82% yields) by ***Sodium Borohydride*** at 25 °C.[16] Reduction to the corresponding hydrazide is achieved with ***Zinc-Acetic Acid*** (~80%)[17] and ***Titanium(IV) Chloride/Magnesium*** (~60%).[16] In nonpolar solvents at 80-100 °C, nitrosoamides decompose in the presence of rhodium(II) carboxylates (see ***Dirhodium(II) Tetraacetate***) to yield, ultimately, the corresponding alkene (eq 5).[6]

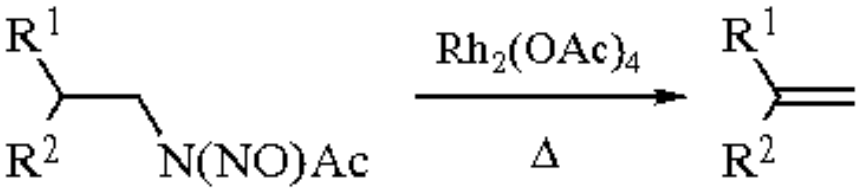

(5)

Photolysis of nitrosoamides results in initial scission of the N-N bond followed by hydrogen abstraction from the solvent by the amido radical. In the final step the nitric oxide generated in the first step reacts with the new carbon radical to yield ketones from alcohols,[18] and oximes, nitrosoalkane dimers, and nitrite esters from hydrocarbons.[19]

Related Alkylating Agents.

A number of alkylating agents utilizing deaminatively formed carbocations are available. Compounds with replaceable protons are alkylated by *syn*- and *anti*-alkanediazotate salts,[20] and by *N*-alkyl-*N*-nitrososulfamates.[21] Conditions can be found for alkylation by *N*-alkyl-*N*-nitro-*O*-acylhydroxylamines[22] and the corresponding *N*-nitroso analogs.[13a,23] These methods are mechanistically related to alkylations with diazoalkanes (see ***Diazomethane***) or with 3-alkyl-1-*p*-tolyltriazenes (see ***3-Methyl-1-p-tolyltriazene***).

The thermal decomposition of *N-nitro*amides in nonreactive solvents yields the same ester/alkene products as are formed from the corresponding *N-nitroso*amides via analogous intermediates. The nitroamides are, like their nitroso analogs, good acylating agents of nucleophiles.[14]

Related Reagents.

Diazomethane; ***1-Methyl-3-nitro-1-nitrosoguanidine***; ***N-[N´-Methyl-N´-nitroso(aminomethyl)]benzamide***; ***N-Methyl-N-nitroso-p-toluenesulfonamide***; ***3-Methyl-1-p-tolyltriazene***; ***N-Nitrosodimethylamine***; ***Nitrosonium Tetrafluoroborate***; ***Nitrosyl Chloride***; ***Sodium Nitrite***; ***Trimethylsilyldiazomethane***.

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N-[*N´*-Methyl-*N´*-nitroso(aminomethyl)]benzamide

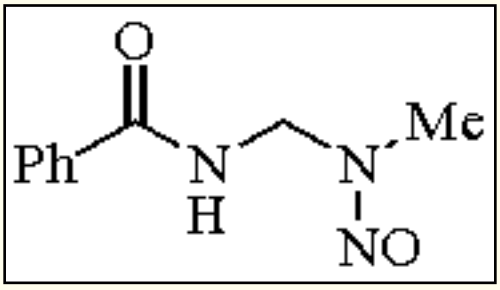

[59665-02-0] · $C_9H_{11}N_3O_2$ · *N*-[*N´*-Methyl-*N´*-nitroso(aminomethyl)]benzamide · (MW 193.23)

(precursor of diazomethane[1])

Alternate Name: N-[(methylnitrosoamino)methyl]benzamide.

Physical Data: mp 128-131 °C.

Solubility: sol acetone, ethanol, dioxane, chloroform; slightly sol ether; insol water, petroleum ether.

Form Supplied in: crystalline solid; commercially available.

Preparative Method: by nitrosation of *N*-[(methylamino)methyl]benzamide hydrochloride, which is itself obtained from methylamine hydrochloride, formaldehyde, and benzamide.[2]

Handling, Storage, and Precautions: stable at rt for many years. Storage in a brown bottle is recommended. Although the mutagenicity of this reagent has not been reported, like all nitroso compounds it should be treated as a highly toxic substance. All handling should be conducted in an efficient fume hood.

General Discussion.

This reagent was introduced[1] in 1976 as a new type of ***Diazomethane*** precursor which may be regarded as a modified Mannich base. It liberates diazomethane in the presence of alkali hydroxide, presumably through β-elimination to form *N,N´*-methylenebisbenzamide and formaldehyde (eq 1).

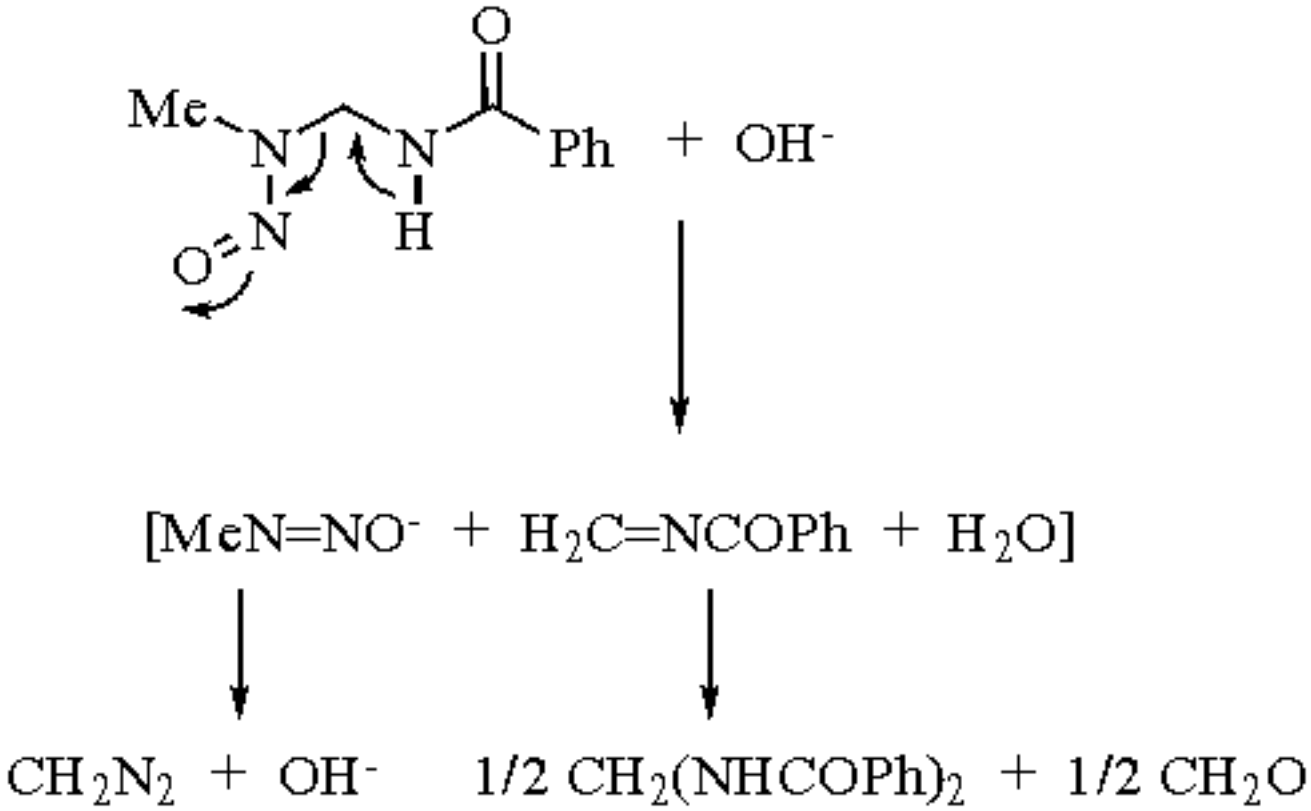

(1)

The generation of diazomethane with this reagent proceeds similarly to that of ***N-Methyl-N-nitroso-p-toluenesulfonamide***, and the procedure can be performed by the use of the same apparatus. The following improved procedure is recommended over that originally described. In a flask are placed a solution of 3 g of potassium hydroxide in 4 mL of water, 5 mL of 2-(2-methoxyethoxy)ethanol, and 10 mL of ether, and a condenser is connected to two receiving flasks in series, both cooled in ice-salt baths. The second receiver contains 10 mL of ether and an inlet tube which dips below the surface of the solvent. The mixture is heated in a water bath at about 70 °C with magnetic stirring, and a solution of 5.8 g (0.03 mol) of *N*-[(methylnitrosoamino)methyl]benzamide in 40 mL of 2-(2-methoxyethoxy)ethanol diluted with 40 ml of ether is added from a dropping funnel over about 20 min. The dropping funnel is rinsed with 30-50 mL of additional ether. The distillation is continued until the distilling ether is colorless. The combined distillate contains 0.77-0.82 g (61-65%) of diazomethane.

A drawback of this reagent is that its poor solubility in ether requires the use of a mixed solvent system of 2-(2-methoxyethoxy)ethanol and ether as described above. In place of 2-(2-methoxyethoxy)ethanol, 2-methoxyethanol (bp 125 °C) (in which the reagent is somewhat more soluble) can be also used. An analog possessing high solubility in ether has been reported: isopropyl *N*-[(methylnitrosoamino)methyl]carbamate,[4] *i*-PrOCONHCH$_2$N(NO)Me. However, this reagent has been reported to exhibit significant mutagenicity.[3]

1. (a) Sekiya, M.; Ohashi, Y.; Terao, Y.; Ito, K. *CPB* **1976**, *24*, 369. (b) Sekiya, M. *Yuki Gosei Kagaku Kyokaishi* **1980**, *38*, 176 (*CA* **1980**, *93*, 94 722).
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N-Methyl-*N*-nitroso-*p*-toluenesulfonamide

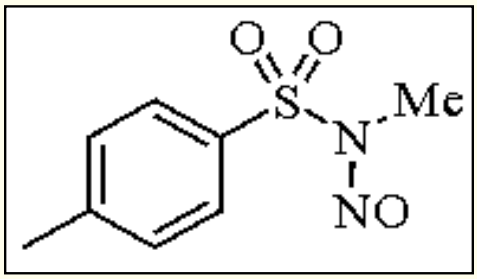

[80-11-5] · $C_8H_{10}N_2O_3S$ · *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide · (MW 214.27)

(precursor of diazomethane[1a])

Alternate Names: Diazald; *p*-tolylsulfonylmethylnitrosamide.

Physical Data: mp 61-62 °C.

Solubility: sol petroleum ether, ether, benzene, alcohol, $CHCl_3$, CCl_4; insol H_2O.

Form Supplied in: pale yellow powder; commercially available.

Preparative Methods: prepared by the reaction of ***p-Toluenesulfonyl Chloride*** with methylamine, followed by nitrosation with ***Sodium Nitrite*** in glacial acetic acid.[1c]

Purification: recrystallization is best achieved by dissolving the reagent in hot ether (1 mL g^{-1}), adding an equal volume of petroleum ether (or pentane), and cooling in a refrigerator overnight.[1c]

Handling, Storage, and Precautions: store in a brown bottle. Has a shelf-life of at least 1 year at rt. For longer periods of storage, it is recommended that the reagent be purified by recrystallization[1c] and refrigerated. Toxic; severe skin irritant; handle only in a fume hood.

General Discussion.

Diazomethane is a yellow gas (bp -23 °C, mp -145 °C) with the dipole structure $CH_2=N^+=N^-$ ⇂ $^+CH_2-N=N^-$ ⇂ $^-CH_2-N=N^+$. This versatile compound behaves as a methylene precursor with release of nitrogen and also functions as a 1,3-dipole in a variety of reactions, as documented in several reviews.[2] Diazomethane itself is both highly toxic and unpredictably explosive, and has been suggested to be a carcinogen.[3] Great care must be taken in handling this substance. However, these risks are minimal when diazomethane is prepared and handled as a dilute solution in an inert solvent such as ether using the proper equipment as discussed below (for further discussion, see

Diazomethane). A large number of compounds which previously served as diazomethane precursors can be represented by the formula RN(NO)Me, where R can be sulfonyl, carbonyl, imidoyl, or similar electron-withdrawing groups. Among these the reagent, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, introduced by de Boer and Backer in 1954,[1a] is the most common reagent used for the preparation of diazomethane. However, in some cases ***N-[N´-Methyl-N´-nitroso(aminomethyl)]benzamide*** and ***1-Methyl-3-nitro-1-nitrosoguanidine*** have advantages as diazomethane precursors. In addition, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide does suffer from some drawbacks, including its relatively short shelf life (1-2 years) and its mutagenic activity.[4]

Diazomethane is prepared as a dilute solution in ether by the decomposition (eq 1) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide catalyzed by alkali hydroxide.

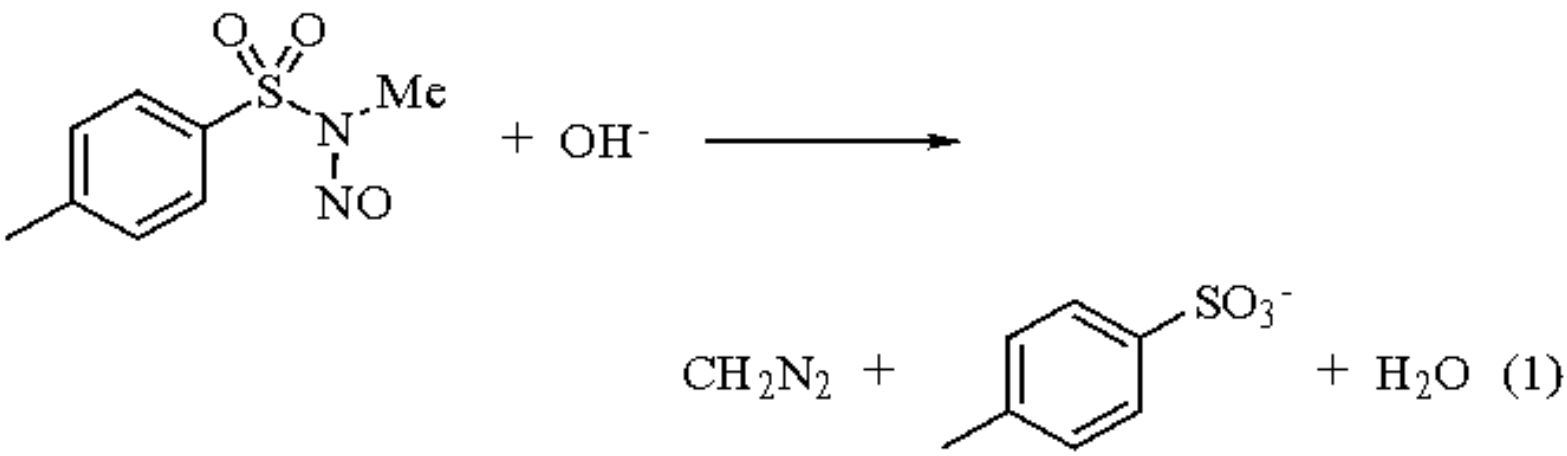

This preparation and all reactions involving diazomethane should be carried out in an efficient fume hood and behind a sturdy safety shield. Rough surfaces and strong sunlight are known to initiate detonation. Carefully fire-polished glassware for diazomethane preparation is commercially available.[5] A typical experimental procedure is as follows.[1b] A 125 mL, 3-neck flask is charged with a solution of 6 g of potassium hydroxide in 10 mL of water, 35 mL of 2-(2-ethoxyethoxy)ethanol (carbitol), and 10 mL of ether, and is then fitted with an efficient condenser set downward for distillation. The condenser is connected to two receiving flasks in series, both cooled in an ice-salt bath. The second receiver contains 25 mL of ether and the inlet tube should dip below the surface of the solvent. The generating flask is heated in a water bath at about 70 °C, stirring is started (Teflon-coated magnetic stirring bar), and a solution of 21.4 g (0.1 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 125 mL of ether is added from the dropping funnel over about 20 min. The rate of addition should about equal the rate of distillation. When the dropping funnel is empty, 50-100 mL of additional ether is added slowly. The distillation is continued until the distilling ether is colorless. The combined ethereal distillate contains 2.7-2.9 g (64-69%) of diazomethane. The content of diazomethane in the codistilled ethereal solution can be determined by titration; excess benzoic acid is added to the solution (to react with diazomethane) and the excess acid is titrated with a standard solution of NaOH. If moisture must be removed from the ethereal diazomethane solution, the drying agent of choice is KOH pellets. It is recommended that diazomethane solutions be used immediately and not stored, even at low temperature.

An alternative popular procedure for the generation of small quantities (1-50 mmol) of diazomethane from Diazald employs a commercial mini-Diazald apparatus with a dry-ice/acetone cold finger in place of the water-jacketed condenser.[5] The generation of diazomethane is carried out by treatment of the Diazald with KOH in aqueous ethanol.[2g]

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5. Aldrich Chemical Company, Inc.

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Methyl 6-Oxo-1-cyclohexenecarboxylate

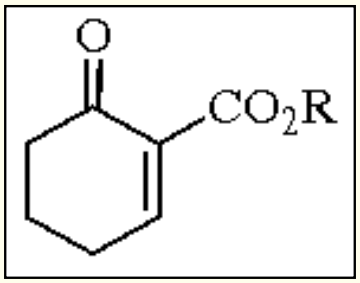

(**1**; R = Me)

[52784-37-9] · $C_8H_{10}O_3$ · Methyl 6-Oxo-1-cyclohexenecarboxylate · (MW 154.18) (**2**; R = Et)

[57205-09-1] · $C_9H_{12}O_3$ · Ethyl 6-Oxo-1-cyclohexenecarboxylate · (MW 168.21)

(dienophile for Diels-Alder reactions[5] and other cycloadditions;[7] Michael acceptor in conjugate additions)

Alternate Name: 2-methoxycarbonyl-2-cyclohexen-1-one.

Physical Data: (**2**) bp 59 °C/0.1 mmHg.

Preparative Methods: the ethyl ester has been prepared by phenylselenylation of the sodium enolate of ethyl 6-oxo-1-cyclohexanecarboxylate with ***Benzeneselenenyl Chloride*** using ***Sodium Hydride*** as the base in THF, followed by oxidation with ***Hydrogen Peroxide*** in a water-dichloromethane system. *Syn* elimination of benzeneselenic acid occurs at rt under essentially neutral condition, allowing the isolation of the compound with an enol content of less than 2%.[1,2] Kügelrohr distillation increases the enol content, which can vary from 5 to 50%. Normally, the crude product is sufficiently pure to be used. The methyl ester has been prepared in a similar way using pyridine as the base in dichloromethane, thus avoiding the use of strong base in anhydrous solvent; isolation of the phenylseleno intermediate is unnecessary.[3] Mention should be made of an efficient synthesis of the methyl ester, which avoids the use of toxic selenium reagents, through Birch reduction of methyl 2-methoxybenzoate followed by acidic hydrolysis.[4]

Handling, Storage, and Precautions: these compounds with doubly activated double bonds are unstable and should be used as soon as possible, although they can be stored for several weeks in solution at -20 °C. Use in a fume hood.

Diels-Alder Reactions.

These reagents are very good dienophiles for different types of cycloaddition. With ***Tin(IV) Chloride*** as catalyst, methyl 6-oxo-1-cyclohexenecarboxylate undergoes Diels-Alder reaction with a variety of dienes to give directly the *cis*-

decalin system with methoxycarbonyl group at the angular position (eq 1).[5] Secondary orbital overlap of the diene with the ester carbonyl rather than the ketone carbonyl is responsible for the stereochemistry of the major isomer. On the other hand, reaction of this dienophile in refluxing benzene with a silyloxydiene derived from 1-acetylcyclopentene gives the *endo* adduct as the major isomer (eq 2).[4] A [2 + 3] cycloaddition of the trimethylenemethane-palladium complex to methyl 6-oxo-1-cyclohexenecarboxylate readily gives the methylenecyclopentane adduct.[6]

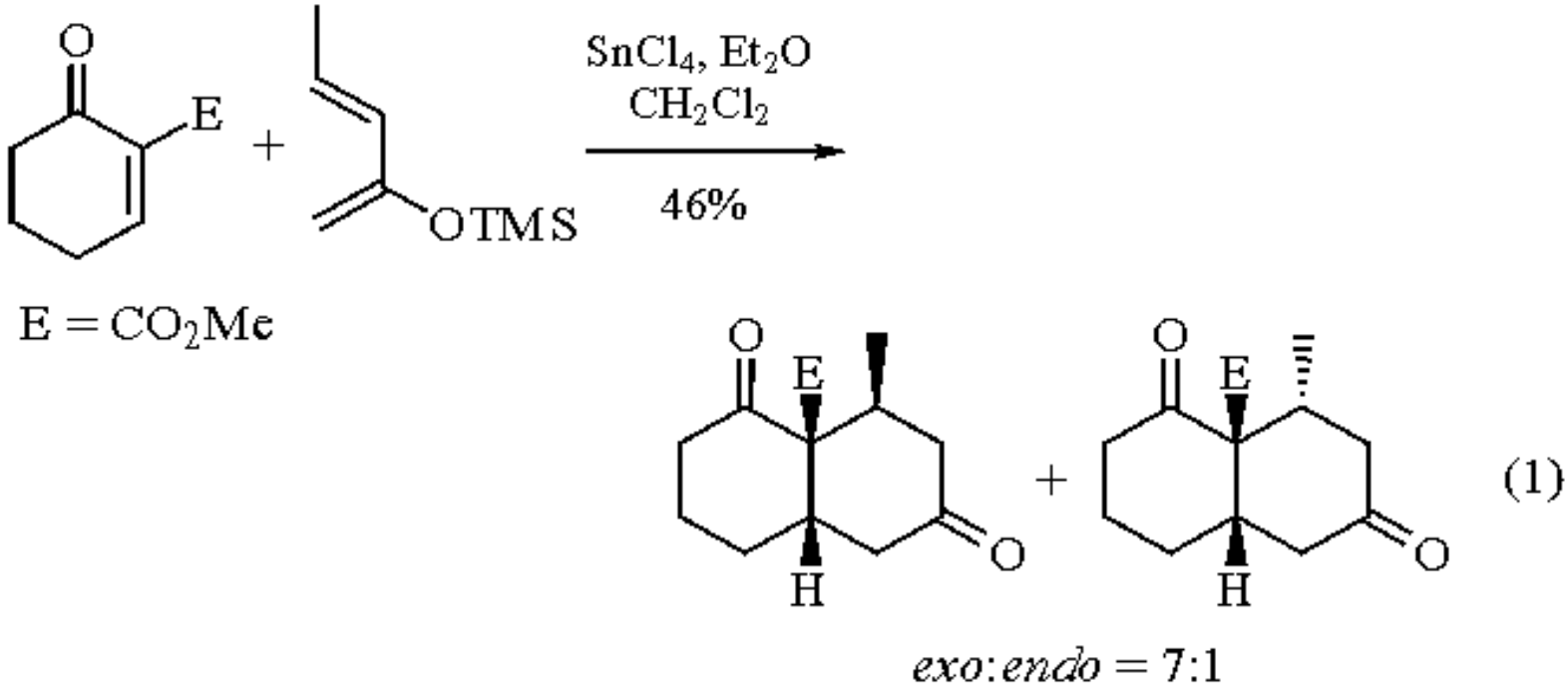

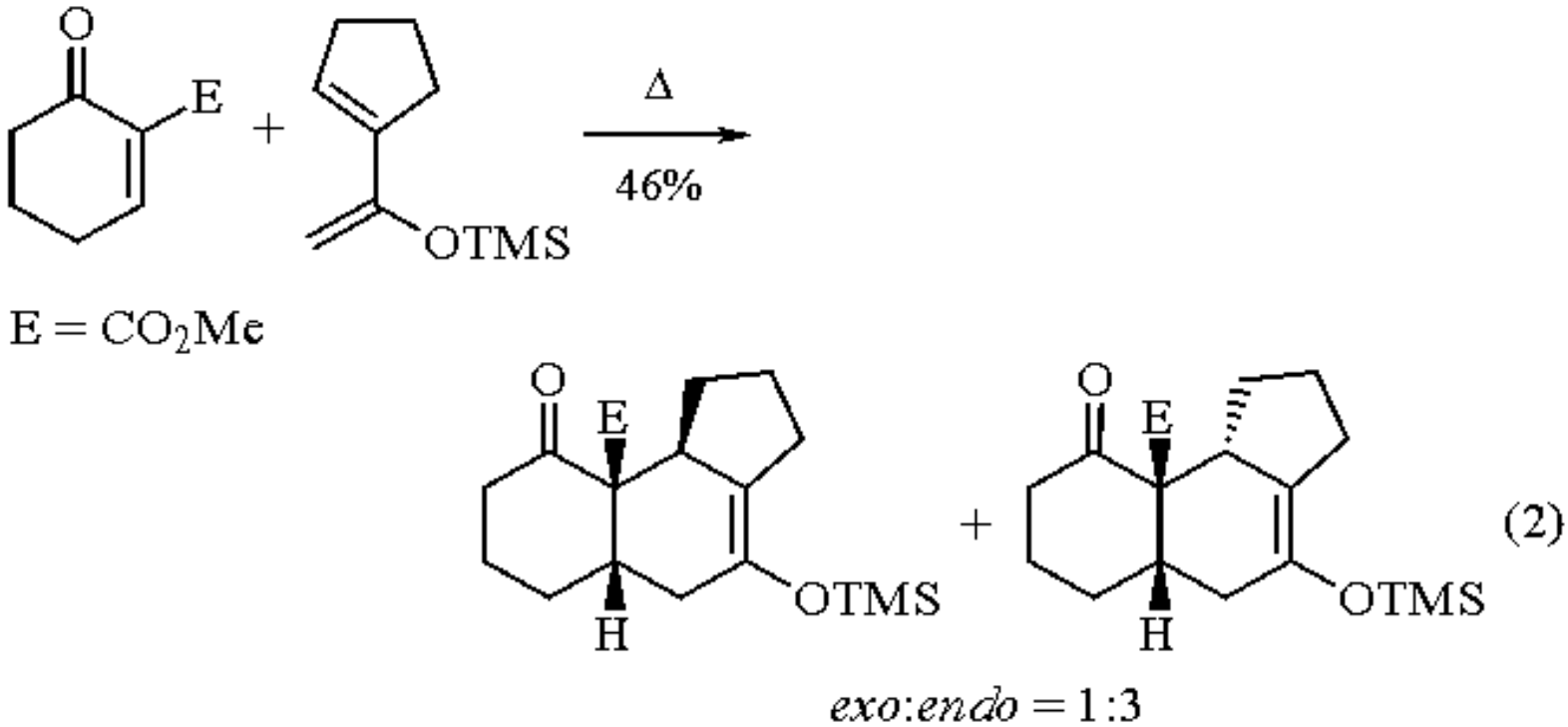

Base-Catalyzed Cycloaddition.

A very closely related transformation by base-catalyzed cycloaddition (or double Michael addition) of methyl 6-oxo-1-

cyclohexenecarboxylate with ***t-Butyl (E)-3-Oxo-4-hexenoate*** gives the corresponding *cis*-decalin, the *t*-butyl ester being selectively cleaved by acid with concomitant decarboxylation (eq 3).[7] High stereoselectivity in favor of the *exo* adduct is achieved using a nonpolar solvent. Several substituted 6-oxo-1-cyclohexenecarboxylates react similarly. Reversal of the methyl group stereochemistry is surprisingly achieved by using the corresponding γ,δ-unsaturated β-keto sulfoxide as the diene (eq 4).[7] Very good selectivity is obtained irrespective of the solvent polarity, in contrast to the reaction with the *t*-butyl ester. This methodology has been applied to the synthesis of 14-α-hydroxy-13α-methyl steroids[8] and optically active 14β-hydroxy steroids.[9]

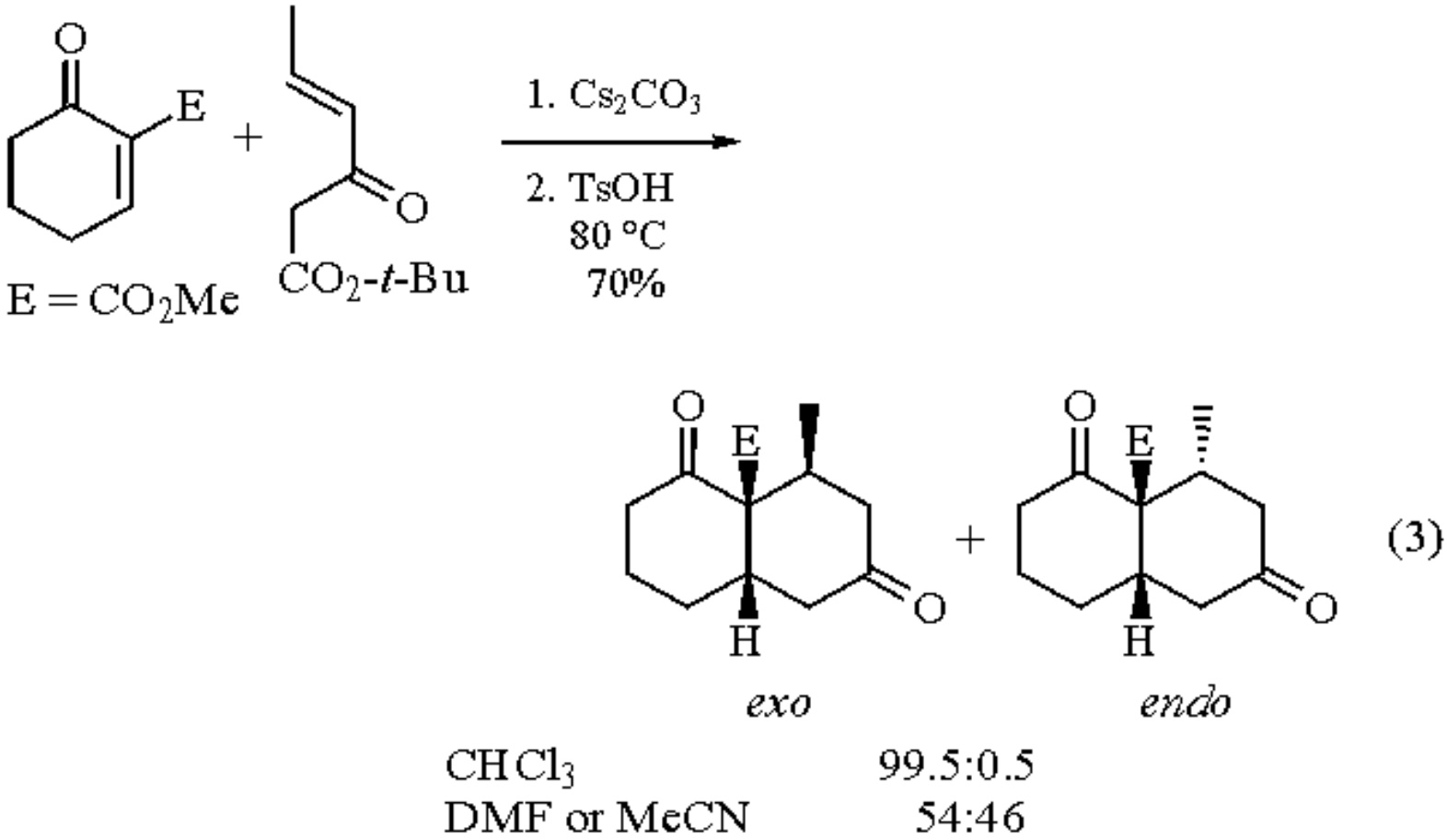

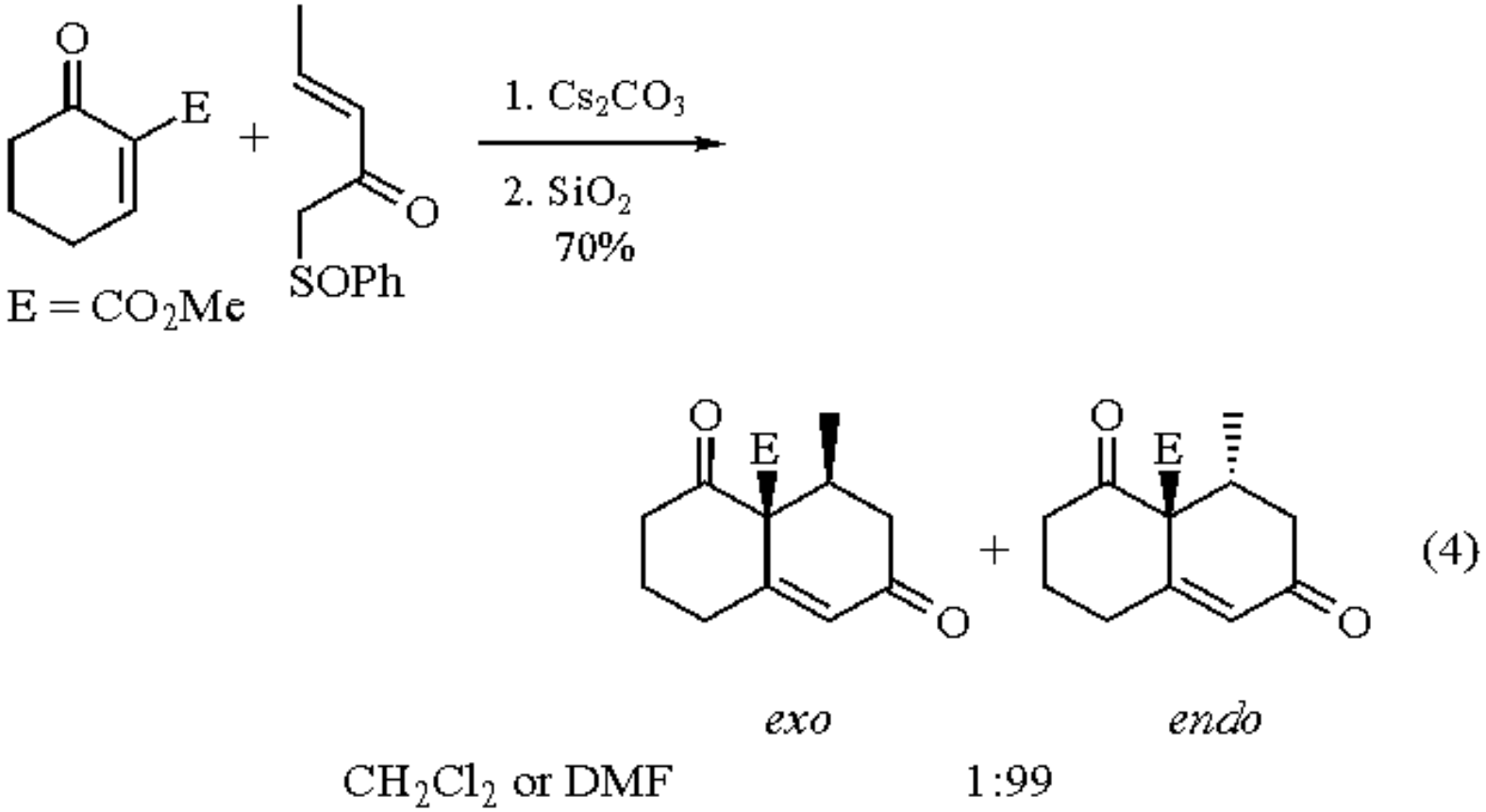

Michael Addition.

Conjugate addition of *O*-silylated ketene acetals to methyl 6-oxo-1-cyclohexenecarboxylate is readily achieved by using high pressure (eq 5).[10] It has been shown that, in other substrates, this procedure overcomes steric and conformational requirements while maintaining conditions compatible with acid-sensitive functionalities. Conjugate addition of allyl,[11] vinyl,[12] tributylstannyl,[13] and dimethylphenylsilyl[14] groups have been reported.

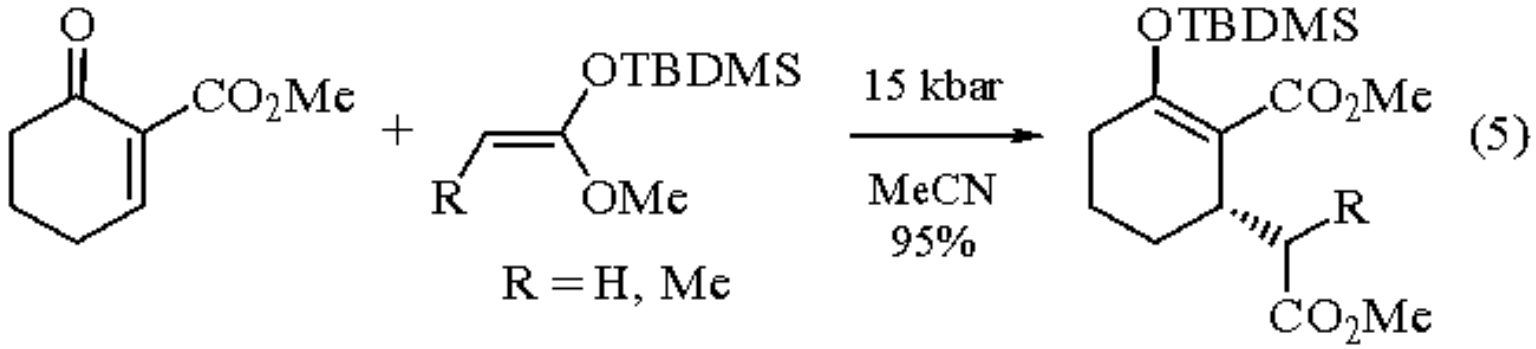

Related Reagents.

t-Butyl (E)-3-Oxo-4-hexenoate; ***Diethyl Ethylidenemalonate***; ***Ethyl Ethoxymethyleneacetoacetate***; ***Ethyl 2-Methyl-4-oxo-2-cyclohexene-1-carboxylate***; ***Methyl 5-Methoxy-3-oxopentanoate***; ***Methyl 3-Oxo-4-pentenoate***.

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Methyl 3-Oxo-4-pentenoate[1]

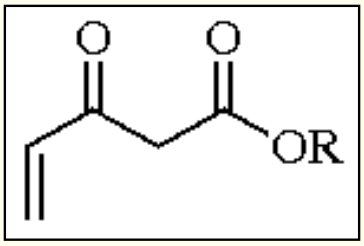

(**1**; R = Me)

[37734-05-7] · $C_6H_8O_3$ · Methyl 3-Oxo-4-pentenoate · (MW 128.14) (**2**; R = Et)

[22418-80-0] · $C_7H_{10}O_3$ · Ethyl 3-Oxo-4-pentenoate · (MW 142.17)

(Michael acceptor in the Robinson annulation[2])

Alternate Names: Nazarov's reagent; methyl acryloylacetate; vinyl β-methoxycarbonylmethyl ketone.

Physical Data: (**1**) bp 65 °C/19 mmHg. (**2**) bp 76-78 °C/18 mmHg.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: exists as a mixture of keto and enol forms; IR (film) cm^{-1} 2984, 1741, 1659, 1588, 1423, 1242, 1150, 1038, and 812; ^1H NMR ($CDCl_3$) δ 1.2-1.3 (overlapping t, 3 H), 3.6 (s, ketonic H at C-2), 4.1-4.3 (m, 2 H), 5.05 (s, enolic H at C-2), 5.50 (appt, 1 H), 5.91-6.43 (m, 2 H), 11.8 (s, enol OH); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 46.4, 60.2, 61.4, 91.8, 122.5, 130.2, 131.2, 135.7, 167.1, 168.6, 172.7, and 192.6.

Preparative Methods: first prepared by Nazarov[3] in 1953 by the reaction shown in eq 1. (**2**) is known as Nazarov's reagent, although (**1**) is often referred to as Nazarov's reagent also.

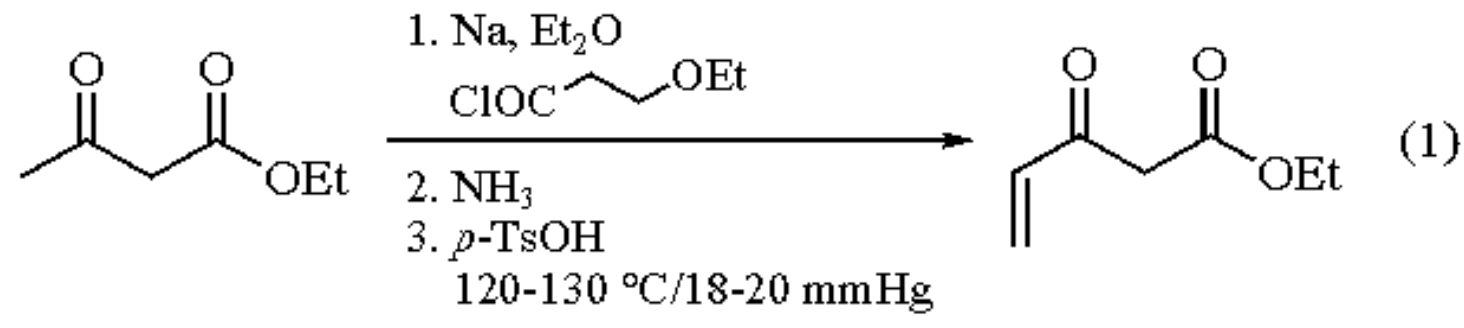

The original preparation of (**2**) suffers several problems. It has been termed tedious[4] and has a low overall yield. Several new syntheses of esters of 3-oxo-4-pentenoic acid have been reported since 1953.[2,4-10]

The most facile preparation of Nazarov's reagent and ester analogs was reported by Zibuck and Streiber in 1989. A variety of ester enolates react with ***Acrolein*** to provide good yields of β-hydroxy esters that can be oxidized to β-keto esters such as Nazarov's reagent and analogs (eqs 2 and 3).[1] The reaction sequence can be safely and successfully carried out on a 1 mol scale. Also, the β-hydroxy ester may be oxidized without purification. Interestingly, (-)-bornyl acetate leads to an annulating agent that contains a chiral auxiliary. ***Methacrolein*** and ***Crotonaldehyde*** give 4- and 5-methyl substituted reagents. C-4 and C-5 substituted analogs of Nazarov's reagent have been prepared by many other research groups, using reactions similar to those presented above.[11-16]

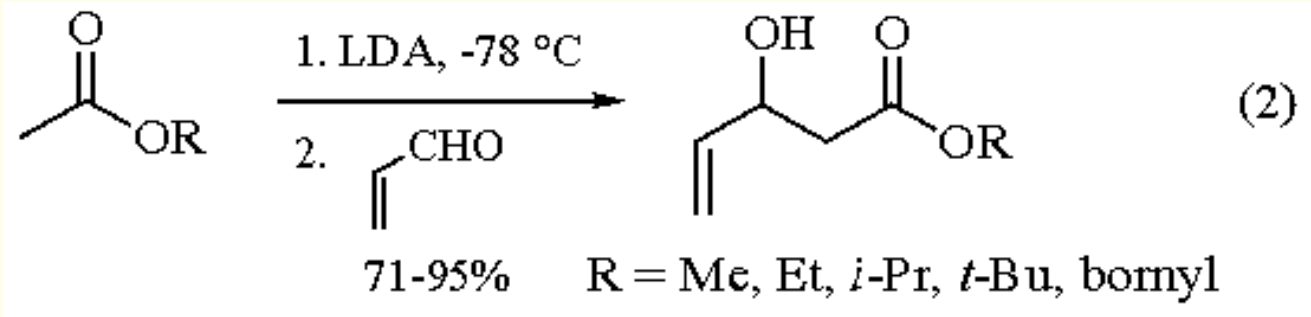

(2)

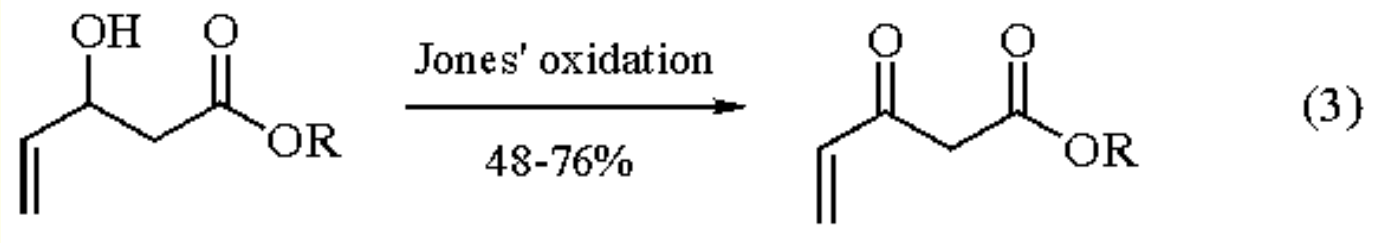

(3)

Purification: by Kugelrohr distillation at 0.6 mmHg (oven temperature 45 °C) with a receiving bulb cooled at -78 °C.

Handling, Storage, and Precautions: polymerizes rapidly at rt; stable to storage at -20 °C under nitrogen for up to 6 months; toxic; handle in a fume hood.

Robinson Annulations and Other Ring-Forming Processes.

Methyl and ethyl 3-oxo-4-pentenoate (**1**) and (**2**) are often used as Michael acceptors in strategies such as the Robinson annulation. Typical examples are shown in eqs 4 and 5.[17]

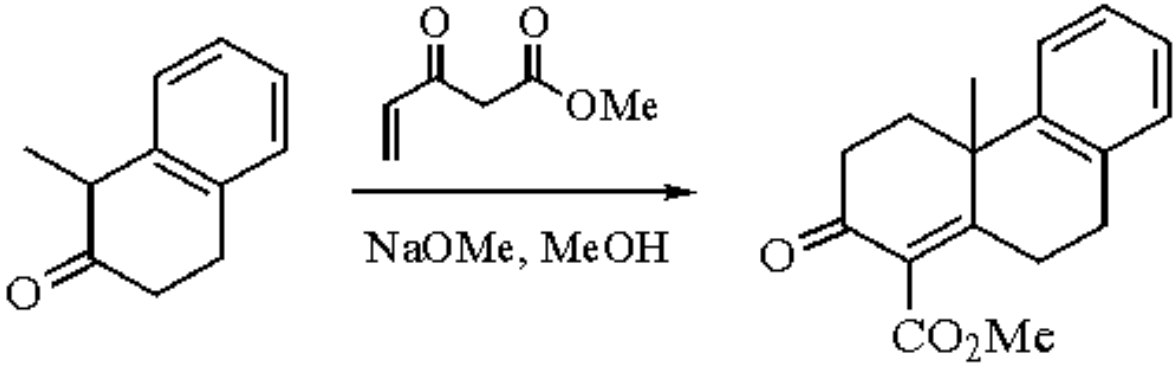

(4)

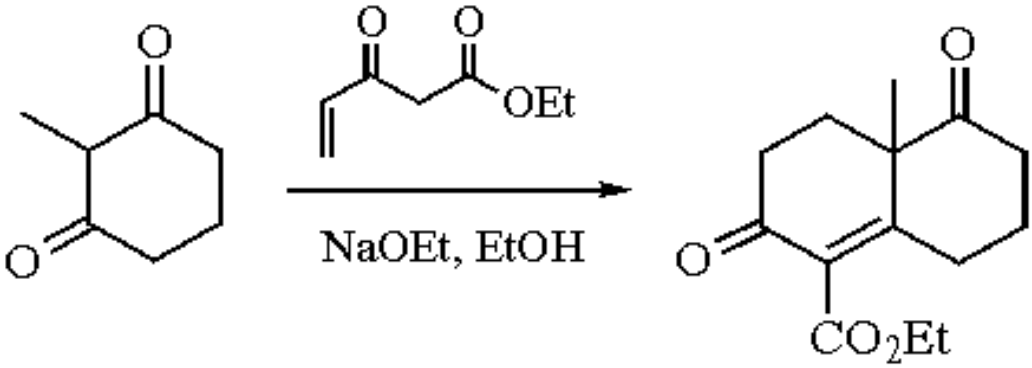

(5)

Other cyclizations involving this reagent include Mannich and Mannich-like reactions (eqs 6-8).[18-20] Thioimidates react as nucleophiles with methyl 3-oxo-4-pentenoate as shown in eq 9.[21]

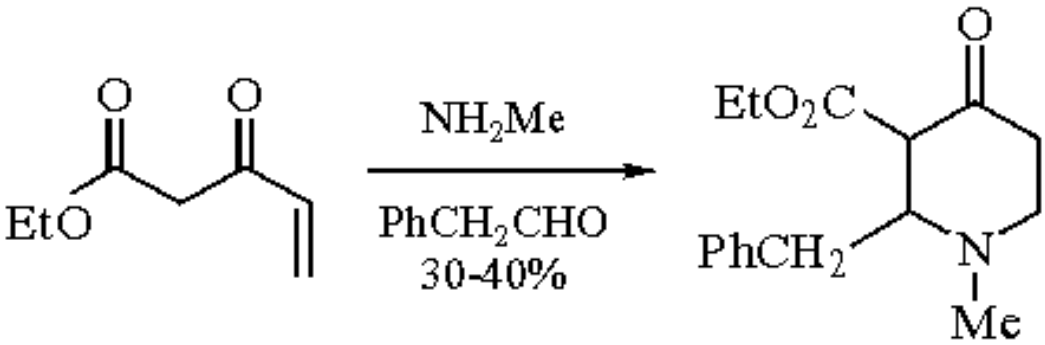

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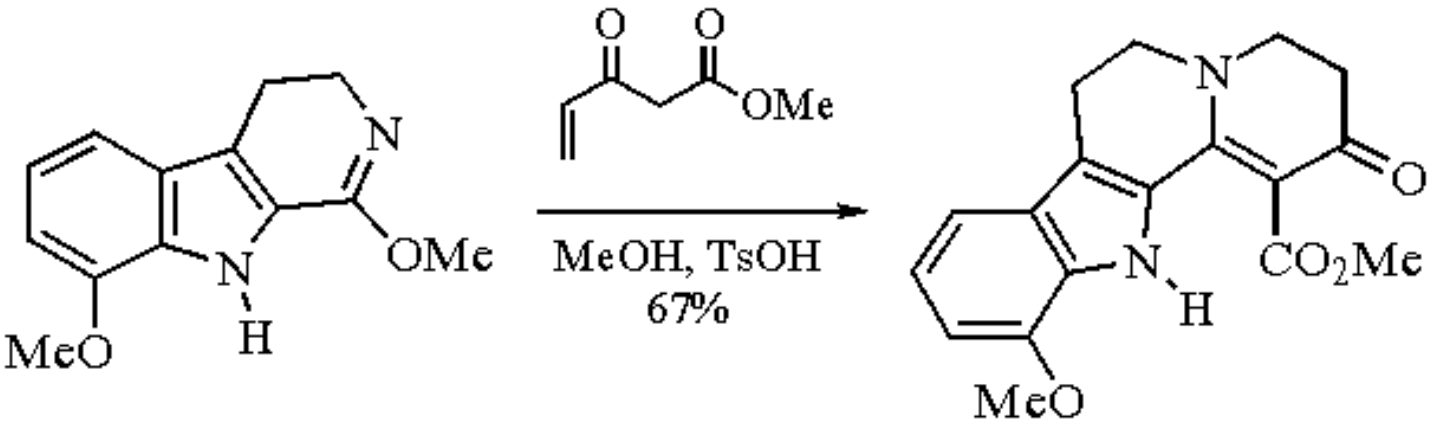

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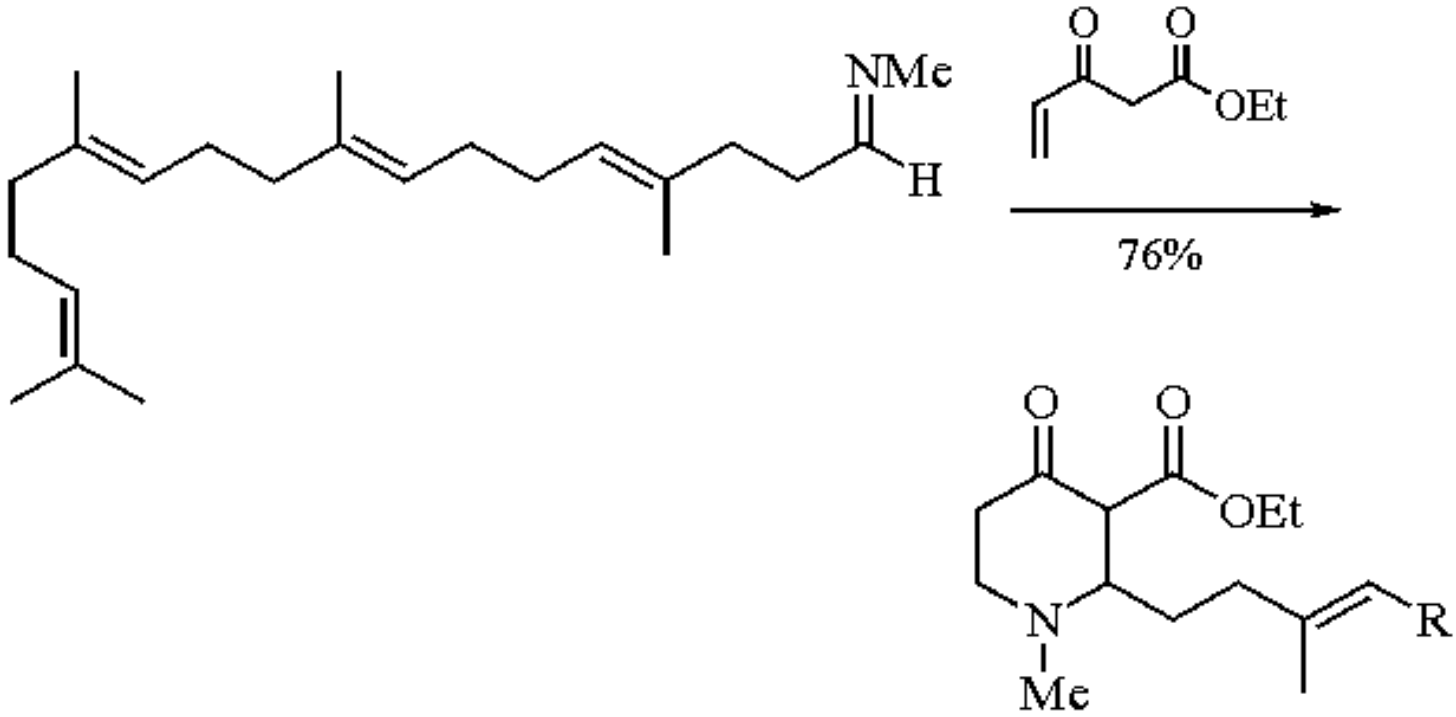

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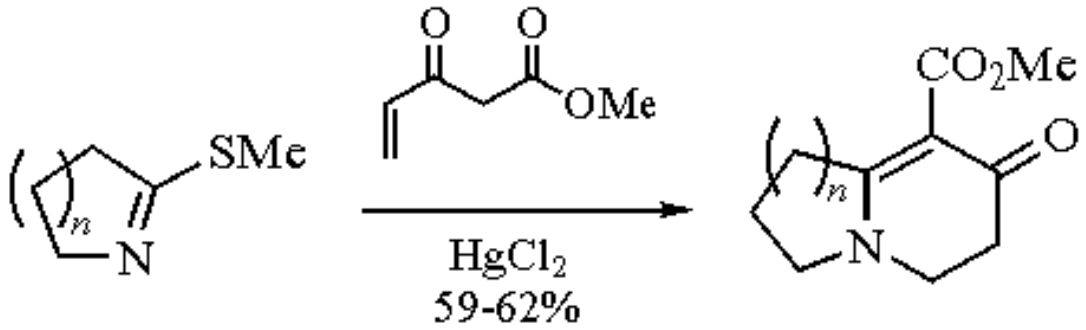

(9)

Methyl 3-oxo-4-pentenoate has also been used in the well-known carbon zip reaction. Cycloheptyl, -octyl, and -dodecyl nitro ketones yield ring-enlarged adducts in 90-93% yield (eq 10).[22] Finally, esters of 3-oxo-4-pentenoate have often been used as Michael acceptors in many other synthetic sequences.[23-27]

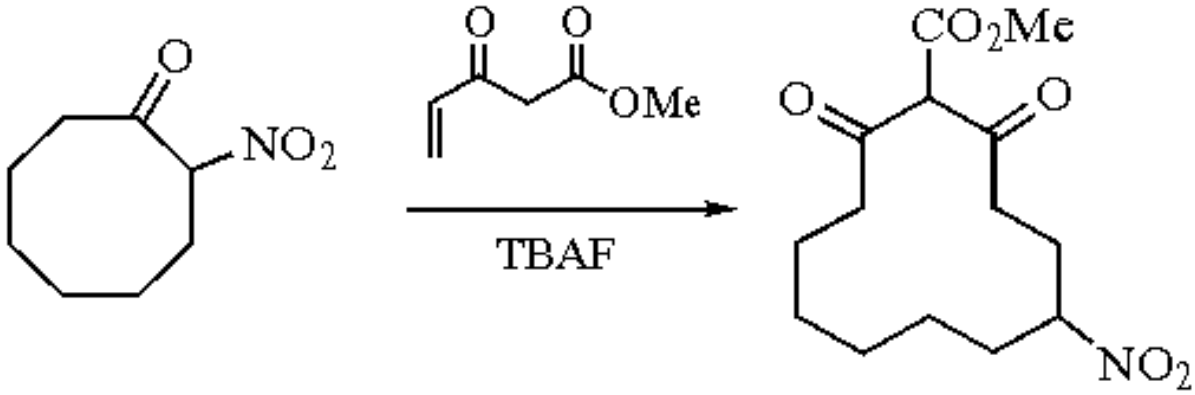

(10)

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(*E*)-Methyl 2,4-Pentadienoate

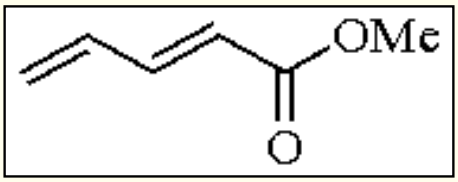

[1515-75-9] · $C_6H_8O_2$ · (*E*)-Methyl 2,4-Pentadienoate · (MW 112.14)

(electron-poor diene capable of cycloaddition reactions with activated dienophiles to form carbocyclic[1] and heterocyclic[2] compounds; metal-promoted [6 + 4] cycloadditions[3] and metal-promoted chain extensions[4])

Physical Data: bp 55-57 °C/14 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: NMR.

Preparative Methods: Wittig alkenation of ***Acrolein*** with ***(Methoxycarbonylmethylene)triphenylphosphorane***;[5] reaction of ***Malonic Acid*** with acrolein, followed by esterification.[6]

Purification: distillation.

Handling, Storage, and Precautions: polymerizes easily.

Diels-Alder Reactions.

As an electron-poor diene, the cycloaddition reactions of (*E*)-methyl 2,4-pentadienoate are optimal when combined with electron-rich dienophiles such as enamines (eq 1).[1] When electron-deficient dienophiles such as benzyljuglone,[7] or relatively nonpolarized dienophiles are employed (eq 2),[8] more forcing conditions are needed.

(E)-Methyl 2,4-Pentadienoate

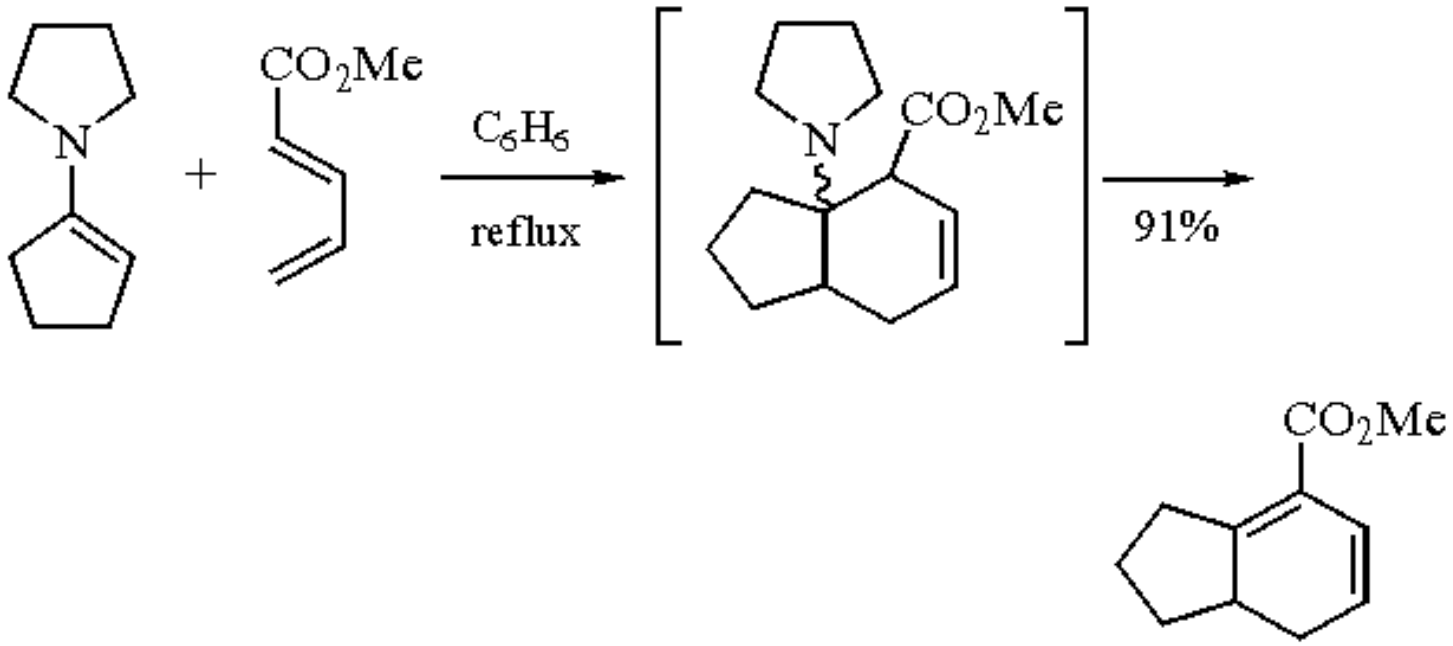

(1)

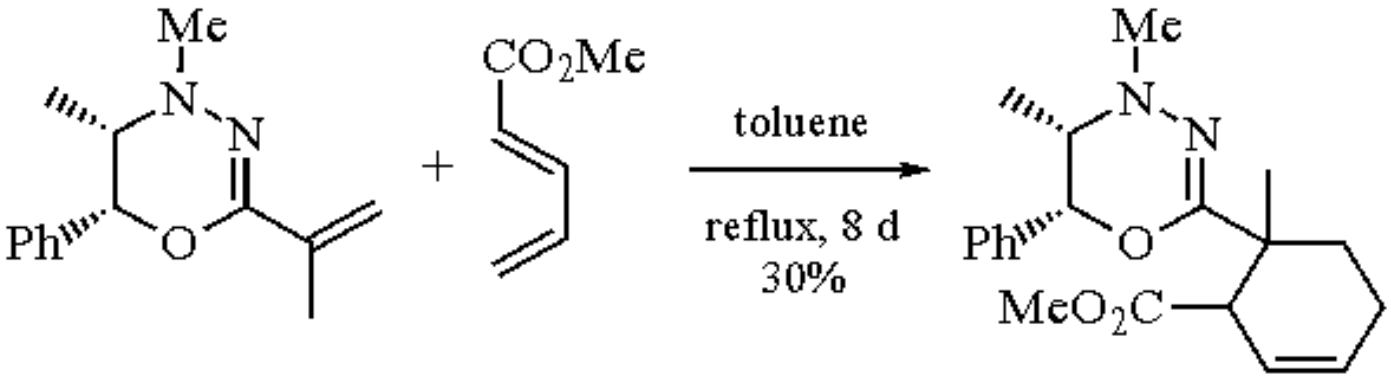

(2)

Heterocycle Synthesis.

Nitroso compounds can react with the dienoate to afford 3,6-dihydro-1,2-oxazines (eq 3).[2] The 3,4-double bond can act as a 2π component in reactions with diphenylnitrilimine (eq 4).[9]

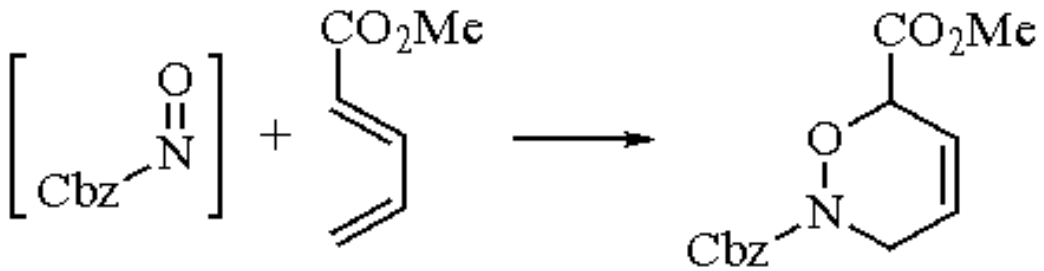

(3)

(E)-Methyl 2,4-Pentadienoate

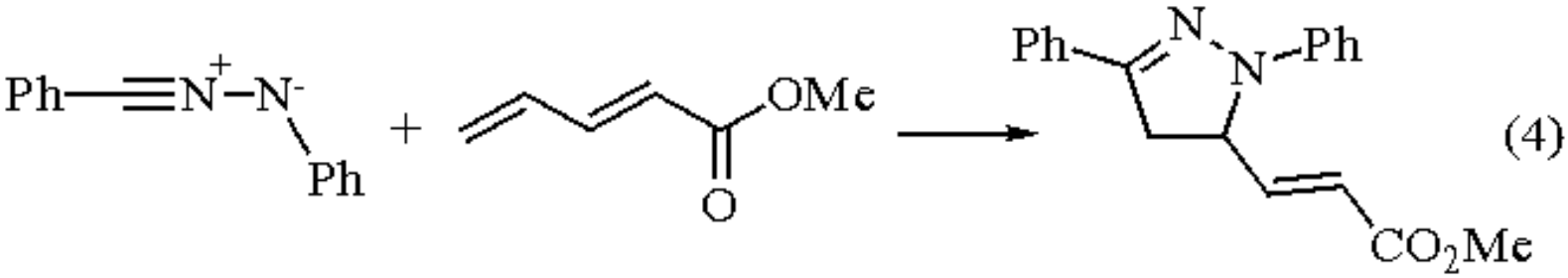

Metal-Promoted Reactions.

The diene is a useful acceptor in the Heck reaction (eq 5).[4] It should be noted that the metal acts in a catalytic fashion in this reaction. When other reactants are not included in the reaction mixture, dimerization and further oligomerization is observed.[10-12] Other metal-promoted reactions can induce cycloaddition processes. In a noncatalytic process, complexation of thiepin dioxide with chromium tricarbonyl brings about [6 + 4] cycloaddition (eq 6).[3]

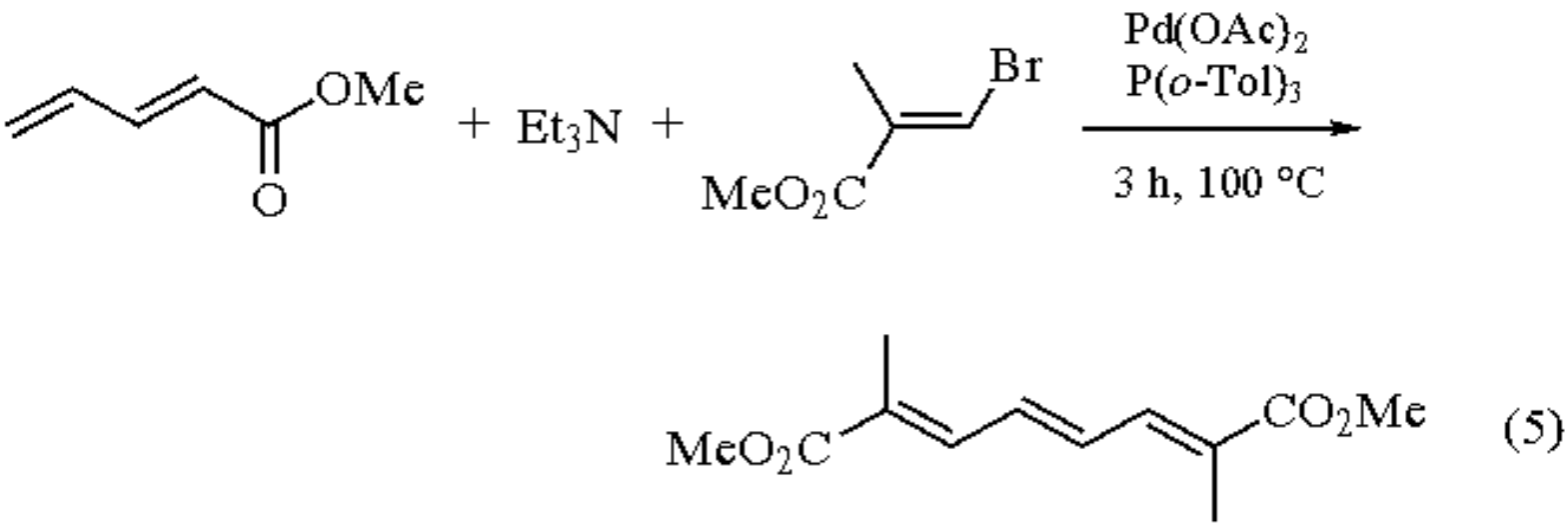

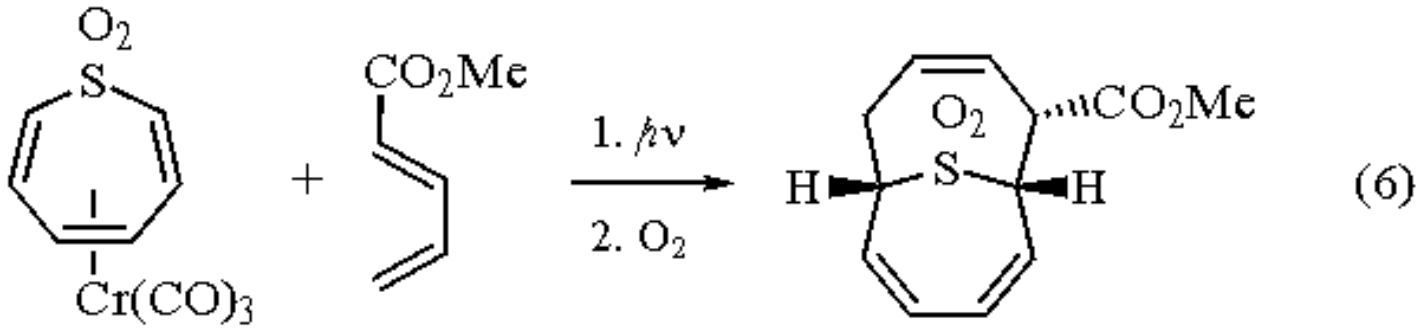

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(Methylphenylamino)triphenylphosphonium Iodide

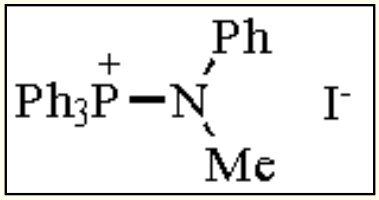

[34257-63-1] · $C_{25}H_{23}INP$ · (Methylphenylamino)triphenylphosphonium Iodide · (MW 495.36)

(synthesis of amines from alcohols; synthesis of unsymmetrical sulfides; synthesis of alkenes from allyl alcohols; synthesis of 1,3-dienes)

Alternate Name: Murahashi's reagent.

Physical Data: mp 237-242 °C (dec); commercial material quotes a higher melting point than material made in the reference.[1]

Solubility: sol DMF, EtOAc. Behaves as a Wittig-type reagent in terms of solubility.

Form Supplied in: solid.

Preparative Method: phenyliminotriphenylphosphorane is reacted with excess ***Iodomethane*** at reflux for 2 h. Removal of MeI followed by recrystallization gives a quantitative yield.[1]

Purification: may be recrystallized from chloroform-ethyl acetate (1:2).

Handling, Storage, and Precautions: store in sealed bottle on bench. Do not breathe dust, fumes, or vapor. Avoid contact with skin and eyes. Use in a fume hood.

Synthesis of Amines from Alcohols.

The reagent is similar to the Mitsunobu reagent in that it converts alcohols to alkylating agents. Hence, the reaction of an alkoxide ion with Murahashi's reagent in the presence of a primary or secondary amine leads to *N*-alkylation in high yield.[2] The reaction is mild and high yielding (eq 1), although replacing benzene for DMF as a solvent for secondary amines is recommended. Analogously, the preparation of azides can be accomplished by using ***Sodium Azide*** as the nucleophile.

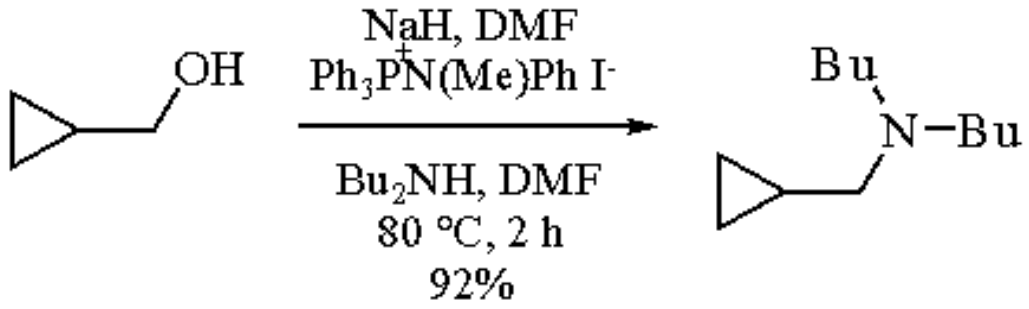

(1)

Synthesis of Unsymmetrical Sufides.

Unsymmetrical sulfides may also be prepared by the reaction of alkoxides and thiols utilizing aminophosphoranes (eq 2). This method has been applied to the synthesis of various thiols, e.g. alkyl, benzyl, phenyl, *t*-butyl, and vinyl thiols.[3] Both *cis*- and *trans*-cinnamyl alcohols have been used, as well as geraniol, yielding the corresponding sulfides with retention of configuration.

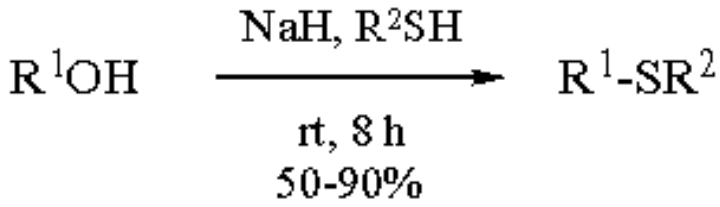

(2)

Synthesis of Alkenes from Allyl Alcohols.

Allylic alcohols may be alkylated by an excess of alkyllithium in the presence of ***Methyllithium***, ***Copper(I) Iodide***, and Murahashi's reagent (eq 3).[4] The detailed structure of the lithium alkoxyallylcuprate and alkylcuprate having the stoichiometry $R^1OCuR^2{}_3Li_3$ is not known.

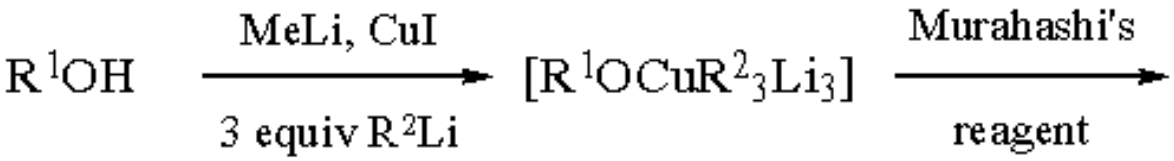

$$R^1\text{-}R^2 + Ph_3PO + R^2{}_2CuN(Me)PhLi_2 \quad (3)$$

γ-Alkylation of allylic alcohols with organolithium reagents using (methylphenylamino)tributylphosphonium iodide proceeds as shown in eq 4.[5] The latter reagent is easily prepared by addition of ***Phenyl Azide*** to ***Tri-n-butylphosphine*** in refluxing ether, followed by treatment with ***Iodomethane*** at reflux (90% yield; mp 120-120.5 °C, recrystallized from ethyl acetate.

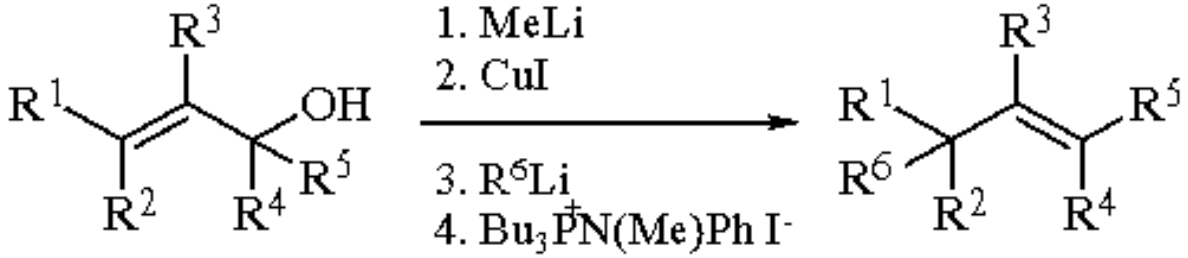

(4)

Thus the reaction provides an efficient single-step process for the regio- and stereoselective synthesis of alkenes. Excellent yields are obtained from primary, secondary, and tertiary alcohols. Importantly, 1-substituted 2-propen-1-ols, which are readily available, can be converted into *trans*-1,2-disubstituted alkenes in a regio- and stereospecific manner. Alkylation of tertiary alcohols occurs with predominant allylic rearrangement, giving trisubstituted alkenes. The *cis*/*trans* ratios of the alkenes are not dependent upon the substitution of the tertiary allylic alcohol nor upon the organolithium compound; constant values of 32-36/68-64 are obtained. A reinvestigation of the regio- and stereochemistry was carried out by Goering.[6] In the initial study, triphenylphosphorane derivatives were used and there was no indication of any regiospecificity. More recently, tributylphosphorane salts have been used and S_N2' regiospecificity is observed (eq 5).

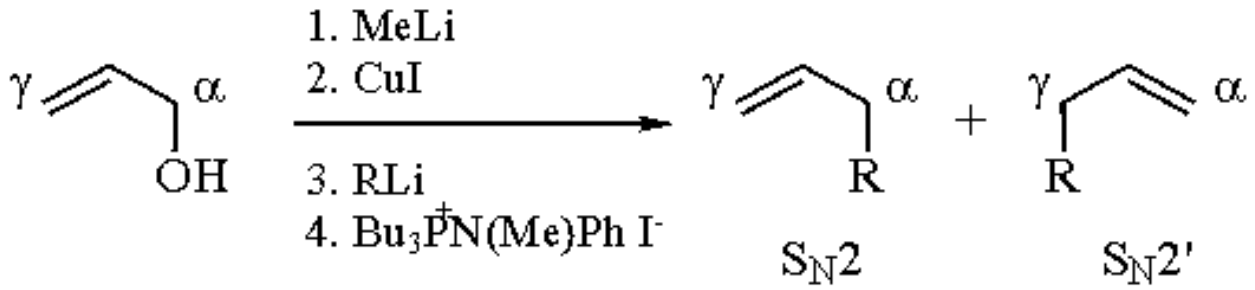

(5)

It is reported that the differences in regiochemistry do not result from using different phosphoranes, but instead result from a change in the experimental procedure. In fact, under the same conditions, the regio- and stereochemistry are the same with both reagents: this would be expected if the mechanistic pathway proposed by Murahashi[5] (eq 6) is followed.

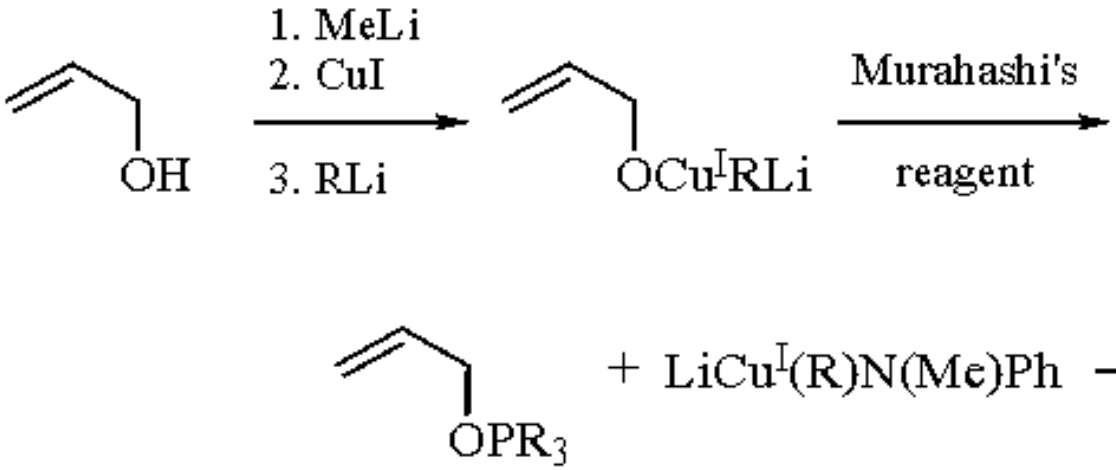

(6)

In a further study of the alkylation of acylic systems by the same group,[7] it was found that *syn* γ-alkylation predominates in acyclic systems, but *anti* γ-alkylation predominates in cyclic systems. The results show that the reaction is highly regioselective.

Synthesis of 1,3-Dienes.

Alkylation of α-allenic alcohols by organolithiums using Murahashi's reagent leads to formation of 1,3-dienes (eq 7).[8] This allows direct nucleophilic substitution of labile or hindered α-allenic alcohols by organolithium reagents; the yields are in the range 35-55%.

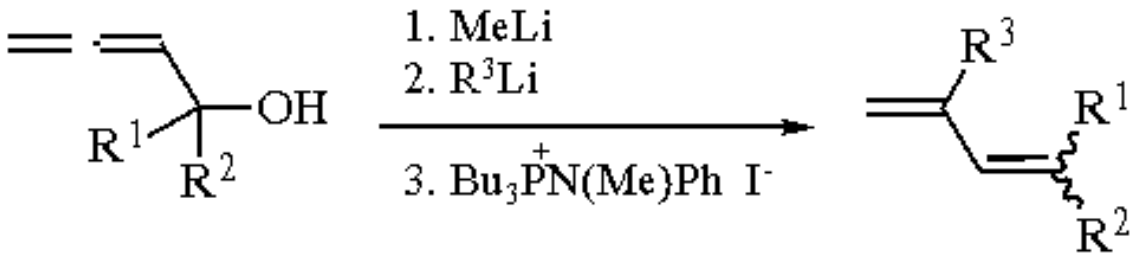

(7)

This procedure invoves the in situ transformation of the hydroxy group of an unsaturated alcohol into an alkoxyphosphonium salt and the reaction of this with a nucleophile. The stereoselectivity seems to be dependent on the nucleophile and the nature of the substituent on the α-allenic carbon atom. The main interest of the reaction lies in the possibility of using various carbonucleophiles.

A review has appeared in the literature concerning the utility of the reagent in preparation and nucleophilic substitution of the hydroxy group of alcohols in organic synthesis.[8]

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(*Z*)-*N*-Methyl-*N*-phenylbenzohydrazonyl Bromide

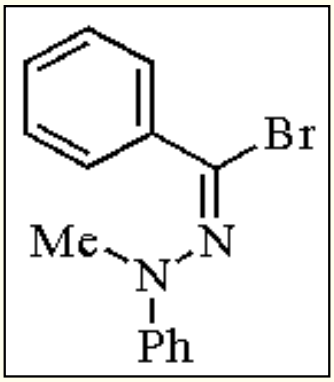

[59259-48-2] · $C_{14}H_{13}BrN_2$ · (*Z*)-*N*-Methyl-*N*-phenylbenzohydrazonyl Bromide · (MW 289.19)

(coupling mediator in peptide synthesis)

Physical Data: bp 82-85 °C/0.5 mmHg.

Solubility: usually used in polar solvents (acetone).

Analysis of Reagent Purity: satisfactory microanalytical data reported.[1]

Preparative Method: from the corresponding hydrazide using either ***Phosphorus(V) Chloride*** in dry benzene or ***Triphenylphosphine-Carbon Tetrabromide*** in acetonitrile for 2 h.[1] The solid material resulting is extracted four times with ether and the resulting organic layer is concentrated to yield the crude product. Distillation provides the pure compound as exclusively the (*Z*)-isomer.

General Discussion.

Imidoyl halide reagents such as (**1**) have been utilized as coupling mediators in peptide synthesis.[2] This reactivity is based on the instability of (**1**) in polar media, in which rapid unimolecular ionization occurs to give nitrilium ions (**2**) (eq 1).[3] These ions exhibit unusual reactivity, being more reactive with carboxylate ions than with simple amines; thus in the presence of equal amounts of acetic acid and morpholine, the major product is the *O*-acyl isoamide (**3**) rather than the amidine (eq 2). This situation is enhanced by pH control so that, when trapping of the nitrilium ion is carried out at pH 6 (i.e. >2 pH units below the pK_a of the amine), the isoamide (**3**) is the exclusive product. Furthermore, (**2**) will discriminate between carboxylate and water as nucleophile and thus the reaction can be carried out in aqueous media. Addition of an amine to (**3**) results in formation of amides in good yields. Use of *N*-protected α-amino acids in reaction with (**1**) gives isoamides (**4**) (eq 3), whose reaction with α-amino esters allows efficient preparation of peptides (eq 4). No racemization occurs during the reaction (as shown by the Anderson[4] method). Base hydrolysis of the crude reaction mixture gives *N*-

protected peptides in 80% overall yield. No acyl migration occurs in the reaction.

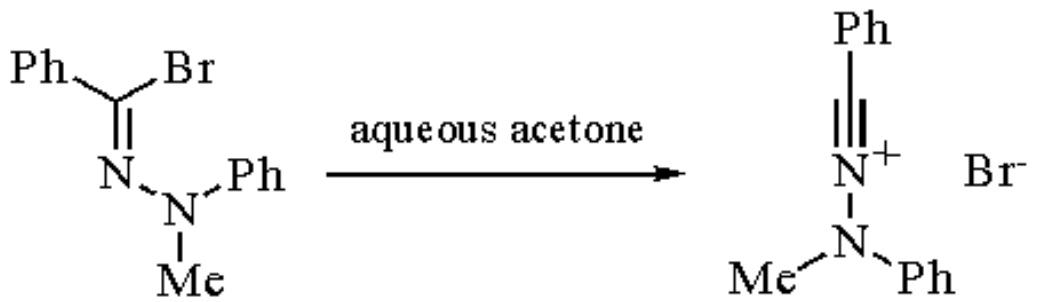

(1)

(1) **(2)**

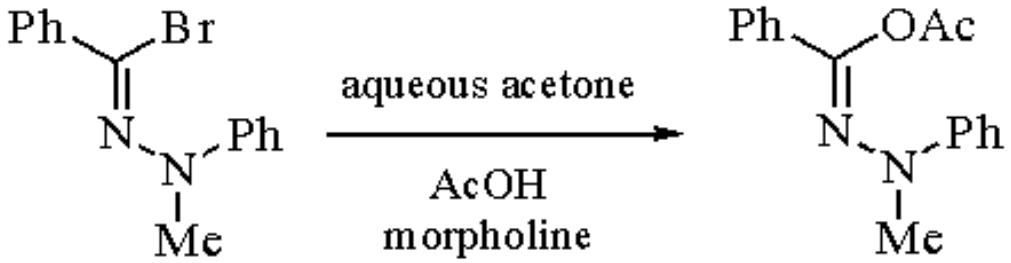

(2)

(3)

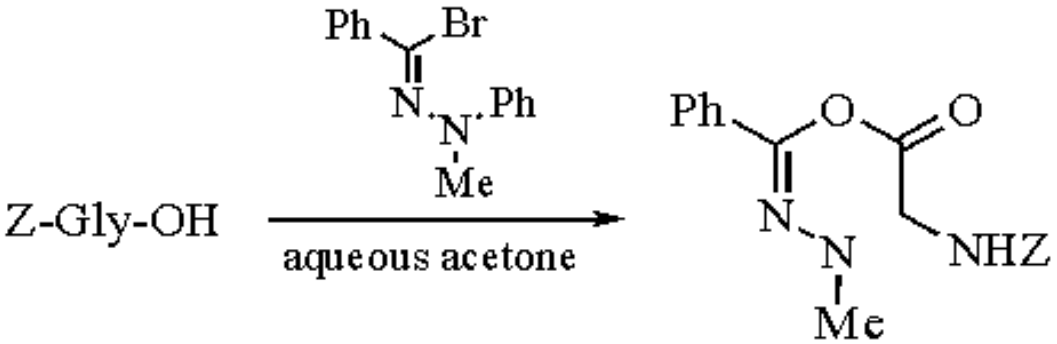

(3)

(4)

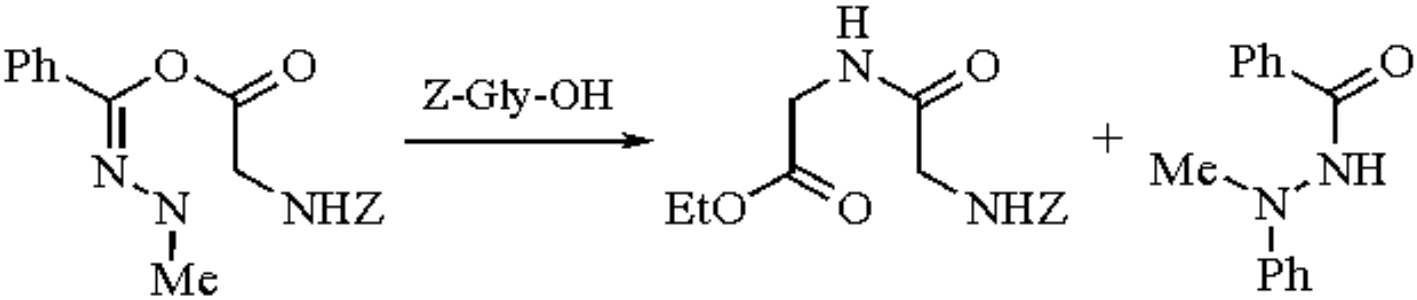

(4)

The unusual reactivity and concomitant pronounced selectivity of (**1**) allows peptides to be synthesized with a minimum number of protecting groups. Indeed, completely unprotected amino acids may be coupled using the above protocol, but best results are obtained when there is a protection of the nitrogen of the first amino acid to be coupled (Table 1). This facilitates separation of the product and subsequent manipulation is simplified.

Table 1 Preparation of Dipeptides using *N*-Methyl-*N*-phenylbenzohydrazonyl Bromide

Acid	Amine	*N*-Protected dipeptide	Yield (%)
Z-Gly-OH	H-Gly-OEt	Z-Gly-Gly-OH	80[a]
Z-Gly-OH	H-Gly-OH	Z-Gly-Gly-OH	78
Z-Gly-OH	H-Trp-OH	Z-Gly-Trp-OH	82
Z-Trp-OH	H-Trp-OH	Z-Trp-Trp-OH	76
Z-Trp-OH	H-Ser-OH	Z-Trp-Ser-OH	80

[a] After base hydrolysis.

1. Wolkoff, P. *CJC* **1975**, *53*, 1333.
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N-Methyl-*N*-phenylcarbamoyl Chloride[1]

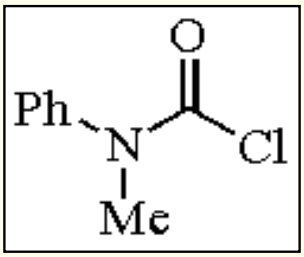

[4285-42-1] · C_8H_8ClNO · *N*-Methyl-*N*-phenylcarbamoyl Chloride · (MW 169.62)

(reagent for formylation of arenes[2])

Physical Data: mp 87-90 °C; bp 280 °C.

Form Supplied in: solid; commercially available.

Purification: recrystallize from dry ether.[3]

Handling, Storage, and Precautions: a corrosive lachrymator. Store under dry nitrogen. Use in a fume hood.

Formylation Reagent.

N-Methyl-*N*-phenylcarbamoyl chloride saw early use for the formation of aromatic aldehydes, through the two-step procedure of a Friedel-Crafts acylation of an arene, followed by reduction of the resultant *N*-methylbenzanilide with ***Lithium Aluminum Hydride***.[2] Yields in both steps are generally only moderate (eq 1).[2] The mechanism of the reduction has been studied.[3] Other reagents for arene formylation have been developed that have greater utility[1] (see ***Bis(1,3-diphenyl-2-imidazolidinylidene)*** and ***N-Ethoxymethyleneaniline***).

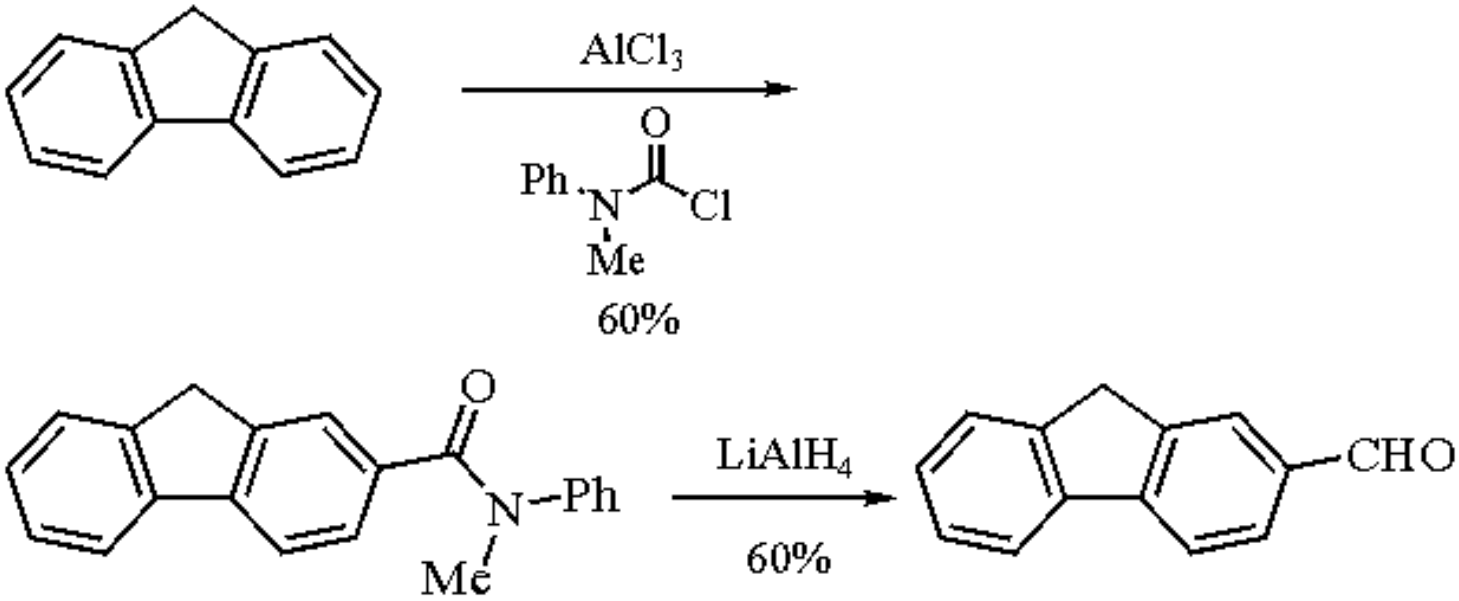

Vinyl and Aryl Amides.

The reagent undergoes reasonably efficient palladium-catalyzed cross coupling with a variety of vinyl- and arylstannanes to give the corresponding amides (eq 2).[4]

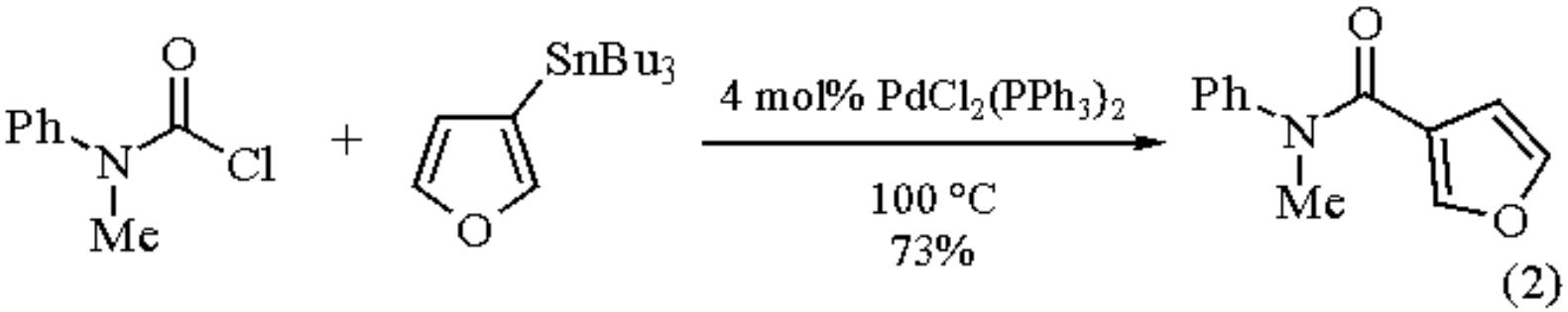

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N-Methyl-*N*-phenyl(chloromethylene)ammonium Phosphorochloridate

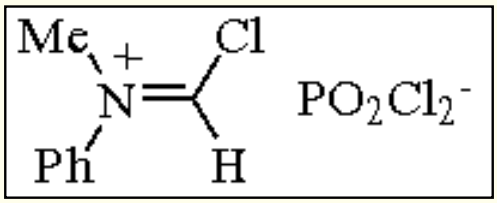

[80984-92-5] · $C_8H_9Cl_3NO_2P$ · *N*-Methyl-*N*-phenyl(chloromethylene)ammonium Phosphorochloridate · (MW 288.50)

(formylation of activated aromatic systems[1,2] and alkenes[2])

Alternate Name: N-methylformanilide-phosphorus oxychloride complex.

Physical Data: see ***N-Methylformanilide*** (MFA) and ***Phosphorus Oxychloride***.

Form Supplied in: prepared in situ.

Preparative Method: $POCl_3$ is slowly added to a small excess of MFA.[3] A solvent may be added,[4] typically 1,2-dichloroethane or 1,2-dichlorobenzene; MFA may also be used as the solvent in the reaction.

Handling, Storage, and Precautions: phosphorus oxychloride is corrosive and lachrymatory. *N*-Methylformanilide is toxic and harmful by absorption. The iminium salt reacts vigorously with water. Use in a fume hood.

Formylation of Arenes.

Simple unactivated aromatic systems do not react with most Vilsmeier reagents (the adduct from ***N,N-Dimethylformamide-Trifluoroacetic Anhydride*** has been reported to formylate unactivated systems;[5]) electron-rich aromatic systems undergo monoformylation with MFA-$POCl_3$ in moderate to good yields.[1] Thus anthracene gives 9-anthracenecarbaldehyde (eq 1);[6] pyrene gives 3-pyrenecarbaldehyde (53%);[7] and azulene gives 1-azulenecarbaldehyde (eq 2).[8] Recent reports suggest that the adduct of ***Pyrophosphoryl Chloride*** ($P_2O_3Cl_4$) and MFA is a more effective formylating agent. For example, formylation of anisole with MFA-$P_2O_3Cl_4$ gives *p*-methoxybenzaldehyde in 72% yield, compared to only 34% with MFA-$POCl_3$.[9]

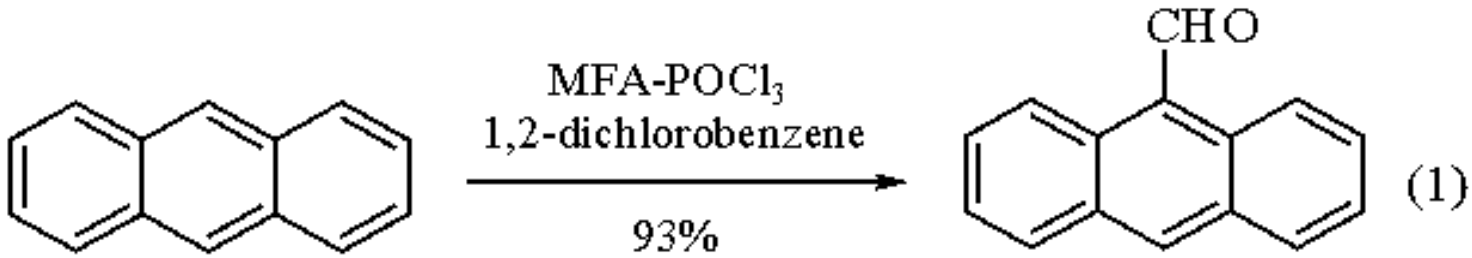

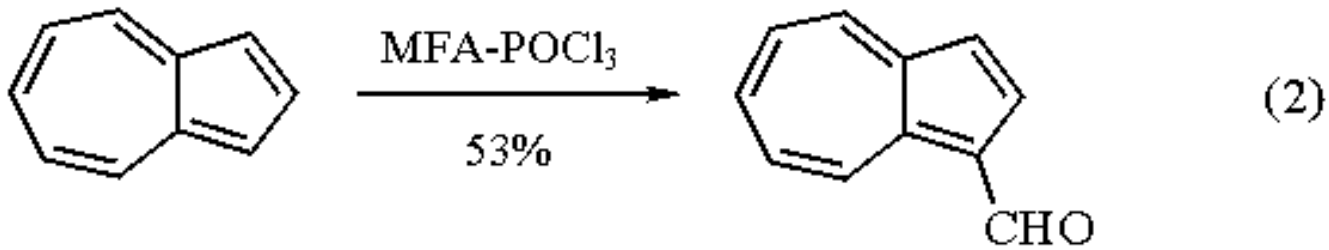

Heterocyclic systems have been formylated in moderate to good yields using MFA-$POCl_3$, e.g. thiophene (eq 3)[3,10] and indole (eq 4).[4] It is notable that poor yields of 3-indolecarbaldehyde (highest yield 37%) are obtained in the absence of a solvent.[4]

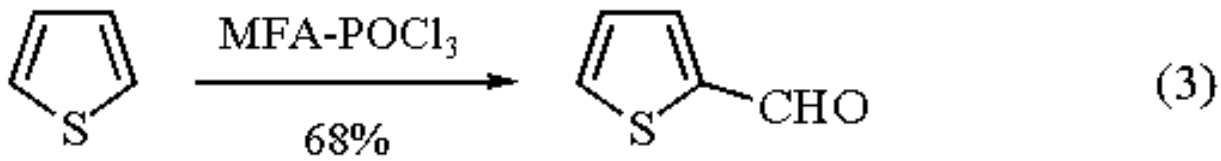

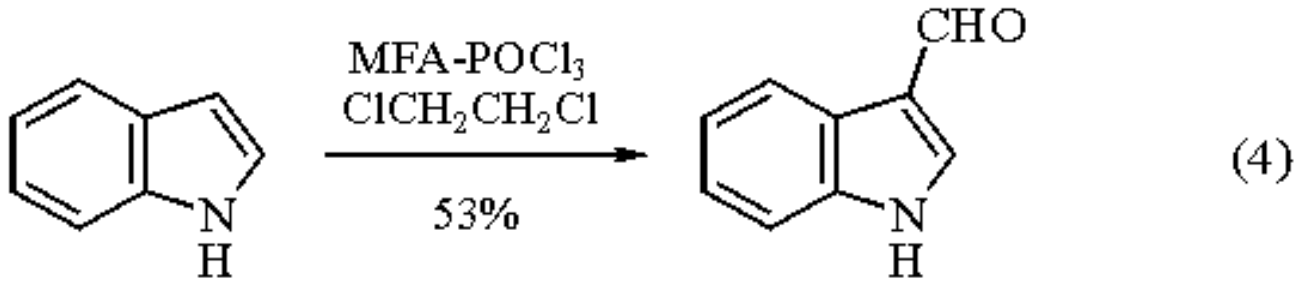

Formylation of Alkenes.

Styrene and several of its derivatives have been converted into the corresponding α,β-unsaturated aldehydes (eq 5).[11] A series of 1,1-diarylethylenes have been similarly converted into α,β-unsaturated aldehydes (eq 6).[12]

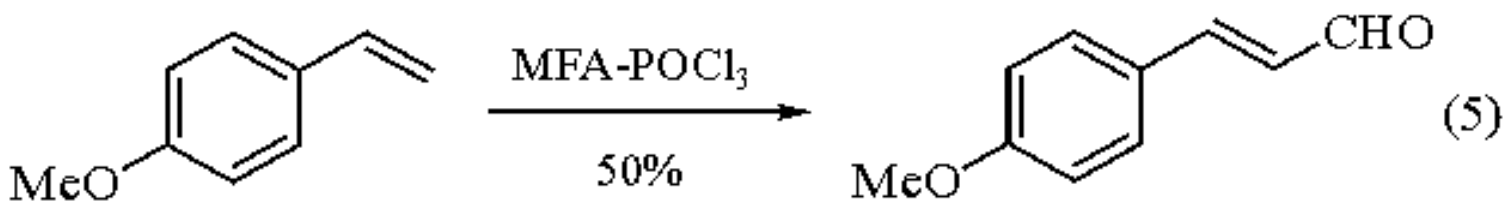

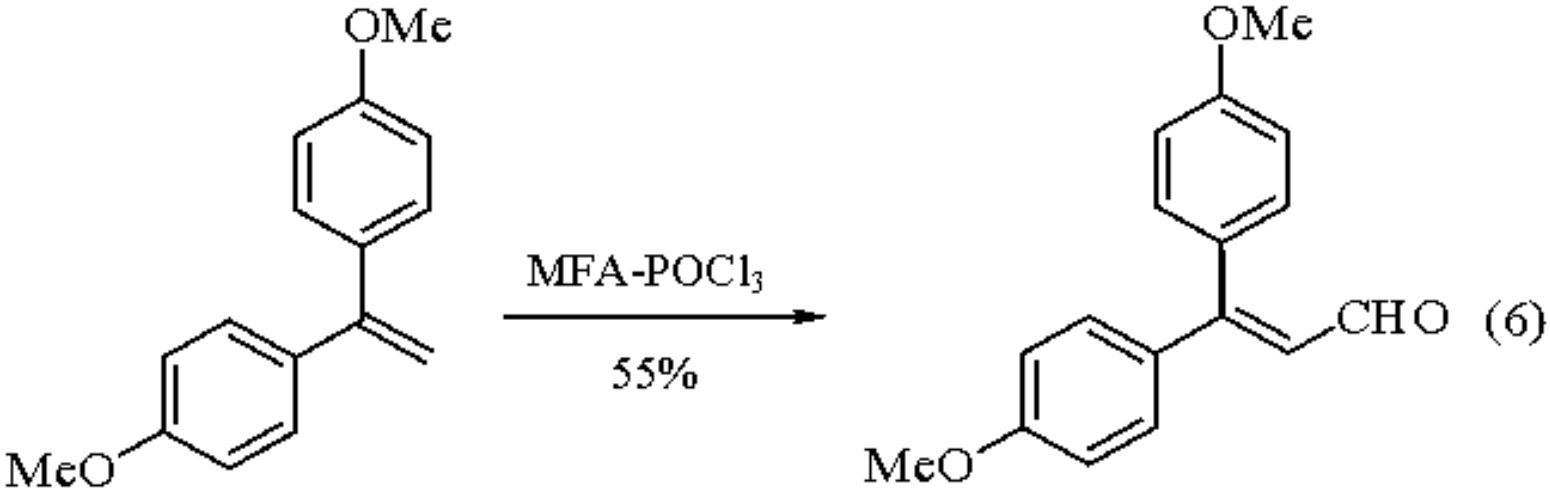

(6)

Reaction with Ketones.

9-Anthraquinone is converted into 10-chloro-9-anthracenecarbaldehyde (eq 7).[13] However, few examples of the synthesis of β-chlorovinyl aldehydes[14] using MFA-$POCl_3$ have been reported.[15]

(7)

Cyclizations under Vilsmeier Conditions.

Numerous cyclizations have been reported when DMF-$POCl_3$ is used as the reagent, but few have been reported using MFA-$POCl_3$.[16] Hippuric acid is converted into a substituted isoxazole by the action of MFA-$POCl_3$ (eq 8).[17] An allylbenzene has been reported to give a dihydronaphthaldehyde (eq 9).[18]

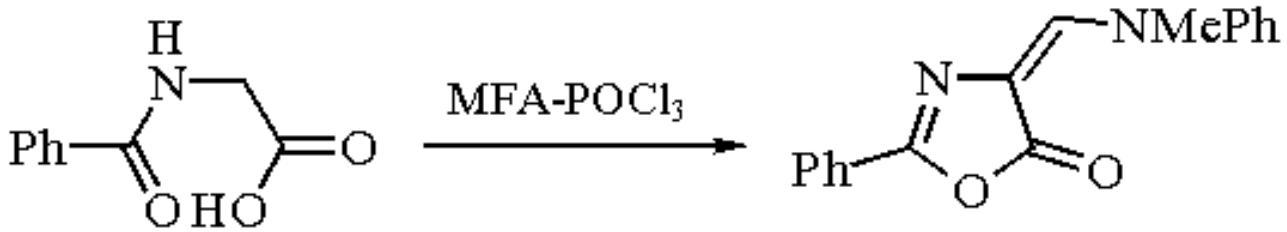

(8)

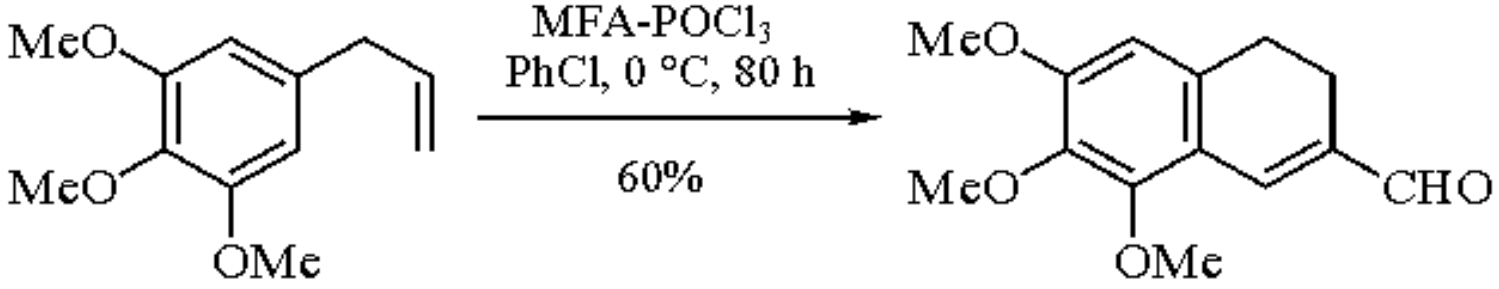

(9)

Although the use of MFA-$POCl_3$ in Vilsmeier reactions has been largely replaced by adducts formed from DMF-$POCl_3$ (see ***Dimethylchloromethyleneammonium Chloride***), MFA-$POCl_3$ often gives aldehydes in higher yield and at lower temperatures than required for reactions with DMF-$POCl_3$.[1a,19] MFA-$POCl_3$ is considered to be more reactive,[19] but extensive decomposition occurs at high reaction temperatures. The cost and low molecular weight favors the use of DMF-$POCl_3$.[1a,19]

---

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Methyl α-Phenylglycinate

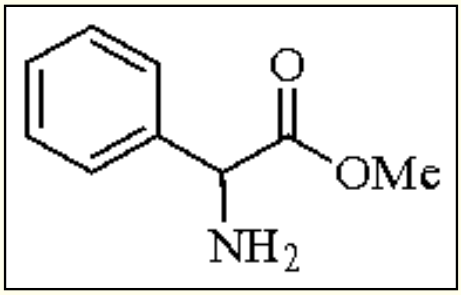

[6591-61-3] · $C_9H_{11}NO_2$ · Methyl α-Phenylglycinate · (MW 165.21) (.HCl)

[15028-40-7] · $C_9H_{12}ClNO_2$ · Methyl α-Phenylglycinate Hydrochloride · (MW 201.67)

(synthesis of β,γ-unsaturated ketones from carboxylic acids and substituted allylic alcohols)

Physical Data: hydrochloride (*RS*)-form: mp 224 °C.[1]

Solubility: hydrochloride: insol ether; sol H_2O, alcohol, benzene.

Form Supplied in: hydrochloride: colorless crystals.

Preparative Method: from α-phenylglycine and methanol.[1,2]

General Discussion.

Methyl α-phenylglycinate is used as a reagent for the conversion of carboxylic acids into β,γ-unsaturated ketones.[3,4] For this purpose, the acid is linked to the amino group of the α-amino acid ester and the resulting methyl *N*-acyl derivative is transesterified with an appropriate allylic alcohol, e.g. geraniol (eq 1). On treatment with ***Triphenylphosphine***/***Hexachloroethane***/***Triethylamine***[5] the geranyl *N*-acyl-α-phenylglycinate is cyclized to a 5-(geranyloxy)oxazole intermediate which immediately rearranges to the 5(2*H*)-oxazolone via a Claisen-aza-Cope sequence.[6] Subsequent reductive cleavage of the oxazolone ring by ***Chromium(II) Acetate***/H_3PO_2 in DMF[7] yields the β,γ-unsaturated ketone. This three-step procedure offers a novel effective means to accomplish nucleophilic acylation with carboxylic acids. Alternatively, the geranyl *N*-acyl-α-phenylglycinate can be synthesized from the preformed amino acid geranyl ester, which can be stored in the form of its hydrochloride.[4]

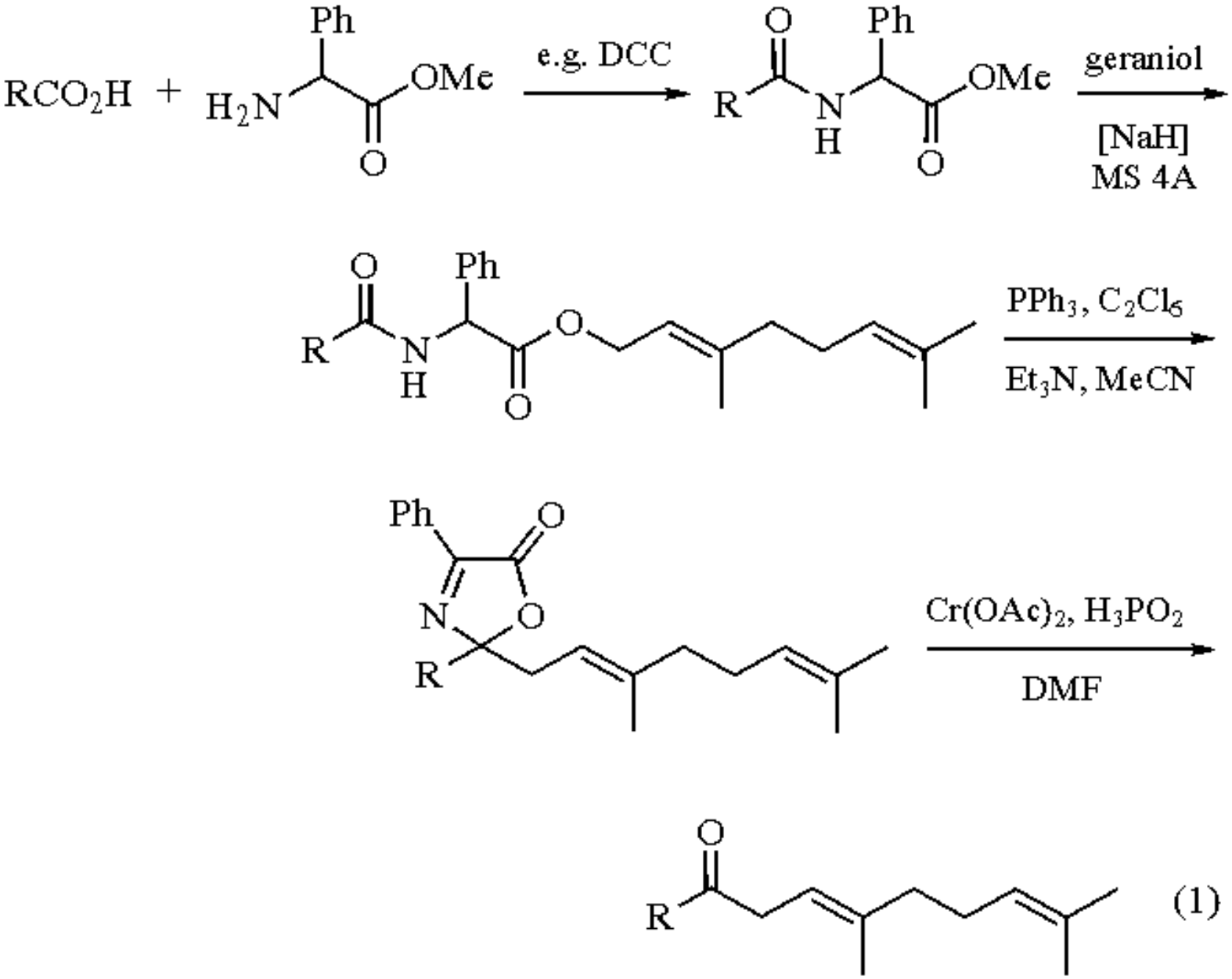

(1)

Whereas the scope of this reaction is nearly unlimited with respect to the carboxylic acid, the choice of the allylic alcohol requires attention. Thus with prenyl alcohols,[4] cinnamyl derivatives,[8] and 2,4-dienols,[4] the sequence proceeds smoothly and in high yields. In the case of crotyl[9] and 3-phenylpropargyl derivatives,[10] the formation of the 5(2*H*)-oxazolone requires elevated temperatures and longer reaction times. Simple allyl esters cannot be used for the chain elongation because the cyclization step in this case leads to stable 4-allyl-5(4*H*)-oxazolones.[3]

The α-phenylglycine technique constitutes an efficient alternative to the use of organometallic reagents for the conversion of carboxylic acid derivatives into β,γ-unsaturated ketones.[11] The mild reaction conditions and absence of strong bases allow even the use of sensitive carboxylic acids, as is illustrated by the conversion of *O*-acetyl protected D-gluconic acid into *C*-farnesyl α-D-glucopyranoside (eq 2).[4] Isomerization of the β,γ-unsaturated ketone to the conjugated enone, a notorious problem with other procedures,[12] is not observed, and stereogenic centers in the α-position to the carboxyl group maintain their stereochemical integrity.[4,13] During the chain elongation, the configuration at the trisubstituted double bond is conserved.[14] This is of importance for the attachment of terpenoid chains to carboxylic acids,[4] e.g. in the synthesis of 12-oxosqualene from farnesoic acid and farnesol (eq 3).[7] Interestingly, both diastereomers of cinnamyl alcohol afford the (*E*)-β,γ-unsaturated ketone (eq 4).[9] In the case of secondary cinnamyl

alcohols, the reaction proceeds with complete transfer of chirality (eq 5).[10]

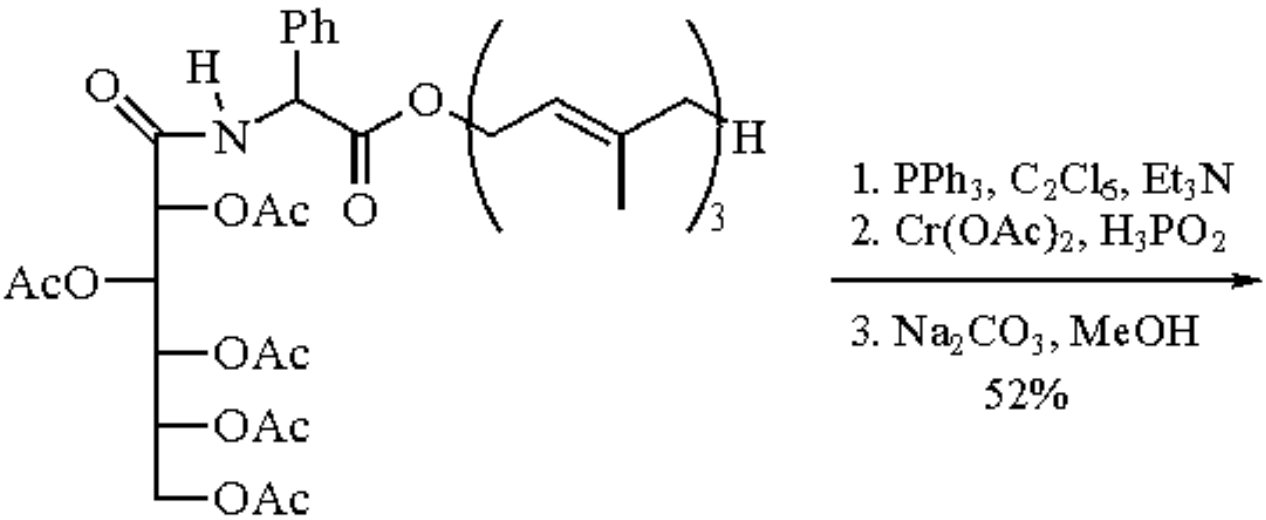

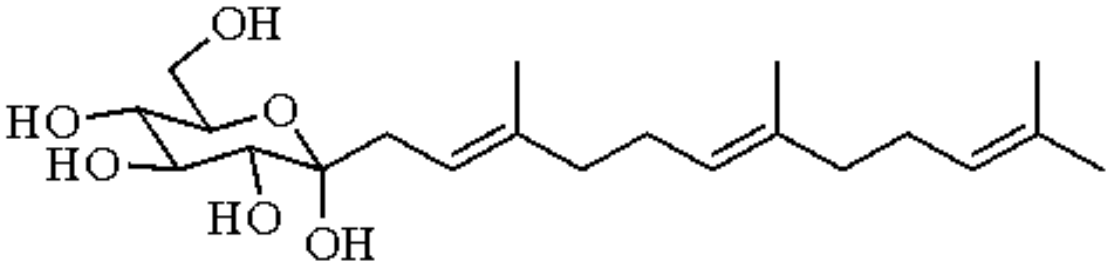

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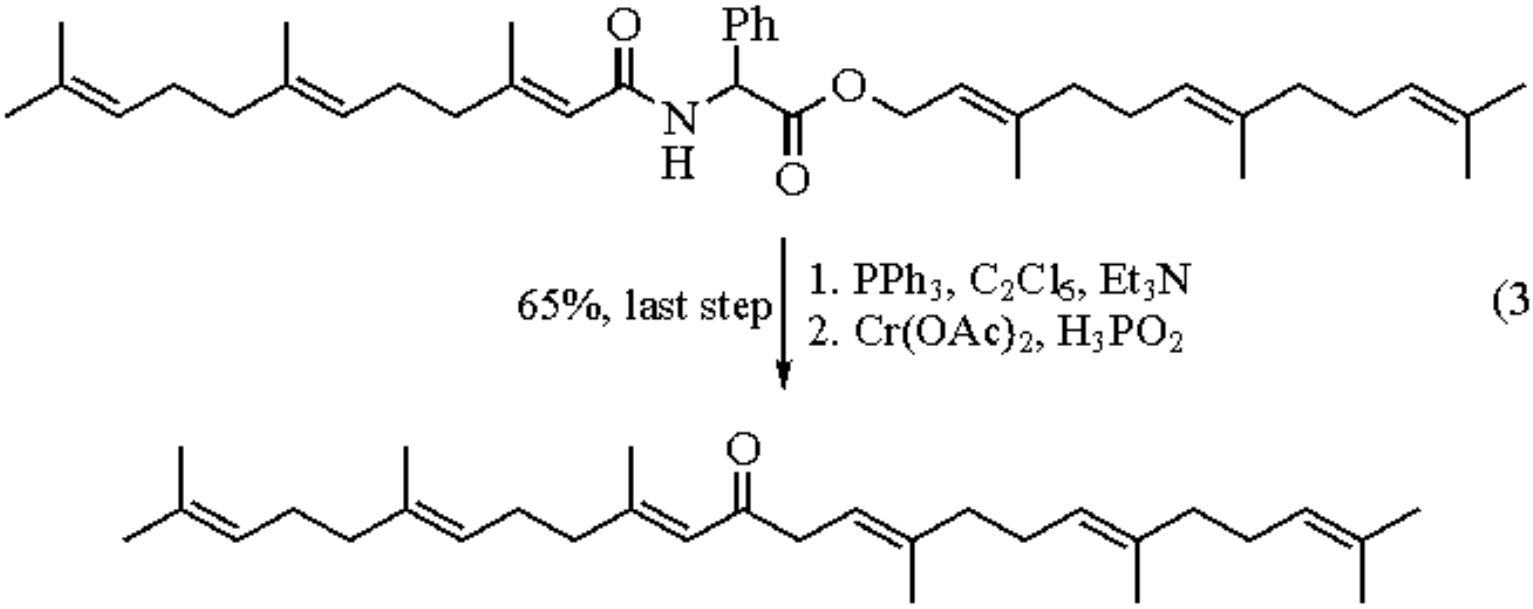

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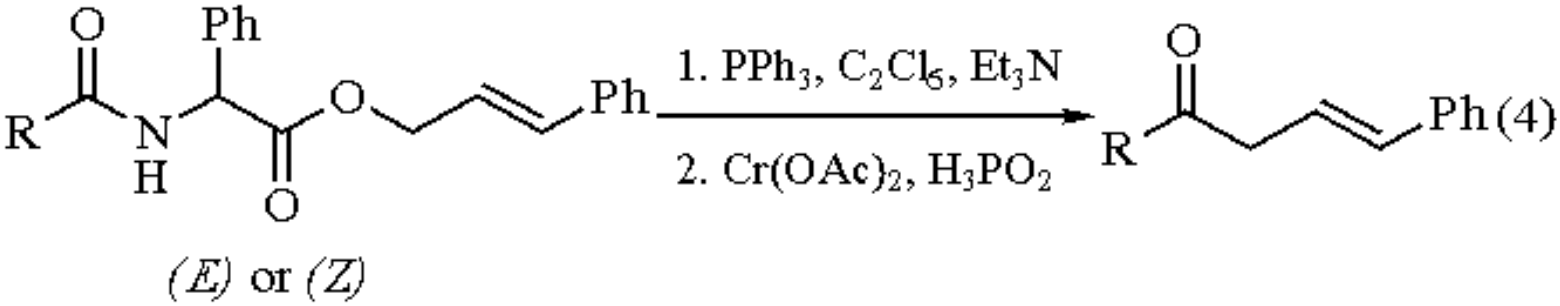

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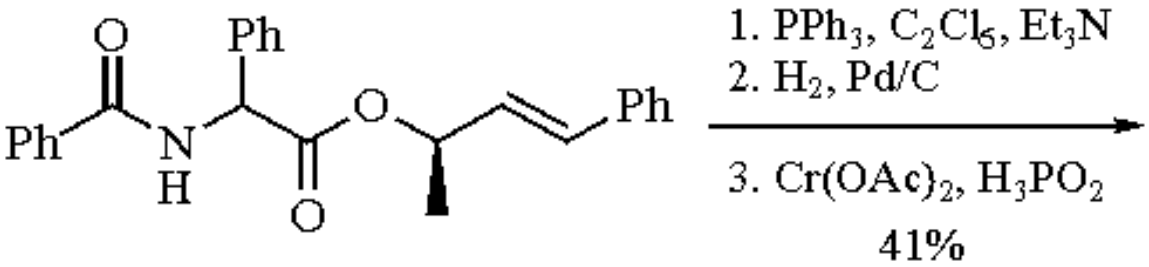

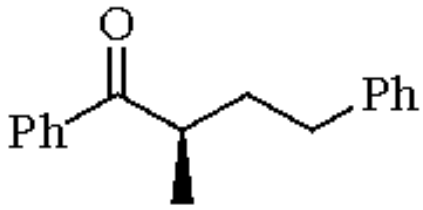

(5)

The chain elongation via allyl *N*-acyl-α-phenylglycinates can be used for the conversion of carboxylic acids into β-keto aldehydes, 1,3-diketones, and β-keto esters, and heterocycles derived therefrom.[8,13] The general procedure is outlined in eq 6 for the synthesis of a *C*-nucleoside.[8]

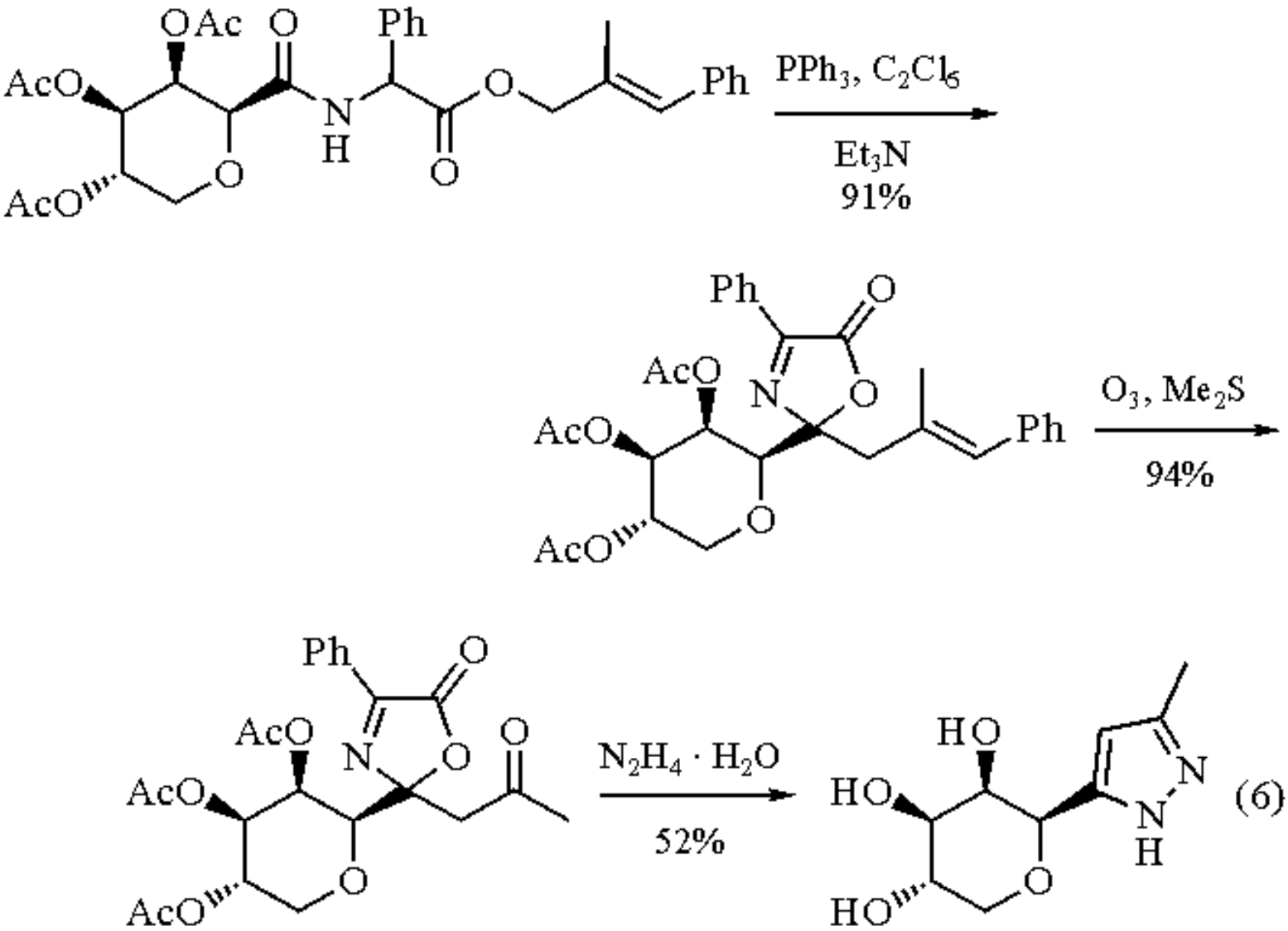

Related Reagents.

Ethyl N-Benzylideneglycinate; ***Methyl N-Benzylidenealaninate***.

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3-Methyl-2-phenyl-1,3,2-oxazaphospholidine

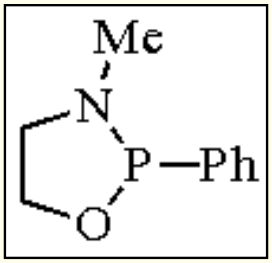

[1885-79-6] · $C_9H_{12}NOP$ · 3-Methyl-2-phenyl-1,3,2-oxazaphospholidine · (MW 181.19)

(formation of thiophosphoramides[1])

Physical Data: bp 75-78 °C/0.05 mmHg.

Solubility: sol chloroform.

Form Supplied in: clear liquid; becomes viscous on standing.

Analysis of Reagent Purity: bp and ^{31}P NMR (143.1 ppm).

Preparative Method: prepared by heating a mixture of phenylphosphorus dichloride and *N*-methylethanolamine at 130 °C (81%).[2]

Purification: distillation in vacuo immediately before use.

Handling, Storage, and Precautions: hygroscopic. Dimerizes and polymerizes on standing.

General Discussion.

The title compound (**1**) undergoes dimerization (eq 1) at rt to form a ten-membered macrocycle. This compound has been isolated as a mixture of two isomers.[3]

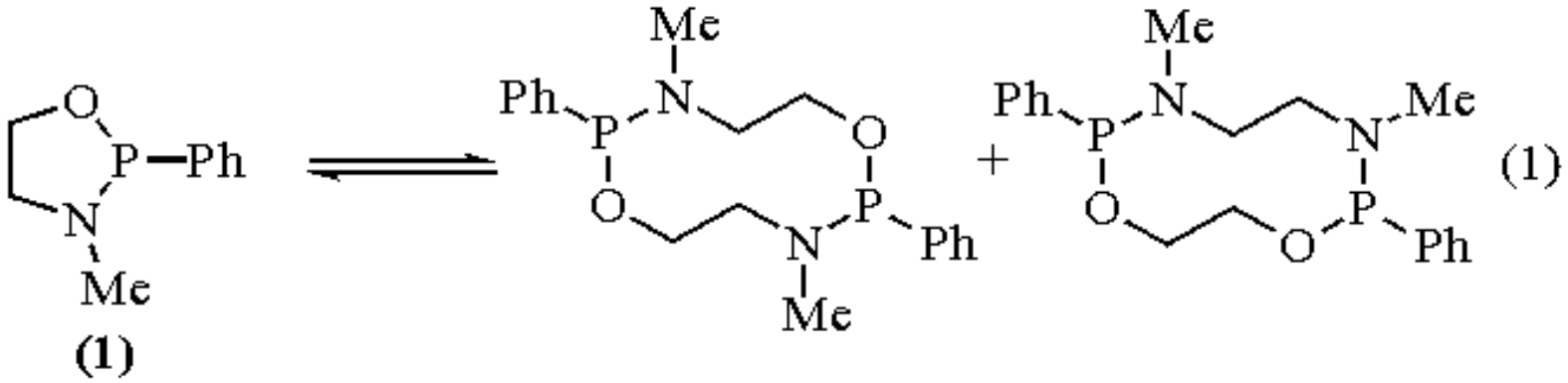

Treatment of (**1**) with ***Diphenyl Disulfide*** results in production of (**2**), presumably by alkylation on phosphorus followed by ring opening by the phenylthiolate anion (eq 2).[1]

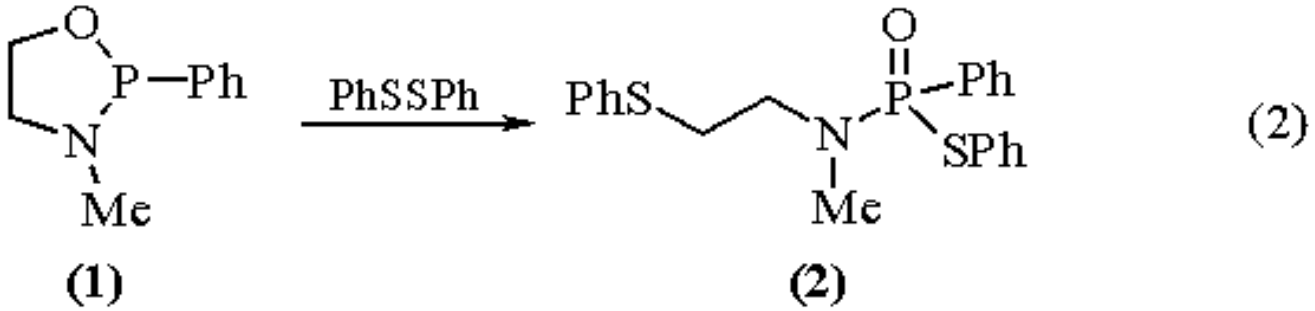

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Methyl 2-(Phenylsulfinyl)acetate

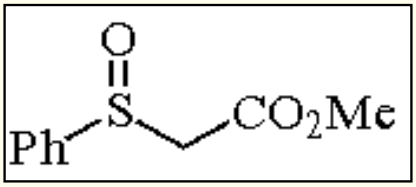

[14090-83-6] · $C_9H_{10}O_3S$ · Methyl 2-(Phenylsulfinyl)acetate · (MW 198.26)

(synthetic equivalent of a vinyl organometallic species; undergoes addition/elimination to aldehydes to give conjugated dienoates or 4-hydroxy (2*E*)-enoates)

Physical Data: mp 53-55 °C; bp 130-131 °C/0.5 mmHg.

Form Supplied in: solid; widely available.

Handling, Storage, and Precautions: fp >100 °C.

Knoevenagel Condensation with Aldehydes.

The sodium and lithium enolates of methyl 2-(phenylsulfinyl)acetate are very stable and tend not to react with aldehydes under normal conditions; however, the Knovenagel amine-catalyzed condensation[1,2] occurs under mild conditions to give 3-aryl-2-(phenylsulfinyl)(2*E*)-propenoate methyl esters stereoselectively (eq 1) in a 98:2 (*E*:*Z*) ratio as determined by Tf_2O/dimethyl sulfide reduction followed by GLC analysis. These compounds are useful because they are powerful dienophiles in a variety of Diels-Alder reactions.

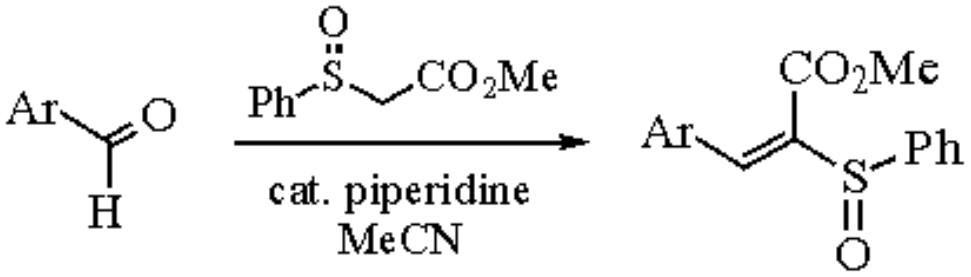

(1)

Preparation of 3-Hydroxy Enoates.

Under similar Knovenagel conditions, methyl 2-(phenylsulfinyl)acetate can undergo addition to afford the sulfinyl condensation product; base-catalyzed deconjugation, a [2,3]-sigmatropic shift, and hydrolysis of the sulfenate ester intermediate then affords 4-hydroxy (2*E*)-enoates[3-5] in one pot (eqs 2 and 3).

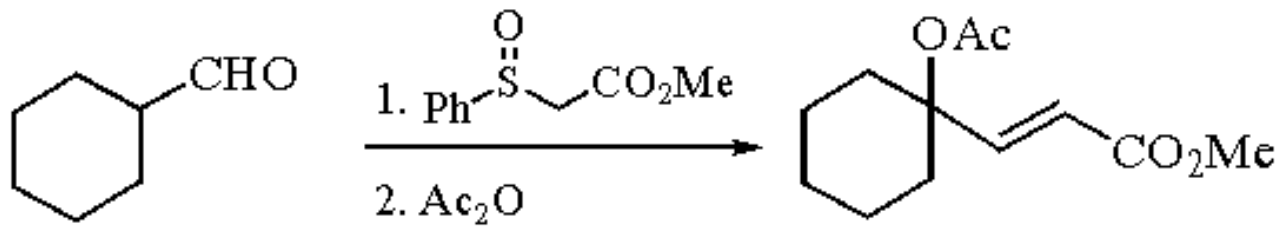

(2)

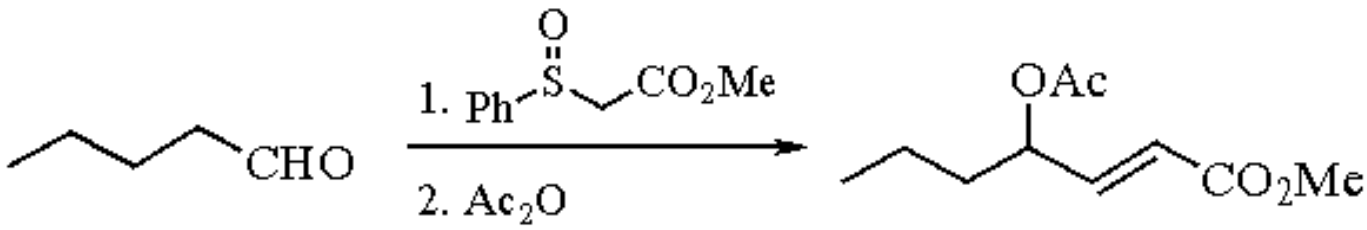

(3)

Preparation of 1,3-Dienoates from Alkenes.

Trost et al.[5] have demonstrated that the palladium-catalyzed addition of methyl 2-(phenylsulfinyl)acetate to palladium π-allyl complexes gives intermediate allylsulfinates, which undergo a standard thermal elimination of the sulfoxide group to afford 2,4-dienoates efficiently from alkenes (eqs 4 and 5).

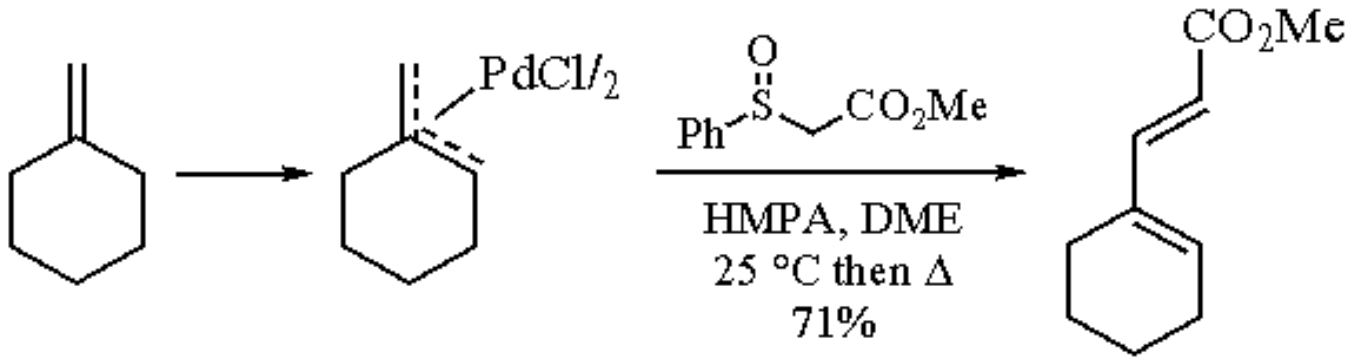

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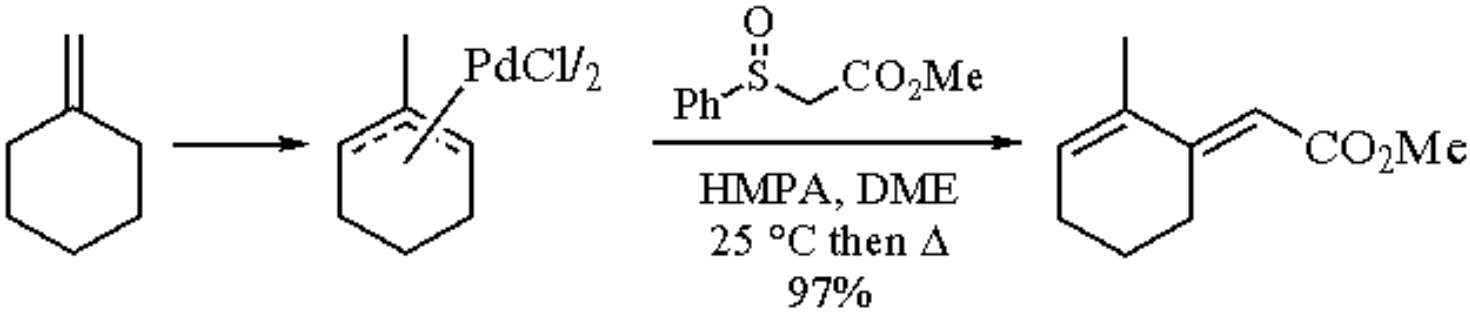

(5)

Alkylation Followed by Elimination to Give Enones.

Despite the low reactivity of the enolates, methyl 2-(phenylsulfinyl)acetate can be induced to undergo nucleophilic attack. Methyl cyclobutenecarboxylate[6] can be prepared by deprotonation of the reagent with a solution of 2 equiv of ***Sodium Hydride*** and ***1,3-Diiodopropane*** in DMF to give the cyclic product; pyrolysis at 160 °C affords the cyclobutene product in a low (39%) overall yield (eq 6).

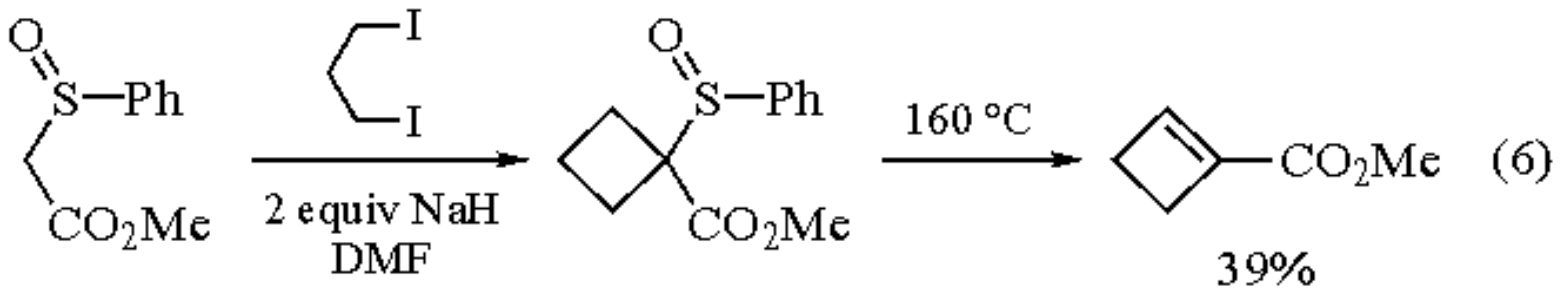

Benzylic bromides also undergo an efficient one-pot alkylation/elimination using ***Potassium Carbonate*** in the presence of a phase-transfer catalyst such as aliquat-336 in DMF to afford *trans*-unsaturated esters in good yields (eq 7).[7]

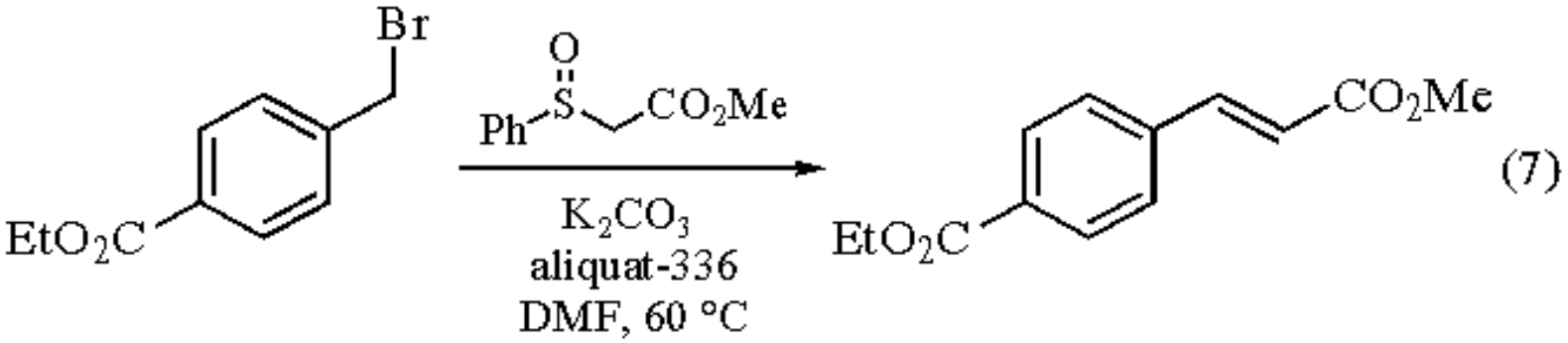

Synthesis of 1,4-Dicarbonyl Compounds via Pummerer Reaction.

Treatment of methyl 2-(phenylsulfinyl)acetate with ***Tin(II) Trifluoromethanesulfonate*** effects conversion of the sulfoxide group to the Pummerer intermediate. This reacts with silyl enol ethers in the presence of ***N-(Trimethylsilyl)imidazole*** to afford 1,4-dicarbonyl compounds[8] containing a phenylthio group, which can be oxidized and thermally eliminated to give unsaturated dicarbonyl compounds or reductively removed to give the saturated analogs (eq 8).

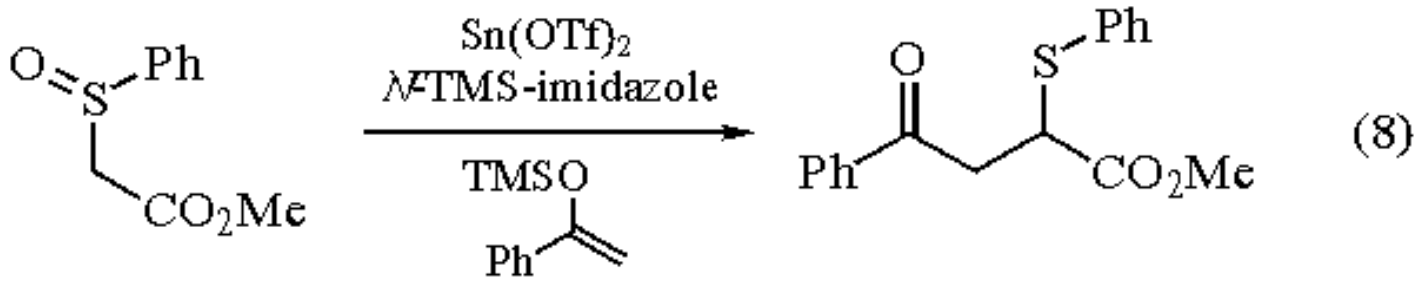

Michael Addition Reactions of Methyl 2-(Phenylsulfinyl)acetate.

The potassium salt of methyl 2-(phenylsulfinyl)acetate can be induced to undergo a Michael addition in the presence of ***18-Crown-6***. Subsequent thermal elimination of the sulfoxide group in refluxing xylenes affords the α,β-unsaturated

enone, via equilibration of the double bond into conjugation with the ketone. This reaction constitutes the synthetic equivalent of an acetate anion addition to an α,β-unsaturated system with retention of unsaturation (eq 9).[9]

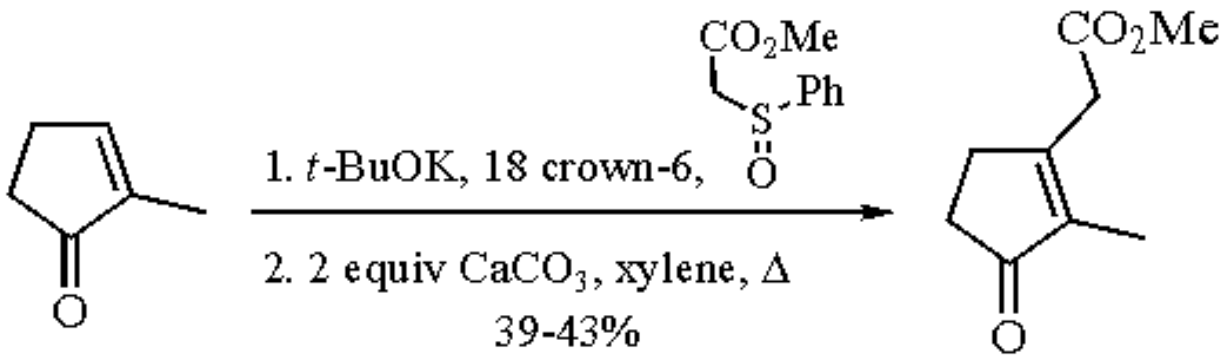

(9)

A tandem Michael addition/enolate acylation reaction with α,β-unsaturated methyl ketones is possible in the presence of ***Magnesium Methoxide***, giving rise to a 1,3-diketocyclohexane system; on heating, this eliminates the sulfoxide group to give an aromatic resorcinol system (eq 10).[10]

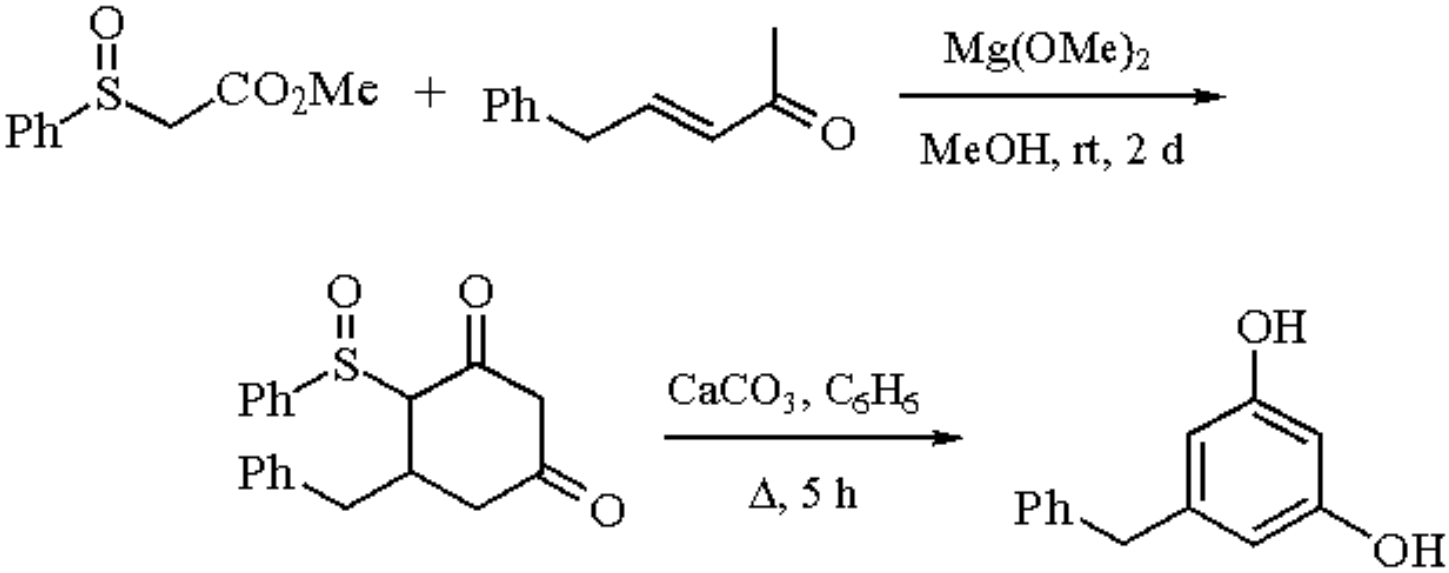

(10)

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Dinos Santafianos

Methyl Phenyl Sulfone

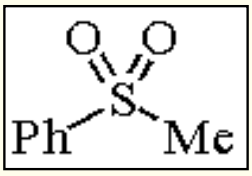

[3112-85-4] · $C_7H_8O_2S$ · Methyl Phenyl Sulfone · (MW 156.22)

(generally used as the lithiated form, which reacts with a variety of electrophiles[1])

Physical Data: mp 86-88 °C.

Solubility: sol ethanol, benzene.

Form Supplied in: white solid; widely available. [^{13}C]Methyl phenyl sulfone is also available.

Preparative Methods: by the reaction of ***Sodium Benzenesulfinate*** with ***Dimethyl Sulfate***; by oxidation of methyl phenyl sulfide with 30% ***Hydrogen Peroxide*** in acetic acid; or by the reaction of polymer-supported benzenesulfinate anion with ***Iodomethane*** in refluxing benzene.[2]

Purification: recrystallized from carbon tetrachloride and 1:3 ethanol-water. On a small scale, water is convenient for recrystallization.[3]

General Discussion.

The lithium salt of methyl phenyl sulfone reacts with electrophiles by alkylation to give homologs which possess acidic methylene protons for further synthetic transformations. Alkylation of [(phenylsulfonyl)methyl]lithium ($PhSO_2CH_2Li$) with primary iodides proceeds smoothly in THF in the presence of HMPA to furnish homologs (eq 1).[4] The factors that control mono- vs. dialkylation of methyl phenyl sulfone have been studied. Alkylation of methyl phenyl sulfone using a lithium base can lead to significant polyalkylation. Use of a potassium base such as ***Potassium Hydride*** enhances formation of monosubstituted product, presumably by decreasing ion pairing.[5]

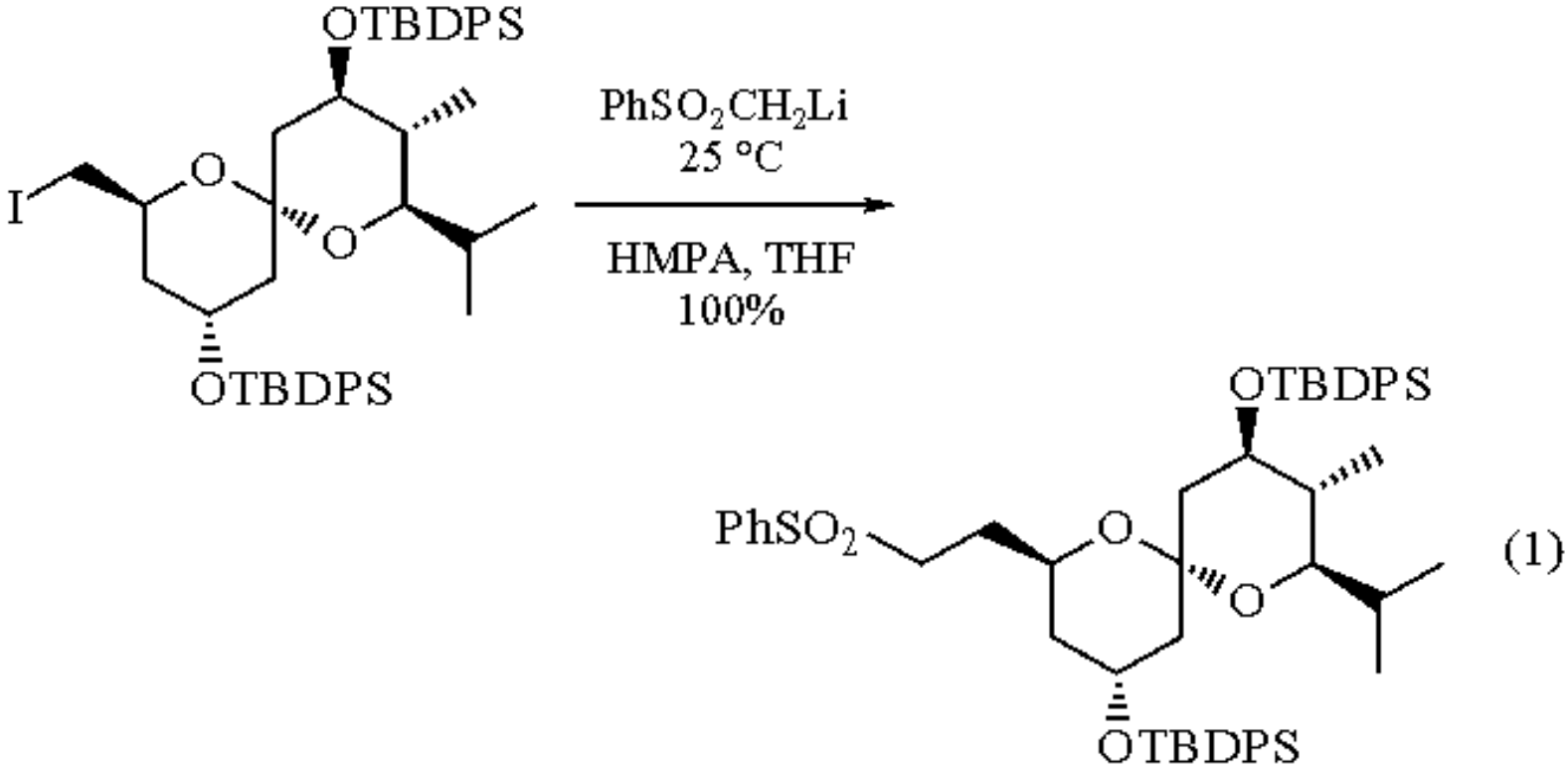

Double coupling reactions of sulfonylmethyl anions with epoxides and then with aldehydes have been developed for the synthesis of homoallyl alcohols (eq 2).[6] The difficulties experienced in the coupling reaction with hindered epoxides may often be overcome by the use of solvent additives (especially ***Hexamethylphosphoric Triamide***) and/or Lewis acids such as ***Boron Trifluoride Etherate***. Indeed, reaction of [(phenylsulfonyl)methyl]lithium (2 equiv $PhSO_2CH_2Li$; HMPA/THF/-78 °C) with the hindered epoxide shown proceeds smoothly in the presence of $BF_3.OEt_2$ (2 equiv) (eq 3).[7]

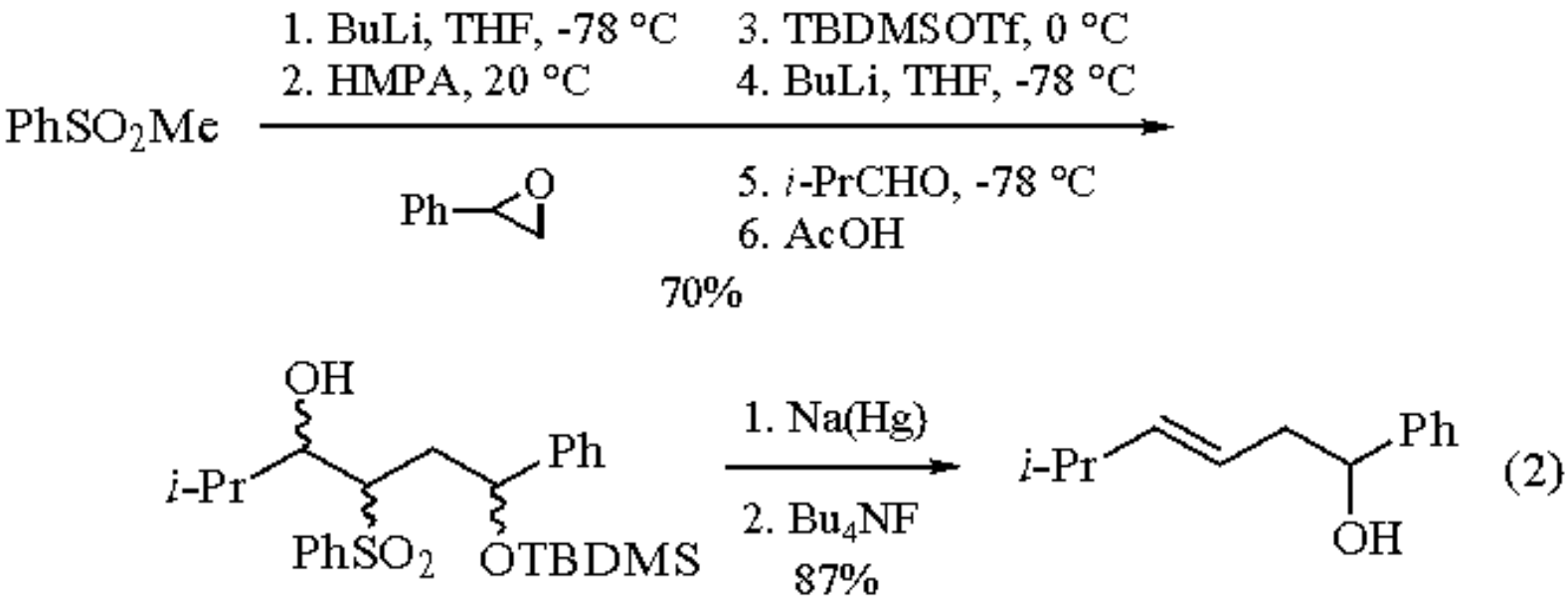

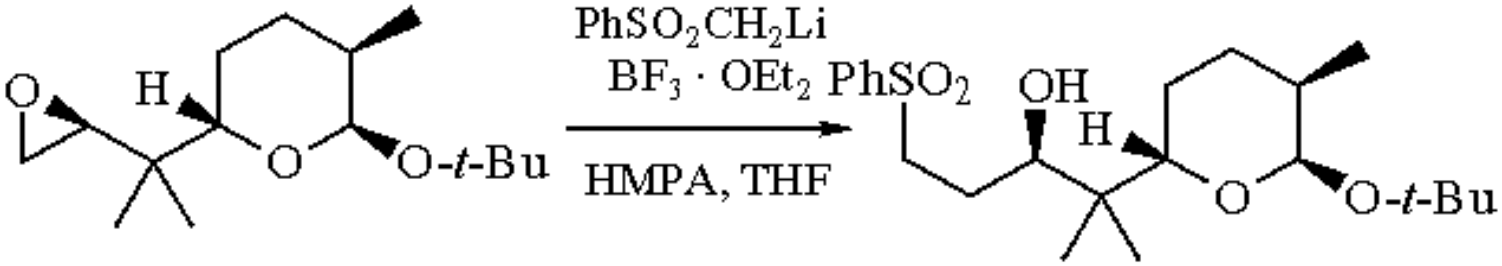

Treatment of methyl phenyl sulfone with 2 equiv of ***n-Butyllithium*** in THF at 0 °C produces [(phenylsulfonyl)methylene]dilithium ($PhSO_2CHLi_2$), which has been used as a powerful nucleophile. Geminal dialkylation of this α,α-dianion with 2 equiv of epoxides has been applied to a synthesis of *trans*-2,6-disubstituted piperidines (eq 4).[8]

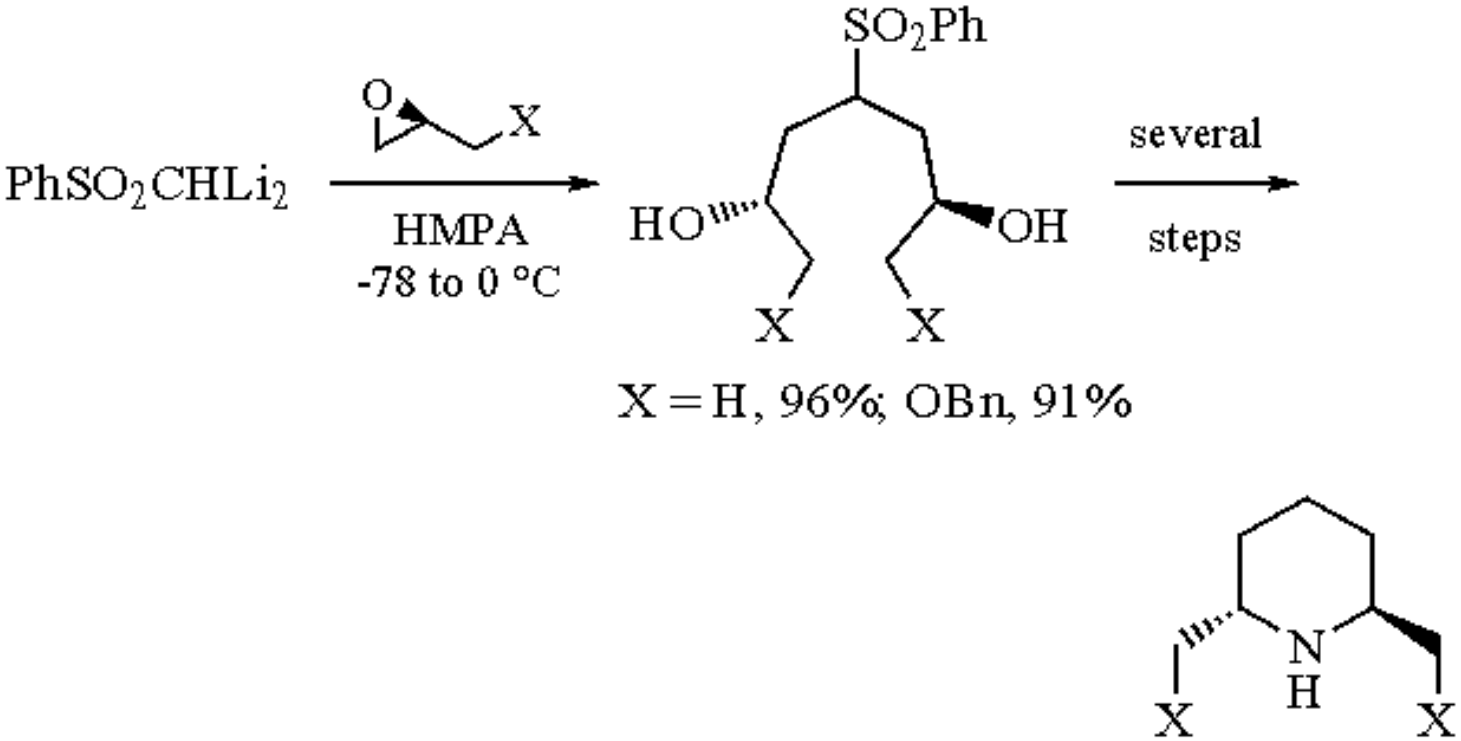

Alkylation followed by intramolecular alkylation with $PhSO_2CHLi_2$ serves as a method for the construction of carbocyclic frameworks. $PhSO_2CHLi_2$ reacts with dihalo alkanes (eq 5), as well as with halo epoxides to furnish cyclic products. In the case of halo epoxides, initial attack occurs on the epoxide terminus to give the larger of the two possible cyclic products (eqs 6 and 7).[9]

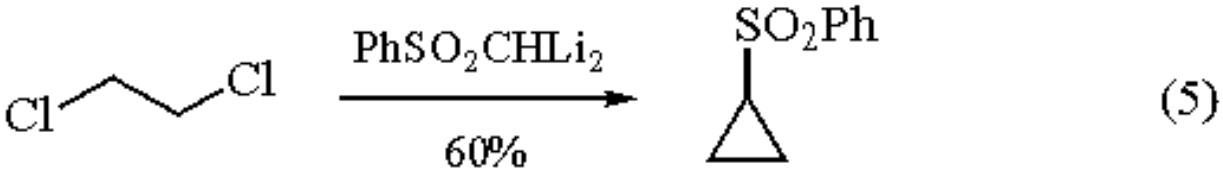

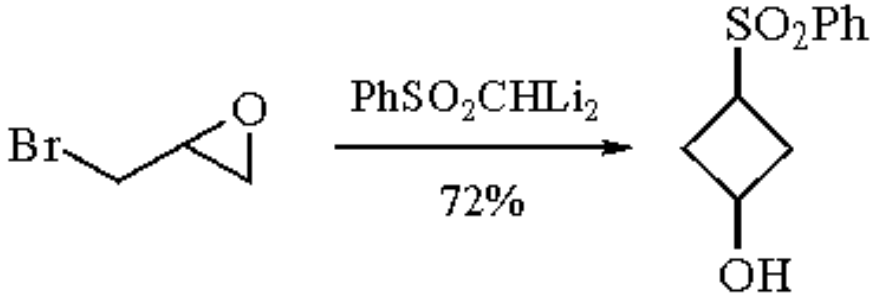

(6)

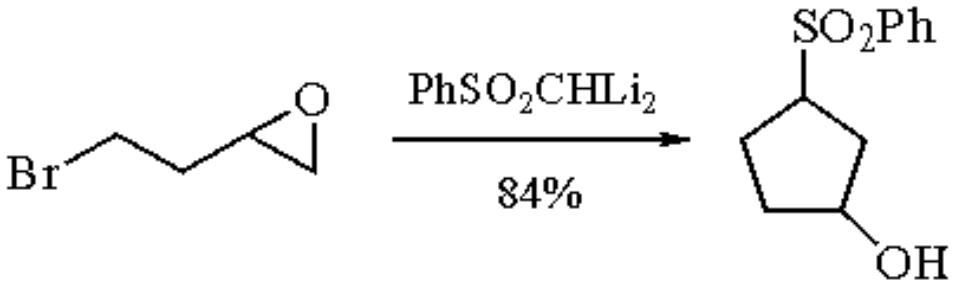

(7)

In acylation reactions, the use of excess base or sulfonyl carbanions is necessary, because the acidic β-keto sulfone product consumes up to half of the starting sulfonyl carbanion by proton transfer. This problem is often overcome by employing $PhSO_2CHLi_2$, which provides directly the anion of the β-keto sulfone product. Condensation of either acid chlorides[10] or esters with $PhSO_2CHLi_2$ gives keto sulfones (eq 8).[11]

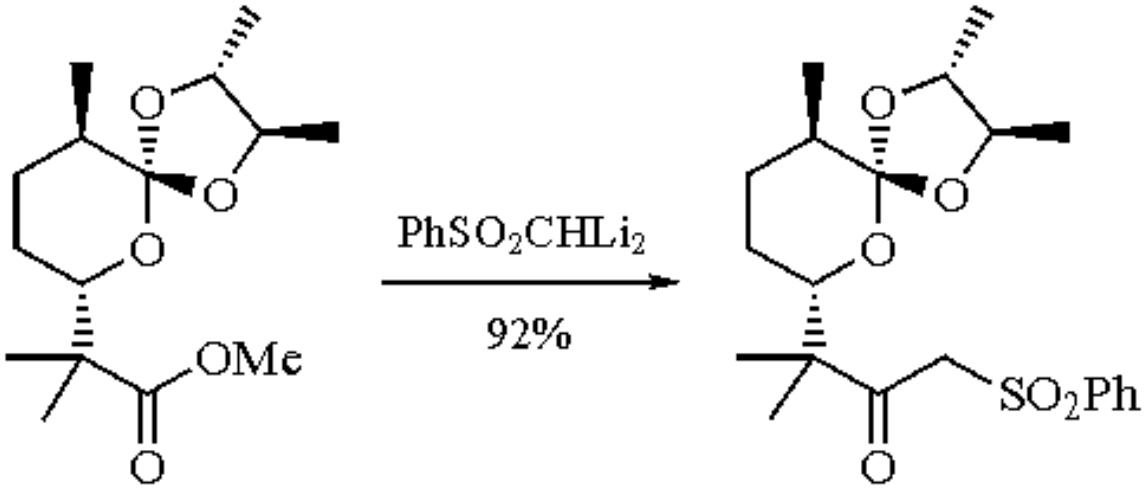

(8)

The reaction of $PhSO_2CHLi_2$ with ethyl 4-bromobutyrate gives the enolate of the β-keto sulfone, which is further converted to vinyl ethers as a mixture of (*E*)- and (*Z*)-isomers (34:44) through intramolecular *O*-alkylation. The cyclopropyl ketone is also observed as a minor product, which presumably arises by equilibration of the enolates (eq 9).[12]

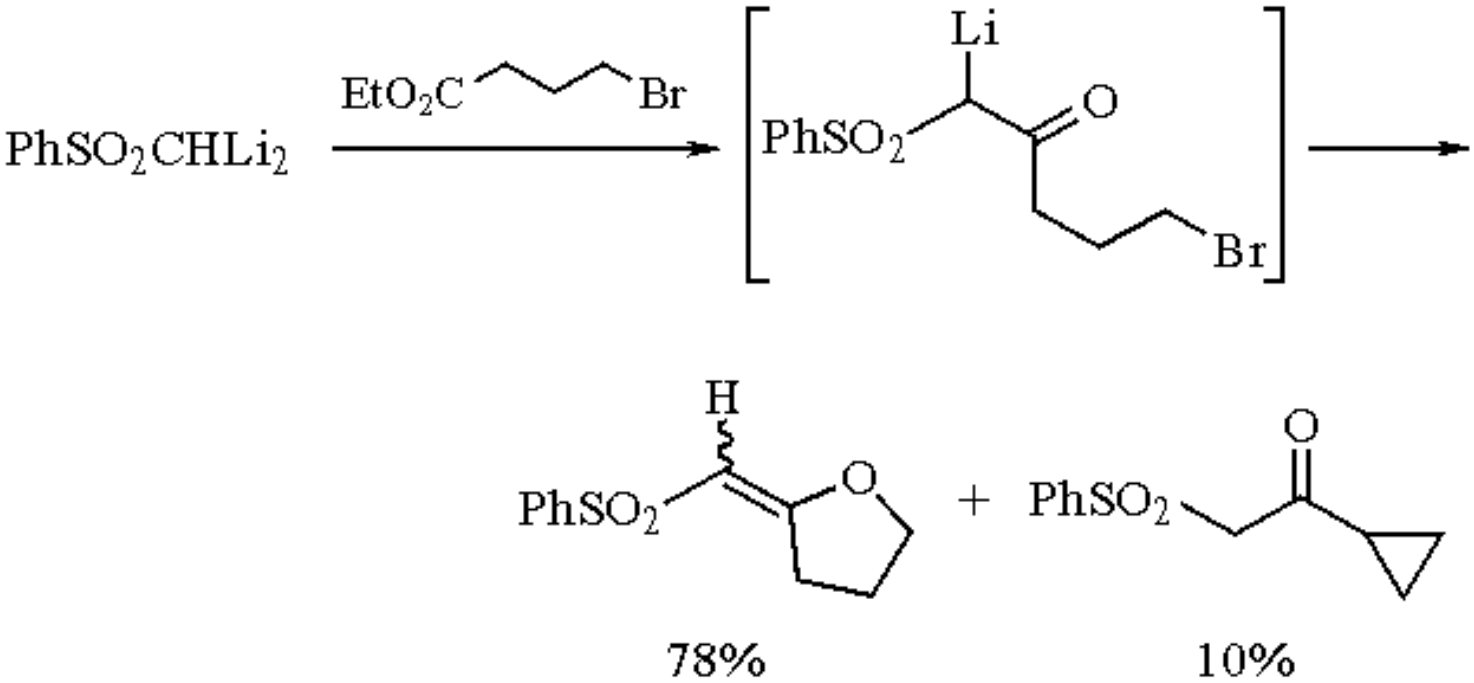

(9)

The counter cations of phenylsulfonylmethide influence the outcome of stereochemistry when added to the chiral aldehyde pentodialdo-1,4-furanose. When the counter cation is magnesium, the *anti*-product is highly favored over the *syn*-product. When $PhSO_2CH_2Li$ is treated with ***Zinc Chloride*** and HMPA, the selectivity reverses to mainly the *syn*-product (eq 10).[13]

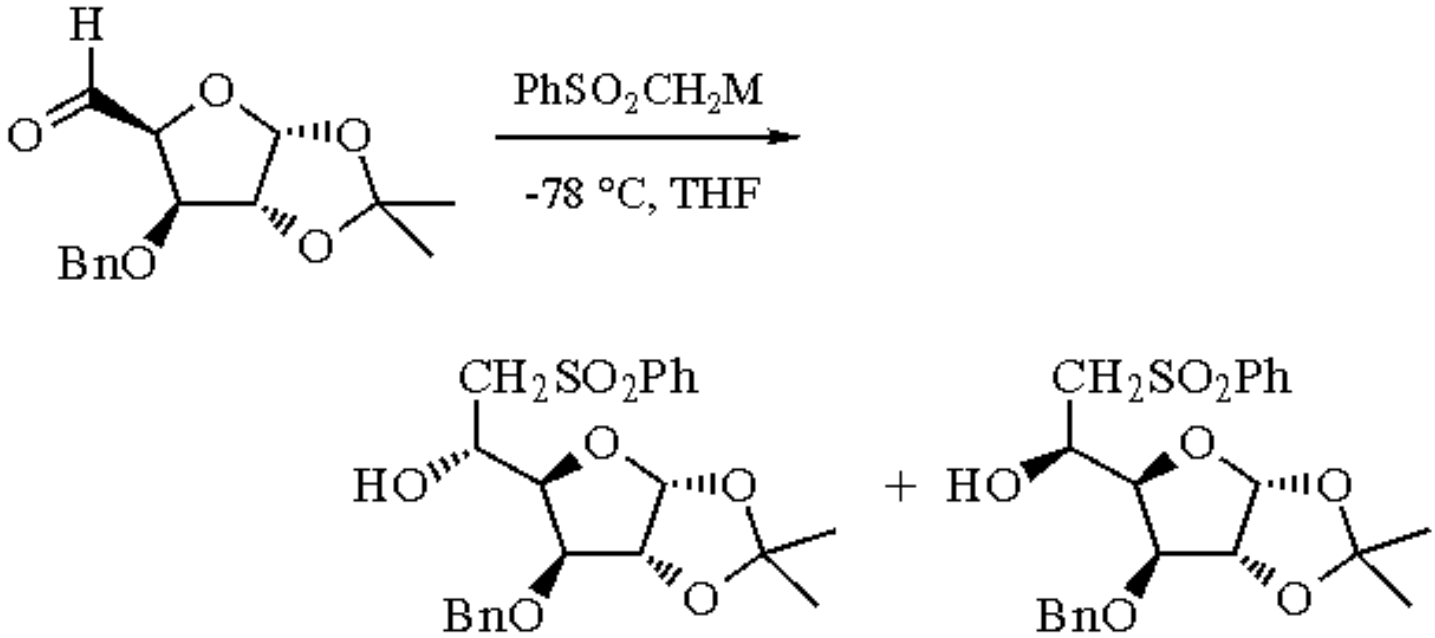

(10)

$PhSO_2CH_2M$	*anti*:*syn*	Yield (%)
$PhSO_2CH_2MgBr$	95:5	85
$PhSO_2CH_2Li$	73:27	92
$PhSO_2CH_2Li$, $ZnCl_2$, HMPA	23:77	92

The homologation of α-diketones using $PhSO_2CHLi_2$ is considered to involve attack on both electrophilic sites followed by ring opening of the cyclopropanediolate involving the expulsion of sulfinate anion. Electron transfer competes in this reaction, judging from the fact that benzoin is isolated in as much as 30% yield (eq 11). In the case of 2-chlorocyclohexanone, the ring-expansion product results (eq 12).[9]

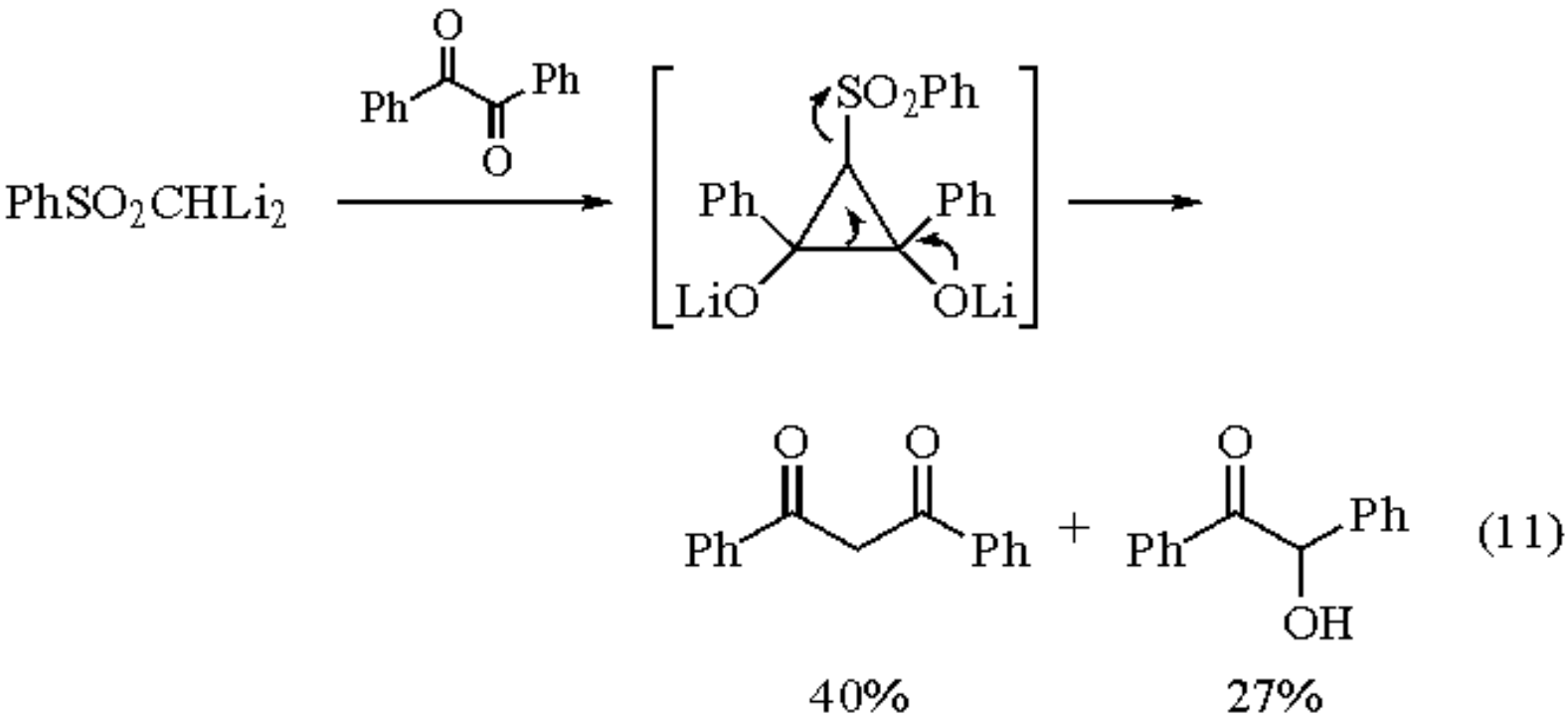

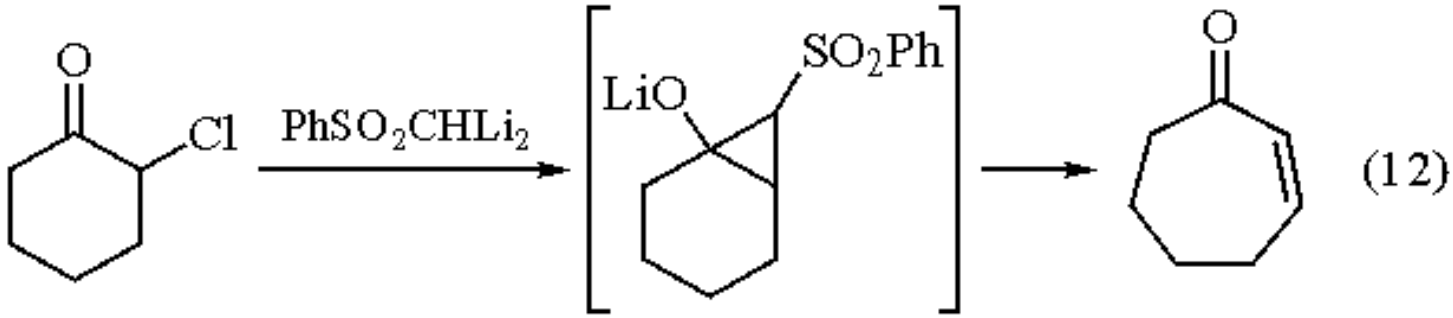

(*E*)-Vinyl sulfones are stereoselectively prepared in one pot through phosphorylation of $PhSO_2CHLi_2$ followed by Horner-Emmons reaction of the resulting phosphonate with aldehydes (eq 13).[14]

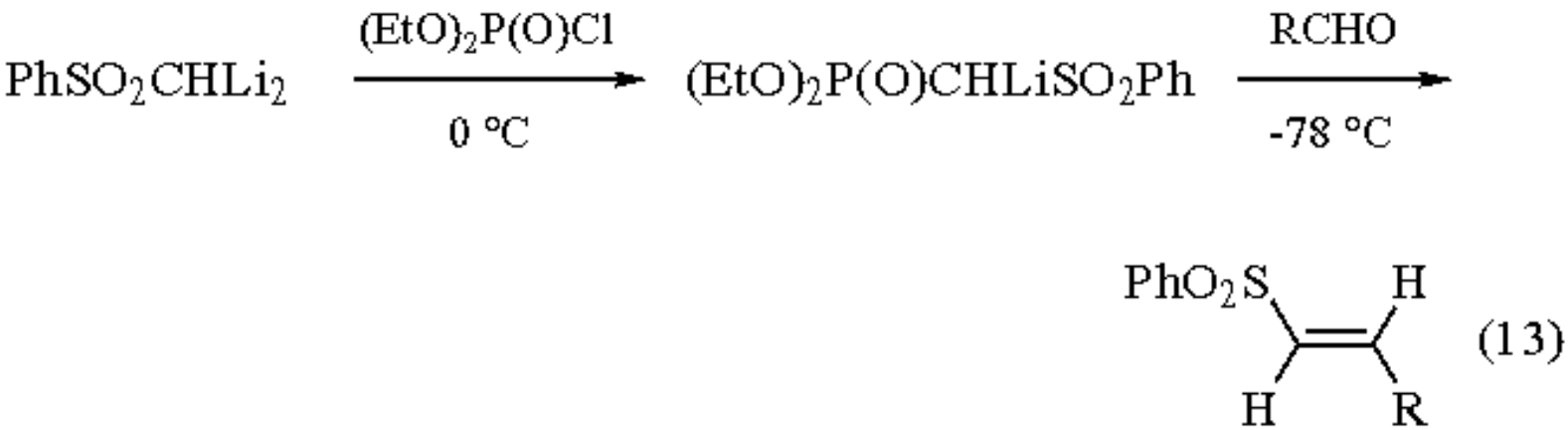

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Methyl Phenylsulfonylacetate

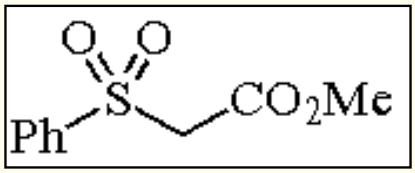

[34097-60-4] · $C_9H_{10}O_4S$ · Methyl Phenylsulfonylacetate · (MW 214.26)

(soft nucleophile which undergoes palladium(0)-catalyzed additions to allylic acetates, pivalates, tosylates, and epoxides; desulfonation affords aliphatic (4*E*)-enoates)

Alternate Name: (methoxycarbonyl)methyl phenyl sulfone.

Physical Data: bp 165 °C/0.05 mmHg; *d* 1.282 g cm^{-3}.

Form Supplied in: liquid/oil; widely available.

Palladium(0)-Catalyzed Addition to Allylic Systems.

Methyl phenylsulfonylacetate has been used as a soft nucleophile in a variety of palladium(0)-catalyzed additions to allylic acetates, allylic pivalates, and allylic epoxides to afford alkyl 2-phenylsulfonyl (4*E*)-enoates. Addition to allylic acetates[1,2] followed by desulfonation[3] leads to the construction of *trans*-4-enoates (eq 1). Addition to allylic tosyl systems can be achieved, giving vinylcyclopropanes (eq 2).[4]

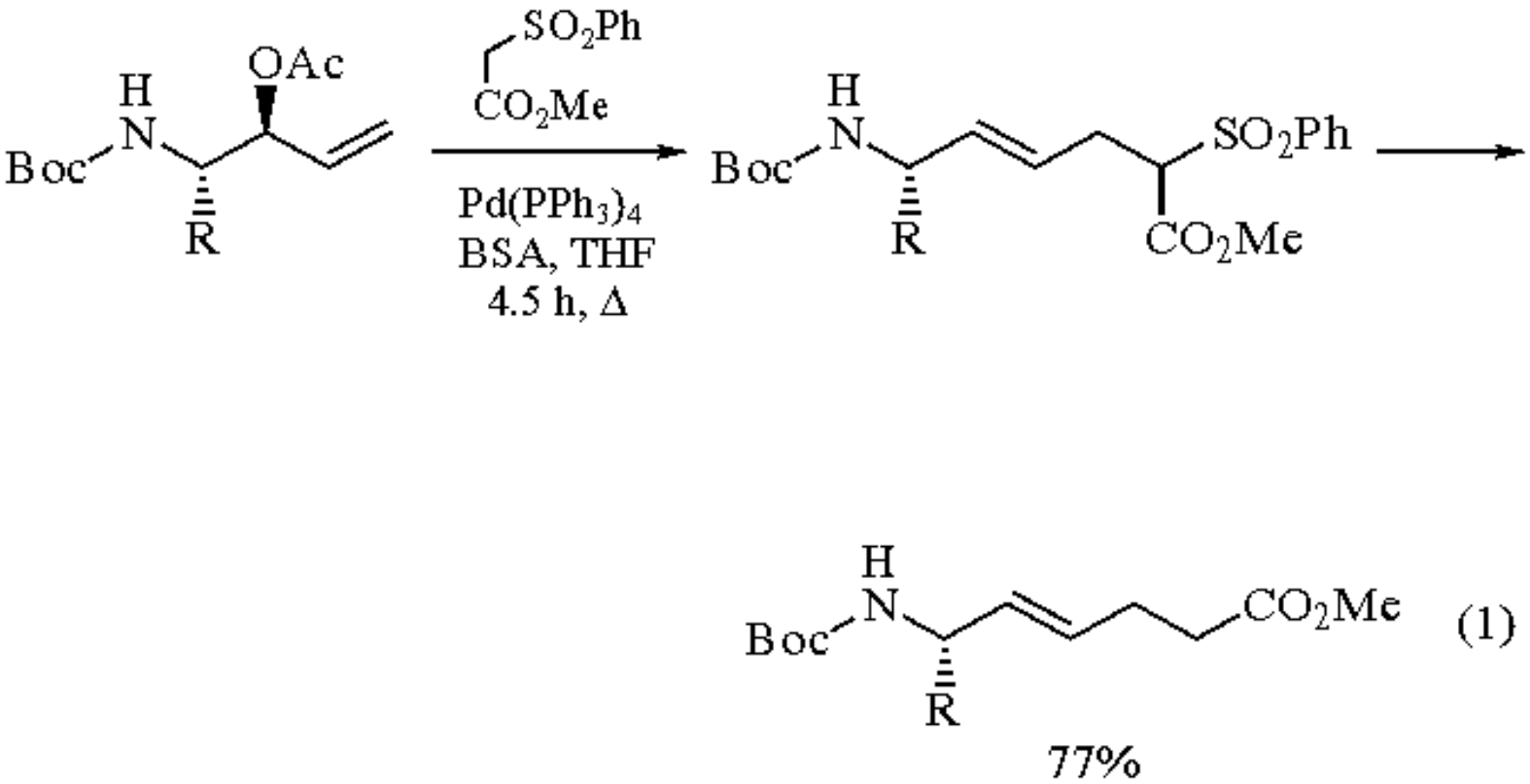

(1)

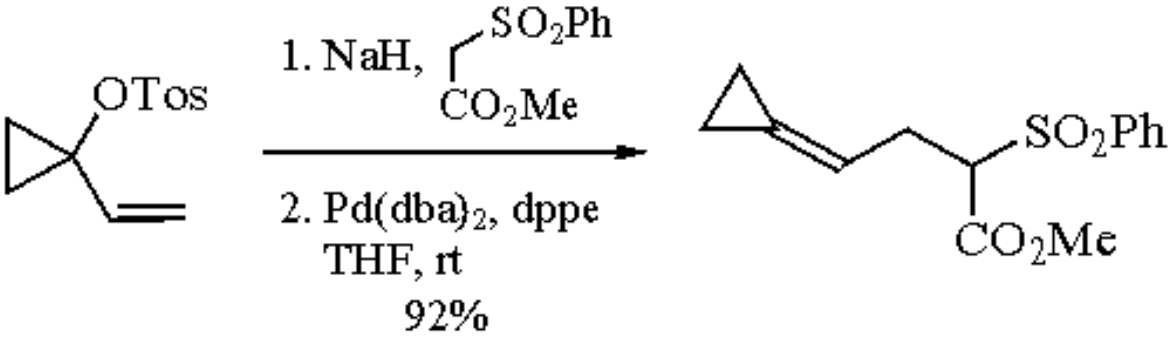

(2)

Cyclopentadiene monoepoxide can undergo palladium-catalyzed ring opening to give a palladium π-allyl complex which reacts with methyl phenylsulfonylacetate to afford *cis*-4-substituted 2-cyclopenten-1-ols[5,6] after desulfonation using ***Sodium Amalgam*** (eq 3).[7] The cyclopentenols can also be prepared in an optically active form starting from *cis*-4-acetoxy-1-hydroxy-2-cyclopentene.[8]

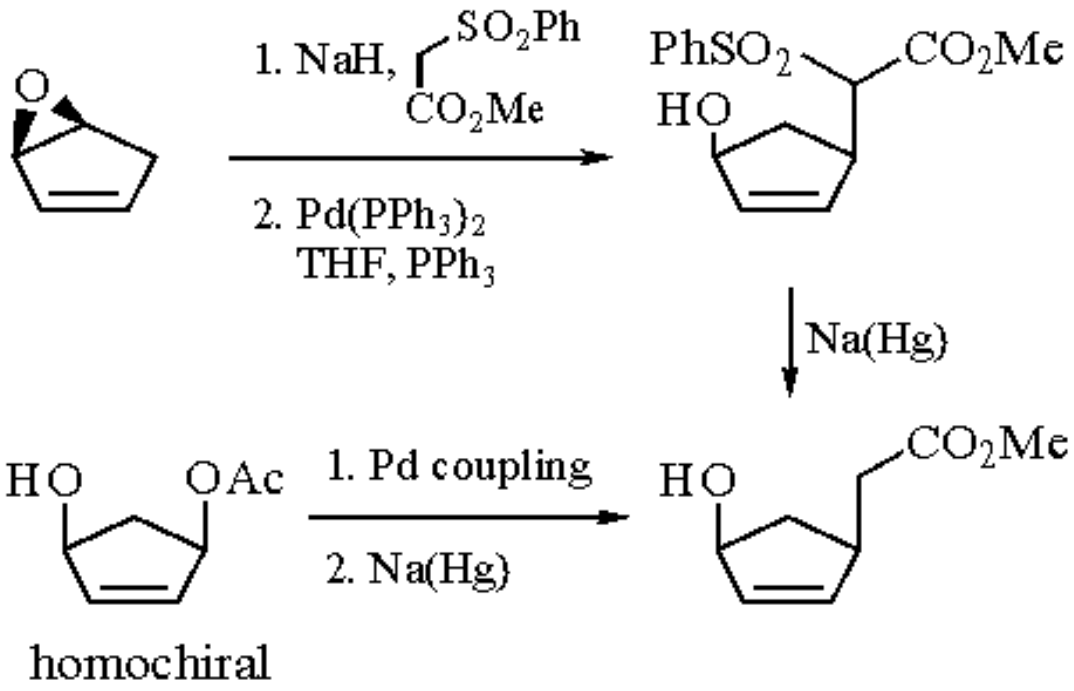

(3)

Methyl phenylsulfonylacetate can be alkylated using π-allyl complexes to afford alk-4-ene functionalities which can be treated with a palladium catalyst to form vinylcyclopropane ring systems. The phenylsulfonyl group can be removed by Na(Hg) reduction and the ester converted to aldehyde by reduction followed by oxidation to give a 60:40 mixture of *cis*- and *trans*-cyclopropanecarbaldehydes (eq 4).[9]

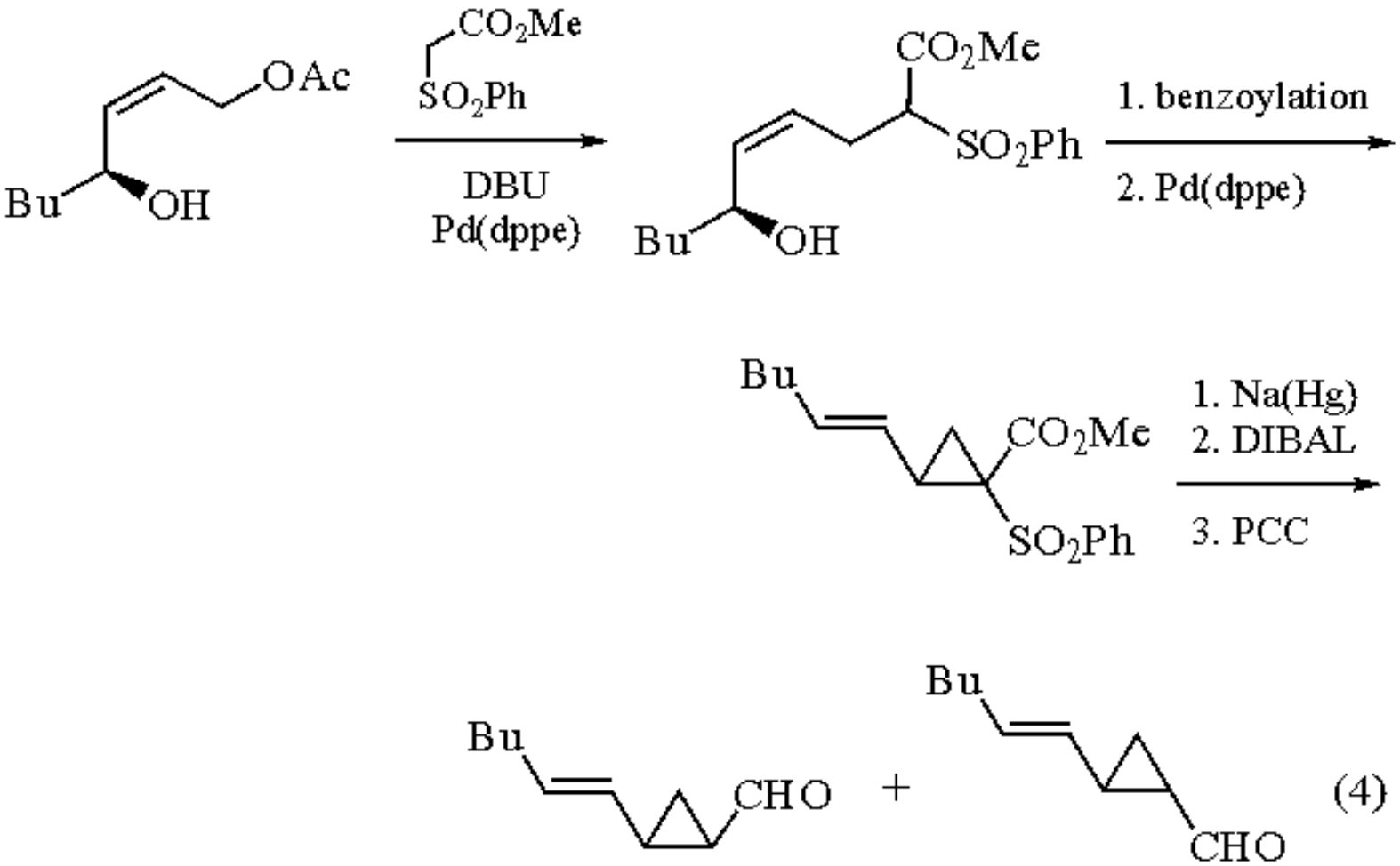

(4)

Alkylation with 5-bromo-1-pentene or 5-bromo-1-pentyne gives the alkenyl and alkynyl derivatives which can undergo palladium-catalyzed cyclization followed by a Heck reaction to give cyclopentanes or vinylidenecyclopentanes (eqs 5 and 6).[10,11]

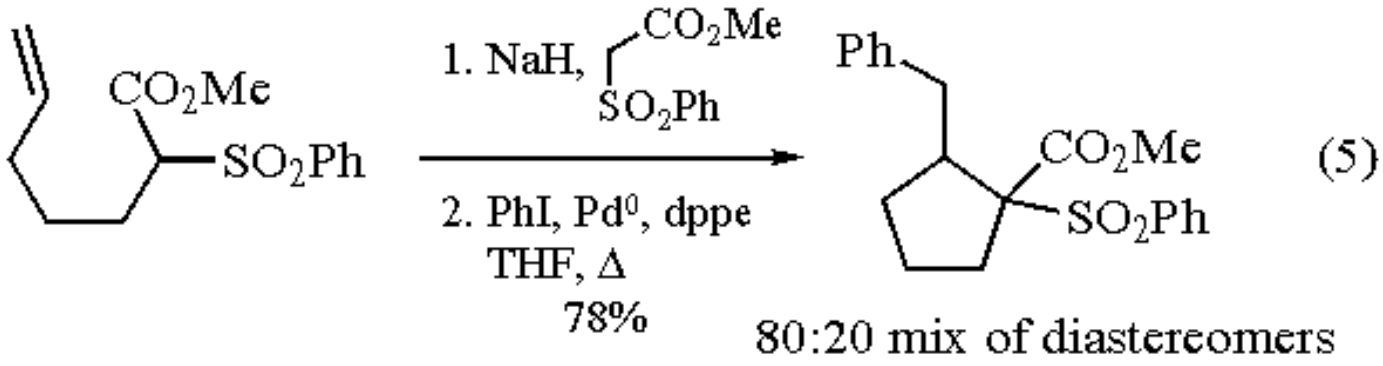

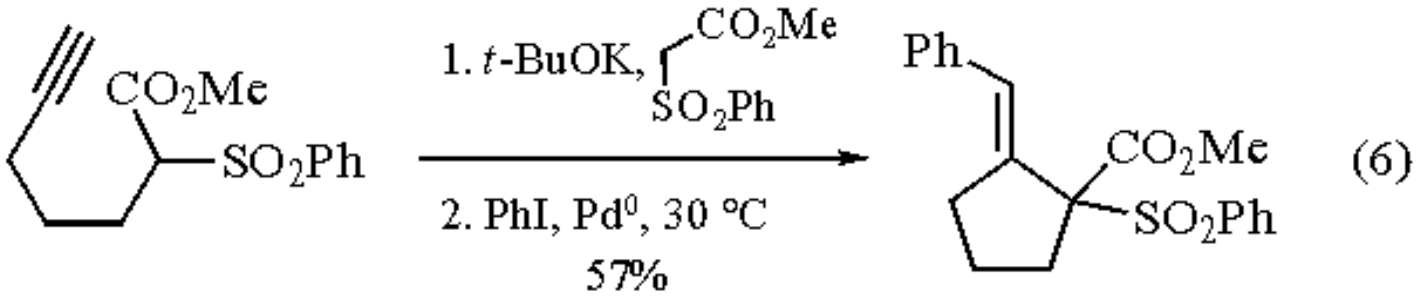

The palladium cyclization reaction using the soft nucleophilic properties of the phenylsulfonylacetate system has been extended to the construction of macrocyclic ring systems.[12,13] Methyl phenylsulfonylacetate can be deprotonated with ***Potassium t-Butoxide*** in *t*-butanol/DMSO and added, via Michael addition, to the unsaturated ketone. Macrocyclization is effected with ***Tetrakis(triphenylphosphine)palladium(0)*** and ***N,O-Bis(trimethylsilyl)acetamide*** in THF at reflux (eq 7).

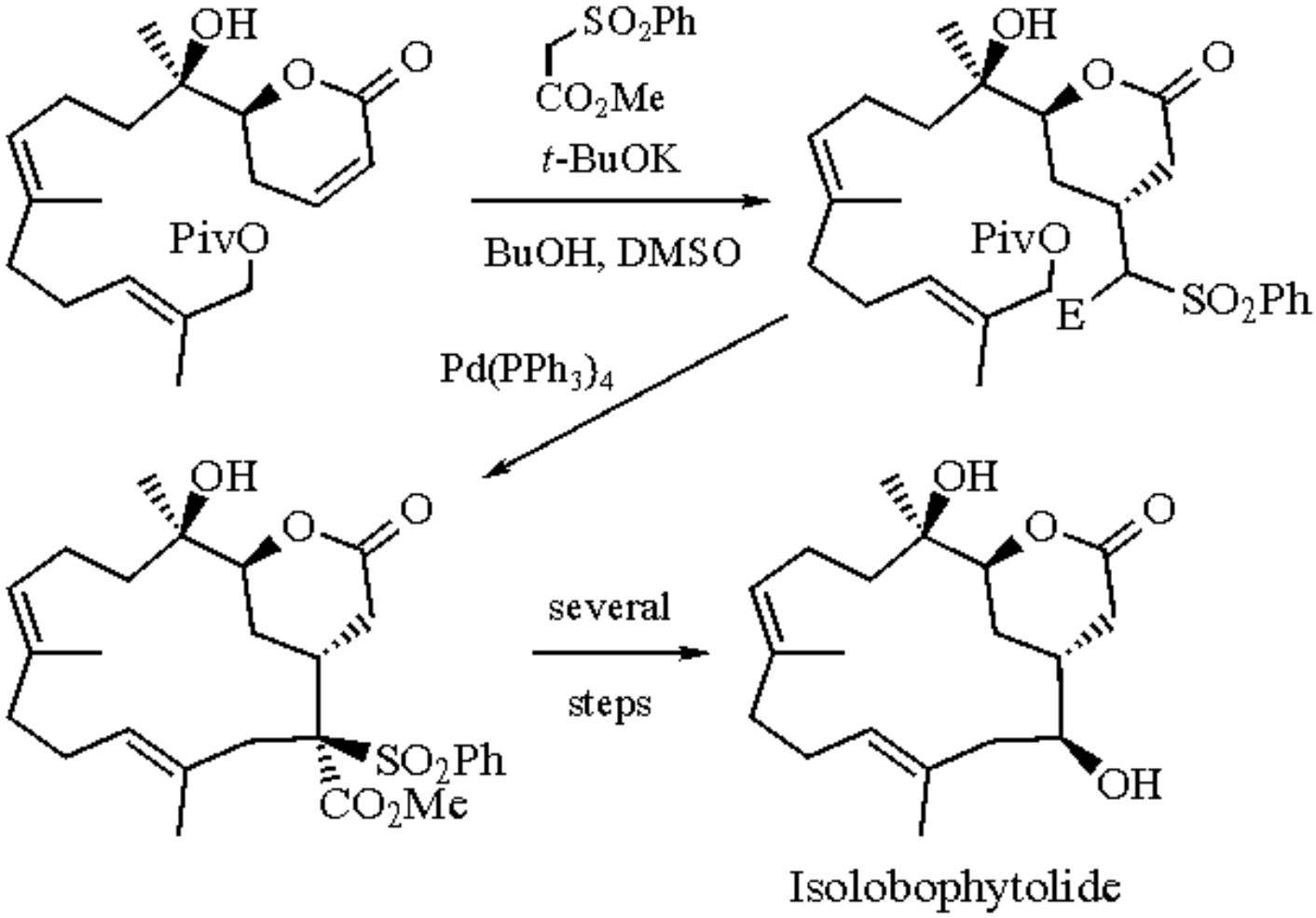

(7)

Methyl phenylsulfonylacetate also undergoes a reductive addition to dienes in the presence of palladium(0) catalysts[14] under basic conditions to give functionalized alkenes (eq 8).

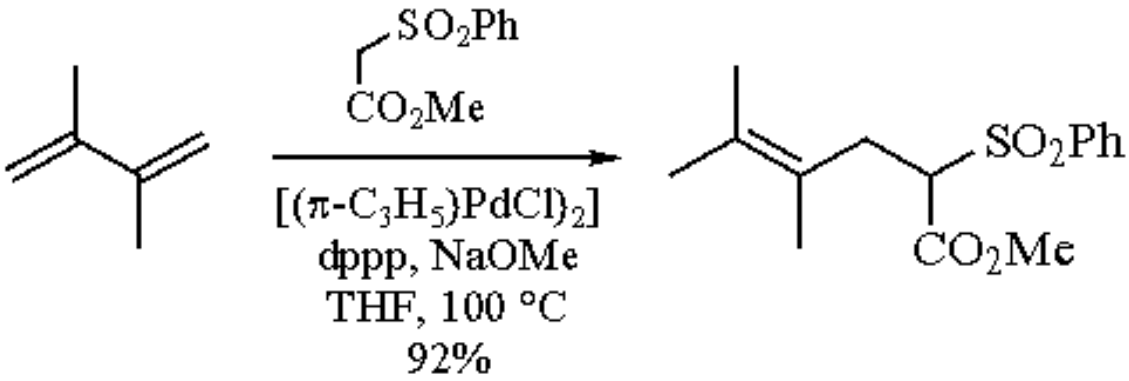

(8)

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Methyl 3-Phenylsulfonyl-2-propenoate

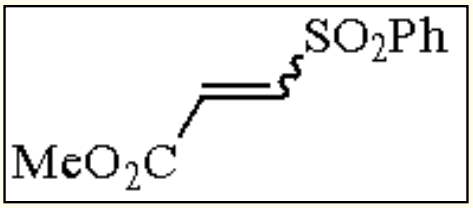

(*E*)

[1865-13-0] · $C_{10}H_{10}O_4S$ · Methyl 3-Phenylsulfonyl-2-propenoate · (MW 226.27) (*Z*)

[91077-67-7]

(used in Michael addition reactions;[1] [2 + 2],[2] [3 + 2],[3] and [4 + 2][4,5] cycloadditions)

Physical Data: (*E*)-isomer mp 100 °C; (*Z*)-isomer mp 50.5-51.5 °C.

Solubility: (*E*)-isomer sol ethanol, methanol; (*Z*)-isomer sol chloroform, toluene; insol pentane.

Form Supplied in: both white crystalline solids.

Preparative Methods: methyl (*E*)-3-phenylsulfonyl-2-propenoate (**1**) is prepared in 70% yield by the reaction of ***Methyl Acrylate*** with benzenesulfonyl iodide followed by treatment with ***Triethylamine***.[3] Methyl (*Z*)-3-phenylsulfonyl-2-propenoate (**2**) is prepared in 88% yield by the ***Boric Acid*** mediated addition of ***Sodium Benzenesulfinate*** to ***Methyl Propiolate***.[5,6]

Handling, Storage, and Precautions: potential alkylating and vesicant. Use in a fume hood.

Midhael Addition Reaction.

Methyl (*E*)-3-phenylsulfonyl-2-propenoate (**1**) has been reported to undergo Michael addition reactions with ***Pyrrolidine*** (eq 1), ***Sodium Methoxide*** (eq 2), and the morpholino enamine of cyclopentanone (eq 3) to produce, initially, β-substituted acrylates.[1] In each case, attack of the nucleophile at the carbon α to the phenylsulfonyl group was followed by irreversible elimination of benzenesulfinic acid to give rise to the observed products.

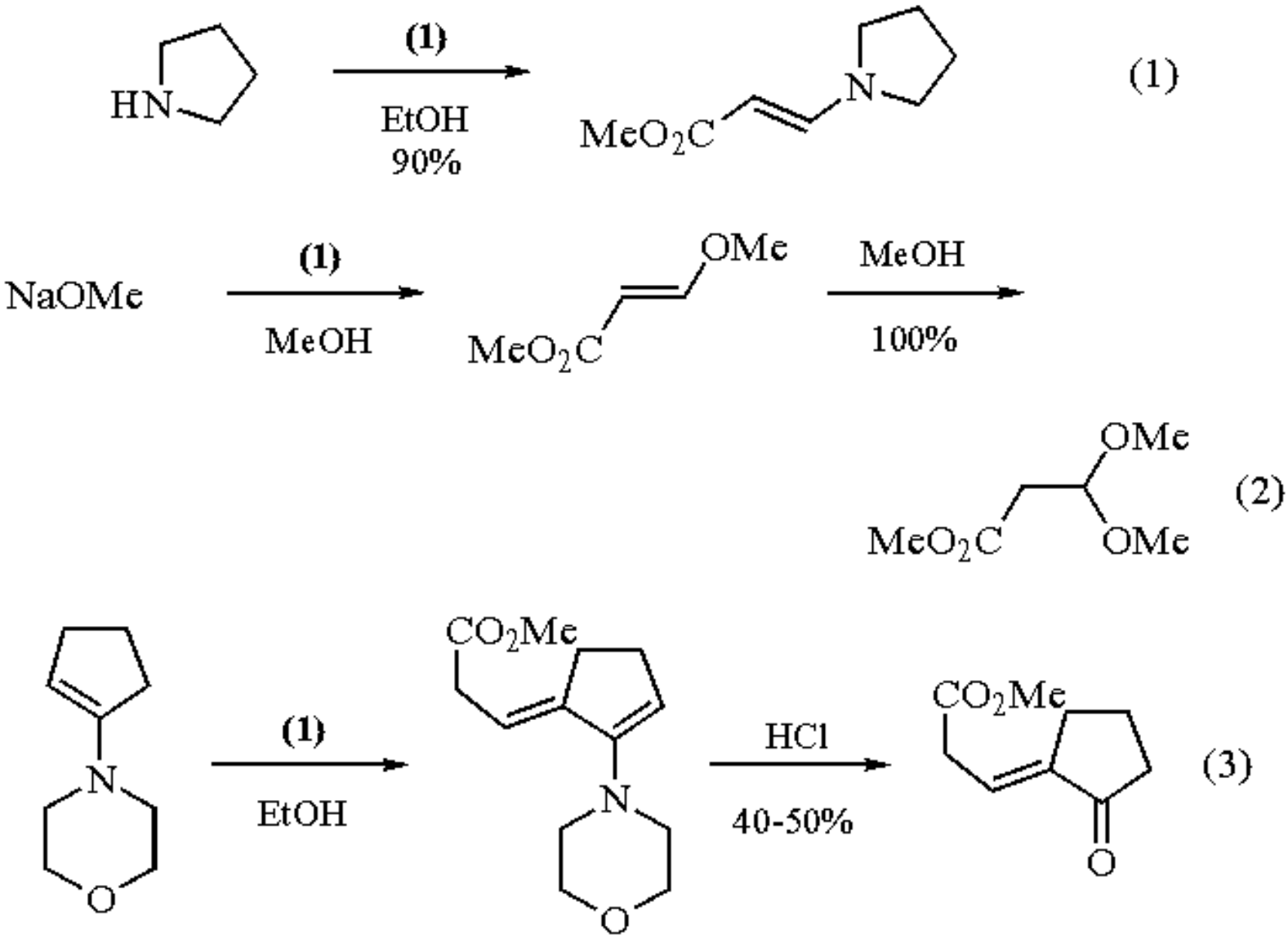

Cycloaddition.

Methyl (*E*)-3-phenylsulfonyl-2-propenoate (**1**) undergoes [2 + 2] cycloaddition with ***N,N-Diethyl-1-propynylamine*** (eq 4) to provide regioselectively the corresponding tetrasubstituted cyclobutene in quantitative yield at 25 °C.[2]

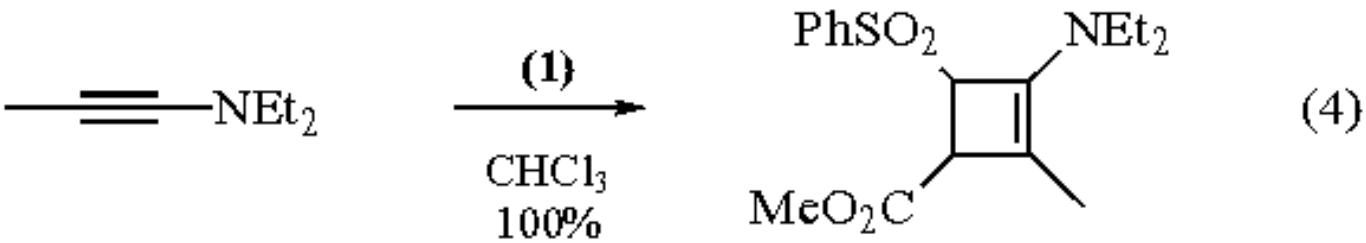

[3 + 2] Cycloaddition.

It has been communicated that methyl (*E*)-3-phenylsulfonyl-2-propenoate (**1**) reacts with the nitrile imine generated in situ from phenylhydrazonyl chloride and triethylamine to afford a single regioisomeric 4,5-dihydropyrazole (eq 5) in

65% yield.[3] The regioselectivity of this process was rationalized in terms of frontier orbital theory.

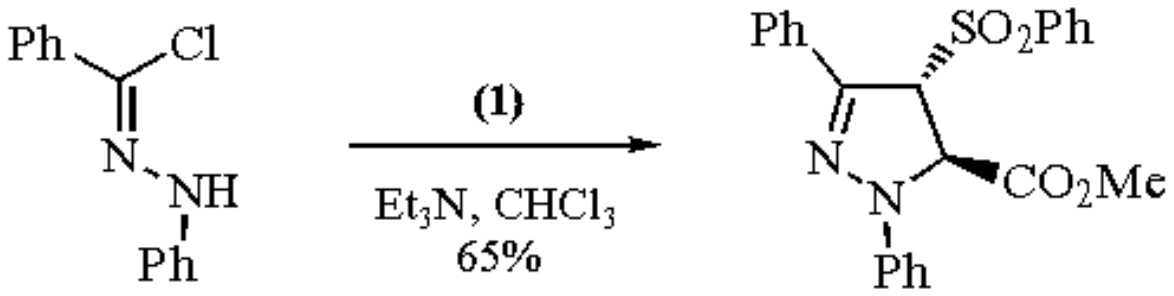

(5)

[4 + 2] Cycloaddition.

Heating methyl (*Z*)-3-phenylsulfonyl-2-propenoate (**2**) with a tricylic triene at 55-60 °C overnight results in the formation of the [4 + 2] cycloadduct in quantitative yield (eq 6).[4] The latter cycloadduct was transformed into a quadricyclane derivative upon photolysis. Methyl (*Z*)-3-phenylsulfonyl-2-propenoate (**2**) also reacts with (*E*)-4-methylhexa-3,5-dien-1-ol in refluxing toluene to give the *endo* Diels-Alder adduct in 81% yield (eq 7).[5] Interestingly, the ethyl ester analogous to methyl (*E*)-3-phenylsulfonyl-2-propenoate (**1**) reacts with this diene to give a quantitative yield of products derived from *endo* addition (eq 8), which have the opposite phenylsulfonyl regiochemistry to that observed with (**2**).

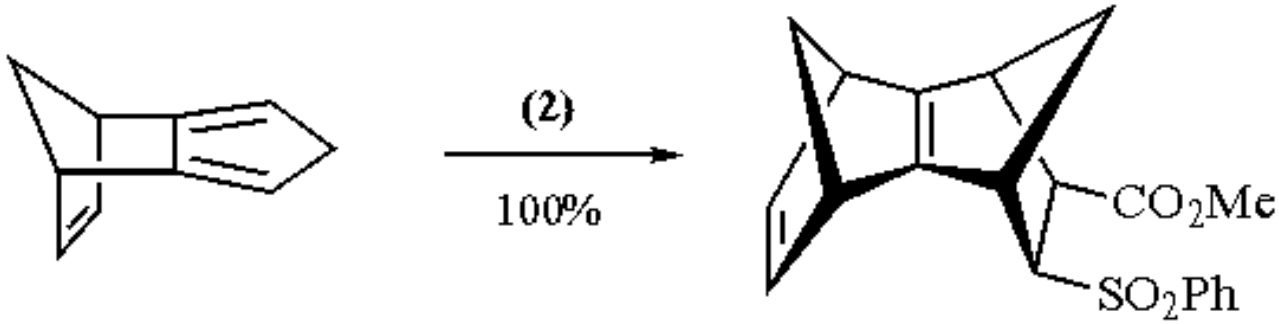

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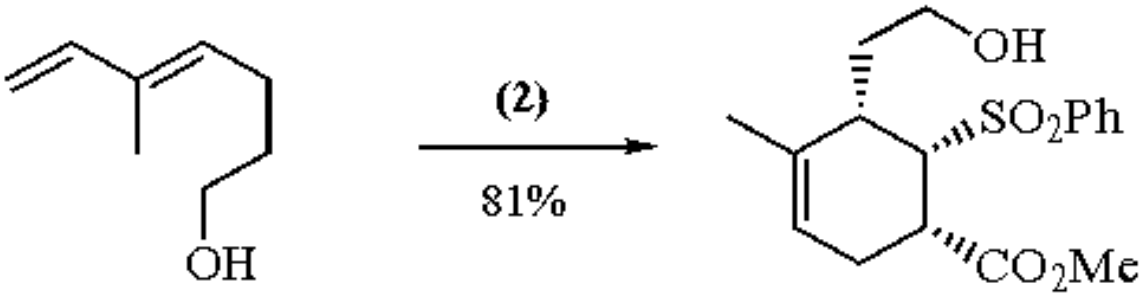

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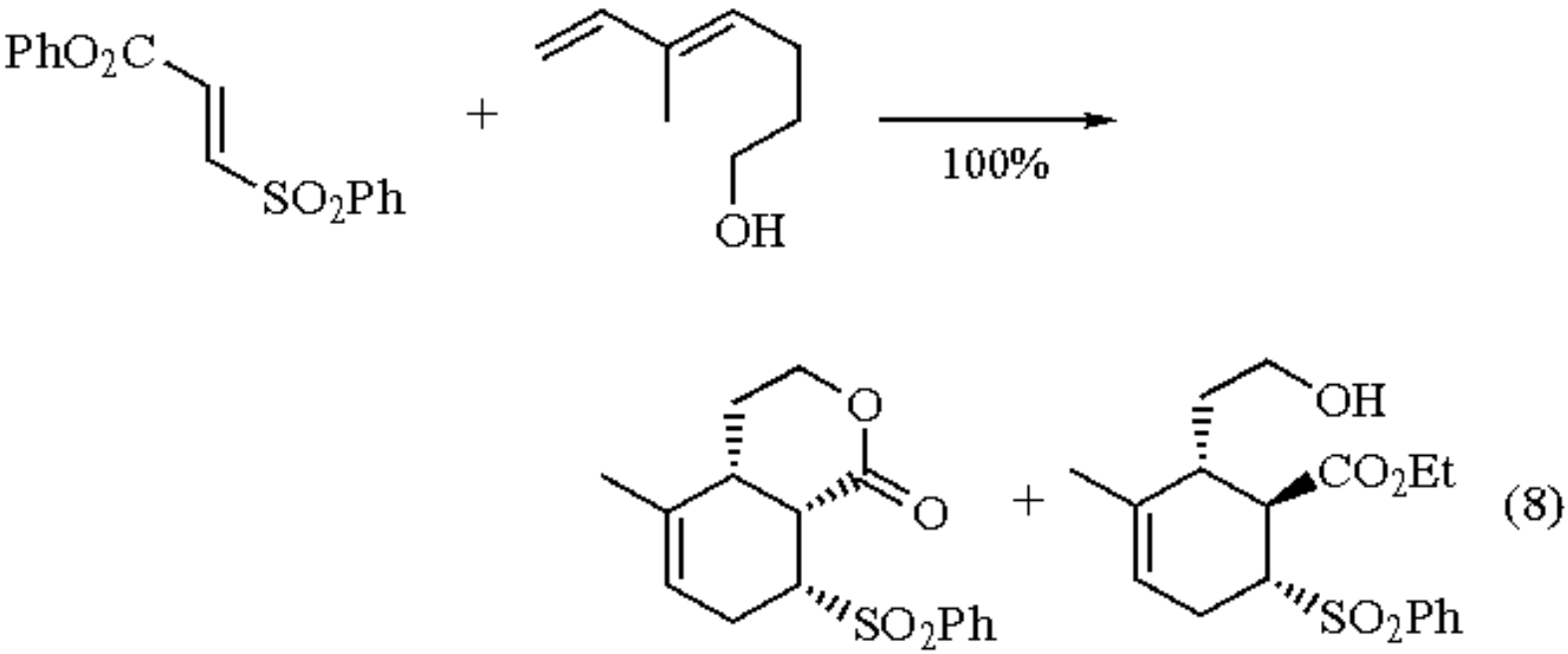

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4-(4´-Methyl-1´-piperazinyl)-3-butyn-2-one

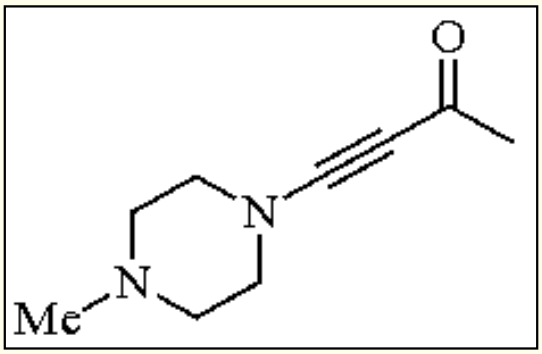

[67543-08-2] · $C_9H_{14}N_2O$ · 4-(4´-Methyl-1´-piperazinyl)-3-butyn-2-one · (MW 166.25)

(peptide coupling)

Physical Data: colorless crystals; mp 18-19 °C.

Preparative Method: can be made in multigram quantities in three steps from commercially available ***4-Methoxy-3-buten-2-one*** in 54% overall yield (eq 1).[1] The intermediates (**2**) and (**3**) are purified by recrystallization or distillation. No chromatography is involved. The final product can be purified by distillation under reduced pressure.

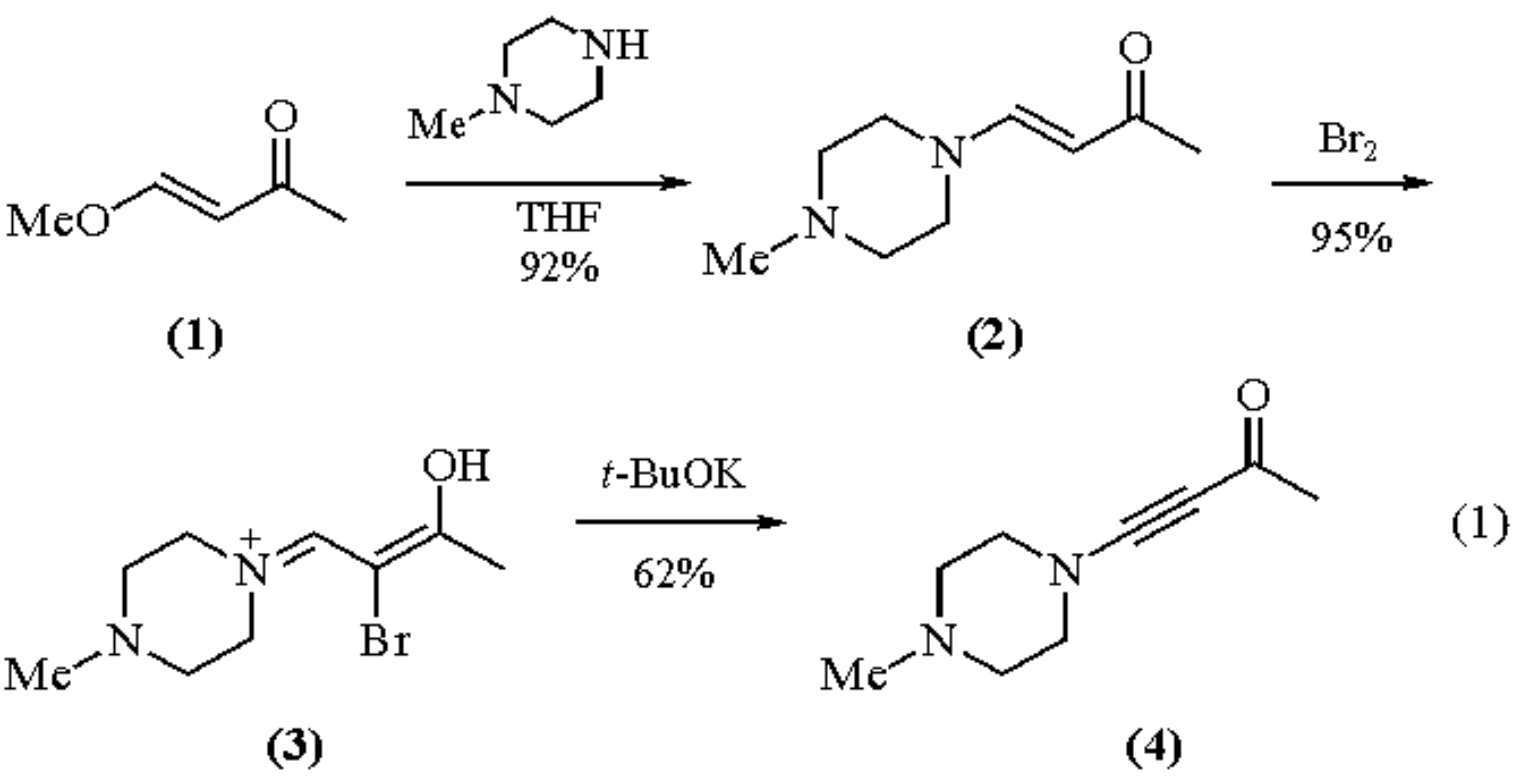

Handling, Storage, and Precautions: stable for a period of hours at rt. It should be stored at refrigerator/freezer

temperatures to prolong its shelf life.

Peptide Coupling.

This push-pull alkyne reagent has found use in the production of amides from carboxylic acids and amines (eq 2).[2] Typically, the carboxylic acid is added to a solution of the ynone in THF at 0 °C and stirred for 30 min. The amine is added at -20 °C and the reaction is allowed to warm to rt. It has been confirmed by isolation that enol esters such as (**7**) are intermediates in the process, which is thought to proceed as shown in (**5**) -> (**8**). A variety of saturated and unsaturated carboxylic acids can be combined with primary and secondary amines to give amides in 73-95% yields.

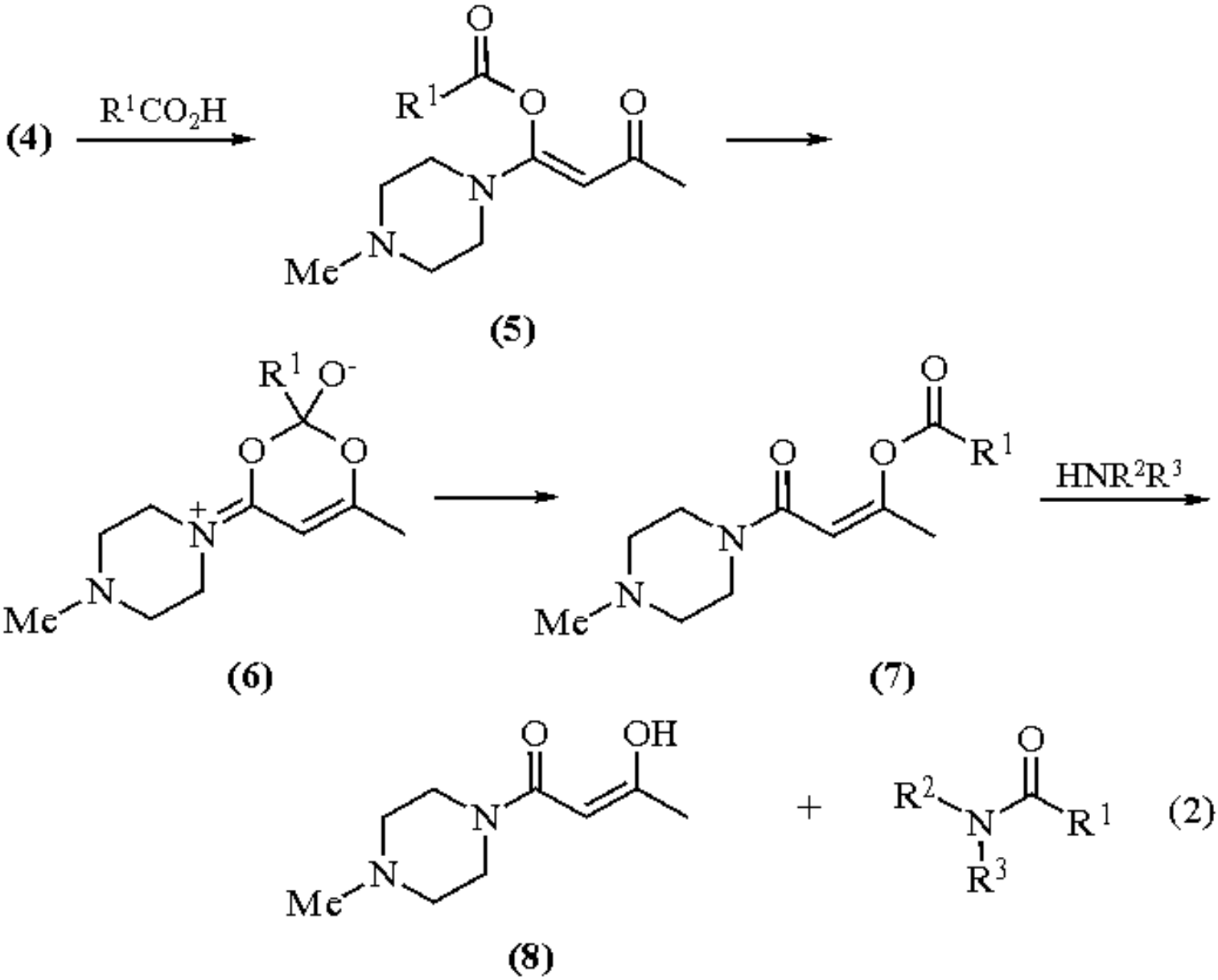

Because of the near-neutral conditions of the coupling process, the reagent is excellent in the formation of peptides (eq 3).[3] Because (**4**) reacts quickly with carboxylic acids to form (**5**), peptide fragments containing unprotected and potentially nucleophilic groups can be used in the coupling process. For example, unprotected serine, methionine, hydroxyproline, tyrosine, and histidine react only at the primary amino group (eq 3). Yields are excellent and little or no racemization is observed.

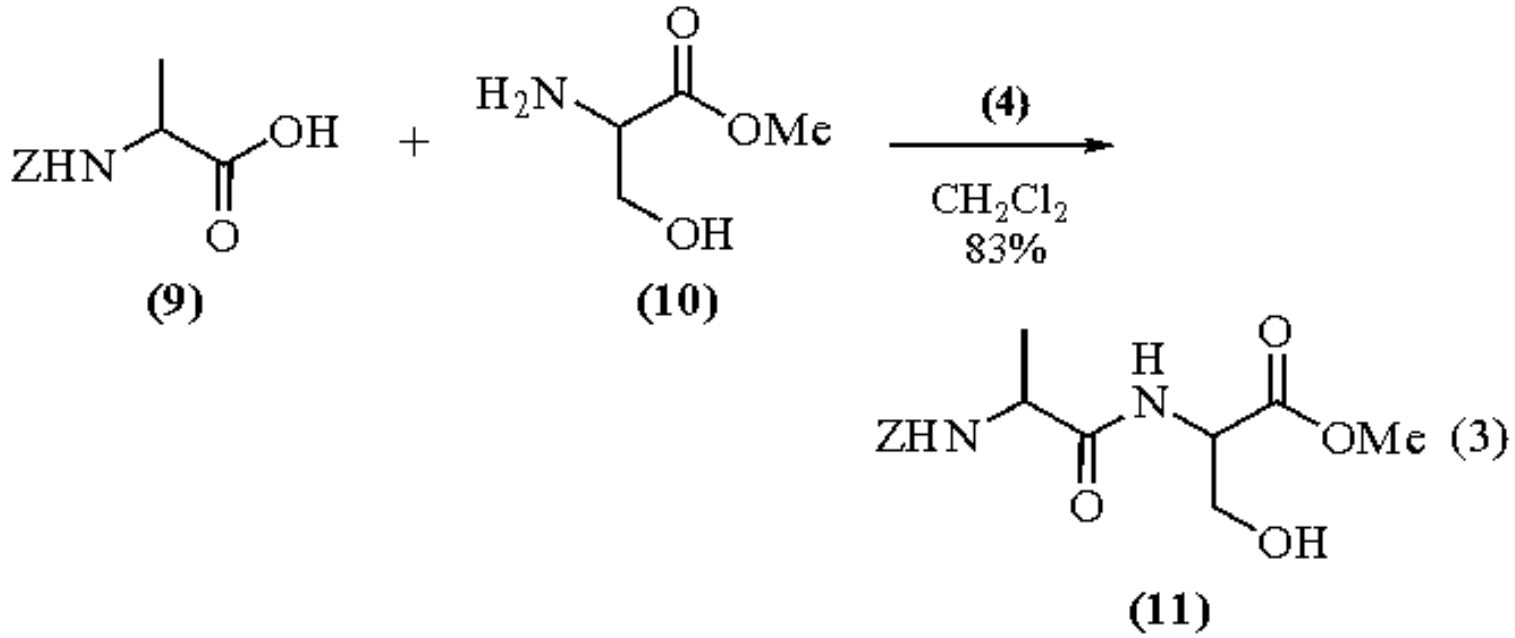

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3. (a) Neuenschwander, M.; Fahrni, H.-P.; Lienhard, U. *HCA* **1978**, *61*, 2437. (b) Neuenschwander, M.; Fahrni, H.-P.; Lienhard, U. *C* **1978**, *32*, 214.

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2-Methyl-1-propenyl Trifluoromethanesulfonate

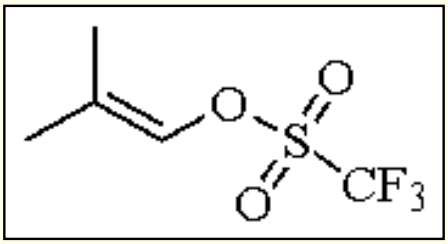

[53282-30-7] · $C_5H_7F_3O_3S$ · 2-Methyl-1-propenyl Trifluoromethanesulfonate · (MW 204.19)

(precursor to dimethylvinylidene carbene,[1] 2-methyl-1-propenyl ethers,[1] isopropylidenecyclopropanes,[2] isopropylidenecyclopropenes,[2] 3-isopropylindazoles,[3] and 2-methyl-1-propenyltriphenylphosphonium triflates[4])

Physical Data: bp 65-66 °C/70 mmHg.

Solubility: sol most organic solvents.

Preparative Method: prepared in a single step from 2-methylpropionaldehyde, ***Trifluoromethanesulfonic Anhydride***, and a hindered pyridine in 1,2-dichloroethane at reflux (eq 1). Distillation gives the product in 45% yield.[5]

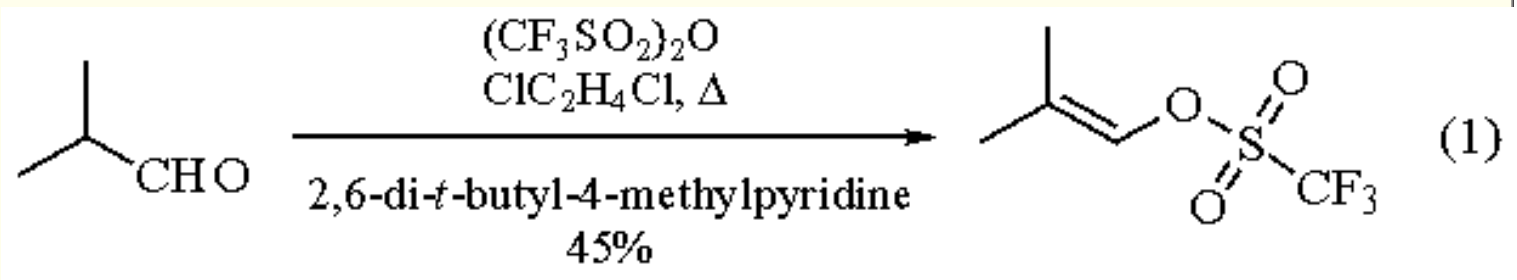

General Discussion.

This reagent is quantitatively converted to the electrophilic carbene (**2**) (eq 2) on treatment with ***Potassium t-Butoxide***.[1] This carbene readily inserts into an oxygen-hydrogen bond, and thus reacts with *t*-butanol to give ether (**3**) (eq 3).[1]

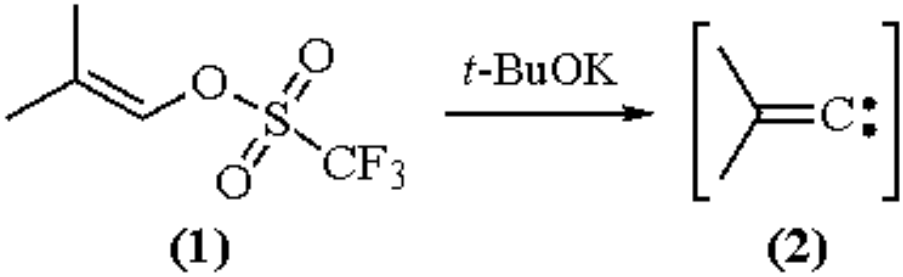

(2)

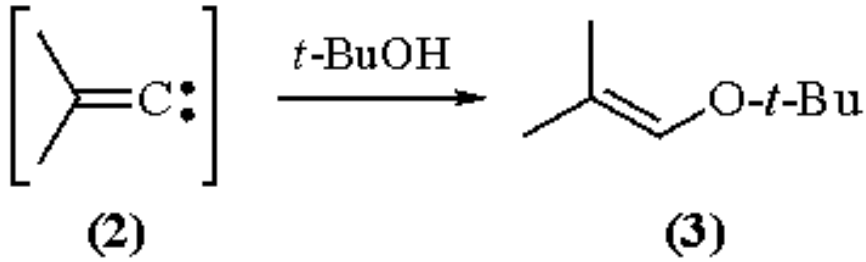

(3)

Carbene (**2**) reacts normally with a variety of substrates. When an alkene is used as solvent (eqs 4 and 5), the corresponding isopropylidenecyclopropanes are generated in good to excellent yield.[1] The silicon-hydrogen bond is an efficient trap (eq 6); the reaction proceeds with retention of configuration at silicon.[6]

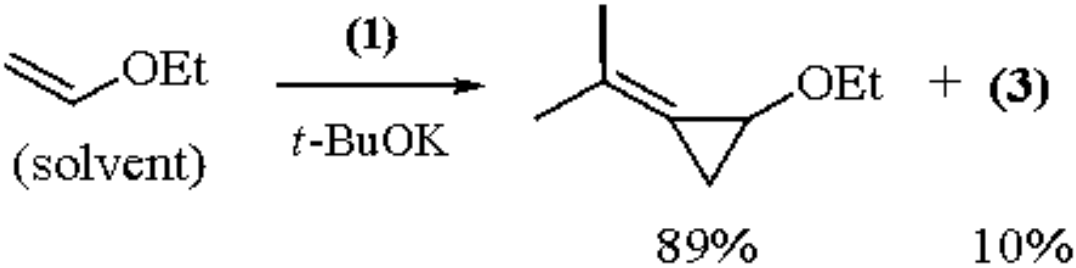

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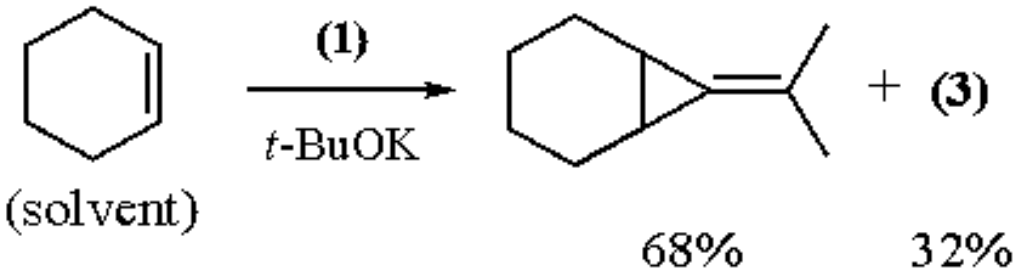

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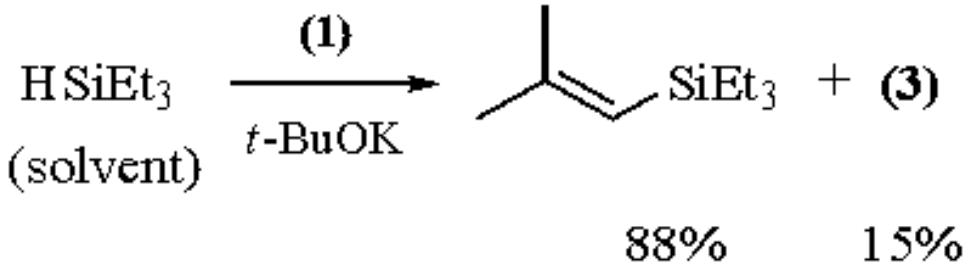

(6)

Alkynes react with (**2**) to yield isopropylidenecyclopropenes (**4**) (eq 7).[2] These products cannot be isolated, but will undergo a facile Diels-Alder reaction. Alternatively, protonation of the product gives isopropylcyclopropenium

ions.

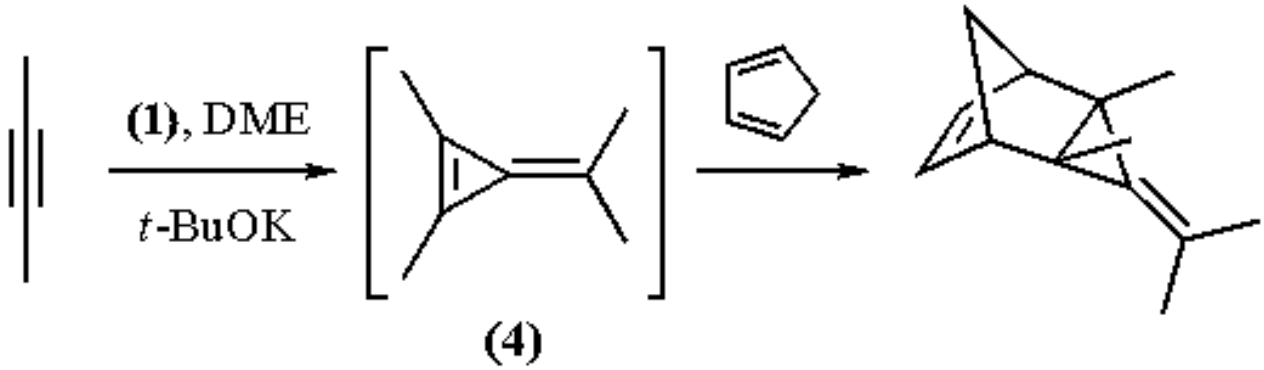

(7)

Reaction of (**1**) in the presence of azoarenes yields the unusual 3-isopropylindazoles (eq 8), presumably via an isopropylidenediaziridine.[3] In the presence of ***Triphenylphosphine***, a palladium catalyst converts (**1**) into the corresponding phosphonium salt in good yield (eq 9).[4]

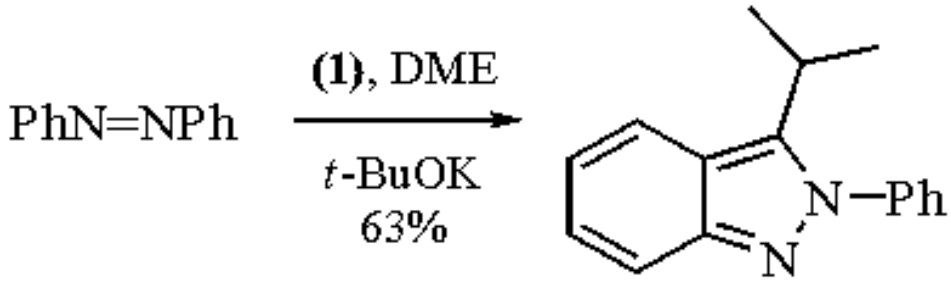

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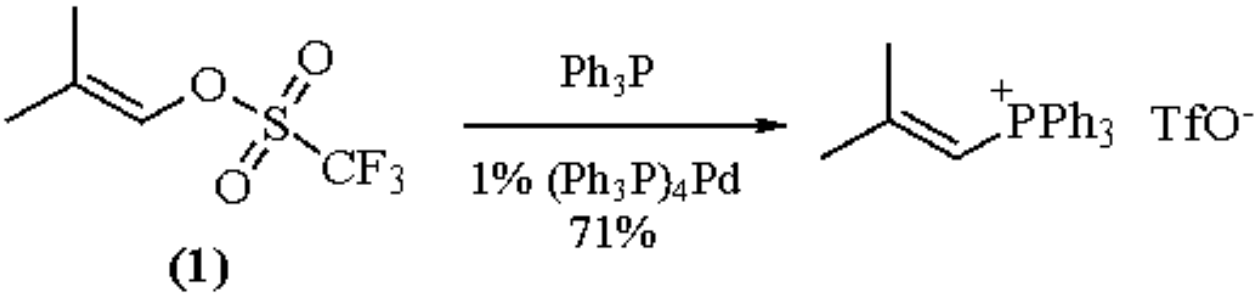

(9)

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Methyl Propiolate

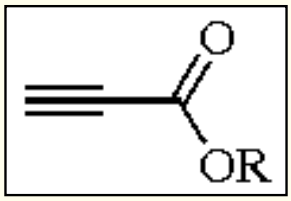

(**1**; R = Me)

[922-67-8] · $C_4H_4O_2$ · Methyl Propiolate · (MW 84.08) (**2**; R = Et)

[623-47-2] · $C_5H_6O_2$ · Ethyl Propiolate · (MW 98.11)

(α,β-unsaturated ester capable of undergoing Diels-Alder[1] and other cycloaddition reactions,[2] Michael additions,[3] acetylide formation,[4] halogen addition,[5] and a variety of cyclization reactions to generate heterocycles[6] and aromatics[7])

Alternate Name: methyl propynoate.

Physical Data: (**1**) bp 104 °C; *d* 0.945 g cm^{-3}. (**2**) bp 120 °C; *d* 0.968 g cm^{-3}.

Form Supplied in: colorless oil; widely available.

Handling, Storage, and Precautions: methyl and ethyl propiolate are lachrymatory liquids; handle in a well-ventilated fume hood.

Diels-Alder Reactions.

Methyl and ethyl propiolate are effective dienophiles and enter into the Diels-Alder reaction with electron-rich (eq 1)[8] and electron-neutral dienes (eq 2)[9] as well as with heterodienes (eq 3).[10] The regiochemical outcome of this transformation is in accord with standard HOMO-LUMO considerations.

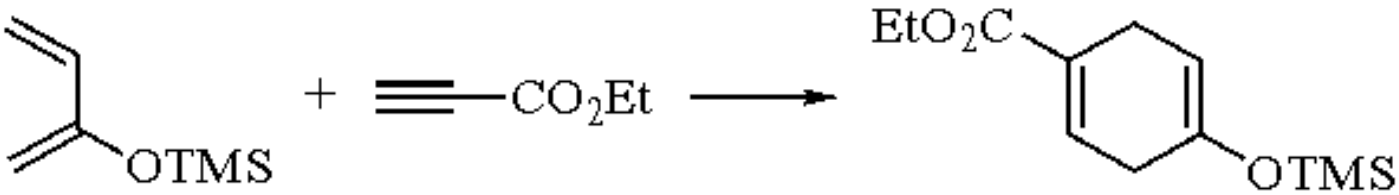

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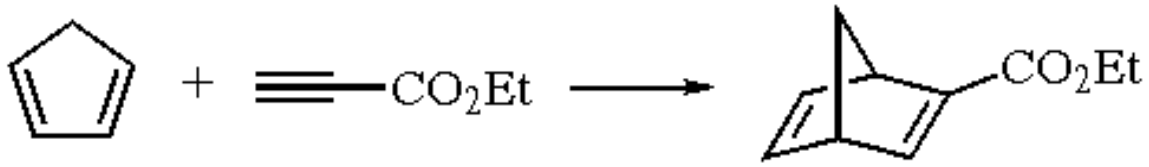

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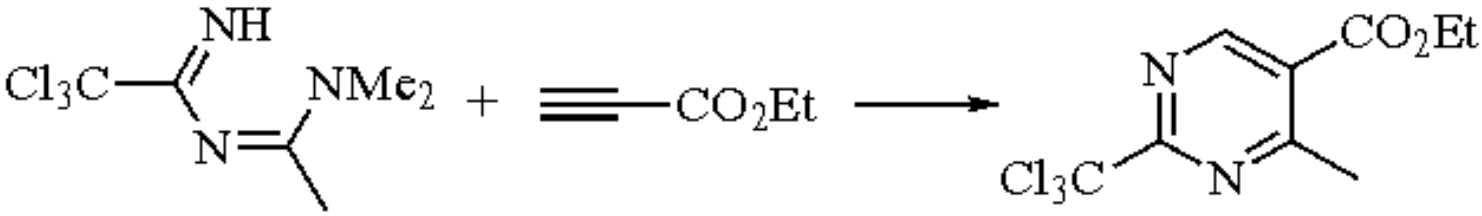

(3)

Other Cycloaddition Reactions.

Methyl and ethyl propiolate are effective partners in [2 + 2] cycloadditions to afford cyclobutenes (eq 4).[11] They also represent good dipolarophiles, undergoing [3 + 2] cycloadditions with a variety of 1,3-dipoles[12] to generate five-membered heterocycles (eq 5).

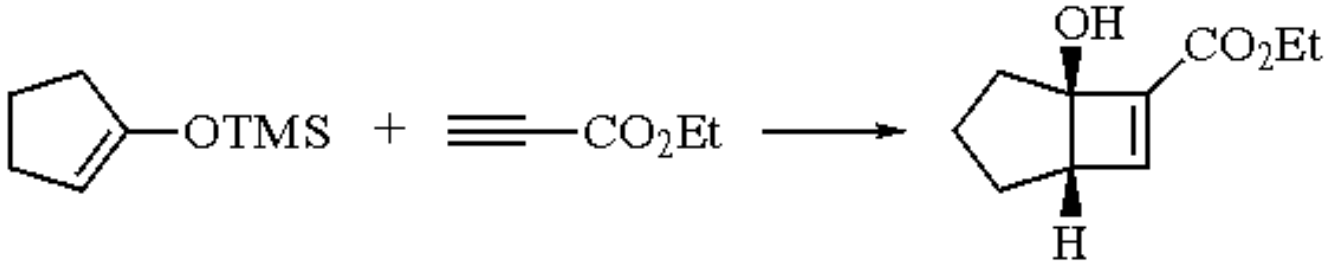

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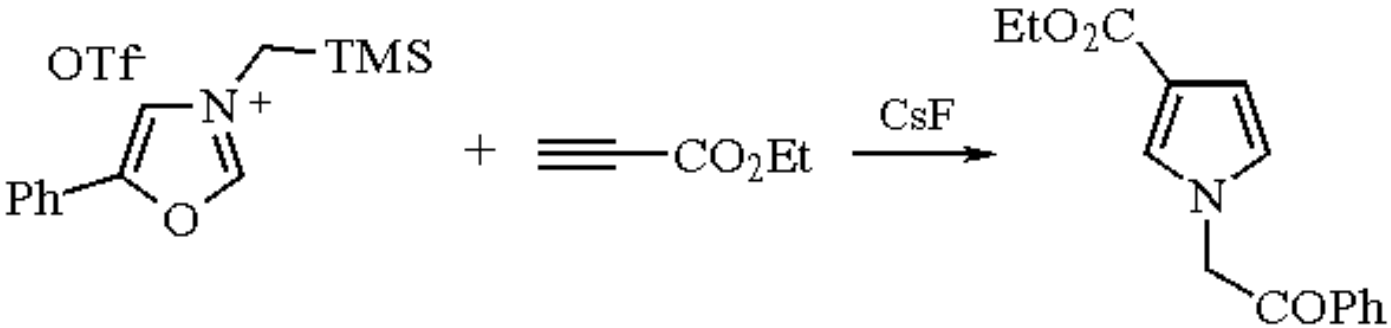

(5)

Halogenation.

Methyl and ethyl propiolate are readily halogenated to afford versatile intermediates such as 3-bromopropiolate esters (eq 6),[13] (*Z*)-haloacrylates (bromo,[14] chloro,[15] and iodo[16]) (eq 7), and 2,3-dihaloacrylates.[17] In the latter case, the stereoselectivity depends on the reaction conditions; both (*E*)-[18] and (*Z*)-[19] dibromides can be prepared specifically (eq 8).

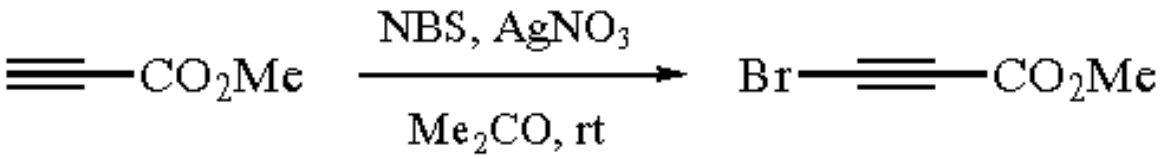

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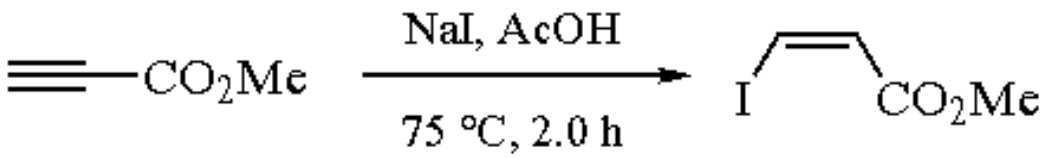

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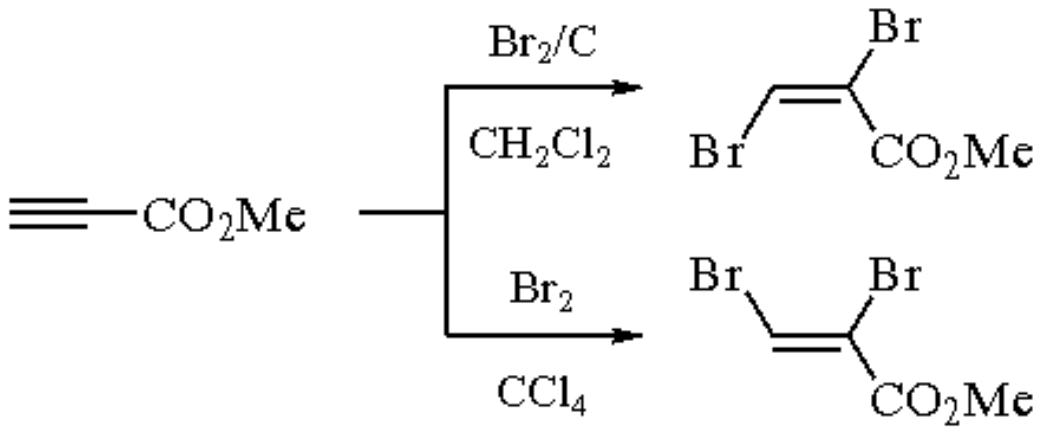

(8)

Conjugate Additions.

Conjugate additions to methyl and ethyl propiolate are well documented, particularly for heterocycle formation. Good Michael donors include thiols,[20] salts of sulfinic acids (which generate potent dienophiles) (eq 9),[21] enolate anions (eq 10),[22] carbon nucleophiles (eq 11),[23] and phenols.[24] In general, heteronucleophiles afford (*Z*)-products and carbon nucleophiles give (*E*)-isomers.

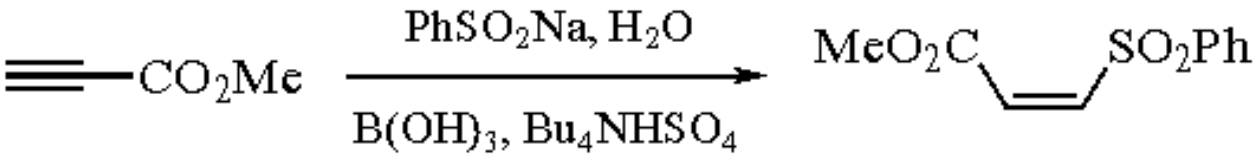

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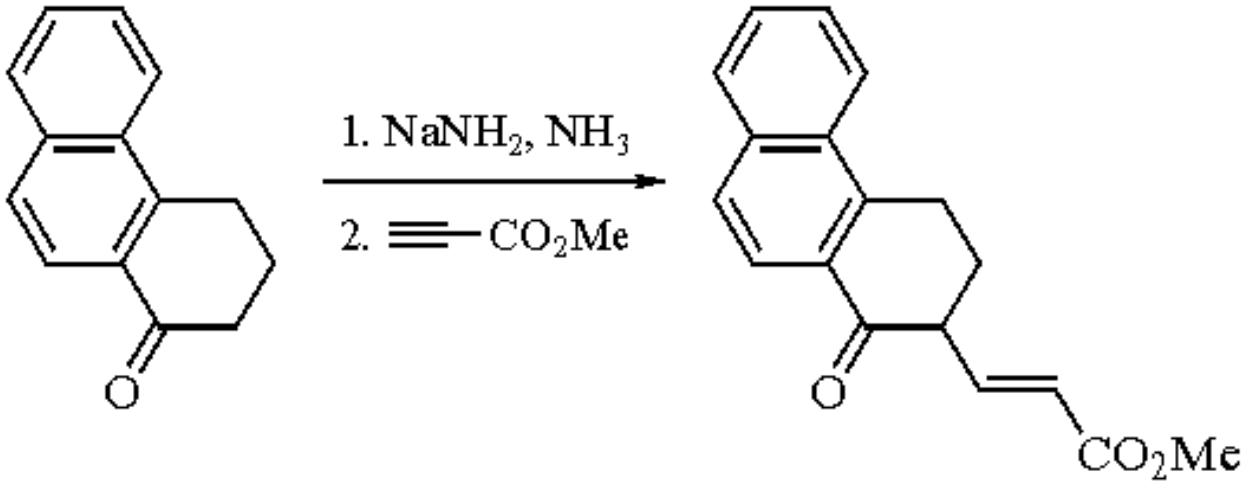

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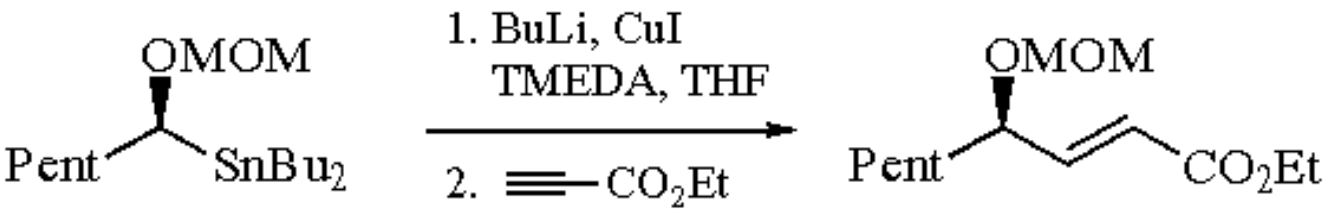

(11)

Heterocycle Formation.

Amidines undergo intermolecular Michael addition followed by cyclization to generate pyrimidones (eq 12).[25] Similar reactions with suitably substituted pyridinium salts afford indazoles (eq 13)[26] and with hydrazines give pyrazolones.[27] Dihydropyridines are prepared using the Michael addition of the elements of ammonia to methyl propiolate with concomitant condensation of the adduct with a simple aldehyde (eq 14).[28] [3 + 2] Cyclizations generate pyrazoles,[29] thiazoles,[30] and oxazoles,[31] among others. Benzofurans are prepared by either the palladium-[32] or copper-catalyzed[33] cyclization of an *o*-halophenol with ethyl propiolate (eq 15).

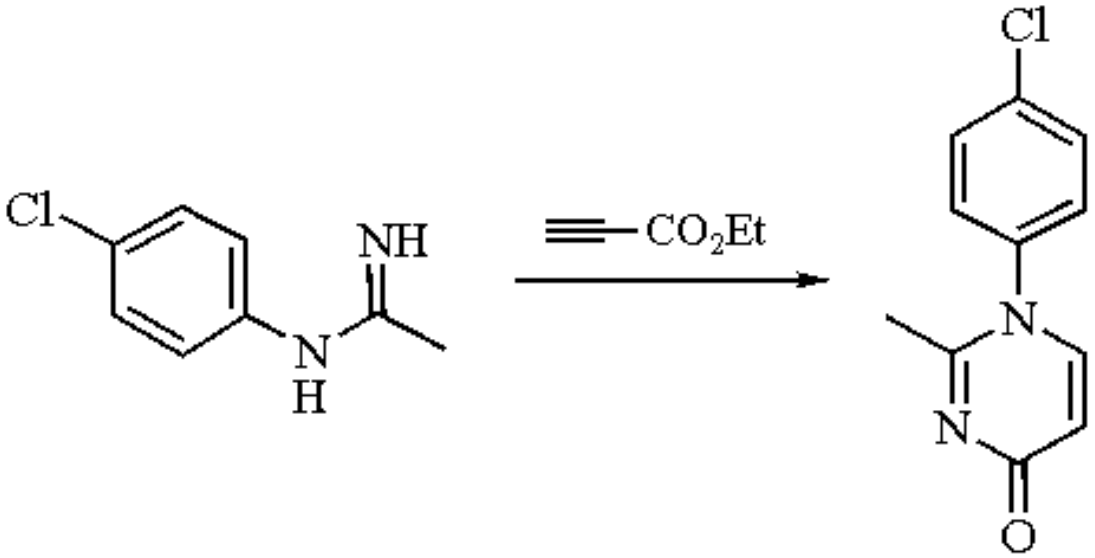

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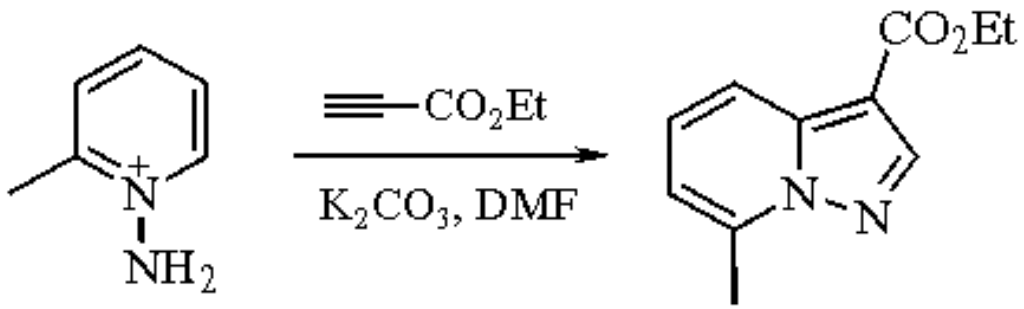

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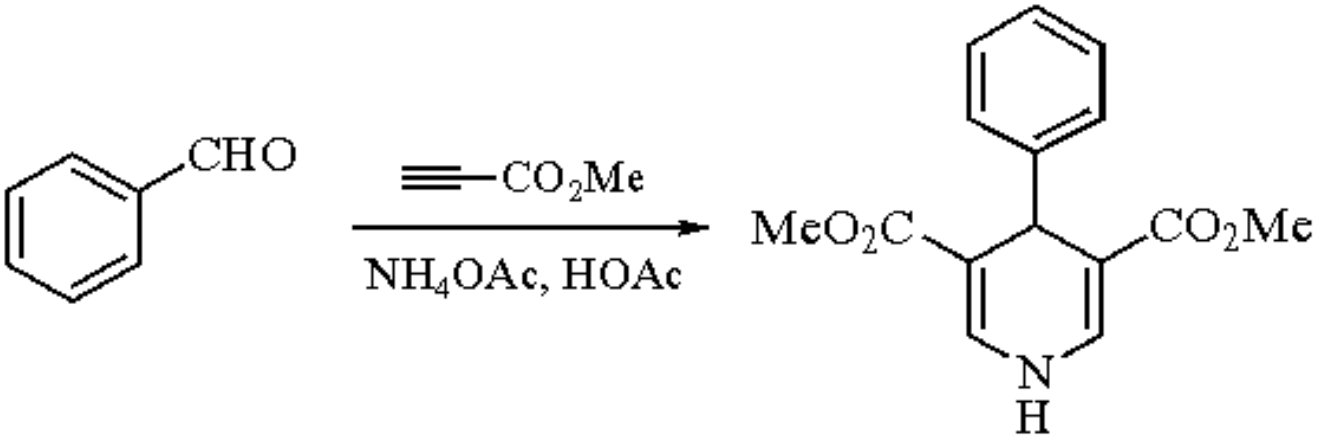

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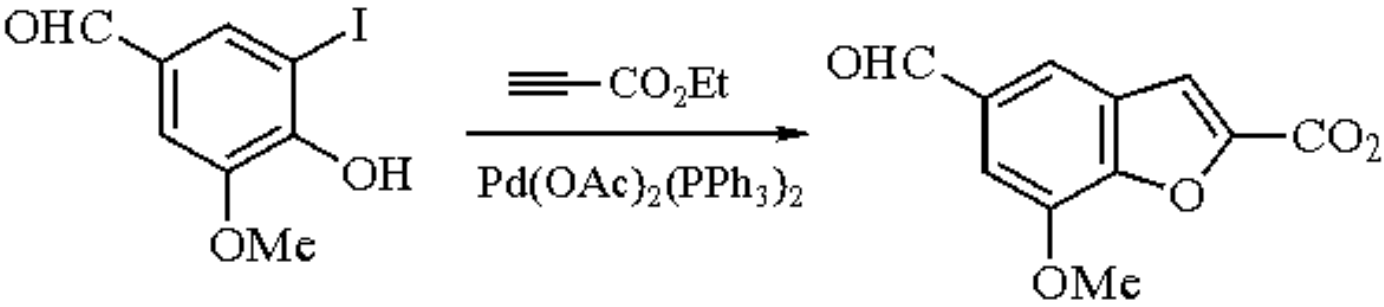

(15)

Acetylide Formation.

Acetylide anions, readily formed with either butyllithium or LDA, undergo nucleophilic addition to a variety of functional groups. These include epoxides,[34] ketones,[35] aldehydes,[36] and carbon dioxide.[37]

Related Reagents.

2-Butynoic Acid; ***3-Butyn-2-one***; ***(E)-(Carboxyvinyl)trimethylammonium Betaine***; ***3,3-Diethoxy-1-propyne***; ***Dimethyl Acetylenedicarboxylate***; ***Propargyl Alcohol***; ***Propargyl Aldehyde***.

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β-Methyl-β-propiolactone[1]

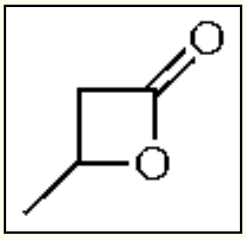

(±)

[3068-88-0] · $C_4H_6O_2$ · β-Methyl-β-propiolactone · (MW 86.10) (*R*)

[32082-74-9] (*S*)

[65058-82-4]

(three-carbon homologating reagent for synthesis of chiral β-methyl carboxylic acids[1])

Physical Data: mp -43.5 °C; bp 71-73 °C/29 mmHg; *d* 1.056 g cm^{-3}. (*R*)-isomer: [α]20D -27.8° (*c* 4.14, $CHCl_3$); (*S*)-isomer: [α]22D +28.8° (*c* 4.30, $CHCl_3$).

Solubility: misc alcohol, acetone, ether, chloroform.

Form Supplied in: colorless oil; the racemic form is widely available.

Preparative Methods: by ring-closure of 3-bromobutyric acid with ***Sodium Carbonate***,[2a] or by hydrogenation of ***Diketene***.[2b] The optically active forms are obtained in the same manner starting from (*R*)- or (*S*)-3-bromobutyric acid, which may be resolved with the (*S*) form of ***1-(1-Naphthyl)ethylamine***.[3] Asymmetric aldol condensation using an enantiopure iron acetyl complex followed by cyclization,[3c] or asymmetric hydrogenation of diketene catalyzed by a chiral ruthenium complex,[3d] also gives the optically active β-lactone.

Handling, Storage, and Precautions: can be stored in the refrigerator for several months without noticeable changes; cancer suspect reagent; should be handled with due care.

General Discussion.

β-Methyl-β-propiolactone is particularly useful as a reactive four-carbon building block. Like β-***Propiolactone***, β-methyl-β-propiolactone undergoes a variety of ring-opening reactions in which the regiochemistry is dependent on the

nature of the nucleophile (eq 1). Addition to the carbonyl carbon predominates in reactions with organolithium[4] or Grignard reagents,[5] giving α,β-unsaturated ketones (**2**) or 1,3-diols (**3**). Organocadmium reagents[4] effect C-O bond fission to give β-methyl carboxylic acids (**4**).

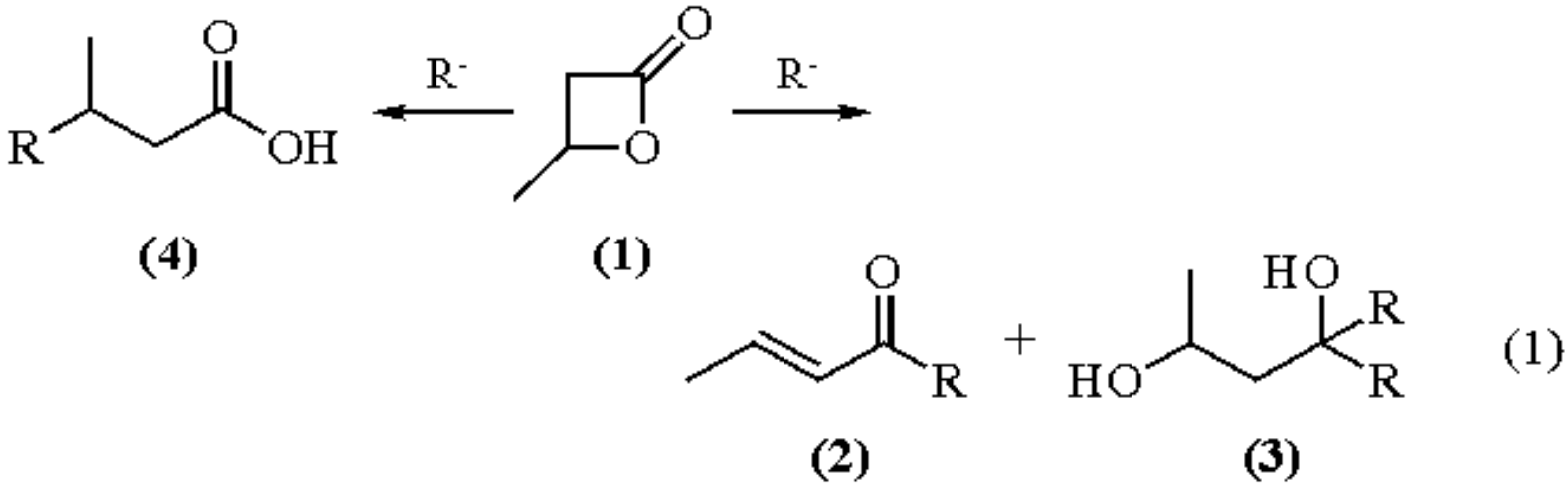

Selective β-attack is best accomplished by the use of organocopper reagents (eq 2).[6] Organocuprates prepared from 2 equiv of Grignard reagents and 1 equiv of ***Copper(I) Iodide*** give β-methyl carboxylic acids (**4**) in better yields than when the corresponding organolithium reagents are used. In the presence of a catalytic amount of a copper(I) salt, Grignard reagents also attack at the β-carbon to give the same products in good yields.[7]

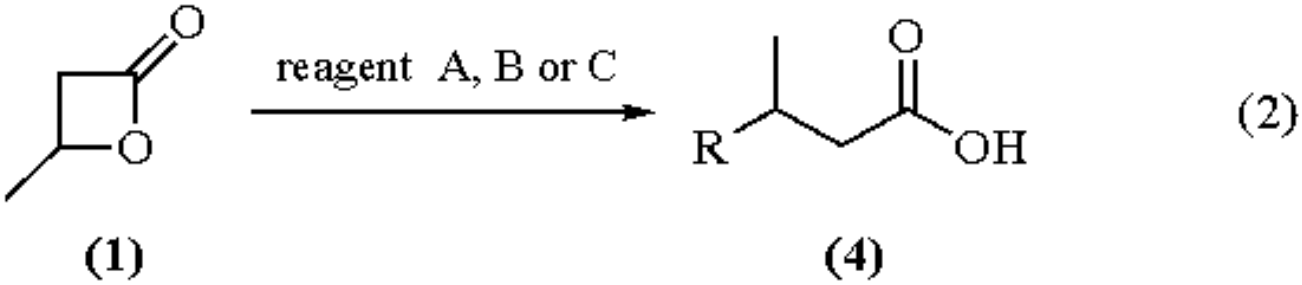

A: R_2CuMgX, THF · Me_2S
B: RMgX, cat CuX, THF
C: RCu · PBu_3, Et_2O

The ***Potassium*** complex of ***18-Crown-6*** or ***Potassium Naphthalenide*** effects ring-opening to give acetates or their alkylated derivatives in good yield (eq 3). Treatment of the reaction mixture obtained from β-methyl-β-propiolactone and potassium-18-crown-6 with hydrochloric acid or alkyl halides gives the acetate (**5**) or its alkylated derivative (**6**), respectively.[8] The α,β-unsaturated carboxylic acid (**7**) or its ester (**8**) is formed by the action of the potassium naphthalenide-18-crown-6 complex.[9]

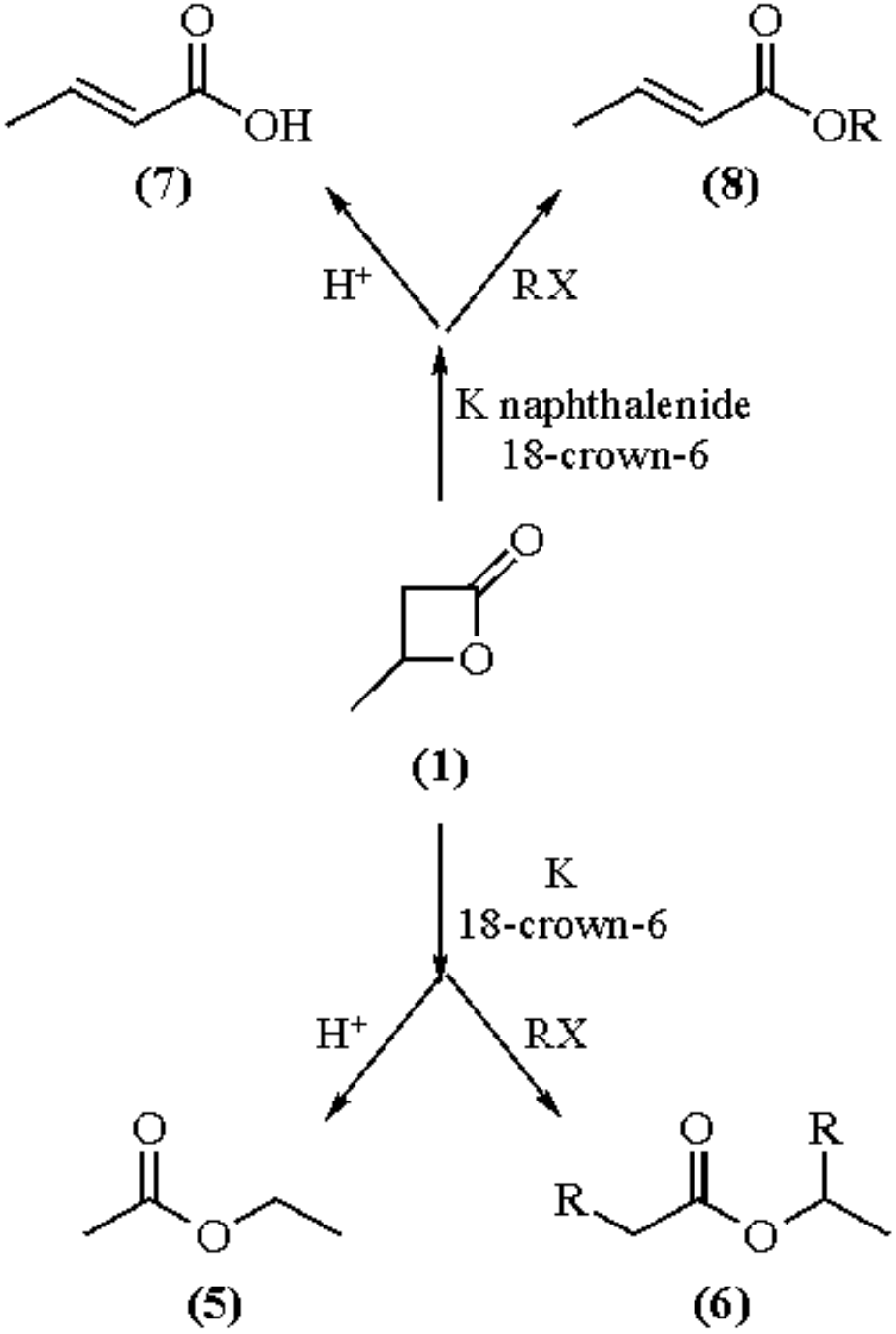

(3)

β-Methyl-β-propiolactone is useful as a four-carbon building block for terpenoid synthesis (eq 4). Citronellic acid (**9**) is prepared by reaction with the homoprenyl Grignard reagent; pulegone (**10**), citronellol (**11**), geraniol, and nerol (**12**) can be obtained by further functional group manipulations.[10]

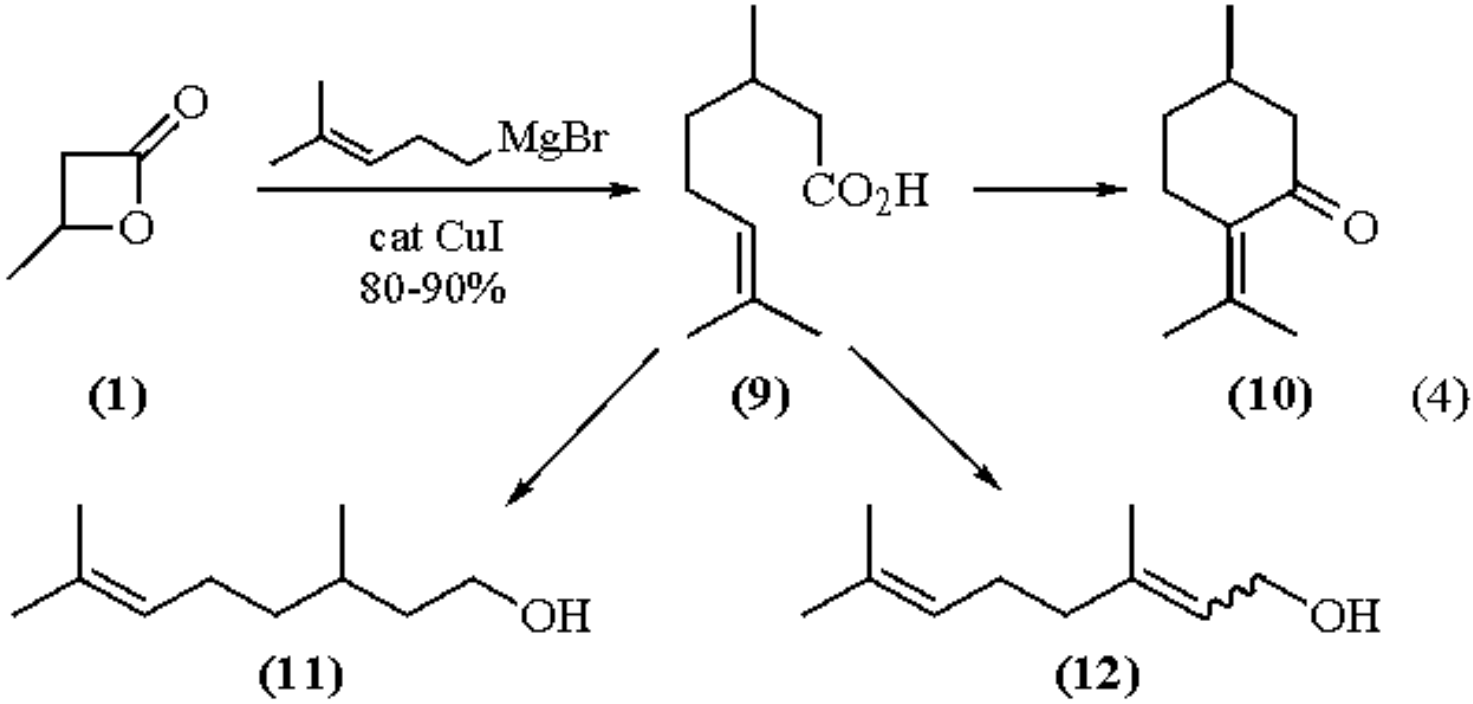

(4)

Optically active (*R*)- and (*S*)-β-methyl-β-propiolactone serve as versatile reagents for the synthesis of 3-sulfinylbutyric acid[11] and for various natural products in optically active form. (*S*)-*ar*-Turmerone (**13**) is obtained by reaction of the (*R*)-enantiomer with a di-*p*-tolylcopper reagent followed by functional group manipulation (eq 5).[3a] (*R*,*R*)-Phytol (**15**) is prepared by ring-opening with the Grignard reagent (**14**) followed by the chain-elongation reaction (eq 6).[12] (*R*,*Z*)-Trogodermal (**18**), an insect pheromone of *Trogoderma inclusum*, is synthesized by using the *cis*-alkenylcopper reagent (**17**) (eq 7).[13] The enantiomeric purity of the final natural products is 83-84% ee. Comparison of this value with that of the starting (*S*)-(+)-3-bromobutyric acid (90% ee) indicates that these magnesiocuprate coupling reactions occur with &egt;92% inversion of configuration at the β-position of the (*R*)-(+)-β-methyl-β-propiolactone.[3a]

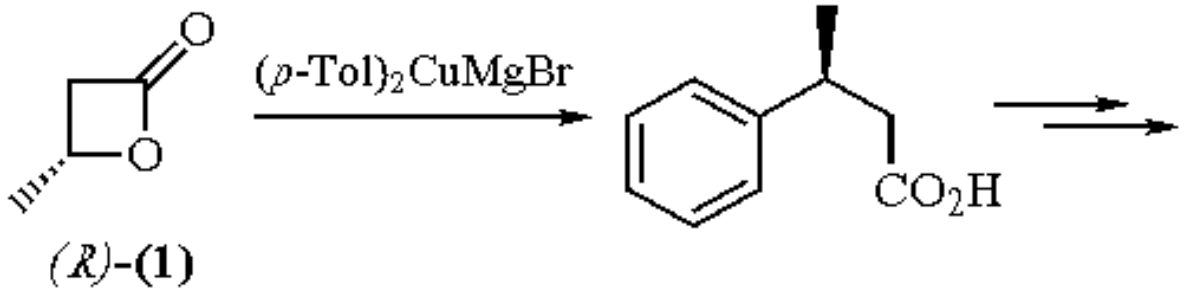

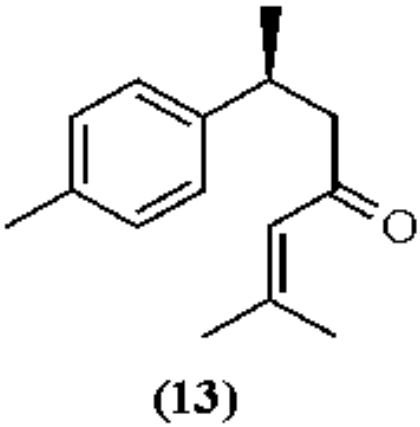

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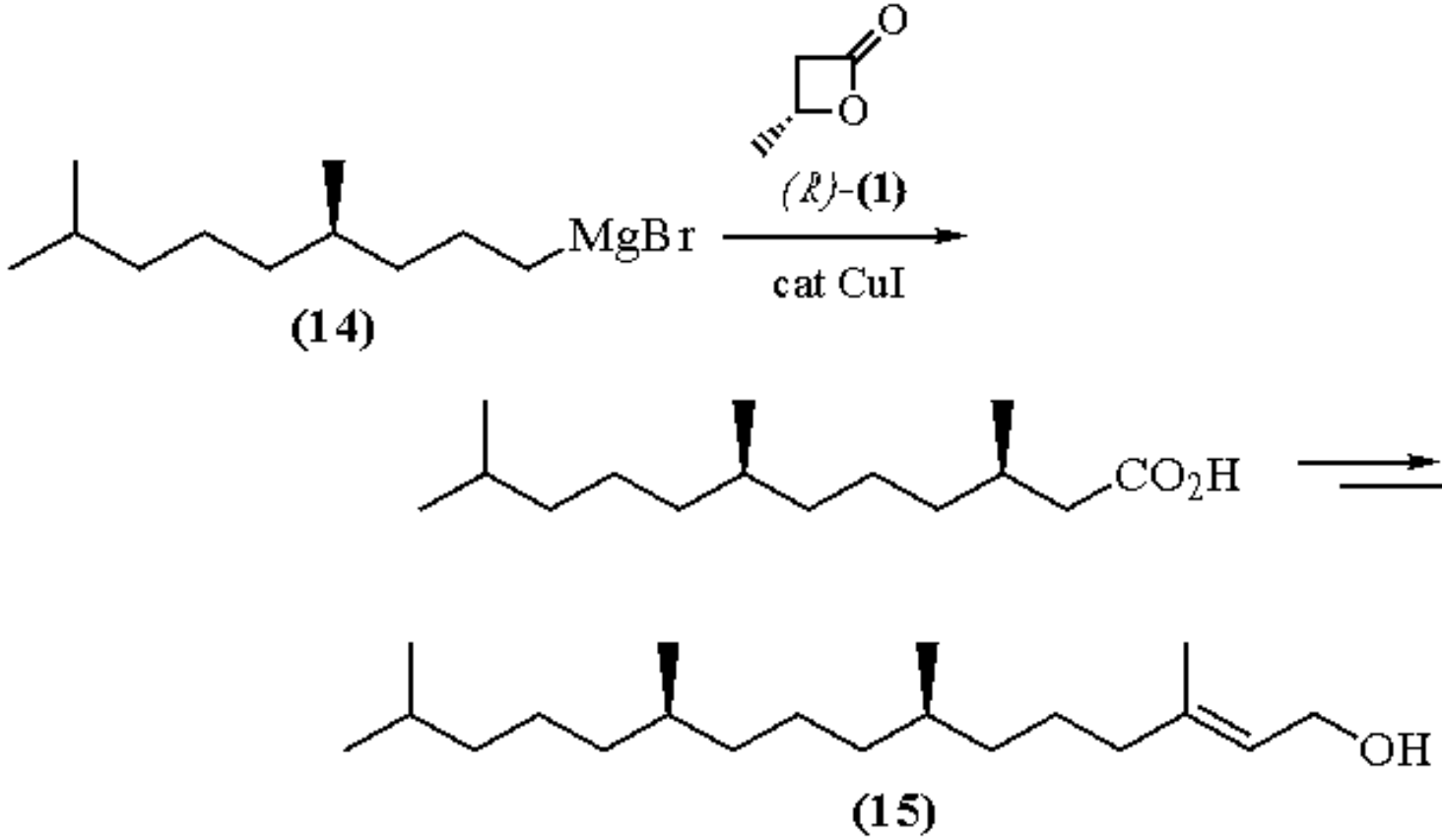

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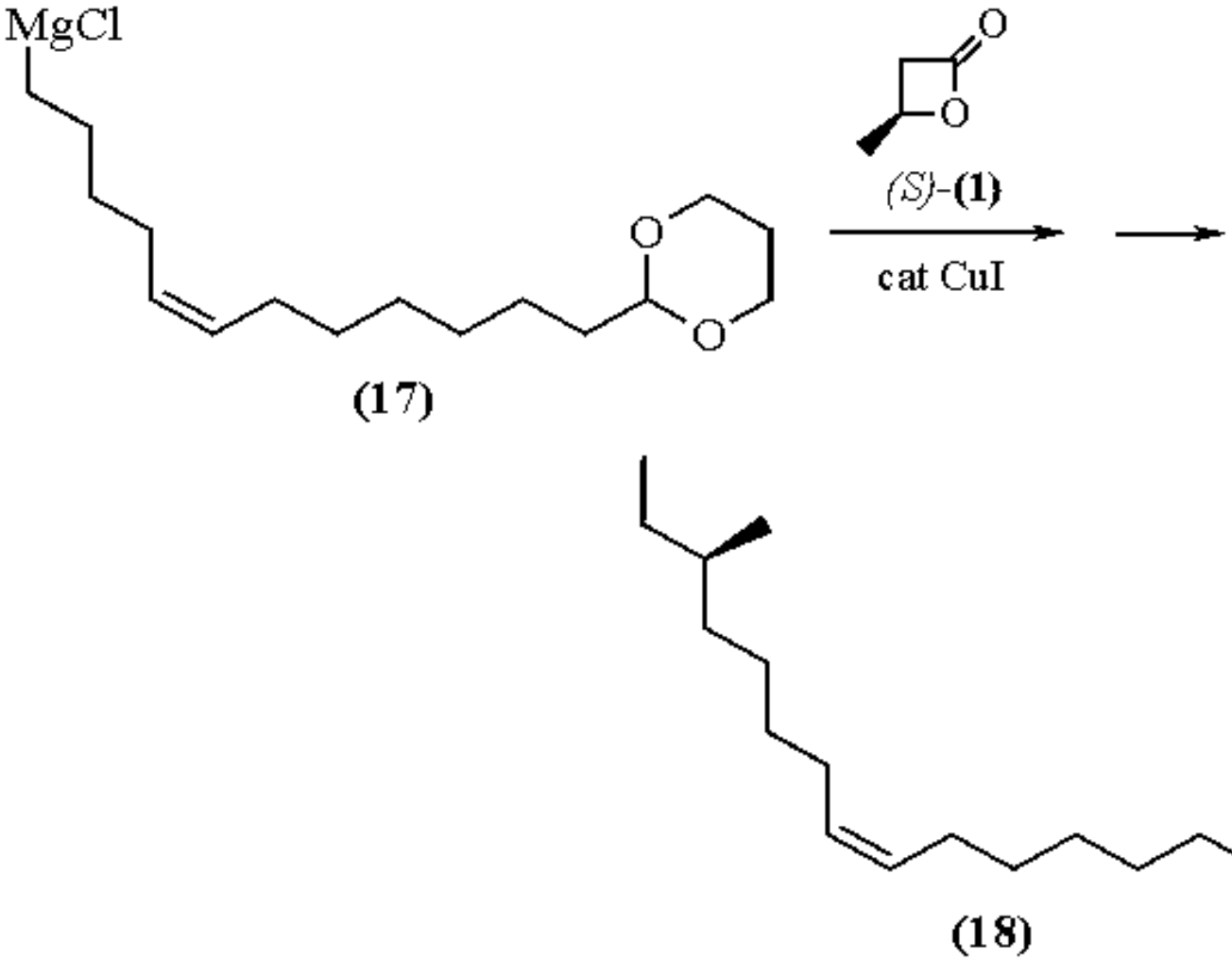

(7)

1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**19**), an insect pheromone, has been synthesized starting from (*R*)-(**1**) via ring-opening at the acyl carbon followed by conjugate addition to the resulting α,β-unsaturated ketone (eq 8).[14]

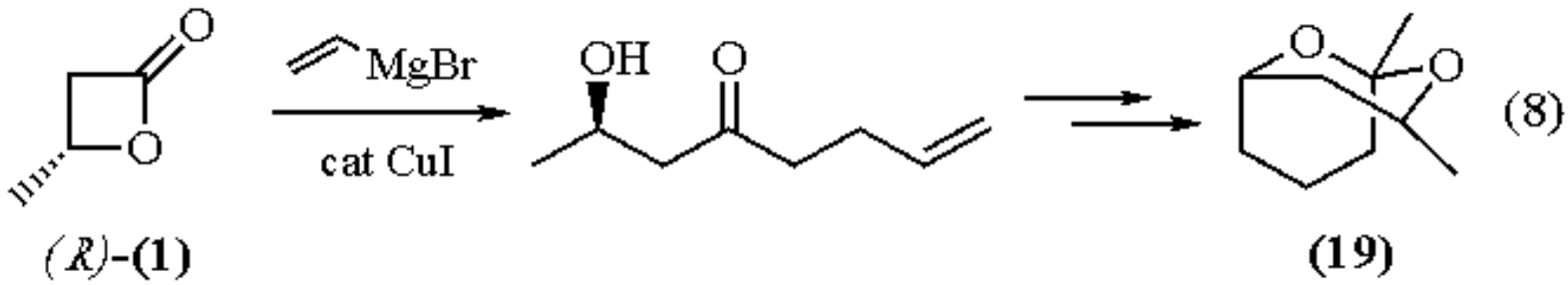

Related Reagents.

N-Benzyloxycarbonyl-L-serine* β-*Lactone; α,β-***Butenolide***; γ-***Butyrolactone***; ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***; β-***Ethynyl*-β-*propiolactone***; β-***Propiolactone***.

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1-Methyl-2(1*H*)-pyridinethione

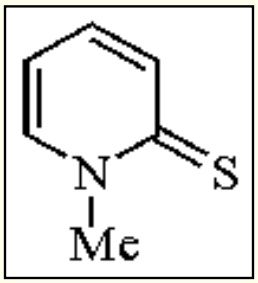

[2044-27-1] · C_6H_7NS · 1-Methyl-2(1*H*)-pyridinethione · (MW 125.21)

(sulfur transfer; carbonyl activation)

Physical Data: pale yellow leaflets; mp 89-90 °C.

Preparative Method: prepared in 80-90% yield from commercially available 1-methyl-2(1*H*)-pyridone by treatment with ***Phosphorus(III) Iodide*** at 130 °C for 4-5 h.

Purification: crystallization from water.[1,2]

Introduction.

The reactivity of 1-alkyl-2(1*H*)-pyridone (and -pyridinethione) derivatives has been studied extensively by Tomisawa.[3]

Carbonyl Activation.

The title reagent (**1**) reacts with acyl chlorides to produce 2-acylthio-1-methylpyridinium salts (**2**) as stable hygroscopic solids (eq 1). These may then be treated with a variety of oxygen and nitrogen nucleophiles in the presence of base to effect transfer of the acyl group to the nucleophilic species to produce (**3**) and regenerate (**1**).[4]

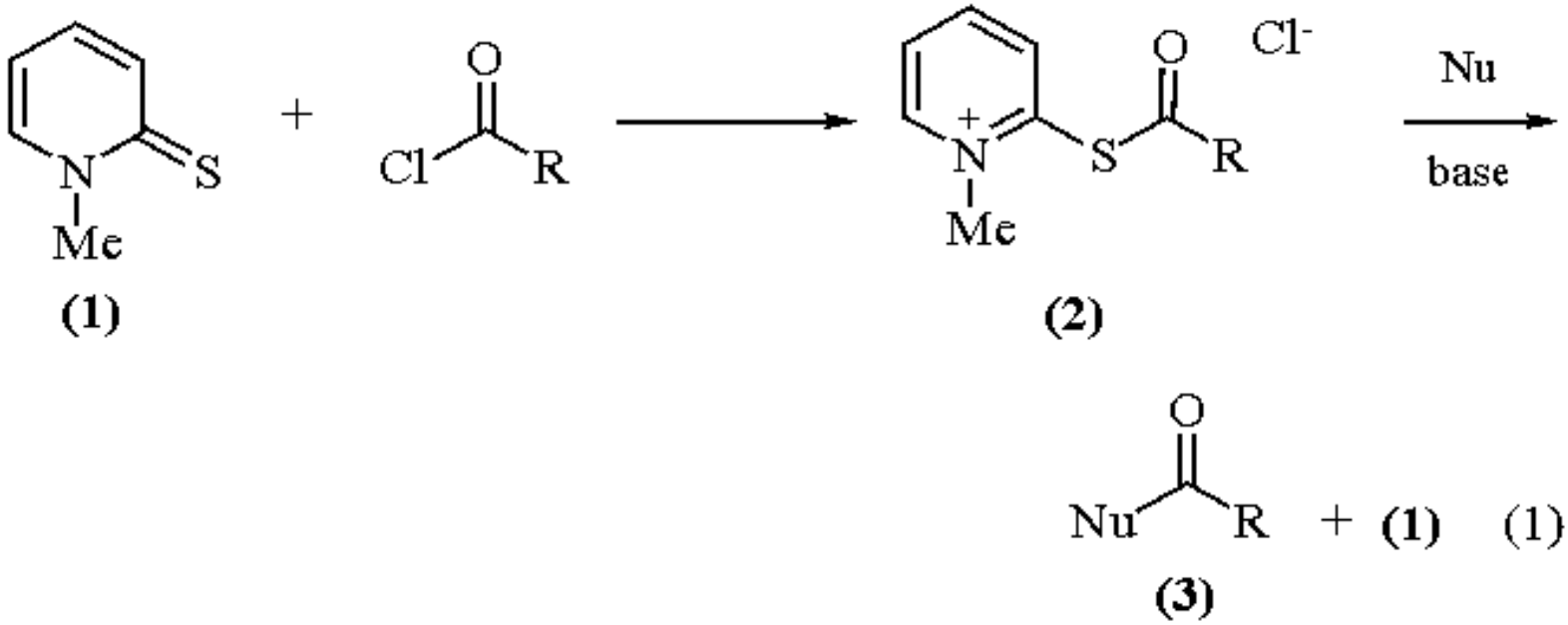

(1)

R = Ph, Me, *i*-Pr, OEt; Nu = primary amines, phenols, carboxylic acids

Sulfur Transfer.

The reagent has been used as a method of producing thiols from halides by alkylation on sulfur followed by hydrolysis.[5] The initial alkylation proceeds best with activated halides such as benzylic halides or α-halo carbonyl compounds, although the conversion of bromocyclohexane to the corresponding thiol occurs in 70% yield. An example (eq 2) shows the compatibility and mildness of the reagent.[6] No β-elimination product was reported.

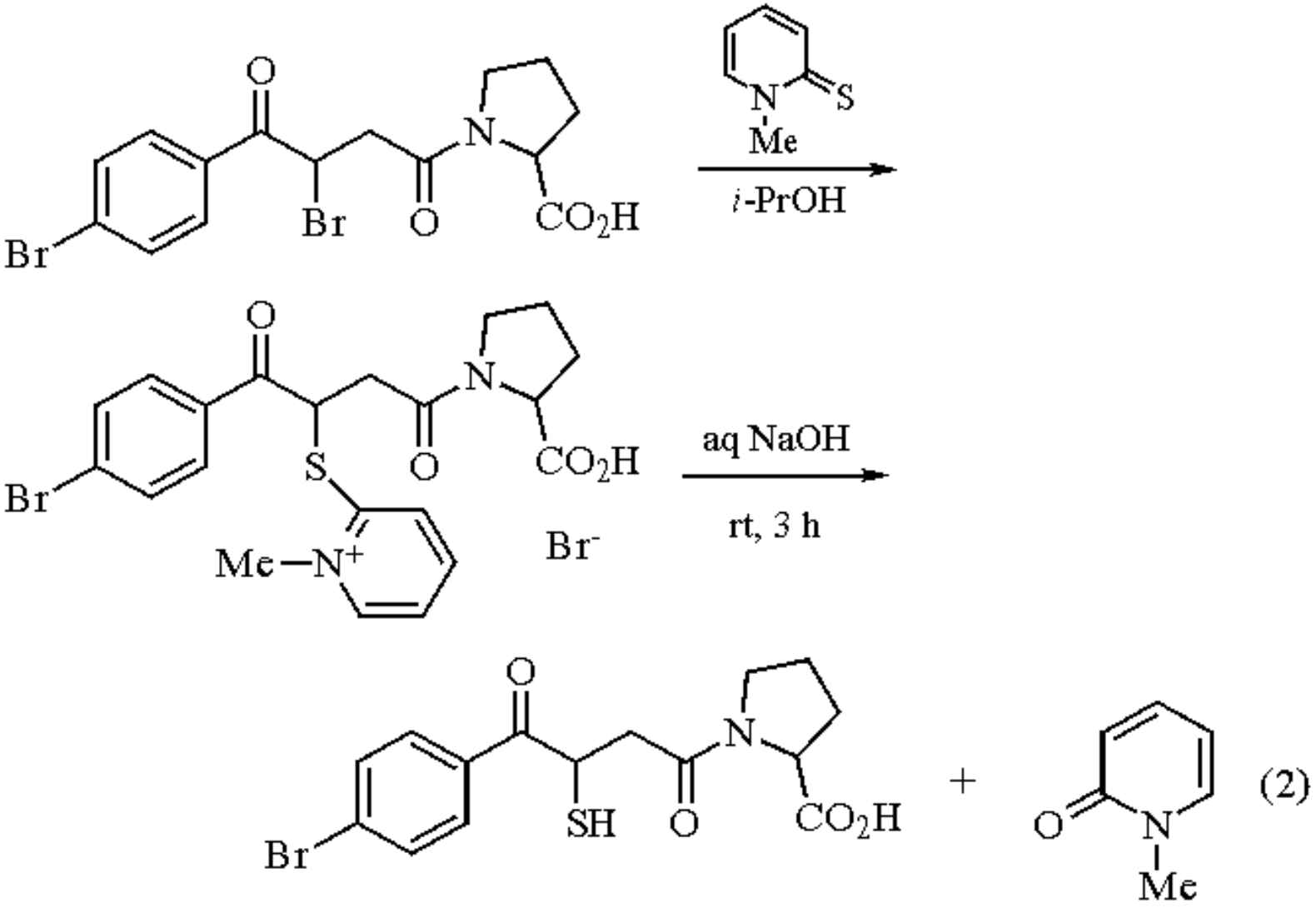

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3. Tomisawa, H.; Wang, C. H. *CPB* **1973**, *21*, 2607 and previous papers in the series.
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N-Methyl-*N*-(2-pyridyl)formamide

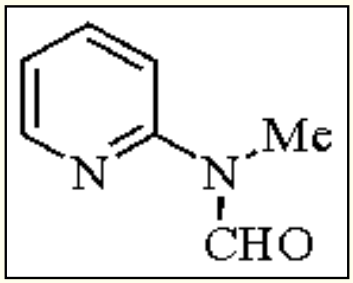

[67242-59-5] · $C_7H_8N_2O$ · *N*-Methyl-*N*-(2-pyridyl)formamide · (MW 136.17)

(formylating reagent for Grignard reagents[1] and certain organolithiums;[6] sequential addition of two Grignard reagents can provide unsymmetrical secondary alcohols[3])

Alternate Name: 2-(*N*-formyl-*N*-methyl)aminopyridine.

Physical Data: bp 71-72 °C/0.05 mmHg; *d* 1.137 g cm^{-3}.

Form Supplied in: colorless liquid; commercially available.

Analysis of Reagent Purity: IR, NMR.

Handling, Storage, and Precautions: moisture sensitive; irritant; should be kept under argon or nitrogen.

General Discussion.

N-Methyl-*N*-(2-pyridyl)formamide (**1**) is a good formylating reagent for certain organometallics. Dropwise addition of Grignard reagents to (**1**) provides good yields of aldehydes (eq 1).[1]

$$\mathrm{RM} \xrightarrow{(1)} \mathrm{RCHO} \qquad (1)$$

$$\mathrm{R = alkyl\ or\ aryl;\ M = MgBr}$$

Various Grignard reagents have been studied and yields are good to excellent. The formylation is effective and facile because of a six-membered chelate complex formed in situ; this inhibits further reaction at low temperature (eq 2).[1,2] On workup with aqueous acid the complex is protonated and dissociates to give the aldehyde and amine salt. The aldehyde is isolated by ether extraction, and the byproduct, 2-(methylamino)pyridine, can be recovered by

neutralization of the aqueous layer with sodium hydroxide and extraction with CH_2Cl_2. The amine can be economically recycled to (**1**) in 90% yield by formylation with a formic acid-acetic anhydride mixture.[3]

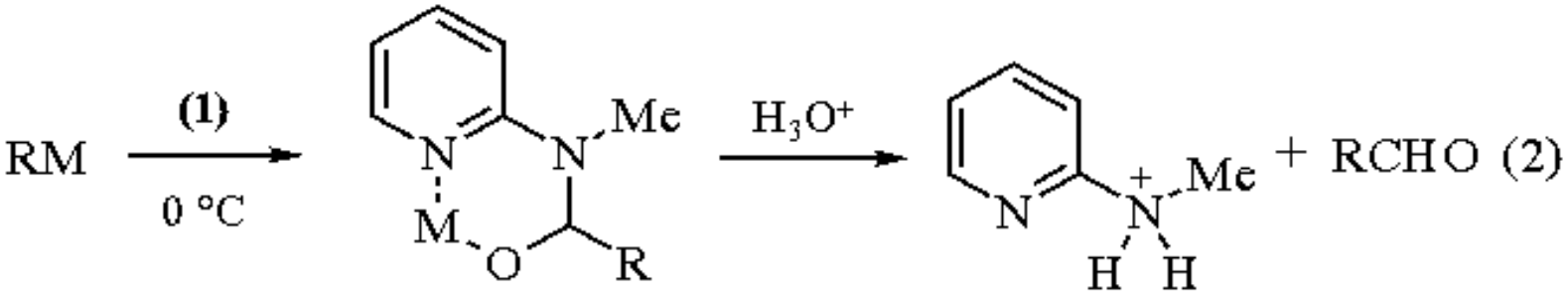

R = alkyl or aryl; M = MgBr

Using a modification of this methodology, unsymmetrical secondary alcohols can be synthesized via a one-pot reaction using two different Grignard reagents (eq 3).[3] Similarly, the vinyl Grignard reagent (**2**) has been formylated using the reagent (**1**) (eq 4).[4]

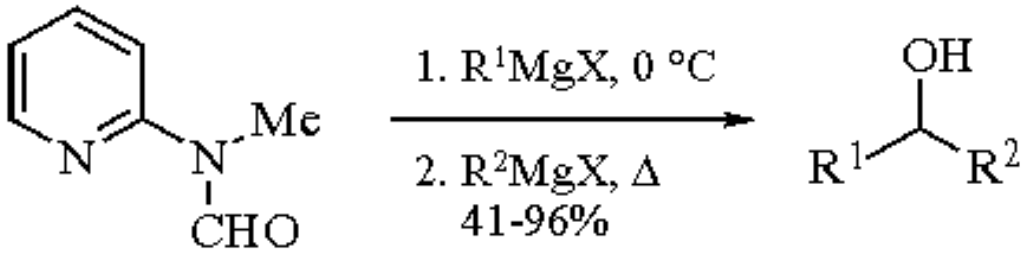

(3)

R^1 = alkyl or aryl; R^2 = alkyl or aryl

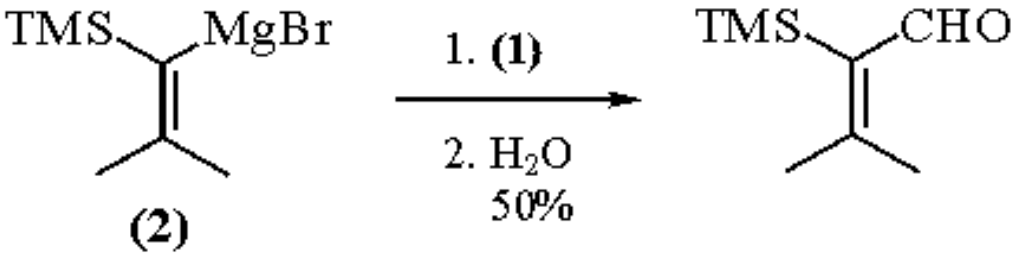

(4)

Using a one-pot reaction, a dithioester has been converted to a protected α-keto carbaldehyde using the reagent (**1**) (eq 5).[5] Heterocycles can be converted to their formyl derivatives by lithiation and reaction with (**1**) (eq 6).[6] The importance of the reagent (**1**) has been demonstrated by its application in natural product synthesis.[7]

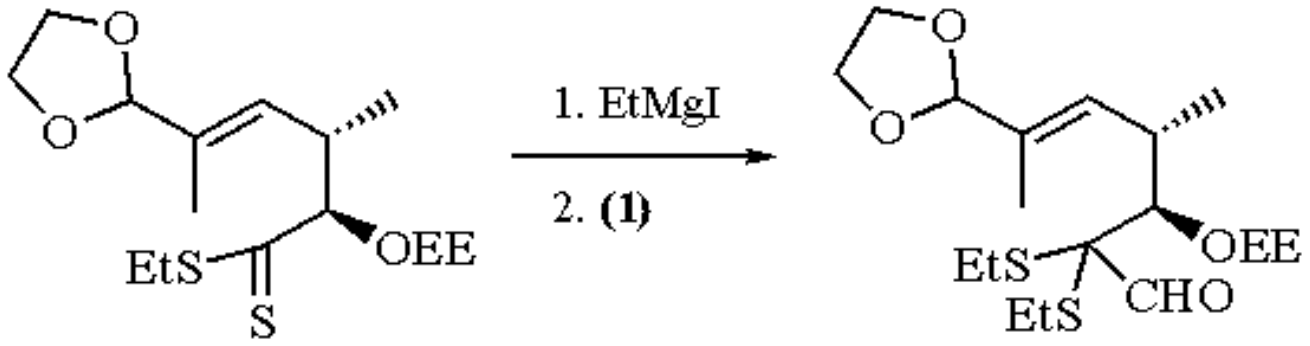

(5)

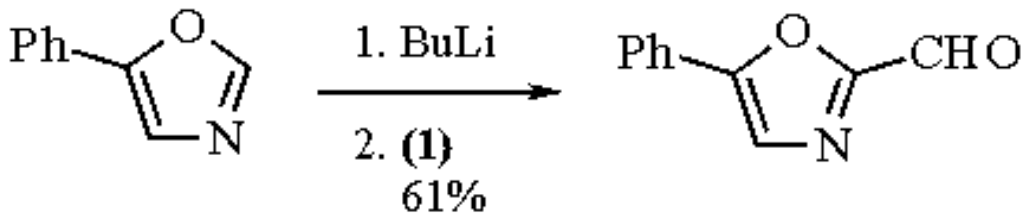

(6)

Related Reagents.

N,N-Dimethylformamide; ***N-Formylpiperidine***; ***N-Methylformanilide***.

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1-Methyl-2-pyrrolidinone[1]

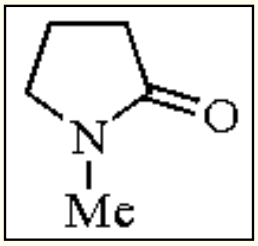

[872-50-4] · C_5H_9NO · 1-Methyl-2-pyrrolidinone · (MW 99.15)

(special solvent;[1] source of enolates[2])

Alternate Names: NMP; *N*-methylpyrrolidone.

Physical Data: mp -24.4 °C; bp 202 °C; *d* 1.030 g cm^{-3}.

Solubility: completely misc H_2O and virtually all organic solvents.

Form Supplied in: colorless liquid. *Drying:* dry over anhydrous K_2CO_3 and anhydrous cerium(IV) sulfate and purify by vacuum distillation through a 50 cm Vigreux column; or distill from CaH_2 and store over 4Å molecular sieves.

Handling, Storage, and Precautions: can be handled safely since it has a high flash point (95 °C), low vapor hazard, high boiling and low freezing points, and good chemical and thermal stability; hydrolyzed by 4% NaOH to the extent of 50-70% in 8 h. The lactam ring is cleaved when exposed to conc HCl for an extended period of time.

Solvent.

NMP is an effective solvent for both inorganic and organic compounds. H-bond basicity in tertiary amides is decreased more by bulky substituents on carbon than by bulky substituents on nitrogen.[3] Thus, the pK_{HB} values for DMF, NMP, and *N*-methyl-2-piperidinone are 2.10, 2.38, and 2.57, respectively. Some measure of the nucleophilicity of NMP is provided by the equilibrium constant for salt formation with trimethylsilyl triflate.[4] The K_{rel} of salt formation decreases in the order: 4-dimethylaminopyridine (32 800) > *N*-methyl-2-pyridone (182) > NMP (1.0) > DMF (0.81) > pyridine (0.10). NMP has advantages over both ***Dimethyl Sulfoxide*** and ***N,N-Dimethylformamide*** for nucleophilic displacement reactions because of its greater stability, and over ***Hexamethylphosphoric Triamide*** because of the lack of adverse physiological properties. NMP has superior properties for several nucleophilic disp lacement reactions:[5] 2- and 4-halo-1,8-naphthalic anhydrides and imides undergo very smooth aromatic substitution with *n*-butylamine, ***Copper(I) Cyanide***, and ***Sodium Methoxide***. The alkylation of lithioalkynes also works exceptionally well in NMP.[5]

Other nucleophilic substitutions have been explored: hydrolysis of halodaunomycinones to adriamycinones,[6] hydrolysis of primary alkyl iodides and bromides to alcohols,[7] and substitution of alkyl iodides and bromides with inorganic Li salts.[1b]

Alkylation of the carbanion from ethyl 6-methylsalicylate *O*-methyl ether[8] has been performed in NMP. The intramolecular nucleophilic displacement of halogen by the carbonyl oxygen of an acylsilane and subsequent cyclization to 2-silyldihydropyrans (eq 1) is accelerated in NMP.[9]

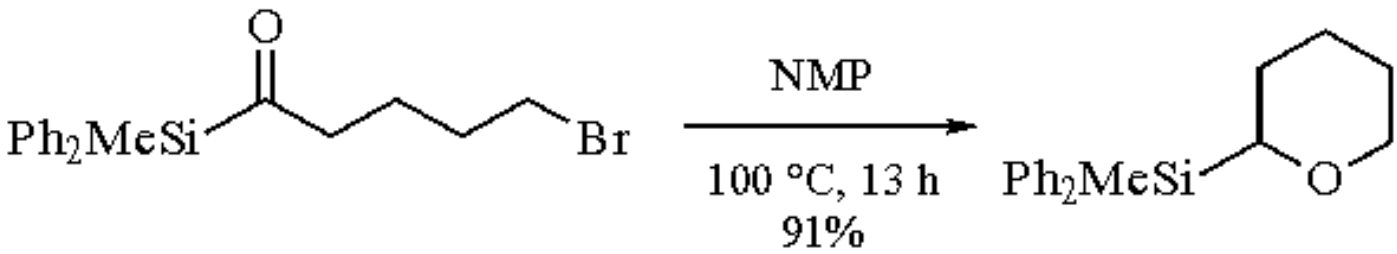

(1)

A simple, safe, and inexpensive synthesis of ***Cyanotrimethylsilane*** has been achieved from ***Chlorotrimethylsilane*** and metal cyanides in NMP (DMF and DMSO are not inert).[10] Some earlier experiments with TMSCN in situ failed. With NMP the product is distilled directly from the pot. The use of NMP raises the yield of the alkynic oxy-Cope rearrangement.[11] The catalytic conversion of ***Methyl Formate*** to ***Acetic Acid*** (eq 2) works best in NMP as solvent, with ***Palladium(II) Acetate*** as catalyst (<1%), and ***Lithium Iodide*** as promoter.[12]

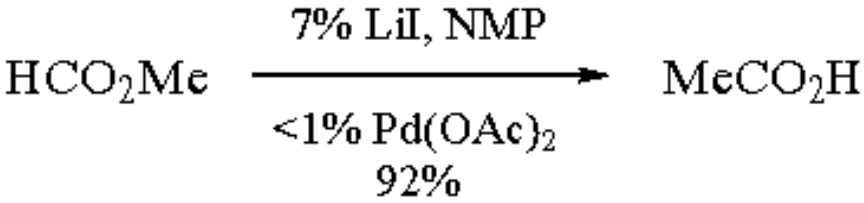

(2)

NMP is also an effective solvent for the decarbonylation of aldehydes. At 110-130 °C in the presence of ***Chlorotris(triphenylphosphine)rhodium(I)***, simple aldoses are converted to the lower alditols. The decarbonylation of sugars has only recently been accomplished, probably for the lack of a compatible solvent.[13] The carbonylation of alkenes (1-decene) to aldehydes by a copper-based catalyst system gives the best yields with $CuCl/PPh_3$/NMP.[14] There are several advantages to using NMP as cosolvent for Cu^{II} catalyzed alkylation of organomanganese chloride reagents. The reactions are easier to perform, no excess of organometallics is required, and higher yields and better selectivity are observed (eq 3).[15]

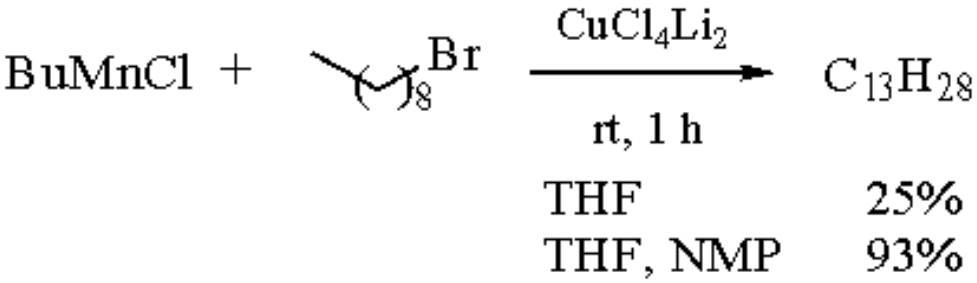

(3)

The reducing power of telluride anion is enhanced in hot NMP.[16] Benzaldehydes and ketones are reduced to the corresponding alcohols (halogens in the molecule are displaced with telluride). Few byproducts are formed, since

Cannizzaro-type disproportionation does not occur. Aromatic nitriles are usually inert to Na_2Te, but in NMP they form 7-deaza-9*H*-purines (eq 4). ***Sodium Telluride*** in NMP is formed at 100-110 °C as a deep purple solution, whereas in DMF it forms a yellow suspension at 140 °C.

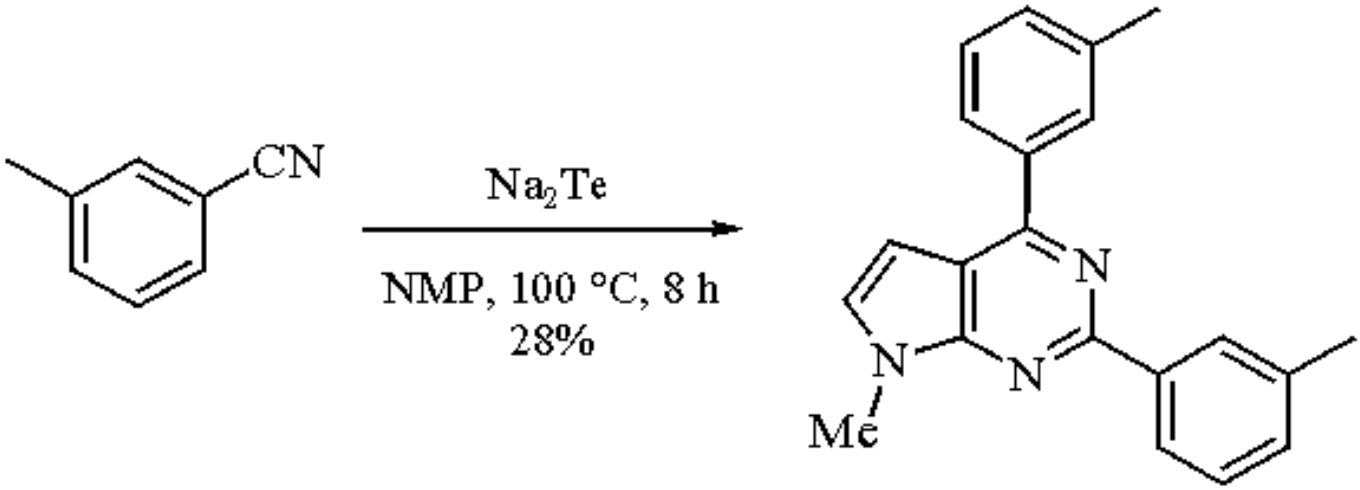

(4)

NMP as a Reagent.

Amidines formed from NMP exist as amidine-enediamine tautomers.[17] *C*-Michael addition leads to functionalized pyrrolidines (eq 5). The stereochemistry of Michael additions of amide or thioamide enolates to α,β-unsaturated ketones has been studied.[2] NMP is a model for an (*E*) lithium enolate (eq 6). Preferential 1,4-addition is observed. Oxo lactams give higher proportions of the *anti*-diastereomers, whereas thiolactams (softer enolates)[18] give mainly the *syn*-diastereomers.[2b] The preference for *syn*-isomers is better seen with K and Na enolates than with the Li analogs.

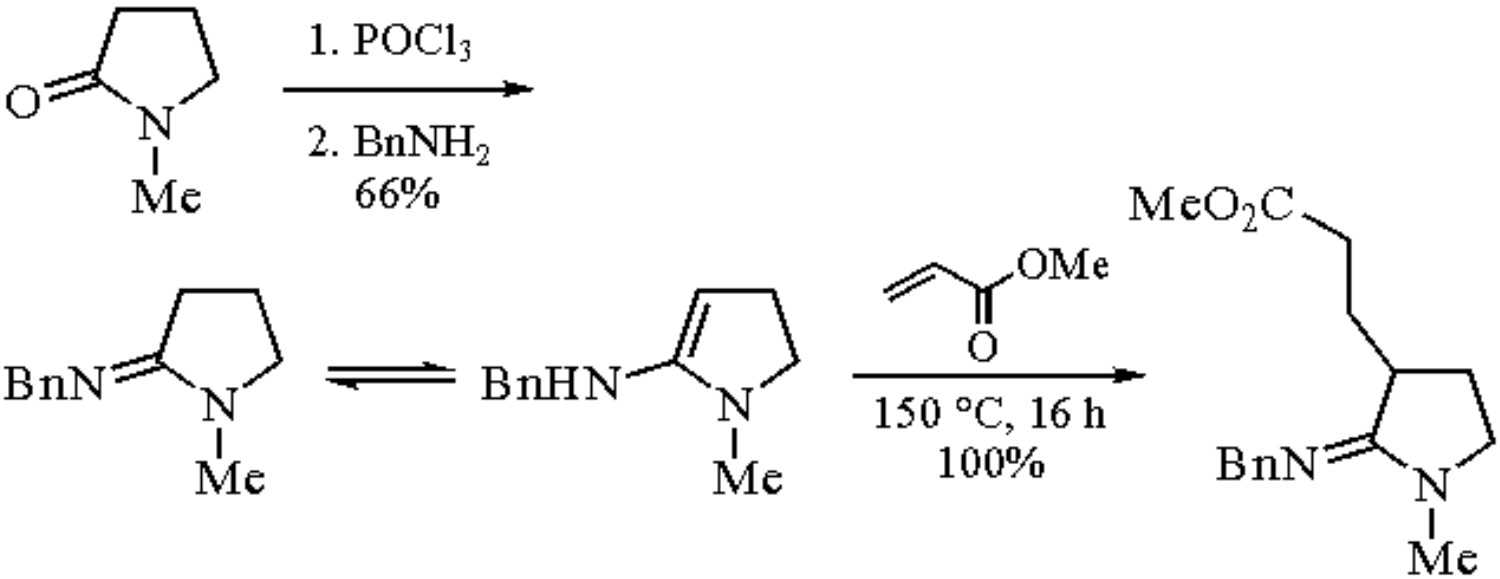

(5)

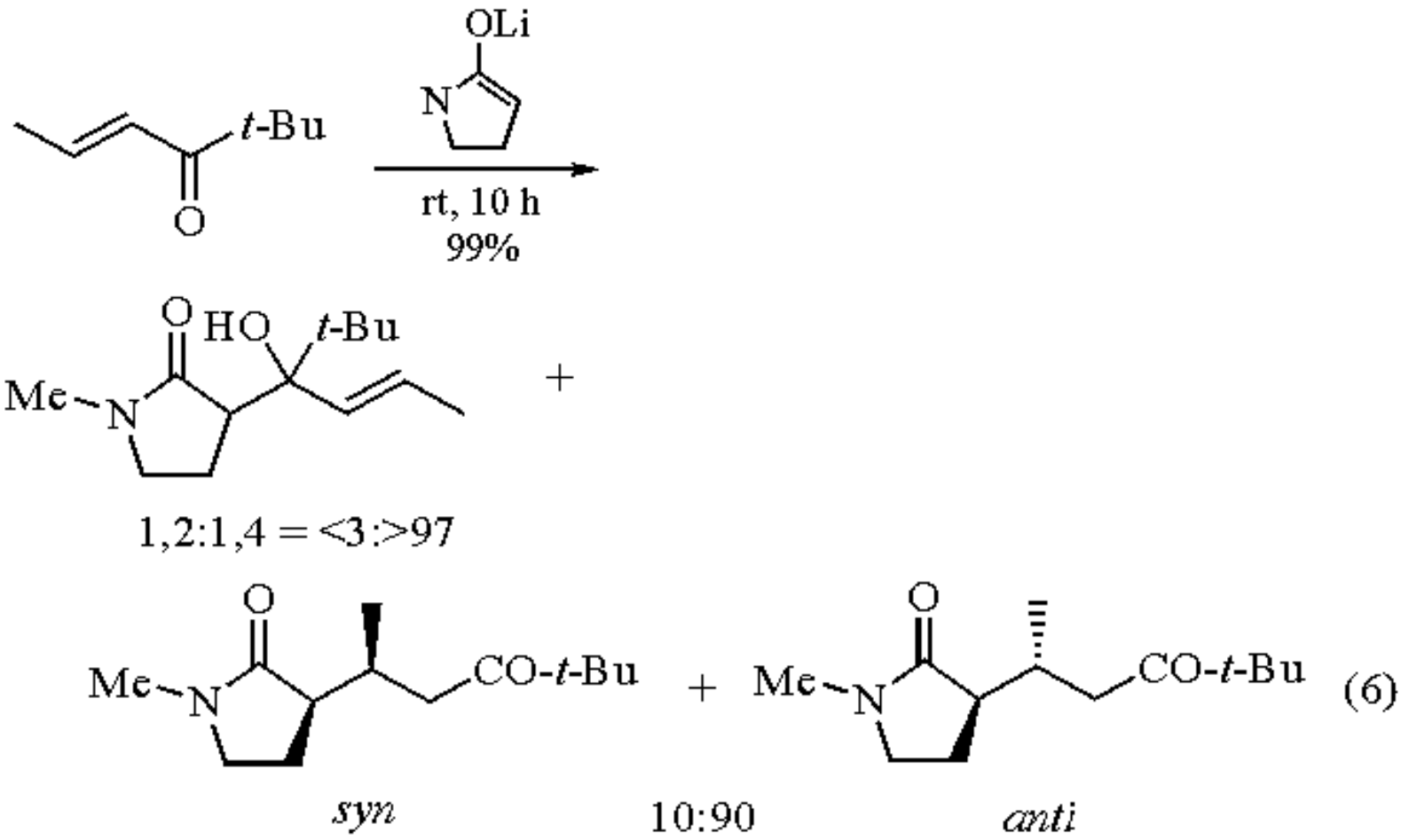

Enamine formation from NMP (unactivated lactam) with various Li reagents has been achieved.[19] The enolate of NMP reacts with many electrophiles to introduce functions into the 3-position of NMP. Thus nitroalkenyl,[20a] bromo,[20b] chloro,[20c] alkyl, allyl,[20a,d] nitro,[20c] and phosphonic acid[20f] derivatives can be formed.

Related Reagents.

N,N´-Dimethylpropyleneurea; ***Dimethyl Sulfoxide***; ***Hexamethylphosphoric Triamide***.

---

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3-Methyl-2-selenoxobenzothiazole

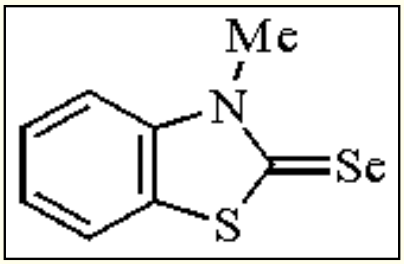

[2786-43-8] · C_8H_7NSSe · 3-Methyl-2-selenoxobenzothiazole · (MW 228.19)

(stereospecifically converts epoxides and episulfides into alkenes[1])

Physical Data: mp 114-116 °C.

Solubility: sol acetone, CH_2Cl_2, THF; slightly sol ether, ethanol; insol H_2O.

Form Supplied in: red solid; commercially available.

Handling, Storage, and Precautions: toxic; light sensitive; store in a dark glass bottle.

General Discussion.

The title reagent (**1**) reacts with epoxides in CH_2Cl_2 in the presence of stoichiometric quantities of ***Trifluoroacetic Acid*** at 0 °C to give the corresponding alkenes almost quantitatively. The method is rapid and stereospecific, proceeding in a fashion that preserves the stereochemistry of the starting epoxide (eq 1).[1] Episulfides react under the same conditions, though slowly, to afford alkenes stereospecifically (eq 2).[1] Another feature of these reactions is the quantitative recovery of selenium, which may be reused in the synthesis of the reagent.

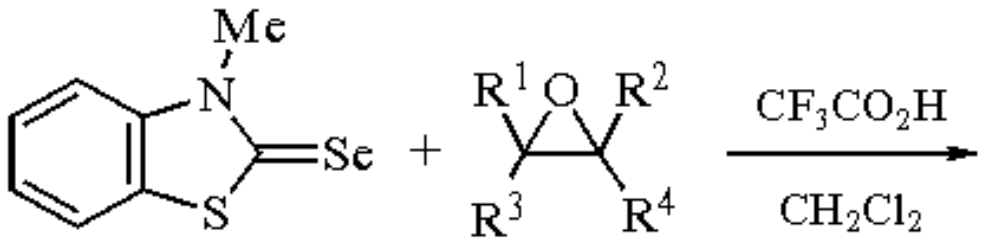

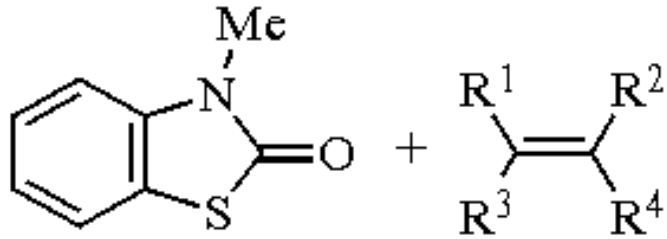

(1)

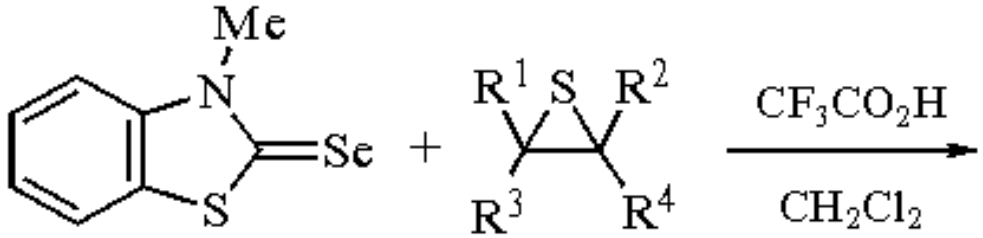

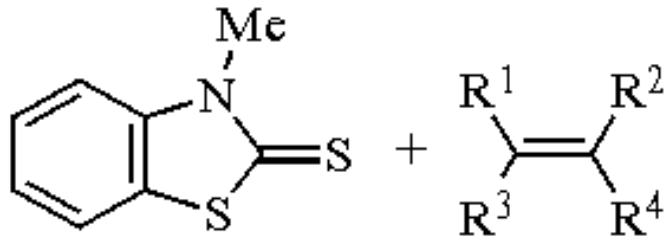

(2)

The mildness of the reaction conditions allows the deoxygenation of epoxides bearing other functionalities, e.g. sugar epoxides (eq 3),[2] for which other reagents such as diphenylsilyllithium[3] or lithium diphenylphosphide[4] cannot be used. In some cases, the deoxygenation occurs with rearrangement (eq 4).[2]

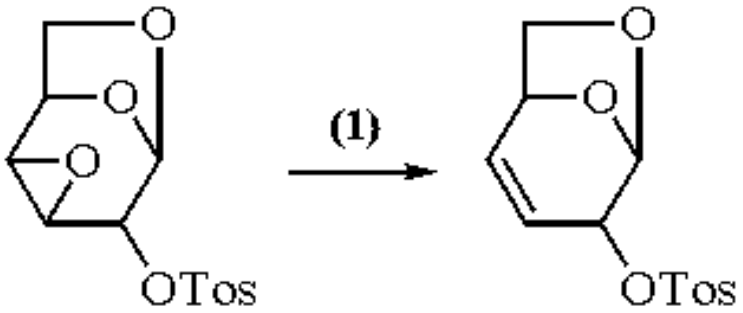

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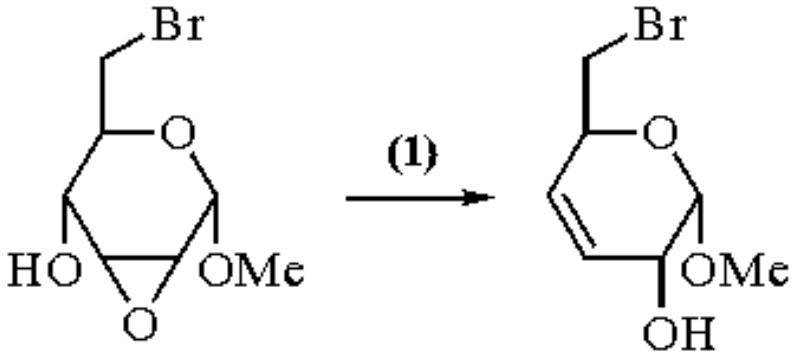

(4)

The synthesis of valienamicin, a branched-chain amino cyclitol, requires a mild deoxygenation of epoxy cyclitol intermediates; this can be accomplished using (**1**) (eq 5).[5]

The reagent has also been used for deoxygenation of sterically crowded epoxides to give bicyclic trienes (eq 6).[6]

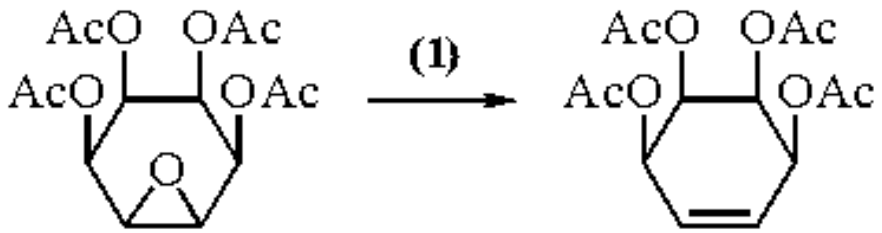

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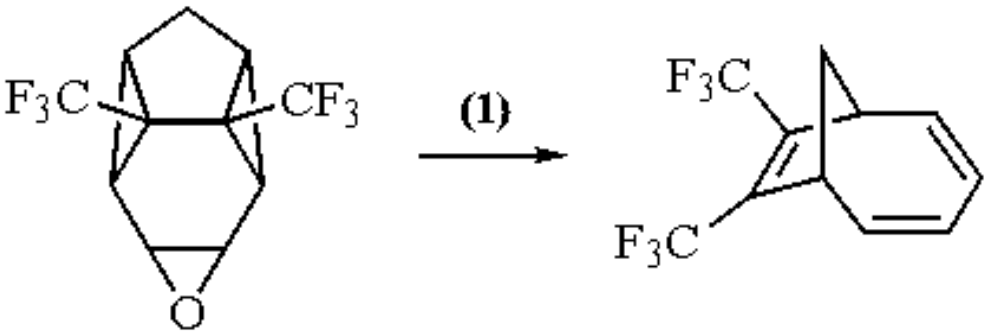

(6)

The related compound 3-methylbenzothiazole-2-thione (**2**) [*2254-94-6*] (mp 91-92 °C, also commercially available) converts epoxides to episulfides stereospecifically under the reaction conditions used for reagent (**1**) (eq 7).[7]

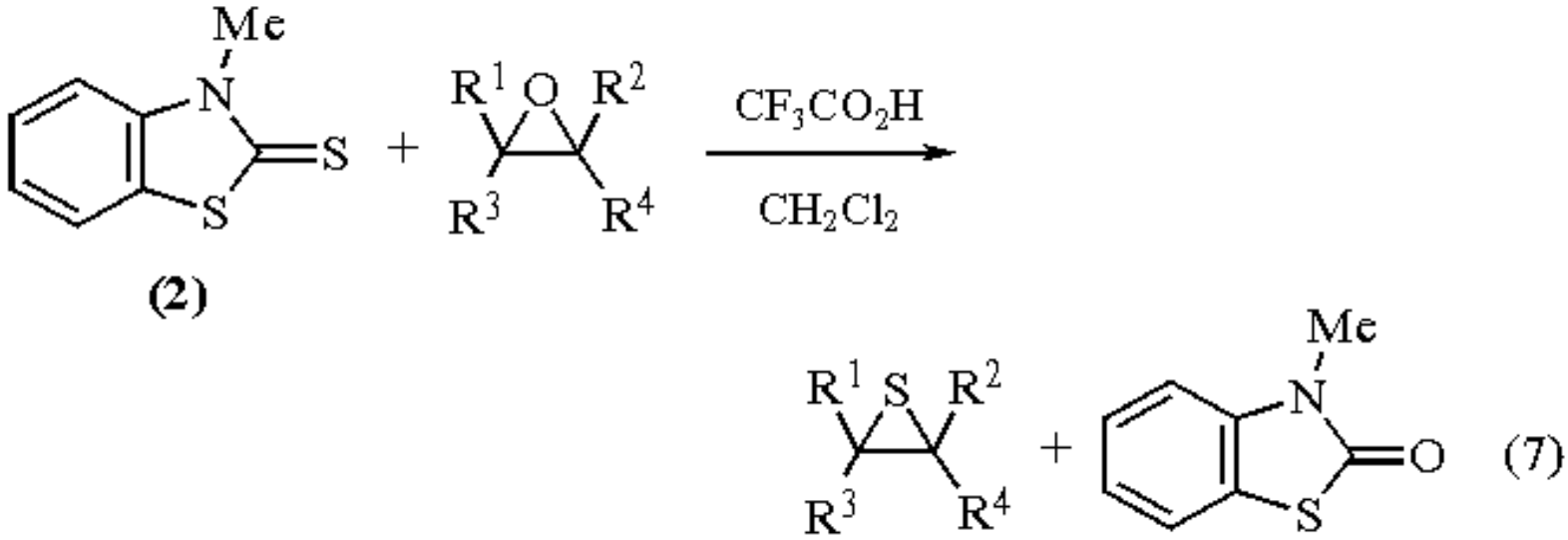

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1. Caló, V.; Lopez, L.; Mincuzzi, A.; Pesce, G. *S* **1976**, 200.
2. Paulsen, H.; Heiker, F. R.; Feldmann, J.; Heyns, K. *S* **1980**, 636.
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Vincenzo Caló

University of Bari, Italy

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Methylsulfenyl Trifluoromethanesulfonate

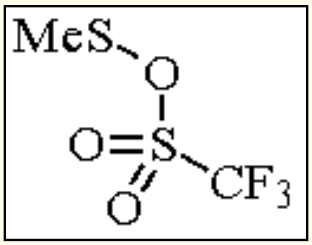

[59259-48-2] · $C_2H_3F_3O_3S_2$ · Methylsulfenyl Trifluoromethanesulfonate · (MW 196.19)

(activator for formation of glycosidic linkages)

Solubility: prepared and used in 1,2-dichloroethane,[1] acetonitrile, or CH_2Cl_2.[1,2]

Form Supplied in: prepared and utilized in situ; no characterization is reported and the compound is not commercially available from the main chemical suppliers.

Preparative Methods: prepared by injecting methylsulfenyl bromide into a light-protected flask containing ***Silver(I) Trifluoromethanesulfonate*** dispersed in dry 1,2-dichloroethane. The resulting supernatant liquid is removed by syringe from the precipitated solids and utilized immediately. Alternatively, the reagent may be generated in situ by addition of methanesulfenyl bromide to a mixture of substrates and silver triflate in the presence of powdered 4Å molecular sieves.

Methylsulfenyl trifluoromethanesulfonate (**1**) is an activator in the thioglycoside-mediated formation of glycosidic linkages.[1-4] (**1**) mediates 1,2-*trans* glycosidation of thioglycosides (**2**) (eq 1) by providing a superior source of the sulfenyl cation; in the absence of silver triflate, sulfenyl bromides are not glycosidation mediators.[1]

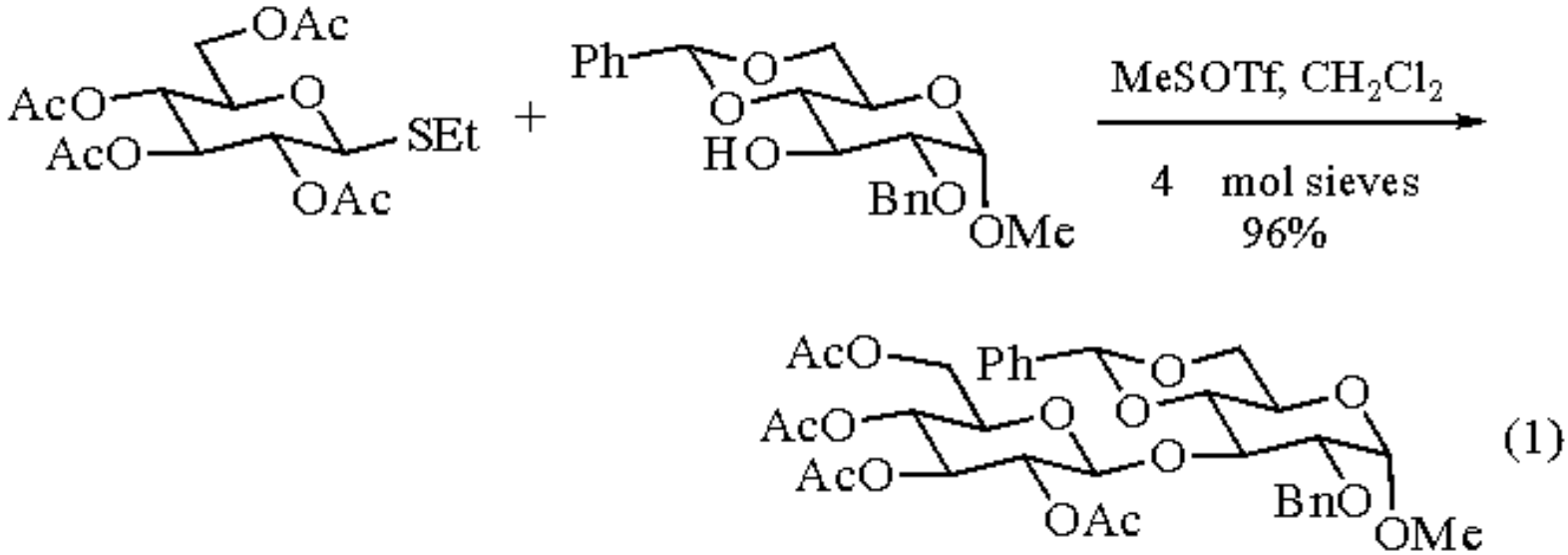

Sialosides may be prepared efficiently using (**1**) (eq 2).[3,4] The high reactivity of (**1**) allows reaction at low temperature, which is essential to minimize side reactions. Trisaccharides may also be prepared in high yield by a similar method.[5] In these reactions, the use of a hindered amine base (such as ***Diisopropylamine***) prevents the formation of methylthioacetamides.

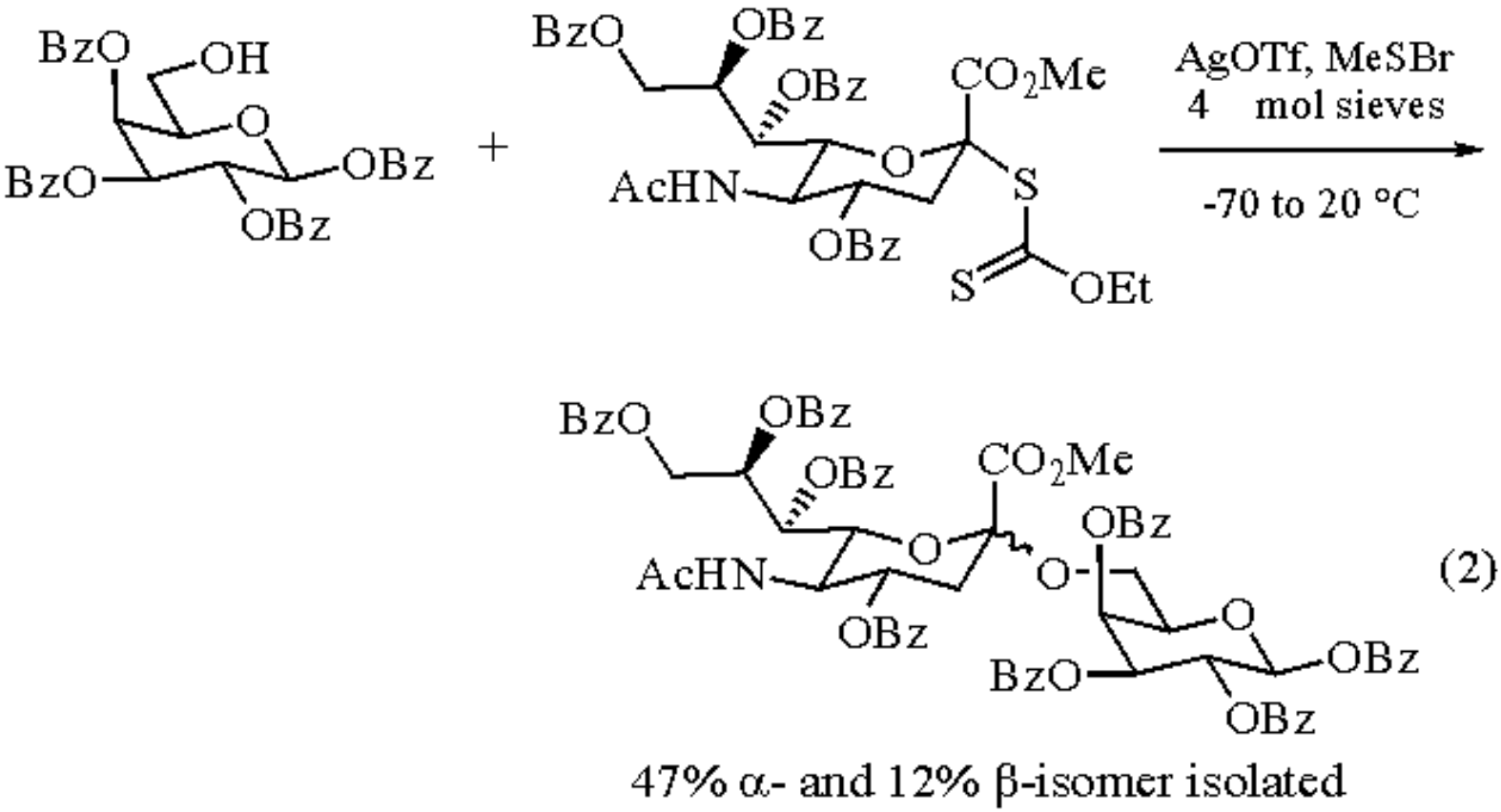

The same amine-modified activation process allows preparation of intermediates (**3**) crucial to the synthesis of highly complex ganglioside lactones such as GM_3 (eq 3).[6]

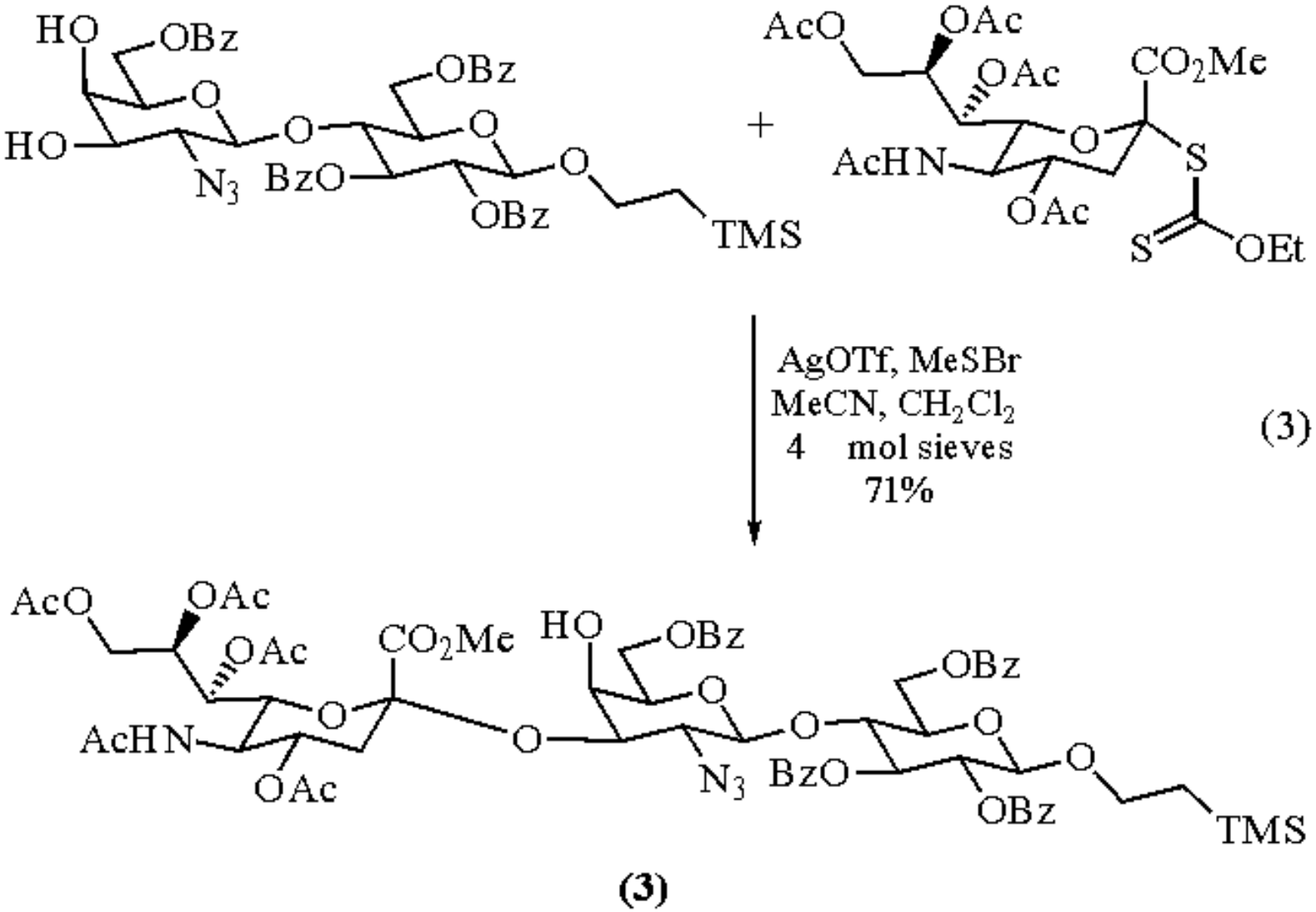

1. Dasgupta, F.; Garegg, P. *J. Carbohydr. Res.* **1988**, *177*, C13.
2. Dasgupta, F.; Garegg, P. *J. Carbohydr. Res.* **1990**, *202*, 225.
3. Birberg, W.; Löhn, H. *TL* **1991**, *32*, 7453.
4. Birberg, W.; Löhn, H. *TL* **1991**, *32*, 7457.
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6. Ray, A. K.; Nilsson, U.; Magnusson, G. *JACS* **1992**, *114*, 2256.

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University of Bristol, UK

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(+)-(*S*)-*N*-Methylsulfonylphenylalanyl Chloride

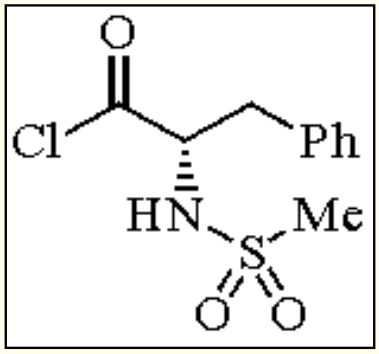

[63640-54-0] · $C_{10}H_{12}ClNO_3S$ · (+)-(*S*)-*N*-Methylsulfonylphenylalanyl Chloride · (MW 261.75)

(chiral reagent for the resolution of racemic alcohols via separation of the corresponding diastereomeric esters[1])

Physical Data: mp 84-85 °C; [α]20D +4.3° (*c* 1.6, THF).

Solubility: readily sol THF, benzene, ether.

Form Supplied in: pale yellow needles; not available commercially.

Preparative Method: prepared from (*S*)-phenylalanine by reaction with ***Methanesulfonyl Chloride***, followed by ***Phosphorus(V) Chloride***.[1b]

Purification: the crude compound can be recrystallized from hexane/ether.

Handling, Storage, and Precautions: best if prepared immediately prior to use. Can be stored at 0 °C under nitrogen for several days without appreciable decomposition.

Introduction.

Enantiomerically pure alcohols can frequently be obtained by physical separation of the diastereomeric esters prepared from the racemic alcohols and chiral acids.[2] Chiral acids that have been successfully employed for this purpose and are available in either enantiomeric form include o-camphanic acid[3] and the monomethyl ester of diacetyltartaric acid.[4] No reagent can be considered generally applicable to all alcohols, since the ease of separation of the diastereomeric esters frequently depends on their crystallinity and/or chromatographic properties. A successful resolution is frequently the result of multiple trials and errors with a variety of acids.

N-Sulfonylated α-Amino Acids.

N-Protected derivatives of the natural α-amino acids offer a wide range of potential derivatizing agents.[5] Particularly useful are *N*-arylsulfonyl-α-amino acids,[6] many of which are commercially available and produce crystalline ester mixtures from which pure diastereomers can often be isolated by recrystallization. *N*-Methylsulfonyl-α-amino acids or the corresponding acid chlorides are generally not commercially available, but in some cases have been shown to be superior to the corresponding *N*-tosyl derivatives (eq 1).[1b,7]

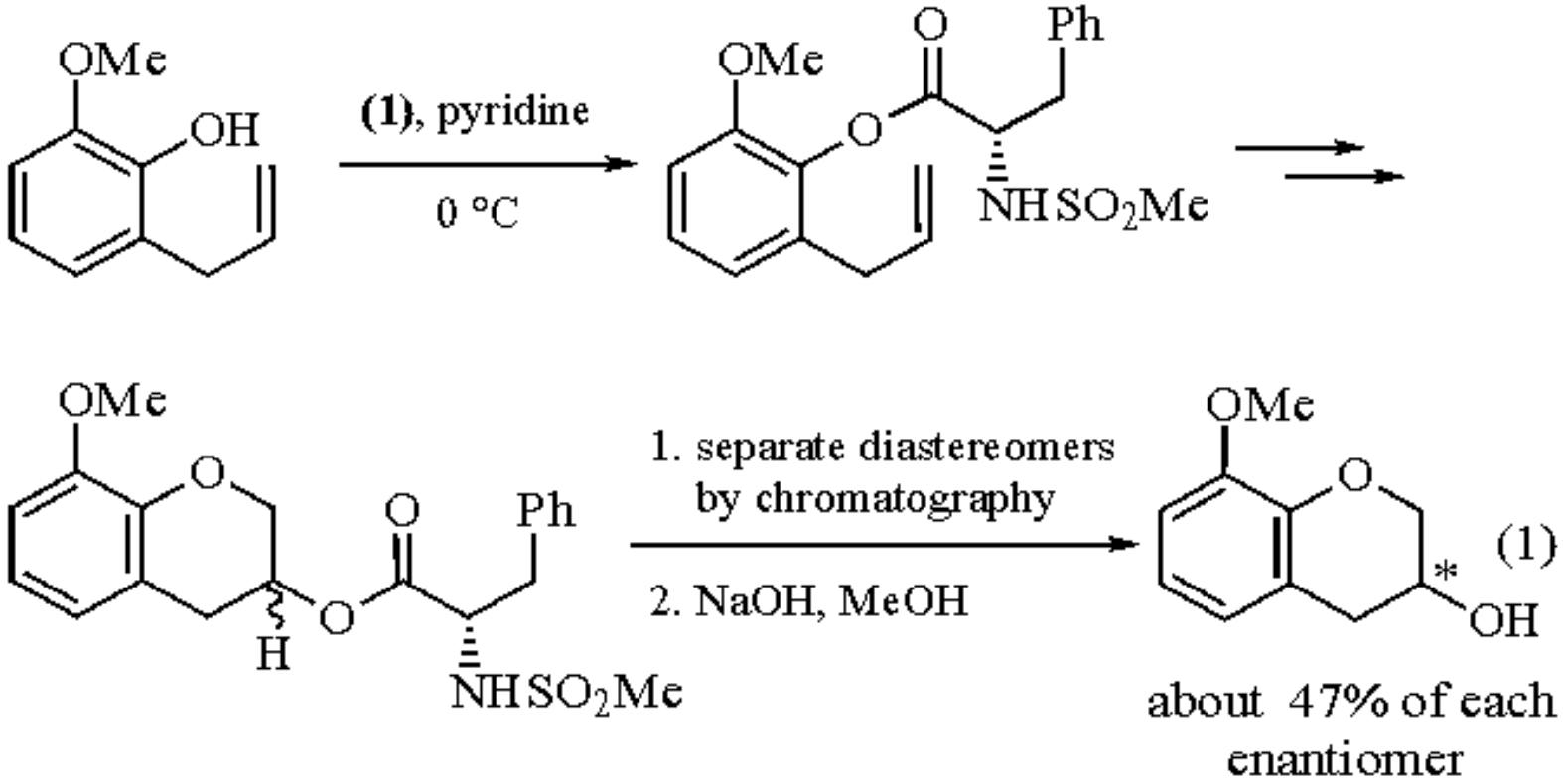

N-Methylsulfonylphenylalanyl chloride (**1**) is particularly useful in the derivatization of *meso*-diols. Mixtures of diastereomeric monoesters can be obtained, from which pure diastereomers are usually isolated by fractional recrystallization and/or chromatography. Chemical transformation of the free hydroxy group, followed by removal of the chiral auxiliary, allows the selective transformation of each prochiral hydroxy group. Isolation of the other diastereomeric ester from the mother liquors, followed by a series of protection-deprotection steps, provides the flexibility of converting 100% of the *meso*-material into one single enantiomer of the product. Alternatively, by rearranging the order of the chemical transformations, both enantiomers of the product can be obtained (eqs 2 and 3).[1,8]

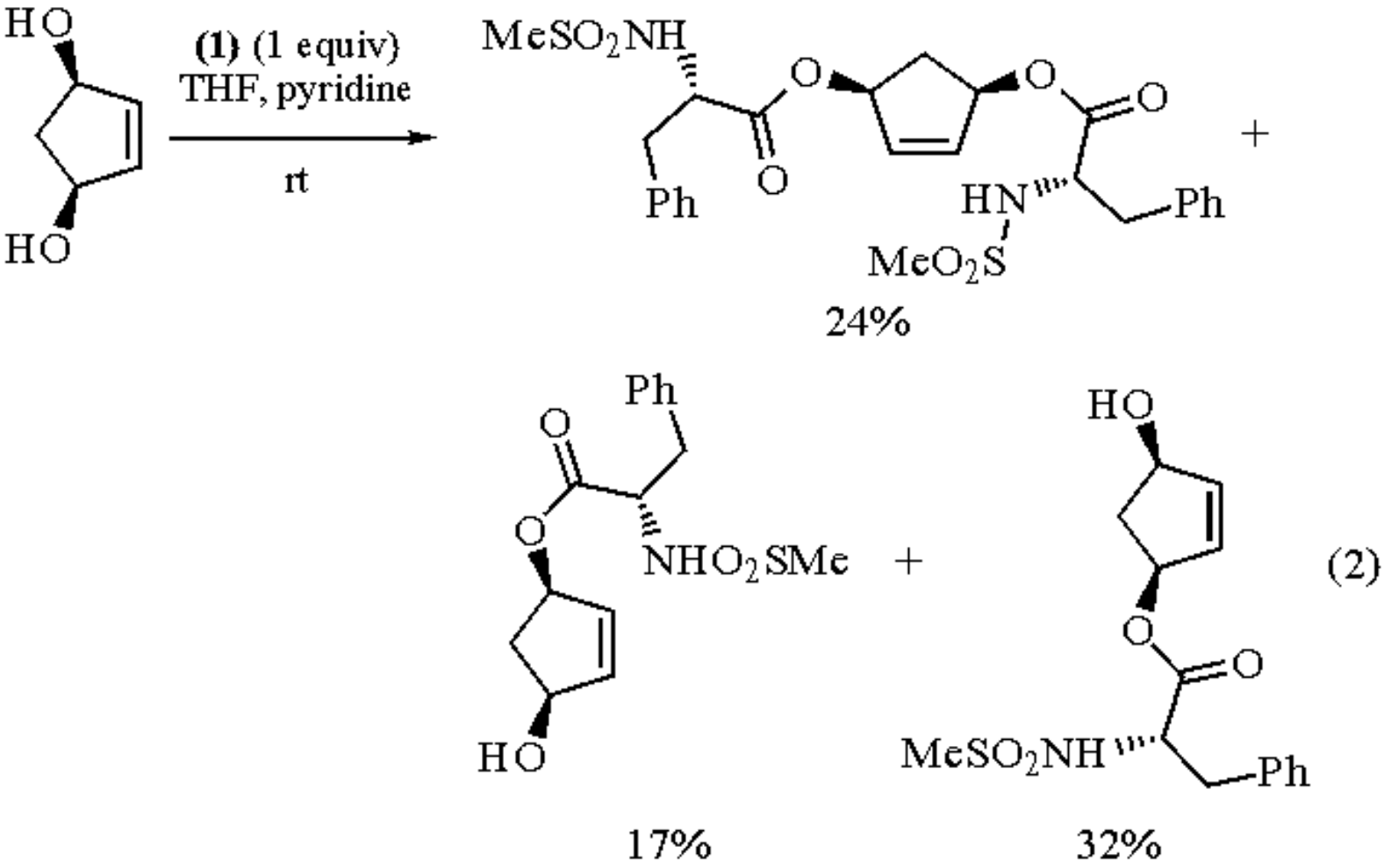
HO
HO
(1) (1 equiv)
THF, pyridine
rt
MeSO2NH
O
O
O
O
Ph
HN
Ph
MeO2S
24%
+
Ph
O
O
NHO2SMe
HO
17%
+
HO
O
O
MeSO2NH
Ph
32%
(2)

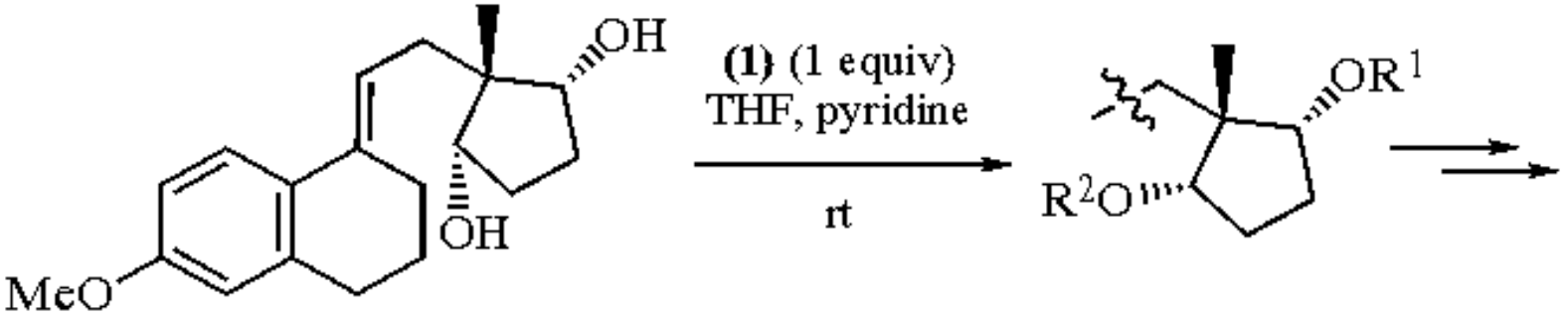

$R^1 = (S)\text{-PhCH}_2\text{CH(NHSO}_2\text{Me)CO};\ R^2 = \text{H};\ 22\%$
$R^1 = \text{H};\ R^2 = (S)\text{-PhCH}_2\text{CH(NHSO}_2\text{Me)CO};\ 19\%$
$R^1 = R^2 = (S)\text{-PhCH}_2\text{CH(NHSO}_2\text{Me)CO};\ 23\%$

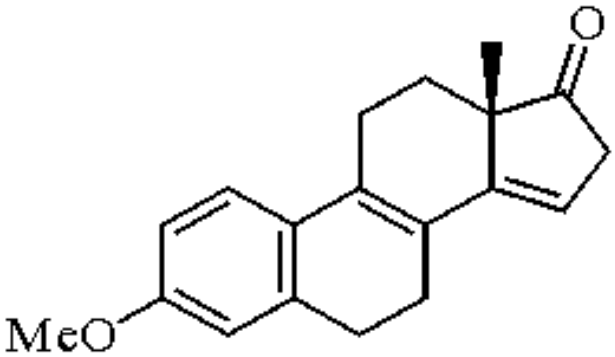

(3)

100% ee

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1. (a) Terashima, S.; Yamada, S. *TL* **1977**, 1001. (b) Nara, M.; Terashima, S.; Yamada, S. *T* **1980**, *36*, 3161.
2. *Enantiomers, Racemates and Resolutions*; Jacques, J.; Collet, A.; Wilen, S. H., Eds.; Wiley: New York, 1981; pp 332-335.
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Juan C. Jaen

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2-Methyl-2-thiazoline

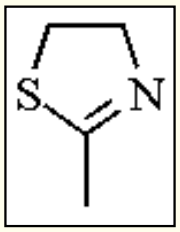

[2346-00-1] · C_4H_7NS · 2-Methyl-2-thiazoline · (MW 101.19)

(lithiation produces an acetaldehyde enolate equivalent for synthesis of mono-, di-, and trisubstituted acetaldehydes,[1,2] β-hydroxy aldehydes,[3] homoallylic alcohols,[3] and α,α-disubstituted β-ethylenic methyl ketones[4])

Alternate Name: 4,5-dihydro-2-methylthiazole.

Physical Data: bp 144.5-145 °C; *d* 1.067 g cm^{-3}.

Form Supplied in: commercially available.

Handling, Storage, and Precautions: no special precautions are warranted. Use in a fume hood.

General Discussion.

2-Methyl-2-thiazoline functions as a latent acetaldehyde equivalent. Lithiation with ***n-Butyllithium*** occurs at -78 °C to produce the thiazoline anion, which can be alkylated with a variety of electrophiles. Reductive hydrolysis of the thiazoline ring then releases the free monoalkylated acetaldehyde (eq 1).[2] Some examples of this methodology are given in Table 1.[2,5] Neutral conditions are employed (***Aluminum Amalgam***/***Mercury(II) Chloride***) for the release of the substituted acetaldehyde. ***Sodium Cyanoborohydride*** in MeOH/TsOH has been utilized instead of Al(Hg) for the reduction of the thiazoline ring to the thiazolidine ring.[6] A variety of methods have been used to convert the thiazolidines to aldehydes (e.g. I_2, MeOH).[7]

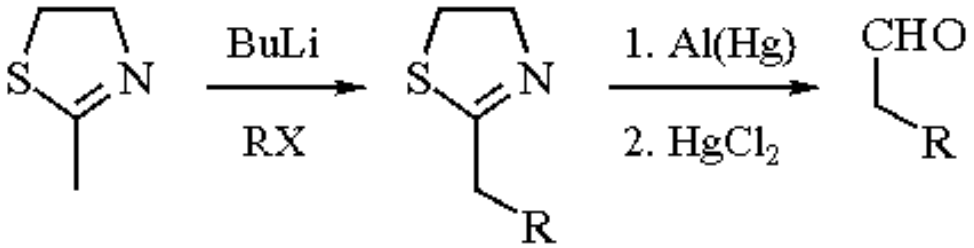

(1)

Table 1 Monosubstituted Acetaldehyde Formation

RX	Product	Yield (%)
		56
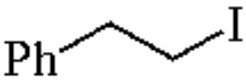		53
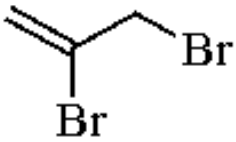	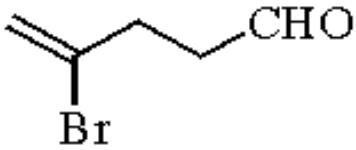	37
		77
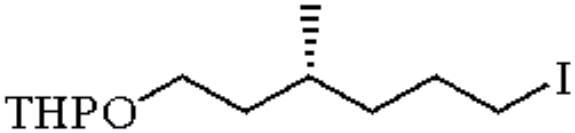	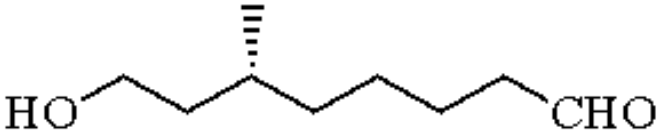	50

If the initially alkylated thiazoline is again metalated and alkylated, dialkylated acetaldehydes are formed (eqs 2-4).[2] Repeating this process (with ***Lithium Diisopropylamide*** as the base) results in trialkylated acetaldehydes (eq 5).[2]

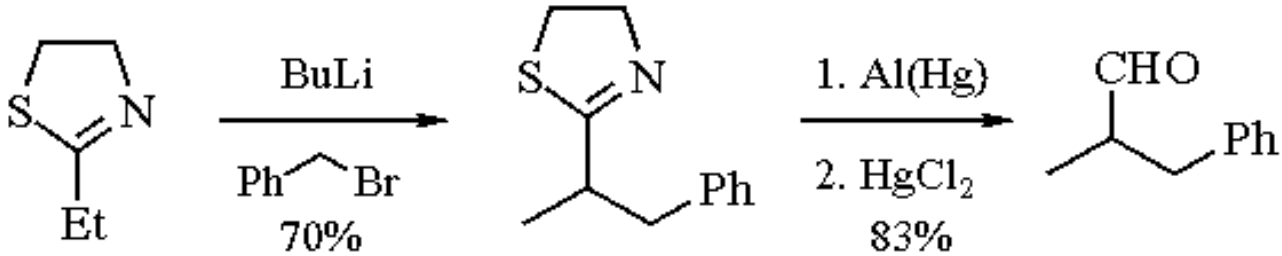

(2)

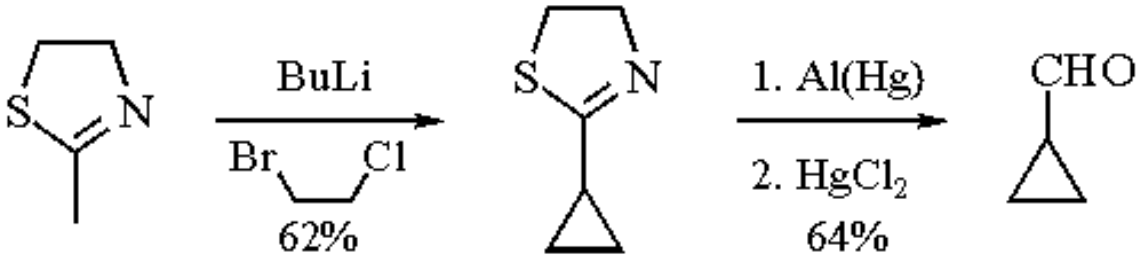

(3)

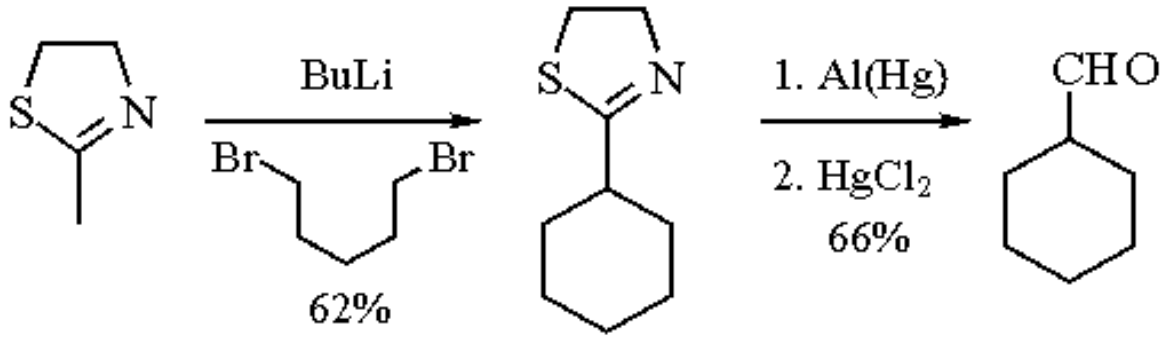

(4)

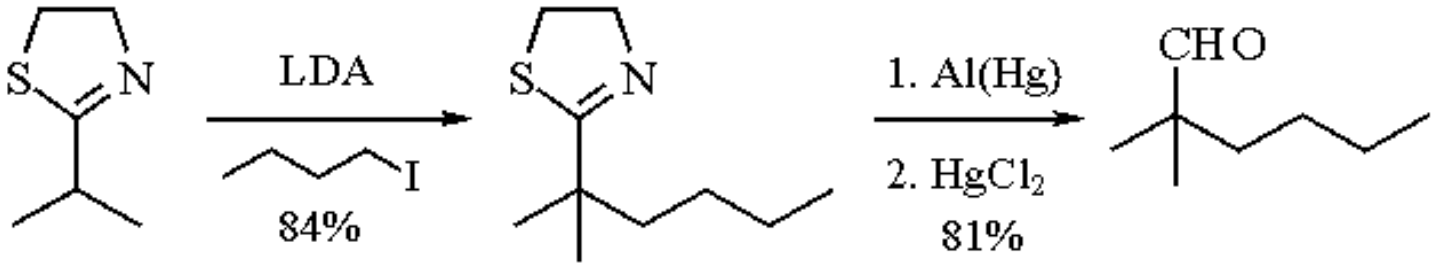

(5)

Deuterated aldehydes are formed when the aluminum amalgam reduction is conducted in the presence of D_2O (eq 6).[2]

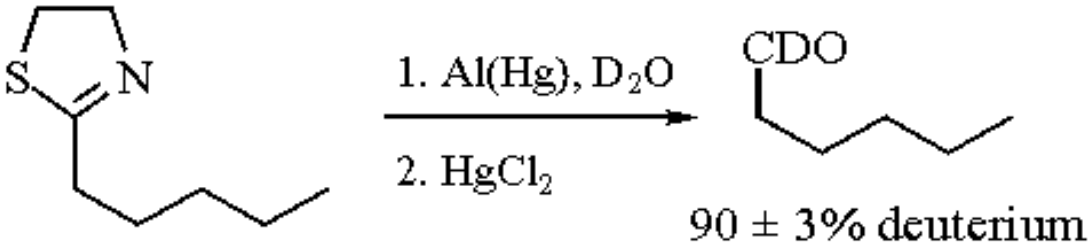

(6)

Treatment of 2-aminoethanethiol with alkyl cyanides results in cyclization to the corresponding thiazolines, which can take part in the above outlined protocol. For example, enantiomerically pure (+)-(*S*)-3-methylpentanenitrile can be converted to the thiazoline in 60% yield (eq 7).[8] Metalation and reaction with 2-iodomethyl-1,3-dioxolane affords the alkylated product in 68% yield. This differentially protected dialdehyde can be selectively deprotected.

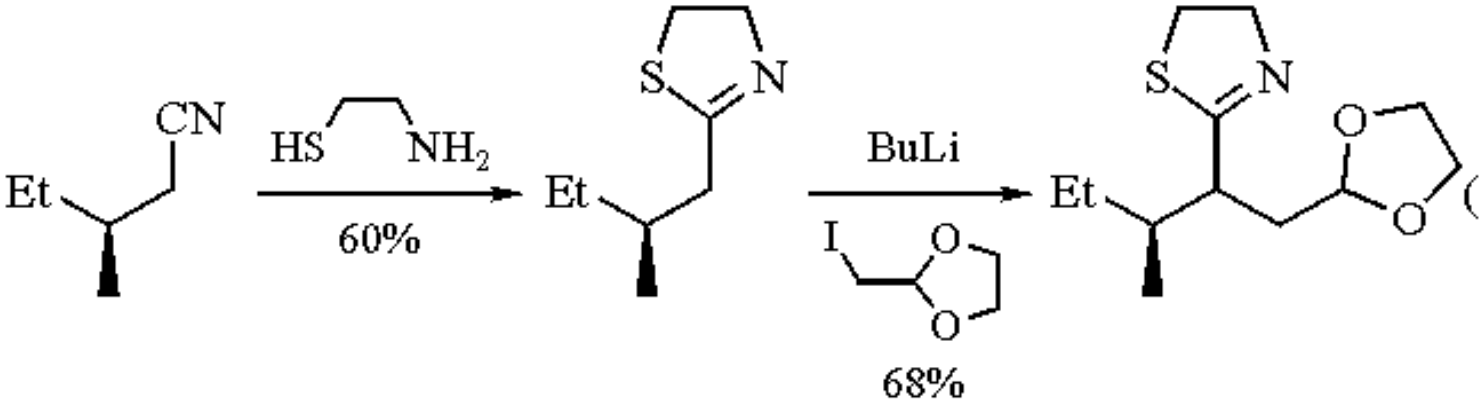

(7)

Addition of the lithio salt of the title reagent to nitriles forms the corresponding enamino thiazoline which can, in principle, be hydrolyzed to β-keto aldehydes (eq 8).[9]

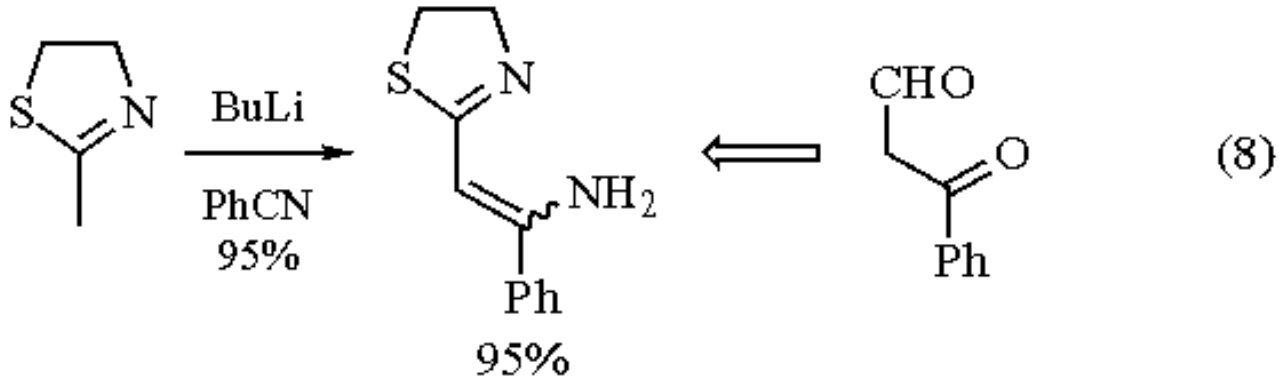

The lithio anion of 2-methyl-2-thiazoline undergoes 1,2-carbonyl addition to aldehydes and ketones.[3] Aldehyde liberation from the thiazoline then results in the corresponding β-hydroxy aldehydes (eq 9).

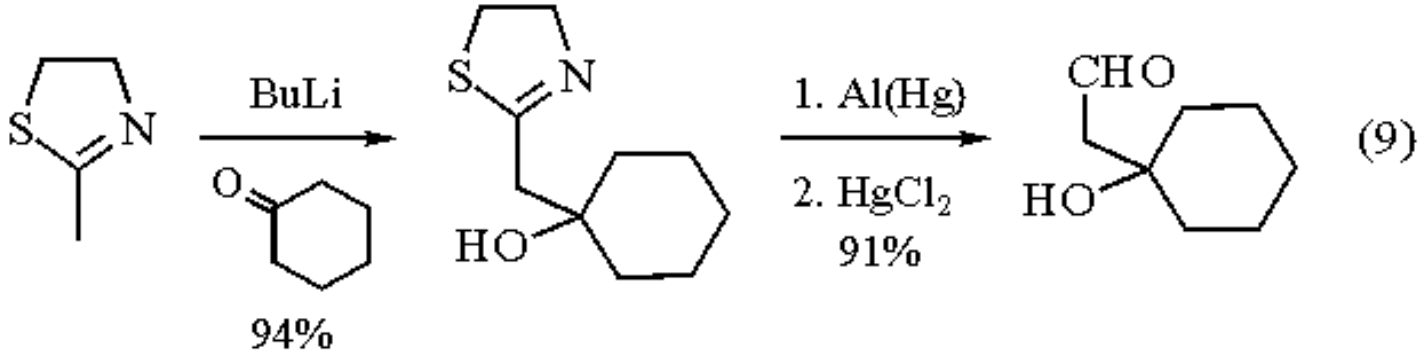

Due to the instability of β-hydroxy aldehydes, in situ methoxymethylation with ***Chloromethyl Methyl Ether*** (MOMCl) is necessary immediately after nucleophilic addition to the carbonyl carbon (eq 10).[3] The MOM group is resistant to the thiazoline cleavage conditions (i.e. Al(Hg) and $HgCl_2$).

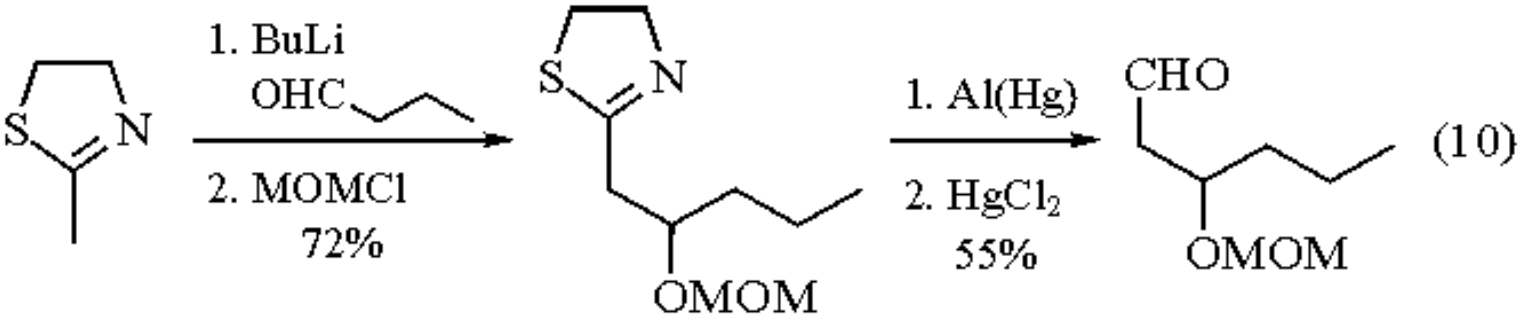

These protected β-hydroxy aldehydes can be conveniently transformed into homoallylic alcohols by treatment with a Wittig reagent and then subsequent alcohol deprotection.[3] 2-Methyl-2-thiazoline has also successfully formed adducts with electrophilic species such as α-oxo ketene dithioacetals,[10] isotopically labeled alkyl halides,[11] and hydroxamates.[12]

1,2-Addition of allylic Grignard reagents to the imine double bond of 2-methyl-2-thiazoline (and derivatives) occurs with transposition of the allylic double bond in good yields (eq 11).[4] Thiazoline hydrolysis affords the two-carbon extended α,α-disubstituted β-ethylenic methyl ketones.

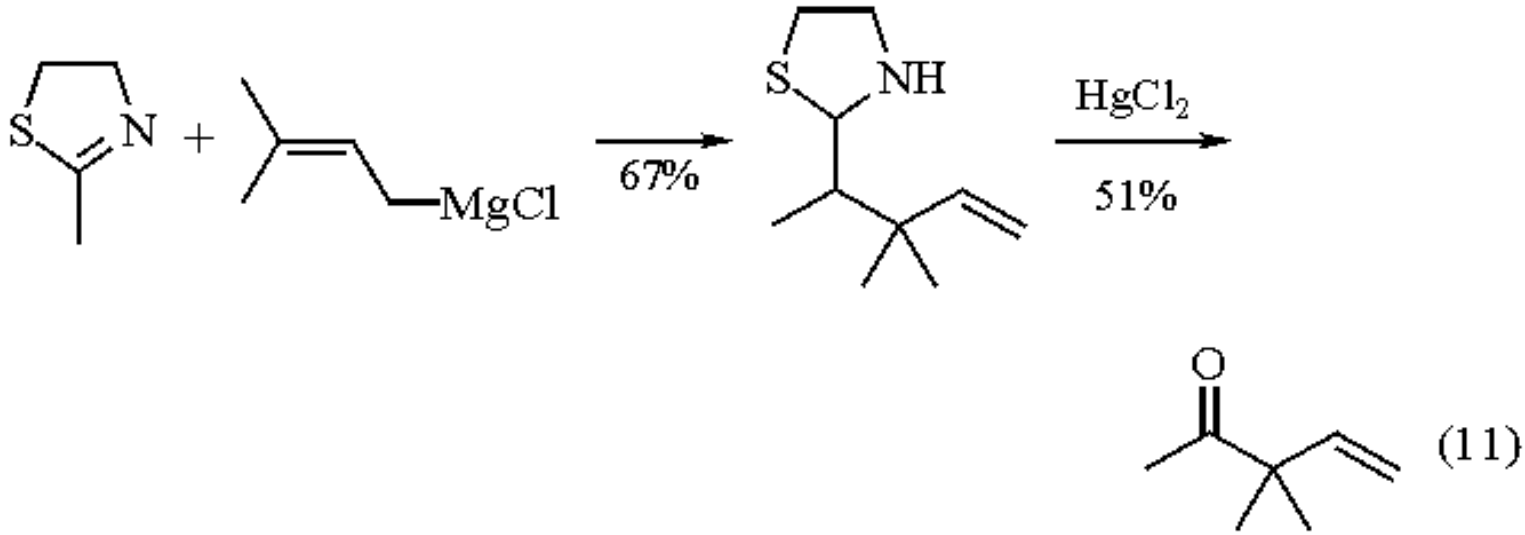

In addition to the title reagent, similar two-carbon extension synthons, such as ***2-Methylbenzothiazole*** (**1**)[13] and 4,5-dihydroimidazoles (e.g. **2**),[14,15] have been utilized in homologation procedures.

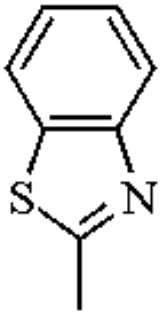

(1)

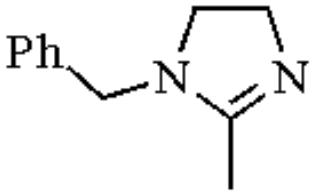

(2)

Related Reagents.

Acetaldehyde N-t-Butylimine; ***Benzothiazole***; ***2-Methylbenzothiazole***; ***5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4H)-oxazine***; ***1,3-Thiazolidine-2-thione***; ***2,4,4-Trimethyl-2-oxazoline***; ***2-Trimethylsilyl-1,3-benzothiazole***; ***2-(Trimethylsilyl)thiazole***.

---

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15. Anderson, M. W.; Jones, R. C. F.; Saunders, J. *JCS(P1)* **1986**, 1995.

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Methylthioacetylene

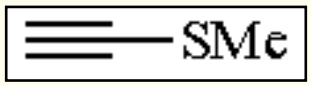

[10152-75-7] · C_3H_4S · Methylthioacetylene · (MW 72.14)

(synthesis of methylthioalkynes;[1] synthesis of methylthiocyclobutenes;[2] synthesis of heterocyclic compounds;[3] synthesis of vinyl sulfides[4] and carbonyl compounds)

Physical Data: bp 70 °C/760 mmHg; *n*20D ~1.485.

Solubility: sol organic solvents.

Form Supplied in: pale yellow to dark brown liquid.

Preparative Methods: by double elimination of HBr from the dibromide (obtained by bromination of methyl vinyl sulfide) (eqs 1 and 2).[5] The preparation of methyl vinyl sulfide from commercially available methylthioethanol has been described.[6] Methylthioacetylene has also been prepared by the reaction of sodium acetylide with sulfur followed by quenching of the resulting sulfide ion with methyl iodide.[7a]

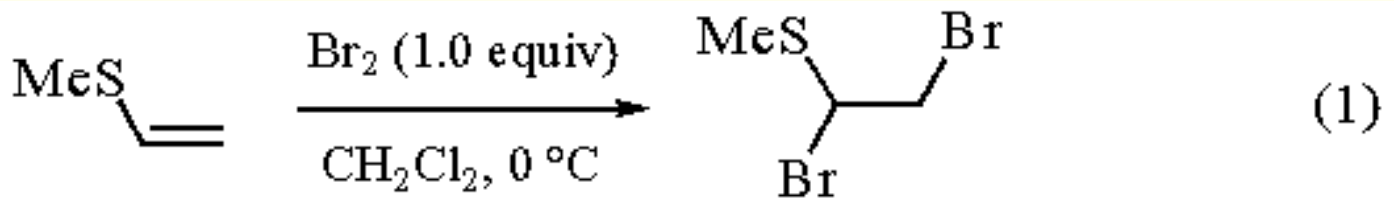

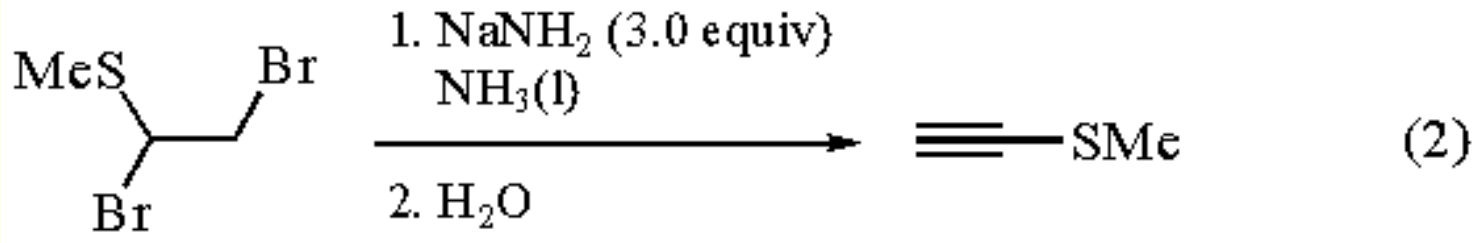

Purification: distillation under nitrogen at atmospheric pressure.

Handling, Storage, and Precautions: should be used freshly distilled for best results (pale yellow). Since methylthioacetylene has limited thermal stability, distillation at normal pressure

should be carried out (under N_2) with relatively small amounts of material.

Reactions of Methylthioacetylene.

Functionalized methylthio-substituted alkynes can be prepared by deprotonation of methylthioacetylene and reaction of the resulting acetylide ion with an appropriate electrophile (eq 3).[1] An interesting thio-Claisen substrate can be constructed in this fashion (eq 4).[7b]

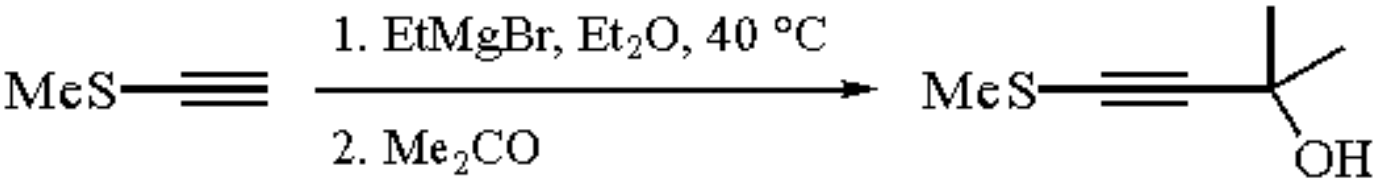

(3)

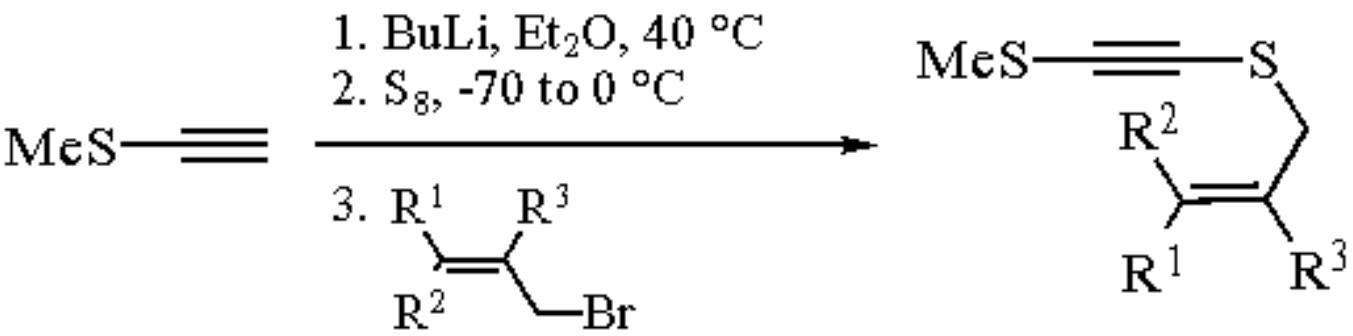

(4)

Methylthioacetylene participates in an asymmetric [2 + 2] cycloaddition with a fumarate amide derivative catalyzed by a chiral Ti^{IV} alkoxide to furnish a methylthiocyclobutene (eq 5).[2] Condensation of methylthioacetylene as the nucleophilic component with thiobenzoyl isocyanate provides a sulfur-containing heterocyclic structure (eq 6).[3] Finally, addition of a [(trimethylsilyl)methyl]copper(I) reagent to methylthioacetylene produces a bifunctional allylic silane (eq 7)[8] and condensation of methylthioacetylene as the electrophilic component with 2-(dialkylamino)arylacetonitriles gives rise to enamino allylic sulfides (eq 8).[9]

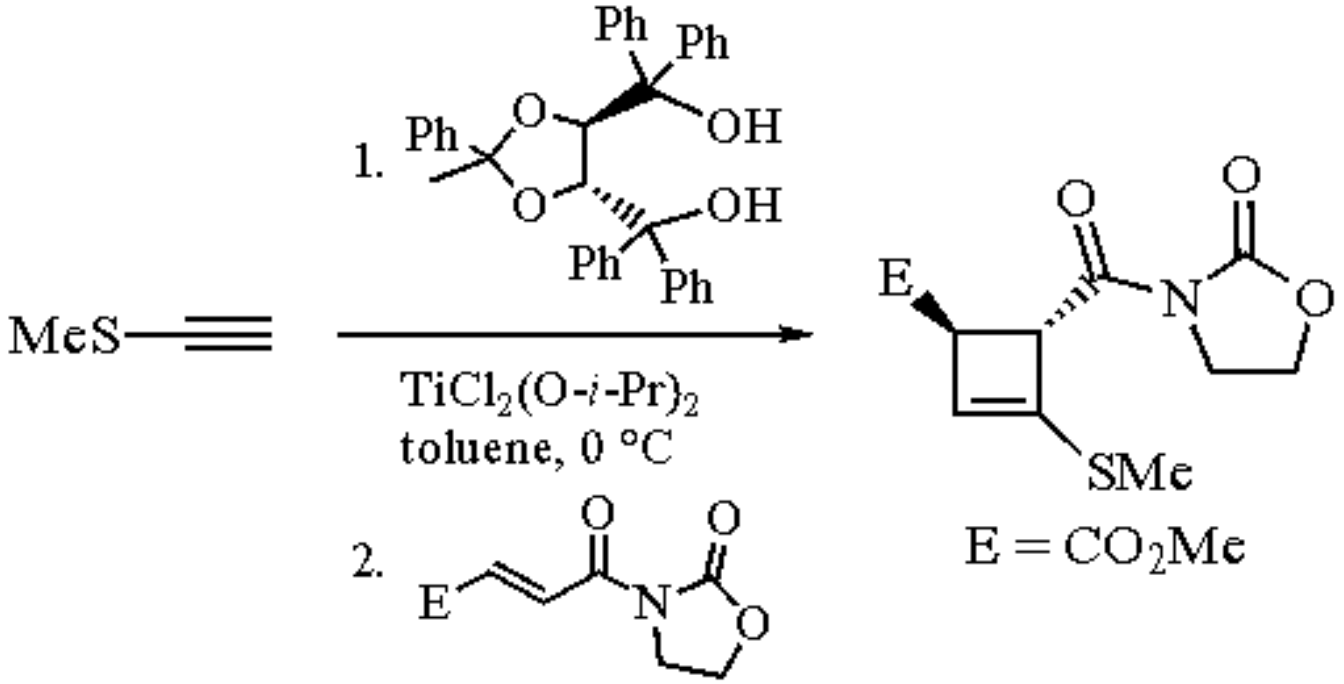
MeS
1.
Ph
Ph
Ph
O
OH
O
OH
Ph
Ph
TiCl2(O-i-Pr)2
toluene, 0 °C
2.
E
O
O
N
O
E
O
O
N
O
SMe
E = CO2Me

(5)

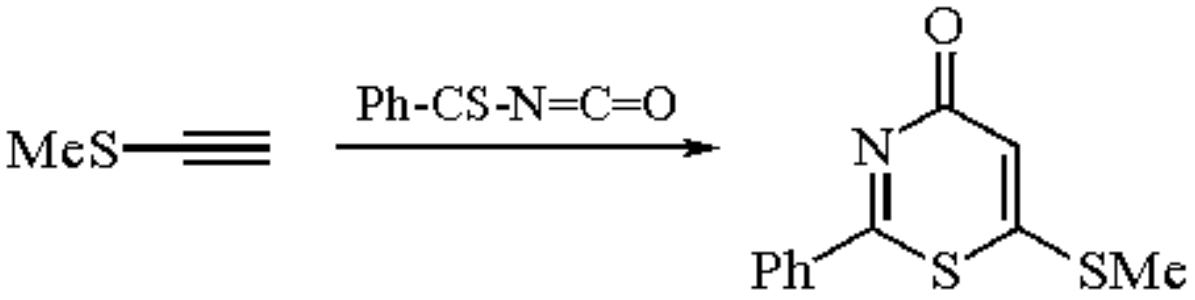
MeS
Ph-CS-N=C=O
O
N
Ph
S
SMe

(6)

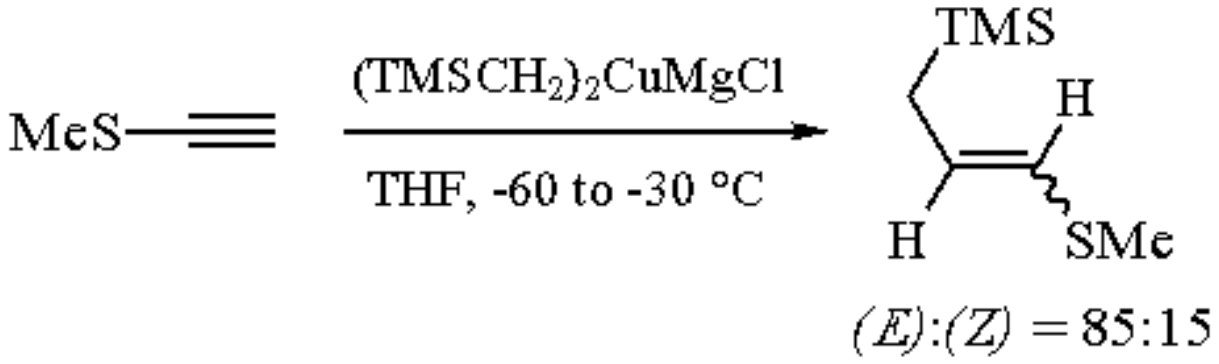
MeS
(TMSCH2)2CuMgCl
THF, -60 to -30 °C
TMS
H
H
SMe
(E):(Z) = 85:15

(7)

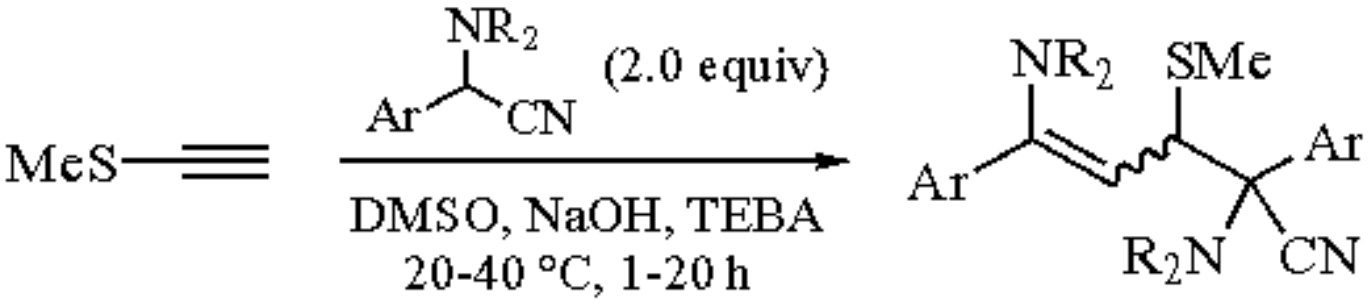
MeS
NR2
Ar
CN
(2.0 equiv)
DMSO, NaOH, TEBA
20-40 °C, 1-20 h
NR2
SMe
Ar
Ar
R2N
CN

(8)

Vinyl Sulfides.

Regio- and stereoselective syntheses of functionalized methyl vinyl sulfides is accomplished by Pd^0-catalyzed hydrostannation (eq 9)[4a,b] and carbocupration (eq 10)[4c] of 1-methylthio-1-alkynes. In turn, vinyl sulfides are very useful intermediates in organic synthesis, not only as carbonyl-masking moieties[10] but also in a variety of other transformations[11] including the Ni^0-catalyzed cross-coupling reaction with Grignard reagents.[12] 1-Methylthio-1-alkynes can in principle be prepared by deprotonation of methylthioacetylene and subsequent reaction with an appropriate electrophile (e.g. eq 3).[13] However, the 1-methylthio-1-alkynes shown in eq 9 and eq 10 were prepared by the reaction of a metal acetylide derivative with either *S*-methyl methylthiosulfonate or dimethyl disulfide.[4b,14]

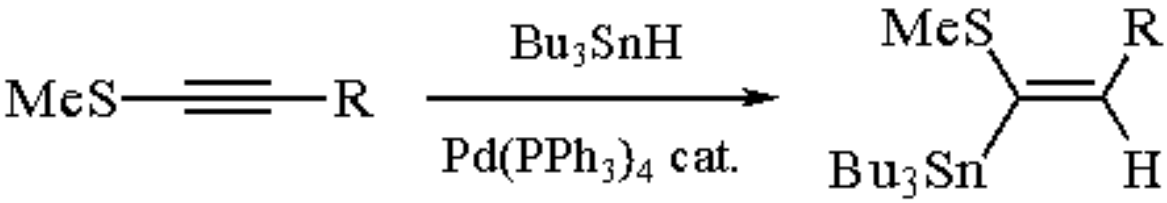

(9)

R = CH_2OH, $CH_2OTBDMS$, Bu, Ph

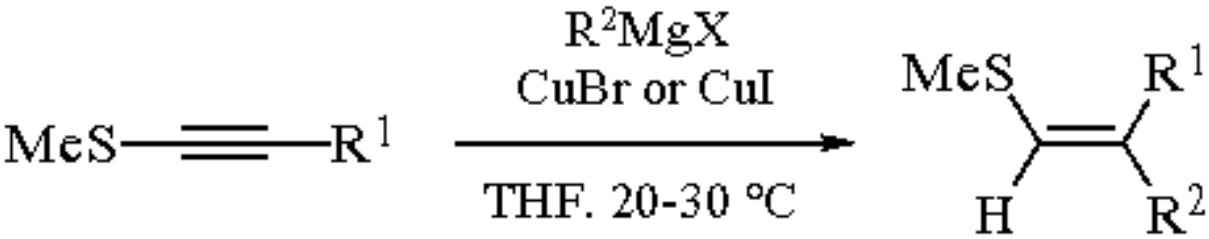

(10)

R^1, R^2 = Me, Et, *i*-Pr, Ph

Related Reagents.

Phenylthioacetylene.

---

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13. For example with phenylthioacetylene, see: Magriotis, P. A.; Brown, J. T. *OS* **1993**, *72*, 252.
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Methylthiomaleic Anhydride

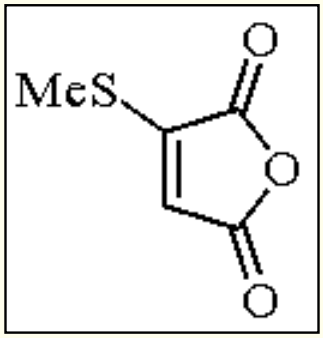

[64810-01-1] · $C_5H_4O_3S$ · Methylthiomaleic Anhydride · (MW 144.16)

(2π partner in [4 + 2] cycloaddition reactions;[1] synthon for methoxycarbonylketene or methyleneketene[5])

Alternate Name: 3-(methylthio)-2,5-furandione.

Physical Data: mp 36-37 °C (ether); bp 123-125 °C/0.5 mmHg.

Analysis of Reagent Purity: IR 1845, 1745, 1566 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28, 2.56; ^{13}C NMR ($CDCl_3$) δ 162.4, 162.1, 155.5, 118.5, 15.2.

Preparative Method: prepared by the addition of ***Methyl Isothiocyanate*** to acetylenedicarboxylic acid (ethanol, 25 °C) to afford a 6:1 mixture of 2-(methylthio)fumaric and -maleic acids, which are dehydrated by dissolution in ***Thionyl Chloride*** for 1 h at 25 °C, then 7 h at 60 °C. Excess $SOCl_2$ is removed at 120 °C at aspirator pressure, followed by distillation of the residue to afford the crystalline anhydride in 68-77% yield.[1]

Reactivity.

Methylthiomaleic anhydride (**1**) has been reported to react as a regioselective, *endo*-selective, electron-deficient 2π partner in [$_\pi4_s$ + $_\pi2_s$] cycloaddition reactions.[1]

Cycloaddition Reactions.[1]

Cycloadditions were carried out by mixing the neat dieneophile (**1**) with the appropriate diene at 0-80 °C in the presence of 2,6-di-*t*-butyl-4-methylphenol (BHT) or hydroquinone as a stabilizer. Exclusive *endo* selectivity was observed in the cycloaddition of cyclopentadiene with dienophile (**1**) to afford the bicyclo[2.2.1]heptene adduct (eq

1). Reaction of (**1**) with ***Isoprene*** afforded the cyclohexene adduct as a single regioisomer (eq 2). Similarly, a single regioisomeric cycloadduct was observed with (**1**) and 1-vinyl-6-methoxy-3,4-dihydronaphthalene (eq 3). The thiomethyl group[2] was postulated to be responsible for the excellent regiocontrol observed in cycloadditions of (**1**), since comparable cycloadditions with methylmaleic anhydride exhibited poor regioselectivity.[3]

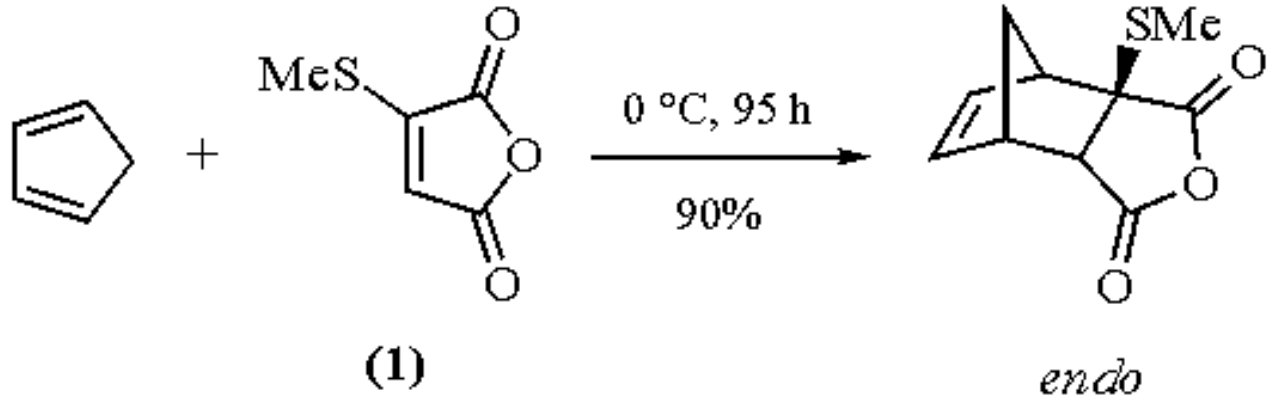

(1)

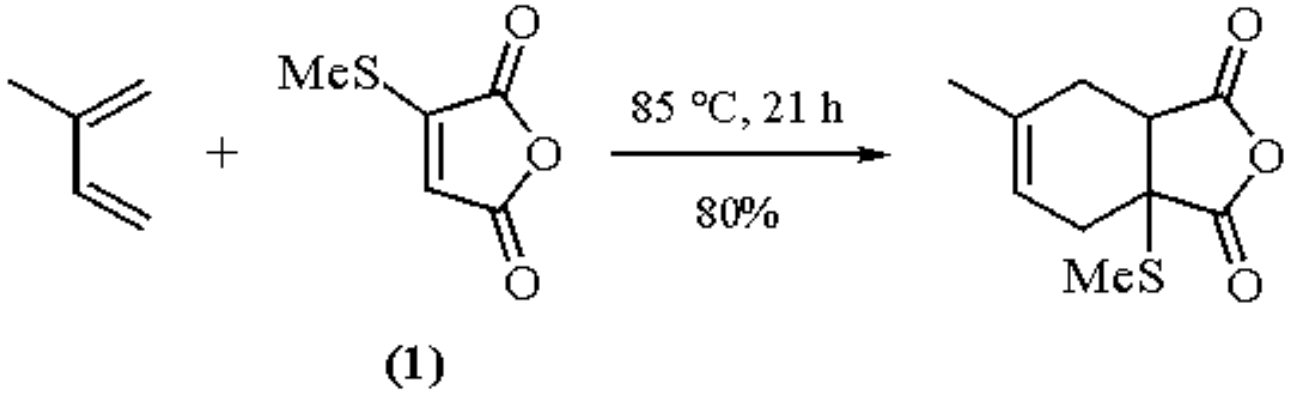

(2)

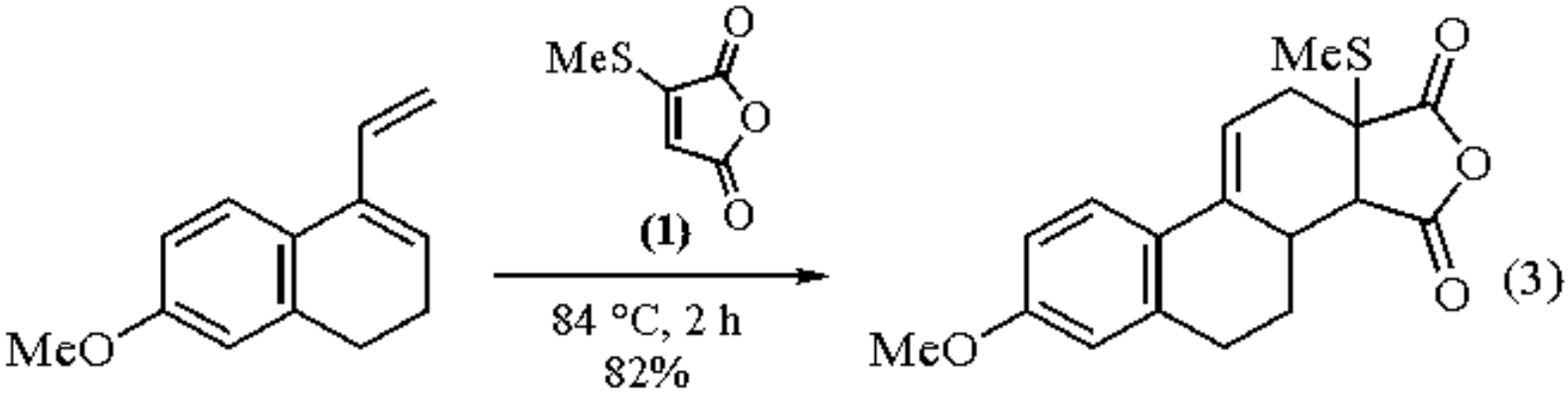

(3)

Oxidative decarboxylation[4] of cycloadducts of (**1**) affords access to β-keto ester functionality. Treatment of the isoprene-(**1**) cycloadduct with methanol followed by ***N-Chlorosuccinimide*** afforded the corresponding dimethyl acetal, which could be hydrolyzed to afford the β-keto ester (eq 4).[1]

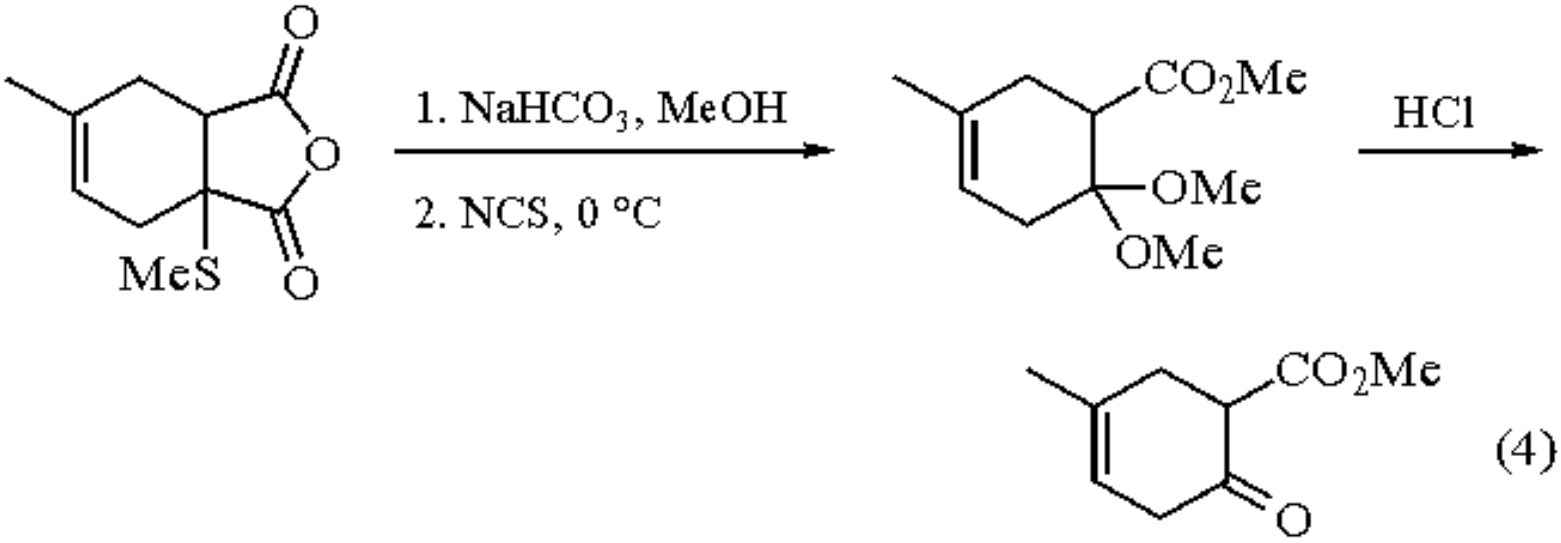

In bicyclic adducts (eq 1), thiol enol ethers are the direct products of oxidative decarboxylation; reduction of the ester and subsequent hydrolysis of the thiol enol ethers affords α-methylene ketones (eq 5).[5] Thus eqs (4) and (5) demonstrate the utility of (**1**) as a methoxycarbonylketene (**2**) or methyleneketene (**3**) synthon in [4 + 2] cycloaddition reactions.

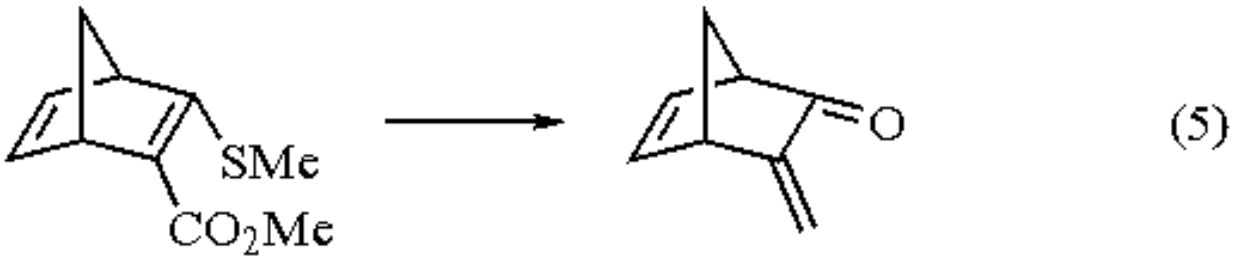

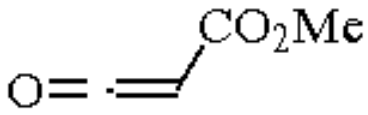

(2)

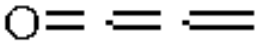

(3)

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1. Trost, B. M.; Lunn, G. *JACS* **1977**, *99*, 7079.
2. (a) Trost, B. M.; Bridges, A. J. *JACS* **1976**, *98*, 5017. (b) Cohen, T.; Mura, A. J., Jr.; Shull, D. W.; Fogel, R. J.; Ruffner, R. J.; Fabek, J. R. *JOC* **1976**, *41*, 3218. (c) Evans, D. A.; Bryan, C. A.; Sims, C. L. *JACS* **1972**, *94*, 2891.
3. Bachman, W. E.; Chemerda, J. M. *JACS* **1948**, *70*, 1468.
4. (a) Trost, B. M.; Tamaru, Y. *JACS* **1977**, *99*, 3101. (b) Trost, B. M.; Tamaru, Y. *TL* **1975**, 3797. (c) Trost, B. M.; Tamaru, Y. *JACS* **1975**, *97*, 3528.
5. Trost, B. M. *ACR* **1978**, *11*, 453.

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N-(Methylthiomethyl)piperidine[1]

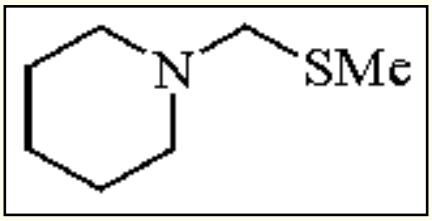

[7257-48-9] · $C_7H_{15}NS$ · *N*-(Methylthiomethyl)piperidine · (MW 145.30) (.HCl)

[7960-22-8] · $C_7H_{16}ClNS$ · *N*-(Methylthiomethyl)piperidine Hydrochloride · (MW 181.76)

(methylthiomethylating agent for 1,3-dicarbonyl compounds[1] and β-keto phosphonates[2])

Physical Data: bp 82 °C/12 mmHg;[3] *n*23D 1.5065;[2] .HCl mp 144-149 °C.[1]

Solubility: insol ether, hexane, benzene; sol CH_2Cl_2, $CHCl_3$, ethanol, methanol; slightly sol hot THF, hot dioxane.

Preparative Methods: ***Methanethiol*** gas (generated by adding conc. ***Sulfuric Acid*** (50 mL) to 15% aqueous sodium methanethiolate (150 mL)) is introduced to a soln of ***Piperidine*** (16 g) and 37% aqueous ***Formaldehyde*** (20 g) at 0 °C. As the reaction progresses an oil separates. The organic layer is extracted with ether, dried, and concentrated. The residual oil (19.5 g) is distilled to give *N*-(methylthiomethyl)piperidine; yield: 16.6 g (61%). An ethereal soln of this amine is added to ether saturated with hydrogen chloride to afford *N*-(methylthiomethyl)piperidine hydrochloride; yield 20 g (58% from piperidine). For alternative preparations, see Mikolajczyk and Balaczewski[2] and Böhme and Hafner.[3]

Handling, Storage, and Precautions: the hydrochloride is very hygroscopic and must be stored in the absence of moisture. The reagent is stable for a few years as long as it is kept in a tightly sealed vessel.

Methylthiomethylation.

Active methylene compounds are heated with the reagent hydrochloride in dioxane to give methylthiomethylated products. β-Diketones,[1,4] β-keto esters,[1] β-keto amides,[1] and β-keto phosphonates[2]

are α-methylthiomethylated in good yields. The closely related reagent *N*-(phenylthiomethyl)piperidine hydrochloride[5] may be used similarly to prepare α-phenylthiomethyl β-diketones (eqs 1 and 2).[4]

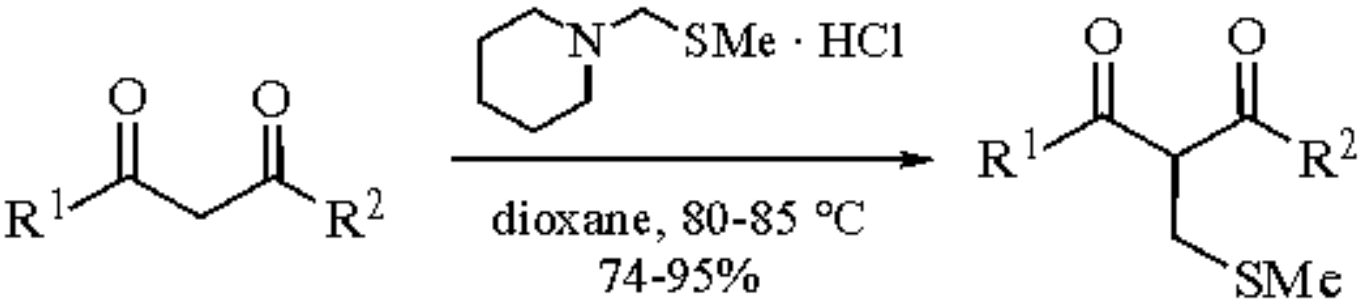

(1)

$R^1 = R, Ar; R^2 = R, Ar, OR, NR_2$

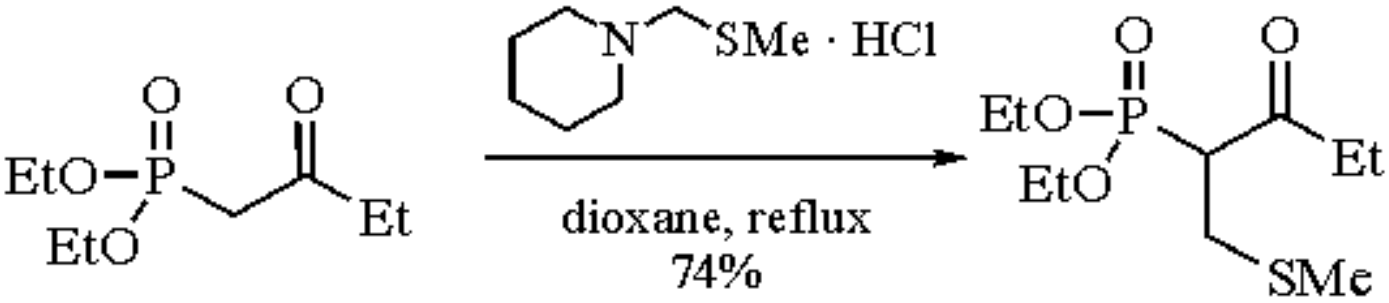

(2)

The α-methylthiomethyl β-diketones are useful intermediates for preparing unstable α-methylene β-diketones[1,4] via oxidation to the sulfoxide and thermal elimination,[6] as illustrated in eq 3.[1] The elimination reactions are conducted in refluxing toluene containing catalytic amounts of ***Calcium Carbonate***[1,4a,4b] or ***Acetic Acid***.[4c] These procedures were instrumental in the synthesis of α-methylene derivatives of acetal-protected aryl 1,3,5-triketones as intermediates in biogentic-type cyclizations producing fulvic acid and the 4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one nucleus of citromycetin.[4a,4b]

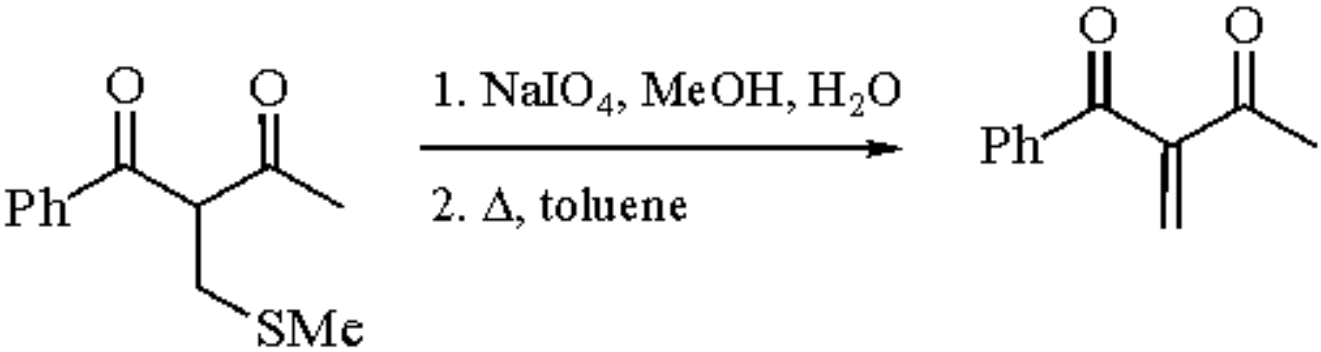

(3)

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2. Mikolajczyk, M.; Balaczewski, P. *S* **1984**, 691.

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4. (a) Watanabe, T.; Katayama, S.; Nakashita, Y.; Yamauchi, M. *CC* **1981**, 761. (b) Yamauchi, M.; Katayama, S.; Nakashita, Y.; Watanabe, T. *JCS(P1)* **1984**, 503. (c) Yamauchi, M.; Katayama, S.; Todoroki, T.; Watanabe, T. *CC* **1984**, 1565; (d) Yamauchi, M.; Katayama, S.; Todoroki, T.; Watanabe, T. *JCS(P1)* **1987**, 389.
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Methylthiomethyl *p*-Tolyl Sulfone[1]

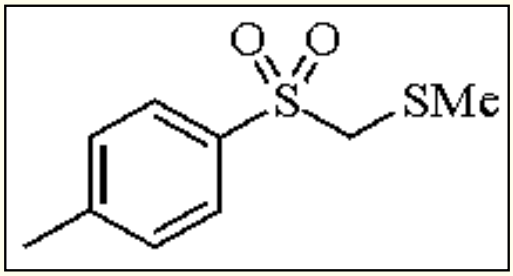

[59662-68-9] · $C_9H_{12}O_2S_2$ · Methylthiomethyl *p*-Tolyl Sulfone · (MW 216.35)

(synthetic reagent for acyclic ketones, cyclic ketones, and conjugated unsaturated ketones)

Alternate Names: MT-sulfone; formaldehyde methyl *p*-tolyl dithioacetal *S,S*-dioxide; methyl *p*-toluenesulfonylmethyl sulfide; methylthio(*p*-toluenesulfonyl)methane.

Physical Data: mp 82-83 °C; bp 164 °C/3 mmHg.

Solubility: sol DMF (87 g/100 mL), acetone (76 g/mL), $CHCl_3$ (57 g/mL), acetic acid (13 g/mL); slightly sol MeOH (5.8 g/mL), ethanol (3.3 g/mL), ethyl ether (3.0 g/mL), CCl_4 (2.2 g/mL); practically insol H_2O, hexane.

Form Supplied in: colorless crystals; commercially available. *Drying:* over P_2O_5 in a desiccator.

Preparative Method: conveniently synthesized from ***Dimethyl Sulfoxide*** in a one-pot reaction, i.e. Pummerer reaction of DMSO with ***Acetic Anhydride*** followed by treatment with ***RS111-***.[2]

Handling, Storage, and Precautions: very stable under alkaline, acidic, and neutral conditions. Handle in a fume hood.

Synthesis of Esters and Aldehydes.

Monoalkylation of methylthiomethyl *p*-tolyl sulfone (MT-sulfone) with an alkyl halide is achieved by the action of a phase-transfer catalyst (PTC) in toluene-50% aq NaOH.[3] ***Sodium Hydride***[3] and ***n-Butyllithium***[4] also generate a carbanion of MT-sulfone. Arylmethyl derivatives of MT-sulfone are prepared by ***Sodium Borohydride*** reduction of the Knoevenagel condensation products with aromatic aldehydes.[5] The monoalkylated products are converted into the corresponding methyl esters (eq 1).[3,6] This functionalization can be utilized for synthesizing α-alkoxy carboxylic esters (eq 2)[3] and α-amino acids (eq 3).[7]

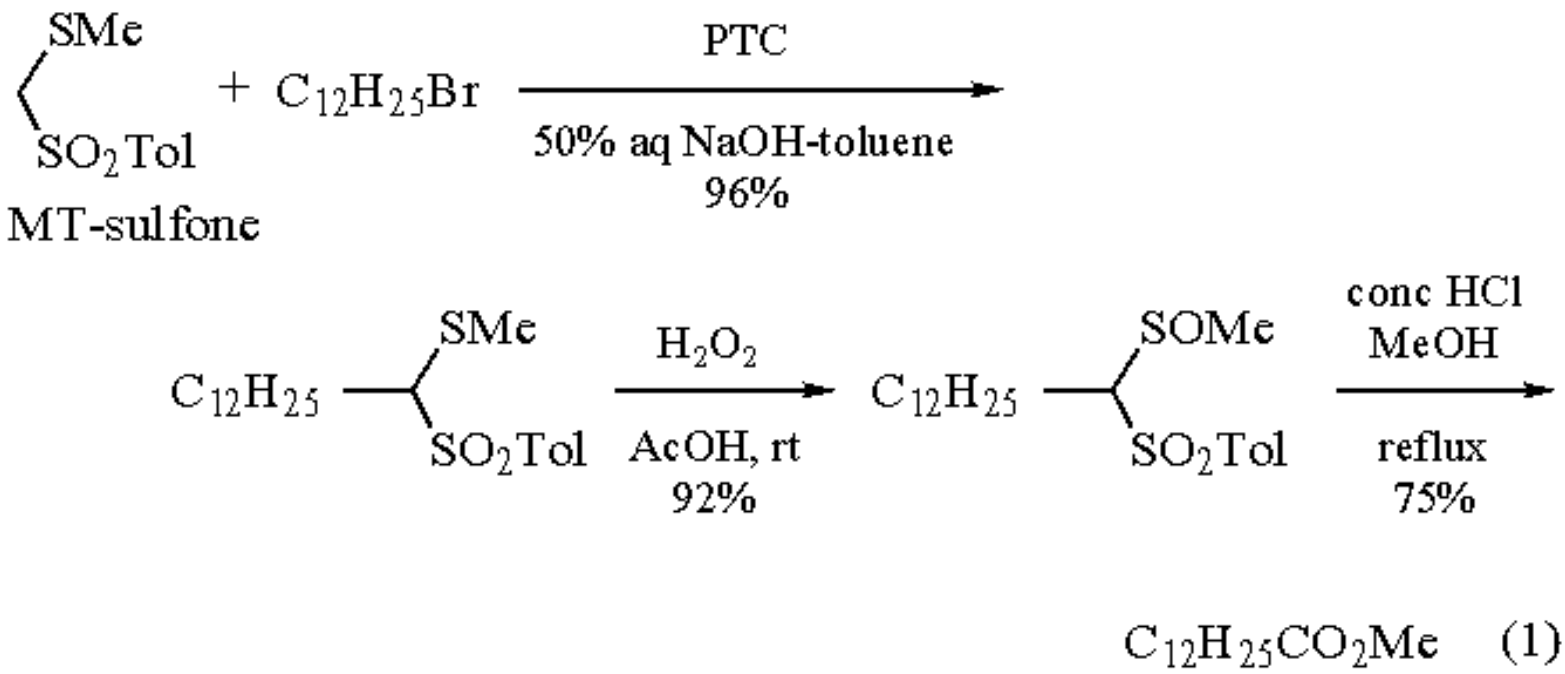
SMe
SO2Tol
MT-sulfone
+ C12H25Br
PTC
50% aq NaOH-toluene
96%
C12H25
SMe
SO2Tol
H2O2
AcOH, rt
92%
C12H25
SOMe
SO2Tol
conc HCl
MeOH
reflux
75%
C12H25CO2Me

(1)

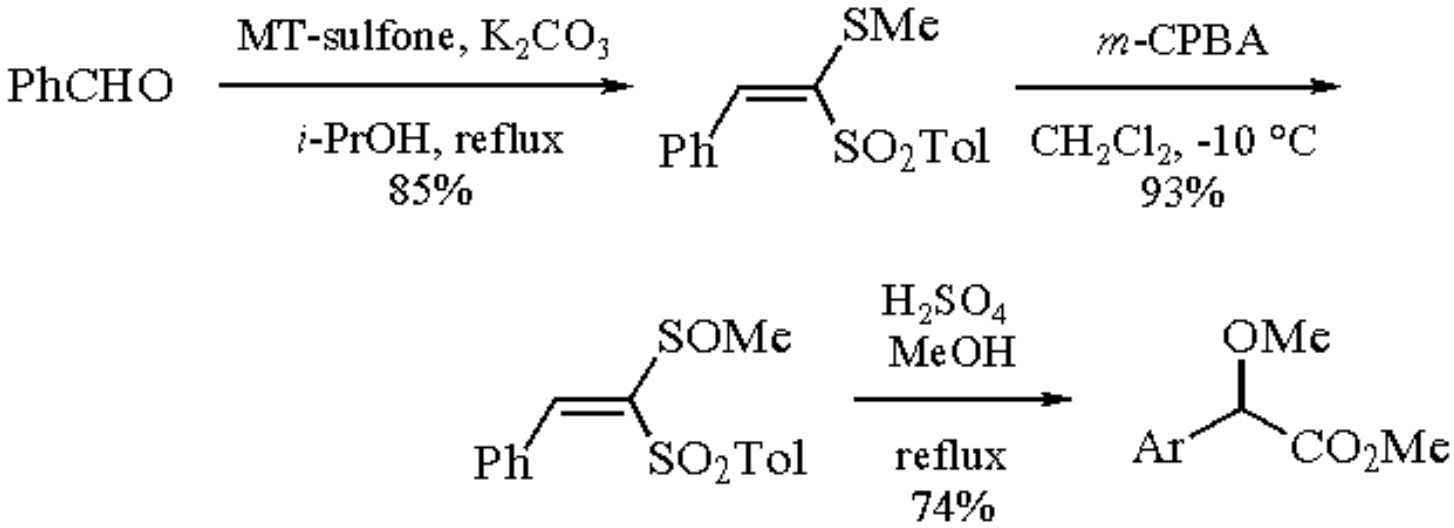
PhCHO
MT-sulfone, K2CO3
i-PrOH, reflux
85%
SMe
Ph
SO2Tol
m-CPBA
CH2Cl2, -10 °C
93%
SOMe
Ph
SO2Tol
H2SO4
MeOH
reflux
74%
OMe
Ar
CO2Me

(2)

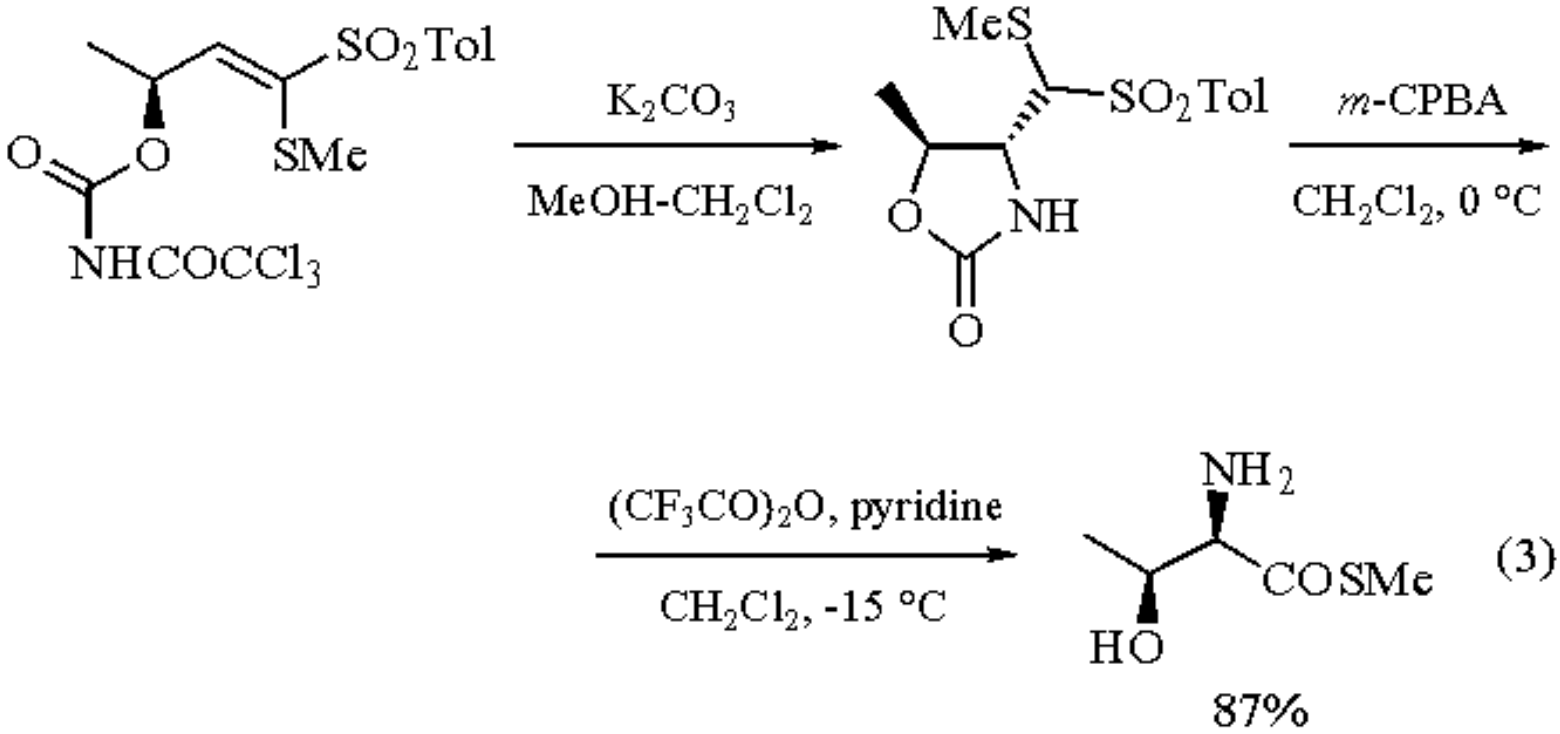

Irradiation (254 nm) of the monoalkylated product in dioxane-H_2O hydrolyzes the dithioacetal *S*,*S*-dioxide to produce an aldehyde. This method is suitably applied to the preparation of aldehydes which are susceptible to acidic conditions (eq 4).[8]

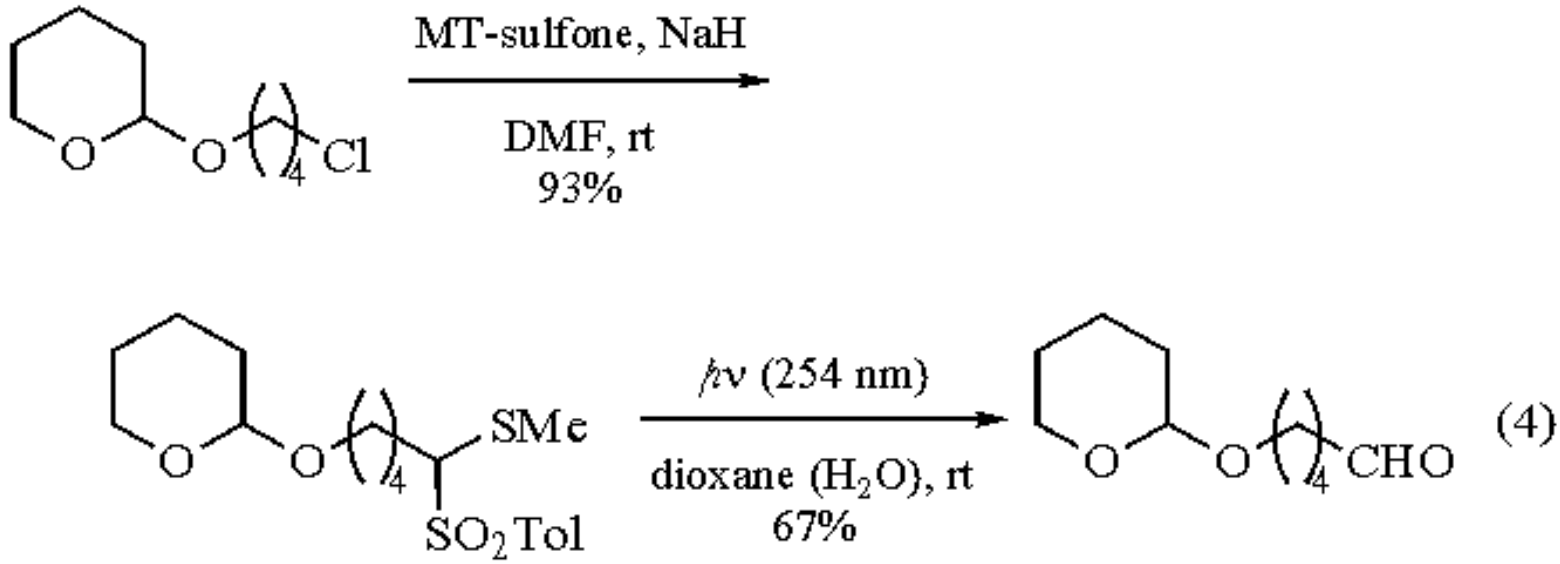

The carbanion of MT-sulfone is stable enough to add to α,β-unsaturated carbonyl compounds in a [1,4] fashion. The (methylthio)(*p*-tolylsulfonyl)methyl group introduced is easily converted into a (methylthio)carbonyl group or a formyl group.[4]

Ketone Synthesis.

The monoalkylated MT-sulfone undergoes further alkylation by action of alkyl halide and NaH or *n*-BuLi to give a dialkylated product. Since the dialkylated product can be hydrolyzed easily, MT-sulfone has proven to be very useful for

synthesizing ketones (eq 5).[5,8,9] Symmetrical ketones are prepared by direct dialkylation with NaH and alkyl halide in DMF and hydrolysis (eq 6).[8] Cyclic ketones are also synthesized from α,o-dihaloalkanes.[3,10] An efficient synthesis of α-hydroxy ketones is also achieved by the addition of the monoalkyl derivative to an aldehyde to give an adduct and subsequent hydrolysis (eq 7).[11]

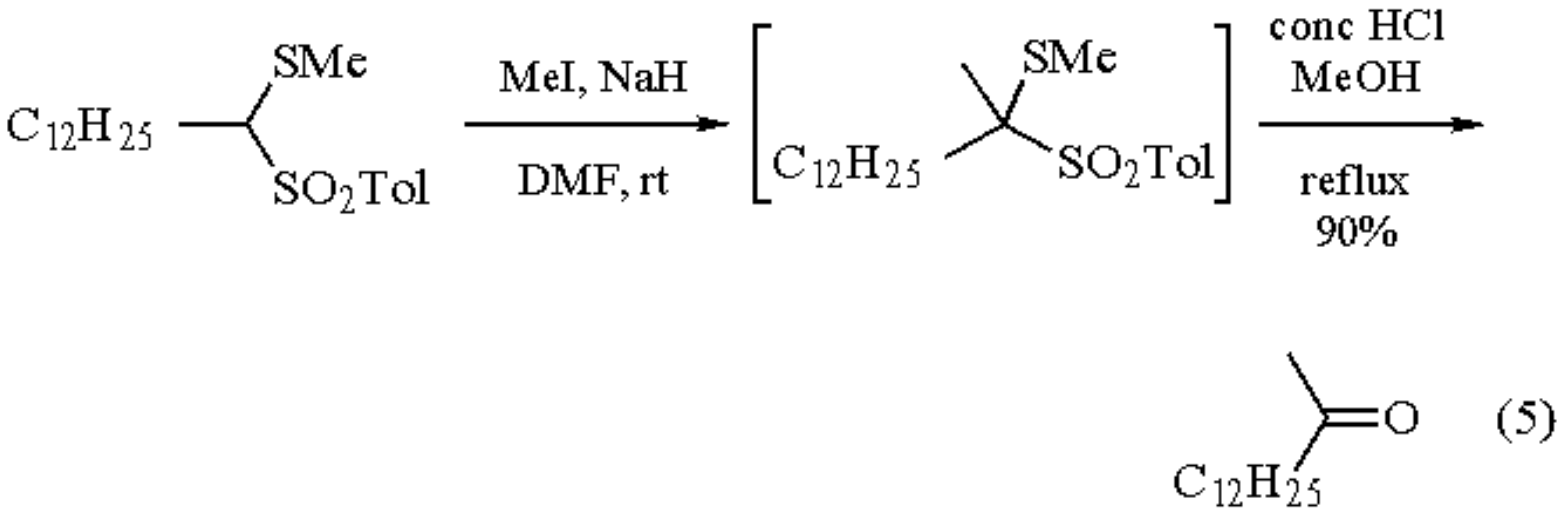

(5)

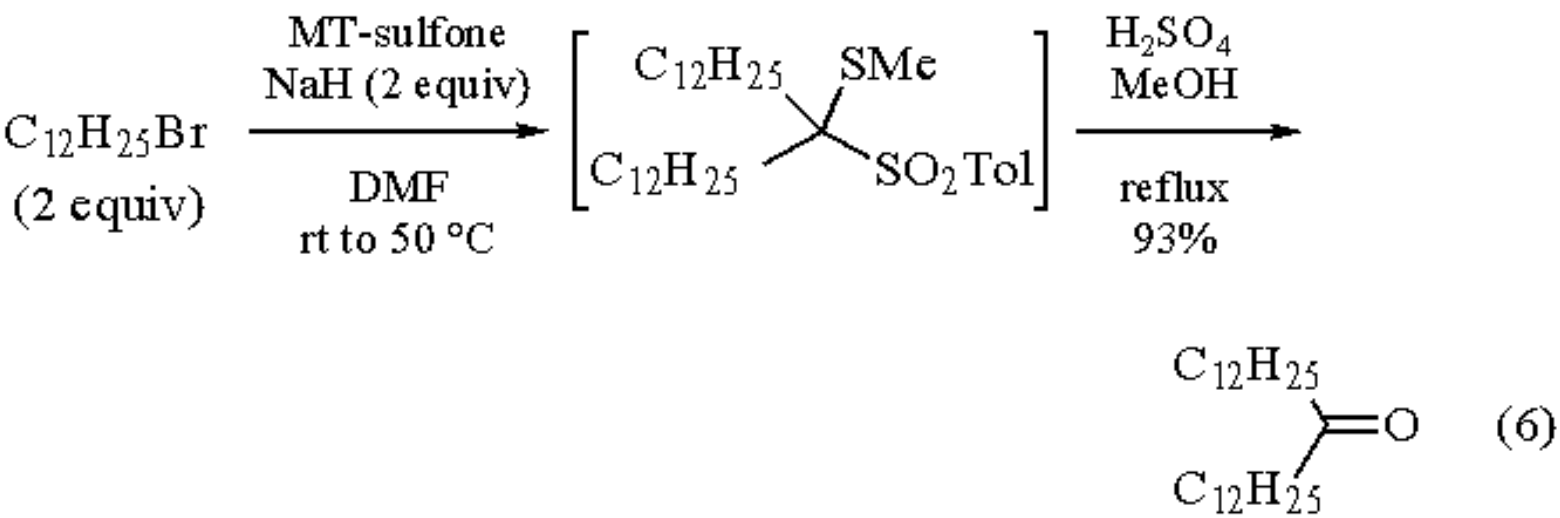

(6)

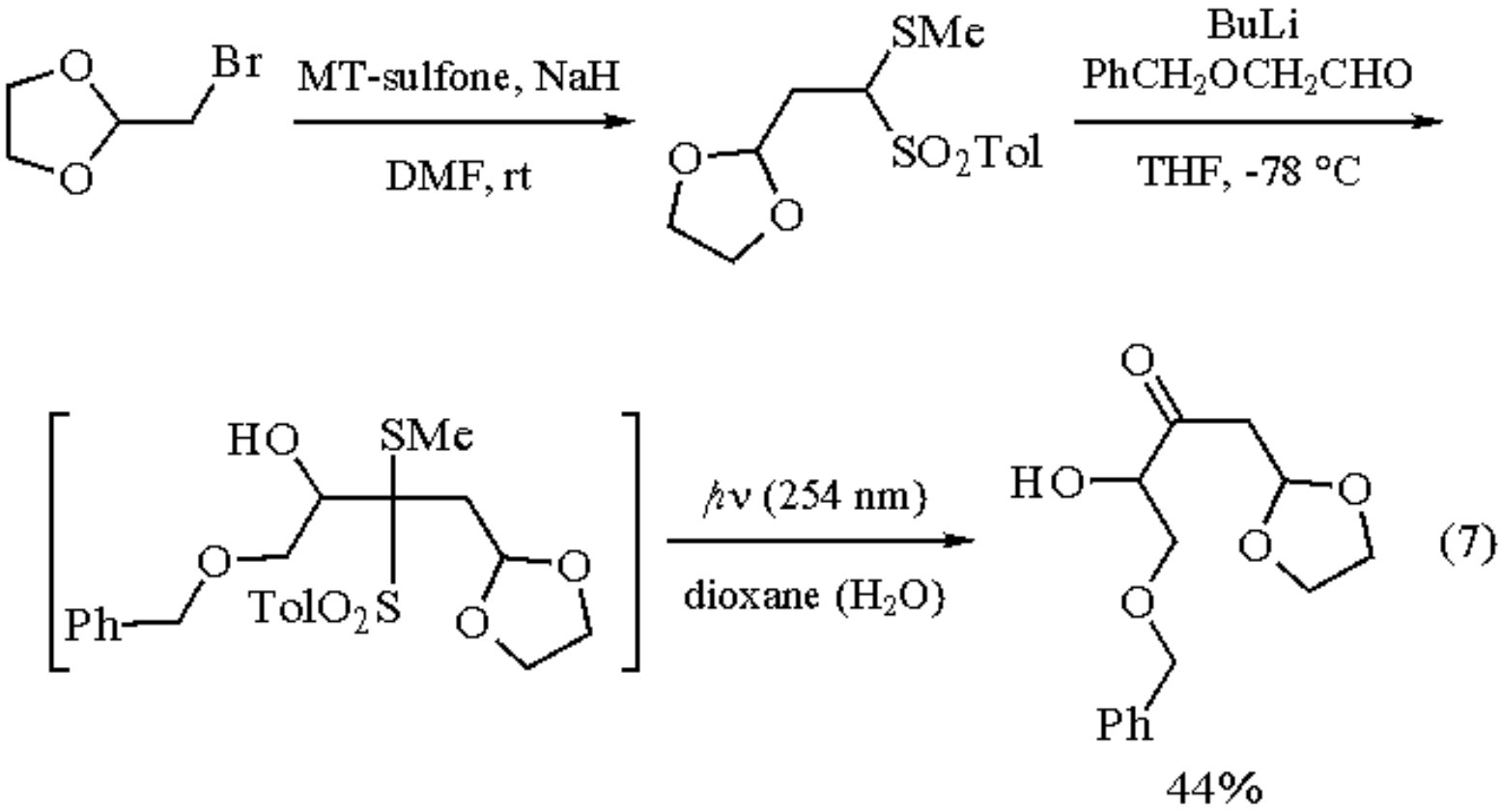

Acylation of MT-sulfone.

MT-sulfone was acylated by treatment with an ester and excess NaH in THF.[3,12,13] The acylated MT-sulfone was oxidized with ***Hydrogen Peroxide*** in ***Acetic Acid***, by slowly warming the reaction to give an *S*-methyl α-keto carbothioate (eq 8).[3]

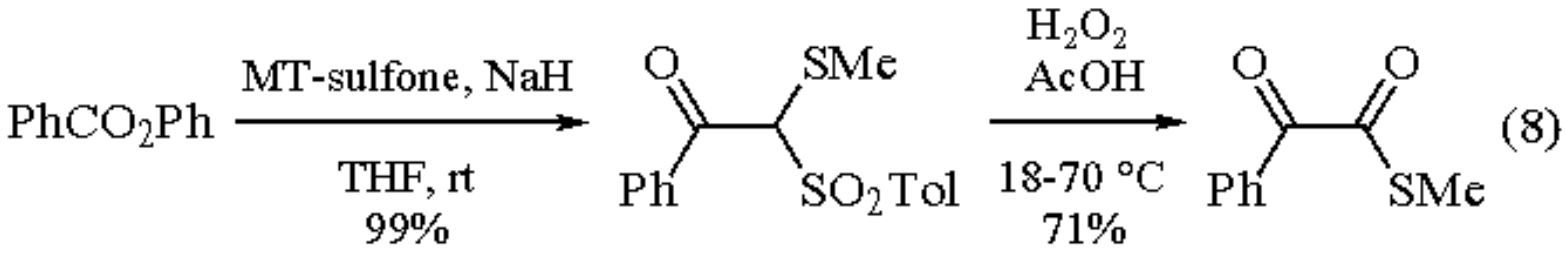

An alkoxyacetyl derivative of MT-sulfone exhibits intriguing behavior on treatment with a weak base to form an acetal of 3-methylthio-2-oxopropanal (eq 9).[14]

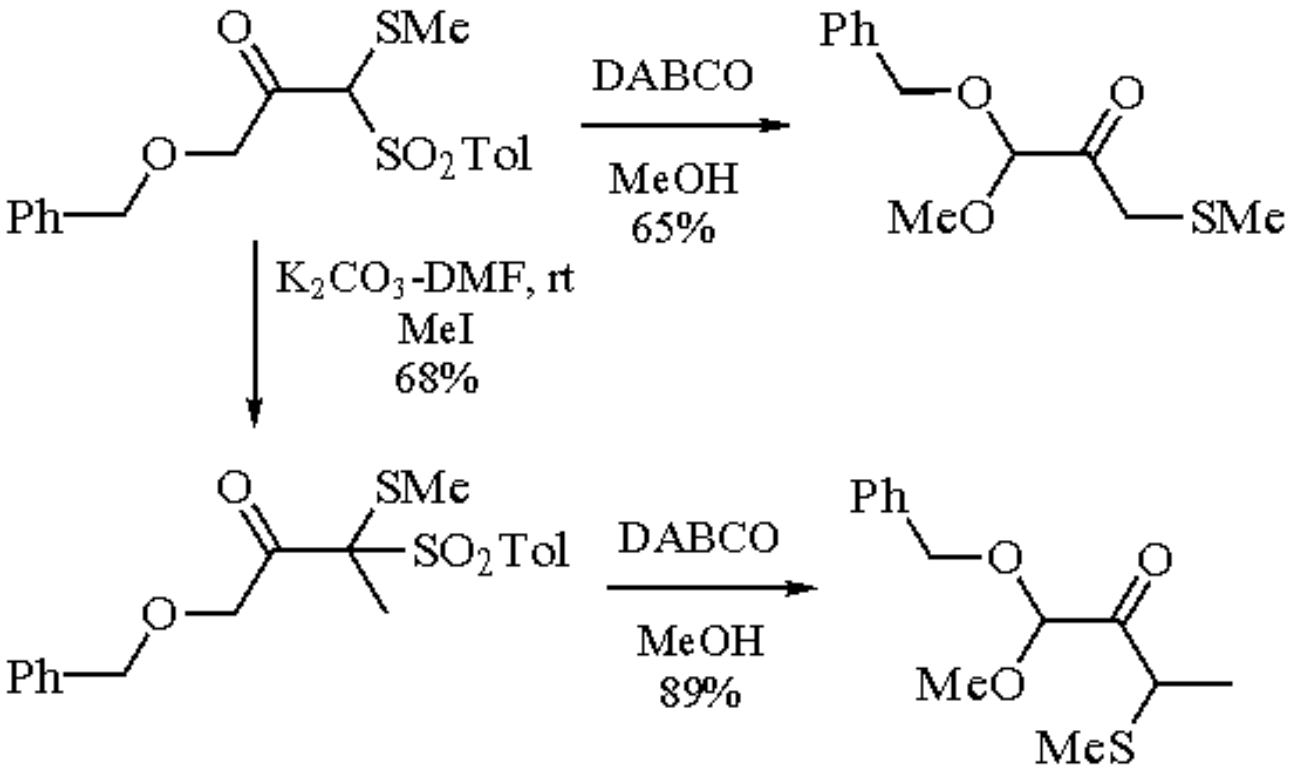

(9)

Synthesis of α,β-Unsaturated Ketones.

Alkylidene derivatives of MT-sulfone are useful synthetic precursors for α,β-unsaturated ketones (eq 10).[15] This method can be extended to provide an efficient synthesis of α,β,γ,δ-unsaturated aldehydes and ketones (eq 11).[16,17]

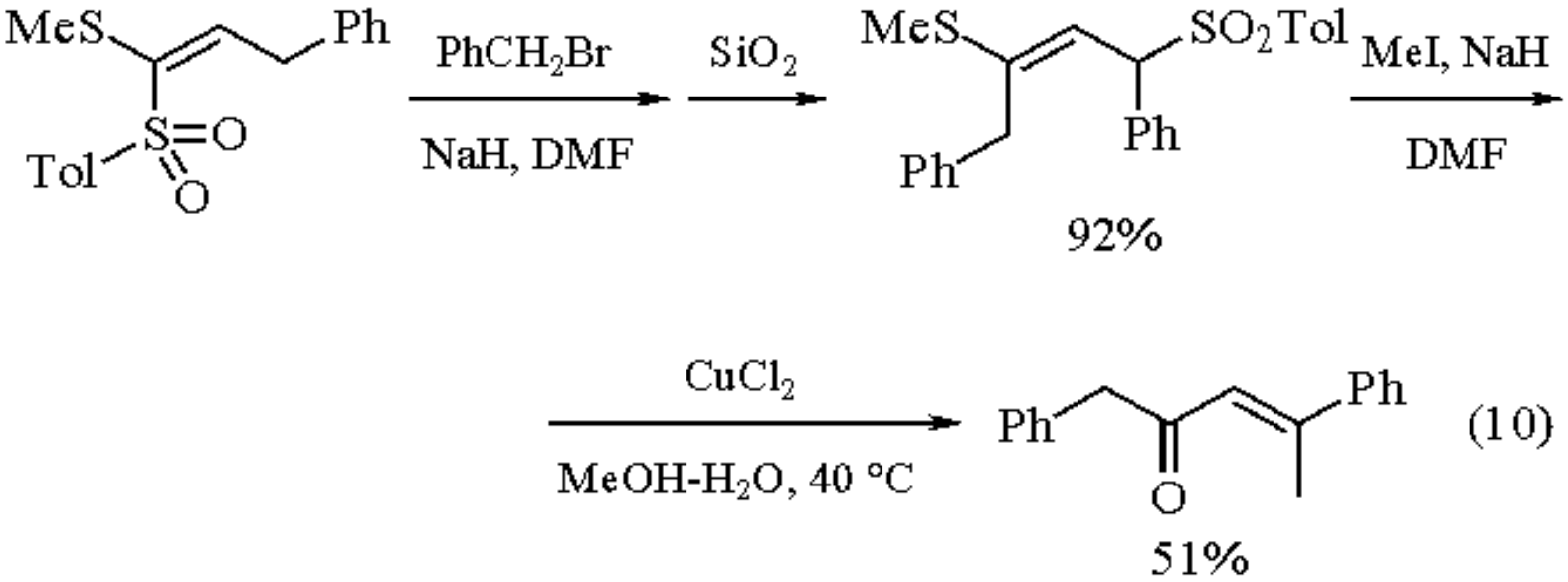

(10)

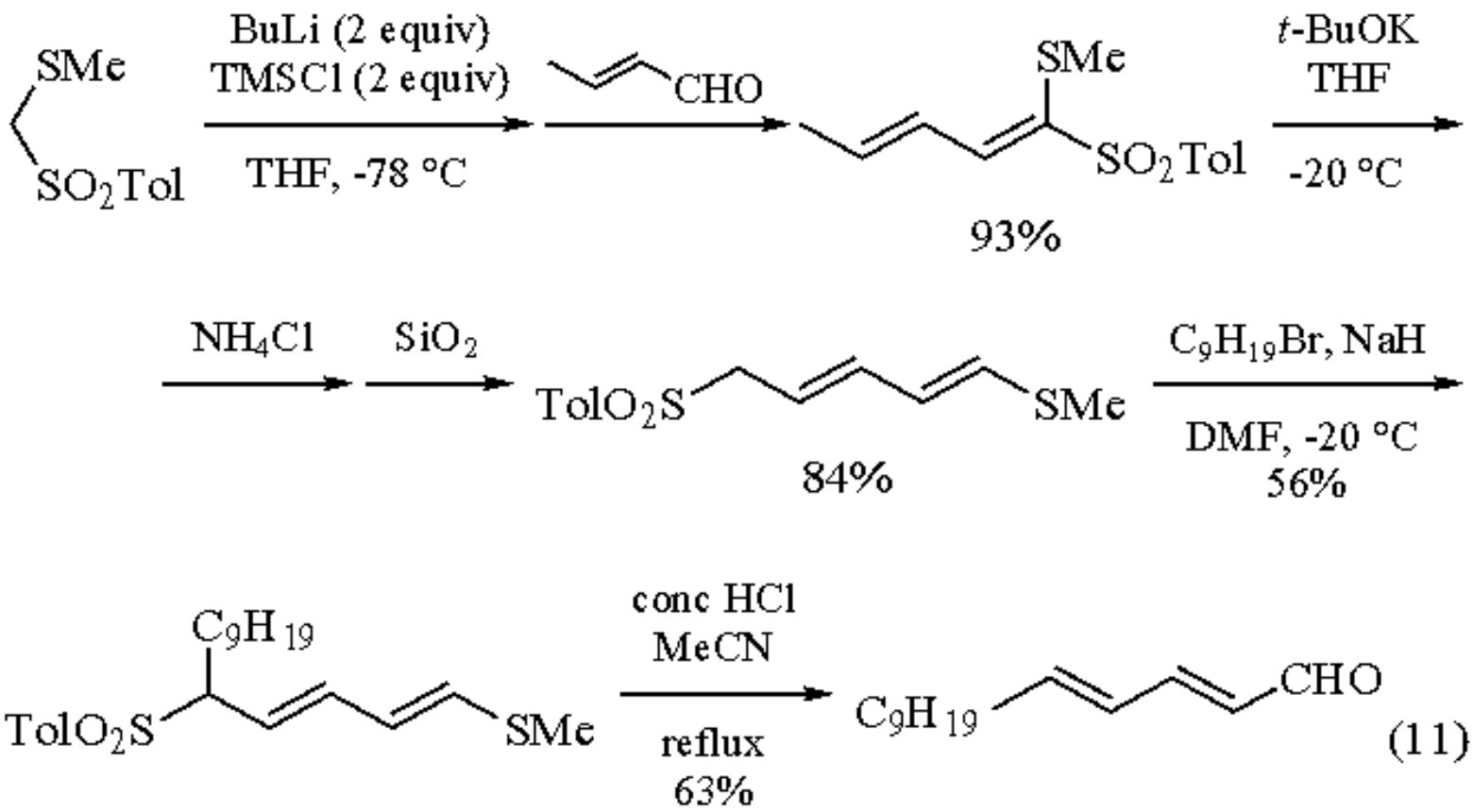

Electrophilic (Methylthio)methylation.

Lewis acids such as ***Aluminum Chloride*** or ***Ethylaluminum Dichloride*** assist the heterolytic cleavage of the C-SO_2 bond of the dithioacetal *S,S*-dioxide to produce a MeS-stabilized carbocation, which reacts with allylsilanes[18] and benzene rings[19] (eq 12).

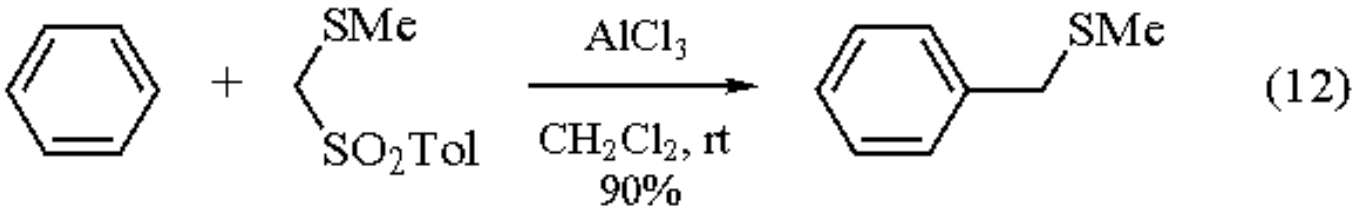

Reactivity of a 1-(Methylthio)-1-(*p*-tolylsulfonyl)-1-alkene.

1-(Methylthio)-1-(*p*-tolylsulfonyl)-1-alkenes show extremely high reactivity towards carbon radicals to provide a synthetic route leading to new types of 1-methylthio-1-(*p*-tolylsulfonyl)alkanes.[20,21] They also undergo nucleophilic epoxidation with ***Lithium t-Butoxide*** to give an α,β-epoxy-α-methylthio sulfone, a precursor for an α-bromo thiol ester (eq 13).[22]

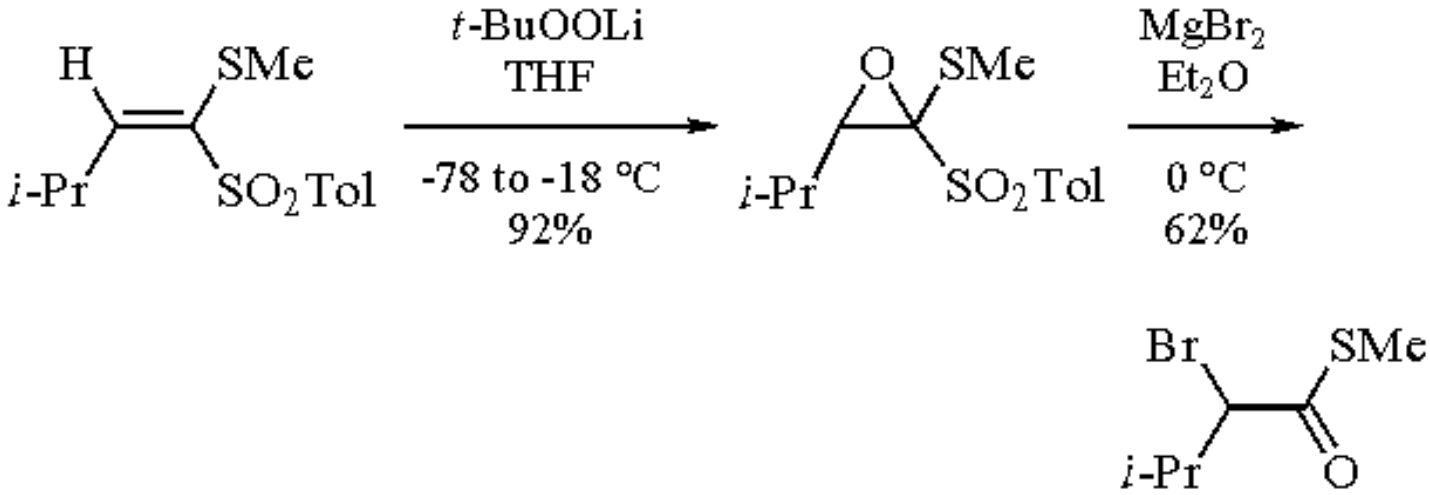

(13)

Methyl Methylthiomethyl Sulfone.

Methyl methylthiomethyl sulfone is the *S*-methyl analog of MT-sulfone and it is conveniently synthesized by oxidation of methyl methylthiomethyl sulfoxide (FAMSO) with ***Potassium Permanganate*** or H_2O_2-NaOH.[23] It is useful for synthetic methods similar to those using MT-sulfone: synthesis of carboxylic esters,[24] ketones,[25] and α-alkoxy-α-arylacetates.[26] In the reaction of this reagent with allylic bromides, α-methylthio-γ,δ-unsaturated sulfones are obtained by stirring the bromide with ***Potassium Carbonate*** and ***Potassium Iodide*** in ***Hexamethylphosphoric Triamide*** (eq 14), which does not occur with MT-sulfone.[24]

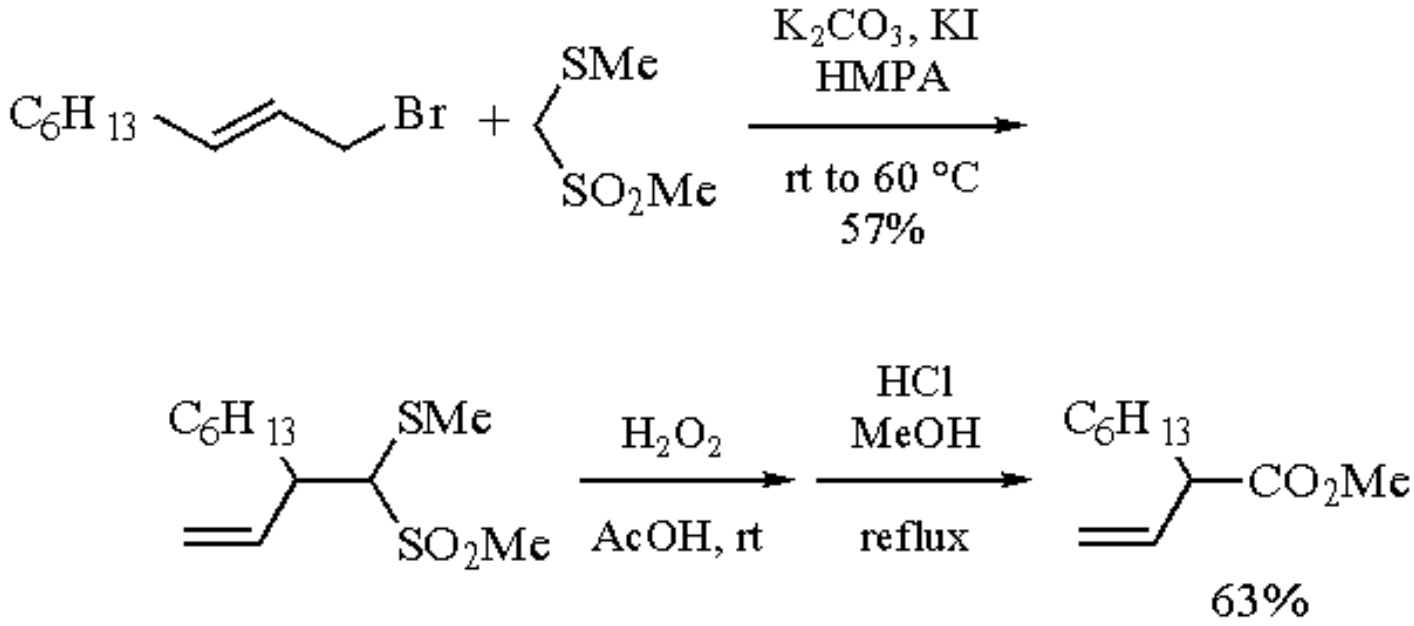

(14)

Related Reagents.

N,N-Diethylaminoacetonitrile; ***N,N-Dimethyldithiocarbamoylacetonitrile***; ***(4aR)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin***; ***2-Lithio-1,3-dithiane***; ***Nitromethane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylsulfonylmethyl Isocyanide***; ***2-(Trimethylsilyl)thiazole***.

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26. Ogura, K.; Watanabe, J.; Takahashi, K.; Iida, H. *JOC* **1982**, *47*, 5404.

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N-Methylthionomaleimide

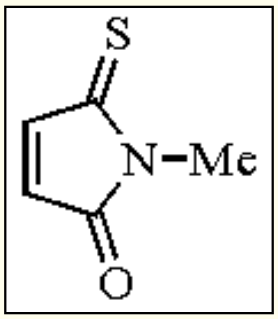

[141707-79-1] · C_5H_5NOS · *N*-Methylthionomaleimide · (MW 127.18)

(dienophile which reacts at the ring double bond;[1] some regioselectivity with unsymmetrical dienes[1])

Physical Data: mp 44-44.5 °C.

Solubility: sol most organic solvents.

Form Supplied in: volatile purple crystals; not commercially available.

Preparative Method: reaction of *N*-methylmaleimide with Lawesson's reagent (***2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide***) under carefully controlled conditions.[1]

Handling, Storage, and Precautions: stable for several months in the freezer; decomposes to yellow crystals at ambient temperature in the presence of light and air.

Introduction.

This is the first thiocarbonyl analog of maleimide with no substituents on the ring carbons. Its use as a dienophile in [4 + 2] reactions has been studied.

Chemoselectivity.

Previously reported thiocarbonyl analogs of maleimide undergo [4 + 2] reactions with a variety of dienes to give reaction at the thiocarbonyl function.[2] *N*-Methylthionomaleimide (**1**) reacts predominantly at the ring unsaturation. Reaction with 2,3-dimethylbutadiene in various solvents leads almost exclusively to the adduct (**2**) (Table 1). Only when reacted in 5 M ethereal ***Lithium Perchlorate***[3] was a significant amount of the adduct (**3**) produced (eq 1).

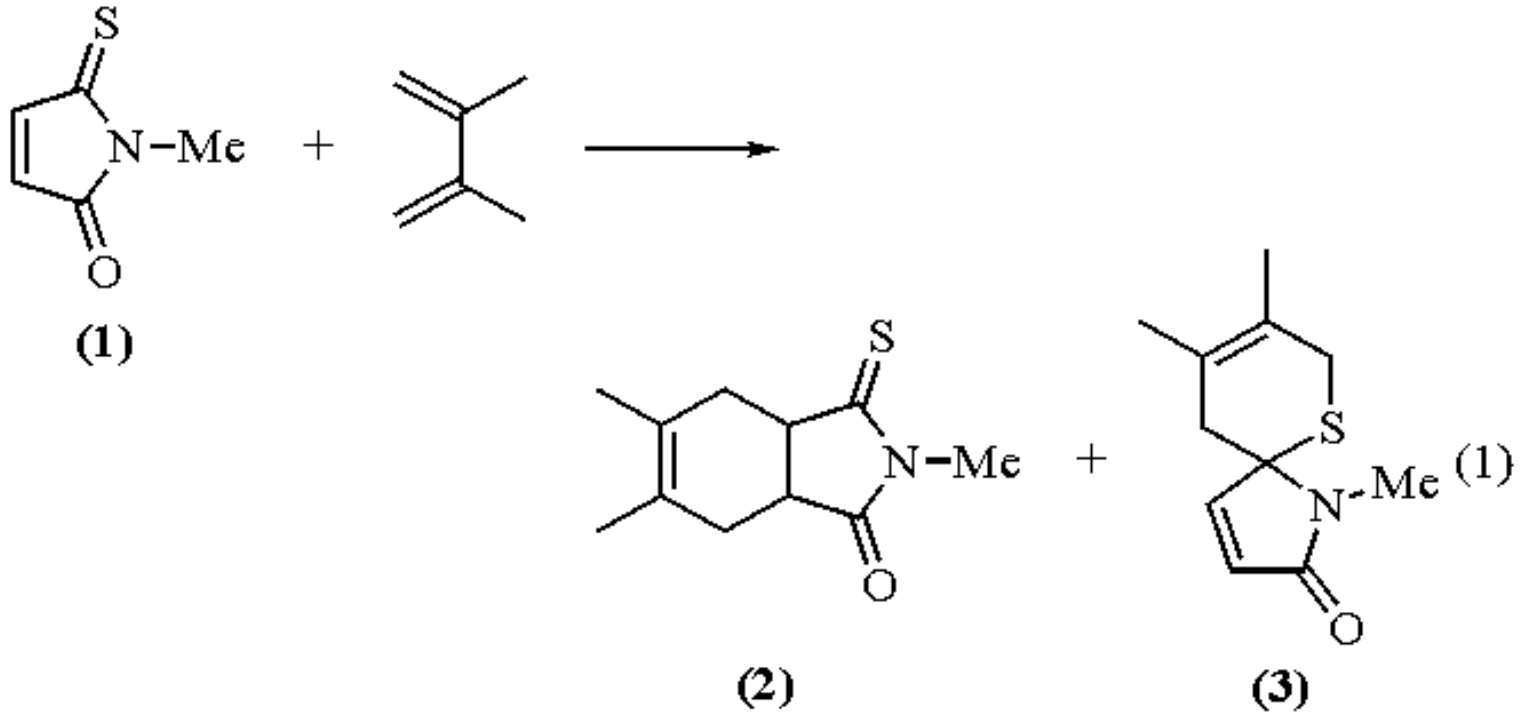

Table 1 Cycloaddition of (**1**) with 2,3-Dimethylbutadiene (eq 1)

Solvent	Temp. (°C)	Reaction time	Product ratio (**2**):(**3**)	Total yield (%)
Toluene	70	5 h	100:0	87
Toluene	rt	3 week	100:0	85
CH_2Cl_2	rt	32 h	90:10	85
$CHCl_3$	rt	32 h	93:7	81
$MeNO_2$	rt	32 h	95:5	88
$LiClO_4$/ether	rt	10 min	44:56	62

Regioselectivity.

Some degree of regioselectivity can be expected in using (**1**) as a dienophile. Reaction of (**1**) with 1-methoxy-1,3-cyclohexadiene (**4**) in toluene at 70 °C gave a 2:1 mixture of the *endo* adducts (**5**) and (**6**) (eq 2). Using ethereal $LiClO_4$ as solvent improved the ratio to 85:15. Reaction with Danishefsky's diene (**7**) gave adduct (**8**) as the only isolated product in

56% yield (eq 3).

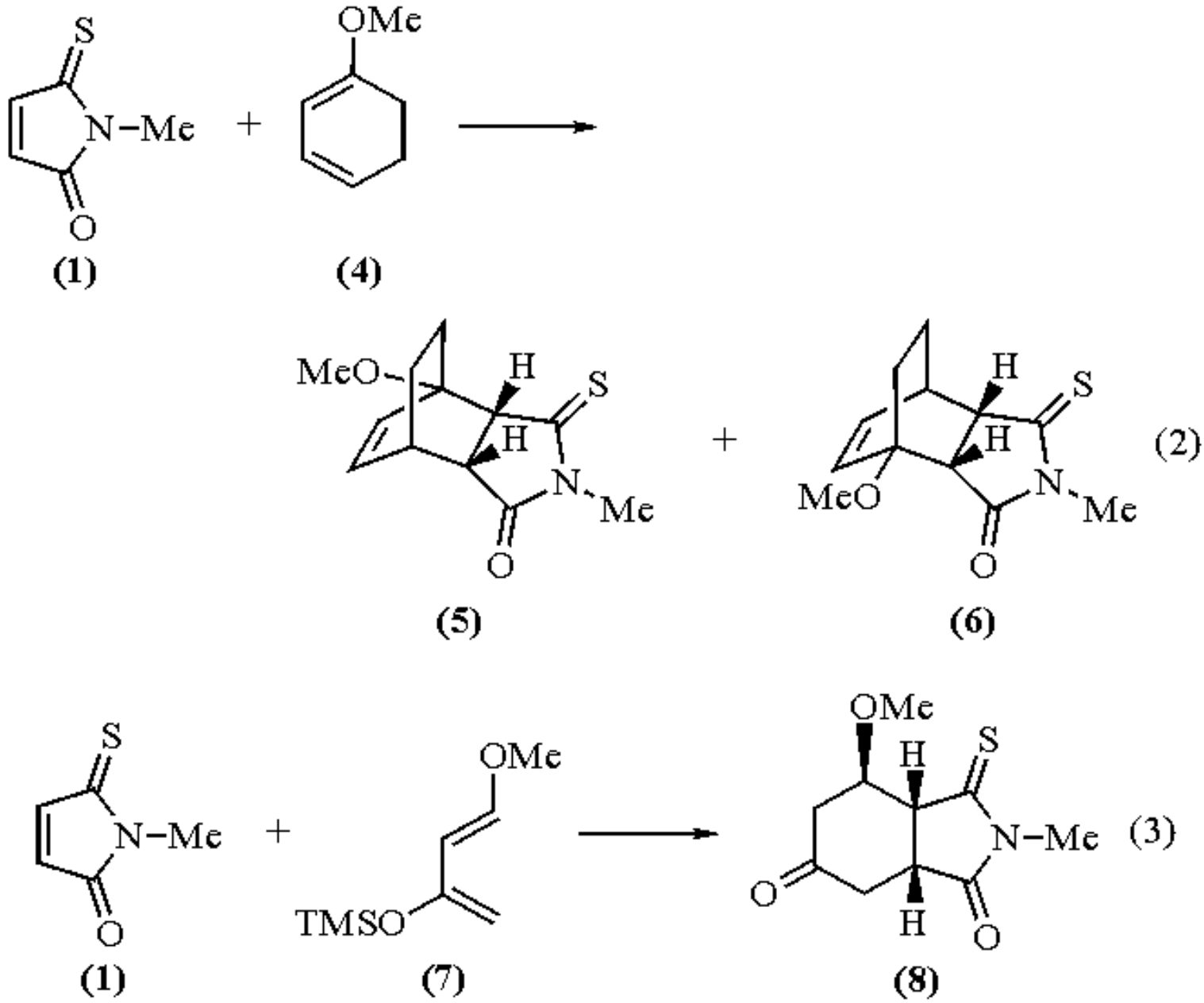

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1. Hu, Z.; Lakshmikantham, M. V.; Cava, M. P.; Becher, J.; Hansen, T.; Jorgenssen, T. *JOC* **1992**, *57*, 3988.
2. (a) Bishop, J. E.; O'Connell, J. F.; Rapoport, H. *JOC* **1989**, *56*, 5079. (b) Gossauer, A.; Hinze, R.-P.; Zilch, H. *AG(E)* **1977**, *16*, 418. (c) Augustin, M.; Köhler, M.; Kazandji, S. *T* **1984**, *40*, 3499. (d) Augustin. M.; Köhler, M. *ZC* **1983**, *23*, 402.
3. (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *JACS* **1990**, *112*, 4595. (b) Braun, R.; Sauer, J. *CB* **1986**, *119*, 1269.

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(*E*)-3-Methylthio-2-propenyl *p*-Tolyl Sulfone[1]

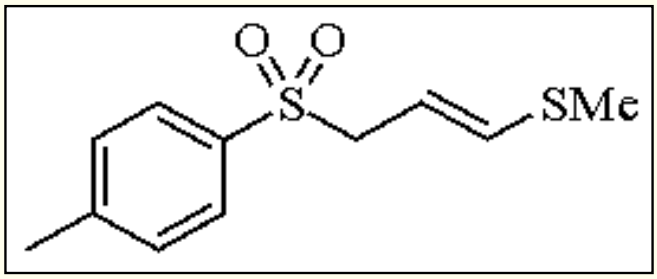

[92610-41-8] · $C_{11}H_{14}O_2S_2$ · (*E*)-3-Methylthio-2-propenyl *p*-Tolyl Sulfone · (MW 242.39)

(a synthetic reagent for preparation of α,β-unsaturated aldehydes and ketones)

Alternate Names: MTPTS; (*E*)-1-methylthio-3-(*p*-toluenesulfonyl)-1-propene.

Physical Data: colorless crystals; mp 79-80 °C (from EtOH).

Solubility: sol DMF, $CHCl_3$; slightly sol MeOH, EtOH, diethyl ether, CCl_4; practically insol H_2O, hexane.

Preparative Methods: either by the reaction of sodium methanethiolate or dimethyl sulfide with 3-chloro-1-propenyl *p*-tolyl sulfone[2] or by α-selenylation of 3-(methylthio)propyl *p*-tolyl sulfone and subsequent oxidative dehydroselenylation.[3]

Handling, Storage, and Precautions: very stable at ambient temperature. Use in a fume hood.

Synthesis of α,β-Unsaturated Aldehydes.

Monoalkylation of MTPTS can be achieved by treatment with an alkyl halide in the presence of ***Potassium Hydroxide***-TOMAC (a phase-transfer catalyst) or ***Sodium Hydride*** in DMF.[4] The reaction of the monoalkylation product with ***Titanium(IV) Chloride*** and ***Copper(II) Chloride*** in acetic acid-water followed by treatment with ***Potassium Carbonate*** in DME affords α,β-unsaturated aldehydes (eq 1).

(E)-3-Methylthio-2-propenyl p-Tolyl Sulfone

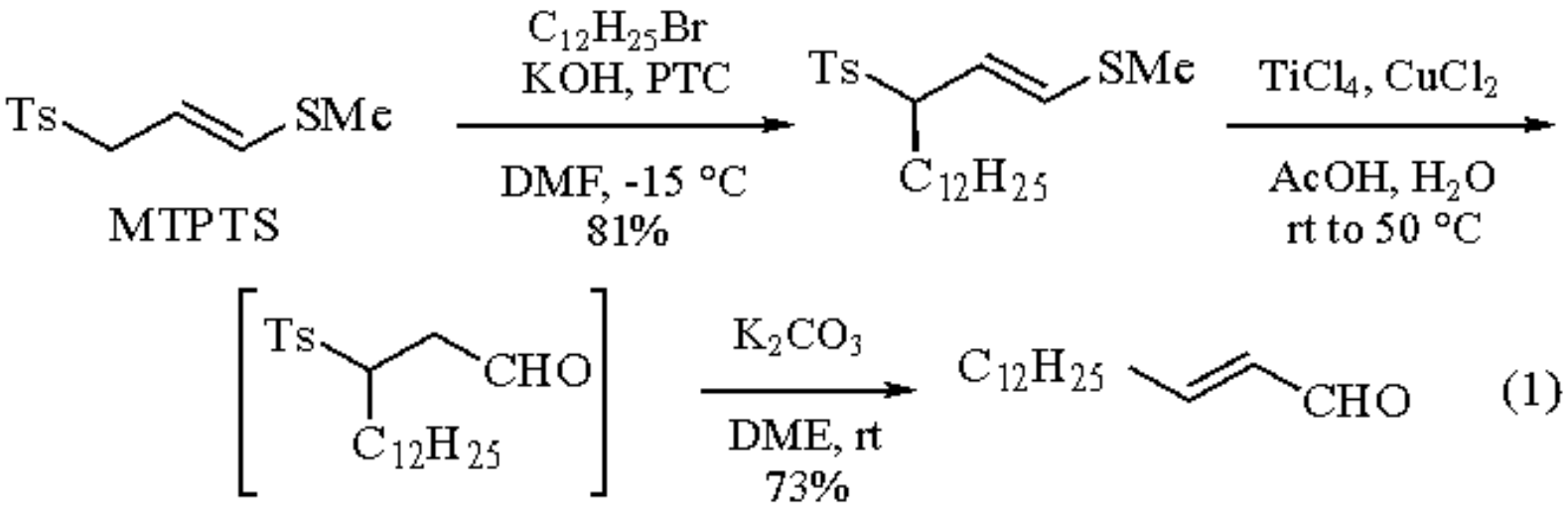

The second alkylation of MTPTS also occurs regiospecifically at the carbon α to the sulfonyl group. Since the dialkylated product is sensitive to silica gel, the reaction mixture is subjected without purification to hydrolysis with $TiCl_4$ and $CuCl_2$ in acetic acid-water to yield directly the corresponding β,β-disubstituted α,β-unsaturated aldehyde (eq 2).

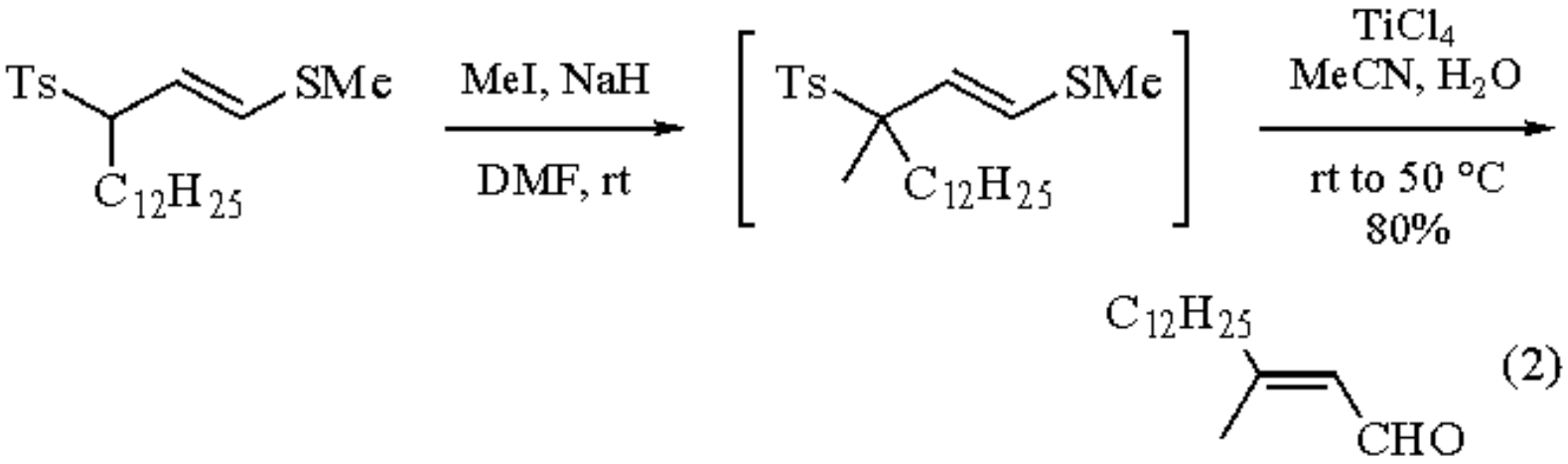

Synthesis of α,β-Unsaturated Ketones.

The dialkylated MTPTS undergoes a facile 1,3-rearrangement of its sulfonyl group on silica gel and a thermodynamically stable 2-alkenal dithioacetal *S,S*-dioxide is produced.[5] Since it has an active proton, the rearrangement product can be further alkylated. Subsequent hydrolysis of the alkylated product with $CuCl_2$ in methanol-water produces α,β-unsaturated ketones (eq 3). The synthetic method using MTPTS is characterized by its wide applicability to make various α,β-unsaturated ketones, three substituents of which are optionally and regiospecifically selected.

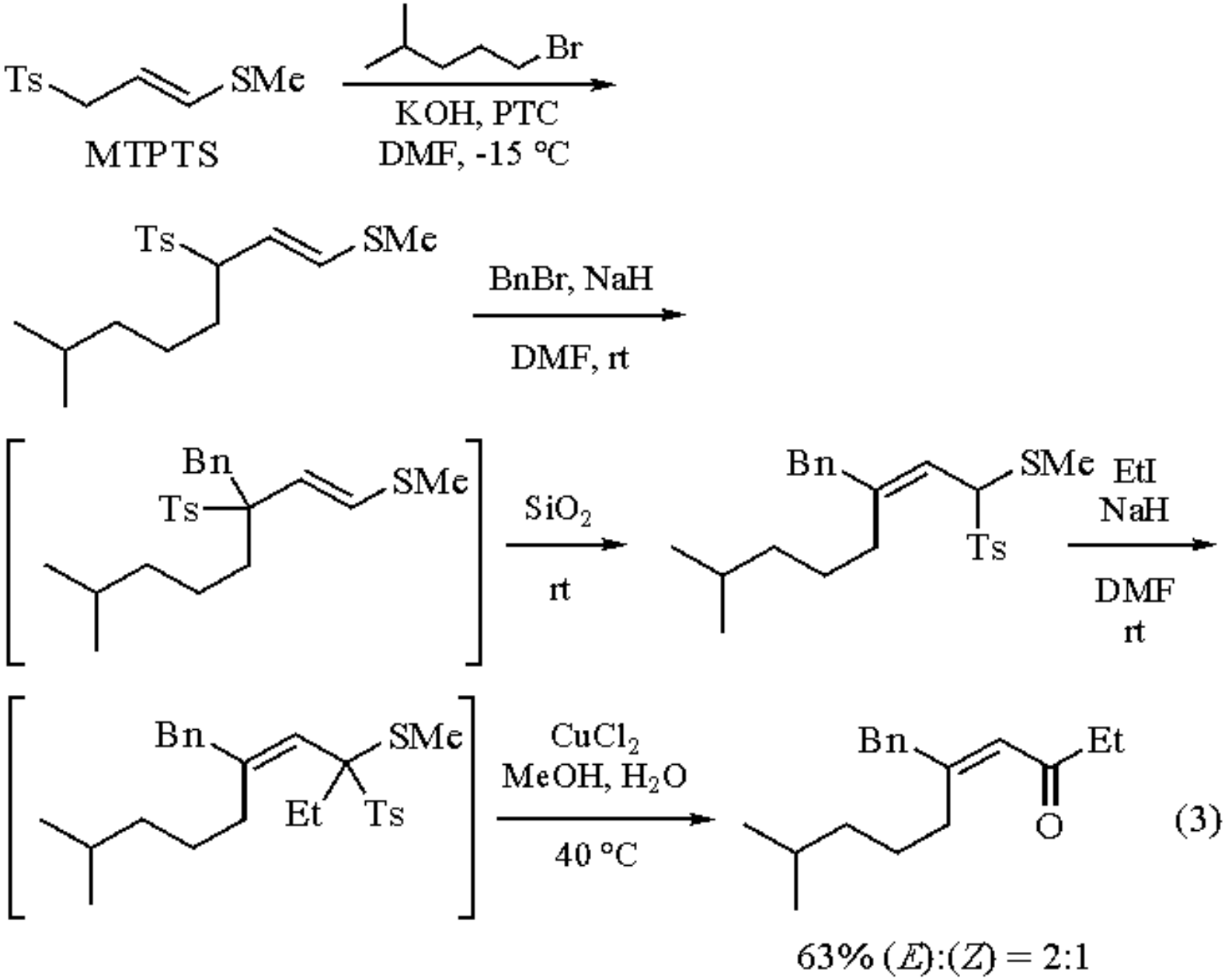

Related Reagents.

1,3-Dibutoxy-1-lithio-1-propene; ***1-Methoxyallenyllithium***; ***3-(Phenylsulfonyl)propanal Ethylene Acetal***.

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1. (a) Ogura, K. *PAC* **1987**, *59*, 1033. (b) Ogura, K. In *Studies in Natural Product Chemistry*; Atta-ur-Raman, Ed.; Elsevier: Amsterdam, 1990, Vol. 6, p 307.
2. Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H. *BCJ* **1984**, *57*, 3347.
3. Hirata, T.; Sasada, Y.; Ohtani, T.; Asada, T.; Kinoshita, G.; Senda, H.; Inomata, K. *BCJ* **1992**, *65*, 75.
4. Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H. *TL* **1984**, *25*, 2671.
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Katsuyuki Ogura

2-(Methylthio)tetrahydrofuran

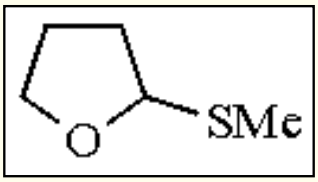

[98194-87-7] · $C_5H_{10}OS$ · 2-(Methylthio)tetrahydrofuran · (MW 118.22)

(methanethiol carbanion, $HSCH_2^-$, equivalent[1])

Physical Data: bp 66-67 °C/21 mmHg; *n*20D 1.4868.[2]

Preparative Methods: conveniently prepared in two steps in 46% yield from THF by light-initiated α-chlorination with ***Sulfuryl Chloride*** at -30 °C followed by reaction with ***Methanethiol***/***Triethylamine*** at -78 °C.[2] Deprotonation with ***n-Butyllithium*** gives 2-tetrahydrofuranyl(thiomethyl)lithium *[98194-88-8]*.[1]

Thiol and Disulfide Synthesis.

Reaction of 2-tetrahydrofuranyl(thiomethyl)lithium with ***t-Butyldimethylchlorosilane***, followed by *n*-BuLi and a second equivalent of *t*-butyldimethylchlorosilane followed by hydrolysis of the adduct with ***Silver(I) Nitrate*** or ***Mercury(II) Chloride*** followed by ***Hydrogen Sulfide*** or ***Hydrogen Chloride*** gives bis(*t*-butyldimethylsilyl)methanethiol ($(t\text{-}BuMe_2Si)_2CHSH$; 91%) (eq 1).[1]

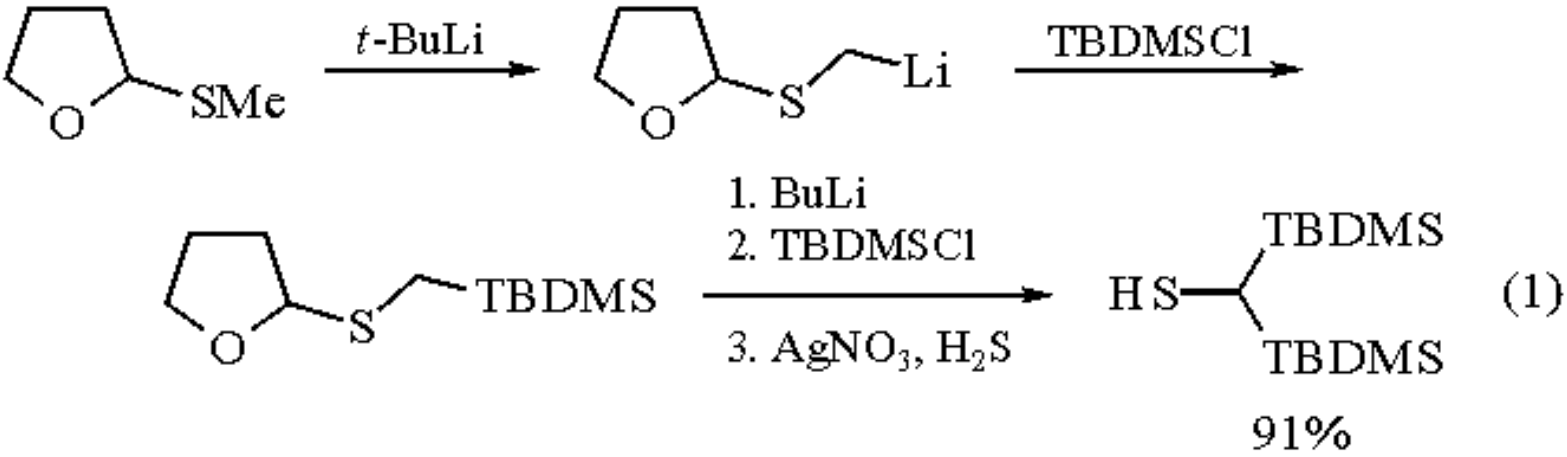

Related Reagents.

2-(Methylthio)tetrahydropyran.

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1. Block, E.; Aslam, M. *JACS* **1985**, *107*, 6729.
2. Brown, H. C.; Midland, M. M. *JACS* **1971**, *93*, 3291.

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2-(Methylthio)tetrahydropyran

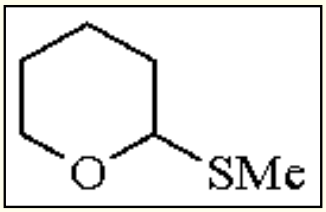

[31053-11-9] · $C_6H_{12}OS$ · 2-(Methylthio)tetrahydropyran · (MW 132.25)

(methanethiol carbanion, $HSCH_2^-$, equivalent[1])

Physical Data: bp 47-48 °C/5 mmHg;[2] *n*20D 1.4910;[3] colorless oil with minty aroma.

Preparative Methods: prepared in 84% yield by ***Pyridinium p-Toluenesulfonate***-catalyzed addition of ***Methanethiol*** to 2,3-dihydropyran;[1] this method is superior to an earlier procedure using HCl as catalyst.[2] Deprotonation with ***t-Butyllithium*** gives 2-tetrahydropyranyl(thiomethyl)lithium *[98194-89-9]*.[1]

Handling, Storage, and Precautions: stable to alkali; decomposed by dilute acid to methanethiol and 5-hydroxypentanal.[2]

Thiol and Disulfide Synthesis.

Reaction of 2-tetrahydropyranyl(thiomethyl)lithium with benzaldehyde, *n*-heptyl iodide, 1,6-dibromohexane, ***Benzyl Bromide***, ***t-Butyldimethylchlorosilane***, or ***Dichlorodimethylsilane***, followed by hydrolysis of the adduct with ***Silver(I) Nitrate*** or ***Mercury(II) Chloride*** followed by ***Hydrogen Sulfide*** or ***Hydrogen Chloride*** gives, respectively, $PhCH(OH)CH_2SH$ (100%), *n*-$C_8H_{17}SH$ (60%), $HS(CH_2)_8SH$ (76%), $PhCH_2CH_2SH$ (93%), *t*-$BuMe_2SiCH_2SH$ (77%), and $Me_2Si(CH_2SH)_2$ (22%). If the adduct is treated instead with iodine, disulfides instead of thiols result.[1] Repetitive treatment of the initial adduct with base and electrophile has been used to prepare $(Me_3Si)_3CSH$.[1] Application of these procedures to the synthesis of *cis*- and *trans*-3-mercaptocyclobutanol has been reported (eq 1).[4] Related work has been reported for the tetrahydropyran derivative of diphenylmethanethiol.[5]

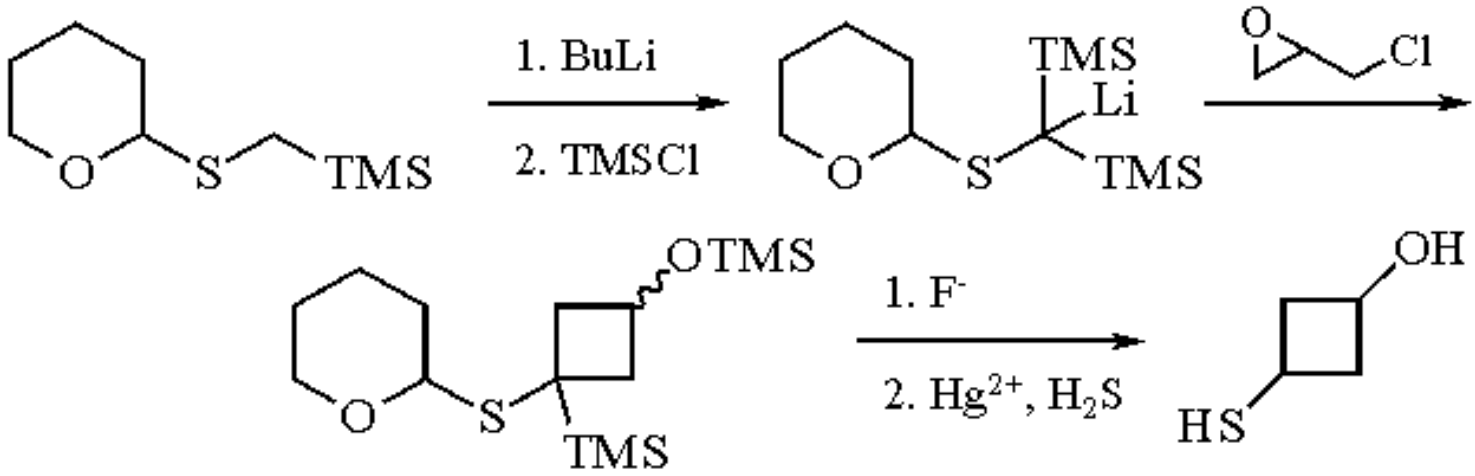

(1)

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1. Block, E.; Aslam, M. *JACS* **1985**, *107*, 6729.
2. Kipnis, F.; Ornfelt, J. *JACS* **1951**, *73*, 822.
3. de Hoog, A. J.; Havinga, E. *RTC* **1970**, *89*, 972.
4. Block, E.; Laffitte, J.-A.; Eswarakrishnan, V. *JOC* **1986**, *51*, 3428.
5. Berg, J. M.; Holm, R. H. *JACS* **1985**, *107*, 917.

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(Methylthio)trimethylsilane

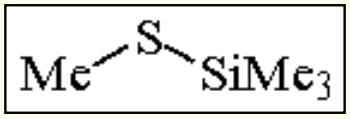

[3908-52-2] · $C_4H_{12}SSi$ · (Methylthio)trimethylsilane · (MW 120.32)

(thioacetalization under neutral conditions;[1,2] cleavage of ethers[3,4])

Physical Data: bp 110-114 °C; *d* 0.848 g cm^{-3}.

Solubility: sol organic solvents (CH_2Cl_2, benzene, acetonitrile, ether).

Form Supplied in: colorless liquid; commercially available.

Preparative Method: prepared as described by Evans et al.[14]

Handling, Storage, and Precautions: the reagent is sensitive to moisture and incompatible with strong oxidizing agents. Should be used in a well-ventilated fume hood.

Carbonyl Protection.

The Lewis acid-catalyzed reaction of aldehydes and ketones with (methylthio)trimethylsilane gives rise to the corresponding thioacetals (eq 1).[1,2] Selective thioacetalization can be achieved with this reagent (eq 2).[1] The reaction with α,β-unsaturated aldehydes and ketones leads to the formation of the 1,4-addition product.

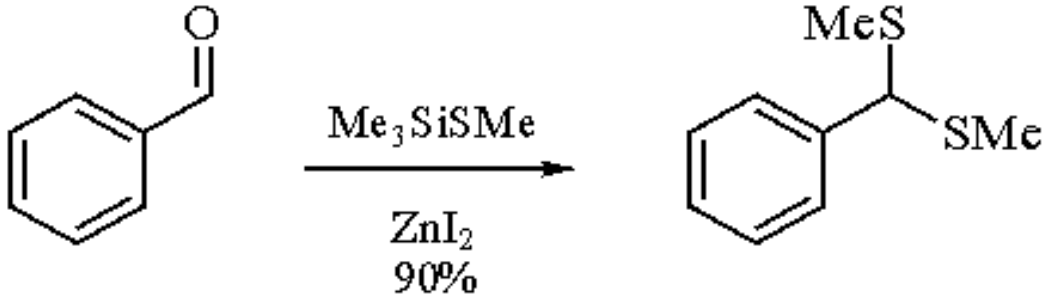

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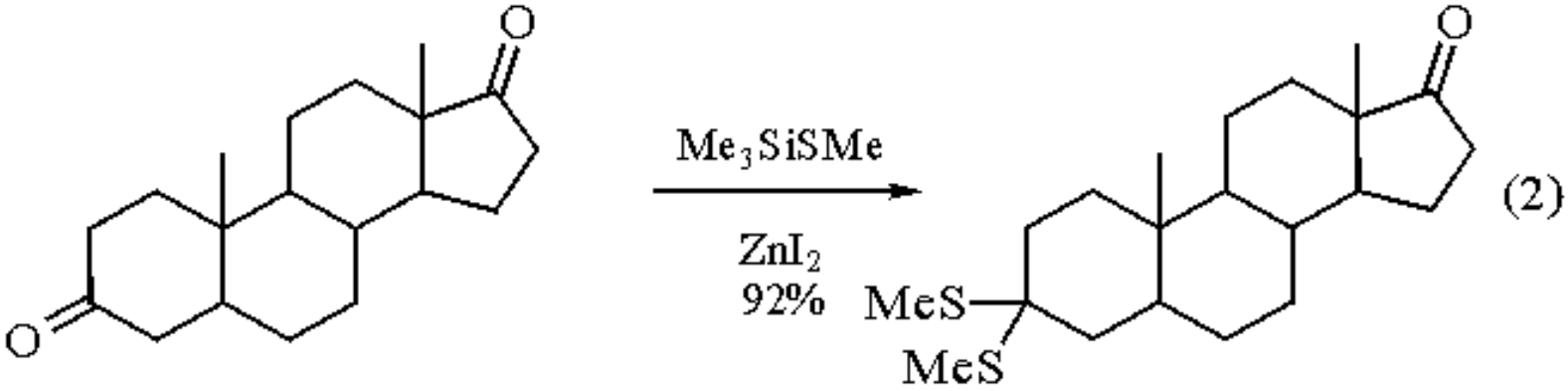

Cleavage of Acyclic and Cyclic Ethers.

Acyclic ethers are readily cleaved by (methylthio)trimethylsilane (eq 3).[3] In contrast to ***Iodotrimethylsilane***, esters are unaffected under the reaction conditions. The reagent is also compatible with acetals and amides.[4] The zinc chloride-catalyzed reaction of oxetanes with (methylthio)trimethylsilane leads to the formation of ring-opened products (eq 4).[5] No reaction takes place in the absence of ***Zinc Chloride***.

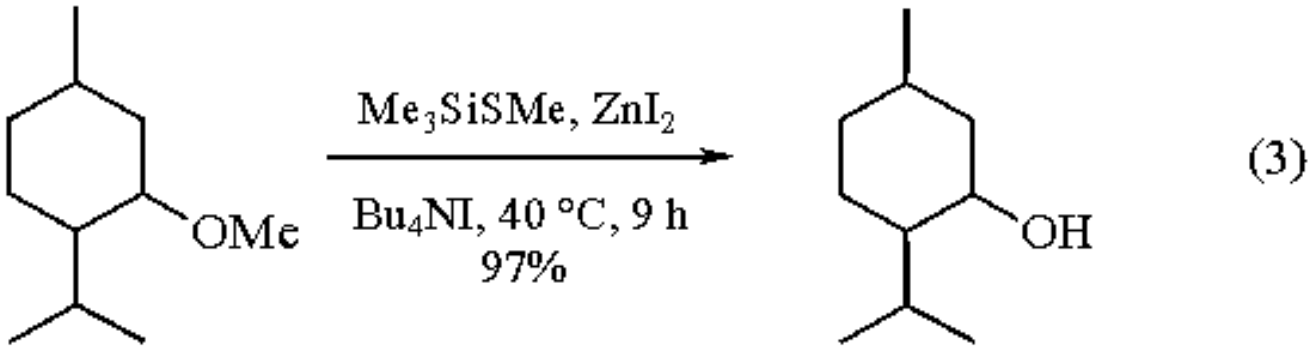

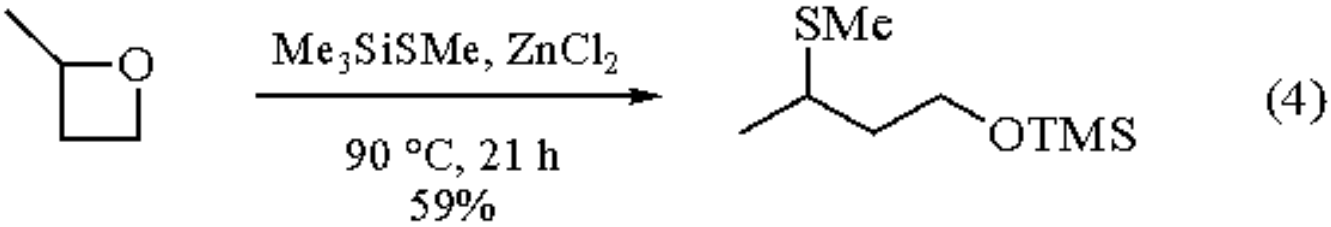

Vinyl Sulfides.

A general route to vinyl sulfides has been achieved through the reaction of thiosilanes with silyl enol ethers in the presence of ***Boron Trifluoride Etherate*** (eq 5).[6]

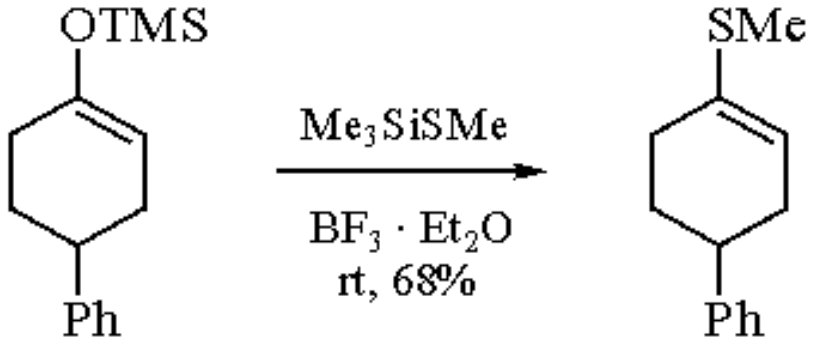

(5)

Miscellaneous Transformations.

The reaction of Me_3SiSMe with glycopyranoses leads to the stereoselective formation of 1-thioglycosides (eq 6).[7,8] When primary nitro compounds are treated sequentially with ***n-Butyllithium*** followed by Me_3SiSMe, the corresponding thiohydroximates are produced in good yields (eq 7).[9] 4-Sulfinylazetidin-2-ones undergo a novel substitution reaction with silylated heteronucleophiles in the presence of a catalytic amount of ***Zinc Iodide*** (eq 8).[10,11] When propenoyltrimethylsilane is treated with Me_3SiSMe, the synthetically useful silyl enol ethers of acylsilanes are formed (eq 9).[12] Orthothioesters are formed when esters are treated with Me_3SSiMe and ***Aluminum Chloride***.[13]

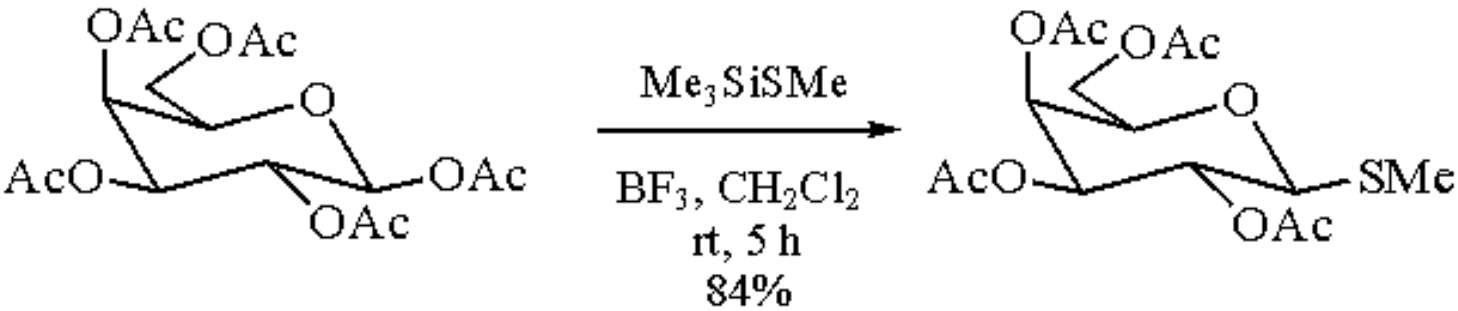

(6)

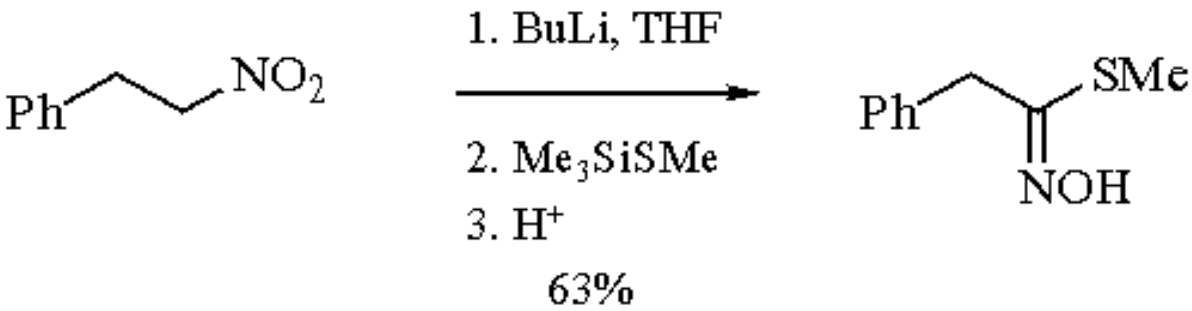

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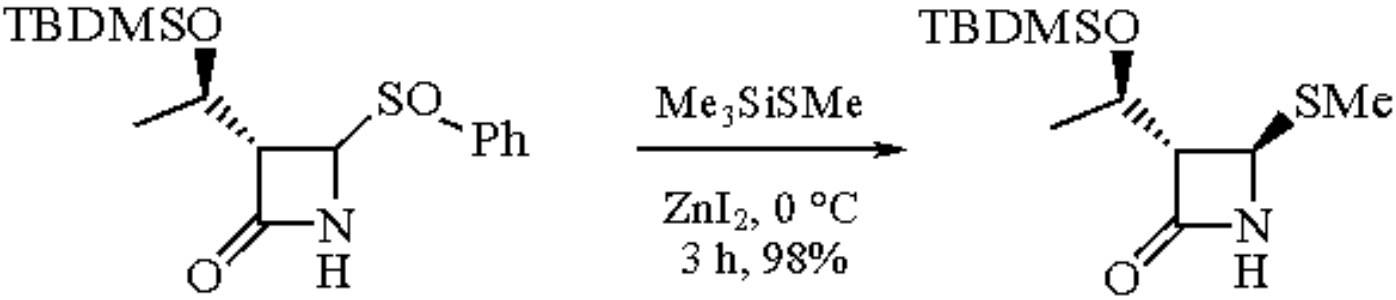

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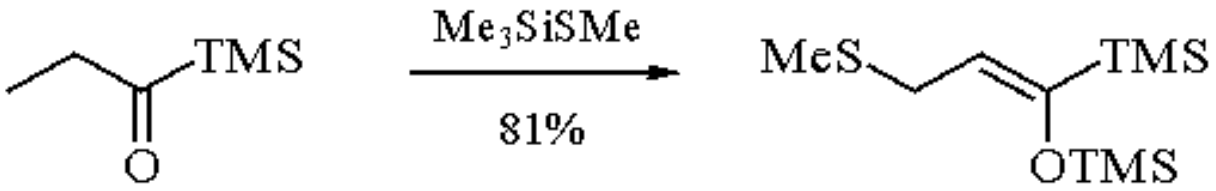

(9)

Related Reagents.

Methanethiol.

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1. Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *JACS* **1977**, *99*, 5009.
2. Groutas, W. C.; Felker, D. S. *S* **1980**, 861.
3. Hanessian, S.; Guindon, Y. *TL* **1980**, *21*, 2305.
4. Guindon, Y.; Young, R. N.; Frenette, R. *SC* **1981**, *11*, 391.
5. Firgo, H. A.; Weber, W. P. *JOM* **1981**, *222*, 201.
6. Degl'Innocenti, A.; Ulivi, P.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A. *SL* **1992**, 499.
7. Pozsgay, V.; Jennings, H. J. *TL* **1987**, *28*, 1375.
8. (a) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277: (b) Kameyama, A.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1990**, *200*, 269.
9. Hwu, J. R.; Tsay, S-C.; *T* **1990**, *46*, 7413.
10. Kita, Y.; Shibata, N.; Yoshida, N.; Tohjo, T. *TL* **1991**, *32*, 2375.
11. de Vries, J. G.; Hauser, G.; Sigmund, G. *H* **1985**, *23*, 1081.
12. Ricci, A.; Degl'Innocenti, A.; Borselli, G.; Reginato, G. *TL* **1987**, *28*, 4093.
13. Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *TL* **1986**, *27*, 4861.
14. Evans, D. A.; Grimm, E. G.; Truesdale, L. K. *JACS* **1975**, *97*, 3229.

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Methyltitanium Trichloride[1]

$MeTiCl_3$

[2747-38-8] · CH_3Cl_3Ti · Methyltitanium Trichloride · (MW 169.27)

(nonbasic nucleophilic reagent with high Lewis acidity;[1,2] adds to aldehydes, ketones, and acetals with high chemo- and stereoselectivity;[1,2] reagent for the S_N1 substitution of tertiary halides[3] and the geminal dimethylation of carbonyl compounds[4,5])

Alternate Names: trichloromethyltitanium; methyltitanium(IV) trichloride.

Physical Data: mp 29 °C; bp 37 °C/1 mmHg.

Solubility: sol most commonly used aprotic solvents, including pentane, Et_2O, THF, CH_2Cl_2. Forms octahedral complexes with bidentate ligands such as glycol ethers, ethylenediamines, and diphosphines as well as with solvents such as Et_2O and THF.

Form Supplied in: purple crystals; not available commercially.

Analysis of Reagent Purity: ^1H NMR: 2.9 ppm (s).

Preparative Methods: $MeTiCl_3$:[6] ether-free reagent, suitable for chelation-controlled carbonyl additions and S_N1 substitutions, can be prepared from a 2:1 mixture of ***Titanium(IV) Chloride*** and Me_2Zn[5] in CH_2Cl_2 at -78 °C. The resulting solution can be used as is or distilled under vacuum. A 1:1 mixture of $TiCl_4$ and Me_2Zn produces ***Dichlorodimethyltitanium***, which is more effective for S_N1 substitutions.[5] MeLi-$TiCl_4$-Et_2O:[2] solutions of $MeTiCl_3$ in Et_2O can be more conveniently prepared from ***Methyllithium*** and $TiCl_4$. Other organometallics, such as ***Methylmagnesium Bromide***, can also be used. In the workup, simple quenching with ice water is preferred. The use of ***Sodium Carbonate*** may lead to cumbersome emulsions of TiO_2, which can be avoided with NH_4F or ***Potassium Fluoride***.

Handling, Storage, and Precautions: moisture sensitive; stable at low temperature in the dark. At rt, it decomposes over several hours. Me_2Zn is very pyrophoric in a pure form.

Organotitanium Reagents.

While many titanium compounds are used widely as key components of Ziegler-Natta polymerization catalysts,[1a,1c] a variety of organotitanium derivatives have found great utility in organic synthesis as well. Compounds of the general type R^1TiX_3 (X = Cl, OR^2, or NR^3_2), studied extensively by Reetz and others,[1] often add to carbonyl groups with a high degree of chemo-, regio-, diastereo-, and enantioselectivity as compared with organomagnesium (RMgX, Grignard) or organolithium reagents (RLi). The synthetic advantages of these organotitanium reagents arise from the modulation of their nucleophilicity and Lewis acidity and basicity, as well as their improved solubility in organic solvents, and their increased steric and electronic requirements. Among the various commonly used derivatives, $MeTiCl_3$ is the most Lewis acidic, while ***Methyltitanium Triisopropoxide*** is the least acidic. Other homologs of type $RTiCl_3$ are more difficult to prepare and have found only limited synthetic use. The similar reagent Me_2TiCl_2 is more nucleophilic than $MeTiCl_3$ and is more effective for S_N1 substitutions.[5]

Chemoselective Addition to Aldehydes and Ketones.

$MeTiCl_3$ reacts quickly with aldehydes at low temperatures, while similar reactions with ketones require higher temperatures. Among other related organometallics, $MeTiCl_3$ exhibits one of the highest levels of aldehyde selectivities (eq 1).[2] In the presence of phosphines, however, an in situ blocking of the aldehyde group allows the reagent to react selectively with ketones in the presence of aldehydes.[7]

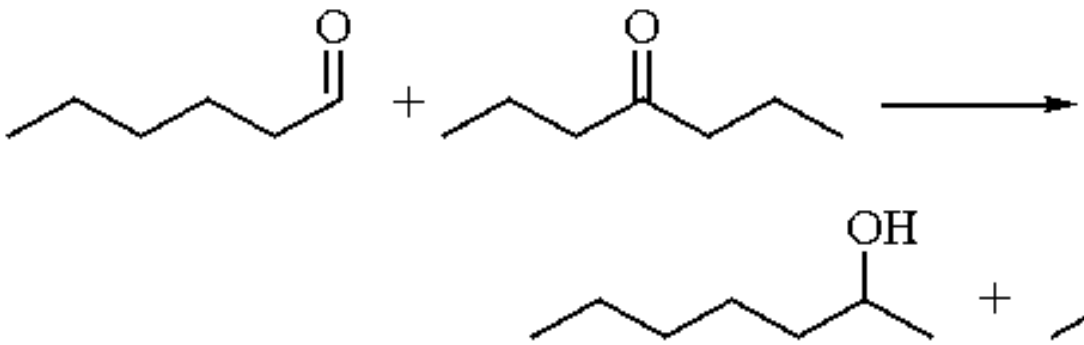

(1)

$MeTiCl_3$	99: 1
$MeTi(O\text{-}i\text{-}Pr)_3$	85:15
$MeZrCl_3$	74:26
MeLi	70:30

In general, $MeTiCl_3$ shows higher reactivity towards ketones than $MeTi(O\text{-}i\text{-}Pr)_3$. Discrimination between different ketones is also most effective with this reagent (eq 2).[2]

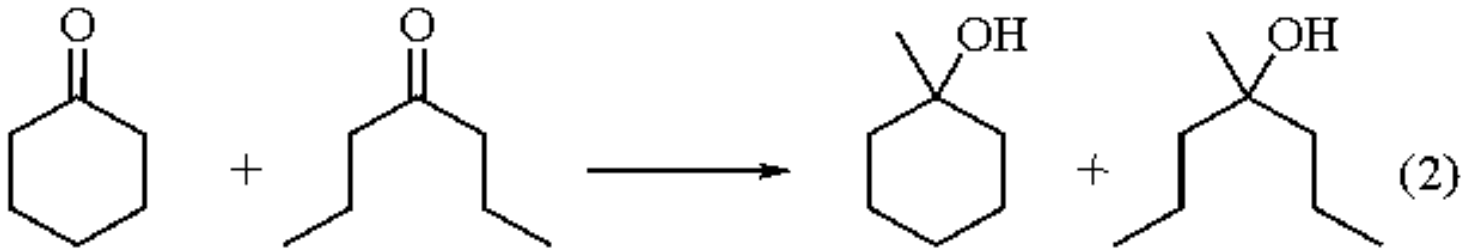

$MeTiCl_3$	99: 1
$MeTi(O\text{-}i\text{-}Pr)_3$	97: 3
MeLi	39:61

A wide variety of functional groups are tolerated under the reaction conditions, including ester, cyano, or nitro groups (eq 3).[2]

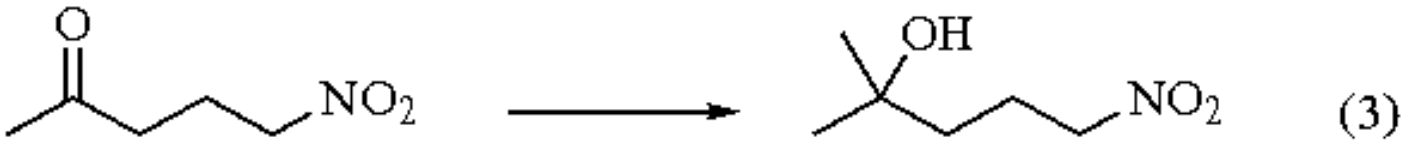

$MeTiCl_3$	76%
$MeTi(O\text{-}i\text{-}Pr)_3$	15%

Being the least basic, $MeTiCl_3$ is the reagent of choice for the addition of methyl groups to highly enolizable ketones (eq 4).[2]

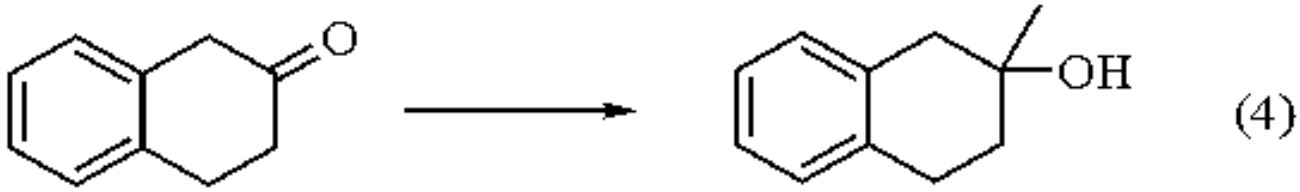

$MeTiCl_3$	90%
MeLi	60%

Stereoselective Additions to Aldehydes and Ketones.

The reagent, formed in situ from the combination of MeLi and $TiCl_4$ in Et_2O, adds to chiral aldehydes according to Cram's rule with higher stereoselectivity than ether-free preformed $MeTiCl_3$ or even $MeTi(O\text{-}i\text{-}Pr)_3$ (eq 5).[2,8]

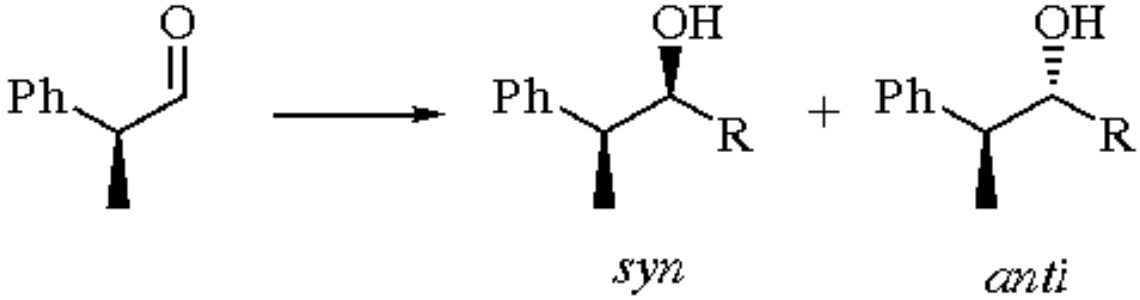

(5)

$MeTi(OPh)_3$	93: 7
$MeZr(O\text{-}i\text{-}Pr)_3$	90:10
$MeLi\text{-}TiCl_4\text{-}Et_2O$	90:10
$MeTi(O\text{-}i\text{-}Pr)_3$	88:12
$MeTiCl_3$	81:19
MeMgBr	66:34
MeLi	65:35

The addition of ether-free $MeTiCl_3$ to α-alkoxy aldehydes proceeds with chelation control[9] and high diastereofacial selectivity, while $MeTi(O\text{-}i\text{-}Pr)_3$ exhibits the opposite selectivity (eq 6).[10,11] The postulated titanium chelates have been observed directly by ^{13}C NMR spectroscopy.[11]

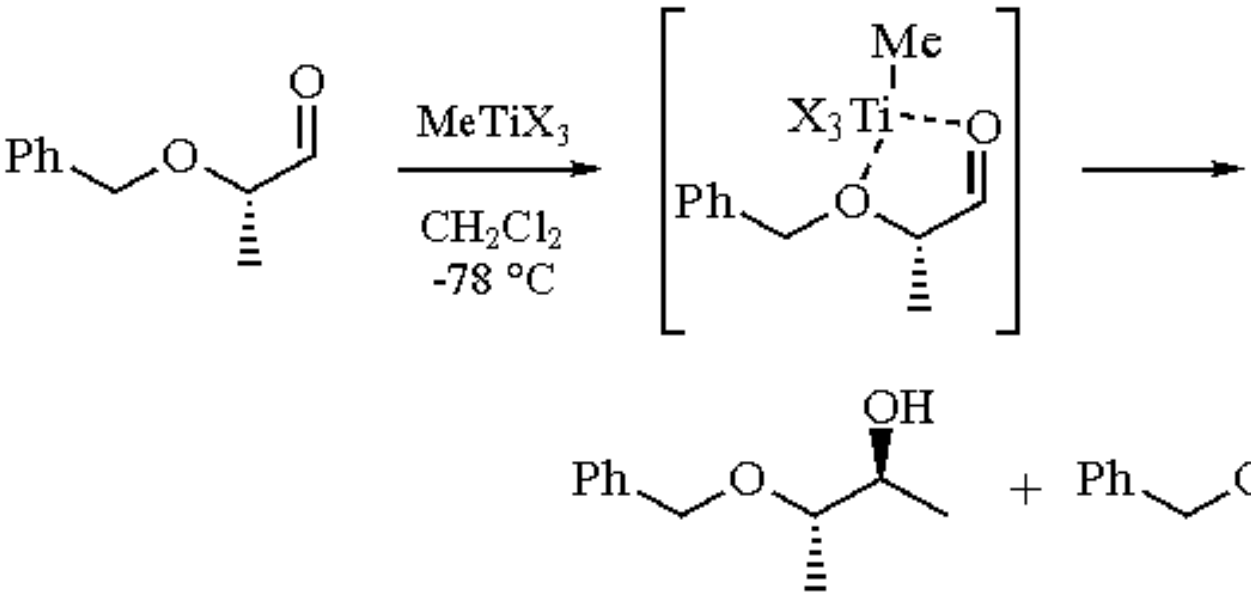

(6)

$MeTiCl_3$	92: 8
$MeTi(O\text{-}i\text{-}Pr)_3$	8:92

Similar chelation control with 1,3-asymmetric induction takes place with β-alkoxy aldehydes (eq 7).[12]

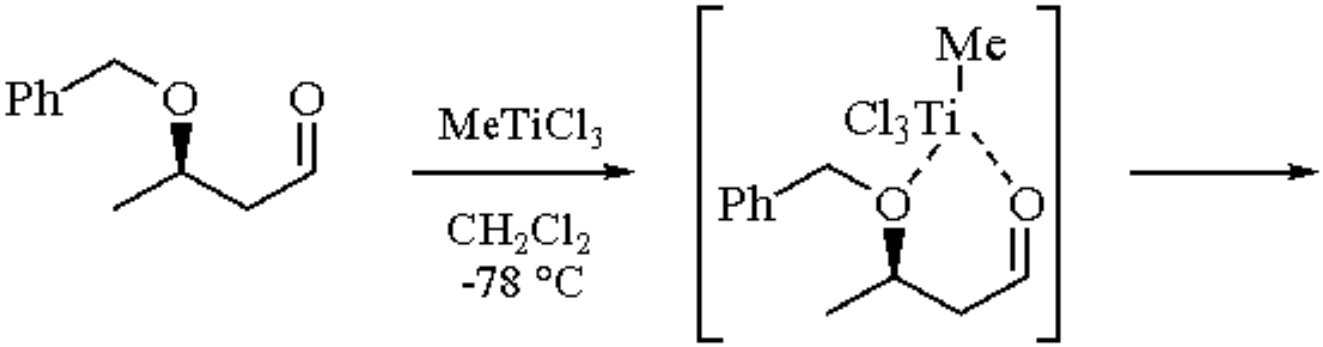

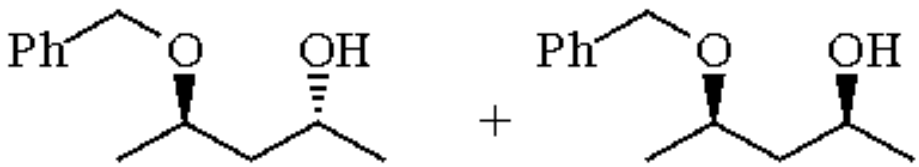

(7)

90:10

Although preformed $MeTiCl_3$ and the combination of Me_2Zn-$TiCl_4$ often behave similarly, in some cases they exhibit significantly different diastereofacial selectivities (eq 8).[13]

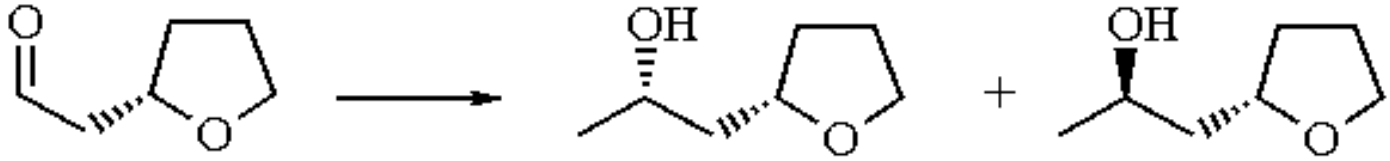

(8)

$MeTiCl_3$	140: 1
Me_2CuLi	80:20
Me_2Zn-$TiCl_4$	68:32
$MeTi(O\text{-}i\text{-}Pr)_3$	58:42
MeLi	58:42
MeMgCl	37:63
MeMgCl-$ZnBr_2$	22:78
Me_2CuLi-Et_3B	15:85

Chelation of $MeTiCl_3$ with neighboring sulfur groups is also possible (eq 9).

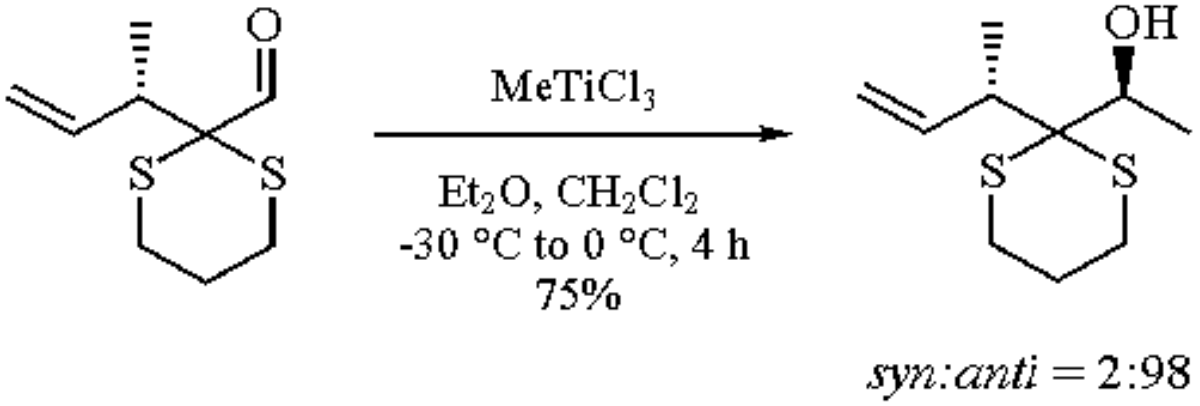

(9)

$MeTiCl_3$ adds efficiently and stereoselectively to the carbonyl group of β-keto sulfoxides, despite the facile enolization of these compounds. Presumably this process involves chelation with the sulfoxide oxygen (eq 10).[14]

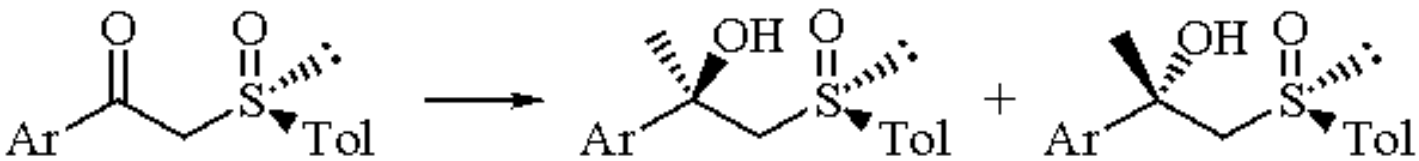

(10)

$MeTiCl_3$, Et_2O	96%	97: 3
Me_2Al, PhMe	71%	13:87

Additions to Acetals.

$MeTiCl_3$ reacts readily with acetals at low temperature even in the presence of ketones. With chiral acetals, the reaction is highly stereoselective (eq 11).[15]

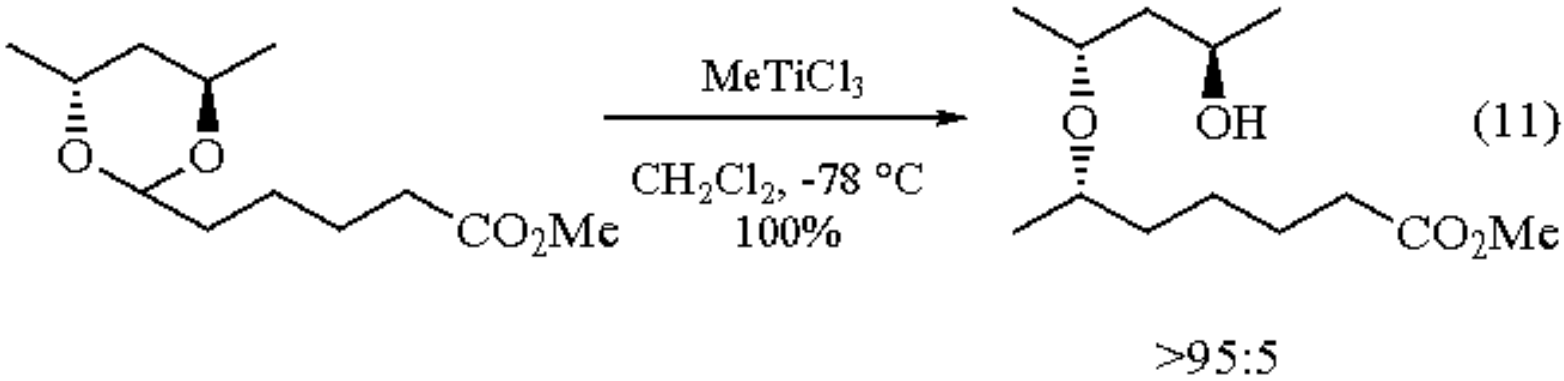

(11)

S_N1 Methylation of Tertiary Alkyl Halides.

The high Lewis acidity of $MeTiCl_3$ and the related derivative Me_2TiCl_2, obtained from $MeTiCl_3$ or Me_2Zn and 1 equiv of $TiCl_4$, makes them suitable for the S_N1 substitution of tertiary chlorides (eq 12)[3] or bromides (eq 13).

Primary or secondary halides do not undergo this reaction, which presumably proceeds via a carbocation.

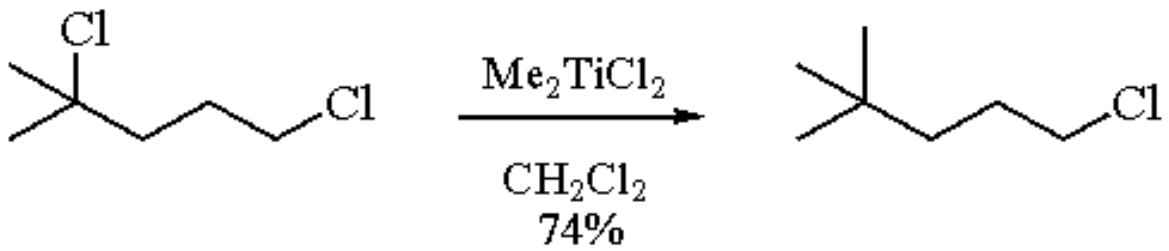

(12)

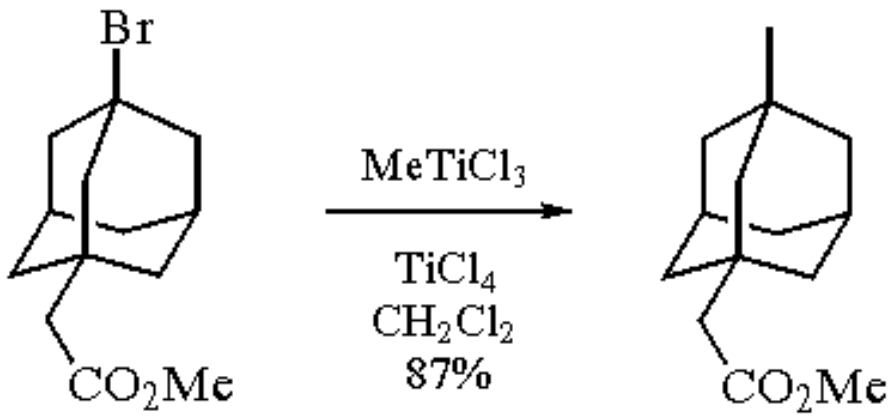

(13)

Geminal Dimethylation of Carbonyl Compounds.

Reaction of ketones with $MeTiCl_3$, or more effectively with Me_2TiCl_2[16,17] or Me_2Zn-$TiCl_4$,[5] gives the corresponding geminal dimethyl derivatives directly[4] (eq 14).[16] This process presumably involves an initial addition to the carbonyl followed by ionization and S_N1 substitution by a second methyl group.

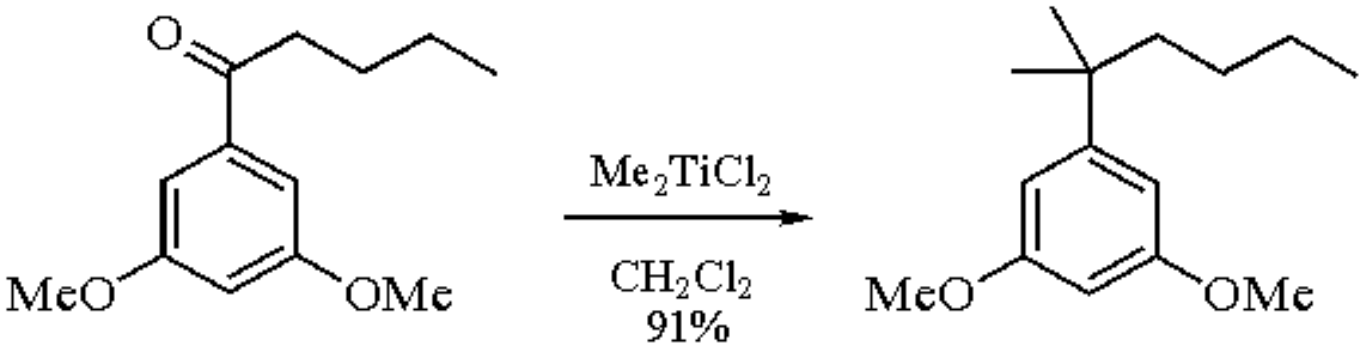

(14)

When a combination of Me_2Zn and $TiCl_4$ is used in this reaction, the geminal dimethylation products are maximized when at least 2 equiv of each is utilized.[5] Otherwise, the corresponding tertiary alcohol or tertiary chloride are obtained as major products (eq 15).[5]

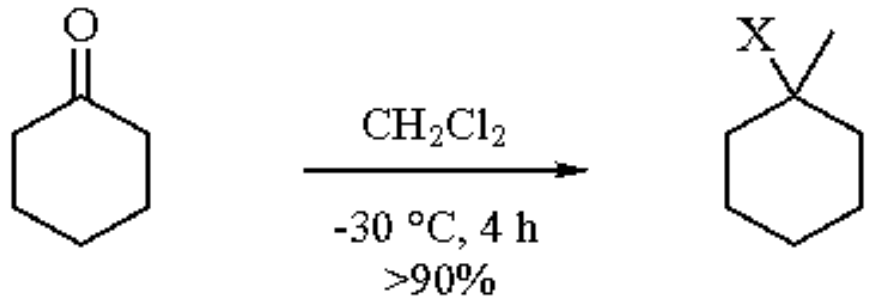

(15)

$TiCl_4$ (equiv)	Me_2Zn (equiv)	X
1	1	OH
3	1	Cl
2	2	Me

The reaction works well with a variety of aliphatic and aromatic ketones, with the exception of α,β-unsaturated derivatives, which give a mixture of products. It is even possible to generate adjacent quaternary carbons in this manner (eq 16).[5]

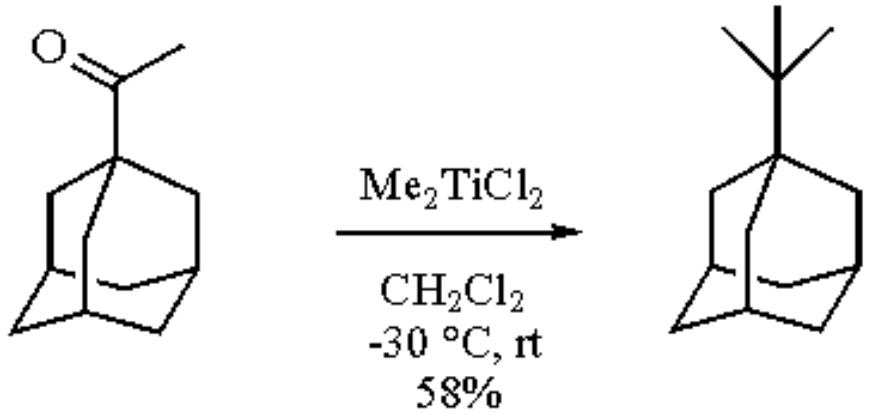

(16)

Although aliphatic aldehydes give alcohols under these reaction conditions, aromatic aldehydes undergo geminal dimethylation to form isopropyl derivatives (eq 17).[17]

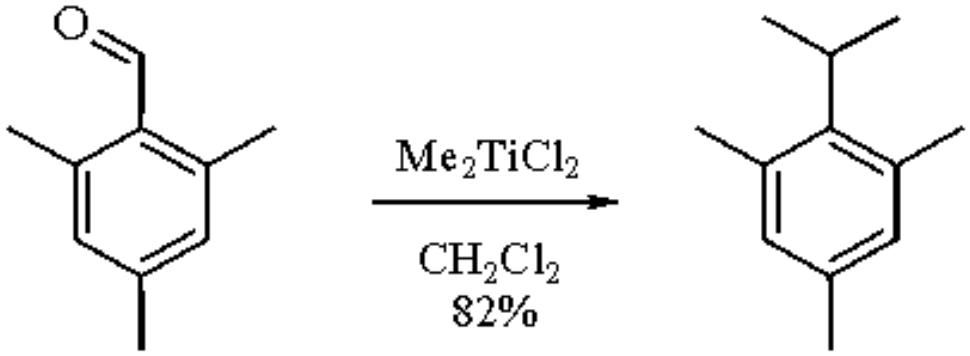

(17)

Similarly, acid chlorides undergo a direct geminal trimethylation (eq 18).[5]

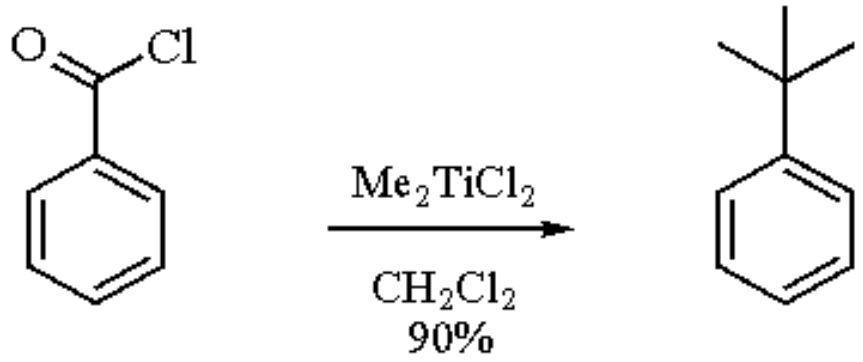

(18)

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10. Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *AG(E)* **1983**, *22*, 989.
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13. Baldwin, S. W.; McIver, J. M. *TL* **1991**, *32*, 1937.
14. Fujisawa, T.; Fujimura, A.; Ukaji, Y. *CL* **1988**, 1541.
15. Mori, A.; Maruoka, K.; Yamamoto, H. *TL* **1984**, *25*, 4421.
16. Reetz, M. T.; Westermann, J.; Steinbach, R. *CC* **1981**, 237.
17. Reetz, M. T.; Kyung, S.-H. *CB* **1987**, *120*, 123.

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Methyltitanium Triisopropoxide[1]

$MeTi(O\text{-}i\text{-}Pr)_3$

[18006-13-8] · $C_{10}H_{24}O_3Ti$ · Methyltitanium Triisopropoxide · (MW 240.22)

(nonbasic nucleophilic reagent;[1] adds to aldehydes and ketones with very high chemo-[1,2] and stereoselectivity;[1,3] adds to lactols stereoselectively[4,5])

Alternate Names: methyltriisopropoxytitanium; methyltitanium tris(isopropoxide); methyltris(2-propanolato)titanium; triisopropoxymethyltitanium.

Physical Data: bp 50 °C/0.01 mmHg; mp 10 °C.

Solubility: miscible with most nonprotic organic solvents, e.g. Et_2O, THF, CH_2Cl_2, toluene. In dilute solutions it is mainly monomeric, while in more concentrated solutions some degree of aggregation occurs.

Form Supplied in: bright yellow liquid; not available commercially.

Analysis of Reagent Purity: ^1H NMR in C_6D_6: 4.61 (m, 3H); 1.26 (d, 18H); 0.98 (s, 3H).

Preparative Methods: pure reagent can be prepared by the addition of a solution of ***Methyllithium*** in Et_2O to an equimolar amount of ***Chlorotitanium Triisopropoxide*** or ***Titanium Tetraisopropoxide*** in Et_2O at -40 °C followed by warming to rt.[2] It can be isolated in excellent yields by removal of the solvent in vacuo and distillation. For carbonyl additions[6] the reagent can be prepared in situ from MeLi and $ClTi(O\text{-}i\text{-}Pr)_3$ (which can be prepared in situ from a 3:1 mixture of $Ti(O\text{-}i\text{-}Pr)_4$ and ***Titanium(IV) Chloride***). The yields from these in situ methods are essentially the same as when purified reagent is employed.

Handling, Storage, and Precautions: moisture and air sensitive. Under N_2 it can be kept in the refrigerator for weeks; at rt it decomposes into a deep blue-green liquid over 12 h.

Organotitanium Reagents.

The nucleophilic addition of alkyl groups to aldehydes and ketones to give alcohols is traditionally performed with organomagnesium (RMgX, Grignard) or organolithium reagents (RLi). The conversion of these carbanion equivalents to derivatives of the general type R^1TiX_3 (X = Cl, OR^2, or NR^3_2) often results in significant improvements in the chemo-, regio-, diastereo-, and enantioselectivity of these processes.[1] Consequently, these organotitanium compounds

have found widespread synthetic utility, beyond their traditional use as components of Ziegler-Natta polymerization catalysts.[1a,1b] The synthetic advantages of these reagents are derived not only from the modulation of their nucleophilicity and Lewis basicity, but also through their improved solubility in organic solvents and their increased steric and electronic requirements. In the case of MeTi(O-*i*-Pr)$_3$, the three bulky alkoxy substituents on the titanium prevent oligomerization and dramatically reduce its Lewis acidity, which decreases in the following order: ***Methyltitanium Trichloride*** > MeTiCl$_2$(O-*i*-Pr) > MeTiCl(O-*i*-Pr)$_2$ > MeTi(O-*i*-Pr)$_3$. Similarly to other organotitanium reagents, MeTi(O-*i*-Pr)$_3$ exhibits much higher chemo- and stereoselectivity than MeLi or ***Methylmagnesium Bromide***.

Chemoselective Additions to Aldehydes and Ketones.[2,7]

MeTi(O-*i*-Pr)$_3$ adds readily to aldehydes in a 1,2-fashion, under mild conditions (-50 °C to 22 °C, over 2-3 h), forming methyl addition products in high yields. It also has low basicity and tolerates a wide variety of functional groups. While the reagent does not add to the carbonyl group of esters, it can promote transesterification to the isopropyl esters. Surprisingly, a similar reaction takes place with acyl chlorides, which are also converted to isopropyl esters. Other functional groups, such as epoxides, alkyl halides, amides, cyano or nitro substituents, do not interfere with the carbonyl addition process (eq 1).[6] The use of MeLi or MeMgBr in these cases gives complex mixtures and low yields of the alcohols.

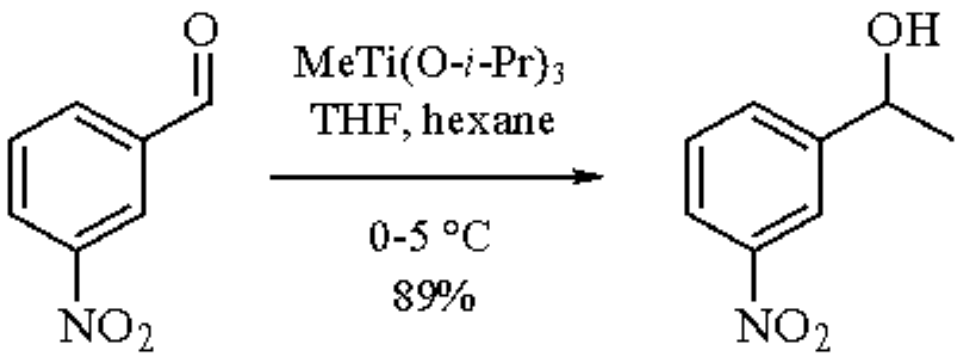

(1)

The reagent reacts with aldehydes at much faster rates than with ketones (up to 10^5:1) and it can be used for the selective addition to aldehydes in the presence of ketones[7] (eq 2).[2]

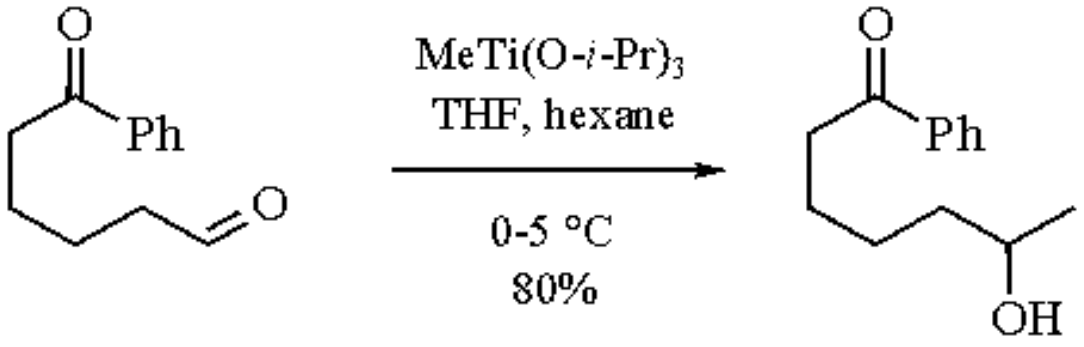

(2)

The reagent is highly regioselective and is sensitive to both steric and electronic effects. Among two aldehydes or two ketones, it adds to the least hindered one with a high degree of preference.[2] The order of relative reactivity for selected carbonyls is shown in eq 3.[8]

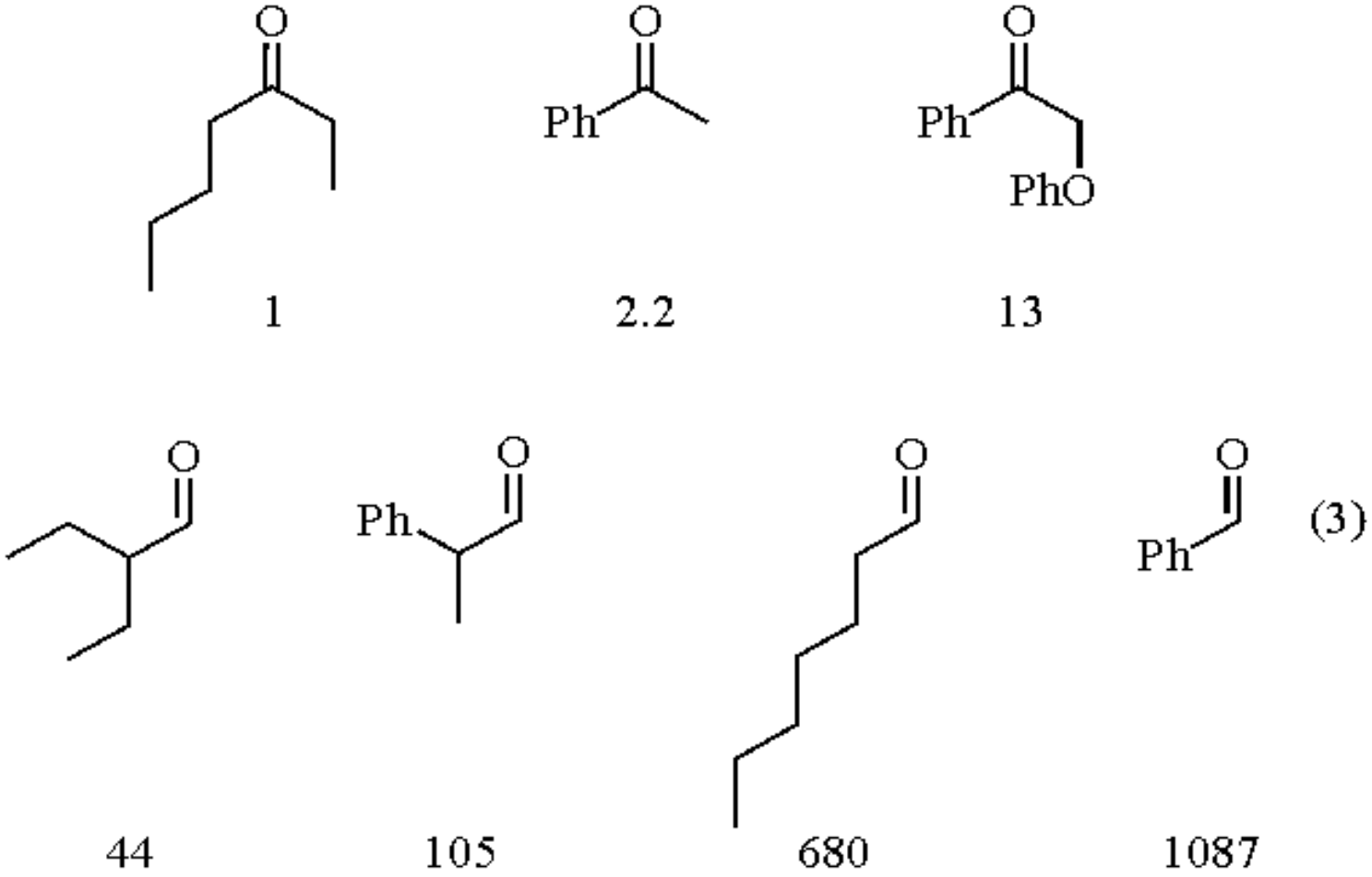

Other reagents of the general type RTi(O-*i*-Pr)$_3$, exhibit analogous selectivities, adding preferentially to the least hindered carbonyls.[9] The reverse selectivity can be achieved via the in situ protection of the least hindered group with a bulky organoaluminum reagent (eq 4).[10]

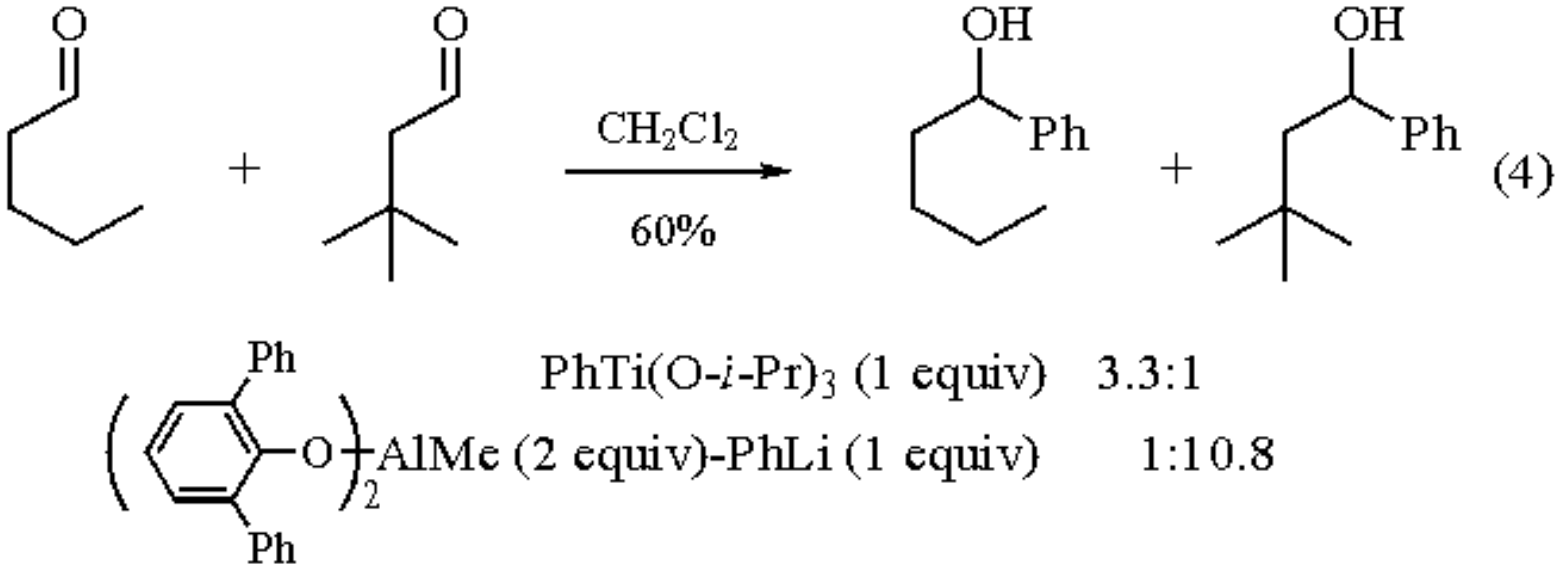

Stereoselective Additions to Aldehydes and Ketones.

The addition of MeTi(O-*i*-Pr)$_3$ to carbonyl groups proceeds according to Cram's rule (Felkin-Anh model), but with enhanced stereoselectivities. Although other reagents can be slightly more selective, overall MeTi(O-*i*-Pr)$_3$ is often the reagent of choice (eq 5).[1c,1f,3]

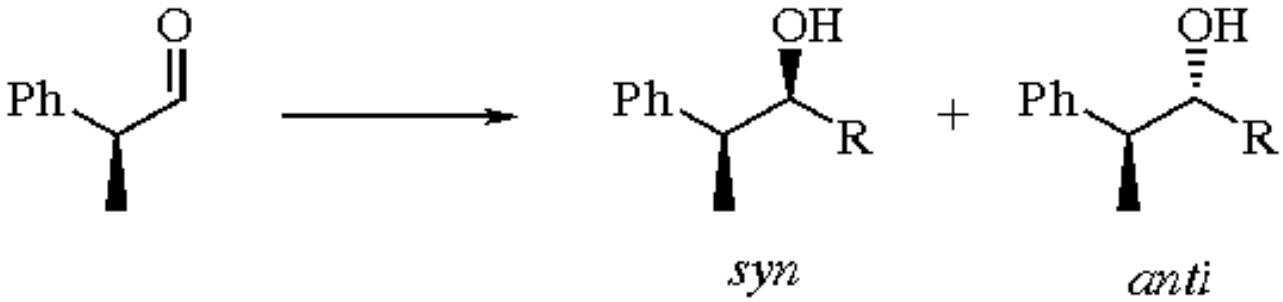

MeTi(OPh)$_3$	93:7
MeZr(O-*i*-Pr)$_3$	90:10
MeLi-TiCl$_4$-Et$_2$O	90:10
MeTi(O-*i*-Pr)$_3$	88:12
MeTiCl$_3$	81:19
MeMgBr	66:34
MeLi	65:35

Although the addition of several organometallics (particularly MeTiCl$_3$) to chiral α- or β-alkoxy aldehydes often proceeds via chelation control,[1h,11] the reactions of MeTi(O-*i*-Pr)$_3$ tend to take place without chelation[8] and with high diastereoselectivity in the opposite sense (eq 6).[12]

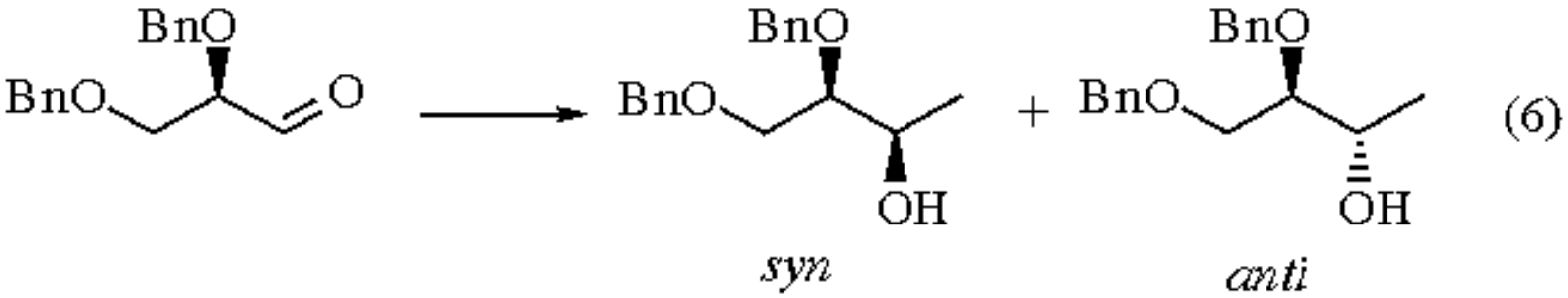

MeTi(O-*i*-Pr)$_3$	7:93
MeLi · LiBr	45:55
MeMgBr	45:55
Me$_2$CuLi	47:53
MeCu · MgBr$_2$	96:4

Despite its low Lewis acidity, however, the additions of MeTi(O-*i*-Pr)$_3$ to ketones with neighboring chelating substituents proceed with rate-accelerating chelation,[1h,8,11] giving tertiary alcohols with a high degree of stereocontrol

(eq 7),[13] including remote asymmetric induction.[14]

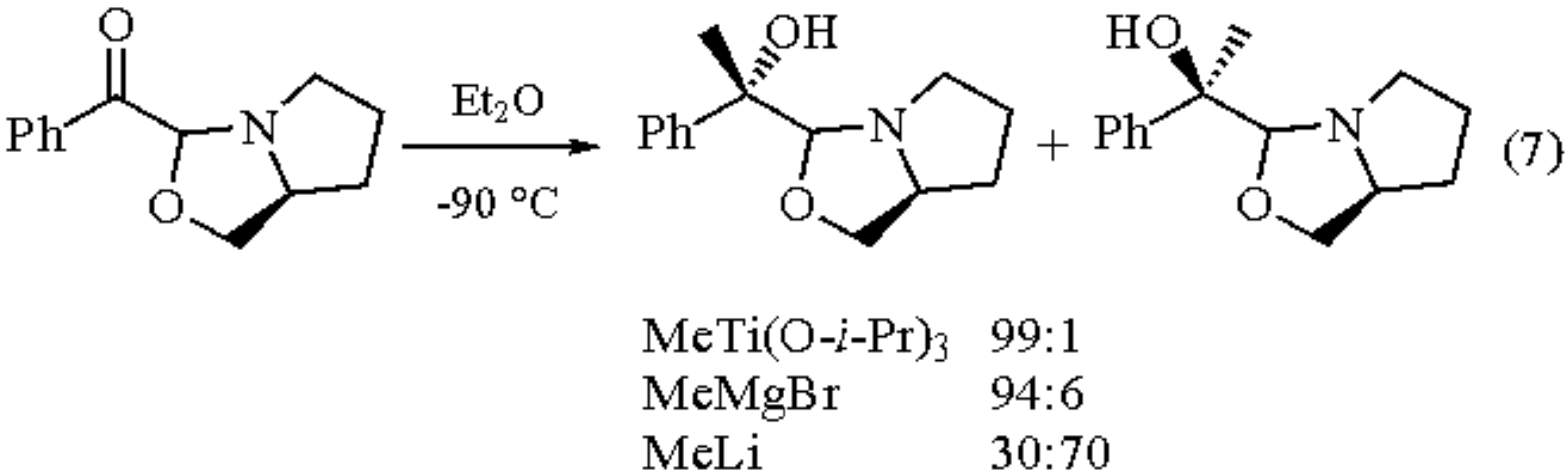

Additions to cyclohexanones take place preferentially from the equatorial direction, even with conformationally labile substrates (eq 8).[3]

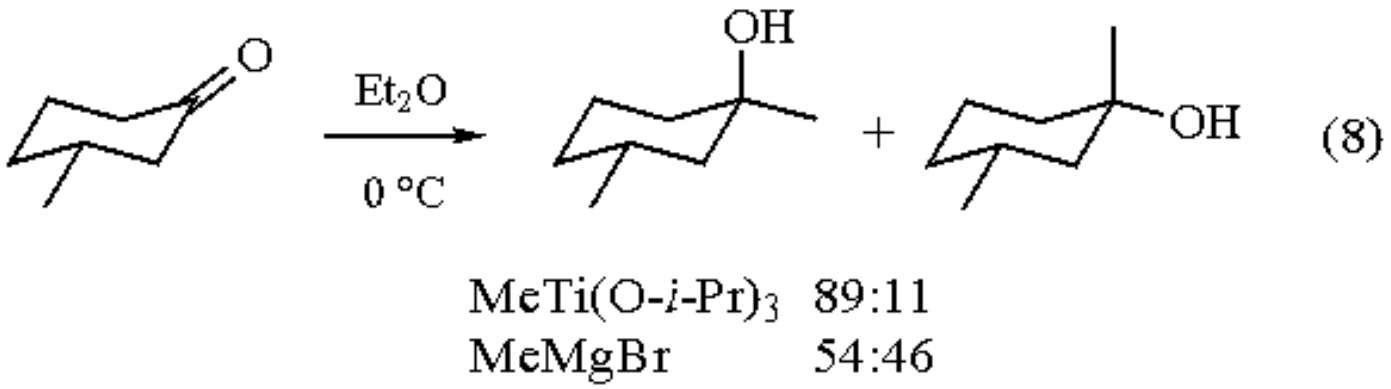

Stereoselective Additions to Lactols.

MeTi(O-*i*-Pr)$_3$ is the reagent of choice for the stereoselective addition to lactol derivatives (eqs 9 and 10).[4,5] These reactions presumably involve chelated alkoxytitanium intermediates.[4,5,15,16]

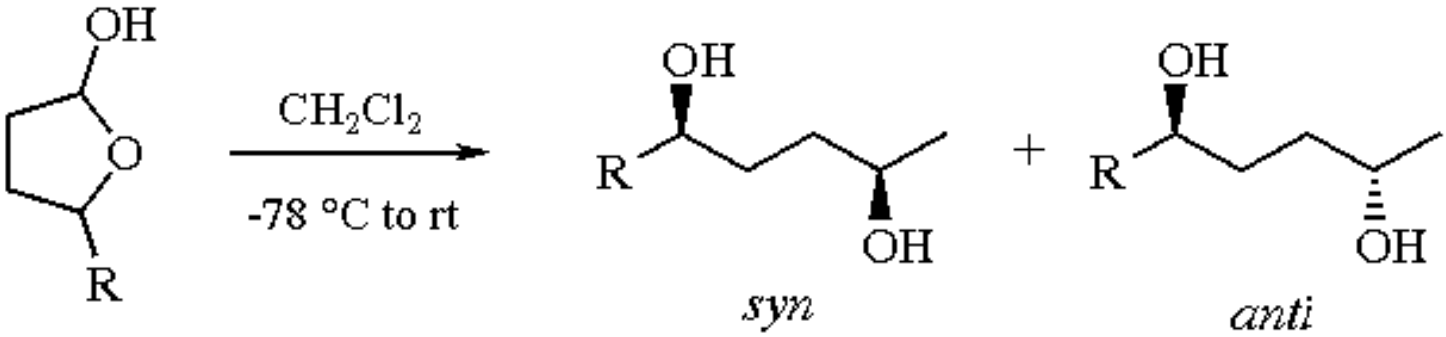

(9)

$MeTi(O\text{-}i\text{-}Pr)_3$	12:1
$MeTiCl_3$	8.4:1
MeLi	1.7:1
MeMgBr	1.3:1
Me_3Al	1.1:1

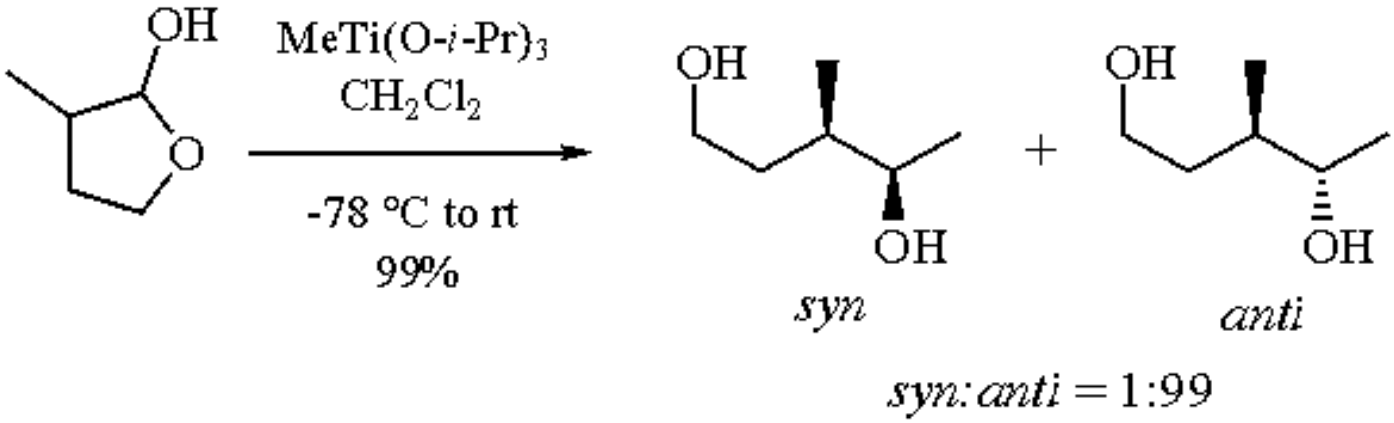

(10)

Copper-Catalyzed S_N2' Alkylations.

Although the $RTi(O\text{-}i\text{-}Pr)_3$ reagents generally behave as poor nucleophiles, in the presence of catalytic amounts of copper salts they react with allyl halides or phosphonates exclusively in an S_N2' manner (eq 11).[17]

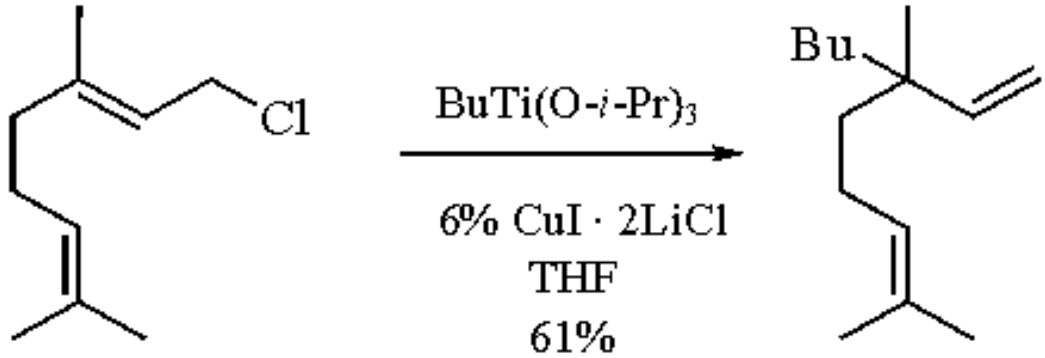

(11)

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Methyltitanium Tris(diethylamide)[1]

$MeTi(NEt_2)_3$

[25483-56-1] · $C_{13}H_{33}N_3Ti$ · Methyltitanium Tris(diethylamide) · (MW 279.37)

(thermally stable reagent useful for alkylative amination of carbonyl compounds[2])

Physical Data: mp 5 °C.

Solubility: sol Et_2O.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: ^1H NMR in C_6D_6: 3.71 (q, 12H); 1.25 (t, 18H); 0.43 (s, 3H).

Preparative Methods: a solution of ***Methyllithium*** (or ***Methylmagnesium Bromide***) in Et_2O is added slowly to a stirred equimolar solution of ***Chlorotris(diethylamino)titanium***[3] or $BrTi(NEt_2)_3$ in Et_2O at -30 °C. After 0.5 h at -30 °C and 1 h at rt, the yellow solution can be used as is[2,4] or can be isolated[5] by sublimation at 60-70 °C/0.001 mmHg.

Handling, Storage, and Precautions: moisture sensitive; thermally stable.

Organotitanium Reagents.

The use of titanium compounds as components of Ziegler-Natta polymerization catalysts[1b,1c] has led to the preparation of numerous organotitanium derivatives that have found other synthetic applications as well.[1d] Among the various titanium ligands the dialkylamido groups produce the least acidic and most thermally stable organotitanium species, presumably due to stronger electron donation and larger steric hindrance. Thus, while ***Methyltitanium Trichloride*** and ***Methyltitanium Triisopropoxide*** decompose at rt over several hours, $MeTi(NEt_2)_3$ is thermally stable at rt and decomposes at temperatures above 120 °C.[6]

Alkylative Amination.

Nonenolizable aldehydes react with $MeTi(NEt_2)_3$ to give tertiary amines through the addition of both the methyl group and one of the NEt_2 ligands. The reaction works in moderate yields with aliphatic (eq 1),[2] aromatic, and α,β-unsaturated aldehydes (eq 2).[2] The reaction proceeds via the initial addition of the amino group to the carbonyl, followed by the formation of an iminium intermediate which undergoes nucleophilic attack by the methyl group. The yields are lowered by a competitive formation of diamine or enamine products (with enolizable aldehydes). Both of these hydrolyze back to the starting material during the acidic aqueous workup.

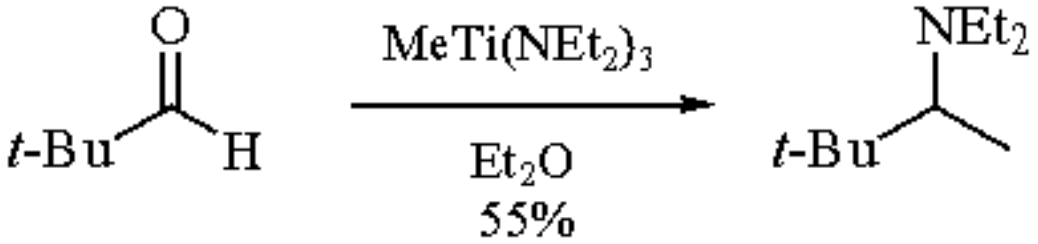

(1)

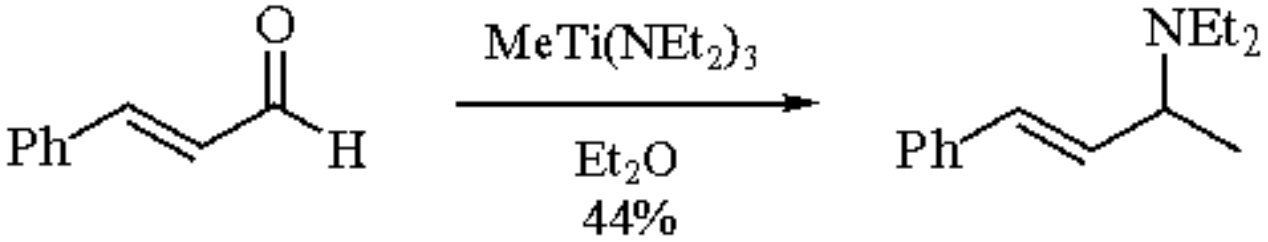

(2)

This reaction also works with the corresponding perfluoroalkyl derivatives (eq 3).[7]

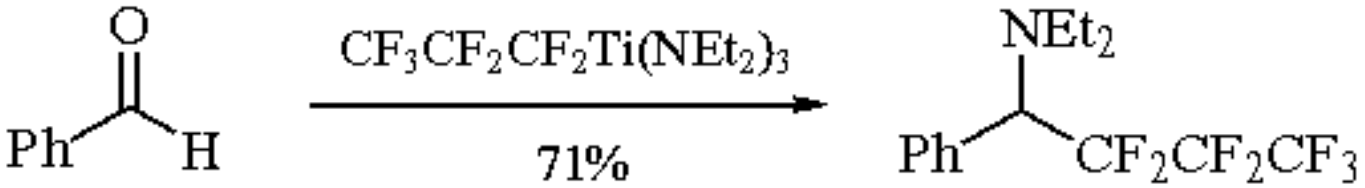

(3)

Additions to Aldehydes.

Unlike $MeTiCl_3$ and $MeTi(O\text{-}i\text{-}Pr)_3$, which carry out Grignard-type additions to aldehydes and ketones, $MeTi(NEt_2)_3$ is not suitable for this type of reaction since the diethylamide group adds to the carbonyl faster than the methyl group. However, with $RTi(NEt_2)_3$ derivatives of more reactive carbon nucleophiles, such as $CH_2{=}CHCH_2Ti(NEt_2)_3$, the carbonyl additions can be efficient (eq 4).[4]

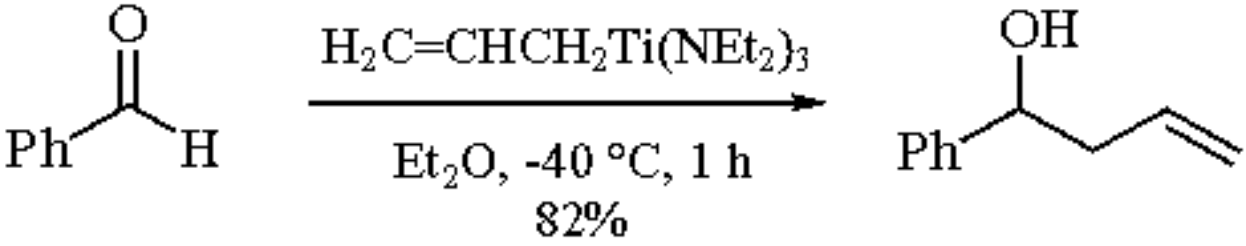

(4)

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α-Methyltoluene-2,α-sultam[1]

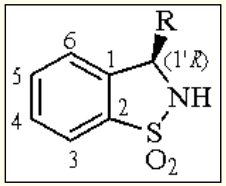

(1´*S*)-(**1a**; R = Me)

[130973-57-8] · $C_8H_9NO_2S$ · α-Methyltoluene-2,α-sultam · (MW 183.25) (1´*R*)-(**1a**)

[130973-53-4] (1´*S*)-(**1b**; R = *t*-Bu)

[137694-01-0] · $C_{11}H_{15}NO_2S$ · α-*t*-Butyltoluene-2,α-sultam · (MW 225.34) (1´*R*)-(**1b**)

[137694-00-9]

(chiral auxiliary: *N*-enoyl derivatives undergo highly stereoselective Diels-Alder reactions with cyclopentadiene[2] and 1,3-dipolar cycloadditions with nitrile oxides;[3] enolates of *N*-acyl derivatives participate in highly stereoselective alkylations, acylations, and aldolizations[4])

Physical Data: (**1a**) mp 92 °C. (1´*S*)-(**1a**) [α]20D -30.0° (*c* 1.21, $CHCl_3$). (1´*R*)-(**1a**) [α]20D +31.0° (*c* 0.6, EtOH). (**1b**) mp 129-130 °C. (1´*S*)-(**1b**) [α]20D -53.9° (*c* 1.00, $CHCl_3$). (**1b**) has been incorrectly assigned.[3]

Preparative Methods: both enantiomers of the α-methyl sultam may be prepared on a multigram scale in optically pure form by asymmetric hydrogenation of imine (**2a**) followed by simple crystallization (eq 1).[5] The (*R*)-enantiomer of the α-*t*-butyl sultam may also be prepared in enantiomerically pure form by asymmetric reduction of imine (**2b**) followed by fractional crystallization.[3] However, multigram quantities of either enantiomer of the α-*t*-butyl sultam may be prepared by derivatization of the racemic auxiliary (obtained in 98% yield from reaction of (**2b**) with ***Sodium Borohydride*** in MeOH) with ***10-Camphorsulfonyl Chloride***, separation of the resulting diastereomers by fractional crystallization, and acidolysis.[3] Prochiral imines (**2a**) and (**2b**) are readily prepared from inexpensive Saccharine by treatment with ***Methyllithium*** (73%) and ***t-Butyllithium*** (66%), respectively.

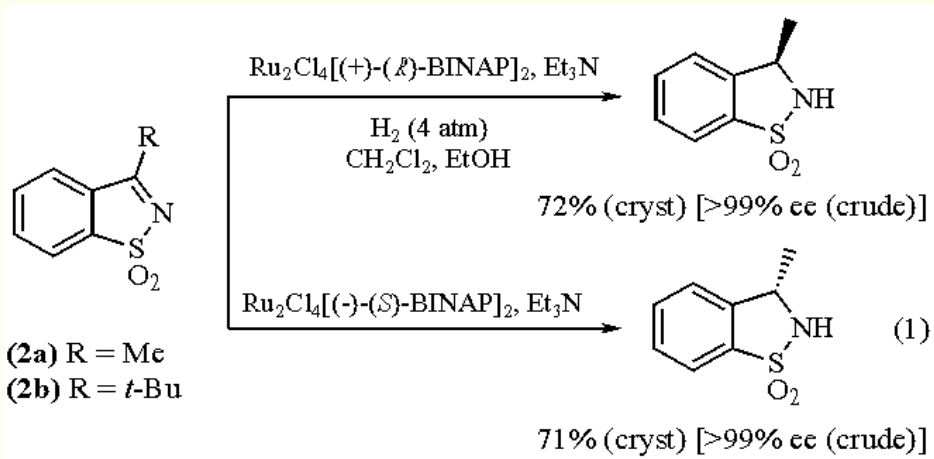

Handling, Storage, and Precautions: these auxiliaries are white crystalline solids which are stable indefinitely at ambient temperature in sealed containers.

Introduction.

alpha-Methyltoluene-2,alpha-sultam

The toluene-2,α-sultams are recently introduced relatives of the well established ***10,2-Camphorsultam*** chiral auxiliary and have been designed to provide similar high levels of face discrimination in reactions of pendent prochiral functionality. Features that distinguish them include high crystallinity and facile NMR and HPLC analysis of derivatives, favorable acylation and aldolization characteristics of derived *N*-acyl enolates, and improved cleavage characteristics.

Preparation of Derivatives.

N-Enoyl[2,3] and *N*-acyl[4] sultam derivatives are readily prepared using either ***Sodium Hydride***-acid chloride or ***Triethylamine***-acid chloride single-step protocols. Various alternative derivatization procedures that work for the 10,2-camphorsultam auxiliary would also be expected to be effective.

Reactions of *N*-Enoyl and *N*-Acyl Derivatives.

[2 + 4] Diels-Alder Cycloadditions (Alkene -> Six-Membered Cycloadduct).[2]

N-Acryloyl-α-methyltoluene-2,α-sultam (**3a**) participates in highly *endo* and C(α)-*re* π-face selective Lewis acid promoted Diels-Alder reactions with ***Cyclopentadiene***, ***1,3-Butadiene*** and ***Isoprene*** (eq 2 and Table 1). These levels of induction compare favorably with most alternative auxiliaries, including the 10,2-camphorsultam. However, *N*-crotonyl-α-methyltoluene-2,α-sultam (*ent*-**3b**) reacts with cyclopentadiene with only moderate π-face selectivity (cf. 93% de with 10,2-camphorsultam). Unusually high *endo* selectivity is observed for the non-Lewis acid-catalyzed reaction of sultam (**3a**) with cyclopentadiene but again the π-face selectivity is only moderate. The corresponding reactions of both α-*t*-butyl- and α-benzyltoluene-2,α-sultams are less selective.

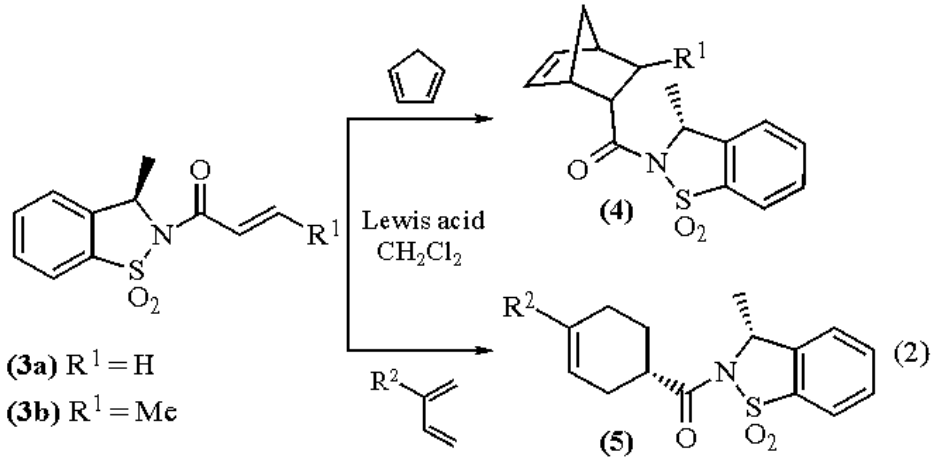

Table 1 Intermolecular Diels Alder Reactions of *N*-Enoyl Sultams (**3a**) or (**3b**) ® (**4**) and (**3a**) ® (**5**) (eq 2)

Dienophile	Diene	Lewis acid[a]	Temp (°C)	Time (h)	Adduct	Yield crude (cryst.) (%)	de crude (cryst.) (%)
(**3a**)	Cyclopentadiene	None	25		(**4**) (R^1 = H)	95[b]	62
(**3a**)	Cyclopentadiene	Me_2AlCl	- 98	0.2	(**4**) (R^1 = H)	97[c] (83)	93 (>99)
(**3a**)	1,3-Butadiene	$EtAlCl_2$	- 78	18	(**5**) (R^2 = H)	79	90
(**3a**)	Isoprene	Me_2AlCl	- 78	7	(**5**) (R^2 = Me)	87	92
ent-(**3b**)	Cyclopentadiene	Me_2AlCl	- 78	24	*ent*-(**4**) (R^1 = Me)	74[d] (58)	59 (>99)

[a] 1.6 2.0 equiv. [b] 96% *endo*. [c] >99% *endo*. [d] 97% *endo*.

1,3-Dipolar Cycloadditions with Nitrile Oxides (Alkene -> Isoxazoline).[3]

1,3-Dipolar cycloaddition reactions of *N*-acryloyl-α-*t*-butyltoluene-2,α-sultam (**6**) with various nitrile oxides give isoxazolines with extremely high C(α)-*re* π-facial control (eq 3). The levels of selectivity exceed those obtainable with the 10,2-camphorsultam auxiliary and are comparable to the highest levels reported for such cycloadditions.[6] The corresponding reactions of α-methyltoluene-2,α-sultams are less selective.

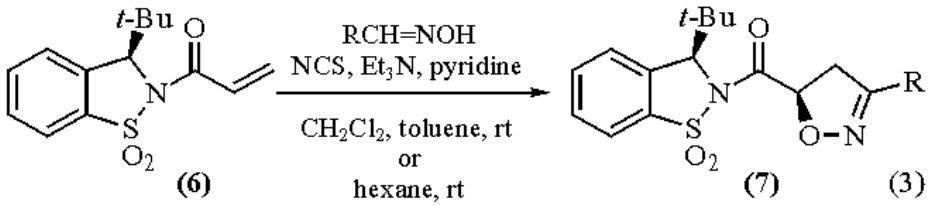

R = Me*, Et*, *t*-Bu, Ph, CH_2O-*t*-Bu
77-88% (cryst) [90-96% de (crude)]
*using *ent*-(**6**) → *ent*-(**7**)

Acylation, Alkylation, and Aldolization (Acyl Species -> α-, β-, or α/β-Functionalized Acyl Product).[3]

Alkylation reactions of sodium enolates of various *N*-acyl-α-methyltoluene-2,α-sultams with selected (both "activated" and "nonactivated") alkyl iodides and bromides proceed with good C(α)-*re* stereocontrol (90-99% de). Analogous acylations with various acid chlorides can also be performed, giving β-keto products (97-99% de). Selective reduction of these latter products with ***Zinc Borohydride*** (chelate controlled, 82.6-98.2% de) or N-Selectride (nonchelate controlled, 95.8-99.6% de) can provide *syn*- and *anti*-aldol derivatives, respectively.[3]

Syn-aldol derivatives may also be obtained directly from boryl enolates of the same *N*-acyl-α-methyltoluene-2,α-sultams by condensation with aliphatic and aromatic aldehydes (eq 4).[3,7] The high C(α)-*si* topicity of these reactions parallels but exceeds that when using the 10,2-camphorsultam auxiliary and is the result of an analogous transition state.[3] It is noteworthy, however, that aldolizations of α-methyltoluene-2,α-sultam derivatives generally proceed to completion with just a small excess of aldehyde (1-1.2 equiv, cf. 2-3 equiv when 10,2-camphorsultam mediated). This may be ascribed to the lack of acidic protons α to the SO_2 group in the Saccharine derived auxiliary.

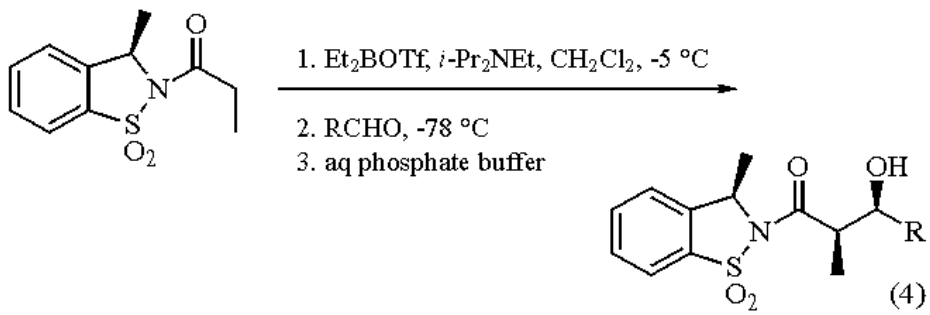

R = Me, *i*-Pr, *i*-Bu, Ph
71-84% (cryst); [R = *i*-Pr, 95% (FC)]
(>99% of crude)

Nondestructive Auxiliary Cleavage.

The toluene-2,α-sultam auxiliaries are even more readily cleaved from derivatives than the 10,2-camphorsultam auxiliary. Following *N*-acyl bond cleavage, simple extraction and crystallization usually effect almost quantitative recovery of enantiomerically pure auxiliary which may be re-used if desired.

Enantiomerically pure carboxylic acids are routinely obtained from *N*-acylsultams by ***Hydrogen Peroxide*** assisted saponification with ***Lithium Hydroxide*** in aqueous THF.[2,4] Alternatively, transesterification can be effected under neutral conditions in allyl alcohol containing ***Titanium Tetraisopropoxide***, giving the corresponding allyl esters which can be isomerized/hydrolyzed with Wilkinson's catalyst (***Chlorotris(triphenylphosphine)rhodium(I)***) in EtOH-H_2O. This provides a convenient route to carboxylic acids containing base-sensitive functionality.[8] Primary alcohols are obtained by treatment with L-Selectride (***Lithium Tri-s-butylborohydride***) in THF at ambient temperature.[3]

The α-methyltoluene-2,α-sultam auxiliary is also displaced by a variety of dilithiated alkyl phenyl sulfones.[7,9] This unique procedure provides direct access to synthetically useful β-oxo sulfones which may be further functionalized or simply subjected to

reductive desulfonation to give alkyl ketones. A particularly striking use of this method is the preparation of β-oxo sulfone (**8**), a key intermediate in a concise synthesis of (-)-semicorole (eq 5).[7] Remarkably, the $MeCLi_2SO_2Ph$ reagent attacks selectively the C(4)-imide C=O group in preference to the C(6)-ester C=O group and no epimerization occurs at C(3) or C(1´).

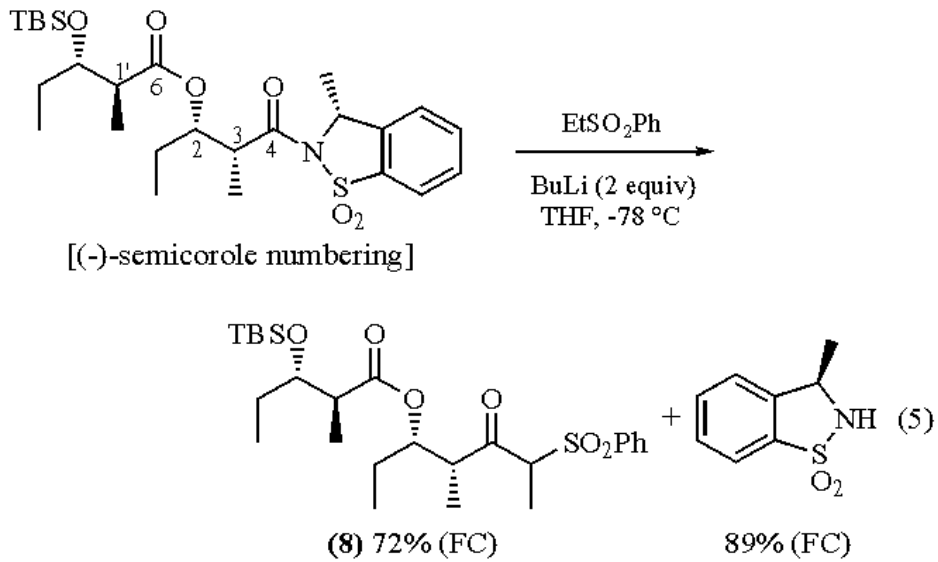

Related Reagents.

10,2-Camphorsultam; ***10-Dicyclohexylsulfonamidoisoborneol***; ***2-Hydroxy-1,2,2-triphenylethyl Acetate***; ***(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline***; ***(S)-4-Benzyl-2-oxazolidinone***.

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Methyl *p*-Toluenethiosulfonate[1]

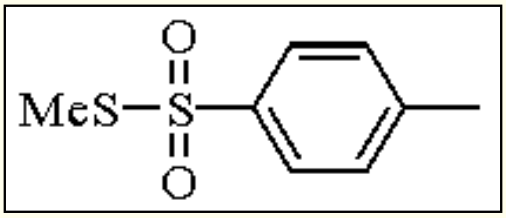

[4973-66-4] · $C_8H_{10}O_2S_2$ · Methyl *p*-Toluenethiosulfonate · (MW 202.32)

(methylsulfenylating agent for formation of useful intermediates which have many applications)

Alternate Name: methyl thiotosylate.

Physical Data: mp 58 °C.

Form Supplied in: white solid.

Preparative Method: prepared by methylation of sodium *p*-toluenethiosulfonate with ***Dimethyl Sulfate*** (65%).[2]

Optically Active Methyl Sulfoxide Derived from Camphor.

(+)-Camphor is converted by methylsulfenylation of the lithium enolate with methyl *p*-toluenethiosulfonate (MeSTs) into *exo*-3-(methylthio)camphor, which upon reduction with ***Diisobutylaluminum Hydride*** gives the corresponding *exo*-(methylthio)isoborneol. Oxidation of the sulfide with ***m-Chloroperbenzoic Acid*** gives optically pure *exo*-3-(methylsulfinyl)isoborneol (eq 1).[3]

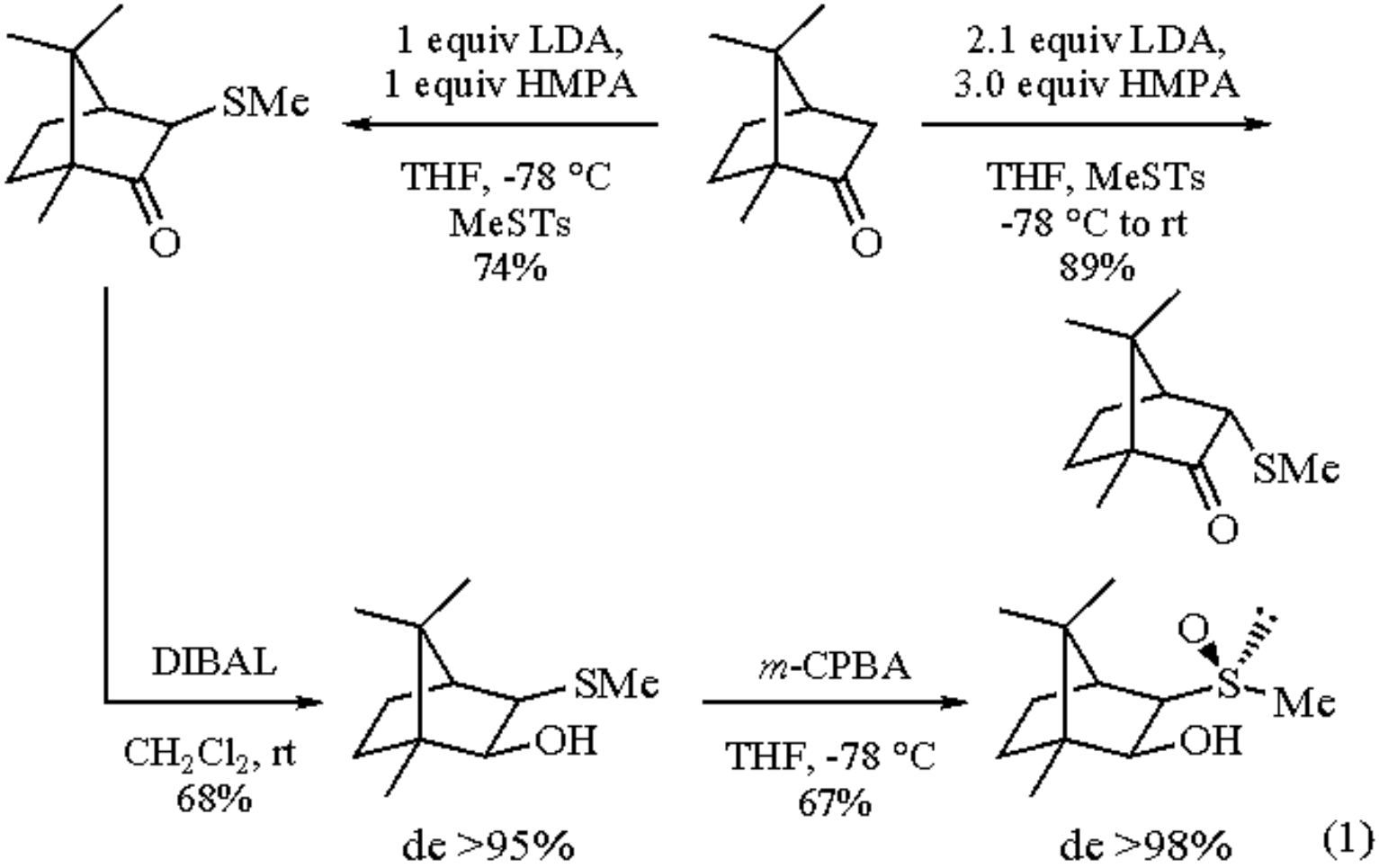

Interestingly, use of excess ***Lithium Diisopropylamide*** and ***Hexamethylphosphoric Triamide*** allows exclusively thermodynamic *endo*-3-(methylthio)camphor formation. The alternative methylsulfenylating agent ***Dimethyl Disulfide*** is not suitable for this highly stereoselective transformation since it gives a mixture of *exo*/*endo* sulfides in low yield. The method is elaborated for use of allyl *p*-toluenethiosulfonates which furnish optically pure *exo*-3-(allylsulfinyl)isoborneols. The derived dianions of these isoborneols undergo diastereoselective conjugate addition reactions with cyclopentenones.[4]

Beckmann Fragmentation of α-Methylsulfenyl Oximes.

It is known that a second-order Beckmann fragmentation is favored by introduction of a methylsulfenyl group α to the oxime group.[5] The termini of the bond that is cleaved are obtained in different oxidation states which can be manipulated for further functionalization. MeSTs is used to prepare an α-methylthio ketone, a precursor to the oxime for the fragmentation. An application of this fragmentation is exemplified by a conversion of a cyclohexanone into a δ-valerolactone (eq 2).[6]

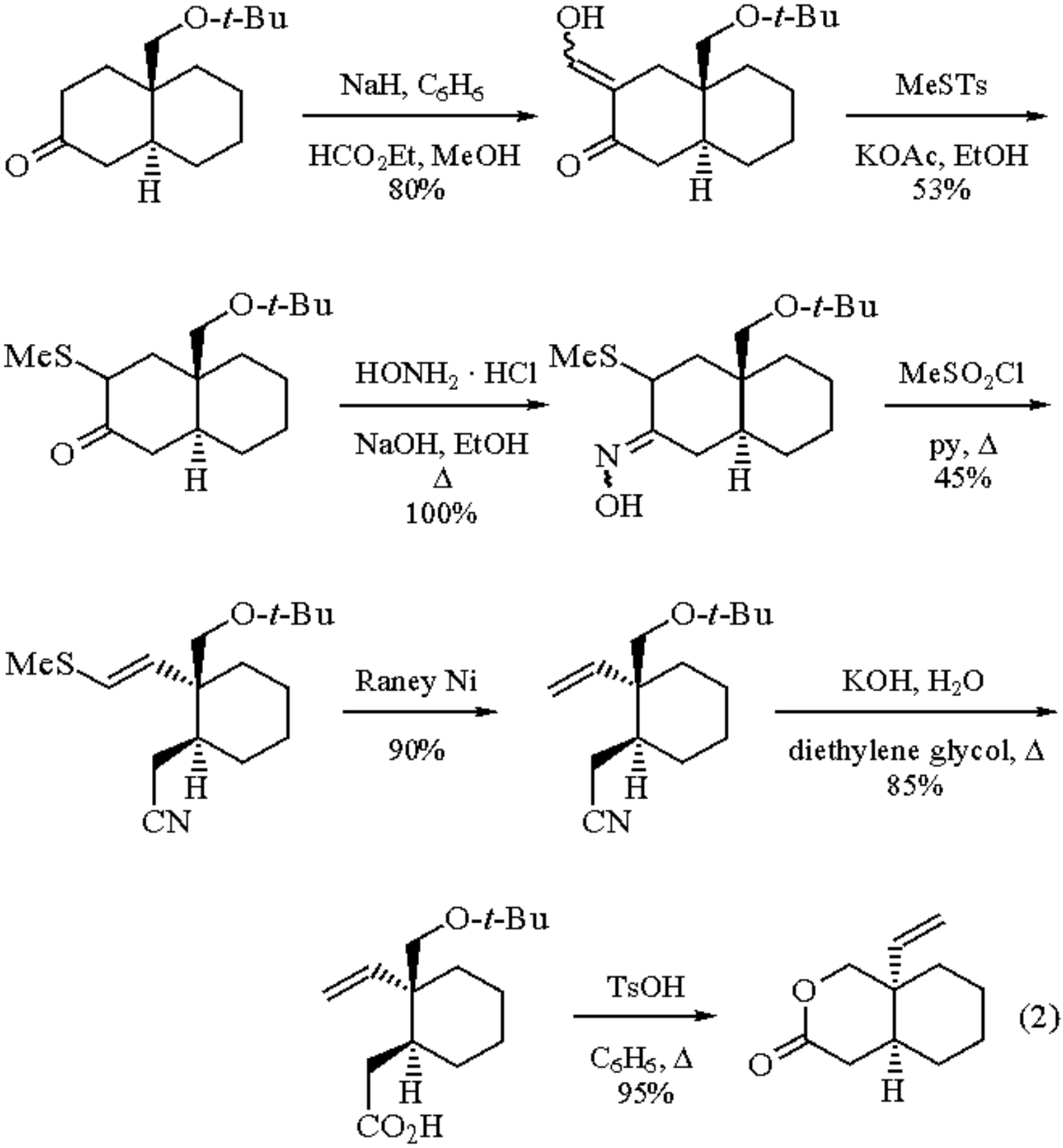

α-Keto Aldehyde from α-(Methylsulfenyl)methyl Ketone.

A two-step conversion of a methyl ketone to an α-keto dimethyl acetal via methylsulfenylation with MeSTs, followed by oxidation with ***N-Chlorosuccinimide*** has been described (eq 3).[7]

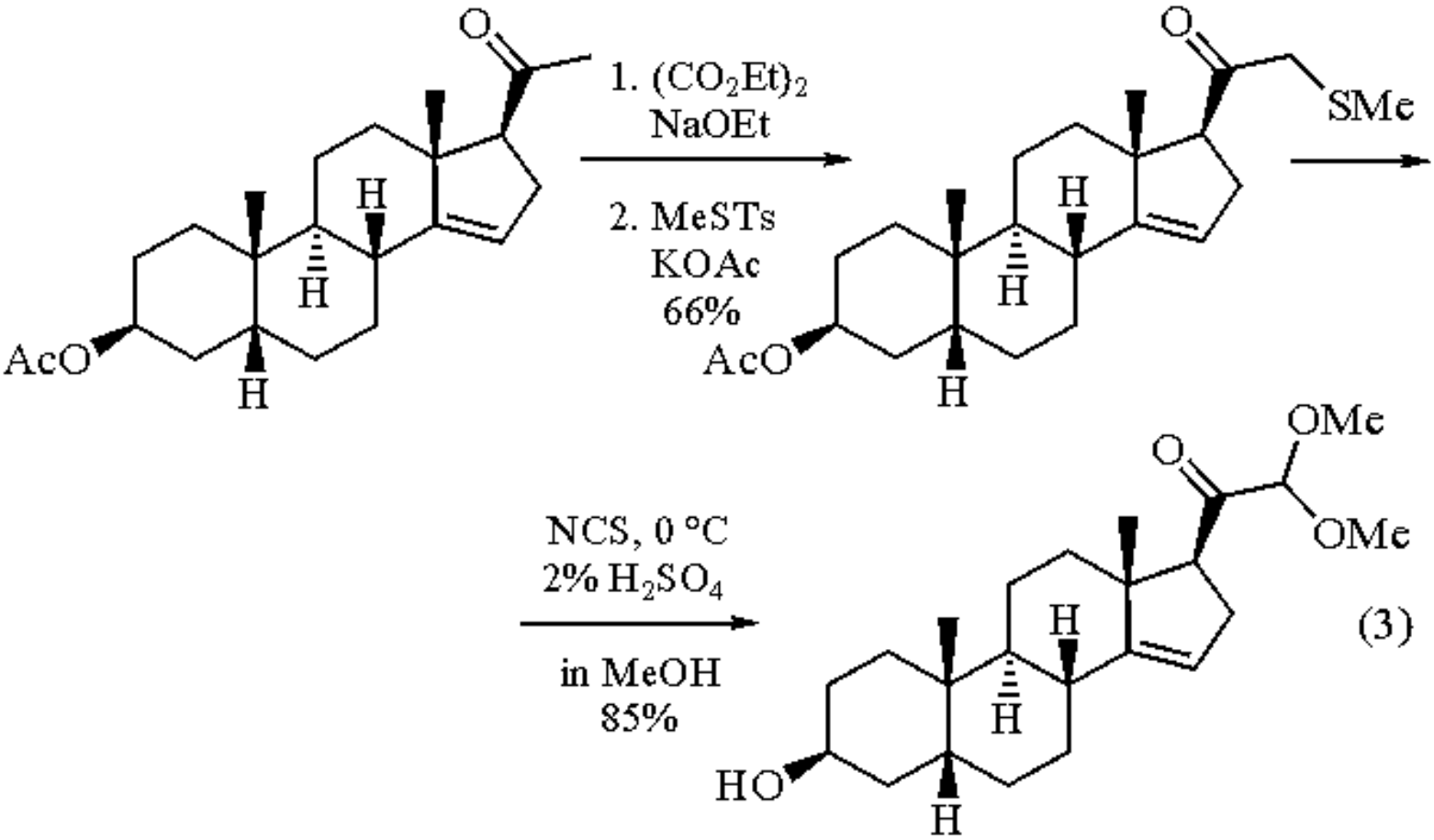

Efficient Synthesis of Cardenolides.

A general and efficient method has been described for the synthesis of cardenolides, consisting of (1) α-methylsulfenylation of pregnen-20-one, (2) Reformatsky reaction, and (3) butenolide formation by alumina chromatography of the epoxy ester obtained from the *S*-methylated Reformatsky product (eq 4).[8]

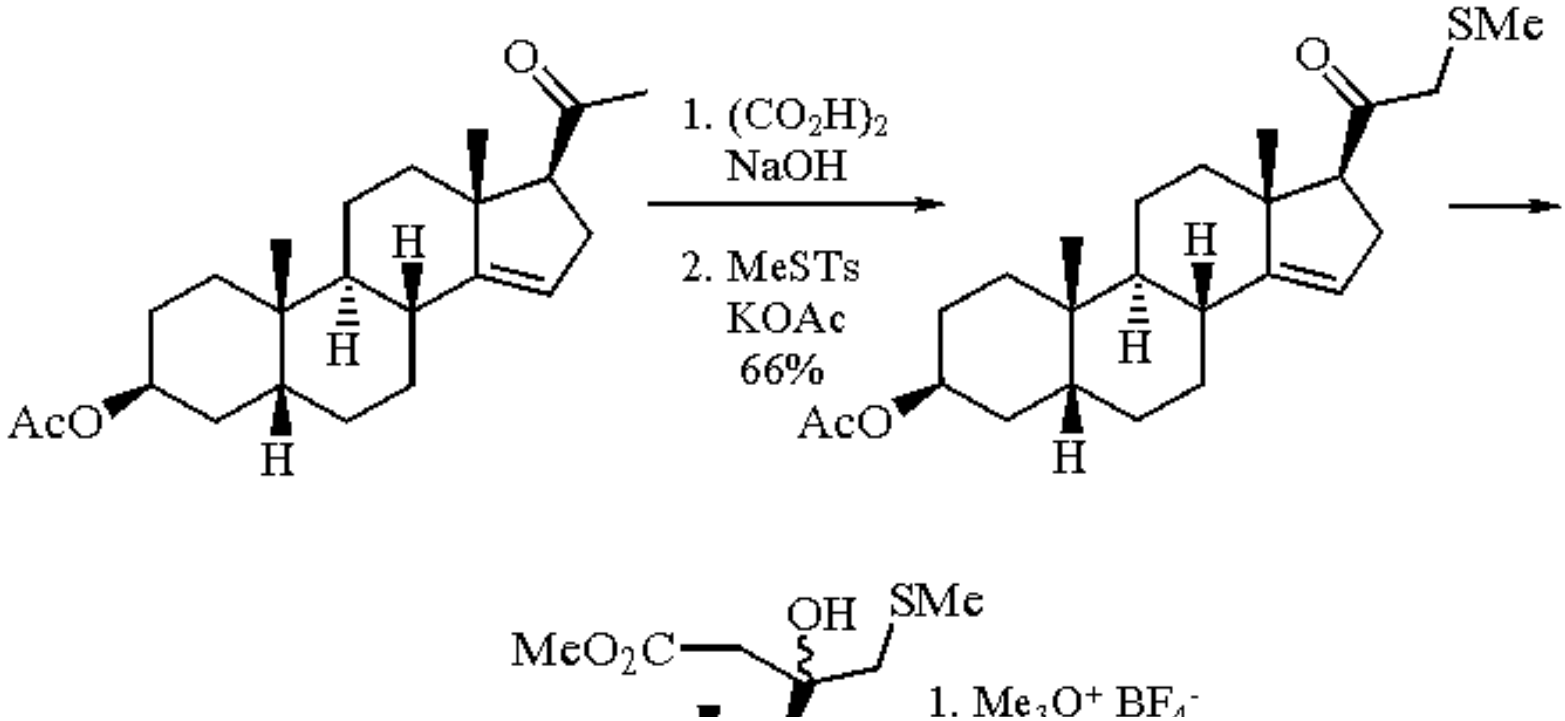

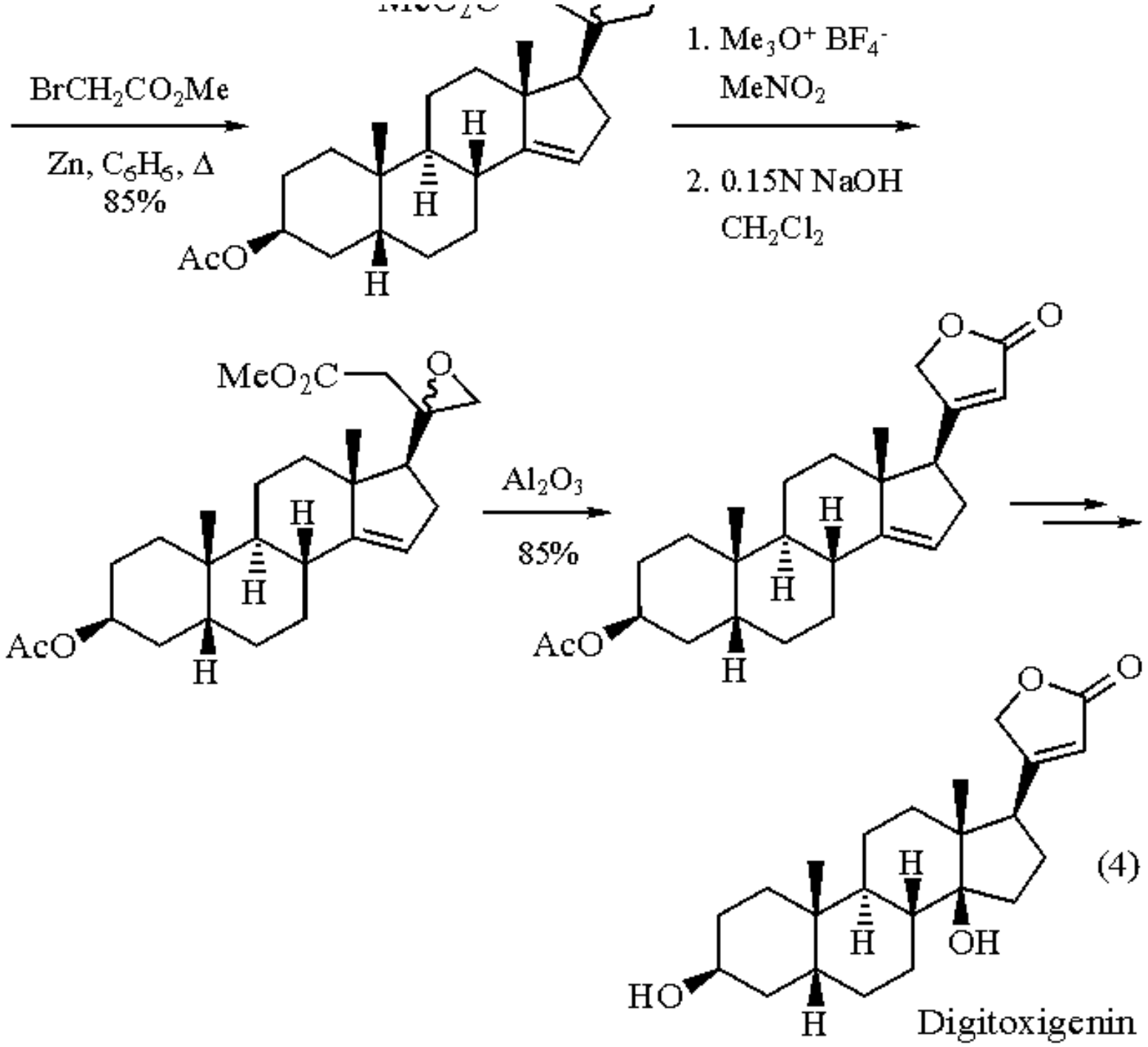

Related Reagents.

Dimethyl Disulfide; ***Methyl Methanethiosulfonate***.

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Kumiko Takeuchi

Eli Lilly and Company, Indianapolis, IN, USA

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(*R*)-(+)-Methyl *p*-Tolyl Sulfoxide

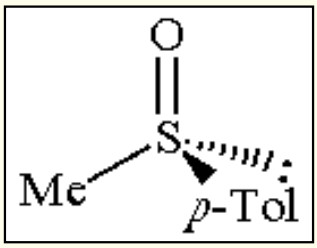

[1519-39-7] · $C_8H_{10}OS$ · (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide · (MW 154.25)

(agent used in the synthesis of chiral β-keto sulfoxides[1b,10])

Physical Data: $[\alpha]_D$ +146° (acetone, *c* = 2), +192° ($CHCl_3$, *c* = 1.2).

Preparative Methods: the most popular means of preparing this reagent is the nucleophilic displacement of ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate*** with methyl Grignard with complete inversion of configuration at sulfur (eq 1).[1]

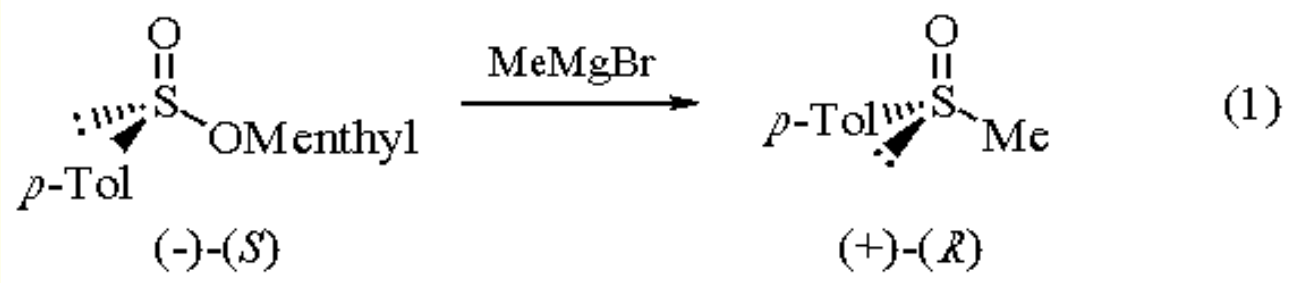

This reagent is also prepared by the reaction of ***Methylmagnesium Bromide*** with optically active (*S*)-*N*-sulfinyloxazolidinone, which is obtained by asymmetric synthesis[2] from the oxazolidinone derived from (4*R*,5*S*)-norephedrine with a low diastereoselectivity (70:30) (eq 2).

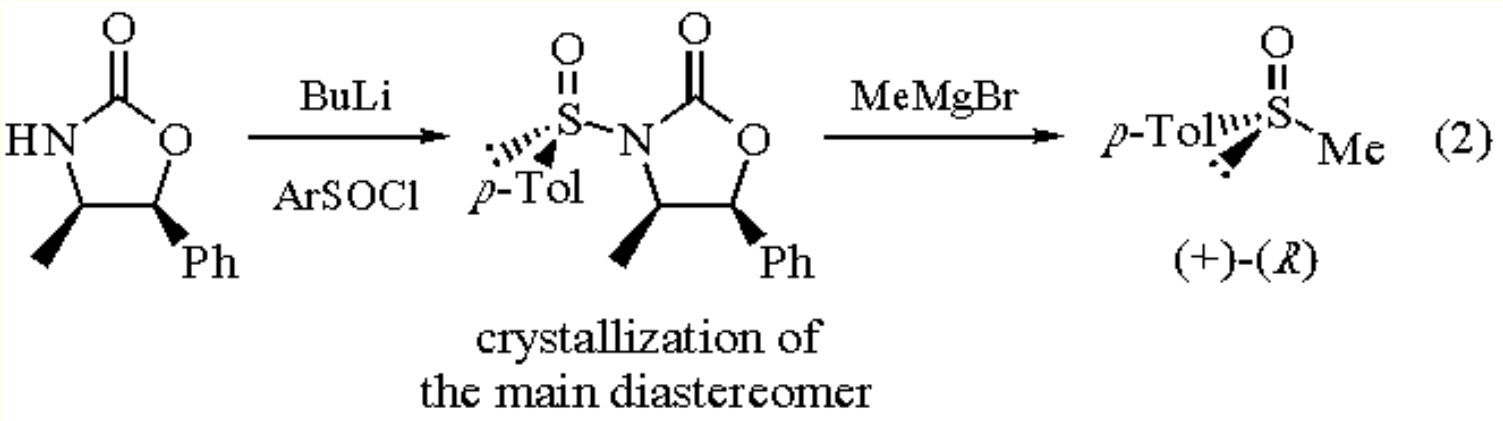

Both enantiomers of methyl *p*-tolyl sulfoxide are also prepared from diacetyl D-glucose giving, with mesyl chloride, and according to the base used, the (*S*)-methyl sulfinate with diisopropylethylamine or the (*R*)-methyl

sulfinate with pyridine, which are then transformed with *p*-tolylmagnesium bromide into the corresponding (*S*)- or (*R*)-methyl *p*-tolyl sulfoxide (eq 3).[3]

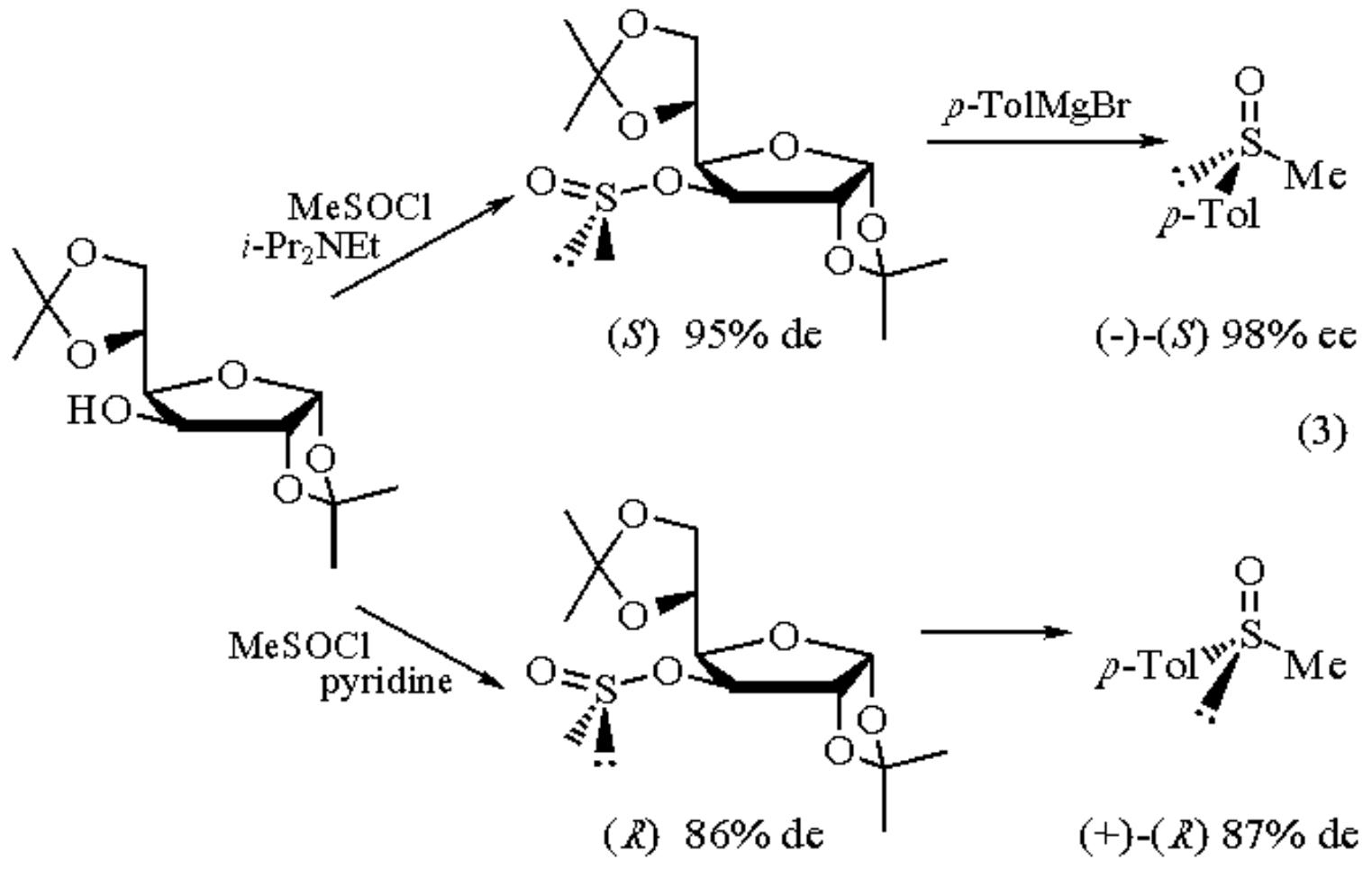

(*R*)-(+)-methyl *p*-tolyl sulfoxide is obtained by asymmetric oxidation of the corresponding sulfide with ***t-Butyl Hydroperoxide*** in the presence of a stoichiometric amount of a modified Sharpless reagent (***Titanium Tetraisopropoxide***)-(+)-(*R*,*R*)-diethyl tartrate-H_2O in a ratio of 1:2:1) in 96% ee.[4]

(-)-α,α-Dichlorocamphorsulfonyloxaziridine (**1**) was shown to be a highly efficient reagent for the asymmetric oxidation of methyl *p*-tolyl sulfide, giving the corresponding (+)-(*R*)-sulfoxide in 95% ee.[5]

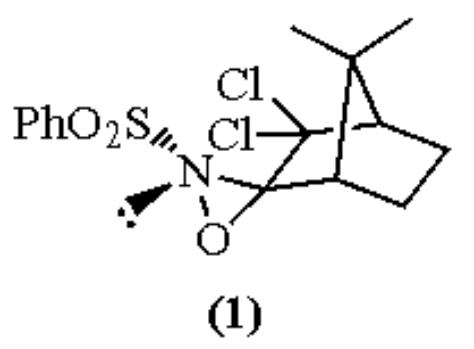

It was shown recently that chloroperoxidase-catalyzed oxidation of methyl *p*-tolyl sulfide, using ***Hydrogen Peroxide*** or *t*-BuOOH as the stoichiometric oxidant, afforded the corresponding (+)-(*R*)-sulfoxide in 99% ee.[6]

Synthesis of β-Keto Sulfoxides.

Optically active β-keto sulfoxides are very useful building blocks (eq 4) because they can be stereoselectively reduced to afford either diastereomer of the corresponding β-hydroxy sulfoxide under appropriate conditions (***Diisobutylaluminum Hydride*** or ***Zinc Chloride***/DIBAL)[8] and thus give access to a wide variety of compounds: chiral carbinols[7] by desulfurization with ***Raney Nickel*** or ***Lithium***/ethylamine in the case of allylic alcohols;[8b] epoxides[8a] via cyclization of the derived sulfonium salt; butenolides[7b] by alkylation of the hydroxy sulfoxide; 1,2-diols via a Pummerer rearrangement followed by reduction of the intermediate.[9]

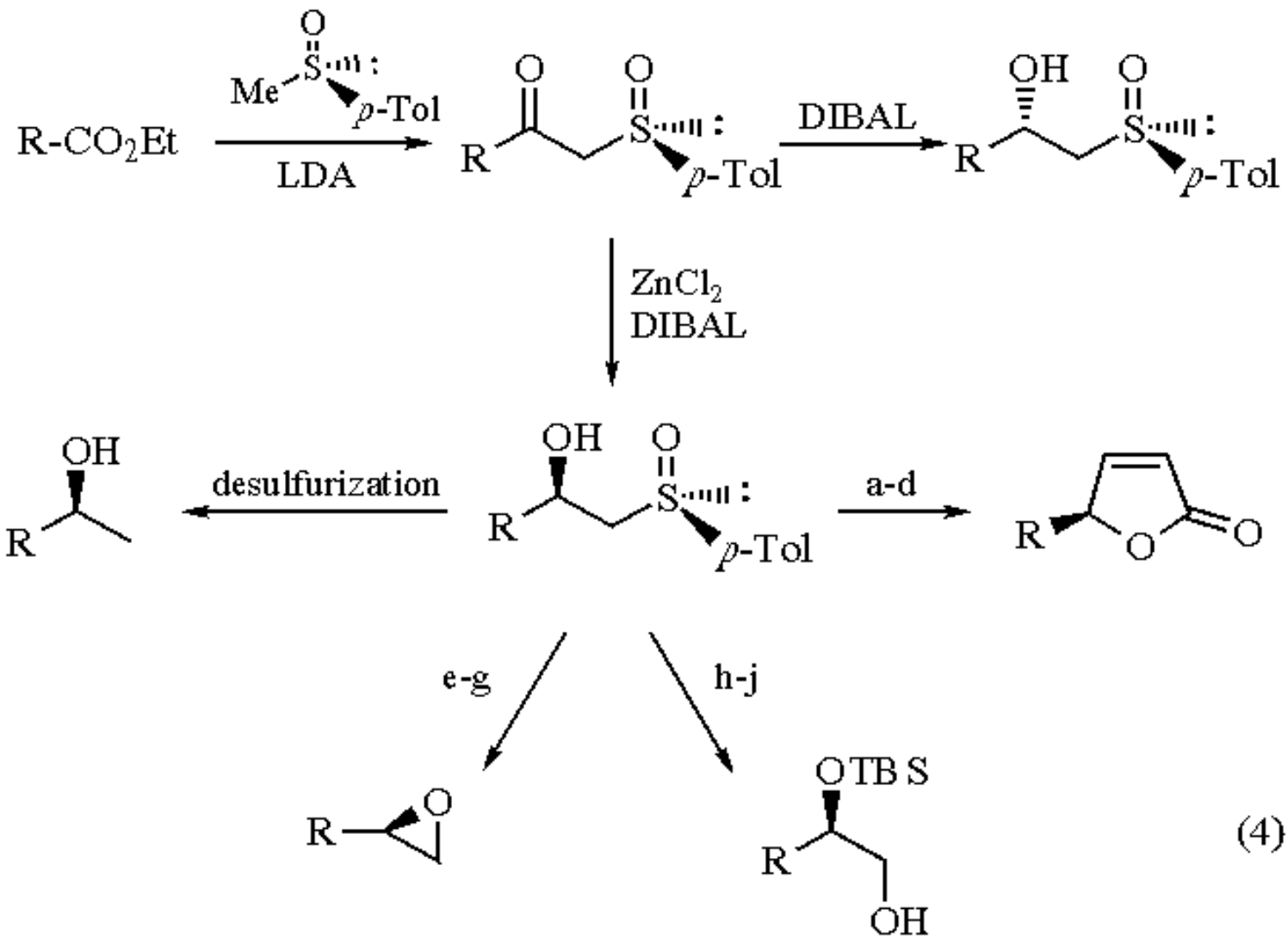

(4)

a) oxidation to sulfone; b) alkylation with sodium iodoacetate;
c) lactonization; d) sulfone elimination;
e) sulfoxide reduction to sulfide with $LiAlH_4$;
f) sulfur methylation with Me_3OBF_4; g) cyclization with a base;
h) OH protection; i) Pummerer rearrangement in Ac_2O;
j) reduction of the Pummerer intermediate.

Numerous applications to total synthesis of natural products have been reported. In the case of the macrolide (*R*)-lasiodiplodin, the achiral ester (eq 5) was reacted with the (+)-(*R*)-methyl *p*-tolyl sulfoxide derived anion to give the corresponding β-keto sulfoxide, which was then reduced with DIBAL to give, after desulfurization, the seco-ester of (*R*)-lasiodiplodin (eq 5).[10] This is an example showing that the chirality can be introduced at the end of the synthesis in the desired configuration.

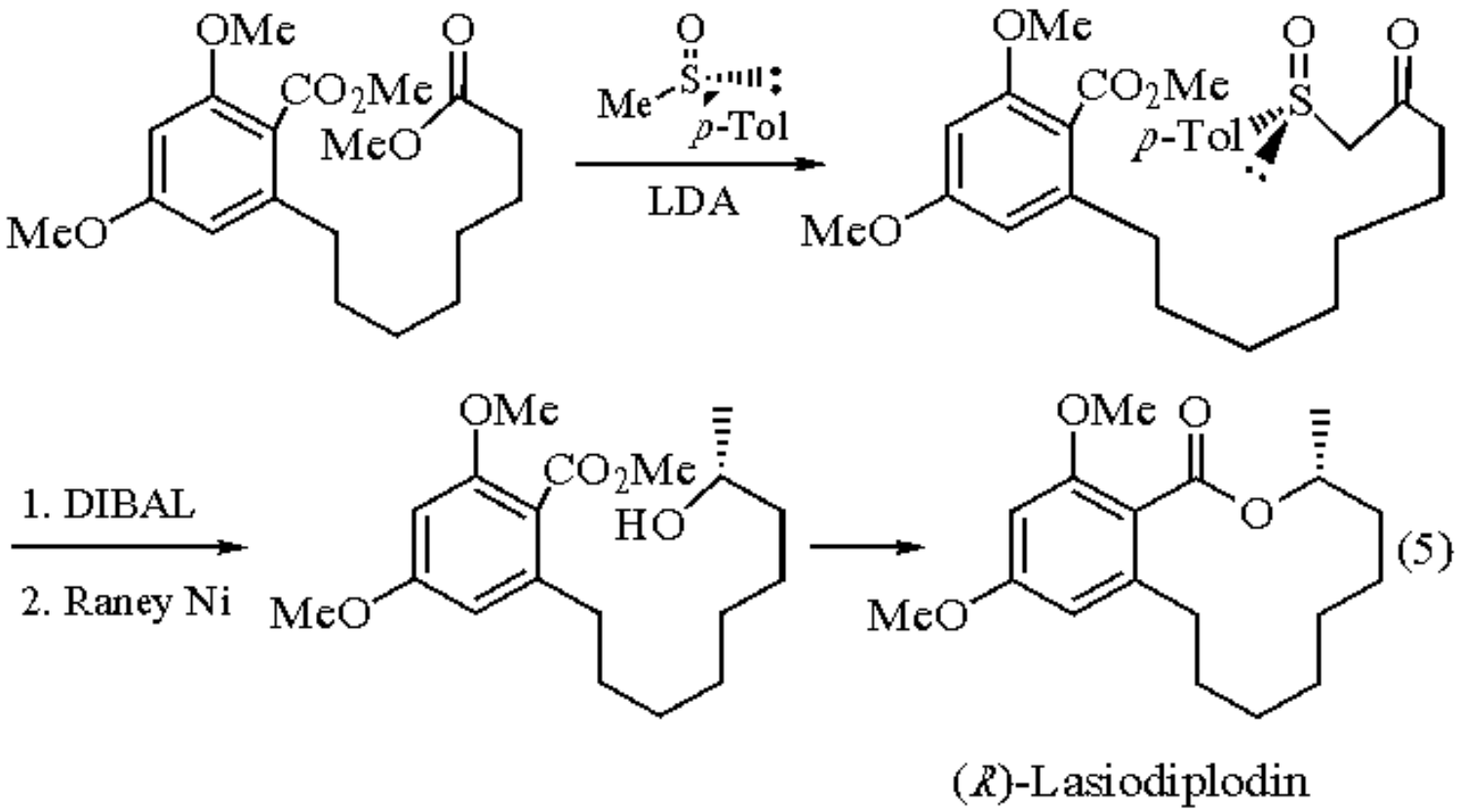

In the synthesis of (*S*)-zearalenone[11] and of a chiral spiroacetal, (2*S*,6*R*)-2-methyl-1,7-dioxaspiro[5.6]dodecane,[12] the starting product was a functionalized β-keto sulfoxide resulting from the reaction of glutaric anhydride with lithiated (+)-(*R*)-methyl *p*-tolyl sulfoxide (eq 6).

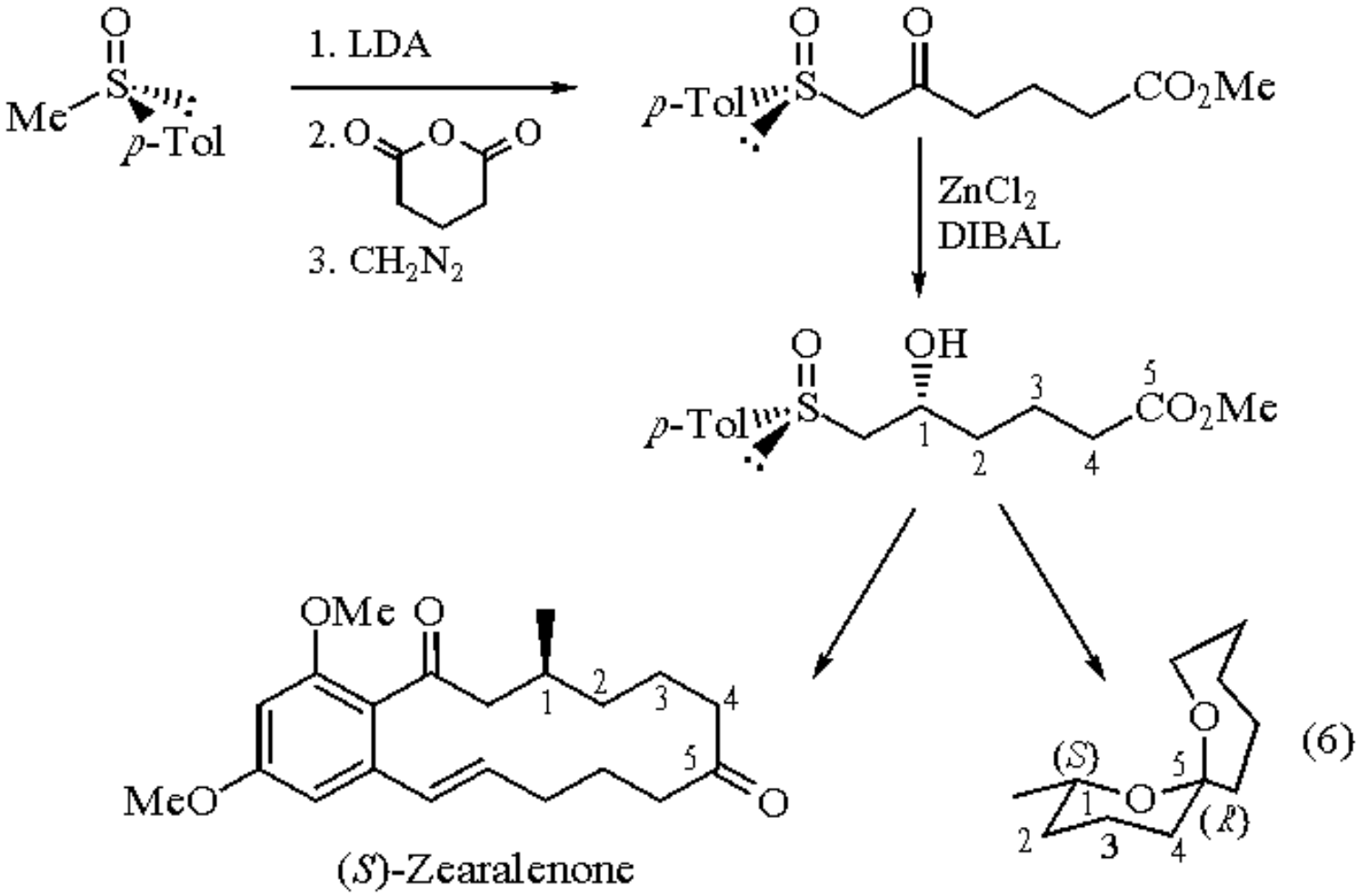

It was also shown in the enantioselective synthesis of the macrolide patulolide A[13] that the anion of methyl *p*-tolyl sulfoxide was more reactive towards the imidazolide, prepared from the hemi ethyl sebacate, than the ester group (eq 7).

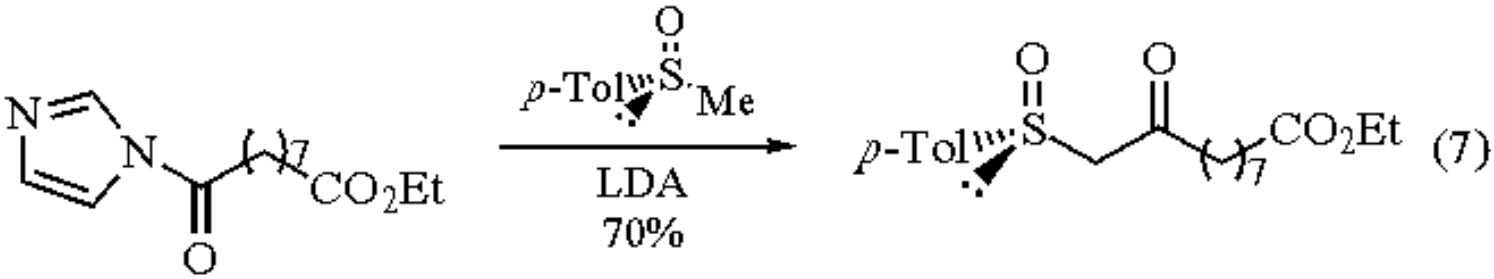

In a similar way,[9] lithiated (+)-(*R*)-methyl *p*-tolyl sulfoxide was able to react only with the methyl ester group in presence of a *t*-butyl ester, as shown in the case of *t*-butyl methyl octadioate (eq 8).

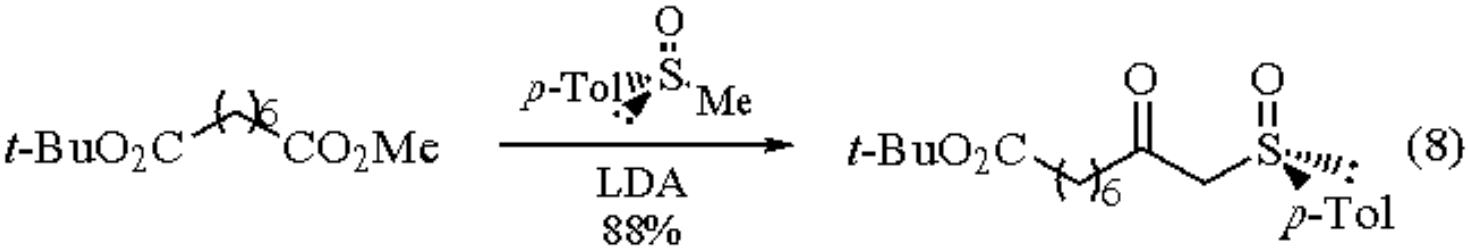

The enantioselective syntheses of yashabushiketol[14] and gingerols[15] showed the synthetic utility of chiral epoxides obtained

from (*R*)-methyl *p*-tolyl sulfoxide (eq 9).

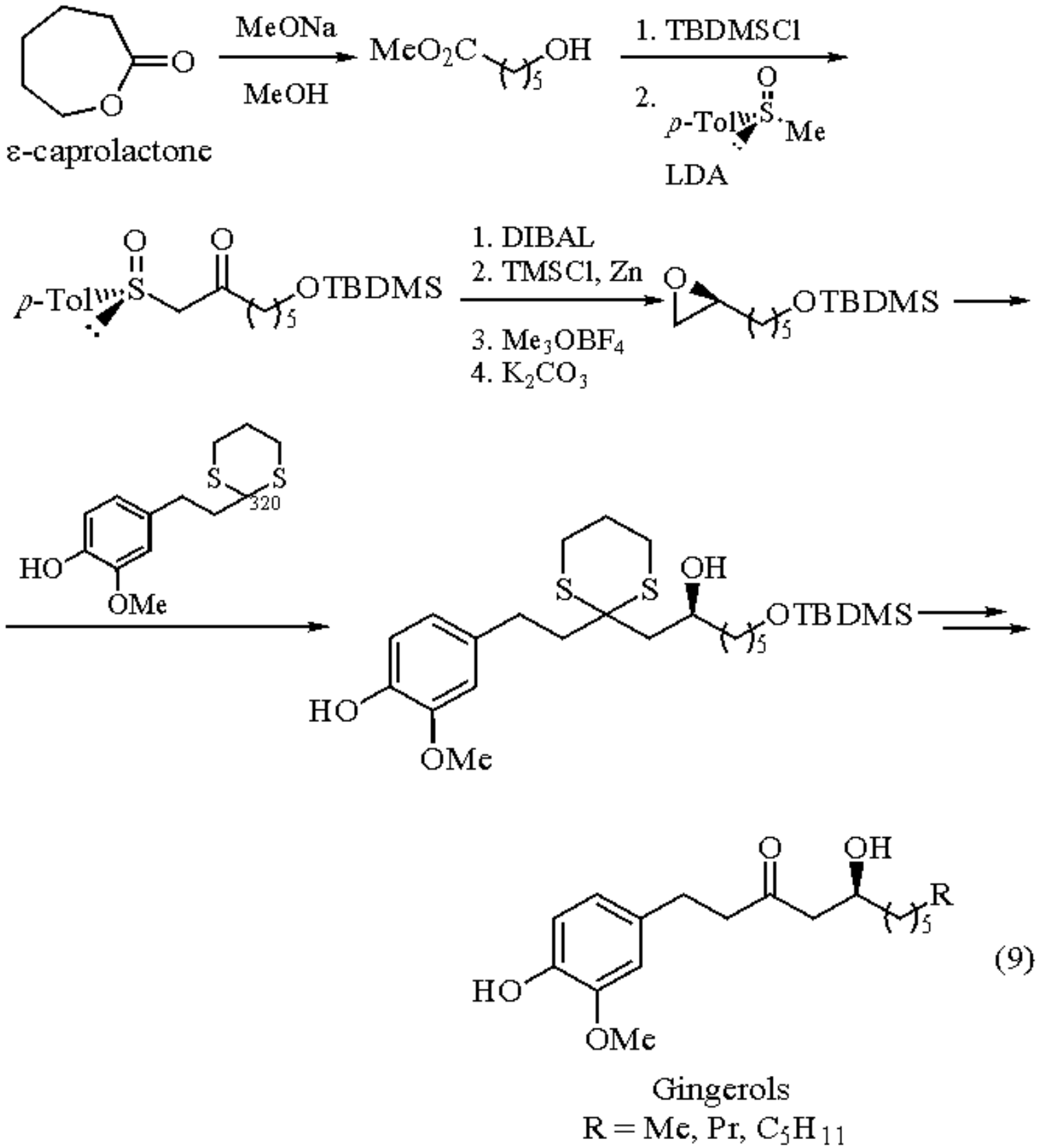

(9)

Methyl chloroacetate reacts with the anion of (*R*)-methyl *p*-tolyl sulfoxide to give the corresponding δ-chloro-β-keto sulfoxide (eq 10), which can be easily transformed into the corresponding β-hydroxy sulfoxide which gives, in presence of a base, the optically active α-sulfinyl epoxides.[16] As illustrated here, α-sulfinyl epoxides can be opened by cuprates, leading

to chiral homoallylic alcohols.[17]

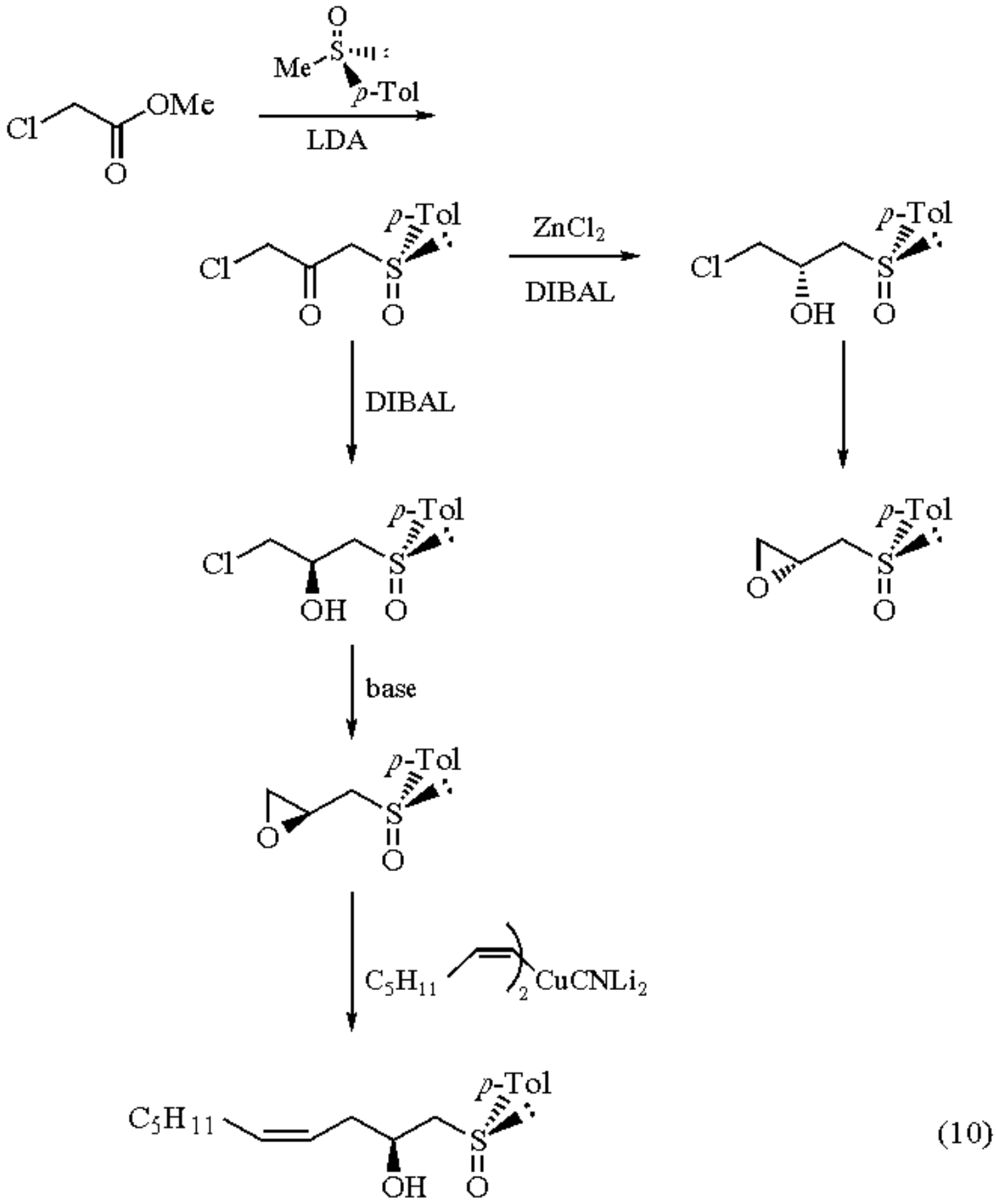

(10)

(*R*)-Methyl *p*-tolyl sulfoxide anion also reacts with β-keto esters to give the corresponding β,δ-diketo sulfoxides,[18] which are useful in the preparation of optically active 1,3-diols (eq 11).[19]

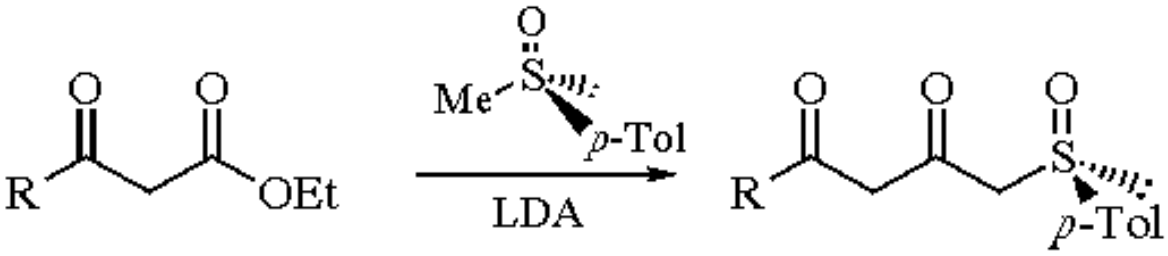

(11)

Difluoroalkyl sulfinylmethyl ketones have been prepared in enantiomerically pure form from (+)-(*R*)-methyl *p*-tolyl sulfoxide in high yield (eq 12).[20] The ketone function was then reduced with complete diastereoselectivity.

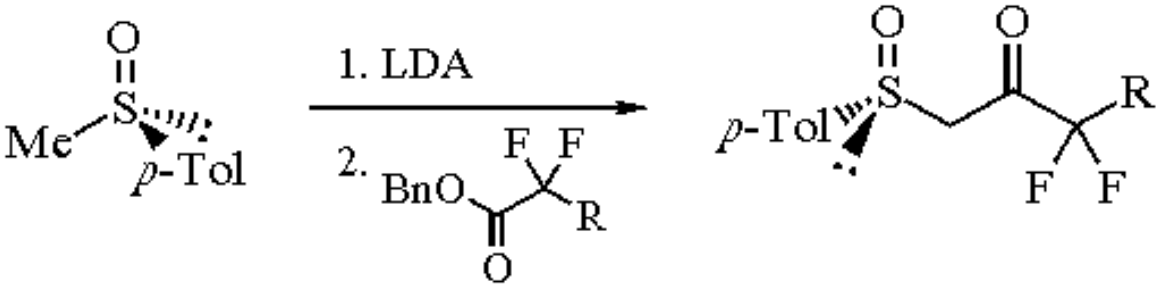

(12)

The absolute configuration at C-32 in recently isolated triterpenoids was assigned by reduction of a β-keto sulfoxide (eq 13).[21]

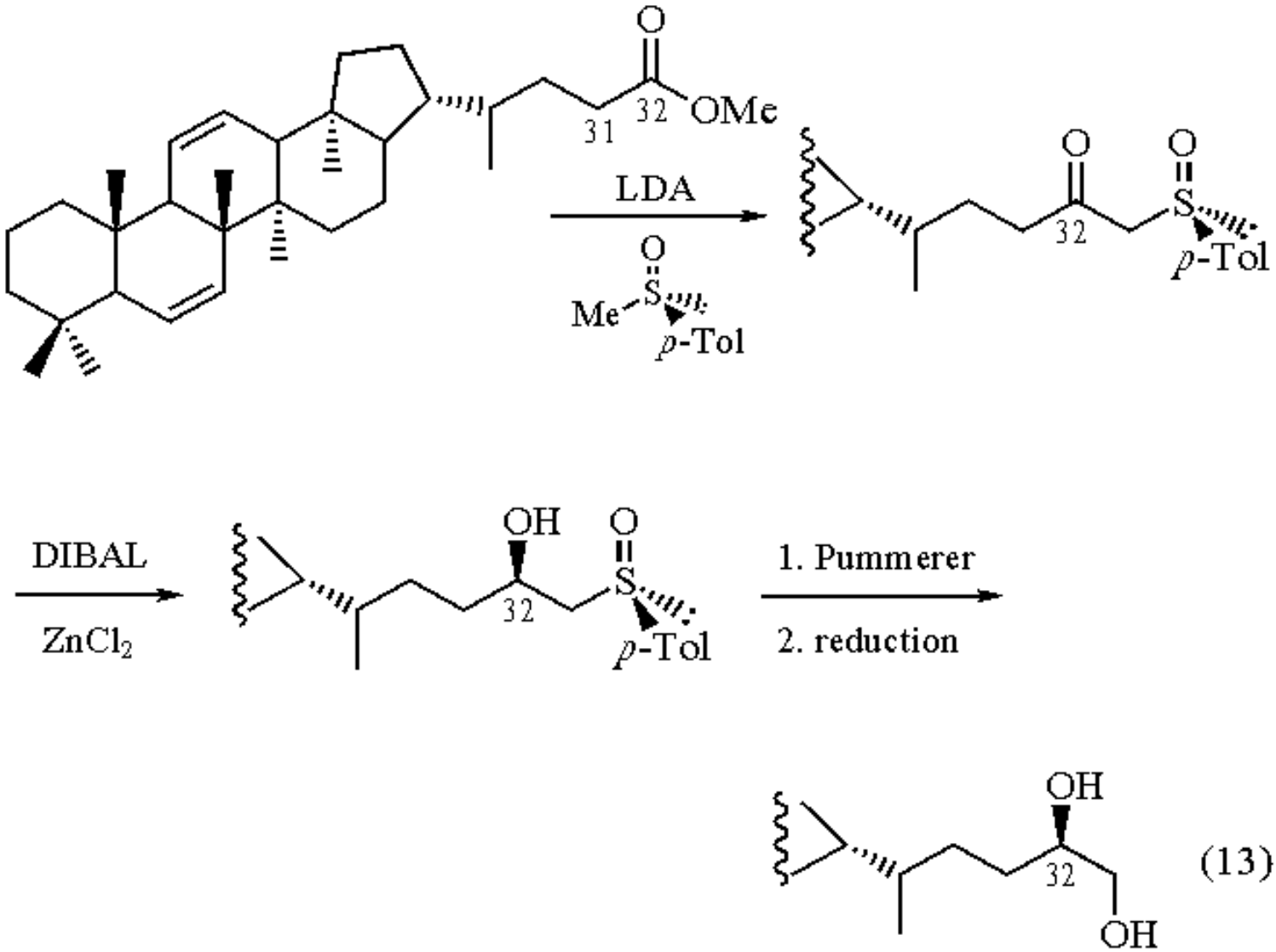

Miscellaneous.

A vinylic sulfoxide was prepared from (*R*)-methyl *p*-tolyl sulfoxide and benzophenone. Cyclopropanation of the double bond with ***Dimethylsulfoxonium Methylide*** gave a good diastereoselectivity (eq 14).[22]

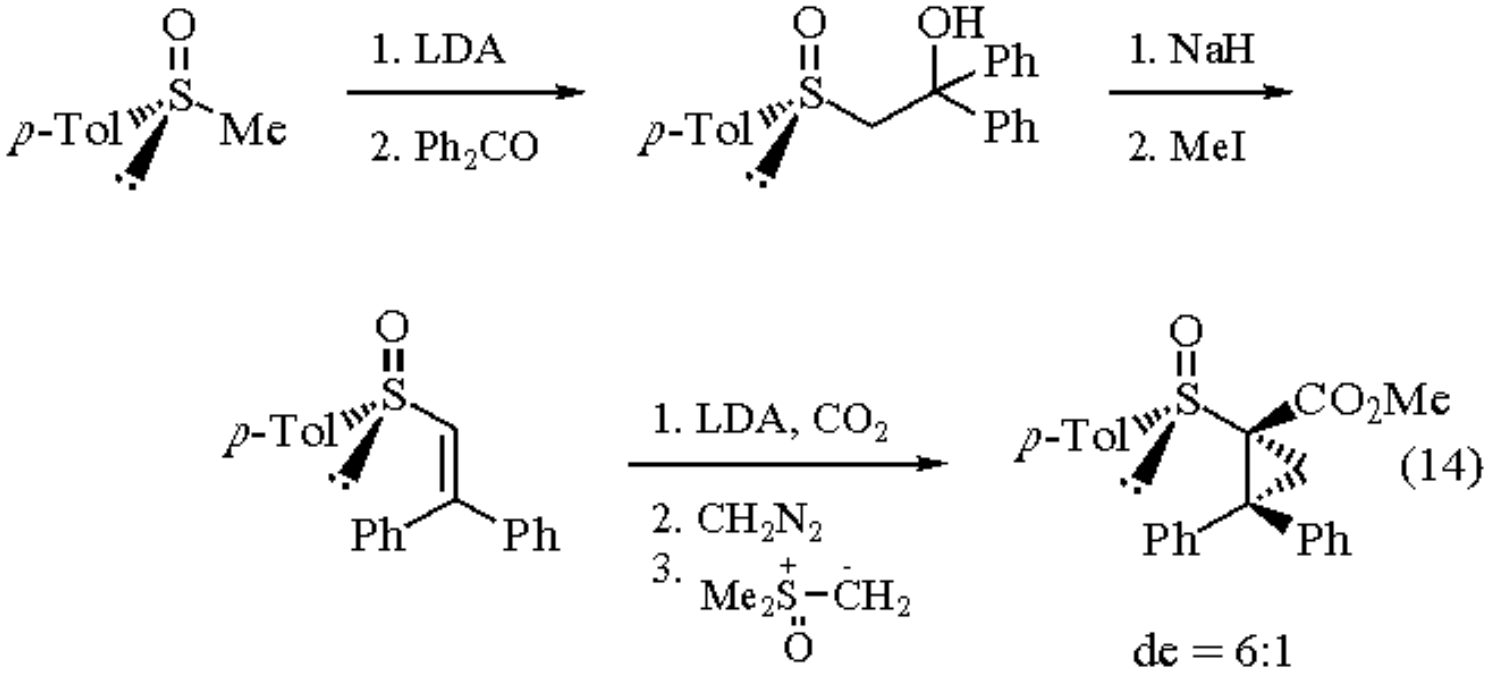

3-Sulfinylpropionic acid was made from lithium 2-bromoacetate and (*R*)-methyl *p*-tolyl sulfoxide (eq 15).[23]

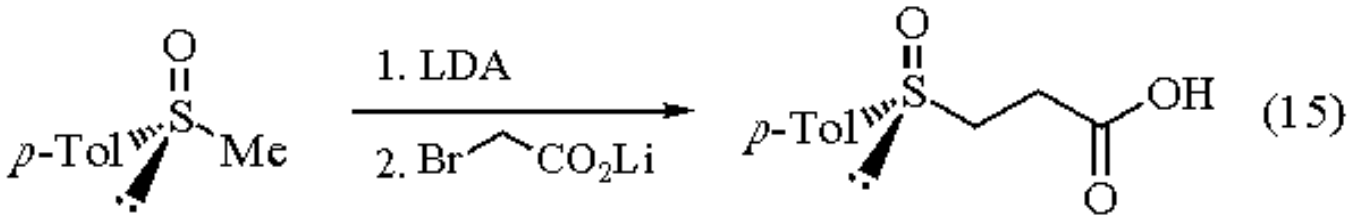

Sulfinyl dienes were made from α,β-unsaturated esters and methyl *p*-tolyl sulfoxide followed by enolization of the ketone group (eq 16).[24]

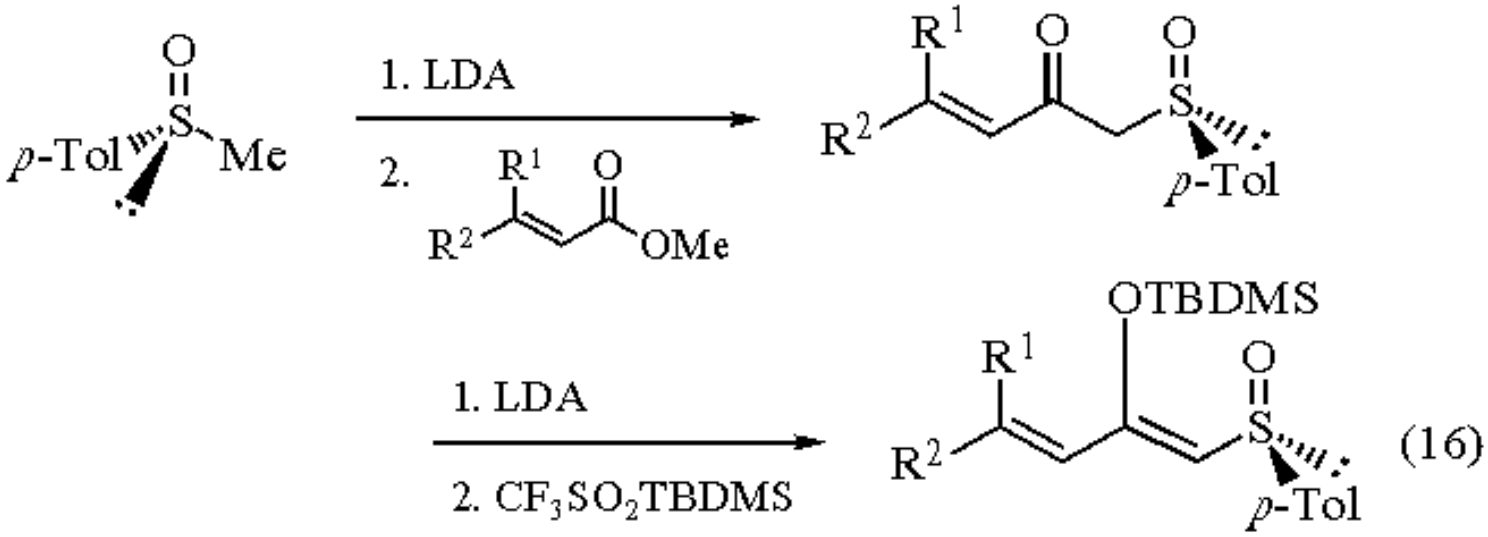

Although the carbanion of (*R*)-methyl *p*-tolyl sulfoxide reacted with aldehydes and ketones with a poor diastereoselectivity,[25] it reacts with imines with a much higher stereoselectivity[25] as long as the imine substituent is an aromatic ring.[26] (*R*)-(+)-Tetrahydropalmatine was synthesized by addition of (*R*)-methyl *p*-tolyl sulfoxide carbanion to 3,4-

dihydro-6,7-dimethoxyisoquinoline (eq 17).[27]

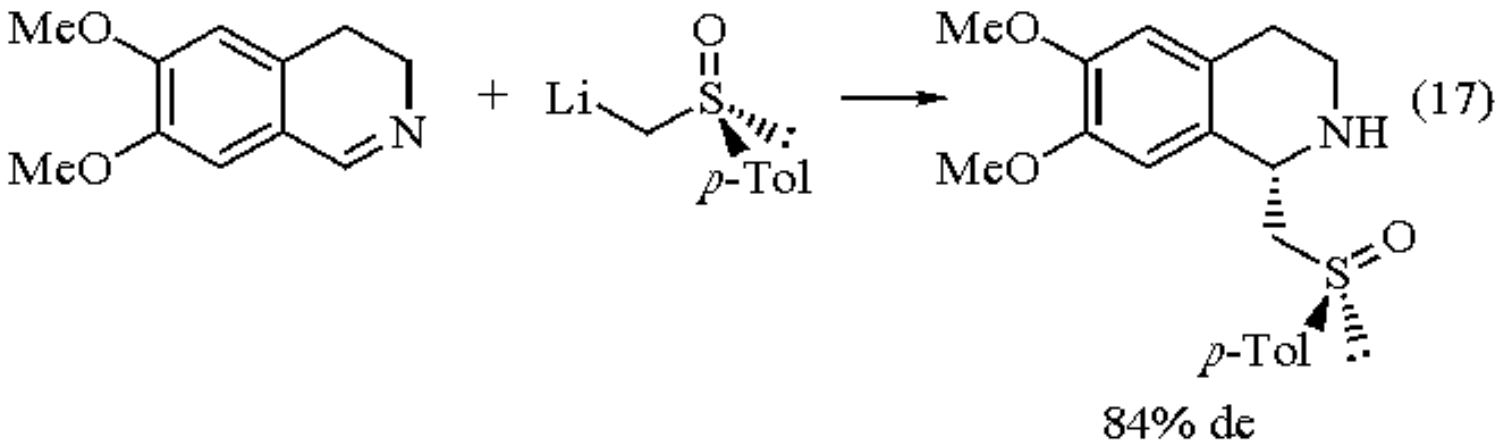

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27. Pyne, S. G.; Dikic, B. *JOC* **1990**, *55*, 1932.

3-Methyl-1-*p*-tolyltriazene[1]

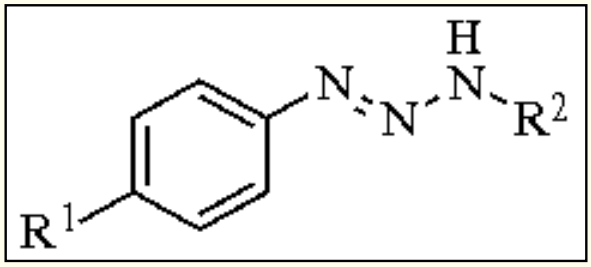

(**1**; R^1 = Me, R^2 = Me)

[21124-13-0] · $C_8H_{11}N_3$ · 3-Methyl-1-*p*-tolyltriazene · (MW 149.22) (**2**; R^1 = NO_2, R^2 = Me)

[40643-39-8] · $C_7H_8N_4O_2$ · 3-Methyl-1-*p*-nitrophenyltriazene · (MW 180.19) (**3**; R^1 = Me, R^2 = Et)

[50707-40-9] · $C_9H_{13}N_3$ · 3-Ethyl-1-*p*-tolyltriazene · (MW 163.25) (**4**; R^1 = OMe, R^2 = Pr)

[74849-15-3] · $C_{10}H_{15}N_3O$ · 3-Propyl-1-*p*-methoxyphenyltriazene · (MW 193.28) (**5**; R^1 = Me, R^2 = *i*-Pr)

[118399-01-2] · $C_{10}H_{15}N_3$ · 3-Isopropyl-1-*p*-tolyltriazene · (MW 177.28) (**6**; R^1 = Br, R^2 = Bn)

[85013-27-0] · $C_{13}H_{12}BrN_3$ · 3-Benzyl-1-*p*-bromophenyltriazene · (MW 290.18)

(methylating agent for carboxylic acids,[2] other acids, alcohols, phenols, and thiols[3])

Physical Data: mp: (**1**) 79-81 °C; (**2**) 112-114 °C; (**3**) 36-38 °C; (**4**) 28-30 °C; (**5**) 29-30 °C; (**6**) 87-88 °C.

Alternate Name: MTT.

Solubility: in general, slightly sol hexane; sol Et_2O, chloroform, acetone, DMSO. May undergo degradation in protic media.

Form Supplied in: (**1**) colorless solid; commercially available in 98% purity.

Preparative Methods: disubstituted triazenes can be prepared by the reaction of Grignard[4] or organolithium reagents[5] with azides, or by the reaction of aryl diazonium salts with primary amines.[6] Chief impurities present in the latter case are the pentazadienes (2:1 condensation products) and diaryltriazenes.

Handling, Storage, and Precautions: can be safely stored for reasonable periods. Alkyltriazenes are potent biological alkylating agents and should be treated as toxic and potentially carcinogenic. Efficient

fumehoods and use of reasonable precautions are recommended when handling these compounds.

Alkylation by Triazenes.

N-Methyltriazenes can achieve low temperature methylation of acidic substances including benzoic acids,[2b,6] fatty acids,[7] enols,[8] polymeric carboxylic acids,[2a,2c] and presumably any compound that can be methylated by ***Diazomethane***. Succinimide and phenols are also methylated directly by 3-methyl-1-*p*-tolyltriazene, but methylation of alcohols and thiols requires aluminum alcoholate catalysis.[3]

In nonpolar solvents the alkylations probably involve displacement reactions on the methyldiazonium ion (eq 1); yields are essentially quantitative. The reaction intermediate is probably identical or very similar to the corresponding intermediate generated from diazomethane. The triazene approach is of special advantage in the case of higher homologs (alkyltriazenes) since most alkyl-substituted diazomethanes are quite unstable; in contrast, primary and secondary alkyltriazenes can be readily prepared.[4,9] 1-Bicyclo[2.2.1]heptyltriazenes are quite stable,[10] but tertiary alkyltriazenes that would lead to relatively stable carbocations, e.g. R^2 = *t*-butyl, are generally not isolable under normal circumstances.

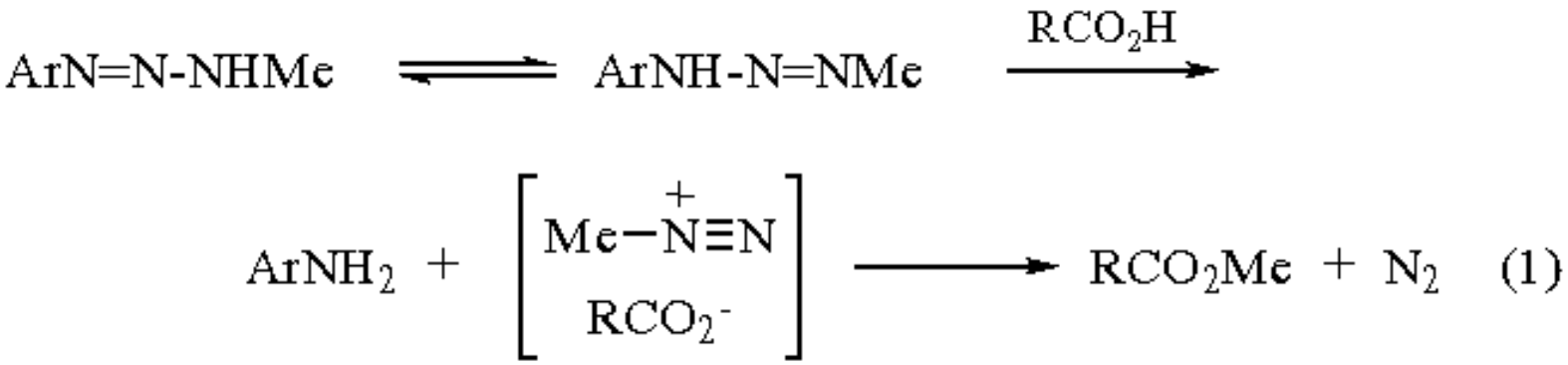

The triazenes have several advantages over diazoalkanes. They are crystalline; they are more stable and need not be freshly prepared; they are far less volatile and thus less toxic via the pulmonary route; they are less prone to explosion; and they do not normally lead to the cycloaddition reactions observed for diazomethane.[11] Finally, chiral triazenes can form chiral esters with retention of configuration[12] (the reactive center of diazoalkanes is achiral) (see eq 3).

Reactions of Higher Triazene Homologs.

Triazenes with alkyl groups bearing β-hydrogens may give elimination products, which can account for ~20-60% (values estimated for reactions of free carbocations) of the alkyl groups (eq 2) (the diazoalkane approach would yield similar amounts of elimination).

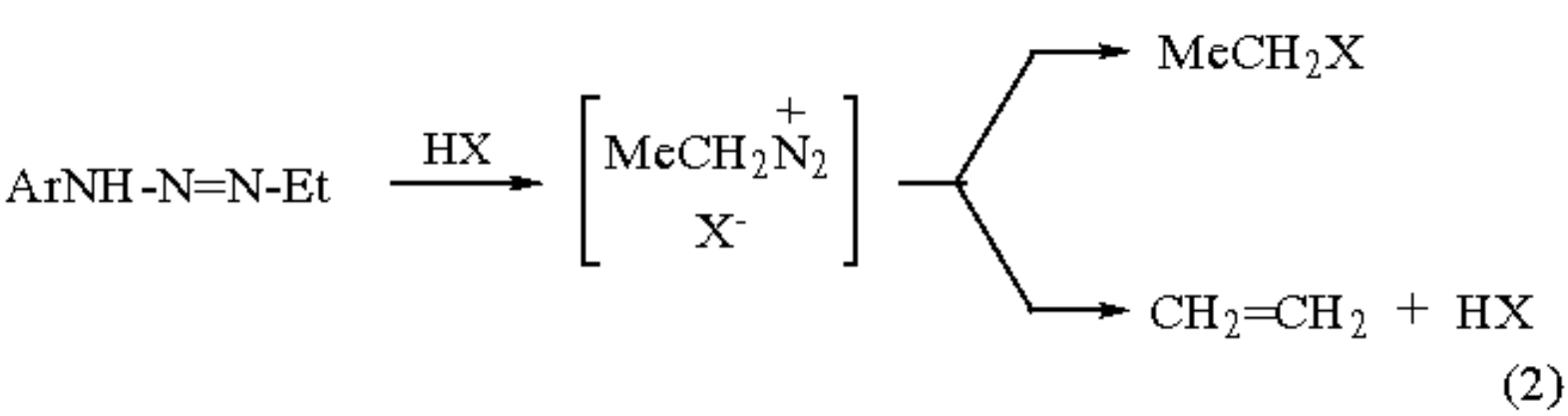

As the electron-donating capacity of the alkyl group increases and as the solvent becomes more polar, the mechanism shifts from S_N2 to S_N1, leading to carbenium ion pair intermediates (eq 3),[12,13] which form the esters with net retention of configuration. In these cases, alkylation of the arylamine also occurs (as well as the elimination reaction), and alkylation of the solvent may become a major reaction,[14] especially when a removable β-hydrogen is not available. This fact can be turned to advantage since, in this way, weakly acidic or nonacidic compounds can be alkylated.[14]

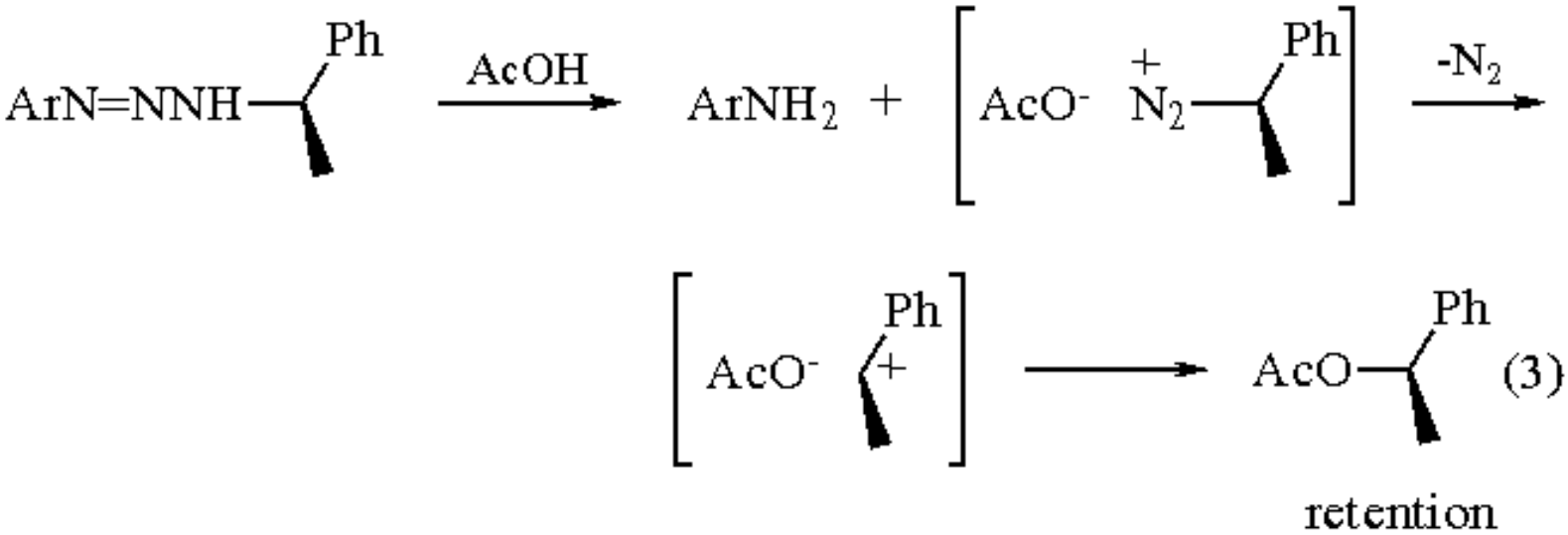

Other Reactions of Triazenes.

The common acylating agents react with mono- and disubstituted triazenes to give the corresponding acyl derivatives; ***Phenyl Isocyanate*** (eq 4) and ***Acetic Anhydride*** have been particularly widely used.[15] These acyl derivatives obtained from dialkyltriazenes still have alkylating capabilities.[16]

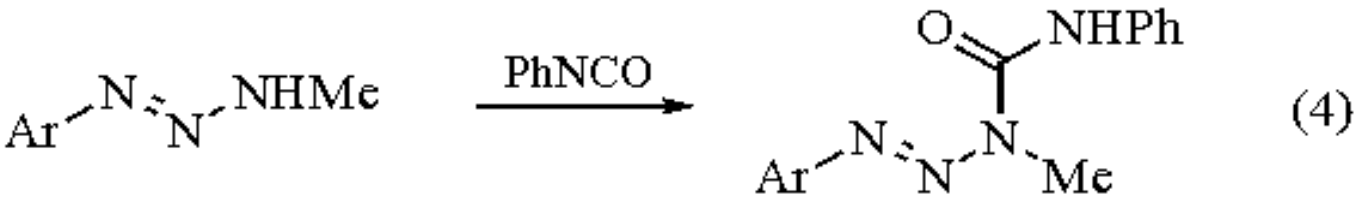

Salts of disubstituted triazenes can be alkylated, and with unsymmetrical triazenes alkylation can occur at either or

both terminal nitrogens.[17] Triazenes are readily reduced to a mixture of amines and hydrazines (the reaction cannot be stopped at the triazane stage).[18] Oxidation of disubstituted triazenes with permanganate produces hexazadienes.[19] Triazenes form complexes with transition metals in the capacity of mono- and bidentate ligands and as bridging agents.[20]

The Triazene Moiety as an Amino Blocking Group.

The isomeric bromoanilines have been converted into the corresponding triazenes, which were subjected to lithium-halogen exchange to yield triazenylaryllithiums.[21] These react with a variety of electrophiles; subsequent deblocking of the products by hydrolysis regenerates the arylamino function.[21]

Biological Alkylation.

Alkyltriazenes are cytotoxic compounds which have carcinogenic,[22] mutagenic,[23] teratogenic,[24] antifungal,[25] bactericidal,[25] and antitumor[26] properties. This broad spectrum of biological activity is commonly attributed to their capacity to alkylate biomolecules, in particular DNA.[27] 5-(3-Methyl-1-triazeno)imidazole-4-carboxamide (MTIC) (**7**), for example, possesses antitumor activity,[26,27] methylating DNA primarily at N-7 and O-6 of the guanine residues.[27]

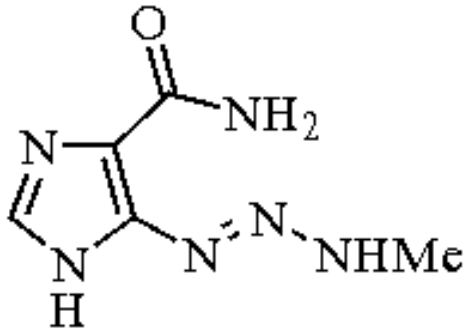

(7)

Related Methylating Agents.

A number of mechanistically related alkylating agents are available, but they are not generally competitive with the triazenes or diazomethane except under specific conditions. For example, acidic compounds are methylated by *syn* and *anti* methanediazoate salts[28] and by *N*-methyl-*N*-nitrososulfamates.[29] Conditions can be found for alkylation by *N*-methyl-*N*-nitro-*O*-acylhydroxylamines[30] and by the corresponding *N*-nitroso analogs.[31] Finally, an elegant approach suitable for isotopically labeled compounds and other valuable compounds involves the prior incorporation of the incipient methylating group and the acidic group (carboxylic acids, carbonic and carbamic acids, sulfonic acids, etc.) into a single molecule, followed by first-order decomposition[32] (see ***N-Methyl-N-nitrosoacetamide***).

Related Reagents.

2-Diazopropane; ***1-Methyl-3-nitro-1-nitrosoguanidine***; ***N-[N´-Methyl-N´-nitroso(aminomethyl)]benzamide***; ***N-Methyl-N-nitroso-p-toluenesulfonamide***; ***N-Nitrosodimethylamine***; ***Phenyldiazomethane***; ***Trimethylsilyldiazomethane***.

---

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Methyl *N*-(*p*-Tolylsulfonylmethyl)thiobenzimidate

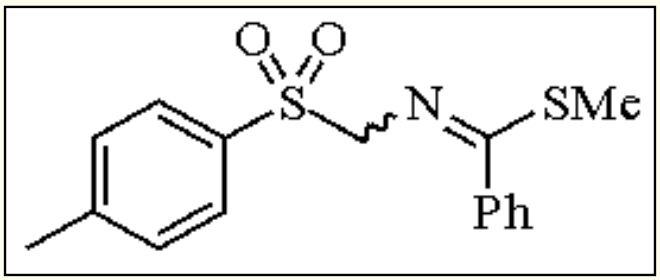

(*E*)

[80224-81-3] · $C_{16}H_{17}NO_2S_2$ · Methyl *N*-(*p*-Tolylsulfonylmethyl)thiobenzimidate · (MW 319.48) (*Z*)

[80224-48-2]

(reagent for the synthesis of 2,3,4-trisubstituted pyrroles[1] from Michael acceptors, and of 2,5-disubstituted oxazoles[2] from aldehydes)

Physical Data: mp 98.5-100.5 °C (*E*,*Z*-mixture).

Form Supplied in: colorless crystalline, shelf-stable material.

Analysis of Reagent Purity: IR (Nujol) 1600 (C=N), 1320 and 1135 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$; *E*/*Z* mixture) δ 2.0 (s), 2.3 (s), 2.4 (s), and 2.5 (s) (2 × Me), 4.7 (s) and 5.0 (s) (CH_2); ^{13}C NMR ($CDCl_3$) δ 74.1 and 74.6 (CH_2).

Preparative Methods: prepared by *S*-methylation of *N*-(*p*-tolylsulfonylmethyl)thiobenzamide in 74% yield using methyl fluorosulfonate,[1a] and in 91% yield using ***Iodomethane***.[1b]

Introduction.

Methyl *N*-(*p*-tolylsulfonylmethyl)thiobenzimidate (**1**) has been designed as a derivative of ***p-Tolylsulfonylmethyl Isocyanide*** (TosMIC). TosMIC is a multipurpose synthesis reagent. One of the major applications of TosMIC is the base-induced cycloaddition of the C-N-C unit of TosMIC across the C=C double bond of Michael acceptors to form 3,4-disubstituted pyrroles, which inherently do not carry substituents at the ring positions 1, 2, and 5. Modified reagents such as (**1**) bearing two substituents on the isocyano carbon of TosMIC may react with Michael acceptors to give 2,3,4-trisubstituted pyrroles, in much the same way as TosMIC does. Thus reagent (**1**) would provide the product

pyrroles with a phenyl substituent at position 2 (next to the ring carbon carrying the electron-withdrawing group of the former Michael acceptor molecule) (eq 1).[1] The second substituent at the isocyano carbon of TosMIC (MeS in **1**) needs to be a leaving group.

Synthesis of Pyrroles.

Reaction of (**1**) with Michael acceptors produces 2,3,4-trisubstituted pyrroles in one operation (eq 1),[1] with a phenyl substituent at C-2. Substituents in (**1**) other than Ph and MeS have also been used.[1]

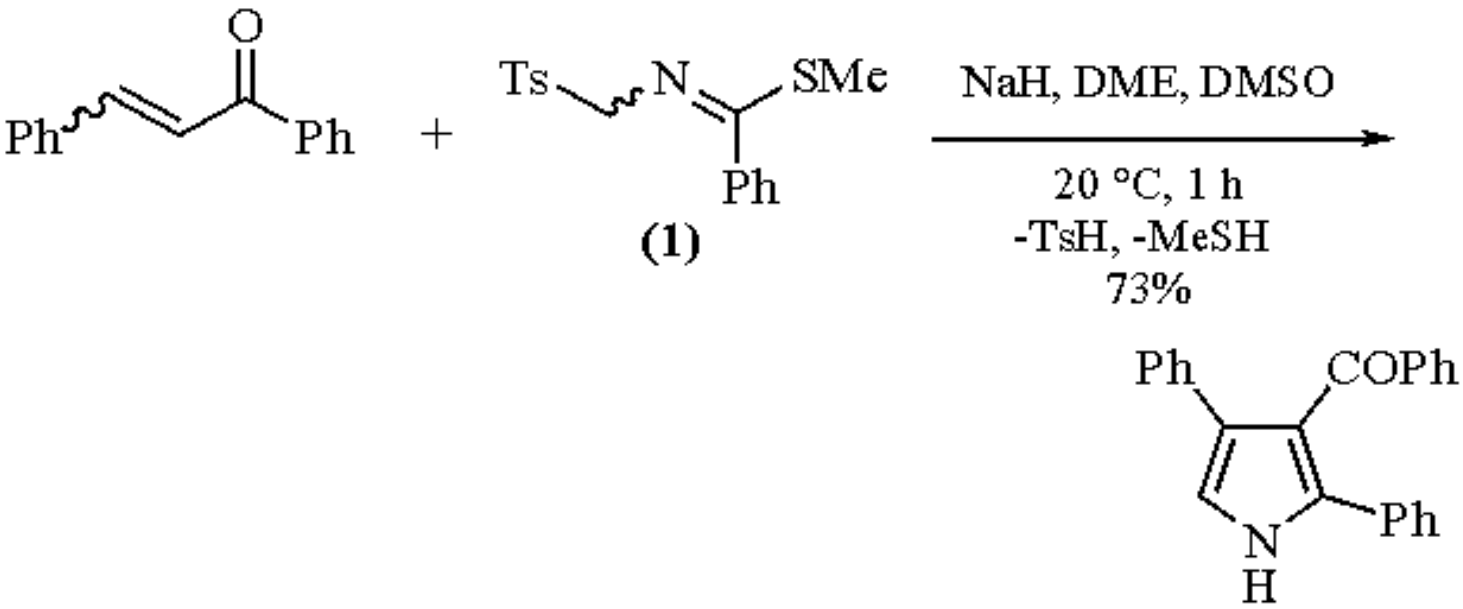

(1)

Synthesis of Oxazoles and Imidazoles.

The reaction of (**1**) with aromatic aldehydes provides 2,5-disubstituted oxazoles (eq 2).[2] 2-Methoxyoxazoles have been prepared by a similar process using dimethyl *N*-(*p*-tolylsulfonylmethyl)iminocarbonate (**2**), instead of (**1**) (eq 3).[2] 1,2,5-Trisubstituted imidazoles are formed accordingly by reaction of (**1**) with imino compounds.[3]

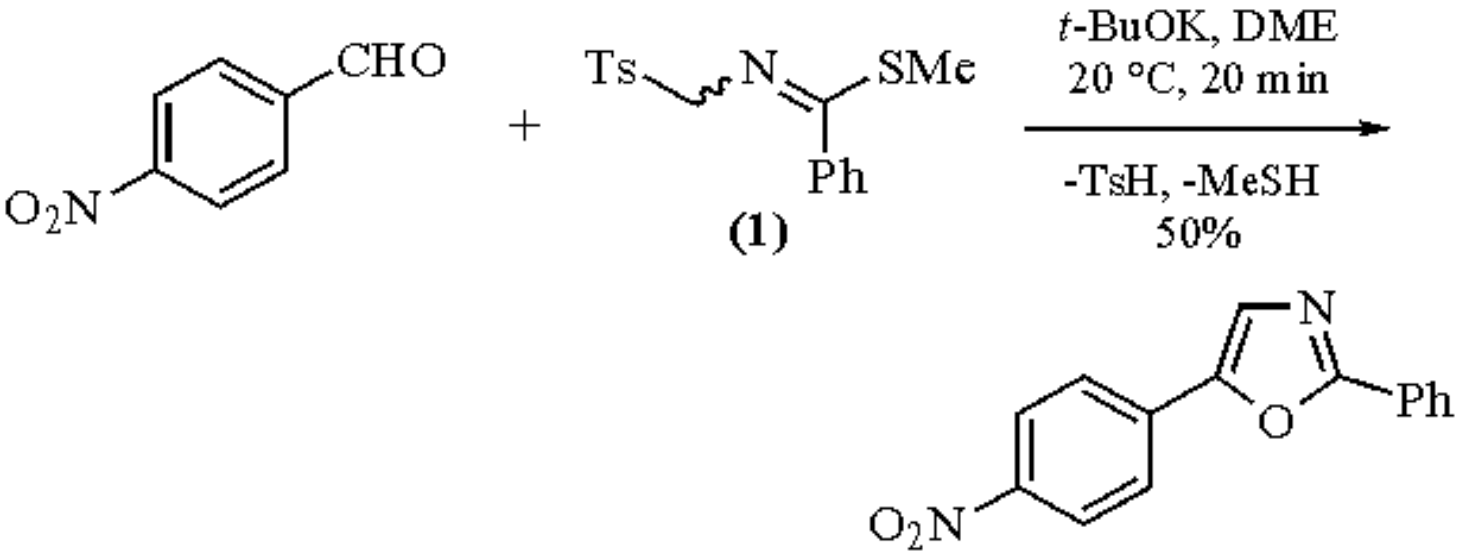

(2)

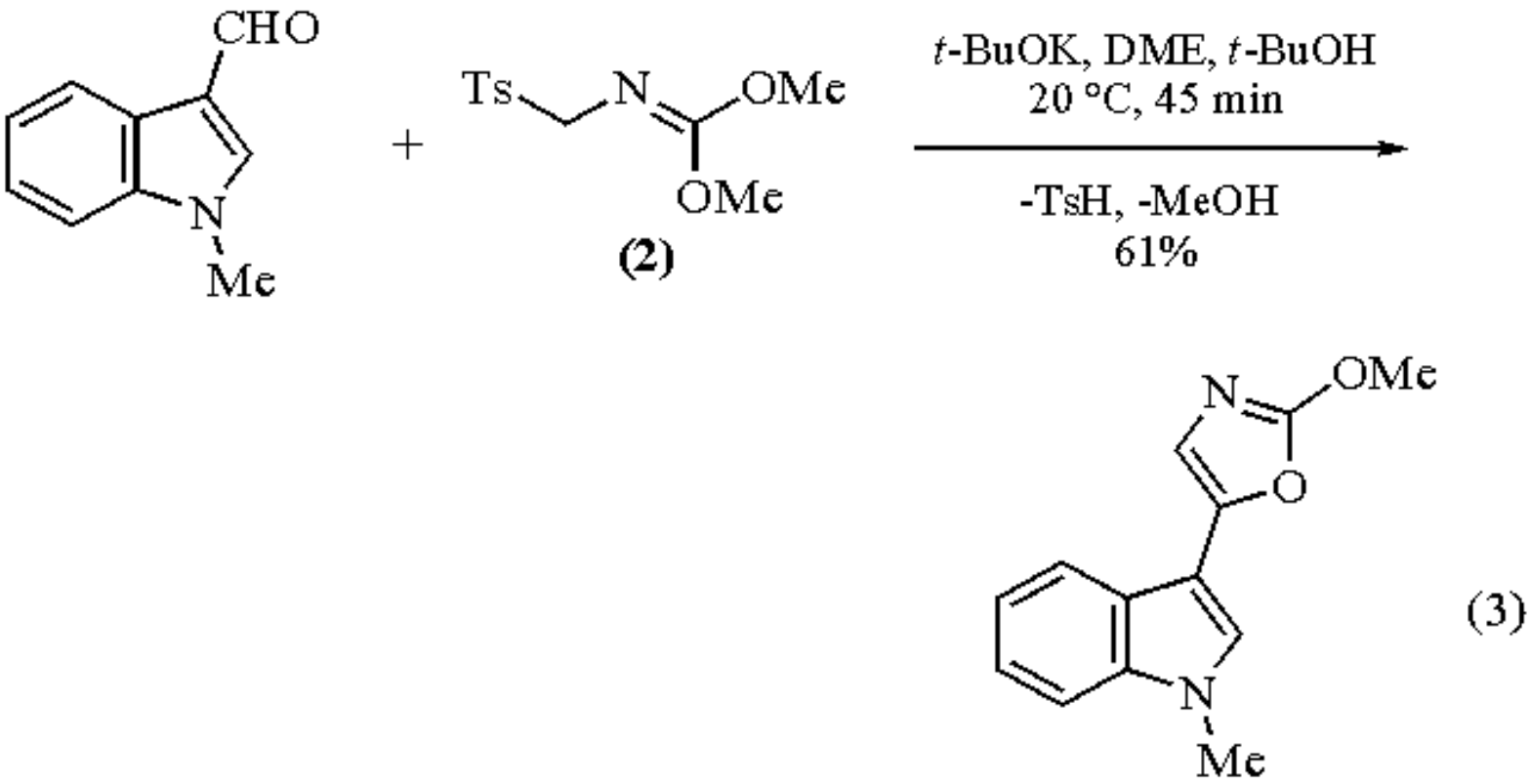

Related Reagents.

Diethyl Isocyanomethylphosphonate; ***Ethyl Isocyanoacetate***; ***Methyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***.

---

1. (a) Houwing, H. A.; van Leusen, A. M. *JHC* **1981**, *18*, 1127. (b) Methyl fluorosulfonate (Magic Methyl, a dangerous methylating agent) is no longer commercially available. However, F. R. Leusink of this laboratory has shown that MeI is an excellent replacement when the procedure of Walter and Saha is followed, using acetonitrile (20 °C, 10 min) instead of acetone. See: Walter, W.; Saha, C. R. *PS* **1983**, *17*, 367.
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N-Methyl-*N*-tosylpyrrolidinium Perchlorate

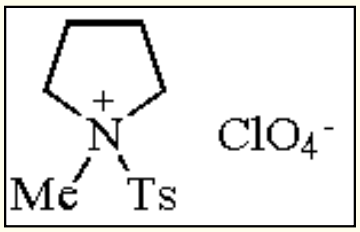

[39830-53-0] · $C_{12}H_{18}ClNOS$ · *N*-Methyl-*N*-tosylpyrrolidinium Perchlorate · (MW 339.84)

(selective tosylating reagent for amines)

Physical Data: mp 148-150 °C.

Solubility: usually used in CH_2Cl_2.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: sharp mp and satisfactory elemental analysis are reported.[1]

Preparative Method: N-methylpyrrolidine is reacted with ***p-Toluenesulfonyl Chloride*** in CH_2Cl_2, in the dark, in the presence of ***Silver(I) Perchlorate***, to yield the required production in 67.7 % yield.[1-3]

Handling, Storage, and Precautions: N-methyl-*N*-tosylpyrrolidinium perchlorate can be stored for six months without significant decomposition. It is reasonably stable in water, with approximately 50% remaining unchanged after 60 min.

Introduction.

N-Methyl-*N*-tosylpyrrolidinium perchlorate is used as a selective tosylating reagent for amines in the presence of alcohols.[1] The use of ClO_4^- as counterion avoids a possible side reaction that occurs when $SbCl_6^-$ is used as counterion, namely attack of Cl^- liberated from $SbCl_6^-$ on the S atom of the sulfonamide. This yields TsCl.

Protection of Primary and Secondary Amines.

The protection of amines is easily achieved by reacting the amine and tosylating agent in CH_2Cl_2 at 0 °C. The hindered amine ***1,3-Dicyclohexylcarbodiimide*** is tosylated in better yield than by previous methods[4] which have used TsCl. However, when the weakly basic diphenylamine is used, slow and forcing conditions are required and tosylation is only achieved in moderate yield (Table 1).

Table 1 Tosylating Conditions and Yields for Amines

Amine	Conditions	Yield (%)
p-Toluidine	0 °C, 1.5 h	97.8
Indoline	0 °C, 2 h	96.7
DCC	0 °C, 1.5 h	65.8
Diphenylamine	40 °C, 2 h	49

Alcohols are not tosylated by *N*-methyl-*N*-tosylpyrrolidinium perchlorate, as exemplified by stirring cholesterol in CH_2Cl_2 with the tosylating reagent, at room temperature for 7 h. No reaction occurs.

Selective Tosylation of Amines in the Presence of Alcohols.

The attempted *N*-tosylation of amino alcohol (**1**), an intermediate in the synthesis of β,β-disubstituted indoline alkaloids, using 10% NaOH and TsCl resulted in 20-40% of the required product, plus a significant amount of the N-Ts/O-Ts compound.[4] However, using *N*-methyl-*N*-tosylpyrrolidinium perchlorate, yields of the required N-Ts compound are improved to 75% (eq 1).

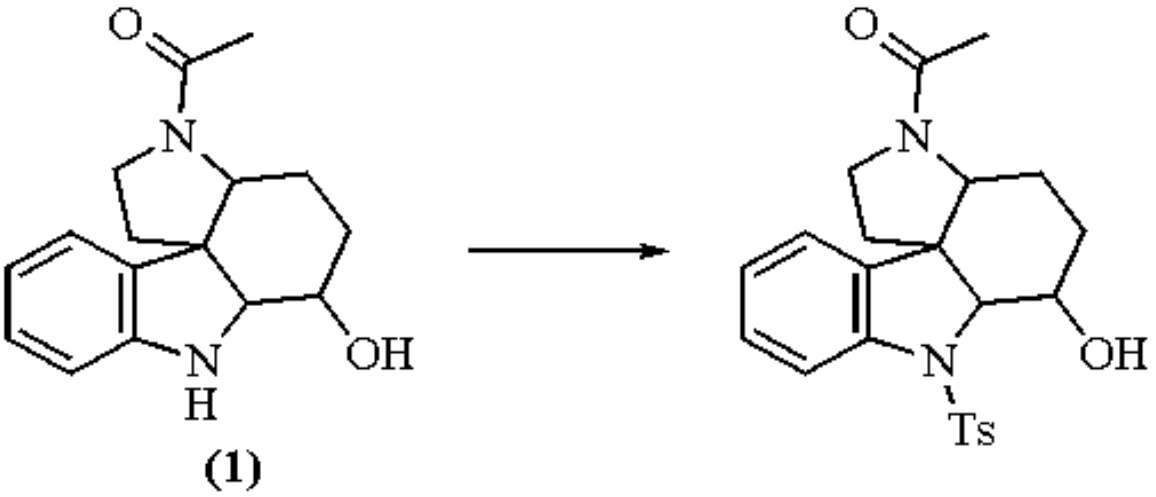

(1)

Similarly, amino alcohol (**2**) is *N*-tosylated in 80% yield with only 5% of the *N*-tosyl-*O*-tosyl compound being formed (eq 2).

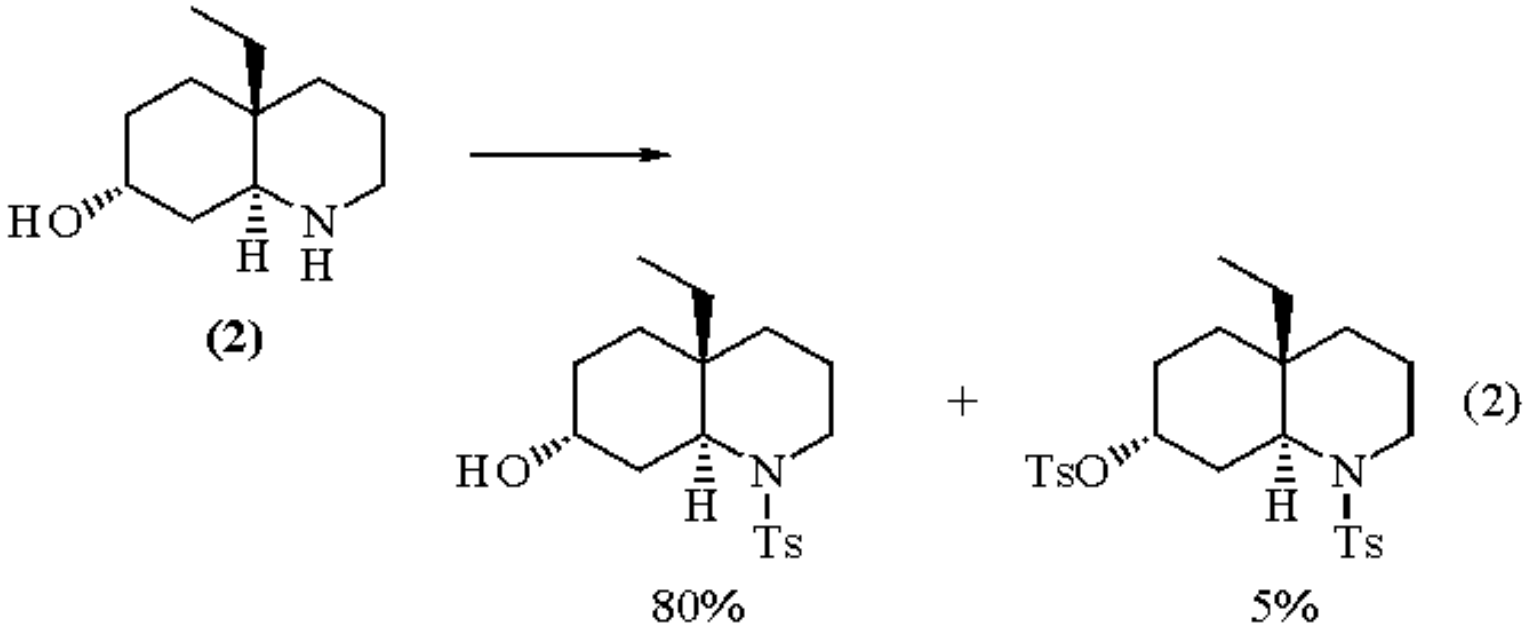

N-Methyl-*N*-tosylpyrrolidinium perchlorate is stable in water (approximately 50% remaining unchanged after 60 min). The authors[1] therefore suggest that it may be applicable to protein modification. However, no reports on this application have been forthcoming.

---

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4. Klamann, D.; Bertsch, H. *CB* **1956**, *89*, 2007.

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4-Methyl-1,2,3-triazine[1]

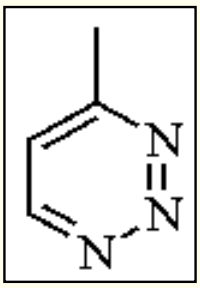

[77202-08-5] · $C_4H_5N_3$ · 4-Methyl-1,2,3-triazine · (MW 95.12)

(an electron-deficient heteroaromatic azadiene capable of participation in inverse electron demand Diels-Alder reactions with electron-rich dienophiles employed for preparation of substituted pyridines[1])

Physical Data: mp 31 °C.

Solubility: sol $CHCl_3$, CH_2Cl_2, EtOH.

Form Supplied in: plates (*i*-Pr_2O).

Preparative Method: an ice-cold solution of 0.01 mol of *N*-amino-5-methylpyrazole in 30 mL of CH_2Cl_2 and 10 mL of H_2O is treated with 0.02 mol of solid ***Sodium Periodate*** or potassium periodate with stirring. The resulting mixture is allowed to stir at 0-5 °C overnight and then extracted repeatedly with $CHCl_3$. The $CHCl_3$ phase is dried over Na_2SO_4, concentrated, and purified by recrystallization or column chromatography on silica gel.[2]

Handling, Storage, and Precautions: stable at room temperature and is probably hygroscopic.

Cycloaddition Reactions.

4-Methyl-1,2,3-triazine (**1**) is an electron-deficient heteroaromatic azadiene that has been shown to participate in inverse electron demand Diels-Alder reactions. It is capable of reacting with electron-rich dienophiles including pyrrolidine enamines and ynamines in a regioselective fashion to give, after a retro Diels-Alder reaction with loss of N_2 and in situ elimination of pyrrolidine, 2,3,6-trisubstituted pyridines (eqs 1 and 2).[3,4] Cycloaddition occurs across N-3/C-6 of the 1,2,3-triazine nucleus and the nucleophilic carbon of the dienophile attaches to C-6 of the 1,2,3-triazine. The utility of this reagent has been demonstrated in the total syntheses of fabianine (eq 3)[5] and guaipyridine (eq 4).[6] A change in the mode of cycloaddition and/or loss of regioselectivity have been observed in reactions conducted under more vigorous conditions (eqs 5 and 6).[7,8]

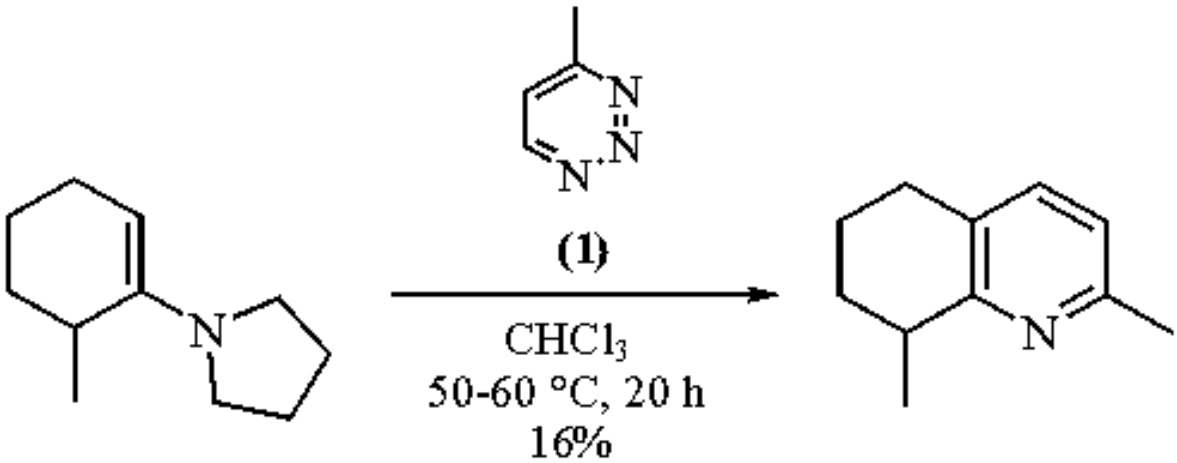
(1)
CHCl3
50-60 °C, 20 h
16%

(1)

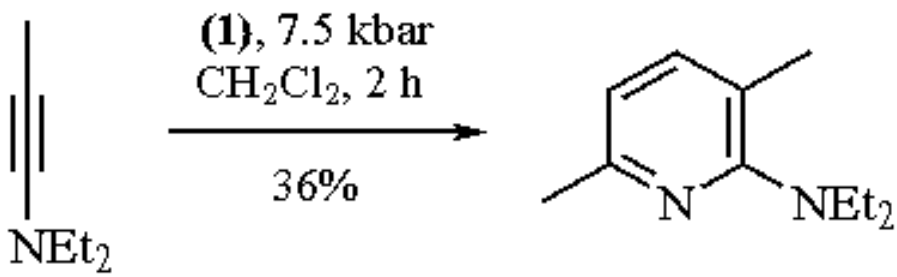
(1), 7.5 kbar
CH2Cl2, 2 h
36%
NEt2

(2)

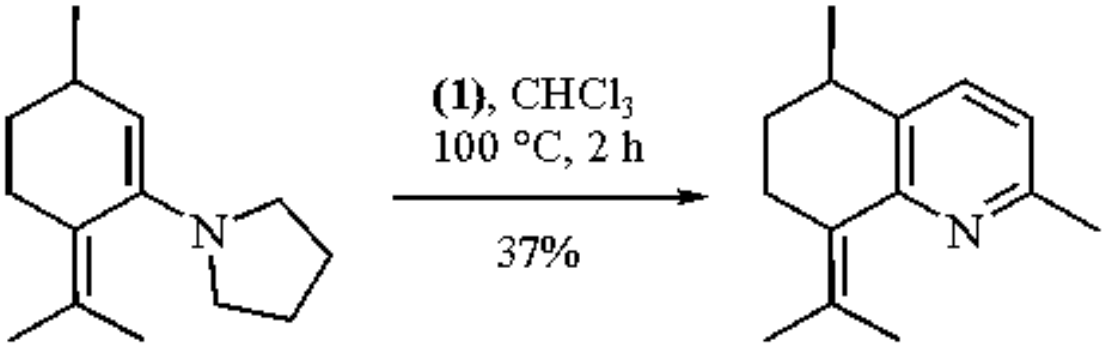
(1), CHCl3
100 °C, 2 h
37%

(3)

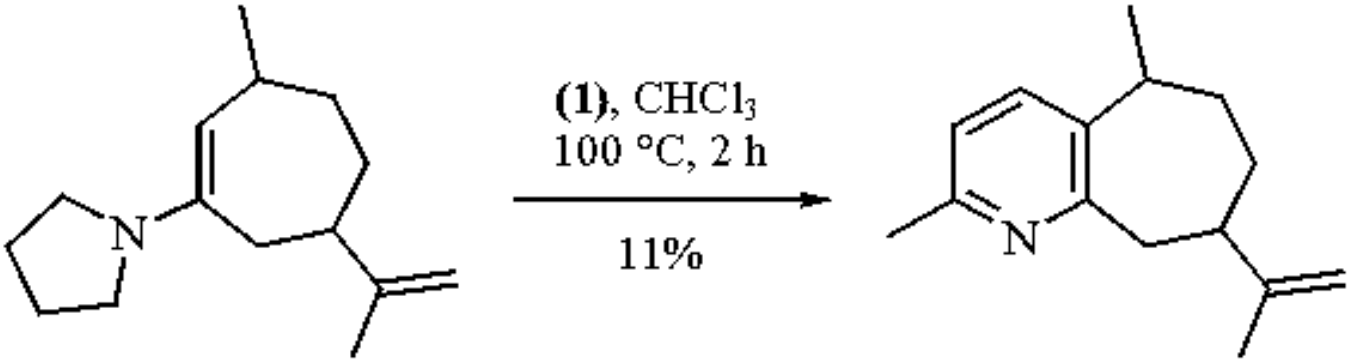
(1), CHCl3
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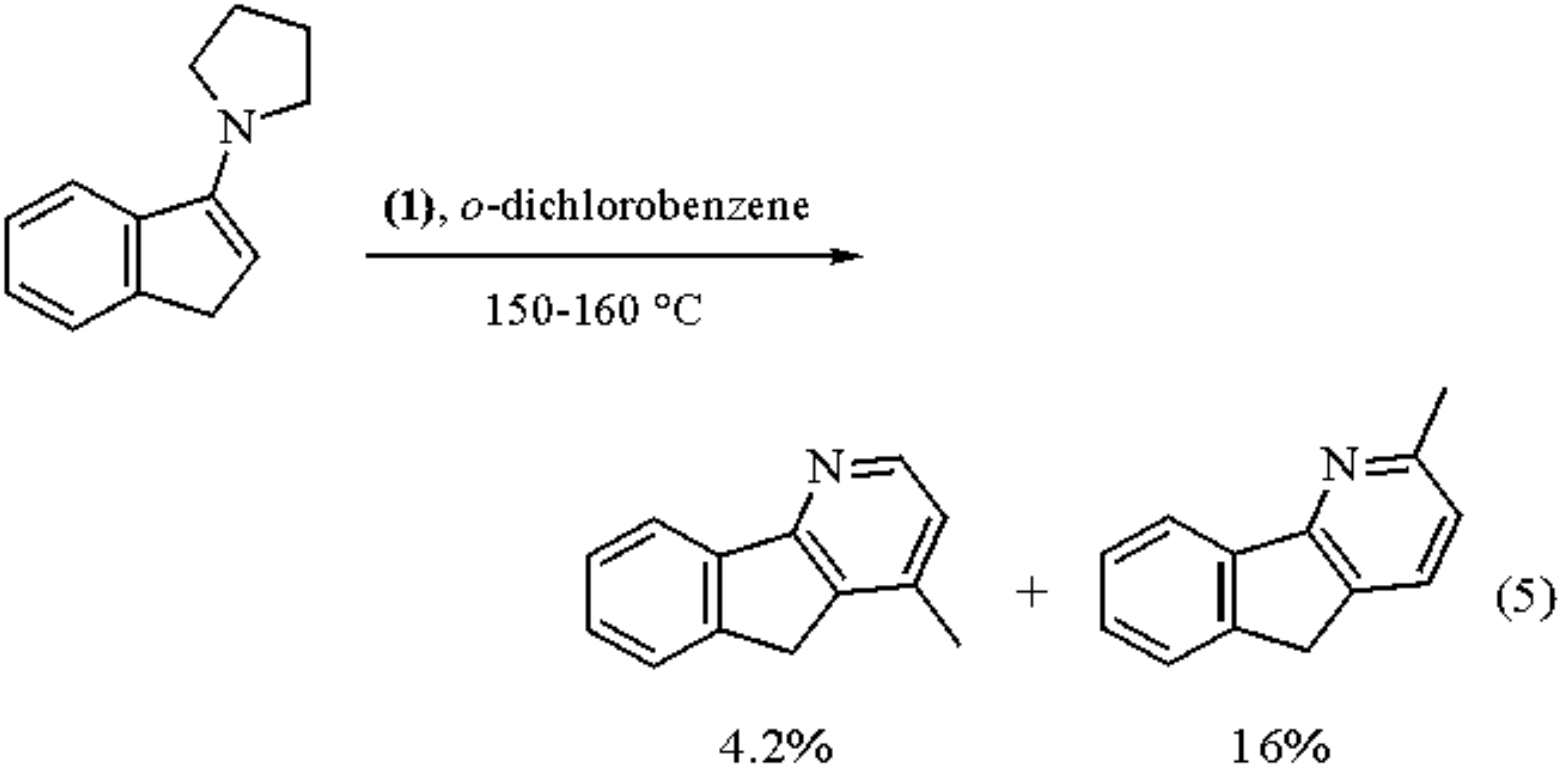

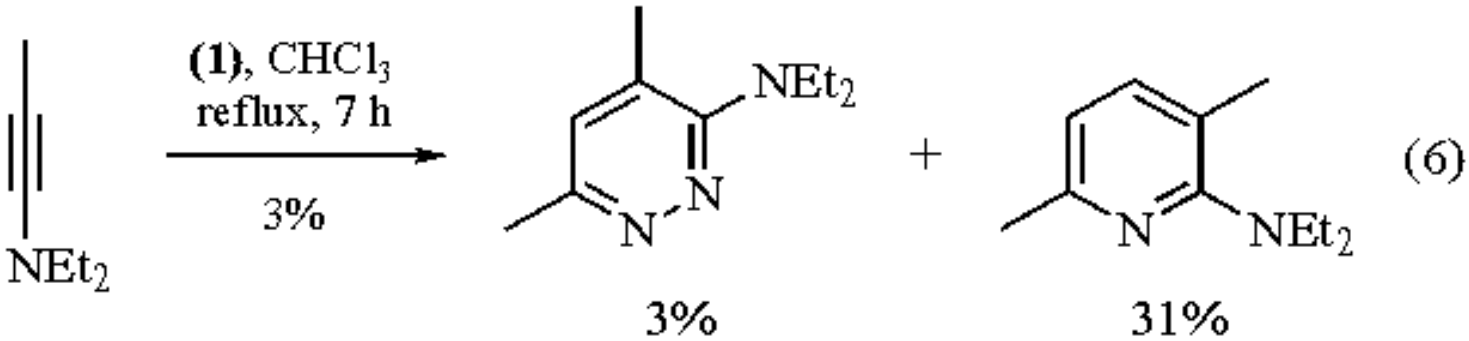

Related Reagents.

Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate; ***3,6-Diphenyl-1,2,4,5-tetrazine***; ***1,2,4-Triazine***; ***1,3,5-Triazine***.

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Dale L. Boger & Minsheng Zhang

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Methyl Tributylstannyl Sulfide

Bu_3SnSMe

[17314-32-8] · $C_{13}H_{30}SSn$ · Methyl Tributylstannyl Sulfide · (MW 337.15)

(methanethiol equivalent in thioglycoside synthesis)

Physical Data: bp 104 °C/0.2 mmHg; *n*22D 1.5110.

Solubility: insol H_2O; sol hexane, acetone, ether.

Analysis of Reagent Purity: reacts readily with iodine and can be titrated against a solution of iodine in carbon tetrachloride.

Preparative Methods: prepared simply by mixing ***Bis(tri-n-butyltin) Oxide*** and ***Methanethiol*** followed by distillation under vacuum.[1] Preparation from ***Tri-n-butylchlorostannane*** and NaSMe is also possible.[2]

Handling, Storage, and Precautions: due to the low volatility, this reagent is much easier to handle than the parent thiol (MeSH; bp 6 °C). However, in addition to the strong odor, it is highly toxic (as is the case with all organotin compounds) and should be handled and stored accordingly.

Thioglycoside Synthesis.

Methyl tributylstannyl sulfide is widely applicable to the preparation of a variety of thioglycosides which are useful synthetic blocks in oligosaccharide synthesis. For instance, glycopyranosyl bromide or acetate gives the corresponding methylthioglycoside in high yield by the action of Bu_3SnSMe in combination with ***Tin(IV) Chloride***.[3] In general, glycosyl bromide gives the product as a mixture of anomers, because of the partial anomerization of the initially formed β-thioglycoside catalyzed by some Lewis acidic species generated in situ. Although the transformation from glycosyl bromide can be achieved without $SnCl_4$, the reaction requires higher temperature and results in incomplete conversion. On the other hand, the reaction of glycopyranosyl acetate gives the 1,2-*trans* product selectively (eq 1). In addition to such stereoselectivity, the ease of preparation and stability makes the use of a glycosyl acetate preferable over the glycosyl bromide as a starting material. A similar reaction using ribofuranosyl acetate gives a mixture of β- and α-anomers (eq 2).

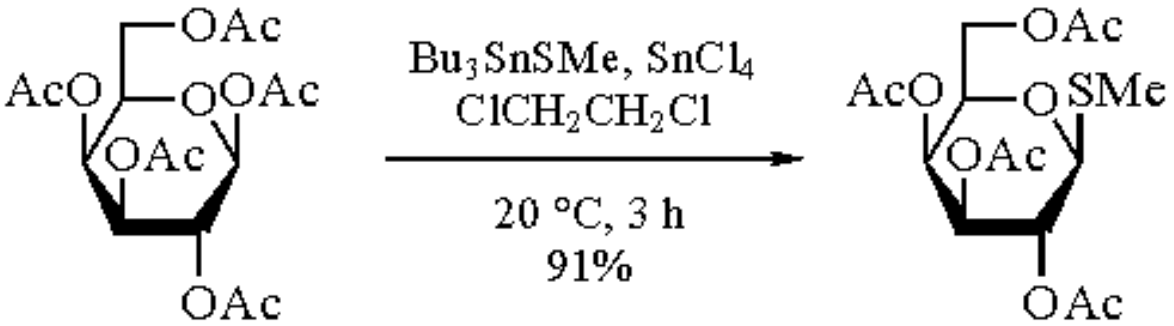

(1)

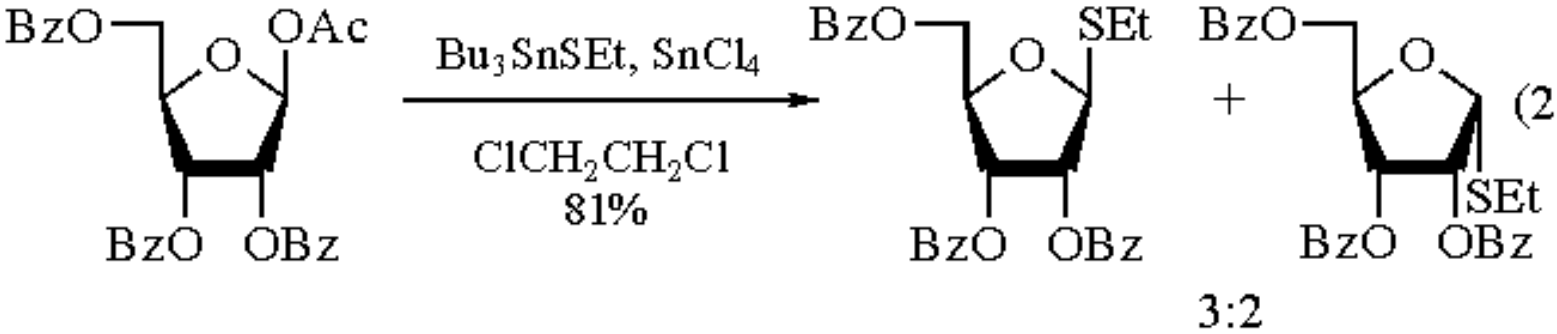

(2)

Since it is known that the reaction of such sugar derivatives with free thiols and ***Zinc Chloride*** sometimes gives a dithioacetal instead of desired thioglycoside,[4] the substitution of hydrogen by a tributylstannyl group seems to attenuate the nucleophilicity of the alkylthio group.

The preparation of complex oligosaccharide-derived thioglycosides is also possible. For this purpose, trichloroacetimidate is the substrate of choice, since it is much more reactive than the corresponding glycosyl acetate (eq 3).[5]

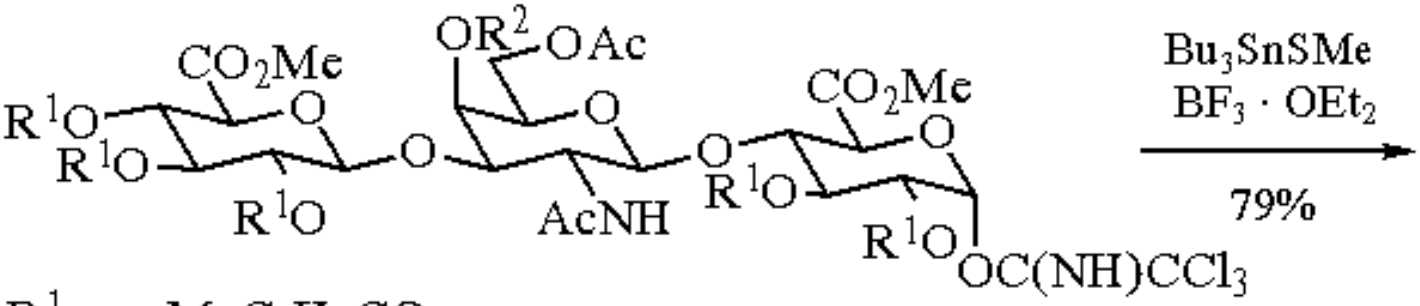

$R^1 = p\text{-}MeC_6H_4CO$

$R^2 = MeCO(CH_2)_2CO$

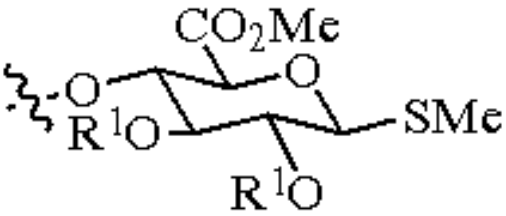

(3)

The use of alkoxystannane (Bu_3SnOR) in place of tributylstannyl sulfide gives *O*-glycosides under similar conditions.[6]

Thioglycosides in Oligosaccharide Synthesis.

Thioglycoside linkages are stable under acidic and basic conditions, which are usually encountered in carbohydrate manipulations such as protection-deprotection of hydroxy groups. In spite of such stability, thioglycosides are powerful glycosyl donors under certain conditions and are widely used in oligosaccharide synthesis (examples[7]). Numerous methods are now available to activate alkylthioglycosides. Some examples of promotors are as follows: $MeOSO_2CF_3$,[8] $PhHgOSO_2CF_3$,[9] $Me_2SSMe^+CF_3SO_2^-$,[10] $CuBr_2$-Bu_4NBr,[11] PhSeCl-$AgOSO_2CF_3$,[12] MeSBr-$AgOSO_2CF_3$,[13] NIS-CF_3SO_3H,[14] $AgOSO_2CF_3$-Br_2.[15]

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Methyltrichlorosilane[1]

[75-79-6] · CH_3Cl_3Si · Methyltrichlorosilane · (MW 149.48)

(precursor to organosilicon compounds;[1] silylating agent;[1] Lewis acid[2])

Physical Data: bp 66 °C; *d* 1.273 g cm^{-3}.

Solubility: sol methylene chloride.

Form Supplied in: liquid; commercially available.

Purification: can be purified by distillation.

Handling, Storage, and Precautions: is corrosive and moisture sensitive. It should be handled in an anhydrous atmosphere in a fume hood.

Organosilicon Compounds.

$MeSiCl_3$ is an important precursor to organosilicon compounds.[1] It reacts with carbanions to form corresponding alkyl(aryl) methylsilanes.[3] Grignard and organolithium reagents are the most frequently used carbanion sources in this transformation. Generally, the organolithiums are preferred over Grignard reagents, especially in the preparation of tetraorganosilanes. However, it was reported that the reaction using Grignard reagents was facilitated by a catalytic amount of cyanide or thiocyanate ions.[4] Stepwise substitution on $MeSiCl_3$ can be accomplished by introducing carbanions sequentially, yielding dichloro-, monochloro-, and tetraorganosilanes, respectively (eq 1). This makes it possible to design a silane with a specific steric bulkiness, a feature often required for the monochlorosilanes to serve as protecting groups.[5]

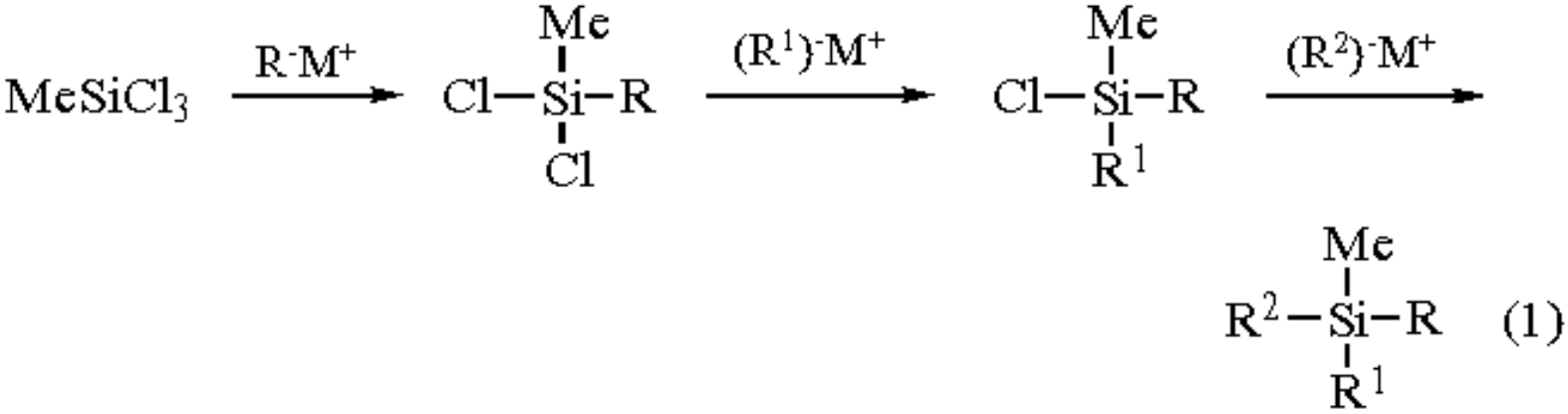

$MeSiCl_3$ has been used as a coupling agent in the preparation of the multidentate ligand (*RRR*)-siliphos {(*RRR*)-$MeSi[CH_2P(t\text{-}Bu)Ph]_3$} (eq 2).[6] The preparation of this optically pure tristertiary phosphine was achieved by deprotonation of optically pure (*R*)-$P(BH_3)Me(t\text{-}Bu)Ph$, followed by silylation of the resulting carbanion with $MeSiCl_3$, and the subsequent removal of the BH_3 protecting group with ***Morpholine***. The function of $MeSiCl_3$ as a coupling agent has also been widely used for the synthesis of star-branched polymers.[7] Cyclic silanes are obtained by treating $MeSiCl_3$ with dicarbanions and tricarbanions, albeit in lower yields (eqs 3 and 4).[8] Treatment of $CFCl_3/(Et_2N)_3P$ with $MeSiCl_3$ led to the formation of $CFCl_2SiCl_2Me$.[9]

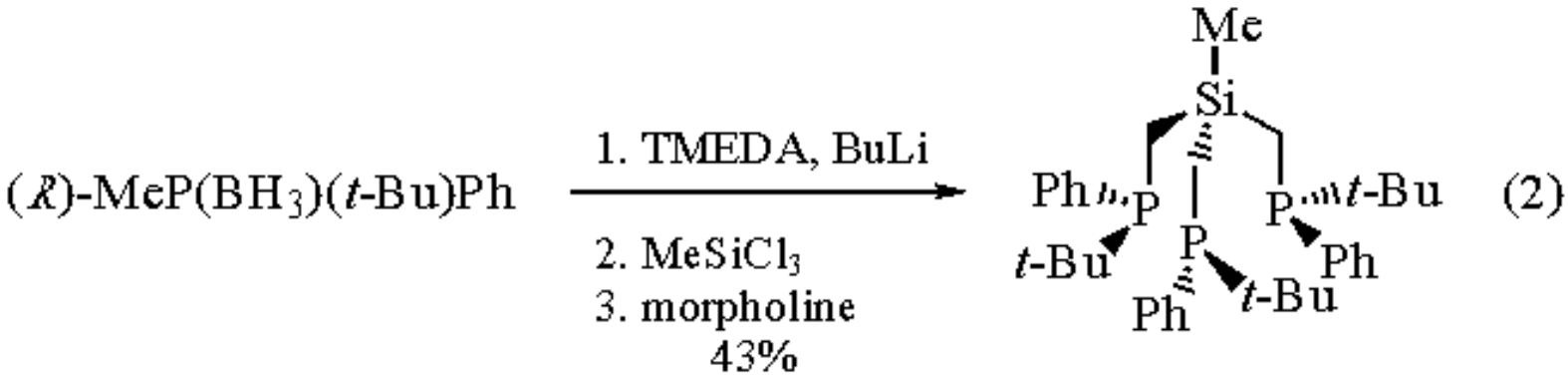

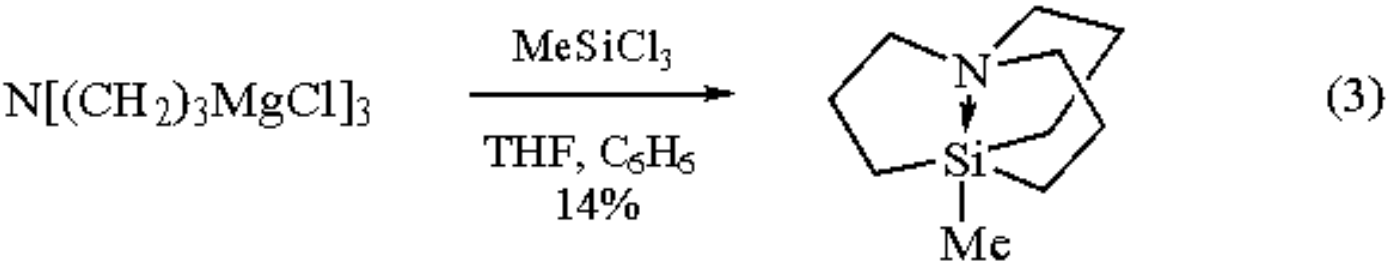

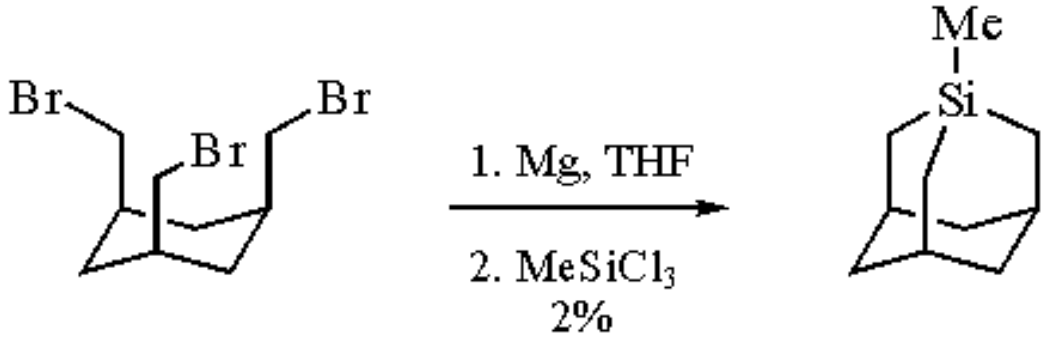

(4)

Substitutions of $MeSiCl_3$ can also be performed under radical conditions or with transition metal catalysis.[1,10] The radical reactions can be initiated either by higher temperature or photolysis. However, the selectivity of the reaction is generally poor.[1] Better results were obtained with transition metal-catalyzed reactions. It was reported that $MeSiCl_3$ reacted with terminal alkynes in the presence of a catalytic amount of ***Copper(I) Chloride*** to form alkynyldichlorosilanes (eq 5).[11]

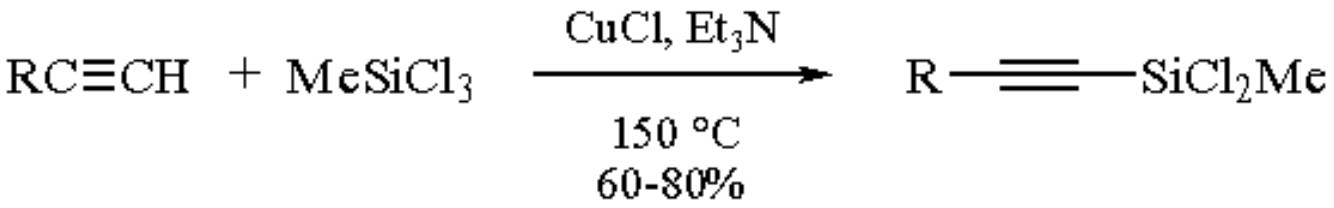

(5)

Besides *C*-silylation, $MeSiCl_3$ is also capable of silylating heteroatoms such as, O, N, and S.[1] It reacts with alcohols, oximes, alkoxysilanes, and esters to form corresponding silylated products.[12] In fact, certain poly- or oligoorganosiloxanes were prepared from $MeSiCl_3$ and hydroxy-containing compounds.[13] When aldehydes and ketones are used, tris(alkenyloxy)silanes are obtained in good yields (eq 6).[14] In the case of 1,3-diketones, organosilicon(IV) β-diketonate complexes are formed (eq 7).[15] Amines are silylated in a similar fashion.[16]

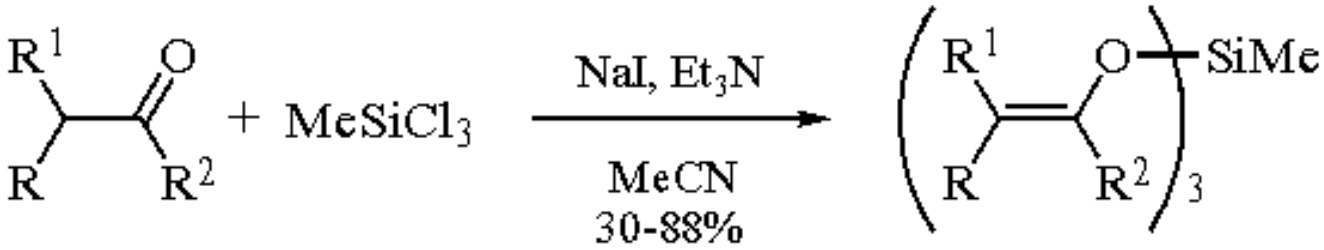

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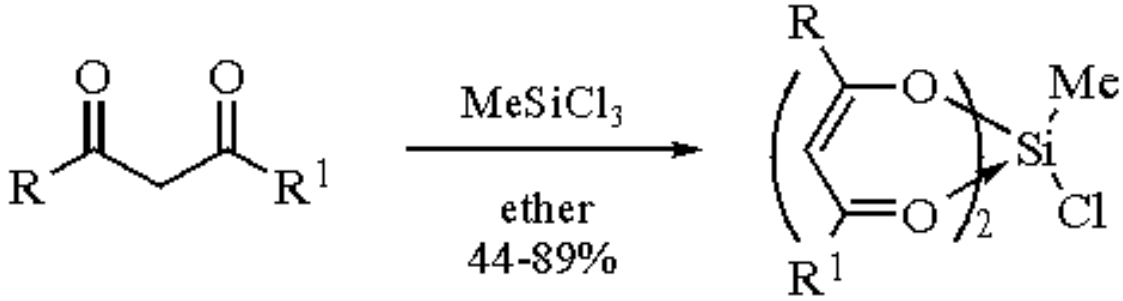

(7)

Reactions as a Lewis Acid.

$MeSiCl_3$ is an effective Lewis acid in the condensation of carboxylic acids with alcohols and amines.[17] Good yields of esters and amides are obtained. $MeSiCl_3$ reacts with epoxides to form β-chloroalkoxysilanes in good yields.[18] It also promotes the addition of allylstannanes to aldehydes (eq 8).[19] Compared to the traditional Lewis acids, $MeSiCl_3$ is relatively mild and less moisture sensitive. The reaction is very selective. When both allylstannanes and allylsilanes are present in the reaction, aldehydes react only with allylstannanes. It was reported that acetylacetone was condensed to pyrylium chloride by using $MeSiCl_3$.[20]

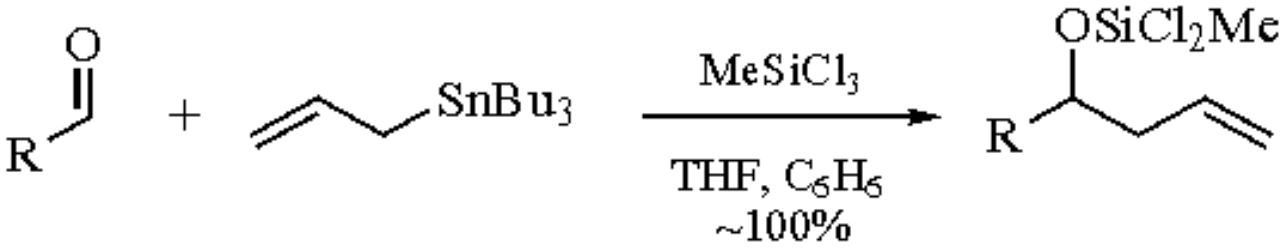

(8)

$MeSiCl_3$ cleaves the ether linkage of *gem*-amino ethers to form dialkyl(methylene)ammonium chloride (Mannich-type salts) in excellent yields (eq 9).[21a] This procedure is much more convenient, efficient, economical, and less dangerous compared to earlier methods. The Mannich salts were also prepared in situ for electrophilic substitution of nucleophilic aromatic compounds (eq 10).[21b,c]

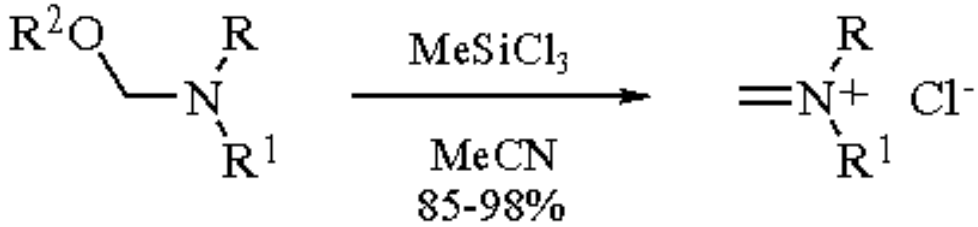

(9)

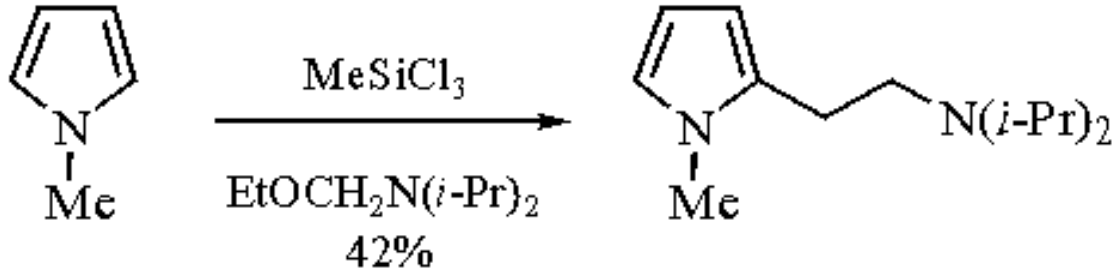

(10)

In conjunction with CuCl, $MeSiCl_3$ promotes conjugate addition of both organomagnesium and manganese(II) reagents to α,β-ethylenic esters (eq 11).[22] These are much higher yield reactions compared to conjugate addition of copper or cuprate reagents to the substrates. The exact role of $MeSiCl_3$ in the reactions is not clear.

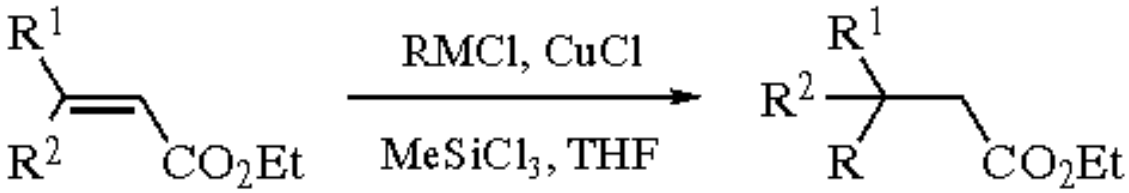

(11)

$M = Mg, Mn^{II}$

$MeSiCl_3$ has been found useful as a deprotecting agent in peptide chemistry.[23] It also promotes, in conjunction with diphenyl sulfoxide, formation of disulfide bonds in peptides (eq 12).[24]

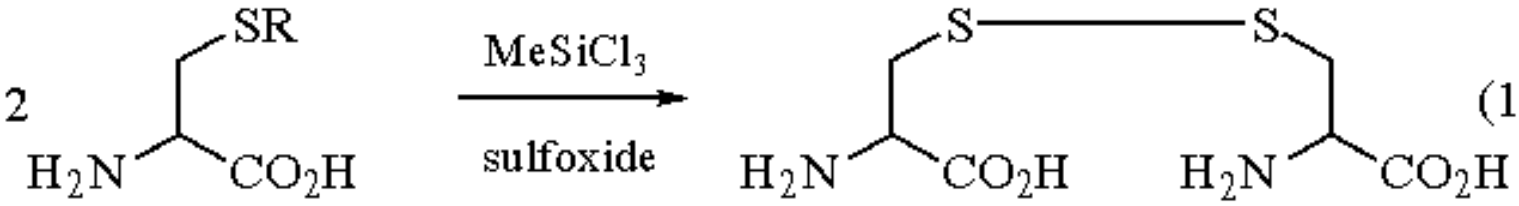

(12)

$MeSiCl_3$/***Sodium Iodide***[2] is an equivalent of ***Iodotrimethylsilane***,[25] a widely used silicon Lewis acid, which has been used for various organic transformations. Compared to Me_3SiI, $MeSiCl_3$/NaI is milder, and thus it is more regioselective when used in ether cleavage (eq 13). Methyl ethers (ROMe) are cleaved affording alcohols as sole products, provided that the alkyl groups are either primary or secondary. Benzyl, trityl, and tetrahydropyranyl ethers are also cleaved regioselectively at ambient temperature to give quantitative yields of alcohols. If a tertiary alkyl group is present in the ethers, an alkyl iodide is then obtained. Esters and lactones are similarly cleaved to carboxylic acids. Acetals are converted to carbonyl compounds by $MeSiCl_3$/NaI (eq 14).

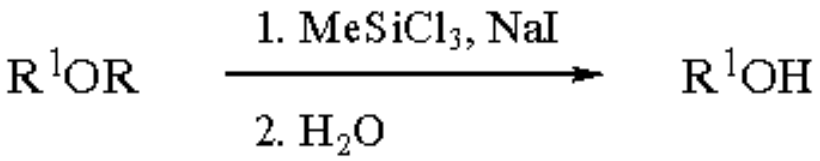

(13)

R^1 = primary and secondary alkyl group;

R = Me, benzyl, trityl, tetrahydropyranyl

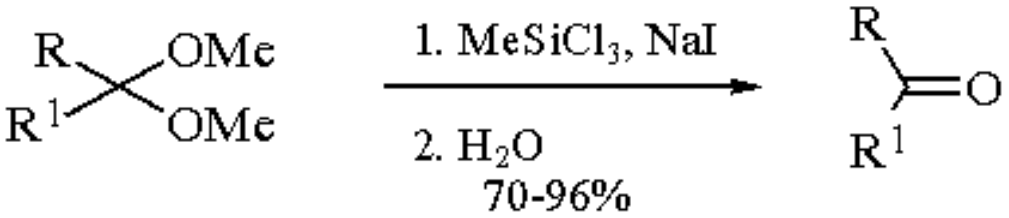

(14)

$MeSiCl_3$/NaI is a good iodinating agent, which converts alcohols to corresponding iodides (eq 15). Primary alcohols react very slowly even under reflux conditions, giving low yields. However, moderate and excellent yields of alkyl iodides can be obtained with secondary, tertiary, and benzylic alcohols.

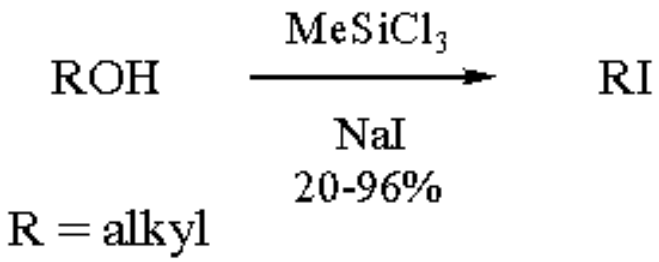

(15)

$MeSiCl_3$/NaI was found to dehalogenate α-halo ketones reductively (eq 16). The conversion of 5-cyano-7-oxabicyclo[2.2.1]hept-2-ene to 2-furanpropanenitrile was also reported (eq 17).[26]

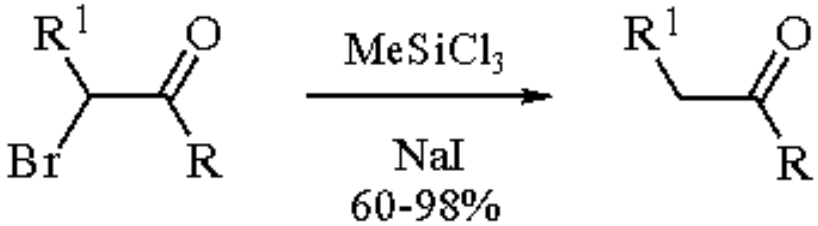

(16)

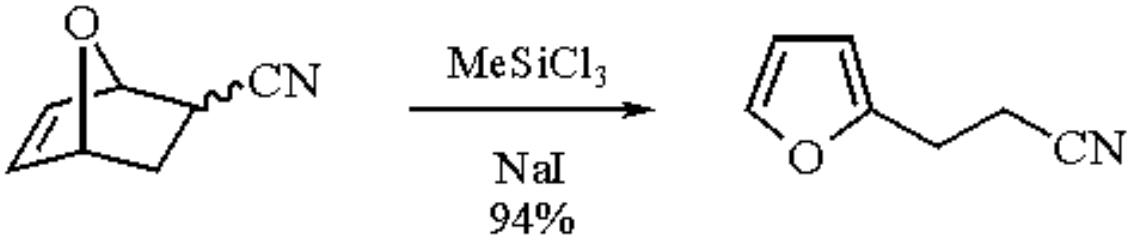

(17)

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N-Methyltrifluoromethanesulfonamide

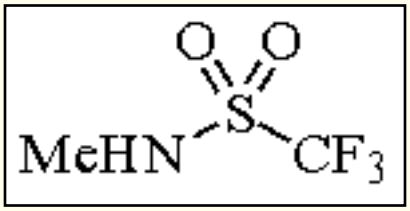

[34310-29-7] · $C_2H_4F_3NO_2S$ · *N*-Methyltrifluoromethanesulfonamide · (MW 163.14)

(methylamine derivative found to react with alcohols under Mitsunobu conditions to give derivatized secondary amines)

Physical Data: bp 90-94 °C/20 mmHg.[1]

Solubility: sol THF, chloroform, methylene chloride.

Form Supplied in: clear liquid.

Preparative Method: prepared from methylamine and ***Trifluoromethanesulfonic Anhydride*** as follows. Methylamine (25.5 g, 0.5 mol) is added to chilled (-70 °C) dichloromethane (250 mL). A solution of triflic anhydride (28.2 g, 0.1 mol) in dichloromethane (20 mL) is added dropwise and the mixture is stirred at -70 °C for 3 h. The mixture is washed with 1N HCl (2 × 250 mL) and the organic layer is separated and dried ($MgSO_4$). The solvent is removed at atmospheric pressure by slow distillation through a column (500 cm × 20 cm) packed with glass helices (product codistills with solvent and evaporation on a rotary evaporator gives very low yields). The residue is distilled to give 9.3 g (57%) of a clear liquid, bp 95-98 °C/30 mmHg.

Secondary Amines.

Alcohols react with this compound in THF under Mitsunobu conditions to give derivatized secondary amines.[2] The reaction proceeds with inversion of configuration (eq 1).[2]

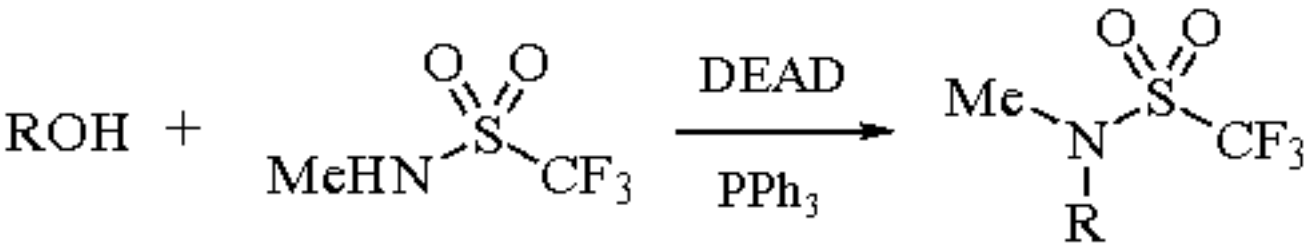

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Methyl Trifluoromethanesulfonate

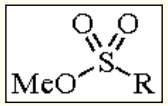

(R = CF_3)

[333-27-7] · $C_2H_3F_3O_3S$ · Methyl Trifluoromethanesulfonate · (MW 164.12) (R = F)

[421-20-5] · CH_3FO_3S · Methyl Fluorosulfonate · (MW 114.11)

(powerful methylating agents[1,2])

Alternate Name: R = CF_3, methyl triflate; R = F, Magic Methyl.

Physical Data: methyl triflate: bp 99 °C, mp -64 °C, *d* 1.50 g cm^{-3}. Methyl fluorosulfonate: bp 92 °C, mp -92.5 °C, *d* 1.45 g cm^{-3}.

Solubility: both reagents are miscible with all organic solvents, but react with many. They are only sl sol water, but hydrolyze rapidly as they dissolve. Useful inert solvents are CH_2Cl_2, SO_2, sulfolane, nitromethane, Me_2SO_4, and Me_3PO_4.

Form Supplied in: methyl triflate (MeOTf) is available as a colorless liquid. Methyl fluorosulfonate ($MeOSO_2F$) was formerly available as Magic Methyl™ but has been withdrawn (see below).

Analysis of Reagent Purity: MeOTf gives a singlet in ^1H NMR at δ 4.18, with ^{13}C absorption at δ 61.60 and 119.32 (q), and a ^{19}F shift of 75.4 ppm. $MeOSO_2F$ absorbs at δ 4.19 in ^1H NMR (J_{HF} &AApprox; 0.4 Hz or less), with ^{13}C absorption at δ 62.45, and a ^{19}F shift of -31.2 ppm. ^{33}S and ^{17}O NMR data have been reported for both compounds.[9]

Preparative Methods: both reagents are prepared[3,4] by distilling an equimolar mixture of the corresponding acid with ***Dimethyl Sulfate*** in an all-glass apparatus with a short Vigreux column. They may be dried by standing over fused K_2CO_3 and redistillation. ***Trifluoromethanesulfonic Acid*** and ***Fluorosulfuric Acid*** are both available, and are comparably priced.

Handling, Storage, and Precautions: both reagents are **extremely hazardous**. All possible precautions should be taken to avoid inhalation or absorption through the skin. A fatality has occurred with $MeOSO_2F$ through inhalation of the vapors leading to pulmonary edema.[5] Dexamethasone isonicotinate (Auxiloson® spray) has been recommended as a first aid in the treatment of such pulmonary irritation.[5] The oral LD_{50} of $MeOSO_2F$ is 112 mg/kg in mice, and an LC_{50} for 1 h exposure for rats between 5 and 6 ppm has been reported; severe eye irritation was noted.[6] It is very unlikely[7] that MeOTf is less dangerous, but no data on toxicity have been reported. Both materials are extremely destructive to the tissue of the mucous membranes and upper respiratory tract, eyes, and skin. Inhalation may be fatal as a result of spasm, inflammation, and edema of the larynx and bronchi, chemical pneumonitis, and pulmonary edema. Use in a fume hood.

The reagents are stable in glass when dry, but storage of $MeOSO_2F$ in bottles with ground glass joints should be avoided as these slowly become fused. It is reported[8] that $MeOSO_2F$ after storage over CaH_2 for two weeks contained 17% Me_2SO_4.

General Reactivity.

MeOTf and $MeOSO_2F$ are two of the most powerful reagents for methylation and are more reactive by a factor of ~10^4 than ***Iodomethane*** and Me_2SO_4.[1,2] The only reagents which are substantially more powerful are ***Methyl Fluoride-Antimony(V) Fluoride*** and related reagents[10] and the dimethylhalonium ions; these reagents pose more severe handling problems. The reactivity of MeOTf and $MeOSO_2F$ is not effectively enhanced by addition of Lewis acids. Thus addition of ***Antimony(V) Chloride*** to $MeOSO_2F$ and ***Dimethyl Sulfone*** led to complexation of the sulfone rather than methylation;[11] it is also reported that addition of $SbCl_5$ leads to formation of MeCl.[12]

The qualitative reactivity of some methylating agents toward a range of functional groups is shown in tabular form (Table 1).[1] Few quantitative data are available, but MeOTf and $MeOSO_2F$ are only a little less reactive than the trimethyloxonium ion, with the dimethoxycarbenium ion probably somewhat more reactive again. Substitution rates with various nucleophiles are reported to be in the order: Me_3O^+ > MeOTf > $MeOSO_2F$ > $MeOClO_3$, with rate ratios of 109:23:8:6:1.0 for reaction with acetonitrile at 0 °C.[13,14] Methyl perchlorate, an explosion hazard, therefore never offers a practical advantage. Our experience is that the relative rates for MeOTf and $MeOSO_2F$ rarely differ by more than a factor of 2-5.

Table 1 Reactivity[a] of Methylating Agents towards Functional Groups

	Approx. pK_a[18]	MeI	Me_2SO_4	$MeOSO_2F$ (MeOTf)	Me_3O^+	$HC(OMe)_2^+$	Me_2Cl^+
Me_3N	9	+	+	++	++	++	++
Pyridine	5	+	+	++	++	++	++
Me_2S	1	+	+	++	++	++	++
Me_2SO	0	+	+	+	+	+	++
$HCONMe_2$	0	-	+	+	+	+	++
MeCN	- 10	-	-	+	+	+	+
Me_2O	- 5	-	-	+	(+)	+	+
PhCHO	- 6	-	-	+	-	+	+
R_2CO	- 6	-	-	±	-	±	+
Lactone	- 7	-	-	+	-	+	+
Ester	- 7	-	-	(+)	-	+	+
MeI	?	-	-	(+)	-	(+)	+
$MeNO_2$	- 10	-	-	-	-	-	+
Me_2SO_2	- 10	-	-	-	-	-	+

[a] Key: ++ methylation occurs and may be strongly exothermic; + methylation occurs; - little reaction; (+) equilibrium transfer reaction; ± reaction is complex.

It is noteworthy that neither MeOTf nor $MeOSO_2F$ shows any reactivity on their own in Friedel-Crafts methylation reactions even with highly reactive substrates (Me_3O^+ ion is similar). Reaction has been observed in the presence of protic or Lewis acids.[15] Olah has recently suggested that this reactivity is associated with generation of superelectrophiles by further protonation.[16] $MeOSO_2F$ has been reported to react as a methylsulfonylating agent towards phenol and anisole,[17] but this alternative reactivity is usually not significant.

The alkylation reactions of MeOTf and $MeOSO_2F$ are discussed according to the atom alkylated. To avoid unnecessary repetition, reactions can be assumed to use MeOTf unless $MeOSO_2F$ is specified. Historically, $MeOSO_2F$ was mainly used up until about 1980, but MeOTf has since become the reagent of choice. In the great majority of cases these reagents can probably be used interchangeably.

Alkylation at Nitrogen.

Most amines react violently with MeOTf or $MeOSO_2F$, and only those with severe steric hindrance or conjugated with strong electron-withdrawing groups really require the use of these reagents. Of derivatives with sp^3 nitrogen, ***Diisopropylamine***, *N*,2,2,6,6-pentamethylpiperidine, and ***1,8-Bis(dimethylamino)naphthalene*** (Proton Sponge™) can all be quaternized by $MeOSO_2F$, and *N*,*N*,2,6-tetramethylaniline reacts on heating.[1] However, it has been reported that *i*-Pr_3N does not react with $MeOSO_2F$.[19] ***2,6-Lutidine*** reacts exothermically with $MeOSO_2F$ at room temperature, and 2,6-dimethoxycarbonylpyridine can be quantitatively quaternized.[1] A range of [*n*](2,6)-pyridinophanes have been methylated with $MeOSO_2F$, with *n* as small as 6 (eq 1).[20]

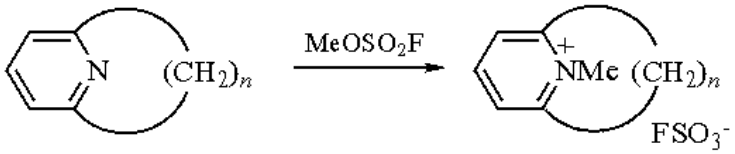

(1)

2,6-Di-t-butylpyridine does not react at normal pressure, and this or 2,6-di-*t*-butyl-4-methylpyridine (synthesis[21]), are often used in applications which require base (see below). Note that 2,6-di-*t*-butylpyridine can be alkylated under high pressure with $MeOSO_2F$ to give >90% of the methylation product when water is carefully excluded.[22]

Simple imines, such as benzylideneaniline, react readily. The *N*-methylation of imine and amidine derivatives of amino acid esters, followed by hydrolysis, has been used as a method for the preparation of *N*-alkylated amino acids with minimal racemization.[23] A convenient synthesis of *N*-methyl nitrones has been developed by alkylation of OTMS oximes with MeOTf, followed by treatment with fluoride ion.[24]

Besides the pyridine derivatives already mentioned, most heterocyclic nitrogens can be alkylated. Aspects of the quaternization of heteroaromatics have been recently reviewed.[25] With respect to the limits of reactivity, it is interesting that dimethylation of 2-phenyl-4,6-dimethylpyrimidine could only be achieved with ***Trimethyloxonium Tetrafluoroborate***; $MeOSO_2F$ only gave monoalkylation.[26] 2-Benzoylbenzothiazole can be *N*-alkylated with $MeOSO_2F$ (but not with MeI) and then acts as an active acylating agent.[27] Formation of an *N*-methylindole from an *N*-ethoxycarbonylindole has been achieved with $MeOSO_2F$.[28]

A number of alkylation products from MeOTf and heterocycles have been advocated as useful intermediates. Thus treatment of 2-substituted thiazoles with MeOTf in acetonitrile, followed by reduction of the salt formed with ***Sodium Borohydride***/CuO in CH_2Cl_2, leads to aldehydes.[29] 1-(Benzenesulfonyl)-3-methylimidazolium and 1-(*p*-toluenesulfonyl)-3-methylimidazolium triflates have been proposed as efficient reagents for the preparation of aryl sulfonamides and aryl sulfonates.[30] MeOTf alkylates 2,5-oxazoles to give salts which can be reduced by $PhSiH_3$/CsF to give 4-oxazolines, and these provide a route to stabilized azomethine ylides.[31]

A novel synthesis of 2-aryl-4-piperidones by Mannich cyclization of imino acetals, initiated by methylation of the imine, has been described.[32] MeOTf has been used in the generation of a munchnone for cycloaddition.[33] Finally, methylation of 1-lithio-2-*n*-butyl-1,2-dihydropyridine with MeOTf gives 2-butyl-5-methylpyridine in 42% yield.[34]

Nitriles, with sp hybridized nitrogen, are unreactive to MeI or Me_2SO_4, but are readily methylated by $MeOSO_2F$,[1] MeOTf,[35] or oxonium ions. Nitrilium salts have been shown to have a number of useful applications. The reduction of nitrilium salts by $NaBH_4$ in alcohols leads first to iminoethers and subsequently to amines.[36] Reduction of *N*-alkylnitrilium ions by organosilicon hydrides gives *n*-alkylaldimines, and thus provides a route to aldehydes from nitriles.[37] Nitrilium triflate salts have been shown to be useful reagents for the synthesis of ketones and ketenimines by electrophilic substitution of reactive aromatics, and also provide good routes to amidinium, imidate, and thioimidate salts.[35] Reaction with 2-amino alcohols gives oxazolidines.[38] Synthesis of either 5-substituted 1-methyl-1*H*-tetrazoles or 3,5-disubstituted 1,4-dimethyltriazolium salts from *N*-methylnitrilium triflate salts can be controlled in reactions with $(Me_2N)_2C{=}NH_2^+N_3^-$.[39] Reaction of nitrilium ions with alkyl azides gives 1,2,3-trisubstituted tetrazolium salts.[40] These can be deprotonated to highly reactive 2-methylenetetrazoles.[41]

Amides are alkylated largely on oxygen, as expected (see below), although some *N*-alkylation can be seen by NMR.[1] *N*-Alkylation is more apparent with carbamates (see the section on ambident nucleophiles). *N*,*N*-Dimethylmethanesulfonamides can be *N*-alkylated ($MeOSO_2F$) to provide salts which are effective reagents for mesylation.[42] *N*,*N*-Dimethylsulfamate esters react with $MeOSO_2F$ to give trimethylammoniumsulfate esters, which rapidly give methyl esters unless the O-group is aryl, showing that $Me_3N^+SO_3^-$ is a very powerful leaving group.[43] $Me_3N^+SO_2OPh$ reacts with nucleophiles at either the sulfur or a methyl carbon atom.[44]

Azo compounds, which do not react with methyl iodide, can be *N*-methylated by $MeOSO_2F$.[45]

A steroidal oxaziridine was converted ($MeOSO_2F$) to an oxaziridinium salt which showed oxidizing properties.[46]

Alkylation at Oxygen.

Most neutral functionalities with lone pairs on oxygen are not alkylated by MeI or Me_2SO_4 but do react with MeOTf or $MeOSO_2F$, although not all such reactions are preparatively useful.[1,2] Ethers react reversibly, and the ultimate product depends on the conditions. Thus good yields of the oxonium ion can be obtained from reaction of THF with stoichiometric amounts of MeOTf, but the use of catalytic amounts leads to polymerization. Cationic ring opening polymerization, initiated by MeOTf and $MeOSO_2F$ among other reagents, has been extensively investigated and recently reviewed.[47]

Reaction of $MeOSO_2F$ with 2-methoxyethyl carboxylates gives 2-alkyl-1,3-dioxolanium ions.[1] The reaction of these ions with trialkylalkynylborate anions provides versatile and direct routes to (*Z*)-α,β-unsaturated ketones (eq 2). Specifically protected 1,3-diketones and other ketonic species can also be prepared from the intermediates.[48]

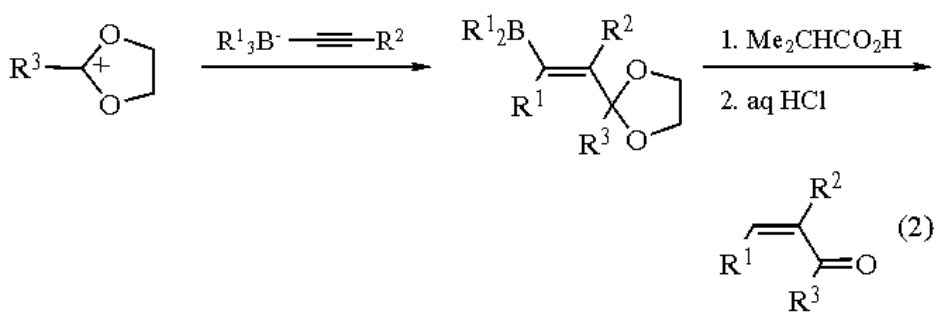

(2)

Almost all carbonyl functions can be methylated. Enolizable aldehydes and ketones usually lead to complex mixtures, probably because of deprotonation to enol ethers, followed by reaction of these with the electrophilic species in the reaction mixture. Nonenolizable aldehydes and ketones give methoxycarbenium ions cleanly, and the relative thermodynamic stabilities of these have been assessed via pairwise equilibrations.[49] Most esters only generate low equilibrium concentrations of dialkoxycarbenium ions, but lactones are readily alkylated.[1]

Amides, carbamates, and ureas are rapidly alkylated, usually on carbonyl oxygen (see the section on ambident nucleophiles). Alkylation of amides with MeOT5f in CH_2Cl_2 followed by reduction of the salts provides a route for the selective reduction of amides; esters, nitriles, acetals, and double bonds are left unaffected by this procedure.[50] Alkylation of isoindolin-1-ones and subsequent deprotonation can provide routes to methoxyisoindoles.[51]

Alcohols can be converted to methyl ethers by the use of MeOTf + 2,6-di-*t*-butylpyridine or 2,6-di-*t*-butyl-4-methylpyridine. This procedure was initially developed in the carbohydrate field.[52] Me_3PO_4 provides a good polar solvent for this process.[53] A recent application, in the synthesis directed at lonomycin, was to methylation of the complex alcohol (**1**) without causing retro-aldol cleaveage.[54]

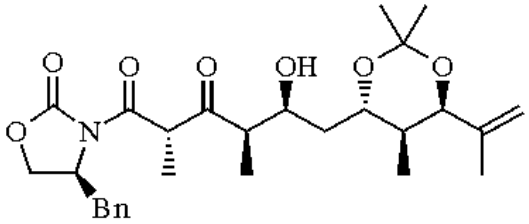

(1)

MeOTf has been reported to effect complete methylation of inositol polyphosphates, P-OMe groups being formed as well.[55] MeOTf will effect *O*-alkylation at the anomeric center, but the stereochemistry is affected by the presence of a crown ether.[56] Reaction of Meisenheimer complexes with $MeOSO_2F$ can lead to capture of the anion as a nitronate ester.[57]

Alkylation at Sulfur and Selenium.

Dialkyl and most arylalkyl sulfides are readily converted into sulfonium salts.[1] Cyclic sulfides, especially dithiolanes, react somewhat faster.[58] Reaction of disulfides with MeOTf gives Me_2SSMe^+ OTf^-; this salt, with ***Triphenylphosphine***, reacts with alkenes in a stereo- and regioselective fashion and the products can be converted into vinylphosphonium salts.[59] Thione groups are also alkylated even when electronegative groups are present. Thus 4,5-bis(trifluoromethyl)-1,3-dithiolane-2-thione was converted into a methylated salt.[60] Sulfoxides are *O*-alkylated,[1] and formation of various oxa- and azasulfonium ions has been reported, up to and including triazasulfonium salts.[61] Alkylation of R_2SO with $MeOSO_2F$, followed by reduction with ***Sodium Cyanoborohydride***, leads to sulfides.[62]

Reaction of MeOTf with the product from P_2S_5/Na_2CO_3 ($Na_2P_4S_{10}O$) gave a useful electrophilic thionation reagent.[63] $MeOSO_2F$ has been used in the conversion of thiols to reactive sulfenating agents (eq 3).[64]

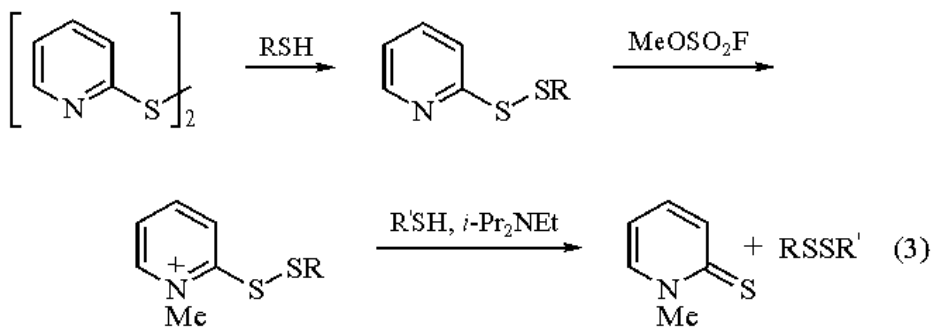

Methylation of dithioacetals by $MeOSO_2F$, followed by reaction with various nucleophiles, has been used for the removal of this protecting group or its conversion into other protecting groups, e.g. acetals (eq 4).[65-68]

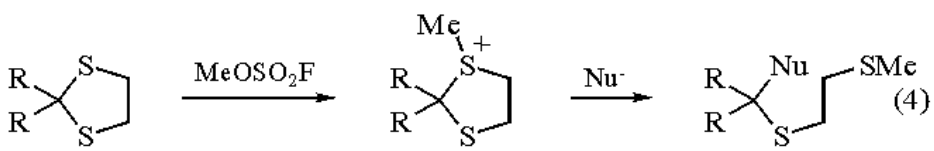

The reaction of the sulfonium intermediate with alcohols leads to their protection as hemithioacetals.[69] Treatment of thioglycosides with MeOTf gives an efficient glycosylating agent,[70] and pyruvic acetal formation from a pyruvyl thioacetal has been achieved in a reaction catalyzed by MeOTf (amongst other electrophiles).[71]

Alkenes can be prepared by methylation of selenides by $MeOSO_2F$ and treatment of the selenonium ions formed with ***Potassium t-Butoxide***.[72]

Alkylation at Phosphorus.

Phosphines and phosphites undergo easy quaternization. Thus methylation of tris(2,6-dimethylphenoxy)phosphine with MeOTf, followed by treatment of the product with sodium 2,6-dimethylphenoxide, gave methyltetrakis(2,6-dimethylphenoxy)phosphane.[73] Methoxyphosphonium triflates are relatively stable intermediates in Arbuzov reactions.[74] Phosphine oxides and sulfides are alkylated. *S*-Methylation of chiral phosphine sulfides, followed by treatment with ***Hexamethylphosphorous Triamide***, has been advocated as a general synthesis of optically active phosphines.[75]

Ambident Nucleophiles.

Amides and related functional groups can be alkylated on oxygen or nitrogen and, as has been noted already, alkylation on carbonyl oxygen normally predominates. In the case of carbamates, *O*-alkylation by $MeOSO_2F$ can be faster, but *N*-alkylation predominates at equilibrium.[76] It has been noted that methylation of secondary amides and thioamides occurs at the protonless heteroatom in the major tautomer.[77] The ionic products of these reactions can be deprotonated to give synthetically useful products, e.g. imidates,[78] but excess $MeOSO_2F$ should be removed before treatment with base.[77]

Reaction of most enolates with MeOTf or $MeOSO_2F$ is always likely to be kinetically controlled. There does not appear to have been a definitive study, but *O*-alkylation is the normal outcome. *O*-Alkylation of a bicyclodecatrienone by $MeOSO_2F$ is enhanced by the use of polar solvents like HMPA.[79] *O*-Alkylation of enolates of appropriate cyclohexadienones by MeOTf has been used to generate various 3a*H*-indenes.[80] A ketene acetal is formed by exclusive *O*-alkylation of the sodium enolate of isopropyl bis(pentachlorophenyl)acetate by MeOTf.[81]

Alkylations at Carbon.

In an important recent development, primary α-alkylation of carbonyl compounds under nonbasic conditions has been achieved (eq 5) by alkylation of silyl enol ethers with MeOTf and other primary alkyl triflates, catalyzed by ***Methylaluminum Bis(4-bromo-2,6-di-t-butylphenoxide)*** (MABR).[82]

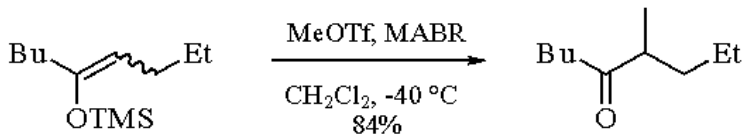

(5)

Related Reagents.

Dimethoxycarbenium Tetrafluoroborate; ***Dimethyliodonium Hexafluoroantimonate***; ***O-Methyldibenzofuranium Tetrafluoroborate***; ***Triethyloxonium Tetrafluoroborate***.

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Methyl(trifluoromethyl)dioxirane[1]

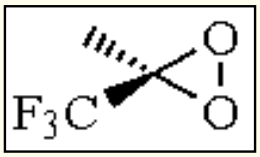

[115464-59-0] · $C_3H_3F_3O_2$ · Methyl(trifluoromethyl)dioxirane · (MW 128.06)

(selective, reactive oxidizing agent capable of epoxidation of unreactive alkenes[5] and arenes,[7] oxyfunctionalization of alkanes,[3] oxidation of alcohols[16] and ethers[19])

Alternate Name: TFDO.

Physical Data: known only as a dilute solution.

Solubility: sol acetone and CH_2Cl_2; sol most other organic solvents, but reacts slowly with many of these.

Form Supplied in: dilute solutions of the reagent in 1,1,1-trifluoro-2-propanone are prepared from Oxone (***Potassium Monoperoxysulfate***) and this ketone as described below. *Drying:* initial drying of reagent solutions is accomplished with reagent grade anhyd $MgSO_4$ in the cold. After filtration, solutions are typically stored over molecular sieves.

Analysis of Reagent Purity: concentrations of the reagent can be determined by classical iodometric titration or by reaction with an excess of an organosulfide and determination of the amount of sulfoxide formed by NMR or gas chromatography.

Preparative Methods: TFDO solutions are prepared by mixing 1,1,1-trifluoro-2-propanone (TFP) and aqueous buffered Oxone in the cold and collecting the volatile TFDO-TFP mixture by transfer into a cold trap in a stream of inert gas under reduced pressure (eq 1).[3]

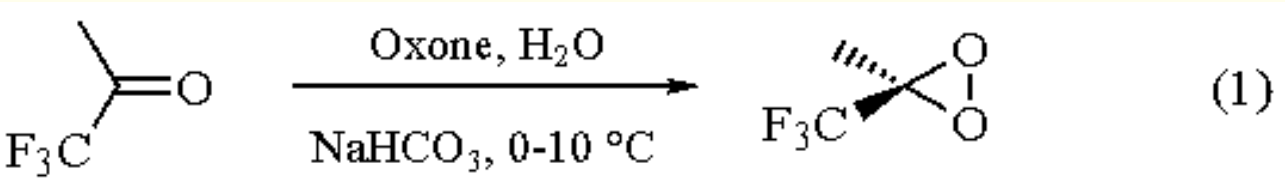

Handling, Storage, and Precautions: solutions of the reagent can be kept in the freezer of a refrigerator at -20 °C for as long as a week. The concentration of the reagent decreases relatively slowly (ca. 6-8% in 48 h), provided solutions are properly stored. It is particularly important that solutions be kept from light and traces of heavy metals, since the reagent is particularly susceptible to their influence. These dilute solutions are not known to decompose explosively, but the usual precautions for handling peroxides should be applied, including the use of a shield. All reactions should be performed in a hood to avoid exposure to the

powerful, volatile oxidant.

Introduction.

Methyl(trifluoromethyl)dioxirane is a fluorinated derivative of the extremely useful oxidant ***Dimethyldioxirane*** (DDO), over which it has several advantages as a reagent. However, it is more expensive and difficult to prepare, since it is obtained from the volatile (bp 22 °C) ketone TFP.[2] Nonetheless, the much greater reactivity of TFDO can be of major advantage for less reactive substrates. Furthermore, the concentration of TFDO (ca. 0.8 M) normally obtained is several times greater than that of DDO. Solutions of TFDO in halocarbon solvents free of starting ketone can be obtained by extraction of the TFP into water, owing to the water solubility of the ketone hydrate.[4] Oxidations with TFDO are performed by adding the reagent to the reactant, often in CH_2Cl_2 solution, and then simply removing the volatile solvents when reaction is complete (usually minutes).

Alkenes and Arenes.

Like DDO, TFDO performs rapid epoxidations of alkenes with retention of alkene stereochemistry.[1,2] Since DDO is adequately reactive towards most double bonds, there is ordinarily no reason to employ TFDO in reactions of this type. One important exception is the epoxidation of trifluoromethyl-substituted alkenes, which are resistant to classic epoxidizing reagents and which require a large excess of DDO during two weeks to complete epoxidation.[5] TFDO rapidly converts such alkenes to epoxides (eq 2). Another example of the beneficial effect of TFDO is in the preparation of the sensitive epoxides of enol ethers, where the short reaction times and facile product isolation are crucial.[6]

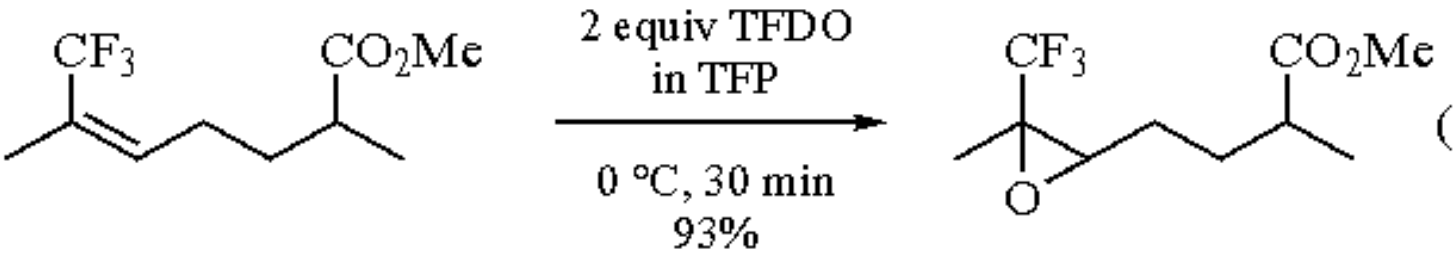

(2)

Polycyclic aromatic hydrocarbons like phenanthrene are converted to epoxides by TFDO.[7] This reactive reagent even permits the epoxidation of naphthalene, which undergoes fast sequential diepoxidation as shown in eq 3. Interestingly, the second epoxidation shows high *anti* stereoselectivity. Catechol is oxidatively cleaved by TFDO into (*Z*,*Z*)-muconic acid in good yield (eq 4).[8] This reagent also oxidizes 2,6-di-*t*-butylphenol to the corresponding quinone and a hydroxyquinone derivative (eq 5).[8]

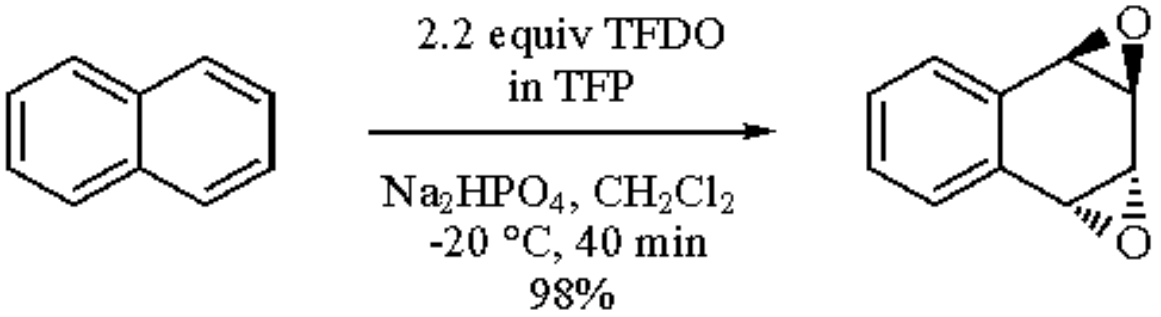

(3)

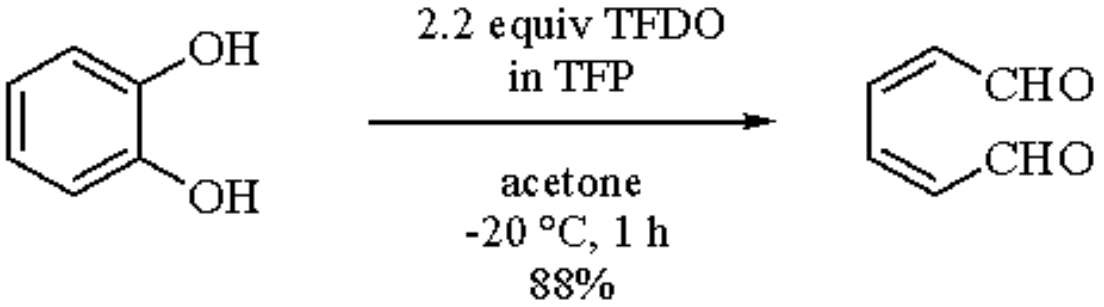

(4)

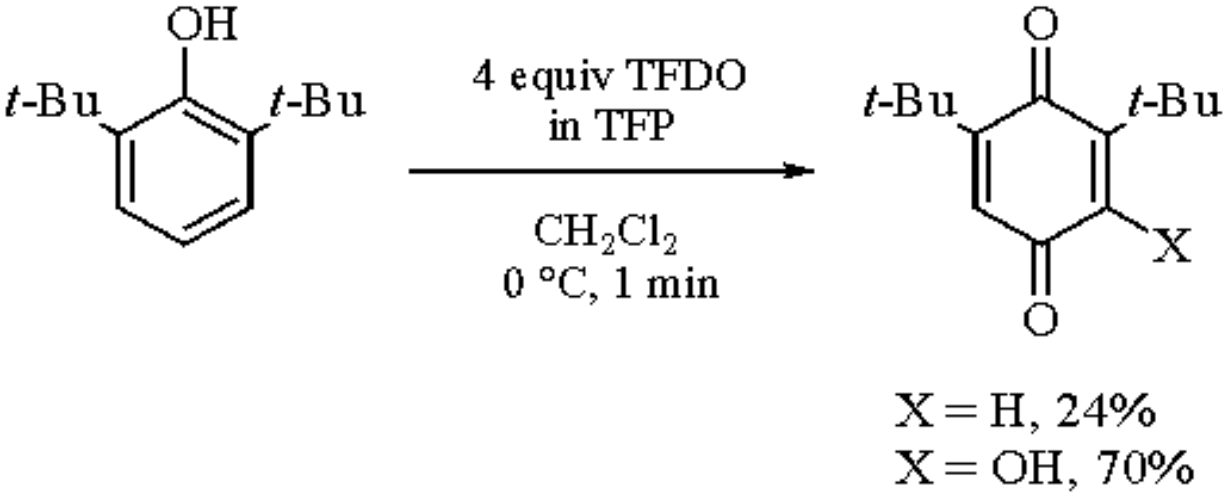

(5)

Alkynes are oxidized by TFDO to give a variety of different products, depending on the nature of the alkynic substituents.[9] Reaction is thought to proceed via an oxirene intermediate. This highly unstable, anti-aromatic heterocycle quickly rearranges to the isomeric α-ketocarbene, which then leads to the observed products by typical carbenoid transformations. For example, cyclodecyne gives bicyclic ketones by transannular insertion processes common to this medium-ring system (eq 6).

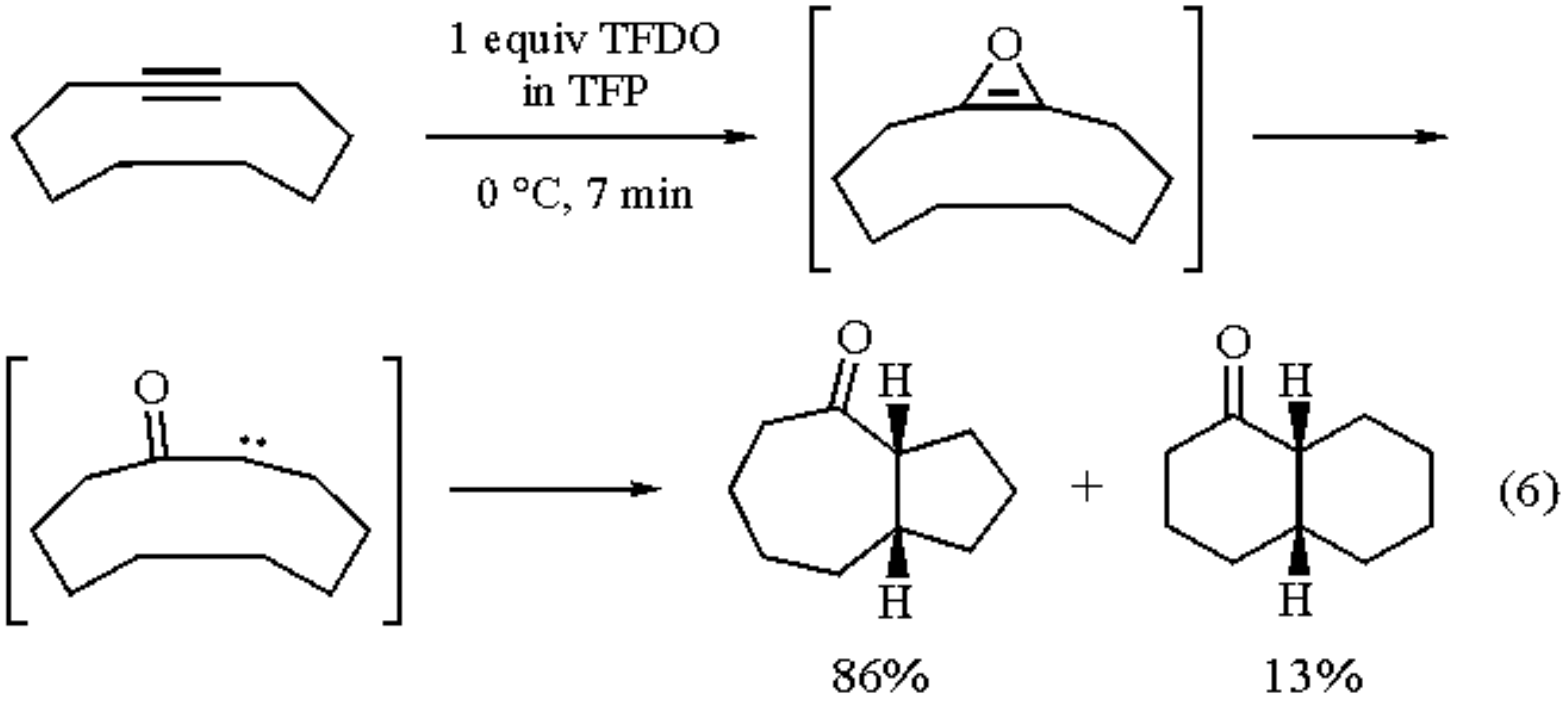

Alkanes.

The most impressive applications of TFDO to date have involved the hydroxylation of unactivated C-H bonds.[1,3] While dimethyldioxirane performs similar reactions, the much greater reactivity of TFDO permits higher conversions of alkanes with less oxidant and in minutes rather than hours. Despite its more reactive nature, TFDO displays selectivity for attack at tertiary > secondary > primary C-H bonds almost as advantageous as that for DDO.[3] Examples include the exclusive formation of the tertiary alcohol from 2,3-dimethylbutane (eq 7) and the stereospecific oxidation of *cis*-1,2-dimethylcyclohexane (eq 8). Cyclohexane is oxidized to cyclohexanone by TFDO in a slower process that involves a fast second oxidation of the initially formed cyclohexanol. Heptane generates a 41:41:18 mixture of 2-, 3-, and 4-heptanone.

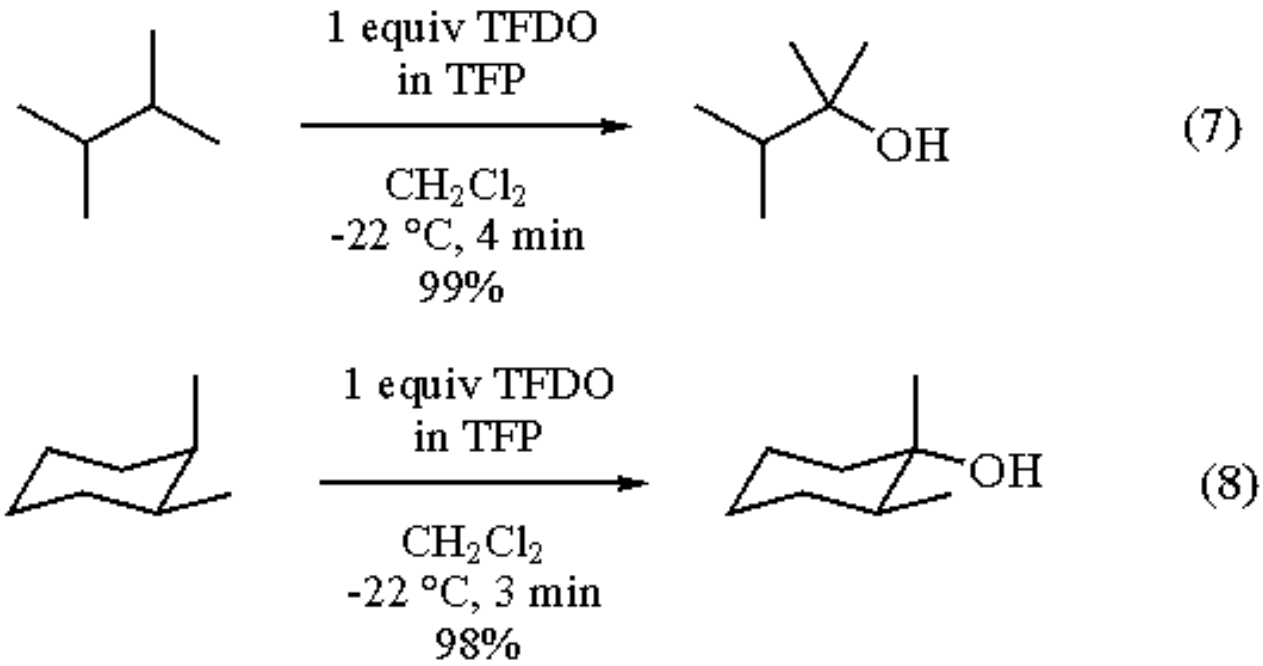

The stereospecificity of these C-H oxidations is illustrated in eq 9 by the benzylic oxidation of optically active (*S*)-(-)-2-phenylbutane, which gives only the tertiary alcohol with total retention of configuration.[10] Interestingly, ketone-free TFDO in CH_2Cl_2 is three times more reactive than TFDO-TFP.

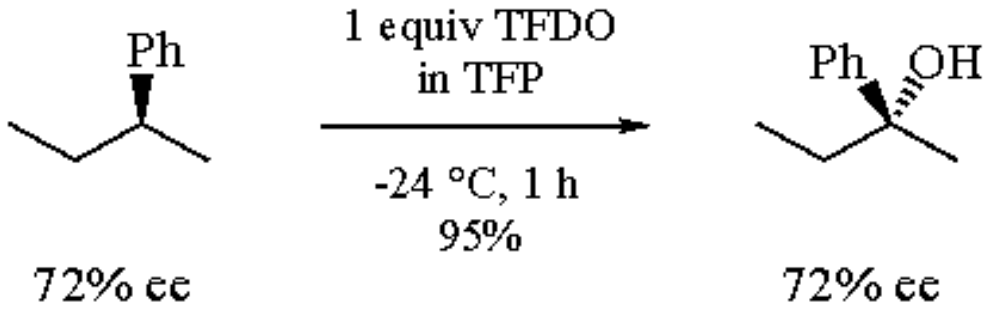

(9)

Adamantane is an informative substrate for oxidation by TFDO; it not only shows very high bridgehead selectivity, but can be converted to mono-, di-, tri-, and even tetrahydroxylated adamantane (eq 10) in good yields by varying the ratio of oxidant to hydrocarbon.[11]

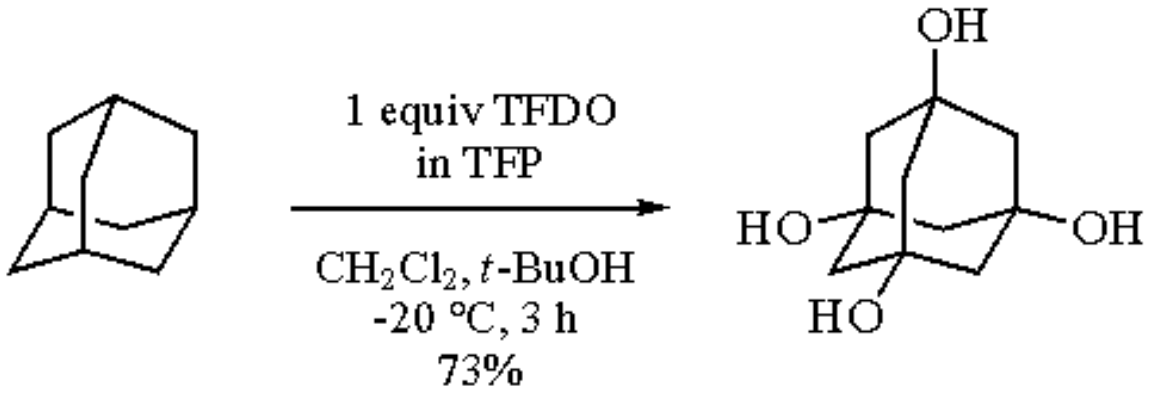

(10)

Several impressive oxyfunctionalization reactions on steroid substrates illustrate the enormous potential of this process. Not only is there a preference for tertiary C-H oxidation, but there is also significant site selectivity, presumably governed by steric features. For example, the cholestane derivative in eq 11 gives rapid, selective C-25 side-chain oxidation without appreciable reaction at other tertiary carbons.[12] Coprostane[13] and estrone[14] derivatives undergo C-5 and C-10 hydroxylation, respectively.

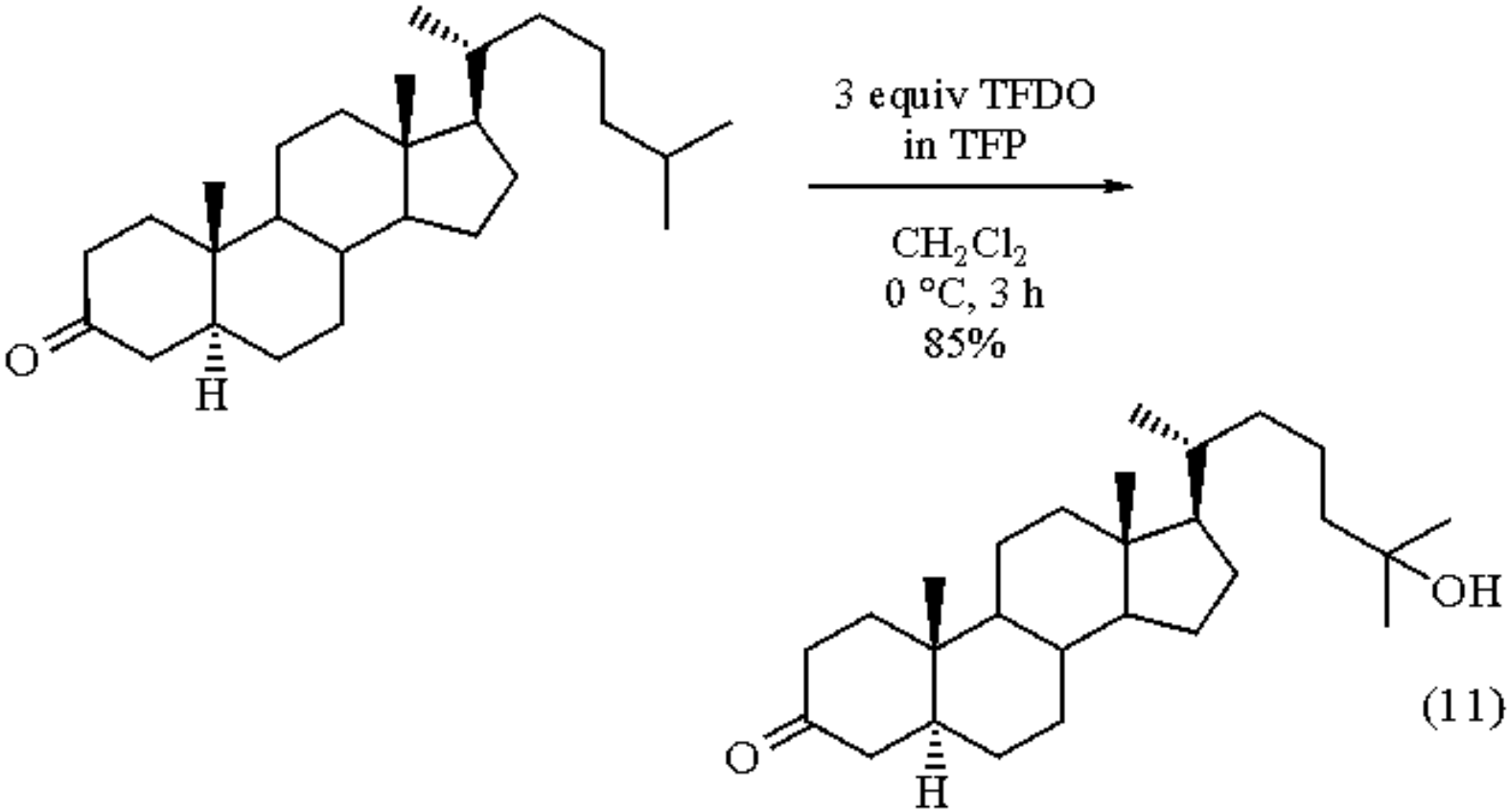

(11)

The stability of TFDO to strong acid adds a further dimension to its chemistry, as illustrated by the reactions of amines in the form of their fluoroborate salts with ketone-free solutions of TFDO.[15] The amino group is deactivated under these conditions and remote C-H hydroxylation takes place (eq 12).

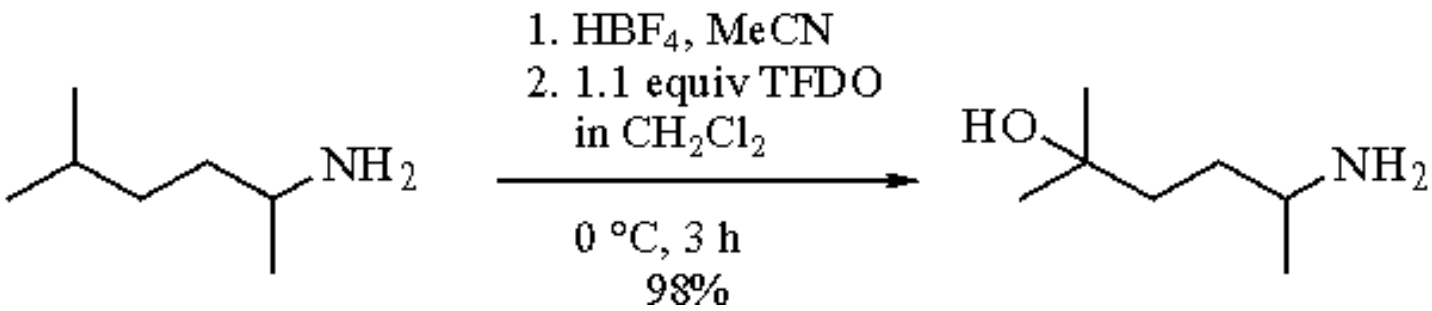

(12)

Alcohols.

Secondary alcohols are smoothly oxidized to the corresponding ketones by TFDO, whereas primary alcohols are converted to acids in a slower process.[16] In view of the many methods for alcohol oxidations, this reagent will be advantageous for such conversions only in special situations. However, TFDO does perform sensitive oxidations under favorable experimental conditions that may be useful with problem cases. Cyclobutanol is oxidized by TFDO without the ring cleavage that is often problematic (eq 13). Other reactive functions can be accommodated as shown for the epoxy alcohol in eq 14.

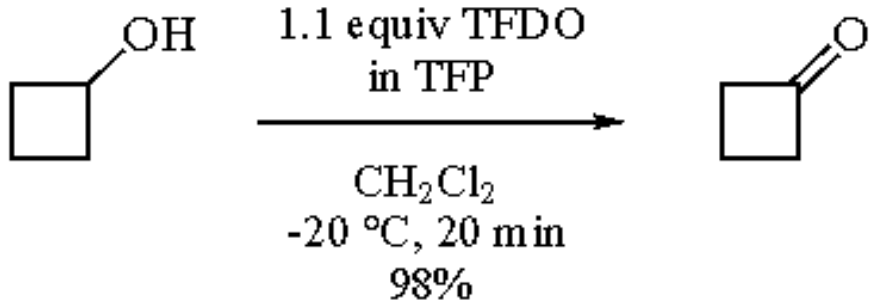

(13)

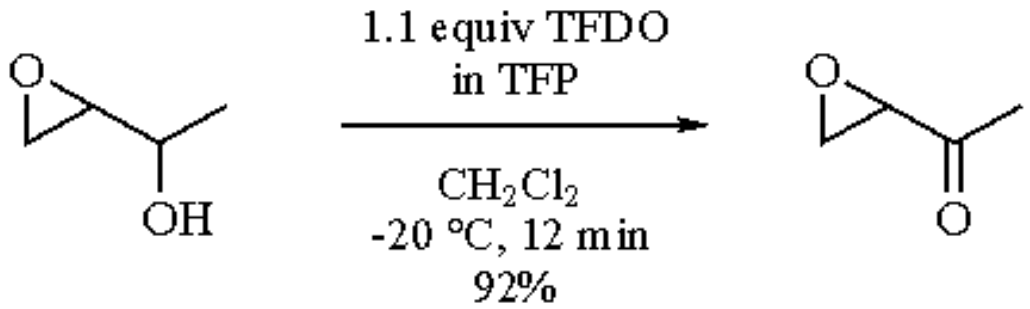

(14)

Vicinal diols are oxidized to α-hydroxy ketones by TFDO without cleavage between the two functional groups. Thus, tertiary-secondary *vic*-diols are usefully oxidized by TFDO (eq 15).[17] Optically active secondary-secondary diols have been converted to α-hydroxy ketones without racemization.[18]

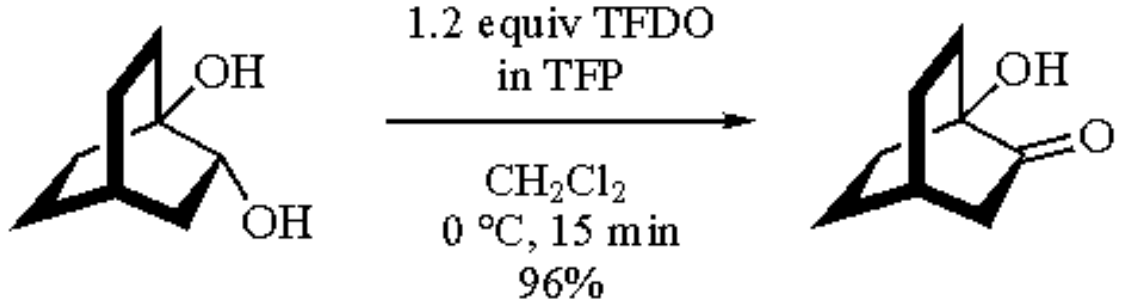

(15)

Ethers and Acetals.

TFDO selectively oxidizes adjacent to an oxygen atom in compounds of these types.[19] The initially generated hemiacetals decompose to carbonyl compounds and alcohols, which may be subject to further oxidation. Ethylene glycol acetals are attacked at the dioxolane ring, leading to an interesting deprotection of the carbonyl unit under nonacid conditions (eq 16). Cyclic ethers like tetrahydropyran yield lactones by subsequent oxidation of a stable cyclic hemiacetal intermediate (eq 17). Even methyl *t*-butyl ether is oxidatively liberated to *t*-butanol upon reaction with TFDO.

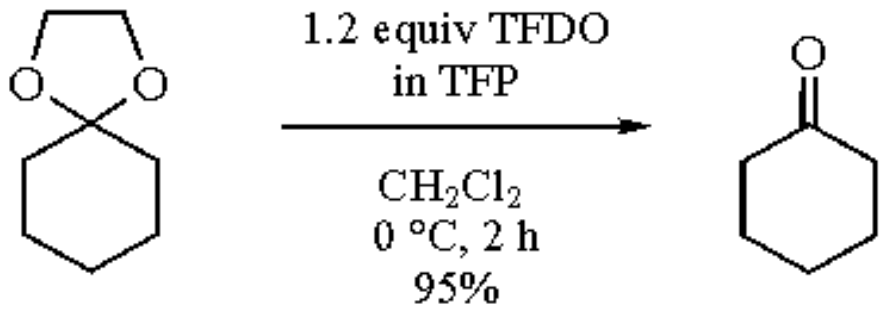

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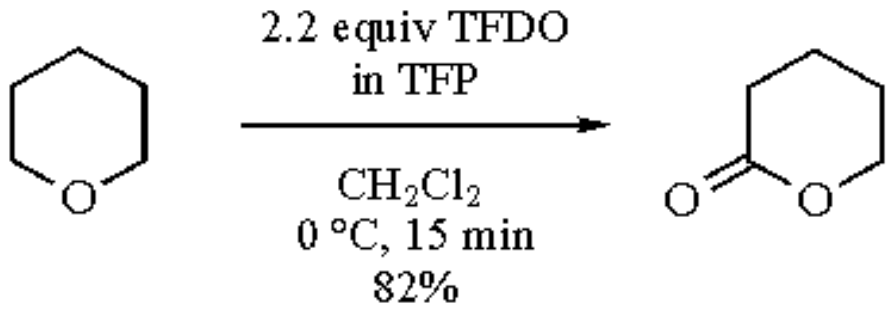

(17)

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Jack K. Crandall

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Methyl 2-Trimethylsilylacrylate

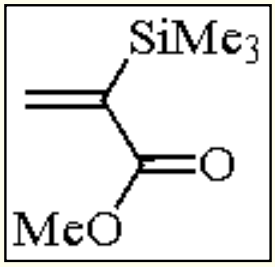

[18269-31-3] · $C_7H_{14}O_2Si$ · Methyl 2-Trimethylsilylacrylate · (MW 158.30)

(reactive, α-silyl Michael acceptor for conjugate addition of carbanions, enolate anions, organolithium reagents, and Grignard reagents; affords 3-cyclopentenecarboxylates and cyclohexanecarboxylates by [3 + 2] and [4 + 2] annulation methods; provides α-silyl esters and vinylsilanes by organolithium conjugate additions[1,3,5])

Physical Data: bp 75 °C/50 mmHg, 152 °C/690 mmHg.

Solubility: sol Et_2O, THF, EtOH, and most organic solvents.

Analysis of Reagent Purity: IR, NMR, GC.

Preparative Methods: prepared[2a,b] by the reaction of ***(E)-2-(Trimethylsilyl)vinyllithium*** with ***Methyl Chloroformate*** or by carbonation of the corresponding Grignard reagent prepared from ***(1-Bromovinyl)trimethylsilane***,[2c] giving 2-trimethylsilylacrylic acid. The methyl ester is prepared from the acid by direct esterification with absolute methanol in the presence of mineral acid, by reaction with ***Diazomethane*** at low temperature, or by treatment with BF_3.MeOH complex. For preparation of various trialkylsilylacrylic acid esters[2d] and *t*-butyl 2-trimethylsilylcrotonate,[8] see the cited references.

Handling, Storage, and Precautions: should be stored in a refrigerator and addition of a few crystals of ionol is recommended in order to prevent polymerization. Use in a fume hood.

Cyclopentenes by [3 + 2] Annulation.

Conjugate addition of allylithium reagents bearing stabilizing groups in the α- and β-positions to methyl 2-trimethylsilylacrylate leads to an anionic [3 + 2] cyclization,[3a,b] generating the trimethylsilyl-substituted 3-cyclopentenecarboxylate in 57% yield (eq 1). α-Unsubstituted Michael acceptors do not give good yields of the cyclopentene product.

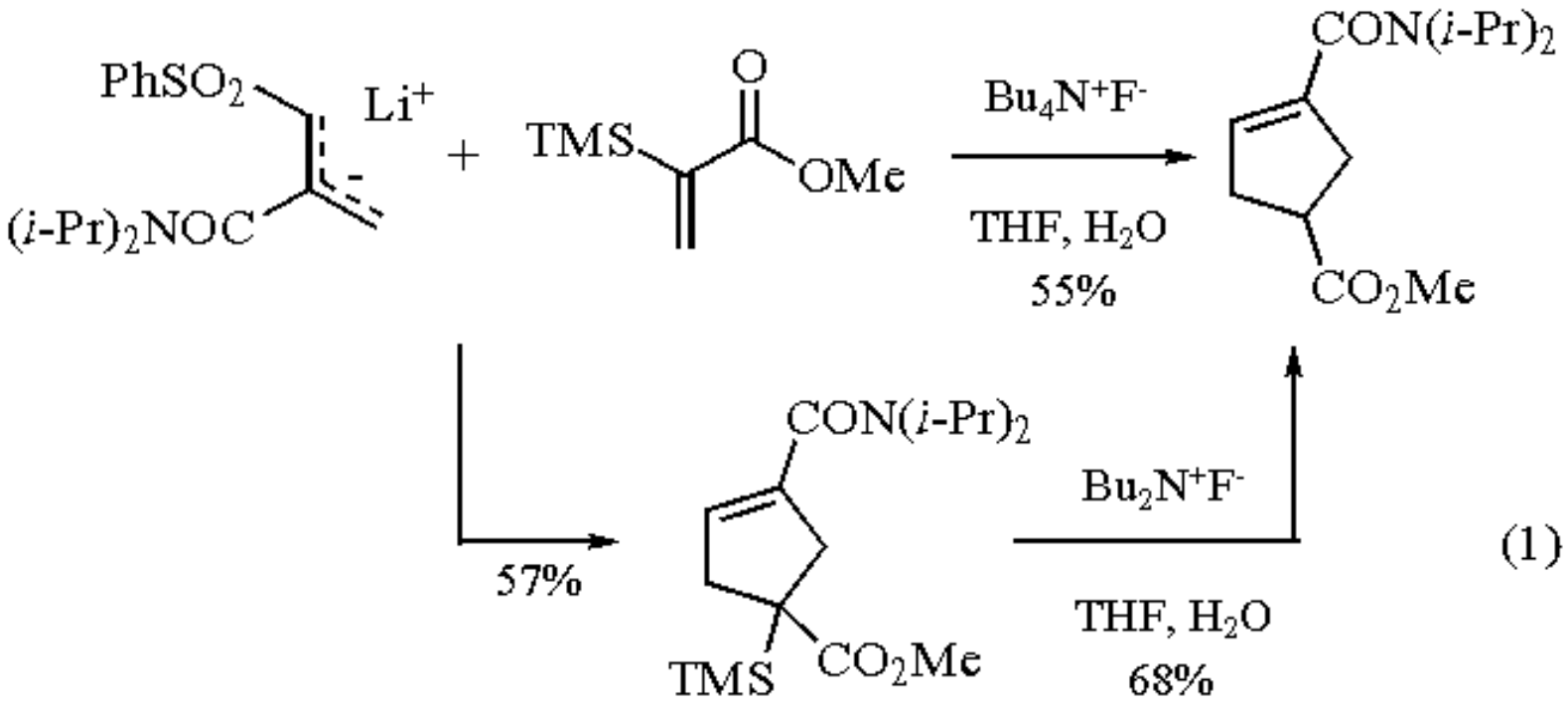

Cyclohexanecarboxylates by [4 + 2] Annulations.

The kinetic enolate of 1-acetylcyclohexene on reaction with methyl 2-trimethylsilylacrylate undergoes a two-fold Michael addition, giving rise to 5-substituted 1-decalones (eq 2), one of which was converted to (±)-khusitone[4a] and (±)-khusilal.[4b]

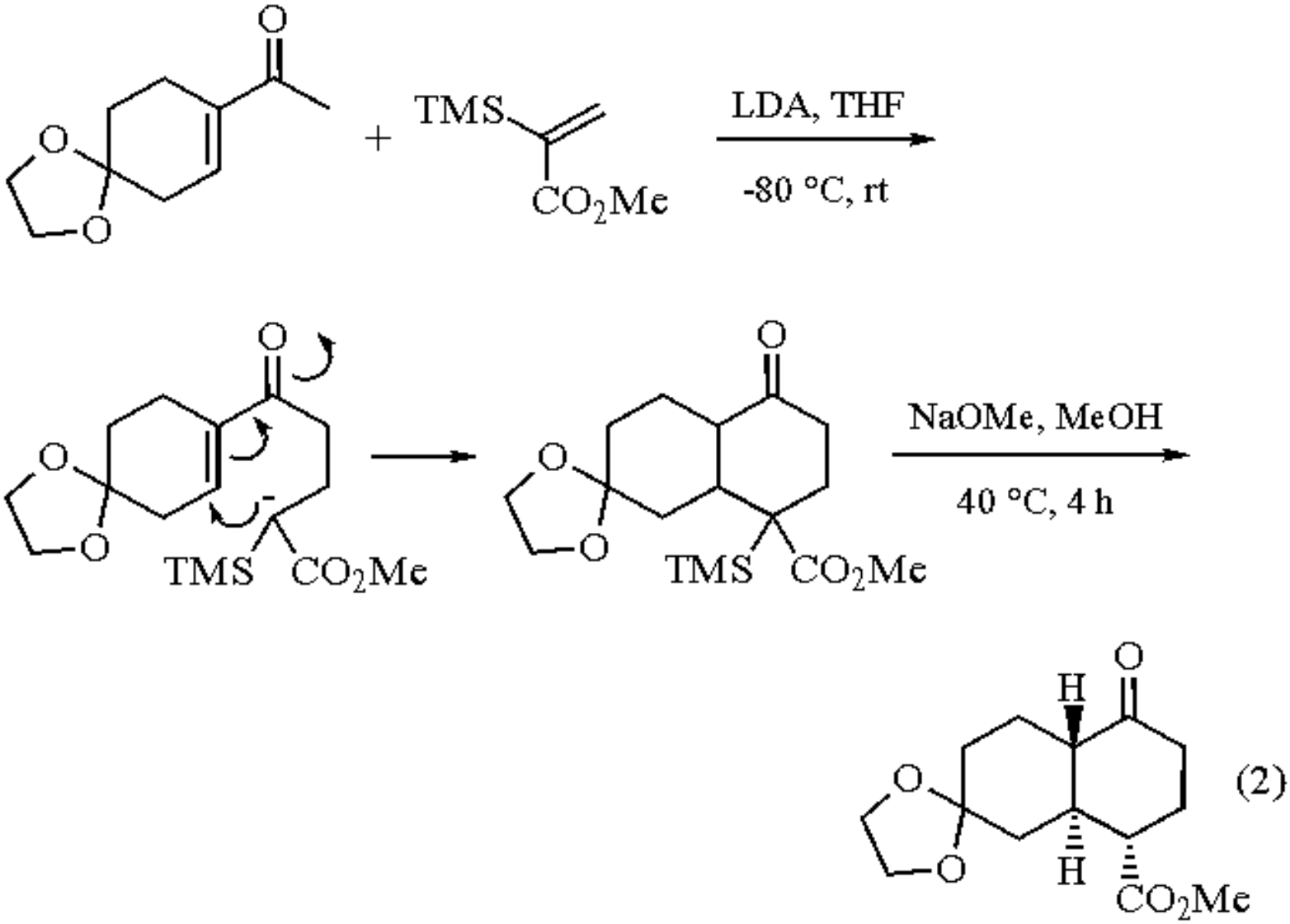

In another annulation sequence,[5] a functionalized aryllithium generated chemoselectively from (2-bromo-4,5-dimethoxyphenyl)ethyl bromide at -100 °C undergoes conjugate addition with methyl 2-trimethylsilylacrylate, and the adduct cyclizes by intramolecular alkylation to give the tetrahydronaphthalenecarboxylate in 80% yield (eq 3).

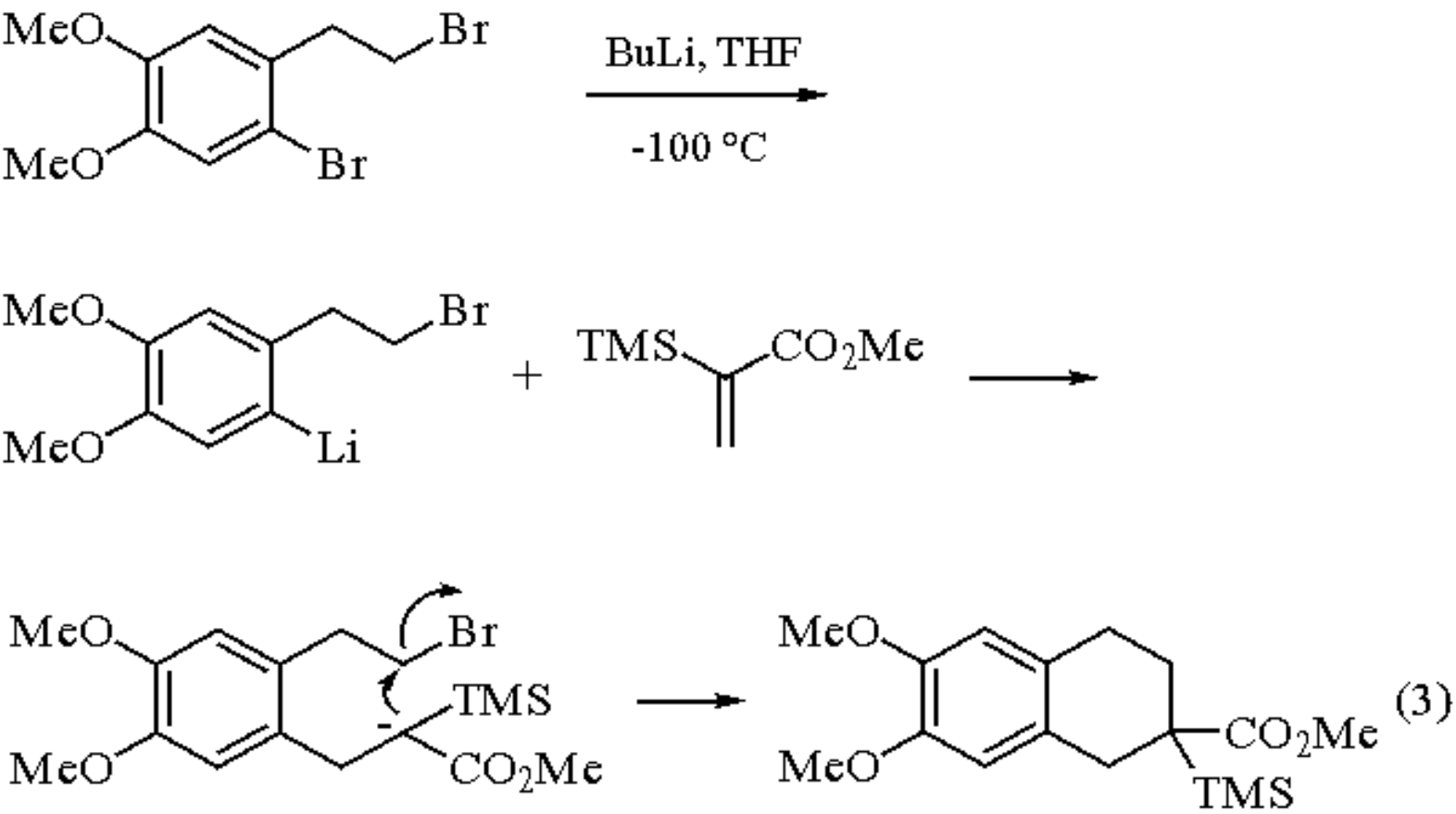

α-Silyl Esters.

Conjugate addition of organometallic reagents (magnesium or lithium) to methyl 2-trimethylsilylacrylate gives either 1:1 or 1:2 adduct[6c] anions (eq 4), depending upon the reaction conditions and reactivity of donor molecules. These anions undergo either alkylation[6b] with a suitable alkylation agent or add to another electrophile[6a] such as ketones, aldehydes, or α,β-unsaturated aldehydes.

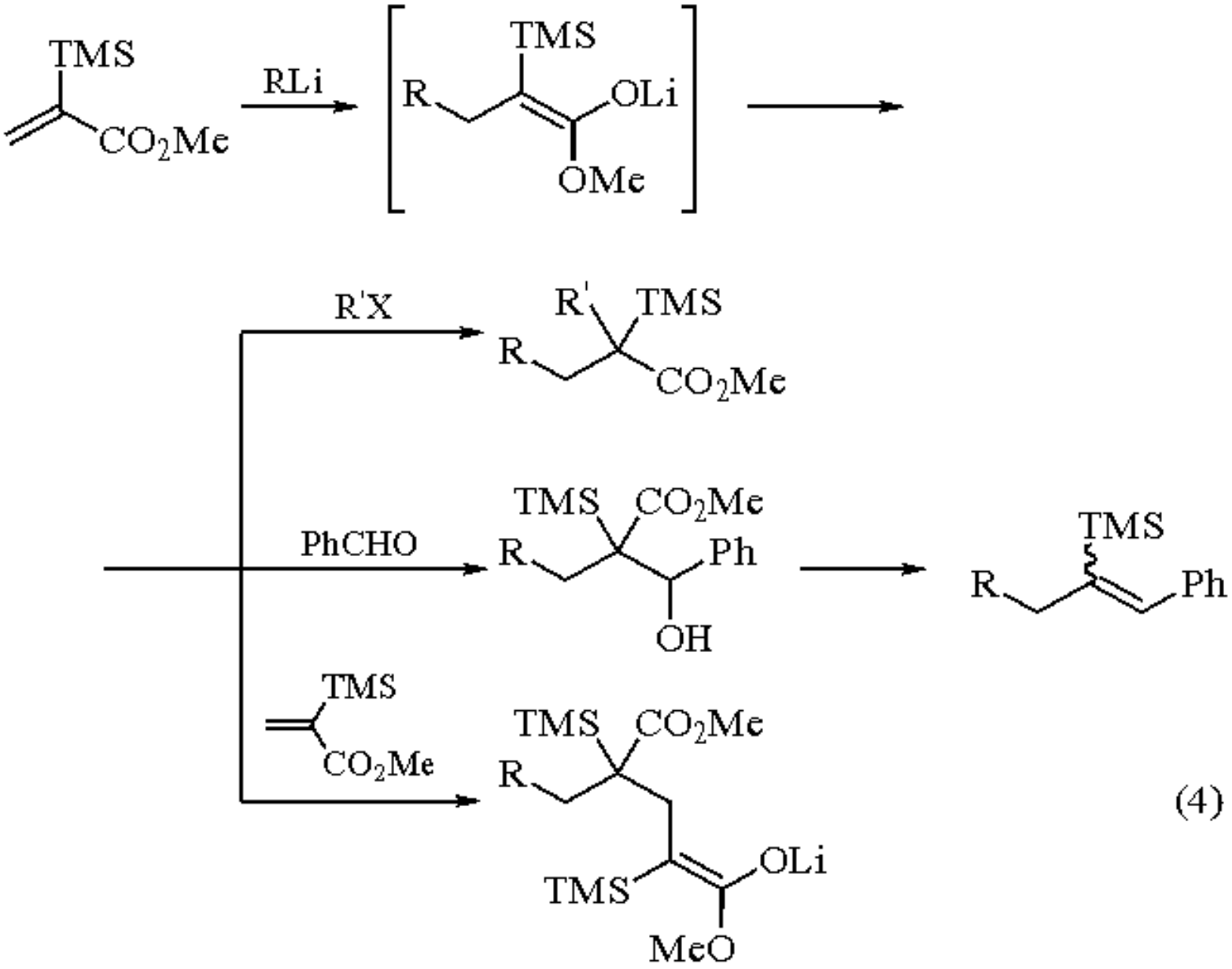

(4)

Synthesis of Pyrrolidones.

2-Azaallyl anions[7] derived from aryl-substituted imines undergo highly diasteroselective Michael addition to methyl 2-trimethylsilylcrotonate. The Michael adducts are converted to pyrrolidones through hydrolytic cyclization (eq 5).

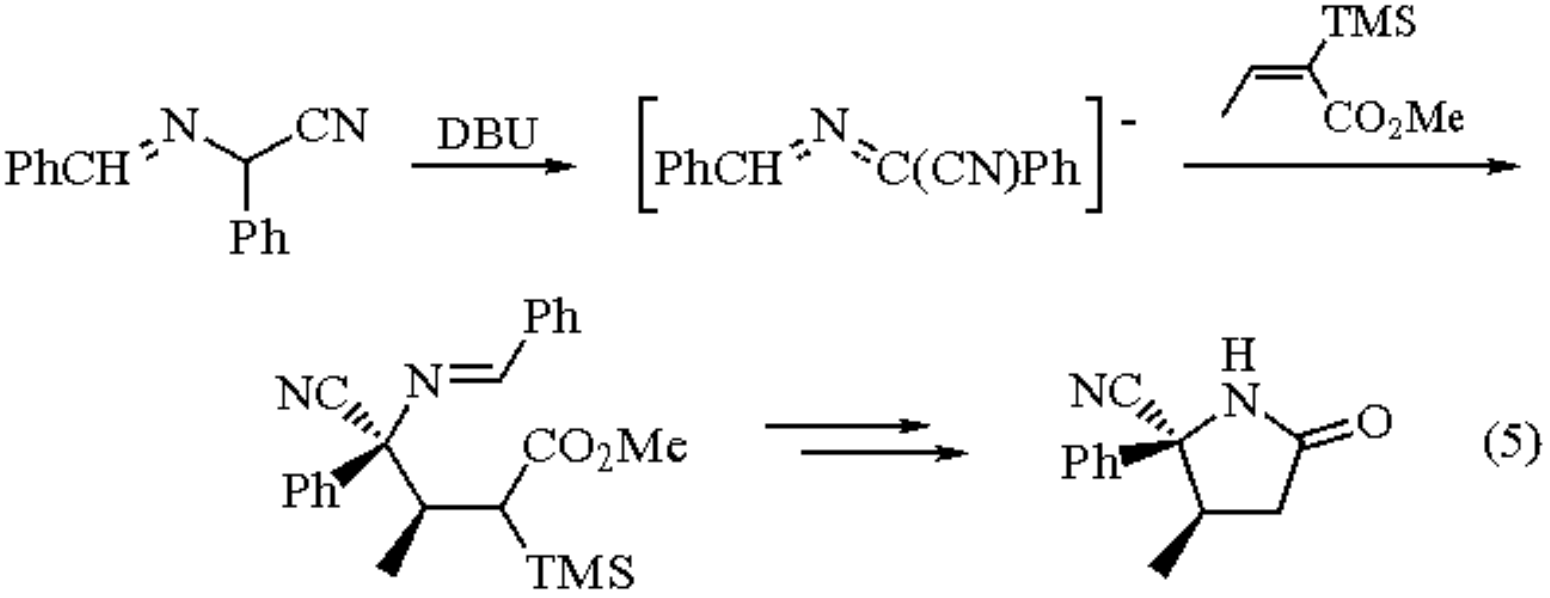

Related Reagents.

Ethyl Acrylate; ***1-(Trimethylsilyl)vinyllithium***; ***Methyl 2-Methylthioacrylate***; ***Trimethyl 2-Phosphonoacrylate***; ***3-Trimethylsilyl-3-buten-2-one***; ***Vinyltrimethylsilane***.

---

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Anubhav P. S. Narula

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1-Methyl-1-(trimethylsilyl)allene[1]

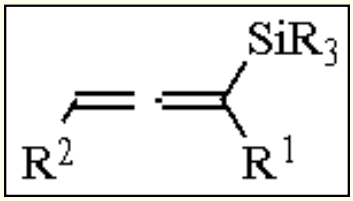

(**1a**; R_3 = Me_3, R^1 = Me, R^2 = H)[4b,9]

[74542-82-8] · $C_7H_{14}Si$ · 1-Methyl-1-(trimethylsilyl)allene · (MW 126.30) (**1b**; R_3 = *t*-$BuMe_2$, R^1 = Me, R^2 = H)[7]

[99035-24-2] · $C_{10}H_{20}Si$ · 1-Methyl-1-(*t*-butyldimethylsilyl)allene · (MW 168.39) (**1c**; R_3 = $(i\text{-Pr})_3$, R^1 = Me, R^2 = H)[7]

[120789-53-9] · $C_{13}H_{26}Si$ · 1-Methyl-1-(triisopropylsilyl)allene · (MW 210.48) (**1d**; R_3 = Me_3, R^1 = H, R^2 = Me)[4b]

[74542-82-8] · $C_7H_{14}Si$ · 3-Methyl-1-(trimethylsilyl)allene · (MW 126.30)

(propargylic anion equivalents;[2,3] three-carbon synthons for [3 + 2] annulations leading to five-membered compounds including cyclopentenes,[4] dihydrofurans,[5] pyrrolines,[5] isoxazoles,[6] furans,[7] and azulenes[8])

Physical Data: (**1a**) bp 111 °C; bp 54-56 °C/90 mmHg; (**1b**) bp 62-65 °C/30 mmHg; (**1d**) bp 107-110 °C.

Solubility: sol CH_2Cl_2, benzene, THF, Et_2O, and most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: (**1a**) IR (neat) 2955, 2910, 2900, 2860, 1935, 1440, 1400, 1250, 935, 880, 830, 805, 750, and 685 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.67 (t, 3H, *J* = 3.3), and 4.25 (q, 2H, *J* = 3.3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -2.1, 15.1, 67.3, 89.1, and 209.1.[4b,9]

Preparative Methods: 1-methyl-1-(trialkylsilyl)allenes can be conveniently prepared by the method of Vermeer.[9,10] Silyl-substituted propargyl mesylates thus undergo S_N2' displacement by the organocopper reagent generated from methylmagnesium chloride, ***Copper(I) Bromide***, and ***Lithium Bromide***. 1-Methyl-1-(trimethylsilyl)allene is produced in 52% yield from commercially available (trimethylsilyl)propargyl alcohol in this fashion (eq 1).[4b,9] The *t*-butyldimethylsilyl and triisopropylsilyl analogs are synthesized by the same method in 90% and 58% yield, respectively.[7] Propargyl alcohols bearing these and other trialkylsilyl groups can be prepared by treatment of ***Propargyl Alcohol*** with ***n-Butyllithium*** and the appropriate trialkylsilyl chloride.[7] Allenylsilanes bearing other C-1 substituents can be prepared in an analogous manner by using the appropriate

Grignard reagents.

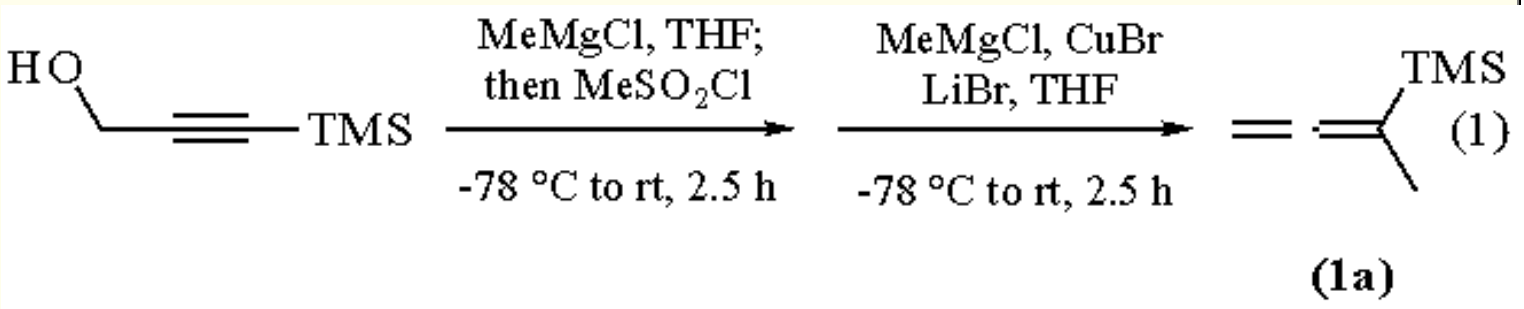

1-Methyl-1-(trialkylsilyl)allenes can be alkylated at C-3 with a variety of alkyl halides by treatment of the allenylsilane with *n*-butyllithium and the desired alkyl halide (e.g. eq 2).[7] In addition to ethyl bromide, alkylating agents such as *n*-heptyl bromide,[6] 1,2-dibromobutane,[7] and 5-bromo-1-pentene[8] have been employed in this reaction.

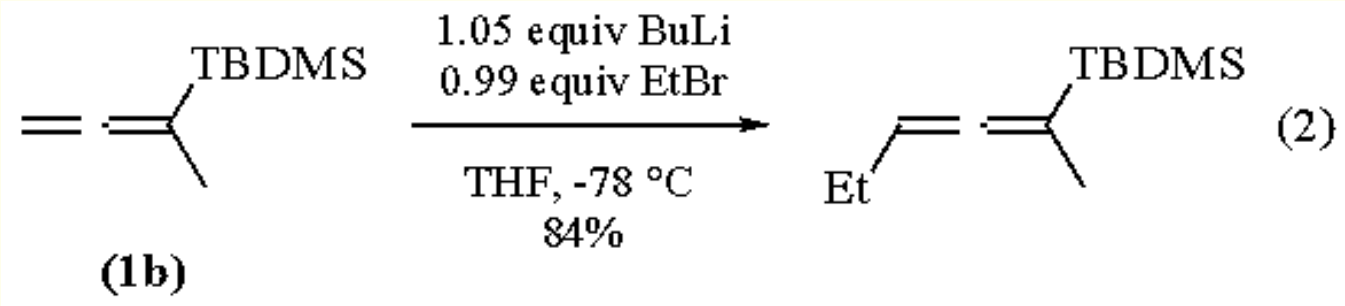

3-Methyl-1-(trimethylsilyl)allene (**1d**) is prepared by the direct silylation of the lithium derivative of 1,2-butadiene.[4b] Sequential treatment of a THF solution of 1,2-butadiene with 1.0 equiv of ***Lithium 2,2,6,6-Tetramethylpiperidide*** (-78 °C, 3 h) and 1.05 equiv of ***Chlorotrimethylsilane*** (-78 °C to 25 °C, 12 h) affords (**1d**) in 41% yield after distillation (eq 3).

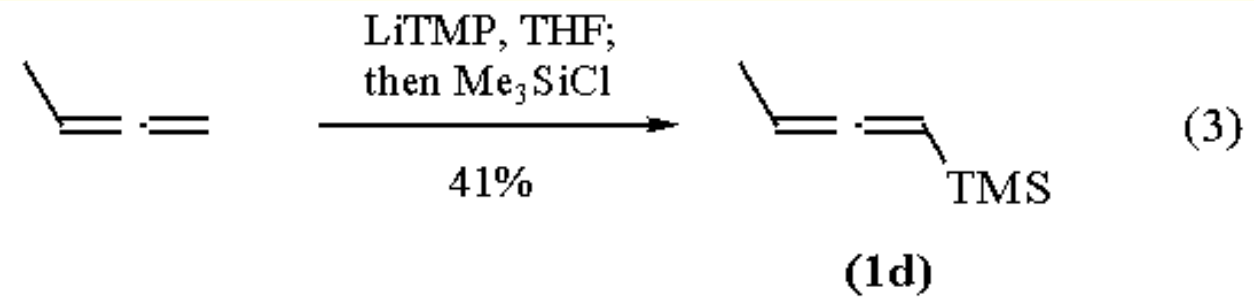

Purification: allenes (**1a**), (**1b**), and (**1c**) are purified by distillation at reduced pressure or by column chromatography. Allene (**1d**) is distilled at atmospheric pressure. The allenylsilanes obtained by the Vermeer method typically contain up to 7-8% of the trialkylsilyl-1-butyne isomer produced by S_N2 reaction. This mixture can be used directly in most subsequent reactions without further purification. If desired, however, the alkynyl contaminant can be selectively removed by treatment of the mixture with ***Silver(I) Nitrate*** in (10:1) methanol-water at room temperature for one hour.[9] 1-Methyl-1-(trimethylsilyl)allene is obtained in 79% yield after pentane extraction and distillation.

Handling, Storage, and Precautions: 1-methyl-1-(trimethylsilyl)allene is stable indefinitely when stored under nitrogen in the refrigerator.

Propargylic Anion Equivalents.

Due to the silicon β-effect, allenylsilanes react with electrophiles at the 3-position in a fashion analogous to the behavior of allyl- and propargylsilanes.[11] Allenylsilanes can thus function as propargylic anion equivalents. Particularly important is the reaction of (trimethylsilyl)allenes with aldehydes and ketones to provide a regiocontrolled route to homopropargylic alcohols of a variety of substitution types. Allenylsilanes substituted at the 1-position undergo the addition to carbonyl compounds in the presence of ***Titanium(IV) Chloride*** to afford homopropargylic alcohols directly (eq 4).[2]

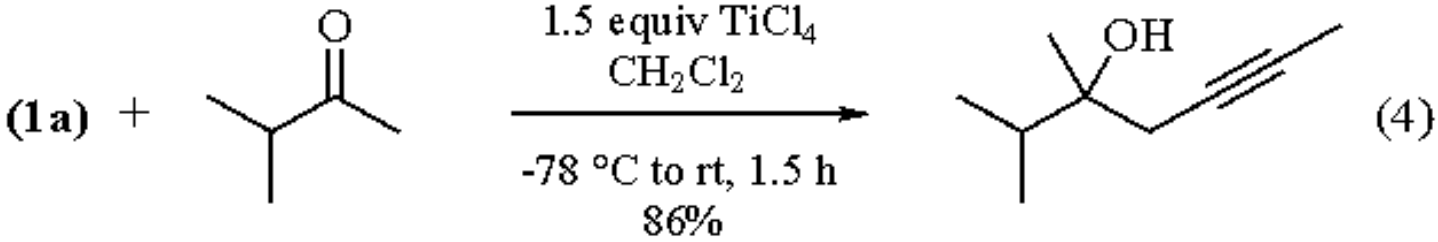

In contrast, allenylsilanes lacking a substituent at C-1 react with carbonyl compounds to produce a mixture of the desired homopropargylic alcohols and (trimethylsilyl)vinyl chlorides. This initial product can be converted to the desired alkyne using the method of Cunico and Dexheimer:[12] exposure of the crude mixture of allenylsilane adducts to 2.5 equiv of ***Potassium Fluoride*** in DMSO furnishes the homopropargylic alcohols in good yield (eq 5).[2]

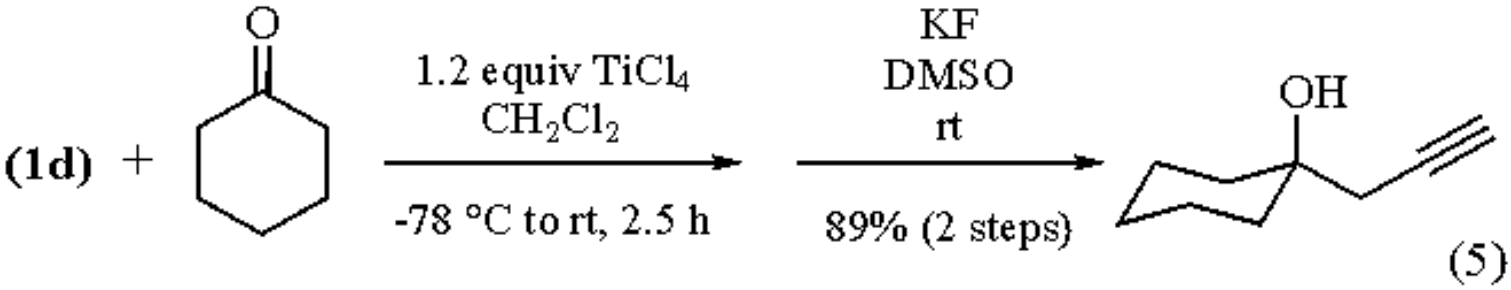

A number of methods have been reported for the preparation of homopropargylic alcohols.[13] Alcohols having the substitution pattern represented in structure (**3**), for example, can be prepared using 3-alkyl-substituted allenyltitanium,[14] -alanate,[15] and -zinc compounds.[16] Unfortunately, these methods are not applicable to the synthesis of type (**4**) products. Zweifel has shown that allenyldialkylboranes (generated via the reaction of lithium chloropropargylide with trialkylboranes) combine with aldehydes (but not ketones) to produce type (**4**) homopropargylic alcohols.[17] The preparation of type (**2**) homopropargylic alcohols is discussed in the article on ***(Trimethylsilyl)allene***.

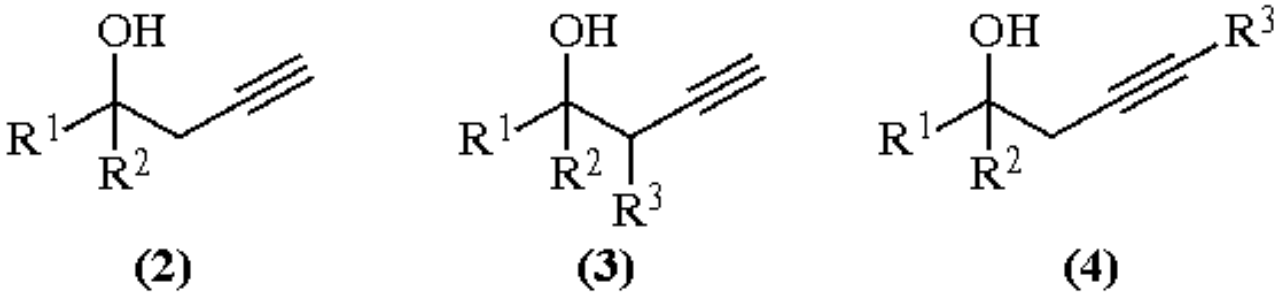

1-Methyl-1-(trimethylsilyl)allene

Santelli has demonstrated that allenylsilanes without a C-1 substituent undergo conjugate addition to α,β-unsaturated acyl cyanides to give δ,ε-alkynic acyl cyanides.[3]

Three-Carbon Synthon for [3 + 2] Annulations.

Danheiser and co-workers have exploited allenylsilanes as the three-carbon components in a [3 + 2] annulation strategy for the synthesis of a variety of five-membered carbocycles and heterocycles. The pathway by which a typical annulation proceeds is shown in eq 6. Reaction of the 2-carbon component (the allenophile) at C-3 of the allenylsilane is followed by rapid rearrangement of the silicon-stabilized vinyl cation. Ring closure then affords the five-membered product.

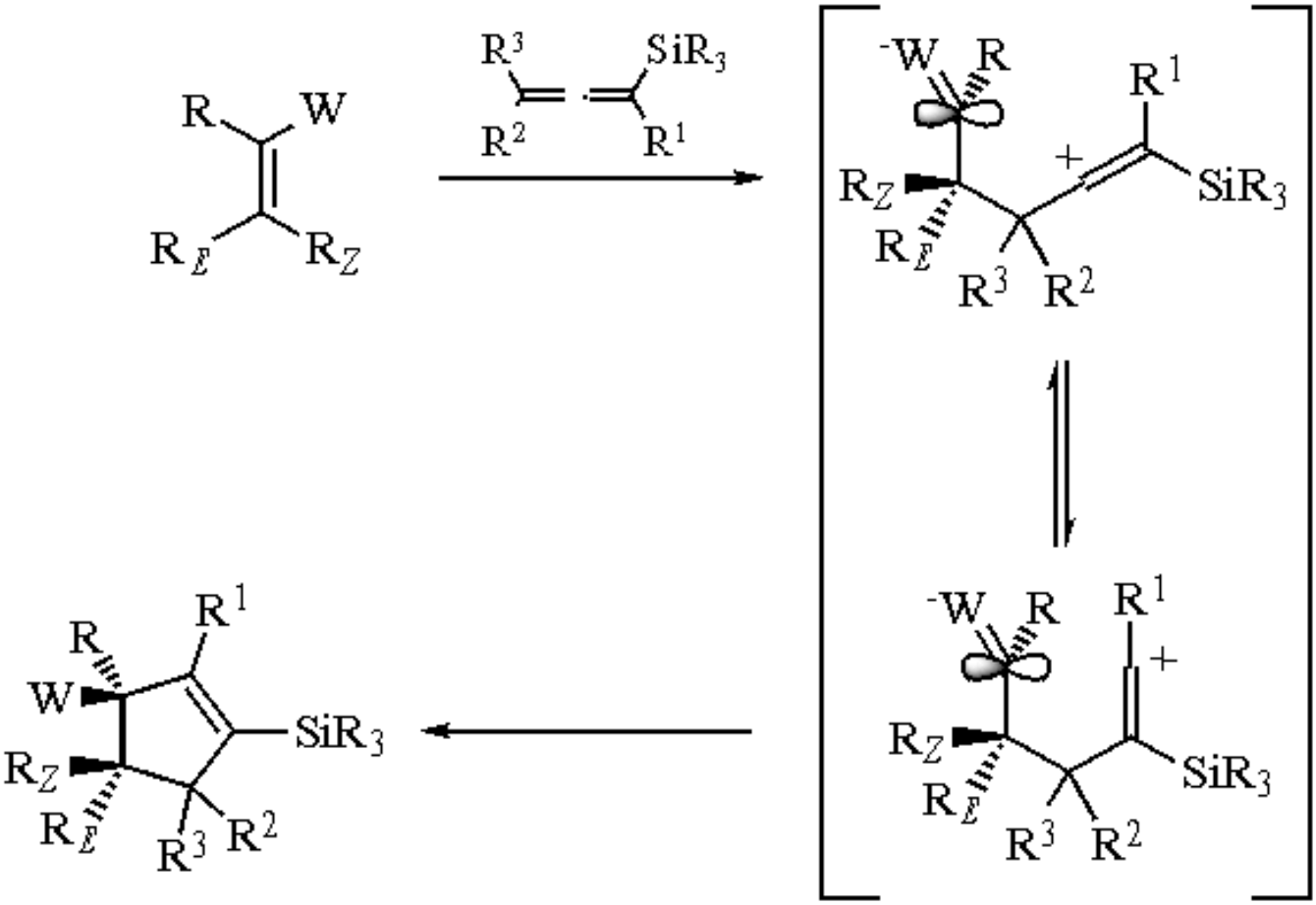

(6)

Synthesis of Five-Membered Carbocycles.

1-Substituted allenylsilanes react with α,β-unsaturated carbonyl compounds in the presence of titanium tetrachloride to produce cyclopentenes.[4] For example, carvone and 1-methyl-1-(trimethylsilyl)allene react smoothly to give a *cis*-fused bicyclic system (eq 7).[4d]

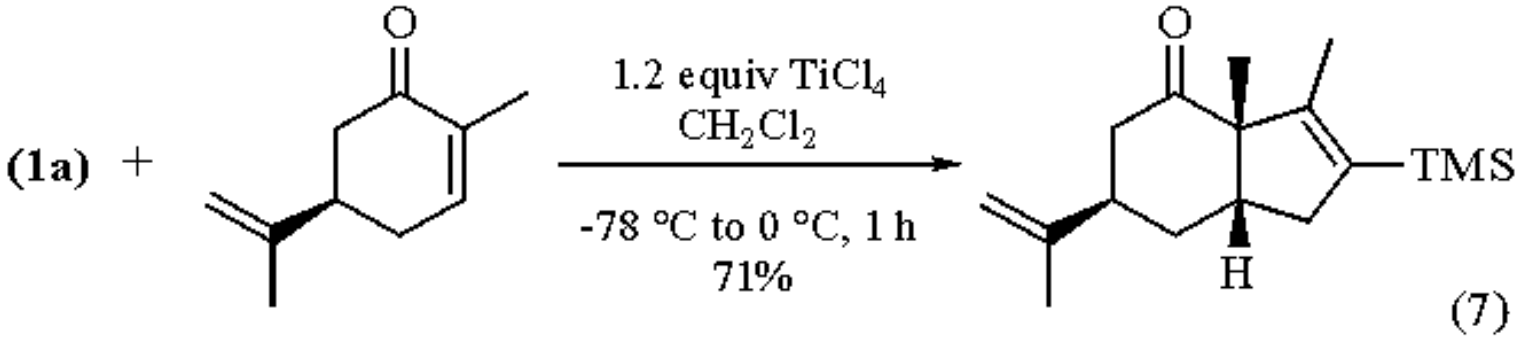

As illustrated above, the reaction proceeds with a strong preference for suprafacial addition of the allene to the allenophile, thus permitting the stereocontrolled synthesis of a variety of mono- and polycyclic systems. Both cyclic and acyclic enones participate in the reaction. Spiro-fused products are obtained from α-alkylidene ketone substrates (eq 8).[4b]

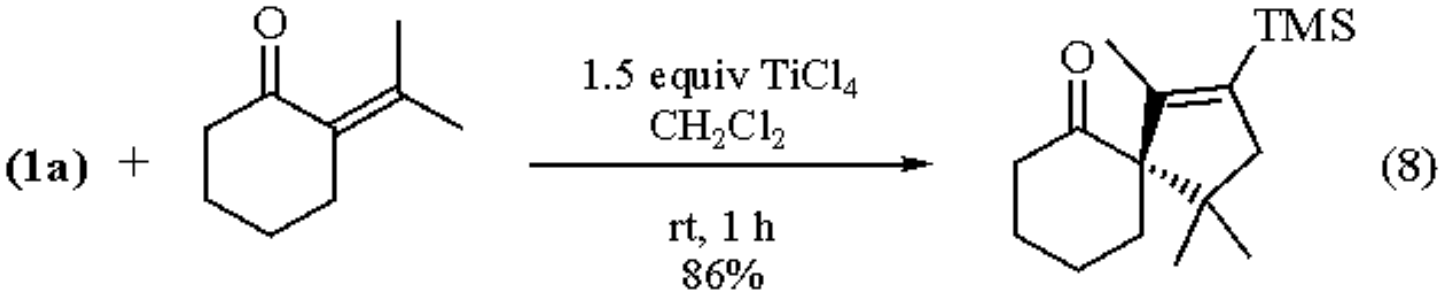

When α,β-unsaturated acyl silanes are employed, the type of product formed varies depending on the trialkylsilyl substituent of the acyl silane: five-membered carbocycles are produced from reaction with *t*-butyldimethylsilyl derivatives, whereas six-membered carbocycles are obtained from trimethylsilyl compounds (eq 9).[4c]

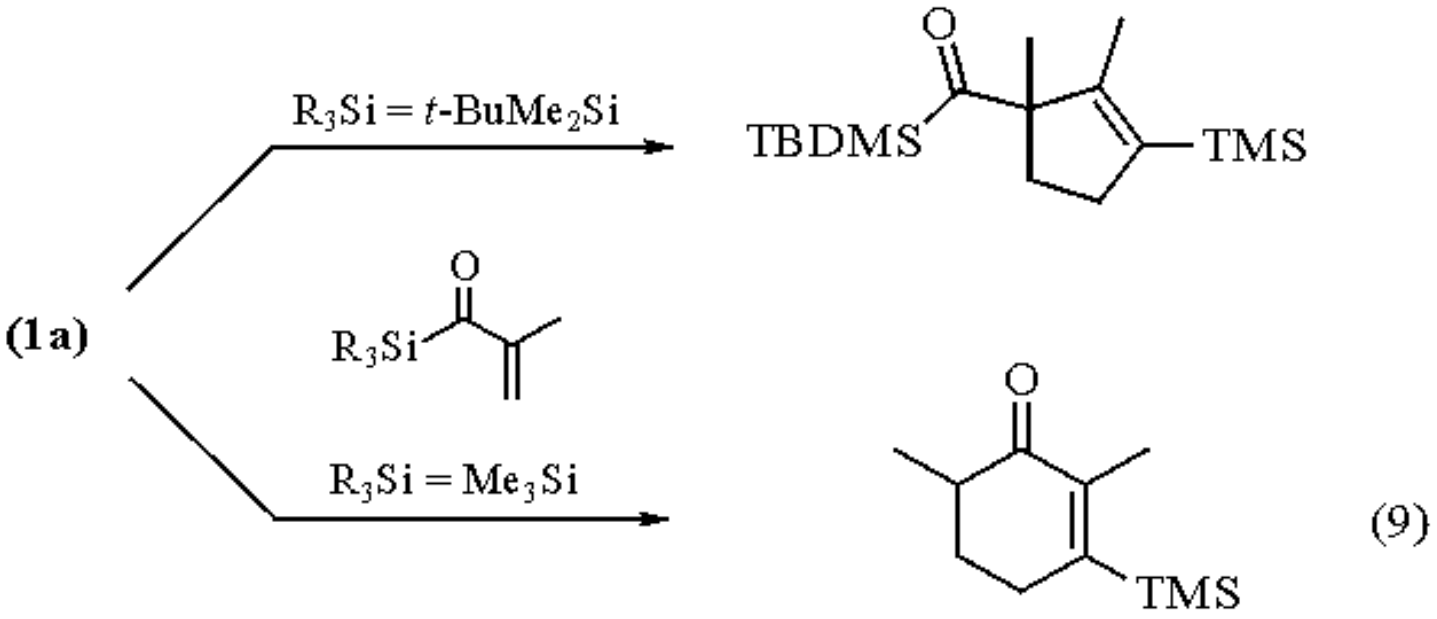

Allenylsilanes lacking a C-1 alkyl substituent do not function efficiently as three-carbon synthons in the [3 + 2] annulation. This phenomenon is attributable to the relative instability of the terminal vinyl cation intermediate required according to the proposed mechanism for the annulations (eq 6). Fully substituted five-membered rings result from annulations employing allenylsilanes substituted at both C-1 and C-3.[4]

Synthesis of 1,3-Dihydrofurans.

(*t*-Butyldimethylsilyl)allenes combine with aldehydes to produce dihydrofurans (eq 10).[5] In a typical reaction, the aldehyde and 1.1 equiv of titanium tetrachloride are premixed at -78 °C in methylene chloride for 10 min. The allenylsilane (1.2 equiv) is then added, and the reaction mixture is stirred in the cold for 15-45 min.

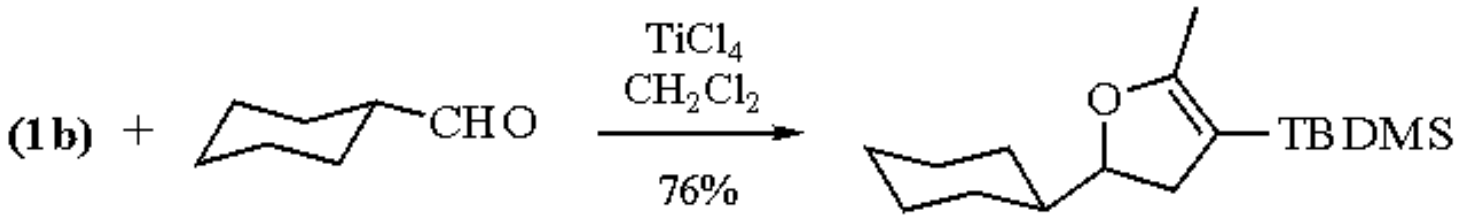

(10)

In reactions of a C-3 substituted allenylsilane with achiral aldehydes, *cis*-substituted dihydrofurans are the predominant products (eq 11).[5]

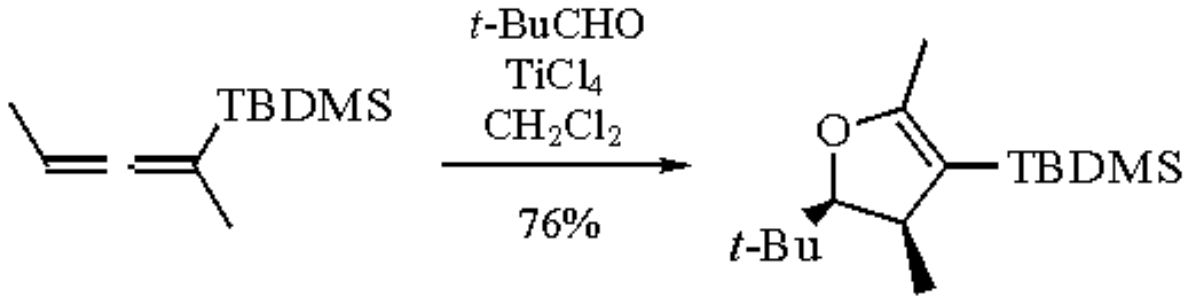

(11)

(Trimethylsilyl)allenes are unsuitable for this [3 + 2] annulation, as the intermediate carbocations undergo chloride-initiated desilylation to produce alkynic byproducts. This unwelcome reaction pathway is suppressed when the bulkier (*t*-butyldimethylsilyl)allenes are employed.

Synthesis of Pyrrolizinones.

Cyclic *N*-acyl imine derivatives combine with (*t*-butyldimethylsilyl)allenes to afford nitrogen heterocycles (eq 12).[5] The *N*-acyliminium ions are generated from ethoxypyrrolidinones in the presence of titanium tetrachloride.

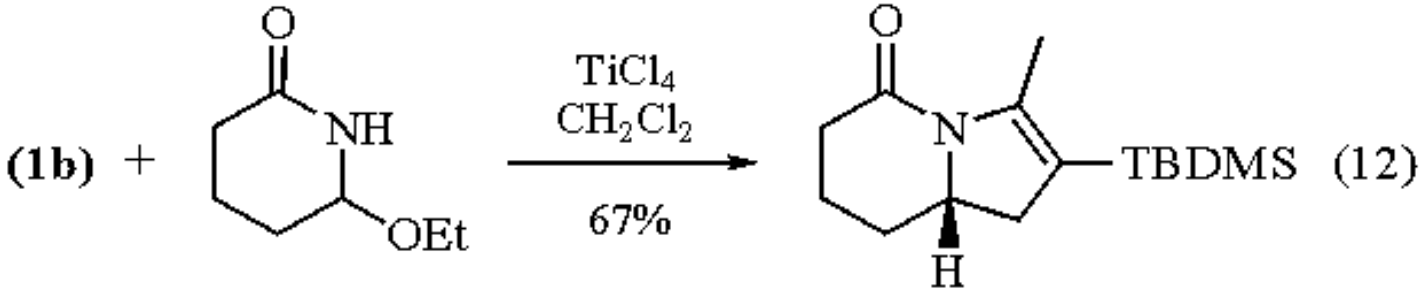

(12)

Synthesis of Furans and Isoxazoles.

Electrophilic species of the general form Y&tbond;X^+ serve as heteroallenophiles, combining with allenylsilanes in a regiocontrolled [3 + 2] annulation method. As illustrated in the mechanism shown in eq 13, addition of the heteroallenophile at C-3 of the allenylsilane produces a vinyl cation stabilized by hyperconjugative interaction with the adjacent carbon-silicon σ-bond. A 1,2-trialkylsilyl shift then occurs to generate an isomeric vinyl cation, which is intercepted by nucleophilic X. Elimination of H^+ furnishes the aromatic heterocycle.

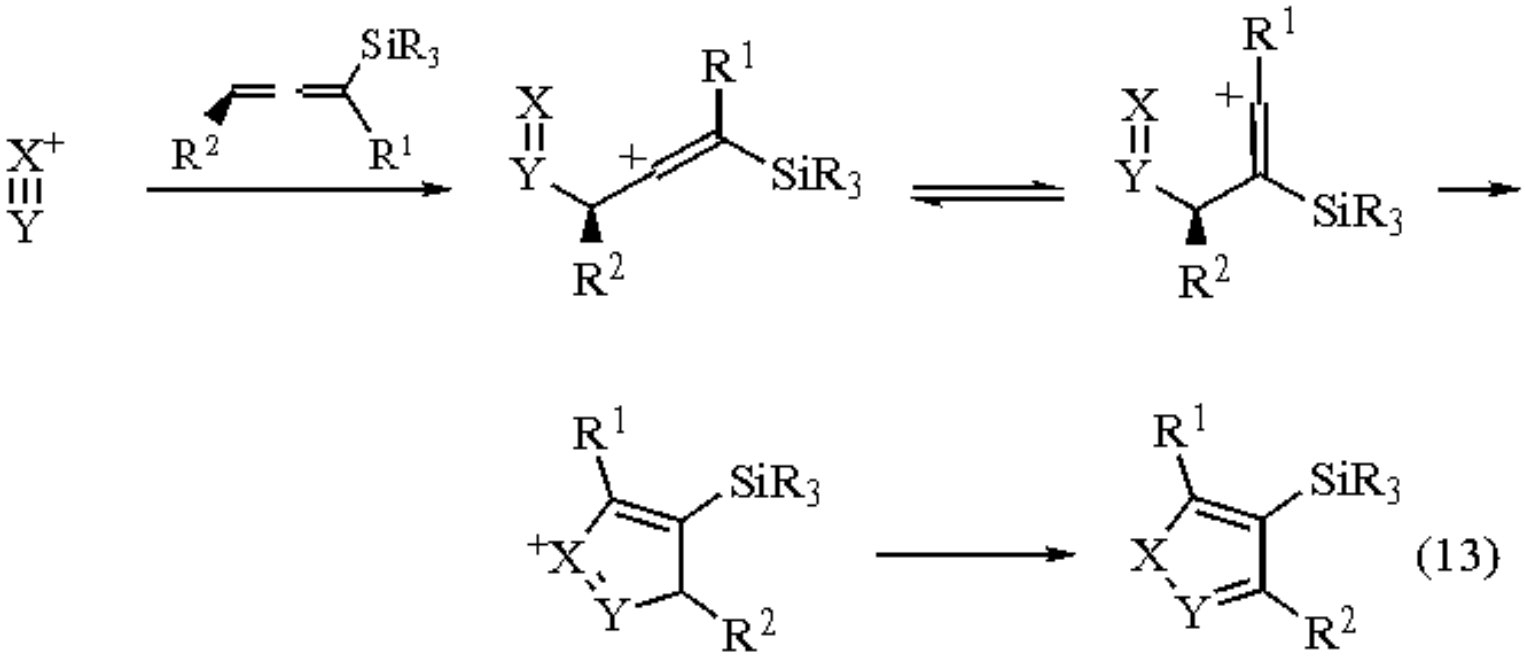

(13)

Isoxazoles are synthesized when the heteroallenophile is nitrosonium ion. Thus, reaction of commercially available ***Nitrosonium Tetrafluoroborate*** with allenylsilanes in acetonitrile at -30 °C affords silyl-substituted isoxazoles in good yield (eq 14).[6]

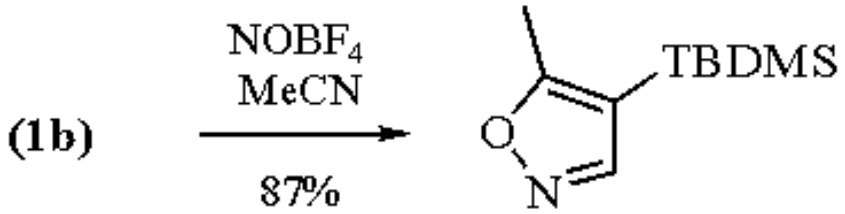

(14)

In a variation of the above procedure, (trimethylsilyl)allenes are employed in a one-pot procedure that produces 5-substituted and 3,5-disubstituted isoxazoles lacking the 4-silyl substituent (eq 15). Desilylation is encouraged by addition of water and warming the reaction mixture to 65-70 °C after the initial annulation.[6] Alternatively, addition of electrophilic reagents to the reaction mixture leads to isoxazoles with C-4 substituents such as Br, COMe, etc.

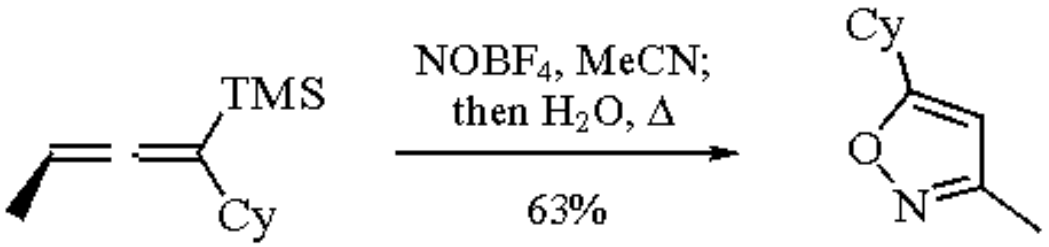

(15)

1-Methyl-1-(trimethylsilyl)allene

The heteroaromatic strategy is extended to the synthesis of furans when acylium ions are employed as the heteroallenophile (eq 16).[7] Acylium ions are generated in situ via the reaction of acyl chlorides and ***Aluminum Chloride***. Typically, the allenylsilane is added to a solution of 1.0 equiv each of $AlCl_3$ and the acyl chloride in methylene chloride at -20 °C. The reaction is complete in 1 h at -20 °C.

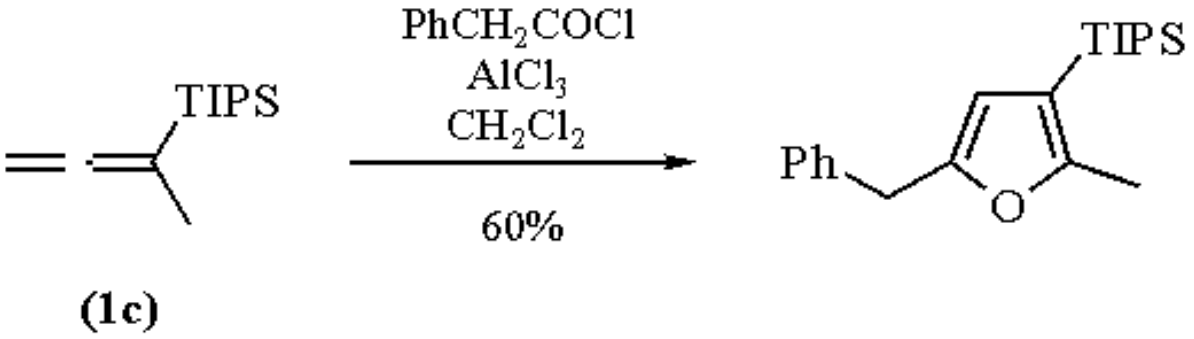

(16)

Intramolecular [3 + 2] annulation affords bicyclic furans (eq 17).[7]

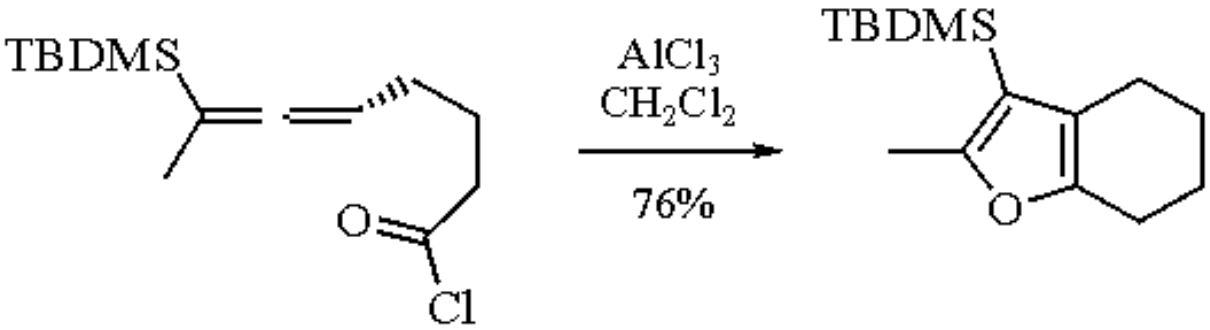

(17)

(*t*-Butyldimethylsilyl)- and (triisopropylsilyl)allenes are superior to their trimethylsilyl counterparts for this annulation, presumably due to the ability of the larger trialkylsilyl groups to suppress undesirable desilylation reactions. In annulations involving allenylsilanes which lack C-3 substituents, the bulkier triisopropylsilyl derivatives are superior to *t*-butyldimethylsilyl analogs.

Synthesis of Azulenes.

Reaction of tropylium cations with allenylsilanes produces substituted azulenes.[8] Typically, commercially available ***Tropylium Tetrafluoroborate*** (2 equiv) is employed. The second equivalent dehydrogenates the dihydroazulene intermediate to produce the aromatic product. ***Poly(4-vinylpyridine)*** (poly (4-VP)) or methyltrimethoxysilane is used to scavenge the HBF_4 produced in the reaction.

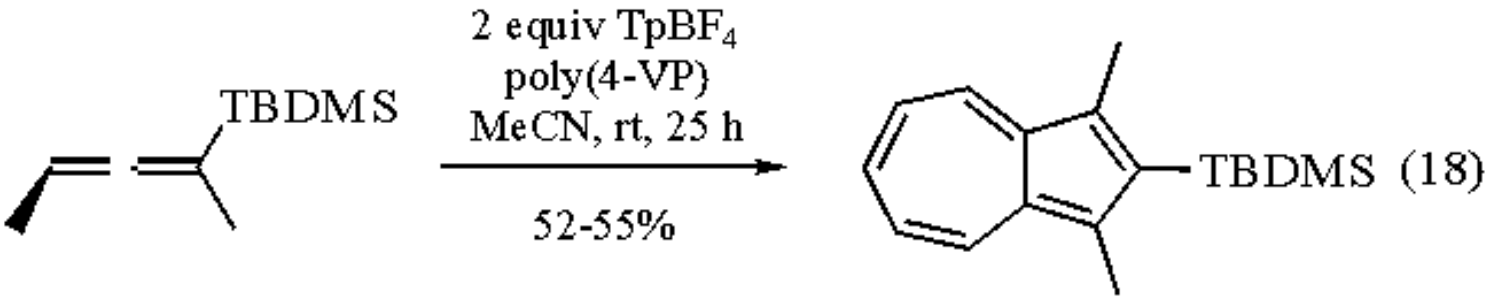

(18)

The azulene synthesis proceeds best with 1,3-dialkyl (*t*-butyldimethylsilyl)allenes. (Trimethylsilyl)allenes desilylate to generate propargyl-substituted cycloheptatrienes as significant byproducts. As observed in the other [3 + 2] annulations discussed already, allenylsilanes lacking C-1 alkyl substituents do not participate in the reaction.

Synthesis of Silylalkynes via Ene Reactions.

(Trimethylsilyl)allenes undergo ene reactions with ***4-Phenyl-1,2,4-triazoline-3,5-dione*** and other reactive enophiles to give silylalkenes.[18]

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2-Methyl-2-(trimethylsilyloxy)-3-pentanone[1]

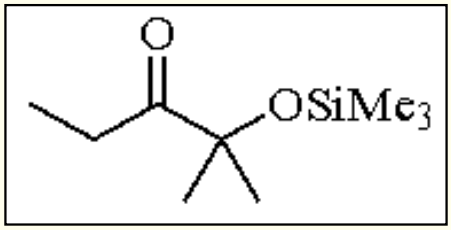

[72507-50-7] · $C_9H_{20}O_2Si$ · 2-Methyl-2-(trimethylsilyloxy)-3-pentanone · (MW 188.38)

(lithium enolate used in the synthesis of *syn*-β-hydroxy acids, aldehydes, and ketones)

Physical Data: bp 71-75 °C/15 mmHg.

Preparative Methods: prepared in four steps from propionaldehyde in 14-33% overall yield;[2] in three steps from ***Acetone Cyanohydrin*** in 40% overall yield;[3] and in two steps from 3-hydroxy-3-methyl-2-butanone in 55% overall yield.[4]

Handling, Storage, and Precautions: use in a fume hood.

Stereoselection in Reactions of Lithium Enolates.

The (*Z*)-lithium enolate (**2**), obtained from the reaction of 2-methyl-2-trimethylsilyloxypentan-3-one (**1**) with ***Lithium Diisopropylamide***, reacts with aldehydes to afford *syn*-β-hydroxy ketones (**3**) exclusively (eq 1).[2,3,5] The synthetic utility of (**3**) is demonstrated by conversion to β-hydroxy acids (**4**), β-hydroxy aldehydes (**5**), and other β-hydroxy ketones by straightforward procedures (eqs 2, 3, and 4).[2,3,5,6] Table 1 illustrates examples of condensations of (**2**) with simple aldehydes and subsequent conversions to (**4**), (**5**), and (**6**).

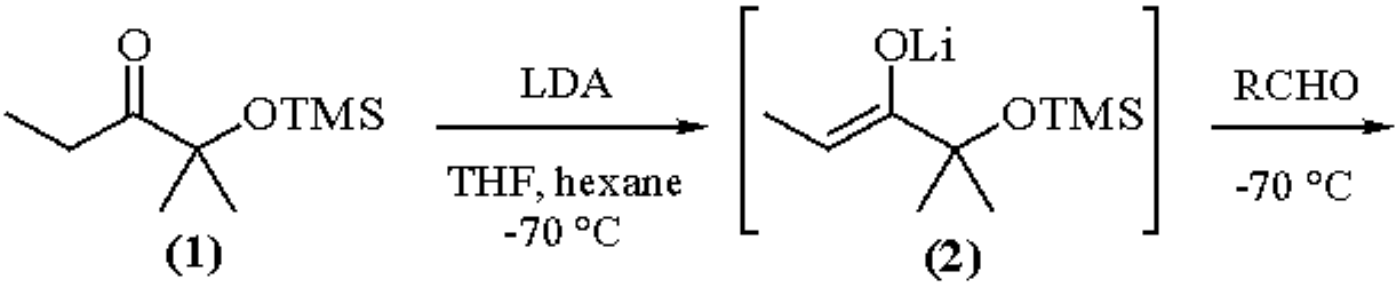
O
OTMS
(1)
LDA
THF, hexane
-70 °C
OLi
OTMS
(2)
RCHO
-70 °C

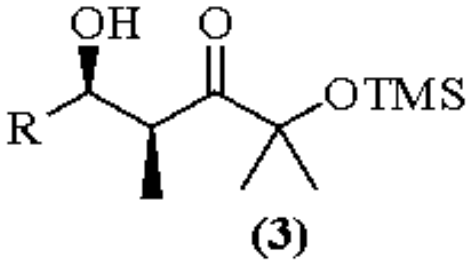
OH
O
R
OTMS
(3)

(1)

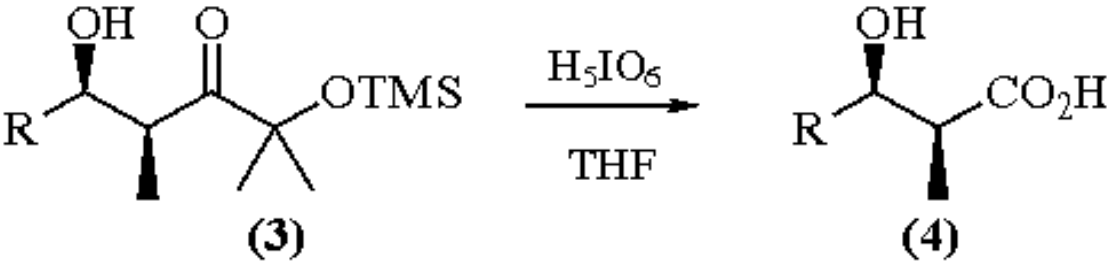
OH
O
R
OTMS
(3)
H_5IO_6
THF
OH
R
CO_2H
(4)

(2)

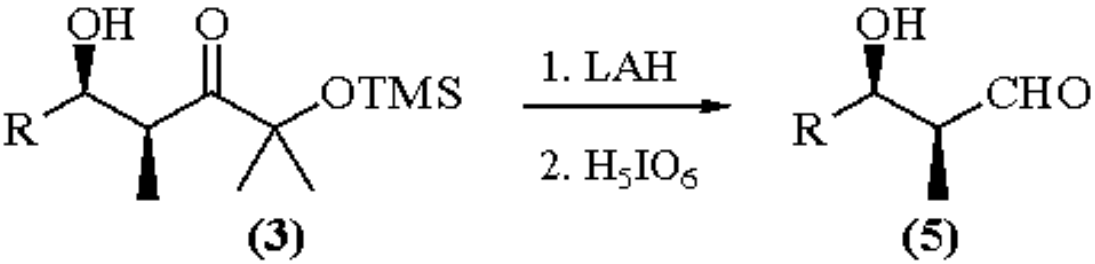
OH
O
R
OTMS
(3)
1. LAH
2. H_5IO_6
OH
R
CHO
(5)

(3)

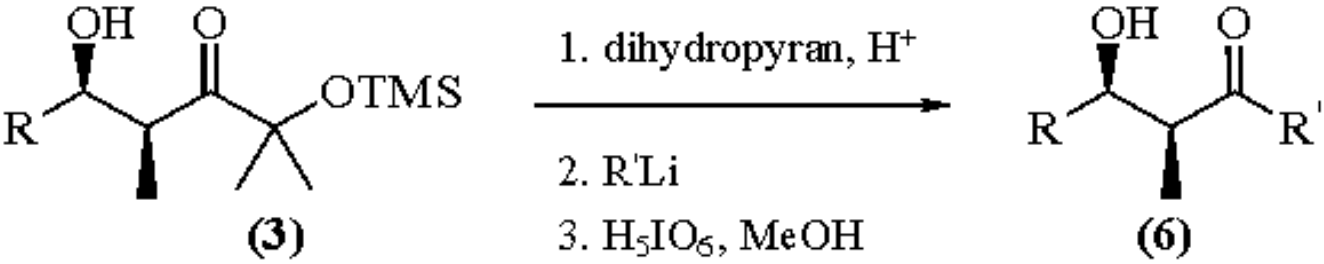
OH
O
R
OTMS
(3)
1. dihydropyran, H^+
2. R'Li
3. H_5IO_6, MeOH
OH
O
R
R'
(6)

(4)

Table 1 Aldol Condensations of Enolate (**2**) with Aldehydes (RCHO) and Subsequent Conversions of (**3**) to *syn*-b-Hydroxy Acids (**4**), Aldehydes (**5**) and Ketones (**6**) (eqs 1 4)

R	Yield of (**3**) (%)	Yield of (**4**) (%)	Yield of (**5**) (%)	Yield of (**6**) (%)	Ref.
Et	82		75[a]		5a
n-C_5H_{11}	43				2
i-Pr	61	77 83			2,3
Bn	51	76			2,3
Ph	78	87		87 (R¢= Me) 65 (R¢= Et) 88 (R¢= *n*-Bu)	2,3,6
2-Thienyl	88	80[b]			5b
CH_2=CH	80	100			5c
trans-MeCH=CH	97	[c]			5c
CH_2=C(Me)	99	[c]			5c

[a] Isolated as an acetate ester. [b] Isolated as a methyl ester after esterification with diazomethane. [c] Yield of this conversion was not reported.

The reaction of (**2**) with aldehydes containing additional functional groups and stereocenters has been reported (eq 5, Table 2).[2,3,9,10] In all instances the stereoselection is high in favor of aldol product of *syn* relative stereochemistry at the α- and β-positions (**7** and **8**), but the degree of stereoselection at the β- and γ-positions is highly variable. Only 2,4-dimethylpent-3-enal exhibits a high level of diastereoselection in formation of the product predicted by Cram's rule (**7**); this product has been used to prepare the C-1 to C-7 fragment of erythronolide A.[10] Additional examples of aldol condensations of (**2**) with complex aldehydes are given in (eq 6).[9] When R and R´ are H, the ratio of (**9**):(**10**) is 5.7:1. When R is Et and R´ is Me, the ratio of (**9**):(**10**) is 3:1. It is noteworthy that significantly higher levels of diastereocontrol are achieved in the synthesis of compounds with the same relative stereochemistry as (**7**) (R = Ph, X = Me; 98:2) and (**9**) (R = Et, R´ = Me; >98:2) using propionate equivalents (**11**)[8a] and (**12**),[8b] respectively.

2-Methyl-2-(trimethylsilyloxy)-3-pentanone

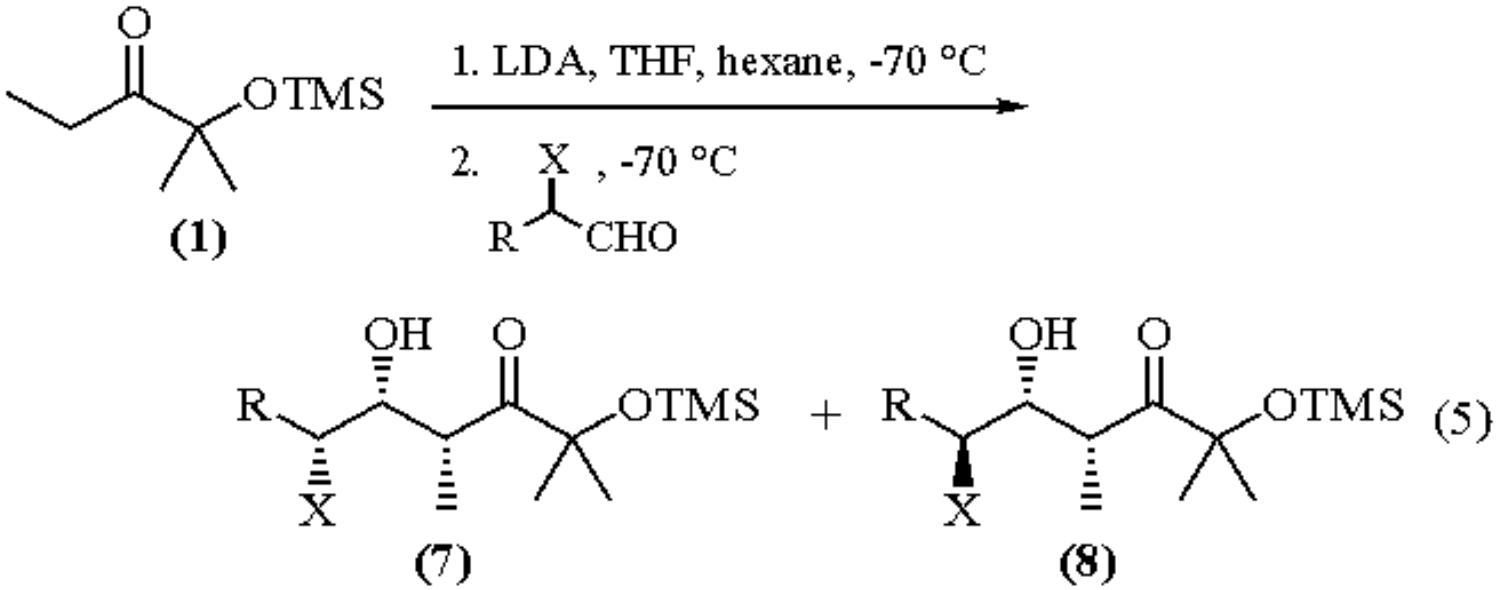

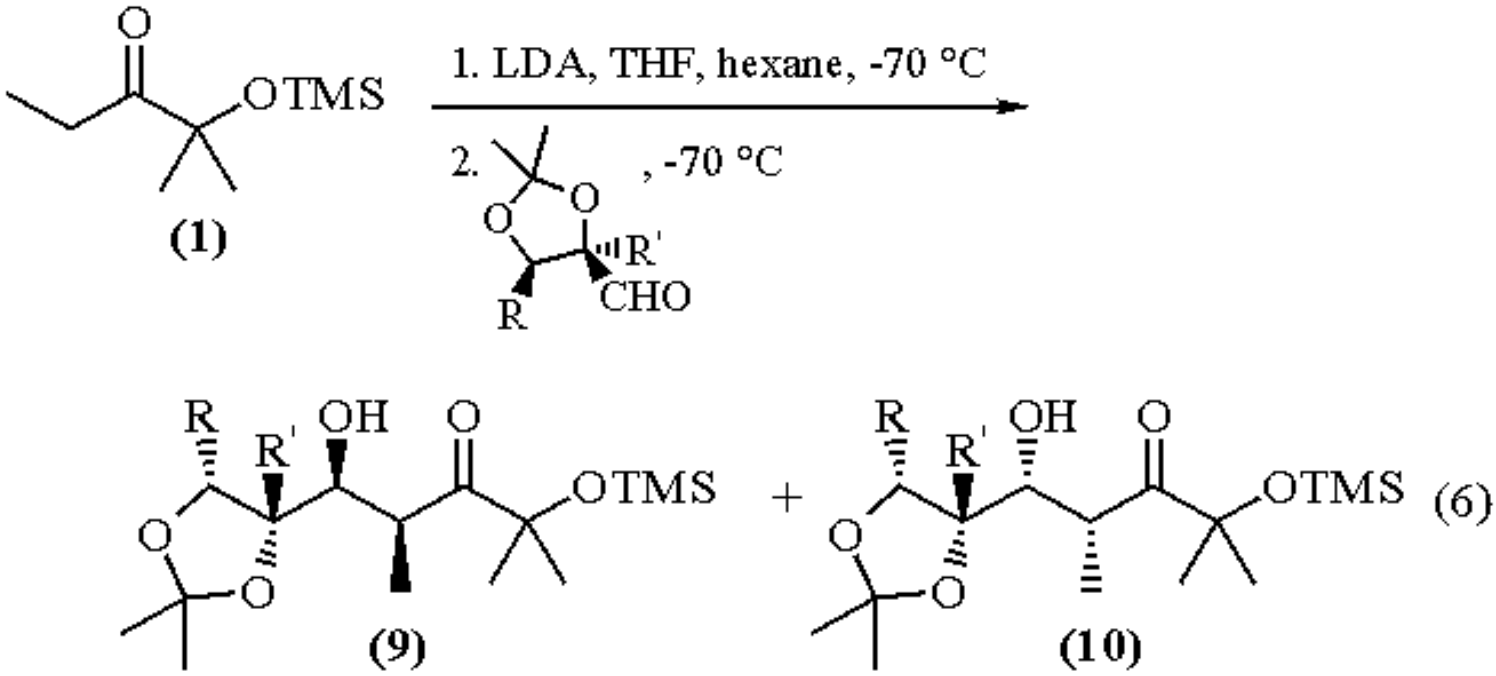

Aldol reactions of lithium enolates of higher homologs of propionate equivalent (**1**) have been studied in the context of natural product syntheses and yield similar levels of stereoselection.[9] The amino sugars (±)-ristosamine and (±)-megalosamine and the nucleus of crassin acetate were prepared using this methodology.[9] Aldol reactions of (**2**) generated from chiral bases or in the presence of chiral solvents yield products of low to moderate levels of optical purity.[10] Asymmetric aldol reactions are best accomplished using other methods.[1] Michael additions of (**2**) have been shown to be highly stereoselective in some instances.[11]

Stereoselection in Reactions of Other Enolates and Enol

Derivatives.

A few examples of reactions of boron, magnesium, and tin enolates of (**1**) and Lewis acid-catalyzed reactions of enol silanes derived from (**1**) have been reported.[12-15] The boron enolate formed by reaction of (**1**) with ***Di-n-butylboryl Trifluoromethanesulfonate*** and ***Diisopropylethylamine*** yields *syn* aldol products.[12] The magnesium enolate formed from (**2**) by exchange with ***Magnesium Bromide*** yields a higher ratio (5:1) of chelation to nonchelation controlled product than (**2**) in reaction with (*R*)-3-benzyloxymethoxy-2-methylpropionaldehyde (see Table 2).[13] Excess tin enolate of (**1**) reacts with β-lactam (**13**) to give (**14**) and its 1α-epimer in a 95:5 ratio.[14] In contrast to the enolates, enol silane (**15**) reacts with benzaldehyde to afford primarily *anti* aldol product (**16**) with ***Boron Trifluoride Etherate*** (**16**:**3** (R = Ph) = 5:1) or ***Titanium(IV) Chloride*** (**16**:**3** (R = Ph) = 9:1) as a catalyst.[15a] Reaction of (**15**) with (*S*)-2-benzyloxypropionaldehyde catalyzed by ***Tin(IV) Chloride*** gave a single isomer (**17**) that possessed the same relative stereochemistry as the minor isomer in the reaction with (**2**) (see Table 2).[15b]

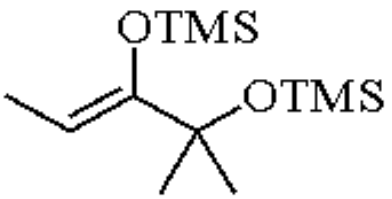

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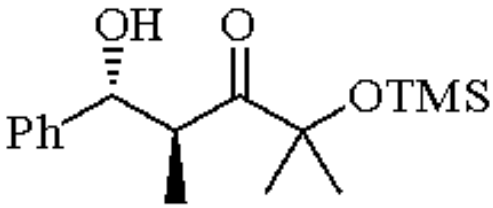

(16)

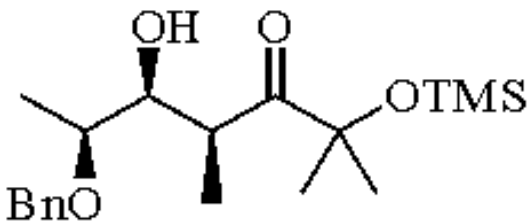

(17)

Related Reagents.

(S)-4-Benzyl-2-oxazolidinone; ***10,2-Camphorsultam***; ***(R)-(+)-t-Butyl 2-(p-Tolylsulfinyl)propionate***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***(R,R)-2,5-Dimethylborolane***; ***2,6-Dimethylphenyl Propionate***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***α-Methyltoluene-2,α-sultam***; ***3-Propionylthiazolidine-2-thione***; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***; ***1,1,2-Triphenyl-1,2-ethanediol***.

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Methyltrioctylammonium Chloride-Alkali

$$[Me(CH_2)_7]_3\overset{+}{N}Me\ \ Cl^-$$

[5137-55-3] · $C_{25}H_{54}ClN$ · Methyltrioctylammonium Chloride · (MW 404.25)

(quaternary ammonium salt; phase transfer catalyst[1])

Alternate Names: Aliquat® 336; tricaprylylmethylammonium chloride.

Physical Data: d 0.884 g cm^{-3}.

Solubility: sol most organic solvents (alcohols, hydrocarbons, aromatics, halogenated solvents), and water.

Form Supplied in: neat liquid; amines are typical impurities.

Purification: toluene solutions (30% by weight) can be washed either twice with equal volumes of 1.5 M HBr solution[2] or three times with equal volumes 4 N NaOH followed by three washes with 1.5 M HCl.[3]

Handling, Storage, and Precautions: hygroscopic; highly toxic; may decompose on prolonged heating (see below).

Introduction.

Methyltrioctylammonium chloride (**1**) has found widespread use in organic synthesis. Typical of phase transfer reagents, (**1**) has been used in dehydrohalogenation, alkylation, saponification, conjugate addition, and carbene reactions. As a caution on catalyst stability and performance, it should be noted that (**1**) has a half-life of 34 h at 110 °C in chlorobenzene, decomposing to a 2:3 mixture of $(Oct)_2NMe$ and $(Oct)_3N$ via Hofmann elimination or dealkylation. Under strongly basic conditions (50% ***Sodium Hydroxide***, PhCl, 60 °C), decomposition is more rapid ($t_{1/2}$ = 9 h), with a greater percentage of Hofmann product formed (95:5).[4]

Carbonyl Transformations.

Saponification of esters can be carried out either in solution[5] or under solvent-free conditions.[6] In the latter case, isolated yields of acids from hindered esters were comparable or better than other methods (eq 1). Similarly, ester formation may be carried out without solvent, but ***Potassium Carbonate*** is preferable to ***Potassium Hydroxide*** as saponification does not occur.

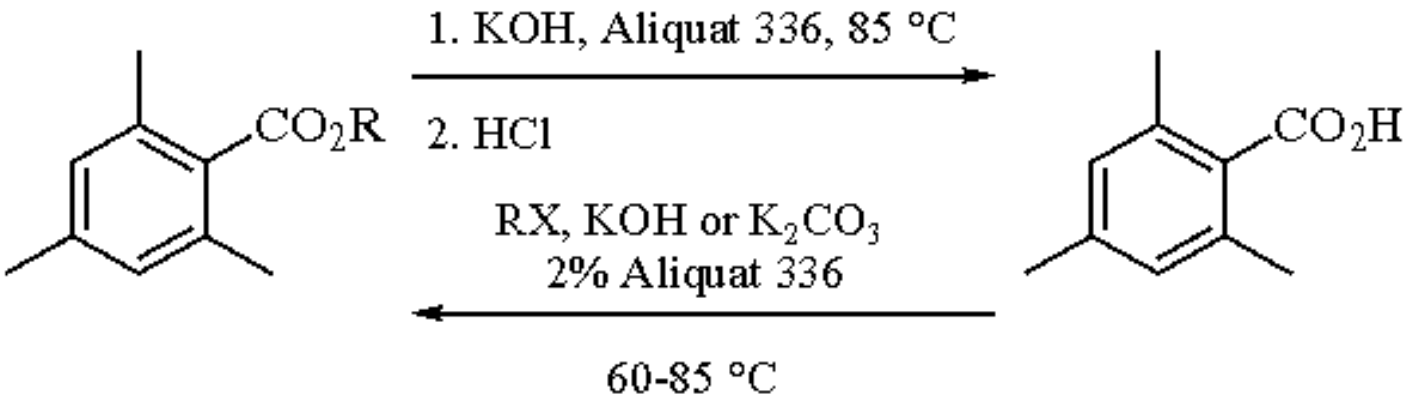

(1)

Alkylations.

At Heteroatoms.

Methyltrioctylammonium chloride (**1**) has been used to effect phase transfer alkylation of phenols,[7] alcohols,[8] and thiols.[9] Care must be taken in solvent choice, as the use of dichloromethane can give rise, under basic conditions, to the formation of acetals (eq 2)[10] or thioacetals[7] in excellent yields (90 +%).

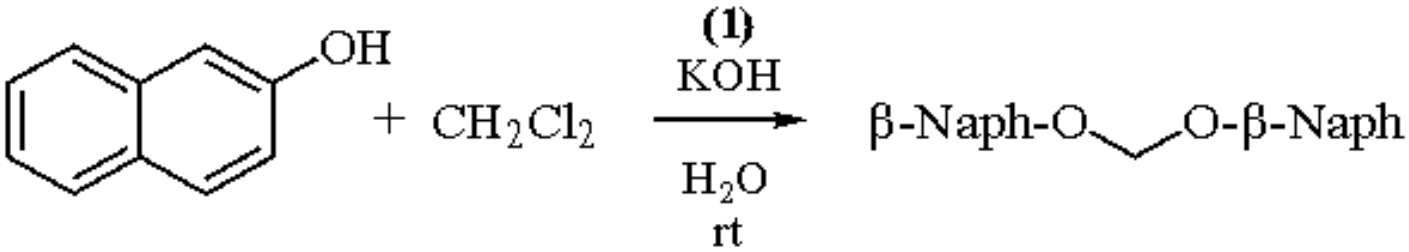

(2)

The reaction may be carried out intramolecularly for the preparation of oxetanes[1a] or β-lactams.[11]

At Carbon.

Substrates bearing acidic protons may be alkylated under phase transfer catalysis (PTC) conditions. For example, cyclopropane-1,1-dicarboxylates have been prepared in 75-91% yields using 1,2-dichloroethane (eq 3).[12] Although catalytic water is necessary for the reaction to proceed, large amounts reduce yields. Reactions carried out under solid/liquid phase transfer conditions suffer less from side reactions such as product saponification than those using aqueous solutions of base. For similar reasons, K_2CO_3 is preferred over KOH in the reaction. Alternatively, if cyclopropanecarboxylic acid products are desired, saponification may be carried out in situ.[13]

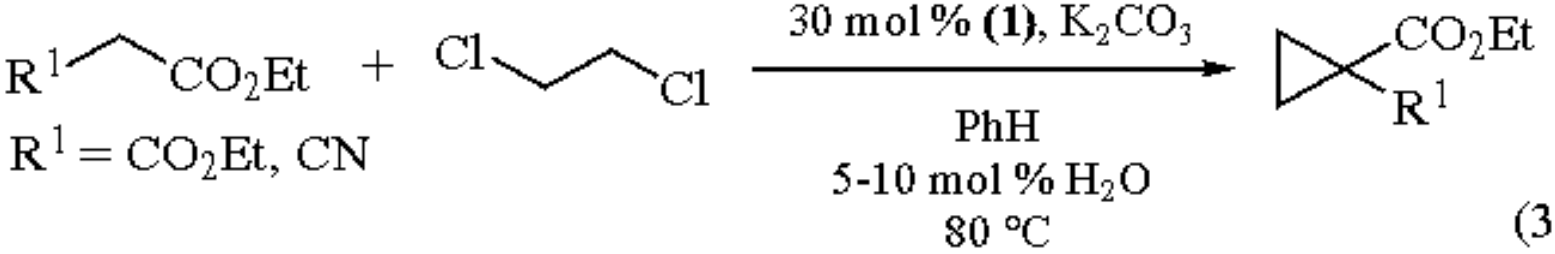

(3)

Alkynes can be deprotonated under PTC conditions (eq 4), and the resulting anions can be trapped.[14] Simple ketones may be alkylated by the combination of (**1**) and potassium hydroxide (eq 5),[15] and α-protons can be exchanged for deuterium in the presence of NaOD/D_2O.[16] Preparation of hydroxycyclopentenones was carried out by the reaction of (**1**) with a keto aldehyde in the presence of ***Lithium Hydroxide*** (eq 6).[17]

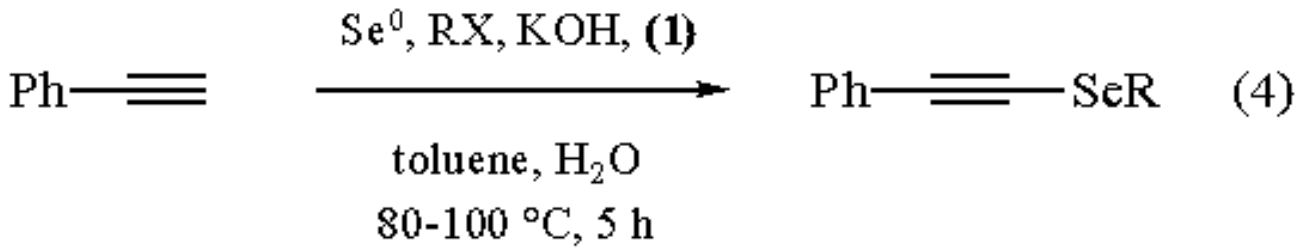

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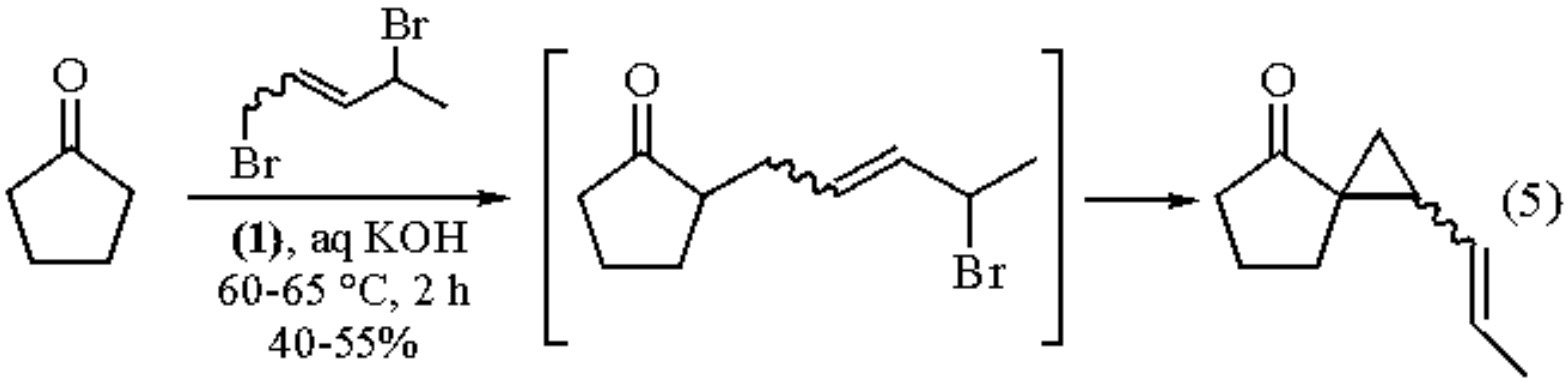

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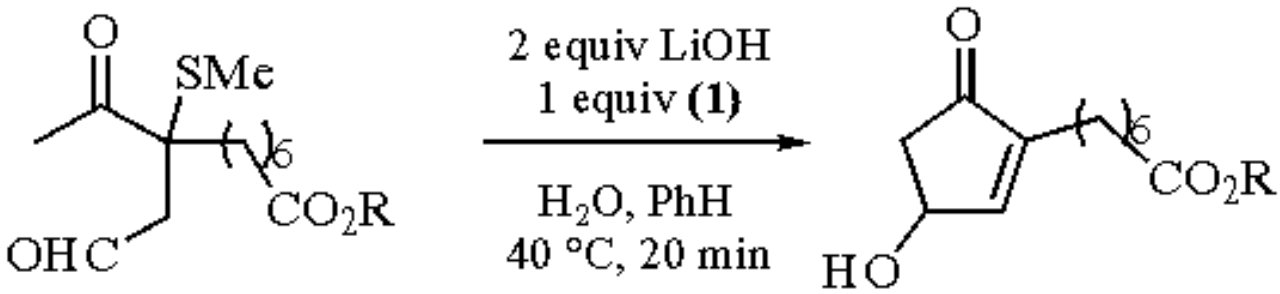

(6)

Carbene Chemistry.

Preparation of dichlorocarbene under phase transfer conditions is well known;[1c] (**1**) is an effective catalyst for the formation of this reactive species,[15] as exemplified in eq 7.[18]

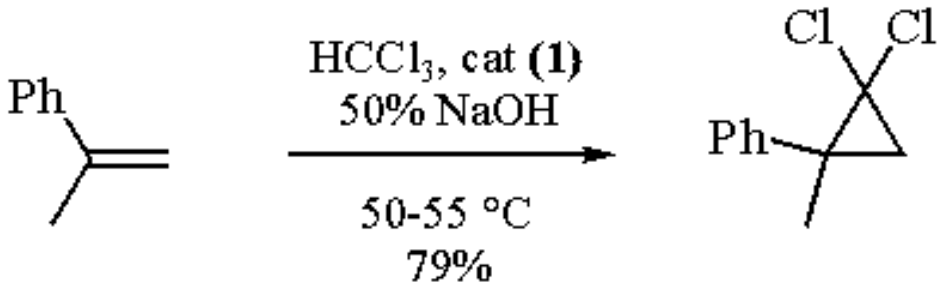

(7)

Miscellaneous.

The Ramberg-Bäcklund reaction of α-halo sulfones has been catalyzed by (**1**) and 10% NaOH solution in excellent yields. A single-pot reaction sequence in which a sulfone is halogenated and rearranged was also described (eq 8).[19]

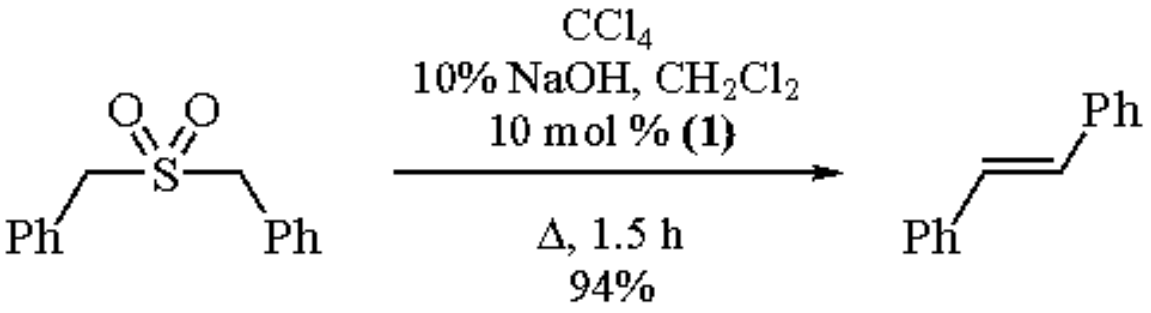

(8)

An improved method of α-diazocarbonyl preparation was reported using (**1**).[20] The method typically produces diazo compounds of high purity, free from starting material and in excellent yield (eq 9).

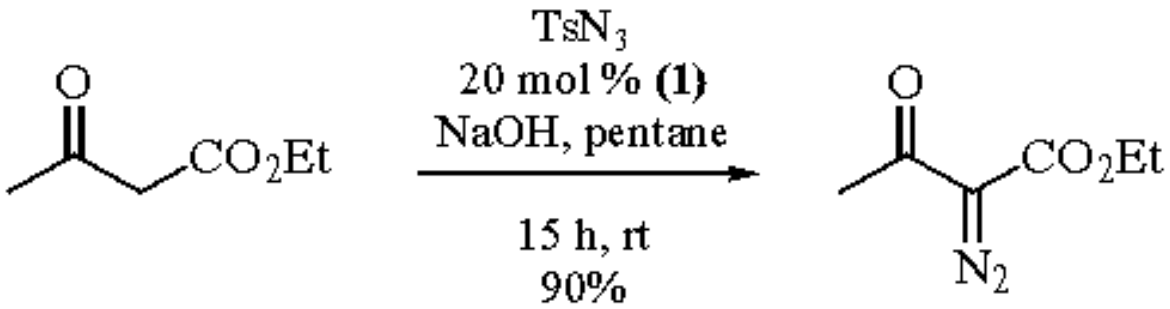

(9)

Related Reagents.

See the entries for benzyltriethylammonium, benzyltrimethylammonium, tetrabutylammonium, tetraethylammonium, and tetramethylammonium salts.

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Methyltriphenoxyphosphonium Iodide[1]

$(PhO)_3$+PMe I^-

[17579-99-6] · $C_{19}H_{18}IO_3P$ · Methyltriphenoxyphosphonium Iodide · (MW 452.24)

(reagent for selective conversion of alcohols to alkyl iodides;[4c,13c] effects dehydration of alcohols[14a] and dehydrohalogenation of alkyl halides[15a] to alkenes; deoxygenates epoxides to alkenes[17])

Alternate Names: MTPI; triphenyl phosphite methiodide; triphenoxy(methyl)phosphonium iodide.

Physical Data: mp 146 °C.

Solubility: sol CH_2Cl_2, DMF, MeCN, THF, HMPA, DMI (1,3-dimethyl-2-imidazolidinone); sl sol PhH.

Form Supplied in: amber to white crystals; commercially available; purity >95%; typical impurity: $MeP(O)(OPh)_2$ (see analytic data below).

Analysis of Reagent Purity: IR (film): 1600, 1500 (Ph), 1160, 980 (P-O-C), 770, 690 (Ph); ^{1}H NMR ($CDCl_3$): 3.1 (d, 3H, $J_{P,H\alpha}$ = 16.5 Hz, Me), 7.45 (m, 15H, OPh). ^{31}P NMR ($CHCl_3$): +41 ± 1 (q). $MeP(O)(OPh)_3$: ^{1}H NMR ($CDCl_3$): 1.8 (d, $J_{P,H\alpha}$ = 18 Hz, Me), 7.2 (m, OPh); ^{31}P NMR ($CHCl_3$): +24 ± 1 (q).

Preparative Methods: further improvements[13c] have been introduced to the original preparation.[4c]

Purification: commercial or synthesized material can, if necessary, be purified by washing with EtOAc or by repetitive (×3) precipitation of the reagent from a CH_2Cl_2 or MeCN solution with ether; the almost colorless solid so obtained is filtered and dried in vacuo.

Handling, Storage, and Precautions: harmful material which may cause irritation; should be handled under N_2 in a dry box; keep container closed; light and moisture sensitive; store in the dark, under N_2 in a cool dry place; avoid breathing dust and contact with eyes, skin, and clothing; incompatibility: strong oxidizing agent.

Introduction.

First described at the beginning of the century[2] the adduct of ***Triphenyl Phosphite*** and ***Iodomethane*** was further developed for use in synthesis 50 years later[4] and has been widely used since that time. Stable in the absence of

moisture, the oxyphosphonium salt MTPI behaves unlike the alkyloxyphosphonium halide analogs; these latter reagents undergo nucleophilic displacement with their own counterions, unless very bulky substituents are involved,[3b] via the Michaelis-Arbuzov reaction. The stability of MTPI arises from the inability of the phenyl group to suffer nucleophilic substitution. ^{31}P NMR data[3] clearly suggest the ionic tetracovalent nature of phosphorus in MTPI.

Preparation of Alkyl Iodides.

In 1951 it was reported[4a] that the Michaelis' salt MTPI reacts with alcohols to form alkyl iodides with release of PhOH and $MeP(O)(OPh)_2$. The reaction appears to involve initial displacement of a phenoxy group by the hydroxyl group of the alcohol, followed by nucleophilic S_N2 substitution to give the iodide (eq 1).

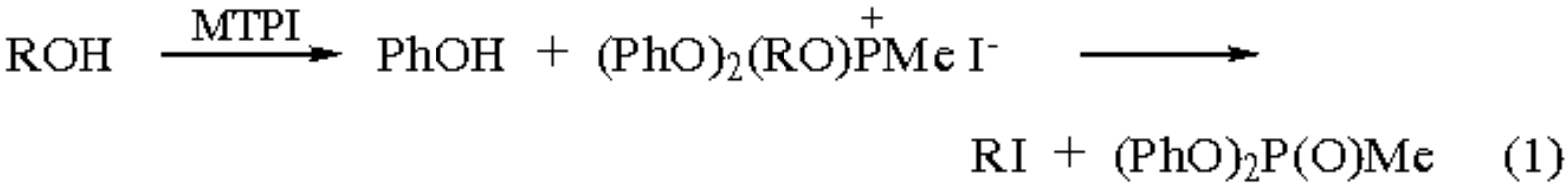

The MTPI reagent has been used to convert alcoholic hydroxyl groups into iodides in saturated and unsaturated aliphatic compounds (eq 2),[4-9] carbohydrates,[10,11] and nucleosides.[13]

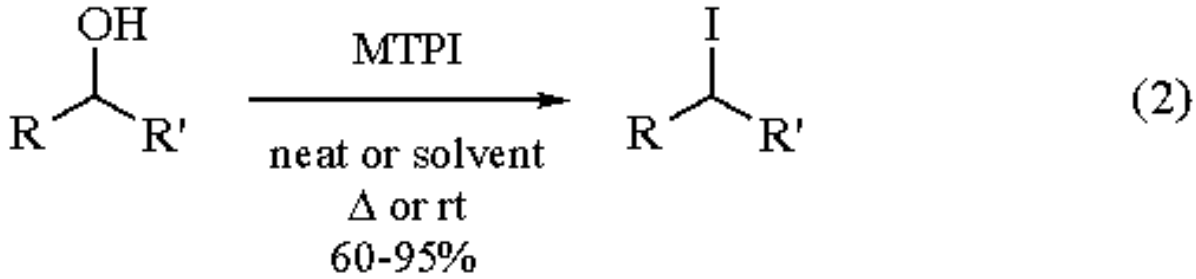

A one-pot procedure involving in situ generation of MTPI from $(PhO)_3P$ and MeI through prolonged heating is generally convenient for reactions of saturated primary and sterically hindered alcohols.[5,6] A two-step procedure[6] using isolated MTPI and milder conditions is preferred for sensitive alcohols and in cases where elimination is expected, such as with all tertiary and many secondary alcohols. Both of these original procedures were conducted without solvent. Subsequent improvements include the use of polar solvents like DMF, which appear to promote the iodination reaction and allows it to proceed at rt in most cases.[13c]

Some carbon skeletal rearrangement is observed with highly hindered alcohols: *t*-pentyl iodide (6%) is formed in the conversion of neopentyl alcohol to neopentyl iodide;[5] steroidal neopentyl alcohols undergo rearrangement followed by an elimination reaction.[8]

MTPI has been used for the synthesis[9] of iodoallenes and iodoalkynes via S_N2' and S_N2 reactions; thus the primary alkynic alcohol prop-2-ynol gives either mainly iodoallene in DMF or mainly the iodoalkyne in CH_2Cl_2 (eq 3).[9a]

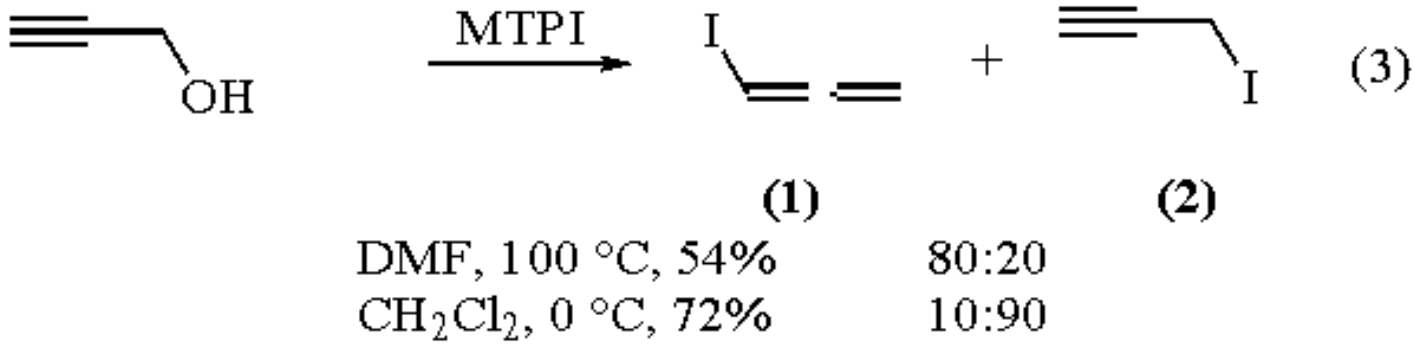

In the carbohydrate field, MTPI provides iodides from primary[10] and secondary alcohols.[10a,b,11] The latter alcohols generally give iodides with inverted configuration by S_N2 reaction, but sometimes isomeric mixtures (resulting from isomerization by iodide ion) are obtained.[11c,d] Some structural rearrangements involving the participation of hydroxyl protecting groups are reported to occur in the preparation of iodides[11a-d] from hindered secondary alcohols; however, this work was later partly questioned in light of subsequent results.[12]

In the sugar moiety of nucleosides the primary 5´-hydroxyl group is converted into iodide[13a-f] in high yield with MTPI, and the reaction can exhibit primary/secondary selectivity (eq 4).[13c] In some cases, with more polar solvents or in presence of an external base, cyclic *N* or *O*,5´-anhydro derivatives, resulting from the attack of the base moiety on the 5´-oxyphosphonium or 5´-iodide intermediate, are obtained.[13c-e,g].

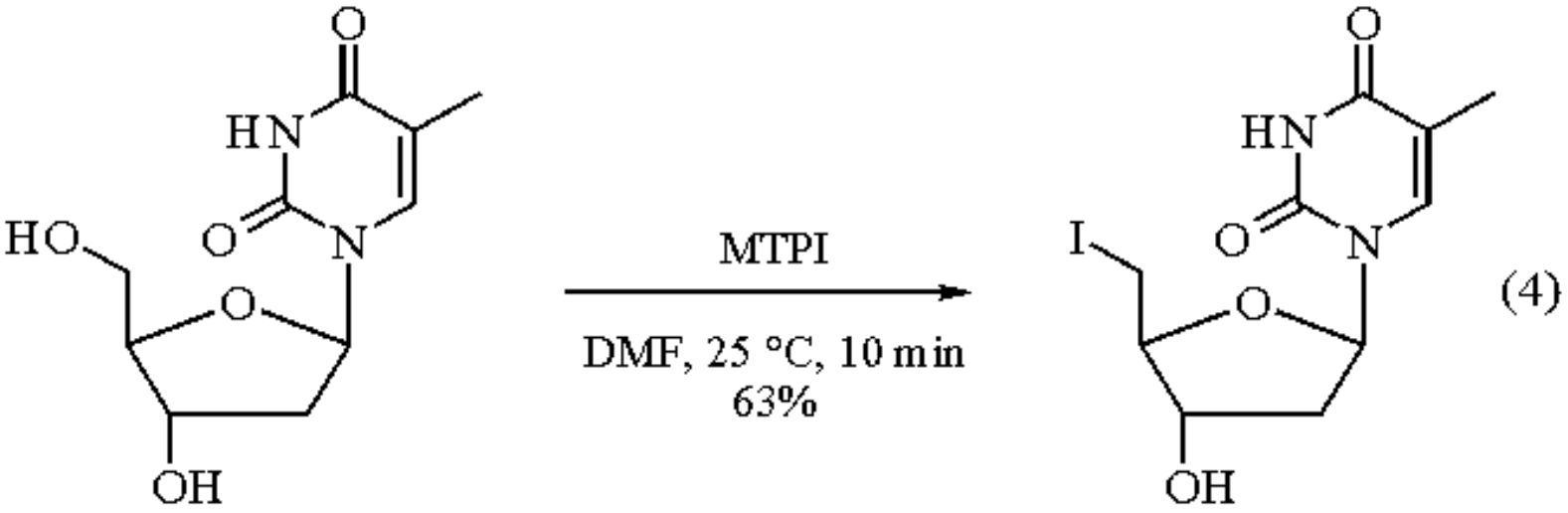

Such cyclic anhydro intermediates, isolated under other reaction conditions, explains the retention of configuration by double inversion observed in the substitution reactions of secondary 2´- or 3´-hydroxyl groups (eq 5).[13c,h]

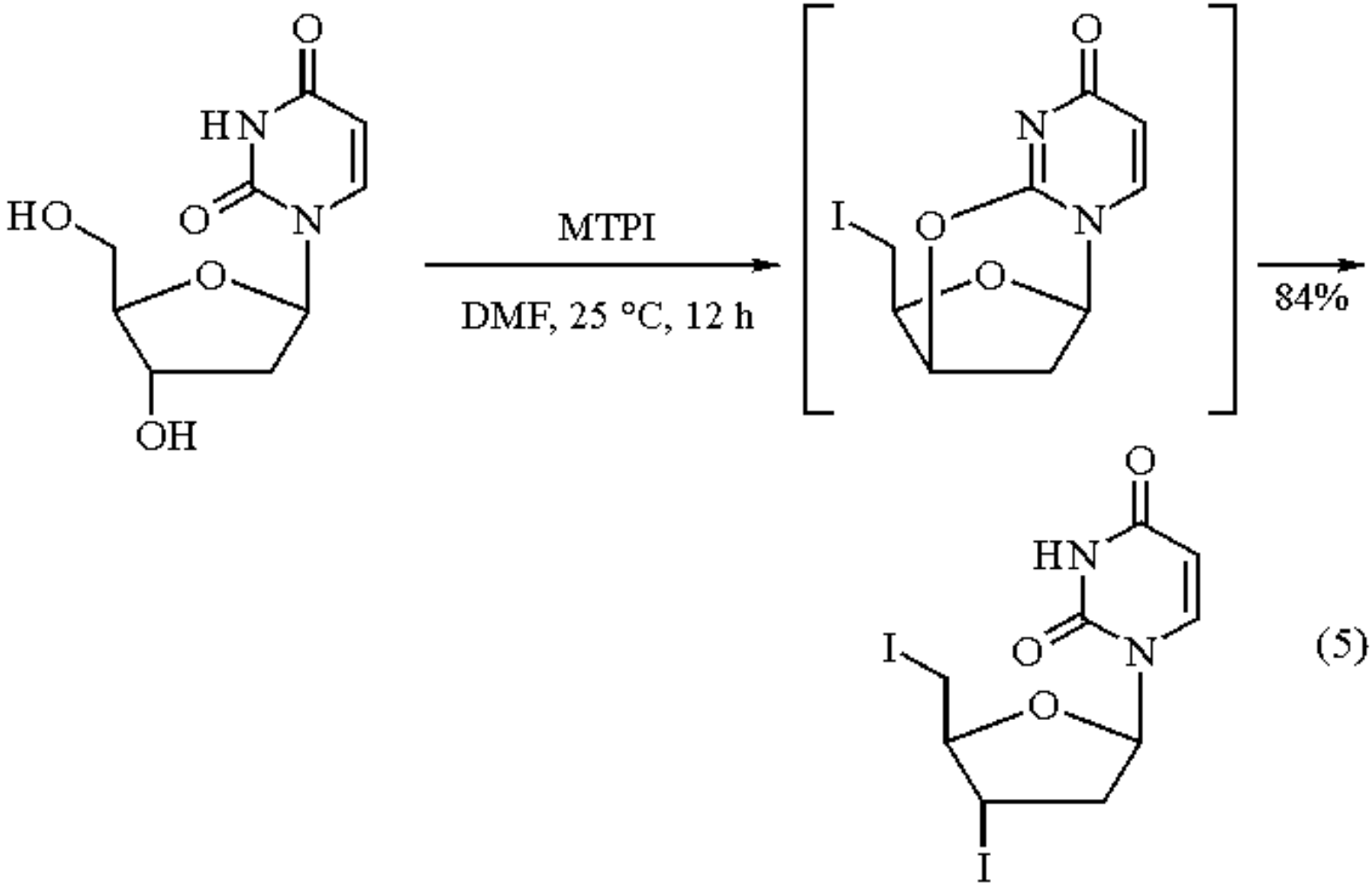

(5)

Reaction of MTPI with *cis*-vicinal glycols, such as nucleosides with secondary 2´- and 3´-hydroxy groups, provides phosphorane intermediates that yield a mixture of 2´- and 3´-phosphonates[13c,h] on hydrolysis. Linear γ-diols can be cyclized by dehydration with MTPI to give *C*-glycoside precursors.[13i]

Alternative agents which convert various kinds of alcohols into iodides with good results include the ***Triphenylphosphine***-additive reagent systems: I_2,[13f] CI_4,[18] triiodoimidazole,[12] NIS, etc.

Alcohol Dehydration and Alkyl Halide Dehydrohalogenation.

MTPI in HMPA at 75 °C selectively dehydrates secondary alcohols under mild conditions,[14a-d] leading predominantly to the more stable Saytzeff alkene with various (*E*/*Z*) stereoselectivity.[14a,c] Tertiary alcohols are unaffected under these conditions.

In eq 6, virtually stereospecific dehydration to the (*E*)-alkene is accompanied by transformation of the pyranyl ether group to the iodide, in high yield.[14c]

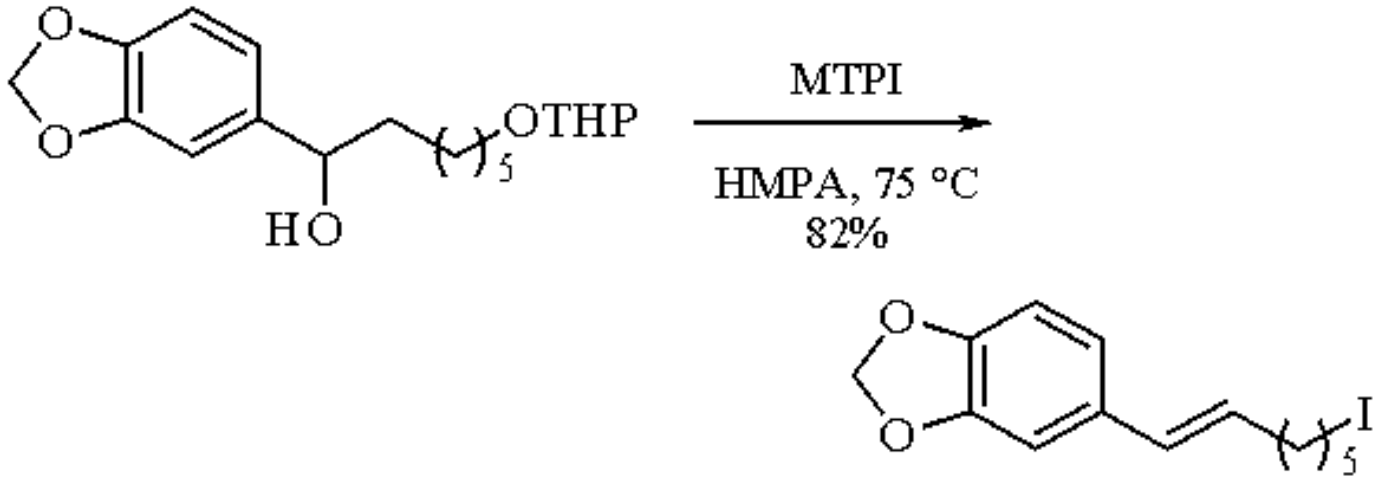

(6)

Conjugated polyenes are formed, either by dehydration of unsaturated alcohols or by dehydrohalogenation of the corresponding bromides, with MTPI in aprotic solvents such as HMPA[15a,b] and DMI.[15c] The suggested mechanism for this transformation involves initial conversion of the alcohol into the iodide with inversion, followed by dehydrohalogenation by either iodide ion or HMPA.

In a special case, leading to the formation of conjugated exocyclic double bond, primary alcohols undergo dehydration with MTPI in DMF under unusually mild conditions. This reaction provides a good method for α-methylenation of γ-butyrolactones.[16]

Deoxygenation of Epoxides to Alkenes.

In combination with ***Boron Trifluoride Etherate***, MTPI converts epoxides into alkenes in 75-99% yields,[17] via *syn* elimination and with retention of stereochemistry. The reaction is conducted at rt in MeCN-C_6H_6 mixtures as solvent. An excess of both MTPI (10 molar equiv) and BF_3 etherate (1-3 molar equiv) are generally required for satisfactory yields. This method compares favorably with another procedure using a ***Potassium Iodide***-crown ether reagent system.

A modification of the MTPI reagent involves the use of ***Methyl Trifluoromethanesulfonate*** (methyl triflate) in place of MeI, thus providing the nonnucleophilic anion $CF_3SO_3^-$ instead of iodide.[19] Treatment of aliphatic alcohols with $MeP(OPh)_3^+$ TfO^- leads to symmetrical dialkyl ethers, whereas alkyl phenyl ethers are formed with sodium alcoholates.[19b]

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Methyltriphenylphosphonium Bromide[1]

Ph_3+PMe Br^-

[1779-49-3] · $C_{19}H_{18}BrP$ · Methyltriphenylphosphonium Bromide · (MW 357.24)

(forms methylenetriphenylphosphorane upon treatment with butyllithium,[2] sodamide,[3] dimsylsodium,[4] or potassium *t*-butoxide;[5] also used as a phase-transfer catalyst[6])

Physical Data: mp 234-235 °C.

Solubility: sol alcohols, DMSO; insol Et_2O, THF, benzene, toluene, hexane.

Form Supplied in: white solid; widely available. *Drying:* when used to prepare methylenetriphenylphosphorane, methyltriphenylphosphonium bromide must be strictly dried immediately prior to use for best results. Drying can be achieved effectively by heating the flask containing the phosphonium salt at 110 °C/0.2 mmHg for several hours, or by repetitive (three times or more) azeotropic removal of water with benzene or toluene.

Preparation of Methylenetriphenylphosphorane.

Methyltriphenylphosphonium bromide can be readily deprotonated with a strong base to give the corresponding methylide (eq 1),[2-5,7,8] the most versatile reagent for Wittig methylenation (see also ***Methylenetriphenylphosphorane***). ***n-Butyllithium*** is the most widely preferred base because of its ready availability. The solvents chosen in this case are invariably Et_2O,[2a,b] THF,[2c,d] or DME.[2e] A typical procedure involves suspension of the dry phosphonium salt in THF and subsequent addition of 1 equiv of 1.6 M solution of butyllithium in hexane at rt followed by stirring at rt for 3 h.[2c] Other lithium bases, although less frequently used, include ***Phenyllithium***, ***Methyllithium***, and ***Lithium Diisopropylamide***.[7]

$$Ph_3\overset{+}{P}-Me\ Br^- \xrightarrow[\text{solvent}]{\text{base}} Ph_3P{=}CH_2 \qquad (1)$$

Sodium Amide[3] is generally used to produce a salt-free ylide. The ylide is generated by stirring a mixture of methyltriphenylphosphonium bromide and $NaNH_2$ in anhydrous liquid ammonia.[2d,3a] Upon completion, ammonia is allowed to evaporate, a dry solvent (Et_2O, THF, or toluene) is added, and the resultant ylide solution is now ready to use. $NaNH_2$ in refluxing THF also can be used instead of liquid ammonia.[3b,c] Dimsylsodium (***Sodium***

Methylsulfinylmethylide) is also widely used to provide the ylide.[4] The required dimsylsodium solution is prepared by stirring a mixture of NaH in dry DMSO at 75-80 °C for ca. 45 min. The resultant solution is cooled to rt followed by addition of methyltriphenylphosphonium bromide in DMSO. In some applications the base used is ***Potassium t-Butoxide***.[5] The reaction is usually run in THF or benzene at rt. Potassium *t*-pentylate is also used occasionally.[8]

Phase-Transfer Catalysis.

Due to the higher thermal stability of phosphonium salts as compared to that of ammonium salts, methyltriphenylphosphonium bromide has been used as a phase-transfer catalyst in a number of reactions.[6] 4,4´-Biphenyldicarboxylic acid has been efficiently converted to the corresponding diacid dichloride with ***Thionyl Chloride*** in the presence of a catalytic amount of methyltriphenylphosphonium bromide (eq 2).[6a] Likewise, the yields of thiocyanatoalkyl methacrylic esters have been increased under phase-transfer conditions (eq 3).[6b] In most cases, however, ammonium salts exhibit far better phase-transfer catalytic activities than phosphonium salts.[6c]

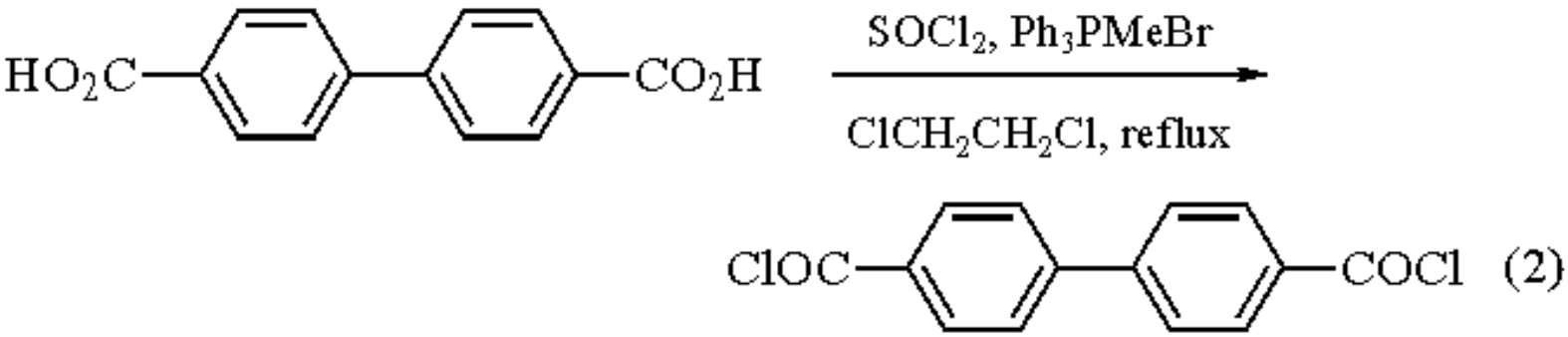

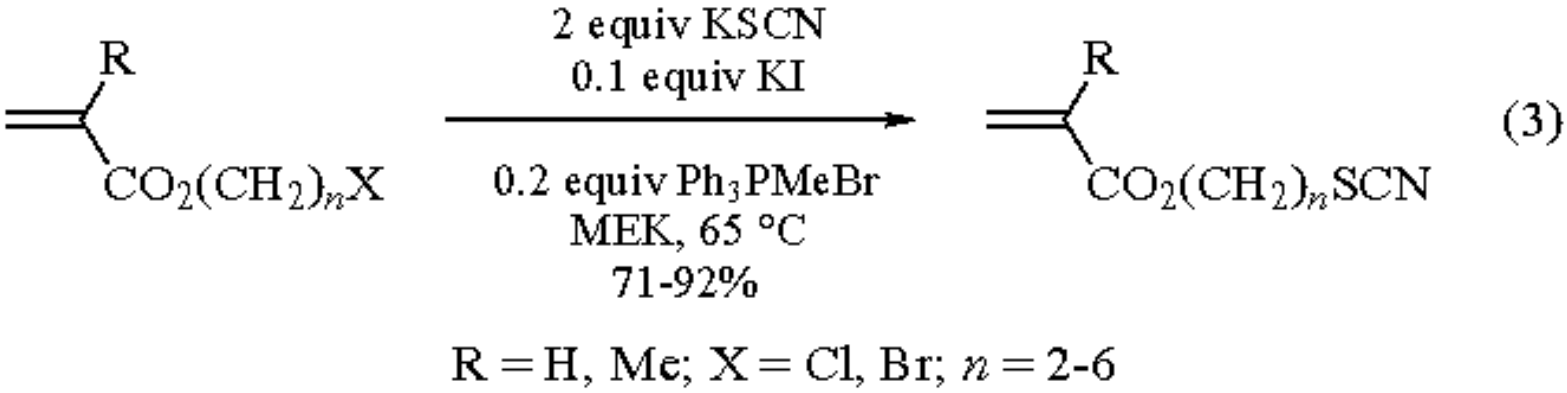

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Methyltriphenylphosphonium Permanganate

Ph_3+PMe MnO_4^-

[73335-41-8] · $C_{19}H_{18}MnO_4P$ · Methyltriphenylphosphonium Permanganate · (MW 396.28)

(oxidant, useful for the conversion of alkenes into *cis*-diols[1])

Physical Data: purple solid; decomposes at 102 °C.[2]

Solubility: 1.17 × 10^{-3} M in H_2O; 1.15 M in CH_2Cl_2; 0.941 M in $CHCl_3$; insol toluene, carbon tetrachloride.[2]

Analysis of Reagent Purity: ε = 2530 ± 30 L mol^{-1} cm^{-1} at 526 nm.[2] IR (KBr) 3420, 3050, 2980, 2890, 1585, 1485, 1435, 1120, 905, 750, 725, and 695 cm^{-1};[3] ^1H NMR (CD_2Cl_2) δ 7.80 and 2.80 ppm.[2]

Preparative Method: ***Potassium Permanganate*** (3.07 g, dissolved in a minimum of H_2O) is added dropwise to ***Methyltriphenylphosphonium Bromide*** (4.63 g in 100 mL of H_2O) with stirring. The purple precipitate is collected, washed with water, dried over P_2O_5, and recrystallized from a solution of CH_2Cl_2 and toluene (2:1, v/v). The yield is 70-75%.[3]

Handling, Storage, and Precautions: oxidant; small quantities may be stored in glass vessels at or below rt. Similar compounds have been known to undergo violent thermal decompositions.[4] Always work behind a protective shield.

cis-Dihydroxylation of Alkenes.

Methyltriphenylphosphonium permanganate has been used to dihydroxylate alkenes using CH_2Cl_2 as the solvent.[1] The reaction is easy to carry out and good yields are observed. Several examples are shown in

eqs 1-3.

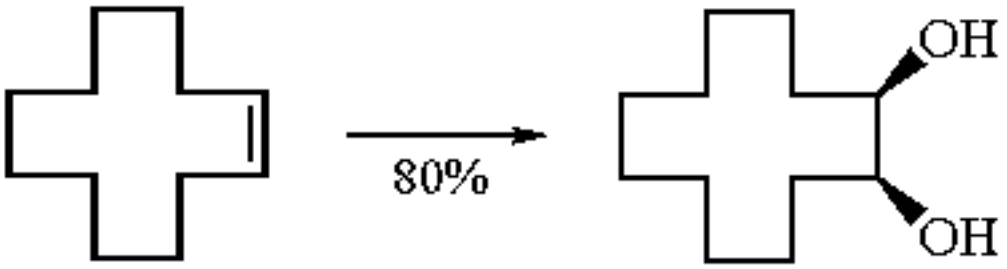

(1)

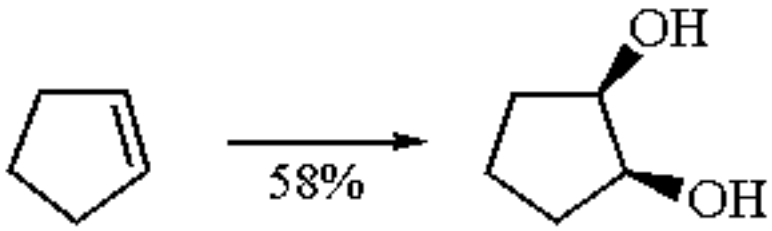

(2)

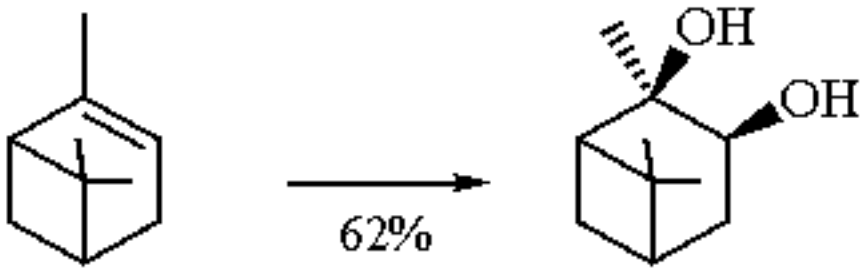

(3)

The reactions of methyltriphenylphosphonium permanganate are very similar to those of quaternary ammonium permanganates such as ***Tetra-n-butylammonium Permanganate*** and ***Benzyltriethylammonium Permanganate***. Similar reactions may also be carried out more simply by use of phase transfer processes that are described under ***Potassium Permanganate***.

---

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Methyl Vinyl Ketone[1]

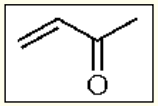

[78-94-4] · C_4H_6O · Methyl Vinyl Ketone · (MW 70.10) (enol)

[59120-04-6]

(reagent for attachment of 3-oxobutyl side chains, i.e. Michael additions;[2] reagent for the annulation of cyclohexenones[3])

Alternate Names: MVK; 3-buten-2-one.

Physical Data: fp -6 °C; bp 81.4 °C, 36.5-36.8 °C/145 mmHg, 33-34 °C/130 mmHg, 32-34 °C/60 mmHg; *d* (20 °C) 0.8636 g cm^{-3}, (25 °C) 0.8407 g cm^{-3}; *n*20D 1.4086; liquid with pungent odor.

Solubility: sol water, methanol, ethanol, ether, acetone, glacial acetic acid; slightly sol hydrocarbons; forms binary azeotrope with water, bp 75 °C (12% water).

Form Supplied in: clear liquid stabilized with 0.1% acetic acid and 0.05% or 1% hydroquinone.

Handling, Storage, and Precautions: should be kept cold. Polymerizes upon standing in the pure form. Readily absorbed through skin; lachrymator; highly toxic and flammable. For best results, dry over K_2CO_3 and freshly distill at reduced pressure. Use in a fume hood.

Introduction.

As a synthetic reagent, methyl vinyl ketone is commonly viewed as a 3-oxobutyl synthon which undergoes predominantly 1,4 conjugate addition (Michael addition) resulting in the attachment of a 3-ketoalkyl side chain. The resulting products are often poised for a subsequent cyclization step, thus resulting in a cyclohexenone derivative; this tandem is the well-known Robinson annulation.[4] In most cases, MVK is the electrophilic partner, but there are a few important nucleophilic (umpolung) derivatives of MVK which also are useful for accomplishing ring construction (see below). MVK itself is particularly susceptible to anionic polymerization, which limited its early use under basic conditions; however, it should be noted that MVK will polymerize under certain acidic and radical conditions as well.[5] The many efforts to improve the Robinson ring synthesis have led to monumental synthetic advances with respect to both nucleophilic reactants and MVK synthetic equivalents (3-oxobutyl synthons).

Aside from inducing the anionic polymerization of MVK, enolates as nucleophilic partners in alkylations are limited by *O*- vs. *C*-alkylation, mono- vs. polyalkylation, rapid proton transfer, and by the ability to control the regioselectivity of their generation. These problems have found solutions through the development of trimethylsilyl enol ethers,[6] in the utilization of enamine chemistry,[7] and by employing metalloenamines (imine anions).[8] With each of these developments in the nucleophilic partner, improvements in MVK alkylation have resulted in a greatly expanded use of the reagent. Nevertheless, a number of MVK synthetic equivalents have been successfully developed and are briefly reviewed in Table 1. Note that in this context, MVK equivalent is defined as any reagent which contains all four carbon atoms; also the 3´-oxo functionality is in place or is one transformation away.

Table 1 Methyl Vinyl Ketone Synthetic Equivalents (3'-Oxobutyl Synthons)

Alkylating agents and Michael acceptors	Conditions to regenerate ketone	Nucleophilic agents (umpolung type)	Conditions to regenerate ketone
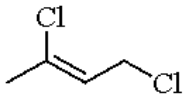 **(1)**	H_2SO_4 (conc.) or $Hg(OAc)_2$, AcOH	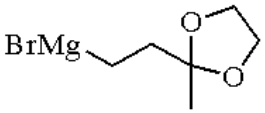 **(8)**	1 N HCl, rt

TMS

Methyl Vinyl Ketone

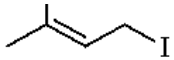

(2)

m-CPBA

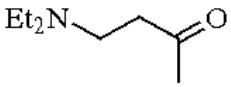

(3)

None

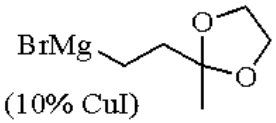

(9)

1 N HCl, rt

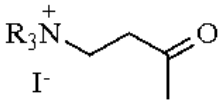

(4)

None

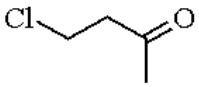

(5)

None

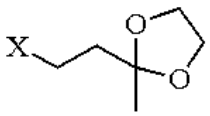

(6) X = Br, I, OTs

1 N HCl, rt

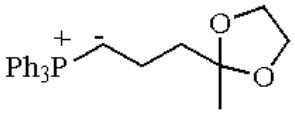

(10)

1 N HCl, rt

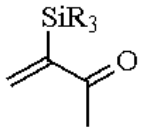

(7) R = Me, Et

NaOMe, MeOH

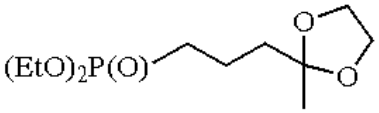

(11)

1 N HCl, rt

Methyl Vinyl Ketone versus its Synthetic Equivalents (as Alkylating Agents).

Primarily to circumvent the polymerization problem, numerous MVK synthetic equivalents have been developed, and these reagents should also be explored as possible sources of the 3-oxobutyl synthon. However, each reagent is handicapped by the fact that there are additional synthetic steps involved in its preparation, and the newly alkylated adduct often must be transformed into the 3-oxobutyl side chain. It should be noted that the manipulation of the side chain to arrive at the keto side chain may require harsh conditions not compatible with the other functional groups present in the molecule.

One of the first reagents developed as an MVK equivalent was ***1,3-Dichloro-2-butene*** (**1**) (the Wichterle reagent).[9] Relative to MVK, it is generally regarded as a superior alkylating agent, but the stringent hydrolytic conditions for conversion of the vinyl chloride to its corresponding ketone limits its application. An excellent alternative reagent of the same type (i.e. allylic halides) is the iodovinylsilane (**2**).[10] The use of this reagent leads to high yields of alkylated adducts, and the subsequent conversion of the alkylated vinylsilanes to their corresponding ketones is achieved by oxidative rearrangement with ***m-Chloroperbenzoic Acid***. These vinylsilanes can be used with enolates and enamines alike.

Robinson himself recognized that MVK polymerization was compromising the efficiency of the annulation protocol and developed the first in a series of compounds which serve as precursors to MVK. The synthetic equivalents (**3**),[11] (**4**),[12] and (**5**)[13] are characterized by β-elimination to generate MVK in situ, but often the results are still not satisfactory (albeit improved) over the use of MVK itself. The principal problems involve poor yields and polyalkylated adducts and, if the synthetic sequence is extended further, unusual cyclization products.

The strategy of carbonyl protection in MVK in order to retard base-catalyzed polymerization fostered interest in a group of β-halo acetals, mixed acetals, and thioacetals of the type (**6**). After alkylation with such reagents, the 3-oxo functionality can be easily regenerated under mildly acidic conditions. The haloacetals (**6**; X = Br, I)[14,15] are prepared in two steps by the conjugate addition of the halo acid to MVK followed by acetalization of the β-halo ketone. The corresponding tosylate (**6**; X = OTs)[16] has also been prepared by a similar, albeit longer, route. At first glance, these reagents would seem ideal for appending the 3-oxobutyl side chain, by alkylation followed by mild acidic deprotection of the carbonyl. Unfortunately, in most cases these reagents are poor alkylating agents. A notable exception is the general annulation procedure (eq 1) which employs imine anions (metalloenamines) as the nucleophilic partner and the bromo acetal (**6**; X = Br) as the MVK equivalent. The sequence commences with the Wadsworth-Emmons alkenation of ketones to afford 2-azadienes, which can be isolated at this point but are usually treated with ***n-Butyllithium*** to generate the highly reactive metalloenamine. The imine anions thus generated can be trapped with the bromoacetal (**6**; X = Br). Hydrolytic workup followed by aldol cyclization-dehydration completes the preparation of 4,4-disubstituted cyclohexenones in yields of 55-65% from the ketones.[17]

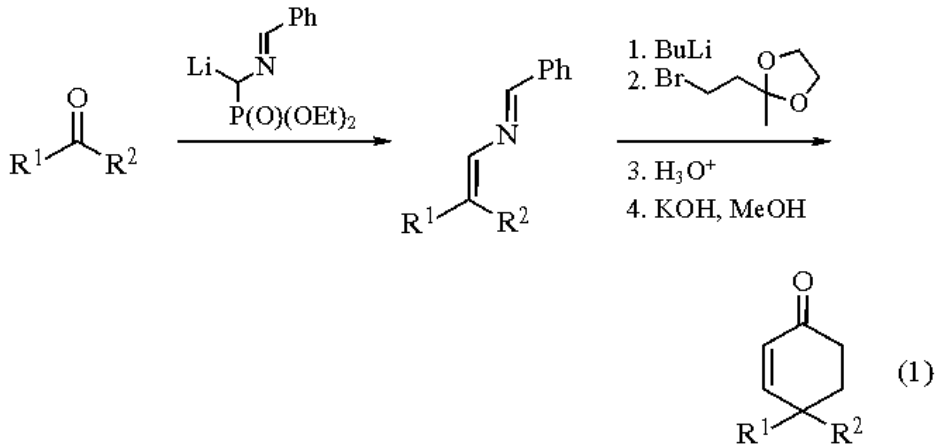

(1)

Another pair of MVK equivalents are the α-trialkylsilyl derivatives of MVK itself (**7**; R = Me, Et).[18,19] The trialkylsilyl group stabilizes the incipient negative charge after Michael addition and provides some steric bulk to impede polymerization. The silyl group can then be removed under basic conditions, usually those employed for a cyclization step. These MVK equivalents are especially important in that they allow effective Michael additions to vinyl ketones under aprotic conditions. The major disadvantage of these reagents is the multistep linear synthesis required for their preparation.

Methyl Vinyl Ketone versus its Synthetic Equivalents (Umpolung Reagents).

In those instances in which the 3-oxobutyl side chain is to be connected to pre-existing carbonyl (or other electrophilic) centers, several umpolung-type MVK equivalents have been developed. Although somewhat capricious in its stability, the Grignard reagent (**8**)[20] derived from the bromo acetal (**6**; X = Br) has been successfully employed in a number of synthetic applications. Particularly useful is the fact that the acetal moiety may be unmasked in the usual hydrolytic workup or carried on as an acetal for removal at a later stage in the synthesis.[21] Special mention should be made of the Grignard reagent's use in the presence of catalytic copper salts (**9**).[22] This technique allows for the conjugate addition of the acetal moiety to α,β-unsaturated ketones as well as the direct attachment of the side chain to less complex systems. The related homologous Wittig reagent (**10**)[23] was developed in the late 1960s and the Horner-Emmons variant (**11**) appeared shortly thereafter.[24] Both compounds have been employed as reacting partners with lactones, ultimately leading to cyclohexanone products via an intramolecular Wittig alkenation process.

1,4-Conjugate Additions (Michael Addition Reactions, Achiral).

There are numerous examples of the use of MVK in conjugate 1,4-addition reactions, i.e. the Michael reaction. Although most of these applications are framed in the context of an annulation procedure (e.g. the Robinson annulation), many of these reactions are worthy of discussion in their own right. The prototypical Michael addition of an enolate with MVK is, in fact, the first step of the Robinson annulation (eq 2).

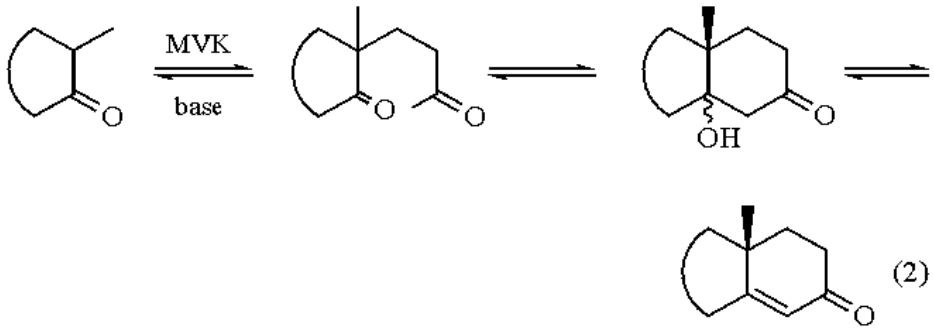

(2)

Under basic conditions (e.g. alkylation reactions employing enolates), MVK suffers a high degree of polymerization, leading to the development of the aforementioned MVK equivalents. However, there are derivatives of ketones which are particularly suitable for Michael addition reactions, most notably the silyl enol ethers.[25] The development of silyl enol ethers addressed the most serious problems encountered in the alkylations of enolates. Firstly, the reactions are conducted in aprotic media under

anhydrous conditions, thus avoiding proton transfer side reactions. Secondly, by judicious choice of the base used to generate the intermediate enolate, the regiochemistry of the alkylation can be controlled. However, the strongly basic conditions required for the regeneration of the enolates themselves preclude successful additions to MVK, resulting in the formation of polymer. Only recently have trimethylsilyl enol ethers been efficiently added to MVK with the assistance of Lewis acid catalysis (eqs 3 and 4).[26,27] The acidic conditions not only serve to activate MVK towards Michael addition, but assist in unmasking the enolate as well. These procedures are usually conducted under relatively mild aprotic conditions which also retard MVK polymerization.

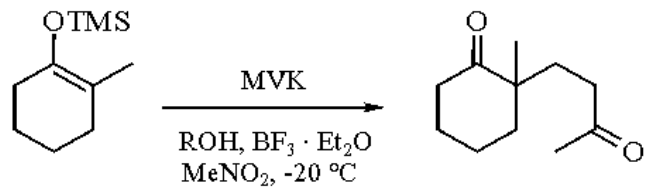

(3)

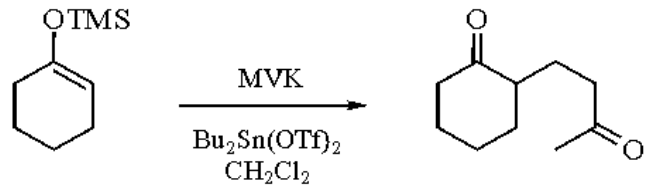

(4)

β-Keto esters, α-nitro ketones, and α-keto sulfones are but a few of the stabilized enolate derivatives which have been used successfully in efficient Michael additions to MVK. One of the most troublesome examples involving β-keto esters was the condensation of cyclohexanone methyl carboxylate with MVK under equilibrating conditions,[28] but this reaction has been developed into a viable synthetic procedure with the use of high pressure techniques under otherwise mild conditions (eq 5).[29]

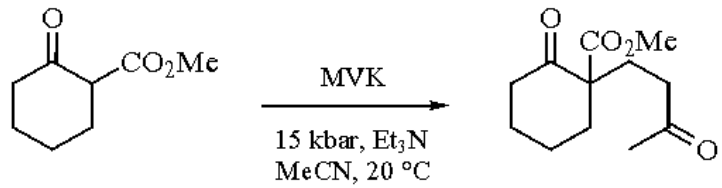

(5)

Another stabilized enolate family includes the α-nitro ketones; although the nitro group activates the formation of the enolate, it is usually necessary to remove it in a subsequent procedure (eq 6).[30] Nevertheless, the overall yields of the products are good.

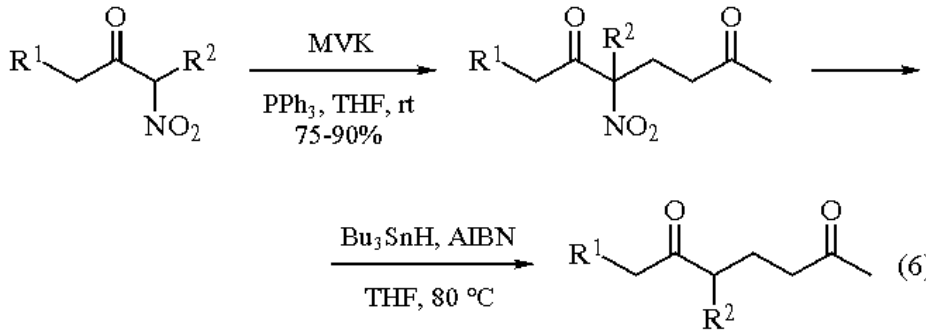

(6)

Simple nitro alkanes have recently been used in an exceptionally mild procedure for the attachment of the 3-oxobutyl side chain using MVK (eq 7). This protocol highlights the use of ***Alumina*** at room temperature for the conditions of the Michael addition, and the yields are good to moderate.[31]

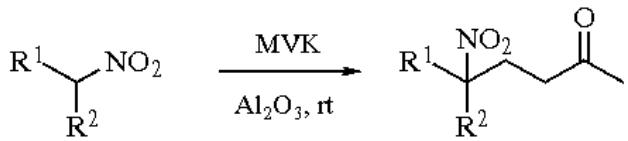

(7)

The Michael addition of α-cyanoamines to MVK (eq 8) has also been used for the preparation of 1,4-dione systems,[32] which are historically difficult to prepare.[33] The reaction occurs under mild conditions; however, the use of ***Hexamethylphosphoric Triamide*** as the solvent limits the scale and the widespread use of this procedure. In this sequence, acidic hydrolysis of the alkylated α-cyanoamine leads to the dione system.

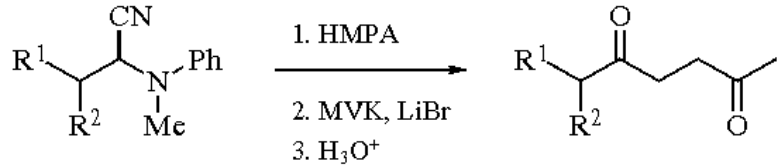

(8)

β-Methylthio allylic systems have also served as the nucleophilic partner in reactions with MVK (eq 9).[34] The procedure employs the hyperbasic media of the ***Lithium Diisopropylamide***/HMPA complex[35] and generates a quaternary carbon center in the product.

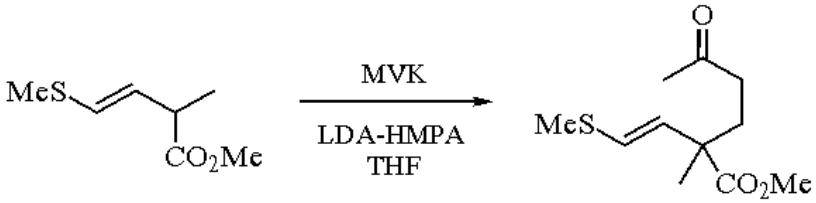

(9)

Recently, dithioenamines have emerged as useful synthetic intermediates in general alkylation methods.[36] In their Michael additions with MVK in the presence of Lewis acid catalysts, an intermediate iminium dithiane is generated which is somewhat sluggishly hydrolyzed; however, the overall yields of alkylated adducts are impressive (eq 10).[37]

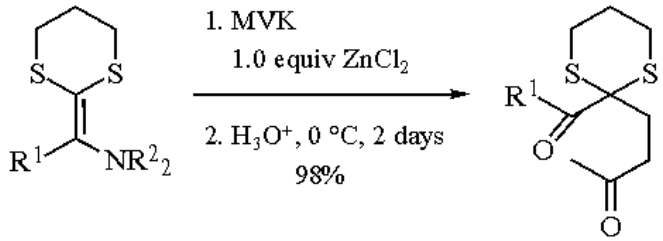

(10)

1,4-Conjugate Additions (Michael Addition Reactions, Chiral).

In recent years, perhaps the most significant development in synthetic organic chemistry has been the explosion in the field of asymmetric induction. As the reactive intermediates of the enolate, enamine, and imine anions were developed into their chiral counterparts, not only were standard alkylation reactions studied but also Michael additions to α,β-unsaturated systems. It is not surprising that the prototypical model studies involved MVK as the Michael acceptor. While most of these methods are used in asymmetric ring synthesis (see below), some examples terminate at the alkylation step with MVK. All of these methods feature the chiral auxiliary in the nucleophilic reagent. One of the earliest examples of asymmetric induction using MVK was developed by Yamada and utilizes chiral pyrrolidino enamines (eq 11).[38] Although the yields of the Michael additions are moderate and the asymmetric induction itself is not particularly impressive by today's standards, this methodology laid the groundwork for many improvements which were to follow. A notable advancement in chiral imine alkylations with MVK is found in the method of d'Angelo, in which the conjugate addition is catalyzed by ***Titanium(IV) Chloride*** (eq 12).[39] A particularly attractive feature of this method is that the chiral auxiliary, ***(S)-α-Methylbenzylamine***, is readily available, and the chemical yields are good with high asymmetric induction.

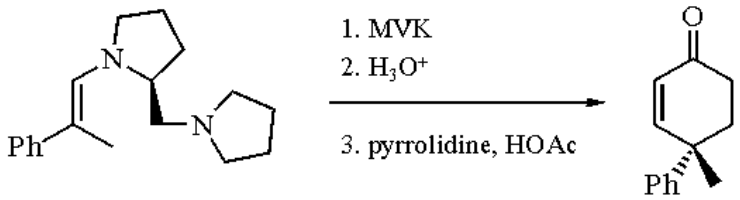

(11)

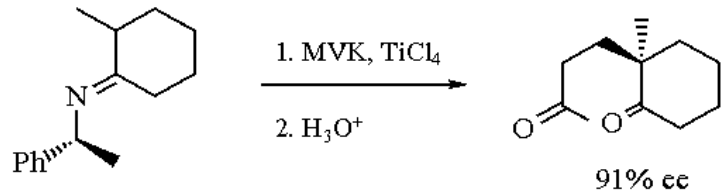

(12)

Another chiral enamine system which has been used with MVK takes advantage of the high nucleophilicity of imine anions (i.e. metalated enamines). In this method the intermediate enolate from the Michael addition is trapped as its TMS enol ether, which is subsequently hydrolyzed in the workup (eq 13).[40] The yields are fair and the asymmetric induction is effective.

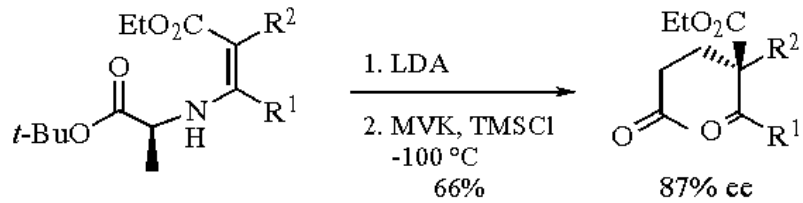

(13)

A chiral reagent within the family of Horner-Emmons phosphonates has been used with MVK, but the results were disappointing in that the major product was the dialkylated adduct (eq 14). In addition, preparations of these reagents are often multistep and tedious.[41]

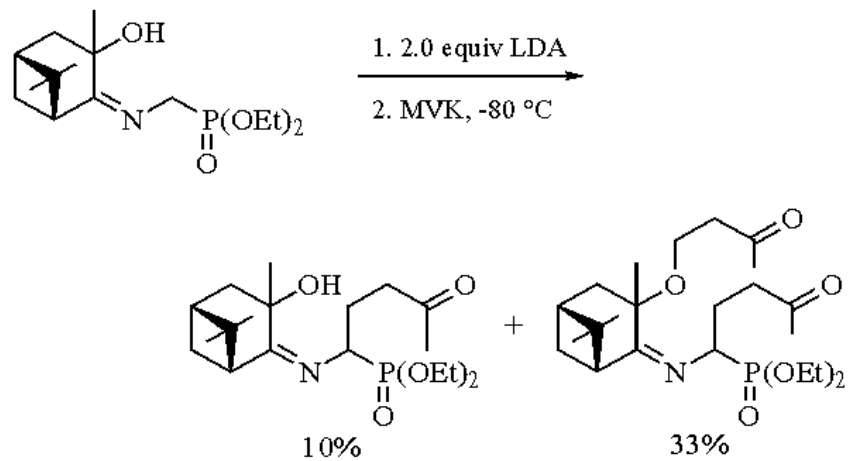

(14)

In a recent synthesis of (+)-*O*-methyljoubertiamine, Taber utilized very mild conditions for the addition of a chiral enolate to MVK in which the chiral auxiliary is the effective naphthyl camphor system (eq 15).[42]

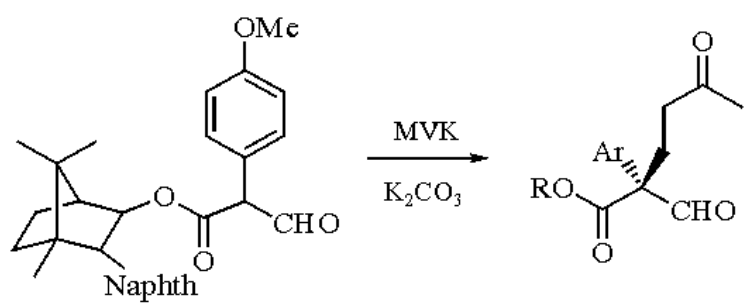

(15)

There are several polymer-based methods which induce some asymmetry to certain substrates. The degree of asymmetric induction is not particularly high (66% ee) and as yet does not appear to be very general. One such example is the cobalt-based diamine polymer which provides modest yields of the Michael adduct (eq 16).[43]

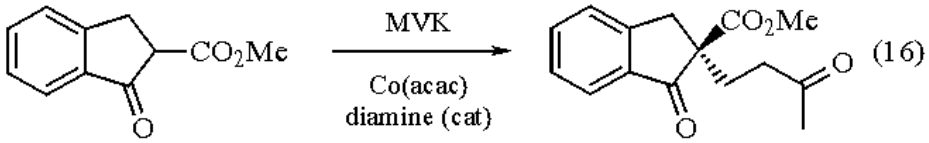

(16)

In terms of high yields and efficiency of asymmetric induction, the Evans procedure using chiral acyl oxazolidones stands apart as a method of choice. In the MVK example the chiral reagent adds, with the assistance of titanium tetrachloride activation at 0 °C, with an impressive 88% chemical yield and 99% ee (eq 17). The oxazolidone can be recycled and the method is general for a variety of α,β-unsaturated systems.[44]

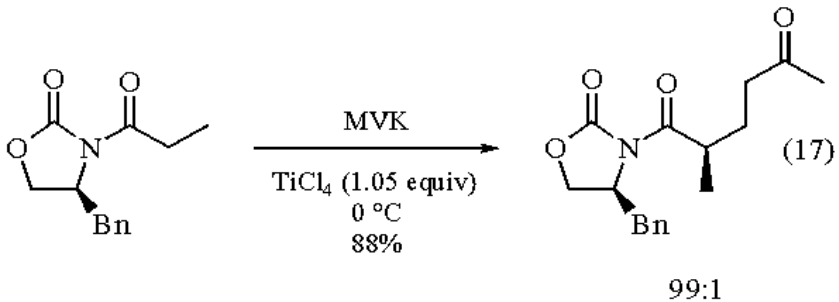

(17)

Alkylation/Cyclization Tandems: The Robinson Annulation.

The most prevalent use of MVK in modern synthesis is the annulation of a six-membered ring onto a pre-existing ketone: the Robinson annulation (see above). In its original format,[45] the sequence involves the generation of an enolate under basic conditions followed by Michael addition to MVK, thus affording a 1,5-dione. The dione can be subjected to basic conditions which induce aldol cyclization-dehydration, resulting in a newly formed cyclohexenone appended to the starting ketone (eq 2). Since its inception, the sequence has been handicapped by a variety of problems: (1) proton transfer; (2) regiochemistry of Michael addition to MVK; (3) *O*- vs. *C*-alkylation; (4) polyalkylation; (5) poor yields in the conjugate addition step; and (6) base-promoted polymerization of MVK itself. In spite of these drawbacks, the procedure is so synthetically important that development and refinement of Robinson's protocol continues to this very day. Most of the problems which are unique to MVK are often overcome by the use of a synthetic equivalent (see above). This section will deal with the annulation procedures which involve MVK itself and can be grouped into linear vs. spiroannulation sequences. In addition, some of these methods involve asymmetric induction, resulting in chiral cyclohexenones. When chirality is involved, it is usually induced in the alkylation (Michael addition) step, but there are a few examples in which the aldol cyclization of the dione or keto aldehyde features the chiral auxiliary.

The Linear Robinson Annulation.

This was the earliest class of Robinson annulation procedure and represents the majority of examples. When simple ketones are used in this sequence with MVK, the results are often unsatisfactory. However, when acidic dicarbonyl compounds are employed, the results are quite viable and practical. For example, 1,3-diones may be treated with a catalytic amount of base to generate a stable enolate which is subsequently trapped with MVK. The alkylated adduct is then cyclized-dehydrated under standard Knoevenagel conditions (eq 18). The acidic conditions of the cyclization help retard reversible β-elimination of MVK.[46]

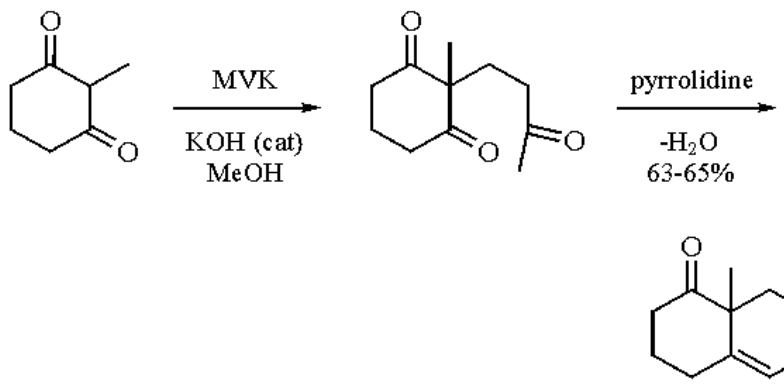

(18)

In a classic case of stereochemical control, chiral auxiliaries were not involved, but rather a simple reversal of order in alkylations of enolates resulting in the preparation of isomeric decalenones (eq 19).[47] Although this is a dialkylation procedure leading to a specific product, the overall strategy of stereochemical control in the Robinson annulation has been extensively studied and discussed.[48]

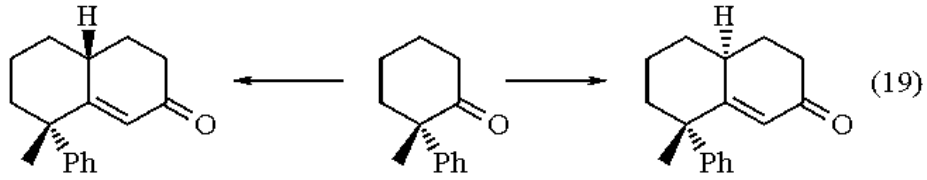

(19)

With the advent of kinetic, sterically hindered bases (such as LDA), which could be used under aprotic conditions, the regiochemistry of enolates could be controlled. In the following sequence, a slight excess of the ketone allows the Michael addition to occur at the most hindered site via the thermodynamic enolate, thus resulting in a quaternary carbon center with stereochemical control. Aldol cyclization-dehydration then affords the cyclohexenone in 60% yield (eq 20).[49]

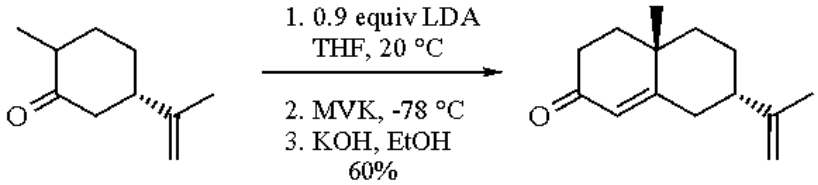

(20)

A highly successful approach to Robinson annulation involves the use of trimethylsilyl enol ethers with MVK under Lewis acid conditions, which thwarts MVK polymerization. The yields of the Michael addition itself are greatly improved (see above), and the resulting diones can be cyclized-dehydrated under standard aldol (basic) conditions. This particular example affords the decalenones in 89% overall yield from MVK (eq 21).[27]

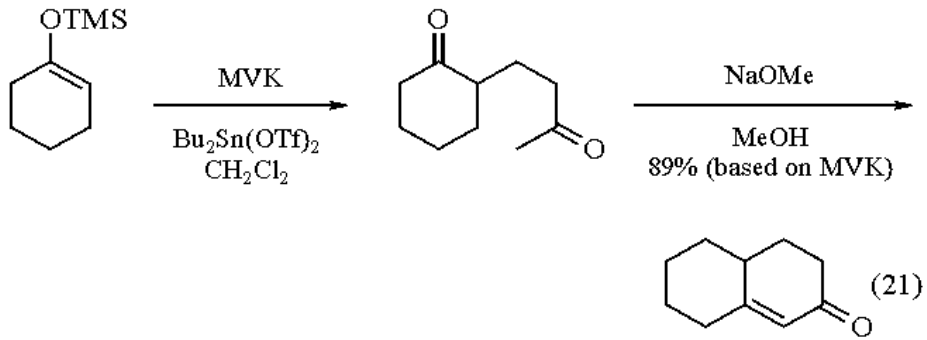

(21)

The Chiral Robinson Annulation.

Perhaps the most important extensions involving the Robinson annulation protocol have concerned the production of chiral cyclohexenones. In general, the asymmetric induction takes place at the Michael addition step with a chiral reactive intermediate and MVK, although there are a few examples in which the aldol cyclization-dehydration step affords the stereochemical control. However, great care must be exercised in the cyclization step in order to avoid epimerization at the newly created chiral center. One of the earliest methods for chiral Robinson annulation is a general procedure in which a chiral ***Pyrrolidine*** enamine is condensed with MVK; the resulting keto imines are then hydrolyzed to give the chiral δ-keto aldehydes, which in turn are cyclized under (acidic) Knoevenagel conditions, finally affording chiral 4,4-disubstituted cyclohexenones (eq 22).

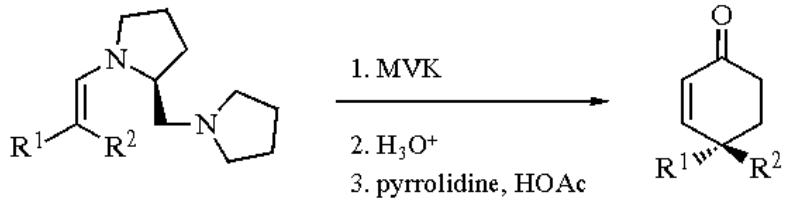

(22)

This methodology was highlighted in the chiral total synthesis of the *Sceletium* alkaloid (+)-mesembrine.[50] More recently, an even milder, shorter sequence was used in the key step for the synthesis of the *Sceletium* alkaloid (+)-*O*-methyljoubertiamine. In this case, the chiral auxiliary was the naphthylcamphor system (see above), which governed the condensation of the enolate with MVK using mild ***Potassium Carbonate*** as the base (eq 23).[42]

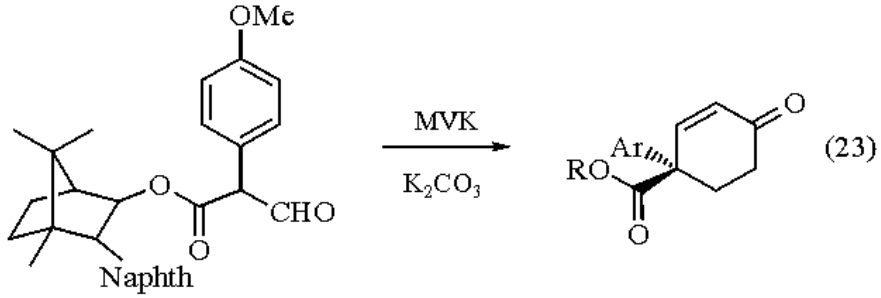

The use of chiral imines has recently received attention as reactive intermediates for Michael additions to MVK. Their advantage is that they are derived from α-methylbenzylamine, which is affordable and can be recycled. The Michael addition itself is activated with titanium tetrachloride and gives good yields (61%) of the Michael adduct with high ee (91%). Hydrolysis concomitant with cyclization provides the decalenone (eq 24).[51]

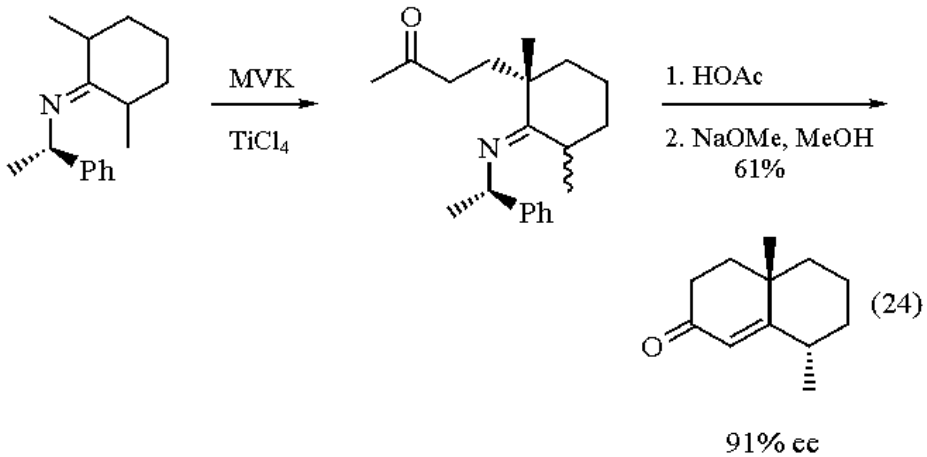

A very useful procedure for inducing chirality in the cyclization step was reported some years ago but has recently been optimized for scale-up. ***2-Methyl-1,3-cyclopentanedione*** serves as the reactive enolate system for the Michael addition with MVK, providing the trione in quantitative yield. The chiral cyclization is a modified Knoevenagel reaction using ***(S)-Proline*** as the asymmetric catalyst. This sequence provides the enedione in 93% optical purity (eq 25).[52]

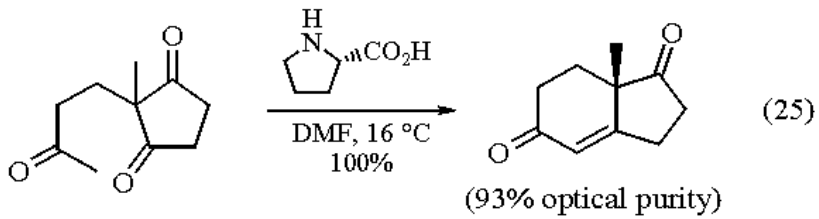

The Spirocyclic Robinson Annulation.

Procedures which attach two carbocyclic rings to one another by a single carbon atom (spiroannulation)[53] are not commonplace. The major synthetic problem to overcome in such an operation is the construction of the common, quaternary carbon center. Although there are a number of ingenious ways to construct quaternary carbon centers,[54] those involving spiroannulations with MVK are generally limited to the reactions of trisubstituted enamines with MVK as the conjugate addition step of the sequence (eq 26).[55] The starting carbonyl compounds are usually aldehydes, but there is also a highly efficient homologation procedure which commences from ketones.[56] In either case, the intermediate at the alkylation stage is a δ-keto imine which is subjected to mild acid hydrolysis, thus generating a δ-keto aldehyde, which is then cyclized-dehydrated with base. Enamines from ***Piperidine*** and ***Morpholine*** have been used successfully in this procedure. There is flexibility in the carbonyl starting materials as well: five-, six-, seven-, and eight-membered carbonyl systems have all been satisfactory substrates in this methodology. The spiroannulation procedure of MVK with enamines is summarized below (Table 2).

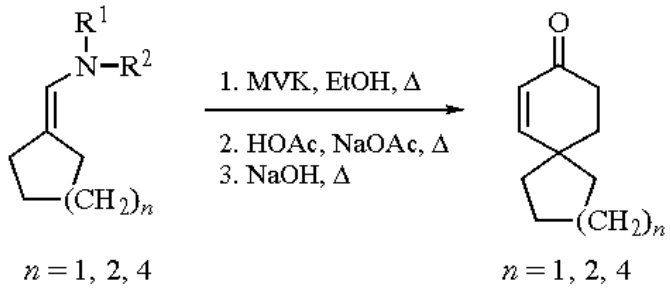

(26)

Table 2 Spiroannulation Procedures Involving Enamines and Methyl Vinyl Ketone

Ketone	Enamine	Yield of spirocycle (%)	Ref.
Cyclopentane-carbaldehyde	Piperidino	59	55c
Isopropylidene-cyclopentane-carbaldehyde	Piperidino	45 65	55a
Cyclohexane-carbaldehyde	Piperidino	45 65	55b,c
Cyclohexanone	Morpholino	41	56
2-Methylcyclo-hexanone	Morpholino	36	56
4-*t*-Butylcyclo-hexanone	Morpholino	41	56
Isophorone	Morpholino	30	56
2-Norbornanone	Morpholino	41	56
Cycloheptane-carbaldehyde	Piperidino	45 65	55b,c
Cyclooctane-carbaldehyde	Piperidino	45 65	55b,c

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2-Methyl-6-vinylpyridine[1]

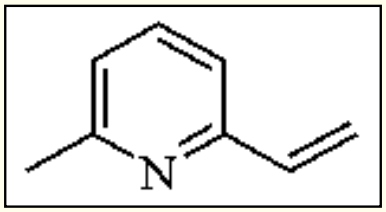

[1122-70-9] · C_8H_9N · 2-Methyl-6-vinylpyridine · (MW 119.18)

(stable, masked methyl vinyl ketone equivalent; bis-annulation reagent useful for the synthesis of fused ring systems;[2,3] 1,5-diketone precursor[4])

Physical Data: clear liquid, bp 65-70 °C/12 mmHg.

Solubility: sol all common organic solvents.

Preparative Method: prepared in a two-step procedure from ***2,6-Lutidine*** in an overall 30% yield.[5]

Handling, Storage, and Precautions: store under nitrogen at rt; unpleasant odor; use in a fume hood.

Annulations.

2-Methyl-6-vinylpyridine is a stable, masked equivalent of two moles of ***Methyl Vinyl Ketone*** that has been utilized in the synthesis of steroid ring systems.[2,3] In addition, 2-methyl-6-vinylpyridine derivatives have found use as a convenient synthon of 1,5-diketones.[4] Alkylation of the vinylpyridine[2,3,6] followed by Birch reduction of the appropriately protected substrate generates a cyclohexenone (eq 1).

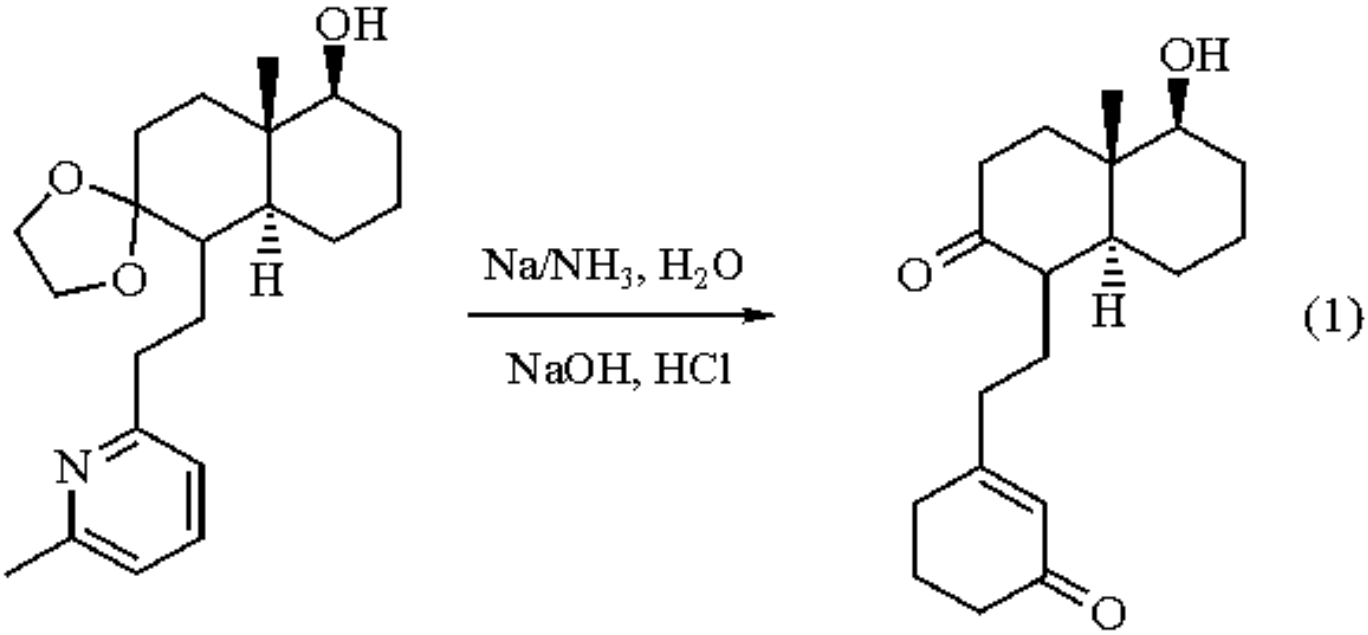

The mode of cyclization of the intermediate 1,5-diketone is predictable and dependent on the substitution pattern (eq 2). Thus Birch reduction of 2-cyclohexylethyl-6-methylpyridine (**1**) (R = cyclohexyl) produces 100% of 3-cyclohexylethylcyclohex-2-enone (**2**) (R = cyclohexyl), while reduction of the corresponding 2-ethyl-6-methylpyridine (**1**) (R = H) affords >90% 2,3-dimethylcyclohex-2-enone (**3**) (R = H).[4c]

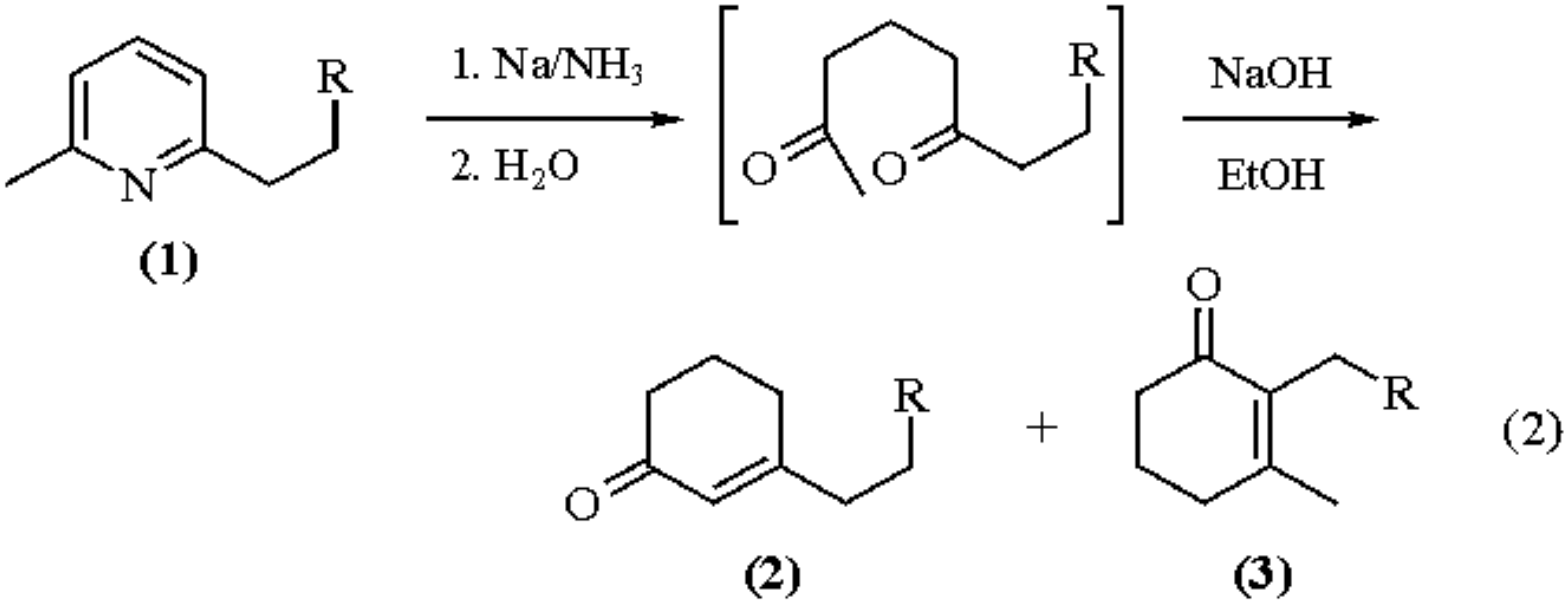

Other examples of heterocyclic bis-annulation reagents include 3-chloromethyl-2,4-dimethylisoxazole,[7] *N*-benzyl-2,6-dicyanopiperidine,[8] and 2,6-dimethyl-4*H*-pyran-4-one.[9]

Related Reagents.

Methyl Vinyl Ketone.

1. Kametani, T.; Nemoto, H. *H* **1978**, *10*, 349.
2. (a) Danishefsky, S.; Nagel, A. *CC* **1972**, 373. (b) Danishefsky, S.; Cain, P.; Nagel, A. *JACS* **1975**, *97*, 380. (c) Danishefsky, S.; Cain, P. *JACS* **1975**, *97*, 5282.
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4. (a) Danishefsky, S.; Nagel, A.; Peterson, D. *CC* **1972**, 374. (b) Danishefsky, S.; Cain, P. *JOC* **1975**, *40*, 3606. (c) Danishefsky, S.; Zimmer, A. *JOC* **1976**, *41*, 4059.
5. Prasad, K. S. N.; Raper, R. *JCS* **1956**, 217.
6. (a) Singerman, G.; Danishefsky, S. *TL* **1964**, 2249. (b) Danishefsky, S.; Cavanaugh, R. *JACS* **1968**, *90*, 520.
7. Stork, G.; Danishefsky, S.; Ohashi, M. *JACS* **1967**, *89*, 5459.
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9. Yamamoto, M.; Iwasa, S.; Takatsuki, K.; Yamada, K. *JOC* **1986**, *51*, 346.

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Methylzirconium Tributoxide

$MeZr(OBu)_3$

[79950-18-8] · $C_{13}H_{30}O_3Zr$ · Methylzirconium Tributoxide · (MW 325.65)

(nucleophile, methylating agent)

Solubility: sol diethyl ether, tetrahydrofuran, CH_2Cl_2.

Form Supplied in: not commercially available.

Preparative Methods: synthesized from $Zr(OBu)_4$ and ***Zirconium(IV) Chloride*** via $ClZr(OBu)_3$.[1] The reaction of ***Methyllithium*** with a solution of tributoxyzirconium chloride in diethyl ether at -10 °C yields the reagent (eq 1). For subsequent reactions the etheral solution of the reagent is used. Both ether and ether solutions in dichloromethane have been used as solvents in the subsequent reactions.[1]

$$ClZr(OBu)_3 \xrightarrow[\text{-10 to 0 °C, 2 h, Ar}]{MeLi,\ Et_2O} MeZr(OBu)_3 \qquad (1)$$

Purification: used as generated in solution.

Handling, Storage, and Precautions: extremely hygroscopic, decomposed by moist air; must be handled under N_2 or Ar; reagent causes burns, and is harmful if inhaled or swallowed. Use in a fume hood.

Nucleophilic Addition to Carbonyls.

Methylzirconium tributoxide, like its higher alkyl, aryl, and vinyl homologs, is a selective nucleophile of low basicity. The selectivity is less, however, than in the titanium analogs, as seen in the preference for aldehydes in the presence of ketones (eq 2).[1]

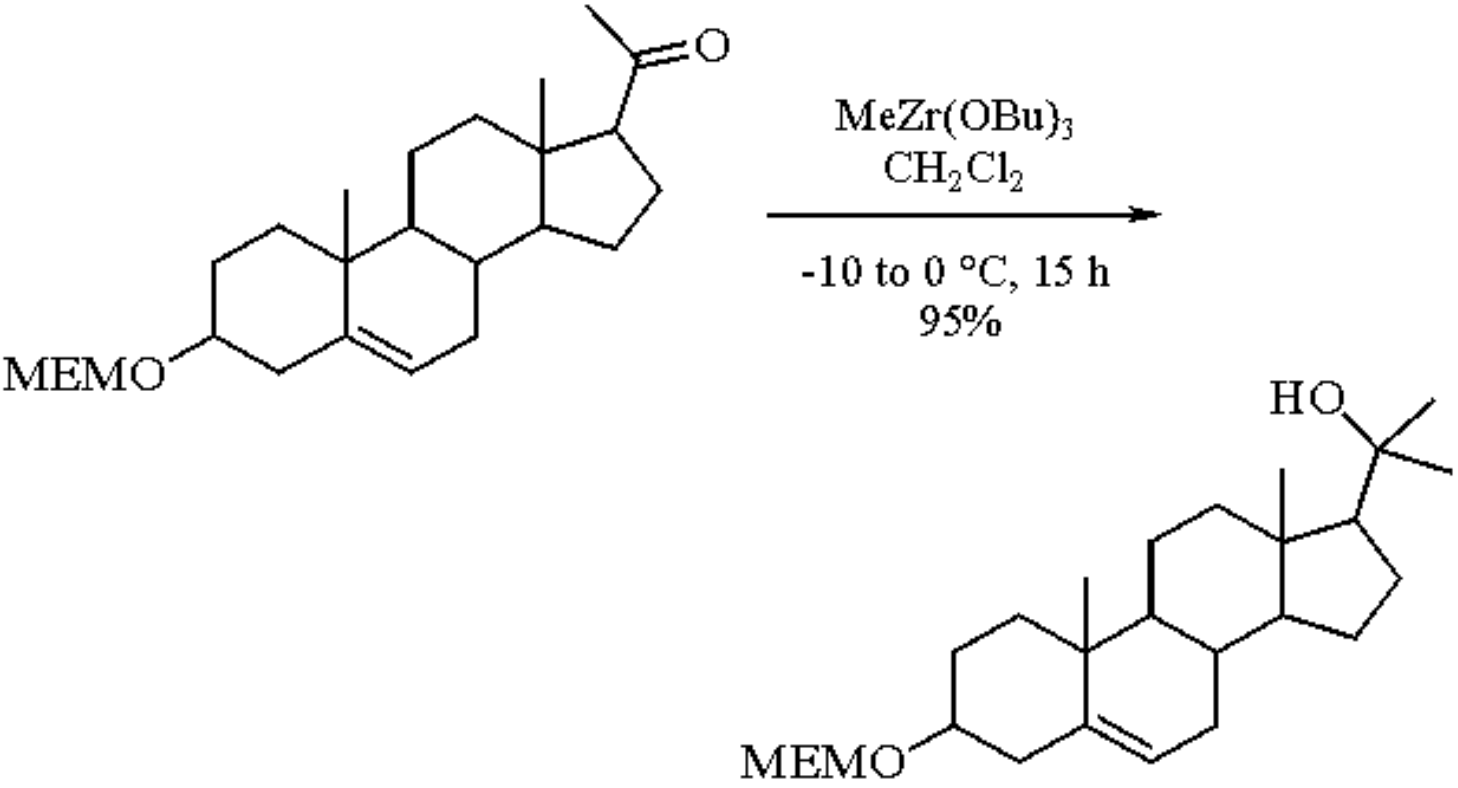

(2)

Several functional groups are compatible (eq 3).

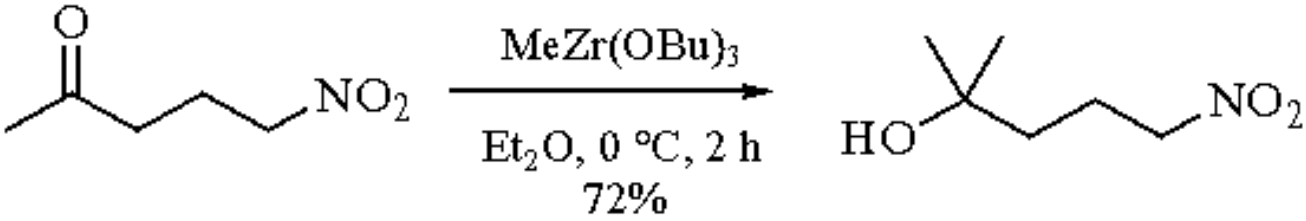

(3)

Basic nitrogen atoms in the substrate molecules do not influence the apparent basicity of the zirconium reagents as much as they do the lithium, Grignard, or titanium derivatives (eq 4).[1]

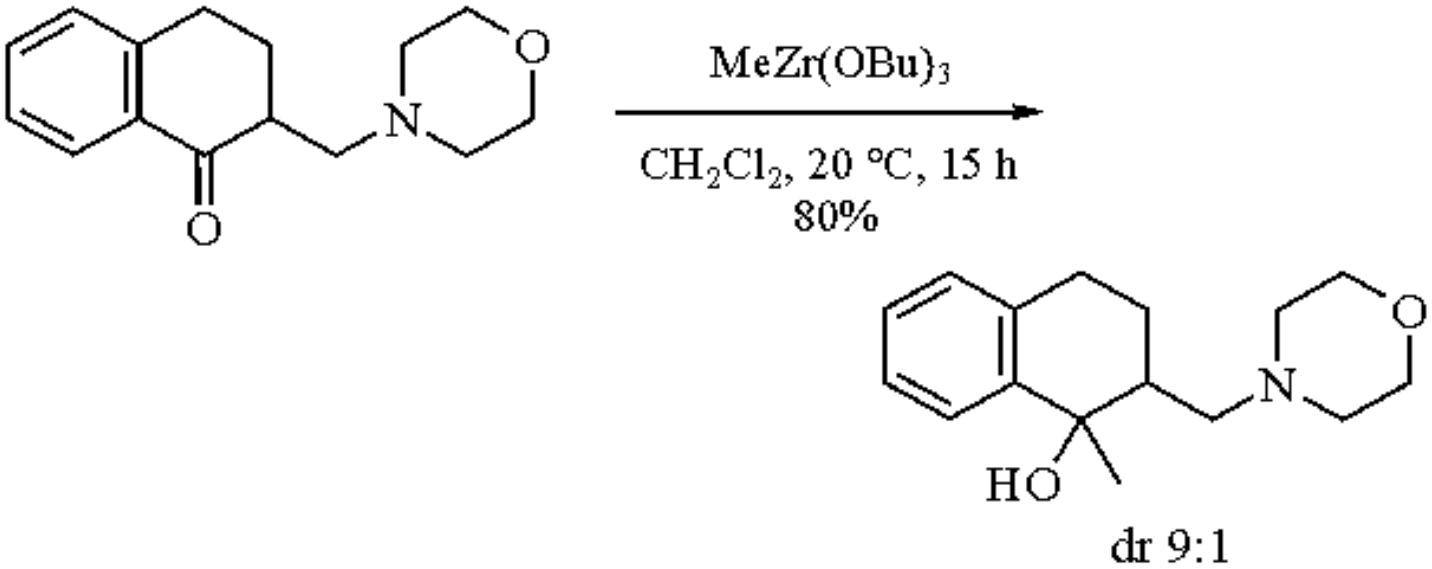

(4)

The alkylzirconium tributoxides are less basic than the titanium analogs, and considerably less basic than the lithium and Grignard reagents and are therefore the reagents of choice in reactions with easily enolizable ketones. In the sugar example given, the reaction is chemo- and stereospecific; only the β-methyl isomer was formed (eq 5).[2] Tetramethylzirconium affords a mixture of the α- and β-stereoisomers, and other organometallic reagents failed because of enolization reactions.

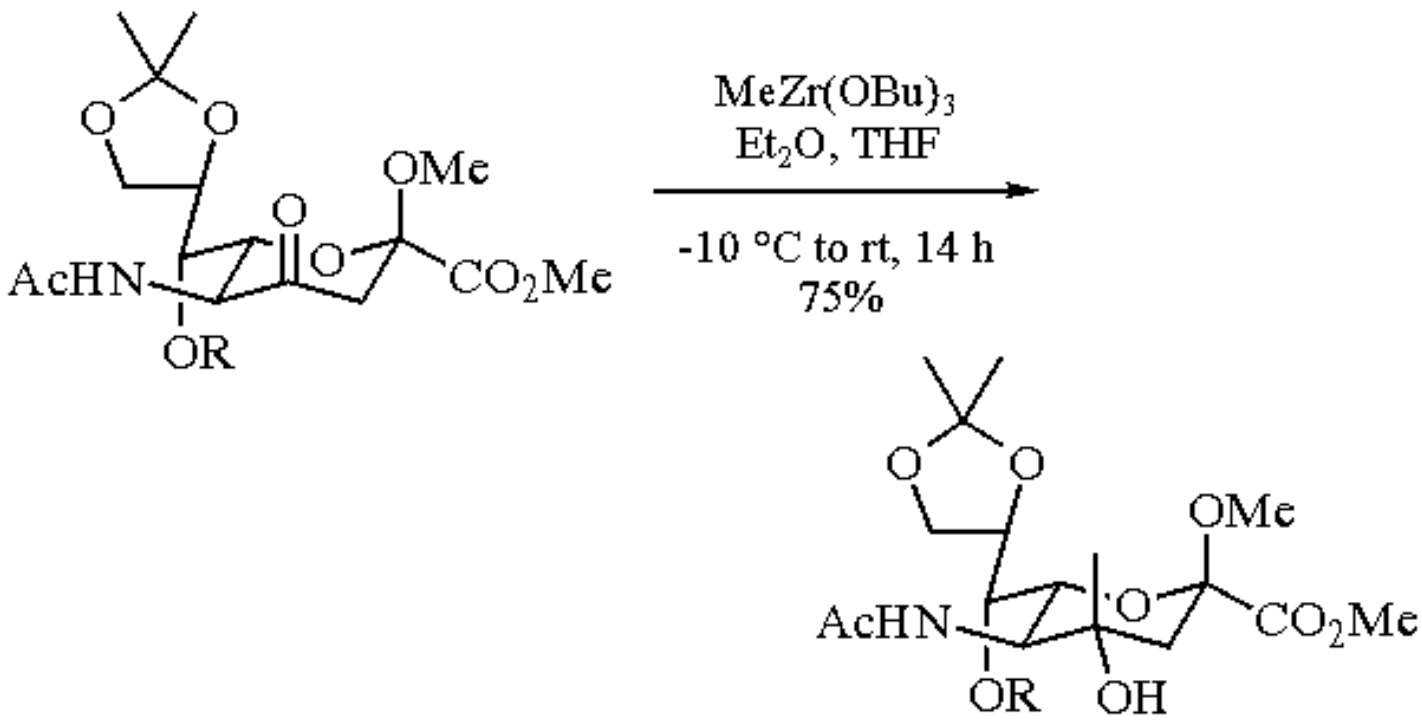

(5)

Related Reagents.

Methyllithium; ***Methylmagnesium Bromide***; ***Methyltitanium Trichloride***; ***Methyltitanium Triisopropoxide***; ***Methyltitanium Tris(diethylamide)***.

---

1. Weidmann, B.; Maycock, C. D.; Seebach, D. *HCA* **1981**, *64*, 1552.
2. Hartmann, M.; Christian, R.; Zbiral, E. *M* **1991**, *122*, 111.

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Molecular Sieves[1]

(electrocyclic reaction cocatalyst; mild acid catalyst; desiccant)

Form Supplied in: the most common forms are bead, pellet, and powdered solids with cavity sizes of 3, 4, 5 and 10 Å. The bead and pellet forms are adequate for drying solvents, while the powdered form is preferred for use in most reactions.

Preparative Methods: sieves are most effective if activated prior to use by drying under vacuum (<1 mmHg) at 300 °C for at least 15 h.

Handling, Storage, and Precautions: all forms of sieves readily absorb water upon exposure to air and are therefore best stored in a desiccator. Sieves can be recycled by (a) washing well with an organic solvent, (b) drying at 100 °C for several hours, and (c) reactivation at &egt;200 °C. Skin contact should be avoided as the desiccant properties of the sieves cause irritation.

General Information.

Molecular sieves are metal aluminosilicates of the general formula $M_{2/n}O.Al_2O_3.xSiO_2.yH_2O$ (where *n* is the valence of the metal, M) characterized by a regular (zeolite) structure and cavity size which is retained even with loss of hydration.[2,3] Although they occur in Nature, most sieves are manufactured commercially as they can be designed with properties specific to their application. Many variations have been synthesized and the field of zeolite design is one of intense investigation.[4] The Linde Division of the Union Carbide Corporation is a major supplier of molecular sieves for synthetic organic applications. Of their products, the 3, 4, and 5 Å as well as 13X sieves are the most commonly employed; these differ both in pore size (3, 4, 5, and 10 Å, respectively) and cation constitution (K, Na, Ca, and Na, respectively).[5] Thus a sieve appropriate to a specific application can be selected.

Diels-Alder Catalysis.

Whether combined with a Lewis acid or used alone, molecular sieves are powerful accelerators of this concerted process. In the former case, great progress has been made toward combining this reagent with a chiral Lewis acid to induce asymmetry during reaction between two achiral molecules.[6-12] This has been achieved through the use of the chiral titanate (**1**) and achiral auxiliary (**2**) which aids in coordination of the dienophile (eqs 1 and 2). Not only is this a highly successful method for the enantioselective generation of the stereocenters, but it is also catalytic. The power of this methodology is elegantly demonstrated in eq 2, taken from Narasaka's synthesis of the hydronaphthalene portions of mevinic acids, where this catalyst system is employed to introduce four contiguous chiral centers with complete diastereoselectivity and very high enantioselectivity from an achiral precursor. Although a less dramatic example, eq 3 displays the ability of sieves to function independently as cycloaddition catalysts,[13] as attested to by the mild temperature and short reaction time.

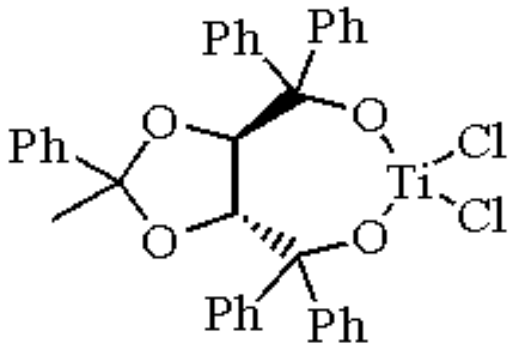
Ph
Ph
Ph
O
O
Ti
Cl
Cl
O
O
Ph
Ph

(1)

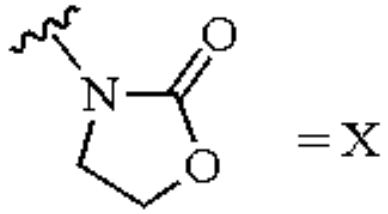
N
O
O
= X

(2)

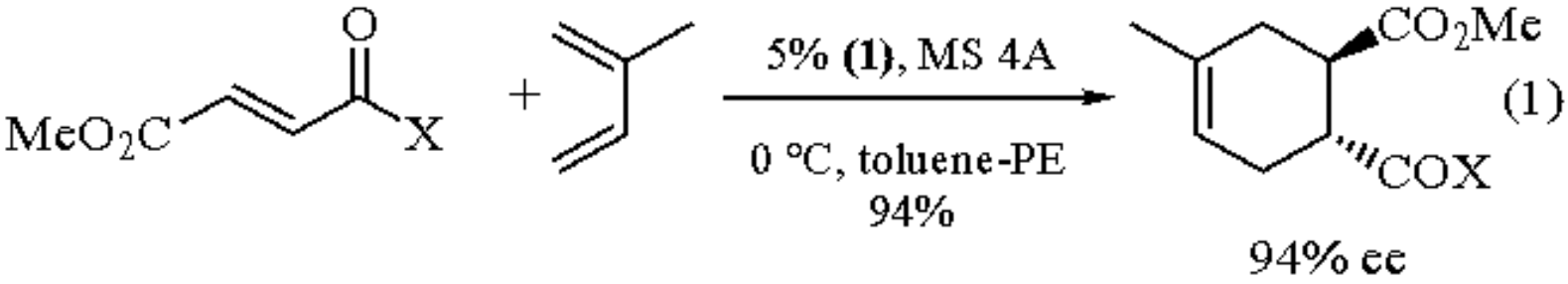
MeO2C
O
X
+
5% (1), MS 4A
0 °C, toluene-PE
94%
CO2Me
COX
(1)
94% ee

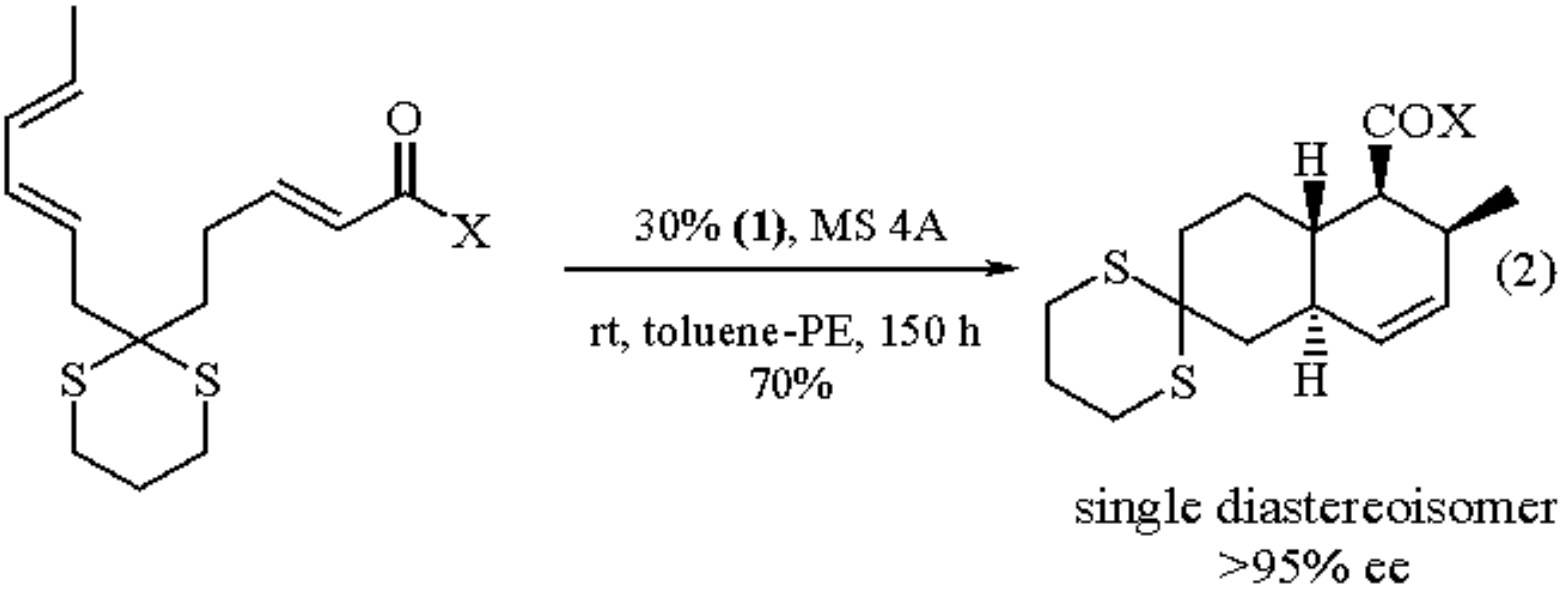
O
X
S
S
30% (1), MS 4A
rt, toluene-PE, 150 h
70%
COX
H
S
S
H
(2)
single diastereoisomer
>95% ee

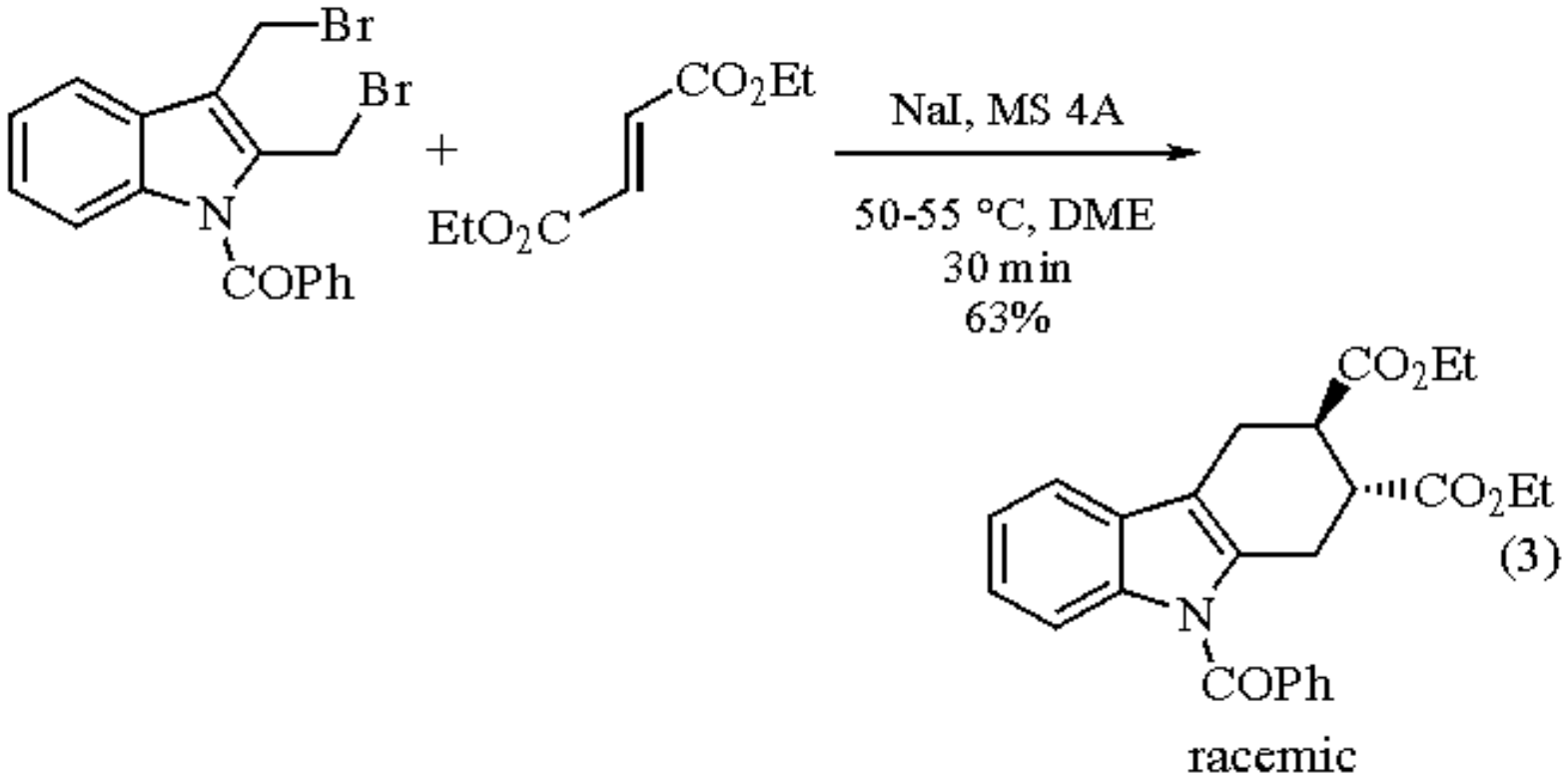

Ene Reactions.

Utilization of the reagent in ene reactions parallels its use in Diels-Alder cycloadditions, although the choice of the Lewis acid cocatalyst is substrate dependent. The three most effective chiral metal complexes employed to date are either the tartrate-based titanate (**1**), titanium-complexed commercially available 1,1´-binaphthol (see ***(R)-1,1´-Bi-2,2´-naphthotitanium Dichloride***), or the more bulky binaphthol-derived system (**3**) (eqs 4-6).[14-16] Performance of these catalytic systems is comparable to those employed in the Diels-Alder reaction in both enantioselectivity and mildness of reaction conditions.

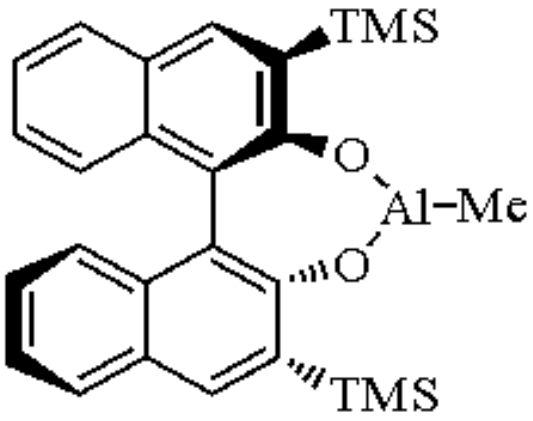

(3)

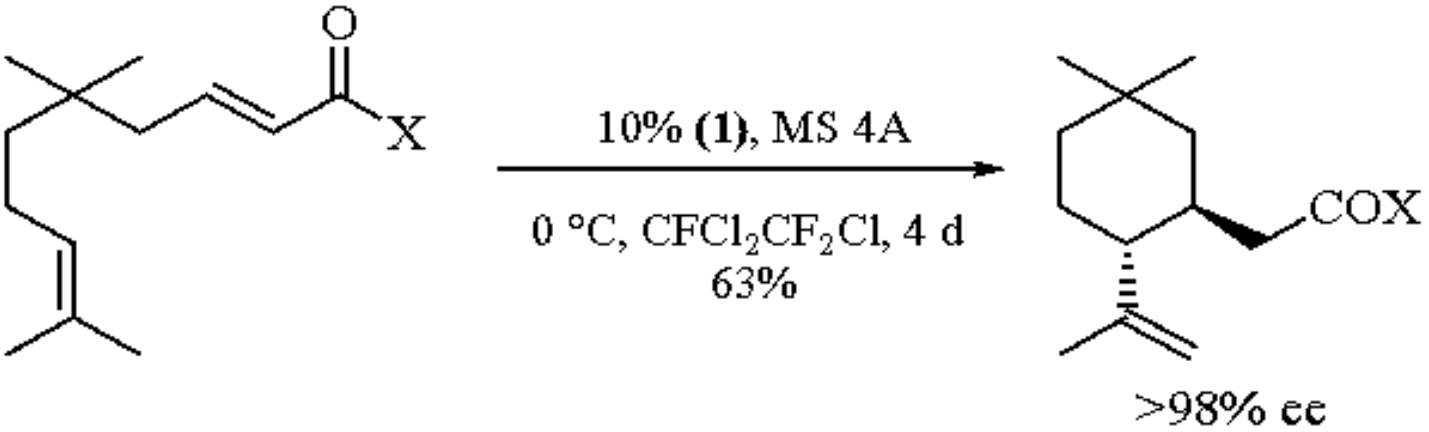

(4)

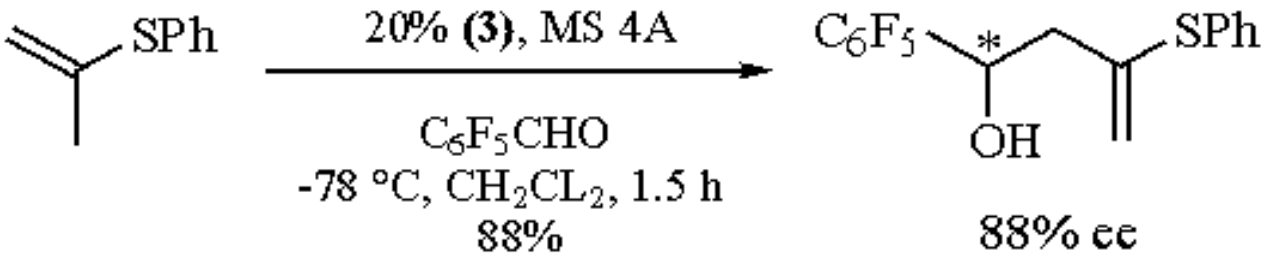

(5)

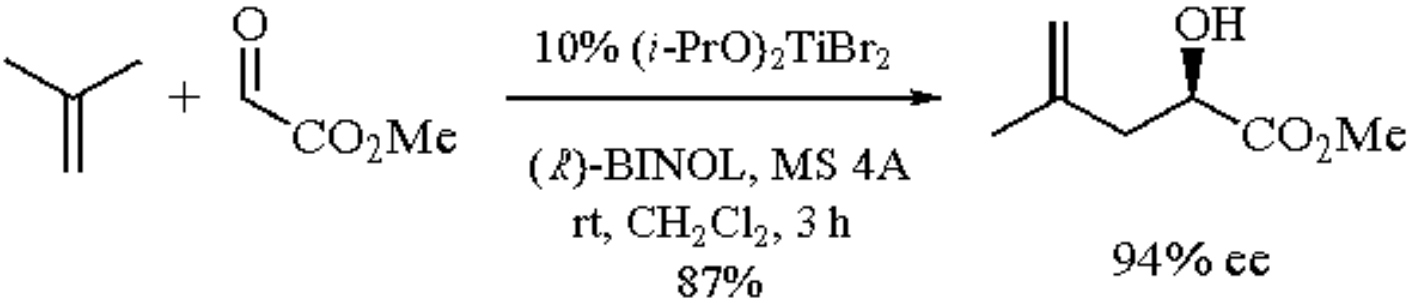

(6)

Other Electrocyclic Reactions.

Finally, molecular sieves have been successful in facilitating asymmetric [2 + 2] cycloadditions when (**1**) is present, and in promoting [3 + 2] dipolar cycloadditions. Again, in the former case, the optical yields are extremely good as can be seen from eqs 7-9.[17-20] In the latter case, the sieves generate the nitrile oxide in situ and this species then reacts with the acrylate acceptor to yield the isoxazole (eq 10). Although this method requires a relatively long reaction time, the mild conditions have the advantage of suppressing side reactions, including dimerization of the nitrile oxide, resulting in high yields of very pure material.[21]

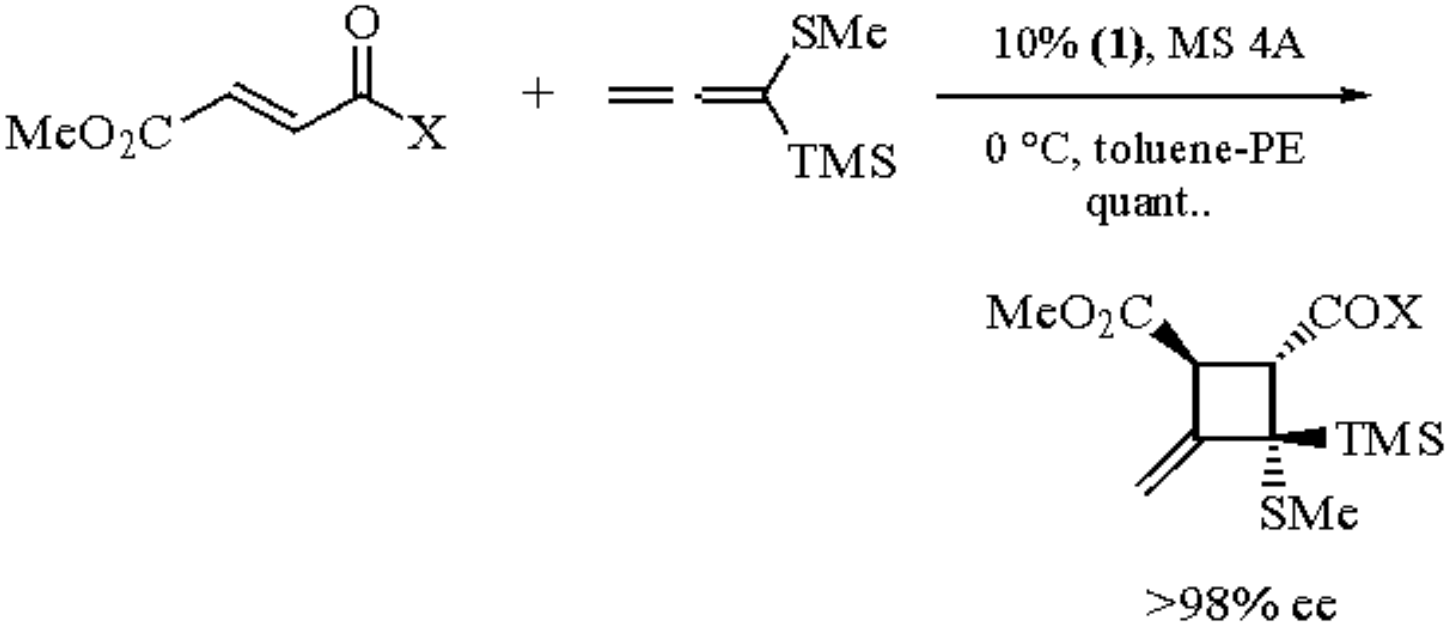
MeO2C
O
X
SMe
TMS
10% (1), MS 4A
0 °C, toluene-PE
quant..
MeO2C
COX
TMS
SMe
>98% ee

(7)

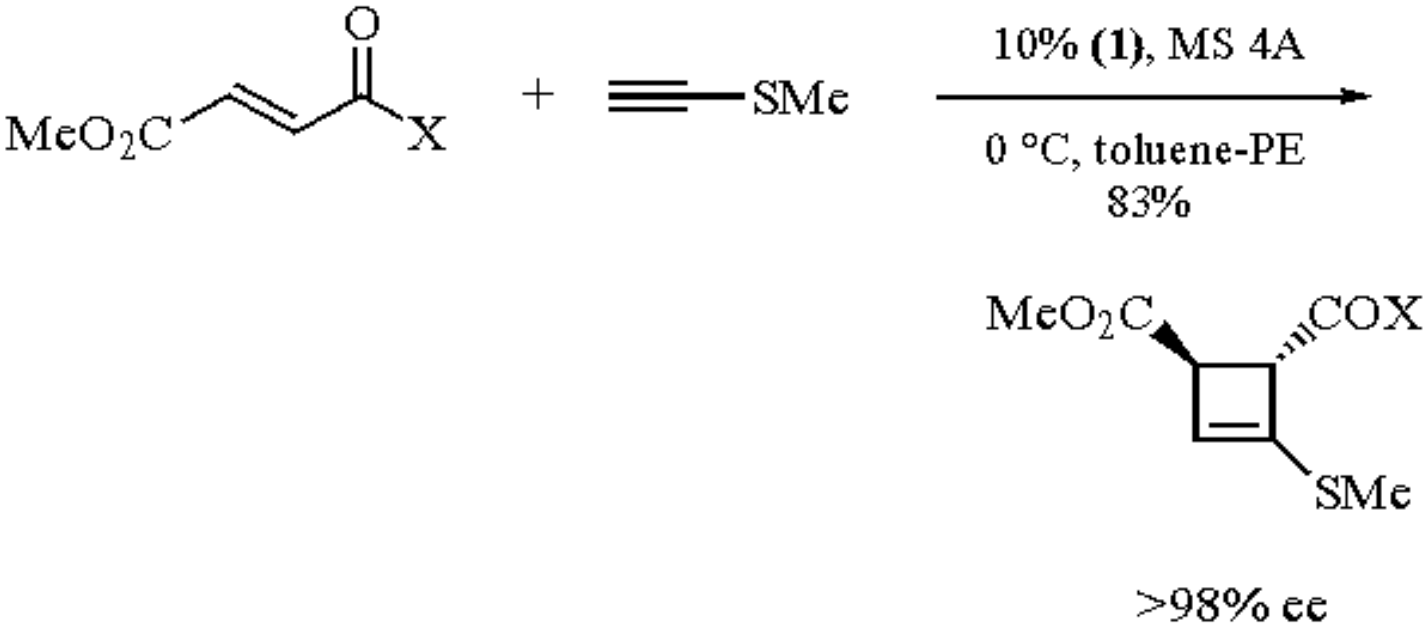
MeO2C
O
X
SMe
10% (1), MS 4A
0 °C, toluene-PE
83%
MeO2C
COX
SMe
>98% ee

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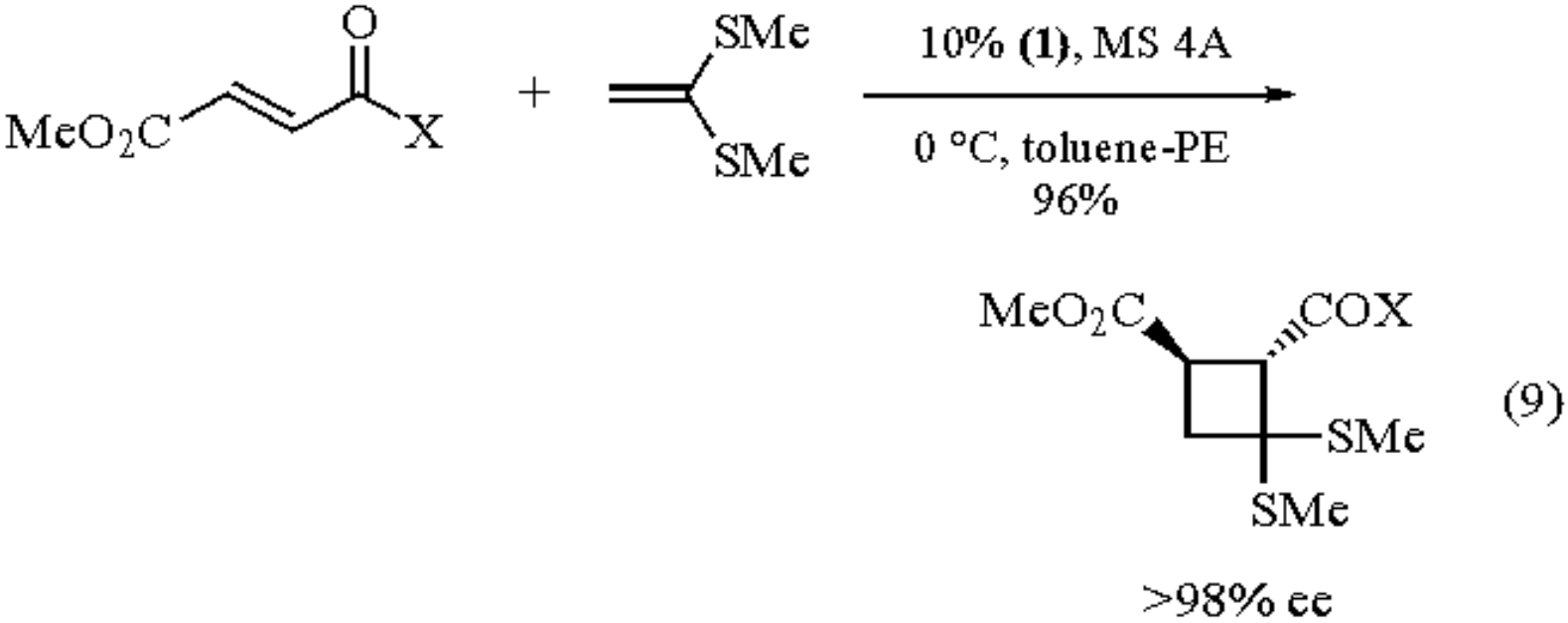

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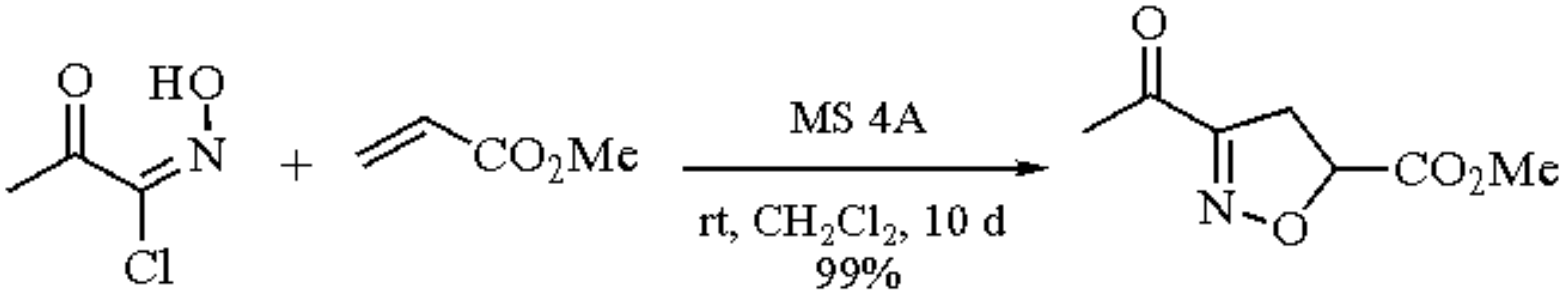

(10)

Acid Scavenging.

In addition to their use as cocatalysts, molecular sieves also function as acid scavengers, making them especially suited to the suppression of acid-catalyzed side reactions such as polymerization. For example, they are employed in the preparation of high-purity methacrylic acid esters from methacryloyl chloride and various alcohols (primary, secondary, tertiary, and benzylic).[22] This acid-scavenging ability has also proven useful in the direct acylation of acid-sensitive, unreactive tertiary hydroxyl groups and of acid- and base-sensitive amides with acyl chlorides.[23,24]

Sorbtion.

The reagent's sorbtion ability has been exploited in a wide range of carbonyl and carboxylate transformations. Key to their utility is the inclusion of molecules such as water and small alcohols into the sieve cavities while excluding the larger compounds, thus allowing greater control of equilibria. By this method, ketimines and enamines derived from sterically encumbered precursors are more accessible.[25,26] Likewise, triphenylphosphazenes can be obtained by reaction of *N*-aminotriphenylphosphinime with various aldehydes and ketones.[27] Reductive amination of carbonyls proceeds in better yield with molecular sieves present to absorb water.[28] When coupled with tertiary amines such as ***1,5-Diazabicyclo[4.3.0]non-5-ene*** or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***, 3 or 4 Å sieves can effect the alkenation of δ-alkoxy-α,β-unsaturated aldehydes efficiently.[29,30] Amide synthesis with molecular sieves provides a general, high yielding, and chemoselective route to secondary amides free of byproducts and impurities.[31] Transesterification of

methyl esters with branched primary, secondary, and tertiary alcohols has been reported with the 5 Å sieve.[3] Zeolites have been utilized in the preparation of an asymmetric hydrocyanating agent by reaction with titanate (**1**) followed by treatment with 2 equiv of ***Cyanotrimethylsilane*** at ambient temperature.[32,33] Addition of this reagent to aldehydes at -78 °C in toluene provides the corresponding cyanohydrins in yields of 67-92% and optical purities ranging from 61% to 93%.

Acid Catalysis.

The Lewis acid reactivity of this reagent can be applied to Michael-type reactions as shown in eqs 11 and 12.[34,35] The resulting ring systems can be further transformed into a variety of useful synthetic building blocks. Molecular sieves can also be coupled with Lewis acids to promote acetal formation and exchange. When used with ***p-Toluenesulfonic Acid*** as a cocatalyst, sieves provide a facile synthesis of acetals from carbonyls, not only when primary but also when secondary alcohols are involved.[36,37] Employment with ***Boron Trifluoride Etherate*** catalyzes exchange between (tributylstannyl)methanol and ***Dimethoxymethane*** to produce the useful hydroxymethyl anion equivalent ***Tri-n-butyl[(methoxymethoxy)methyl]stannane*** in high yield.[38,39]

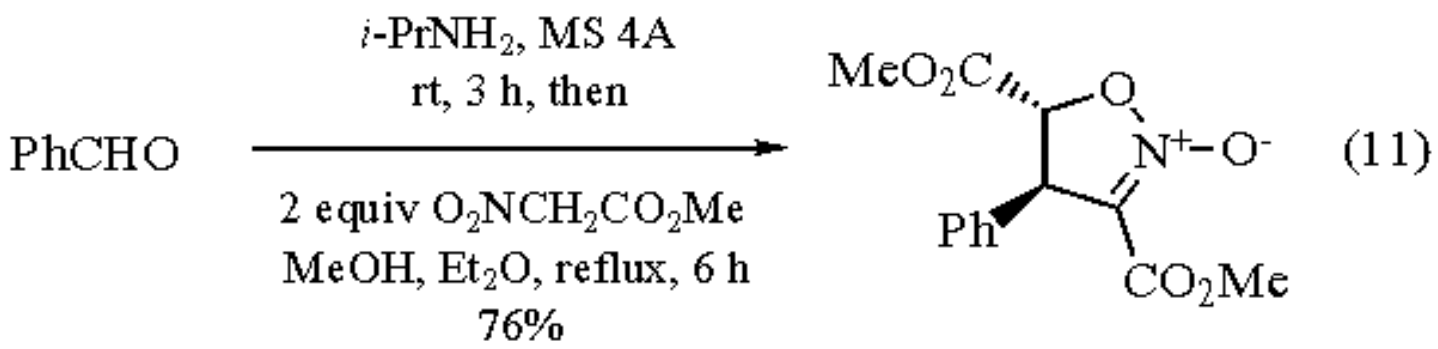

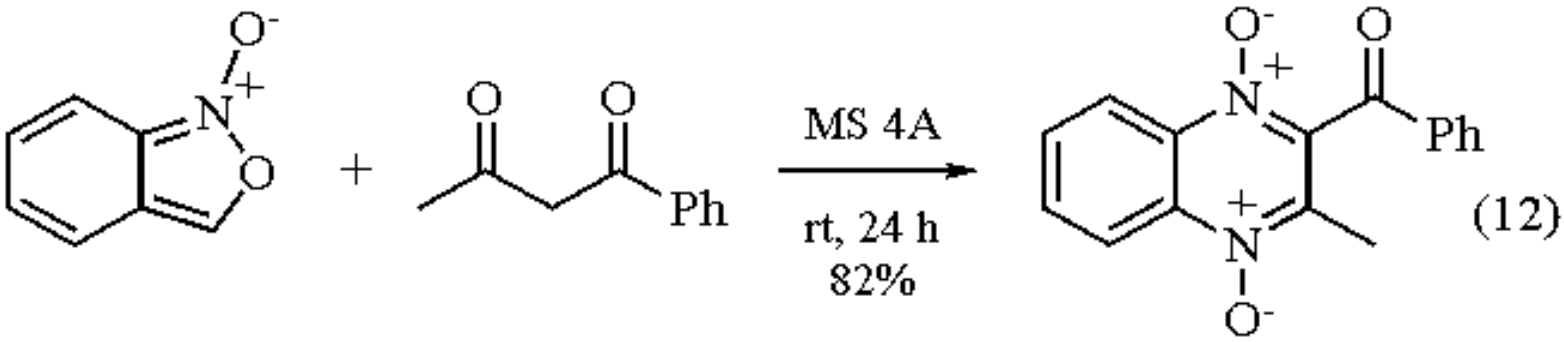

Oxidations.

Titanium silicate molecular sieves have served as catalysts in the selective oxidation of thioethers to sulfoxides.[40] They effect this transformation under mild conditions (1 equiv of H_2O_2 in refluxing acetone) with little over-oxidation to the sulfone. When used as a promoter in ***Pyridinium Chlorochromate*** and ***Pyridinium Dichromate*** oxidations of nucleoside derivatives, sieves work remarkably well, in contrast to other additives such as ***Alumina***, Celite, or silica gel which fail to accelerate these reactions.[41] As drying agents, sieves are a crucial component of the Sharpless catalytic asymmetric epoxidation.[42]

Miscellaneous Reactions.

The shape selectivity of zeolites has been exploited to selectively brominate either a hindered double bond in the presence of an unhindered double bond or vice versa, depending on the reaction conditions.[43] If the hindered and unhindered alkene mixture is allowed to equilibrate prior to bromine addition, bromination of the hindered alkene is greatly favored (up to a 95:5 preference). Conversely, inclusion of the bromine in the sieves followed by addition of the alkene mixture shows opposite selectivity.

Molecular sieves have been employed as acid scavengers in the transition metal-catalyzed synthesis of carboxylic acids and esters from iodides under base-free conditions, as represented in eq 13.[44] Another transition metal-catalyzed reaction (eq 14) applies sieves as a cocatalyst with ***Iron(III) Chloride*** to form a nonreducing disaccharide in an alternative to the conventional Koenigs-Knorr method.[45] In concert with ***Tin(II) Trifluoromethanesulfonate*** and ***2,4,6-Collidine***, molecular sieves promote the coupling of acetobromoglucose with various protected sugar derivatives to form exclusively *trans*-β-D-glucosides with glucose as the reducing unit.[46] Finally, the use of zeolites as cocatalysts in palladium-catalyzed oxidative cyclizations has led to substantial improvements in the diastereoselectivity of these reactions.[47,48] This is exemplified in eq 15, which shows only a 17% de in the absence of molecular sieves.

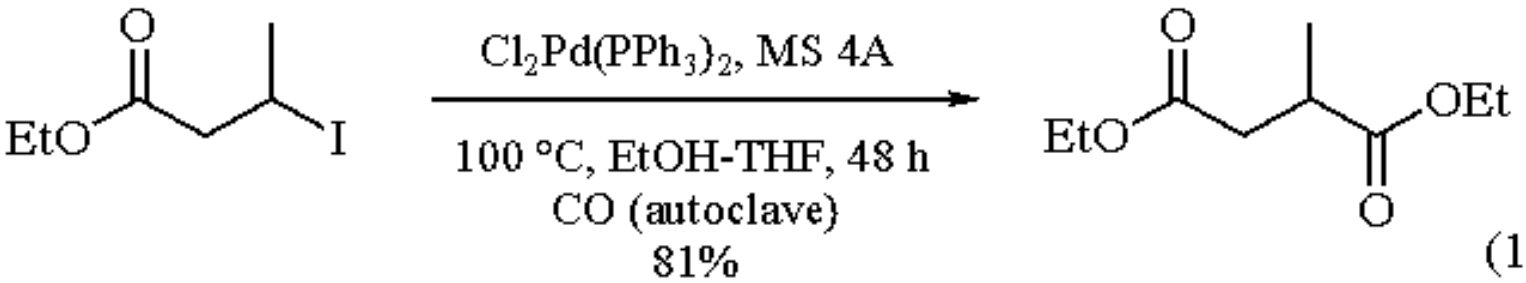

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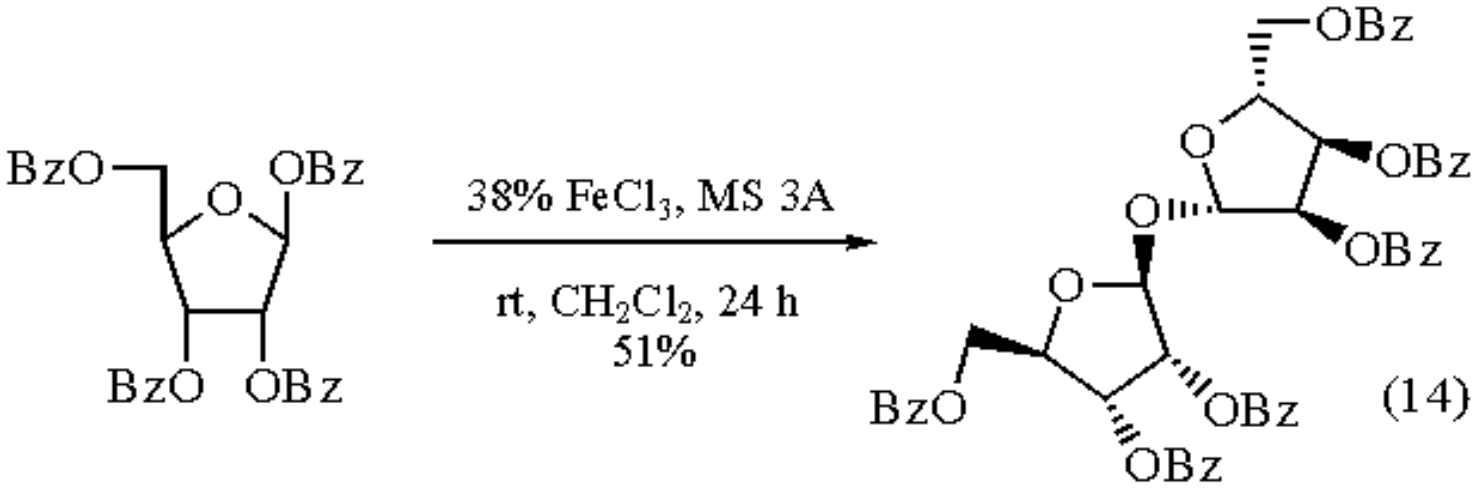

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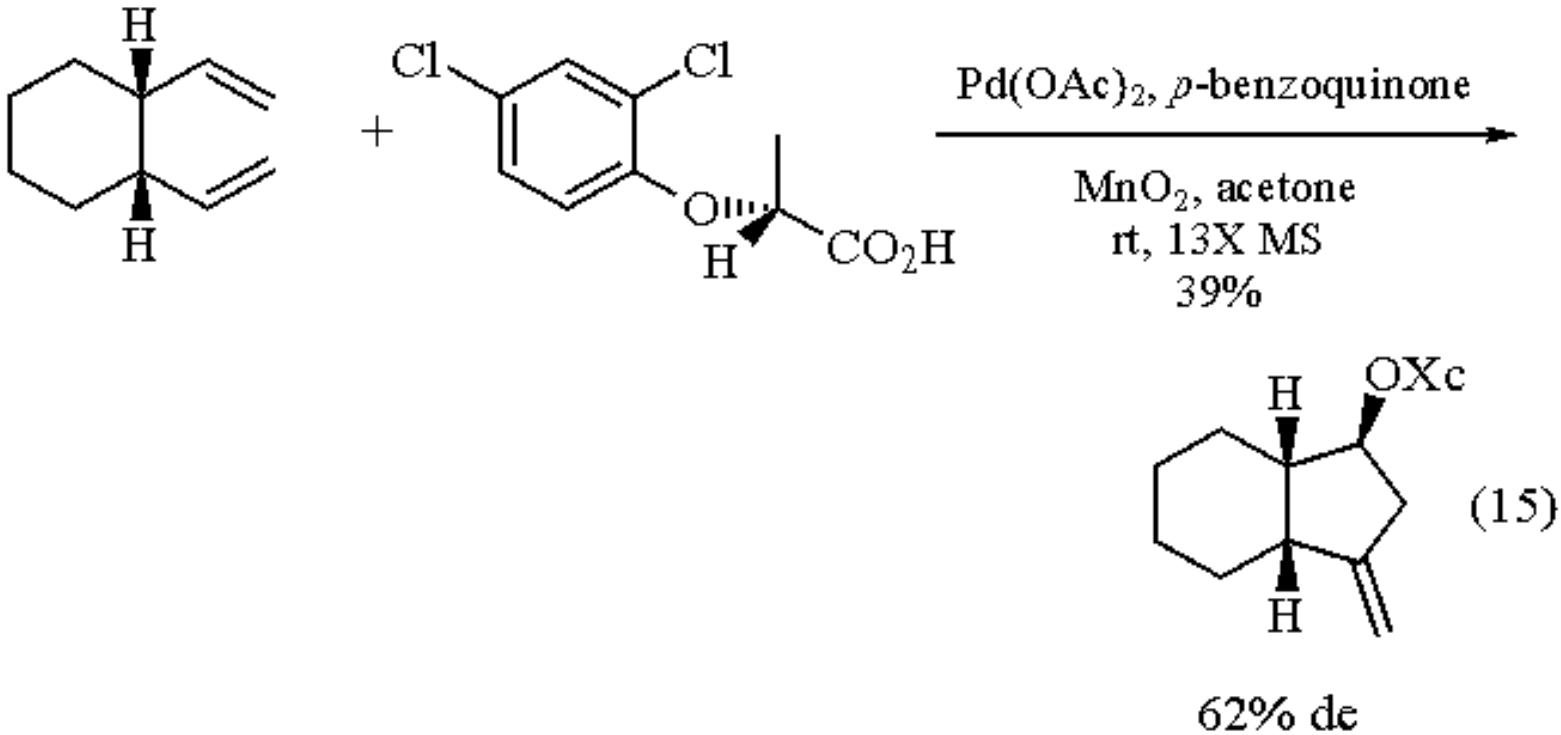

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Molybdenum(V) Chloride

$MoCl_5$

[10241-05-1] · Cl_5Mo · Molybdenum(V) Chloride · (MW 273.19)

(chlorinating agent for alkyl halides,[5] alkenes,[7] and alkynes;[8] used as a Lewis acid and as a catalyst for CO_2 insertion to oxiranes,[9] for C-C coupling of alkenyllithium reagents,[10] and for condensation of nitrobenzene with alcohols;[11] easily reduced to Mo^{III} species, useful as a reagent of deoxygenation;[12,13] methylenemolybdenum reagents for chemoselective carbonyl alkenation are prepared from $MoCl_5$[17,18])

Alternate Name: molybdenum pentachloride.

Physical Data: mp 204 ± 1 °C; bp 276.5 °C; *d* 2.936 g cm^{-3}.

Solubility: sol H_2O, where it undergoes hydrolysis; slightly sol $TiCl_4$, diethyl ether.

Analysis of Reagent Purity: pure reagent (99.9%) is commercially available, packaged in ampules.

Preparative Methods: by the reaction of molybdenum(VI) oxide and carbon tetrachloride or $CCl_2{=}CClCCl_3$ as very dark-colored crystals.[1-3] The industrial method is the direct chlorination of molybdenum metal. A convenient laboratory technique is the liquid-phase reaction system that uses refluxing thionyl chloride and MoO_3.[4]

Handling, Storage, and Precautions: moisture sensitive; store under nitrogen. Use in a fume hood.

Chlorination of Alkyl Halides.[5]

Alkyl iodides, bromides, and fluorides are converted to alkyl chlorides in fair to good yields by reaction with $MoCl_5$ in CH_2Cl_2 at room temperature (eq 1). The reaction sequence is applicable to the conversion of secondary and tertiary halides (I, Br, or F). $MoCl_5$ does not effect halogen interchange with primary alkyl bromides. The conversion of 1-fluorooctane to 1-chlorooctane is accompanied by rearrangement producing 2-chlorooctane (eq 2). A Lewis acid-assisted ionization of the carbon-halogen bond followed by conversion of the carbonium ion to chlorocarbon by the reaction with halometallo-ate complex is a likely mechanism for this transformation.

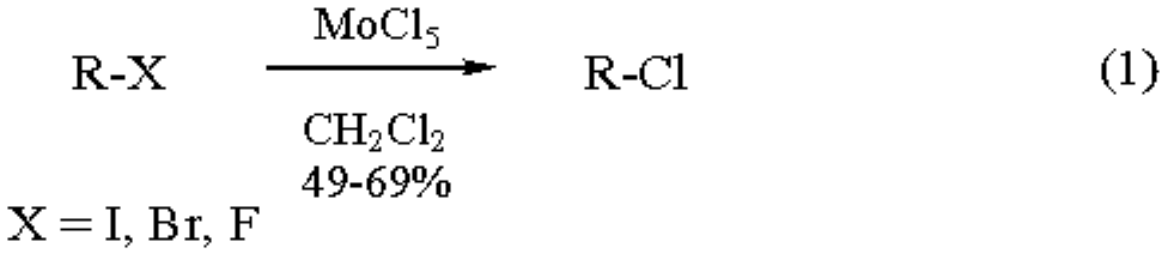

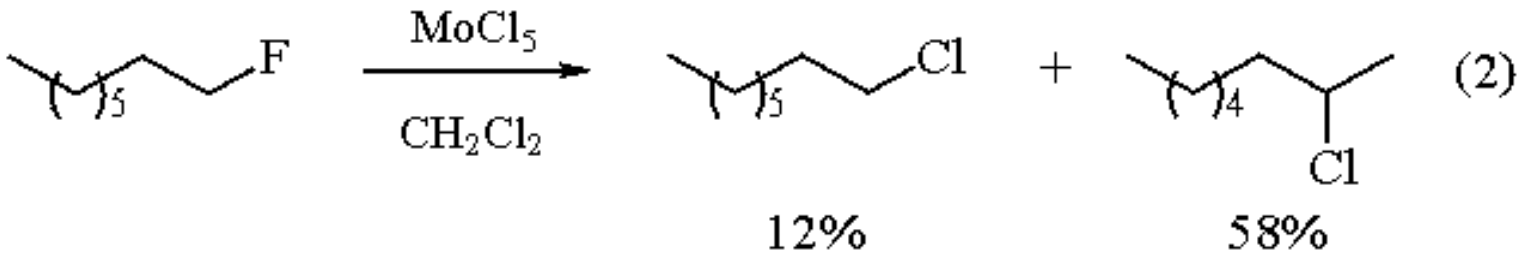

Vicinal Chlorination.[6]

The reaction of alkyl chlorides with an excess of $MoCl_5$ leads to vicinal chlorides in fair to excellent yields. For example, 2-chlorobutane is converted (eq 3) to (±)-2,3-dichlorobutane (58%) and *meso*-2,3-dichlorobutane (38%). The reaction sequence has been applied to the chlorination of alkyl halides containing either a secondary or tertiary vicinal carbon (eq 4).

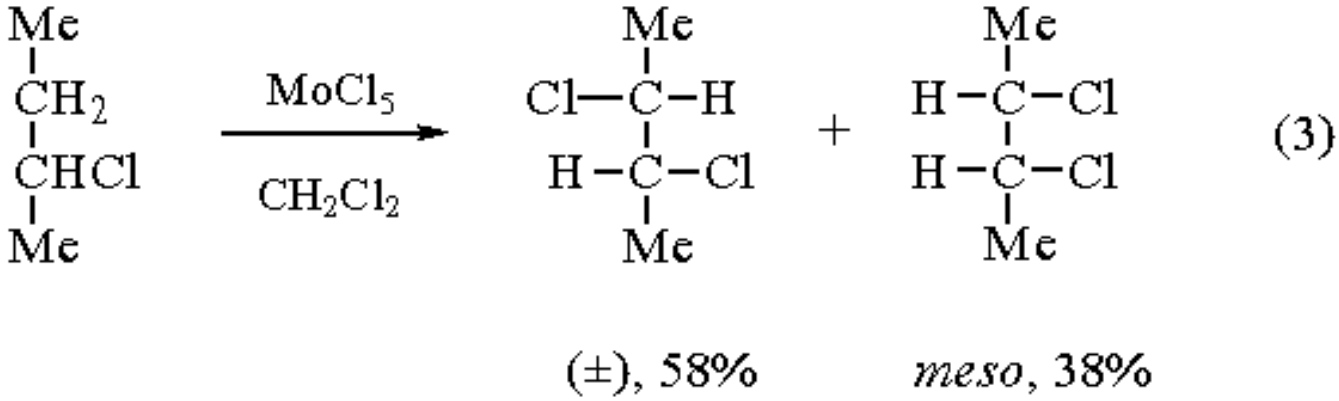

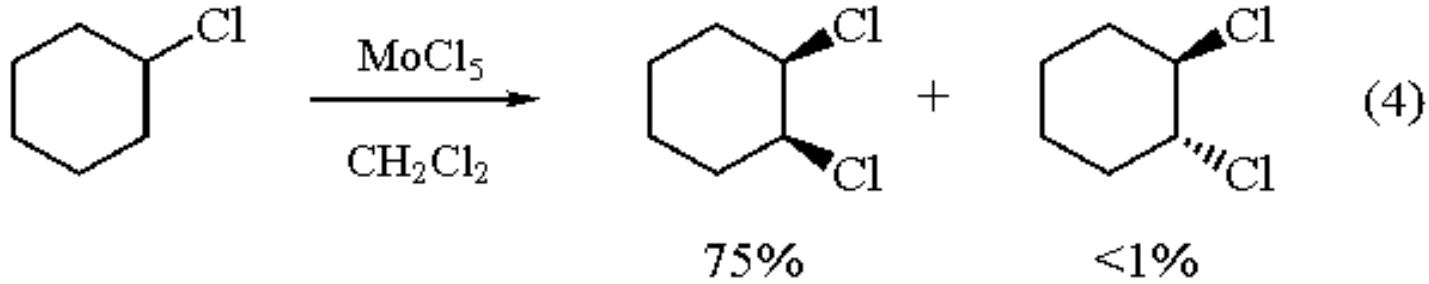

Chlorination of Alkenes and Alkynes.[7,8]

Chlorination of alkenes with $MoCl_5$ was first observed in the preparation of molybdenum(IV) chloride under irradiation, where upon hexachloroethane was produced from tetrachloroethylene (eq 5). Molybdenum(V) chloride

reacts with vicinal disubstituted alkenes and internal alkynes to produce dichloroalkanes and -alkenes, respectively, in fair to good yields. In this case, irradiation is not necessary. Typically (eq 6), cyclohexene in CH_2Cl_2 was treated with $MoCl_5$ to give *cis*-1,2-dichlorocyclohexane (68%), *trans*-1,2-dichlorocyclohexane (2%), cyclohexylcyclohexane (2%), and chlorocyclohexane (2%). Vicinal dichlorination may not proceed via the ionic or radical pathway characteristically observed in the reaction of alkenes with molecular chlorine. Chlorination of alkynes gives *cis*-addition (eq 7).

$$Cl_2C{=}CCl_2 \xrightarrow[\substack{CH_2Cl_2 \\ -2\ MoCl_4}]{2\ \text{equiv}\ MoCl_5} Cl_3C\text{-}CCl_3 \qquad (5)$$

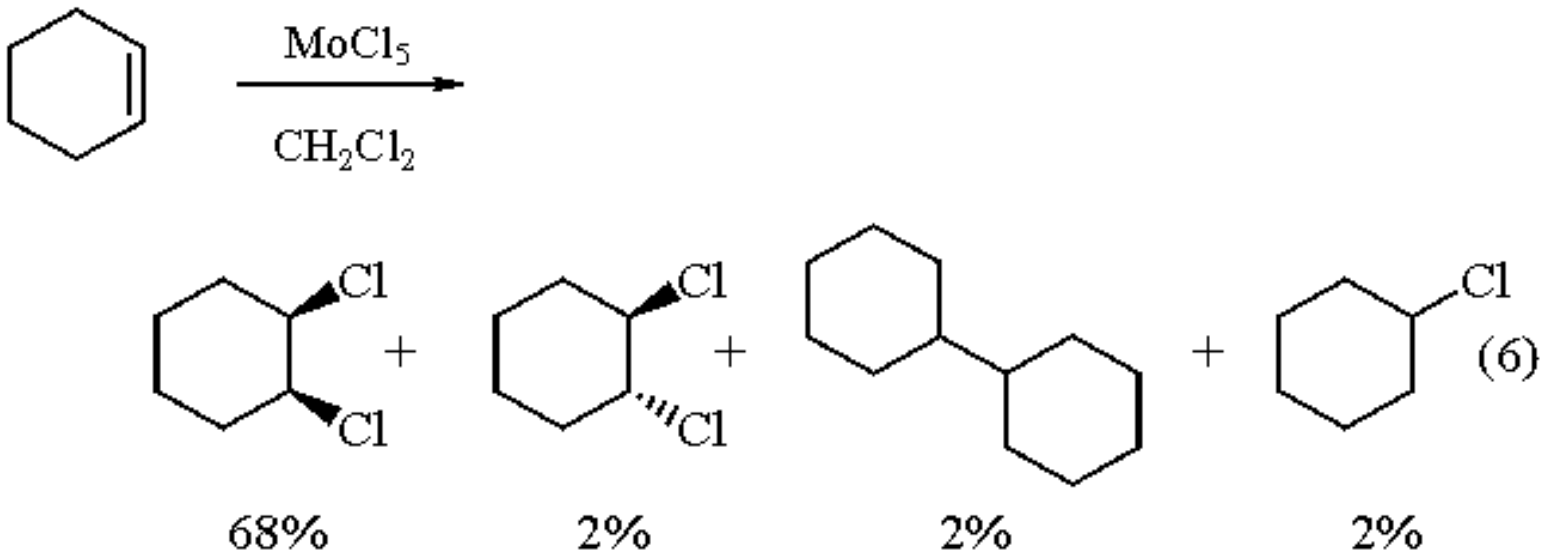

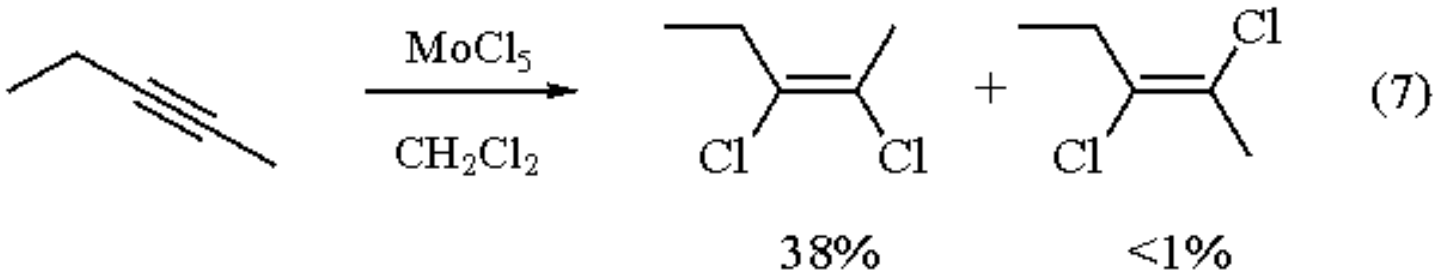

Catalyst for Insertion and Coupling Reactions.

The reagent ***Molybdenum(V) Chloride-Triphenylphosphine*** (1:6) promotes the insertion of CO_2 into methyloxirane at 20 °C under 1 atm (eq 8). This catalyst system gave best conversions and yields when using a 100- to 200-fold excess of oxirane relative to $MoCl_5$.[9]

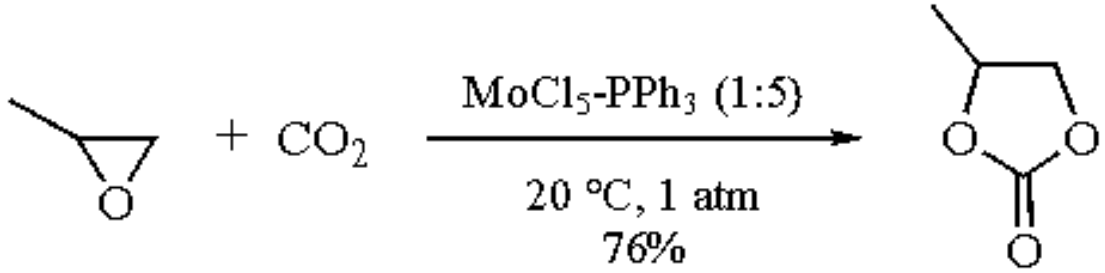

(8)

The conversion of *trans*-propenyllithium to 2,4-hexadiene is catalyzed by $MoCl_5$ (eq 9). Comparable yields were obtained with $MoCl_5$ and Ni^{II} reagents.[10]

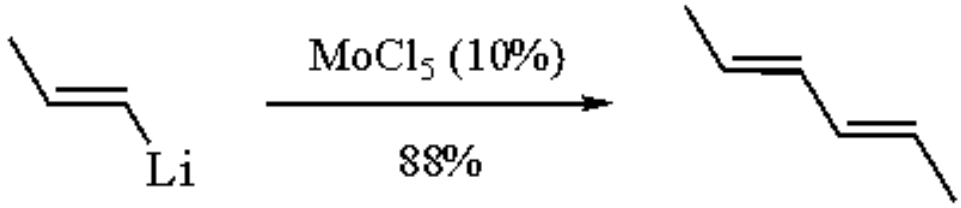

(9)

Nitrobenzene reacts with ethanol and higher alcohols in the presence of this reagent to form 2-methyl- or 2,3-dialkylquinolines (eq 10). The best yields and conversions are obtained in the presence of about equimolar or 0.5:1.0 mixtures of ***Tetracarbonyl(di-μ-chloro)dirhodium*** and $MoCl_5$ at 180 °C. Molybdenum species, due to their Lewis acidity, catalyze mainly the condensation reaction.[11]

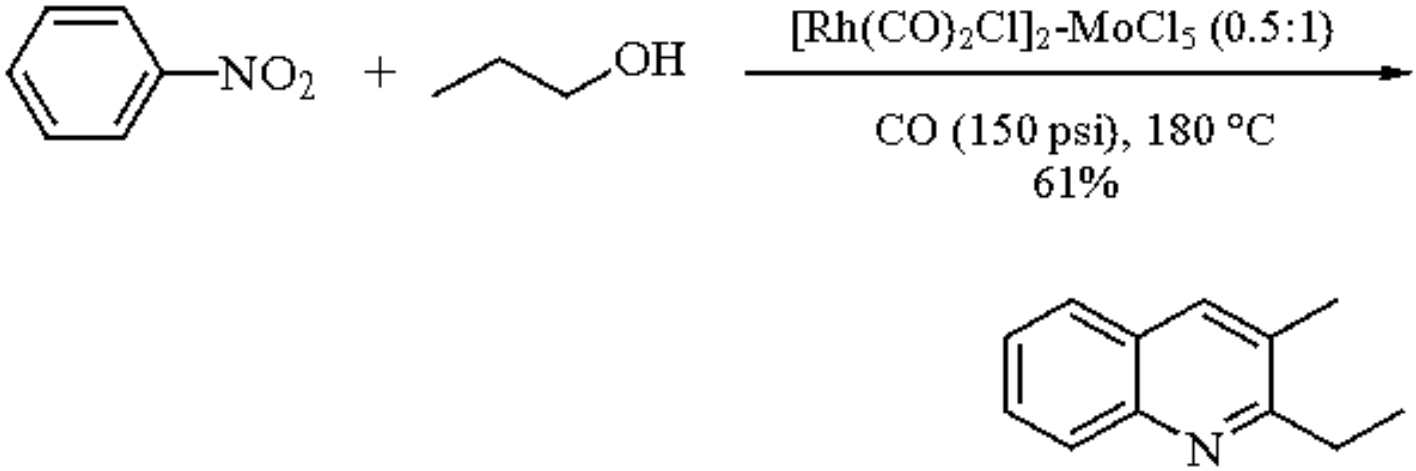

(10)

Deoxygenation with $MoCl_5$/Zn.[12,13]

An Mo^{III} species obtained by reaction of $MoCl_5$ with ***Zinc*** in aqueous THF reduces sulfoxides to sulfides in 78-91% yields (eq 11) and aromatic *N*-oxides in 45-65% yield (eq 12). The reagent also reduces aromatic and heteroaromatic nitro compounds to amines in 30-70% yields (eq 13). See also ***Molybdenum(V) Chloride-Zinc***.

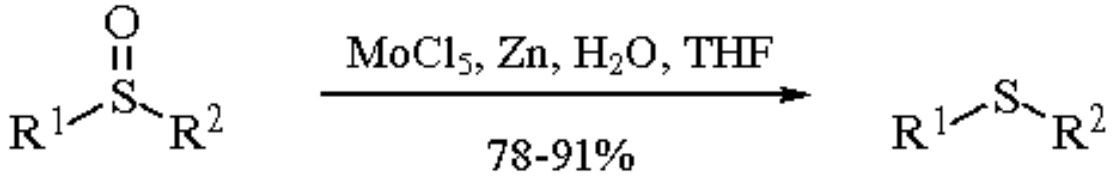

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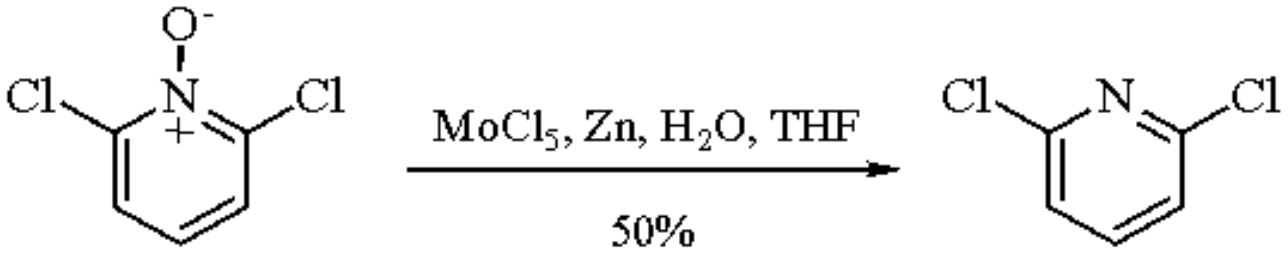

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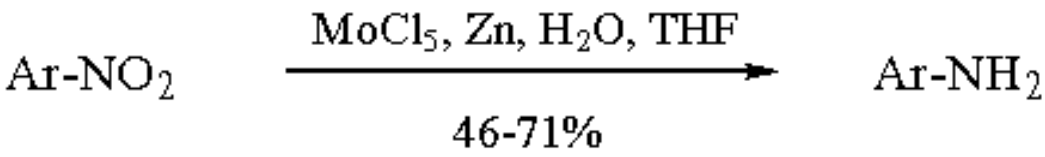

(13)

Lewis Acid-Catalyzed Reactions.[14,15]

Molybdenum(V) chloride is used as a Lewis acid for selective cleavage of carbon-oxygen bond of *O,S*-acetals and acetals in the reaction of trimethylstyrylsilanes, leading to the corresponding styryl adducts (eqs 14 and 15).

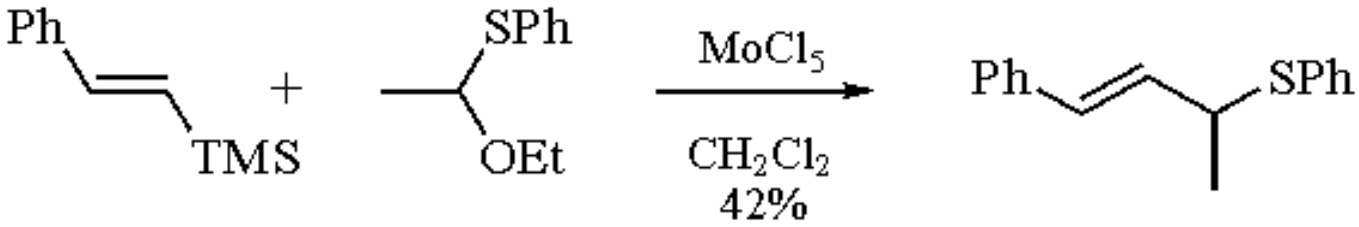

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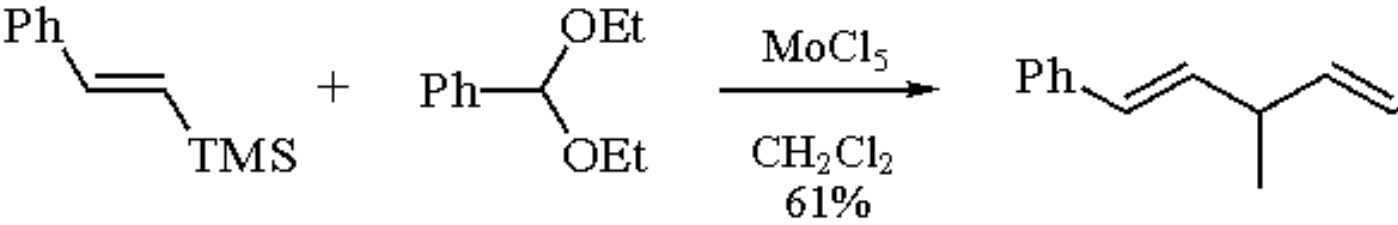

(15)

Chemoselective Carbonyl Methylenating Reagents.

$MoCl_5$ and substitution products of $MoCl_5$, such as $MoOCl_3(THF)_2$ or $(MeO)_2MoCl_3$ (= $MoCl_5$ + addition of THF or MeOH), are educts for a series of carbonyl methylenating reagents which are generated by reaction with ***Methyllithium***[16-18] or ***Trimethylaluminum***.[19] The reaction with MeLi is believed to occur according to eq 16 and yields carbonyl methylenating μ-methylene complexes which are in contrast to the carbonyl alkenating reagents of Wittig, Horner-Emmons, Peterson, Schrock, and Tebbe Lewis-acids and are highly chemoselective.

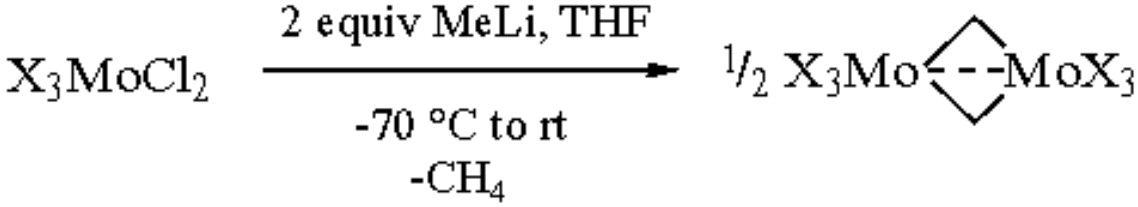

(16)

A limiting factor is the high thermolability of the reagents. The most closely investigated reagents are the following.

Reagent $MoCl_5$ + 2 MeLi.[17]

This reagent is inert towards the groups -COCl, $-CO_2R$, and $-CONR_2$, but methylenates aldehydes and ketones in good yields and discriminates well between aldehyde and keto groups in favor of the aldehyde group (e.g. eq 17). A corresponding reaction occurs with azomethines. The reaction with aromatic epoxides yields the corresponding alkenes, whereas in the case of aliphatic epoxides, chlorohydrins are produced.

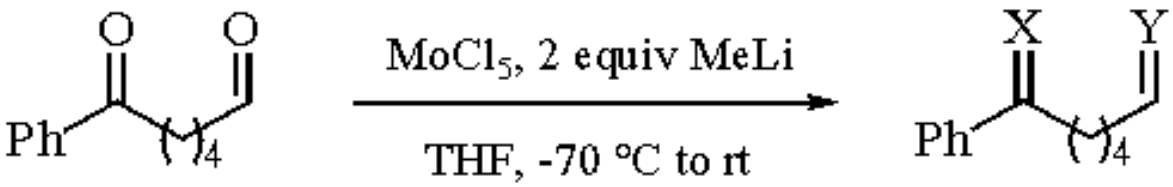

(17)

$X = O, Y = CH_2$; 80%
$X = CH_2, Y = O$; 0%
$X = Y = CH_2$; 1%

Reagent $MoOCl_3(THF)_2$ + 2 MeLi.[18]

This reagent allows regioselective carbonyl methylenation due to high aldehyde vs. ketone selectivity and cheleselectivity (preference of a keto group in the α- or β-position to a hydroxy group before an isolated keto group, e.g. eq 18), and tolerates the groups -COCl, $-CO_2R$, and $-CONR_2$ as well as water or alcohols in the solvent. It allows highly selective monomethylenation of dialdehydes, diketones, and triketones (e.g. eq 19).[16]

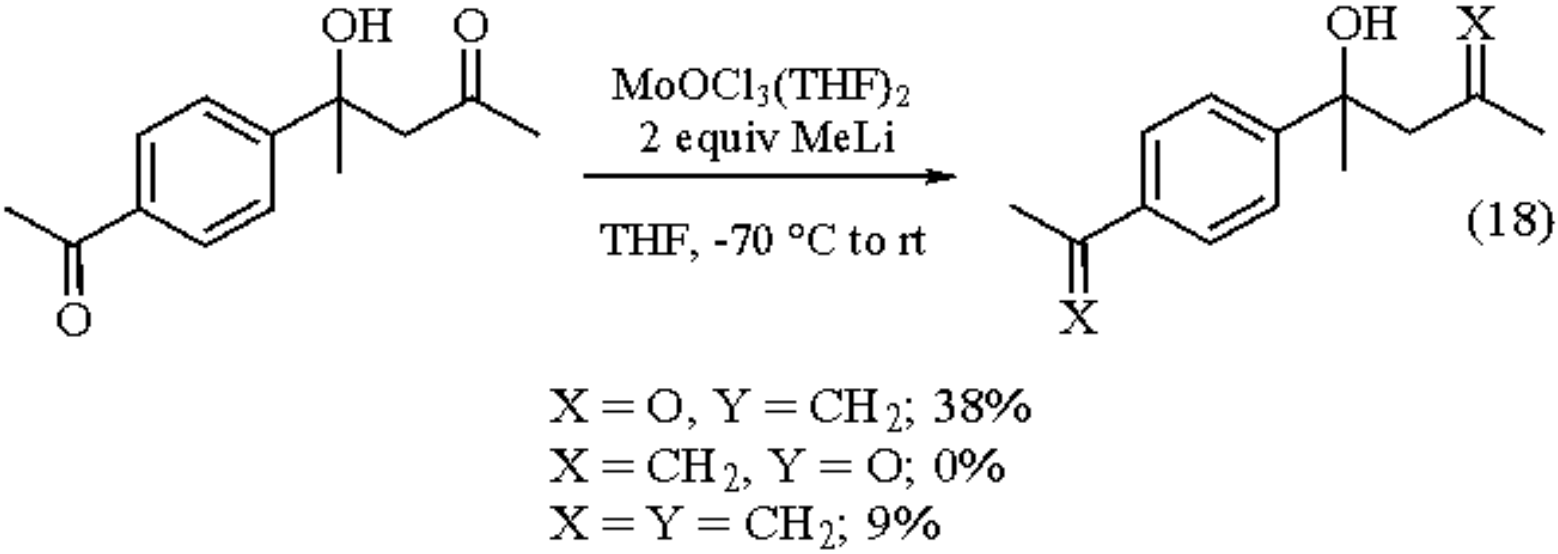

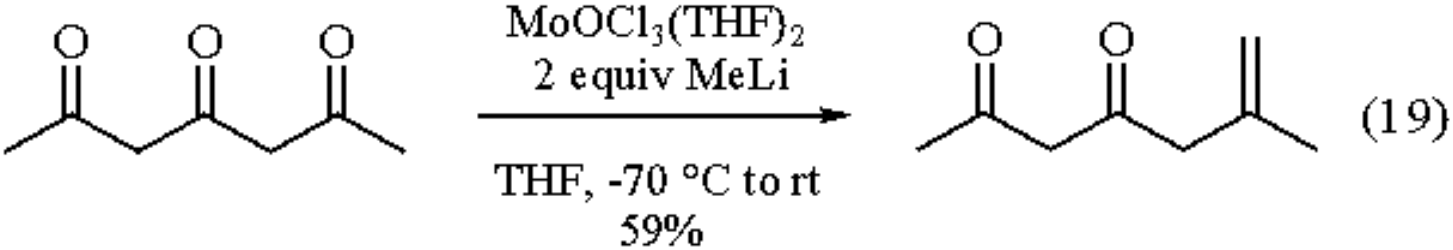

Molybdenocenes.

Stirring NaCp with $MoCl_5$ in THF at rt produces $Mo^{IV}Cp_2Cl_2$; CpMgCl reacts with $MoCl_5$ to give $[Cp_2Mo^{IV}Cl]^+$ ions, which can be precipitated by Reinecke acid.[20]

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18. (a) Kauffmann, T.; Fiegenbaum, P.; Wieschollek, R. *AG* **1984**, *96*, 500; *AG(E)* **1984**, *23*, 531. (b) Kauffmann, T.; Fiegenbaum, P.; Papenberg, M.; Wieschollek, R.; Wingbermühle, D. *CB* **1993**, *126*, 79. (c) Kauffmann, T.; Baune, J.; Fiegenbaum, P.; Hansmersmann, U.; Neiteler, C.; Papenberg, M.; Wieschollek, R. *CB* **1993**, *126*, 89.
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Molybdenum(V) Chloride-Triphenylphosphine

$MoCl_5$-PPh_3

($MoCl_5$)

[10241-05-1] · Cl_5Mo · Molybdenum(V) Chloride-Triphenylphosphine · (MW 273.19)
(PPh_3)

[603-35-0] · $C_{18}H_{15}P$ · Molybdenum(V) Chloride-Triphenylphosphine · (MW 262.30)

(carbon dioxide insertion;[2] cyclic carbonate preparation; Lewis acid catalysis)

Physical Data: see ***Molybdenum(V) Chloride*** and ***Triphenylphosphine***.

Solubility: $MoCl_5$: sol most organic solvents. PPh_3: sol Et_2O, $CHCl_3$, and most common organic solvents; slightly sol EtOH; insol H_2O.

Form Supplied in: $MoCl_5$: green-black solid; widely available. PPh_3: white crystalline solid; widely available.

Handling, Storage, and Precautions: $MoCl_5$ is air- and moisture-sensitive and somewhat corrosive. Ph_3P is fairly air-stable, but is slowly converted to its oxide, Ph_3PO, upon prolonged exposure. Ph_3P can be recrystallized from Et_2O. Use in a fume hood.

Cyclic Carbonates.

Molybdenum(V) chloride-triphenylphosphine (1:5) catalyzes the insertion of CO_2 into methyloxirane to afford the cyclic carbonate of propane-1,2-diol in 78% yield (eq 1). The reaction proceeds at room temperature and 1 atm CO_2 pressure. Other Lewis acids can be used in place of $MoCl_5$, although the molybdenum reagent is the most efficient.[1] Previously reported catalytic processes required elevated CO_2

pressure (5-200 atm) and temperature (100-200 °C).[2,3]

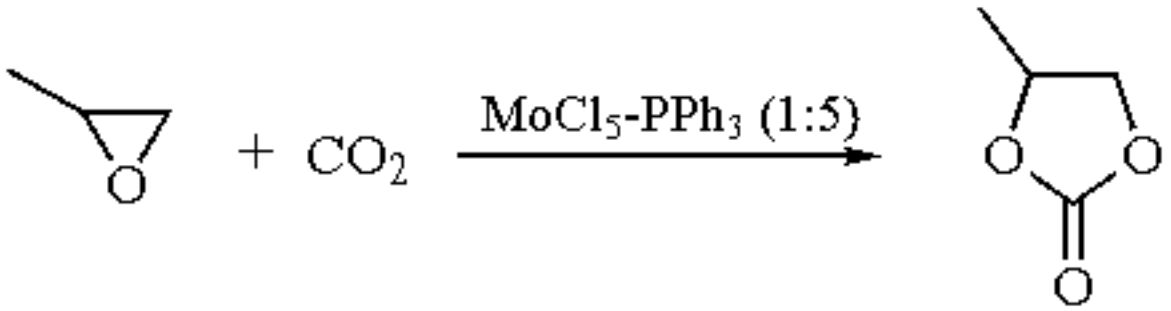

(1)

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Molybdenum(V) Chloride-Zinc

$MoCl_5$-Zn

($MoCl_5$)

[10241-05-1] · Cl_5Mo · Molybdenum(V) Chloride-Zinc · (MW 273.19) (Zn)

[7440-66-6] · Zn · Molybdenum(V) Chloride-Zinc · (MW 65.39)

(nitro group, *N*-oxide reduction;[5] amine preparation[4])

Physical Data: see ***Molybdenum(V) Chloride*** and ***Zinc***.

Solubility: $MoCl_5$: sol organic solvents. Zn: insol.

Form Supplied in: $MoCl_5$: green-black solid; widely available. Zn: metallic solid; widely available as powder, wire, or granular solid.

Handling, Storage, and Precautions: $MoCl_5$ is air- and moisture-sensitive and somewhat corrosive. Use in a fume hood.

Sulfoxide Reduction by Low-Valent Molybdenum Species.

Olah reported that treatment of a THF solution of $MoCl_5$ with H_2O followed by Zn metal produces a low-valent molybdenum species which effectively converts organic sulfoxides to sulfides at room temperature in high yields (78-91%). The active deoxygenating species in solution is believed to be some form of Mo^{III}. ***Vanadium(II) Chloride*** was found to mediate the same deoxygenation, although somewhat less efficiently.[1] Sulfoxide reduction has also been reported for low-valent molybdenum and tungsten species obtained by other means.[2,3]

Deoxygenation of *N*-Oxides and Reduction of Nitro Groups.[4]

Molybdenum(V) Chloride-Zinc is a mild, selective reagent for the deoxygenation of pyridine and pyridazine *N*-oxides and for the reduction of aromatic and heteroaromatic nitro groups to amines. Reported yields are moderate (29-71%); however, potentially sensitive functionality is tolerated (eqs 1-3).

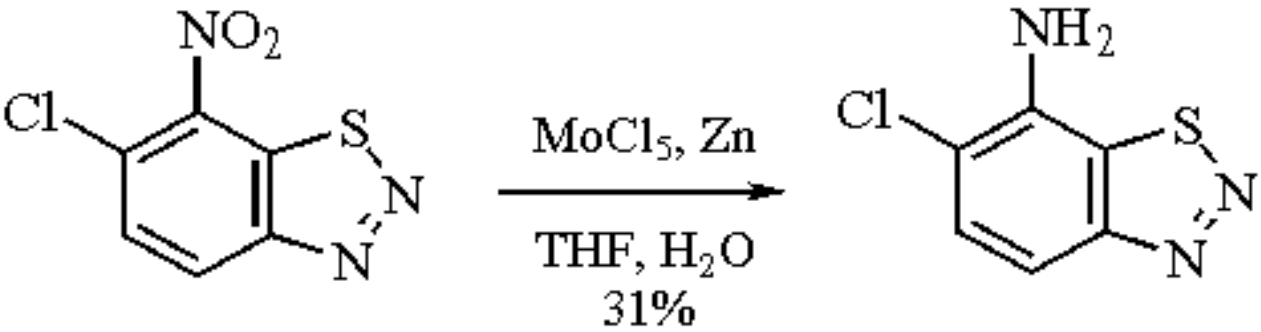

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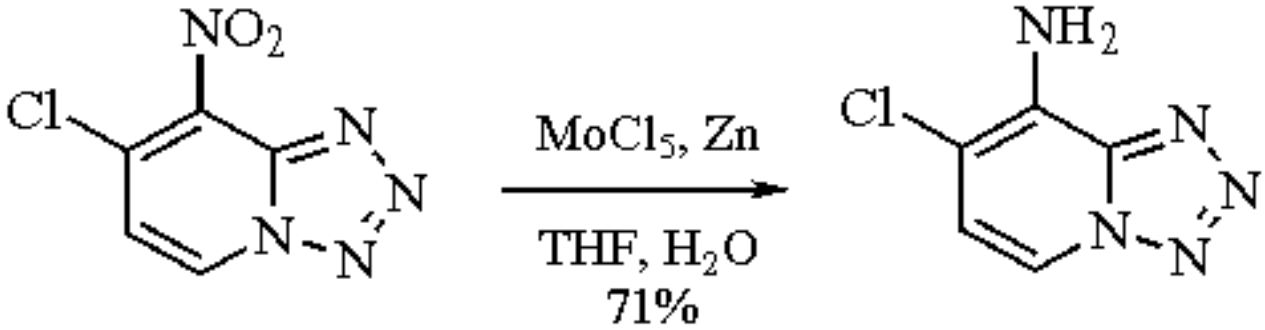

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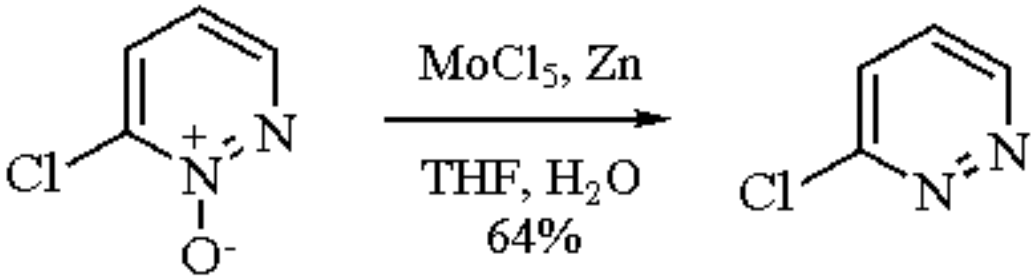

(3)

Other Reductions Mediated by Low-Valent Transition Metal Species.

The reduction of organic compounds by low-valent transition metal species has been reviewed by Ho.[5]

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Molybdenum(VI) Fluoride[1]

MoF_6

[7783-77-9] · F_6Mo · Molybdenum(VI) Fluoride · (MW 209.94)

(metathetic fluorination of carbonyl groups;[2] oxidation[3] or oxidative fluorination[4] of selected organic compounds)

Alternate Name: molybdenum hexafluoride.

Physical Data: mp 17.5 °C; bp 35 °C; *d* 2.543 g cm^{-3} (l, 19 °C).

Solubility: sol saturated hydrocarbons, chlorinated and fluorinated hydrocarbons. The rate of decomposition of the solution of MoF_6 in *n*-hexane is 1% h^{-1}. The reaction of MoF_6 with CCl_4 takes place at ca. 150 °C. MoF_6 reacts violently with H_2O and protic solvents.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: the purity of a MoF_6 solution can be checked by ^{19}F NMR: $\delta^{19}F$ (MoF_6) +290 ($MeCN/CFCl_3$, δ +ve for downfield shifts); $\delta^{19}F$ ($MoOF_4$) +148.

Handling, Storage, and Precautions: can be handled in normal glassware at or below room temperature. It attacks silica at 120-150 °C to give $MoOF_4$[5] and must be handled in stainless steel autoclaves for reactions at high temperature. Any leak can be detected by the deep blue color which results from the reaction of MoF_6 with moisture. Normal precautions when working with MoF_6 include gloves, glasses, and a good fume hood. Contact of a CH_2Cl_2 solution with the skin leads to superficial burnings, readily detected by their blue color. Molybdenum is reputed to be of low toxicity.

Oxygen to Fluorine Exchange Reactions.

The difference between the formation enthalpies of MoF_6(g) and $MoOF_4$(g) is ca. 55 kcal mol^{-1},[6] which may be compared with ca. 2 × 50 kcal mol^{-1} for the SF_4/SO_2 system. Hence, MoF_6 is expected to reproduce the oxygen to fluorine exchange reactions performed by ***Sulfur Tetrafluoride***. Indeed, in methylene chloride at room temperature with ***Boron Trifluoride*** as a catalyst, MoF_6 readily reacts with ketones and aldehydes to give the corresponding *gem*-difluoro compounds (eq 1).[2,7]

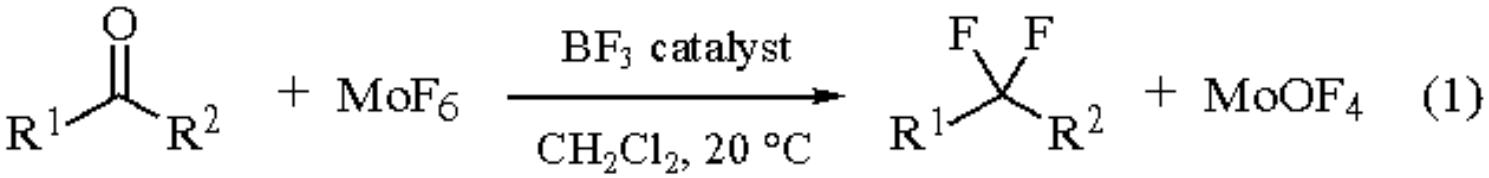

The transformation is compatible with organic functionalities such as Cl, Br, CO_2R, $C(O)NR_2$, CN, NO_2, and $P(O)R_2$. Alcohols, amines, ethers, and double bonds are attacked. MoF_6 is significantly stronger than SF_4 as a Lewis acid. This technique has been used inter alia for the preparation of *gem*-difluoro-substituted fatty acids.[8]

At high temperature and without a catalyst, MoF_6 is also able to convert aliphatic[9] and aromatic[10] carboxylic acids into *gem*-trifluoro derivatives (eqs 2 and 3).

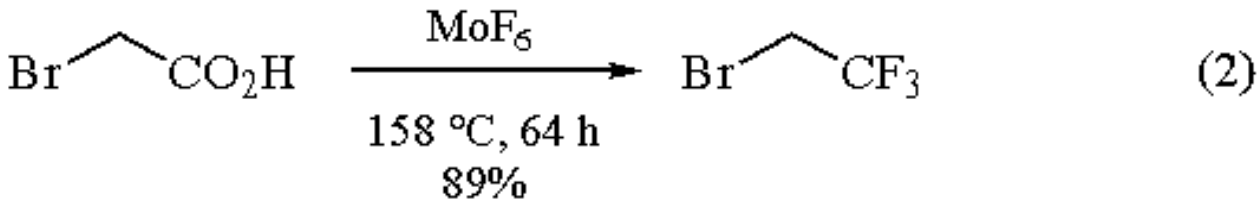

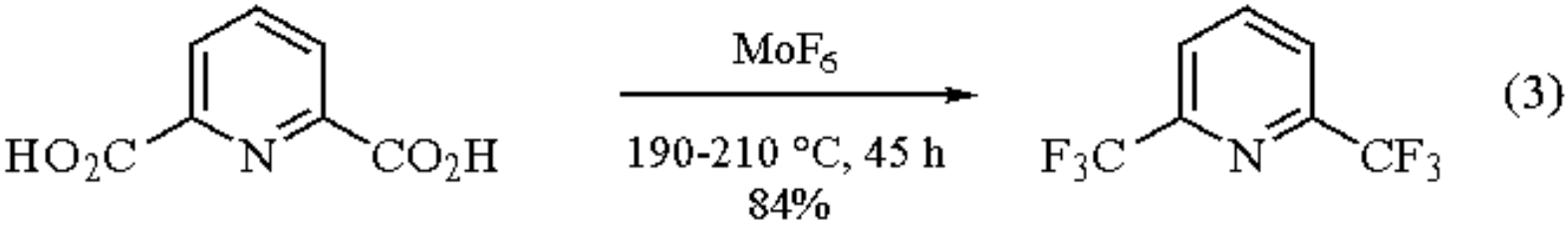

Aryl trifluoromethyl derivatives can also be obtained under less drastic conditions by fluorination of aromatic acid chlorides (eq 4).[11]

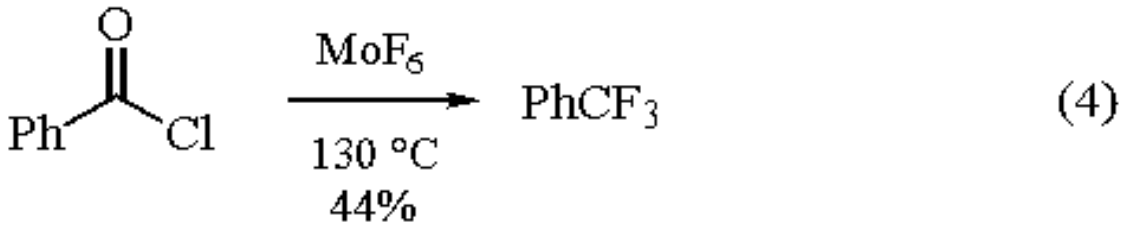

Ortho substitution of the arene ring blocks the reaction. In a related transformation, aryl chlorothioformates can be converted into aryl trifluoromethyl ethers (eq 5).[12]

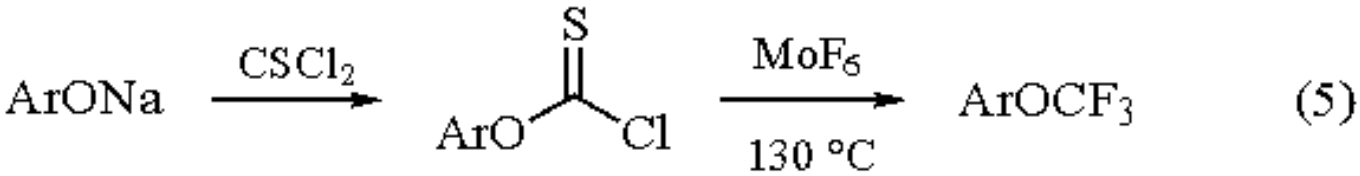

Owing to the presence of the oxygen spacer, the interconversion is no longer sensitive to *ortho* substitution and the yields are consistently high. Finally, two results worthy of note: MoF_6 converts ***Ethylene Oxide*** and trifluoroethanol,

respectively, into 1,1-difluoroethane (42%) and 1,1,1,2-tetrafluoroethane (85%).[9]

Oxidizing Agent.

Electrochemical studies in acetonitrile have shown that MoF_6 is a rather powerful oxidizing agent. The order $UF_6 > MoF_6 > NO^+ > Cu^{2+}$ &egt; WF_6 has been proposed.[13]

This property of MoF_6 can be used in organic synthesis. For example, Olah et al. have described the oxidative cleavage of hydrazones (eq 6).[3]

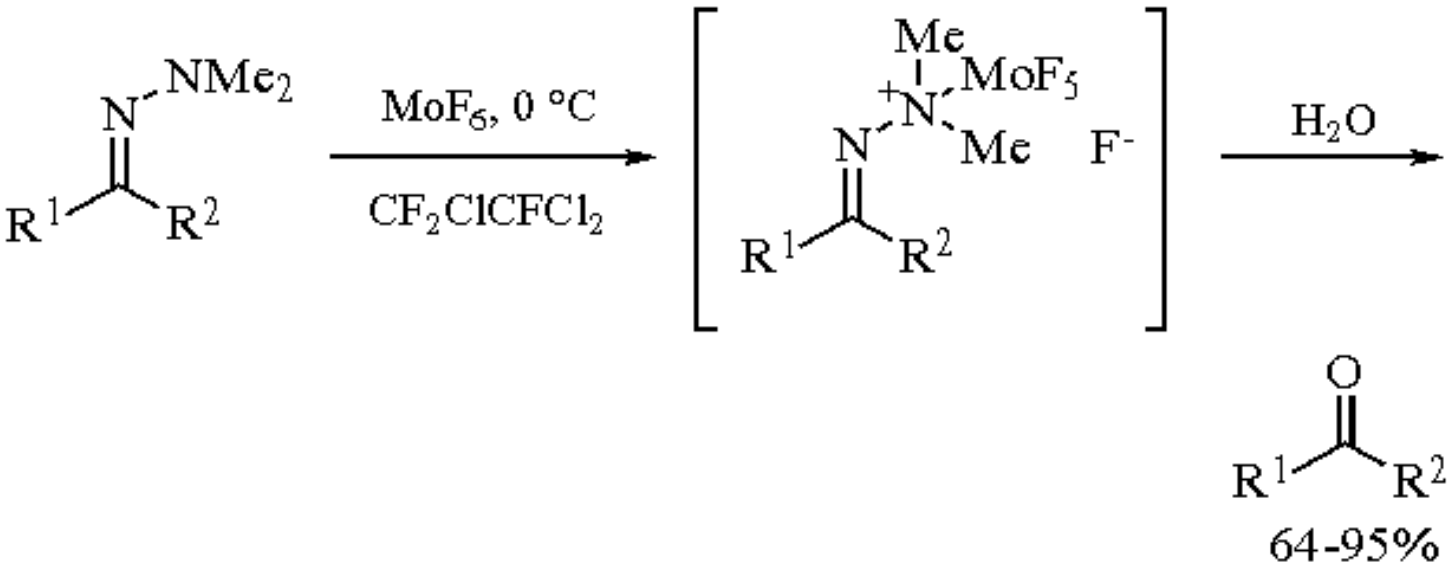

(6)

MoF_6 has also been used for the oxidative fluorination of phosphines into fluorophosphoranes (eqs 7 and 8).[4]

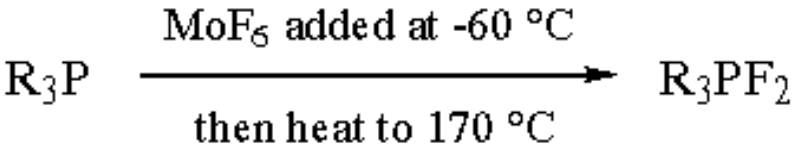

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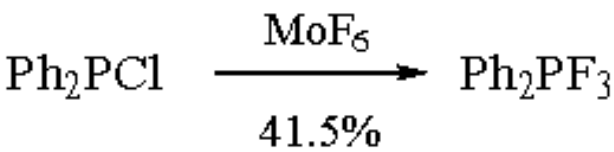

(8)

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Monochloroalane[1]

AlH_2Cl

[14644-71-4] · $AlClH_2$ · Monochloroalane · (MW 64.45)

(reducing agent for a variety of functional groups[1])

Alternate Name: aluminum chloride hydride.

Physical Data: the reagent is generated and used in situ. See ***Aluminum Chloride*** and ***Lithium Aluminum Hydride***.

Solubility: sol ether.

Preparative Methods: (a) A solution of 0.57 g (15 mmol) of $LiAlH_4$ in 15 mL of dry ether is mixed with a solution of 1.99 g (15 mmol) of $AlCl_3$ in 15 mL of dry ether at -5 °C. The resulting mixed hydride solution is stirred at room temperature for 15 min.[2] (b) To a precooled (0-5 °C) 20 mL of ether are added ground $AlCl_3$ (400 mg, 3.00 mmol) and $LiAlH_4$ (114 mg, 3.00 mmol), and the suspension is heated under reflux for 30 min.[3] This procedure provides AlH_2Cl as a suspension in ether.

Analysis of Reagent Purity: Metal Hydrides Technical Bulletin No. 401 describes an apparatus and methodology for assay by means of hydrogen evolution. See also Rickborn and Quartucci.[4] The IR spectrum of AlH_2Cl shows a strong Al-H stretching absorption band at 1852 cm^{-1}.[5]

Handling, Storage, and Precautions: solutions or suspensions of AlH_2Cl in ether are highly flammable and must be stored in the absence of moisture. Tetrahydrofuran is cleaved by AlH_2Cl to yield the corresponding aluminum alkoxide and is thus not a suitable solvent.

General Discussion.

This reagent readily reacts with aldehydes, ketones, esters, and epoxides to give alcohols, and also with amides, nitriles, and azides to give amines. Unlike ***Lithium Aluminum Hydride***, this reagent does not reduce nitro groups (eq 1).[6] Simple alkyl halides and tosylates are not readily reduced (eq 2).[7] Optically active azetidin-2-ones are reduced to the corresponding azetidines without cleavage of the β-lactam ring or loss of enantiomeric purity (eqs 3 and 4).[3]

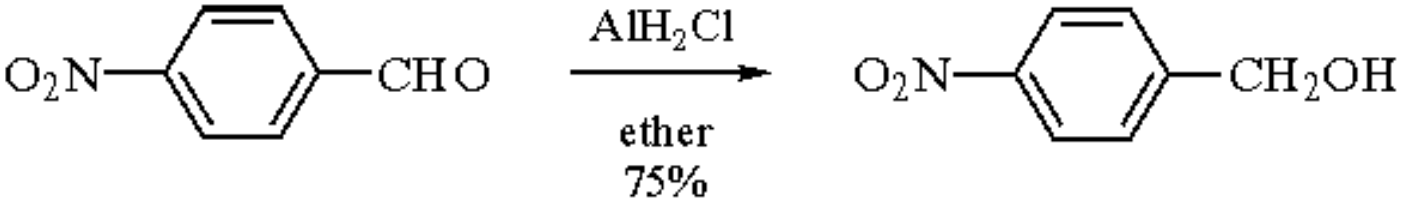

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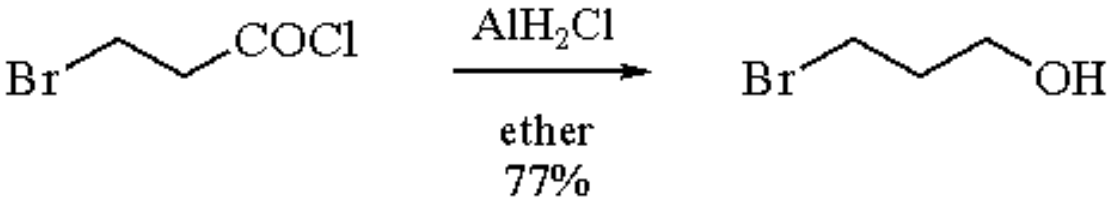

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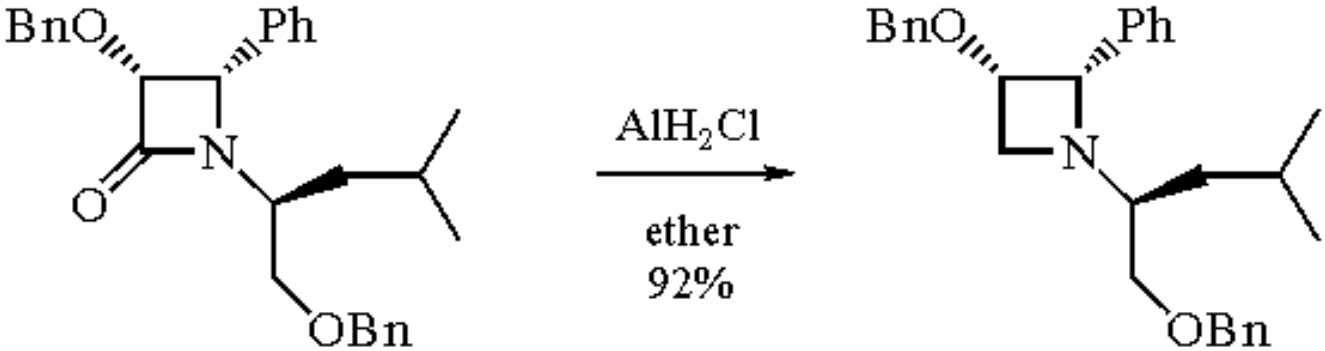

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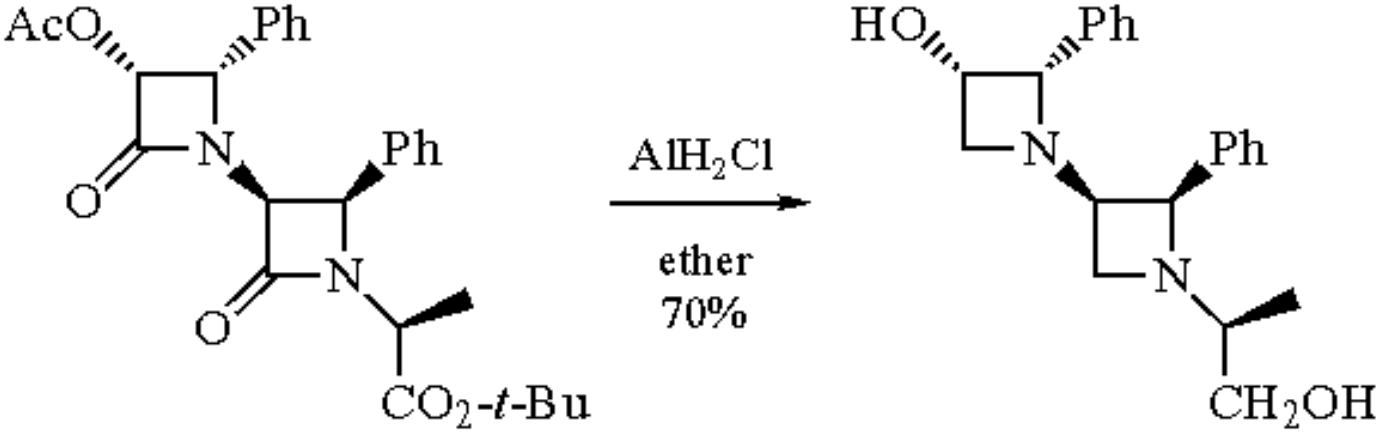

(4)

Aluminum chloride hydride is a milder reducing agent than $LiAlH_4$, which acts as a Lewis acid as well as a hydride donor. For example, epoxides are reduced to the corresponding alcohols, where the ring cleavage takes place at the more substituted carbon (eqs 5 and 6).[8] These results clearly show the strong Lewis acidity of this reagent.

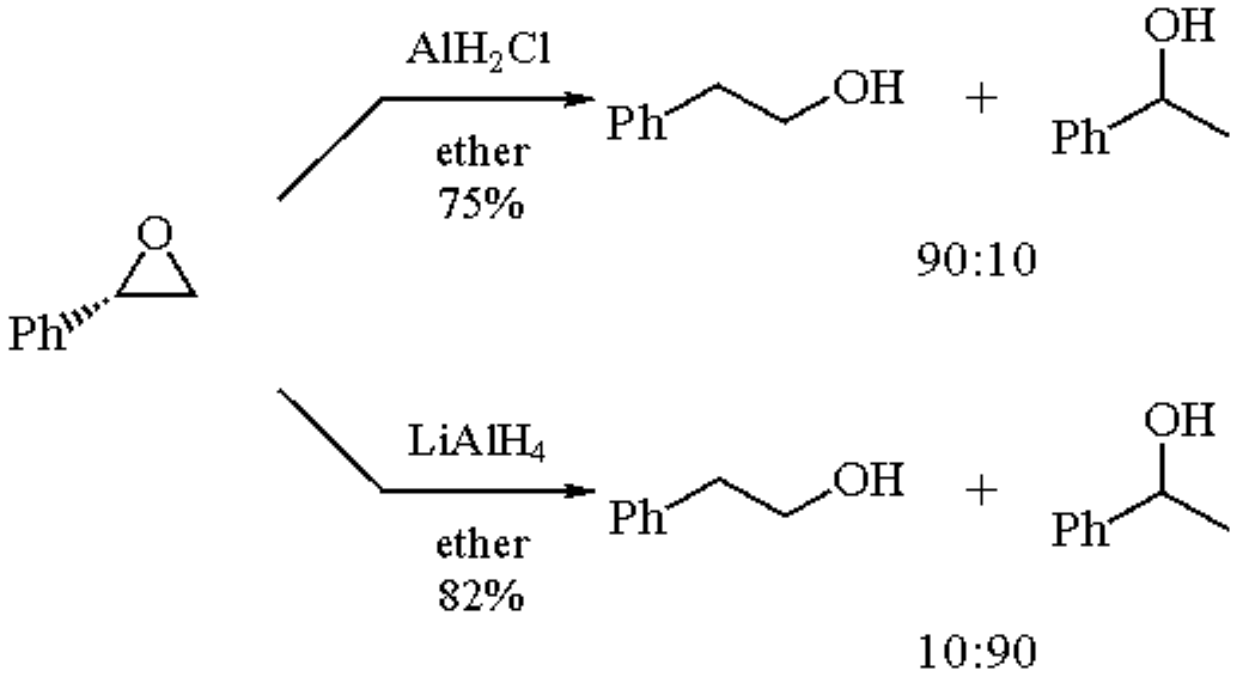

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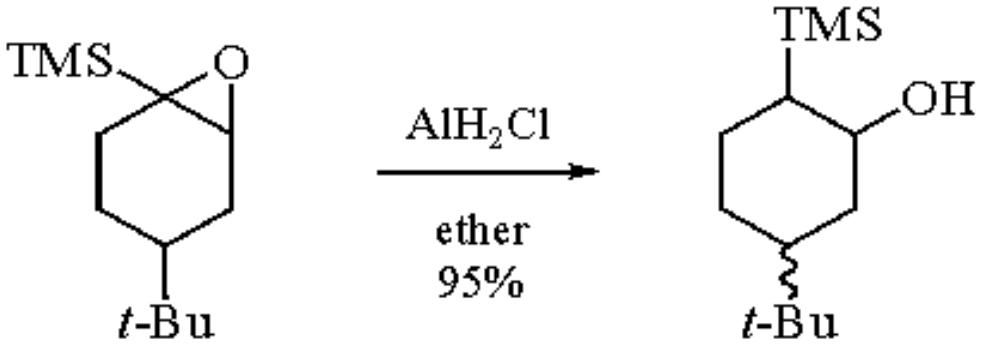

(6)

Reduction of cyclopropene esters proceeds with carbon-carbon bond migration, giving cyclobutenes in good yield (eq 7).[9] Reaction of 6β-methoxy-3α,5-cyclocholestane with AlH_2Cl gives 3α,5-cyclo-5α-cholestane as the major product (eq 8).[10]

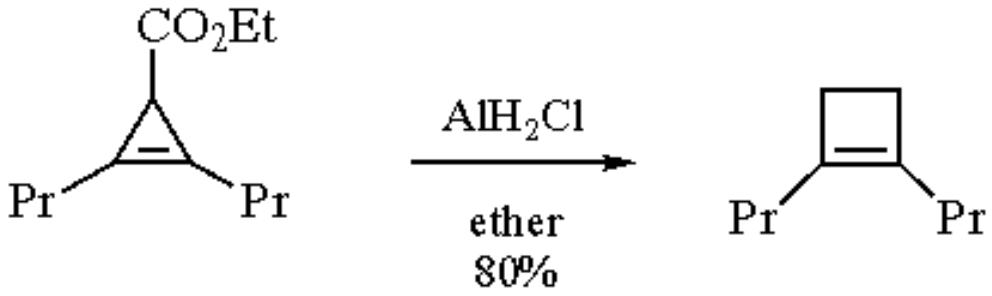

(7)

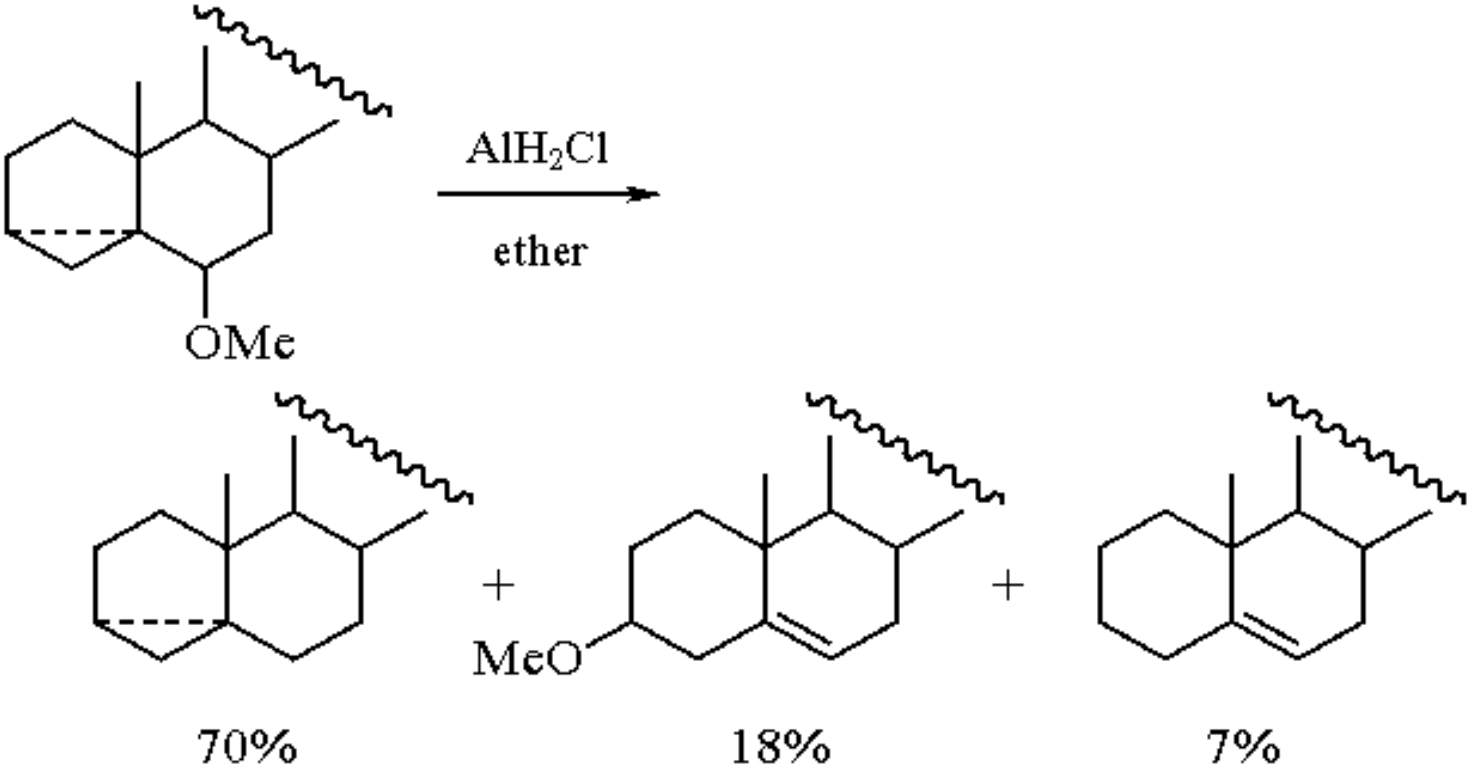

(8)

This reagent has a greater tendency to bring about hydrogenolysis than $LiAlH_4$. Conjugated ketones and esters are frequently reduced to hydrocarbons (eqs 9-11).[11]

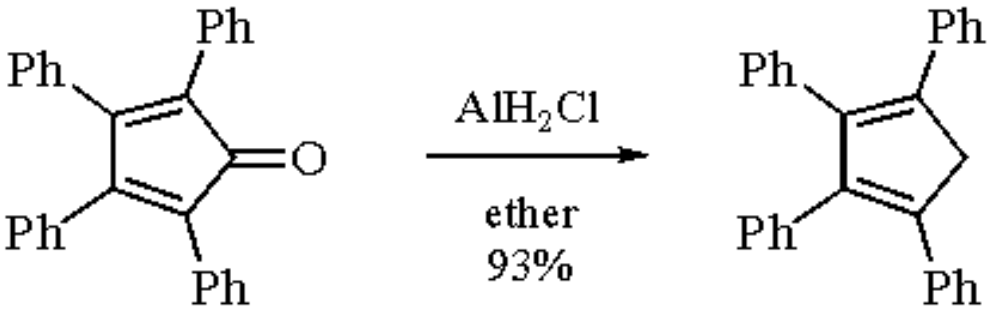

(9)

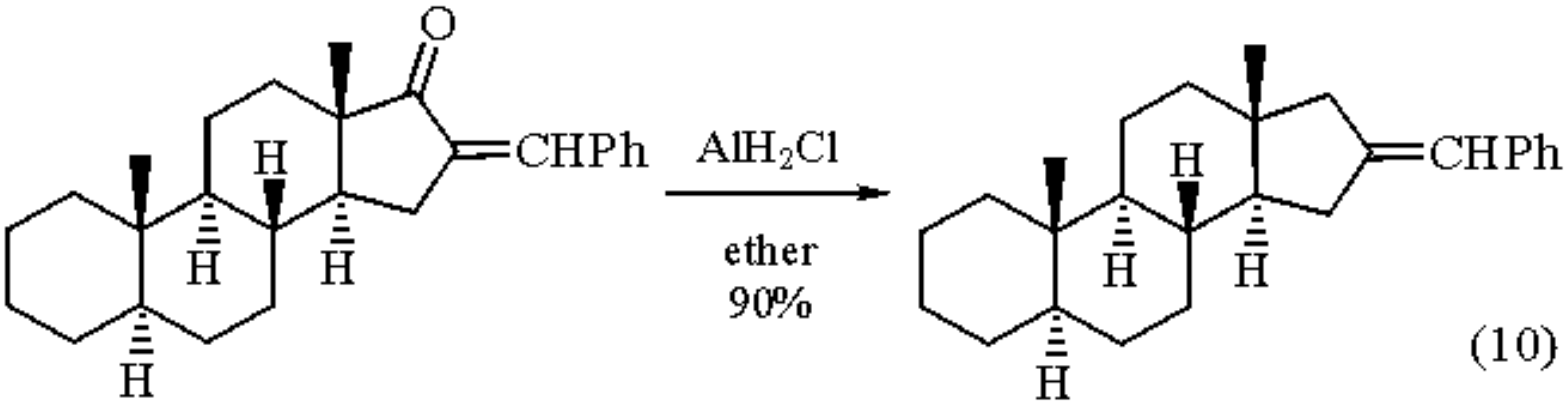

(10)

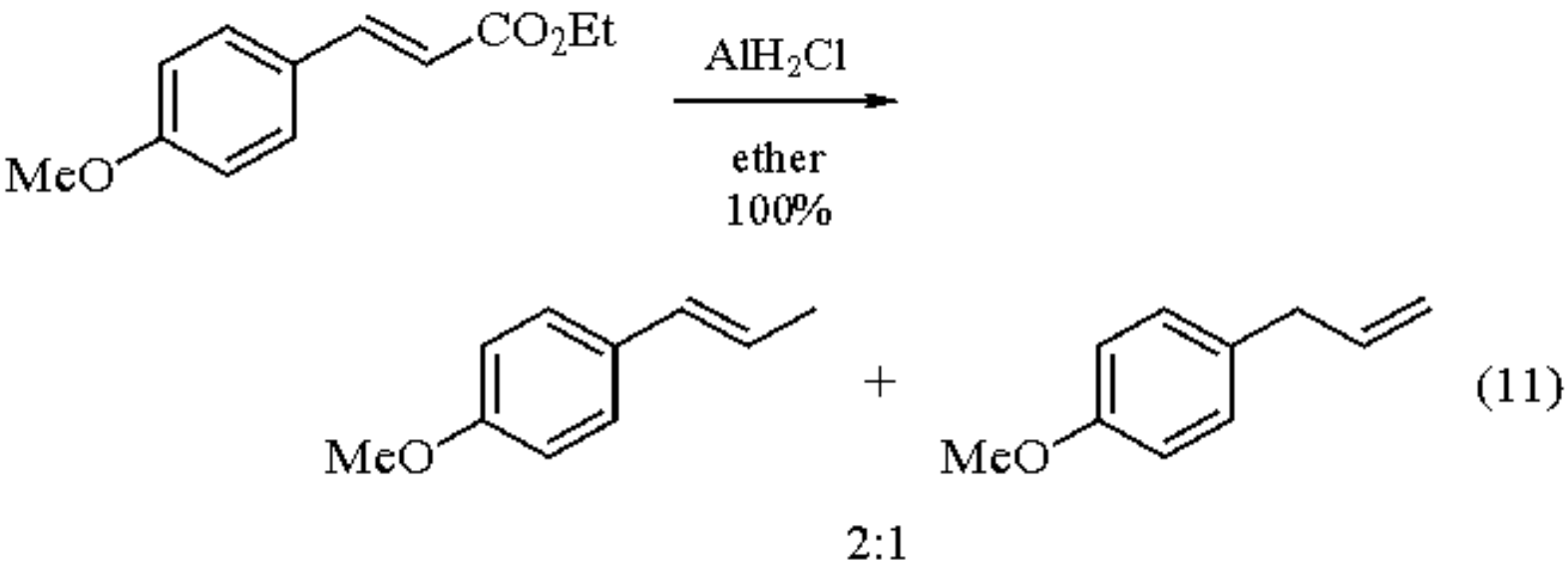

Aluminum chloride hydride is a convenient reagent for reductive cleavage of acetals to the corresponding ethers (eq 12),[1] and hemithioacetals to thioethers (eq 13).[12] Cyclic acetals are converted into hydroxy ethers (eqs 14 and 15).[13,14] The regioselectivity of the reaction is governed by the electronic and steric effects of the substituents of the acetals (eq 16).[15]

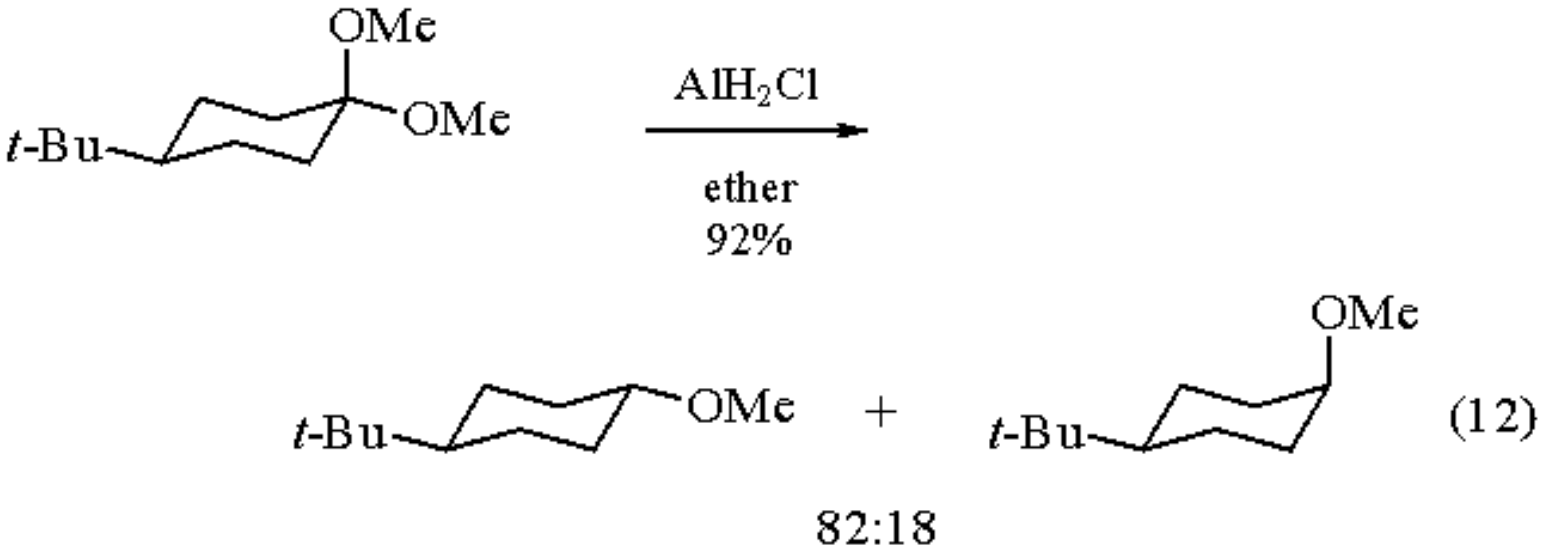

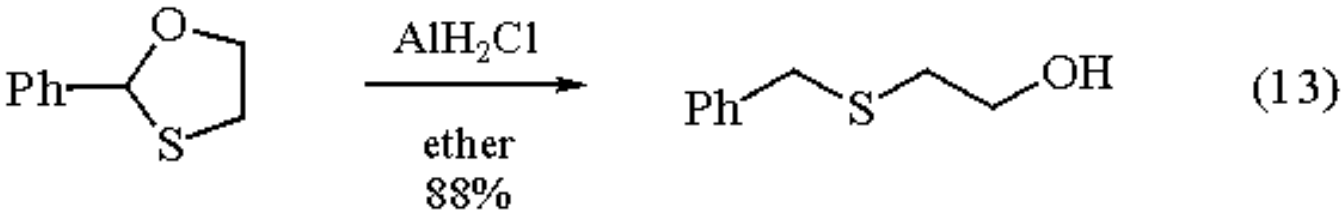

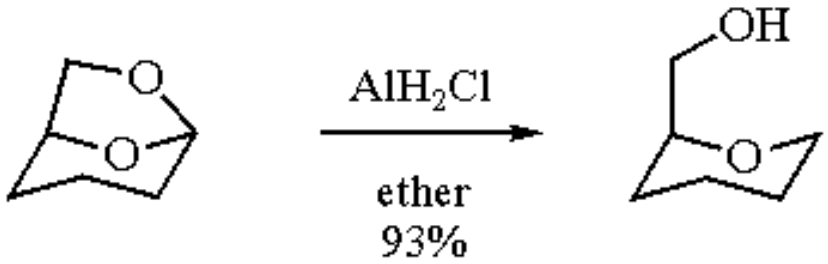

(14)

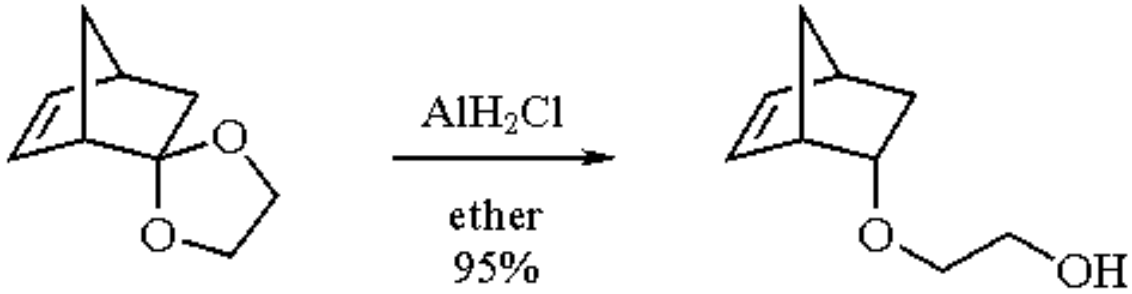

(15)

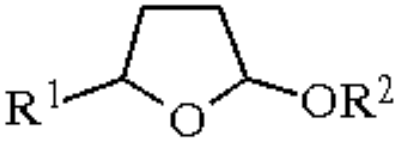

$\xrightarrow[\text{ether}]{AlH_2Cl}$ 80-86%

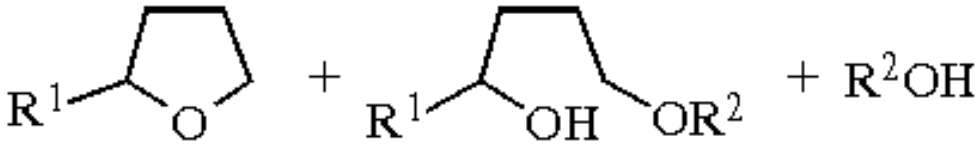

(1) **(2)** (16)

$R^1 = H$;	$R^2 =$ Me, Et, *i*-Pr, *t*-Bu	0:100
$R^1 = H$;	$R^2 =$ Ph	100:0
$R^1 =$ *t*-Bu;	$R^2 =$ Me	100:0
$R^1 =$ *i*-Pr;	$R^2 =$ Me	86:14
$R^1 =$ Ph	$R^2 =$ Me	15:85

Enamines are reduced to alkenes and amines in ether at reflux for 5-24 h, as exemplified in eq 17.[16]

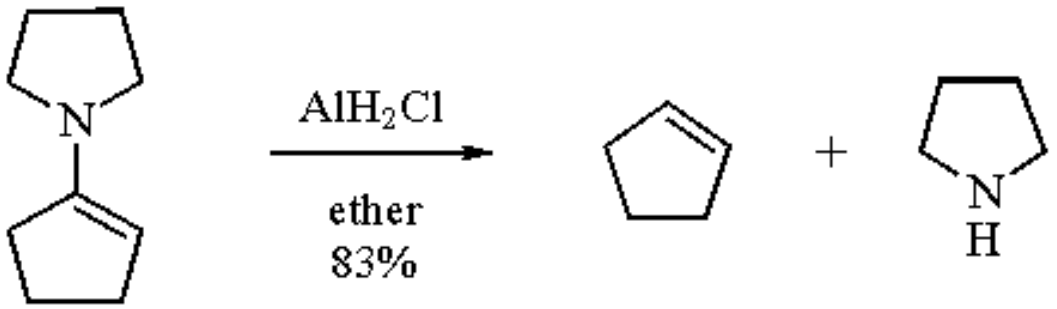

(17)

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Monochloroborane Diethyl Etherate[1]

$BH_2Cl.OEt_2$

[36594-41-9] · $C_4H_{12}BClO$ · Monochloroborane Diethyl Etherate · (MW 122.42)

(hydroborating agent providing access to dialkylchloroboranes,[2] dialkenylchloroboranes,[2] and *B*-chloro bora heterocycles,[3] all useful intermediates for the synthesis of alkenes, dienes, ketones, esters, secondary amines, hydroperoxides, and aminoboranes)

Physical Data: mp -105 to -85 °C.[4]

Solubility: sol diethyl ether.

Preparative Methods: conveniently prepared by the reaction of ***Lithium Borohydride*** with ***Boron Trichloride*** in diethyl ether.[2] The reaction can be monitored by ^{11}B NMR analysis. A 1.0-1.5 M solution of monochloroborane is obtained, existing in an equilibrium with a small amount of dichloroborane and borane (eq 1).[1a] The solution cannot be concentrated to obtain a neat product, since it loses diborane when excess ether is removed.[5]

$$\underset{\sim 90\%}{2\,BH_2Cl \cdot OEt_2} \rightleftharpoons \underset{\sim 5\%}{BHCl_2 \cdot OEt_2} + \underset{\sim 5\%}{BH_3 \cdot OEt_2} \quad (1)$$

Analysis of Reagent Purity: concentration of the reagent is determined by the analysis for hydride, chloride, and boron.[2,6] If the hydride and chloride are not in the proper ratio of 2:1, a calculated quantity of the solution in deficiency is added. In the ^{11}B NMR spectrum, the resonances for dichloroborane and borane should be of equal intensity; δ (ppm) 5.0 (t, $J_{B\text{-}H}$ = 131 Hz).[2a]

Handling, Storage, and Precautions: corrosive, flammable liquid; reacts violently with water. Monochloroborane solutions in diethyl ether are stable for several weeks when kept at 0 °C, protected from moisture and air. Handle and store under nitrogen or argon. Use in a fume hood.

Hydroboration of Alkenes.

Monochloroborane diethyl etherate reacts readily at 0 °C with alkenes to give dialkylchloroboranes in quantitative

yields (eq 2).[2] Regioselectivity of the hydroborations is greater than with ***Borane-Tetrahydrofuran*** (Figure 1).

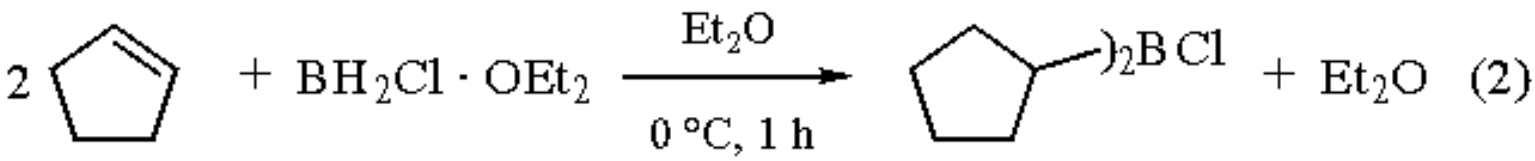

The hydroboration of alkenes with monochloroborane diethyl etherate can be controlled to stop at the monoalkylchloroborane stage by the addition of 1-2 equiv. of THF. Monoalkylchloroboranes can be isolated and characterized as complexes with ***Trimethylamine***. However, in diethyl ether solution, monoalkylchloroboranes readily disproportionate.[7] The stepwise hydroboration of two different alkenes with monochloroborane diethyl etherate in the presence of THF or ***Dimethyl Sulfide*** does not provide the mixed dialkylchloroboranes cleanly.[1a] Other procedures leading to these products and totally mixed trialkylboranes have been developed.[7-11]

Dialkylchloroboranes are useful synthetic intermediates. Since they are formed in excellent purity, they can often be used without isolation. Thus dialkylchloroboranes undergo facile reaction with ***Ethyl Diazoacetate*** at -78 °C to give the corresponding ethyl alkylacetates in nearly quantitative yield (eq 3).[12] Bulky alkyl groups are readily accommodated. Consequently, the reaction provides a general two-carbon homologation under remarkably mild conditions.

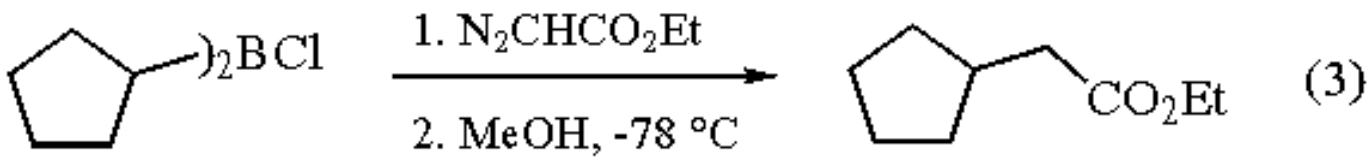

Treatment of dialkylchloroboranes with alcohols provides esters of dialkylborinic acids. These compounds react with ***Dichloromethyl Methyl Ether*** in the presence of lithium triethylcarboxide (DCME reaction) to give α-chloroborinic esters (eq 4). The esters are converted into alkenes by mild thermal treatment,[13,14] while oxidation provides ketones (eq 5).[14]

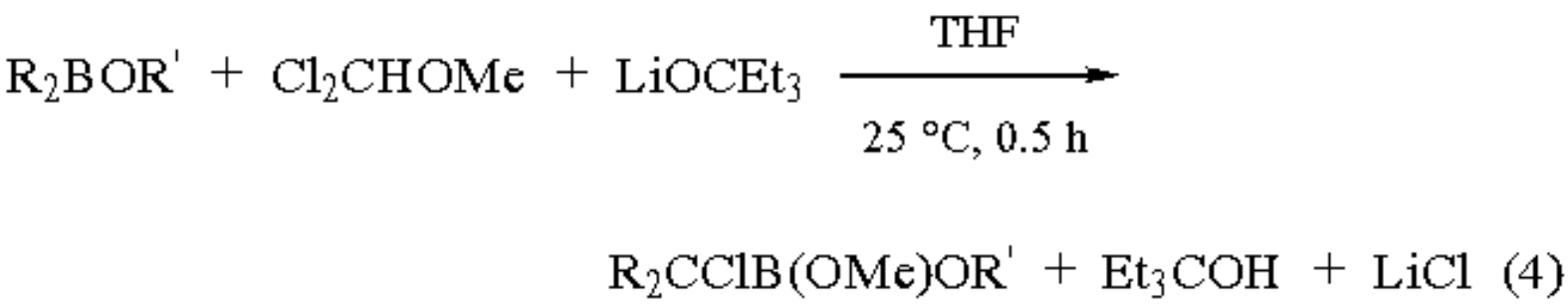

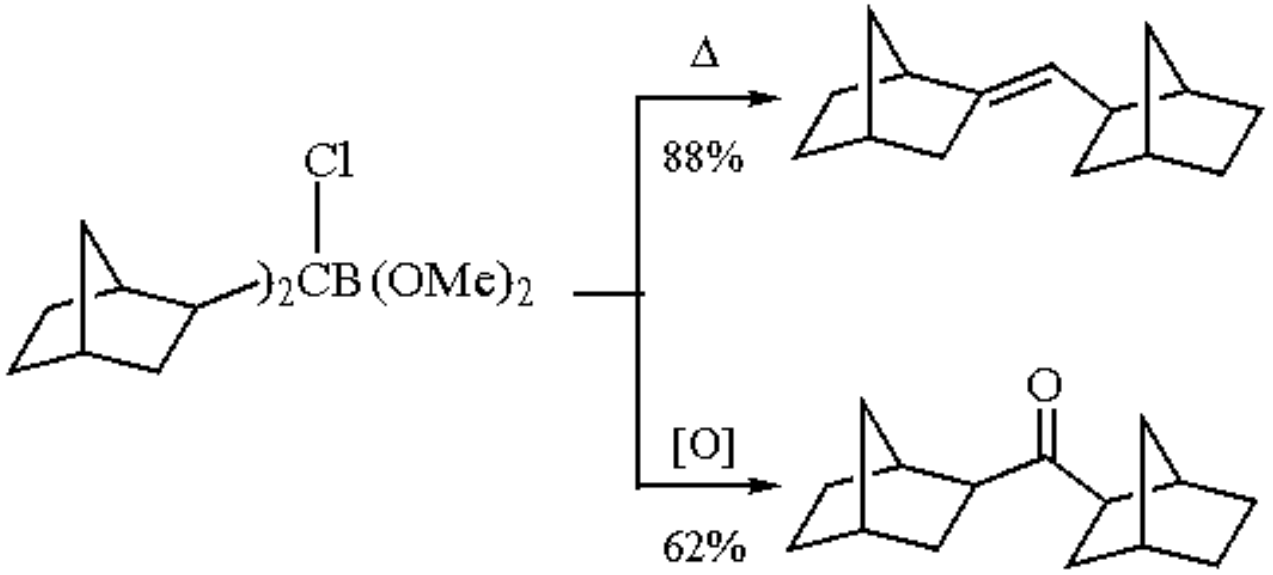

(5)

Unsymmetrical ketones can be synthesized by the reaction of dialkylchloroboranes with lithium aldimines (eq 6).[15]

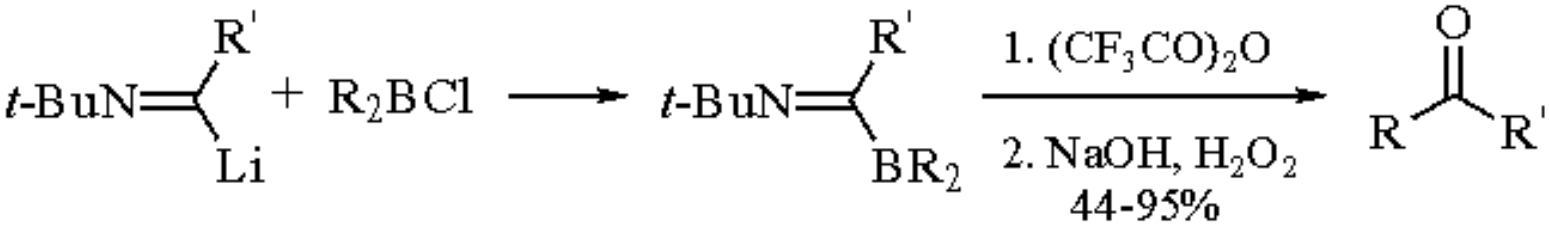

(6)

Dialkylchloroboranes react with organic azides to give secondary amines in 50-60% yields (eq 7).[16]

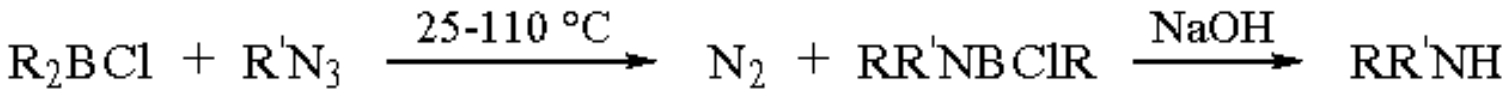

(7)

All reactions described above proceed with retention of configuration of the alkyl group.

B-Chlorodiisopinocampheylborane (Dip-chloride), an asymmetric dialkylchloroborane, can be prepared by hydroboration of α-pinene with $BH_2Cl.OEt_2$[17] (see also ***Monochloroborane-Dimethyl Sulfide***). It is a highly enantioselective reducing agent for ketones,[18] and is also used as a chiral catalyst in the asymmetric Diels-Alder reaction (see ***(+)-B-Chlorodiisopinocampheylborane***).[19] Other chiral dialkylboranes have been used in the asymmetric aldol reaction.[20] Alkyl hydroperoxides can be prepared by oxidation of dialkylchloroboranes with molecular oxygen under controlled conditions.[21] The reaction of $BH_2Cl.OEt_2$ with silazenes has been used for the synthesis of silylated aminoboranes.[22]

Hydroboration of Dienes.

α,o-Dienes react with monochloroborane to give a mixture of monomeric and polymeric products. Heating the mixture under vacuum provides *B*-chloroboracycloalkanes in good yields (eq 8).[3]

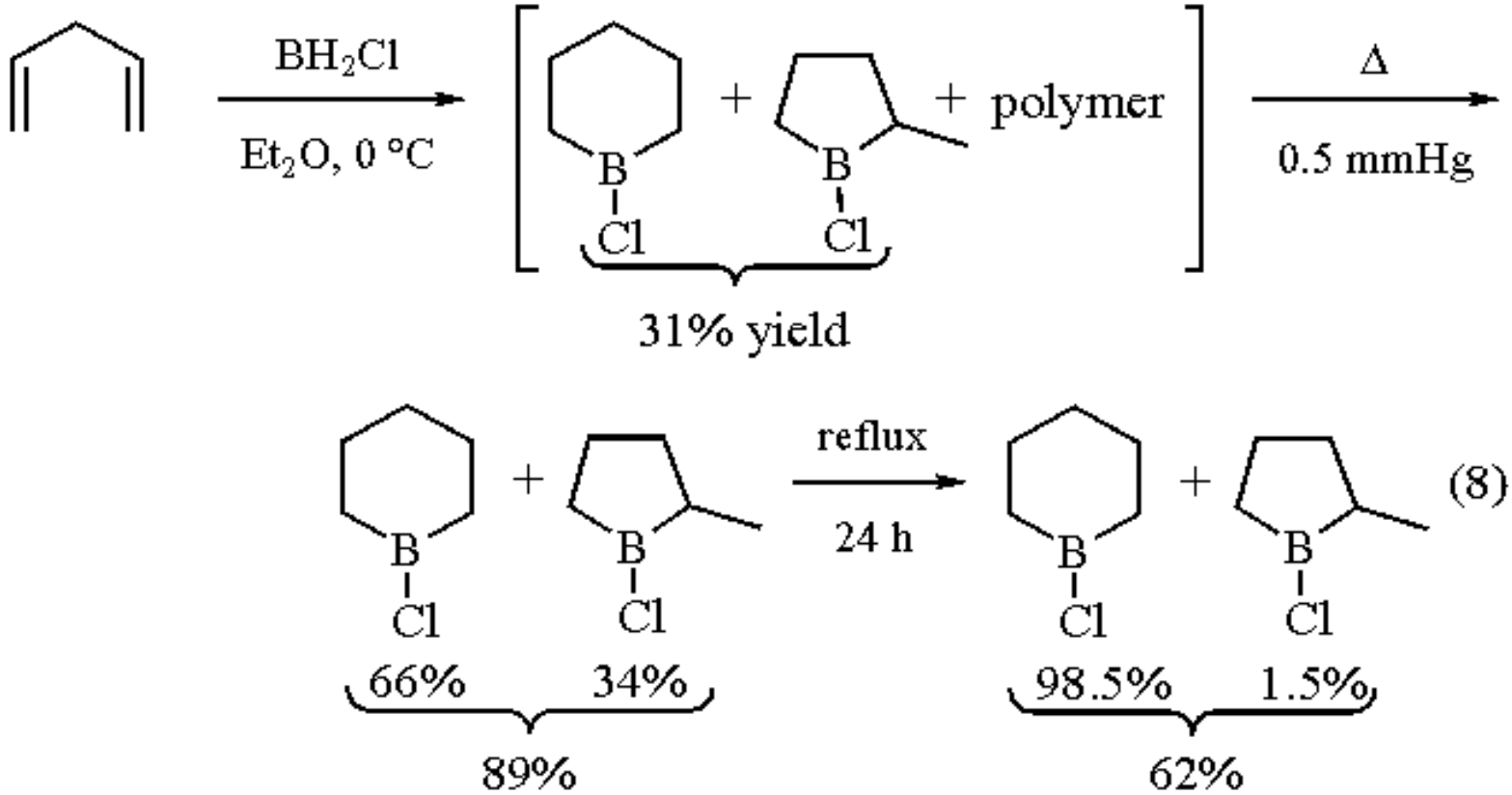

Pure *B*-chloroborinane, *B*-chloro-3,5-dimethylborinane, and *B*-chloroborepane are readily isolated. They find application in the synthesis of pheromones.[23-26] *B*-Chloroborocane, an eight-membered ring bora heterocycle, can also be prepared. However, higher medium-ring bora heterocycles are not available by this method. They can be prepared by a stepwise ring enlargement.[27]

Limonene is transformed into *B*-chlorolimonylborane which, upon reduction, gives limonylborane, an asymmetric hydroborating agent.[28] The monohydroboration of limonene and other cycloalkadienes gives unsaturated alcohols in 30-80% yields.[29]

Hydroboration of Alkynes.

The monohydroboration of alkynes with monochloroborane diethyl etherate proceeds cleanly at 0 °C to give dialkenylchloroboranes (eq 9).[2]

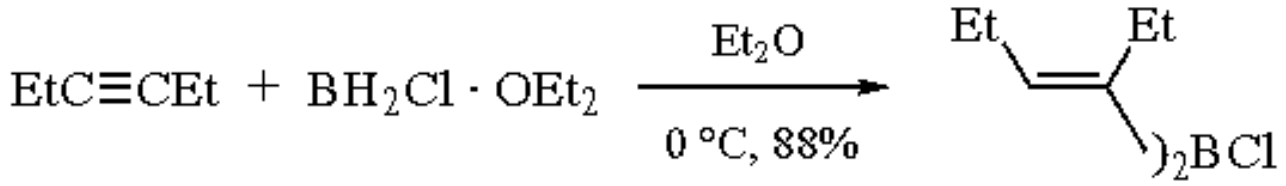

(9)

Internal alkynes react in a stoichiometric ratio, whereas 30-40% excess of a terminal alkyne must be used to avoid undesired dihydroboration. Dialkenylchloroboranes undergo the usual reactions of vinylboranes, e.g. protonolysis with ***Acetic Acid*** to alkenes and oxidation with alkaline ***Hydrogen Peroxide*** to carbonyl compounds. The most useful reactions of dialkenylchloroboranes is their conversion to stereochemically pure (*E*,*Z*)-1,3-dienes by the Zweifel reaction,[2] and to symmetrical (*E*,*E*)-1,3-dienes,[30] 1,4-dienes, and alkenes via vinylcopper intermediates[31] (eq 10).[2,30]

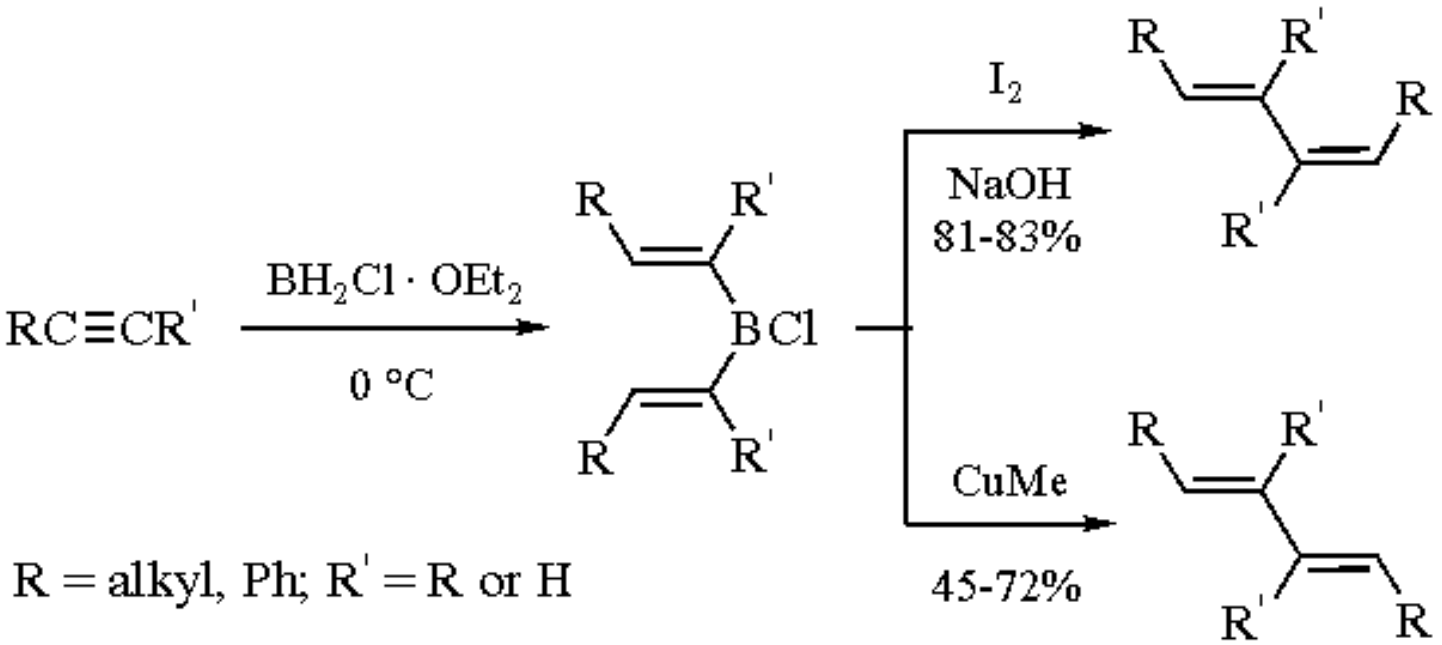

(10)

Dialkenylchloroboranes have been used for the preparation of dialkenylaminoboranes.[32]

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Monochloroborane-Dimethyl Sulfide[1]

$BH_2Cl.SMe_2$

[63348-81-2] · C_2H_8BClS · Monochloroborane-Dimethyl Sulfide · (MW 110.43)

(hydroborating agent providing access to thexylmonochloroborane,[2] dialkylchloroboranes,[3a] *B*-chloro bora heterocycles[4]; reagent for the cleavage of acetals[5] and epoxides[6])

Alternate Name: MCBS.

*Physical Data: d*204 1.059 g cm^{-3}.

Solubility: sol dichloromethane, pentane, diethyl ether.

Form Supplied in: colorless liquid.

Preparative Methods: by redistribution of ***Borane-Dimethyl Sulfide*** (BMS) and ***Boron Trichloride***.SMe_2[7] and by the reaction of BMS with CCl_4.[8] The reagent is in an equilibrium with approximately 15% each of $BHCl_2.SMe_2$ and BMS.[2,8-10]

Analysis of Reagent Purity: active hydride is determined by hydrolysis of an aliquot and measuring the hydrogen evolved according to the standard procedure.[11] ^{11}B NMR (CCl_4; δ, ppm) -7.2 (t),[9] -6.7 (t, J_{B-H} = 131 Hz).[7]

Handling, Storage, and Precautions: corrosive liquid; flammable; stench; reacts violently with water. Handle and store under nitrogen or argon. Stable indefinitely when stored under nitrogen at 25 °C. Use in a fume hood.

Hydroboration of Alkenes.

Monochloroborane dimethyl disulfide is a more convenient reagent than ***Monochloroborane Diethyl Etherate***. It is stable at room temperature, has higher concentration (9.5 M in BH_2Cl), and is soluble in various solvents. MCBS hydroborates both terminal and internal alkenes in less than 2 h at 25 °C in dichloromethane, pentane, or diethyl ether.[3a] The regioselectivity of addition to alkenes is similar to monochloroborane diethyl etherate. Even relatively hindered alkenes produce dialkylchloroboranes, e.g. α-pinene and 2-ethylapopinene are transformed into *B*-chlorodiisopinocampheylborane (Dip-chloride)[12a] and *B*-chlorobis(2-ethylapoisopinocampheyl)borane (Eap_2BCl),

respectively. Both are highly enantioselective reducing agents for ketones (see ***(+)-B-Chlorodiisopinocampheylborane***).[12]

With very hindered alkenes, the hydroboration stops at the monoalkylborane stage. Thus 2,3-dimethyl-2-butene gives cleanly ***Chloro(thexyl)borane-Dimethyl Sulfide*** (eq 1),[2] a useful hydroborating and reducing agent;[2,13-17] for example, it reduces carboxylic acids to aldehydes.[17]

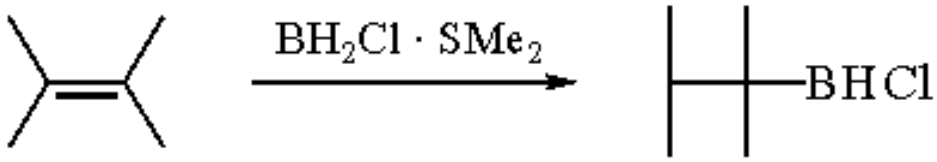

(1)

Nopol methyl ether also reacts with MCBS in 1:1 molar ratio, the intramolecular complexation halting further reaction (eq 2).[9]

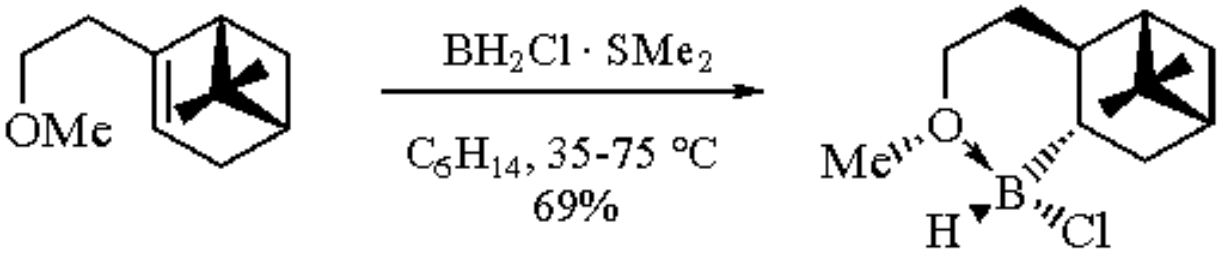

(2)

Synthesis of (*E*)- and (*Z*)-Alkenes and Ketones.

Dialkylchloroboranes are useful synthetic intermediates. They are readily methanolyzed, affording methyl dialkylborinates, which can be further transformed into ketones by the ***Dichloromethyl Methyl Ether*** (DCME) reaction (eq 3).[3]

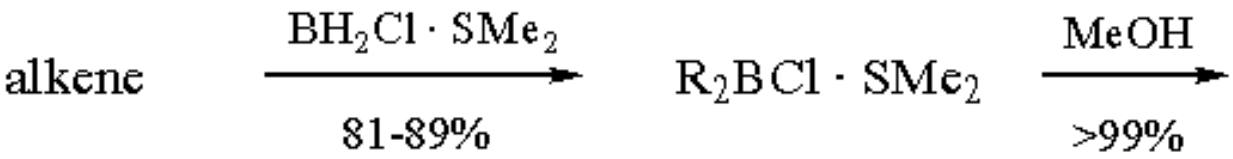

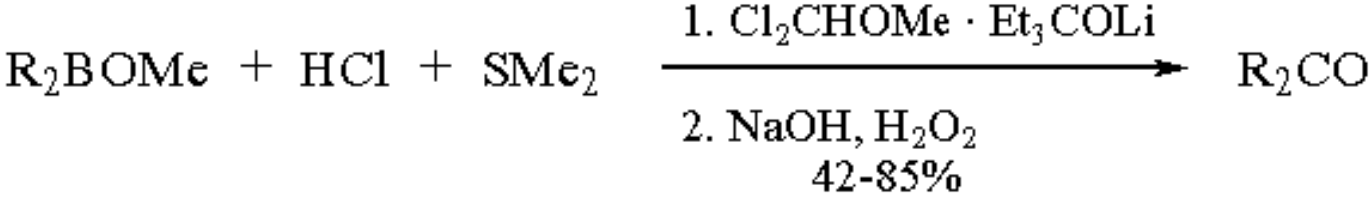

(3)

The hydride reduction (hydridation) of dialkylchloroboranes provides access to a variety of dialkylboranes not available by direct hydroboration with borane itself.[18] These dialkylboranes are convenient intermediates for the Zweifel synthesis of (*E*)-[19] (eq 4) and (*Z*)-disubstituted[20] alkenes and trisubstituted alkenes.[21]

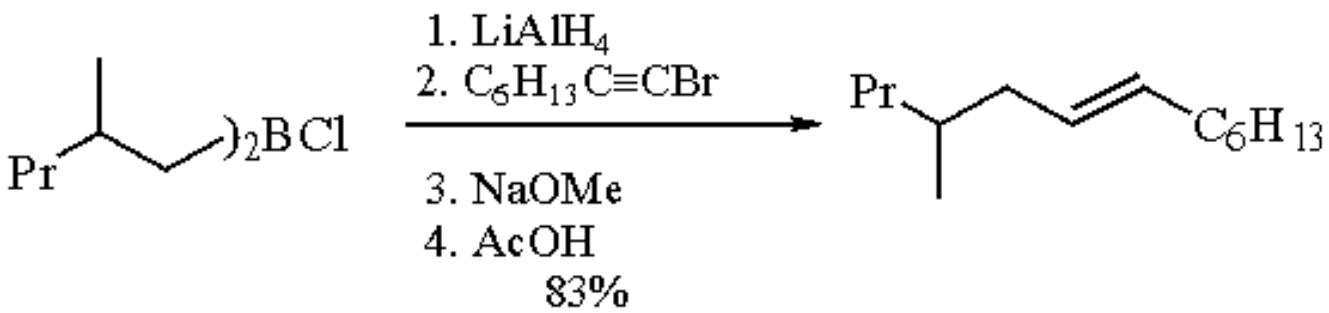

(4)

Only one R group of R_2BCl is utilized in these reactions and an excess of a terminal alkyne has to be used to minimize dihydroboration. These inconveniences can be circumvented by using alkenylborinate intermediates[22] or alkyldibromoboranes (see ***Dibromoborane-Dimethyl Sulfide***).

Cyclic Hydroboration of Dienes.

Hydroboration of 1,5-cyclooctadiene[4] and 1,3,5,7-cyclooctatetraene[23] with MCBS gives *B*-chloro-9-BBN and the 2,6-diboraadamantane skeleton, respectively. *B*-Chloro-9-BBN is useful for the preparation of ***9-Borabicyclo[3.3.1]nonane*** derivatives not directly available by hydroboration with 9-BBN, e.g. allenyl-9-BBN, a reagent for the synthesis of homopropargylic alcohols.[24]

Cyclic hydroboration with MCBS has been used in the synthesis of a hydrozaulene skeleton with three contiguous chiral centers (eq 5).[25] MCBS is more reactive than ***Thexylborane*** in this transformation.

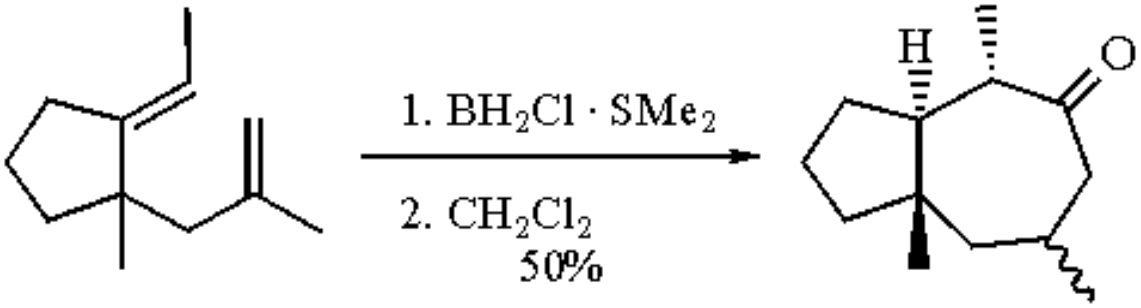

(5)

Synthesis of Aldehydes, Ketones, and Acids.

Oxidation of dialkylchloroboranes derived from terminal alkenes with ***Pyridinium Chlorochromate*** and ***Chromium(VI) Oxide*** in acetic acid produces aldehydes and acids, respectively[26,27] (eq 6).[27] Similarly, ketones can be obtained from internal alkenes.[26]

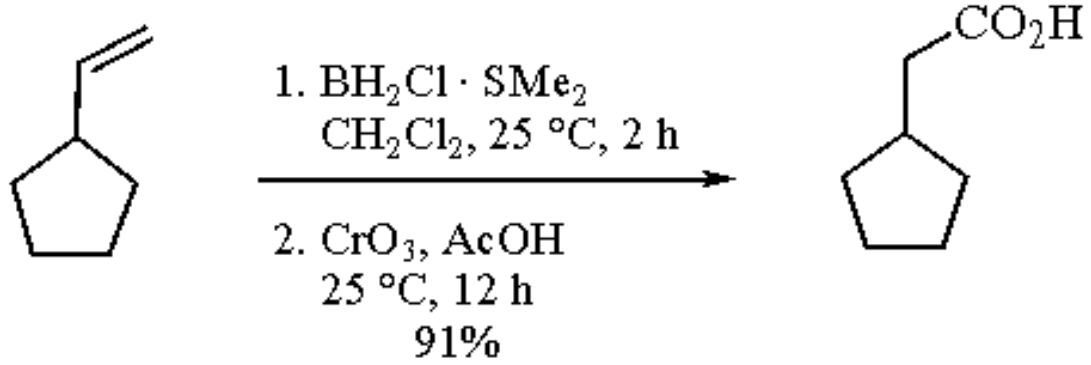

(6)

Reagents for Enolboration.

Aldol reactions of boron enolates are remarkably stereoselective.[28] Consequently, generation of stereodefined boron enolates is of primary synthetic importance. Dialkylchloroboranes obtained by hydroboration of alkenes with MCBS and also by other methods are convenient reagents for enolboration of ketones and other carbonyl derivatives;[29] for example, dicyclohexylchloroborane gives the (*E*)-enolate predominantly for diethyl ketone and exclusively for propiophenone (eq 7).[30]

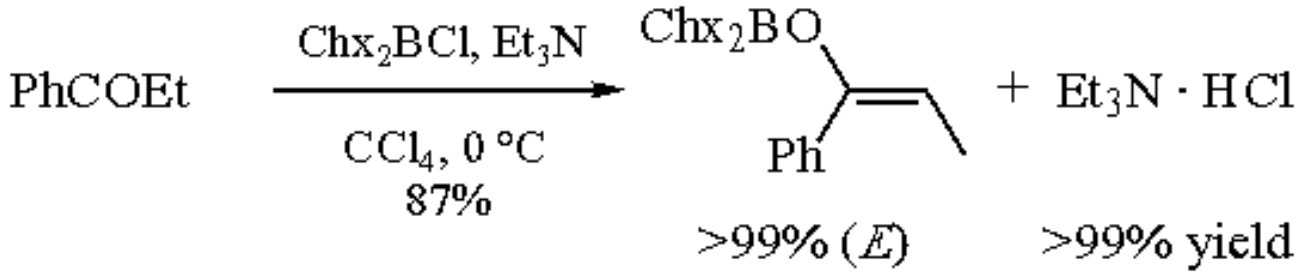

(7)

Computer modeling applied to design boron enolates effective for asymmetric *anti*-aldol reactions has led to the preparation of $[(Menth)CH_2]_2BCl$ (eq 8).[31]

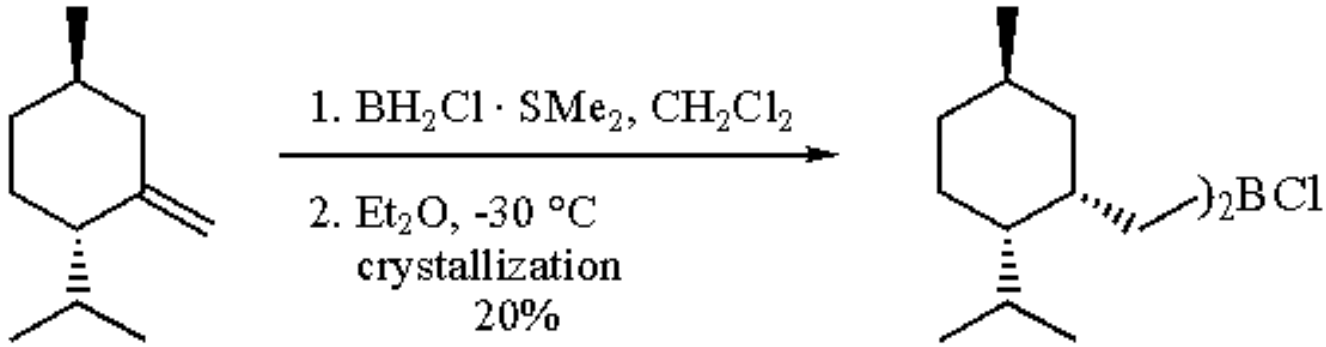

(8)

(1)

Highly selective formation of (*E*)-enolates is achieved by treating ketones with (**1**). Addition to aldehydes gives *anti*-aldols with diastereoselectivity of 86:14 to 100:0 (*anti*:*syn*) in 56-88% ee.[31]

Cleavage of Acetals, Ketals, and Epoxides.

MCBS chemoselectively cleaves acetals of cyclic ketones, even in the presence of double bonds. Unsaturated aliphatic acetals undergo preferential hydroboration of the double bond[5] (for opposite chemoselectivity, see ***Monochloroborane Diethyl Etherate***). Epoxides are stereoselectively cleaved to *anti*-chlorohydrins[6,32] (eq 9).[6]

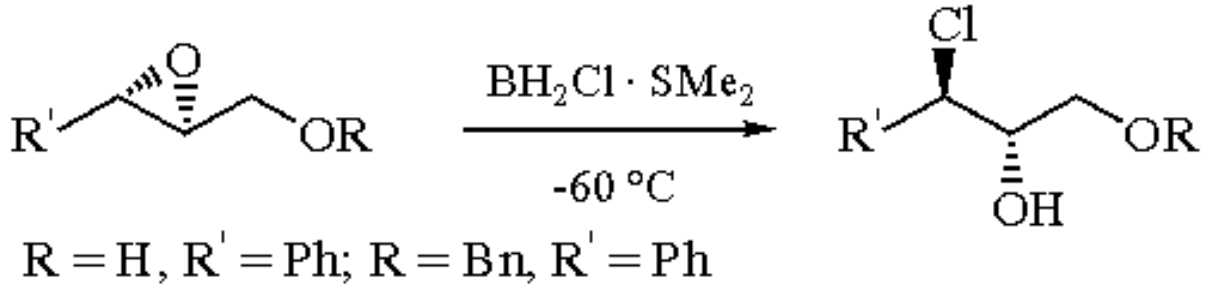

(9)

Certain dialkylhaloboranes are also effective reagents for the epoxide cleavage, e.g. Dip-chloride cleaves *meso*-epoxides with high enantioselectivity[33] (see also ***Chlorodiethylborane***).

Other Applications.

MCBS has been used for the synthesis of metallacarboranes,[34] boron-metal cluster compounds[35] and boron-containing polymers.[36]

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Monoisopinocampheylborane[1]

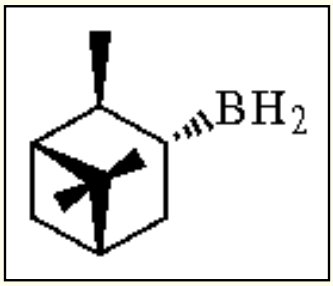

[64234-27-1] · $C_{10}H_{19}B$ · Monoisopinocampheylborane · (MW 150.10)

(asymmetric hydroboration of *trans* and trisubstituted alkenes;[2] asymmetric reduction of ketones[3])

Physical Data: a crystalline adduct with ***N,N,N´,N´-Tetramethylethylenediamine*** ($2IpcBH_2$.TMEDA) has mp 140.5-141.5 °C; [α]23D +69.03° (*c* 9.33, THF).

Solubility: sol THF, Et_2O.

Analysis of Reagent Purity: the optical purity of the reagent is assayed by oxidation (NaOH, H_2O_2) to give isopinocampheol, [α]27D -35.8° (*c* 0.9, benzene).

Handling, Storage, and Precautions: best used as prepared. Guidelines for the handling of air- and moisture-sensitive materials should be followed.[1c]

Preparation.

Hydroboration of alkenes with ***Borane-Tetrahydrofuran*** or ***Borane-Dimethyl Sulfide*** proceeds rapidly past the monoalkylborane stage with all but the most sterically demanding alkenes. Thus, attempts to prepare a solution of monoisopinocampheylborane ($IpcBH_2$) by simple admixture of 1:1 (+)-α-pinene:borane result in an equilibrium mixture of $IpcBH_2$, diisopinocampheylborane (Ipc_2BH), and borane.[4] Although several indirect methods for the preparation of $IpcBH_2$ have been devised,[5a-f] the preparation of $IpcBH_2$ by displacement of α-pinene from Ipc_2BH with TMEDA is recommended (eq 1).[5e,6] It is unique to this procedure that the crystalline adduct[7] incorporates two $IpcBH_2$ units which are of higher optical purity than the starting (+)-α-pinene used. Analysis of the mother liquor reveals that the minor enantiomer accumulates in the more soluble diastereomeric adduct.

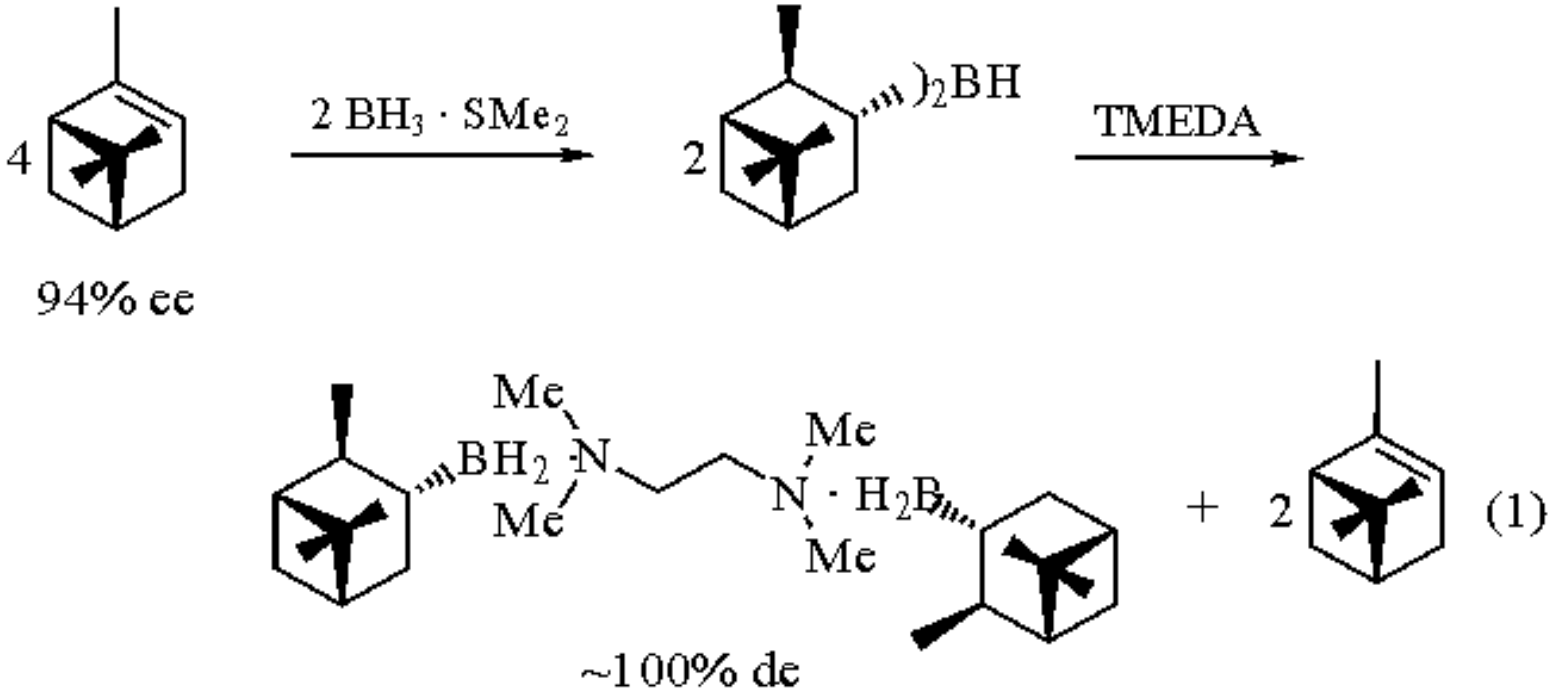

$IpcBH_2$ of essentially 100% ee is liberated from the TMEDA adduct by addition of ***Boron Trifluoride Etherate*** in THF. Filtration of the TMEDA.$2BF_3$ adduct provides a solution of $IpcBH_2$ in THF ready for subsequent hydroboration reactions (eq 2).

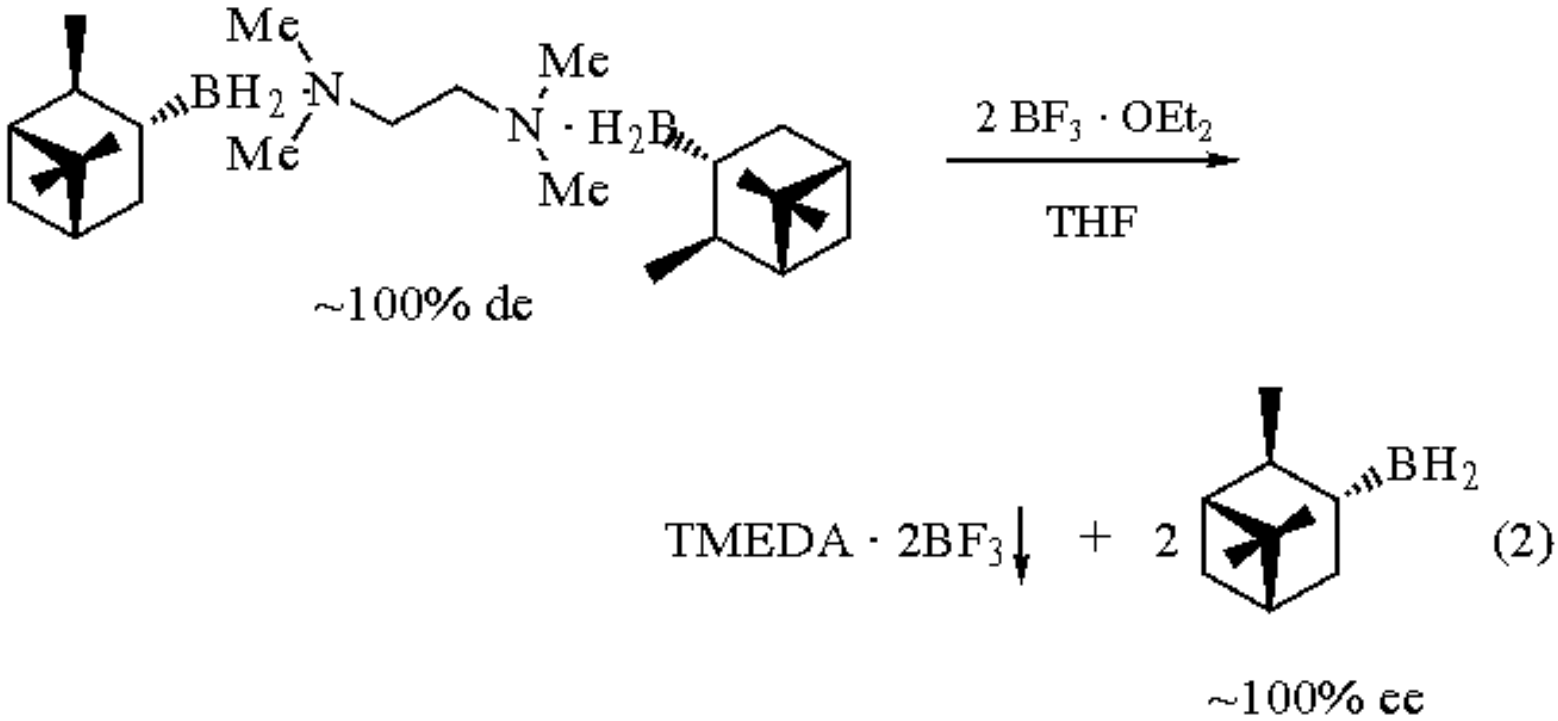

Asymmetric Hydroboration.

The steric requirements of $IpcBH_2$ are such that hydroboration of *trans* and trisubstituted alkenes proceeds with little or no displacement of α-pinene from the reagent, a phenomenon which is observed with the more hindered

Diisopinocampheylborane (Ipc_2BH). Ipc_2BH is most effective for the hydroboration of relatively unhindered *cis* alkenes, which are hydroborated with low asymmetric induction by $IpcBH_2$ (eq 3). The two reagents are therefore complementary in this respect. (For a reagent which hydroborates *cis*, *trans*, and trisubstituted alkenes with excellent asymmetric induction, see also ***(R,R)-2,5-Dimethylborolane***)

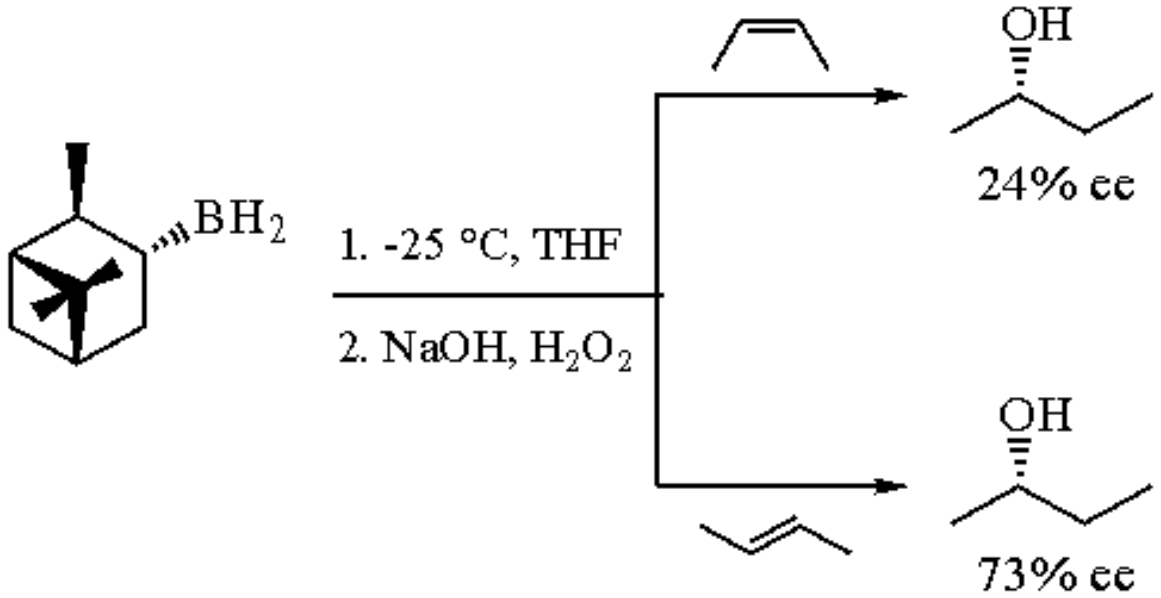

(3)

Representative *trans* alkenes are asymmetrically hydroborated by $IpcBH_2$ derived from (+)-α-pinene to give (*S*)-alcohols in the range of 65-76% ee. With highly hindered *trans* alkenes, the enantioselectivity can be somewhat higher (eq 4).[2]

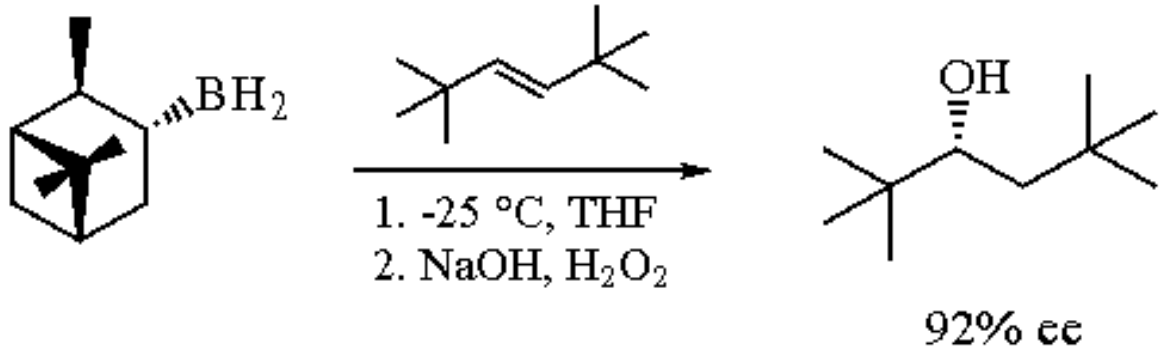

(4)

Aliphatic trisubstituted alkenes are likewise hydroborated to give (*S*)-alcohols in the range of 53-72% ee. When the trisubstituted alkene bears a phenyl substituent, a significant increase in enantioselectivity is observed (eq 5).[2,8]

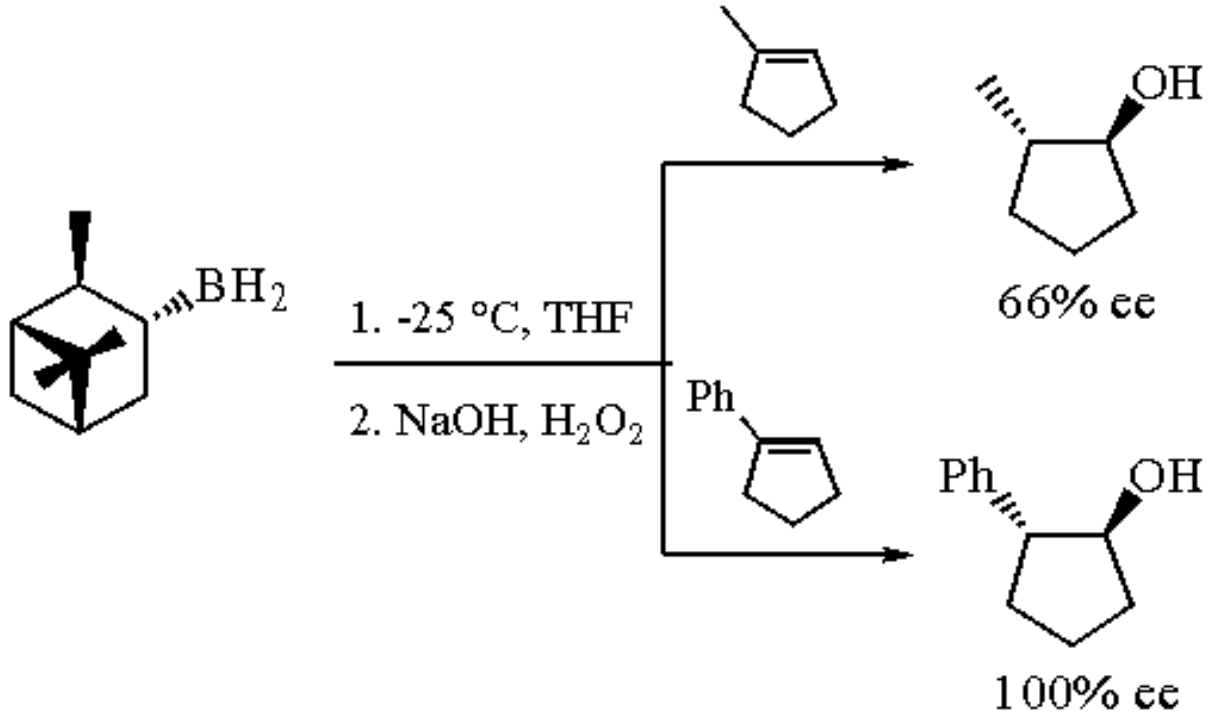

(5)

In the asymmetric hydroboration of 1-heteroarylcycloalkenes,[9] $IpcBH_2$ exhibits enantioselectivities of 83-90% ee, comparable to the phenyl-substituted alkenes examined (eq 6).

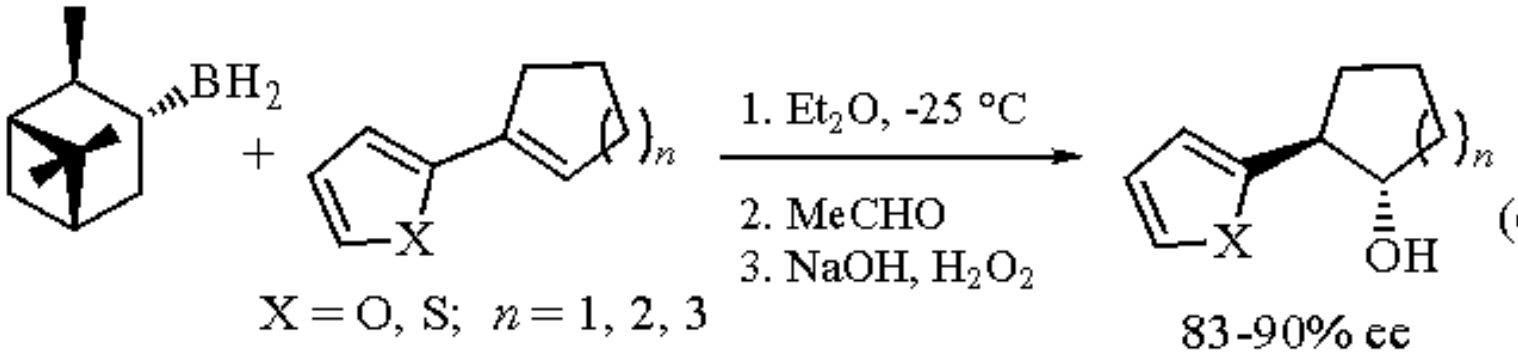

(6)

Many intermediate dialkylboranes derived from hydroboration with $IpcBH_2$ can be recrystallized to enantiomeric purities approaching 100%, thus giving alcohols of 98-99% ee upon oxidation.[10] If, instead of being oxidized in situ, the dialkylborane intermediate is treated with ***Acetaldehyde***,[11] α-pinene is displaced for recovery and a chiral boronate bearing the R group of the alkene is obtained (eq 7).

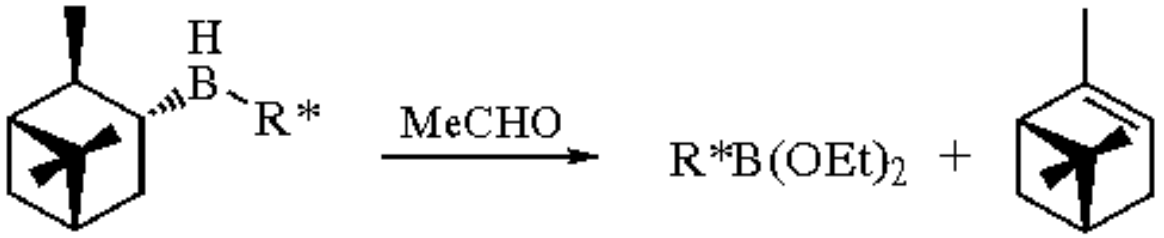

(7)

This reaction is general, and these boronic esters are versatile synthetic intermediates in their own right.[12]

Asymmetric Reduction of Ketones.

The reduction of prochiral ketones with $IpcBH_2$ is mechanistically complex. Although the secondary alcohols obtained are consistantly enriched in the (*S*) enantiomer when the reagent is prepared from (+)-α-pinene, the degree of asymmetric induction observed, 11-46% ee, varies with the reaction stoichiometry.[3] This has been attributed to the ability of the 1:1 $IpcBH_2$:ketone addition product to serve as a reducing agent for an additional equivalent of ketone (eq 8).

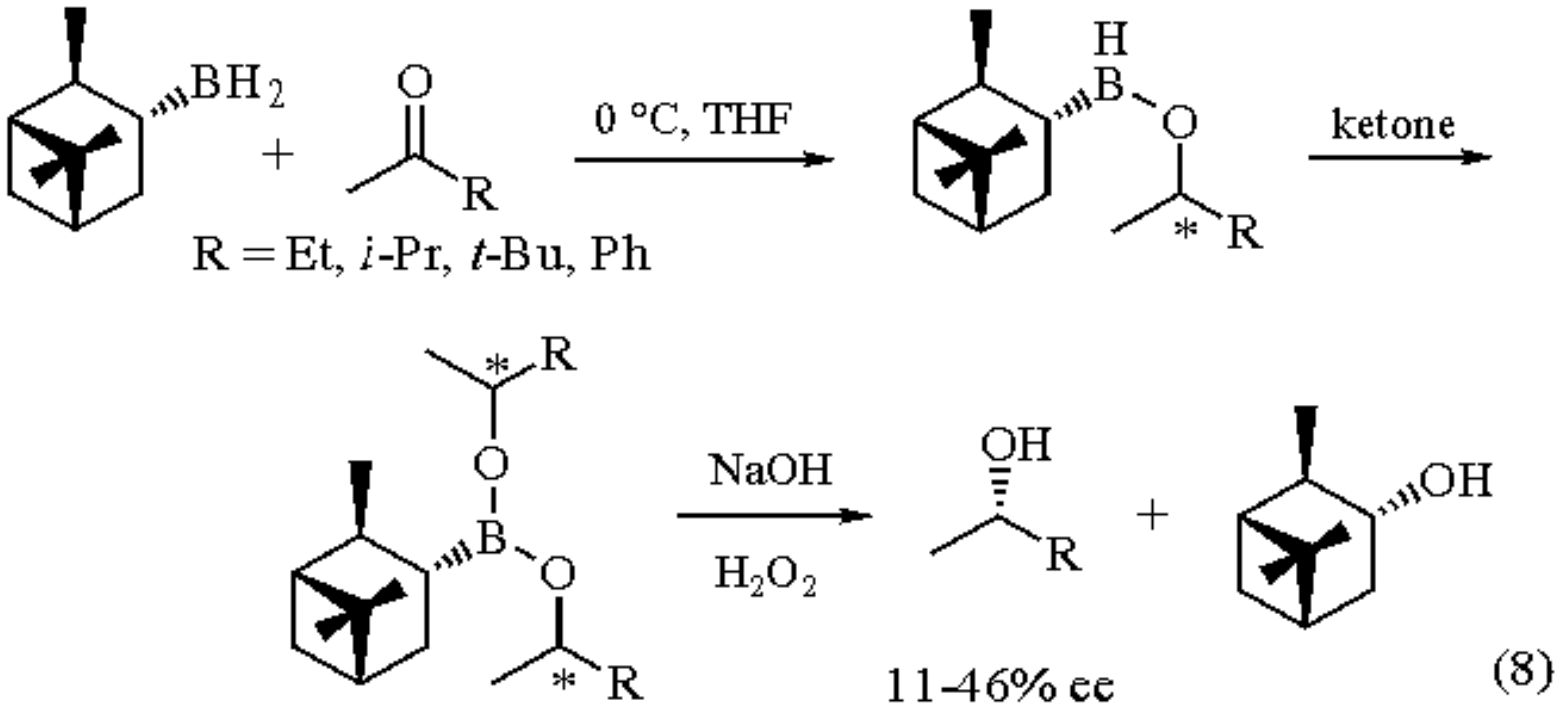

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Monoperoxyphosphoric Acid[1]

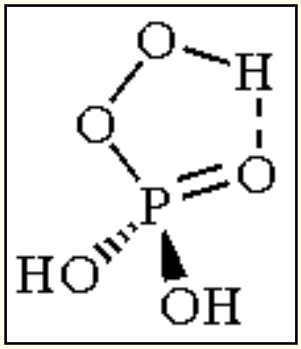

[13598-52-2] · H_3O_5P · Monoperoxyphosphoric Acid · (MW 114.00)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes,[2] alkynes,[3] arenes,[4] and amines[5])

Alternate Names: peroxymonophosphoric acid; PMPA.

Solubility: sol acetonitrile, dioxane.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: assay using iodometry.[6]

Preparative Methods: (a) to a stirred suspension of 14.2 g of ***Phosphorus(V) Oxide*** in 60 mL of acetonitrile at 0 °C, 10 g of 70% ***Hydrogen Peroxide*** (**caution**!) in 20 mL of acetonitrile was added over a period of 45 min. The mixture was stirred at rt for 16 h.[6] (b) 87% H_2O_2 is used;[7] the latter is the more common procedure.

Handling, Storage, and Precautions: should be used immediately after preparation; reagent stored at 5 °C for 26 days lost 30% of active oxygen. Since H_3PO_5 is a peroxy acid, care should be exercised while carrying out the reactions; during workup, check for peroxides before solvent removal. This reagent should be handled in a fume hood.

Oxidations of Alkenes, Arynes, and Arenes.

Epoxides which are not readily opened by acids can be prepared by reacting alkenes with H_3PO_5. *trans*-Stilbene oxide (**1**) has been prepared in 74% yield through epoxidation of *trans*-stilbene with H_3PO_5 in dioxane.[2] Oxidation of diphenylacetylene with H_3PO_5 at rt in acetonitrile furnishes the diketone (**2**) in 48% yield;[3] this reaction can be carried out with ***Trifluoroperacetic Acid*** (TFPAA) but not with the normal peroxycarboxylic acids.

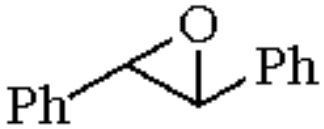

(1)

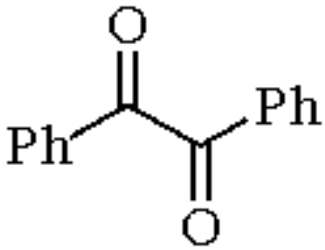

(2)

H_3PO_5 is an effective reagent for aromatic hydroxylation, the reactivity being comparable to that of TFPAA; oxidation of mesitylene in acetonitrile (25 °C, 4 h) furnishes mesitol in 77% yield.[4]

Baeyer-Villiger Reaction.

Reaction of acetophenone (**3**) with H_3PO_5 in acetonitrile at 30 °C furnished the aryl acetate (**6**) in 91% yield. The ketones (**4**) and (**5**) were also oxidized to (**7**) and (**8**) in yields of 95% and 98%, respectively; the corresponding methyl benzoates were not obtained. Baeyer-Villiger reaction of acetophenones with H_3PO_5 has nearly 100-fold higher rate than that with peroxycarboxylic acids such as ***Perbenzoic Acid***.[8]

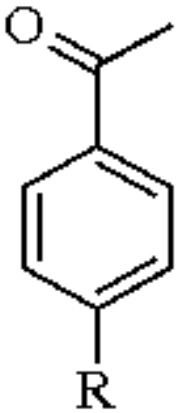

(3) R = H
(4) R = Cl
(5) R = Me

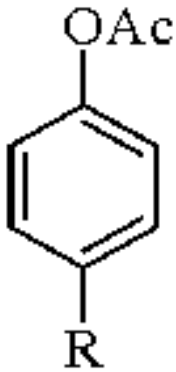

(6) R = H
(7) R = Cl
(8) R = Me

Baeyer-Villiger reaction of (**9**) with H_3PO_5 furnished the phenol (**10**) (eq 1).[6] However, the reagents ***Peracetic Acid*** or TFPAA furnished the carboxylic acid (**11**).

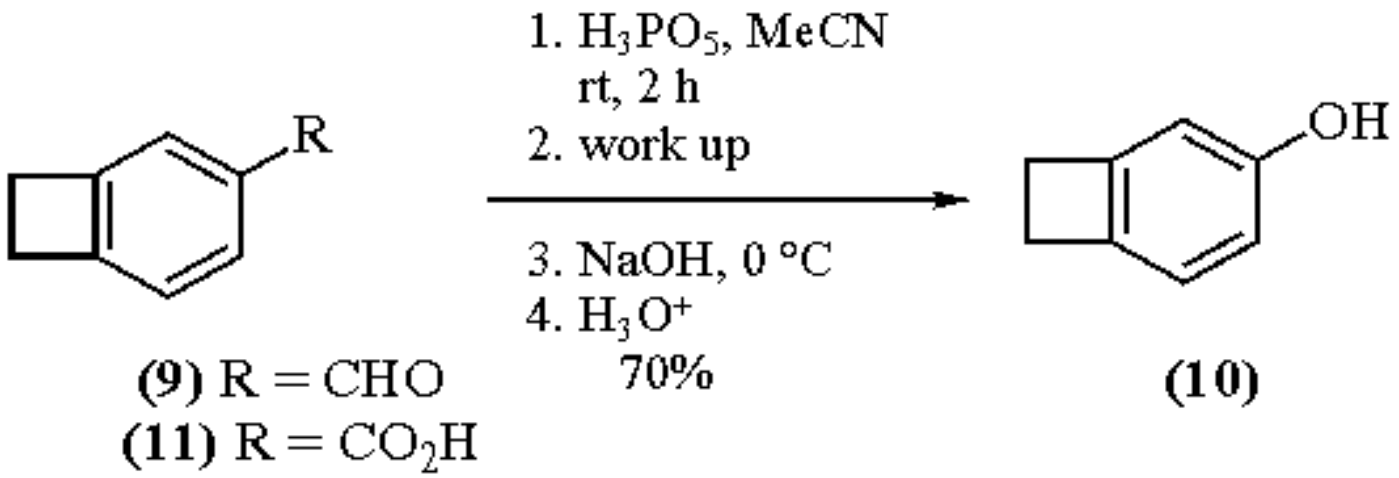

(1)

Other Applications.

Oxidation of *N*,*N*-dimethylaniline in aqueous acetonitrile at 30 °C afforded the *N*-oxide in 82% yield.[5] Oxidation of THF with H_3PO_5 in acetonitrile or without solvent at 25 °C furnishes γ-butyrolactone in 40-45% yield.[9] This oxidation cannot be performed with percarboxylic acids such as $MeCO_3H$.

Related Reagents.

Peroxymaleic Acid; ***Trifluoroperacetic Acid***.

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1. Ogata, Y. *Kogaku no Ryoiki* **1979**, *33*, 223 (*CA* **1979**, *91*, 82 304t).
2. Ogata, Y.; Tomizawa, K.; Ikeda, T. *JOC* **1979**, *44*, 2362.
3. Ogata, Y.; Sawaki, Y.; Ohno, T. *JACS* **1982**, *104*, 216.
4. Ogata, Y.; Sawaki, Y.; Tomizawa, K.; Ohno, T. *T* **1981**, *37*, 1485.
5. Ogata, Y.; Tomizawa, K.; Morikawa, T. *JOC* **1979**, *44*, 352.
6. Thomas, P. J.; Pews, R. G. *SC* **1991**, *21*, 2335.
7. Boyland, E.; Manson, D. *JCS* **1957**, 4689.
8. Ogata, Y.; Tomizawa, K.; Ikeda, T. *JOC* **1978**, *43*, 2417.
9. Ogata, Y.; Tomizawa, K.; Ikeda, T. *JOC* **1980**, *45*, 1320.

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Monoperoxyphthalic Acid[1]

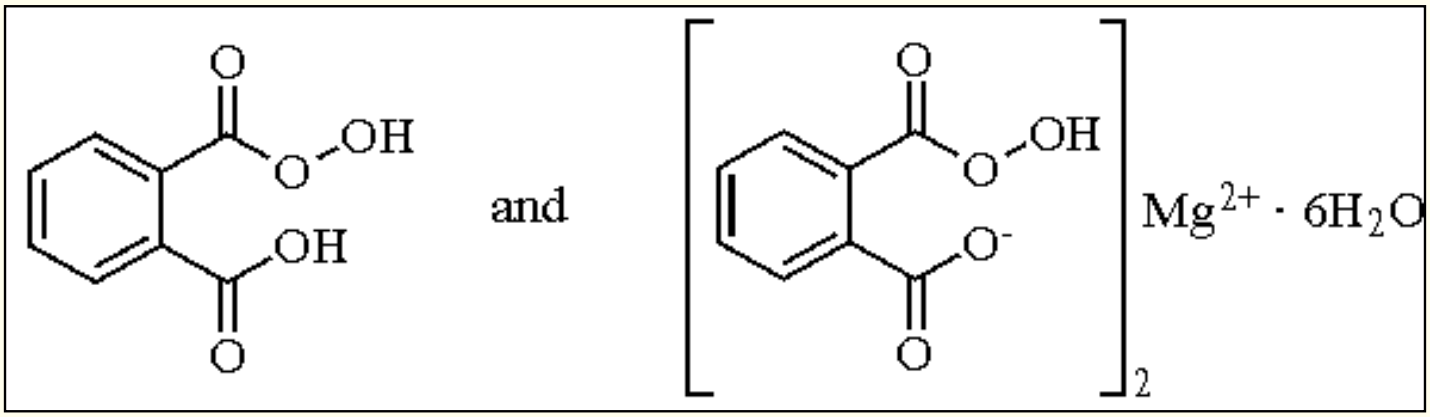

[2311-91-3] · $C_8H_6O_5$ · Monoperoxyphthalic Acid · (MW 182.14) (Mg salt.$6H_2O$)

[84665-66-7] · $C_{16}H_{22}MgO_{16}$ · Magnesium Monoperoxyphthalate Hexahydrate · (MW 494.69)

(mild peroxycarboxylic acids for effecting epoxidation of π-bonds, Baeyer-Villiger reactions, and the oxidation of diverse heteroatoms including nitrogen, sulfur, and selenium)

Alternate Name: MPP.

Physical Data: monoperoxyphthalic acid: mp 110-112 °C (dec).[2]

Solubility: monoperoxyphthalic acid: sol ether; magnesium monoperoxyphthalate: sol water, low molecular weight alcohols; very low sol organic solvents such as dichloromethane.

Form Supplied in: magnesium monoperoxyphthalate: white crystalline powder; commercially available as the hexahydrate.

Preparative Methods: monoperoxyphthalic acid is prepared as required by the addition of phthalic anhydride to 30% aqueous ***Hydrogen Peroxide***,[3a] in the presence of ***Sodium Hydroxide***[3b] or ***Sodium Carbonate***.[3c] Magnesium monoperoxyphthalate is prepared by the addition of phthalic anhydride and ***Magnesium Oxide*** to aqueous hydrogen peroxide.[3d] *Drying:* magnesium monoperoxyphthalate should be dried over calcium chloride in a desiccator.

Handling, Storage, and Precautions: magnesium monoperoxyphthalate may be stored at room temperature. *All work should be carried in an efficient fume hood behind a polycarbonate safety screen.*

Monoperoxyphthalic Acid.

Before the introduction of ***m-Chloroperbenzoic Acid*** (*m*-CPBA), one of the most frequently used peroxy acids was monoperoxyphthalic acid (MPP). Although MPP is a weaker acid than *m*-CPBA, the fact that phthalic acid is essentially insoluble in ether is an advantage with MPP. A disadvantage of the reagent is that MPP has to be made each time that it is used, whereas *m*-CPBA (60%) is commercially available admixed with *m*-chlorobenzoic acid and water. The epoxidation of a number of alkenes can be achieved in reasonable yields using MPP. Cyclohexene, limonene, and α-pinene were converted into the respective epoxides in 64, 71, and 48% yields, respectively.[3a] The oxidation of bicyclo[2.2.1]heptadiene gave, in addition to a low yield of the expected epoxide, bicyclo[2.2.1]hex-2-ene-5-carbaldehyde.[4] The epoxidation of a number of acid-sensitive alkenes, such as α-keto enol ethers, has been achieved in good yields in the presence of disodium phthalate as a buffer and is exemplified in eq 1.[5] It is of interest to note that the yields in these reactions were halved in the absence of the buffer.

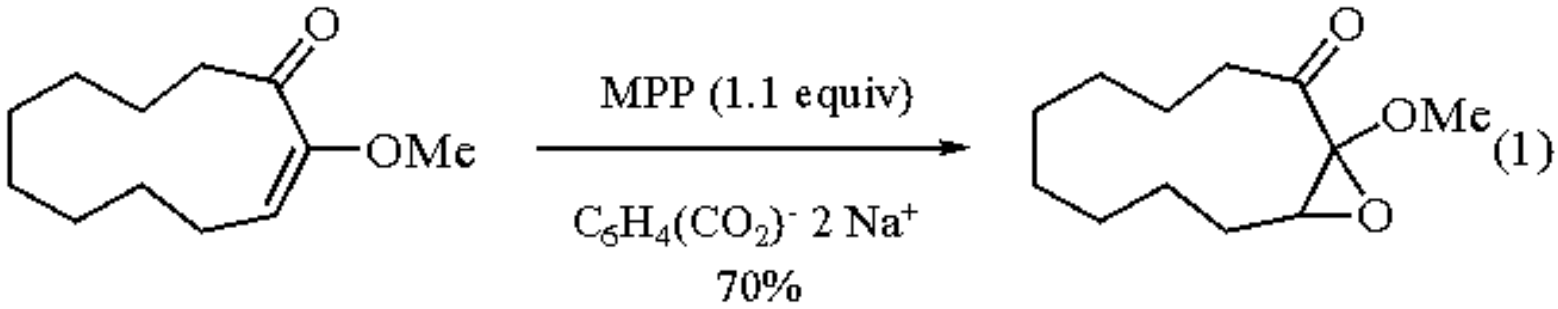

The oxidation of indole derivatives gives rise to a number of products, including those where ring fragmentation has occurred. Thus 2-*t*-butylindole affords *N*-pivaloylanthranilic acid.[6] Monoperoxyphthalic acid has also been used to prepare *N*-oxides; for example, quinoline derivatives have been converted into their *N*-oxides.[7] Although MPP is now not used as frequently as formerly, some useful examples have been published recently. The epoxidation reactions shown in eqs 2 and 3 and the Baeyer-Villiger type rearrangement (eq 4) are illustrative.[8-10]

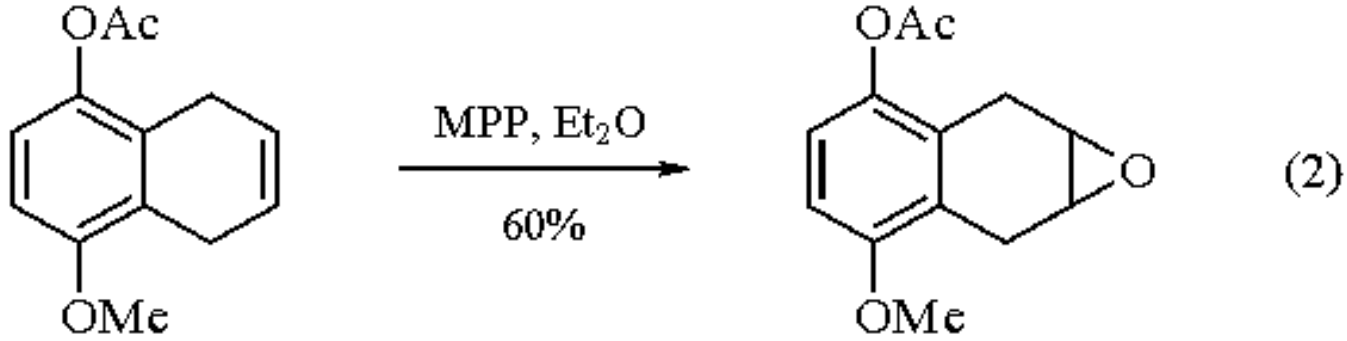

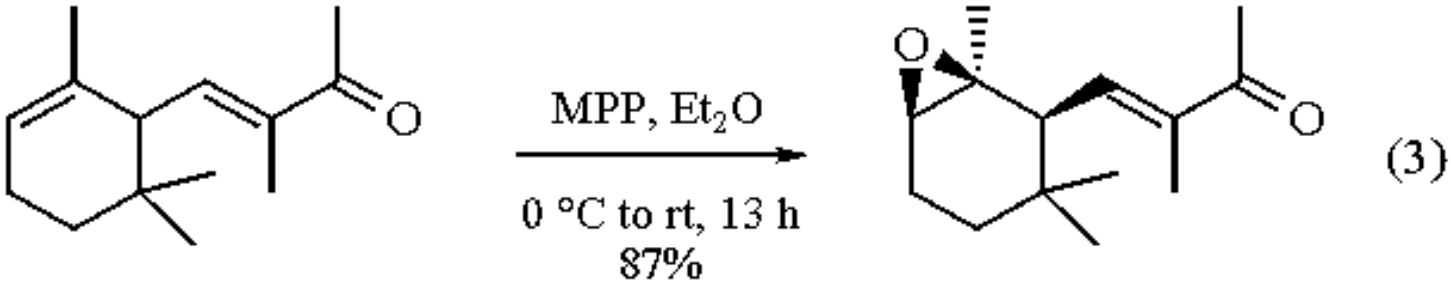

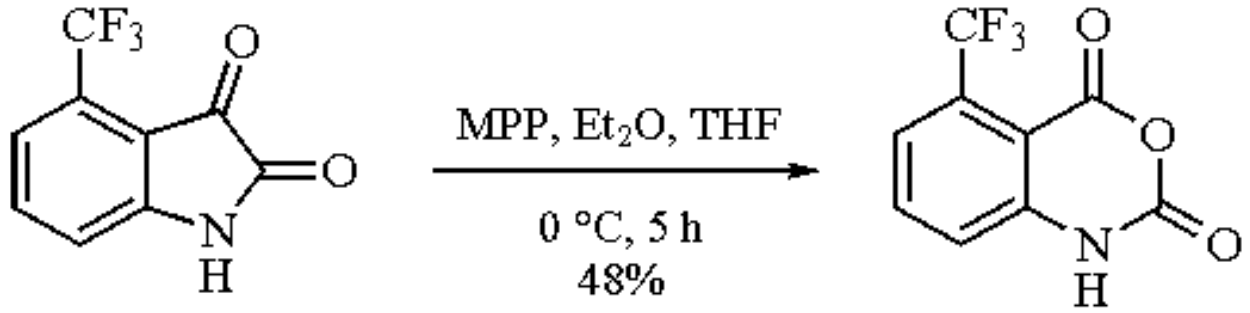

(4)

Magnesium Monoperoxyphthalate.

The production of magnesium monoperoxyphthalate (MMPP) in commercial quantities has led to its use in a number of different types of oxidation reactions since its introduction.[11] The use of MMPP has been reviewed in detail to early 1993.[1c] The different reaction types are outlined and exemplified in the following sections.

Epoxidation Reactions.

The majority of the successful examples of epoxidation reactions using MMPP have been carried out using water or a low molecular weight alcohol as a solvent. Where the substrate to be epoxidized is insoluble in such a solvent, water has been used together with a phase-transfer agent to take the monoperoxyphthalate ion into an organic phase, for example chloroform or dichloromethane. The formation of the monoepoxide from [$^2H_6$]buta-1,3-diene has been reported in a reaction where one atmosphere of the gas was kept over an aqueous solution of MMPP.[12] There have also been cases reported where attempted epoxidation reactions have failed in the presence of MMPP.[13] Typically these involve terminal alkenes where electron density in the double bond is relatively low. Epoxidation may then be successful using Kishi's high-temperature method in which the radical inhibitor 4,4´-thiobis(6-*t*-butyl-3-methylphenol) is employed together with *m*-CPBA.[14] An efficient alternative method for the epoxidation of terminal alkenes involves the use of ***Trifluoroperacetic Acid*** (TFPAA) generated by the interaction of urea-hydrogen peroxide (UHP) with trifluoroacetic anhydride (see ***Hydrogen Peroxide-Urea***).[15] It is of interest to note that the epoxidation of cholesterol proceeds efficiently in dichloromethane in the absence of a phase-transfer catalyst. Presumably in this case the hydroxyl group that is present in cholesterol acts as a crystal disrupting agent. This explanation may also apply to the observation that the MMPP epoxidation of *cis*-but-2-ene-1,4-diol proceeds efficiently, whereas a reaction of the diacetate does not.[16] As with all peroxycarboxylic acid epoxidations of cholesterol, a reaction using MMPP results in the formation of a mixture of products in which the α:β ratio is about 4:1. It appears that the larger the peroxycarboxylic acid, the larger the amount of the α-epoxide formed. A direct comparison with *m*-CPBA can be made in the case of the epoxidation of 1,2-dimethylcyclohexa-1,4-diene,[17,18] and also in the reactions with ***Ethyl Vinyl Ether***.[19] The oxidation shown in eq 5 gave about a 4:1 mixture of diastereomers in very good yield when carried out in a water-isopropanol mixture.[20] Hydrogen bonding between the peroxy acid and the hydroxyl group is presumed to be responsible for the preferred formation of the α-epoxide. The failure of *m*-CPBA to effect epoxidation of the diene ester shown in eq 6 is surprising. However, MMPP and TFPAA both gave the α-epoxide exclusively. On the other hand, a reaction using 3,5-dinitroperbenzoic acid gave a 3:1 mixture of the α- and β-epoxides.[21] As with epoxidation reactions carried out using *m*-CPBA, the reactions of MMPP with dienes (for example limonene) involve initial reaction at the more electron-rich double bond.

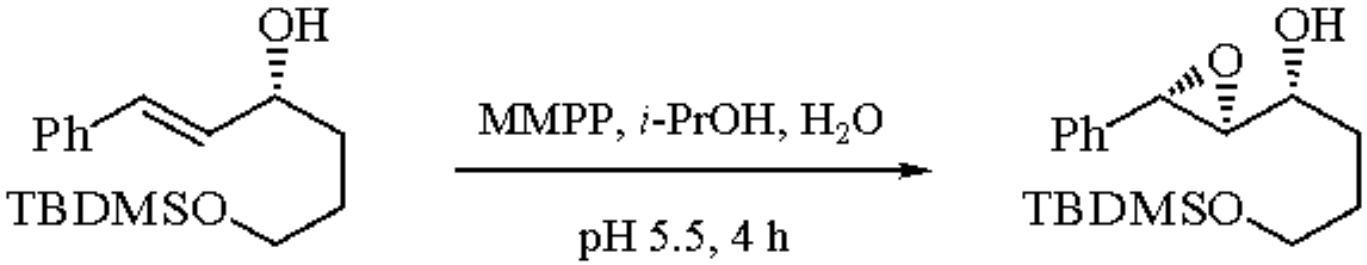

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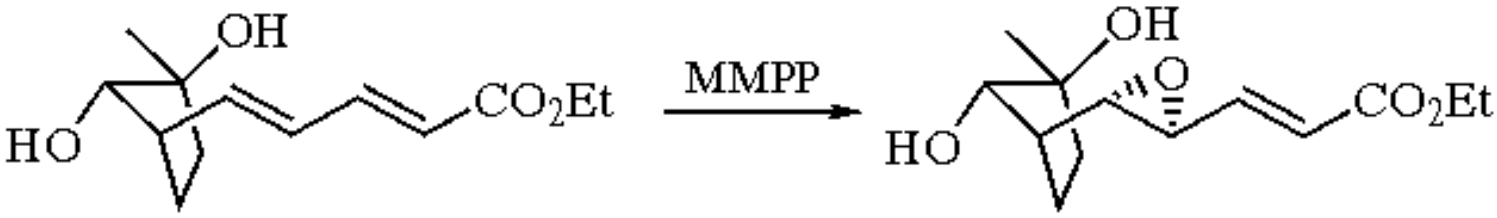

(6)

High diastereofacial selectivity can be anticipated where a neighboring functional group can be involved to control the stereochemical course of the reaction. Both of the diastereomers of the phosphine oxides shown in eq 7 are epoxidized with de values in excess of 95%.[22] Very low selectivities were observed where the chirality only involved the phosphorus center. Evidently the stereoselectivity is dominated by the effect of the chiral carbon center. Control may be less satisfactory when two functional groups have opposite influences. The epoxidation reaction shown in eq 8 was used in a study involving an enantiospecific synthesis of the nonproteinogenic α-amino acid anticapsin.[23] The desired product (**1**) was formed along with (**2**) in the ratio 5:2 using MMPP, whereas a 1:1 mixture was obtained using *m*-CPBA. Hydrogen bonding of the peroxy acid to the amide group evidently competes with the sterically demanding *t*-butyldiphenylsilyl residue in this reaction.

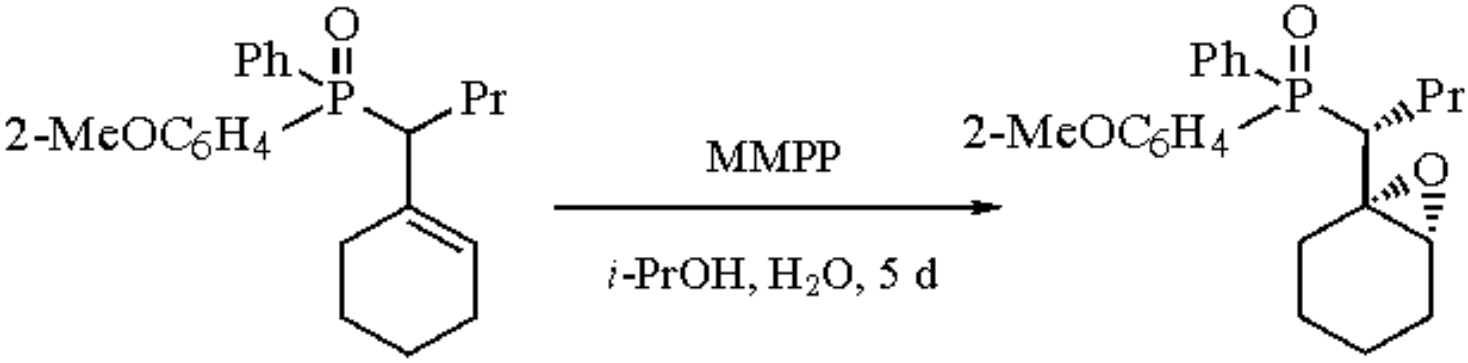

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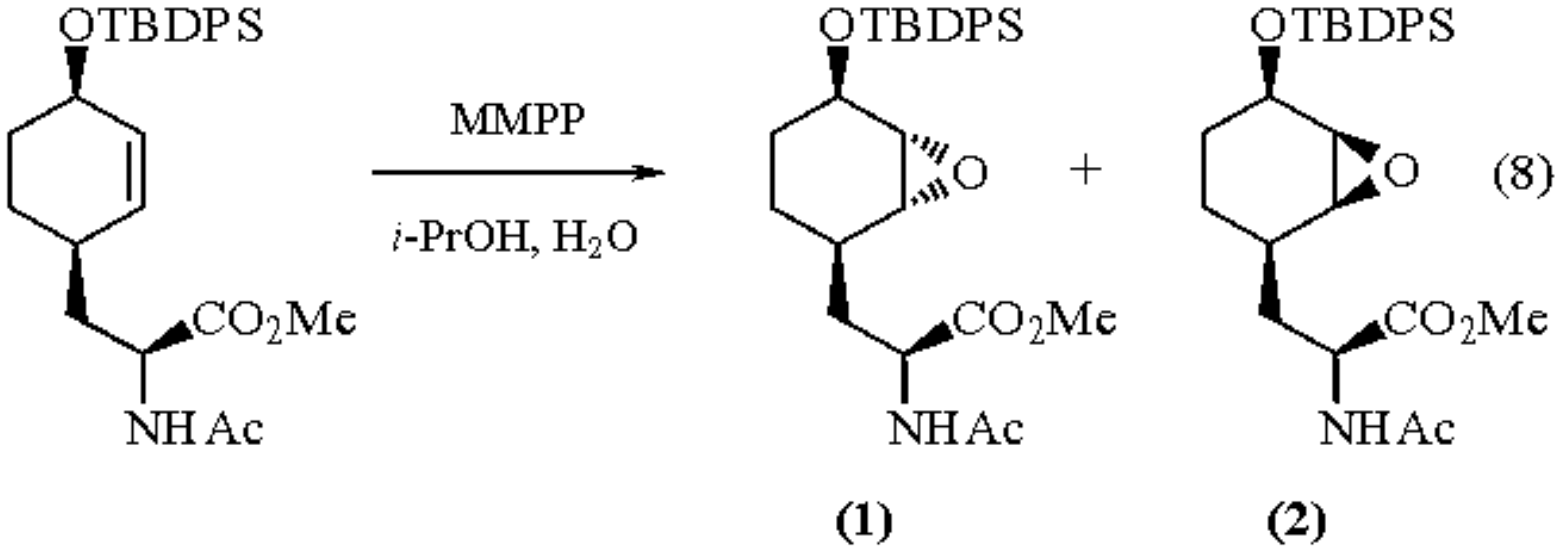

The synthesis of a number of naturally occurring fused 3-methylfuran derivatives was achieved using, as a key step, the epoxidation-aromatization shown in eq 9.[24] The oxidation of a number of heteroaromatic compounds has also been studied using MMPP and some of the products clearly result from initial epoxidation. A number of furan derivatives that carry electron-releasing substituents in the 2- and 5-positions are oxidized to give acyclic dienones in reactions with either *m*-CPBA or MMPP.[25] The oxidation shown in eq 10 was used in a synthesis of bromobeckerelide,[26] and the oxidation of 1-benzenesulfonylindole using MMPP gives the indoxyl derivative shown in eq 11.[27]

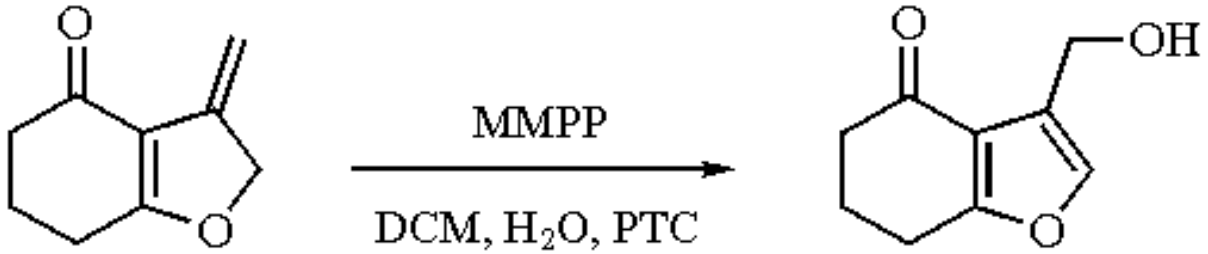

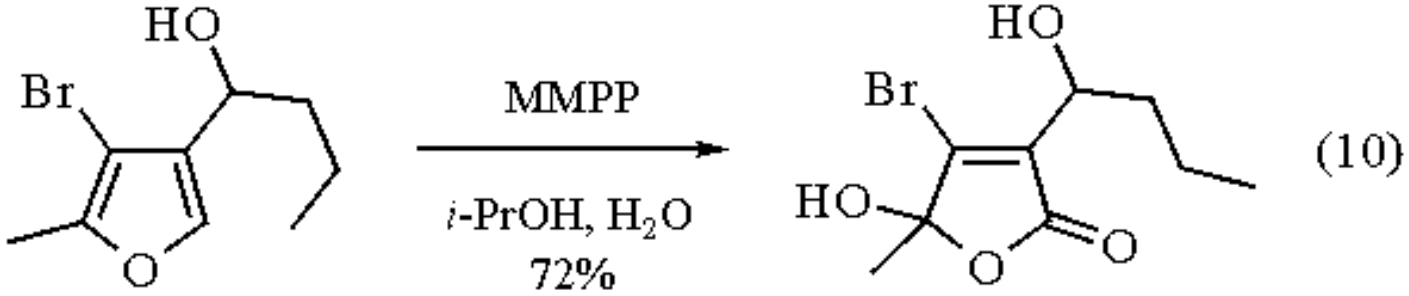

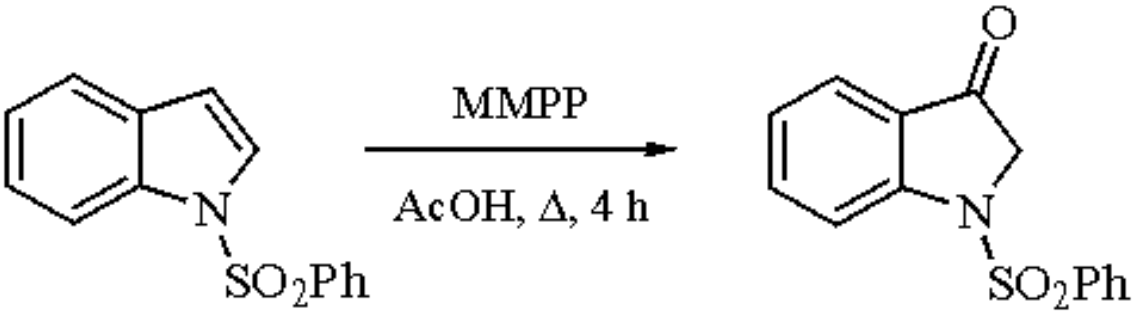

(11)

Baeyer-Villiger and Related Reactions.

The ease with which Baeyer-Villiger oxidation reactions of ketones occur is related to the strength of the conjugate acid of the leaving group. Since phthalic acid is not a particularly strong acid, it is not surprising that monoperoxyphthalic acid and MMPP are not used as frequently as trifluoroperacetic acid in Baeyer-Villiger reactions. Cyclohexanone and 3,3-dimethylbutanone are converted into ε-caprolactone and *t*-butyl acetate, respectively, in good yields.[11] The oxidative rearrangement reactions of the β-lactams shown in eq 12 have been reported to give higher yields when using MMPP than using *m*-CPBA.[28] The conversion of an aromatic aldehyde into a phenol via the formate ester (the Dakin reaction) is evidently related to the Baeyer-Villiger reaction. These reactions proceed well when the aromatic aldehyde has an electron releasing substituent *ortho* or *para* to the formyl residue. A number of peroxy acids have been used, for example *m*-CPBA and ***Peracetic Acid***, including cases where the peroxy acid was generated using UHP and ***Acetic Anhydride***. A limited number of examples have been reported using MMPP; the example shown in eq 13 is illustrative.[29]

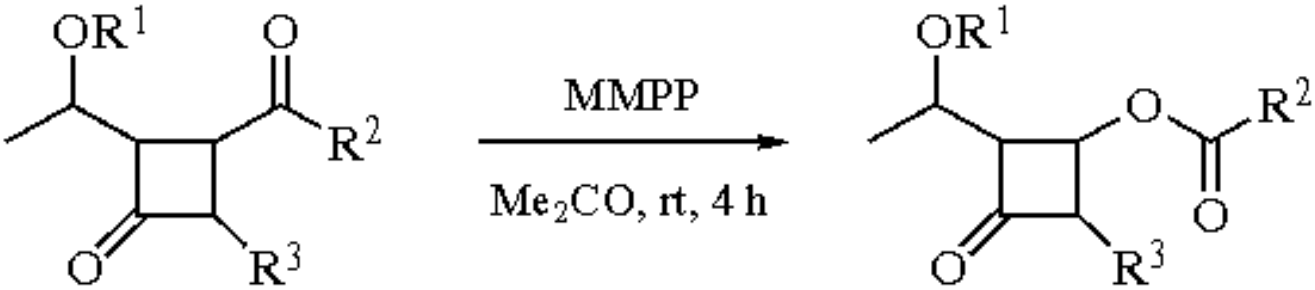

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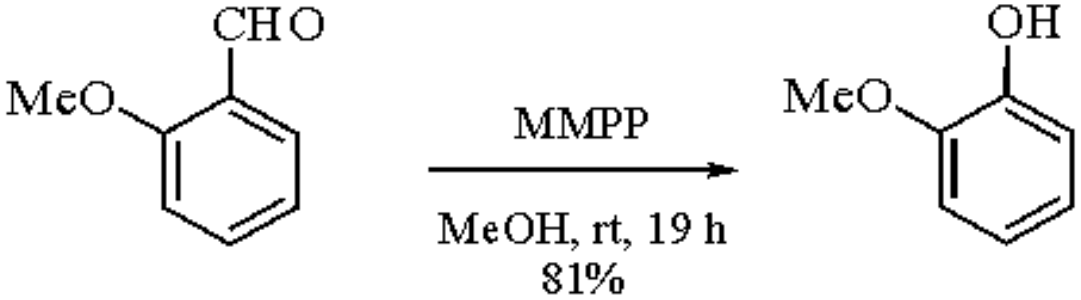

(13)

Oxidation of Sulfur and Selenium.

The oxidation of sulfides to sulfoxides and sulfones can be achieved with a wide range of oxidizing agents, including various peroxycarboxylic acids. The second oxidation step is normally slower than the first and so using a controlled amount of peroxy acid normally allows the formation and isolation of either product. Thus tetrahydrothiophene can be

oxidized either to the sulfoxide or to the sulfone using MMPP.[11] A number of cases have been reported where good yields of sulfoxides have been obtained,[30-32] including the example shown in eq 14 which was used in a synthesis of artemisinin.[32] The oxidation of the selenide that is involved in the sequence shown in eq 15 also proceeds in high yield.[33]

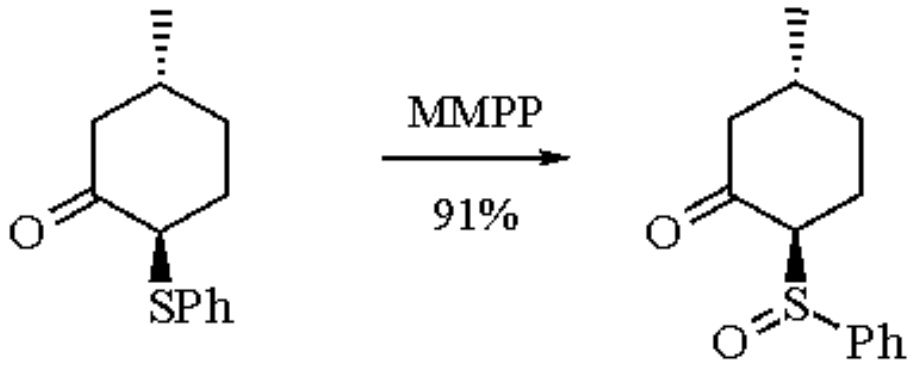

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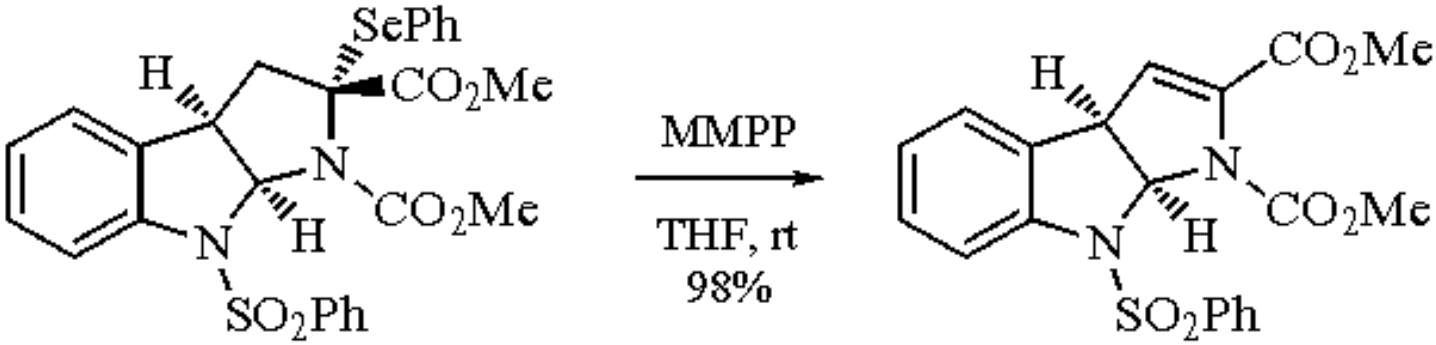

(15)

The use of an excess of MMPP has allowed a number of research groups to obtain sulfones from sulfides in good yields.[34 -37] The oxidation of phosphothionate to phosphate has been studied using a wide variety of oxidants. It was shown that MMPP was better than *m*-CPBA in the oxidation of malathion to malaoxon.[38] The example shown in eq 16 exemplifies the successful use of a phase-transfer catalyst.[34]

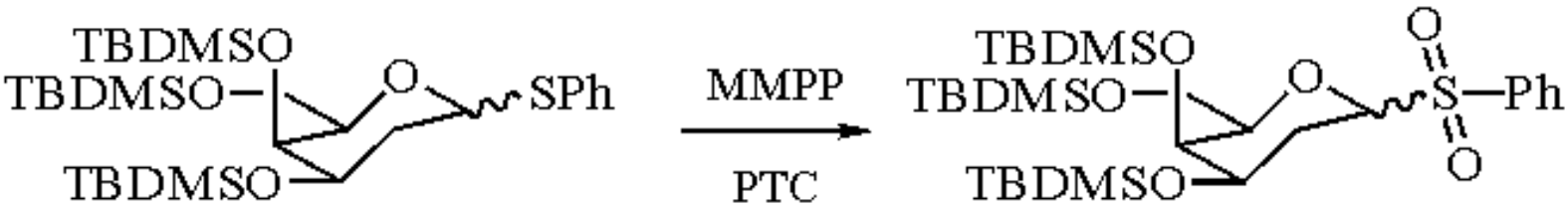

(16)

Oxidation of Nitrogen Functional Groups.

The oxidations of a number of pyridine derivatives,[11] pyrimidines,[39] and pyridothiophenes[40] to the related *N*-oxides have been reported. The oxidation of quinoxaline (eq 17) to the di-*N*-oxide also proceeds efficiently.[29] The oxidative cleavage of suitable bicyclic isoxazolidines has been studied in connection with the synthesis of indolizidine alkaloids.[41] In the example shown in eq 18 the use of *m*-CPBA afforded a mixture of the products (**3**) and (**4**) in which (**3**) predominated. Regiochemical control was better when using MMPP and in that case the nitrone (**4**) was the only

product.

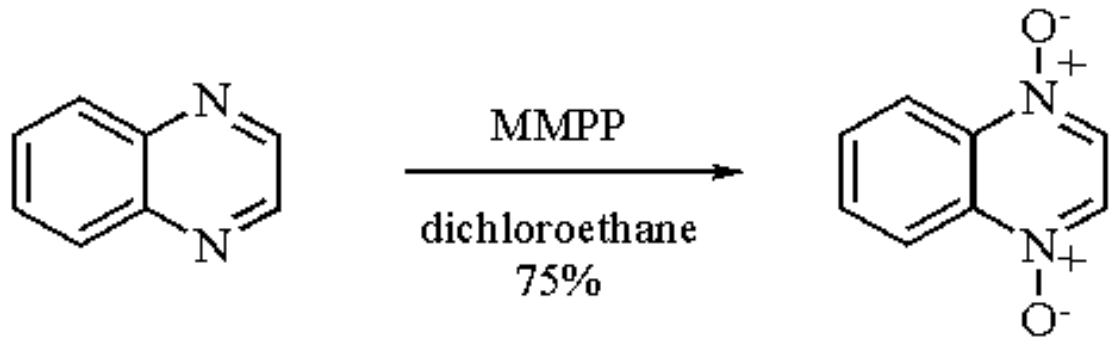

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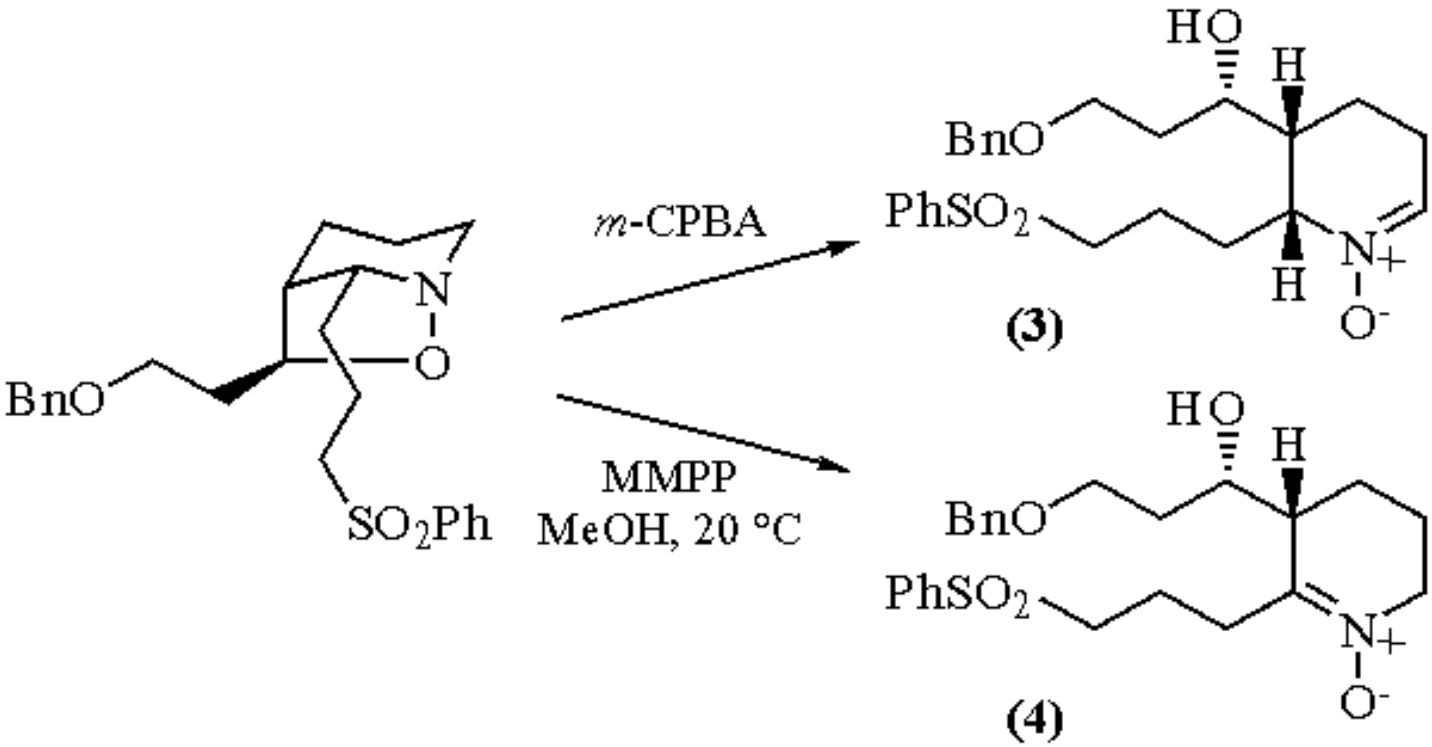

(18)

A number of methods are available for the oxidative regeneration of ketones from hydrazones. Very good yields have been reported for the conversion of *N*,*N*-dimethyl- and SAMP-hydrazones into their precursor ketones using MMPP. In the latter case (eq 19), the stereochemical integrity of the chiral center α to the carbonyl group was maintained.[42] The oxidation of *N*,*N*-dimethylhydrazones derived from aldehydes has also been studied using MMPP. Nitriles are obtained in high yields in these reactions and once again (eq 20) there is no racemization of a chiral center α to the original formyl group.[43]

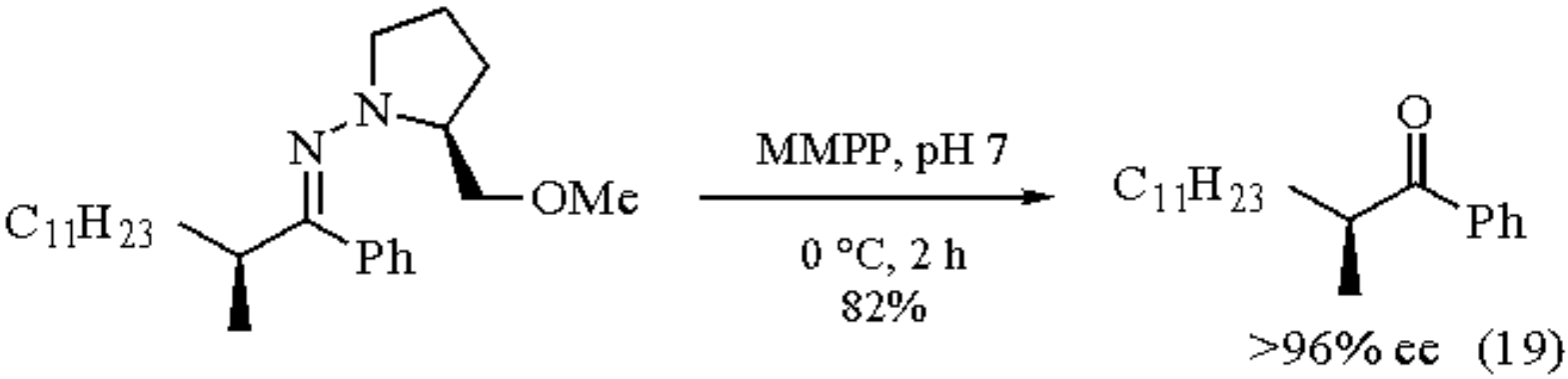

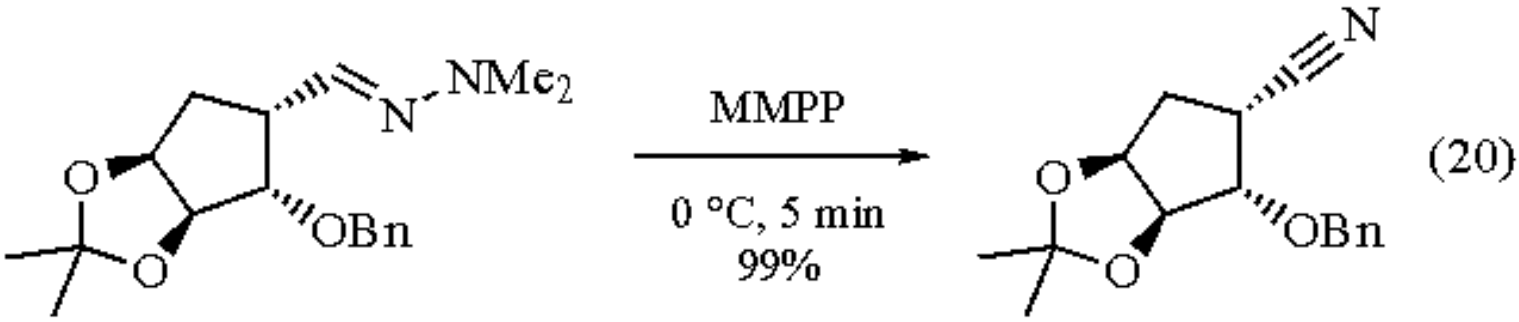

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Monoperoxysulfuric Acid[1]

H_2SO_5

[7722-86-3] · H_2O_5S · Monoperoxysulfuric Acid · (MW 114.07)

(strong oxidizing agent for many functional groups;[1] can selectively oxidize amines;[2] in alcohol solvent can directly convert conjugated aldehydes to esters;[3] can effect regioselective Baeyer-Villiger oxidations;[4] can promote regioselective oxidative rearrangement of tertiary alcohols to o-hydroxy ketones[5])

Alternate Name: Caro's acid.

Physical Data: mp 45 °C.

Solubility: sol water (see also ***Potassium Monoperoxysulfate*** (Oxone)).[1c,d]

Analysis of Reagent Purity: a spectrophotometric method is available for analysis of the components of an $H_2SO_5/H_2S_2O_8/H_2O_2$ mixture.[6]

Preparative Methods: prepared as needed from $K_2S_2O_8$ (see ***Ammonium Peroxydisulfate***), concentrated ***Sulfuric Acid***, and water;[1b,e,f] or ***Hydrogen Peroxide*** (60-90%) and concentrated H_2SO_4.[3]

Handling, Storage, and Precautions: may react explosively with acetone, and primary or secondary alcohols.

Selective Oxidations.

Neutralized Caro's acid can chemoselectively oxidize arylamines to nitroso compounds (eq 1);[1b,2a,7] a simpler procedure for this transformation uses ***Acetic Acid/Hydrogen Peroxide*** 30%.[2b] An alternative pathway leading to the formation of azoxybenzenes (eq 1);[7] or nitro compounds (eq 2)[8] is also possible and depends upon substrate, solvent, pH, and reaction conditions. Caro's acid oxidation of polyhalodiazines is unfruitful, except for pyrazines. While chloropyrazines and chloroquinoxalines react with 30% H_2O_2 in glacial acetic acid to give mono-*N*-oxides with selective *N*-4 oxidation,[9] Caro's acid affords mono-*N*-oxides with regioselective oxidation at *N*-1 (eq 3).

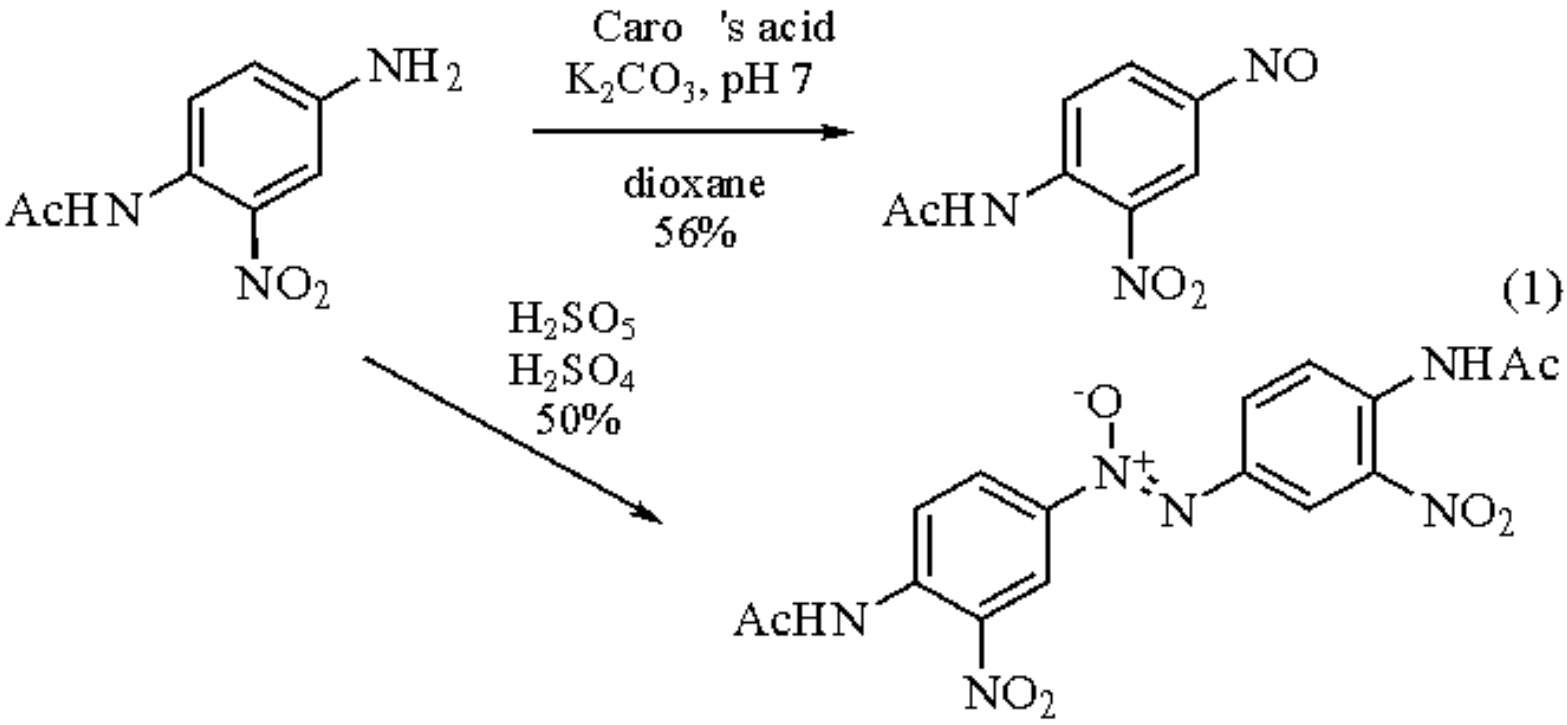

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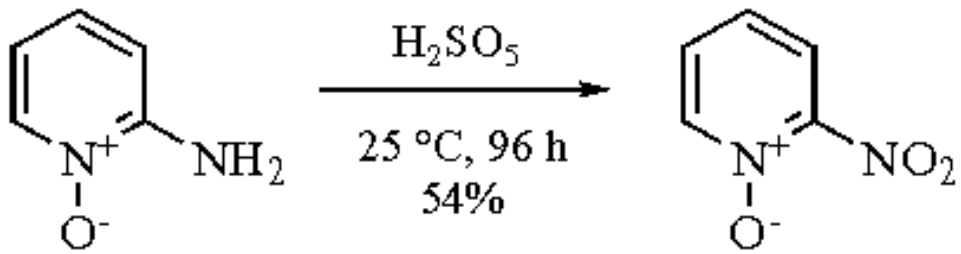

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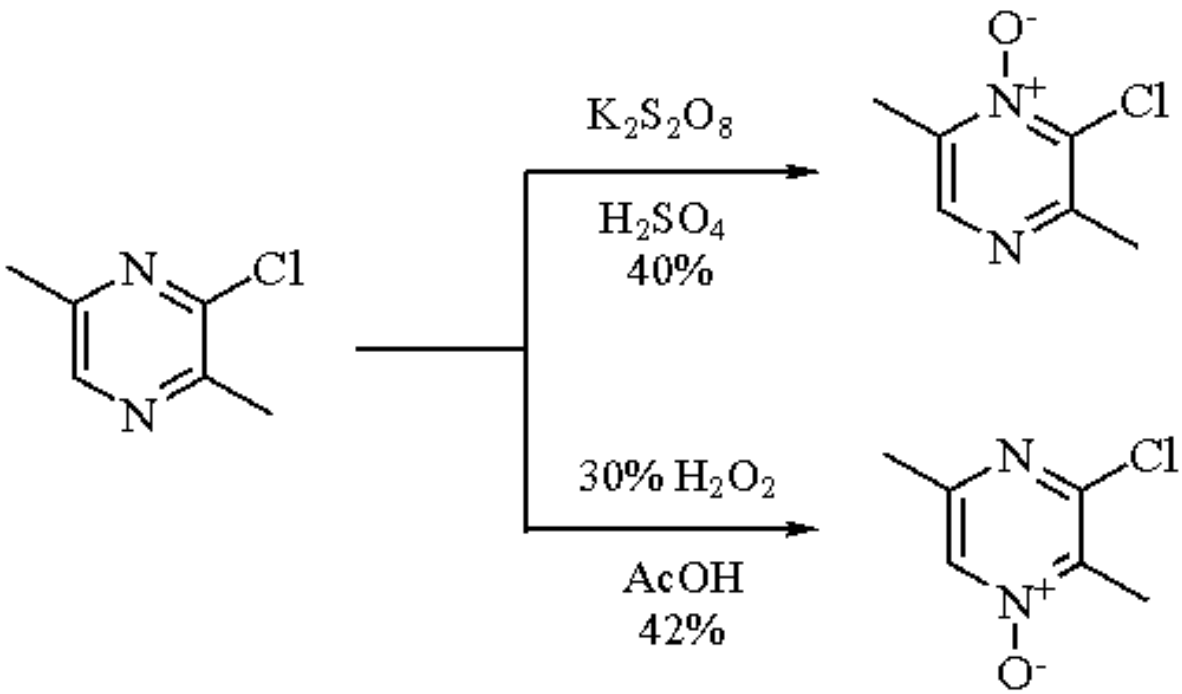

(3)

Conjugated aldehydes can be oxidized directly to α,β-unsaturated esters by Caro's acid in alcoholic media (eq 4).[3] The reaction probably proceeds through a hemiacetal and not the carboxylic acid.

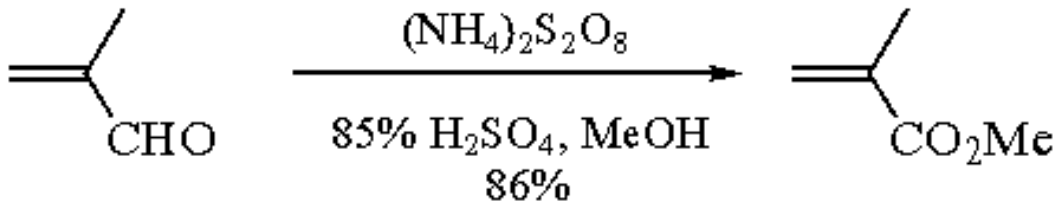

(4)

Baeyer-Villiger Oxidation.

Caro's acid has proven useful in the Baeyer-Villiger oxidation of cyclic ketones and steroids.[4] The regioselective Baeyer-Villiger oxidation of isatins to 2,3-dioxo-1,4-benzoxazines observed with Caro's acid contrasts sharply with formation of isatoic anhydrides using ***Peracetic Acid*** (eq 5).[4a] The related buffered reagent ***Bis(trimethylsilyl) Monoperoxysulfate*** is a strong Baeyer-Villiger oxidant. This aprotic reagent is soluble in methylene chloride and generally gives higher yields and purer product than Caro's acid.[10]

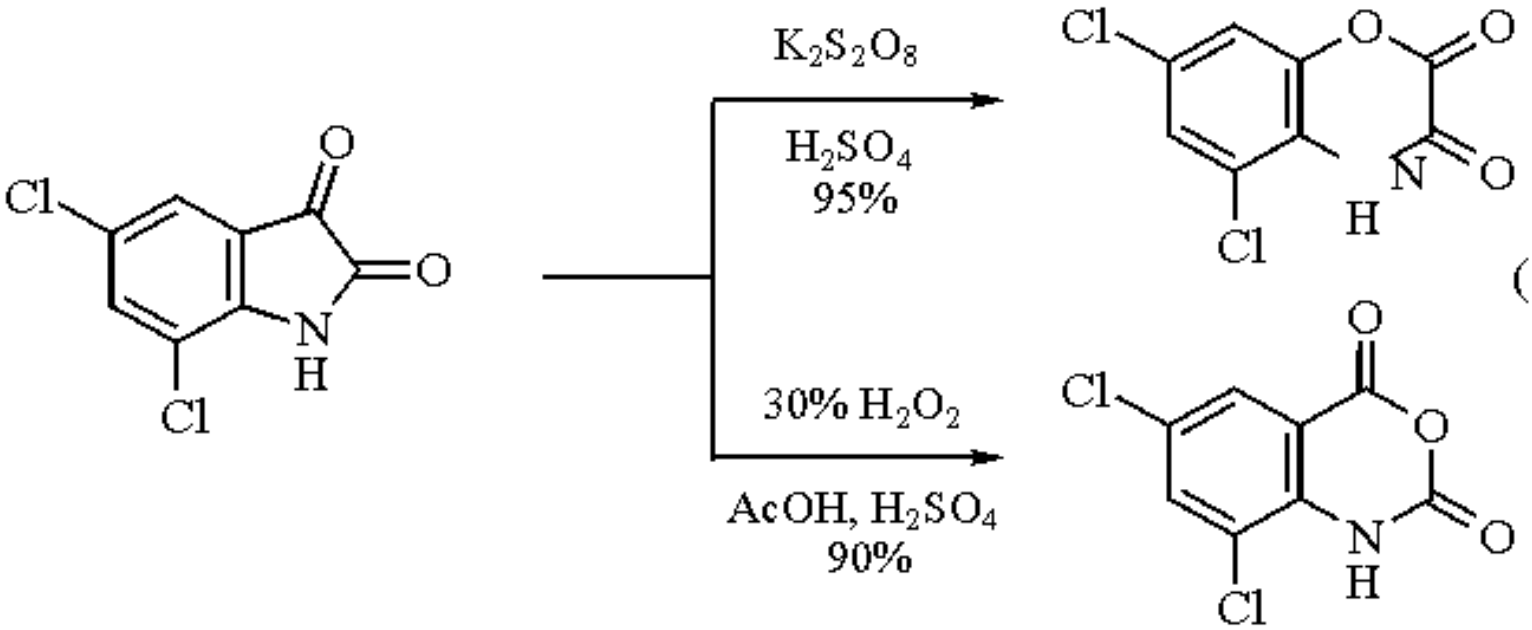

(5)

Alkyl Hydroperoxide Synthesis and Rearrangement.

Caro's acid oxidizes tertiary alcohols to hydroperoxides, which rearrange in the acid medium. The procedure is useful for the conversion of cycloalkanols to o-hydroxy ketones (eq 6).[5] Cyclic o-hydroxy ketones exist as oxonium ions in sulfuric acid and thus are resistant to further Baeyer-Villiger oxidation.

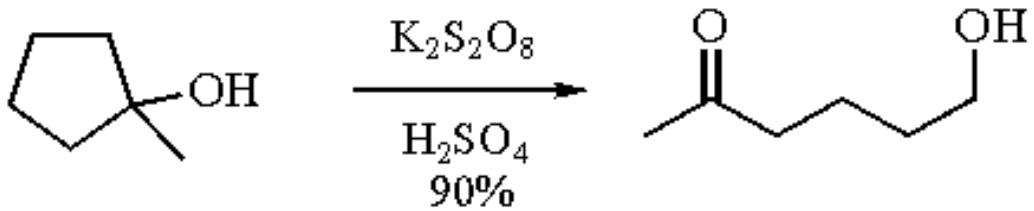

(6)

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Montmorillonite K10

[1318-93-0]

(catalyzes protection reactions of carbonyl and hydroxy groups; promotes ene,[22] condensation,[25] and alkene addition[27] reactions)

Physical Data: the surface acidity of dry K10 corresponds to a Hammett acidity function H_0 = -6 to -8.[13]

Form Supplied in: yellowish-grey dusty powder. Forms with water a mud that is difficult to filter, more easily separated by centrifugation; with most organic solvents, forms a well-settling, easy-to-filter suspension.[6]

Handling, Storage, and Precautions: avoid breathing dust; keep in closed containers sheltered from exposure to volatile compounds and moisture.

General.

Montmorillonite clays are layered silicates and are among the numerous inorganic supports for reagents used in organic synthesis.[1,2] The interlayer cations are exchangeable, thus allowing alteration of the acidic nature of the material by simple ion-exchange procedures.[3,4] Presently, in fine organic synthesis, the most frequently used montmorillonite is K10, an acidic catalyst, manufactured by alteration of montmorillonite (by calcination and washing with mineral acid; this is probably a proprietary process).

The first part of this article specifically deals with representative laboratory applications to fine chemistry of clearly identified, unaltered K10, excluding its modified forms (cation-exchanged, doped by salt deposition, pillared, etc.) and industrial uses in bulk. This illustrative medley shows the prowess of K10 as a strong Brønsted acidic catalyst. The second part deals with cation-exchanged (mainly Fe^{III}) montmorillonite. Clayfen and claycop, versatile stoichiometric reagents obtained by metal nitrate deposition on K10,[5] are used in oxidation and nitration reactions. They are treated under ***Iron(III) Nitrate-K10 Montmorillonite Clay*** and ***Copper(II) Nitrate-K10 Bentonite Clay***.

K10 is often confused, both in name and in use, with other clay-based acidic catalysts (KSF, K10F, Girdler catalyst, acid treated or H^+-exchanged montmorillonite or clay, etc.) that can be effectively interchanged for K10 in some applications. Between the 1930s and the 1960s, such acid-treated montmorillonites were common industrial catalysts, especially in petroleum processing, but have now been superseded by zeolites.

Activation.[6]

K10 clay may be used crude, or after simple thermal activation. Its acidic properties are boosted by cation exchange

(i.e. by iron(III)[7] or zinc(II)[8]) or by deposition of Lewis acids, such as zinc(II)[9,10] or iron(III)[11] chloride (i.e. clayzic and clayfec). In addition, K10 is a support of choice for reacting salts, for example nitrates of thallium(III),[12] iron(III) (clayfen),[5] or copper(II) (claycop).[5] Multifarious modifications (with a commensurate number of brand names) result in a surprisingly wide range of applications; coupled with the frequent imprecise identification of the clay (K10 or one of its possible substitutes mentioned above), they turn K10 into a Proteus impossible to grab and to trace exhaustively in the literature.

Preparation of Acetals.

Trimethyl orthoformate (see ***Triethyl Orthoformate***) impregnated on K10 affords easy preparation of dimethyl acetals,[14] complete within a few minutes at room temperature in inert solvents such as carbon tetrachloride or hexane (eq 1). The recovered clay can be reused.

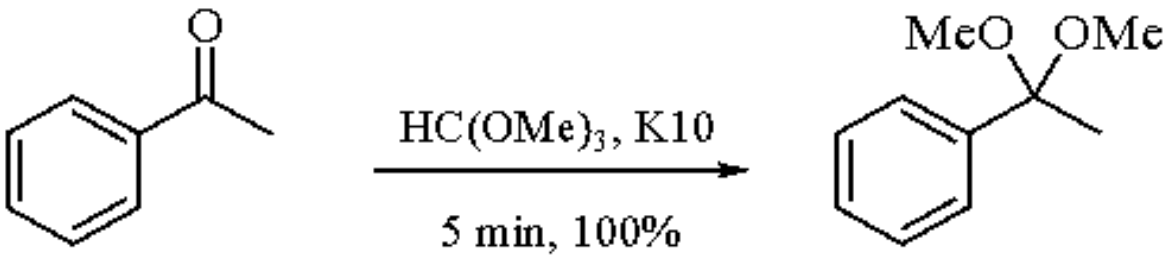

(1)

Cyclic diacetals of glutaraldehyde are prepared in fair yields by K10-promoted reaction of 2-ethoxy-2,3-dihydro-4*H*-pyran with diols, under benzene azeotropic dehydration (eq 2).[15]

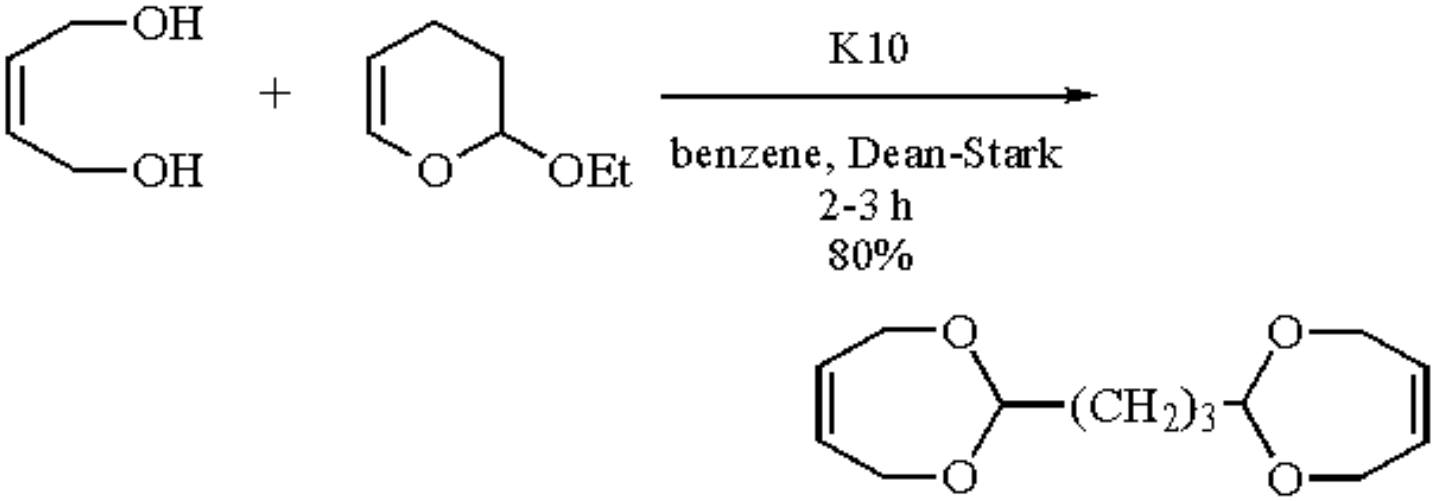

(2)

Diastereoisomeric acetal formation catalyzed by K10 has been applied to the resolution of racemic ketones, with diethyl (+)-(*R*,*R*)-tartrate as an optically active vicinal diol.[16]

1,3-Dioxolanes are also prepared by K10-catalyzed reaction of 1-chloro-2,3-epoxypropane (***Epichlorohydrin***) with aldehydes or ketones, in carbon tetrachloride at reflux (eq 3).[17] In the reaction of acetone with the epichlorohydrin, the efficiency of catalysts varies in the order: K10 (70%) > ***Tin(IV) Chloride*** (65%) > ***Boron Trifluoride*** (60%) = ***Hydrochloric Acid*** (60%) > ***Phosphorus(V) Oxide*** (57%).

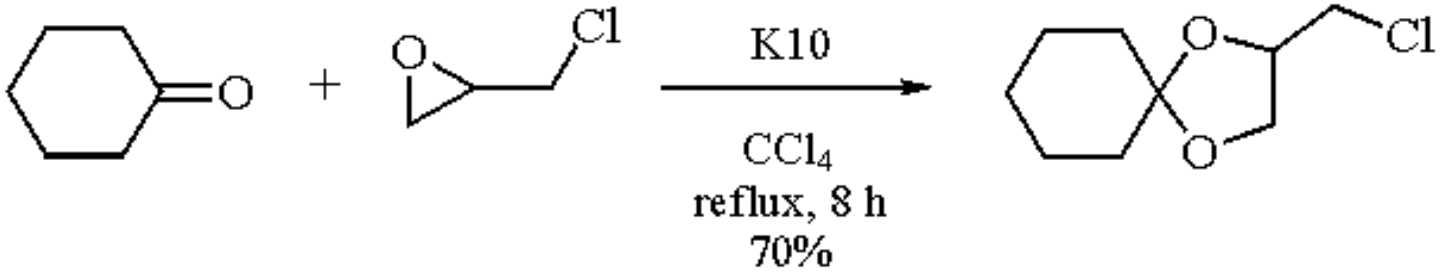

(3)

Preparation of Enamines.

Ketones and amines form enamines in the presence of K10 at reflux in benzene or toluene, with azeotropic elimination of water (eq 4). Typical reactions are over within 3-4 h. With cyclohexanone, the efficiency depends on the nature of the secondary amine: ***Pyrrolidine*** (75%) > ***Morpholine*** (71%) > ***Piperidine*** (55%) > ***Dibutylamine*** (34%).[18] Acetophenone requires longer heating.[19]

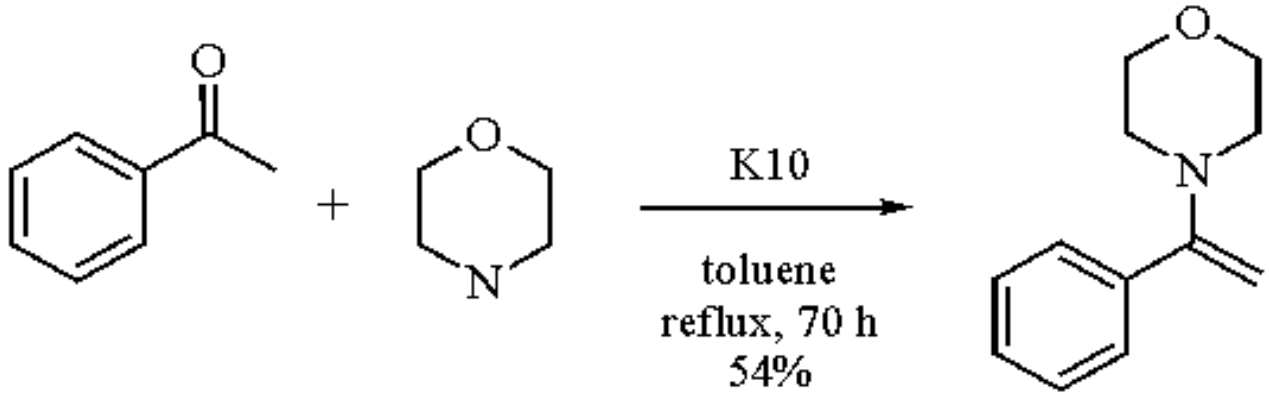

(4)

The K10-catalyzed reaction of aniline with β-keto esters gives enamines chemoselectively, avoiding the competing formation of anilide observed with other acidic catalysts.[20,21]

Synthesis of γ-Lactones via the Ene Reaction.

K10 catalyzes the ene reaction of diethyl oxomalonate and methyl-substituted alkenes at a rather low temperature for this reaction (80 °C), followed by lactonization (eq 5).[22] When alkene isomerization precedes the ene step, it results in a mixture of lactones. Using kaolinite instead of K10 stops the reaction at the ene intermediate, before lactonization.

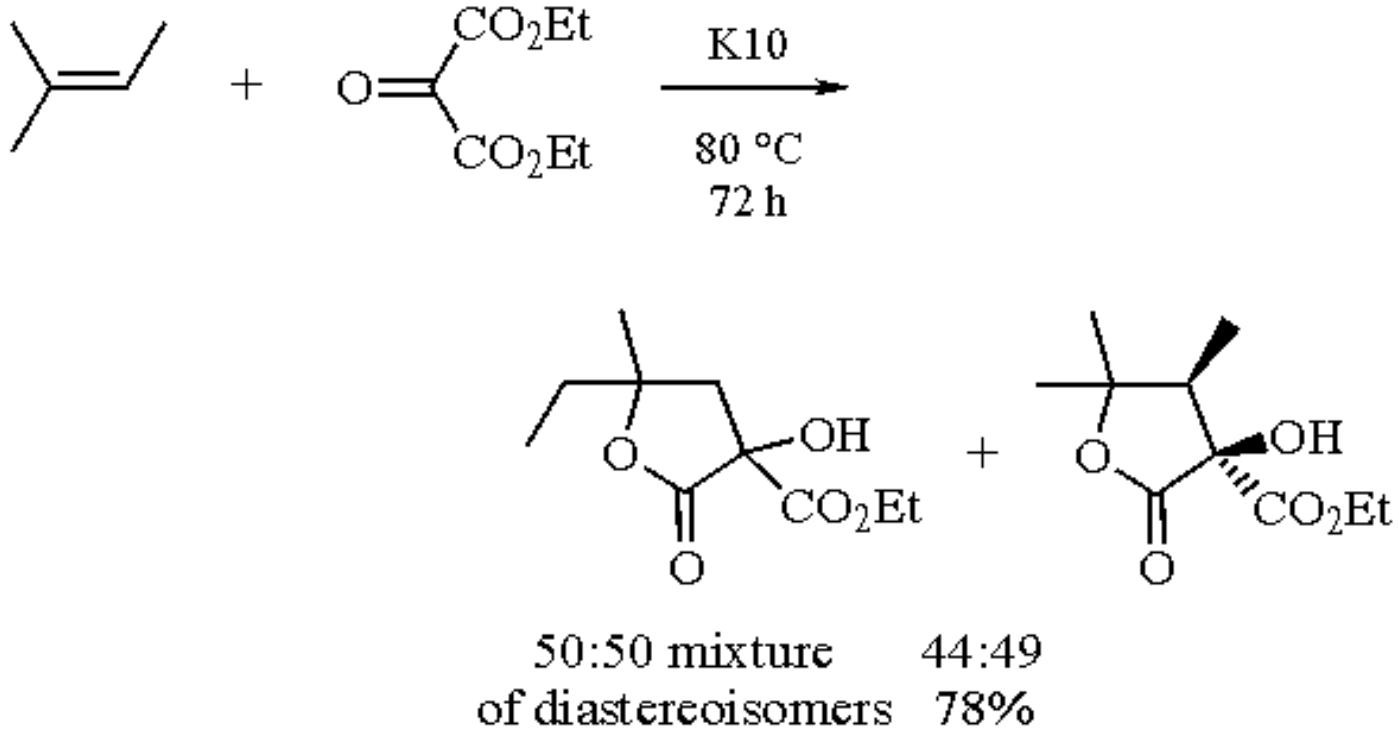

(5)

Synthesis of Enol Thioethers.

Using a Dean-Stark water separator, K10 catalyzes formation of alkyl- and arylthioalkenes from cyclic ketones and thiols or thiophenols, in refluxing toluene (eq 6). A similar catalysis is effected by KSF (in a faster reaction) and K10F.[23] The isomer distribution is under thermodynamic control.

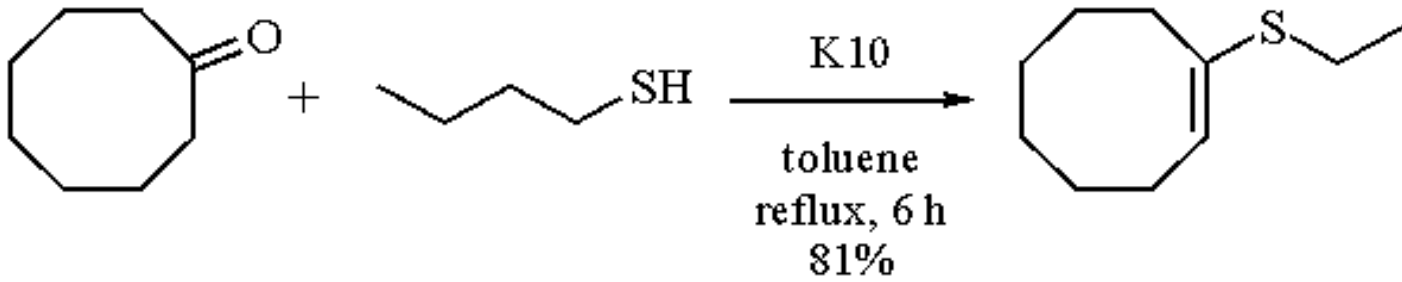

(6)

Preparation of Monoethers of 3-Chloro-1,2-propanediol.

Alcohols react regioselectively with 1-chloro-2,3-epoxypropane to form 1-alkoxy-2-hydroxy-3-chloropropanes. The K10-catalyzed process is carried out in refluxing carbon tetrachloride for 2.5 h (eq 7).[24] Yields are similar to those obtained by ***Sulfuric Acid*** catalysis.

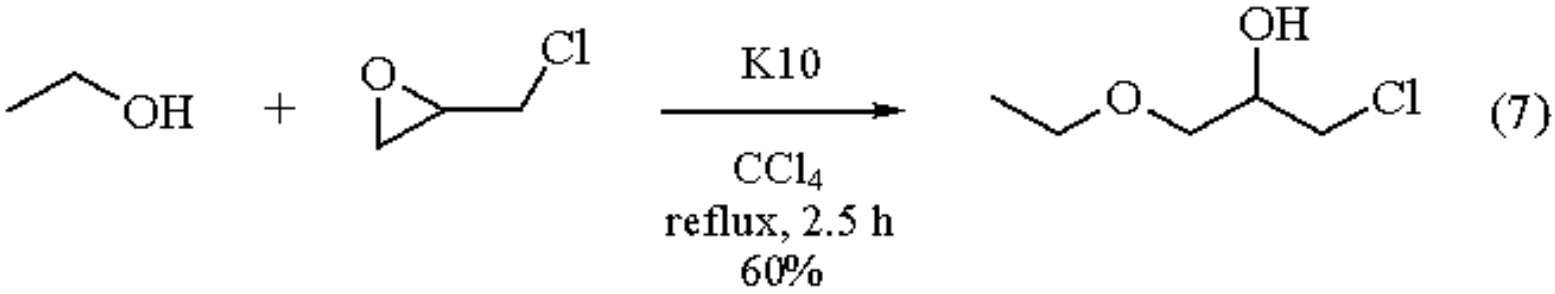

α,β-Unsaturated Aldehydes via Condensation of Acetals with Vinyl Ethers.

K10-catalyzed reaction of diethyl acetals with ***Ethyl Vinyl Ether*** leads to 1,1,3-trialkoxyalkanes. Hydrolysis turns these into *trans*-α,β-unsaturated aldehydes.[25] The reaction is performed close to ambient temperatures (eq 8). K10 is superior to previously reported catalysts, such as ***Boron Trifluoride*** or ***Iron(III) Chloride***. The addition is almost instantaneous and needs no solvent. Cyclohexanone diethyl acetal gives an analogous reaction.

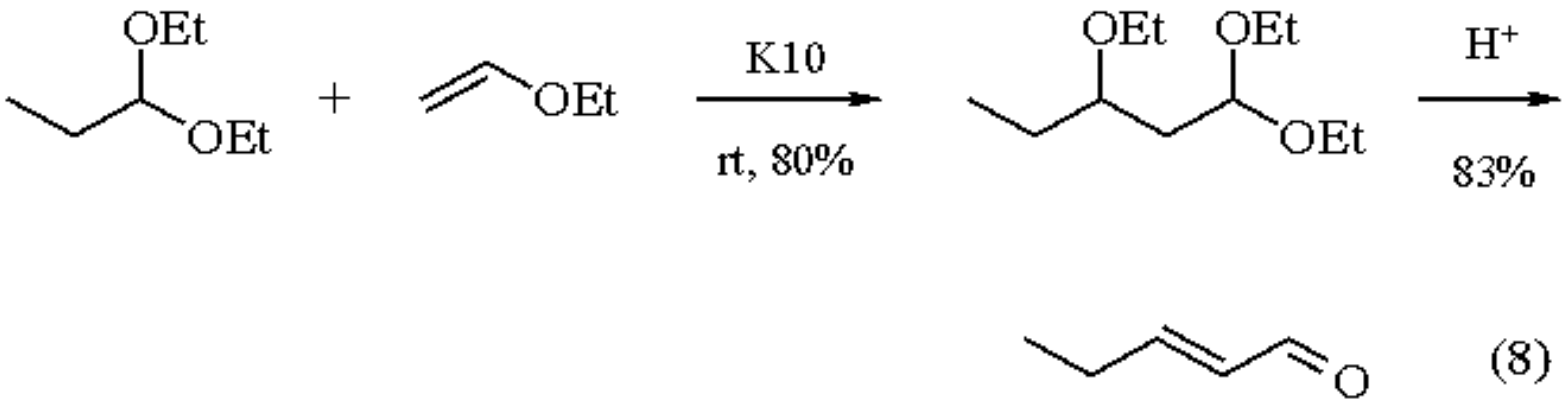

Protective Tetrahydropyranylation of Alcohols and Phenols.

With an excess of ***3,4-Dihydro-2H-pyran***, in the presence of K10 at room temperature, alcohols are transformed quantitatively into their tetrahydropyranyl derivatives. Run in dichloromethane at room temperature, the reaction is complete within 5-30 min (eq 9). The procedure is applicable to primary, secondary, tertiary, and polyfunctional alcohols as well as to phenols.[26]

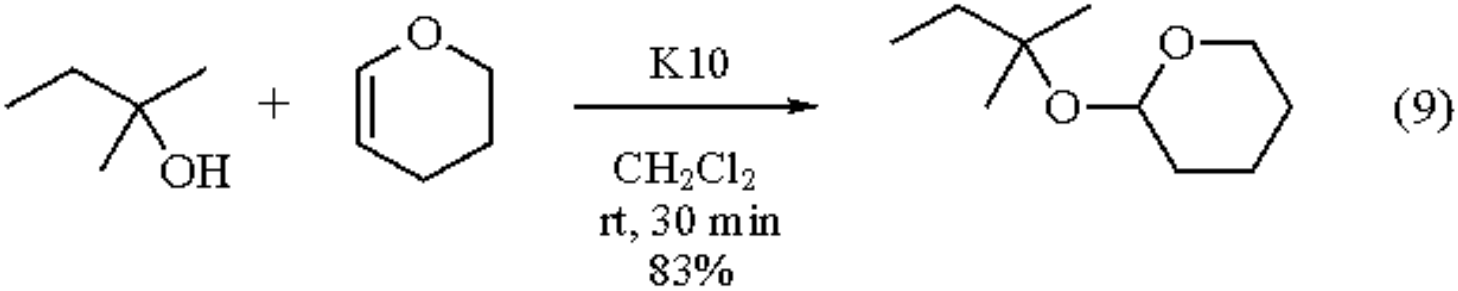

Markovnikov Addition of Hydrochloric Acid to Alkenes.

1-Chloro-1-methylcyclohexane, the formal Markovnikov adduct of hydrochloric acid and 1-methylcyclohexene, becomes largely predominant when ***Sulfuryl Chloride*** is the chlorine source and K10 the solid acid.[27] The reaction at 0 °C, in dry methylene chloride, is complete within 2 h (eq 10).

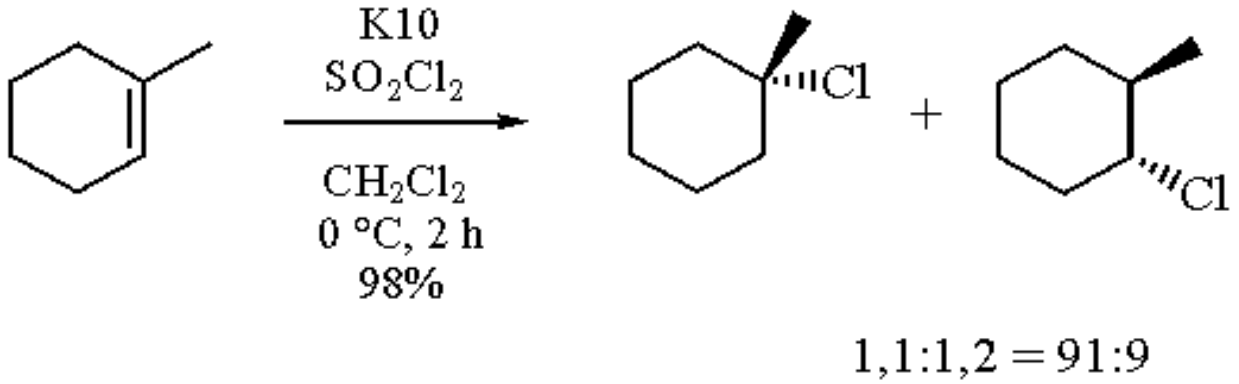

(10)

Porphyrin Synthesis.

Meso-tetraalkylporphyrins are formed in good yields from condensation of aliphatic aldehydes with pyrrole; thermally activated K10 catalyzes the polymerization-cyclization to porphyrinogen, followed by ***p-Chloranil*** oxidation (eq 11).[28]

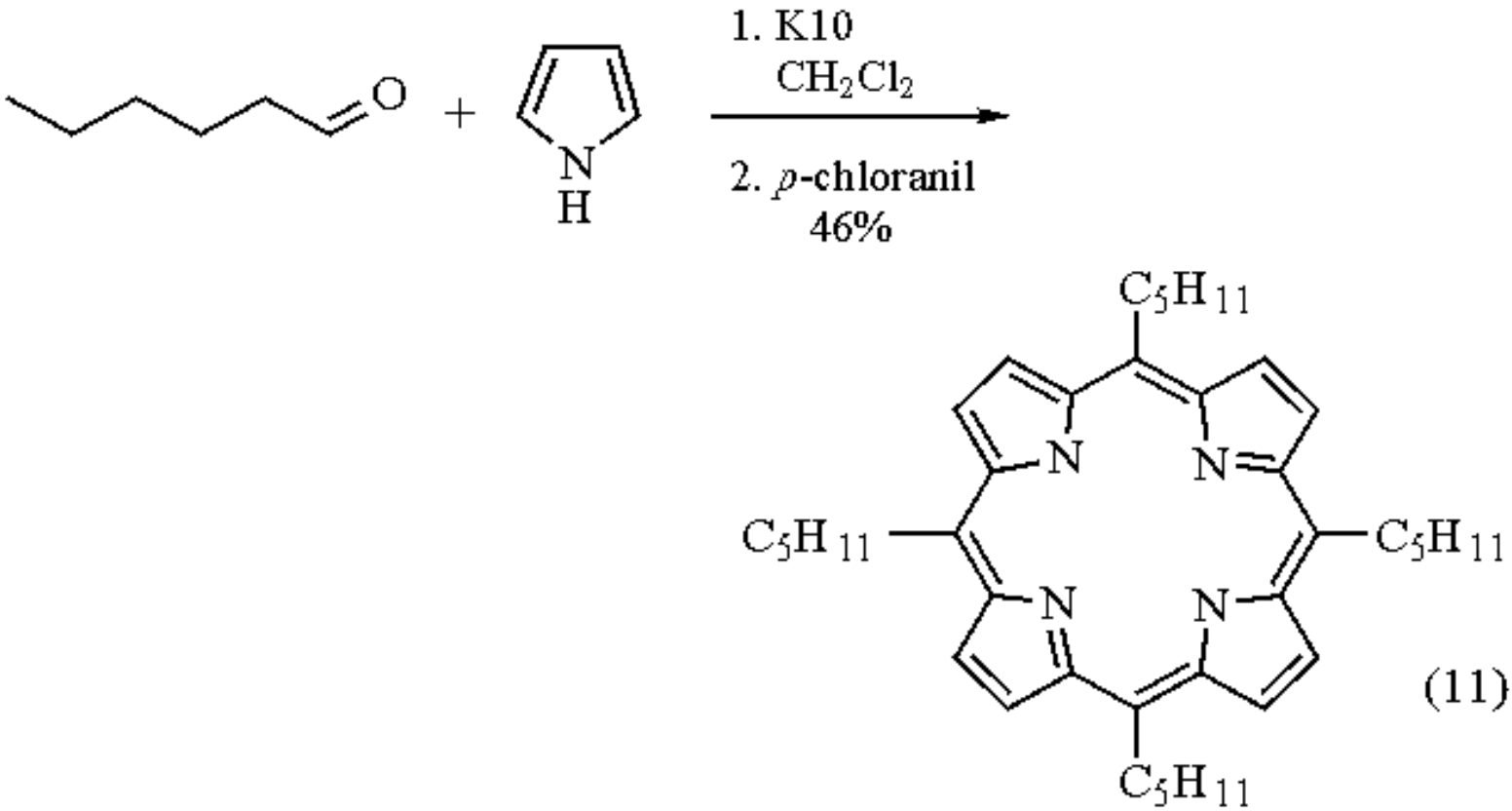

(11)

Meso-tetraarylporphyrins, with four identical or with tuneable ratios of different aryl substituents, are made by taking

advantage of modified K10 (clayfen or Fe^{III}-exchanged) properties.[29,30]

Iron(III)-Doped Montmorillonite.

General Considerations.

The acid strength of some cation-exchanged montmorillonites is between ***Methanesulfonic Acid*** (a strong acid) and ***Trifluoromethanesulfonic Acid*** (a superacid) and, in some instances, their catalytic activity is greater than that of a superacid.[31] Iron montmorillonite is prepared by mixing the clay with various Fe^{III} compounds in water.[8,32] The resulting material is filtered and dehydrated to afford the active solid-acid catalyst. These solid-acid catalysts are relatively inexpensive and are generally used in very small quantities to catalyze a wide variety of reactions, including Friedel-Crafts alkylation and acylation, Diels-Alder reactions, and aldol condensations.[1,5]

Diels-Alder Reactions.[33]

Stereoselective Diels-Alder reactions involving an oxygen-containing dienophile are accelerated in the presence of Fe^{III}-doped montmorillonite in organic solvents (eq 12).[34] Furans also undergo Diels-Alder reactions with ***Acrolein*** and ***Methyl Vinyl Ketone*** in CH_2Cl_2 to give the corresponding cycloadducts in moderate yield (eq 13).[35] The iron-doped clay also catalyzes the radical ion-initiated self-Diels-Alder cycloaddition of unactivated dienophiles such as 1,3-cyclohexadiene and 2,4-dimethyl-1,3-pentadiene (eq 14).[36]

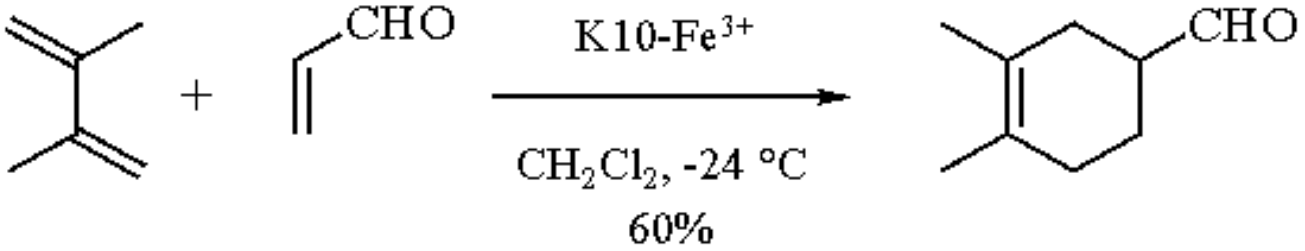

(12)

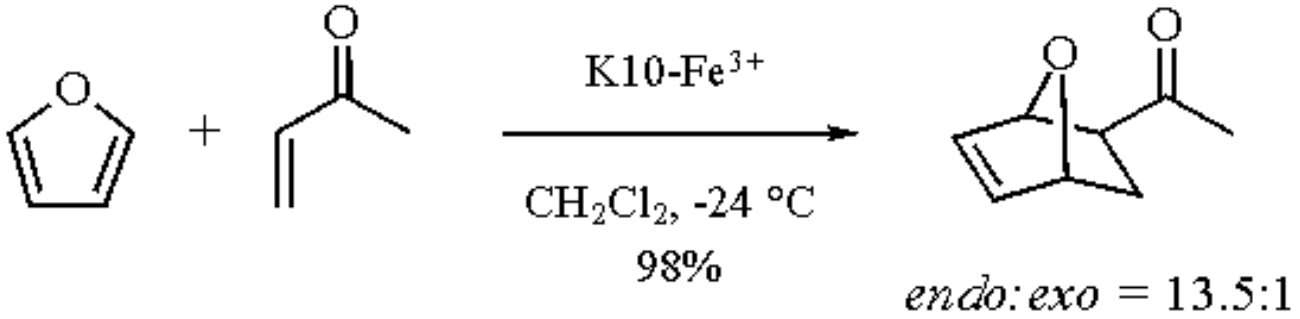

(13)

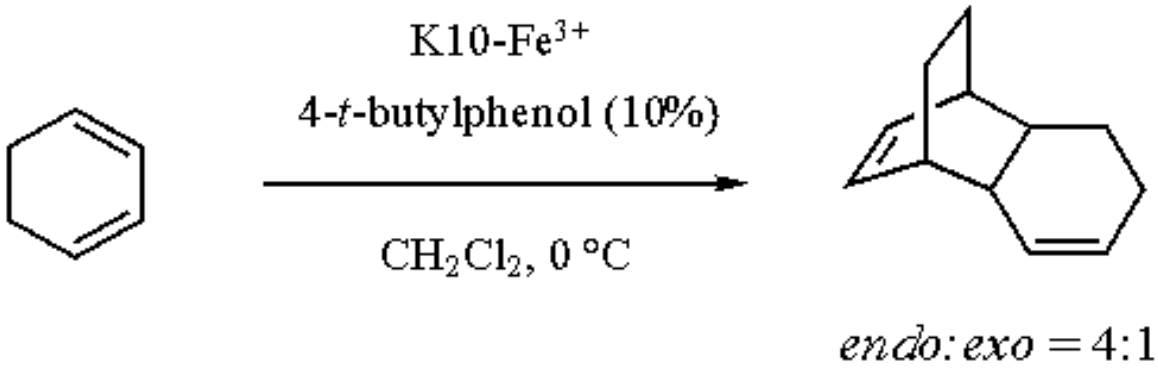

(14)

The role of Fe^{III}-impregnated montmorillonite, and other cation-exchanged montmorillonites, in asymmetric Diels-Alder reactions was found to be limited to the use of small chiral auxiliaries; the results obtained from these reactions are similar to those of homogeneous aluminum catalysts (eq 15).[33]

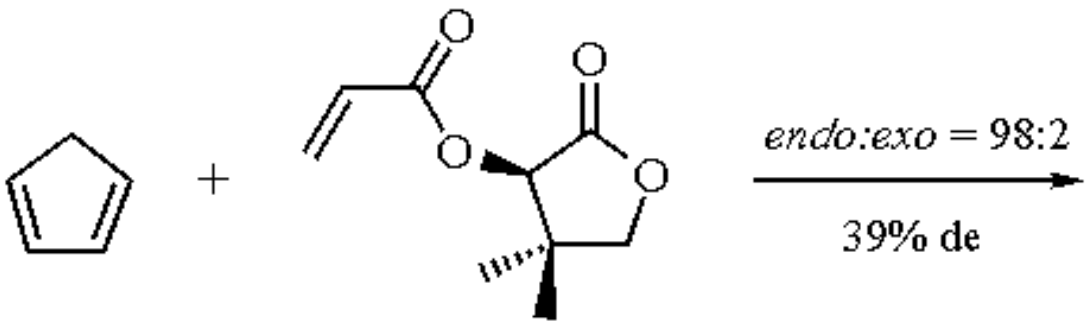

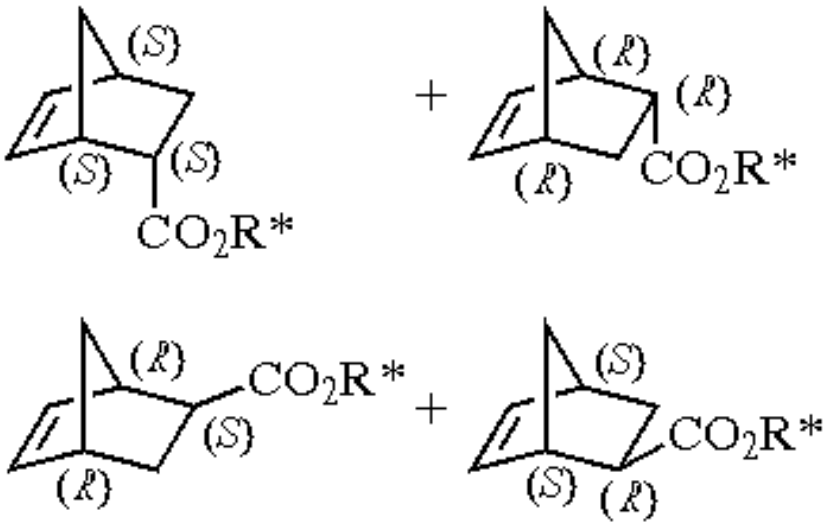

(15)

Friedel-Crafts Acylation and Alkylation.[37,38]

The Friedel-Crafts acylation of aromatic substrates with various acyclic carboxylic acids in the presence of cation-exchanged (H^+, Al^{3+}, Ni^{2+}, Zr^{2+}, Ce^{3+}, Cu^{2+}, La^{3+}) montmorillonites has been reported.[39] Curiously, the use of iron-doped montmorillonite was not included in the report; however, some catalysis is expected. Under these conditions, the yield of the desired ketones was found to be dependent on acid chain length and the nature of the interlayer cation.

The direct arylation of a saturated hydrocarbon, namely adamantane, in benzene using $FeCl_3$-impregnated K10 was recently reported.[11] Additionally, Friedel-Crafts chlorination of adamantane in CCl_4 using the same catalyst was also reported. The alkylation of aromatic substrates with halides under clay catalysis gave much higher yields than conventional Friedel-Crafts reactions employing ***Titanium(IV) Chloride*** or ***Aluminum Chloride*** as catalyst.[8] Higher levels of dialkylation were observed in some cases. The alkylation of aromatic compounds with alcohols and alkenes was also found to be catalyzed with very low levels of cation-exchanged montmorillonites, as compared to standard Lewis acid catalysis; however, iron-doped clays performed poorly compared to other metal-doped clays.

Aldol Condensations.

Cation-exchanged montmorillonites accelerate the aldol condensation of silyl enol ethers with acetals and aldehydes.[40] Similarly, the aldol reaction of silyl ketene acetals with electrophiles is catalyzed by solid-acid catalysts. Neither report discussed the use of iron montmorillonite for these reactions; however, some reactivity is anticipated.

Miscellaneous Reactions.

The coupling of silyl ketene acetals (enolsilanes) with pyridine derivatives bearing an electron-withdrawing substituent, namely cyano, in the *meta* position is catalyzed by iron montmorillonite and other similar solid-acid catalysts (eq 16).[41]

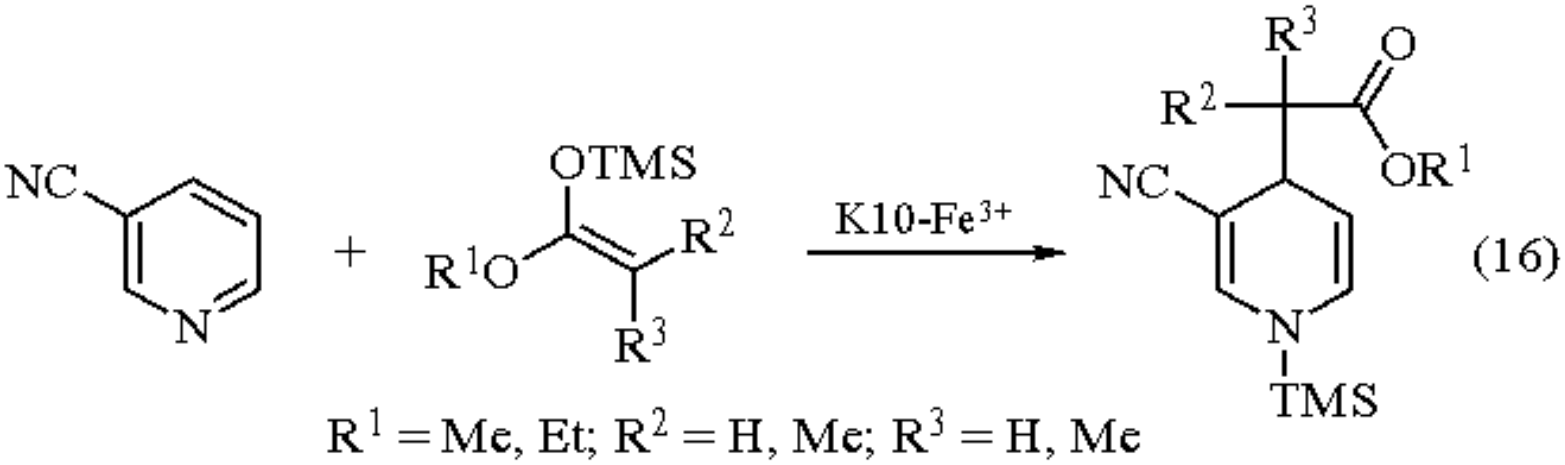

The resulting *N*-silyldihydropyridines easily undergo desilylation by treatment with ***Cerium(IV) Ammonium Nitrate*** to afford the desired dihydropyridine derivative. The reactivity was found to be dependent on the montmorillonite counterion and to follow the order: Fe^{3+} > Co^{2+} > Cu^{2+} &AApprox; Zn^{2+} > Al^{3+} &AApprox; Ni^{2+} &AApprox; Sn^{4+}.

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Morpholine

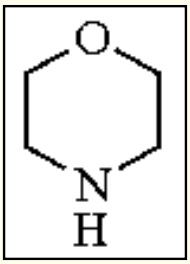

[110-91-8] · C_4H_9NO · Morpholine · (MW 87.14)

(secondary amine base; reagent for enamine formation and utilization; condensation catalyst for Mannich condensations)

Physical Data: bp 128.9 °C; *d* 1.007 g cm^{-3}; pK_a 8.8.

Solubility: miscible with water, acetone, diethyl ether.

Form Supplied in: liquid, >99%.

Purification: dried with KOH, fractionally distilled, dried for a second time over sodium metal, then redistilled.[1]

Handling, Storage, and Precautions: eye and skin irritant; flammable liquid; use in a fume hood.

Willgerodt Reaction.[2]

Morpholine is employed as the amine component of the Kindler modification of the Willgerodt reaction. The process effects the rearrangement of aryl alkyl ketones to carboxylic acid derivatives (eqs 1 and 2).[3,4] Morpholine is particularly useful in the reaction as its high boiling point makes the use of sealed tubes unnecessary.

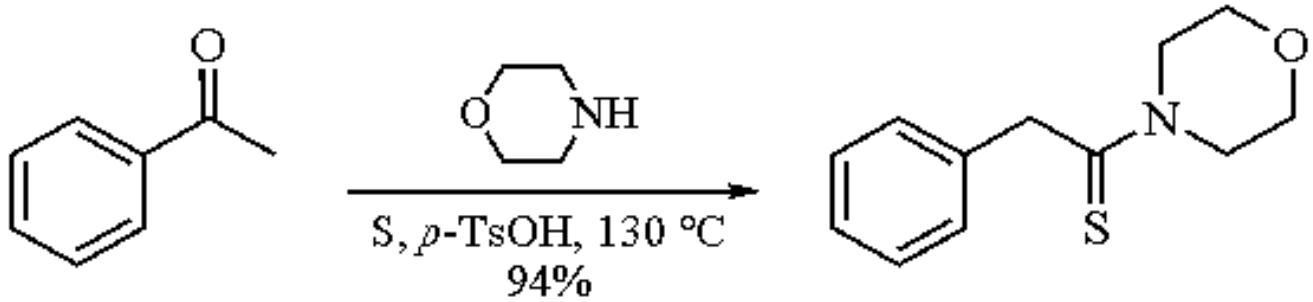

(1)

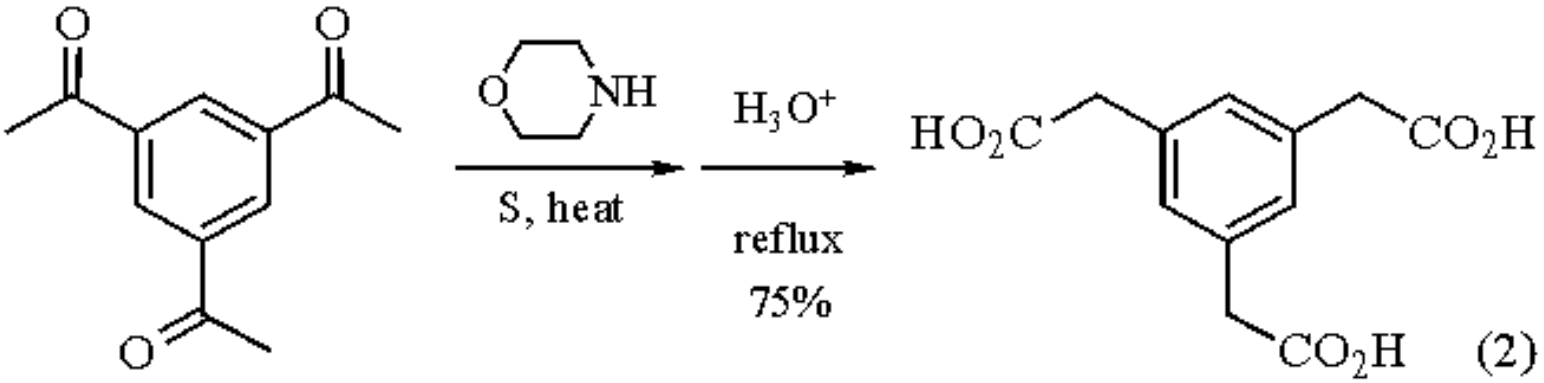

Willgerodt-like processes are effected by treatment of benzylphosphonates[5] and chlorides[6] with morpholine and ***Sulfur*** (eqs 3 and 4).

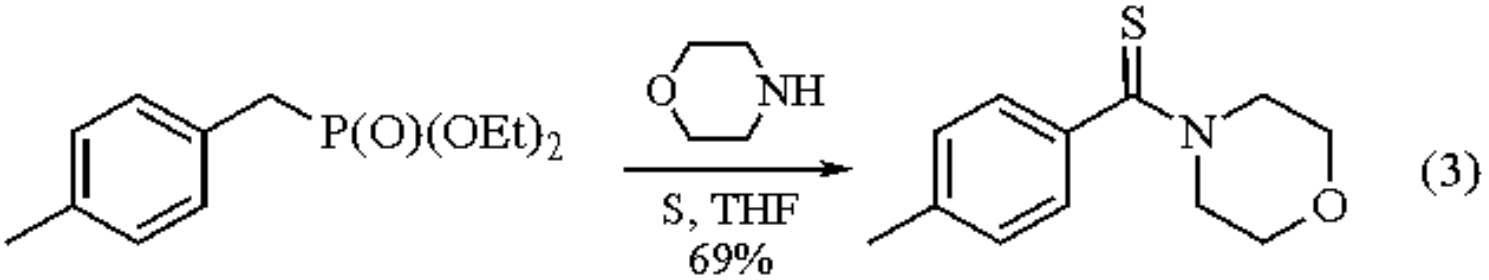

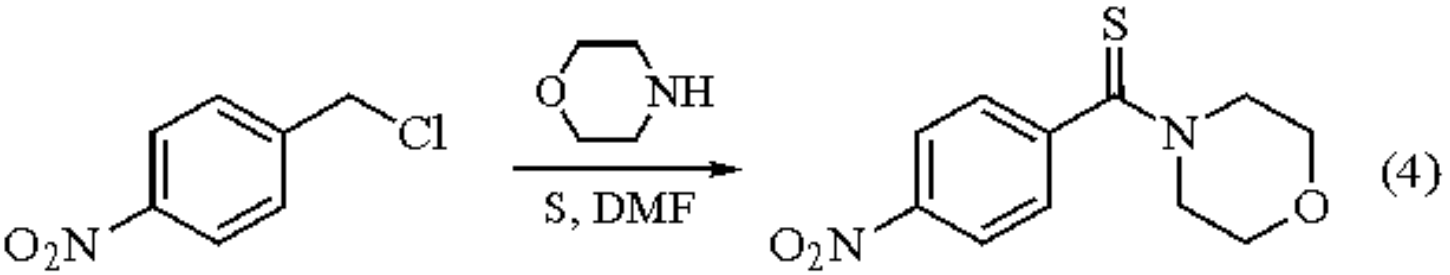

Enamine Formation and Utilization.

Morpholine is one of the three principal secondary amines used in the formation of enamines.[7-10] A weaker base than either ***Piperidine*** or ***Pyrrolidine***, it forms enamines more slowly than the other two bases. The regioselectivity of morpholine enamine formation is significantly less than with pyrrolidine.[11]

The lower reactivity of morpholine has been used as a method for the separation of monoalkylated cyclohexanones from unalkylated material (eq 5).[12]

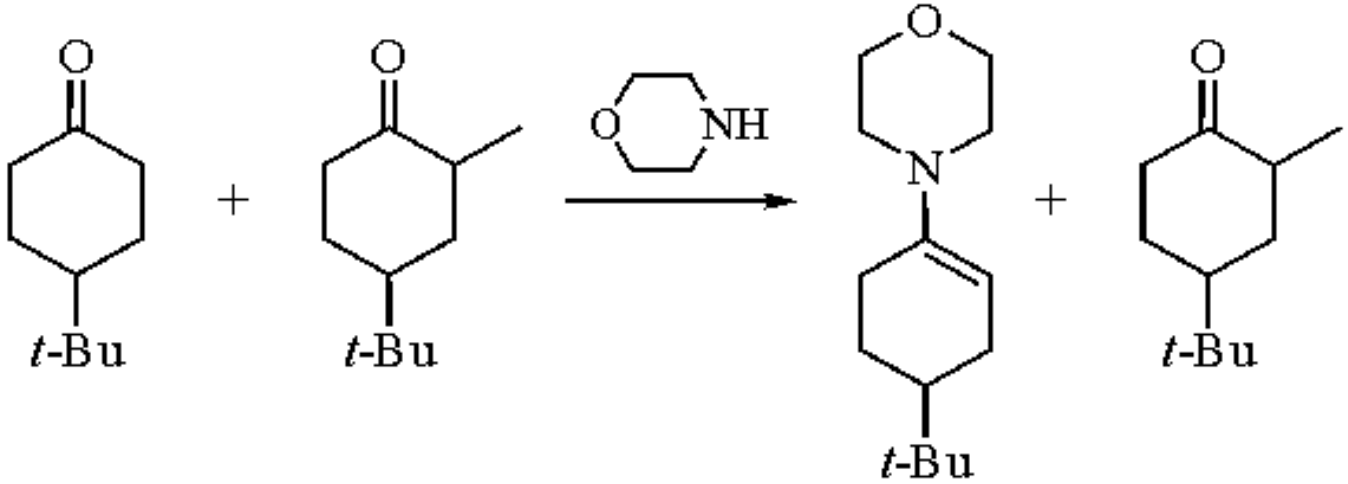

(5)

Morpholine enamines of saturated ketones and aldehydes are prepared by heating the base and the carbonyl compound alone in benzene solution (eq 6),[10] by catalysis with ***p-Toluenesulfonic Acid*** in toluene (eq 7),[13] and by catalysis with ***Titanium(IV) Chloride*** (eq 8).[14] Aldehyde enamines may also be prepared by decarboxylation of the morpholine enamines of substituted pyruvic acids (eq 9).[15]

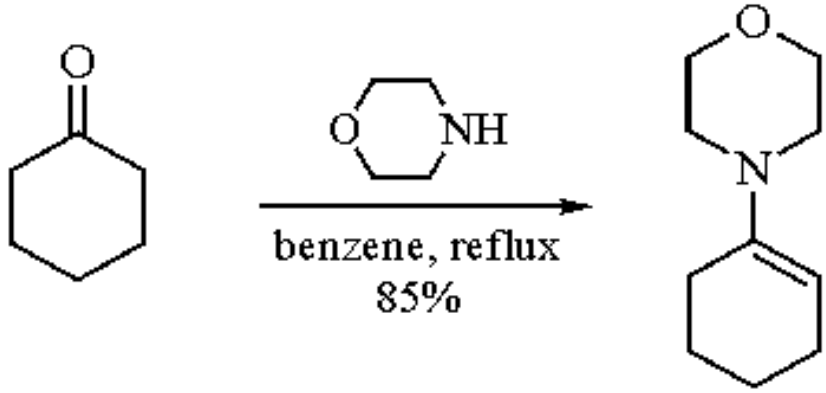

(6)

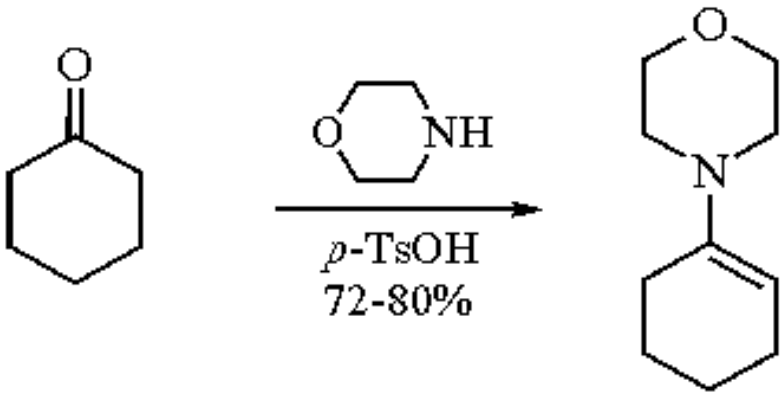

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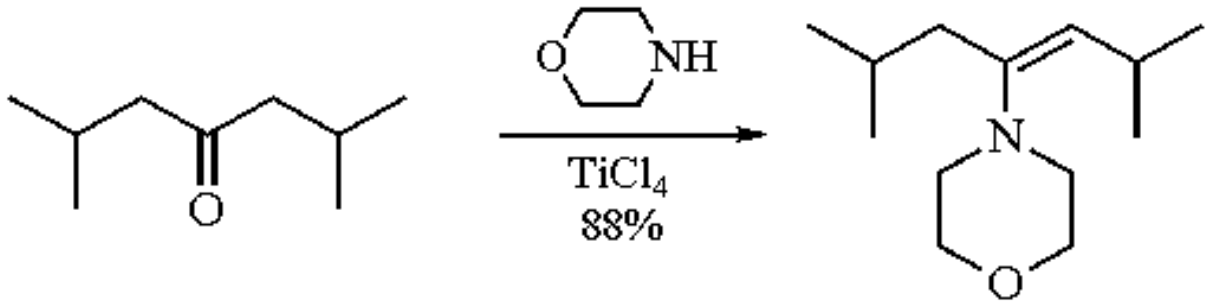

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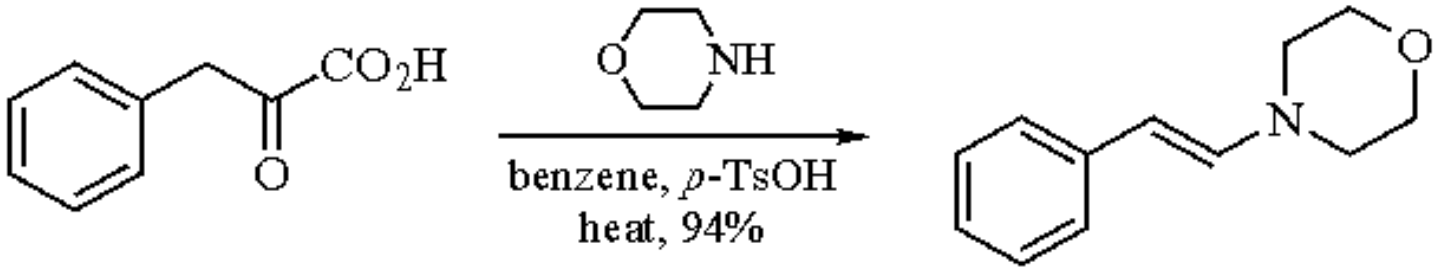

(9)

Enaminones may be prepared by conjugate addition of morpholine to an alkynic ketone (eq 10),[16] and the morpholine enamine of pyruvaldehyde has been prepared by conjugate addition and rearrangement of 2-chloroacrolein (eq 11).[17]

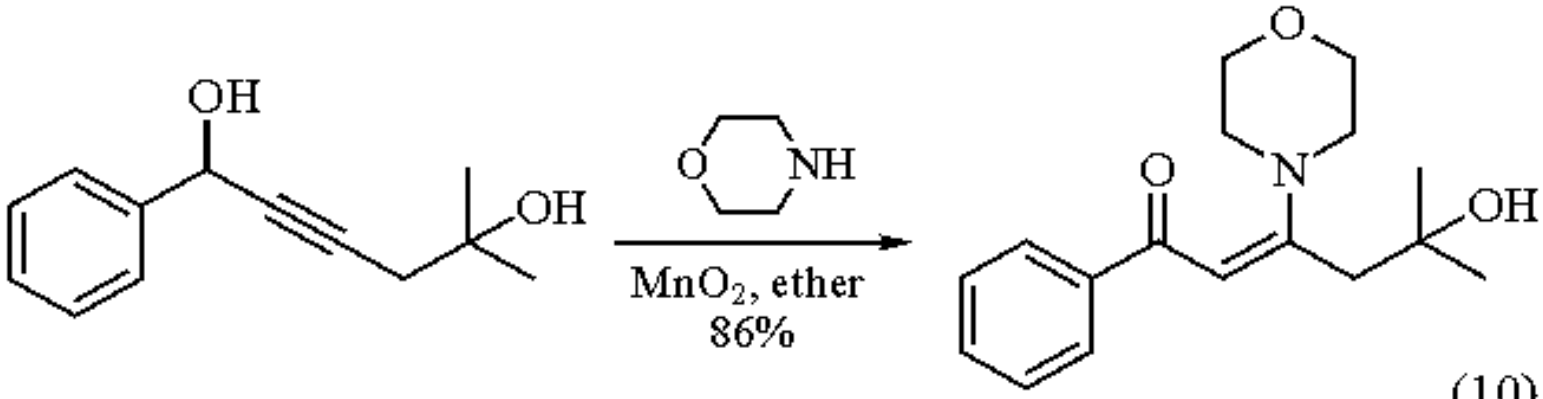

(10)

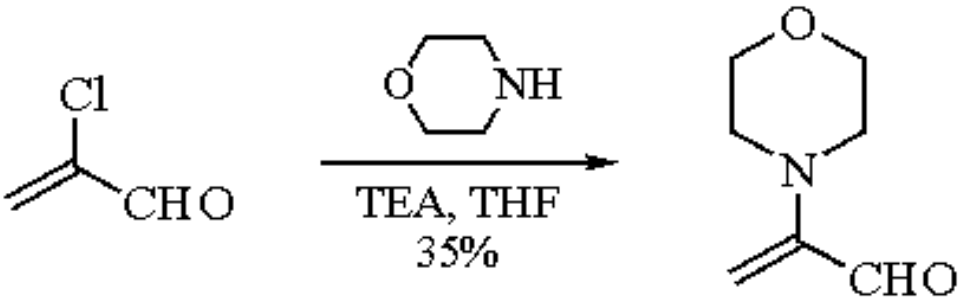

(11)

Utilization of Morpholine Enamines.

The less reactive morpholine enamines have been shown to acylate in better yield than the corresponding pyrrolidine derivatives.[10] A typical example is the acylation of the morpholine enamine of cyclopentanone (eq 12).[18]

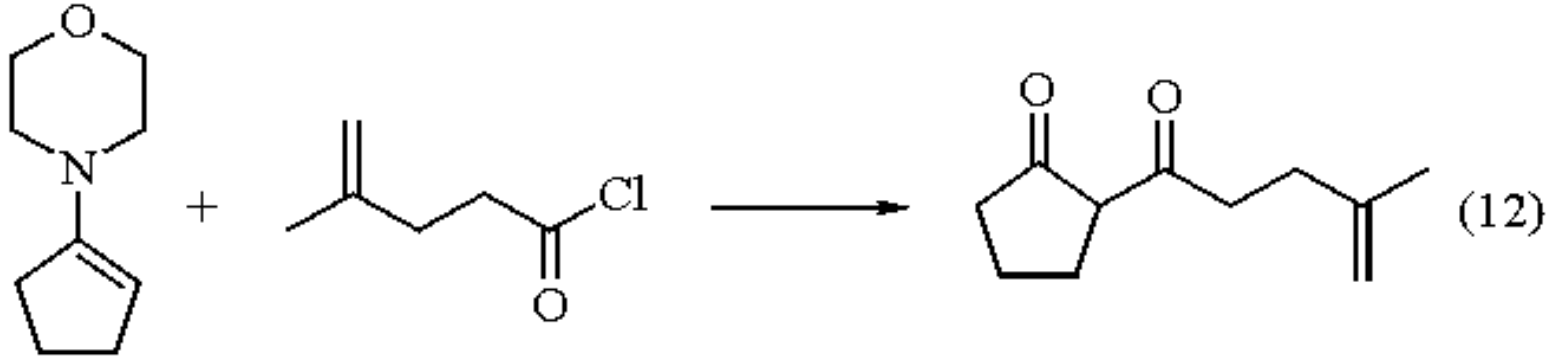

Miscellaneous Reactions.

Morpholine is used as a base for dehydrobromination (eq 13)[19] and in conjunction with molecular ***Iodine*** for the iodination of alkynic alcohols (eq 14).[20]

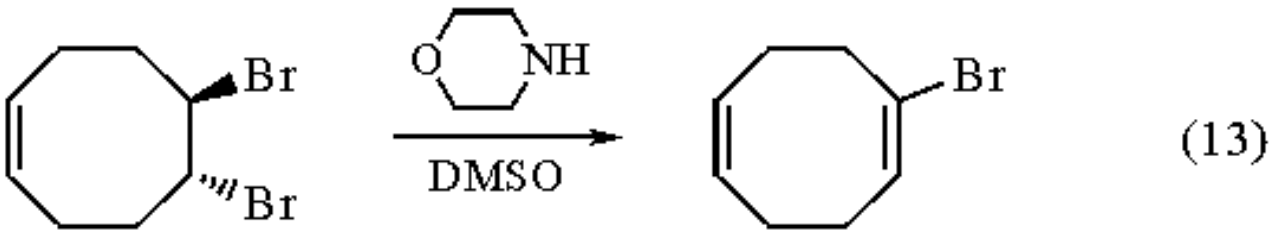

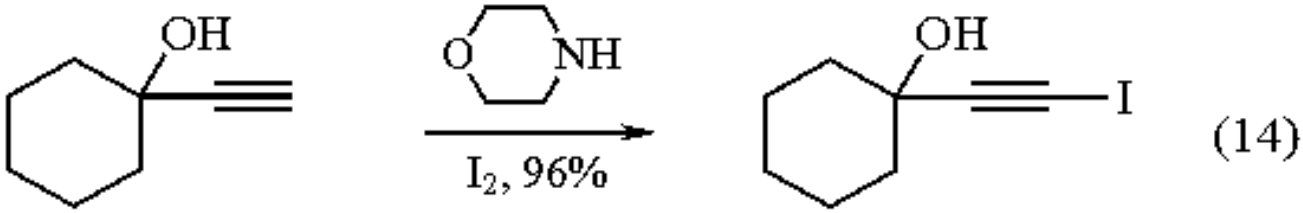

Treatment of benzyl phenyl ketone with ***Thionyl Chloride*** and morpholine results in the formation of benzil, a reaction which presumably occurs through the intermediacy of the ketone enamine (eq 15).[21]

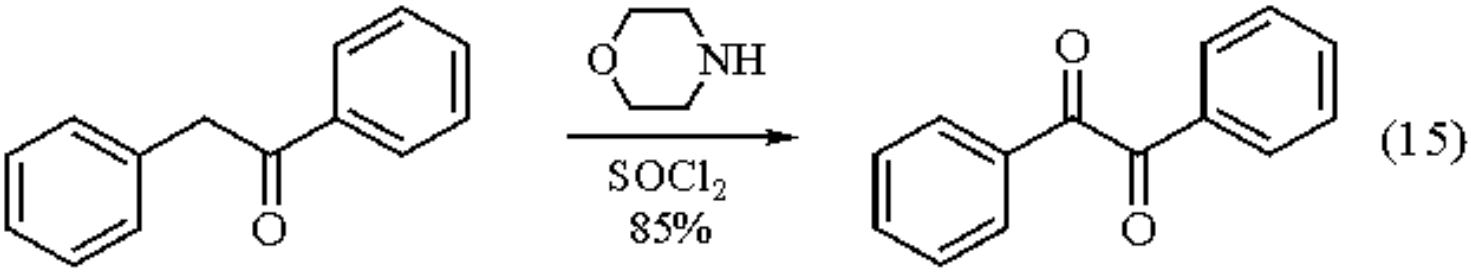

Under high pressure, *p*-nitrophenyl triflate undergoes addition-elimination with morpholine (eq 16).[22]

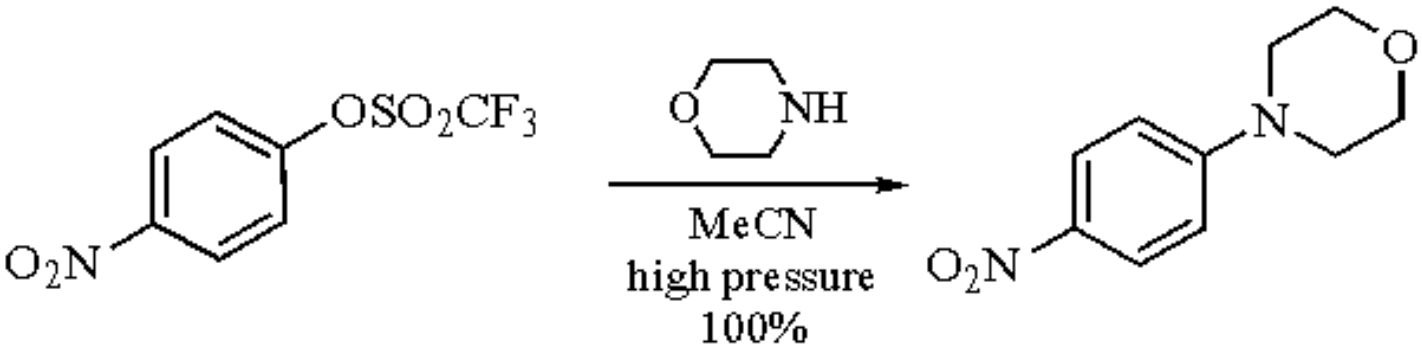

(16)

Morpholine, like other secondary amines, may be used for Mannich-type condensations (eq 17).[23]

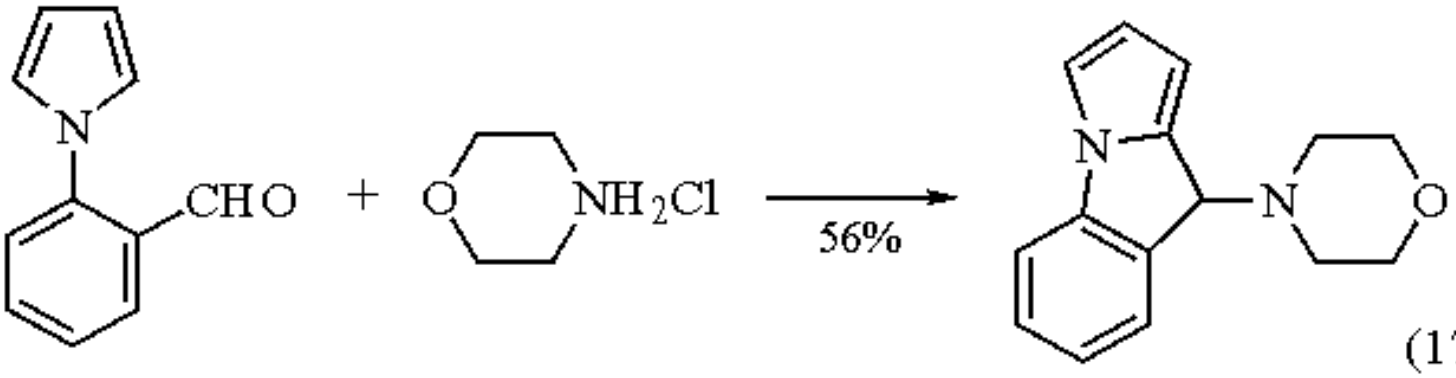

(17)

Related Reagents.

N-Chloromorpholine; ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide***; ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-p-toluenesulfonate***; ***N,N´-Dicyclohexyl-4-morpholinecarboximidamide***; ***Diethyl Morpholinomethylphosphonate***; ***Lithium Morpholide***; ***N-Methylmorpholine N-Oxide***; ***2-Morpholinoethyl Isocyanide***; ***N-Morpholinomethyldiphenylphosphine Oxide***; ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***.

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2-Morpholinoethyl Isocyanide

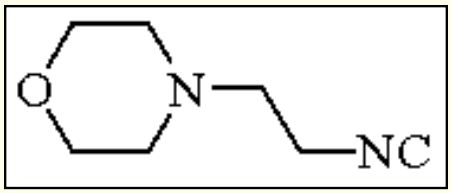

[78375-48-1] · $C_7H_{12}N_2O$ · 2-Morpholinoethyl Isocyanide · (MW 140.21)

(coupling reagent for amino acids; amide synthesis)

Physical Data: bp 72-73 °C/0.7 mmHg; *d* 1.017 g cm^{-3}; n_D 1.469.

Solubility: usually used in CH_2Cl_2.

Form Supplied in: liquid, >98% pure.

Analysis of Reagent Purity: comparison with literature boiling point; also ν_{max} (liquid film) at 2150 cm^{-1} is indicative of isocyanide functionality.

Preparative Methods: by the reaction of 2-morpholinoethylamine with ***Formic Acid*** in boiling toluene with a water separator, to yield the formamide which is treated either with ***Phosgene*** and ***Triethylamine*** in CH_2Cl_2 or with ***Phosphorus Oxychloride*** and ***Diisopropylamine***.[1,2] The use of diisopropylamine as base is favored as yields are improved, typically to 68%. ***Trichloroacetic Anhydride*** has also been used as an alternative for $COCl_2$, giving a yield of 74%.[3]

Purification: when phosphorus oxychloride and diisopropylamine are employed, purification is not required.[2]

Introduction.

The principal synthetic application of 2-morpholinoethyl isocyanide is as a coupling reagent of amino acids to yield peptides.[2] It also reacts with aldehydes or ketones to yield amides,[4] with acids to yield imidazolinium salts,[5] and has been used as a ligand in spectroscopic studies to examine shielding effects.[6]

Coupling of Amino Acids.[2]

The coupling reaction is performed in CH_2Cl_2 with ***N-Hydroxysuccinimide*** or ***1-Hydroxybenzotriazole*** and 2-

morpholinoethyl isocyanide (**1**) to yield products in 61-95% yield (eq 1).

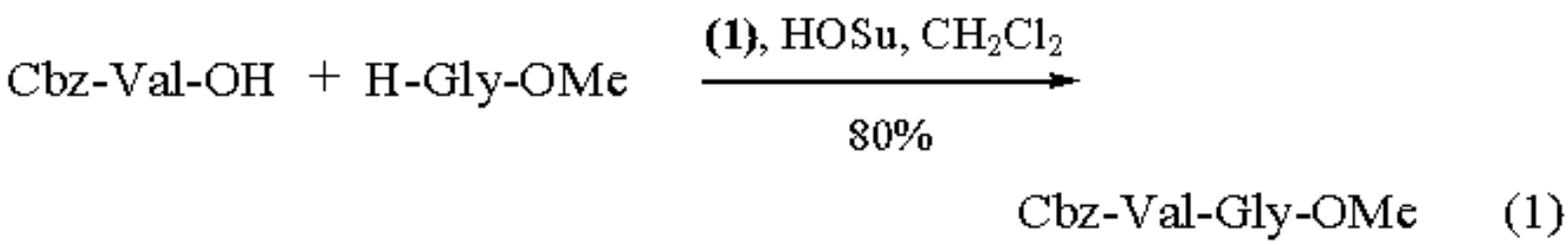

No racemization is observed, as determined by the coupling reaction of CF_3CO-Phe-OH with H-Phe-O-*t*-Bu in the presence of HOSu.

Formation of Amides.[4]

The isocyanide moiety of 2-morpholinoethyl isocyanide reacts with aldehydes and ketones to form amides in good yields (eq 2).

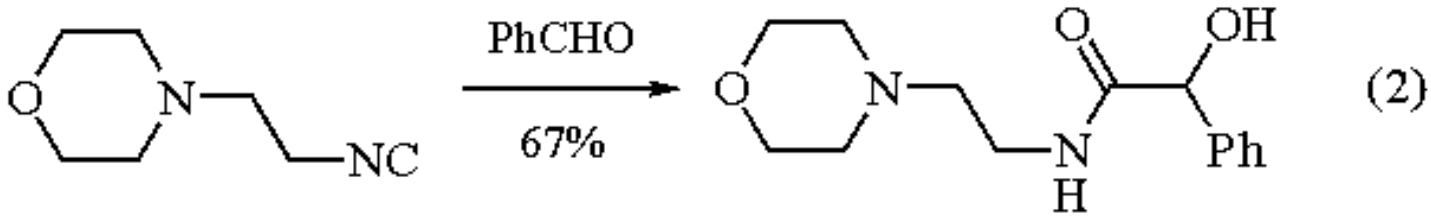

Formation of Imidazolinium Salts by Cyclization.[5]

Treatment of the isocyanide with HZ (Z = Cl, TsO) gives 40-60% of the spiroimidazolium salt which on addition of excess HZ provides the imidazolinium salt in 70-95% yield (eq 3).

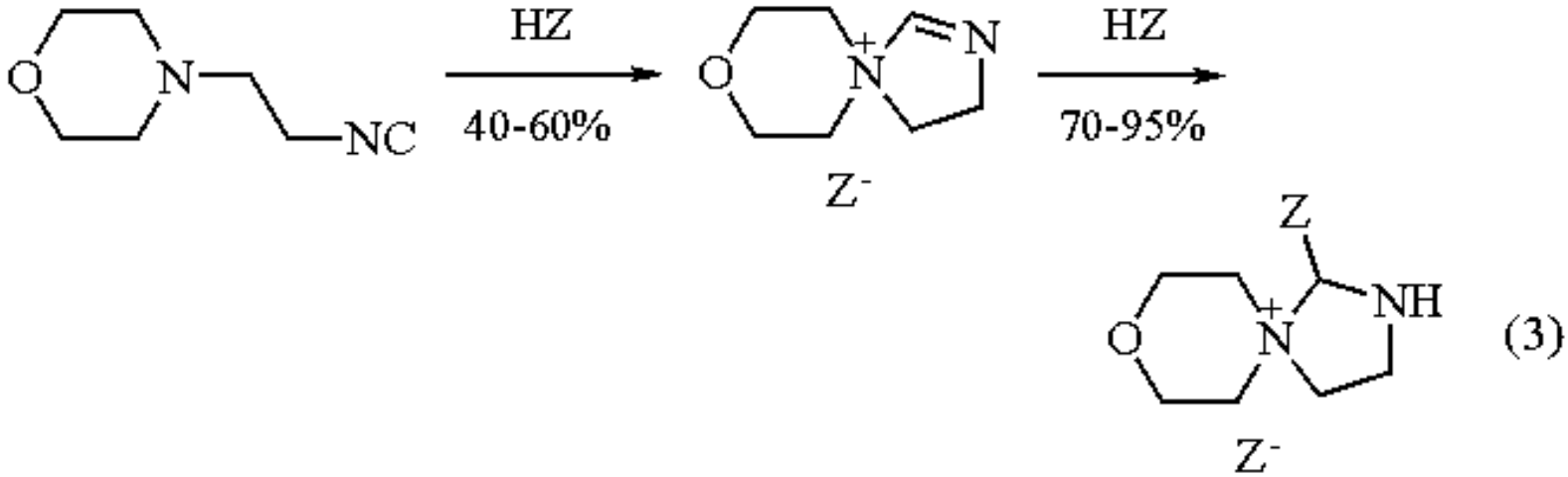

Use in Spectroscopic Studies.[6]

2-Morpholinoethyl isocyanide has been used to study the NMR ^{14}N NMR signals of molybdenum (^{95}Mo) and tungsten (^{183}W) carbonyl isocyanide complexes $M(CO)_{6-n}(CNR)_n$ (n = 0-6). When isocyanide is coordinated to the metal center, the ^{14}N signal is deshielded but, with further substitution, the N becomes more shielded again. With UV and IR studies, substitution of CO by isocyanide shifts the absorption toward longer wavelength so that the color of the complexes changes from white to orange-red.

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N-Morpholinomethyldiphenylphosphine Oxide[1]

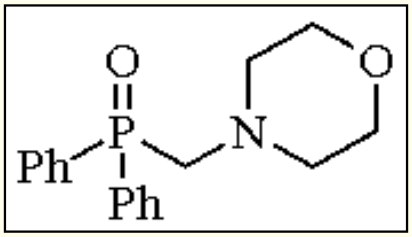

[20684-76-8] · $C_{17}H_{20}NO_2P$ · *N*-Morpholinomethyldiphenylphosphine Oxide · (MW 301.35)

(Horner-Wittig reagent useful for the preparation of homologous aldehydes,[2] their morpholino enamines,[2a,b,3] and α-morpholinomethyl ketones[4])

Physical Data: mp 159 °C.

Solubility: insol H_2O; sol THF, $CHCl_3$.

Form Supplied in: white crystalline solid, not commercially available.

Preparative Methods: has been prepared in several ways, most efficiently by two related sequences involving an Arbuzov reaction (eqs 1 and 2).[3,5] In both approaches the crude product is sufficiently pure for use in subsequent synthesis applications.

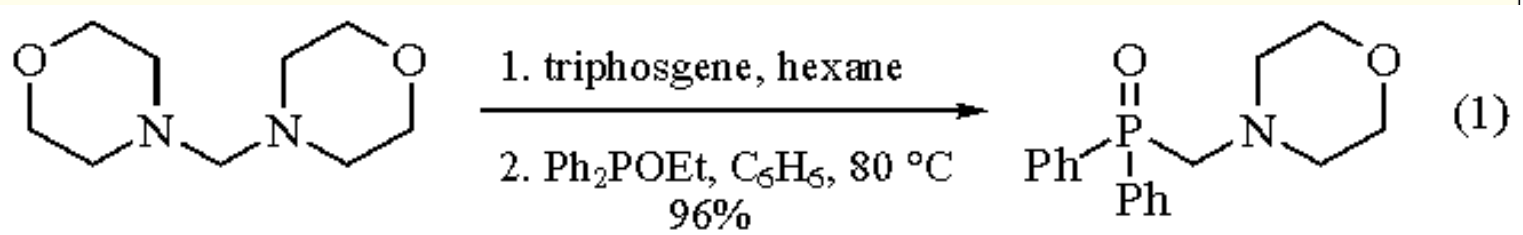

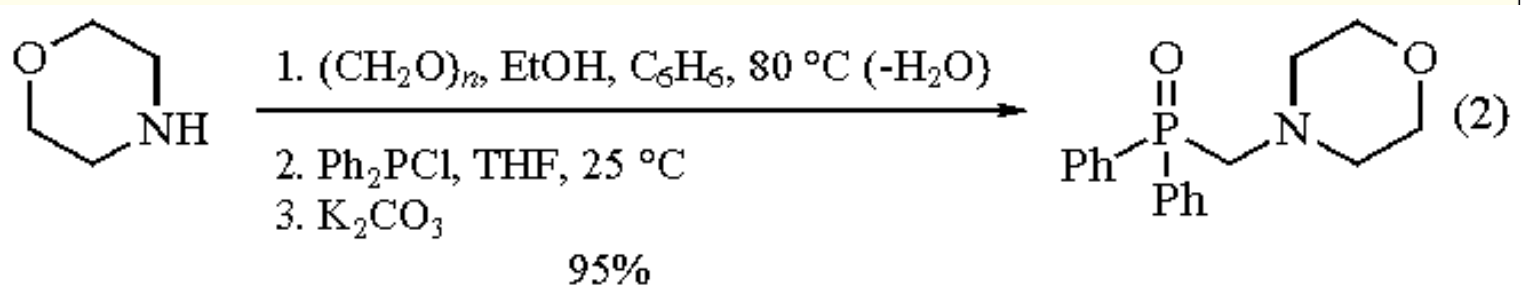

Purification: most easily purified by recrystallization from benzene or from CH_2Cl_2/hexane. It can also be purified by column chromatography on silica gel.

Handling, Storage, and Precautions: stable for extended periods of storage under nitrogen; its toxicity is unknown.

Horner-Wittig Formation of Enamines.

The utility of the title reagent lies in its application as an α-amino-substituted Horner-Wittig reagent. Deprotonation with ***n-Butyllithium*** in THF at 0 °C gives a reasonably stable, orange-colored anion (**1**). This anion adds to aliphatic, aromatic, and α,β-unsaturated aldehydes to give good yields of the addition adducts as lithium alkoxides, which are sufficiently stable that they do not undergo direct elimination of lithium diphenylphosphinate.[2a] Rather, protonation yields the alcohols as diastereomeric mixtures of products (eq 3). Treatment with ***Potassium t-Butoxide***, ***Potassium Hydride***, or ***Sodium Hydride*** forms the corresponding potassium or sodium alkoxide which eliminates potassium or sodium diphenylphosphinate to give mixtures of (*E*)- and (*Z*)-enamines; these isomerize to the more stable (*E*)-enamines upon purification (eq 4).

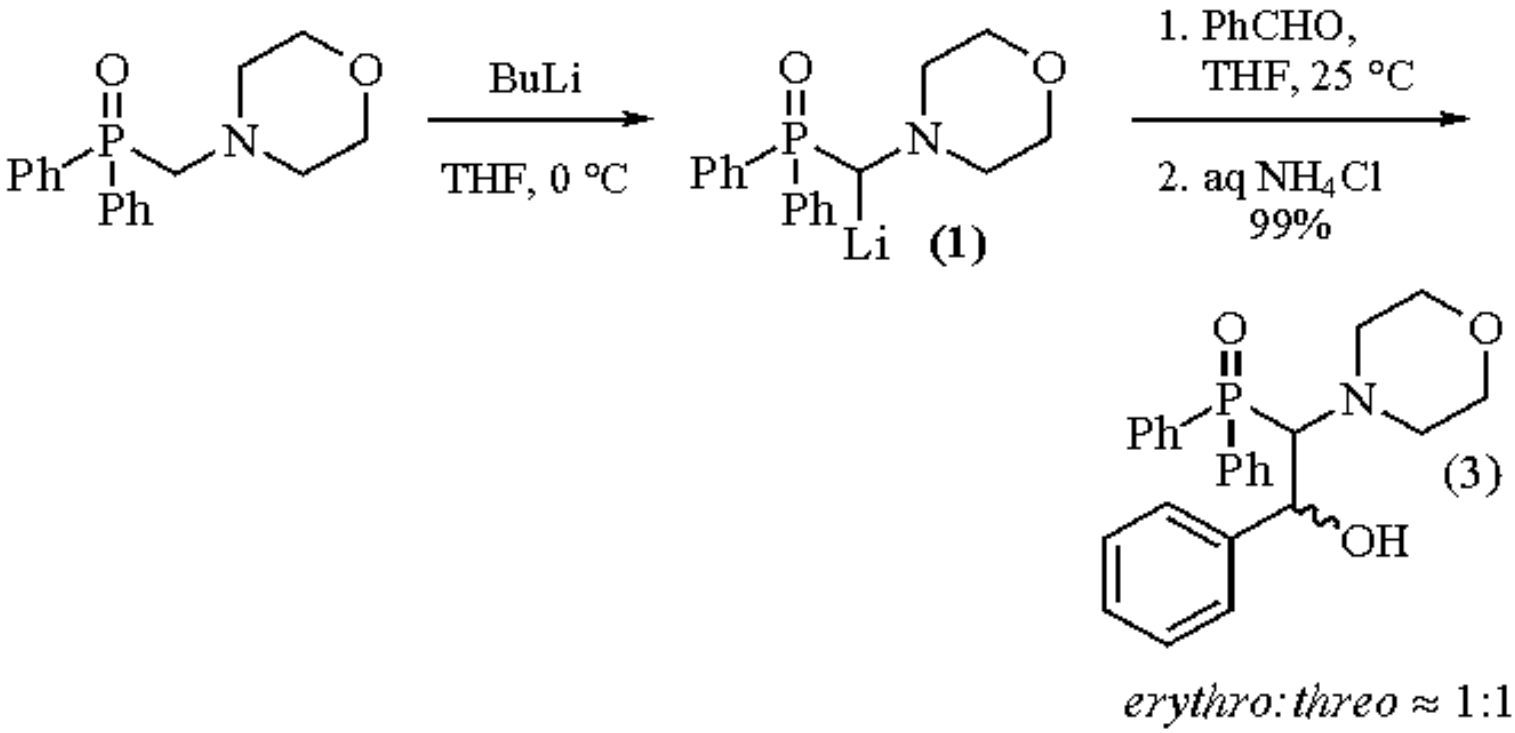

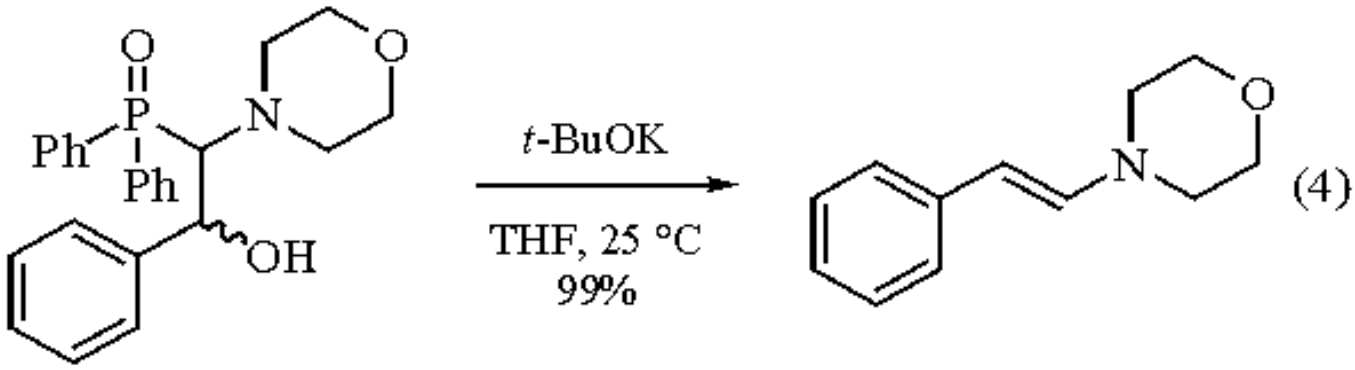

This reagent has certain advantages over related phosphonates[6] and phosphonium salts,[7] both of which have shown only limited success for the synthesis of homologous enamines of aldehydes. However, the utility of this reagent is limited by

the basicity of the anion (**1**) in that its reaction with ketones results in partial to complete enolization.[2b] The related reagent [(*N*-methylanilino)methyl]diphenylphosphine oxide has been used successfully with ketones, due to the lower basicity of its derived anion relative to (**1**).[8]

Formation of Homologous Aldehydes.

The enamines prepared with the title reagent can be readily hydrolyzed to the corresponding aldehydes (eq 5).[2a] Thus, the overall transformation exemplified by eqs 3-5 represents a method for the one-carbon homologation of aldehydes. Related reagents having an additional α-substituent, which can be prepared by Mannich-type condensation of ***Diphenylphosphine Oxide*** with aldehydes and morpholine,[5b] show promise as acyl anion equivalents.[9]

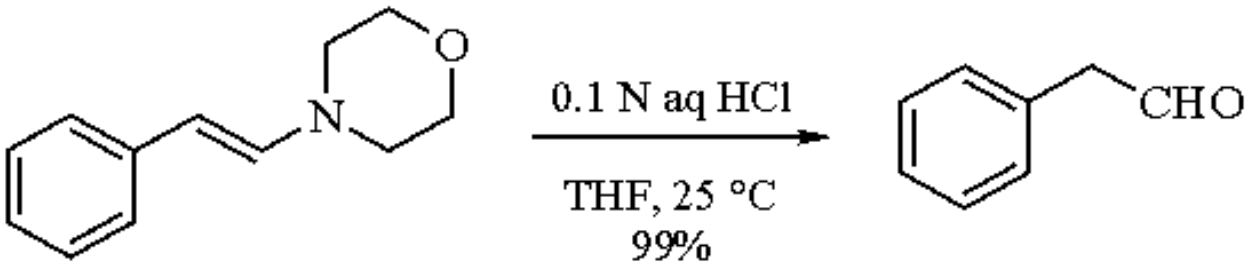

(5)

Formation of α-Morpholinomethyl Ketones.

The initial addition adduct of (**1**) with aldehydes can also be elaborated to α-morpholinomethyl ketones by heating in a protic solvent (e.g. ethylene glycol) or by heating in an aprotic solvent in the presence of a catalytic amount of ***p-Toluenesulfonic Acid*** (eq 6).[4] This reaction is consistent with following an E1-type mechanism in which the β-hydroxyl group is not directly involved in the elimination step.

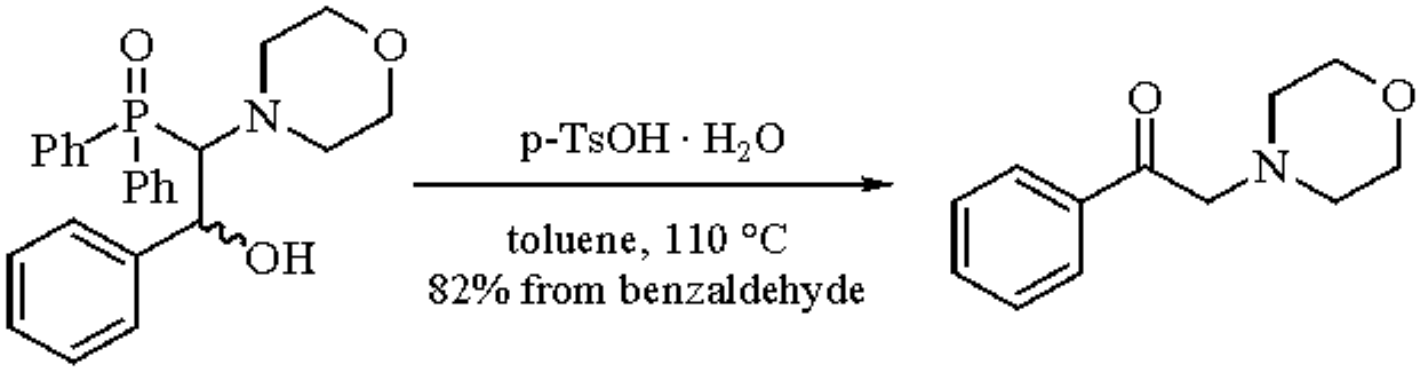

(6)

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John M. Fevig

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Nafion-H

$$(\sim CF_2CF_2)_n\text{-}CF_2\text{-}(CF\sim)\text{-}O\text{-}(CF_2CF(CF_3)O)_m\text{-}CF_2CF_2\text{-}SO_3H$$

[63937-00-8] · - · Nafion-H · (MW ~1250 maximum)

(highly acidic solid; used as an acid catalyst for alkylation, aroylation, and nitration reactions; also used for ether, ester, and acetal synthesis[1])

Alternate Name: Nafion ND50

Solubility: insol polymer; will swell with solvent, but will not dissolve.

Form Supplied in: available commercially (Nafion ND50 in 10-35 mesh beads) as a white powder.

Handling, Storage, and Precautions: irritant; hygroscopic.

Introduction.

Nafion-H is a perfluorinated resinsulfonic acid, and its primary use in organic synthesis is as a superacid catalyst. The acidity of the surface acid groups on Nafion-H is comparable to that of 96-100% ***Sulfuric Acid***,[1] and as such will promote a wide variety of acid-catalyzed reactions.

Alkylation Reactions.

Gas-phase alkylations of aromatic hydrocarbons over Nafion-H catalyst give superior yields and cleaner products than the usual Friedel-Crafts alkylations in solution.[2] Several methods of alkylation are available.

Alkylation with Alkenes.

It should be noted that alkylation with alkenes (eq 1) results in a slow reduction in the catalytic activity of Nafion-H due to surface polymerization, which deactivates the catalytic sites.[1]

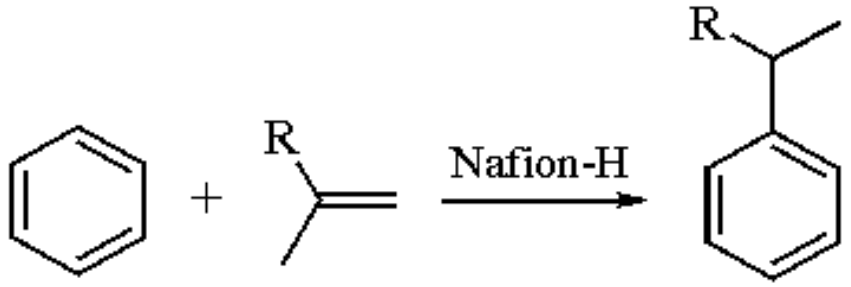

(1)

Alkylation with Alcohols.

The life of the catalyst is improved with this method.[3] The best example of this case is the methylation of phenol with methyl alcohol (eq 2).[4]

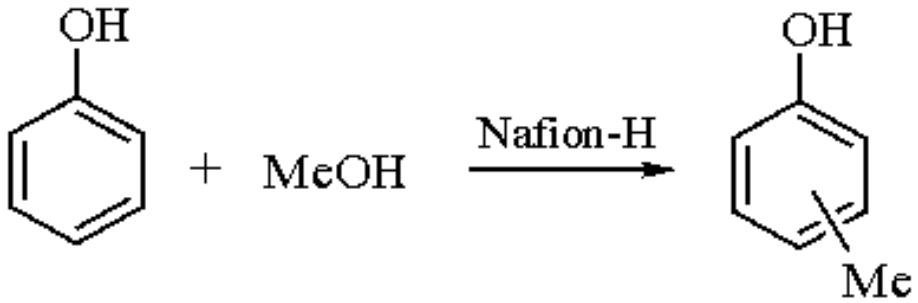

(2)

Alkylation with Alkyl Halides.

Unlike Friedel-Crafts alkylation in which polyalkylation is a problem, the gas-phase alkylation reaction over the Nafion-H catalyst shows a high selectivity for monoalkylation (eq 3).[5]

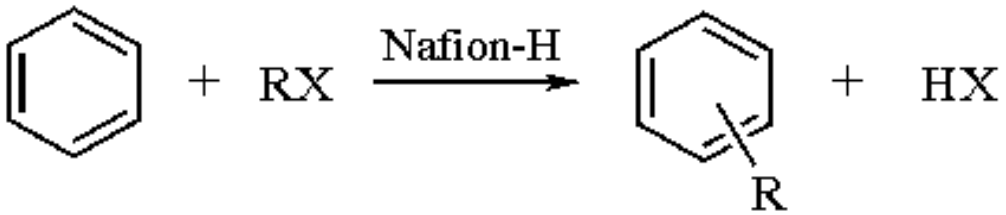

(3)

Alkylation with Alkyl Esters.

This may be performed in either the gas or liquid phase over Nafion-H.[6] Unlike the Friedel-Crafts method which may produce both alkylated and acylated products, the Nafion-H catalyst shows high selectivity for alkylation (eq 4).[7]

$$\mathrm{ArH} + \mathrm{R^1CO_2R^2} \xrightarrow{\text{Nafion-H}} \mathrm{ArR^2} + \mathrm{R^1CO_2H} \qquad (4)$$

Acylation.

Nafion-H may be used to catalyze the acylation of benzene with aroyl chlorides and anhydrides (eq 5).[8] A great advantage of the Nafion-H catalyst over the typical Friedel-Crafts catalyst is that only 10-30% of the Nafion-H catalyst is needed, unlike acylations typically performed in solution where more than a molar equivalent of the catalyst is required.[8]

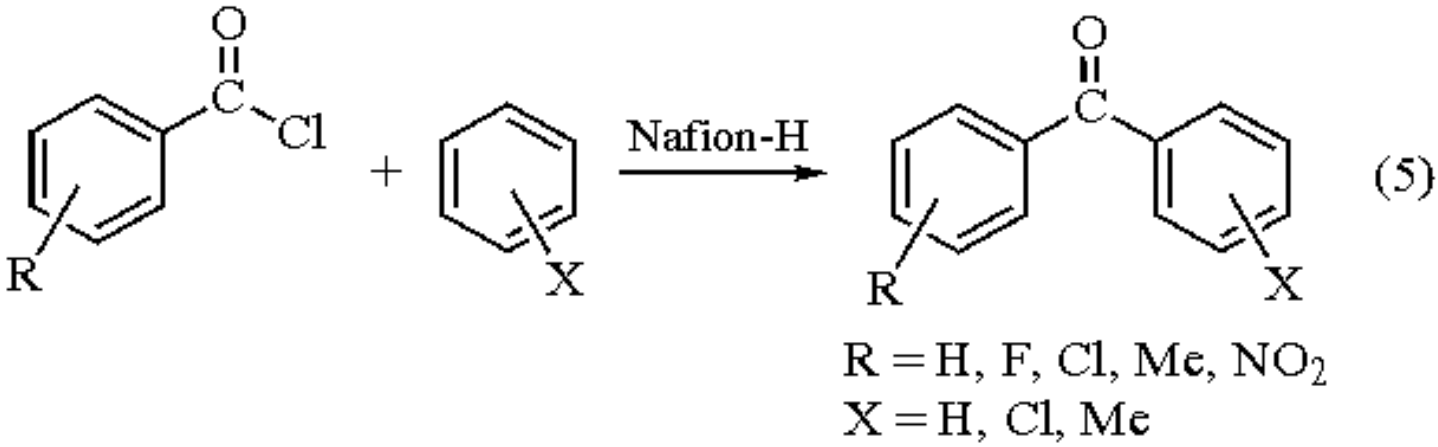

Nitration.

Nitration of substituted benzenes and other aromatic hydrocarbons may be performed with *n*-butyl nitrate,[9] acetone cyanohydrin nitrate,[10] or ***Nitrogen Dioxide***.[10] The advantage of nitration with Nafion-H catalyst over electrophilic aromatic substitution of nitrate using ***Nitric Acid*** in solution is that no aqueous workup is required. Also, the nitro compounds produced may be easily isolated by filtration of the catalyst.[10]

Ether Synthesis.

Ethers are commonly synthesized by an acid-catalyzed mechanism, but require basic workup procedures in typical methods. Nafion-H, however, provides a method for ether synthesis that does not require basic workup, but only filtration of the solid catalyst and evaporation of the solvent.[11] ***Dimethoxymethane*** may be reacted with primary and secondary alcohols over the Nafion-H catalyst to produce good yields of methoxymethyl ethers,[11] which are commonly used as a means for protecting hydroxyl groups (eq 6).[12] Tertiary alcohols give only the dehydration products.[11]

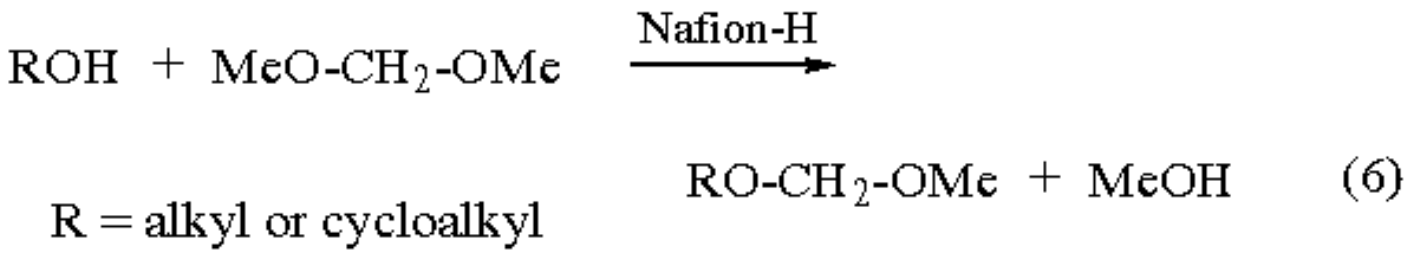

Cyclization of 1,4-butanediols to the corresponding tetrahydrofurans may also be accomplished by simply heating the 1,4-butanediol over the Nafion-H catalyst (eq 7). No workup is required, high yields are obtained (~90%),[13] and product isolation is very easy. This method is far superior to the aqueous mineral-acid version of the same reaction, which does require elevated reaction temperatures and aqueous basic workup.[13]

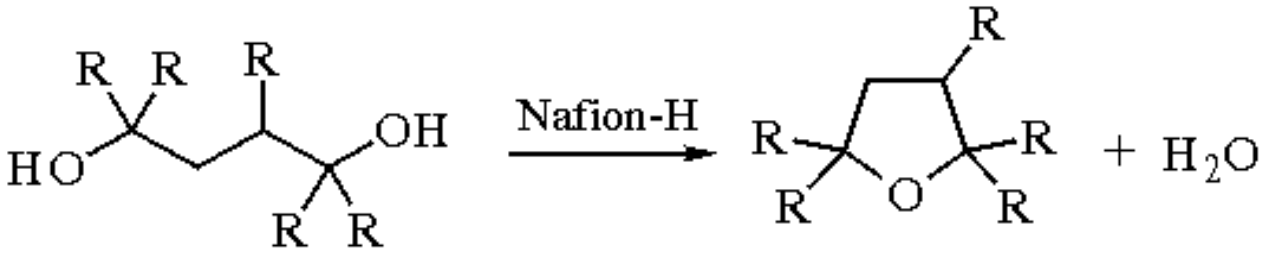

Acetal Synthesis.

Acid-catalyzed acetal synthesis is possible with Nafion-H, particularly in the reaction of trimethyl orthoformate with ketones or aldehydes (eq 8).[14]

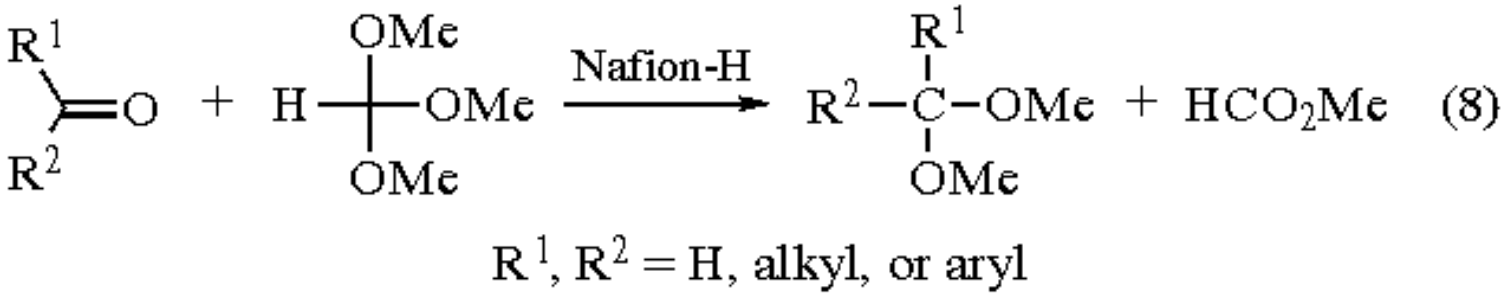

Other Reactions.

Synthesis of 1,3 Dioxanes.

Nafion-H is capable of catalyzing the reaction of ketones with ***Paraformaldehyde*** to form 1,3-dioxanes in high yield (eq 9).[15]

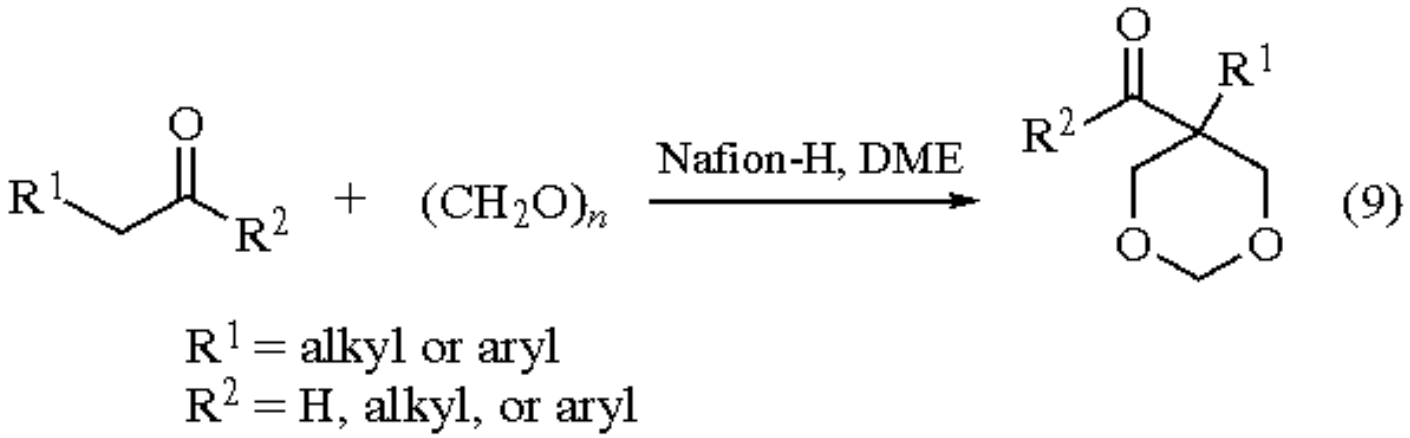

Diels-Alder Reaction Catalyst.

Nafion-H has a particular advantage as a catalyst for the Diels-Alder reaction. Nafion-H may be used in catalytic amounts and provides high yields of product with no diene polymerization in many cases.[16] Also, product isolation is

easy as it involves only filtration of the catalyst.[16] Lewis acid catalysts may be used, but these cause polymerization of the diene. Two molar equivalents of the Lewis acid are usually necessary, and Lewis acid complexes with reactants and products may form. All of this causes difficulties in the workup.[17,18] As an example of the effectiveness of Nafion-H catalysis, the uncatalyzed reaction of 1,3-cyclohexadiene with ***Acrolein*** gives only 25% of the Diels-Alder product when heated to 100 °C for 3.5 h. However, Nafion-H catalysis gives 88% yield after stirring for 40 h at 25 °C (eq 10).[16]

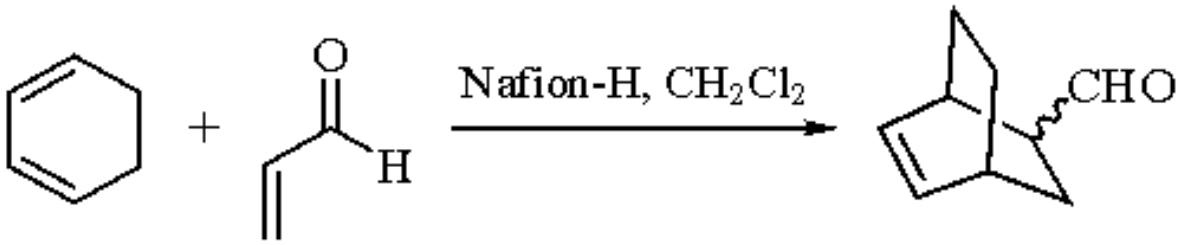

(10)

Condensation of Acetone to Mesitylene.

Nafion-H catalyzes the condensation of ***Acetone*** to mesitylene with a selectivity of greater than 99%.[19] Unlike other acid-catalyzed condensations which may produce other condensation products such as propene,[19] isobutene,[19] and pentenes,[19] the Nafion-H-catalyzed mechanism is superior in its selectivity for mesitylene (eq 11). It should be noted, however, that overall percentage yields are lower for the Nafion-H-catalyzed mechanism than for other acid-catalyzed mechanisms.[19]

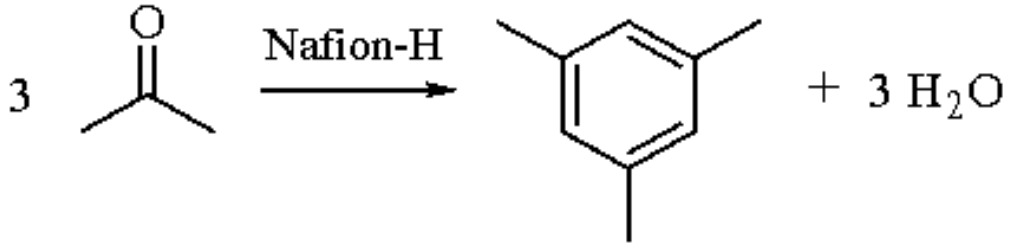

(11)

Azidobromination of Alkenes.

Nafion-H catalyzes the azidobromination of alkenes to form β-bromoalkyl azides.[20] ***N-Bromosuccinimide*** and ***Azidotrimethylsilane*** are reacted over the Nafion-H surface in a solvent that is 3:1 in methylene chloride-nitromethane. One postulated mechanism is outlined by eqs 12 and 13.[20]

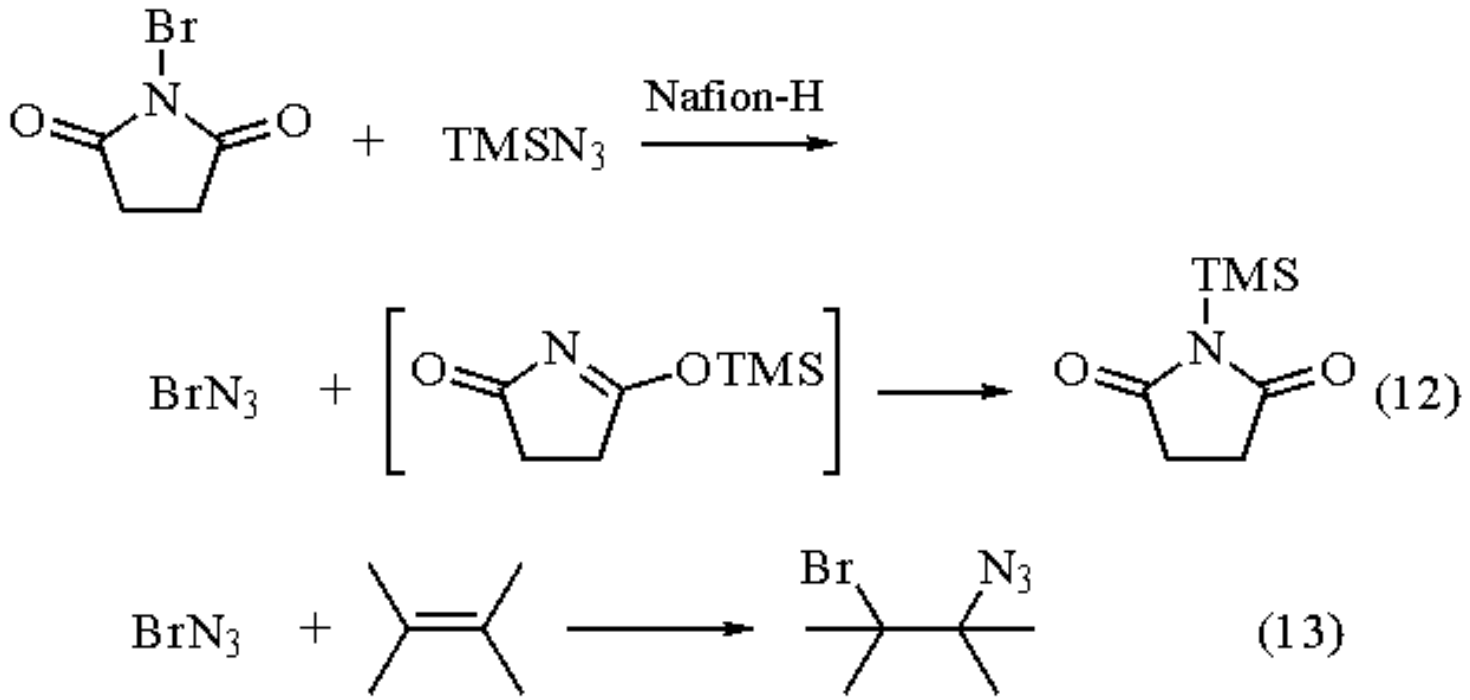

Nafion-H and Pd/C.

The combination of the acid catalyst Nafion-H with the ***Palladium on Carbon*** hydrogenation catalyst in the presence of hydrogen is useful for performing an aldol condensation followed by hydrogenation of the condensation product.[21] Pittman and Liang have effected one-step conversions of acetone to methyl isobutyl ketone,[21] benzaldehyde and acetone to 4-phenyl-2-butanone,[21] and 2,5-hexanedione to 2,5-dimethyltetrahydrofuran.[21] The reaction is simply carried out by reacting the anhydrous starting materials over a mixture of 30-60 mesh Nafion-H into which dry Pd/C catalyst has been mixed. The reacting system is pressurized with H_2 gas, and is heated to promote the reaction (eq 14). In the example of the condensation of acetone to methyl isobutyl ketone, Nafion-H acts as a simple acid catalyst to cause condensation to mesityl oxide.

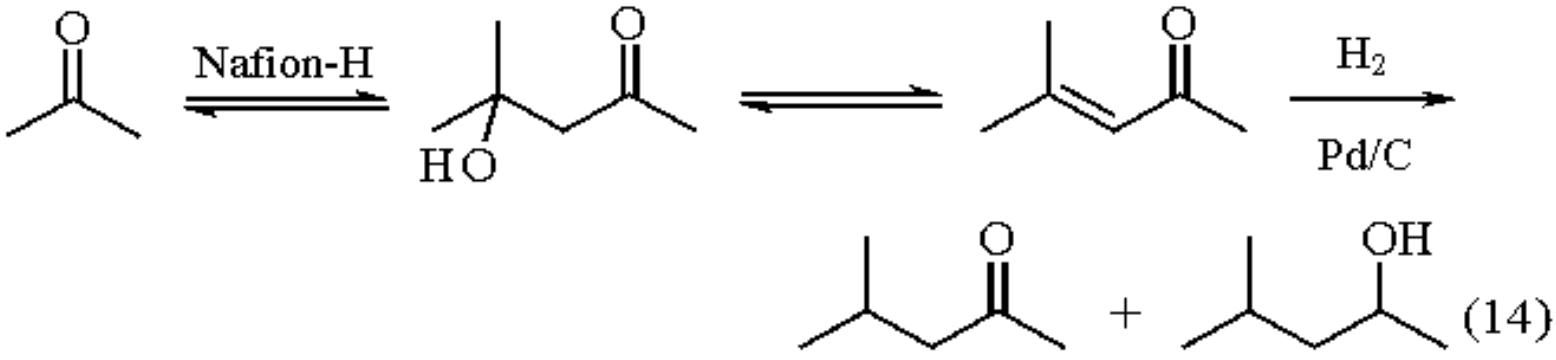

Overall production of mesityl oxide is limited by the equilibrium between it and the original starting materials. If mesityl oxide were isolated and then hydrogenated, yields of methyl isobutyl ketone would be only about 20%. However, the sequential condensation/hydrogenation that may be performed by the Nafion-H and Pd/C catalyst combination results in a yield of methyl isobutyl ketone that is about twice as high. This is because mesityl oxide is continuously removed from the equilibrium by hydrogenation, which pulls the equilibrium to the right.[21]

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1,4-Naphthoquinone[1]

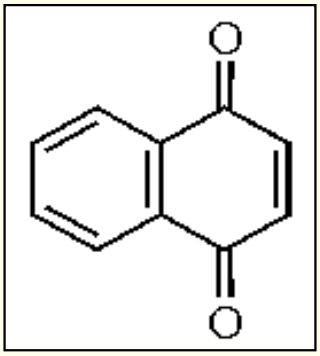

[130-15-4] · $C_{10}H_6O_2$ · 1,4-Naphthoquinone · (MW 158.16)

(dienophile used to synthesize various aromatic rings via Diels-Alder or cycloaddition-type reactions;[1] undergoes amination,[2] allylation,[3] cyclooligomerization,[4] and Thiele-Winter acetoxylation to give the 1,2,4-triacetoxynaphthalene[5])

Physical Data: mp 126 °C, begins to sublime below 100 °C; *d* 1.422 g cm^{-3}.

Solubility: sparingly sol cold water; slightly sol pet ether; freely sol hot alcohol, ether, benzene, chloroform, carbon disulfide, acetic acid; sol alkali hydroxide solutions, giving a reddish brown solution.

Form Supplied in: yellow triclinic needles from alcohol or pet ether.

Handling, Storage, and Precautions: toxic and irritant.

Synthesis of Aromatic Systems.

1,4-Naphthoquinone is used to synthesize various products that contain an aromatic ring. These syntheses are most commonly executed via Diels-Alder and cycloaddition-type reactions.

Diels-Alder Reactions.

A method for preparing naphthacenequinones employs a very convenient, three-step, one-pot sequence consisting of an initial Diels-Alder cycloaddition of an isobenzofuran with an appropriate dienophile such as 1,4-naphthoquinone (eq 1).[6]

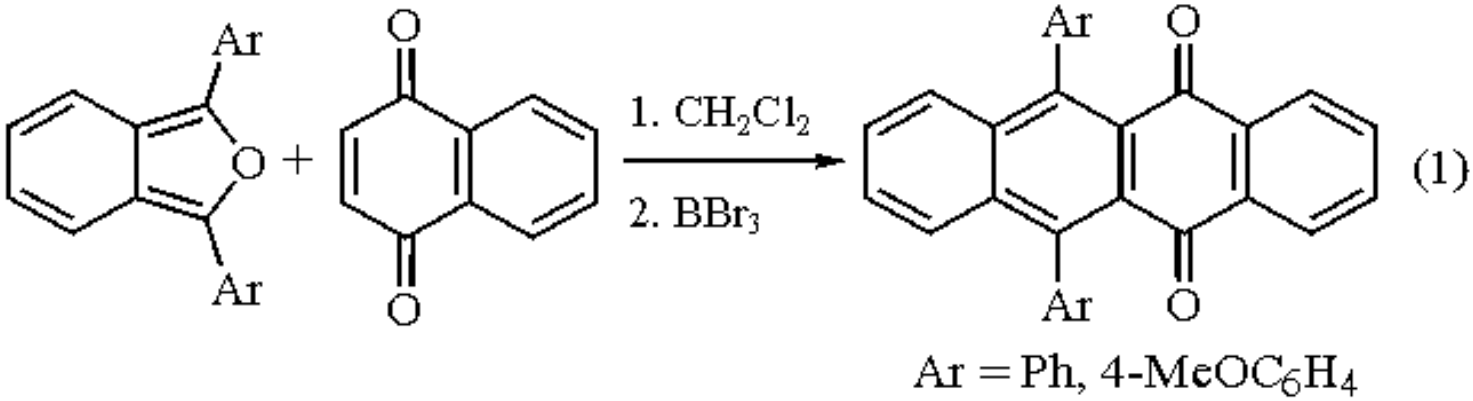

The Diels-Alder reactivity of in situ-generated *N*-benzoylindole-2,3-quinodimethane has been expanded considerably to include reactions with carbon dienophiles (e.g. 1,4-naphthoquinone) which furnish a variety of [*b*] annulated indoles as well as functionalized and annulated carbazoles.[7] In another variation of this reaction, 2- and 3-vinylindoles react with 1,4-naphthoquinone to afford new six-ring annulated carbazoles (eqs 2 and 3).[8]

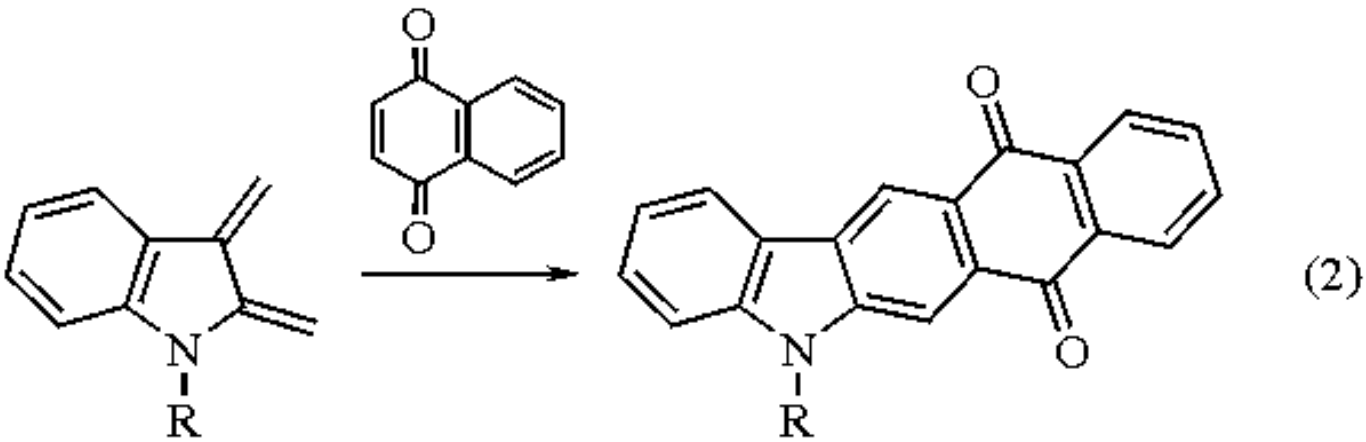

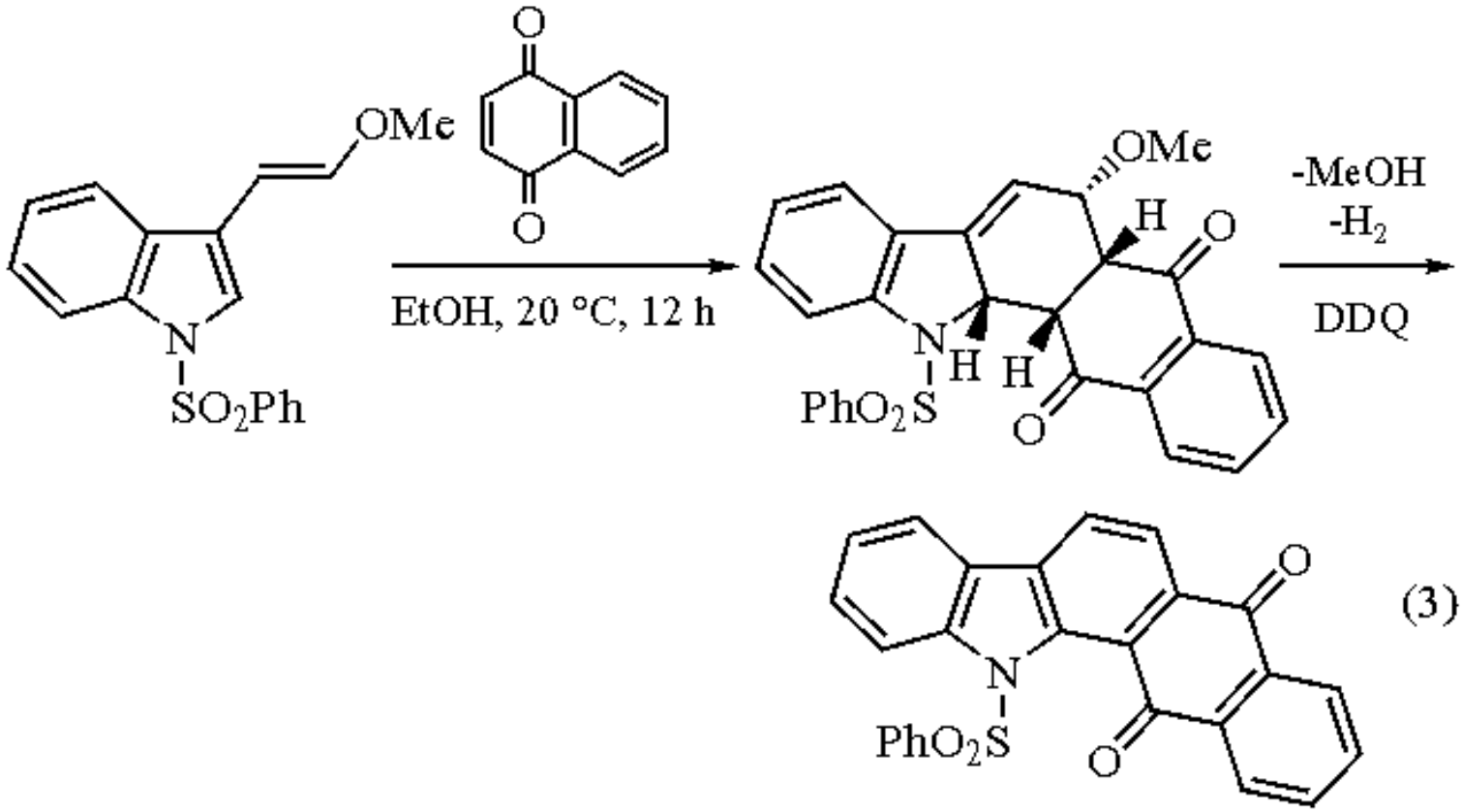

1,4-Naphthoquinone is the reagent of choice in a new approach to the synthesis of 2*H*-isoindole-4,7-diones (eq 4).[9]

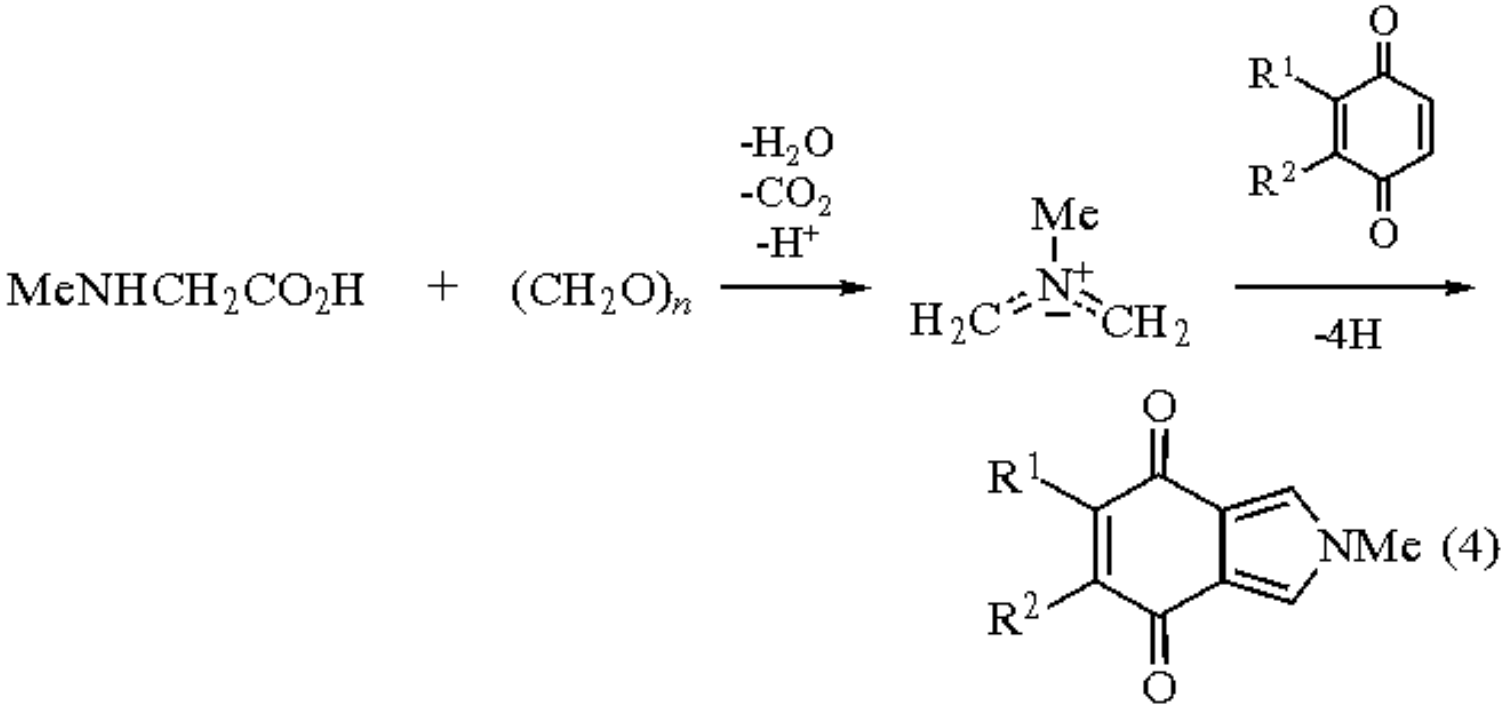

A simple synthesis of spirodiones via $_{\pi}6_{s}$ + $_{\pi}2_{s}$ photocyclization of the Diels-Alder adducts obtained by reaction of spiro[4.2]heptadiene and spiro[4.4]nonadiene with 1,4-naphthoquinone in homogeneous and miscellar media is illustrated in eq 5.[10]

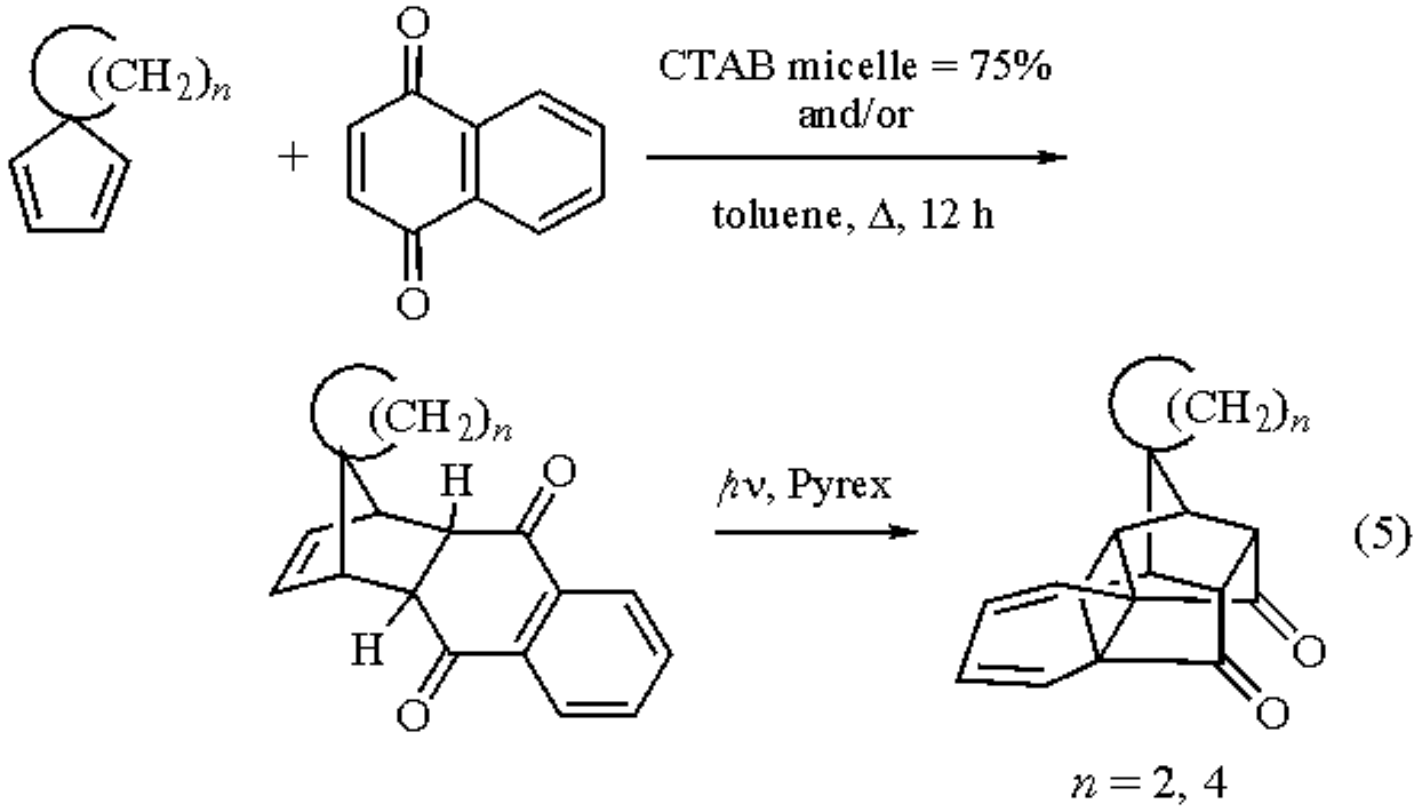

Stereoselective syntheses of quinone-annulated 2,3-bis(methylene)-7-oxabicyclo[2.2.1]heptanes involves 1,4-naphthoquinone as a dienophile. The products are promising building blocks for the synthesis of antineoplastic antibiotics.[11] Treatment of furan-annulated 3-sulfones with 1,4-naphthoquinone at 150 °C for 4 h gave 1,4-epoxy-2,3-bis(methylene)-1,4,4a,9a-tetrahydroanthraquinone in 58% yield (eq 6).[11]

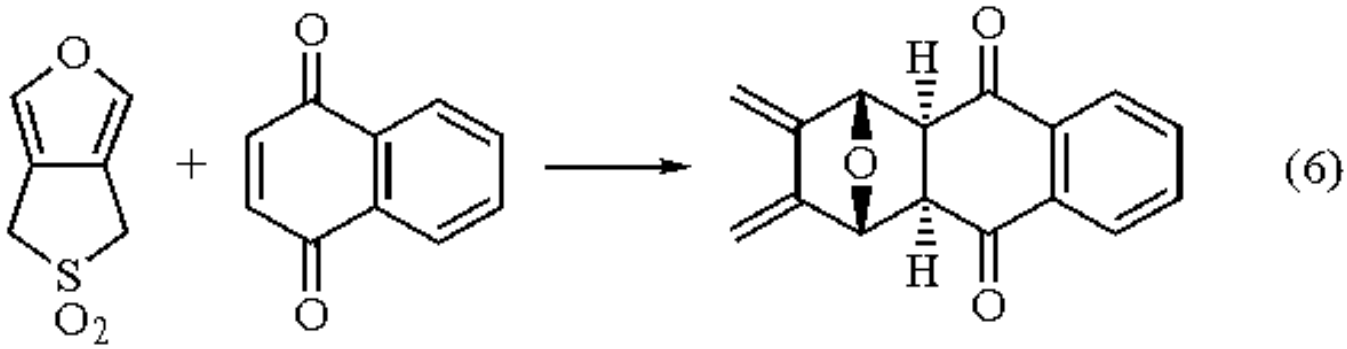

Biologically Significant Products.

Several Diels-Alder reactions involving 1,4-naphthoquinone have importance for the preparation of biologically active compounds. For example, the trifluoromethyl group is an increasingly popular aromatic substituent in compounds synthesized for biological applications. However, only a handful of methods are available for its introduction into aromatic compounds. Its use was consequently limited, but a new method using 1,4-naphthoquinone was found to be effective for this purpose. Triethyl(trifluoromethyl)silane and tri-*n*-butyl(trifluoromethyl)silane were found to react with the quinone by addition to one of the carbonyl atoms, giving dienones containing geminal trifluoromethyl substituents.[12]

Another application involves the reaction of 1,4-naphthoquinone and pyrroline, giving one major new product (eq 7) which was isolated in moderate yield (25%).[13] This new product has significance in the synthesis of ansamyocin and mitomycin

antibiotics.

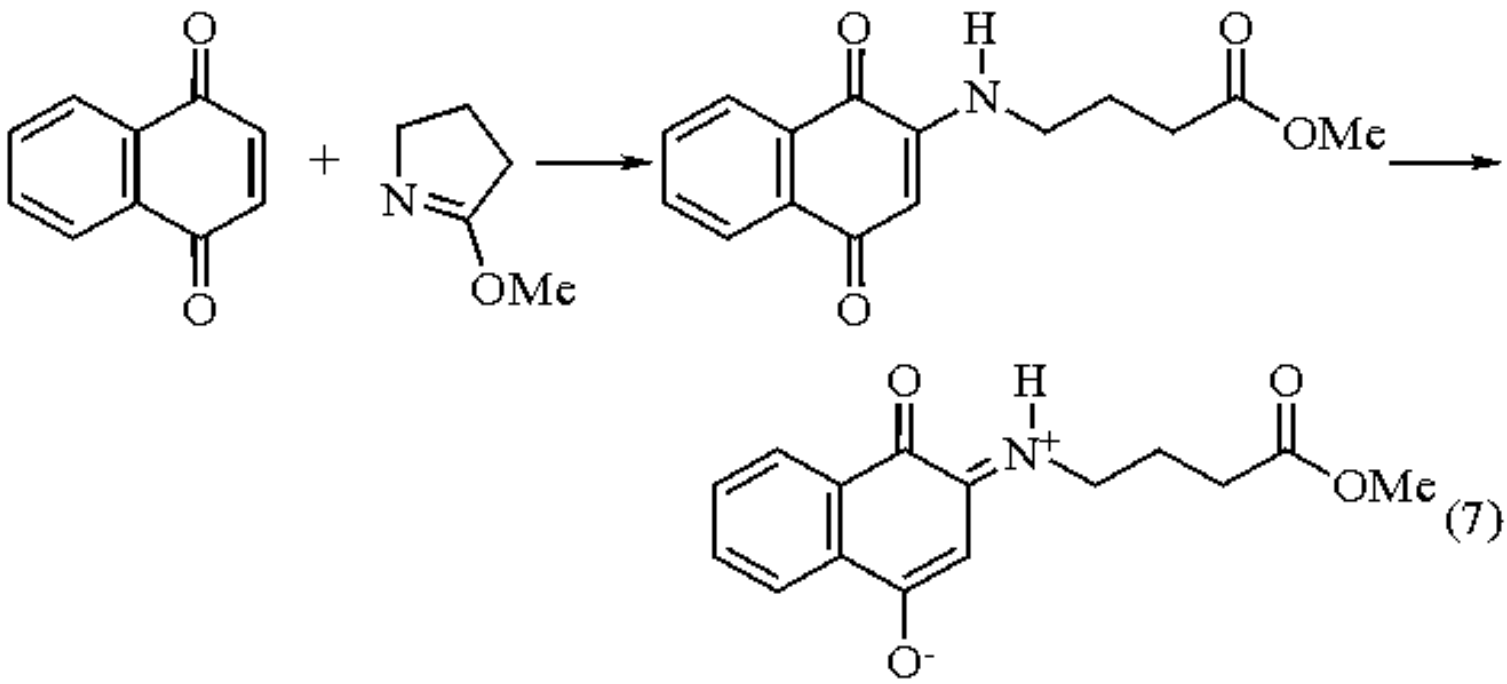

(7)

Aromatic polyketide antibiotics generally fall into two structural classes, linear and nonlinear polyketides. Although enormous effort has been devoted to the synthesis of the linear polyketides, the nonlinear aromatic polyketides have received relatively little attention.[14] With a vinylquinone acetal as the diene and 1,4-naphthoquinone as the dienophile, the nonlinear benzathracenedione can be synthesized in 24% yield (eq 8).[14]

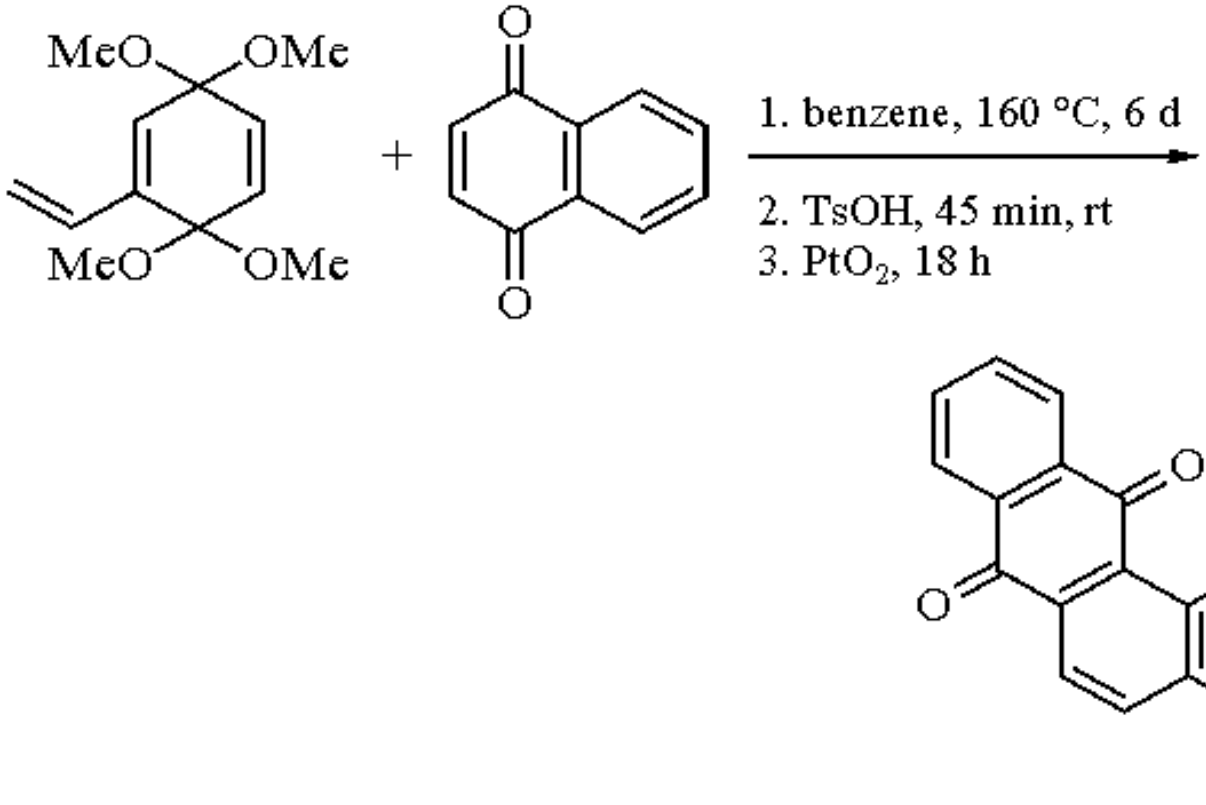

(8)

Additional Cycloadditions.

Allylic cyanides cycloadd to 1,4-naphthoquinone at room temperature. Treatment of the crude mixture with ***Potassium Fluoride*** in refluxing methanol gives compound (**1**) in 61% yield (eq 9).[15]

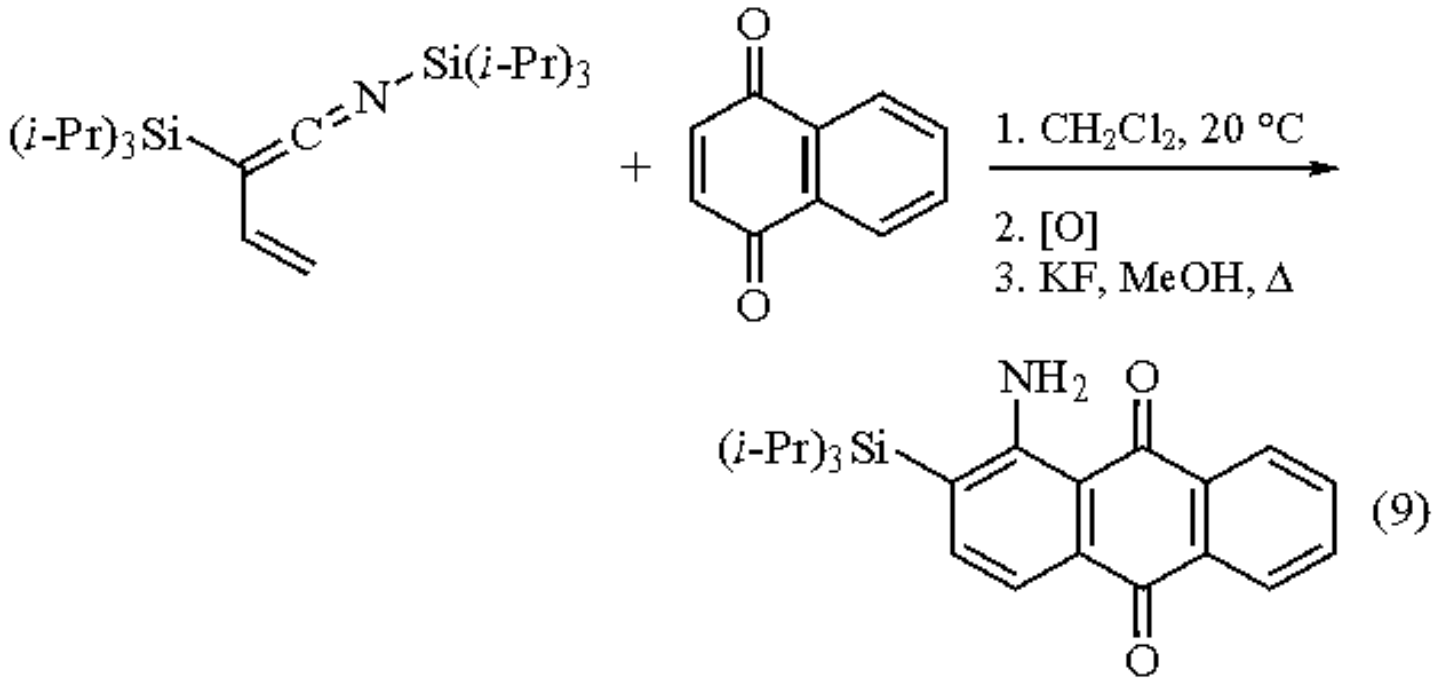

(9)

(1)

A general and simple route to the synthesis of triptycene derivatives involves cycloaddition of 1,4-naphthoquinone with anthracene and subsequent treatment of the resulting adduct with ***Lithium Aluminum Hydride*** followed by ***p-Toluenesulfonyl Chloride*** in pyridine (eq 10).[16]

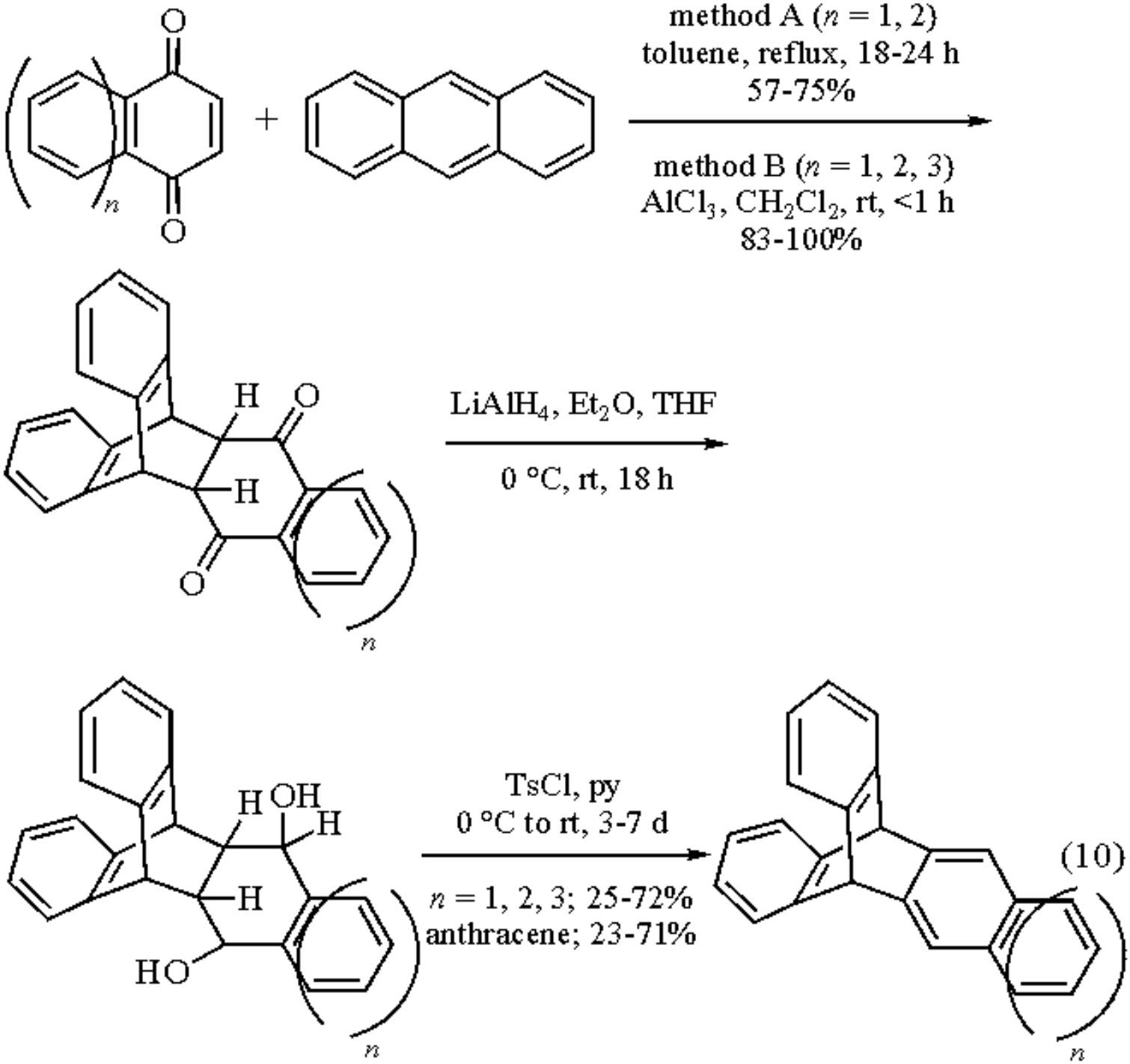

A reaction of 1,4-naphthoquinone with the diene 3-vinylpyrrole gives an indole in 21% yield (eq 11).[17]

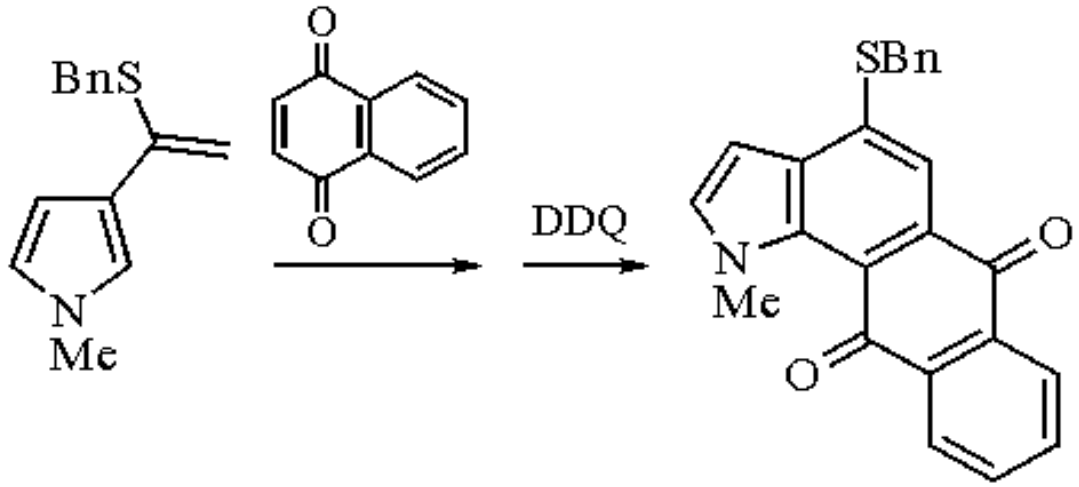

(11)

Amination of Naphthoquinones.

A new method for the synthesis of aminonaphthoquinones uses 1,4-naphthoquinone and ***Azidotrimethylsilane*** (eq 12).[2]

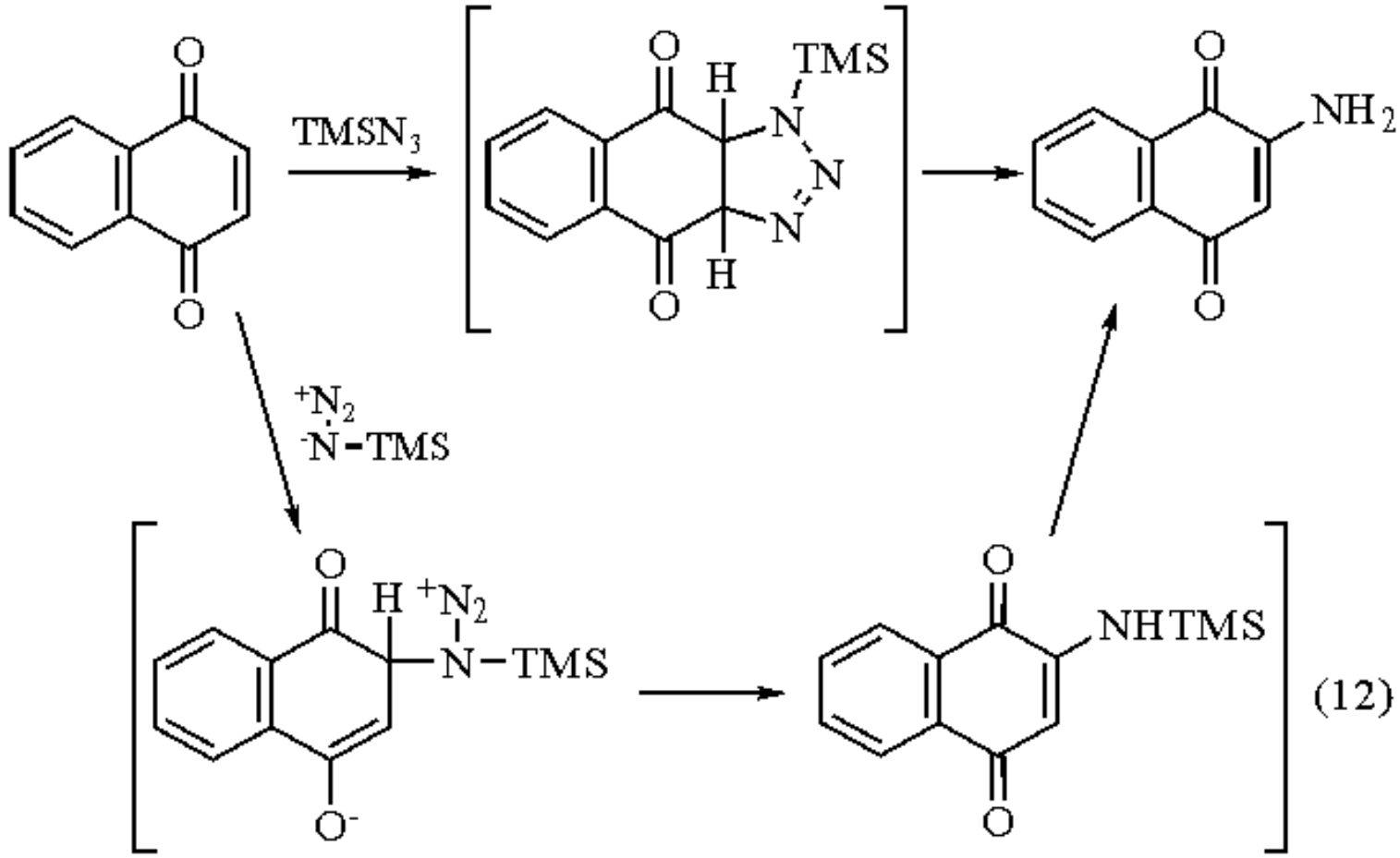

(12)

Allylation of Substituted *p*-Quinones.

1,4-Naphthoquinone reacts with allylindium sesquiiodide to give allylquinols in excellent yield.[3] This reaction has been extended to prenylation and nerylation of napthoquinone as well (Table 1; Scheme 1).

Table 1 Prenylation and Nerylation of 2,3-Disubstituted Quinones

Quinone	Allyl-indium	Molar ratio of quinone: allylindium	Product ratio monoallyl:diallyl	Total Yield %
1,4-Naphtho-quinone	Prenyl	1:1	61:39	86
		2:1	22:78	100
		4:1	77:23	79
		6:1	97:3	100
	Neryl	2:1	29:71	92
		3:1	71:29	97
		6:1	100:0	84

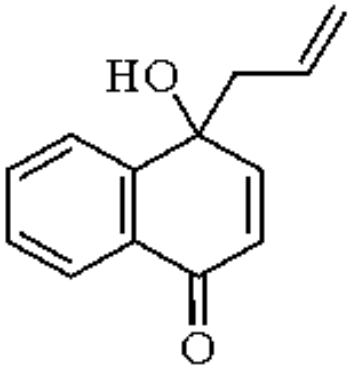

Allylquinone

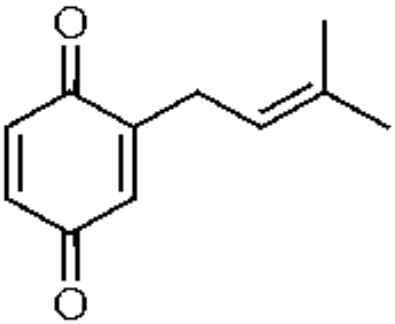

Prenyl

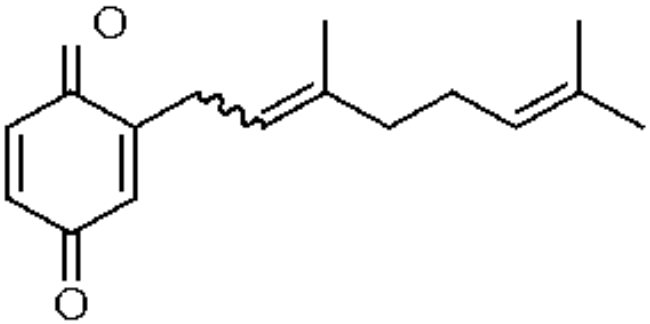

Neryl

Scheme 1

Cyclooligomerization of Quinones.

When treated with acid, 1,4-naphthoquinone gives a dimer, 5,8-dihydroxydinaphtho[1,2-*b*:2´,1´-*d*]furan (**2**), 15,18-dihydroxydinaphtho[2,1-*d*:2´,1´-*d*]naphtho[1,2-*b*:4,3-*b*´] difuran (**3**) and a tetramer, tetranaphthyleno[5,6-*bcd*:11,12-*b*´*c*´*d*´:17,18-*b*´´*c*´´*d*´´]tetrafuran (**4**).[4]

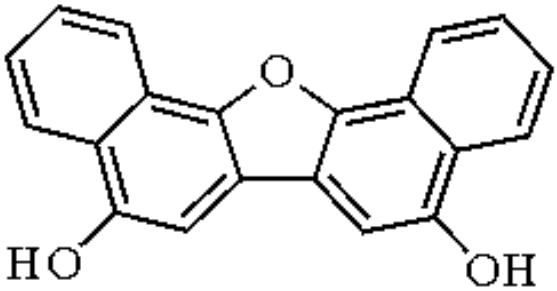

(2)

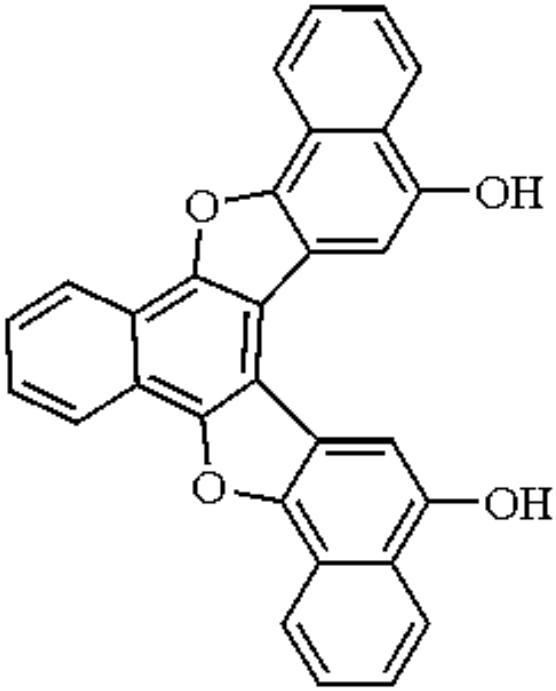

(3)

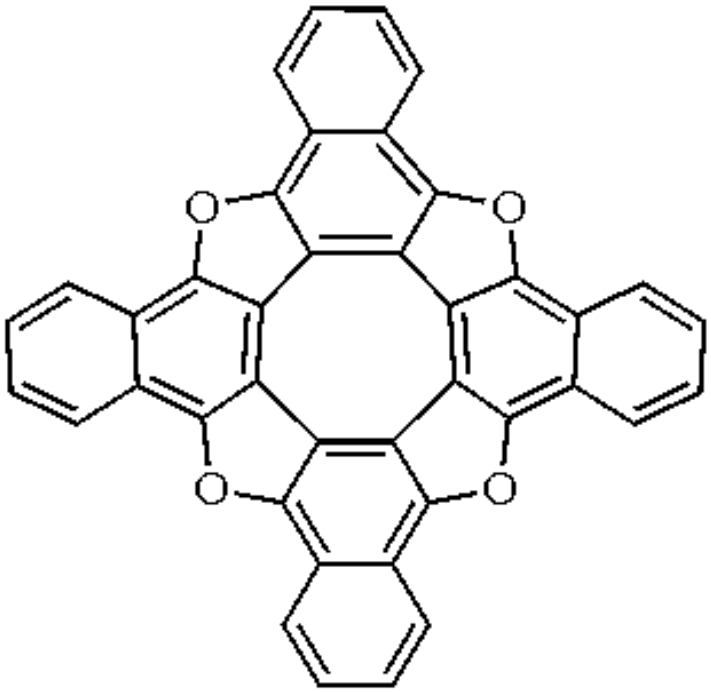

(4)

Thiele-Winter Acetoxylation.

1,4-Naphthoquinone can undergo the Thiele-Winter reaction.[19] From a synthetic point of view the most important feature is the introduction of an oxygen onto an aromatic nucleus. Burton and Praill showed that perchloric acid is probably the most effective catalyst for effecting the transformation (eq 13).[19]

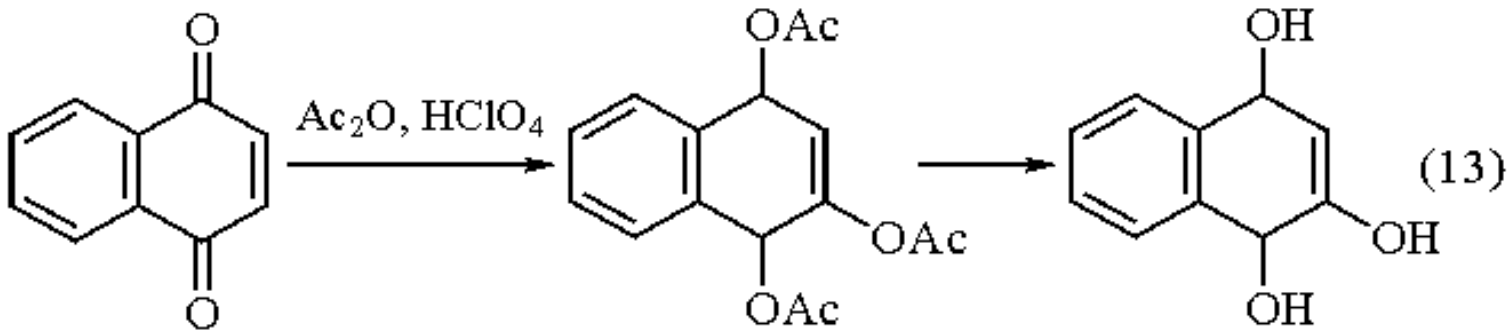

Related Reagents.

1,4-Benzoquinone; ***1,3-Diphenylisobenzofuran***.

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1-(1-Naphthyl)ethylamine

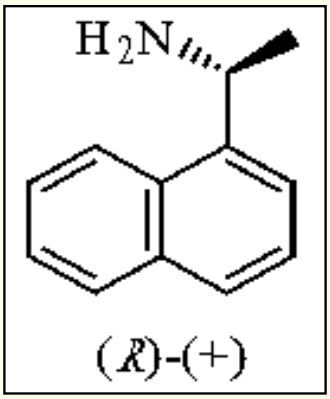

(±)

[42882-31-5] · $C_{12}H_{13}N$ · 1-(1-Naphthyl)ethylamine · (MW 171.26) (+)

[3886-70-2] (-)

[10420-89-0]

(chiral reagent used for resolution of carboxylic acids,[1] alcohols,[2] and lactones;[3] a chiral derivatization agent used for chromatographic resolution of carboxylic acids[4] and alcohols;[5] can serve as a chiral solvating agent[6])

Alternate Name: NEA.

Physical Data: (±) form: bp 156 °C/15 mmHg; *d* 1.063 g cm^{-3}. Oxalate: mp 221 °C (dec). (*S*)-(-) isomer: bp 153 °C/11 mmHg; *d* 1.060 g cm^{-3}; $[\alpha]^{25}$ -80.8° (neat); $[\alpha]^{20}$ -59° (*c* = 5, MeOH). Oxalate: mp 232 °C (dec). (*R*)-(+) isomer: bp 153 °C/11 mmHg; *d* 1.060 g cm^{-3}; $[\alpha]^{25}$ +82.8° (neat); $[\alpha]^{20}$ +60° (*c* = 5, MeOH). Oxalate: mp 240 °C.

Solubility: sol alcohol, ether; insol H_2O.

Form Supplied in: clear liquid; both enantiomers and the racemate are all widely available.

Analysis of Reagent Purity: the enantiomeric purity of the reagent can be determined by either NMR or HPLC analysis of derivatives produced from α-methoxy-α-(trifluoromethyl)benzyl isocyanate,[7] α-methoxy-α-(trifluoromethyl)benzyl acid chloride,[8] or 2´-methoxy-1,1´-binaphthyl-2-carboxylic acid chloride.[9]

Preparative Methods: racemic 1-(1-naphthyl)ethylamine can be resolved with camphoric acid,[10] tartaric acid,[11] L-menthyl hydrogen phthalate,[11] di-*O*-isopropylidene-2-ketogulonic acid,[11,12] and (*S*)-(-)-(2-

phenylcarbamoyloxy)propionic acid.[13] These procedures can also be used to enhance the enantiomeric purity of the reagent.

Handling, Storage, and Precautions: use in a well-ventilated fume hood.

Resolution of Carboxylic Acids.

The enantiomers of 1-(1-naphthyl)ethylamine are used to resolve racemic carboxylic acids by selective crystallization of diastereomeric salts. For example, crystallization of racemic 3-bromobutyric acid with (*R*)-(+)-NEA followed by acidification of the diastereomeric salt afforded (*S*)-(+)-3-bromobutyric acid (eq 1).[1] In the same manner, resolution with (*S*)-(-)-NEA yielded (*R*)-(-)-3-bromobutyric acid after liberation of the amine (eq 1).[1]

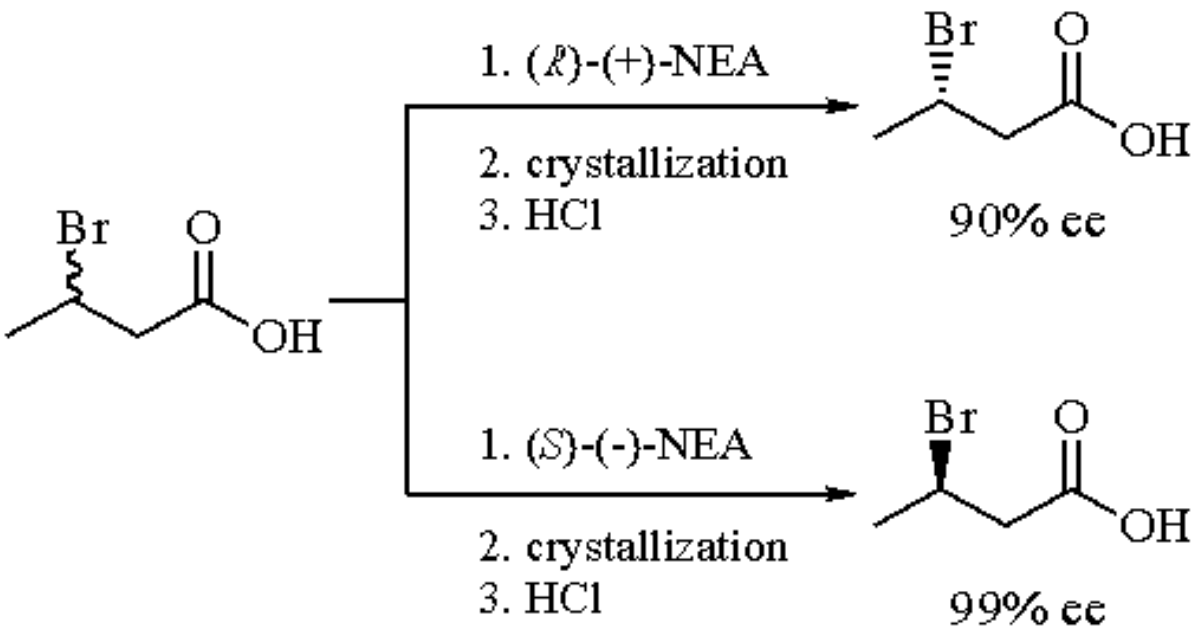

(1)

Resolution of alcohols can be achieved following derivatization with phthalic anhydride.[2] Racemic 1-undecyn-3-ol was converted into a phthalic monoester derivative and resolved with (*R*)-(+)-NEA (eq 2). Liberation of the resolved phthalic ester and saponification yielded (*R*)-(+)-alcohol in 92% optical purity (eq 2). Similarly, the (*S*)-(-) alcohol is obtained upon resolution with (*S*)-(-)-NEA (eq 2).

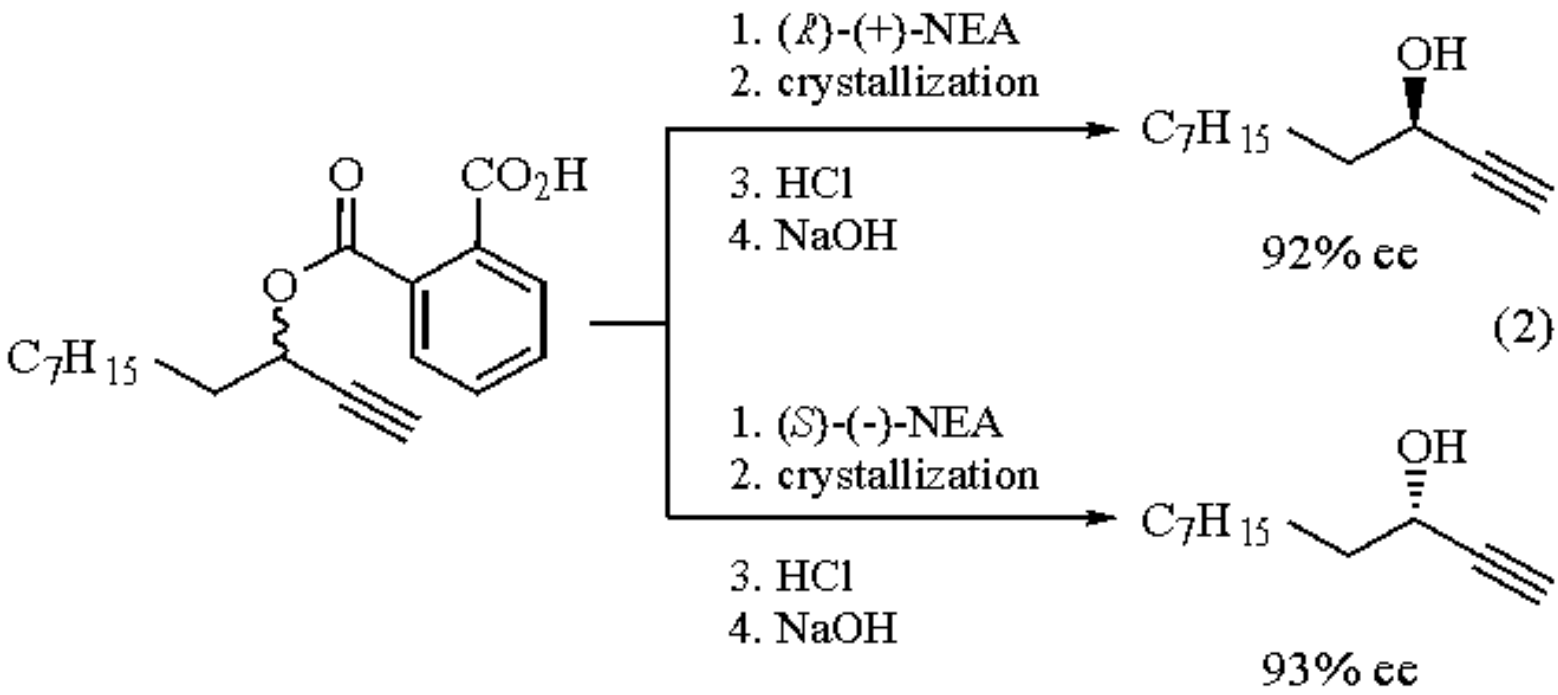

Optically active lactones are also readily available through this classical resolution technique. The racemic lactone is hydrolyzed to the hydroxy acid and resolved with (*S*)-(-)-NEA (eq 3).[3] After crystallization, the *dextro* (+)-lactone is regenerated upon acidification of the chiral salt. Resolution of the lactone with (R)-(+)-NEA leads to the *levo* (-)-lactone (eq 3).[3]

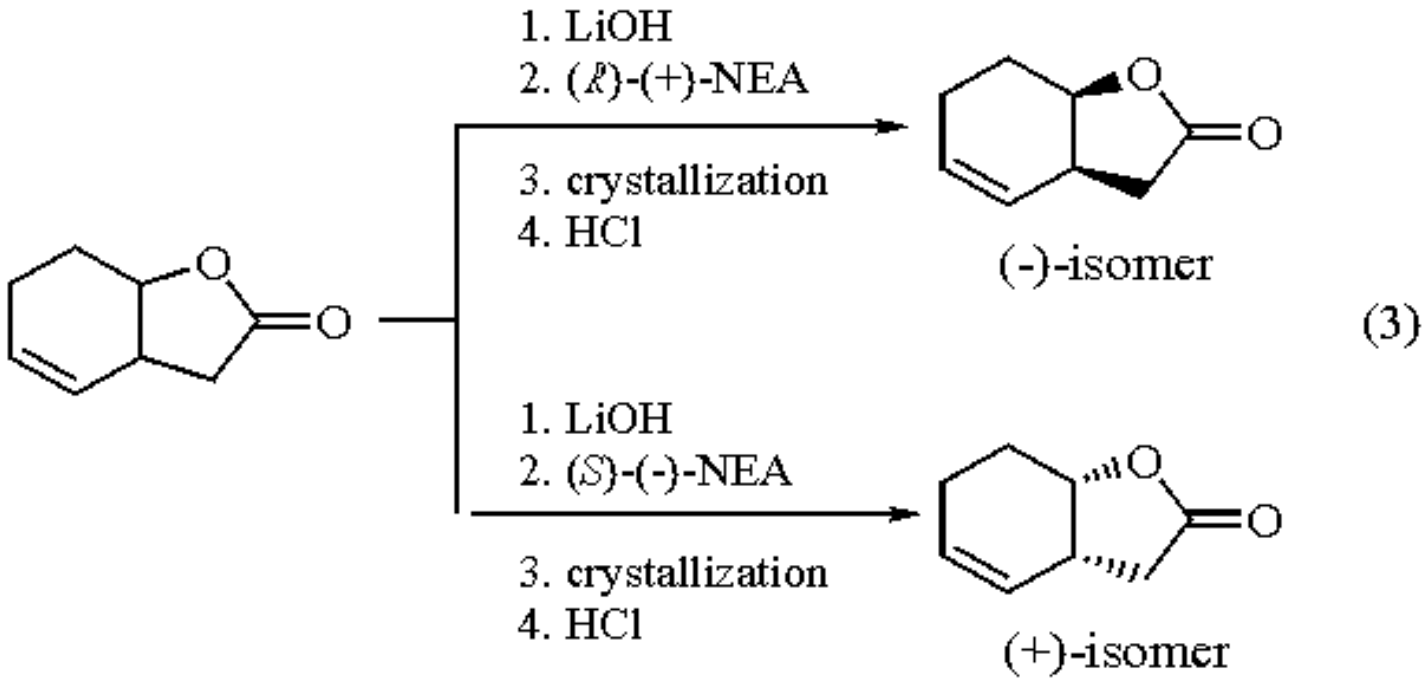

Chromatographic Resolutions.

1-(1-Naphthyl)ethylamine serves as a chiral derivatization agent useful in preparing diastereomeric amides from racemic acids for chromatographic resolution.[4] For example, various terpenoid acids, after conversion to the diastereomeric amides using (*R*)-(+)-NEA, were analyzed by HPLC to define the enantiomeric composition (eq 4).[4]

Application of the procedure has been used to analyze the enantiomeric purity of several carboxylic acid derivatives.[14]

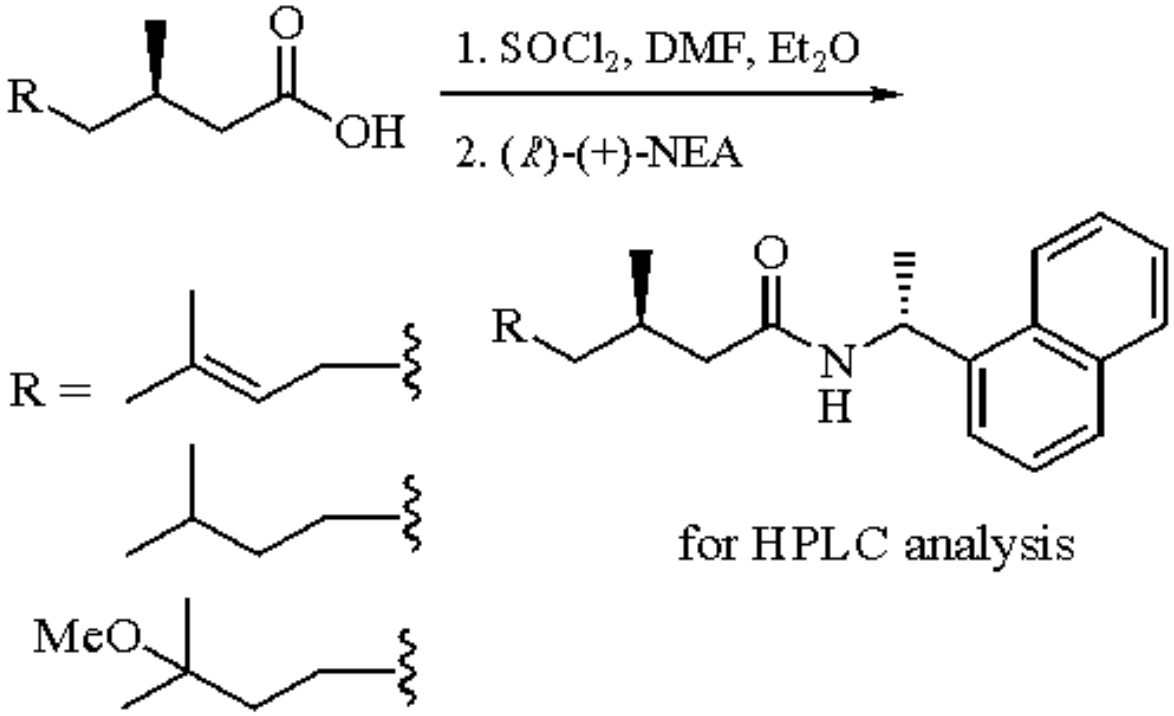

(4)

In some cases the resolution of the diastereomeric amides on silica gel is sufficiently large to achieve preparative separation. The preparative separation of diastereomeric hydroxy amides has proved useful in supplying quantities of enantiomerically pure lactones (eq 5).[15]

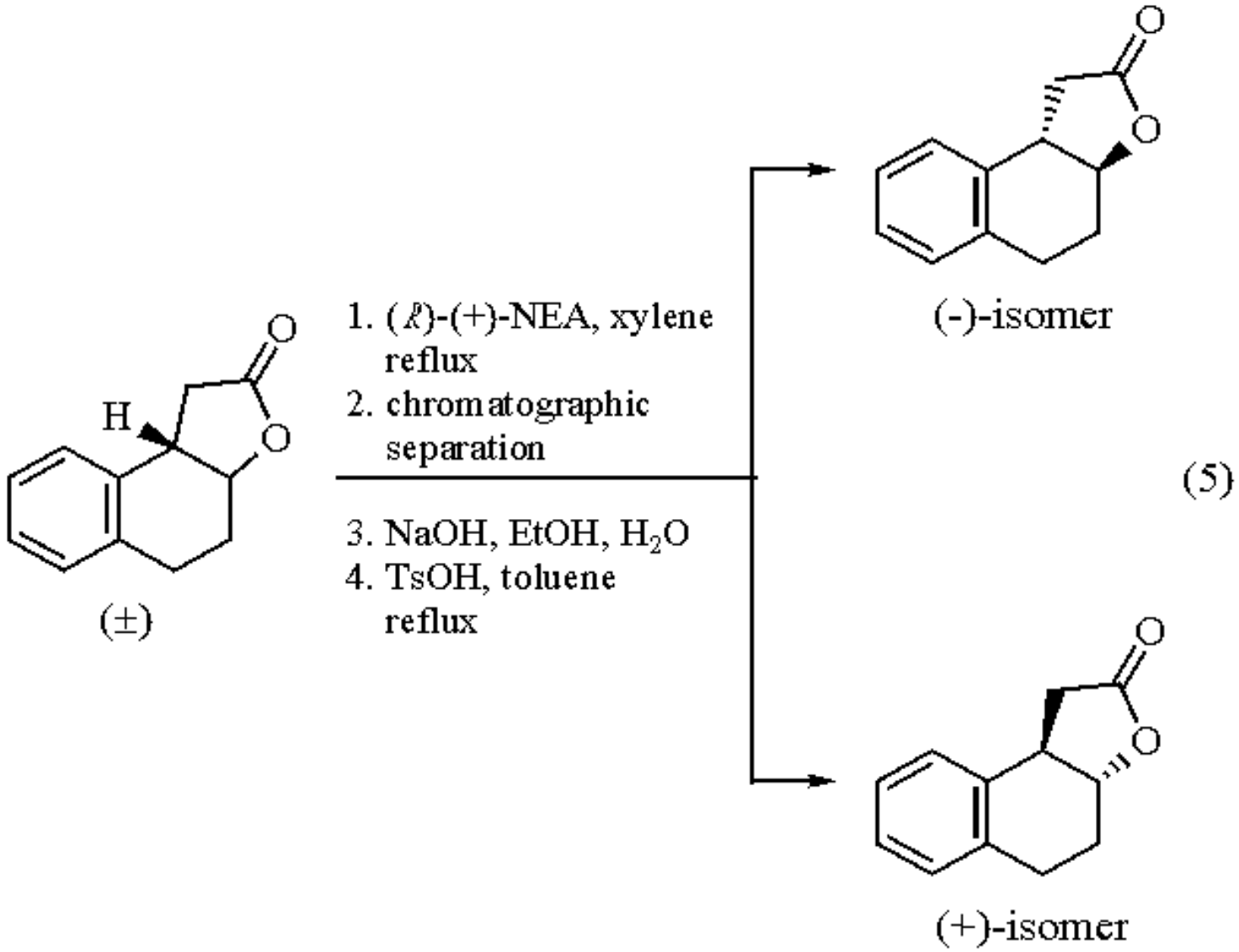

Nonracemic NEA is equally useful in preparing diastereomeric carbamates. Typically, the carbamates are derived from alcohols and (*R*)-(+)-naphthylethyl isocyanate,[16] which is conveniently prepared from (*R*)-(+)-NEA (see ***(R)-1-(1-Naphthyl)ethyl Isocyanate***). However, the diastereomeric carbamates may also be produced by treating the chloroformate derivative of a racemic alcohol with (*R*)-(+)-NEA.[5] Preparative separation of racemic 1-heptyn-3-ol was achieved through chromatographic separation of the diastereomeric carbamates prepared via the chloroformate derivative (eq 6).[17] The carbamates are conveniently cleaved by the action of trichlorosilane (see ***Trichlorosilane***).[18]

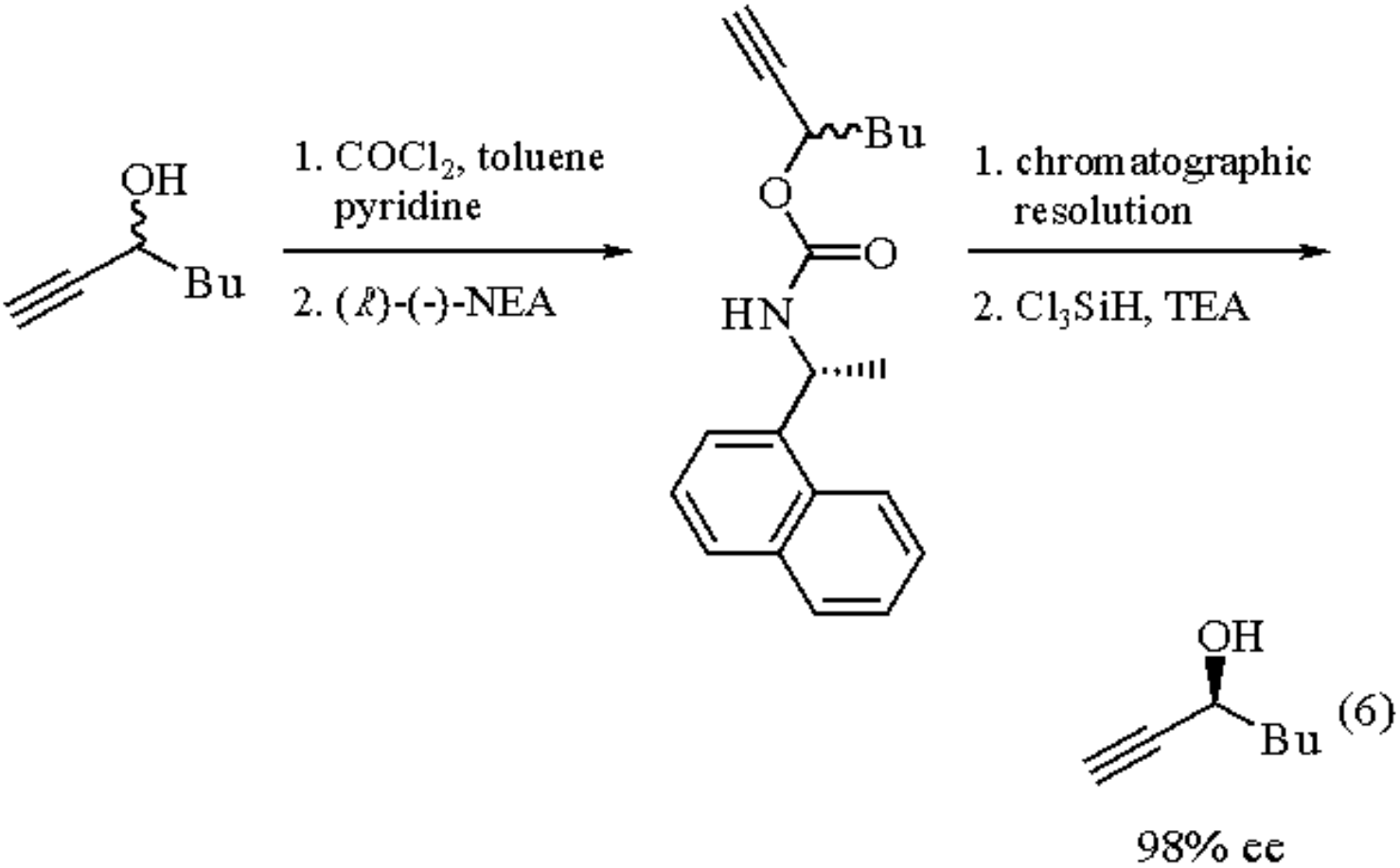

Chiral Solvating Agent.

NEA is an effective chiral solvating agent for NMR determination of enantiomeric purity.[6,19] The combination of enantiomerically pure NEA (3-5 mol excess) and racemic solute causes the NMR spectra of the diastereomerically solvated enantiomers to differ. Since NEA is an efficient hydrogen-bond acceptor, it solvates better if the solute is a hydrogen-bond donor. (*R*)-(+)-NEA has been used to determine the enantiomeric purity of a variety of substrates.[20]

Chiral Stationary Phases for GC and HPLC.

Enantiomerically pure NEA has been used to prepare a variety of chiral stationary phases for liquid,[21] gas,[22] and supercritical fluid[23] chromatography. These stationary phases are used to separate enantiomers without derivatization of the substrate with a chiral agent.

Related Reagents.

(R)-1-(1-Naphthyl)ethyl Isocyanate.

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(*R*)-1-(1-Naphthyl)ethyl Isocyanate

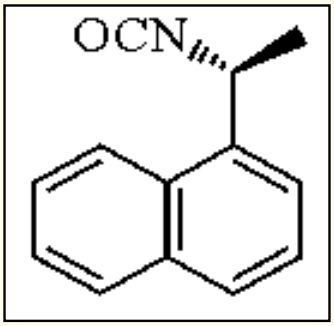

(*R*)-(-)

[42340-98-7] · $C_{13}H_{11}NO$ · (*R*)-1-(1-Naphthyl)ethyl Isocyanate · (MW 197.25) (*S*)-(+)

[73671-79-1]

(enantiomeric resolving agent for alcohols,[1,2] thiols,[1,3] sulfonamides,[4] and amines[5] (forms diastereomers separable by chromatography or crystallization); used in creating enantiomeric stationary phases for liquid chromatography;[6,7] reagent in the synthesis of chiral nonracemic allenes[8])

Alternate Names: NEI; (*R*)-1-isocyano-1-naphthylethane.

Physical Data: bp 106-108 °C; fp 93 °C; *d* 1.13 g cm^{-3}; optical rotation [α]20D = -47° (*c* 3.5, toluene), [α]24.1D = -50.5° (*c* 27.9, benzene).

Solubility: freely sol benzene, toluene, and a variety of dry organic solvents; reacts with water.

Form Supplied in: colorless liquid; available commercially >99% pure.

Preparative Methods: from (*R*)-(+)-***1-(1-Naphthyl)ethylamine*** by reaction with ***Phosgene*** or by a method using ***Trichlorosilane***.[1]

Handling, Storage, and Precautions: stable when stored between 0 and 4 °C; reacts with water; highly toxic; should be handled with proper skin and eye protection in a well-ventilated fume hood.

Resolution of Alcohols.

The reagent (*R*)-(-)-1-(1-naphthyl)ethyl isocyanate, (*R*)-NEI, as well as its enantiomer, (*S*)-NEI, forms diastereomeric carbamates with racemic secondary alcohols (eq 1);[1,2] the reaction may be facilitated by base or Lewis acid

catalysts.[4] The diastereomers can usually be separated by liquid chromatography on silica or alumina, providing a convenient means for analysis or preparative purification of the enantiomers: the resolved alcohols are recovered in high yield under mild, or nonracemizing, conditions by treatment with trichlorosilane/triethanolamine (TEA) (eq 1).[9]

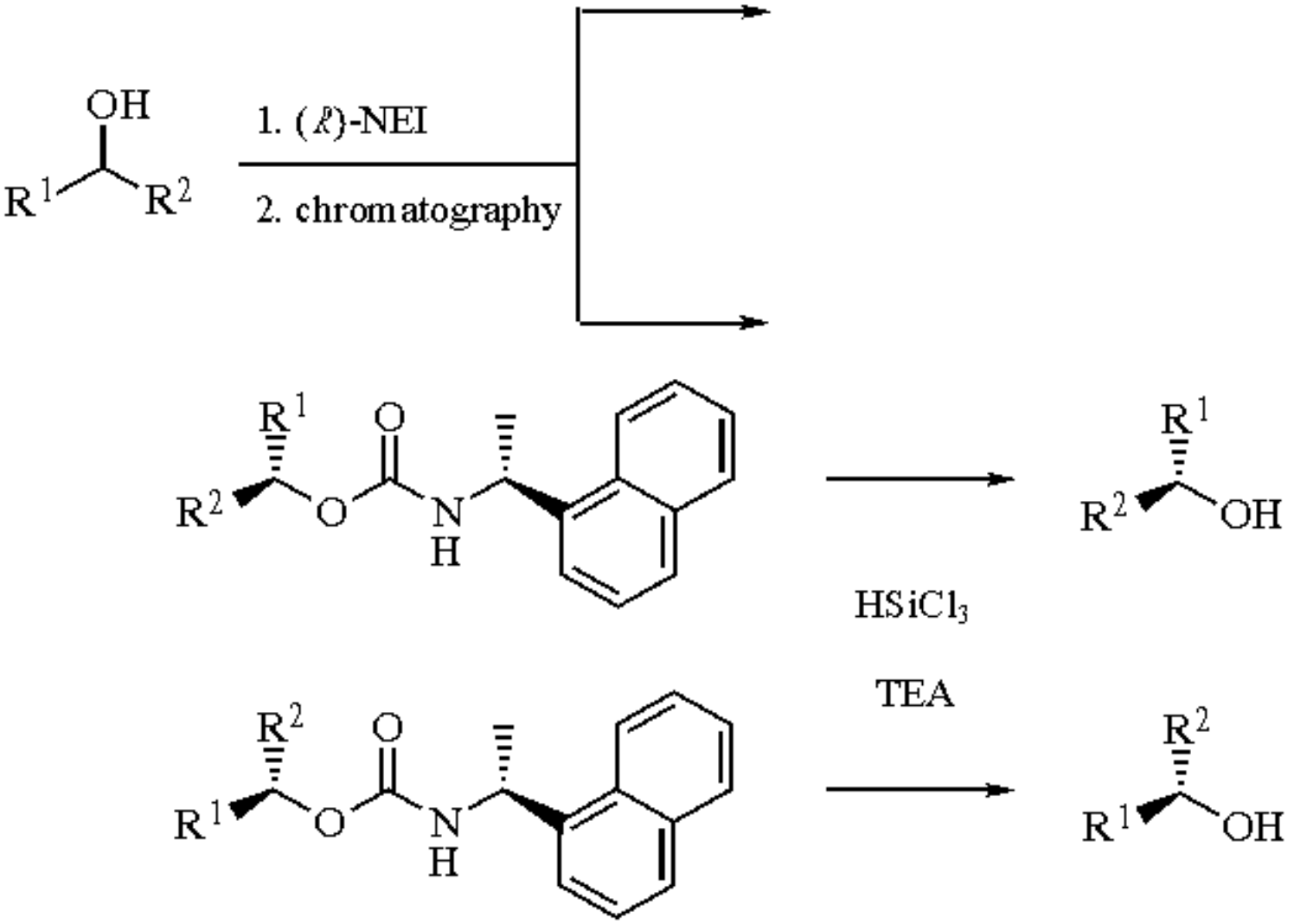

(1)

This general strategy has found wide application in synthesis. Enantiomerically pure cyano alcohols obtained in this way are starting materials in the synthesis of uni- and multicyclic lactones.[10-13] High purity enantiomeric epoxides can be prepared by resolution of the appropriate alcohol precursor followed by ring closure.[14] Propargylic alcohol enantiomers resolved by this technique are intermediates in the synthesis of the four stereoisomers of 1,2,3-decanetriol,[15] and of the sesquiterpene fungal metabolite (+)-sterpurene.[16,17] The purification of stereoisomers of secondary alkan- and alkenols by this method is an essential step in the synthesis of biologically active enantiomers of 8-methyl-2-decanol propanoate,[18] and of the germination inhibitor (-)-gloeosporone.[19] The general method given in eq 1 is used to isolate enantiomerically pure intermediates in the synthesis of the fungal metabolites ascofuranone and ascofuranol,[20] of the fungitoxic hydroquinone zonarol,[21] and of naturally occurring *C*-nucleosides and their analogs.[22] A hindered *endo* alcohol is also resolved after derivatization with (*R*)-NEI.[23] In the synthesis of vitamin D_3 metabolites, an enynyl alcohol intermediate is resolved with the help of both (*R*)- and (*S*)-NEI using crystallization rather than chromatography to separate the diastereomers.[24]

Indirect analysis of the enantiomeric ratio of an alcohol can be accomplished via separation and quantitation of the diastereomers of eq 1 by high-performance liquid chromatography (HPLC), gas-liquid chromatography (GLC), or

supercritical fluid chromatography (SFC). For example, diastereomeric diacylglycerol 1-(1-naphthyl)ethyl carbamates are separated by HPLC on a silica gel column,[25] as are the diastereomeric derivatives of the tertiary monoterpene alcohol linalool,[26] diastereomers of (unsymmetrically substituted) 1,3-dialkylglycerol ethers are separable by GLC,[27] and secondary alcohol enantiomers are derivatized with (*R*)-NEI and separated by SFC using several different stationary phases.[28] The use of a bonded amine HPLC column is reported for the analysis of enantiomers of several 2,3-epoxy-1-propanols following derivatization with (*R*)- and (*S*)-NEI.[29] Enantiomeric purity of a thiol, a derivative of the enkephalinase inhibitor thiorphan, is also determined after derivatization with (*R*)-NEI.[3]

Resolution of Amines.

Amines react with (*R*)- or (*S*)-NEI to form the corresponding urea diastereomers which can be separated in a manner analogous to the alcohols in eq 1. Secondary amines thus resolved can be recovered from the diastereomers by hydrolysis, as in the synthesis of chiral nonracemic lactams,[5] or by decomposition in refluxing alcohols, as demonstrated by the resolution of several amine drugs.[30]

Analysis of the enantiomeric ratios of several β-blocking drugs (1-aryloxy-3-isopropylamino-2-propanol derivatives) is carried out by HPLC with UV or fluorescence detection after derivatization with (*R*)-NEI or (*R*)-(+)-1-(1-phenyl)ethyl isocyanate (in a reversed-phase system),[31,32] or (*S*)-NEI (on silica gel);[33] only the amine function of the drugs reacts with the NEI; the hydroxy group does not.[31] Similar schemes for HPLC determination of enantiomeric purity of tetrahydrofolate derivatives[34] and of fluoxetine[35] are also reported.

In analysis, the original compound need not be recovered after separation, and therefore primary amines such as amino acids can be derivatized and analyzed in the same manner.[36] (*S*)-NEI is employed as a derivatizing reagent in an Edman-like sequencing scheme to assess the extent of racemization of amino acid residues in synthetic peptides.[37]

Enantiomeric Stationary Phases.

Chiral nonracemic chromatographic stationary phases prepared from β-cyclodextrin, derivatized with (*R*)- and (*S*)-NEI, and covalently bonded to a silica support are useful for the direct separation of enantiomers of a wide variety of compounds in both normal-phase and reversed-phase HPLC.[6,7,38]

Determination of Absolute Configuration of Enantiomeric Compounds.

Empirical rules for the elution order in normal-phase chromatography of diastereomeric carbamates are used to assign absolute configurations of chiral nonracemic compounds resolved by the general method of eq 1.[2] Owing to the inflexibility of the carbamate linkage, the relative positions of the most hydrophobic (or repulsive) group on the original compound and the naphthyl group of NEI are fixed in either a *syn* or an *anti* configuration in the two diastereomers. The *syn* conformer is likely to elute last, as its less repulsive moieties are more directly available for interaction with the silica surface.[2] The rules fail occasionally.[39] ^{1}H NMR[39,40] and single crystal X-ray diffraction[41,42] of purified diastereomers are also used in determining absolute conformation.

Synthesis of Chiral Nonracemic Allenes.

Enantiomerically enriched chiral allenes can be prepared by derivatization of a racemic propargyl alcohol with (*R*)-NEI, followed by chromatographic separation of the resulting diastereomers and reaction of the purified diastereomers with lithium dialkylcuprates at -78 °C, as shown in eq 2.[8,43]

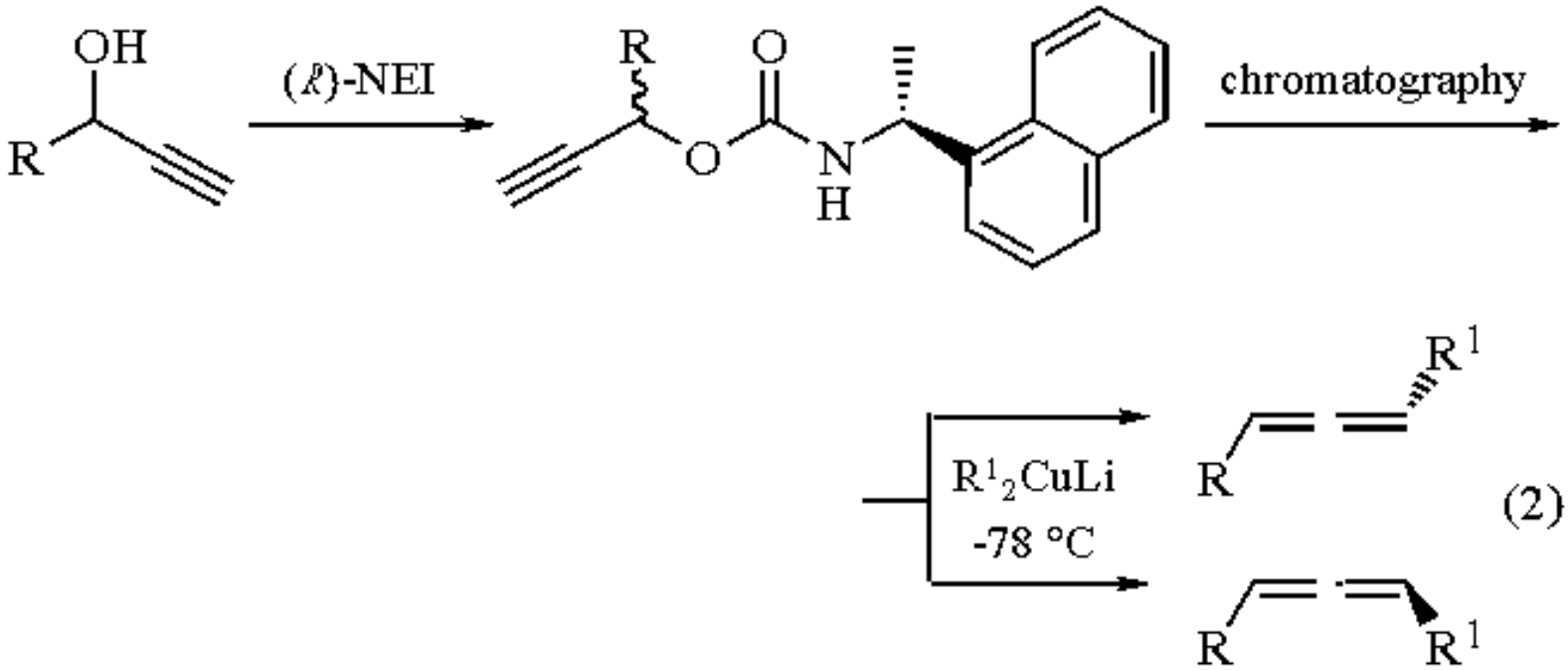

(2)

Alternative Reagents.

1-(1-Phenyl)ethyl isocyanate (PEI) is a cheaper alternative to NEI; however, diastereomers formed from NEI are usually easier to separate by liquid chromatography.[2,5,9] Other alternatives are also used, e.g. in determining the enantiomeric purity of 3-aminoquinuclidine, PEI, NEI, 2,3,4,6-tetraacetyl-β-D-glucopyranosyl isothiocyanate, and (*R,R*)- and (*S,S*)-*O,O*-dibenzoyltartaric acid anhydride are all employed successfully.[44] ***Mandelic Acid*** and Mosher's reagent, α-methoxytrifluoromethylphenylacetyl chloride, may not be quite as effective as NEI when resolutions are carried out by liquid chromatography.[2]

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Nickel

Ni^0

[7440-02-0] · Ni · Nickel · (MW 58.71)

(homocoupling of halobenzenes;[1,2] benzyl halide coupling;[3,4] synthesis of β-hydroxynitriles;[5] xylylene cycloadditions;[6] synthesis of 3-arylpropanenitriles[7])

Form Supplied in: black powder; activated nickel is not commercially available and must be prepared prior to use.

Preparative Methods: activated nickel is prepared by the reduction of nickel iodide with ***Lithium*** metal under argon with a catalytic amount of naphthalene in glyme.[6]

Handling, Storage, and Precautions: all reactions should be carried out in an inert atmosphere. Appropriate precautions are necessary since the reagent is a cancer suspect agent. Use in a fume hood.

Homocoupling Reactions of Halobenzenes.

Activated metallic nickel powder is a simple and convenient reagent for coupling iodobenzenes and bromobenzenes (eqs 1 and 2).[1] Best results are obtained with unsubstituted or 4-substituted iodobenzenes. *Ortho* substitutents, particularly nitro groups, seem to inhibit coupling. Electron-donating substitutents seem to lower the reactivity. Carbonyl groups and nitriles are compatible and afford good yields of the corresponding biphenyls. Glyme, DMSO, and DMF have all been used as solvents with very little difference in yields.

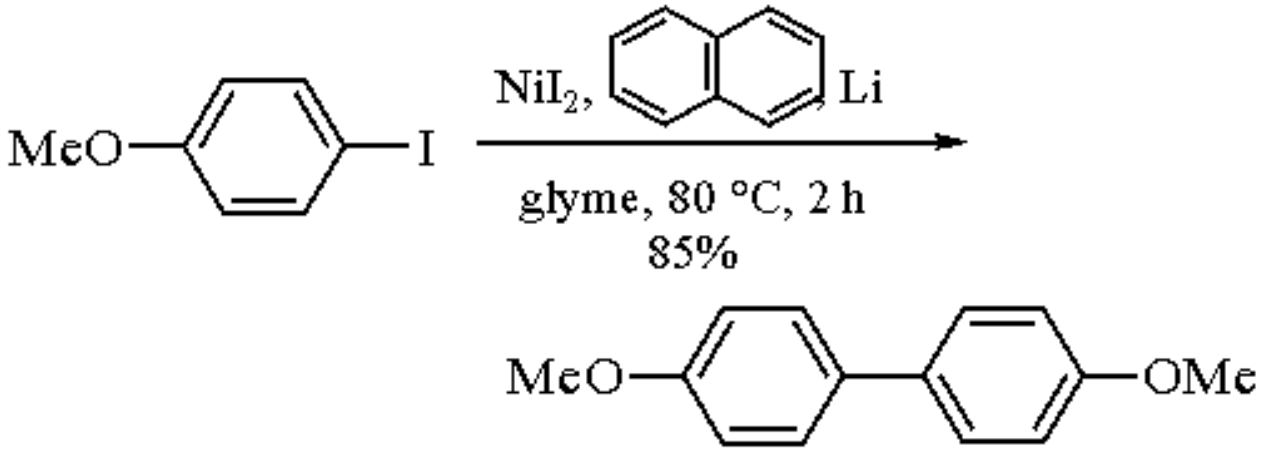

(1)

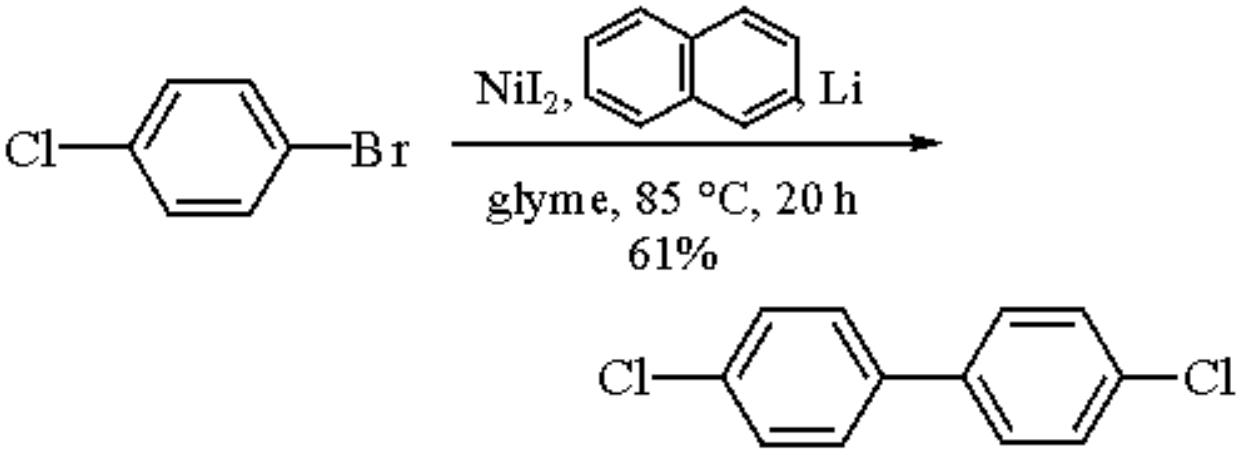

(2)

The use of activated nickel powder is superior to the Ullmann synthesis in that reaction temperatures are much milder (80 °C compared to 150-280 °C) and yields are generally better.

Unsubstituted and monosubstituted benzylic halides react with metallic nickel at room temperature to afford the corresponding 1,2-diarylethanes in good yield (eq 3).[2] Substituents such as methoxy, chloro, bromo, nitro, cyano, and alkoxycarbonyl groups are well tolerated. Reactions of benzylic di- and trihalides gives mixtures of *cis*- and *trans*-ethylenes (eq 4).[2]

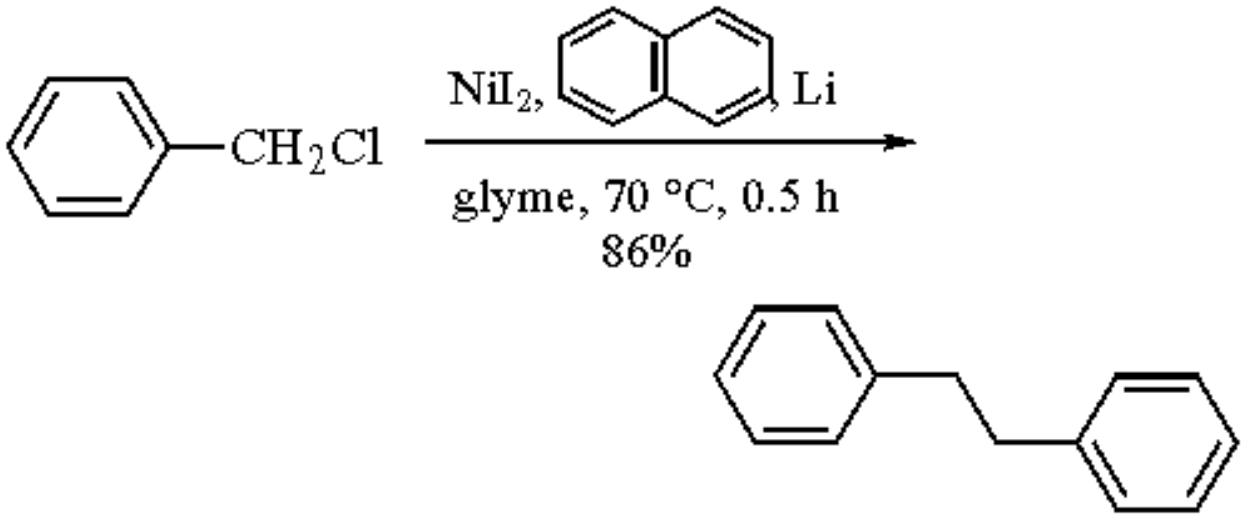

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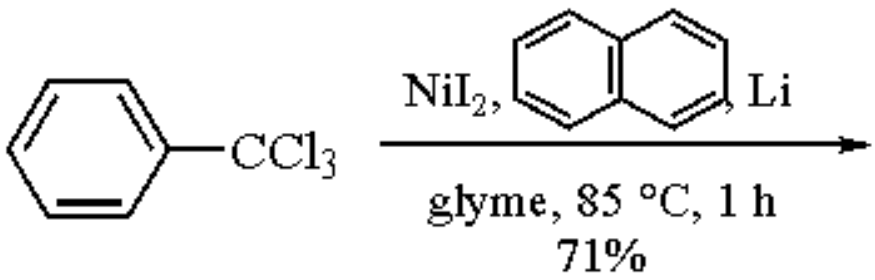

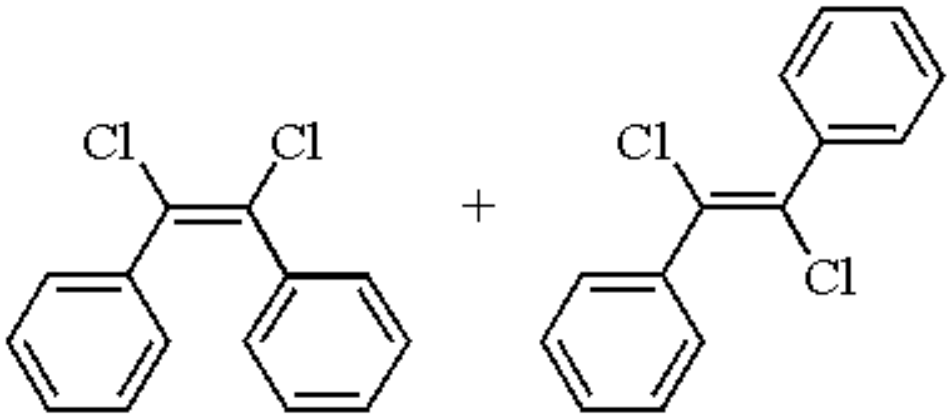

74% *cis* 26% *trans*

(4)

Coupling of Benzyl Halides.

Metallic nickel is a convenient reagent for the reductive coupling of benzyl halides with acyl halides to afford benzyl ketones (eq 5).[4] Best results are obtained in refluxing glyme, although some reactions proceed even at room temperature.

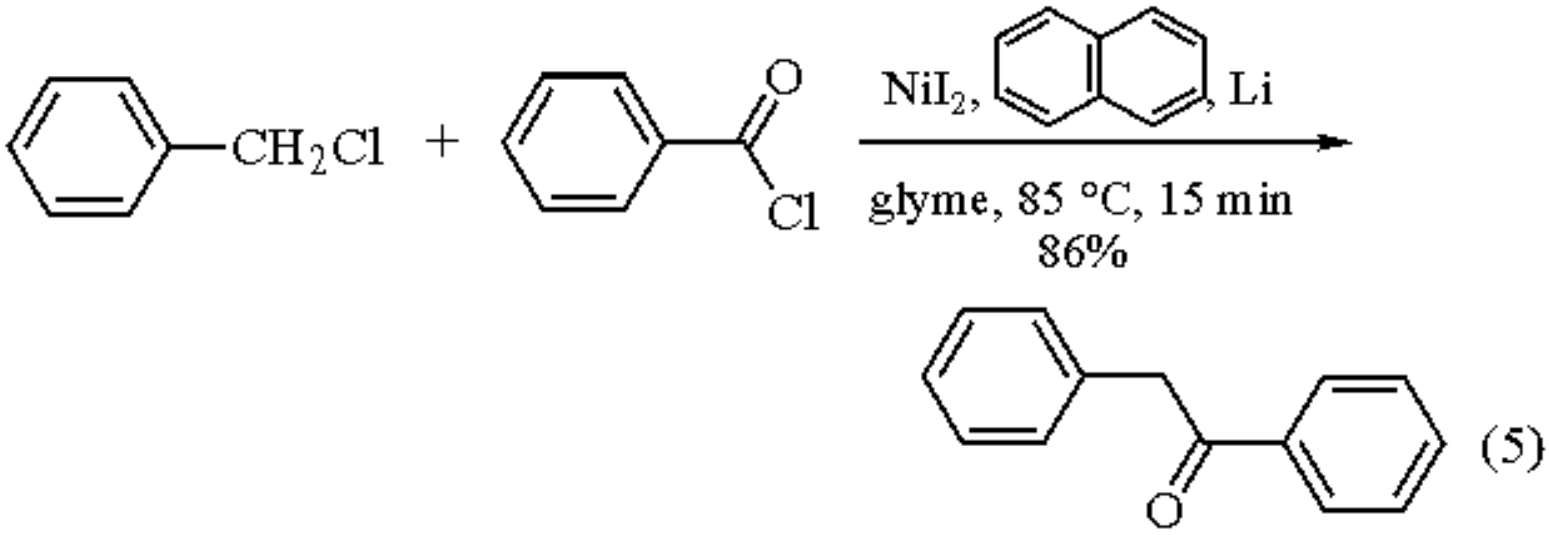

Synthesis of β-Hydroxynitriles.

Metallic nickel can effect Reformatsky-type addition of haloacetonitriles to aldehydes at 85 °C in glyme to give β-hydroxynitriles (eq 6).[5] Bromoacetonitriles give the best results, but chloro- and iodoacetonitriles also react.

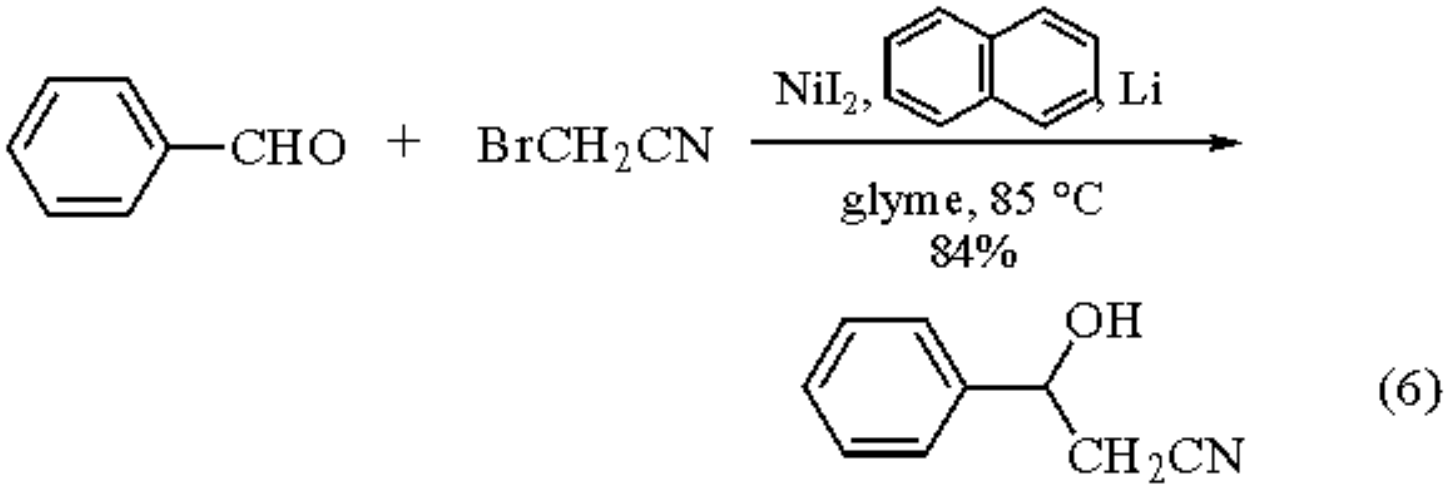

Cycloadditions of *o*-Xylylenes with Dienophiles.

Activated nickel reacts with α,α´-dihalo-*o*-xylene in the presence of electron-deficient alkenes to yield 1,2,3,4-tetrahydronaphthalene derivatives in moderate yield (eq 7).[6] This reaction proceeds, presumably, via an *o*-xylylene intermediate. A variety of alkenes give the expected cycloaddition products. In general, *cis*-alkenes yield a mixture of *cis* and *trans* products (eq 8), while *trans*-alkenes only give *trans* products (eq 9).[6] Although the cycloaddition has not been proven to be either concerted or stepwise, the mixtures of *cis* and *trans* products can be explained by isomerization of the alkenes prior to the cycloaddition.

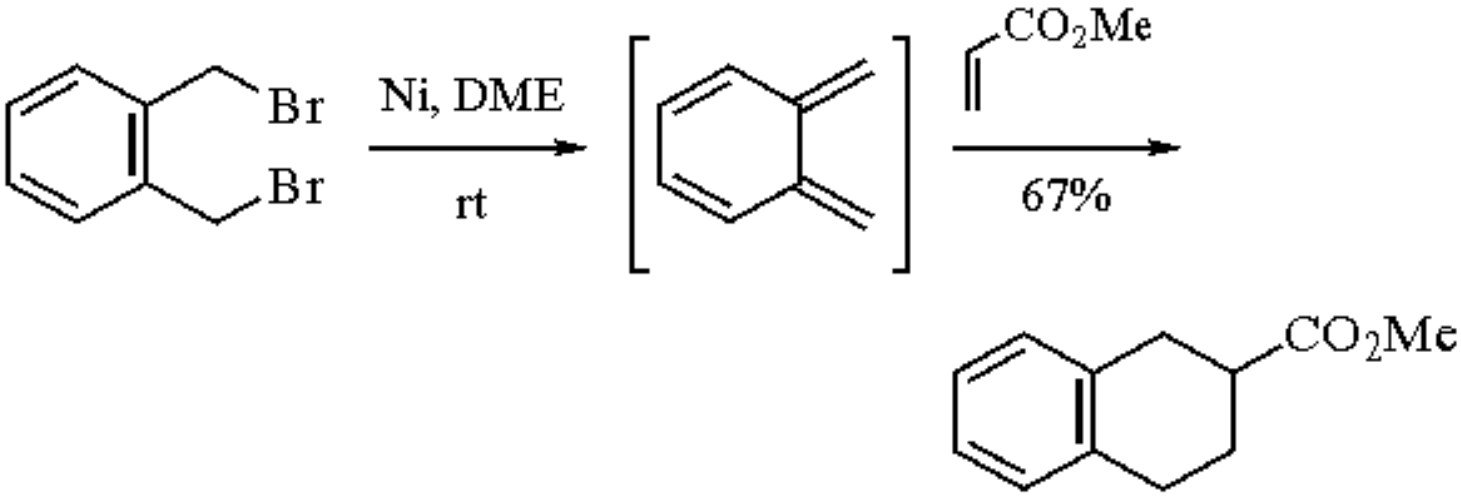

(7)

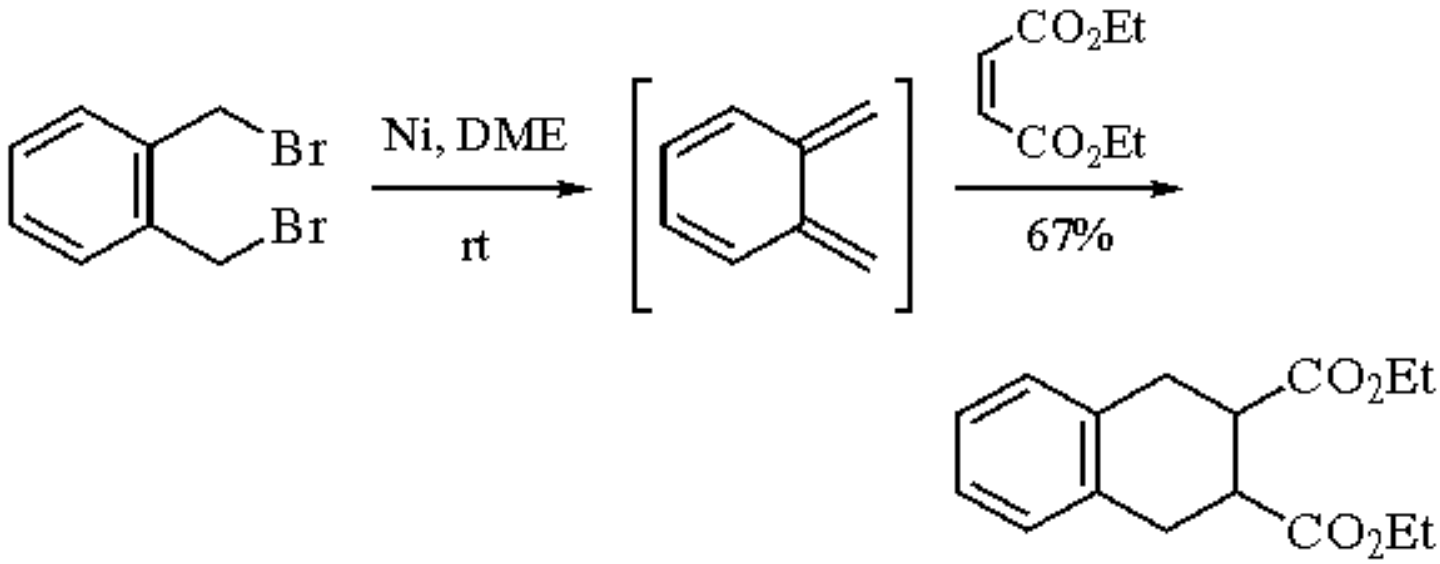

(8)

cis:*trans* = 1:1

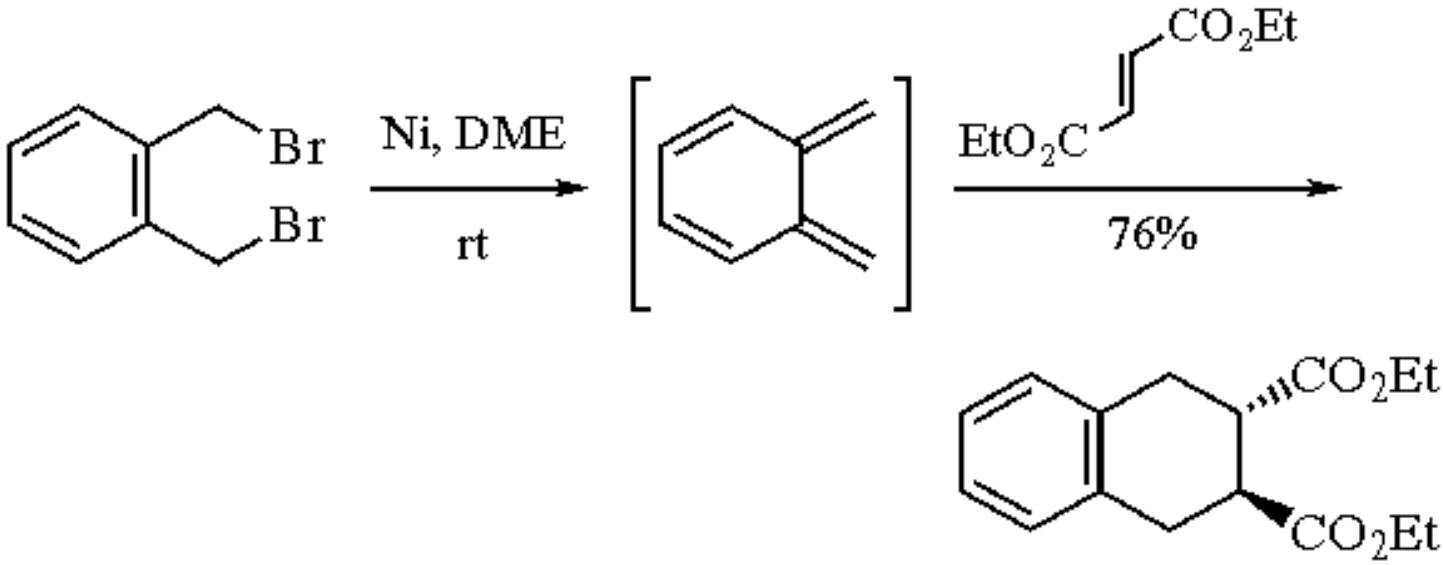

(9)

Preparation of 3-Arylpropanenitriles.

Benzylic halides react with haloacetonitriles in the presence of nickel to form 3-arylpropanenitriles (eq 10).[7] The reaction conditions are compatible with a variety of substituents including halogens, nitriles, and alkoxycarbonyl groups (eqs 11 and 12).

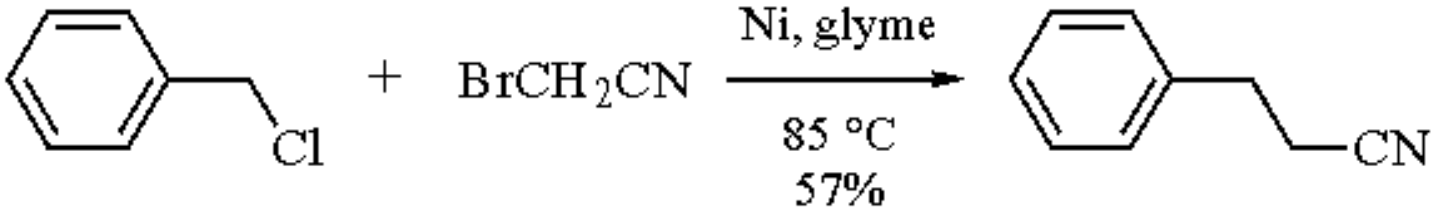

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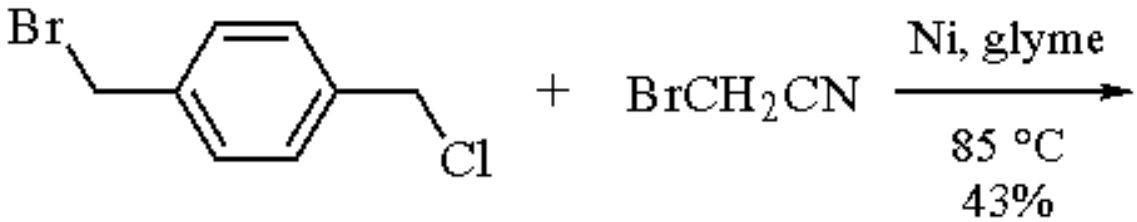

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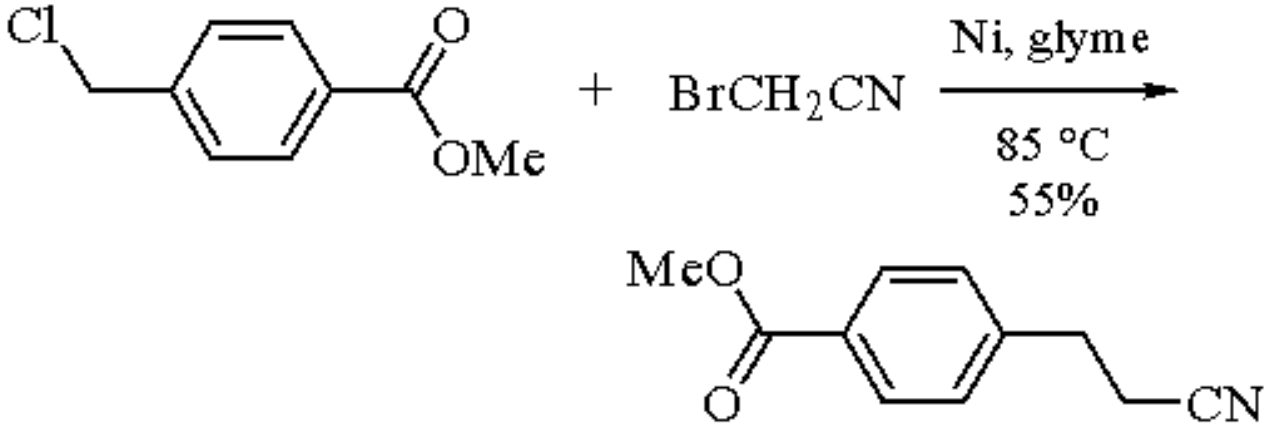

(12)

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2. Inaba, S.; Matsumoto, H.; Rieke, R. D. *JOC* **1984**, *49*, 2093.
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Nickel(II) Acetate

$(AcO)_2Ni.4H_2O$

[6018-89-9] · $C_4H_{14}NiO_8$ · Nickel(II) Acetate · (MW 248.87)

(autoxidation catalyst;[1] hydrogenation catalyst;[2] catalyst for isomerization of aldoximine[4] to amides;[3] template for Schiff base condensations[4])

Physical Data: decomposition above 250 °C; d = 1.798 g cm^{-3}.

Solubility: sol H_2O and MeOH; insol most organic solvents.

Form Supplied in: widely available as tetrahydrate in high purity as a green powder or small crystals.

Purification: anhydrous nickel acetate can be obtained by heating the tetrahydrate to 100 °C under vacuum over P_2O_5 or other desiccants.

Handling, Storage, and Precautions: excellent shelf life, carcinogen, toxic.

Autoxidation of Benzoin.

Anhydrous nickel acetate in methanol can be used to catalyze the autoxidation of benzoin to benzil.[1] The reaction is first order in nickel acetate and in benzoin, and extensive mechanistic studies suggest that a complex is formed between nickel acetate and benzoin that subsequently reacts rapidly with dioxygen. Both formaldehyde and H_2O_2 were identified as byproducts. No other α-hydroxy ketones have been studied.

Hydrogenation.

A heterogeneous catalyst for hydrogenation can be prepared from ***Sodium Hydride***, RONa, and $Ni(OAc)_2$ and used for hydrogenation of alkynes, alkenes, and carbonyl compounds at room temperature and atmospheric pressure.[2] The catalyst is prepared by adding a stirred suspension of 1 equiv anhydrous $Ni(OAc)_2$ in THF to 6 equiv NaH. After heating to 45 °C, 2 equiv of the desired alcohol, for example *t*-pentyl alcohol, is added and heating is continued for 3 h. The resulting solution is used directly for reduction of 1 equiv of substrate at room

temperature for reaction times of 5-60 min. This catalyst selectively reduces alkynes to *cis*-alkenes in reaction times of 10-20 min. Conjugated dienes react more slowly, so that a mixture of dienes may be selectively reduced as well. Ketones are reduced to alcohols more slowly, requiring 2-9 h for completion of the reaction. See ***Sodium Hydride-Nickel(II) Acetate-Sodium t-Pentoxide***.

Isomerization of Aldoximes to Amides.

Aldoximes are isomerized to amides by heating in xylenes in the presence of 0.2-5.6 mol % $Ni(OAc)_2$ as catalyst.[3] For example, benzaldoxime is converted to benzamide in 91% purified yield by heating to reflux in xylenes for 5 h with 2 mol % catalyst (eq 1). Aliphatic oximes, including acid-sensitive ones, and aromatic oximes with either electron-donating or -withdrawing substituents are all good substrates for this reaction.

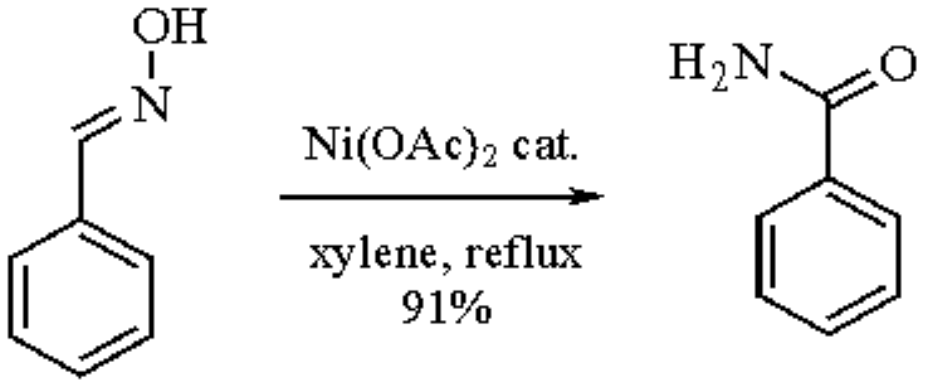

(1)

Schiff Base Condensations.

Simple nickel(II) salts such as $Ni(OAc)_2$ are used as templates for Schiff base condensation of amines with carbonyl compounds to form polydentate nickel chelates.[4] In particular, acetylacetone and its analogs will condense with ***1,2-Diaminoethane*** to form a macrocyclic complex. The reaction is exemplified with phenyldiazomalondialdehyde (eq 2).

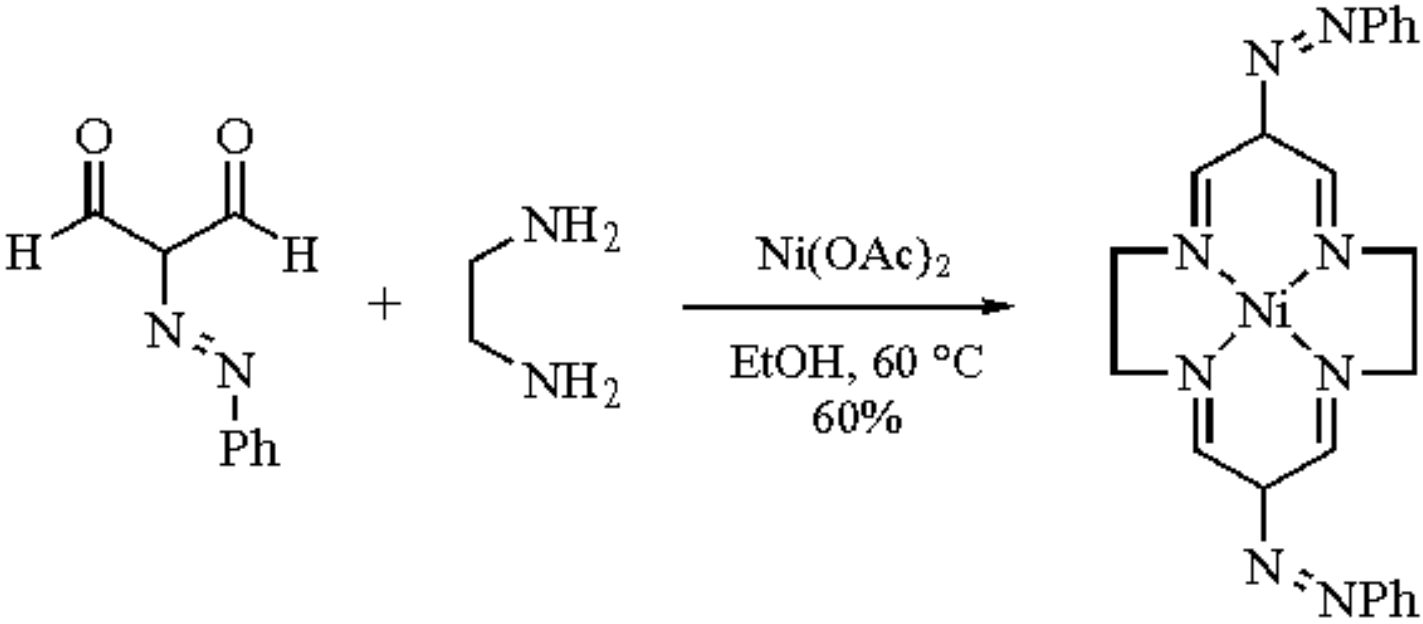

(2)

1. Hammond, G. S.; Wu, C. S. *JACS* **1973**, *95*, 8215.
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State University of New York at Stony Brook, NY, USA

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Nickel(II) Acetylacetonate[1]

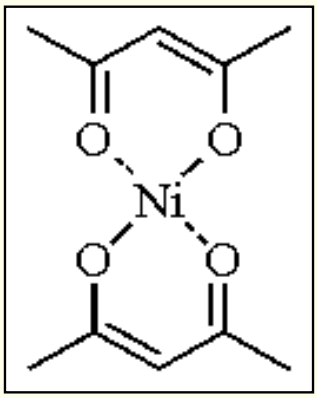

[3264-82-2] · $C_{10}H_{14}NiO_4$ · Nickel(II) Acetylacetonate · (MW 256.93)

(catalyst for oligomerization, telomerization, hydrosilylation, hydrogenation, reduction, cross-coupling, oxidation, conjugate addition, addition to multiple bonds, and rearrangements[1])

Alternate Name: bis(acetylacetonato)nickel(II).

Physical Data: pale green solid, mp 240 °C (dec); see also ***2,4-Pentanedione***.

Solubility: sol ethers and aromatic and halogenated hydrocarbons.

Analysis of Reagent Purity: atomic absorption is the method most commonly used.

Preparative Methods: commercially available; can be prepared from ***Nickel(II) Chloride***.[1d]

Purification: recrystallize from benzene and sublime under vacuum (10^{-3} mmHg).[1c]

Handling, Storage, and Precautions: nickel is now recognized as a cancer suspect agent as well as a possible teratogen and due precautions should be taken when handling the reagent. The anhydrous solid is stable, but is an irritant and hygroscopic and should preferably be stored in a sealed container to preclude contact with air and moisture. Solutions are more susceptible to atmospheric oxidation.

Catalysts for Oligomerization, Cooligomerization, and Telomerization.

Active catalytic systems used for these reactions have been prepared from many Ni^{II} salts and Ni^0 complexes. The most common are $Ni(acac)_2$, nickel halides, and nickel-alkene complexes. The reactive species are formed from the

combination of Ni^0, a Lewis acid usually based on aluminum, and a suitable ligand. They are referred to as Ziegler catalysts. When Ni^{II} salts are used, a reducing agent is required to produce the active Ni^0. The Lewis acid present, commonly a trialkylaluminum, is generally sufficiently reactive to reduce the nickel salt. Other reducing agents such as ***n-Butyllithium***,[2] ***Sodium Borohydride***,[3] or an electric current[4] have also been used. The oligomerization reactions are usually done in hydrocarbon or halogenated solvents. The mechanism is believed to involve nickel hydride, formed in situ via β-hydride elimination. First, an alkene inserts into the Ni-H bond. Further insertion of a second alkene into the C-Ni bond and reductive elimination regenerates nickel hydride and produces the oligomer. While some very interesting carbocyclic systems can be accessed via these catalysts, the product distribution can vary depending on the nickel precatalyst/Lewis acid/ligand combination chosen. The better activity resulting from using one precatalyst over another for a specific transformation is not always well understood, and often results from careful tuning of the catalytic system. Below are those in which $Ni(acac)_2$ has been successful. Other articles and monographs on ***Nickel*** should also be consulted.[1a,1b]

Oligomerization and Cooligomerization of Alkenes.

Cooligomerization of monoalkenes is generally of limited synthetic interest due to the formation of many isomers and oligomers and the difficulty in establishing conditions displaying suitable selectivity. It is, however, very important in the industrial production of lower alkenes. This topic is certainly well beyond the scope of this article. Some cyclic and bicyclic alkenes have proven more suitable (eq 1), the rigidity of which provides lesser oportunities for isomerizations by ways of insertion/migration.[5,6]

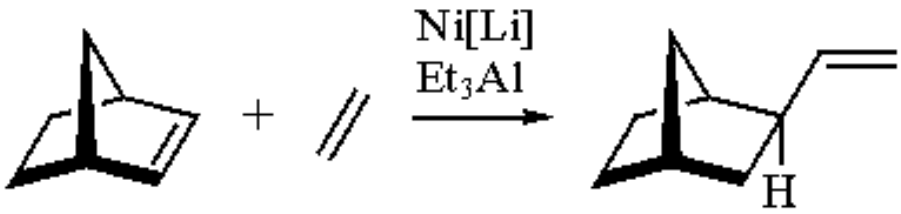

(1)

Cooligomerization of 1,3-Dienes.

The cyclotrimerization of butadiene is performed in the presence of a ligand-free nickel catalyst, giving cyclododecatrienes (eq 2),[7] with the all-*trans*-1,5,9-isomer as the major product. Lesser amounts of the other double-bond isomers are also found, the quantity of which are temperature and concentration dependent.[8] Substituted 1,3-dienes have not received as much attention due to the large number of isomers formed during the reaction, as well as the much lower reaction rates. The cyclooligomerization can be stopped at the stage of the dimer by introducing a phosphite or phosphine ligand.[9] In the reaction of butadiene the major product is 1,5-cyclooctadiene (eq 3),[9] which is accompanied by small amounts of divinylcyclopropane and 4-vinylcyclohexene. The three products are believed to originate from the same di-π-allylnickel intermediate (eq 4).[10] The proportion of these intermediates and consequently the product distribution is affected by the presence of a ligand, effects of which have been related to their electronic and steric nature. The less basic and more bulky ligands favor a di-π-allyl intermediate which eventually closes by reductive elimination to the 1,5-cod via a terminal, rather than internal, di-σ-allyl complex.[10]

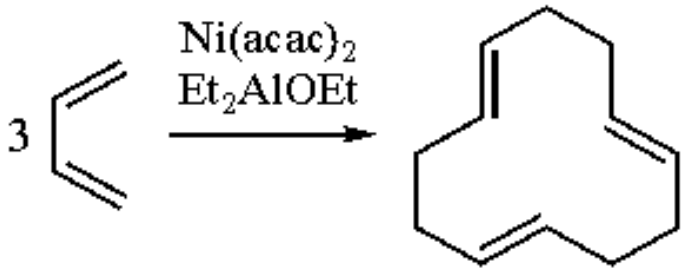

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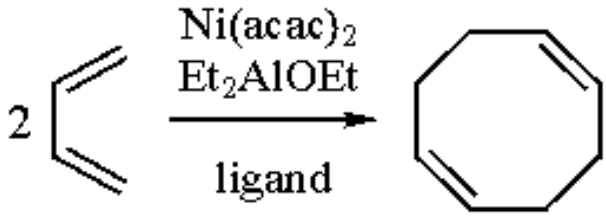

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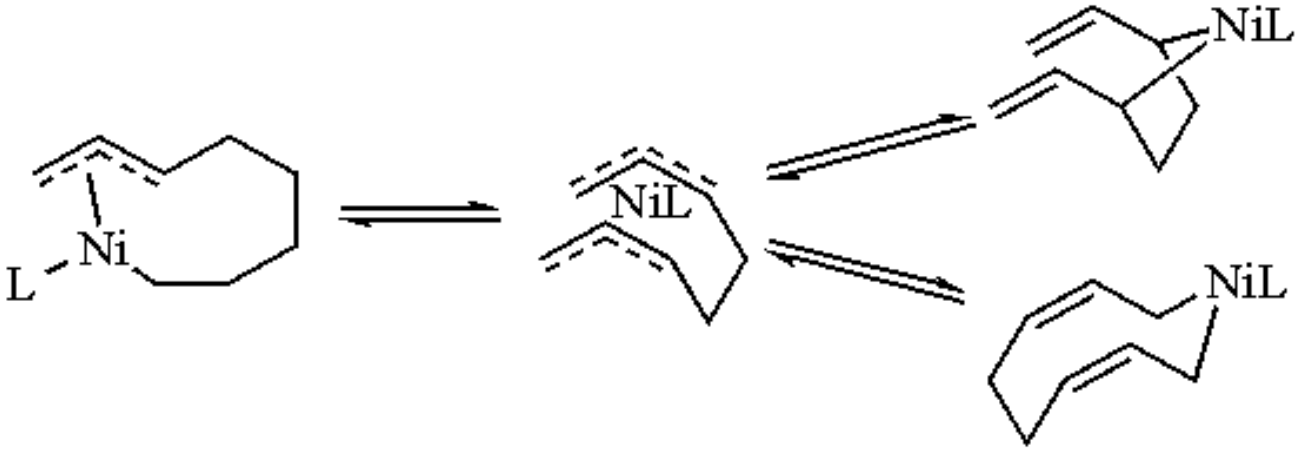

(4)

Codimerizations of a variety of 1,3-dienes provide a convenient access to substituted 1,5-cyclooctadienes (eq 5)[11] and cyclohexenes (eq 6).[12] The presence of an activating group such as an ester can provide further stabilization of the σ-allyl/π-allyl complex, increasing the selectivity of the reaction (eq 7).[13]

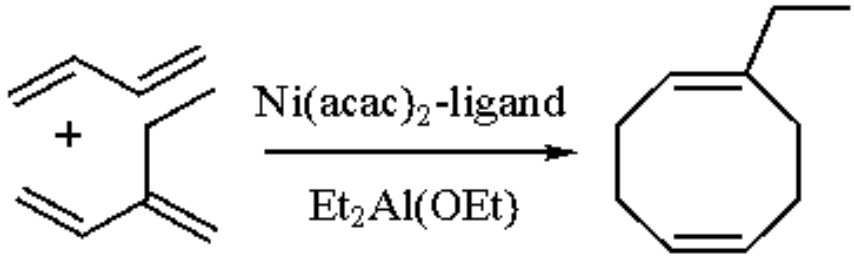

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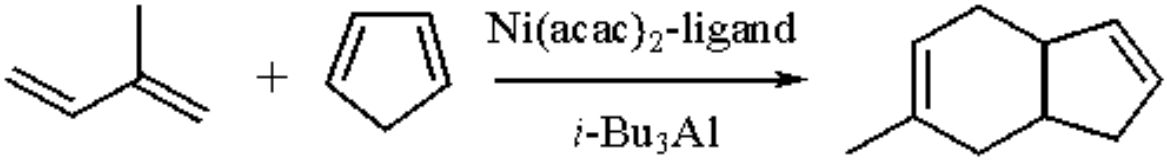

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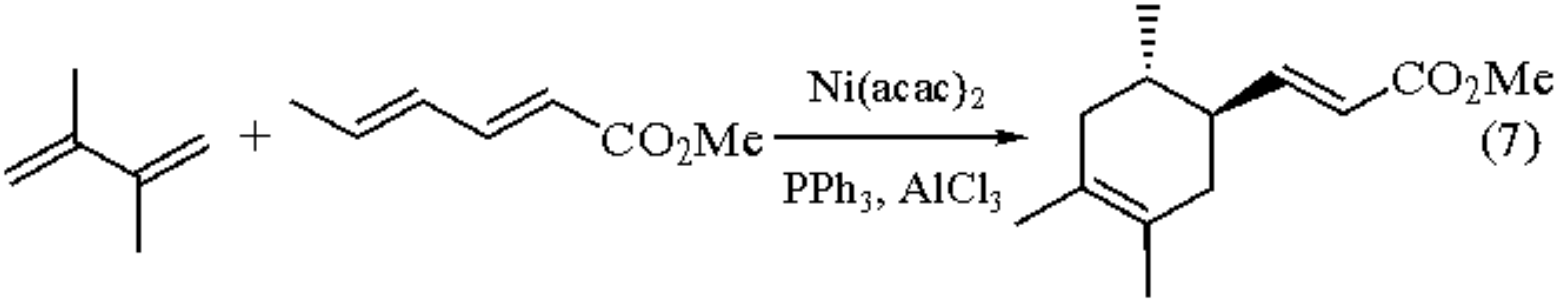

(7)

The cooligomerization of 1,3-dienes and alkenes involves two molecules of the diene and one of the alkene to form substituted cyclodecadienes (eq 8)[14] and variable amounts of the linear cotrimers. In the case of symmetrical alkenes it is possible to obtain a single product, in contrast to unsymmetrical alkenes in which mixtures of isomers result, in addition to those resulting from the other modes of oligomerization (i.e. linear vs. cyclic). These reactions work best in the presence of the catalytic system $Ni(acac)_2$/ligand/diethylethoxyaluminum. This is among the few methods giving direct access to 10-membered rings.

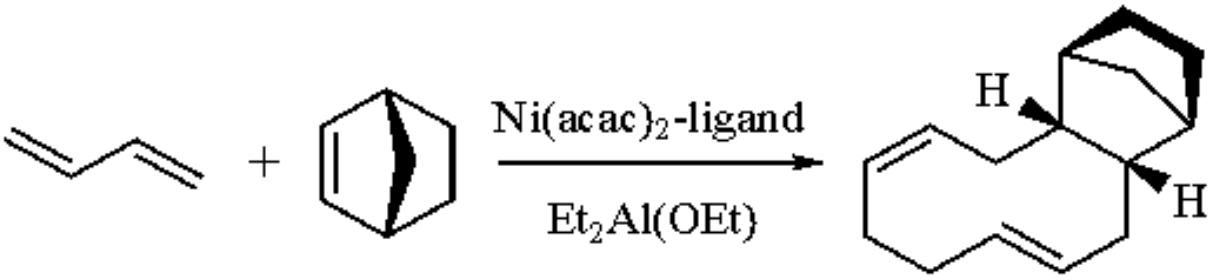

(8)

Disubstituted alkynes as well as allenes have also served as substrates in cooligomerizations with butadienes. With the former, *cis*-4,5-divinylcyclohexenes and mixtures of cyclodecadienes result. Other nickel precatalysts, such as ***Bis(1,5-cyclooctadiene)nickel(0)***, have, however, proved to be more specific with regard to the type and number of products formed.[15]

Alkynes.

The oligomerization of unsubstituted (eq 9)[16] and monosubstituted alkynes, also known as the Reppe reaction, produces variable mixtures of linear dimers, 1,2,4- and 1,3,5-trisubstituted benzenes, and cyclooctatetraene[17] isomers. Disubstituted alkynes are known not to undergo such a process although they can be used in cooligomerizations with mono- and unsubstituted alkynes. The product distribution depends on the nature of the ligands.[18] Weak ligands such as acac[19] or cod favor cyclotetramerization while stronger ones such as PPh_3 induce cyclotrimerization.[20] When coordinating solvents such as pyridine or DMF are used, only the linear dimer is formed.[21]

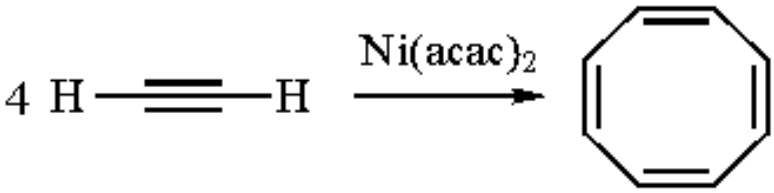

(9)

Strained systems are also reactive and their synthetic utility has been elegantly demonstrated.[22] In the synthesis of 12-

nor-13-acetoxymodhephene, advantage was taken of the facile Ni^0-induced transannulation that can take place in eight-membered rings, made possible by coordination of Ni^0 to the two double bonds (eq 10).[23]

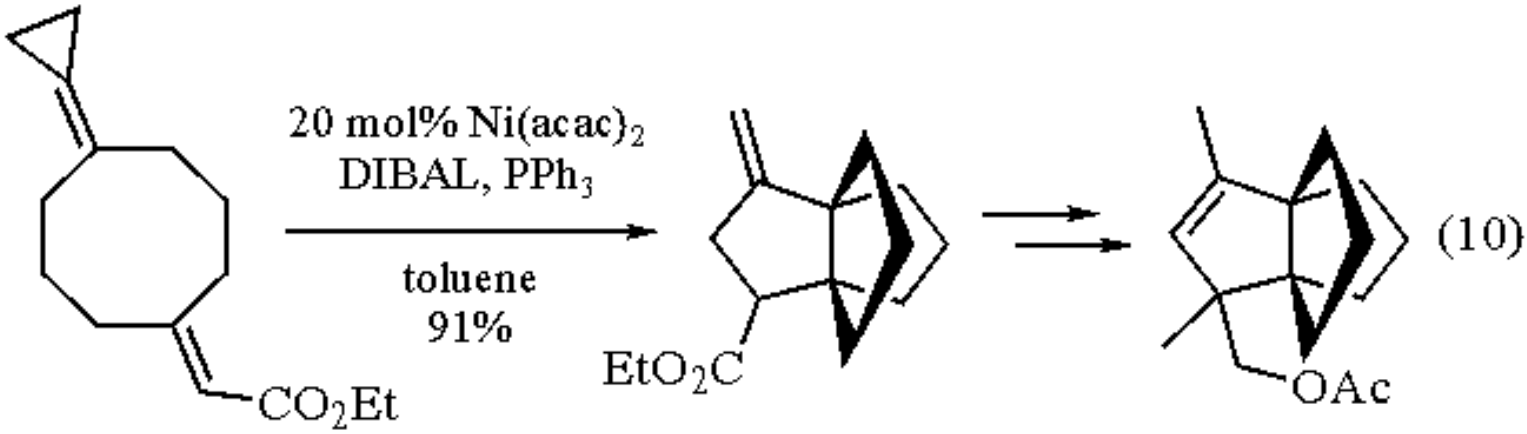

Telomerization is also an important reaction catalyzed by $Ni(acac)_2$ and other nickel species in the presence of ligands and reducing agents.[24] In this process, a diene is inserted in a 1,2- or 1,4-fashion into an activated C-H bond (eq 11)[25] or into the X-H bond of an alcohol (eq 12),[26] phenol, amine, or silane.[27]

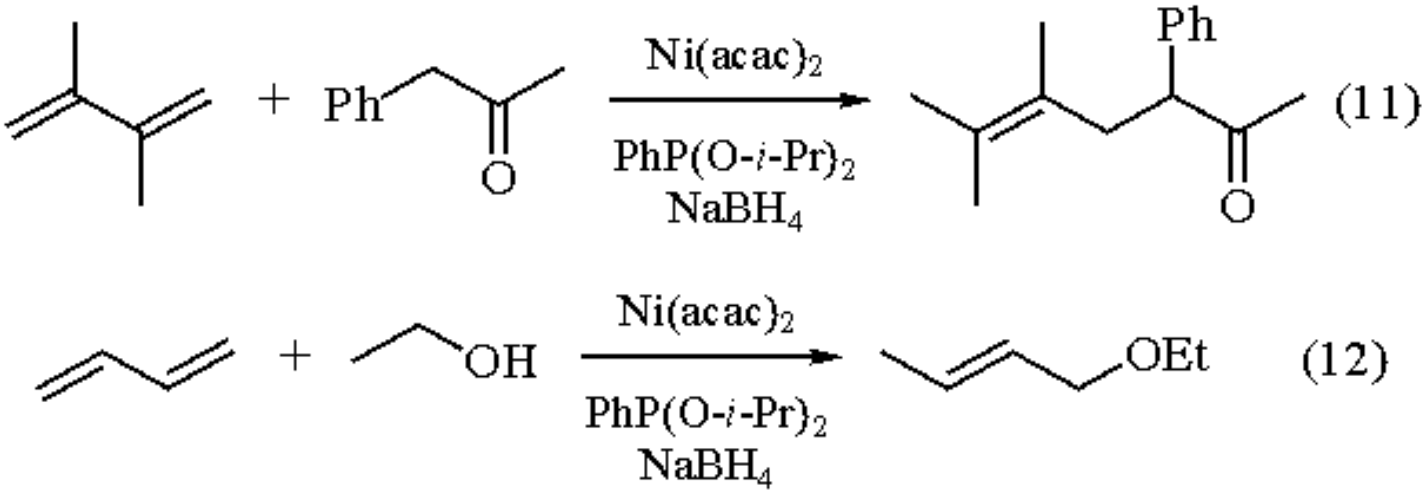

1,7-Diynes also undergo cyclization with 1,8-insertion into a Si-H bond.[28] Finally, dimethylsilane adds efficiently and with excellent regioselectivity to functionalized electron-rich or -poor alkenes in a 1,2-fashion, providing access to a wide variety of silane-containing substrates.[29]

A catalytic asymmetric version of the codimerization of alkenes has also appeared.[30] Homochiral phosphine ligands are used to induce chirality and, in selected examples, have resulted in appreciable levels of asymmetric induction (eq 13).[31,32]

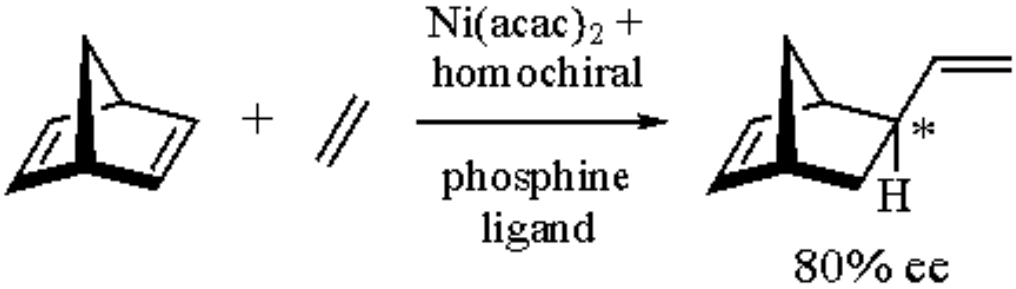

(13)

Nickel hydride generated in situ has been postulated as the active catalyst in the transformations described above and, not surprisingly, a large number of precatalysts have been reported. Only those dealing specifically with $Ni(acac)_2$ have been described here. A more comprehensive account is provided in the excellent reviews by Jolly and Wilke.[1a,1b]

Catalyst for Oxidations.

A very efficient protocol for the air oxidation of ketones, alkenes, and aldehydes, catalyzed by nickel (1,3-diketonates) has been developed by Mukaiyama and co-workers. Baeyer-Villiger oxidation of ketones to esters and lactones (eq 14)[33] is achieved in moderate to high yields with 1% $Ni(acac)_2$ or $Ni(dpm)_2$ (dpm = dipivaloylmethanato) and 2-3 molar equivalents of isovaleraldehyde or benzaldehyde under one atmosphere of air or oxygen, in 1,2-dichloroethane at ambient temperature. High regioselectivities were observed for unsymmetrical ketones (eq 15).[33] The aldehyde, which functions as a reducing agent, is converted to the acid in high yield.[34] This represents a mild, convenient, and ecologically sound oxidation protocol.

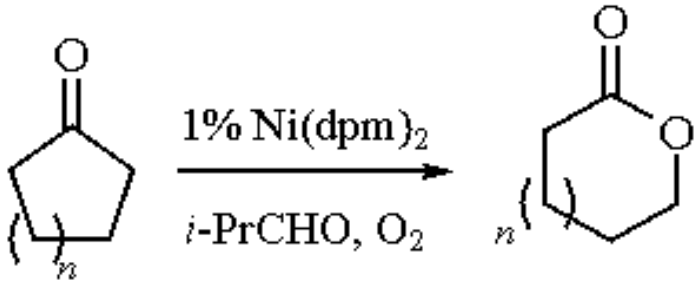

n	%
1	84
2	91
3	33

(14)

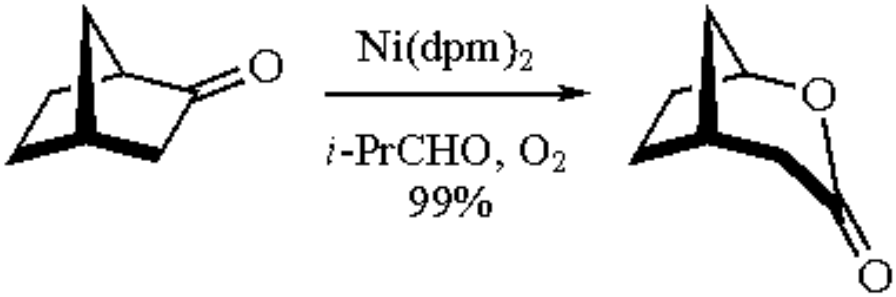

(15)

The epoxidation of alkenes[35] can also be realized in moderate to high yields under the same conditions using an aldehyde, or under more forcing conditions using an alcohol,[36] as the coreducing agent. Very low stereospecificity is obtained for disubstituted alkenes, which provide nearly equal mixtures of *cis*- and *trans*-epoxides, irrespective of the initial alkene geometry. This is, however, a good protocol for some 1,1-symmetrical trisubstituted alkenes.[37] Little information is available on the chemoselectivity and compatibility of other functional groups under the reaction conditions.

Catalyst for Conjugate Additions.

The conjugate addition of organozinc reagents in a 1,4-fashion to α,β-unsaturated ketones in the presence of 1-10 mol% of $Ni(acac)_2$ in ethereal or aromatic solvents proceeds in good to excellent yields (eq 16).[38] The reaction is fast and the conditions are very mild. This represents a nice alternative to organocopper reagents since diorganozinc reagents are much more stable than their organocopper analogs and can be used at ambient temperatures without decomposition. Addition occurs even with the most sterically demanding substrates, as demonstrated by the synthesis of (±)-β-cuparenone by Greene and co-workers (eq 17).[39] Aryl-, *t*-butyl-, cyclohexyl-, and alkenylzinc reagents have also been used. It should be noted that only one of the two alkyl groups is transferred and monoalkylzinc halides do not add, which results in the loss of one equivalent of the nucleophile. Articles on copper reagents should be consulted for related transformations.

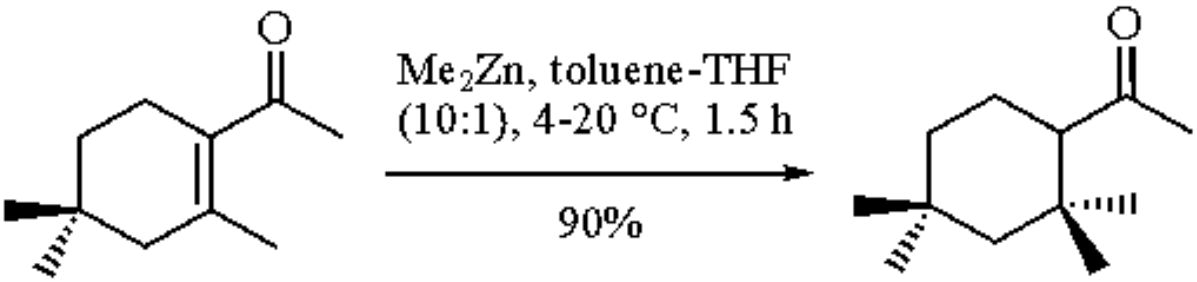

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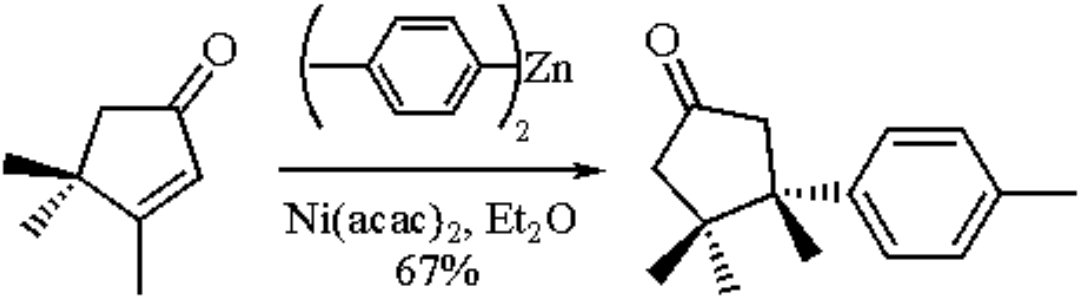

(17)

In the presence of $Ni(acac)_2$ and a coreducing agent such as ***Diisobutylaluminum Hydride*** (DIBAL), alkenylzirconium reagents[40] (but not alkylzirconium[41] undergo 1,4-additions to α,β-enones in 60-95% yield, which decrease with substitution at C-1 of the organometallic. Similarly, the complex formed by addition of $Ni(acac)_2$ and DIBAL (1:1) catalyzes the 1,4-addition of dialkylaluminum acetylides to α,β-enones (eq 18).[42] Again, the reaction works well even with highly hindered substrates. Trimethylsilylalkynes add efficiently but the yields are considerably lower with acetylene itself. Trialkylaluminums have been used directly on enones with in situ generation of the active nickel species.[43] Other nucleophiles such as lithium thiophenoxide[43] and 1,3-dicarbonyls (eq 19)[44,45] can be used but generally require more forcing conditions. Although the mechanism of these nickel-catalyzed additions has not been clearly established, it is believed to involve ketyl radicals resulting from single-electron transfer (SET) from a nickel(I) species.[46]

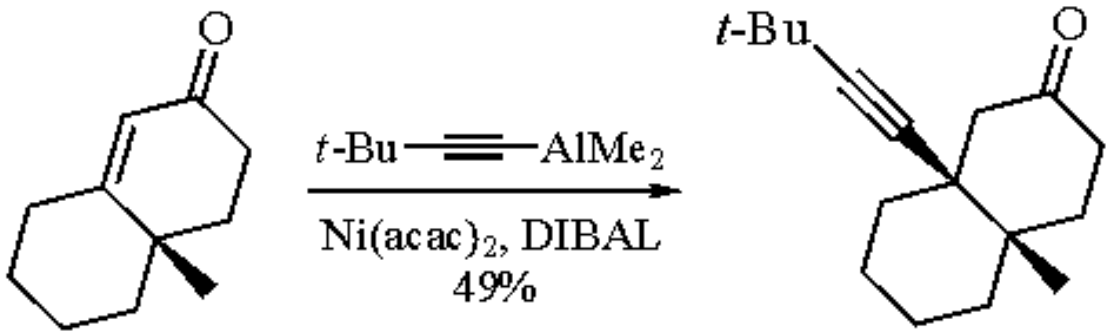

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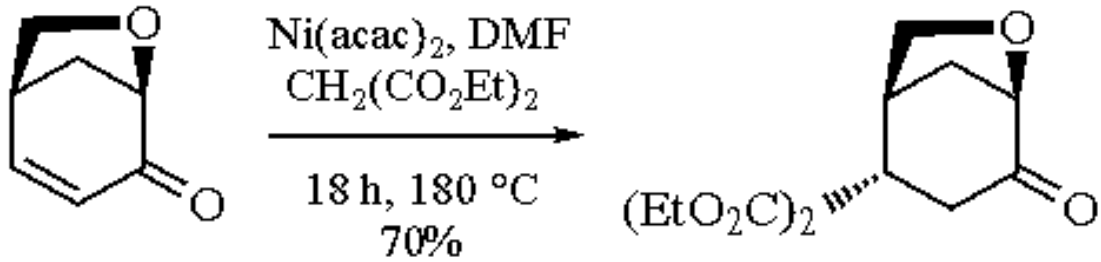

(19)

Catalytic Enantioselective Conjugate Additions.

In recent years, much work has been done to achieve enantioselective addition of organozinc reagents to various enones using homochiral ligands.[47,46b] Respectable levels of induction have been achieved with selected aromatic substrates, but attempts with simpler enones such as cyclohexenone have been unsuccessful. The accepted model to test the activity of a particular catalytic system is the addition of ***Diethylzinc*** to chalcone. Yields are generally good and enantiomeric excesses (ee) range from 25 to 95%. A variety of bi- and tetradentate ligands have been designed and the most successful are shown in eq 20. Nonlinear relationships between the ee of the ligand and the ee of the final product have been frequently observed.[48,46b]

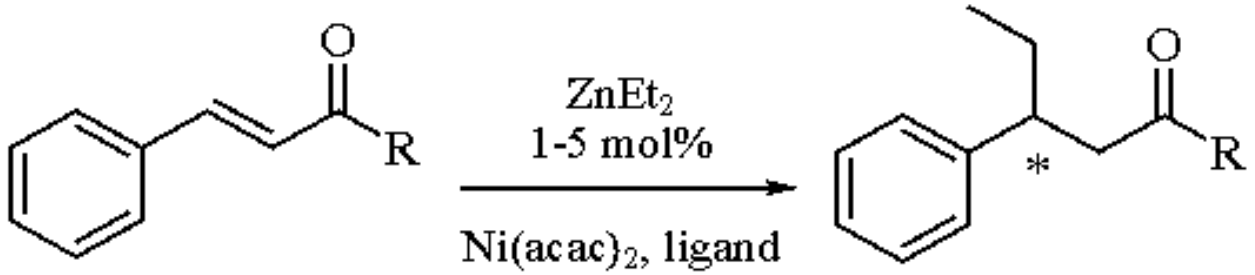

(20)

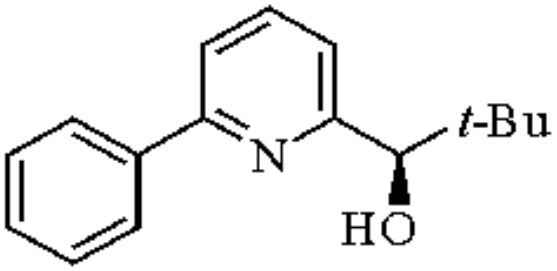

90% ee

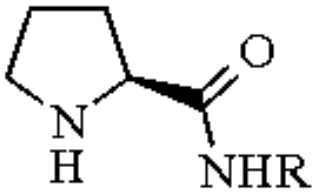

R = *t*-Bu, $CH_2Si(OEt)_3$
95% ee

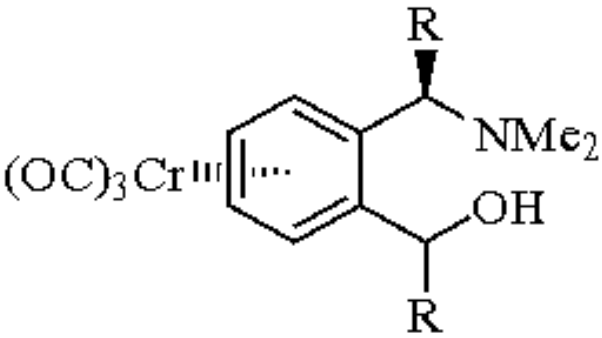

78% ee

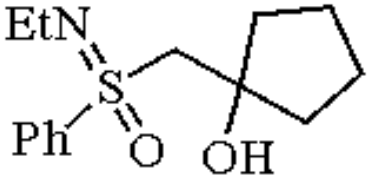

70% ee

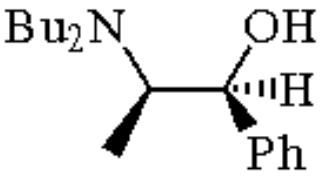

90% ee

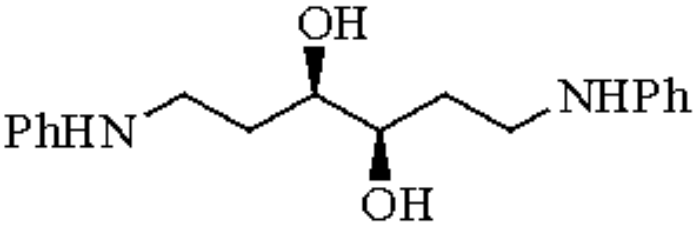

60% ee

Catalyst for Cross-Coupling Reactions.

While not as popular as other Ni^{II} precatalysts, Ni^0 complexes, or other metals such as Pd^0 complexes, $Ni(acac)_2$ has found many applications as a catalyst for cross-coupling reactions. It is fairly stable and sufficiently soluble to be used in a large variety of solvents. Aryl halides,[49] silyl enol ethers,[50] enol phosphates[51] and, more recently, aryl-*O*-carbamates and triflates[52] have been successfully coupled with alkyl, aryl, and alkenyl organometallics (eq 21).[53] The yields are generally good and chemoselectivity can be achieved in some cases (eq 22).[54,52]

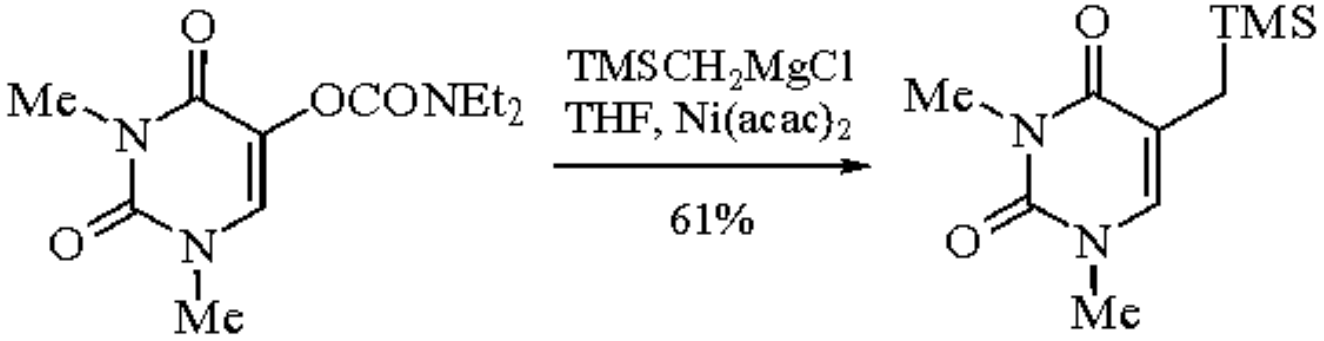

(21)

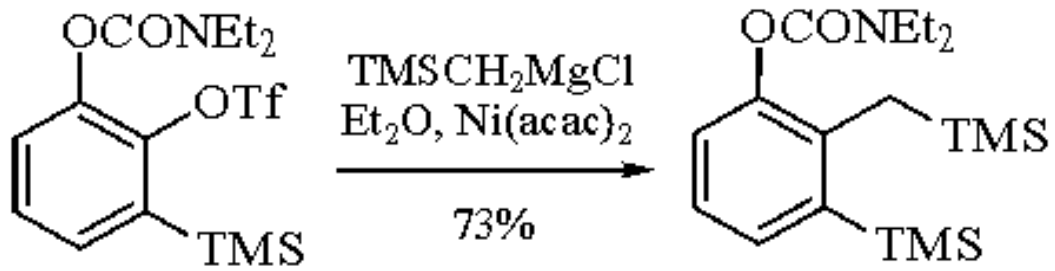

(22)

The addition of mono- and bidentate phosphine ligands in ethers or aromatic solvents often has a beneficial effect on the yield and speed of the reaction. The mechanism has been well documented and involves an oxidative addition of the aryl halide to Ni^0 followed by addition of the organometallic species to the Ni^{II} complex. Reductive elimination of the cross-coupling product and regeneration of Ni^0 completes the catalytic cycle. The coupling of stereodefined 1-alkenylalanes and zirconium with a variety of aryl halides proceeds in good yield and stereospecifically (eq 23).[55] Vinylic sulfones can serve as the electrophilic partner, coupling efficiently with phenyl- or methylmagnesium bromide (eq 24).[56] An interesting example was reported in which both electrophilic and nucleophilic components are borne by the same carbon. In this example, an α-(bromomagnesium)sulfone dimerizes head-to-head to produce a mixture of *cis*- and *trans*-alkenes (eq 25).[57]

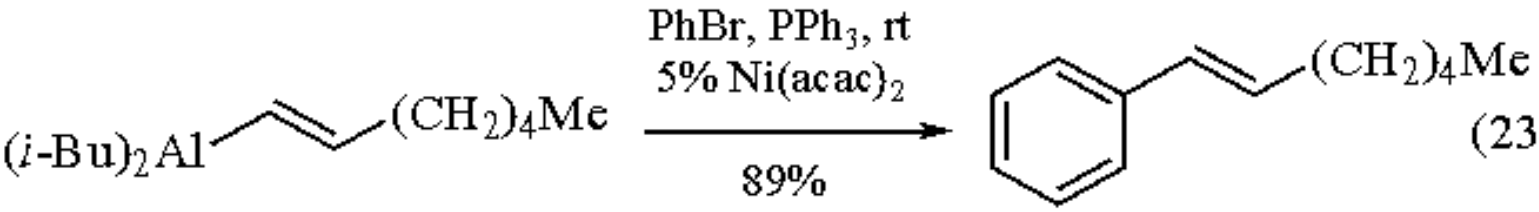

(23)

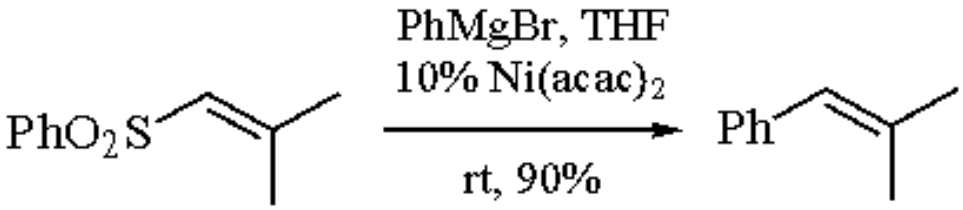

(24)

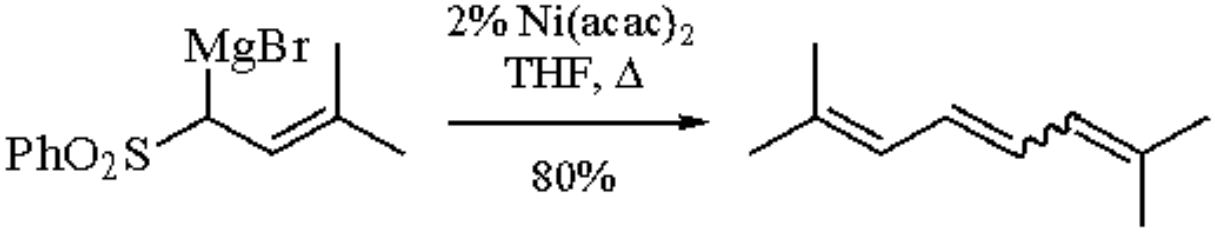

(25)

Again, $Ni(acac)_2$ is only one of the many precatalysts which have been used (often interchangeably) for these transformations. The choice of proper precatalyst has, in many instances, been the result of a more or less exhaustive screening of the five or six most common ligands. Other metal ions such as palladium, copper, or chromium are often similarly effective in promoting the transformation.

Other Additions.

Grignard reagents add regioselectivity and stereoselectively to substituted trimethysilylalkynes, in presence of $Ni(acac)_2$ and ***Trimethylaluminum***, to give a *syn* addition product (9:1). These additions occur exclusively at the carbon-substituted end of the alkyne.[58] If a heteroatom, such as an ether or an amine, is present on the carbon chain, isomerization to the *trans* product occurs (eq 26). The intermediate organometallic species can be subsequently trapped with a variety of electrophiles.

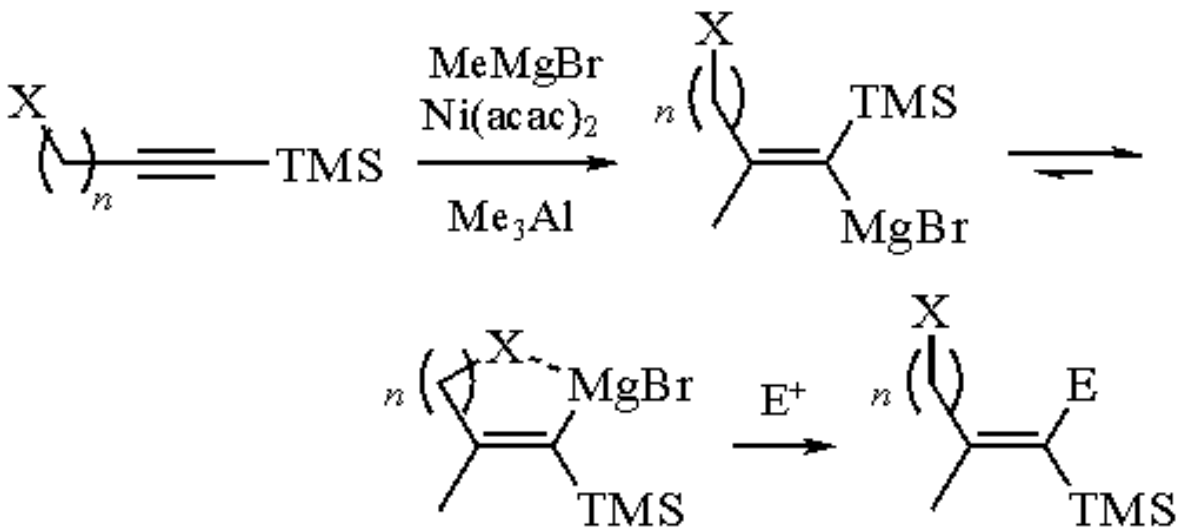

(26)

Functionalization of an unactivated terminal alkene is possible via remote chelation of a halomagnesium alkoxide (eq 27).[59] Addition of Grignard reagents to propargyl chlorides proceeds in a S_N2' fashion to provide good yields of the corresponding allenes. Methyl ketones can be prepared by $Ni(acac)_2$-catalyzed addition of trimethylaluminum to a nitrile followed by hydrolysis.[60a]

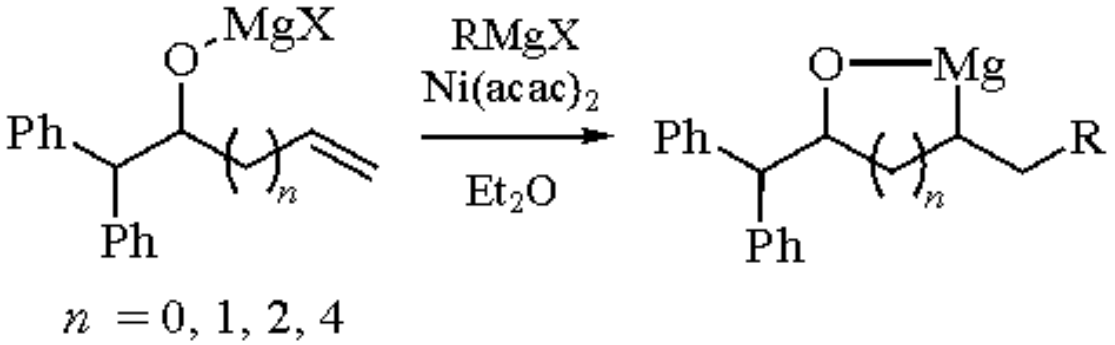

(27)

$Ni(acac)_2$ has been shown to promote the intramolecular coupling of a vinyl iodide with an aldehyde in the presence of ***Chromium(II) Chloride***, to form a 13-membered ring lactone. However, only a moderate stereoselectivity was observed, as both diastereomeric alcohols were produced (60% yield).[60b]

In the presence of a catalytic amount of $Ni(acac)_2$ (in addition to other metals), ***Cyanotrimethylsilane*** reacts smoothly with acetals or orthoesters derived from α,β-unsaturated carbonyls to give the corresponding *O*-methylcyanohydrins under neutral conditions (eq 28).[61]

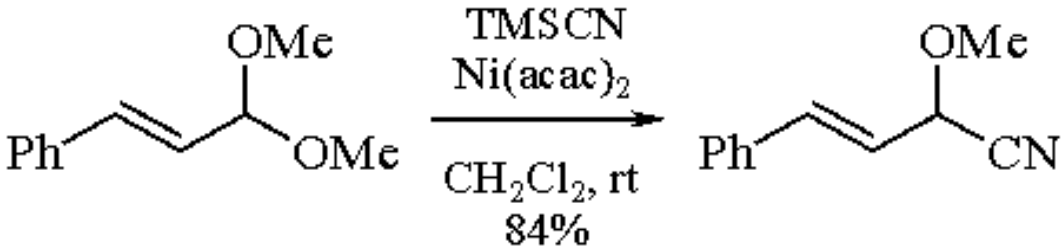

(28)

β-Diketonates add to ***Malononitrile*** in moderate yield to give β-amino cyanides (eq 29).[62] In contrast, β-keto esters, 1,3-diesters, and β-keto amides are all poor substrates. Other electrophiles have been used such as cyanogen, benzoyl cyanide,[63] and ***Trichloroacetonitrile***.[64] Reaction of acetylacetonate with cyanogen has been reported to produce highly substituted pyrimidines in moderate yields.[65]

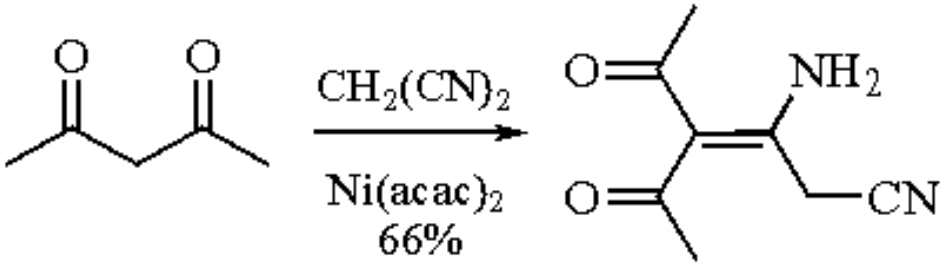

(29)

Optically active trialkylsilanes react with ***Vinylmagnesium Bromide*** via a pentacoordinate intermediate to produce, after loss of a hydride, tetrasubstituted silanes with almost complete retention of configuration.[66]

Reductions.

$Ni(acac)_2$ has seldom been used as a reduction catalyst. Hydrogenation of alkenes has been realized under photochemical conditions in the presence of a ketone as a sensitizer.[67] Monohydrogenation of 1,4-cyclohexadiene was effected using a homogeneous nickel catalyst generated from $Ni(acac)_2$, $Et_3Al_2Cl_3$, and PPh_3. Substituted cyclohexadienes produce mixtures of cyclohexene isomers, isomerization of which was shown to be promoted by the catalyst itself. A zeolite-supported complex formed between $Ni(acac)_2$ and an optically active 2-(aminocarbonyl)pyrrolidine ligand catalyzes the asymmetric hydrogenation of ethyl (*Z*)-α-benzoylaminocinnamate with ee values up to 85%. Other metals that have been studied have resulted in even higher enantioselectivities.[68]

Vinylic sulfones are reduced in fair to good yield to the corresponding alkenes with retention of configuration upon treatment with *n*-butylmagnesium bromide and a catalytic amount of $Ni(acac)_2$.[69] 2-Arenesulfonyl-1,3-dienes are also reduced stereospecifically to conjugated (*Z*,*E*)-dienes under the same conditions (eq 30).[70]

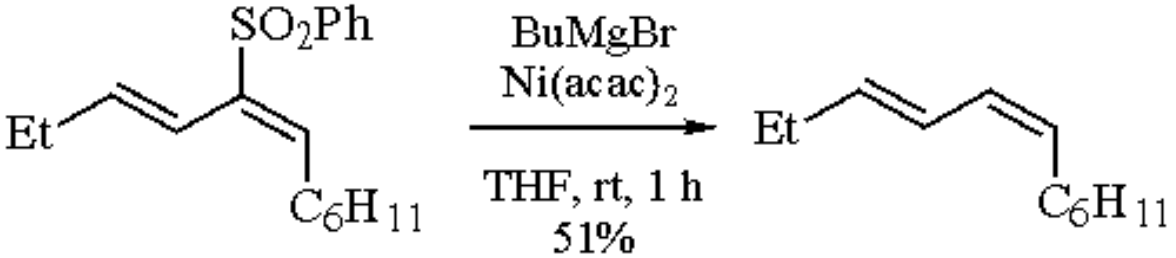

(30)

Miscellaneous Uses of Ni(acac)$_2$.

The isomerization of aldoximes to amides catalyzed by Ni(acac)$_2$ and ***Palladium(II) Acetylacetonate*** has been described.[71] The determination of the absolute configuration of vicinal glycols and amino alcohols complexed with Ni(acac) in protic or aprotic organic solvents has been claimed to be feasible by examination of the induced CD.[72] However, this method is not very general.

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Nickel Boride[1]

Ni_2B

(Ni_2B)[2]

[12007-01-1] · BNi_2 · Nickel Boride · (MW 128.19)

(selective hydrogenation catalyst,[1a,c,3] desulfurization catalyst;[4] reduces nitro[5] and other functional groups;[1a] dehalogenation catalyst;[1b,6] hydrogenolysis[7] catalyst)

Physical Data: mp 1230 °C.[8]

Solubility: insol aqueous base and most organic solvents; reacts with concentrated aqueous acids.

Form Supplied in: black granules, stoichiometry varies with supplier.

Preparative Methods: to a stirred suspension of 1.24 g (5 mmol) of powdered ***Nickel(II) Acetate*** in 50 mL of 95% ethanol is added 5 mL of a 1 M solution of ***Sodium Borohydride*** in 95% ethanol at room temperature (control frothing). Stirring is continued until the gas evolution ceases (usually 30 min). The flask is used directly in the hydrogenation.[1c,9a] This catalyst is nonpyrophoric.

Handling, Storage, and Precautions: caution must be taken in handling nickel salts. Ingestion of soluble nickel salts causes nausea, vomiting, and diarrhea. Nickel chloride has an LD_{50} (iv) = 40-80 mg kg^{-1} in dogs. Many nickel salts will sublime in vacuo. Nickel metal is carcinogenic and certain nickel compounds may reasonably be expected to be carcinogenic.

Catalyst Composition and Structure.

The composition of the catalyst produced by the reaction of Ni^{II} salts and ***Sodium Borohydride*** is dependent on reaction conditions (solvent, stoichiometry, temperature, etc.).[9] X-ray photoelectron spectroscopy[10] showed that the main difference between the P1 form of nickel boride (P1 Ni) and the P2 form of nickel boride (P2 Ni) is the amount of $NaBO_2$ adsorbed on to the surface of the catalyst. P1 Ni (which is prepared in water) has an oxide:boride ratio of 1:4, while P2 Ni (which is prepared in ethanol) has a ratio of 10:1. Early studies of the reaction of borohydrides with transition metal salts[11] (Fe^{II}, Cu^{II}, Pd^{II}, Ni^{II}, Co^{II}, etc.) showed that the reaction product is either the metal (as in the case of Pd^{II}) or a black granular solid (as in the case of Ni^{II}); in both cases, H_2 is evolved.[11c,12] Analysis of the black solid formed from the Ni^{II} suggested the catalyst to be a boride.[11c,13] Paul et al.[11b] examined several Ni^{II} salts and found nickel acetate to be most acceptable.

Hydrogenation of Alkenes and Alkynes.

Brown has described two forms of nickel boride (P1 Ni and P2 Ni)[9] which are hydrogenation catalysts. In a comparison of P1 Ni to W2 ***Raney Nickel*** (Ra Ni) as a hydrogenation catalyst, P1 Ni was found to be somewhat more active (as measured by the $t_{1/2}$ for hydrogenation of several alkenes).[9a] What is more important in the comparison of Ra Ni and P1 Ni is the lower incidence of double-bond isomerization observed with P1 Ni vs. Ra Ni (3% vs. 20%). P1 Ni reduces mono-, di-, tri-, and tetrasubstituted alkenes under mild conditions (1 atm H_2, rt) while leaving many groups unaffected (e.g. a phenyl ring). There is a significant difference in the rate of reduction among the various substituted alkenes allowing for selectivity. However, P2 Ni is very sensitive to steric hindrance and to the alkene substitution pattern. Little or no hydrogenolysis of allylic, benzylic, or propargylic substituents is observed with this catalyst; partial reduction of alkynes and dienes are also possible. Some examples of the use of P2 Ni as a hydrogenation catalyst are shown in Table 1.

Table 1 Reduction of Alkenes, Dienes, and Alkynes with P2 Ni

Substrate	Product	Yield (%)	Ref.
1-Hexyne	Hexane	16	9a
	1-Hexene	68	
	Starting material	16	
3-Hexyne	Hexane	1	9a
	cis-3-Hexene	96	
	trans-3-Hexene	3	
2-Methyl-1,5-hexadiene	2-Methylhexane	2	9a
	2-Methyl-1-hexene	96	
	Other methylhexenes	2	
1,3-Cyclohexadiene	Cyclohexane	2	9a
	Cyclohexene	89	
	Benzene	9	
1-Penten-3-ol	3-Pentanol	100	9a
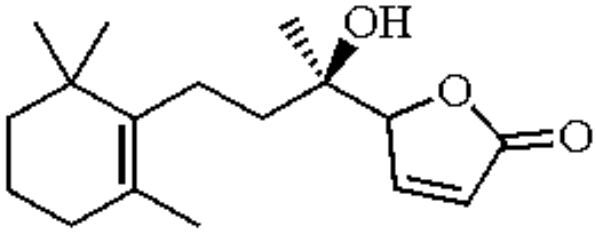	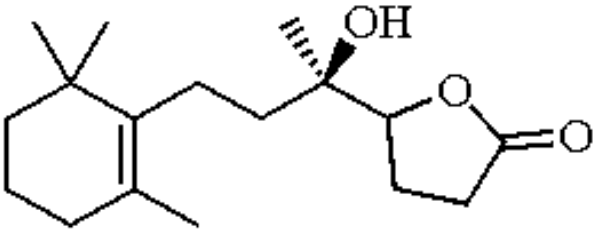	94	14
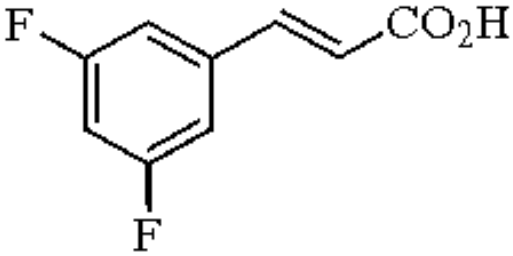	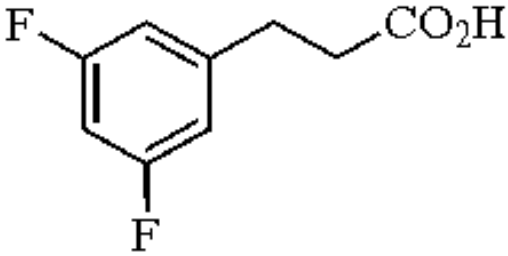	75	15

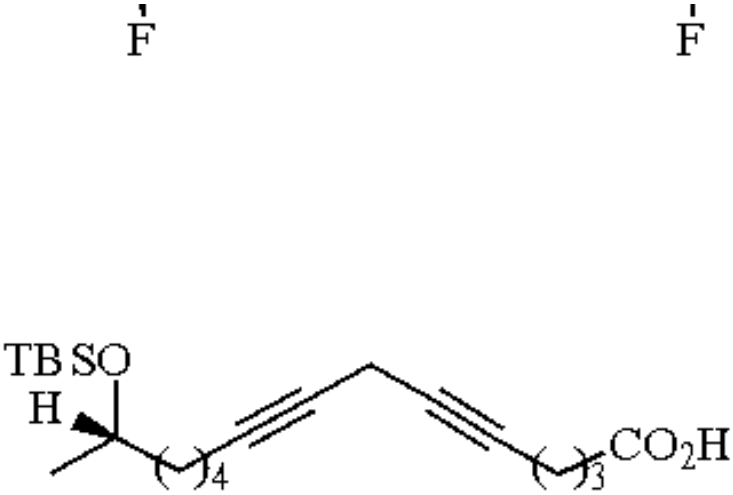	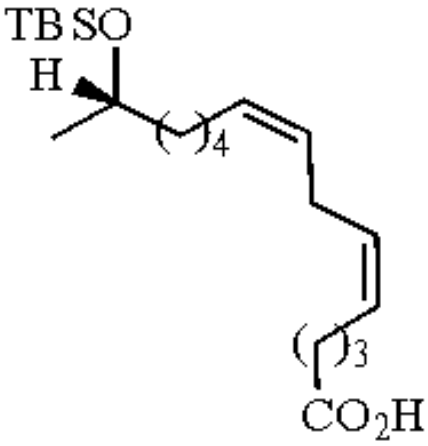	100	16
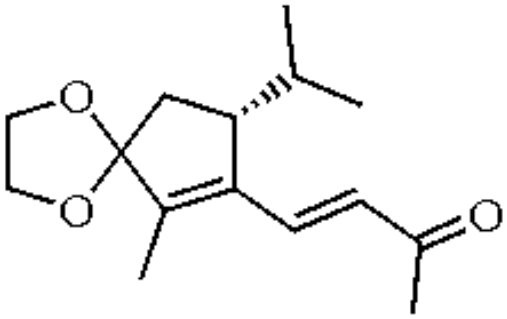	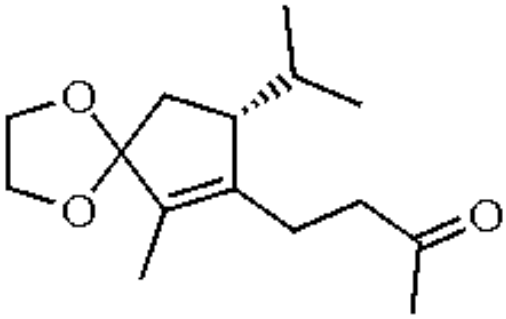	70	17
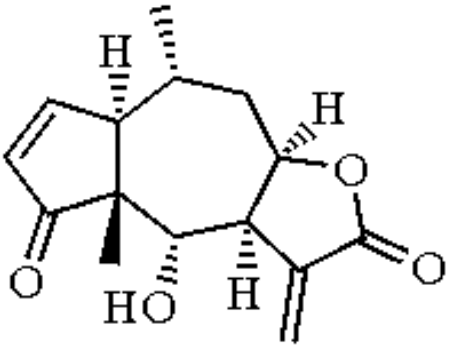	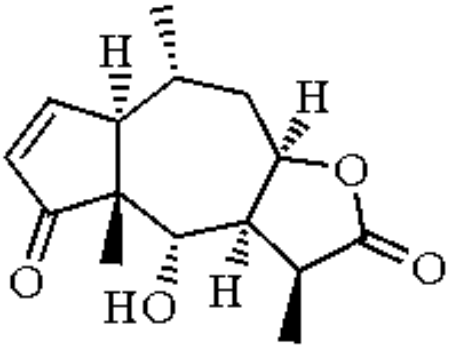	50	18

Under more forcing conditions (30 psi in a Parr apparatus), Russell[19] was able to reduce unsaturated ethers, alcohols, aldehydes, esters, amines, and amides to their saturated counterparts without hydrogenolysis. Unsaturated nitriles[19b] were reduced to primary amines while epoxides were unaffected by the reagent. Both dimethoxyborane (eq 1)[20] and ***Lithium Aluminum Hydride*** (eq 2)[21] can replace $NaBH_4$ in these reactions.

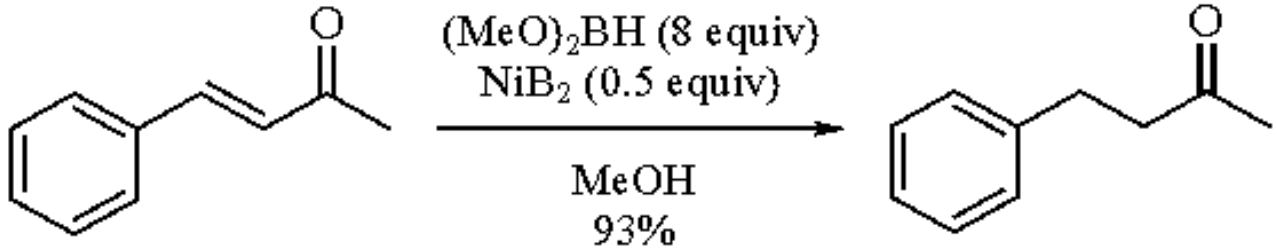

(1)

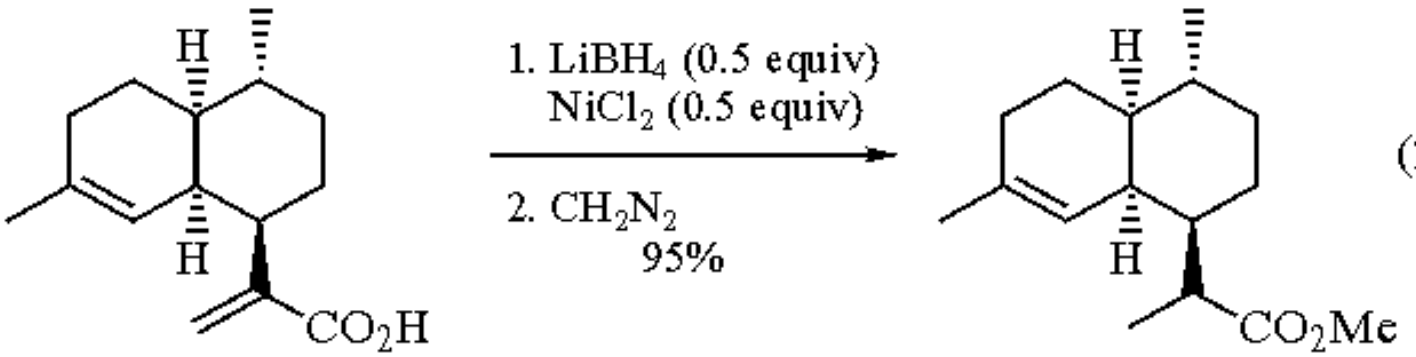

(2)

Heteroarenes.

Nose and Kudo[22] examined the reduction of quinaldine (**1**) with a variety of transition metal salts ($CoCl_2$, $NiCl_2$, $CuCl_2$, $CrCl_3$) in the presence of $NaBH_4$; only ***Nickel(II) Chloride*** was effective (eq 3).

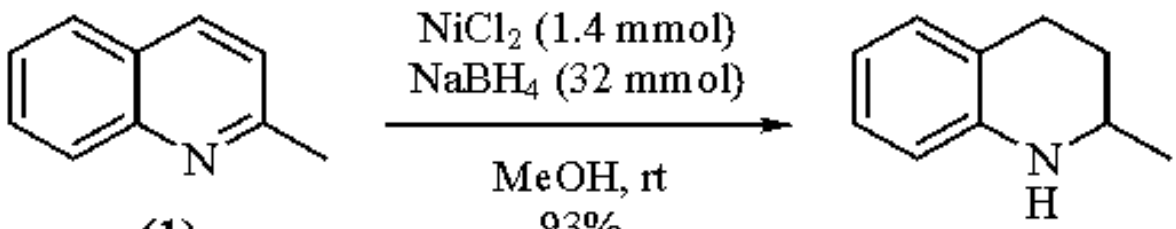

(1) (3)

Partial reduction of a series of heteroaromatics was examined using $NiCl_2/NaBH_4$ in methanol at room temperature (Table 2). The authors suggest that the reduction proceeds through a $NiCl_2$ complex of the arene; however, other workers[1a] dispute this mechanism.

Table 2 Reduction of Heteroaromatics with $NiCl_2/NaBH_4$

Substrate	Product	Yield (%)
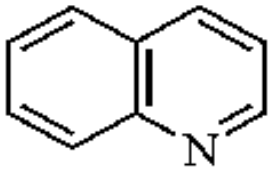	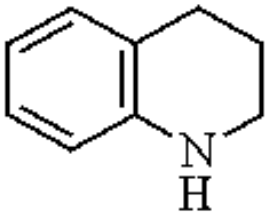	83

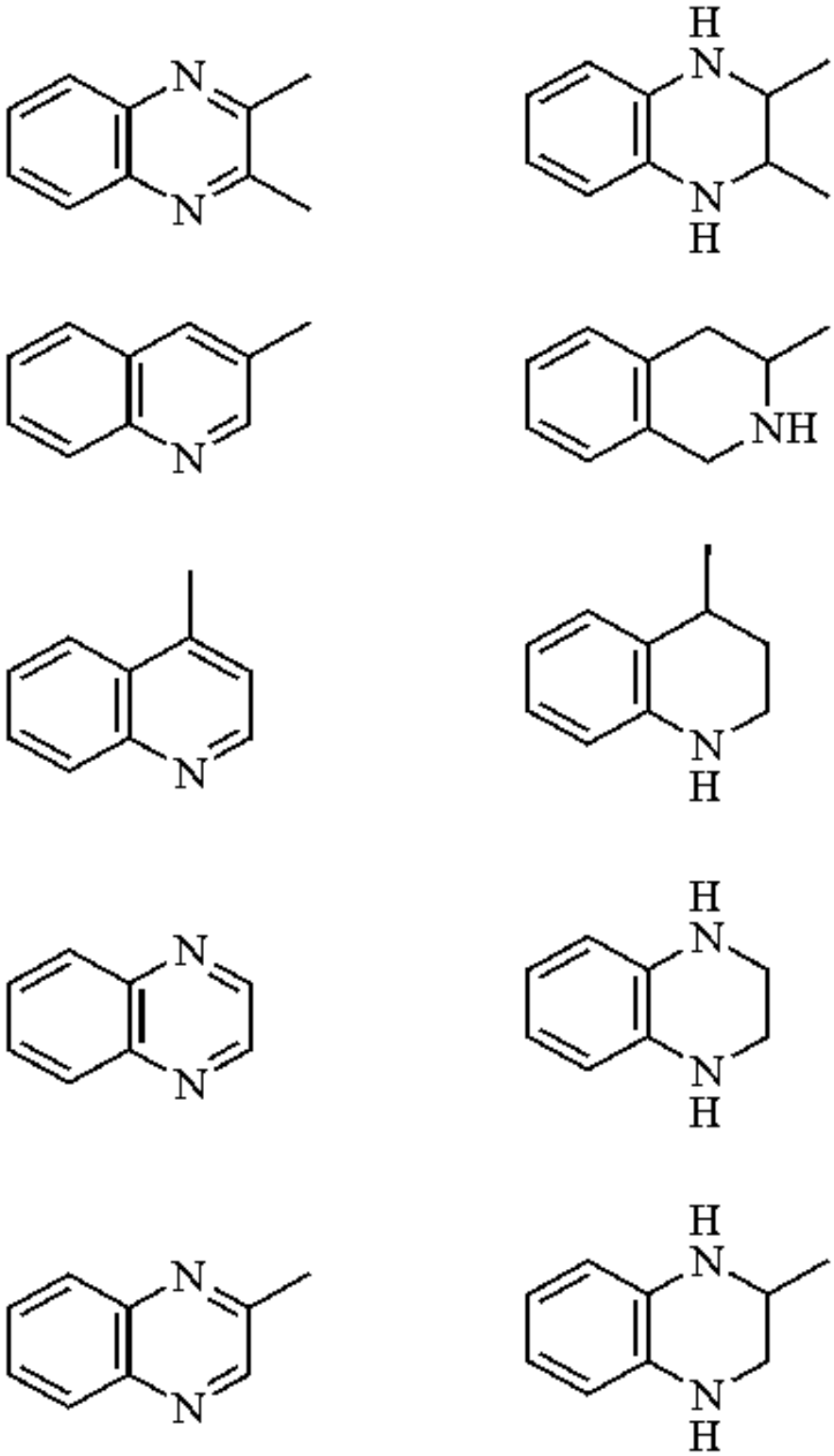

	99
	96
	83
	54
	52

Desulfurization.

While Raney nickel[23] is the traditional reagent for desulfurization reactions, it has several drawbacks (i.e. strongly basic, pyrophoric, sensitivity to air and moisture). In 1963, Truce and Roberts[24] reported the use of $NiCl_2/NaBH_4$ in the partial cleavage of a dithioacetal (eq 4).

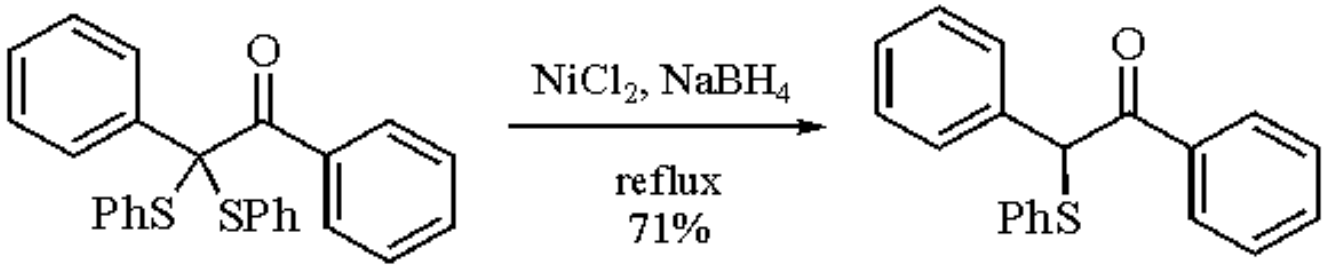

(4)

Since then, there have been numerous examples of the use of Ni^{II} salt/$NaBH_4$ in desulfurization reactions;[4] in many cases the yields are greater than those seen with Raney nickel[25] (eq 5) *(note: caution must be exercised when using $NaBH_4$ in DMF)*.

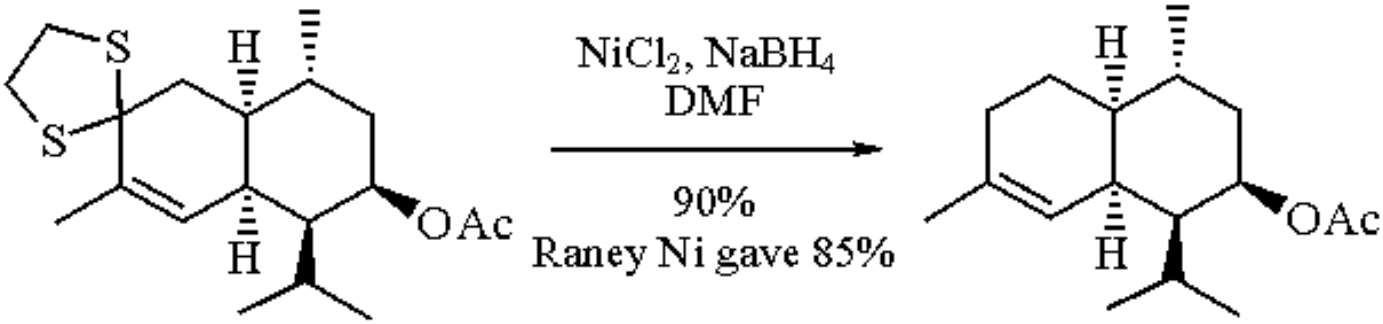

(5)

Boar et al.[26] used nickel boride in a protection-deprotection scheme for triterpenoid ketones (eq 6).

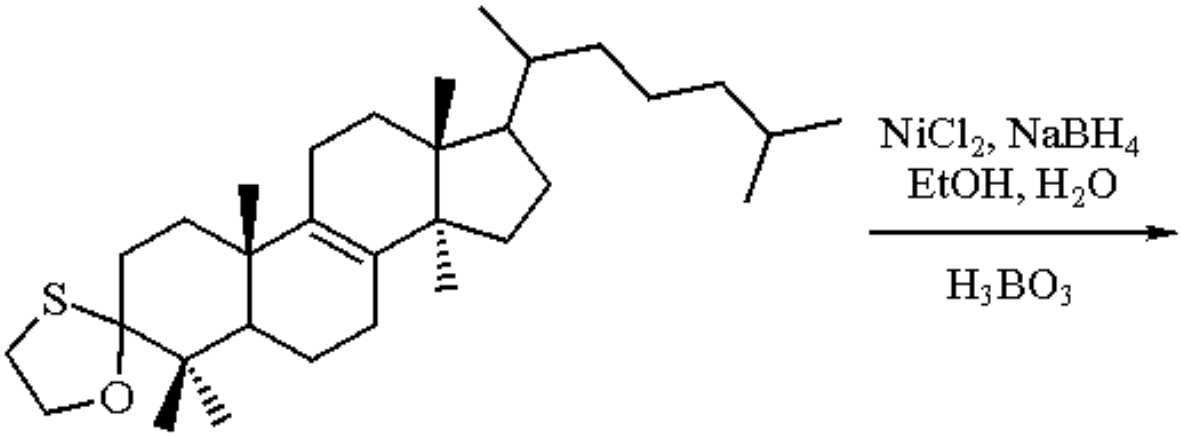

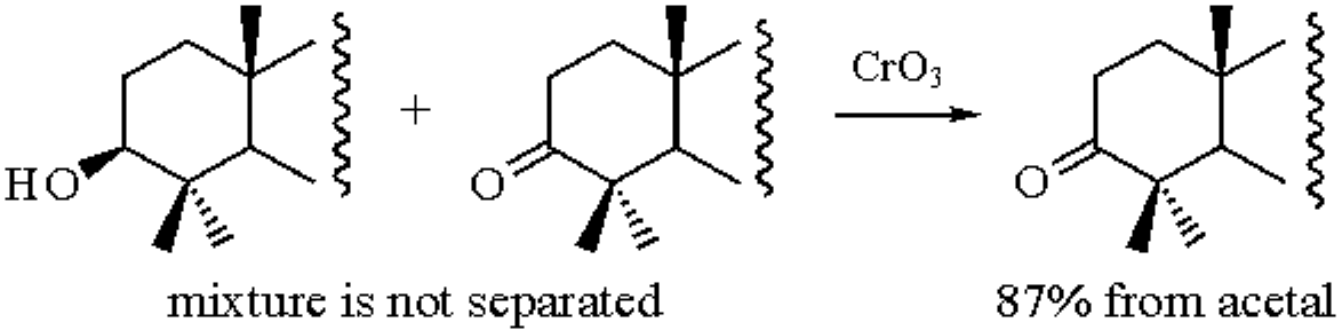

(6)

$Ni^{II}/NaBH_4$ is an effective reagent for desulfurization of thioamides,[27] thioethers,[28] and sulfides.[4,29] Back and co-

workers[4,30] has reported extensive studies of the scope, stereochemistry, and mechanism of nickel (and cobalt) boride desulfurizations. In general, nickel boride is a more effective desulfurization catalyst than ***Cobalt Boride*** (other metals such as Mo, Ti, Cu, and Fe were completely ineffective). ***Lithium Borohydride*** can be used in place of $NaBH_4$ while ***Sodium Cyanoborohydride*** cannot. Sulfides, thioesters, thiols, disulfides, and sulfoxides are reduced to hydrocarbons by Ni_2B, while sulfoxides are stable. Esters, chloro groups, and phenyl groups are stable to Ni_2B. Iodides, nitro groups, nitriles, and alkenes are reduced completely by Ni_2B, while bromides, aldehydes, ketones, and cyclopropanes show variable reactivity (eqs 7-10).

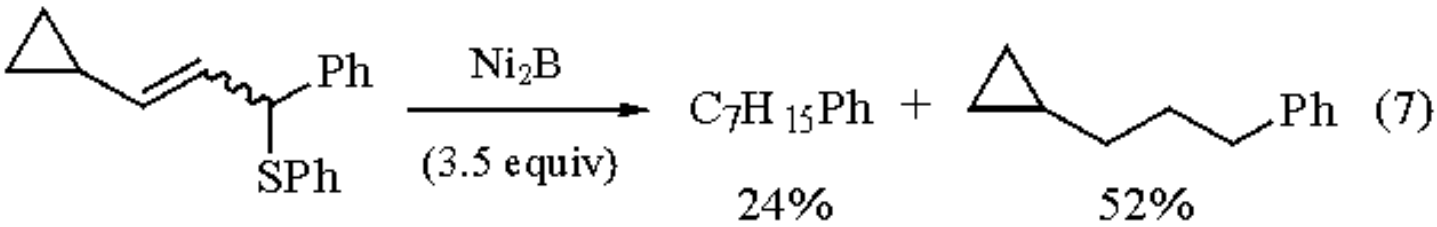

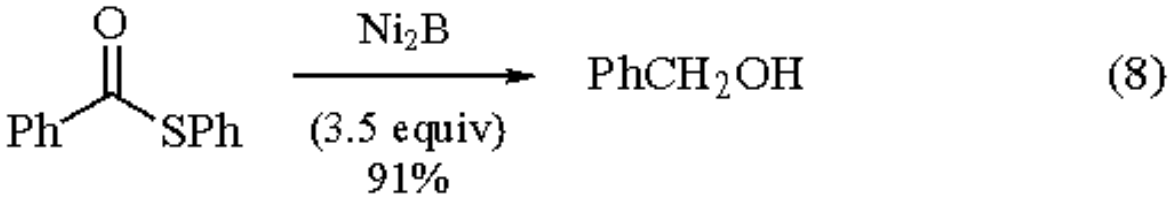

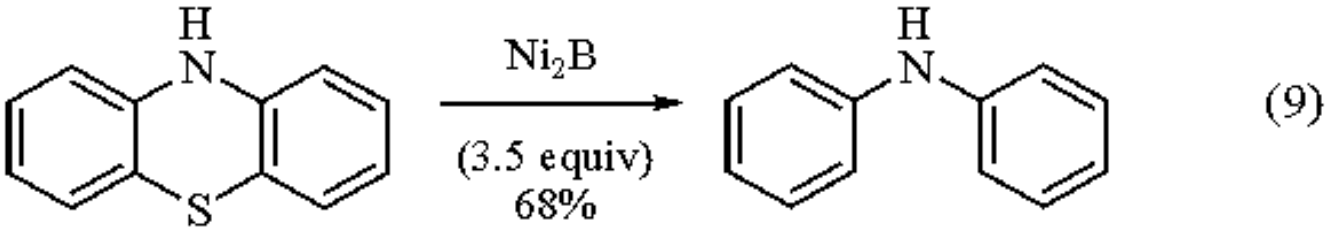

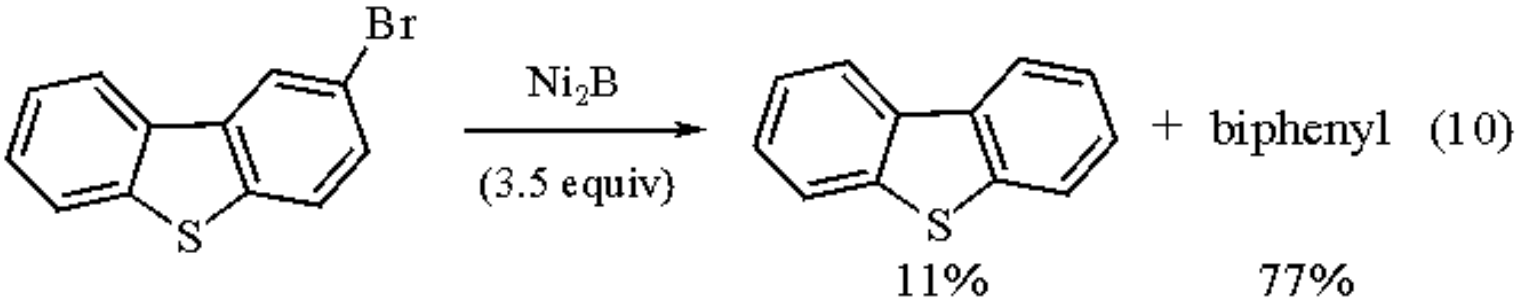

Using deuterium labelling, Back showed that desulfurization occurs with retention of configuration, unlike Raney nickel, which involved a radical mechanism. The suggested mechanism of desulfurization involves an oxidative addition-reductive elimination sequence via a nickel hydride intermediate.

Reduction of Other Nitrogenous Functional Groups.

Primary, secondary, and tertiary aliphatic nitro groups are reduced to amines with $NiCl_2/NaBH_4$.[5c] ***Hydrazine*** hydrate has also been used with Ni_2B to reduce both aryl and aliphatic nitro groups in a synthesis of tryptamine (eqs 11 and 12).[31]

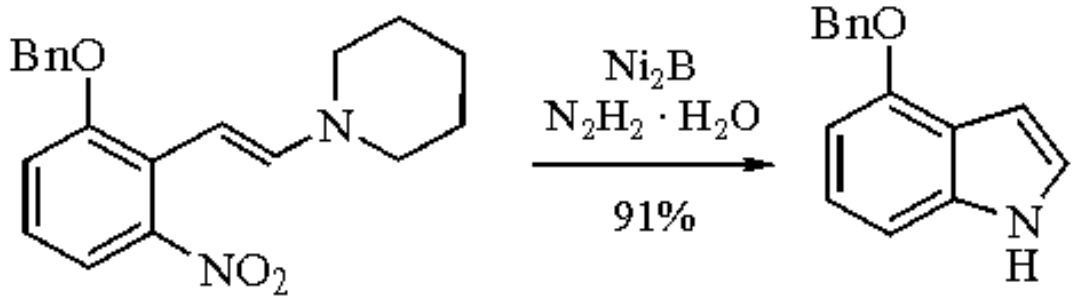

(11)

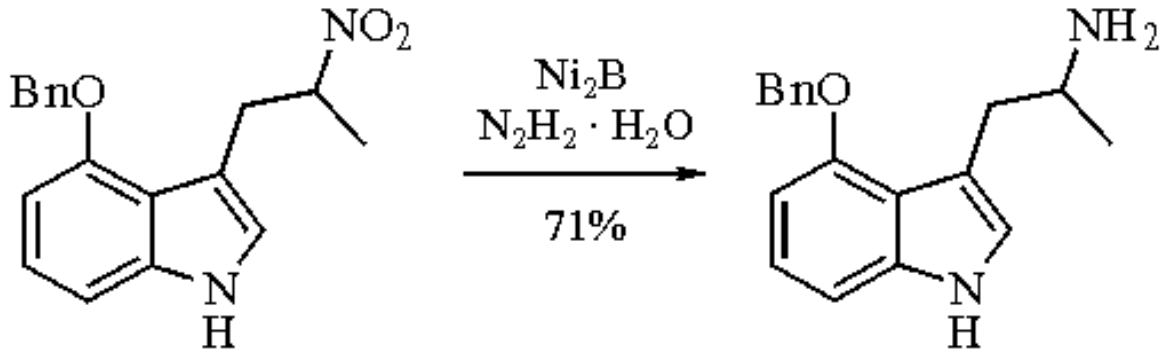

(12)

Reductive cleavage of thioethers and reduction of nitro groups has been combined in a synthesis of pyrrolidones (eq 13).[32]

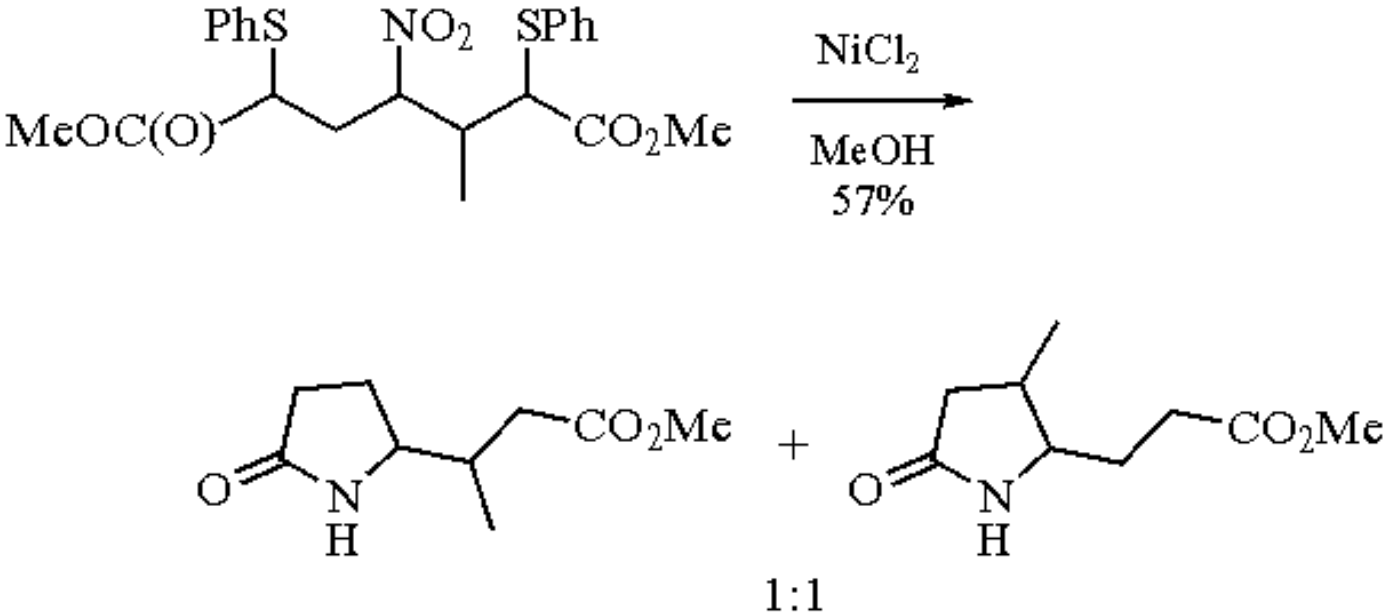

(13)

Like Co_2B, Ni_2B[5b] reduces nitroarenes to anilines and azoxybenzenes to azobenzenes (Table 3); unlike Co_2B, Ni_2B reduces oximes[33] to amines (Table 4).

Table 3 Reduction of Nitroarenes with Ni^{II}/Borohydride Reagents

Substrate	Reagent	Product	Yield (%)
$PhNO_2$	2 equiv Ni_2B, MeOH	$PhNH_2$	3[5a]
$PhNO_2$	1 equiv Ni_2B, 15N NH_4OH	$PhNH_2$	96[5a]
$PhNO_2$	0.1 equiv Ni_2B, 5 equiv $NaBH_4$	Azoxybenzene	89[5b]
$4\text{-}ClC_6H_4NO_2$	1 equiv Ni_2B, 3N HCl	$4\text{-}ClC_6H_4NH_2$	96[5a]
$4\text{-}CNC_6H_4NO_2$	2 equiv Ni_2B, 3N HCl	$4\text{-}CNC_6H_4NH_2$	60[5a]
6-Nitroquinoline	1 equiv Ni_2B, 15N NH_4OH	6-Aminoquinoline	86[5a]
1-Nitronaphthalene	$NiCl_2$-$NaBH_4$ (2:1)	1-Aminonaphthalene	85[5d]
$4\text{-}IC_6H_4NO_2$	4 equiv Ni_2B, 1N HCl	$4\text{-}IC_6H_4NH_2$	76[34]
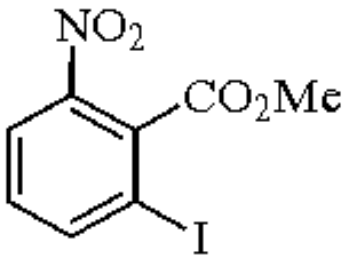	4 equiv Ni_2B, 1N HCl	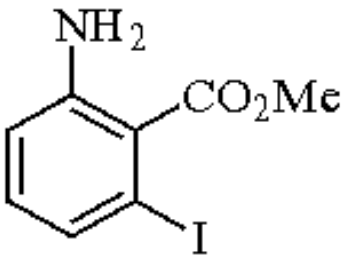	85[34]

Table 4 Reduction of Oximes to Amines with $NiCl_2/NaBH_4$

Substrate	Product	Yield (%)
	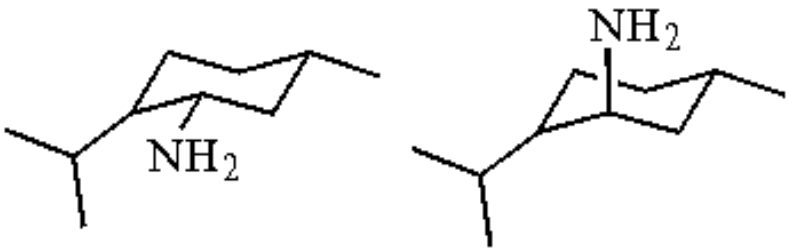 1:2	92
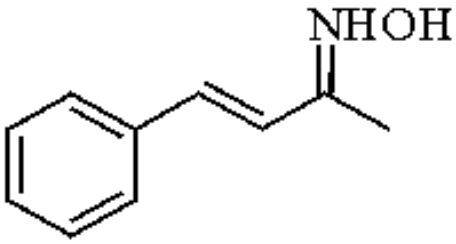	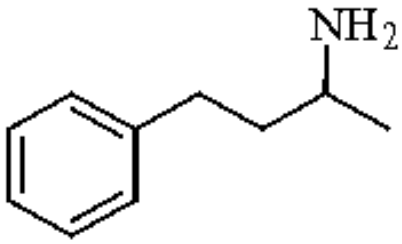	95
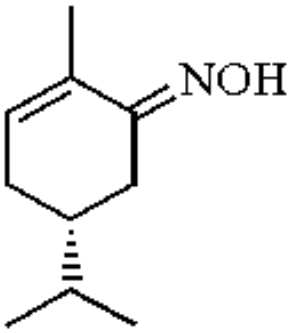	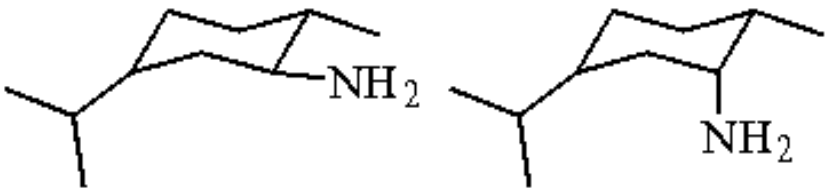 1:1	90
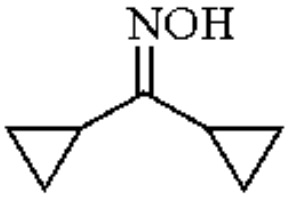	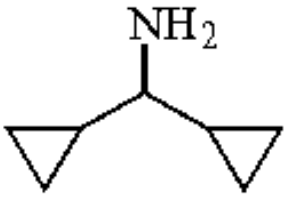	70

Reduction of Other Nitrogenous Functional Groups.

Borane-Tetrahydrofuran/$NiCl_2$ has been used to reduce chiral cyanohydrins to ethanol amines in high yield.[35] Azides are cleanly reduced to amines in good yield with nickel boride.[36] Azides are reduced in preference to hindered aliphatic nitro groups (eq 14).[37]

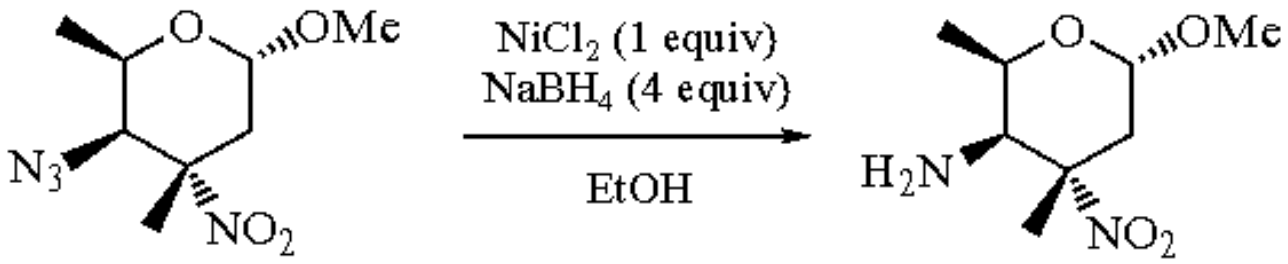

(14)

Isoxazoles are reduced to β-amino enones in high yield using the $NiCl_2/NaBH_4$ system.[38] Dihydroisoxazolones are reduced with a high degree of diastereoselectivity with the $NiCl_2/NaBH_4$ system.[39]

Dehalogenation.

Many α-bromo ketones[6a] are cleanly reduced to the parent ketone with nickel boride in DMF (caution). Vicinal dibromides are reduced to alkenes (eq 15).

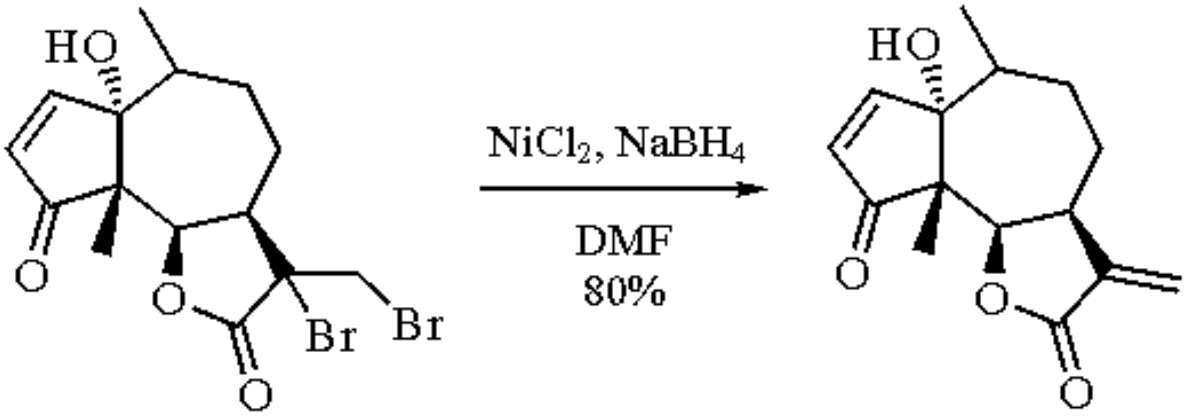

(15)

Aryl and certain alkyl chlorides can be dehalogenated[1a,1b,6b] with a variety of Ni^{II}/hydride agents (e.g. $NaBH_2(OCH_2CH_2OMe)_2$, ***Triethylsilane***, $NaBH_4$). Lin and Roth have effected the clean debromination of aryl bromides[40] using ***Dichlorobis(triphenylphosphine)nickel(II)***/$NaBH_4$ in DMF (**caution**); ***Tris(triphenylphosphine)nickel(0)*** is assumed to be the active catalyst. Russel and Liu[41] demonstrated that reductive cleavage of an iodide goes with retention when $NiCl_2/NaBH_4$ is used (cf. inversion seen with $LiAlH_4$; eq 16).

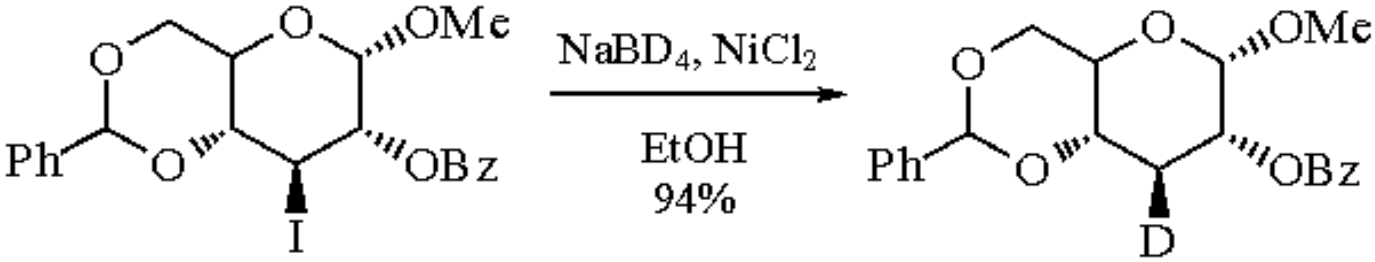

(16)

Hydrogenolysis.

Ni_2B has been used to hydrogenolyze benzylic (eqs 17-19),[7a] allylic (eqs 20-22),[7b,42] and propargylic (eq 23)[7b] esters in good yields.

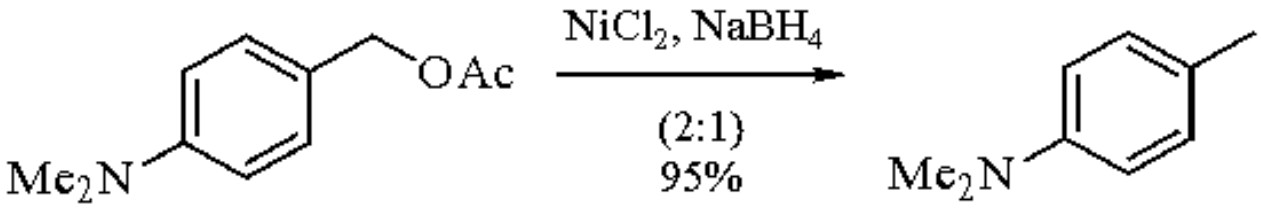

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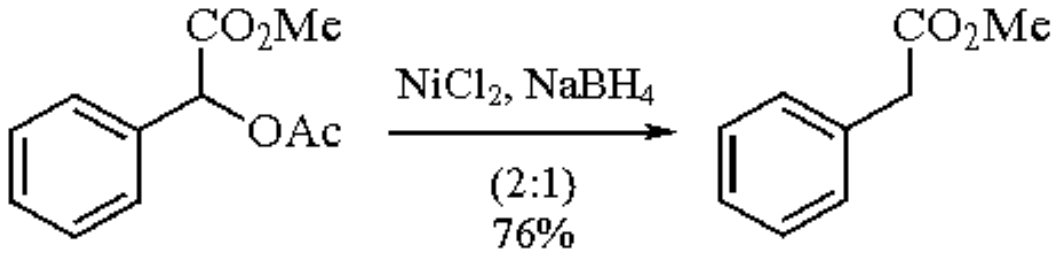

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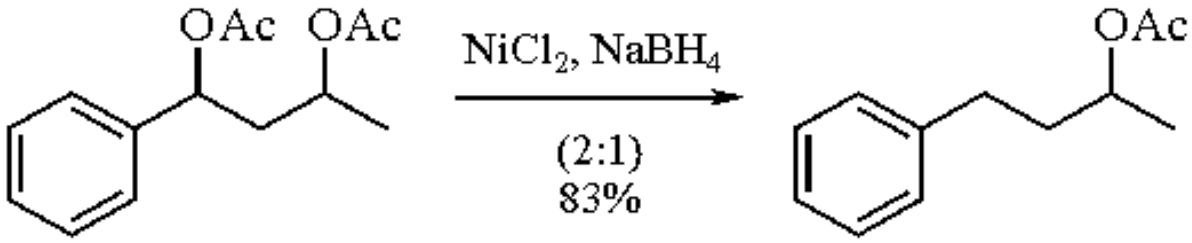

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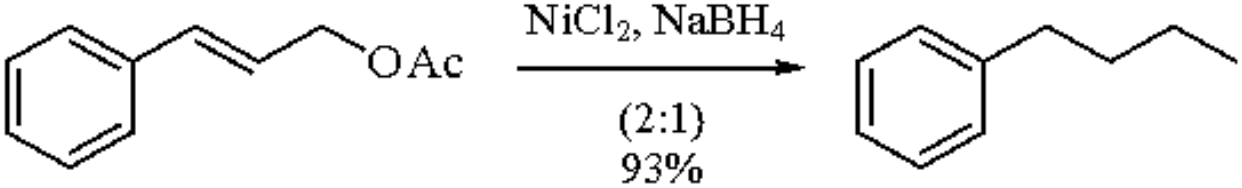

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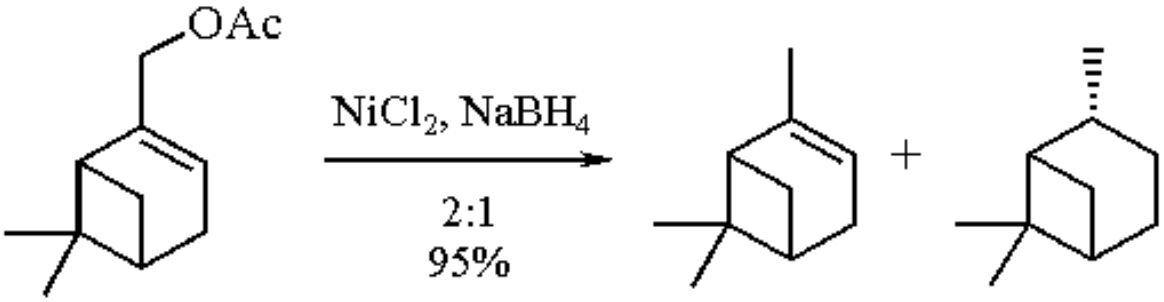

(21)

1:1

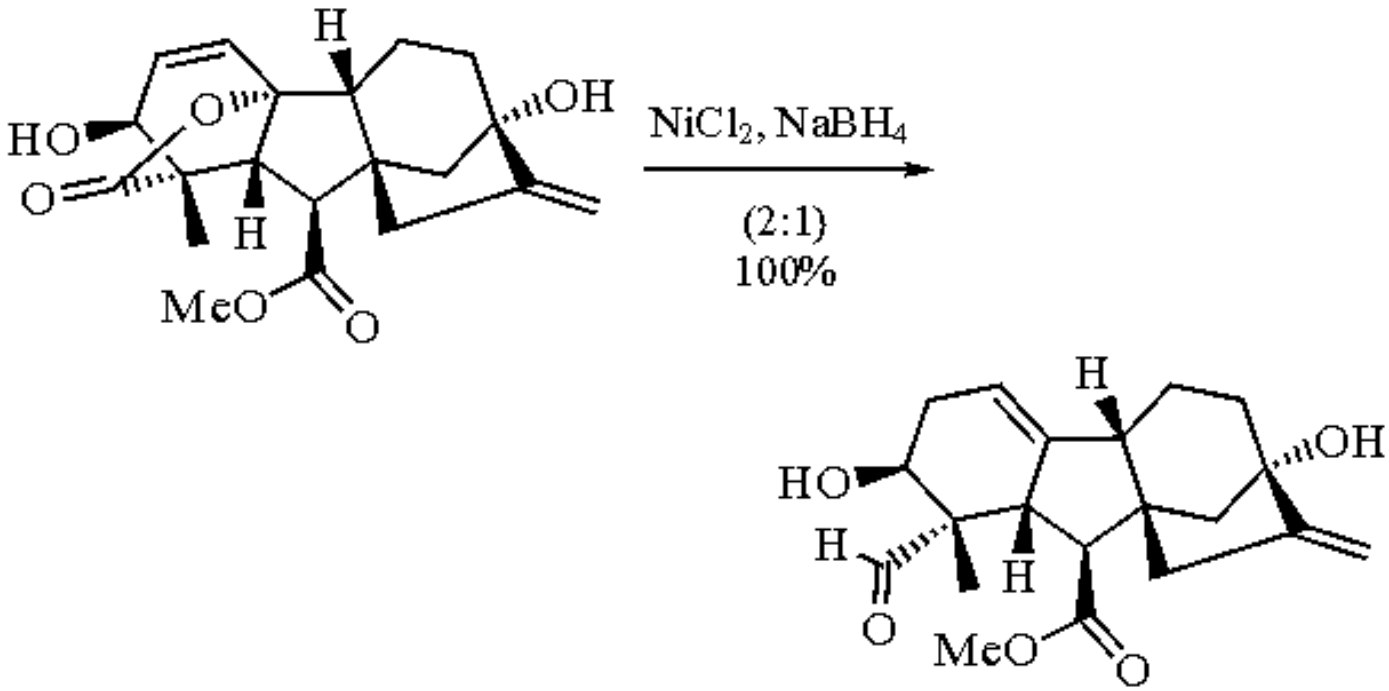

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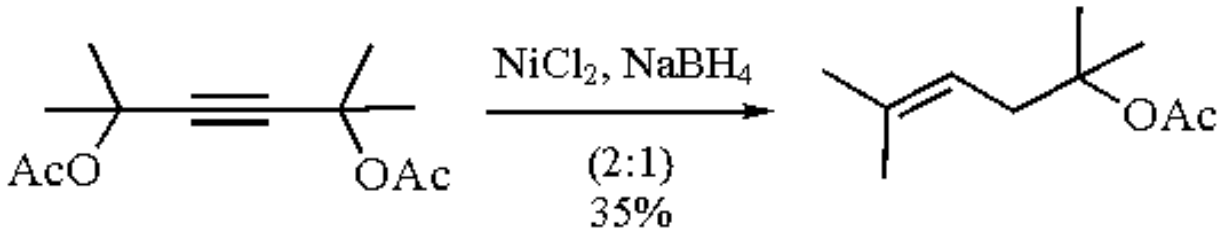

(23)

Enol tosylates and aryl tosylates are deoxygenated in good to excellent yields[43] (eqs 24 and 25)

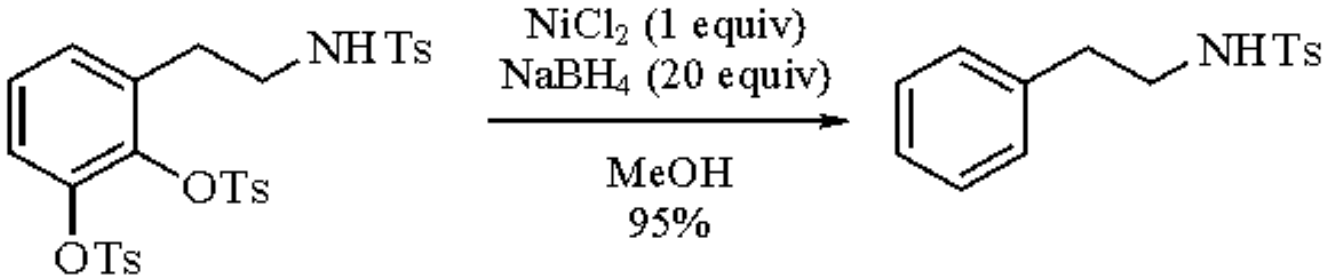

(24)

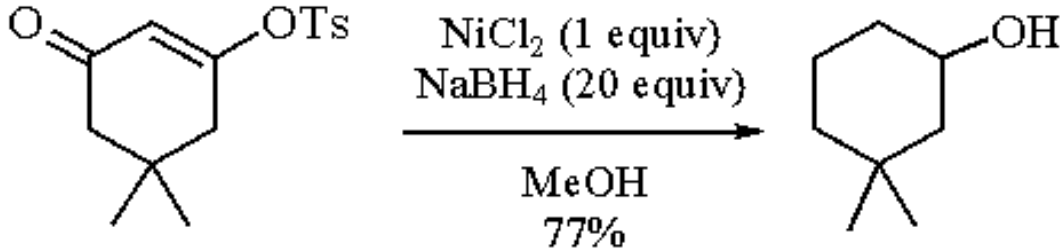

(25)

A variety of allylic functional groups[44] (alcohols, esters, silyl ethers, ketones, and hydroperoxides) have been reduced with Ni_2B. The combination of ***Chlorotrimethylsilane***/Ni_2B will selectively reduce an aldehyde in the presence of a ketone.[45]

Selenides[46] and tellurides[47] are reductively cleaved by Ni_2B with retention of stereochemistry. The phenyl selenyl group is

cleaved in preference to the thio phenyl group.

---

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2. It should be noted that Ni_2B represents a nominal stoichiometry for the reagent prepared by the action of $NaBH_4$ on a Ni^{II} salt. Several Ni_xB_y species have been described in the literature. *Chemical Abstracts* uses the registry number [*12619-90-8*] to designate nickel boride of unspecified stoichiometry. [*12007-02-2*] and [*12007-00-0*] are the registry numbers for Ni_3B and NiB, respectively. These are the most widely cited synthetically useful reagents.
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8. This is the melting point of Ni_2B formed by fusion of the elements *Adv. Chem. Ser.* **1961**, *32*, 53). Material prepared by the reduction of $NiCl_2$ with $NaBH_4$ begins to decompose at 100 °C when heated in vacuo with liberation of H_2 (Maybury, P. C.; Mitchell, R. W.; Hawthorne, M. F. *JCS(C)* **1974**, 534).
9. (a) This procedure provides the P2 form of nickel boride, which is a selective hydrogenation catalyst. Brown, H. C.; Brown, C. A. *JACS* **1963**, *85*, 1005. (b) Brown, H. C.; Brown, C. A. *JACS* **1963**, *85*, 1003. This paper reports the preparation and properties of P1 nickel boride. P1 nickel boride is more active, in some applications, than Raney nickel. (c) Destefanis, H.; Acosta, D.; Gonzo, E. *Catal. Today* **1992**, *15*, 555. This group describes the use of BH_3.THF complex to prepare Ni_3B and Ni_4B_3 using $Ni(OAc)_2$ and $NiCl_2$, respectively, and their use as hydrogenation catalysts.
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Nickel(II) Bromide

$NiBr_2$

($NiBr_2$)

[13462-88-9] · Br_2Ni · Nickel(II) Bromide · (MW 218.49) ($NiBr_2.2H_2O$)

[13596-19-5] · $Br_2H_4NiO_2$ · Nickel(II) Bromide · (MW 254.53) ($NiBr_2.3H_2O$)

[7789-49-3] · $Br_2H_6NiO_3$ · Nickel(II) Bromide · (MW 272.55) ($NiBr_2.6H_2O$)

[18721-96-5] · $Br_2H_{12}NiO_6$ · Nickel(II) Bromide · (MW 326.61)

(mild Lewis acid for displacement;[1-4] catalyst in cross-coupling reactions,[5-9] and in combination with reducing agent for homocoupling reactions[11-15])

Physical Data: mp 963 °C; *d* 5.098 g cm^{-3}.

Solubility: sol water, alcohol, ether.

Form Supplied in: yellowish green for hydrate; golden yellow when anhydrous; widely available.
Drying: anhydrous nickel bromide can be obtained by heating at 300 °C and storing in a desiccator.

Handling, Storage, and Precautions: nickel(II) is reputed to be toxic and a cancer suspect agent. Use in a fume hood.

General Considerations.

Most reactions promoted by ***Nickel(II) Chloride*** can also be mediated by nickel(II) bromide. This section covers certain specific applications using nickel bromide as a reagent.

Displacement Reactions.

Li_2NiBr_4 prepared from anhydrous ***Lithium Bromide*** and $NiBr_2$ in THF serves as a source of soft nucleophilic bromide and reacts regioselectively with epoxides to give bromohydrins in high yield (eq 1).[1]

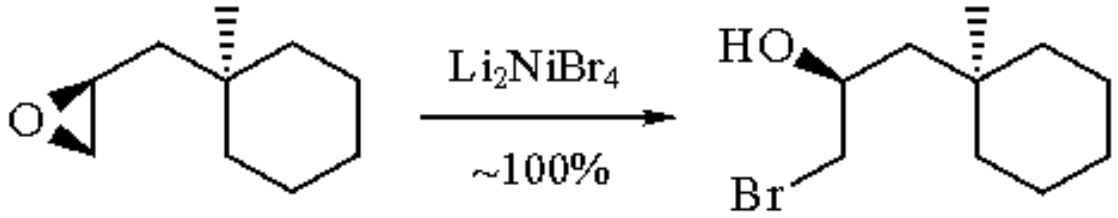

(1)

Like $NiCl_2$, reduction of $NiBr_2$ with a number of reducing agents generates useful catalytic species. To illustrate this, $NiBr_2$-***Zinc*** can catalyze the halogen exchange reaction of aryl bromides with ***Potassium Iodide*** under mild conditions.[2] At elevated temperature, $NiBr_2$-***Tri-n-butylphosphine*** is also an effective catalyst for this transformation. With a catalytic amount of a Ni^0 complex generated in situ from $NiBr_2$, ***1,1´-Bis(diphenylphosphino)ferrocene***, and zinc powder, aryl thiols react with an equimolar amount of aryl iodide at 25 °C or bromide at 60 °C to afford symmetric aryl sulfides in excellent yields (eq 2).[3]

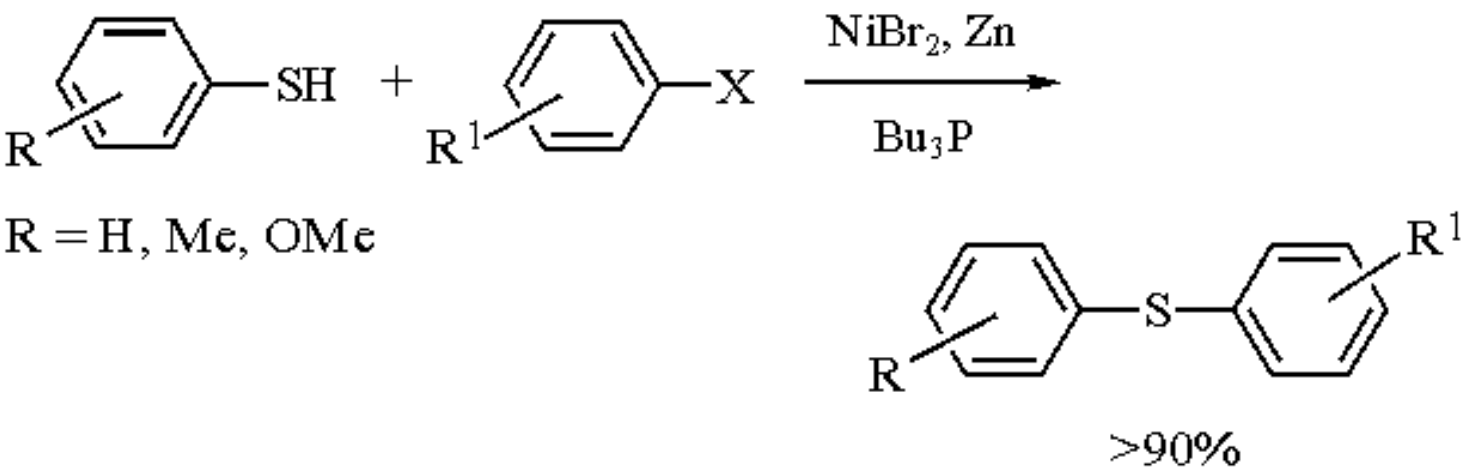

(2)

The conversion of aryl and vinyl bromides into the corresponding iodides is also achieved using a low-valent nickel catalyst generated in situ.[4] This reaction turns out to be useful to activate the carbon-chlorine bond in aryl chlorides in the Heck reaction (eq 3).[4e]

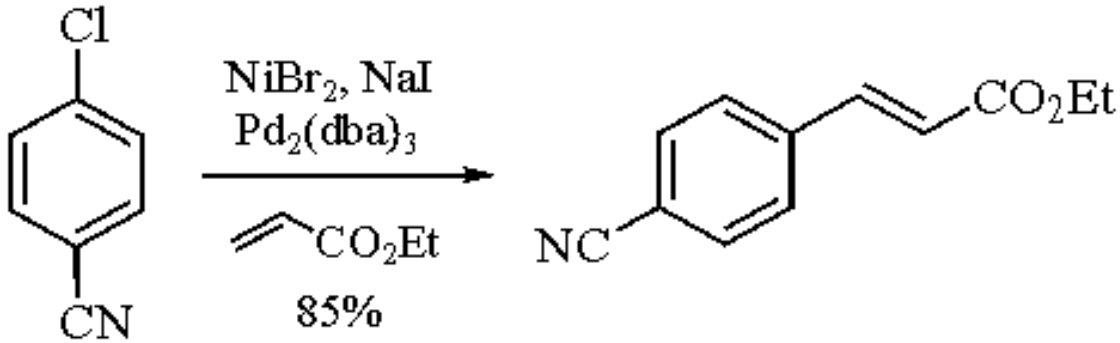

(3)

$NiBr_2$-BuLi.

The addition of ***n-Butyllithium*** to a suspension of $NiBr_2$ in THF at -78 °C forms material which catalyzes an efficient substitution reaction of lithium ester enolates with aryl or vinyl bromides or iodides (eqs 4 and 5).[5] The reaction occurs with clean retention of stereochemistry at the halogen-bearing carbon. Addition of phosphine ligands gives

totally inactive material.

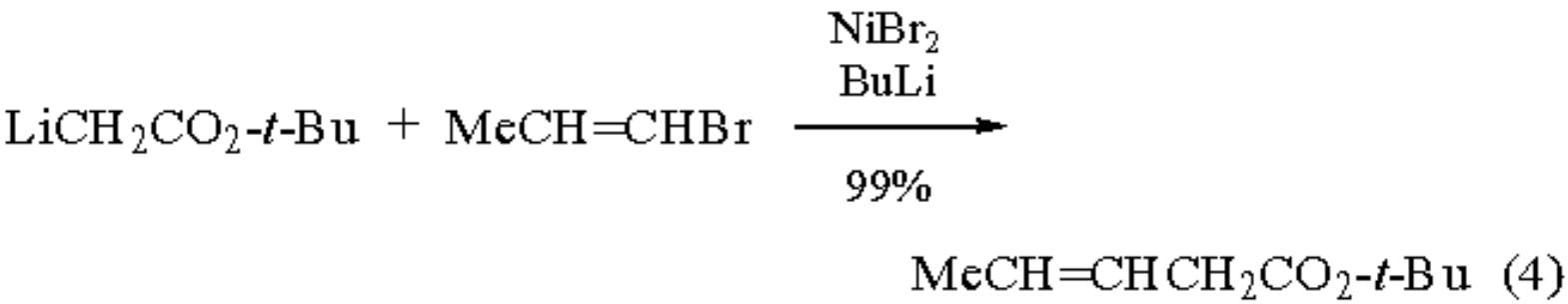

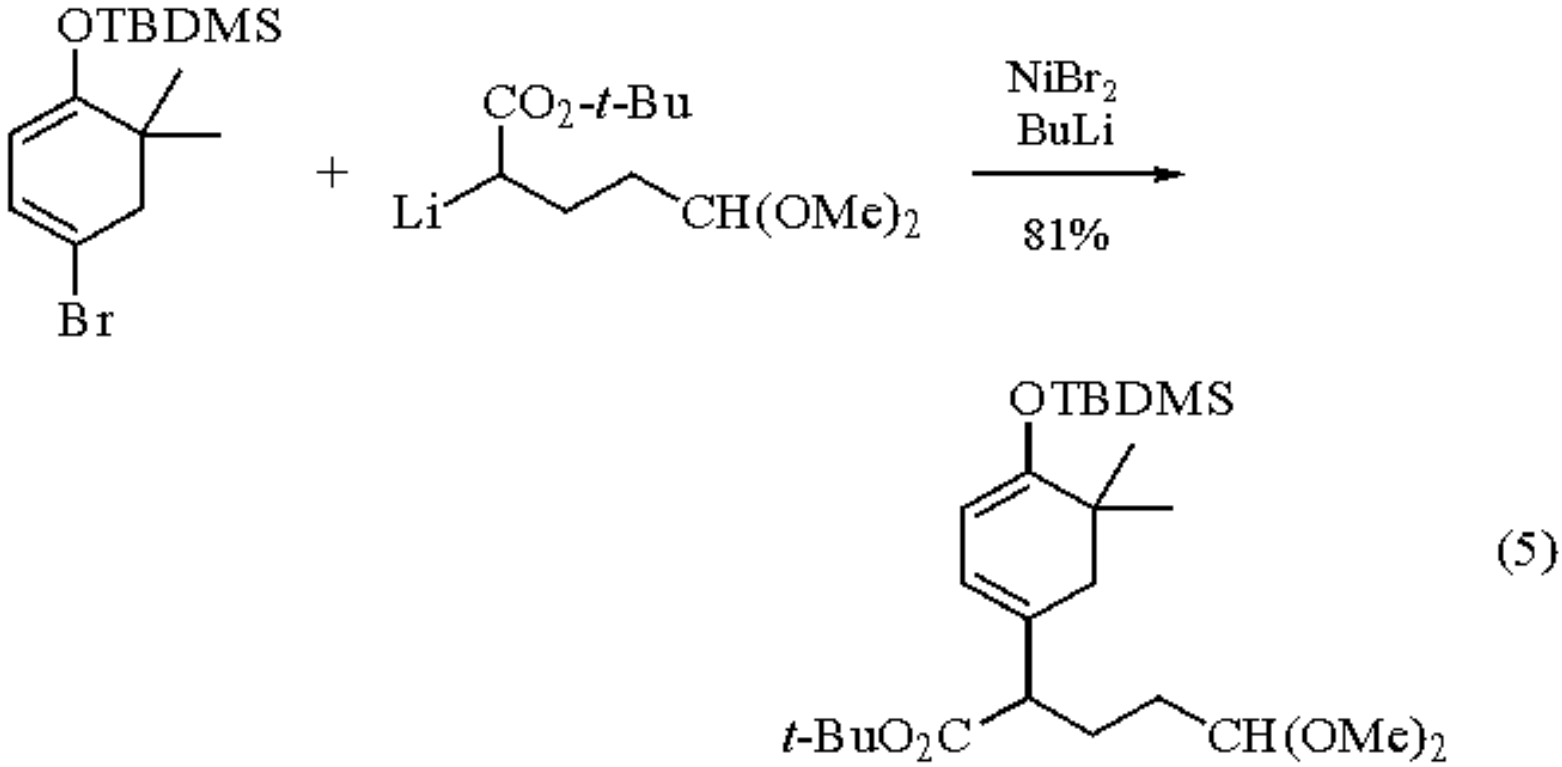

Cross-Coupling Reactions.

Most nickel-promoted cross-coupling reactions use nickel halide phosphine complexes as the catalyst and are discussed under ***Nickel(II) Chloride***. The addition of the phosphine ligand to a solution of nickel bromide also serves as a useful catalytic system for this purpose. For example, enol phosphates are converted into the corresponding allylsilanes when trimethylsilylalkyl Grignard reagents are employed (eq 6).[6]

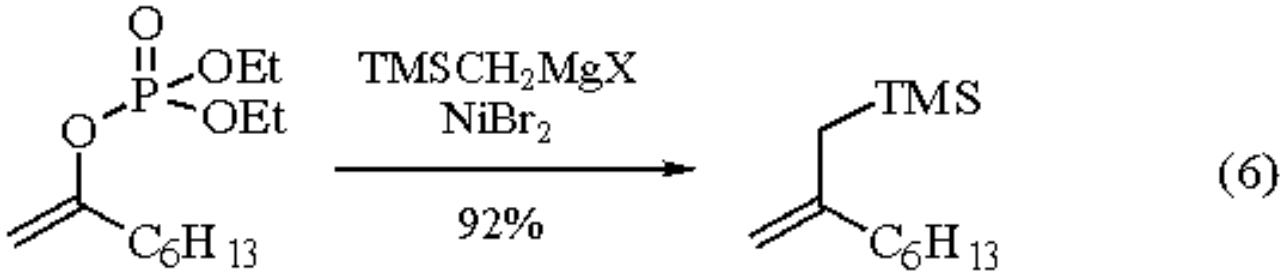

Nickel bromide has been shown to convert aryl bromides into the corresponding aryl phosphine derivatives (eqs 7-9).[7]

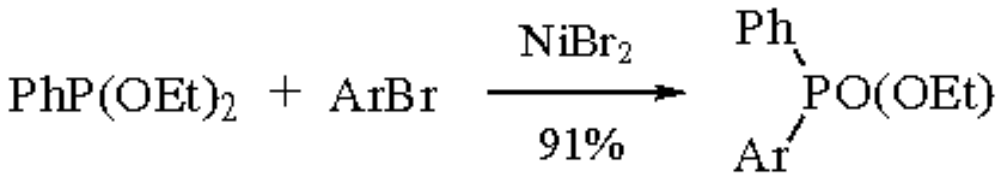

(7)

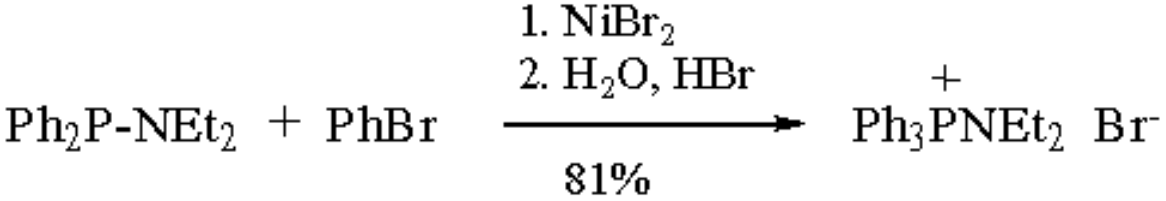

(8)

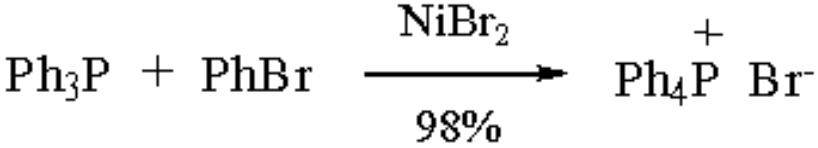

(9)

$NiBr_2$ catalyzes the reaction of aryl iodides with red phosphorus to give triphenylphosphine oxide in excellent yield after hydrolysis (eq 10). Under modified conditions, triphenylphosphine is obtained (eq 11).[8]

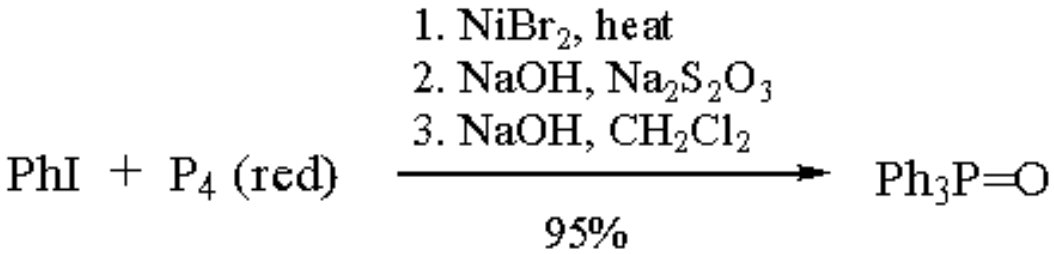

(10)

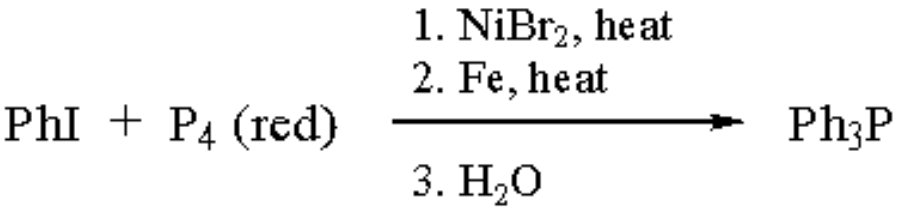

(11)

Five- and six-membered cyclic 3-iodo enones undergo spiroannulation with symmetric internal alkynes in the presence of $NiBr_2$ and zinc powder to afford spiro[4.4]nonadienones and spiro[4.5]decadienones in good to excellent yields at temperatures of 60-100 °C (eq 12).[9]

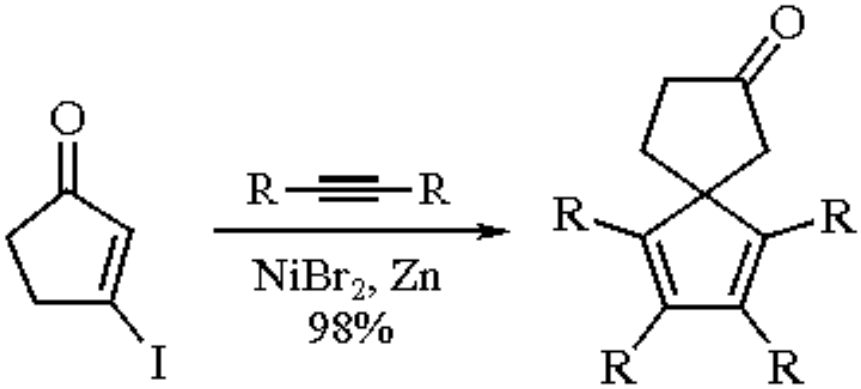

(12)

Miscellaneous.

Primary and secondary alcohols are oxidized to their respective carbonyl compounds in high yield by ***Dibenzoyl Peroxide*** through the action of $NiBr_2$, which serves as an effective mediative catalyst and as an alcohol template in these transformations.[10]

The Ni^0 species generated by electrochemical reduction of the $NiBr_2$(bipy) complex exhibits catalytic activity for the dimerization of aryl, benzyl, alkyl, or vinyl halides in good yields.[11] Zinc plays a similar role as reducing agent in the homocoupling reactions.[12] Like the nickel chloride-mediated reactions, the presence of iodide ion and thiourea accelerates the reaction (eq 13).[13] Aryl bromides can also be efficiently reduced with ***Sodium Hydride*** in the presence of $NiBr_2$.[14] In a manner similar to that observed with the $NiCl_2$ catalyst, the reduction of $NiBr_2$ by magnesium in a boiling THF solution of symmetrical alkynes quantitatively leads to cyclotrimerization products.[15]

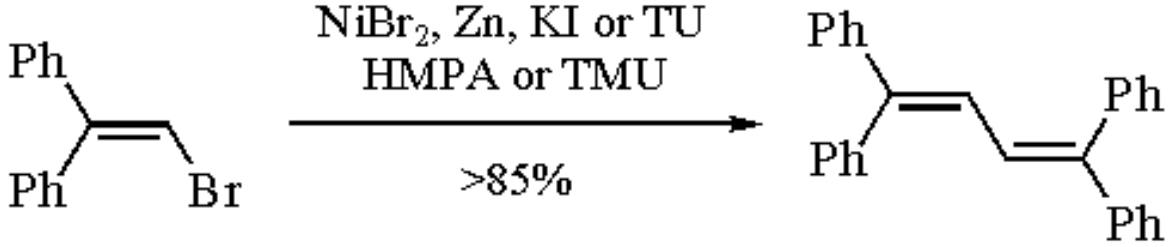

(13)

The reaction of divinylphenylphosphine with 1-phenyl-3,4-dimethylphosphole in the presence of anhydrous $NiBr_2$ leads to the formation of a single diastereomer of the product as the result of two sequential stereoselective intermolecular [4 + 2] Diels-Alder cycloadditions. This reaction provides a facile route to a new type of conformationally rigid tridentate phosphine (eq 14).[16]

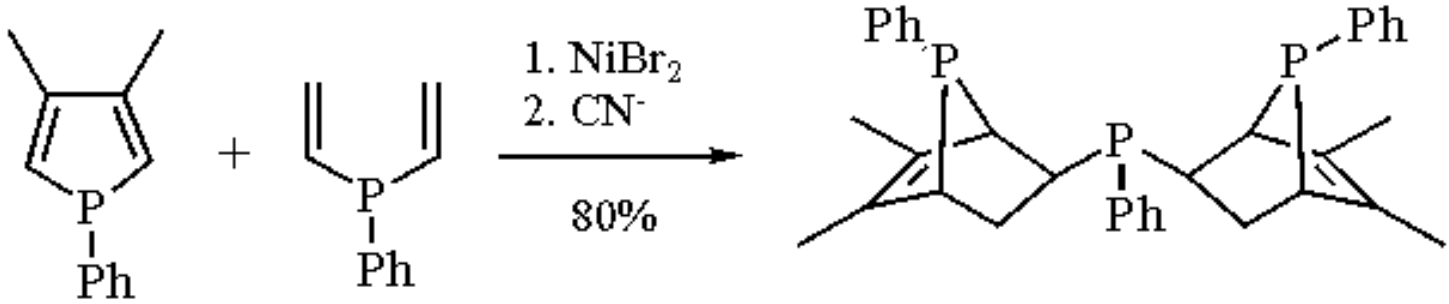

(14)

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Nickel Catalysts (Heterogeneous)

Ni^0

[7440-02-0] · Ni · Nickel Catalysts (Heterogeneous) · (MW 58.71)

(hydrogenolyses and hydrogenations[1])

Physical Data: mp 1453 °C; bp 2730 °C; *d* 8.908 g cm^{-3}.

Form Supplied in: powder, rod, wire, foil, or pellet; 75% nickel on graphite is available.

Preparative Methods: nickel on alumina can be prepared from $Ni(NO_3)_2.6H_2O$ slurried with ***Alumina*** and then dried at 120 °C. The catalyst is activated before use by heating at 400 °C for 30 min.[2]

Handling, Storage, and Precautions: nickel is stable to air, yet care should be taken to avoid moisture when using finely divided nickel catalysts. Nickel is a possible carcinogen. Use in a fume hood.

Heterogeneous Nickel Catalysts.

This class of compounds covers Ni^0 on a variety of supporting media. Raney nickel and Urushibara nickel are discussed under separate headings (see ***Raney Nickel*** and ***Urushibara Nickel***). There have been many significant contributions to this field, yet a comprehensive study of reactions involving these heterogeneous processes has not been produced. Therefore, many of the catalysts described have been applied to only a limited subset of substrates.

Hydrogenolyses.

Hydrogenolysis reactions have been the subject of many studies involving heterogeneous nickel catalysts.[3-6] Most of these reactions have involved the use of substituted adamantanes in the gas phase over supported nickel catalysts (i.e. 30% nickel on alumina). These gas phase hydrogenolyses have been performed upon a variety of functional groups such as halides, amines, alcohols, carboxylic acids, esters, nitriles, ethers, hydroxymethylenes, and halomethylenes.[3] The removal of alkyl groups from substituted adamantanes at elevated temperatures is even possible.[4] Eq 1 demonstrates the temperature dependence of hydrogenolyses utilizing nickel on alumina.[5]

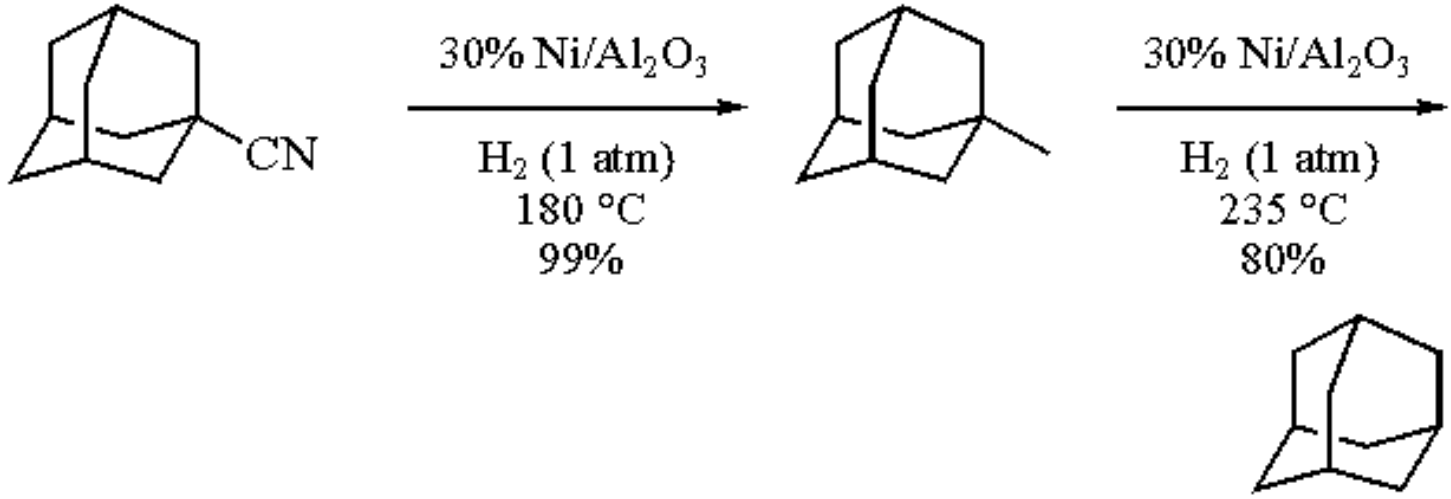

(1)

At lower temperatures the nitrile is hydrogenolyzed to a methyl group, yet at higher temperatures the resulting methyl group can be removed. Similar hydrogenolysis reactions have been performed using platinum and palladium catalysts; however, these reactions tend to be low yielding (<10%) due to random cracking of the parent hydrocarbon.[6]

Hydrogenations.

Supported nickel catalysts have been used to hydrogenate both alkynes and alkenes in high yield. Nickel on graphite has been used extensively to semihydrogenate alkynes to (*Z*)-alkenes using notably mild conditions (eq 2).[7]

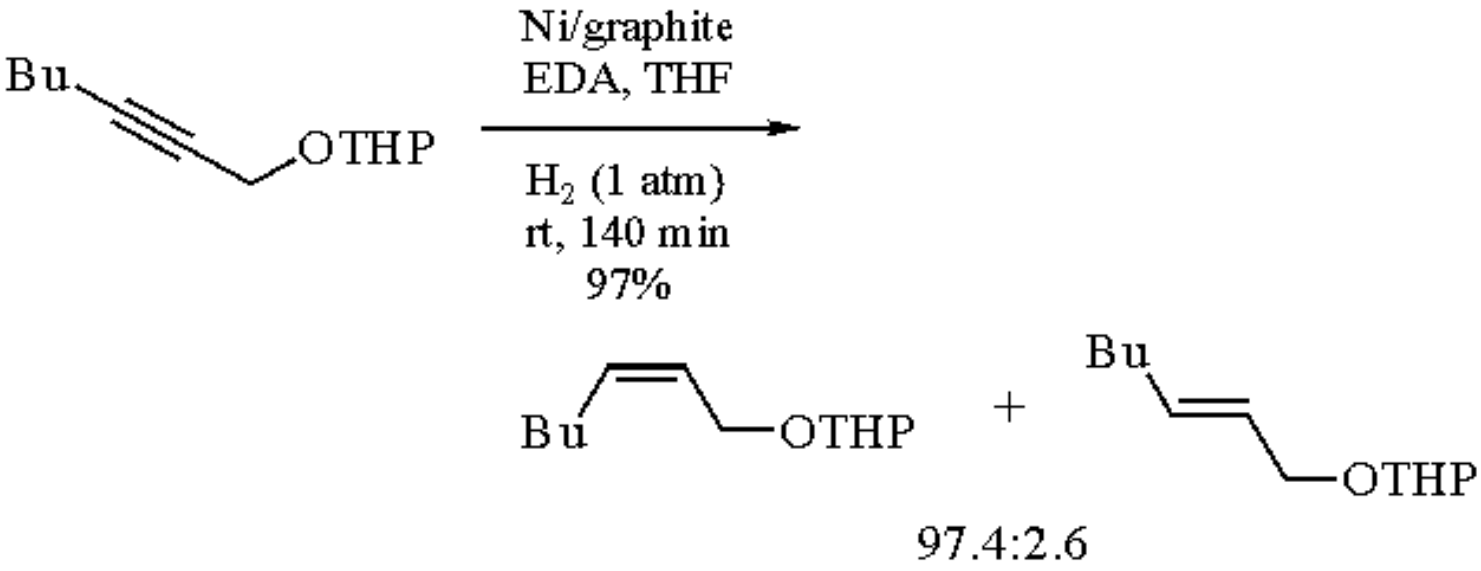

(2)

Similar hydrogenations have been performed using supported palladium with similar stereoselectivity. However, nickel on graphite offers a reasonably priced alternative that can produce results comparable with, and in some cases better than, those with palladium catalysts. Further, nickel catalysts are nonpyrophoric, making filtration during workup safer than with other catalysts. A disadvantage of nickel on graphite is that the catalyst should be prepared fresh prior to each hydrogenation.

Caubere[8] has described a heterogeneous catalyst (Nic), which is a complex reducing agent of the type NaH-RONa-NiX_2 (see ***Nickel Complex Reducing Agents***). Nic is highly reactive, capable of rapidly reducing alkenes, alkynes, and

carbonyls. Reduction of alkynes occurs with high stereoselectivity to the corresponding (*Z*)-alkene. Nic offers several advantages over Raney nickel in that it is nonpyrophoric, stable to long-term storage, and provides higher stereoselectivity.

There have also been reports of aromatic saturation in excellent yields by passing hydrogen and gaseous substrate over nickel on alumina.[9] Hydrogenation of nitriles to the corresponding amines are known. For example, hydrogenating propionitrile with nickel on silica in methanolic ammonia at 125 °C for 45 min resulted in a 97% yield of *n*-butylamine.[10]

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Nickel(II) Chloride[1]

$NiCl_2$

($NiCl_2$)

[7718-54-9] · Cl_2Ni · Nickel(II) Chloride · (MW 129.59) ($NiCl_2.6H_2O$)

[7791-20-0] · $Cl_2H_{12}NiO_6$ · Nickel(II) Chloride · (MW 237.71)

(mild Lewis acid;[2-5] catalyst for coupling reactions,[1a,7-12] and in combination with complex hydrides as a selective reducing agent[16,33,36-38])

Physical Data: mp 1001 °C; *d* 3.550 g cm^{-3}.

Solubility: sol H_2O, alcohol; insol most organic solvents.

Form Supplied in: yellow solid when anhydrous, green solid for the hydrate; widely available. *Drying:* for anhydrous nickel chloride, standard procedure for drying metal chlorides can be used by refluxing with ***Thionyl Chloride*** followed by removal of excess $SOCl_2$.[45]

Handling, Storage, and Precautions: nickel(II) is reputed to be toxic and a cancer suspect agent. Use in a fume hood.

Mild Lewis Acid.

Nickel chloride serves as a mild Lewis acid which promotes the regioselective rearrangement of dienols in aqueous *t*-BuOH at 60 °C in satisfactory yield (eq 1).[2] Brønsted acids give dehydration products, whereas other Lewis acids such as ***Nickel(II) Acetate***, ***Palladium(II) Chloride***, and ***Copper(II) Chloride*** proved less effective than nickel chloride and yield a mixture of rearranged and dehydration products. When anhydrous alcohol solvent is used, rearranged products bearing terminal alkoxy groups are obtained.

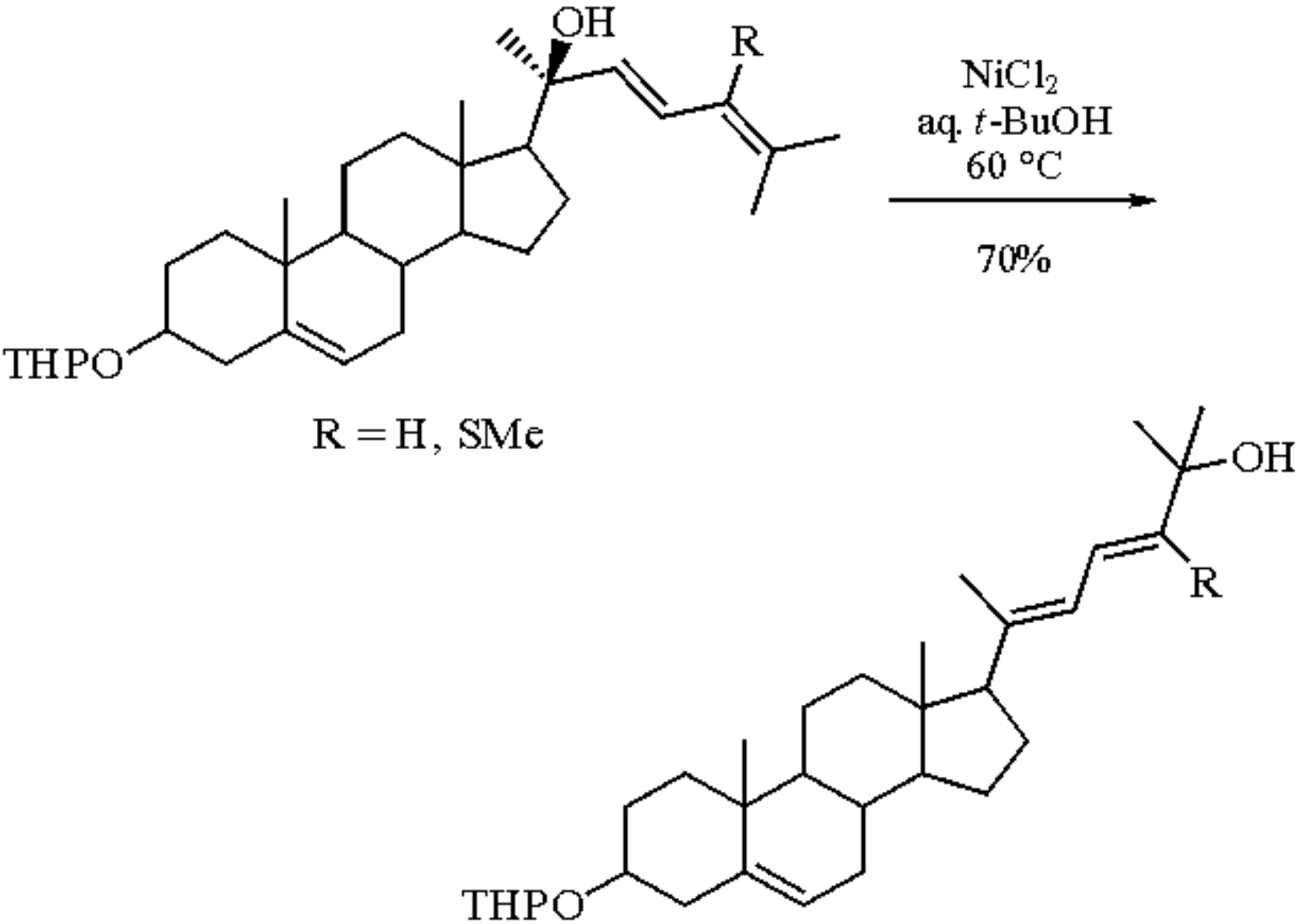

(1)

In the presence of a catalytic amount of $NiCl_2$, ***Cyanotrimethylsilane*** smoothly reacts with acetals or orthoesters derived from aromatic and α,β-unsaturated carbonyl compounds to give the corresponding α-cyano derivatives under neutral conditions (eq 2).[3] $NiCl_2$ can also accelerate the conversion of acrylamide to ethyl acrylate[4a] and catalyze the amination of 5,8-quinolinediones.[4b] The ring-opening reaction of epoxides with $LiAlR_4$ is catalyzed by $NiCl_2$ or ***Nickel(II) Bromide*** (eq 3).[5]

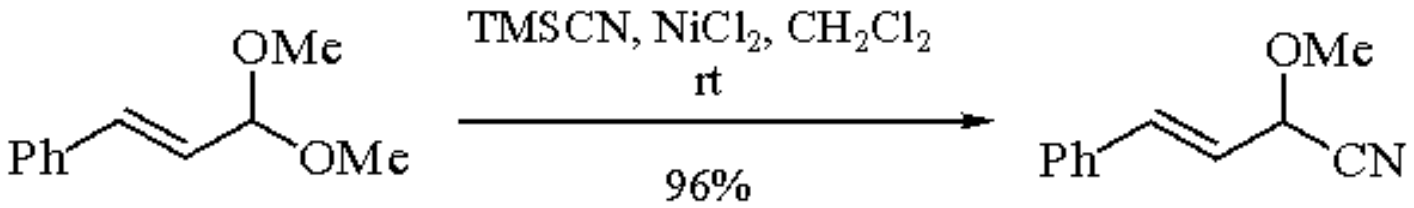

(2)

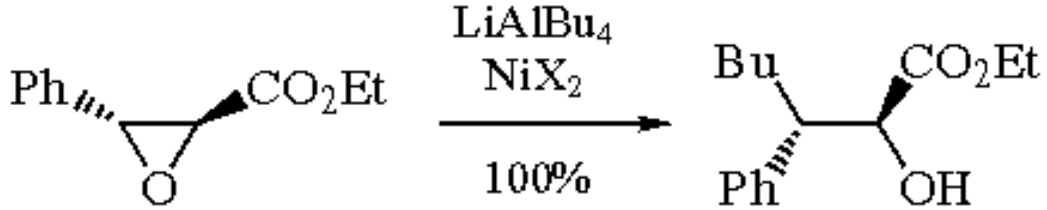

(3)

Nickel(II) Chloride-Chromium(II) Chloride.

Although the ***Chromium(II) Chloride***-mediated reaction of an aldehyde with a vinylic iodide provides a useful entry for the preparation of allylic alcohol,[1a,6] the presence of a catalytic amount of $NiCl_2$ is essential to ensure the completion of the reaction.[7-12] Vinyl iodides (eq 4)[7] or triflates[8a] are commonly used. Alkynyl iodides behave similarly (eq 5).[9] Silyl enol ethers or enol phosphates are unreactive. The stereochemistry of iodoalkenes is retained in the majority of cases with the exceptions of trisubstituted *cis*-iodoalkenes and *cis*-iodoenones, which afford exclusively the *trans*-alkenes instead of the expected *cis*-alkenes.[7a]

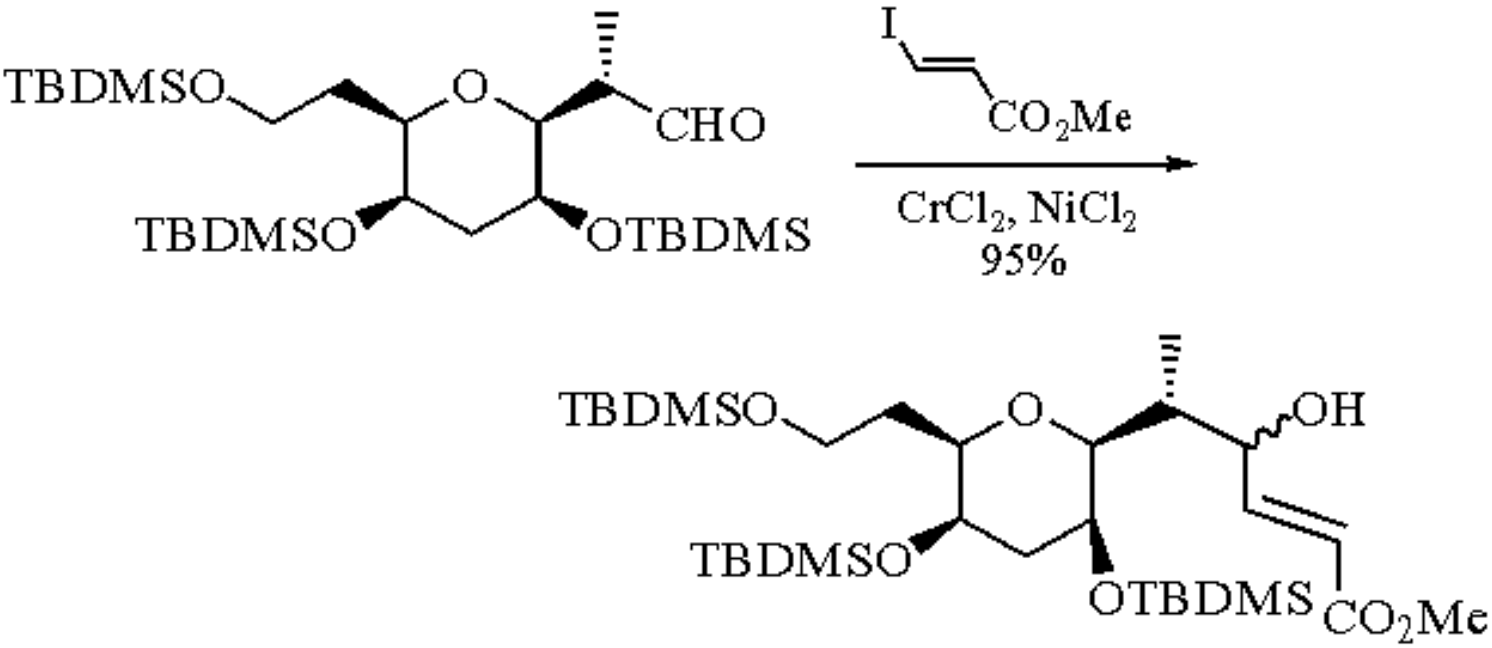

(4)

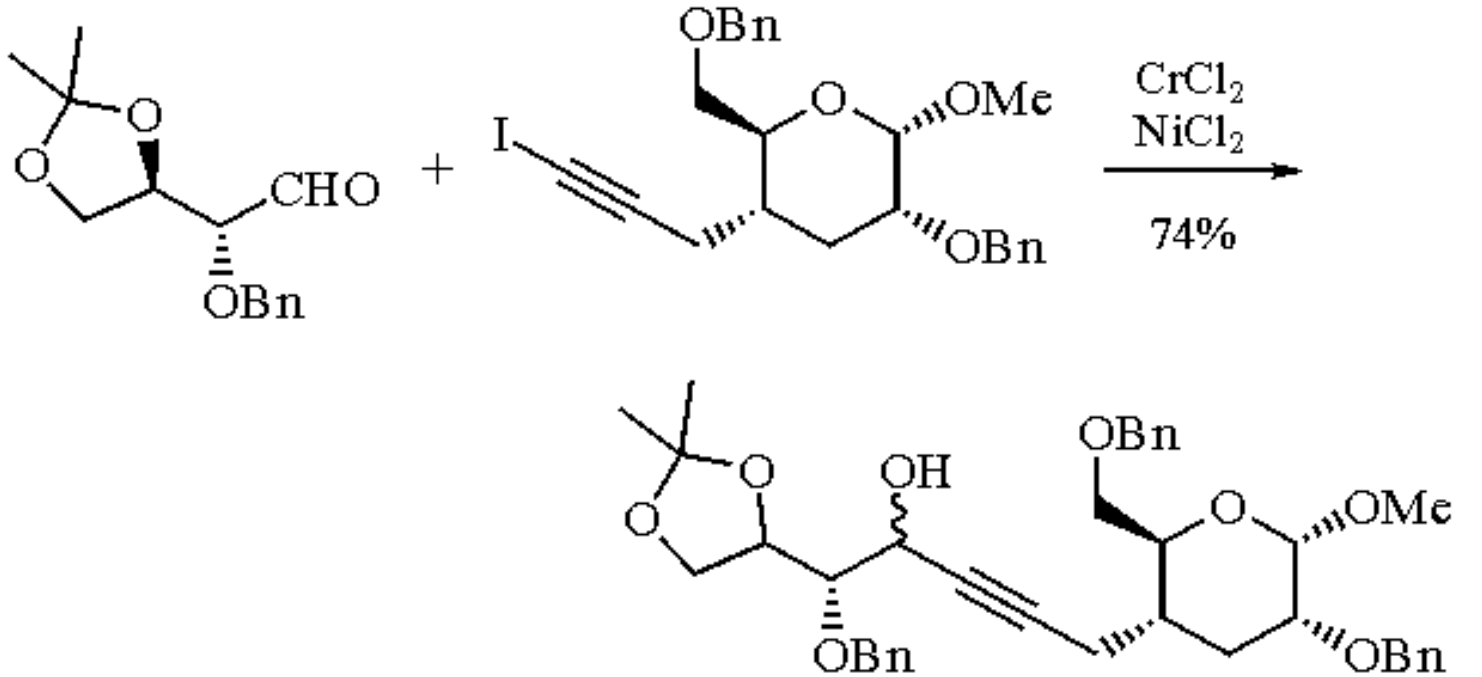

(5)

Functional groups such as esters, amides, nitriles, ketones, acetals, ethers, silyl ethers (TBDMS or TBDPS), alcohols, alkenes, and triple bonds are stable under the reaction conditions. Substrates containing structural complexity can be

employed in this transformation. Thus, the reaction served as the key step for the formation of C(7)-C(8) and C(84)-C(85) bonds in the total synthesis of palytoxin,[10] as well as for the synthesis of other natural products and C-saccharides. The reagent has also been proved to be useful in the intramolecular cyclization of the aldehyde (eqs 6 and 7).[11,12]

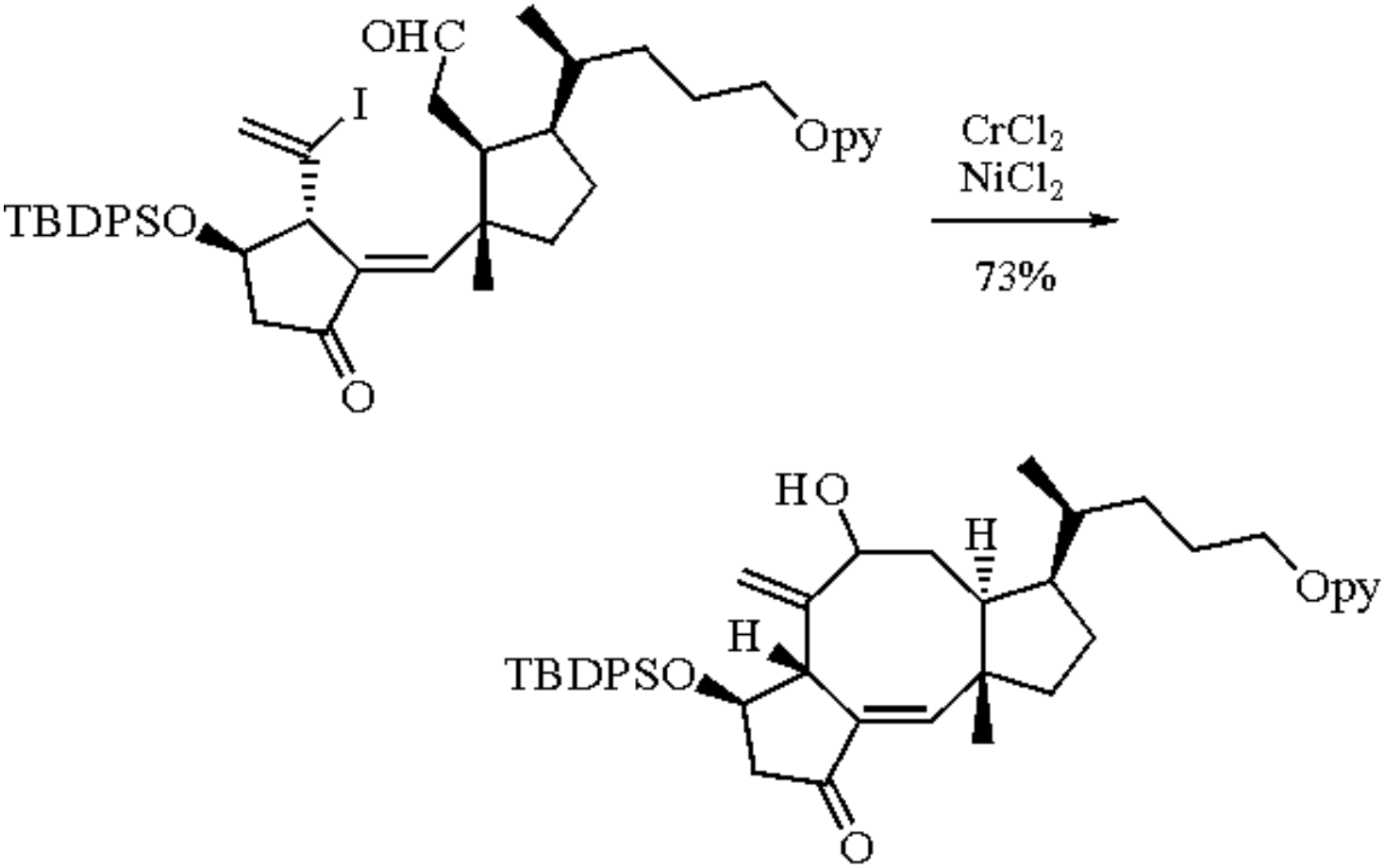

(6)

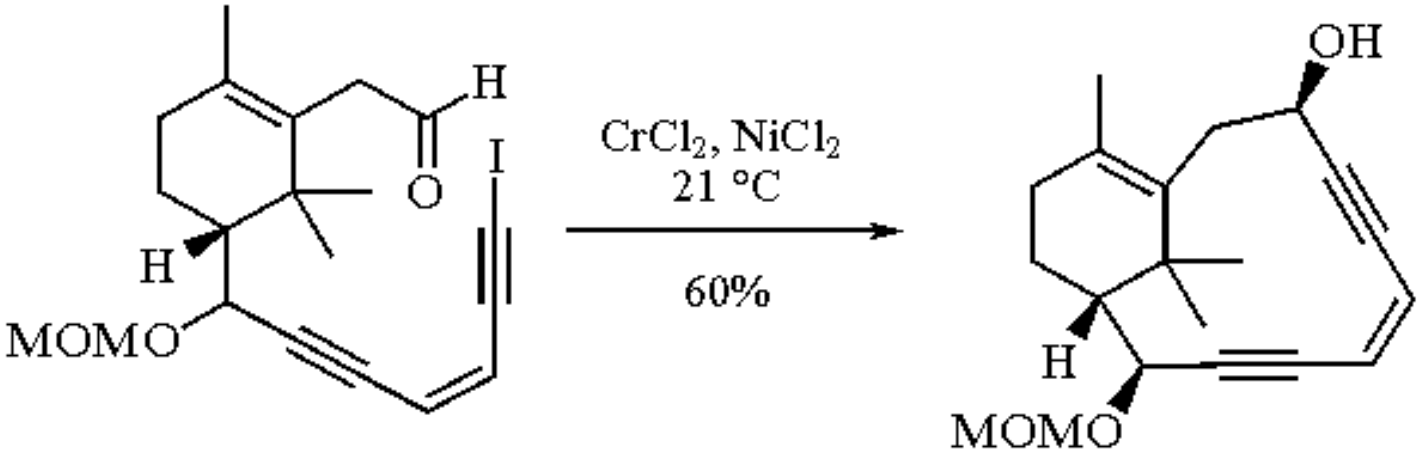

(7)

A simple and selective method for the conversion of an aldehyde to vinyl iodides, (*E*)-RCH=CHX, by means of a $CHX_3/CrCl_2$ system has been developed (eq 8).[13]

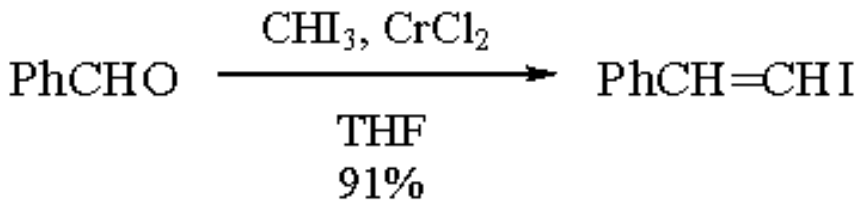

(8)

DMF happens to be the most effective solvent for this coupling reaction. The reaction goes slowly but cleanly in the DMSO solvent.[8a] The presence of a phosphine ligand in the nickel catalyst gives a diene sideproduct.[4a] Nevertheless, this later system has been used in the intramolecular cyclization of enynes (eq 9).[14]

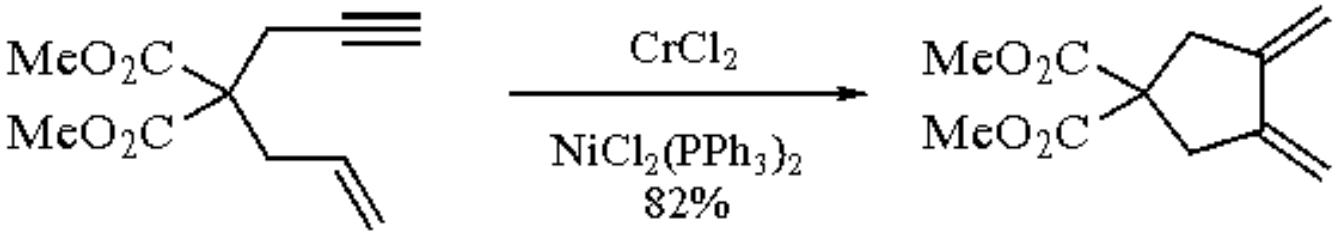

(9)

Monosubstituted α,β-unsaturated aldehydes are converted to cyclopropanols in the presence of $NiCl_2/CrCl_2$ in moderate yields (eq 10).[15]

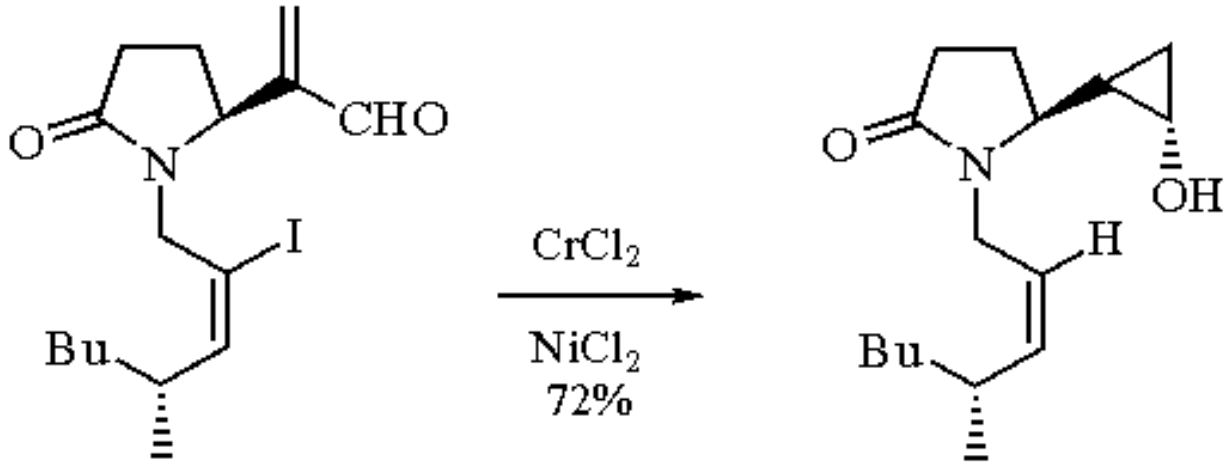

(10)

Selective Reductions.

Low-valent transition metal complexes generated in situ from metal halides and reducing agents are particularly useful for the selective reduction of various functionalities.[16] Nickel chloride and nickel bromide have demonstrated a unique role in these reduction reactions. To illustrate this, in the presence of an equimolar quantity $NiCl_2$, ***Lithium Aluminum Hydride*** can reduce alkenes to alkanes in excellent yields.[17] Under similar conditions at -40 °C, alkynes are reduced to *cis*-alkenes in good yield.[17] Haloalkanes are also smoothly converted into the corresponding hydrocarbons under these conditions.[18a,b] Even chlorobenzene and 1-bromoadamantane can be reduced efficiently by this reagent. ***Sodium Hydride*** in the presence of $NiCl_2$ or $NiBr_2$ and a sodium alkoxide can also serve a similar purpose.[16c,18c]

The N-O bond in isoxazolidines is cleaved efficiently by $LiAlH_4/NiCl_2$ at -40 °C (eq 11).[19] Styrene oxide yields β-phenylethanol in 95% yield by this complex reagent, whereas $LiAlH_4$ alone gives α-phenylethanol.[19]

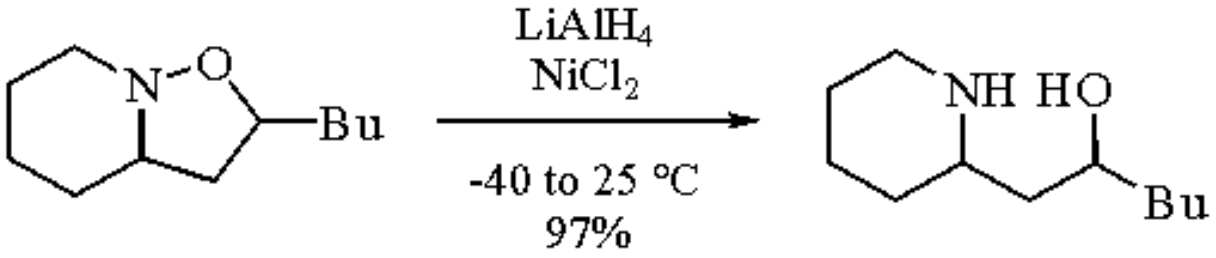

(11)

Nickel Boride, prepared in situ from the reaction of nickel chloride and ***Sodium Borohydride***, behaves like ***Raney Nickel***.[1b] In DMF, the dark brown/black solution comprises an efficient system for alkene hydrogenation. The carbon-carbon double bonds of the α,β-unsaturated carbonyl compounds are reduced selectively (eq 12).[20] It is noted that carbon-sulfur bonds are selectively reduced under similar conditions (eq 13).[16b,21] Thiols, sulfides, disulfides, dithioacetals, as well as sulfoxides can all be hydrodesulfurized smoothly. Sulfones, on the other hand, remain intact under the reaction conditions.[21d,e]

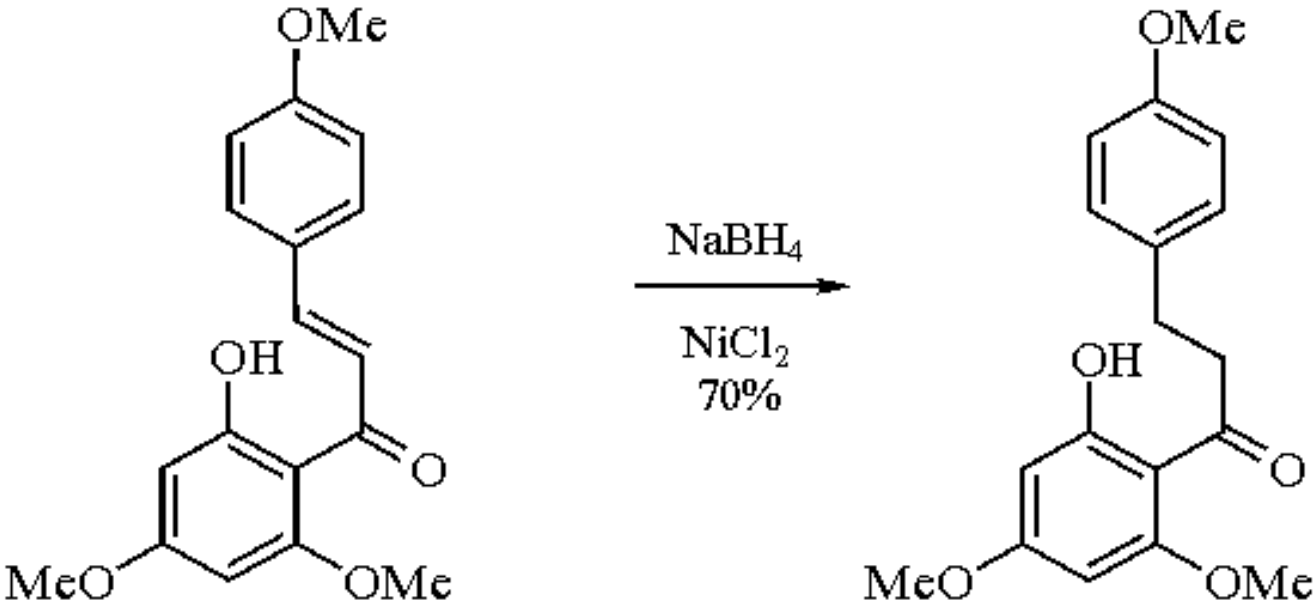

(12)

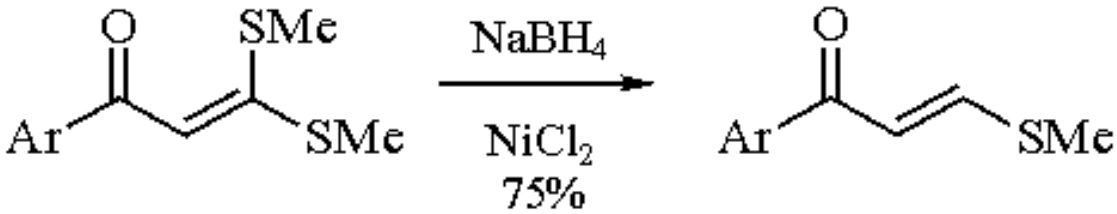

(13)

Reduction of α-halo ketones with nickel boride produces the corresponding ketones.[22] The carbon-oxygen bonds in allylic ethers,[23a] benzylic esters,[23b] as well as aryl tosylates[23c] are reduced to the corresponding C-H bonds (eq 14).

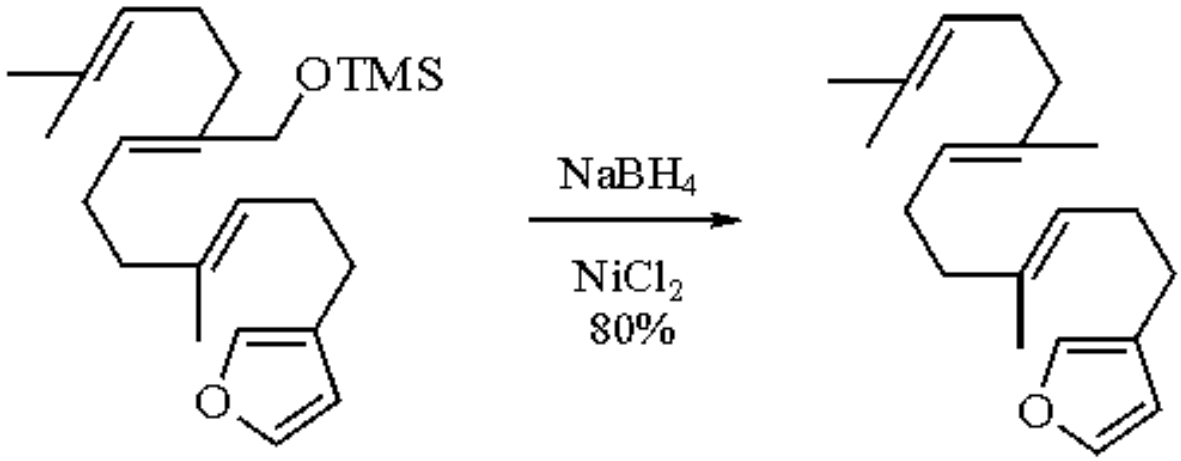

(14)

Upon treatment with $NiCl_2/NaBH_4$, nitro,[24a-c] azide,[24d,e] and oxime[24f] groups are smoothly transformed into amino groups in good yields. Carbon-carbon double bonds are occasionally reduced under these conditions.[24a,f] Nitro and cyano groups are also reduced to amines by the reagent mixture $NiCl_2/B_2H_6$.[25] Ketones, aldehyde, carboxylic acid, alkene, ester, and amide moieties are unaffected under these conditions.

Addition of TMSCN to an allene is catalyzed by nickel boride generated in situ, although the reaction is nonstereoselective (eq 15).[26]

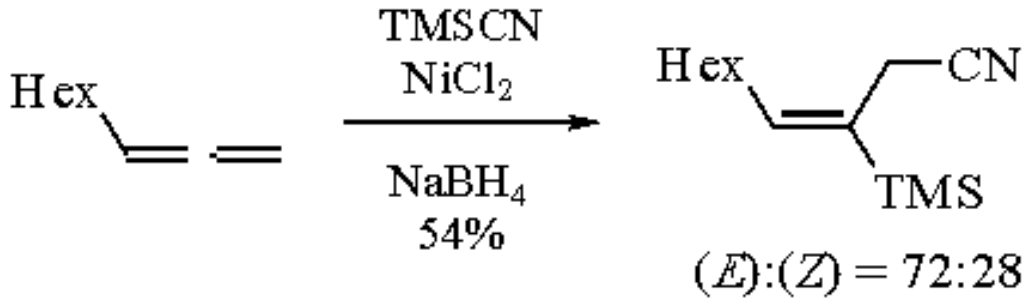

(15)

Treatment of ***Diphenylacetylene*** with excess TMSCN in the presence of the $NiCl_2$/***Diisobutylaluminum Hydride*** or $NiCl_2$/***Triethylaluminum*** catalyst affords a substituted pyrrole in high yield (eq 16).[27]

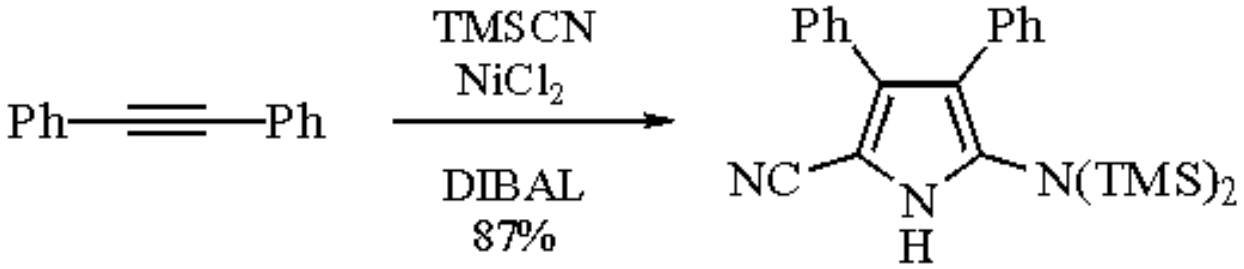

(16)

Hydrosilylation of conjugated dienes with $HSiR_3$ is catalyzed by $NiCl_2/Et_3Al$ in excellent yield; 1,4-addition is observed exclusively (eq 17).[28]

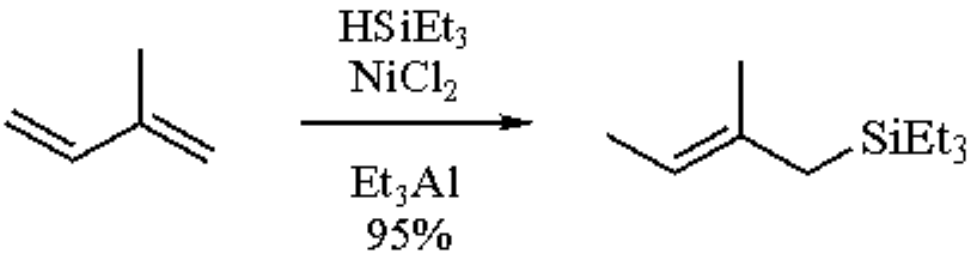

(17)

A combination of ***Aluminum*** and $NiCl_2$ promotes the selective reduction of α,β-enones to the corresponding saturated carbonyl compounds (eq 18).[29] Both nitro groups[30] and aryl ketones[29] are reduced to amines and benzylic alcohols, respectively.

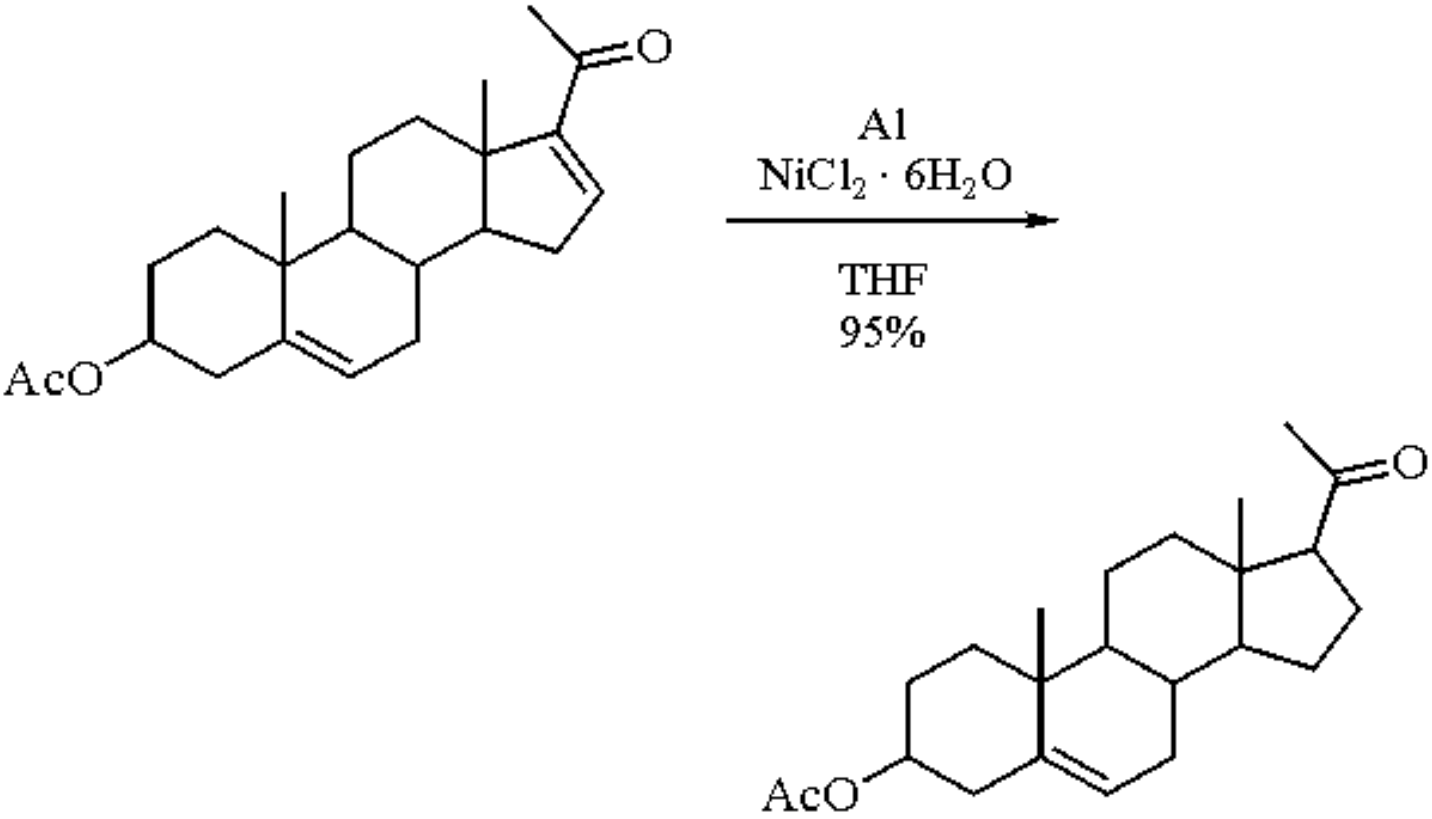

(18)

Nickel(II) Chloride-Zinc.

Finely divided nickel with high catalytic activity is readily obtained by the treatment of $NiCl_2$ with ***Zinc*** dust.[31] This reagent reduces aldehydes, alkenes, and aromatic nitro compounds in good yields.[32a] Nitriles as well as aryl ketones give a mixture of reduced products under these conditions. Zn/$NiCl_2$ in the presence ***Ammonia***/NH_4^+ buffer (pH 6-10)[3] has been shown to effect the selective reduction of α,β-enones to the corresponding saturated carbonyl compounds.[32b] Aryl, allyl, and alkyl halides are reduced by water, zinc, and a catalytic amount of $NiCl_2$, ***Triphenylphosphine***, and iodide ion.[32c]

Reductive Heck-Like Reactions.

Reductive Heck-like reactions (eq 19) can be achieved when alkyl, aryl, and vinyl bromides are treated with

zinc/$NiCl_2.6H_2O$ in the presence of an excess quantity of α,β-unsaturated esters.[33] A trace amount of water is essential for this conversion. Similar reactions are observed when alkenes are treated with iodofluoroacetate or iododifluoroacetate under the same conditions (eq 20).[34] Tandem reaction can also occur to give cyclic products (eq 21).[35]

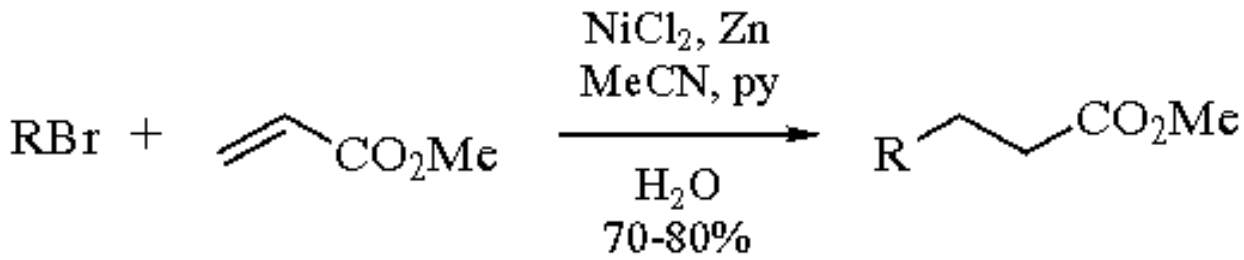

(19)

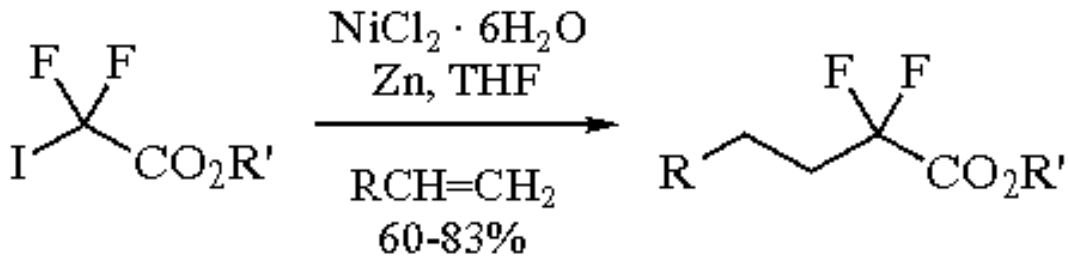

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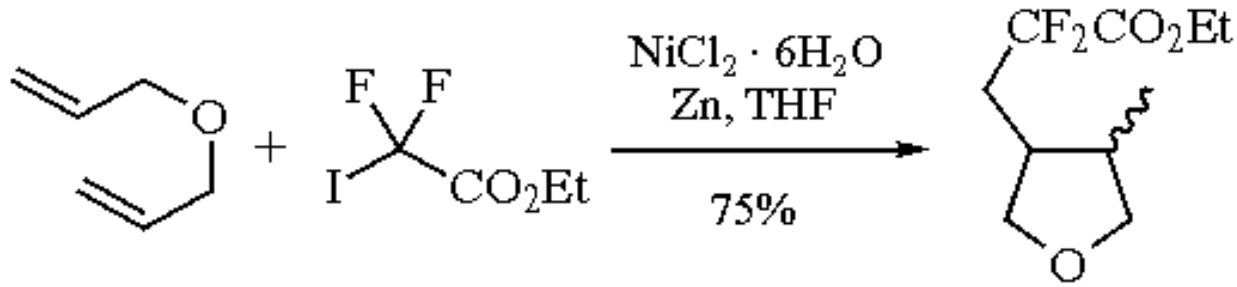

(21)

Homocoupling Reactions.

In the absence of a Michael acceptor, aryl and vinyl halides undergo dimerization reaction upon treatment with the $NiCl_2$/Zn reagent.[36-38] Under sonication conditions and in the presence of excess Ph_3P and ***Sodium Iodide*** in DMF, the $NiCl_2$/Zn reagent promotes homocoupling of aryl triflates in good yields.[36] Bipyridyls having electron-donating groups, such as methoxy groups, are obtained in satisfactory yields under these conditions (eq 22).[37] Thiophene derivatives behave similarly.[38] Vinyl bromides dimerize to yield the corresponding butadienes.[39] It is interesting that the presence of iodide ion or thiourea can accelerate the reaction.

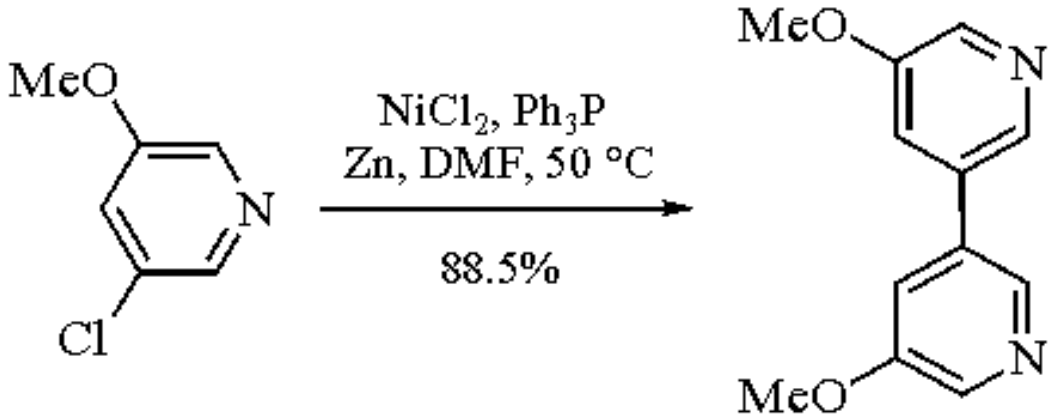

(22)

Cross-Coupling Reactions.

Most cross-coupling reactions using nickel catalysts require phosphine ligands and are therefore discussed in detail under ***Dichlorobis(triphenylphosphine)nickel(II)***. The reaction of aryl iodides or bromides with trialkyl phosphites in the presence of $NiCl_2$ is the premier method for preparing dialkyl arylphosphonates (eq 23).[40a,b] Thermolysis of allyl phosphite in the presence of $NiCl_2$ yields the corresponding allyl phosphonates (eq 24).[40c]

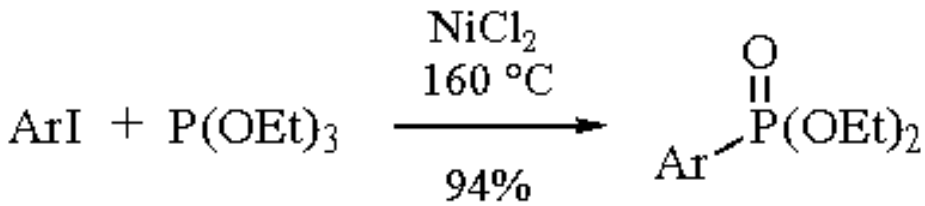

(23)

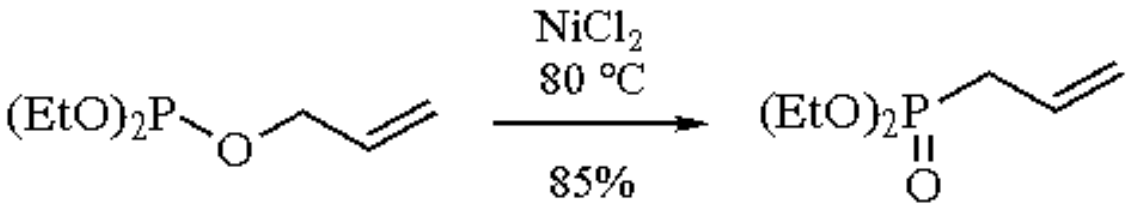

(24)

Miscellaneous Reactions.

Symmetrical alkynes in the presence of $NiCl_2$ or $NiBr_2$ and ***Magnesium*** undergo trimerization to give the corresponding hexasubstituted aromatic compounds (eq 25). Terminal alkynes yield a mixture of regioisomers.[41]

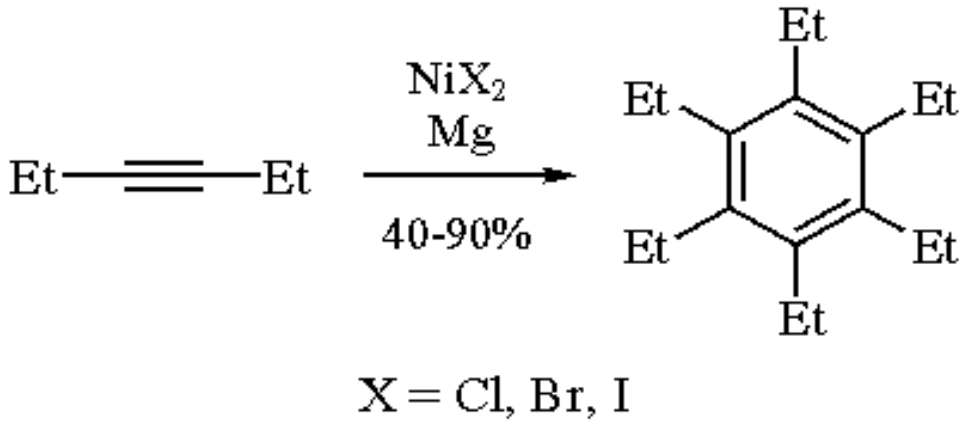

(25)

Grignard reagents activated by a catalytic quantity of $NiCl_2$ can substitute the germanium-hydrogen bond with a germanium-carbon bond (eq 26).[42] It is noted that the stereochemistry of the original organogermane is retained.

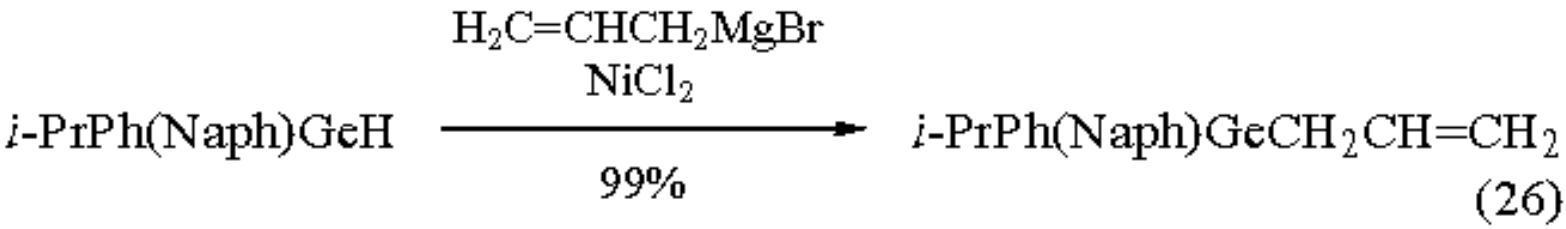

(26)

Hydromagnesiation of a styrene with ***Ethylmagnesium Bromide*** followed by treatment with ***Carbon Dioxide*** gives the 2-arylpropionic acid in good yield (eq 27).[43]

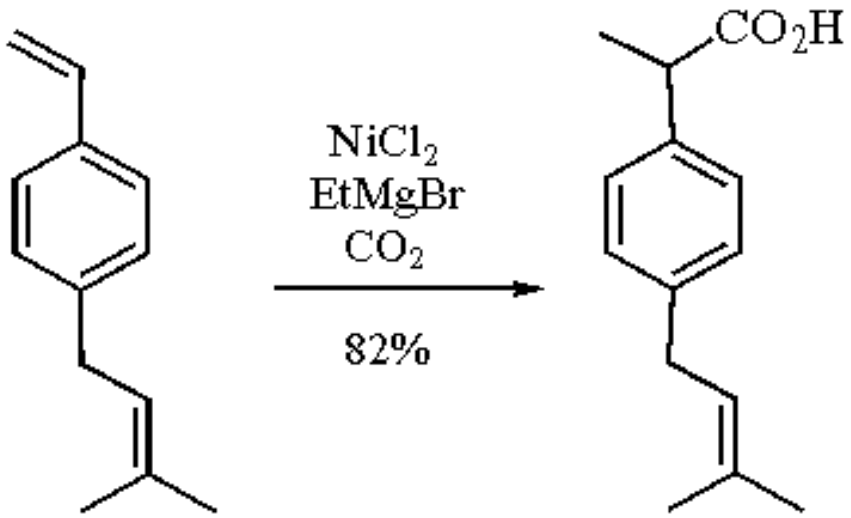

(27)

Thermolysis of 1-phenyl-3,4-dimethylphosphole in the presence of $NiCl_2$ yields the corresponding nickel complex of the dimeric product. The ligand can be liberated upon treatment with ***Sodium Cyanide*** (eq 28).[44]

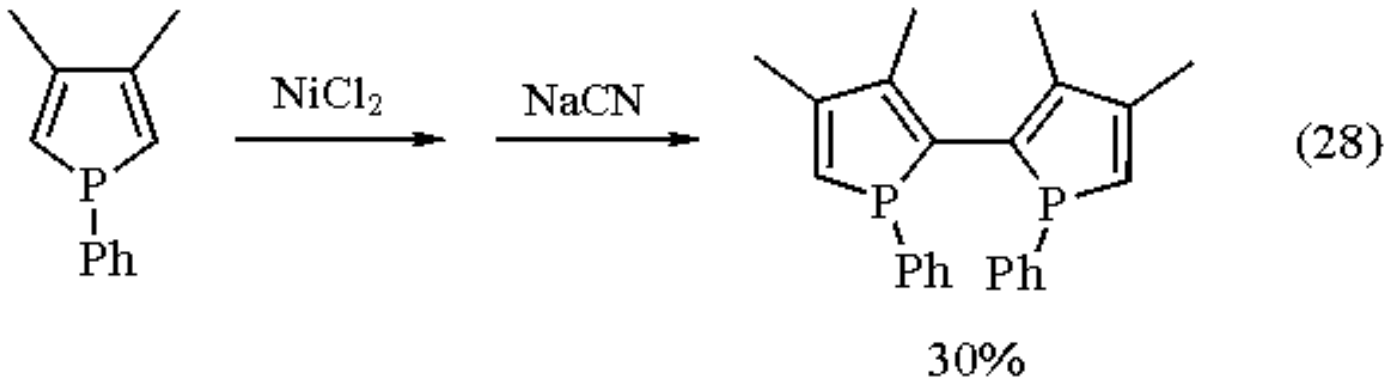

Related Reagents.

Chromium(II) Chloride-Nickel(II) Chloride; ***Lithium Aluminum Hydride-Nickel(II) Chloride***.

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Nickel Complex Reducing Agents[1]

NaH-*t*-$C_5H_{11}ONa$-$Ni(OAc)_2$

(NaH)

[7646-69-7] · HNa · Nickel Complex Reducing Agents · (MW 24.00) (*t*-$C_5H_{11}ONa$)

[14593-46-5] · $C_5H_{11}NaO$ · Nickel Complex Reducing Agents · (MW 110.15) ($Ni(OAc)_2.4H_2O$)

[6018-89-9] · $C_4H_{14}NiO_8$ · Nickel Complex Reducing Agents · (MW 248.87)

(reduces many functional groups; couples organic halides; desulfurizes organic substrates; source of hydrogenation catalyst[1])

Alternate Name: nickel-containing complex reducing agents (NiCRAs).

Physical Data: black solid of uncertain structure containing Ni^0 species.[2]

Solubility: insol organic solvents.

Preparative Methods: *t*-$C_5H_{11}ONa$-NiCRA (*x.y.z*) is conveniently prepared by the reaction of *t*-$C_5H_{11}OH$ (*y* equiv) with a mixture of ***Sodium Hydride*** (*x* + *y* equiv) and ***Nickel(II) Acetate*** (*z* equiv) in THF or DME. Commercial NaH (55-60% in oil) is used after three washings with anhydrous THF or DME under N_2. *t*-$C_5H_{11}OH$ is distilled from sodium. $Ni(OAc)_2$ is dried in vacuo (15 mmHg) for 16 h at 120-130 °C. Note: *t*-$C_5H_{11}ONa$-NiCRA (*x.y.z*) means a reagent obtained from *x*,*y*, and *z* equivalents of NaH, *t*-$C_5H_{11}ONa$, and $Ni(OAc)_2$, respectively.

Handling, Storage, and Precautions: NiCRAs are nonpyrophoric but are handled and stored under inert atmosphere (N_2 or, better, Ar). Hydrolysis must be performed by slow addition of cold water or EtOH to destroy the hydride.

Reductions.

t-$C_5H_{11}ONa$-NiCRAs are significantly less basic than NaH and *t*-$C_5H_{11}ONa$. *t*-$C_5H_{11}ONa$-NiCRA (4.2.1) reduces under mild conditions and in good yields aryl halides, including aryl fluorides,[3] vinyl, allyl, benzyl, and alkyl halides (I > Br > Cl; primary &egt; secondary &egt; tertiary)[4] and monoreduces *gem*-dihalocyclopropanes.[5] It thus allows the removal of a tertiary hydroxy group (eq 1) while all other classical methods were unsuccessful.[6]

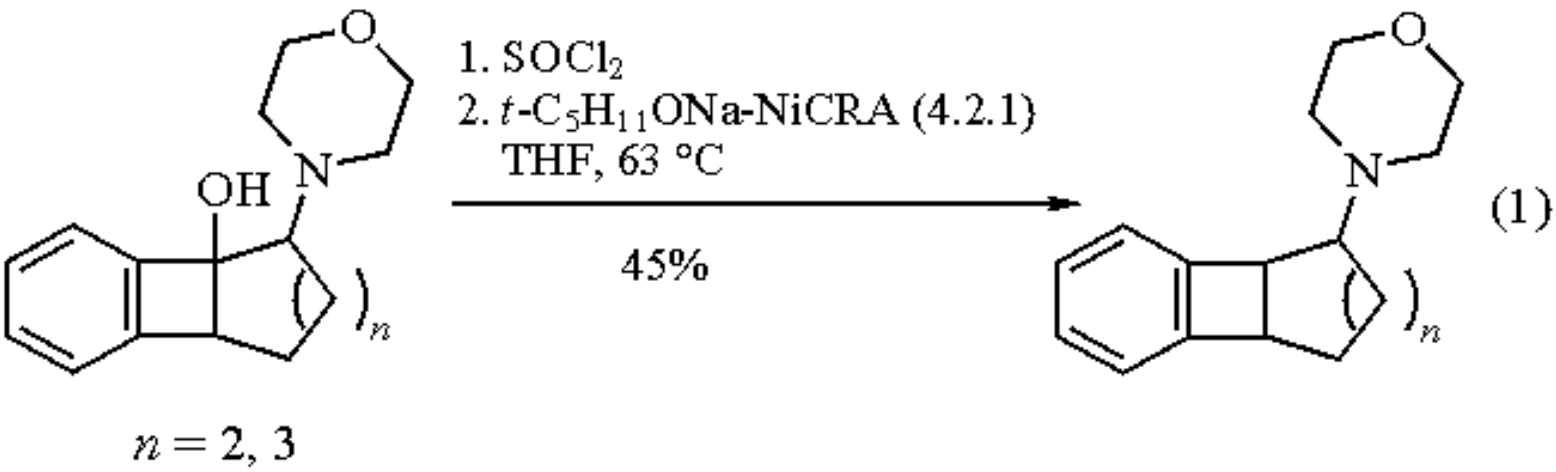

NiCRAs are sensitive to the nature and structure of the halides and allow selective reductions of polyhalogenated substrates, as exemplified in eq 2.[5]

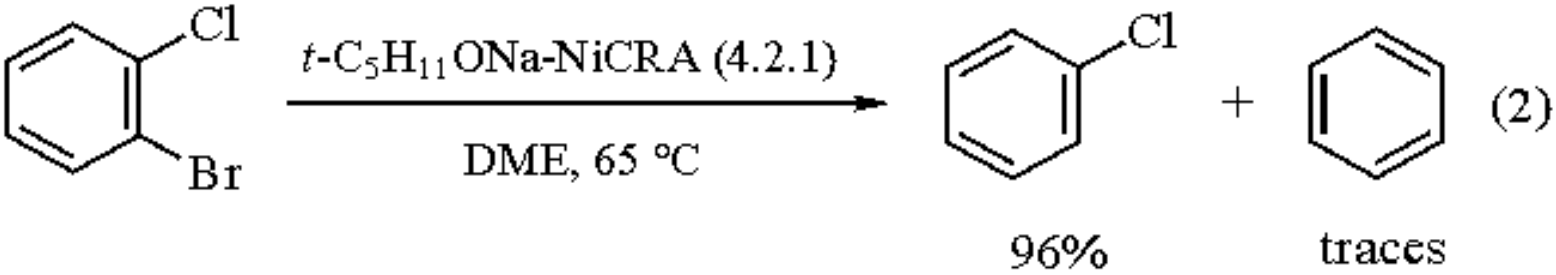

Except with substrates very sensitive to bases, chemoselective reduction of halides may be easily performed in the presence of alkoxy, acetal, hydroxy, OTHP, carboxy, alkoxycarbonyl, keto, and cyano groups.[5] No elimination takes place with 1,2-alkoxy halides (eqs 3 and 4).

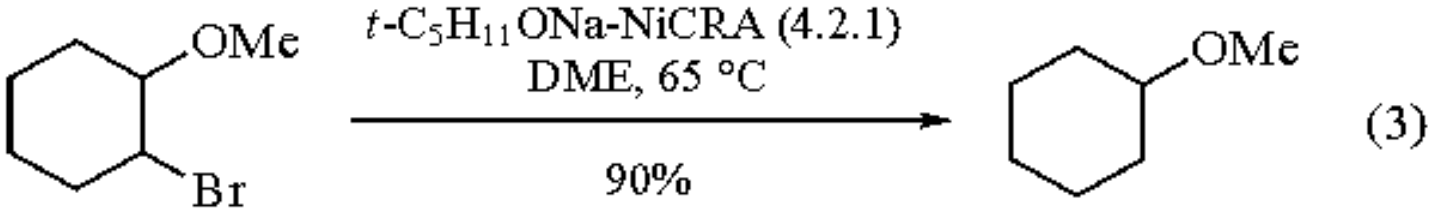

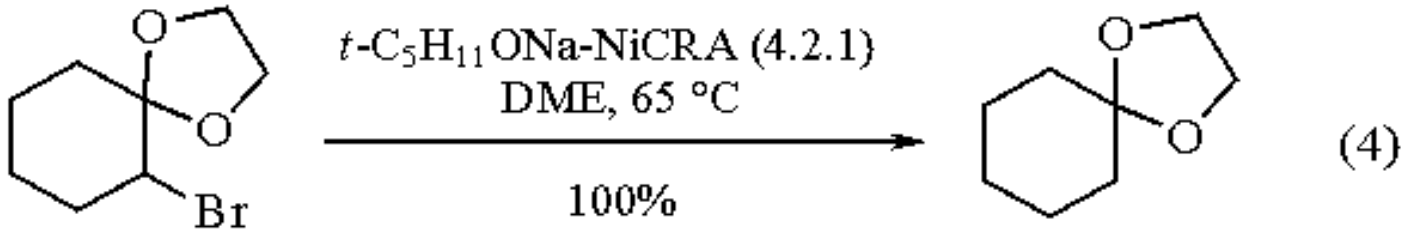

NiCRAs are much more powerful than ZnCRAs (see ***Zinc Complex Reducing Agents***) in the reduction of halides. *t*-C_5H_{11}ONa-NiCRA (4.1.1) reduces all classes of ketones or aldehydes and is not very sensitive to steric hindrance.[7,8] The efficiency of the reduction may be increased by the addition of electrophilic salts such as ***Magnesium Bromide*** or ***Lithium Chloride*** (eqs 5 and 6).

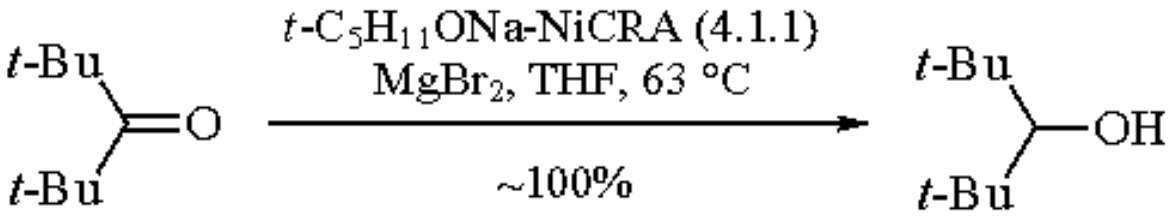

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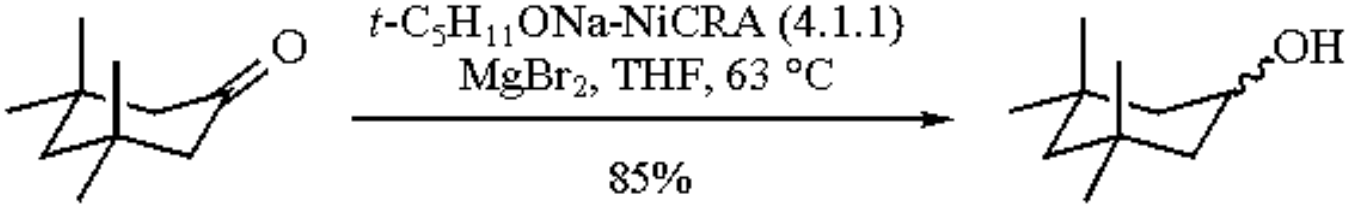

(6)

Under appropriate conditions, t-$C_5H_{11}ONa$-NiCRAs easily epimerize alcohols.[9] This property may be used to reduce ketones with a very high selectivity for the most stable alcohol. In such reactions t-$C_5H_{11}ONa$ may be advantageously replaced by the sodium salt of 2,5-dimethyl-2,5-hexanediol.[8b]

In the presence of ***Chlorotrimethylsilane*** (1 equiv), t-$C_5H_{11}ONa$-NiCRA (5.2.1) (or 5.1.1) (t-$C_5H_{11}ONa$-NiCRASi) very efficiently reduces carbon-carbon double bonds. The reagent is sensitive to steric hindrance as well as to electronic effects and allows the selective reduction of dienes, unsaturated ketones, esters, and acids.[10] The high selectivity is illustrated in eqs 7-9.

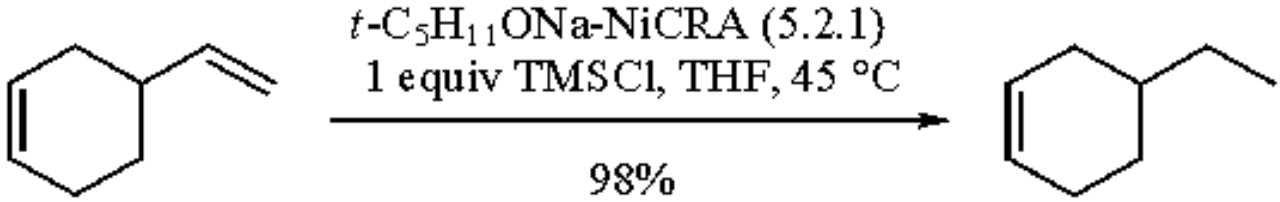

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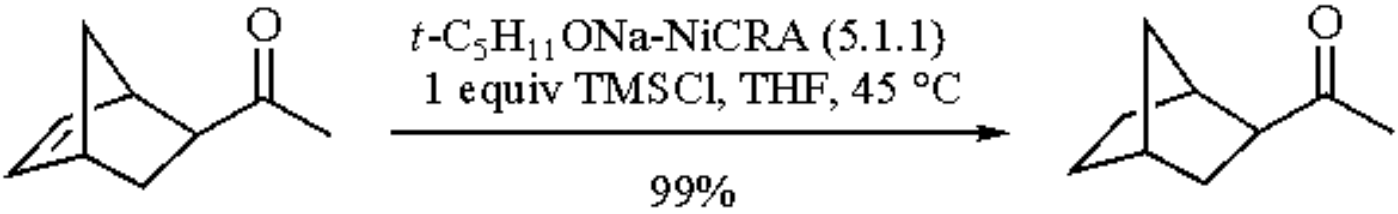

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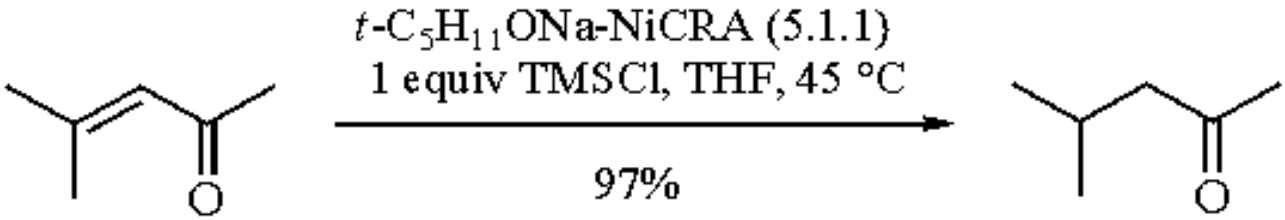

(9)

t-$C_5H_{11}ONa$-NiCRA (4.1.1) also selectively reduces a number of α,β-unsaturated ketones, although sometimes less efficiently than t-$C_5H_{11}ONa$-NiCRASi.[11] In the reduction of unsaturated carbonyl substrates, NiCRAs are complementary to ZnCRAs, which only reduce the carbonyl groups.

t-C_5H_{11}ONa-NiCRA (4.2.1) regioselectively reduces epoxides,[12] with the major or only product formed coming from the regioselective attack on the most hindered carbon. This regioselectivity is opposite to that observed with ZnCRAs.

Finally, anilines are easily prepared from the corresponding nitro derivatives using *t*-C_5H_{11}ONa-NiCRA (7.1.1) as the reducing agent.[13]

Reductive Desulfurization.

t-C_5H_{11}ONa-NiCRAs as such or in the presence of a ligand (*t*-C_5H_{11}ONa-NiCRALs) very efficiently and chemoselectively desulfurize thiols, thioethers, dithioacetals, sulfoxides, and sulfones.[14] Ketones, esters, and carbon-carbon double bonds are tolerated (eqs 10-12). Under appropriate conditions, monodesulfurization of dithioacetals may be easily performed (eq 13).

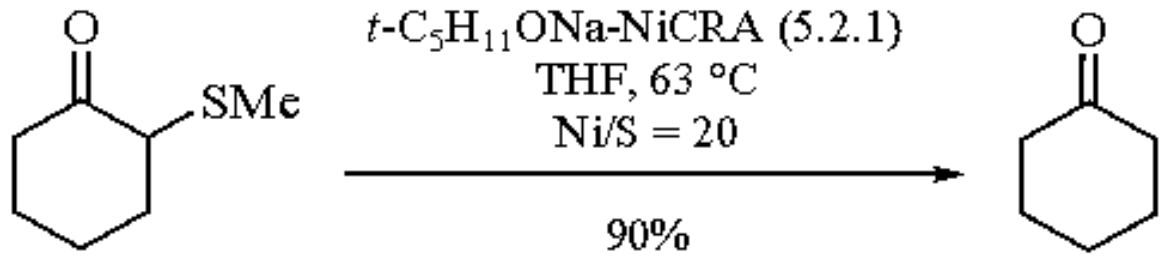

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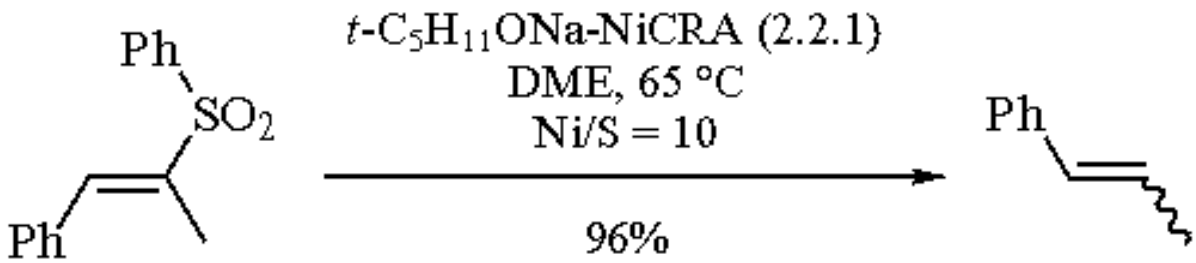

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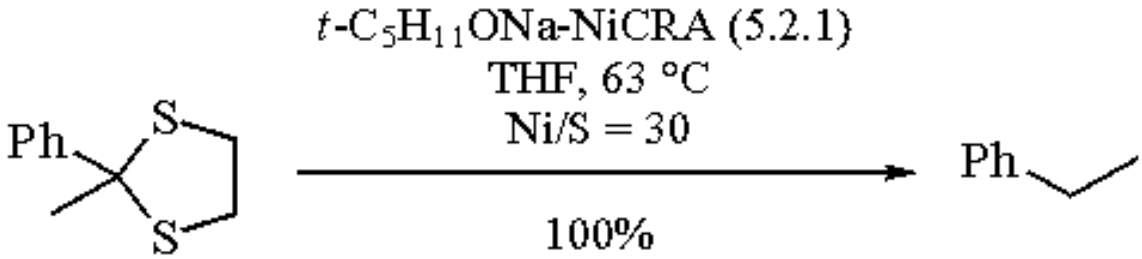

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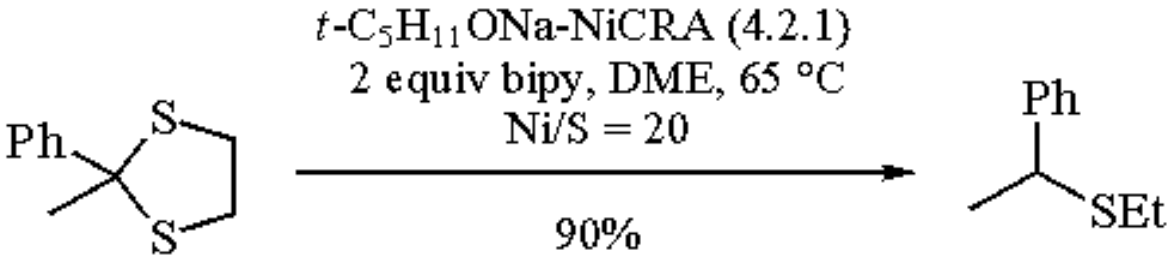

(13)

Coupling Reactions.

t-C_5H_{11}ONa-NiCRALs very efficiently couple aryl as well as heteroaryl halides (eqs 14 and 15).[15]

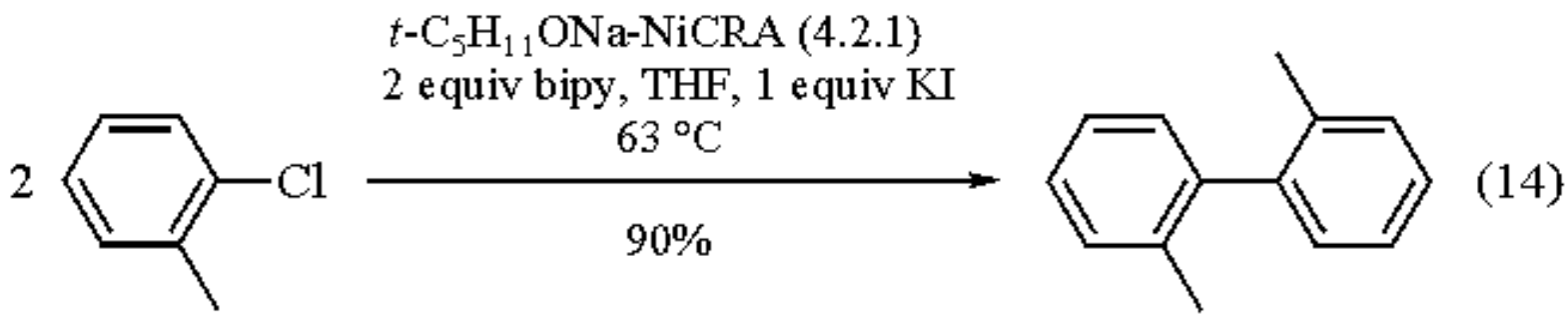

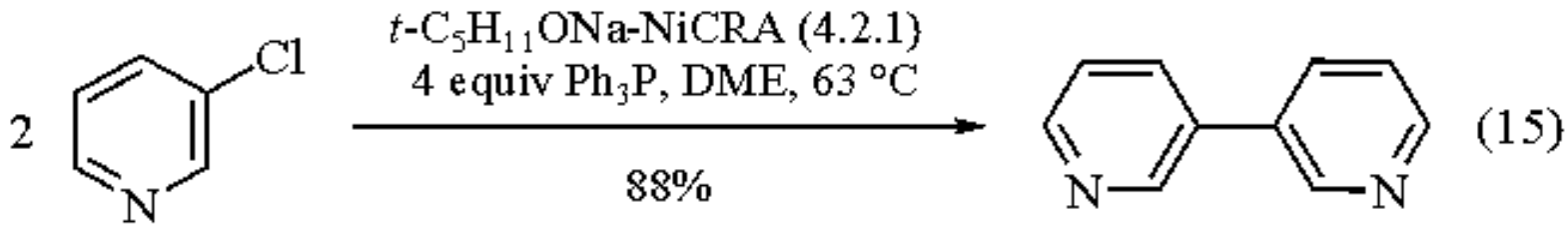

Unsymmetrical cross-couplings may be performed in fair to good yields simply by addition of two aryl halides to the reagent (eq 16).

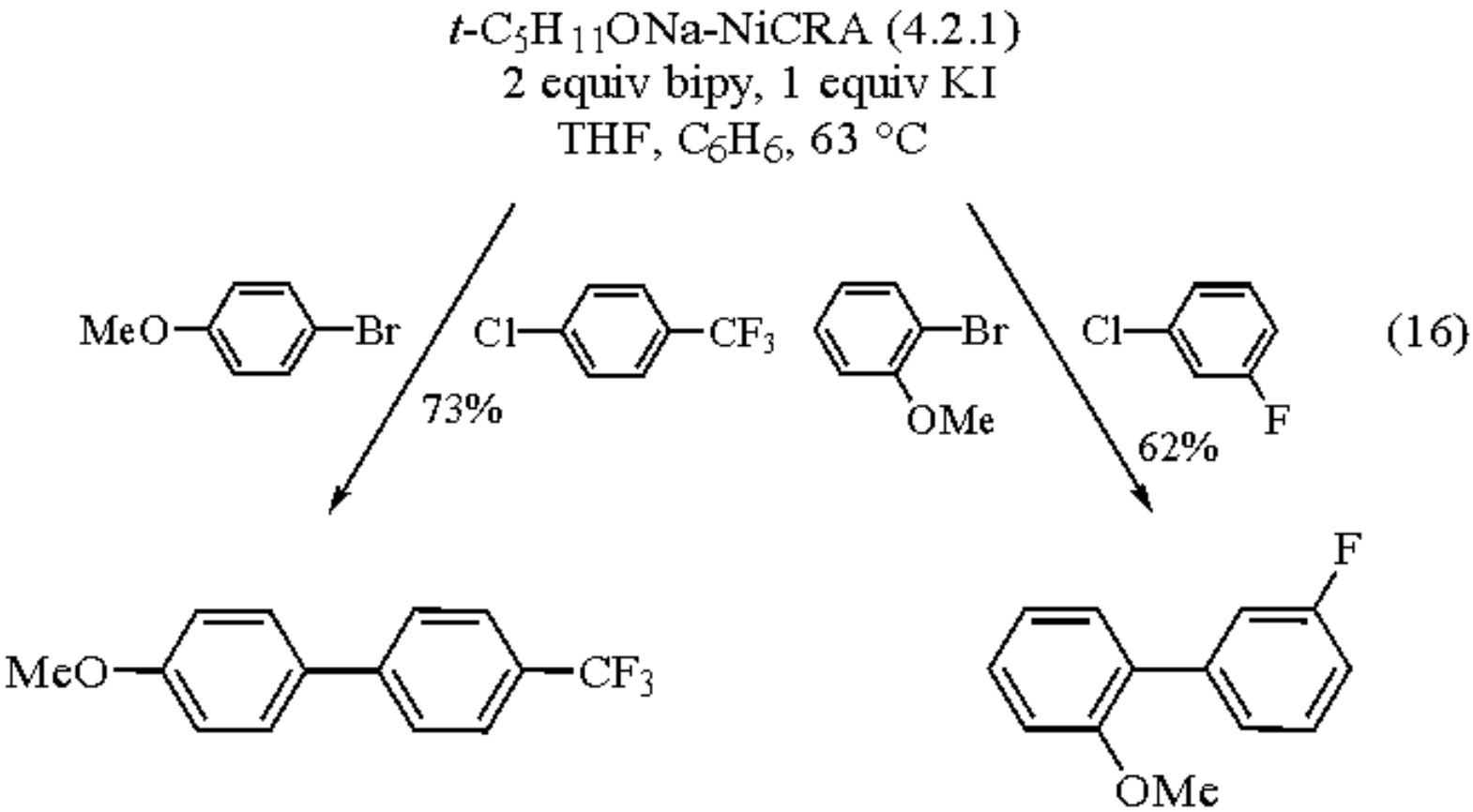

Hydrogenation Catalyst.

A nonpyrophoric hydrogenation catalyst, referred to as Nic, may be easily obtained from *t*-$C_5H_{11}ONa$-NiCRA by simple addition of a catalytic amount of the reagent to the reaction medium when the solvent is protic. In aprotic solvent, NaH is neutralized with *t*-$C_5H_{11}OH$ before use. If necessary, soluble alkoxide is removed by washing with EtOH (Nic_w). Nic is very efficient in atmospheric hydrogenation of carbon-carbon double bonds, ketones, and aldehydes and in the selective partial hydrogenation of carbon-carbon triple bonds.[16]

Related Reagents.

Sodium Hydride-Nickel(II) Acetate-Sodium t-Pentoxide.

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University of Nancy I, France

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Nickel(II) 2-Ethylhexanoate

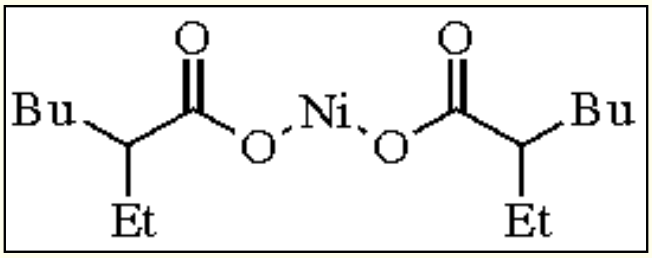

[4454-16-4] · $C_{16}H_{30}NiO_4$ · Nickel(II) 2-Ethylhexanoate · (MW 345.15)

(catalyst in conjunction with bromine for regioselective oxidation of diols and conversion of diols to lactones[1,2])

Solubility: sol toluene, xylenes; slightly sol hexane.

Form Supplied in: available as a viscous solution in mineral spirits containing 10-15 wt % Ni. Contains excess 2-ethylhexanoic acid.

Analysis of Reagent Purity: elemental analysis of Ni (weight percent).

Handling, Storage, and Precautions: not hygroscopic; nickel compounds are cancer suspect agents.

Oxidation of Alcohols.

Nickel(II) 2-ethylhexanoate is used in conjunction with anhydrous ***Bromine*** in acetonitrile for the selective oxidation of 1,4-diols in which one alcohol moiety is primary and one is secondary.[1] The reaction leads to selective oxidation of the primary alcohol and concomitant cyclization to a lactone. In the case of 1,4-butanediols with substituents in the 2 position, the less sterically hindered of the two primary alcohol groups is preferentially oxidized (eq 1).[2] The steric bulk of 2-ethylhexanoate is also an important factor in comparison to other nickel carboxylates such as ***Nickel(II) Acetate***, nickel(II) benzoate, and nickel(II) pivalate. Use of chlorine or NaOCl in place of bromine gives inferior results.

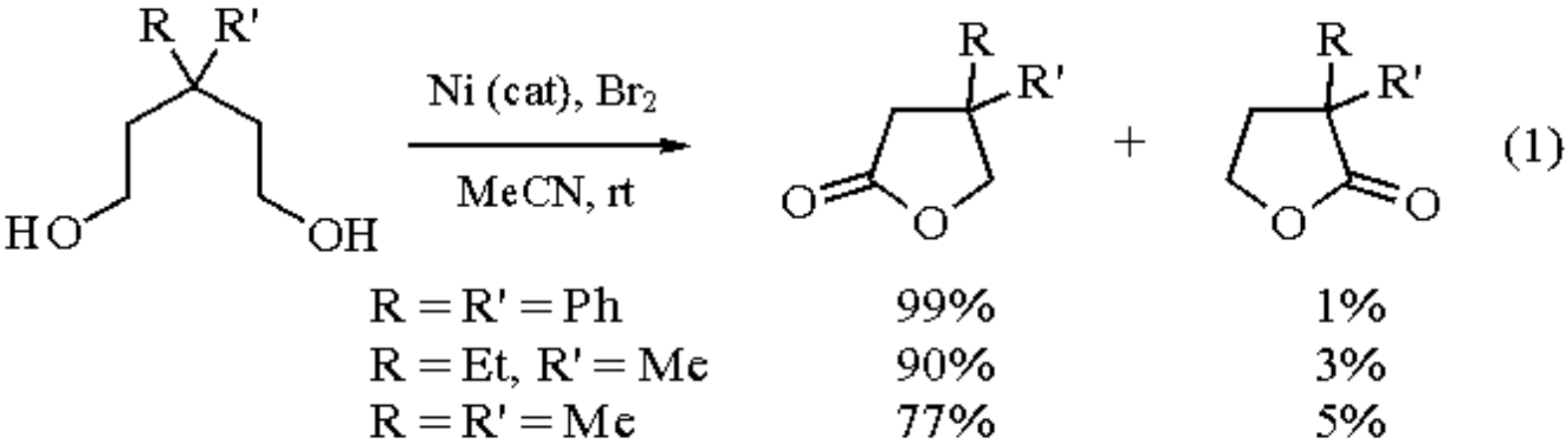

Reactions are carried out in acetonitrile at room temperature for 1 h using 8 mol Br_2 and 5 mol nickel compound per mol of diol. Some adjustment of the molar ratio of bromine may be necessary to give optimal regioselectivity.

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Nickel-Graphite

Ni-Gr

[134067-47-3] · Ni · Nickel-Graphite

(Ni-Gr1 is a hydrogenation catalyst for alkynes;[1] Ni-Gr2 reduces carbon-carbon, carbon-oxygen, and carbon-nitrogen multiple bonds and is selective for unsaturated carbonyl compounds and β-diketones[2])

Form Supplied in: not commercially available.

Preparative Methods: Ni-Gr1 catalyst is prepared in situ by reduction of bis(dimethoxyethane)dibromonickel ($NiBr_2$.2DME) by ***Potassium-Graphite*** in THF/HMPA at room temperature under argon.[1] Exposure of Ni-Gr1 to air produces Ni-Gr2, a less active catalyst.[2]

Handling, Storage, and Precautions: due to the air sensitivity of Ni-Gr1, it is advisable to prepare and use it in situ for each application. Exposure of Ni-Gr1 to air produces a less active catalyst, Ni-Gr2, which can be stored in polyethylene bottles for at least four months before catalytic activity is decreased. Neither form of the catalyst is pyrophoric.

Hydrogenation Catalyst.

Catalytic hydrogenation of terminal alkynes with Ni-Gr1 affords the alkene as the major product (eq 1).[1] Prolonged exposure to hydrogen will result in complete conversion to the alkane regardless of the presence of ethylenediamine. Disubstituted unconjugated alkynes are stereospecifically converted to the corresponding (*Z*)-alkenes (eq 2). The specificity is comparable to that obtainable with other catalysts such as Lindlar's catalyst and P2 nickel. Ni-Gr2 also reduces disubstituted alkynes, but with slightly lower stereoselectivity than Ni-Gr1.[2] Attempts to improve the selectivity by addition of amines such as ethylenediamine, quinoline, or piperidine failed, due to complete loss of activity.

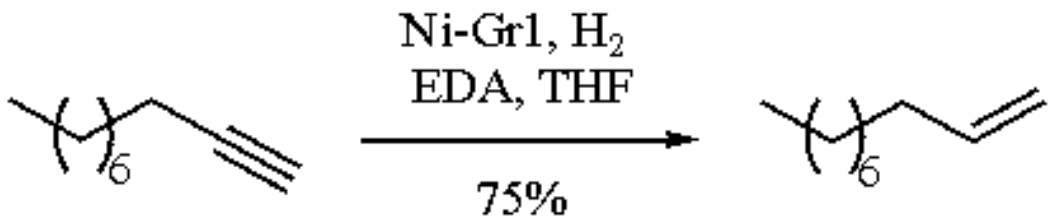

(1)

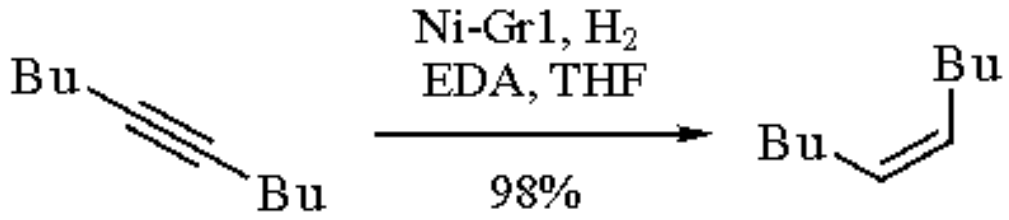

(2)

The reactivity of Ni-Gr2 is in agreement with most common catalysts. Reactivity towards catalytic hydrogenation decreases in the following order: alkyne > alkene &AApprox; nitro > carbonyl > nitrile. Stereoselective reduction of disubstituted alkynes affords (*Z*)-alkenes, although further reduction to the alkane also takes place (eqs 3 and 4).[2] Alkenes are quantitatively reduced to alkanes (eq 5).[2] Conjugation of the double bond with an aromatic ring increases reactivity toward alkenes and ketones.

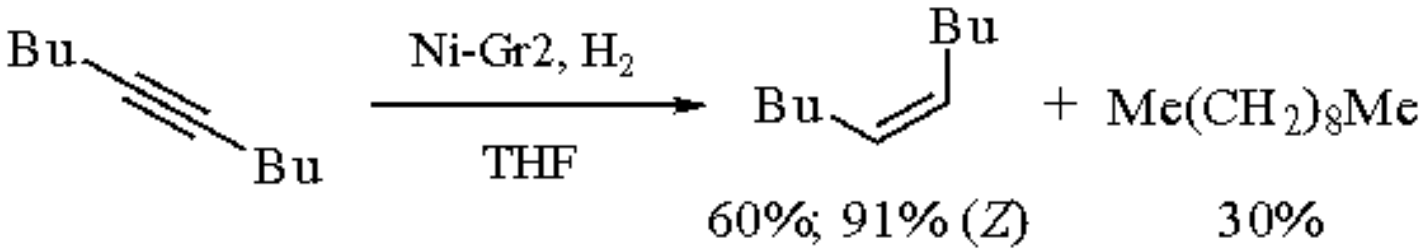

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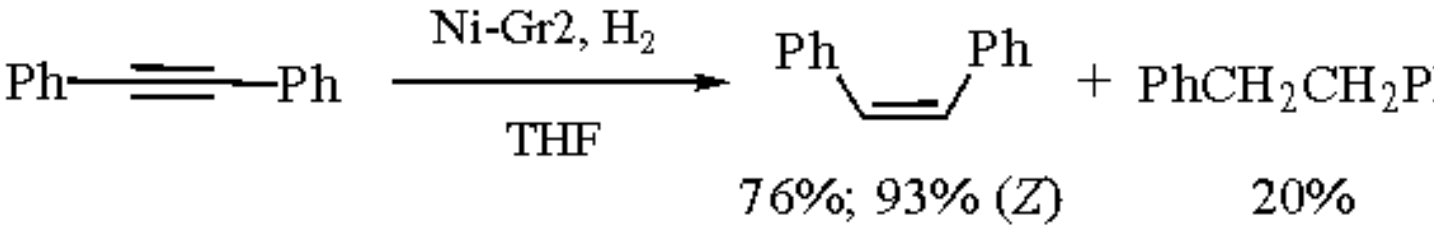

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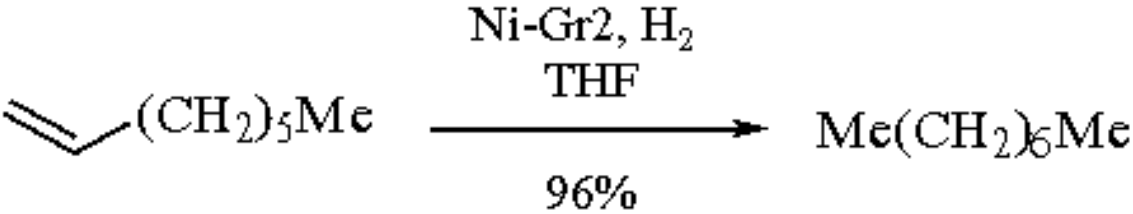

(5)

Ni-Gr2 is a poor catalyst for reduction of nitro groups,[2] presumably due to poisoning of the catalyst. In order to achieve some reaction, a large excess of catalyst relative to substrate is needed.[2] Additionally, nitriles can be reduced to amines even in the presence of ketones.[2]

Selective Hydrogenation of Unsaturated Carbonyls

and β-Diketones.

As a consequence of its reduced activity, Ni-Gr2 selectively reduces the double bond of an α,β-unsaturated ketone in the presence of other alkenes (eq 6),[2] although the reactivity appears to be temperature dependent. In all cases, no reaction takes place at room temperature and elevated temperatures are needed to reduce carbonyl groups as well as hindered double bonds. Similarly, in unsymmetrical β-diketones the less hindered carbonyl group is reduced most easily (eq 7).[2]

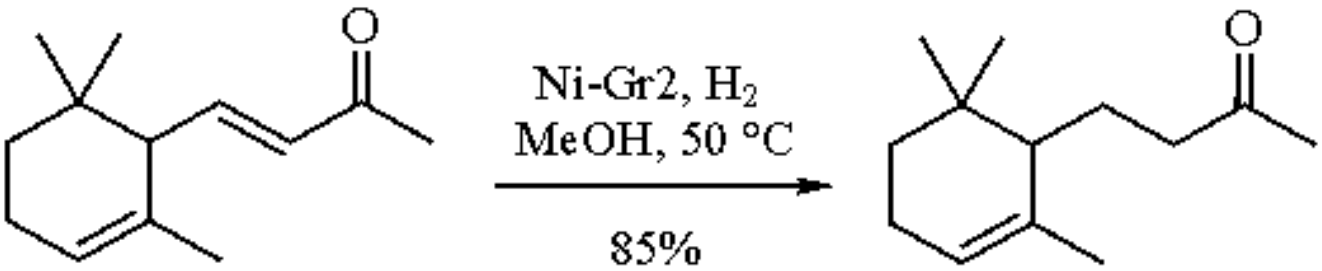

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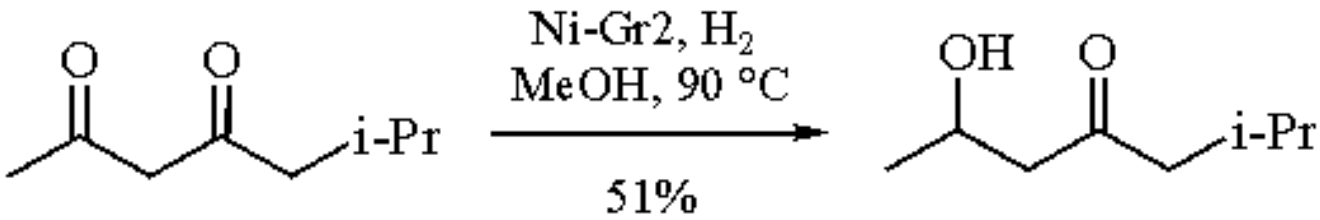

(7)

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Nickel(II) Peroxide[1]

NiO_2

[12035-36-8] · NiO_2 · Nickel(II) Peroxide · (MW 90.69)

(reagent for oxidation of alcohols,[2] phenols,[3] and amines,[4] and for dehydrogenation of heterocycles[5])

Physical Data: black hydrous powder, reportedly a mixture of higher nickel oxides.

Form Supplied in: supplied as nickel peroxide hydrate, $NiO_2.xH_2O$, with Ni content >25%, active oxygen content >30%.

Preparative Methods: by treatment of alkaline nickel sulfate with sodium hypochlorite.[2]

Handling, Storage, and Precautions: as with most nickel compounds, a presumed carcinogen which should be handled with extreme care. Irritating to mucous membranes and upper respiratory tract. Causes dermatitis and may cause allergic respiratory reactions. Use in a fume hood.

Alcohol Oxidations.

Nickel peroxide has been used as a mild, selective reagent for the oxidation of a variety of primary alcohols to the corresponding carboxylic acids in alkaline medium. Saturated primary aliphatic alcohols oxidize cleanly, but some unsaturated alcohols, such as allyl alcohol, give mostly cleavage products. The scope of the reaction is illustrated by the oxidation of 1-butanol and cinnamyl alcohol to the corresponding acids (eqs 1 and 2).[6] Oxidation of 6-hydroxymethyl-1-methyl-2-thiouracil to 1-methylorotic acid also involves replacement of sulfur by oxygen in the thiocarbonyl group (eq 3).[7]

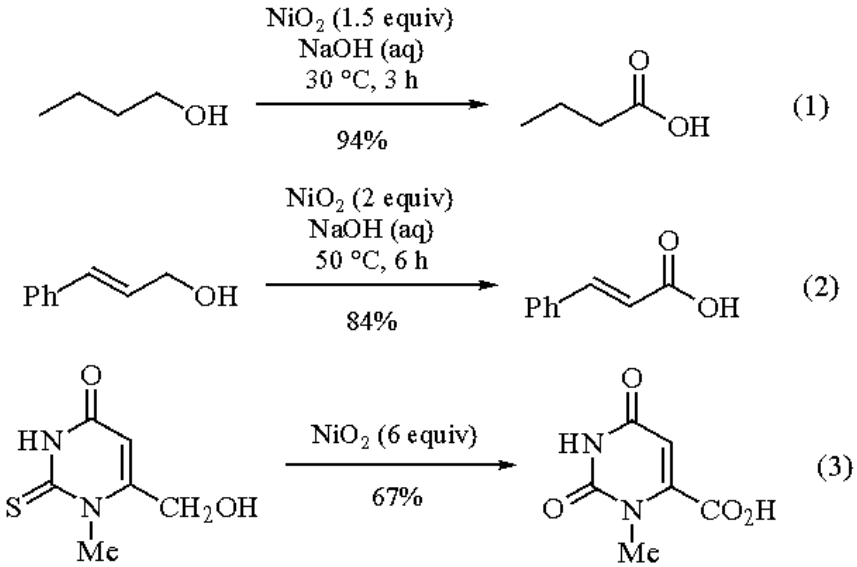

When organic solvents such as petroleum ether or benzene are used in place of water, conversion of alcohols to the corresponding carbonyl compounds is observed. Although the reaction is poor with simple aliphatic alcohols, good to excellent yields of allylic or benzylic aldehydes and ketones are obtained using 1.0-1.2 equiv NiO_2. Allyl alcohol, furfuryl alcohol, benzyl alcohol, and diphenylmethanol in benzene are all smoothly converted to the corresponding aldehyde or ketone in 78-98% yield.[6] Oxidation of 3-phenylpropargyl alcohol under these conditions reportedly gives the aldehyde in 70% yield.[8] The conversion of geraniol to citral (eq 4) is illustrative of the selectivity of this process.[6] Oxidation of vitamin A_1 to retinene[6] and monooxidiation of the terpenoid diol lutein to 3-hydroxy-3´-α-carotene[9] are similarly achieved. Related alcohol oxidations were recently reported using NiO_2 deposited on alumina.[10] Oxidation of polyhydroxy compounds with NiO_2 gives rise to various cleavage products similar to periodate oxidations, depending on the solvent and reaction conditions.[11]

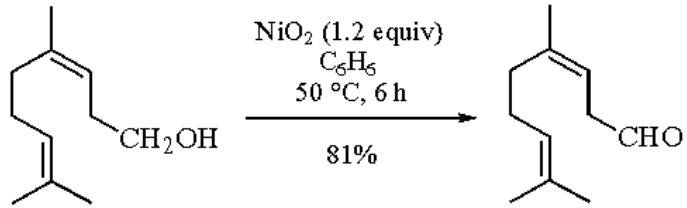

(4)

Oxidation of Phenols.

Treatment of most simple phenols with NiO_2 leads to polymerization, although oxidation of sterically cluttered phenols may lead to dimers, oligomers, or quinonoid structures, depending on the substitution pattern of the phenol.[12] Thus oxidation of 2,6-di-*t*-butyl phenol gives rise to the dimeric 4,4´-diphenoquinone (eq 5),[12] while oxidation of more hindered phenols affords 3,5-disubstituted fuchsones (eq 6).[3] NiO_2 also oxidizes 4-cyanocatechol to the corresponding *ortho*-quinone, whereas Ag_2O oxidation fails.[13]

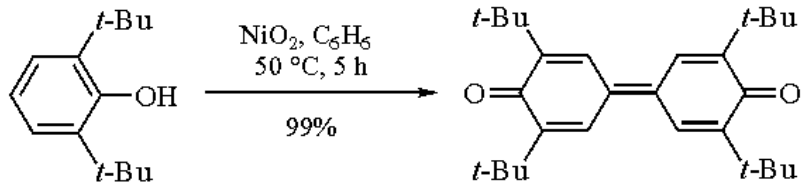

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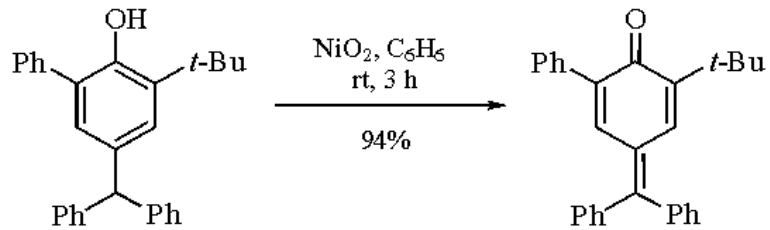

(6)

Amides from Alcohols or Aldehydes.

Primary allenic alcohols are cleanly oxidized to the corresponding aldehydes with NiO_2 in benzene (eq 7), but are converted to amides when the oxidation is carried out in the presence of ammonia (eq 8).[14] Secondary allenic alcohols give the corresponding ketones when oxidized.

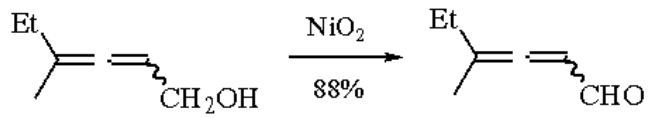

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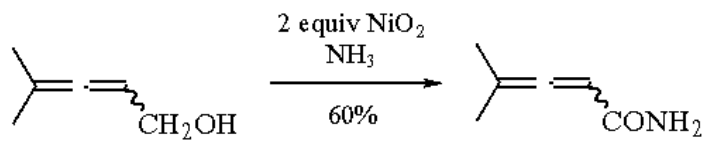

(8)

Oxidation of allylic and benzylic aldehydes with NiO_2 in ether at -20 °C in the presence of ammonia also gives the corresponding amides in good yield, as illustrated by the conversion of piperonal to piperonamide (eq 9).[15] At higher temperatures, an intermediate imine forms which is oxidized to the corresponding nitrile.[15] In the absence of ammonia, oxidation of aldehydes leads to the corresponding acid,[16] while oxidation of ketones in some cases affords 1,4-diketones via a dehydrodimerization process.[17]

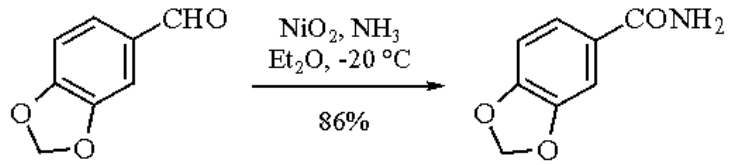

(9)

Amine Oxidations.

NiO_2 oxidation of primary aliphatic and benzylic amines affords the corresponding nitriles, while primary aromatic amines afford the symmetrical azo compounds. Thus oxidation of *n*-heptylamine gives *n*-hexyl cyanide (eq 10), while *p*-nitroaniline gives 4,4´-azonitrobenzene (eq 11).[4]

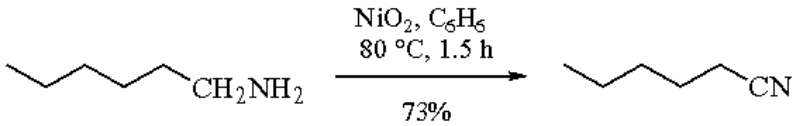

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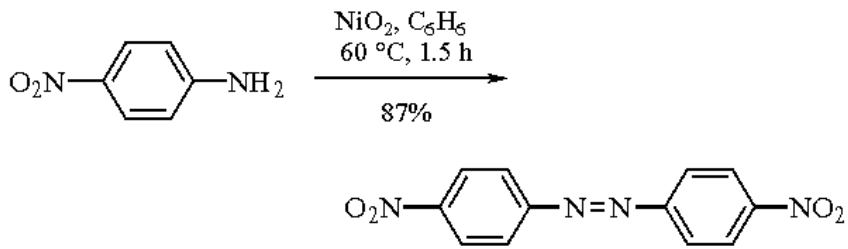

(11)

Secondary aromatic amines undergo oxidative dimerization, affording the symmetrical hydrazines (eq 12).[18]

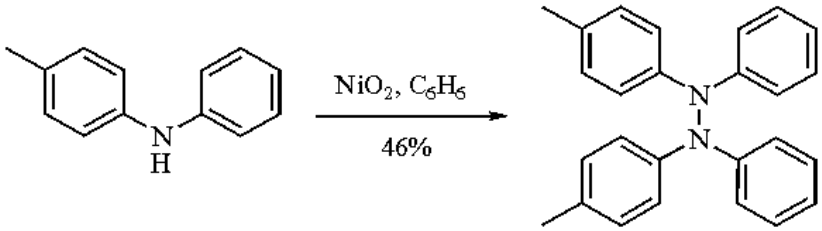

(12)

Oxidation of 1,2-diaminoaromatics leads to ring-opened dinitriles, although the yields are uniformly poor.[19] Thus oxidation of *o*-phenylenediamine with NiO_2 gives *cis,cis*-1,4-dicyano-1,3-butadiene (eq 13), whereas oxidation with ***Manganese Dioxide*** gives only 2,2´-diaminoazobenzene.[20]

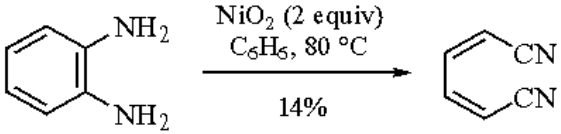

(13)

Heterocycle Synthesis.

Early work indicated that pyrazolines[21] or indolines[22] could be dehydrogenated to pyrazoles or indoles using NiO_2 in refluxing benzene. Subsequent efforts showed that a variety of partially reduced oxygen-, sulfur-, and nitrogen-containing heterocycles could be cleanly dehydrogenated in hydrocarbon or halogenated solvents using NiO_2.[5] These findings included the previously unreported conversion of oxazolines to oxazoles. More recently, it has been found that dihydrotriazoles[23] and flavanones[24] are converted to triazoles and flavones, respectively, by oxidation with NiO_2. Table 1 shows some representative examples of these transformations.[5]

Table 1 NiO_2-Induced Dehydrogenation of Selected Heterocycles

Heterocycle	Equiv of NiO_2	Solvent	Conditions	Product	Yield (%)
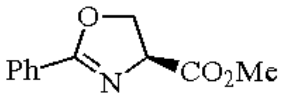	1.5	C_6H_{12}	6 h, reflux	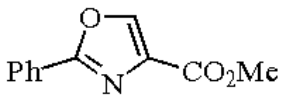	69
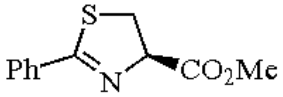	2.0	$CHCl_3$	3 d, 25 °C	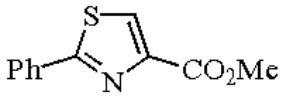	81
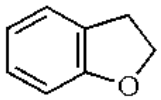	2.2	C_6H_6	11 h, reflux	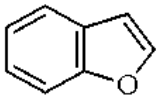	52
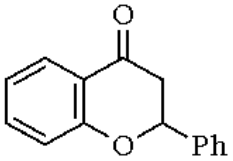	1.6	C_6H_6	4 h, reflux	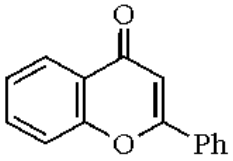	71
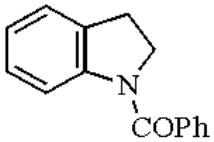	4.4	C_6H_6	24 h, reflux	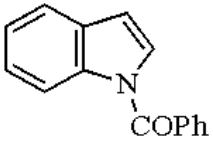	54
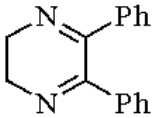	1.7	C_6H_6	4 h, reflux	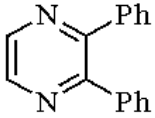	92

Treatment of Schiff bases derived from *o*-aminophenols and benzaldehyde with NiO_2 in benzene leads to benzoxazoles via an intramolecular oxidative cyclization (eq 14).[25] The monoimines derived from *o*-phenylendiamine and substituted benzaldehydes are similarly cyclized to benzimidazoles.[26] Hydrazones of pyridine-2-carbaldehyde and 2-acetylpyridine are also oxidatively cyclized to ring-fused triazoles by NiO_2 in benzene (eq 15).[27]

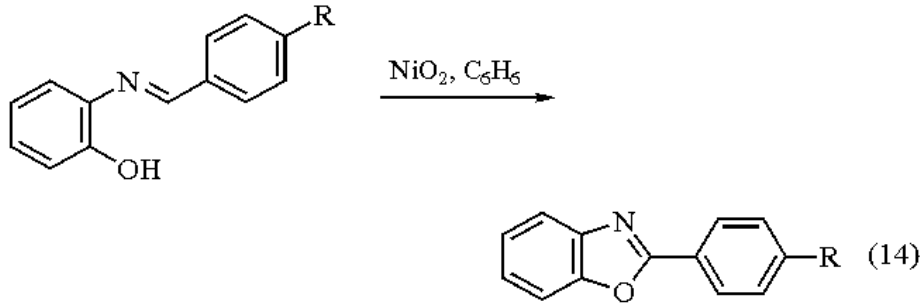

R = OMe, 72%; H, 73%; NO_2, 73%

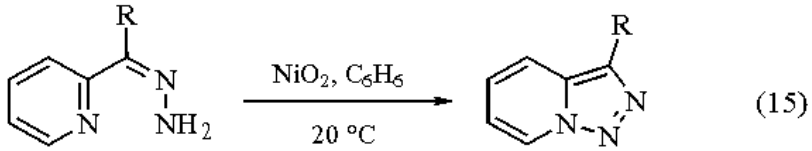

R = H, 97%; Me, 94%

Miscellaneous Reactions.

NiO_2 oxidizes benzophenone hydrazone to diphenyldiazomethane in quantitative yield[28] and, in the absence of solvent, converts diphenylmethane and fluorene to benzophenone and fluorenone in 79% and 66% yields, respectively.[21] Thiols and sulfides give disulfides in high yield when treated with the reagent.[29,30]

---

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Nickel(II) Tetraphenylporphyrinate

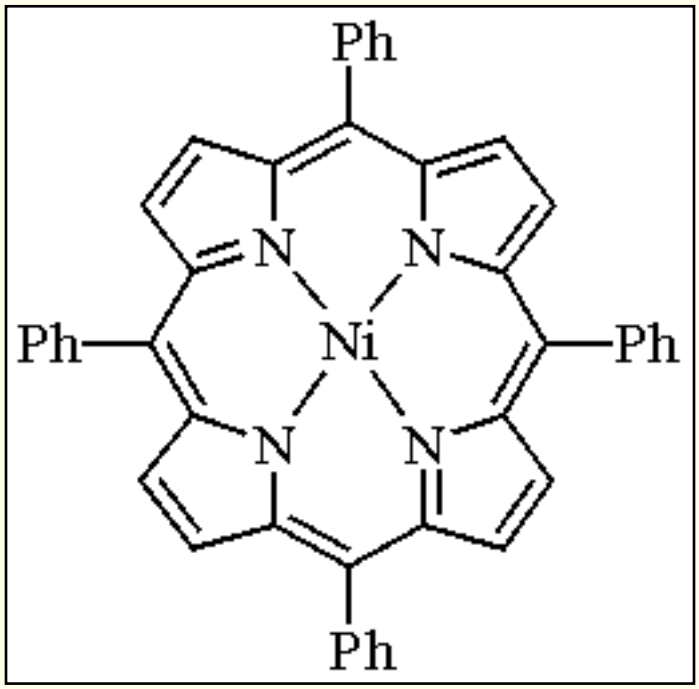

[14172-92-0] · $C_{44}H_{28}N_4Ni$ · Nickel(II) Tetraphenylporphyrinate · (MW 671.45)

(electron transfer agent and catalyst for aryl halogen exchange reactions;[1] used in cyclizations of saturated o-iodo ketones[2] and hydrogenation of alkenes[3])

Alternate Name: NiTPP.

Physical Data: sublimes with decomp at 400-450 °C.

Solubility: insol H_2O; sol $CHCl_3$; slightly sol ether, benzene, hexane, methanol.

Form Supplied in: purple powder, widely available.

Handling, Storage, and Precautions: stable in air and water. Some nickel compounds are known carcinogens so standard safety precautions apply.

Aryl Halogen Exchange.

Simple aryl bromides have been converted to aryl chlorides using aqueous ***Sodium Hypochlorite*** under phase-transfer conditions and NiTPP as a catalyst (eq 1).[1] Yields were quantitative when aryl bromides were used. Chlorination of aryl iodides led to competitive I-chlorination, and substrates with alkyl substituents gave poorer yields because of benzylic chlorination.

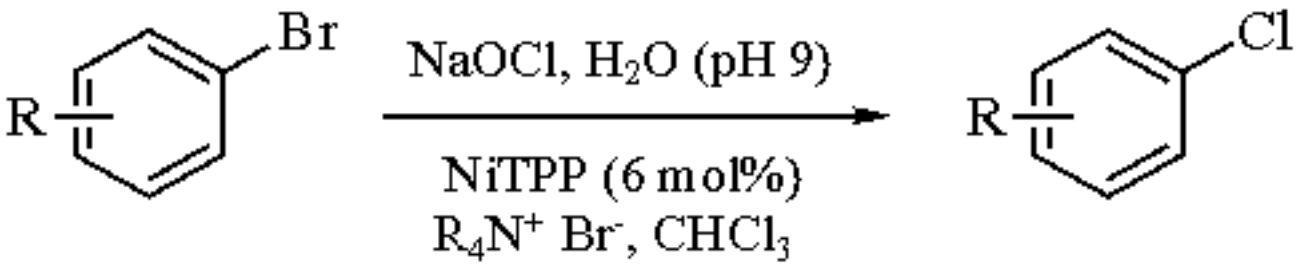

(1)

Cyclization of Iodo Ketones.

The dianion of NiTPP has been prepared by reaction with ***Lithium Naphthalenide*** in THF at 0 °C.[2] It has proved to be effective in converting o-iodo ketones to cyclic alcohols (eq 2). Other reagents (Li/NH_3, Na/naphthalene, or Na/phenanthrene) gave lower yields.[2] $NiTPP^{2-}$ failed to convert vinylic iodo ketones to cyclic alcohols.

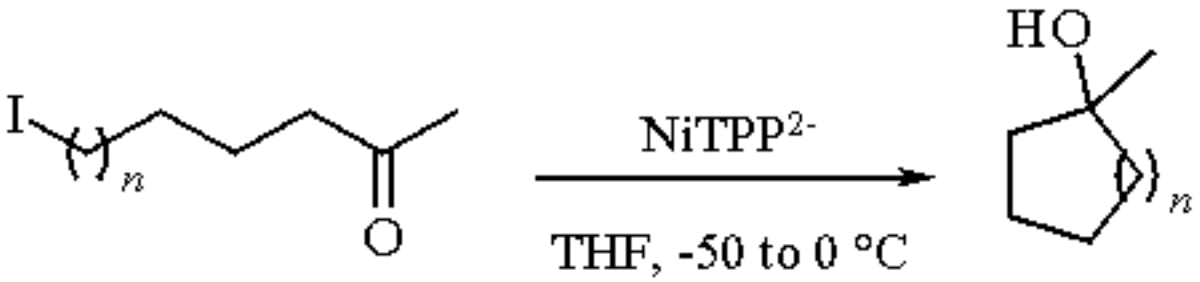

(2)

$n = 1$, 61%; $n = 2$, 88%

Hydrogenation of Alkenes.

$NiTPP^{2-}$ has been deposited on silica wool by reaction of a 1:3 mixture of NiTPP with Na or Na benzophenone ketyl in THF. In the presence of H_2 at 90 °C, this catalyst has been used to hydrogenate alkenes and alkynes. For example, butadiene gave 1-butene, and hydrogenation of propyne to propene was fast compared to subsequent reduction to propane.[3]

---

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Niobium(IV) Chloride

$NbCl_4$

($NbCl_4$)

[13569-70-5] · Cl_4Nb · Niobium(IV) Chloride · (MW 234.71) ($NbCl_4(THF)_2$)

[61247-55-2] · $C_8H_{16}Cl_4NbO_2$ · Niobium(IV) Chloride · (MW 378.95)

(reductively couples imines and nitriles[1])

Physical Data: $NbCl_4$: subl. 200 °C/10^{-4} mmHg. $NbCl_4(THF)_2$: mp 110 °C (dec), yellow crystals.

Solubility: sol ethereal and thioether solvents.

Form Supplied in: not commercially available.

Preparative Method: tetrachlorobis(tetrahydrofuran)niobium is prepared from commercially available niobium(V) chloride in two steps.[2]

Purification: filter and wash with THF and dry under vacuum.

Handling, Storage, and Precautions: corrosive; moisture sensitive. Use in a fume hood.

Reductive Coupling of *N*-Silylimines and Nitriles.

Treatment of *N*-silylimines with niobium(IV) chloride leads to 1,2-diamines (eq 1). The reaction is the nitrogen analog of the pinacol coupling reaction. The reaction produces initially the bis(metal imido) complex, which is hydrolyzed to the corresponding diamine by reaction with aqueous ***Potassium Hydroxide***. Alternatively, reaction of nitriles, ***Tri-n-butylchlorostannane***, and niobium(IV) chloride produces a similar coupling product (eq 2). Both aryl- and alkyl-substituted imines are suitable substrates for the reaction. Predominantly the (±)-isomer is produced in the coupling reaction; however, the selectivity is considerably greater when imines derived from aryl aldehydes are employed in the reaction.

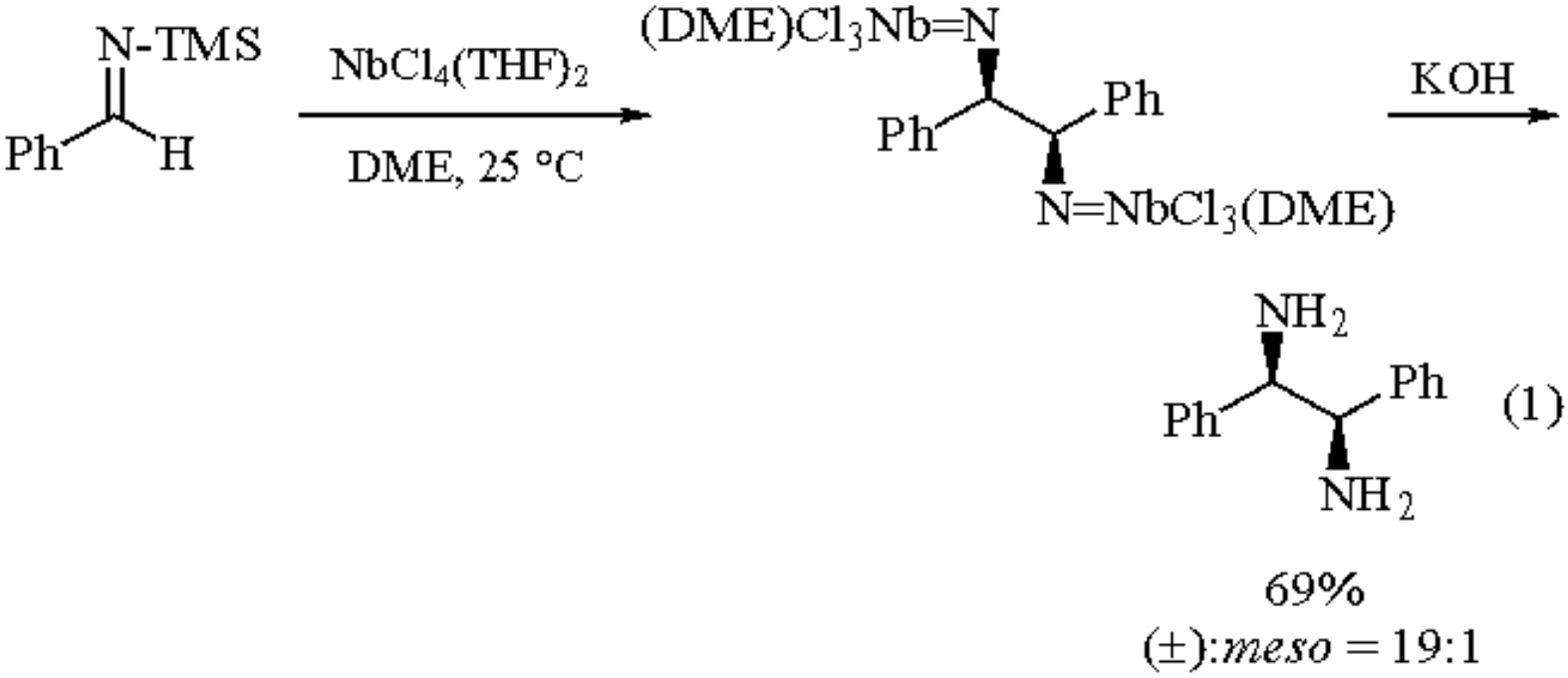

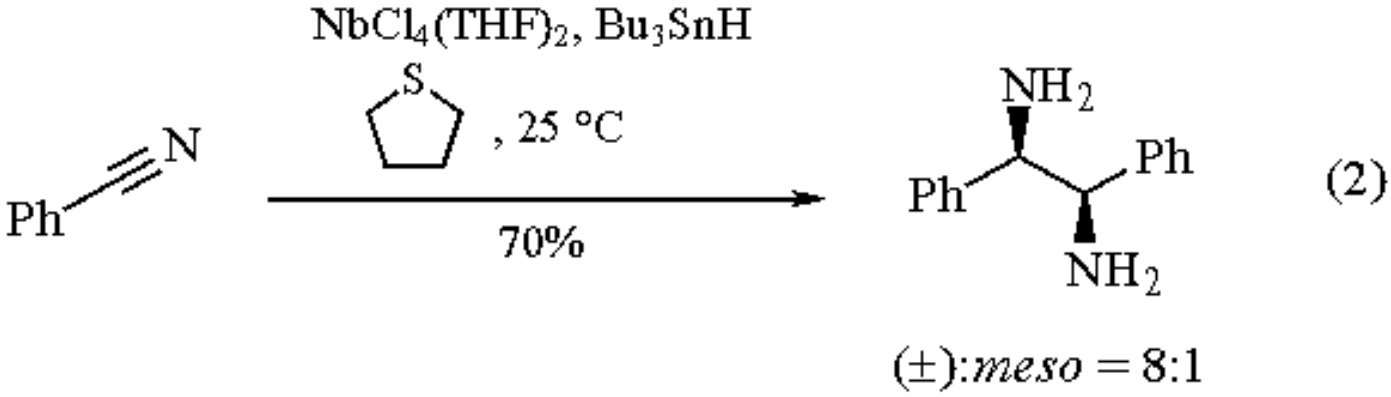

Related Reagents.

Niobium(V) Chloride-Zinc; ***Samarium(II) Iodide***; ***Titanium(III) Chloride***.

---

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Niobium(V) Chloride-Zinc

$NbCl_5$-Zn

($NbCl_5$)

[10026-12-7] · Cl_5Nb · Niobium(V) Chloride-Zinc · (MW 270.15) (Zn)

[7440-66-6] · Zn · Niobium(V) Chloride-Zinc · (MW 65.37)

(synthesis of allylic alcohols, dienes, and naphthols; selective reduction of alkynes to (*Z*)-alkenes)

Solubility: sol THF-PhH, DME-PhH, HMPA.

Preparative Method: generated in situ from pentachloroniobium and ***Zinc***.

Handling, Storage, and Precautions: should be prepared and used under an inert atmosphere of nitrogen or argon.

A combination of $NbCl_5$ with Zn in either THF or DME presumably generates a $NbCl_3(L)_2$ species, which reacts with alkynes to give intermediate metallacyclopropenes.[1] These metallacyclopropenes can then be quenched with $NaOD/D_2O$ to give *cis*-dideuterated alkenes (eq 1). In addition, reaction of the metallacyclopropenes with aldehydes or ketones gives either allylic alcohols or dienes, and reaction with phthalic dicarbaldehyde yields naphthols. The latter two transformations can be effected in higher yield using $TaCl_5$-Zn and $NbCl_3$(DME), respectively.

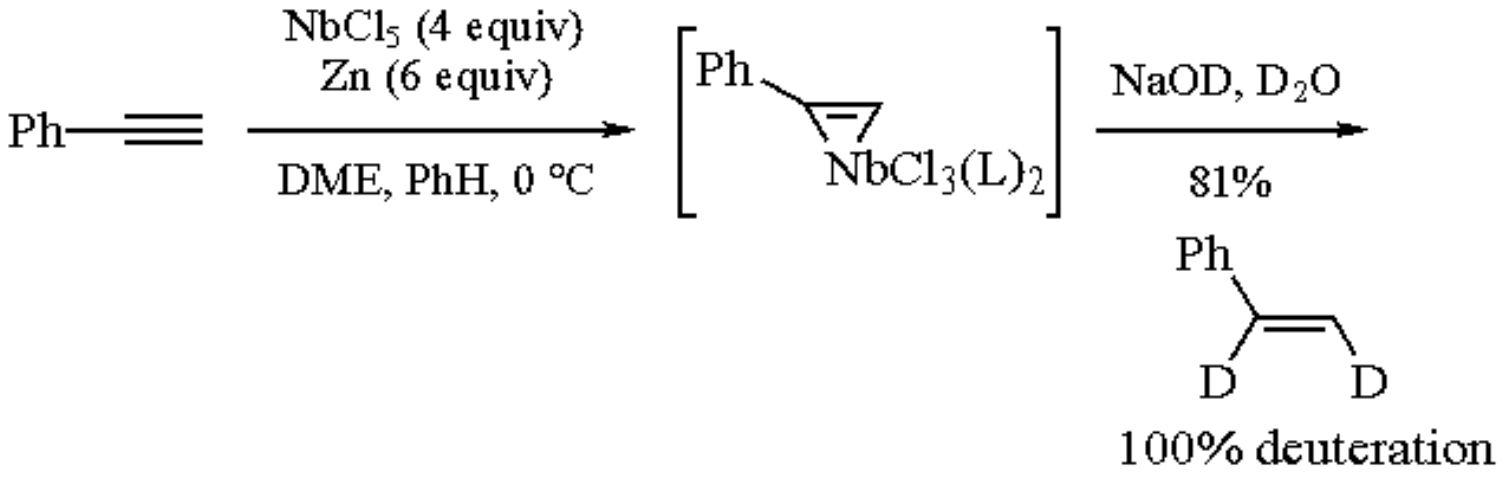

(1)

1. (a) Kataoka, Y.; Takai, K.; Oshima, K.; Utimoto, K. *JOC* **1992**, *57*, 1615. (b) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K.; Utimoto, K. *JOC* **1992**, *57*, 1973. (c) Kataoka, Y.; Miyai, J.; Tezuka, M.; Takai, K.; Oshima, K.; Utimoto, K. *TL* **1990**, *31*, 369.

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Nitric Acid

HNO_3

[7697-37-2] · HNO_3 · Nitric Acid · (MW 63.02) (fuming)

[52583-42-3]

(nitration and oxidation of organic molecules)

Physical Data: mp -41.6 °C; bp 83 °C; *d* 1.50 g cm^{-3}.[1]

Solubility: sol H_2O.

Form Supplied in: clear colorless liquid (69-71% in H_2O); fuming nitric acid is a colorless to pale yellow liquid, HNO_3 content >90% widely available.

Preparative Methods: anhydrous nitric acid can be prepared by distilling fuming nitric acid from an equal volume of concentrated sulfuric acid.

Handling, Storage, and Precautions: strong acid; oxidizing agent. Colorless acid may discolor on exposure to light. Anhydrous nitric acid decomposes above the freezing point to give NO_2, H_2O, and O_2. Emits toxic fumes of nitrogen oxides. Hygroscopic. Contact with other material may cause fire. Poison. Corrosive. Avoid contact and inhalation. May be fatal if inhaled, swallowed, or absorbed through skin. Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract, eyes, and skin.[2] Many of the reactions mentioned in this article require special care in order to avoid uncontrollable reactions and the possibility of explosions. Many nitrated compounds are unstable. The reader is therefore strongly urged to refer to original literature procedures.

Nitric acid holds an important place in the history of organic synthesis. It is used primarily for the nitration of organic molecules and to effect a wide variety of oxidative transformations. The advantage of nitric acid as a reagent is that it allows simple and straightforward isolation of products. However, it is not a very selective oxidant.

Nitration of Simple Aromatic Systems.[3]

Nitration of aromatics has been studied extensively. The mechanism by which nitration occurs is believed to involve electrophilic attack by NO_2^+. The concentration of the active species increases in the presence of the more acidic ***Sulfuric Acid***. With this mixed reagent, the nitration of simple benzene derivatives[4] and polyaromatic ring systems[5]

has been accomplished. For example, treatment of methyl benzoate with concentrated nitric acid gives methyl 3-nitrobenzoate in 81-85% yield.[4a] In polyaromatic ring systems, nitration usually occurs selectively on the more electron rich aromatic ring (eq 1).[6] Under the reaction conditions, anilines are protonated and the aniline ring is relatively unreactive (eq 2).[5e]

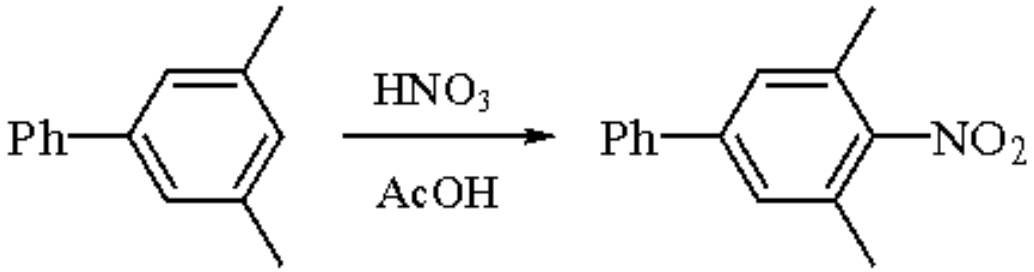

(1)

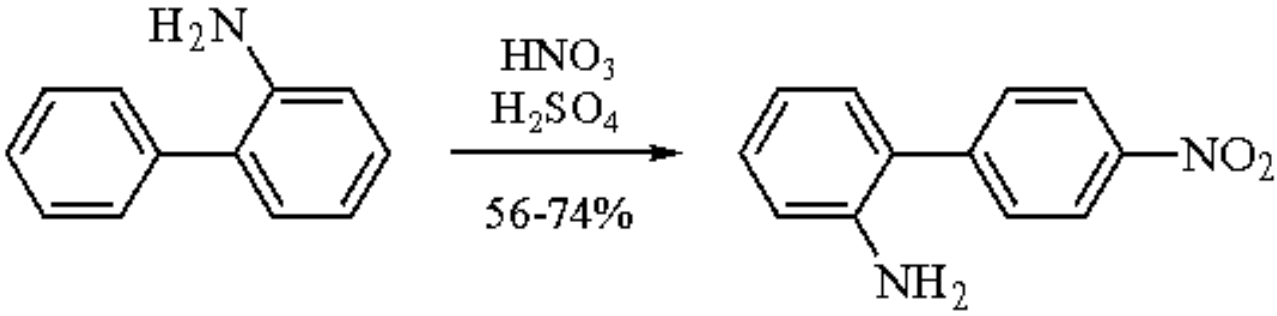

(2)

Nitration of Aromatic Heterocycles.

Several types of aromatic heterocycles have been nitrated with nitric acid.[7] For example, when thiophene is treated with nitric acid in acetic anhydride, 2-nitrothiophene is formed in 70-85% yield. In order to prepare 3-nitrothiophene, a deactivating strategy is required (eq 3). 2,4-Dinitrothiophene can be obtained by nitration of either 2-nitro- or 3-nitrothiophene.[7a] Nitration of the *N*-oxide of 2-methylpyridine allows the introduction of a nitro group at the 4 position in good yield (eq 4).[7b]

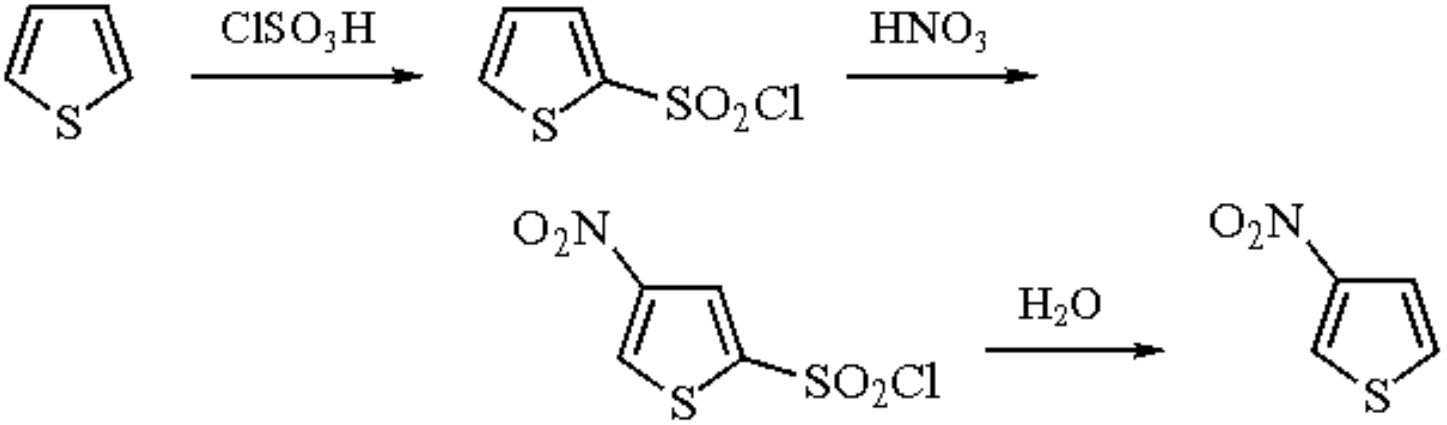

(3)

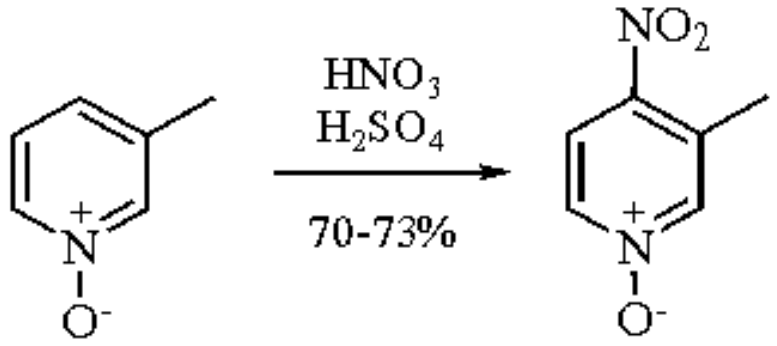

(4)

Nitration of Alkenes.[8]

Alkenes may also be nitrated by nitric acid. This reaction has been exploited in the synthesis of a number of steroid derivatives.[9] Fuming nitric acid converts cholesteryl acetate to 6-nitrocholesteryl acetate in good yield (eq 5). The nitration of the more highly functionalized dienyl acetate (eq 6) provides the corresponding nitro steroid. Treatment of 1,1-dichloro-2-fluoroethylene with nitric acid in concentrated sulfuric acid provides fluoronitroacetyl chloride in 16% yield.[10] 2-Sulfolenes have also been nitrated.[11]

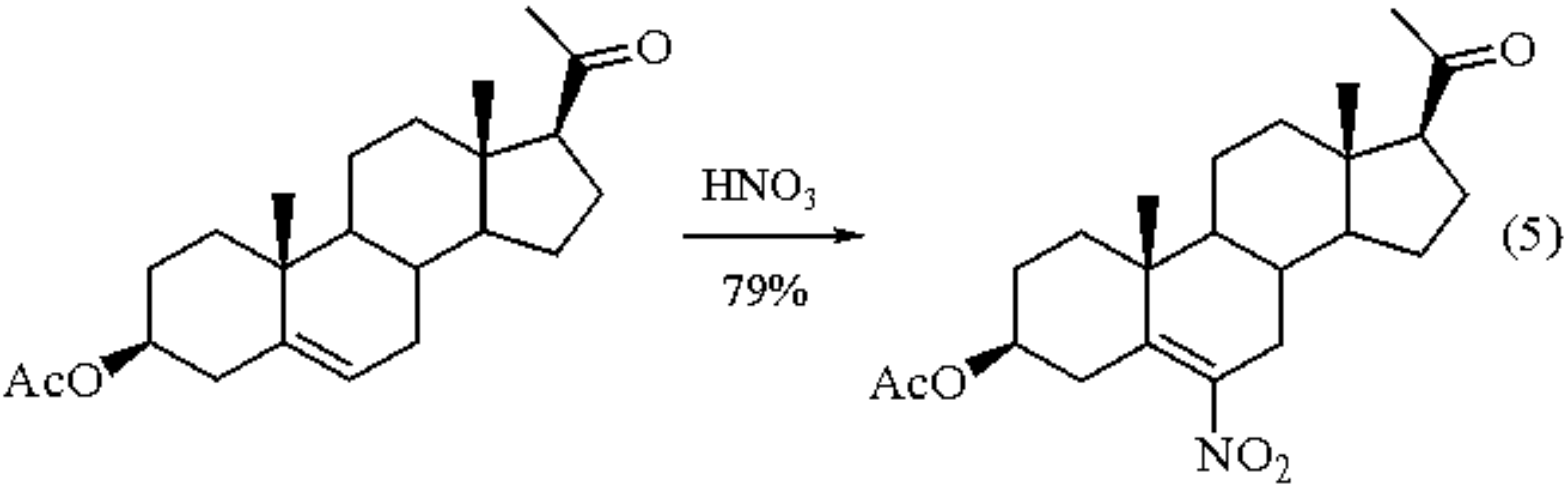

(5)

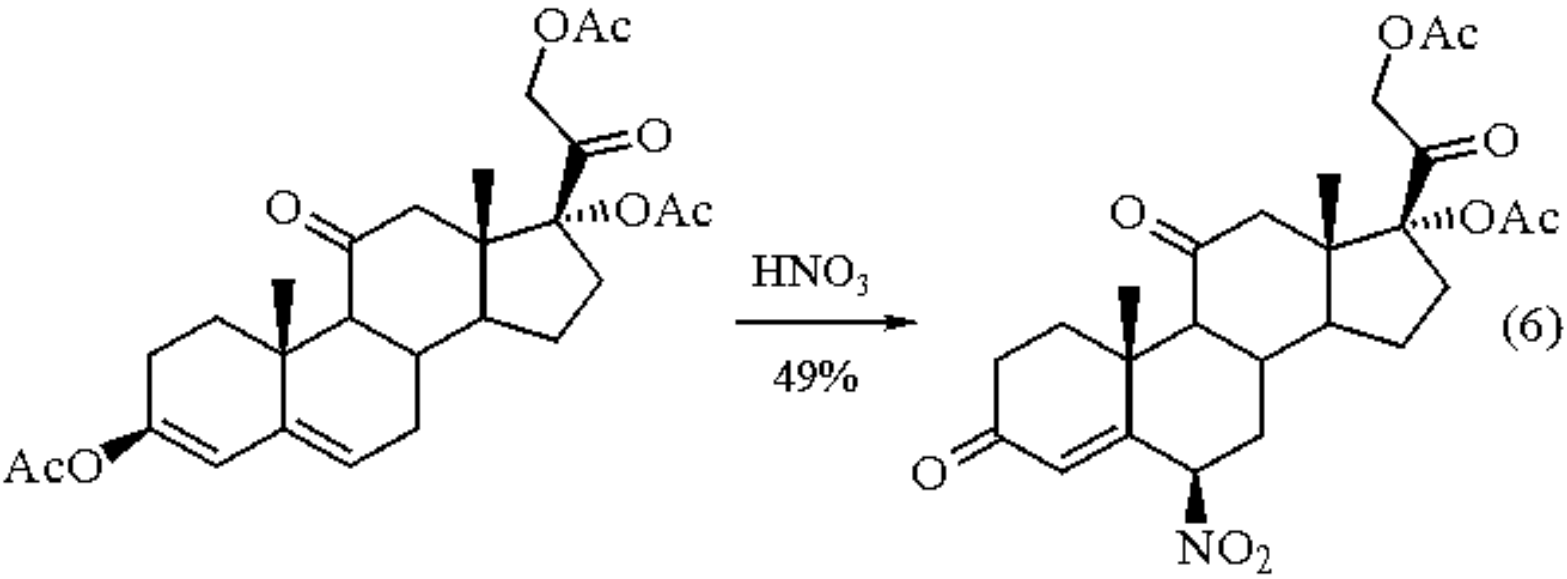

(6)

Nitration of Active Methylene Carbons.[8,12]

Active methylene carbons are nitrated by a number of reagents.[12,13] With nitric acid the nitration of β-diketones can be achieved (eq 7). Nitration of diethyl malonate provides diethyl nitromalonate in 92% yield. α-Nitro ketones are obtained by nitration of ketones or enol acetates with the reagent derived from nitric acid and ***Acetic Anhydride*** in moderate to good yields (eq 8).[14]

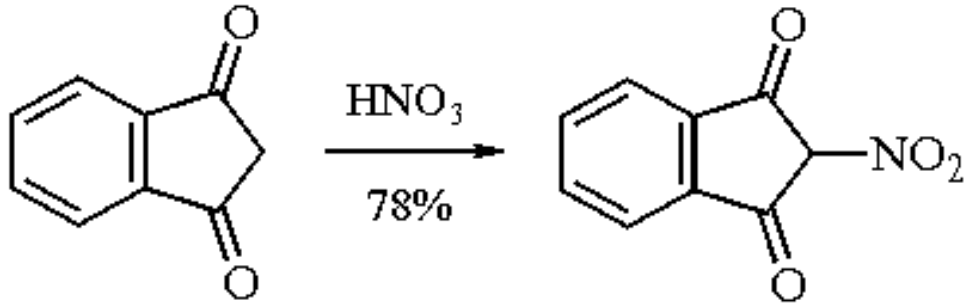

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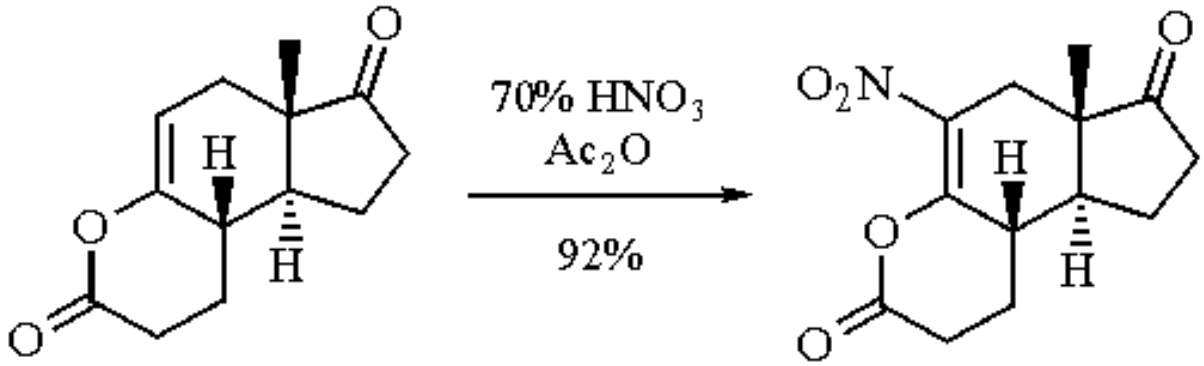

(8)

Nitration of Heteroatoms.

Secondary amines and primary and secondary amides can be converted to *N*-nitro compounds by direct nitration with nitric acid.[15,16] Although most primary amines cannot be nitrated directly, it is possible to obtain primary nitramines by nitration of the corresponding dichloroamines (eq 9).[17] Treatment of pyrrolidone with nitric acid and acetic acid in the presence of copper provides *N*-nitroso-2-pyrrolidone in 70% yield;[18] note that this transformation represents *N*-nitrosation.

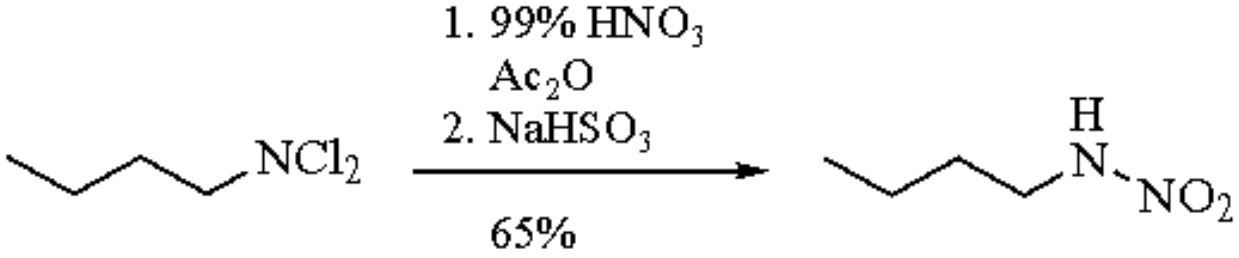

(9)

Nitrolysis of dialkyl *t*-butylamines with nitric acid and sulfuric acid or acetic anhydride provides secondary nitramines (eq 10).[19] More recently, Suri has shown that the reagent derived from ammonium nitrate and trifluoroacetic acid is effective for *N*-nitration.[20]

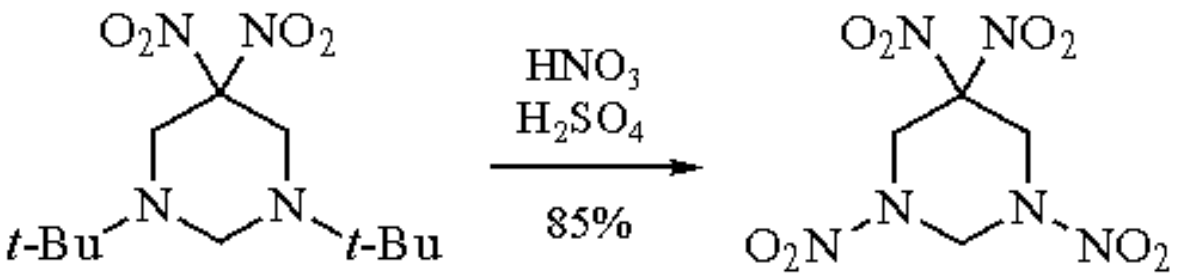

(10)

Acyl nitrates can be prepared conveniently on a laboratory scale by treatment of 90% nitric acid with a tenfold excess of the corresponding acid anhydrides.[21]

Oxidation of Alcohols, Aldehydes, and Esters.

Nitric acid oxidizes alcohols and aldehydes to the corresponding carboxylic acids. For example, 1-chloro-3-propanol is oxidized to 3-chloropropanoic acid in 78-79% yield.[22] 3-Chloropropionaldehyde affords the same product.[23] Primary alcohols protected as esters are oxidized to the carboxylic acids (eq 11).[24] In a two-phase solvent system (for example dimethyl ether and water), the oxidation of benzyl alcohols can be controlled so that aldehydes are obtained.[25]

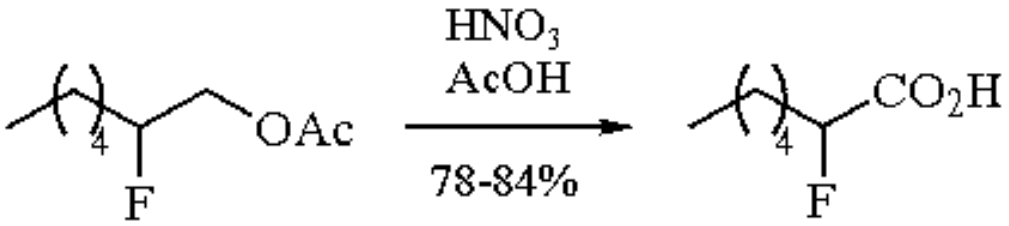

(11)

Oxidative Cleavage.

Treatment of cyclohexanone with 33% nitric acid gives adipic acid in quantitative yield;[26] oxidation of cyclohexanol affords the same product (eq 12).[27] Glutaric acid is obtained in 70-75% yield by oxidative cleavage of 3,4-dihydro-2*H*-pyran.[27]

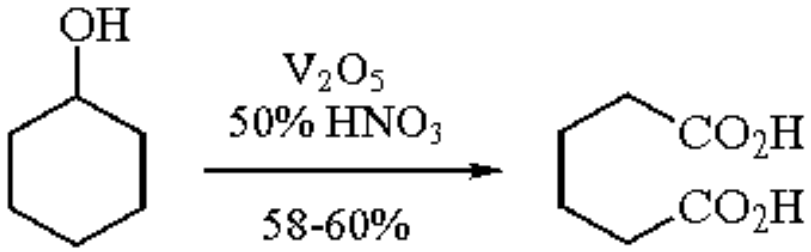

(12)

Oxidation at Benzylic Position.

Nitric acid oxidizes many aromatic alkyl substituents to the carboxylic acid group. Thus toluene is oxidized to

benzoic acid in 85-90% yield.[28] Oxidation of ethylbenzene with 15% nitric acid also gives benzoic acid in 80% yield. The reaction is general and has also been applied to the oxidation of pyridine derivatives. When 4-methylpyridine is treated with 10% nitric acid in phosphoric acid at elevated temperature and pressure, 4-pyridinecarboxylic acid is obtained in 93% yield.[29] The reaction of *p*-isopropyltoluene can be controlled to give the partially oxidized product, *p*-methylbenzoic acid, in 56-59% yield.[27] Additional examples of selective benzylic oxidations are shown in eqs 13 and 14.[30,31]

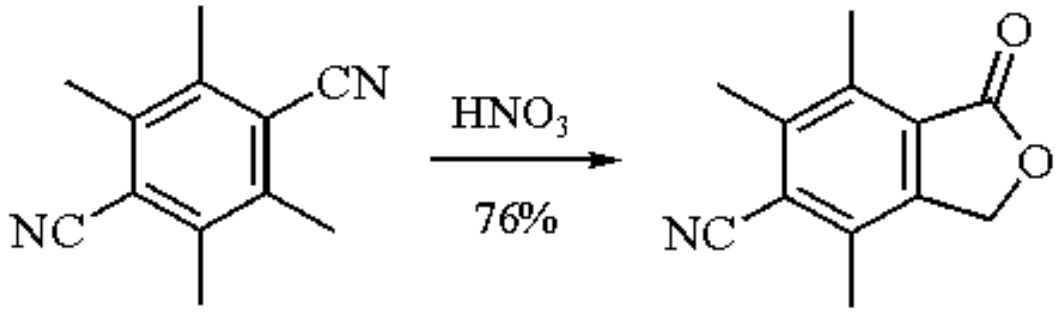

(13)

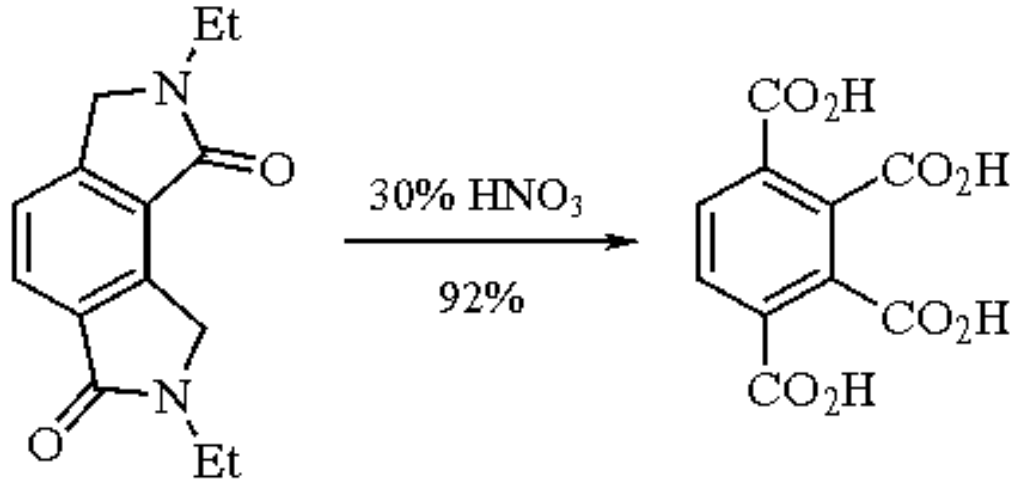

(14)

Oxidation to Quinones.

Nitric acid oxidizes a wide variety of hydroquinone derivatives to quinones (eq 15).[32] Aminonaphthols can be converted to naphthoquinones by treatment with nitric acid (eq 16).[27] Perhalogenated aromatic systems have also been oxidized to quinones (eq 17).[33]

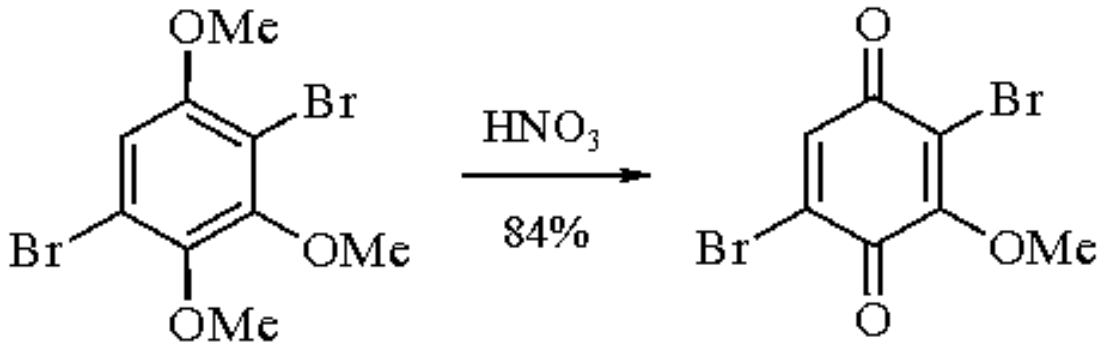

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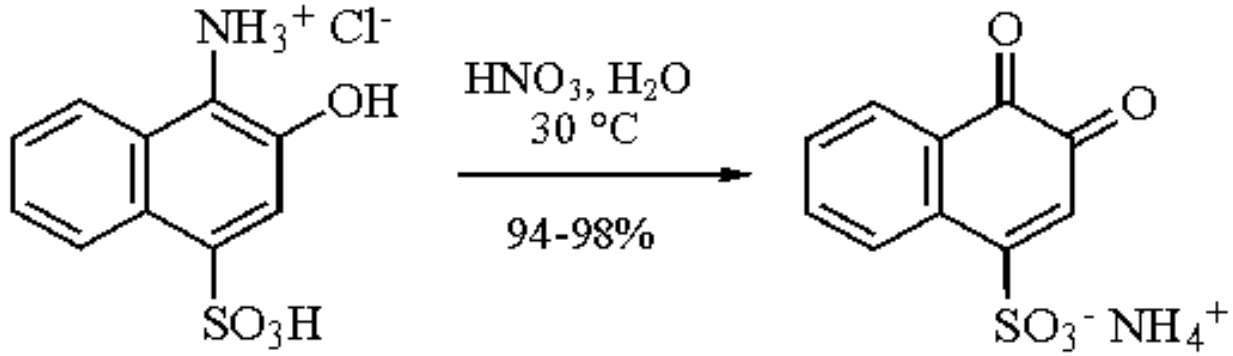

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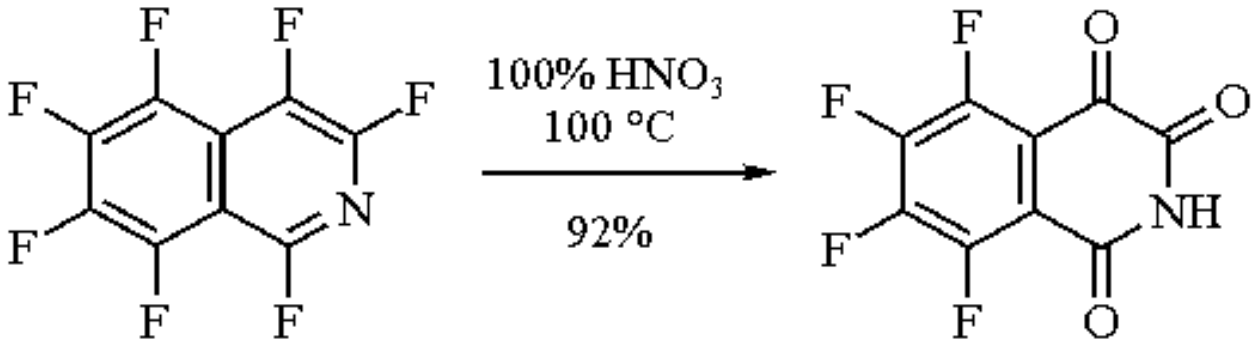

(17)

Dehydrogenation and Aromatization.

Dihydropyridines can be aromatized by dilute nitric and sulfuric acid (eq 18).[34] Diethyl hydrazodicarboxylate is dehydrogenated by fuming nitric acid to diethyl azodicarboxylate in 70-80% yield.[35]

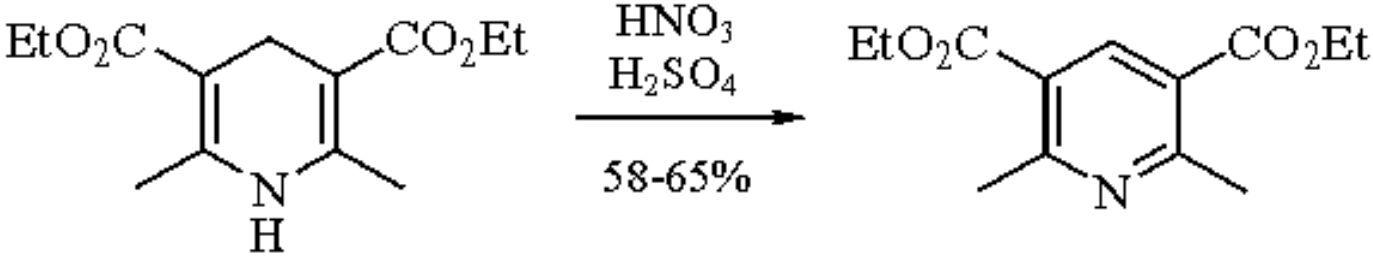

(18)

Oxidation of Heteroatoms.

The nitroso group is oxidized efficiently to the nitro group by nitric acid.[36] For example, 2,4-dinitrosoresorcinol is converted efficiently to 2,4,6-trinitroresorcinol with concentrated nitric acid (eq 19).[37]

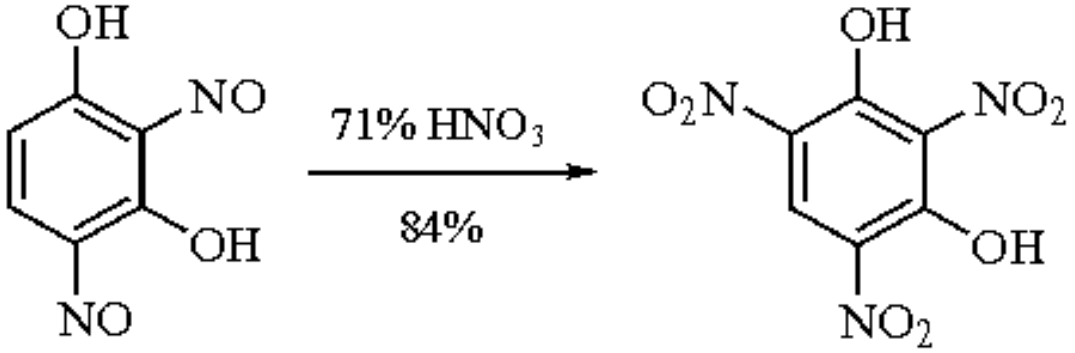

(19)

Azoxycyclohexane can be obtained by oxidation of azocyclohexane.[38] Dialkyl sulfides have been oxidized to the corresponding sulfones[39] and sulfoxides;[40] thiols provide sulfonic acids (eq 20).[41] Iodoso compounds have been obtained from oxidation of aryl iodides (eq 21).[42] Nitric acid converts 2-amino-6-nitrobenzonitriles to substituted 1,2,3-benzotriazin-4(3*H*)-one N^2-oxides (eq 22).[43]

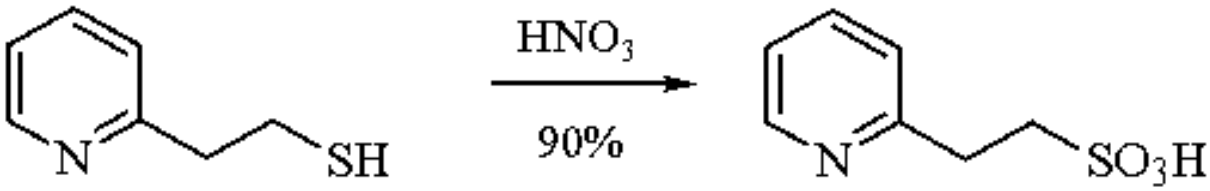

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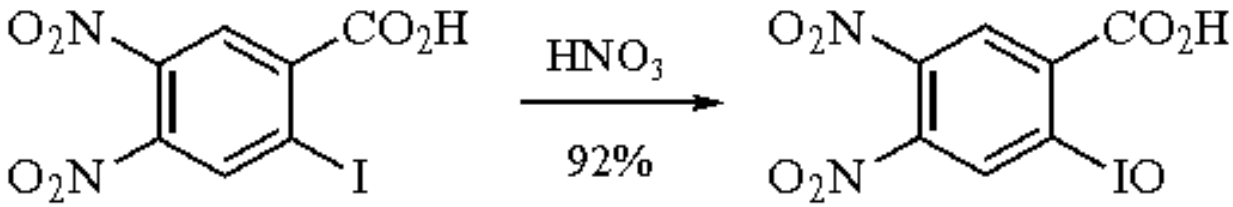

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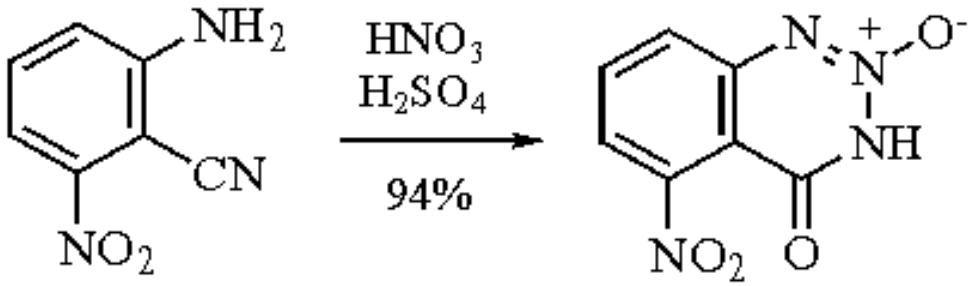

(22)

Other Uses.

Dichloromaleic anhydride has been obtained in 81% yield by treatment of hexachlorobutadiene with fuming nitric acid followed by concentrated sulfuric acid.[25] Pyrroles react rapidly with nitric acid to give pyrrolinones (eq 23).[44] Desulfurization of 1,2,4-triazole-3-thiol with nitric acid presumably involves the formation of the sulfonic acid, which is then hydrolyzed to triazole in 52-58% yield.[27,45]

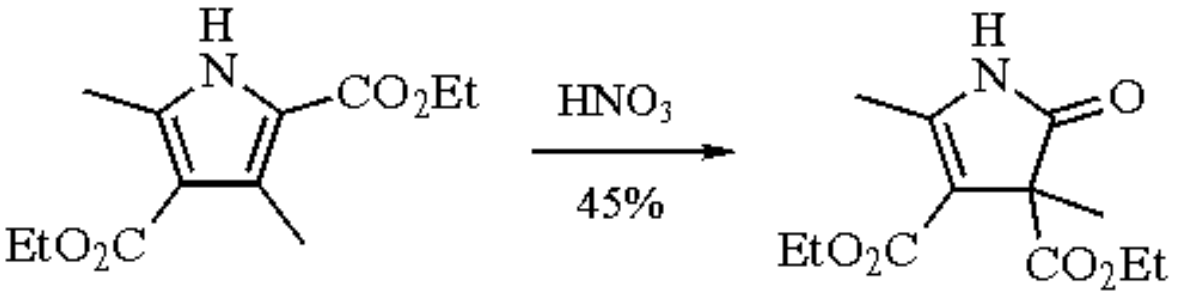

(23)

Primary alkyl halides have also been oxidized to provide the corresponding carboxylic acids. On treatment with concentrated nitric acid, *trans*-2,3-bis(iodomethyl)-*p*-dioxane provides *trans*-*p*-dioxane-2,3-dicarboxylic acid in 73% yield.[46]

---

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o-Nitrobenzeneseleninic Acid

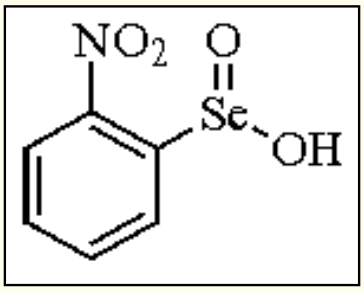

[56790-59-1] · $C_6H_5NO_4Se$ · *o*-Nitrobenzeneseleninic Acid · (MW 234.08)

(catalyst with hydrogen peroxide for the epoxidation of alkenes,[1,2] the oxidation of sulfides,[2] the Baeyer-Villiger oxidation of aromatic aldehydes and ketones,[3] and the conversion of aldehydes to esters[4] and nitriles[5])

Physical Data: mp 184-186 °C (dec).

Solubility: slightly sol water; sol DMF.

Preparative Methods: obtained from the oxidation of bis(2-nitrophenyl) diselenide with 30% ***Hydrogen Peroxide***[6] or concd ***Nitric Acid***.[7] Bis(2-nitrophenyl) diselenide is prepared by reaction of ***Lithium Diselenide*** with 2-nitrochlorobenzene[8] or from the base hydrolysis of 2-nitrophenyl selenocyanate.[1]

Handling, Storage, and Precautions: both 2-nitrobenzeneseleninic acid and bis(2-nitrophenyl) diselenide are stable indefinitely at room temperature. Selenium compounds are potentially toxic and should be handled in a fume hood.

2-Nitrobenzeneseleninic acid catalyzes the epoxidation of alkenes in CH_2Cl_2 under two-phase reaction conditions with 30% ***Hydrogen Peroxide*** (eq 1).[1,2,9,10] Bis(2-nitrophenyl) diselenide is typically used as an in situ source for 2-nitrobenzeneseleninic acid, and anhydrous $MgSO_4$ is added to facilitate epoxidation by scavenging excess water (see also ***2,4-Dinitrobenzeneseleninic Acid***).[1]

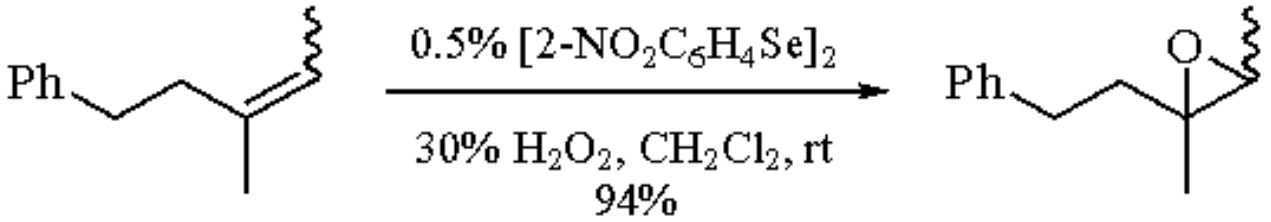

(1)

As a safe, convenient, and inexpensive alternative to peroxycarboxylic acids, 2-nitroperoxybenzeneseleninic acid (eq

2),[11] catalytically generated, converts sulfides either to sulfoxides (>95%) or cleanly to sulfones depending on the amount of H_2O_2 used.[2] The low solubility of catalyst in both CH_2Cl_2 and H_2O allows acid-sensitive substituents to remain intact during the Baeyer-Villiger oxidation of aromatic aldehydes (eq 3).[3] α,β-Unsaturated aldehydes give vinyl formates as the major products, but the oxidation of ketones is limited to polymethoxyacetophenones, with 90% H_2O_2 being recommended to obtain reasonable reaction rates.[12]

(2)

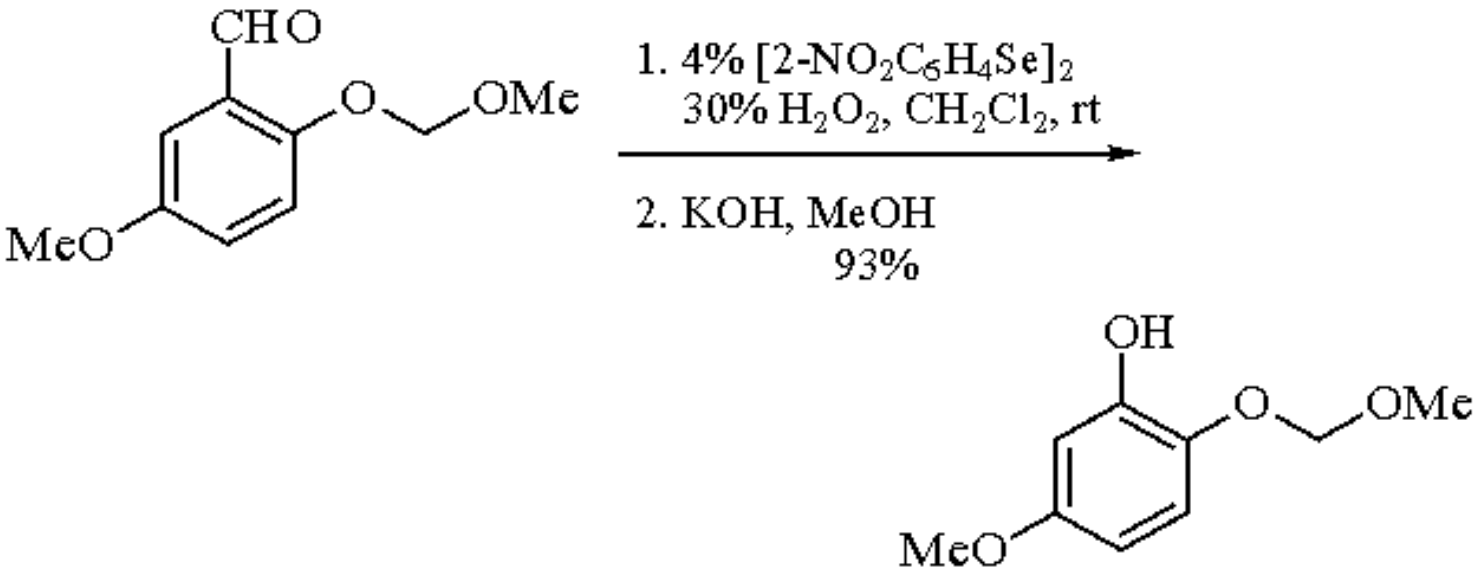

(3)

Aromatic and aliphatic aldehydes are converted into esters via their aldoximes or aldoxime *O*-methyl ethers by treatment with alcohol solutions of 30% H_2O_2 in the presence of a catalytic amount of 2-nitrobenzeneseleninic acid (eq 4).[4] These oxidation conditions are also effective for converting aldehyde dimethylhydrazones to nitriles (eq 5).[5] ***Selenium(IV) Oxide*** catalyzes both transformations, but the yields are generally lower.

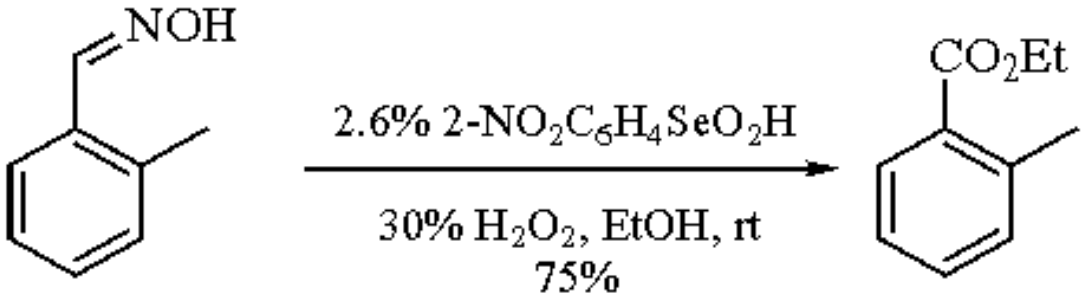

(4)

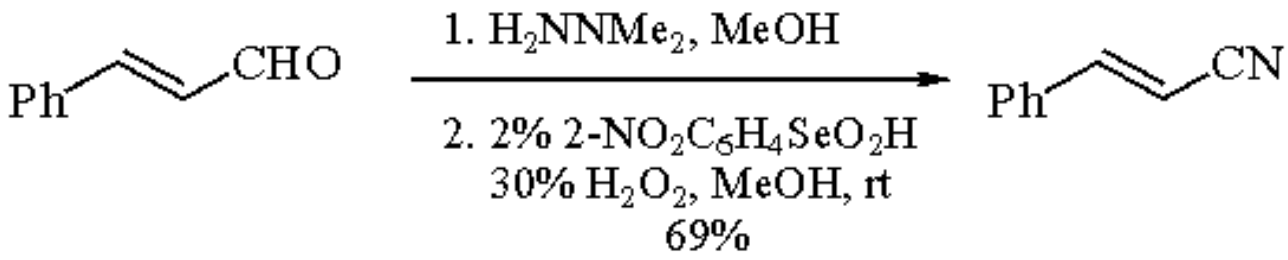

(5)

Related Reagents.

Benzeneseleninic Acid.

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o-Nitrobenzenesulfenyl Chloride[1]

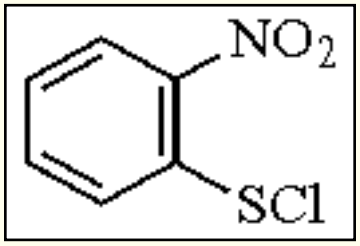

[7669-54-7] · $C_6H_4ClNO_2S$ · *o*-Nitrobenzenesulfenyl Chloride · (MW 189.63)

(protection of amino groups[1d,2] and thiols;[3] sulfenylation of alkenes;[4] preparation of sulfoxides from alcohols[5])

Alternate Name: NPS-Cl.

Physical Data: mp 74-76 °C.

Preparative Methods: by addition of ***Chlorine*** to (*o*-$O_2NC_6H_4S)_2$.[6]

Form Supplied in: yellow solid; widely available.

Handling, Storage, and Precautions: corrosive and moisture sensitive; decomposes within a few days when exposed to moist air, with liberation of HCl.

Protection of Amines.

Reaction of amines with *o*-$O_2NC_6H_4SCl$ in the presence of a base produces the corresponding sulfenamide (eq 1). Such 2-nitrophenylsulfenyl (NPS)-protected amines have been used primarily in peptide chemistry.[2] They have also seen service in the synthesis of cephalosporins,[7] nucleosides,[8] and *N*-acyl β-lactones.[9] The NPS group is cleaved by acid hydrolysis (e.g. HOAc or HCl),[2] by nucleophiles (e.g. $HSCH_2CH_2OH$, $HSCH_2COOH$, 2-mercaptopyridine,[10] NaI,[7] thioacetamide,[11] Bu_3P[8,12]), or with Raney nickel.[13] Other arylsulfenyl chlorides have been used for amine protection, but those with *ortho*-nitro groups provide the most stable derivatives.[1d] *N*-NPS-saccharin has been proposed as a more stable substitute for NPS-Cl.[14]

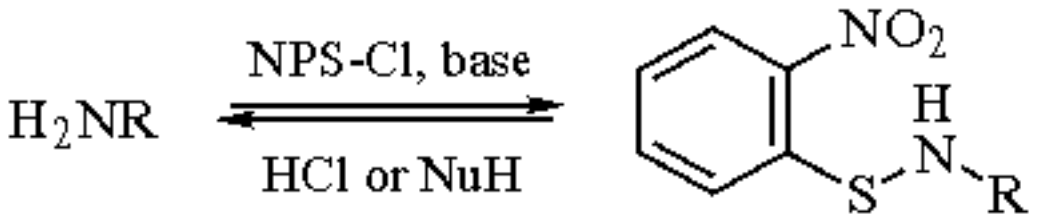

(1)

Protection of Thiols.

Mercapto groups (e.g. on cysteine) may be protected as mixed disulfides using NPS-Cl (eq 2).[3] The free thiol may be regenerated by reduction ($NaBH_4$) or by treatment with other thiols (e.g. $HSCH_2CO_2H$, $HSCH_2CH_2OH$). Treatment of *t*-butyl thiols with NPS-Cl followed by reduction constitutes a useful method for the removal of the *t*-butyl group.[3c,3d] Sulfenates of sugar derivatives have been prepared but sulfenates have not been widely used as hydroxyl protecting groups in synthesis.[15]

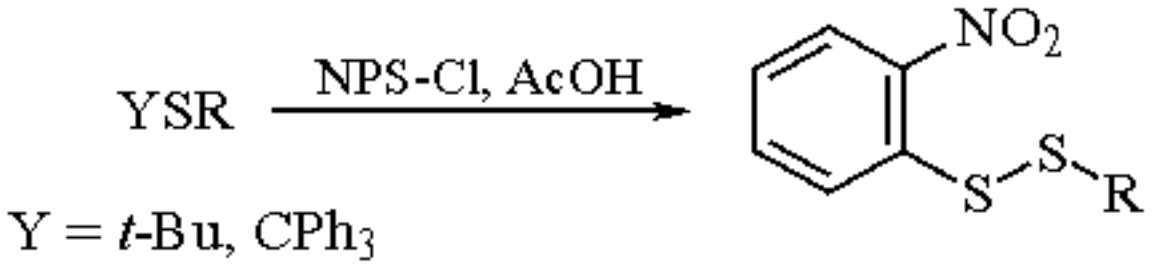

(2)

Sulfenylation of Alkenes.

Treatment of alkenes bearing suitably disposed nucleophilic functionalities with sulfenyl chlorides gives rise to cyclic products (eq 3). ***Benzenesulfenyl Chloride*** has been used most commonly in this capacity,[1a-c] but NPS-Cl has also been employed.[4]

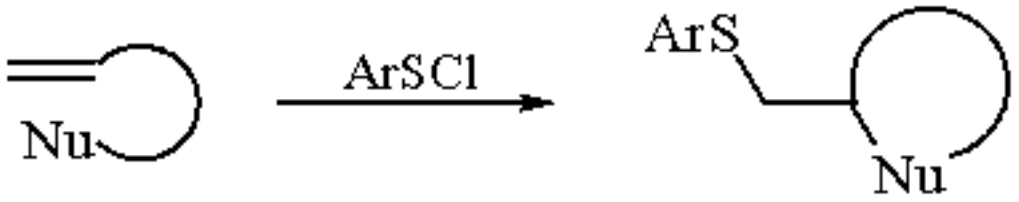

(3)

Preparation of Sulfoxides from Alcohols.

Allylic and propargylic alcohols react with sulfenyl chlorides to produce intermediate sulfenates which undergo a [2,3]-sigmatropic rearrangement to allylic and allenic sulfoxides, respectively (eq 4).[5] There has been considerable interest in the mechanism, stereochemistry, and synthetic applications of this

reaction.[5,16] Many sulfenyl chlorides have been used, including NPS-Cl.[17]

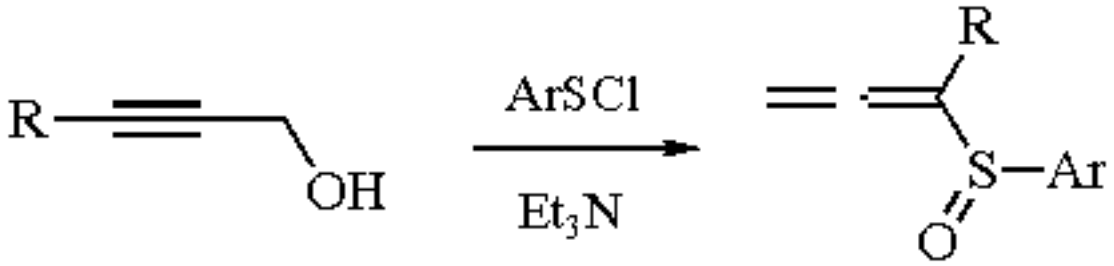

(4)

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p-Nitrobenzenesulfonyloxyurethane[1]

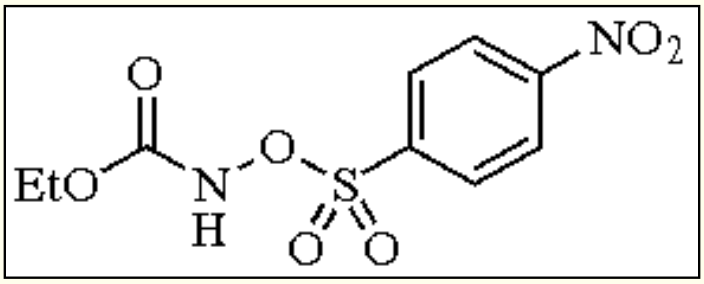

[2955-74-0] · $C_9H_{10}N_2O_7S$ · *p*-Nitrobenzenesulfonyloxyurethane · (MW 290.28)

(generation of ethoxycarbonylnitrene by α-elimination[2,3] under mild conditions, including phase-transfer conditions[4])

Physical Data: mp 116.4-116.8 °C.

Solubility: sol ether, acetone, $CHCl_3$, CH_2Cl_2, DMSO, DMF, ethyl acetate, alcohols; moderately sol benzene; insol hydrocarbon solvents, CCl_4, H_2O.

Preparative Method: by the reaction of *N*-hydroxyurethane with *p*-nitrobenzenesulfonyl chloride.[2]

Treatment of the title compound with a base such as ***Triethylamine*** leads to deprotonation followed by α-elimination to generate singlet ethoxycarbonylnitrene.[2,3] The mild conditions required offer an advantage over ***Ethyl Azidoformate*** as a source of the ethoxycarbonylnitrene. The synthetic utility of this nitrene is limited to two types of reactions: (1) aziridination of alkenes and (2) addition to heteroatoms, which is often followed by rearrangement. A common side-reaction is the insertion of the nitrene into C-H bonds. The synthetic utility of the insertion reaction itself is severely limited since ethoxycarbonylnitrene shows poor selectivity toward different types of C-H bonds. The development of procedures to generate this nitrene under phase-transfer conditions has enhanced its utility.[4,5]

Ethoxycarbonylnitrene generated by α-elimination adds to alkenes to give the corresponding aziridines in moderate yields. Thus reaction of ethoxycarbonylnitrene with the strained alkene 2-azabicyclo[2.2.0]hex-5-ene under phase-transfer conditions produces the aziridine in 42% yield (eq 1).[6] Thermolysis of the adduct gives rise to a 1,4-diazepine. This method has been used to access a variety of substituted 1,4-diazepines, 1*H*-1,4-diazepines,[7] and other heterocyclic ring systems.[8]

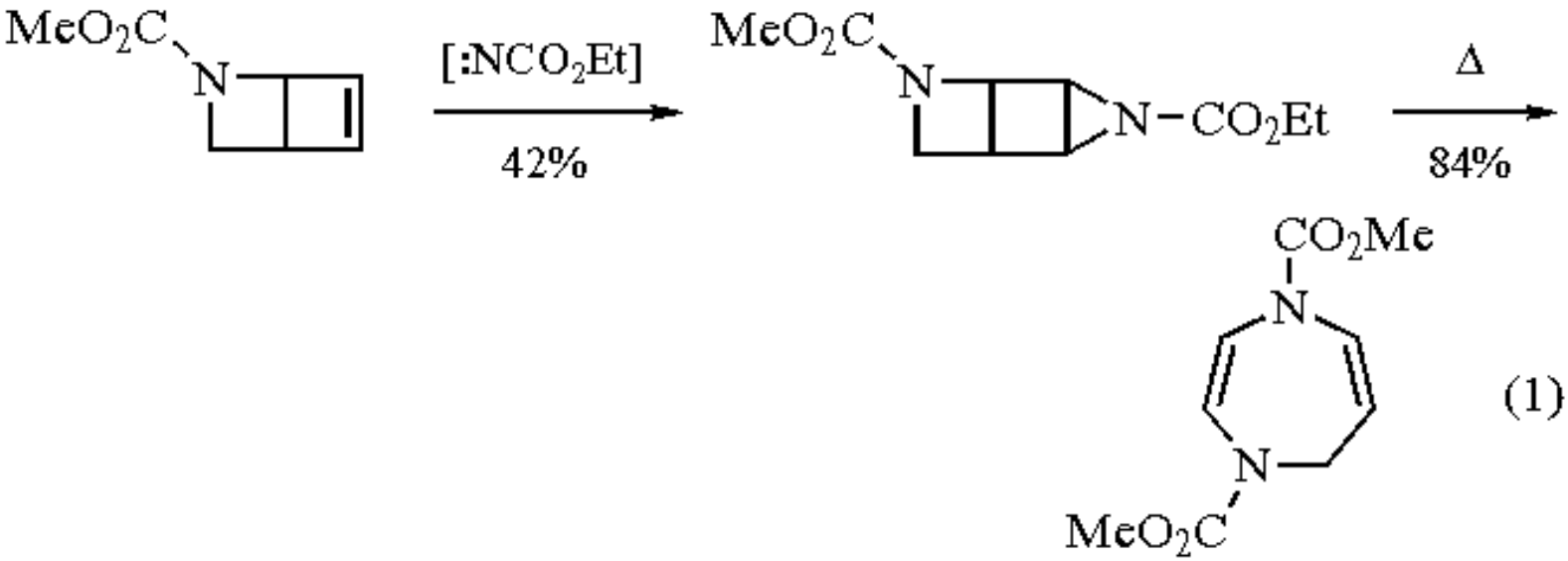

Addition of ethoxycarbonylnitrene across the double bond of a symmetric propelladiene has been reported to give a mixture of stereoisomeric aziridines in 46% yield.[9] Additions to vinylsilanes under phase-transfer conditions[10] and to vinyl chlorides[11] produce the corresponding aziridines in moderate yields. Addition to azo compounds yields azimines which, on subsequent photolysis, give the triaziridines.[12] Aziridination of isolated double bonds occurs preferentially over the double bond of allylic ethers.[13] Attempted addition to enamines[14] and allenes[15] gives very low yields of the desired products. Addition to a chiral, optically active enol ether has been reported to proceed in low yield, but with high diastereoselectivity.[16] Additions to allylic and homoallylic acetals have also been reported.[17]

There are few examples of synthetically useful reactions involving addition of ethoxycarbonylnitrene to heteroatoms. Addition to phospholes gives the corresponding iminophospholes in good yield.[18] Addition of ethoxycarbonylnitrene to trialkylboranes gives the corresponding *N*-alkyl carbamates after rearrangement and hydrolysis (eq 2).[19] This procedure allows access to a variety of ethyl *N*-alkylcarbamates in high yields.

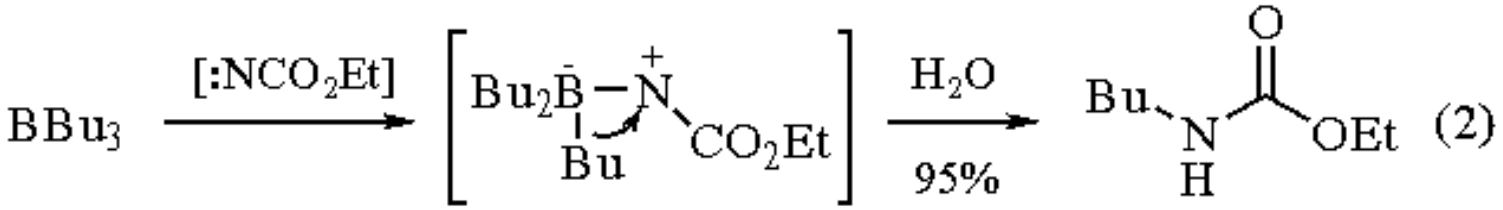

Related Reagents.

t-Butyl Azidoformate; ***Ethyl Azidoformate***.

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o-Nitrobenzenesulfonyl Azide

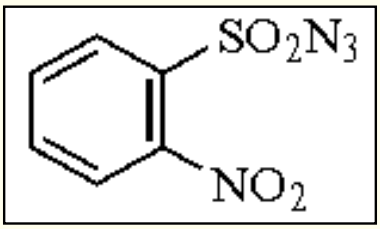

[6655-31-8] · $C_6H_4N_4O_4S$ · *o*-Nitrobenzenesulfonyl Azide · (MW 228.21)

(1,3-dipolar reagent that undergoes cycloaddition to alkenes, enamines, enol ethers, and enynes[1])

Physical Data: mp 71-73 °C.

Solubility: sol most organic solvents.

Preparative Method: by the reaction of *o*-nitrobenzenesulfonyl chloride with an aqueous acetone solution of ***Sodium Azide***, first at 0 °C and then at 25 °C.[2]

Purification: crystallization from ethanol.[2]

Handling, Storage, and Precautions: azides should be expected to be sensitive to electrical, thermal, and/or mechanical shock. The parent sulfonyl azide, benzenesulfonyl azide, in the crude state, detonates violently when heated.

Dipolar Cycloaddition.

o-Nitrobenzenesulfonyl azide has been used for the ring enlargement-conversion of methylenecycloalkanes into the homologous *o*-nitrobenzenesulfonimidocycloalkanes. For example, methylenecycloheptane affords the imido product in quantitative yield. Hydrolysis of the imide with acid then affords the corresponding ketone (eq 1).[3]

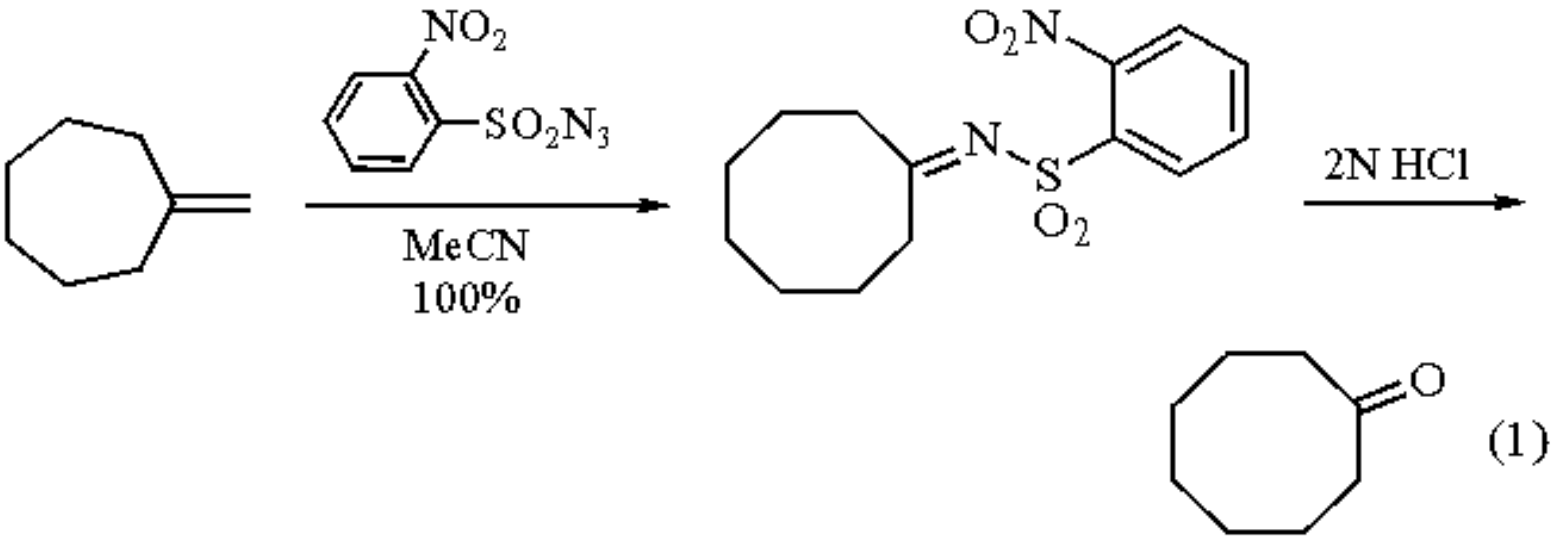

The reagent has also been employed for the cycloaddition-rearrangement of both methyl and trimethylsilyl enol ethers (eqs 2 and 3).[4,5]

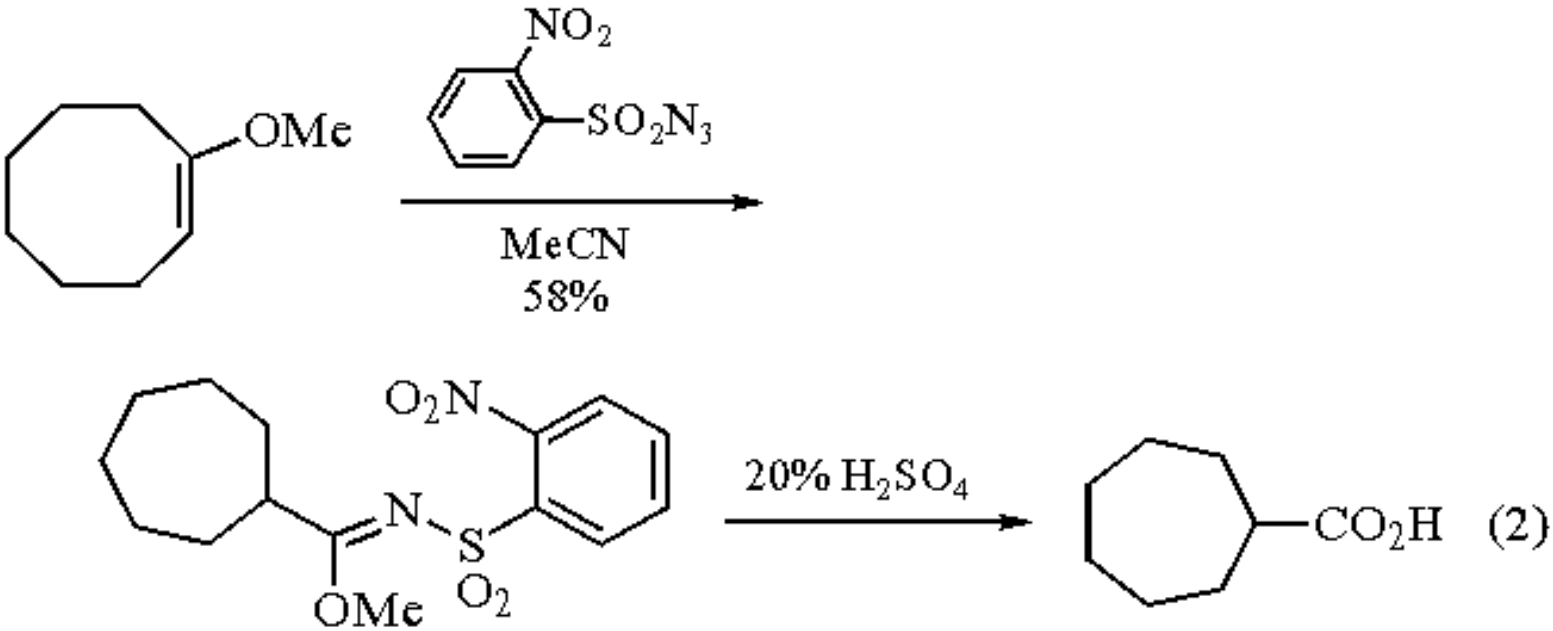

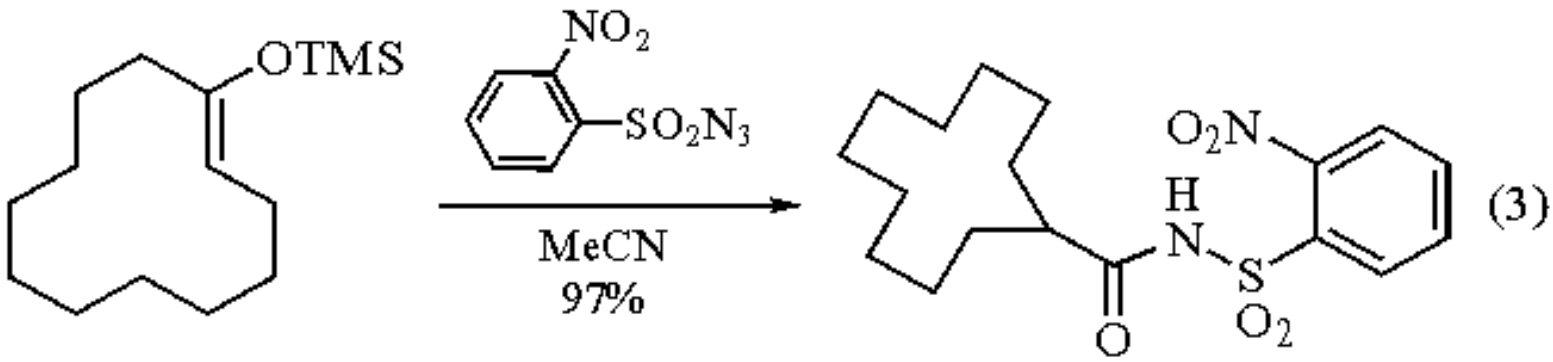

Decomposition of the reagent in boiling benzene-cyclohexene affords a quantitative yield of a 3:1 mixture of imide and enesulfonamide (eq 4).[6]

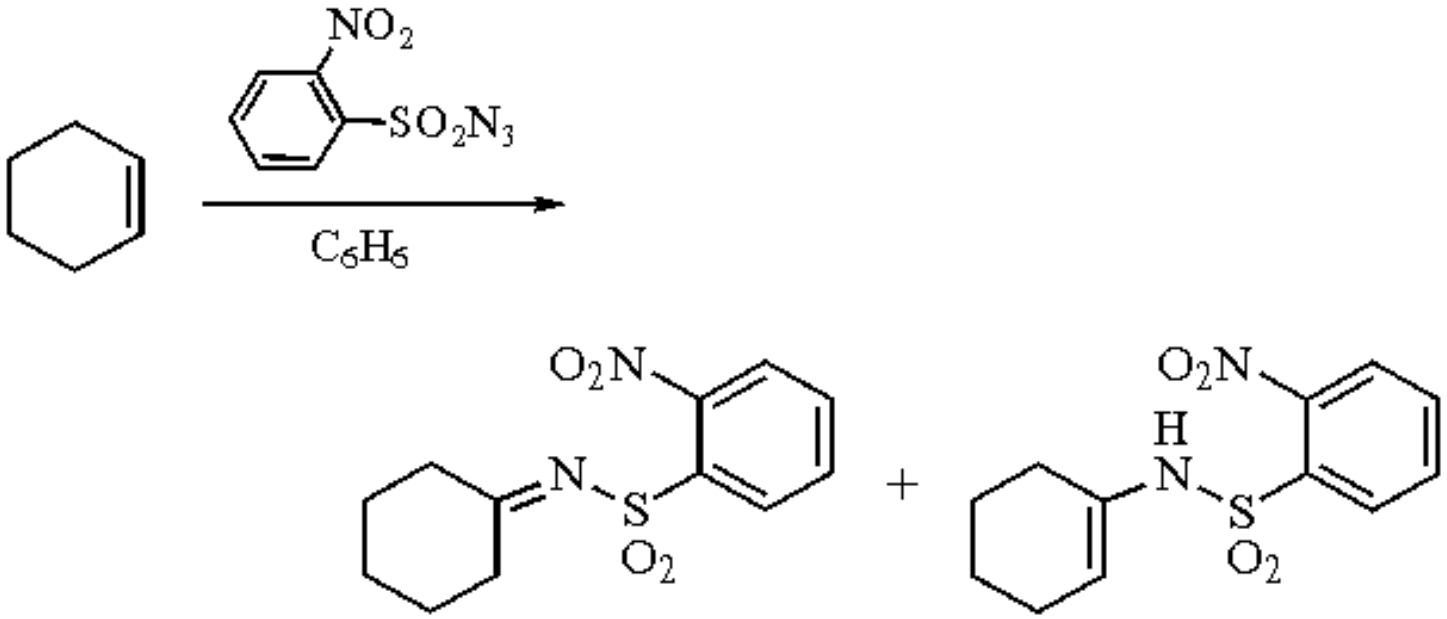

(4)

With a cyclic enamine, *o*-nitrobenzenesulfonyl azide affords an *N*-sulfonyl amidine following decomposition of an unstable intermediate triazoline (eq 5).[7]

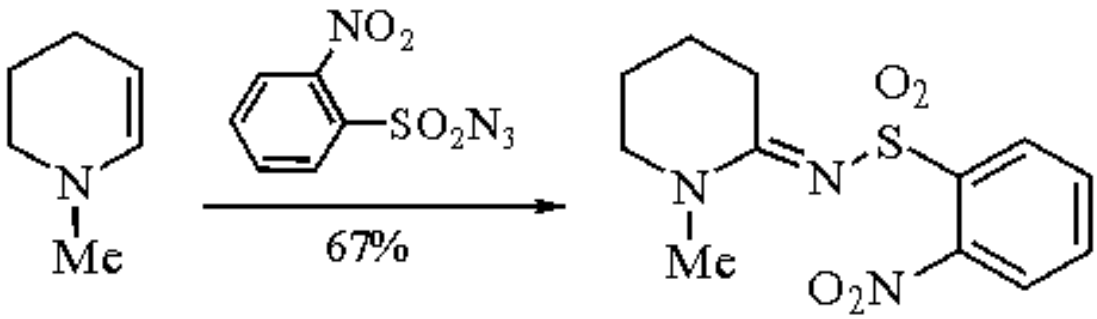

(5)

The reaction of *o*-nitrobenzenesulfonyl azide with an ynamine leads to a 2-diazoalkanamidine as the only isolable product. An equilibrium between the amidine and the ring-closed triazole exists, however, in solution (eq 6).[8]

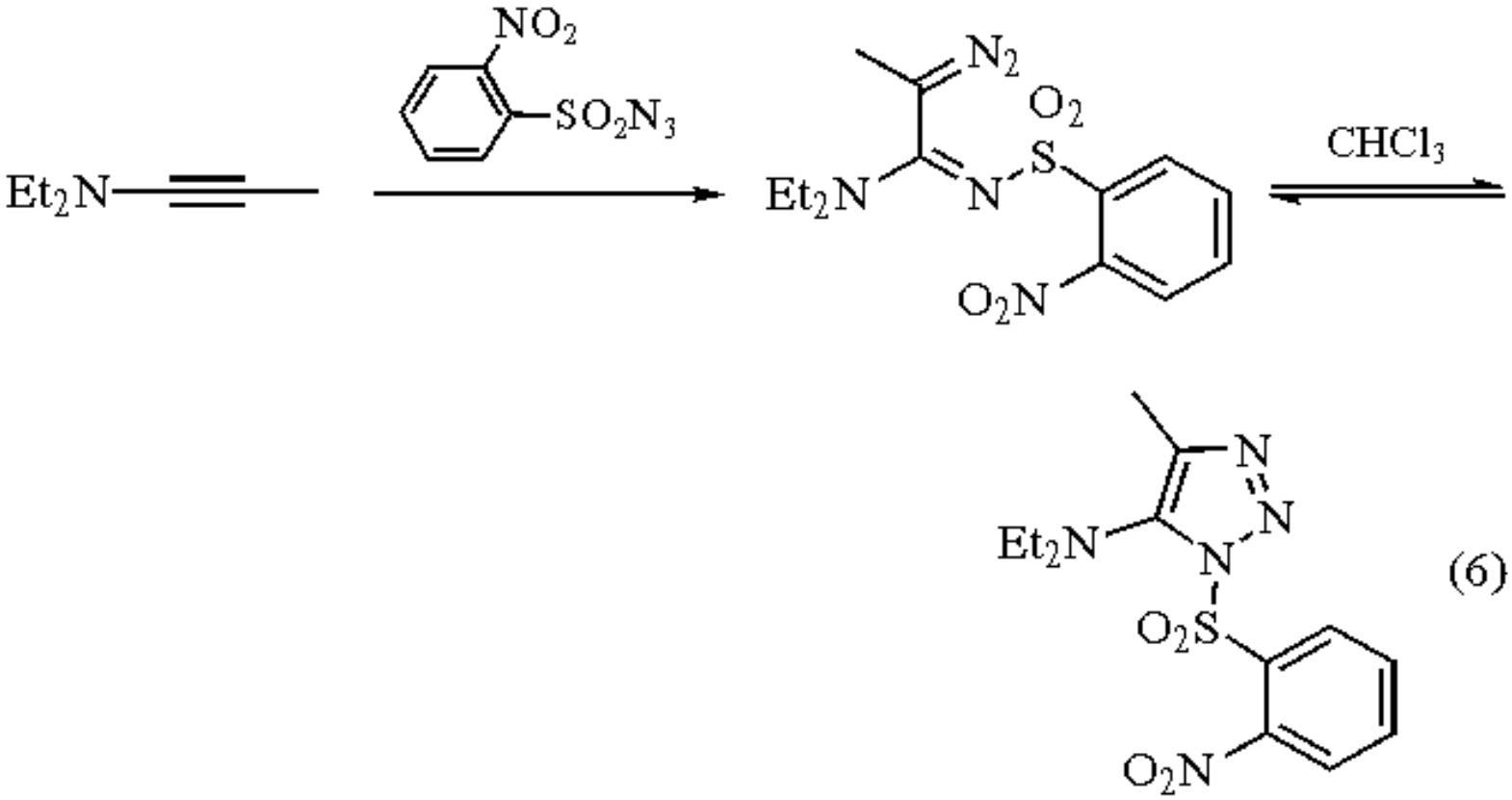

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p-Nitrobenzenesulfonyl-4-nitroimidazole

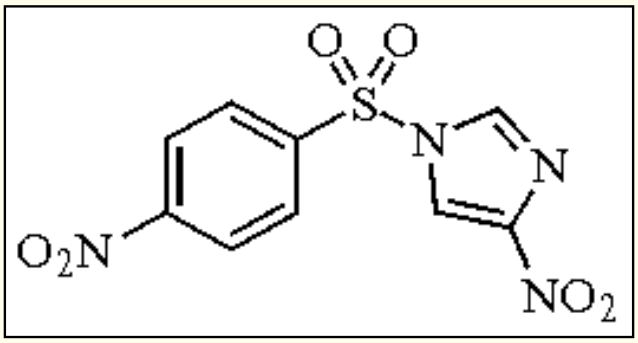

[81006-79-3] · $C_9H_6N_4O_6S$ · *p*-Nitrobenzenesulfonyl-4-nitroimidazole · (MW 298.26)

(condensing agent for the triester coupling of nucleotide fragments[1])

Alternate Name: p-NBSNI.

Physical Data: mp (sealed tube) 179-185 °C (dec); UV (dioxane) 253 nm.

Solubility: sol pyridine, DMSO; slightly sol dioxane, ethyl acetate.

Form Supplied in: white needles; not available commercially; may be contaminated with *p*-nitrobenzenesulfonic acid.

Analysis of Reagent Purity: ^{1}H NMR (60 MHz, DMSO-d_6) δ 8.45 (s, 4H); 8.55 (d, J = 2 Hz, 1H); 9.10 (d, J = 2 Hz, 1H); sulfonic acid impurities are easily detected as higher field signals.

Preparative Method: by treatment of 4-nitroimidazole (1.025 equiv) and *p*-nitrobenzenesulfonyl chloride (1.0 equiv) with ***Triethylamine*** (1.1 equiv) in dry dioxane at 0 °C.[1]

Purification: recrystallization from ethyl acetate.

Handling, Storage, and Precautions: stable to air and moisture in screw cap bottles at rt for over six months.

Condensing Agent.

p-Nitrobenzenesulfonyl-4-nitroimidazole has been used as a condensing agent in the triester synthesis of oligonucleotides. The reagent activates the phosphodiester towards attack by the incoming 5´-hydroxyl through formation of a mixed phosphoric-sulfonic anhydride. Typically, the suitably protected nucleotide fragments, in pyridine solution, are treated with *p*-NBSNI (2.5 equiv) and stirred at rt for approximately 15 h. After workup,

purification is achieved through two chromatographic separations over silica gel, affording the desired polynucleotide in 60-83% yield (eq 1).[1]

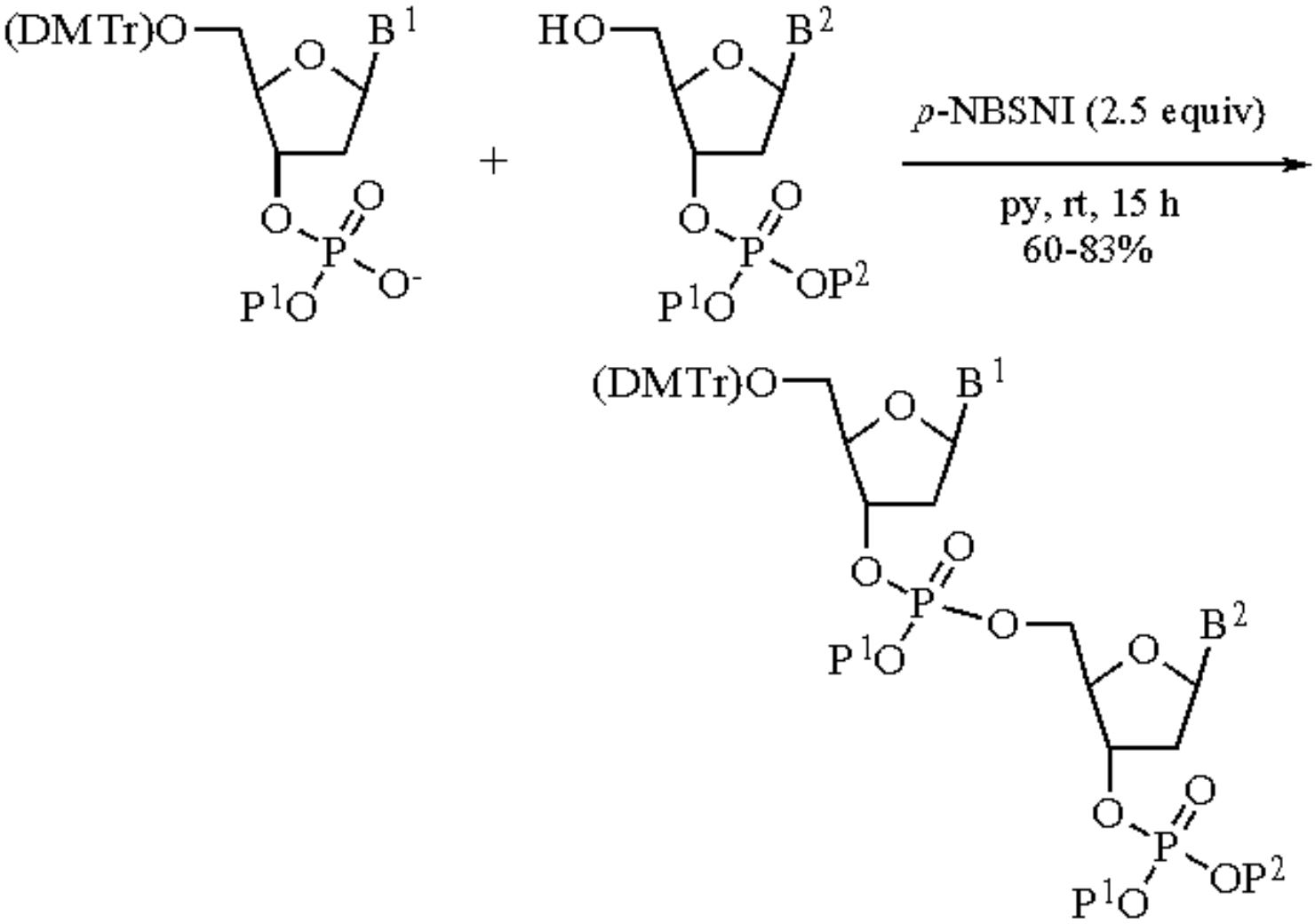

DMTr = 5'-*O*-dimethoxytrityl; P^1 = *p*-ClC_6H_4; P^2 = cyanoethyl

p-Nitrobenzenesulfonyl-4-nitroimidazole holds the advantage over older reagents, such as triisopropylbenzenesulfonyl chloride, of giving fewer side products resulting from sulfonation of the free 5´-hydroxyl. The long reaction times necessary are a disadvantage and the condensing agents 2,4,6-triisopropylbenzenesulfonyl-1,2,3,4-tetrazole (TPSTe) and 1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT) are preferable.[2]

---

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m-Nitrobenzenesulfonyl Peroxide[1]

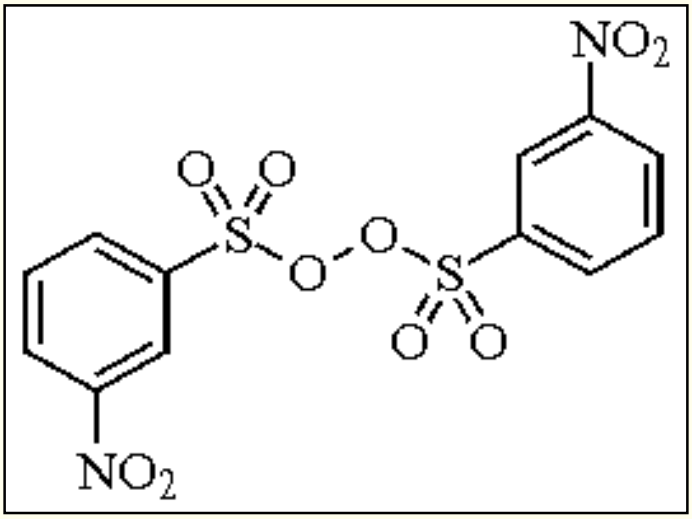

[6209-71-8] · $C_{12}H_8N_2O_{10}S_2$ · *m*-Nitrobenzenesulfonyl Peroxide · (MW 404.36)

(oxidation of heteroatoms including selenium,[4] tellurium,[5] sulfur,[5] and nitrogen;[6] electrophilic aromatic substitution[7])

Alternate Name: m-NBSP.

Physical Data: mp 107 °C (dec); decomposition at the melting point is exothermic.

Solubility: (>1 g 100 mL^{-1}) ethyl acetate, acetone, acetonitrile; slightly sol dichloromethane, diethyl ether, chloroform; insol pentane, water.

Form Supplied in: off-white or pale yellow powder.

Analysis of Reagent Purity: purity is determined by iodometric titration. A weighed quantity (70 mg) of the peroxide is dissolved in ethyl acetate (20 mL) and treated with glacial acetic acid (10 mL) and 10% potassium iodide (10 mL). The solution is titrated to a starch endpoint with standardized thiosulfate (~0.01 N).

Preparative Method: m-nitrobenzenesulfonyl chloride (11.1 g, 0.05 mol) is dissolved in chloroform (15 mL) and added with stirring to a cold (-20 °C) solution of ***Potassium Carbonate*** (8.5 g) in water (140 mL), ethanol (70 mL), and 30% ***Hydrogen Peroxide*** (20 g) in a Waring blender cup. Agitation is slowly increased to full power and held there for 1 min. Ethanol (100 mL), is then added and the mixture is agitated slowly for a few minutes. The resulting precipitate is collected by filtration, washed thoroughly with water, and dried under vacuum.

Purification: the crude product is dissolved in acetone at room temperature, the solution is filtered, and the filtrate is concentrated under reduced pressure to yield 97% pure peroxide (5.0 g, 49%) which decomposes at 107 °C.[2,3]

Handling, Storage, and Precautions: can be stored at -20 °C for a considerable time without loss of purity. Plastic spatulas are recommended for transfer. It can decompose vigorously in the presence of electron donors,[3] and should only be handled with suitable protection. Use in a fume hood.

Being a strong electrophile, *m*-nitrobenzenesulfonyl peroxide reacts readily with good electron donors. This reactivity has been exploited in several useful synthetic processes. Heteroatom oxidations, aromatic substitutions, and additions to unactivated alkenes have been reported. In addition *m*-nitrobenzenesulfonyloxy radicals can be produced homolytically.

Electrophilic Additions to Alkenes and Arenes.

m-NBSP reacts with diselenides,[4] ditellurides,[5] and disulfides[5] to generate electrophilic intermediates (**1**) (eq 1), which react with alkenes in the presence of various nucleophiles to give addition products (**2**) (eq 2).

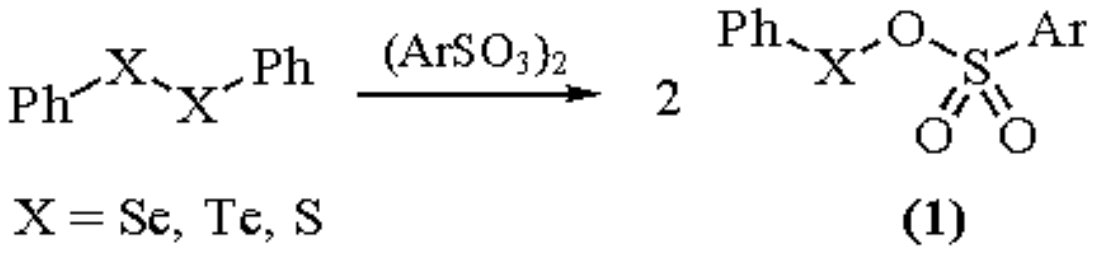

(1)

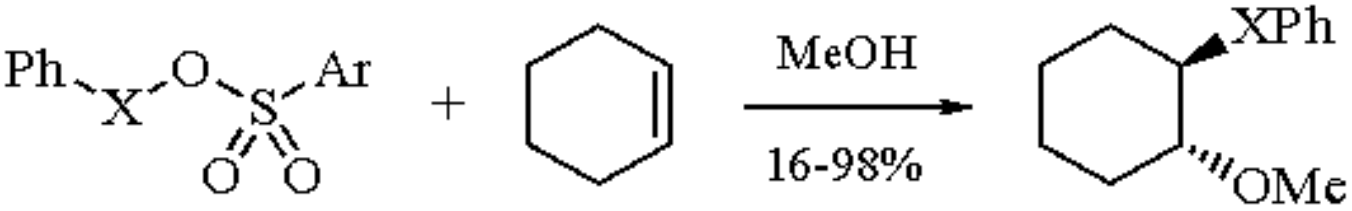

(2)

(1) (2)

The intermediate (**1**) initiates the electrophilic cyclization of unsaturated alcohols to form cyclic ethers and can be used for phenylsulfolactonization or phenylselenolactonization of unsaturated carboxylic acids to lactones (eq 3).[4,5] Selenium works particularly well in these reactions. Furthermore, intermediate (**1**) (X = Se) is sufficiently electrophilic to react with aromatic compounds such as anisole, phenol, acetanilide, and toluene to produce benzeneselenated aromatic products in variable yields (12-94%).[4b]

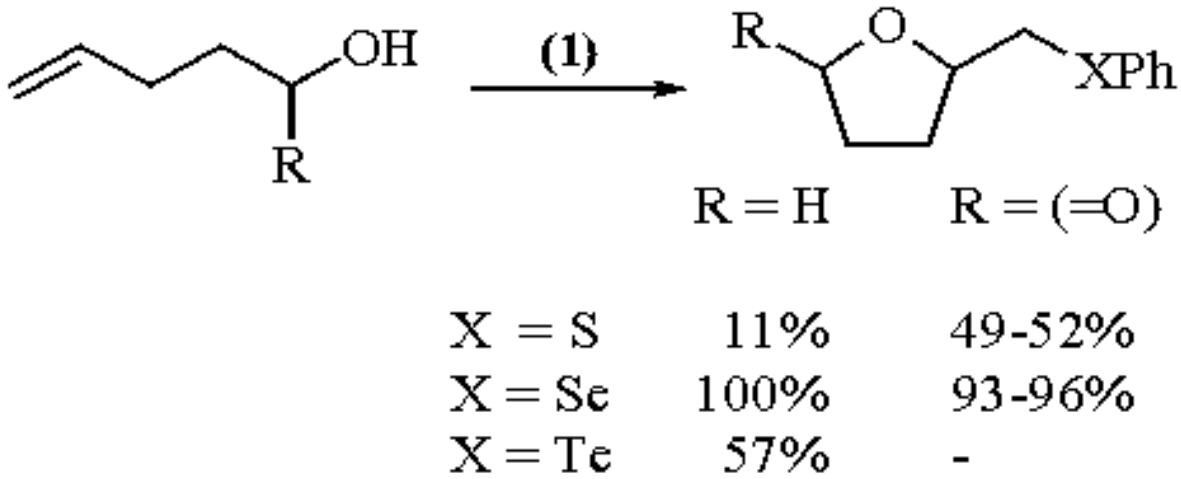

(3)

The reaction of *m*-NBSP with the nitrogen atom of substituted benzylamines has been used to produce *N*-[(*m*-nitrobenzenesulfonyl)oxy]benzylamines, which undergo base induced elimination to imines.[6] It has also been reported that *O*-(*m*-nitrobenzenesulfonyl) hypochlorites and *O*-(*m*-nitrobenzenesulfonyl) hypobromites formed by the reaction of *m*-NBSP with chloride and bromide ions, respectively, are effective reagents for the electrophilic halogenation of aromatic rings (50-93%).[7]

Aromatic Substitution.

m-NBSP reacts with methyl benzoate, anisole, nitrobenzene, halobenzenes, and alkylbenzenes (as well as many other aromatic compounds) to give aryl *m*-nitrobenzenesulfonates (**3**) (eq 4).[1] Hydrolysis or reductive cleavage of these products gives phenols.[8] Attempted oxygenation of toluene failed in the presence of salts known to catalyze radical reactions.[9]

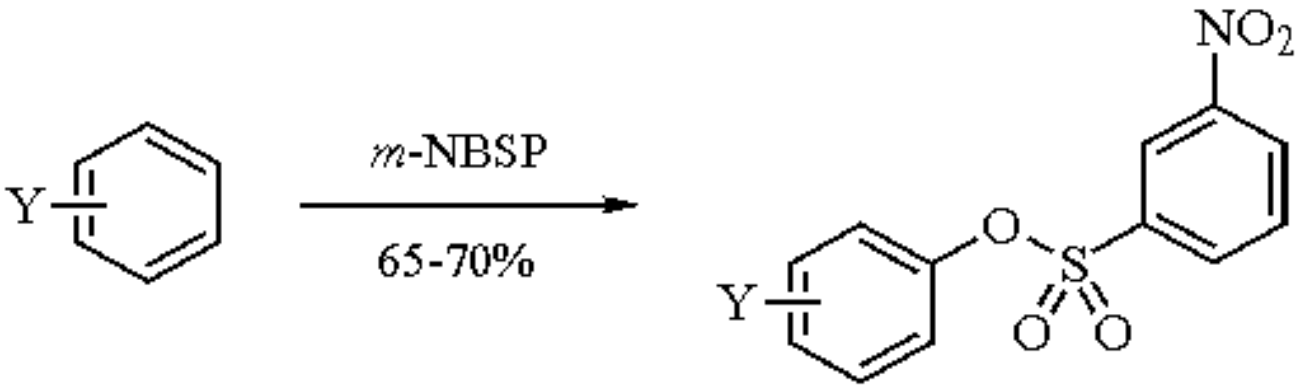

(4)

(3)

Radical Reactions.

Decomposition of *m*-NBSP in chloroform solution gives *m*-nitrobenzenesulfonic acid (eq 5), in addition to hexachloroethane and phosgene.[10] The same process is also found for other arylsulfonyl peroxides and constitutes an excellent method for the preparation of arylsulfonic acids.[11] Activation parameters and the

reaction products indicate that the decomposition in chloroform proceeds by homolytic cleavage of the O-O bond.[10]

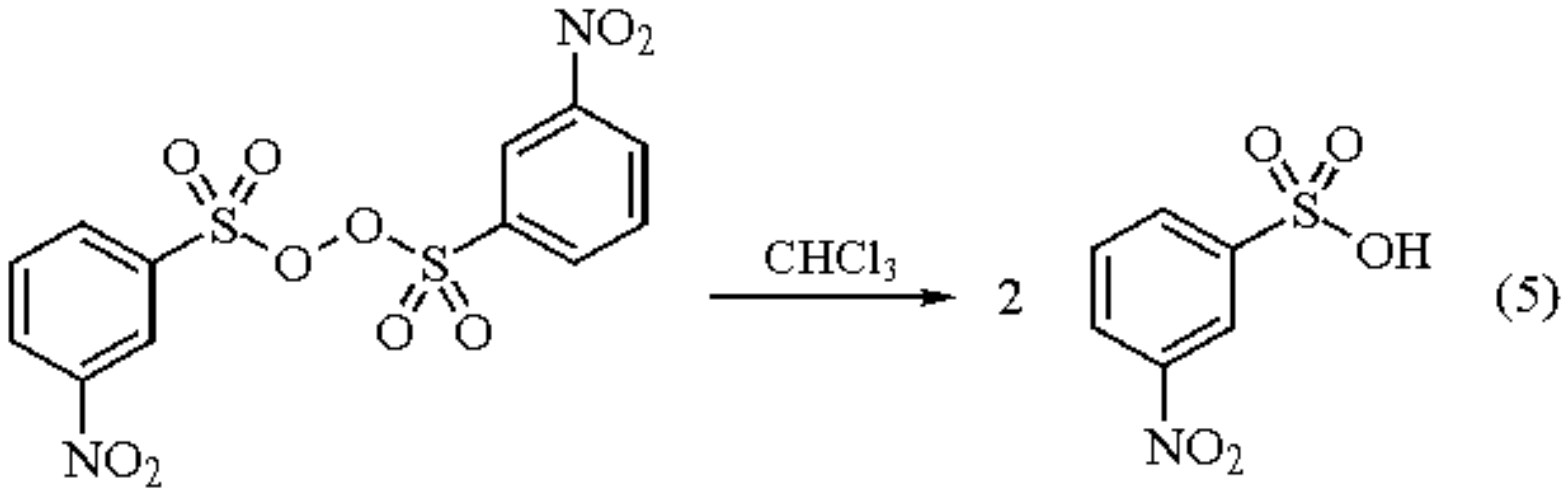

Additions to Alkenes.

m-NBSP undergoes electrophilic addition to alkenes such as norbornene and gives *syn*-7-(arylsulfonyloxy)norbornene and 2,7-bis(arylsulfonyloxy)norbornane. Norbornadiene reacts with *m*-NBSP to give arylsulfonyloxytricycloheptane products.[12]

Related Reagents.

p-Nitrobenzenesulfonyl Peroxide.

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1. (a) Hoffman, R. V. In *Advances in Oxygenated Processes*; Baumstark, A. L.; Ed.; JAI Press: Greenwich, CT, 1991; Vol. 3, pp 43-70. (b) Hoffman, R. V. *OPP* **1986**, *18*, 179. (c) Hoffman, R. V. In *The Chemistry of Peroxides*; Patai, S.; Ed; Wiley: New York, 1983; pp 259-278.
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p-Nitrobenzenesulfonyl Peroxide[1]

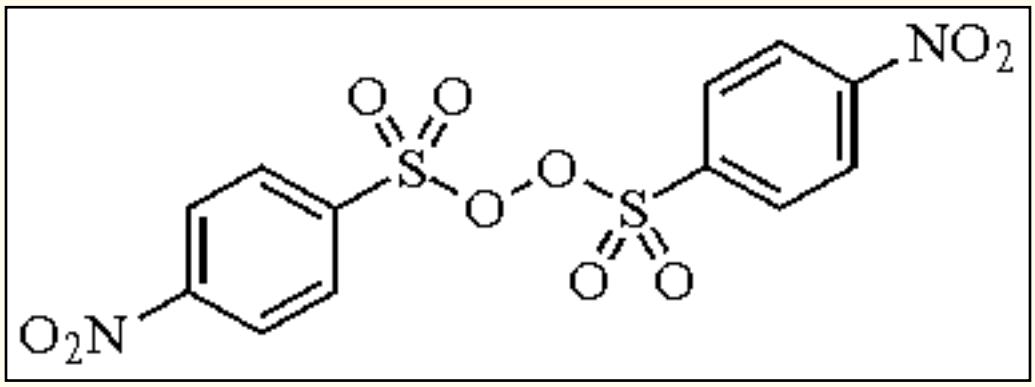

[6209-72-9] · $C_{12}H_8N_2O_{10}S_2$ · *p*-Nitrobenzenesulfonyl Peroxide · (MW 404.36)

(oxygen electrophile for addition to unsaturated compounds;[1] preparation of α-nosyloxy ketones and esters;[3] addition to 1-alkoxy-1-silyloxy-1,3-dienes;[6] addition to enols[3] to give tricarbonyl esters and amides;[3] addition to amines to give *N*-nosyloxyamines[1])

Alternate Name: *p*-NBSP.

Physical Data: mp 128 °C (dec); decomposition at the melting point is exothermic; typical preparations with mp >124 °C are generally satisfactory.

Solubility: sol (>1 g 100 mL^{-1}) ethyl acetate, acetone, acetonitrile; slightly sol dichloromethane, ether, chloroform; insol pentane, water.

Form Supplied in: off-white or pale yellow powder; typical impurities are *p*-nitrobenzenesulfonic acid and water.

Analysis of Reagent Purity: purity is determined by iodometric titration. A weighed quantity (~70 mg) of the peroxide is dissolved in ethyl acetate (20 mL) and treated with glacial acetic acid (10 mL) and 10% potassium iodide (10 mL). The solution is titrated to a starch endpoint with standardized thiosulfate (~0.01 N).

Preparative Method: prepared by the addition of *p*-nitrobenzenesulfonyl chloride (20 g) in chloroform (40 mL) to a -20 °C solution of ***Potassium Carbonate*** (15.6 g) and 30% ***Hydrogen Peroxide*** in 2:1 water-ethanol (360 mL).[2] The mixture is agitated in a chilled Waring Blender cup at full power for 1.5 min. The mixture is filtered on a large Buchner funnel and the oily

solid is washed copiously several times with water. A good washing protocol is to suspend the solid in water and stir in the Waring Blender at medium power for 1 min and refilter. The faintly yellow solid is dried by passing air through the solid on the filter, and then in vacuo at room temperature. It is prudent to use plastic implements when manipulating the peroxide.

Purification: the crude peroxide is dissolved in reagent grade acetone (360 mL), the solution is cooled to -78 °C, and a vigorous stream of air is directed onto the surface of the stirred solution. When the volume has been reduced to 180 mL, the mixture is filtered and air is passed through the solid until it is completely dry. Purities of >97% normally result if care is taken to completely dry the peroxide when it is first isolated. Yields of 40-50% of purified product are normal. An alternate method of purification which delivers material suitable for most purposes (>95% purity) is to suspend the peroxide in acetone (150 mL) and stir at -78 °C for 1.5-2 h. Filtration and air drying give acceptable product. It is even more crucial that the crude product be quite dry before using this procedure as the major impurity seems to be water that is not easily removed by this method of purification.

Handling, Storage, and Precautions: can be stored for long periods of time at -20 °C without loss of purity and can be handled in the laboratory using normal laboratory procedures and precautions. Plastic spatulas are recommended for transfer. Vigorous reaction occurs with neat or concentrated solutions of good electron donors such as amines, alkenes, or alkoxides, but *p*-NBSP is relatively stable towards oxygen, water, acids, and a variety of common solvents such as acetone, ethyl acetate, dichloromethane, and acetonitrile. Because *p*-NBSP can decompose exothermically (but not explosively), personal protection in the form of eye protection, gloves, etc. is necessary when handling the peroxide.

Electrophilic Addition.

p-Nitrobenzenesulfonyl peroxide is a pseudohalogen reagent whose reactivity is comparable to that of chlorine. It provides a source of electrophilic oxygen for attachment of the *p*-nitrobenzenesulfonyloxy (nosyloxy) group to electron donors. Subsequent chemistry depends on the donor function and the reactions that the *p*-nitrobenzenesulfonate adduct undergoes.[3]

Enol Derivatives.

Electrophilic addition of *p*-NBSP to compounds with electron-rich double bonds provides a smooth method for the electrophilic attachment of the nosylate group. Reaction with enol derivatives of ketones (R^1,R^2 = alkyl, aryl) gives 2-nosyloxy ketones in generally high yields (60-90%) (eq 1).[4] These are excellent precursors for α-amino ketones, α-hydroxy acetals, and α-hydroxy ketones.[3] Reaction with ketene silyl acetals (X = Me_3SiO, R^1 = alkoxy, R^2 = alkyl, aryl) gives 2-nosyloxy esters, also in excellent

yields (65-90%);[5] these are easily converted in high yields to amino acids and their *N*-substituted derivatives.[3] Reactions with other nucleophiles give other 2-substituted esters.[3]

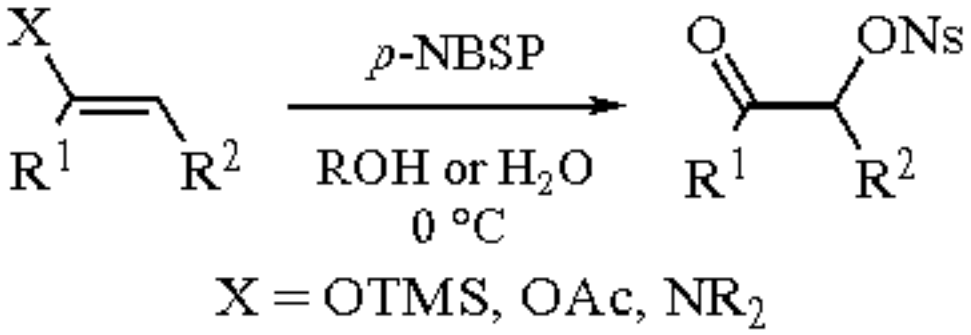

(1)

Silyloxy dienes.

Silyl enol ether derivatives of unsaturated esters (1-alkoxy-1-trimethylsilyloxy-1,3-dienes) react with *p*-NBSP to give both 2-nosyloxy and 4-nosyloxy unsaturated esters.[6] Replacement of the nosyloxy group by nucleophiles yields 4-substituted 2,3-unsaturated esters.[3]

Enols.

Compounds with naturally high enol contents react directly with *p*-NBSP to give α-nosyloxy carbonyl compounds. β-Keto esters[7] and β-keto amides[8] react readily to give the corresponding 2-nosyloxy β-keto esters and amides (eq 2). These derivatives undergo reductive elimination to give tricarbonyl esters and tricarbonyl amides in high yields. They can also be reduced to 3-hydroxy-2-nosyloxy esters, which are convertible to many densely functionalized products.[3]

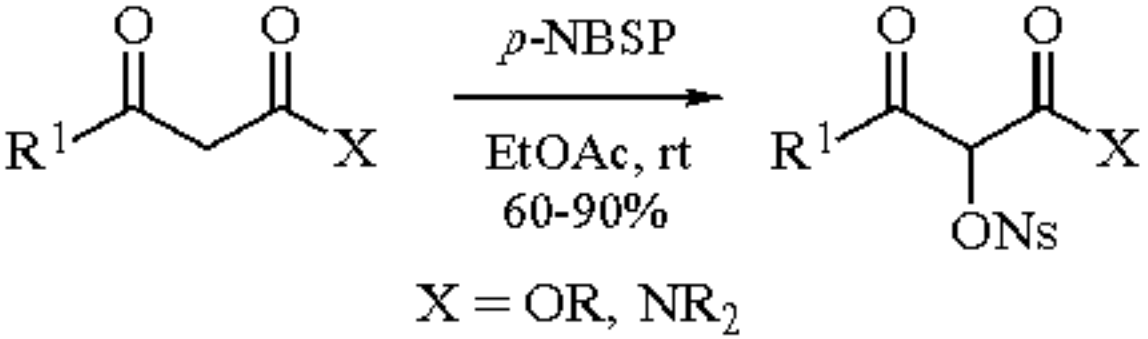

(2)

Amines.

Amines react with *p*-NBSP at -78 °C to give *N*-[(*p*-nitrobenzene)sulfonyl]oxy amines (eq 3).[1] These adducts undergo facile base-promoted eliminations to imines.[9] In the absence of base, they undergo

ionization-rearrangement reactions which yield skeletally rearranged iminium ions. These adducts are also effective reagents for the preparation of *N*-substituted lactams from cyclic ketones and acetals.[3]

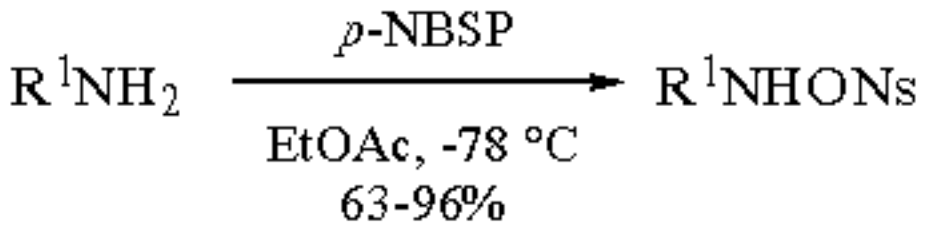

(3)

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1. (a) Hoffman, R. V. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; Jai Press: Greenwich, CT, 1991; Vol. 3, pp 43-70. (b) Hoffman, R. V. *OPP* **1986**, *18*, 179. (c) Hoffman, R. V. In *The Chemistry of Peroxides*; Patai, S., Ed; Wiley: New York, 1983; pp 259-278.
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5-Nitro-3*H*-1,2-benzoxathiole *S,S*-Dioxide

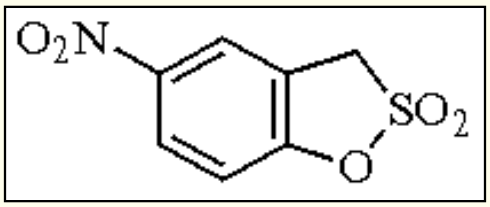

[14618-10-1] · $C_7H_5NO_5S$ · 5-Nitro-3*H*-1,2-benzoxathiole *S,S*-Dioxide · (MW 215.20)

(peptide coupling reagent)

Physical Data: very pale yellow crystals; mp 148.5-149.5 °C.

Analysis of Reagent Purity: satisfactory microanalytical data have been reported.[1]

Preparative Method: by nitration of the corresponding sultone.[1]

5-Nitro-3*H*-1,2-benzoxathiole *S,S*-dioxide is a peptide coupling reagent.[2,3] Its reactivity derives from the inherent strain present in cyclic five-membered sulfonate esters. These species react with nucleophiles such as carboxylates to form mixed carboxylic sulfonic anhydrides (**1**) (eq 1), which rearrange via an intramolecular acyl transfer to phenyl esters (**2**) (eq 2). When the carboxylate nucleophile in eq 1 is that of an *N*-protected α-amino acid, (**2**) reacts with α-amino esters to give peptides (eq 3 and Table 1). The process offers the advantage that the byproduct of the coupling reaction (sulfonate (**3**)) is water-soluble and, therefore, easily removed from the reaction mixture.

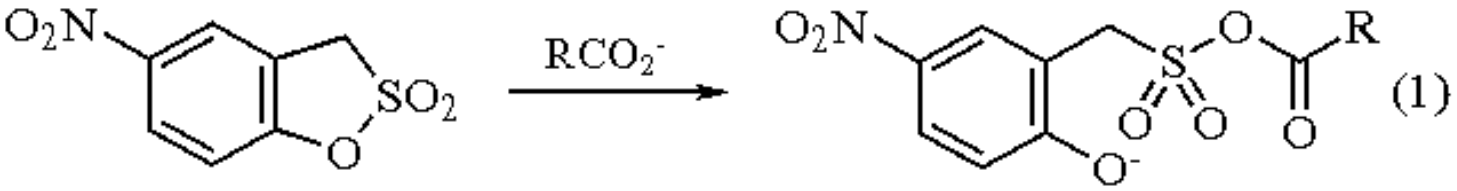

(1)

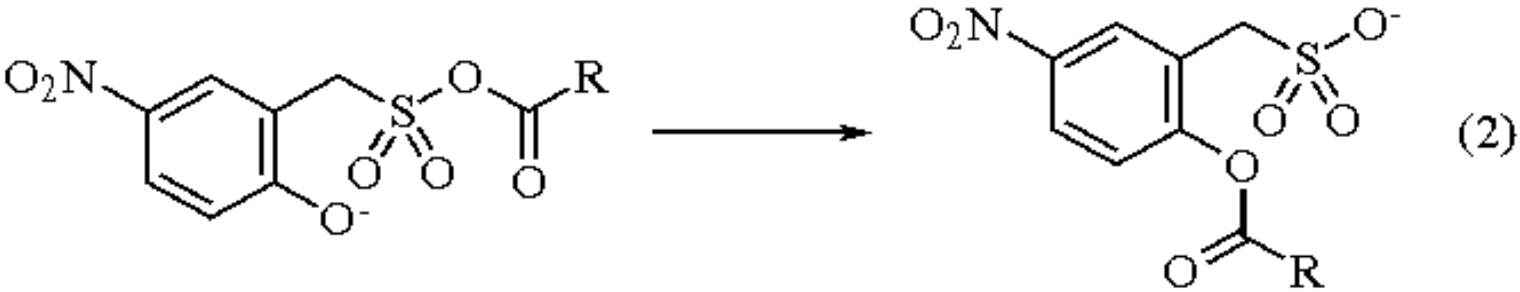

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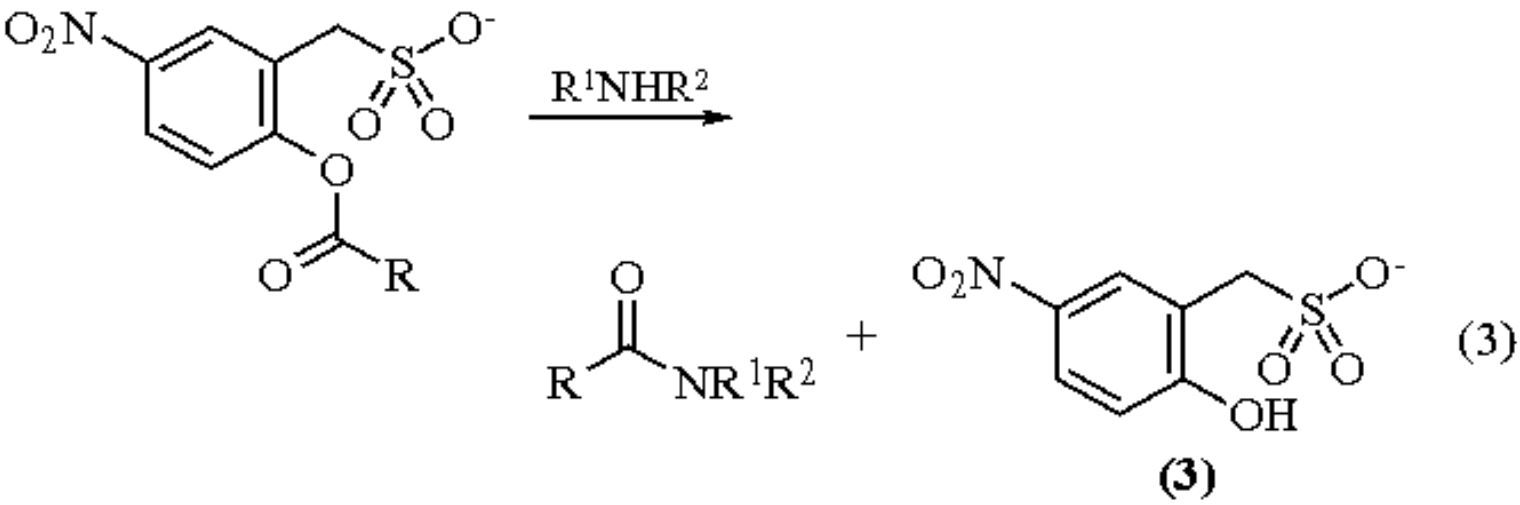

Table 1 Preparation of Dipeptides using 5-Nitro-3 *H*-1,2-benzoxathiole *S,S*-Dioxide

Acid	Amine	Yield of *N*-protected dipeptide (%)
Z-Gly-OH	H-Ala-OMe	60
Z-Gly-OH	H-Ser-OMe	60
Z-Phe-OH	H-Gly-OEt	52
Z-Pro-OH	H-Gly-OEt	63
Z-Met-OH	H-Gly-OEt	63
Z-Val-OH	H-Gly-OEt	55
Z-Asn-OH	H-Gly-OEt	40
Z-Ser-OH	H-Gly-OEt	49
Z-Gly-Phe	H-Gly-OEt	56

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o-Nitrobenzoyl Chloride

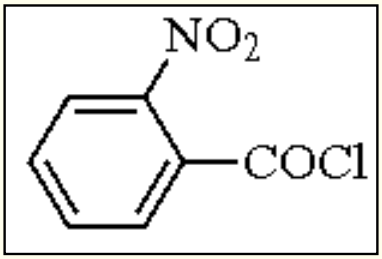

[610-14-0] · $C_7H_4ClNO_3$ · *o*-Nitrobenzoyl Chloride · (MW 185.57)

(acylating agent in reaction with amines and alcohols; produces crystalline esters from alcohols; building block for the synthesis of several classes of heterocycles)

Physical Data: mp 17-20 °C; bp 148-149 °C/9 mmHg; *d* 1.404 g cm^{-3}.

Solubility: sol THF, CH_2Cl_2, $CHCl_3$; reacts with water and alcohols.

Form Supplied in: commercially available; low melting solid.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: extremely irritating to skin and eyes. Can cause burns. Use in a fume hood. Reacts with water, liberating HCl. Explosion of distillation residue has been reported.[1]

Ester Formation.

o-Nitrobenzoyl chloride forms crystalline esters with alcohols (see ***p-Nitrobenzoyl Chloride***) and these esters are readily hydrolyzed under standard conditions for benzoyl removal (eqs 1 and 2). The crystalline nitrobenzoyl esters enable enhancement of enantiomeric excess by recrystallization.[2]

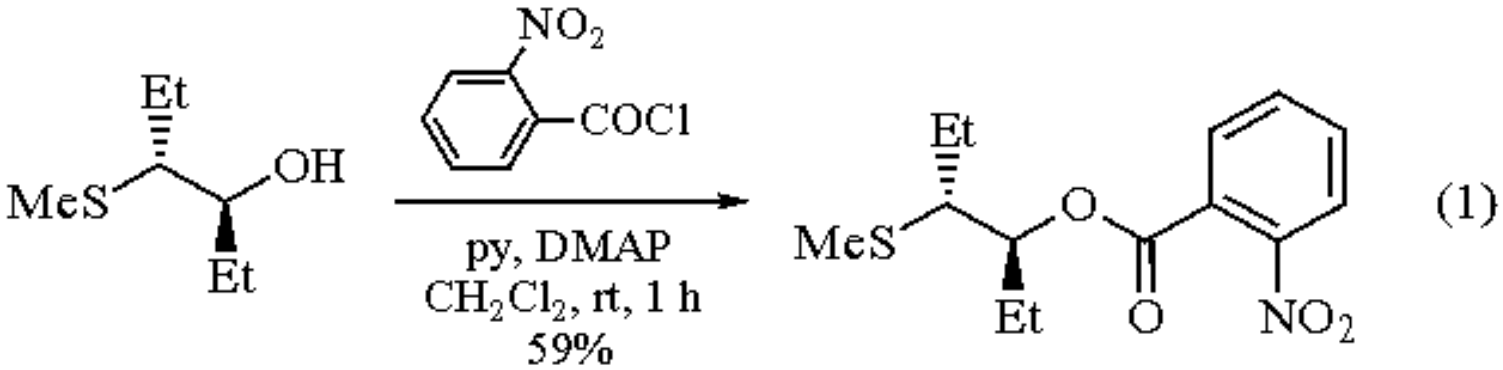

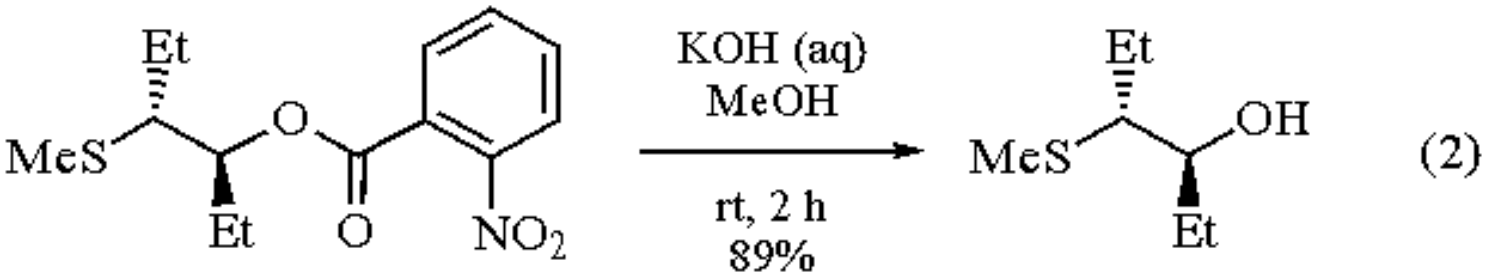

Synthesis of Heterocycles.

o-Nitrobenzoyl chloride has been used in the synthesis of various heterocycles, particularly quinazolinones (eq 3),[3] benzodiazepines (eq 4),[4] and xanthones.[5] In the quinazolinone synthesis (eq 3), and in many other cases, the nitro group acts as a masked amine. Initial condensation of the acetyl chloride is followed by nitro reduction to the free amine which then participates in further condensation and cyclization. In other cases, *o*-nitrobenzoyl chloride undergoes initial Friedel-Crafts acylation before cyclization of the amine.[5]

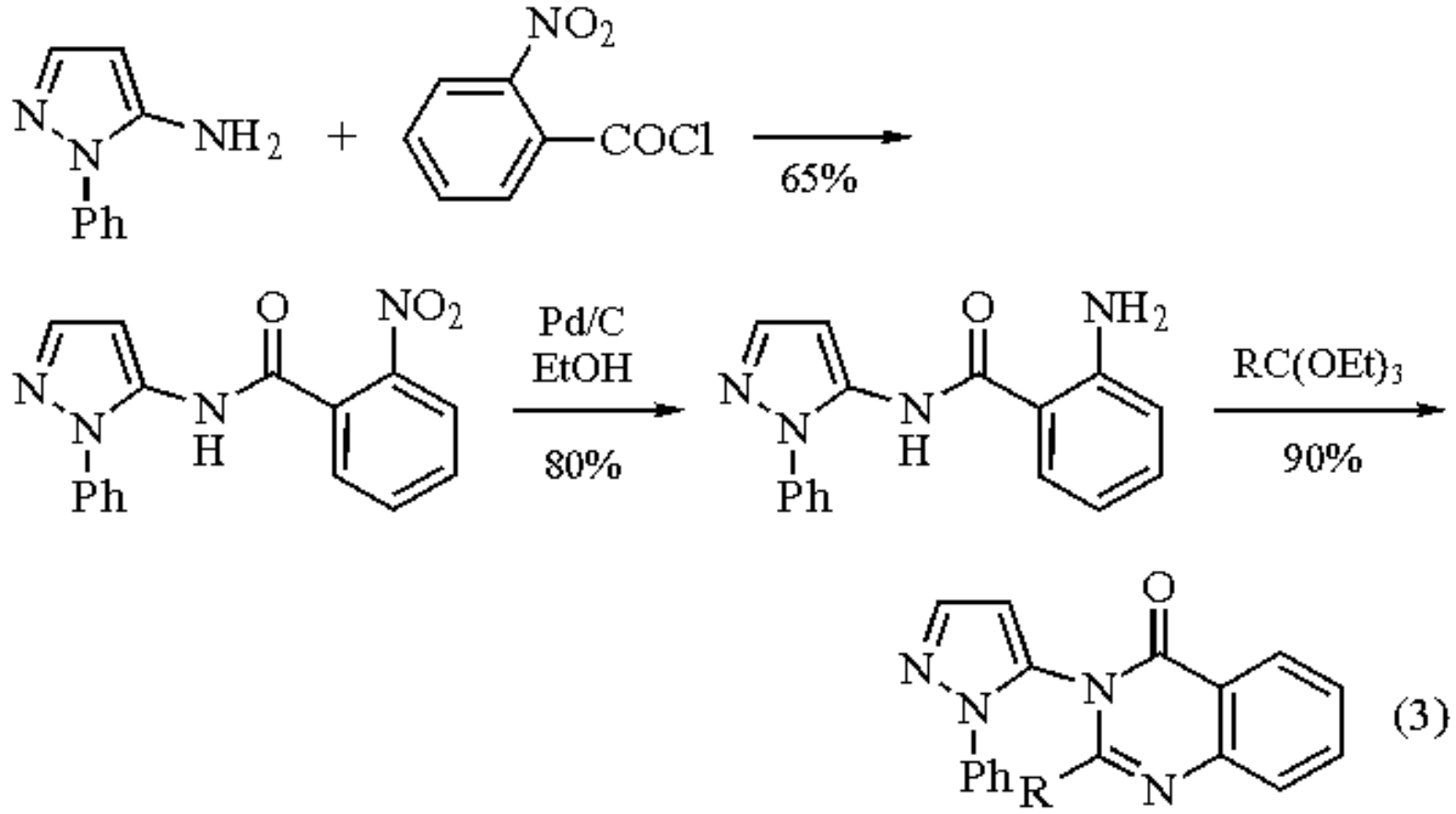

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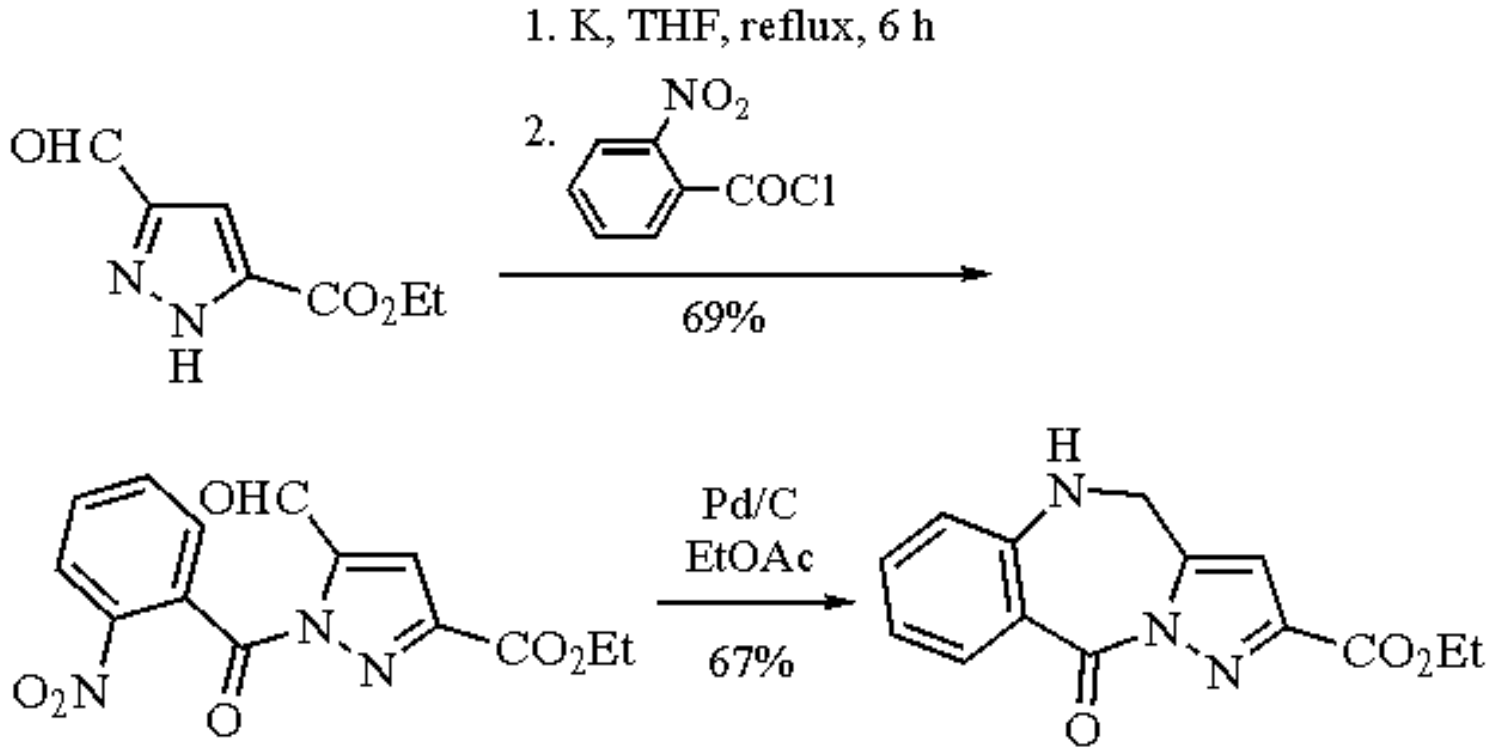

(4)

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p-Nitrobenzoyl Chloride

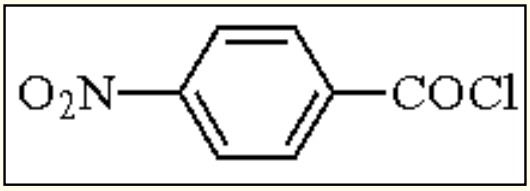

[122-04-3] · $C_7H_4ClNO_3$ · *p*-Nitrobenzoyl Chloride · (MW 185.57)

(characterization of amines and alcohols by formation of crystalline amide and ester derivatives; forms suitable directing group for glycosidation reactions)

Physical Data: mp 72-74 °C; bp 202-205 °C/105 mmHg.

Solubility: sol THF, CH_2Cl_2, $CHCl_3$, pyridine; reacts with water and alcohols.

Form Supplied in: commercially available; yellow crystalline solid.

Purification: recrystallization from CCl_4 or C_6H_6.

Handling, Storage, and Precautions: extremely irritating to skin and eyes. Can cause burns. Use in a fume hood. Reacts with water, liberating HCl.

Amide Formation.

p-Nitrobenzoyl chloride forms *p*-nitrobenzamides by reaction with amines and these have been used in the characterization of amphetamines.[1] These derivatives are chemically stable, easily prepared (eq 1), and have enhanced UV detectability.

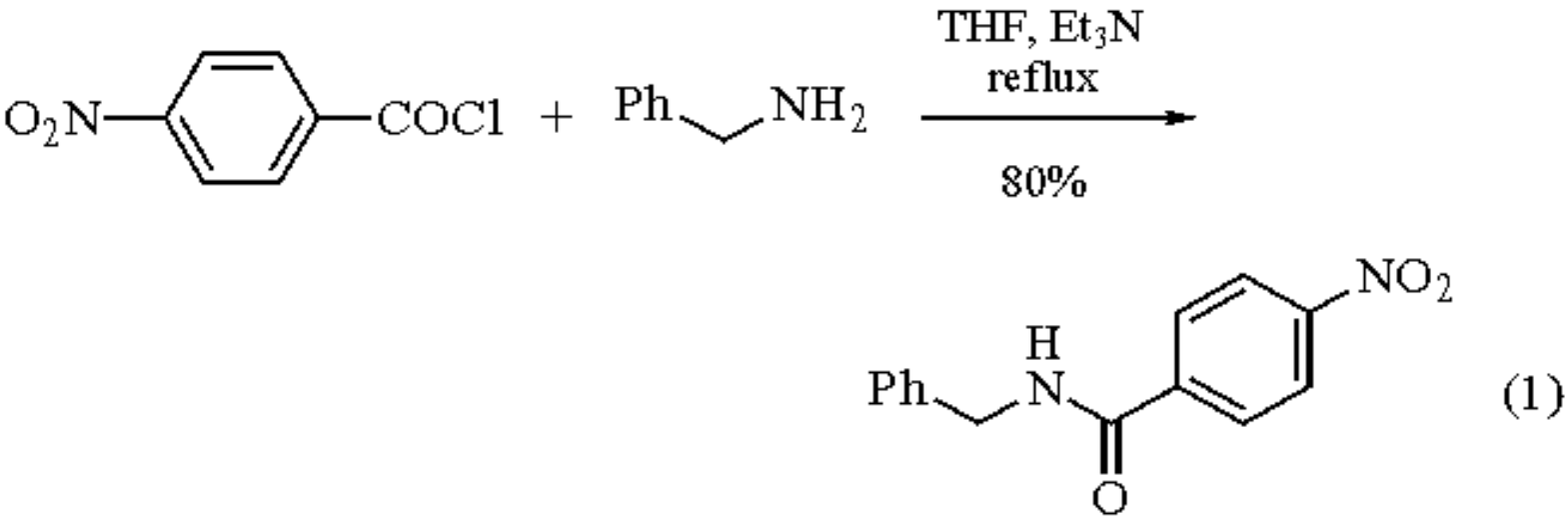

Ester Formation.

The crystalline *p*-nitrobenzoate (PNB) esters formed by reaction of alcohols and *p*-nitrobenzoyl chloride are widely used in simplifying the characterization,[2] purification, and isolation[3,4] of alcohols. In certain cases, they allow ready enhancement of enantiomeric excess by recrystallization.[3] They can be prepared from the alkoxide (eq 2)[5] (useful for acid sensitive alcohols) or, more commonly, from the free alcohol, *p*-nitrobenzoyl chloride, and amine base such as pyridine[4] (often as solvent), lutidine,[2] or triethylamine.[3]

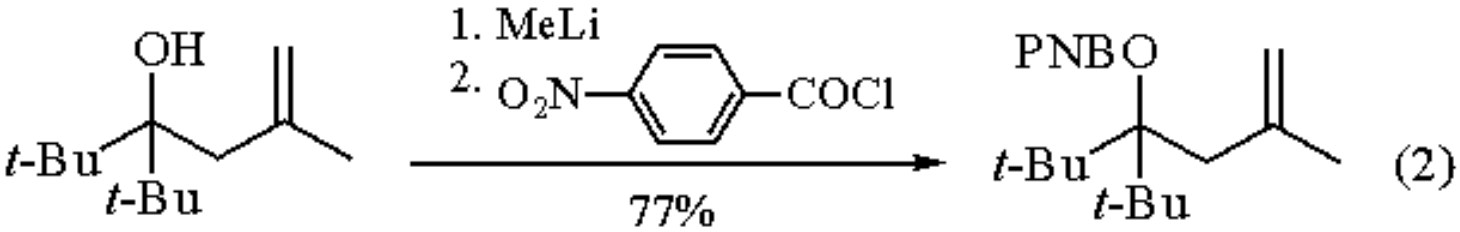

p-Nitrobenzoyl chloride has been used for the in situ derivatization of low molecular weight, water-soluble epoxy alcohols (eq 3).[3]

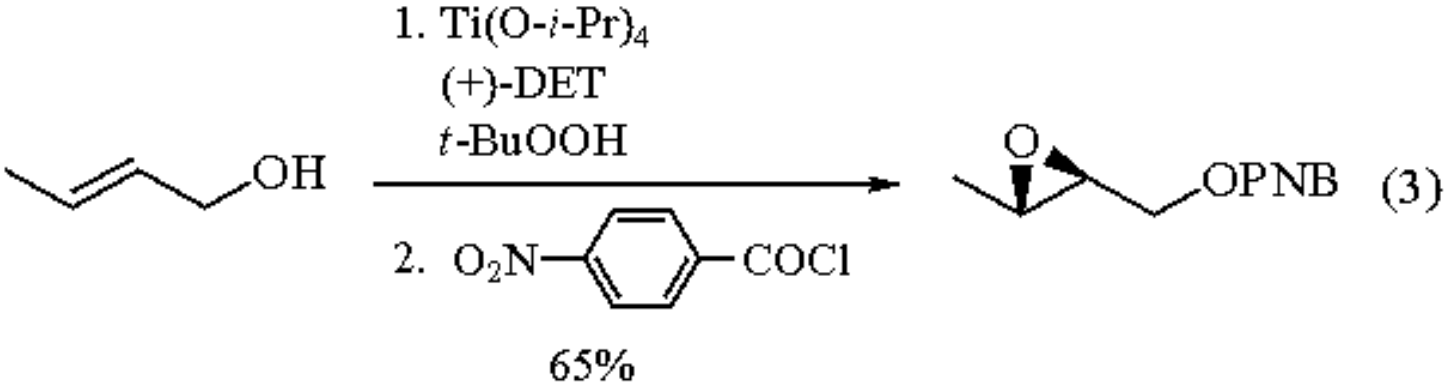

Glycosidations.

p-Nitrobenzoyl chloride forms *O*-*p*-nitrobenzoyl esters which are used in carbohydrate chemistry as protecting groups that can also direct the steric course of glycosidation reactions. The 4-*O*-*p*-nitrobenzoyl group gives steric control (by anchimeric assistance) in the coupling reactions of certain sugars to give *trans*-C-1,C-4 products.[6,7] The *O*-PNB esters can also act as precursors to the glycosyl halides required for the Koenigs-Knorr coupling reaction. The example in eq 4 illustrates both these features.[7] The 4-*O*-PNB group gives somewhat better selectivities than the 4-*O*-trifluoroacetyl or the 4-*O*-acetyl group.[8] *p*-Nitrobenzoyl chloride is also used in the synthesis of highly crystalline *p*-nitrobenzoylaminobenzoyl esters of sugars.[9]

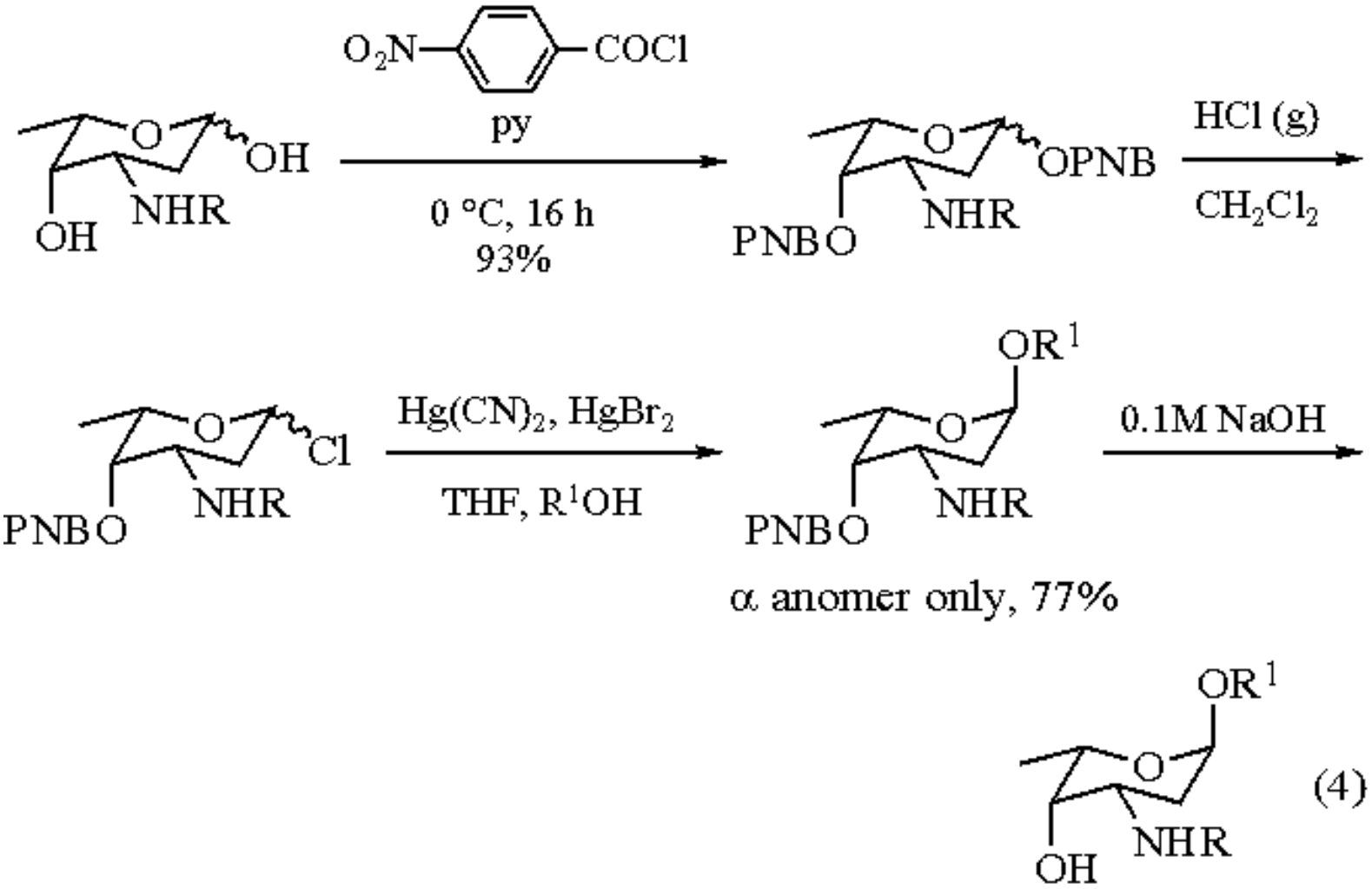

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o-Nitrobenzyl Alcohol

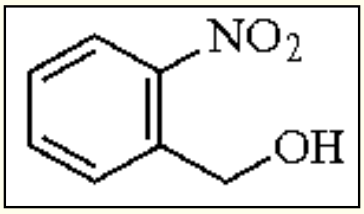

[612-25-9] · $C_7H_7NO_3$ · *o*-Nitrobenzyl Alcohol · (MW 153.15)

(photoremovable protective group for ketones and aldehydes,[1] carboxylic acids,[2] anhydrides,[3] acid chlorides,[4] and amines;[5a] reaction with isocyanates to generate protected amines;[5b,c,d] protection of amino acids;[2b,6] protection of the hydroxyl groups of ribonucleotides,[7a,b,c] dinucleotides,[7d] and furanoses;[7e] synthesis of a novel catalyst in the polymerization of epoxides;[8] formation of leaving groups of enhanced ability;[9] reaction with formyl Meldrum's acid to afford the formylacetate;[10] oxidation to the corresponding aldehyde[11] or carboxylic acid[12])

Alternate Name: *o*-NBA.

Physical Data: mp 70-72 °C; bp 270 °C. The thermal stability of nitrobenzyl alcohols has been examined.[17] Its conformation in solution has been studied using ^{17}O NMR[18a] and ^{13}C NMR[18b] analysis.

Form Supplied in: light tan powder.

Handling, Storage, and Precautions: light-sensitive. Harmful if swallowed or inhaled.

Mechanism of Action.

Under photolysis,[19] acidic,[20] and electron bombardment[21] conditions, the transformation of *o*-nitrobenzyl alcohol or its derivatives involves an internal redox reaction sequence followed by liberation of the deprotected alcohol or amine (eq 1). Analogously, the photorearrangement of esters of *o*-NBA, obtained through its reaction with acid chlorides[2a,4] or anhydrides,[3] also induces an internal redox reaction (eq 2).

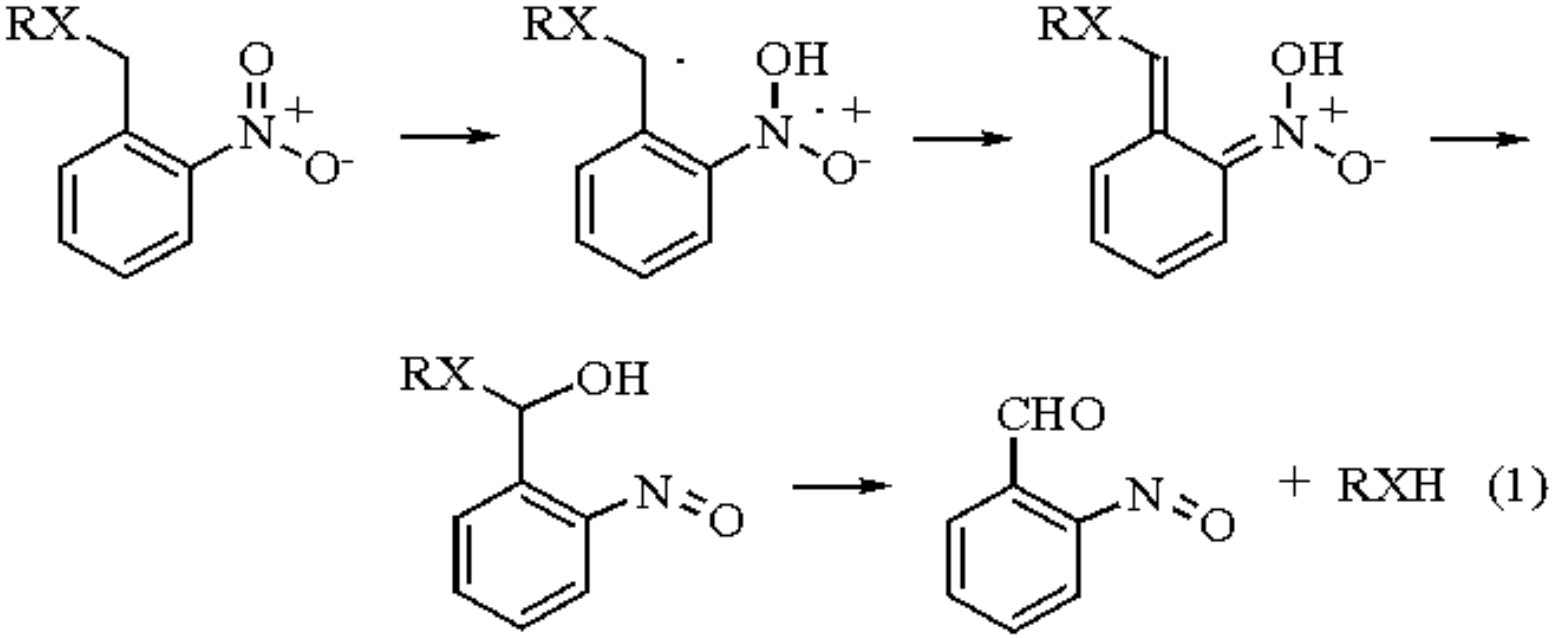

R = H or protected functionality, X = O or N

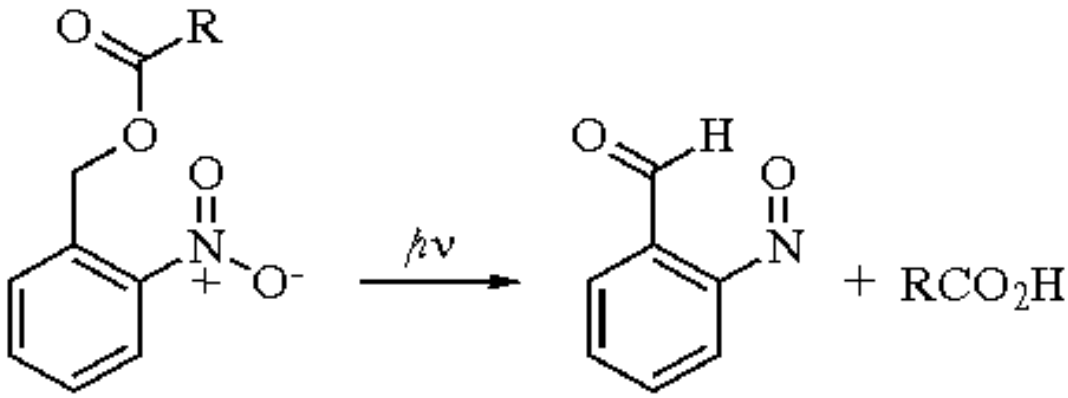

Protection of Ketones and Aldehydes.

o-NBA serves as a photoremovable protective group for aldehydes and ketones. Bis-acetals are prepared in a high-yield exchange reaction, except with hindered ketones for which it is necessary to employ the diol *o*-$O_2NC_6H_4CH(OH)CH_2OH$. The acetals are removed in excellent yield by irradiation at 350 nm in benzene (eq 3).[1]

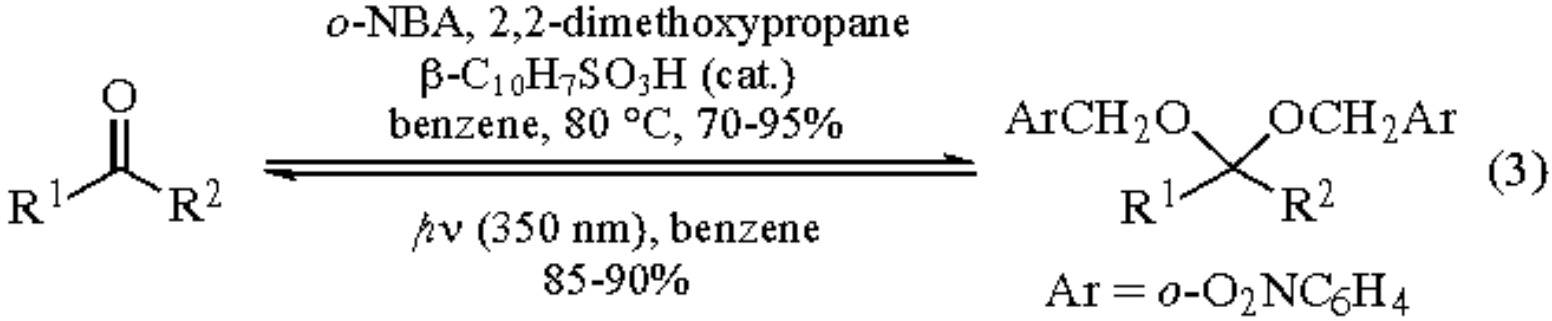

Generation of Carboxylic Acids.

Photolabile phosphatidylcholine (PLPC) has been synthesized by reaction of *o*-NBA with dodecanedioyl dichloride followed by ***1,3-Dicyclohexylcarbodiimide*** coupling. Subsequent photolysis of the resulting 2-nitrobenzyl esters results in the instantaneous disintegration of the PLPC liposomes, thus opening up the possibility of their use as drug carriers in vivo.[4] Irradiation of copolymers with *o*-nitrobenzyl ester side groups, synthesized from methacrylyl chloride, generates free carboxylic acids, as illustrated in eq 4.[2a] The positive photosensitive polyiimide biphenyl precursor pictured in eq 5 has been made by treatment of biphenyltetracarboxylic acid dianhydride (BPDA) with *o*-NBA.[3]

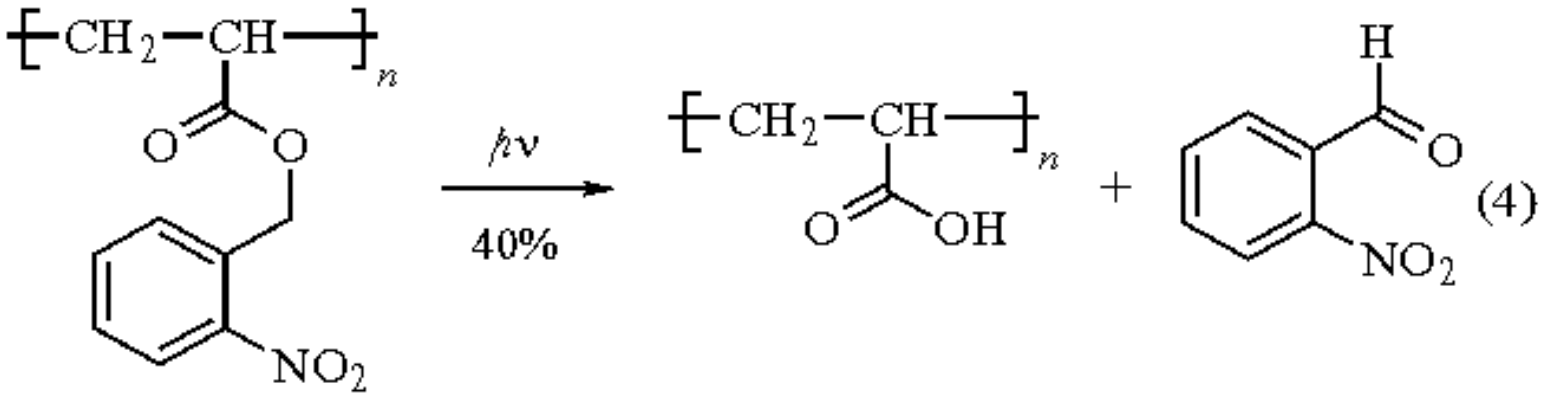

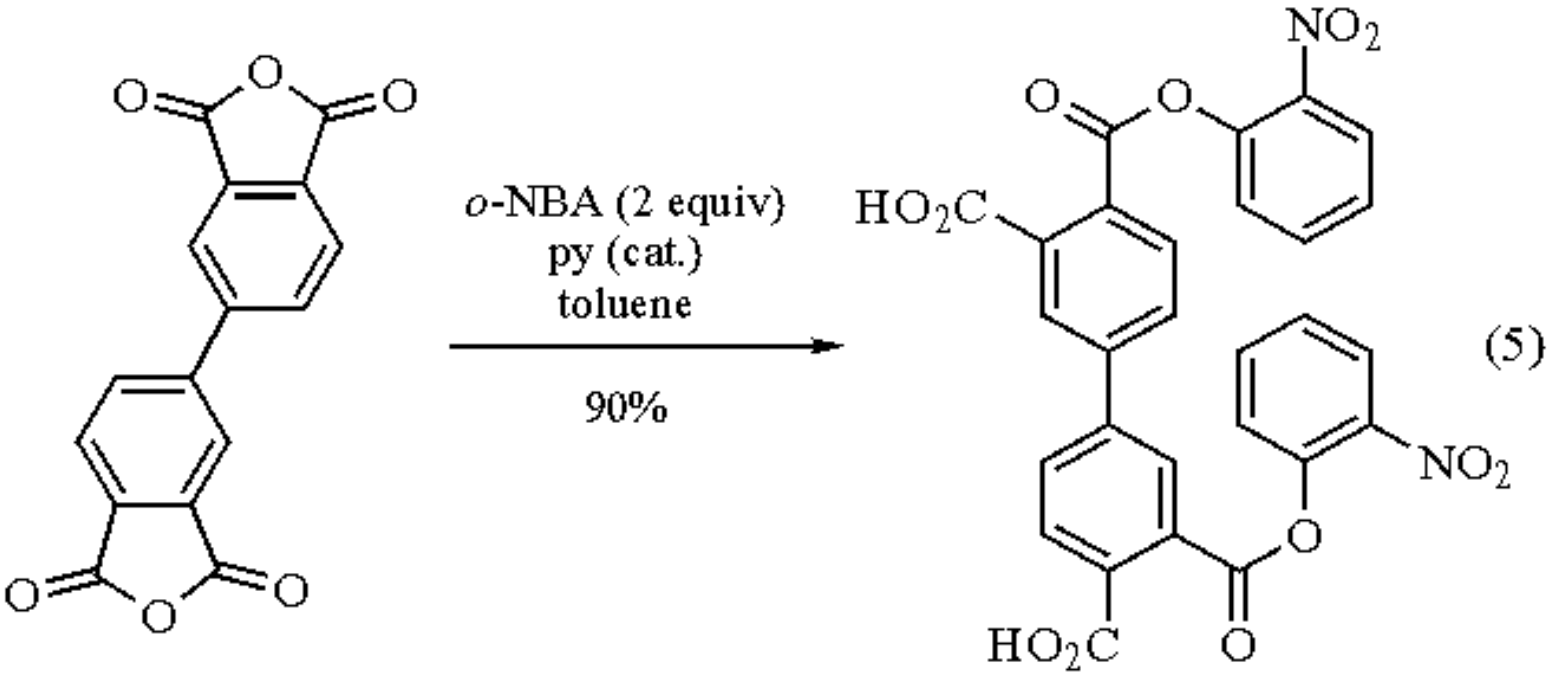

Protection of Amines.

Reaction of *o*-NBA with ***Phosgene*** yields the stable compound *o*-nitrobenzyloxycarbonyl chloride (eq 6).[5a] Subsequent reaction with 2-amino-2-deoxy-D-glucose cleanly affords the protected amine. The yields of the free amines obtained upon irradiation (eq 7) are lowered by side reactions with the *o*-nitrobenzaldehyde generated under the reaction conditions.[2a,5a,b] Yields are increased by the addition of polymeric aldehydes or sulfuric acid to the reaction mixture during irradiation,[5a] or by utilizing the related 2,6-dinitrobenzyl alcohol in the first step.[5b] Functional group tolerance

for this entire reaction sequence is impressively high.

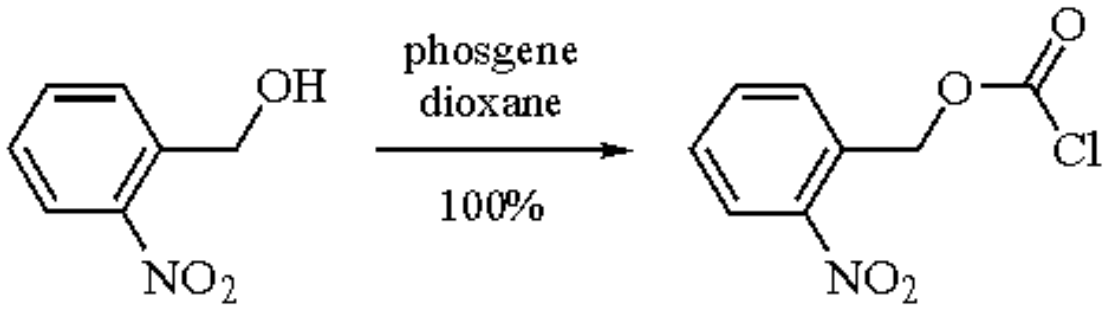

(6)

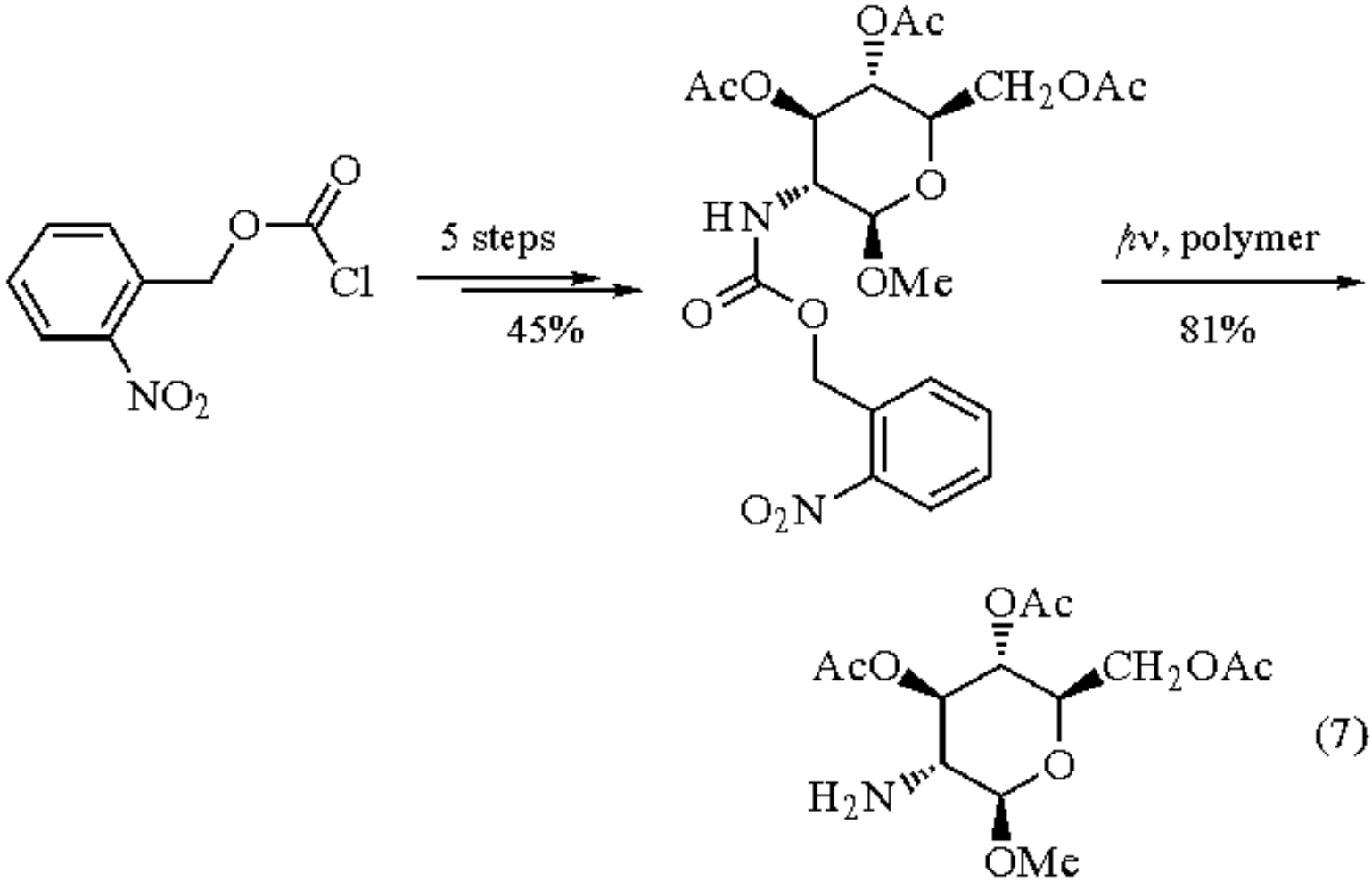

(7)

Reaction with isocyanates also provides a route to carbamates, which serve as masked amines[5b,c] (eq 8) or as diamines[5d] for epoxy resin curing. Carbamates of *o*-NBA possess moderate antitumor activity.[22]

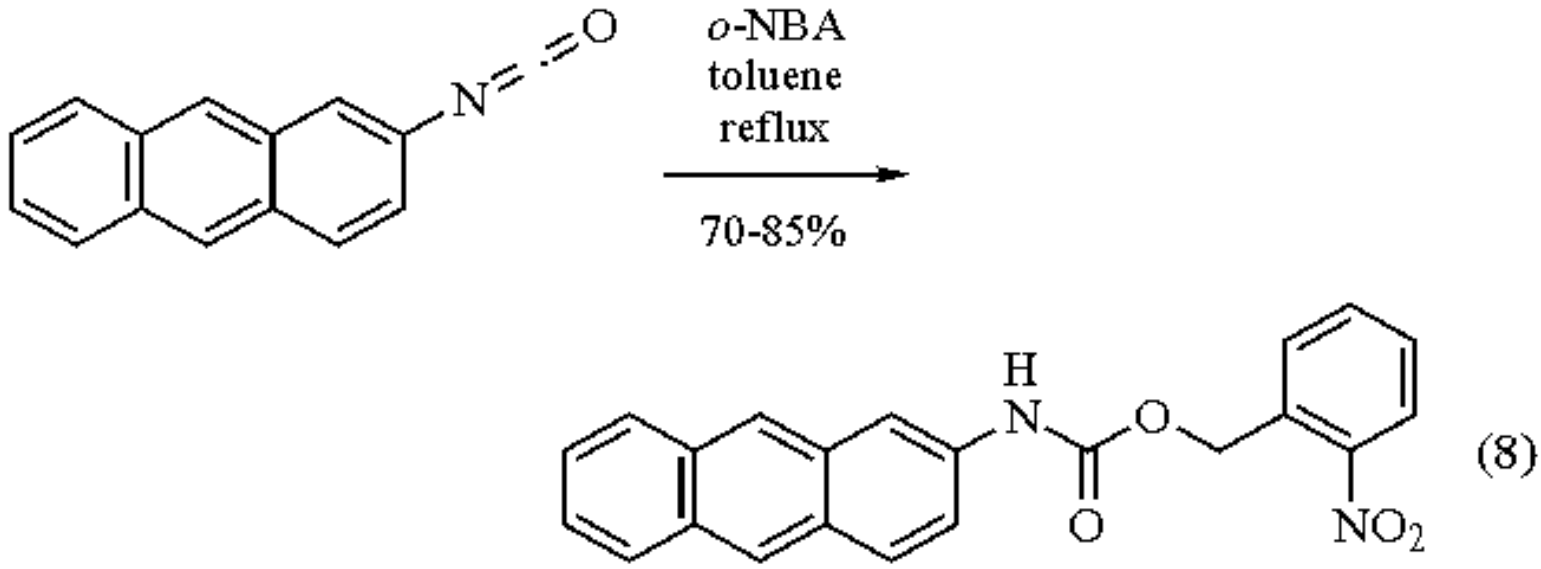

Protection of Amino Acids.

Photolabile *N*-protected amino acids and peptides have also been synthesized via their chloroformates.[2b,6] Quantitative deprotection proceeds without racemization[23,24] when an excess of ***Sulfuric Acid*** or ***Semicarbazide*** hydrochloride is added to the reaction mixture (eq 9). Conversely, treatment of serine with *o*-NBA in the presence of catalytic ***p-Toluenesulfonic Acid*** provides the *o*-nitrobenzyl ester of serine (eq 10).[2b]

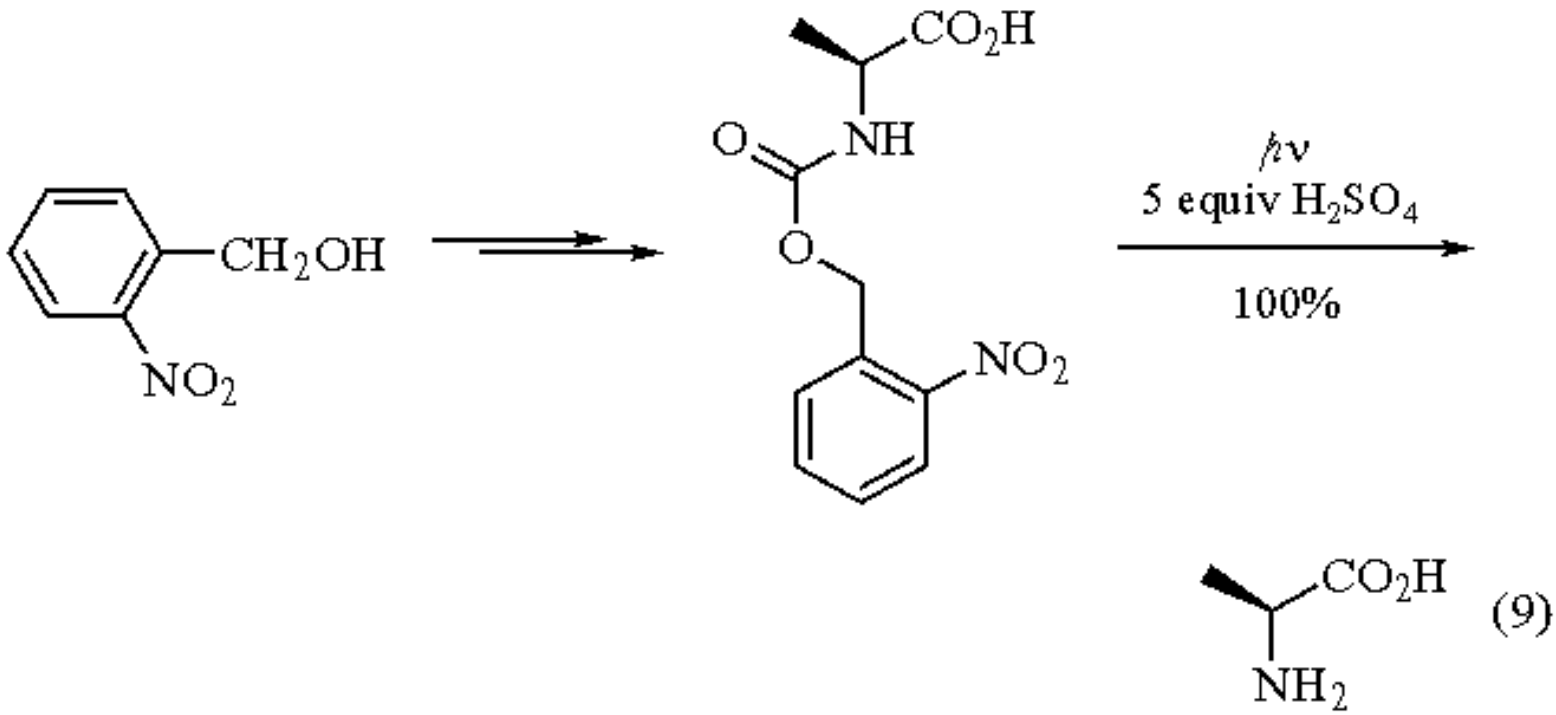

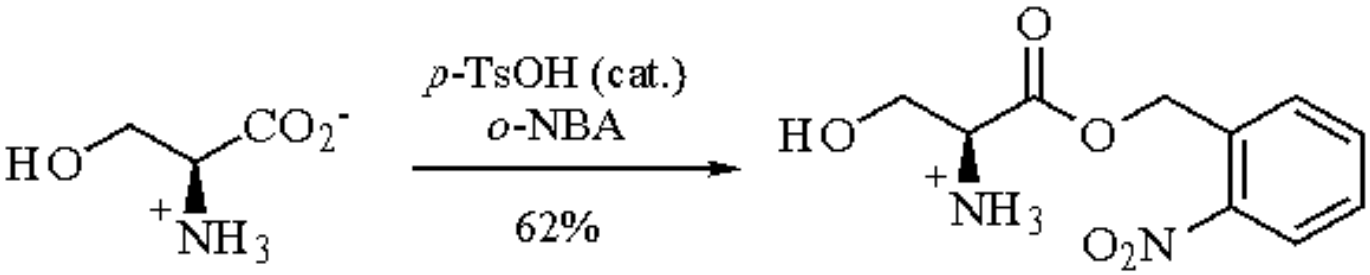

(10)

Protection of Hydroxyl Groups.

Photolabile 2´-*O*-(*o*-nitrobenzyl) derivatives of various ribonucleotides[7a-c] as well as dinucleotides[7d] have been synthesized, and their subsequent photodeprotections, which yield the corresponding alcohols, examined (eq 11). Protection of the anomeric hydroxyl functionality of 2-deoxy-D-ribofuranose has been accomplished using *o*-NBA (eq 12).[7e] This protective group is quite stable to acidic conditions, and has proven invaluable in the synthesis of abasic oligonucleotides. Similar conditions are employed in the synthesis of bis(*o*-nitrobenzyl) ethers.[25]

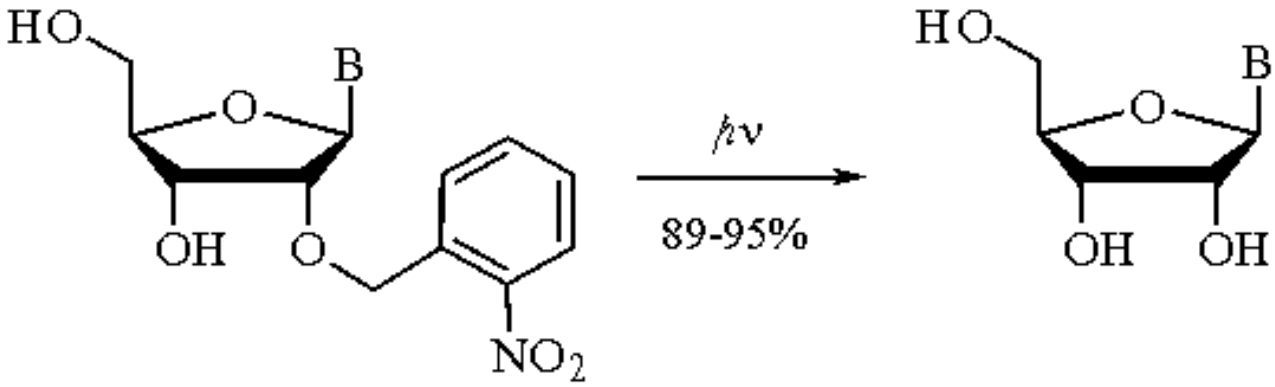

(11)

B = purine or pyrimidine

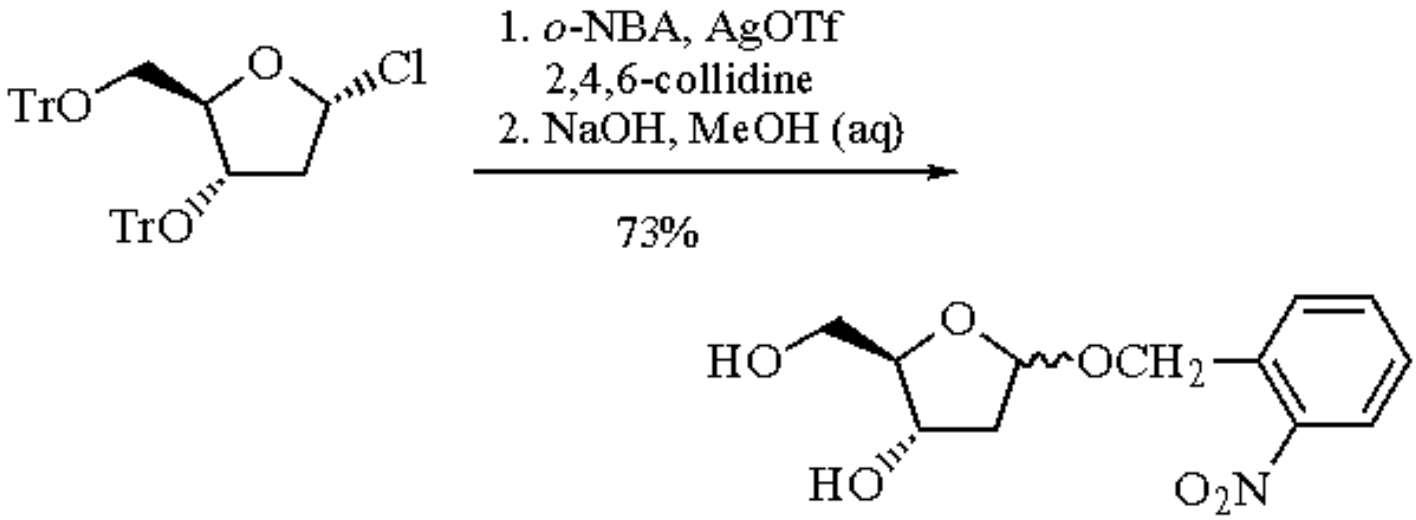

(12)

Miscellaneous Reactions.

o-Nitrobenzyl triphenylsilyl ether, a latent photogenerated source of triphenylsilanol, has been synthesized from *o*-NBA (eq 13). This new catalyst, upon irradiation at 365 nm, serves as a coinitiator in the polymerization of epoxides.[8]

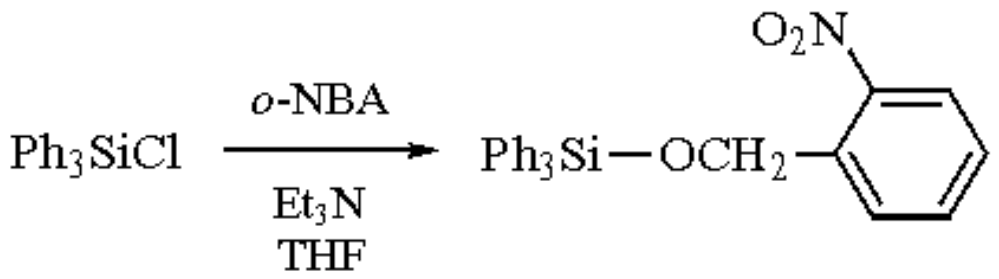

(13)

Greatly enhanced leaving group ability has been realized by use of *o*-NBA. Steroidal sulfonates synthesized from the sulfonylating agent formed in eq 14 undergo bimolecular azide displacements more efficiently than traditional sulfonates.[9]

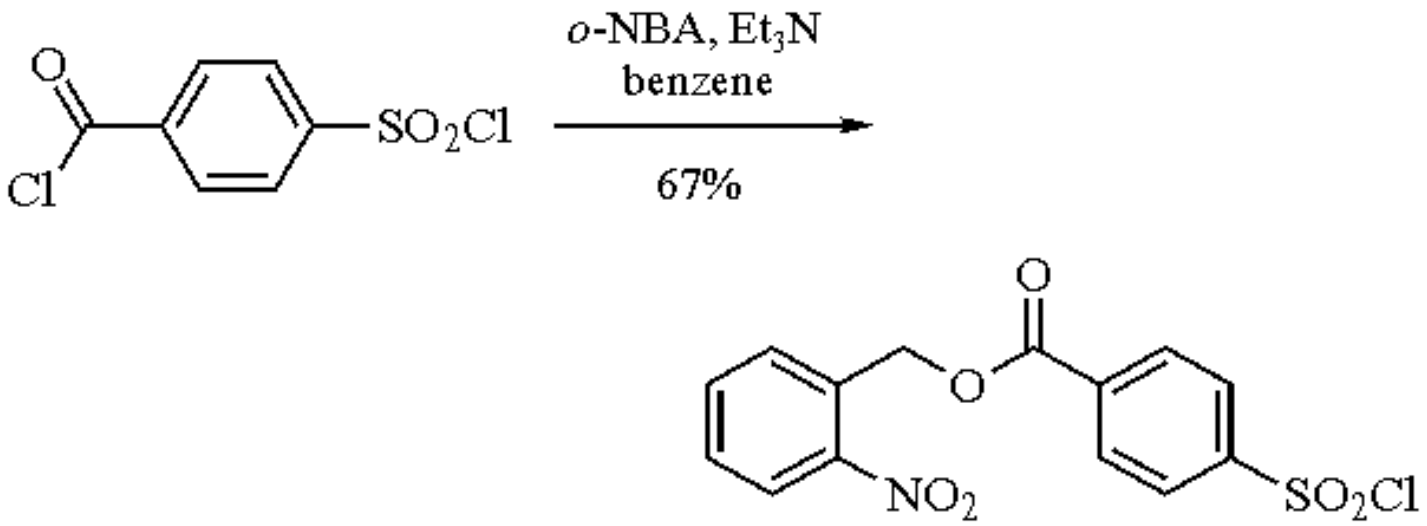

(14)

o-Nitrobenzyl formylacetate has been made by the reaction of formyl Meldrum's acid with *o*-NBA in dry toluene (eq 15).[10] α-Hydroxyimino phosphonates can serve as precursors to alkyl metaphosphates when photolabile ester groups are incorporated (eq 16).[26]

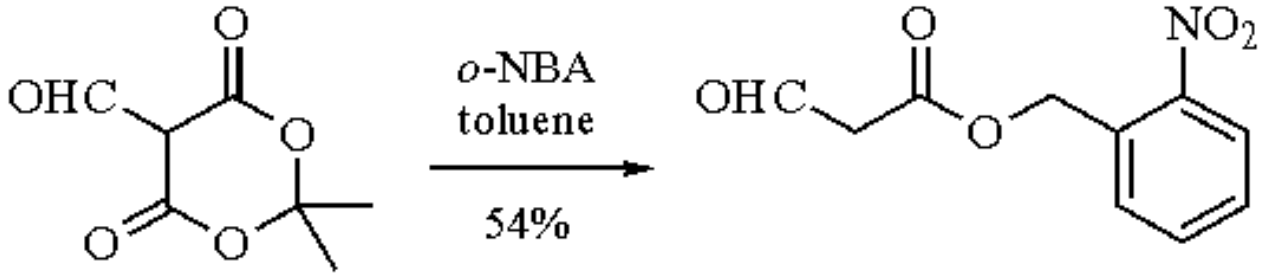

(15)

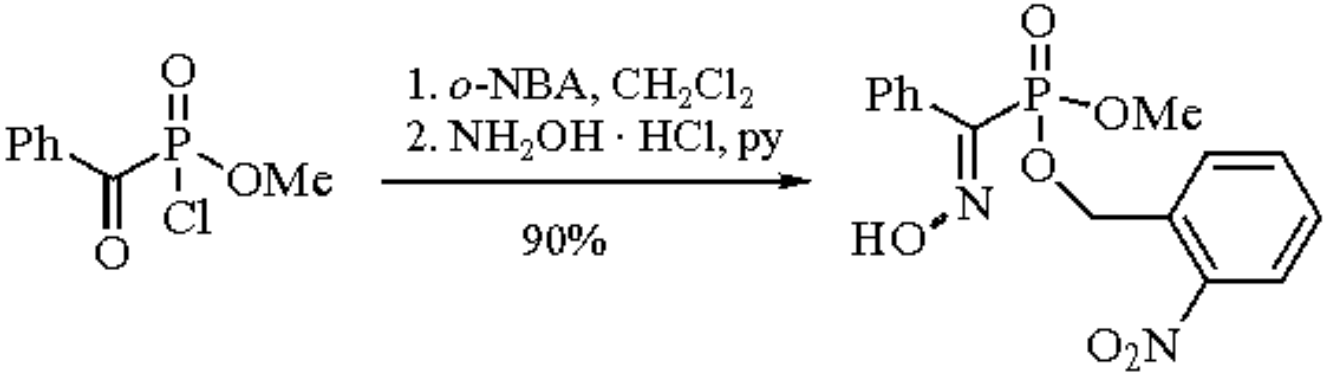

(16)

Oxidations and Reductions.

Oxidation of *o*-nitrobenzyl alcohol to its aldehyde has been accomplished using bis(dihydrogentellurato)M^{III} where M = Cu^{III} and Ag^{III},[11a] chromium trioxide and alumina,[11b] biphasic nitric acid,[11c] bromamine-B,[11d] ethyl chlorocarbamate,[11e] potassium bromate in aqueous HCl,[11f] pyridinium fluorochromate,[11g] *N*-bromoacetamide,[11h] thallium(III),[11i] ammonium molybdate tetrahydrate in 6 M HCl,[11j] 1-chlorobenzotriazole,[11k] pyridine oxodiperoxychromium(VI),[11l] cobalt(III) hydroxide,[11m] cerium(IV) perchlorate,[11n] or silver(II) oxide in acidic media.[11o] Oxidation to *o*-nitrobenzoic acid is possible using methyltrioctylammonium tetrakis(oxodiperoxotungsto)phosphate,[12a] electrogenerated superoxide,[12b] $(NH_4)VO_3$ and dilute $HClO_4$,[12c] or benzyltrimethylammonium tribromide.[12d] Biological oxidation of *o*-nitrotoluene to *o*-NBA by *Pseudomonas* sp. strain JS150 and *Pseudomonas putida* F1 has also been reported.[13]

Reduction of esters of *o*-nitrobenzyl alcohol to yield *o*-NBA can be accomplished using sodium borohydride in aqueous media.[14] Reductions of *o*-nitrobenzaldehyde to *o*-NBA using sodium borohydride under phase transfer conditions,[15a] dimethoxyborane-$CoCl_2$,[15b] and trimethoxysilane-lithium methoxide[15c] have been reported. Reduction of the nitro group of *o*-NBA to the amine using catalytic hydrogenation with Pd^0 and polybenzimidazole resin in DMF is likewise known.[16]

Related Reagents.

o-Nitrobenzyl Bromide.

---

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o-Nitrobenzyl Bromide

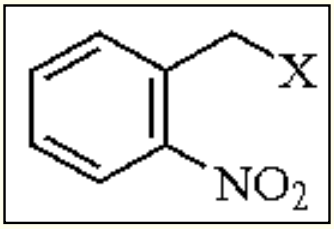

(R = Br)

[3958-60-9] · $C_7H_6BrNO_2$ · *o*-Nitrobenzyl Bromide · (MW 216.04) (R = Cl)

[612-23-7] · $C_7H_6ClNO_2$ · *o*-Nitrobenzyl Chloride · (MW 171.58)

(introduction of the 2-nitrobenzyl protecting group which can be cleaved selectively by photolysis[1-4])

Alternate Name: 2-nitrobenzyl bromide.

Physical Data: (X = Br) mp 45-48 °C. (X = Cl) mp 46-48 °C, bp 127-133 °C/10 mmHg.

Solubility: sol most solvents; alkylations are frequently carried out in polar solvents such as DMF.

Form Supplied in: commercially available from many sources.

Handling, Storage, and Precautions: 2-nitrobenzyl halides are lachrymators and should be used in a well-ventilated fume hood.

The 2-Nitrobenzyl Group as a Protecting Group.

The 2-nitrobenzyl group is one of an increasing number of functions that have been employed as photolabile protecting groups in organic synthesis,[1-4] and photolytic cleavage usefully adds to the range of deprotecting strategies in the armory of the organic chemist. One of the first examples of such a protecting group was in the use of 2-nitrobenzyl esters as protected carboxylic acids.[5] UV irradiation of the esters yields the free acid and initially 2-nitrosobenzaldehyde (the mechanism of the rearrangement has been studied extensively[1-4]). The benzaldehyde is further converted to azobenzene-2,2´-dicarboxylic acid which then acts as an internal light filter and so severely hampers the reaction. Benzylic substituents remove this problem and derivatives such as the α-phenyl-2-nitrobenzyl esters give much better yields (eq 1). The 2-nitrobenzyl unit has also been incorporated into a wide variety of photolabile polymer supports for solid phase peptide synthesis.[6] Polystyrene supported 2-nitrobenzyl bromide has been used as a resin for anchoring the *C*-terminus amino acid residue to the solid phase as its 2-nitrobenzyl ester.[7]

Phosphate esters incorporating the photolabile 2-nitrobenzyl group have also been synthesized.[8]

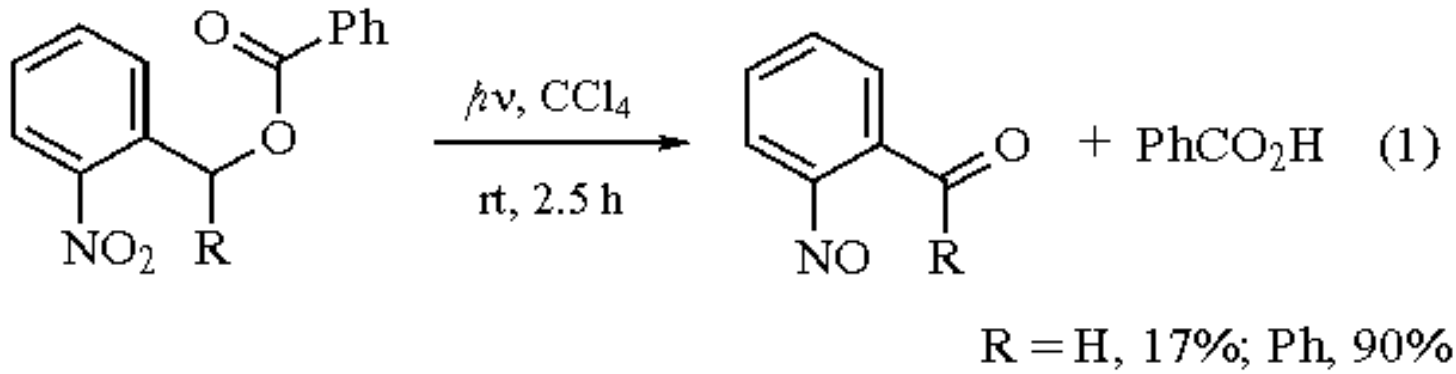

2-Nitrobenzyl halides have been used extensively in the field of oligonucleotide synthesis[9-15] as a protecting group (eqs 2 and 3) for the 2´-OH of uridine,[9] adenosine,[10] cytidine,[10] and guanosine.[11] Treatment of the nucleoside with a strong base such as ***Bis(tri-n-butyltin) Oxide***[9] or ***Sodium Hydride***[10,11] followed by 2-nitrobenzyl bromide gives the expected ethers, though in very poor yields (ca. 25-30%). The benzylic protons of nitrobenzyl halides are quite acidic and so decomposition of the halides is significant under the strongly basic conditions. To bypass this problem some workers have used 2-nitrophenyldiazomethane instead of the substituted benzyl halide,[16] but the increased yields are accompanied by poorer selectivity for the 2´-OH over the 3´-OH and introduce the problem of product separation. Another method, which has been used for making 4-nitrobenzyl ethers of simple alcohols, is to use *p*-nitrobenzyl trifluoromethanesulfonate derived from the corresponding alcohol.[17]

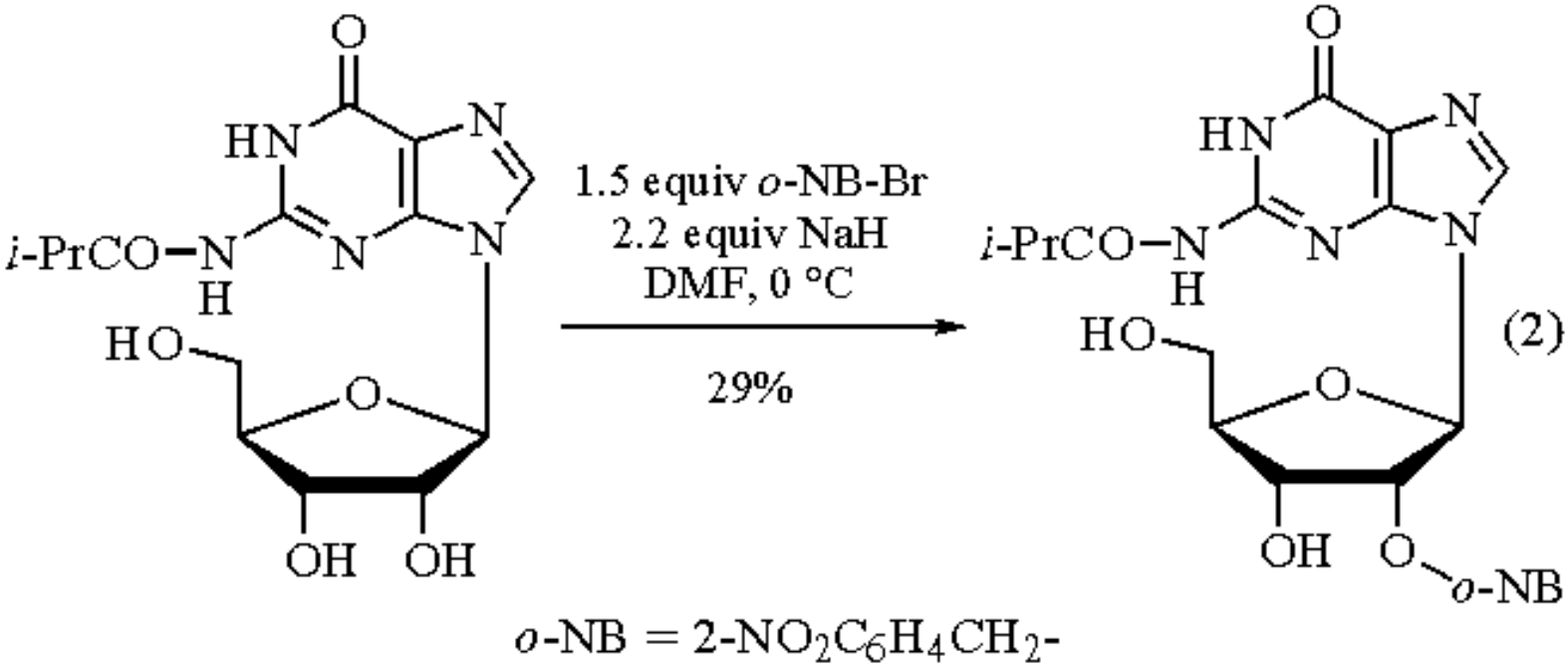

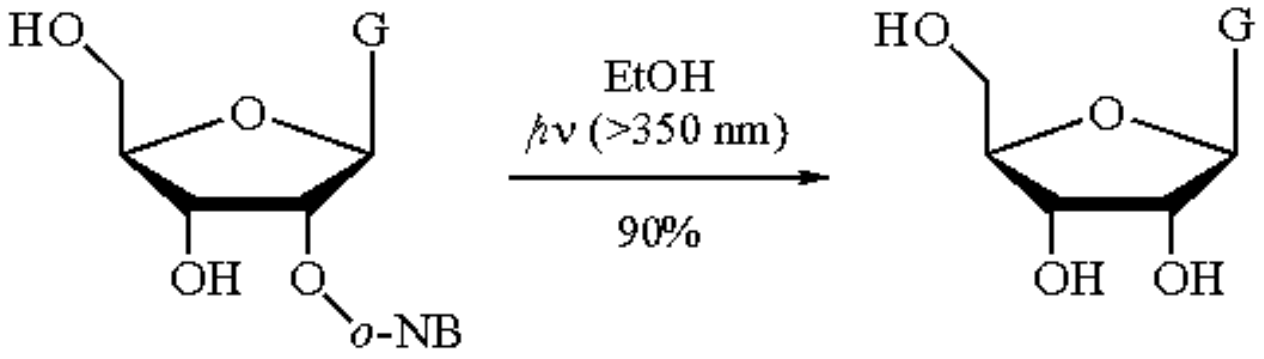

(3)

In the etherification of an alcohol using 2-nitrobenzyl bromide, Ireland[18] used BaO/***Barium Hydroxide*** instead of the stronger bases mentioned above (eq 4). The reaction is still capricious, and investigation of silver-assisted alkylations resulted in failure. Deprotection near the end of the synthesis though is effected smoothly and cleanly with UV irradiation (eq 5). For the protection of phenolic hydroxyl groups both ***Silver(II) Oxide*** in benzene[19] and a ***Potassium Carbonate***/***Cesium Carbonate*** mixture[20] (eq 6) have been used successfully.

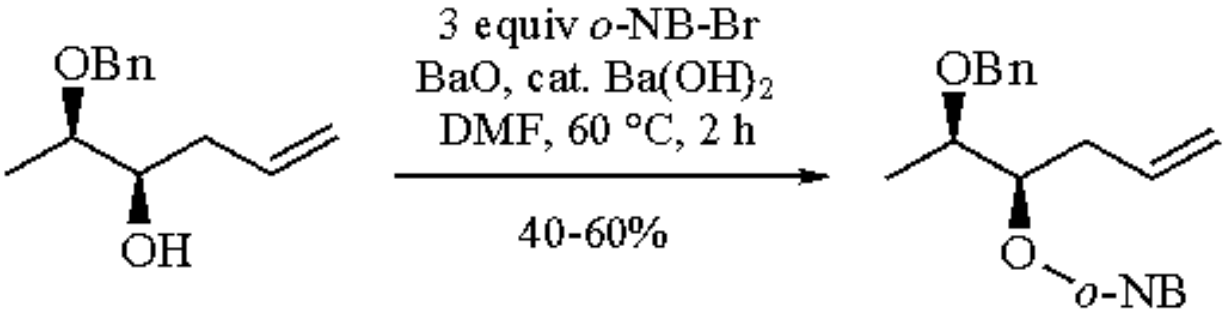

(4)

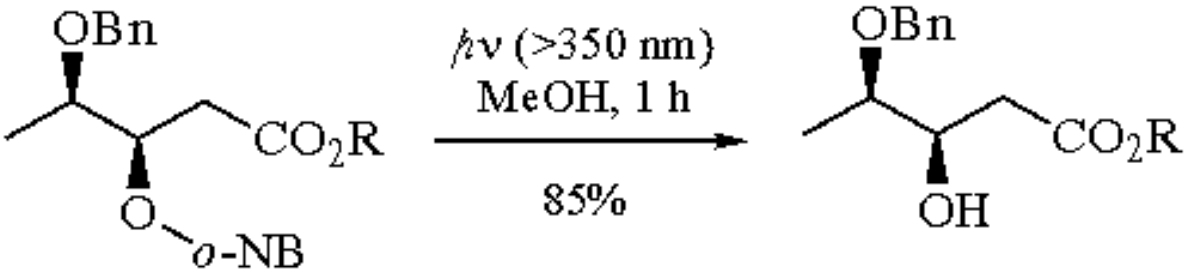

(5)

R = complex spiroacetal

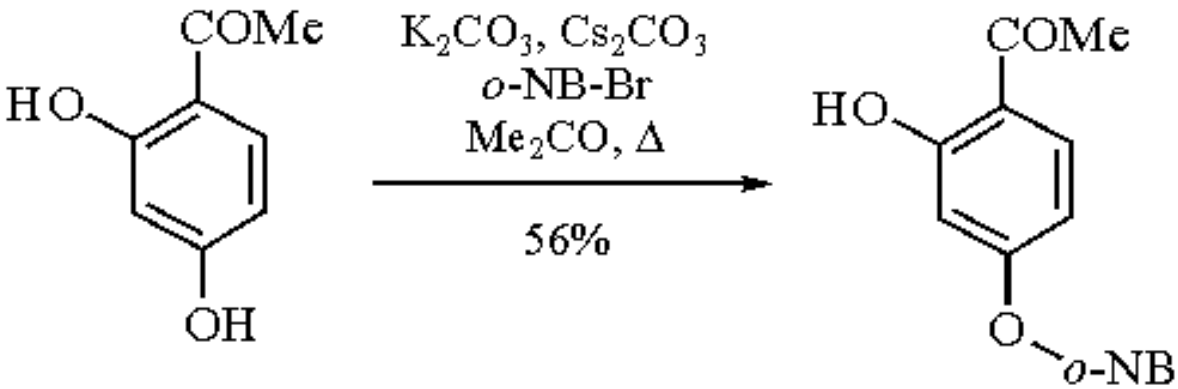

(6)

The photolabile 2-nitrobenzyl group has been employed in carbohydrate chemistry[21] for the protection of anomeric hydroxyl groups, and has also been used for other acetals.[22] These derivatives, synthesized from 2-nitrobenzyl alcohol, are particularly useful as they impart greater crystallinity to the compounds and aid in purification.

The 2-nitrobenzyl group has been used to protect heteroatoms other than oxygen. The sulfur atom in the phosphorothioate group of some nucleotides has been protected as the *S*-(2-nitrobenzyl)phosphorothioate (eq 7), and with this protection the nucleotides can be successfully coupled and deprotected to give di- and trinucleotides.[23]

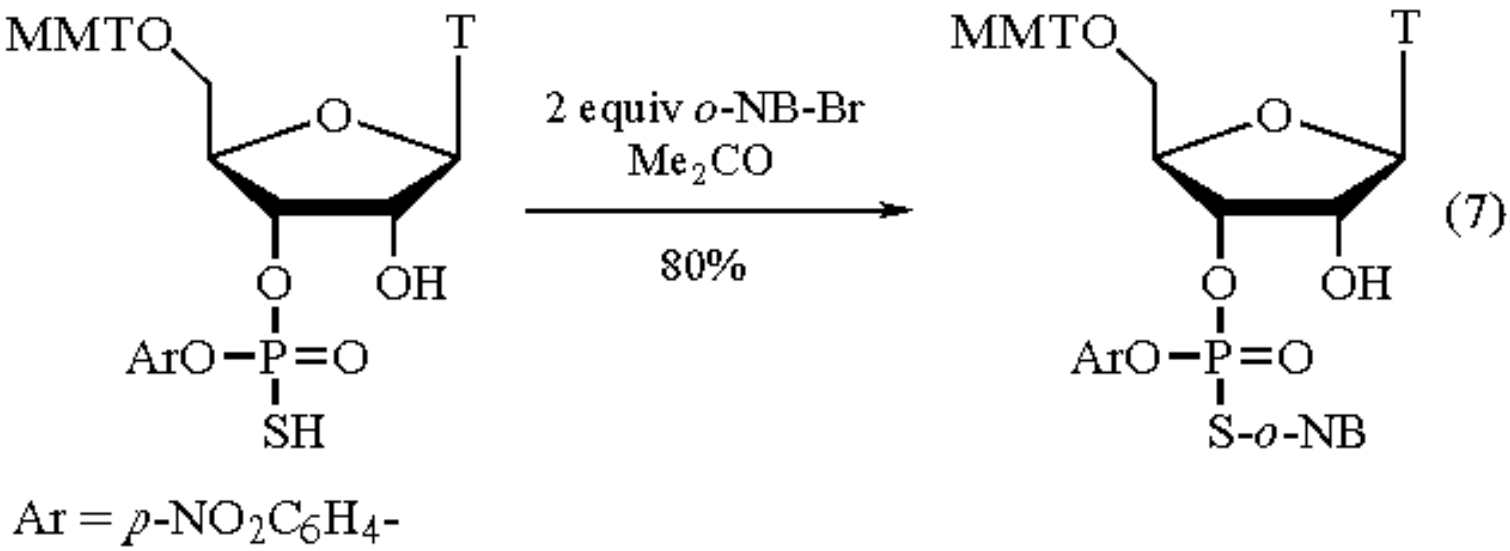

The N-1 atom in pyrazolidin-3-ones has been protected using 2-nitrobenzyl bromide in DMF (eq 8),[24] as has the N^{im}-3 atom in histidine (eqs 9 and 10).[25]

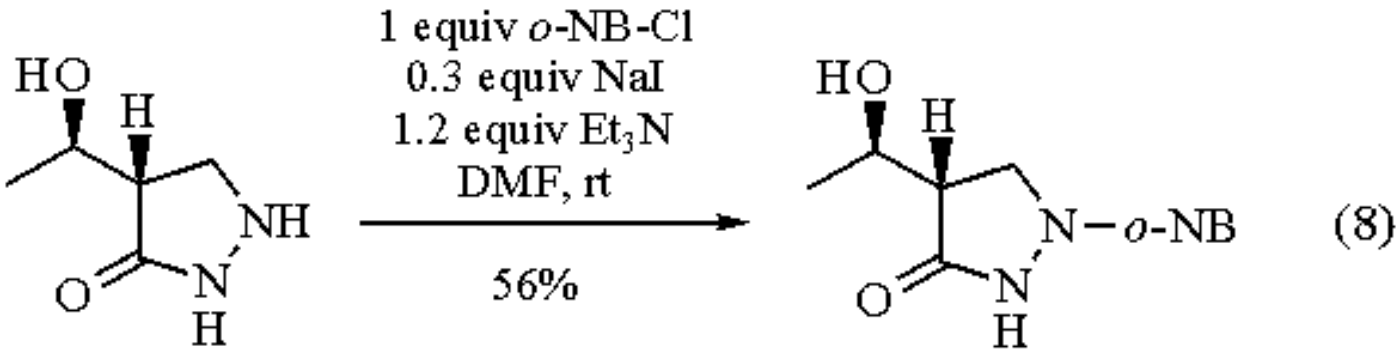

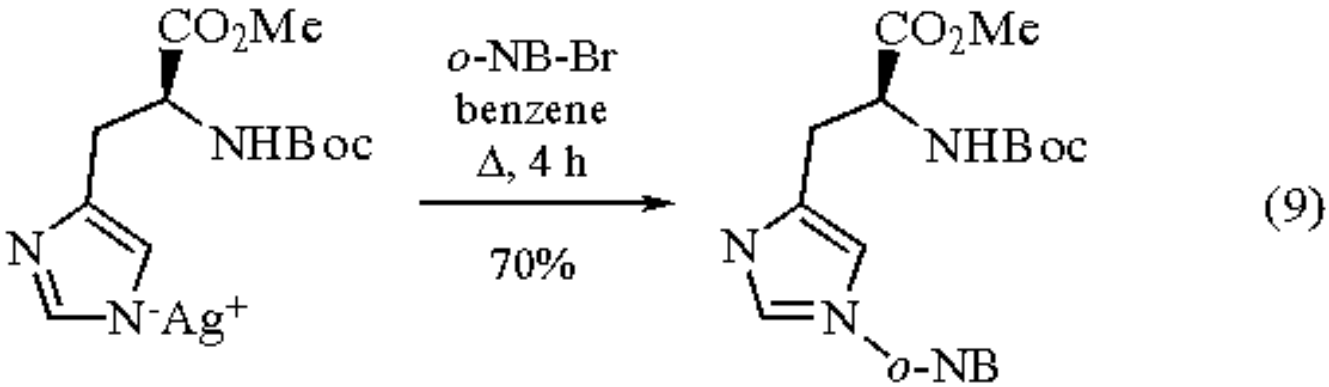

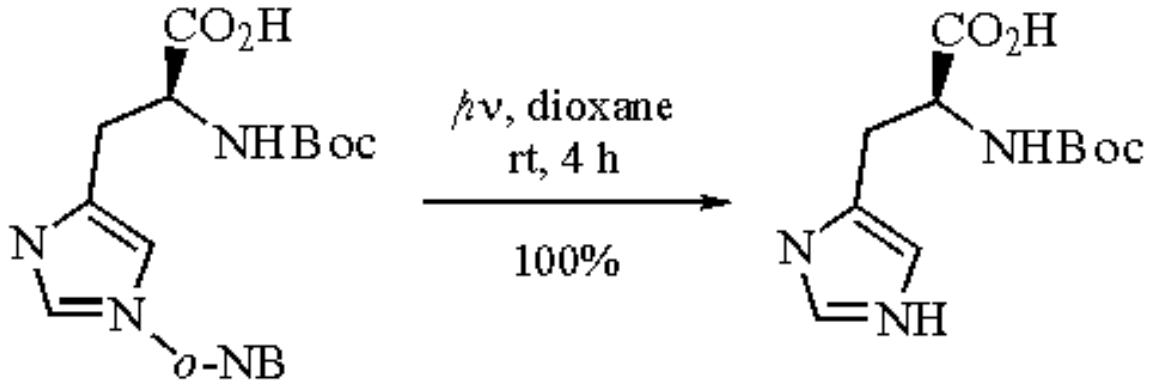

(10)

In Williams' synthesis of (±)-aplysiatoxin, he used a *N*-(2-nitrobenzyl) protected glycine unit.[26] The 2-nitrobenzyl group has been used to *N*-protect other biologically important compounds such as 5-fluorouracil, 2´-deoxy-5-fluorouridine (eq 11),[27] and purine bases.[28] Glycine, an important inhibitory neurotransmitter, has been *N*-derivatized with the 2-nitrobenzyl group so that the biologically active compound can be released with UV photolysis as desired.[29] This use of photolabile protecting groups for biologically active molecules has been reviewed recently.[30]

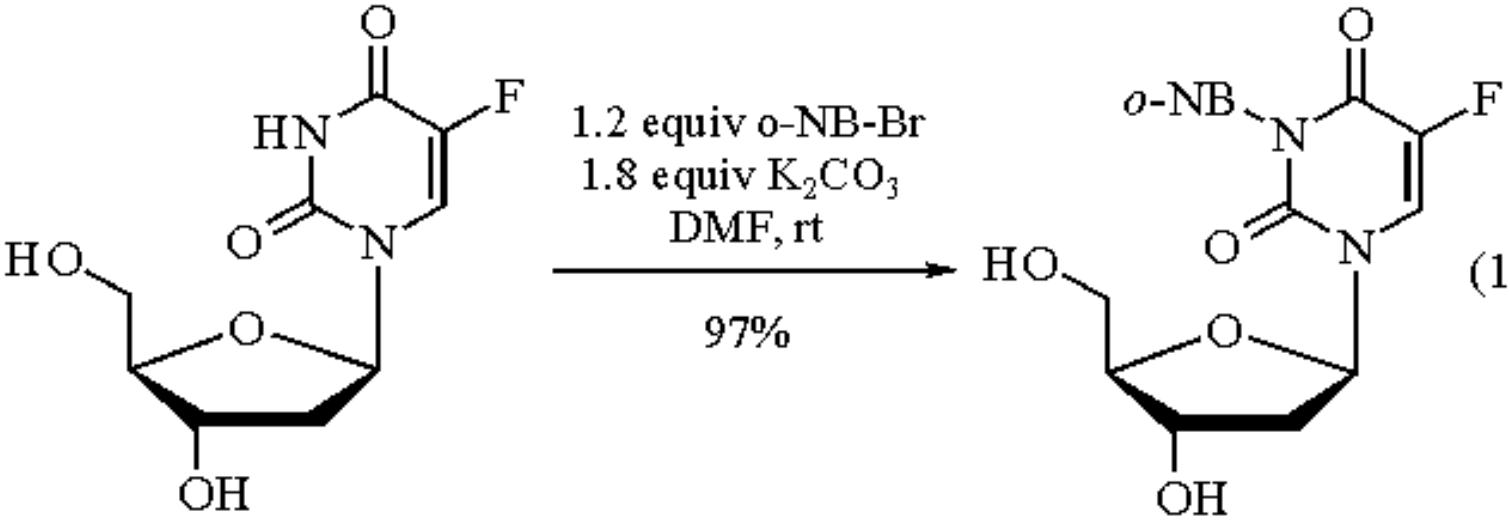

(11)

The 2-nitrobenzyl substituent has also found a use in the protection of amino groups (eq 12) as urethanes using 2-nitrobenzyloxycarbonyl chloride, giving a photolabile equivalent to the benzyloxycarbonyl (Z) group.[31]

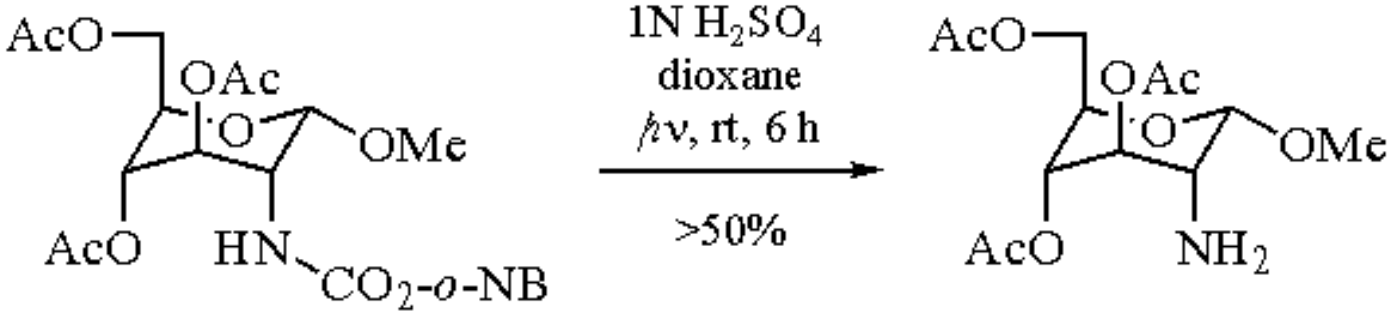

(12)

Related Reagents.

o-Nitrobenzoyl Chloride; ***o-Nitrobenzyl Alcohol***.

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p-Nitrobenzyl 2-Diazo-3-trimethylsilyloxy-3-butenoate

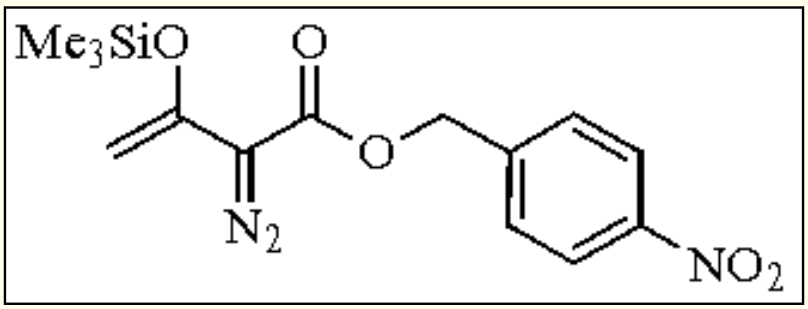

[93788-47-7] · $C_{14}H_{17}N_3O_5Si$ · *p*-Nitrobenzyl 2-Diazo-3-trimethylsilyloxy-3-butenoate · (MW 335.43)

(annulation of β-lactams[1] and aromatic aldehydes and ketones[13])

Physical Data: mp 75 °C (dec).[4] The corresponding TBDMS ether has mp 133 °C (dec).

Solubility: sol acetonitrile, ethyl acetate, ether, methylene chloride, toluene; poorly sol hexane.[4] The reagent hydrolyzes in water and protic solvents, whereas the TBDMS enol ether is stable to neutral aqueous workup.[2]

Form Supplied in: stored and used in methylene chloride or toluene solution. *p*-Nitrobenzyl 2-diazoacetoacetate, the hydrolysis product, is the expected impurity.

Analysis of Reagent Purity: ^{1}H NMR.[1,2]

Preparative Methods: by silylation of the corresponding diazoacetoacetate[2] with a silyl triflate (***Trimethylsilyl Trifluoromethanesulfonate*** or ***t-Butyldimethylsilyl Trifluoromethanesulfonate***) and ***Triethylamine*** in CH_2Cl_2.[2] For large scale preparations the use of ***Chlorotrimethylsilane***, ***Potassium Iodide*** (one equivalent), and Et_3N in acetonitrile is more advantageous.[6]

Handling, Storage, and Precautions: should be stored in solution in a dry, dark, cold place. The solid form is stable for several months in the refrigerator. The solid reagent is not shock sensitive but exothermic decomposition takes place on melting, generating 200 cal g^{-1} (138 cal g^{-1} for the TBDMS ether).[5] Decomposition can also be initiated by metallic impurities (Cu, Rh, etc.).

Annulation of β-Lactams.

This bifunctional reagent was developed for the stereospecific construction of the carbapenem skeleton in the conversion of penicillin to thienamycin.[1a] The annulation scheme is based on condensation of the enol silane with the iminium ion intermediate followed by ring closure via rhodium-catalyzed carbenoid insertion into the NH bond (eq 1).

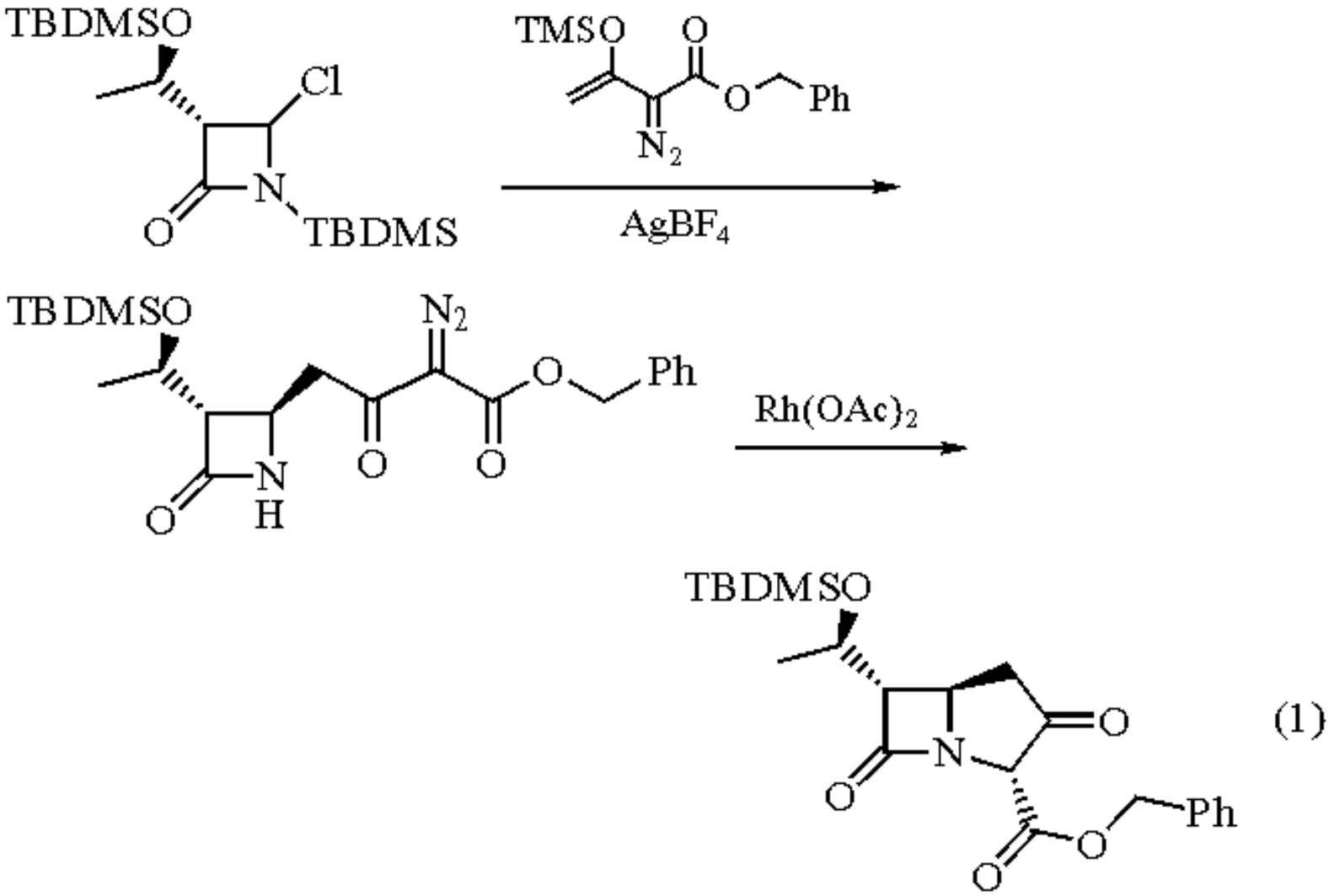

(1)

Subsequently, it was shown that the condensation is more facile when the nitrogen is not silylated[1b,7] and that acetoxy[1b] or benzoyloxy[8] groups may serve as the leaving group for generation of the iminium ion. Lewis acids such as $ZnCl_2$, $ZnBr_2$, ZnI_2, and TMSOTf in CH_2Cl_2 initiate the reaction (eq 2). This mode of annulation has formed the basis of the syntheses of thienamycin [R = MeCH(OH)-],[1,2,7-9] asparenomycin [R = $HOCH_2C(Me)$=],[10] PS-5 (R = Et),[3,11,12] and PS-6 (R = *i*-Pr).[3] The [3*R*(1´*R*),4*R*]-4-acetoxy-3-(1-hydroxyethyl)-2-azetidinone is commercially available. The patent literature contains numerous examples of this type of annulation. Variations of this annulation scheme, such as condensation of the β-lactam with bis-silylated acetoacetate (unstable reagent), followed by diazo transfer[1a] and nucleophilic displacement with the lithium enolate of diazoacetoacetate (3.2-14.1% yield),[12] are clearly inferior alternatives.

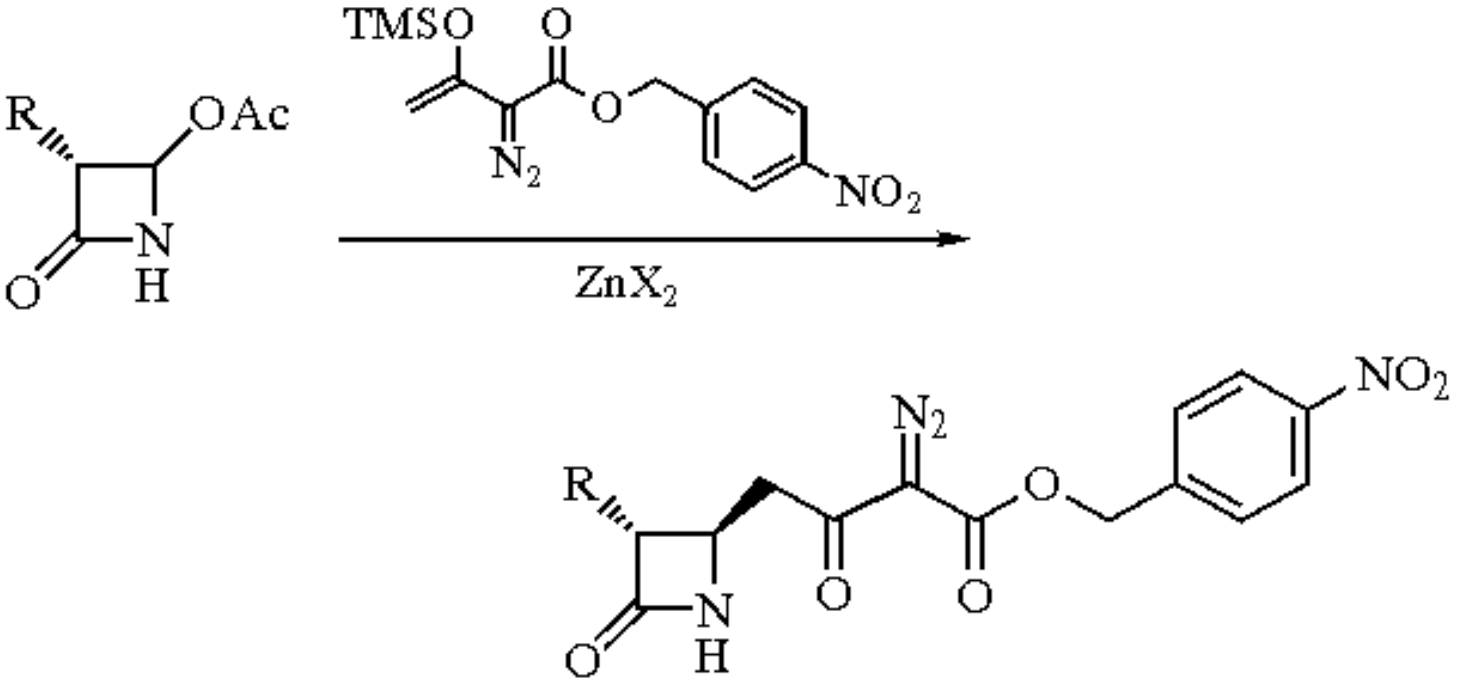

(2)

Annulation of Aldehydes and Ketones.[13]

Titanium(IV) Chloride-catalyzed condensation of the reagent and aldehydes or ketones followed by rhodium-catalyzed carbene insertion into the OH bond affords furanone derivatives (eq 3).

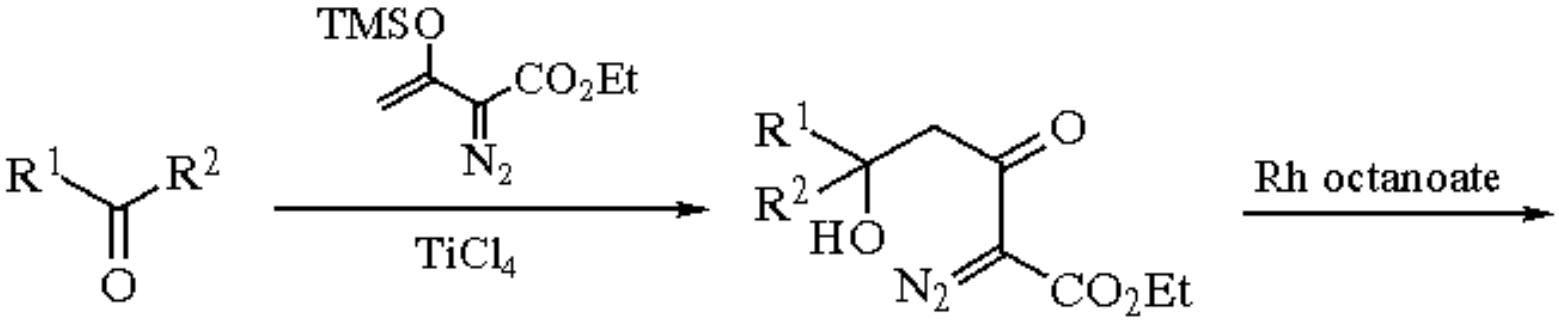

$R^1 = Ph; R^2 = H, Me$

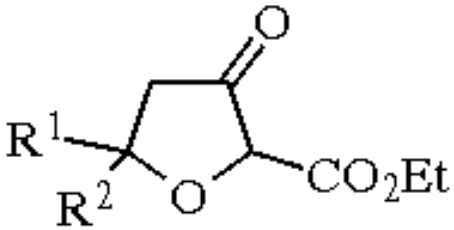

(3)

Analogous condensation with benzophenone using 2 equiv of $TiCl_4$ yields the unsaturated diazo ketone in 80% yield. ***Boron Trifluoride***-initiated ring closure produces the β-naphthol analog, while rhodium-promoted reaction generates the isomeric α-naphthol via Wolff rearrangement, followed by ketene cyclization, in quantitative yield (eq 4).

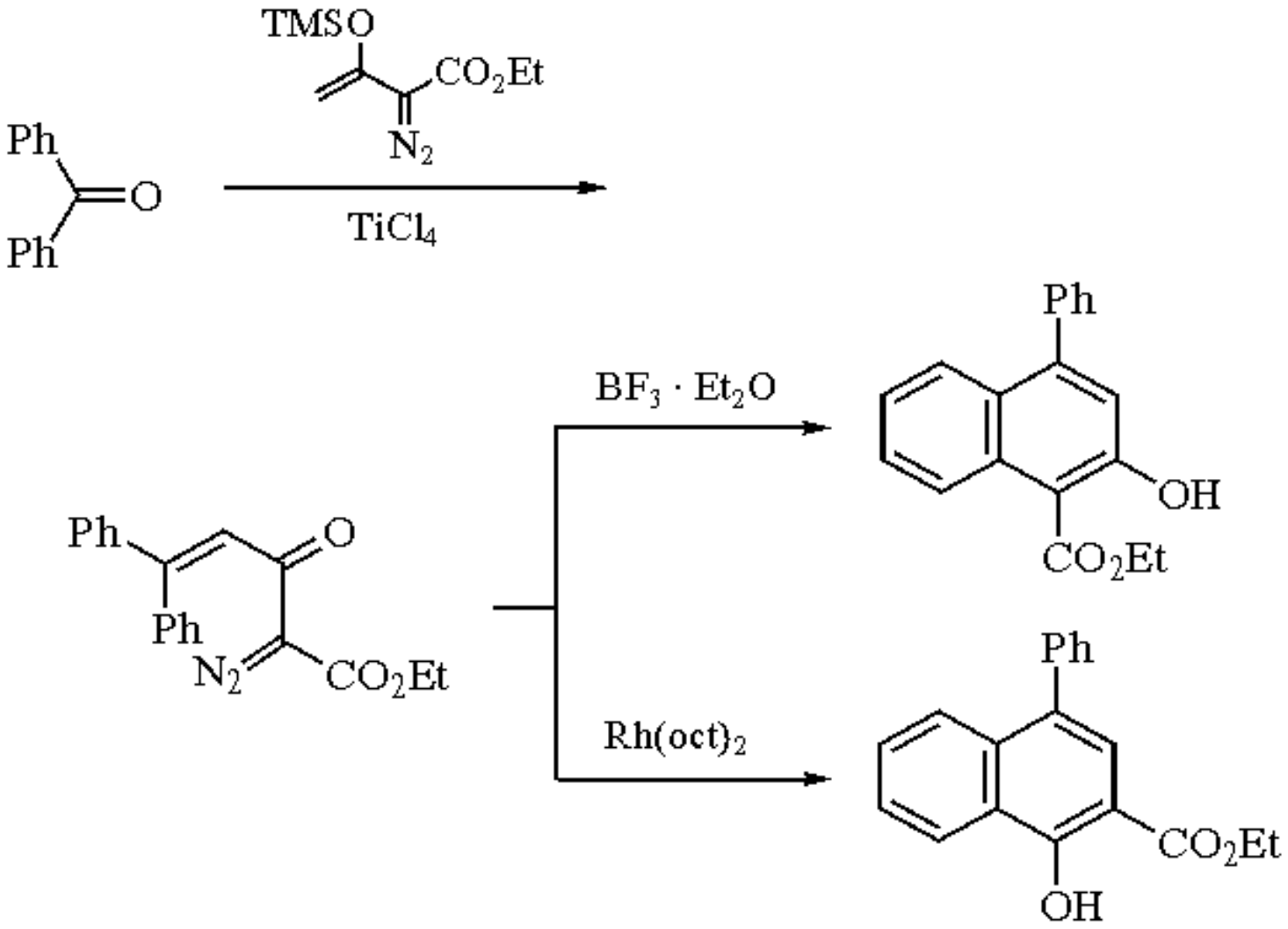

(4)

It is expected that this versatile bifunctional reagent will find application in other areas of synthetic chemistry. The *t*-butyldimethylsilyl ether analog is frequently used. The benzyl,[1] *p*-methoxybenzyl,[2] diphenylmethyl,[3] allyl,[2] and trimethylsilyl esters[2] have also been used.

---

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p-Nitrobenzyl *p*-Toluenesulfonate[1]

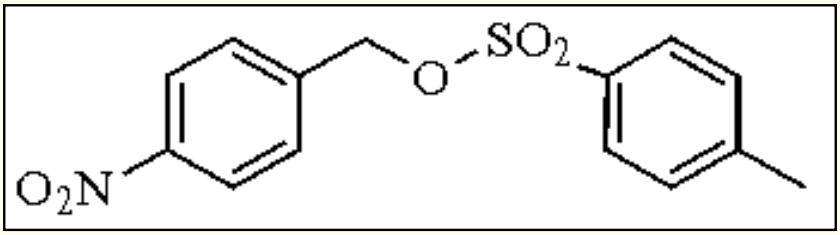

[4450-68-4] · $C_{14}H_{13}NO_5S$ · *p*-Nitrobenzyl *p*-Toluenesulfonate · (MW 307.35)

(conversion of a carboxylate anion into the *p*-nitrobenzyl ester, principally for use as a protecting group[1,2])

Physical Data: mp 103-104 °C.

Solubility: sol most organic solvents.

Form Supplied in: not commercially available.

Preparative Methods: by reaction of (a) ***p-Toluenesulfonyl Chloride*** with *p*-nitrobenzyl alcohol[3] for 30 min in dry pyridine at -10 °C; or (b) dry ***Silver(I) p-Toluenesulfonate*** with *p*-nitrobenzyl bromide in refluxing dry $CHCl_3$ for 24 h in the dark.[2]

Purification: recrystallize from 2-propanol-petroleum ether,[2] ligroin,[3] or anhydrous ethyl ether.[4]

Handling, Storage, and Precautions: mutagenic in the Ames *Salmonella* plate incorporation assay (using strain TA100);[5] should be treated as a potential carcinogen; can induce skin sensitization in guinea pigs.[6] Can be kept for long periods without apparent decomposition.[3]

p-Nitrobenzyl *p*-toluenesulfonate (PNB-OTs) is used as a reagent for protecting carboxylic acids. Formation of the ester involves conversion of the acid to a carboxylate salt (e.g. to the sodium salt using NaOMe in methanol,[2] or to the Et_3NH^+ salt using Et_3N[7]), followed by reaction with PNB-OTs in Me_2CO[2,7] or Me_2CO-DMF (2:1).[2,8] The PNB esters are stable to HBr/HOAc at room temperature (permitting cleavage of *N*-Cbz groups) and are readily cleaved by catalytic hydrogenation[2] (or NaOH/aq acetone[8]); the conditions of protection and deprotection minimize racemization of amino acids and peptides. In the example in eq 1, the protection-deprotection sequence was used[9] to avoid formation of a lactone along with the diacetate.

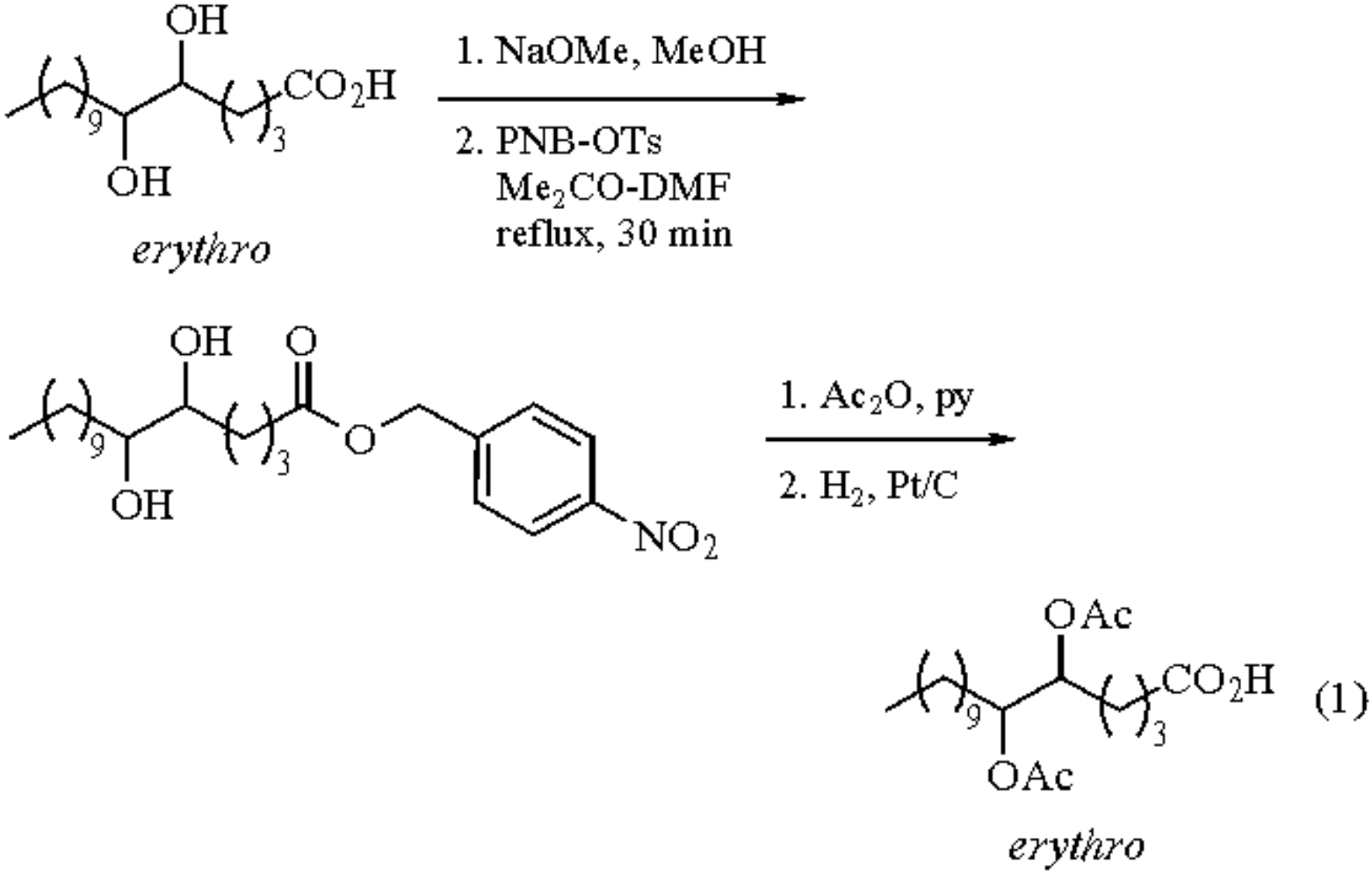

PNB-OTs has also been used as a UV labeling agent for detecting monocarboxylic acids in HPLC analyses.[10]

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Nitroethane

$EtNO_2$

[79-24-3] · $C_2H_5NO_2$ · Nitroethane · (MW 75.08)

(building block in synthesis; polar solvent)

Physical Data: mp -90 °C; bp 115 °C; *d* 1.04 g cm^{-3}; pK_a 8.5.

Solubility: completely misc most organic solvents; slightly sol water; sol alkaline solution.

Form Supplied in: colorless liquid, widely available; contains 2-nitropropane as the chief contaminant.

Purification: by drying over $MgSO_4$ and distillation at reduced pressure; a small acidic forerun is discarded.

Handling, Storage, and Precautions: stable compound. Flammable; toxic.

Introduction.

The reactions of nitroethane discussed here can, in principle, be applied to most primary nitroalkanes. Nitroethane reacts with metal alkoxides and hydroxides to form metal nitronates which are often applied as in situ generated reagents. They are unstable and it is advisable not to isolate them.

The Nitroaldol Reaction (Henry Reaction).[1,2]

Reactions with Aldehydes.

In the presence of base, nitroethane reacts with aliphatic aldehydes in an aldol-type reaction with formation of 2-nitro alcohols (nitroaldols). Due to its reversibility, the reaction is normally carried out in the presence of only catalytic quantities of base. The reaction of nitroethane with an aldehyde in the presence of one equivalent of base gives the salt of the *aci*-nitro tautomer of the product, which must be carefully acidified to avoid the Nef reaction. Alkali metal hydroxides, alkoxides, or carbonates and tertiary amines have been applied as catalysts.[2a] Elimination of water, the aldol reaction, and the Cannizzaro reaction are competing side reactions.[2a,b] 2-Nitro alcohols are unstable compounds and care has to be exercised during workup (decomposition during distillation). Higher yields are often obtained when

the reaction is catalyzed in heterogeneous systems with catalysts such as powdered NaOH,[3] Al_2O_3,[4] and Al_2O_3-supported KF.[5] The 2-nitro alcohols are readily converted into a variety of functionalities (eq 1).[1b,4-10,13-17]

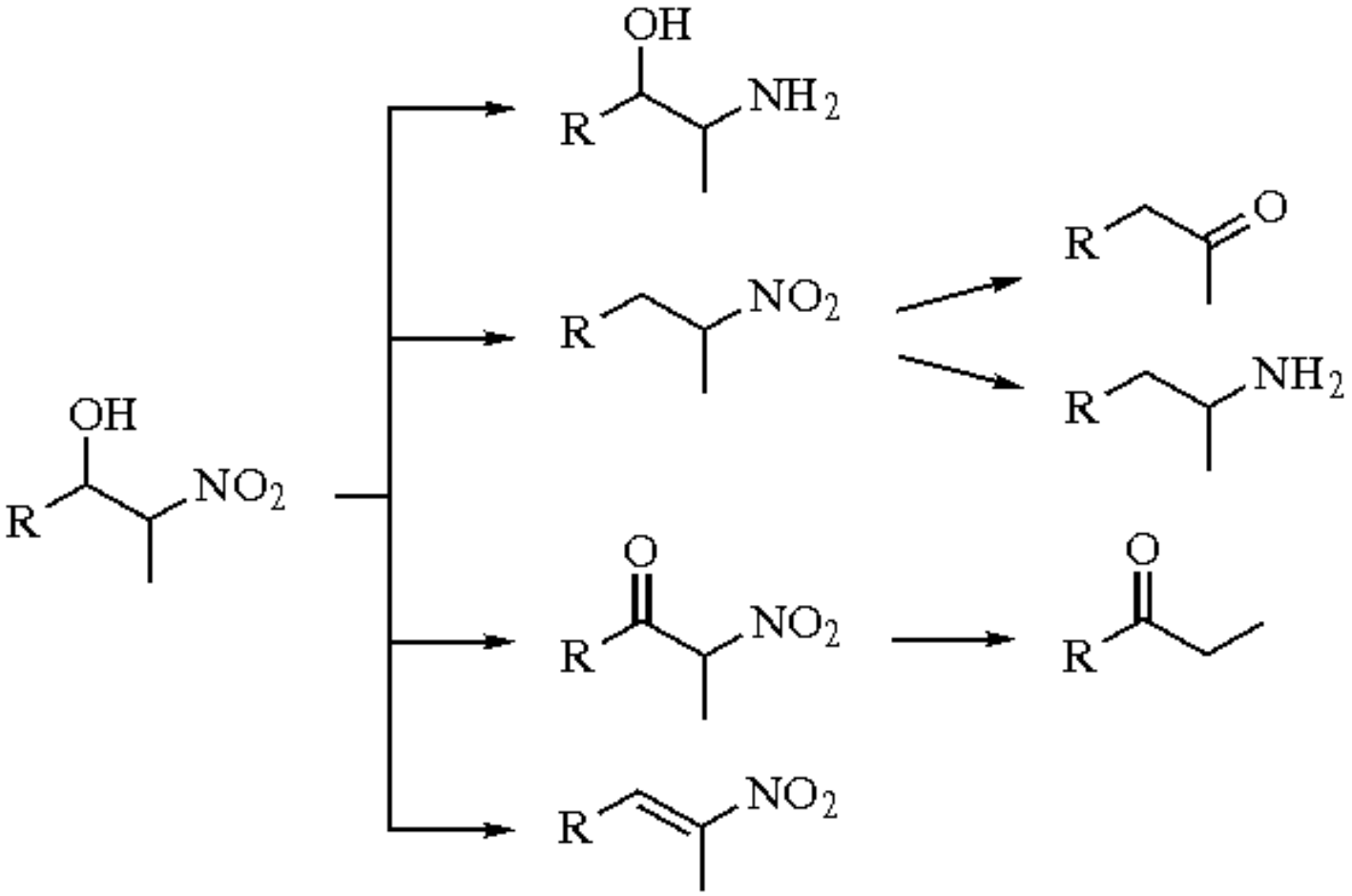

(1)

Aromatic aldehydes react with nitroethane under the same conditions.[11] Elimination of water to give β-nitrostyrenes takes place on acidification.[2a] Synthesis of β-nitrostyrenes can be accomplished in one step by heating aromatic aldehydes in acetic acid with NH_4OAc as catalyst.[12] In the presence of NaOAc in refluxing acetic acid, aldehydes are converted into nitriles (eq 2).[12b]

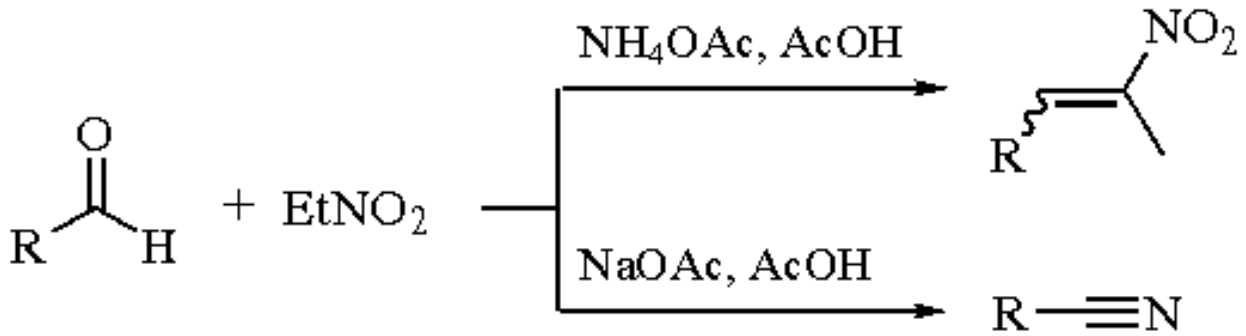

(2)

Dehydration of 2-nitro alcohols to nitroalkenes has been accomplished with ***Methanesulfonyl Chloride***,[13], phthalic anhydride,[14] ***1,3-Dicyclohexylcarbodiimide***,[15] pivaloyl chloride,[16] ***Trifluoroacetic Anhydride***,[17] and ***Acetic Anhydride***.[17] Heating 2-nitro alcohols in dichloromethane in the presence of basic aluminium oxide is another mild method for the synthesis of nitroalkenes.[18] Nitroalkenes can be converted into a variety of functionalities (eq

3),[2,19a,21-26] and have found utility as heterodienes in hetero Diels-Alder reactions and as reactants in Lewis acid promoted tandem [4 + 2]/[3 + 2] cycloadditions (eq 4).[20]

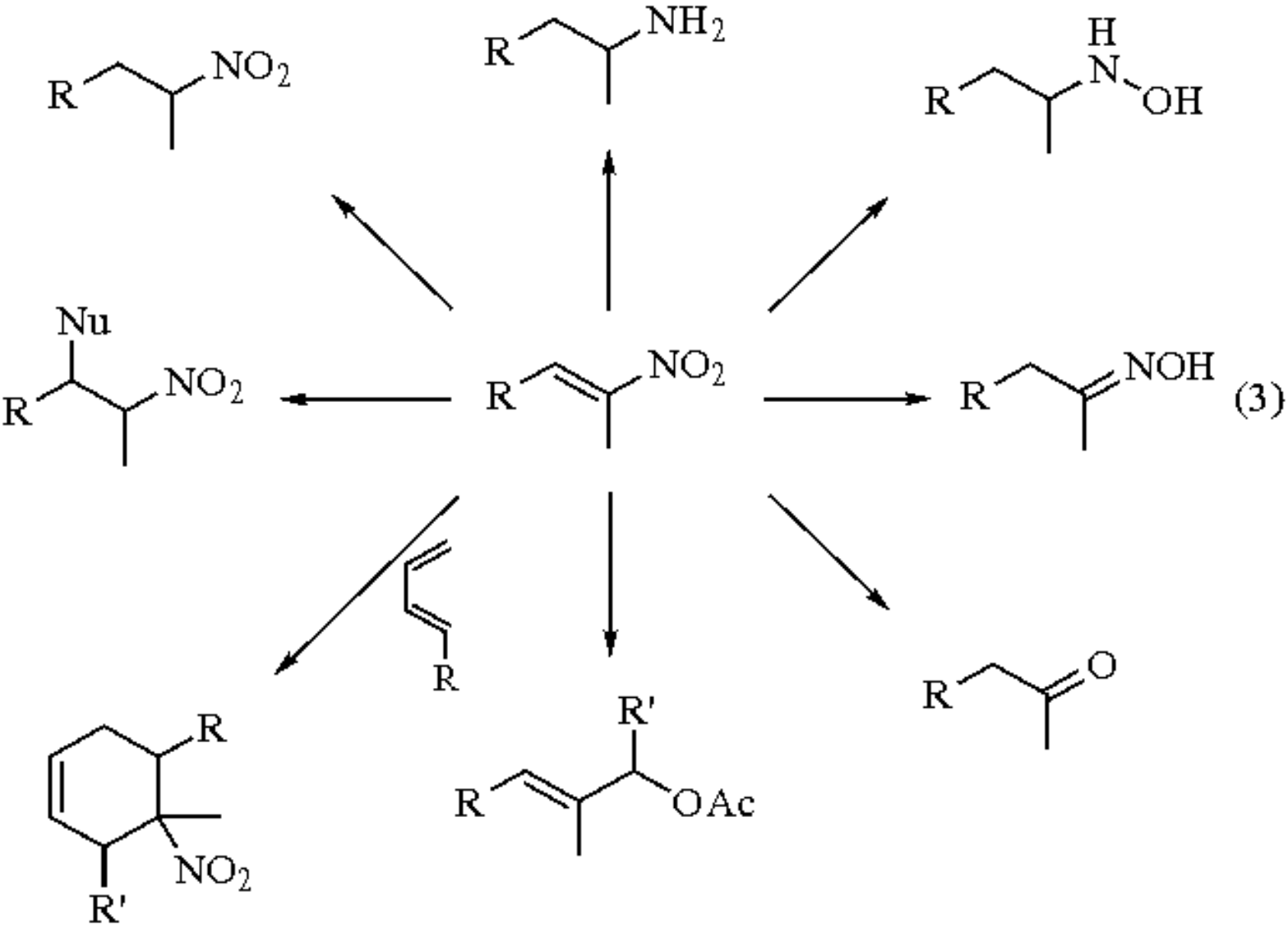

(3)

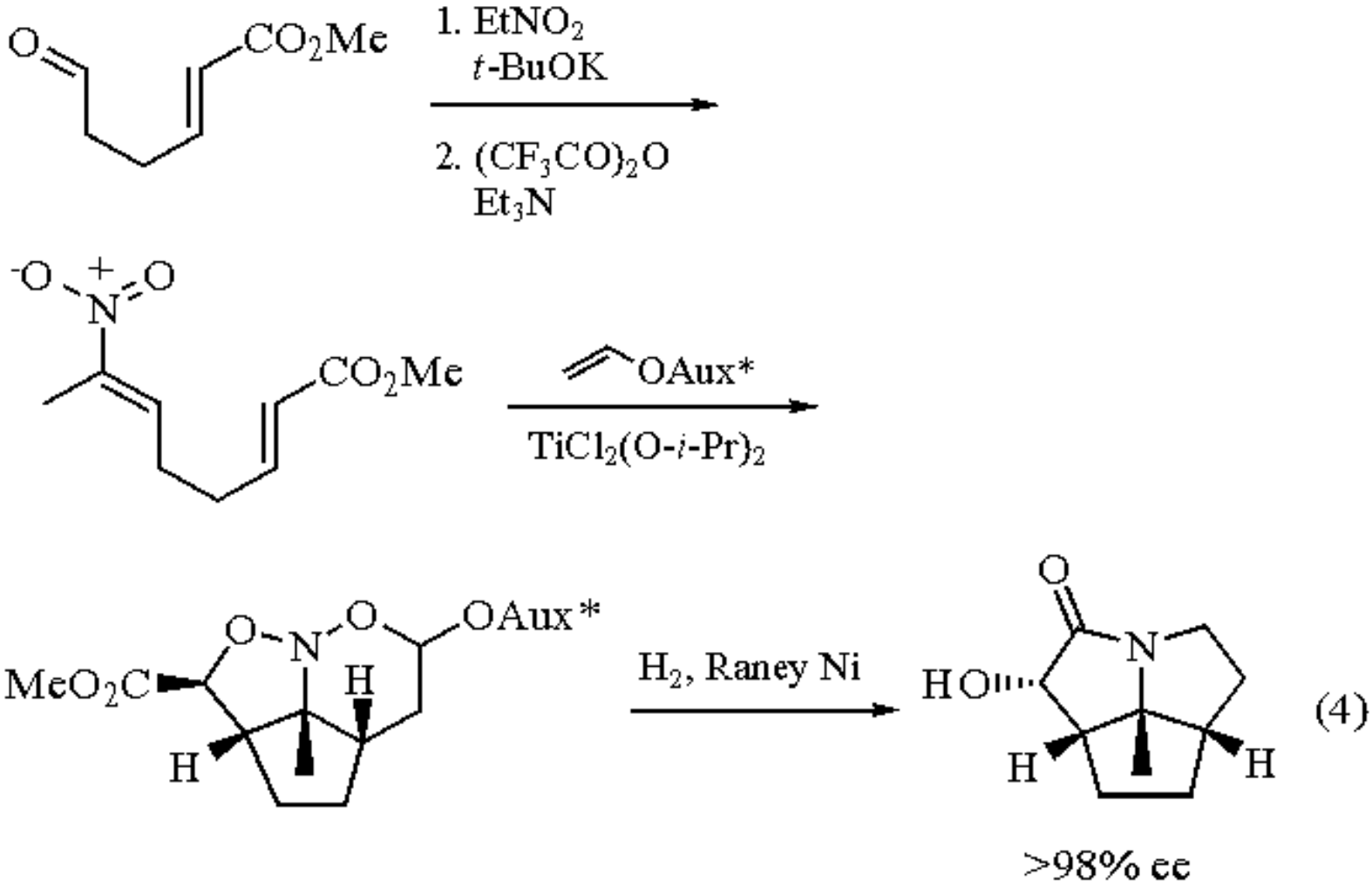

Nitroethane can be silylated to form stable trimethylsilyl or *t*-butyldimethylsilyl nitronates.[27] In the presence of a catalytic amount of ***Tetra-n-butylammonium Fluoride*** at -78 °C in THF, the silyl nitronates react with aldehydes to give 2-nitro alcohol *O*-silyl ethers in high yields.[6b,28] The TBDMS nitronate reacts in the presence of freshly dried Bu_4NF to give the *erythro*-isomer of the product in >95% de (eq 5).

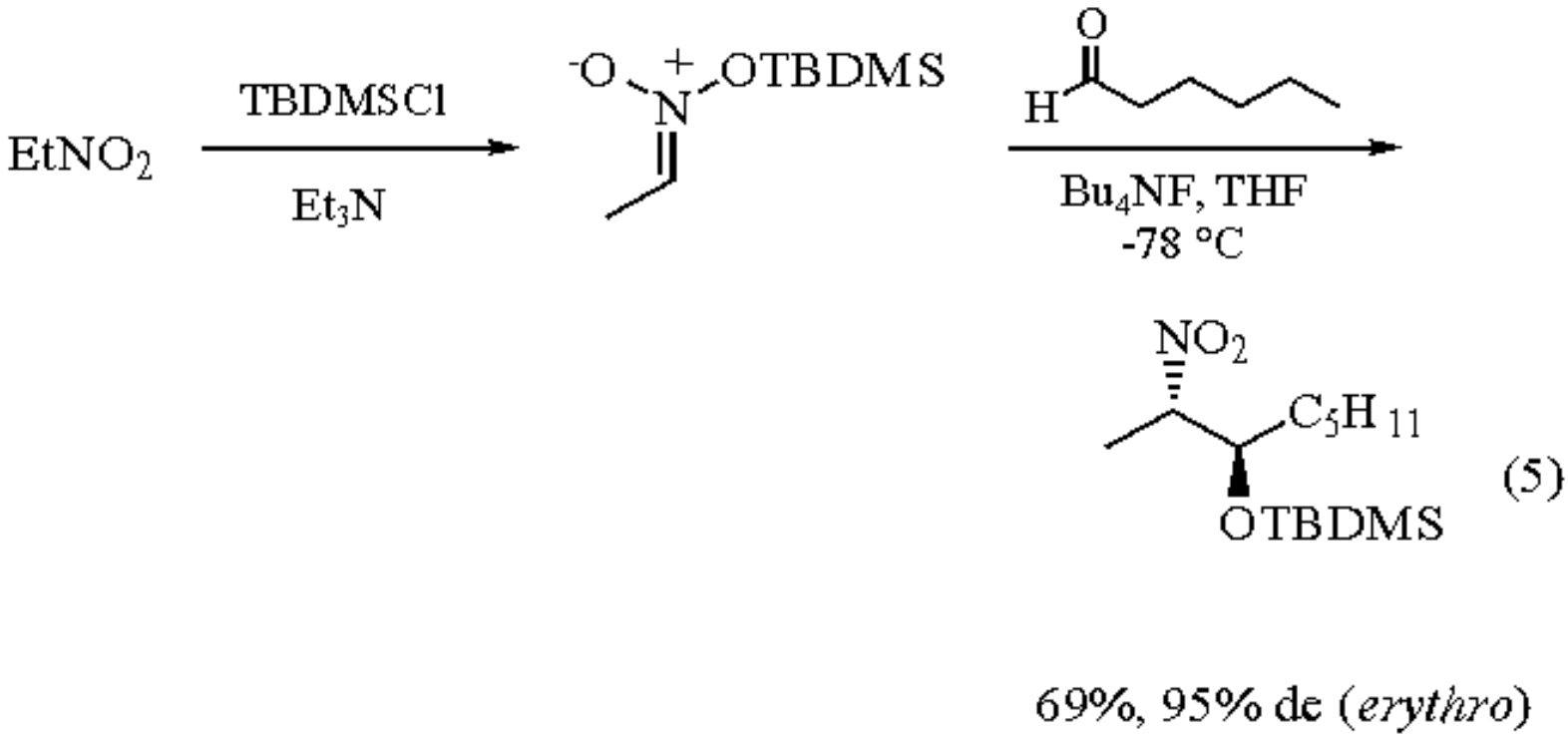

The dilithium salt of nitroethane is formed by treatment of nitroethane with 2 mol equiv of ***n-Butyllithium*** in THF/HMPA at -90 °C.[28,29] It reacts with aldehydes at -70 to -60 °C to form the doubly deprotonated nitro alcohols which must be carefully acidified at -90 °C with acetic acid. The dilithium salt is a much harder carbon nucleophile than the sodium nitronate and the reaction with carbonyl compounds is irreversible; this often leads to higher yields of 2-nitro alcohols than the conventional Henry reaction. The reaction proceeds diastereoselectively to give the *threo* and *erythro* isomers in a ratio of characteristically 3-5:1 (eq 6).[28]

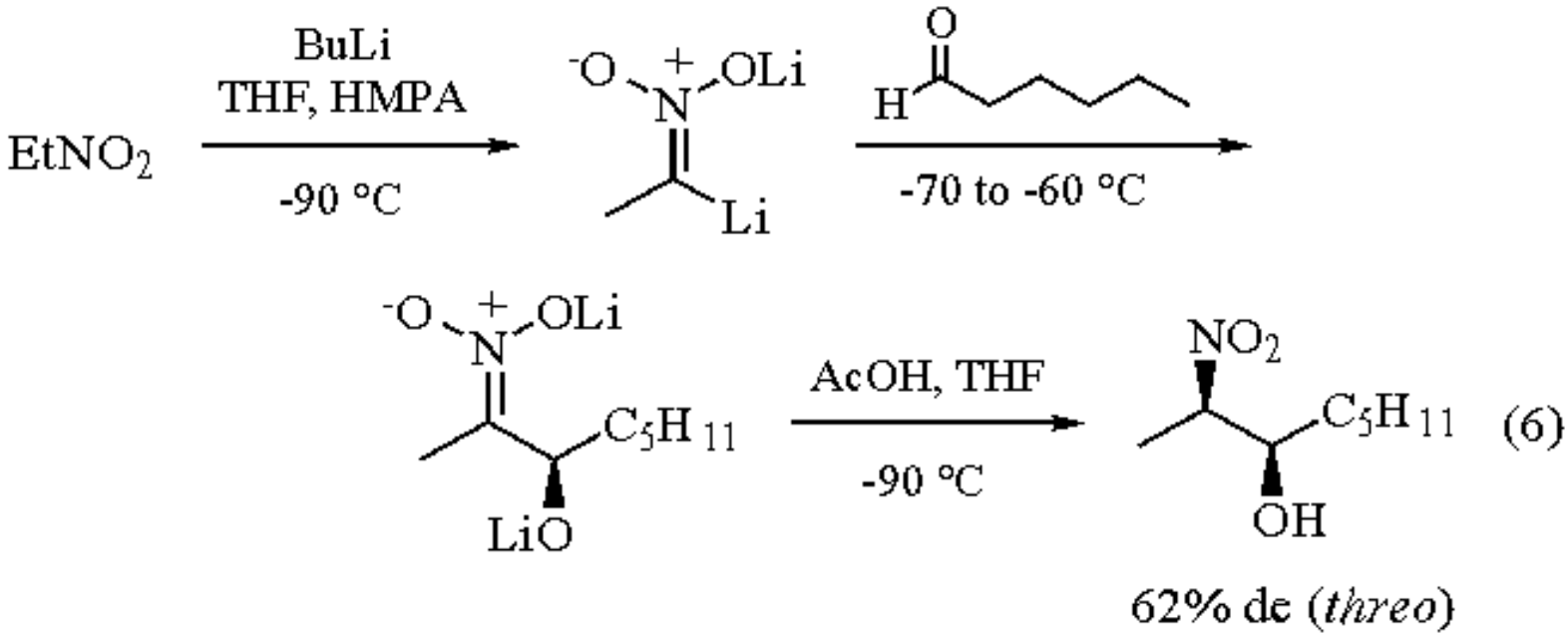

Diastereomeric mixtures of nitro alcohols derived from nitroethane can be transformed to the *threo*-isomer, predominantly, by double deprotonation and protonation or to the *erythro*-isomer by double deprotonation, silylation with ***t-Butyldimethylchlorosilane***, protonation, and desilylation (eq 7).[28]

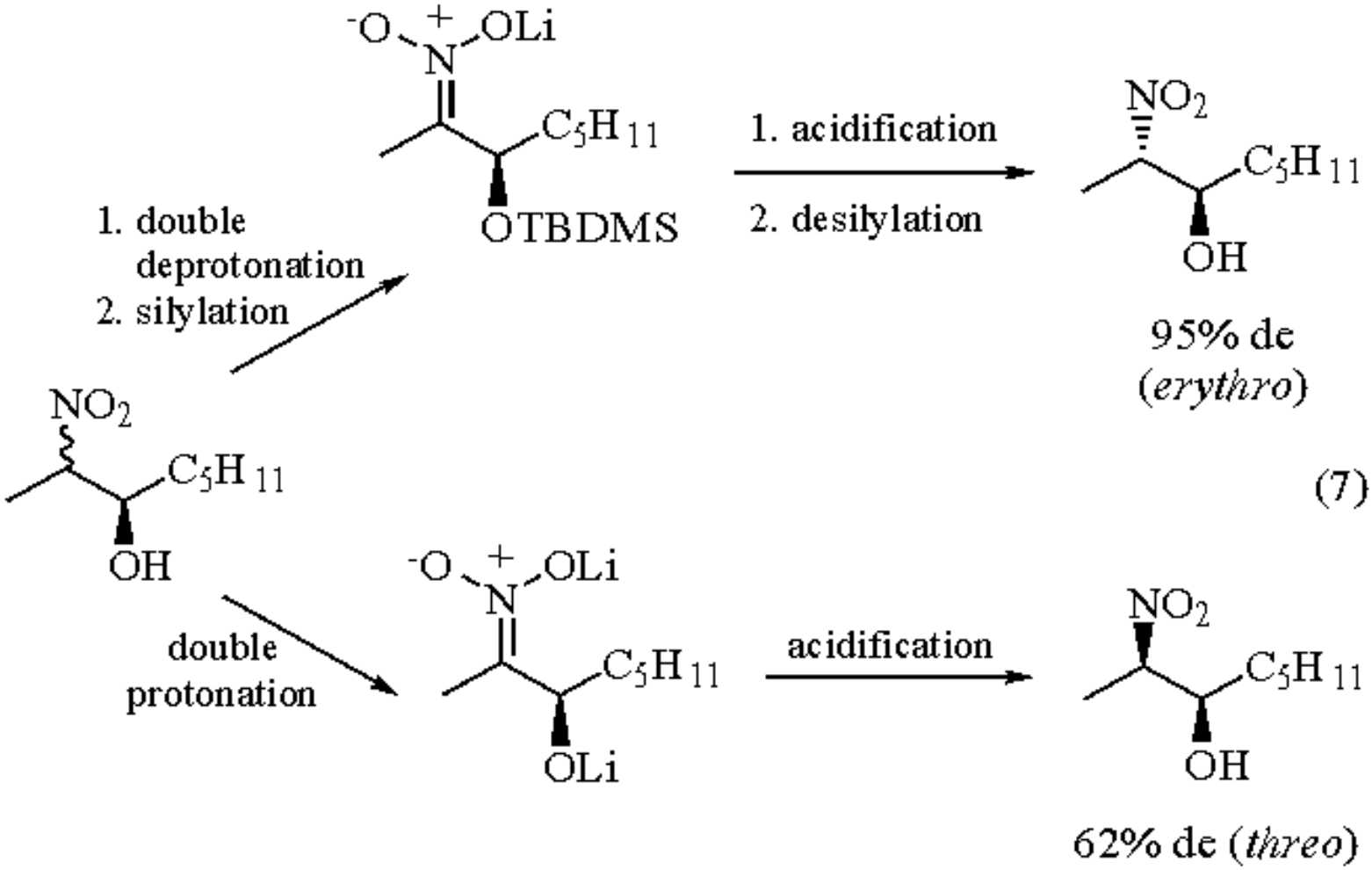

Nitroethane can react with two mol equiv of formaldehyde.[2a] With acetaldehyde and higher analogs, the reaction with a second molecule is difficult.[2b,d]

Dialdehydes derived from periodate cleavage of a sugar react with nitroethane in an one-pot cyclization reaction to give predominantly one stereoisomer (eq 8).[30]

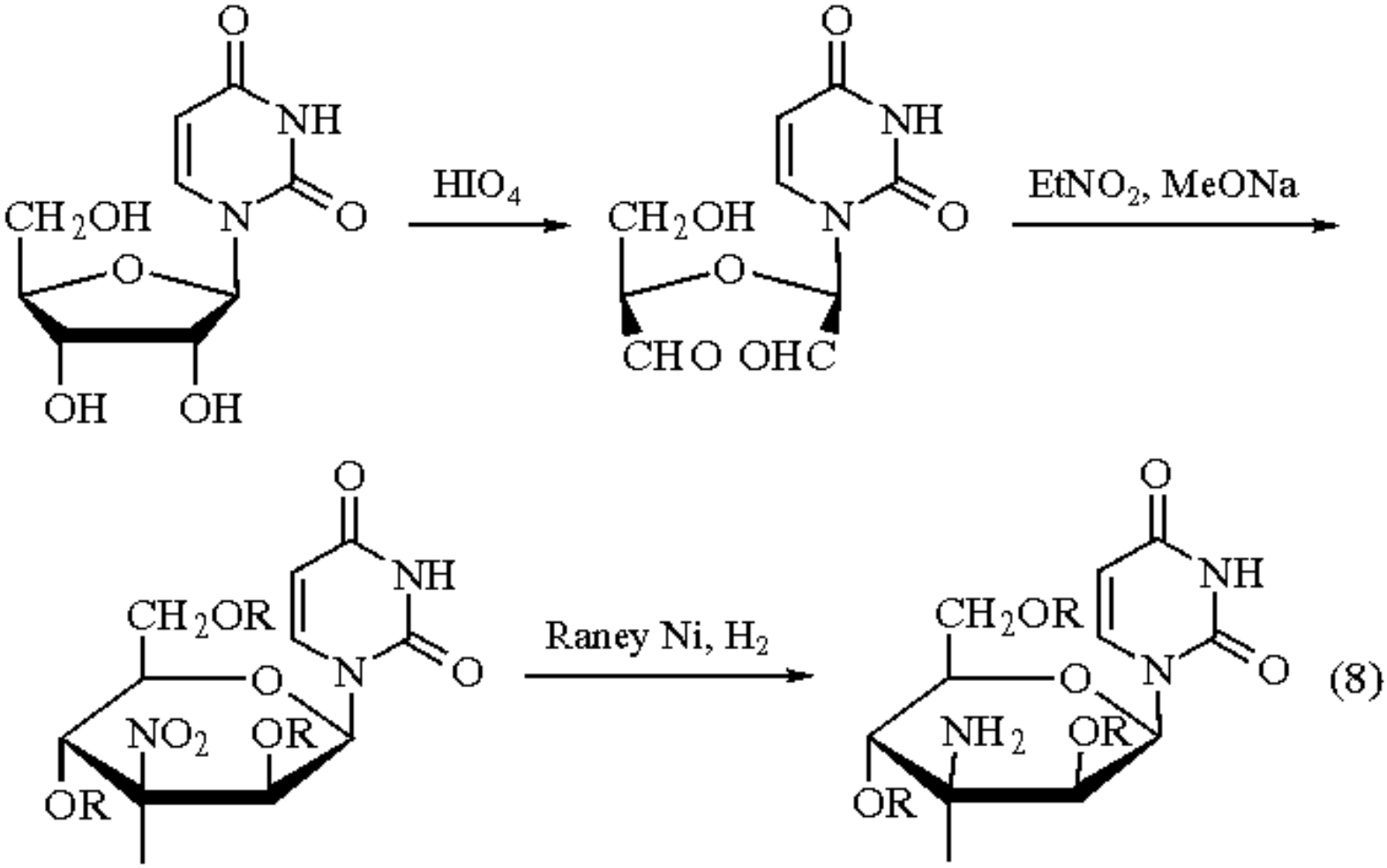

meso-1,5-Dialdehydes react with nitroethane in methanol in the presence of a catalytic amount of NaOH to give a crude mixture of 2,6-dihydroxynitrocyclohexanes from which the major *trans,trans*-isomer precipitates (eq 9).[31] The diacetate of 2,6-dihydroxy-1-methyl-1-nitrocyclohexane formed by this reaction can be saponified enantioselectively with pig liver esterase (PLE) to give the monoacetate of >95% ee (eq 9).[31]

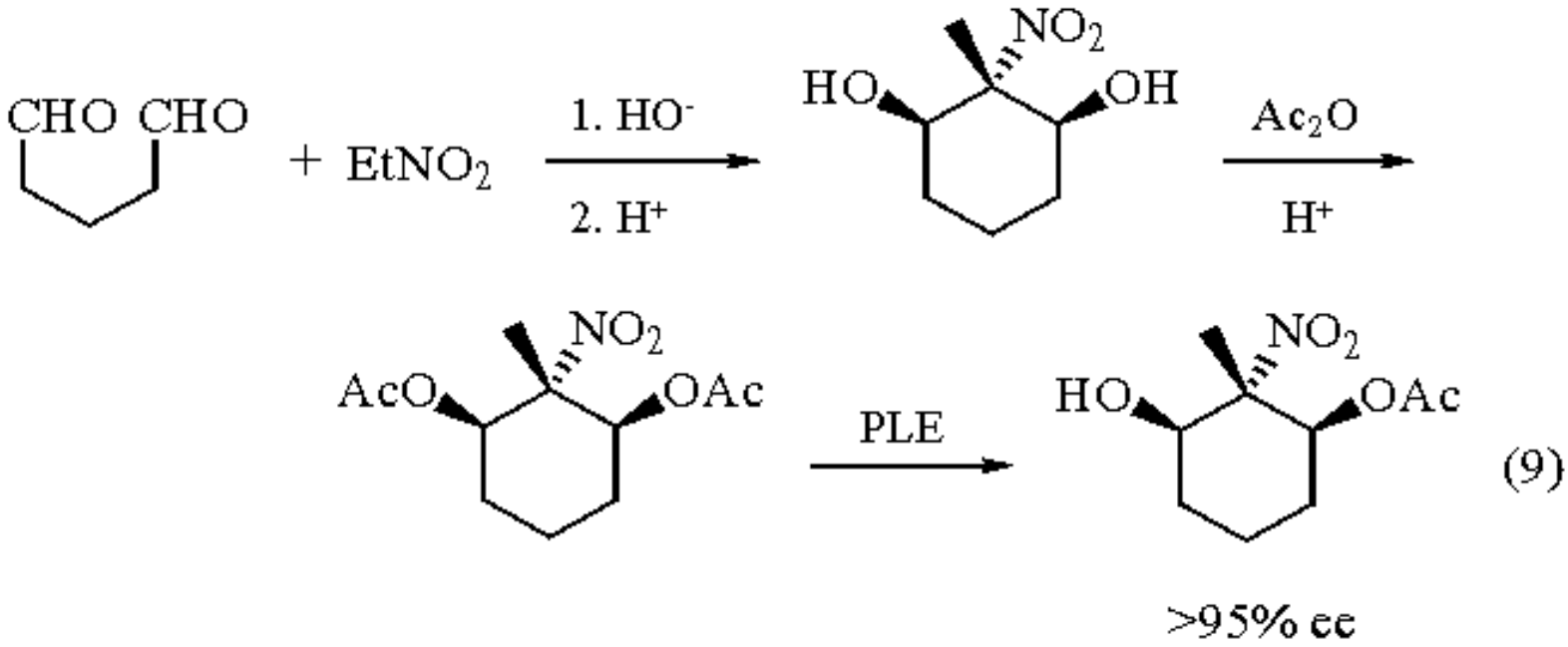

In the presence of primary or secondary amines, aldehydes react with nitroethane in a Mannich-type reaction.[2d]

Reactions with Ketones.

The reaction is complex and depends on the ratio of reactants, base, temperature, and time (eq 10).[2a]

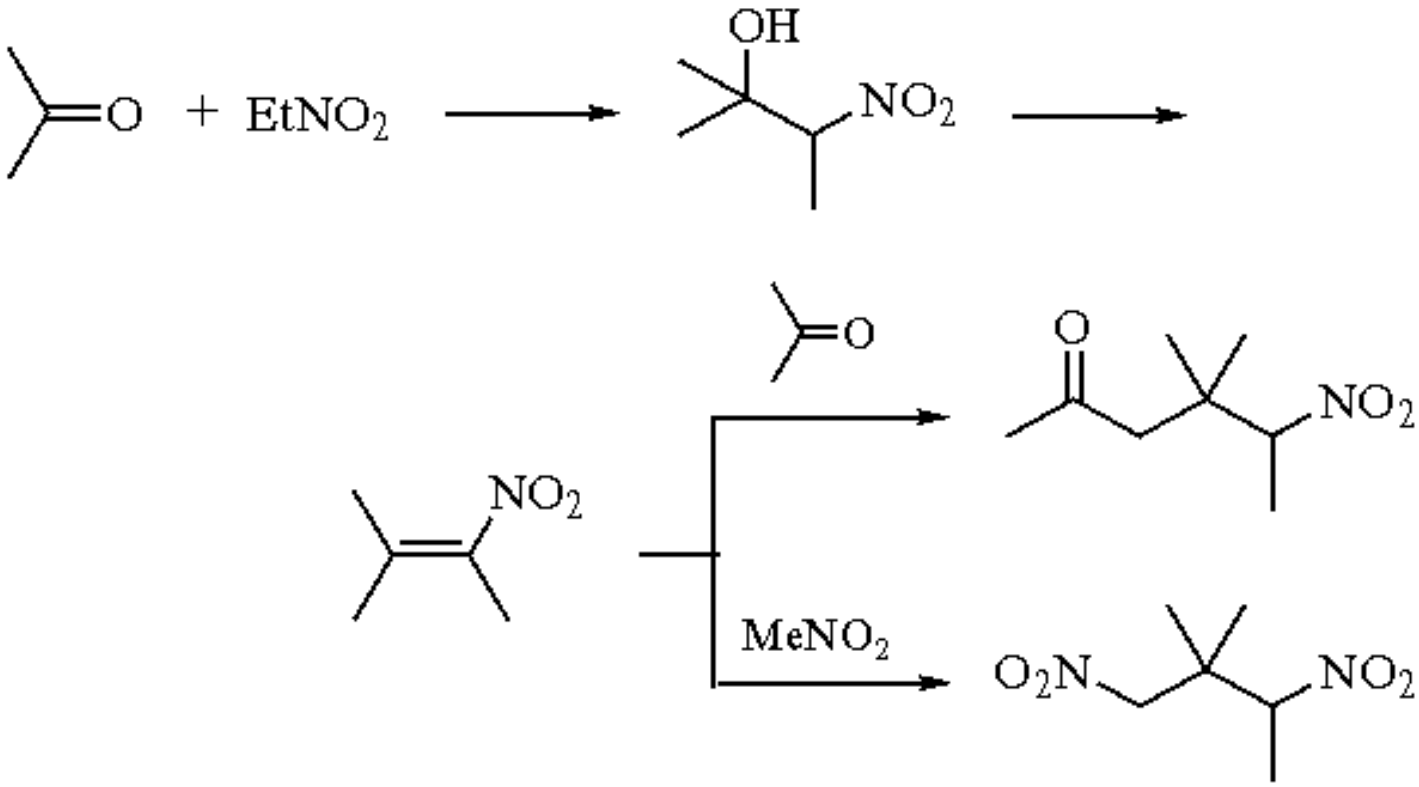

(10)

With alkali metal hydroxides or alkoxides, quaternary ammonium hydroxides, or primary or tertiary amines, low yields (10-30%) of nitro alcohols are normally obtained.[2a,b] Nitroethane reacts with methylcyclohexanones under pressure with TBAF as catalyst to give nitro alcohols in 41-87% yields.[32] With *N*,*N*-dimethylethylenediamine as base, it is possible to selectively synthesize allylic nitro compounds in moderate to high yields from both acyclic and alicyclic ketones (eq 11).[33] The doubly deprotonated forms of primary nitroalkanes give (with nitromethane as an exception) higher yields of 2-nitro alcohols in the reaction with ketones.[34]

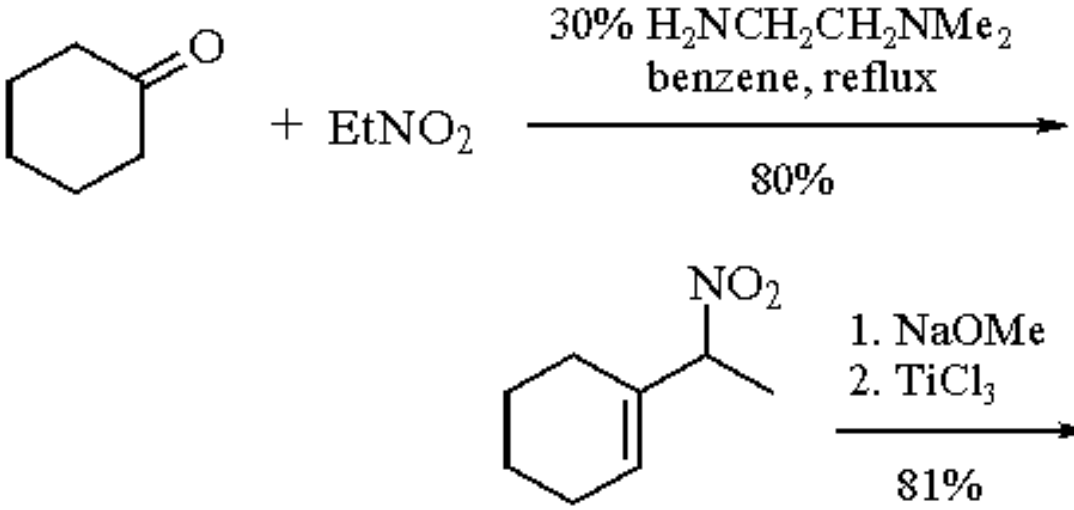

(11)

Michael Reactions.

Conjugate addition of nitroethane to activated double bonds is an important C-C bond forming reaction (eq 12).

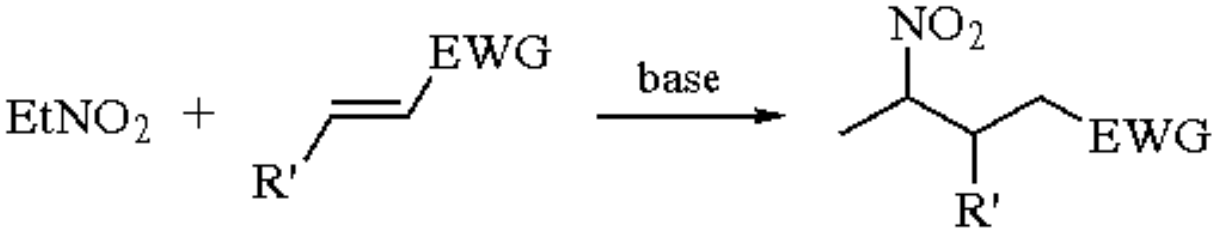

(12)

EWG = CHO, COR, CO_2R, CN, SOR, SO_2R, NO_2

Michael additions with nitroethane are catalyzed in homogeneous solution with catalysts such as alkali metal hydroxides in alcohol,[35] organic nitrogen bases,[36] fluoride ion,[37] and sodium hydride.[8] The reaction is also catalyzed in heterogeneous systems with alumina[38] and Al_2O_3-supported KF or CsF.[39] When combined with the Nef reaction,[1a,9] synthetically useful 1,4-dicarbonyl compounds can be synthesized. Nitroethane reacts with 2 mol equiv of Michael acceptors to give a variety of coupling products (eq 13).[37]

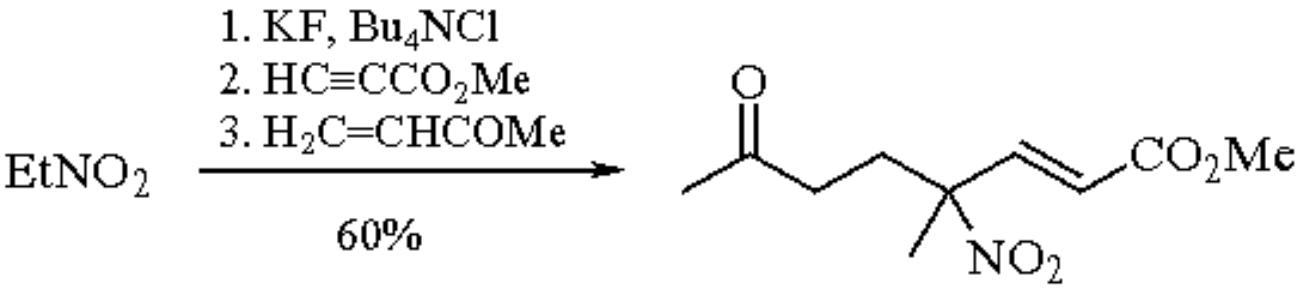

(13)

Acylation of Nitroethane.

With few exceptions, acylation of sodium ethanenitronate with acyl halides or anhydrides occurs on oxygen. The

unstable products rearrange into hydroxamic acid derivatives.[40] *C*-Acylation can be accomplished with acylimidazoles[41] and acyl cyanide (eq 14).[42] Carboxylation can be accomplished by reaction with methoxymagnesium methyl carbonate (Stiles reagent).[43]

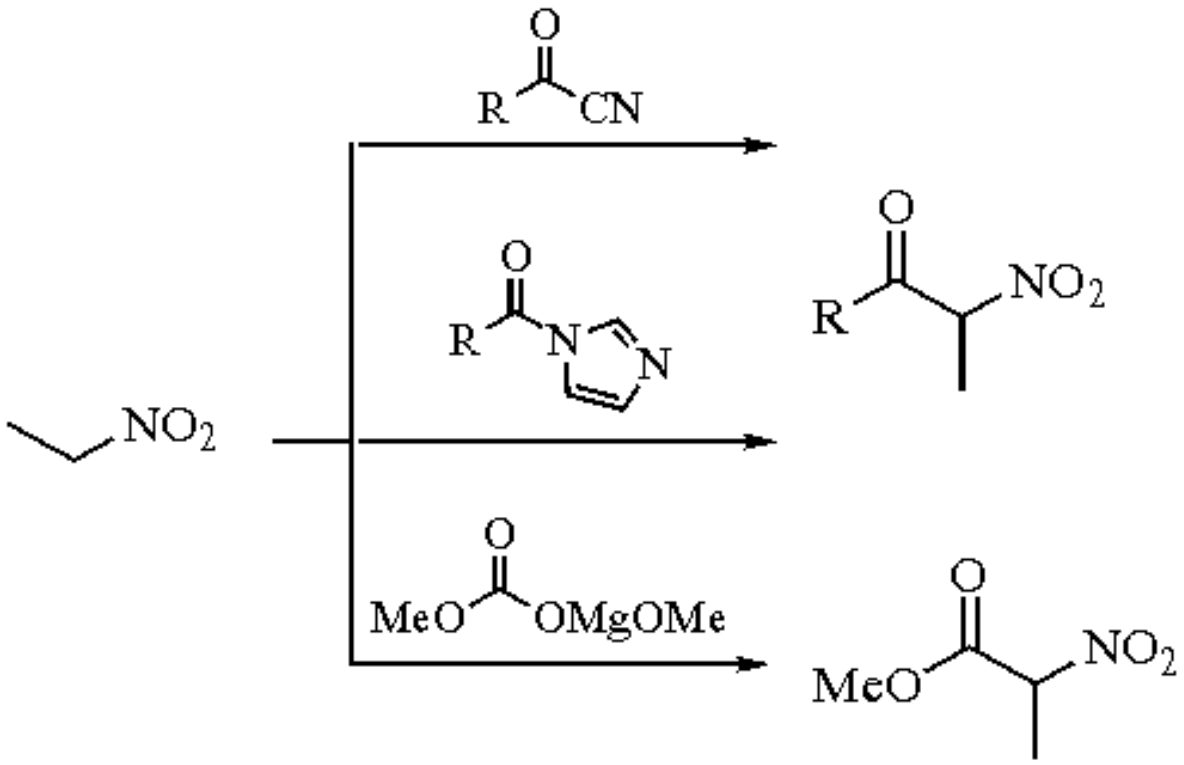

(14)

The dilithium salts of nitroethane and higher primary nitroalkanes react with carboxylic esters, anhydrides, and dialkyl carbonates to form β-oxo nitronates or β-carboxy nitronates, which must be carefully acidified at -90 °C to avoid Nef reaction with acetic acid.[34]

Alkylation of Nitroethane.

The ambident ethanenitronate ion reacts with alkyl iodides to give a mixture of *C*-alkylated and, primarily, *O*-alkylated compounds. The alkyl nitronates of nitroethane are unstable and decompose to carbonyl compounds and acetaldoxime.[44] The reaction has found some utility in the oxidation of primary alkyl iodides to aldehydes.[45] The methyl and ethyl nitronate of nitroethane are stable below -78 °C and can be synthesized from the sodium nitronate and ***Trimethyloxonium Tetrafluoroborate*** and ***Triethyloxonium Tetrafluoroborate***, respectively, at -60 °C in excellent yields.[44] The sodium salt of nitroethane can selectively be *C*-benzylated with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate in moderate yields.[46] The pyridinium cations are readily available from ***2,4,6-Triphenylpyrylium Tetrafluoroborate*** and the corresponding benzylamines. The dilithium salts of primary nitroalkanes are *C*-alkylated with primary iodo- and bromoalkanes.[47] A homoallylic nitro compound is formed when nitroethane, after treatment with lithium methoxide in methanol, reacts with cinnamyl acetate in the presence of 10 mol % ***Tetrakis(triphenylphosphine)palladium(0)*** as catalyst (eq 15).[48]

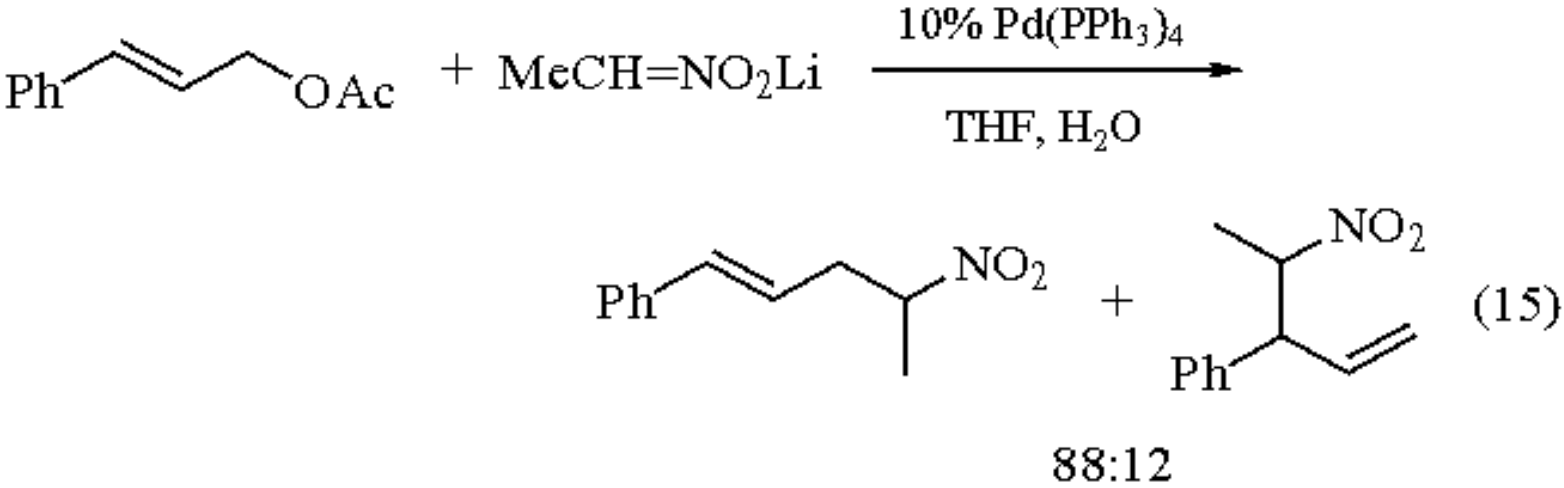

1,3-Dipolar Cycloadditions of Nitroethane.[49]

The in situ generated trimethylsilyl ethanenitronate reacts with activated terminal alkenes in a 1,3-dipolar cycloaddition to form 5-substituted 3-methyl-*N*-trimethylsilyloxyisoxazolidines which, upon acid treatment or heating, give isoxazolines.[27a,50] Asymmetric isoxazolines have been synthesized in this manner. The cycloaddition of *N*-acryloyl-(2*R*)-bornane-10,2-sultam (acrylate of ***10,2-Camphorsultam***) with the silyl nitronate, followed by acid-catalyzed elimination of trimethylsilyl alcohol, gives the corresponding isoxazoline in high yields and 78% ee of the C-5 (*R*)-isomer (eq 16).[51]

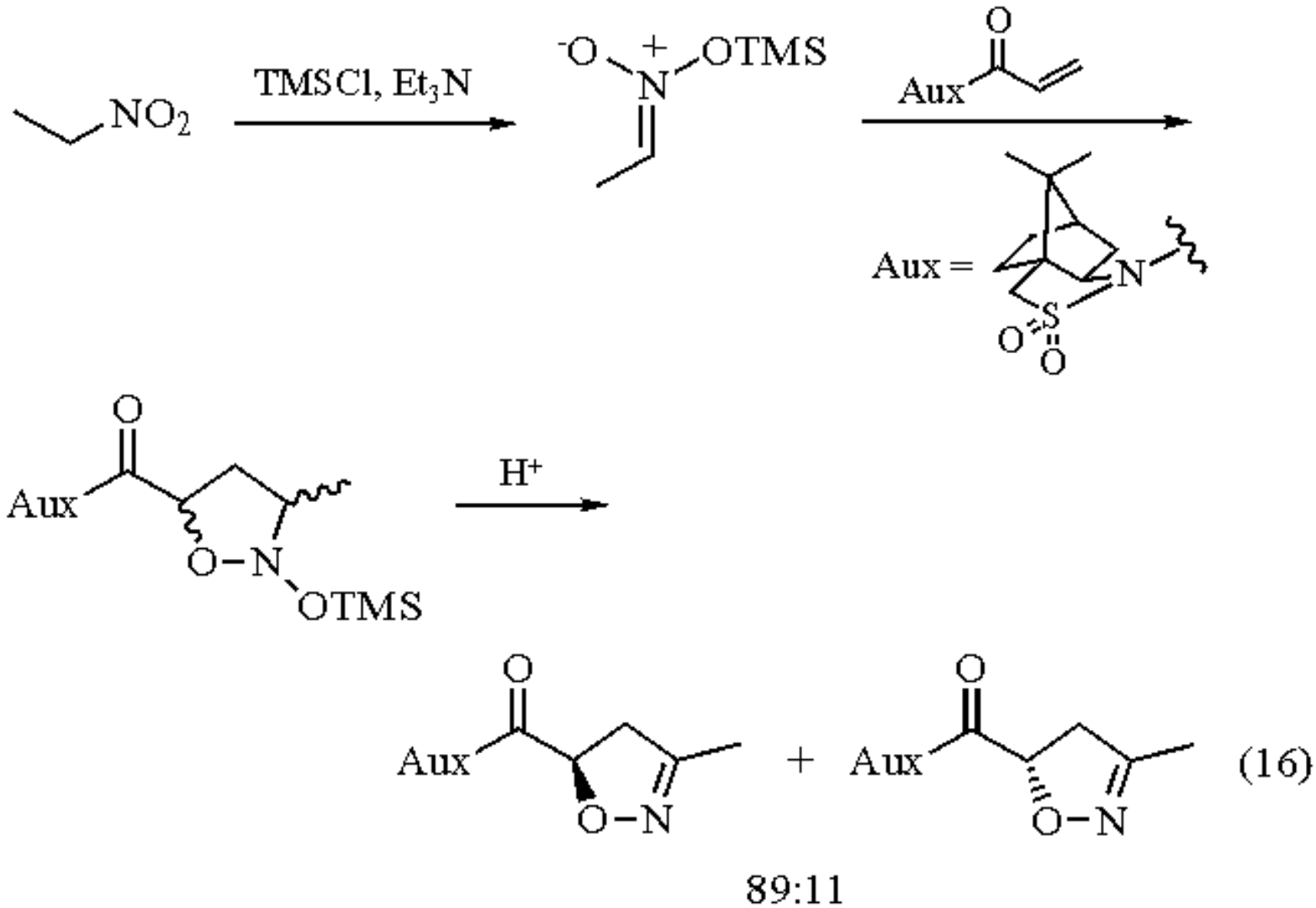

Acetonitrile N-Oxide is formed when nitroethane is treated with ***Phenyl Isocyanate*** in the presence of ***Triethylamine*** in the Mukayiama reaction.[52] The nitrile oxide is a potent dipole and reacts with alkenes and alkynes to give isoxazolines and isoxazoles, respectively. With terminal alkenes or alkynes, the reaction is regioselective, giving 5-substituted 3-methylisoxazolines or -isoxazoles. 1,2-Disubstituted *cis*- and *trans*-alkenes react in a stereospecific manner giving *cis*- and *trans*-4,5-substituted isoxazolines, respectively.[49] Acetonitrile oxide reacts stereoselectively with optically active acrylic esters and amides to give the isoxazolines illustrated in eq 17.[53-56] With Curran's bis-lactam chiral auxiliaries, products with about 98% ee are obtained (eq 17).[53]

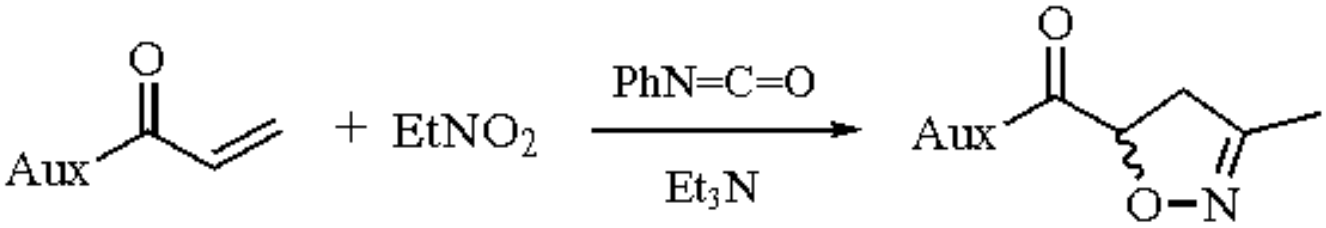

(17)

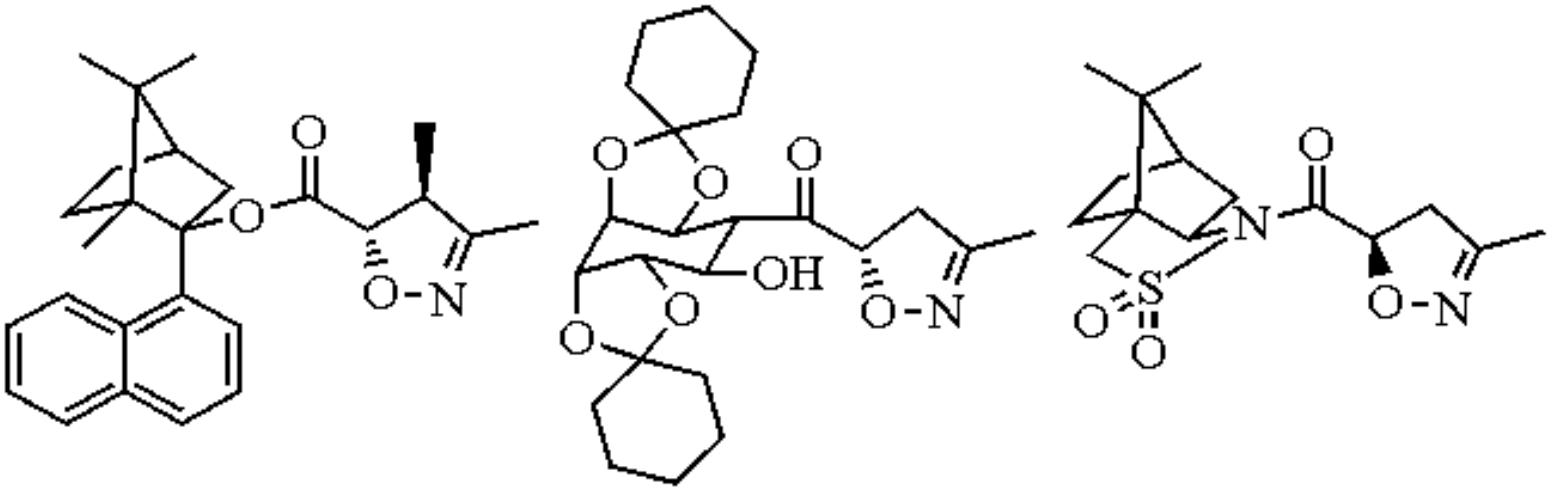

75% ee 82% ee >80% ee

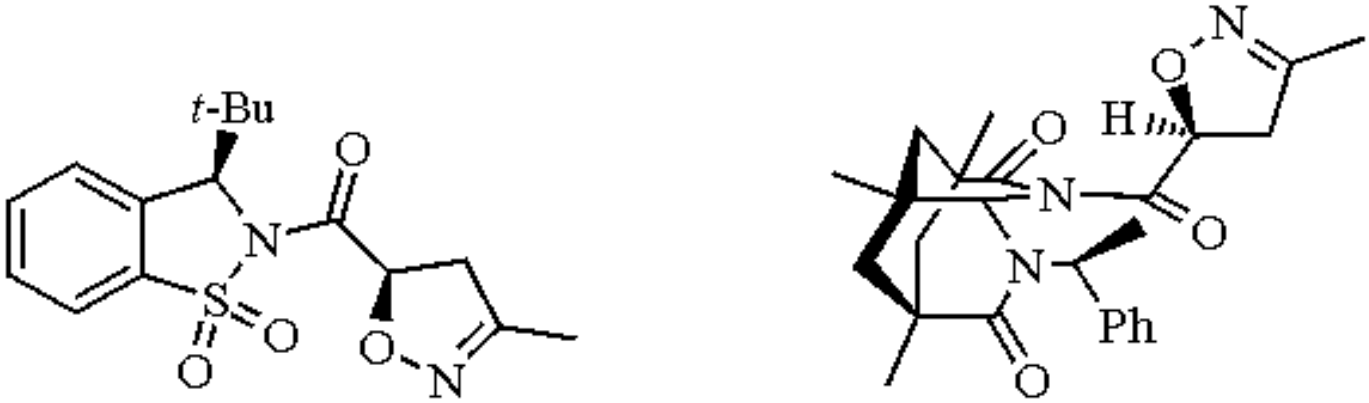

>90% ee 98% ee

3-Methylisoxazolines can easily be reduced to β-hydroxy ketones (an alternative route to the products from aldol reactions with acetone)[57] and 3-amino alcohols (eq 18).[58]

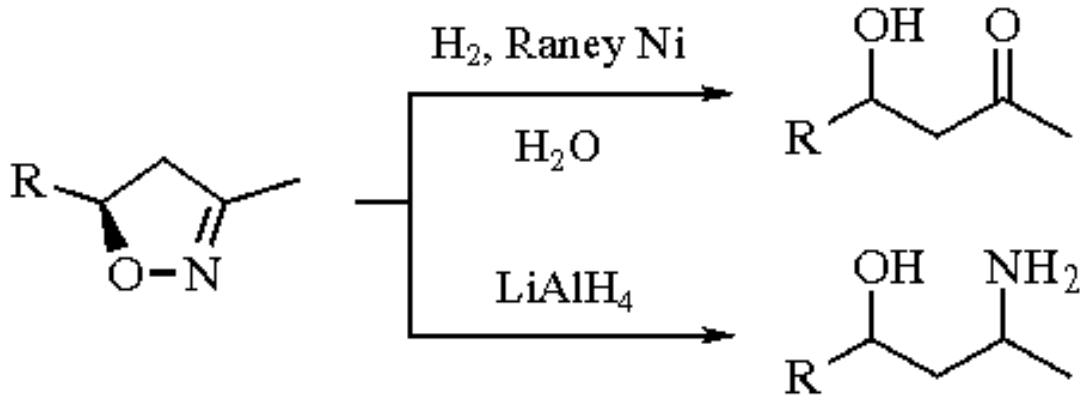

(18)

Related Reagents.

t-Butyldimethylsilyl Ethylnitronate; ***Lithium α-Lithiomethanenitronate***; ***O,O-Dilithio-1-nitropropene***; ***Nitromethane***; ***1-Nitropropane***; ***1-Nitro-1-propene***.

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Kurt B. G. Torssell & Kurt V. Gothelf

Nitroethylene[1]

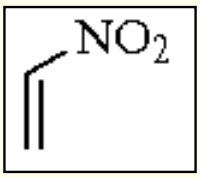

[3638-64-0] · $C_2H_3NO_2$ · Nitroethylene · (MW 73.06)

(Diels-Alder dienophile;[3] Michael acceptor[3])

Physical Data: bp 38-39 °C/80 mmHg.[2]

Analysis of Reagent Purity: titration against tetraphenylcyclopentadienone.[3]

Preparative Methods: best prepared by dehydration of 2-nitroethanol using phthalic anhydride (eq 1).[2,3] It can also be generated for reactions in situ from several precursors, especially 2-nitroethyl phenyl sulfoxide.[4]

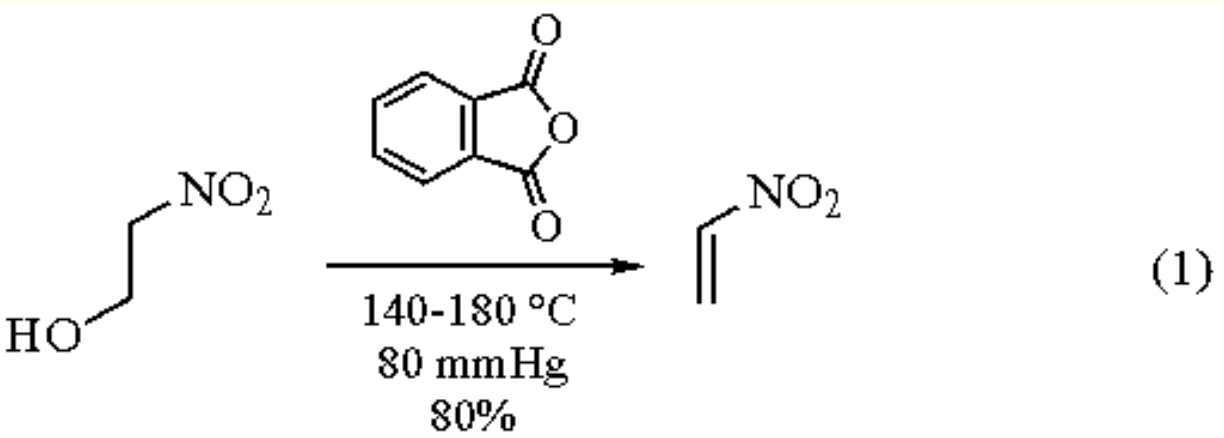

Handling, Storage, and Precautions: lachrymatory oil. Polymerizes readily in the presence of water and violently with base. Purified compound darkens quickly, but 10% solutions in dry benzene can be kept for 6 months or longer when refrigerated.[3]

Cycloadditions.

Nitroethylene is a very electron-deficient and highly reactive dienophile in Diels-Alder reactions with electron-rich or unactivated dienes. Its reactions with cyclopentadiene derivatives exhibit particularly high reactivity and selectivity, proceeding at temperatures as low as -100 °C to form only the *endo* product (eq 2).[3,5] Many other cyclic dienes show

similar selectivity.[6] The adducts are readily converted to ketones, making nitroethylene a useful ketene equivalent.[5]

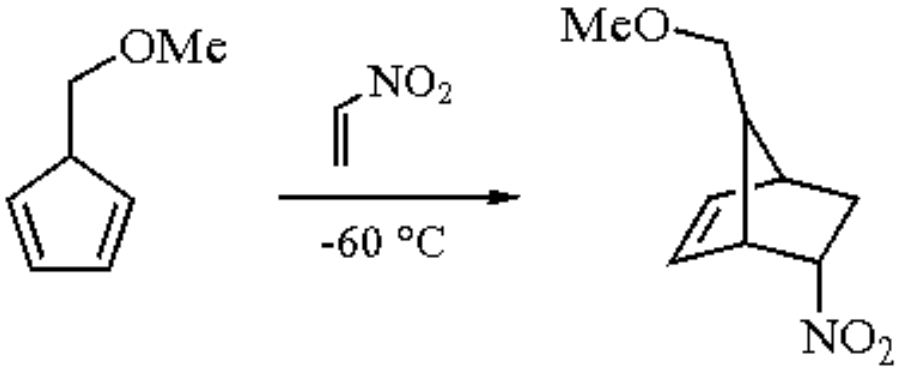

(2)

Reactions with acyclic dienes proceed much more slowly, and are often carried out at 80-120 °C.[7] These reactions exhibit high regioselectivity with simple dienes.[8] Subsequent alkylation and denitration (***Tri-n-butylstannane***) of the adducts (eq 3) effects the overall synthetic equivalent of a regiocontrolled Diels-Alder reaction with 1-alkenes.[8]

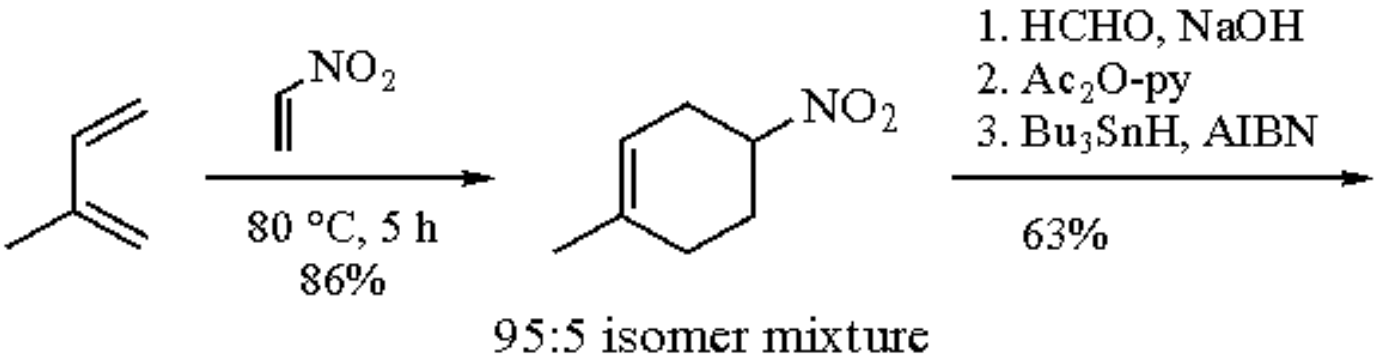

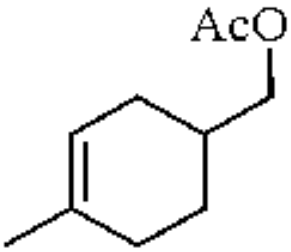

(3)

Nitroethylene is also a reactive dipolarophile in 1,3-dipolar cycloadditions.[3,9] An interesting observation, rationalizable from FMO considerations, is that the regiochemistry of nitroethylene reactions with nitrones is often reversed from that observed with less electron-deficient alkenes (eq 4).[9a,c]

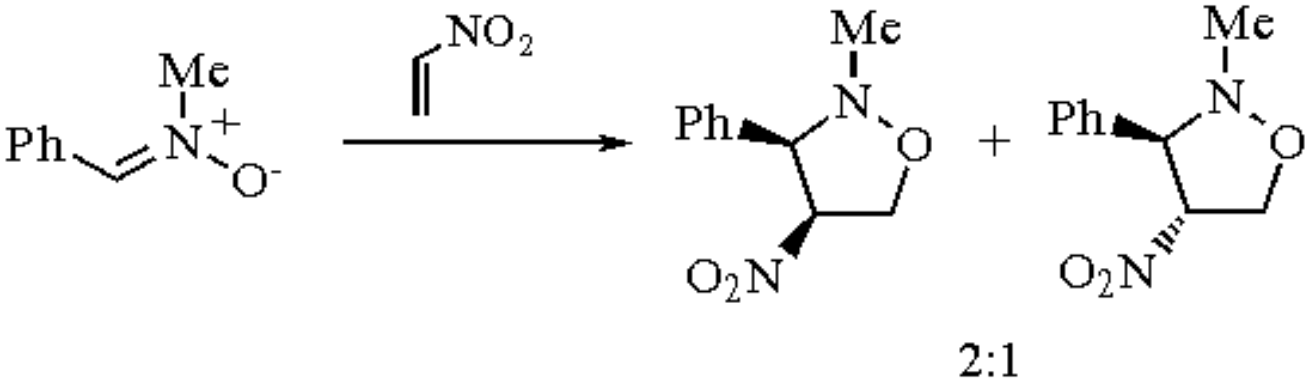

(4)

Radical Additions.

Nitroethylene is a reactive and useful acceptor for nucleophilic radicals (eq 5).[10]

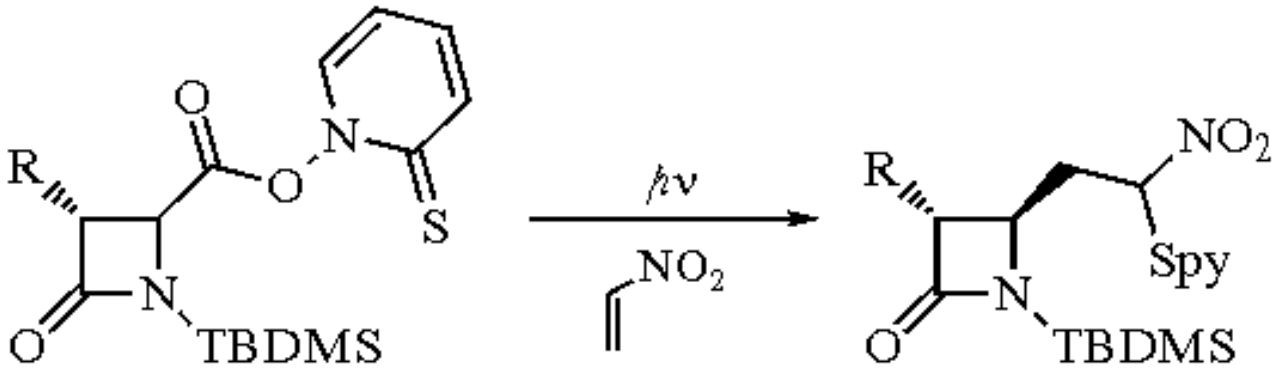

(5)

Nucleophilic Additions.

A wide variety of nucleophiles have been used in conjugate additions to nitroethylene.[3,11] Avoiding the facile base-mediated polymerization of nitroethylene is crucial to the success of these additions. A broad study found that additions of amines with pK_a values between 2 and 8 are highly successful, while more basic amines lead to polymerization.[12] An exception is the pyrrolidine synthesis in eq 6, in which a second Michael addition traps the intermediate nitronate anion.[13]

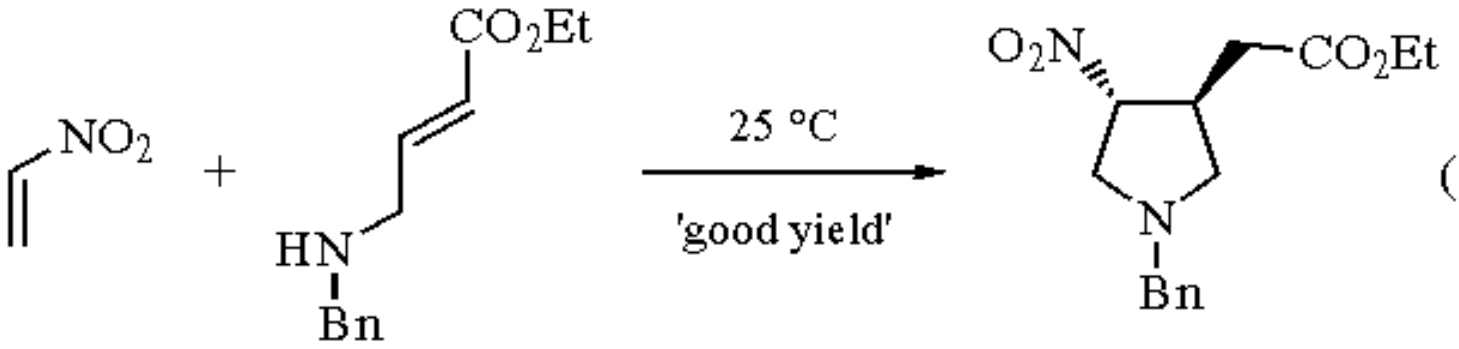

(6)

Traditional Michael additions of β-dicarbonyl compounds to nitroethylene in protic solvents are best carried out under the most mildly basic conditions possible (KF catalyzed,[14] for example). Kinetic Michael additions of preformed

enolates at low temperatures have also been reasonably successful.[15]

Related Reagents.

2-Acetoxyacrylonitrile; ***2-Chloroacrylonitrile***.

---

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Nitrogen Dioxide

NO_2

(NO_2)

[10102-44-0] · NO_2 · Nitrogen Dioxide · (MW 46.01) (N_2O_4)

[10544-72-6] · N_2O_4 · Nitrogen Dioxide · (MW 92.02)

(nitration of aromatic[1,2] and unsaturated[3,4] compounds; conversion of oximes into dinitromethanes;[3,5,6] halogenation of arenes;[7,8] oxidation of many functional groups.[9-11])

Alternate Names: nitrogen tetroxide; dinitrogen tetroxide.

Physical Data: a reddish-brown gas above 21.15 °C and a brown or yellow-brown liquid below 21.15 °C; mp 11.2 °C; bp 21.15 °C; *d*204 1.448 g cm^{-3}, *d*21.3(gas) 3.3 g L^{-1}; exists as N_2O_4 in liquid and solid state; as a mixture of NO_2 and N_2O_4 in the gas phase; and as NO_2 above 135 °C.

Solubility: sol CCl_4, CH_2Cl_2, DMF, ether, concd sulfuric and nitric acids.

Form Supplied in: brown liquid under pressure.

Preparative Methods: prepared by thermal decomposition of lead nitrate or from N_2O_5.[12]

Handling, Storage, and Precautions: deadly poison! One of the most insidious gases. 100 ppm is dangerous and 200 ppm may be fatal. Decomposes in water or alkaline solutions. Use in a fume hood.

Nitration of Aromatic Compounds.

Examples of arene nitration with nitrogen dioxide at high temperature or in the presence of concentrated acids are numerous, but they are often messy.[1] In the best cases, mixtures of *o*- and *p*-nitro compounds are formed with predomination of the former (eq 1).[13]

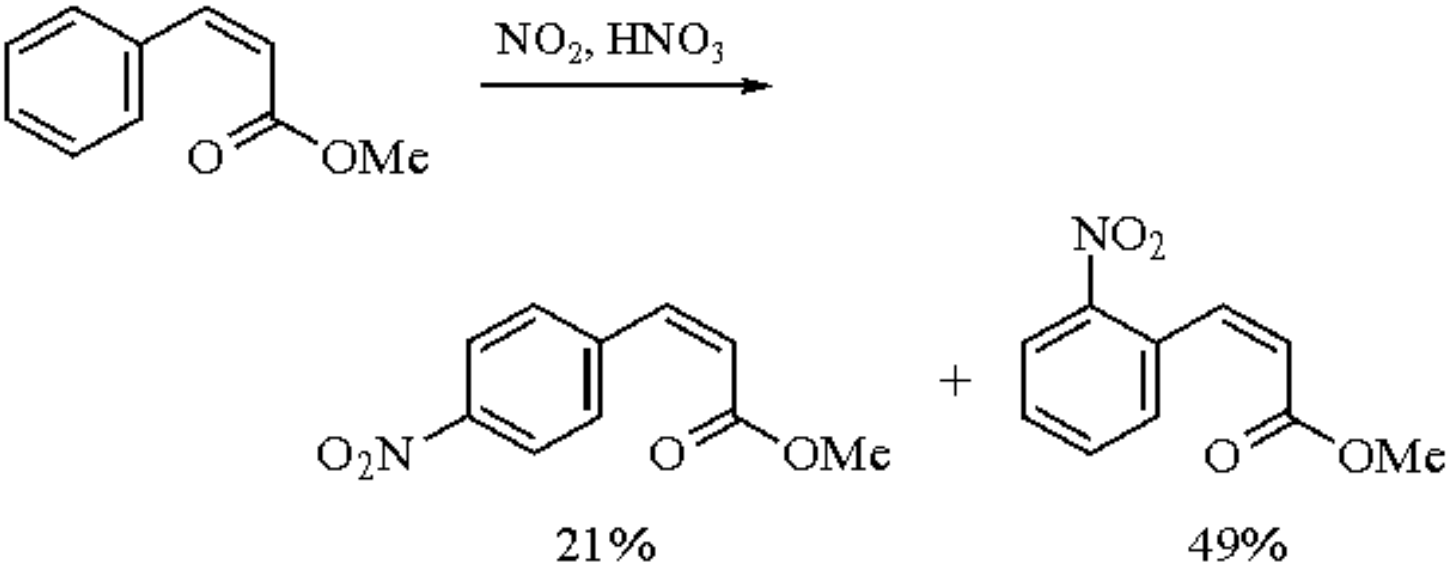

(1)

Activated arenes and even porphyrins can be nitrated directly by nitrogen dioxide in benzene or dichloromethane solution.[14,15] Phenols usually give di-*o*-nitro substituted compounds as well as 4-nitrocyclohexadienones (eq 2).

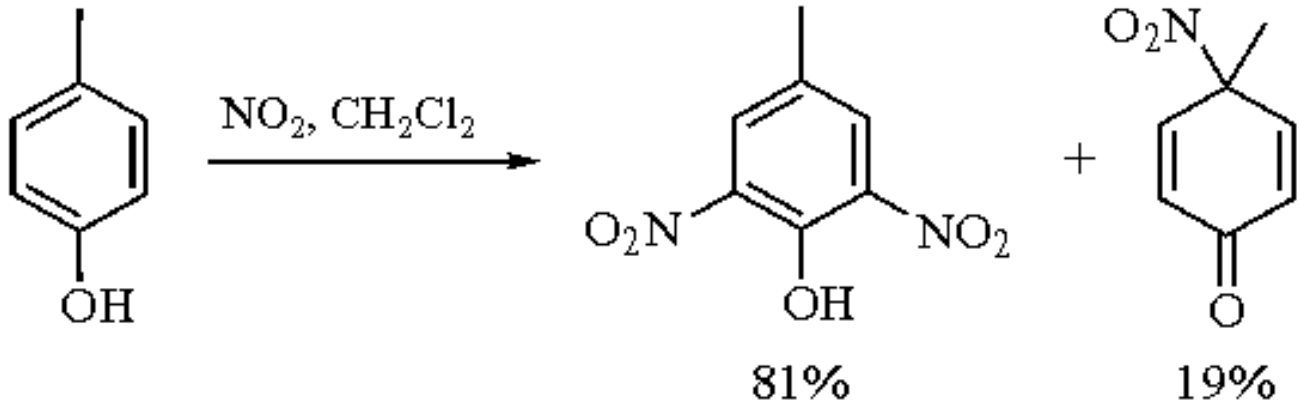

(2)

o-Nitrophenols have been obtained in high yield using pyridinium salts as NO_2 transfer agents.[16] Anthracene reacts with nitrogen dioxide to give *cis*- and *trans*-9,10-dinitro-9,10-dihydroanthracene.[17] Compounds of lower reactivity than benzene can be nitrated by nitrogen dioxide in the presence of ***Ozone*** even at low temperatures.[18,19] Thus, treatment of acetanilides with nitrogen dioxide and ozonized air gives a high proportion of *o*-nitro derivatives in good yields (eq 3).[19] Polynitration of arenes or nitration of strongly deactivated compounds requires the use of catalysts such as ***Boron Trifluoride Etherate*** or ***Methanesulfonic Acid***.[18]

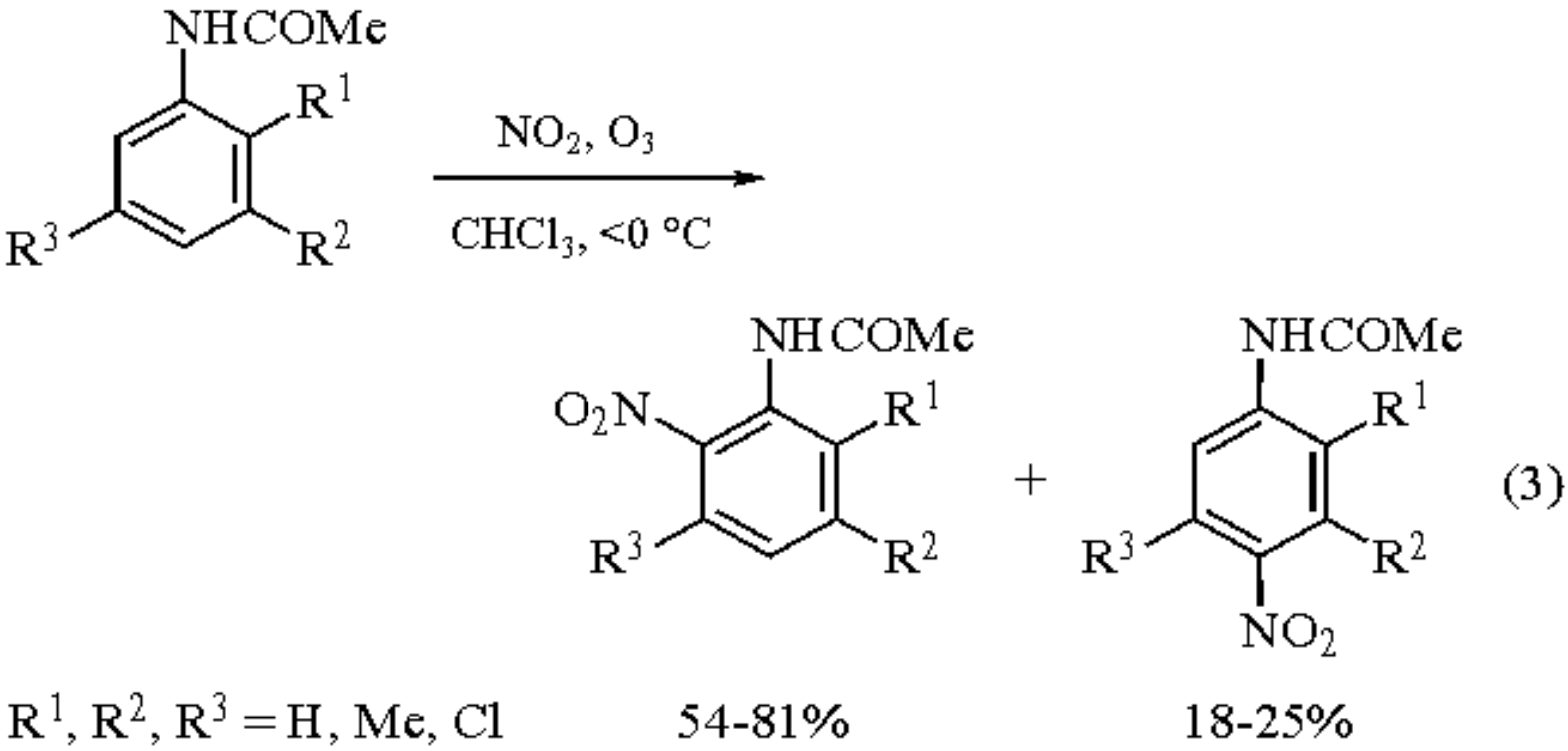

Nitration of Unsaturated Compounds.

Alkenes react with liquid nitrogen dioxide to give a complex mixture of compounds that include mainly 1,2-dinitroalkanes and 1-nitro-2-nitrosooxyalkanes.[3,5,9] However, tetrasubstituted or halogenated alkenes usually give good yields of dinitro compounds (eq 4).

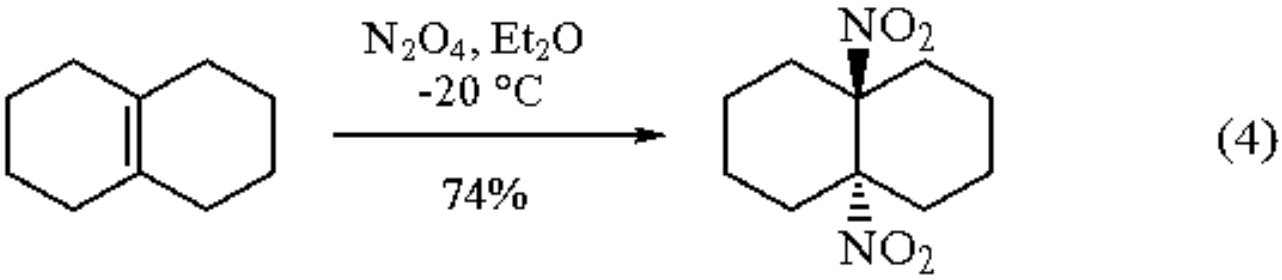

Addition of nitrogen dioxide to 1,1-dialkyl substituted alkenes affords good yields of nitroso nitrates.[3,9] The same reaction in the presence of halogens leads to 1-nitro-2-haloalkanes which may undergo dehydrohalogenation to nitroalkenes.[3,20] Alkynes react with nitrogen dioxide to give moderate yields of 1,2-dinitroalkenes.[3,10]

Oxidation.

Oxidation of alcohols and ethers with nitrogen dioxide gives aldehydes or ketones (eq 5).[9,10,21] Nitrogen dioxide oxidizes primary amines to nitroalkanes, trialkylphosphines to phosphine oxides, and dialkyl sulfides to sulfoxides (without further oxidation to sulfones).[9-11,22] Sulfides react with nitrogen dioxide to afford good yields of sulfonic acid anhydrides.[9]

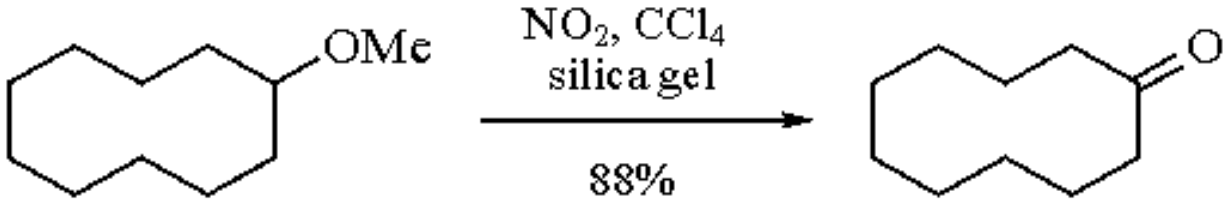

(5)

Ponzio Reaction.

A general method for direct preparation of dinitromethylarenes is the oxidation of oximes with nitrogen dioxide (eq 6).[3,5,6,10,11]

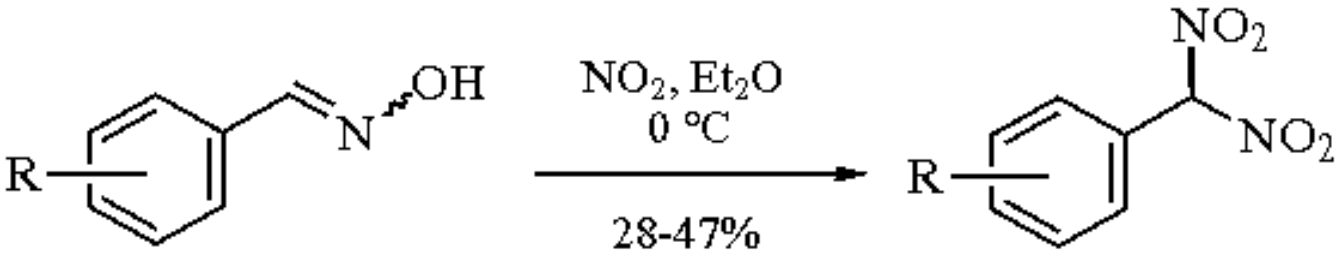

(6)

Halogenation.

Nitrogen dioxide has been used in combination with halogens and metal halogenides for the halogenation of unreactive aromatic compounds and adamantane (eq 7).[7,8,23]

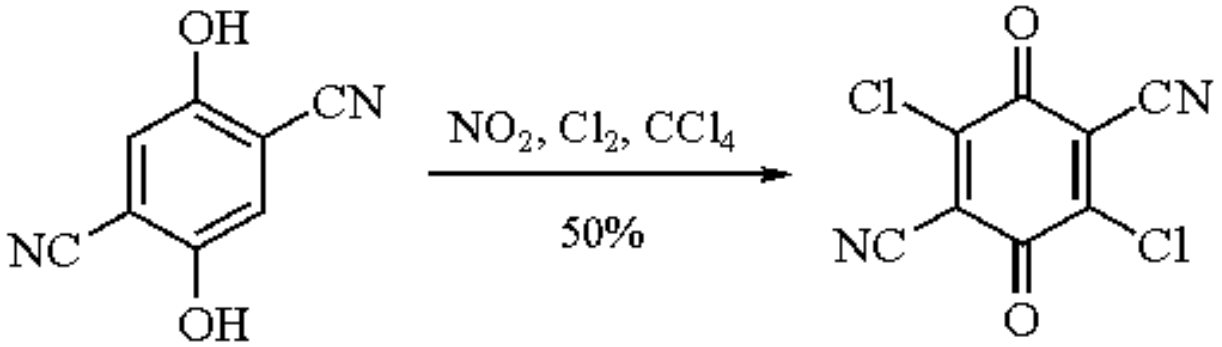

(7)

Related Reagents.

Iodine-Nitrogen Tetroxide.

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Nitromethane

$MeNO_2$

[75-52-5] · CH_3NO_2 · Nitromethane · (MW 61.05)

(building block in synthesis; polar solvent)

Physical Data: mp -28.5 °C; bp 101 °C; *d* 1.13 g cm^{-3}; dipole moment 3.5 D.

Solubility: completely misc most organic solvents; slightly sol petroleum ether, water; sol alkaline solution.

Form Supplied in: colorless liquid, widely available.

Purification: purified by drying over $MgSO_4$ and distilling; a small acidic forerun is discarded.

Handling, Storage, and Precautions: stable compound. It is advised not to distill large quantities at reduced pressure. Flammable; toxic. Gives shock- and heat-sensitive alkali and heavy metal salts. Do not dry the sodium salt.

Introduction.

Nitromethane is a common starting material for the synthesis of aliphatic nitro compounds, which serve as valuable building blocks, providing access to a variety of other functionalized products such as 2-nitro alcohols, nitroalkanes, nitroalkenes, hydrocarbons, amines, oximes, carbonyl compounds, and heterocycles.[1] Nitromethane reacts with alkali metal hydroxides and alkoxides to form the metal nitronates which are used as in situ generated reagents. The alkali metal nitronates are unstable and it is advisable not to isolate them. The sodium salt of nitromethane undergoes violent decomposition or detonation on heating and drying.

The Nitroaldol Reaction (Henry Reaction).[2]

Reactions with Aldehydes.

In the presence of base, nitromethane reacts with aliphatic aldehydes in an aldol-type reaction with formation of 2-nitro alcohols (nitroaldols). Due to its reversibility, the reaction is normally carried out in the presence of only catalytic quantities of base, although in certain cases stoichiometric amounts are used to precipitate the product.[3] The reaction of nitromethane with aldehydes in the presence of one equivalent of base gives the salt of the *aci*-nitro tautomer of the

product, which must be carefully acidified to avoid the Nef reaction. Alkali metal hydroxides, alkoxides or carbonates, and tertiary amines are effective catalysts.[2a] Elimination of water, the aldol reaction, and the Cannizzaro reaction are competing side reactions.[2a,b] 2-Nitro alcohols are unstable compounds and care has to be exercised during workup (decomposition during distillation). Fluoride ion catalysts often give higher yields.[4] The reaction has been carried out in the absence of solvent using powdered NaOH,[5] Al_2O_3,[6] and Al_2O_3-supported KF[7] as catalysts. The 2-nitro alcohols are readily converted into a variety of functionalities (eq 1).[1b,4,5,7-13,16-21]

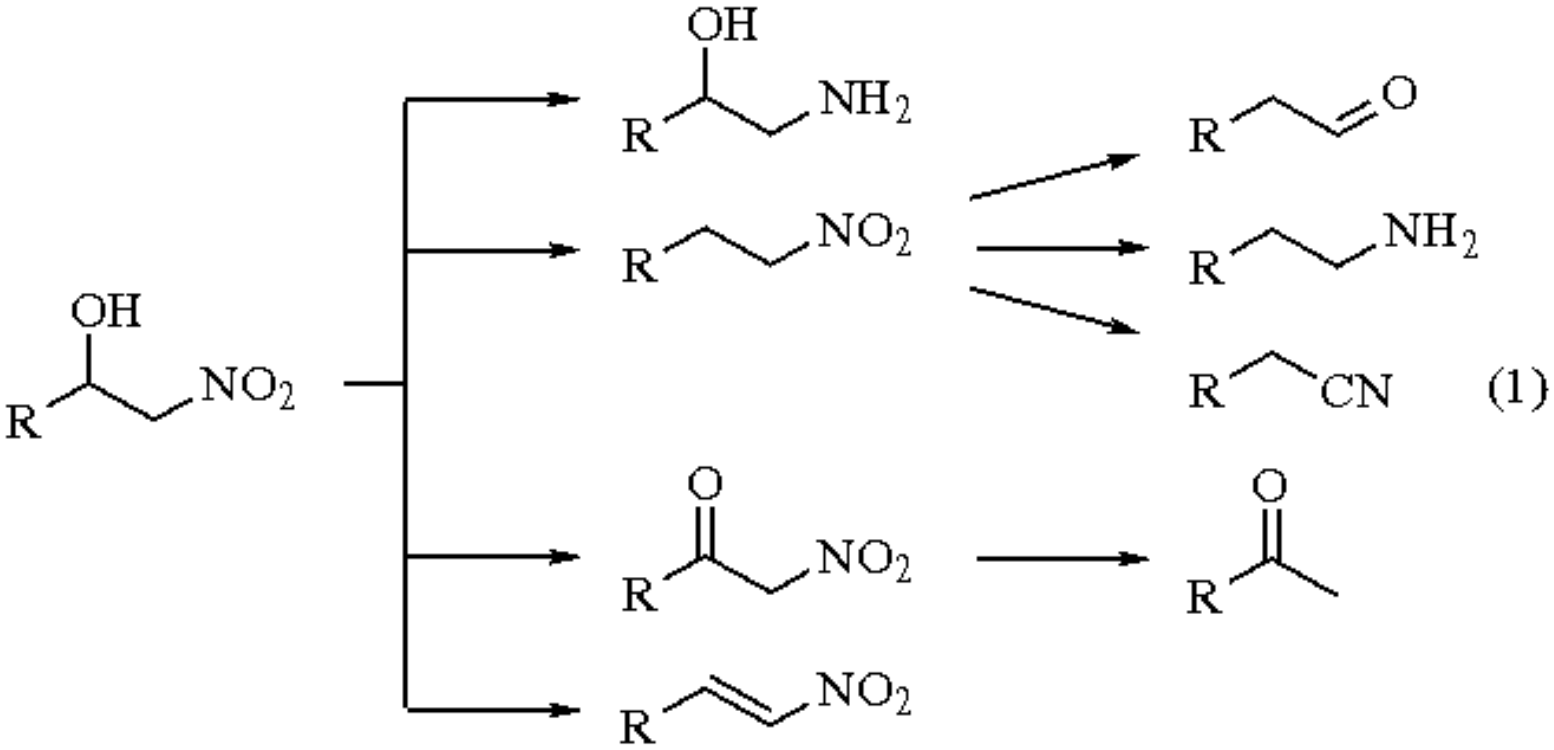

Aromatic aldehydes react smoothly with nitromethane under the same conditions.[14] Elimination of water to give β-nitrostyrenes takes place on acidification.[2a] Synthesis of β-nitrostyrenes can be accomplished in one step by heating aromatic aldehydes in acetic acid and with NH_4OAc as catalyst.[15] Dehydration of 2-nitro alcohols to nitroalkenes has been accomplished with ***Methanesulfonyl Chloride***,[16] phthalic anhydride,[17] ***1,3-Dicyclohexylcarbodiimide***,[18] pivaloyl chloride,[19] ***Trifluoroacetic Anhydride***,[20] and ***Acetic Anhydride***.[20] Heating 2-nitro alcohols in dichloromethane in the presence of basic aluminium oxide is another mild method for the synthesis of nitro alkenes.[21] Nitroalkenes can be converted into a variety of functionalities (eq 2)[2,5,22,24-30] and have found utility as heterodienes in hetero Diels-Alder reactions and as reactants in Lewis acid promoted tandem [4 + 2]/[3 + 2] cycloadditions.[23]

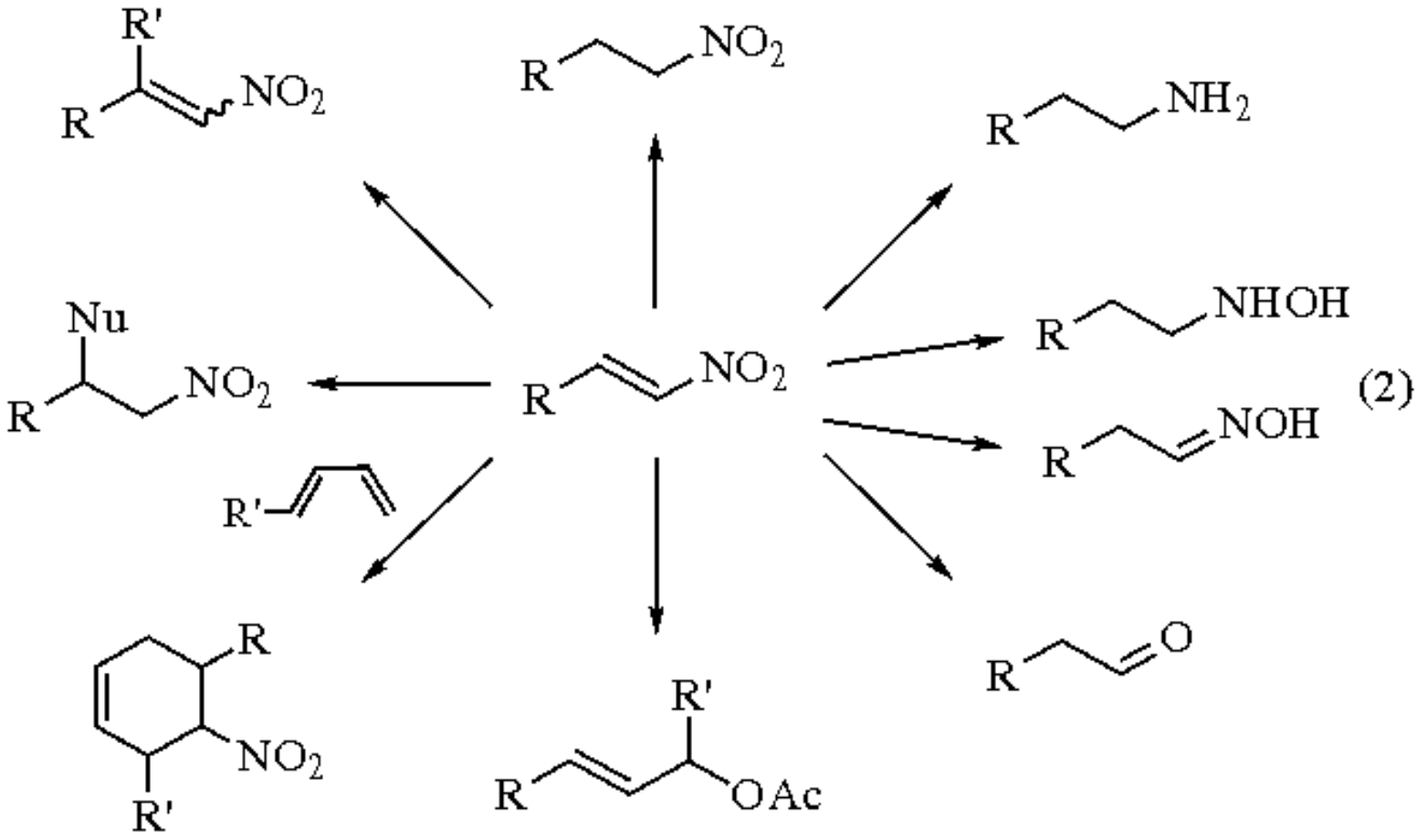

(2)

A catalytic asymmetric nitroaldol reaction has been developed.[31] The catalyst is formed from ***Lanthanum(III) Chloride***, the dilithium salt of ***(R)-1,1´-Bi-2,2´-naphthol***, NaOH, and H_2O in a 1:1:1:10 molar ratio in THF. Nitromethane reacts with various aldehydes in the presence of 10% of the catalyst to give 2-nitro alcohols in high yields and with an ee as high as 93% (eq 3). Chiral binaphthol complexes of other rare earth metal trichlorides show similar catalytic effects. The optical purities of nitroaldols obtained using these rare earth metal complexes as asymmetric catalysts are highly dependent on the amount of water present and on the relation between substrate and radius of the rare earth metals.

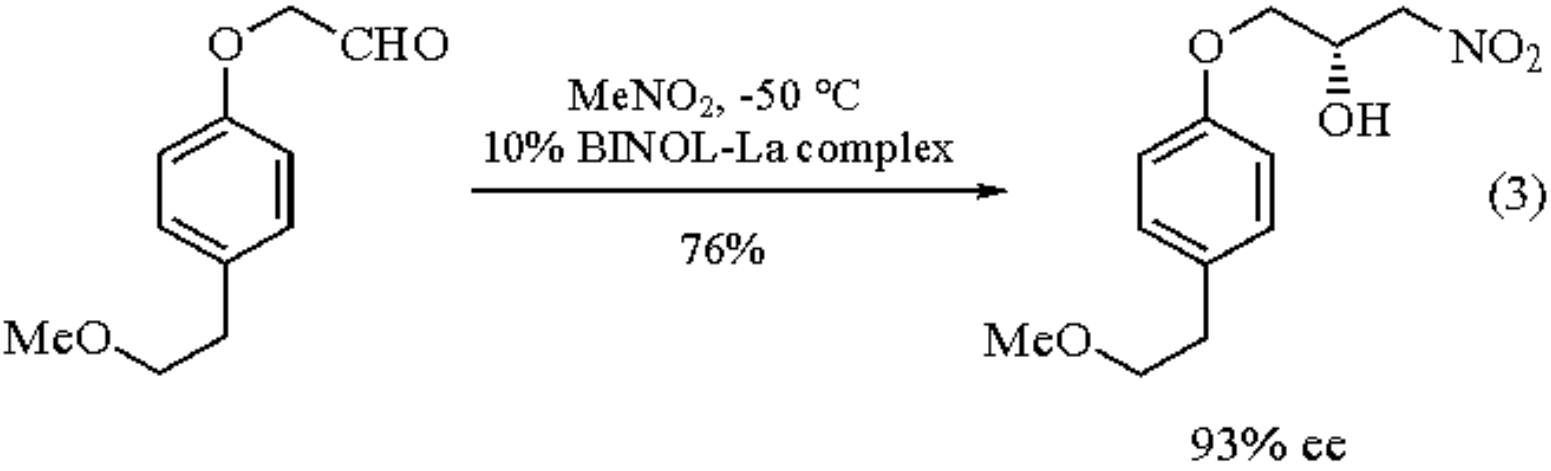

(3)

Nitromethane can react with two mol equiv of an aldehyde.[2a] The reaction with the second aldehyde molecule proceeds slower than that with the first due to the lower acidity of the α-proton in 2-nitro alcohols and enhanced steric

hindrance. With sterically hindered aldehydes, the reaction with the second aldehyde is difficult.[2b,d] Seebach et al.[32] synthesized the multiple coupling reagent 2-nitro-2-propenyl 2,2-dimethylpropanoate (NNP) from nitromethane. In the initial step, nitromethane reacts with two moles of formaldehyde to give 1,3-dihydroxy-2-nitropropane in 95% yield. Subsequent acylation with two mol equiv of pivaloyl chloride and elimination of pivalic acid gives NNP. The reaction may be run on a 40 to 200 g scale without problems (eq 4). NNP allows succesive introduction of two different nucleophiles Nu^1 and Nu^2 (eq 5).

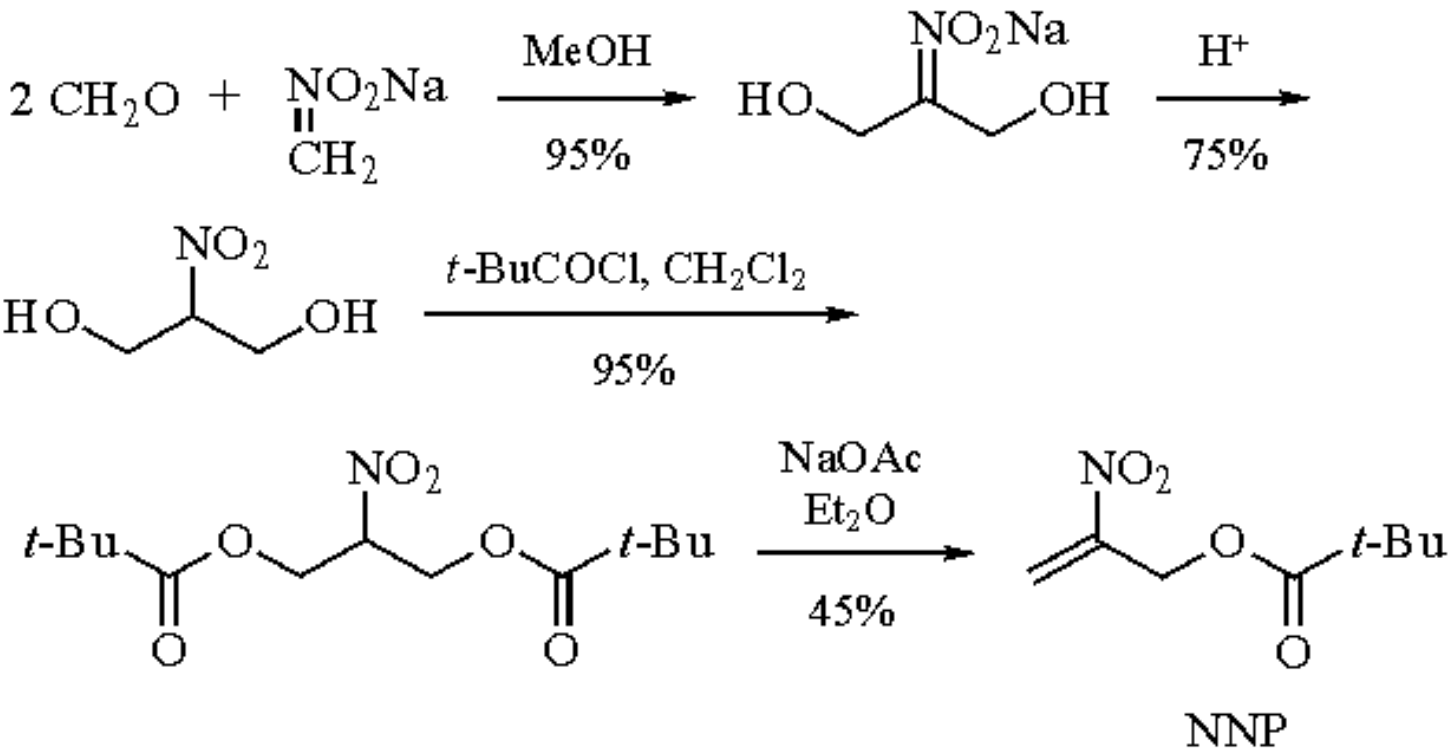

(4)

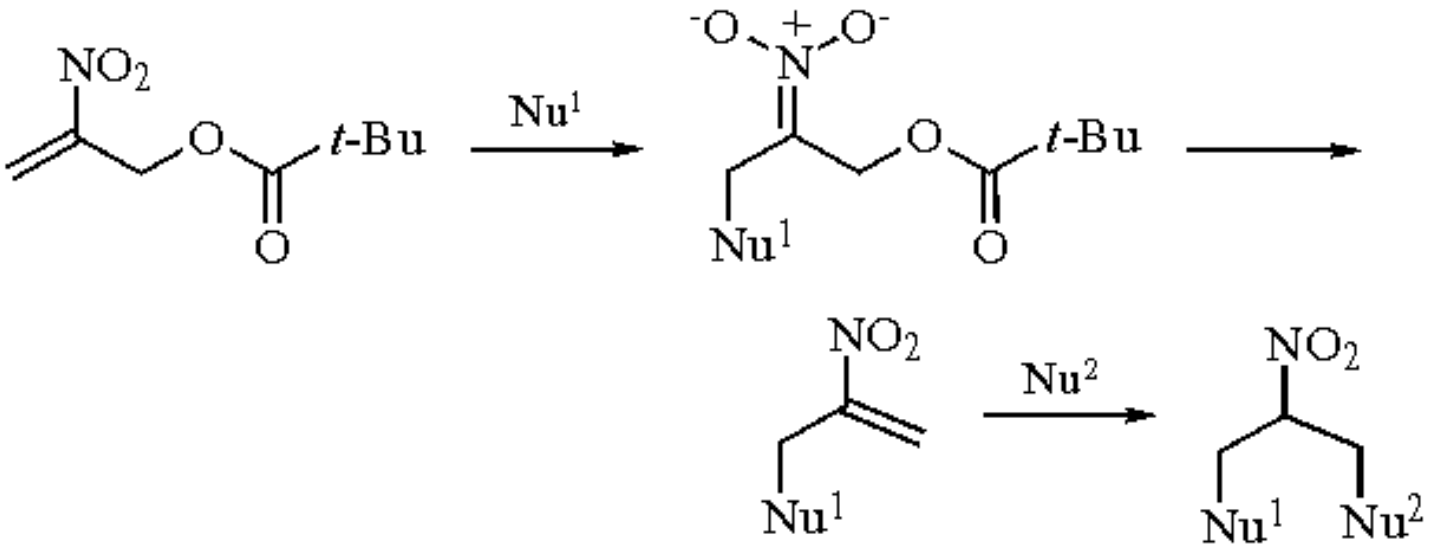

(5)

With dialdehydes, nitromethane forms cyclic nitro compounds.[33] Nitromethane reacts with glyoxal at pH 10 to give a mixture of isomeric inositol derivatives from which *neo*-inositol, one of 14 possible diastereomers, precipitates (72% yield) (eq 6).

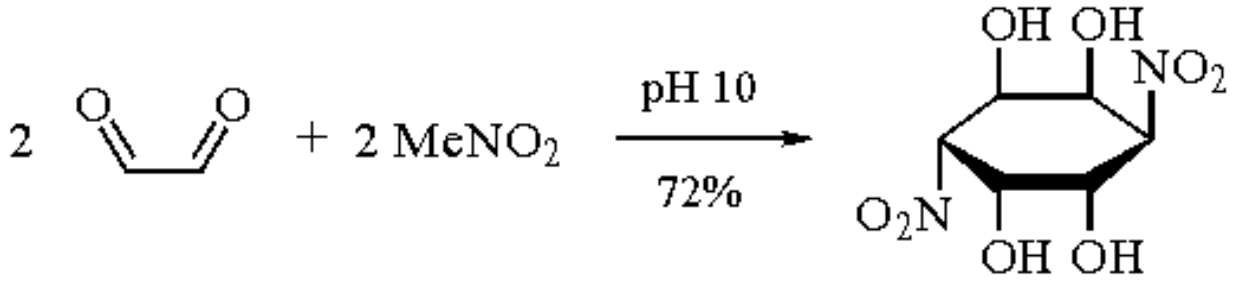

(6)

Tartaraldehyde gives a mixture of stereomeric nitro-2,3,4,5-cyclopentanetetraols.[33] With *o*-phthalaldehydes, nitromethane reacts in alcoholic alkali to give, after acidification, 2-nitro-3-hydroxyindenes.[33] Dialdehydes derived from periodate cleavage of sugars react with nitromethane in a one-pot cyclization reaction to give, frequently, one predominant stereoisomer (eq 7).[33,34]

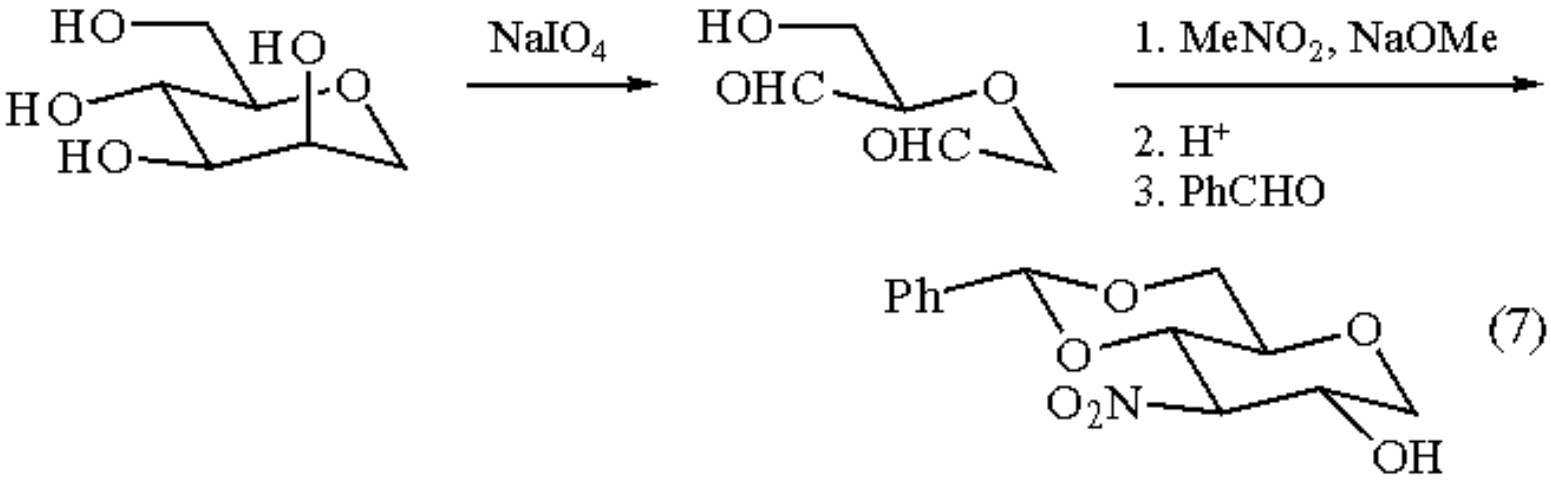

(7)

meso-1,5-Dialdehydes react with nitromethane in methanol and a catalytic amount of NaOH to give a crude mixture of 2,6-dihydroxynitrocyclohexanes from with the major *trans*,*trans*-isomer precipitates (eq 8).[35] The diacetates of carbocyclic and heterocyclic six-membered compounds formed by this reaction can be saponified enantioselectively with pig liver esterase (PLE) to give monoacetates of >95% ee.[35]

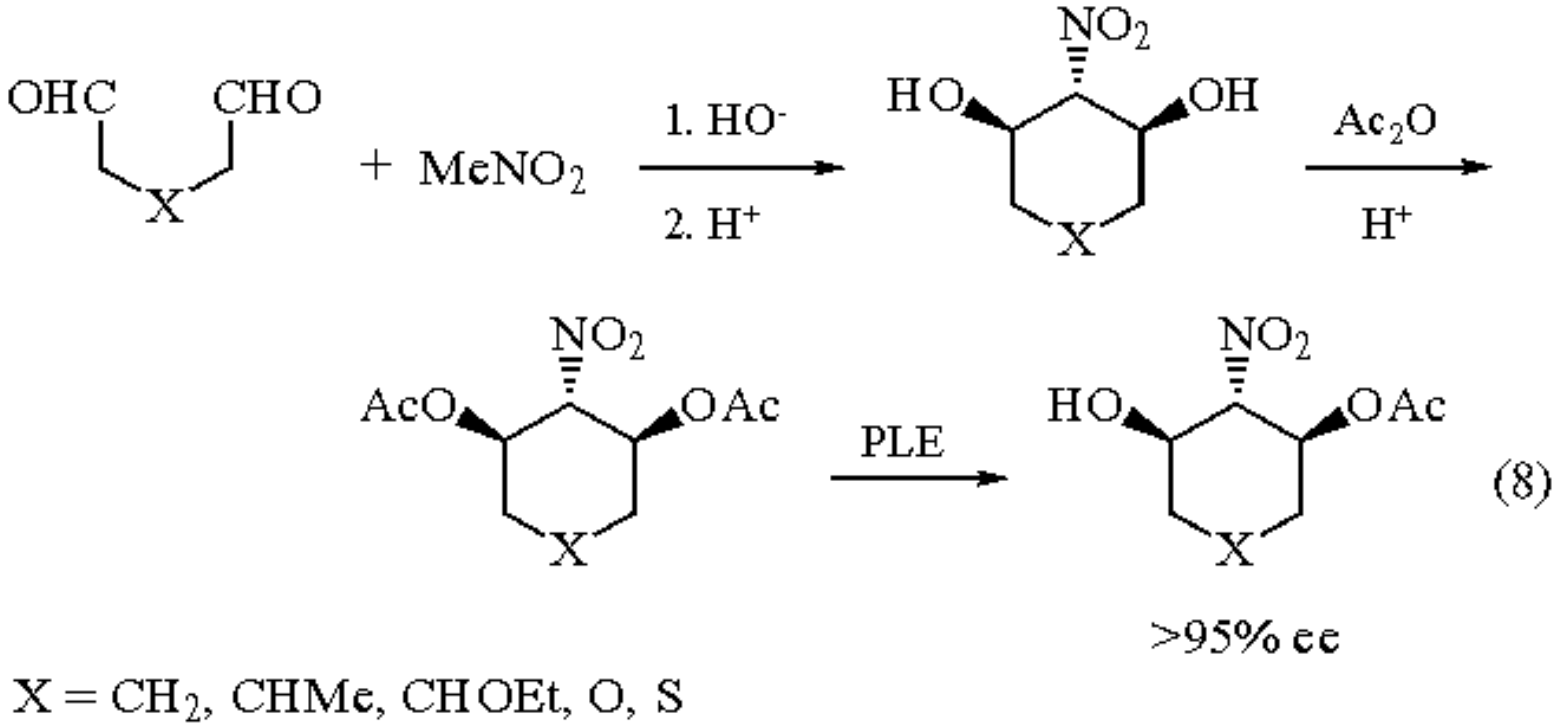

In the presence of primary or secondary amines, aldehydes react with nitromethane in a Mannich-type reaction.[2d]

Reactions with Ketones.

Unlike other nitroalkanes, nitromethane often gives satisfactory yields in the reaction with ketones.[2b] The reaction is complex and depends on the ratio of reactants, base, temperature, and time (eq 9).[2a]

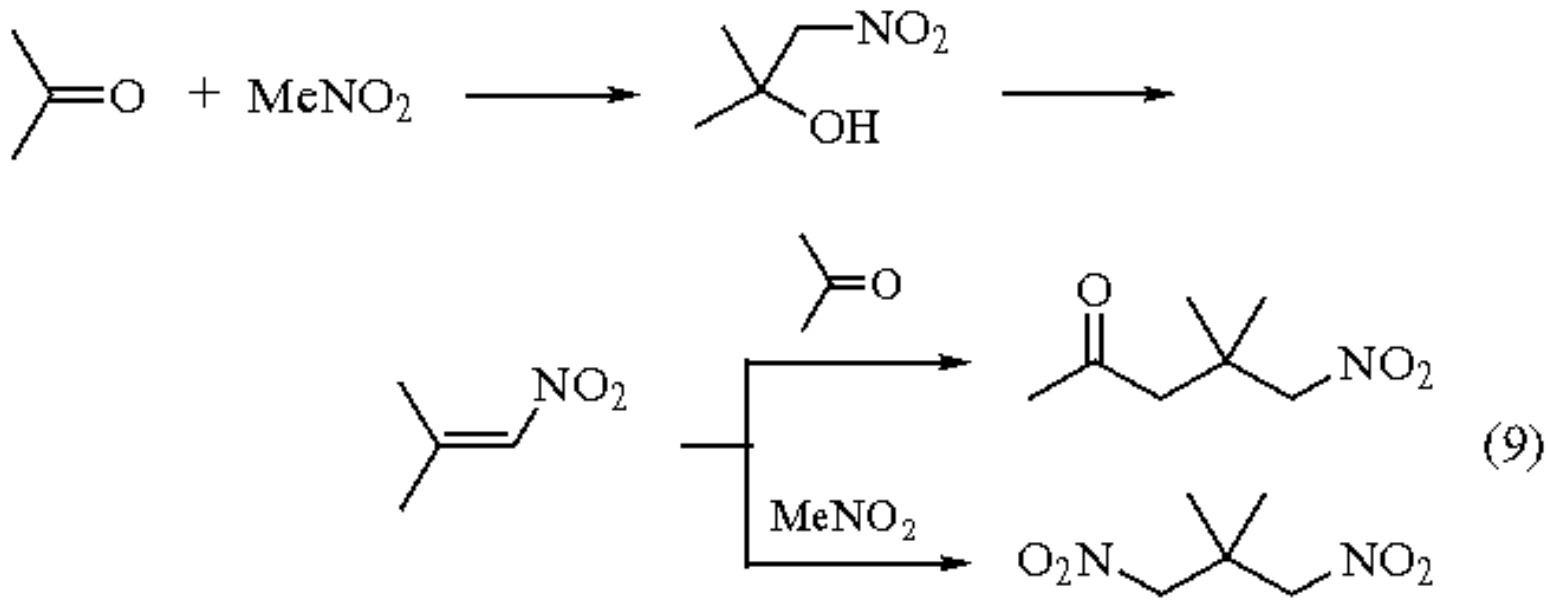

With alkali metal hydroxides or alkoxides, quaternary ammonium hydroxides, primary or tertiary amines, or ***Tetra-n-butylammonium Fluoride*** under pressure[36] it is usually possible to stop the reaction at the nitro alcohol stage.[2d] When the reaction is catalyzed by secondary amines, nitroalkenes are isolated.[37] From 3β-hydroxyandrost-5-en-17-one, nitromethane, and 1% ***1,2-Diaminoethane*** as catalyst, an exocyclic nitroalkene is obtained (eq 10),[38] although

exocyclic nitroalkenes often rearrange to the endocyclic β,γ-nitroalkenes. With *N*,*N*-dimethylethylenediamine as base, it is possible to selectively synthesize allylic nitro compounds from both acyclic and alicyclic ketones (eq 11).[39]

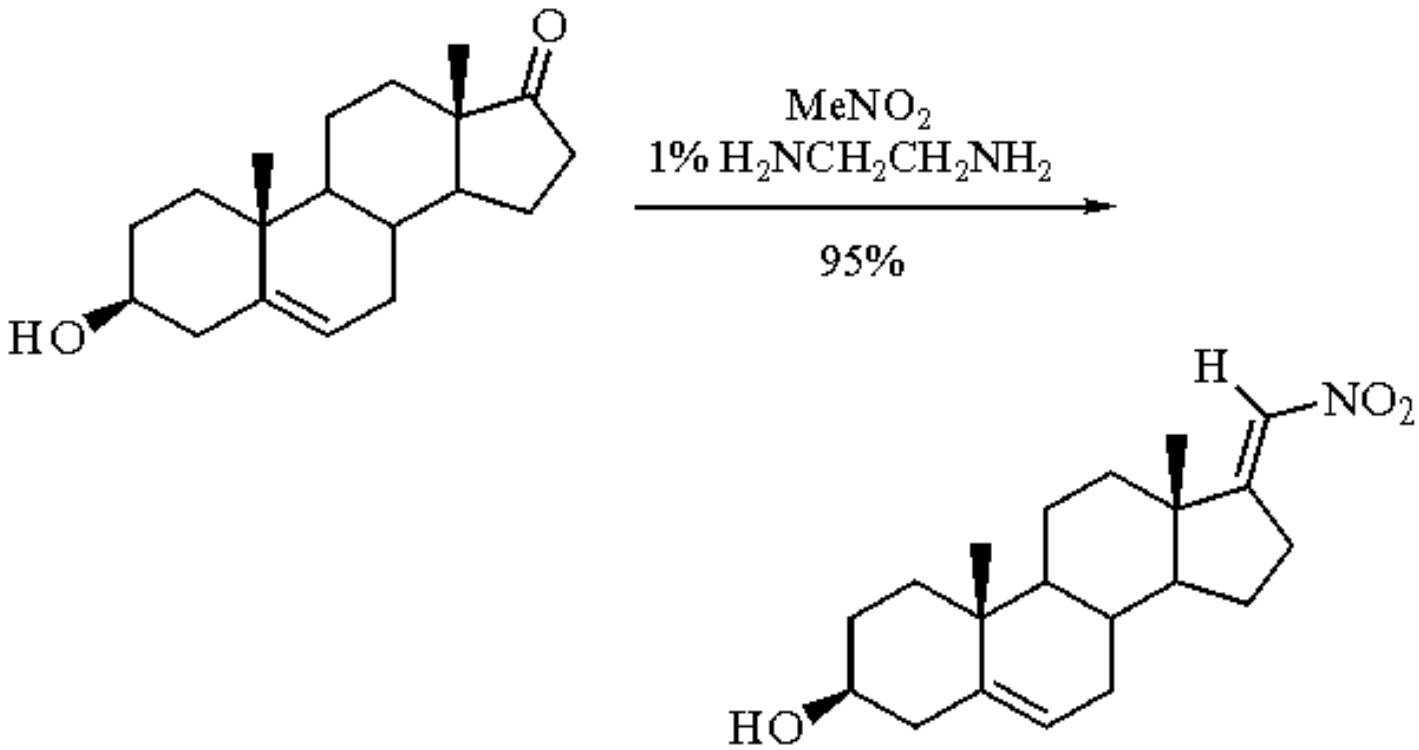

(10)

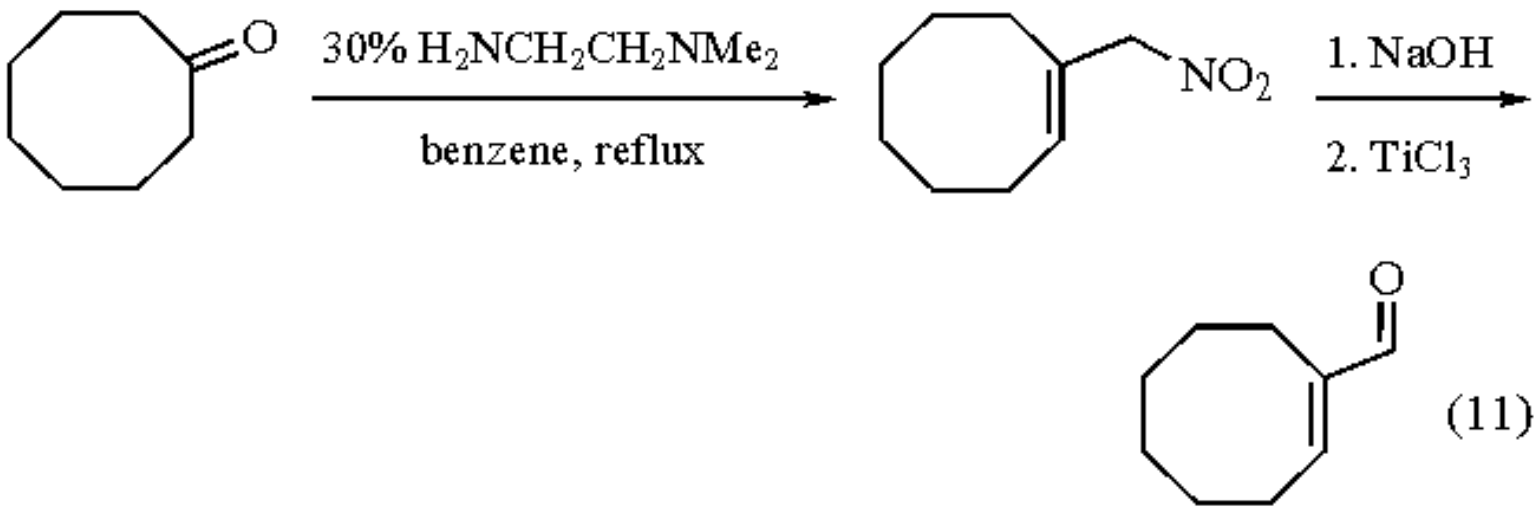

(11)

Nitromethane has been used in the Tiffeneau-Demjanov ring expansion of cyclic ketones by reduction of the nitro alcohol to the β-hydroxy amine and diazotization (eq 12).[40]

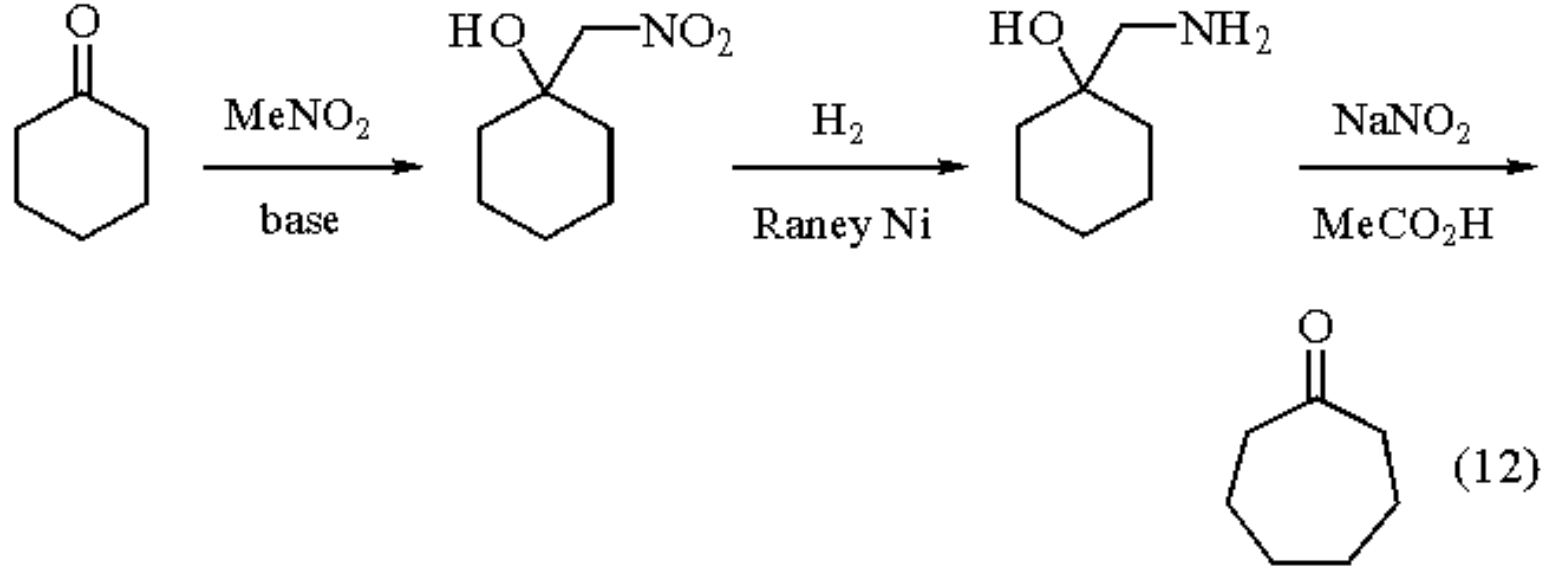

(12)

Michael Reactions.

Conjugate addition of nitromethane to activated double bonds is another important C-C bond forming reaction (eq 13). Unsaturated aldehydes give rise to competing 1,2-addition (Henry reaction), which can be controlled to some extent by the choice of catalyst.[2a] Michael additions with nitromethane are catalyzed in homogeneous solution with catalysts such as alkali metal hydroxides in alcohol,[41] organic nitrogen bases,[42] and fluoride ions.[43] The reaction is also catalyzed in heterogeneous systems with alumina[44] or Al_2O_3-supported KF or CsF.[45] Nitromethane reacts smoothly with two moles of Michael acceptors to give a variety of coupling products (eq 13).[43,44]

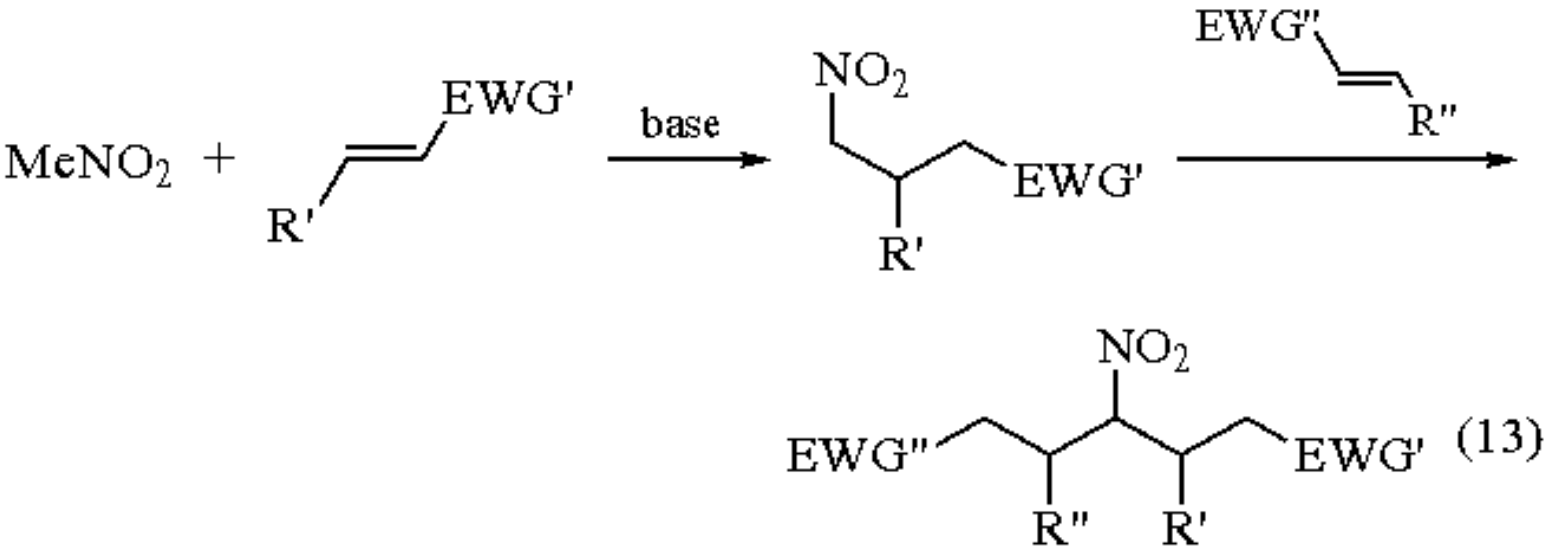

(13)

EWG = CHO, COR, CO_2R, CN, SOR, SO_2R, NO_2

Nitromethane has been employed in cyclopropanation.[46] The product is formed by Michael addition of nitromethane to a double bond with two geminal electron withdrawing groups followed by elimination of the nitro group (eq 14).

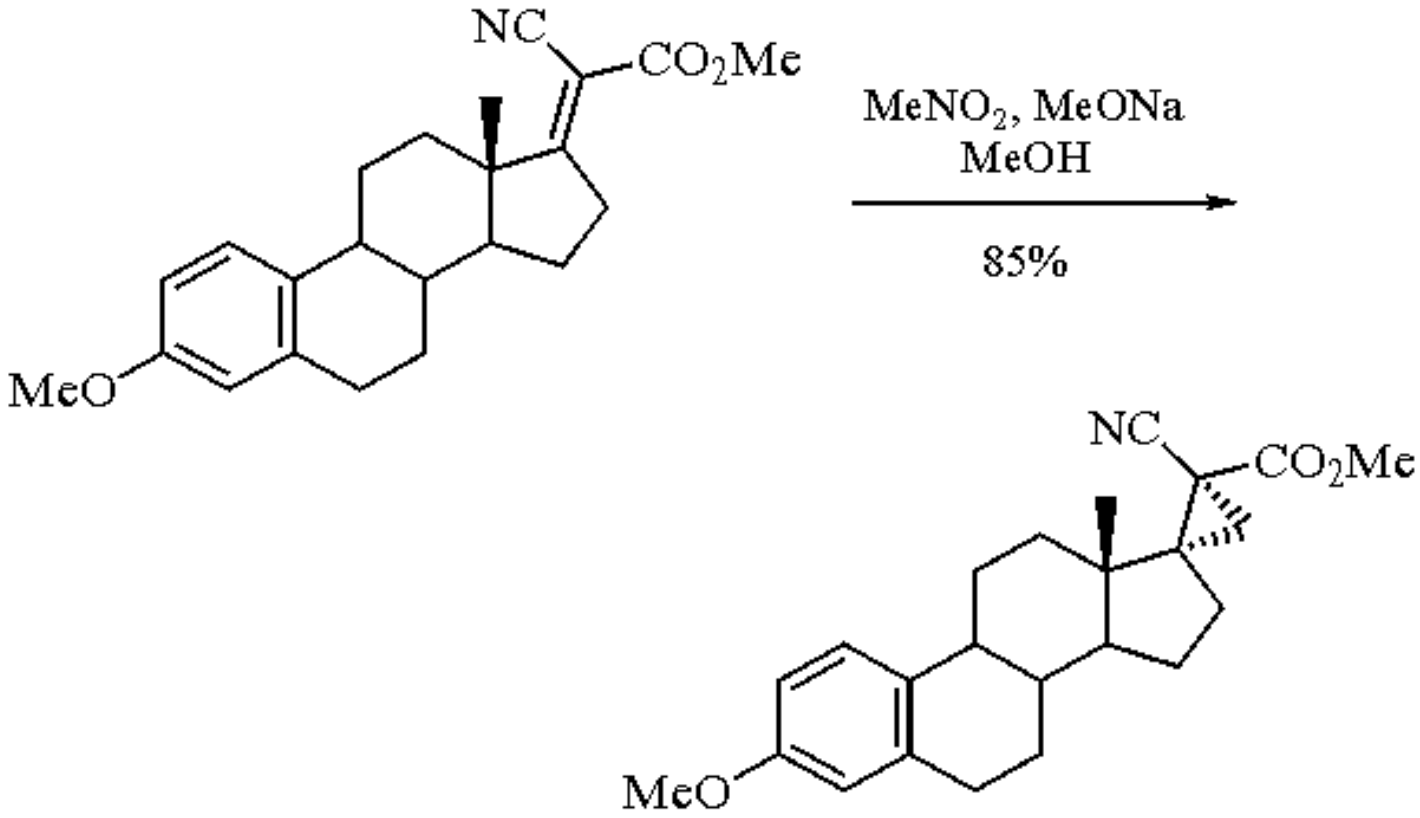

(14)

Acylation of Nitromethane.

With few exceptions, acylation of sodium methanenitronate with acyl halides or anhydrides occurs on oxygen. The unstable products rearrange into hydroxamic acid derivatives. *C*-Acylation can be accomplished with acylimidazoles,[47] acyl cyanide,[48] and phenyl benzoates[49] and from benzoic acids by the action of ***Diethyl Phosphorocyanidate*** (eq 15).[50]

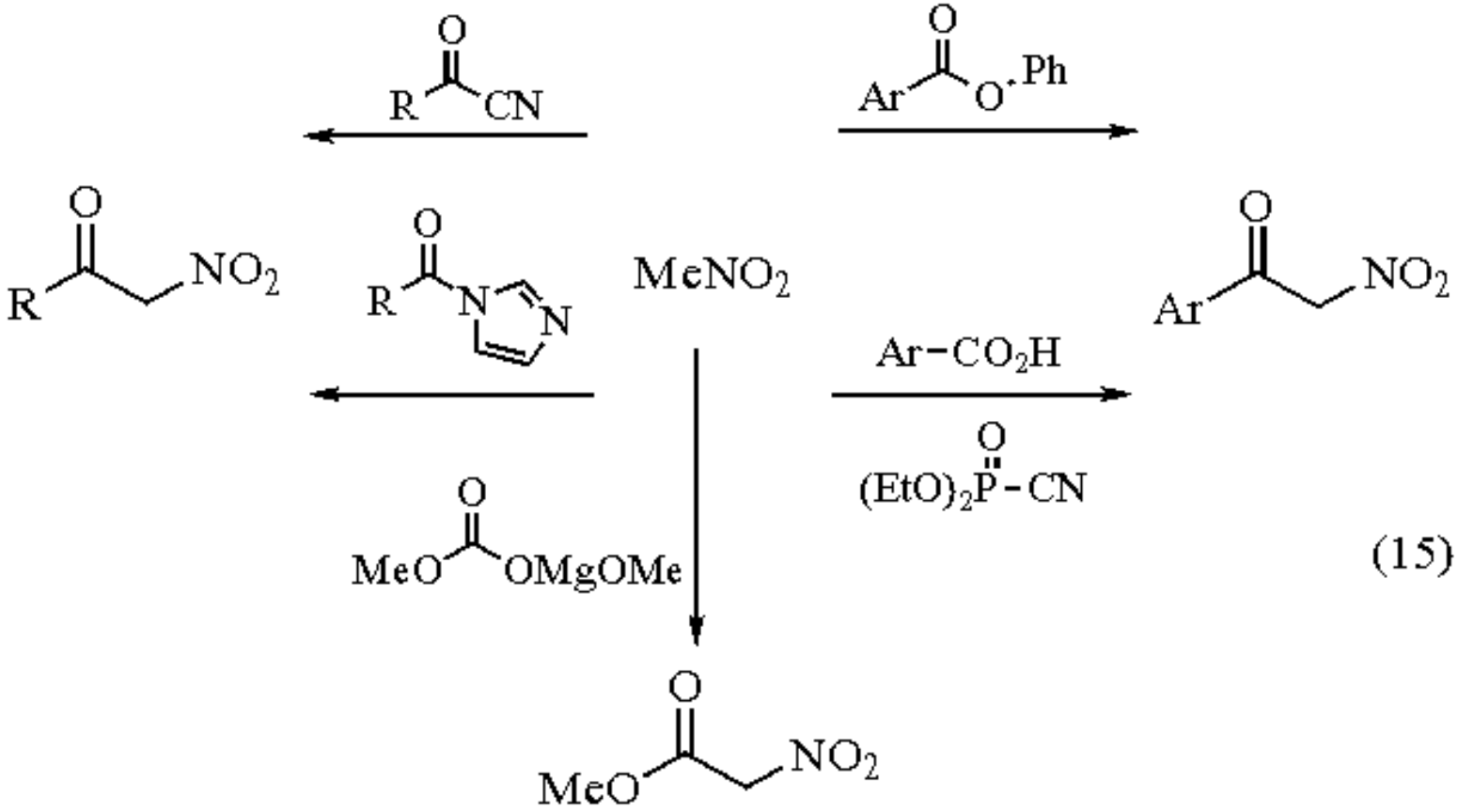

(15)

Carboxylation can be accomplished by reaction with methoxymagnesium methyl carbonate (Stiles reagent).[51] Another method for the preparation of methyl 2-nitroacetate is by heating nitromethane at 160 °C in the presence of KOH, followed by acidification of the nitronate salt at -15 °C in the methanolic solution (eq 16).[52]

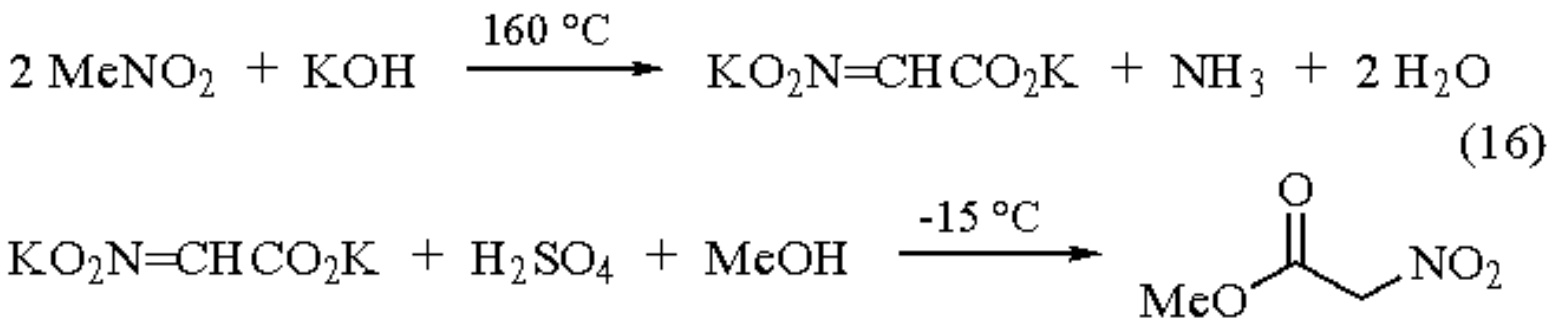

(16)

The dilithium salt of nitromethane reacts with carboxylic esters at -30 °C to form the β-oxo nitronate, which must be carefully acidified at -90 °C with acetic acid (eq 17).[53] The dilithium salt of nitromethane is formed by treatment of nitromethane with ***n-Butyllithium*** in THF/HMPA at -65 °C.[53] The dilithium salt is a much harder carbon nucleophile than the sodium nitronate.

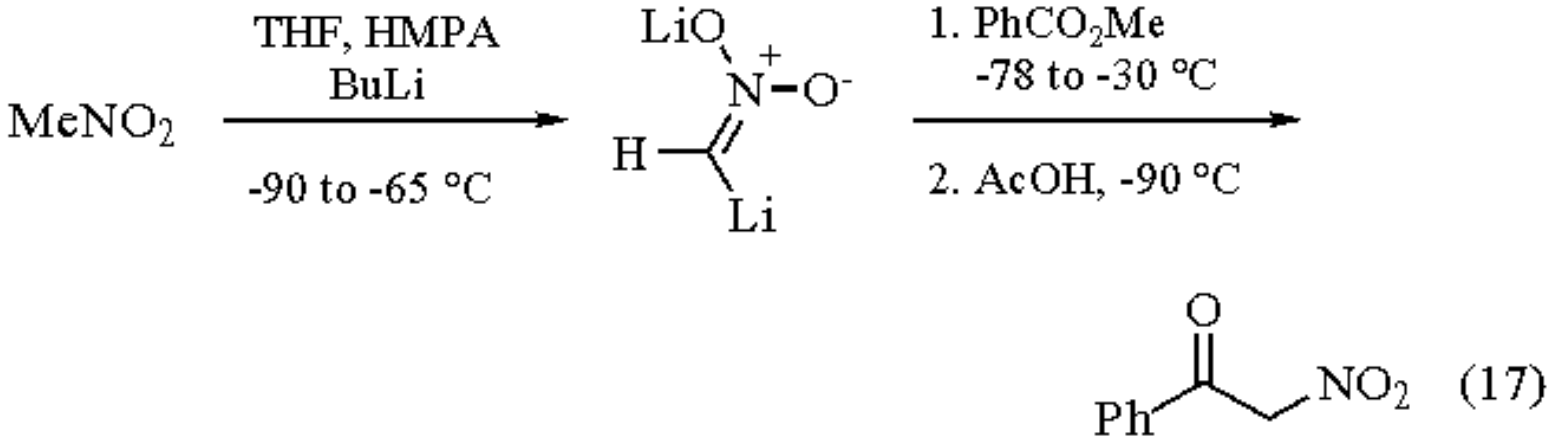

Alkylation of Nitromethane.

The ambident methanenitronate ion reacts with alkyl iodides to give a mixture of *C*-alkylated and primarily *O*-alkylated compounds. The alkyl nitronates of nitromethane are very unstable and decompose to carbonyl compounds and formaldoxime.[54] The sodium salt of nitromethane can be selectively *C*-benzylated with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate in good to moderate yields.[55] The pyridinium cations are readily available from ***2,4,6-Triphenylpyrylium Tetrafluoroborate*** and the corresponding benzylamines.[55]

The dilithium salt of nitromethane is *C*-alkylated with 1-iodohexane in moderate yield.[56] Kornblum et al. has reported on a general high yielding method for the *C*-alkylation of nitromethane with tertiary nitro compounds (eq 18).[57] The tertiary nitro group is substituted with nitromethane in a radical chain process. The reaction is carried out at 25 °C in DMSO with exposure to fluorescent light and the molar ratio of tertiary nitro compound, nitromethane, and NaH is 1:4:8.

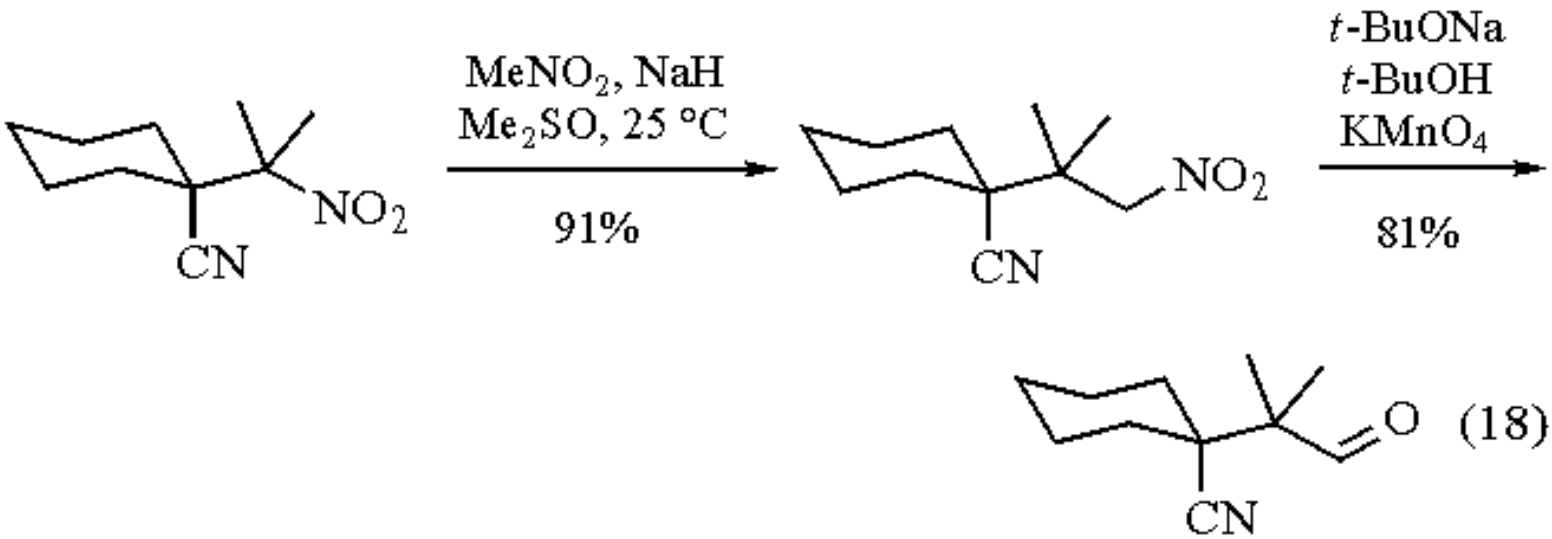

1,3-Dipolar Cycloadditions of Nitromethane.

Nitromethane can be *O*-silylated with ***Chlorotrimethylsilane*** in the presence of ***Triethylamine***.[58a] The trimethylsilyl methanenitronate is unstable and dimerizes, but it can be trapped with an activated alkene in a 1,3-dipolar cycloaddition to give isoxazolidines which, upon acid treatment, give isoxazolines (eq 19).[58]

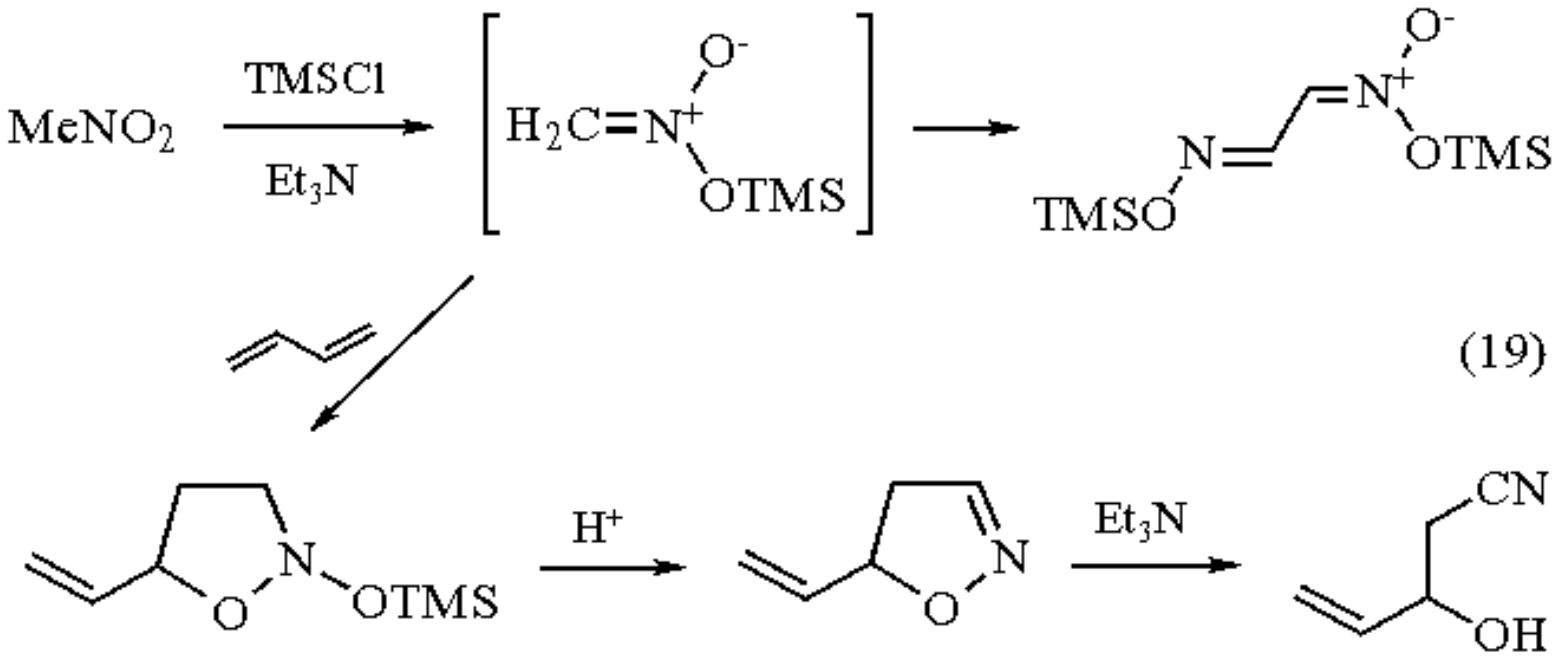

(19)

In contrast to other primary nitro compounds, the corresponding nitrile oxide (fulminic acid) of nitromethane is not formed in the Mukaiyama reaction.[59] When nitromethane is treated with ***Phenyl Isocyanate***, α-nitroacetanilide is formed first and is subsequently transformed to the nitrile oxide with a second mol equiv of phenyl isocyanate (eq 20). The nitrile oxide reacts with terminal double bonds in a regioselective manner to give 3,5-substituted isoxazolines.[59]

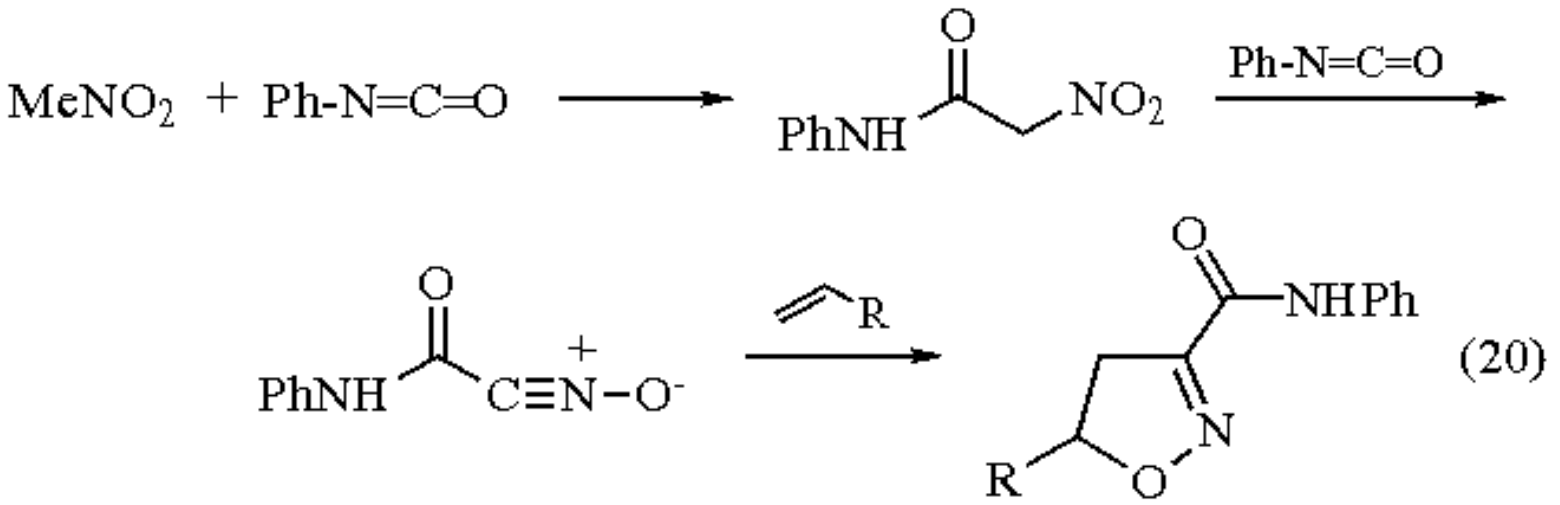

(20)

Related Reagents.

t-Butyldimethylsilyl Ethylnitronate; ***Lithium α-Lithiomethanenitronate***; ***O,O-Dilithio-1-nitropropene***; ***Nitroethane***; ***1-Nitropropane***; ***1-Nitro-1-propene***.

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3-Nitro-9-nitrosocarbazole

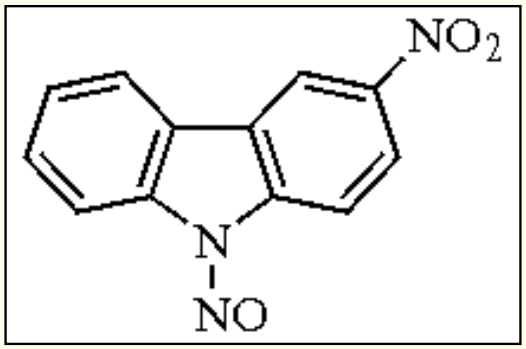

[5393-41-9] · $C_{12}H_7N_3O_3$ · 3-Nitro-9-nitrosocarbazole · (MW 241.22)

(mild nitrosating reagent[1])

Physical Data: mp 166-168 °C.

Solubility: sol benzene; insol methanol.

Form Supplied in: brown-yellow needles.

Analysis of Reagent Purity: IR (KBr, cm^{-1}) 3050, 1530, 1440, 1310, 840, 780, 760, 725; MS (m/e (intensity)) 242 (3.8), 241 (M^+, 13.5), 222 (11.5), 211 (90.4), 210 (86.5), 204 (9.6), 181 (32.7), 167 (13.5), 166 (52.9), 165 (28.8), 153 (46.1), 150 (13.5), 149 (100.0).

Preparative Methods: an aqueous solution of ***Sodium Nitrite*** (1.5 g, 22 mmol) is added to a suspension of carbazole (3.0 g, 18 mmol) in nitrobenzene (30 mL), and HCl (2 mL) is then introduced dropwise for 1 h. The reaction mixture is kept at 15 °C for 1 h. To the resulting solution of 9-nitrosocarbazole is added HNO_3 (1 mL) slowly for 30 min, and the solution is kept for 1.5 h. Crystalline 3-nitro-9-nitrosocarbazole (3.5 g, 14 mmol) is obtained when the solvent is evaporated.[2] 3-Nitro-9-nitrosocarbazole (6.65 g, 28 mmol) is also prepared by the reaction of 3-nitrocarbazole (6.39 g, 30 mmol) and sodium nitrite (2.76 g, 40 mmol) in acetic acid (120 mL) at 70 °C.[3]

Purification: recrystallization from acetone or 2-butanone.

Nitrosation.[1]

3-Nitro-9-nitrosocarbazole is a mild nitrosating reagent, which is suitable for nitrosating secondary amines. *N*-Methylaniline (**1**) reacts with 3-nitro-9-nitrosocarbazole (**2**) in refluxing benzene to afford *N*-nitrosomethylaniline (**3**) in 55% yield (eq 1). 3-Nitrocarbazole (**4**) is obtained as a byproduct. However, attempted nitrosation of aziridine (**5**) by

(**2**) does not produce *N*-nitrosoaziridine. Instead, ethylene (42%) and nitrous oxide (50%) are isolated; these might arise from decomposition of *N*-nitrosoazirine (eq 2).

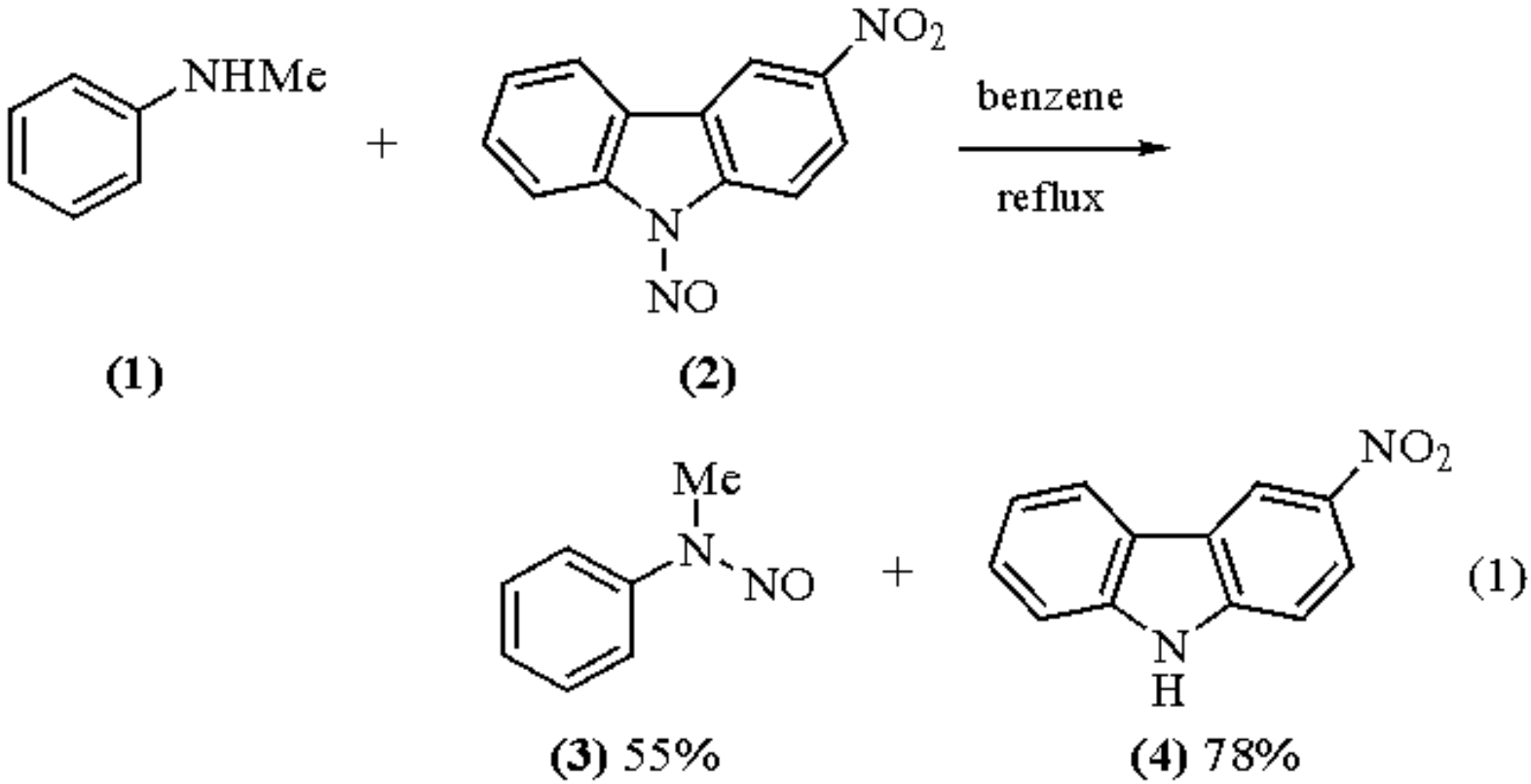

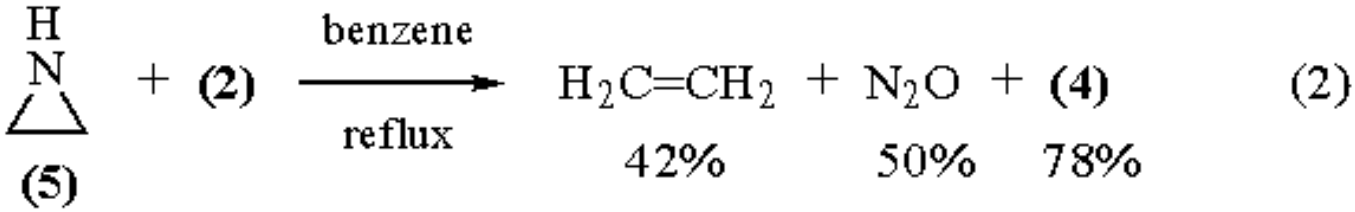

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Nitronium Tetrafluoroborate[1]

$NO_2^+BF_4^-$

[13826-86-3] · BF_4NO_2 · Nitronium Tetrafluoroborate · (MW 132.82)

(electrophilic nitrating agent;[1] mild oxidant;[2] hydride and halide abstracting agent[2])

Physical Data: decomposes to NO_2F and BF_3 at temperatures >180 °C.

Solubility: sol sulfolane, acetonitrile; slightly sol nitromethane. Compared with $NO_2^+BF_4^-$, $NO_2^+PF_6^-$ has much higher solubility in organic solvents.

Form Supplied in: colorless crystalline compound; commercially available.

Handling, Storage, and Precautions: due to its hygroscopic nature, $NO_2^+BF_4^-$ should be stored and used under anhydrous conditions. Commercial $NO_2^+BF_4^-$ often contains varying amounts of $NO^+BF_4^-$. Removal of the NO^+ from $NO_2^+BF_4^-$ is difficult. Therefore, pure nitronium tetrafluoroborate should be prepared directly from urea-treated purified HNO_3.[3]

Nitration.

$NO_2^+BF_4^-$ is a highly efficient electrophilic nitrating agent for organic compounds.[1] A variety of arenes have been nitrated by this reagent (eq 1). The ability of $NO_2^+BF_4^-$ to nitrate under anhydrous conditions makes it a reagent of choice for the nitration of aromatics with acid sensitive functional groups, such as nitriles, acid halides, and esters. The nitrations are conveniently carried out in sulfolane solution, although methylene chloride and nitromethane are also used. With severely deactivated arenes such as polyhaloarenes and 1,3-dinitrobenzene, superacids such as ***Fluorosulfuric Acid*** and ***Trifluoromethanesulfonic Acid*** are used as solvents to achieve satisfactory results.[4] The increased reactivity of the nitronium ion in strongly acidic solution results from protosolvation (protonation) of the lone pair electron of NO_2^+ to form the protonitronium dication.[5] Nitration of hexamethylbenzene, nitropentamethylbenzene, bromopentamethylbenzene, and pentamethylbenzoic acid with excess $NO_2^+BF_4^-$

leads to formation of 1,2-dinitro-3,4,5,6-tetramethylbenzene.[6] $NO_2^+BF_4^-$ reacts with methylheptafluoronaphthalene to form addition products.[7]

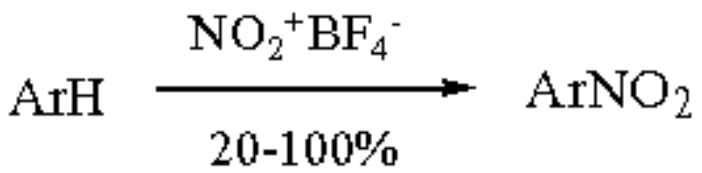

(1)

Due to its less oxidative nature compared with conventional mixed acids (HNO_3/H_2SO_4), $NO_2^+BF_4^-$ is widely applied in the nitration of heterocyclic compounds. Alkylpyridines,[8] thiophene,[9] and furan,[9] as well as polyheteroatom cyclic compounds[10-12] such as uracils and pentaazaphenalenes, are nitrated under mild conditions. Even macroheterocyclic compounds like porphyrins and metal phthalocyanines (metal = iron, cobalt, nickel) are nitrated with $NO_2^+BF_4^-$.[13]

Electrophilic nitration of alkanes is still of little preparative value in organic synthesis. However, in special cases such as adamantane, nitration with $NO_2^+BF_4^-$ occurs readily to give 1-nitroadamantane in 66% yield (eq 2).[14]

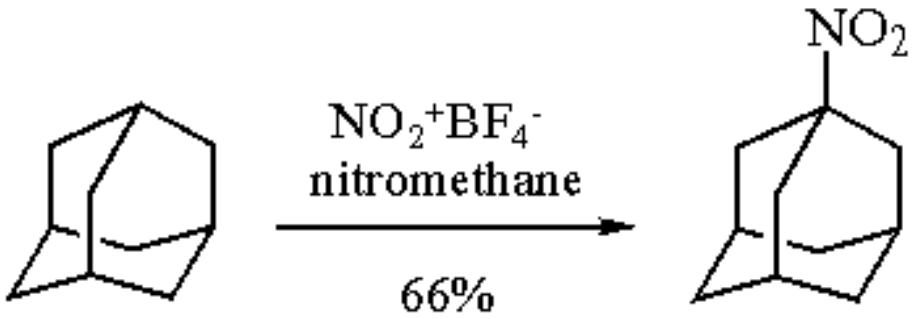

(2)

The reaction of $NO_2^+BF_4^-$ with alkenes generally gives a mixture of addition, addition-elimination, and oligomerization products, with the ratio depending on the nature of the substrates and the reaction conditions.[1c] However, with alkenes such as allyl esters[15] and vinyl halides[16] which contain functional groups capable of stabilizing the reaction intermediates, the addition (nitrofluorination) products can be obtained preferentially. When ***Pyridinium Poly(hydrogen fluoride)*** is used as additional fluoride source, alkenes react with $NO_2^+BF_4^-$ to give β-nitroalkyl fluorides in good yields.[17] With acetonitrile[18] and acetic anhydride,[19] solvoaddition products are also obtained (eq 3).

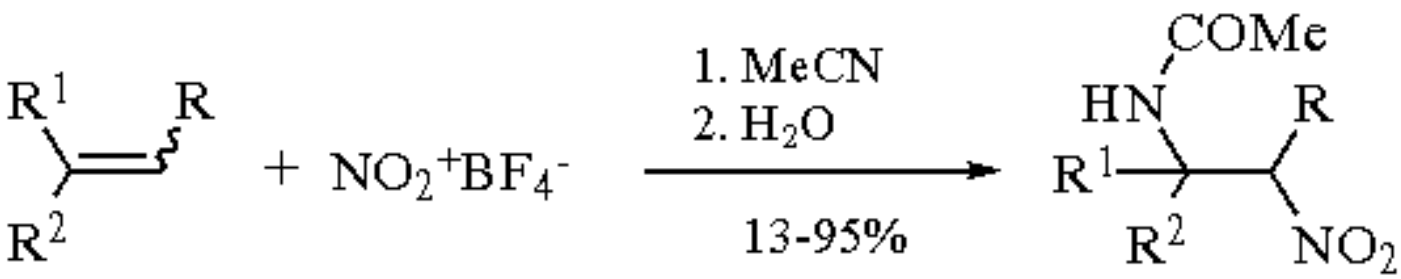

(3)

Nitration of alkenyloxysilanes and enol acetates with $NO_2^+BF_4^-$ leads to formation of α-nitro ketones.[20] Allylsilanes react with the salt readily to yield nitroalkenes.[21] Nitration of trimethylsilylacetylene or alkynylstannanes with $NO_2^+BF_4^-$ leads to formation of nitroalkynes.[22]

Both primary and secondary amines react with $NO_2^+BF_4^-$ to form nitro amines (eq 4).[1,23] Pyridines are *N*-nitrated to form *N*-nitropyridinium tetrafluoroborates, which have been widely used as transfer nitrating agents.[24] The advantage of using *N*-nitropyridinium salts as nitrating agents is that they react under acid-free conditions. Unsubstituted sulfodiimides or their *N*,*N*-bis(trimethylsilyl) derivatives react with $NO_2^+BF_4^-$ to afford interesting *N*,*N*-dinitrosulfodiimides.[25]

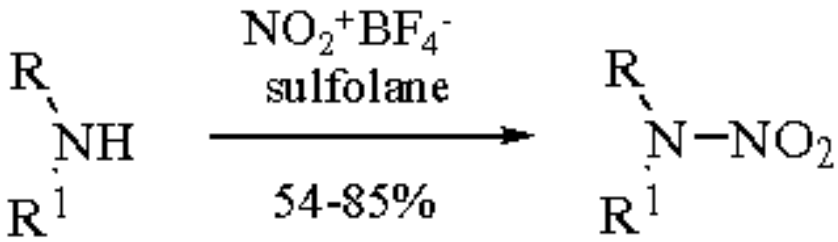

(4)

Nitration of amides with $NO_2^+BF_4^-$ yields *N*-nitroamides.[26] The nitroamides of benzoic and chloroacetic acid are obtained in satisfactory yields but the yield of nitroacetamide is only 12%. *N*-alkyl- and *N*,*N*-dialkylamides are nitrolyzed to form corresponding nitroamines and *N*,*N*-dinitroamines in satisfactory yields.[27] *N*-Alkyl-*N*-nitroamides react similarly with $NO_2^+BF_4^-$ to form dinitroamines in good yields.[28]

Aliphatic isocyanates react with $NO_2^+BF_4^-$ in ethyl acetate or acetonitrile to form nitroamines (after hydrolysis).[29] On the other hand, in conjunction with HNO_3, $NO_2^+BF_4^-$ reacts with isocyanates to yield *N*,*N*-dinitroamines.[30] Alcohols are nitrated with $NO_2^+BF_4^-$ to alkyl nitrates (eq 5).[31] In the presence of other nucleophiles, epoxides are ring-opened by $NO_2^+BF_4^-$.[32]

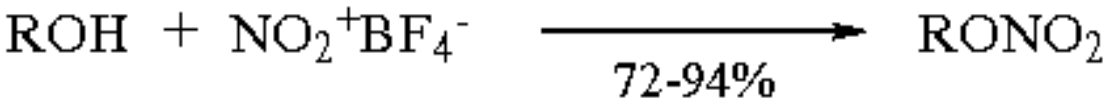

(5)

Oxidation.

$NO_2^+BF_4^-$ is a mild oxidant. The oxidative ability of the salt is manifested by the formation of products resulting either from coupling or from oxidation in its reaction with electron rich aromatics.[33] The oxidative property of $NO_2^+BF_4^-$ has been utilized to regenerate the masked carbonyls from 1,3-dithioacetals, oximes, and dimethylhydrazones.[34] $NO_2^+BF_4^-$ is also capable of oxidizing ethers to carbonyls,[35a] or converting them into *N*-alkylacetamides by trapping the intermediates with acetonitrile.[35b]

Organic sulfides are oxidized with $NO_2^+BF_4^-$ to form sulfoxides (eq 6).[36] With additional added $NO_2^+BF_4^-$, the sulfoxides can be further converted to sulfones.[36] Phosphines are similarly oxidized to phosphine oxides in quantitative yield.[36] More recently, fullerene (C_{60}) has been oxidized to fullerols by $NO_2^+BF_4^-$ in the presence of carboxylic acids.[37]

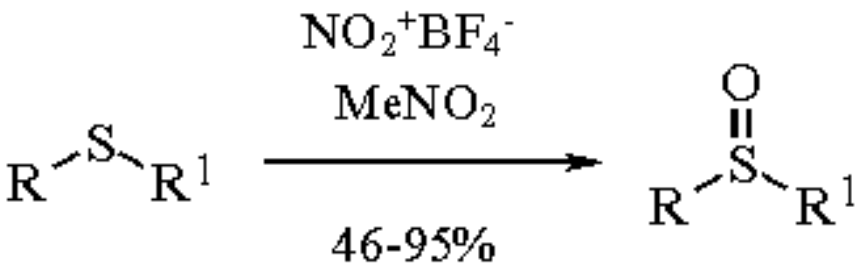

(6)

Hydride and Halide Abstraction.

Like ***Nitrosonium Tetrafluoroborate***, $NO_2^+BF_4^-$ is a hydride and halide abstracting agent.[38-41] However, it is less efficient in this aspect compared to $NO^+BF_4^-$.

Related Reagents.

Nitric Acid.

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George A. Olah, G. K. Surya Prakash, Qi Wang & Xing-ya Li

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p-Nitroperbenzoic acid[1]

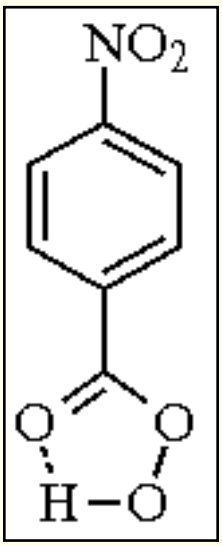

[943-39-5] · $C_7H_5NO_5$ · *p*-Nitroperbenzoic acid · (MW 183.13)

(electrophilic reagent which delivers oxygen to alkenes[2])

Alternate Names: *p*-nitroperoxybenzoic acid; PNPBA.

Physical Data: white crystalline solid; mp 136-137 °C.

Solubility: sol THF, ether, $CHCl_3$, benzene.

Form Supplied in: white powder, 80% purity.

Analysis of Reagent Purity: iodometric titration.

Preparative Method: the reaction between Na_2O_2 and ***p-Nitrobenzoyl Chloride*** in THF in the presence of small quantities of water below -5 °C furnishes the sodium salt of PNPBA. *p,p´*-Dinitrobenzoyl peroxide and *p*-nitrobenzoic acid are removed from the reaction mixture during workup. PNPBA (purity 94-96%) is obtained in 85% yield (0.1 mol scale).[2]

Purification: recrystallization from ether-petroleum ether.

Handling, Storage, and Precautions: at room temperature, PNPBA is stable for long periods.

It should be stored in polyethylene containers in a refrigerator. Since PNPBA is a peroxide and potentially explosive, care should be exercised when carrying out reactions with it; during workup, check for the presence of peroxide before evaporating solvent.

Epoxidation of Alkenes.

Due to the presence of the electron withdrawing NO_2 group, PNPBA epoxidizes alkenes about ten times more rapidly than ***Perbenzoic Acid*** (PBA); ***m-Chloroperbenzoic Acid*** is only slightly more reactive than PBA. *trans*-Stilbene is thus oxidized to *trans*-stilbene oxide (eq 1).[3] A solution of 5.4 g of stilbene (30 mmol) in 60 mL of $CHCl_3$ is added dropwise with stirring to a suspension of 7.5 g (33 mmol) of 80% PNPBA in 100 mL of $CHCl_3$; the reaction mixture is kept at rt for 24 h with occasional shaking, and filtered. The filtrate is washed with 10% aq Na_2CO_3, dried, and the solvent is evaporated. The residue is recrystallized from petroleum ether to give 5.5 g (93%) of the epoxide.

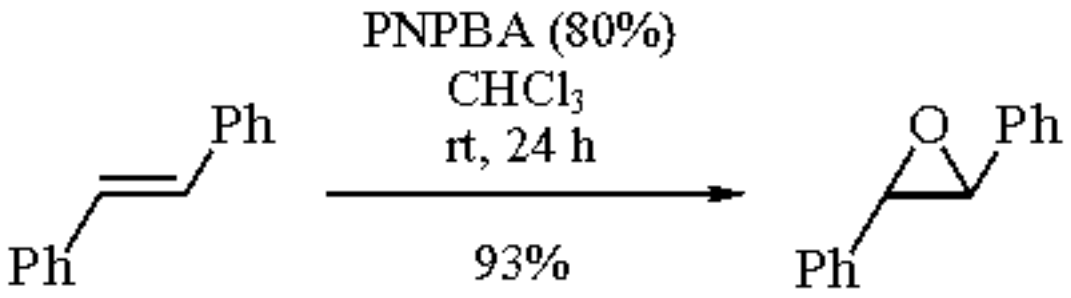

(1)

The monosubstituted alkene (**1**) reacts with PNPBA (22 h, rt) to furnish the epoxidation product in 75% yield.[4] The epoxide (**2**), an intermediate for the synthesis of cyclobutanone, has been prepared in 90% yield by treating methylenecyclopropane with PNPBA in CH_2Cl_2 at -10 °C.[5]

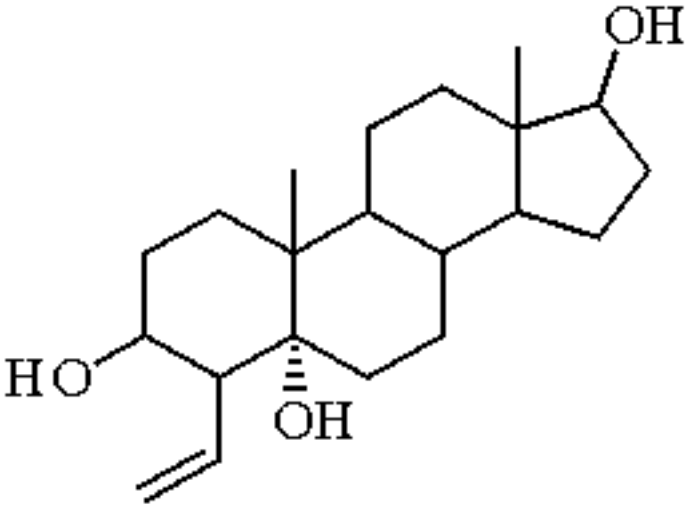

(1)

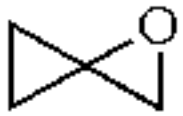

(2)

Reaction of the α,β-unsaturated ketone (**3**) with PNPBA in benzene (24 h, rt) furnishes the 5β,10β-epoxide in 91% yield.[6] This epoxide cannot be prepared from (**3**) using *m*-CPBA or H_2O_2/MeOH/NaOH. Reaction of the alkene (**4**) with PNPBA in $CHCl_3$ (reflux, 3 days) in the presence of the radical inhibitor 4,4´-thiobis(6-*t*-butyl-3-methylphenol) furnishes the 4α,5α-epoxide in 30% yield.[7] *m*-CPBA and benzonitrile/H_2O_2 are not useful reagents for the epoxidation of (**4**); TBHP/$Mo(CO)_6$ furnishes the epoxide in low yields.

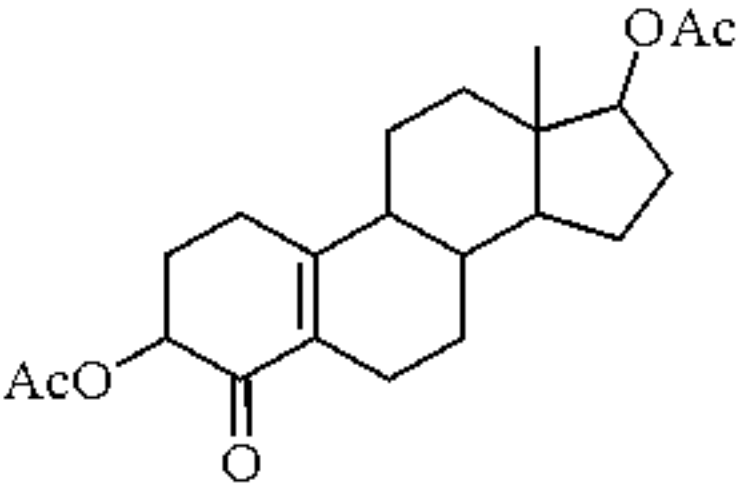

(3)

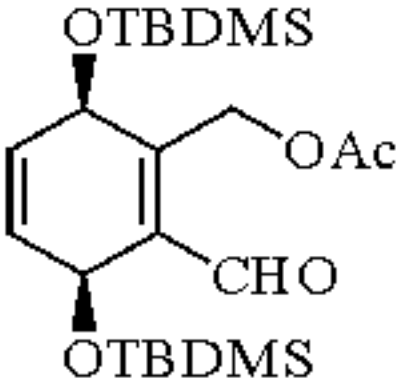

(4)

Oxidation of Unactivated Hydrocarbons.

Reaction of alicyclic hydrocarbons with PNPBA results in regio- and stereoselective hydroxylation (eq 2).[8] Tertiary alcohols are obtained with high selectivity (>97%); hydroxylation takes place with retention

(>98%) of configuration. Dioxiranes are excellent reagents for the hydroxylation of alicyclic hydrocarbons under mild conditions (see ***Dimethyldioxirane***).[9]

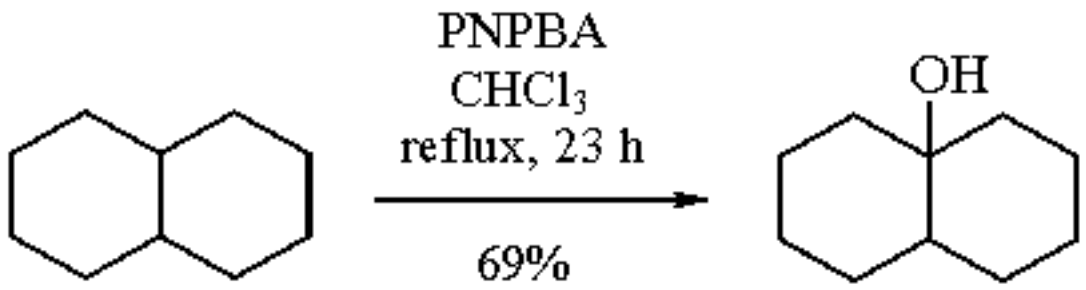

(2)

Baeyer-Villiger reaction.

For an example, see eq 3.[10]

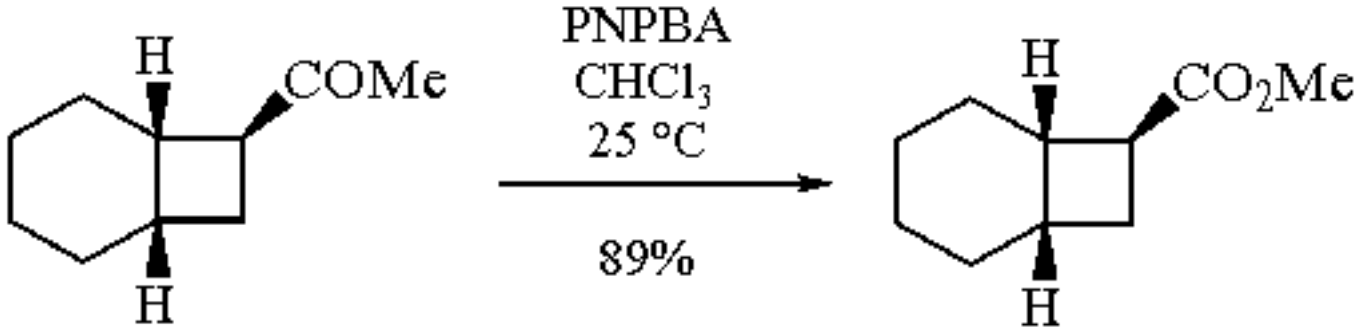

(3)

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A. Somasekar Rao & H. Rama Mohan

o-Nitrophenol

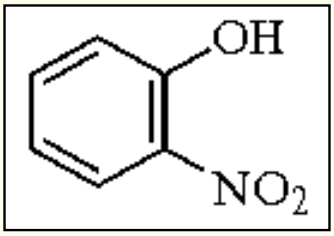

[88-75-5] · $C_6H_5NO_3$ · *o*-Nitrophenol · (MW 139.12)

(preparation of active esters for peptide synthesis[1])

Physical Data: mp 45 °C; bp 216 °C; pK_a 7.23 (at 25 °C).

Solubility: sol ether, benzene; sparingly sol H_2O.

Form Supplied in: yellow solid, commercially available.

Purification: crystallizes as yellow needles or prisms from ethanol or ether.

Handling, Storage, and Precautions: moderately toxic by inhalation and skin absorption.

Preparation of Active Esters for Peptide Synthesis.

Esters of *o*-nitrophenol, prepared by the ***1,3-Dicyclohexylcarbodiimide*** coupling method, can be used in peptide synthesis (eq 1)[1] in the same way as are the corresponding *p*-nitrophenyl esters (see ***p-Nitrophenol***). *o*-Nitrophenol is less reactive than *p*-nitrophenol in the DCC coupling step; use of pyridine as solvent instead of ethyl acetate increases the nucleophilicity of the hydroxyl group and minimizes side reactions. In the aminolysis step, the *o*-nitrophenyl esters are more reactive than the *p*-isomers, and the reaction rates are less sensitive to changes in solvent or to steric hindrance. *o*-Nitrophenyl esters have been used in a stepwise synthesis of a nonapeptide in which all synthetic operations are performed in the same reaction vessel, without isolation of intermediates (in situ peptide synthesis).[1]

o-Nitrophenol

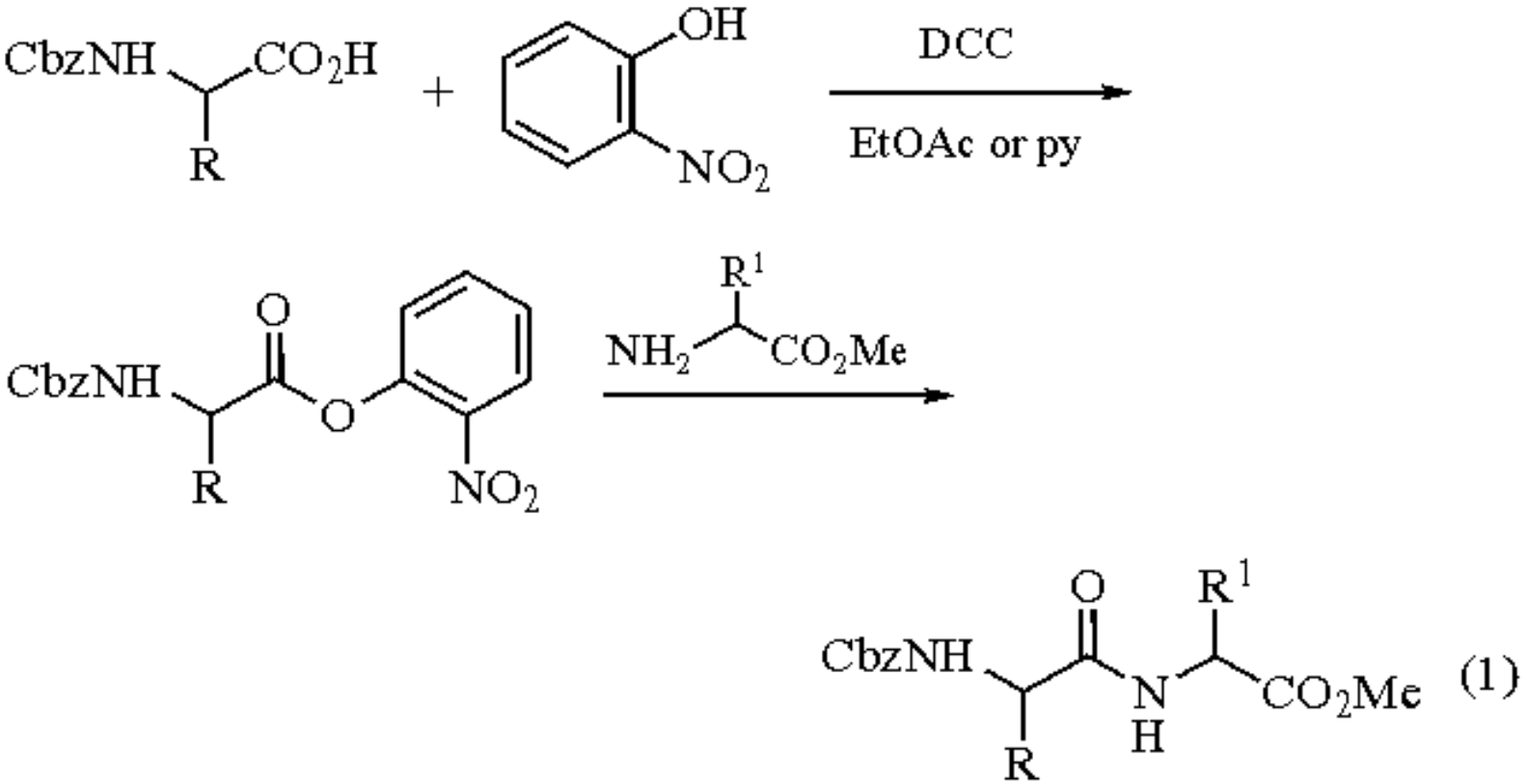

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1. Bodanszky, M.; Funk, K. W.; Fink, M. L. *JOC* **1973**, *38*, 3565; Bodanszky, M.; Kondo, M.; Yang Lin, C.; Sigler, G. F. *JOC* **1974**, *39*, 444.

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p-Nitrophenol

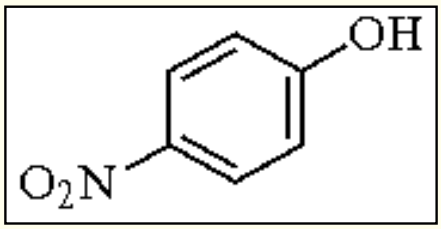

[100-02-7] · $C_6H_5NO_3$ · *p*-Nitrophenol · (MW 139.12)

(preparation of active esters for peptide synthesis[1])

Physical Data: mp 114 °C; pK_a 7.15 (at 25 °C); dimorphous.

Solubility: moderately sol cold water; sol alcohol, chloroform, ether.

Form Supplied in: generally obtained as a mixture of the two crystalline forms.

Purification: recystallization from toluene gives the metastable α-form if performed at >63 °C; the β-form is obtained as yellow prisms at <63 °C.

Handling, Storage, and Precautions: the α-form is light stable, whereas the yellow β-form gradually turns red in light. Moderately toxic by inhalation and skin absorption.

Preparation of Active Esters for Peptide Synthesis.

p-Nitrophenyl esters, prepared by ***1,3-Dicyclohexylcarbodiimide***-mediated coupling between *N*-protected amino acids and *p*-nitrophenol, are among the most useful activated esters for peptide synthesis (eq 1).[1] They are readily purified by recrystallization, often from alcoholic solvents with which they do not react. Aminolysis occurs at a reasonable rate, generally at room temperature without a catalyst. The *p*-nitrophenol generated as a byproduct in this step is easily removed. *o*-Nitrophenyl esters can be used similarly (see ***o-Nitrophenol***); a study of the rates of aminolysis of Boc-L-leucine nitrophenyl esters showed the *o*-isomer to react 4-9 times faster than the *p*-isomer.[2]

p-Nitrophenol

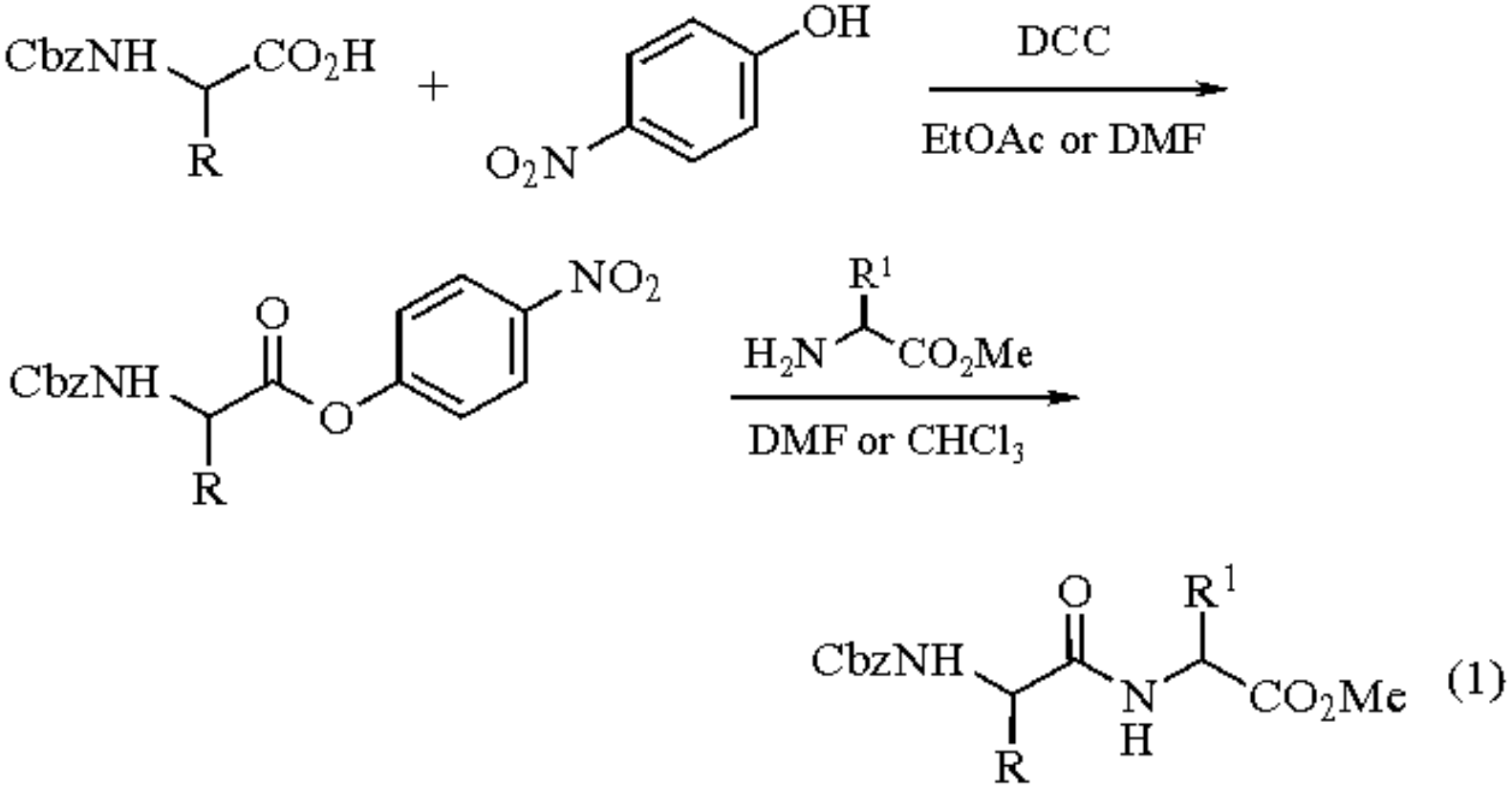

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1. Bodanszky, M.; Du Vigneaud, V. *JACS* **1959**, *81*, 5688; Bodanszky, M.; Meienhofer, J.; Du Vigneaud, V. *JACS* **1960**, *82*, 3195.
2. Bodanszky, M.; Bath, R. J. *CC* **1969**, 1259.

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o-Nitrophenyl Selenocyanate[1]

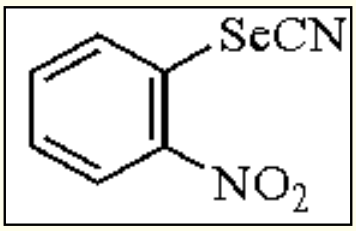

[51694-22-5] · $C_7H_4N_2O_2Se$ · *o*-Nitrophenyl Selenocyanate · (MW 227.09)

(reagent for alkene synthesis[2-4])

Physical Data: light brown crystals; mp 139-141 °C.

Solubility: sol common organic solvents such as dichloromethane, THF, DMF, and ethanol.

Form Supplied in: commercially available in 98% purity.

Preparative Method: obtained in 66% yield from *o*-nitroaniline by diazotization followed by treatment with ***Potassium Selenocyanate*** in buffer solution containing sodium acetate.[2,5]

Purification: recrystallization from ethanol.

Handling, Storage, and Precautions: highly toxic and irritant agent. Use in a fume hood.

Specific Features of the Reagent.

o-Nitrophenyl selenocyanate is used as an analog of ***Phenyl Selenocyanate*** and is a useful reagent for introducing an *o*-nitrophenylselenenyl group into organic molecules. Advantages of the reagent are: (1) the more facile oxidative elimination ability of the *o*-nitrophenylselenenyl group than that of a simple phenylselenenyl group (~24 times as fast) (eq 1);[2] and (2) the large steric effect of the nitro group at the *ortho* position which allows enantioselective oxidation of prochiral selenides (eq 2).[6] 4,4´-Dichlorodiphenyl diselenide is also a useful reagent for alkene synthesis because of its easy access and facile oxidative elimination.[2a] The yields in elimination reactions of phenyl selenoxides can be improved by a proper choice of reaction conditions.[2b]

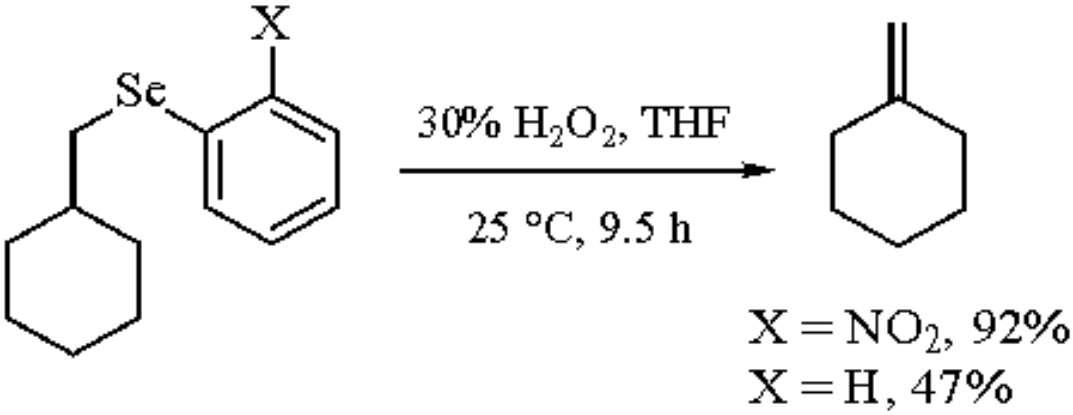

(1)

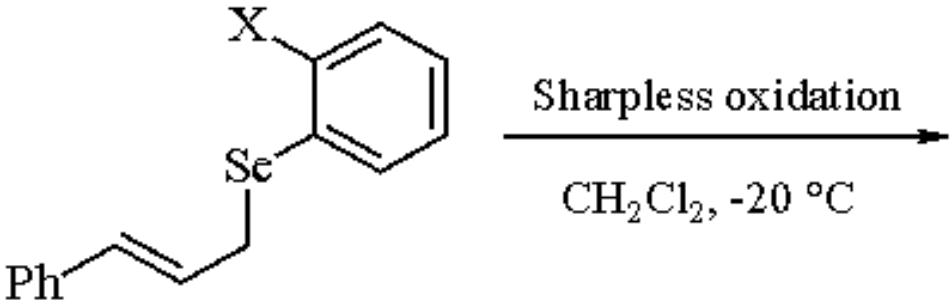

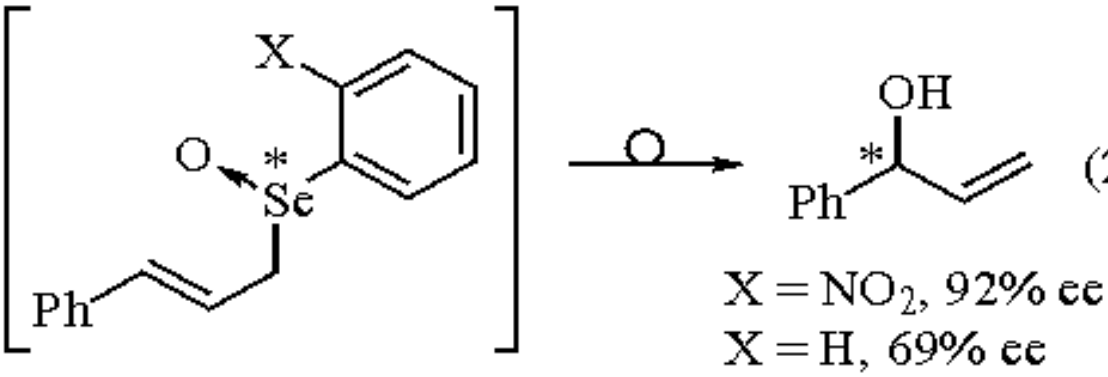

(2)

Alkene Synthesis.

Because of its excellent functional group selectivity and facile elimination ability, the reagent has been widely used for the conversion of primary alcohols into terminal alkenes in the synthesis of numerous natural products. In early applications by Grieco et al., primary alcohols were first transformed to the corresponding bromides or mesylates and then substituted with the *o*-nitrophenylselenolate anion, which was quantitatively generated by treatment of *o*-nitrophenyl selenocyanate or di-*o*-nitrophenyl diselenide with ***Sodium Borohydride***. The substitution products were finally subjected to oxidative rearrangement to afford terminal alkenes (eqs 3 and 4).[7,8]

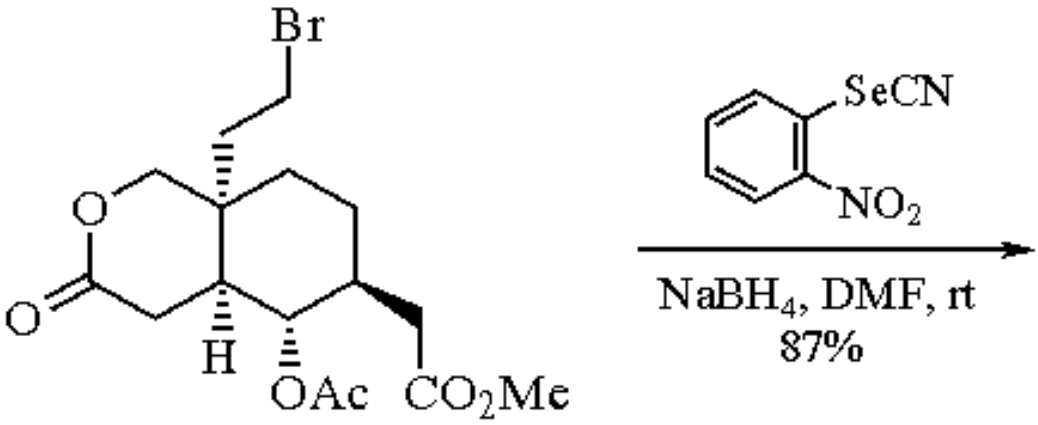
Br
O
O
H
OAc
CO2Me
SeCN
NO2
NaBH4, DMF, rt
87%

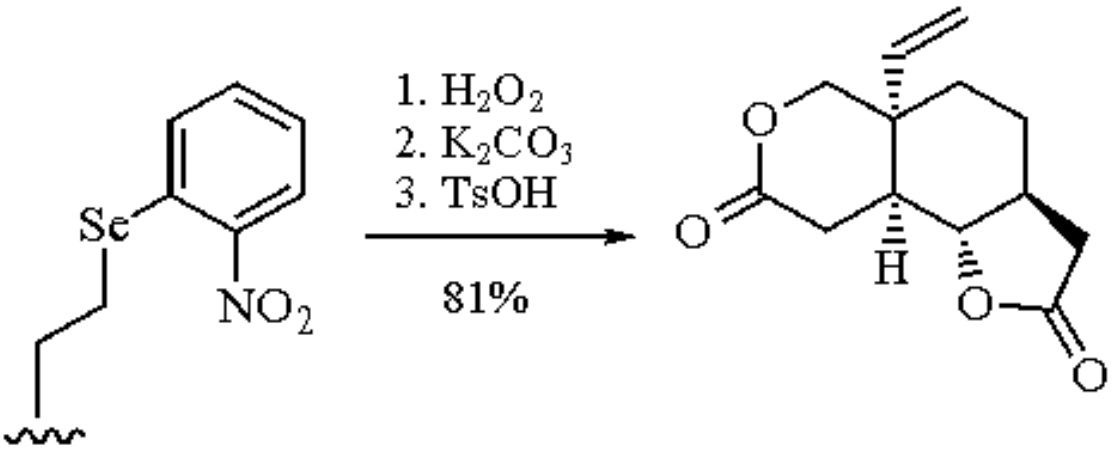
Se
NO2
1. H2O2
2. K2CO3
3. TsOH
81%
O
O
H
O
O

(3)

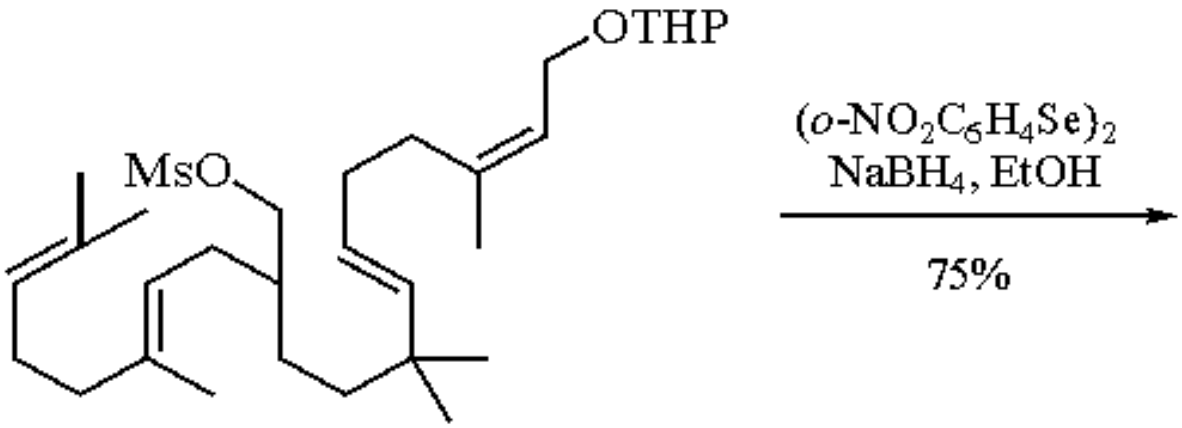
OTHP
MsO
(o-NO2C6H4Se)2
NaBH4, EtOH
75%

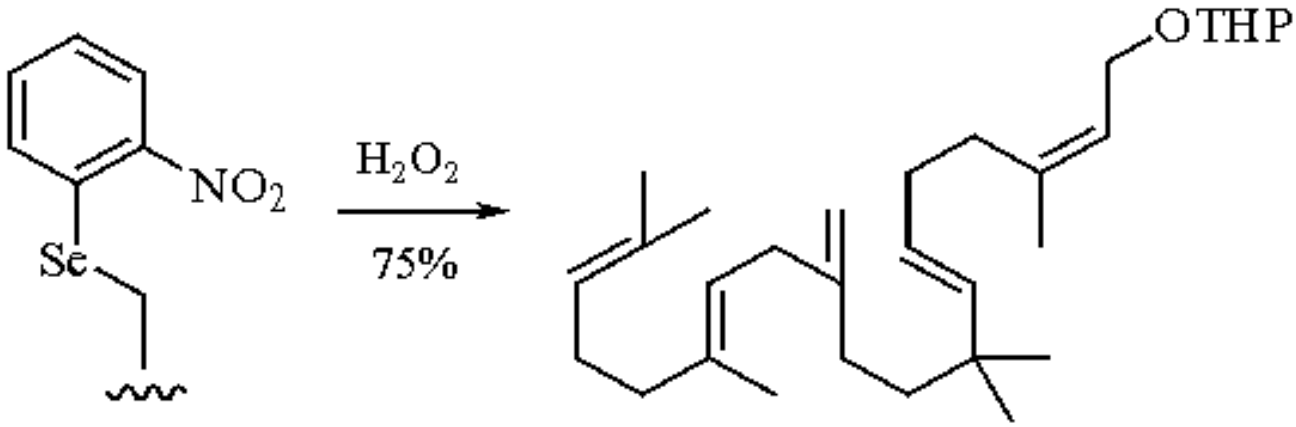
NO2
Se
H2O2
75%
OTHP

(4)

More useful methodology for the transformation of primary alcohols to terminal alkenes is the direct reaction with *o*-nitrophenyl selenocyanate in the presence of ***Tri-n-butylphosphine*** to produce the corresponding *o*-nitrophenyl selenides (eq 5),[3] followed by oxidative elimination. This methodology has been extensively employed in the stereoselective synthesis of (±)-antirhine (eq 6),[9] in the total synthesis of erythromycin (eq 7),[10] and in other syntheses.[11]

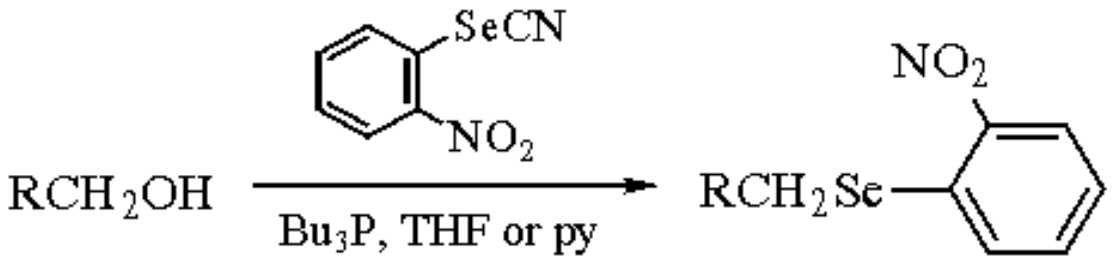

(5)

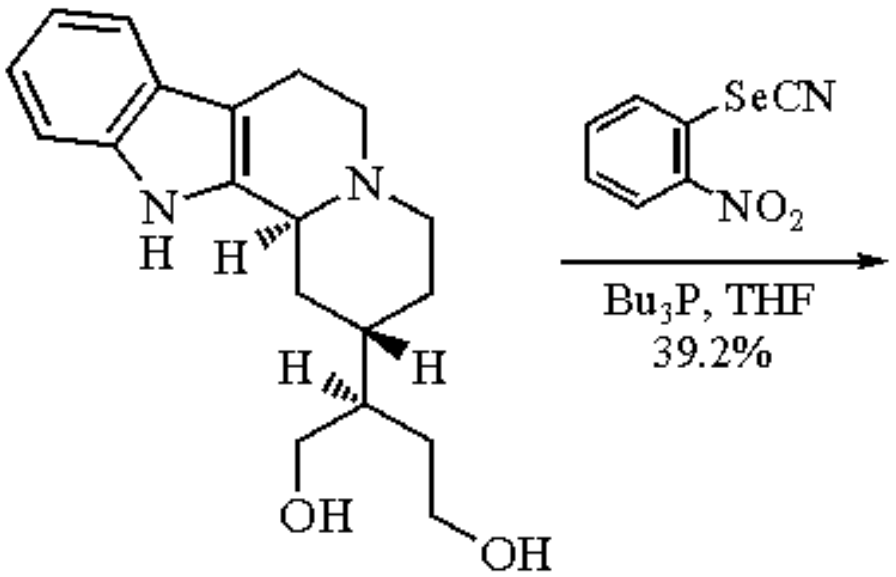

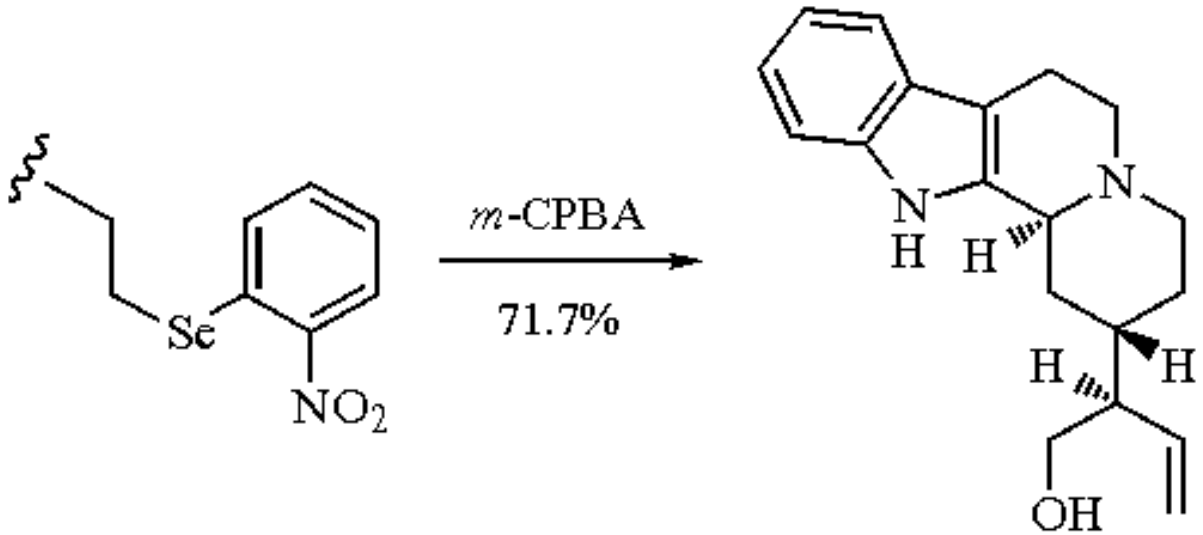

(6)

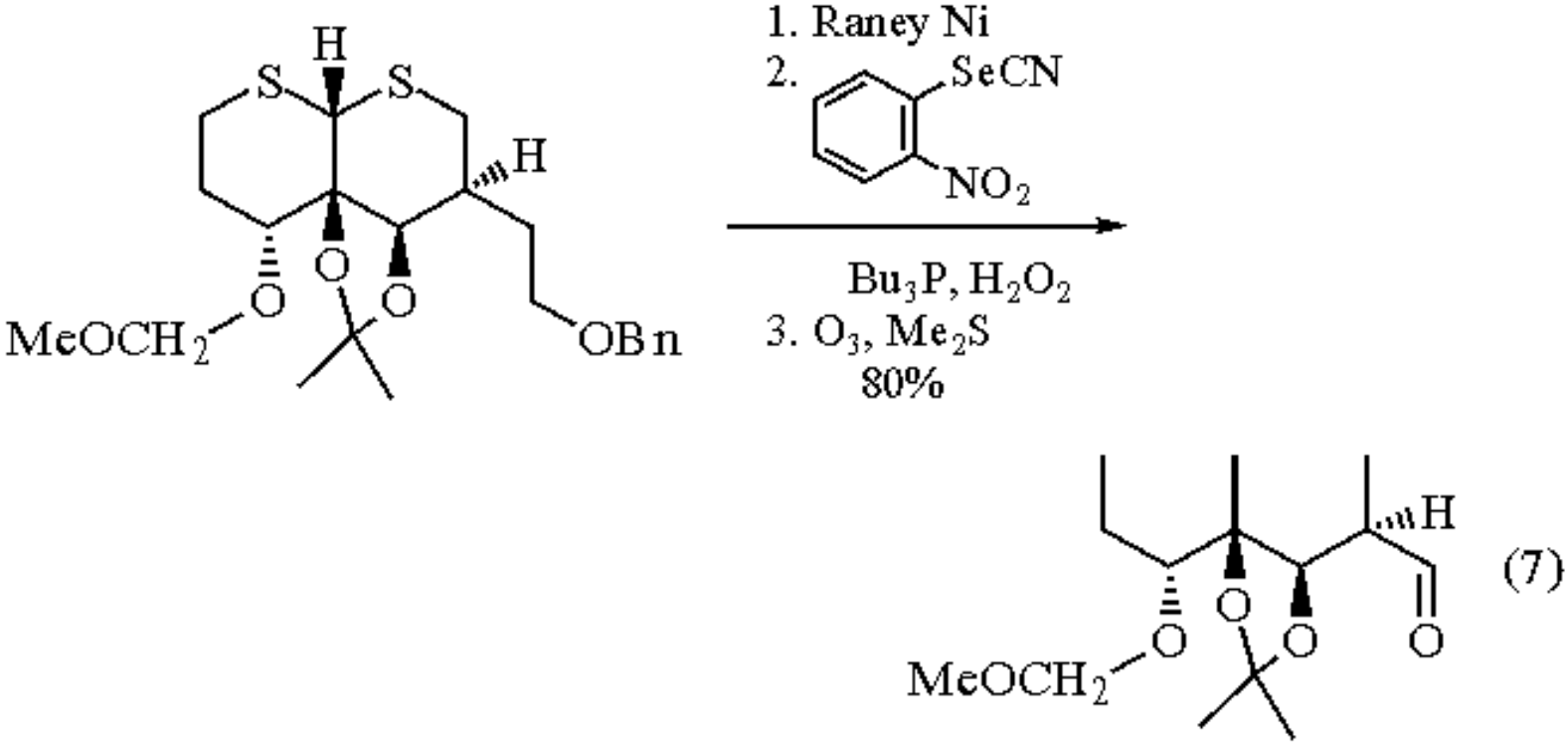

In the presence of tri-*n*-butylphosphine, *o*-nitrophenyl selenocyanate reacts with aldehydes to produce cyanoselenenylation adducts. Oxidation of the adducts with ***Hydrogen Peroxide*** gives α,β-unsaturated nitriles in high yields (eq 8).[4]

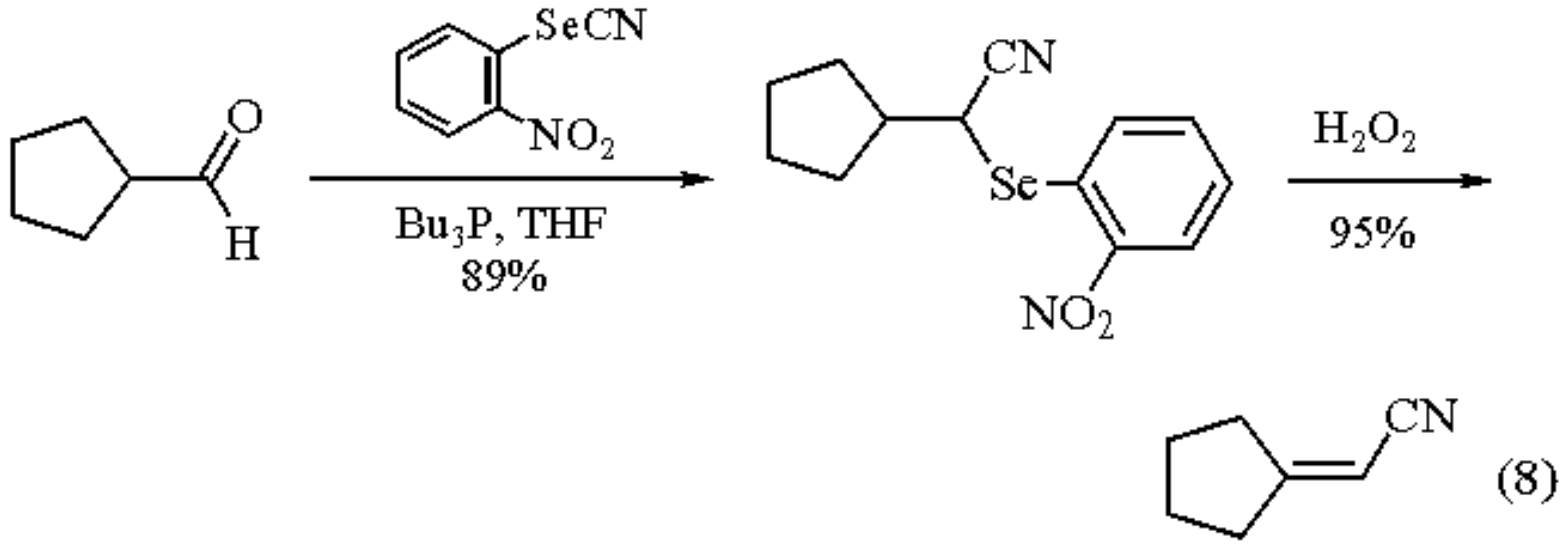

Rearrangement of Allylic Alcohols.

Oxidation of allylic selenides provides allylic alcohols via 2,3-sigmatropic rearrangement of the allylic selenoxides.[12] This rearrangement is useful for the conversion of primary allylic alcohols into the rearranged compounds (eq 9).[13]

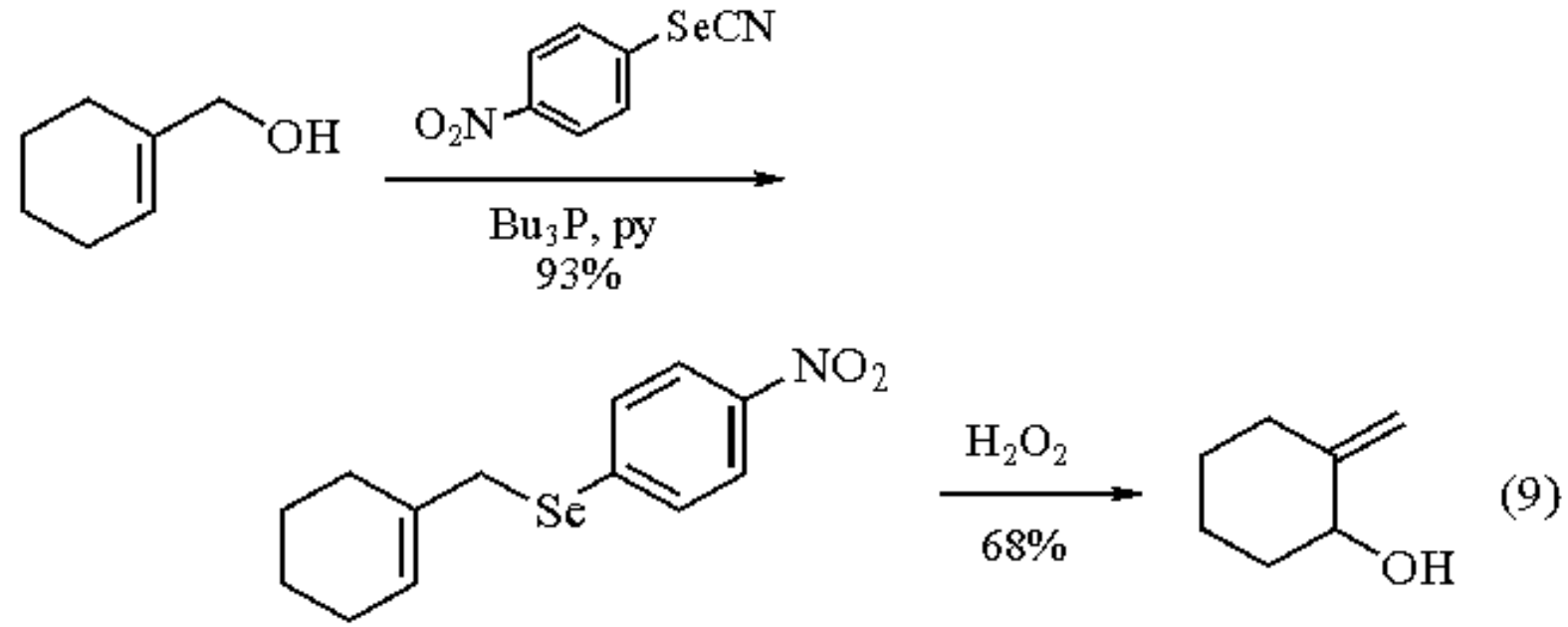

Ketone Synthesis.

o-Nitrophenylselenolate anions react with epoxides to form ring-opened adducts. These adducts can be easily transformed to ketones by oxidation with hydrogen peroxide (eq 10).[14] This methodology is useful for the one-step synthesis of deoxy-keto sugars.[14]

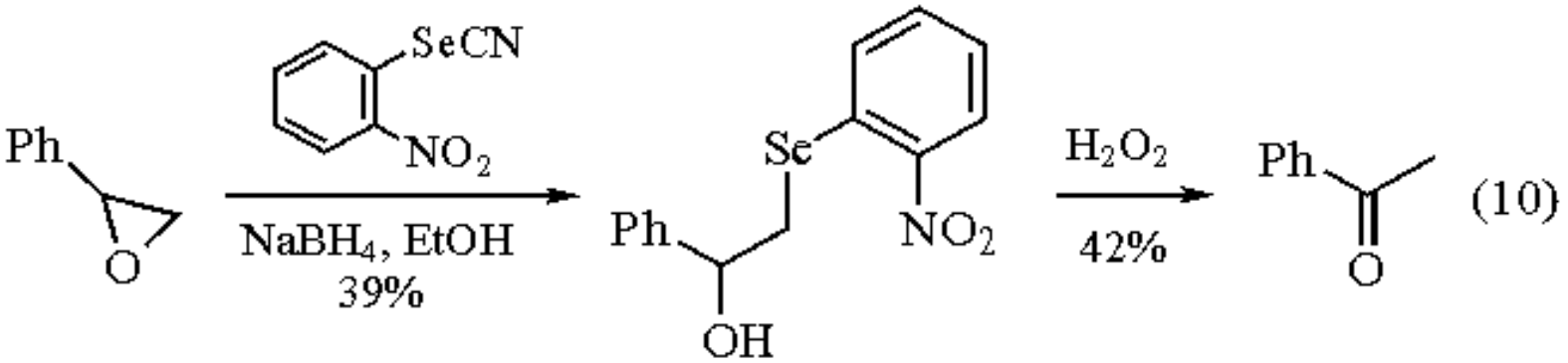

Synthesis of Selenol Esters.

Like phenyl selenocyanate, *o*-nitrophenyl selenocyanate reacts with carboxylic acids to give selenol esters in the presence of tri-*n*-butylphosphine (eq 11),[15] but the yield is normally modest.

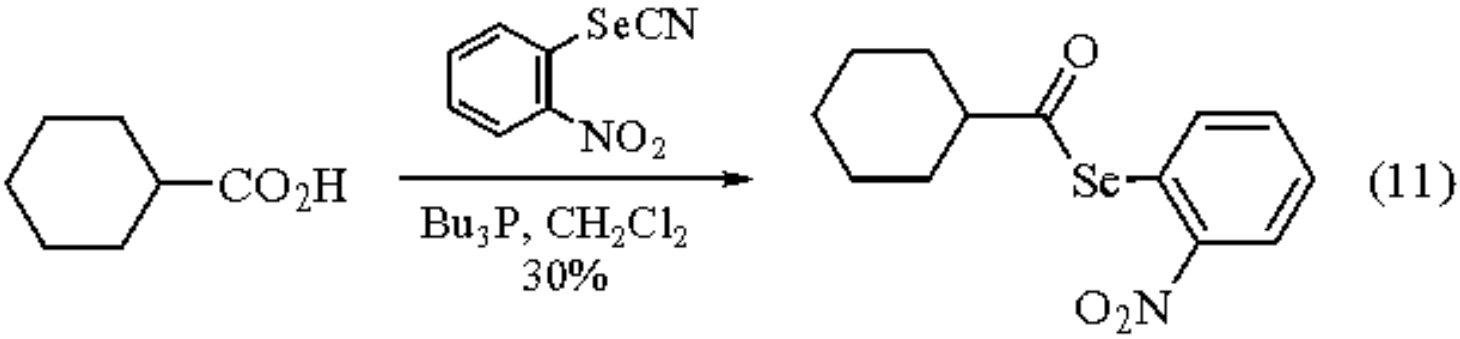

Related Reagents.

Diphenyl Diselenide; ***Phenyl Selenocyanate***.

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1. (a) Clive, D. L. J. *T* **1978**, *34*, 1049. (b) Reich, H. J. *ACR* **1979**, *12*, 22. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1984. (d) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S; Rappoport, Z., Eds.; Wiley: 1986; Vol. 1. (e) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (f) *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley: New York, 1987.
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14. Furuichi, K.; Yogai, S.; Miwa, T. *CC* **1980**, 66.
15. Grieco, P. A.; Yokoyama, Y.; Williams, E. *JOC* **1978**, *43*, 1283.

Michio Iwaoka & Shuji Tomoda

The University of Tokyo, Japan

1-Nitro-2-phenylsulfonylethylene[1]

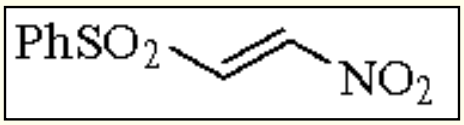

[101933-29-3] · $C_8H_7NO_4S$ · 1-Nitro-2-phenylsulfonylethylene · (MW 213.23)

(Michael acceptor;[3-5] acetylene equivalent in the Diels-Alder reaction[8,9])

Alternate Name: 1-phenylsulfonyl-2-nitroethylene.

Physical Data: mp 148-150 °C.

Solubility: sol THF, Et_2O, $CHCl_3$, CH_2Cl_2.

Analysis of Reagent Purity: IR 1160, 1350, 1550 cm^{-1}; NMR δ 7.50-7.96.

Preparative Method: by oxidation of ***1-Nitro-2-phenylthioethylene*** with ***m-Chloroperbenzoic Acid*** (2 equiv).[2]

Michael Acceptor.

Addition-elimination reactions of various nucleophiles to this reagent provide a useful method for the preparation of various 1-nitroalkenes. Polyfunctional organozinc and copper reagents react with this reagent to give polyfunctional 1-nitroalkenes. Organometallics bearing an ester (eq 1),[3] diene (eq 2),[4] or oxygen function (eq 3)[5] give terminal nitroalkenes substituted with these functional groups. Thus a precursor for an intramolecular Diels-Alder reaction and new allylic acetates bearing terminal nitroalkenes are readily prepared by this procedure.

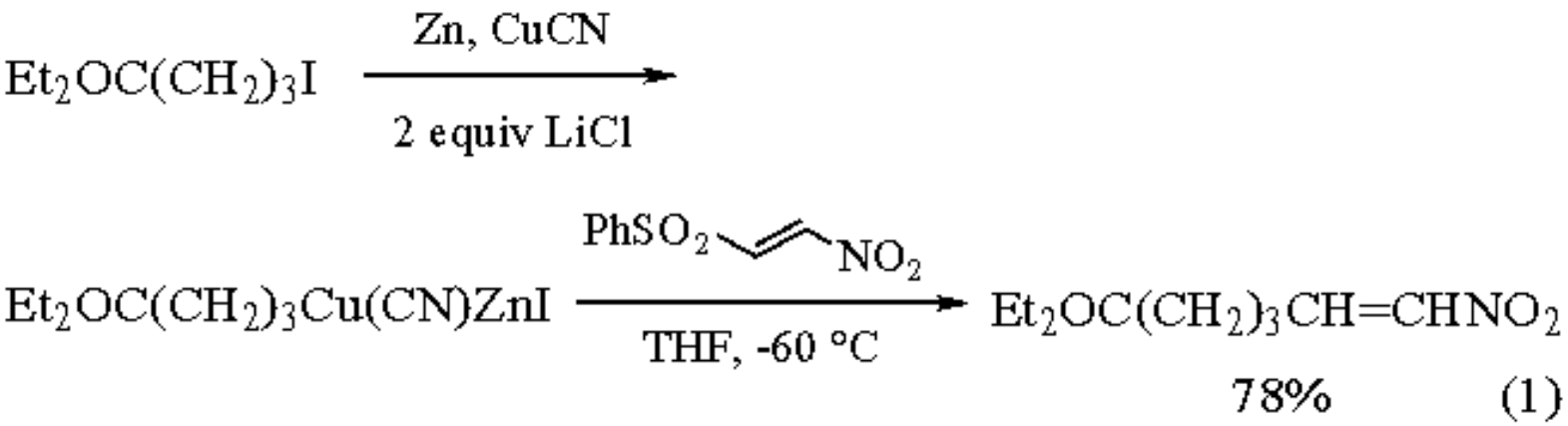

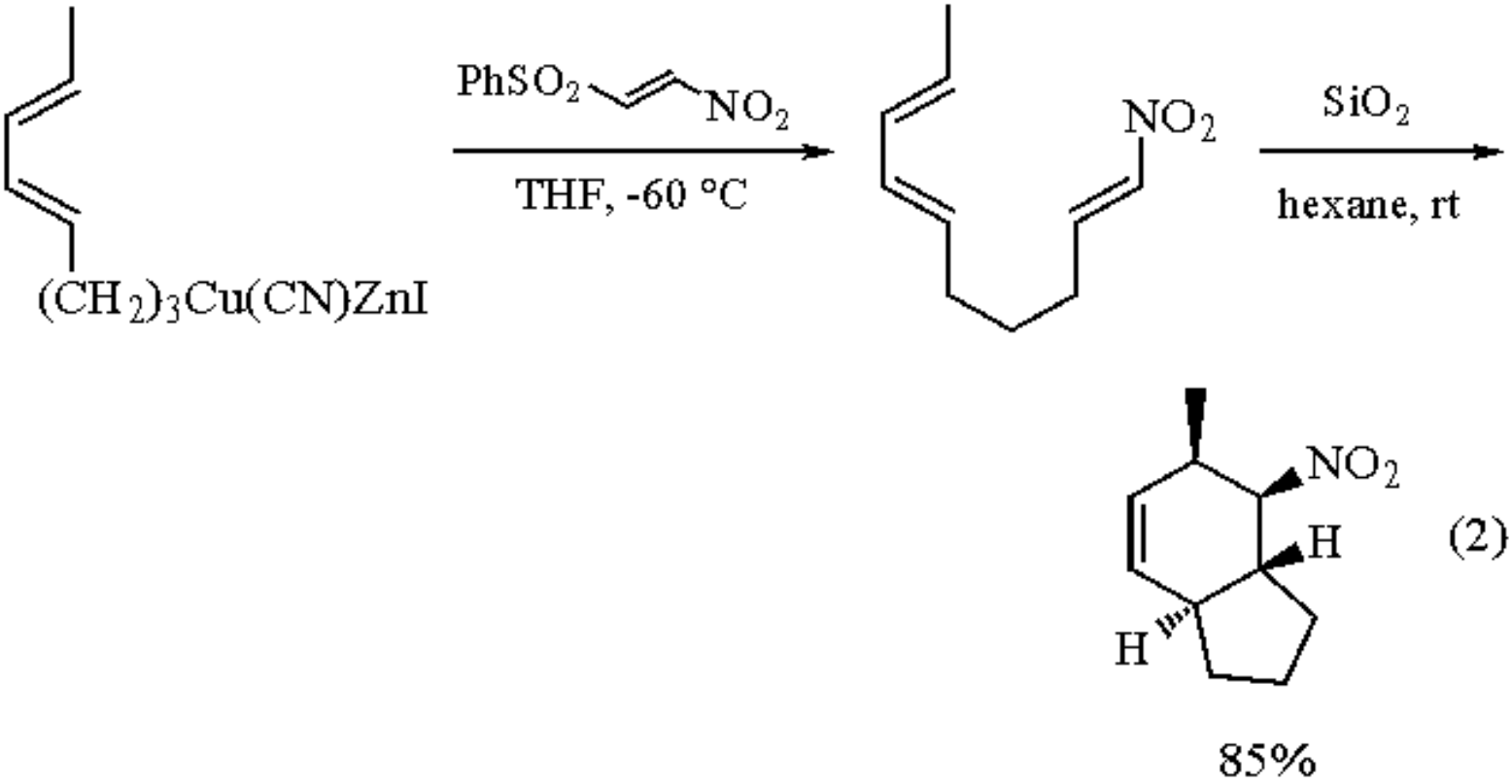

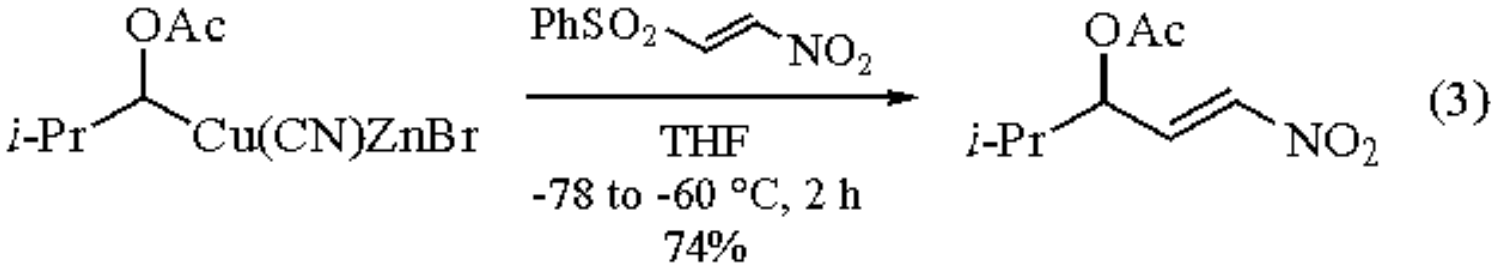

Acetylene Equivalent.

This reagent is an excellent dienophile in the Diels-Alder reaction and reacts with various dienes to give the adducts under mild conditions. Subsequent treatment of the resulting β-nitro sulfones with ***Tri-n-butylstannane*** results in the reductive elimination of the nitro and sulfonyl groups[6] to give 1,4-cyclohexadienes. Thus this reagent serves as a very reactive ***Acetylene*** equivalent,[7] and various dienes have been converted into 1,4-cyclohexadienes by this procedure (eqs 4 and 5).[8,9]

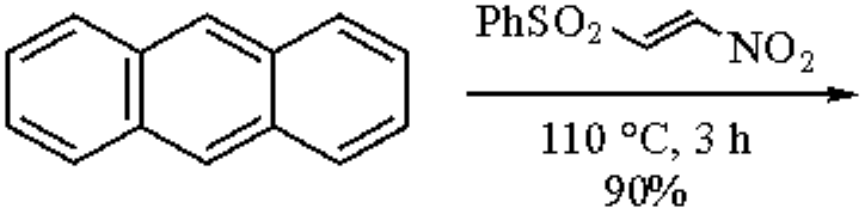

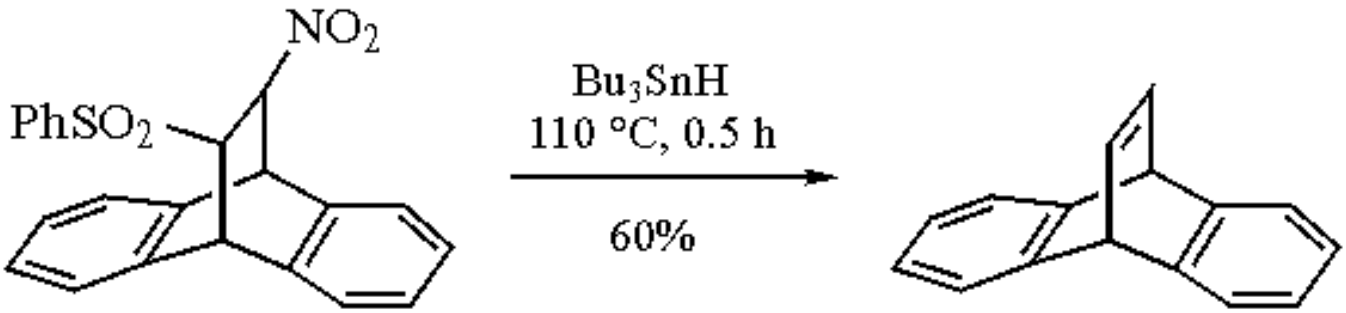

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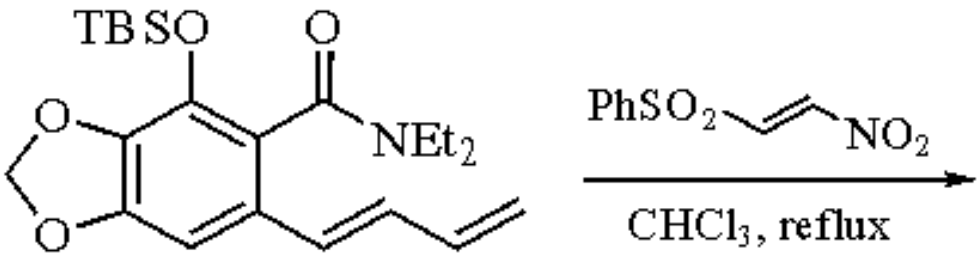

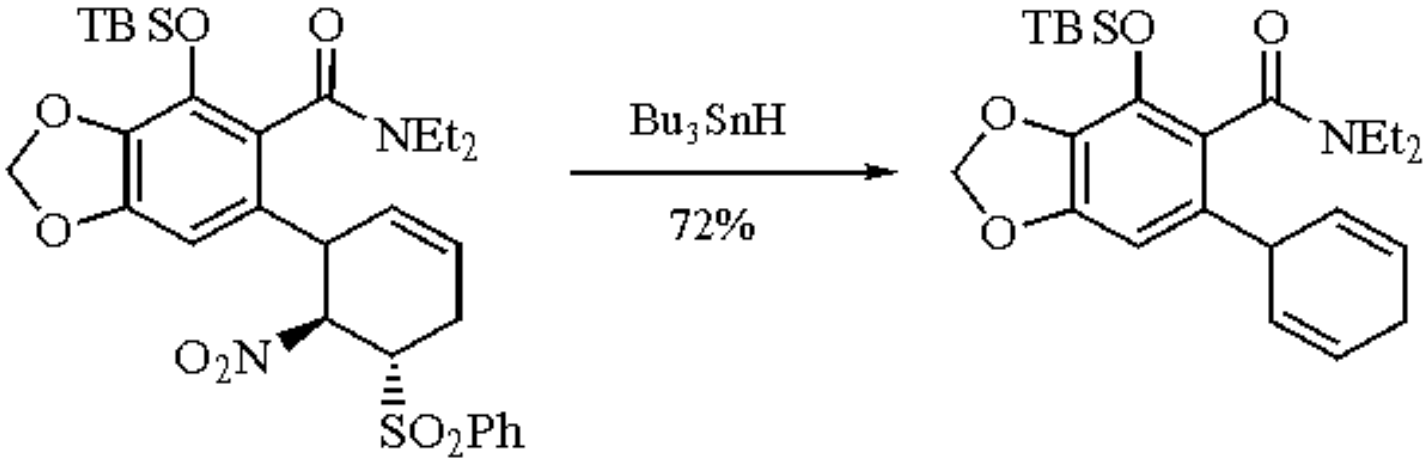

(5)

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1. (a) Ono, N.; Kaji, A. *S* **1986**, 693 (b) Ono, N. *Nitro Compounds : Recent Advances in Synthesis and Chemistry*; Feuer, H.; Nielsen, A. T., Eds.; VCH: New York, 1990; p 1.
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1-Nitro-2-phenylthioethylene[1]

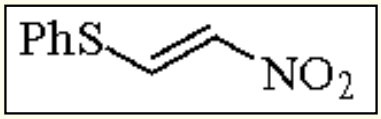

[101933-27-1] · $C_8H_7NO_2S$ · 1-Nitro-2-phenylthioethylene · (MW 181.23)

(Michael acceptor for the preparation of nitro enamines,[3,4] α-nitro aldehyde acetals,[5] and indolizines;[6] dienophile in the Diels-Alder reaction[3,7])

Alternate Name: 1-phenylthio-2-nitroethylene.

Solubility: sol EtOH, acetone, THF, Et_2O, $CHCl_3$, CH_2Cl_2.

Analysis of Reagent Purity: NMR δ 6.66 (d, *J* = 12 Hz, 1H), 7.24-7.56 (m, 5H), 8.18 (d, *J* = 12 Hz, 1H).

Preparative Method: from 2-nitroethanol[2] by the sequence shown in eq 1,[3] which can be extended into a general synthesis of β-phenylthio nitroalkenes.[3]

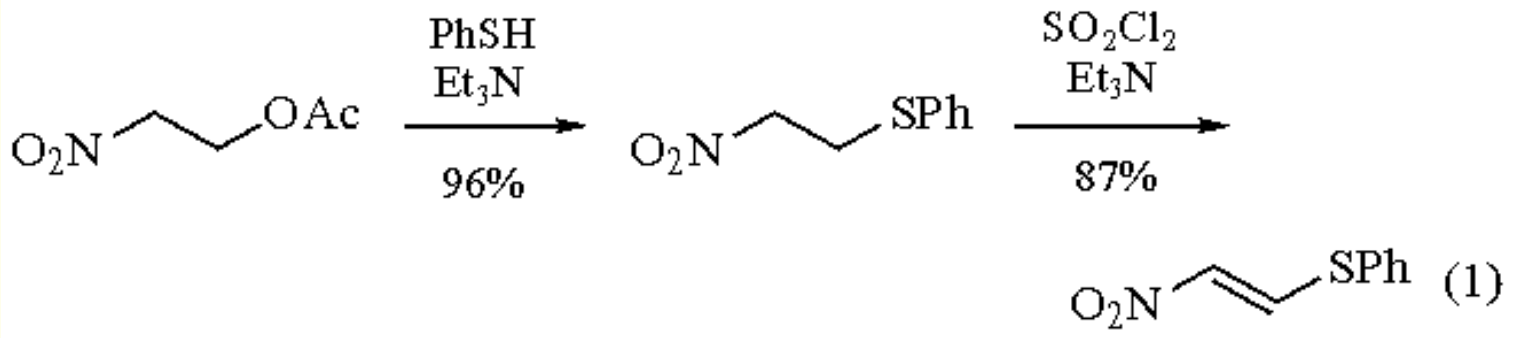

Michael Acceptor.

Electron-deficient alkenes substituted with nitro and phenylthio groups are useful reagents for the preparation of 1-nitroalkenes via the addition-elimination sequence. The reaction with various amines affords a general method for the synthesis of nitro enamines (eq 2).[3,4] However, the reaction with alkoxides does not give 1-alkoxynitroethylenes, but gives 2,2-dialkoxynitroethanes; this affords a useful method for the synthesis of α-nitro aldehyde acetals (eq 3).[5]

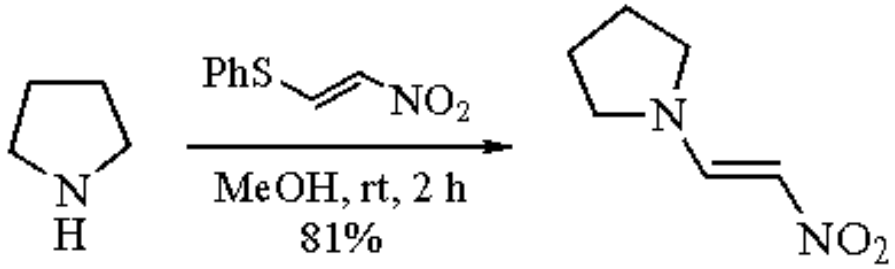

(2)

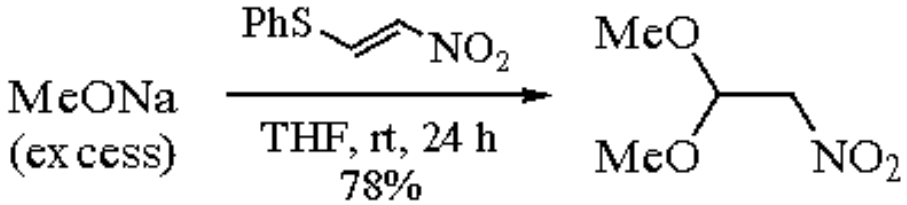

(3)

This reagent reacts with the pyridinium salts in the presence of ***Triethylamine*** to give the indolizine (eq 4)[6] via the azomethine ylide.

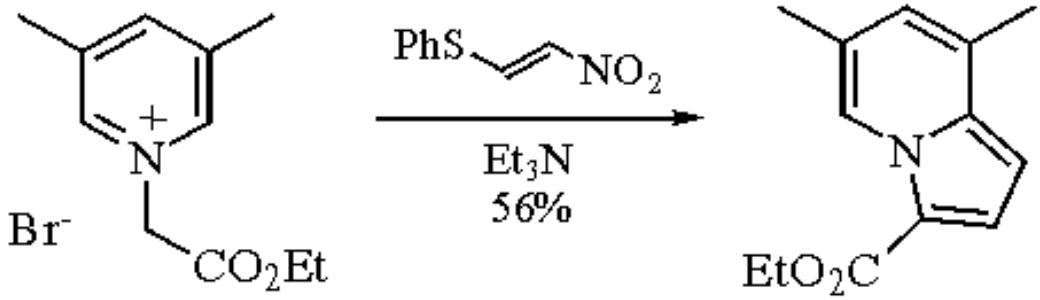

(4)

Dienophile.

Although this reagent undergoes the Diels-Alder reaction with reactive dienes (eq 5),[3] its reactivity is low compared to that of the corresponding sulfoxide and sulfone.

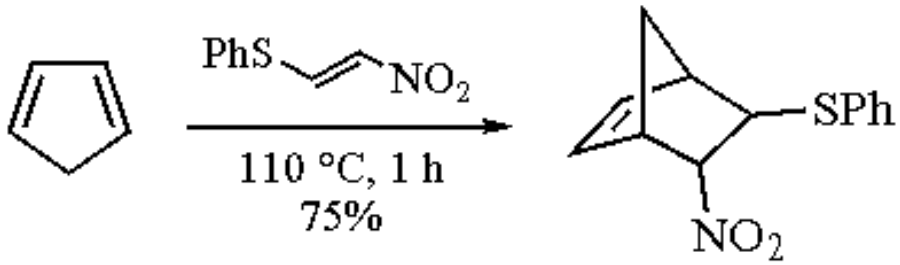

(5)

Oxidation of this reagent with ***m-Chloroperbenzoic Acid*** gives 1-phenylsulfinyl-2-nitroethylene, which is an excellent dienophile and acts as a nitroacetylene equivalent in the Diels-Alder reaction (eq 6).[7]

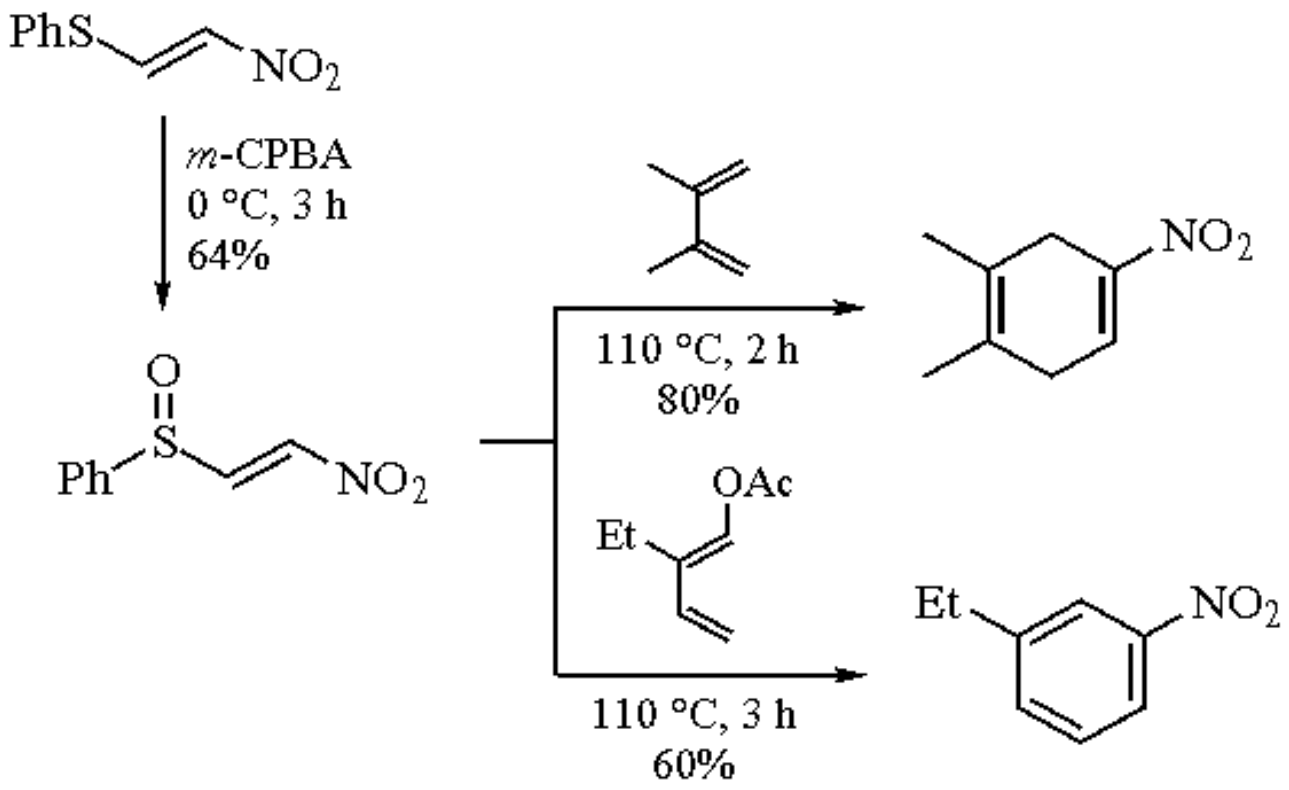

(6)

Related Reagents.

1-Nitro-2-phenylsulfonylethylene.

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1. (a) Ono, N.; Kaji, A. *S* **1986**, 693. (b) Ono, N. *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H.; Nielsen, A. T., Eds; VCH: New York, 1990; p 1.
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7. (a) Ono, N.; Kamimura, A.; Kaji, A. *JOC* **1988**, *53*, 251. (b) Jung, M. E.; Grove, D. *CC* **1987**, 753.

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p-Nitrophenyl Trifluoroacetate

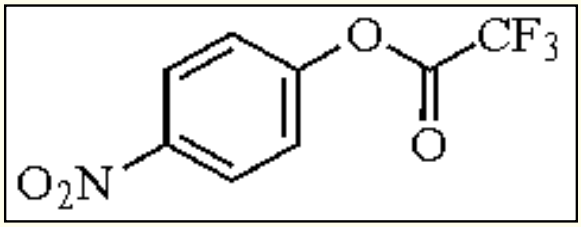

[658-78-6] · $C_8H_4F_3NO_4$ · *p*-Nitrophenyl Trifluoroacetate · (MW 235.13)

(preparation of active esters for peptide synthesis[1,2])

Physical Data: mp 36-38 °C (sublimed material).

Form Supplied in: commercially available solid.

Preparative Method: prepared in quantitative yield by heating at reflux a mixture of ***p-Nitrophenol*** and ***Trifluoroacetic Anhydride*** in benzene. Evaporation gives crude, crystalline material (mp 37-39 °C) of sufficient purity for use in peptide synthesis.[1]

Purification: by vacuum sublimation.

Handling, Storage, and Precautions: water sensitive; should be stored in a tightly closed bottle.

Preparation of Active Esters for Peptide Synthesis.

p-Nitrophenyl trifluoroacetate reacts readily with *N*-Cbz protected amino acids in pyridine to give the corresponding *p*-nitrophenyl esters (eq 1),[1,2] without racemization; these activated esters can be employed in peptide synthesis (see also ***p-Nitrophenol***). Protection of side-chain functionality such as hydroxyl or amino groups is necessary in order to avoid side reactions. The only coproduct, trifluoroacetic acid, is water soluble. Isolation of the active ester is not necessary; direct addition of an amino component and 2 equiv of ***Triethylamine*** allows amide formation in the same reaction vessel as active ester formation.[2] This procedure is particularly useful when the activated ester will not crystallize. Formation of the active esters of *N*-Cbz protected peptides by this method is slower and requires heating or longer reaction times. Presumably for this reason, complete racemization is observed in the Anderson test (coupling of CbzGly-L-Phe to Gly-OEt).[3]

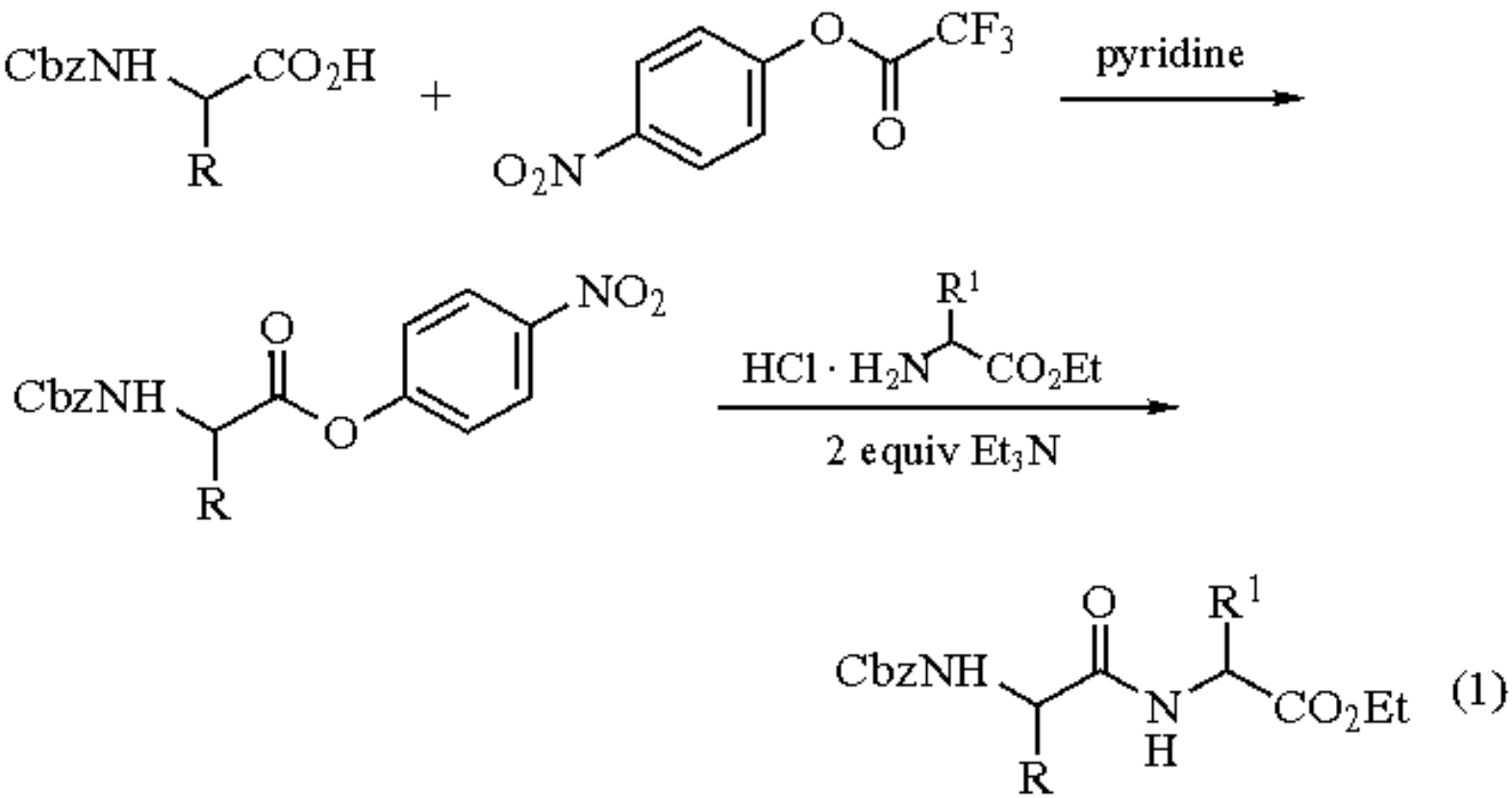

1. Sakakibara, S.; Inukai, N. *BCJ* **1964**, *37*, 1231.
2. Sakakibara, S.; Inukai, N. *BCJ* **1965**, *38*, 1979.
3. Sakakibara, S.; Inukai, N. *BCJ* **1966**, *39*, 1567.

Alan Armstrong

University of Bath, UK

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2-Nitro-3-pivaloyloxypropene[1]

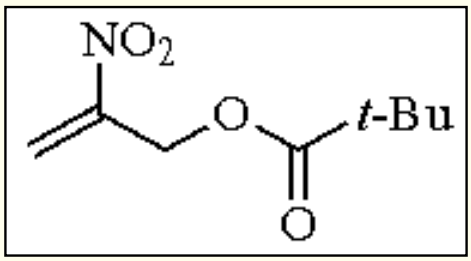

[78551-14-1] · $C_8H_{13}NO_4$ · 2-Nitro-3-pivaloyloxypropene · (MW 187.22)

(multicoupling reagent; reacts stepwise with two different nucleophiles[1])

Alternate Name: NPP.

Physical Data: mp 18 °C; bp 40-45 °C/0.01 mmHg.

Solubility: sol all organic solvents; decomposes in pyridine and slowly in protic solvents.

Preparative Method: prepared in four steps from ***Formaldehyde***, ***Nitromethane***, and pivaloyl chloride (ca. 25% overall yield at a 0.7 mol scale).[1]

Handling, Storage, and Precautions: can be stored six months at -10 °C without decomposition. Use in a fume hood.

Selective Multicoupling Reagent.

2-Nitro-3-pivaloyloxypropene (NPP) is an exceptionally reactive nitroalkene, since both the nitro group and the allylic pivaloyloxy group contribute to enhance the acceptor properties of the double bond. It reacts under very mild conditions with a broad range of nucleophiles producing polyfunctional nitroalkenes which under the reaction conditions do not react further with the nucleophile added (eq 1).[1-3] The resulting nitroalkenes can react with a different second nucleophile, providing highly functionalized nitroalkanes (eq 2).[3] They also can be converted into ketones by a Nef reaction (eq 3)[3] or reduced to amines.[3] NPP readily undergoes Diels-Alder reactions with various dienes; after an elimination reaction, cyclic enol pivalates are obtained (eqs 4 and 5).[4] The related reagent 2-nitro-3-acetoxypropene can also be prepared. It reacts selectively with the functionalized zinc-copper reagents RCu(CN)ZnI (eq 6).[5]

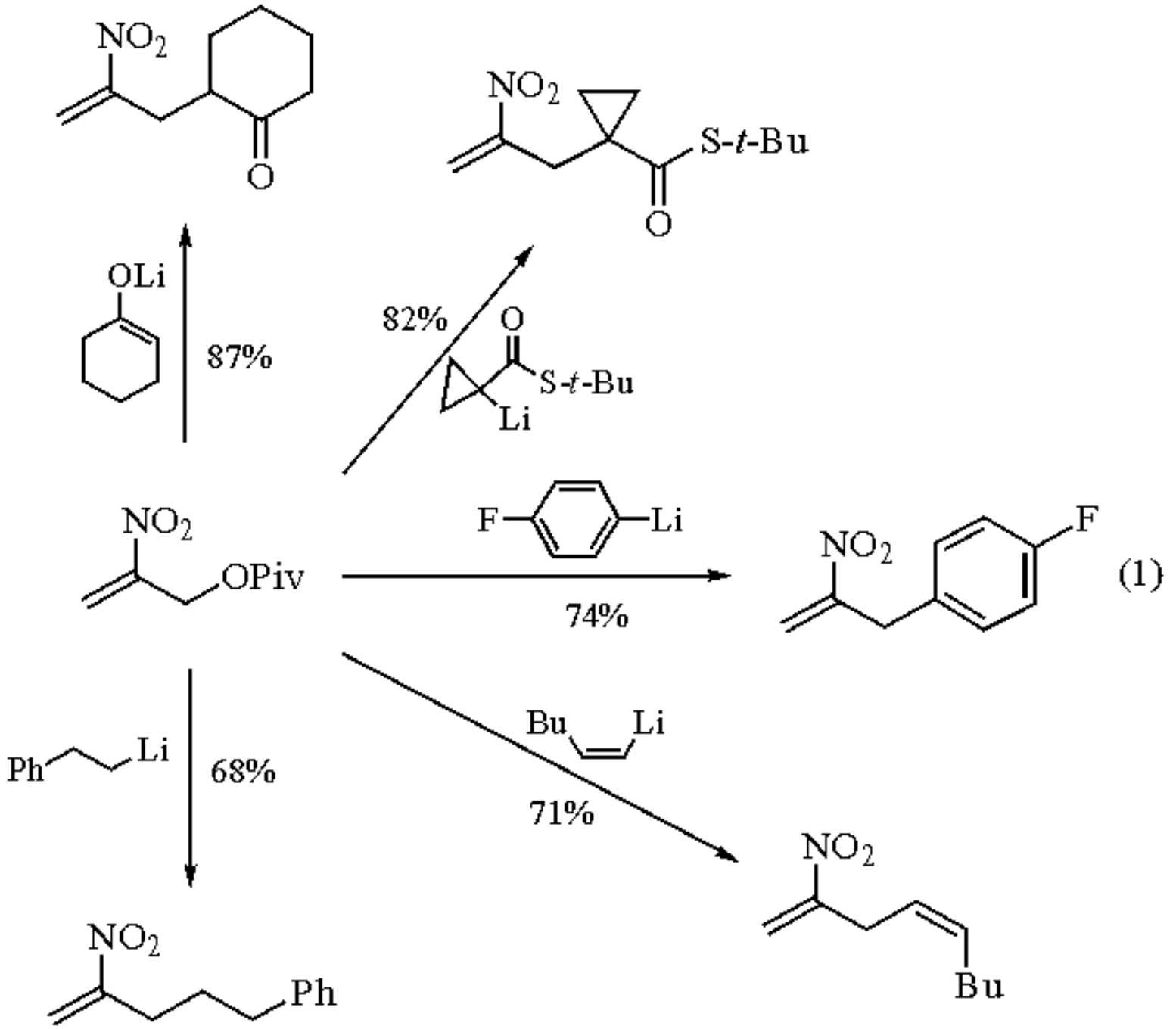
NO2
O
NO2
S-t-Bu
O
OLi
87%
82%
O
S-t-Bu
Li
NO2
OPiv
F
Li
74%
NO2
F
(1)
Ph
Li
68%
Bu
Li
71%
NO2
Bu
NO2
Ph

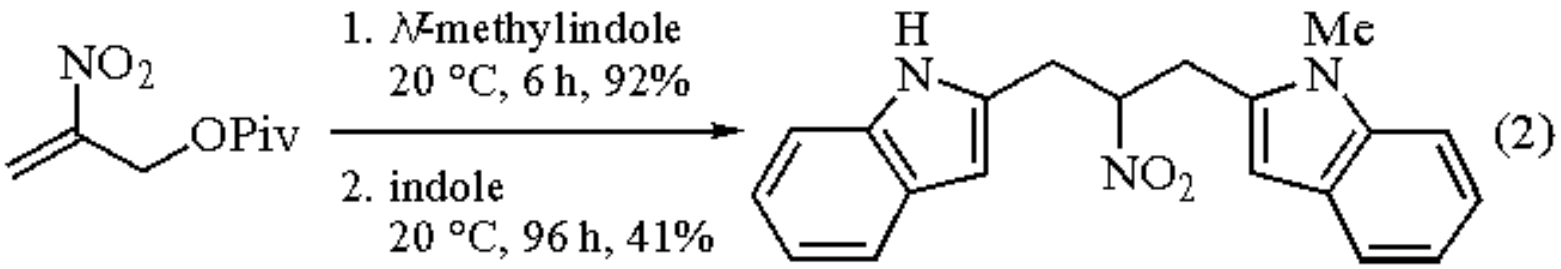
NO2
OPiv
1. N-methylindole
20 °C, 6 h, 92%
2. indole
20 °C, 96 h, 41%
H
N
Me
N
NO2
(2)

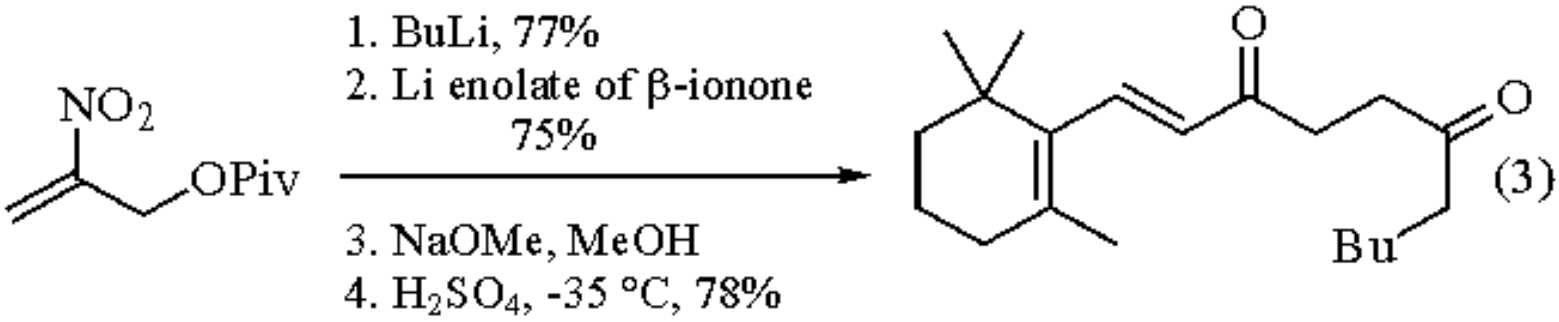

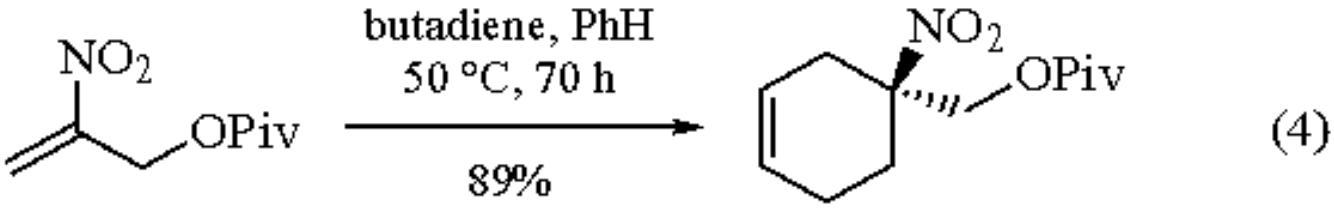

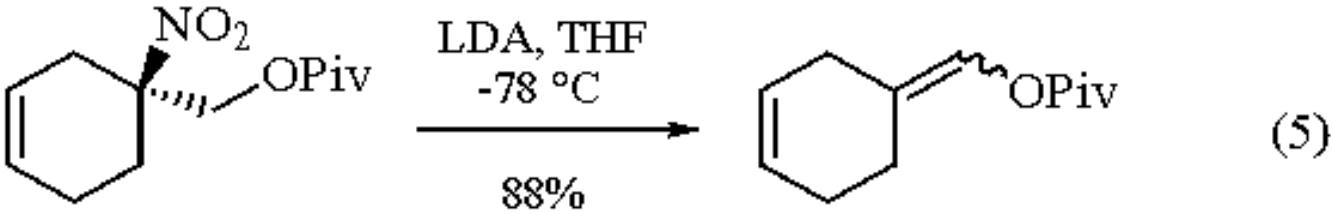

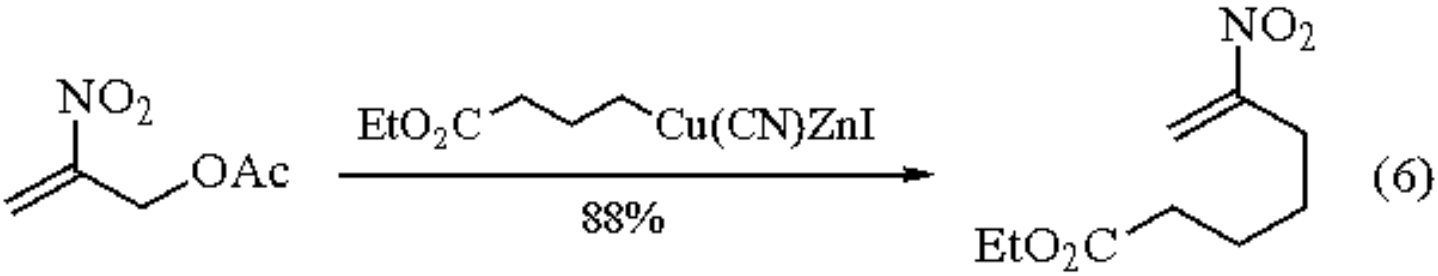

Substituted NPP Reagents.

A wide range of substituted NPP reagents can be prepared regio- and enantioselectively.[6,7] They display the same reactivity pattern (eqs 7 and 8)[7] and can be used for performing highly diastereoselective cyclizations with chiral enamines (eq 9)[8,9] or β-enamino esters (eq 10).[10]

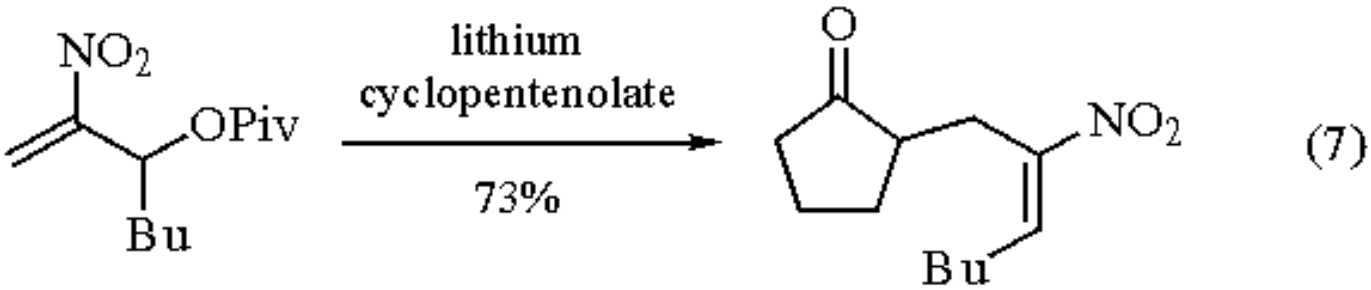

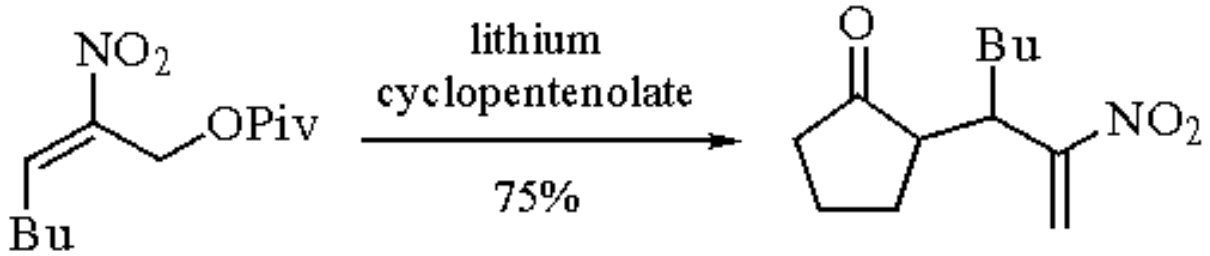

(8)

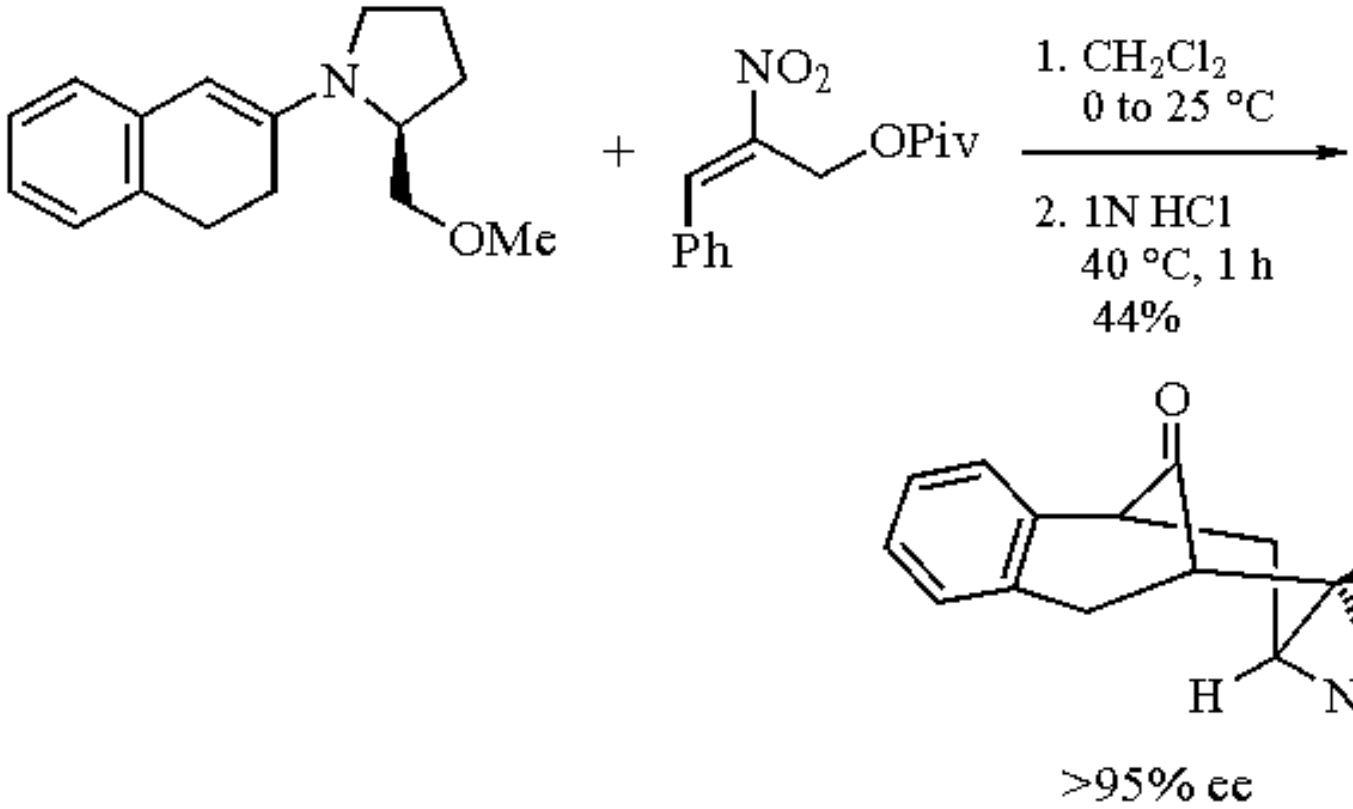

(9)

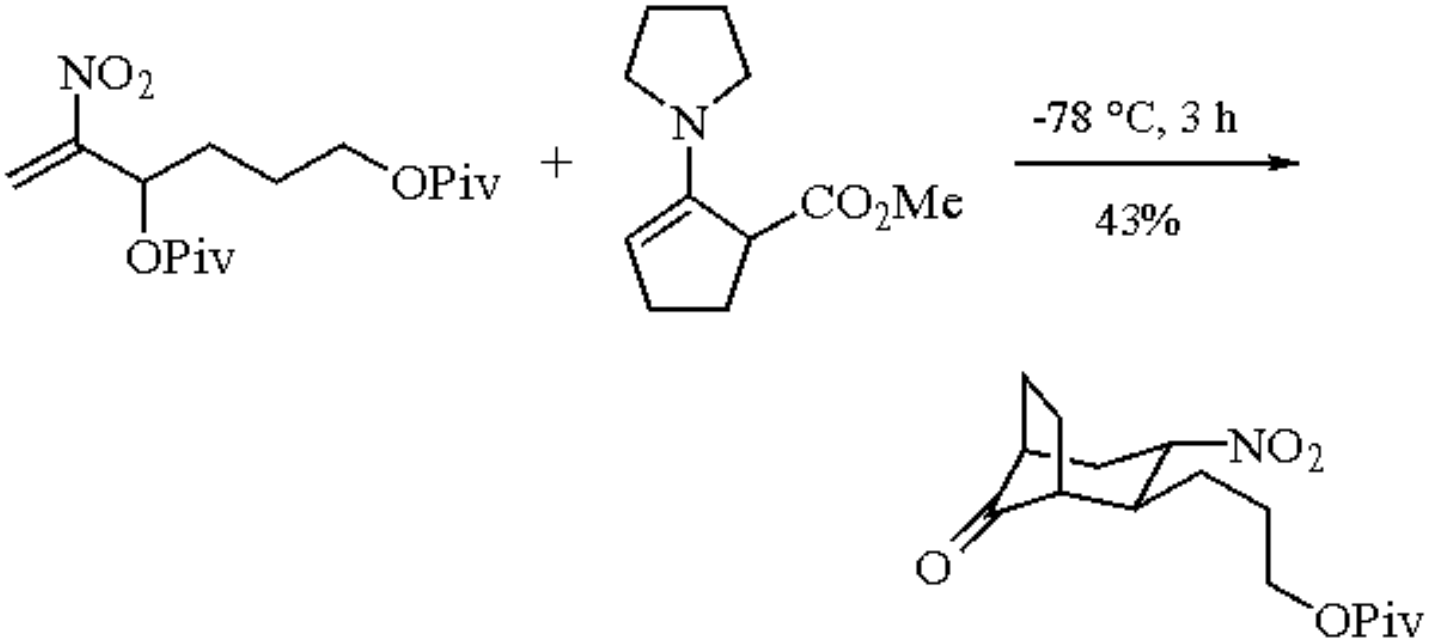

(10)

Interestingly, using enzymatic methods, the preparation of enantiomerically pure NPP derivatives becomes

possible.[11,12] These chiral reagents have been used successfully for performing the above-mentioned [3 + 3] carbocyclization.[9] The NPP reagents demonstrate well the synthetic utility of multicoupling building blocks in organic synthesis.[13,14]

---

1. Seebach, D.; Knochel, P. *HCA* **1984**, *67*, 261.
2. Knochel, P.; Seebach, D. *NJC* **1981**, *5*, 75.
3. Knochel, P.; Seebach, D. *TL* **1981**, *22*, 3223.
4. Knochel, P. PhD Thesis, ETH Zürich 1982, No. 7170.
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2-Nitropropane[1]

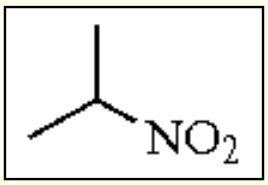

[79-46-9] · $C_3H_7NO_2$ · 2-Nitropropane · (MW 89.11)

(as nitronate, oxidant for allyl and benzyl halides;[2] acyl anion equivalent of acetone, reacts with electrophiles;[3] reactant in electron-transfer reactions;[4] isopropylidene equivalent in cyclopropanations[5])

Physical Data: mp -91 °C; bp 120 °C; *d* 0.988 g cm^{-3}.

Solubility: 1.7 g wt % in H_2O at 25 °C; sol ethanol and ether at 20 °C.

Form Supplied in: liquid; widely available. *Drying:* use calcium chloride, calcium sulfate, or magnesium sulfate.

Handling, Storage, and Precautions: flammable; avoid contact with base; cancer suspect agent; dry nitronate salts can be explosive; bases such as NaOH, TEA, DBU, TMG, NaH, or LDA can be used to deprotonate 2-nitropropane (pK_a = 7.67) to give the ambident nucleophile 2-nitropropane nitronate, which is the reactive form of the reagent. Use in a fume hood.

Oxidizing Agent.

Primary benzylic halides,[2] including heterocyclic halides,[6] are converted to aldehydes by means of 2-nitropropane-***Sodium Ethoxide*** (eq 1).

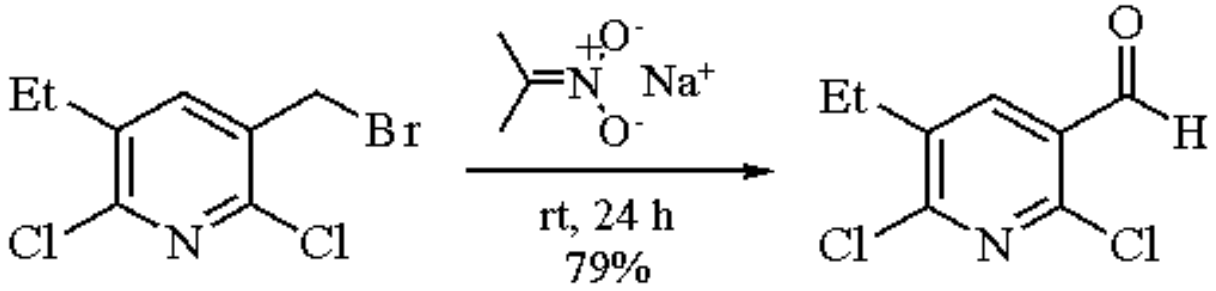

(1)

Secondary benzylic halides are not oxidized, but secondary allyl halides are oxidized regioselectively and

stereoselectively to α,β-unsaturated aldehydes with sodium 2-nitropropane nitronate in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** (eq 2).[7]

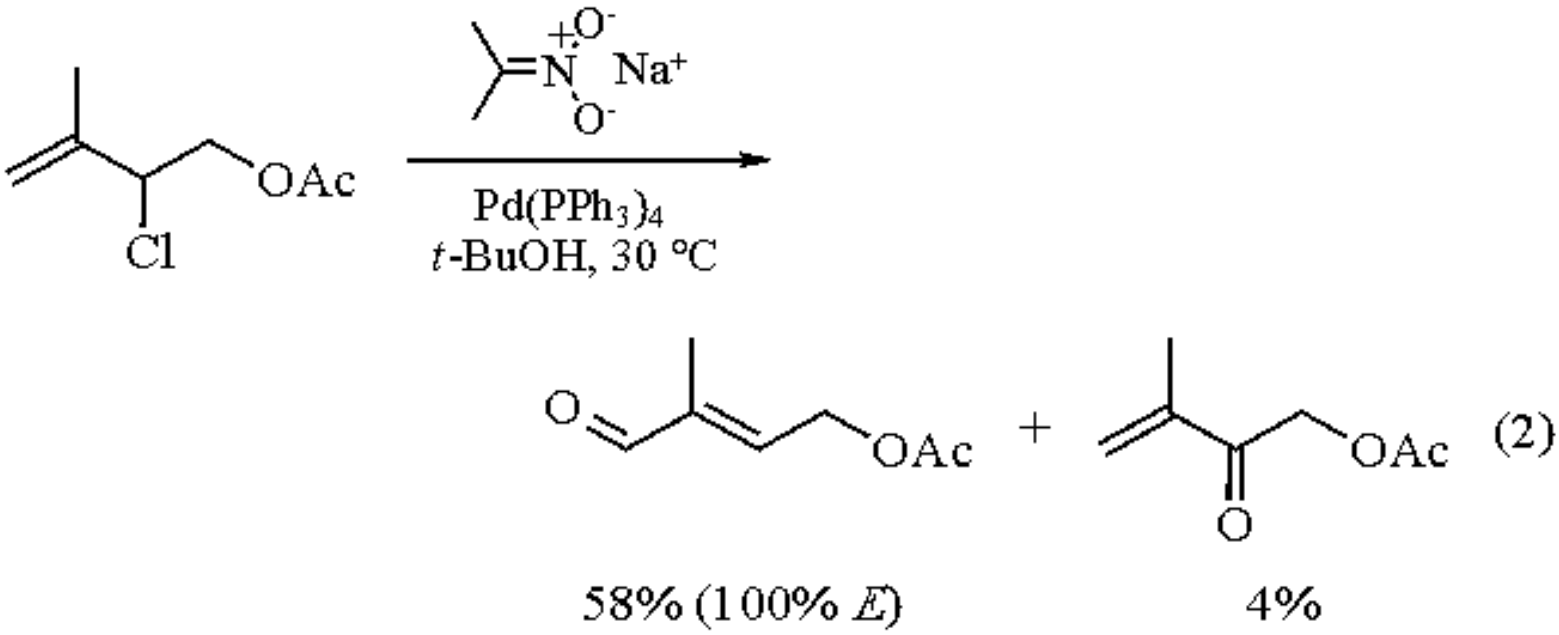

C-Allylation.

Unlike secondary allyl halides, which alkylate the oxygen atoms of the nitronate of 2-nitropropane, primary allyl alcohols, acetates, and phenyl ethers alkylate the carbon atom, leading to *C*-allylated 2-nitropropanes (eq 3).[8] Dichlorobis(triphenylphosphine)palladium(II) with 2 additional equiv of ***Triphenylphosphine*** is used as catalyst.

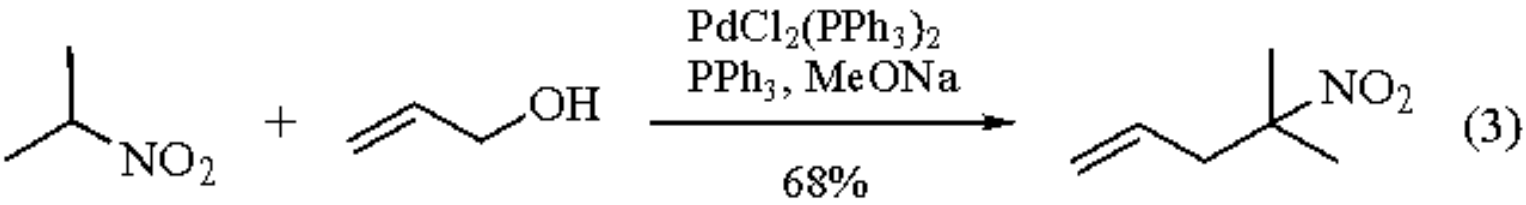

C-Alkylation.

A variety of alkylating reagents, including *o*- and *p*-nitrobenzyl chlorides,[3] *N*-substituted pyridinium salts,[9] hypervalent iodofluoroalkanes,[10] and organomercury compounds,[11] can be used to alkylate the potassium salt of 2-nitropropane (eq 4).

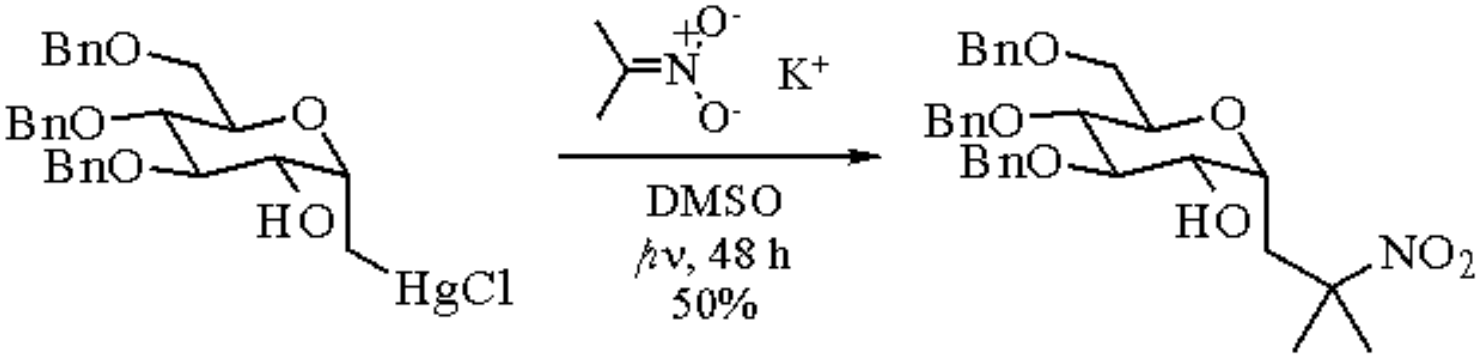

(4)

Conjugate Addition.

The nitronate salt of 2-nitropropane adds to electron-deficient alkenes (Michael reaction) and with subsequent radical denitration serves as an isopropyl anion equivalent (eq 5).[12]

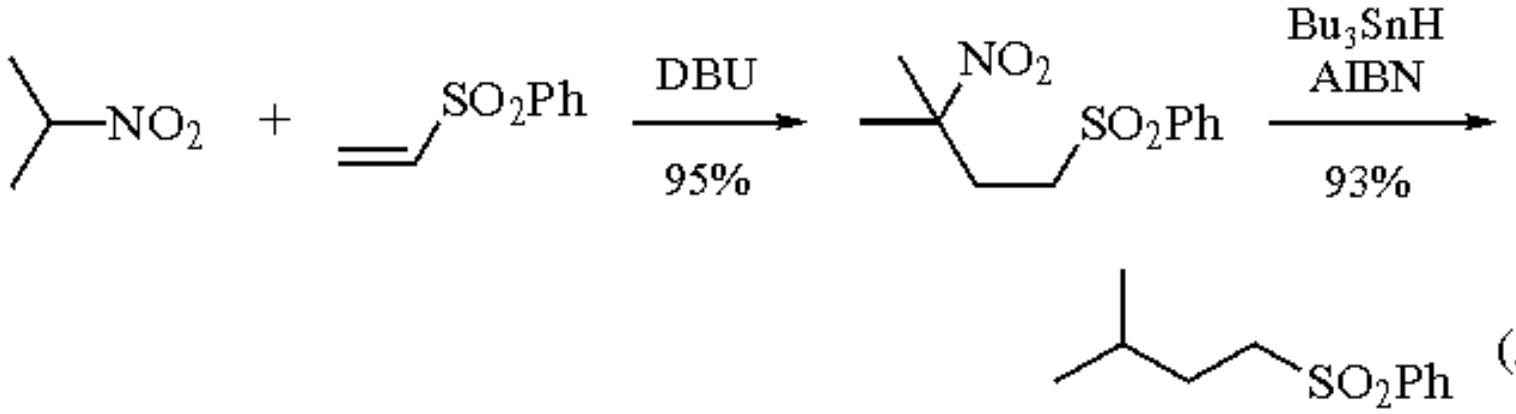

(5)

Synthesis of 1,1-Dimethylethylenes.

The nitronate salt of 2-nitropropane reacts with geminal dinitroalkanes, resulting in vicinal dinitroalkanes[13a] which can be converted to tetrasubstituted alkenes by reduction (eq 6).[13b]

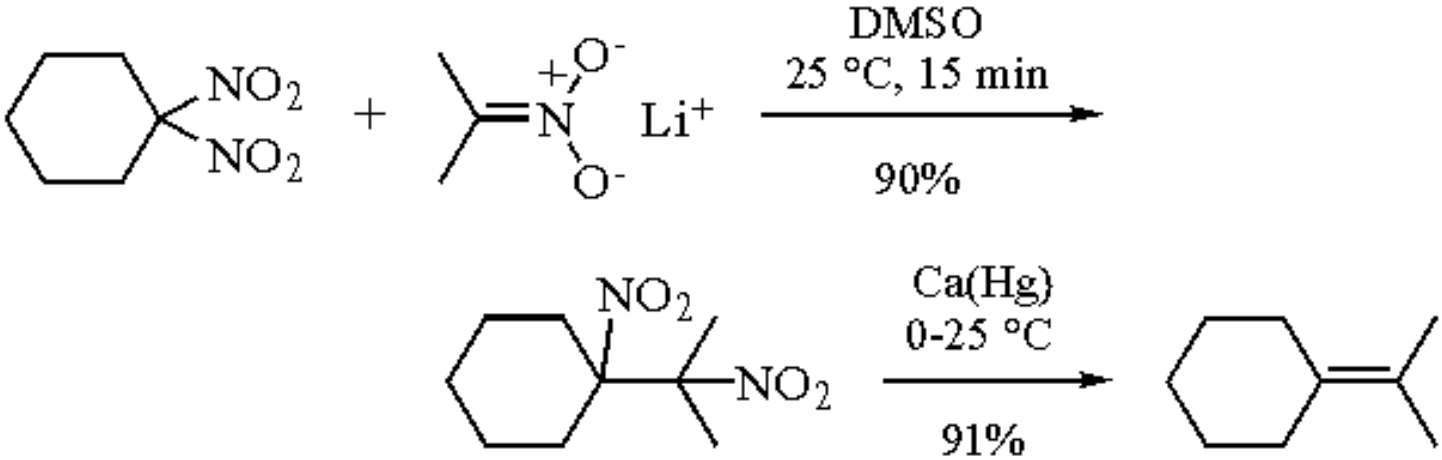

(6)

Synthesis of Substituted *gem*-Dimethylcyclopropanes.

The sodium or potassium salts of 2-nitropropane can be used as isopropylidene-transfer reagents. In a one-pot, tandem Michael addition-nitrite displacement sequence of reactions, electron-deficient alkenes react with the nitronate salt of 2-nitropropane to give *gem*-dimethylcyclopropanes in good yields (eq 7).[5] The reaction appears to be stereoselective with the various substrates that have been used.[5]

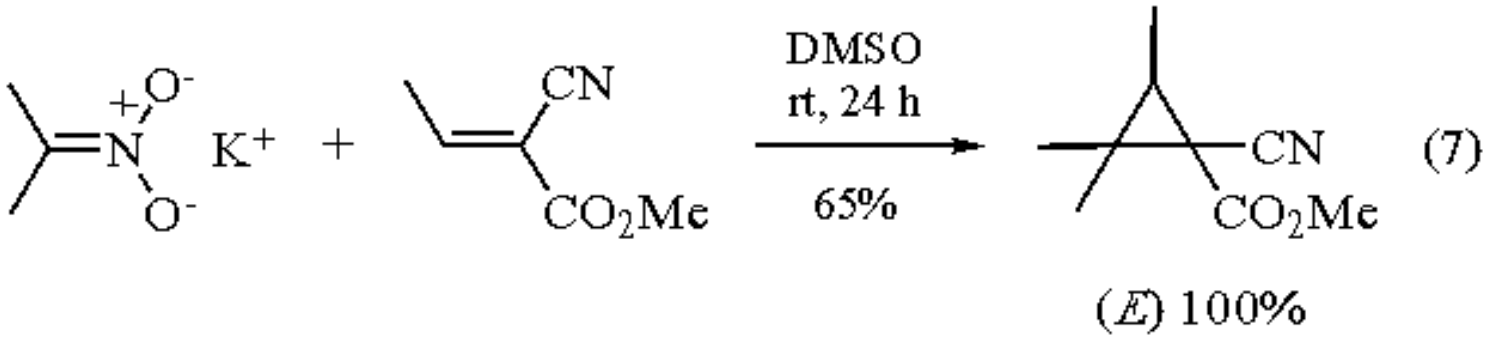

C-C Coupling at β-Carbon.

The α,β-doubly deprotonated 2-nitropropane can be benzylated, benzoylated, and hydroxybenzylated at the β-carbon in modest yields (eq 8).[14]

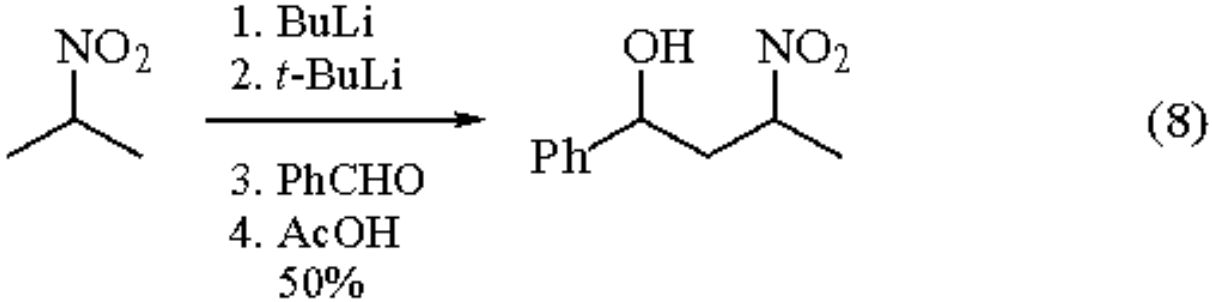

Related Reagents.

O,O-Dilithio-1-nitropropene; ***1-Nitropropane***.

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1. (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988. (b) *The Chemistry of the Nitro and Nitroso Groups*, Part 2; Feuer, H., Ed.; Interscience: New York, 1970. (c) *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1982. (d) *Nitroparaffins, TDS1*; Angus Chemical Co.: Northbrook IL, 1989. (e) *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H; Nielsen, A. T., Eds.; VCH: New York, 1990.
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1-Nitropropane[1]

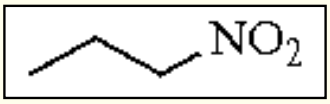

[108-03-2] · $C_3H_7NO_2$ · 1-Nitropropane · (MW 89.11)

(for aromatic aldehyde to nitrile conversion;[2] nitronate, as acyl anion equivalent of *n*-propanal, as a *n*-propyl anion equivalent, reaction with electrophiles[3])

Physical Data: mp -104 °C; bp 131 °C; *d* 1.001 g cm^{-3}.

Solubility: 1.5 g wt % in H_2O at 25 °C; sol ethanol, ether.

Form Supplied in: liquid, widely available. *Drying:* use calcium chloride, calcium sulfate, magnesium sulfate.

Handling, Storage, and Precautions: flammable; avoid contact with bases; toxic; dry nitronate salts can be explosive; 1-nitropropane (pK_a = 8.98) can be deprotonated by bases such as NaOH, TEA, DBU, TMG, NaH, or LDA. The resulting 1-nitropropane nitronate is the usual reactive form of the reagent.

Conversion of Aromatic Aldehydes to Nitriles.

A one-step method for the conversion of aromatic and heterocyclic aldehydes to nitriles utilizes 1-nitropropane (as the source of hydroxylamine) and $(NH_3)_2HPO_4$ as the reagents (eq 1).[4]

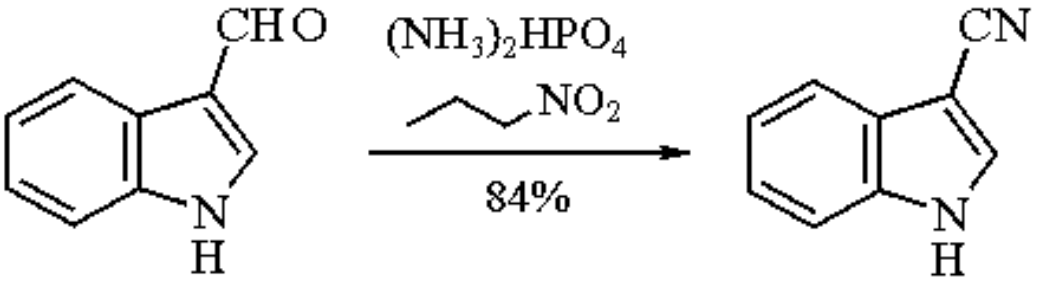

(1)

1,2-Addition to Carbonyl Compounds.

As a nucleophile, 1-nitropropane nitronate reacts with the carbonyl group of aldehydes and ketones (Henry reaction[5]); this is a method of chain extension by three carbon atoms (eq 2).[6]

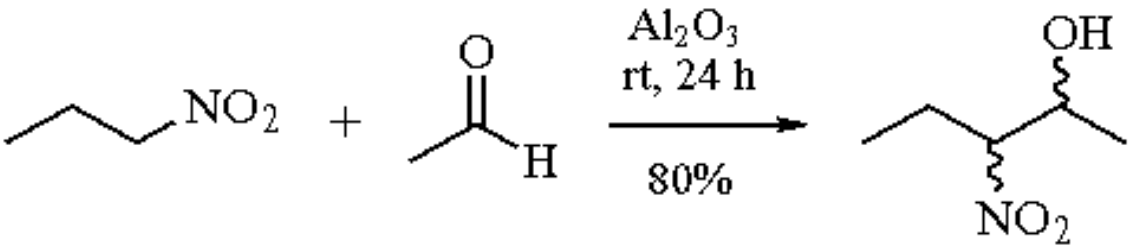

(2)

The diastereoselectivity of the products obtained from the reaction with aldehydes is dependent upon the reaction conditions employed. The nitro aldol products have been used extensively in synthesis.

1,4-Addition to Carbonyl Compounds.

In the Michael reaction,[7] 1-nitropropane can serve as an *n*-propanoyl equivalent by a subsequent Nef reaction of the conjugate addition product (eq 3).[8]

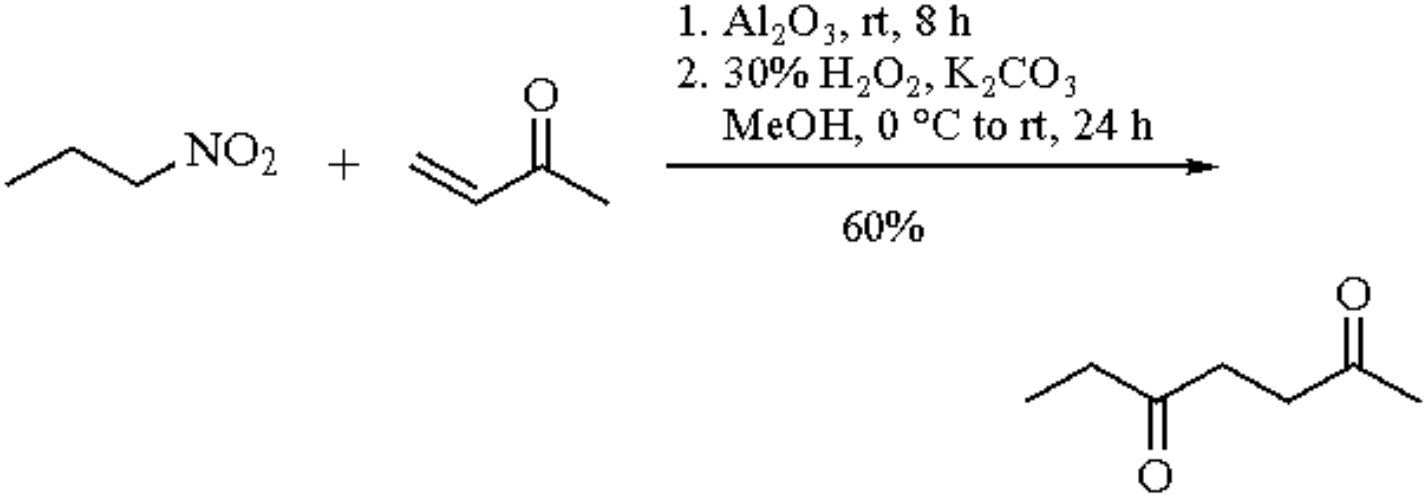

(3)

Alternatively, 1-nitropropane can serve as an *n*-propyl anion equivalent in the Michael reaction by subsequent radical denitration of the conjugate addition product (eq 4).[9]

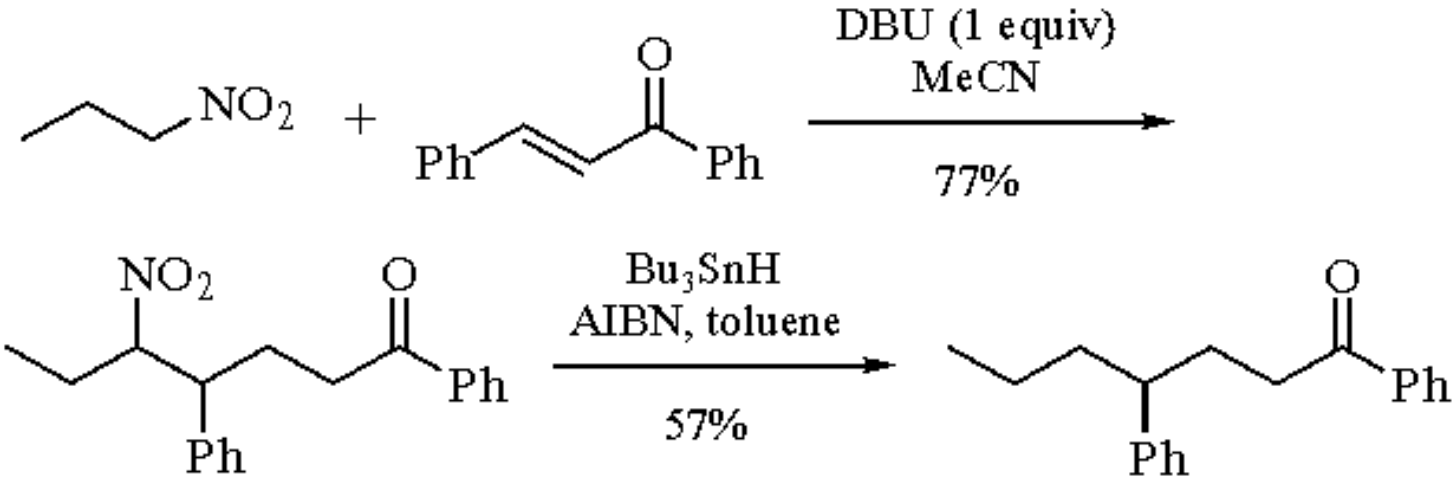

(4)

α,α-Doubly Deprotonated 1-Nitropropane.

C-Alkylation, *C*-acylation, and *C*-hydroxyalkylation products are obtained in good yields by the reaction of α,α-doubly deprotonated 1-nitropropane with alkyl halides, carboxylic acid derivatives, and aldehydes and ketones (Henry reaction). In the Henry reaction of the dianion with aldehydes, *threo*-enriched products are obtained. With ketones, better yields of the nitro aldol products are realized than under classical conditions (eq 5).[10]

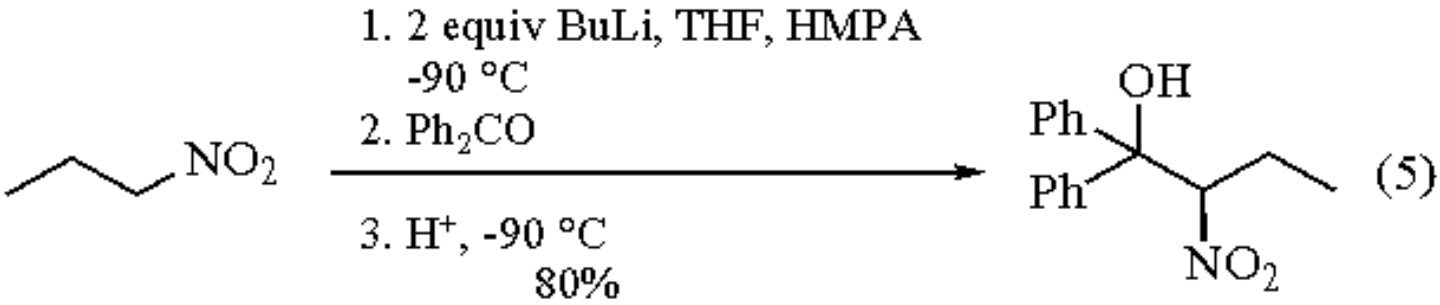

Silyl Esters of *aci*-1-Nitropropane.

Nitropropane is converted to its *O*-*t*-butyldimethylsilyl ester, which is used as a reagent in the fluoride ion-catalyzed Henry reaction with aldehydes. The reaction gives good yields of products with a >95% *erythro* stereoselectivity (eq 6).[11]

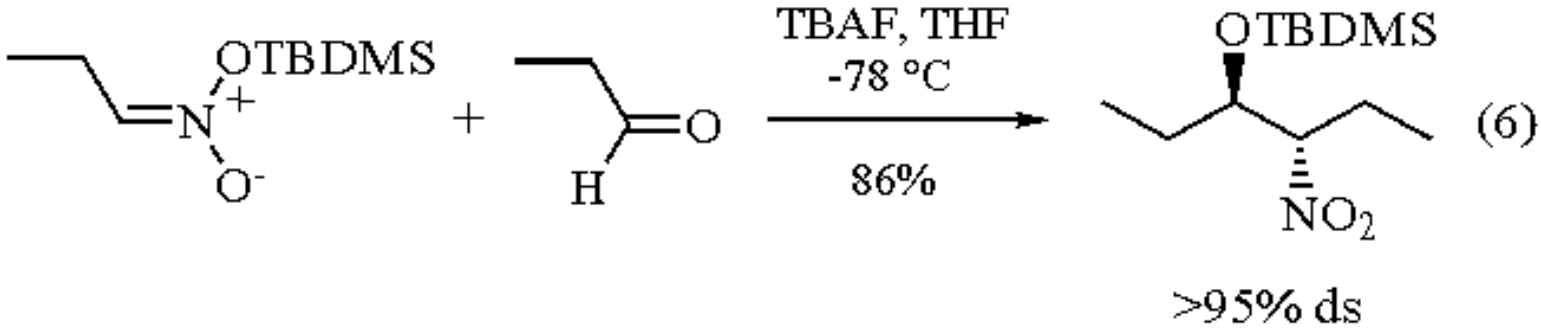

1,3-Dipolar cycloaddition reactions of the silyl nitronates of 1-nitropropane with alkenes have been used to prepare 2-oxazolines, which can be transformed into a variety of nonheterocyclic compounds (eq 7).[12]

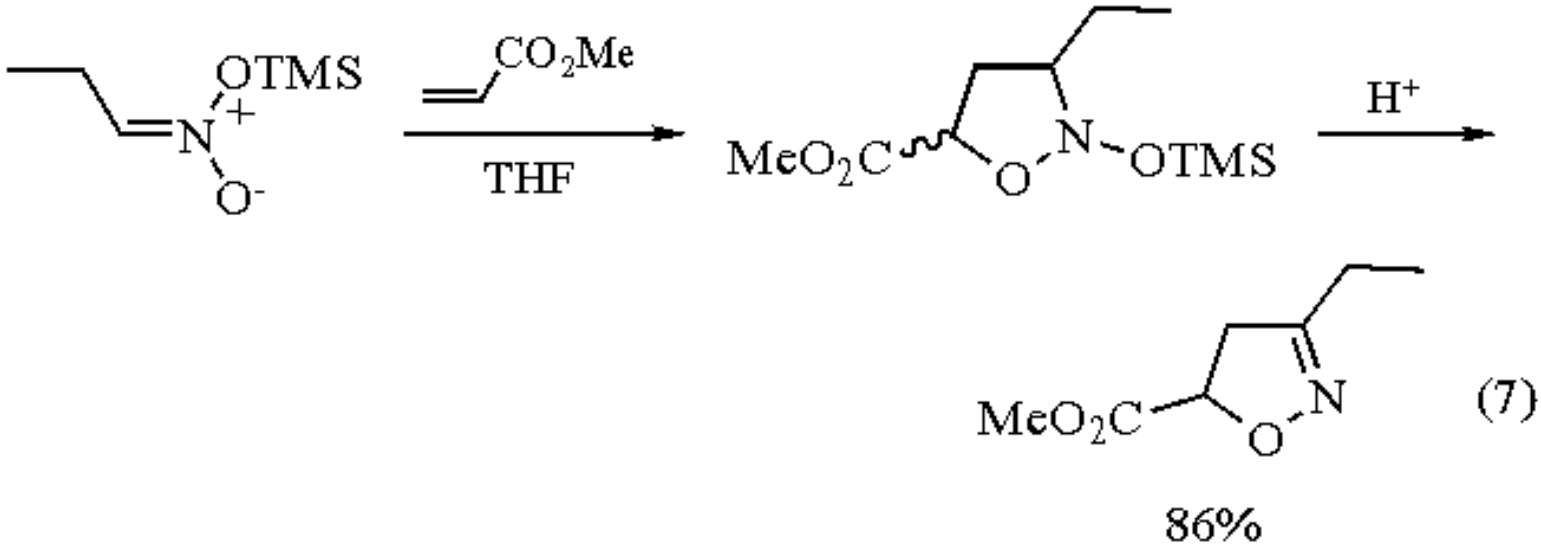

Propanenitrile Oxide Precursor.

The 1,3-dipolarophile propanenitrile oxide is prepared from 1-nitropropane for use in situ[13] and can be used to synthesize heterocycles (eq 8).[14]

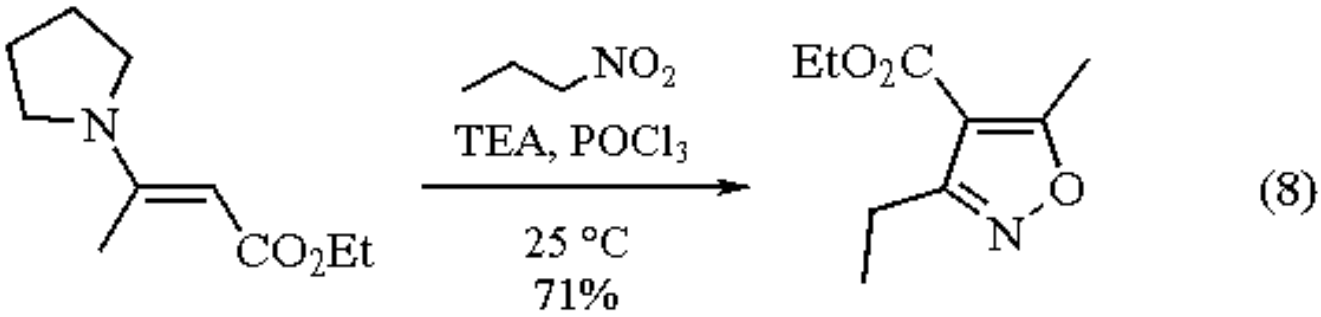

Related Reagents.

t-Butyldimethylsilyl Ethylnitronate; ***O,O-Dilithio-1-nitropropene***; ***Nitroethane***; ***Nitromethane***.

---

1. (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988. (b) *The Chemistry of the Nitro and Nitroso Groups*, Part 2; Feuer, H., Ed.; Interscience: New York, 1970. (c) *The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: Chichester, 1982. (d) *Nitroparaffins, TDS1*; Angus Chemical Co.: Northbrook, IL, 1989. (e) *Nitro Compounds: Recent Advances in Synthesis and Chemistry*; Feuer, H.; Nielsen, A. T., Eds.; VCH: New York, 1990.
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1-Nitro-1-propene[1]

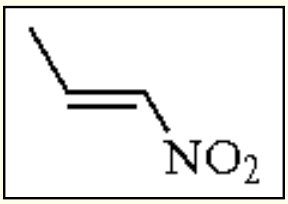

[3156-70-5] · $C_3H_5NO_2$ · 1-Nitro-1-propene · (MW 87.09)

(Michael addition of various nucleophiles such as organolithium reagents,[5,6] enamines,[13,15,19] allylstannane,[9] and alkyl radicals[22])

Physical Data: bp 58 °C/35 mmHg, 54 °C/28mmHg.

Solubility: sol THF, Et_2O, acetone, CH_2Cl_2, toluene.

Analysis of Reagent Purity: IR: 1655, 1520 cm^{-1}; NMR: δ 1.95 (d, 3H, *J* = 6Hz), 6.83-7.55 (m, 2H).

Preparative Methods: dehydration of 1-nitro-2-propanol with ***Methanesulfonyl Chloride*** and ***Triethylamine*** (30% yield),[2] ***Acetic Anhydride***-AcONa (85% yield),[3] or phthalic anhydride (55% yield).[4]

Handling, Storage, and Precautions: see ***2-Nitro-1-propene***.

Michael Acceptor.

1-Nitropropene is a useful reagent as a Michael acceptor for the addition of various nucleophiles (eq 1) including amines,[1] alcohols,[1] thiols,[1] organolithium reagents (eqs 2 and 3[5,6]), Grignard reagents,[7] enamines,[8] allylstannanes (eq 4),[9] and lithium trialkylalkynylborates.[10] Other organometallic reagents such as organoaluminum compounds[11] and zinc-copper reagents RCu(CN)ZnI[12] are also good candidates as nucleophiles.

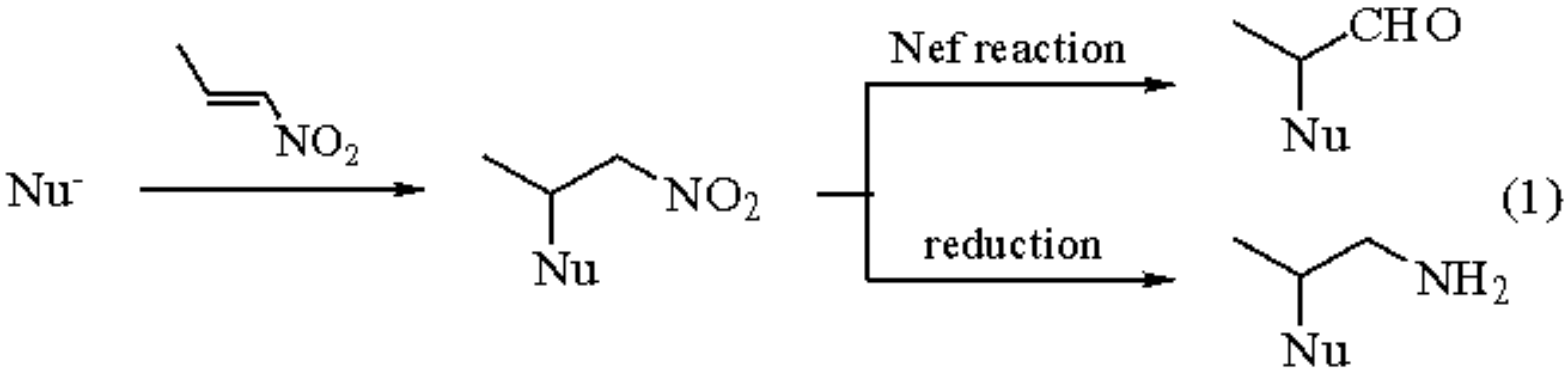

(1)

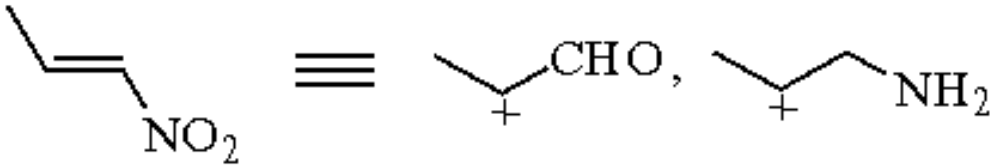

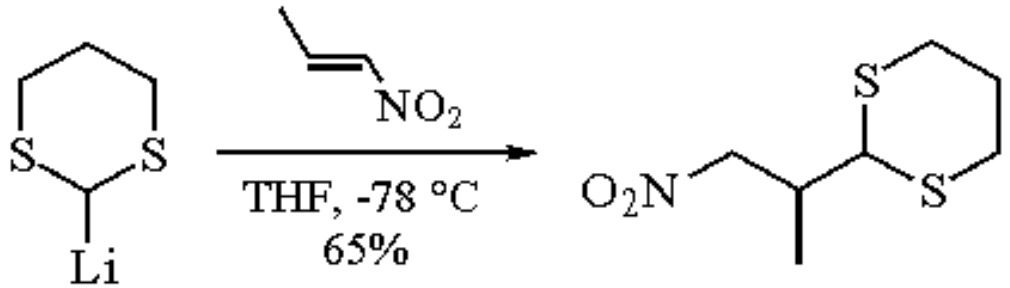

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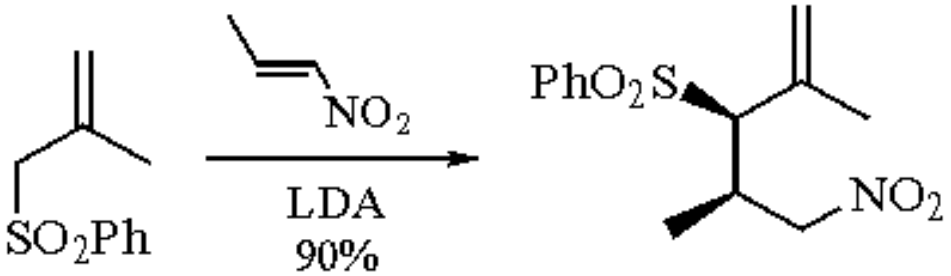

(3)

syn:*anti* = 84:16

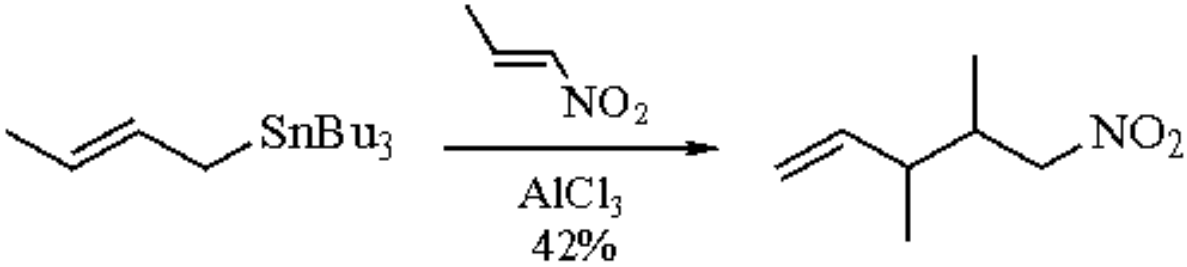

(4)

Formaldehyde dimethylhydrazone readily adds to 1-nitropropene in the absence of base, giving the β-nitrodimethylhydrazone, which is converted into the β-nitroaldehyde by ozonolysis (eq 5).[13]

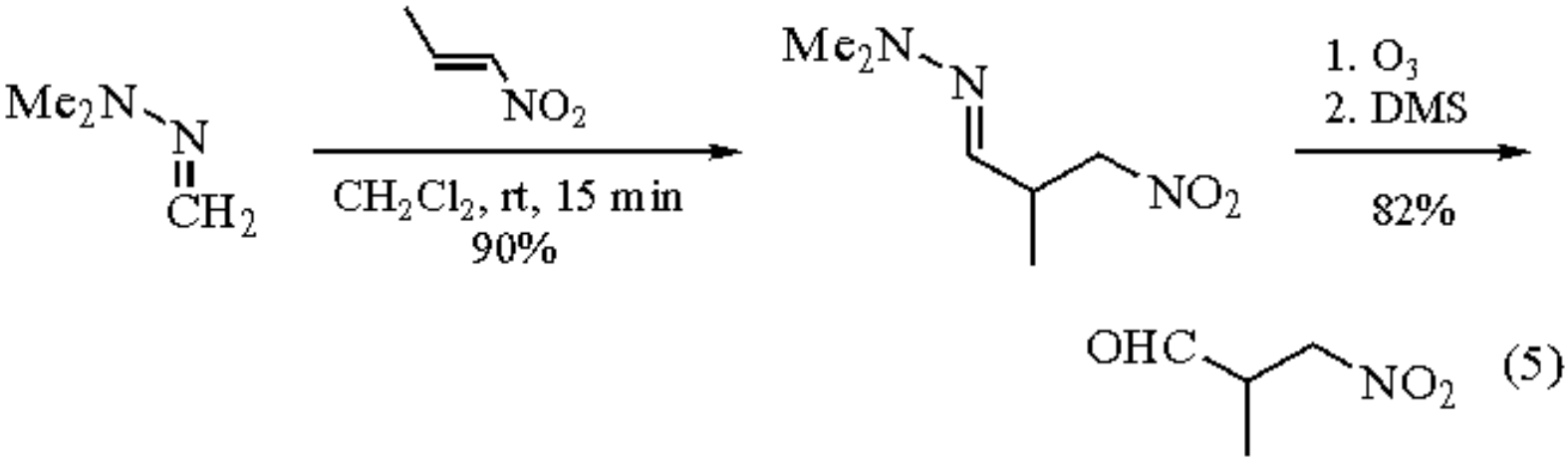

The Michael addition of 1,3-diketone dianions or 2-aminoenones to 1-nitropropene and subsequent aldol reaction (eqs 6, 7 and 8[14,15,16]) provides a useful strategy for organic synthesis. In addition 1-nitropropene is an efficient reagent for bicycloannulation, as illustrated in eq 7.[17]

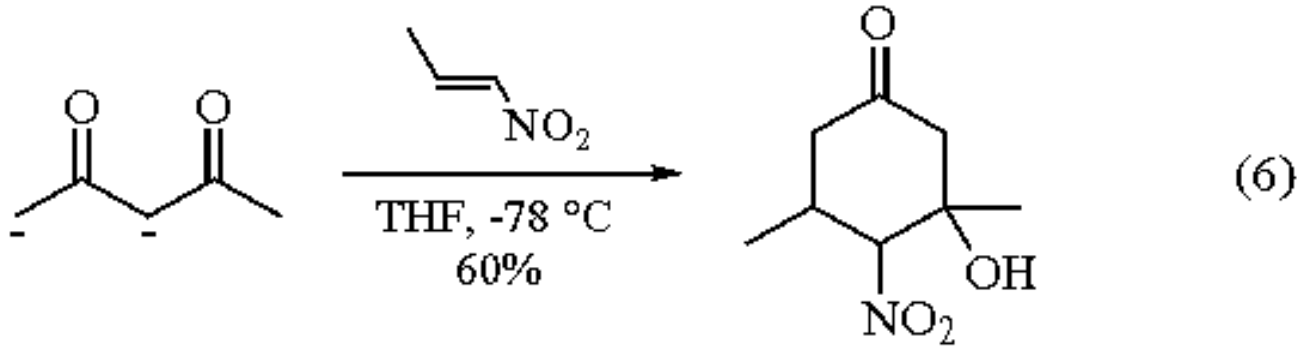

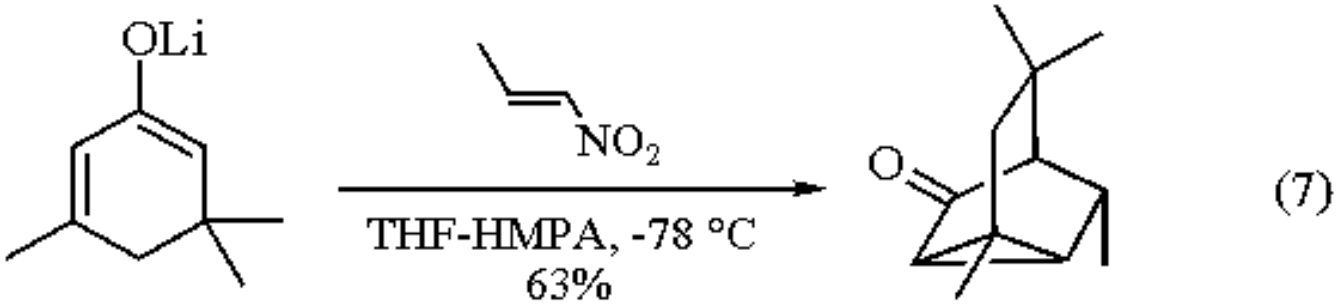

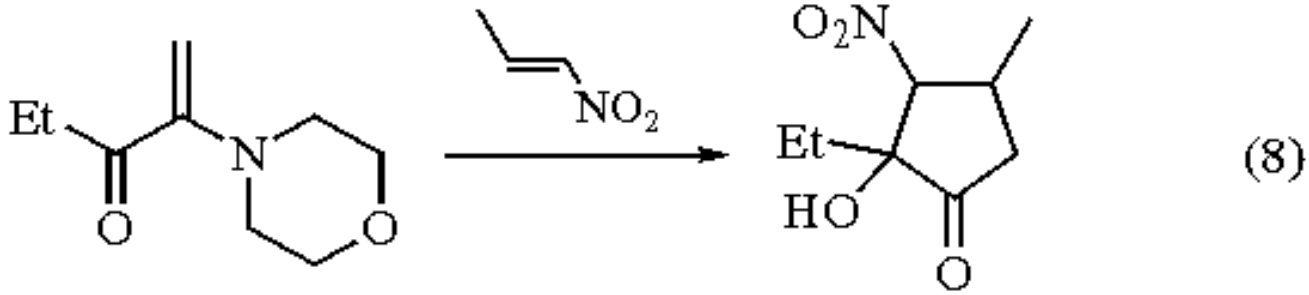

Allyl alcohols are prepared by the reaction of 1-nitropropene with thiols and aldehydes followed by reductive elimination of β-nitro sulfides with ***Tri-n-butylstannane*** (eq 9).[16]

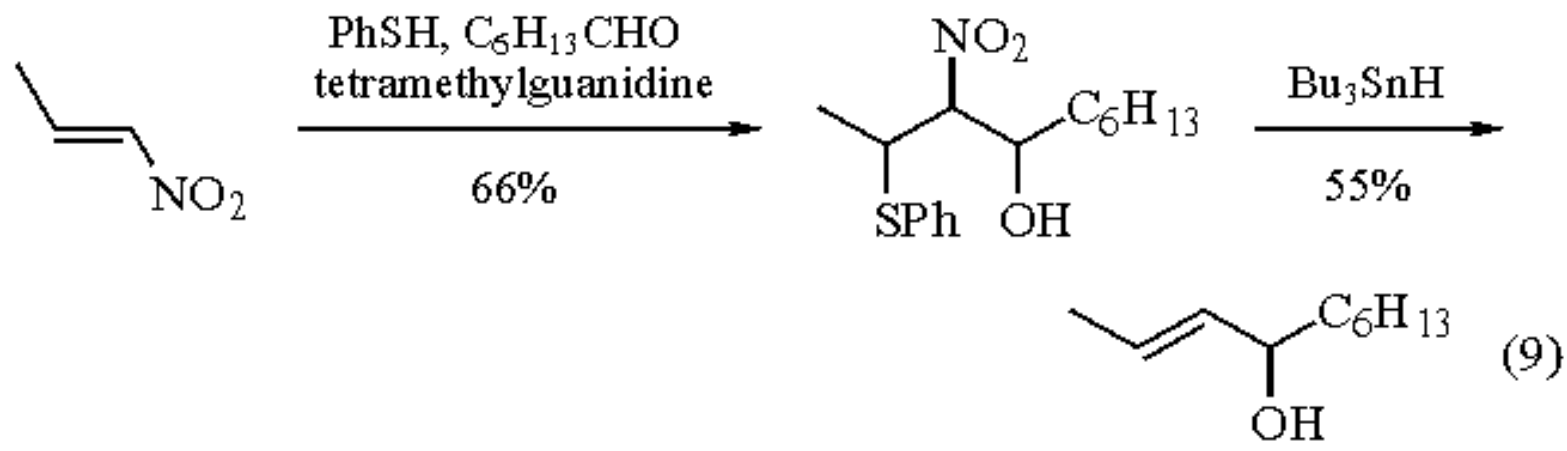

As the addition of enolates[18] or enamines[19] to 1-nitropropene proceeds in a stereoselective way, asymmetric Michael addition is possible using chiral enolates (eq 10)[20] or the titanated bislactim ether of cyclo(L-Val-Gly) (eq 11).[21]

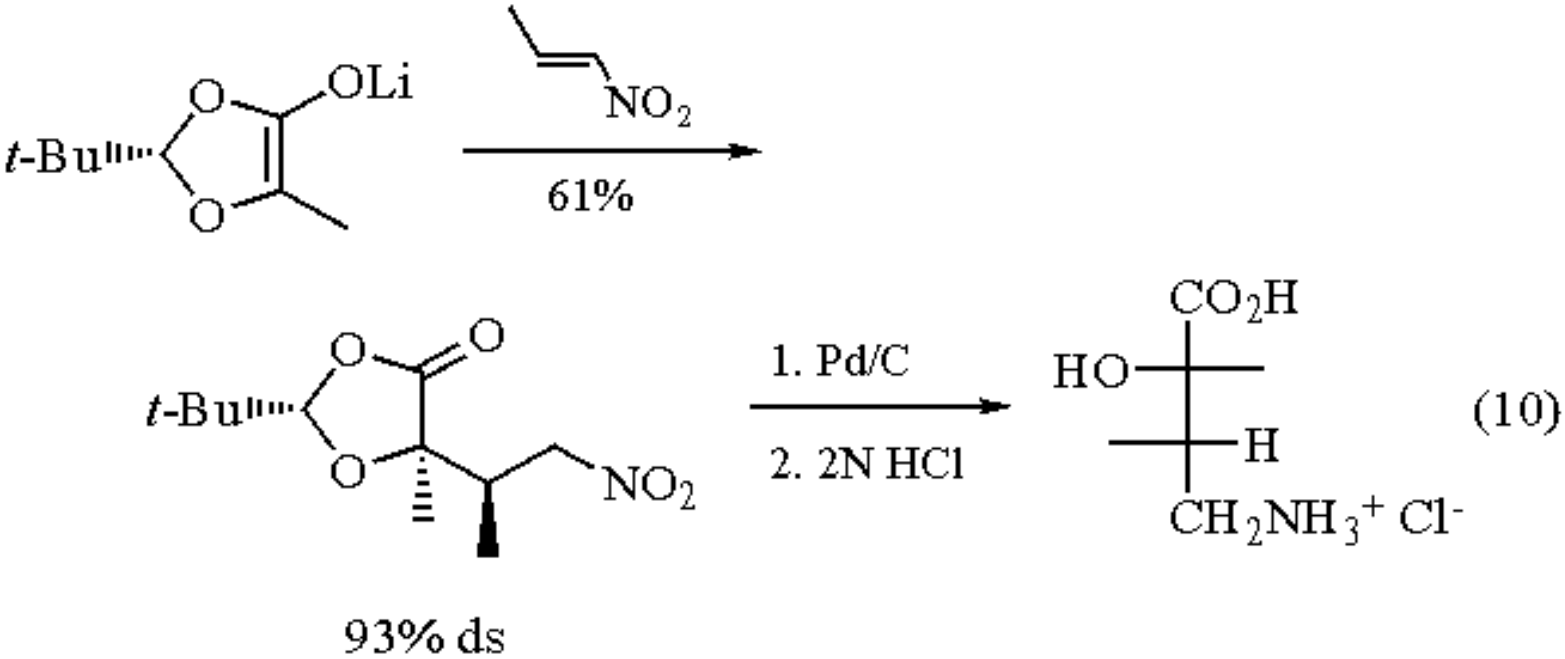

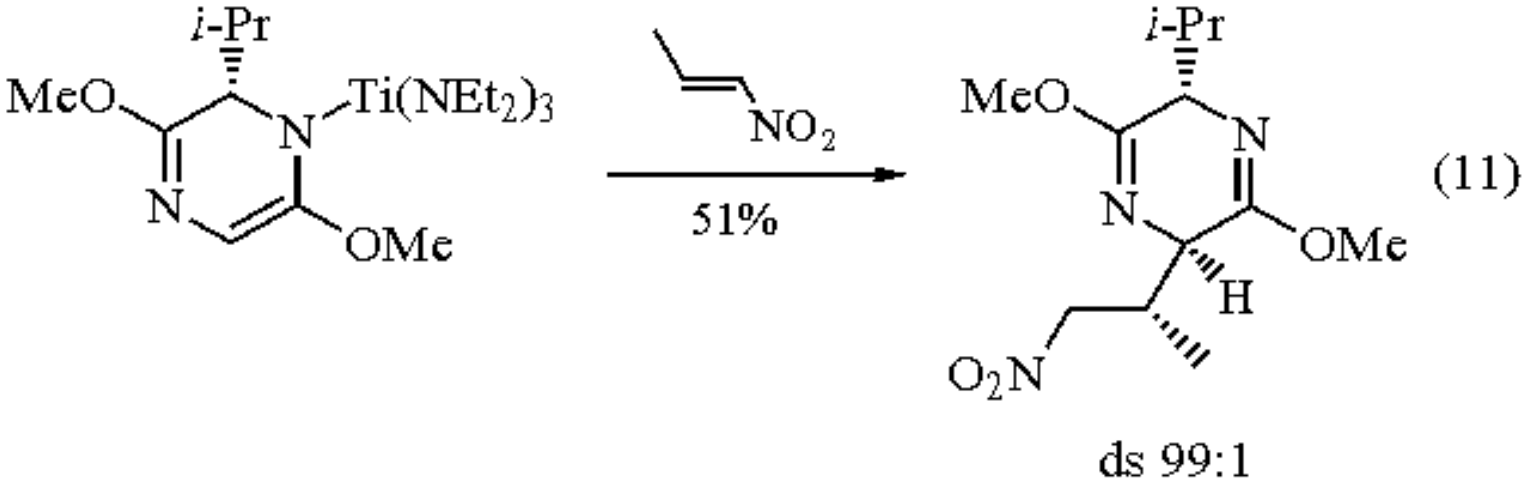

1-Nitropropene reacts with alkyl radicals derived from *O*-acyl 2-thiopyridylhydroxamate to from new carbon-carbon bonds (eq 12).[22]

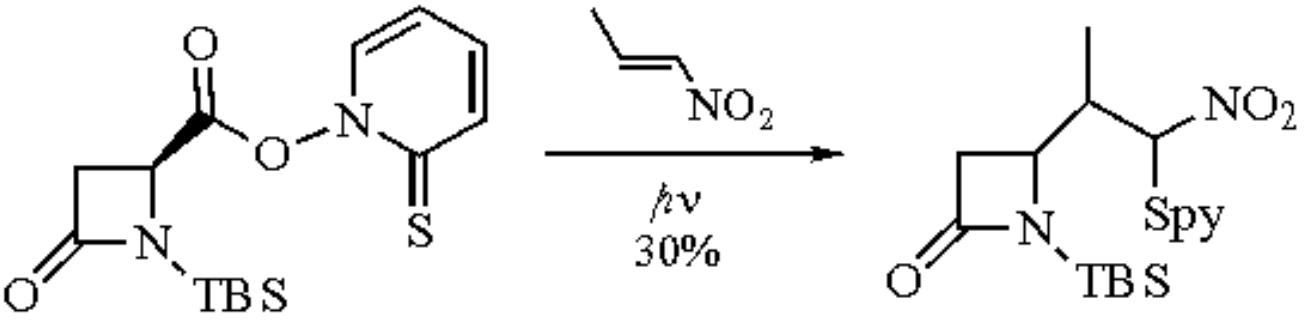

(12)

Diels-Alder Reaction.

1-Nitropropene is a very reactive dienophile in the Diels-Alder reaction, and the regiochemistry is controlled by the nitro group (eq 13).[23]

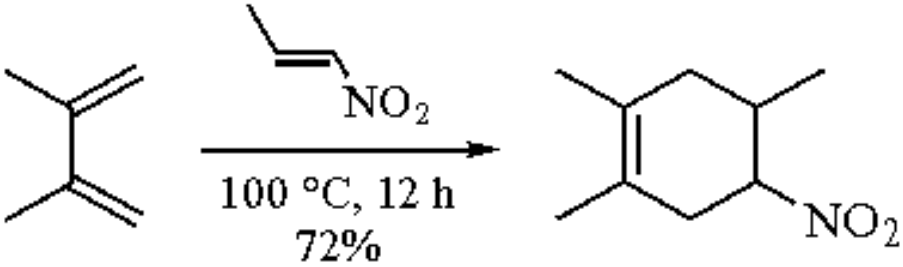

(13)

Related Reagents.

Nitroethylene; ***2-Nitro-1-propene***.

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1. (a) Schickh, O.; Apel, G.; Padeken, H. G.; Schwartz, H. H.; Segnitz, A. *MOC* **1971**, *10*, 9-462. (b) Barrett, A. G. M.; Graboski, G. G. *CRV* **1986**, *86*, 751. (c) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *C* **1979**, *33*, 1. (d) Rossini, G.; Ballini, R. *S* **1988**, 833. (e) Baer, H.; Urbas, L. *The Chemistry of the Nitro and Nitroso Groups*; Feuer, H., Ed.; Interscience: New York, 1970; Part 2, pp 75-200. (f) Tamura, R.; Kamimura, A.; Ono, N. *S* **1991**, 423.
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18. Häner, R.; Laube, T.; Seebach, D. *C* **1984**, *38*, 255.
19. Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *HCA* **1985**, *68*, 162.
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2-Nitro-1-propene[1]

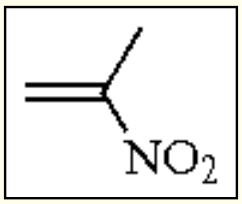

[4749-28-4] · $C_3H_5NO_2$ · 2-Nitro-1-propene · (MW 87.09)

(Michael addition to afford 1,4-diketones,[4] furans,[7] and pyrroles,[11] and an electrophilic reagent for α-keto cation in the Friedel-Crafts reaction[12])

Physical Data: bp 56-57 °C/86 mmHg, 50 °C/60 mmHg; *n*20D 1.4348, d^{20} 1.0492 g cm^{-3}.

Solubility: sol Et_2O, THF, acetone, CH_2Cl_2.

Preparative Methods: by dehydration of 2-nitro-1-propanol (ca. 98% purity commercially or prepared from ***Nitroethane*** and formalin, yield 70%[2]) with phthalic anhydride (73%)[3] or ***Acetic Anhydride***-AcONa (85%).[4]

Handling, Storage, and Precautions: pure 2-nitro-1-propene may be stored in a freezer for several weeks; best prepared immediately before use since it tends to polymerize; this reagent is a powerful lachrymator. Use in a fume hood.

Michael Acceptor.

This reagent readily undergoes addition reactions with many different nucleophiles to give saturated nitro compounds,[5] which are readily converted into a variety of compounds such as amines or ketones via reduction or the Nef reaction, respectively (eq 1).[1]

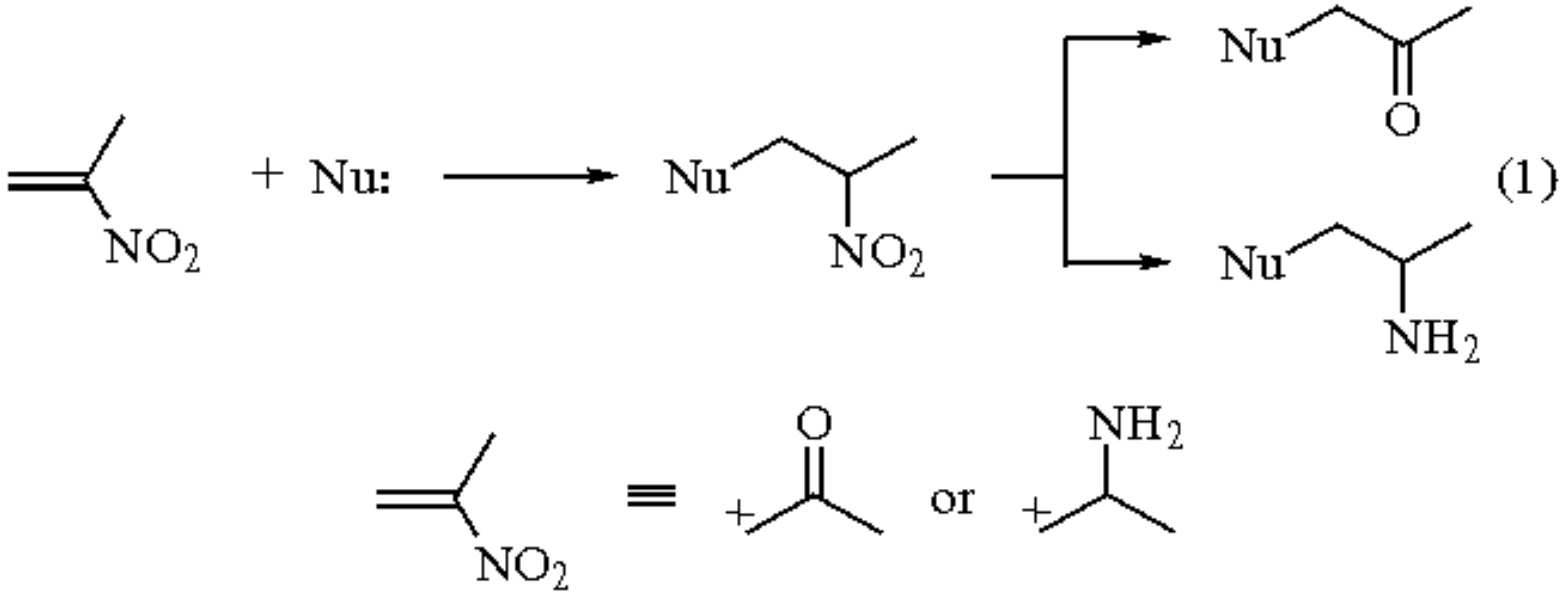

Lewis acid-promoted addition of silyl enol ethers to this reagent provides a very useful method for the preparation of 1,4-diketones (eq 2).[4] The 1,4-diketones thus obtained are converted into cyclopentenones in high yields.[5]

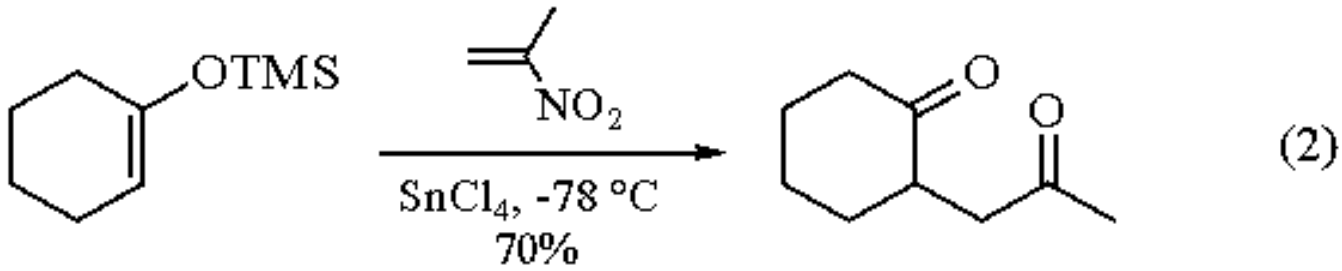

Carboxylic acid dianions or ester enolates react with this reagent to give γ-keto acids after hydrolysis (eq 3). However, a low temperature is required to suppress the polymerization of the nitroalkene.[6]

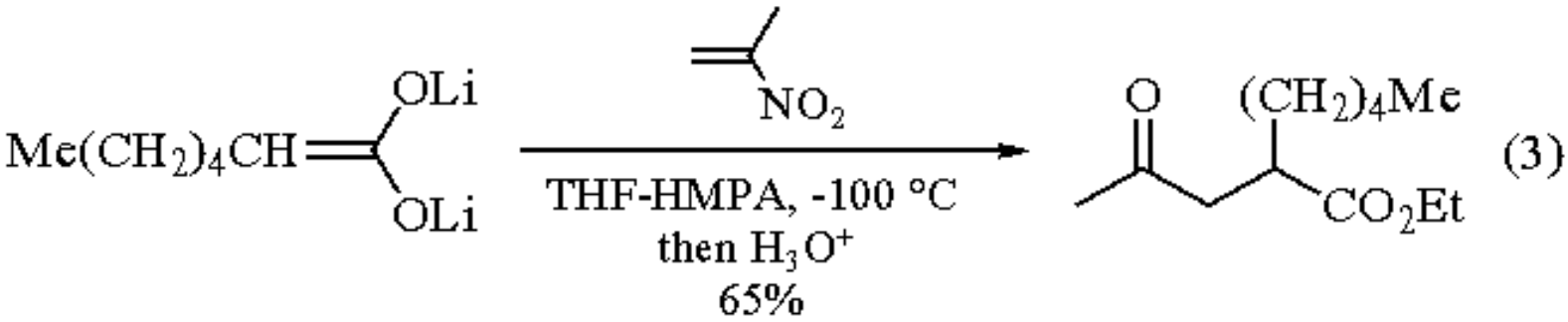

The base-catalyzed addition of 1,3-diketones to 2-nitropropene followed by heating the initial Michael adducts results in the formation of furans. Thus dimedone and acetylacetone react with 2-nitropropene to give the furans shown in eqs 4 and 5.[7]

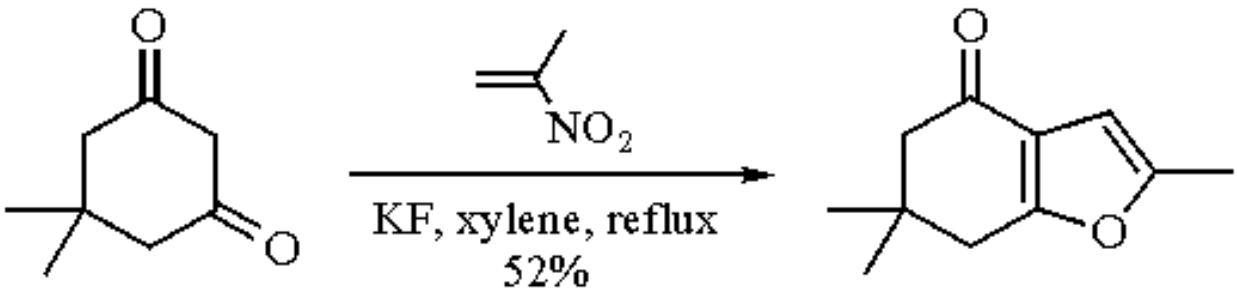

(4)

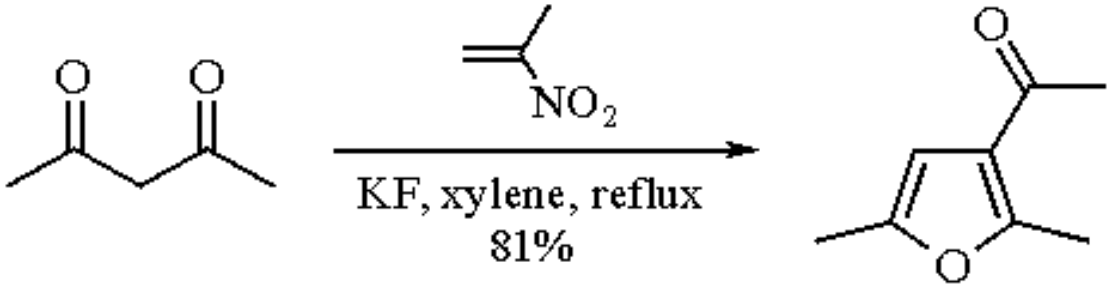

(5)

The reaction of this reagent with ketone enolates followed by treatment with ***Acetic Anhydride*** gives acetic nitronic anhydrides, which are converted into 1,4-diketones or pyrroles (eq 6).[8]

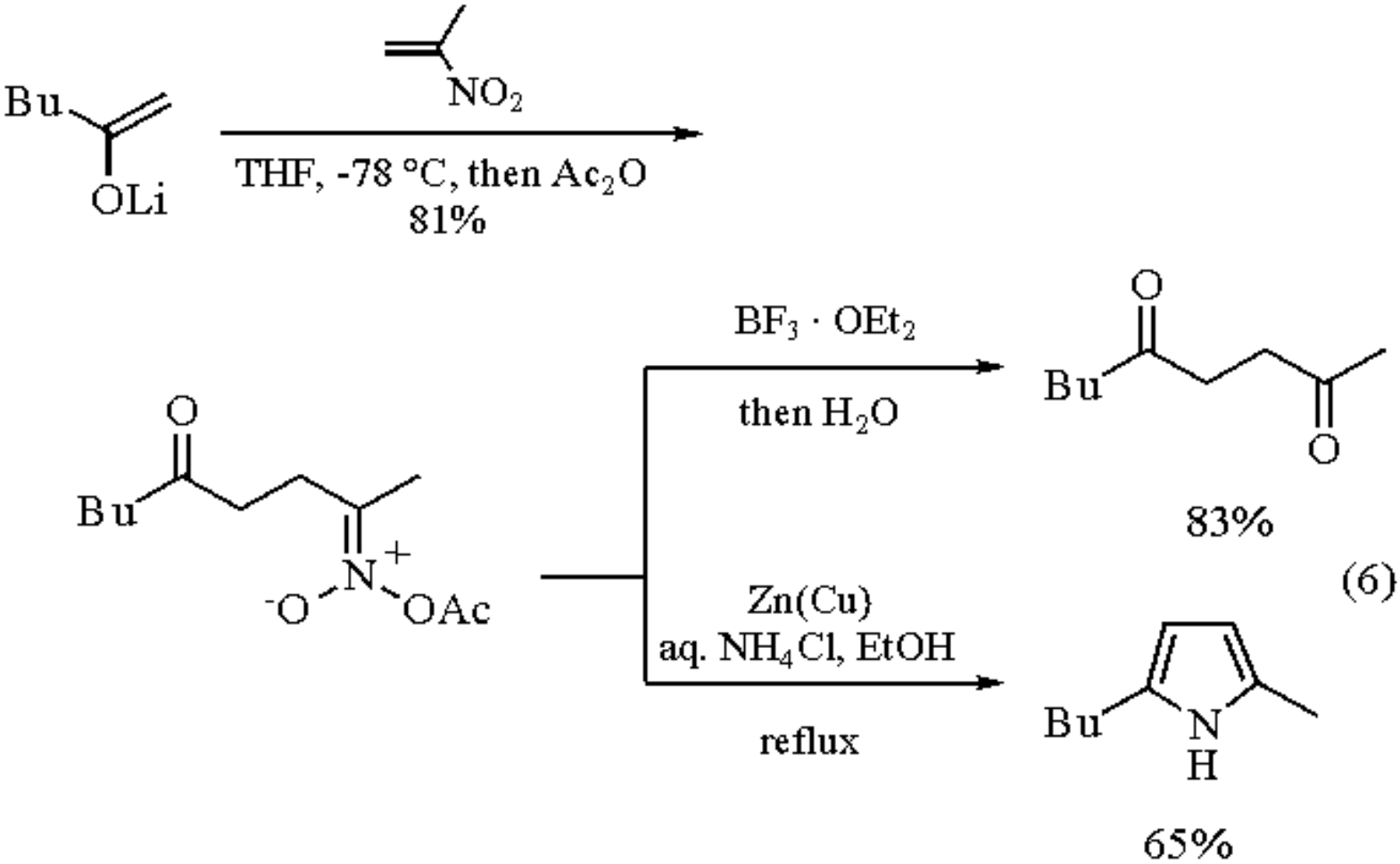

(6)

The conjugate addition of sulfonyl carbanions to 2-nitropropene, followed by ozonolysis or acid treatment of the

resulting nitronates (Nef reaction[9]) and subsequent elimination of sulfinic acid from β-ketosulfones with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU), gives α,β-unsaturated ketones (eq 7).[10]

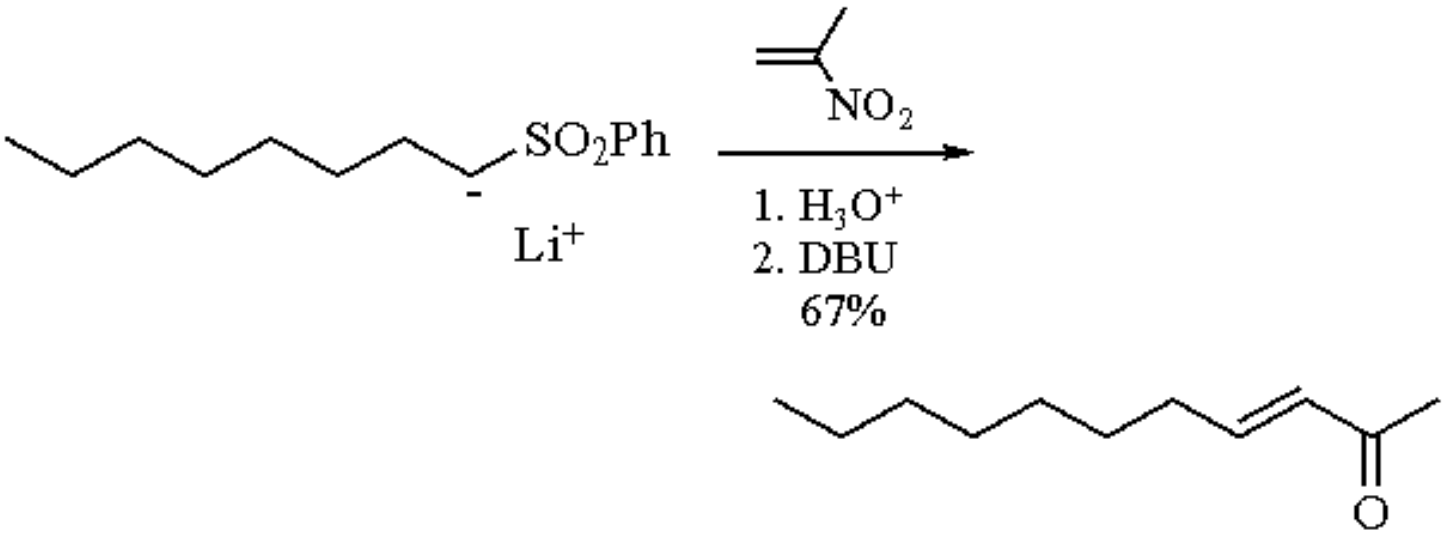

(7)

A unique pyrrole synthesis is realized by the reaction of nitroalkenes with isocyanoacetates. For example, 2-nitropropene condenses with methyl isocyanoacetate in the presence of DBU to produce the pyrrole which is a trail marker pheromone (eq 8).[11]

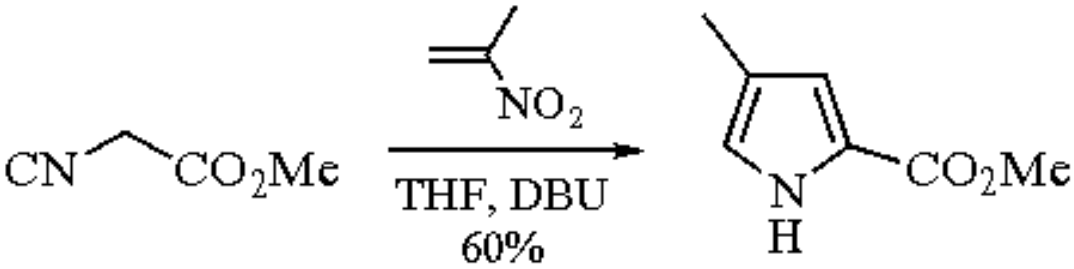

(8)

Friedel-Crafts-Type Reactions.

A novel electrophilic reagent is formed by diprotonation of nitroalkenes in ***Trifluoromethanesulfonic Acid***. *O,O*-Diprotonated 2-nitropropene undergoes two alternative electrophilic reactions with benzene which yields α-phenylacetone[12] or 4*H*-1,2-benzoxazine,[13] depending on the reaction conditions. These products are not readily synthesized by the conventional Friedel-Crafts reaction. Benzoxazine acts as a precursor of *o*-benzoquinone methide (eq 9).[14]

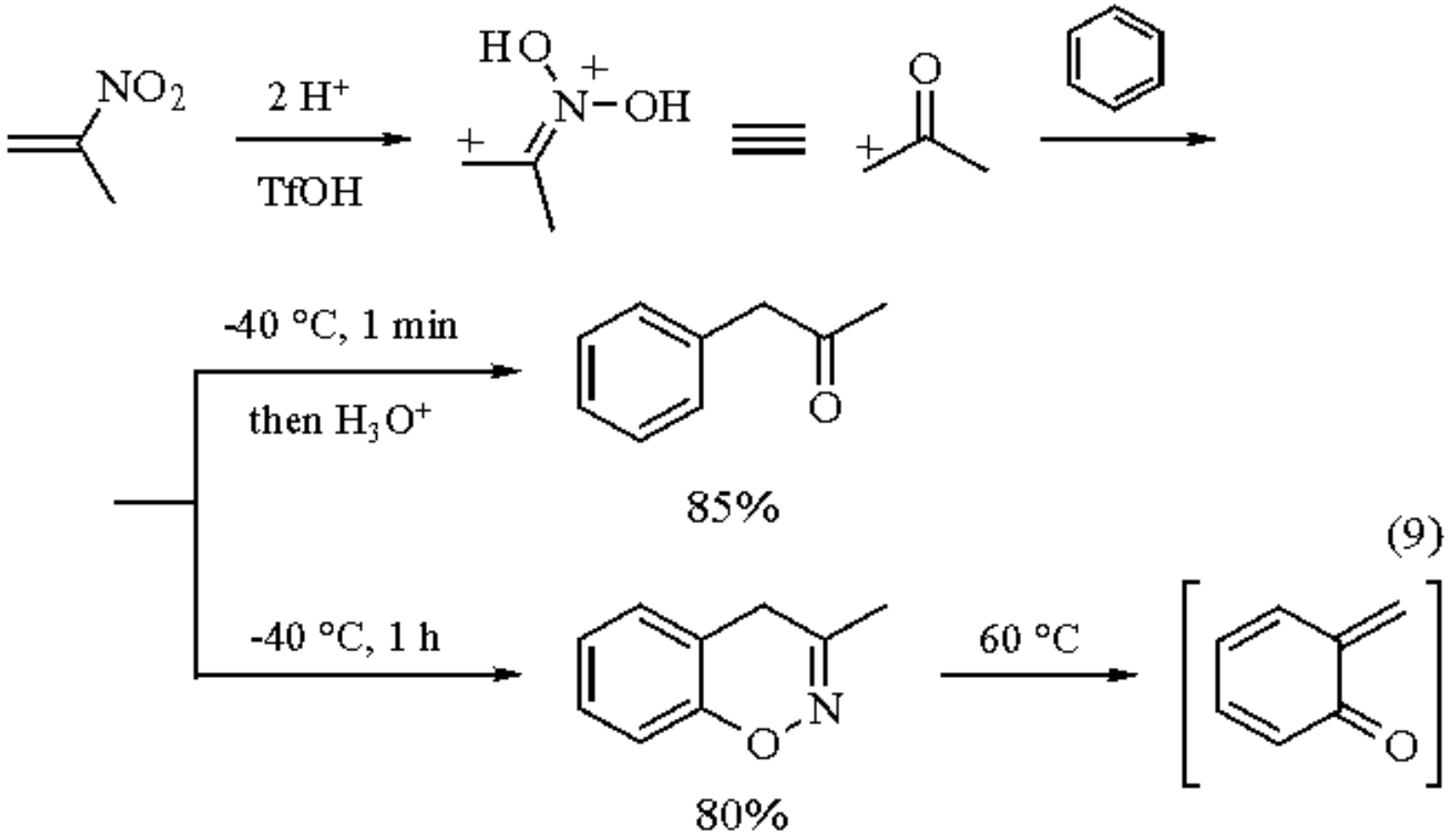

Diels-Alder Reaction.

This reagent is an excellent dienophile in the Diels-Alder reaction and it reacts with various dienes.[15] The regiochemistry of the Diels-Alder reaction is effectively controlled by the nitro group.[16]

Related Reagents.

Nitroethylene; ***1-Nitro-1-propene***.

---

1. (a) Schickh, O.; Padeken, H. G.; Segnitz, A. *MOC* **1971**, *10*, pp 9-462. (b) Bauer, H. H.; Urbas, L. *The Chemistry of the Nitro and Nitroso Group*; Feuer, H., Ed.; Interscience: New York, 1970; Part 2. (c) Yoshikoshi, A.; Miyashita, A. *ACR* **1985**, *18*, 284.
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3-Nitro-2-pyridinesulfenyl Chloride

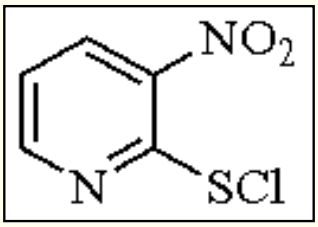

[68206-45-1] · $C_5H_3ClN_2O_2S$ · 3-Nitro-2-pyridinesulfenyl Chloride · (MW 190.60)

(for transfer of the 3-nitro-2-pyridinesulfenyl (Npys) group, used as a protecting group both for terminal NH_2 groups and also side-chain NH_2, OH, and SH groups in amino acid chemistry, and for activation of RS groups)

Alternate Name: NpysCl.

Physical Data: mp 217-222 °C (dec).

Solubility: sol CH_2Cl_2.

Analysis of Reagent Purity: may be determined by standard analytical techniques, although one group[1] reports that it observed a melting point different from that previously published.[2]

Preparative Method: may be prepared by chlorination of bis(3-nitro-2-pyridyl) disulfide with gaseous chlorine.[2]

Handling, Storage, and Precautions: moisture sensitive, but stable for several weeks at rt under dry conditions; no decomposition is seen after 6 months in a refrigerator.

Synthesis of N$^{\alpha}$Npys Amino Acids and Peptides.[3,4]

The amino acid or peptide is reacted with the title reagent (**1**) (1.3 equiv) in the presence of ***Triethylamine*** (1.2 equiv) (eq 1). If the amino acid used is in its zwitterionic form, it may be reacted under aqueous conditions, using aqueous ***Sodium Hydroxide*** as the base.

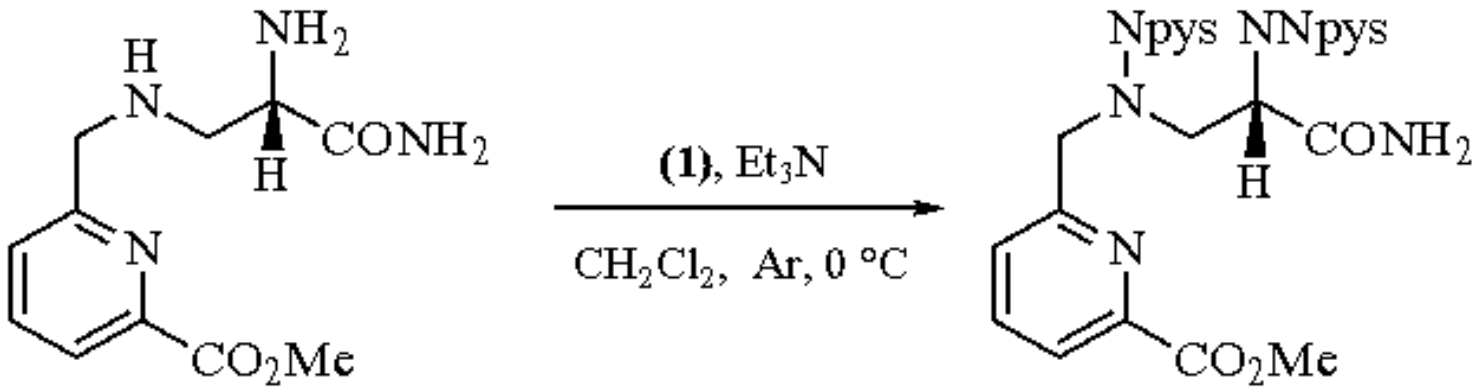

(1)

Protection of Side-Chain Functionalities of Boc-N Amino Acids.[5,6]

The *N*-protected amino acid is reacted with NpysCl (1.3 equiv) in the presence of a base (1.2 equiv), which can be either triethylamine or ***4-Dimethylaminopyridine*** (eq 2). Yields are moderate to good.

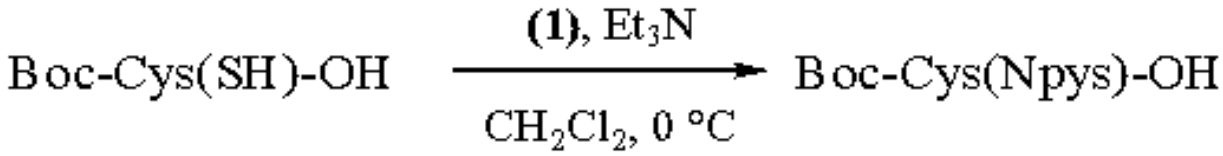

(2)

Activation of RS groups.[1,6]

Npys-protected thiols are activated towards attack by free thiols (eq 3). This leads to the formation of disulfides, and is particularly useful in the formation of disulfide bridges in peptide chemistry.

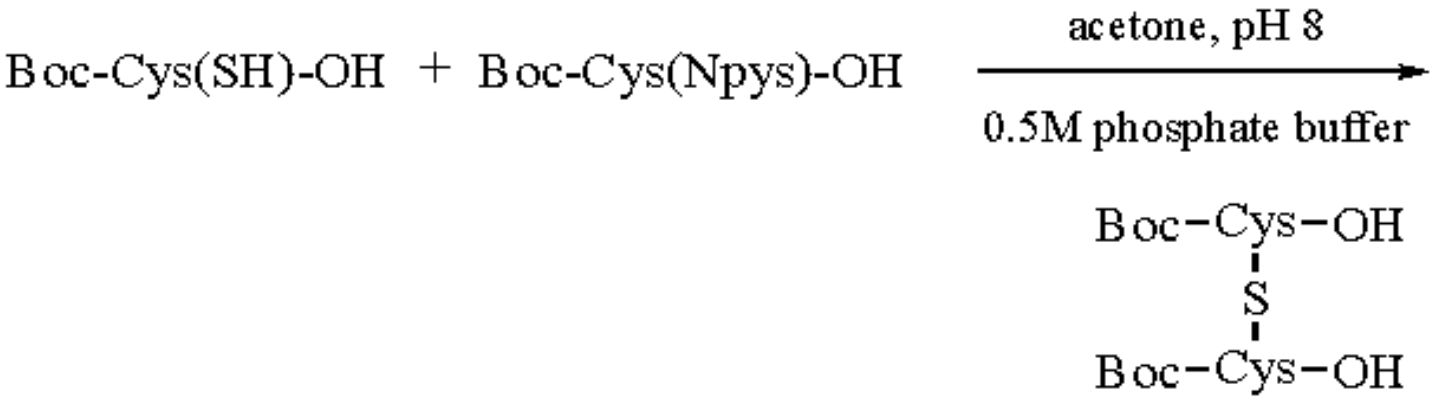

(3)

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1. Ploux, O.; Chassaing, G.; Marquet, A. *Int. J. Peptide Protein Res.* **1987**, *27*, 162.
2. Matsueda, R.; Aiba, K. *CL* **1978**, 951.
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6. Matsueda, R.; Kimura, T.; Kaiser, E. T.; Matsueda, G. R. *CL* **1981**, 737.

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5-Nitro-2-pyridyl Diphenylphosphinate

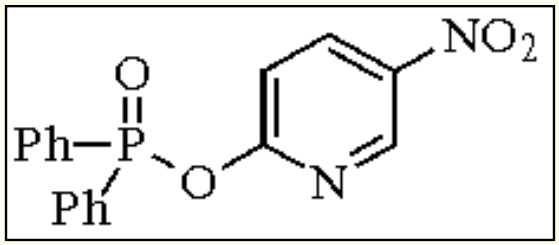

[80944-63-4] · $C_{17}H_{13}N_2O_4P$ · 5-Nitro-2-pyridyl Diphenylphosphinate · (MW 340.29)

(reagent for peptide synthesis[1])

Physical Data: mp 125-127 °C.

Preparative Method: from diphenylphosphinyl chloride and 2-hydroxy-5-nitropyridine in the presence of ***Triethylamine***.[1]

Peptide Synthesis.

Tetrabutylammonium salts of *N*-protected amino acids can be coupled with amino acid methyl or ethyl esters in the presence of 5-nitropyridyl diphenylphosphinate (**1**).[1] Reaction between tetrabutylammonium *N*-benzoyl-L-leucinate and glycine ethyl ester hydrochloride (Young test) proceeded with little racemization (98% L-isomer) (eq 1). The 2-hydroxy-5-nitropyridine byproduct is water soluble and so is easily separated from the dipeptide. Protection of side-chain functionality such as aliphatic or phenolic hydroxyl groups or imidazole or indole rings is unnecessary.

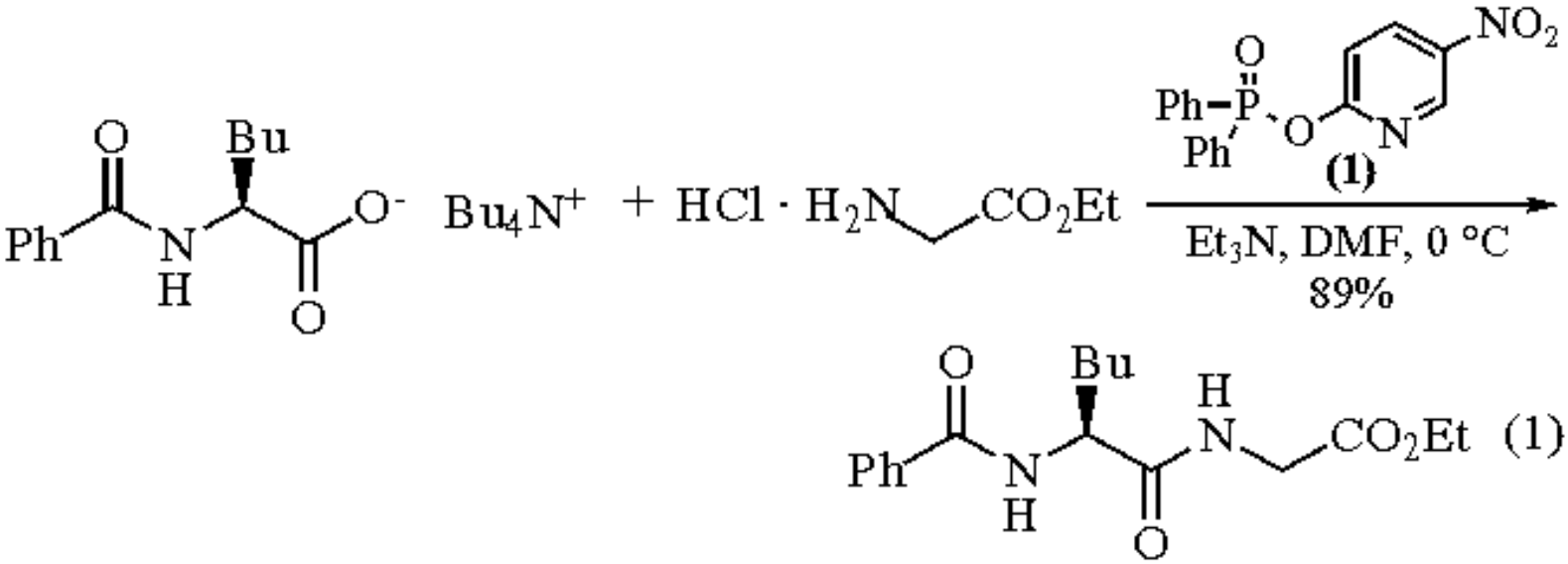

Using pyridine as solvent, the method was applied to the one-pot cyclization of linear peptides, including the synthesis of gramicidin S (eq 2).[1]

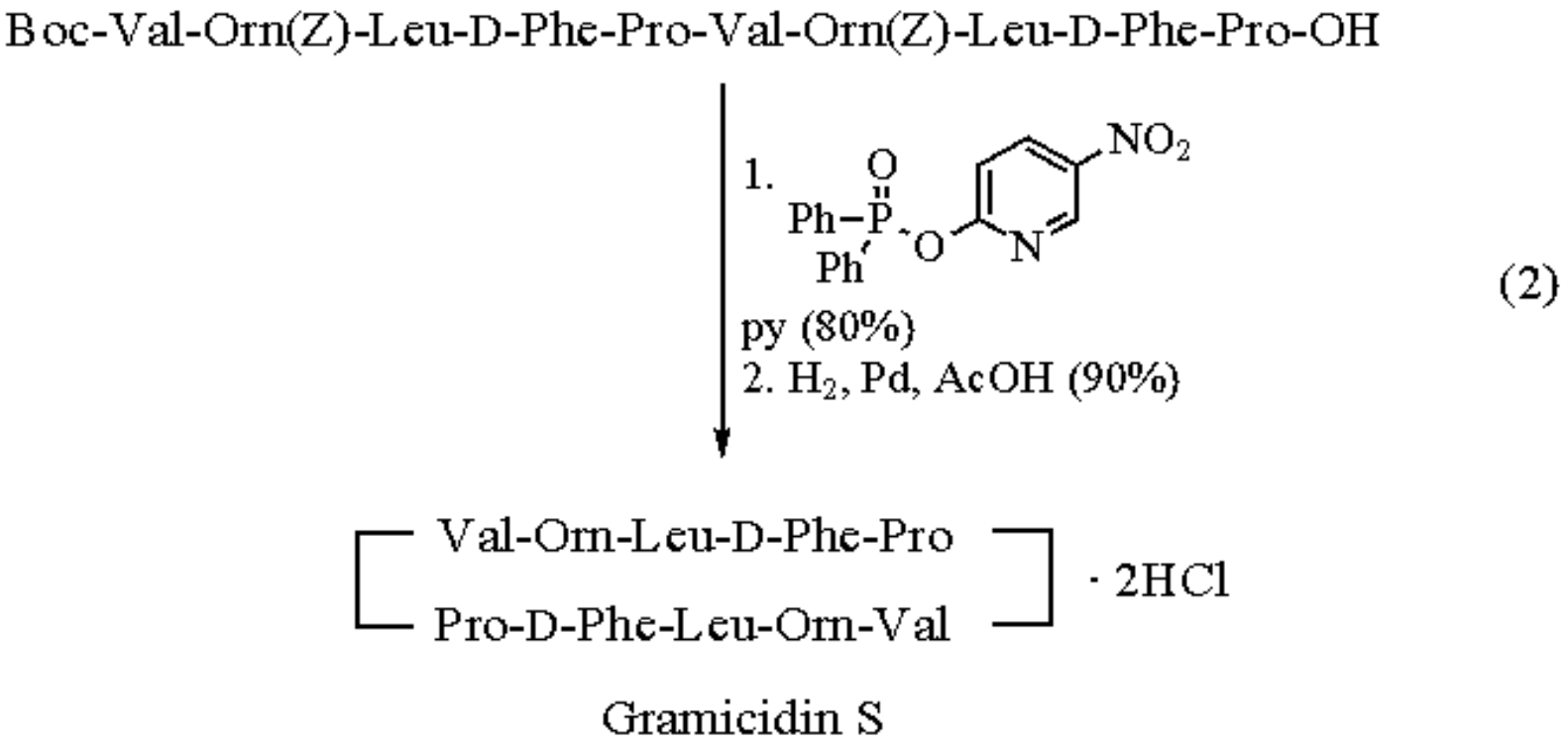

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1. Mukaiyama, T.; Kamekawa, K.; Watanabe, Y. *CL* **1981**, 1367.

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Nitrosocarbonylmethane

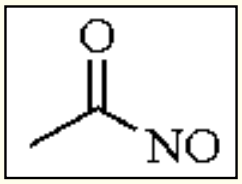

[63115-45-7] · $C_2H_3NO_2$ · Nitrosocarbonylmethane · (MW 73.06)

(ene reactions and [4 + 2]cycloadditions)

Solubility: sol commonly used organic solvents.

Preparative Method: prepared in situ by oxidation of acetohydroxamic acid with tetrapropylammonium periodate.

General Discussion.

Nitrosocarbonylmethane, like other acylnitroso compounds, is an exceptionally reactive substance which must be generated in situ. It participates in a variety of reactions, most notably [4 + 2] cycloadditions and ene reactions. A review by Kirby summarizes much of the early work on this class of compounds.[1]

Two methods for generation of nitrosocarbonylmethane have been most commonly employed. The first is via oxidation of acetohydroxamic acid. Tetraalkylammonium periodates such as ***Tetra-n-butylammonium Periodate*** or tetrapropylammonium periodate have been widely used for this process. Keck examined tetraethyl-, tetrapropyl-, and tetra-n-butylammonium periodates and found the tetrapropylammonium periodate to provide the best balance between ease of preparation and solubility properties. Commonly used solvents include DMF, $CHCl_3$, and CH_2Cl_2.

Nitrosocarbonylmethane generated in this way undergoes [4 + 2] cycloaddition with simple dienes in which the nitroso moiety functions as the dienophile (eq 1).

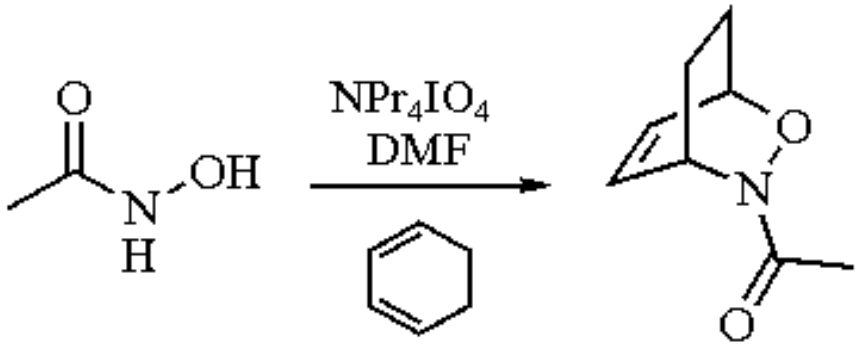

(1)

Oxidation of acetohydroxamic acid in the presence of 9,10-dimethylanthracene leads to the Diels-Alder adduct in good yield. As originally demonstrated by Kirby, this [4 + 2] adduct serves as a very convenient source of nitrosocarbonylmethane under strictly neutral nonoxidizing conditions. Thus (**1**) is a crystalline solid which is easily purified and stable upon storage as the solid; however, heating to 80-110 °C in solution results in release of nitrosocarbonylmethane (and 9,10-dimethylanthracene) (eq 2).[1] The nitrosocarbonylmethane can be employed as a dienophile with other dienes present.

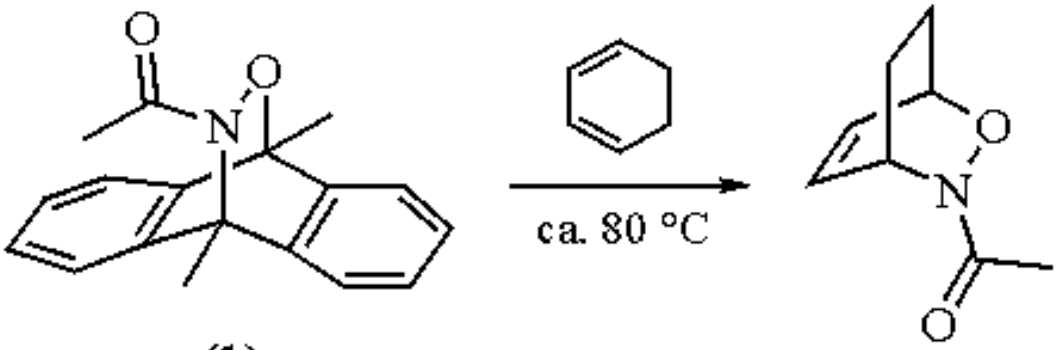

(1)

+ 9,10-DMA (2)

Diels-Alder adducts of other simple nitrosocarbonyl compounds with 9,10-dimethylanthracene can be utilized in similar fashion.

Nitrosocarbonylmethane also participates in ene reactions with appropriate alkenes, and here generation of nitrosocarbonylmethane from (**1**) is preferred. Keck and Yates have provided several examples of ene reactions of simple alkenes using this method (eqs 3 and 4).[2]

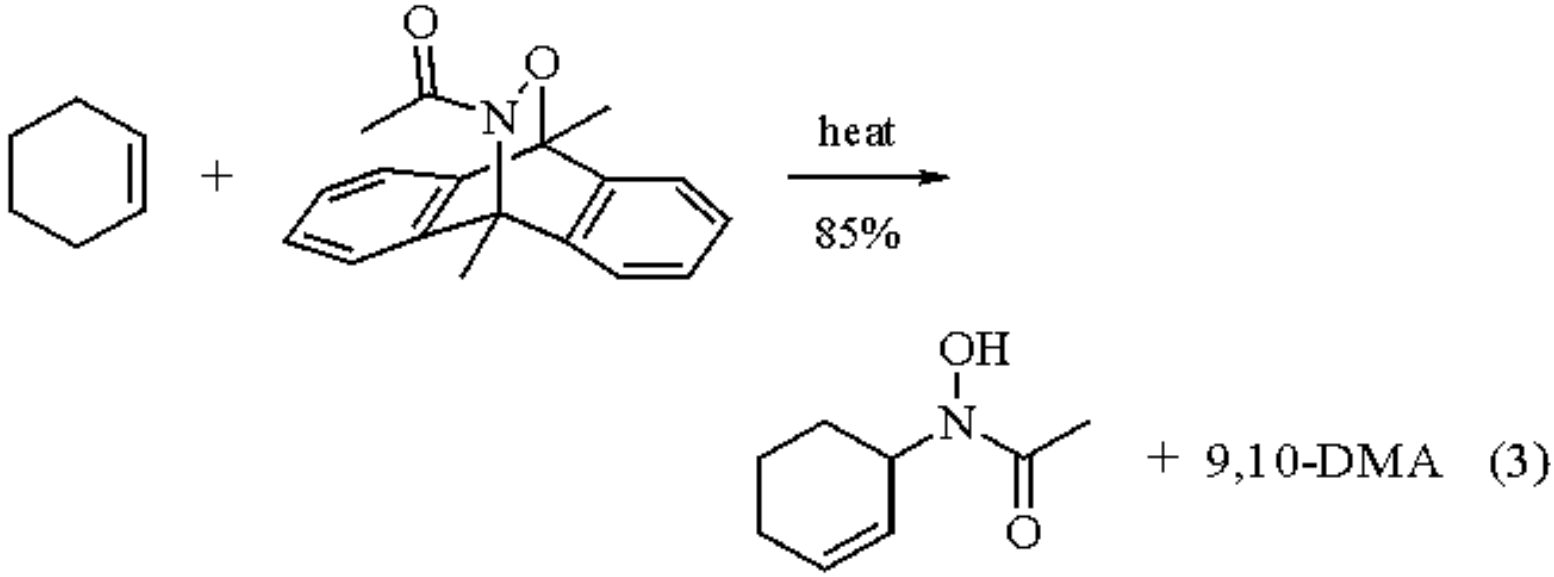

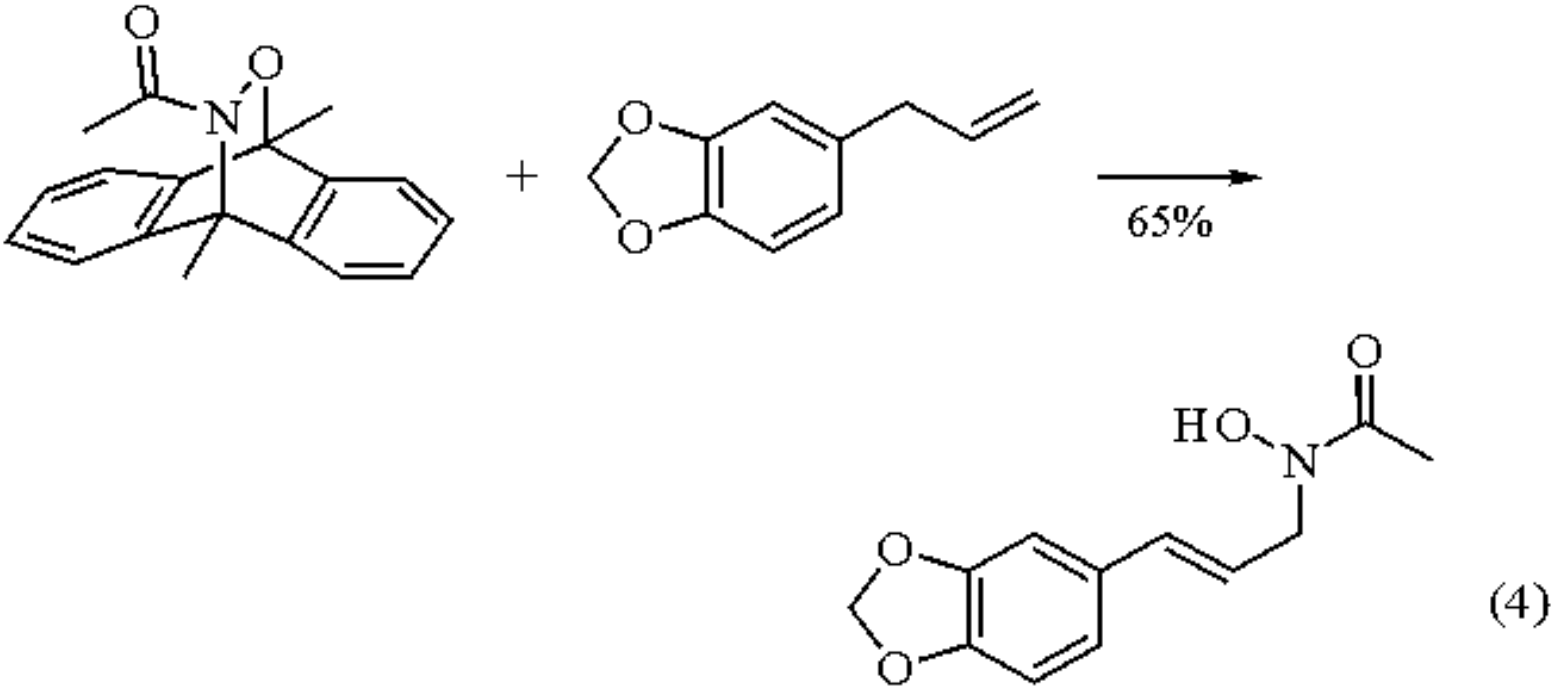

Diels-Alder adduct (**1**) is very useful in the preparation of other more complex nitrosocarbonyl compounds. Keck has demonstrated that the lithium enolate of (**1**) can be generated uneventfully with ***Lithium Diisopropylamide*** and used in a variety of alkylation and condensation reactions (eq 5). This methodology thus provides a surrogate for the enolate of nitrosocarbonylmethane, which is, of course, inaccessible by direct means.

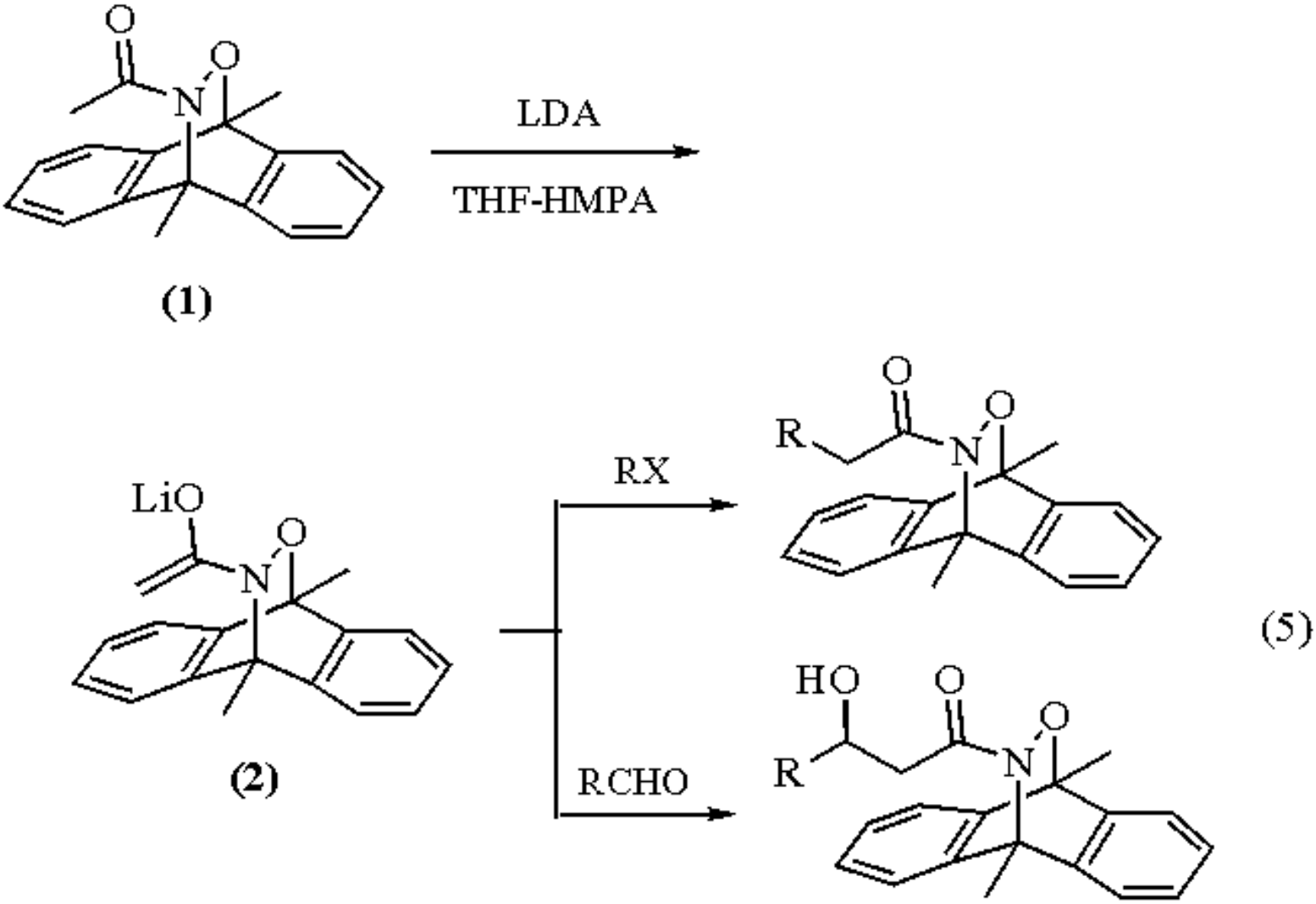

Keck and co-workers have utilized this methodology to effect intramolecular [4 + 2] cycloadditions and intramolecular ene reactions of such substituted derivatives of nitrosocarbonylmethane.[3] For example, condensation of (**2**) with sorbaldehyde affords (**3**); subsequent heating of (**3**) in refluxing benzene then affords (**4**) in very high yield (eq 6).

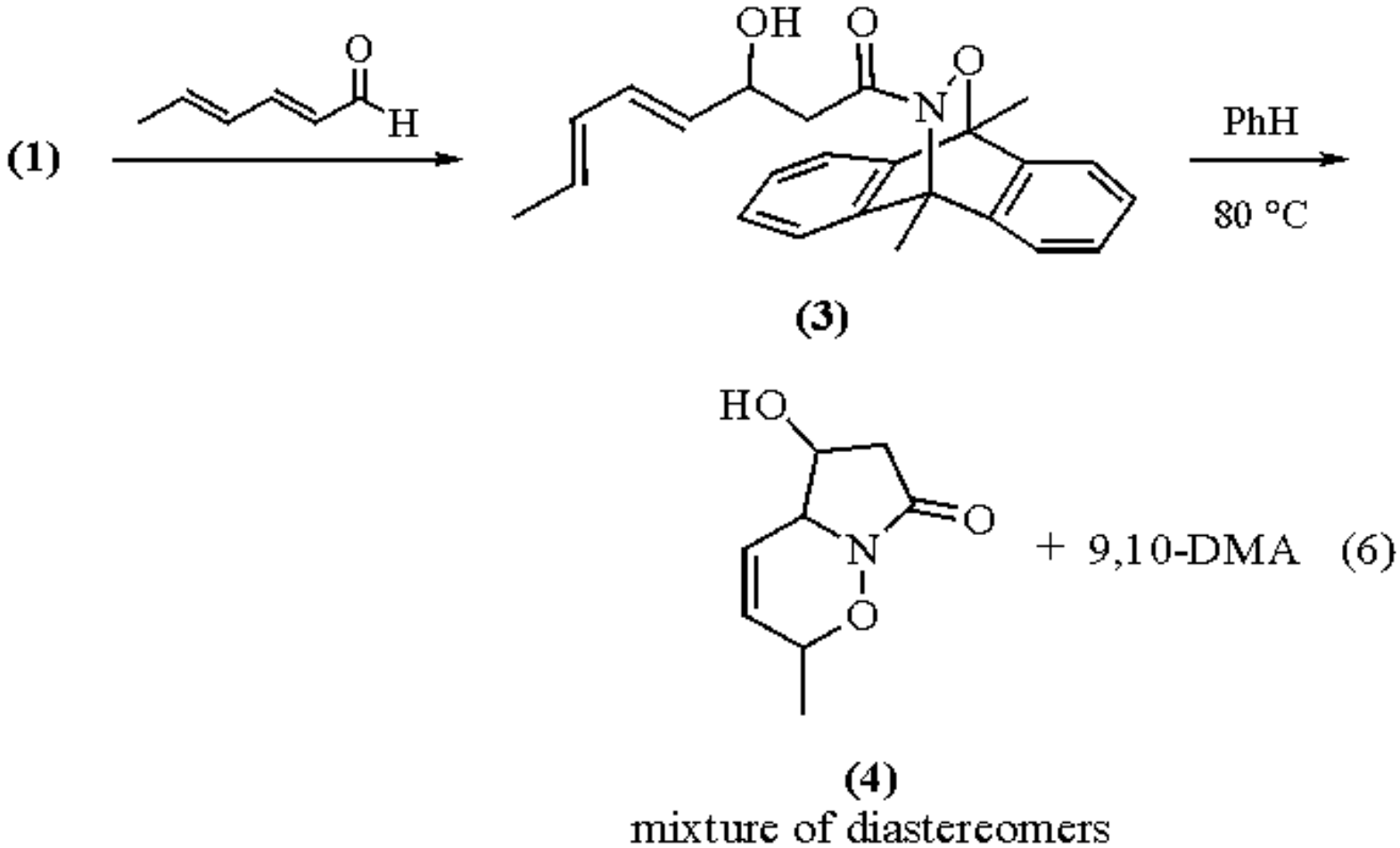

In a synthesis of (+)-perhydrohistrionicotoxin, Keck and Yates used this approach to effect an intramolecular type ene reaction (eq 7).[4]

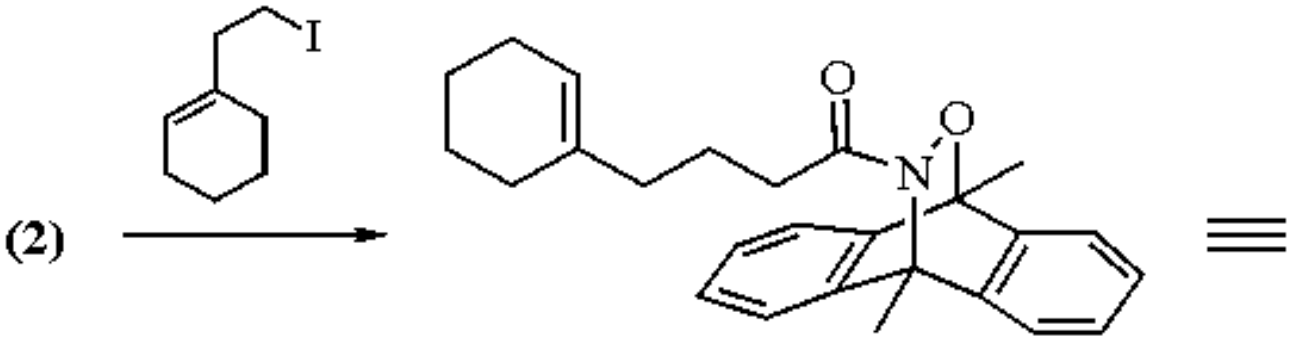

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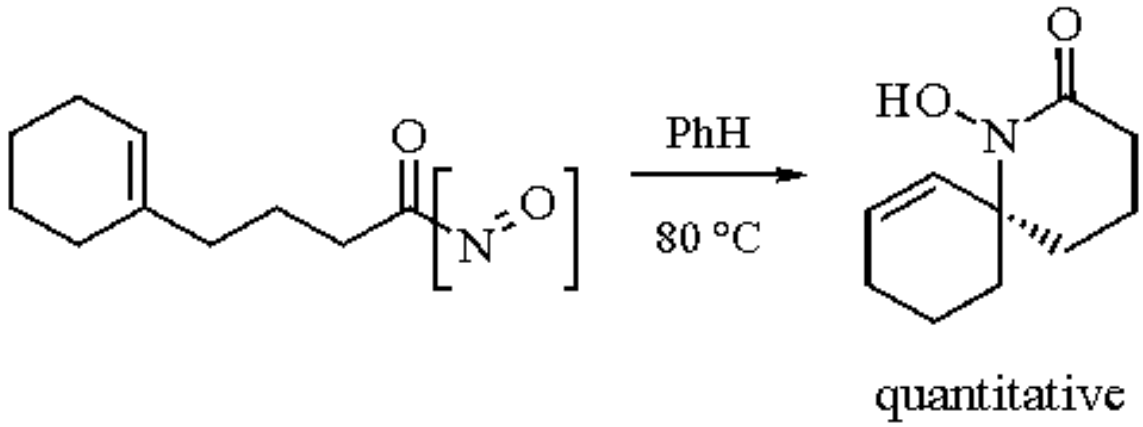

(7)

quantitative

Additional selected examples of this methodology, i.e. utilization of enolate (**2**) to construct substrates for intramolecular Diels-Alder reactions or ene reactions of substituted derivatives of nitrosocarbonylmethane, are shown (eqs 8 and 9).[5]

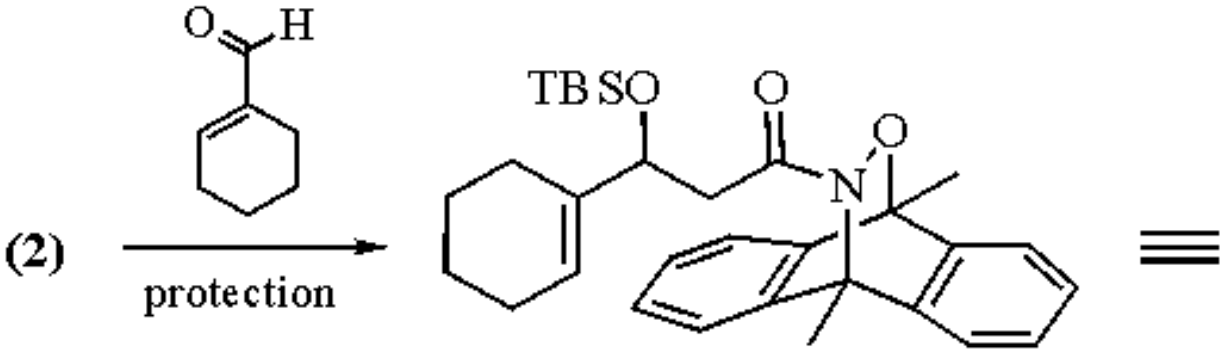

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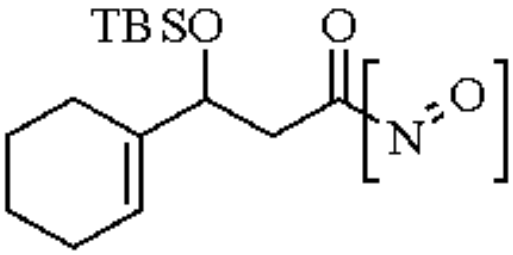

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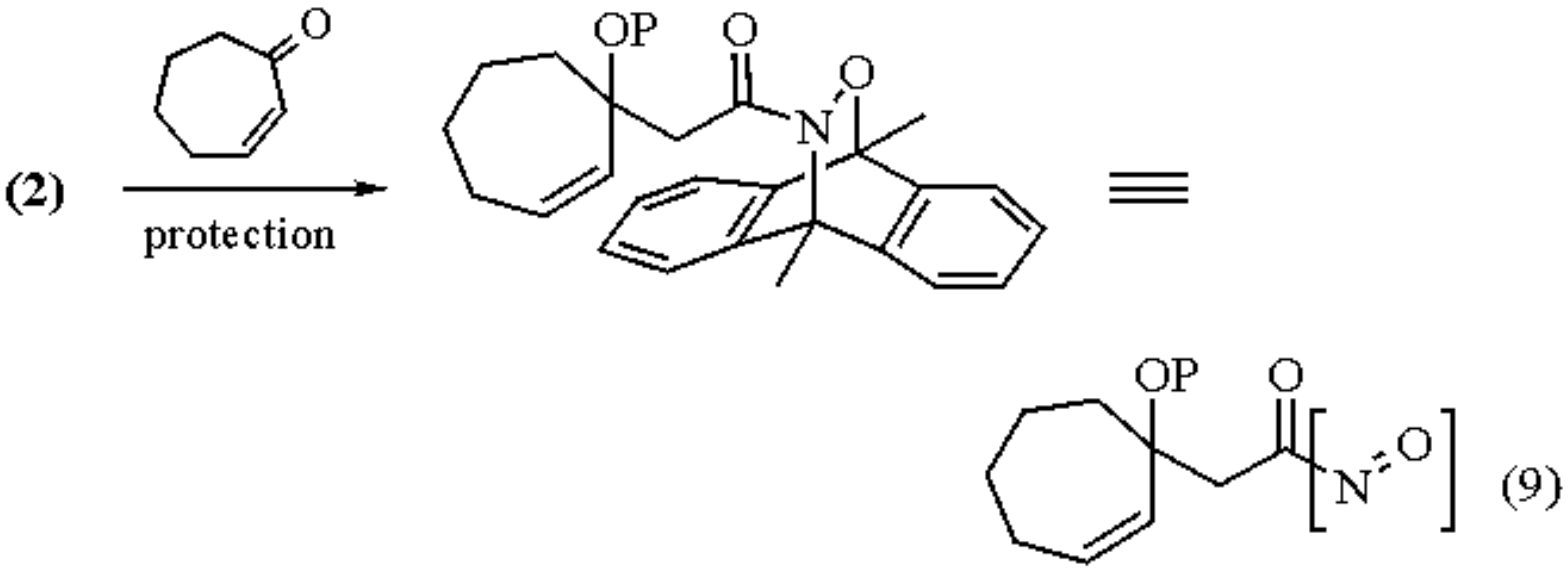

The N-O bond in such Diels-Alder or ene products is easily cleaved reductively. Reagents commonly employed include ***Zinc-Acetic Acid***, ***Aluminum Amalgam***, ***Sodium Amalgam***, ***Titanium(III) Chloride***, and various catalytic hydrogenation protocols. The ease of this reduction, and the possibility for hydroxylation of the C=C double bond produced in the [4 + 2] cycloaddition, has made this a popular strategy for the synthesis of numerous polyhydroxylated nitrogen containing compounds.

For nitrosocarbonylmethane itself, the regioselectivity of bimolecular Diels-Alder reactions is often low. For example, reaction with 1-*t*-butyldimethylsilyloxybutadiene leads to a 1:1 mixture of regioisomeric Diels-Alder adducts (eq 10).[6]

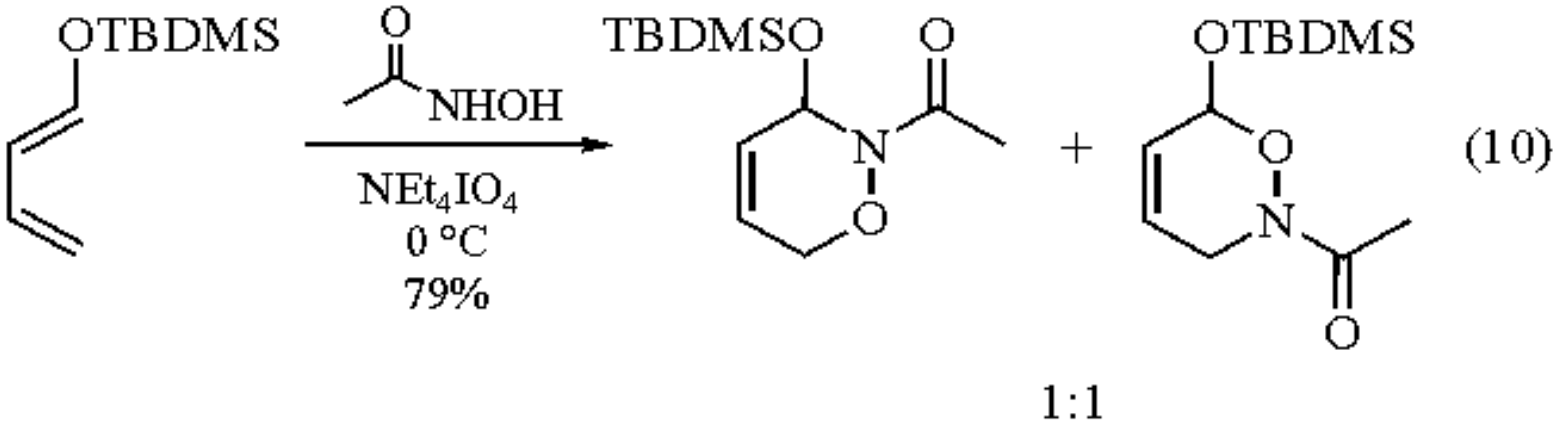

Kirby has also noted the formation of a very unusual product upon reaction of nitrosocarbonylmethane with dienamine (**5**) (eq 11).[7]

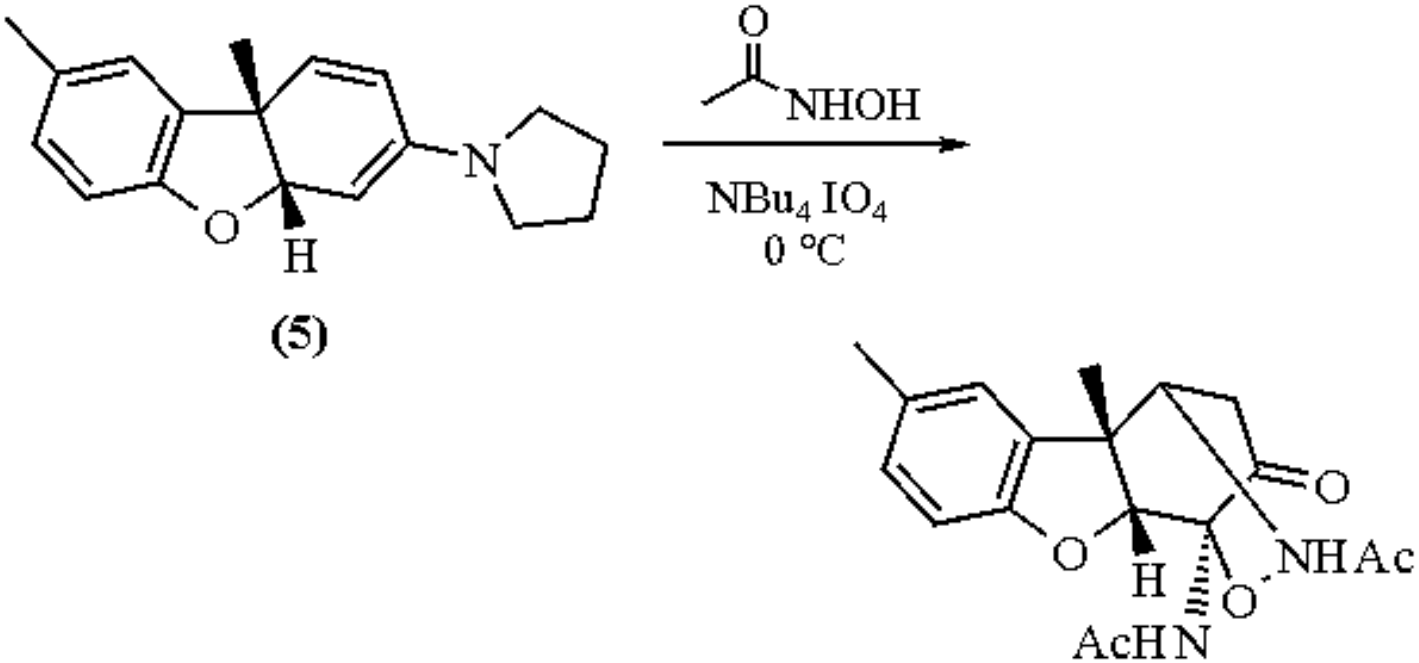

Related Reagents.

Benzyloxyhydroxamic Acid.

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1. Kirby, G. W. *CSR* **1977**, *1*, 6.
2. Keck, G. E.; Yates, J. B. *TL* **1977**, *48*, 4627.
3. Keck, G. E.; Nickell, D. G. *JACS* **1980**, *102*, 3632.
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6. Streith, J.; Pires, J.; Defoin, A. *SL* **1990**, *2*, 111.
7. Kirby, G. W.; Freer, A.; Islam, A.; Mahajan, M. *H.* **1989**, *28*, 147.

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N-Nitrosodimethylamine[1]

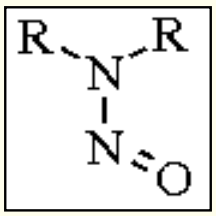

(R = Me)

[62-75-9] · $C_2H_6N_2O$ · *N*-Nitrosodimethylamine · (MW 74.10) (R = Et)

[55-18-5] · $C_4H_{10}N_2O$ · *N*-Nitrosodiethylamine · (MW 102.16) (R = $-(CH_2)_4-$)

[130-55-2] · $C_4H_8N_2O$ · *N*-Nitrosopyrrolidine · (MW 100.14)

(lithiation of the title reagent and its analogs generates α-amino carbanion equivalents which can be alkylated and denitrosated to form secondary amines, 1,2-amino alcohols, α-amino acids, and related compounds[1])

Physical Data: R = Me: bp 154 °C/760 mmHg; *d* 1.006 g cm^{-3}. R = Et: bp 177 °C/760 mmHg; *d* 0.943 g cm^{-3}. R = $(CH_2)_4$: bp 104-106 °C/20 mmHg; *d* 1.085 g cm^{-3}.

Form Supplied in: the three nitrosamines shown are commercially available; others may be prepared from secondary amines and ethyl nitrite by transfer of the nitroso group.

Handling, Storage, and Precautions: nitrosodialkylamines are carcinogenic;[2] use a fume hood; handling and precautions are described by Seebach and Enders.[1]

Introduction.

Nitrosodimethylamine and analogous compounds are important for synthesis of 1.1-dialkylhydrazines (being substrates, not reagents for this purpose). Nitrosodimethylamine (**1**) can be a source of either the dimethylamino group or the nitroso group,[3] but due to its carcinogenicity it is no longer a competitor to other sources of these groups. It is, however, very useful for C-C bond formation with carbon electrophiles. By the reaction sequence lithiation (in this case a typical umpolung), action of an electrophile El-X, and denitrosation, the starting amine is converted to another secondary amine with formal substitution of an α-H by the electrophile (eq 1).

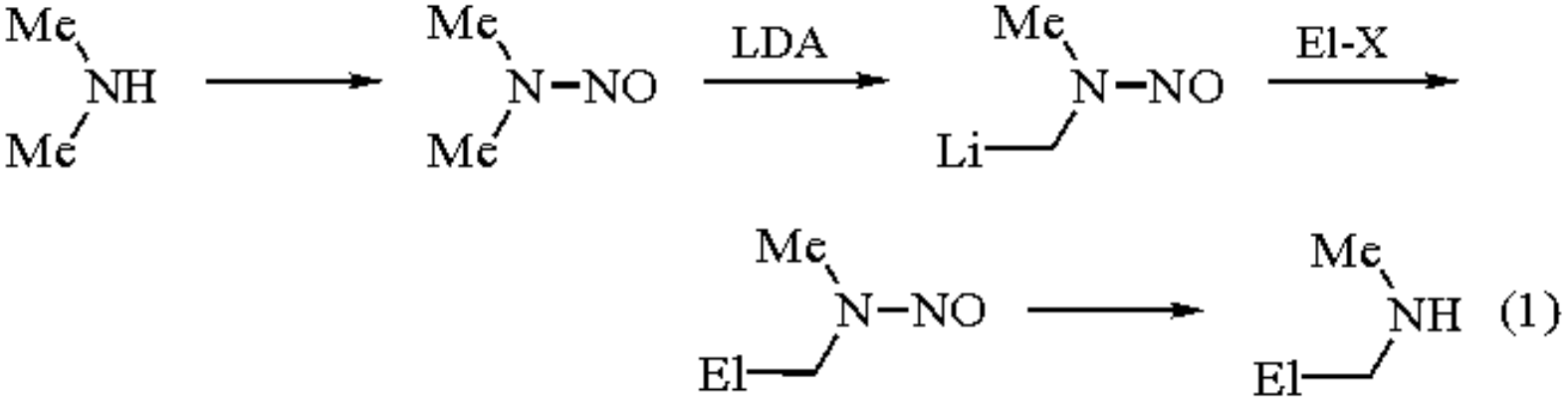

Lithiation.

Solutions of the nitrosamine can be used after removal of the ethanol without isolation or purification. Lithiation is carried out with ***Lithium Diisopropylamide***; 5 min at -80 °C is sufficient time for metalation of a methyl group, 1 h at rt is necessary for a methylene group. Kinetically controlled regiospecific lithiation at the methyl group of an unsymmetrical *N*-nitrosamine can be effected. ***Hexamethylphosphoric Triamide*** increases the metallation rate and stabilizes the solutions of the reagents. Metalation yields of simple aliphatic *N*-nitrosamines often exceed 90%, whereas those of cyclic aliphatic *N*-nitrosamines with four- to seven-membered rings are in the 50-70% range.

C-Alkylation.

C-Alkylation proceeded smoothly in all investigated cases. Alkylation yields for lithiated *N*-nitrosodimethylamine with ***Iodomethane***, *n*-butyl iodide, ***Allyl Bromide***, and ***Benzyl Bromide*** were 75, 75, 90, and 95%, respectively. Alkylation of alkyl lithiomethylnitrosamines with the same alkyl halides gave the corresponding products in ca. 90% yields, whereas alkylation of the cyclic *N*-nitrosamines occurred in ca. 60% yield. Aldehydes and ketones undergo addition to give 1,2-amino alcohols. Thus the pharmaceutically important arylamino alcohols are easily accessible (eq 2). Carboxylations proceed smoothly (eq 3); reaction with acid halides leads to derivatives of α-amino ketones (eq 4). Michael additions to α,β-unsaturated ketones (eq 5) lead to nitrosamines of γ-amino ketones. Additions to nitroalkenes are also possible (eq 6).

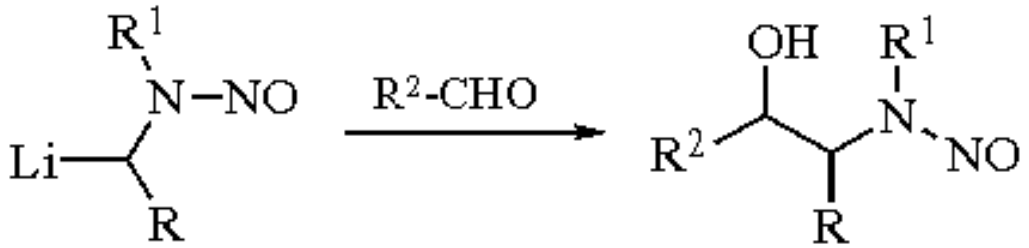

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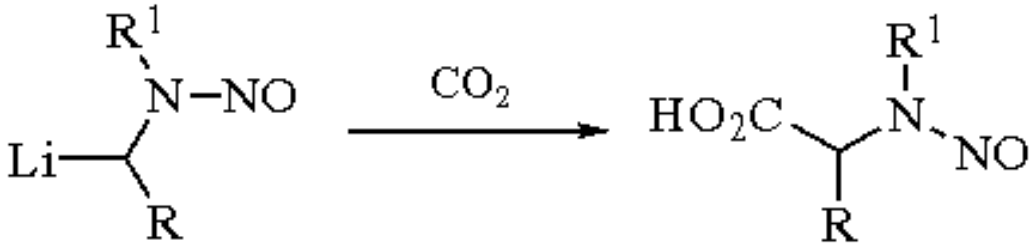

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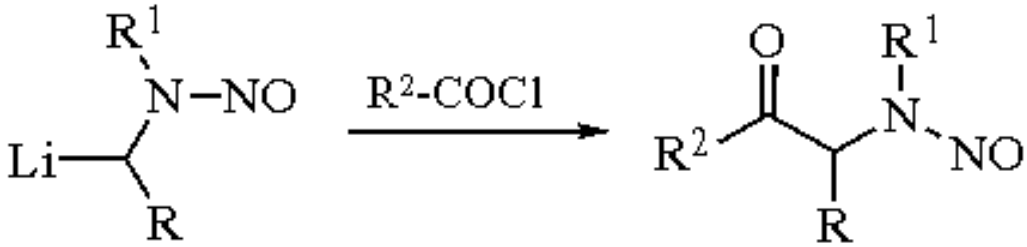

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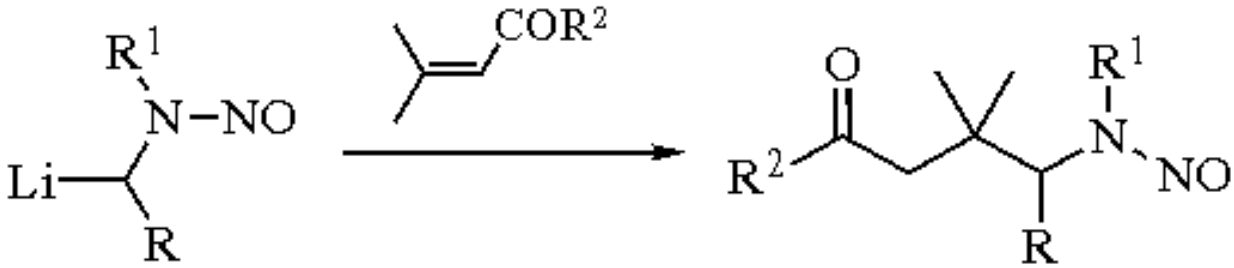

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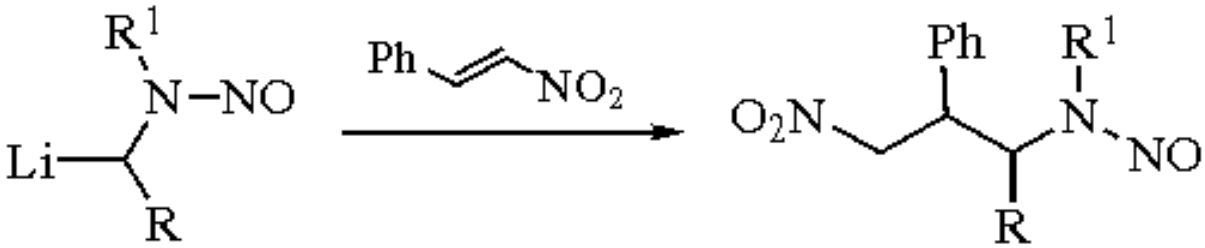

(1) (6)

Nitriles react with subsequent formation of triazoles (eq 7). The following hetero electrophiles also afforded the expected substitution products: ***Chlorotrimethylsilane***, ***Chlorotrimethylstannane***, disulfides, and diselenides.[4]

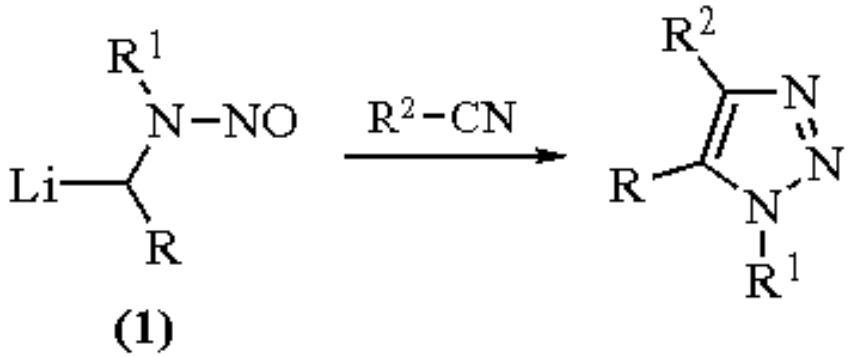

(7)

Denitrosation.

Denitrosation by acid alone is a very slow reaction,[5] and a reducing species must be present. Preference is given to either ***Hydrogen Bromide/Acetic Acid*** or ***Raney Nickel***. Catalysis by a copper salt is also reported. The review of the inventors of the method recommends a one-pot procedure combining nitrosation, metalation, alkylation, and denitrosation without isolation of any intermediates.

When the lithiation-alkylation sequence is to be carried out twice, the conformation of the nitrosamino group controls the kinetic position of lithiation.[6] The position of entry of the second alkyl group also depends on temperature.

When two alkylations are carried out at the two α-positions of e.g. nitrosopyrrolidine, the steric result depends on the final protonation step,[7] and may be controlled by the conditions of protonation.

Related Reagents.

N-t-Butoxycarbonyl-N-methylaminomethyllithium; ***N´-t-Butyl-N,N-dimethylformamidine***; ***Dimethylaminomethyllithium***; ***N-(Diphenylmethylene)methanamine***.

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1. (a) Seebach, D.; Enders, D. *AG(E)* **1975**, *14*, 15. (b) Seebach, D.; Enders, D. *CB* **1975**, *108*, 1293.
2. Druckrey, H. *AG(E)* **1970**, *9*, 777.
3. *FF* **1975**, *5*, 479; **1977**, *6*, 336.
4. Seebach, D.; Enders, D. *JMC* **1974**, *17*, 1225.
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Nitrosonium Tetrafluoroborate[1]

$NO^+BF_4^-$

[14635-75-7] · BF_4NO · Nitrosonium Tetrafluoroborate · (MW 116.82)

(efficient nitrosating and diazotizing agent;[1] mild oxidant;[2] hydride- and halide-abstracting agent[2])

Physical Data: d 2.185 g cm^{-3}.[3]

Solubility: sol acetonitrile.

Form Supplied in: colorless crystalline compound; commercially available.

Purification: commercial $NO^+BF_4^-$ frequently contains some $NO_2^+BF_4^-$; NO_2^+ can be removed from $NO^+BF_4^-$ by washing with dry benzene; sublimation (200-250 °C/0.01 mmHg) can be used if highly pure $NO^+BF_4^-$ is needed.[3]

Handling, Storage, and Precautions: due to its hygroscopic nature, $NO^+BF_4^-$ should be stored and used under anhyd conditions; use in a fume hood.

Nitrosation.

$NO^+BF_4^-$ is a highly efficient nitrosating agent, and has been used widely for synthetic purposes. Alcohols and secondary amines react readily with $NO^+BF_4^-$ to form alkyl nitrites and nitrosamines, respectively, in high yields (eqs 1 and 2).[4] Nitrosation of less reactive *N*-alkylamides and sulfonamides can also be achieved without difficulty, where other nitrosating agents are not effective.[5,6] Reaction of $NO^+BF_4^-$ with pyridine yields *N*-nitrosopyridinium tetrafluoroborate.[7] Aziridines react with $NO^+BF_4^-$ to yield nitrosoaziridines. Extrusion of N_2O from the products under thermal decomposition conditions led to formation of carbon-carbon double bonds.[8] This reaction has been employed for the synthesis of *cis*-diazabis-σ-homobenzene.[8a]

$$ROH + NO^+BF_4^- \longrightarrow RONO \qquad (1)$$

$$R^1R^2NH + NO^+BF_4^- \longrightarrow R^1R^2NNO \qquad (2)$$

$$R^1 = \text{alkyl};\ R^2 = \text{alkyl, acyl}$$

Diazotization and Related Reactions.

When primary amines react with $NO^+BF_4^-$, diazonium tetrafluoroborates are generated.[1] This reaction has been extensively studied with arylamines, since it is particularly useful for the isolation of the corresponding diazonium tetrafluoroborates (eq 3).[9] Decomposition of these salts produces fluoroarenes.[10] Isocyanates also react with $NO^+BF_4^-$ to yield diazonium salts.[2a,11] Primary amides can be converted to acids by $NO^+BF_4^-$ via diazotization and subsequent hydrolysis.[12]

$$ArNH_2 \xrightarrow{NO^+BF_4^-} ArN_2^+BF_4^- \longrightarrow ArF \qquad (3)$$

Treatment of alkyl azides with $NO^+BF_4^-$ led to the formation of carbenium ions, which can be intercepted with various nucleophiles such as fluoride, hydroxide, carboxides, and nitriles.[13] The reaction using nitriles has been utilized to prepare dihydroisoquinolines and oxazoles. Vinyl azides react with $NO^+BF_4^-$ to form 1,2,5-oxadiazoles and/or 1,2,4-oxadiazoles, depending on the structures of the substrates.[14] When 1,2-dialkylvinyl azides are used, 1,2,5-oxadiazoles were obtained as the only heterocyclic compounds in 75-80% yields.

Various substituted hydrazines react with $NO^+BF_4^-$ to form azides.[15]

Oxidation.

$NO^+BF_4^-$ is a mild oxidant, with NO/NO^+ having 1.5 V standard oxidation-reduction potential in acetonitrile.[16] It has been widely used as a single electron transfer oxidant. Many arene- and sulfur-containing radical cations have been prepared by treatment of corresponding precursors with $NO^+BF_4^-$ (eq 4).[17,18] The easy removal of the side-product NO makes the procedure especially convenient. These radical cations have played a significant role in the development of organic ferromagnets and conductors.

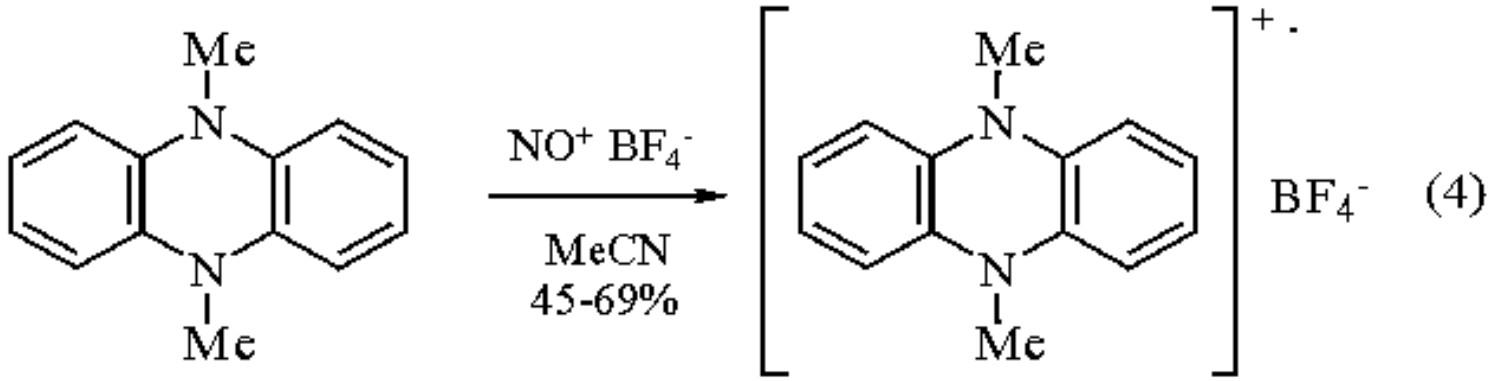

The oxidative property of $NO^+BF_4^-$ has also been synthetically utilized to regenerate carbonyl groups from masked derivatives such as 1,3-dithioacetals, oximes, and dimethylhydrazones.[19]

The same principle was applied to stereospecific construction of *O*-glycosidic linkages.[20] Treatment of readily available methyl *S*-glycosides with an equimolar amount of $NO^+BF_4^-$ in dry methylene chloride at temperatures between 0 and 25 °C gives high yields of *O*-glycosides in the presence of a hydroxylic component (eq 5). The stereospecificity and lack of complications compared with earlier methods make this procedure very attractive.

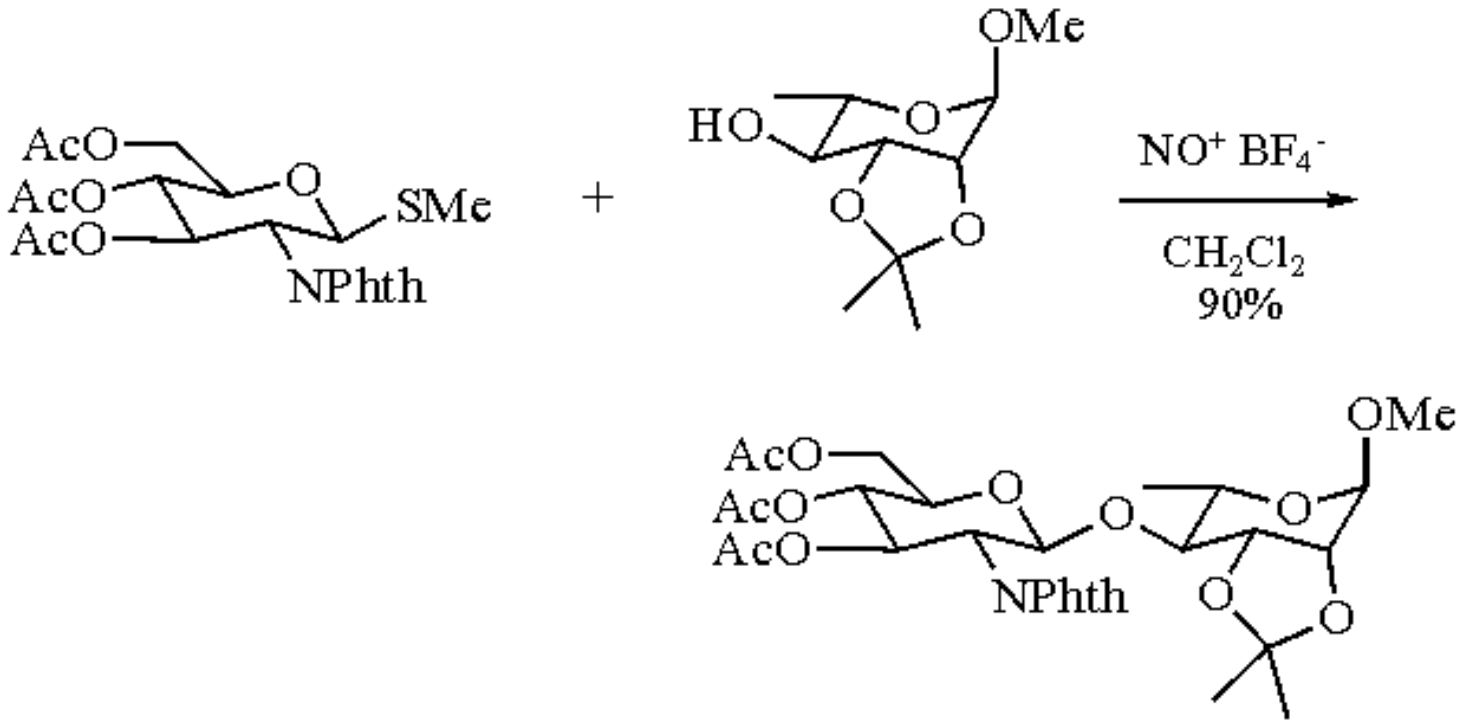

(5)

Noteworthy is the oxidative iodination of aromatic compounds with $NO^+BF_4^-$ as catalyst.[21] A wide range of arenes were iodinated with the system $I^-/O_2/NO^+BF_4^-$.[21b] This method is not as effective as I_2/Ag^+, but much more efficient than the use of other oxidative iodination systems such as I_2/Ce^{IV} salts and $I_2/(NH_4)_2S_2O_8$. The more important feature of this transformation is the suppression of side-chain oxidation of alkylarenes.[21c]

Electrophilic Addition to Unsaturated Carbon-Carbon Bonds.

As an electrophilic agent, $NO^+BF_4^-$ is able to initiate electrophilic addition to unsaturated carbon-carbon bonds. Reaction of alkenes with $NO^+BF_4^-$ in the presence of acetonitrile yields imidazoles after reduction (eq 6).[22a] Changing acetonitrile to dimethyl sulfide led to formation of nitrososulfonium tetrafluoroborate (in dimer form).[22b] The dimer can be depolymerized, tautomerized, and hydrolyzed to give oxosulfonium salt, which can be utilized synthetically. $NO^+BF_4^-$ was reported to dimerize certain alkenes and alkynes.[22c,d] In the latter case, the true identity of the reagent that initiates the reaction (whether it is NO^+ or NO_2^+) is unclear. $NO_2^+BF_4^-$ is known to induce the same reaction.[22d]

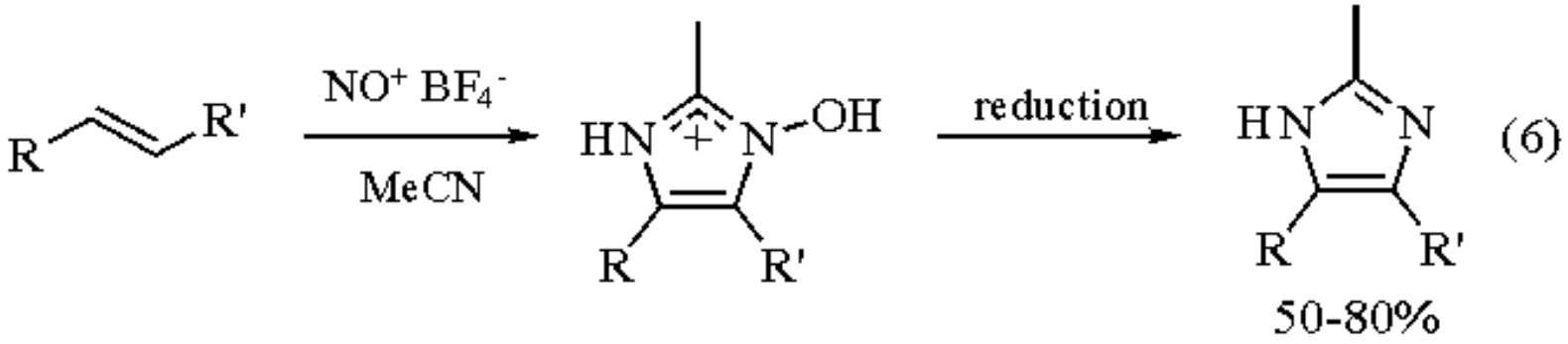

NO^+ can also insert into the cyclopropane ring, offering a new route to 2-isoxazolines.[23]

Hydride and Halide Abstraction.

$NO^+BF_4^-$ is able to abstract a hydride from a tertiary C-H bond, generating a carbocation. The carbocationic intermediate can be trapped by a fluoride or alkyl nitriles, forming alkyl fluorides or *N*-alkylamides respectively.[24] Silanes also react with $NO^+BF_4^-$ to form fluorosilanes.[25]

In a similar fashion, NO^+ can also abstract a halogen atom from alkyl halides. In the presence of alkyl nitriles, *N*-alkylamides were obtained as a consequence of the Ritter reaction.[26]

Addition to Allenylsilanes.

Allenylsilanes react with nitrosonium tetrafluoroborate in acetonitrile at -30 °C to form 4-trialkylsilylisoxazole derivatives in good yield.[27] This method provides a regiospecific [3 + 2] annulation route to unsymmetrically substituted isoxazoles. The silylisoxazole products can be further elaborated by electrophilic substitution in the same operation (eqs 7 and 8). In these [3 + 2] annulations, $NOBF_4$ is distinctly superior to other nitrosating agents such as ***Nitrosyl Chloride*** and ***Nitrosylsulfuric Acid***.

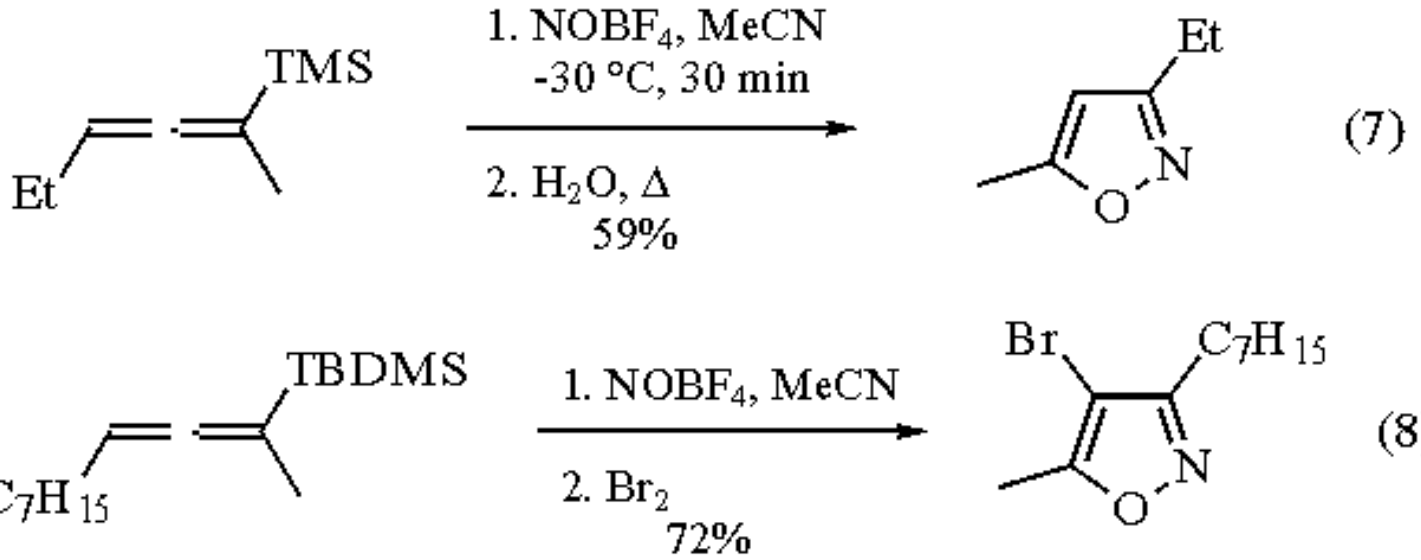

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Nitrosyl Chloride[1]

ClNO

[2696-92-6] · ClNO · Nitrosyl Chloride · (MW 65.46)

(electrophilic and radical nitrosating agent for synthesis of a wide range of nitroso compounds, diazotization, and deamination; addition to alkenes yields chloronitroso derivatives; at high temperatures will chlorinate alkanes)

Physical Data: mp -61.5 °C; bp -6.4 °C; *d* (-12 °C) 1.417 g cm^{-3}; *d* (gas) 2.99 g L^{-1}.

Solubility: sol alcohols, ethers, $CHCl_3$; hydrolyzed in water to give HNO_2, HNO_3, NO, and HCl.

Form Supplied in: readily available as an orange-yellow gas in cylinders, easily condensed to a deep red liquid; often more convenient to generate ClNO in situ from alkyl nitrites and HCl in ether, ethanol, or other organic solvents, or in water from HNO_2 and HCl (or H^+ and Cl^-).

Handling, Storage, and Precautions: ClNO gas is highly irritating to the skin, eyes, and mucous membranes; very irritating odor; can cause fatal pulmonary edema; use in a fume hood; can react violently with acetone.

Nitrosation.

ClNO acts as a powerful electrophilic nitrosating agent,[2] reacting with primary amines to give diazonium ions, secondary amines to give nitrosamines (eq 1), alcohols to give alkyl nitrites, thiols to give thionitrites, and carbonyl compounds to give (usually) keto oximes.[3] The product of *C*-nitrosation can be the monomeric nitroso compound (blue), dimeric nitroso compound (white), or the tautomeric oxime, depending on substrate structure. Cyclic ketones often yield dioximes. ClNO is the effective reagent when diazotization, etc., is carried out in hydrochloric acid[4] (using ***Sodium Nitrite***) due to the equilibrium given in eq 2, for which the equilibrium constant at 25 °C is 1.1×10^{-3} L^2 mol^{-2}.[5]

$$R_2NH + ClNO \longrightarrow R_2NNO + H^+ + Cl^- \quad (1)$$

$$HNO_2 + H^+ + Cl^- \rightleftharpoons ClNO + H_2O \quad (2)$$

The use of ClNO dissolved in organic solvents (or generated in situ from alkyl nitrites and HCl) has some advantage synthetically over acidic aqueous solutions of HNO_2, for reactions of compounds (for example, amines or amides) which only have a limited solubility in water.

ClNO is a very reactive species and reacts with aromatic amines of pK_a >~4 at the encounter limit.[6] BrNO is, as expected, less reactive but bromide ion (and thiocyanate ion) catalysis of nitrosation in water is more pronounced because of the much larger equilibrium constant for BrNO formation.

Ring opening of cyclic ketones can occur by reaction with ClNO and EtOH in liquid SO_2 (eq 3).[7]

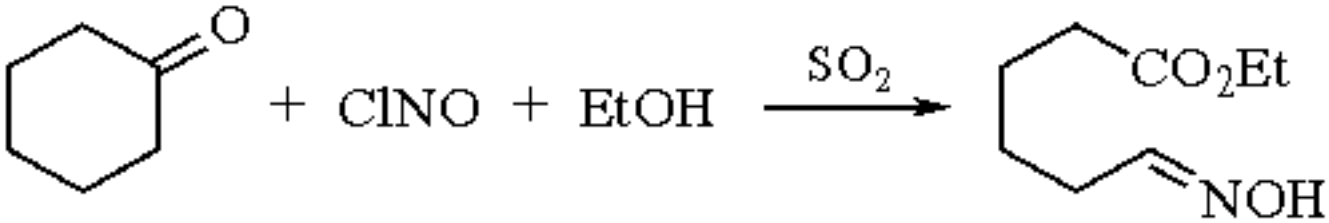

(3)

With alkenes, addition occurs to give chloronitroso products (eq 4),[8] a reaction which has some synthetic utility, for example in aziridine synthesis[9] (after reduction of the NO group to NH_2 and ring closure). Generally, ClNO addition follows the Markovnikov rule for unsymmetrical alkenes (and is interpreted as proceeding via a nitroso carbocation intermediate). This reaction was much used in the past to characterize terpenes.[10] With some bicyclic systems (including norbornene and norbornadiene), there is evidence of *syn* addition via a four-center transition state.[11] Generally good yields for this reaction can be obtained by using $NaNO_2$ and HCl.

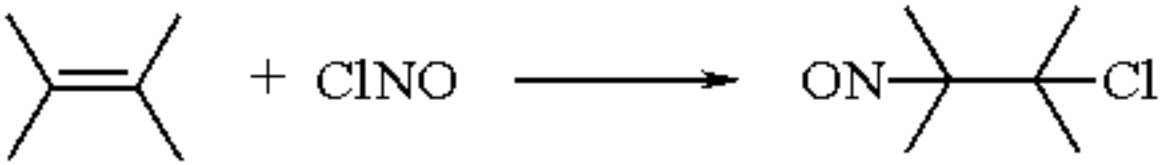

(4)

Nitroso products can also be obtained photochemically via a radical pathway.[12] An example is shown in eq 5. Under some conditions, *gem*-chloronitroso products are formed (eq 6). The former reaction is used industrially with cyclohexanecarboxylic acid in the manufacture of ε-caprolactam.

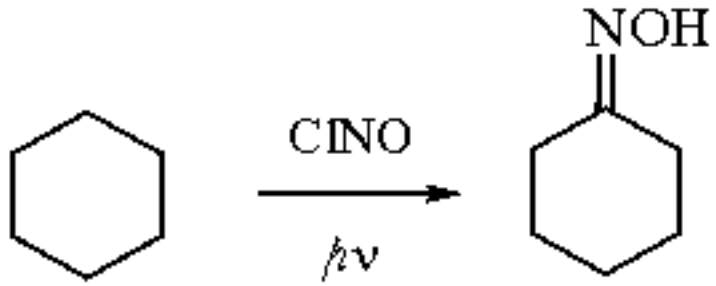

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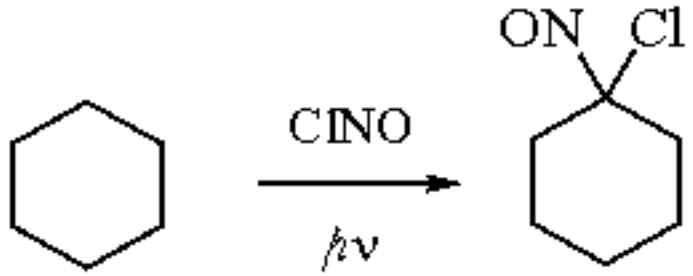

(6)

Peroxycarboxylic acids react with ClNO to give *C*-nitroso compounds.[13] Organometallic compounds such as alkyl (and aryl) Grignard reagents[14] also give nitroso compounds with ClNO.

Chlorination.

At higher temperatures than those used for nitrosation, ClNO will act as a chlorinating agent, particularly for alkanes, again probably by a radical pathway. Chlorinations have also been achieved in other solvents; for example, that of sulfoxides in $CHCl_3$-pyridine (eq 7)[15] and the conversion of thioamides to imidoyl chlorides (eq 8).[16]

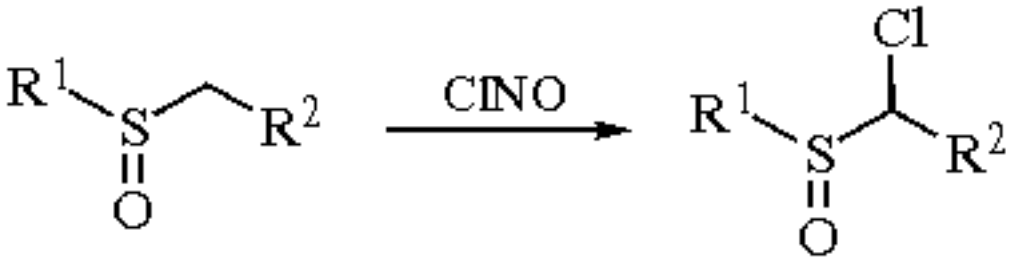

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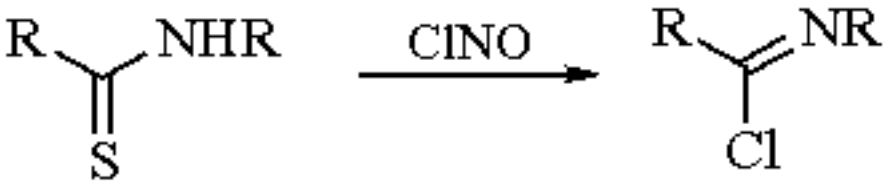

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Nitrosylsulfuric Acid

$NOHSO_4$

[7782-78-7] · HNO_5S · Nitrosylsulfuric Acid · (MW 127.09)

(nitrosating and diazotizing agent; moderate oxidizing agent)

Physical Data: mp 70 °C.

Solubility: sol sulfuric acid; slightly sol acetic acid, acetonitrile, nitromethane, DMF insol most other organic solvents.

Form Supplied in: pale yellow crystals; commercially available.

Preparative Method: dry SO_2 is allowed to pass into a mixture of 98% nitric acid and acetic acid (3:1) at 0 °C; the precipitated $NOHSO_4$ is washed with acetic acid and carbon tetrachloride and dried under vacuum to give the analytically pure reagent.[1]

Handling, Storage, and Precautions: stable at rt; protect from moisture; use in a fume hood.

Nitrosation.

Like other nitrosonium salts, namely ***Nitrosonium Tetrafluoroborate*** and $NOPF_6$, nitrosylsulfuric acid is an efficient nitrosating agent. It has been reported that $NOHSO_4$ is superior to ***Nitrosyl Chloride*** for the nitrosation of *N*-acylarylamines such as 4-methoxy-3-nitroacetoanilide and 5-acetamido-6-methoxyquinoline (eq 1).[2] $NOHSO_4$ has also been shown to be more efficient than other classical nitrosating agents such as ***Isopentyl Nitrite***, phenyl nitrite, and ***Sodium Nitrite***. For example, successful nitrosation of 3-methyl-5-acetamidoisothiazole was achieved by utilizing nitrosylsulfuric acid in DMF, whereas previous attempts using isopentyl nitrite or sodium nitrite in acetic acid had failed (eq 2).[3] Nitrosation of thebaine in methanol under different conditions using nitrosyl chloride, phenyl nitrite, and $NOHSO_4$ all gave the oxime together with varying amounts of other bimolecular products.[4]

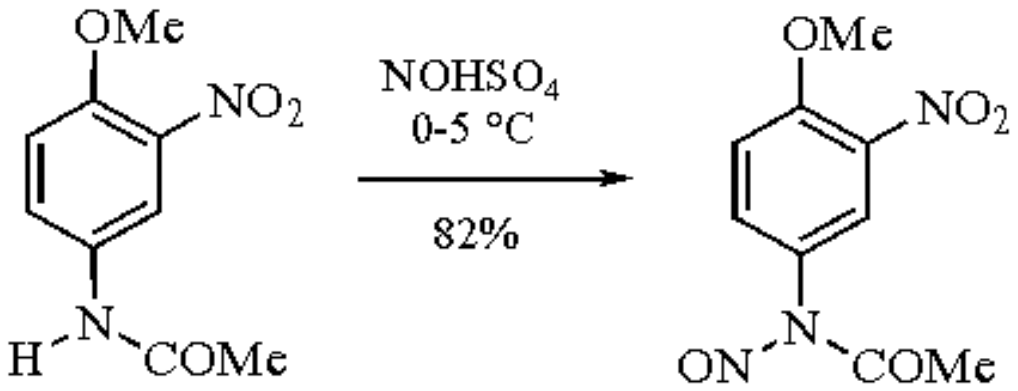

(1)

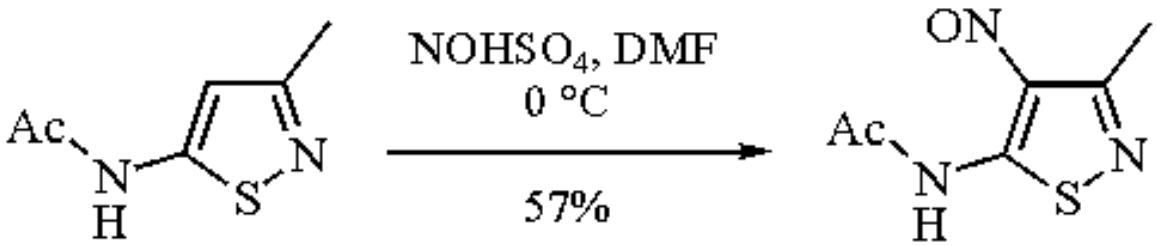

(2)

The conversion of cyclohexanecarboxylic acid or cyclohexyl aryl ketone to ε-caprolactam by treatment with $NOHSO_4$ in the presence of SO_3 (eq 3) may involve the nitrosation of an enol and Beckmann rearrangement.[5] Nitrosation of pentamethyleneketene under similar conditions also gives ε-caprolactam.[6] Lactams with 11 and 12 carbon atoms in their rings were obtained in good yields by treating cycloundecanoic acid and cyclododecanoic acid with $NOHSO_4$ in chloroform.[7]

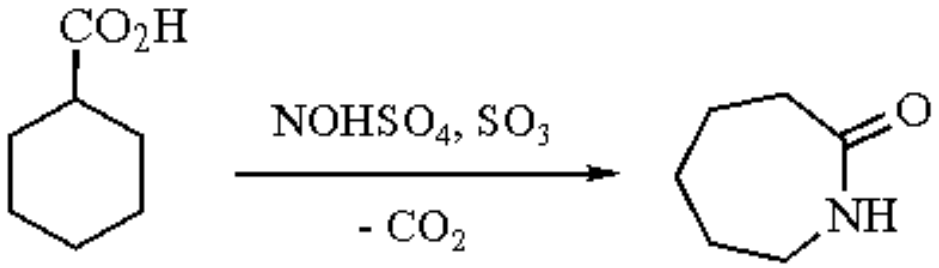

(3)

Diazotization and Related Reactions.

Ar-NH_2 to Ar-N_2^+.

Aromatic amines are readily diazotized by $NOHSO_4$ to give the corresponding diazonium hydrogen sulfates. Although solutions of sodium nitrite in concentrated H_2SO_4, instead of pure $NOHSO_4$, have been used for diazotization, the yields of solid diazonium salts were in some cases relatively poor. For the purpose of preparation of pure diazonium hydrogen sulfates free from other mineral acids and salts, solutions or suspensions of the amines in acetic acid were added to a solution of solid $NOHSO_4$ in acetic acid, then ether was added to precipitate the diazonium salts.[8] Nitrosylsulfuric acid is also suitable for the diazotization of weakly basic amines such as nitroanilines (eq 4) and polynitroanilines,[8,9] tetrafluoroanthranilic acid,[10] aminonaphthoquinones,[11] 1,4-diaminoanthraquinones (eq 5)[12] and 2-cyano-4-nitroaniline.[13] In some cases the diazonium salts formed undergo

intramolecular coupling with aryl rings to give azo compounds (eq 6).[14,15]

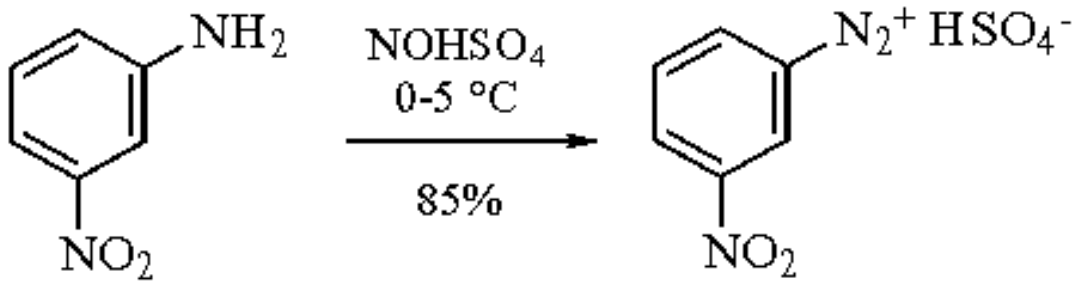

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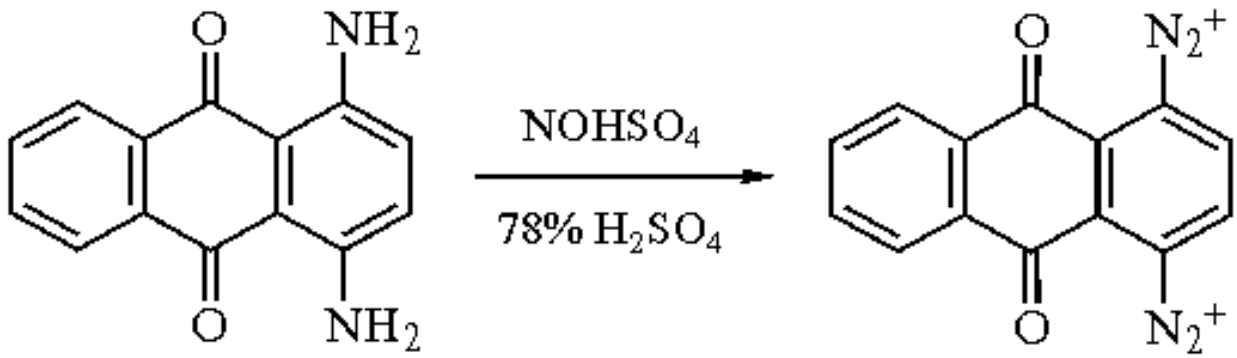

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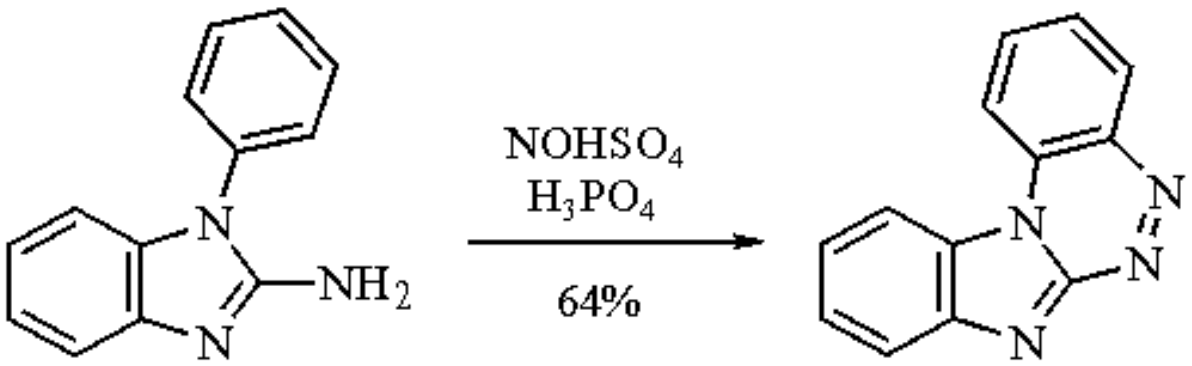

(6)

Ar-NHNH$_2$ to Ar-N$_3$.

Aryl and acyl hydrazines are converted to azides in good yields on treatment with an equimolar amount of $NOHSO_4$ or $NOBF_4$ (eq 7).[16]

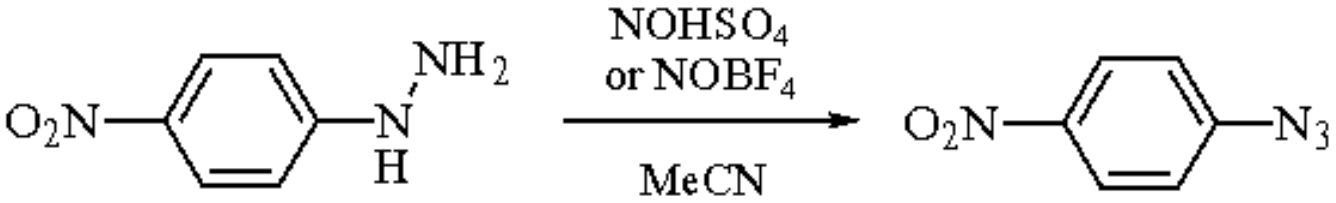

(7)

Addition to Alkenes and Dienes.

$NOHSO_4$ adds to trisubstituted alkenes to give β-sulfatooximes (eq 8), which are relatively unstable and react readily with nucleophiles such as ***Piperidine***, MeOH, or AcOK to give the corresponding α-substituted oximes.[17] Conjugated dienes react with $NOHSO_4$ at low temperature in liquid SO_2, giving 1,4-addition products which spontaneously cyclize to 6*H*-1,2-oxazine hydrogen sulfates (eq 9).[18]

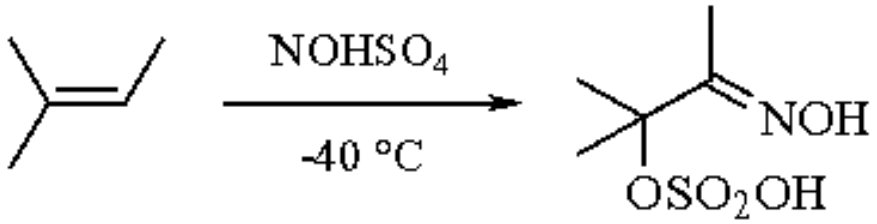

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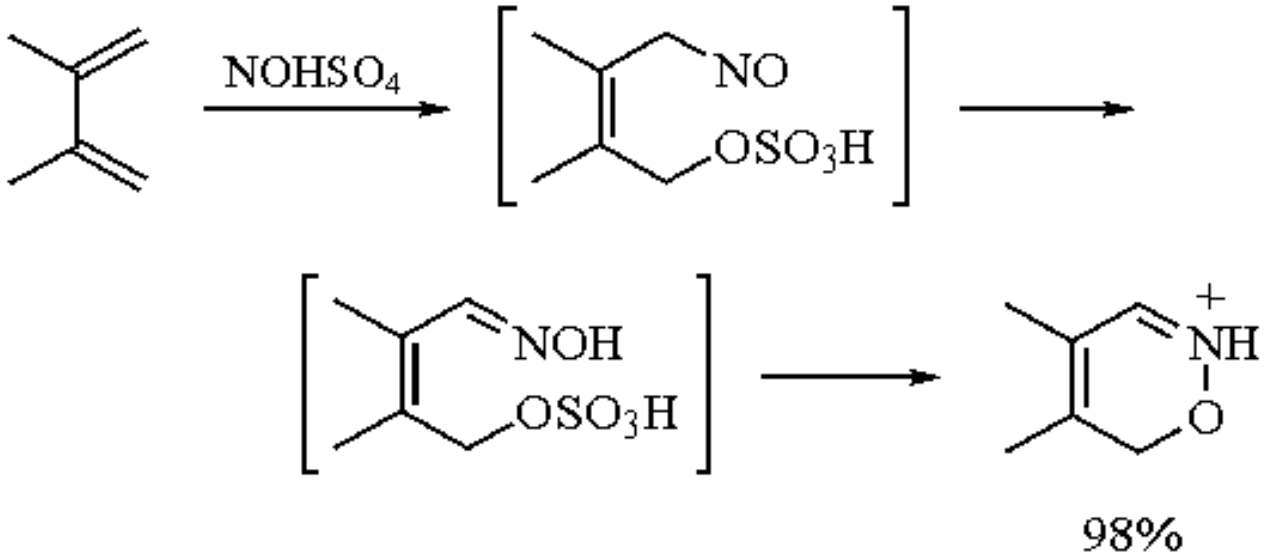

(9)

Other Applications.

Amides and sulfonamides are converted to the corresponding acids by $NOHSO_4$ and other nitrosonium salts at low temperature in acetonitrile or nitromethane (eq 10).[19] Sterically hindered amides also react with ease and good yields, although higher reaction temperatures are needed. A mild cleavage of ethylene dithioacetals to ketones has been achieved with $NOHSO_4$ in methylene chloride or $NaNO_2$ in aq CF_3CO_2H (eq 11).[20]

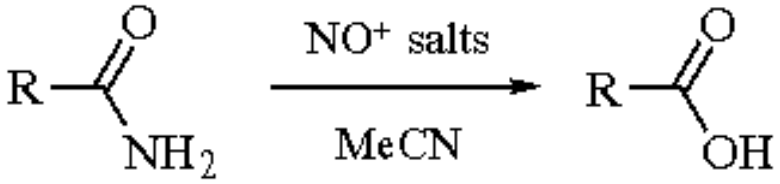

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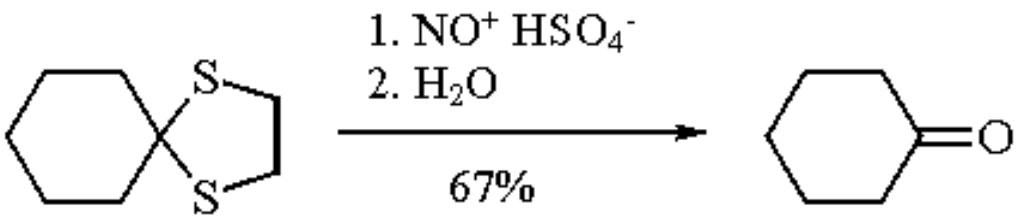

(11)

The treatment of 2-amino-4*H*-pyrans with nitrosylsulfuric acid brings about their transformation into 2-pyridones (eq 12).[21]

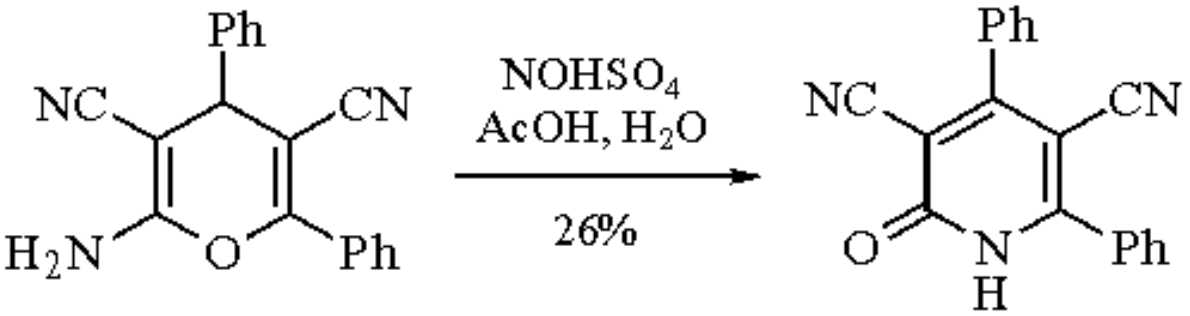

(12)

All nitrosonium ions are in principle hydride-abstracting agents, and nitrosylsulfuric acid has occasionally been used as a dehydrogenating agent (eq 13).[22]

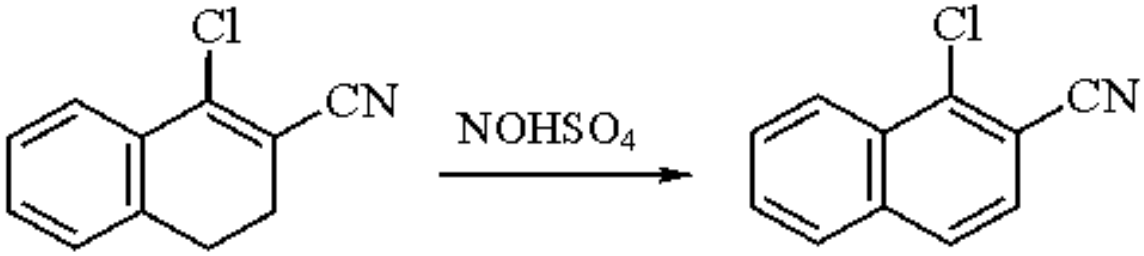

(13)

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Nonacarbonyldiiron[1]

$Fe_2(CO)_9$

[15321-51-4] · $C_9Fe_2O_9$ · Nonacarbonyldiiron · (MW 363.79)

(precursor for iron carbonyl complexes, carbonylation, dehalogenation, deoxygenation, and reduction reactions)

Alternate Names: diiron enneacarbonyl; diiron nonacarbonyl; tri-μ-carbonylhexacarbonyldiiron.

Physical Data: mp 100-120 °C (dec); *d* 2.08 g cm^{-3}; X-ray diffraction study.[3]

Solubility: insol organic solvents.

Form Supplied in: orange flaky solid.

Preparative Method: formed by exposing ***Pentacarbonyliron*** to light (eq 1).[1] The complex contains six terminal carbonyl groups and three bridging carbonyl groups.[2]

$$2\ Fe(CO)_5 \xrightarrow[74\%]{h\nu} Fe_2(CO)_9 + CO \qquad (1)$$

Handling, Storage, and Precautions: because of its much lower solubility and volatility, $Fe_2(CO)_9$ is less dangerous to handle than $Fe(CO)_5$, though it should be remembered that $Fe(CO)_5$ is often formed in reactions using $Fe_2(CO)_9$; when handling $Fe_2(CO)_9$, avoid dust formed by this light flaky substance; use in a fume hood; store in a freezer; when fully dried, commercial samples can be pyrophoric.[4]

Diene Complexation.

Cyclohexadiene Series.

Tricarbonyliron complexes are formed by reaction of $Fe(CO)_4$ with dienes. $Fe_2(CO)_9$ is an important starting material for this reaction because it offers a convenient source of $Fe(CO)_4$ generated under much milder conditions than from pentacarbonyliron (eq 2).

$$Fe_2(CO)_9 \longrightarrow Fe(CO)_4 + Fe(CO)_5 \qquad (2)$$

Starting from a cisoid 1,3-diene, $Fe_2(CO)_9$ can yield, under mild thermal conditions, tricarbonyl(η^4-1,3-diene)iron complexes. Cyclohexa-1,4-dienes (readily available from the Birch reduction of substituted benzenes) often require prior conjugation, but conjugated 1,3-dienes (both cyclic and acylic) can be converted into tricarbonyliron complexes directly. Some of the earliest examples[5-9] of complexation of 1,3-dienes employed $Fe_2(CO)_9$ (eq 3, dates shown in parentheses). (Alternative reagents in the early days were ***Pentacarbonyliron*** or ***Dodecacarbonyltriiron***.)

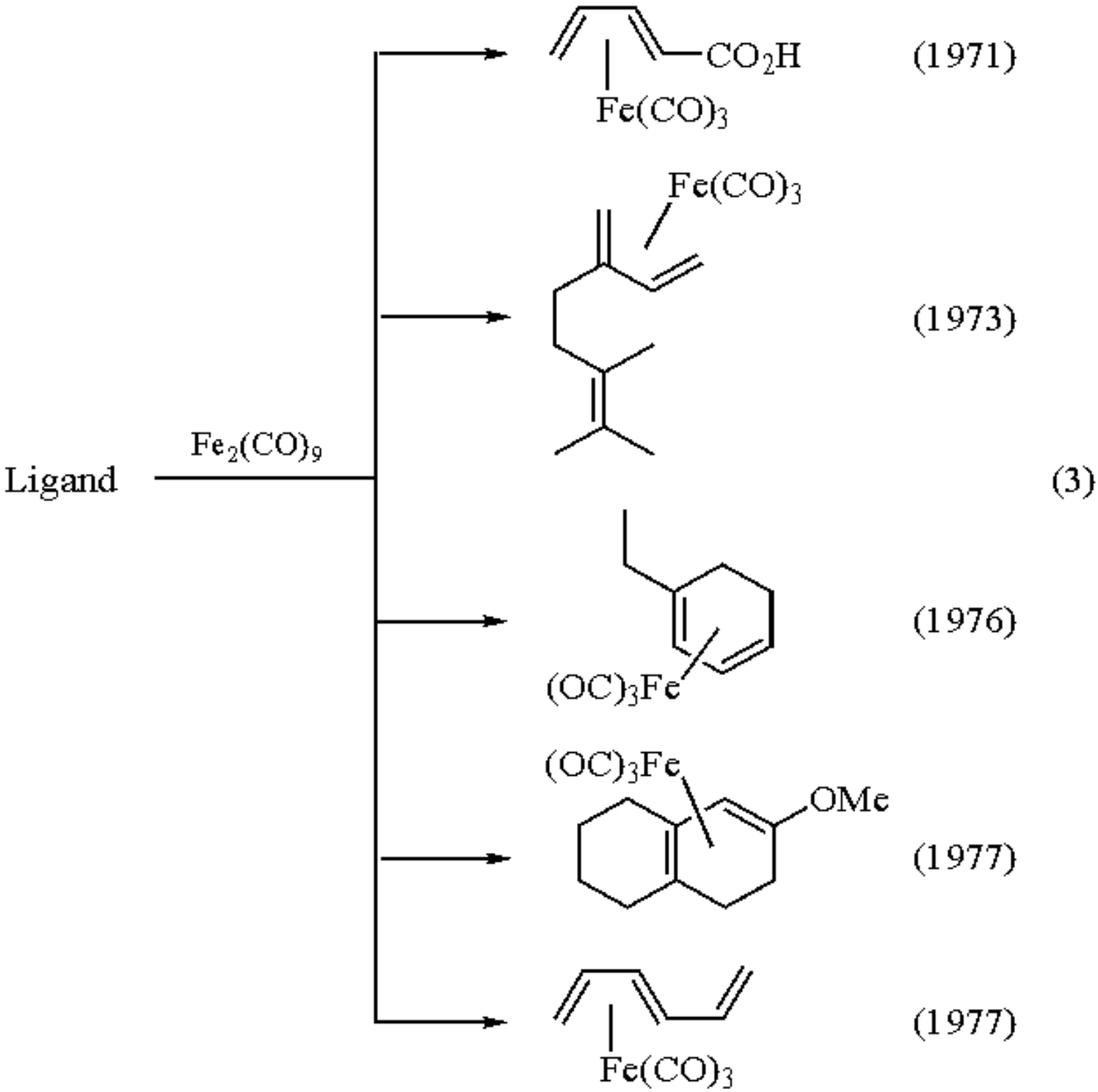

More recently, the use of $Fe_2(CO)_9$ has been increasingly valued because, under mild conditions, improved regio- and stereocontrol are possible, and sensitive functionality is less severely affected by the complexation conditions. Regiocontrol is often a problem in the complexation of 1,4-dienes by high-temperature direct reaction with $Fe(CO)_5$. Preparation of the diene complex (**1**), for example, can be improved by preconjugation of the 1,4-diene with ***p-Toluenesulfonic Acid***[10] and by complexation of the resulting equilibrium concentration of the 1,3-diene with $Fe_2(CO)_9$ under conditions in which the 1,4-isomer does not react (eq 4). Bis-alkene complexes are formed when rearrangement to bring the double bonds into conjugation is not possible.[11]

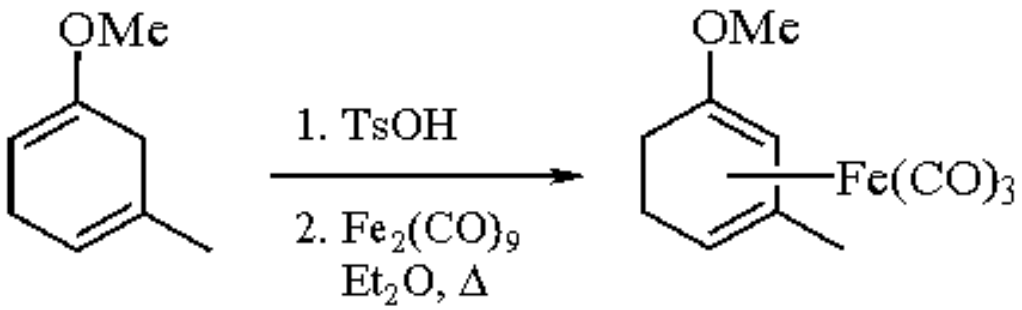

(4)

(1)

Good diastereoselectivity can also be a significant advantage. The dioxygenation of arenes by *Pseudomonas putida* provides optically active *cis*-diol products.[12] In the mild complexation conditions using $Fe_2(CO)_9$, the chirality of the diol is relayed to tricarbonyliron complexes, providing enantiopure intermediates for use in asymmetric synthesis.[13]

Cycloheptadiene Series.

The treatment of (**2**) with $Fe_2(CO)_9$ in acetone at 35 °C gives a 1:4 mixture in favor of (**4**). Enriched samples of (**3**) or (**4**) are accessible directly (eq 5), according to the reaction conditions.[14]

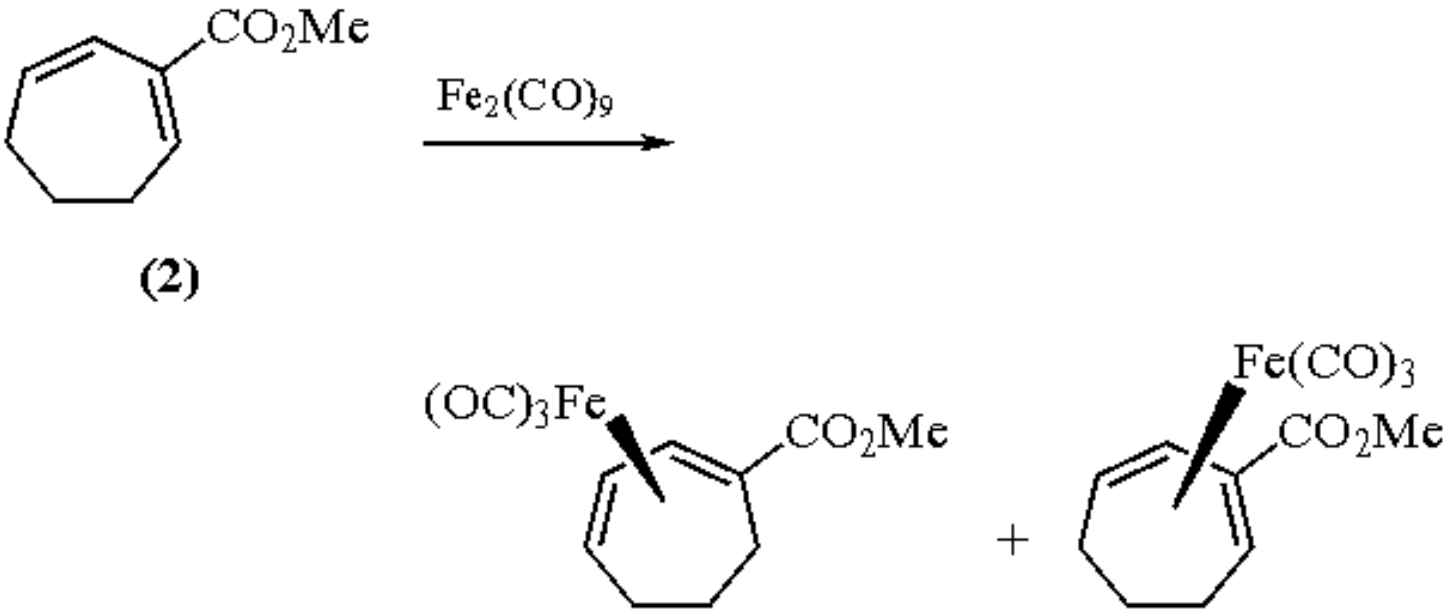

(5)

(2)

(3) **(4)**

Cycloheptatrienone (tropone) reacts efficiently in 60% yield with $Fe_2(CO)_9$ to give a complex (**5**) in which one double bond remains uncomplexed (eq 6).[15] This double bond displays normal reactivity, while the remaining unsaturation is effectively protected. Dinuclear bis-η^3-tricarbonyliron complexes can also be formed.[16]

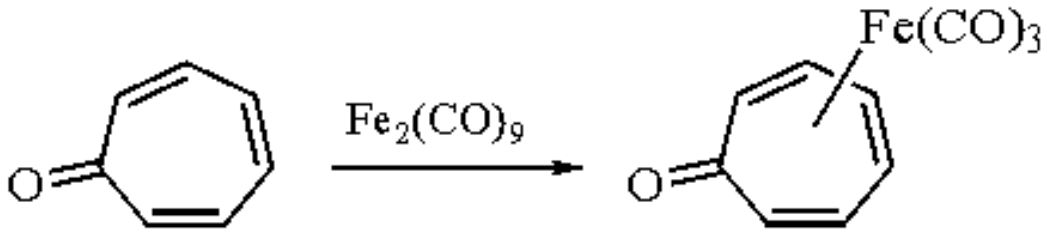

(6)

(5)

Complexation of Natural Products.

The $Fe(CO)_3$ moiety can provide a method for diene protection. Steroid interconversions employed tricarbonyl(ergosteryl acetate)iron(0)[17] and tricarbonyl(ergosteryl benzoate)iron(0).[18] Thus treatment of ergosteryl acetate or benzoate with tricarbonyl(4-methoxybenzylideneacetone)iron(0) (preformed by complexation using $Fe_2(CO)_9$, or with $Fe_2(CO)_9$ in the presence of 4-methoxybenzylideneacetone[19]), gives the pure desired steroid complex in good yield (60% and 80%, respectively). Nopadiene has been complexed by reaction with $Fe_2(CO)_9$ to form an optically active metal complex.[20]

Exocyclic Diene Complexation.

Formation of iron carbonyl complexes of (**6**) illustrates the mild nature of the complexation conditions (eq 7).[21]

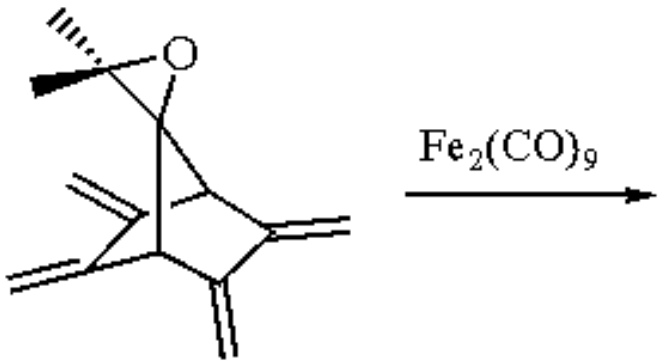

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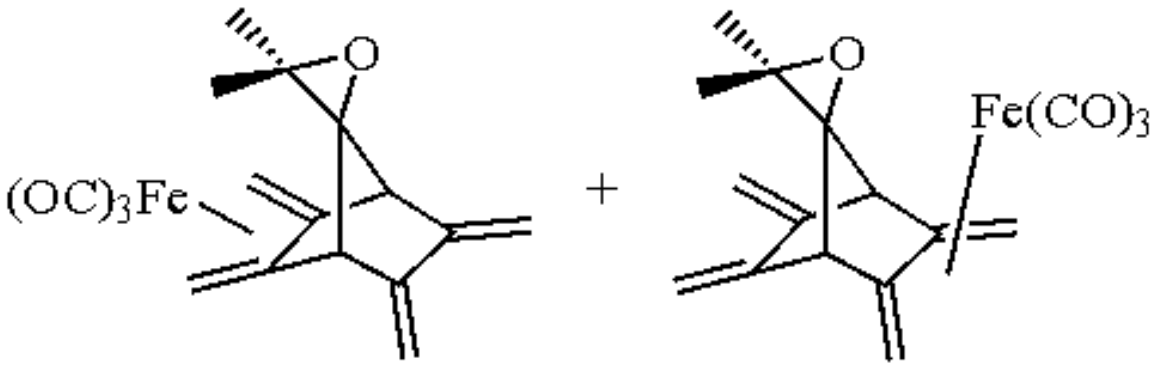

(7)

(7) **(8)**

Reaction with $Fe_2(CO)_9$ is *exo* face selective, giving a mixture of the corresponding mono complexes (**7**) (*anti-exo*) and (**8**) (*syn-exo*). Further complexation of (**8**) with $Fe_2(CO)_9$ occurs in a nonstereoselective fashion to give mixtures of the diiron complexes (*anti-exo, syn-endo*), (*anti-exo, syn-exo*), and (*anti-endo, syn-exo*).

On treatment of (**9**) with $Fe_2(CO)_9$, the endocyclic double bond is first coordinated to yield the *exo*-$Fe(CO)_4$ complex (**10**), which then further reacts with $Fe_2(CO)_9$ to afford the diiron complex as a major product (eq 8).

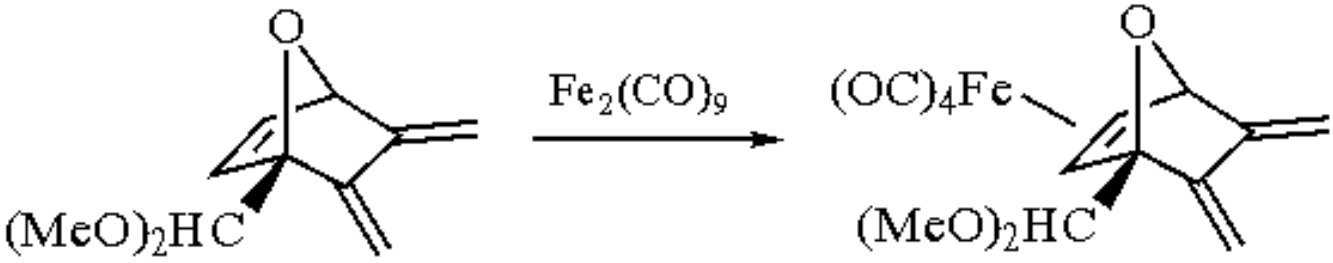

(8)

(9) **(10)**

Heating promotes deoxygenation to form the substituted tricarbonyl(*o*-quinodimethide)iron complex (**11**). Oxidative removal of the $Fe(CO)_3$ moiety in (**11**) affords the indanone derivative (**12**) by CO insertion (eq 9).[22]

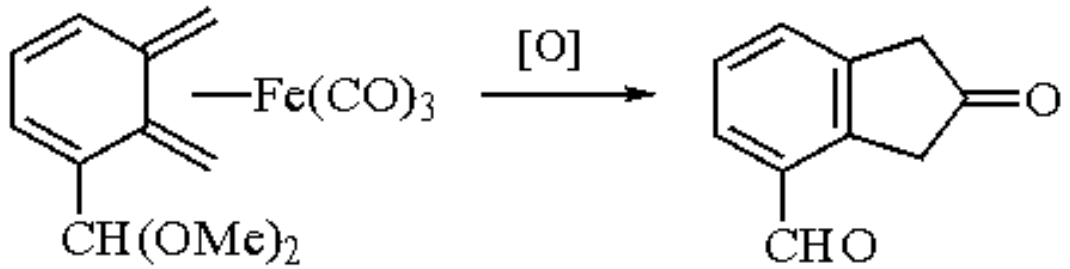

(9)

(11) **(12)**

Complexes of 7-azanorbornadienes have been examined as sources of nitrenes.[23]

Complexation of Acyclic Dienes.

Complexation of *trans*-4-methyl-2,4-pentadienol (**13**) with $Fe_2(CO)_9$ gives the dienol complex (**14**) as a yellow oil. The product is valuable as a precursor for the cation (**15**) by reaction with $HPF_6/Ac_2O/Et_2O$ (eq 10).[24] Substituted dienes with the (*Z*) configuration at a methyl-bearing terminus complex less efficiently.[25]

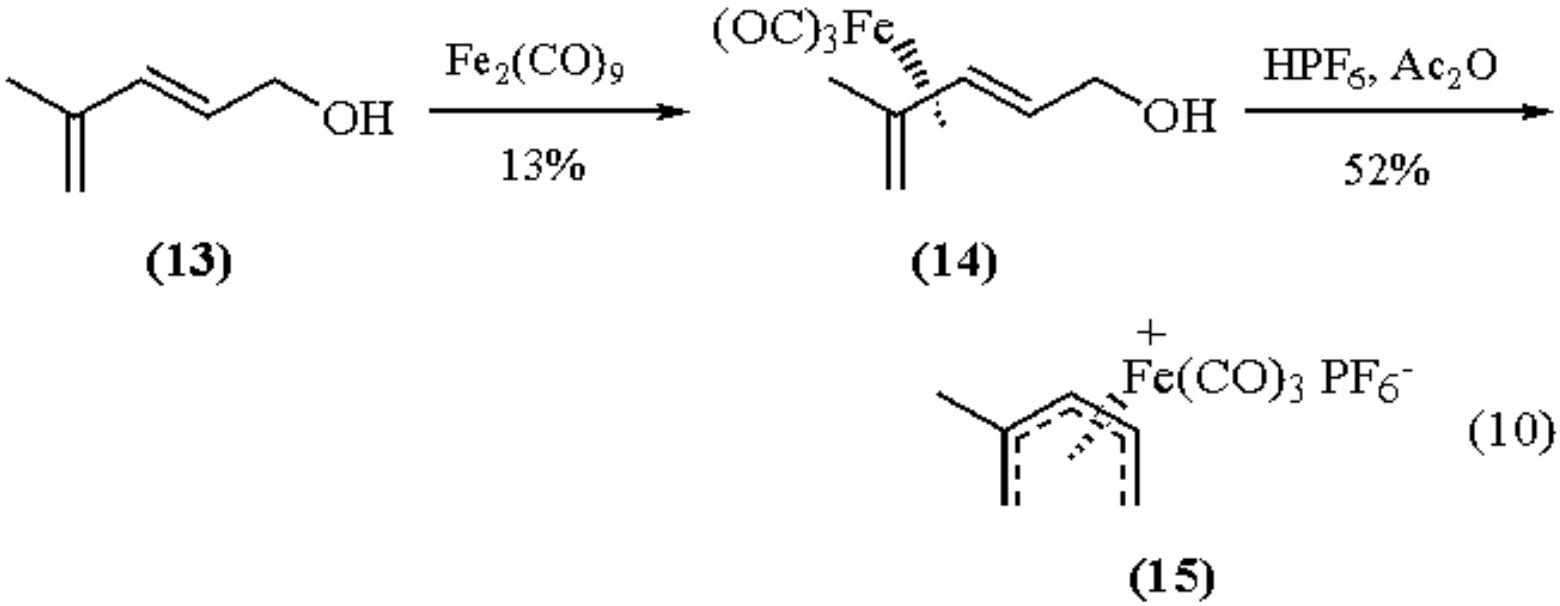

(10)

(13) **(14)** **(15)**

$Fe(CO)_3$-diene aldehydes have been formed using $Fe_2(CO)_9$ in work that culminated in an efficient asymmetric induction using chiral allylborane reagents to give access to metal complexes in high optical purity.[26]

1-Methoxybutadiene has been complexed photochemically using $Fe_2(CO)_9$, instead of the more conventional thermal conditions.[27] Complexation of acyclic dienes with $Fe_2(CO)_9$ constituted the first step toward trimethylenemethane complexes.[28] All details concerning the preparation and spectral properties of tricarbonyl(butadiene)iron complexes are gathered in recent reviews.[29]

$Fe_2(CO)_9$/Ultrasound Method of Complexation.

The reaction of $Fe_2(CO)_9$ with sensitive dienes can be promoted by ultrasound (eq 11). Syntheses of a variety of tricarbonyl(η^4-diene)iron(0) complexes (**16**) use the convenient high-yielding sonication method.[30]

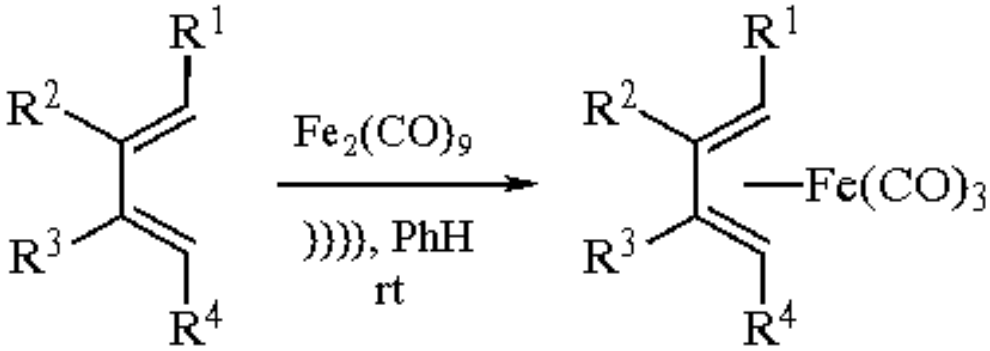

(11)

(16)

$R^1 = OAc$; R^2, R^3, $R^4 = H$; 100%

$Fe_2(CO)_9$ Used with a Tertiary Amine.

Aliphatic trialkylaminotetracarbonyliron(0) complexes result from direct reaction between R_3N and $Fe_2(CO)_9$.[31] Fair to good yields of (**17**) can be obtained (eq 12).

$$R_3N + Fe_2(CO)_9 \xrightarrow[\text{rt, } N_2]{\text{hexane or THF}} R_3N \cdot Fe(CO)_4 + Fe(CO)_5 \quad (12)$$

(17)

The complex (**17**) transfers $Fe(CO)_4$ to dienes, monoenes (resulting in isomerization), and $Fe(CO)_5$ (to form $Fe_2(CO)_9$ and $Fe_3(CO)_{12}$). The R_3N unit can also be replaced by other amines and by phosphines. The amine/phosphine exchange was performed with $Me_3N.Fe(CO)_4$ at 60 °C in quantitative yield after 0.5 h. The amine/diene exchange reaction has been studied with 1,3-cyclohexadiene in hydrocarbon solution at 52 °C (eq 13).

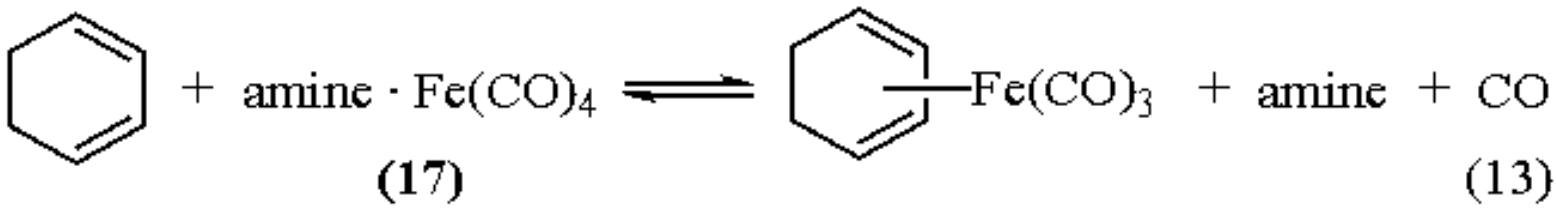

(13)

Other Routes to η^4 Complexes.

Alternative access to $Fe(CO)_3$ complexes are afforded by a variety of more unusual starting materials: cyclopropenes, dibromides, dihydrothiophene dioxides, alkynes/CO, allenes, and cyclohexadienones are all discussed below.

Enone Complexation.

Various α,β-unsaturated ketones form moderately stable tricarbonyliron complexes (**18**),[32,37] and offer access to 1,4-diketones (**19**) by reaction with Grignard reagents, organolithium reagents (eq 14), or organocuprates.[33] Trimethylsilyloxybutadienes require phenyl substituents to form stable complexes by reaction with $Fe_2(CO)_9$.[34] Enone complexes are also useful as transfer reagents to place $Fe(CO)_3$ on diene ligands.[32,35] A related procedure employs complexes of α,β-unsaturated imines in the same way.[36]

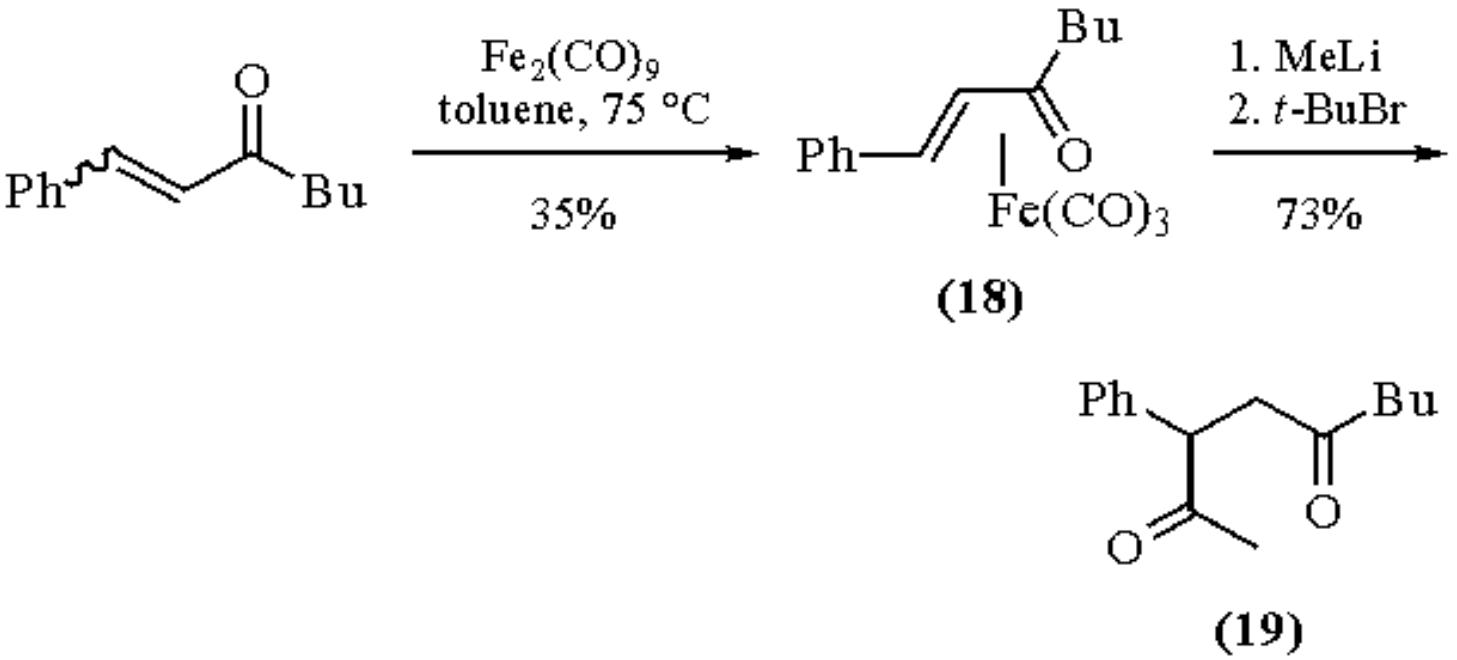

(14)

Reagents for asymmetric transfer of $Fe(CO)_3$ to dienes have been obtained thermally from (+)-pulegone[37,38] and (-)-3β-acetyloxypregna-5,16-dien-20-one[38] by reaction with $Fe_2(CO)_9$. The chiral enone complexes are used without isolation to provide a direct synthesis of optically active (diene)$Fe(CO)_3$ complexes in up to 40% ee.[38,39]

Complexes from Alkenediols.

2-Butene-1,4-diols react with $Fe_2(CO)_9$ in the presence of Lewis acids under ultrasound conditions to form η^3-allyliron complexes.[40]

Ferralactone Complexes.

From Oxazines.

The first ferralactone complex (**21**) was obtained during studies on π-allyliron complexes by Heck. The same compounds are also obtained by treatment of oxazines (**20**) with $Fe_2(CO)_9$ (eq 15).[41]

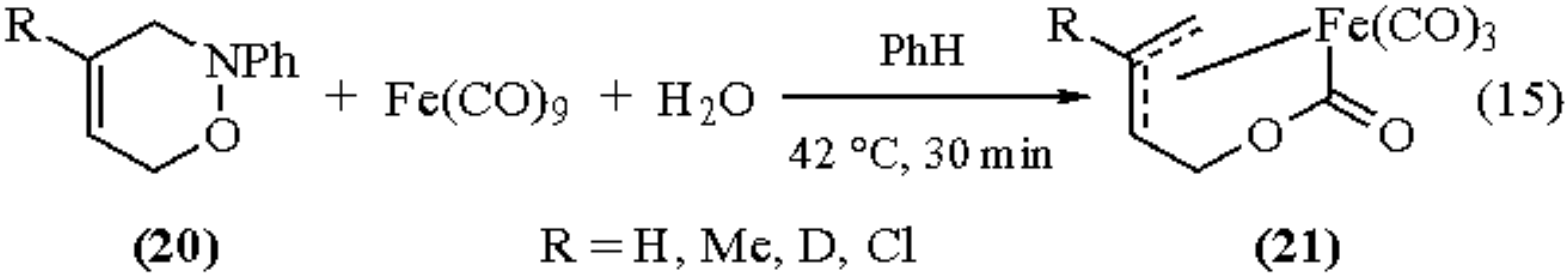

Formation of β- and α-Lactones from Vinyloxiranes.

An oxidative addition of vinyloxiranes (**22**) to iron(0) complexes provides the most usual synthesis of ferralactone complexes (**21**) (eq 16).[42,43]

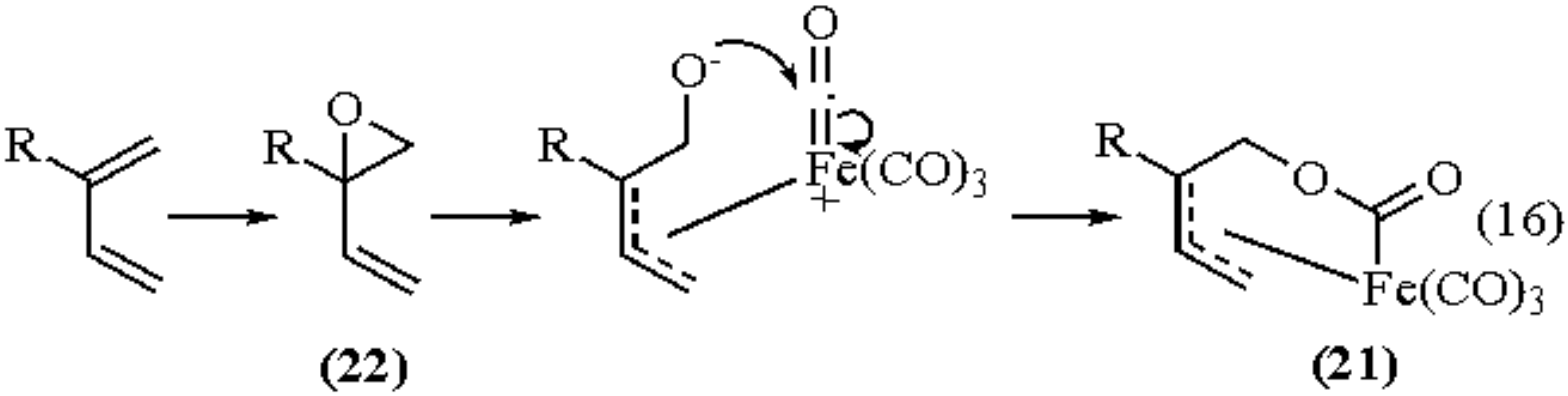

Efficient preparations are possible using $Fe_2(CO)_9$ according to two different methods (in THF, or in lower polarity solvents with ultrasound) to produce the ferralactone complexes in moderate to excellent yields.[44] Removal of the metal to form δ-lactones has been successfully applied to total syntheses of parasorbic acid (**23**), the carpenter bee pheromone (**24**), and malyngolide (**25**).[45] Epoxide-derived ferralactone complexes have provided key intermediates in syntheses of routiennocin,[46] avermectin B1a,[47] and (-)-valilactone.[48]

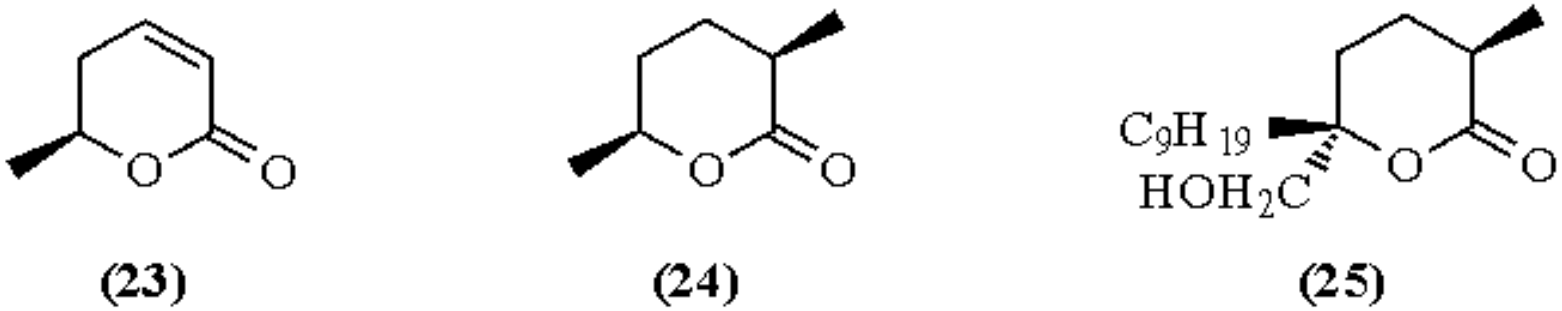

Demetalation of ferralactone complexes with ***Cerium(IV) Ammonium Nitrate*** produces β-lactones (at low temperature) and/or δ-lactones (at high temperature, under a high pressure of carbon monoxide).

Formation of β-Lactams.

The synthesis and oxidative demetallation of ferralactam complexes affords a route to β-lactams.[42] The difficulty of preparation of the monoaziridines limits the scope of direct ring opening, but ferralactam complexes are more readily obtained from ferralactones by reaction with an amine and a mild Lewis acid catalyst.[49] This methodology has been successfully applied to the synthesis of (+)-thienamycin (**28**),[50] via the key intermediates (**26**) and (**27**).

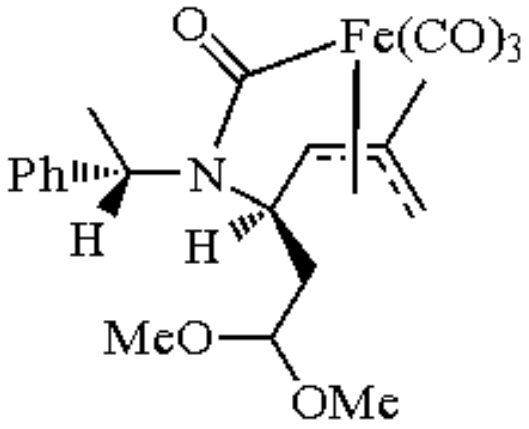

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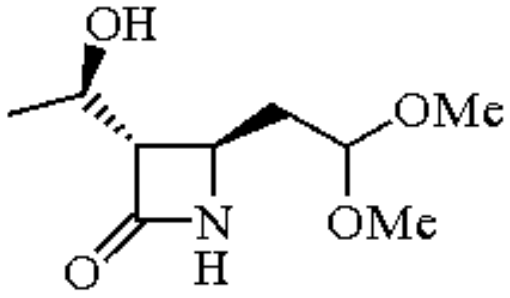

(27)

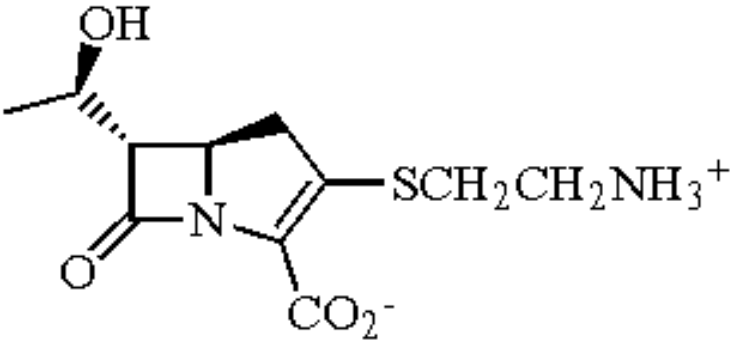

(28)

Complexes from Electrophilic Cyclopropenes.

Methyl- and phenyl-substituted cyclopropenes have been shown to react with iron carbonyls by ring opening and carbonylation to yield tricarbonyl(η^3,η^1-allylcarbonyl)iron complexes (eq 17).[51]

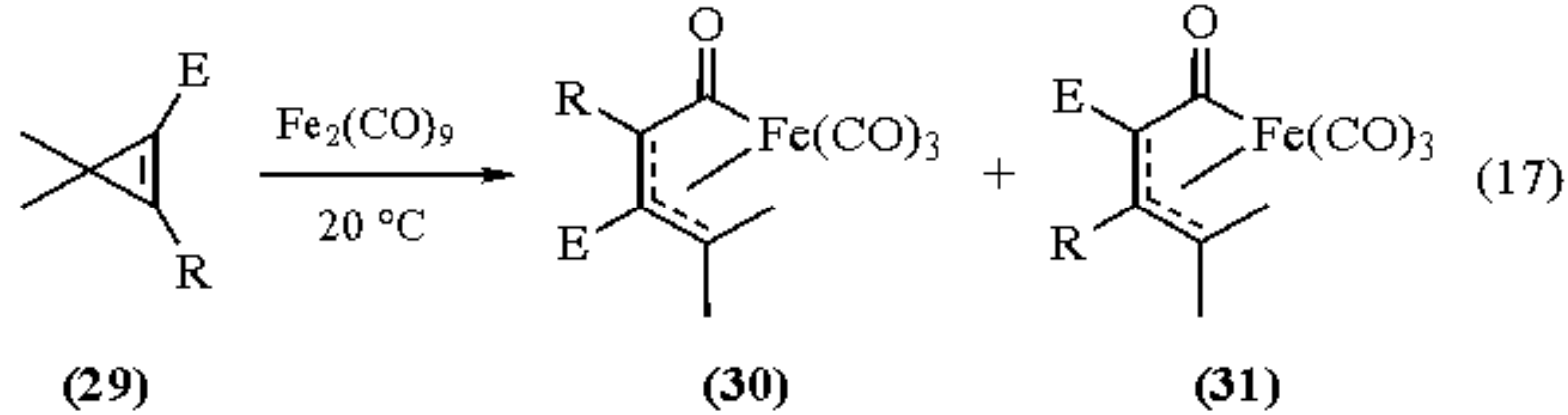

Franck-Neumann, starting from the easily accessible electrophilic *gem*-dimethylcyclopropenes (**29**), could obtain the carbonyliron adducts (**30**) and (**31**) in excellent yields.[52,53] The reaction of $Fe_2(CO)_9$ with the isomers of Feist's ester (**32**) leads first to the formation of the corresponding tetracarbonyliron alkene complexes (**33**) (eq 18).[54] Reaction of naphthalenocyclopropene with $Fe_2(CO)_9$ has also been studied.[55]

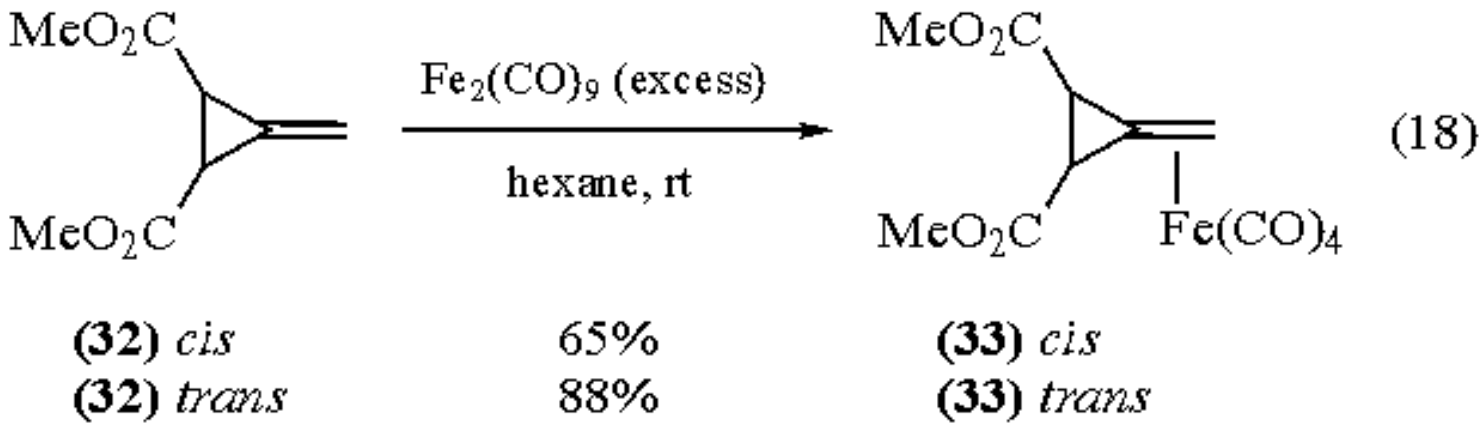

The products from cyclopropene ring opening have the advantage of easy conversion into tricarbonyl(η^4-diene)iron complexes (**34**), its regioisomer and (**35**), by thermal loss of carbon monoxide, or photochemically without CO evolution (eqs 19 and 20).[52,56]

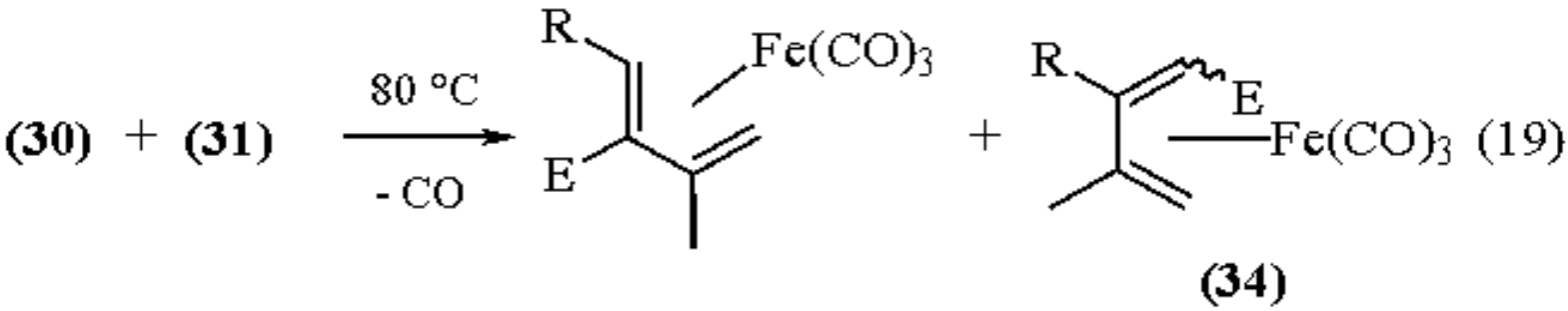

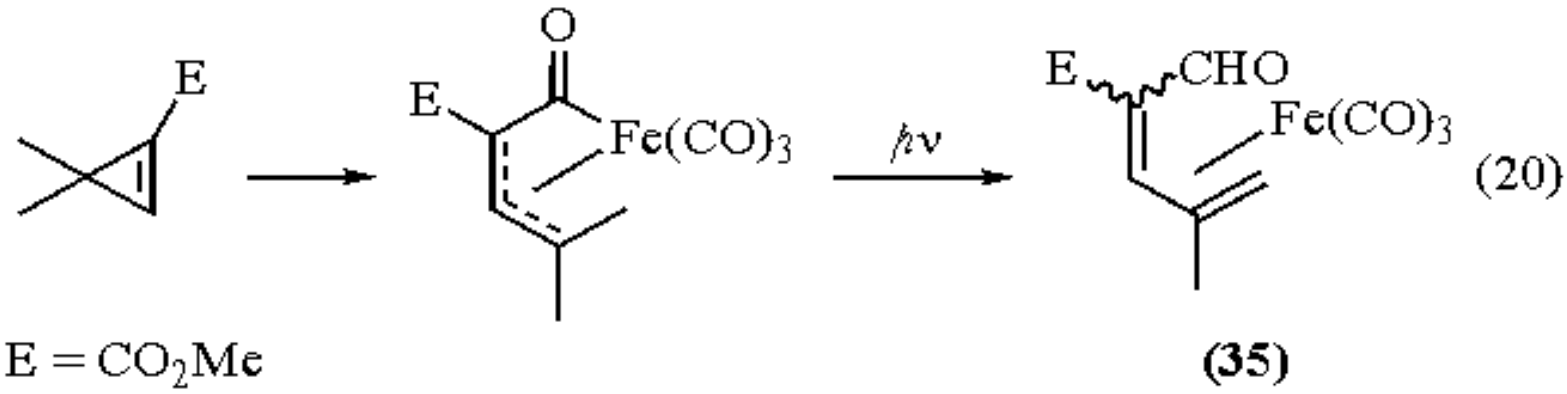

Opening of Cyclopropane Rings.

Ring enlargement of compounds such as bicyclo[4.1.0]hept-2-ene (**36**) or its derivatives (+)-2-carene (**37**) or (+)-3-carene (**38**) by carbonylation results in the formation of bicycloheptenones or cycloheptadiene complexes, depending on the reaction conditions.[57]

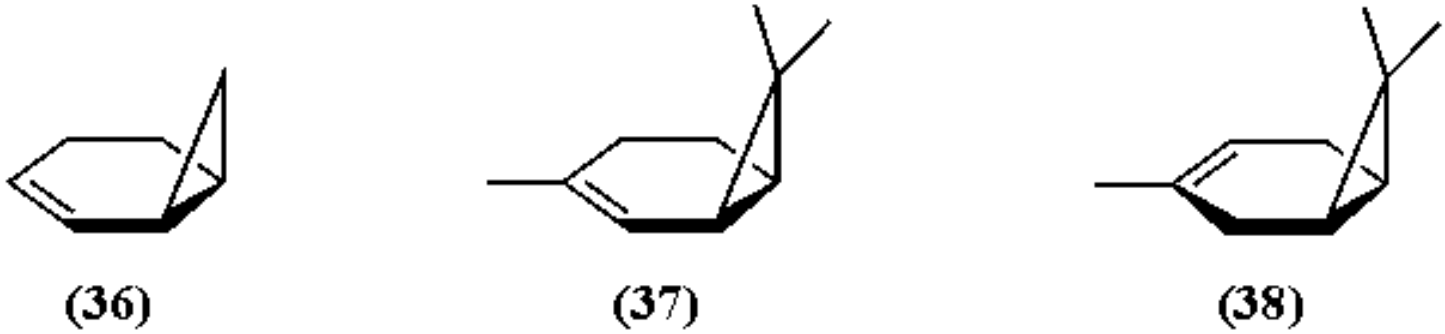

Under mild reaction conditions, (+)-2-carene affords the optically active (η^1,η^3) complex (**39**) (eq 21).

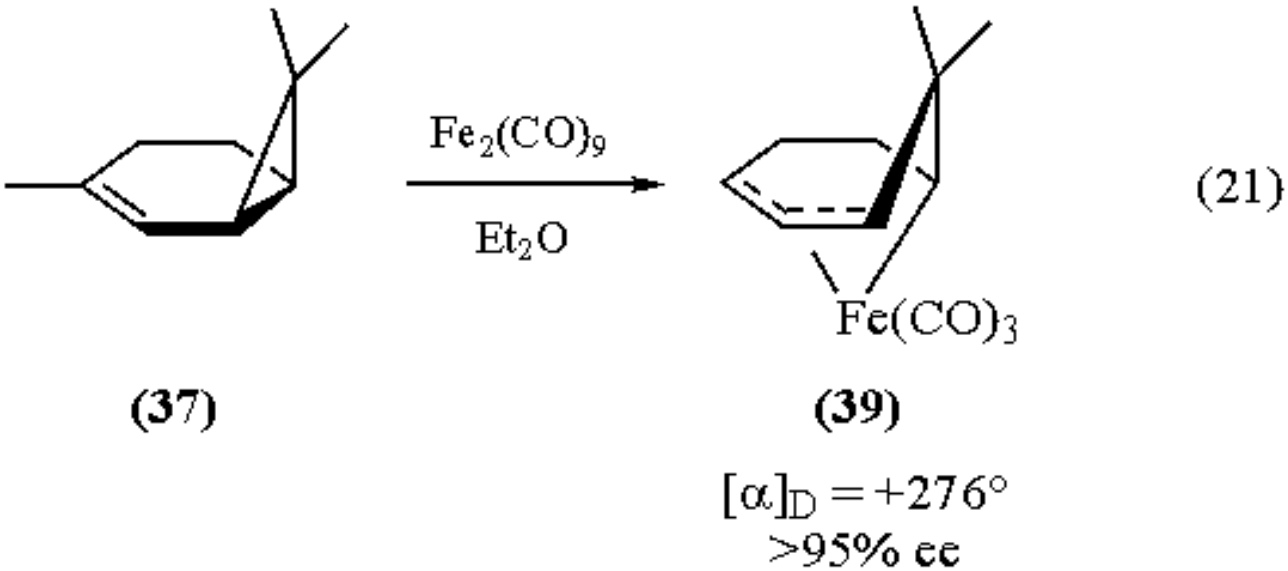

Metal and Lewis acid induced carbonylative ring enlargement of chiral and prochiral cyclohexadienes can give access to bicyclo[3.2.1]octanes.[58]

Dehalogenation Reactions.

Formation of Quinonedimethide Complexes.

Formation of a stable quinonedimethide complex (**40**) can be achieved by dehalogenation.[59] The product (**40**) decomposes to benzocyclobutene at 500 °C (eq 22).

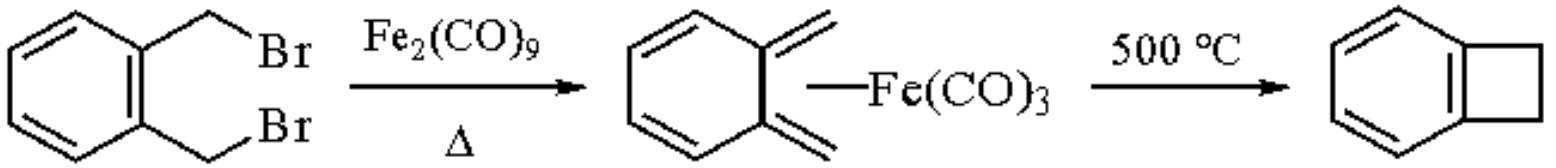

(40) (22)

In the bis(bromomethyl)naphthalene series, a σ-bonded $Fe(CO)_4$ product has been reported.[60]

Formation of Cyclobutadiene Complexes.

Cyclobutadiene can be prepared as the stable complex tricarbonyl(cyclobutadiene)iron(0) (**41**), by reaction of 3,4-dichlorocyclobutene with $Fe_2(CO)_9$ (eq 23).[61]

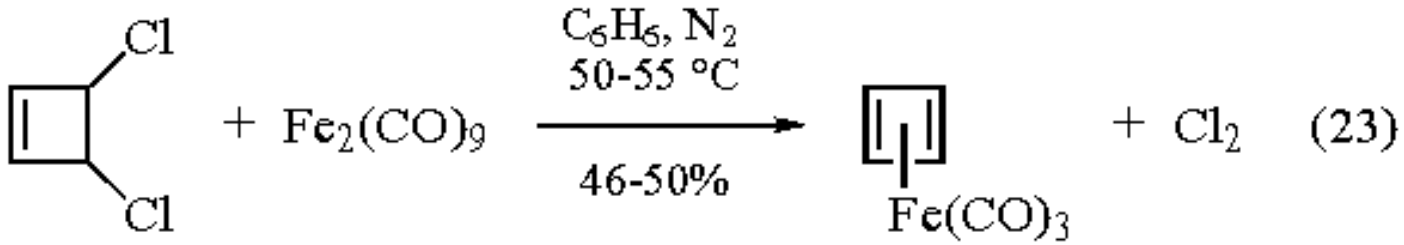

(23)

(41)

Dehalogenation of α,α´-dihaloalkenes and Ketones.

The preparation (eq 24) of the iron carbonyl complex of trimethylenemethane (**42**)[62] and some $Fe_2(CO)_9$-mediated rearrangements of dibromo ketones[63] constitute the pioneering work in this area. Noyori has extended the dehalogenation reaction of α-halo ketones to α,α´-dibromo ketones and α,α,α´,α´-tetrabromo ketones which can be dehalogenated with $Fe(CO)_5$ or $Fe_2(CO)_9$.[64]

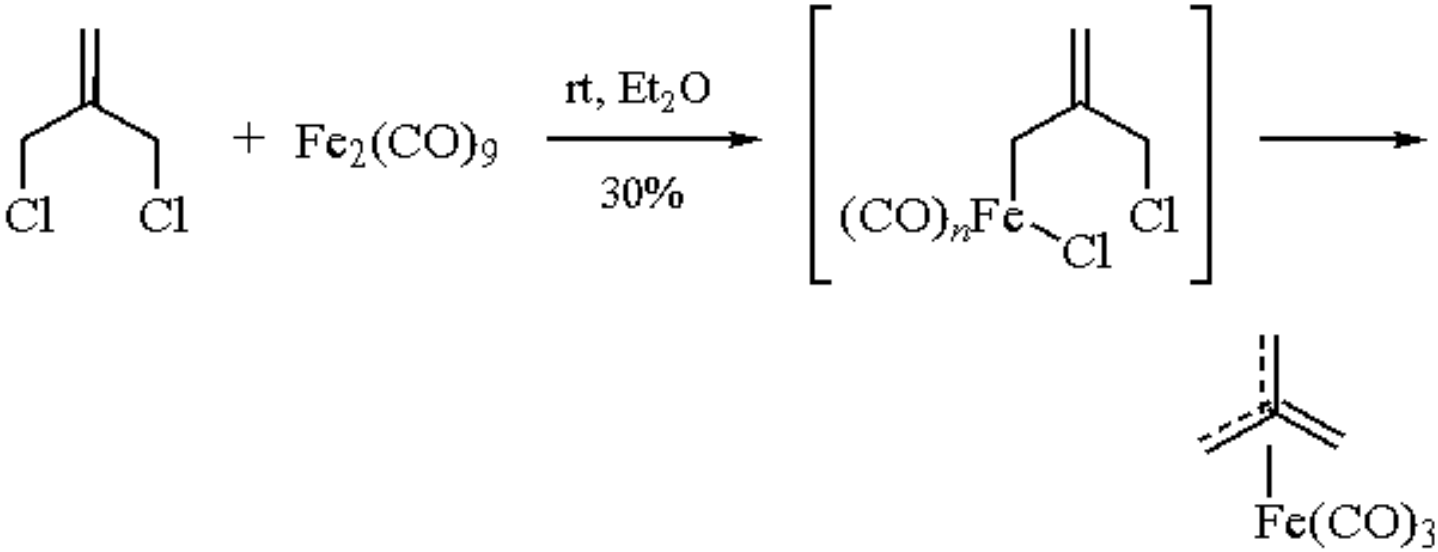

(24)

(42)

Iron-stabilized oxallyl cations (generated in situ (eq 25) from α,α´-dibromo ketones and $Fe_2(CO)_9$) react with alkenes. Noyori used this [3 + 2] cycloaddition reaction to produce cyclopentanone or cyclopentanone derivatives, as illustrated by a single-step synthesis of (±)-α-cuparenone (**43**) (eq 26).[65] The reaction of α,α´-dibromo ketones with enamines and $Fe_2(CO)_9$ yields substituted cyclopentenones in 50-100% yield (eq 27), as illustrated by the reaction with the α-morpholinostyrene (**44**).[66]

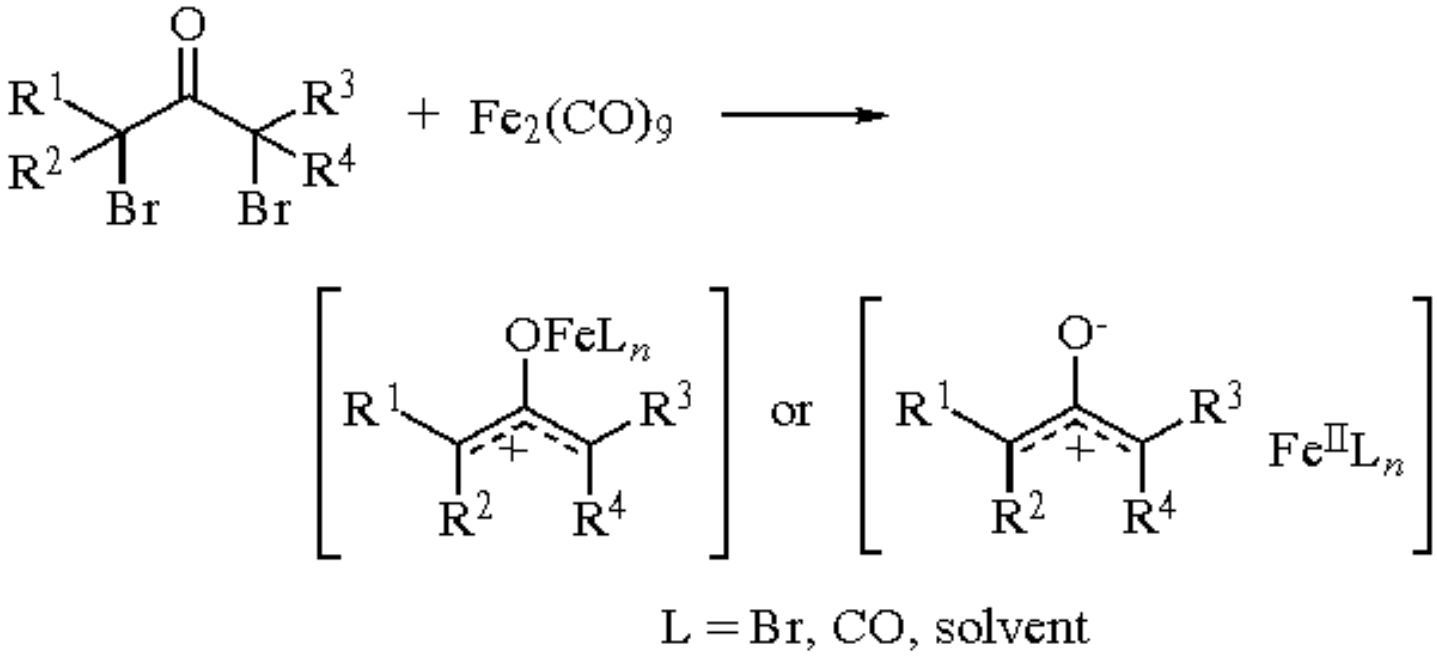

(25)

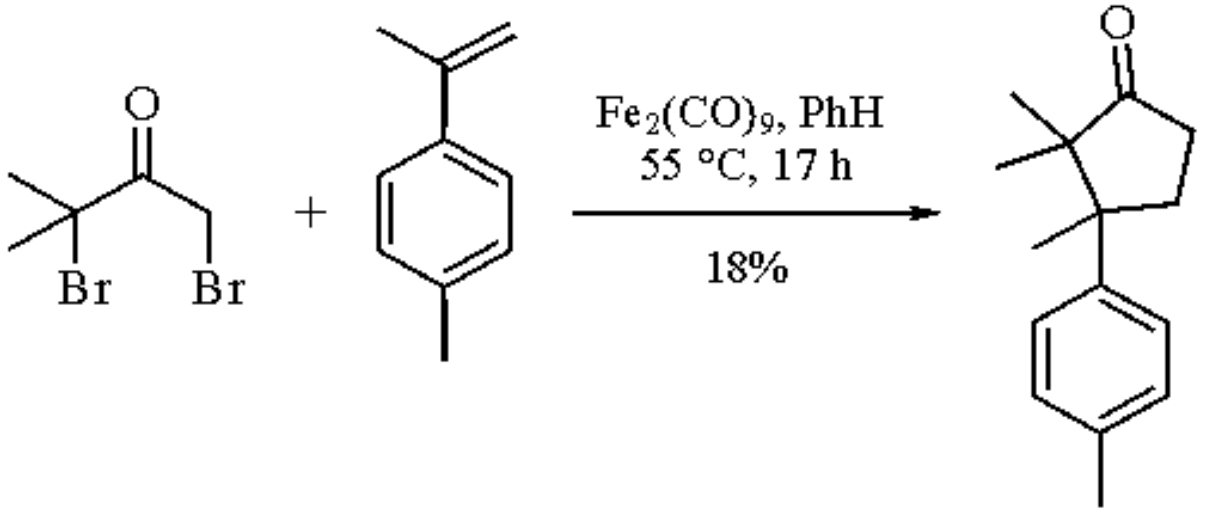

(26)

(43)

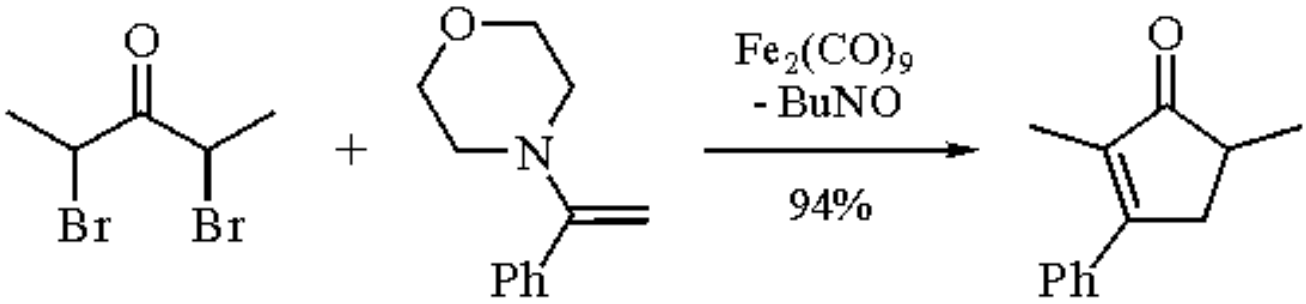

(27)

(44)

The reaction with dienes can be carried out either in benzene at 60-80 °C using α,α´-dibromo ketone, diene, and $Fe_2(CO)_9$ (1:large excess:1.2), in benzene at room temperature with irradiation (same ratio of reagents), or in benzene at 80-120 °C using the dibromide and tricarbonyl(η^4-diene)iron(0) complex (1:1.3). Formation of (**45**) (eq 28) provides a typical example.[67]

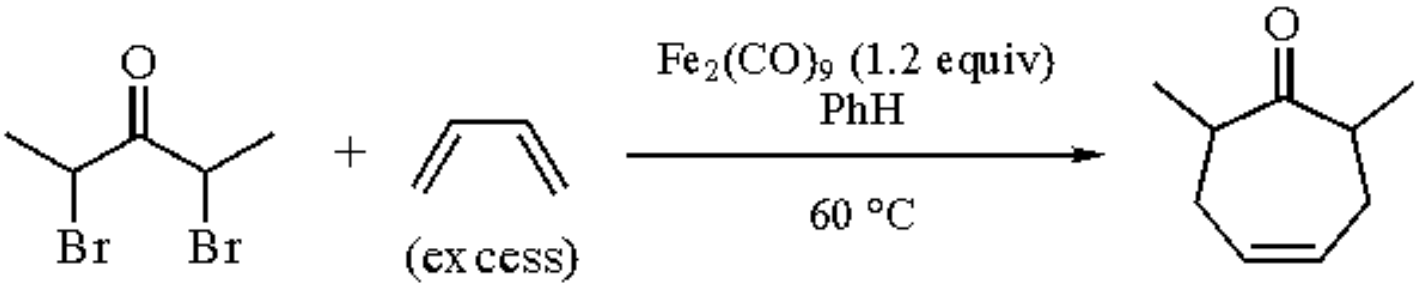

(28)

(45) 44%

Noyori et al. have reported a general synthesis of tropane alkaloids from α,α´-dibromo ketones.[68] Reaction of tetrabromoacetone, *N*-methoxycarbonylpyrrole, and $Fe_2(CO)_9$ (3:1:1.5 mol ratio) in benzene (50 °C, N_2) produces two isomeric cycloadducts in a 2:1 mixture, which can be used in the preparation of the alcohol (**46**), a key intermediate in the synthesis of scopine and other tropane alkaloids.[69] A more recent example gives access to the

bicyclo[5.2.0]nonene skeleton.[70]

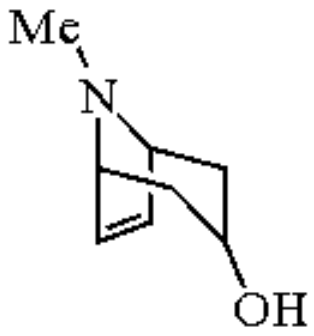

(46)

Reactions with Sulfur Compounds.

Desulfurization of Episulfides.

The reaction of cyclohexene episulfide with $Fe_3(CO)_{12}$, reported by King[71] to produce cyclohexene, has been improved:[72] 2-butene episulfides, e.g. (**47**) ($R^1 = R^2 = Me$, $R^3 = R^4 = H$), yield alkenes by treatment with $Fe_2(CO)_9$ in refluxing benzene (eq 29). The reaction occurs with retention of the stereochemistry in yields superior to 80%.

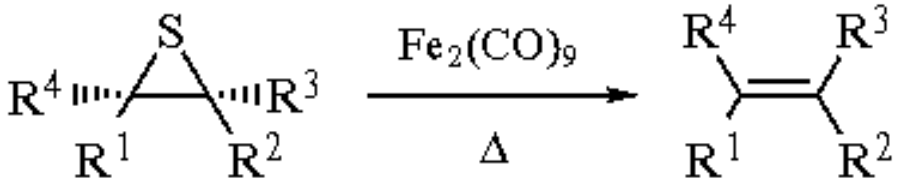

(47)

(29)

Tetramethylallene episulfide, on the other hand, affords a thioallyl $Fe(CO)_3$ complex.[73]

Reaction with Thioketones.

The reaction of thiobenzophenone derivatives (**48**) and similar compounds with $Fe_2(CO)_9$ has been studied by Alper.[74] It has been shown to result in the formation of *ortho*-metalated complexes (**49**) in reasonable to high yields (eq 30). Treatment of the complexes (**49**) with ***Mercury(II) Acetate*** effects *ortho*-mercuration.[75] Thioketene complexes have also been examined.[76] Complexes of type (**49**) offer a new route to lactones.[74]

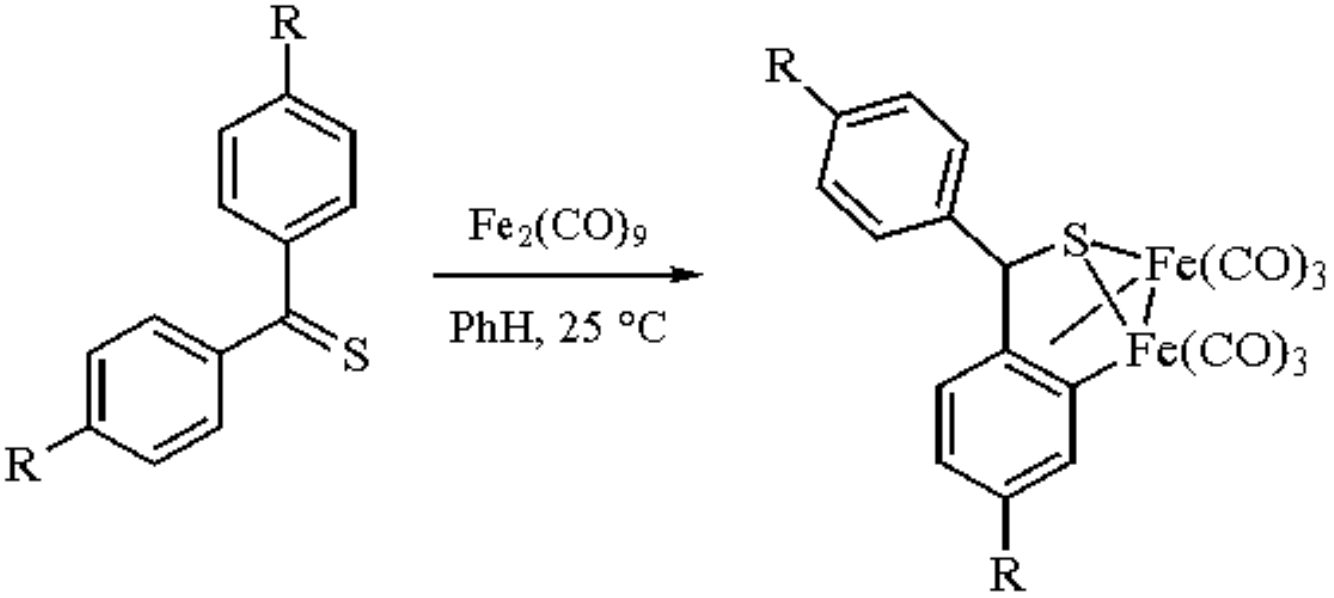

(48) **(49)**

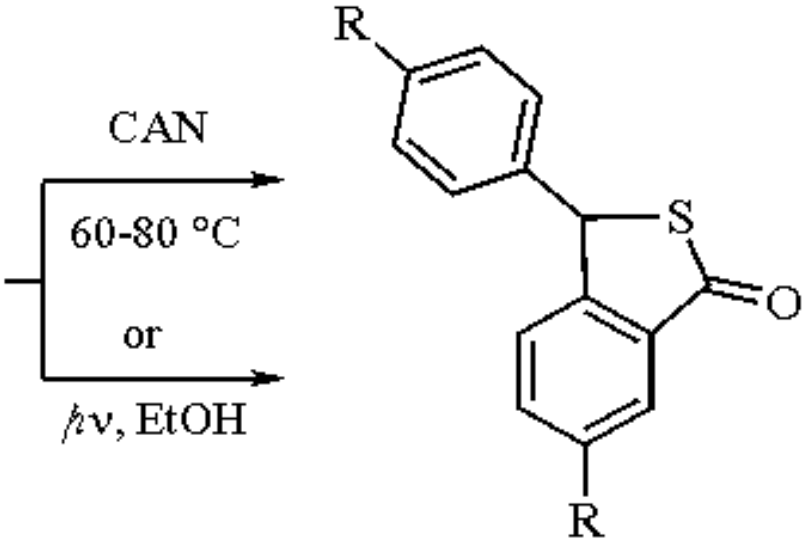

(30)

R = H, Me, OMe, NMe_2

Reaction with 2,5-Dihydrothiophene 1,1-Dioxide.

2,5-Dihydrothiophene 1,1-dioxides are known to be converted into 1,3-dienes after thermal displacement of sulfur dioxide.[77] Reaction in situ with $Fe_2(CO)_9$ offers a general preparation of highly functionalized tricarbonyl(η^4-buta-1,3-diene)iron(0) complexes (**50**) (eq 31).[78]

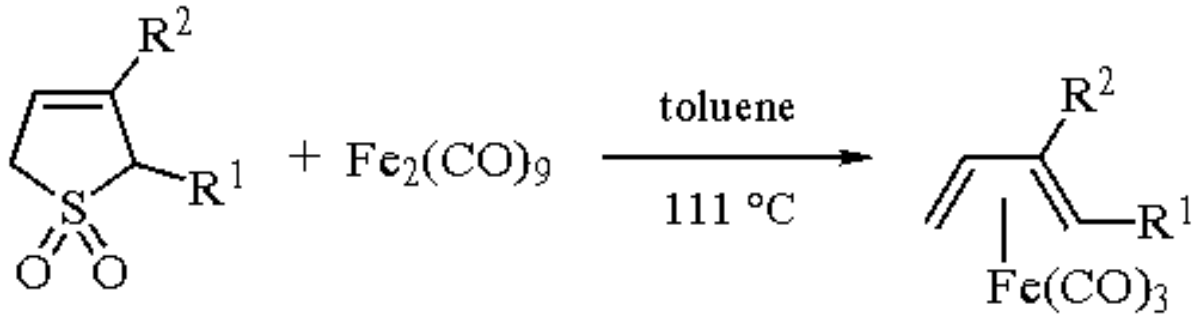

(31)

(50)

Reactions with Alkynes.

$Fe_2(CO)_9$ reacts with acetylene by carbonylation/cyclotrimerization leading to the formation of tricarbonyl(tropone)iron(0) (**51**) (eq 32). (For comparison with direct complexation of tropone, see eq 6.) This complex is obtained in low yield (28%) with $Fe_2(CO)_9$, but this represents a significant improvement on results obtained with $Fe(CO)_5$.[79]

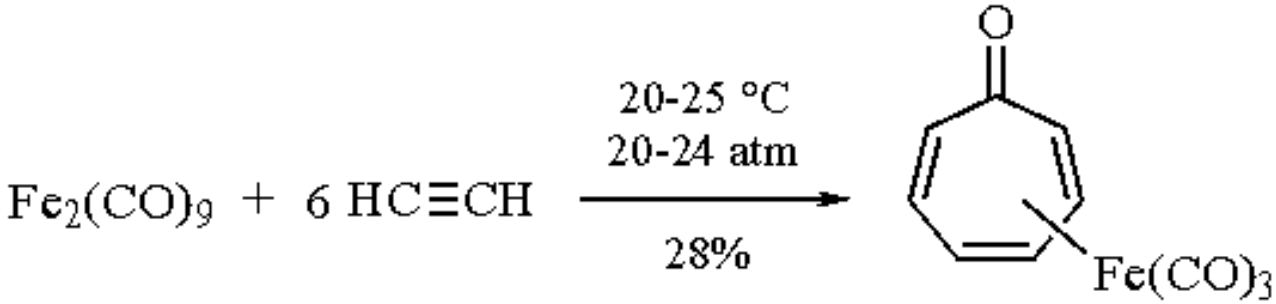

(32)

(51)

Hexyne is carbonylated by $Fe_2(CO)_9$. An intermediate can be isolated.[80] Alkylthioalkynes are not desulfurized but form iron complexes.[81]

Reaction with Acid Chlorides.

The reaction of an acid chloride with one equivalent of $Fe_2(CO)_9$ affords symmetrical ketones.[82]

Formation of 1,2,4-Triazines.

1,2,4-Triazines, e.g. (**54**), are formed regioselectively (eq 33) by cocyclization of adiponitrile (**52**) and a nitrile (**53**) in the presence of $Fe_2(CO)_9$.[83]

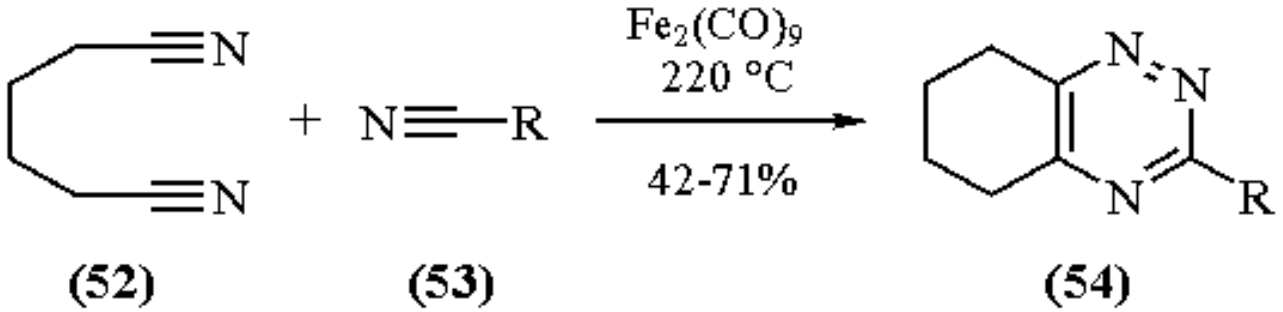

(33)

Deprotection and Deoxygenation Reactions of Oximes and Isobenzofurans.

Oximes, oximic ethers, or oxime *O*-acetates can be converted into the corresponding ketones by reaction with $Fe_2(CO)_9$ in methanol at 60 °C.[84] Deoxygenation of 7-oxabicyclo[2.2.1]dienes with $Fe_2(CO)_9$ affords aromatic products.[85] This method is particularly recommended for deoxygenation of (**55**) in the formation of (**56**) (eq 34).[86]

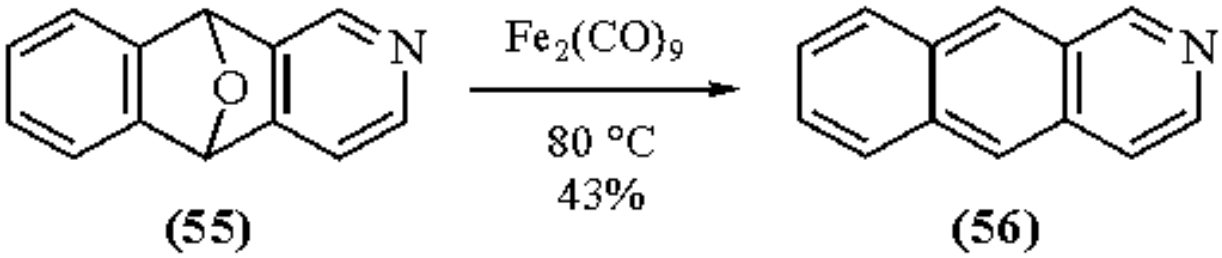

(34)

Reaction with Electrophilic Allenes.

Formation of tricarbonyl(1,3-butadiene)iron(0) complexes from allenes (e.g. **57**) is possible via tricarbonyl(trimethylenemethane)iron(0) intermediates (eq 35).[87]

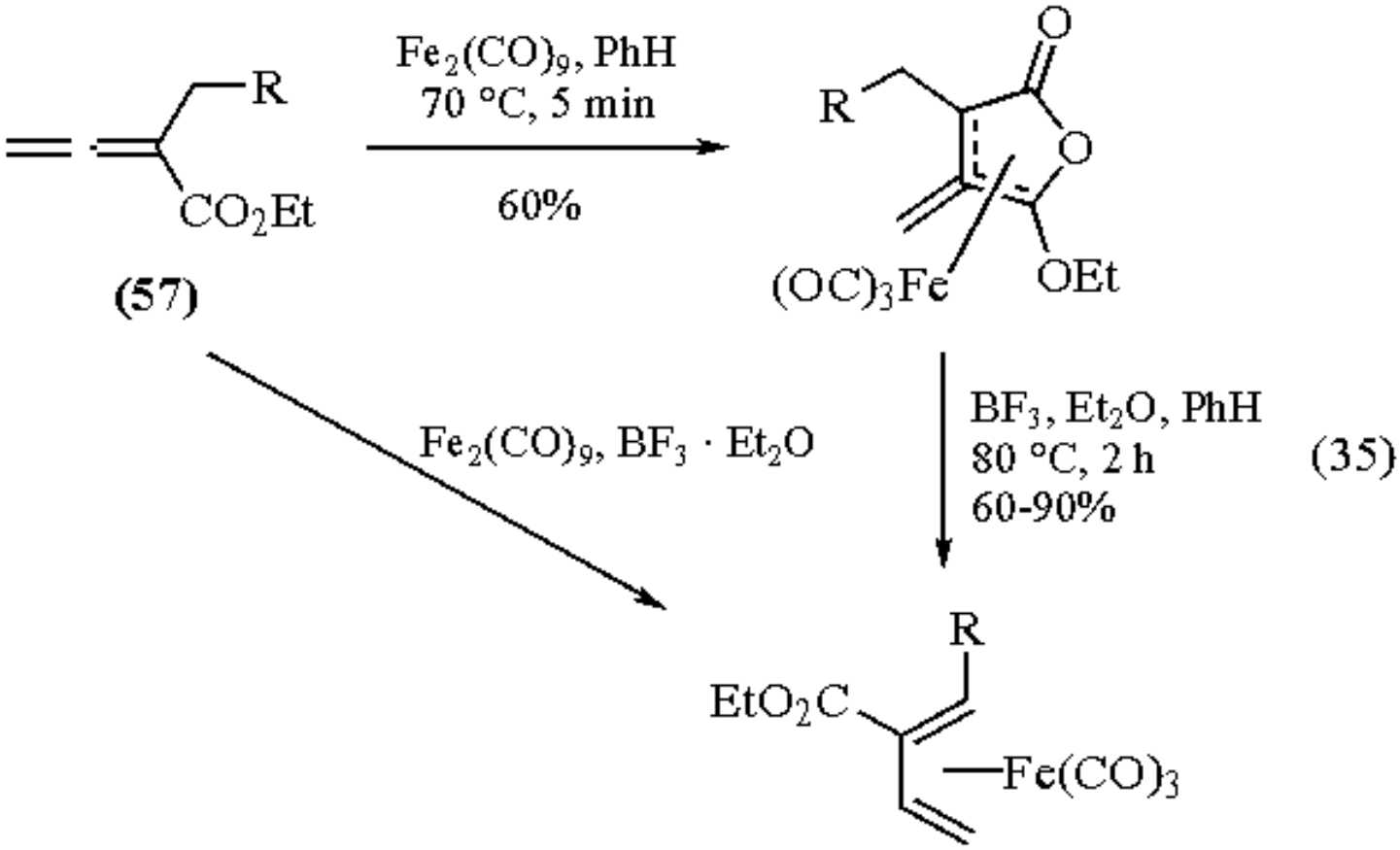

Cyclohexadienone Reductions with $Fe_2(CO)_9$ and Water.

Tricarbonyl(cyclohexadienol)iron(0) complexes are formed by selective monohydrogenation of cyclohexadienones (**58**) by reaction with $Fe_2(CO)_9$ and water, under unusually mild conditions (eq 36).[88]

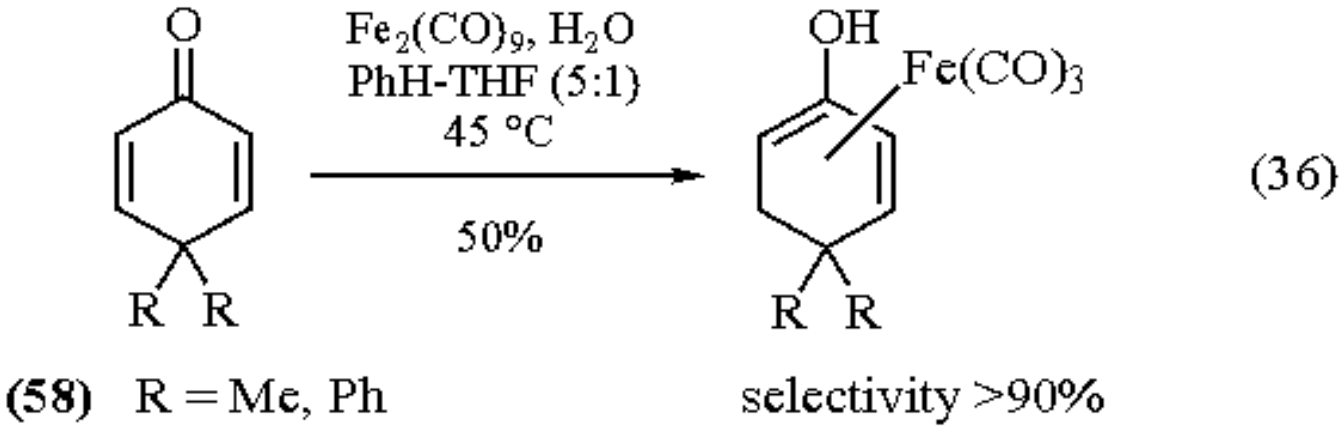

These reactions have been examined with a variety of substrates.[88,89] Regio- and stereoselectivity depends on the pH of the reaction mixture.

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Nonafluorobutanesulfonyl Fluoride[1]

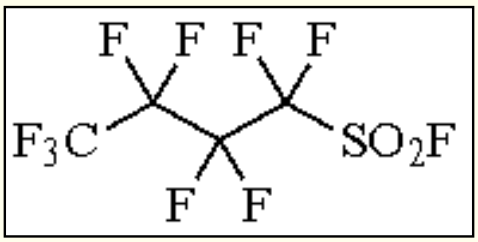

[375-72-4] · $C_4F_{10}O_2S$ · Nonafluorobutanesulfonyl Fluoride · (MW 302.11)

(mild alkylating reagent for amines and alkoxysilanes; precursor for nonafluorobutanesulfinic and -sulfonic acids and various nonafluorobutyl sulfones)

Alternate Name: NfF.

Physical Data: bp 65-66 °C/760 mmHg; *d* 1.682 g cm^{-3}.

Solubility: sol ether, THF; insol CH_2Cl_2.

Form Supplied in: colorless to pale yellow liquid of 90% purity; impurities are branched nonafluorobutanesulfonyl fluorides.

Analysis of Reagent Purity: ^{19}F NMR;[1] MS.[2]

Preparative Methods: by electrochemical fluorination of alkanesulfonyl halides in anhyd HF at 4-6 V,[3] or, better, by electrochemical fluorination of sulfolene.[1]

Purification: dried over $CaCl_2$ and distilled.

Handling, Storage, and Precautions: store in amber colored bottles protected from light; for prolonged storage, PVC bottles are recommended.

Reactions with Alcohols and Phenols.

The title reagent reacts with alcohols containing electronegative groups in the presence of ***Triethylamine*** to afford the nonafluorobutanesulfonate esters (nonaflates) (eqs 1 and 2).[4,5] Under these conditions ethanol, for example, affords diethyl ether by alkylation of the ethanolate anion (from EtOH and Et_3N) with the formed ethyl nonaflate (eq 3).

$$Cl_3CCH_2OH + C_4F_9SO_2F \xrightarrow[\text{40\%}]{Et_3N,\ CH_2Cl_2,\ -HF} Cl_3CCH_2ONf \quad (1)$$

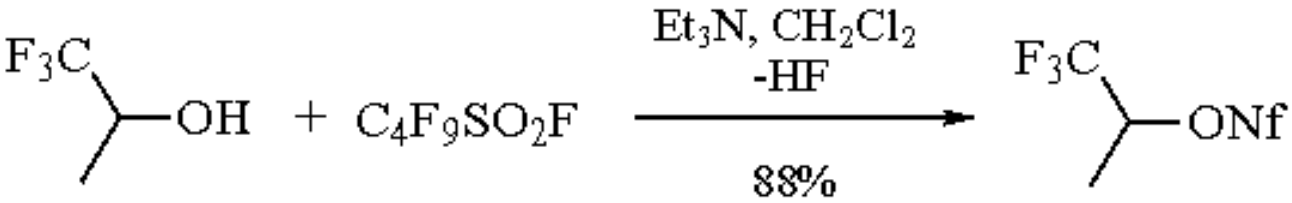

$$EtOH + C_4F_9SO_2F \xrightarrow{Et_3N,\ CH_2Cl_2} EtONf \xrightarrow{EtO^-} EtOEt \quad (3)$$

Phenols react with NfF in the presence of Et_3N to form aryl nonaflates in good yields, and these were hydrogenated using Pd/C (10%) as catalyst to give arenes (eq 4).[6] This has found application in the steroid field.[7]

$$ArOH + C_4F_9SO_2F \xrightarrow[\text{80-93\%}]{Et_3N,\ Et_2O} ArONf \xrightarrow[\text{81-100\%}]{\text{10\% Pd/C, MeOH}} ArH \quad (4)$$

Sodium phenolates also react with NfF in ether to afford aryl nonaflates (eq 5).[8a] For ether insoluble systems, especially heterocyclic hydroxy compounds, dimethoxyethane can be substituted as a more suitable solvent.[6]

$$ArOH \xrightarrow[\text{ether or DME}]{NaH} ArONa \xrightarrow[\text{81-98\%}]{C_4F_9SO_2F} ArONf \quad (5)$$

A milder method of preparation of aryl nonaflates is the reaction of aryloxysilanes with NfF in the presence of fluoride ion (eq 6).[9] This reaction has been extended to prepare vinyl nonaflates from the corresponding silyl ethers (eq 7).[8b,c]

$$ArOTMS + C_4F_9SO_2F \xrightarrow[\text{80-93\%}]{Et_3NF,\ -TMSF} ArONf \quad (6)$$

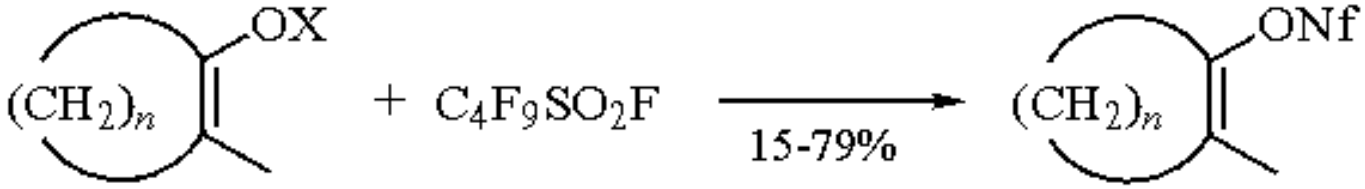

(7)

X = Na, TMS
n = 3-6

Reaction with Amines.

Nonafluorobutanesulfonamides have been prepared by the reaction of NfF with an excess of NH_3 (eq 8).[10] The corresponding ammonium salt formed during this reaction has been isolated,[11] and on acidification with HCl liberates the weakly acidic sulfonamide (eq 9). The sulfonamides have been used in preparing imides and their chemistry studied.[12]

$$C_4F_9SO_2F + 2\ NH_3 \longrightarrow C_4F_9SO_2NH_2 + NH_4F \qquad (8)$$

$$C_4F_9SO_2F + 3\ NH_3 \xrightarrow[-\ NH_4F]{} C_4F_9SO_2NHNH_4 \xrightarrow[-\ NH_4Cl]{HCl} C_4F_9SO_2NH_2 \qquad (9)$$

Other Applications.

NfF was hydrolyzed with aqueous ***Barium Hydroxide***, and the barium salt formed was acidified to give nonafluorobutanesulfonic acid. This acid was converted to the nonafluorobutanesulfonic anhydride (Nf_2O) by treatment with ***Phosphorus(V) Oxide*** (eq 10).[13] Nf_2O can be used instead of ***Trifluoromethanesulfonic Anhydride*** to prepare the homologous nonaflates, which solvolyze about twice as fast as do the triflates.[13]

$$C_4F_9SO_2F + Ba(OH)_2 \xrightarrow{Ba(OH)_2} (C_4F_9SO_3)_2Ba \xrightarrow{H_2SO_4} C_4F_9SO_3H \xrightarrow{P_2O_5} (C_4F_9SO_2)_2O \qquad (10)$$

Hydrazine is found to reduce NfF in ether to give hydrazinium nonaflinate (eq 11), which is hydrolyzed by passing gaseous HCl into the mixture (eq 12).[14] The nonafluorobutanesulfinic acid obtained is useful in preparing nonafluorobutane sulfones (nonaflones) (eq 13).[14]

$$C_4F_9SO_2F + 2\,N_2H_4 \longrightarrow C_4F_9SO_2H \cdot N_2H_4 + 1/2\,[N_2H_4 \cdot 2HF] + 1/2\,N_2 \quad (11)$$

$$C_4F_9SO_2H \cdot N_2H_4 \xrightarrow[-\,N_2H_4 \cdot HCl]{HCl} C_4F_9SO_2H \quad (12)$$

$$C_4F_9SO_2H \xrightarrow{MeI,\ Et_3N,\ HMPA} C_4F_9SO_2Me \quad (13)$$

Nonaflones are also obtained by the reaction of NfF with Grignard reagents (eq 14)[15] and with organolithium reagents (eq 15).[16]

$$C_4F_9SO_2F + RMgBr \xrightarrow{THF} C_4F_9SO_2R \quad (14)$$

$$C_4F_9SO_2F + LiCH_2CN \xrightarrow{THF} C_4F_9SO_2CH_2CN \quad (15)$$

NfF reacts with the sodium salt of ***Diethyl Malonate*** at 20 °C to afford the corresponding nonaflone, which can be hydrolyzed with 40% H_2SO_4 (eq 16).[17]

$$C_4F_9SO_2F + NaCH(CO_2Et)_2 \longrightarrow C_4F_9SO_2CH(CO_2Et)_2 \xrightarrow{40\%\ H_2SO_4} C_4F_9SO_2CHCO_2Et \quad (16)$$

The nonaflones are useful synthetic intermediates in preparing vinyl nonaflones.[16]

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Norephedrine-Borane[1]

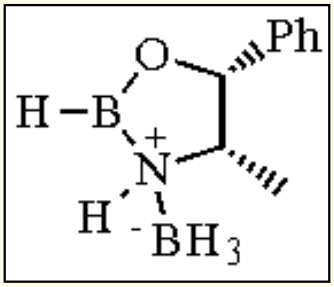

(+)

[154145-14-9] · $C_9H_{15}B_2NO$ · Norephedrine-Borane · (MW 174.87) (-)

[161512-50-1]

(chirally modified hydride reagent[1])

Alternate Name: (4*S*,5*R*)-(4-methyl-5-phenyl-1,3,2-oxazaborolidine).borane

Physical Data: the title reagent has never been isolated; the structure shown above has been assigned on the basis of related studies[2] and by analogy to other well-characterized 1,3,2-oxazaborolidines.[3]

Solubility: THF.

Preparative Method: a 1M THF solution of BH_3 (3.0 mmol) was added to a THF solution of (-)-norephedrine (1.5 mmol) at -30 °C and the resulting mixture was warmed to 20 °C; the thus-formed chiral hydride reagent was used in situ for enantioselective reductions.

Handling, Storage, and Precautions: moisture sensitive; handle under a dry, inert atmosphere.

Enantioselective Reductions.

This chiral hydride reagent reduces aromatic ketones to the corresponding alcohols with high enantioselectivity (eq 1).[4]

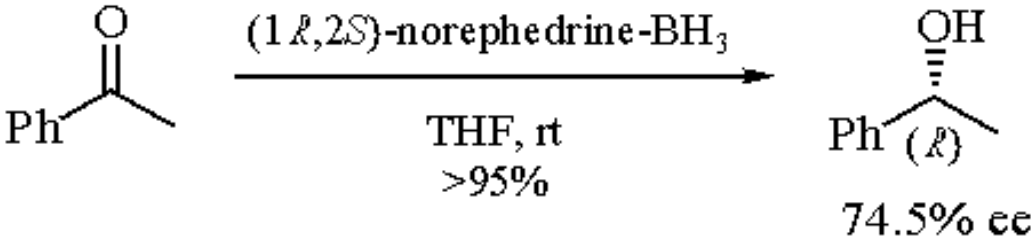

(1)

Anti and *syn* ketoxime ethers are also reduced by this reagent to the corresponding amines in up to 92% ee. The absolute configuration of the resulting amine is dependent on the geometry of the starting oxime ethers: *anti* oximes give (*S*) configurated amines whereas *syn* oximes afford the (*R*) antipodes (eqs 2 and 3); see Table 1.[4,5]

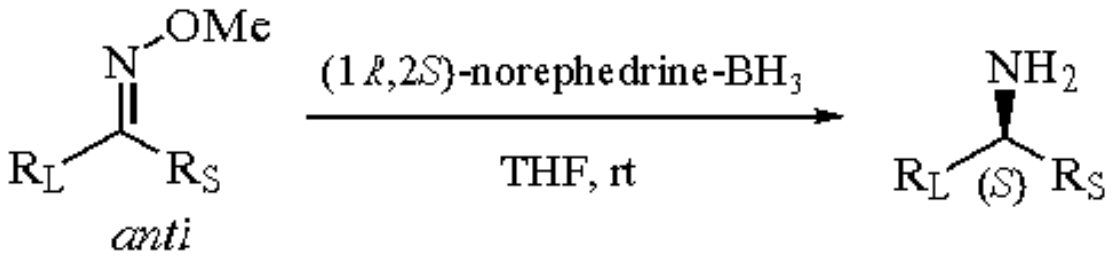

(2)

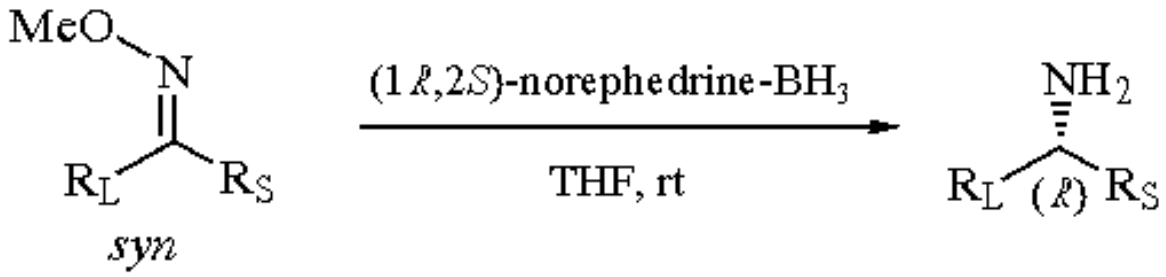

(3)

Table 1 Enantioselective Oxime Reductions[2,3]

Oxime	R_L	R_S	Config	ee (%)	Yield (%)
anti	Ph	*p*-TolCH_2	*S*	92	64
syn	*p*-TolCH_2	Ph	*R*	92	58
anti	2-Naphthyl	Me	*S*	92	73
syn	Me	2-Naphthyl	*R*	92	
anti	Ph$(CH_2)_2$	Me	*S*	86	40
syn	Me	Ph$(CH_2)_2$	*R*	81	46
anti	Ph	Me	*S*	93	99

Similar results can be obtained if the borane is substituted for the system ***Sodium Borohydride*/*Aluminum Chloride***.[6]

On the basis of experimental[3b] as well as theoretical[7] studies on similar systems, the mechanism of carbonyl reduction is expected to involve:

- 1)In situ formation of the 1,3,2-oxazaborolidine from borane and the 1,2-amino alcohol with 2 equiv of H_2 uptake;
- 2)coordination between the N atom of the oxazaborolidine and a second equivalent of borane;
- 3)coordination at the heterocyclic B atom by the oxygen of the solvent and then by that of the carbonyl compound;
- 4)hydride transfer from the NBH_3^- unit to the substrate via a six-membered transition state.

Although these reactions are expected to be catalytic in oxazaborolidine, the reported examples use the chiral ligand in stoichiometric amounts.

Related Reagents.

Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole.

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Octacarbonyldicobalt

$Co_2(CO)_8$

[10210-68-1] · $C_8Co_2O_8$ · Octacarbonyldicobalt · (MW 341.94)

(catalyst for carbonylation and related reactions; major source of other synthetically useful organocobalt compounds)

Alternate Names: di-μ-carbonylhexacarbonyldicobalt; cobalt carbonyl.

Physical Data: mp 51-52 °C (dec); subl 40 °C/vac.

Solubility: insol H_2O; sol common org solvents.

Form Supplied in: dark orange crystals (commonly stabilized with 5-10% hexane).

Handling, Storage, and Precautions: toxic, moderately air sensitive, and unstable at ambient temperature, slowly releasing carbon monoxide (residual finely divided metal may become pyrophoric); may be stored for long periods at or below 0 °C in tightly closed vessels under inert gas (N_2, Ar) or (best) CO; brief handling (including weighing) in air causes no problems; heating in inert solvents yields the less reactive $Co_4(CO)_{12}$; use in a fume hood.

Introduction.

In the crystal, the molecule of this reagent consists of two cobalt atoms linked both directly and by two bridging carbonyls and each carrying three terminal carbonyls (cf. eq 33).[1] In solution this form is in equilibrium with unbridged $(OC)_4Co\text{-}Co(CO)_4$.

Halogen oxidation only leads to a halocarbonyl species in the case of iodine; the unstable and incompletely characterized product, probably $ICo(CO)_4$, has found little use. The anion $Co(CO)_4^-$, readily formed by reduction (***Sodium Amalgam***) or by disproportionation on reaction with bases, including not only pyridine and other nitrogen bases but also such donor solvents as methanol and acetonitrile, is treated separately. (See ***Sodium Tetracarbonylcobaltate***.) However, reactions which utilize $Co_2(CO)_8$ as starting material are included here even if the reaction conditions imply that this anion or its conjugate acid, $HCo(CO)_4$ (also formed from $Co_2(CO)_8 + H_2$), may be the active intermediate. The chemistry of the reagent has been reviewed.[2,3]

Catalytic Uses.

Hydroformylation and Hydrogenation.

Octacarbonyldicobalt catalyzes a wide range of reactions of carbon monoxide (alone or with hydrogen),[2,4-8] of which the best known is probably the hydroformylation (oxo reaction) of alkenes. Depending on reaction conditions, notably $CO:H_2$ ratio and temperature, the products are aldehydes (eq 1) or alcohols (hydroalkylation) (eq 2).

$$RCH{=}CH_2 + CO + H_2 \xrightarrow{130\text{-}180\ ^\circ C} RCH_2CH_2CHO + RCH(Me)CHO \quad (1)$$

$$RCH{=}CH_2 + CO + 2\,H_2 \xrightarrow{160\text{-}200\ ^\circ C} RCH_2CH_2CH_2OH + RCH(Me)CH_2OH \quad (2)$$

A valuable feature is the preference for straight chain over branched chain products; since $HCo(CO)_4$ is an efficient alkene isomerization catalyst, this is true even for internal alkenes. Much research has been devoted to optimizing the product ratio for specific uses, e.g. by adding phosphines or other catalyst modifiers. While cobalt carbonyl (probably as $HCo(CO)_4$) is an effective catalyst for these and many related reactions and has found extensive industrial use (albeit commonly generated in situ rather than introduced as such), it has largely been superseded by related rhodium catalysts; the greater cost of the latter is offset by much higher activity and hence efficient conversions using small catalyst concentrations under much milder reaction conditions. Alkyl halides and alcohols can replace alkenes in many such reaction.

Whereas, in general, reduction of the formyl group (cf. eqs 1 and 2) requires a higher temperature than hydroformylation, reduction of the C=C double bond can be a major side-reaction of cobalt-catalyzed hydroformylation. Thus, in the reaction of eugenol, which is accompanied by cyclization (eq 3), 40% of the starting material is reduced to dihydroeugenol.[9]

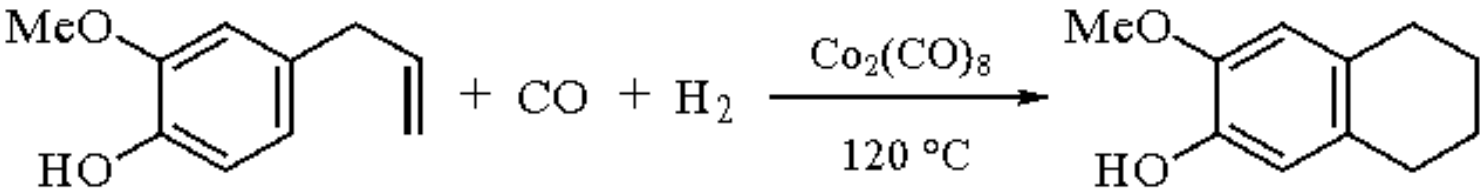

(3)

The $Co_2(CO)_8$-catalyzed alkene hydrogenation can be useful, as in the smooth reduction of alkylcinnamaldehydes (eq 4),[10] the highly selective hydrogenation of methyl (*E*,*E*)-octadeca-9,11-dienoate to methyl elaidate (eq 5),[11] and of a range of polycyclic aromatics,[12] e.g. naphthacene (eq 6).

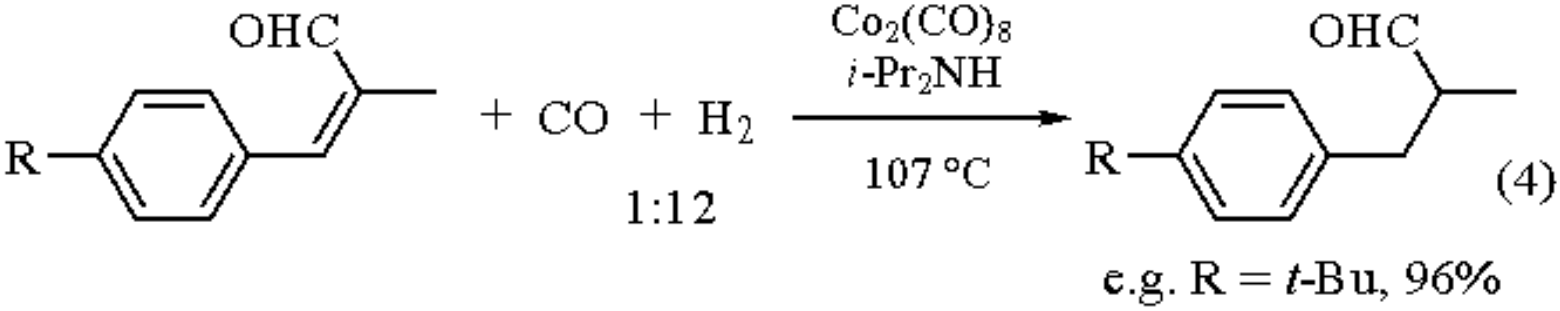

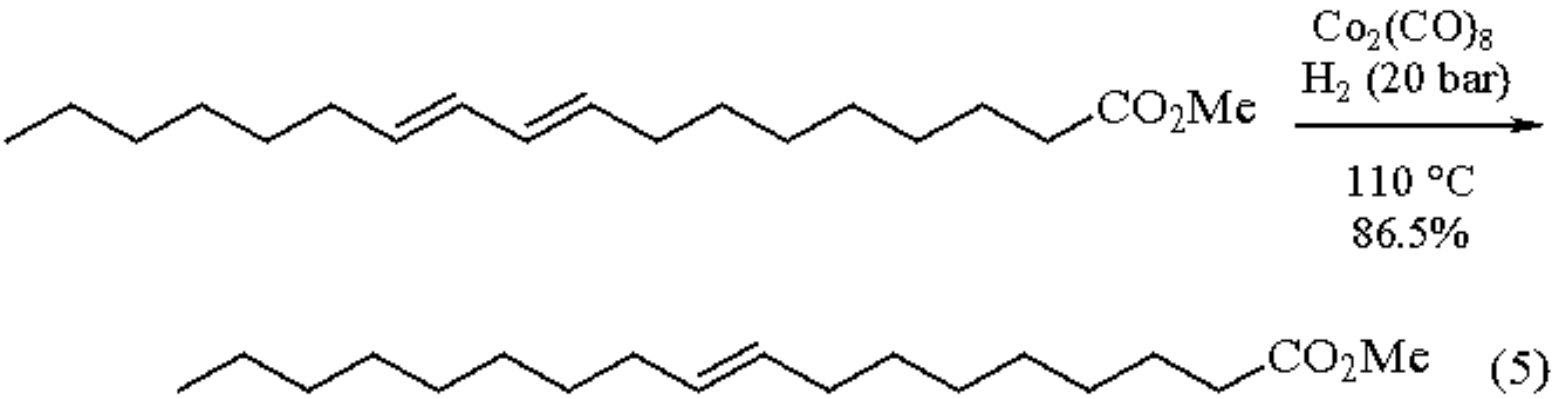

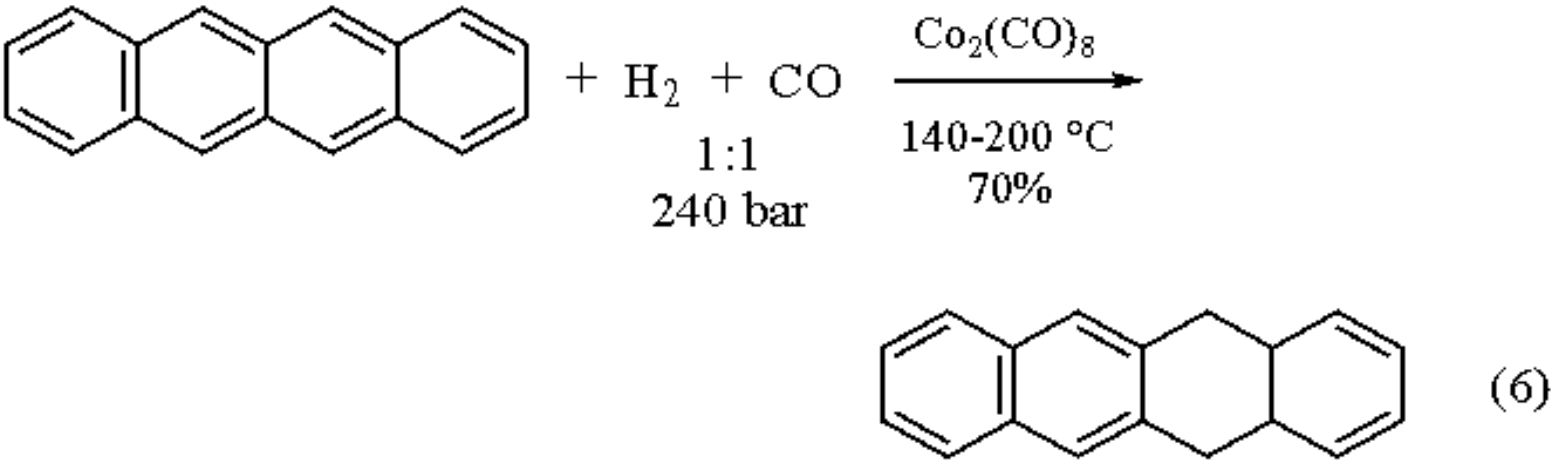

Dehydration or loss of alcohol accompanies hydroalkylation (eq 2) when applied to allylic alcohols (giving tetrahydrofurans rather than 1,4-diols) or to acrylic acids or esters, which give butyrolactones (eq 7) in moderate to excellent yields.[13]

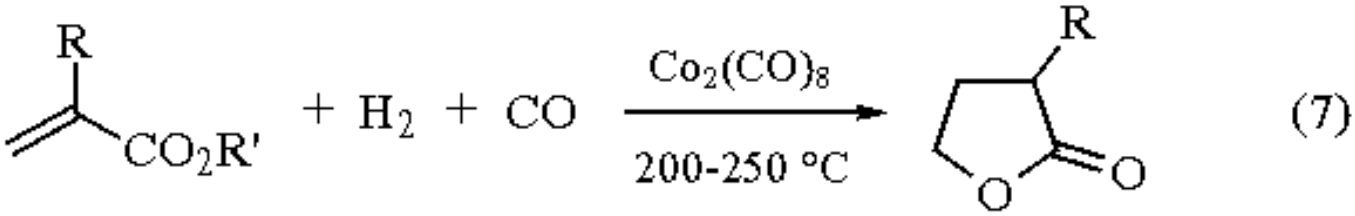

In more or less related reactions, $Co_2(CO)_8$ is a useful catalyst in carboxylation (viz. alkoxycarbonylation) and a wide range of carbonylation reactions. Both catalysis of the water-gas shift reaction[14] and of Fischer-Tropsch processes[15] have been demonstrated on solid supports and probably involve $Co_2(CO)_8$-derived polynuclear carbonyls.[16]

Carboxylation and Related Reactions.

Although nickel, palladium, and other catalysts have been widely studied for carboxylation reactions and are clearly preferable in the case of alkynes, octacarbonyldicobalt (especially in combination with ***Pyridine***) is an effective catalyst for the conversion of alkenes into acids and esters (eq 8) and differs significantly in selectivity from the nickel-based systems. Thus, whereas styrene gives predominantly the branched esters with both types of catalyst, terminal *n*-alkenes give predominantly branched esters with nickel catalysts, but straight-chain esters with $Co_2(CO)_8$, as in eq 9.[4] The related hydrocyanation reaction, on the other hand, gives branched-chain products and, except with the most reactive alkenes, poor yields[17] when using $Co_2(CO)_8$ and better nickel-based catalysts are available.

$$\mathrm{RCH{=}CH_2} + \mathrm{CO} + \mathrm{R'OH} \xrightarrow{\mathrm{Co_2(CO)_8,\ py}} \mathrm{RCH_2CH_2CO_2R'} + \mathrm{RCH(Me)CO_2R'} \quad (8)$$

$\mathrm{R' = H, Me, etc}$

$$+ \mathrm{CO} + \mathrm{H_2} + \mathrm{MeOH} \xrightarrow[\text{(1:12), 175 °C; 95\% conversion}]{\mathrm{Co_2(CO)_8,\ py}}$$

190 bar 10 bar

$$\underset{79\%}{\mathrm{C_8H_{17}CO_2Me}} + \underset{14\%}{\mathrm{Me(CH_2)_5CHMeCO_2Me}} + \underset{4\%}{\mathrm{Me(CH_2)_4CHEtCO_2Me}} + \underset{3\%}{\mathrm{Me(CH_2)_3CHPrCO_2Me}} \quad (9)$$

The condensation of two alkene molecules with ***Carbon Monoxide*** to yield ketones [e.g. ethylene -> 3-pentanone (95%)][4] succeeds well only in special cases, e.g. with methyl acrylate (eq 10).[18]

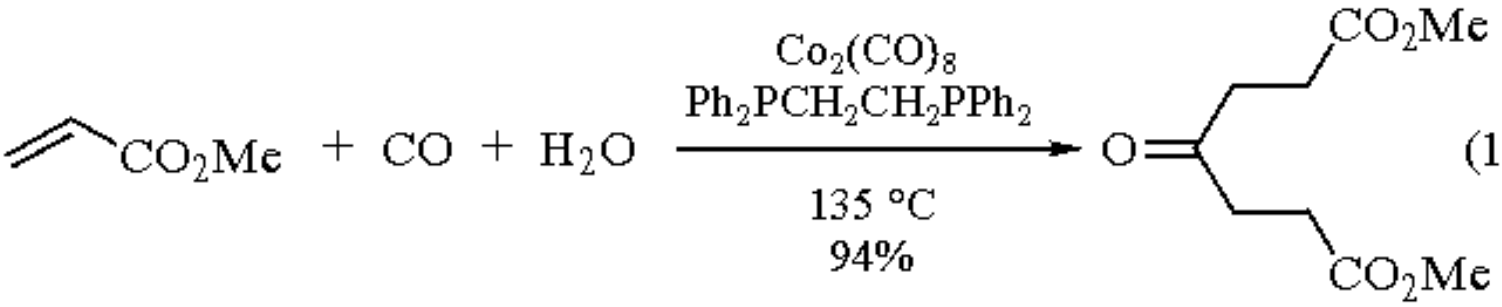

(10)

Octacarbonyldicobalt-catalyzed homologation of alcohols (eq 11) is difficult to control and of little practical value, while the related carboxylation of methanol to acetic acid requires such extreme conditions that it cannot compete with the technically important rhodium-catalyzed process.

$$ROH + CO + 2\,H_2 \xrightarrow[135\ ^\circ C]{Co_2(CO)_8,\ I_2} RCH_2OH \qquad (11)$$

Relatively mild conditions suffice for the regioselective carbonylation (eq 12)[19] and carboxylation of epoxides (eq 13).[20] The rather poor yields quoted in these examples have been attributed to extensive side-reactions, but specific cases giving excellent results are also known, e.g. with a carbohydrate epoxide (eq 14).[21]

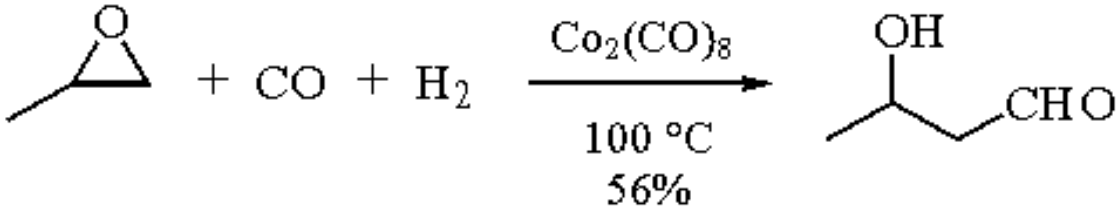

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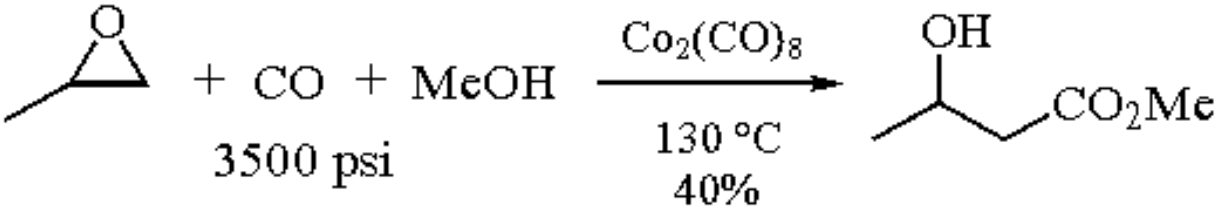

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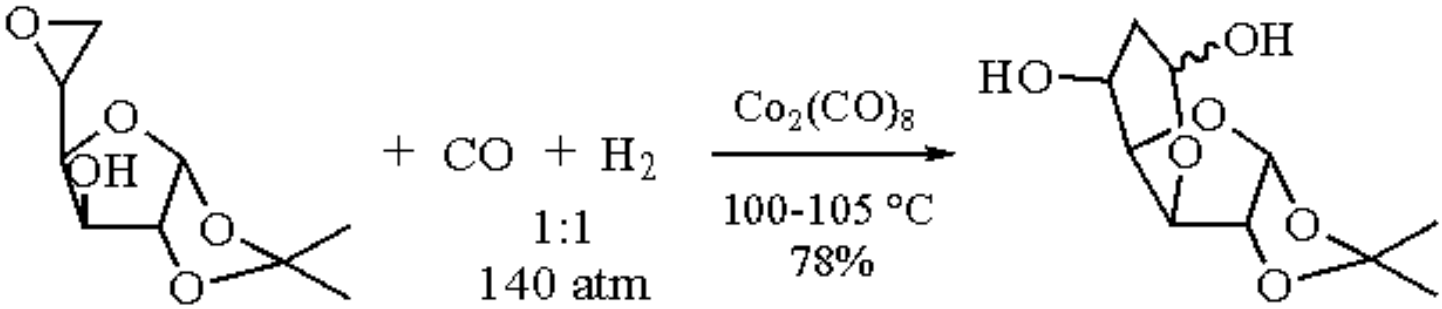

(14)

Carboxylations of halogen compounds include the technically useful conversion of chloroacetate to malonate (eq 15),[22] and several patent reports of quantitative conversion of ***Benzyl Chloride*** to phenylacetic acid.[23] The incorporation of two molecules of carbon monoxide to give α-keto-acids, as exemplified by the reaction of benzyl chloride (eq 16), is remarkably solvent-dependent[24] and almost certainly involves reaction of the halide with $Co(CO)_4^-$.

$$ClCH_2CO_2Et + CO + NaOEt \xrightarrow[\substack{7\ bar \\ 55\ ^\circ C \\ 85\%}]{Co_2(CO)_8} CH_2(CO_2Et)_2 \qquad (15)$$

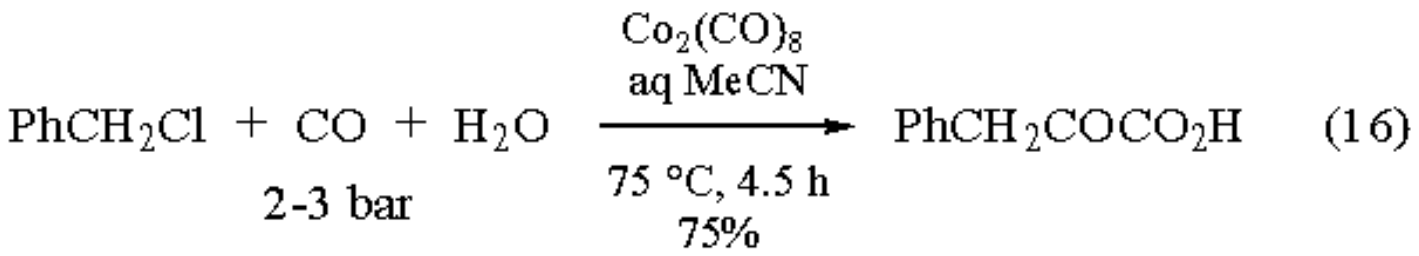

A carboxylation which is followed by a Michael addition occurs with high overall efficiency when ***Acrylonitrile*** reacts in the presence of an alcohol and pyridine (eq 17).[25]

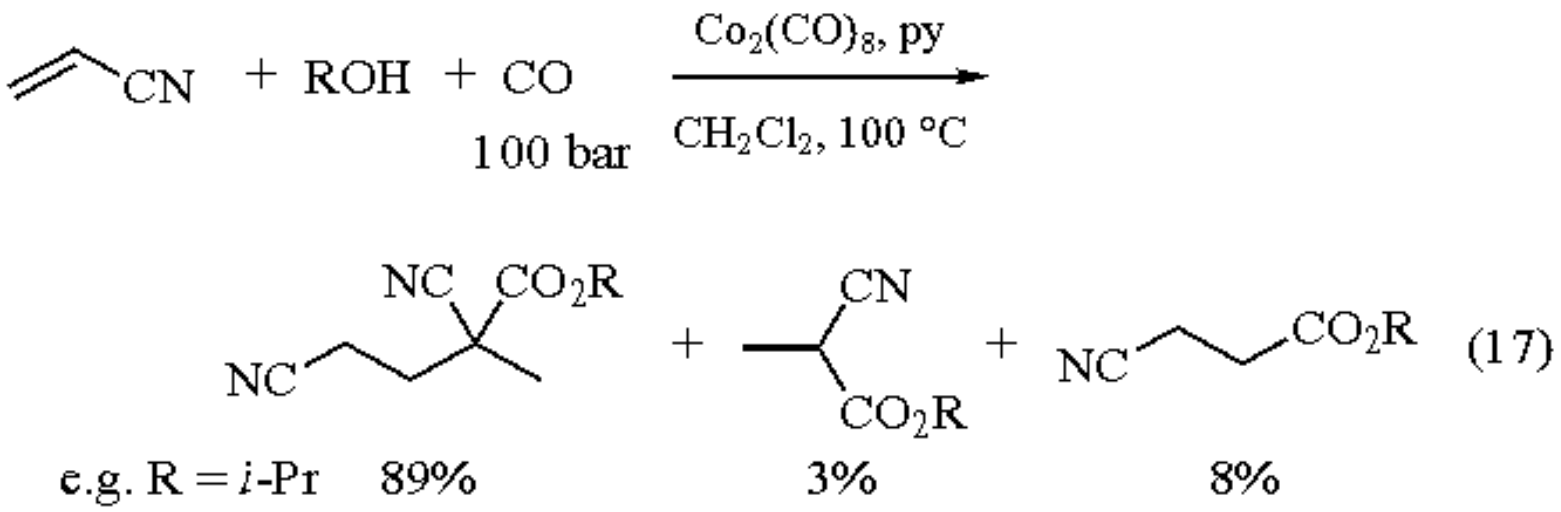

Carbonylation.

This term is used here to denote carbon monoxide insertions (with or without cyclization) which do not involve H_2 or ROH.

Unlike epoxides, oxetanes react with carbon monoxide in the presence of $Co_2(CO)_8$ by ring expansion to γ-butyrolactones, rather than ring opening; thietanes (eq 18) as well as azetidines (eqs 19 and 20) behave similarly. Mixtures of cobalt and ruthenium carbonyls (1:1) are reported to give better yields than either catalyst separately.[26] The examples shown illustrate the strong dependence of regioselectivity on substitution pattern in the azetidine case.[27]

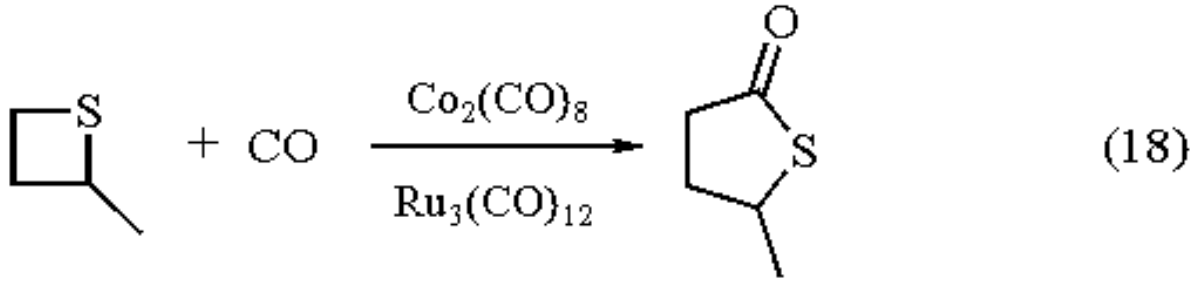

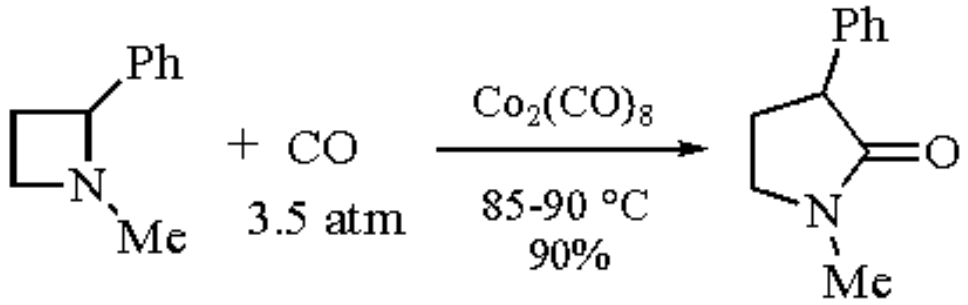

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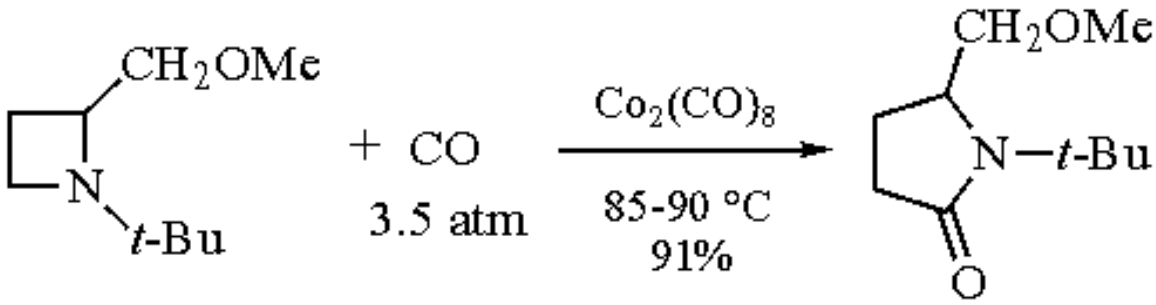

(20)

$Co_2(CO)_8$-catalyzed reactions of a variety of other nitrogen compounds, e.g. azo compounds (eq 21),[28] imines (eq 22),[29] and amides (eq 23),[30] involve CO insertion into N-N and N-H bonds and cyclizations which probably proceed via cyclometalation.

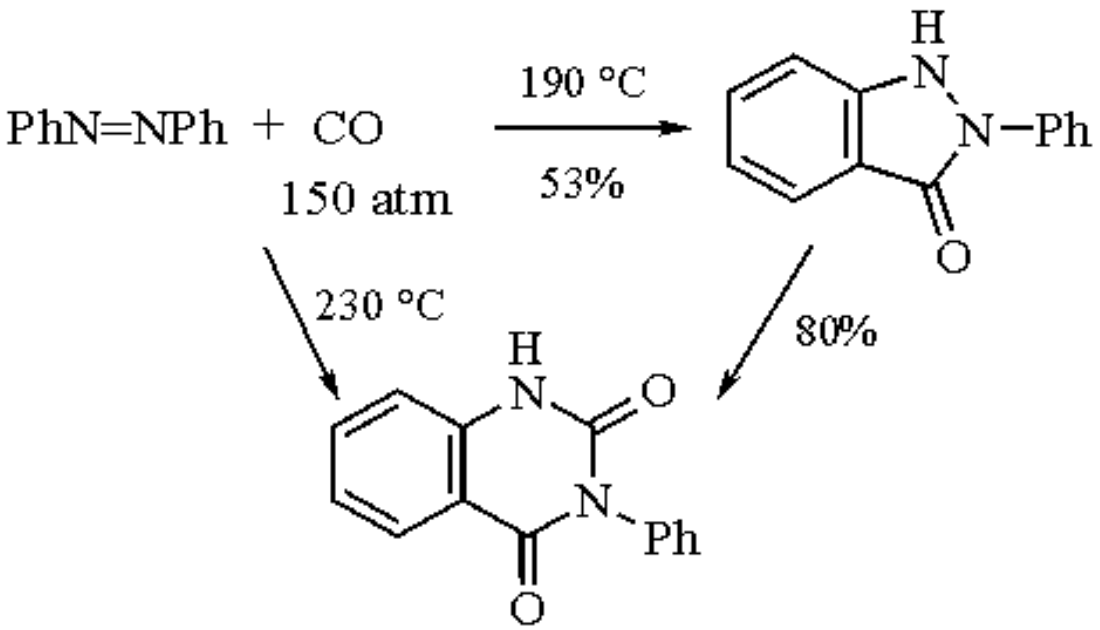

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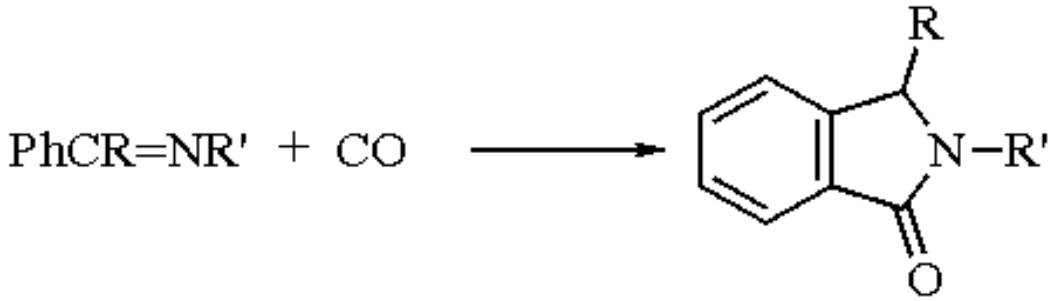

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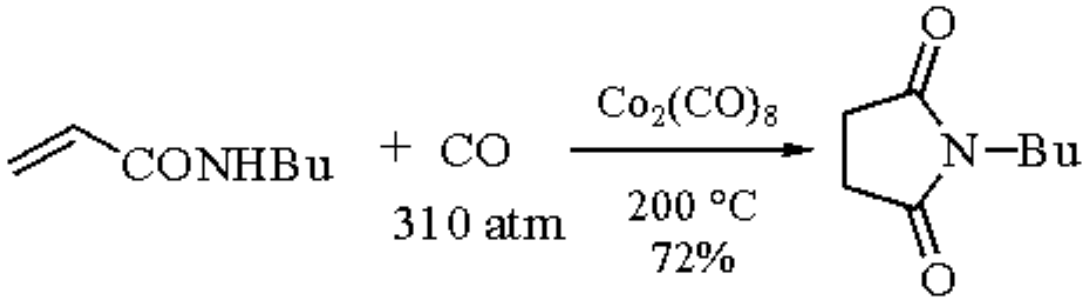

(23)

The mechanism of the remarkable formation of furans[31] from 3-diethylamino-1-propyne (or -butyne) (eq 24) (R = H or Me) is unknown, but it must involve CO insertion into a C-N bond.

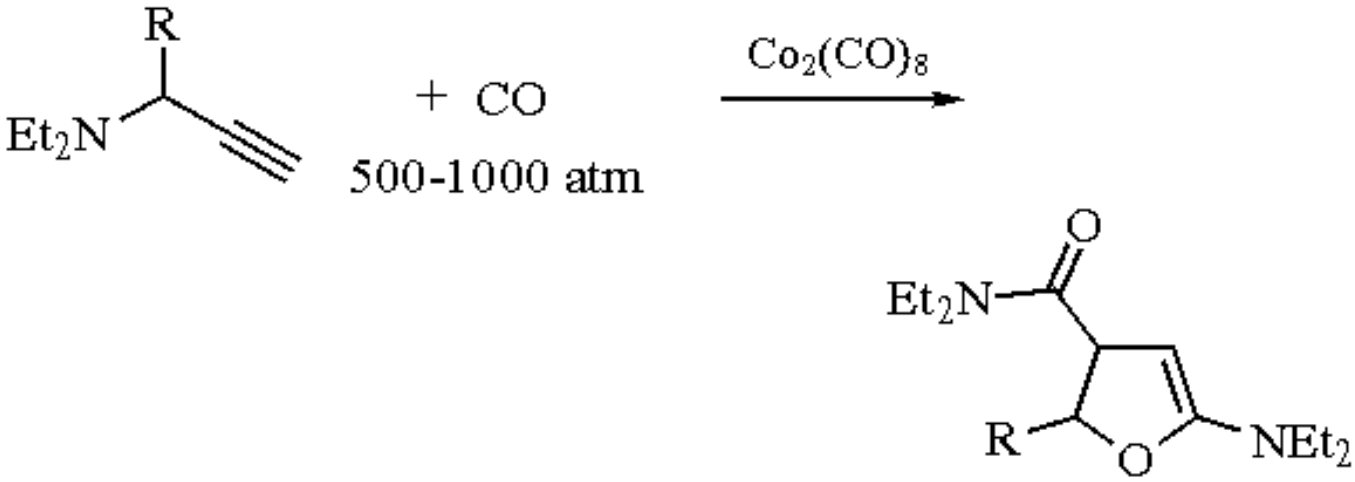

(24)

The carbonylation of ***Diphenyl Diselenide*** (eq 25) illustrates the general behavior of diaryl diselenides and ditellurides,[32] but proceeds more smoothly than most other examples studied.

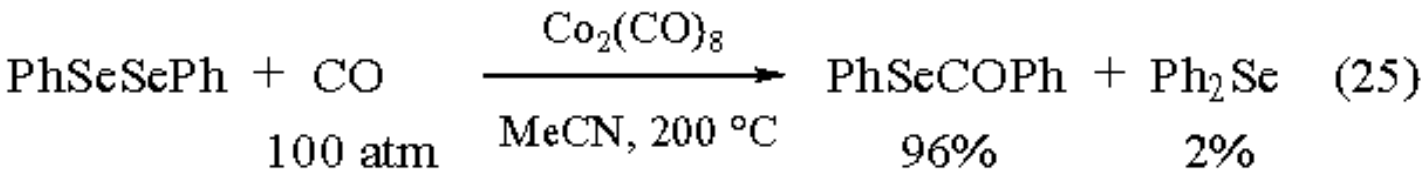

(25)

Reversibility of carbonylation processes is illustrated by decarbonylation of phthalic anhydride by $Co_2(CO)_8$ under H_2 to benzoic acid,[33] and of ***Diphenylketene*** to tetraphenylethylene.[34]

Carbonylation of alkynes is discussed below in connection with the stoichiometric reactions of alkyne-cobalt compounds.

Amidocarbonylation.

The reaction of aldehydes with primary amides and carbon monoxide in the presence of cobalt carbonyl (eq 26) provides a valuable alternative to the Strecker reaction as a route to *N*-acyl-α-amino acids.[8,34-36] Its convenience is enhanced by the possibility of generating the aldehyde in situ by isomerization of an allylic alcohol for which a cocatalyst [$PdCl_2(PPh_3)_2$, ***Carbonylhydridotris(triphenylphosphine)rhodium(I)***, or ***Nonacarbonyldiiron***] is advantageous,[37] (e.g. eq 27), or by hydroformylation of an alkene (e.g. by the reactions of eq 28 which can be combined

to give the *N*-acetylamino acid in 83% yield[8,38]), or of an alcohol (e.g. eq 29). In the last example[39] the product is isolated (as the methyl ester after ***Diazomethane*** treatment) in 73% total yield as a mixture of *threo* and *erythro* isomers.

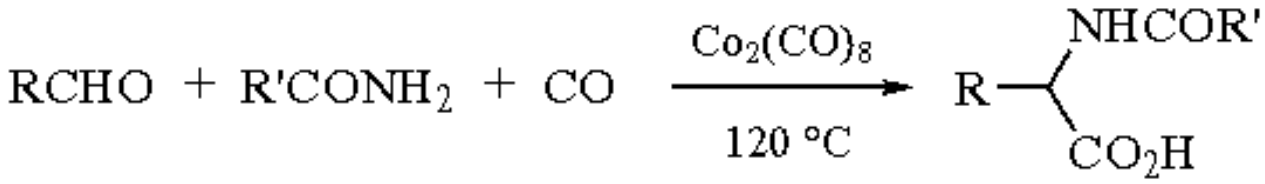

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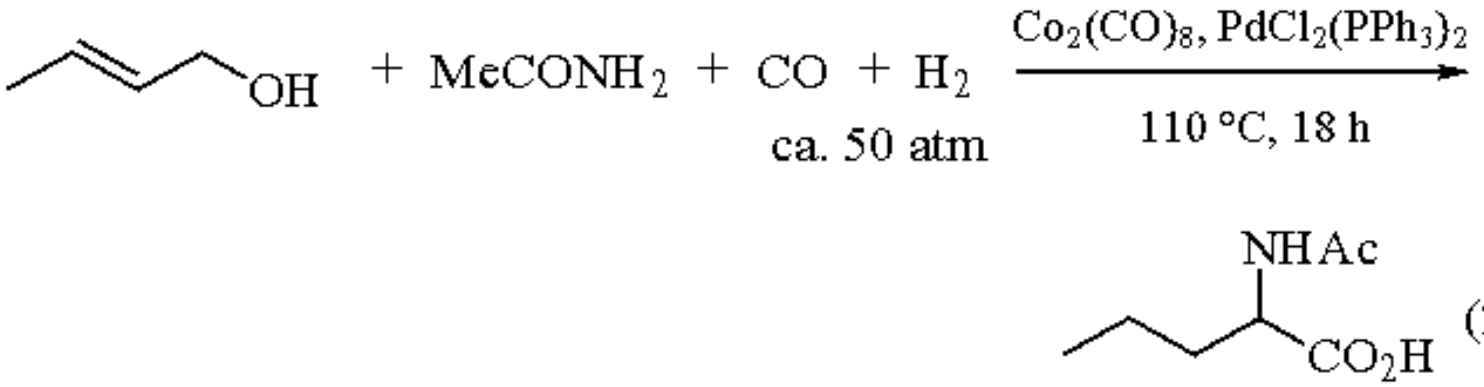

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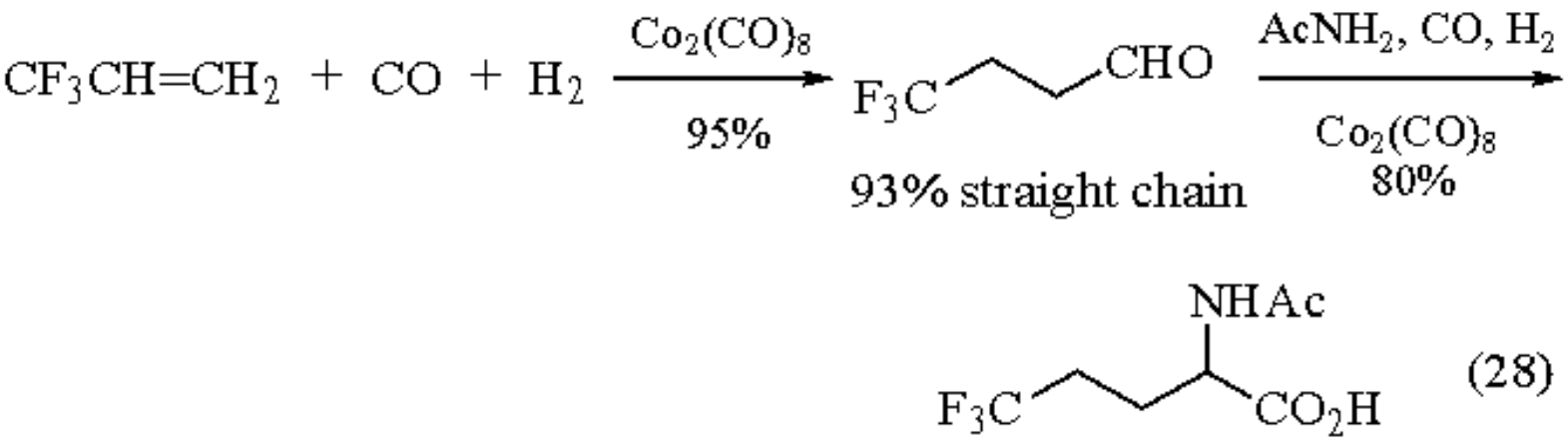

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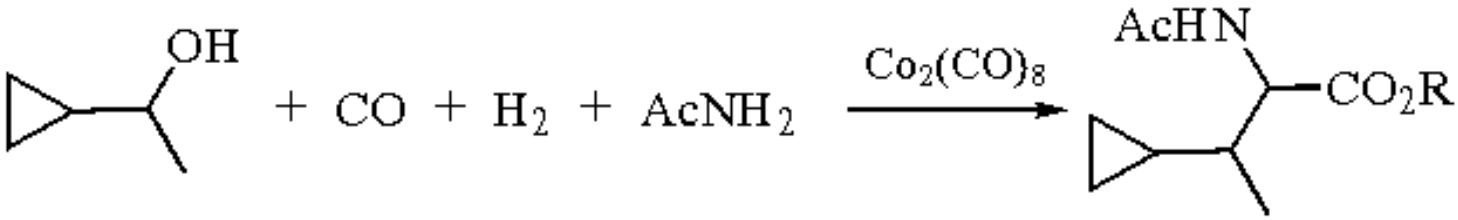

(29)

Other Octacarbonyldicobalt-Catalyzed Reactions.

A retro-Diels-Alder reaction catalyzed by $Co_2(CO)_8$ was observed in which a barrelene derivative loses a C_2H_2 fragment (eq 30).[40] An analogous cleavage accompanies the cyclopentenone synthesis (see below) when norbornadiene reacts in certain solvents with alkynehexacarbonyldicobalts, as shown by the formation of dicarbonylcyclopentadienylcobalt,[41] whereas a Diels-Alder addition catalyzed by a cobalt carbonyl species is involved when the same reaction is applied to cyclohexadiene.[42]

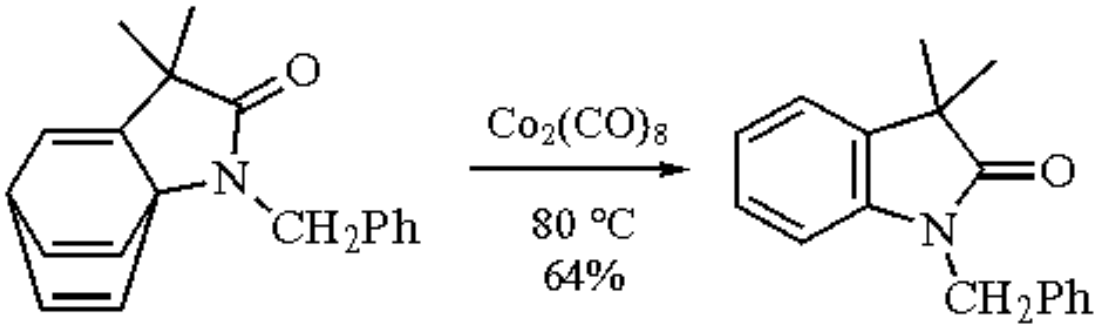

(30)

Efficient and appreciably regioselective ring-opening addition of ***Cyanotrimethylsilane*** to tetrahydrofurans is illustrated by the example shown (eq 31).[43] The same reagent undergoes $Co_2(CO)_8$ (or ***Dicarbonyl(cyclopentadienyl)cobalt(I)***) catalyzed addition to alkynes to give pyrrole derivatives (eq 32).[44]

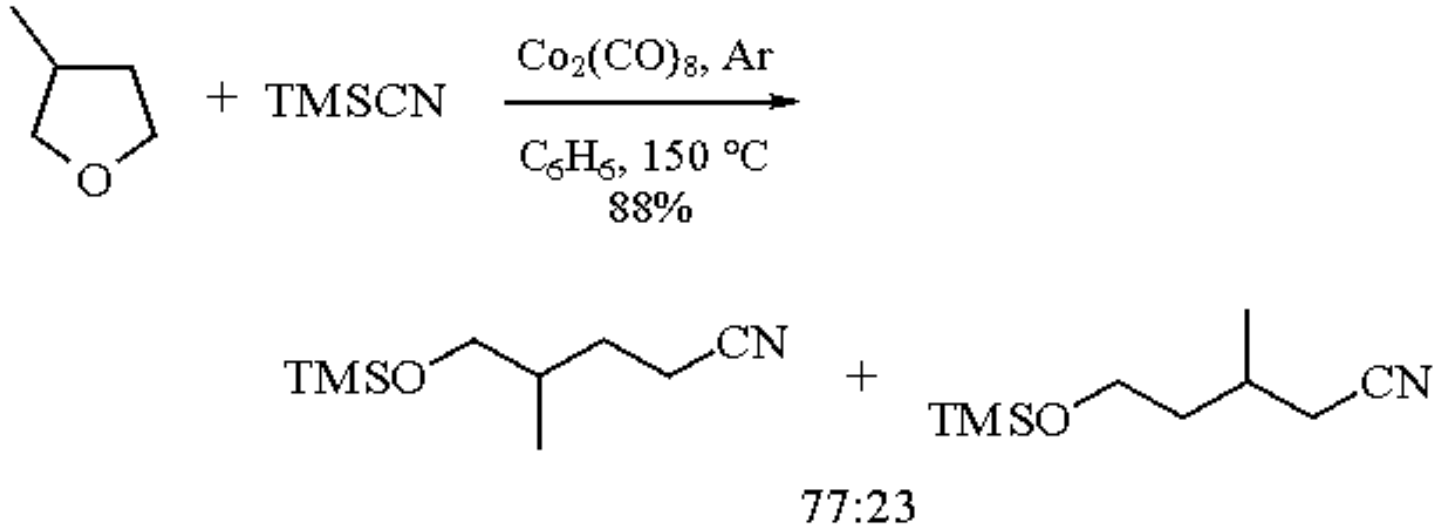

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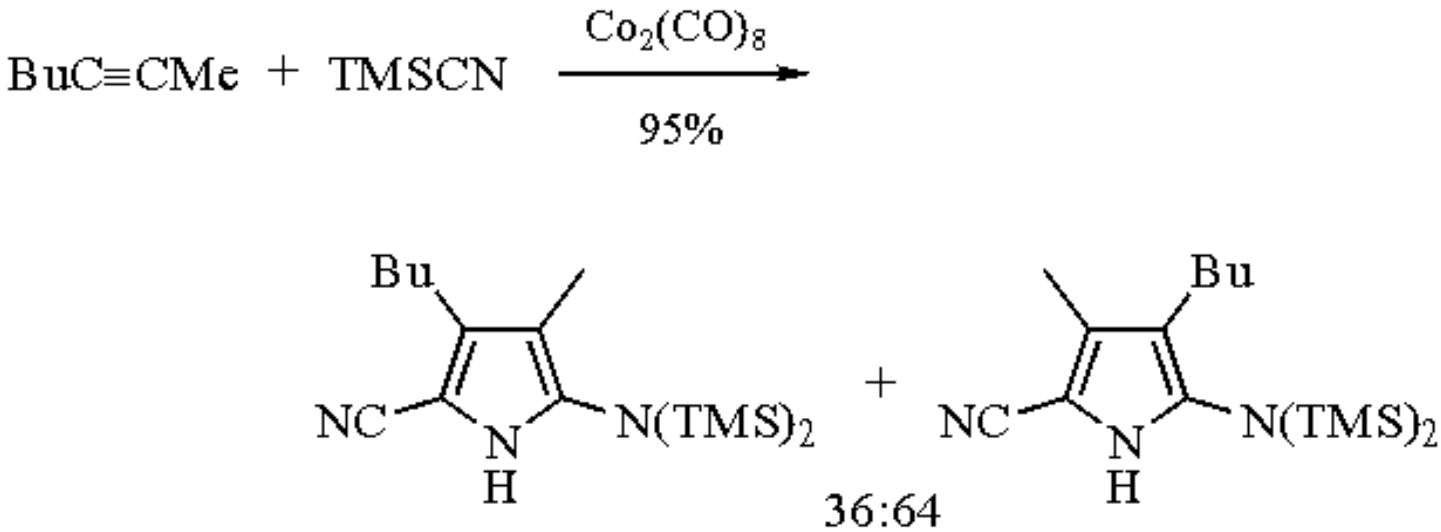

(32)

Octacarbonyldicobalt shares with many other metal carbonyls and other organometallics the ability to catalyze the cyclotrimerization of alkynes[45] and related condensations, e.g. of two alkyne and one nitrile molecule to give pyridines. Derived compounds including $Hg[Co(CO)_4]_2$, $Co(CO)_3NO$ (obtained from $Co_2(CO)_8$ with NO or other nitrosating agents) and the alkyne complexes $(RC_2R')Co_2(CO)_6$ (see below) all share this activity, but none of these compare in

efficiency with the preferred $CpCoL_2$ catalysts.

The few examples of catalytic cyclopentenone formation from alkyne, alkene, and CO are discussed below, as is the bifurylidenedione synthesis from alkyne and CO. It should also be noted that $Co_4(CO)_{12}$, obtained by heating the dinuclear carbonyl, can probably replace the latter in most of the above catalytic reactions, but without obvious advantage.

Stoichiometric Reactions.

Reactions with Dienes.

Conjugated dienes and norbornadiene displace two terminal carbonyl groups from first one and then both metal atoms of the octacarbonyl (eq 33).[46]

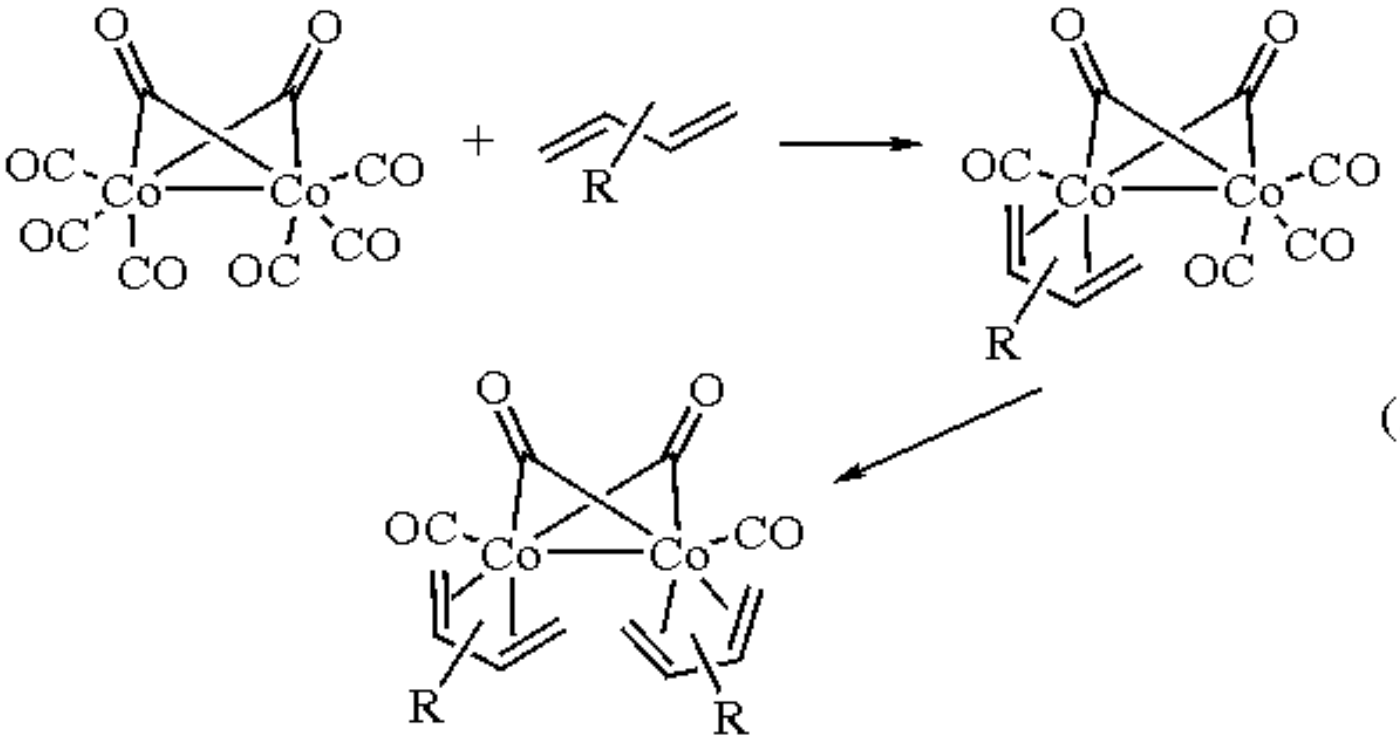

(33)

Either of these products can be oxidized to $[(diene)Co(CO)_3]^+$ salts,[47] whose synthetic potential arises from their reactivity towards nucleophiles.[47b,48] Whether 1- or 2-substituted butadiene ligands react highly regioselectively at the 4-position (e.g. eq 34),[47b] or at both C-1 and C-4, depends both on the substituent and on the nucleophile, but attack at C-2 has only been found in the reaction of the butadiene complex with ***Lithium Diisopropylamide***.[48b]

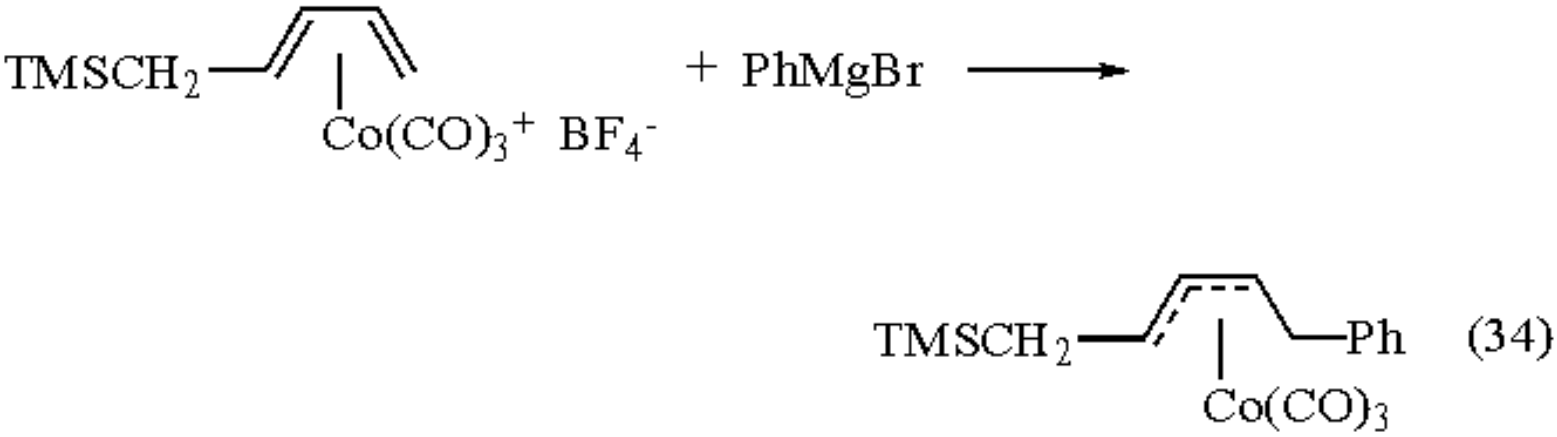

Greater synthetic interest attaches to the cycloaddition of dienolates of β-diketones or β-keto esters, illustrated for the cyclohexadiene complex (eq 35), which leads, after ***Tetra-n-butylammonium Fluoride*** treatment of an intermediate (not isolated), to dihydrofuran derivatives.

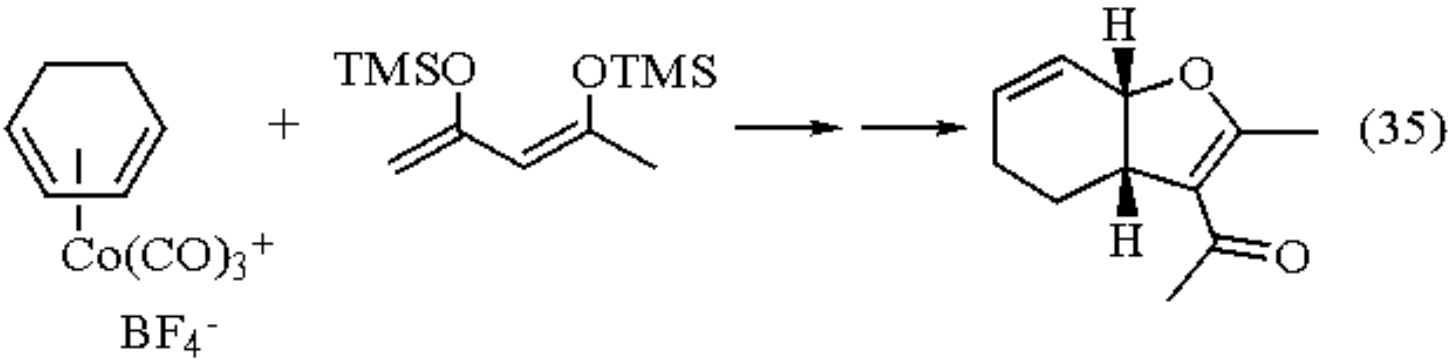

Cyclopentadiene does not yield an isolable diene complex when reacting with $Co_2(CO)_8$, yielding instead ***Dicarbonyl(cyclopentadienyl)cobalt(I)***.

Reactions with Alkynes.

In contrast to dienes (see above), alkynes replace the two bridging carbonyls of $Co_2(CO)_8$ producing stable, readily isolated complexes in reactions which are normally rapid at room temperature (eq 36).[49] The alkyne moiety lies at right angles to the Co-Co bond, so that the alkyne carbons form a tetrahedron with the two cobalt atoms. If the alkyne is terminal (R^2 = H), these products (hereafter drawn in the simplified form of eq 37) react with acids (e.g. ***Sulfuric Acid*** in MeOH) to give the trinuclear compounds $RCH_2C[Co_3(CO)_9]$,[50] which also form directly from the alkyne with $Co_2(CO)_8$ at 85 °C.[49b] (For further elaboration of such trinuclear complexes see ***Sodium Tetracarbonylcobaltate***, from which a wider range of such compounds is most conveniently prepared.)

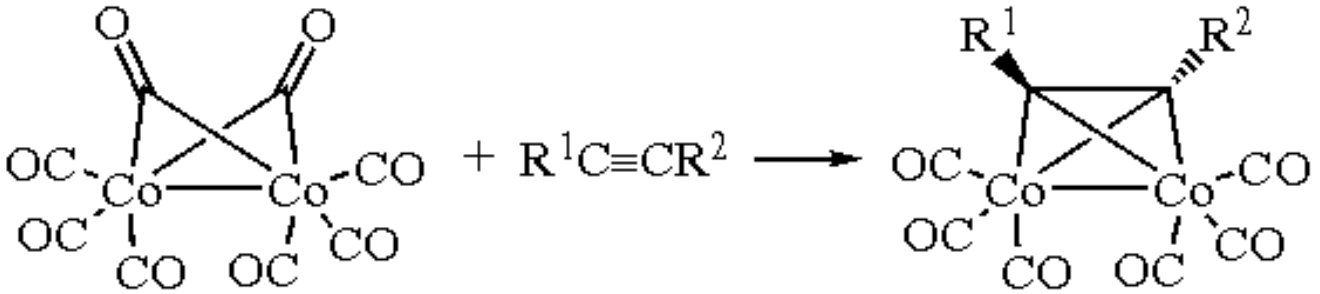

(36)

Reactions of the $(RC_2H)Co_2(CO)_6$ complexes with carbon monoxide under pressure give lactone complexes[51a,b] (reducible to γ-butyrolactones[51c]) by insertion of two CO groups into the Co-C bonds (eq 37); the further stepwise insertion of CO and alkyne provides the mechanism for the efficient $Co_2(CO)_8$-catalyzed synthesis of 2,2´-bifurylidene-5,5´-diones (eq 38).[52] Under relatively mild conditions and with a 1:1 ratio of C_2H_2:CO, the extended bifurandiones of eq 39 also become significant products.[53]

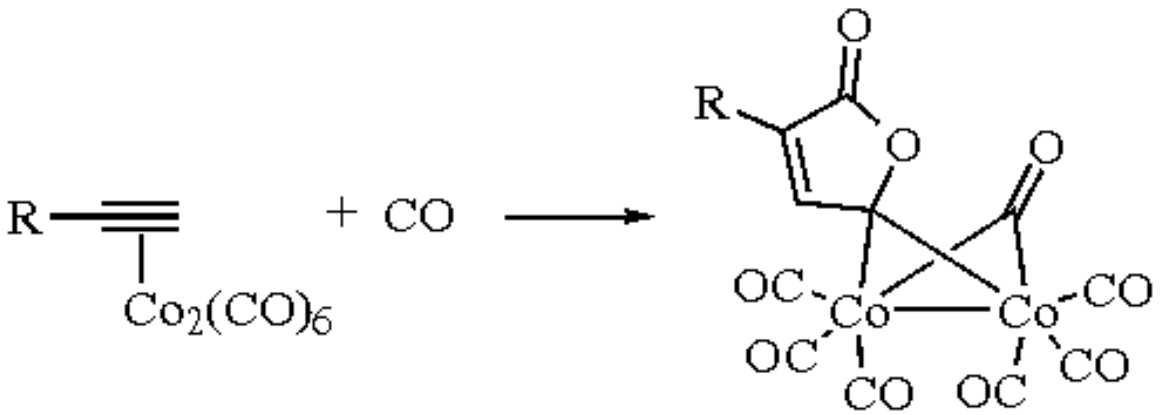

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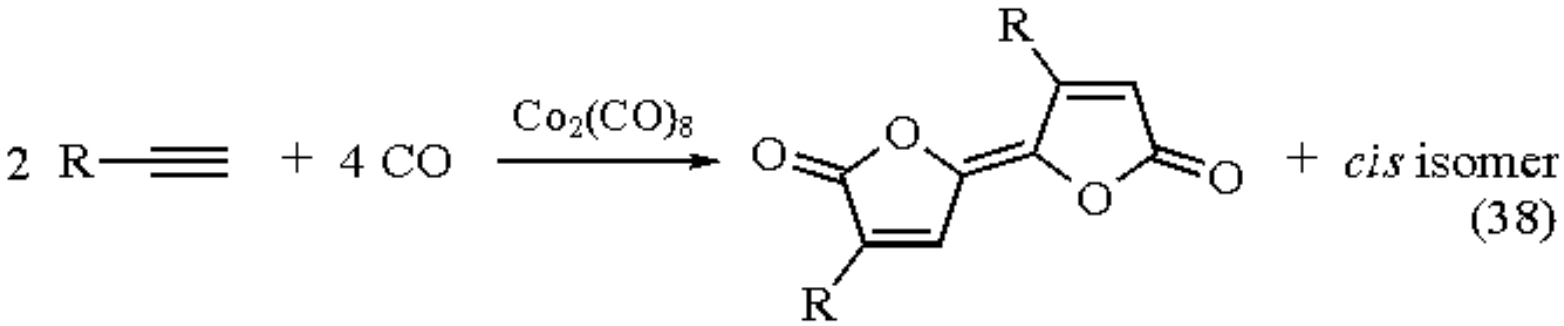

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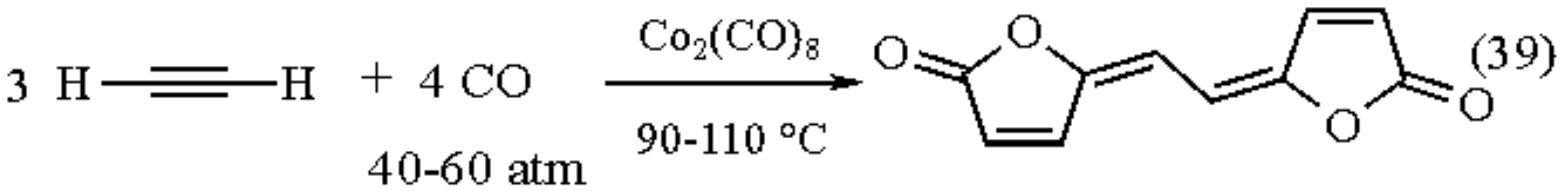

(39)

The lactone complexes react with tertiary propynylamines at room temperature in moderate to good yield to give unsaturated aminolactones (eq 40),[54] while bifurandiones incorporating the propynyl group and a solvent-derived hydrogen atom result when quaternary propynylammonium salts are employed under similar conditions (eq 41).[54]

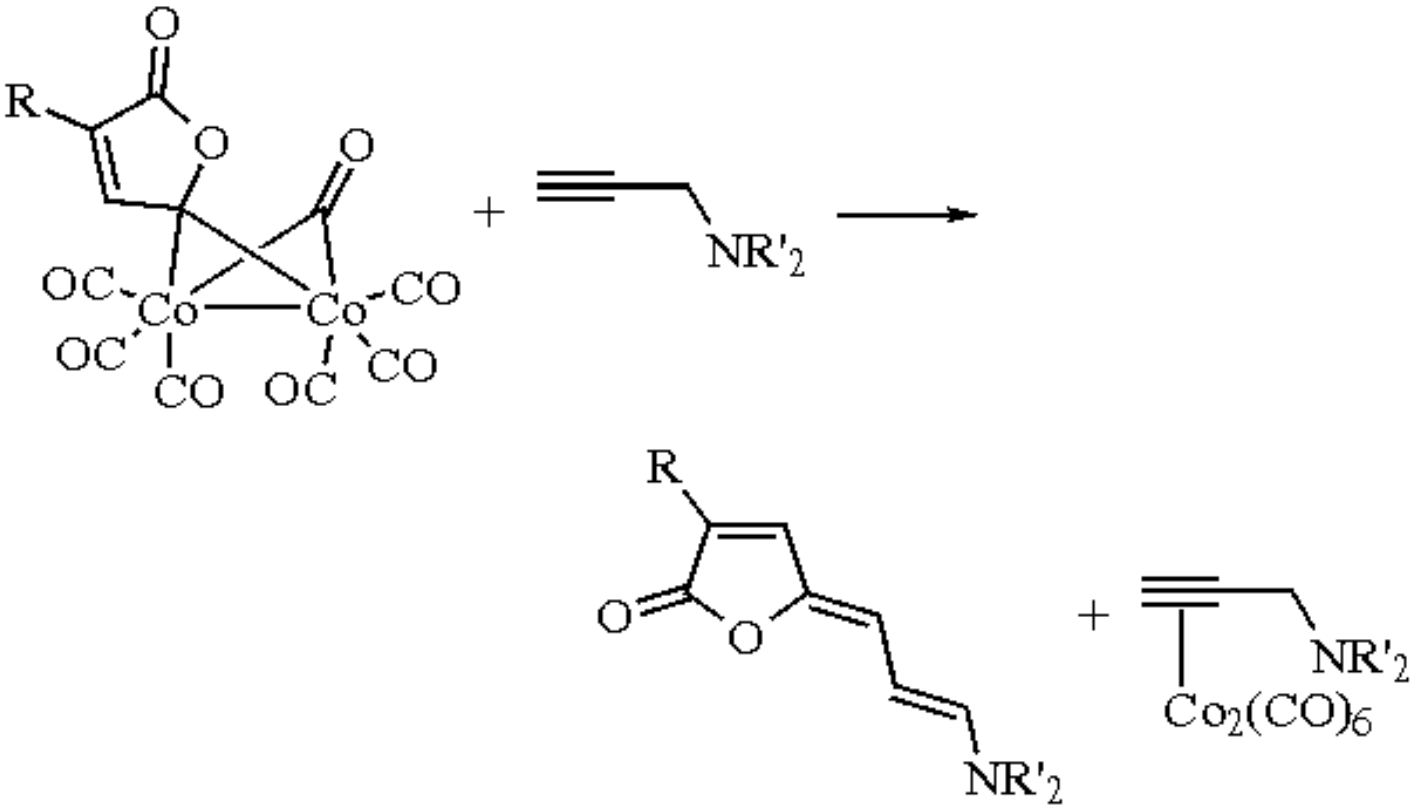

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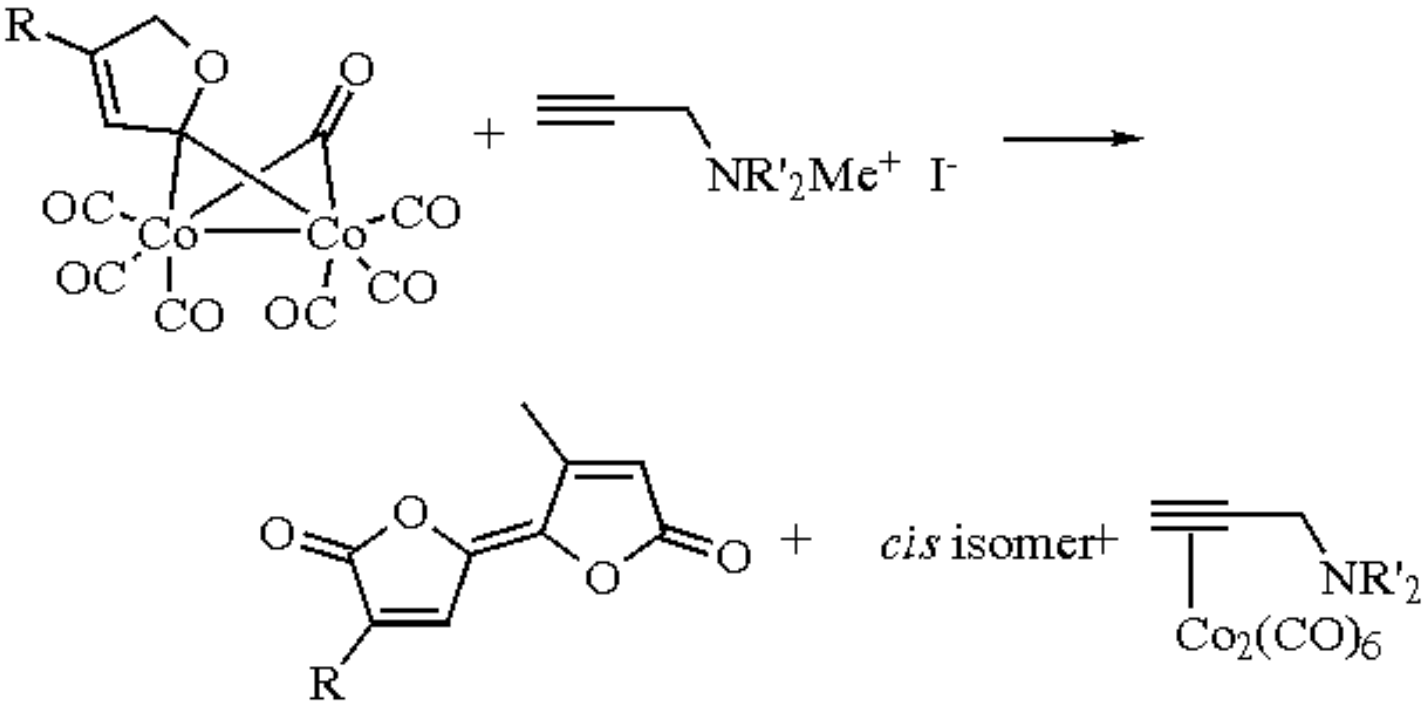

(41)

Without CO pressure, the monoalkyne complexes react on warming with an excess of alkyne to incorporate two more molecules of the latter, giving flyover complexes (eq 42).[55] These cyclize on oxidation (by Br_2) or on heating (typically to 150-170 °C, but in refluxing toluene in the case of the flyover complex from 3 moles of PhC_2COMe[55b]), yielding benzene derivatives. This reaction sequence represents a significantly different mechanism for alkyne cyclotrimerization under $Co_2(CO)_8$ catalysis compared, for example, to the dicarbonylcyclopentadienylcobalt-catalyzed process. The possibility of employing two different alkynes (eq 42) should permit synthesis of a wider range of benzene derivatives and, indeed, the use of alkynes with bulky R^2 groups (e.g. R^2 = *t*-Bu) provides a route to benzene derivatives with two

such groups in adjacent positions (e.g. 1,2-di-*t*-butyl- and 1,2,4,5-tetra-*t*-butylbenzenes from the flyovers with R^1 = H or *t*-Bu and R^2 = *t*-Bu).[56] However, since the initial complex, $(R^1C_2H)Co_2(CO)_6$, also undergoes alkyne exchange with the added alkyne, yields are severely limited and product mixtures are inevitably formed.[56]

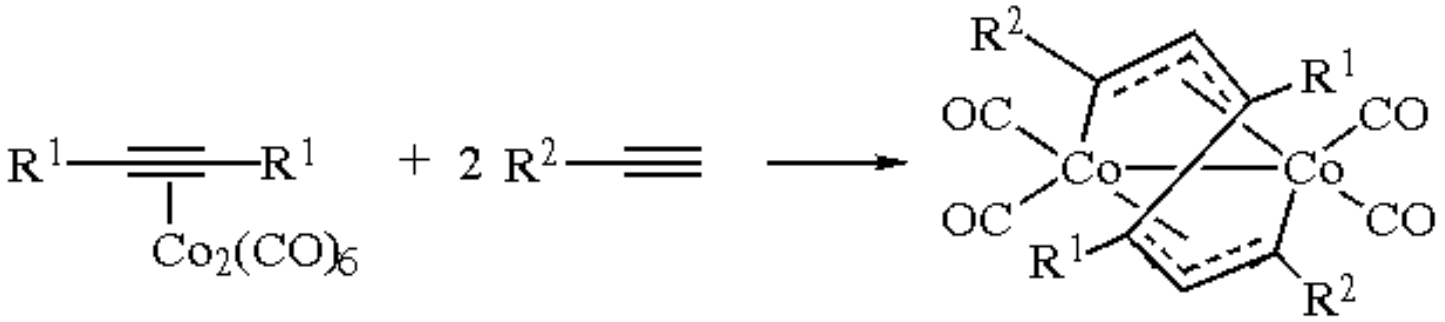

(42)

Intermediates of the reaction of eq 42 are not normally observed, but some examples of complexes formed from octacarbonyldicobalt and two alkyne moieties are known, e.g. from cyclooctyne, giving a product which promotes the cyclotrimerization of cyclooctyne (eq 43),[57] and also from $MeN(CMe_2C_2H)_2$.[58] The product of the latter reaction has been treated with phenylacetylene,[58] forming an arene system (eq 44). Thus, both of these examples show that this type of bis(alkyne)cobalt complex can also be on the cyclotrimerization pathway.

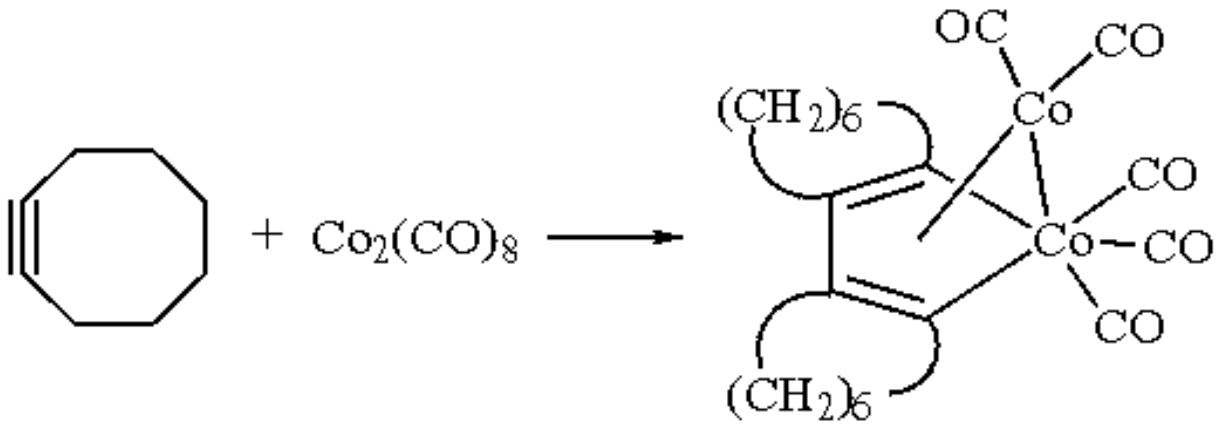

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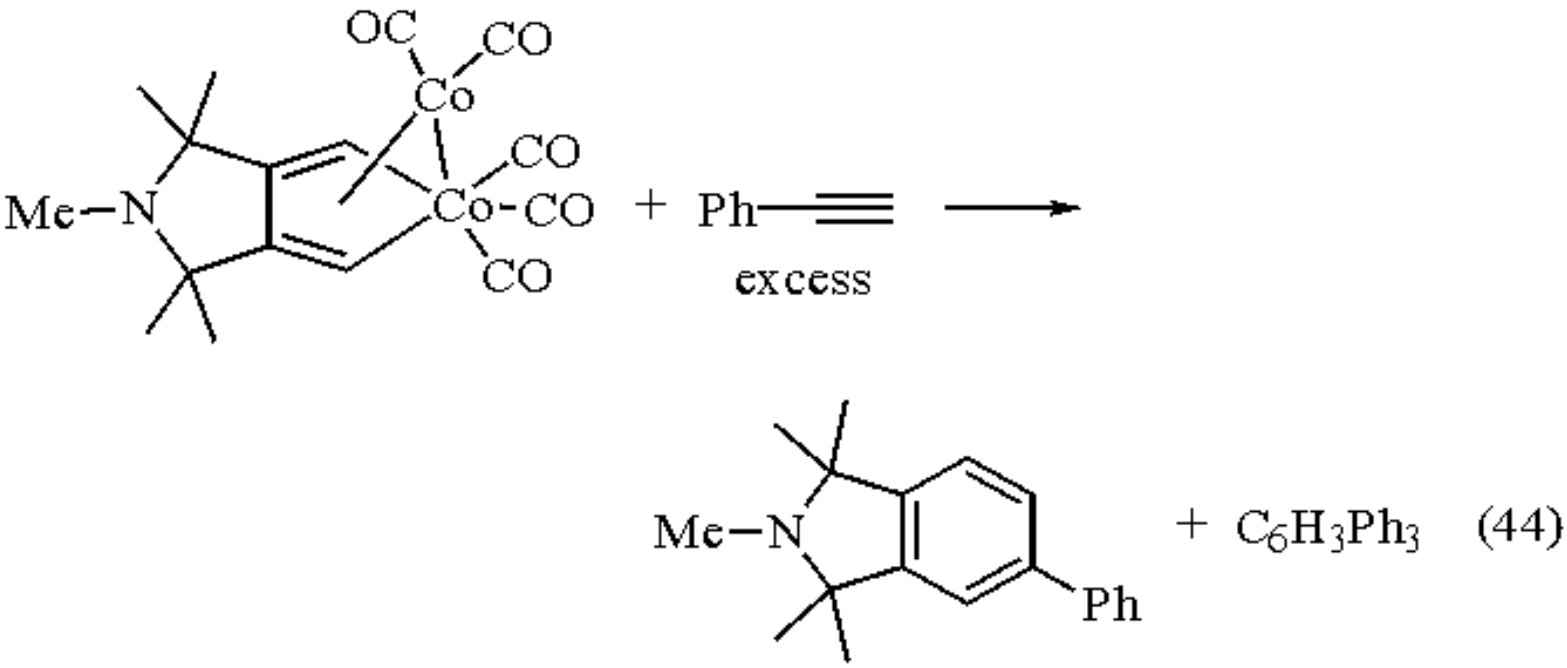

Alkyne Protection, Distortion, and Altered Substituent Reactivity.

The hexacarbonyldicobalt moiety of the bridged alkyne complexes $(R^1C_2R^2)Co_2(CO)_6$ can serve as a valuable protecting group which allows one to perform on other parts of the organic ligand reactions which would not be possible with the free alkyne. At the same time, complexation reduces the bond order from triple to approximately that of a double bond, with corresponding change in bond angles. Hence substituents are in much more favorable locations for many cyclization reactions. Some of the most elegant synthetic applications use both of these features in combination with the α-cation stabilization discussed in the next subsection.

The first demonstration of the stabilizing effect[59] involved Friedel-Crafts acetylation of the tolane complex to give regioselectively the 4-acetyl and 4,4´-diacetyl derivatives and the smooth liberation of the free alkynes by cerium(IV) oxidation. Open-chain enyne complexes (even with the double and triple bonds conjugated) were shown[60] to undergo smooth acid-catalyzed hydration and hydroboration/***Hydrogen Peroxide*** oxidation (e.g. eq 45), as well as reduction of the double bond (by N_2H_2) and again oxidative decomplexation, while the 5,6-double bond of complexed Δ^5-17-ethynylandrostene-3,17-diol was reduced by hydroboration followed by acetic acid treatment.[60] The protective effect has also been utilized to prevent alkyne-to-allene isomerization during oxidation of an allylic alcohol function.[61]

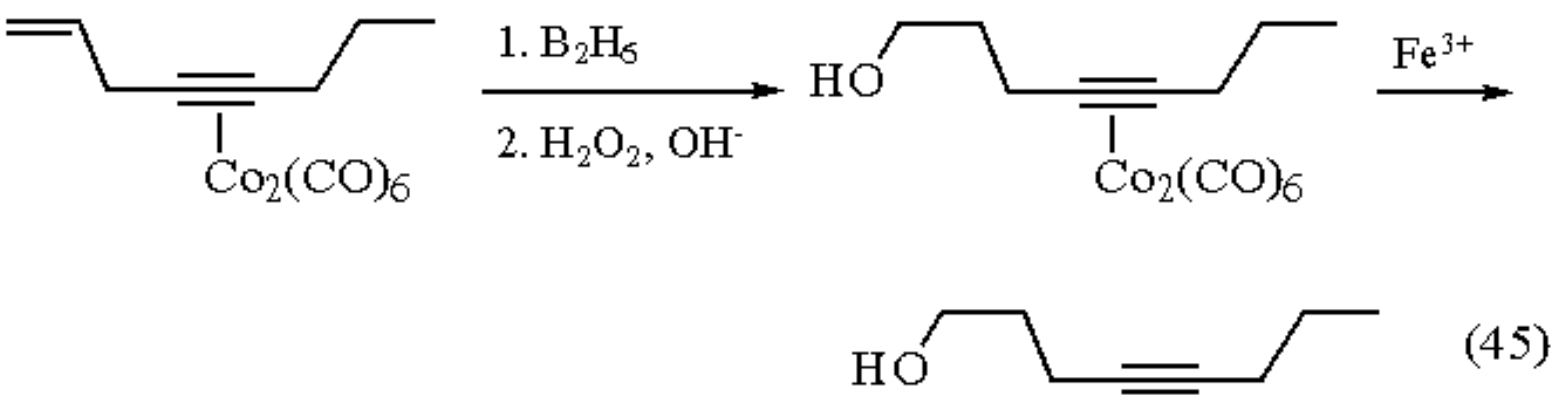

The effect of distortion is clearly revealed in the macrocyclization of the but-2-yne-1,5-diol complex with diphenyldichlorosilane (eq 46),[62] by elegant syntheses of cycloene-diynes related to calicheamicin (e.g. eq 47),[63] 10- and 11-membered ring lactones (e.g. eq 48),[64] but most strikingly in the construction of the cyclooctadecanonayne system by oxidative coupling of 1,3,5-hexatriyne, complexed to phosphine-substituted cobalt carbonyl (eq 49).[65]

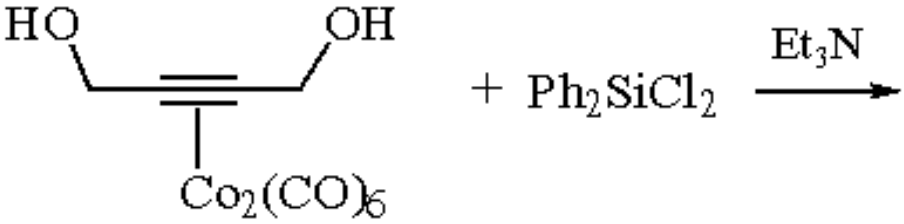

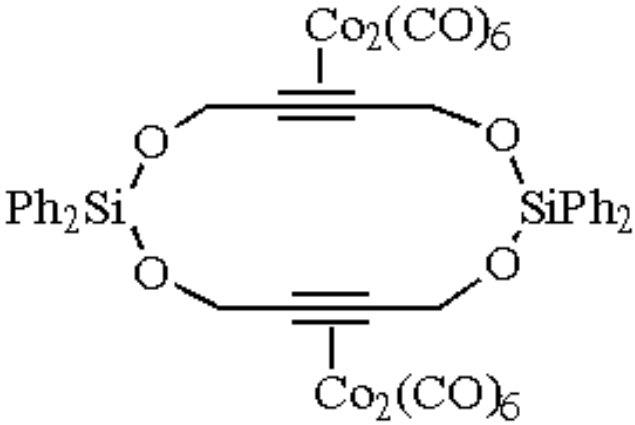

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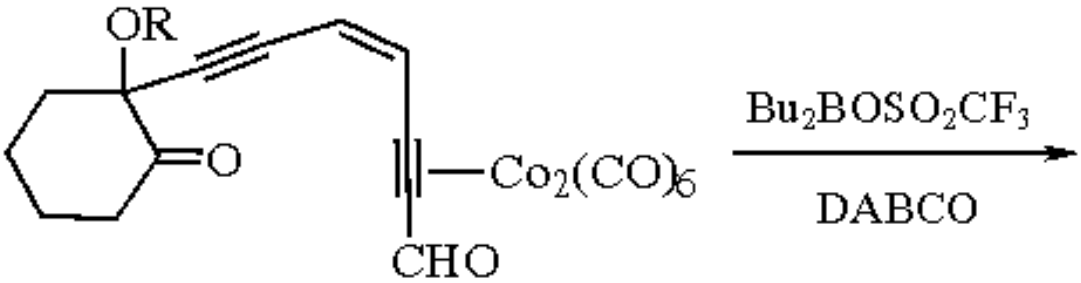

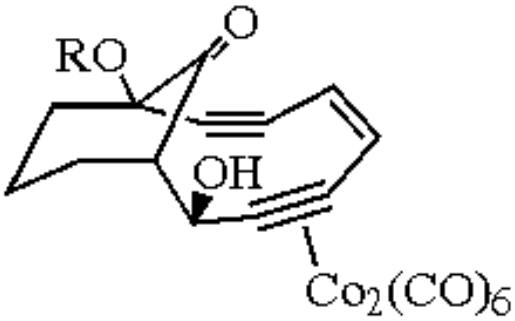

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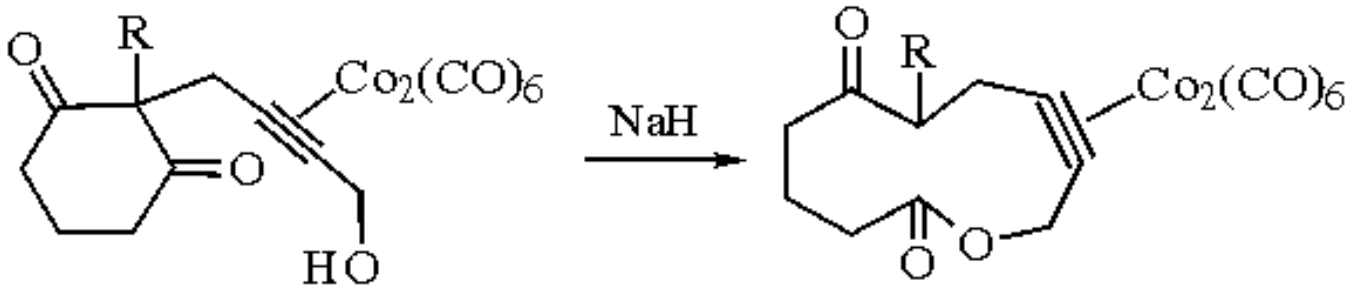

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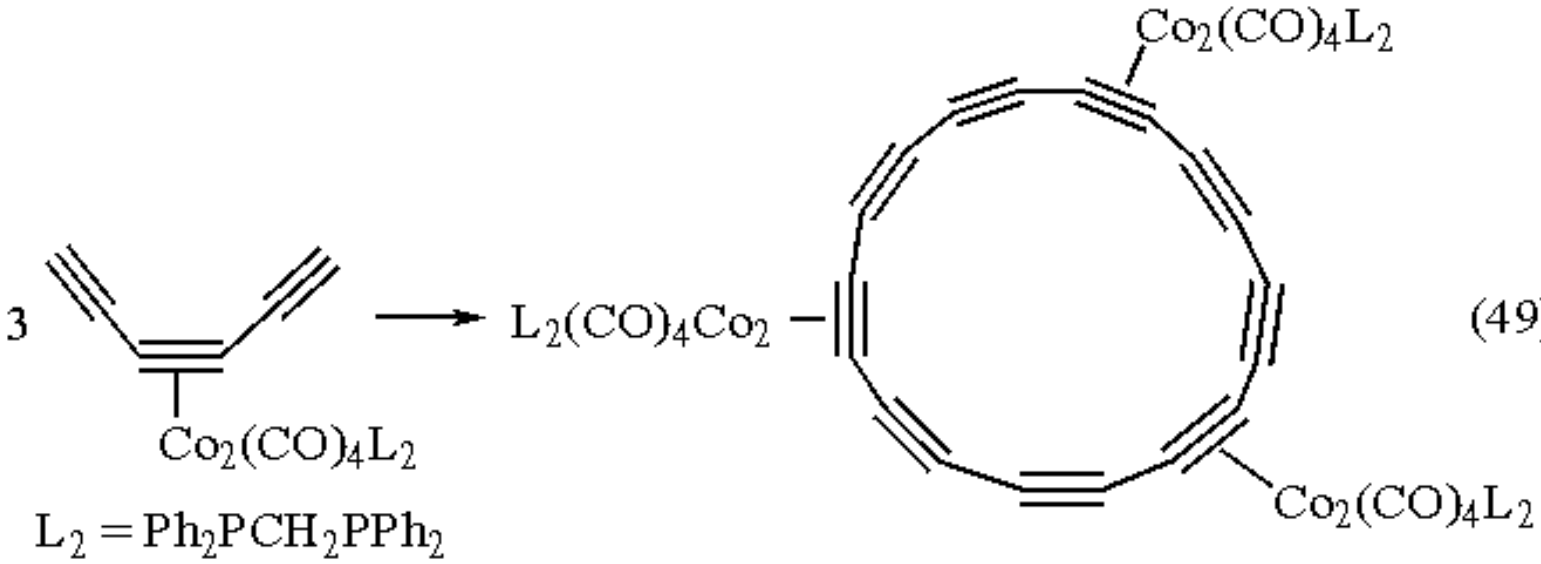

(49)

Steric effects of the hexacarbonyldicobalt moiety may be responsible for altered reactivity, notably enhanced stereoselectivity in reactions of adjacent substituents, e.g. formyl groups in aldol condensations.[66] Thus, condensation of trimethylsilylpropynal with the silyl enol ether of cyclopentanone gives a 90% yield of the aldol product (eq 50) as a 40:60 *erythro:threo* mixture, whereas reaction of the $Co_2(CO)_6$-complexed aldehyde followed by cerium(IV) oxidation gives the same total yield, but in an 87:13 diastereomeric ratio.[66a]

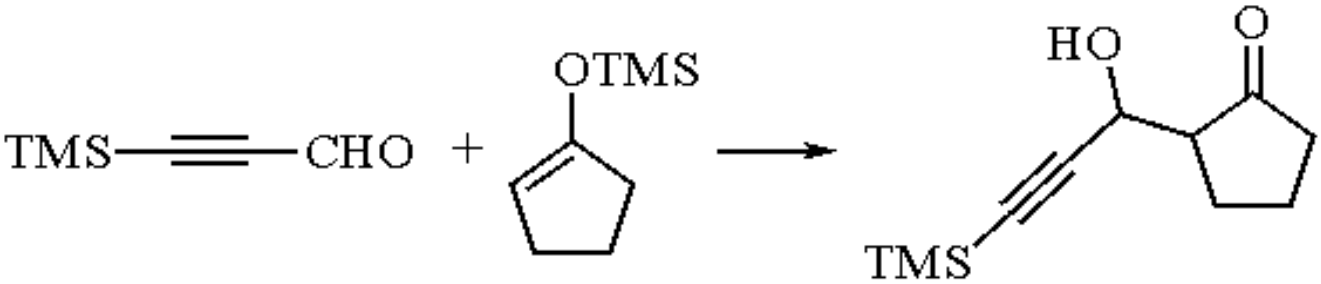

(50)

Cobalt-Complexed Propargyl Cations and Their Reactions.

The stability and synthetic utility of hexacarbonyldicobalt complexed cations was first reported in 1971.[60,67] They are readily formed by protonation of propargyl alcohol complexes or addition of electrophiles (protons, or alkyl or acyl cations) to vinylacetylene complexes. They can be isolated in pure form, usually by precipitation as hexafluorophosphates or tetrafluoroborates, but are more commonly generated in situ and used directly. Most of the early work is due to Nicholas, who has comprehensively reviewed the work up to 1986.[68] A detailed description of the procedure for generating the 1-methyl-2-propynyl complex and for its reaction with trimethylsilyloxycyclohexene (eq

51) has been given.[69]

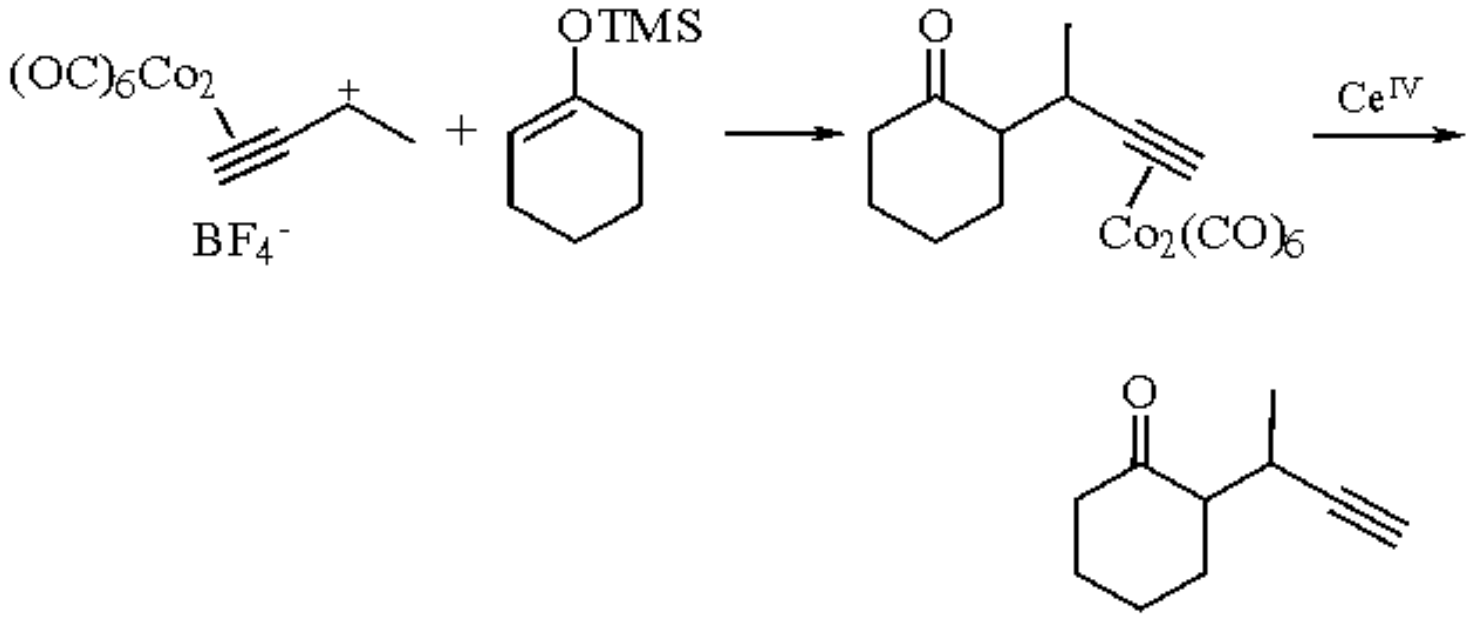

(51)

More recent studies of the utility of the complexed cations in synthesis have paid particular attention to stereoselectivity in their reaction with silyl enolates[70] and enol borates,[71] e.g. eq 52; in this case the same products result, but with only 2.5:1 stereoselection when using the triethylsilyl enol ether and ***Boron Trifluoride Etherate*** catalysis.

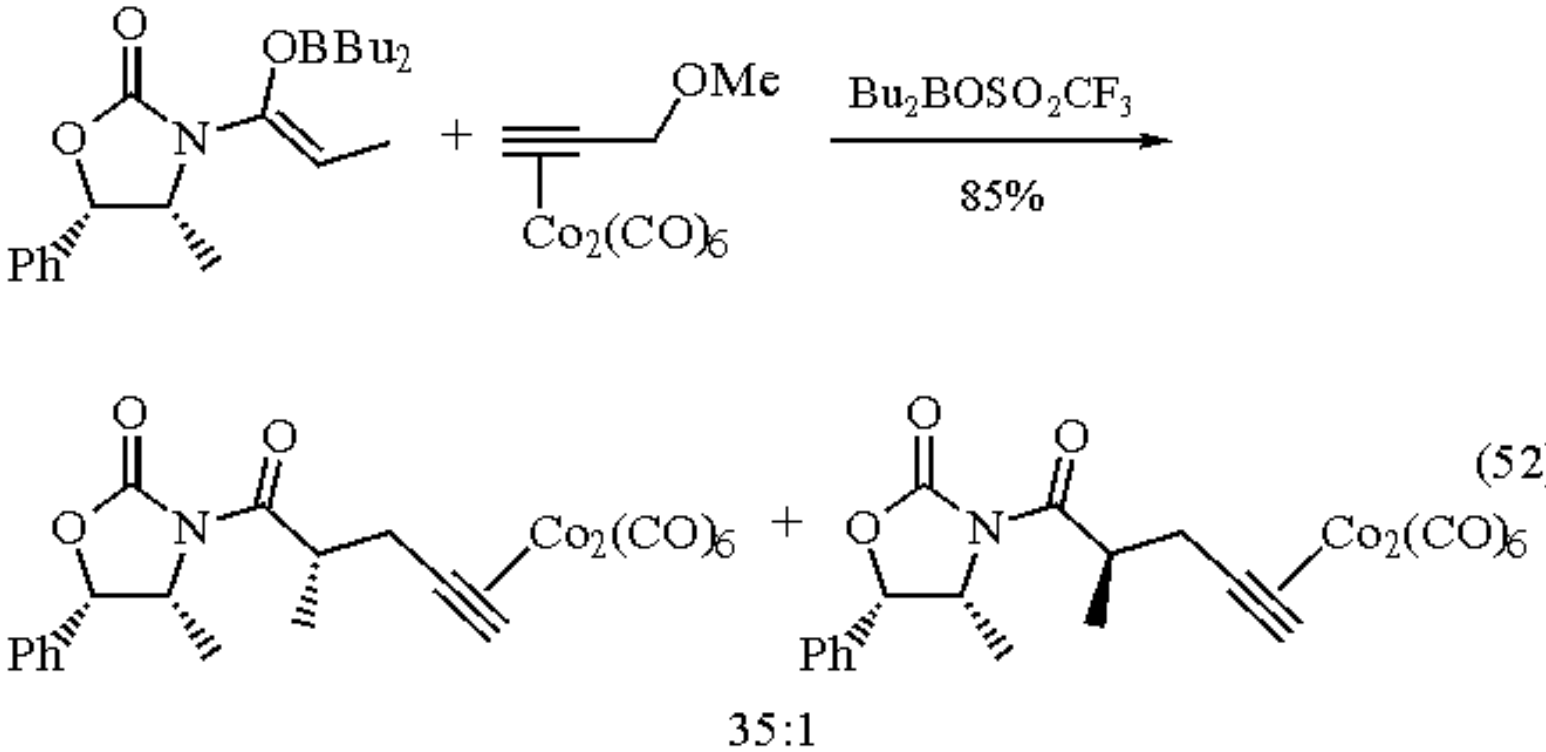

(52)

Replacement of one carbonyl group by phosphine (thus creating chirality at cobalt) has been shown to permit enantioselective addition of nucleophiles to the cations.[72] Regioselectivity of aromatic substitution by the cations has been studied in resorcinol derivatives[73] and examples of aromatic substitution extended to include indoles.[74]

An alternative approach to the antitumor active enediyne systems (cf. eq 47) using Nicholas cations has been

extensively studied[75] and applied to the dynemycin core structure (eq 53).[75c] Another example of the use of such cations in forming strained rings is the preparation of a cobalt complex of a trithia-crown ether (eq 54), which has been shown to complex Cu^I and Ag^I.[76]

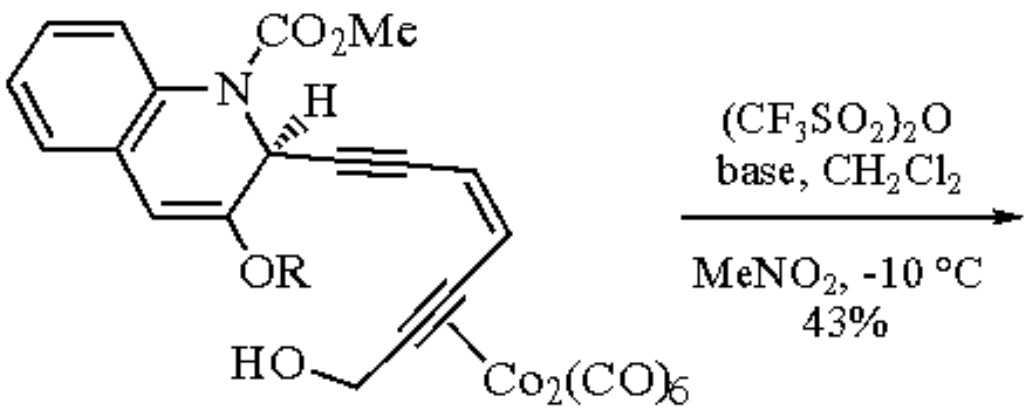

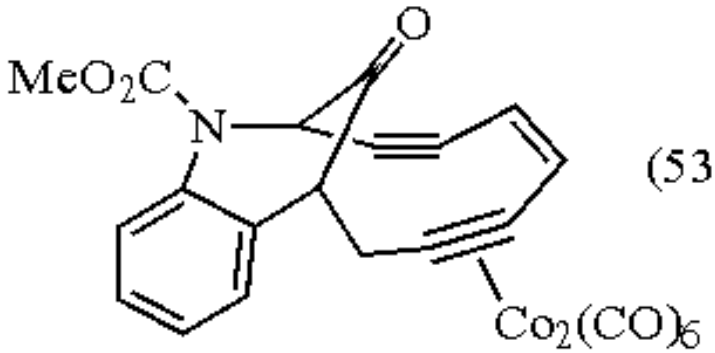

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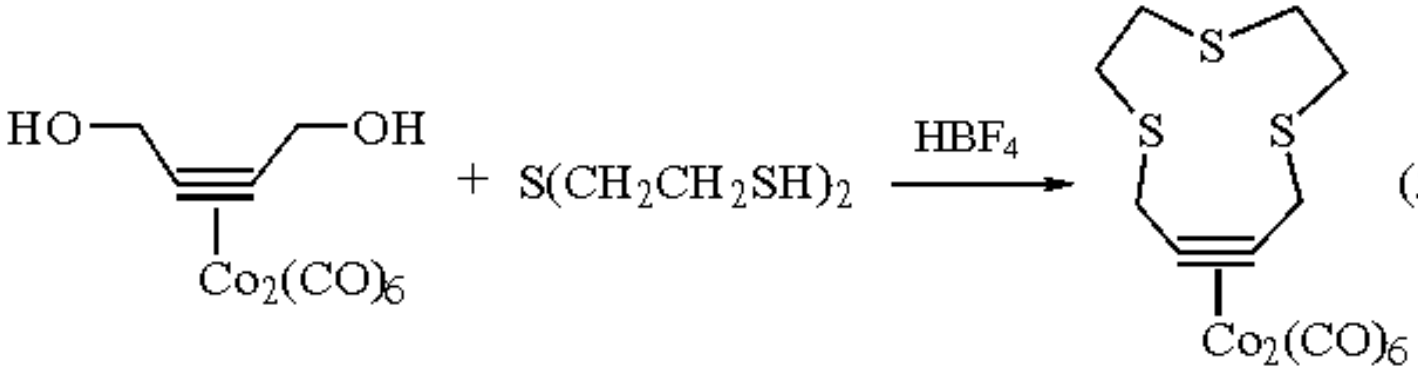

(54)

Cyclopentenone Synthesis.

Synthesis of cyclopentenones from alkynes + alkenes + CO has become a widely used process and is variously known as the Khand reaction or the Pauson-Khand reaction. Although inter alia examples promoted by ***Pentacarbonyliron***, ***Hexacarbonylmolybdenum***, tetracarbonylbis(cyclopentadienyl)ditungsten or -molybdenum, and carbene(pentacarbonyl)chromium have been described, octacarbonyldicobalt is the generally used reactant. The method has been extensively reviewed.[52a,77]

The general reaction (eq 55) is most commonly conducted by preparing the intermediate alkyne complex $(R^1C_2R^2)Co_2(CO)_6$, with or without isolation, before adding the alkene component, but this is not necessary. Under a

CO atmosphere, regeneration of this complex from added free alkyne occurs and in at least one case[78] efficient catalytic synthesis has been achieved (eq 56). Under conditions of complete conversion of 1-heptyne, the product was obtained in 47-49% yield and contained only 1-2% of the regioisomer, 3-pentylcyclopent-2-en-1-one.

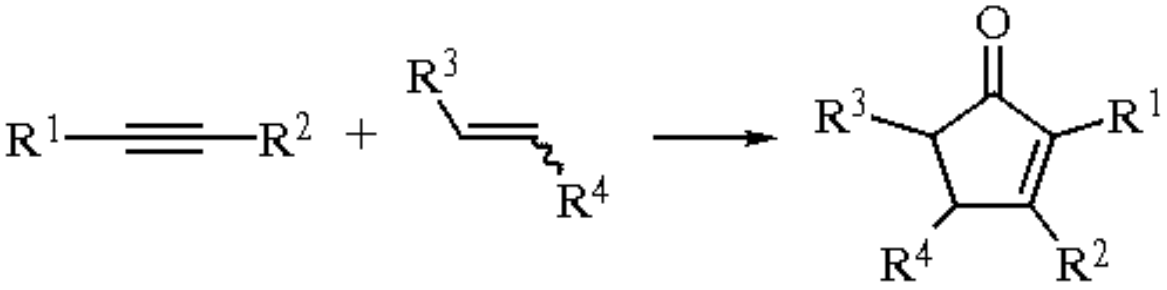

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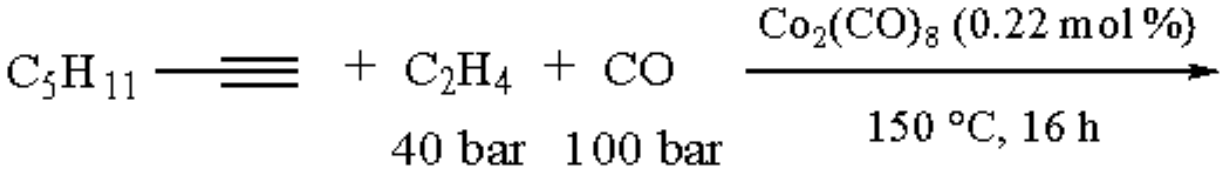

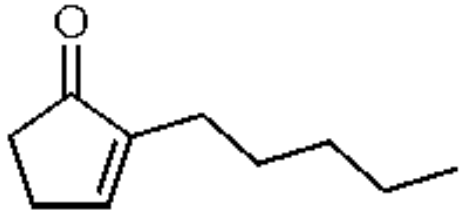

(56)

Such high regioselectivity is typical of terminal alkynes, and the less reactive internal alkynes show only slightly lower selectivity in forming the products with the bulkier group (R^1) in the 2-position. Only strong electronic effects may override this sterically determined preference (e.g. see eq 63 below). Regioselectivity with respect to the alkene is much more variable. Simple terminal alkenes show little or no selectivity when the alkyne is also terminal, but significant preference for 5-substitution (R^3 in eq 55) when the alkyne is internal. More efficient regioselection may be achieved with functional substituents, notably electron-donor groups in the homoallylic position, which favor formation of the 5-substituted product.[79] Thus, the example shown in eq 57 is the key step in a formal synthesis of PGA_2;[80] it also illustrates the good yields obtainable by the simple thermal reaction in the case of alkenes with donor substituents.

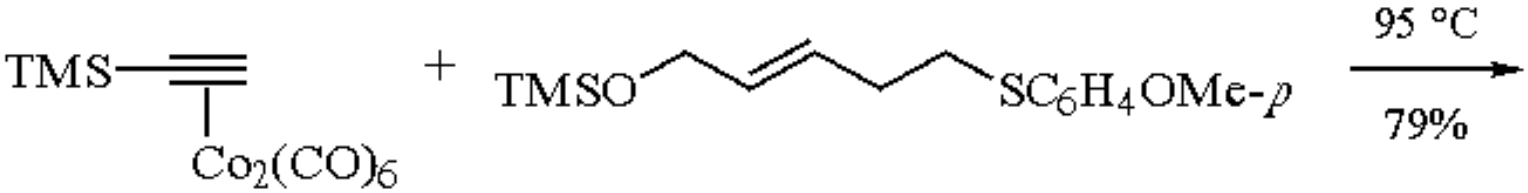

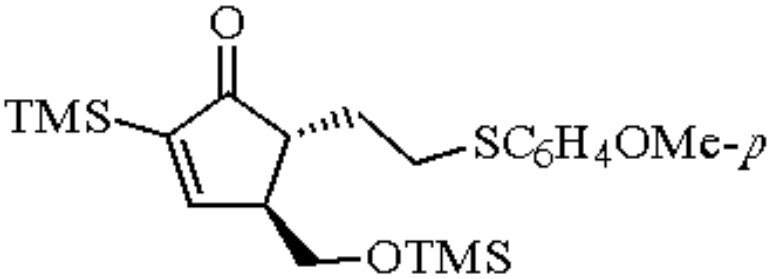

(57)

Three more general techniques have greatly improved the earlier yields. Discussion of the solid-phase adsorption method is included in more recent reviews.[77a-d] It probably remains the method of choice in selected cases and sometimes has results different from those of other methods. For example, the predominant reduction to cyclopentanone in the intramolecular reaction of *N*-acetyl-*N*-allylpropargylamine (eq 58)[81] and the reductive ether cleavage when related ethers react on alumina (eq 59),[82] is avoided on silica, in the presence of oxygen, with formation of the expected bicyclic products.

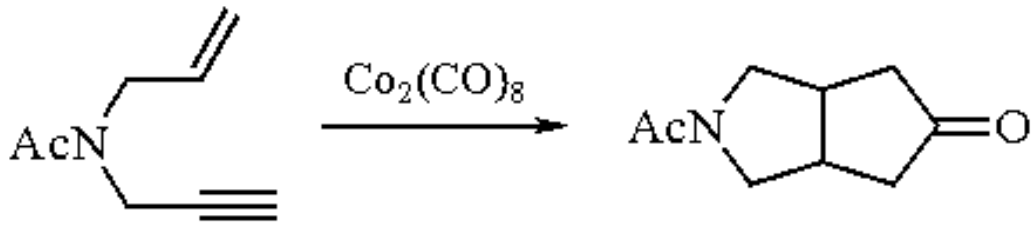

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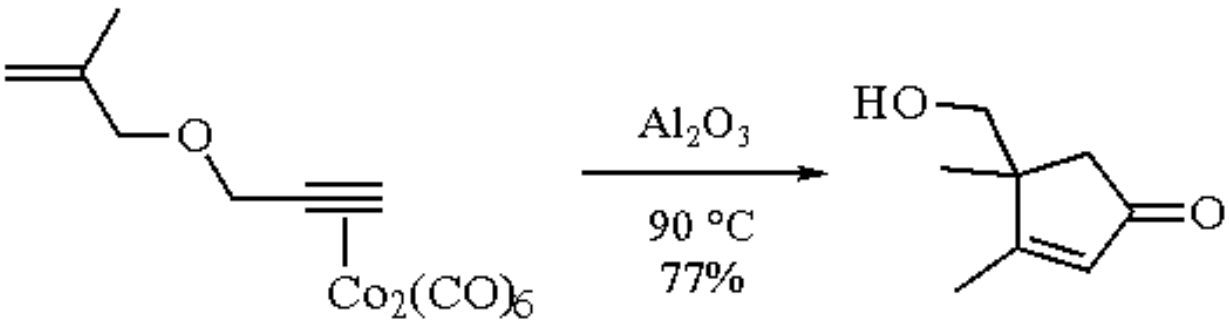

(59)

This solid-phase technique has made possible efficient syntheses of bi- and polycyclic systems from precursors frequently generated via Nicholas cations, (e.g. eq 60)[83] and has been used for intermolecular reactions with methylenecyclopropane (eq 61) and methylenecyclobutane to give spirocyclic cyclopentenone derivatives. (**1**) is the major product when the alkyne is terminal (R^2 = H), but only (**2**) was isolated when EtC_2Et or Me_3SiC_2Me were used.[84]

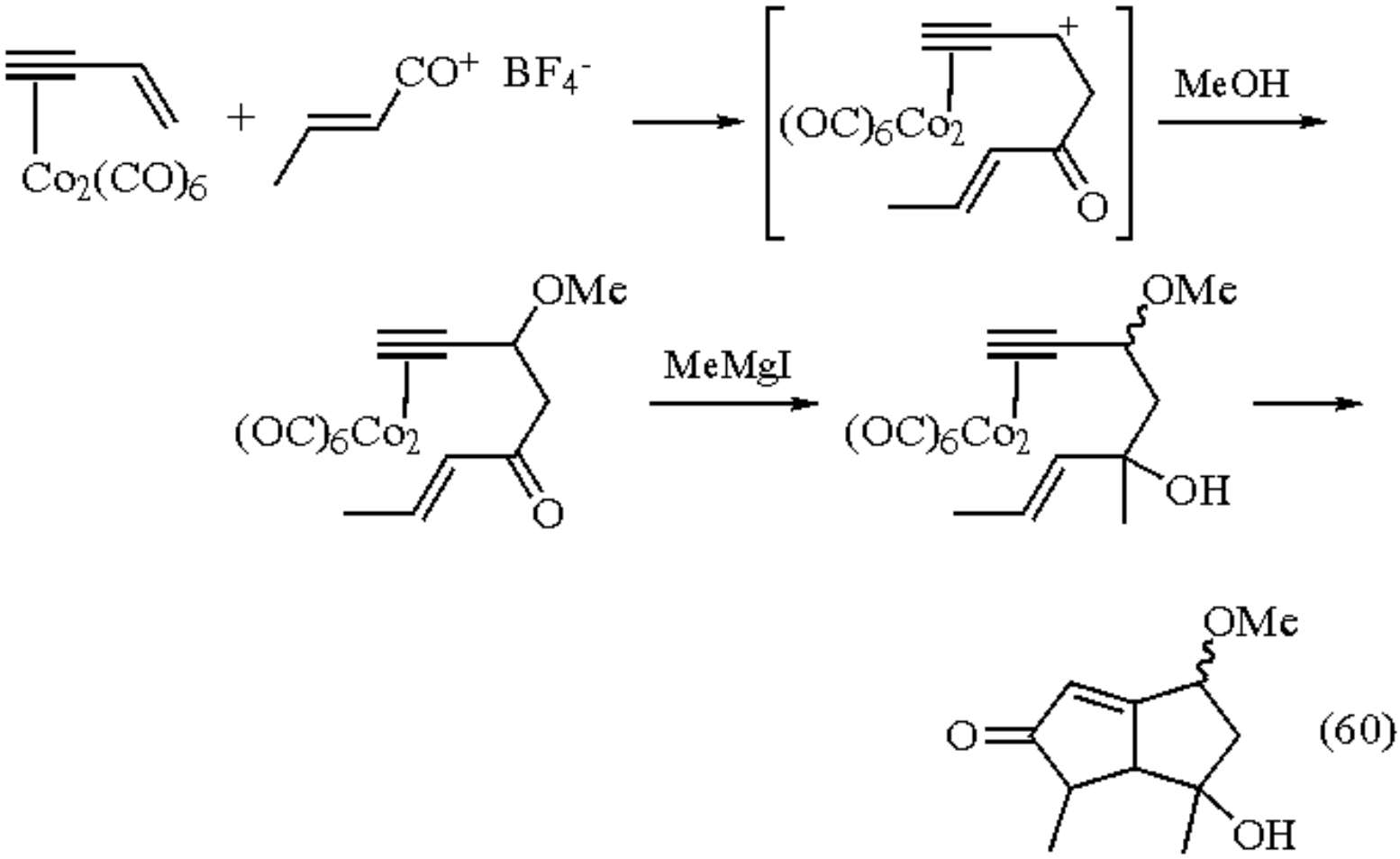

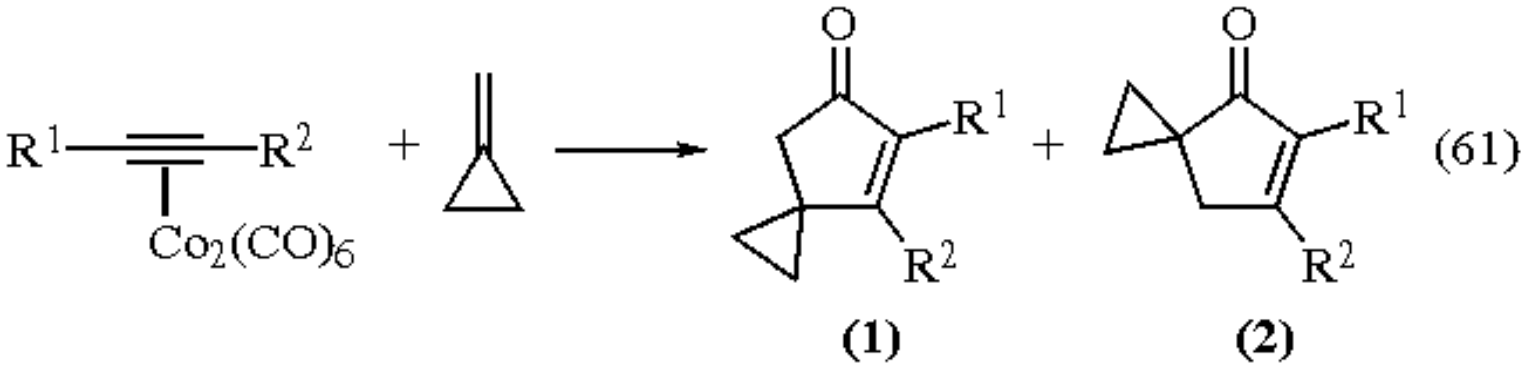

The more recent and now widely used improvement involves the use of amine oxides, usually ***Trimethylamine N-Oxide***[85a] or ***N-Methylmorpholine N-Oxide***.[86] Alternatively, while requiring slightly higher temperature and longer reaction time, DMSO (or other sulfoxides) can give equally good yields. A range of other polar solvents (e.g. MeOH, MeCN, HCO_2Et) also exert a distinct, but smaller, promoting effect.[87]

N-Methylmorpholine *N*-oxide, preferably as monohydrate,[79b] as well as Me_3NO not only induces cyclopentenone formation under very mild conditions (0-20 °C) and in frequently excellent yields, but also removes some earlier limitations. The reductive processes (eqs 58 and 59) do not occur when these promoters or DMSO are used under oxygen.[85,87] Hence two efficient syntheses of (-)-kainic acid[88] have employed cyclizations of allylpropargylamine derivatives as the key step; in one of these (eq 62), as well as in a synthesis of the dendrobine skeleton,[89] use of a chiral precursor was shown to result in enantiospecific bicyclization.[88a]

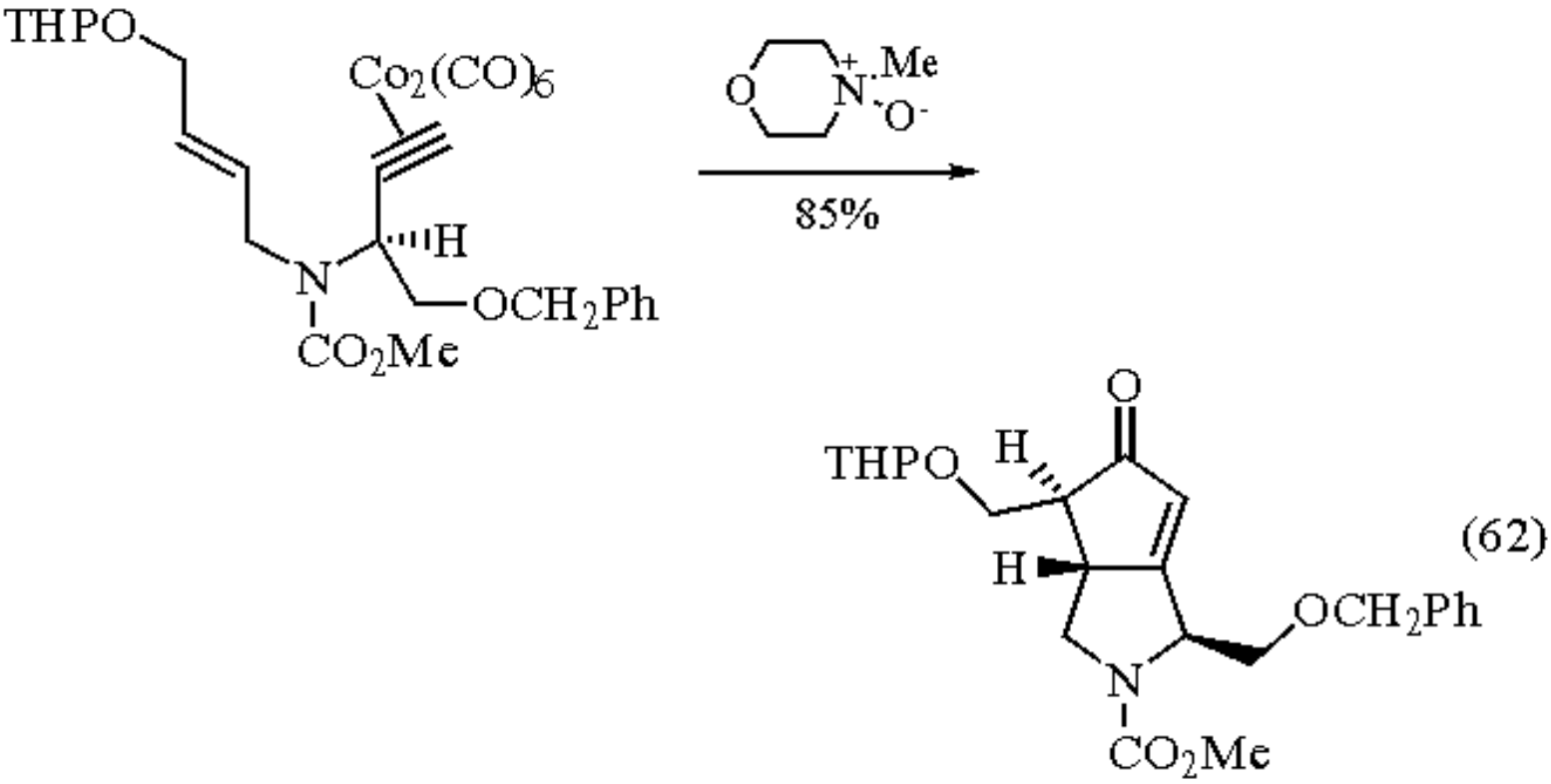

Intramolecular cyclizations of enynes using catalytic amounts of octacarbonyldicobalt (3 mol %) succeed in the presence of biphenyl phosphite (10 mol %) undr 3 atm of CO, typically in DMF at 120 °C.[85b]

Whereas in earlier work the (uncatalyzed) reaction of alkenes bearing electron-withdrawing groups with the alkynecobalt complexes gave conjugated dienes as the only or major products,[77] intramolecular cyclizations involving such groups have now been accomplished by both the solid-state method[90] and using *N*-oxide promotion.[91] Moreover, electron-deficient alkynes have been successfully employed in both inter- and intramolecular cases. The use of ethyl 2-butynoate (eq 63) illustrates the preferred orientation in this case.[92]

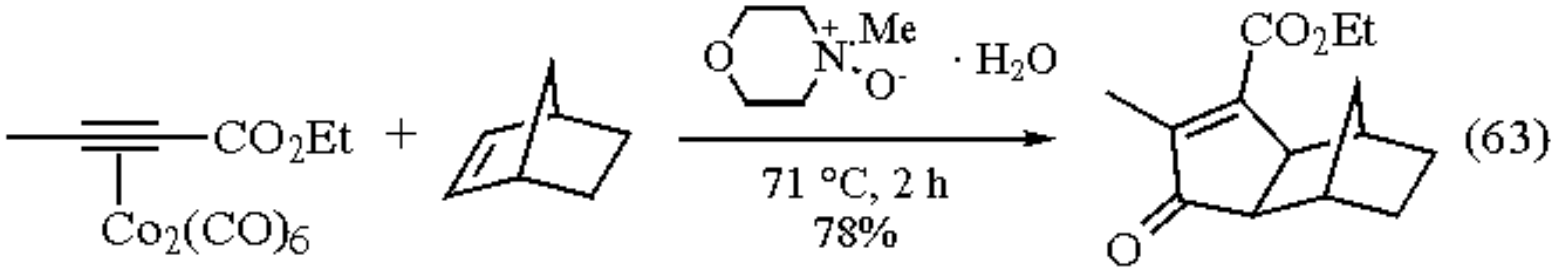

Further examples of the efficiency of the *N*-oxide method are the formation of bicyclic lactols (e.g. eq 64), utilized in a synthesis of (±)-loganin,[93] and the quantitative cyclization (eq 65) which is the key step in a synthesis of decarboxydemethylquadrone.[94]

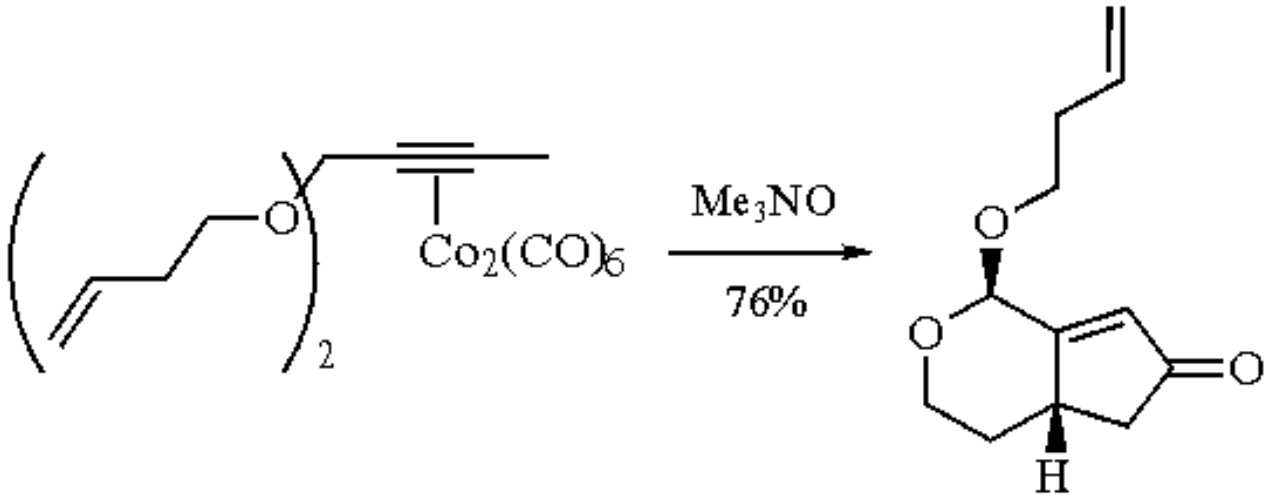

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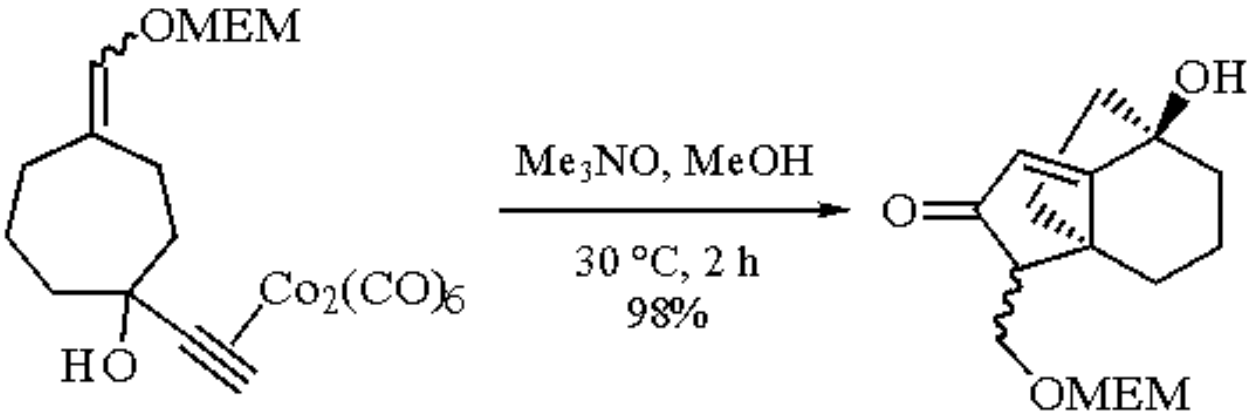

(65)

Finally, reference is made to the remarkably facile cyclization which alkynyl Fischer carbene complexes can undergo[95] under conditions normally leading only to alkyne-cobalt complex formation (eq 66) (M = Cr or W; R = Ph or Et).

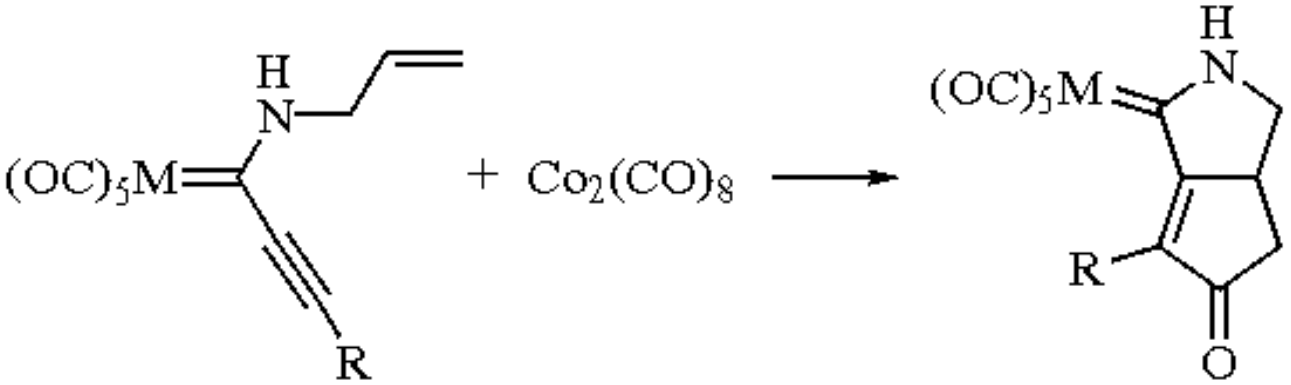

(66)

Related Reagents.

Dicarbonyl(cyclopentadienyl)cobalt(I); ***Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide***; ***Sodium Tetracarbonylcobaltate***.

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Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide[1]

$Co_2(CO)_8$-$HSiEt_2Me$-CO

($Co_2(CO)_8$)

[10210-68-1] · $C_8Co_2O_8$ · Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide · (MW 341.94)
($HSiEt_2Me$)

[760-32-7] · $C_5H_{14}Si$ · Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide · (MW 102.28)
(CO)

[630-08-0] · CO · Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide · (MW 28.01)

(silyloxymethylenation of alkenes,[2] esters,[3] and aldehydes;[4] silyloxymethylation of epoxides,[8] glycosyl acetates,[11] benzylic esters,[12] and orthoesters;[13] carbonylative ring expansion[5])

Physical Data: $HSiEt_2Me$: bp 77.4 °C; *d*204 0.705 g cm^{-3}; *n*20D 1.3984.

Form Supplied in: $HSiEt_2Me$: colorless oil.

Handling, Storage, and Precautions: see ***Octacarbonyldicobalt*** and ***Carbon Monoxide***.

Silyloxymethylenation.

The $Co_2(CO)_8$/$HSiEt_2Me$/CO reaction of alkenes results in incorporation of CO to give enol silyl ethers (eq 1).[2] The reaction of terminal alkenes such as 1-hexene gives four possible regio- and stereoisomers.[2b]

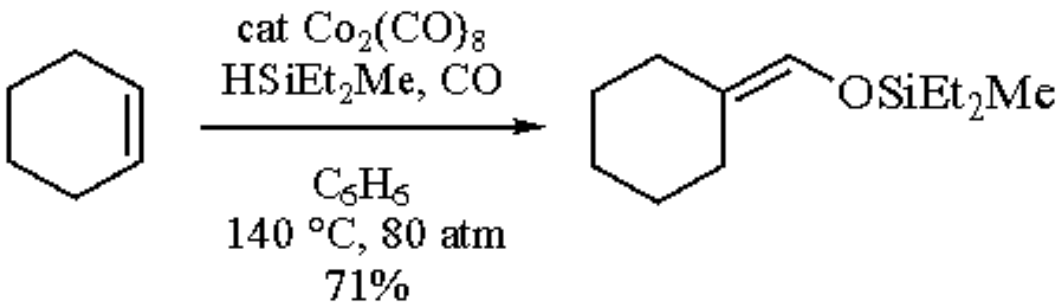

(1)

The reaction of oxygen-containing compounds with the catalytic system at higher reaction temperatures (140-200 °C) under higher CO pressure (50-80 atm) results in silyloxymethylenation with concomitant cleavage of a carbon-oxygen bond. Esters derived from secondary alcohols are converted to (silyloxymethylene)alkanes (enol silyl ethers), which are useful synthetic intermediates (eq 2).[3] The reaction of lactones can proceed at 120-140 °C when pyridine is used as an additive. $HSiMe_3$, ***Triethylsilane***, and ***Dimethyl(phenyl)silane*** are also effective for the synthesis of enol silyl ethers. For handling of $HSiMe_3$ (bp 6.7 °C) a special syringe has been devised,[4] which should be also useful for storing and handling other low-boiling materials. The reaction of aldehydes affords 1,2-bis(siloxy)alkenes (enediol disilyl ethers) (eq 3).[5] Carbonylative ring-expansion of cyclobutanones to 1,2-bis(siloxy)cyclopentenes can also be achieved (eq 4).[6]

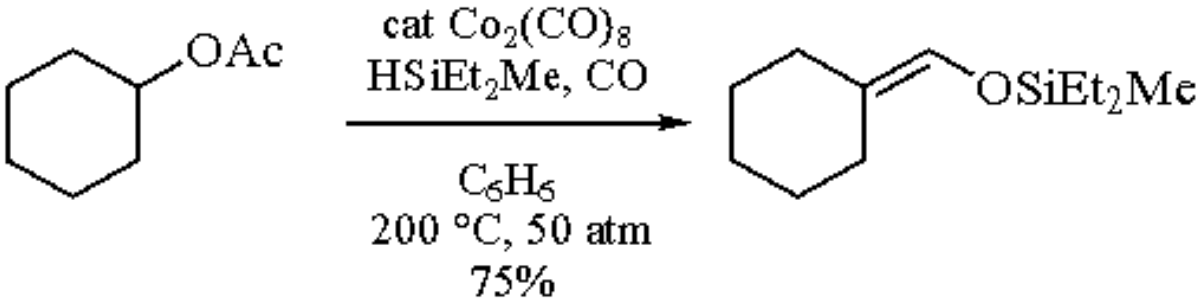

(2)

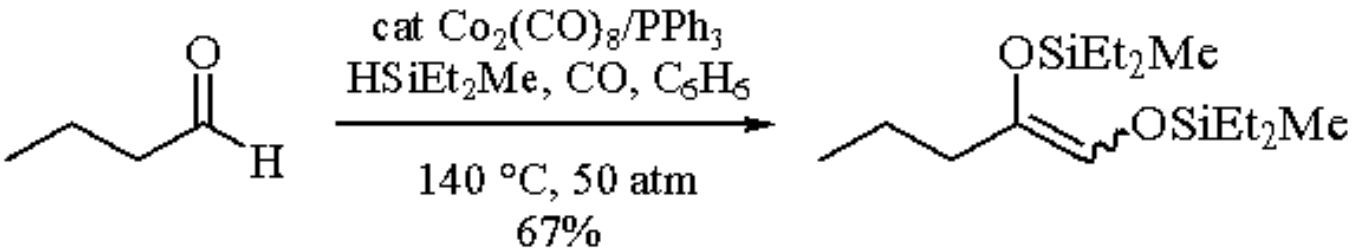

(3)

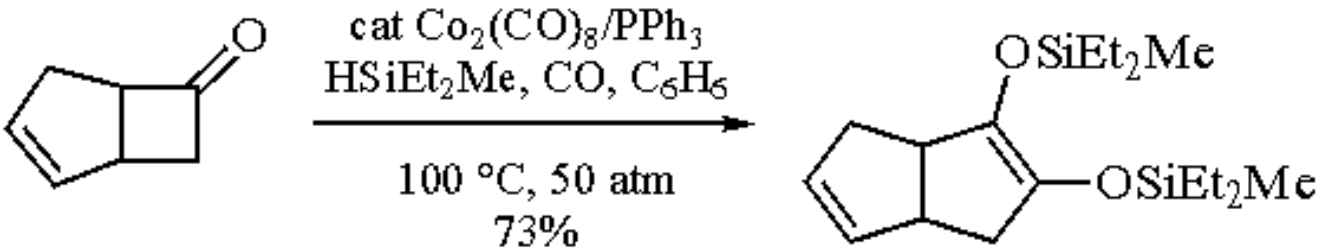

(4)

Silylformylation.

Aldehydes are catalytically converted into homologated α-silyloxyaldehydes (eq 5).[7] Ring-opening silylformylation of cyclic ethers, including oxiranes, oxetane, and THF, are also effective (eq 6).[8]

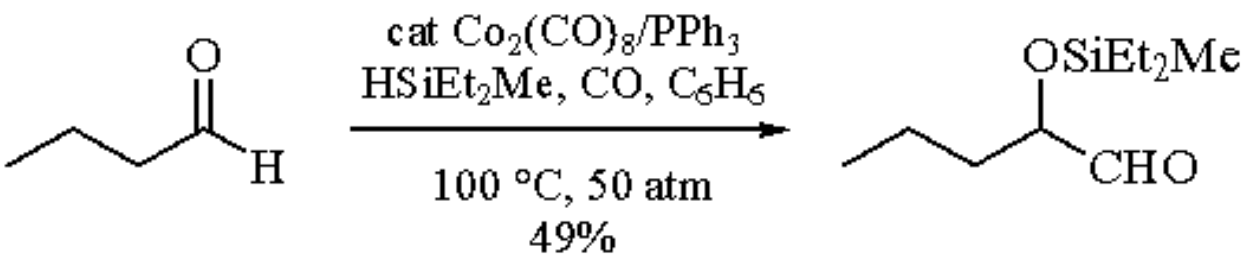

(5)

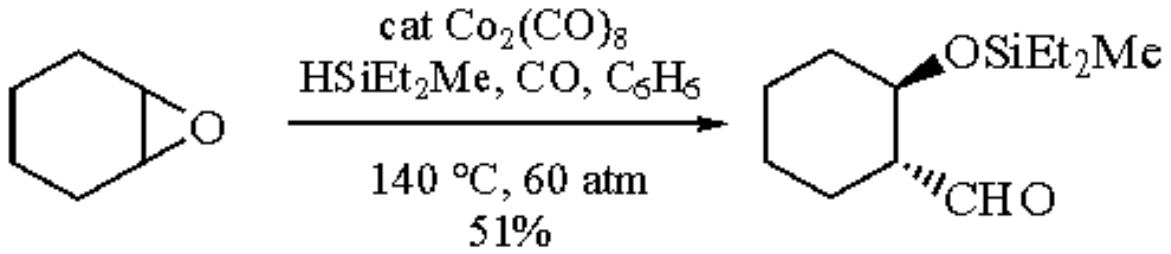

(6)

Silyloxymethylation.

The catalytic silyloxymethylation has been revealed to have wide applicability to various oxygen-containing compounds such as oxiranes, oxetanes, tetrahydrofurans, glycosyl acetates, benzylic esters, and orthoesters. The reactions are carried out at near-ambient temperatures (0-40 °C) under 1 atm of CO. Generally, the reaction is faster in the order of $HSiMe_3$ > $HSiEtMe_2$ > $HSiEt_2Me$ > $HSiEt_3$. The use of $HSiMe_3$ sometimes causes reduction of substrates, depending on the substrates and solvent used.

Various oxiranes react with $HSiEt_2Me$ and CO in the presence of $Co_2(CO)_8$ to afford 1,3-diol disilyl ethers with *trans* ring opening (eq 7).[4,9] Stereospecific silyloxymethylation is demonstrated in the reaction of *cis*- and *trans*-2-butene oxide. The reactions of oxetanes[10] and tetrahydrofurans[11] also involve ring-opening silyloxymethylation.

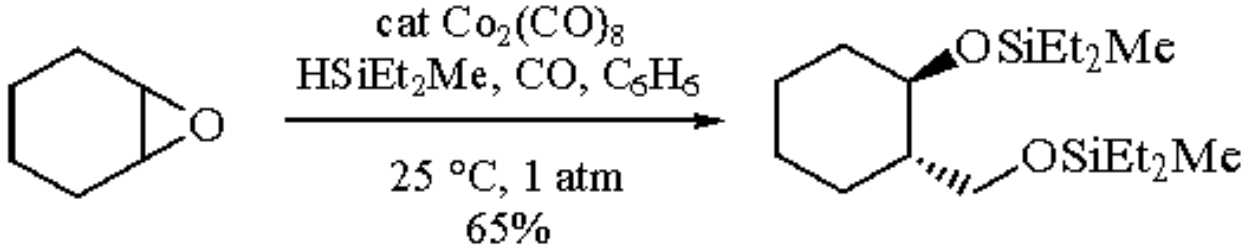

(7)

Highly stereoselective silyloxymethylation at the anomeric center of glycosyl acetates can be attained with the $Co_2(CO)_8$/$HSiMe_3$/CO catalytic system under mild reaction conditions (eq 8).[12] The reaction of benzyl acetates gives β-phenethyl alcohol derivatives (eq 9).[13] The reaction is applicable to furanyl-, thienyl-, and ferrocenylmethyl acetates. The reaction of cyclic orthoesters results in CO incorporation to give diols having one additional carbon atom (eq 10).[14]

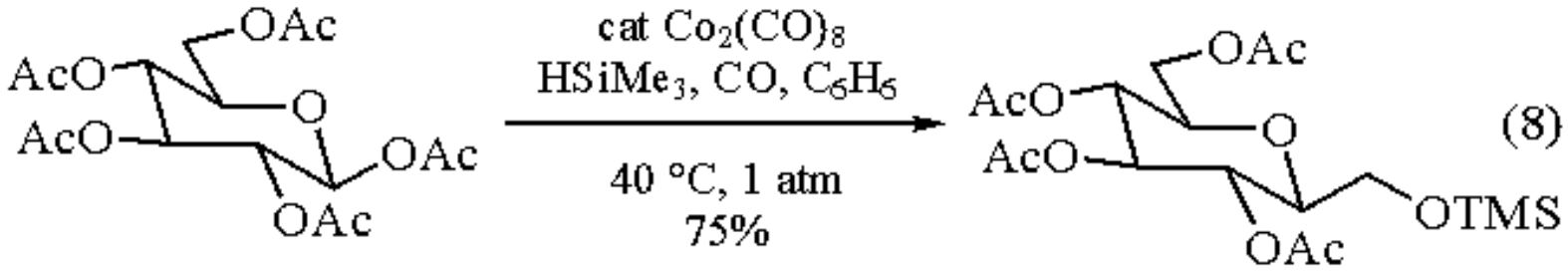

(8)

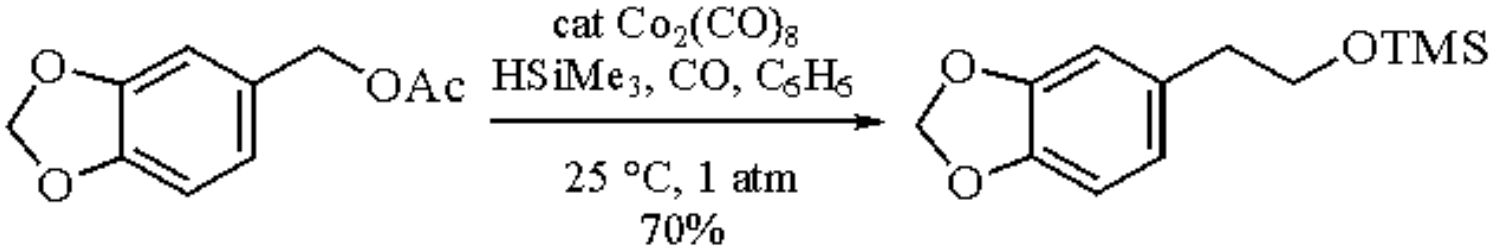

(9)

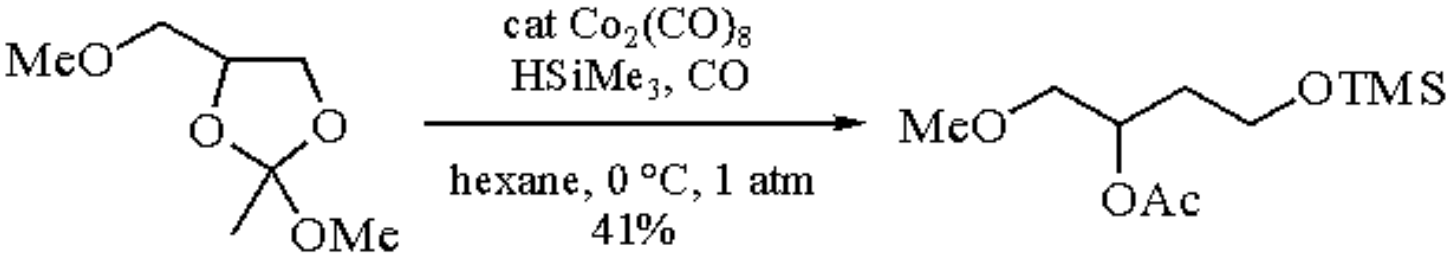

(10)

Related Reagents.

Carbon Monoxide; ***Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide***; ***Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide***.

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Octacarbonyl(zinc)dicobalt

$Zn[Co(CO)_4]_2$

(*2Co-Zn*)

[16985-99-2] · $C_8Co_2O_8Zn$ · Octacarbonyl(zinc)dicobalt · (MW 407.33) ($Cd[Co(CO)_4]_2$(*2Co-Cd*))

[16986-00-8] · $C_8CdCo_2O_8$ · Octacarbonyl(cadmium)dicobalt · (MW 454.35) ($Hg[Co(CO)_4]_2$(*2Co-Hg*))

[13964-88-0] · $C_8Co_2HgO_8$ · Octacarbonyl(mercury)dicobalt · (MW 542.54)

(air-sensitive yet readily available organometallic species capable of catalyzing the selective dimerization of norbornadiene;[1] in an isolated example catalyzes the linear dimerization of a propargyl amine[2])

Alternate Names: bis(tetracarbonylcobalt)zinc; di(cobalttetracarbonyl)zinc.

Physical Data: mp 71-72.5 °C; subl 60 °C/0.005 mmHg. X-ray crystal structure shows each Co to be trigonal bipyramidal (with CO and Zn occupying axial positions) and unbridged Co-Zn-Co.[3]

Solubility: sol heptane, hexane, benzene, toluene, THF, and in acetone to provide enhanced stability; forms complexes with THF from which solvent is difficult to remove.

Form Supplied in: commercially not readily available.

Purification: IR,[4] ^{59}Co NQR,[5] MS,[4a] and Raman.[4b,c]

Preparative Methods: most conveniently prepared from the analogous mercury compound, $Hg[Co(CO)_4]_2$, by reaction with Zn (granular or powder) at 25 °C under argon at atmospheric pressure (93% yield).[4a,b] A variety of procedures which utilize high pressures of CO with ***Octacarbonyldicobalt*** (or various Co salts) and ***Zinc*** are also known.[1a,6] Preparation from ***Sodium Tetracarbonylcobaltate*** and ***Zinc Chloride*** at atmospheric pressure is disfavored due to the numerous manipulations of air-sensitive materials required.[7] A less widely used method from $Co_2(CO)_8$ and powdered Zn in hexanes at atmospheric pressure has been reported[8] as has a simple, yet lower yielding, electrochemical synthesis.[9] The cadmium analog, $Cd[Co(CO)_4]_2$ (recrystallized from hexane at -60 °C;[4a] yellow/orange plate-like crystals mp 79-81 °C;[4b] IR,[4a,c,9,10] ^{59}Co NQR,[5] MS,[4a,11] and Raman[4c,12]), is also available by the techniques described above,[1a,4a,b,6,9] as well by an alternative route from $Hg[Co(CO)_4]_2$.[13]

Octacarbonyl(mercury)dicobalt ($Hg[Co(CO)_4]_2$, recrystallized from acetone/H_2O[13,14] or MeOH;[4a] orange air-stable crystals mp 81-82 °C,[14] partially sublimed at 50 °C/0.1 mmHg;[14] sol heptane, hexane, benzene,

Et_2O, acetone, insol H_2O; IR,[4a,c,10,15] ^{59}Co NQR,[16] MS,[4a,17] Raman,[4c,12,18] and X-ray[19]) is a useful intermediate in the preparation of other cobalt carbonyl derivatives which, unlike $Zn[Co(CO)_4]_2$, $Cd[Co(CO)_4]_2$, and $Co_2(CO)_8$, is stable in air for prolonged periods (in excess of one year). This mercury derivative is conveniently and commonly prepared without the requirement for high-pressure equipment by two general routes. In the first technique, readily available cobalt(II) nitrate hexahydrate is used in a room temperature reaction with CO and mercury(II) cyanide (90% yield).[13,14] Alternatively, $Co_2(CO)_8$ can be treated with either Hg (quantitative yield)[20a] or 1% ***Sodium Amalgam*** (62% yield),[20] again at room temperature and atmospheric pressure. Procedures which utilize higher pressures of CO have also been reported.[6]

Purification: can be recrystallized from toluene at -80 °C,[4a] sublimed at 60 °C/0.005 mmHg;[4b] yellow prismatic crystals.[4b]

Handling, Storage, and Precautions: decomposes readily in air and has been reported as being pyrophoric.[6] Can be handled and stored as a solid or solution in the organic solvents quoted above under inert gas (argon or nitrogen).

Dimerization of Norbornadiene.

The dinuclear catalyst $Zn[Co(CO)_4]_2$ has two cobalt centers connected by zinc and is capable of catalyzing the dimerization of norbornadiene (eq 1).[1] The product of this dimerization has been shown unequivocally to be Binor-S (**1**) and is obtained exclusively and quantitatively when a high catalyst to monomer ratio (1:28) is used in nonpolar solvents (e.g. heptane or toluene) under an inert atmosphere (N_2 or Ar). At lower catalyst to monomer ratios (e.g. 1:238) a mixture of isomeric dimers of norbornadiene results. Furthermore, it was found that Lewis acids (as co-catalysts) activate the dimerization and enhance the formation of Binor-S (**1**). In particular, ***Boron Trifluoride Etherate*** and ***Aluminum Bromide*** were the most effective co-catalysts for the specific dimerization reaction. In the presence of Lewis acids, $Cd[Co(CO)_4]_2$, $In[Co(CO)_4]_3$, and $Co_2(CO)_8$ (all with $BF_3.OEt_2$) also gave quantitative yields of (**1**).

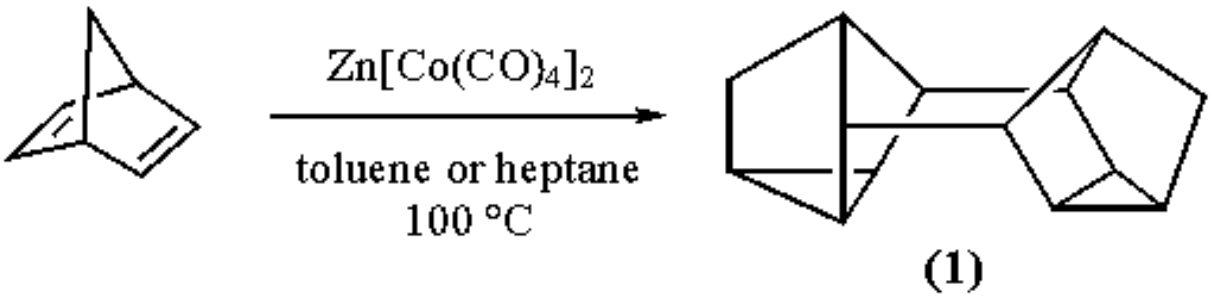

(1)

The use of $Zn[Co(CO)_4]_2$ has significant advantages over other metal-catalyzed dimerizations of norbornadiene (e.g. with $Fe(CO)_5$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$ or, when used in isolation, $Co_2(CO)_8$), where an array of dienes, ketones, and saturated hydrocarbons result in relatively low yields under similar conditions.[21] Additionally, in the reaction with acetylene, octacarbonyl(zinc)dicobalt produces benzene as the main volatile product and approximately 3% of cyclooctatetraene.[1]

By way of a comparison to the use of the title compound as a catalyst for the dimerization shown in eq 1, a range of alternative catalysts which are nearly as effective but which are more readily accessible have been reported.[22] These include $CoBr_2.2PPh_3$, $CoI_2.2PPh_3$, and $RhCl(PPh_3)_3$, all being used with $BF_3.OEt_2$ as the co-catalyst. The complexes are air-stable and are readily obtained from the corresponding anhydrous halides and ***Triphenylphosphine***. When compared to the original $Zn[Co(CO)_4]_2$, these mononuclear catalysts have an induction period prior to reaction. Following initial gentle heating, caution must be observed since the dimerization is exothermic and occasional cooling is required. As with the Zn system, metal-metal bonded intermediates are proposed as the catalytically active species. As part of independent studies, the $CoBr_2.2PPh_3$ catalyst has been utilized to prepare Binor-S (**1**) in 85% yield as part of an efficient synthetic route towards diamantane.[23]

The intermolecular condensation product of $Zn[Co(CO)_4]_2$, the mixed-metal cluster (**2**), can be prepared by heating the title compound in *n*-octane at 70 °C in the dark under a partial vacuum (eq 2).[24] The orange needle-like crystals of bis[μ-(tetracarbonylcobalt)zincio](μ-carbonyl)hexacarbonyldicobalt(*Co-Co*) (**2**) when dissolved in toluene and heated with norbornadiene catalyze the dimerization to Binor-S (**1**) in 70% yield.[24a] This reaction proceeds without the induction periods observed for the previously discussed catalysts.

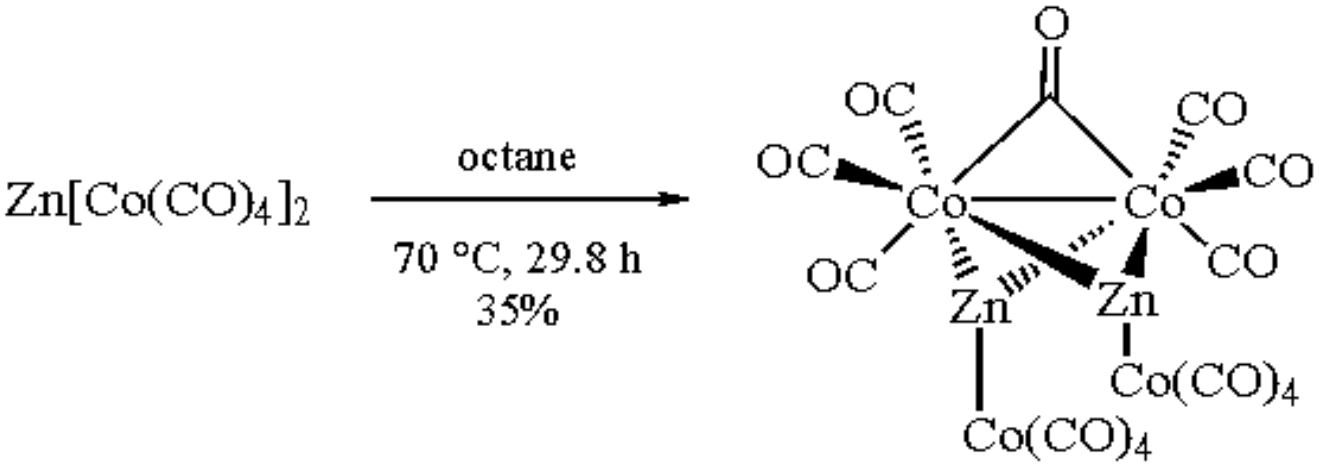

(2)

(2)

Propargyl Amine Linear Dimerization.

During a study, which generally shows the title compound to be a less efficient catalyst for the isomerization of allyl ethers and the cyclotrimerization of propargyl ethers and amines than alternative cobalt complexes, one unusual reaction is observed. In this isolated example, when 3-diethylaminopropyne is treated with $Zn[Co(CO)_4]_2$ a linear dimer is formed from reaction of the methylene carbon of an amino ethyl group (eq 3).[2]

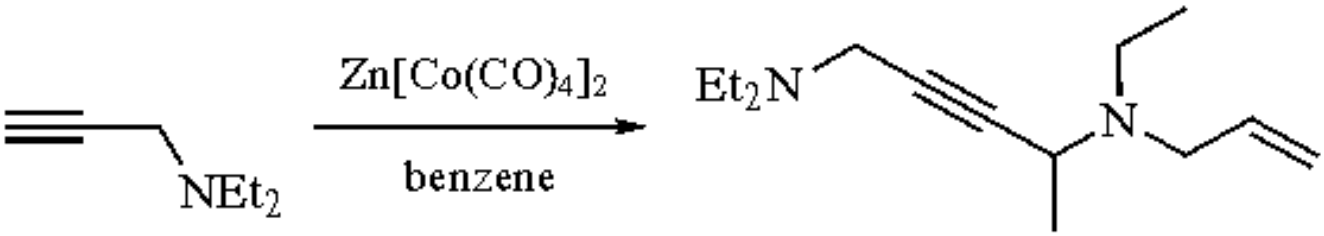

(3)

Reactions of the Analogous Mercury Compound, $Hg[Co(CO)_4]_2$.

Cyclotrimerization reactions of alkynes in the presence of metal carbonyls is a well-known phenomenon in organometallic chemistry.[25] In particular, octacarbonyl(mercury)dicobalt is an efficient catalyst for this process and, furthermore, when unsymmetrical alkynes are used, good selectivities for the 1,2,4-trisubstituted products are observed (eq 4).[26] In addition, partial intramolecular cyclization resulted when terminal 1,7- or 1,8-diynes were used.[27] The zinc species has not been shown to be an efficient catalyst for the alkyne cyclotrimerization process.

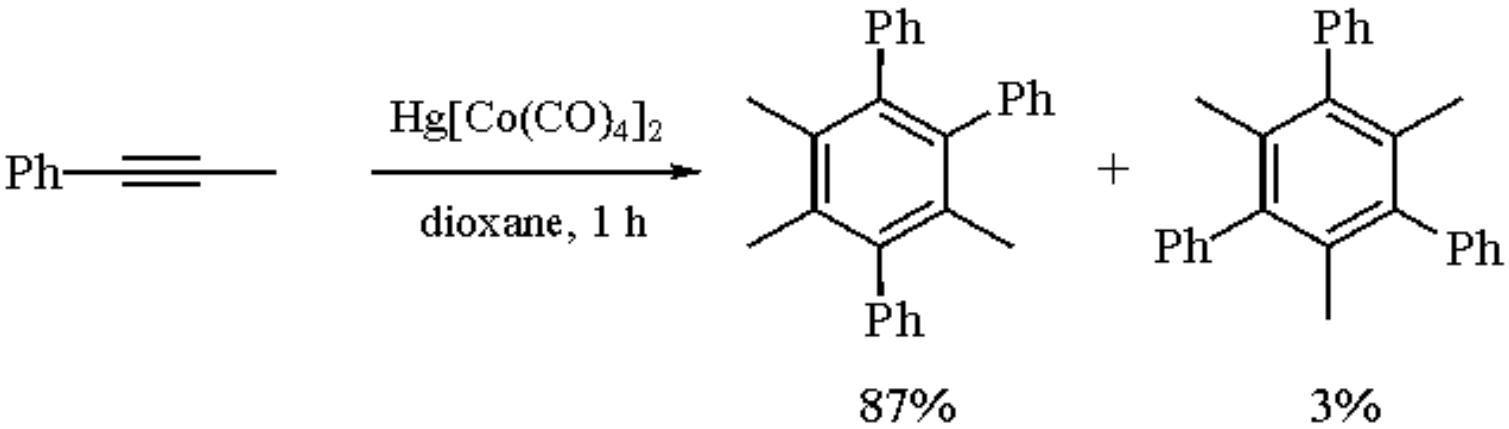

(4)

Two further $Hg[Co(CO)_4]_2$ catalyzed reactions which have not been reported as being mediated by the analogous zinc species are illustrated in eqs 5 and 6. In the former case, symmetrical diaryl ketones can be formed from the corresponding diarylmercury compound under photolysis conditions.[28] Despite good to high yields being observed for diaryl ketones, this process is not applicable to the synthesis of dialkyl ketones. In the latter procedure, *gem*-dihalides can be coupled to give tetrasubstituted alkenes (eq 6).[29] When $Hg[Co(CO)_4]_2$ is employed as the catalyst, higher yields are observed when the reaction is carried out photolytically. A number of alternative metal-cobalt carbonyl species also mediate this transformation.

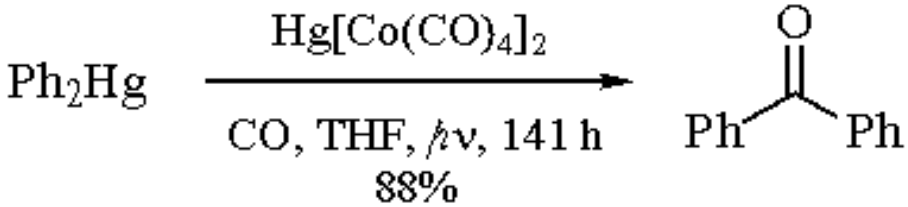

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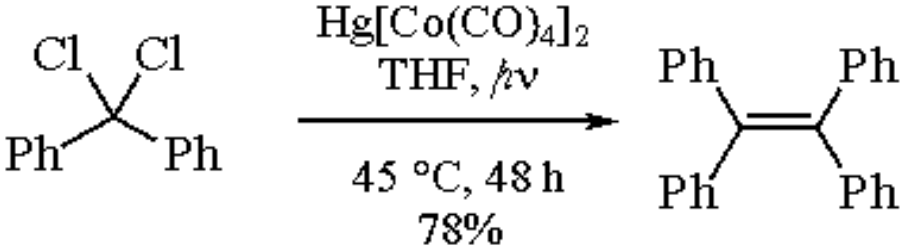

(6)

Related Reagents.

Octacarbonyldicobalt; ***Sodium Tetracarbonylcobaltate***.

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1,7-Octadien-3-one

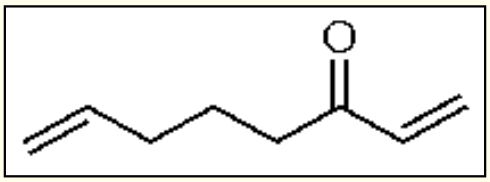

[70855-06-0] · $C_8H_{12}O$ · 1,7-Octadien-3-one · (MW 124.20)

(used mainly as a bisannulation reagent to prepare two annulated six-membered rings)

Physical Data: colorless liquid, bp 38-42 °C/3 mmHg, 65 °C/20 mmHg; semicarbazone: mp 180-182 °C.

Solubility: sol most organic solvents.

Preparative Methods: prepared most conveniently by the palladium-catalyzed reaction of ***1,3-Butadiene*** with ***Acetic Acid*** affording an equilibrium mixture (1:3) of 1-acetoxy-2,7-octadiene (**2**) and 3-acetoxy-1,7-octadiene (**1**) (eq 1);[1,2] the lower-boiling (**1**) (90-95 °C/25 mmHg) can be separated from the higher-boiling (**2**) (103-108 °C/25 mmHg) by distillation. The desired allylic acetate (**1**) can also obtained by the palladium-catalyzed allylic rearrangement of the isomeric allylic acetate (**2**); hydrolysis of (**1**) affords 1,7-octadien-3-ol; this allylic alcohol is oxidized with ***Manganese Dioxide*** in CCl_4, or with CrO_3-pyridine in CH_2Cl_2, to afford the title reagent.

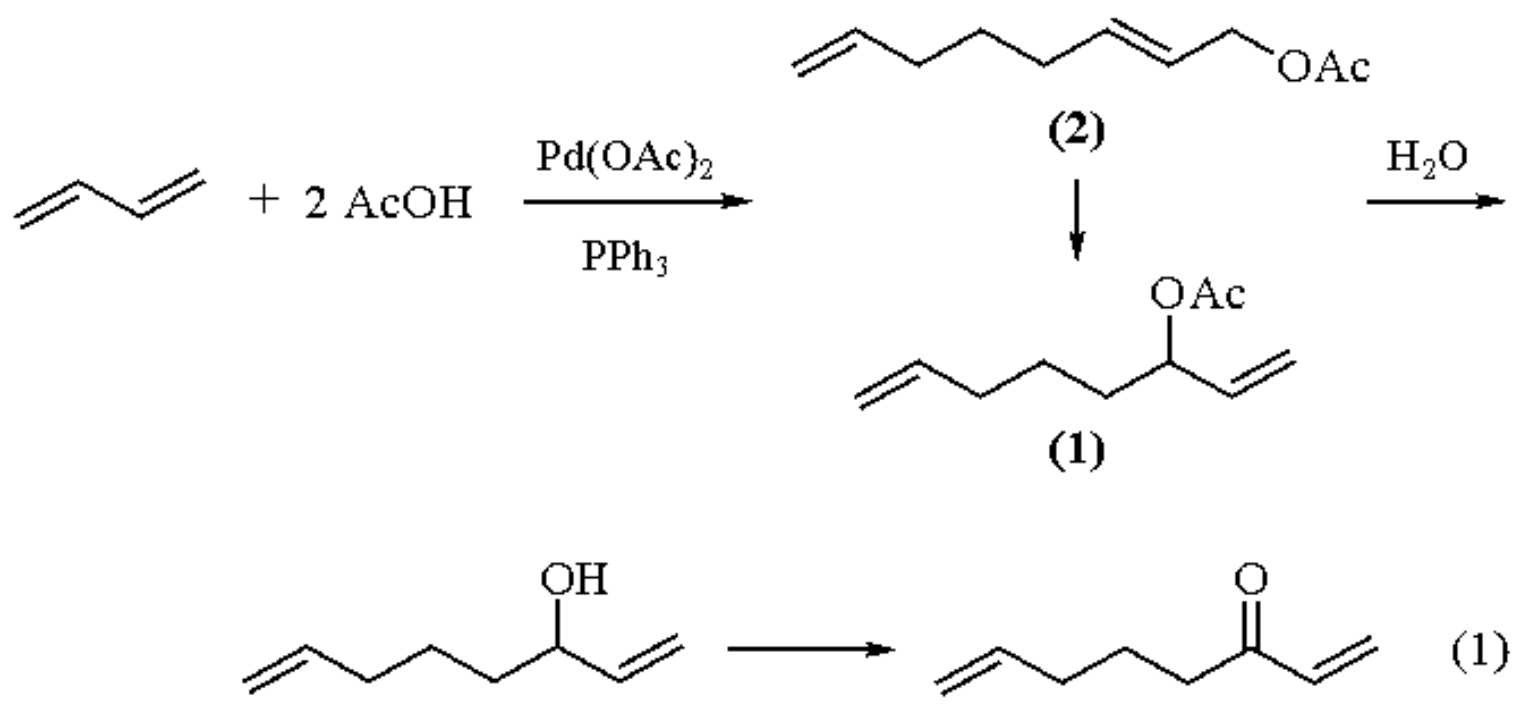

In another method, 1,7-octadien-3-ol is prepared in 80% yield by the reaction of ***Acrolein*** with the Grignard reagent prepared from 4-pentenyl bromide (eq 2); Jones oxidation of the alcohol affords 1,7-octadien-3-one in 89% yield.[3]

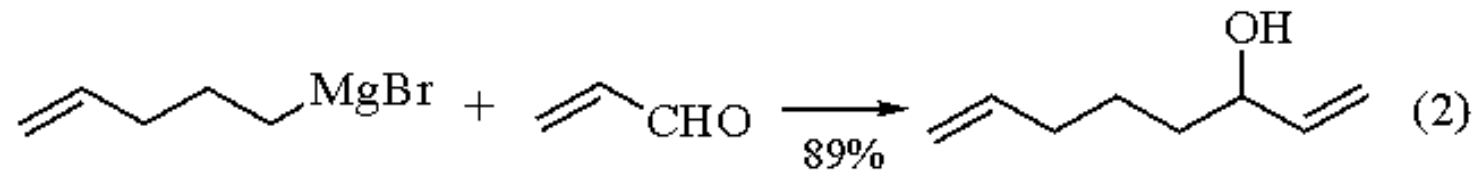

(2)

Handling, Storage, and Precautions: use in a fume hood.

Bisannulation.

1,7-Octadien-3-one can be regarded as a masked equivalent for 1-octene-3,7-dione, and can be used as a bisannulation reagent for the preparation of two annulated cyclohexene rings. The enone portion of the reagent is used for Michael and aldol reactions, while the terminal double bond serves as a masked methyl ketone which can be unmasked by Wacker-type oxidation with ***Palladium(II) Chloride-Copper(I) Chloride*** in aq DMF.[4] A typical application is shown by the annulation of 2-methylcyclopentane-1,3-dione (eq 3).[1] The first step involves Michael addition to the diketone, which is followed by aldol condensation to give the annulated cyclohexenone. The terminal double bond is then oxidized with catalytic $PdCl_2$/CuCl, yielding the trione. The last step is aldol condensation to generate a new cyclohexenone ring.

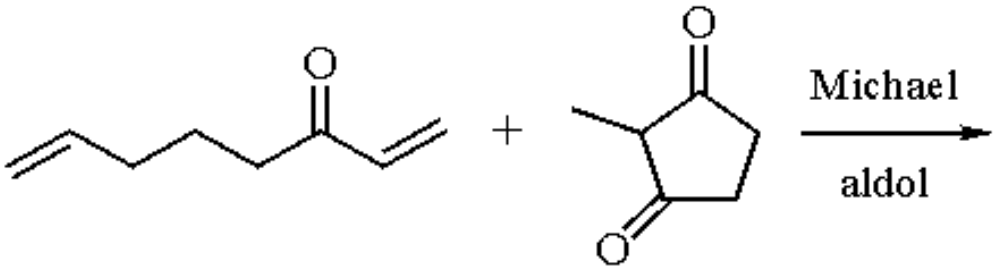

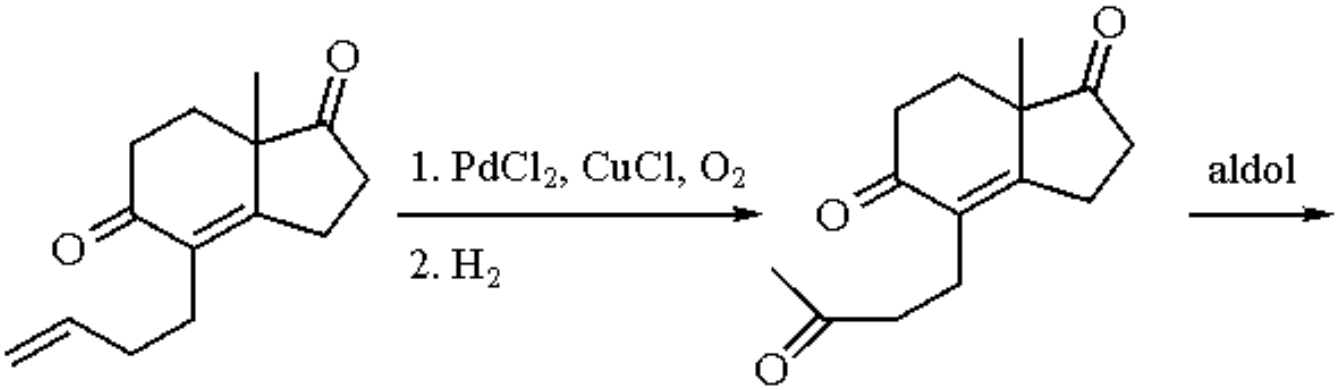

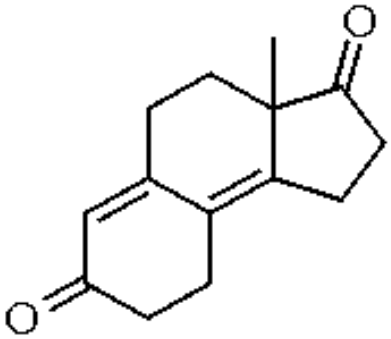

(3)

1,7-Octadien-3-one

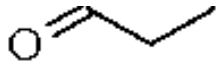

(+)-19-Nortestosterone has been prepared from a CD ring intermediate by the bisannulation method using 1,7-octadien-3-one according to the sequence of reactions summarized in eq 4.[1,5]

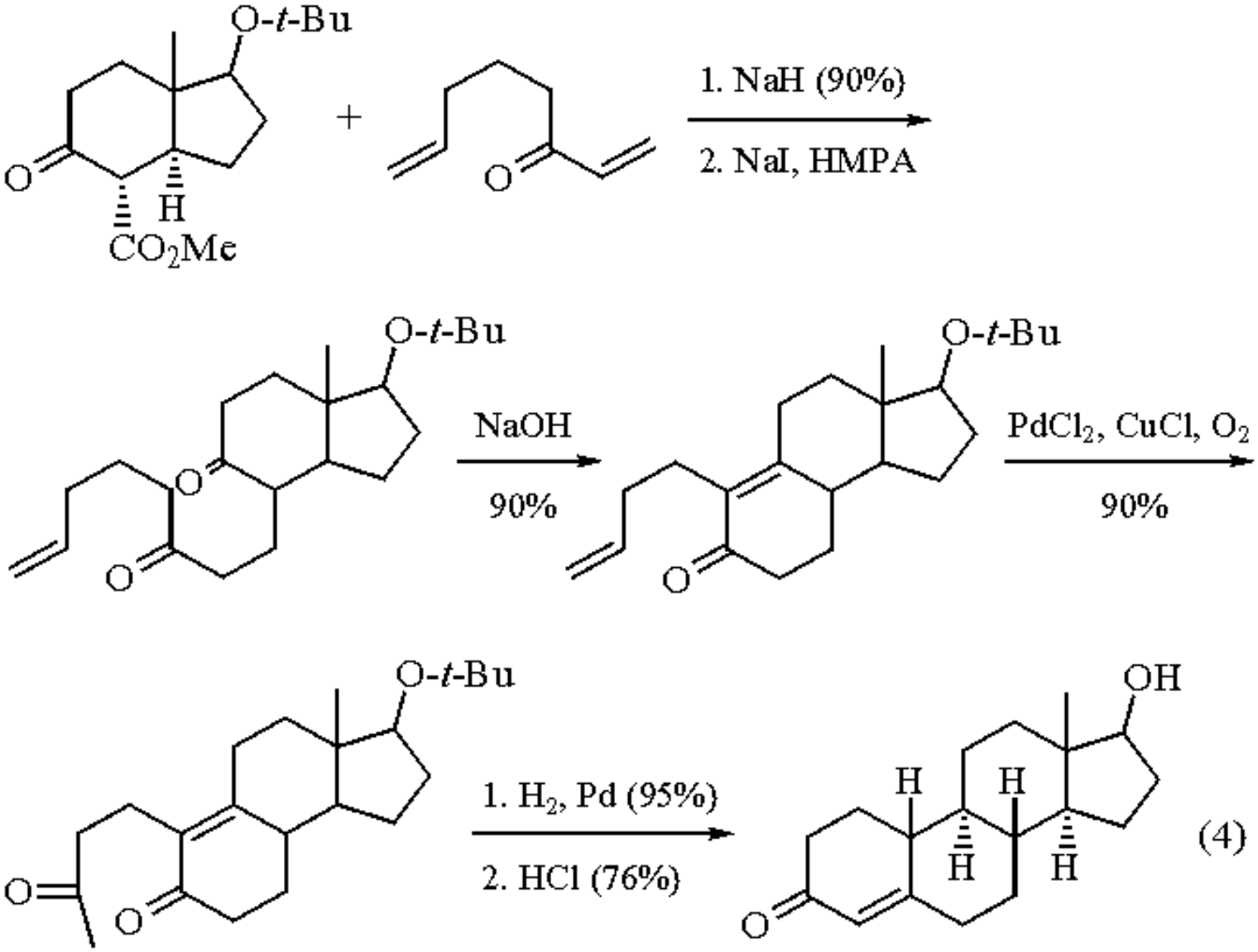

Synthesis of a Trisannulation Reagent.

1,7-Octadien-3-one is converted to 7-acetoxydodeca-1,11-dien-3-one, used as a trisannulation reagent, by the sequence of reactions shown in eq 5.[6] This compound is a masked equivalent for 1-dodecene-3,7,11-trione, with the C-7 and C-11 ketones masked as an acetoxy group and terminal double bond, which can be unmasked in a stepwise manner to generate the ketones.

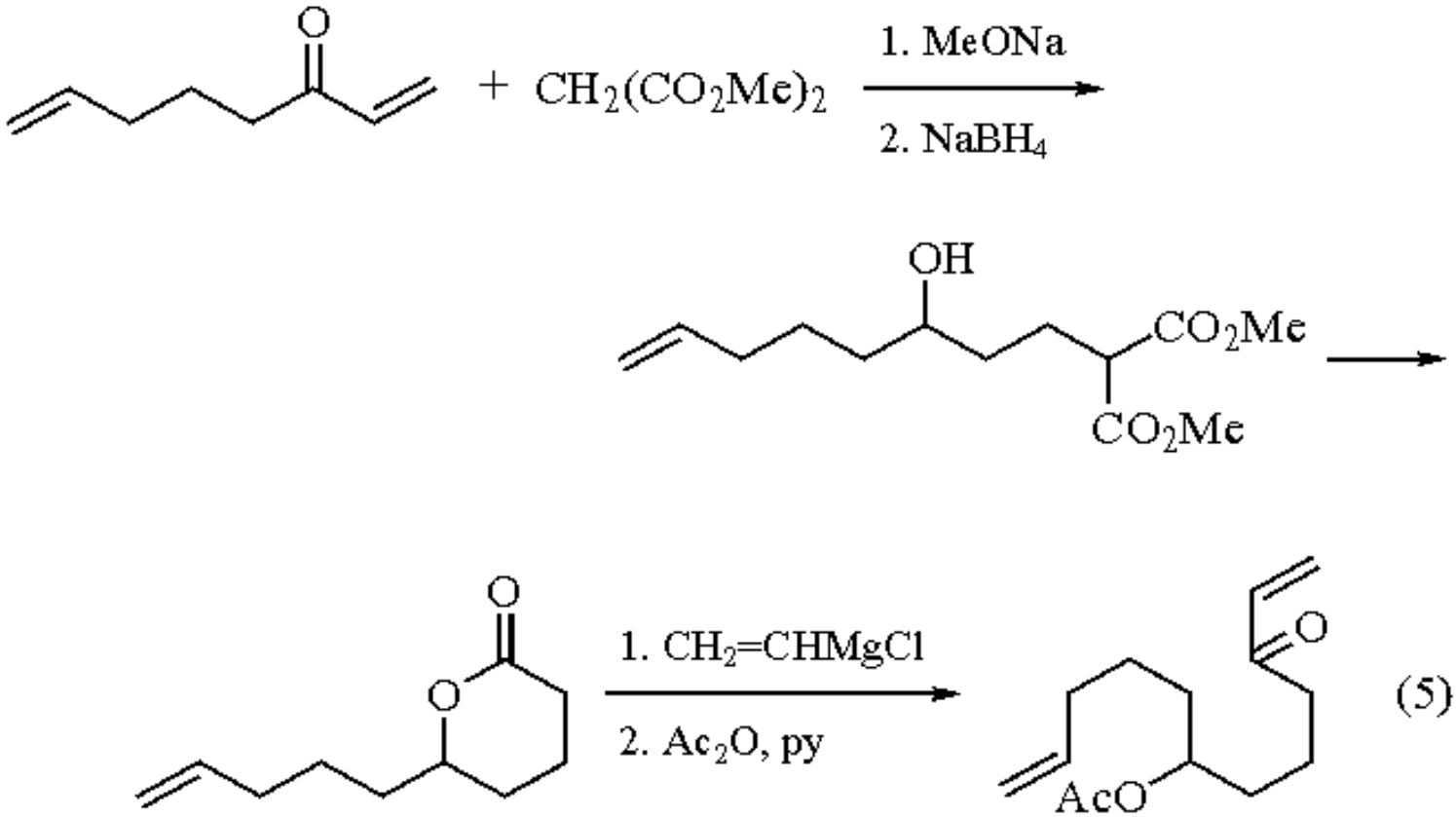

A steroid synthesis based on the trisannulation is also carried out using the trisannulation reagent described above (eq 6).[6]

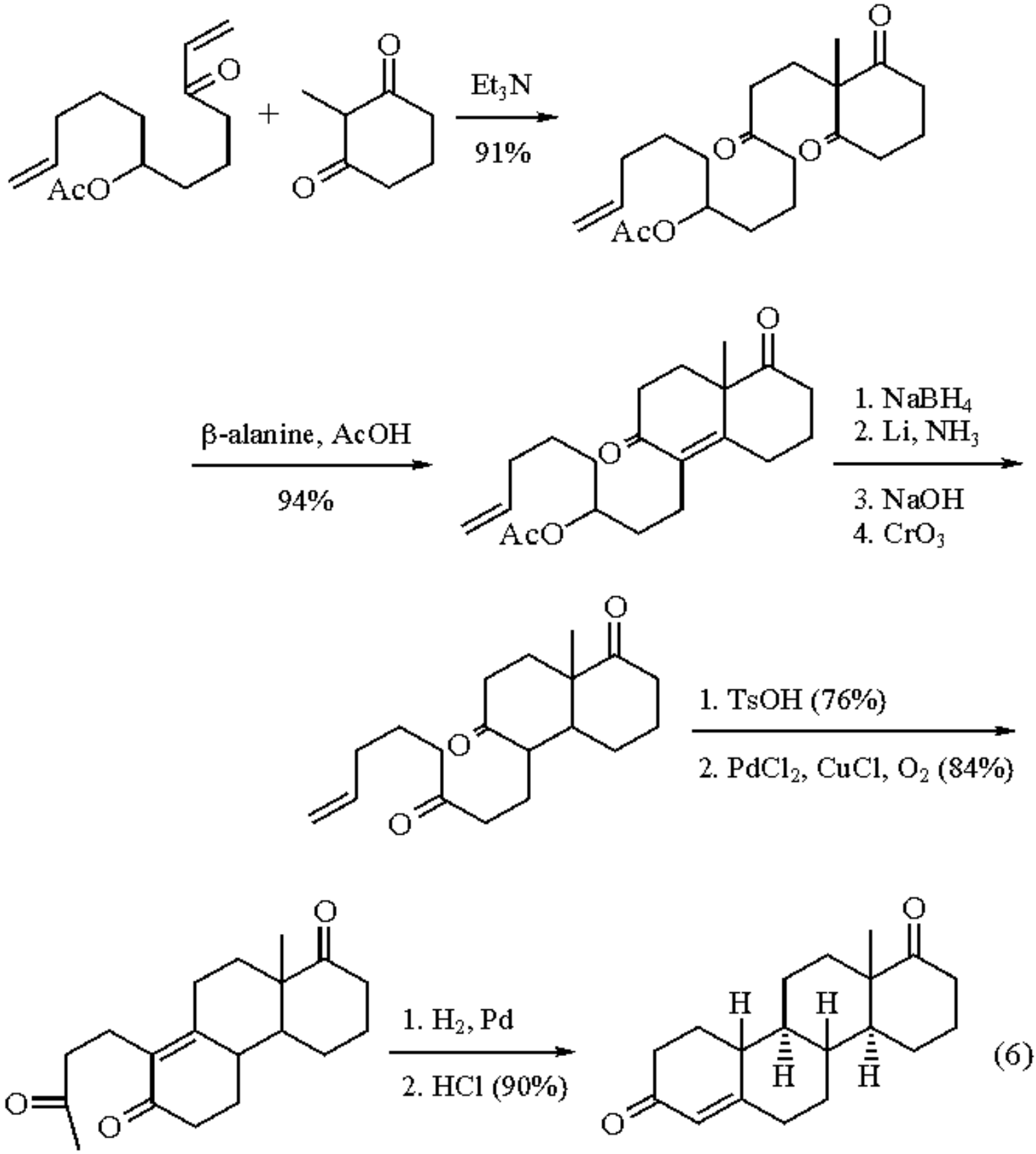

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Jiro Tsuji

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[(2*S*)-(2α,3aα,4α,7α,7aα)]-2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol

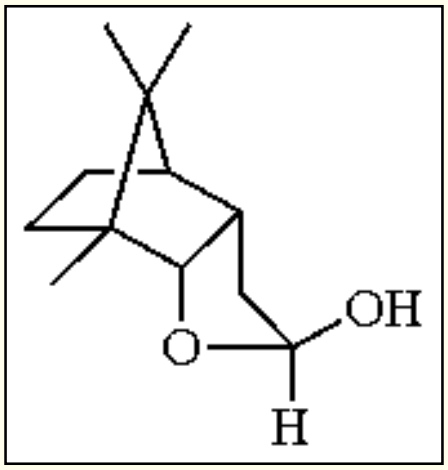

([(2*S*)-(2α,3aα,4α,7α,7aα)]-isomer)

[81925-09-9] · $C_{12}H_{20}O_2$ · [(2*S*)-(2α,3aα,4α,7α,7aα)]-2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol · (MW 196.32) (enantiomer)

[108031-75-0] (2*S*) acetal dimer (**1**)

[87248-50-8] · $C_{24}H_{38}O_3$ · [(2*S*)-(2α,3aα,4α,7α,7aα)]-2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol Acetal Dimer · (MW 374.62) (enantiomeric acetal dimer)

[108031-79-4]

(useful for resolving racemic alcohols via formation of diastereomeric acetals,[1] and also for determining the absolute configuration of certain types of chiral alcohols[2])

Alternate Name: MBF-OH.

Physical Data: monomeric lactol: bp 120 °C/0.005 mmHg, [α]20D + 100° (*c*, 11.24, THF); acetal dimer: mp 150-151 °C, $[\alpha]^{21}$ + 199.1° (*c*, 2.25, THF).

Solubility: monomeric lactol: sol ether, $CHCl_3$, THF; acetal dimer: sol $CHCl_3$, THF, hot petroleum ether.

Form Supplied in: the acetal dimer, and its enantiomer, are available as the neat solids.

Analysis of Reagent Purity: NMR,[3] mp.

Preparative Methods: the [(2*S*)-(2α,3aα,4α,7α,7aα)]-isomer is prepared from (+)-camphor,[3a] and the (2*R*)-enantiomer from (-)-borneol via oxidation to (-)-camphor.[3b]

Purification: the monomeric lactols can be purified by distillation, and the acetal dimers by recrystallization from petroleum ether.

Handling, Storage, and Precautions: no reported instability or toxicity.

Resolving Agent for Chiral Alcohols.

The title lactol reagent (known as the Noe reagent) has been used mainly for resolving racemic alcohols through formation of diastereomeric, separable acetals.[1] From each alcohol enantiomer, a single diastereomer of the product acetal is formed with high selectivity. Separation of the diastereomeric derivatives by chromatography or crystallization, followed by mild methanolysis, gives the resolved alcohol in good yield and high enantiomeric purity. If an excess of the racemic alcohol is employed, enantiomer-selective acetal formation results in one of the product diastereomers being produced in excess, which increases the yield of pure diastereomer obtained (eq 1).[4]

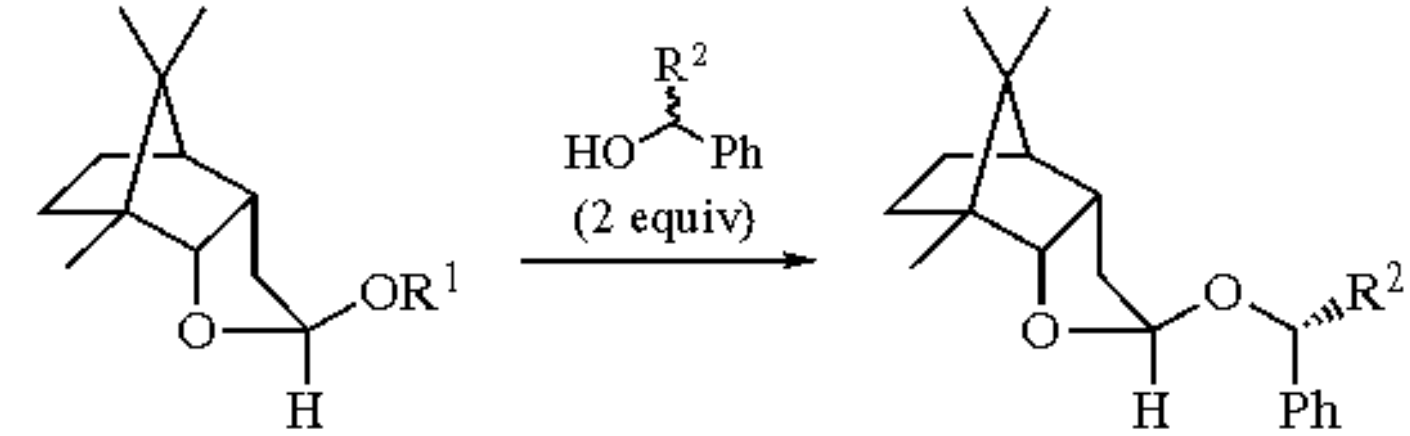

(1)

$R^1 = H$ or MBF

major diastereomer

$R^2 = Me$, 49%; $R^2 = t\text{-Bu}$, 64%

The commercially available acetal dimer (**1**), and the enantiomeric dimer, can also be used as reagents instead of the lactols.[1] As an alternative to the (2*R*)-enantiomer of the *endo*-lactol, one can use the *exo*-lactol (**2**), or the corresponding acetal dimer.[5] Compound (**2**) is prepared from (+)-camphor, as is the (2*S*)-enantiomer of the *endo*-lactol, but the two reagents show opposite sense of enantiomer selectivity in acetal formation.

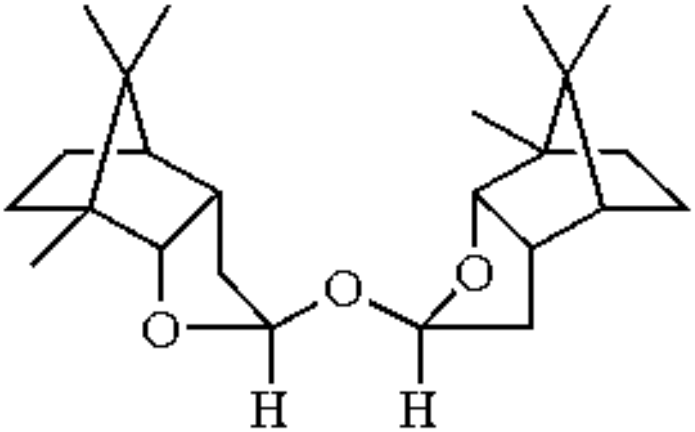

(1)

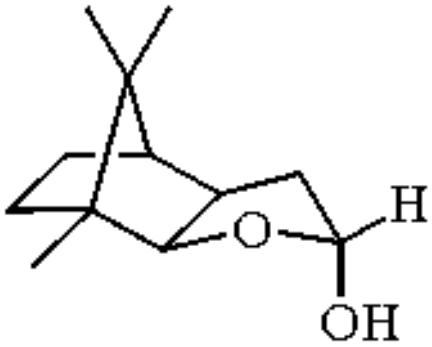

(2)

Using these reagents, resolutions of various types of racemic alcohols, including alkylarylcarbinols,[1] alkylthienylcarbinols,[6] cyanohydrins,[1,7] α-hydroxyalkynes,[2b] and α-hydroxyphosphonates,[8] and also of a thiol[1] and an amine,[1] have been performed.

An alternative procedure has been reported for the resolution of alcohols through separation of diastereomeric *O*-methylmandelates;[9] a drawback of this approach is that partial racemization of the mandelic acid derivative sometimes occurs during the esterification. In contrast, the Noe reagents are configurationally stable; also, complete separation of the derived diastereomeric acetals can usually be achieved, which gives access to enantiomerically pure alcohols when the selectivity of the acetal formation is low. An additional advantage of the title reagents is that the derived acetal can be used as an ordinary hydroxyl-protecting group in subsequent synthetic operations, with a reactivity similar to a THP group.[7,10] Of other alternative methods for resolution of racemic alcohols, kinetic resolutions by enzyme-catalyzed transformations often give very high selectivities.[11]

Determination of Absolute Configuration for Chiral Alcohols.

Using NMR data for the derived acetals, in combination with the known sense of enantiomer selectivity for the Noe reagent used, one can also determine the absolute configuration of the starting alcohol.[2] Gas chromatography data can be used as well.[2c] This method for determining absolute configuration should be a useful complement to the more commonly used methods based on NMR analysis of Mosher esters[12] or *O*-

methylmandelates.[9]

---

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Osmium Tetroxide[1]

O_4sO

[20816-12-0] · O_4Os · Osmium Tetroxide · (MW 254.20)

(*cis* dihydroxylation of alkenes; osmylation; asymmetric and diastereoselective dihydroxylation; oxyamination of alkenes)

Physical Data: mp 39.5-41 °C; bp 130 °C; *d* 4.906 g cm^{-3}; chlorine- or ozone-like odor.

Solubility: sol water (5.3% at 0 °C, 7.24% at 25 °C); sol many organic solvents (toluene, *t*-BuOH, CCl_4, acetone, methyl *t*-butyl ether).

Form Supplied in: pale yellow solid in glass ampule, as 4 wt % solution in water, and as 2.5 wt % in *t*-BuOH.

Handling, Storage, and Precautions: vapor is toxic, causing damage to the eyes, respiratory tract, and skin; may cause temporary blindness; LD_{50} 14 mg/kg for the rat, 162 mg/kg for the mouse. Because of its high toxicity and high vapor pressure, it should be handled with extreme care in a chemical fume hood; chemical-resistant gloves, safety goggles, and other protective clothing should be worn; the solid reagent and its solutions should be stored in a refrigerator.

Dihydroxylation of Alkenes.

The *cis* dihydroxylation (osmylation) of alkenes by osmium tetroxide to form *cis*-1,2-diols (*vic*-glycols) is one of the most reliable synthetic transformations (eq 1).[1]

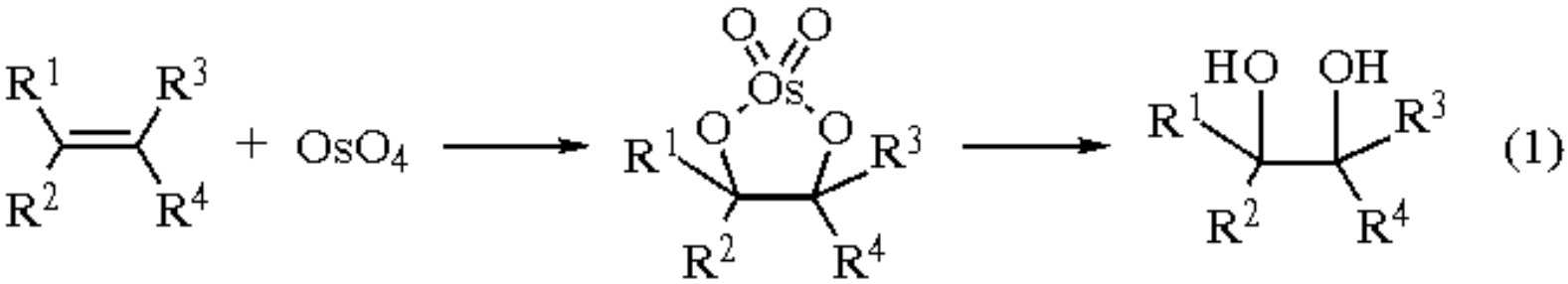

The reaction has been proposed to proceed through a [3 + 2] or [2 + 2] pathway to give the common intermediate osmium(VI) monoglycolate ester (osmate ester), which is then hydrolyzed reductively or oxidatively to give the *cis*-1,2-

diol (eq 2). The *cis* dihydroxylation of alkenes is accelerated by tertiary amines such as ***Pyridine***, quinuclidine, and derivatives of dihydroquinidine (DHQD) or dihydroquinine (DHQ) (eq 3).

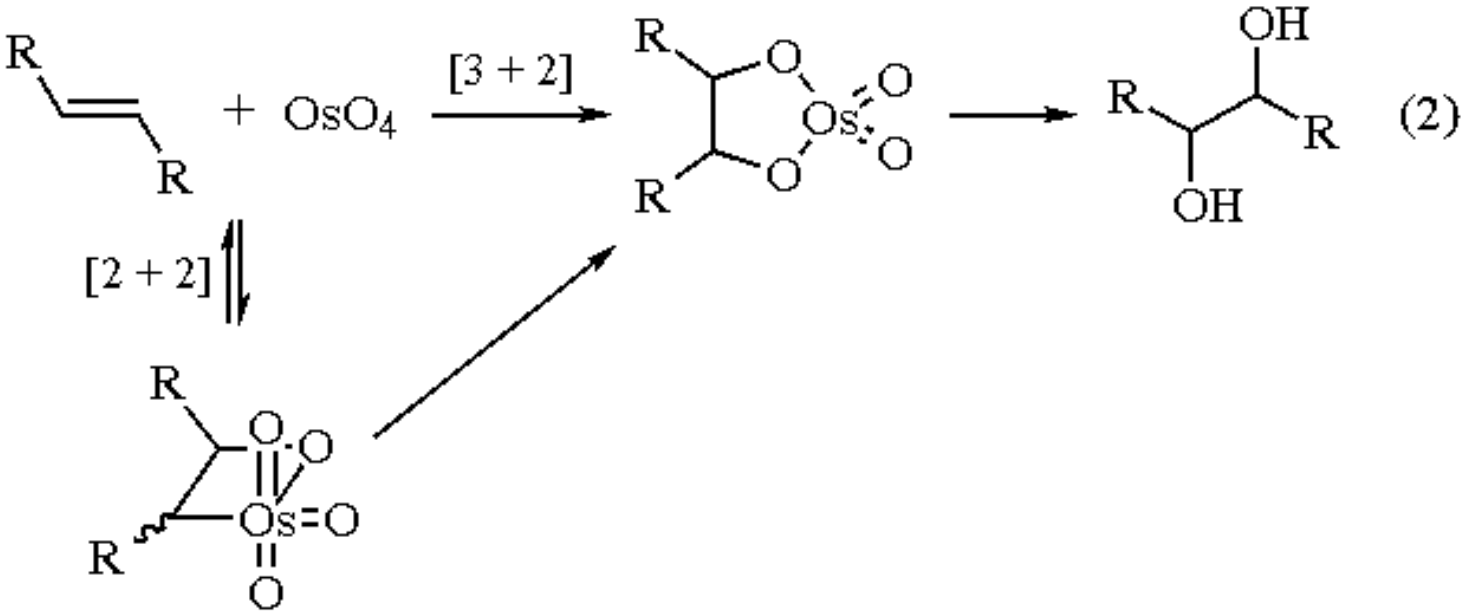

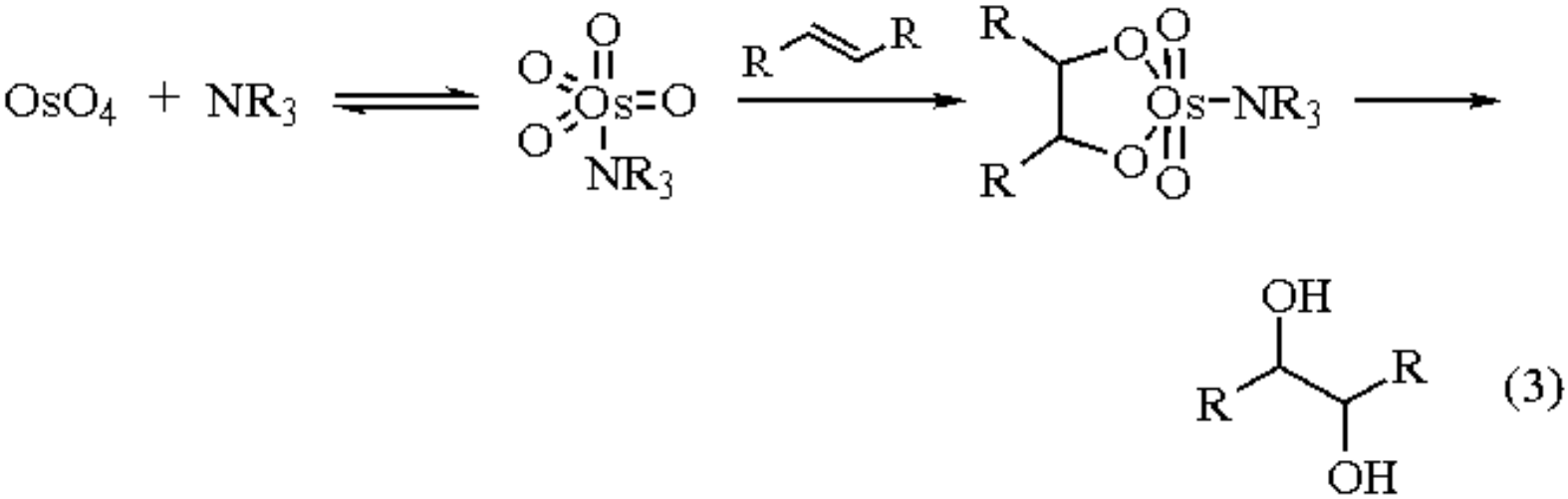

Due to the electrophilic nature of osmium tetroxide, electron-withdrawing groups connected to the alkene double bond retard the dihydroxylation.[2] This is in contrast to the oxidation of alkenes by ***Potassium Permanganate***, which preferentially attacks electron-deficient double bonds. However, in the presence of a tertiary amine such as pyridine, even the most electron-deficient alkenes can be osmylated by osmium tetroxide (eq 4).[3] The more highly substituted double bonds are preferentially oxidized (eq 5).

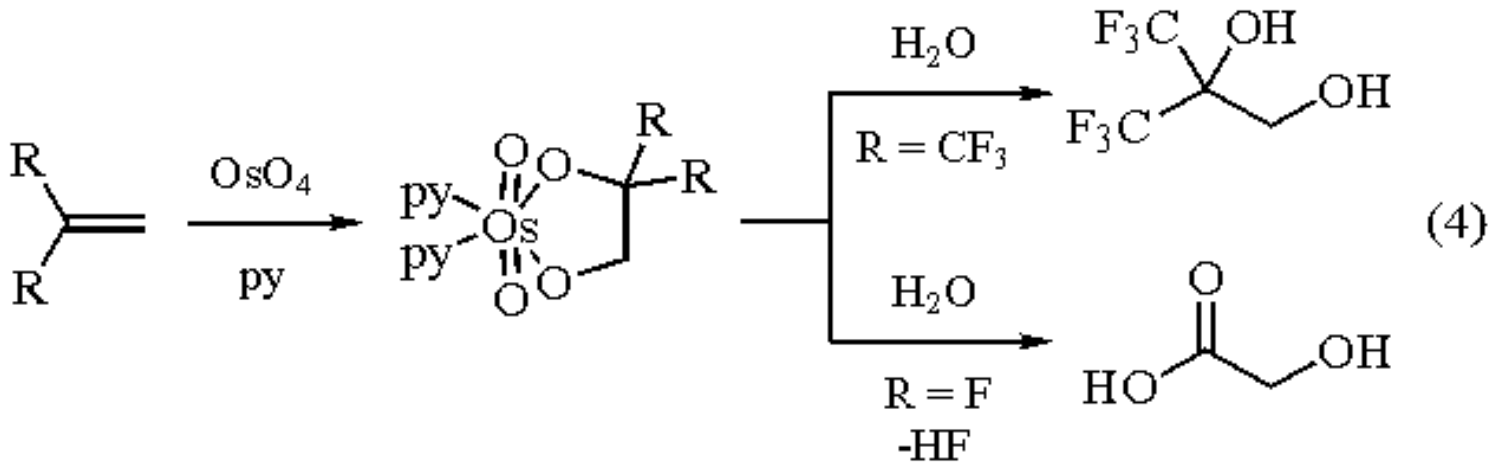

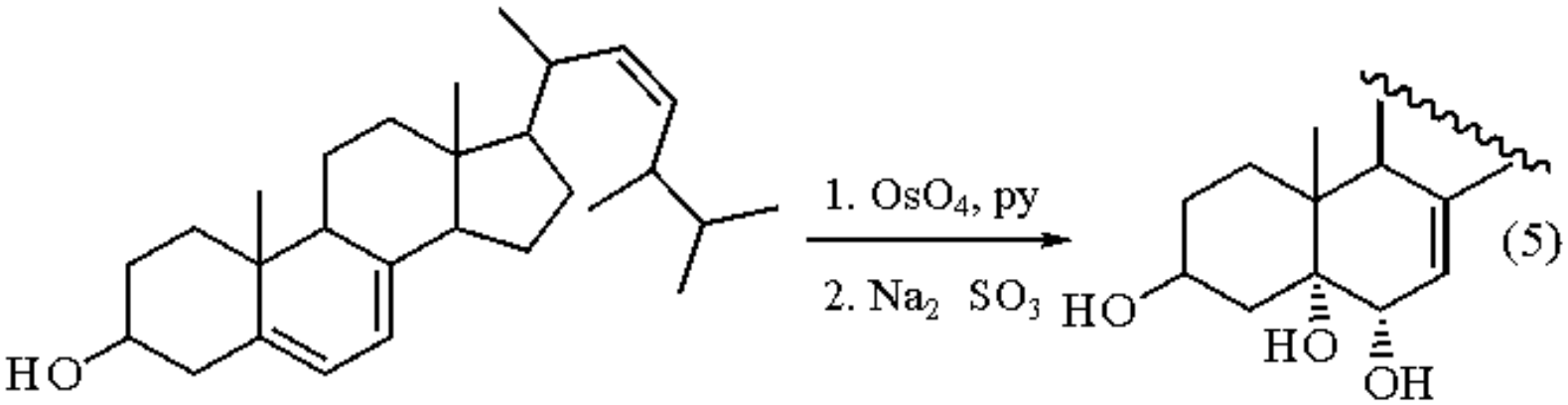

Under stoichiometric and common catalytic osmylation conditions, alkene double bonds are hydroxylated by osmium tetroxide without affecting other functional groups such as hydroxyl groups, aldehyde and ketone carbonyl groups, acetals, triple bonds, and sulfides (see also ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***).

The *cis* dihydroxylation can be performed either stoichiometrically, if the alkene is precious, or more economically and conveniently with a catalytic amount of osmium tetroxide (or its precursors such as osmium chloride or potassium osmate) in conjunction with a cooxidant. In the stoichiometric dihydroxylation, the diol product is usually obtained by the reductive hydrolysis of the osmate ester with a reducing agent such as ***Lithium Aluminum Hydride***, ***Hydrogen Sulfide***, K_2SO_3 or Na_2SO_3, and $KHSO_3$ or $NaHSO_3$. The reduced osmium species is normally removed by filtration. Osmium can be recovered as osmium tetroxide by oxidation of low-valent osmium compounds with hydrogen peroxide.[4] In the catalytic dihydroxylation, the osmate ester is usually hydrolyzed under basic aqueous conditions to produce the diol and osmium(VI) compounds, which are then reoxidized by the cooxidant to osmium tetroxide to continue the catalytic cycle. Normally 0.01% to 2% equiv of osmium tetroxide or precursors are used in the catalytic dihydroxylation. Common cooxidants are metal chlorates, ***N-Methylmorpholine N-Oxide*** (NMO), ***Trimethylamine N-Oxide***, ***Hydrogen Peroxide***, ***t-Butyl Hydroperoxide***, and ***Potassium Ferricyanide***. ***Oxygen*** has also been used as cooxidant in dihydroxylation of certain alkenes.[5] Excess cooxidant and osmium tetroxide are reduced with a reducing agent such as those mentioned above during the workup. The stoichiometric dihydroxylation can be carried out in almost any inert organic solvent, including most commonly MTBE, toluene, and *t*-BuOH. In the catalytic dihydroxylation, in order to dissolve the inorganic cooxidant and other additives, a mixture of water and an organic solvent are often used. The most common solvent combinations in this case are acetone-water and *t*-BuOH-water. Because of the high cost and toxicity of osmium tetroxide, the stoichiometric dihydroxylation has been mostly replaced by the catalytic version in preparative organic chemistry (see also ***Osmium Tetroxide-t-Butyl Hydroperoxide***, ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***, and ***Osmium Tetroxide-Potassium Ferricyanide***).

Diastereoselective Dihydroxylation.

Dihydroxylation of acyclic alkenes containing an allylic, oxygen-bearing stereocenter proceeds with predictable stereochemistry. In general, regardless of the double-bond substitution pattern and geometry, the relative stereochemistry between the pre-existing hydroxyl or alkoxyl group and the adjacent newly formed hydroxyl group of the major diastereomer will be *erythro* (i.e. *anti* if the carbon chain is drawn in the zig-zag convention) (eq 6).[6,7]

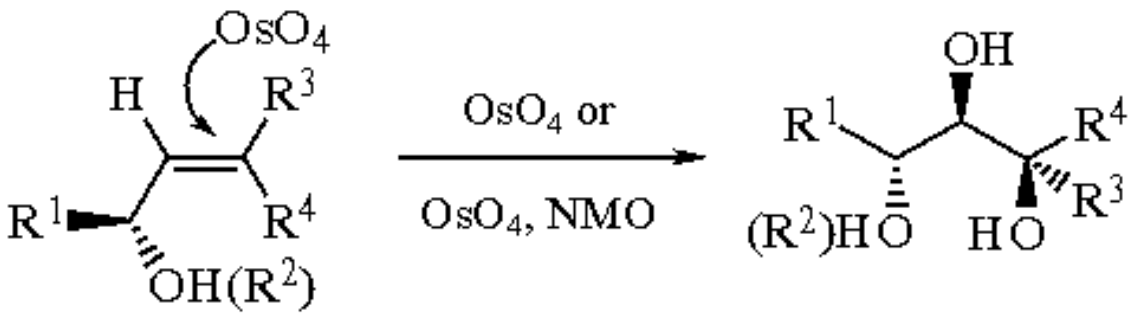

(6)

In the osmylation of 1,2-disubstituted allylic alcohols and derivatives, *cis*-alkenes provide higher diastereoselectivity than the corresponding *trans*-alkenes (eqs 7 and 8).[6] Opposite selectivities have been observed in the osmylation of (*Z*)-enoate and (*E*)-enoate esters (eqs 9 and 10).[8] High selectivity has also been observed in the osmylation of 1,1-disubstituted[9] and (*E*)-trisubstituted allylic alcohols and derivatives[10] and bis-allylic compounds[11] (eqs 11-13).

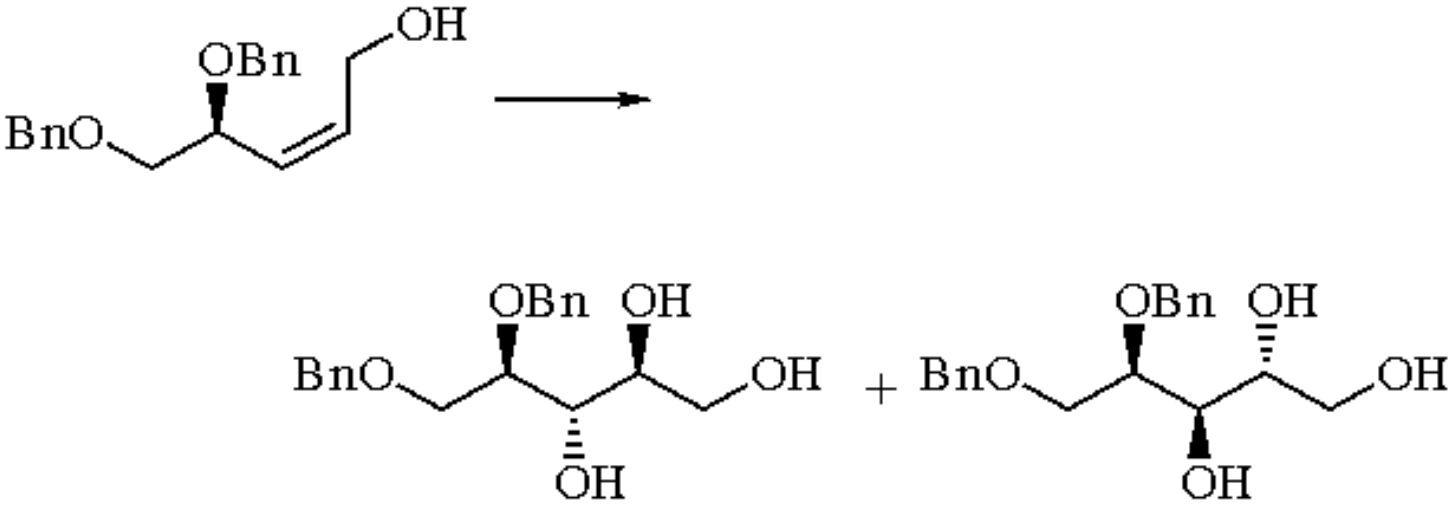

(7)

OsO_4	8.0:1.0
OsO_4, NMO	7.0:1.0

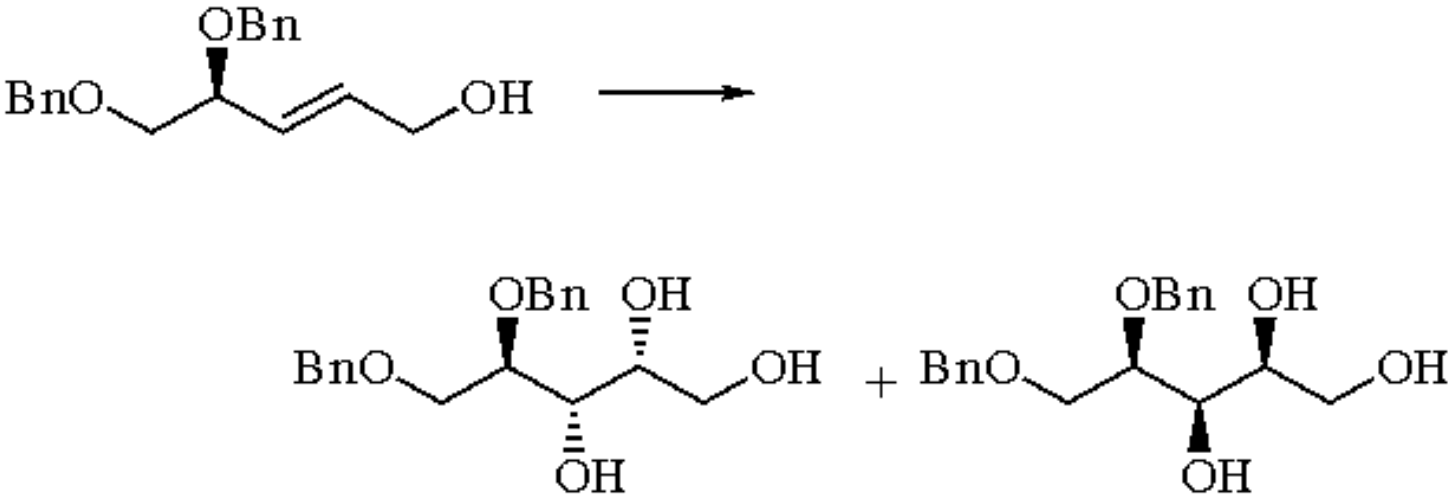

(8)

OsO_4	4.2:1.0
OsO_4, NMO	3.1:1.0

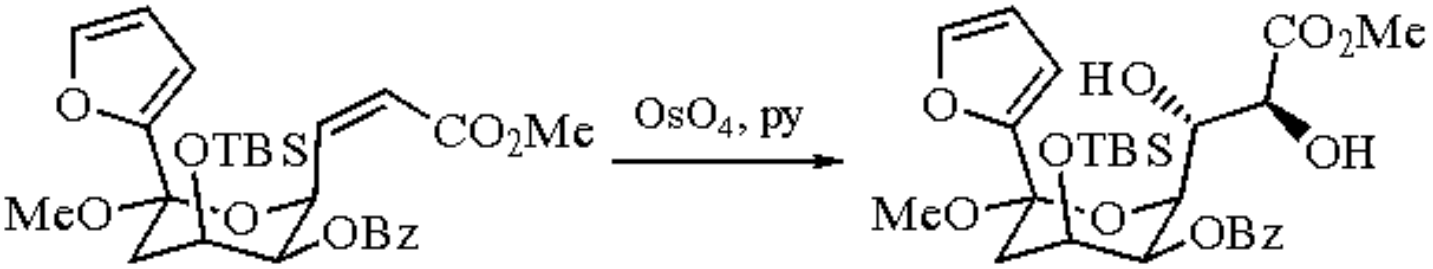

(9)

de > 18:1

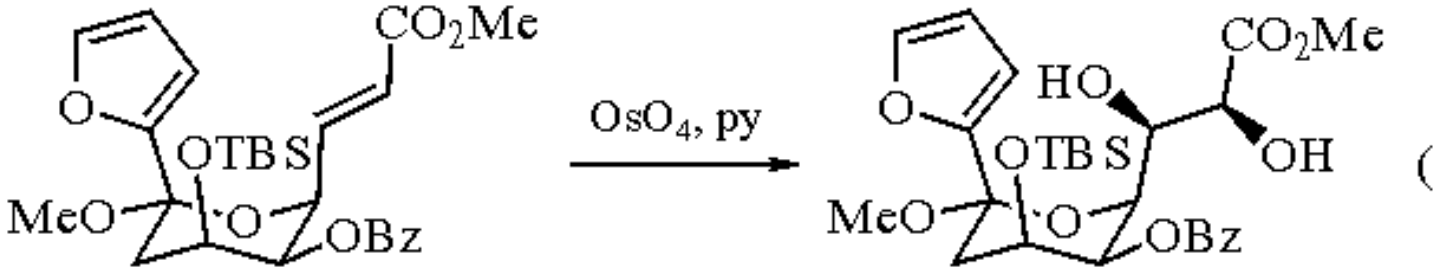

(10)

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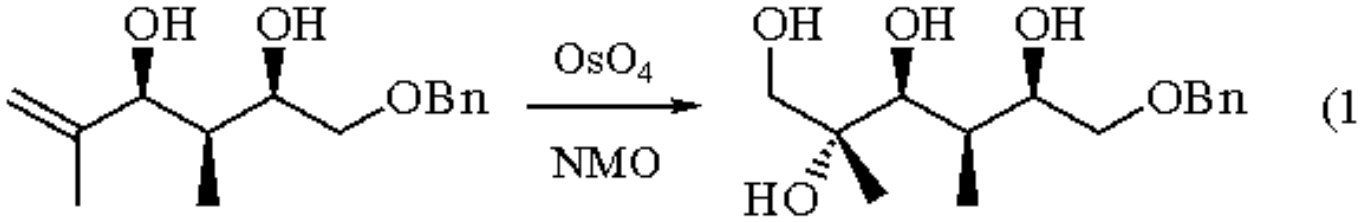

(11)

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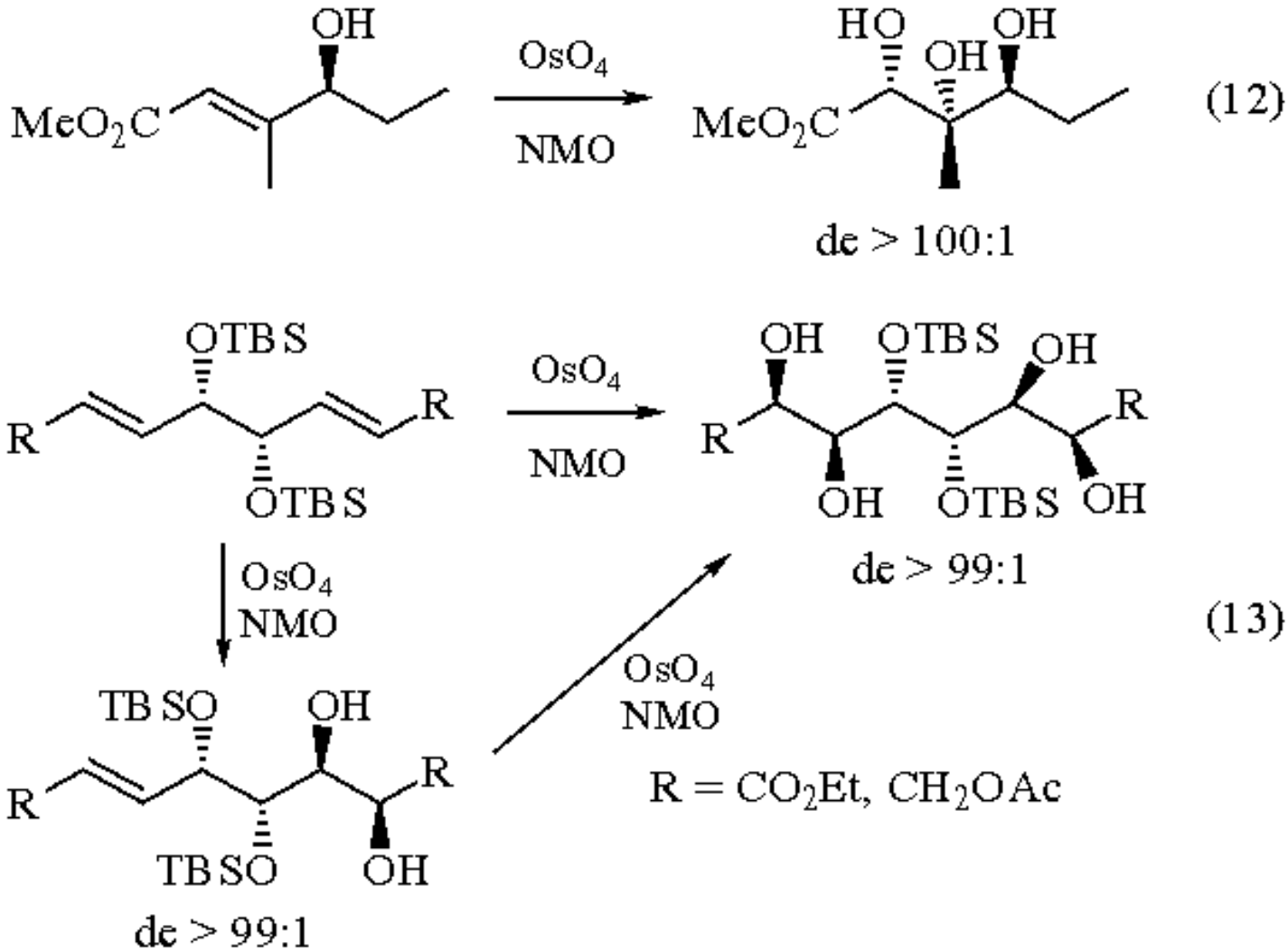

The diastereoselective osmylation has been extended to oxygen-substituted allylic silane systems, and the general rule observed for the allylic alcohol system also applies (eq 14).[12] High selectivity is also observed in the osmylation of allylsilanes where the substituent on the chiral center bearing the silyl group is larger than a methyl group (eq 15).[13] These diastereoselectivities have been achieved in both stoichiometric and catalytic dihydroxylations. Slightly higher selectivity has been observed in the stoichiometric reaction than in the catalytic reaction; this may be due to less selective bis-osmate ester formation in the catalytic reaction using NMO as the cooxidant. Use of $K_3Fe(CN)_6$ may solve this discrepancy. Several rationales have been proposed for the observed selectivity.[14] The conclusion appears to be that the osmylation of these systems is controlled by steric bias, rather than by the electronic nature of the allylic system, and osmylation will occur from the sterically more accessible face. The high diastereoselectivity of osmium tetroxide in the dihydroxylation of chiral unsaturated compounds has been applied widely in organic synthesis.[8,15]

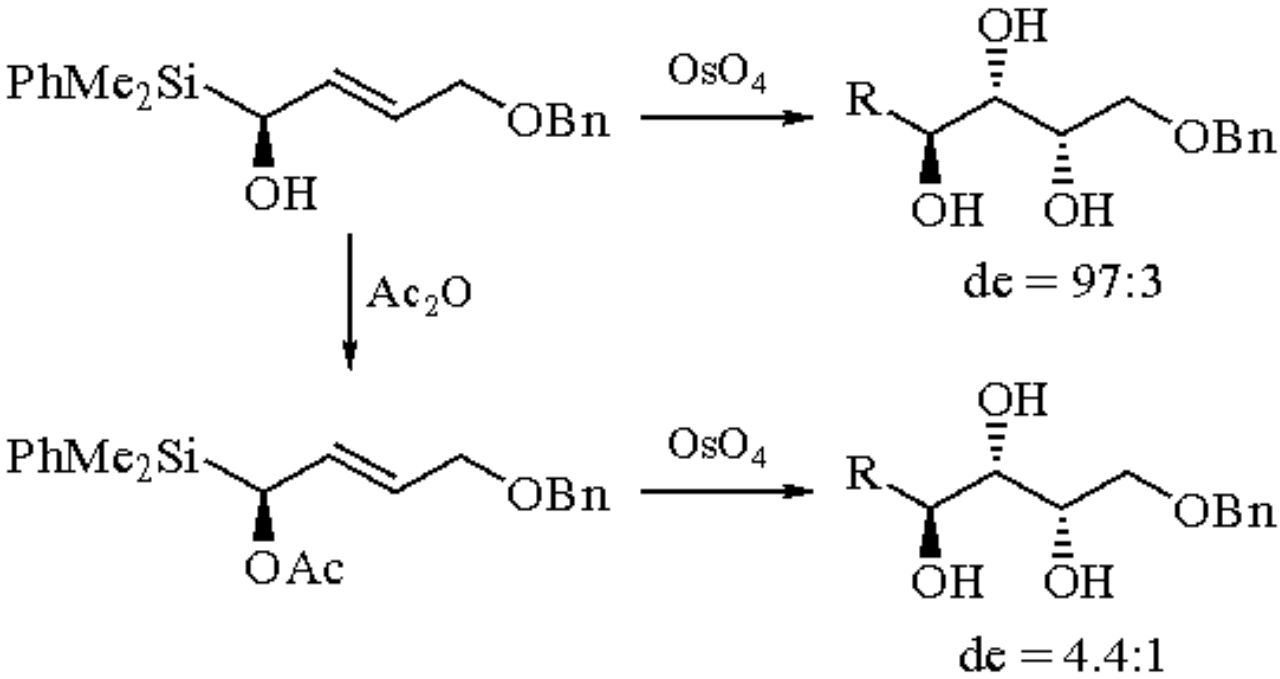

(14)

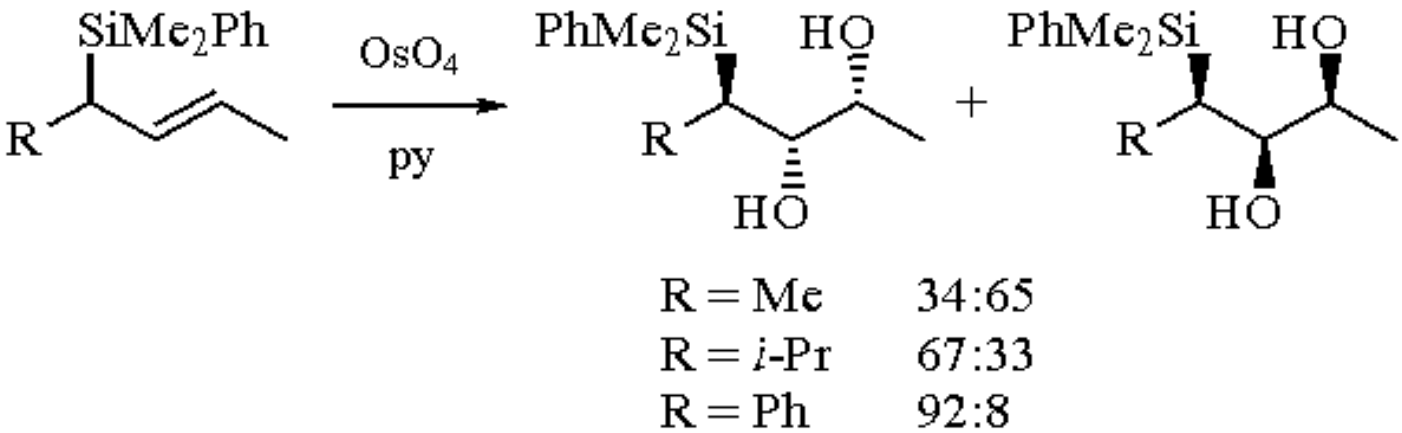

(15)

Sulfoxide groups direct the dihydroxylation of a remote double bond in an acyclic system perhaps by prior complexation of the sulfoxide oxygen with osmium tetroxide (eqs 16 and 17).[16] Chiral sulfoximine-directed diastereoselective osmylation of cycloalkenes has been used for the synthesis of optically pure dihydroxycycloalkanones (eq 18).[17] Nitro groups also direct the osmylation of certain cycloalkenes, resulting in dihydroxylation from the more hindered side of the ring. In contrast, without the nitro group the dihydroxylation proceeds from the less hindered side (eq 19).[18]

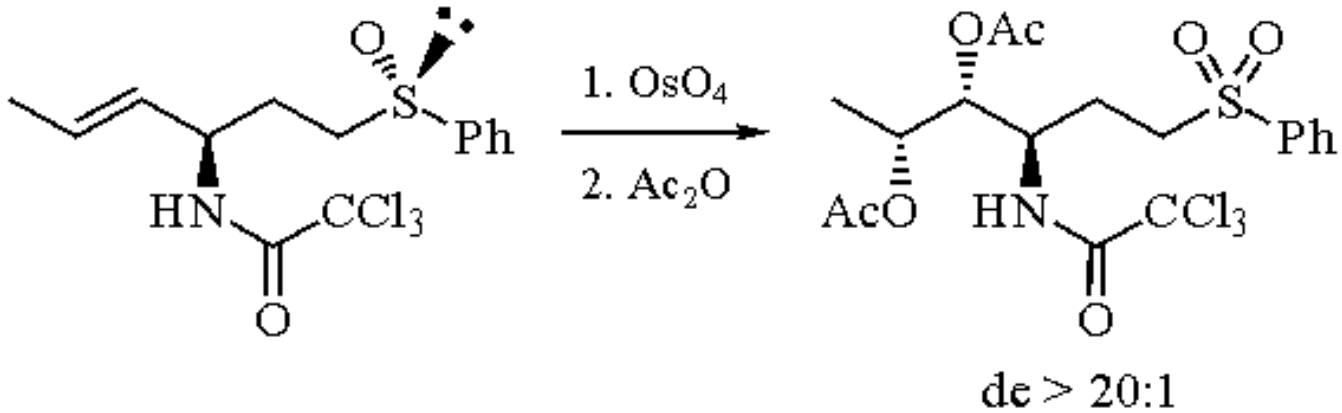

(16)

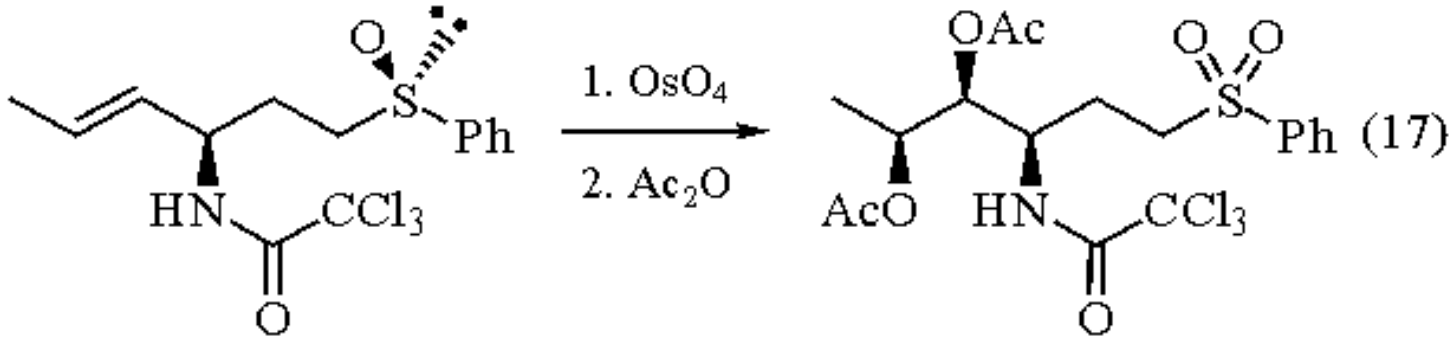
O
S
Ph
HN
CCl3
O
1. OsO4
2. Ac2O
OAc
O O
S
Ph
AcO
HN
CCl3
O

(17)

de > 20:1

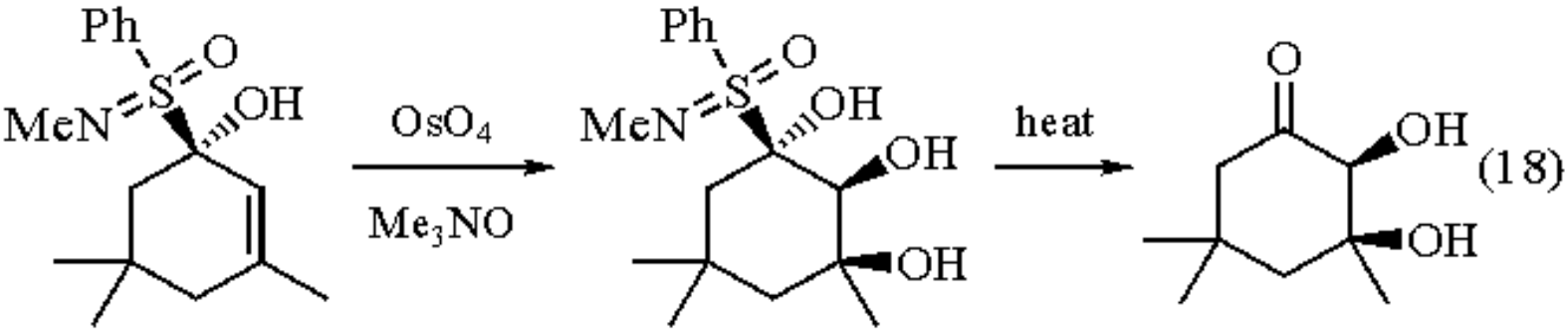
Ph
MeN
S
O
OH
OsO4
Me3NO
Ph
MeN
S
O
OH
OH
OH
heat
O
OH
OH

(18)

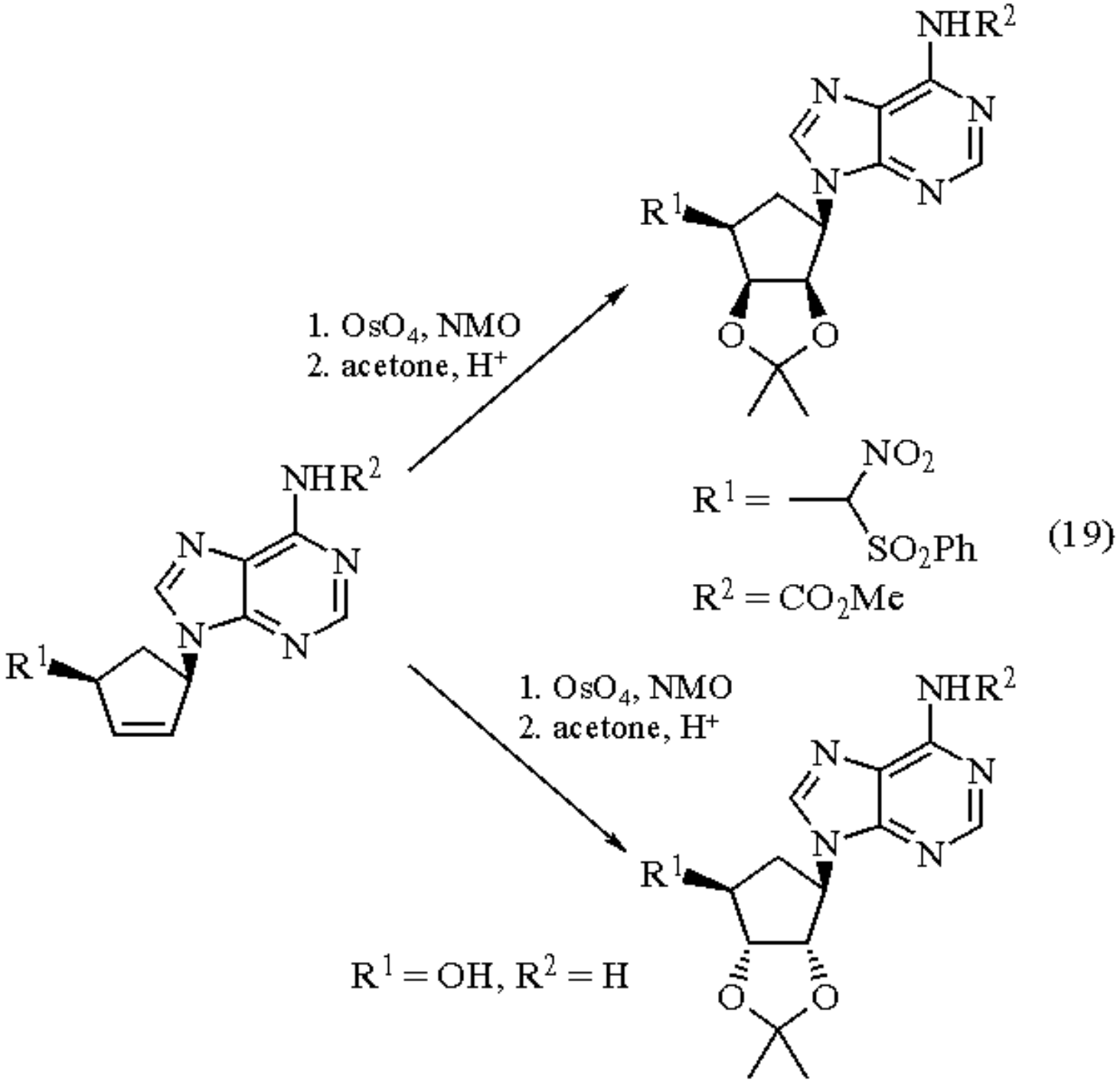

Enantioselective Dihydroxylation.

The acceleration of osmylation by tertiary amines brought about the use of chiral amines as chiral ligands for the asymmetric dihydroxylation (AD).[1] The AD can be classified into two types: (a) noncatalytic reaction, where stoichiometric amounts of ligand and osmium tetroxide are used, and (b) catalytic reaction, where catalytic amounts of ligand and osmium tetroxide are employed in conjunction with stoichiometric amounts of cooxidant. Generally, in the stoichiometric AD systems, chiral chelating diamines are used as chiral auxiliaries with osmium tetroxide for the introduction of asymmetry to the diol products.[1,19] Although high asymmetric inductions have been achieved in these systems, the stoichiometric ADs have limited use in practical organic synthesis because of the cost of both ligand and osmium tetroxide. The discovery of the ligand-accelerated catalysis in AD made the transition from stoichiometric to

catalytic AD possible.[1c,1d,20] In the most effective catalytic system, osmium tetroxide or its precursors and chiral ligands derived from cinchona alkaloids, dihydroquinidine (DHQD), or dihydroquinine (DHQ), are used catalytically in the presence of a stoichiometric amount of cooxidant such as NMO or $K_3Fe(CN)_6$. Besides alkaloid-derived ligands, other types of ligand have been designed and used in the catalytic AD with moderate success.[21] (see also ***Osmium Tetroxide-N-Methylmorpholine N-Oxide*** and ***Osmium Tetroxide-Potassium Ferricyanide***).

Double Diastereoselective Dihydroxylation.

AD of homochiral alkenes gives matched and mismatched diastereoselectivities due to the steric interaction of the chiral osmium tetroxide-ligand complex with the chiral center in the vicinity of the alkene double bond. For example, in the noncatalytic osmylation of the monothioacetal (eq 20),[22] the ratio of (2*S*,3*R*) to (2*R*,3*S*) diastereomers is 2.5:1 with the achiral quinuclidine as ligand, 40:1 with ***Dihydroquinidine Acetate*** (DHQD-OAc) as ligand in the matched case, and 1:16 with ***Dihydroquinine Acetate*** (DHQ-OAc) as ligand in the mismatched case.

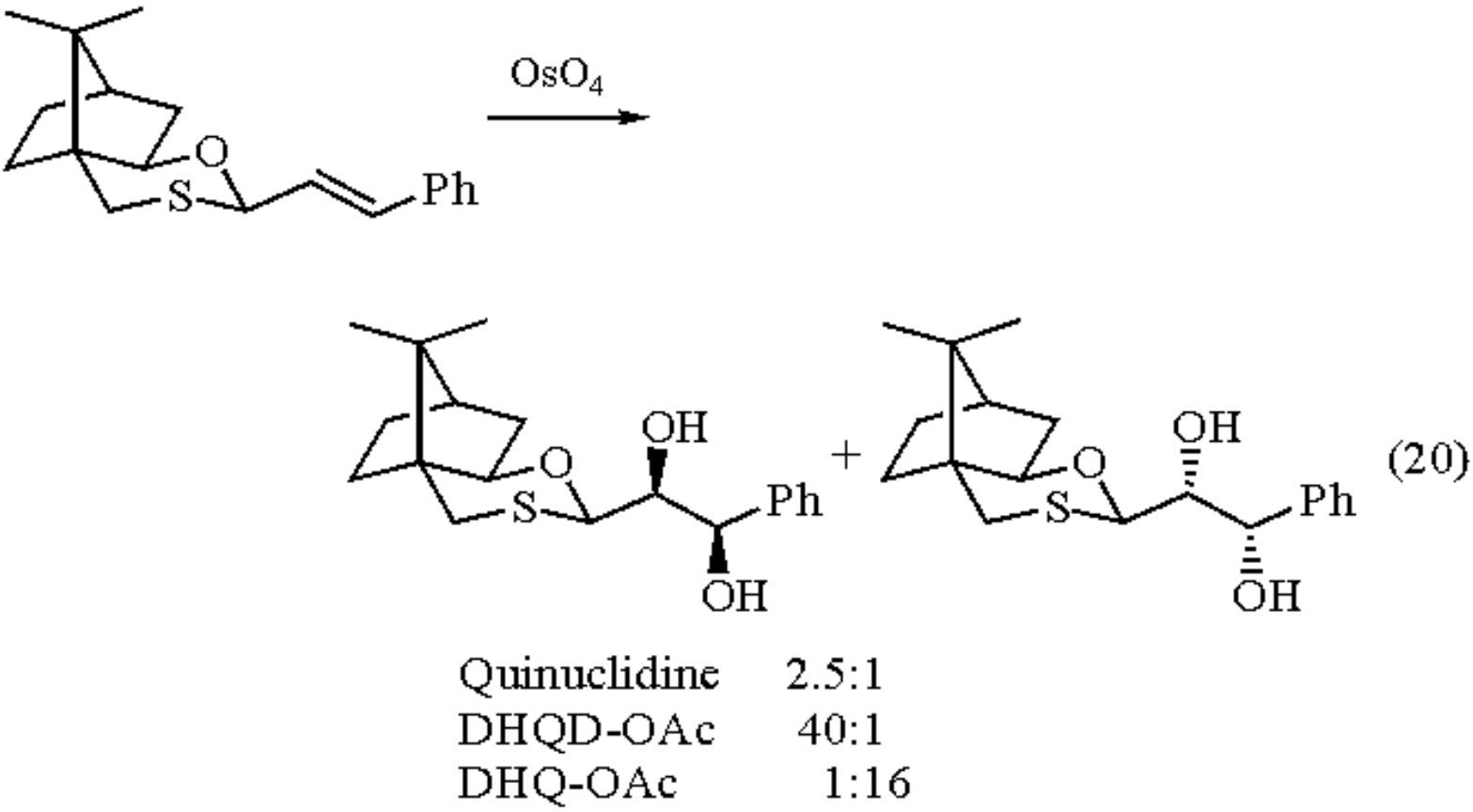

Diastereoselectivities in the catalytic AD with OsO_4-NMO of several α,β-unsaturated uronic acid derivatives are significantly enhanced when the alkenes are matched with the chiral ligands DHQ-CLB (dihydroquinine *p*-chlorobenzoate) and DHQD-CLB (dihydroquinidine *p*-chlorobenzoate) (eq 21).[23] Using the chiral ligands $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL, the double diastereoselective dihydroxylation of a chiral unsaturated ester has been tested using ***Osmium Tetroxide-Potassium Ferricyanide*** (eq 22).[1c] These results show that enhanced diastereoselectivity in the dihydroxylation can be achieved by matching of alkene diastereoselectivity with catalyst enantioselectivity. Double diastereoselective dihydroxylation with a bidentate ligand has also been reported.[24] Kinetic resolutions of racemic alkenes with OsO_4 in the presence of a chiral ligand have been demonstrated.[25] An elegant example is the kinetic resolution of the enantiomers of C_{76}, the smallest chiral fullerene, by asymmetric osmylation in the presence of DHQD-

and DHQ-derived ligands.[26]

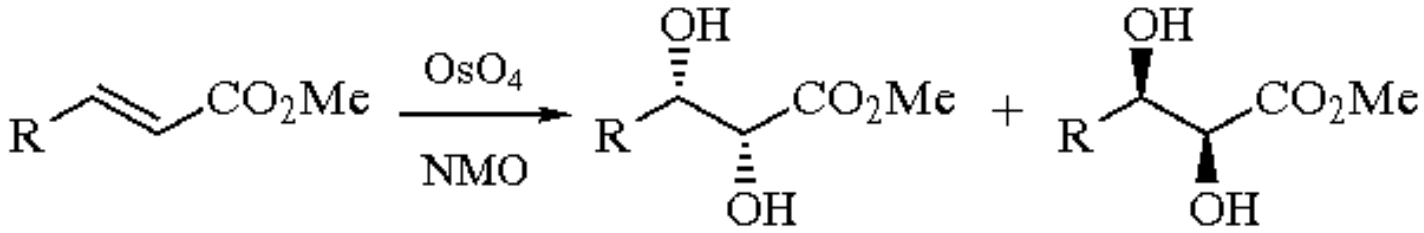

R	Reagent	Ratio
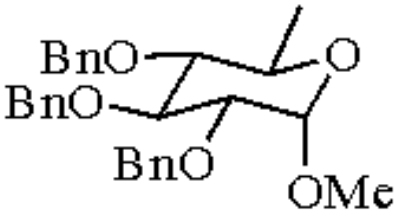	OsO_4 only	10.3:1
	DHQD-CLB	1.3:1
	DHQ-CLB	20.5:1
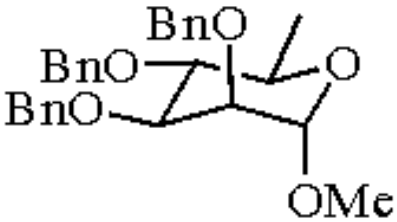	OsO_4 only	7.4:1
	DHQD-CLB	3.4:1
	DHQ-CLB	15.9:1

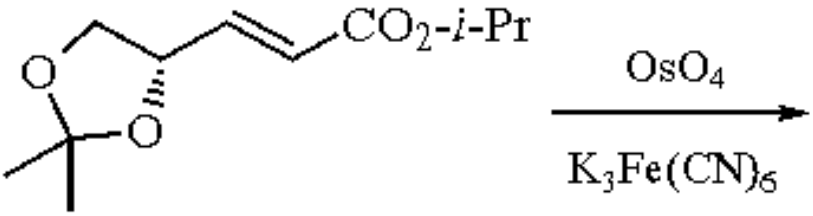

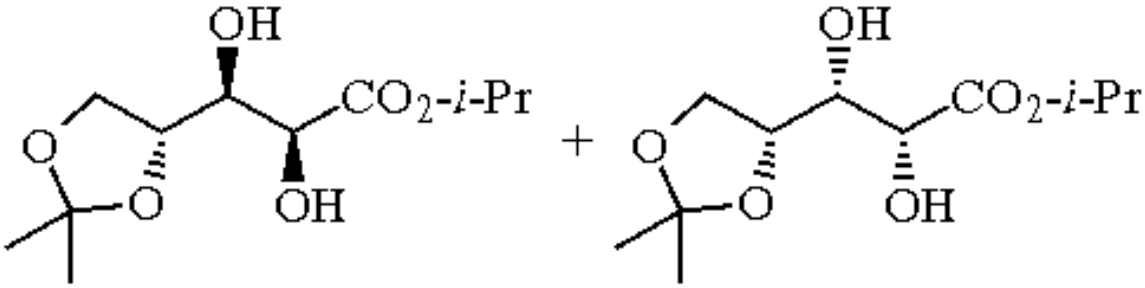

no ligand	2.8:1
$(DHQD)_2$-PHAL	39:1
$(DHQ)_2$-PHAL	1:1.3

Oxyamination of Alkenes and Oxidation of Other

Functional Groups.

Osmium tetroxide catalyzes the vicinal oxyamination of alkenes to give *cis*-vicinal hydroxyamides with ***Chloramine-T*** (eq 23)[27] and alkyl *N*-chloro-*N*-argentocarbamate, generated in situ by the reaction of alkyl *N*-chlorosodiocarbamate (such as ethyl or *t*-butyl *N*-chlorosodiocarbamate) with ***Silver(I) Nitrate*** (eq 24).[28]

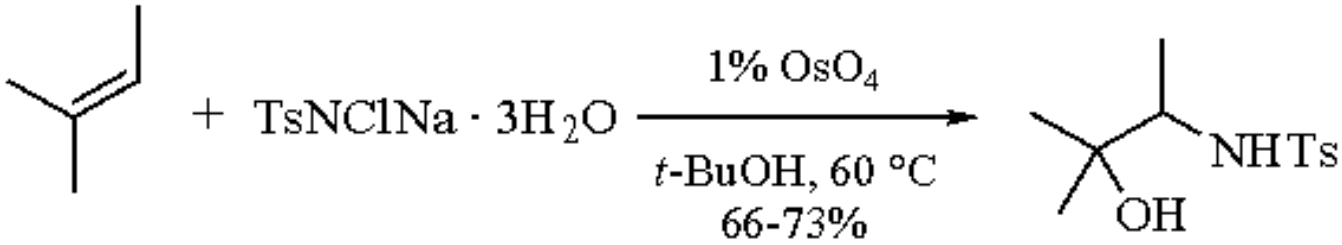

(23)

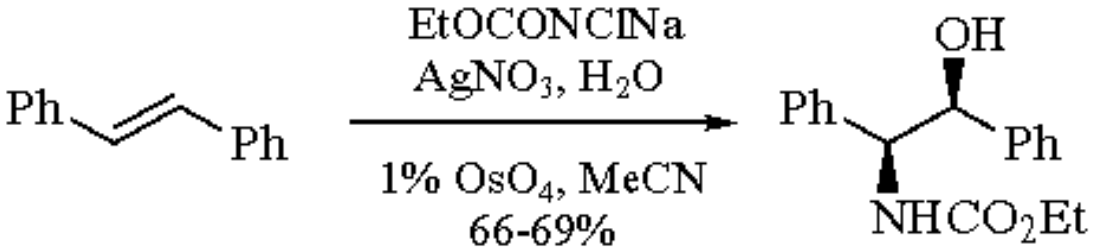

(24)

Since chloramine-T is readily available, the former method offers a practical and direct method for introducing a vicinal hydroxyl group and a tolylsulfonamide to a double bond. While the sulfonamide protecting group is difficult to remove (and undesirable in some cases), the *N*-chloro-*N*-argentocarbamate system provides an alternative method, since the carbamate group can be easily removed to give free amine. This latter system is also more regioselective and reactive towards electron-deficient alkenes such as ***Dimethyl Fumarate*** and (*E*)-stilbene than the procedures based on chloramine-T. In all of these oxyamination reactions, monosubstituted alkenes react more rapidly than di- or trisubstituted alkenes. In the presence of tetraethylammonium acetate, trisubstituted alkenes can be oxyaminated with catalytic OsO_4 and *N*-chloro-*N*-metallocarbamates. So far, attempts to effect catalytic asymmetric oxyamination have not been successful.

Osmium tetroxide also catalyzes the oxidation of organic sulfides to sulfones with NMO or trimethylamine *N*-oxide (see ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***). In contrast, most sulfides are not oxidized with stoichiometric amounts of OsO_4. Oxidations of alkynes and alcohols with OsO_4 without and in the presence of cooxidants have also been reported.[1a,1b] However, these reactions have not found wide synthetic applications because of the availability of other methods.

Related Reagents.

Sodium Periodate-Osmium Tetroxide.

---

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Osmium Tetroxide-*t*-Butyl Hydroperoxide[1]

OsO_4-*t*-BuOOH

(OsO_4)

[20816-12-0] · O_4Os · Osmium Tetroxide-*t*-Butyl Hydroperoxide · (MW 254.20) (TBHP)

[75-91-2] · $C_4H_{10}O_2$ · Osmium Tetroxide-*t*-Butyl Hydroperoxide · (MW 90.14)

(*cis* dihydroxylation of alkenes; osmylation)

Physical Data: for 70% aq TBHP: bp 96 °C; mp -2.8 °C; *d* 0.935 g cm^{-3}. See also ***Osmium Tetroxide***.

Solubility: TBHP: sol acetone, *t*-butyl alcohol.

Form Supplied in: 70% aq TBHP (remaining water) in plastic bottle.

Handling, Storage, and Precautions: TBHP is an eye and skin irritant. Safety goggles and gloves should be worn when handling TBHP solution. Avoid contamination of high-strength TBHP solution with strong acids and transition metal salts known to be good autooxidation catalysts (e.g. Mn, Fe, and Co). Never work with pure TBHP. Do not distill reaction mixtures containing TBHP without prior reduction with reducing agents such as Na_2SO_3. Store 70% aq TBHP in plastic containers below 38 °C but not much below 25 °C. Keep away from bright light and heat sources. See also ***Osmium Tetroxide***.

Dihydroxylation of Alkenes.

Although, in some cases, catalytic *cis* dihydroxylation with OsO_4 using ***Hydrogen Peroxide*** or metal chlorates as cooxidant gives good yields of diols, over-oxidation leading to high yields of ketols or aldehyde products becomes a problem.[1] Thus alkaline ***t-Butyl Hydroperoxide*** was introduced as a superior cooxidant in the catalytic *cis* dihydroxylation. In the OsO_4-TBHP system, 70% aq TBHP is normally used and the reaction is usually performed in *t*-BuOH or acetone when tetraethylammonium acetate (Et_4NOAc) is used as the base (see below). In most cases, only 0.2 mol % OsO_4 is sufficient for completion of the oxidation.[2]

The key to the success of the OsO_4-TBHP system is the presence of a nucleophile in the form of tetraethylammonium hydroxide (Et_4NOH) or Et_4NOAc. The role of the nucleophile is to increase the turnover rate of the catalytic cycle by facilitating the hydrolysis of the osmate ester intermediate. For example, it is possible to dihydroxylate even some tetrasubstituted alkenes using the OsO_4-TBHP-Et_4NOH combination (eq 1).[2a]

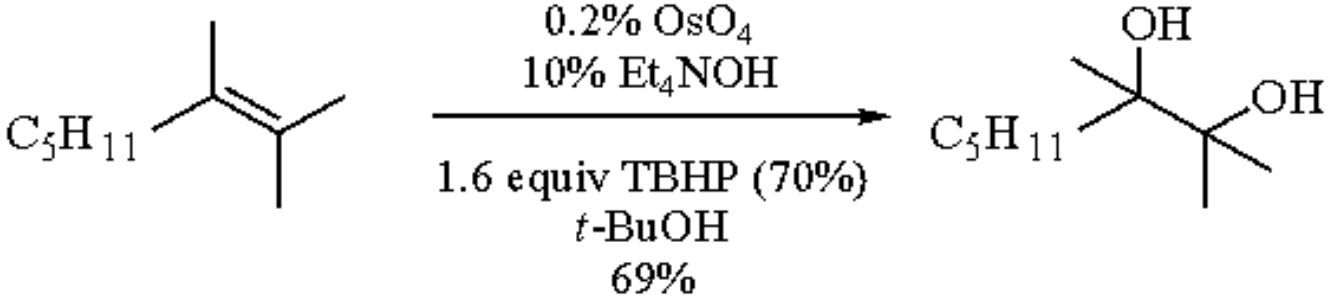

(1)

Tetraethylammonium acetate gives higher yields of diol than Et_4NOH in the *cis* dihydroxylation of base-sensitive alkenes even though, as a weaker base, it fails with tetrasubstituted alkenes (eq 2).[2b] In another example, alkenylphosphonates are dihydroxylated with OsO_4-TBHP in acetone in the presence of Et_4NOAc to give *threo*-dihydroxyalkylphosphonates in >80% yields. In contrast, using OsO_4-H_2O_2, a mixture of diol and ketol is obtained.[3] The OsO_4-TBHP system does not work well in the dihydroxylation of sterically hindered tri- and tetrasubstituted alkenes such as cholesterol (for oxidation of these alkenes, see ***Osmium Tetroxide-Potassium Ferricyanide***).

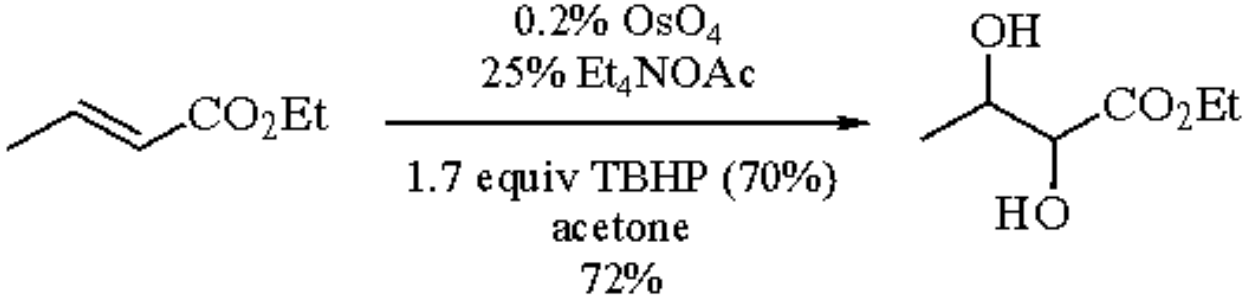

(2)

The OsO_4-TBHP system and OsO_4-NMO system (see ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***) are quite comparable for the dihydroxylation of simple alkenes. The ability to use less OsO_4 and the lower expense of TBHP are the main advantages with the OsO_4-TBHP system. However, no asymmetric catalytic dihydroxylation using the OsO_4-TBHP system has been developed, and probably due to safety concerns there have been few synthetic applications of the OsO_4-TBHP system.[3,4]

Osmium tetroxide-TBHP is also used for the oxidation of 1-trimethylsilylalkynes to produce α-keto esters in about 60% yield (eq 3). It is most likely that the oxidation involves an α-keto acylsilane which then undergoes a Brook-type rearrangement to the final product.[5]

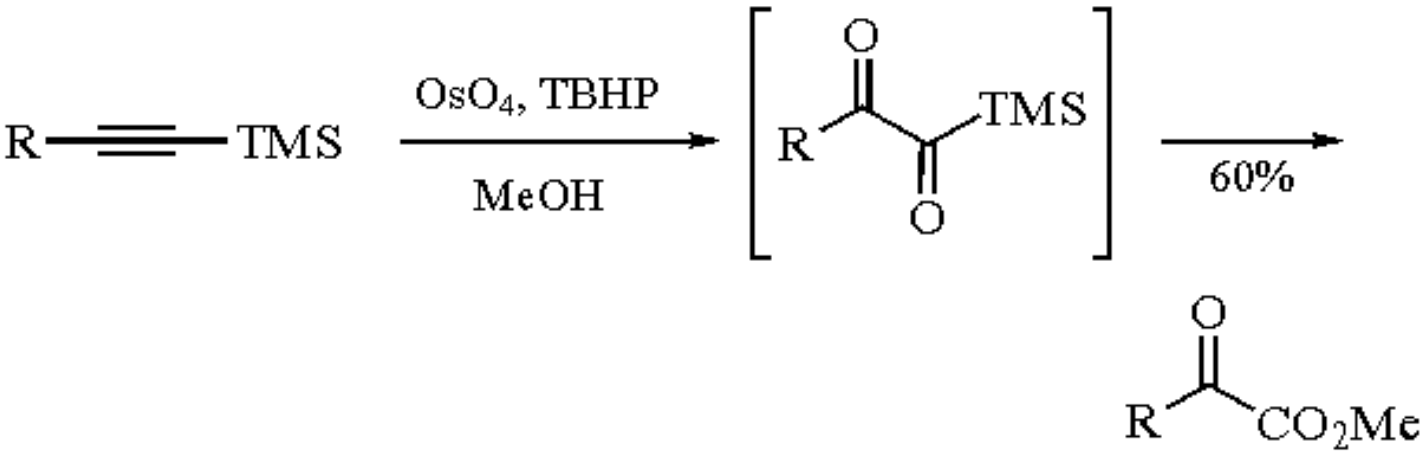

(3)

1. (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. (b) Singh, H. S. In *Organic Synthesis by Oxidation with Metal Compounds*, Mijs, W. J.; De Jonge, C. R. H. I., Eds.; Plenum: New York, 1986; Chapter 12.
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Osmium Tetroxide-*N*-Methylmorpholine *N*-Oxide[1]

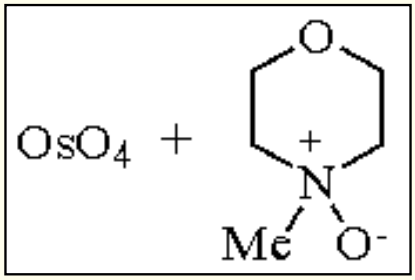

(OsO_4)

[20816-12-0] · O_4Os · Osmium Tetroxide-*N*-Methylmorpholine *N*-Oxide · (MW 254.20) (NMO)

[7529-22-8] · $C_5H_{11}NO_2$ · Osmium Tetroxide-*N*-Methylmorpholine *N*-Oxide · (MW 117.17)

(*cis* dihydroxylation of alkenes; osmylation; asymmetric dihydroxylation of alkenes; oxidations of enol ethers, sulfides)

Physical Data: NMO monohydrate: mp 75-76 °C; 60 wt % aqueous solution: bp 118.5 °C, mp -20 °C, *d* 1.13 g cm^{-3}. See also ***Osmium Tetroxide***.

Solubility: NMO: sol water, acetone, *t*-butyl alcohol, THF.

Form Supplied in: NMO: as monohydrate or 60 wt % aqueous solution.

Handling, Storage, and Precautions: NMO is irritating to eyes, respiratory system, and skin. Store refrigerated. Use in a fume hood. See also ***Osmium Tetroxide***.

Dihydroxylation of Alkenes.

The use of an amine *N*-oxide such as ***N-Methylmorpholine N-Oxide*** as cooxidant for osmium tetroxide-catalyzed *cis* dihydroxylation has become the standard method for the preparation of *cis*-1,2-diols because of the higher yield of diol product and less byproduct formation compared with oxidations carried out with ***Hydrogen Peroxide***, metal chlorates, and ***t-Butyl Hydroperoxide***.[1] Other alkylamine *N*-oxides such as ***Trimethylamine N-Oxide*** have also been used in the catalytic *cis* dihydroxylation. NMO (as monohydrate and 60 wt % aq solution) is commercially available and readily prepared or regenerated by treatment of *N*-methylmorpholine (NMM) with H_2O_2. Normally, aqueous acetone or aqueous *t*-BuOH is used in the catalytic *cis* dihydroxylation with OsO_4-NMO. Workup involves reduction by sodium sulfite or

sodium bisulfite and extraction with ethyl acetate. A detailed procedure for the preparation of NMO (eq 1) and dihydroxylation of cyclohexene with OsO_4-NMO (eq 2) has been published.[2] Functional groups such as alcohols, esters, lactones, carboxylic acids, ketones, and electron-poor alkenes such as α,β-unsaturated ketones are not affected. For unstable or water-soluble diols, the osmylation can be performed in the presence of ***Dihydroxy(phenyl)borane*** and the product is isolated as the borate ester (eq 3).[3]

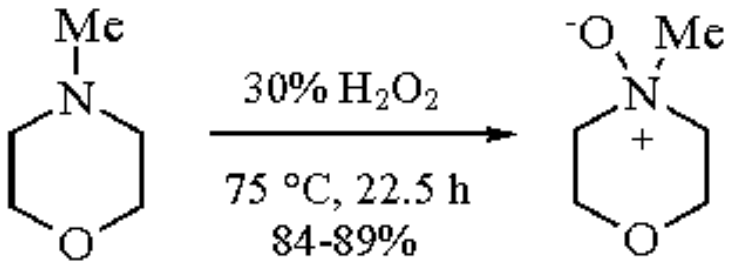

(1)

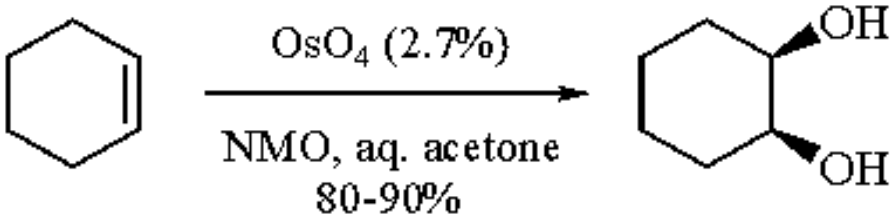

(2)

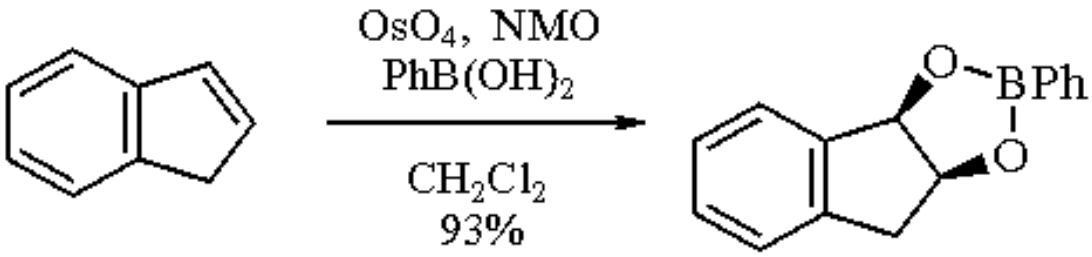

(3)

The OsO_4-NMO system works well with mono- and disubstituted alkenes. Bases such as ***Pyridine*** accelerate the *cis* dihydroxylation in the OsO_4-amine *N*-oxide system, especially for hindered alkenes.[4,5] For example, the α-pinene derivative nopol is hydroxylated in low yield by the ***Osmium Tetroxide-t-Butyl Hydroperoxide*** system; however, it is hydroxylated in 62% yield with OsO_4-Me_3NO in the presence of pyridine in aqueous *t*-BuOH. Other hindered alkenes are also oxidized by this system in 78-93% yield. By switching the solvent to aqueous acetone, the OsO_4-Me_3NO-pyridine system has been used for the *cis* dihydroxylation of an intermediate for the preparation of an HMG-CoA reductase inhibitor on a 20-kg scale with 95% diastereoselectivity in 78% yield (eq 4).[6]

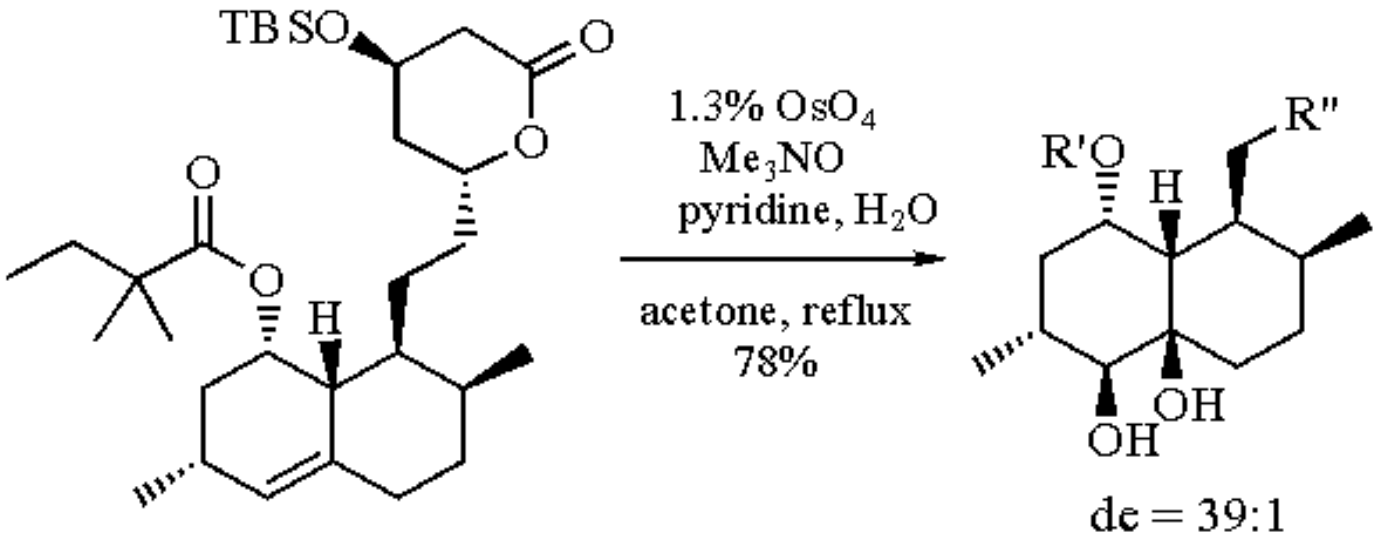

(4)

Diastereoselective Osmylation.

Diastereoselective dihydroxylations with OsO_4-NMO have been extensively studied (see also ***Osmium Tetroxide***). In general, in the osmylation of acyclic alkenes containing an allylic, oxygen-bearing stereocenter, the relative configuration between the pre-existing hydroxyl or alkoxyl group and the adjacent newly formed hydroxyl group in the major diastereomer is *erythro* (*anti*).[7] Taking advantage of the high diastereoselectivity in the osmylation reaction, the OsO_4-NMO or OsO_4-Me_3NO system has been used in many stereoselective organic syntheses. One example is the synthesis of octoses based on the catalytic osmylation of allylic alcohols with OsO_4-NMO (eq 5).[8]

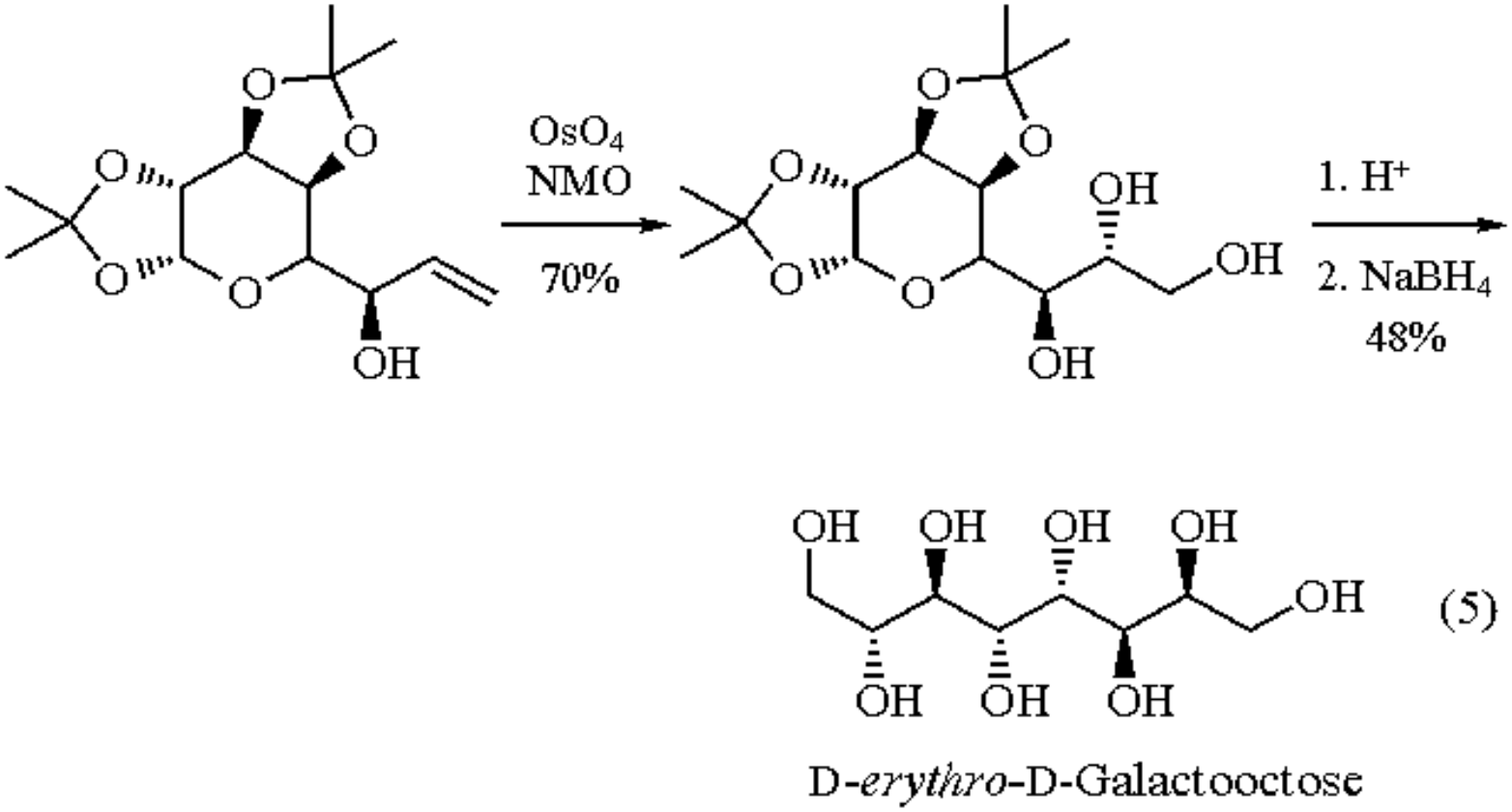

(5)

Opposite selectivity has been observed in the dihydroxylation of a cyclopentene derivative for the synthesis of

carbonucleoside aristeromycin (eq 6).[9] Dihydroxylation of (**1**) with alkaline permanganate proceeds from the less hindered side to give the desired diol, which is then converted to aristeromycin (**2**). However, dihydroxylation of (**1**) with OsO_4-NMO proceeds from the more hindered side to give the *cis*-diol, which is subsequently transformed to *lyxo*-aristeromycin (**3**). This surprising stereoselectivity is attributed to the complexation of osmium tetroxide with the nitro group, resulting in a nitro-directed osmylation from the more hindered side.

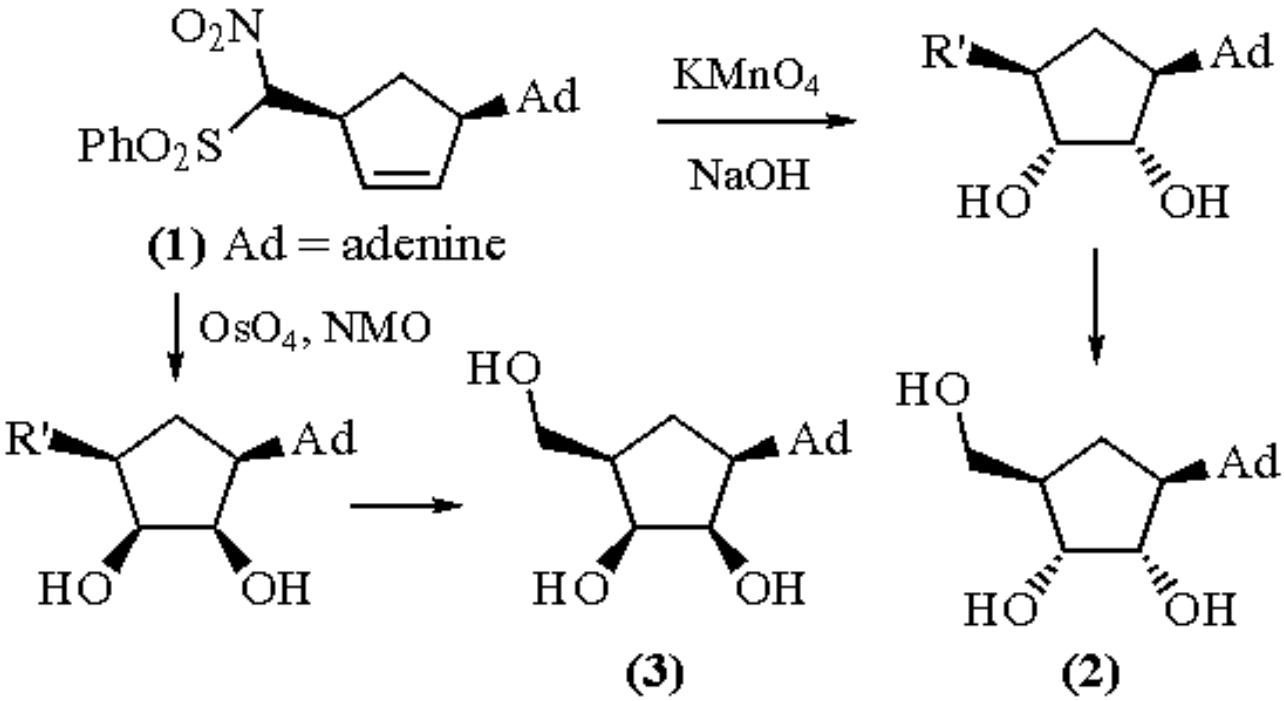

(6)

Asymmetric Dihydroxylation (AD).

AD of alkenes with OsO_4-NMO is usually performed in aqueous acetone in the presence of dihydroquinidine (DHQD) or dihydroquinine (DHQ) derived chiral ligands such as dihydroquinidine *p*-chlorobenzoate (DHQD-CLB) or dihydroquinine *p*-chlorobenzoate (DHQ-CLB) (eq 7) (see also ***Osmium Tetroxide-Potassium Ferricyanide***).[10]

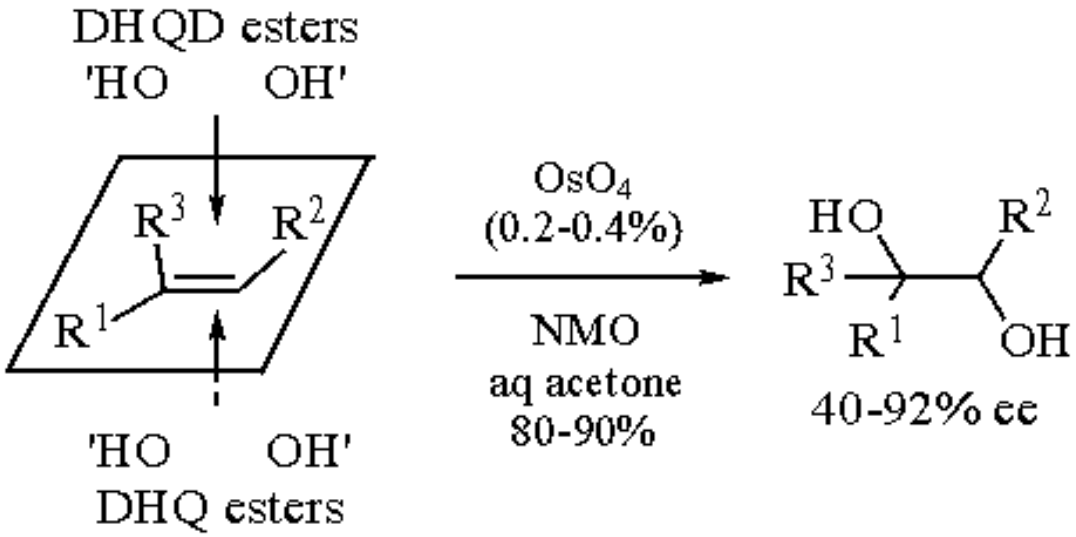

(7)

For example, using OsO_4-NMO in the presence of the DHQD-CLB ligand, *trans*-stilbene is converted to (*R*,*R*)-

stilbenediol in 88% ee, which is further enriched by recrystallization to >99% ee.[11] This method has also been used for the preparation of optically pure (2*S*,3*R*)-methyl 2,3-dihydroxyphenylpropionate, useful for the synthesis of the taxol sidechain.[12] A catalytic cycle of AD with OsO_4-NMO has been proposed.[13] The presence of a second catalytic cycle results in a reduced ee for some alkenes in comparison with the ee obtained under stoichiometric conditions, due to the slow hydrolysis of the intermediate osmate ester. Although addition of base such as tetraethylammonium acetate accelerates the hydrolysis of the osmate ester, thereby diminishing the second cycle, the best solution is to add the alkene slowly to prevent the build-up of the osmate ester. In this manner, many alkenes have been dihydroxylated to the corresponding diols in ee close to those obtained under stoichiometric conditions.[14]

Since the AD with OsO_4-$K_3Fe(CN)_6$ suppresses the second cycle in the aqueous *t*-BuOH solvent system, the OsO_4-NMO system has been largely superseded by the OsO_4-$K_3Fe(CN)_6$ system in catalytic AD. However, by employing the most effective ligands such as $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL and using the slow-addition technique, higher enantioselectivity in the AD with OsO_4-NMO can be expected.

Other Oxidations.

Vinylsilanes are converted to silyl enol ethers with retention of the double bond configuration by dihydroxylation with OsO_4-Me_3NO followed by an anti β-elimination with ***Sodium Hydride*** (eqs 8 and 9).[15] α-Keto acylsilanes are prepared in over 40% overall yields from (*Z*)-vinylsilanes by dihydroxylation with OsO_4-NMO followed by oxidation with ***Dimethyl Sulfoxide-Oxalyl Chloride*** (eq 10).[16]

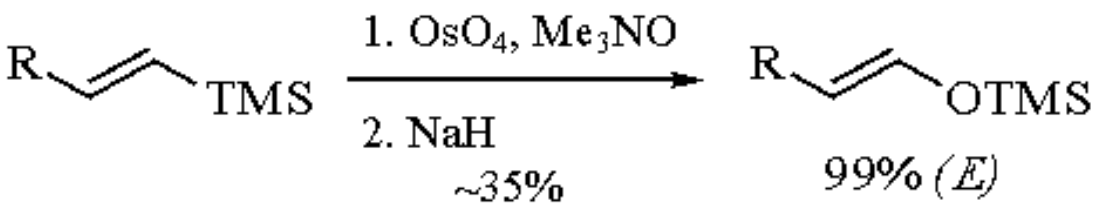

(8)

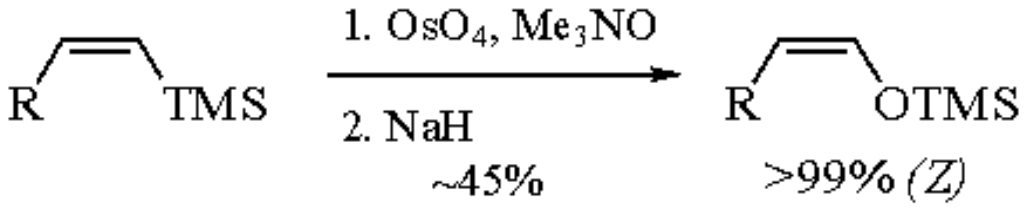

(9)

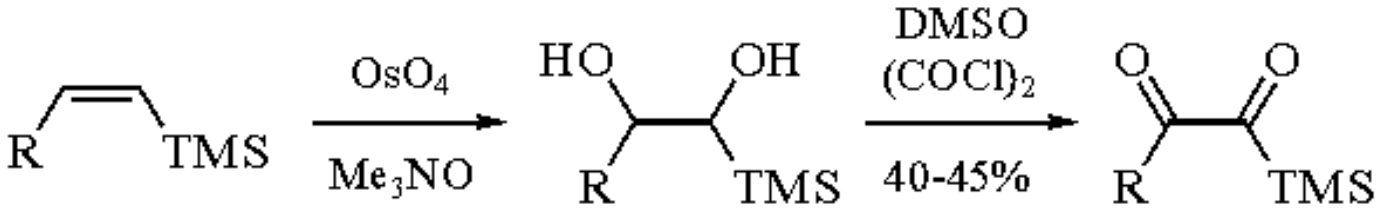

(10)

Enol ethers are transformed to α-hydroxy ketones with OsO_4-NMO (eq 11).[17] In the presence of a chiral ligand, optically active α-hydroxy ketones are obtained (also see ***Osmium Tetroxide-Potassium Ferricyanide***).[14] Although OsO_4 does not normally oxidize organic sulfides, the OsO_4-NMO system can oxidize sulfides to sulfones in good yields (eq 12).[18]

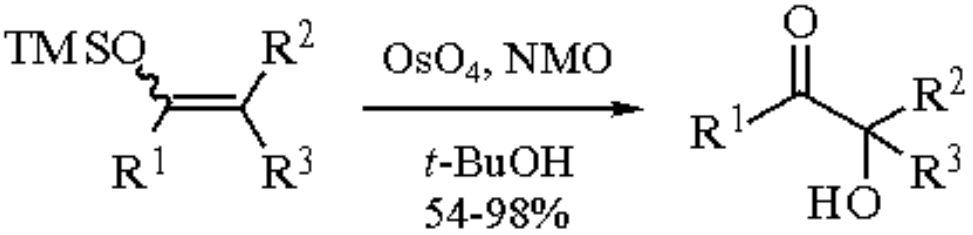

(11)

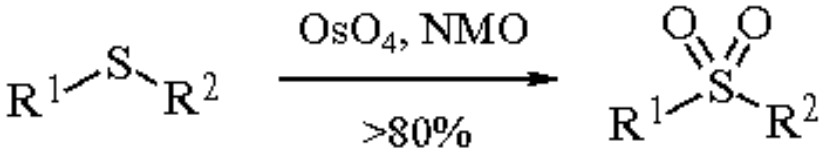

(12)

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Osmium Tetroxide-Potassium Ferricyanide[1]

OsO_4-$K_3Fe(CN)_6$

(OsO_4)

[20816-12-0] · O_4Os · Osmium Tetroxide-Potassium Ferricyanide · (MW 254.20) ($K_3Fe(CN)_6$)

[13746-66-2] · $C_6FeK_3N_6$ · Osmium Tetroxide-Potassium Ferricyanide · (MW 329.27)

(*cis* dihydroxylation of alkenes; asymmetric dihydroxylation of alkenes, enynes, polyenes, and enol ethers)

Physical Data: $K_3Fe(CN)_6$: orange crystals, *d* 1.89 g cm^{-3}. See also ***Osmium Tetroxide***.

Solubility: $K_3Fe(CN)_6$: sol water (0.33 g mL^{-1} at 4 °C, 0.78 g mL^{-1} at 100 °C); slightly sol alcohol; decomposed by acids.

Handling, Storage, and Precautions: $K_3Fe(CN)_6$: wear gloves and goggles. The aqueous solution decomposes slowly on standing. Store away from light. This reagent system should be used in a fume hood. See also ***Osmium Tetroxide***.

Dihydroxylation of Alkenes.

Alkali metal ferricyanides, notably ***Potassium Ferricyanide***, have been used as cooxidants in the studies of OsO_4-catalyzed oxidations of lower molecular weight organic compounds.[1a] For example, propene is dihydroxylated with OsO_4-$K_3Fe(CN)_6$ in aqueous alkaline solutions to propylene glycol in almost quantitative yield. Potassium ferricyanide and alkali consumed in the reaction have been regenerated electrochemically, resulting in an overall reaction with consumption of alkene, water, and electricity to produce the glycol (eq 1).[2]

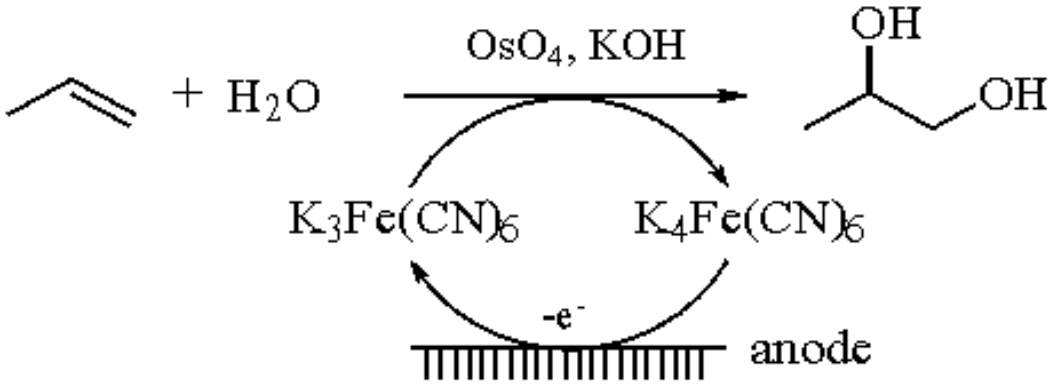

(1)

Recently, it has been found that water-insoluble alkenes can be dihydroxylated with the OsO_4-$K_3Fe(CN)_6$ system in an alkaline aqueous *t*-BuOH solution to give 1,2-diols in good yields.[3] Addition of tertiary amines such as quinuclidine or ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO) accelerates the dihydroxylation with OsO_4-$K_3Fe(CN)_6$, resulting in an increased yield of diol product. For example, in the presence of DABCO the yield of dihydroxylation of cholesterol increases from 19% to 74%. In this case it appears that DABCO or quinuclidine promotes the hydrolysis of the stable osmate ester intermediate.

The use of $K_3Fe(CN)_6$ as a cooxidant for the osmium-catalyzed asymmetric dihydroxylation (AD) in place of ***N-Methylmorpholine N-Oxide*** results in across-the-board increases in the level of asymmetric induction for all classes of alkenes.[1b,1c] The enhanced enantioselectivity is due to the complete suppression of the second cycle observed in the OsO_4-NMO system (see ***Osmium Tetroxide-N-Methylmorpholine N-Oxide***) and the use of the *t*-BuOH-water solvent system, which under the reaction conditions forms a biphasic mixture.[4] Both osmium(III) chloride hydrate and potassium osmate(VI) dihydrate [$K_2OsO_4.2H_2O$] have been used in place of osmium tetroxide. For safety and convenience in handling reasons, potassium osmate is used in the standard set of conditions for the catalytic AD with OsO_4-$K_3Fe(CN)_6$ and in the commercially available AD mixes.[5] Many ligands derived from dihydroquinidine (DHQD) and dihydroquinine (DHQ) have been developed for catalytic AD.[1b,6] 1,4-Bis(dihydroquinidine) phthalazine ether [$(DHQD)_2$-PHAL] and its diastereomer 1,4-bis(dihydroquinine) phthalazine ether [$(DHQ)_2$-PHAL] have shown significant improvements in enantioselectivity over other ligands for the AD of most alkenes. Polymer-supported DHQD and DHQ derived ligands have been examined for the purpose of recycling of the catalyst.[7]

For most alkenes, 0.2 mol % of osmium and 1.0 mol % of ligand are sufficient to provide a satisfactory rate of reaction even at 0 °C using 3.0 equiv each of $K_3Fe(CN)_6$ and K_2CO_3. Ready-made mixture containing the four solid components named AD-mix-β (containing $(DHQD)_2$-PHAL) and AD-mix-α (containing $(DHQ)_2$-PHAL) are currently commercially available. Increasing the amount of osmium and ligand and the reaction temperature up to 25 °C can accelerate the AD of more substituted and sterically hindered alkenes.[8] In addition, for 1,2-disubstituted, tri- and tetrasubstituted alkenes, addition of up to 3 equiv of sulfonamide (usually methanesulfonamide) enhances the overall rate of the AD by accelerating the hydrolysis of the osmate ester intermediate.[5] A mnemonic scheme showing alkene orientation and face selectivity is illustrated in eq 2. However, this mnemonic should be considered as only suggestive of new diol configurations due to the large structural diversity of alkenes.

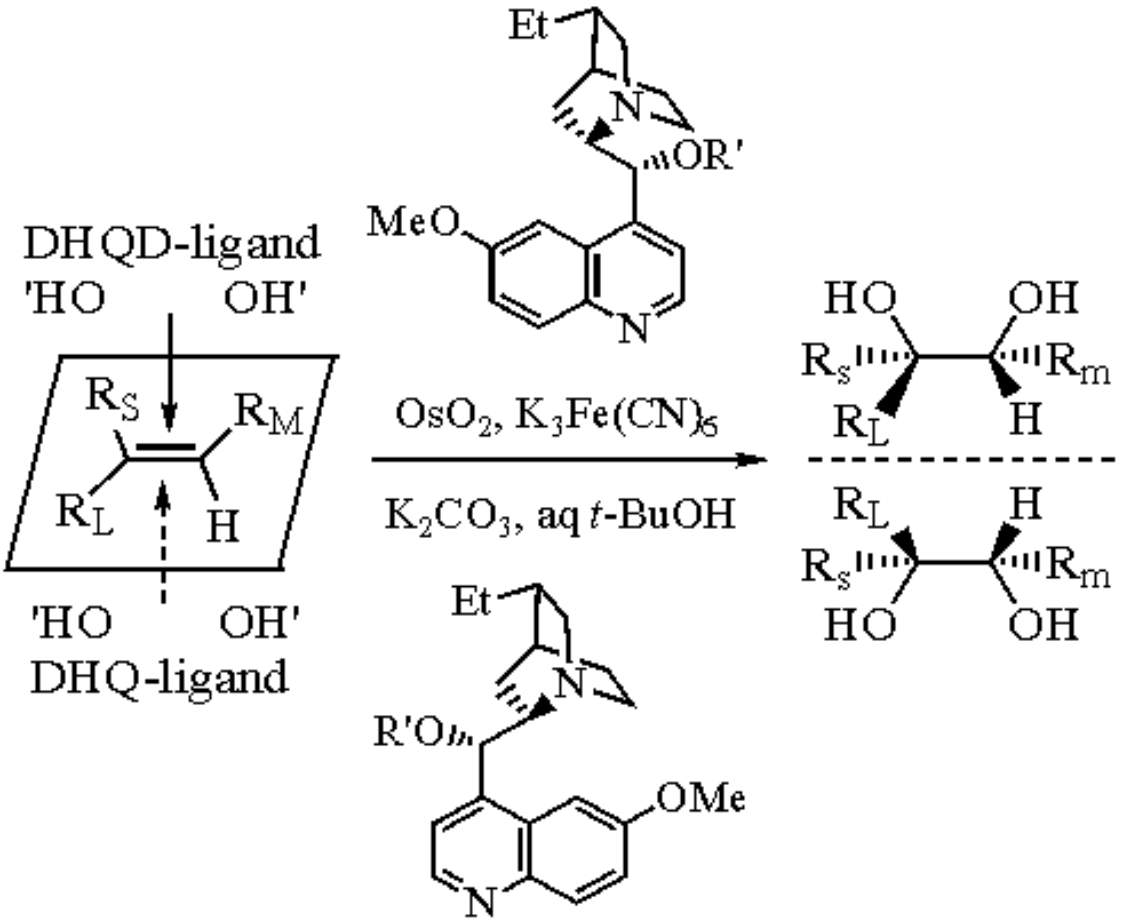

(2)

Table 1 summarizes results of the AD of six types of alkenes using the OsO_4-$K_3Fe(CN)_6$ system with the preferred DHQD- or DHQ-derived ligands. In general, slightly lower ees are observed in the AD with DHQ-derived ligands than with DHQD-derived ligands.

Table 1 Results of AD of Six Types of Alkenes with Preferred Ligands

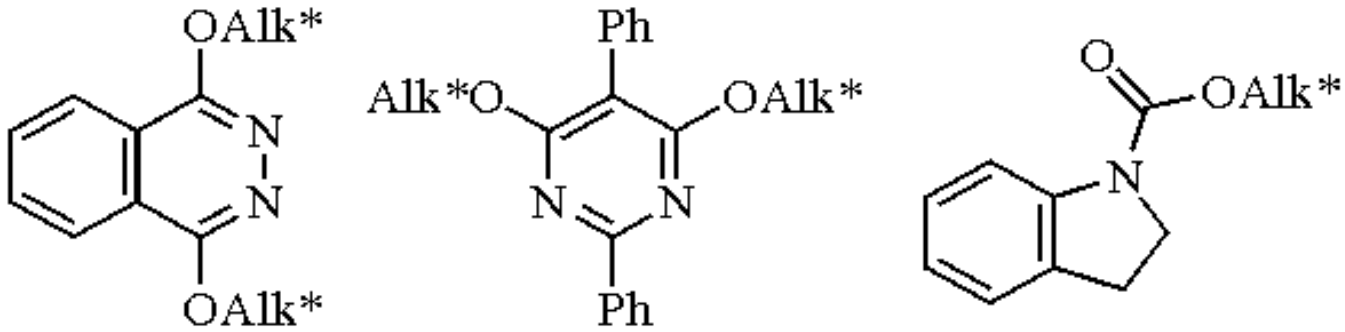

PHAL class	PYR class	IND class		
Alkene type	Alkene example	Preferred ligand	ee range (%)	Ref.

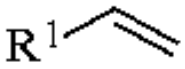	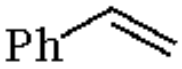 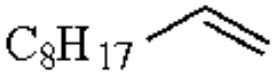	PHAL, PYR	80-97	5, 8
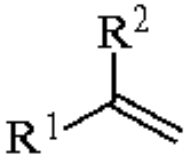	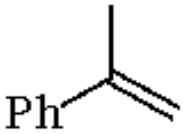	PHAL	70-97	5
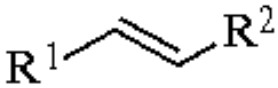		PHAL	90-99.5	5
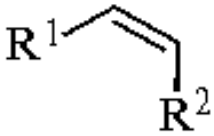	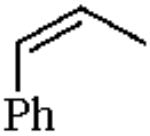	IND	20-80	5
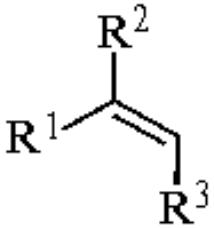	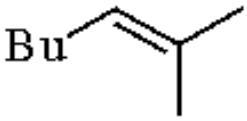	PHAL	90-99	5
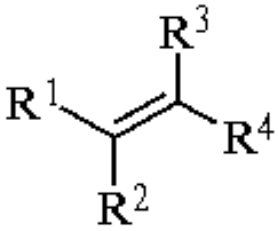	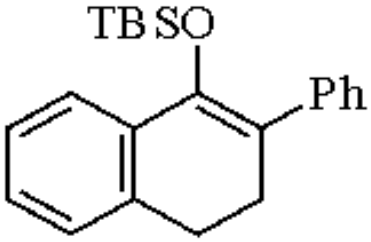	PYR, PHAL	20-97	5, 8

Besides simple alkenes, enol ethers can be oxidized enantioselectively to give optically active α-hydroxy ketones (eq 3).[10]

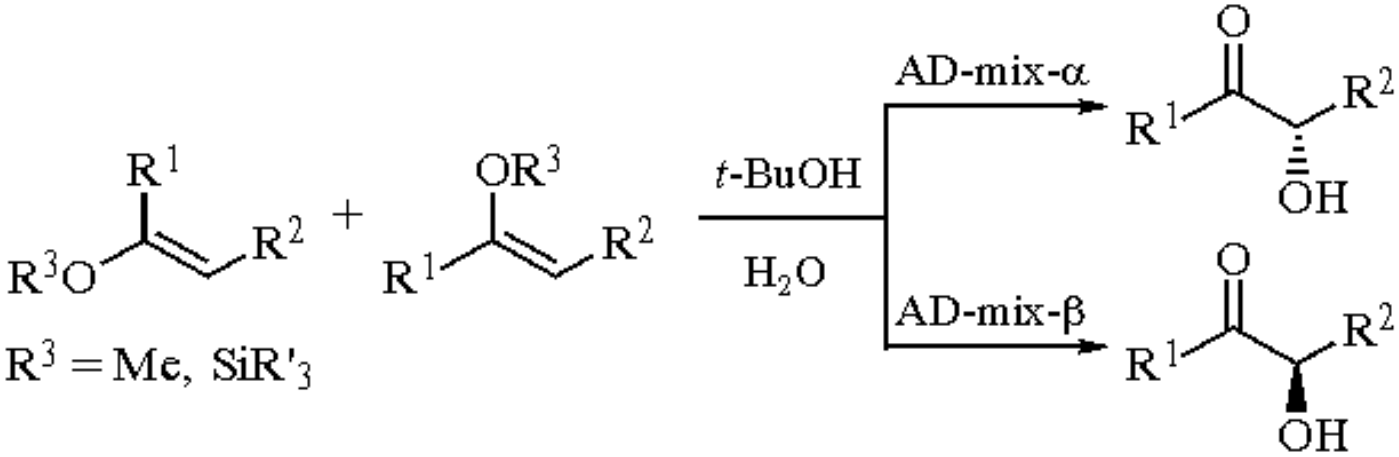

(3)

Enynes are dihydroxylated selectively at only the double bond[11] and dienes at the more substituted and/or more electron-rich double bond.[12] Polyenes such as squalene have been enantioselectively perhydroxylated with OsO_4-$K_3Fe(CN)_6$ in the presence of $(DHQD)_2$-PHAL or $(DHQ)_2$-PHAL.[13] Under buffered condition (in the presence of $NaHCO_3$), even α,β-unsaturated ketones can be dihydroxylated to the corresponding optically active α,β-dihydroxy ketones.[14] Kinetic resolution of racemic alkenes have also been reported.[15] Diastereoselective dihydroxylation of optically pure alkenes with OsO_4-$K_3Fe(CN)_6$ in the presence of DHQD- or DHQ-derived ligand results in matched and mis-matched selectivities (also see ***Osmium Tetroxide***). Synthetic transformations of optically pure 1,2-diols to other useful intermediates such as chiral cyclic sulfites, cyclic sulfates,[16] and epoxides[17] have been developed (eq 4). These new synthetic transformations and the catalytic AD are being increasingly used in the synthesis of optically pure natural products, pharmaceuticals, and other interesting compounds.[1,18]

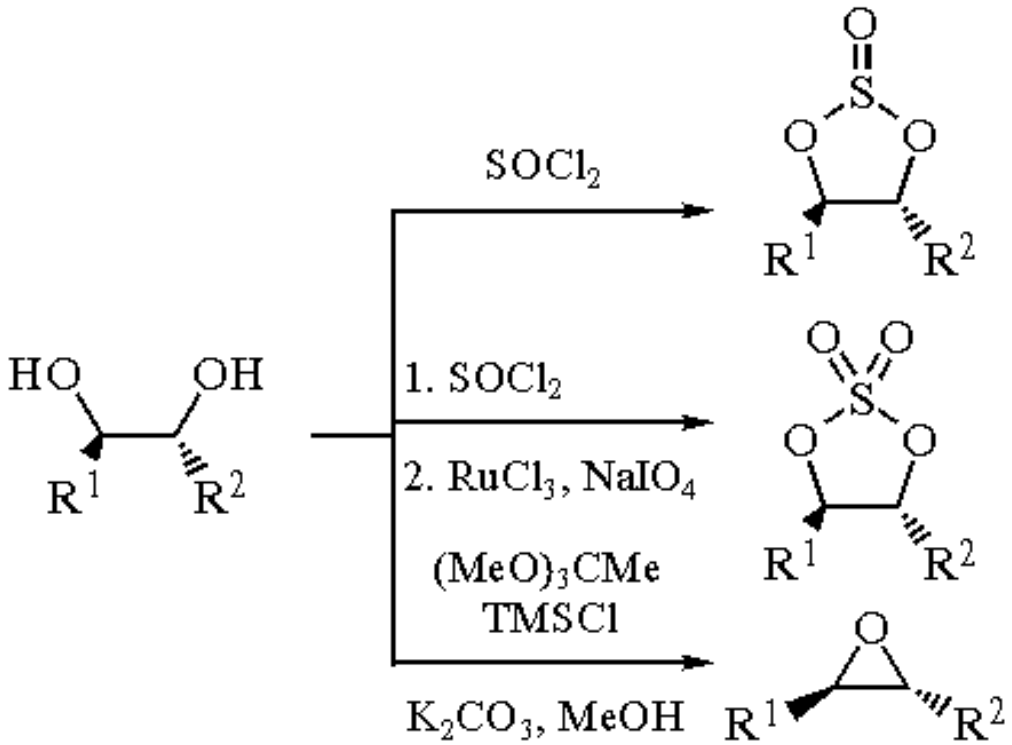

(4)

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1-Oxa-2-azaspiro[2.5]octane[1]

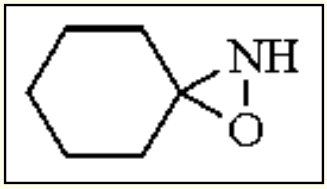

[185-80-8] · $C_6H_{11}NO$ · 1-Oxa-2-azaspiro[2.5]octane · (MW 113.18)

(selective electrophilic aminating agent for N-, S-, C-, and O-nucleophiles;[1] transfers either the NH function or the entire cyclohexylideneamino unit)

Alternate Name: 3,3-pentamethyleneoxaziridine.

Solubility: sol toluene, ether, chloroform, and other organic solvents; insol H_2O.

Form Supplied in: freshly prepared solutions in organic solvents, preferably toluene, 0.2-0.5 M; main impurities are excess cyclohexanone from the preparation and *N*-chlorocyclohexylimine (5-10%), both in most applications without influence.

Preparative Methods: a mixture containing 125 mL of toluene, 25 mL of cyclohexanone, 25 mL of 2 N NH_3 soln, and 100 g of finely crushed ice is shaken in a separatory funnel with 50 mmol NaOCl soln. (e.g. 31 mL of a 1.6 M soln.) for 30 s. The upper layer is washed with 0.1 N HCl and can be used directly for amination reactions or it can be dried with Na_2SO_4 or by removing of some solvent in vacuo.[2] Solutions having less remaining cyclohexanone can be obtained from the reaction of hydroxylamine-*O*-sulfonic acid with cyclohexanone and NaOH.[3]

Analysis of Reagent Purity: redox titration:[2] a 2 mL aliquot of the reagent soln. is added to 12 mL of acetic acid and 3 drops of a concentrated solution of KI in H_2O; titration of the liberated iodine by 0.2 N thiosulfate soln. until decolorization (concn. in mol L^{-1} = 0.05 mL of $S_2O_3^{2-}$ soln.).

Handling, Storage, and Precautions: solutions of the reagent are stable at 0-20 °C for 1-6 weeks without loss of more than 15% of the initial activity. Appropriate precautions should be taken for some evolution of gases during storage. With 0.2-0.4 M solutions, no problems have been encountered on a 0.1-2000 L scale. Use in a fume hood. *Caution*: no experience with solutions having reagent concentration of more than 0.5 mol L^{-1} has been acquired in the authors' laboratory or is reported in the literature.

N-Amination.

Secondary amines are aminated by oxaziridine (**1**) at 20-30 °C within a few minutes, yielding cyclohexanone hydrazones which can be hydrolyzed to the free hydrazines or used for further transformations (eq 1),[1] e.g. morpholine,[2] tetrahydroisoquinolines.[4] With 2,4-dibromo-6-(*trans*-4-hydroxycyclohexylaminomethyl)aniline, the amination takes place at the aliphatic amino group exclusively.[1]

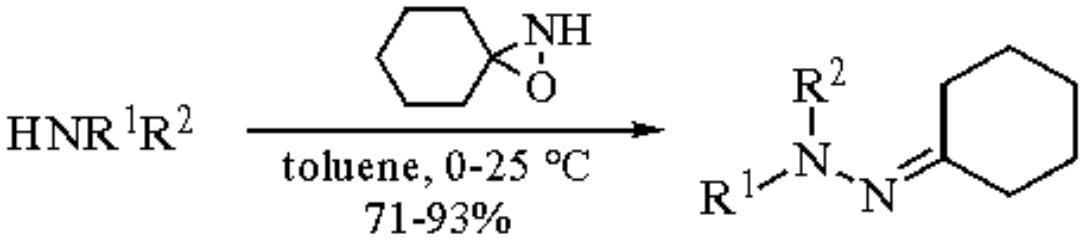

(1)

Primary aliphatic amines are not aminated selectively or, if deactivated, they need higher temperatures (80-100 °C), e.g. amino acids,[1] peptides,[5] and 2-aminophosphonates.[6] Aromatic and heteroaromatic amines can be aminated after acetylation and (partial) deprotonation (***1,4-Diazabicyclo[2.2.2]octane***). Thus even 3-hydrazinopyridines can be obtained, whereas other amination reagents exclusively attack the ring nitrogen.[7]

S-Amination.

All (potential) thiols react exothermically with the reagent. Hydrolysis of the primary intermediate yields cyclohexanone and sulfenamides (eq 2). Elimination of water yields cyclohexanone thioximes (eq 3). Depending on the nature of the other functional groups in the starting material, the sulfenamides or thioximes can be stable or undergo further reactions to give a variety of heterocyclic products. A third possibility to be considered is the formation of sulfur-free final products.[1]

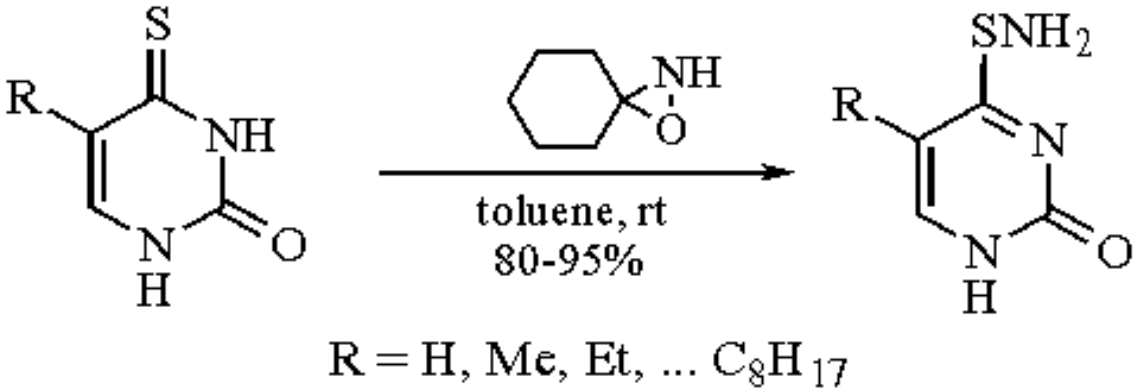

(2)

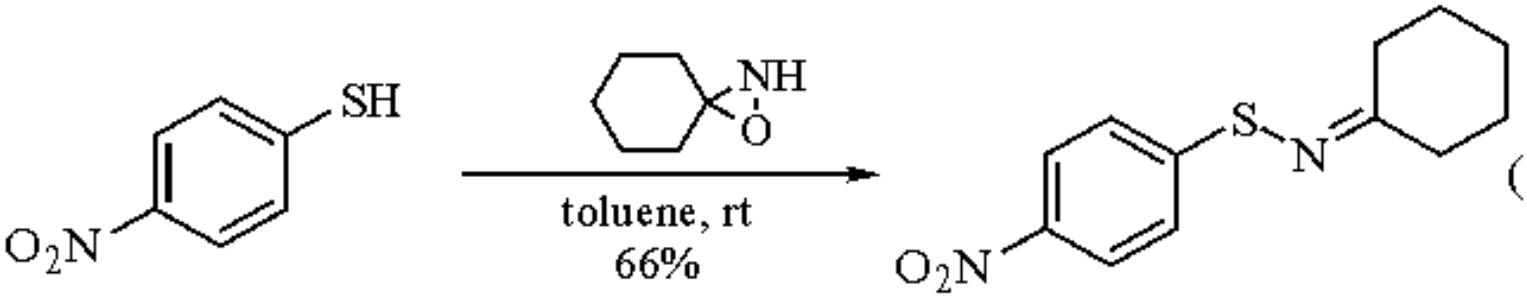

(3)

For example, the following heterocyclic compounds can be prepared using oxaziridine (**1**):

- 1)via cyclohexanone thioximes: 1,2,4-thiadiazolidines,[9] 5a-amino-5a,6,7,8,9,9a-hexahydro-4*H*-pyrimido[2,1-*b*]benzothiazoles,[10] 2-(2-hydroxycyclohexenethio)benzothiazoles and -benzoxazoles;[10]
- 2)via sulfenamides: 1,2-thiazoles,[1] 1,2-thiazolones,[1] 1,2,4-thiadiazoles,[8] and benzothiazoles;[1]
- 3)via desulfurization reactions: 2-amino-5-substituted 1,2,4-oxadiazoles,[1] triazino[3,4-*a*]azepines,[1] and nitriles (from thioamides).[1]

C-Amination.

Hydrophilic cyanoacetic amides are converted into α-amino malondiamides by (**1**) in toluene/2 N NaOH (eq 4). Less hydrophilic cyanoacetic amides yield cyclic spirocyclohexane glycine amides with DABCO as base. Cyanoacetic amides, monosubstituted at the N-function, can give ring transformed amination products. Double amination often predominates, giving stable α,α-diamino acid derivatives (eq 5).[11] All reactions are finished after few minutes at 0-20 °C, with complete hydration of the nitrile group. In some cases only 5 mol % of the base DABCO is necessary.[11]

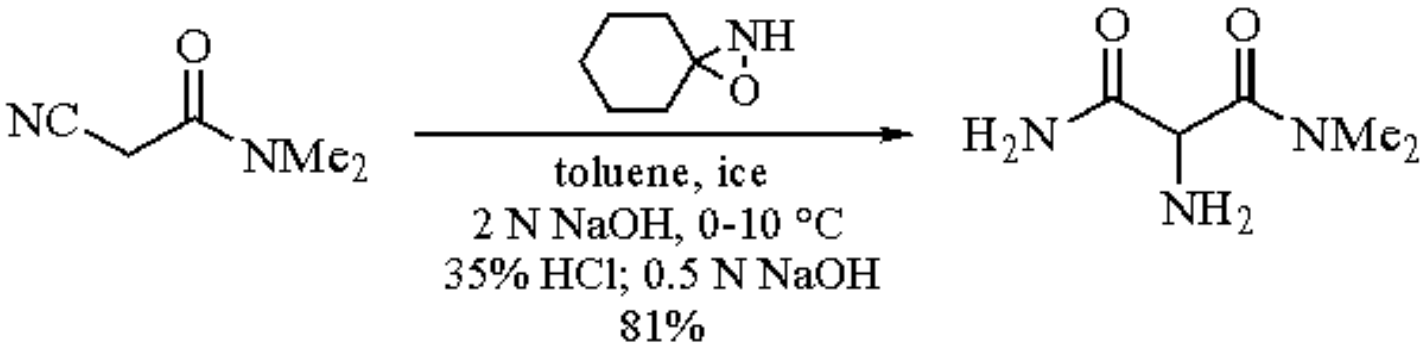

(4)

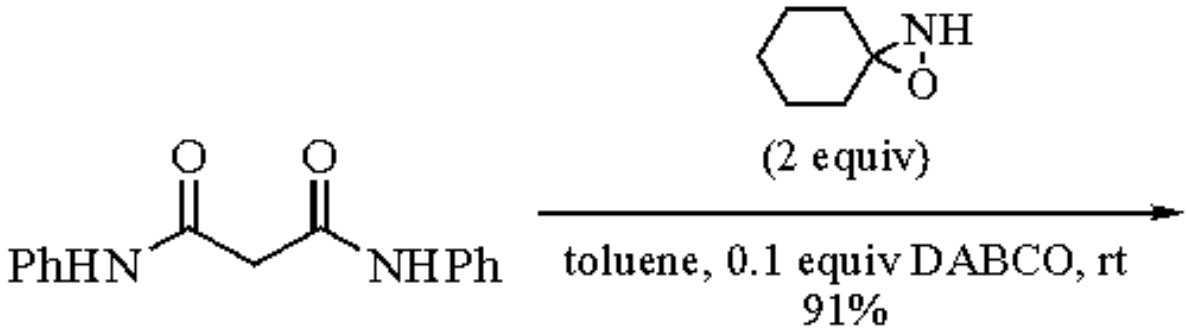

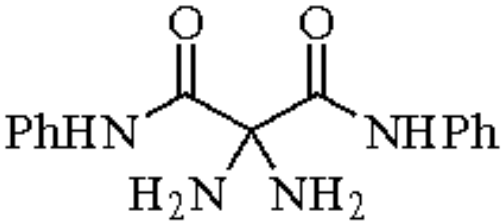

(5)

Many other CH acidic compounds can be aminated by oxaziridine (**1**) if the generation of the carbanion can be realized under mild conditions.[11] However, nitrobenzyl aryl sulfones are converted into aryl aldehydes or ketones.[12] In contrast to other oxaziridines no direct hydroxylation reactions have been observed with (**1**).

Aziridination of Alkenes.

Aziridines are obtained in 20-68% yield from substituted styrenes, acrylonitrile (41% 2-cyanoaziridine), and norbornene (20% *exo*-product). Cyclohexene gives the corresponding *N*-aminoaziridine by successive *C*- and *N*-amination.[13]

O-Amination.

Possible conversions, e.g. water to hydroxylamine, methanol to cyclohexanone oxime *O*-methyl ether (40%),[14] are not of preparative value.

Related Reagents.

(Camphorylsulfonyl)oxaziridine; ***Chloramine***; ***Hydroxylamine-O-sulfonic Acid***; ***O-Methylhydroxylamine***; ***(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine***.

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Oxalic Acid

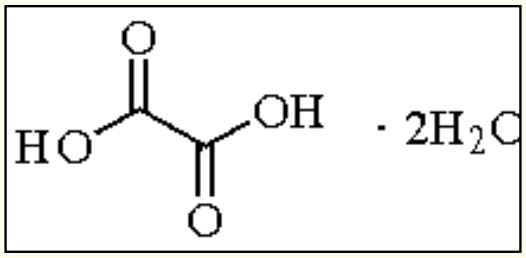

(free acid)

[144-62-7] · $C_2H_2O_4$ · Oxalic Acid · (MW 90.04) (dihydrate)

[6153-56-6] · $C_2H_6O_6$ · Oxalic Acid · (MW 126.08)

(mild Brønsted acid; chelating[5] and quenching[23-25] agent; catalyst for hydrolysis,[6-9] protection-deprotection,[10-21] dehydration-elimination,[28-33] decarboxylation,[34] and condensation[35-40] reactions)

Alternate Name: ethanedioic acid.

Physical Data: anhydrous acid: hygroscopic, exists in rhombic and monoclinic forms; mp (rhombic) 189.5 °C; pK_{a1}, 1.46; pK_{a2}, 4.40. Anhydrous acid has substantial vapor pressure; begins to sublime at slightly below 100 °C; sublimes rapidly at 125 °C. Dihydrate: monoclinic crystals, mp 101 °C.[1]

Solubility: anhydrous acid: v sol H_2O, alcohol; sl sol ether; insol benzene.

Purification: crystallized from distilled water;[43] see below for drying.

Form Supplied in: readily available as the dihydrate; anhydrous form also available.

Analysis of Reagent Purity: by titration of reductive capacity; impurity tests known.[42]

Preparative Methods: preparation of the anhydrous acid may be accomplished by refluxing the dihydrate in carbon tetrachloride with removal of water;[2] alternatively, the hydrate may be heated in an oven at 98 °C for several hours.[3] The latter process may be harmful to the oven.

Handling, Storage, and Precautions: the dihydrate should be stored in a cool area at 50-70% relative humidity to prevent caking. Oxalic acid and its solutions are corrosive and highly toxic; ingestion of oxalic acid and its salts can cause death. Use of gloves, aprons, and goggles when handling the material is strongly recommended. A review of oxalic acid as a hazardous material, with extensive references, is available.[4] Use in a fume hood.

Introduction.

Oxalic acid is the simplest of the dicarboxylic acids and is typical of its class with respect to the preparation of its simple salts and esters. Several of its simple derivatives are important reagents in organic chemistry (see ***Diethyl Oxalate***, ***Oxalyl Chloride***); these will not be discussed here. Oxalic acid has been widely used in inorganic chemistry as a precipitant and chelating agent; a review of metal oxalato complexes may be consulted for these uses.[5] Oxalic acid is utilized extensively in synthetic organic chemistry as a mild Brønsted acid for various acid-catalyzed processes. It is particularly useful in cases where the reactants or products contain potentially acid-labile functionality. In many cases it furnishes a degree of selectivity which would otherwise be difficult to attain.

Protections/Deprotection and Hydrolyses.

Aqueous oxalic acid is an excellent reagent for the hydrolysis of enol ethers to ketones.[6] Hydrolysis of the enol ethers obtained by Birch reduction of aromatic ethers, by mineral acid, typically gives the conjugated ketone. In contrast, use of oxalic acid provides the ketone without concomitant migration of the double bond.[7-9] In the example shown (eq 1),[9] hydrolysis and closure of the hydroxy acid to the lactone occurred simultaneously.

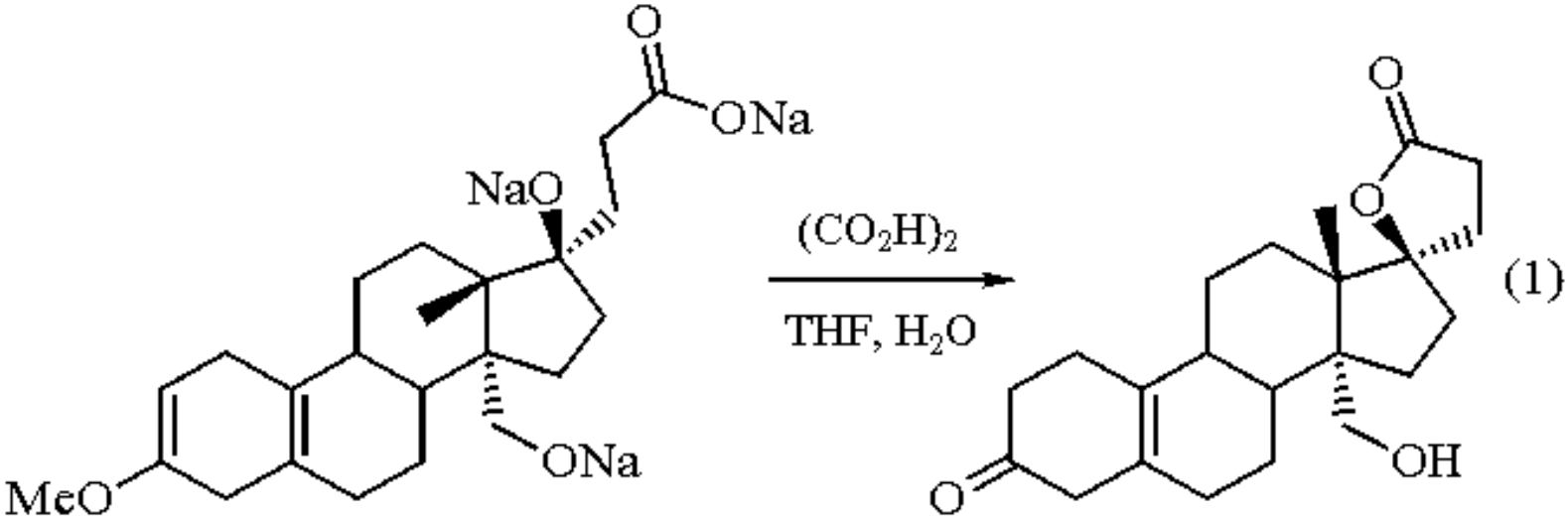

Oxalic acid may be used for both incorporation and removal of acetal and ketal functionalities. Ketones and aldehydes may be reacted with ethylene glycol or methanol in the presence of oxalic acid (anhyd) to effect conversion to the ketals and acetals, respectively.[10,11] Dimethylmethoxymethyl ethers have been prepared by stirring alcohols with 2-methoxypropene in the presence of oxalic acid.[12] Ketalization of progesterone with oxalic acid proceeds without isomerization of the double bond, whereas use of ***p-Toluenesulfonic Acid*** results in migration to the 5,6-position.[13] Cleavage of acetals to regenerate the carbonyl group may be accomplished in aqueous solution.[14-17] Acid-sensitive functionality is well tolerated by this method (eq 2).[16] A two-phase system of methylene chloride and water has also been used.[18]

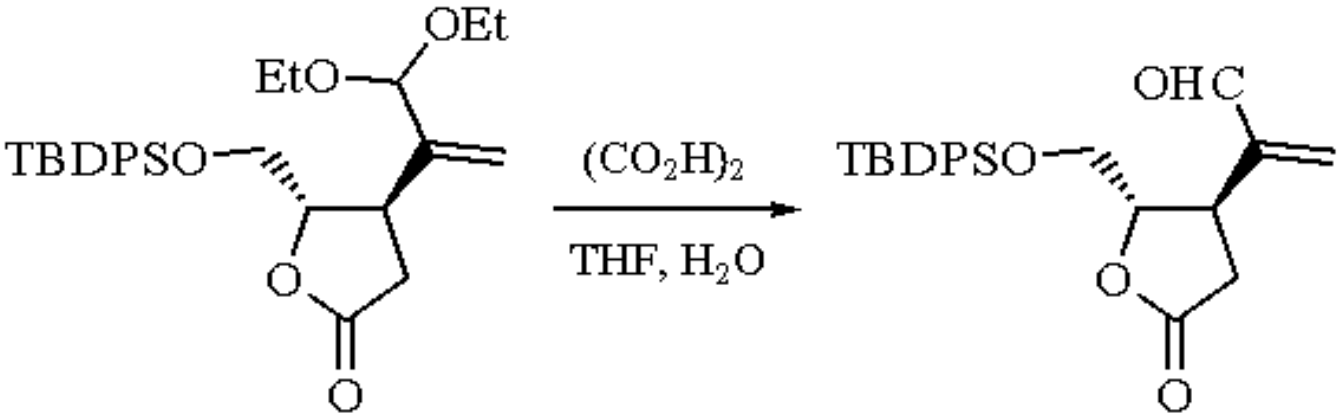

(2)

A particularly mild method for deacetalization is the use of oxalic acid and moist silica gel.[19] Cleavage of β-hydroxy ketals to the corresponding hydroxy ketones may be effected without accompanying dehydration (eq 3),[20] and vinylsilanes have not undergone protodesilylation under these conditions.[21] Vinylogous phosphoramides have been hydrolyzed to ketophosphonates using this method.[22]

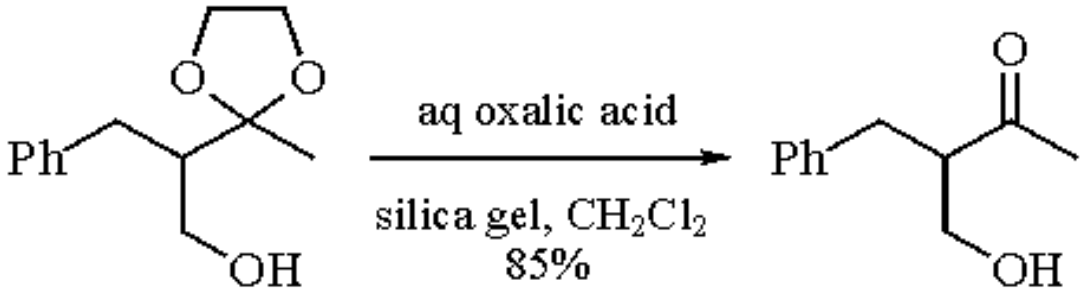

(3)

Oxalic acid is a frequently used mild acid quench for a variety of reaction types, including oxidations with ***Dimethyl Sulfoxide*** activated with ***1,3-Dicyclohexylcarbodiimide***[23,24] and ***Phenyl Dichlorophosphate*** (Pfitzner-Moffatt oxidation),[25] as well as organometallic reactions and anion additions. Oxalic acid in methanol has been used to effect protodesilylation[26] and protodestannylation[27] of dihydropyridine compounds.

Heating alcohols with anhydrous oxalic acid[28] or refluxing in aqueous oxalic acid[29] effects dehydration to alkenes, often with results superior to other methods. Appropriately disposed hydroxy ketones have been cyclodehydrated to cyclic ethers (eq 4).[30-32] Elimination of amines from Mannich adducts with oxalic acid in ethanol, to yield unsaturated ketones, has also been reported.[33]

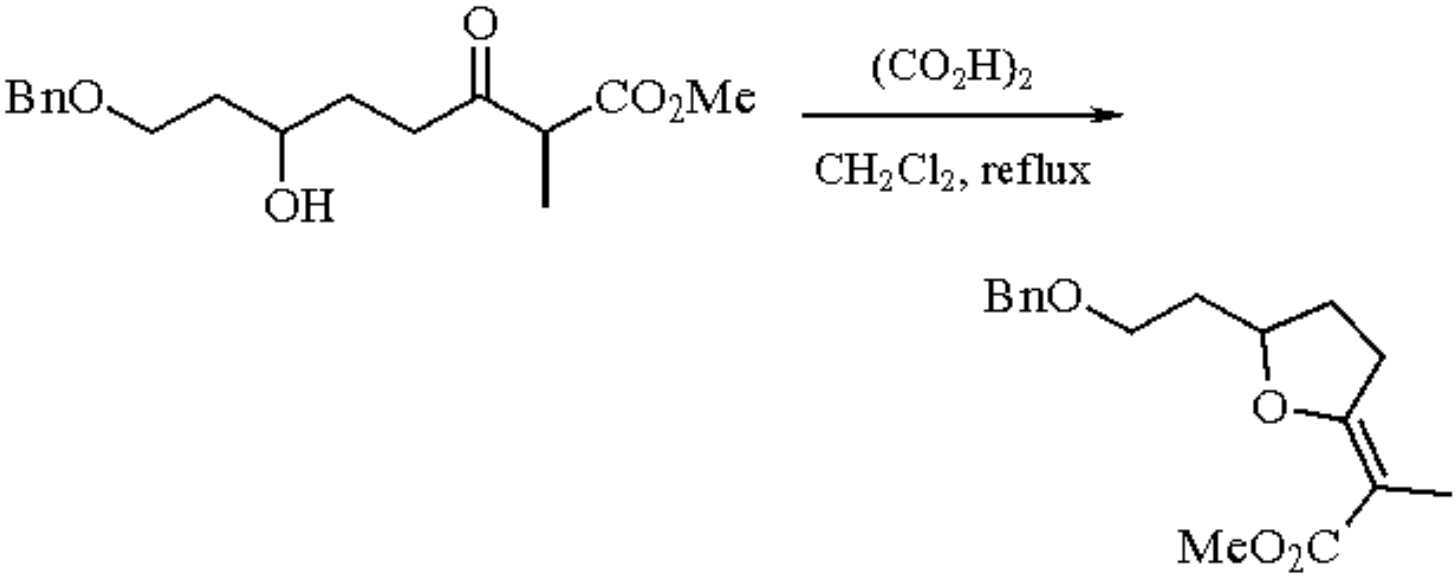

(4)

β-Ketoesters may be decarboxylated by aqueous oxalic acid in dioxane (eq 5).[34]

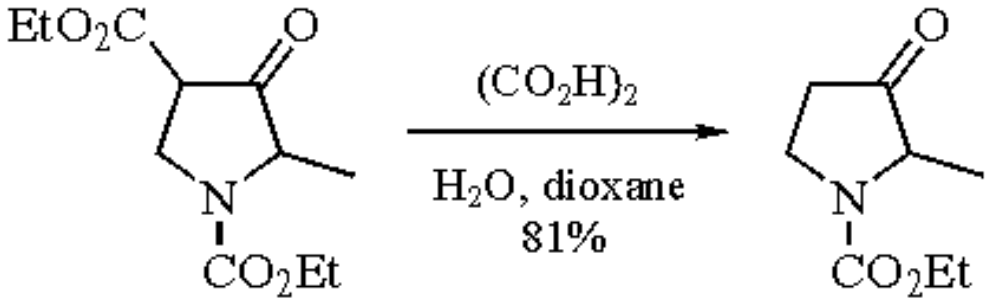

(5)

Oxalic acid has been used as an acidic agent in a number of condensation processes, including condensation of allylic alcohols with aromatic rings[35] and condensations with carbonyl groups.[36] Oxalic acid can itself serve as a reaction partner in such processes, for example in condensations between aromatic amines and aldehydes,[37] and between phenols.[38] Oxalic acid has been utilized as a bifunctional condensation partner in the synthesis of heterocyclic systems.[39] Palladium-catalyzed hydroxycarboxylation of alkenes and alkynes by oxalic acid provides alkanoic and alkenoic carboxylic acids, respectively.[40]

Oxalic acid is frequently used for the characterization of amines as their oxalate salts.[41]

Related Reagents.

Acetic Acid; ***Hydrochloric Acid***; ***Methanesulfonic Acid***; ***Pivalic Acid***; ***Sulfuric Acid***; ***p-Toluenesulfonic Acid***; ***Trifluoroacetic Acid***.

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Oxalyl Bromide

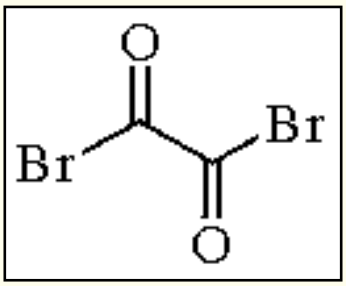

[15219-34-8] · $C_2Br_2O_2$ · Oxalyl Bromide · (MW 215.82)

(reactive acid halide;[1] heterocycle synthesis[2])

Physical Data: bp 16-17 °C/10 mmHg; *d* 2.30 g cm^{-3}.

Form Supplied in: liquid or solution in CH_2Cl_2; commercially available

Preparative Methods: originally prepared by Staudinger in 1913 by treating ***Oxalyl Chloride*** with HBr;[3] a more recent report describes a convenient alternative using ***Bromotrimethylsilane*** which provides the reagent in 85% yield.[4]

Handling, Storage, and Precautions: corrosive; lachrymator. Use in a fume hood.

Brominations.

Oxalyl bromide is useful for the preparation of acid bromides from carboxylic acids or salts.[5] These acid bromides are quite reactive and will often acylate nucleophiles under milder conditions than those required for the corresponding acid chlorides.[1]

Oxalyl bromide has found use for the preparation of a number of brominated heterocycles. Reaction of oxalyl bromide with α-amino- or α-hydroxynitriles yields substituted 2(1*H*)-pyrazinones (eq 1)[2a] and 2*H*-1,4-oxazin-2-ones (eq 2),[2b] respectively.

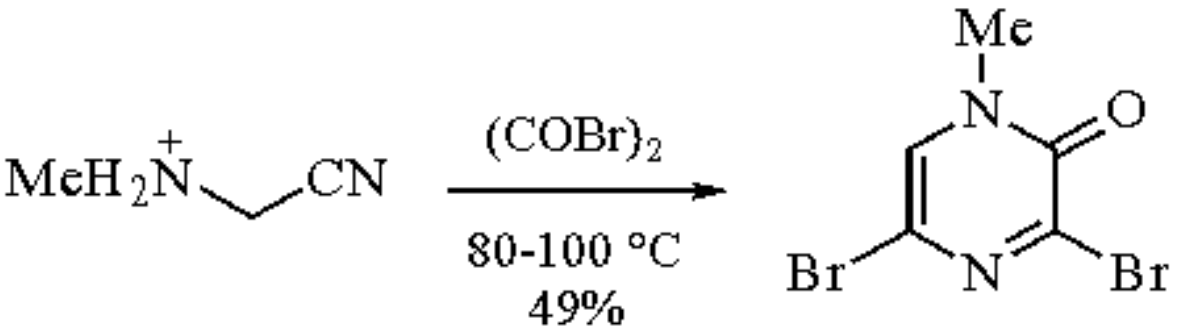

(1)

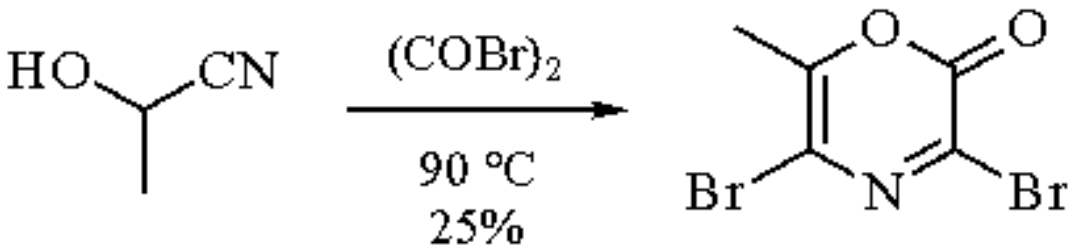

(2)

Reaction of cyanogen with oxalyl bromide affords the tetrabromopyrazine (**1**) in greater than 70% yield (eq 3).[6] A completely different product is obtained in this reaction when ***Oxalyl Chloride*** is used.

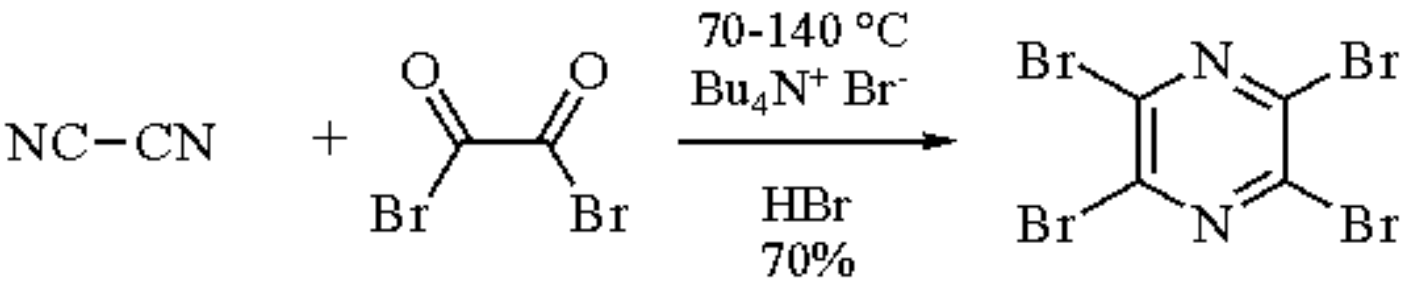

(3)

(1)

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Michael D. Ennis

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Oxalyl Chloride

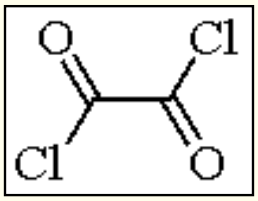

[79-37-8] · $C_2Cl_2O_2$ · Oxalyl Chloride · (MW 126.92)

(versatile agent for preparation of carboxylic acid chlorides;[1] phosphonic acid dichlorides;[2] alkyl chlorides;[3] β-chloro enones;[4] acyl isocyanates[5])

Physical Data: mp -12 °C; bp 63-64 °C/763 mmHg; *d* 1.48 g cm^{-3}; *n*20D 1.4305.

Solubility: sol hexane, benzene, diethyl ether, halogenated solvents, e.g. dichloromethane and chloroform, acetonitrile.

Form Supplied in: colorless, fuming liquid; widely available; 2M soln in dichloromethane.

Handling, Storage, and Precautions: liquid and solution are toxic, corrosive, and severely irritating to the eyes, skin, and respiratory tract. Use in a fume hood and wear protective gloves, goggles, and clothing. Bottles should be stored in a cool, dry place and kept tightly sealed to preclude contact with moisture. Decomposes violently with water, giving toxic fumes of CO, CO_2, HCl.

Preparation of Carboxylic Acid Chlorides (and Anhydrides).

Oxalyl chloride has found general application for the preparation of carboxylic acid chlorides since the reagent was introduced by Adams and Ulich.[1] Acid chlorides produced by this means have subsequently featured in the synthesis of acyl azides,[6] bromoalkenes,[7] carboxamides,[8] cinnolines,[9] diazo ketones,[10] (thio)esters,[11] lactones,[12] ketenes for cycloaddition reactions,[13] intramolecular Friedel-Crafts acylation reactions,[14] and the synthesis of pyridyl thioethers.[11]

Like ***Thionyl Chloride***, oxalyl chloride gives gaseous byproducts with acids and the chlorides can be readily isolated in a pure form by evaporation of the solvent and any excess reagent, or used in situ for further elaboration (eq 1).

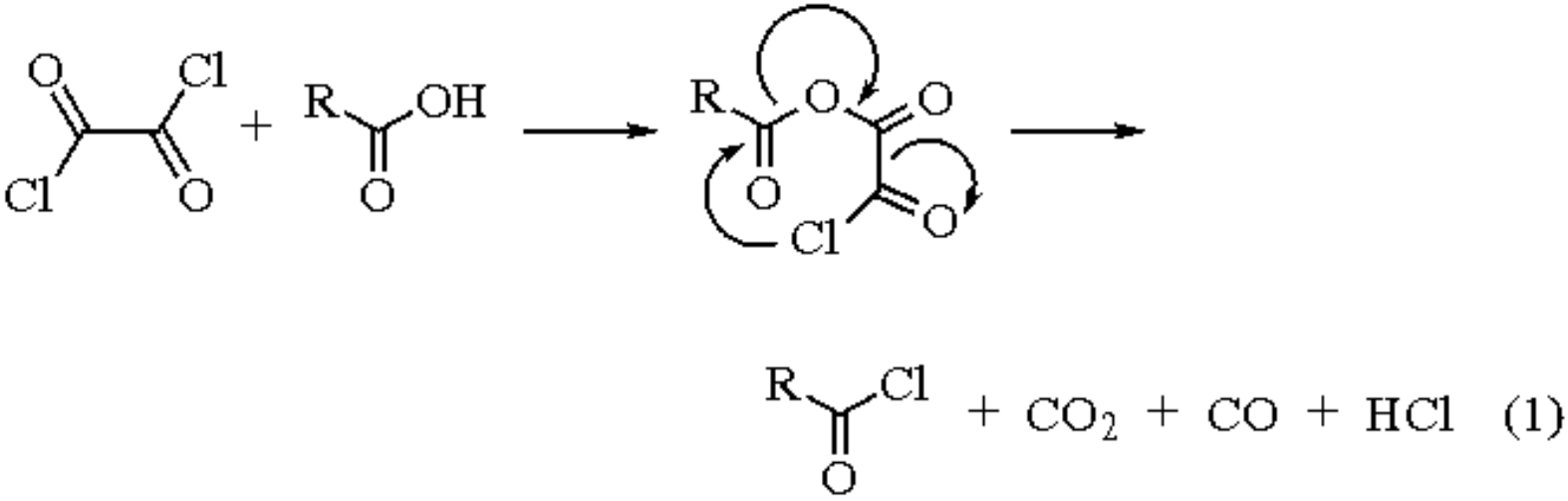

Prior formation of an amine or alkali metal salt, with or without pyridine,[1] has been used to advantage with substrates that are sensitive to strong acids or are bases (see also ***Oxalyl Chloride-Dimethylformamide*** for a procedure conducted under neutral conditions using silyl esters). By adjusting the molar proportions of oxalyl chloride to substrate, anhydrides can also be prepared using these methods (eq 2).[15] *N*-Carboxy-α-amino acid anhydrides can also be made this way.[16]

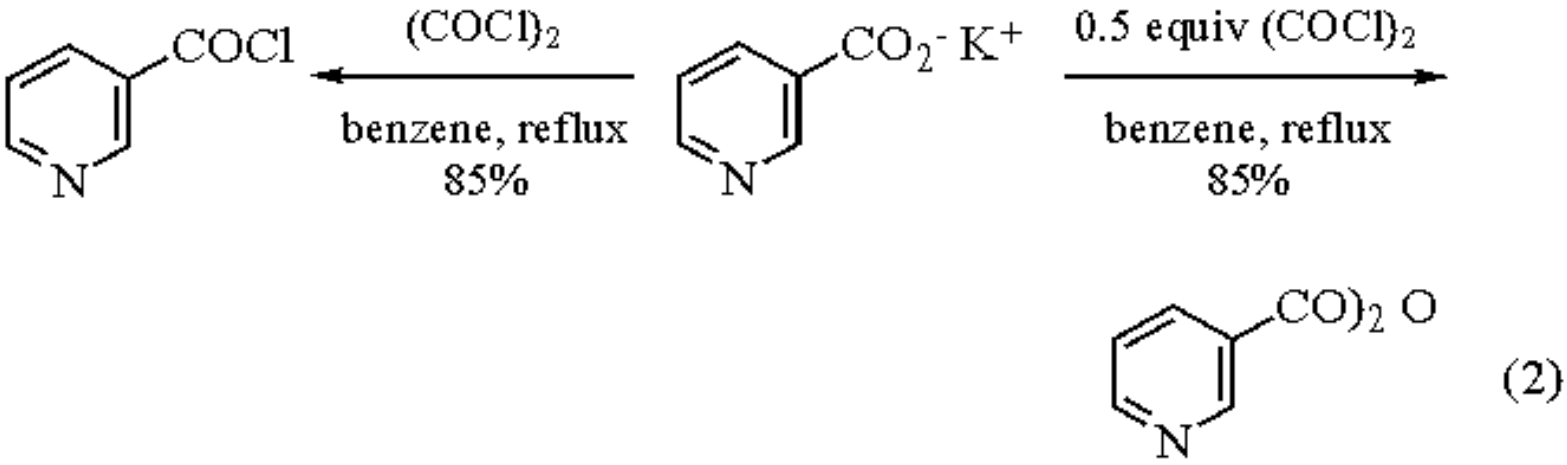

The use of nonpolar solvents such as hexane or toluene allows for the removal of inorganic or amine salts which may otherwise interfere with subsequent reactions.

Under the mild conditions employed (eqs 3 and 4),[17] racemization of stereogenic centers, skeletal rearrangement, or byproduct formation, seen with other reagents such as thionyl chloride/pyridine,[18] are seldom observed.

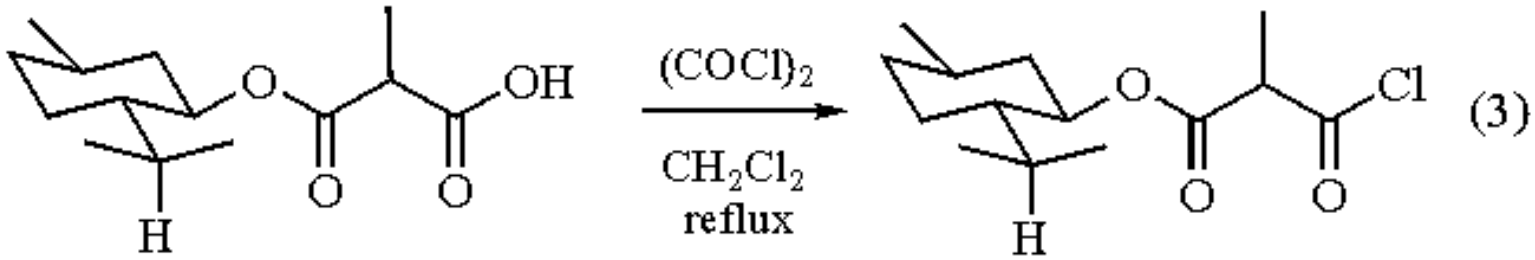

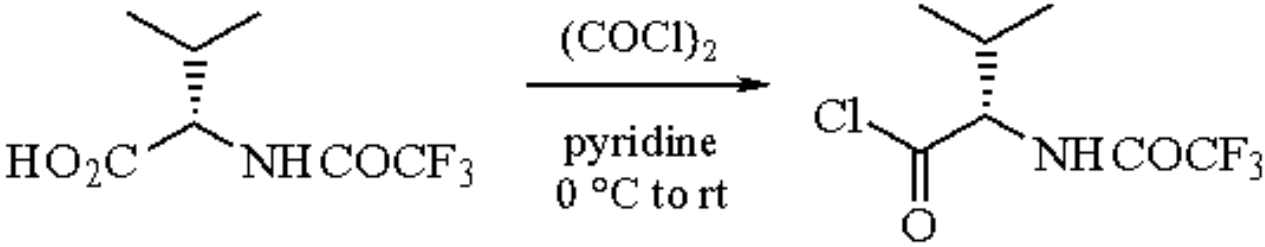

(4)

Conversion of β-bromoacrylic acid to the acid chloride using thionyl chloride/DMF, ***Phosphorus(III) Chloride***, or benzotrichloride/zinc chloride also resulted in bromine for chlorine exchange. Use of oxalyl chloride with the preformed ammonium salt provided a mild, general method to β-bromoacryloyl chlorides (eq 5)[19] without halogen exchange or (*E*/*Z*) equilibration. β-Fluoro- and iodoacrylic acids have been cleanly converted to the acid chlorides without prior salt formation.

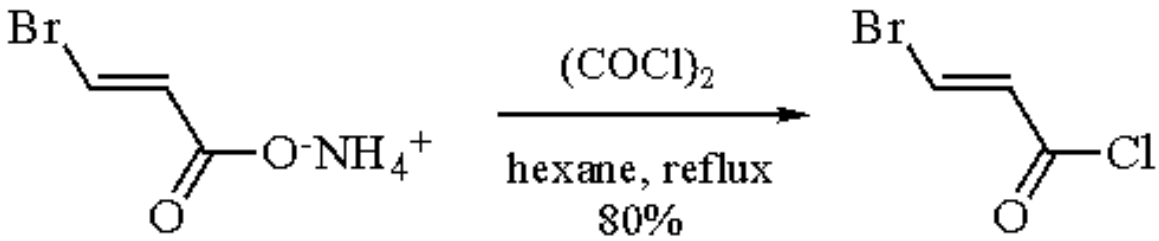

(5)

As well as forming acid chlorides, α-tertiary amino acids can react with oxalyl chloride and undergo an oxidative decarboxylation to give iminium salts, or ring expansion, depending on the substituents and their stereochemistry (eq 6).[20]

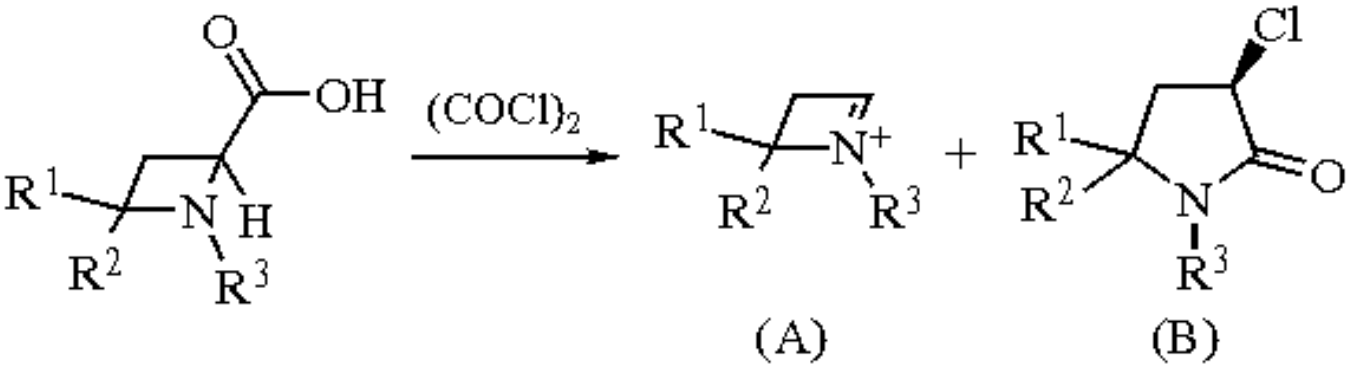

(6)

			% Yield	
R^1	R^2	R^3	(A)	(B)
Me	H	*t*-Bu	0	69
H	CO_2Me	*c*-Hex	0	59
H	Me	Me	30	0

Preparation of Phosphonic Acid Chlorides.

Phosphonic acid dichlorides have been obtained in high yield (determined by ^{31}P NMR) at low temperature from the corresponding acids using oxalyl chloride and ***Pyridine*** (eq 7).[2]

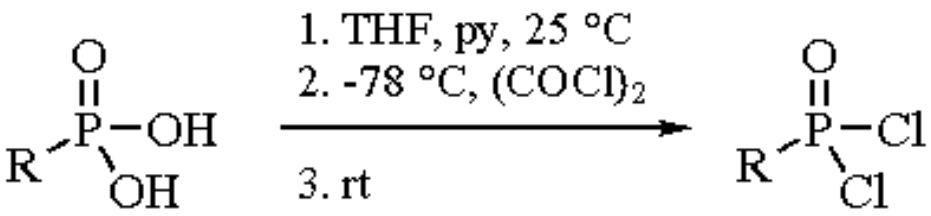

(7)

R = Et, $PhCH_2$, CF_2H, arabinomethyl, phthalidyl

Similarly, monoalkyl methylphosphonochloridates (eq 8)[21] can be made from dialkyl esters; thionate acid chlorides could not be made by this method. Thionyl chloride and PCl_5 were also used to make this type of compound (see also ***Oxalyl Chloride-Dimethylformamide***).

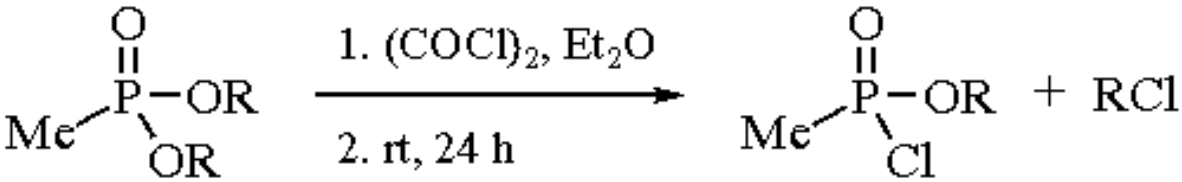

(8)

R = Me, Et, Pr, *i*-Pr, Bu

Numerous other reagents such as PCl_3, PCl_5, $POCl_3$, and Ph_3P/CCl_4 are available for the preparation of acid chlorides and anhydrides but may not be as convenient as the byproducts are not so easily removed, or the reactions require more vigorous conditions.

Direct Introduction of the Chlorocarbonyl Group (Halocarbonylation).

Alkanes or cycloalkanes react with oxalyl chloride under radical conditions; typically, mixtures are produced.[22] However, bicyclo[2.2.1]heptane undergoes regio- and stereospecific chlorocarbonylation, giving the ester on subsequent methanolysis (eq 9).[23]

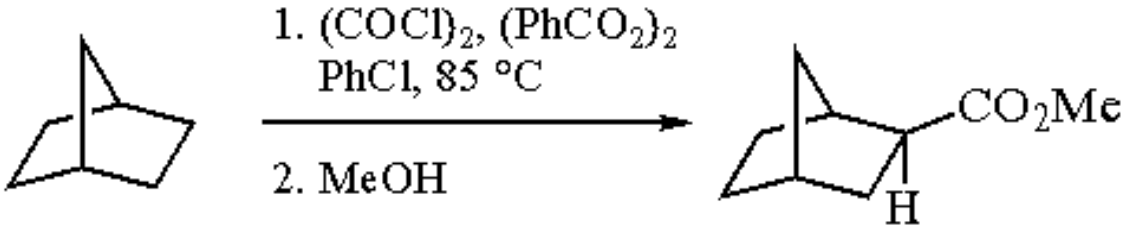

(9)

Certain alkenes such as 1-methylcyclohexene and styrene react with oxalyl chloride, under ionic conditions without added catalyst, to give alkenoic acid chlorides in variable yields. Alkenes such as octene and stilbene did not react under these conditions.[24]

Reactions of aromatic compounds with oxalyl chloride/Lewis acid catalysts have been reviewed.[25] Anthracene is unusual as it undergoes substitution without added catalyst (eq 10).[26]

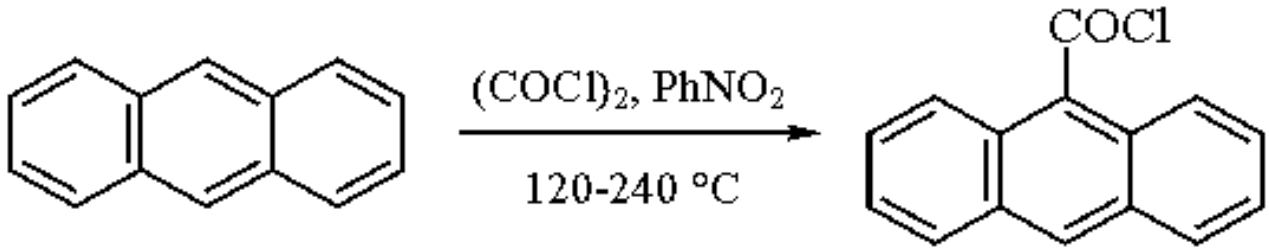

(10)

Preparation of Chloroalkanes.

Alcohols react with oxalyl chloride to give oxalyl monoalkyl esters, which if heated in the presence of pyridine give the alkyl chloride (eq 11).[3]

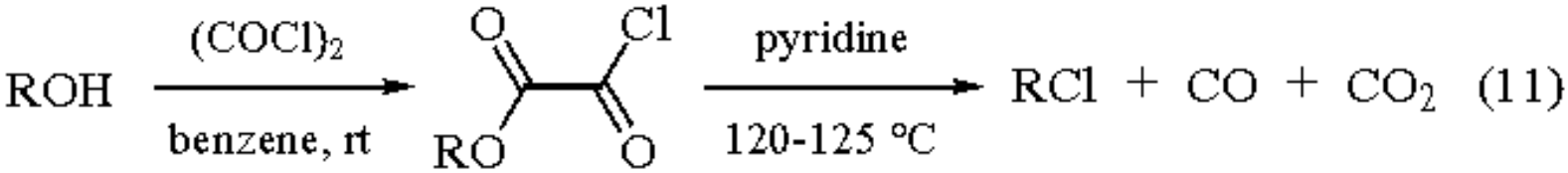

(11)

Tertiary alcohols have been converted to tertiary chlorides in a Barton-Hunsdiecker type radical process using hydroxamate esters (eq 12).[27]

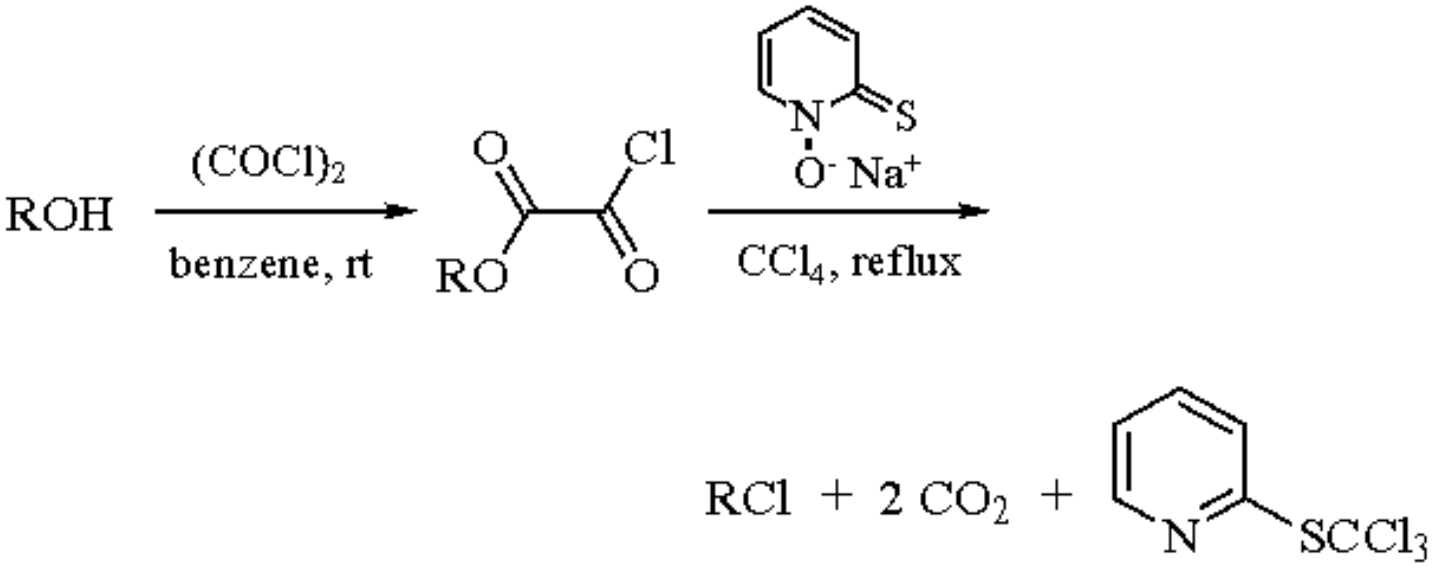

(12)

e.g. R = $Me(CH_2)_{16}CMe_2$-

Chlorination of Alkenes.

A novel stereospecific dichlorination of electron rich alkenes has been reported using a manganese reagent generated

from ***Benzyltriethylammonium Chloride*** and oxalyl chloride (eqs 13-17).[28] No oxygenation byproducts are observed.

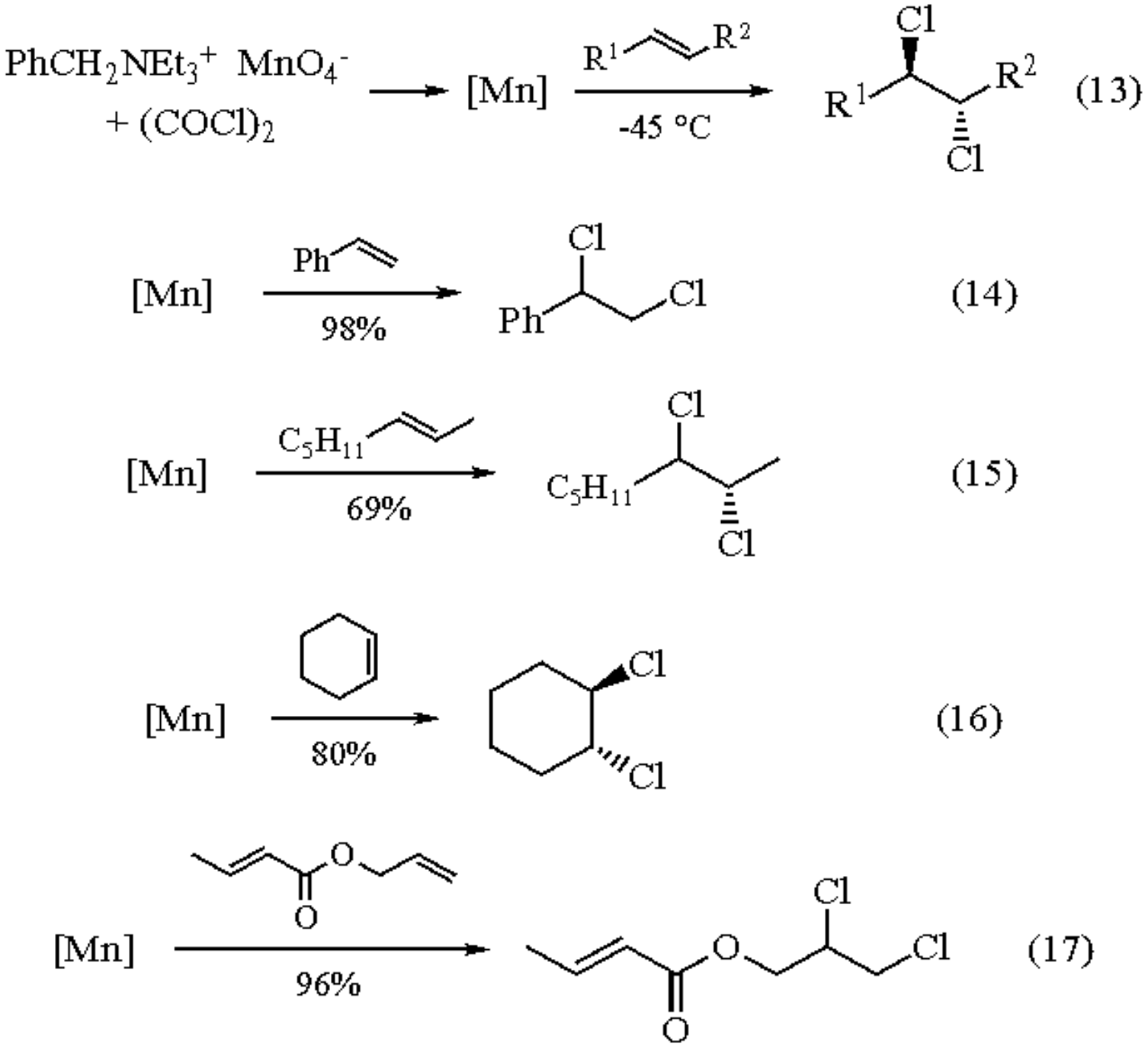

Reactions with Carbonyl Groups.

Unsaturated 3-keto steroids give the corresponding 3-chloro derivatives with oxalyl chloride (eq 18).[4] Prolonged heating can give rise to aromatization.[4] Tropone gives the chlorotropylium chloride in high yield.[4] In a related reaction, 1,2-dithiol-3-ones and -3-thiones give dithiolium salts when heated in toluene or chloroform with the reagent.[4] A range of β-chloro enones has been prepared from diketones. Dimedone gives the β-chloro enone in high yield (eq 19).[29] Keto esters did not react to give β-chloro esters.

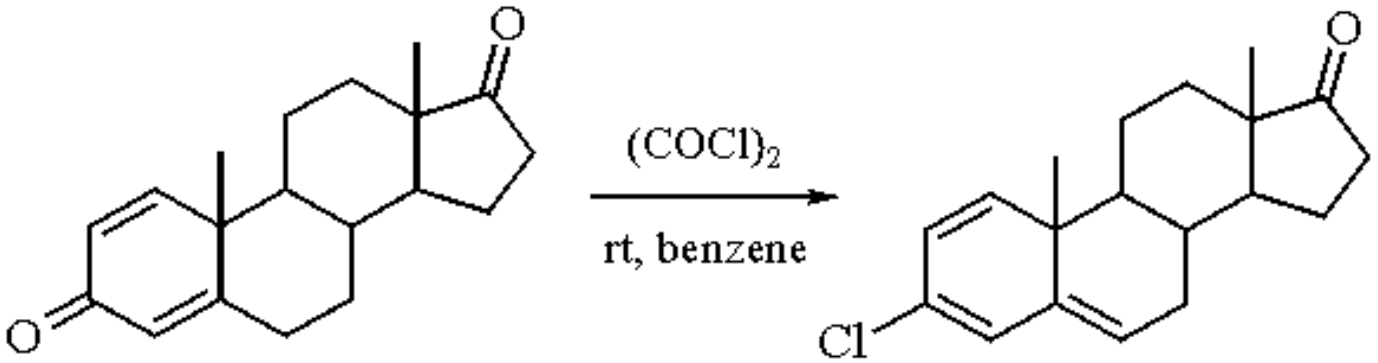

(18)

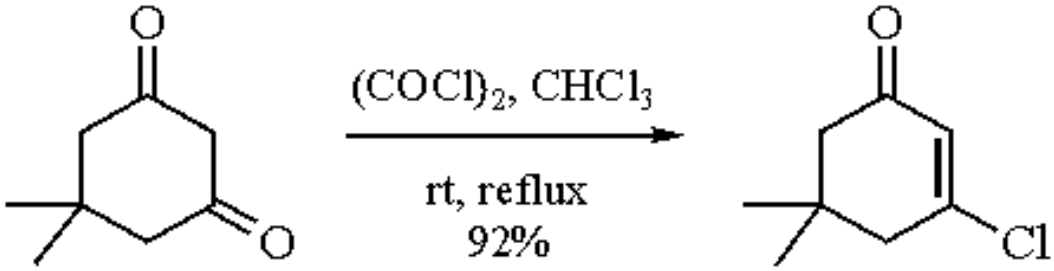

(19)

β-Keto aldehydes give a single regio- and stereospecific isomer, the chlorine being *cis* to the carbonyl group (eq 20).

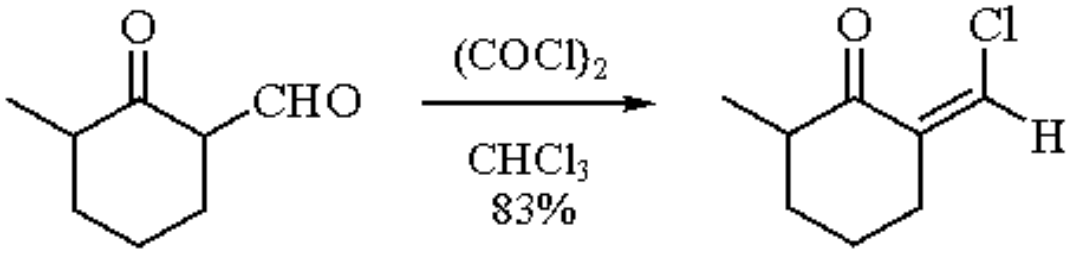

(20)

Certain triketones give 3-chlorides with excess oxalyl chloride, in good yield (eq 21).[30]

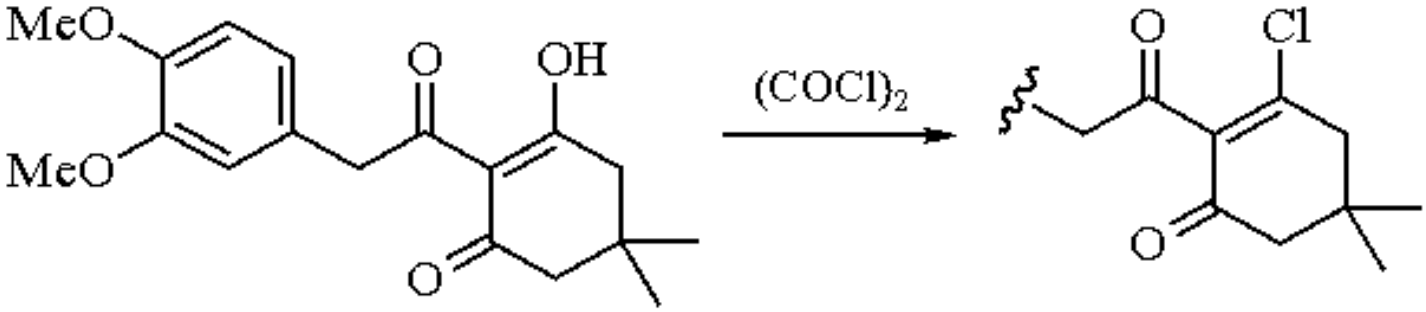

(21)

Preparation of Acyl Isocyanates and Aryl Isocyanates.

Certain primary carboxamides can be converted to acyl isocyanates in yields from 36-97% with the reagent (eq 22);[5] ***Phosgene*** gives nitriles under similar conditions. Oxalyl chloride has found limited application for the preparation of triazine and quinone isocyanates.[5]

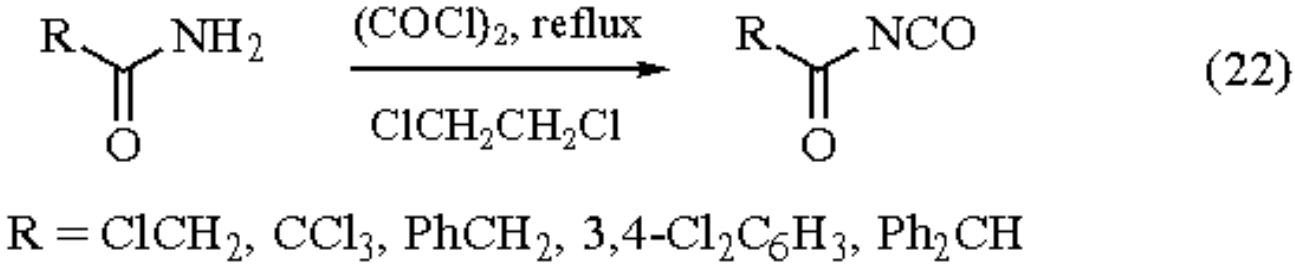

Miscellaneous Applications.

Oxalyl chloride has been used in the preparation of 2,3-furandiones from alkenyloxysilanes,[31] *o*-aminophenols from *N*-aryl nitrones,[32] dihydroquinolines via a modified Bischler-Napieralski ring closure,[33] 2,3-β-furoquinoxalines from quinoxazolones,[34] sterically hindered salicylaldehydes from phenoxyoxalyl chlorides,[35] and in mild cleavage of 7-carboxamido groups in cephalosporin natural products, without cleavage of the lactam ring or disruption of optical centers.[36]

Related Reagents.

Dimethyl Sulfoxide-Oxalyl Chloride; ***Oxalyl Chloride-Aluminum Chloride***.

---

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Oxalyl Chloride-Aluminum Chloride

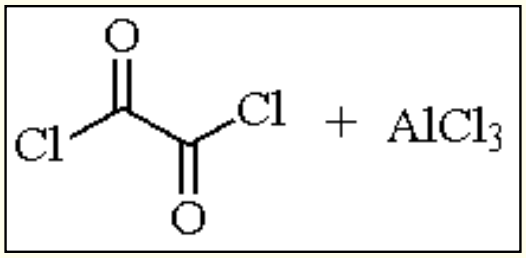

$(COCl)_2$

[79-37-8] · $C_2Cl_2O_2$ · Oxalyl Chloride-Aluminum Chloride · (MW 126.92) ($AlCl_3$)

[7446-70-0] · $AlCl_3$ · Oxalyl Chloride-Aluminum Chloride · (MW 133.33)

(useful for the preparation of benzoyl chlorides and derivatives;[1] 2-acylpyrrole synthesis[2])

Physical Data: see entries for ***Oxalyl Chloride*** and ***Aluminum Chloride***.

Handling, Storage, and Precautions: Caution! Both phosgene and carbon monoxide are formed upon mixing equimolar amounts of oxalyl chloride and aluminum chloride at room temperature. Use this reagent only in an efficient fume hood.

General Discussion.

The combination of oxalyl chloride and aluminum chloride is a reagent system which has proven generally useful for the preparation of substituted benzoic acid derivatives. For example, 4-alkyl- or 4-halobenzoyl chlorides can be prepared in good yield and free of any positional isomers using this reagent combination.[1] The reaction is equivalent to a Friedel-Crafts acylation using ***Phosgene***, and in fact the presence of both carbon monoxide and phosgene has been detected by IR spectroscopy in the gases formed upon mixture of these reagents. The reaction works best for alkylated aromatic substrates and fails when attempted on those bearing either activating (such as alkoxy) or deactivating substituents. Carbon disulfide appears to be the solvent of choice for these reactions. The acid chloride products obtained by this method can also be directly subjected to either hydrolysis[3] or alcoholysis[4] to provide the corresponding carboxylic acids or esters (eqs 1 and 2).

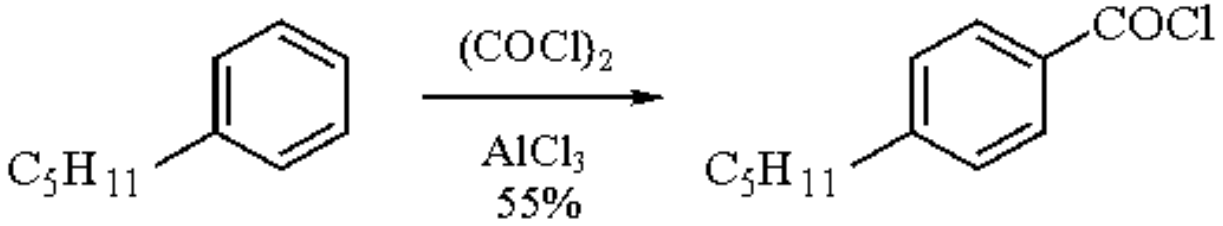

(1)

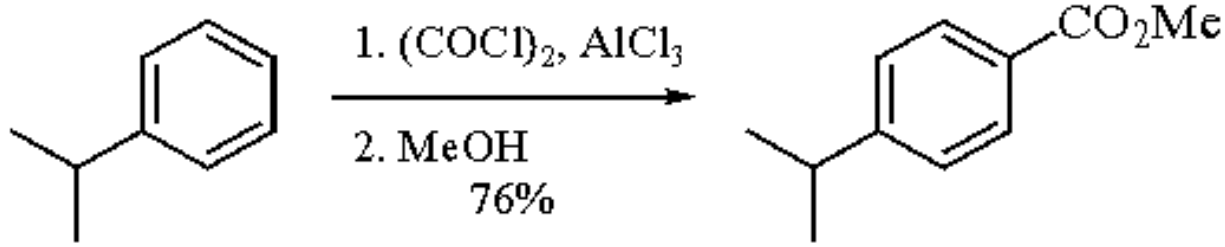

(2)

Similarly, the combination of oxalyl chloride/aluminum chloride will introduce an acyl group at the 2-position of 1-(phenylsulfonyl)pyrrole (**1**) to give the corresponding acid chloride (**2**) (eq 3).[2]

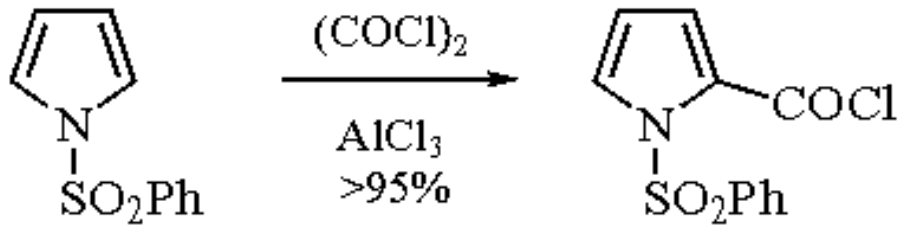

(3)

(1) **(2)**

There is a report describing the reaction of paracyclophane (**3**) with oxalyl chloride/aluminum chloride under mild conditions (-10 °C) to produce the glyoxyl chloride derivative (**4**) in quantitative yield.[5] Refluxing (**4**) for 3 h in chlorobenzene effects complete decarbonylation to the acid chloride (**5**).

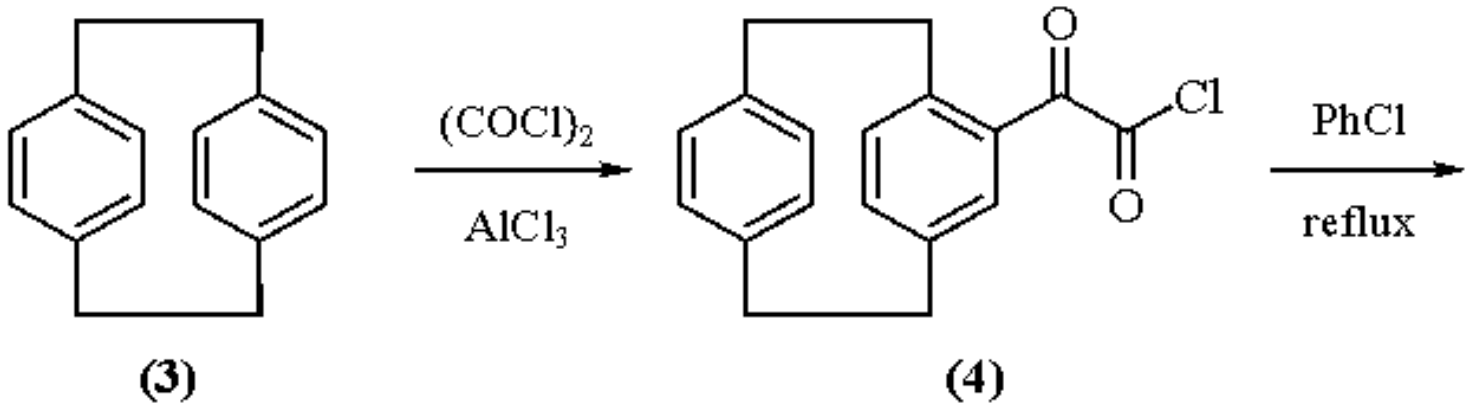

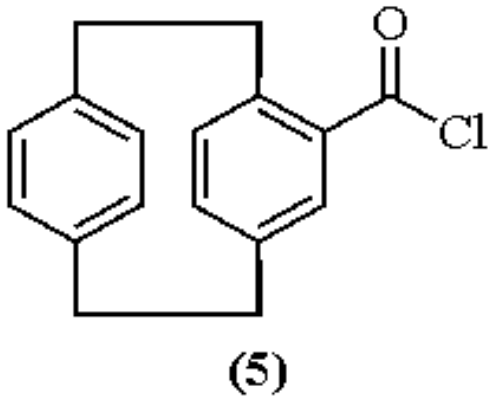

(4)

An interesting ring closure of the tricarbonylmyrceneiron complex (**6**) has been reported.[6] Treatment of (**6**) with oxalyl chloride/aluminum chloride (1:2) in dichloromethane at -78 °C led to the immediate formation of two diastereomeric keto chlorides (**7**). Dehydrohalogenation of one of the stereoisomers using ***Silver(I) Nitrate*** afforded the enone (**8**) (eq 5).

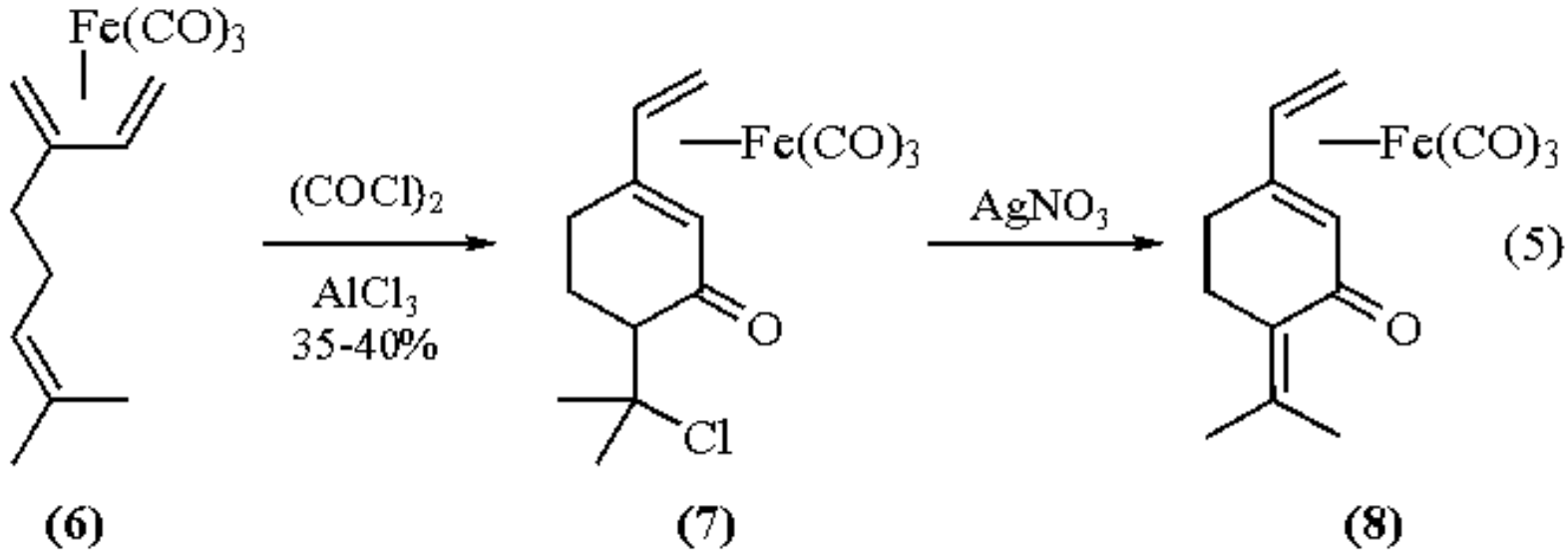

(5)

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Oxalyl Chloride-Dimethylformamide

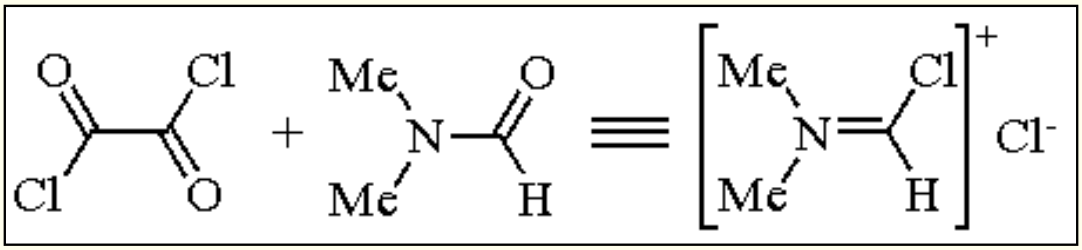

$(COCl)_2$

[79-37-8] · $C_2Cl_2O_2$ · Oxalyl Chloride-Dimethylformamide · (MW 126.92) (DMF)

[68-12-2] · C_3H_7NO · Oxalyl Chloride-Dimethylformamide · (MW 73.11)

(versatile agent combination for in situ generation of Vilsmeier reagent used in preparation of carboxylic acid chlorides and other acid derived products,[1] phosphonic acid chlorides,[2] β-chloro enones,[3] ketoximes[4] and formyl derivatives[5])

Physical Data: see entries for ***Oxalyl Chloride*** and ***N,N-Dimethylformamide***.

Form Supplied in: generated in situ under anhydrous conditions from oxalyl chloride and either catalytic or stoichiometric dimethylformamide, typically in halogenated solvents such as dichloromethane; acetonitrile, or hexane. The intermediate dimethylforminium chloride (DMFCl) can be isolated as a hygroscopic solid, mp 140 °C (see also ***Thionyl Chloride***, ***Phosphorus Oxychloride***).

Handling, Storage, and Precautions: (see also ***Oxalyl Chloride***); reagent generated in situ under anhydrous conditions; corrosive, toxic. Oxalyl chloride should be used in the fume hood.

Synthesis of Carboxylic Acid Chlorides and Anhydrides.

Carboxylic acids, including amino acids,[6] readily react with DMFCl generated in situ to produce acid chlorides on heating (eq 1).[1] The procedure has been shown to be general, and may provide acid chlorides not available with oxalyl chloride alone.[7,8]

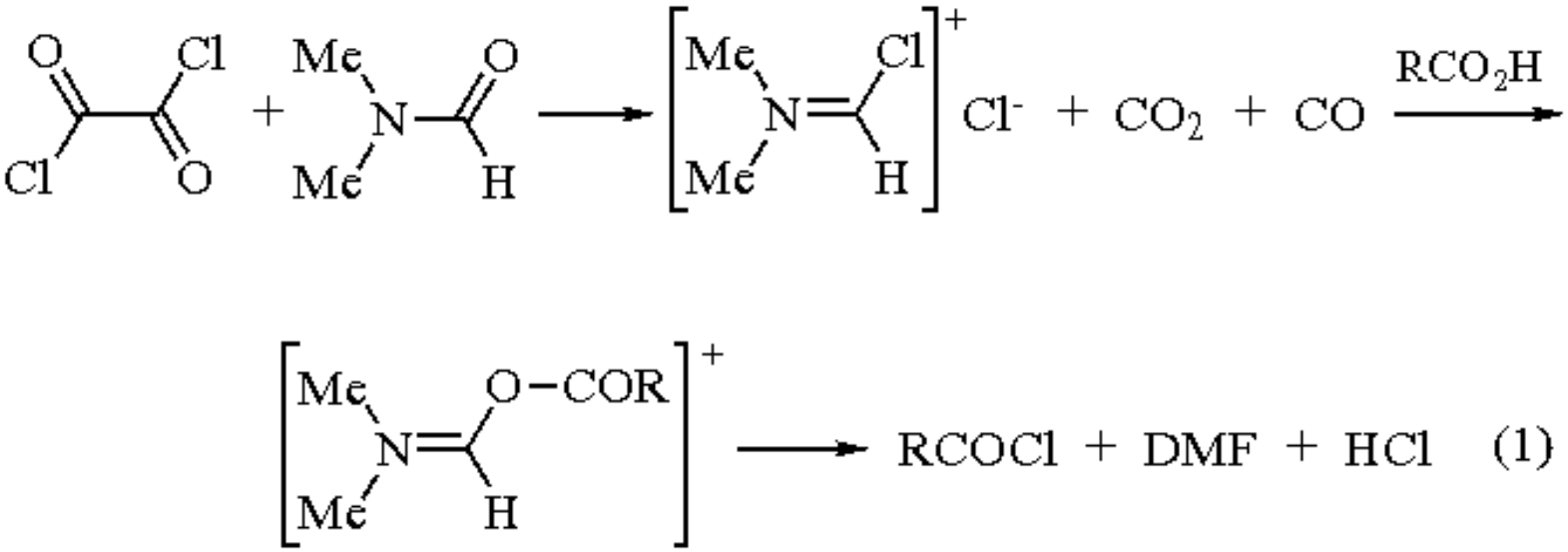

The mild reaction conditions employed enables the preparation of chlorides without disrupting chiral or other sensitive functionality. The use of hexane has been found particularly suitable for microscale preparation of high purity Mosher's acid chloride as it enables residual DMFCl to be filtered from solution (eq 2).[9]

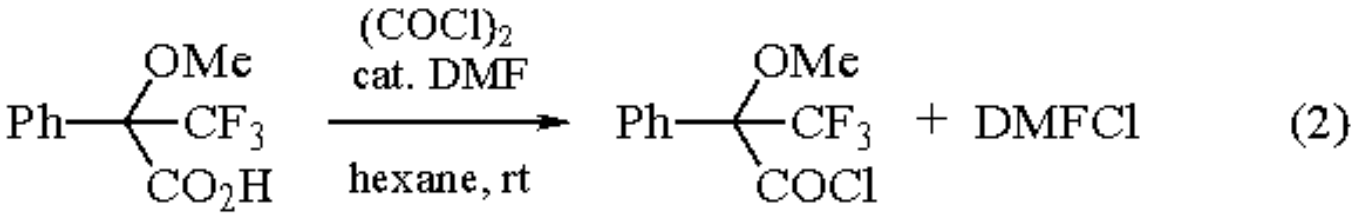

DMFCl has been used to prepare carboxylic esters (eq 3),[10] *N*-hydroxycarboxamides and *O*,*N*-dimethylcarboxamides,[11] and α-hydroxycarboxamides (eq 4),[12] via a one pot process.

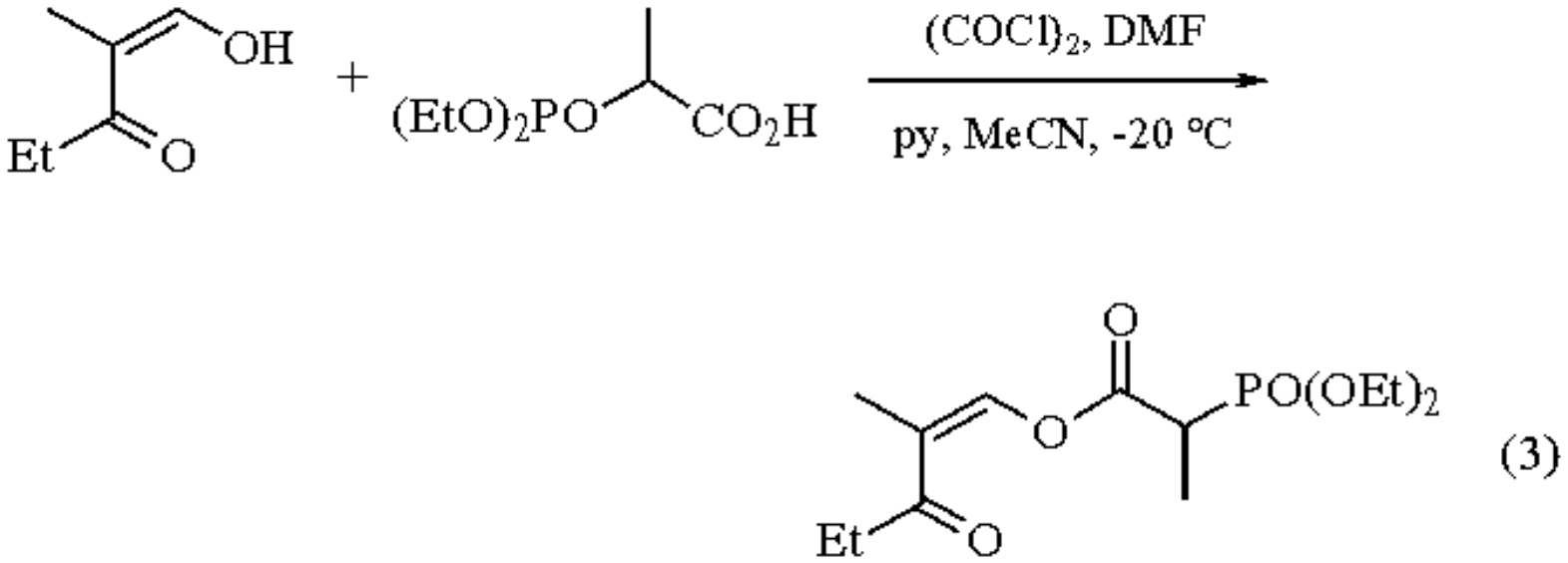

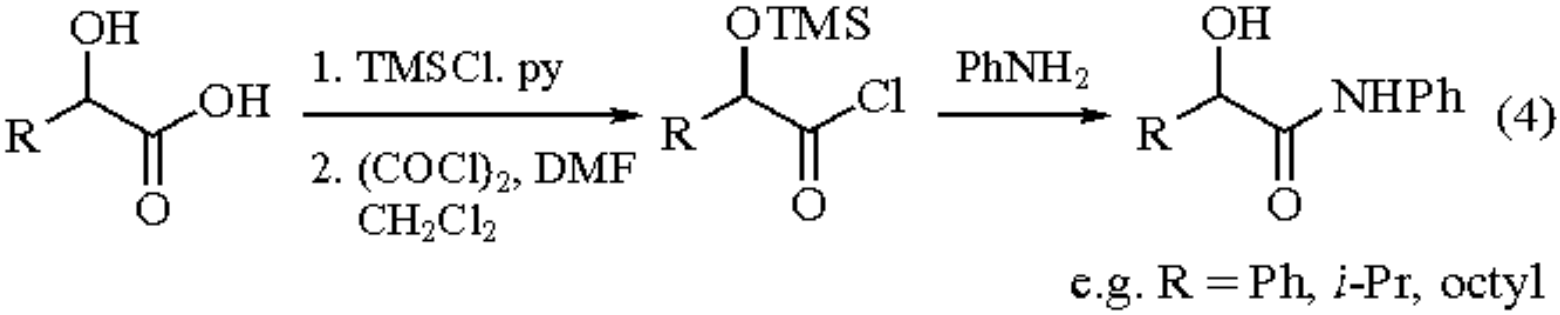

A procedure using silyl esters, developed to allow synthesis of acid chlorides under neutral conditions, has been applied to a range of substrates (eq 5),[13] including amino acid anhydrides.[1]

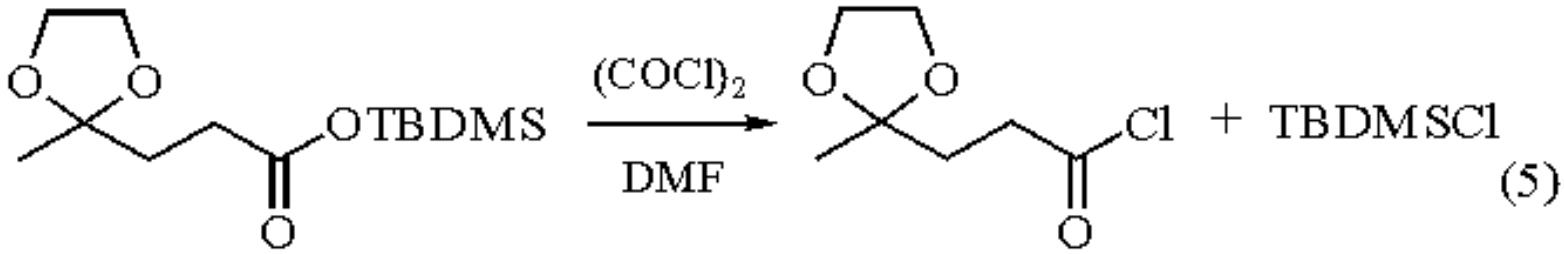

Reduction of the intermediate generated from a carboxylic acid and DMFCl provides aldehydes with ***Lithium Tri-t-butoxyaluminum Hydride***,[14] and alcohols with ***Sodium Borohydride***,[15] both in high yield and chemoselectivity.

Preparation of Phosphonic Acid Chlorides.

Disilyl esters of phosphonic acids react with oxalyl chloride-DMF to give the phosphonyl chlorides and silyl chlorides under mild conditions (eq 6).[2] Prior treatment of an acid-sensitive phosphonate monoester with ***Trimethylsilyldiethylamine*** was used to minimize exposure to HCl (eq 7).[16]

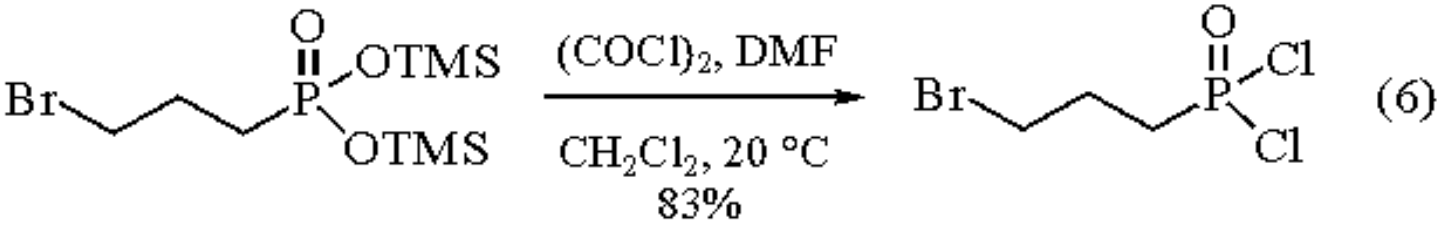

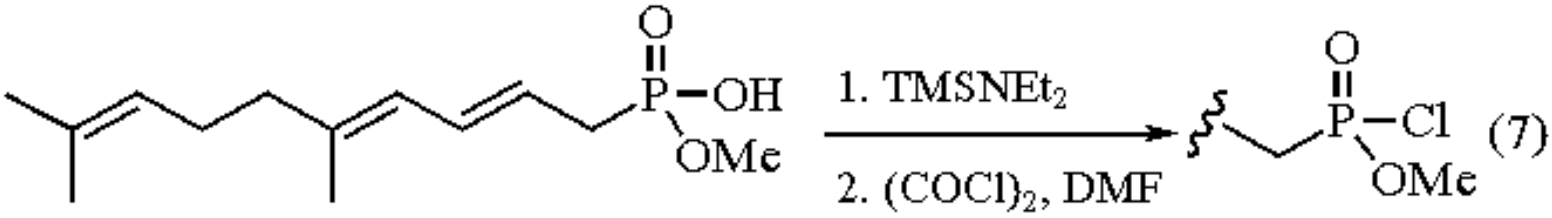

A general process suitable for large scale synthesis of phosphonic acid dichlorides, which avoids the need for preforming silyl esters, has been reported (eq 8).[17]

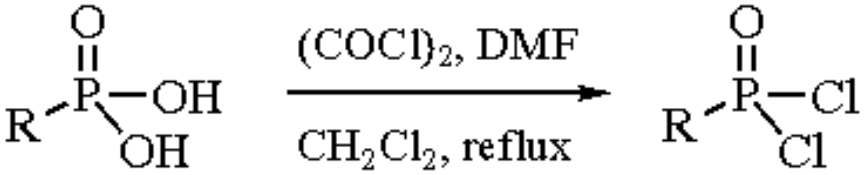

(8)

β-Chloro (or Bromo) Enones.

Cyclic diketones in solution with DMF and dichloromethane react with oxalyl chloride (or bromide) to give β-halo enones in high yield (eq 9).[3] The reported procedure reduces overall reaction time and avoids solubility problems.

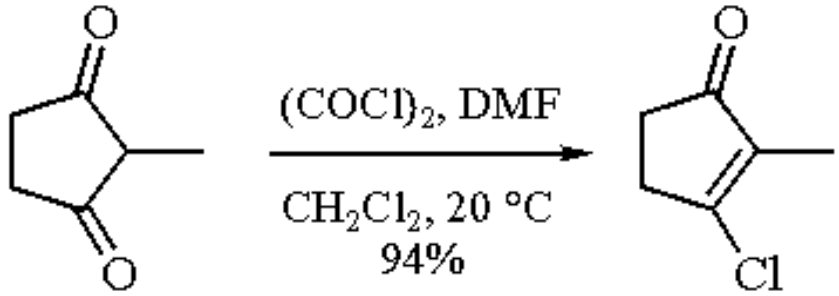

(9)

Formylation.

Vilsmeier formylation reactions have been reviewed.[1] Oxalyl chloride-dimethylformamide has found occasional use; one application has been preparation of a piperidine substituted dialdehyde (eq 10).[5]

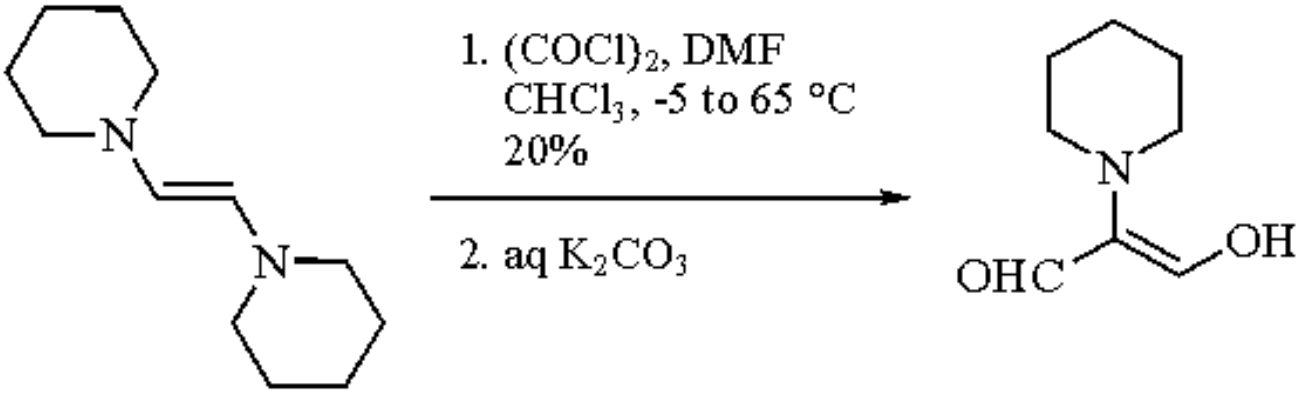

(10)

Alkyl Chlorides.

N,*N*-Diphenylformamide is reported to be an improvement on DMF when used with oxalyl chloride to prepare primary and secondary alkyl chlorides from alcohols.[18]

Ketoximes.

Lithium salts of nitroalkanes react with DMFCl, preformed from oxalyl chloride and DMF, to give intermediates which

on reaction with Grignard reagents give ketoximes on workup (eq 11).[4]

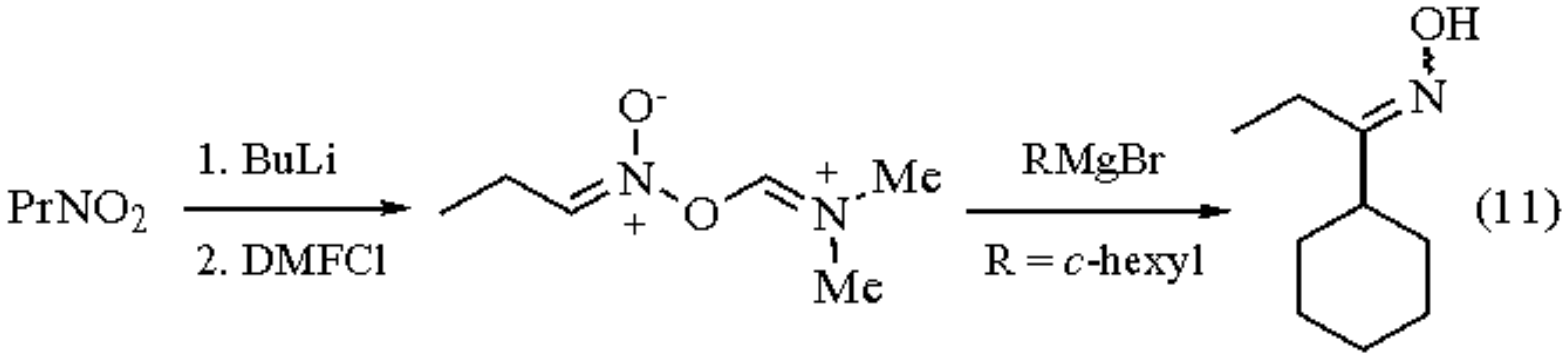

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Oxazole[1,2]

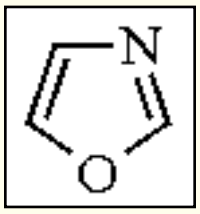

[288-42-6] · C_3H_3NO · Oxazole · (MW 69.07)

(2-aza Diels-Alder diene,[2] precursor to *N*-formylformamide[3])

Physical Data: mp -87 to -84 °C; bp 69-70 °C; *d* 1.050 g cm^{-3}; λ_{max} 205 nm (ε 3900).

Form Supplied in: colorless oil.

Preparative Methods: two methods have been reported for the preparation of oxazole.[4,5] The more recent approach entails three steps (eqs 1 and 2) and an overall yield of 39%.

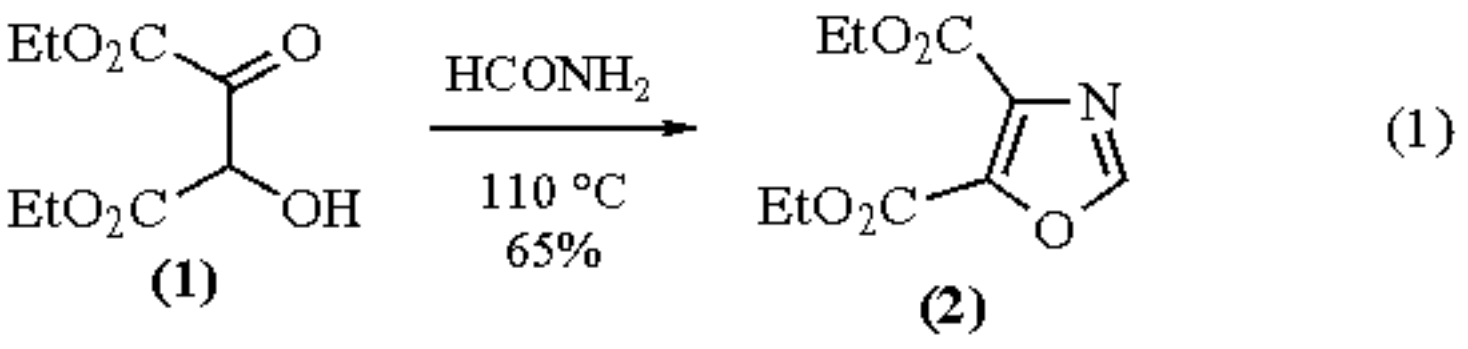

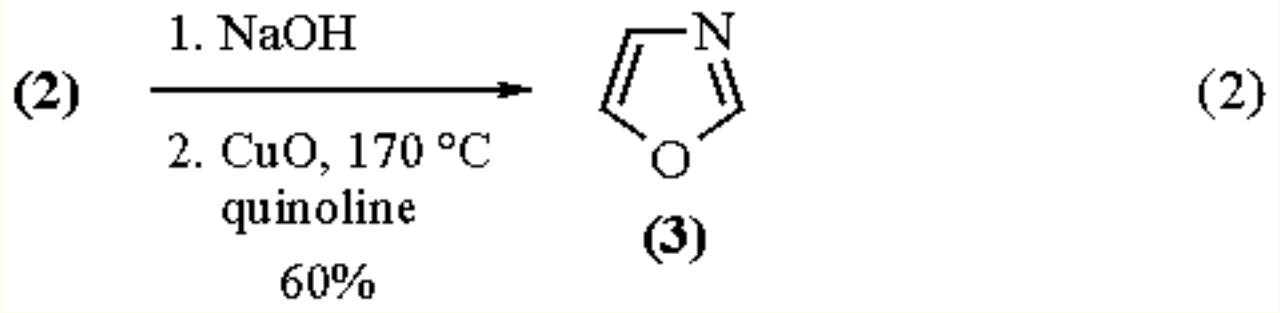

General Discussion.

Oxazole functions as an azadiene in the Diels-Alder reaction.[2] The resulting [4 + 2] product is normally not isolated, instead rearranging to pyridines (eq 3). High regioselectivity has been reported[6] for this reaction (see also ***4-Phenyloxazole***). Oxazole can also perform as a dienophile, as in the reaction with tetrazines (eq 4).[7]

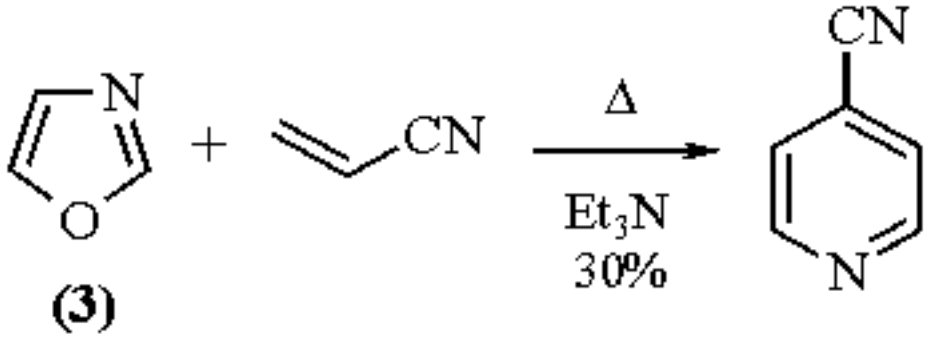

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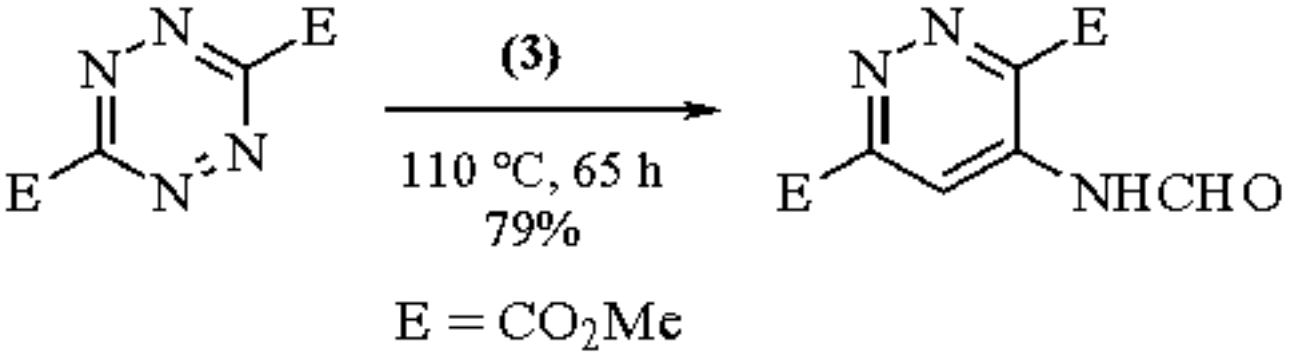

(4)

Treatment of oxazole with one equivalent of ***Ozone*** cleaves the C-C bond and yields *N*-formylformamide (**4**) (eq 5).[3] Subsequent addition of primary or secondary amines gives high yields of formamides (eq 6). Formylation of alcohols is substantially slower.

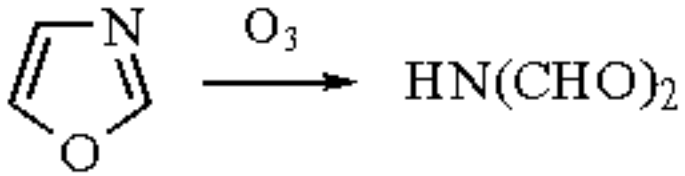

(3) (4) (5)

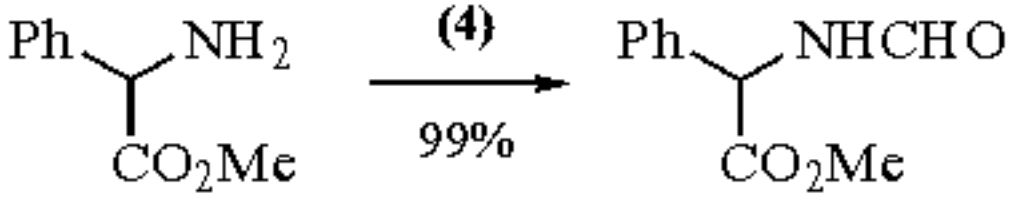

(6)

Metalation at C-2 of oxazole is rapid with ***n-Butyllithium***, and the metalated product is in equilibrium with the ring-opened isocyanide (eq 7). Highly reactive electrophiles yield products from the enolate form of (**5**) (eqs 8 and 9), while less reactive electrophiles react with the carbanion form (eqs 10 and 11).[8]

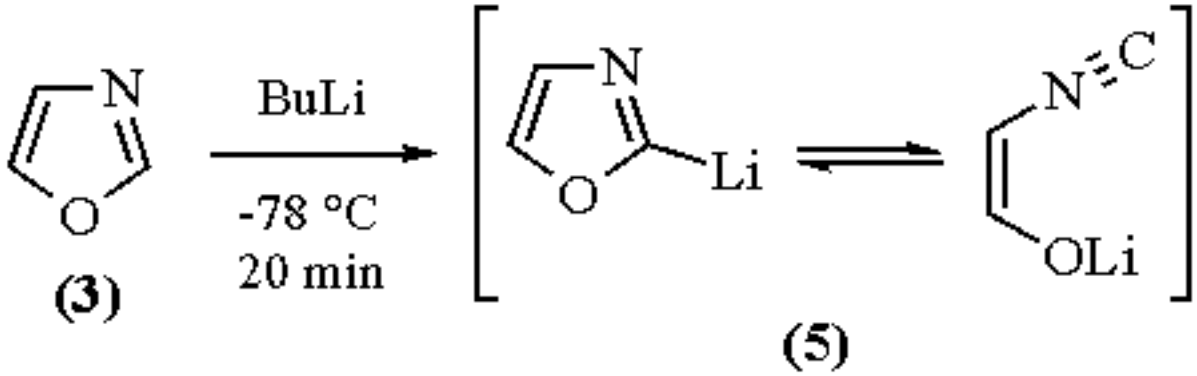

(7)

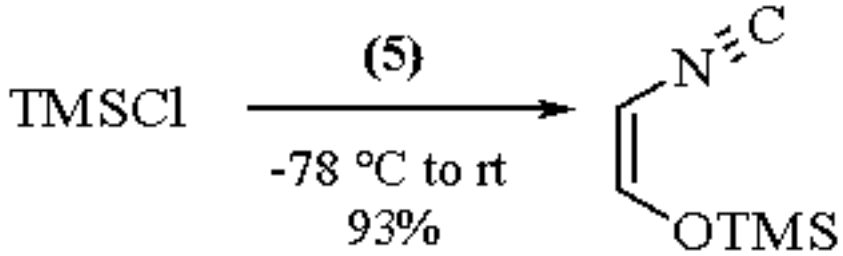

(8)

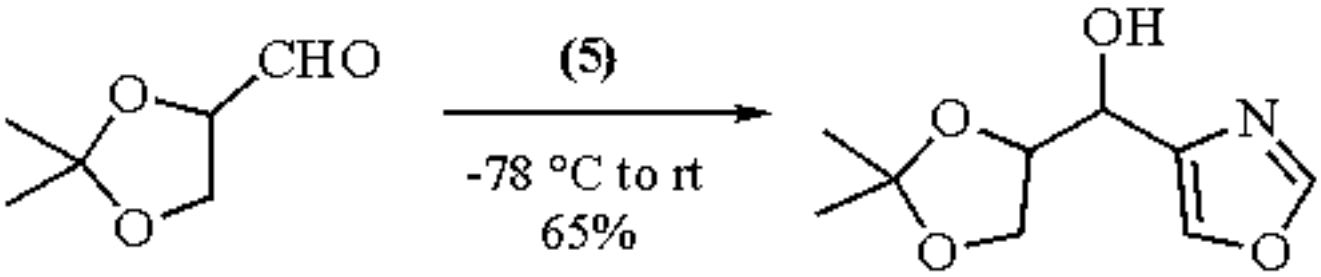

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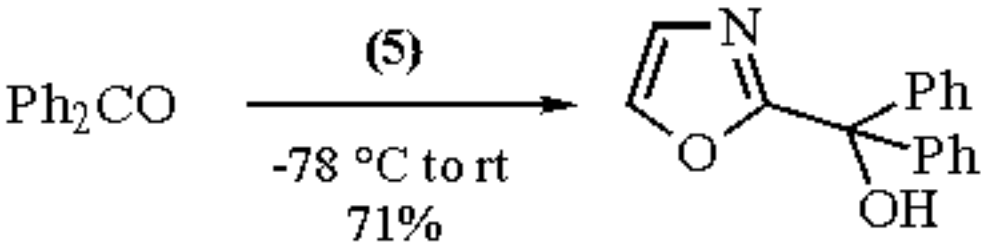

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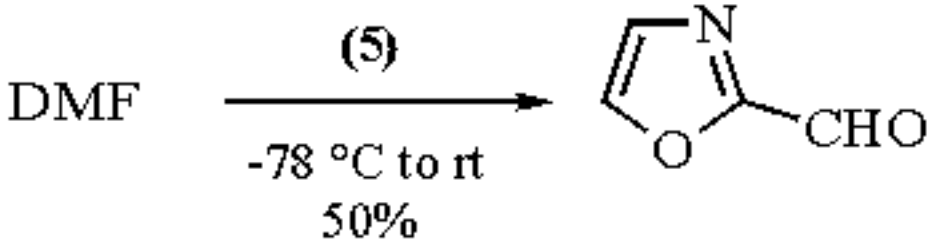

(11)

Palladium-catalyzed coupling of chloropyrazines with oxazole occurs at C-2, yielding the diaryl in good yield (eq 12).[9]

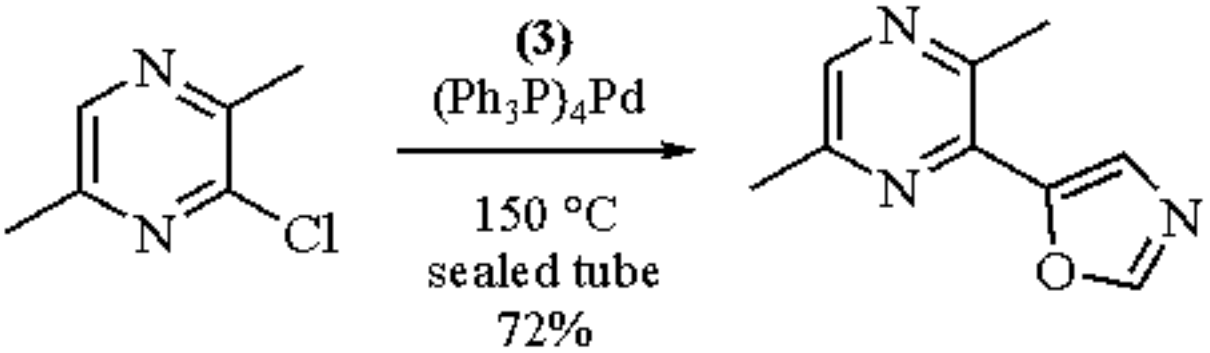

(12)

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(2-Oxoisopentyl)triphenylarsonium Bromide

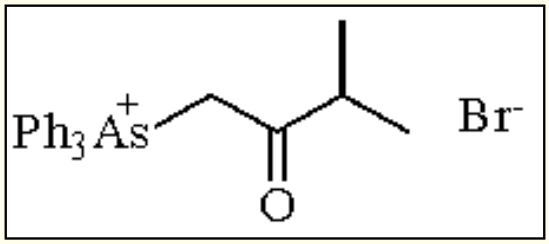

[-] · $C_{23}H_{24}AsBrO$ · (2-Oxoisopentyl)triphenylarsonium Bromide · (MW 471.29)

(highly stereoselective alkenation reagents for the synthesis of (*E*)-β-enones; especially suitable for unstable aldehyde substrates in natural products synthesis)

Physical Data: mp 181-182 °C.

Solubility: insol ether; sol THF, MeCN, etc.

Preparative Methods: from ***Triphenylarsine*** and 1-bromo-3-methyl-2-butanone, which is obtained from 3-methyl-2-butanone and bromine in methanol.[1]

Handling, Storage, and Precautions: the toxicity of this reagent is unknown at present; use in a fume hood.

General Discussion.

The synthesis of (*E*)-β-enones is usually accomplished by the Wittig or Horner-Emmons reaction. It has been shown that arsonium ylides with electron-withdrawing substituents in the alkylidene moiety are more reactive than the corresponding phosphorane[2,3] and a facile approach to achieve the alkenation using arsonium salts has been disclosed.[4,5]

β-(*E*)-Enones are prepared in high yields with high stereoselectivity by reaction of (**1**) with aldehydes under PTC conditions (eq 1).[6]

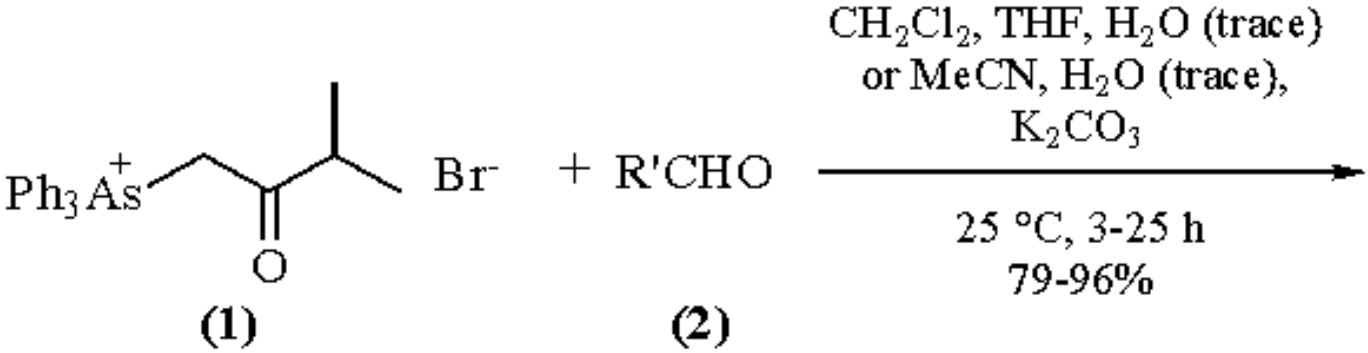

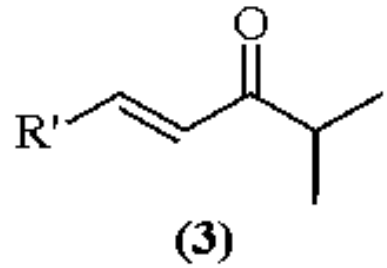

(1)

Similarly, 2-(oxoheptyl)triphenylarsonium bromide ($C_{25}H_{28}OAsBr$, mp 156-159 °C) (**4**) reacts with aldehydes to give (**5**) (eq 2).[6]

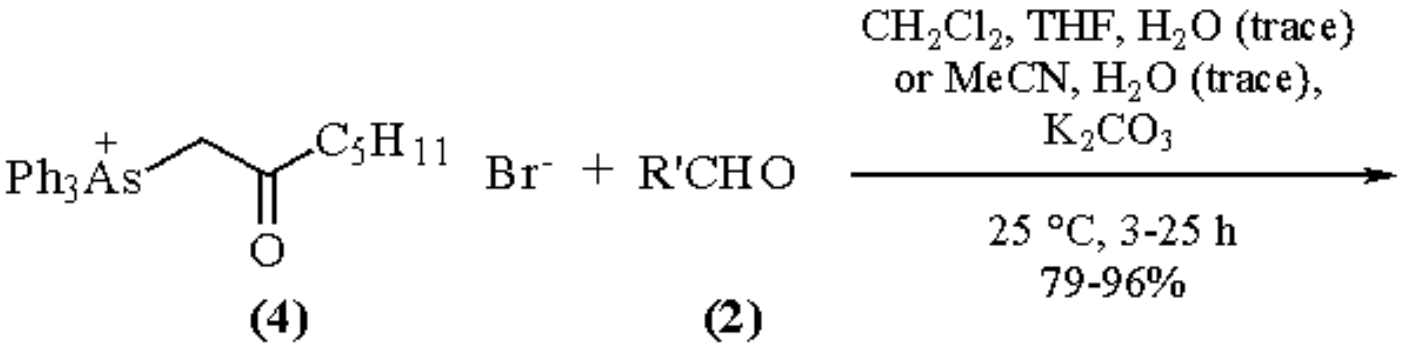

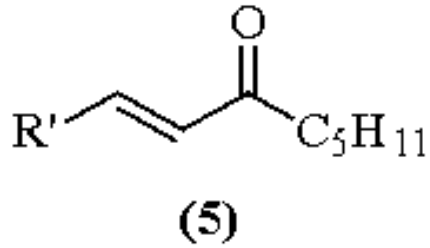

(2)

The aldehyde (**6**) reacts with the arsonium salt (**1**) in acetonitrile to give the key intermediate (**7**) for the synthesis of brassinosteroid in 78% yield (eq 3).

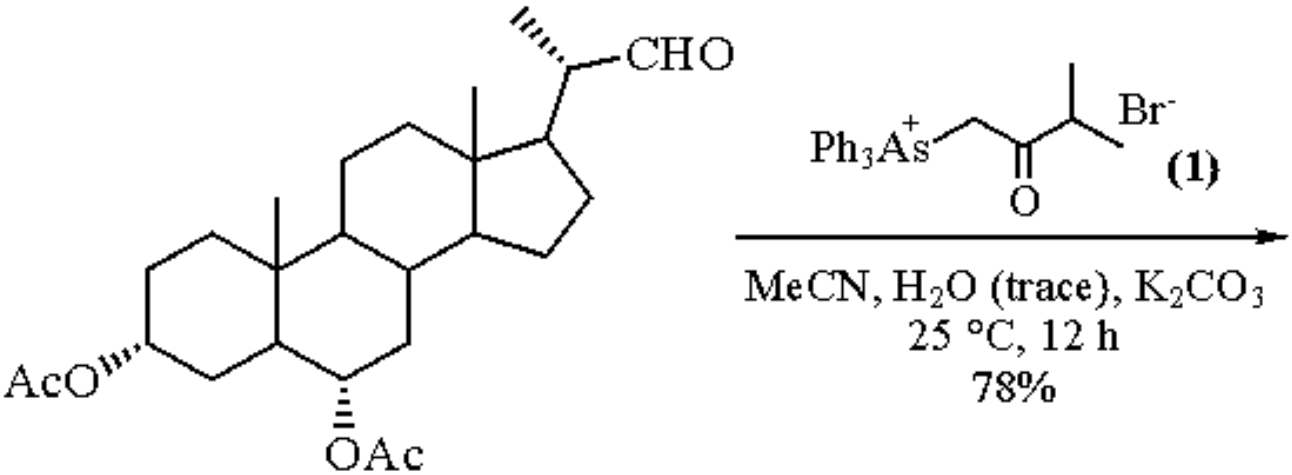

(6)

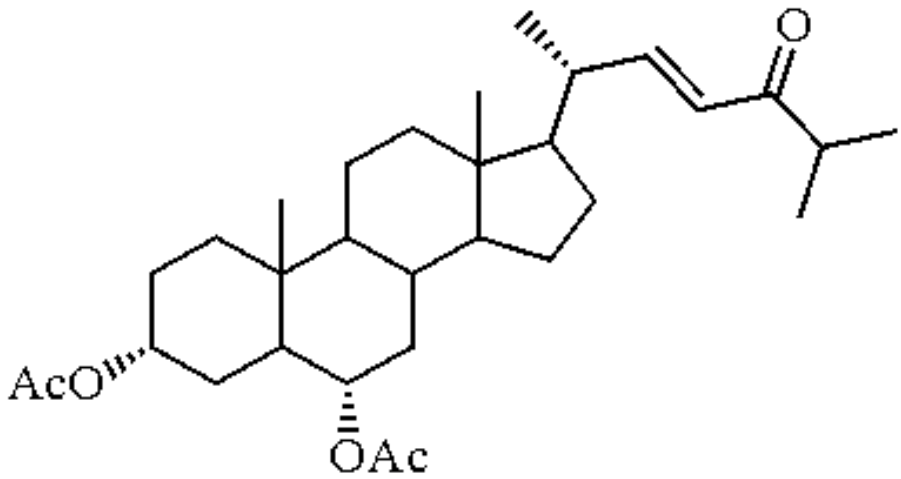

(3)

(7)

The construction of the alkenyl side chain of $PGF_{2\alpha}$ and its analogs has frequently been accomplished by alkenation of the Corey aldehyde (**8**) with phosphonic esters or phosphoranes.[7] However, the reactions must be strictly controlled and elimination of the acetoxy group often occurs in large scale reactions. When the reaction of (**9**) and (**4**) is carried out in acetonitrile, the elimination product is formed predominantly. However, with the CH_2Cl_2/THF solvent system in which the salt (**4**) is more soluble, the elimination is completely prevented. Thus the unstable aldehyde (**9**) reacts smoothly with (**4**) to give $PGF_{2\alpha}$ intermediate (**10**) in 63% overall yield from (**8**) (eq 4).[6]

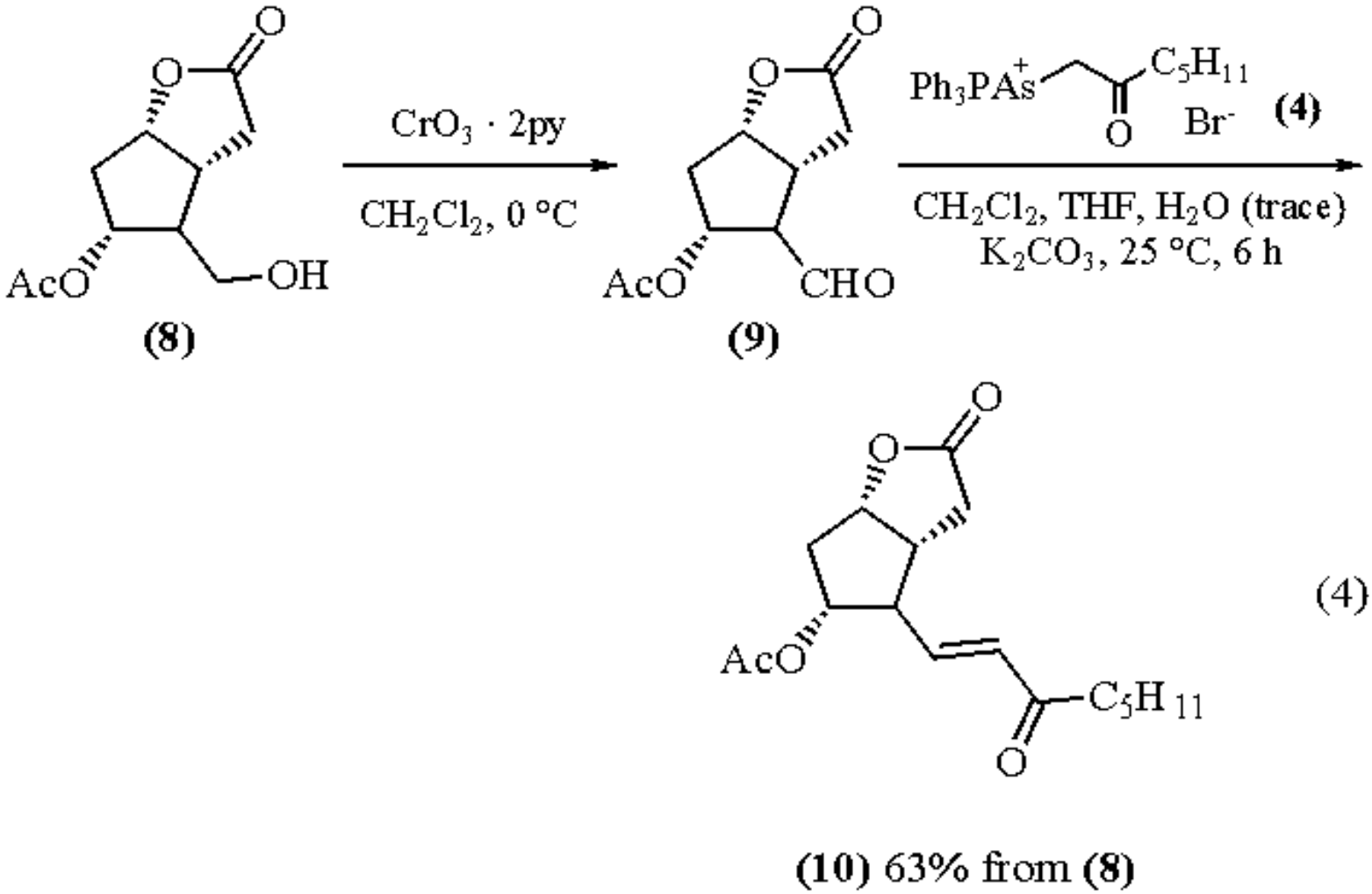

The related arsonium salt (4-oxopent-2(*E*)-enyl)triphenylarsonium bromide (**11**) (mp 127-128 °C) is prepared from triphenylarsine and (*E*)-5-bromo-3-penten-2-one without solvent at 50 °C for 4 h in 43% yield (eq 5).

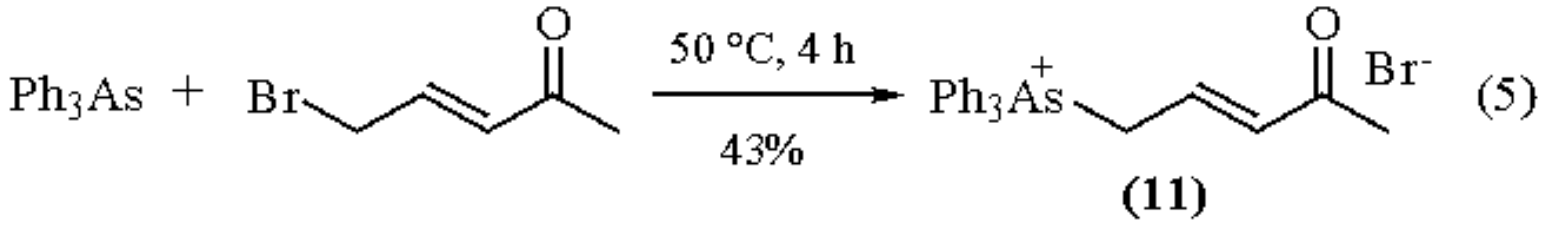

Aldehydes react with (**11**) in ether (trace H_2O) and K_2CO_3 at 0-3 °C to give a mixture of (*E*,*E*) and (*E*,*Z*) isomers in 81% yield, with the former predominating. The latter can be easily isomerized to the (*E*,*E*) isomer when treated with catalytic amount of I_2 under daylight.

A naturally occurring trail-breaking alarm pheromone of sea slug, navenone A, has been synthesized in 46% yield by a two-step alkenation sequence (eq 6).[8] In contrast, an alternative seven-step sequence provided navenone A in 1.1% overall yield.[9]

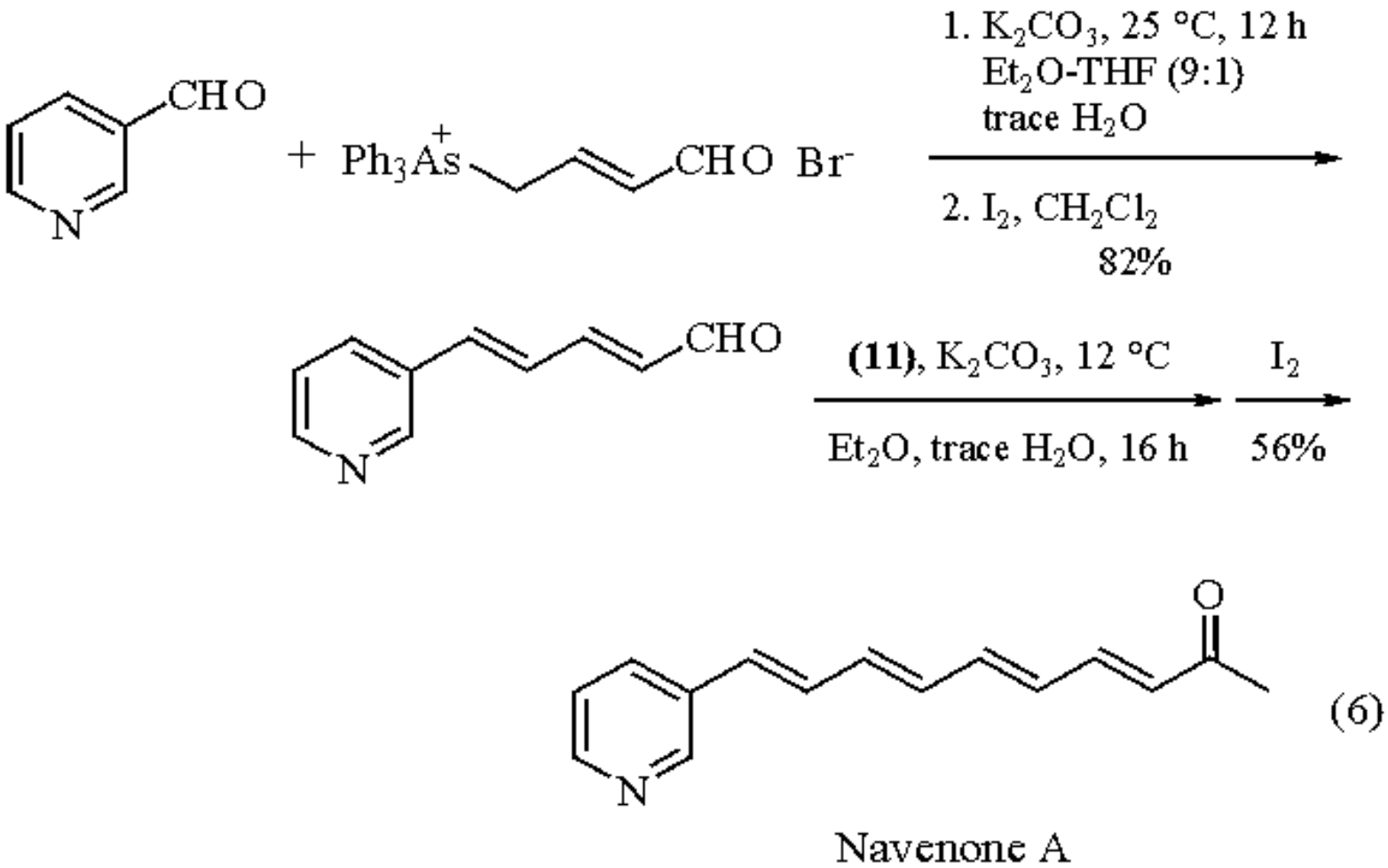

1. Gaudry, M. G.; Marquet, A. *OS* **1976**, *55*, 24.
2. (a) Huang, Y. Z.; Shen, Y. C. *Adv. Organomet. Chem.* **1982**, *20*, 115 and references cited therein. (b) Huang, Y. Z.; Xu, Y. Y.; Li, Z. *OPP* **1982**, *14*, 373.
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9. Sakakibara, M.; Matsui, M. *ABC* **1979**, *43*, 117.

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μ-Oxobis(chlorotriphenylbismuth)[1]

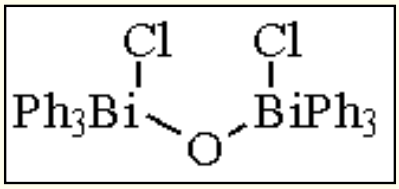

[35952-85-3] · $C_{36}H_{30}Bi_2Cl_2O$ · μ-Oxobis(chlorotriphenylbismuth) · (MW 967.52)

(mild oxidant for alcohols and α-glycol cleavage[4])

Physical Data: mp 148-154 °C.[2]

Solubility: sol CH_2Cl_2, $CHCl_3$, THF, hot benzene.

Preparative Methods: by treatment of ***Triphenylbismuth Dichloride*** with NaOH in MeOH-acetone.[3]

Handling, Storage, and Precautions: stable white solid. Can be stored in the refrigerator under inert gas (N_2 or Ar) for some weeks. This reagent should be handled in a fume hood.

Oxidation of Alcohols.[3,4]

Oxobis(chlorotriphenylbismuth) is a mild oxidant for primary, secondary, allylic, and benzylic alcohols, which are converted smoothly and in high yields to the corresponding carbonyl derivatives under mild conditions of pH and temperature. The oxidation is generally performed by addition of the alcoholic substrate to a solution of the reagent in CH_2Cl_2 in the presence of K_2CO_3 or $KHCO_3$ at rt or under reflux. The carbonyl products are easily separated from the triphenylbismuth byproduct, either by chromatography on silica gel, or by heating the reaction mixture with acetic acid followed by aqueous workup and ether extraction. Unfortunately this latter procedure curtails the advantage of the near neutral reaction conditions. The reagent is especially effective for the oxidation of allylic alcohols. Examples of the efficiency of the reagent are found in the oxidation of natural products. The oxidation of methyl hederagenin to methyl hederagonate was performed in 24 h with a 36% yield (eq 1), significantly better than the previously reported oxidation.[5] In the synthesis of digitoxin derivatives, the oxidation of a furyl alcohol to the 15-keto derivative was achieved in 94% yield (eq 2).[6] In the oxidation of cembranolide diterpenes,[7] the reaction was accomplished without disturbing the oxirane ring (eq 3).

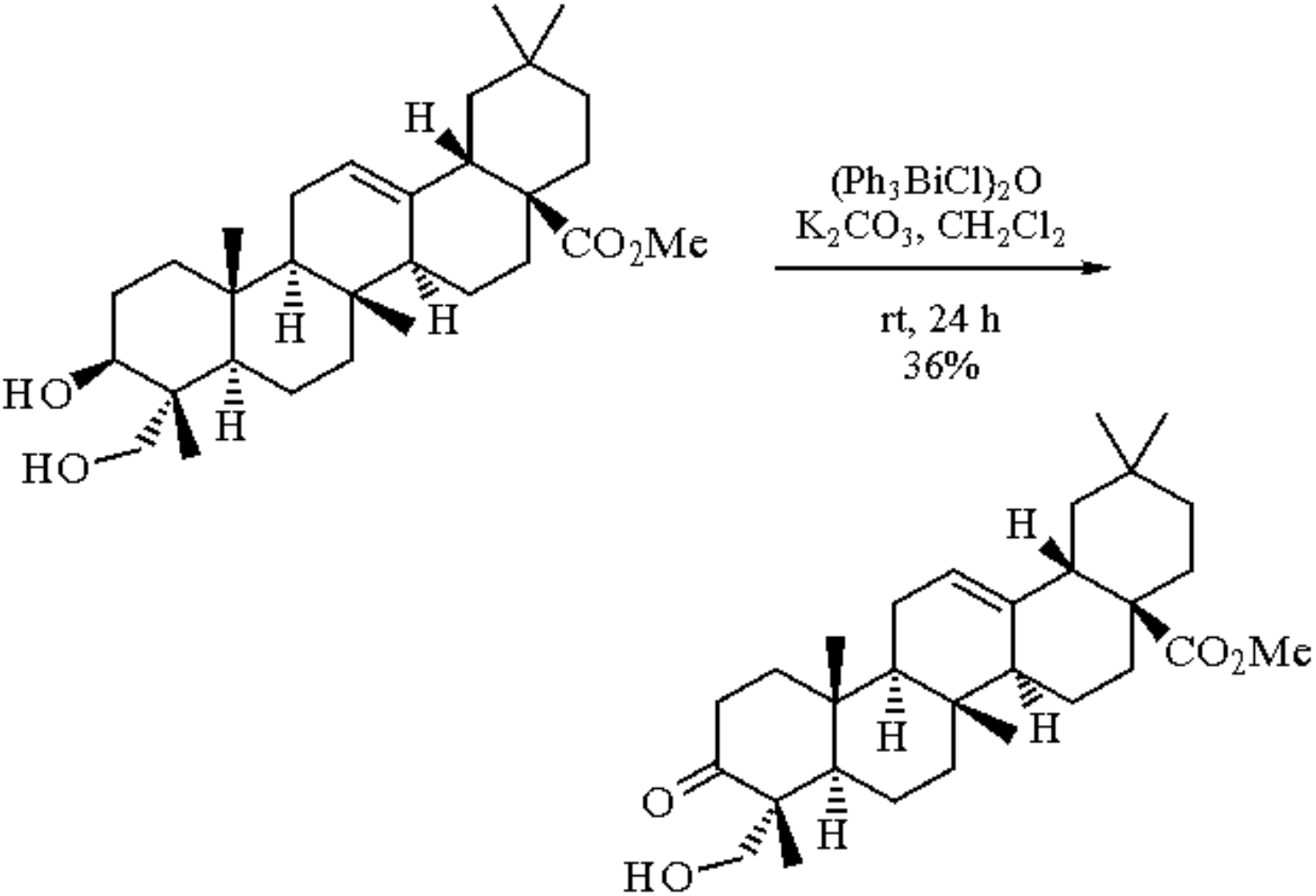
H
CO2Me
H
H
HO
H
HO
(Ph3BiCl)2O
K2CO3, CH2Cl2
rt, 24 h
36%
H
CO2Me
H
H
O
H
HO

(1)

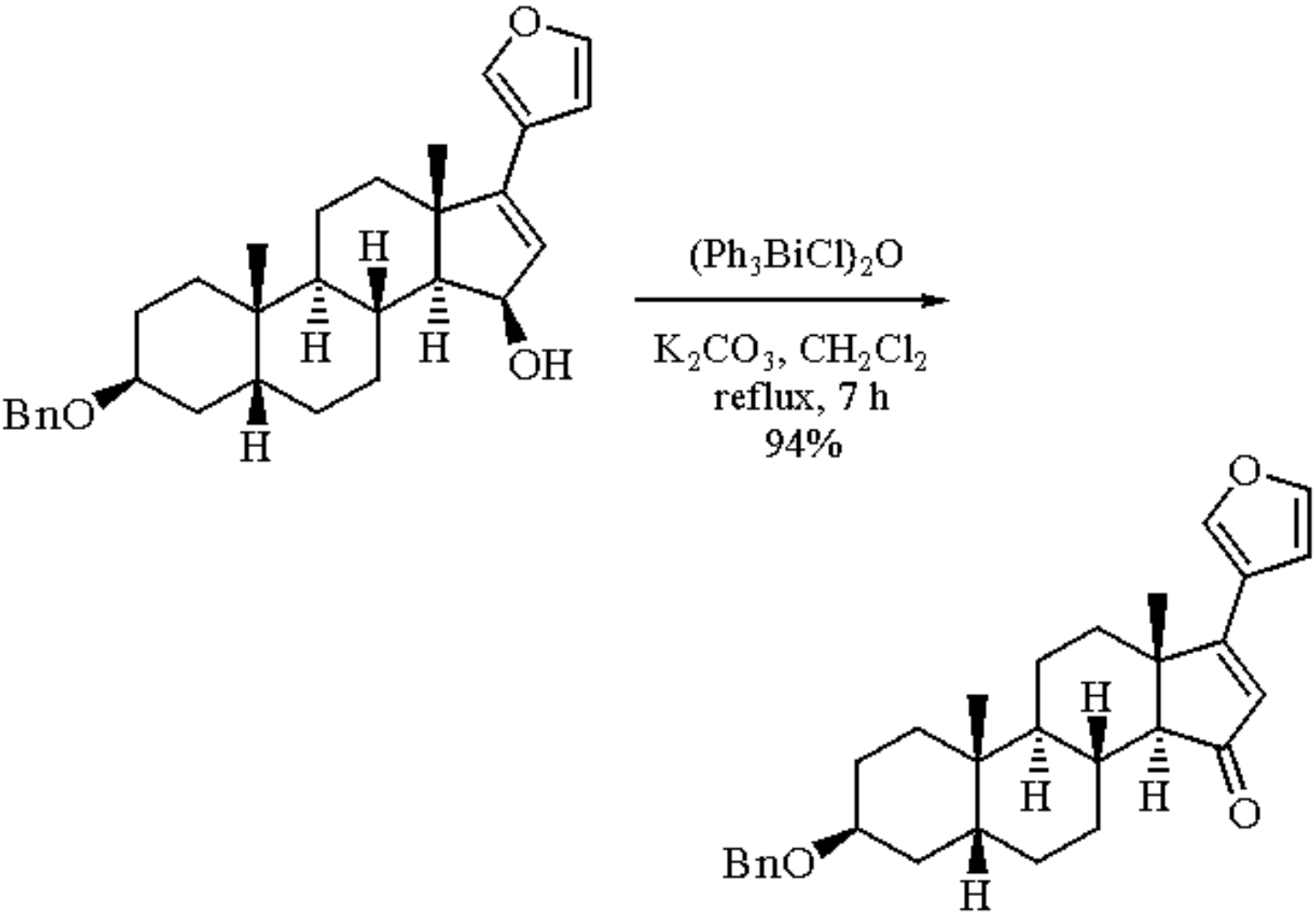
O
H
H
H
OH
BnO
H
$(Ph_3BiCl)_2O$
K_2CO_3, CH_2Cl_2
reflux, 7 h
94%
O
H
H
H
O
BnO
H

(2)

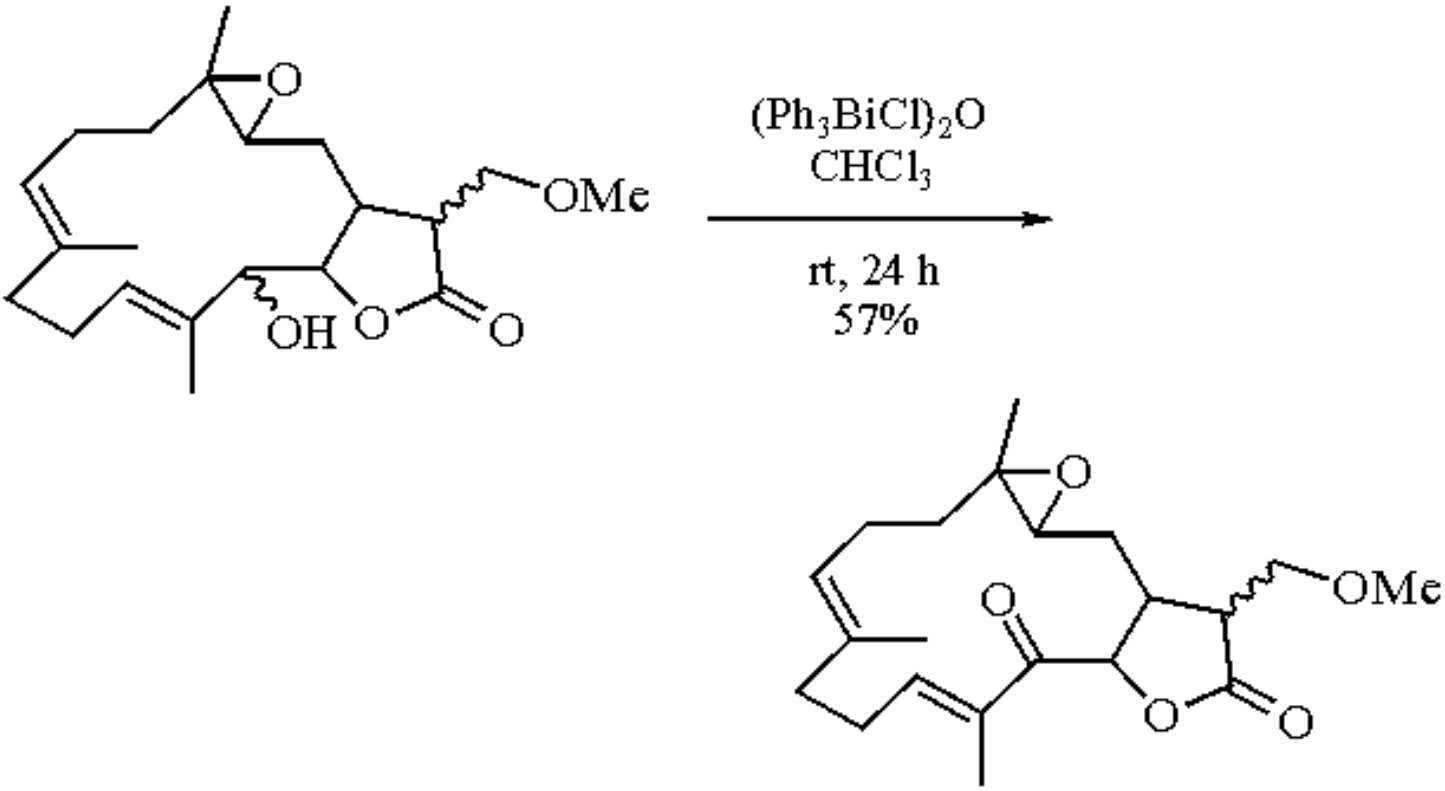
O
OMe
OH
O
O
$(Ph_3BiCl)_2O$
$CHCl_3$
rt, 24 h
57%
O
OMe
O
O
O

(3)

1,2-Glycols are cleaved under the same reaction conditions to afford the two derived carbonyl components. However, this reaction has not been developed as much as the glycol cleavage by triphenylbismuth carbonate.

Related Reagents.

See also the oxidizing reagents ***Triphenylbismuth Carbonate***, ***Triphenylbismuth Diacetate***, and ***Triphenylbismuth Dichloride***; for glycol cleavage, see ***Triphenylbismuthine*** and ***Triphenylbismuth Carbonate***.

---

1. (a) Barton, D. H. R.; Finet, J. P. *PAC* **1987**, *59*, 937. (b) Abramovitch, R. A.; Barton, D. H. R.; Finet, J. P. *T* **1988**, *44*, 3039. (c) Kitchin, J. P. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J.; De Jonge, C. R. H. I., Eds.; Plenum: New York, 1986; p 817.
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7. Ahond, A.; Bowden, B. F.; Coll, J. C.; Fourneron, J. D.; Mitchell, S. J. *AJC* **1979**, *32*, 1273.

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μ-Oxobis[tris(dimethylamino)phosphonium] Bis(tetrafluoroborate)[1]

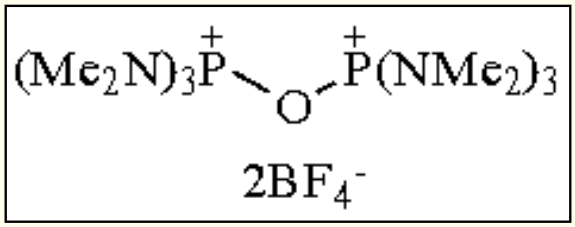

[55881-03-3] · $C_{12}H_{36}B_2F_8N_6OP_2$ · μ-Oxobis[tris(dimethylamino)phosphonium] Bis(tetrafluoroborate) · (MW 516.10)

(a mild dehydrating agent, useful in peptide synthesis,[2] dehydration of aldoximes to nitriles[3] and Beckmann or Lossen-type rearangements[3])

Alternate Name: Bates' reagent.

Physical Data: mp 194-204 °C.

Solubility: insol ether, EtOAc, THF, CH_2Cl_2, $CHCl_3$; sol MeCN, DMF, HMPA.

Form Supplied in: white crystalline solid; limited commercial availability.

Preparative Methods: by treatment of ***Hexamethylphosphoric Triamide*** with *p*-toluenesulfonic anhydride at 55 °C for 3 h, isolation of the bis(*p*-toluenesulfonate), then treatment with $NaBF_4$ in MeCN.[2]

Handling, Storage, and Precautions: can be used with care without special precautions; however, it reacts with water to produce HMPA (carcinogenic) and HBF_4 (corrosive).

Peptide Synthesis.

Bates' reagent is a dehydrating agent used in the synthesis of peptides (eq 1).[1] It has the advantage over ***1,3-Dicyclohexylcarbodiimide*** (DCC) that the byproducts of the reaction (HMPA, etc.) are water-soluble and easily removed. A disadvantage is that it results in extensive racemization. This can be overcome, however, by the addition of ***1-Hydroxybenzotriazole*** (HOBT).[1] Bates' reagent, even in conjunction with HOBT, is not as popular as the closely related reagent ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate*** (BOP).[4] The latter

reagent is more readily available, considerably cheaper, has a lower molecular weight (less reagent is required), produces less acid (less base is required), and is more efficient for solid-phase peptide synthesis.[5]

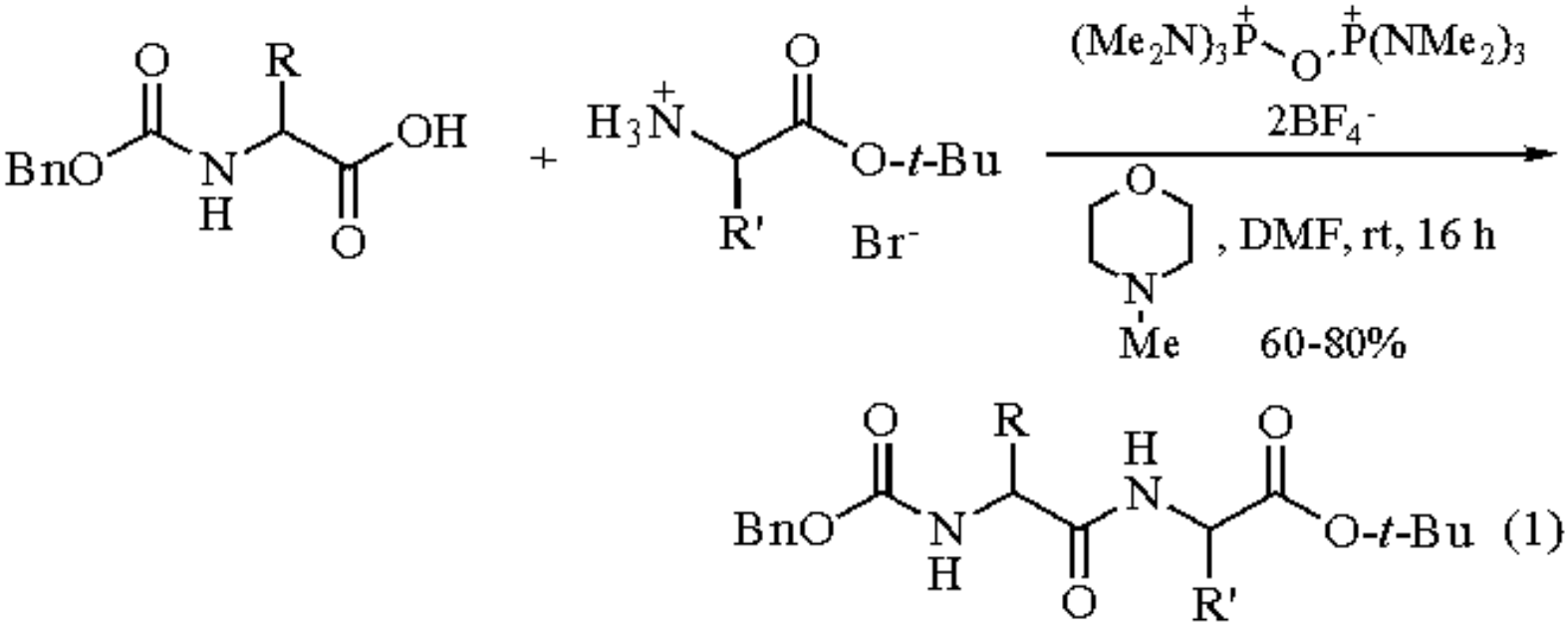

Activation of *N*-Hydroxy Compounds.

Bates' reagent is a useful reagent for the Beckmann rearrangement of ketoximes (eq 2), dehydration of aldoximes to nitriles (eq 3), and Lossen-type rearrangement of hydroxamic acids (eq 4).[3]

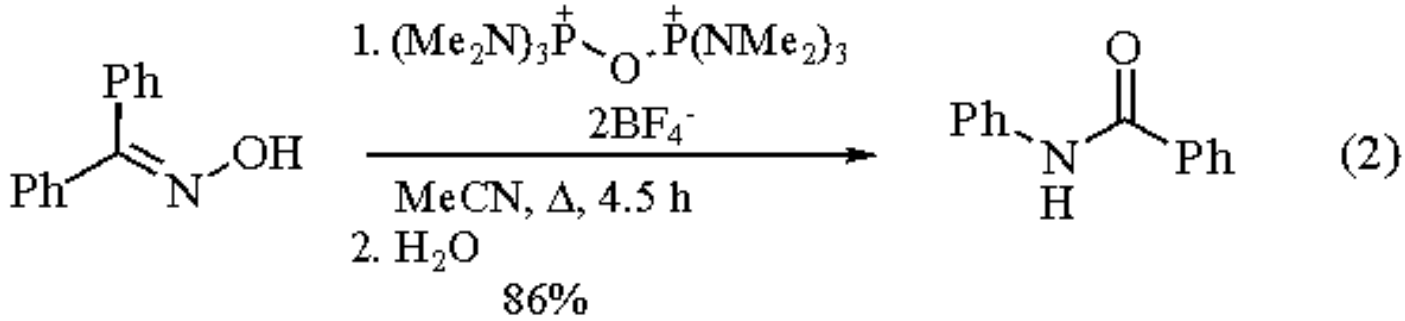

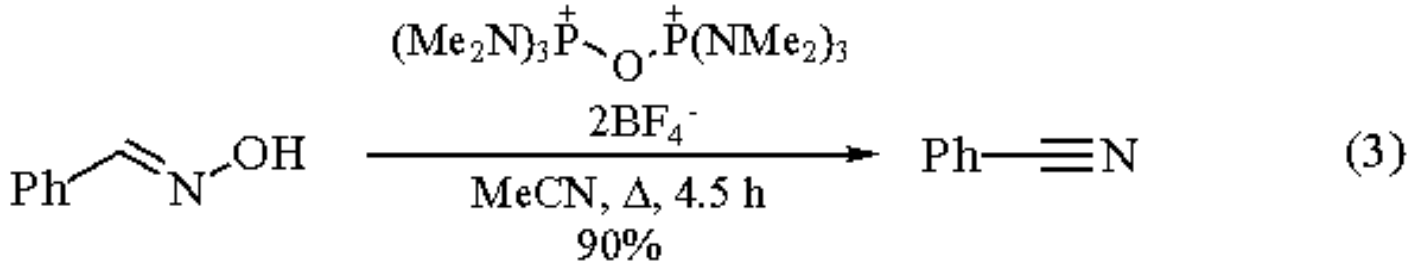

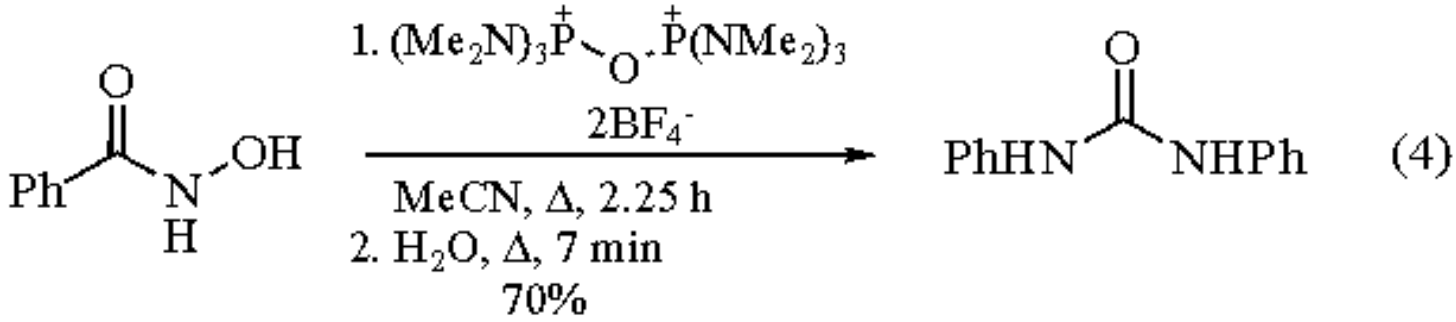

It is much less reactive as an activating/dehydrating agent than is the analogous Ph_3+P-O-+PPh_3 2OTf$^-$,[6] where reactions are often complete in a few minutes at rt. However, a disadvantage of the latter reagent is the difficulty of separating the product from Ph_3PO.

---

1. *FF* **1977**, *6*, 425.
2. Bates, A. J.; Galpin, I. J.: Hallett, A.; Hudson, D.; Kenner, G. W.; Ramage, R. *HCA* **1975**, *58*, 688.
3. Galpin, I. J.; Gordon, P. F.; Ramage, R.; Thorpe, W. D. *T* **1976**, *32*, 2417.
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6. Hendrickson, J. B.; Hussoin, Md. S. *JOC* **1987**, *52*, 4137; **1989**, *54*, 1144.

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Oxodimethoxyphosphoranesulfenyl Chloride[1]

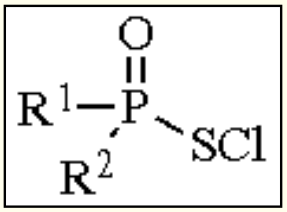

(**1**; $R^1 = R^2 = OMe$)

[13894-35-4] · $C_2H_6ClO_3PS$ · Oxodimethoxyphosphoranesulfenyl Chloride · (MW 176.57) (**2**; $R^1 = R^2 = OEt$)

[1186-08-9] · $C_4H_{10}ClO_3PS$ · Oxodimethoxyphosphoranesulfenyl Chloride · (MW 204.63) (**3**; $R^1 = R^2 =$ O-*i*-Pr)

[55655-36-2] · $C_6H_{14}ClO_3PS$ · Oxodimethoxyphosphoranesulfenyl Chloride · (MW 232.69)

(reacts as a pseudohalogen;[1] adds across alkenes and alkynes with little regioselectivity;[2-5] can thiophosphorylate aldehydes and ketones α to the carbonyl[6])

Physical Data: (**1**) bp 50 °C/0.06 mmHg. (**2**) bp 50 °C/0.2 mmHg. (**3**) bp 86 °C/2 mmHg.

Solubility: sol CH_2Cl_2, CCl_4, benzene, diethyl ether, THF.

Form Supplied in: yellow liquids; not commercially available.

Preparative Methods: prepared from a variety of different precursors using the procedures shown in eq 1.[1]

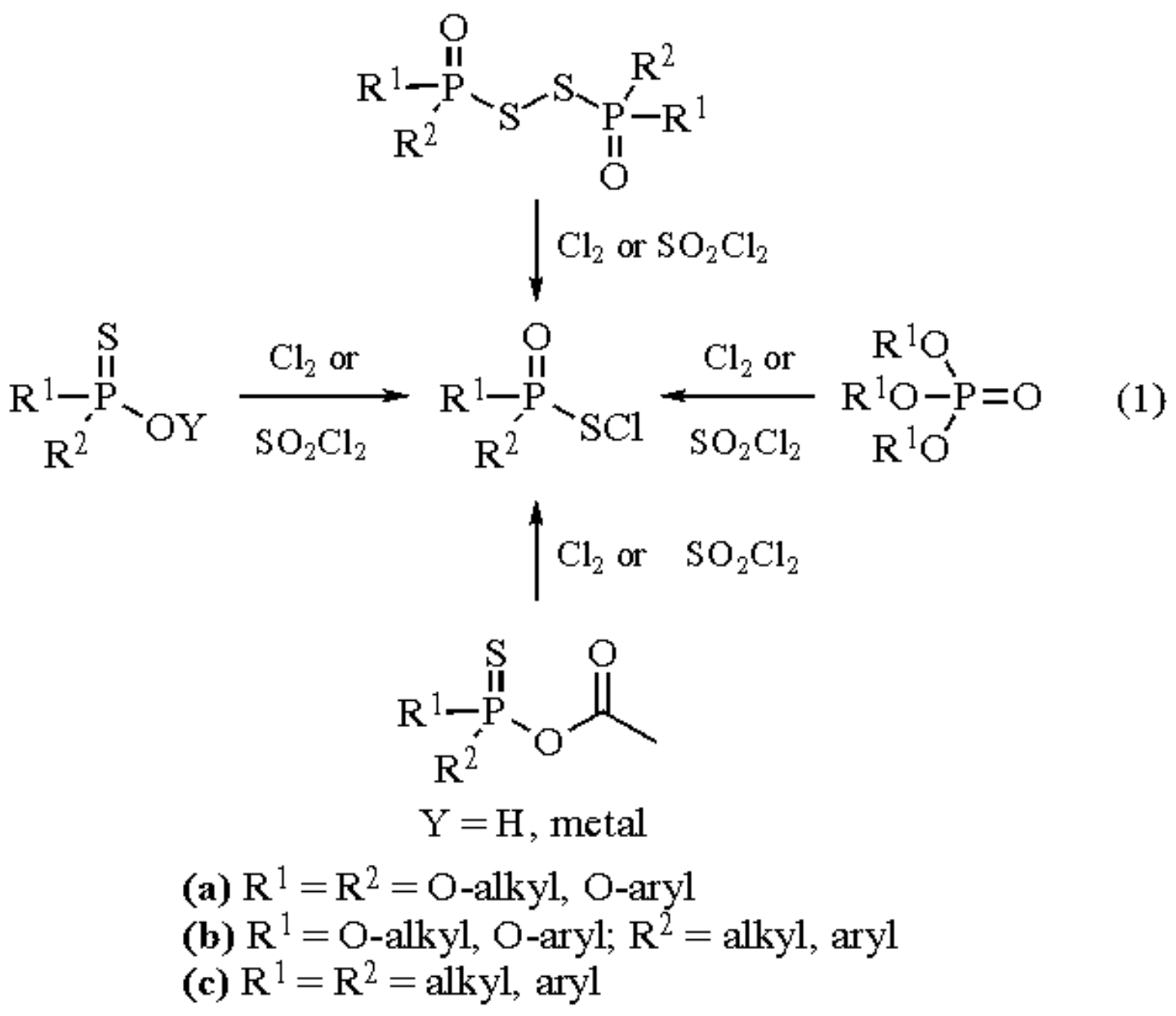

Handling, Storage, and Precautions: stability is in the order: phosphoro, $(R^1O)_2P$- > phosphono, $(R^1O)R^2P$- > phosphino, R^1R^2P-. Phosphoryl derivatives are quite stable and may be distilled under vacuum. They decompose upon storage, even at low temperatures, and are often prepared and used in situ. Phosphono derivatives lose sulfur on heating and phosphino derivatives lose sulfur at 20 °C and are only moderately stable at 0 °C.

Additions to Alkenes.

The addition of phosphoranesulfenyl chlorides to alkenes is not as regioselective as similar additions of methanesulfenyl chloride or other alkyl- and arylsulfenyl chlorides where anti-Markovnikov products tend to predominate.[2] This is due to the fact that additions of phosphoranesulfenyl chlorides proceed by an Ad_E2 mechanism which does not necessarily involve a thiiranium ion intermediate, in contrast to those of *C*-sulfenyl chlorides.[3,7] The electron-withdrawing property of the phosphorus impairs the bridging ability of the sulfur atom sufficiently to make

the intermediate possess more carbonium ion character, with the chloride counterion more closely associated with the sulfur atom.[2,8] Also, the oxygen atom attached to phosphorus may contribute to stabilization of cationic intermediates (eq 2).[3]

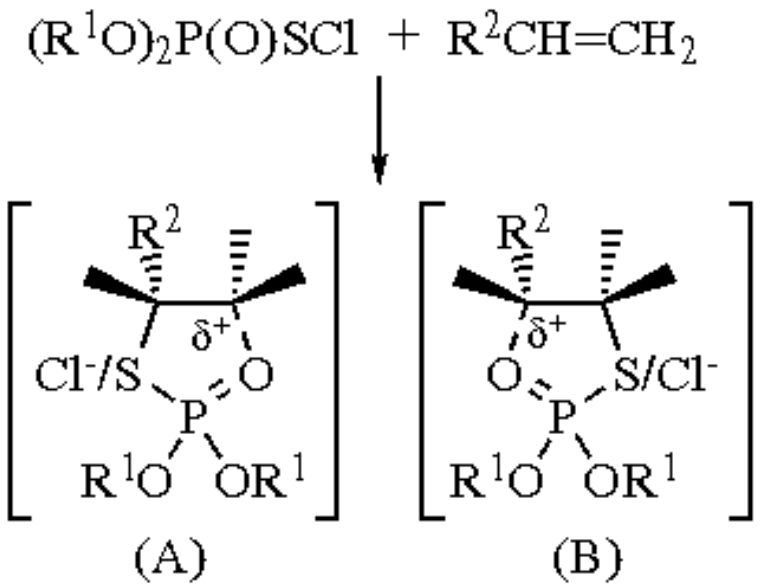

(2)

The additional regiochemical dependence of these additions on the steric and electronic effects of the alkene and phosphorus substituents can contribute to the low regioselectivity of these reactions (eqs 3 and 4).[3,4]

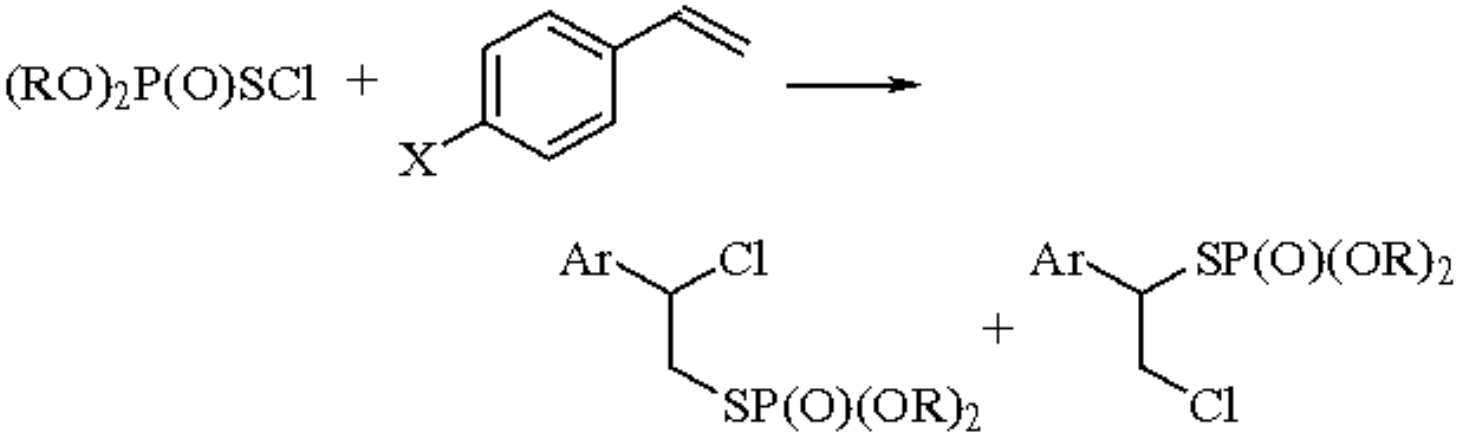

(3)

R = Me	X = Cl, Br, CH_2Cl, NO_2	100:0
R = *i*-Pr	X = Cl, Br, CH_2Cl, NO_2	50:50

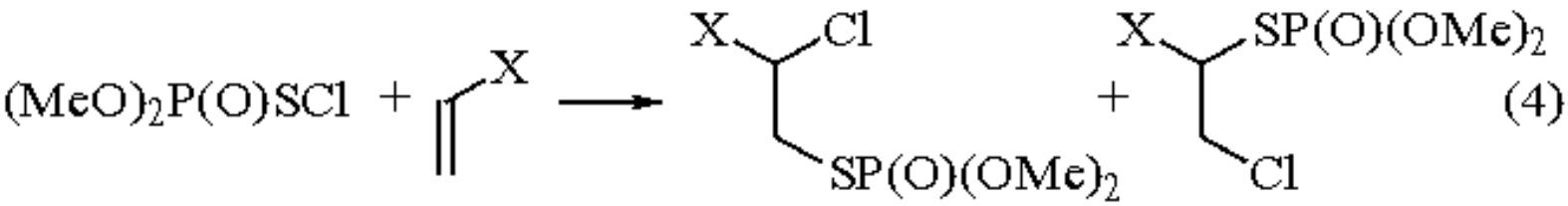

X = CN, SO_2Me, $SiEt_2Me$	0:100
X = Ph	100:0
X = CO_2Me	66:34
X = P(O)(OEt)$_2$	50:50

Addition to Alkynes.

The substantial amount of *cis* product produced in the addition of phosphoranesulfenyl chlorides to alkynyl compounds is evidence for an unsymmetrical reaction intermediate in which an appreciable amount of positive charge is localized on one carbon atom (eq 5).[5]

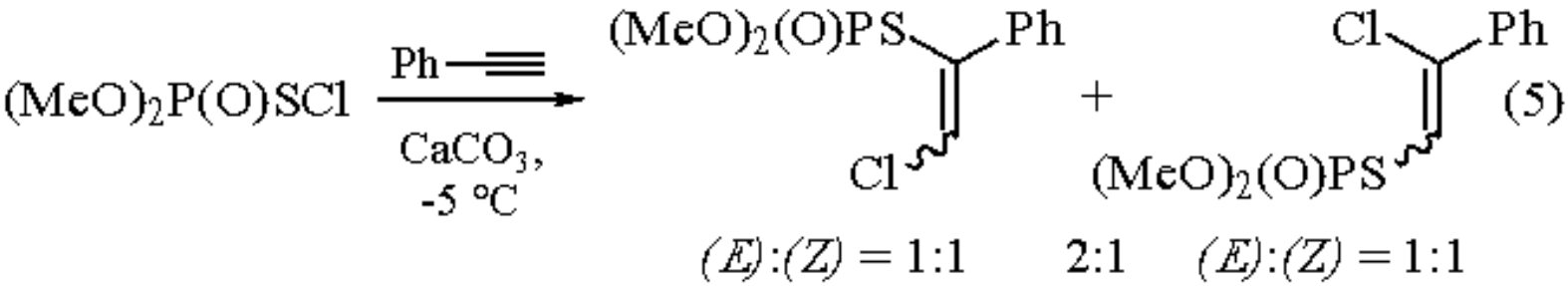

Addition to Allylsilanes and Allylstannanes.

Reaction of phosphoranesulfenyl chlorides with allylsilanes and allylstannanes is similar, with both giving the products of an S_E2' mechanism (although this mechanistic pathway has not been proven).[5] In the case of allylsilanes, however, other products are also formed (eq 6).

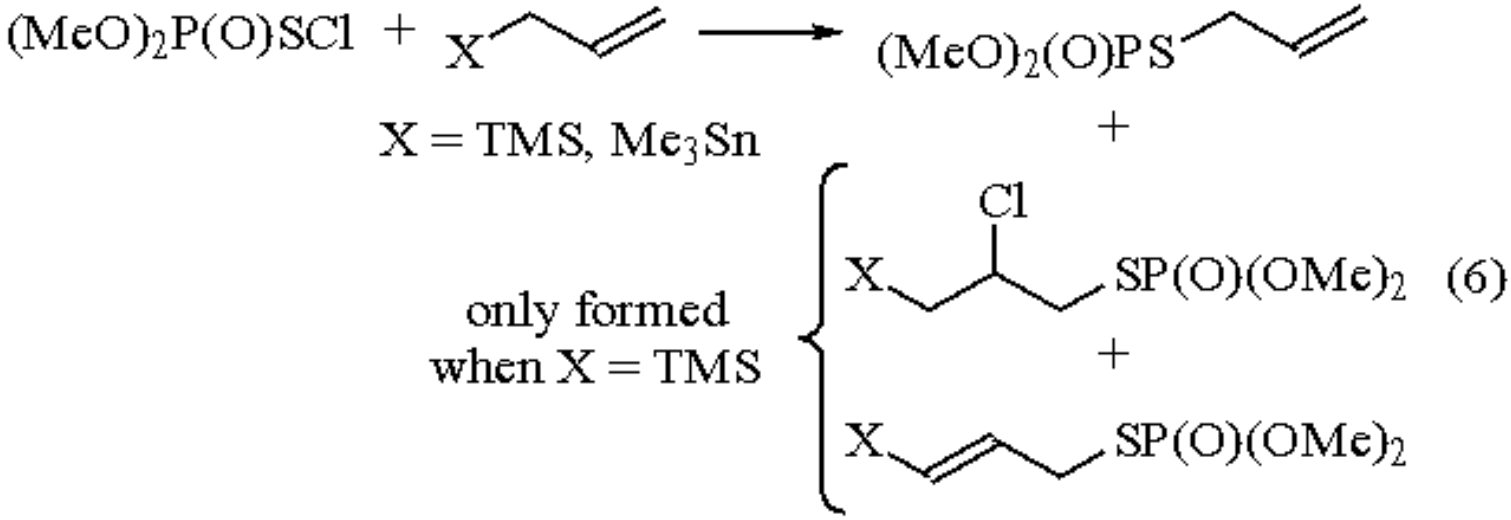

Reaction with Aldehydes and Ketones.

Aldehydes and ketones may be thiophosphorylated α to the carbonyl by reaction of silyl enol ethers with phosphoranesulfenyl chlorides (eq 7).[6]

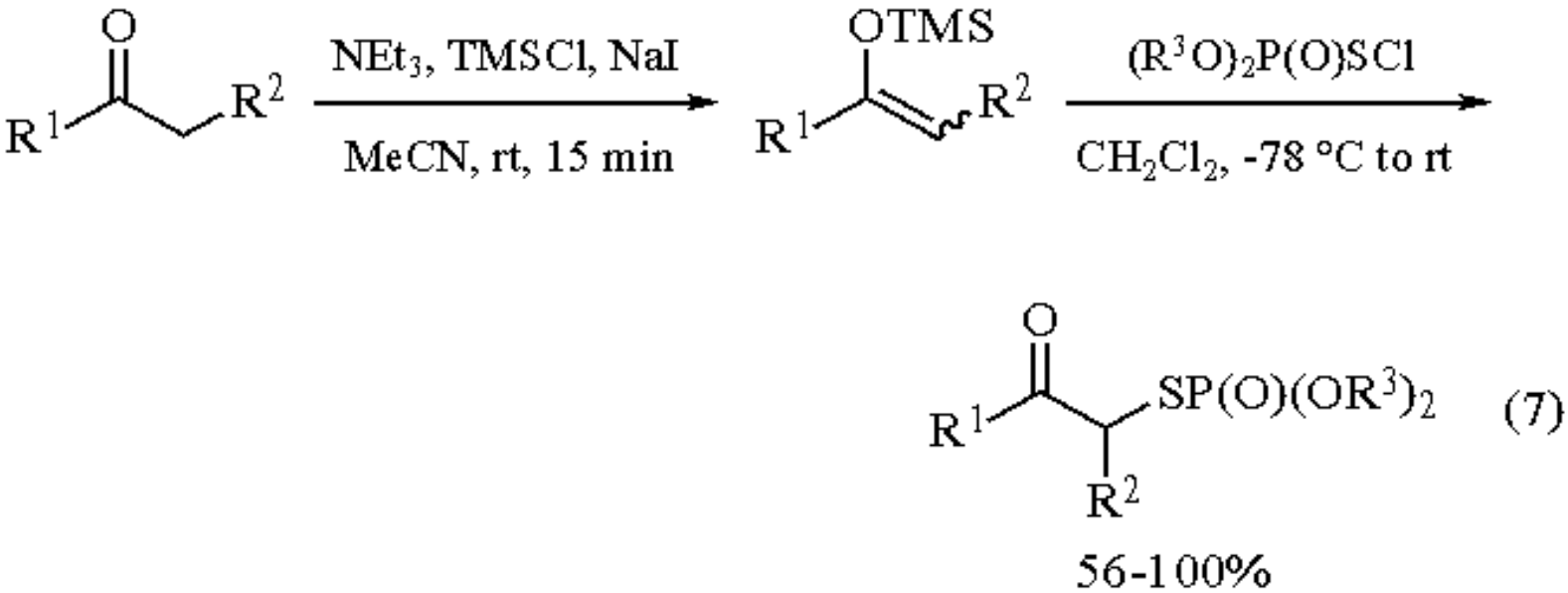

Reaction with Acetylide Anions.

The preparation of *S*-ethynyl esters of thiophosphoric acids occurs in moderate yield by the reaction of phosphoranesulfenyl chlorides with ***Ethynylmagnesium Bromide*** (eq 8).[9]

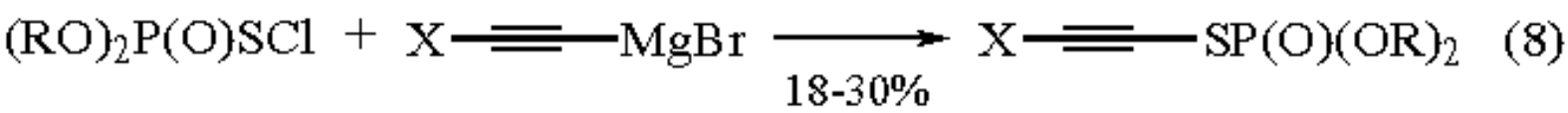

R = Et, Pr, Bu
X = H, Bu, CH_2SEt, CH_2Bu, $S(O)P(OEt)_2$

Reaction with α-Diazo Ketones.

Reaction of phosphoranesulfenyl chlorides with α-diazo ketones may be performed in CH_2Cl_2 or ether at -15 °C, or in benzene at 6 °C. Since these reaction conditions preclude the formation of a carbene intermediate, the reaction is thought to proceed via a diazonium cation to give α-chloro-substituted esters of thiophosphoric acid (eq 9).[10]

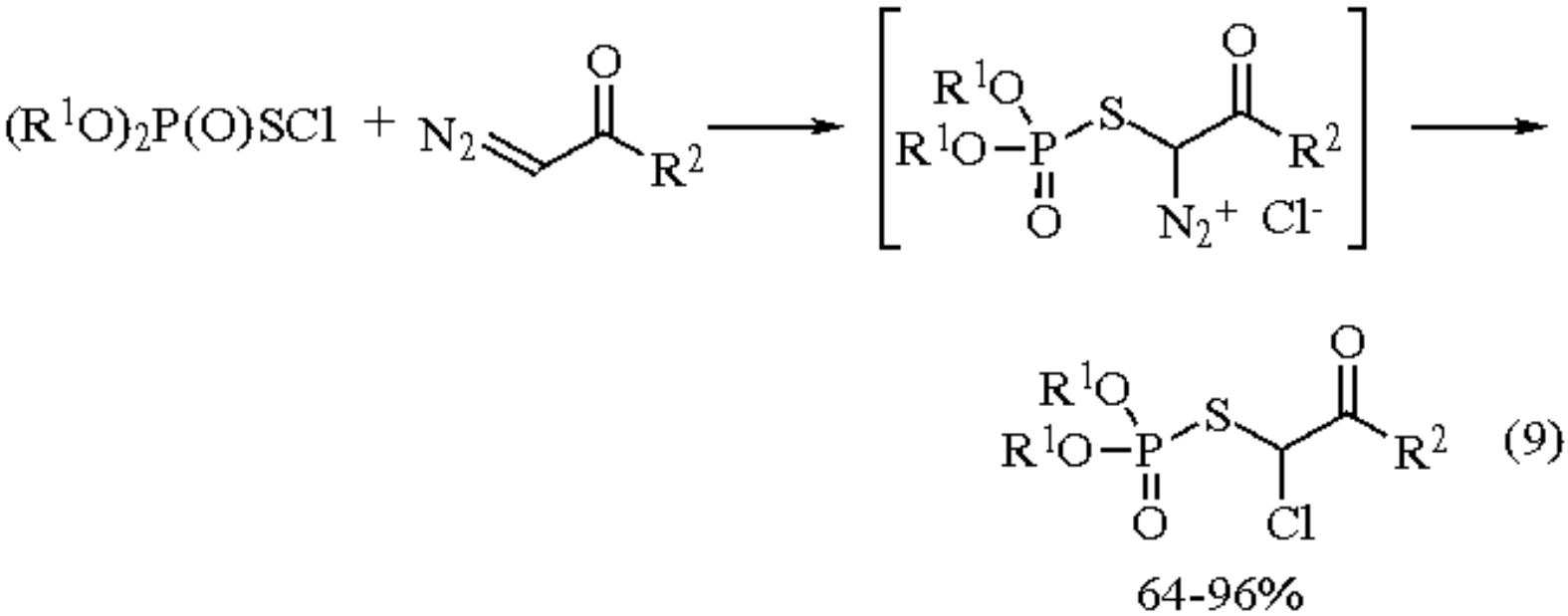

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Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)

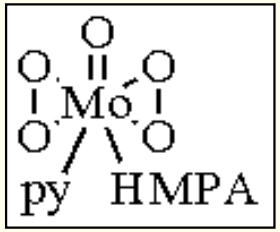

[23319-63-3] · $C_{11}H_{23}MoN_4O_6P$ · Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) · (MW 434.29)

(hydroxylation of enolates[1] and nitrile anions;[2] preparation of carbonyl compounds by oxidative degradation of anions of sulfones;[3] nitroalkanes;[4] phosphonates;[5] for *N*-hydroxylation of amides;[6] for oxidative cleavage of C-B bonds[7])

Alternate Name: MoOPH.

Physical Data: mp 103-105 °C (dec).

Solubility: insol ether; sparingly sol THF; sol dichloromethane.

Form Supplied in: finely divided yellow crystals; not available commercially.

Analysis of Reagent Purity: no convenient assay has been reported. Decomposition is indicated if the reagent smells of pyridine or becomes sticky.[1b]

Preparative Methods: a detailed procedure is available:[1b] (1) MoO_3 + 30% H_2O_2 (<40 °C); (2) add HMPA; vacuum dry MoO_5.HMPA.H_2O to MoO_5.HMPA; (3) pyridine in THF gives MoOPH.

Purification: attempted recrystallization causes decomposition of MoOPH. Purity depends on the quality of MoO_5.HMPA.H_2O, which can be recrystallized from methanol.

Handling, Storage, and Precautions: MoOPH should be stored in the freezer and protected from light.[1b] The reagent should be treated as an

explosion hazard due to its peroxidic nature.[1b,8] Properly stored MoOPH is a freely flowing, yellow crystalline powder, and can be handled in the air at room temperature using a safety shield and protective gloves.

Enolate Hydroxylation.

MoOPH[1,9] is a useful reagent for the hydroxylation of lithium, sodium, and potassium enolates of ketones,[1,10] aldehydes,[11] esters,[1,12] and lactones,[1,13,14] and related anions.[15] Similar hydroxylations can be performed with 1-*p*-toluenesulfonyl-2-phenyloxaziridine (Davis' reagent; see ***(±)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine***), but the latter reagent works best with Na or K enolates that are sensitive to equilibration.[16] MoOPH oxidation of the lithium enolate in THF is the method of choice when regiospecific hydroxylation is desired [examples (**1**)-(**6**)].

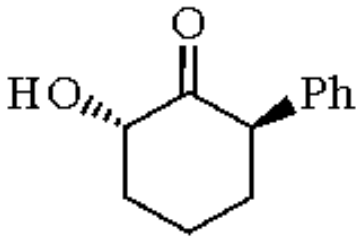

(1) 70%

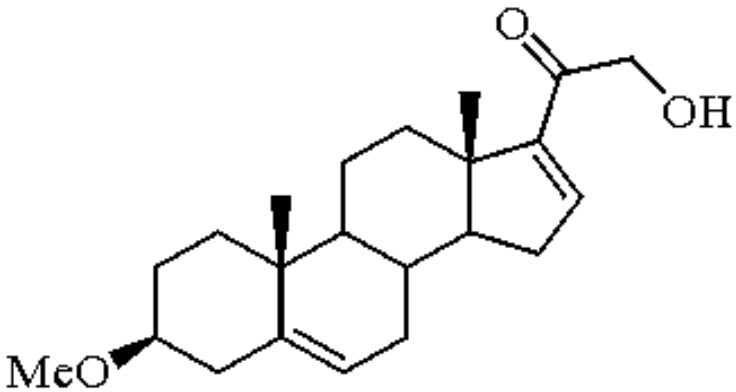

(2) 52%

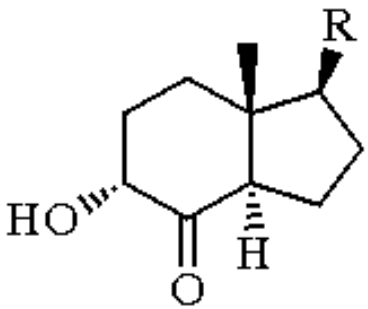

(3) 75%

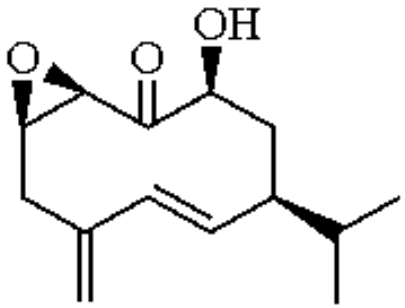

(4) 86%

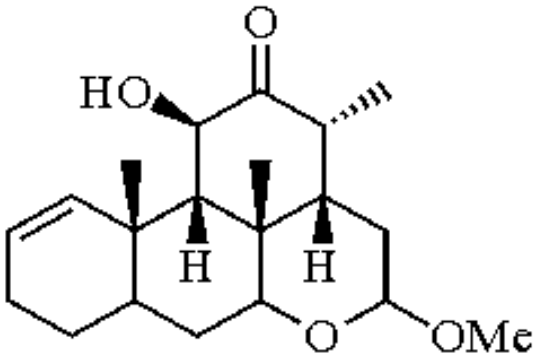

(5) 45%

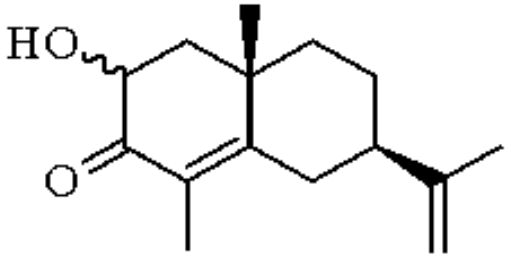

(6) 62%

Byproducts may include α-diketones (with aryl *n*-alkyl ketone enolates) or aldol adducts (methyl ketone or enone enolates), and recovery of 5-20% unreacted ketone is common. Inverse addition techniques and temperature optimization (usually -78 to -20 °C) may prevent side reactions with difficult substrates.[1a] Cyclohexanone enolates prefer axial hydroxylation [(**1**) 7:1 α:β;[1a] (**3**) only isomer reported;[10a] (**6**) 2:1 β:α[10d]]. Several stereoselective ester[12] and lactone[13,14] hydroxylations have also been reported [(**8**) 7:1 α:β;[13a] (**9**) 8.5:1 α:β[14a]]. The MoOPH hydroxylation of the Evans imide enolates has a small selectivity advantage compared to the Davis oxaziridine, but yields are lower.[15a] MoOPH is relatively bulky, and prefers bonding to the less hindered enolate face in the absence of stereoelectronic factors. These oxidations involve enolate attack at the O-O bond (eq 1).

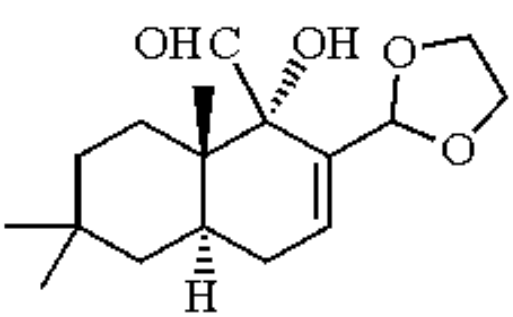

(7) 85%

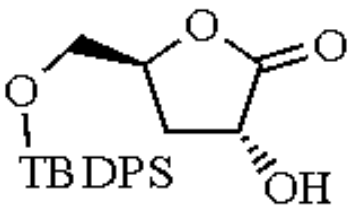

(8) 80%

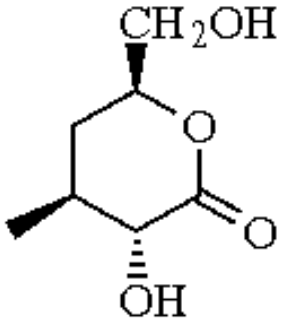

(9) 58%

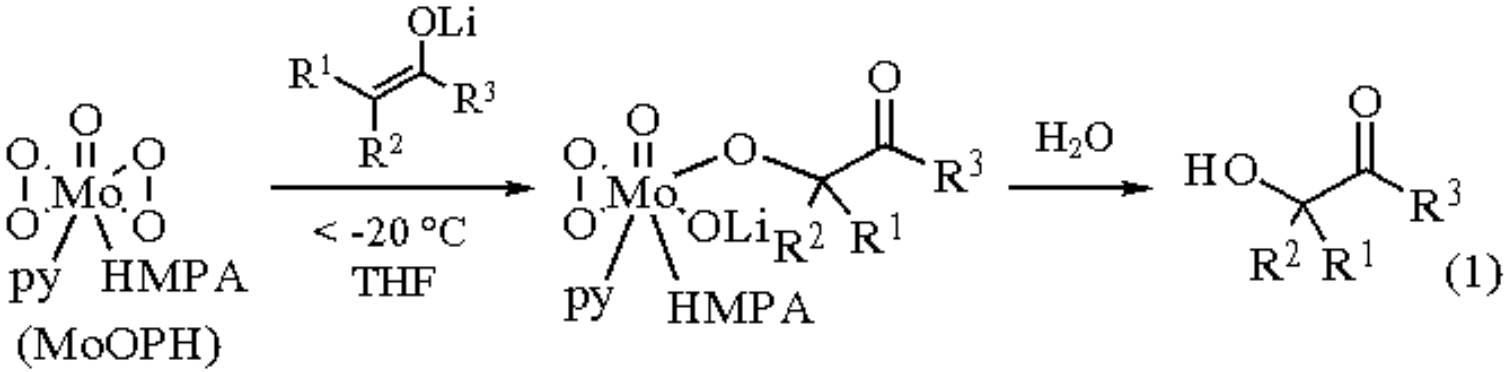

Hydroxylation of Other Stabilized Anions.

Nitrile anions are hydroxylated by MoOPH to afford cyanohydrins.[2,17] The cyanohydrins can be isolated starting from unbranched nitriles[2,17c] or strained cyclic nitriles (eq 2).[17a] More typical α-branched nitrile anions afford the ketones directly,[2,17b] and condensation of this ketone with the starting nitrile anion may complicate these reactions.[2]

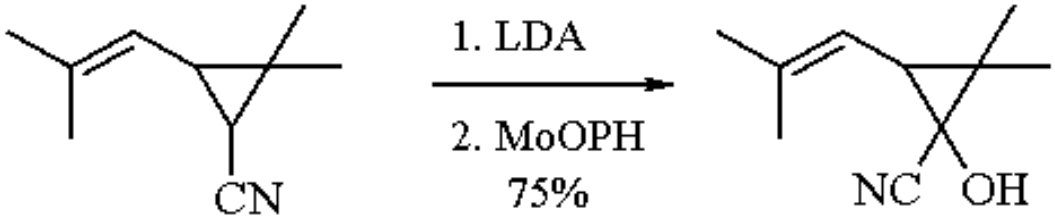

(2)

Sulfone anions can also be hydroxylated.[3] The resulting α-hydroxy sulfones fragment spontaneously to the corresponding ketone[3,18] or aldehyde.[19] Condensation between the carbonyl product and the sulfone anion can be a major reaction pathway.[19b] Similar oxidative degradation occurs with nitroalkane and phosphonate anions.[4,5]

Miscellaneous Hydroxylations with MoOPH.

Other strongly basic carbanions have been hydroxylated with MoOPH, including an aryllithium derivative,[20] a dipole-stabilized benzyllithium PhC(O)N(Me)CH(Li)Ph,[21] and a lithiated vinylogous amide.[22] Certain relatively nonbasic substrates can also react with MoOPH, resulting in net hydroxylation. The reagent cleaves C-B bonds with retention,[7] and is useful for the oxidative workup of boron enolate aldol reactions.[23] In the presence of ***t-Butyl Hydroperoxide***, MoOPH converts α- or β-naphthols into ketols derived from *ortho* hydroxylation of the naphthalene ring.[24] Finally, MoOPH reacts with *N*-trimethylsilylamides to afford the *N*-hydroxy amides (eq 3).[6,25]

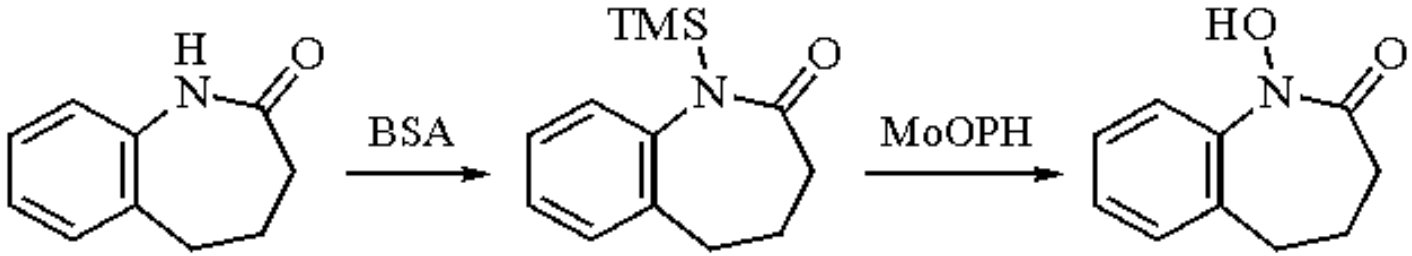

(3)

90%

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Edwin Vedejs

University of Wisconsin, Madison, WI, USA

μ_3-Oxohexakis(μ-trimethylacetato)tris(methanol)triiron(III) Chloride

$[Fe_3O(OCOCMe_3)_6(MeOH)_3]Cl$

[55216-31-4] · $C_{33}H_{66}ClFe_3O_{16}$ · μ_3-Oxohexakis(μ-trimethylacetato)tris(methanol)triiron(III) Chloride · (MW 921.99)

(one of several (μ_3-oxo)triiron cluster complexes used to catalyze the epoxidation of alkenes with molecular oxygen[1])

Physical Data: orange-yellow crystalline solid.

Preparative Methods: equimolar aqueous solutions of $Fe^{III}Cl_3$ and sodium pivalate are mixed and the resulting precipitate is filtered and dried in vacuo.[2]

Purification: recrystallization from chloroform-methanol.

Epoxidation of Alkenes.[3]

$[Fe_3O(OPiv)_6(MeOH)_3]^+Cl^-$ (Piv = $OCCMe_3$) is a useful catalyst for the epoxidation of alkenic alcohol acetates with molecular oxygen. The reaction requires one equivalent of oxygen to effect the peroxidation, half of which is apparently consumed in undesirable side reactions. The regiospecificity of the oxidation is similar to that observed when conventional peroxy acid epoxidation reagents are used,[4] but is opposite to that observed under Sharpless epoxidation conditions.[5] This polynuclear transition metal catalyst affords higher yields and better selectivity than alternative transition metal catalysts known to effect alkene epoxidation with oxygen. However, two particularly good alternatives are $[Fe_3O(OAc)_6(H_2O)_3](OAc)$ *[60797-92-4]* and $[Fe_3O(OAc)_6(py)_3]Cl$ *[69554-73-0]*.[6] Mononuclear iron catalysts, such as $FeCl_3$, failed under the prescribed conditions. Depending on the substrate, the reaction may be performed in the absence of a solvent. For instance, 6,7-epoxygeranyl acetate was produced from geranyl acetate in the absence of a solvent (60 °C, 20 h) and without formation of the 2,3-epoxide isomer (eq 1).

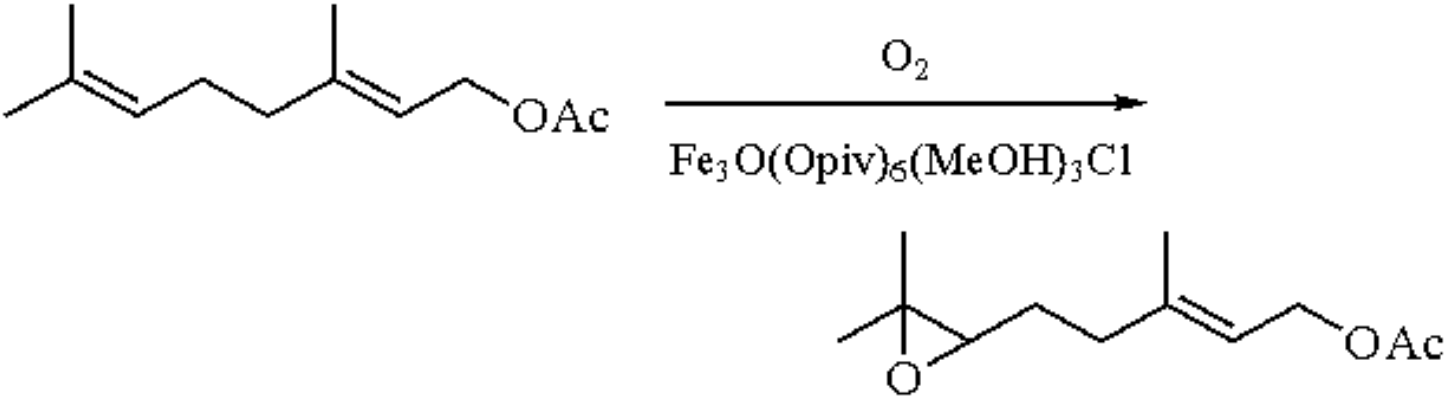

(1)

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Mark W. Zettler

The Dow Chemical Company, Midland, MI, USA

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Oxo(methoxy)molybdenum(V) 5,10,15,20-Tetraphenylporphyrin

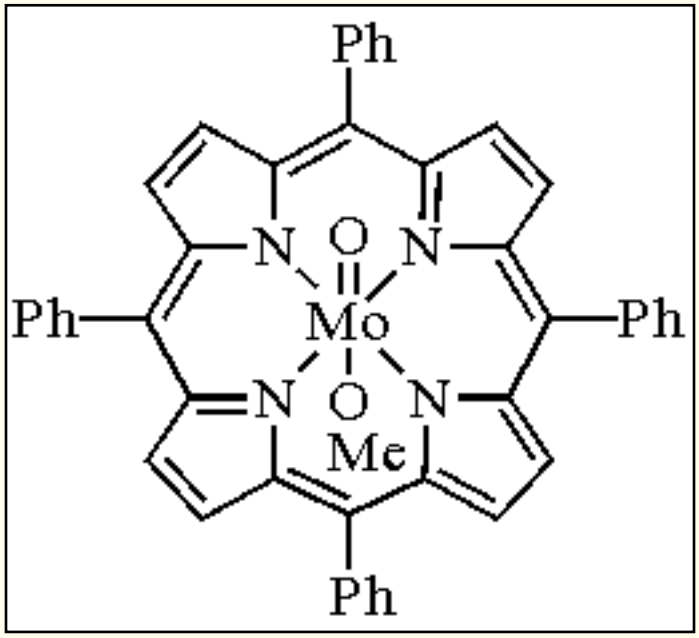

[74751-79-4] · $C_{45}H_{31}MoN_4O_2$ · Oxo(methoxy)molybdenum(V) 5,10,15,20-Tetraphenylporphyrin · (MW 755.74)

(able to catalyze selective and specific oxidation of alkenes by peroxy-bond heterolysis[1,2])

Solubility: sol methylene chloride, benzene.

Preparative Methods: the alkoxo complex is obtained[1,2] by chromatography of O=Mo(TPP)Cl[1] over alumina using 20% MeOH in methylene chloride as eluant, followed by crystallization from MeOH-CH_2Cl_2.

Stereoselective Epoxidation.[2]

The reagent has been used as a catalyst in the selective epoxidation of alkenes with ***t-Butyl Hydroperoxide***. In a typical experiment, OMo(TPP)OMe (5×10^{-6} mol) was dissolved in dry oxygen-free benzene. Cyclohexene (24.6 mmol) was added. The accurate catalyst concentration was measured by

UV-Vis spectrometry, and the mixture was heated to 80 °C under argon. After equilibration, *t*-BuOOH (5 mmol) was added and aliquots were periodically monitored.

O=Mo(TPP)OMe, O=Mo(TPP)Cl, and *cis*-O_2Mo(TPP) catalyze the epoxidation of cyclohexene with *t*-butyl hydroperoxide with formation of the insoluble $[OMo(TPP)]_2O$. These Mo complexes are comparable to ***Hexacarbonylmolybdenum***, but exhibit a longer induction period. A high selectivity to cyclohexene oxide was obtained at total conversion of the hydroperoxide. The rates of epoxide formation, expressed as the turnover number of the catalyst, are, respectively, $Mo(CO)_6$ 283 and OMo-(TPP)OMe 51 h^{-1}. Monitoring the reaction by UV-Vis spectrometry revealed a complicated spectrum evolution during the induction period. However, after a time of reaction corresponding to three times the duration of the induction period, i.e. when the reaction had reached its stage of full catalytic activity, the concentration of Mo^V porphyrin complexes in solution was still 98-100% of that measured before addition of *t*-BuOOH.

OMo(TPP)Cl-catalyzed epoxidation of *cis*- and *trans*-2-hexene was found to be highly stereoselective, affording, respectively, 97% and 99% of the corresponding *cis*- and *trans*-2-epoxides. Relative rates of formation of *cis*- and *trans*-2-hexene oxides are significantly different. The *cis*-2-hexene oxide is formed 3.5 times faster than the *trans* isomer, showing a specific behavior of the porphyrin complex. The higher rate of formation observed for *cis*-2-hexene oxide indicates a more efficient steric control, as expected if the bulky rigid porphyrin ligand is present in the activated complex.

This effect is clearly evidenced in the case of 2-methylbutadiene (isoprene) where 3-methyl-3,4-epoxy-1-butene and 2-methyl-3,4-epoxy-1-butene, corresponding respectively to the epoxidation of the di- and monosubstituted double bond, are obtained in a 4:1 ratio by using $Mo(CO)_6$[3] compared to 0.7:1 with OMo(TPP)OMe (eq 1).

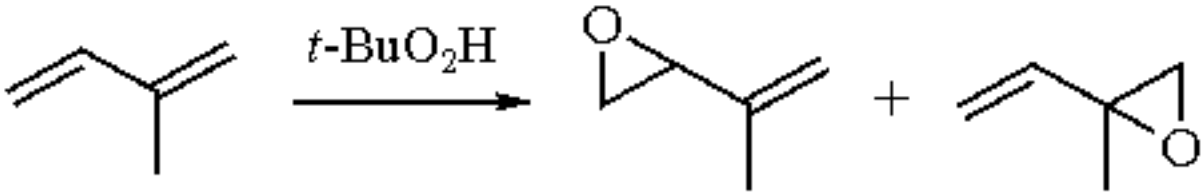

(1)

$Mo(CO)_5$	1:4
O=Mo(TPP)OMe	1:0.7

OMo(TPP)X complexes represent the first example of metalloporphyrins able to catalyze selective and specific oxidation of alkenes by peroxy-bond heterolysis.[2] With other transition metals like iron or cobalt, radical chain processes are observed for the oxidation of alkenes, giving only extremely low selectivity to epoxide[4] or the hydroxylation of saturated hydrocarbons.[5] This oxomolybdenum porphyrin-*t*-butyl hydroperoxide system may be considered as a simple chemical model for activation of hydroperoxides by cytochrome P-450 dependent monooxygenases.

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Oxoperoxobis(*N*-phenylbenzohydroxamato)molybdenum(VI)

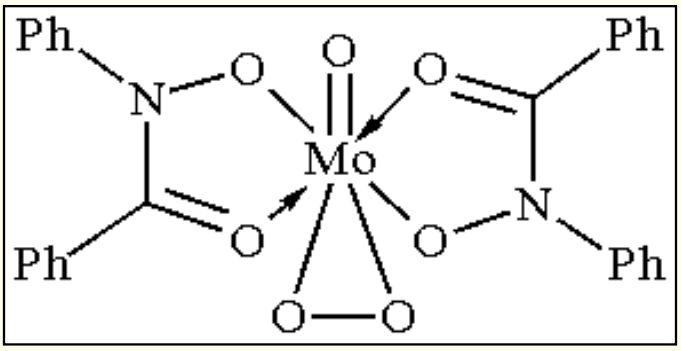

[77402-46-1] · $C_{26}H_{20}MoN_2O_7$ · Oxoperoxobis(*N*-phenylbenzohydroxamato)molybdenum(VI) · (MW 568.42)

(oxidizes primary and secondary alcohols to the corresponding carbonyl compounds;[1] can epoxidize allylic alcohols stereoselectively[1])

Physical Data: mp 150 °C (dec).

Solubility: sol dichloromethane, 1,2-dichloroethane; insol water, hexane.

Form Supplied in: orange-yellow crystals.

Preparative Methods: by stirring a mixture of $MoO_2(acac)_2$ (1 mmol) and hydroxamic acid (PhCON(Ph)OH) (2 mmol) at 25 °C for 3 h, followed by treating the white solid of $MoO_2(PhCON(Ph)O)_2$, so formed, with excess of 30% H_2O_2 at 25 °C.

Oxidation of Primary and Secondary Alcohols.[1]

Primary alcohols are oxidized to aldehydes and secondary alcohols to ketones. Yields are fair to good. The mixture of the Mo complex and the alcohol in 1,2-dichloroethane is refluxed for 4 h. The product is isolated after the usual workup. Cyclododecanol and 2-octanol have been oxidized in >95% yield to their corresponding ketones, whereas aldehydes are obtained from benzyl alcohol and dodecanol in 80 and 63% yield, respectively.

Epoxidation of Alkenic Alcohols.

The reagent is quite reluctant to react with simple alkenes, although molybdenum diperoxo compounds such as Mimoun's reagent are known to epoxidize alkenes.[2] However, allylic alcohols were converted easily to α,β-epoxy alcohols in fair yields (60-70% isolated). It is worth noting that more stereoselectivity is obtained in this reaction using a stoichiometric

amount of the monoperoxo complex than that observed with ***t-Butyl Hydroperoxide*** in combination with ***Hexacarbonylmolybdenum***.[3] This is illustrated in Table 1.

Table 1 Epoxidation of Alkenic Alcohols

Alcohol	Monoperoxo complex		$Mo(CO)_6$/*t*-BuOOH	
	threo (%)	*erythro* (%)	*threo* (%)	*erythro* (%)
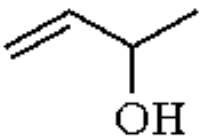	7	93	44	56
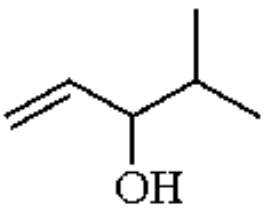	9	91	35	65
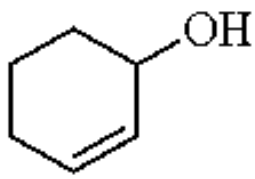	6	94	16	84
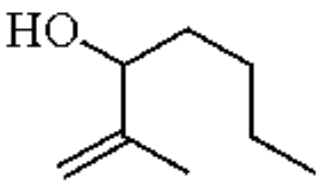	<0.5	>99.5	2	98

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Oxo(trimanganese) Heptaacetate[1]

$Mn_3O(OAc)_7$

[19513-05-4] · $C_{14}H_{21}Mn_3O_{15}$ · Oxo(trimanganese) Heptaacetate · (MW 594.17)

(selective oxidizing agent; mediates addition of carboxylic acids to alkenes; reagent for allylic acetoxylation)

Alternate Name: manganese triacetate.

Solubility: insol most organic solvents; sol hot acetic acid; hydrolyzed by water.

Form Supplied in: brown or gray powder and chunks; widely available.

Preparative Methods: often referred to as anhydrous $Mn(OAc)_3$, which does not exist.[2] Can be prepared from $Mn(OAc)_2$ and $KMnO_4$ in $AcOH/Ac_2O$, or prepared in situ from $Mn(OAc)_2$ and $KMnO_4$ in AcOH.[3,4]

Purification: not usually necessary.

Handling, Storage, and Precautions: hygroscopic; avoid heat, sparks, and open flames.

Preparation of Lactones from Alkenes.

In the presence of manganese triacetate, simple alkenes react with carboxylic acids (often solvent ***Acetic Acid***) to give γ-lactones (eqs 1 and 2)[3,4] in a reaction which is thought to involve radical intermediates. This reaction can be performed on dienes[5] and on alkenes which possess other potentially reactive groups such as alkynes[6] (eq 3).[7] A range of other carboxylic acids has been used in place of acetic acid.[8,9]

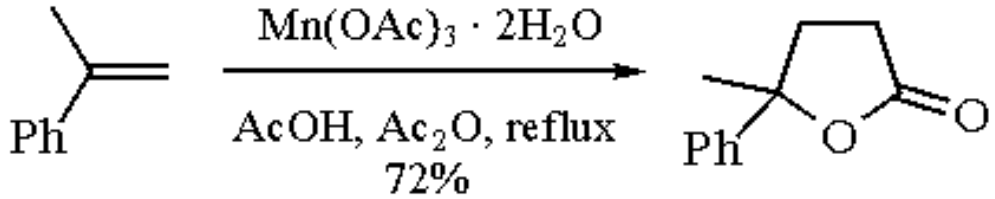

(1)

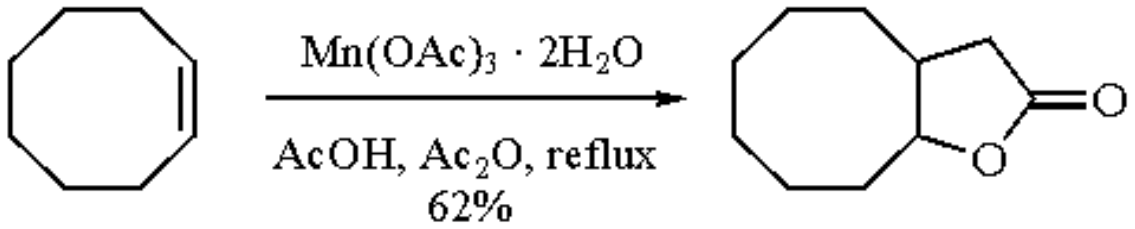

(2)

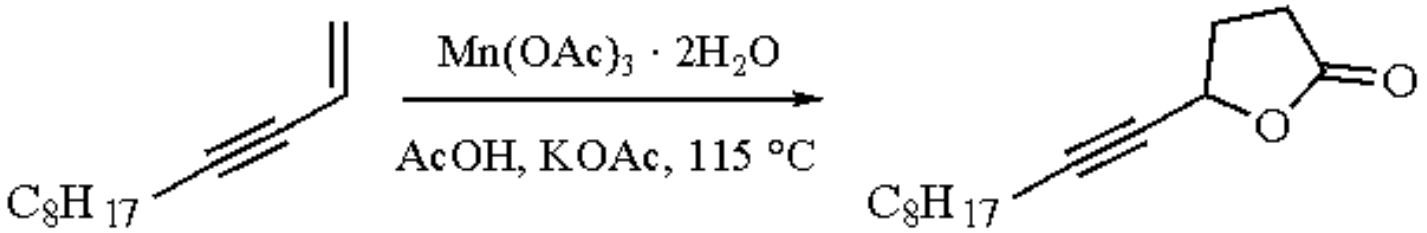

(3)

In addition to simple carboxylic acids, a variety of β-keto acids also undergo reaction with alkenes to give lactones (eq 4),[9] and the intramolecular version of this reaction can be used effectively to produce polycyclic lactones (eq 5).[10] This latter reaction has been adapted to the total synthesis of polycyclic natural products.

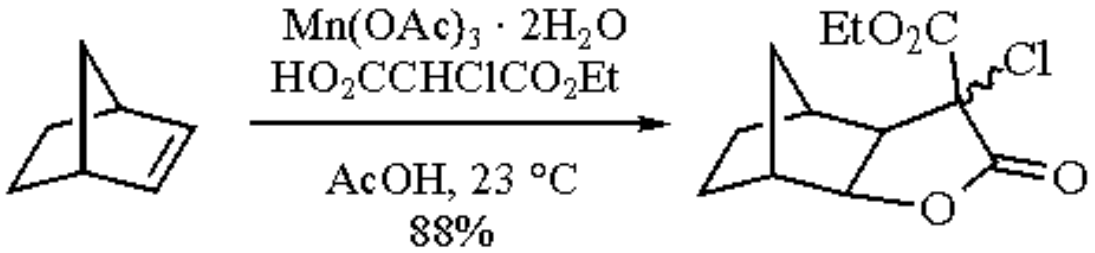

(4)

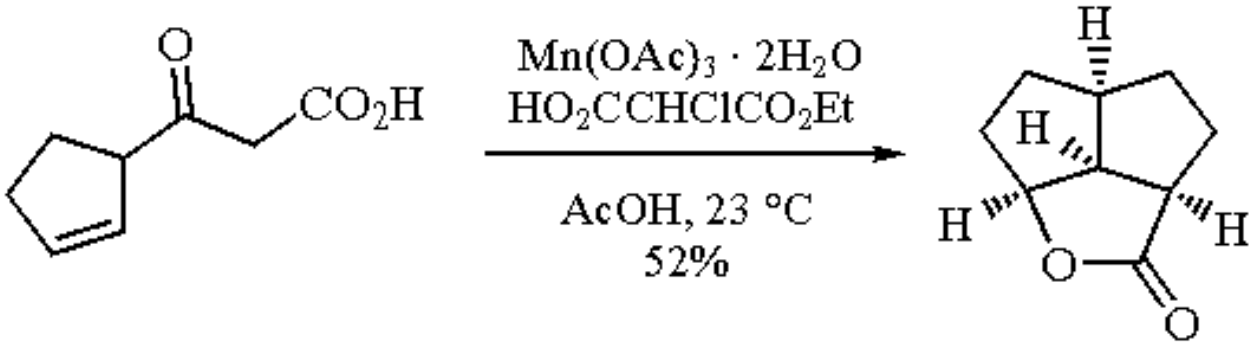

(5)

The formation of C-C bonds using Mn^{III} salts is not restricted to the reaction of alkenes and carboxylic acids. A range of β-dicarbonyl compounds will also undergo additions to give dihydrofurans (eq 6)[11] and other types of products. In particular, the intramolecular cyclization can be used to construct a variety of cyclic systems, using both monocyclizations (eq 7)[12] and tandem cyclizations (eq 8).[13] A sulfoxide group can take the place of one of the carbonyl groups, and in this case the chirality of the sulfoxide controls the absolute configuration of the product. In effect, the sulfoxide group has been used as a chiral auxiliary in this cyclization (eq 9).[14]

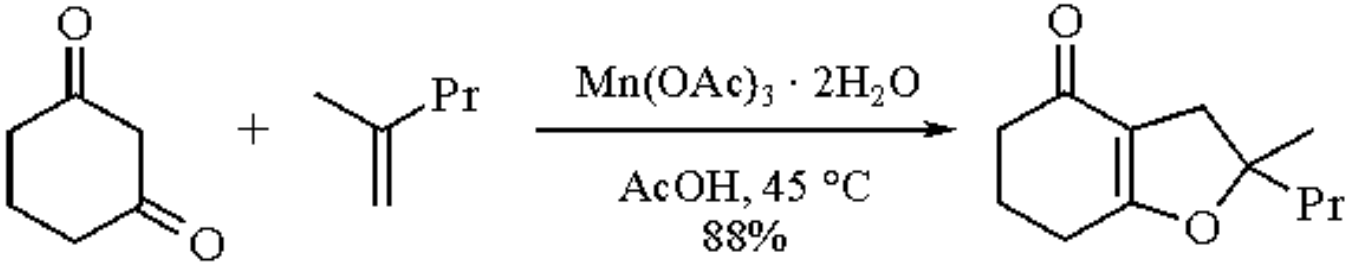

(6)

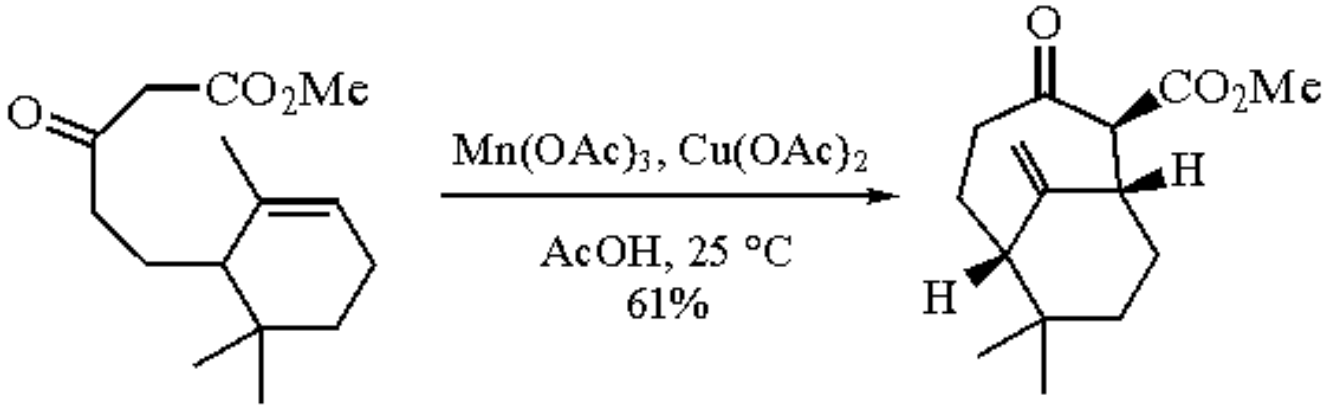

(7)

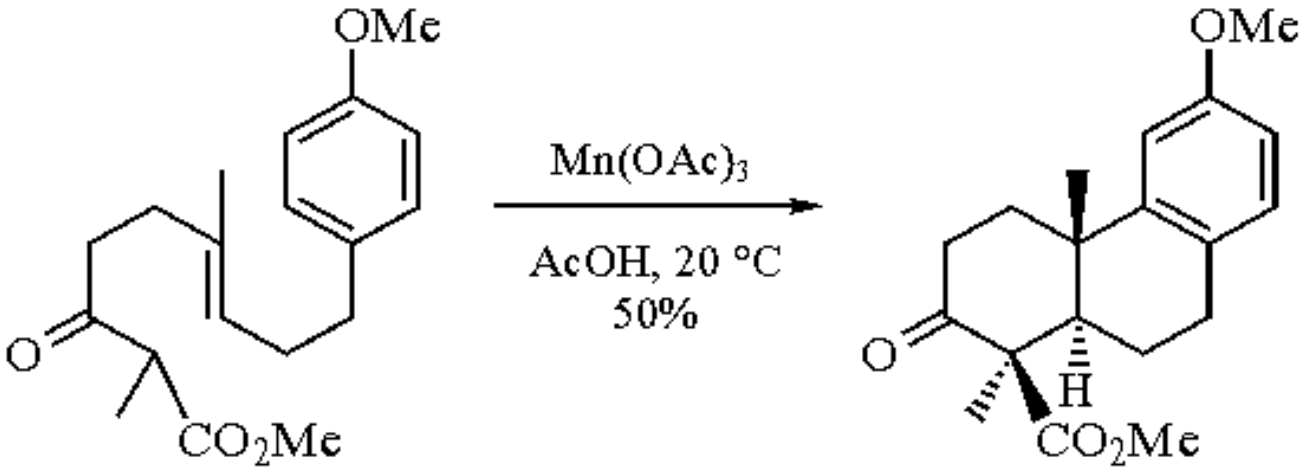

(8)

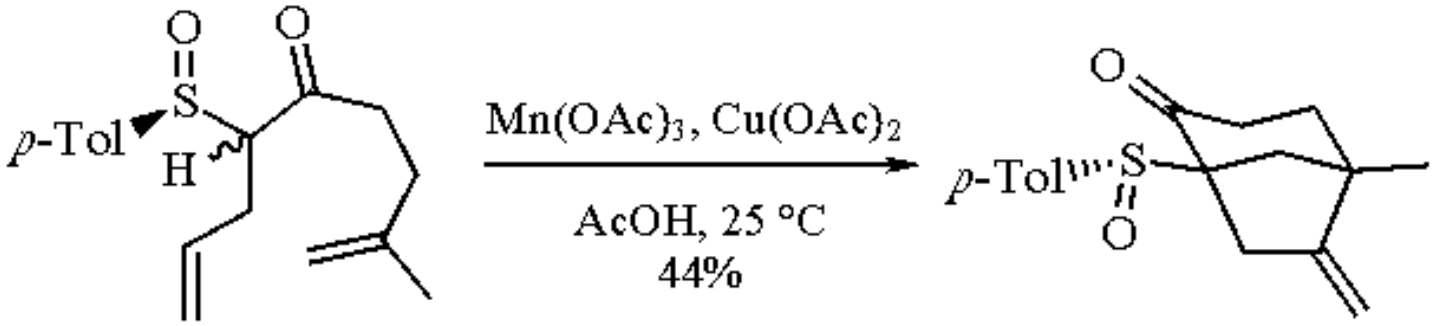

(9)

Enol ethers and enol esters can also serve as the alkene component of this type of reaction, the products being useful as precursors for furans and 1,4-dicarbonyl compounds (eqs 10 and 11).[15,16] It is also possible to use simple ketones as the carbonyl component, although the yields are relatively low, and if the ketone is unsymmetrical, mixtures of products are obtained.[17]

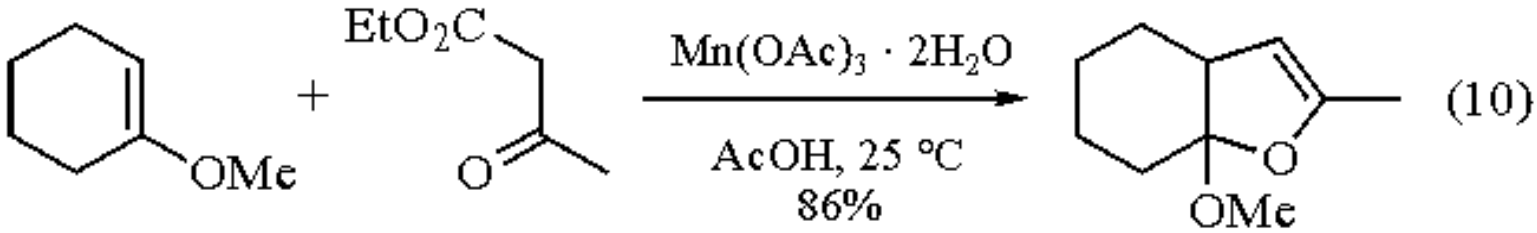

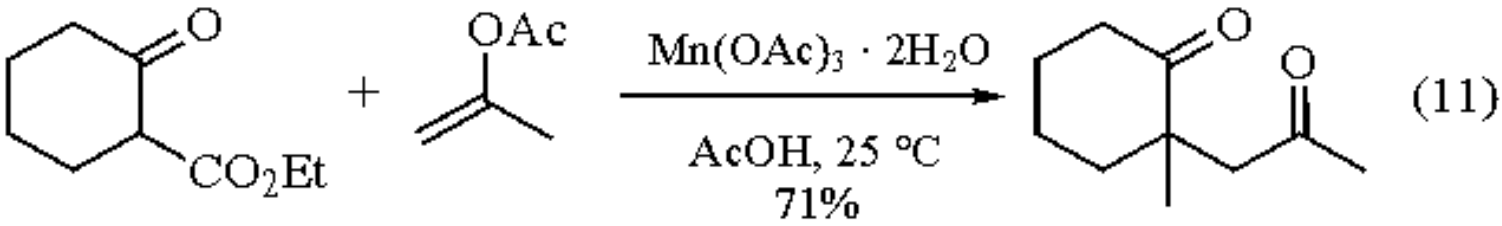

Allylic Oxidation and Oxidation α to Carbonyl Groups.

Acetoxylation adjacent to both C=C and C=O double bonds is possible using manganese triacetate.[18,19] Although the reaction tends to be substrate dependent and the yields variable (eq 12),[19] it has been used to good effect in the synthesis of relatively complex polyfunctional systems that contain groups which might interfere (eqs 13 and 14).[20,21]

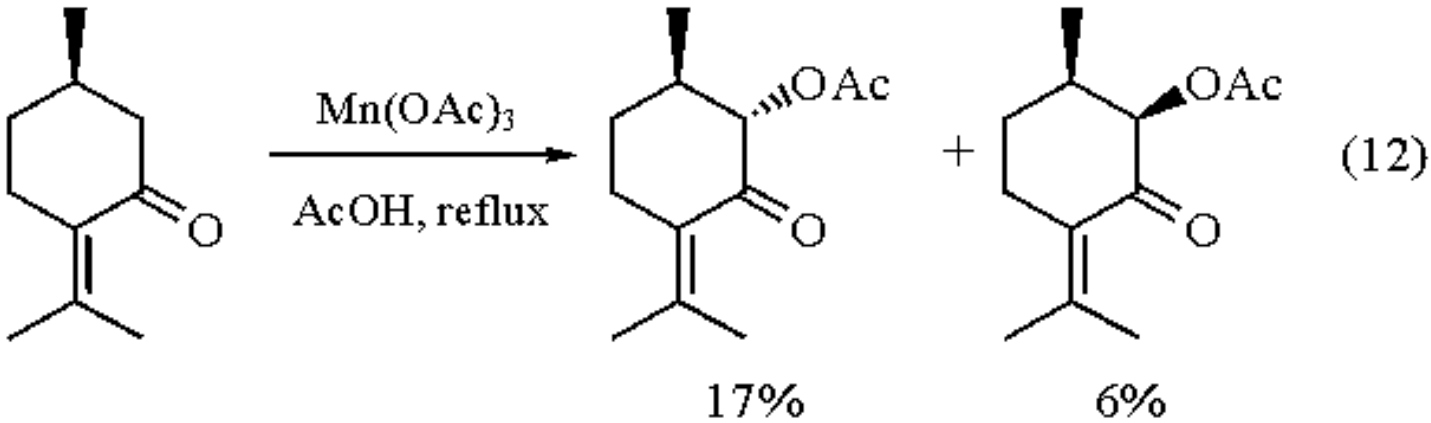

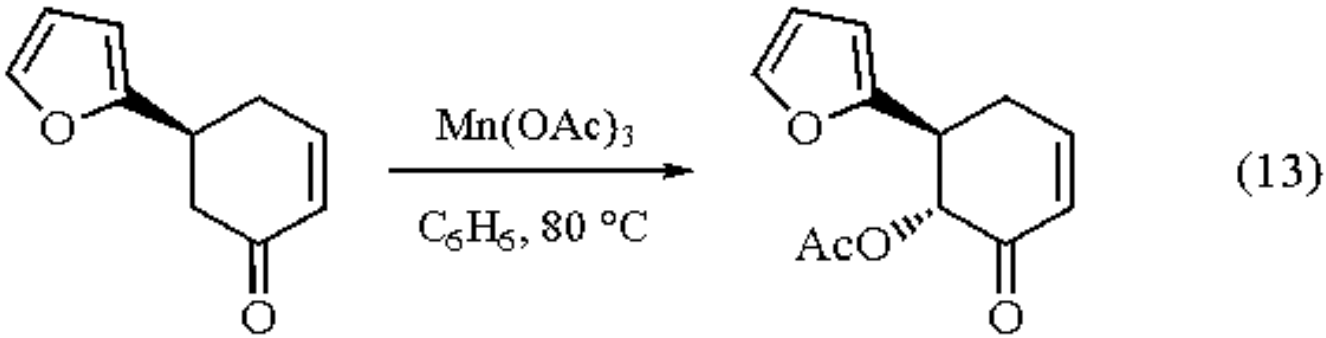

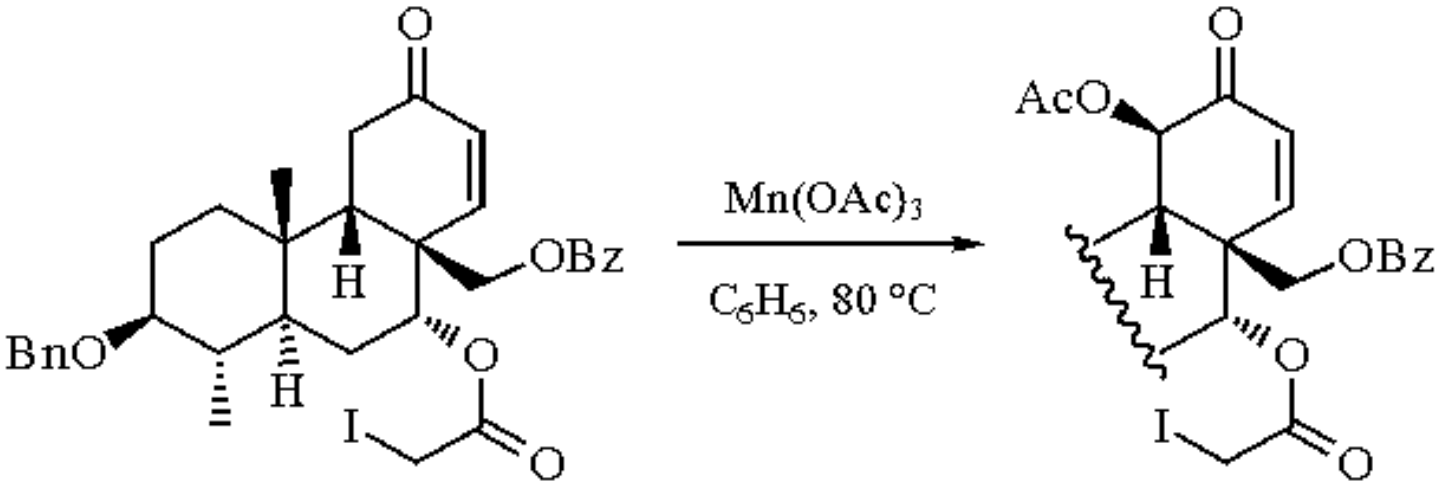

(14)

Other Applications.

Manganese triacetate is reported to be superior to ***Ruthenium(VIII) Oxide*** and ***Cerium(IV) Ammonium Nitrate*** for the oxidation of *N*-protected indolines to indoles (eq 15).[22] On treatment with manganese triacetate, aryldialkylamines undergo dealkylation, in which one alkyl group is replaced by an acetyl group,[23] and in combination with ***Diphenyl Disulfide*** alkenes undergo regioselective addition of PhS and OH.[24] Manganese triacetate was found to be the reagent of choice for the final step in a total synthesis of cyanocycline, which required the oxidation of the *p*-methoxyphenol to the corresponding quinone (eq 16).[25]

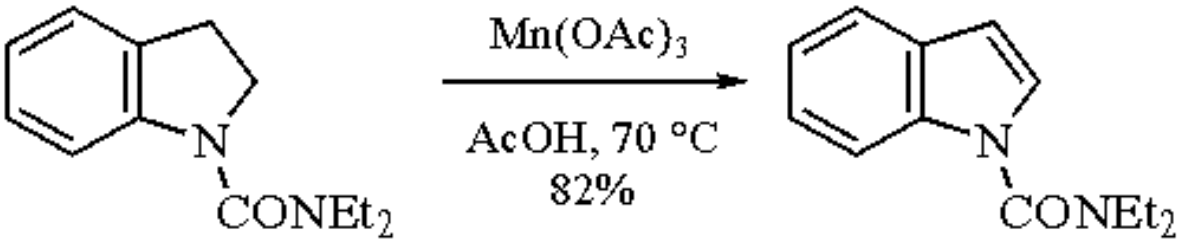

(15)

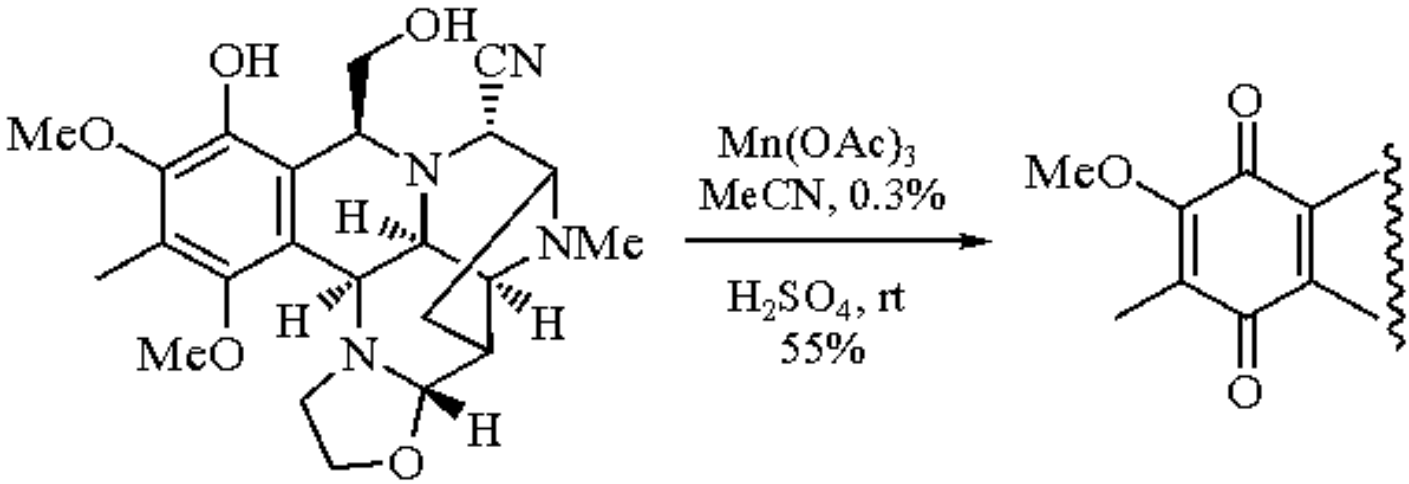

(16)

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Oxygen

[7782-44-7] · O_2 · Oxygen · (MW 32.00)

(oxidizing agent for many organic systems, including, most commonly, organometallic compounds, carbon radicals, and heteroatoms such as sulfur)

Physical Data: mp -218 °C; bp -183 °C; *d* 1.429 g L^{-1} (0 °C), 1.149 g L^{-1} (-183 °C).

Solubility: sol to some extent in most solvents. Selected data, expressed as mL of O_2 (at 0 °C/760 mmHg) dissolved in 1 mL of solvent when the partial pressure of the gas is 760 mmHg, are as follows: Me_2CO (0.207/18 °C), $CHCl_3$ (0.205/16 °C), Et_2O (0.415/20 °C), EtOAc (0.163/20 °C), MeOH (0.175/19 °C), petroleum ether (0.409/19 °C), PhMe (0.168/18 °C), H_2O (0.023/20 °C).

Form Supplied in: dry gas; dilutions in Ar, He, or N_2; $^{18}O_2$; $^{17}O_2$.

Handling, Storage, and Precautions: of itself, oxygen gas is essentially nontoxic. However, it will support and vigorously increase the rate of combustion of most materials. It may ignite combustibles and can cause an explosion on contact with oil and grease. The potential for autoxidative formation of explosive peroxides (e.g. with Et_2O) should always be borne in mind.

Oxygenation of Carbanions and Organometallic Compounds.

Many organometallic species react with triplet oxygen to form the corresponding hydroperoxides,[1,2] although the products are more usually reduced in situ or during workup to afford alcohols as the isolated products. A number of other sources of electrophilic oxygen have been developed (e.g. ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** (MoOPH), sulfonyloxaziridines) and compete for this niche, but no single reagent is universally preferable. As carbon anion equivalents, Grignard reagents are optimal for simple hydrocarbons,[2] but organolithiums are more frequently employed. The potential for radical-mediated oxidative dimerization can constrain utility (particularly for aryl organometallics). Useful oxygenations of alkyl,[3] vinylic,[4] allylic,[5] benzylic,[6] and aryl (eq 1)[6] organolithium compounds have been reported. 1,1-Diorganometallics give the corresponding carbonyl derivatives (eq 2).[7]

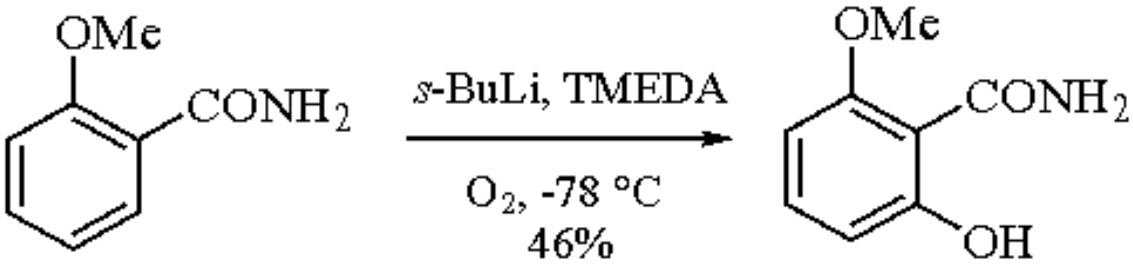

(1)

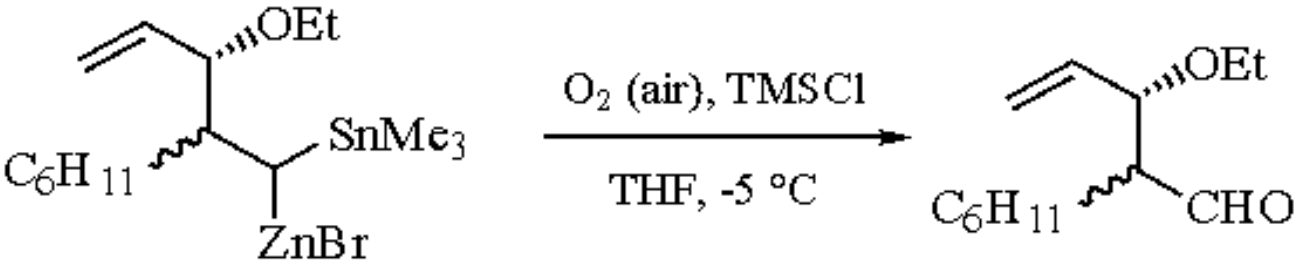

(2)

Effective oxygenation of enolate anions is generally restricted to tertiary centers where over-oxidation is not possible.[8] Nonetheless, ketones (eq 3),[9] esters/lactones,[8] amides/lactams (eq 4),[10] and carboxylic acids[8] can all be usefully α-hydroxylated. In most cases the intermediate α-hydroperoxides are reduced in situ (usually with ***Triethyl Phosphite***),[11] although they can be isolated if desired.[12] The small size of the electrophile and the potential for radical involvement[8] do not encourage stereochemical chastity in these processes, but where sufficient bias exists, good discrimination can be observed (see eqs 3 and 4). A slightly different approach uses enolates derived from aqueous base treatment. These species have been usefully hydroxylated where there was little or no ambiguity in the direction of enolization[8] and this process forms the basis for a surprisingly effective catalytic, enantioselective oxygenation (eq 5).[13]

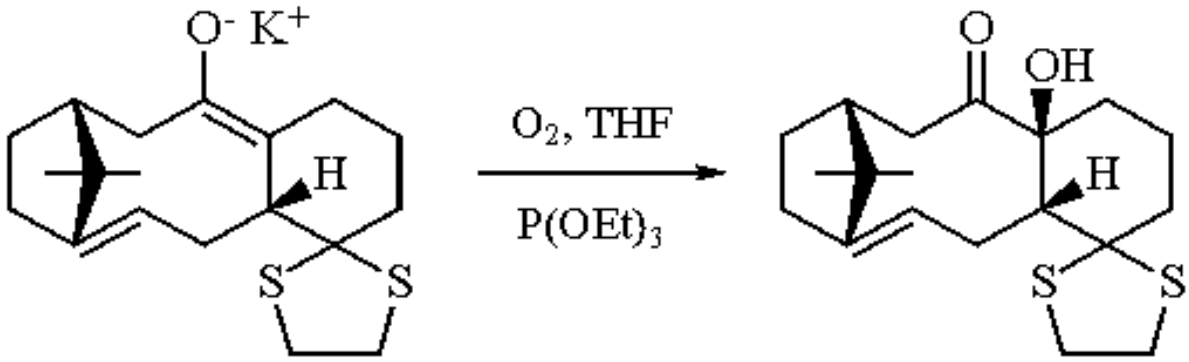

(3)

from anionic oxy-Cope

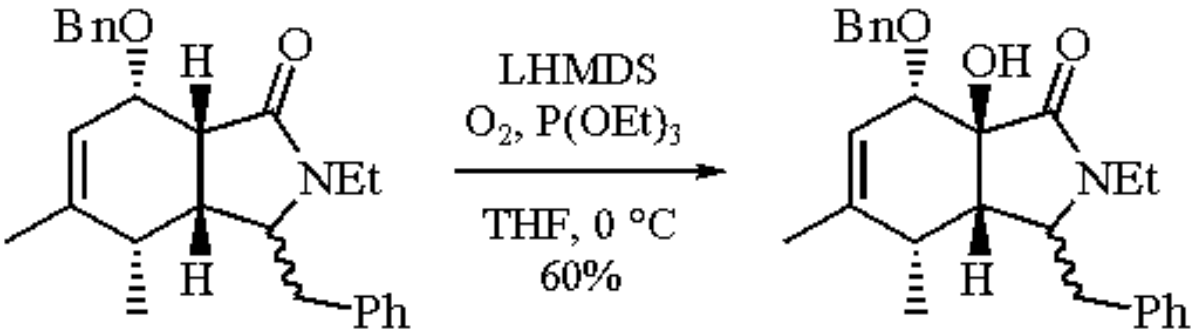

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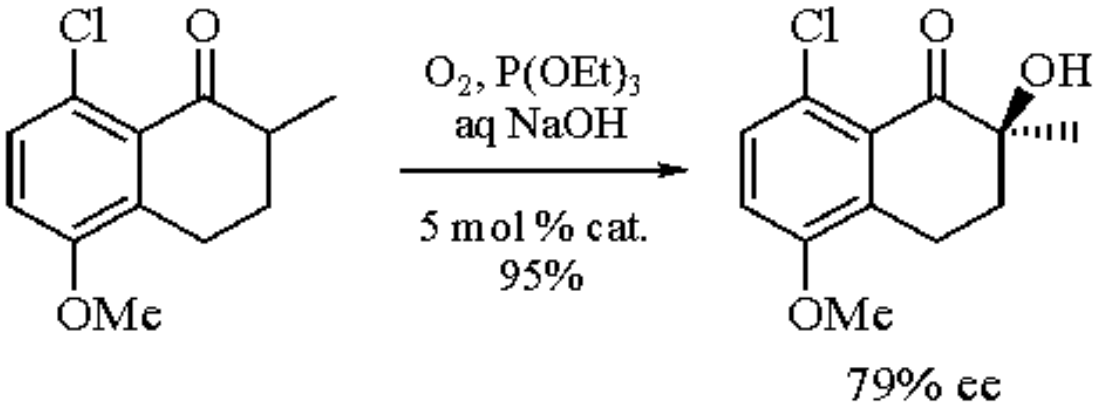

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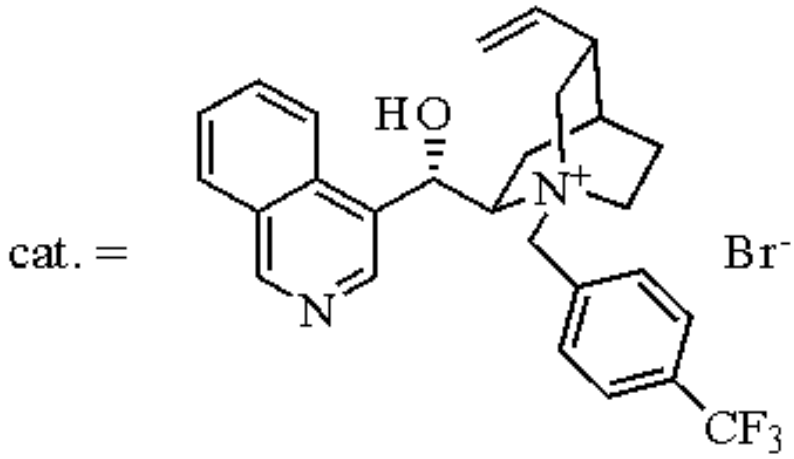

In cases where the activating group is also a leaving group, oxygenation can provide the corresponding carbonyl compound. Thus oxidative decyanation can be effected under either phase transfer[14] or anhydrous conditions (eq 6).[15] The latter procedure is more general, although it does require treatment with ***Tin(II) Chloride*** and base to reduce and fragment the α-hydroperoxide, and this method is not effective for the primary nitrile to aldehyde conversion. α,β-Unsaturated nitriles generally react at the α-position to give α,β-unsaturated ketones.[15]

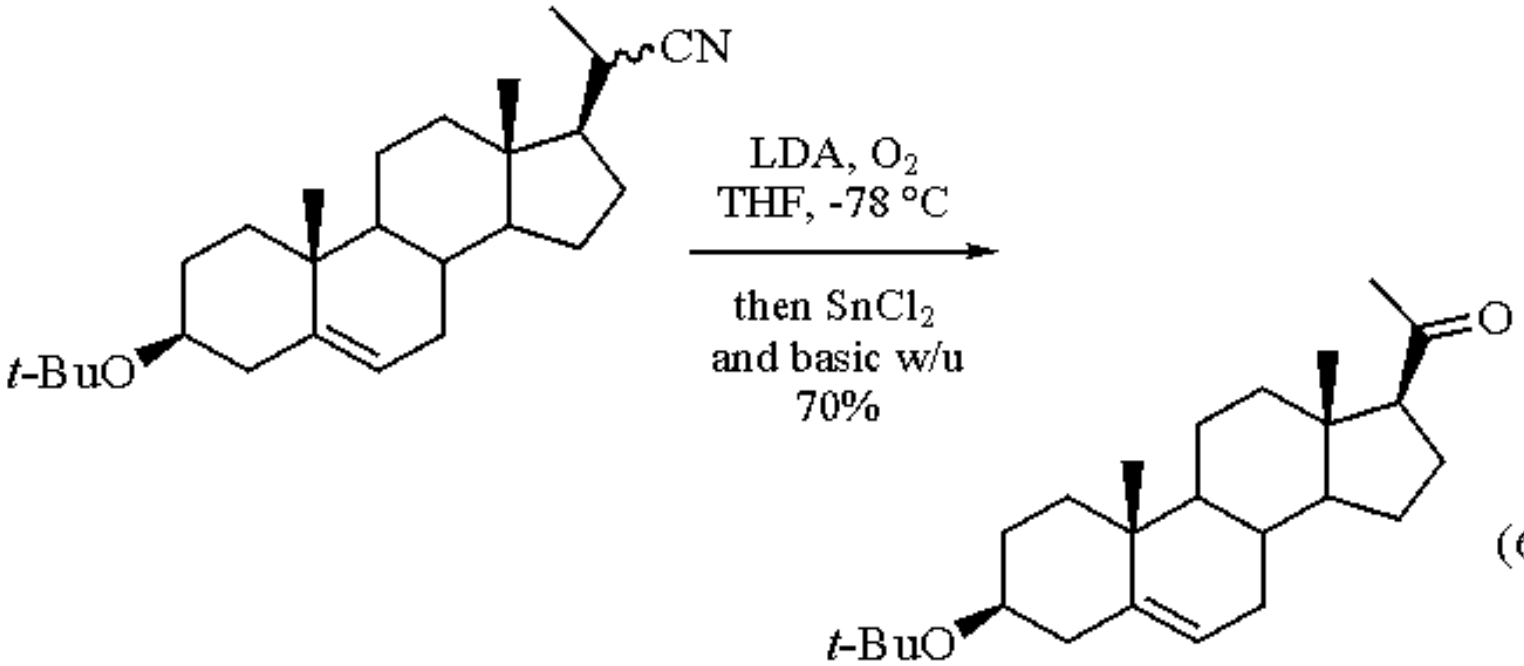

(6)

Oxygenation of sulfone anions and the consequent desulfonylation is frequently effected with the MoOPH reagent. In

some cases, however, molecular oxygen has proved effective where MoOPH failed.[16] This perhaps illustrates a functional advantage over more bulky reagents and a counterpoint to the stereochemical disadvantages (see above). It should be noted that one such attempt resulted in a minor explosion[17] although, of course, any reaction involving peroxides bears this possibility. A similar process, preceded by nickel transmetalation, demonstrated the oxidation of the C-Ni bond, but the synthetic advantage is not clear.[18] However, this report did demonstrate the conjugative oxygenation of an allylic sulfone anion to give a γ-hydroxy sulfone.

Oxygenation of phosphorus-stabilized anions also produces the corresponding carbonyl compounds. The anions derived from phosphonates[19] (eq 7)[20] (including α-heteroatom substituted phosphonates)[19] and phosphine oxides[21] react smoothly with oxygen. Similarly, phosphorane ylides are readily oxidized.[22] In all these cases, however, the reaction of primary substrates suffers from competing self-condensation, giving alkenes.[22] It should be noted that a two-stage procedure involving the reaction of phosphonate anion with chlorodimethyl borate followed by oxidation with ***m-Chloroperbenzoic Acid*** has been advocated as a more efficient method[23] (and, interestingly, allows isolation of the intermediate hydroxy phosphonate).

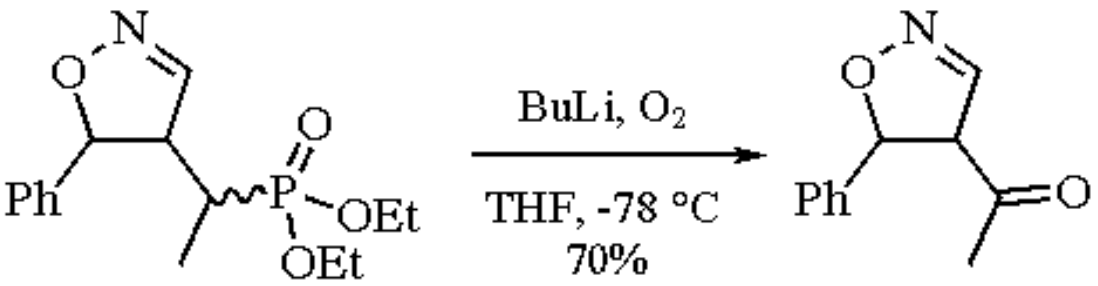

(7)

Oxygenation of Carbon Radicals.

Not surprisingly, triplet oxygen reacts rapidly with carbon centered radicals.[24] Classical autoxidation is the most obvious example of this behavior. Traditionally, autoxidation refers to hydroperoxide formation from alkanes, aralkanes, alkenes, ethers, alcohols, and carbonyl compounds, where the initiating homolysis is induced thermally or photochemically.[25,26] There is an extensive literature concerning these processes dating back many years. While very important commercially, they are generally too promiscuous to be of wide synthetic value, particularly when dealing with complex molecules. Interestingly, however, a deformylative hydroxylation of an allylic neopentyl aldehyde has been observed that bypasses the classical autoxidative fate of aldehydes (eq 8).[27]

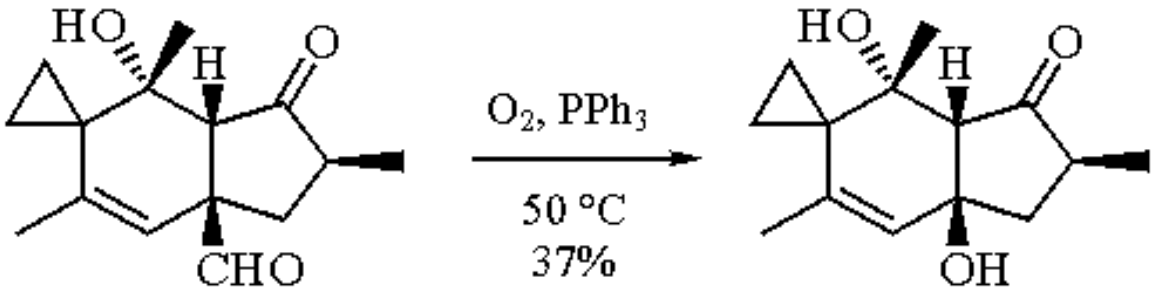

(8)

Radical oxygenation is most valuable where there is more strict control over the site of radical formation and subsequent oxygenation. Good stereochemical control is, of course, not usually achieved, although exceptions can be found in most cases. The mild and controlled methods of radical generation that have seen much use in synthesis are readily applicable to oxygenation. The thermal or photochemical decarboxylation of the esters of thiohydroxamic acids,[28] or their room temperature decomposition in the presence of tris(phenylthio)antimony[29] (i.e. Barton's methodology), can be intercepted

by triplet oxygen to generate the nor-alcohols. The addition of heteroatom radicals to alkenes can provide the source of carbon centered radicals for trapping. An interesting example of oxygenation initiated by phenylthio or phenylseleno radical addition to vinylcyclopropanes showcases the use of this methodology (eq 9).[30] Here, instances of moderately successful stereocontrol in the C-O bond forming step were noted. This transformation also demonstrates the potential of the initially formed hydroperoxy radical to participate in further steps (where higher levels of stereochemical discrimination are observed as a consequence of the intramolecular nature of the radical trapping). ***Samarium(II) Iodide*** induced radical processes have been quenched with oxygen to provide hydroxyl functionalized products.[31]

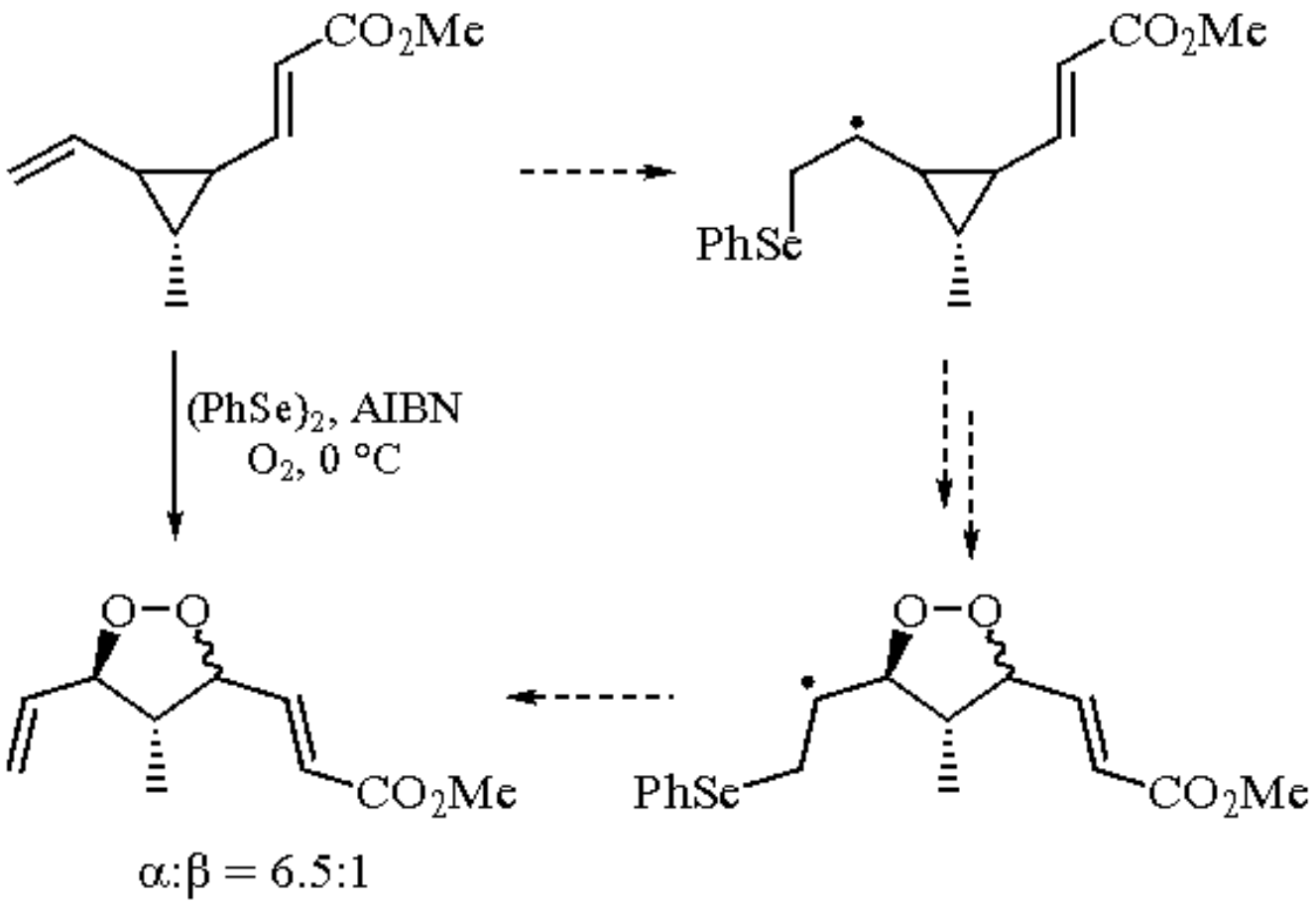

(9)

One of the most prevalent uses of molecular oxygen in modern synthesis is for oxidative demercuration.[32] Carbon radicals generated by the reduction of organomercurials with borohydride are efficiently trapped by oxygen, most frequently in DMF solution, to give hydroperoxides which are reduced under the reaction conditions to generate the corresponding alcohols directly.[33] The alkene oxymercuration-oxidative demercuration sequence is commonly practised (usually through a β-alkoxymercury species, since β-hydroxy fails[33]), particularly where the oxymercuration is an intramolecular cyclization (eq 10).[34] Typically, any stereocontrol observed in the oxymercuration (or other C-Hg bond forming step) is effaced in the oxygenation (as in eq 10).

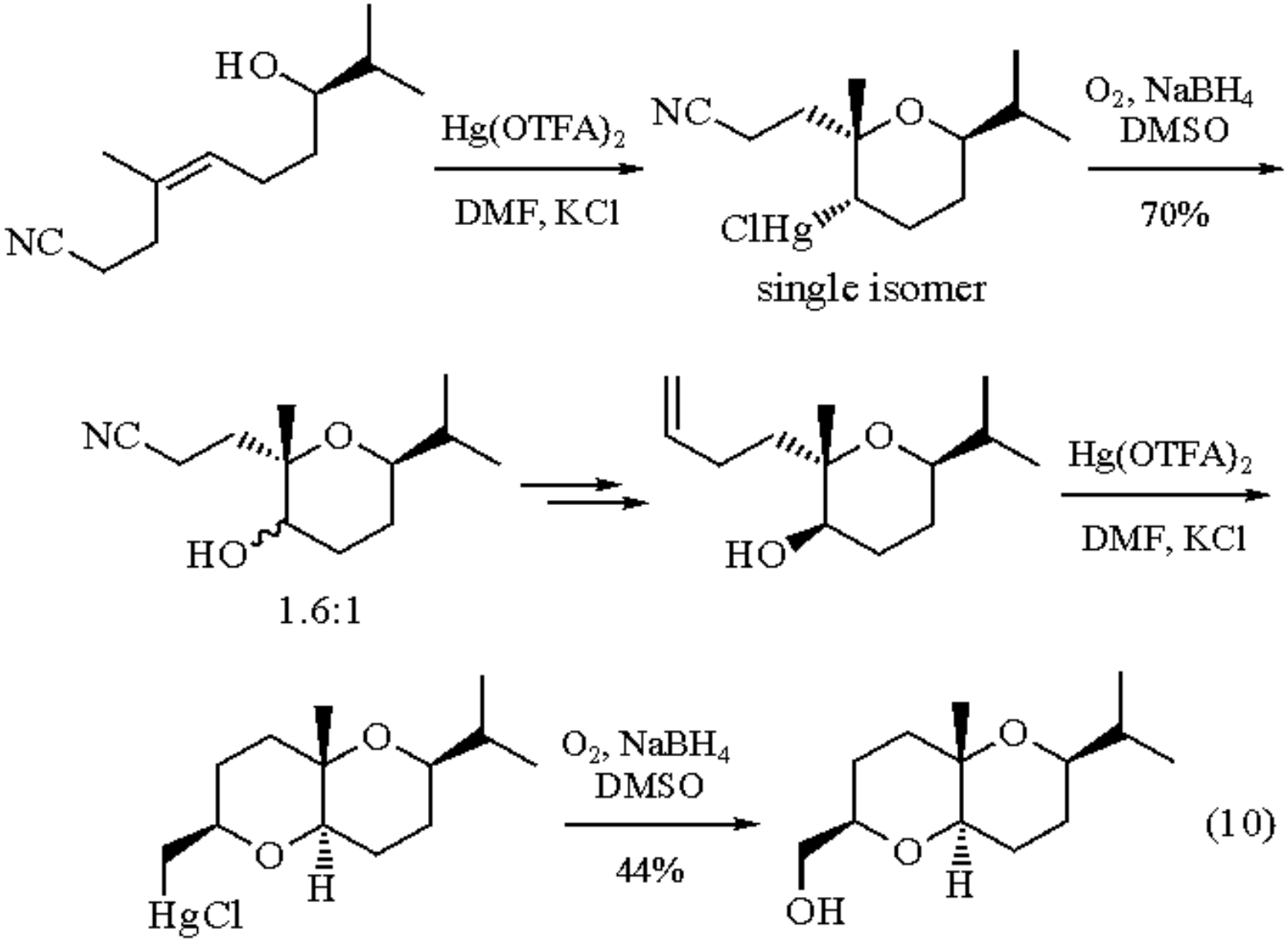

Oxidation of Organoboranes.

Boranes, most frequently accessed by hydroboration of alkenes, can be oxidized by triplet oxygen.[35,36] If the oxidation is carried out in fairly concentrated solution (~0.5 N) at 0 °C, intermolecular redox reaction of the intermediate diperoxyborane is facilitated and workup provides the corresponding alcohol.[36] While this is quite efficient, ***Hydrogen Peroxide*** is more commonly used in synthetic applications. This is partly for convenience, but also a consequence of stereochemical issues. The oxidation with H_2O_2 occurs with retention of configuration at the carbon center. The radical characteristics of the dioxygen reaction generally lead to at least partial racemization. That this stereochemical corruption is not always complete is an indication of the uncertainty about the mechanism.[35] Interestingly, rhodium(III) porphyrin has been shown to promote stereoselective oxidation in the dioxygen procedure (eq 11).[37] In dilute solution (0.01-0.05 N) the intermolecular redox process is suppressed and diperoxyboranes are produced. Oxidation of the third B-C bond with H_2O_2 or peroxy acid and workup allows isolation of the corresponding alkyl hydroperoxides.[36] Alternatively alkyl hydroperoxide formation is facilitated by the use of alkyldichloroboranes.[36] This is one of the most convenient approaches to this functionality. The oxygen mediated approach to alcohols may be more convenient than H_2O_2 for radiolabeling; ^{17}O (eq 12) and ^{15}O alcohols have been prepared in this way.[38,39]

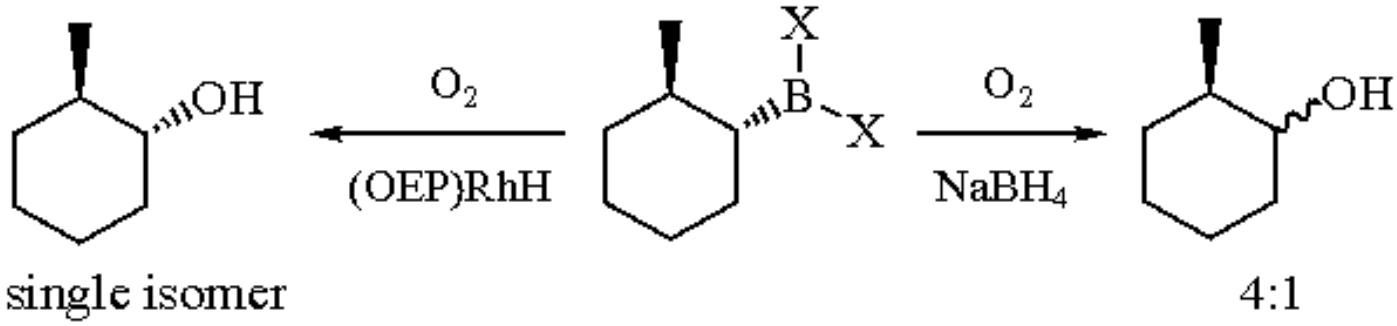

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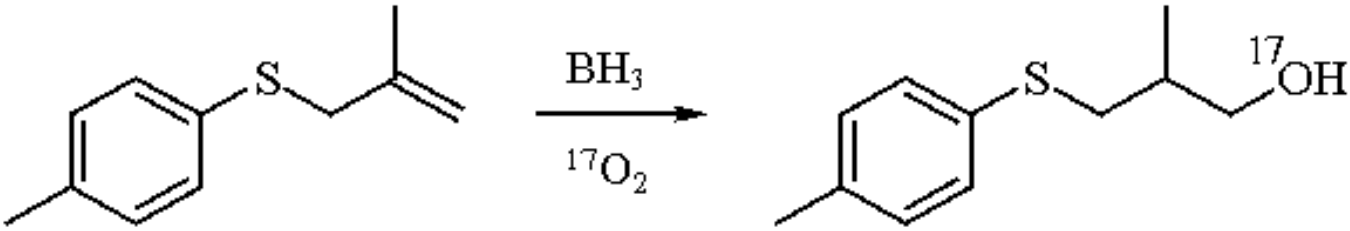

(12)

Heteroatom Oxidation.

Oxidation of nitrogen functionality with oxygen, while well precedented[40] and of continuing interest,[41,42] does not generally represent the method of choice for those processes of synthetic significance. However, a report of a mild procedure for the oxidation of silylamines to carbonyl compounds bears some synthetic potential (eq 13).[43] Oxidation of phosphorus functionality by oxygen can be quite facile.[44] For example, tertiary phosphines are very readily oxidized to their phosphine oxides, and secondary chlorophosphines can give the phosphinic acids.[44] Perhaps the most common heteroatom air oxidations are those of Group 16 RX-H bonds to their corresponding dimers ($(RX)_2$) and particularly the thiol to disulfide oxidation.[45] This, of course, is related to the importance of the disulfide bond to peptide and protein secondary structure. One example that reflects current interest in the control of multiple disulfide bond formation in synthetic peptides is given in eq 14.[46] Oxidation may be promoted by heavy metal ions.[45] Higher oxidations (for example sulfide to sulfoxide) are best performed with other reagents (oxone, peroxy acid, etc.).

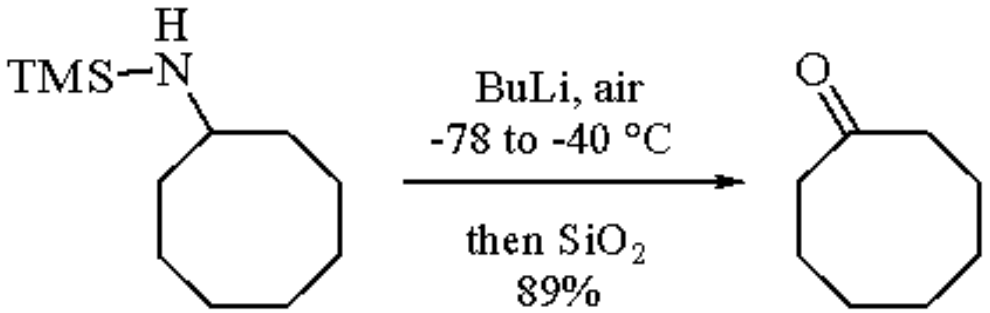

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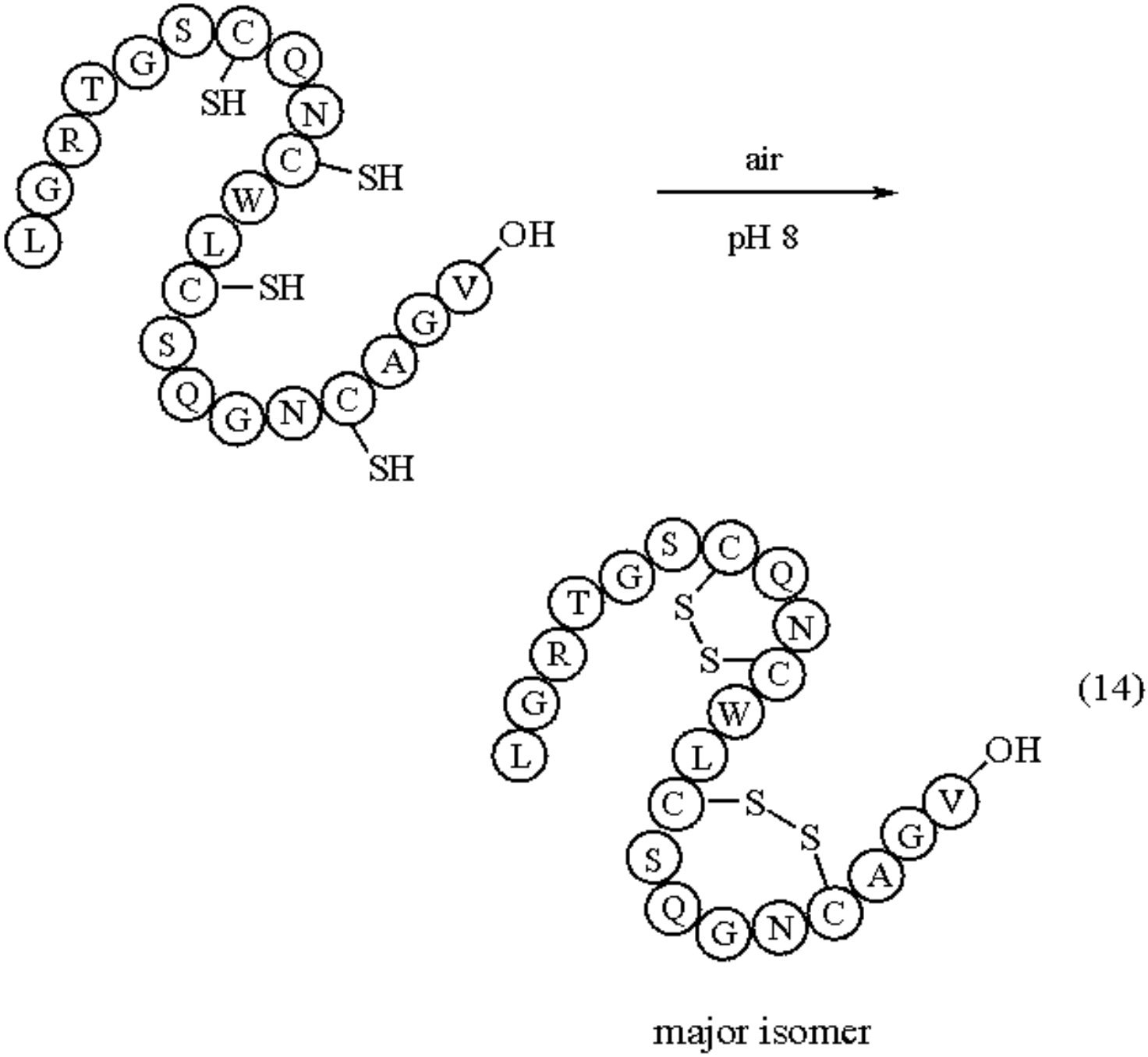

Other Uses.

The oxidative dimerization of organometallics, alluded to above, is particularly prevalent for organocuprates,[47] although not totally unavoidable.[48] In fact it is efficient enough to be regarded as a synthetic strategy and has been used as such (eq 15).[49] Baeyer-Villiger oxidations generally employ peroxy acids, but a recent report indicates that 1 atm of oxygen can effect the rearrangement even in the absence of either metal catalysts or light.[50] Epoxidation by oxygen is possible[51] but, of course, is not usually the method of choice for laboratory synthesis.

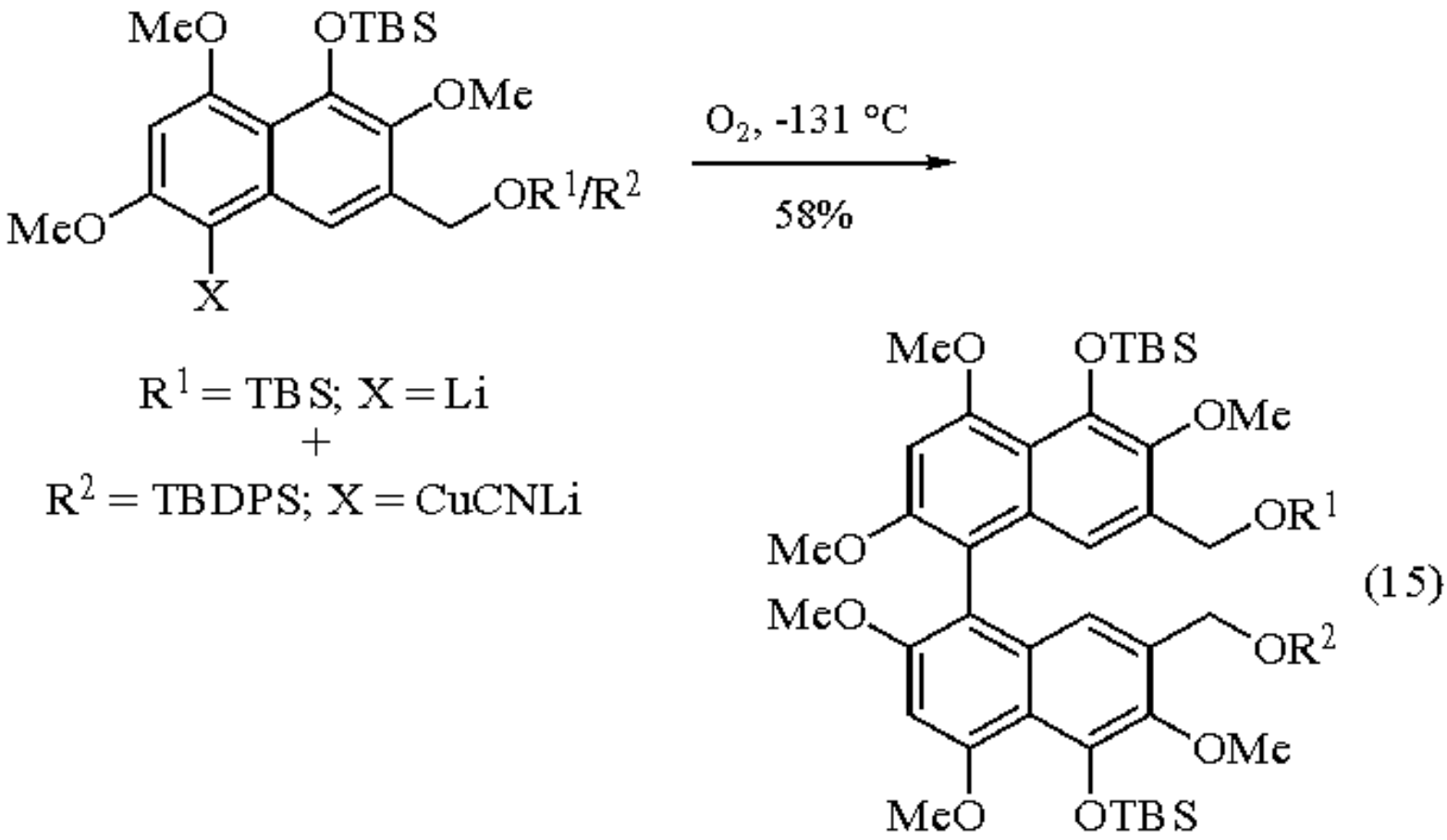

(15)

There is a vast literature concerning metal-catalyzed oxidative processes involving molecular oxygen,[52] of which only a fraction have seen synthetic use. Many metal catalysts behave as oxygen fixing species, that deliver oxygen to the substrate through a peroxo complex. Reports frequently concern experimental systems, probing substrate reactivity and/or asymmetric induction. The function of oxygen in metal-catalyzed oxidations is not necessarily that of a reagent. Thus, for example, in the Wacker oxidation of terminal alkenes it operates as a re-oxidant for copper(II) chloride which in turn is a re-oxidant for the Pd^{II} species. All of these applications are best regarded as functions of the metal component and, for this reason, are not discussed here.

Related Reagents.

Copper(I) Chloride-Oxygen; ***Diethylzinc-Bromoform-Oxygen***; ***Iron(II) Sulfate-Oxygen***; ***Oxygen-Platinum Catalyst***; ***Singlet Oxygen***.

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A. Brian Jones

Oxygen-Platinum Catalyst[1]

O_2-Pt

[7740-06-4] · Pt · Oxygen-Platinum Catalyst · (MW 195.08)

(selective oxidant; highly regioselective oxidant for cyclic polyols; lactones obtained from diols; primary alcohols oxidized to carboxylic acids)

Solubility: reaction usually heterogeneous.

Form Supplied in: fine powder; widely available.

Preparative Methods: various methods[1] are employed, depending on the catalyst: for Pt/C, charcoal, concentrated HCl, and aqueous chloroplatinic acid are reduced with hydrogen or formaldehyde; Adams catalyst (PtO_2) is hydrogenated in the solvent to be used for the oxidation; after purging hydrogen, store under chosen solvent.

Purification: dry at 50 °C under reduced pressure.

Handling, Storage, and Precautions: avoid sources of ignition; take precautions against static discharge.

Introduction.

Oxygen (often as air) and a platinum catalyst are used in the oxidation of primary alcohols to yield usually carboxylic acids (eq 1)[2] and for oxidation of secondary alcohols. It has been widely used in the selective oxidation of carbohydrates and related systems, and some general guidelines have been developed. Primary alcohols are oxidized more rapidly than secondary alcohols; for secondary cyclic alcohols, axial hydroxyl groups are oxidized more rapidly than equatorial hydroxyl groups.

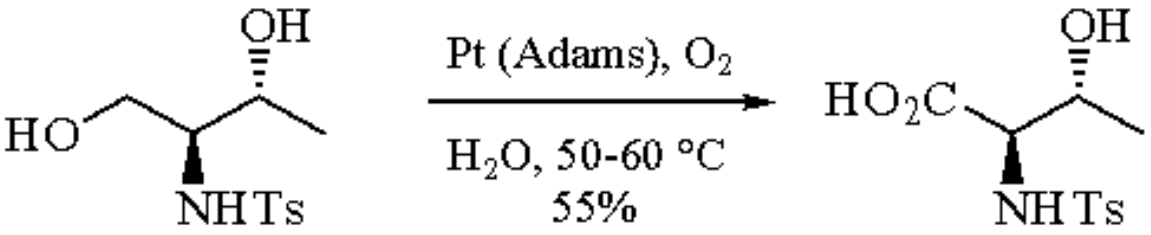

(1)

Oxidation of Aldoses and Ketoses.

Aldonic acids are produced by oxidation of aldoses (eq 2)[3] and ketoses undergo reaction at the primary position (eq 3).[4] Oxidation of reducing sugars at positions other than the aldehyde position is simply achieved by protection of this position as the corresponding acetal or acetonide, and, as expected, oxidation of the next most reactive position takes place (eq 4).[5] For deoxyamino sugars, the amino function is usually protected as a suitable acyl derivative (eq 5).[6]

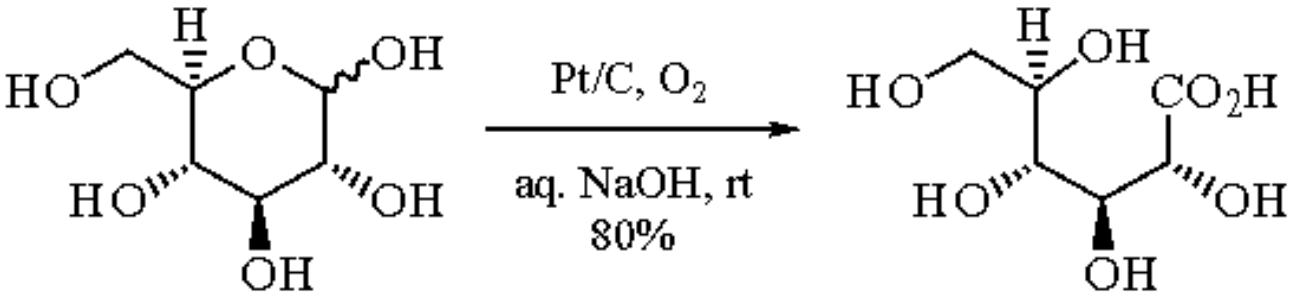

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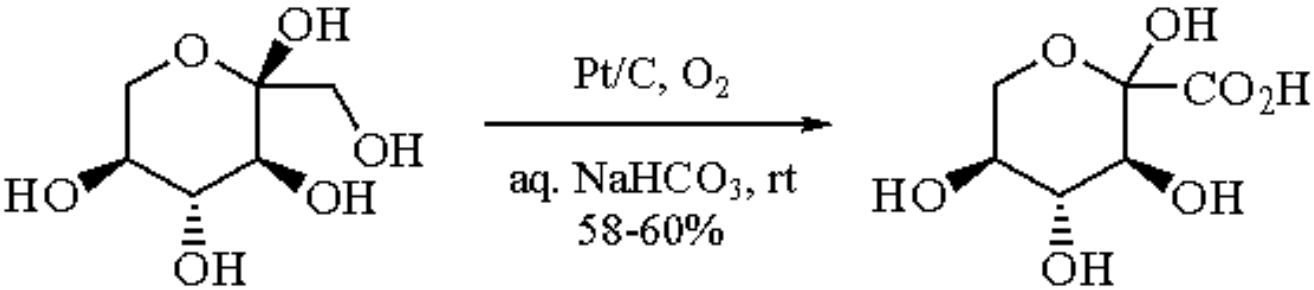

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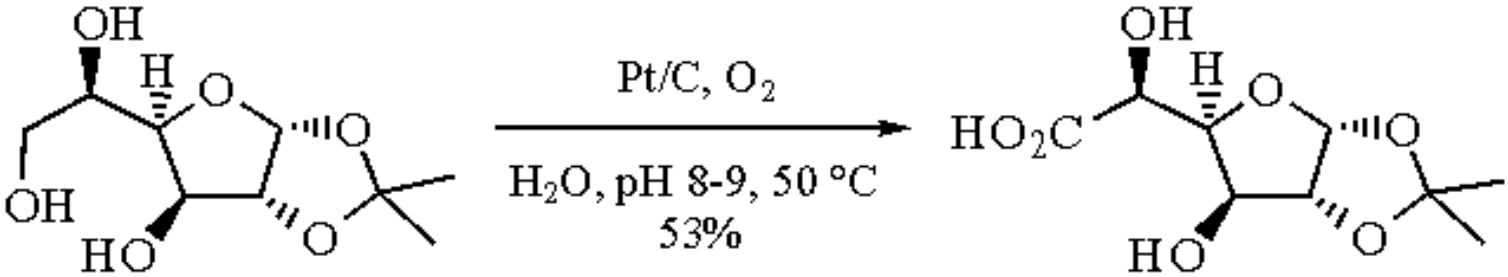

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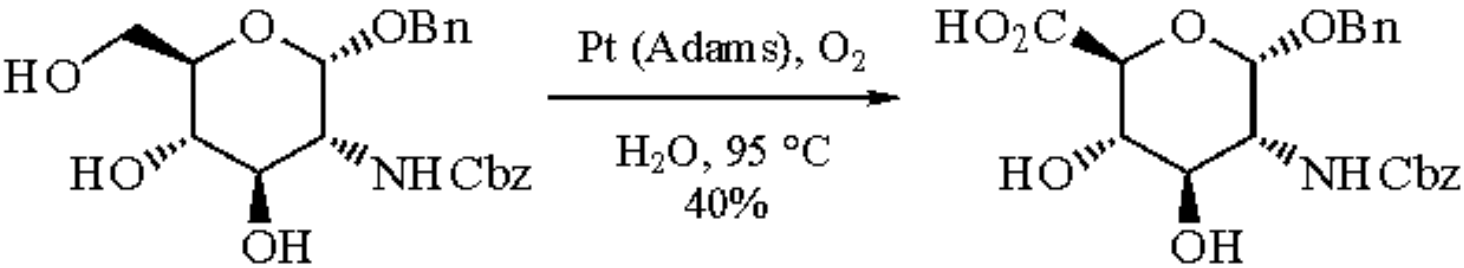

(5)

Oxidation of Cyclitols.

A considerable amount of work has been carried out on the oxidation of cyclitols with oxygen-platinum catalysts[1] and a set of general rules has been developed: (a) only axial hydroxyl groups are oxidized; (b) oxidation stops at the monoketone even when more than one axial hydroxyl is present; (c) if several nonequivalent axial hydroxyl groups are present, then usually oxidation of only one of these will take place. These general rules are exemplified by eqs 6 and 7.[7]

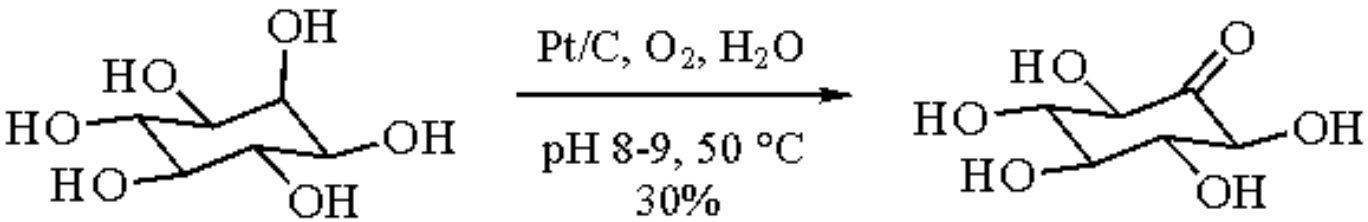

(6)

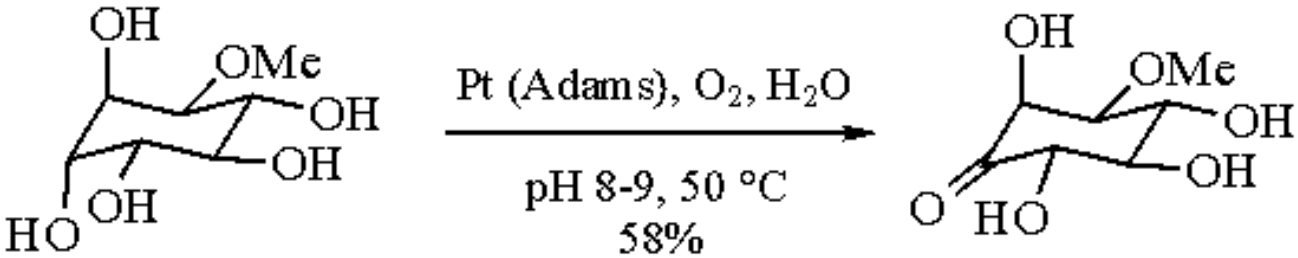

(7)

Oxidation of Diols to Lactones.

The oxidation of 1,4-diols in which one of the hydroxyls is primary gives the corresponding lactones, a reaction which has found use in natural product synthesis,[8] including hydroazulenes (eq 8)[9] and prostaglandins (eq 9).[10]

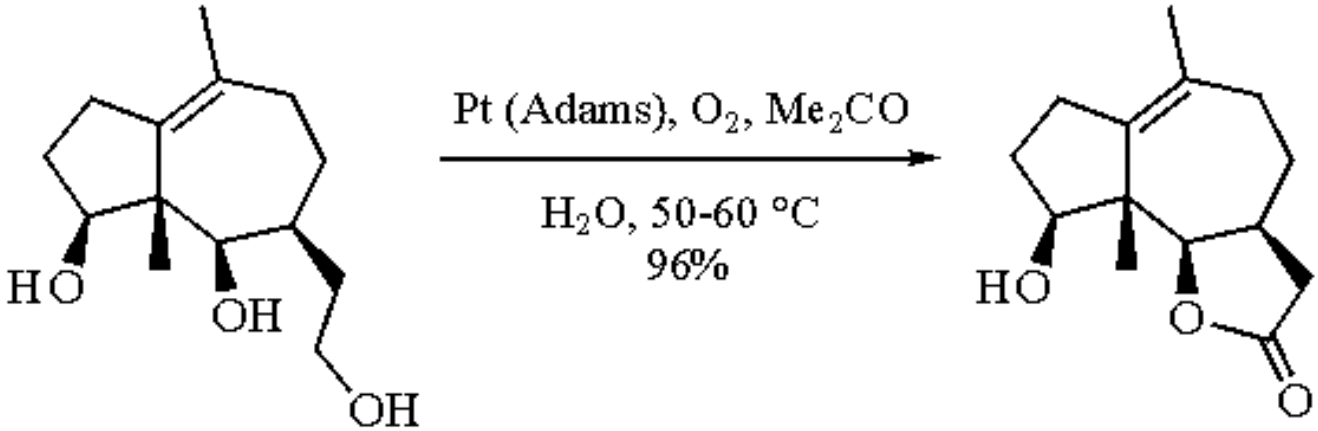

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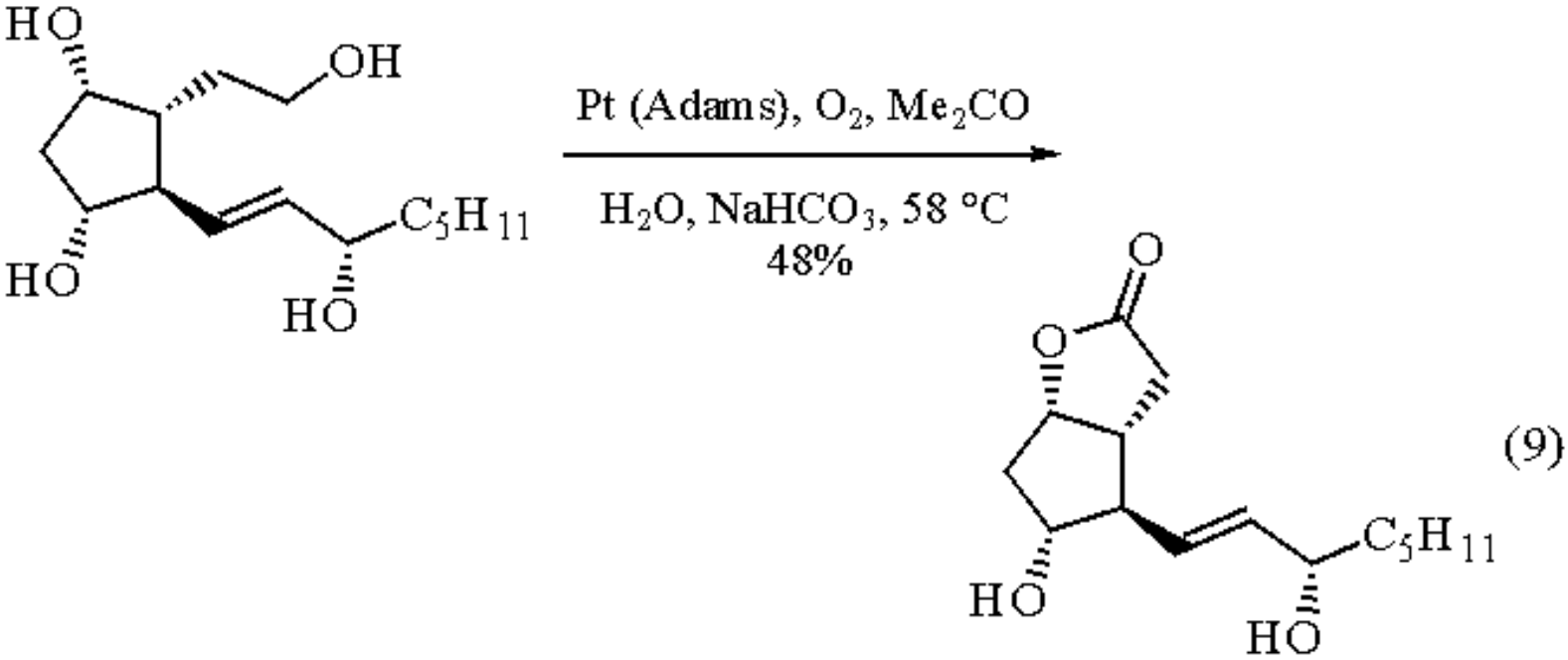

Other Applications.

It has been shown that visible light and a catalyst of H_2PtCl_6-$CuCl_2$ (1:2) can be used to oxidize a series of alcohols,[1c] and that the oxidation of reducing sugars does not need oxygen if platinum catalysts are used under basic conditions.[11] 12a-Hydroxylation of a deoxytetracycline has been carried out using oxygen and a platinum catalyst,[12] although the usefulness this reaction appears to depend strongly on the structure of the substrate.[13]

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1. (a) Heyns, K.; Paulsen, H. *Newer Methods Prep. Org. Chem.* **1963**, *2*, 303. (b) Heyns, K.; Paulsen, H. *Adv. Carbohydr. Chem.* **1962**, *17*, 169. (c) Cameron, R. E.; Bocarsly, A. B. *JACS* **1985**, *107*, 6116.
2. Maurer, P. J.; Takahata, H.; Rapoport, H. *JACS* **1984**, *106*, 1095.
3. Heyns, K.; Heinemann, R. *LA* **1947**, *558*, 187.
4. Heyns, K. *LA* **1947**, *558*, 177.
5. Mehltretter, C. L.; Alexander, B. H.; Mellies, R. L.; Rist, C. E. *JACS* **1951**, *73*, 2424.
6. Heyns, K.; Paulsen, H. *CB* **1955**, *88*, 188.
7. Post, G. C.; Anderson, L. *JACS* **1962**, *84*, 471.
8. For a comparison of this reagent with Ag_2CO_3, see: Boeckman, Jr., R. K.; Thomas, E. W. *TL* **1976**, 4045.
9. (a) Kretchmer, R. A.; Thompson, W. J. *JACS* **1976**, *98*, 3379. (b) Lansbury, P. T.; Hangauer, Jr., D. G.; Vacca, J. P. *JACS* **1980**, *102*, 3964.
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11. de Wit, G.; de Vlieger, J. J.; Kock-van Dalen, A. C.; Heus, R.; Laroy, R.; van Hengstrum, A. J.; Kieboom, A. P. G.; van Bekkum, H. *Carbohydr. Res.* **1981**, *91*, 125.
12. Muxfeldt, H.; Buhr, G.; Bangert, R. *AG(E)* **1962**, *1*, 157.
13. Muxfeldt, H.; Haas, G.; Hardtmann, G.; Kathawala, F.; Mooberry, J. B.; Vedejs, E. *JACS* **1979**, *101*, 689.

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Ozone[1]

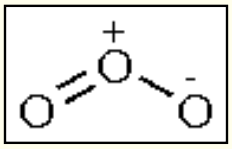

[10028-15-6] · O_3 · Ozone · (MW 48.00)

(powerful oxidant; capable of oxidizing many electron rich functional groups;[1c,d] most widely used to cleave alkenes, affording a variety of derivatives depending on workup conditions[1b,2])

Physical Data: mp -193 °C; bp -111.9 °C; *d* (0 °C, gas) 2.14 g L^{-1}.

Solubility: 0.1-0.3% by weight in hydrocarbon solvents at -80 to -100 °C.[3]

Preparative Methods: ozone is a colorless to faint blue gas which is usually generated in the laboratory by passing dry air or oxygen through two electrodes connected to an alternating current source of several thousand volts. From air, ozone is typically generated at concentrations of 1-2%; from oxygen, concentrations are typically 3-4%. Several laboratory scale generators are commercially available.

Analysis of Reagent Purity: the amount of ozone generated can be determined based on the liberation of iodine from potassium iodide solution followed by thiosulfate titration to determine the amount of iodine produced.[4] Photometric detectors are available which can determine the concentration of ozone in a metered gas stream. In this manner, exact amounts of ozone introduced into a reaction can be determined.

Handling, Storage, and Precautions: ozone is irritating to all mucous membranes and is highly toxic in concentrations greater than 0.1 ppm by volume. It has a characteristic odor which can be detected at levels as low as 0.01 ppm. All operations with ozone should be carried out in an efficient fume hood and scrubbing systems employing thiosulfate solutions can be used to destroy excess ozone. Liquefied ozone poses a severe explosion hazard.

Ozonolysis of Alkenes.

Ozone has been most widely used for cleavage of carbon-carbon double bonds to produce carbonyl compounds or alcohols, depending on workup conditions. These reactions usually are performed by passing a stream of ozone in air or oxygen through a solution of the substrate in an inert solvent at low temperature (-25 to -78 °C). Useful solvents include pentane, hexane, ethyl ether, CCl_4, $CHCl_3$, CH_2Cl_2, EtOAc, DMF, MeOH, EtOH, H_2O, or HOAc. The solvents most commonly used are CH_2Cl_2 and MeOH or a combination of the two. Reaction endpoint can be determined using photometric monitors to detect ozone in the exit gas stream, or by the appearance of a blue color in the reaction medium, which indicates excess ozone in solution. A wide variety of alkenes undergo ozonolysis, and those in which

the double bond is connected to electron-donating groups react substantially faster than alkenes substituted with electron-withdrawing groups.[1b,5] With haloalkenes, the rate of ozone attack is decelerated and a greater variety of products are obtained, although double bond cleavage is still prevalent.[6]

The reaction mechanism for ozonolysis has been studied extensively and is thought to involve a 1,3-dipolar cycloaddition to afford an initial 1,2,3-trioxolane or primary ozonide, which cleaves to a carbonyl compound and a carbonyl oxide (eq 1).[7] The carbonyl oxide generally forms at the fragment containing the more electron donating group. Recombination of the fragments affords a 1,2,4-trioxolane or ozonide which is sometimes isolated, but due to the danger of explosion is usually directly converted to carbonyl compounds via either a reductive or oxidative procedure. If alcoholic solvents are used, trapping of the carbonyl oxide can occur to afford an α-alkoxy hydroperoxide.

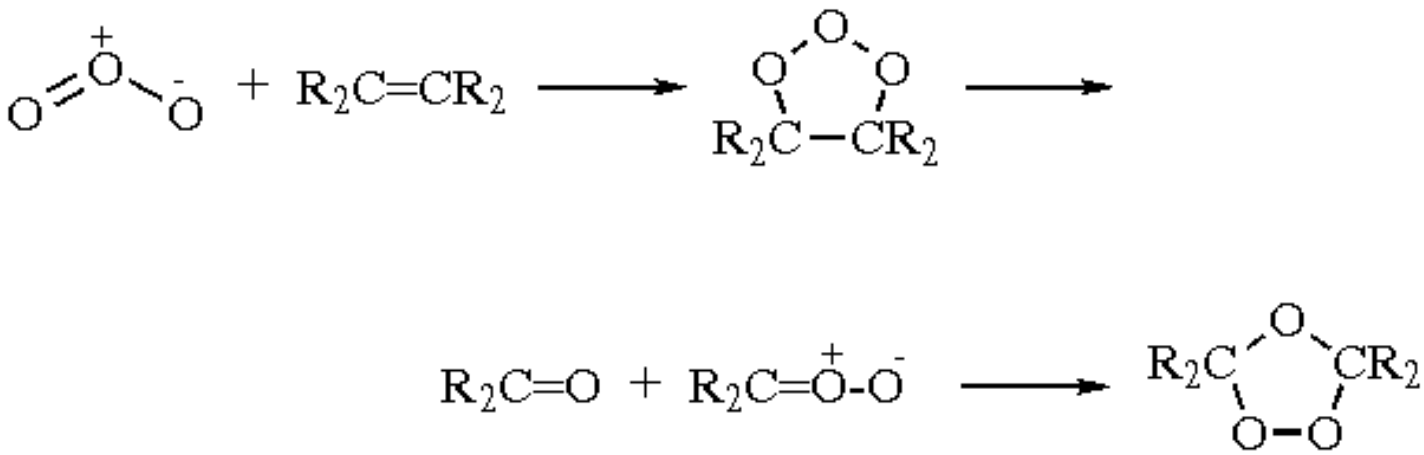

(1)

Reductive workup procedures afford aldehydes, ketones, or alcohols. An extensive number of reducing agents have been used including catalytic hydrogenation, sulfite ion, bisulfite ion, iodide, phosphine, phosphite, tetracyanoethylene (TCNE), Zn-HOAc, BH_3, $SnCl_2$, Me_2S, thiourea, or, to obtain alcohols, $LiAlH_4$ or $NaBH_4$.[1a,b,8] ***Dimethyl Sulfide*** offers several advantages. It rapidly reduces peroxidic ozonolysis products to carbonyl compounds, it operates under neutral conditions, excess sulfide is easily removed by evaporation, and the oxidation product is DMSO.[9] In cases where the odor of Me_2S is a problem, ***Thiourea*** is a convenient substitute: results are comparable to those obtained with Me_2S, and thiourea *S*,*S*-dioxide separates out from the reaction mixture.[10] A polymer-based diphenylphosphine system also has been developed which offers the advantage of a simple filtration and evaporative workup and eliminates potential product contamination by PPh_3 or its oxide.[11] A comparison of these workup options is shown in eq 2.

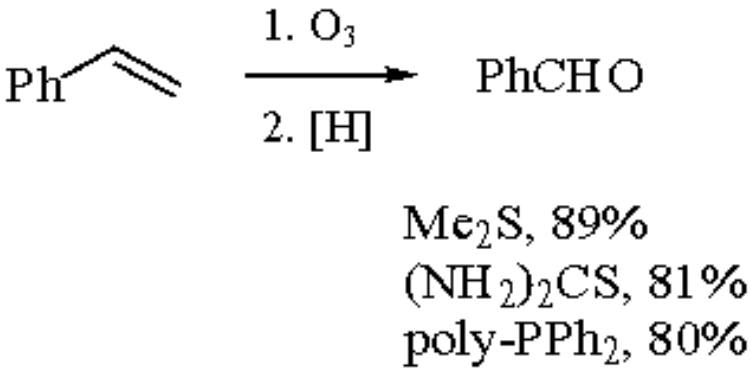

(2)

Oxidative workup procedures convert peroxidic ozonolysis products to ketones or carboxylic acids. Typical oxidative

reagents include peroxy acids, silver oxide, chromic acid, permanganate, molecular oxygen, and the most widely used reagent, ***Hydrogen Peroxide***.[1a,b,8]

Additional terminal functionalization can be accomplished by several methods. Schreiber has developed general ozonolysis and workup procedures which enable a variety of products to be prepared from cycloalkenes (eq 3).[12] Also, iron or copper salts can be used to convert ozonides or α-alkoxy hydroperoxides to chlorides or alkenes with one less carbon atom than in the original alkene (eqs 4 and 5),[13] and treatment of ozonides with hydrogen and an amine in the presence of a catalyst provides a direct route for the production of amines from alkenes (eq 6).[14] In a more specific case, stilbenes can be converted to alkyl benzoates by treatment of the intermediate α-alkoxybenzyl hydroperoxides with amines or DMSO.[15]

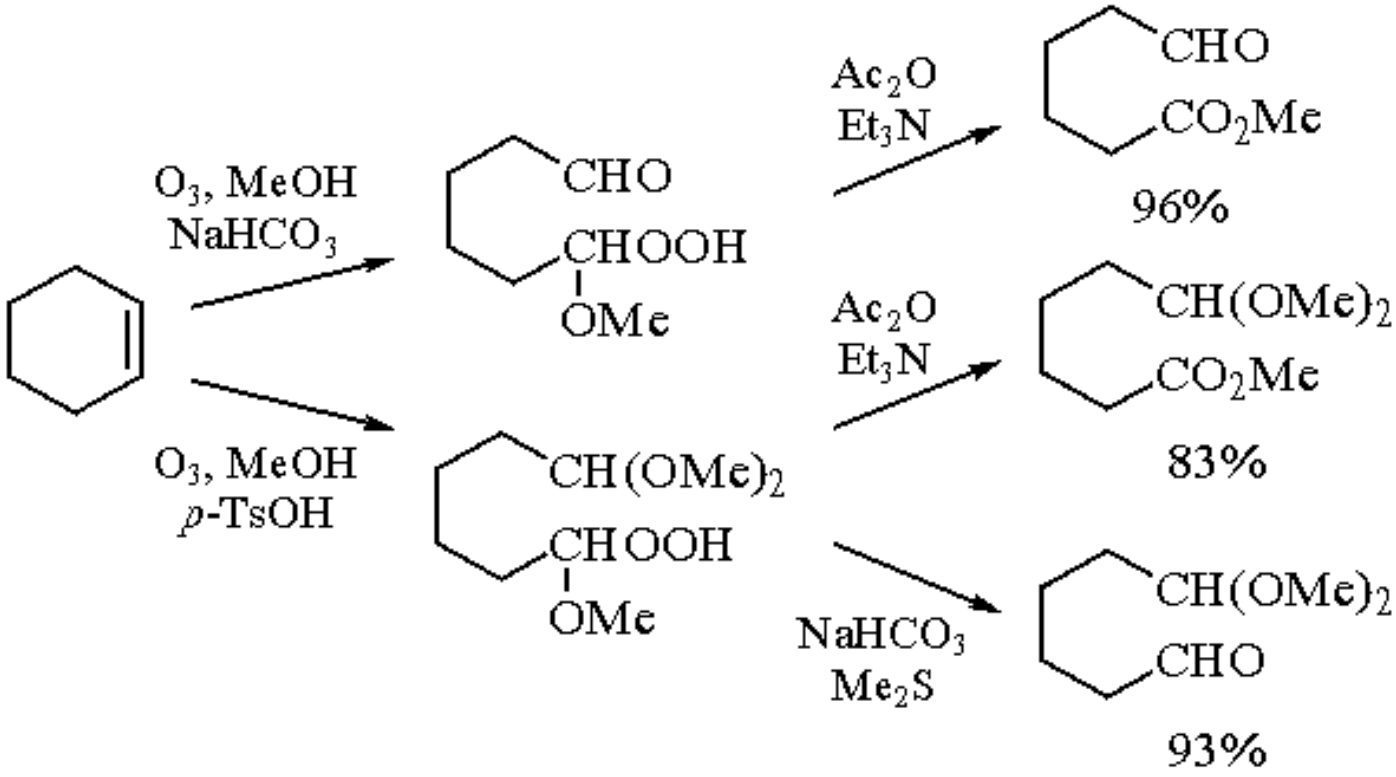

(3)

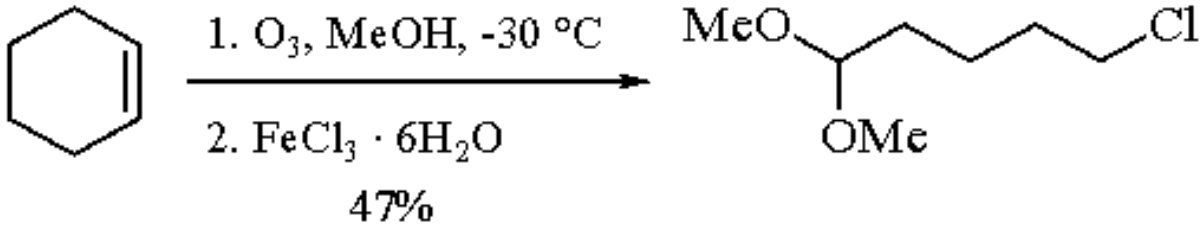

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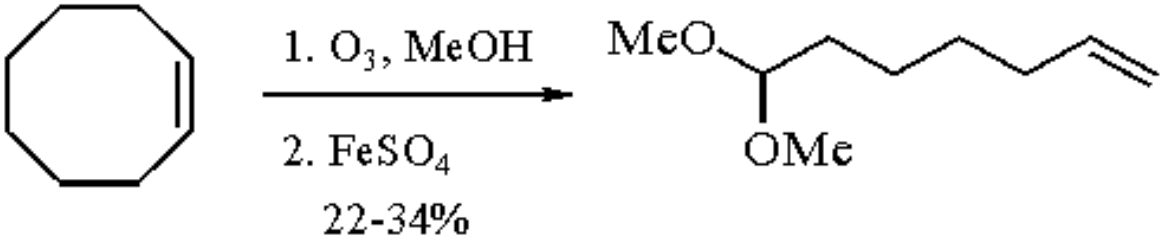

(5)

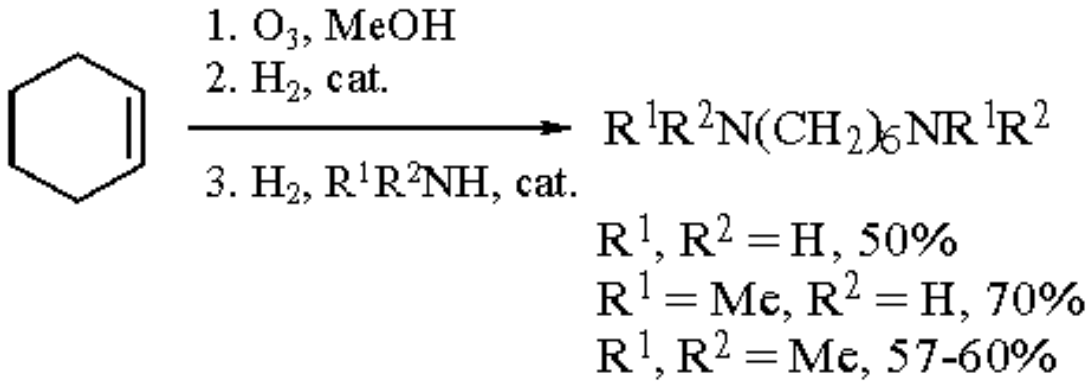

(6)

Vinyl ethers are more reactive toward ozone than alkenes due to the electron-donating oxygen substituent and double bond cleavage products are often obtained.[16] Notably, the ozonolysis of cyclic vinyl ethers provides a path to aldol and homoaldol type products.[17] In addition, silyloxyalkenes undergo clean oxidative cleavage with ozone to afford diacids by using oxidative workups (eq 7),[18] or hydroxyl or oxo derivatives by using reductive workups (eqs 8-10).[19] Overall, the two-step process of forming and cleaving a silyloxyalkene provides a method for regiospecific cleavage of an unsymmetrical ketone. Eq 10 shows that the silyloxyalkene double bond is sufficiently nucleophilic to allow for selective oxidative cleavage of this bond in the presence of less activated double bonds; with appropriate workup conditions, the method can thus complement Baeyer-Villiger oxidation.

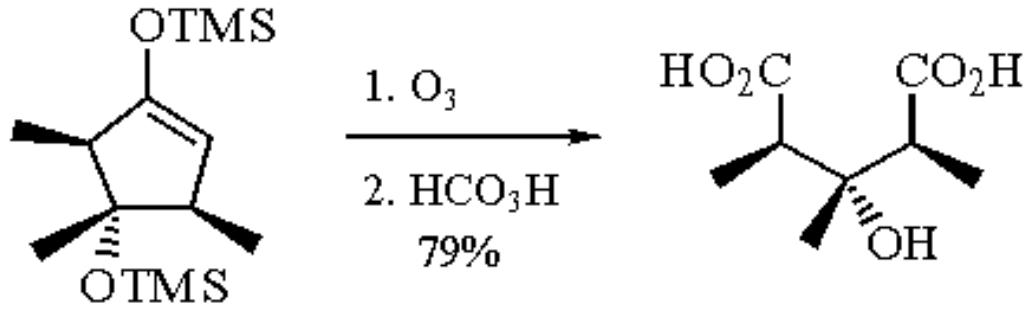

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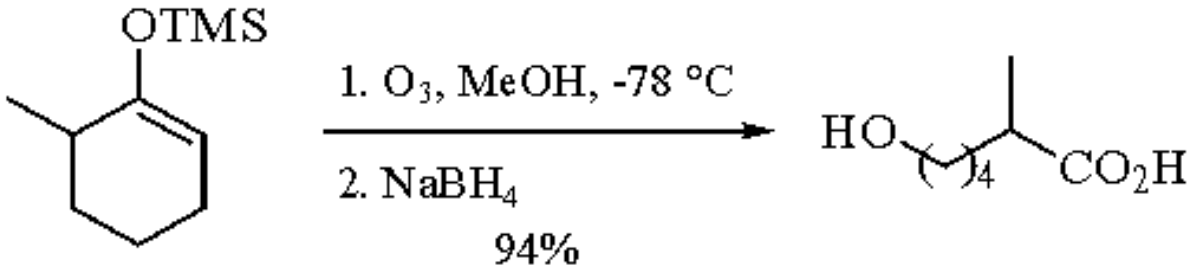

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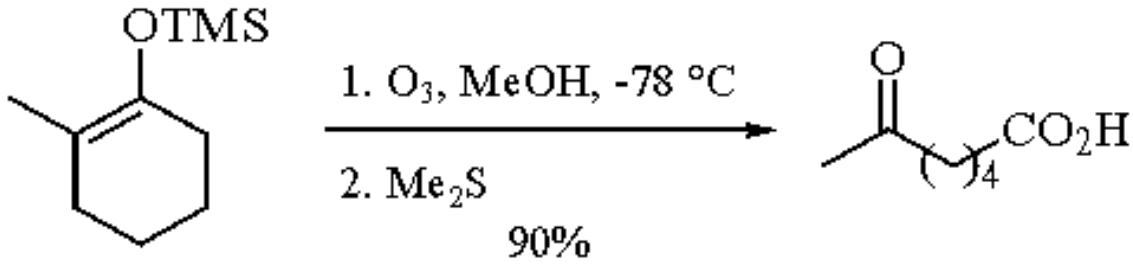

(9)

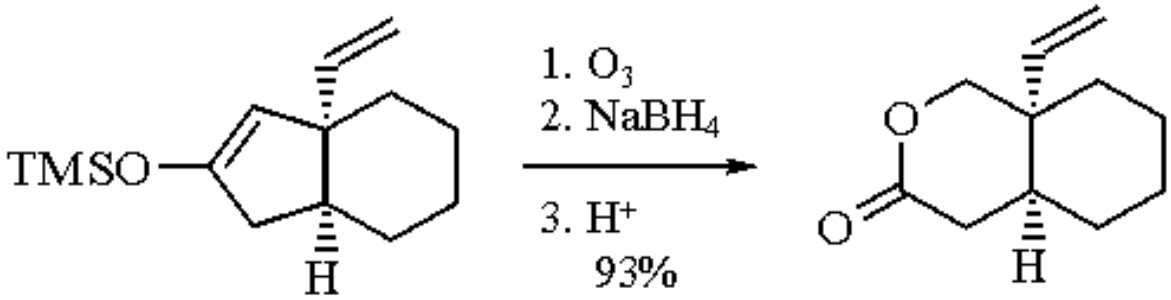

(10)

While ozone generally reacts with vinyl sulfides and enamines to provide both the expected products of double bond cleavage and anomalous products,[20,21] ketene dithioacetals have been efficiently cleaved to ketones using ozone (eq 11).[22]

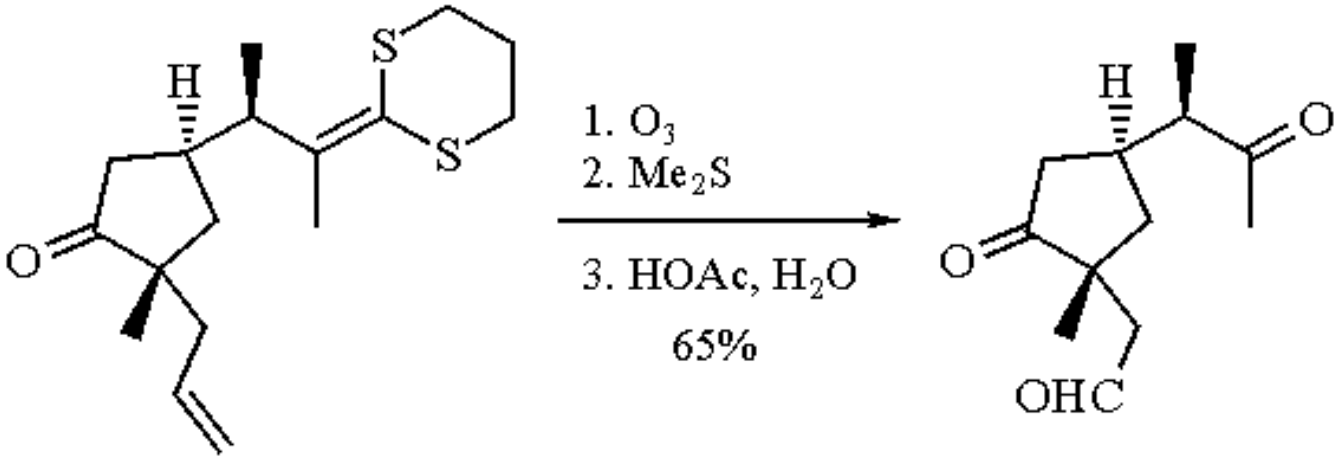

(11)

The reaction of α,β-unsaturated ketones with ozone usually affords keto acids containing one less carbon than in the original molecule (eq 12).[23]

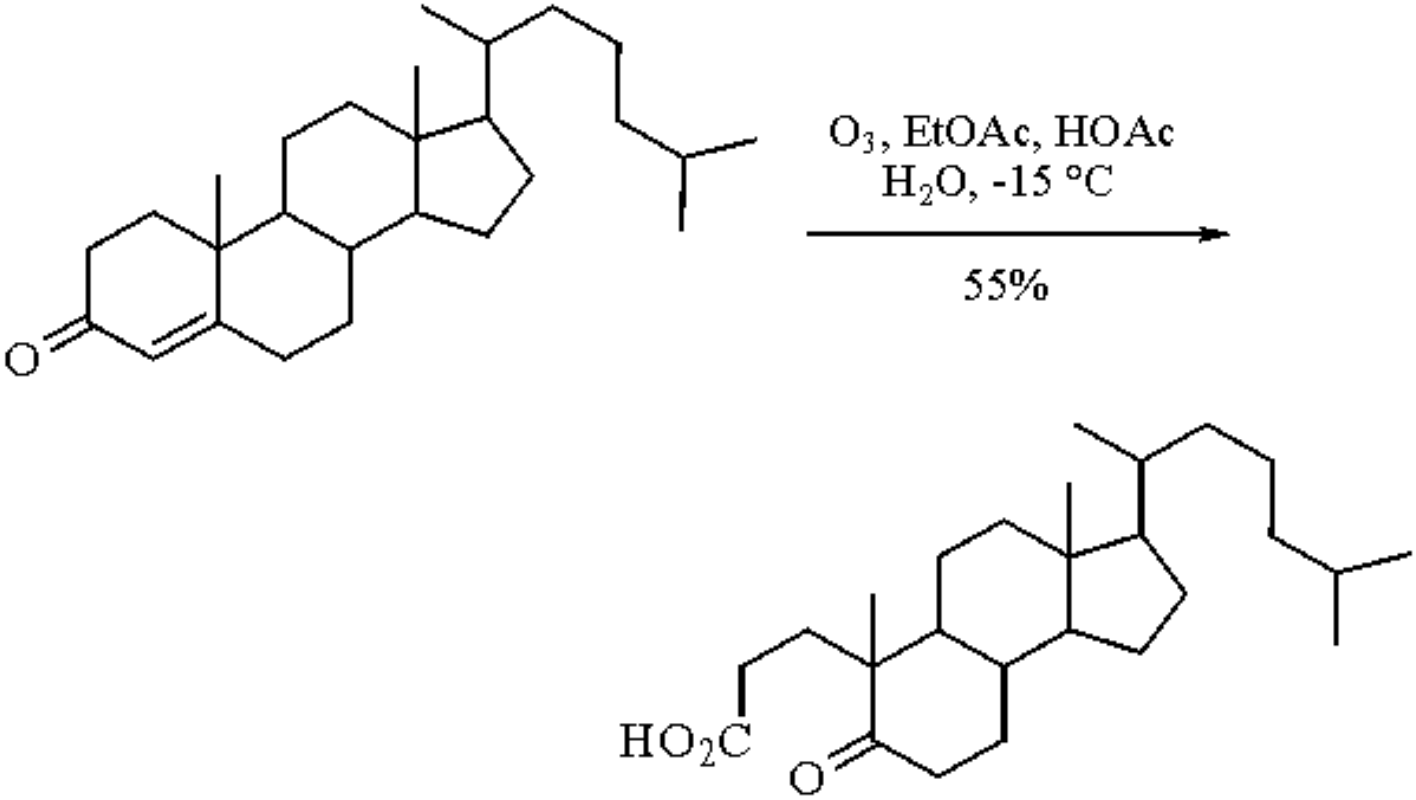

(12)

In the ozonolysis of 1,3-dienes, one double bond often can be cleaved selectively, and in 1,3-cyclodienes, the regioselectivity in fragmentation of the primary ozonide depends upon the size of the rings (eq 13).[24] Eq 13 shows that as the ring size contracts from cyclooctadiene to cyclohexadiene, the α,β-unsaturated ester becomes favored over the enal.

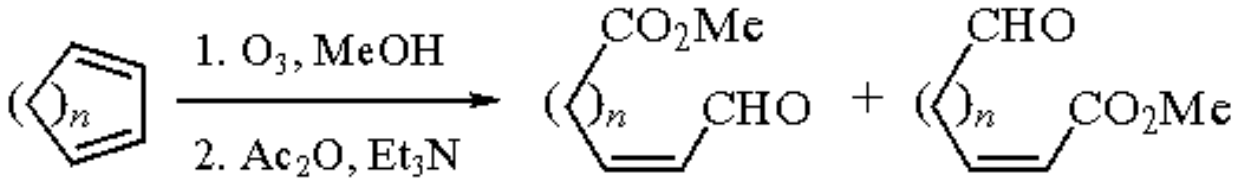

(13)

$n = 4$, 71% 15:1
$n = 2$, 50% 1:8

Hindered alkenes often afford epoxides upon ozonation due to difficulty in forming the primary ozonide by a cycloaddition process.[25] Examples are displayed in eqs 14 and 15.[26,27]

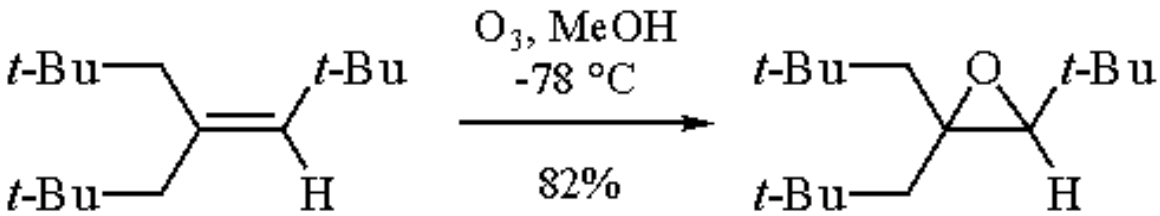

(14)

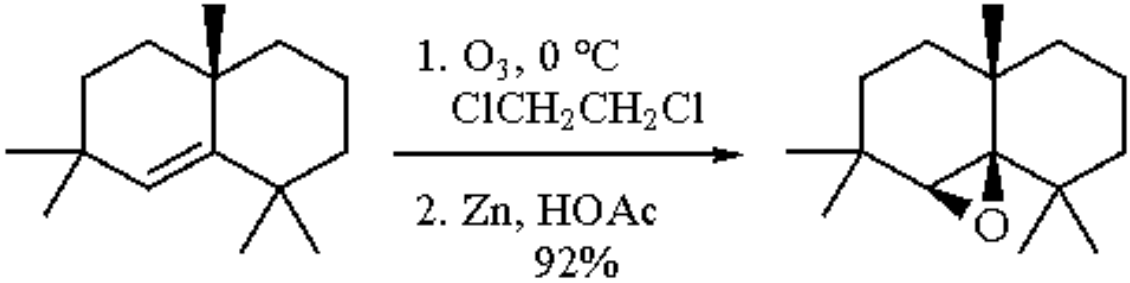

(15)

Overall, ozone compares favorably with other approaches for oxidative alkene cleavage involving ***Osmium Tetroxide***, ***Potassium Permanganate***, ***Ruthenium(VIII) Oxide***, ***Sodium Periodate***, or chromyl carboxylates which are costly, toxic, involve metal wastes, and may require detailed workup procedures.

Ozonation of Alkynes.

Reactions of alkynes with ozone afford either carboxylic acids or, if reductive procedures are used, α-dicarbonyl compounds.[1c] For the production of carboxylic acids, MeOH has been shown to be superior to CH_2Cl_2 as reaction solvent.[28] As with alkenes, a number of reducing agents can be used to produce α-dicarbonyl compounds. An easy option which results in high yields of α-dicarbonyl compounds involves the addition of ***Tetracyanoethylene*** directly to an ozonation reaction mixture as an in situ reducing agent (eq 16).[29]

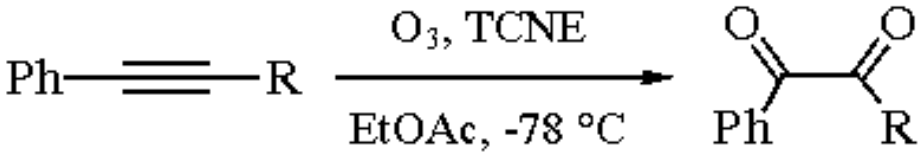

(16)

R = Ph, 92%; H, 60%; Pr, 71%

Alkynes react slower with ozone than do alkenes and selective reaction of alkenes can be achieved in the presence of alkynes (eq 17).[30] Conversely, the example of eq 18 shows that alkynes are more reactive toward ozone than aromatic rings.[31]

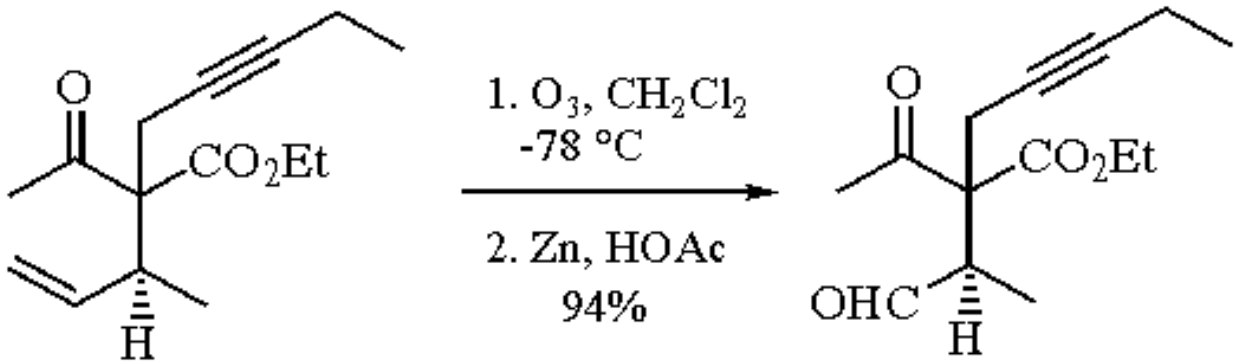

(17)

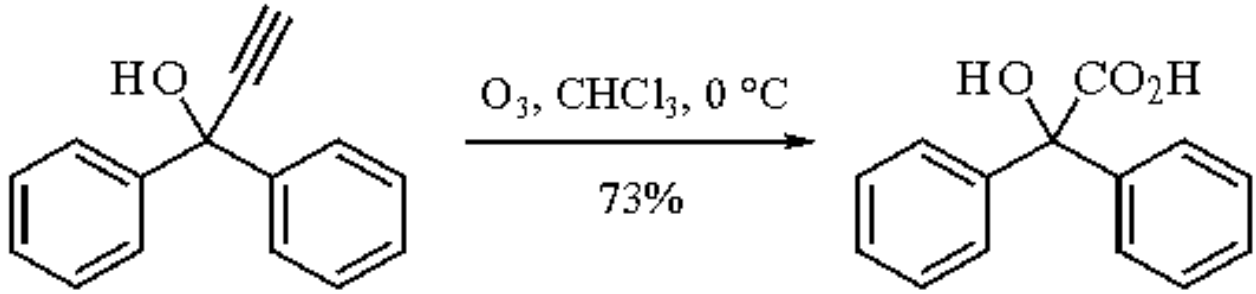

(18)

The ozonation of terminal alkynes to afford α-oxoaldehydes is significant (see eq 16). While reagents such as $KMnO_4$, RuO_4, OsO_4, and ***Thallium(III) Nitrate*** can be used to convert internal alkynes to α-dicarbonyl compounds, terminal alkynes are generally cleaved to carboxylic acids. Only ***Mercury(II) Acetate***-catalyzed oxidations using a molybdenum peroxide complex afford α-oxoaldehydes.[32] However, high catalyst loads are required, the oxidant is not commercially available, and metal wastes are generated.

Oxygenated alkynes also can be ozonated. The reaction of ozone with alkynyl ethers followed by reductive workup provides a convenient method for the production of α-keto esters in moderate yields (eq 19).[33]

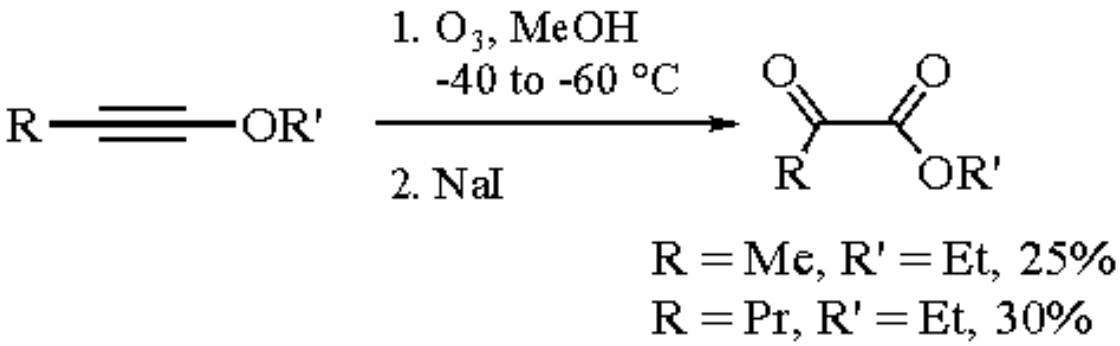

(19)

Ozonation of Aromatic Systems.

Aromatic compounds are less reactive toward ozone than either alkenes or alkynes. As a consequence, more forcing conditions are required to ozonize aromatic systems. These conditions typically involve the use of acetic acid as solvent, excess ozone, and oxidative decomposition often using H_2O_2. Electron-withdrawing groups deactivate aromatic systems toward electrophilic ozone attack, while electron-donating groups activate aromatic systems toward ozone attack. An example of this is provided in Woodward's strychnine synthesis where methoxy substitution allows for selective oxidation of one aromatic ring over two others to afford an often difficult to prepare, terminally functionalized, conjugated (*Z*,*Z*)-diene (eq 20).[34]

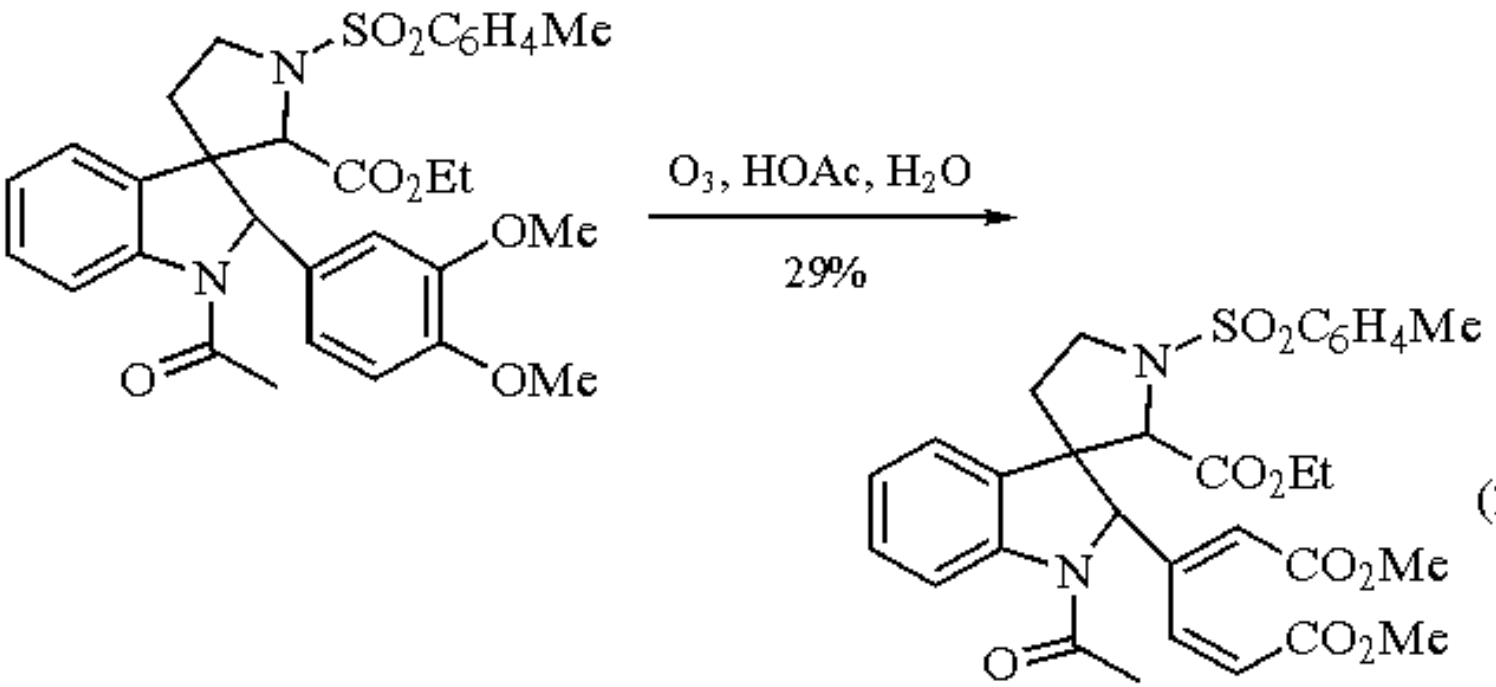

(20)

With polycyclic aromatic hydrocarbons, the site of ozone attack may be dependent upon substrate structure and reaction solvent (eq 21).[35]

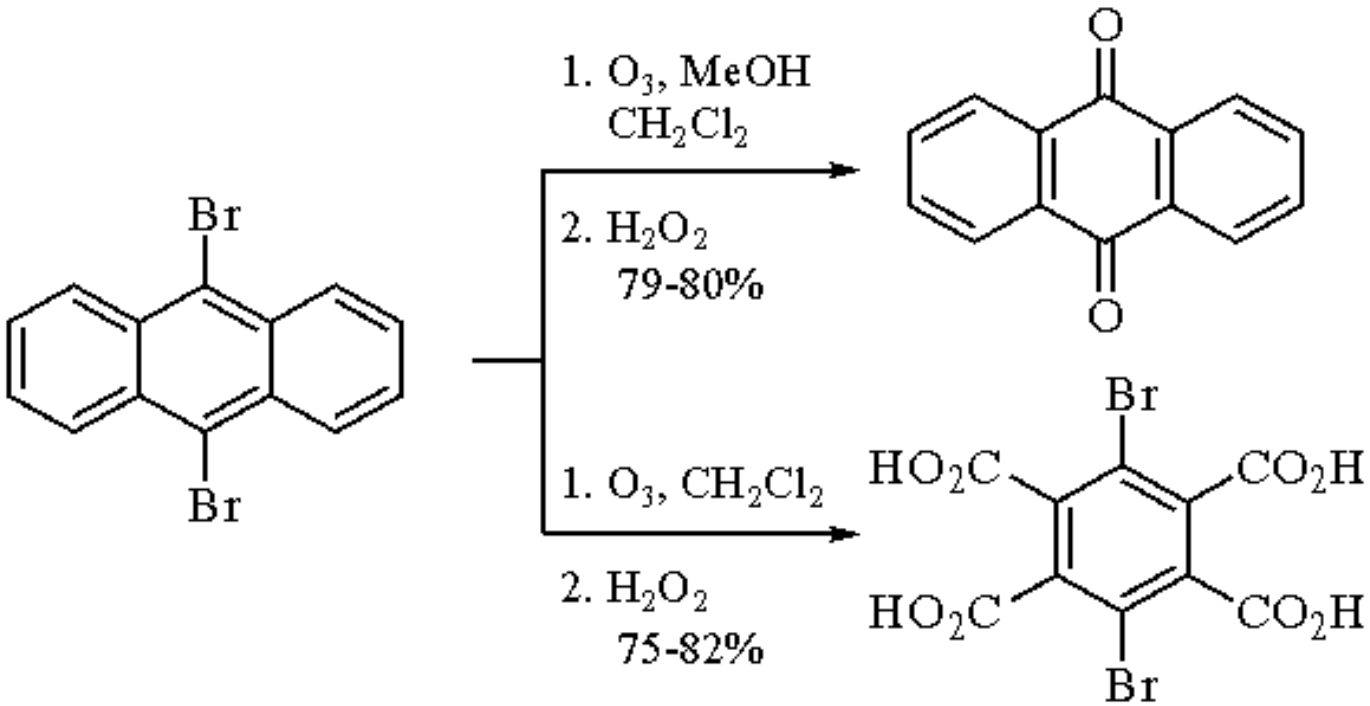

(21)

Synthetically useful ozonolyses of heteroaromatic systems include the preparation of pyridine derivatives from quinolines (eq 22),[36] the preparation of versatile *N*-acyl amides by the ozonolysis of imidazoles (eq 23),[37] and the unmasking of a latent carboxylic acid function by the ozonolysis of a furan system (eq 24).[38]

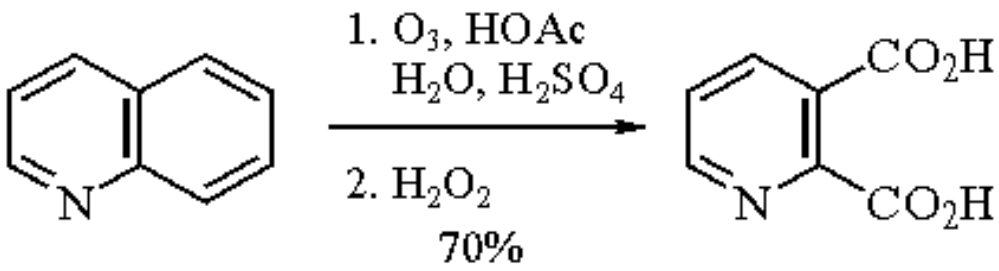

(22)

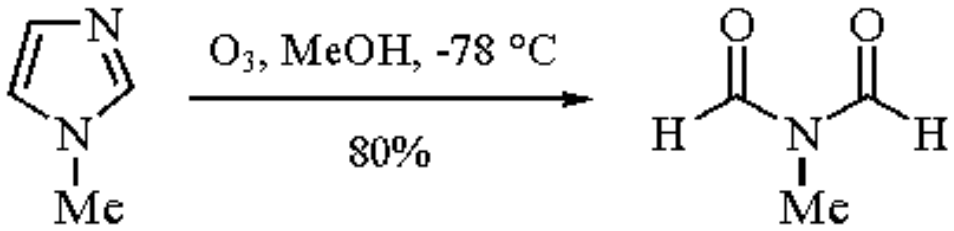

(23)

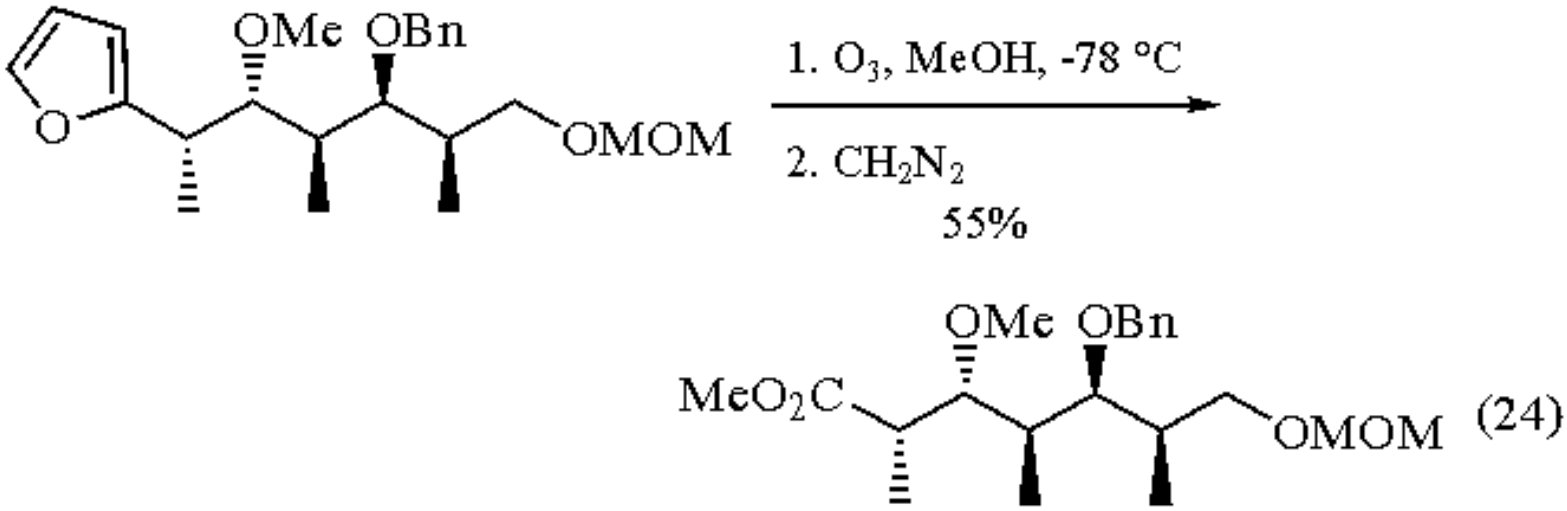

(24)

Ozonation of Heteroatoms.

Phosphines are converted to phosphine oxides and phosphites to phosphates by ozone.[39,40] These reactions are quite general and a wide range of substitutents can be tolerated. Phosphine oxides also can be produced by the ozonation of alkylidenetriphenylphosphoranes or of thio- or selenophosphoranes.[41,42] Organic sulfides are converted to sulfoxides and sulfones by ozonation.[40,43] Tertiary amines are converted to amine oxides, while nitro compounds can be produced in modest yields by ozonation of primary amines.[43,44] This preparation of nitroalkanes compares well with alternate approaches using peroxides, peroxy acids, permanganate, or ***Monoperoxysulfuric Acid***, but ozonation on silica gel has proven to be superior (see ***Ozone-Silica Gel***). Selenides are converted to selenoxides by ozone and this reaction is often used to achieve overall production of unsaturated carbonyl compounds. An example is shown in eq 25.[45]

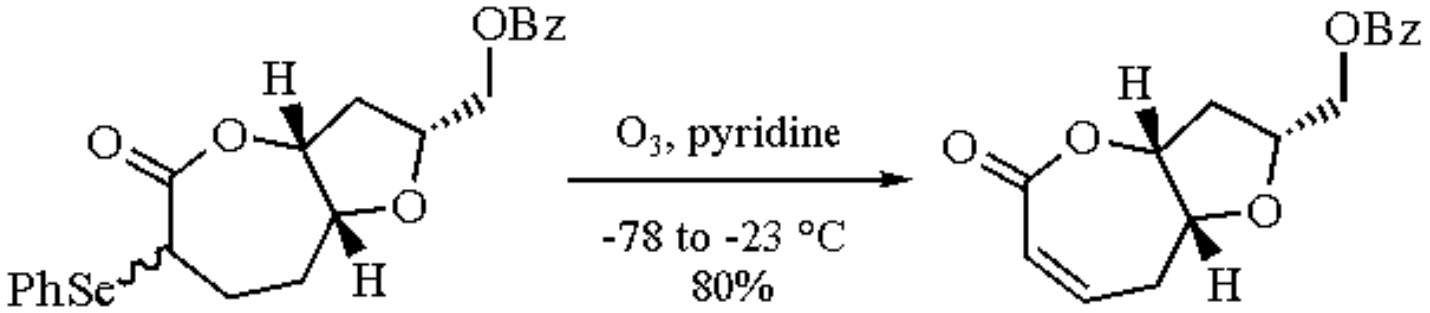

(25)

Modification of Ozone Reactivity.

The reactivity of ozone toward various unsaturated moieties can be moderated by the addition of either Lewis acids or pyridine to the ozonations. Enhanced electrophilic ozone reactivity toward aromatic substrates is observed when the Lewis acids ***Aluminum Chloride*** or ***Boron Trifluoride*** are added to reaction mixtures.[46] Conversely, an apparent decrease in ozone reactivity and a concurrent increase in the regioselectivity of ozone attack can be achieved by adding small amounts of pyridine to ozonolyses (eq 26).[47] It is thought that coordination of either the Lewis acid or basic pyridine to ozone results in the modified reactivity.

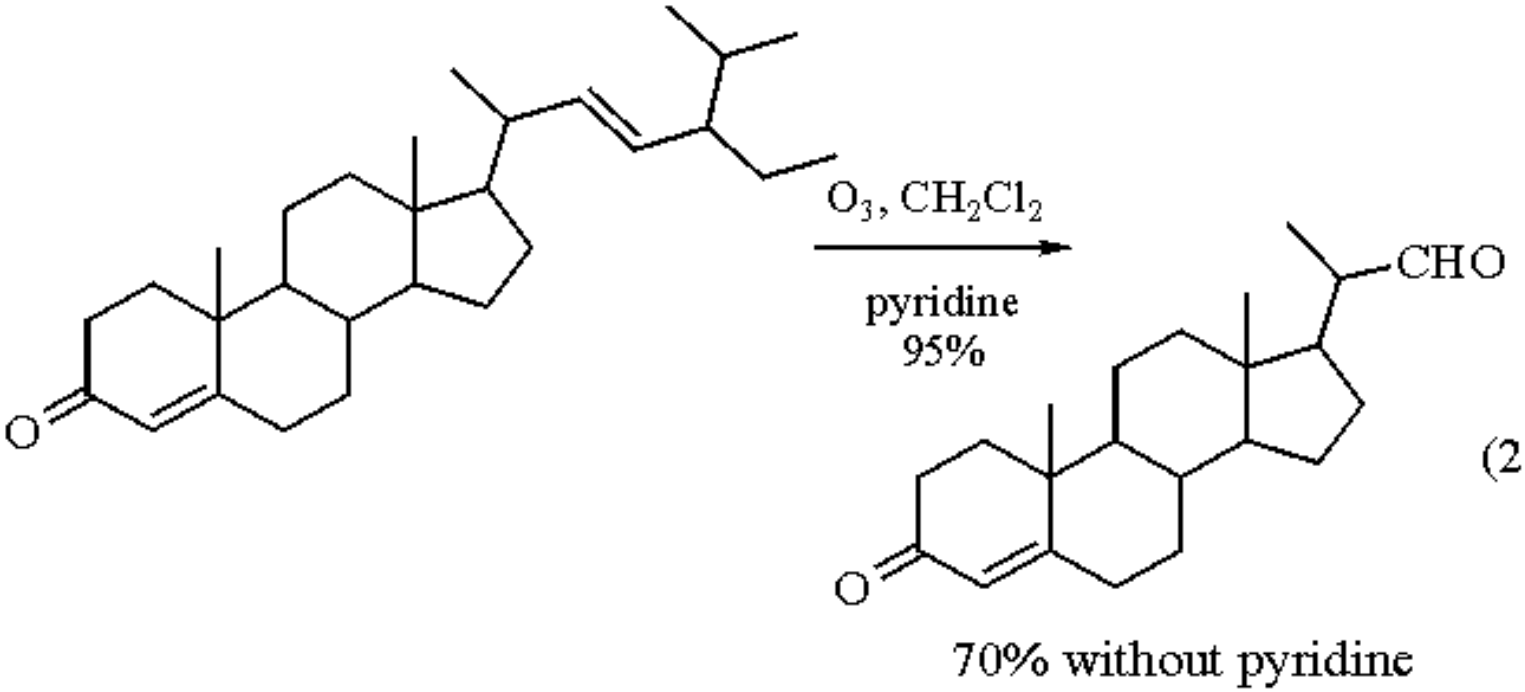

(26)

In a related procedure, ozonizable dyes have been used as endpoint indicators for selective ozonation of substrates containing multiple unsaturated linkages.[48] The dye affords colored solutions and the ozonation is carried out just until the color is discharged. If the dye is of suitable reactivity such that the most reactive substrate unsaturated linkage reacts first, and the dye second, the reaction can be stopped before further oxidation of the substrate occurs.

Interestingly, addition of BF_3 etherate to the ozonolysis of *o*-dimethoxybenzene derivatives results in increased yields of (*Z*,*Z*)-dienes (eq 27, compare to eq 20).[49] In this case, it is thought that coordination of the Lewis acid to the diene reduces its electron density and suppresses further attack by ozone. Also, the fact that the BF_3 is already coordinated to ether may limit its ability to coordinate to ozone and increase its electrophilic reactivity.

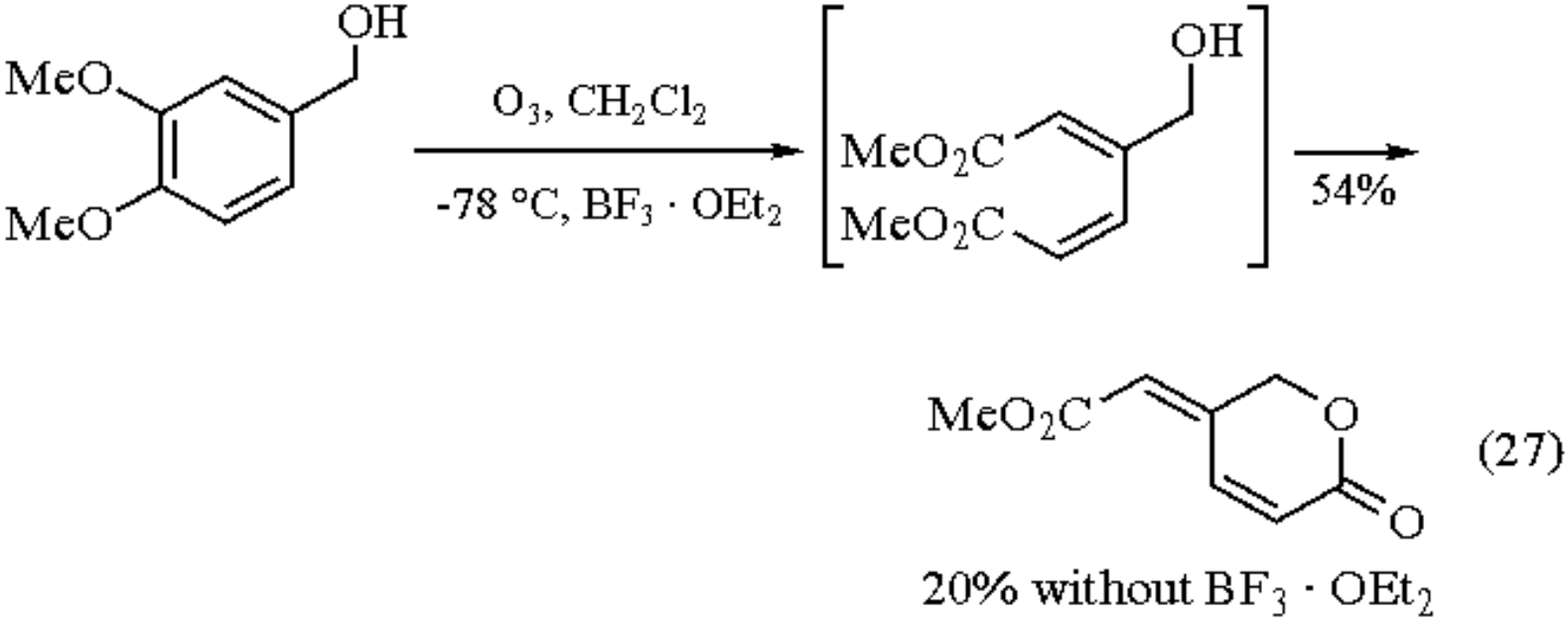

Ozonation of Acetals.

Ozone reacts very efficiently with acetals to afford the corresponding esters (eqs 28 and 29).[50] The aldehyde and alcohol components of the acetal function can be varied and yields are excellent. Cyclic acetals react much faster than acyclic acetals as a result of conformational effects.

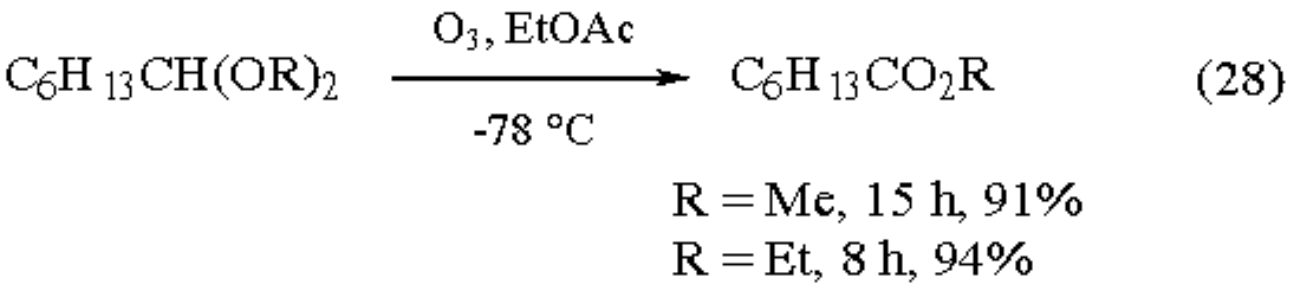

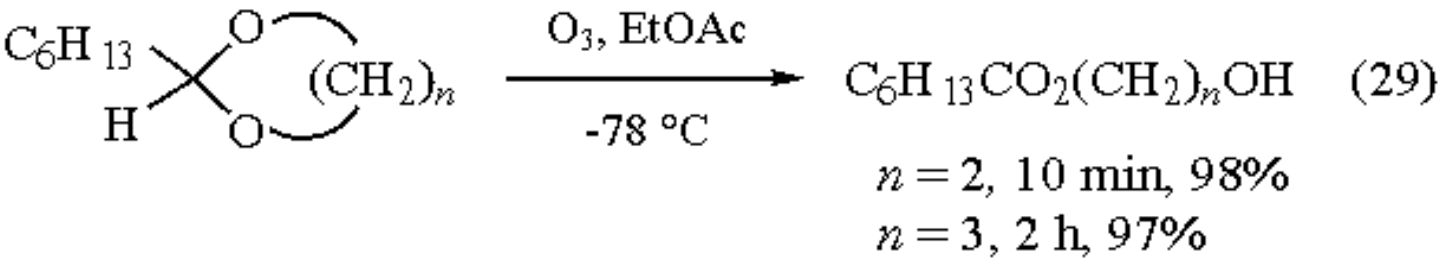

Miscellaneous Ozonations.

Ozonation offers a simple neutral alternative for oxidation of secondary alcohols to ketones (eq 30).[51]

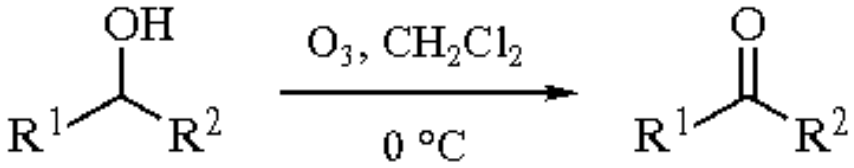

(30)

R^1	R^2	%
Me	Me	83
Me	Me	72
$-(CH_2)_4-$		53
$-(CH_2)_5-$		65

Upon reaction of allene with one equivalent of ozone, trisection occurs to provide carbon monoxide derived from the central carbon atom and carbonyl compounds from the remaining carbon atoms.[52] In the example of eq 31, allene ozonolysis is used to prepare a versatile protected α-hydroxyaldehyde.[53]

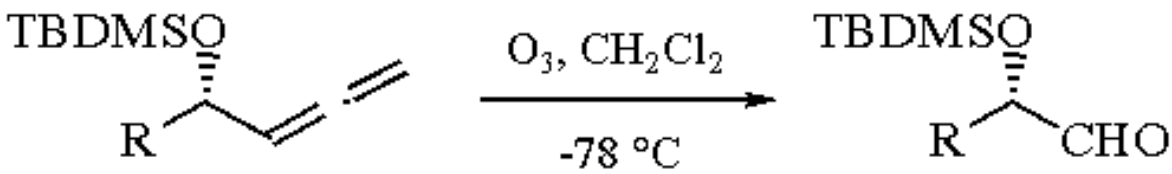

(31)

$R = C_5H_{11}$, Ph, *t*-Bu, 89-99%

Ozonation of benzyl ethers affords high yields of benzoate esters (eq 32).[54] Coupled with deacylation by NaOMe, this reaction offers a mild alternative for removal of benzyl ether protecting groups (eq 33).[55] However, due to the higher reactivity of alkenes, selective oxidative cleavage of carbon-carbon double bonds can be accomplished in the presence of benzyl ethers (eq 34).[56]

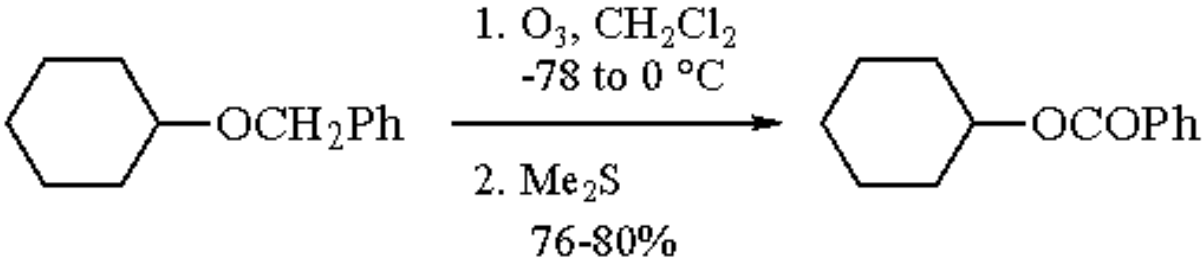

(32)

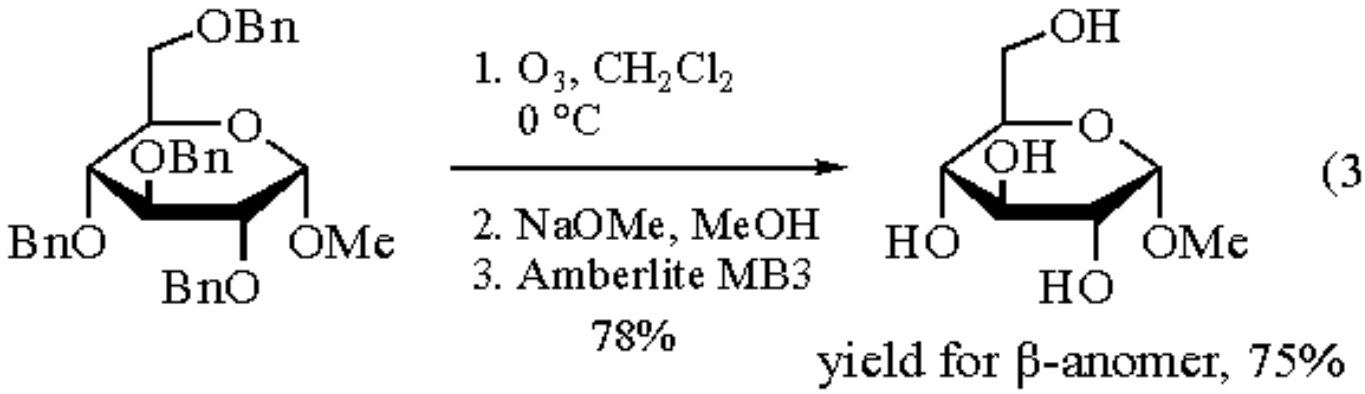

(33)

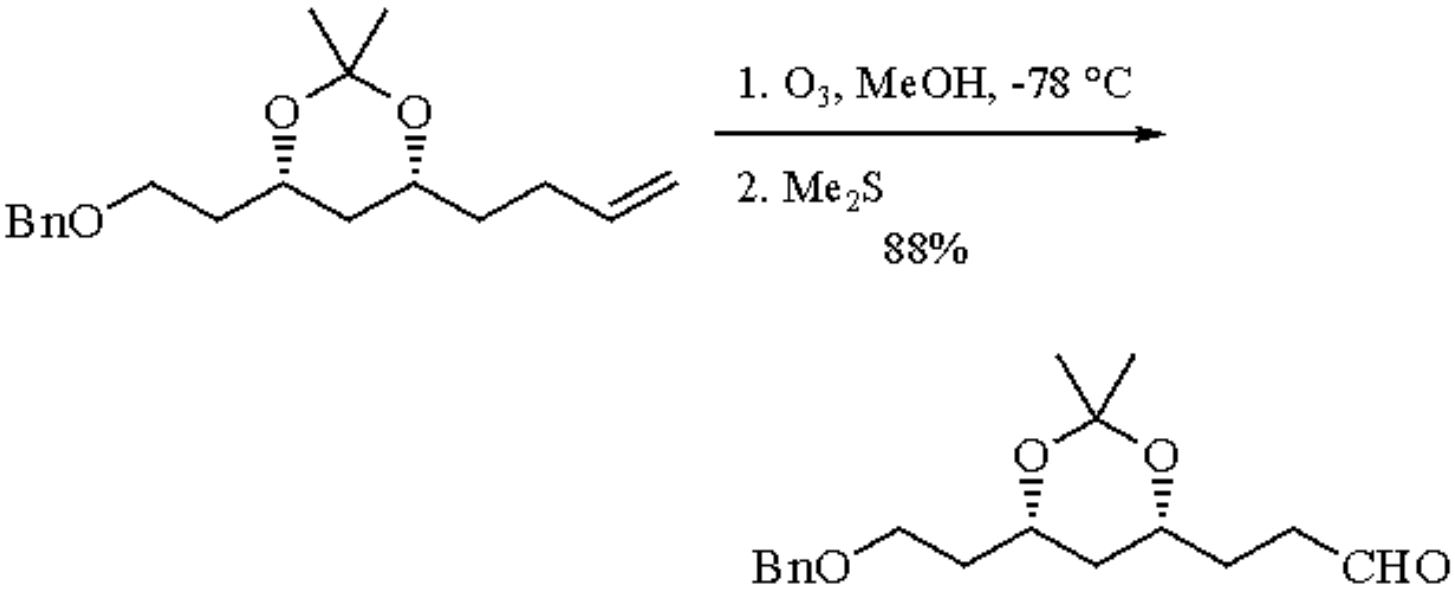

(34)

Ozone has been used to cleave nitronate anions, resulting in the high yield production of either aldehydes or ketones.[57] An example of this reaction is shown in eq 35.[57a] This is a very general method and has advantages over the Nef reaction which requires strong acid conditions, and other procedures utilizing permanganate or ***Titanium(III) Chloride***.

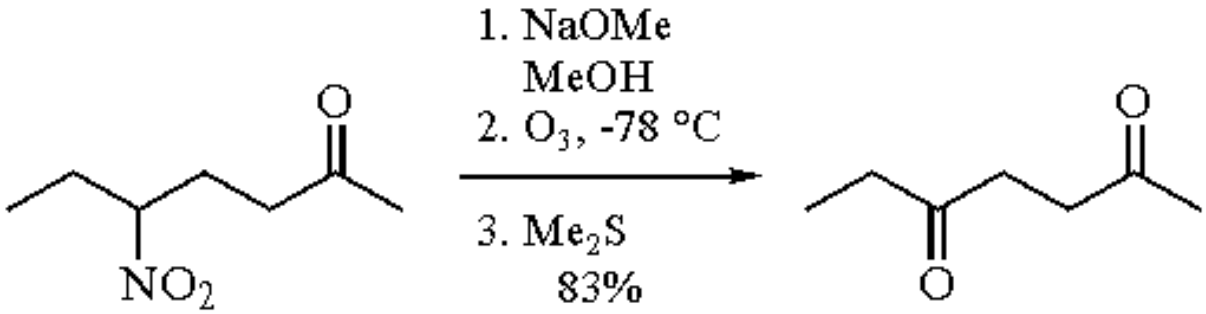

(35)

Aldehydes can be converted to peroxy acids via ozonation in methyl or ethyl acetate,[58] or to methyl esters via ozonation in 10% methanolic KOH (eq 36).[59] Ethyl esters can be produced analogously, but the use of higher alcohols results in low KOH solubility and poor conversion. This problem can be overcome by adding the aldehyde to a solution of lithium alkoxide in THF at -78 °C and treating this mixture with ozone (eq 37). Additionally, the direct preparation of methyl esters can be accomplished via alkene ozonolysis in methanolic NaOH or by addition of NaOMe to a MeOH-CH_2Cl_2 ozonolysis solvent system.[60]

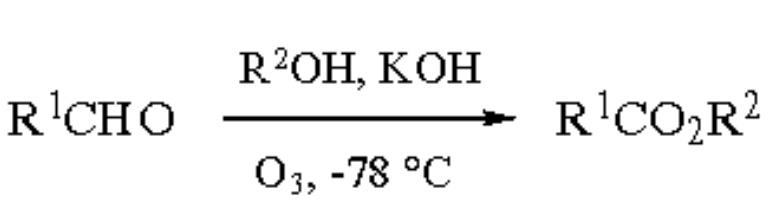

R^1	R^2	%
Cy	Me	58
	Et	60
Ph	Me	66
	Et	60
3-Oxobisnor-	Me	85
4-cholenyl	Et	87

(36)

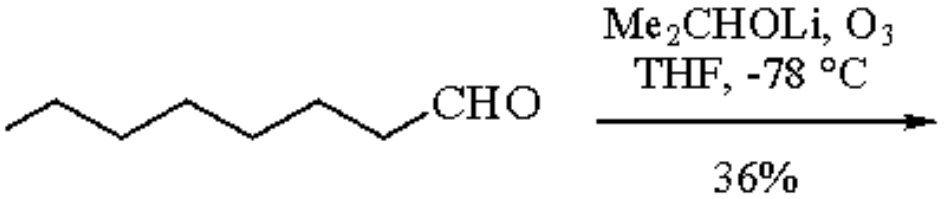

(37)

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Richard A. Berglund

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Ozone-Silica Gel[1]

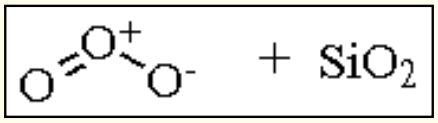

[10028-15-6] · O_3 · Ozone-Silica Gel · (MW 48.00)

(powerful oxidizing agent; capable of oxidizing carbon-hydrogen bonds[2] and a variety of electron-rich functional groups; provides a high effective concentration of ozone[2a])

Physical Data: ozone, mp -193 °C; bp -111.9 °C; *d* (0 °C, gas) 2.14 g L^{-1}.

Solubility: 4.5% ozone by weight is adsorbed on silica gel at -78 °C.[2]

Preparative Methods: ozone is generated in the laboratory by passing dry air or oxygen through two electrodes connected to an alternating current source of several thousand volts. Silica gel 60 (70-230 mesh, available from several suppliers) usually is dried prior to use and is saturated with ozone at low temperature.

Handling, Storage, and Precautions: ozone is irritating to all mucous membranes and is highly toxic in concentrations greater than 0.1 ppm by volume. It has a characteristic odor which can be detected at levels as low as 0.01 ppm. All operations with ozone should be carried out in an efficient fume hood and scrubbing systems employing thiosulfate solutions can be used to destroy excess ozone. Liquified ozone poses a severe explosion hazard.

General Procedure.

The organic substrate is preadsorbed on silica gel either by direct mixing or by slurrying in an appropriate solvent followed by removal of the solvent under vacuum. A stream of ozone then is passed through the silica gel at low temperature (usually -78 °C) until it is saturated and a deep blue color. The mixture is then warmed slowly to rt and organic material is isolated by elution. Multiple saturation and warming cycles may be necessary to achieve complete consumption of substrate. This dry ozonation procedure complements ozonation carried out in organic solvents. The high ozone concentration which can be achieved on silica gel allows for a more facile oxidation of substrates normally difficult to ozonize, and problems associated with solvent interference are eliminated.

Oxidation of Carbon-Hydrogen Bonds.

Dry ozonation most often has been used for hydroxylation of tertiary centers in saturated cyclic hydrocarbons with stereoselective retention of configuration. Hydrotrioxides have been detected as intermediates in these reactions.[3] The yields of tertiary alcohols from dry ozonation typically are higher than those obtained using either ***Chromic Acid*** or

solution ozonolysis (eq 1).[2,4,5]

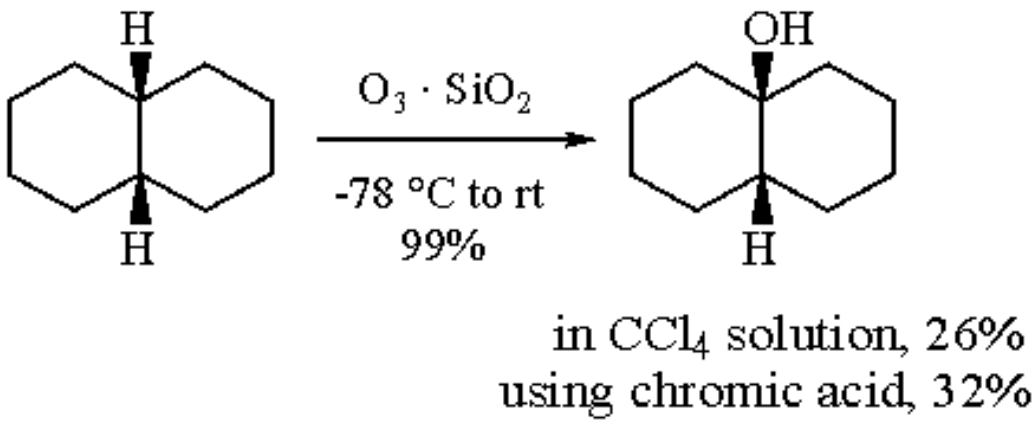

(1)

While the method is generally applicable to cyclic hydrocarbons, the use of acyclic substrates often results in the production of significant amounts of ketones due to carbon-carbon bond cleavage (eq 2).[6] Eq 2 shows that in dry ozonation, ozone attack is directed at exposed positions remote to the silica gel binding site. This results from molecules being ordered in a close packed array on the solid support with steric effects hindering reactivity at the proximal positions. Bridgehead hydroxylation of polycyclic hydrocarbons,[2,7] and derivatization of terpenoids[8] and steroidal systems,[9] have been accomplished using dry ozonation. Additionally, remote methylene units have been transformed to ketones in cyclic acetates.[10]

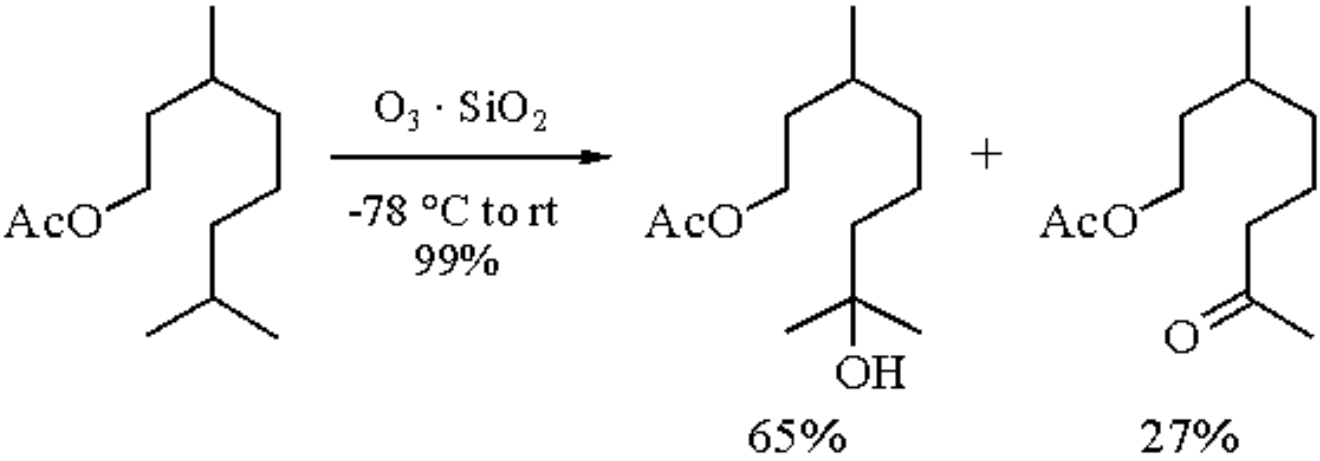

(2)

Dry ozonation also can be used to functionalize cyclopropyl hydrocarbons at the α-position, affording cyclopropyl alkyl ketones.[11] The method is quite general and reaction α to the cyclopropyl group is preferred over hydroxylation at tertiary positions (eqs 3 and 4).[12]

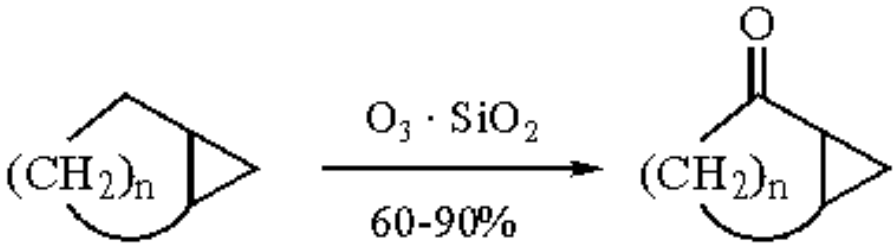

(3)

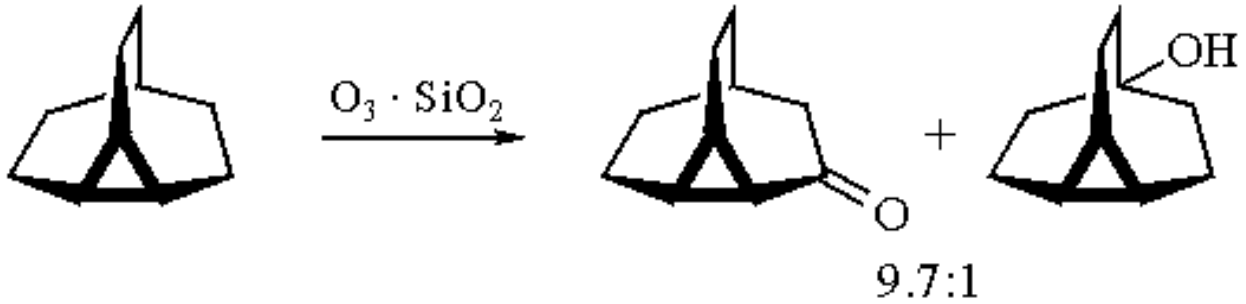

(4)

Ozonolysis of Alkenes and Alkynes.

Alkene ozonolysis on dry silica gel results in the efficient formation of ozonides, while reaction on nontreated or hydrated silica gel affords mixtures of aldehydes, ketones, or carboxylic acids (eq 5).[13-15] Products from these reactions usually are obtained directly upon elution from the silica gel without the need for either a reductive or oxidative workup.

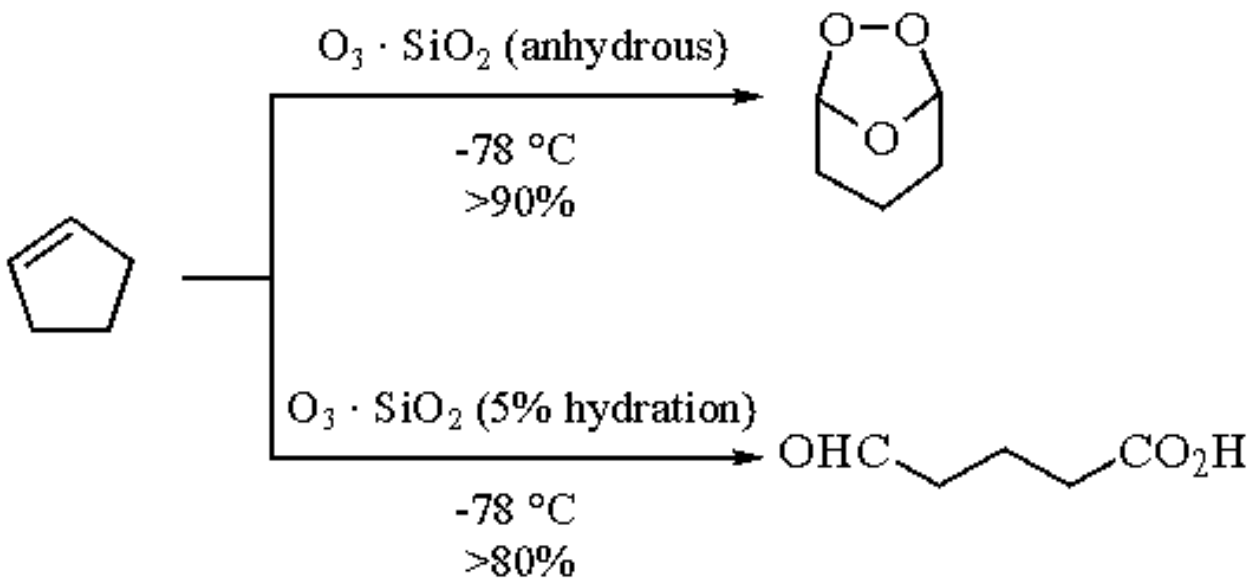

(5)

Notably, ozonides of tetrasubstituted alkenes,[16] vinyl ethers,[17] vinylic esters,[18] and α,β-unsaturated ketones[19] (which are normally not observed in solution reactions) can be obtained using ozonation on polyethylene as the solid support. It is believed that solid-supported ozonolysis favors ozonide formation due to the proximity of initial cleavage products and the resulting ease of recombination. Also, since cleavage fragments are fixed on the support, combination to form cross ozonides is reduced dramatically.

In addition to providing a route to otherwise inaccessible ozonides, dry ozonation has been used to cleave normally unreactive alkenes directly to carbonyl compounds (eq 6).[20] In another example, bulky tetramethylethylene affords acetone in 95% yield upon dry ozonation using untreated or hydrated silica gel.[14]

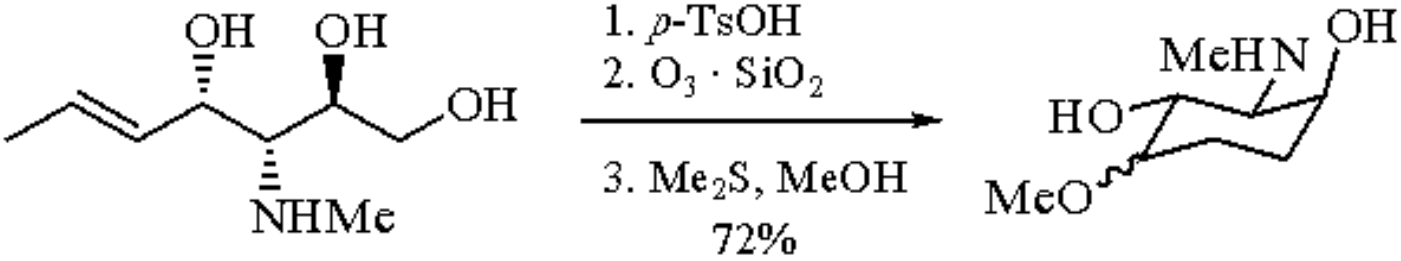

(6)

An overall hydroxylation of alkenes using the dry ozonation procedure can be accomplished if the more reactive alkene functionality is first converted to a dibromide. After hydroxylation, deblocking liberates the alkene (eq 7).[21]

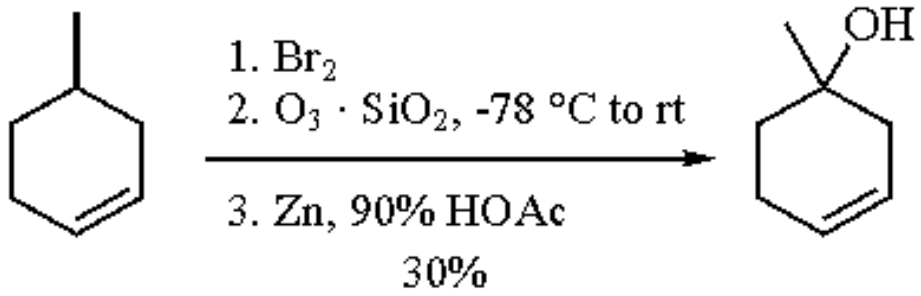

(7)

Dry ozonation of alkynes generally results in cleavage to carboxylic acids and carbonyl compounds. Only in the case of diphenylacetylene has a diketone been observed.[14,15]

Oxidation of Primary Amines.

Aliphatic primary amines are efficiently oxidized by ozone on silica gel to the corresponding nitro compounds (eq 8).[22] This procedure is an improvement over solution ozonations in which yields are lower due to solvent interaction with partial oxidation products and competing oxidation of the α-carbon atom (see ***Ozone***).

R	%
t-Bu	70
Bu	65
Bn	66

(8)

Ozonation of Aromatic Systems.

Phenyl rings are cleaved to carboxylic acids using dry ozonation, although multiple ozone saturation and warming cycles may be required for high conversions (eq 9).[23] Compared to oxidations utilizing ***Ruthenium(VIII) Oxide***, yields are significantly higher.[24]

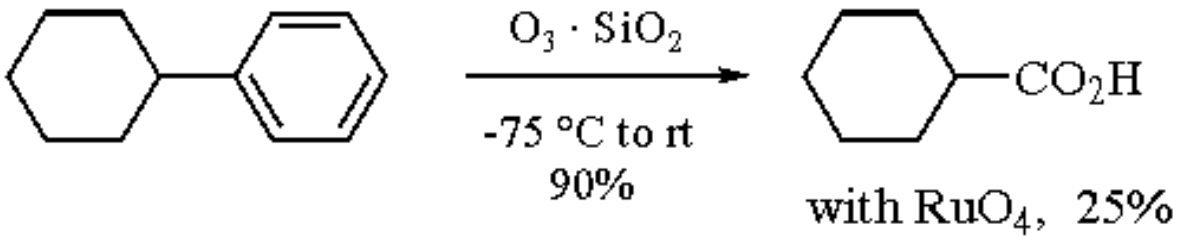

(9)

Alternate Procedure.

A modification of the dry ozonation procedure employs a microwave discharge of a He-O_2 or a He-CO_2 gas stream to produce ground-state oxygen atoms [O(^{3}p) atoms] which, when passed over silica gel or Florisil preadsorbed with substrate at low temperature, combine with oxygen on the adsorbent to slowly form ozone in low concentration in situ. The ozone then can react with the absorbed organic substrate.[25] This is a milder method than conventional dry ozonation, and this procedure can afford regiospecific ozonation of polyunsaturated compounds or partial oxidative cleavage of polycyclic aromatics (eq 10).[26] Conventional solvent ozonolyses or standard dry ozonations often result in cleavage of several bonds.

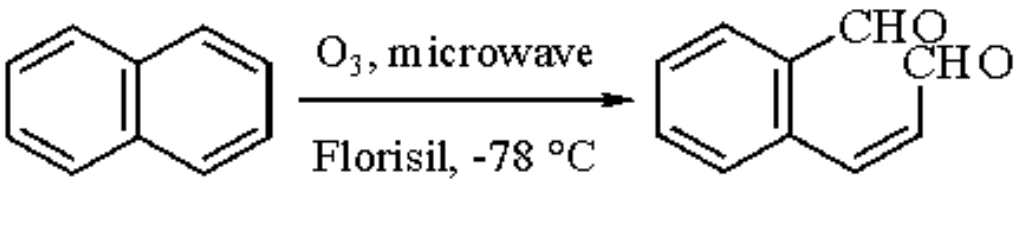

(10)

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Eli Lilly and Company, Lafayette, IN, USA

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Palladium(II) Acetate[1]

$Pd(OAc)_2$

[3375-31-3] · $C_4H_6O_4Pd$ · Palladium(II) Acetate · (MW 224.52) (trimer)

[53189-26-7]

(homogenous oxidation catalyst[3] that, in the presence of suitable co-reagents, will effect the activation of alkenic and aromatic compounds towards oxidative inter- and intramolecular nucleophilic attack by carbon, heteroatom, and hydride nucleophiles[1,3,4,5])

Alternate Name: bis(acetato)palladium; diacetatopalladium(II); palladium diacetate.

Physical Data: mp 205 °C (dec).

Solubility: sol organic solvents such as chloroform, methylene chloride, acetone, acetonitrile, diethyl ether. Dissolves with decomposition in aq HCl and aq KI solutions. Insol water and aqueous solutions of NaCl, NaOAc, $NaNO_3$ as well as in alcohols and petroleum ether. Decomposes when heated with alcohols.

Form Supplied in: orange-brown crystals; generally available.

Preparative Methods: preparation of palladium diacetate from palladium sponge was developed by Wilkinson et al.[2]

Purification: palladium nitrate impurities can be removed by recrystallization from glacial acetic acid in the presence of palladium sponge.

Handling, Storage, and Precautions: can be stored in air. Low toxicity.

General Considerations.

Salts of palladium that are soluble in organic media, for example $Pd(OAc)_2$, ***Dilithium Tetrachloropalladate(II)***, and $PdCl_2(RCN)_2$, are among the most extensively used transition metal complexes in metal-mediated organic synthesis. Palladium acetate participates in several reaction types, the most important being: (i) Pd^{II}-mediated activation of alkenes towards nucleophilic attack by (reversible) formation of Pd^{II}-alkene complexes, (ii) activation of aromatic, benzylic, and allylic C-H bonds, and (iii) as a precursor for Pd^0 in Pd^0-mediated activation of aryl, vinyl, or allyl halides or acetates by oxidative addition to form palladium(II)-aryl, -vinyl and -(π)-allyl species, respectively.[1b] All reactions proceed via organopalladium(II) species which can undergo a number of synthetically useful transformations.

Alkenes complexed to Pd^{II} are readily attacked by nucleophiles such as water, alcohols, carboxylates, amines, and stabilized carbon nucleophiles (eq 1). Attack occurs predominantly from the face opposite to that of the metal (*trans* attack), thus forming a new carbon-nucleophile bond and a carbon-metal σ-bond.

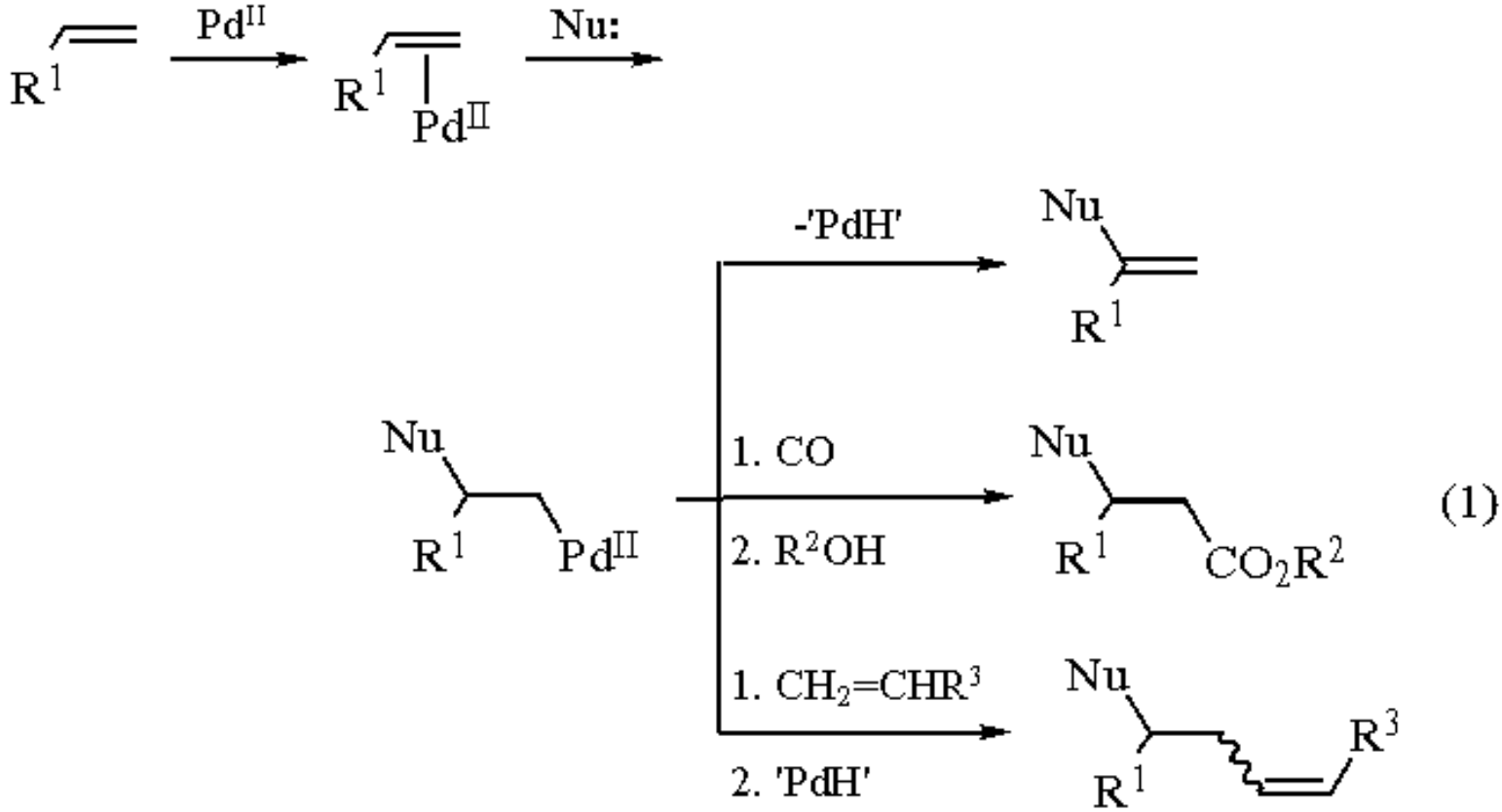

The σ-complex obtained is usually quite reactive and unstable, and can undergo a number of synthetically useful transformations such as β-hydrogen elimination (eq 1) to give a vinyl substituted alkene and insertion of CO (eq 1) or alkenes (eq 1) into the carbon-palladium bond, which permit further functionalization of the original alkene. The same general chemistry is observed for complexes generated from Pd^0 (eq 2). Heck vinyl couplings and carbonylations together with allylic nucleophilic substitution reactions are among the synthetically most interesting reactions employing palladium acetate.[5]

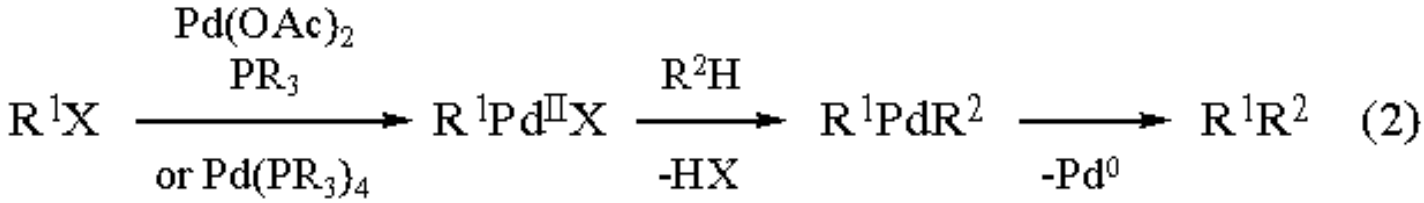

The transformations in eqs 1 and 2 ultimately produce palladium(0), while palladium(II) is required to activate alkenes (eq 1). Thus, if such a process is to be run using catalytic amounts of the noble metal, a way to rapidly regenerate palladium(II) in the presence of both substrate and product is required. Often this reoxidation step is problematic in palladium(II)-catalyzed nucleophilic addition processes, and reaction conditions have to be tailored to fit a particular type of transformation. A number of very useful catalytic processes, supplementing the processes that employ stoichiometric amounts of the metal, have been developed.[1,3-5]

Oxidative Functionalization of Alkenes with Heteroatom Nucleophiles.

Oxidation of Terminal Alkenes to Methyl Ketones.

The oxidation of ethylene to acetaldehyde with water acting as the nucleophile using a $Pd^{II}Cl_2$-$Cu^{II}Cl_2$ catalyst (see ***Palladium(II) Chloride*** and ***Palladium(II) Chloride-Copper(II) Chloride***) under an oxygen atmosphere is known as the Wacker process. On a laboratory scale the reaction conveniently allows the transformation of a wide variety of terminal alkenes to methyl ketones.[6] Some synthetic procedures that employ $Pd(OAc)_2$ in chloride-free media have been developed (eq 3).

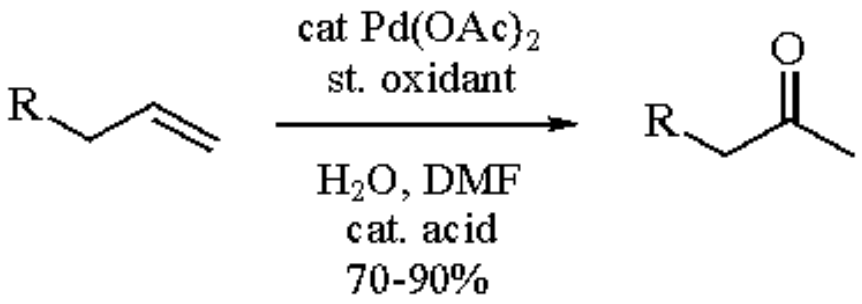

(3)

By this, both the use of the highly corrosive reagent combination $PdCl_2$-$CuCl_2$ and the occurrence of chlorinated byproducts are avoided. The stoichiometric oxidant used in these reactions can be a peroxide,[7] ***1,4-Benzoquinone***,[8] or molecular ***Oxygen***.[8a,9] An electrode-mediated process has also been described.[10]

Other Heteroatom Nucleophiles.

Alcohols and carboxylic acids also add to metal-activated alkenes,[1a] and processes for the industrial conversion of ethylene to vinyl acetate and acetals are well established.[1c] However, these processes have not been extensively used with more complex alkenes. In contrast, a number of intramolecular versions of the processes have been developed, a few examples of which are given here. Allylphenols cyclize readily in the presence of palladium(II) to form benzofurans (eq 4). Catalytic amounts of palladium acetate can be used if the reaction is carried out under 1 atm of molecular oxygen with copper diacetate as cooxidant, or in the presence of ***t-Butyl Hydroperoxide***. If instead of palladium acetate a chiral π-allylpalladium acetate complex is used, the cyclization proceeds to yield 2-vinyl-2,3-dihydrobenzofuran with up to 26% ee.[11]

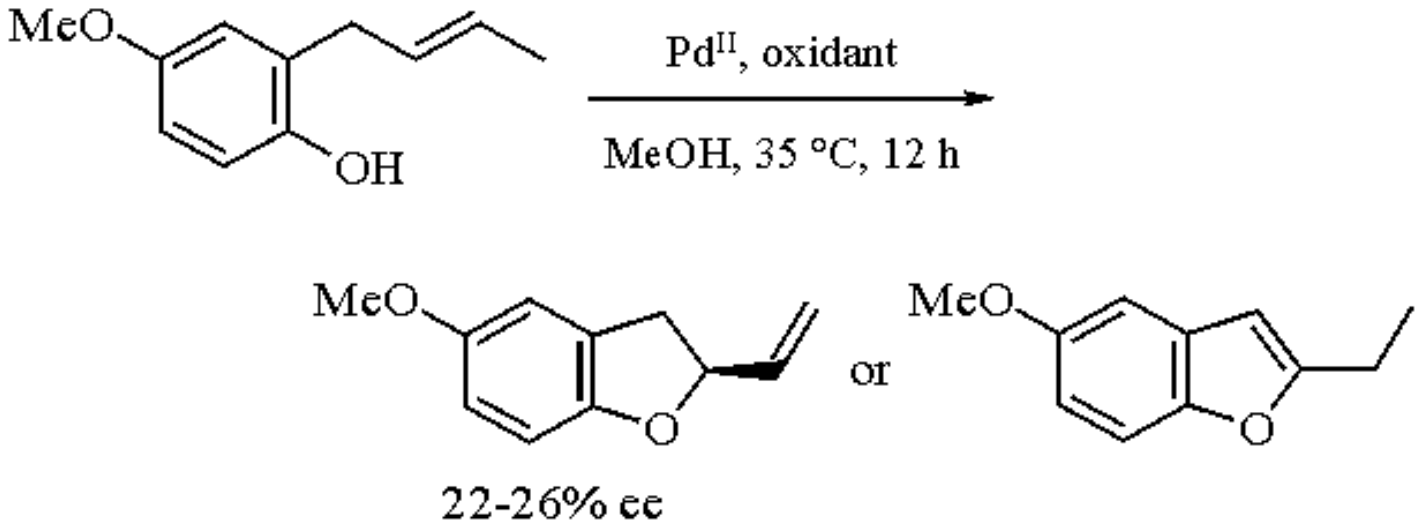

(4)

Methyl glyoxylate adducts of *N*-Boc-protected allylic amines cyclize in the presence of a catalytic amount of palladium acetate and excess ***Copper(II) Acetate*** to 5-(1-alkenyl)-2-(methoxycarbonyl)oxazolidines (eq 5).[12] These heterocycles are easily converted to unsaturated *N*-Boc protected β-amino alcohols through anodic oxidation and mild hydrolysis.

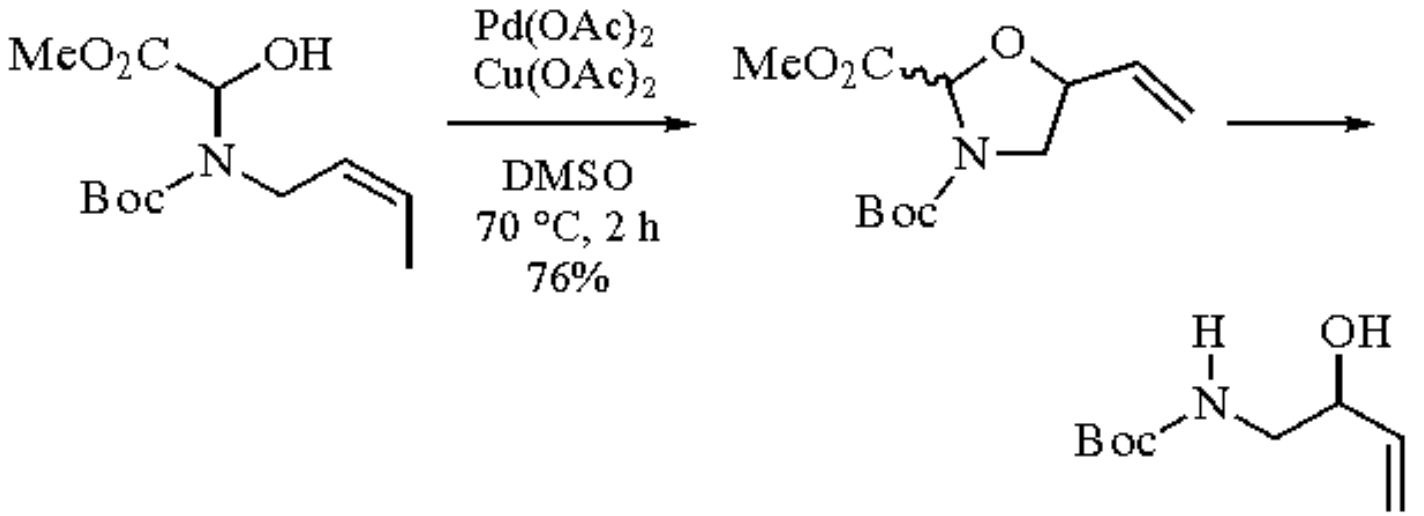

(5)

Nitrogen nucleophiles such as amines, and in intramolecular reactions amides and tosylamides, readily add to alkenes complexed to Pd^{II} derived from $PdCl_2(RCN)_2$ (see ***Palladium(II) Chloride***) with reactivity and regiochemical features paralleling those observed for oxygen nucleophiles.[3,4] Intramolecular nucleophilic attack by heteroatom nucleophiles also occurs in conjunction with other palladium-catalyzed processes presented in the following sections.

Allylic C-H Bond Activation.

Internal alkenes, in particular cyclic ones, can be transformed into allylic acetates in a palladium-catalyzed oxidation (eq 6).[13] With benzoquinone as stoichiometric oxidant or electron transfer mediator,[9a] the allylic acetoxylation proceeds with high selectivity for the allylic product and usually in excellent yield.

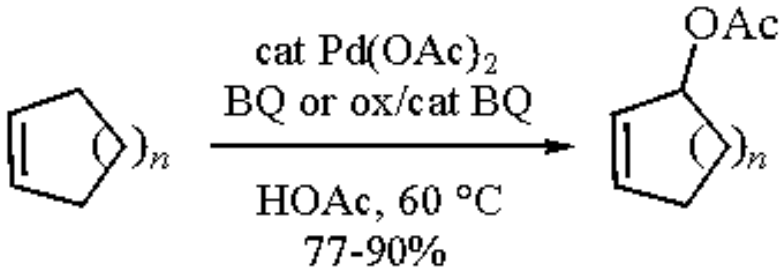

(6)

This one-step transformation of an alkene to an allylic acetate compares well with other methods of preparation such as hydride reduction of α,β-unsaturated carbonyl compounds followed by esterification. The scope and limitations of the reaction have been investigated.[14] The allylic acetoxylation proceeds via a π-allylpalladium intermediate,[15] and as a result, substituted and linear alkenes generally give several isomeric allylic acetates. With oxygen nucleophiles the reaction is quite general, and reactants and products are stable towards the reaction conditions. This is normally not yet the case with nitrogen nucleophiles, although one intramolecular palladium-catalyzed allylic amination mechanistically related to allylic acetoxylation has been reported.[16]

Functionalization of Conjugated Dienes.

Electrophilic transition metals, particularly palladium(II) salts which do not form stable complexes with 1,3-dienes, do activate these substrates to undergo a variety of synthetically useful reactions with heteroatom nucleophiles.[17] Some examples are presented below.

Telomerization.

Conjugated dienes combine with nucleophiles such as water, amines, alcohols, enamines and stabilized carbanions in the presence of palladium acetate and ***Triphenylphosphine*** to produce dimers with incorporation of one equivalent of the nucleophile.[1,18] Telomerization of butadiene (eq 7) yields linear 1,6- and 1,7-dienes and has been used for the synthesis of a variety of naturally occurring materials.[19]

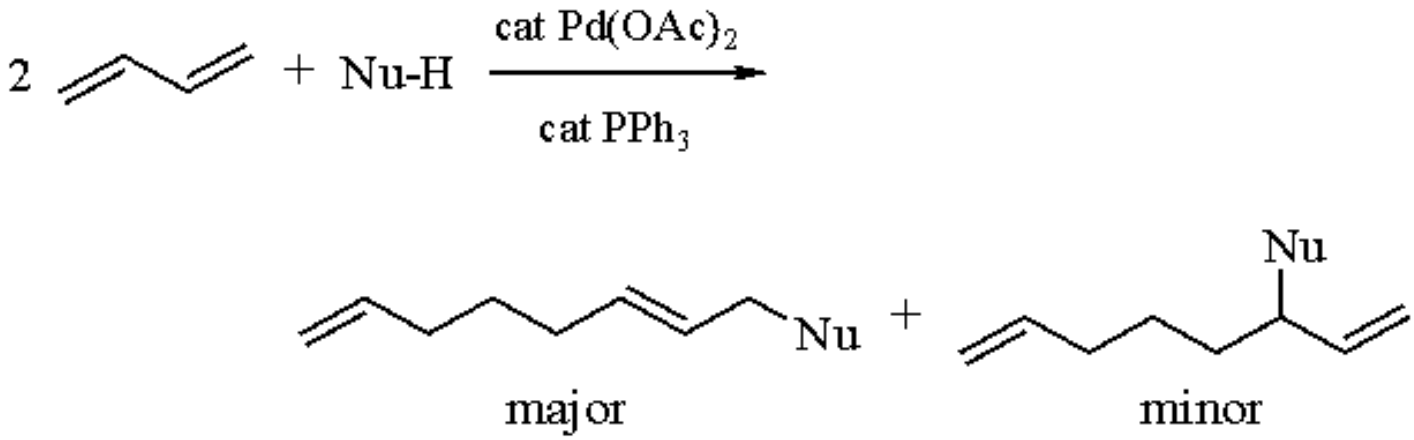

(7)

Oxidative 1,4-Functionalization.

The regio- and stereoselective palladium-catalyzed oxidative 1,4-functionalization of 1,3-dienes (eq 8) constitutes a synthetically useful process.[20-23]

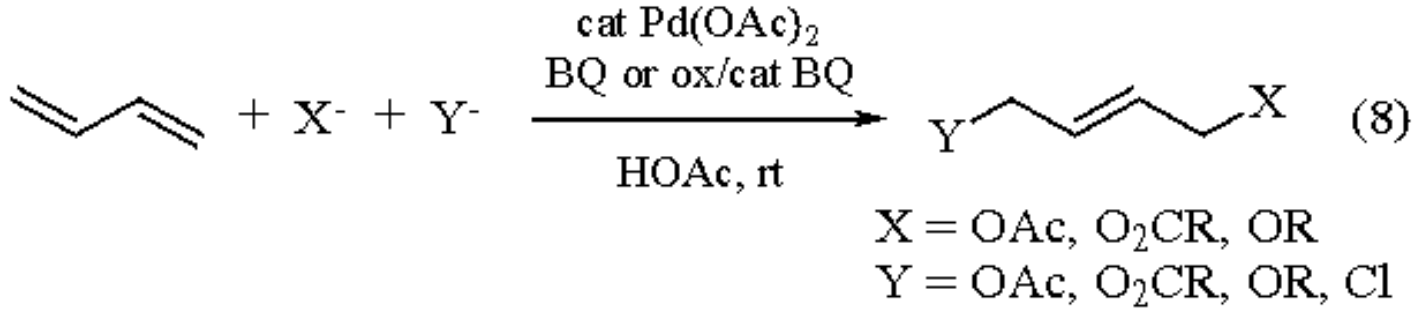

A selective catalytic reaction that gives high yields of 1,4-diacetoxy-2-alkenes occurs in acetic acid in the presence of a lithium carboxylate and benzoquinone. The latter reagents act as the activating ligand and reoxidant for palladium(0).[24] The reaction can be made catalytic also in benzoquinone by the use of ***Manganese Dioxide***,[20] electrochemistry,[25] or metal-activated molecular oxygen[9a] as stoichiometric oxidant. If the reaction is carried out in alcoholic solvent in the presence of a catalytic amount of a nonnucleophilic acid, *cis*-1,4-dialkoxides can be obtained.[23] An important feature of the 1,4-diacetoxylation reaction is the ease by which the relative sterochemistry of the two acetoxy substituents can be controlled (eq 9).

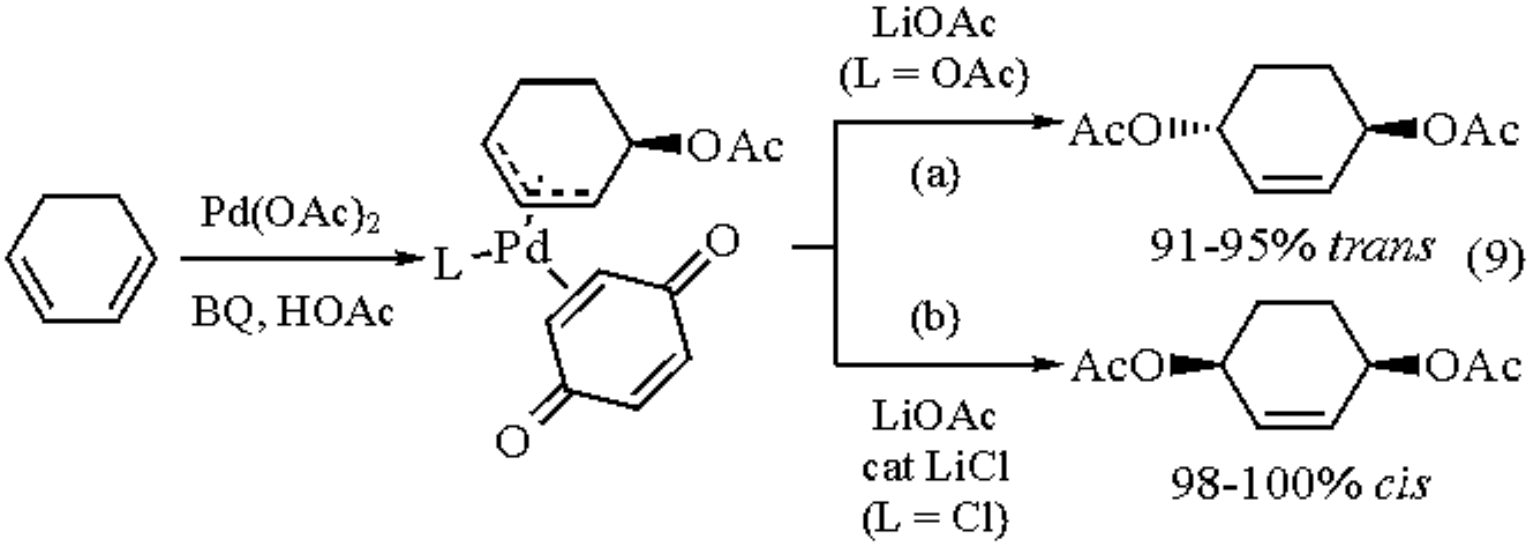

The first step in the reaction sequence is a regioselective and stereoselective *trans*-acetoxypalladation of one of the double bonds, thus forming a π-allylpalladium(II) intermediate, which is then attacked by a second nucleophile. By variation of the concentration of chloride ions, reactions selective for either the *trans*-diacetate or the *cis*-diacetate (eq 9) can be accomplished. The use of other chloride salts resulted in poor selectivity. The selectivity for the *trans* product at chloride-free conditions is further enhanced if the reaction is carried out in the presence of a sulfoxide co-catalyst.[26] Enzymatic hydrolysis of the *cis-meso*-diacetate yields *cis*-1-acetoxy-4-hydroxy-2-cyclohexene in more than 98% ee,[27] thus giving access to a useful starting material for enantioselective synthesis.[28]

In a related catalytic procedure, run in the presence of a stoichiometric amount of ***Lithium Chloride*** (eq 10), it is possible to obtain *cis*-1-acetoxy-4-chloro-2-alkenes with high 1,4-selectivity and in high chemical yield.[21] A selective nucleophilic substitution of the chloro group in the chloroacetate, either by palladium catalysis or by classical methods (eq 10), and subsequent elaboration of the acetoxy group, offer a number of useful transformations.[22] The methodology has been applied to, for example, a synthesis of a naturally occurring 2,5-disubstituted pyrrolidine, some tropane alkaloids, and perhydrohistrionicotoxin.[29]

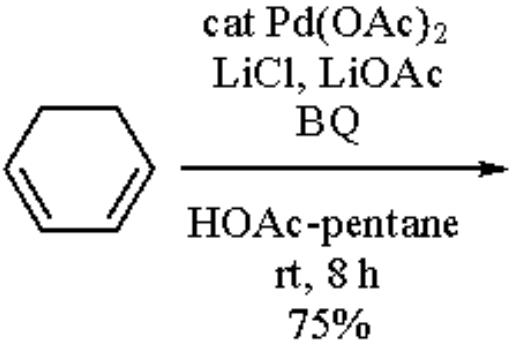

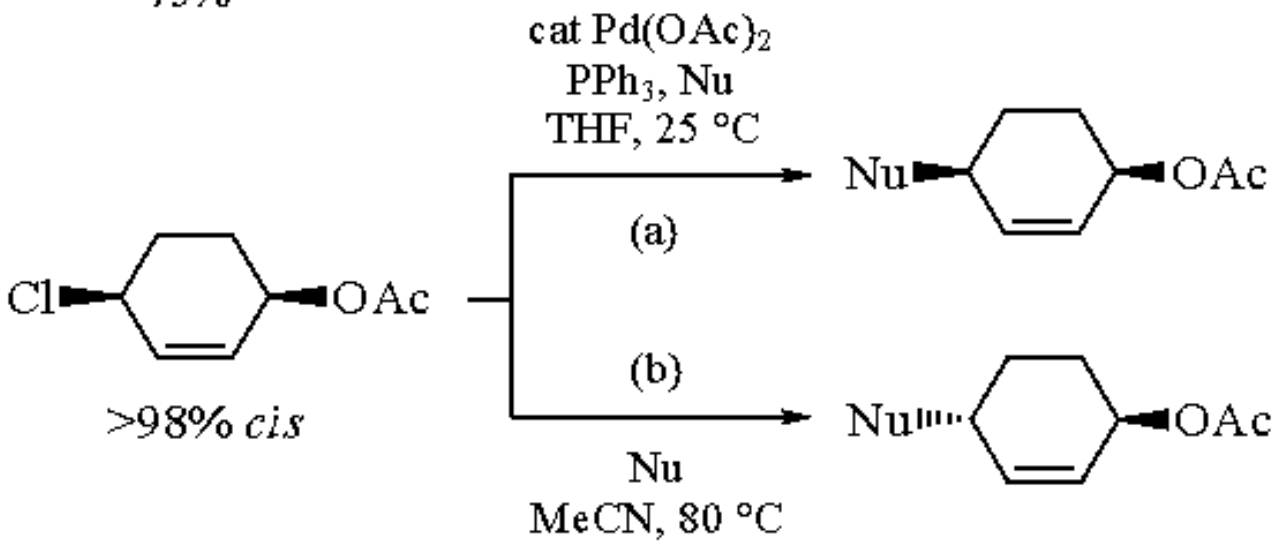

(10)

The use of two different nucleophiles can lead to unsymmetrical dicarboxylates.[30] Palladium-catalyzed oxidation of 1,3-cyclohexadiene in acetic acid in the presence of CF_3CO_2H/LiO_2CCF_3, with MnO_2 and catalytic benzoquinone, yielded 70% of *trans*-1-acetoxy-4-trifluoroacetoxy-2-cyclohexene (more than 92% *trans*), with a selectivity for the unsymmetrical product of more than 92%. 1,3-Cycloheptadiene afforded the *cis* addition product in 58% yield with a selectivity for the unsymmetrical product of more than 95%. Since the two carboxylato groups have different reactivity, for example toward hydrolysis, further transformations can be carried out at one allylic position without affecting the other.

Intramolecular versions of the 1,4-oxidations have been developed.[31] In these reactions the internal nucleophile can be a carboxylate, an alkoxide, or nitrogen functionality, and the result of the first nucleophilic attack is the regioselective and stereoselective formation of a *cis*-fused heterocycle (eq 11).

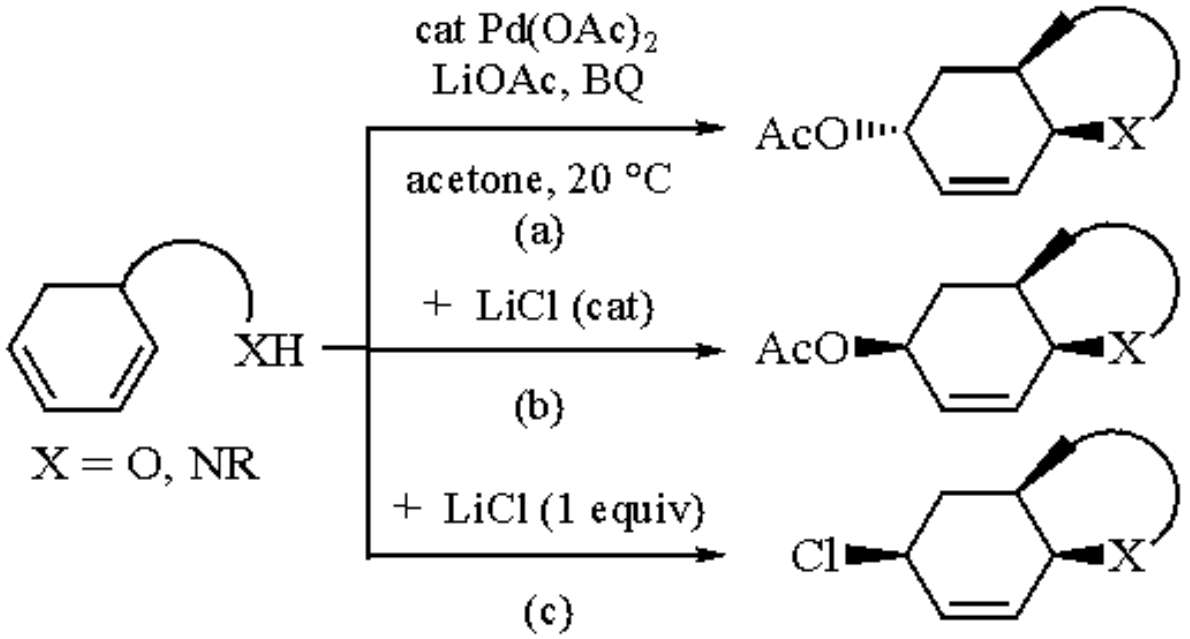

(11)

The second attack can be directed as described above to yield either an overall *trans* or *cis* product in >70% yield. With internal nucleophiles linked to the 1-position of the 1,3-diene, spirocyclization occurs. The synthetic power of the method has been demonstrated in the total syntheses of heterocyclic natural products,[32] and further developed into a tandem cyclization of linear diene amides (eq 12) to yield bicyclic compounds with trisubstituted nitrogen centers.[33]

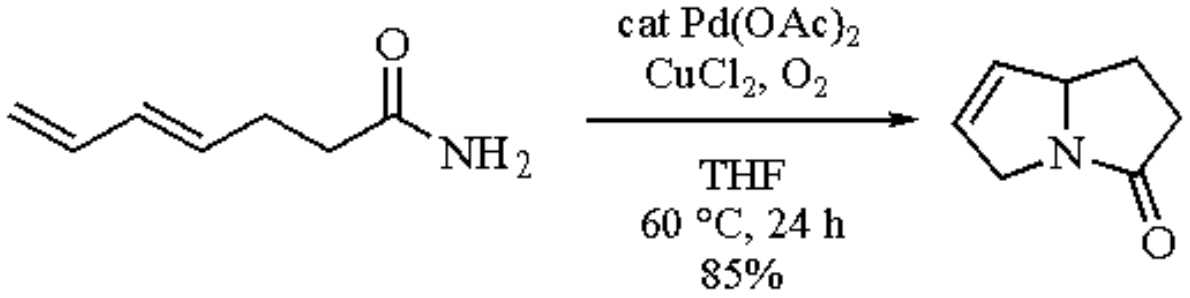

(12)

Functionalization of Alkenes with Palladium-Activated Carbon Nucleophiles.

Heck Coupling.[5]

The Heck reaction is the common name for the coupling of an organopalladium species with an alkene and includes both inter- and intramolecular reaction types. However, no general reaction conditions exist and the multitude of variations can sometimes seem confusing.

The original version of the Heck reaction involved the coupling of an alkene with an organomercury(II) salt in the presence of stoichiometric amounts of palladium(II),[34] a method still used in nucleoside chemistry.[35] The finding that the organomercury reagent can be replaced by an organic halide, however, greatly increased the versatility of the process.[36] The modified process is catalyzed by zerovalent palladium, either in the form of preformed tertiary phosphine complexes or, preferentially, formed in situ from palladium acetate (eq 13).

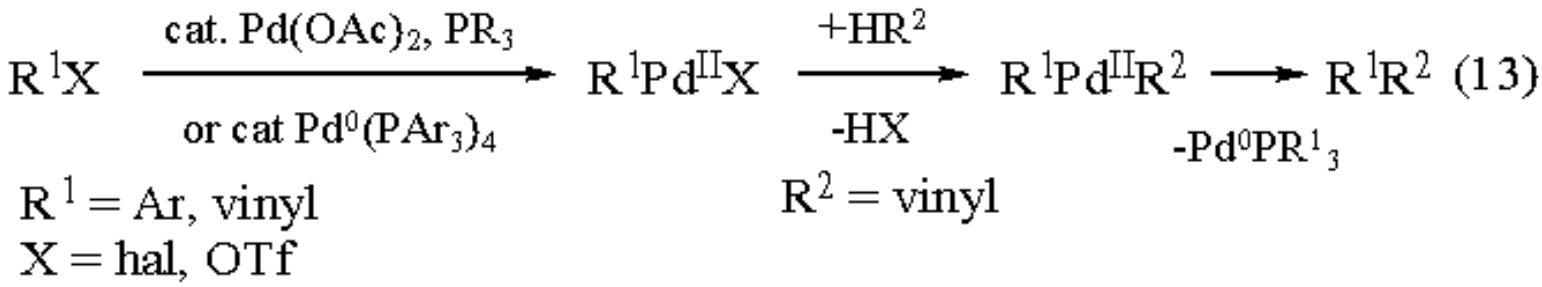

To keep the active catalyst in solution, reactions are often carried out in the presence of tertiary phosphines such as ***Triphenylphosphine***,[37] or rather tri(*o*-tolyl)phosphine,[38] which is now the phosphine most widely employed in Heck coupling reactions.[5] Other ligands successfully employed include tris(2,6-dimethoxyphenyl)phosphine and the bidentate ligands ***1,2-Bis(diphenylphosphino)ethane*** (dppe), ***1,3-Bis(diphenylphosphino)propane*** (dppp), ***1,4-Bis(diphenylphosphino)butane*** (dppb), and ***1,1´-Bis(diphenylphosphino)ferrocene*** (dppf). Coupling reactions can occur in homogenous aqueous media if a water-soluble palladium ligand, trisodium 3,3´,3´-(phosphinetriyl)tribenzenesulfonate, is employed. This greatly facilitates workup procedures, and good yields of coupled products were obtained from reacting aryl and alkyl iodides with alkenes, alkynes, and allylic acetates.[39] In all cases, an inert atmosphere and the presence of a base, normally ***Triethylamine***, is required.

Phase-Transfer Conditions.

The Heck conditions described above are not useful, however, for a large number of alkenic substrates.[40] A sometimes serious drawback is the high temperature (ca. 100 °C) often required. Upon addition of tetrabutylammonium chloride (phase-transfer conditions or Jeffery conditions), aromatic halides or enol triflates react under mild conditions with vinylic substrates or allylic alcohols.[5,41] Variations of these conditions include the optional or additional presence of silver or thallium salts. The effect of using different salts, bases, catalysts, solvents, and protecting groups in the coupling of aminoacrylates with iodobenzene has been studied.[42]

Cross Coupling.

In cross-coupling reactions, an aryl, vinyl, or acyl halide or triflate undergoes a palladium-catalyzed Heck-type coupling to an aryl-, vinyl-, or alkyl-metal reagent (eq 14) to give a new carbon-carbon bond.[5]

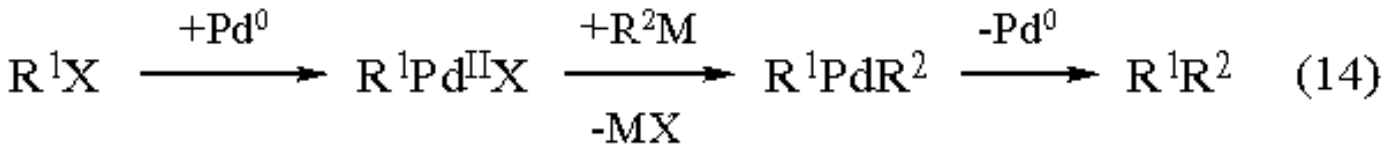

Mg, Zn, and Zr are examples of metals used in cross-coupling reactions,[43] but, in particular, organostannanes have been employed in mild and selective palladium acetate-catalyzed couplings with organic halides and triflates.[44] Aryl arenesulfonates undergo a cross-coupling reaction with various organostannanes in the presence of palladium diacetate, dppp, and LiCl in DMF.[45] An advantage of the arylsulfonates over triflates is that the former are solids whereas the latter are liquids. Also, arylboranes and boronic acids also undergo a palladium-catalyzed cross-coupling with alkyl halides, although the catalysts of choice are ***Tetrakis(triphenylphosphine)palladium(0)***, ***Dichloro[1,4-bis(diphenylphosphino)butane]palladium(II)***, or ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***.[46]

Arylation of Alkenes by Coupling and Cross Coupling.

Alkenes can be functionalized with palladium-activated arenes, yielding styrene derivatives in a process applicable to a wide range of substrate combinations. An early demonstration of the possibilities of the Heck arylation was the coupling of 3-bromopyridine with *N*-3-butenylphthalimide (eq 15), the first step of four in a total synthesis of nornicotine.[47]

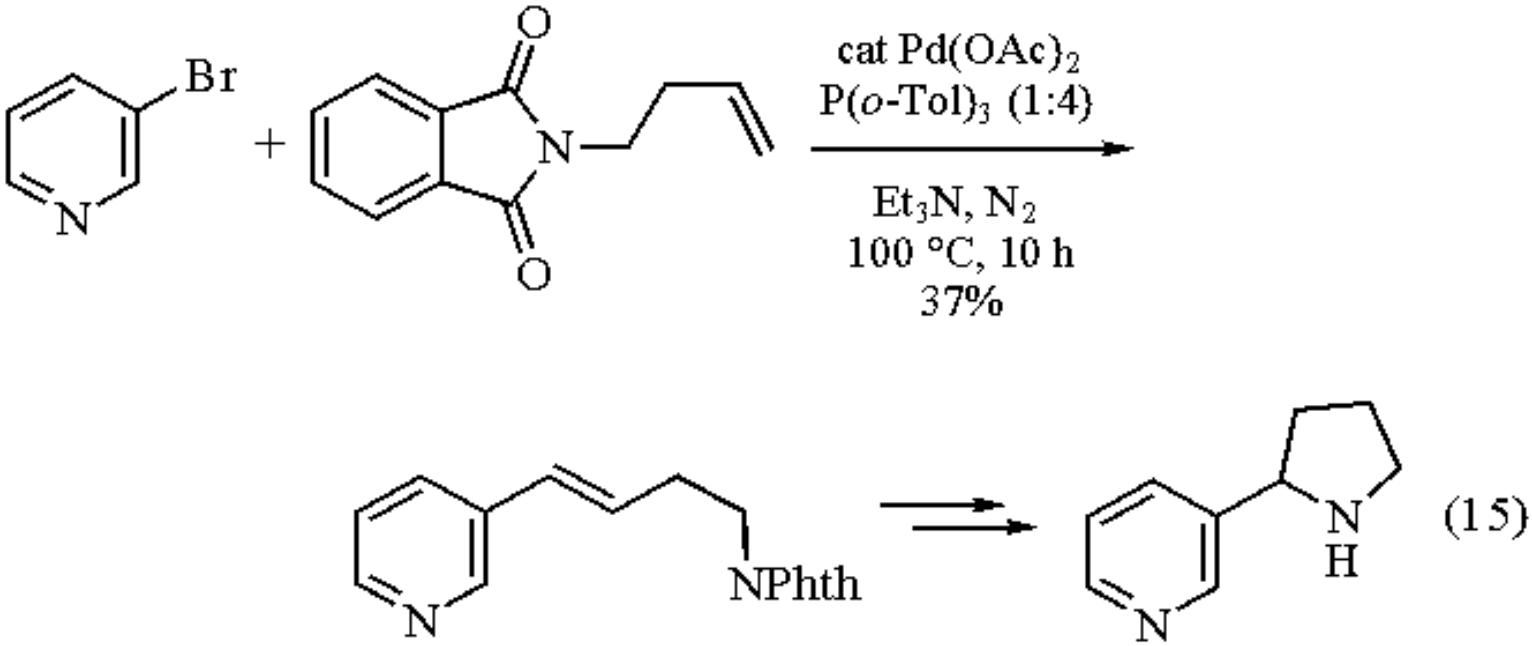

N-Vinylimides readily undergo palladium-catalyzed vinylic substitution with aryl bromides to yield 2-styryl- and 2-phenylethylimines. With aryl iodides (eq 16), the reaction proceeds even in the absence of added phosphine,[48] which opens the possibility of a sequential disubstitution of bromoiodoarenes.

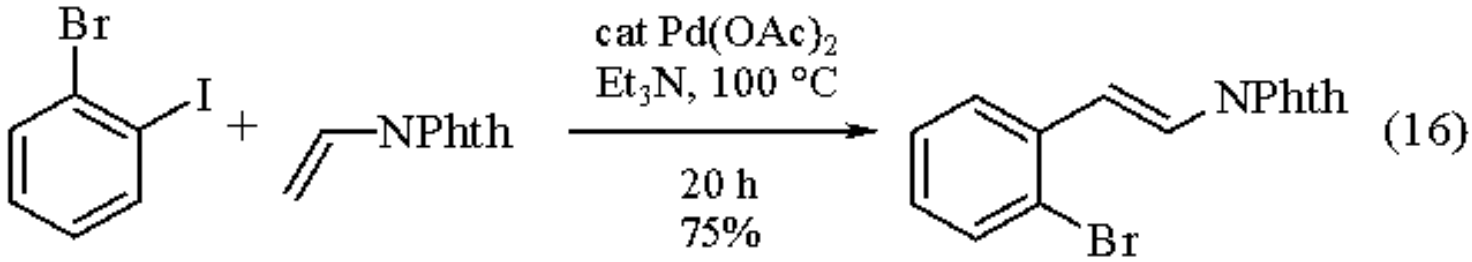

Vicinal dibromides undergo a twofold coupling reaction with monosubstituted alkenes to yield 1,3,5-trienes (eq 17). The reaction, catalyzed by palladium acetate in the presence of triphenylphosphine and triethylamine, can also be applied to aromatic tri-and tetrabromides.[49]

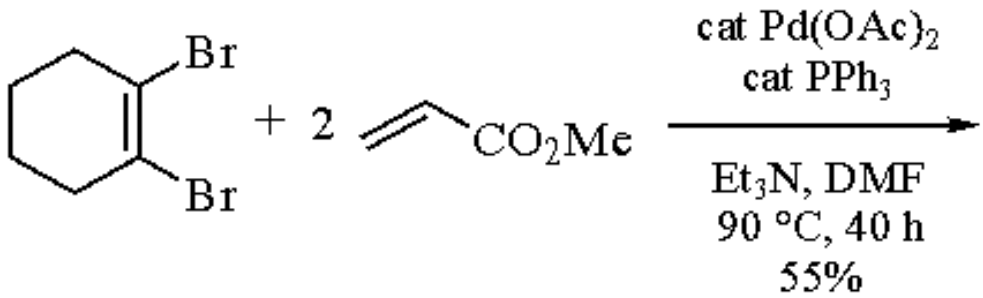

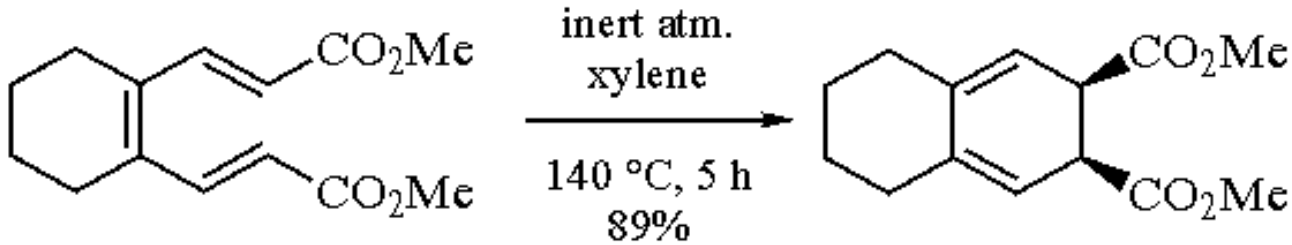

(17)

A double coupling of 2-amidoacrylates with 3,3´-diiodobiphenyl constitutes a key step in a short preparation of a biphenomycin B analog.[50] Palladium acetate-catalyzed double coupling reactions of 1,8-diiodonaphthalene with substituted alkenes and alkynes under phase-transfer conditions are useful also for the synthesis of various acenaphthene and acenaphthylene derivatives.[51]

1,2-Disubstituted alkenes are generally less reactive towards coupling than are monosubstituted alkenes. However, the use of the more reactive aryl iodides can result in reasonable yields of the coupled product, usually as a mixture of (*E*) and (*Z*) isomers.[52] The reaction has been applied to a coupling of 2-iodoaniline derivatives with ***Dimethyl Maleate*** (eq 18), the product of which spontaneously cyclizes to form quinolone derivatives in 30-70% yield. If, instead, the 2-iodoaniline is coupled with ***Isoprene*** or cyclohexadiene in the presence of palladium acetate, triphenylphosphine, and triethylamine, indole and carbazole derivatives are obtained by a coupling followed by intramolecular nucleophilic attack by the heteroatom.[53]

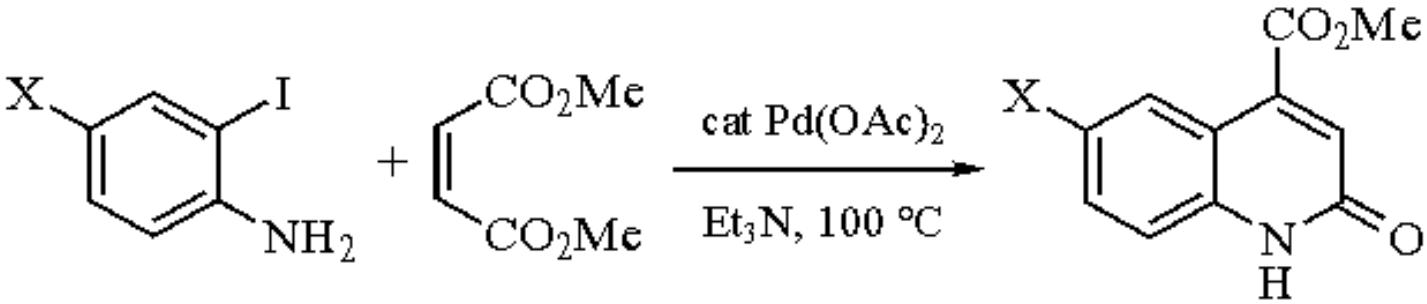

(18)

X = H (71%), OH (55%), Br (30%)

2-Alkylidenetetrahydrofurans can be prepared via intramolecular oxypalladation and subsequent coupling by treatment of aryl or alkyl alkynic alcohols with ***n-Butyllithium*** followed by palladium acetate and triphenylphosphine. The reaction proceeds to yield furans in moderate yields.[54]

Formation of Dienes and Enynes by Coupling and Cross Coupling.

The vinylation of methyl acrylate, methyl vinyl ketone, or acrolein with (*E*) or (*Z*) vinylic halides under phase-transfer conditions gives high yields of (*E*,*E*) (eq 19) or (*E*,*Z*) (eq 20) conjugated dienoates, dienones, and dienals, respectively.[55] Coupling of vinyl halides or triflates with α,β- or β,γ-unsaturated acids under phase-transfer conditions yields vinyl lactones.[56]

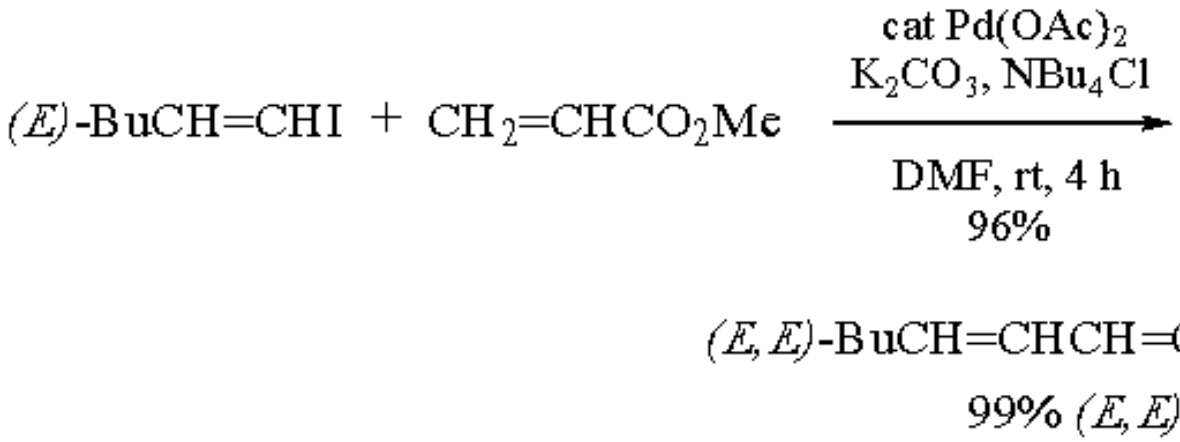

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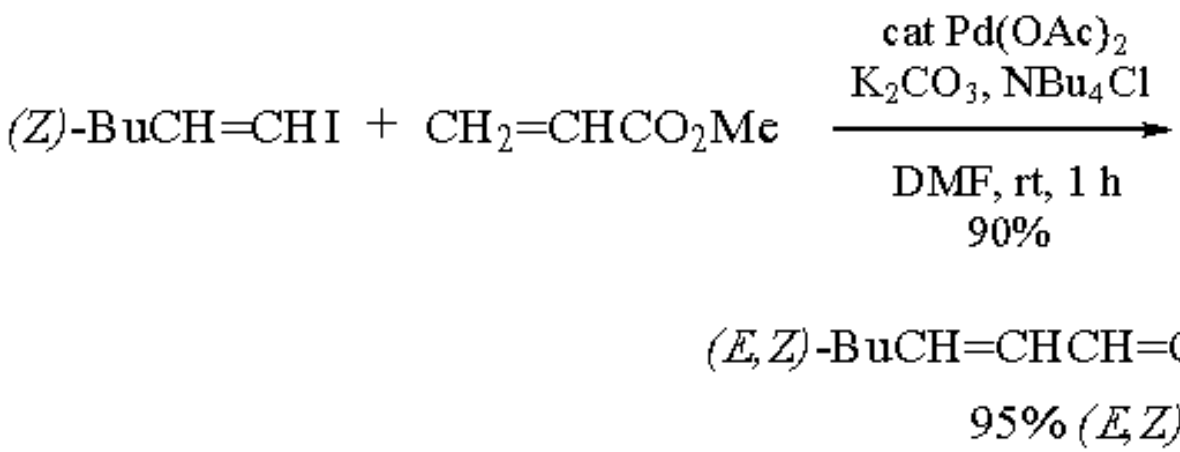

(20)

Commercially available trimethylvinylsilanes can be vinylated using either vinyl triflates or vinyl iodides in the presence of silver salts, in a reaction catalyzed by palladium acetate in the presence of triethylamine. The resulting 3-substituted 1-trimethylsilyl-1,3-dienes are obtained in reasonable to good yields.[57]

Alkenylpentafluorosilicates derived from terminal alkynes react readily with allylic substrates in a palladium-catalyzed cross-coupling reaction to yield (*E*)-1,4-dienes (eq 21).[58] Treatment of 1-alkenylstannanes with t-BuOOH in the presence of 10% of palladium acetate gives 1,3-dienes (eq 22), whereas coupling between 1- and 2-alkenylstannanes provides 1,4-dienes in good yields (eq 23).[59]

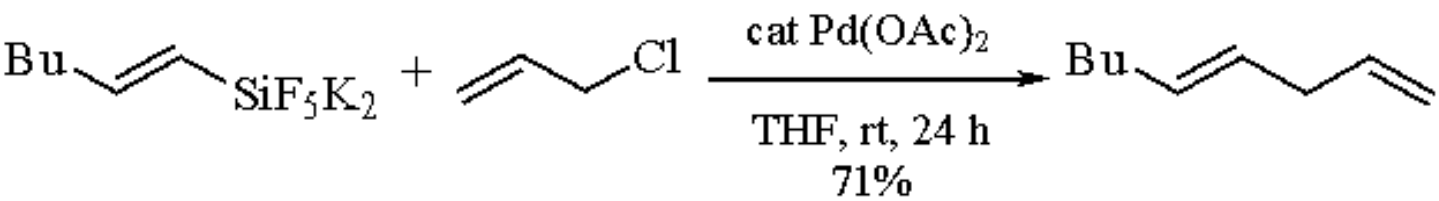

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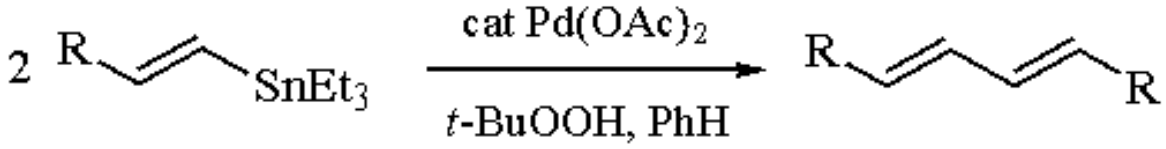

(22)

R = Ph, 80%, (*E*):(*Z*) = 4:1
R = C_6H_{13}, 76%, only (*E*)

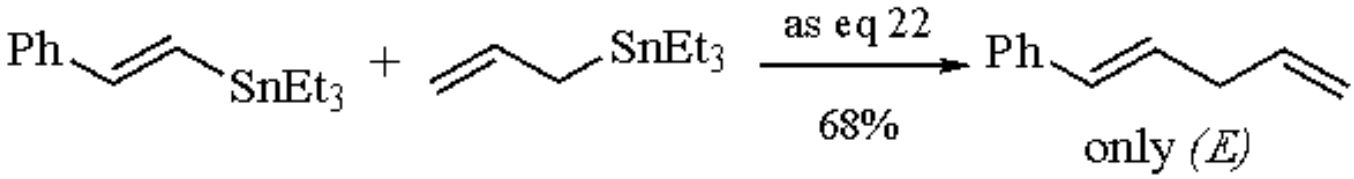

(23)

Cross coupling of enol triflates under neutral conditions with allyl-, vinyl-, or alkynylstannanes in the presence of palladium diacetate and triphenylphosphine proceeds to give high yields of 1,4- and 1,3-dienes and 1,3-enynes, respectively (eq 24).[60]

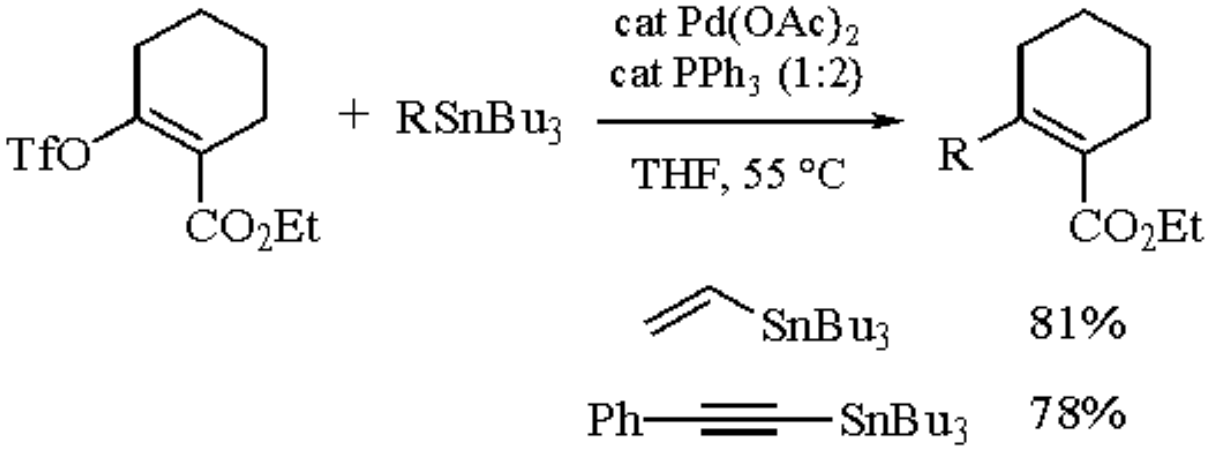

(24)

Terminal alkynes react to form 1-en-3-ynes in a process catalyzed by palladium acetate and tris(2,6-dimethoxyphenyl)phosphine. A number of functional groups such as internal alkenes, esters, and alcohols are tolerated, and good yields of homo- (eq 25) as well as hetero-coupled enynes (eq 26) are obtained.[61]

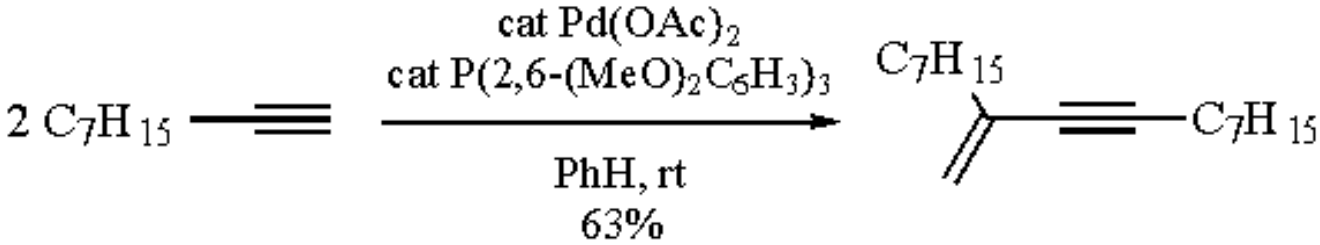

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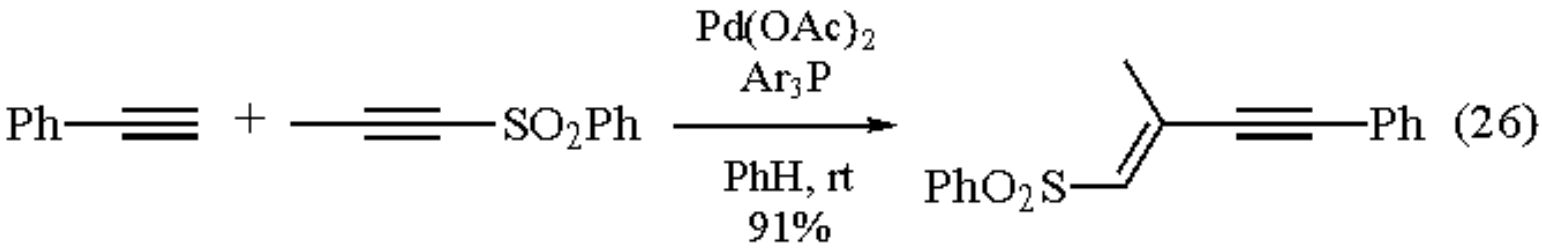

An interesting approach to 1-en-5-ynes is the palladium-catalyzed tandem coupling of a *cis*-alkenyl iodide, a cyclic alkene, and a terminal alkyne (eq 27). With norbornene as the alkene, the coupling occurs in a stereodefined manner, and the enyne products are obtained in good yields.[62] ***Potassium Cyanide*** can be used instead of an alkyne to yield the corresponding cyanoalkene.[63]

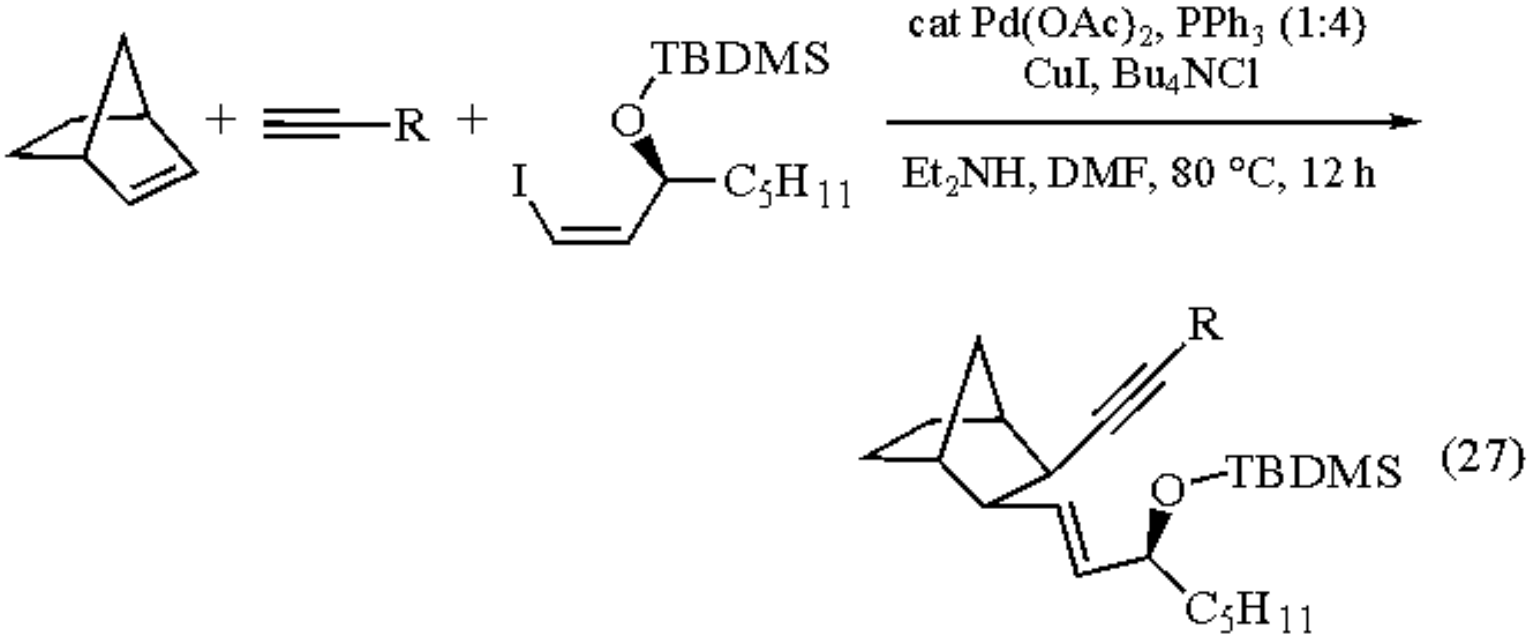

Formation of Aldehydes, Ketones, and Allylic Dienols by Coupling to Allylic Alcohols.

Allylic alcohols can be coupled with aryl or vinyl halides or triflates. The outcome of the reaction depends on the coupling agent and the reaction conditions. Thus arylation of allylic alcohols under Heck conditions constitutes a convenient route to 3-aryl aldehydes and 3-aryl ketones (eq 28).[64]

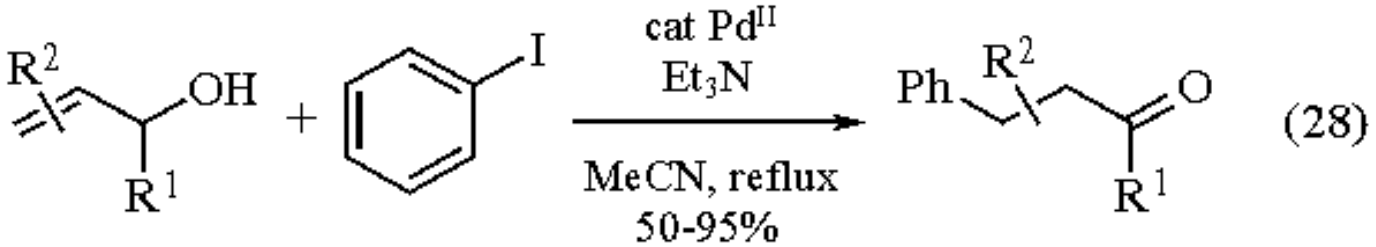

Coupling of primary allylic alcohols with vinyl halides carried out under phase-transfer conditions (cat $Pd(OAc)_2$ in the presence of Ag_2CO_3 and *n*-Bu_4NHSO_4 in acetonitrile) gave 4-enals,[65] whereas secondary allylic alcohols, when treated

with a vinyl halide or enol triflate, afforded conjugated dienols with good chemoselectivity, regiochemistry, and stereoselectivity.[66] Since the coupling reaction under these conditions proceeds without touching the carbon bearing the alcohol functional group, it was possible to prepare optically active dienols from vinyl iodides and optically active allylic alcohols (eq 29).[67]

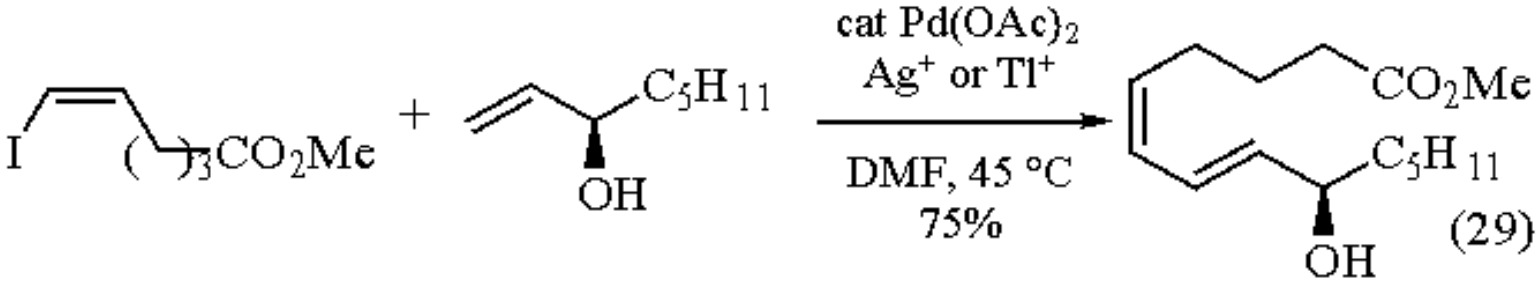

Formation of Allyl and Aryl Primary Allylic and Homoallylic Alcohols from Vinyl Epoxides and Oxetanes.

Vinylic epoxides can be coupled with aryl (eq 30) or vinyl (eq 31) iodides or triflates to form allylic alcohols in 40-90% yield.[68] When employing palladium acetate as the catalyst, a reducing agent such as sodium formate is required in addition to the salts normally present under phase transfer conditions.

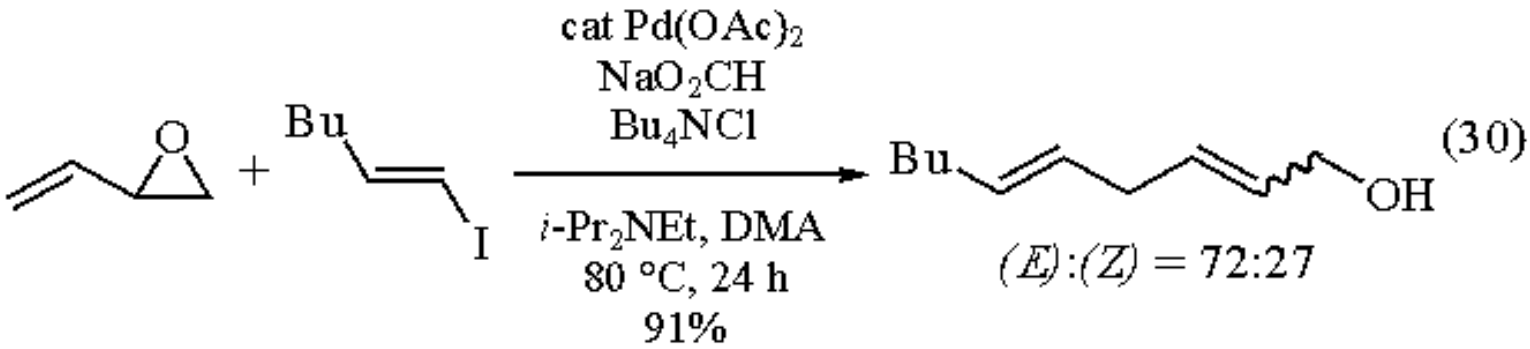

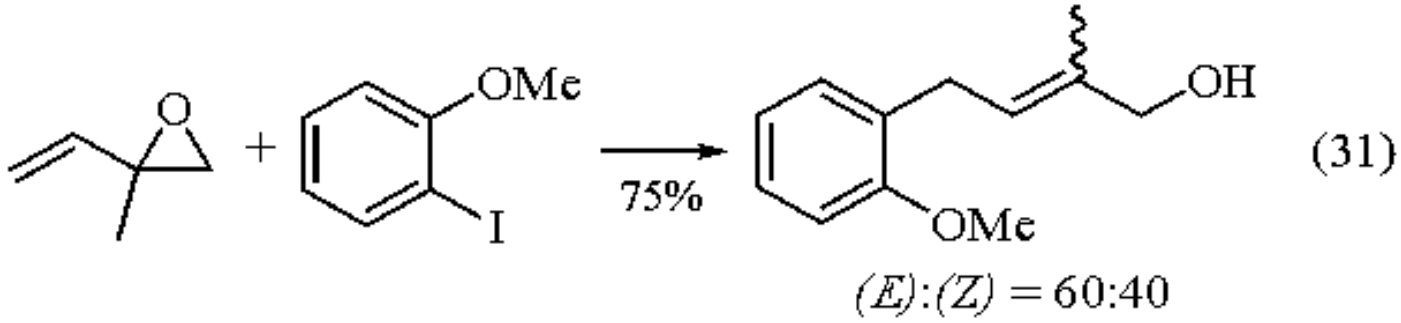

Vinyloxetane couples with aryl or vinyl iodides or triflates to form homoallylic alcohols under essentially the same reaction conditions (eq 32).[69] The process has also been applied to the preparation of aryl-substituted 3-alkenamides from 4-alkenyl-2-azetidinones (eq 33).[70]

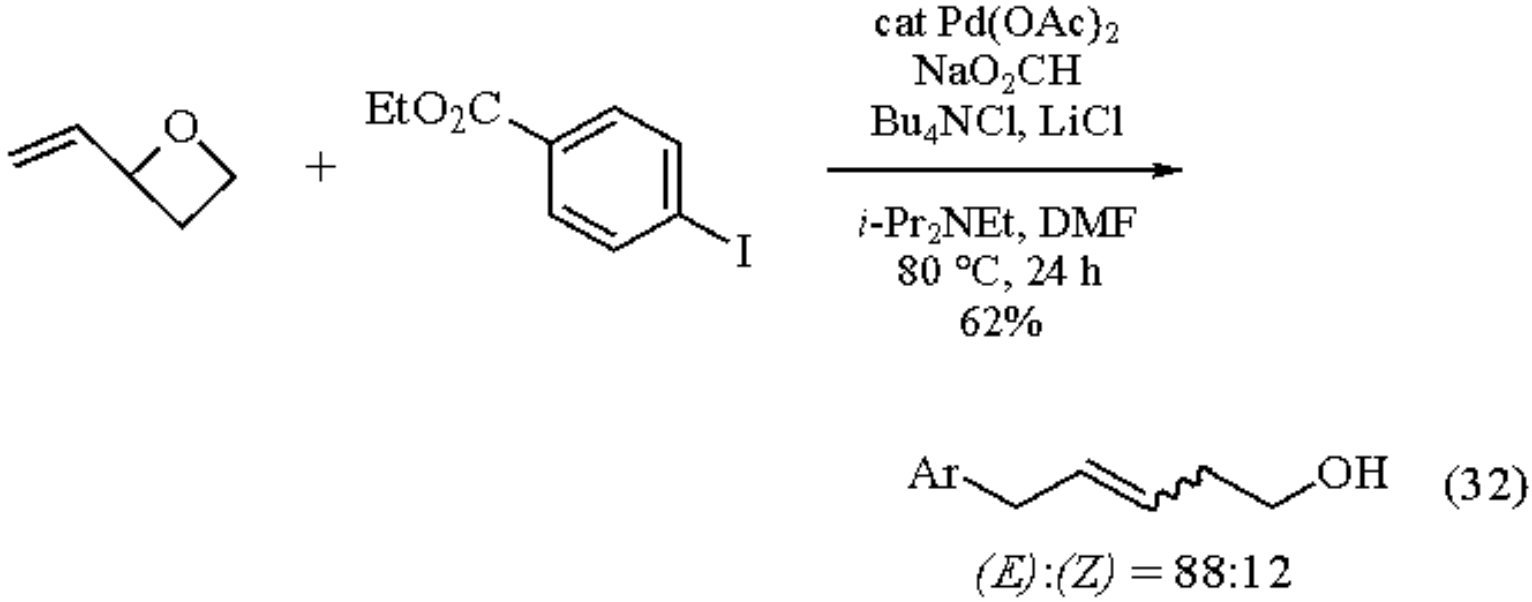

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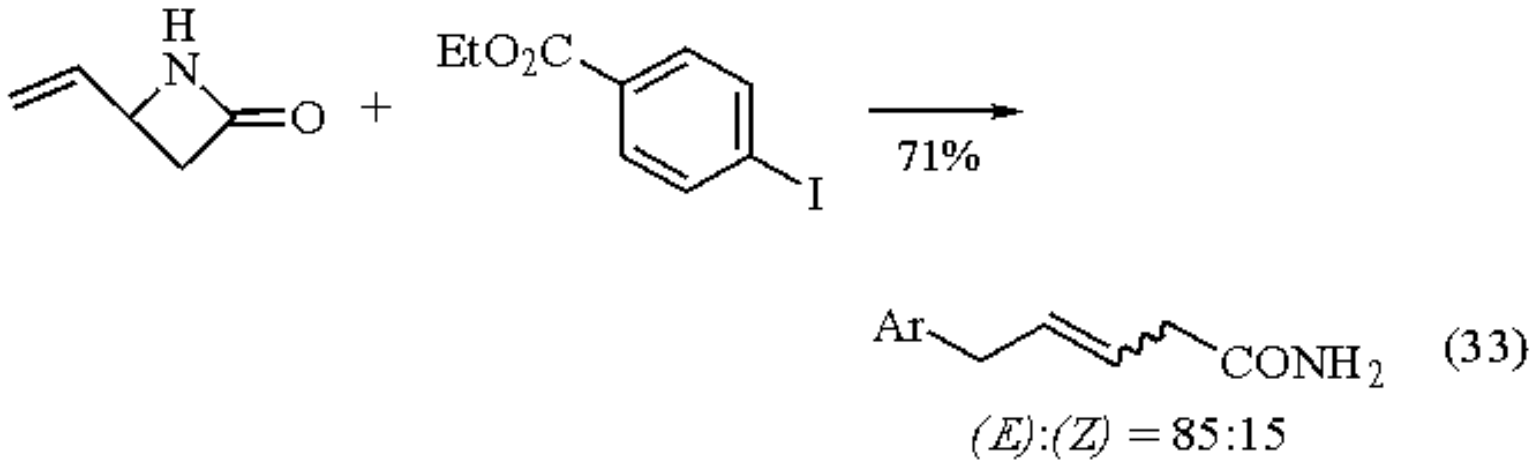

(33)

Homoallylic alcohols can also be prepared using a one-pot transformation of homopropargyl alcohols. Intramolecular hydrosilylation followed by a palladium-catalyzed coupling of the in situ generated alkenoxysilane with an aryl or alkenyl halide, in the presence of fluoride ions, affords the alcohol product.[71] This process has also been applied to the preparation of 1,3-dienes.

Carbonylation.

Carbon monoxide readily inserts into Pd-C σ-bonds. The resulting acylpalladium intermediate can react intermolecularly or intramolecularly with amines or alcohols to form ketones, amides, or esters, respectively, or with alkenes to yield unsaturated ketones.[1a,5] Thus treatment of vinyl triflates with $Pd(OAc)_2$, PPh_3, and MeOH in DMF results in one-carbon homologation of the original ketone to α,β-unsaturated esters.[72] Benzopyrans with a *cis*-fused γ-lactone can be prepared in high yield from *o*-disubstituted arenes by carbonylation of the intermediate formed upon intramolecular attack of the phenol on the terminal alkene (eq 34). The sequence affords the *cis*-fused lactone, regardless of the relative stereochemistry of the hydroxide and the methylenepalladium in the intermediate.[73]

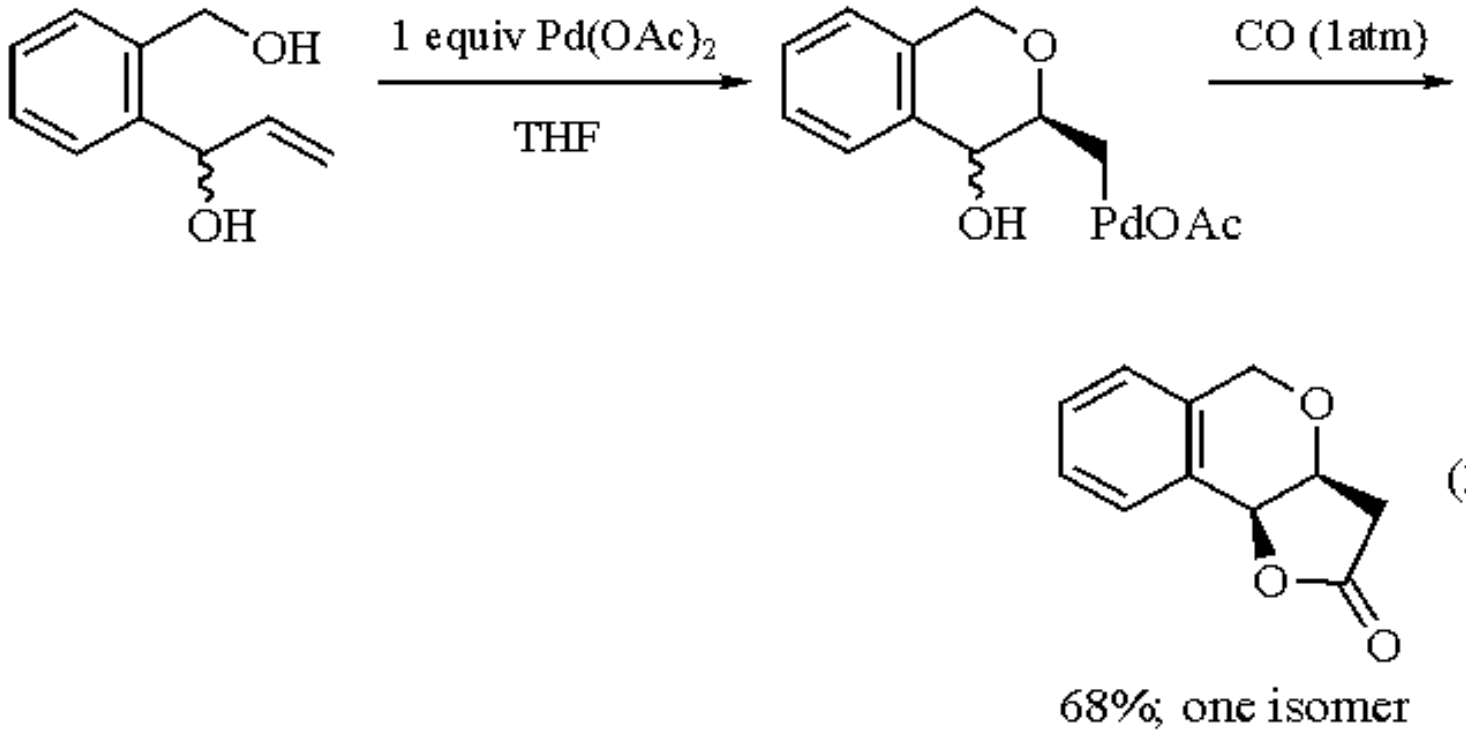

Vinyl triflates undergo carbonylative coupling with terminal alkynes to yield alkenyl alkynyl ketones in a reaction catalyzed by palladium acetate and dppp in the presence of triethylamine.[74] When applied to 2-hydroxyaryl iodides (eq 35), subsequent attack by the hydroxyl group on the alkyne yielded flavones and aurones. The cyclization result depends on the reaction conditions. ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** as base in DMF yields mainly the six-membered ring flavone, whereas the only product observed when employing potassium acetate in anisole was the five-membered ring aurone.[75]

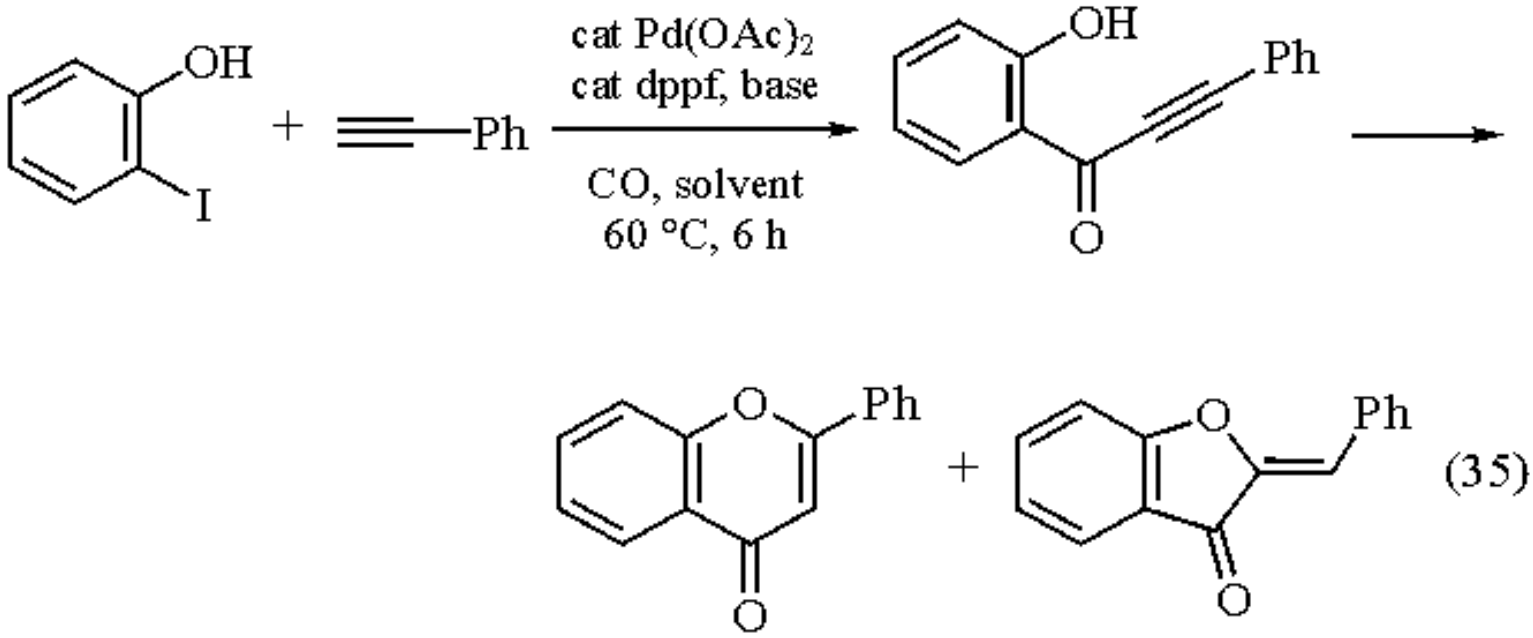

base	sol	
AcOK	anisole	0:100
DBU	DMF	92:8

Chiral α,β-unsaturated oxazolines can be obtained by a carbonylation-amidation of enol triflates or aryl halides with chiral amino alcohols (eq 36).[76] The palladium catalyst can be either $Pd(PPh_3)_4$, ***Bis(dibenzylideneacetone)palladium(0)*** and PPh_3, or $Pd(OAc)_2$ and dppp in the presence of triethylamine.

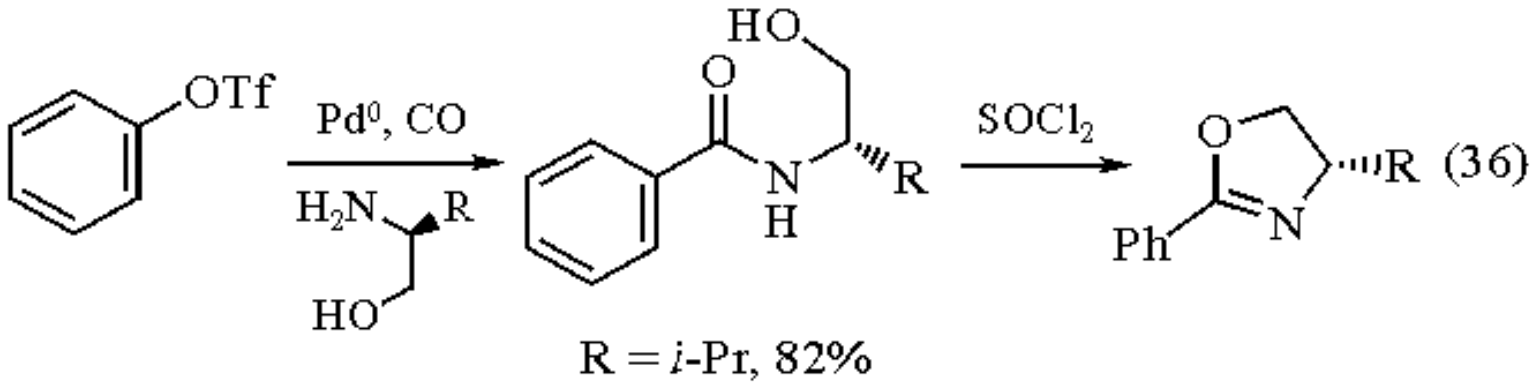

N-Substituted phthalimides are obtained from coupling *o*-dihalo aromatics with carbon monoxide and primary amines. The best catalysts for this reaction, however, were $PdCl_2L_2$ species.[77]

Formation of Heterocyclic Compounds.

Coupling reactions of 2-halophenols or anilines with molecules containing functionalities that allow the heteroatom nucleophile to form a heterocycle either by intramolecular oxy- or amino-palladation of an alkene, or by lactone or lactam formation, has already been mentioned in the preceding sections.[78] In addition to these powerful techniques, carbon-heteroatom bonds can be constructed in steps prior to the cyclization. For example, the enamine 3-((2-bromoaryl)amino)cyclohex-2-en-1-one undergoes a palladium-catalyzed intramolecular coupling to yield 1,2-dihydrocarbazoles in moderate yields.[79] Intramolecular coupling of 2-iodoaryl allyl amines gave high yields of indoles under phase-transfer conditions (eq 37).[80] The corresponding aryl allyl ethers require the additional presence of sodium formate in order to give benzofurans in good yields (eq 38).

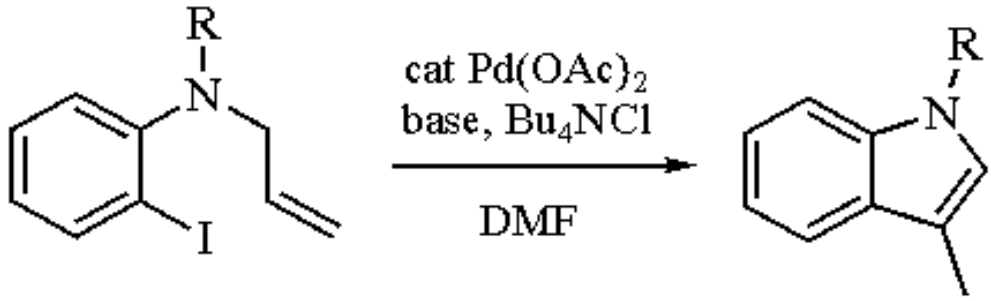

R	Base	Time	Temp.	Yield
H	Na_2CO_3	24 h	25 °C	97%
Me	Et_3N	48 h	25 °C	81%
MeCO	NaOAc	24 h	80 °C	90%

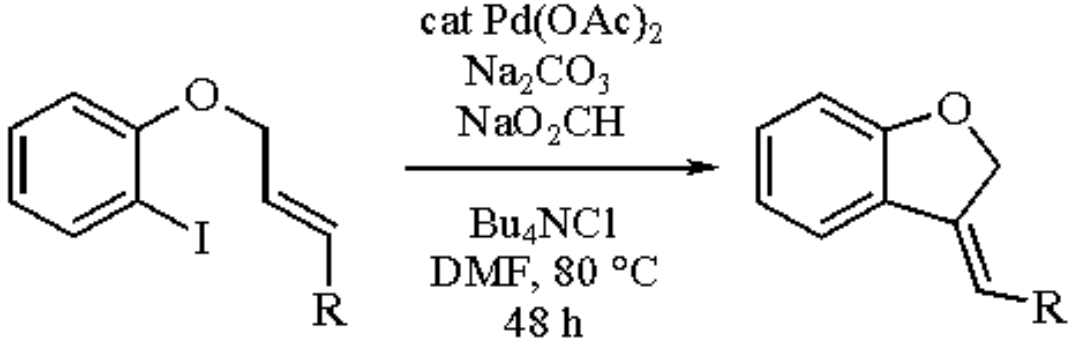

(38)

R = H (47%), Me (83%), C_5H_{11} (83%), Ph (81%)

The principle has been applied to the preparation of pharmaceutically interesting heterocyclic compounds,[81] and to the assembly of fused or bridged polycyclic systems containing quaternary centers.[82]

Formation of Carbocycles.

By Intramolecular Heck Coupling.

1-Bromo-1,5-dienes and 2-bromo-1,6-dienes cyclize in the presence of ***Piperidine*** and a palladium acetate-tri-*o*-tolylphosphine catalyst to produce cyclopentene derivatives (eq 39).[83] 2-Bromo-1,7-octadiene, when subjected to the same reaction conditions, cyclized to yield a mixture of six and five-membered ring products, whereas competing dimerization and polymerization was observed for the more reactive 2-bromo-1,5 dienes.

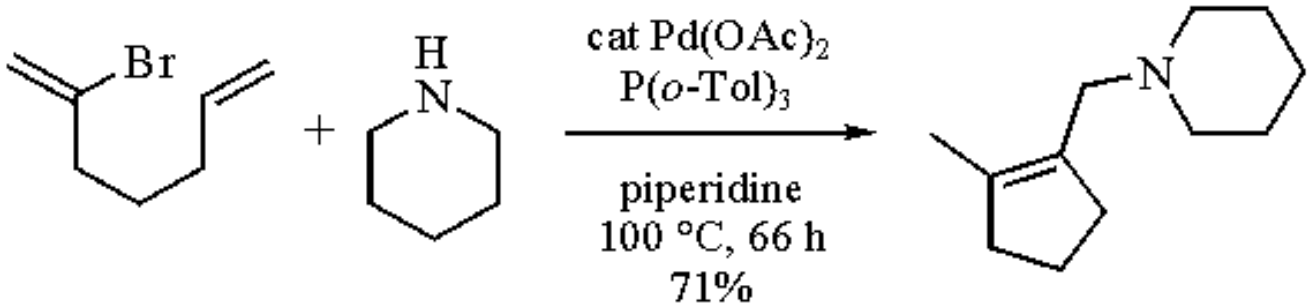

(39)

The influence of phosphine ligands, added salts, and the type of metal catalyst on the selectivity of the cyclization have been studied.[84] With K_2CO_3 as base, Wilkinson's catalyst (***Chlorotris(triphenylphosphine)rhodium(I)***) showed higher selectivity for the formation of 1,2-dimethylenecyclopentanes over 1-methylene-2-cyclohexenes than the palladium acetate-triphenylphosphine catalyst.

The palladium-catalyzed cyclization of acyclic polyenes to form polycyclic systems (eq 40) constitutes a very powerful further development of the above method. σ-Alkylpalladium intermediates, produced in an intramolecular Heck reaction, can be efficiently trapped by neighboring alkenes to give bis-cyclization products of either spiro or fused geometry. The second cyclization also produces a σ-alkylpalladium intermediate which can also be trapped.

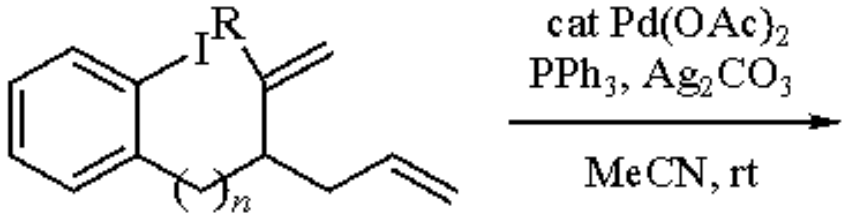

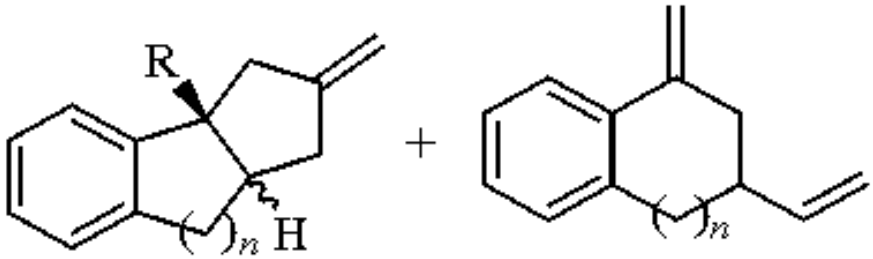

(40)

R	*n*	Ratio	
Me	1	1:1.5	
Me	2	100:0	(1:1 H_α:H_β)
H	1	0:100	

1-Iodo-1,4- and -1,5-dienes can be transformed into α-methylenecyclopentenones and -hexenones, respectively, by palladium-catalyzed carbonylation and subsequent intramolecular coupling.[85] Better results, however, were obtained using ***Tetrakis(triphenylphosphine)palladium(0)***.

Via (π-Allyl)palladium Intermediates.

Allylic substitution, by nucleophilic attack on (π-allyl)palladium complexes generated from allylic substrates, are most often catalyzed by Pd^0-phosphine complexes.[86,87] There are, however, a few examples of intramolecular reactions where the active catalyst is generated in situ from palladium acetate. For example, ethyl 3-oxo-8-phenoxy-6-octenoate reacts to yield cyclic ketones in the presence of catalytic amounts of palladium diacetate and a phosphine or phosphite ligand (eq 41).[88] The product distribution between five- or seven-membered rings depends on the ligand employed and the solvent used. With a chiral phosphine, (*E*)-methyl 3-oxo-9-methoxycarbonyloxy-7-nonenoate was cyclized to give (*R*)-3-vinylcyclohexane with 41-48% ee.[89]

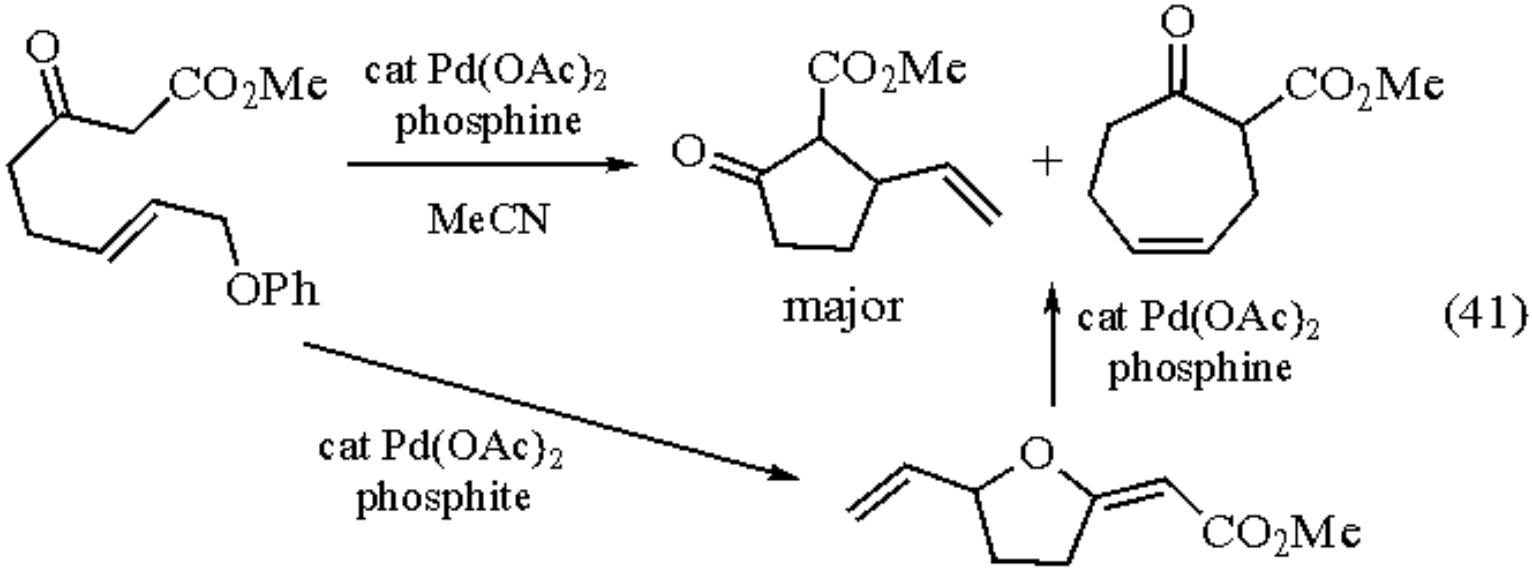

Another example is based on the palladium-catalyzed 1,4-chloroacetoxylation methodology,[21,22,29] where a common intermediate, by proper choice of reaction conditions, can be transformed into *cis*- or *trans*-annulated products.[89]

By Cyclization of Alkenyl Silyl Enol Ethers.

Treatment of alkenyl silyl enol ethers with stoichiometric amounts of palladium acetate induces an intramolecular attack to form carbacycles (eqs 42 and 43). Good to high yields of α,β-unsaturated ketones were obtained.[90]

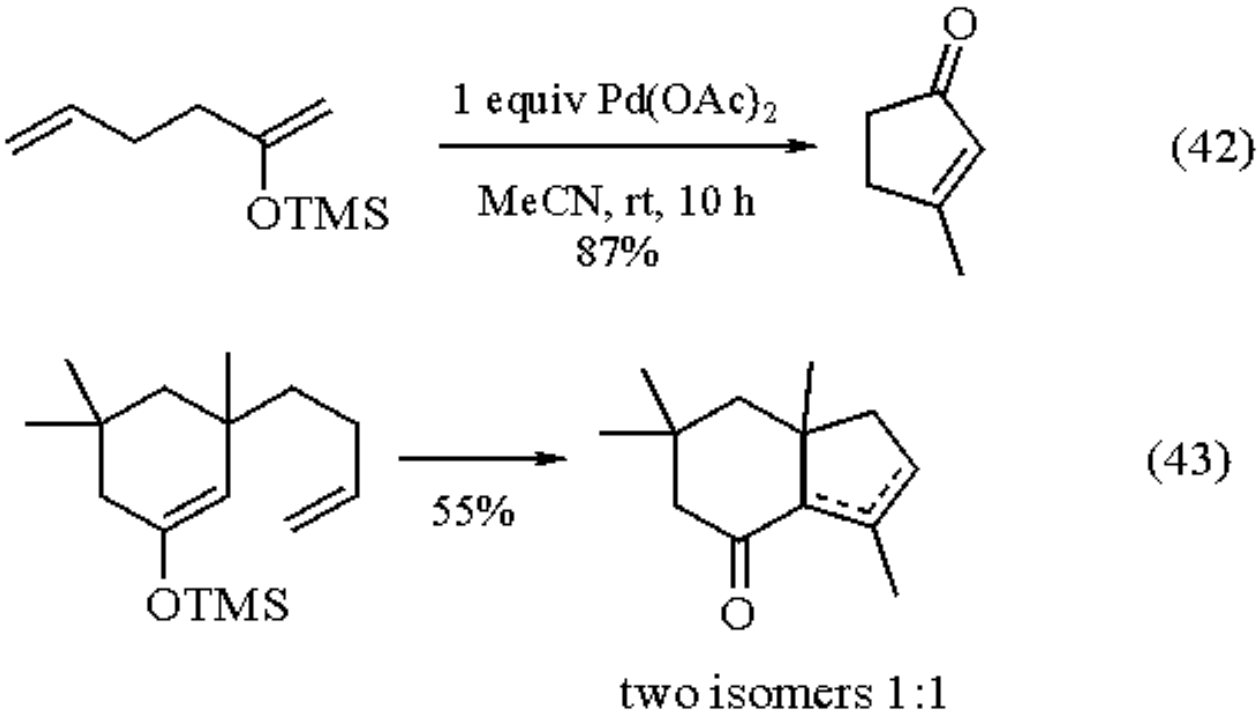

With slightly different substrates, the observed products were not α,β-unsaturated ketones but nonconjugated bicycloalkenones.[91] The method, which affords bridged (eq 44) as well as spirocyclic (eq 45) bicycloalkenones in acceptable to good yields, has been applied to the preparation of bicyclo[3.3.1]nonadienones[92] and to a total synthesis of quadrone.[93]

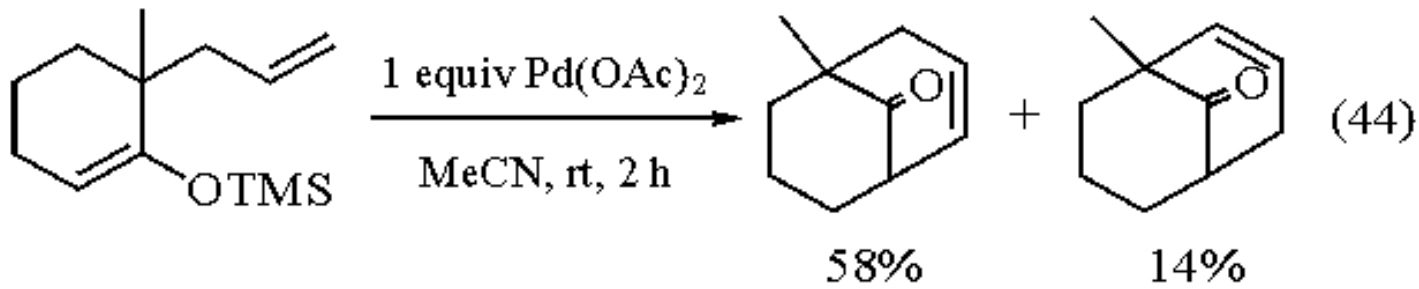

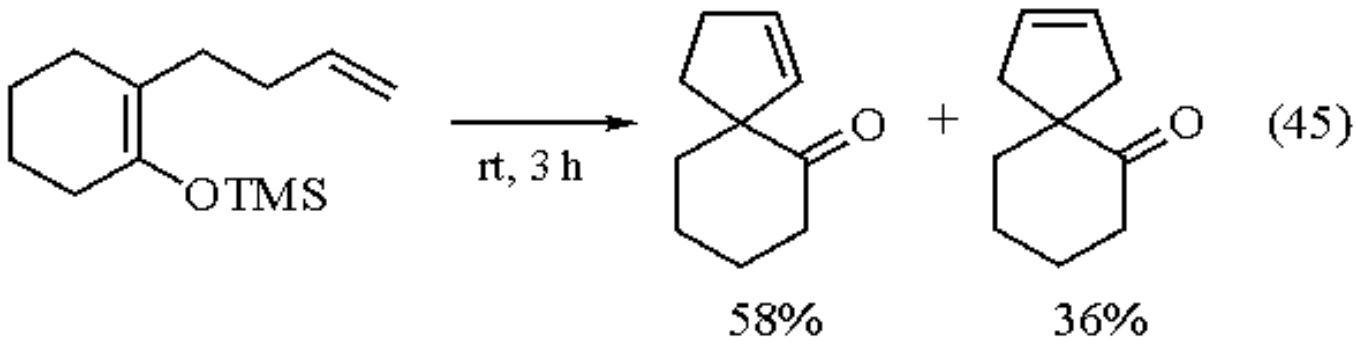

By Cyclization of Simple Dienes.

Treatment of 1,5-dienes with catalytic amounts of $Pd(OAc)_2$ and benzoquinone with MnO_2 as stoichiometric oxidant in acetic acid leads to an oxidative cyclization reaction (eqs 46, 47).[94] The reaction normally yield cyclopentanes with acetate and exomethylene groups in a 1,3-configurational relationship.[95]

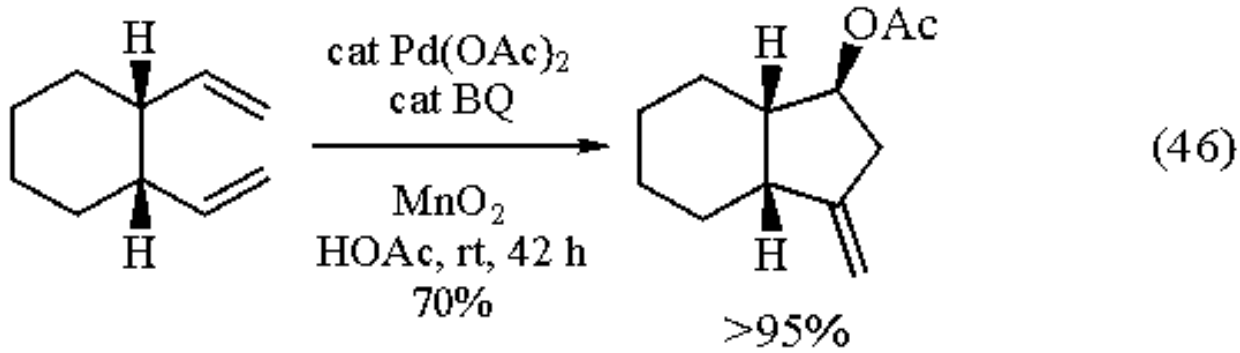

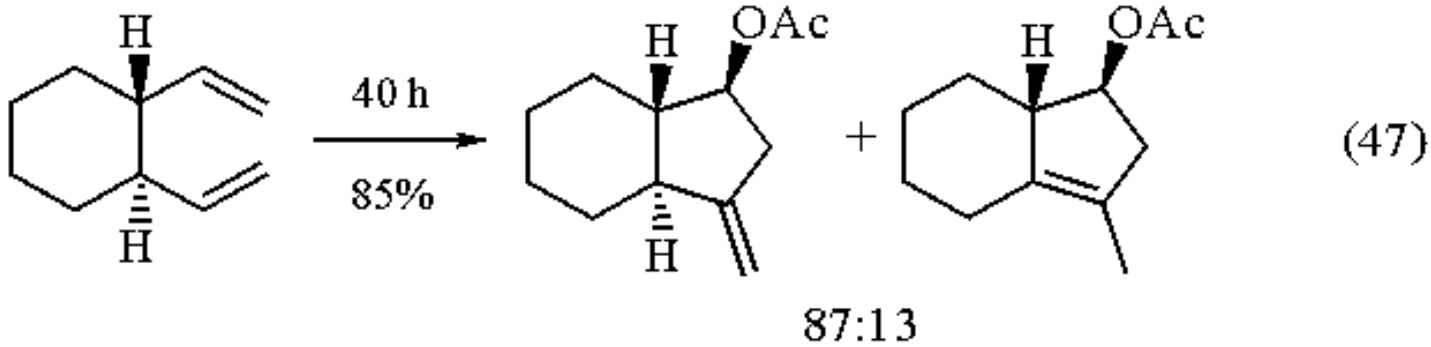

The selectivity of the reaction depends strongly upon the structure of the starting alkene. Substituents in the 1,3- and/or 4-positions of the diene are tolerated, but not in the 2- and 5-positions; thus the reaction most likely proceeds via an

acetoxypalladation of the 1,2-double bond followed by insertion of the 5,6-alkene into the palladium-carbon σ-bond and subsequent reductive elimination.[96] The cyclization is compatible with the presence of several types of functional groups such as alcohols, acetate (even in the allylic position), ethers, nitriles, and carboxylic acids. An improved diastereoselectivity was observed in reactions carried out with chiral nucleophiles in the presence of water-containing molecular sieves.[97] The synthetic utility of the reaction was demonstrated by a synthesis of diquinanes.[98]

By Cycloisomerization of Enynes.

When 1,6-enynes, prepared by a $Pd(PPh_3)_4$-catalyzed coupling of an allylic carboxylate with dimethyl propargylmalonate anion, is treated with a catalytic amount of a palladium(II) species, a carbocyclization leading to cyclopentanes carrying an exocyclic double bond occurs (eq 48).[99] Yields of 1,4-dienes ranging from 50% to 85% are observed. If the enyne has oxygen substituents in the allylic positions, the reaction instead yields a 1,3-diene (eq 49).[100] Cycloisomerization could also be induced for internal enynes carrying alkynic electron-withdrawing substituents.[101]

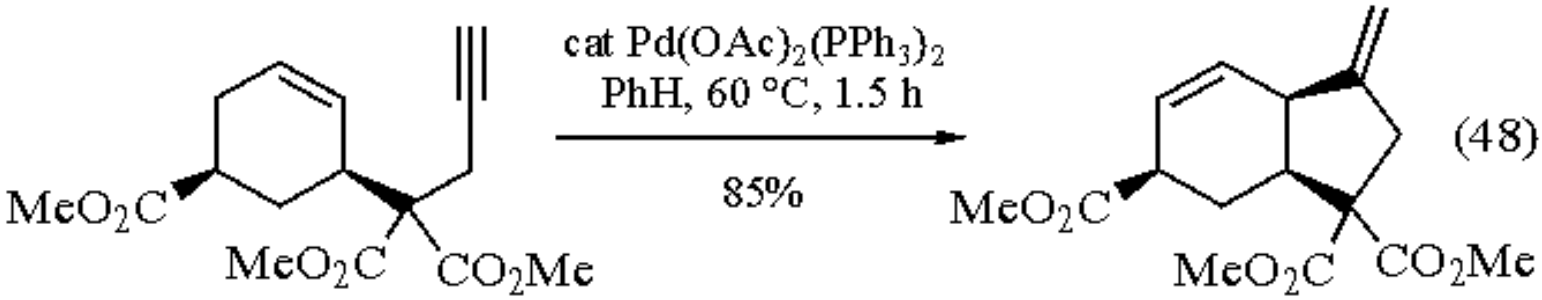

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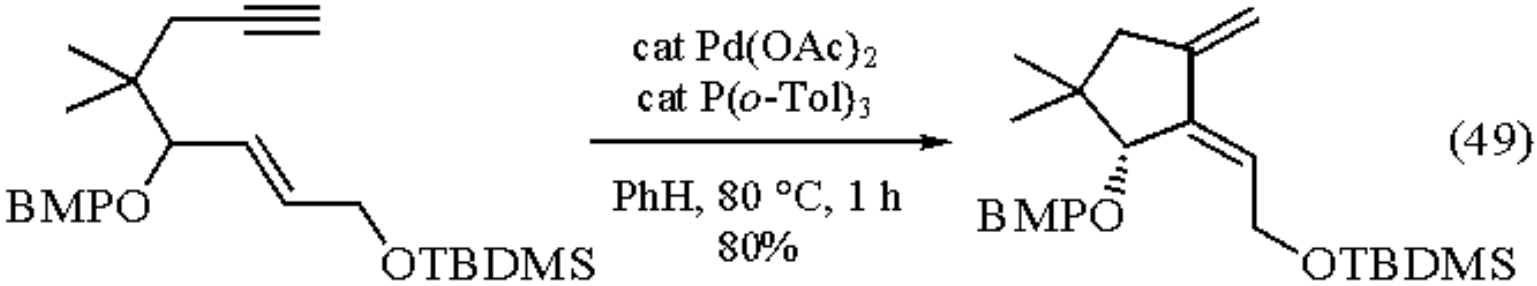

(49)

By Cycloaddition.

Palladium acetate, combined with $(i\text{-PrO})_3P$, catalyzes the [2 + 3] cycloaddition of trimethylenemethane to alkenes carrying electron-withdrawing substituents (eq 50). The yields of five-membered carbocycle varied from 35-89%.[102] With 1,3-dienes, a [4 + 3] cycloaddition gave seven-membered ring products in good yield (eq 51), and in some cases excellent diastereomeric ratios were observed.[102]

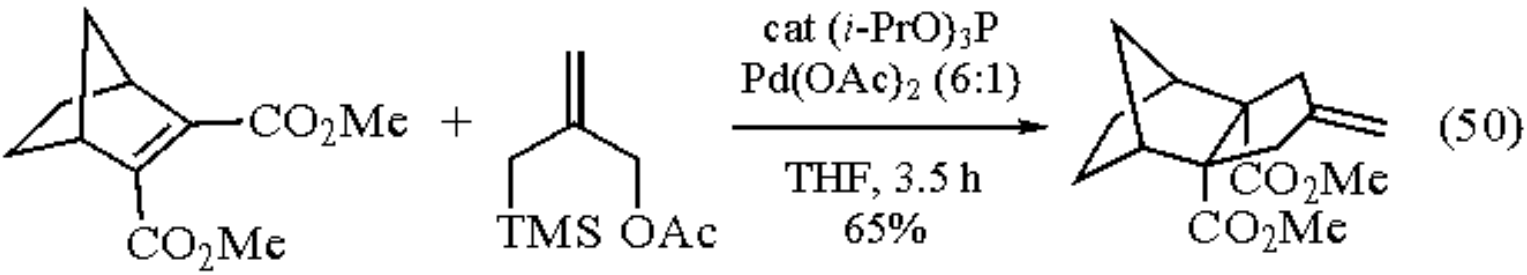

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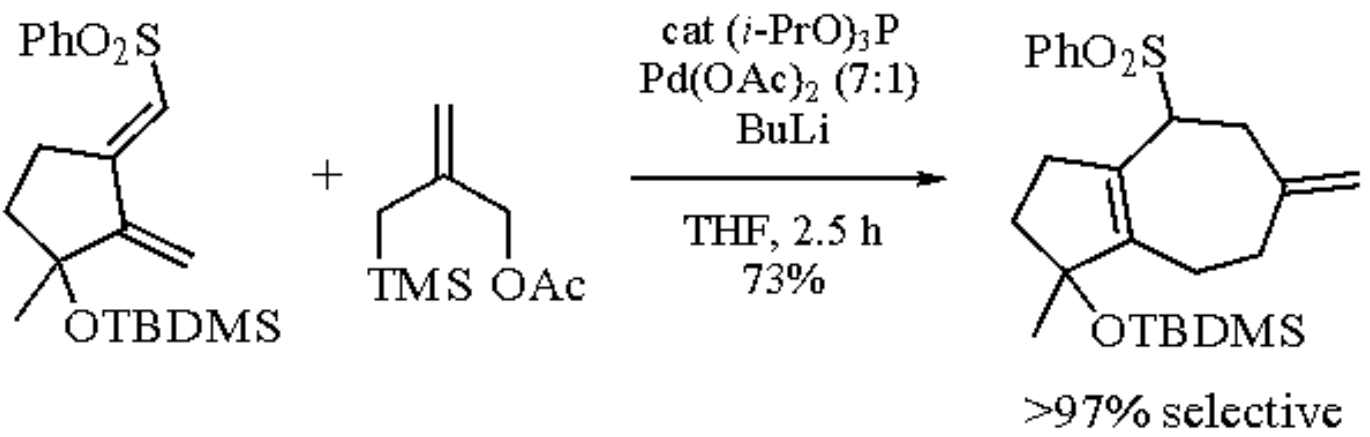

(51)

By Cyclopropanation.

Alkenes undergo a cyclopropanation reaction with diazo compounds (caution)[103] such as ***Diazomethane*** or ***Ethyl Diazoacetate*** in the presence of a catalytic amount of palladium acetate.[104] With diazomethane, a selective cyclopropanation of terminal double bonds can be obtained (eq 52).[105]

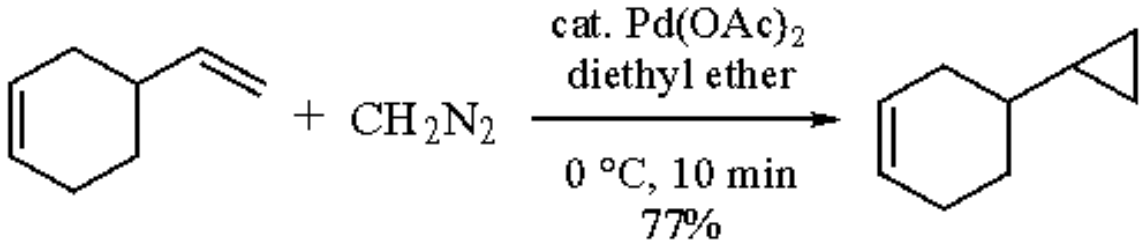

(52)

With diazo esters, the regioselectivity in transition metal-catalyzed cyclopropanation of dienes and trienes was generally not as good with palladium acetate as with a rhodium carboxylate catalyst,[106] although both palladium and rhodium carboxylates were better catalysts for the reaction than ***Copper(II) Trifluoromethanesulfonate***. α,β-Unsaturated carbonyl compounds also undergo palladium-catalyzed cyclopropanation, yielding the corresponding cyclopropyl ketones (eq 53) and esters (eq 54).[107]

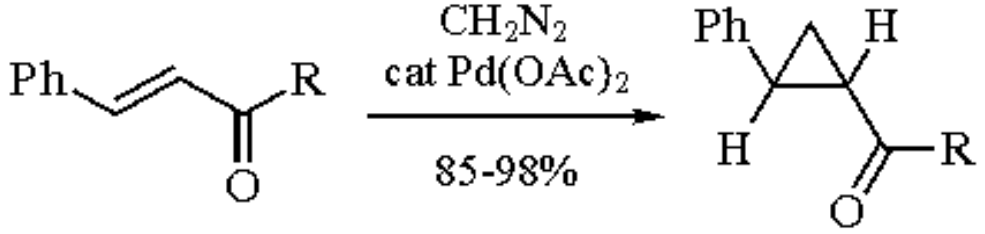

(53)

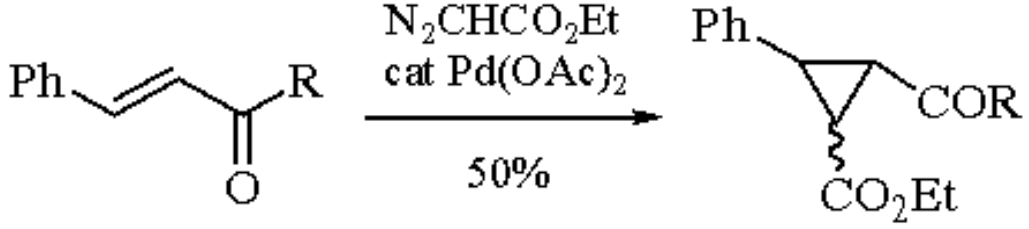

(54)

Asymmetric cyclopropanations of α,β-unsaturated carboxylic acid derivatives with CH_2N_2 proceeds in greater than 97.6% diastereomeric excess when Oppolzer's sultam is used as a chiral handle.[108] The stereoselectivity of the reaction was found to be temperature dependent, with the best results obtained at higher temperatures. A coupling of norbornene and a *cis*-alkenyl iodide in the presence of a hydride donor resulted in a cyclopropanation of the norbornene (eq 55).[65]

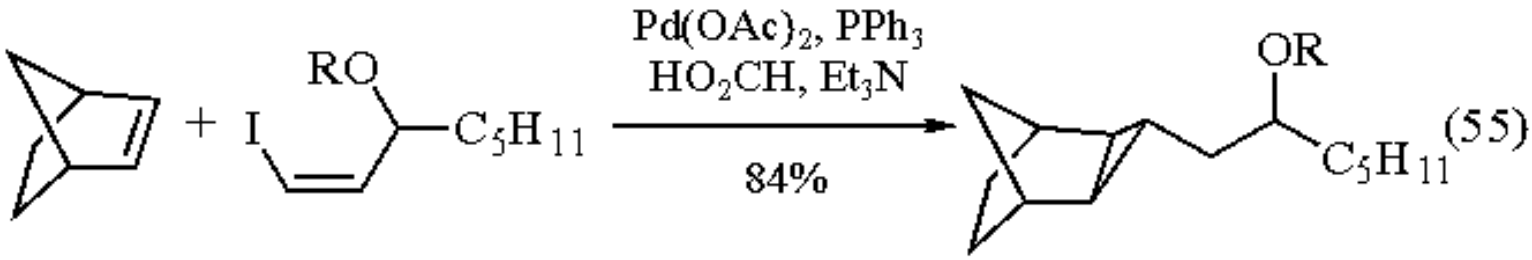

Other examples of palladium-catalyzed cyclopropanation are intramolecular processes catalyzed by, for example, ***Dichloro[1,2-bis(diphenylphosphino)ethane]palladium(II)***,[109] ***Tetrakis(triphenylphosphine)palladium(0)***,[110] or ***Bis(allyl)di-μ-chlorodipalladium***.[111]

Oxidations.

Carbonyl Compounds by Oxidation of Alcohols and Aldehydes.

Salts of palladium, in particular $PdCl_2$ in the presence of a base, catalyze the CCl_4 oxidation of alcohols to aldehydes and ketones. Allylic alcohols carrying a terminal double bond are transformed to 4,4,4-trichloro ketones at 110 °C, but yield halohydrins at 40 °C. These can be transformed to the corresponding trichloro ketones under catalysis of palladium acetate (eq 56).[112] The latter transformation could be useful for the formation of ketones from internal alkenes provided the halohydrin formation is regioselective.

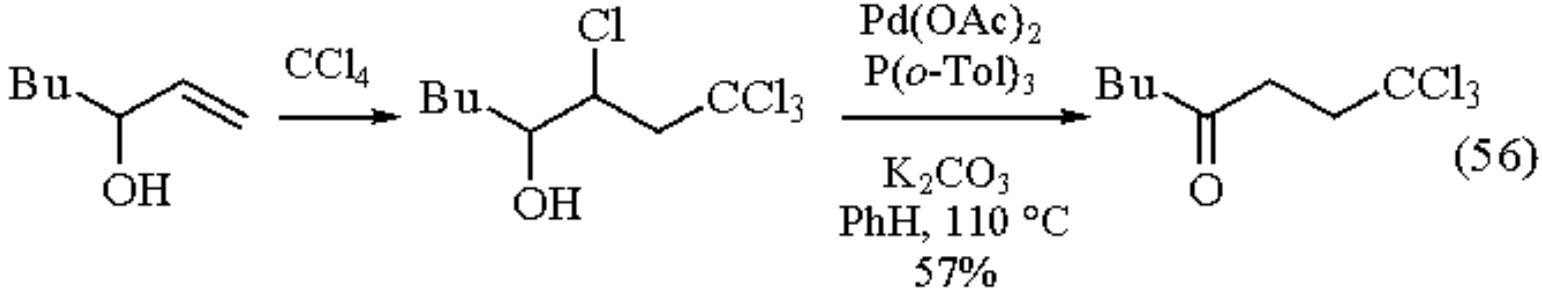

Secondary alcohols can be oxidized in high yield to the corresponding ketones by bromobenzene in a reaction catalyzed by palladium acetate in the presence of a base and a phosphine ligand. These reaction conditions, when applied to Δ^2-, Δ^3-, and Δ^4-unsaturated secondary alcohols, yielded product mixtures. When the stoichiometric oxidant was bromomesitylene and a $Pd(OAc)_2$:PPh_3 ratio of 1:2 was used, the oxidation proceeded smoothly for a wide variety of alcohols (eqs 57 and 58).[113]

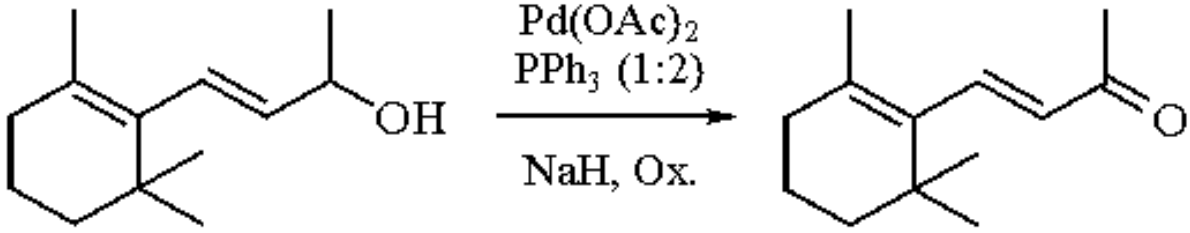

(57)

Ox = PhBr, 48%, MesBr, 77%

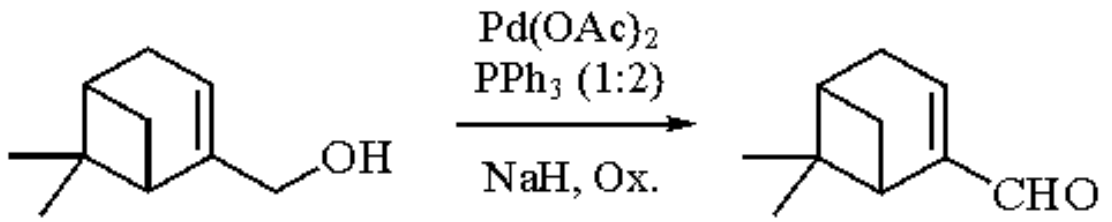

(58)

Ox = PhBr, 100%

Oxidation of aldehydes in the presence of ***Morpholine*** proceeded effectively to yield 50-100% of the corresponding morpholine amides.[114]

α,β-Unsaturated Ketones and Aldehydes by Oxidation of Enolates.

Palladium diacetate-mediated dehydrosilylation of silyl enol ethers proceeds to yield unsaturated ketones in high chemical yield and with good selectivity for the formation of (*E*)-alkenes (eqs 59 and 60).[115] Although stoichiometric amounts of $Pd(OAc)_2$ are employed, this method for dehydrogenation has been employed in key steps in the total synthesis of some polycyclic natural products.[116]

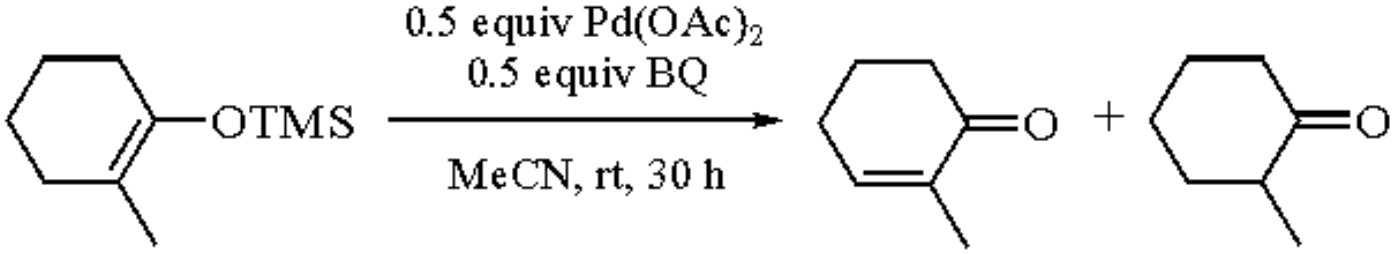

(59)

94% 5%

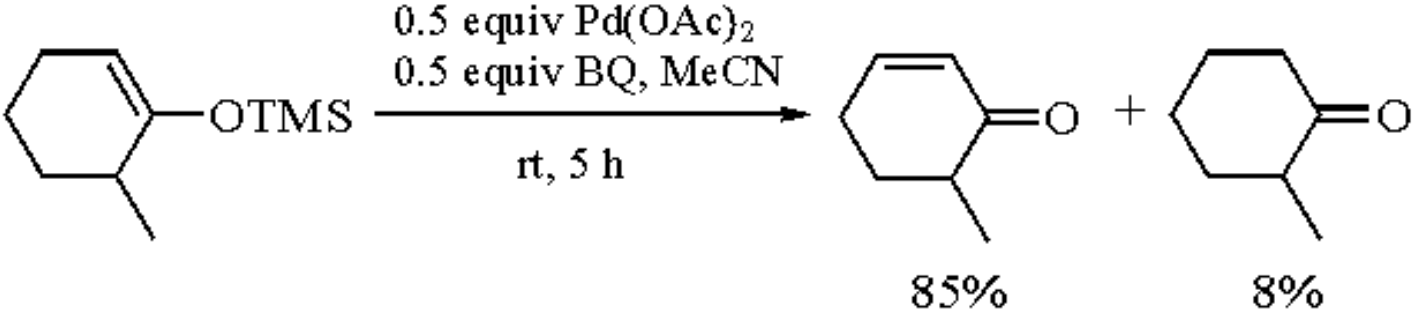

(60)

Oxidation of primary vinyl methyl ethers yields α,β-unsaturated aldehydes. The method has been applied to a transformation of saturated aldehydes to one-carbon homologated unsaturated aldehydes (eq 61) by a Wittig reaction and subsequent palladium acetate-mediated oxidation.[117] The oxidations, which were carried out in $NaHCO_3$-containing aqueous acetonitrile, yielded 50-96% of the unsaturated aldehydes.

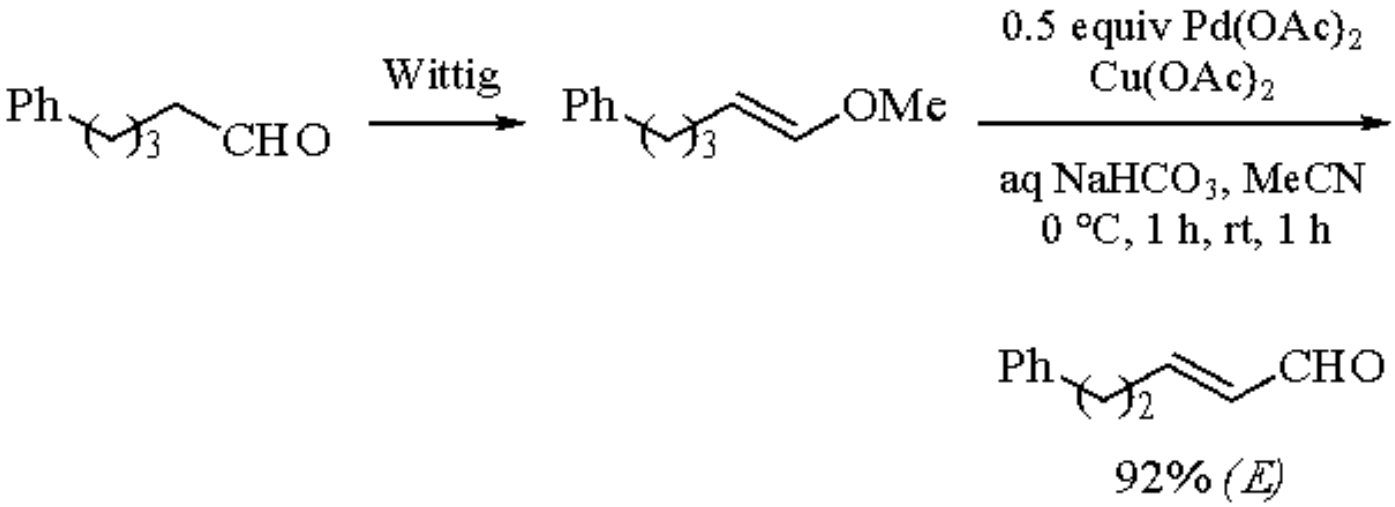

(61)

Allyl β-keto carboxylates and allyl enol carbonates undergo a palladium-catalyzed decarboxylation-dehydrogenation to yield α,β-unsaturated ketones in usually high chemical yield and with good selectivity.[118] Following this approach, it was possible to obtain 2-methyl-2-cyclopentenone in two steps from diallyl adipate in a procedure that could be convenient for large-scale preparations (eq 62).[119]

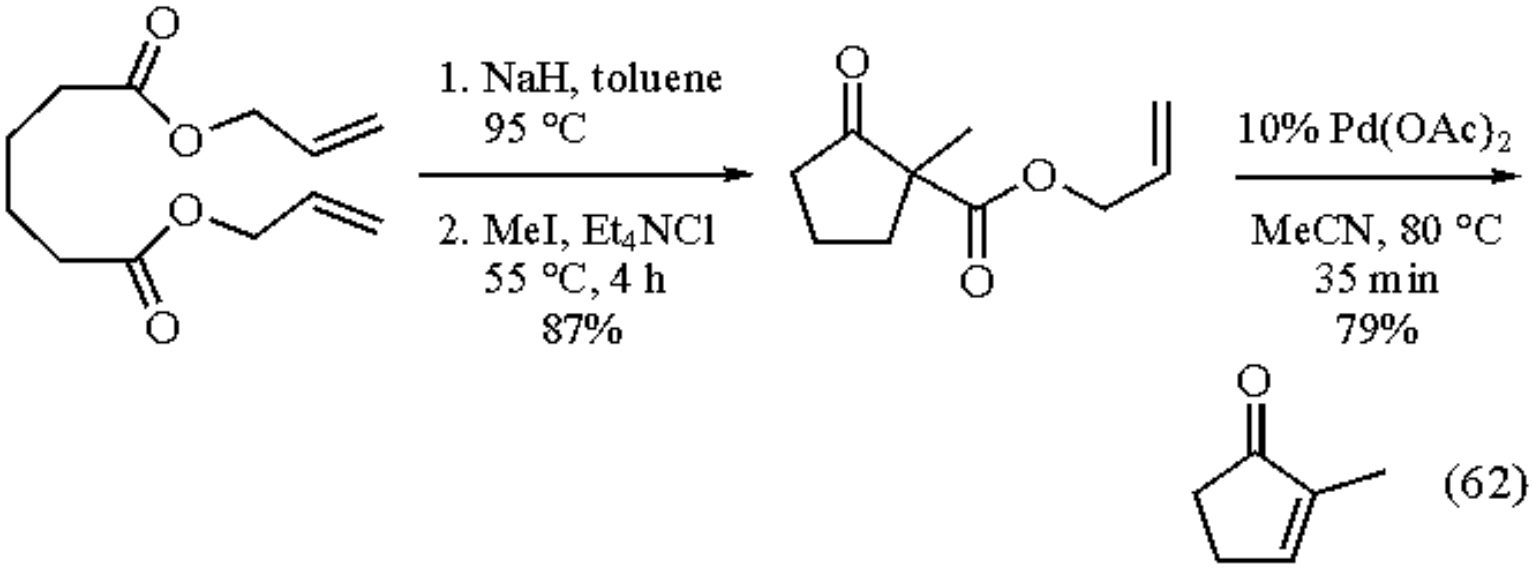

(62)

Activation of Phenyl and Benzyl C-H bonds: Oxidation of Aromatics.

If palladium diacetate is heated in an aromatic solvent, oxidation of the solvent by cleavage-substitution of a C-H bond occurs, resulting in a mixture of products.[120] Depending on the reaction conditions, biaryls and phenyl or benzyl acetates are isolated. Seemingly small changes can result in large changes in product distribution (eq 63). For example, the oxidation of toluene by a palladium(II) salt yields benzyl acetate in reactions mediated by palladium acetate, whereas bitolyls are the major products in reactions carried out in the presence of chloride ions (eq 63).[121]

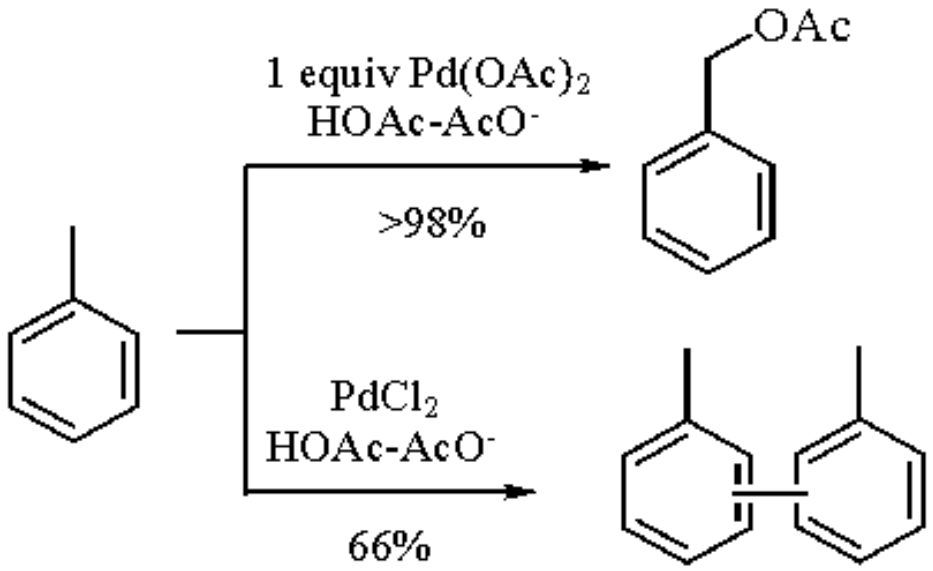

(63)

Oxygen Nucleophiles.

A reagent such as permanganate oxidizes toluene to benzoic acid,[122] whereas benzylic oxidation by palladium acetate results in benzyl alcohol derivatives. The oxidation is favored by electron-releasing substituents in the phenyl ring.[123] Catalytic amounts of palladium acetate and tin diacetate, in combination with air, effects an efficient palladium-catalyzed benzylic oxidation of toluene and xylenes. For the latter substrates, the α,α´-diacetate is the main product.[124] A mixed palladium diacetate-copper diacetate catalyst has also been found to selectively catalyze the benzylic acyloxylation of toluene (eq 64).[125]

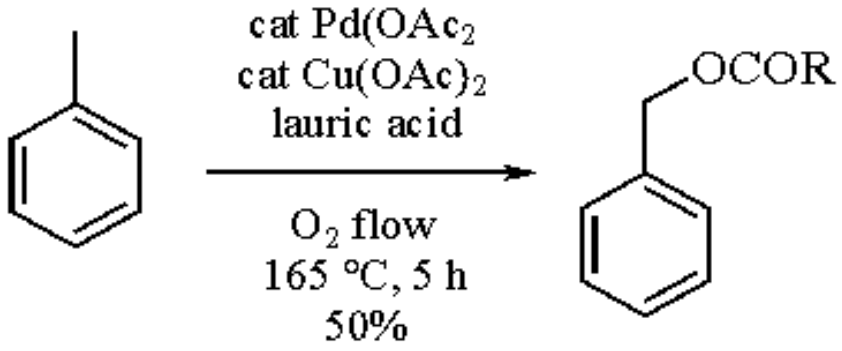

(64)

Benzene can be oxidized to phenol by molecular oxygen in the presence of catalytic amounts of palladium diacetate and 1,10-phenanthroline (eq 65).[126] If potassium peroxydisulfate is used as a stoichiometric oxidant with 2,2´-bipyridyl as a

ligand, a process yielding mainly *m*-acetoxylated aromatics results (eq 66).[127]

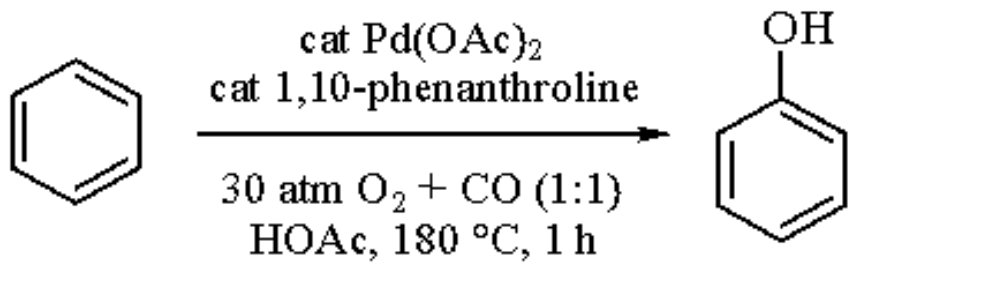

(65)

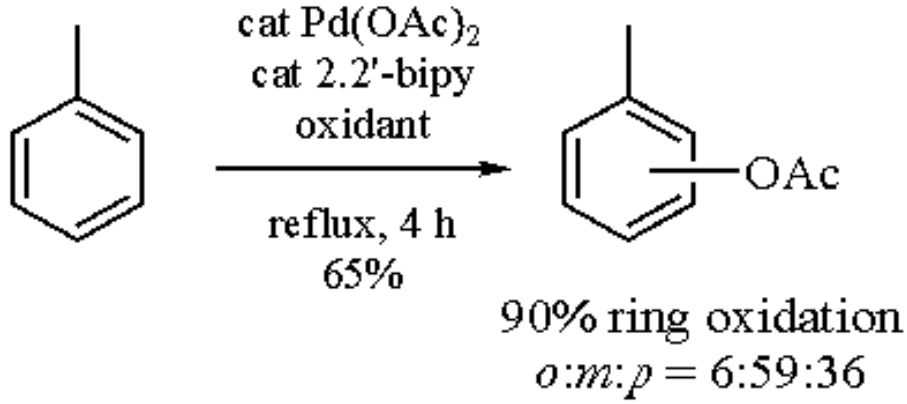

(66)

Palladium diacetate in ***Trifluoroacetic Acid*** ($Pd(O_2CCF_3)_2$) gives a mixture of *o*- and *p*-trifluoroacetoxylated products.[128] The reagent is also capable of oxidizing saturated hydrocarbons such as adamantane and methane. In the presence of carbon monoxide and with sodium acetate as co-catalyst, carbonylation of aromatic C-H bonds occurs, eventually yielding acid anhydrides.[129]

Naphthalenes and methylbenzenes can be oxidized to *p*-quinones by aqueous H_2O_2 in acetic acid catalyzed by a Pd^{II}-DOWEX polystyrene resin. Yields and selectivities are generally higher for the methylnaphthalenes (50-65% *p*-quinone) than for methylbenzenes (3-8%).[130]

Carbon Nucleophiles.

Palladium-mediated homocoupling of substituted arenes generally yields mixtures of all possible coupling products. If the reaction is carried out with a catalytic amount of palladium diacetate and with ***Thallium(III) Trifluoroacetate*** as stoichiometric oxidant (eq 67), aryls carrying substituents such as alkyl or halide afford mainly the 4,4´-biaryls in yields ranging from 60% (R = ethyl) to 98% (R = H).[131] Biaryls can also be formed without the palladium catalyst.[132]

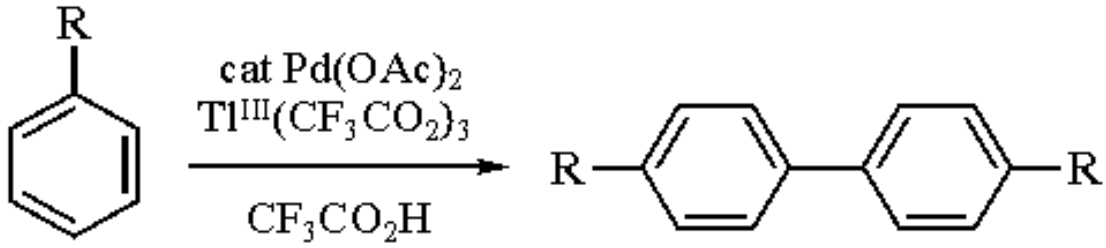

(67)

R = Me, 40 h, 95% (74% 4,4')

Oxidative substitution of aromatics with a heteroatom substituent in a benzylic position generally yields *o*-substituted products.[1b,5] The reaction probably proceeds via a cyclopalladated phenylpalladium species (eq 68), which decomposes to form substituted products. For example, the alkylation of a number of acetanilides proceeds with high selectivity for the *o*-alkylated product.[133]

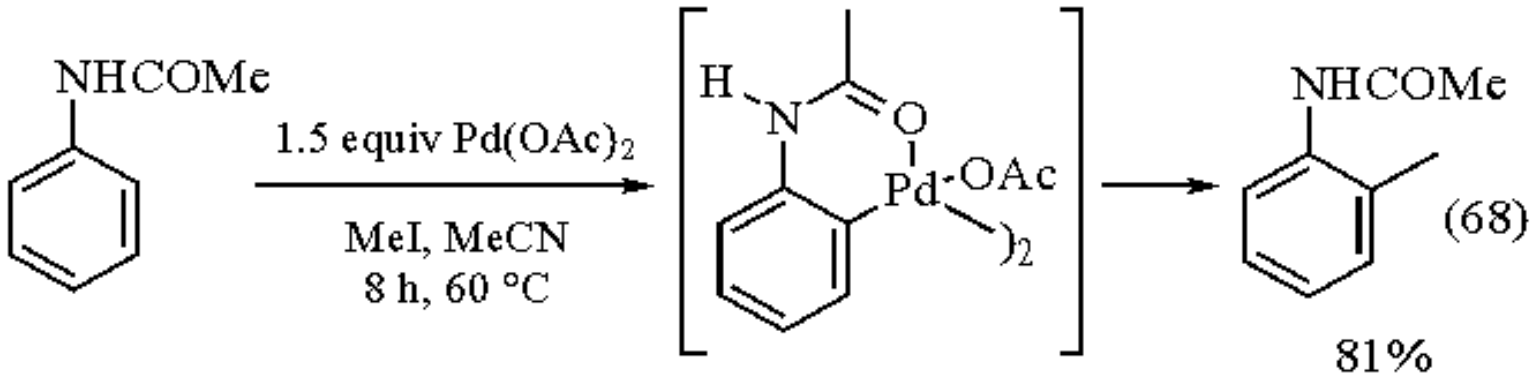

(68)

81%

With *t*-butyl perbenzoate as hydrogen acceptor, it is possible to couple benzene or furans with alkenes. In the absence of alkene, benzoxylation of the aromatic compound is observed.[134]

When heated in palladium acetate-containing acetic acid, diphenyl ether, diphenylamine, benzophenone, and benzanilide gave high yields of cyclized products (eq 69). A large number of ring substituents were tolerated in the cyclization.[135]

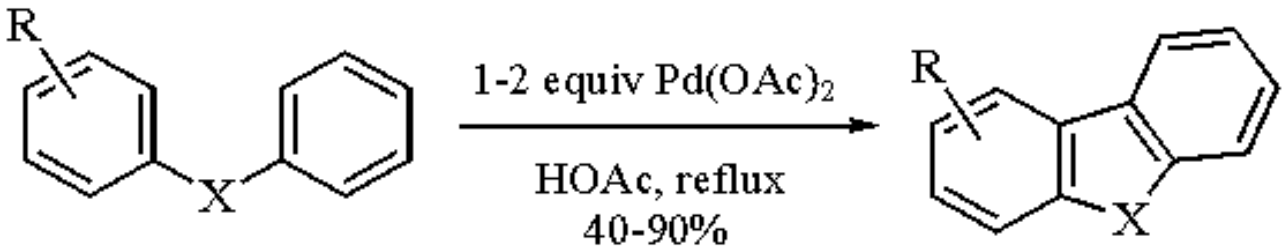

(69)

X = O, NH, CO

Oxidation of benzoquinones and naphthoquinones by palladium diacetate in arene-containing acetic acid gave the corresponding aryl-substituted quinones (eq 70).[136] Treatment of 1,4-naphthoquinone with aromatic heterocycles, for example furfural, 2-acetylfuran, 2-acetylthiophene, and 4-pyrone, yielded the corresponding 2-heteroaryl-substituted 1,4-naphthoquinones.

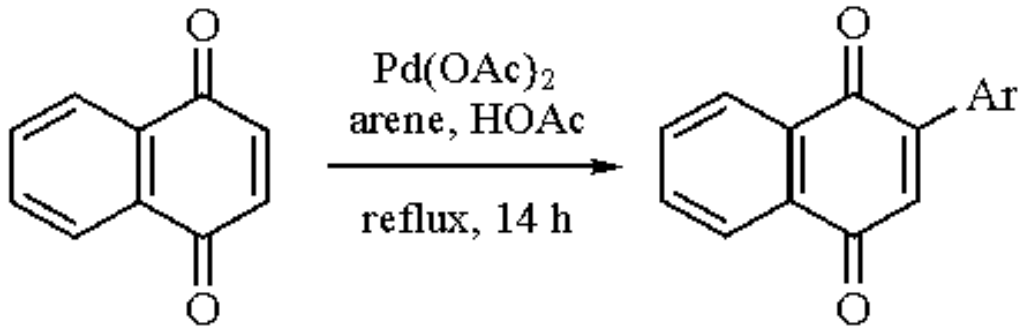

(70)

arene = C_6H_6 (85%), 2,5-$Me_2C_6H_4$ (78%), 2,5-$Cl_2C_6H_4$ (70%)

Palladium-Catalyzed Reductions.

Reduction of Alkynes.

Alkynes are selectively reduced to (*Z*)-alkenes by a reduction catalyst prepared from NaH, *t*-$C_5H_{11}OH$, and $Pd(OAc)_2$ (6:2:1) in THF. The reactions, carried out in the presence of quinoline under near atmospheric pressure of H_2, are self-terminating at the semihydrogenated stage, and are more selective than the corresponding reductions catalyzed by Lindlar's catalyst. Omitting the *t*-$C_5H_{11}OH$ gave a catalyst that effected complete reduction.[137]

Alkenyldialkylboranes from internal alkynes undergo palladium acetate-catalyzed protonolysis to yield (*Z*)-alkenes under neutral conditions and (*E*)-alkenes in the presence of Et_3N.[138]

Hydrogenolysis of Allylic Heterosubstituents.

Chemoselective removal of an allylic heterosubstituent in the presence of sensitive functional groups is a sometimes difficult transformation since nucleophilic displacement with hydride donors is efficient only if the heterosubstituent is a good leaving group or the hydride donor is powerful. However, removal of an allylic heterosubstituent is a reaction readily performed by Pd^0.[87] The resulting (π-allyl)palladium complexes are readily attacked by hydride nucleophiles (eq 71). Thus, mild hydride donors such as ***Sodium Borohydride*** or ***Sodium Cyanoborohydride*** can be employed.[139] Treatment of allylic oxygen, sulfur, and selenium functional groups with a combination of $Pd(PPh_3)_4$ and ***Lithium Triethylborohydride*** yielded the corresponding hydride-substituted compounds with good regio- and stereoselectivity, with the more highly substituted (*E*)-alkene as the predominant product (eq 71).[140] Similar results are observed for all hydride donor systems but one: that derived from formic acid yields predominantly or exclusively the less substituted alkene (eq 71).[142]

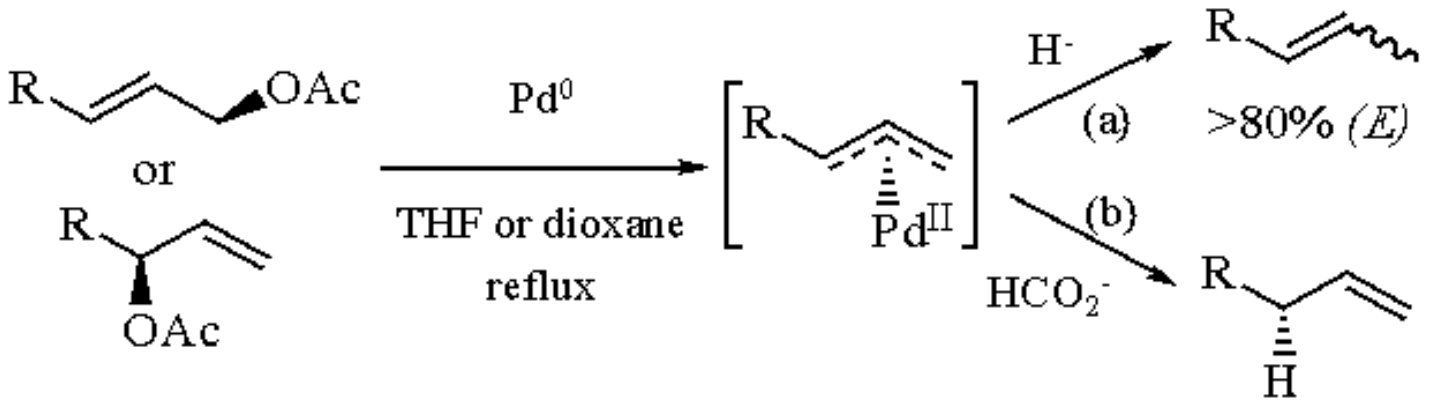

The regio- and stereoselective hydride attack on the more substituted terminus of (π-allyl)palladium complexes derived from allylic formates has been applied to the palladium acetate-*n*-Bu_3P-catalyzed formation of ring junctions in hydrindane, decalin, and steroid systems, and to stereospecific generation of steroidal side-chain epimers.[141]

Deoxygenation of Carbonyls.

Carbonyl compounds can be deoxygenated to form alkenes in a palladium-catalyzed reduction of enol triflates (eq 72). The reaction is quite general, and has been applied to aryl as well as alkyl enol triflates.[142]

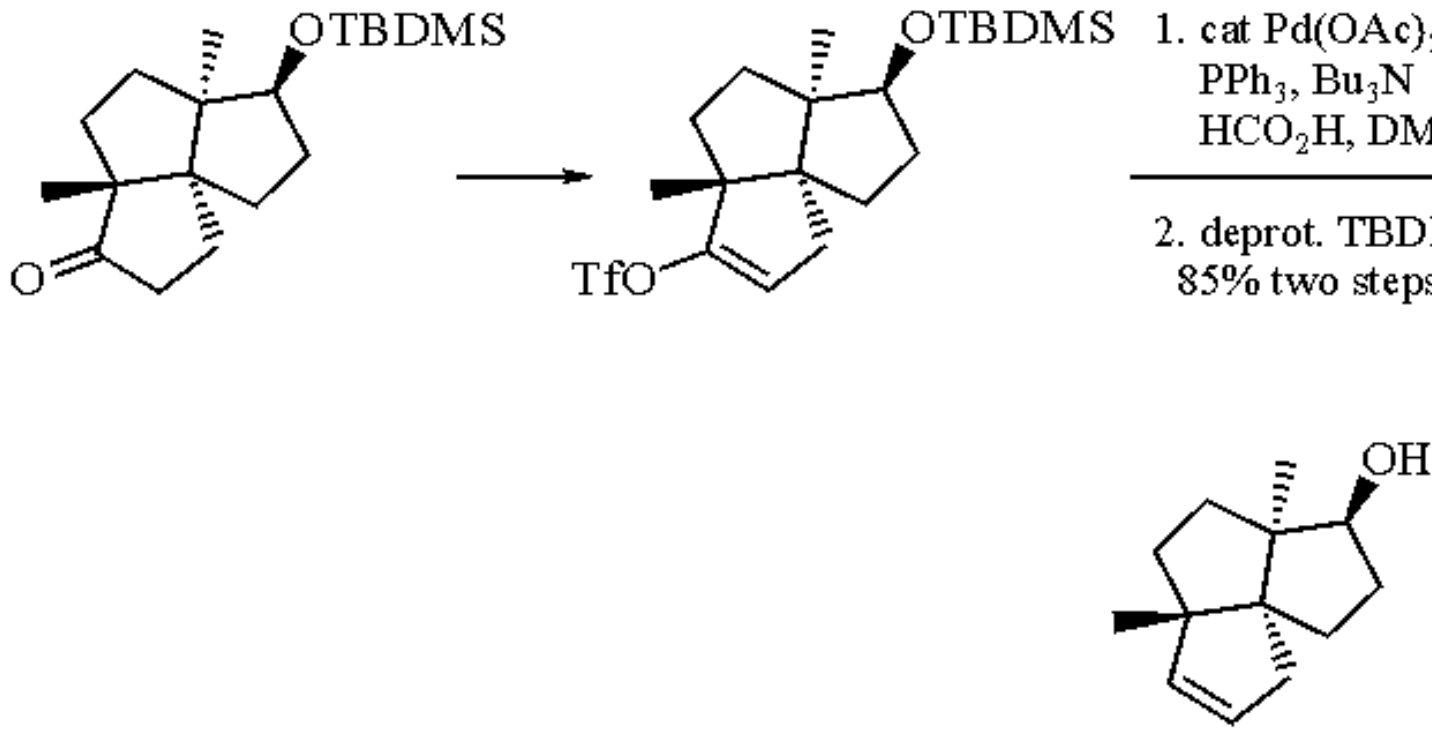

Related Reagents.

Sodium Hydride-Palladium(II) Acetate-Sodium t-Pentoxide; ***Thallium(III) Trifluoroacetate--Palladium(II) Acetate***.

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Palladium(II) Acetylacetonate

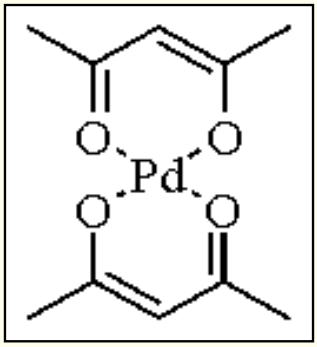

[14024-61-4] · $C_{10}H_{14}O_4Pd$ · Palladium(II) Acetylacetonate · (MW 304.66)

(occasionally used as a homogeneous Pd^{II} catalyst; used mainly as source of Pd^0 catalysts after reduction in the presence or absence of ligands)

Physical Data: mp 205 °C (dec).

Solubility: insol H_2O; slightly sol benzene, ether, ethanol; sol chloroform.

Form Supplied in: orange needle-like crystals; widely available.

Purification: recrystallization from benzene.

Generation of Carbenes from Diazo Compounds.

$Pd(acac)_2$ is used as a catalyst for carbene generation from diazo compounds. For example, treatment of the α-diazo-β-keto ester shown in eq 1 with $Pd(acac)_2$ (9 mol %) at 80 °C in benzene gave the cyclopropane derivative in 78% yield as the only isolated product.[1] This product is different from the furan derivative obtained by the catalysis of $Rh_2(OAc)_4$.

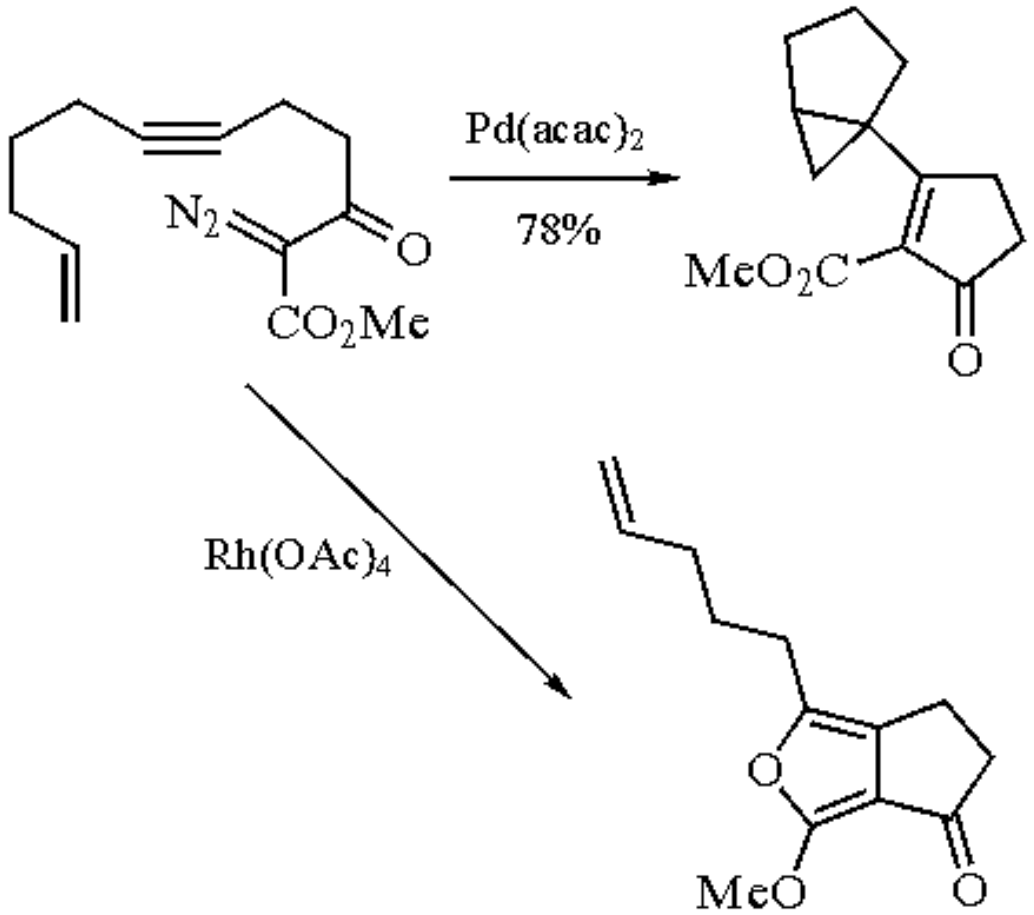

(1)

Generation of Pd^0 Species.

Many reactions are catalyzed by Pd^0 catalysts.[2] The Pd^0 complexes ***Tetrakis(triphenylphosphine)palladium(0)*** and ***Bis(dibenzylideneacetone)palladium(0)*** are commercially available. More conveniently, Pd^{II} salts are reduced in situ to Pd^0. For this purpose, ***Palladium(II) Acetate*** is most widely used, but $Pd(acac)_2$ is sometimes preferable because it can be easily obtained in better quality by recrystallization. $Pd(acac)_2$ is reduced in situ in the presence or absence of a ligand (L) to form Pd^0L_n complexes, which can be used as catalysts. Various reducing agents such as metal hydrides ($NaBH_4$, $LiAlH_4$, *i*-Bu_2AlH), RLi, RMgX, CO, alkenes, and phosphines are used. In the most convenient method of reduction, $Pd(acac)_2$ is treated with ***Tri-n-butylphosphine*** in THF (eq 2). The solution turns quickly to pale yellow, and a very active Pd^0 catalyst is generated.[3] Reactions catalyzed by Pd^0 in the presence, or absence, of a phosphine ligand are shown below.

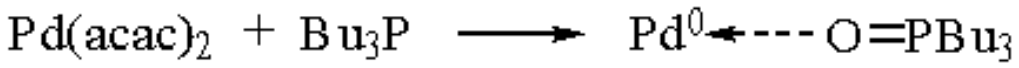

(2)

Hydrogenolysis of Allylic Formates and Carbonates.

The catalyst shown in eq 2 has been used for the regioselective and stereoselective generation of either C-20 epimer in steroid side chains by the Pd^0-catalyzed hydrogenolysis of C-20 allylic carbonates.[4] The unnatural stereochemistry at C-20 was generated from the *trans*-allylic carbonate (eq 3), and the natural stereochemistry was generated by the hydrogenolysis of the *cis*-allylic carbonate (eq 4). Commonly used $Pd(Ph_3P)_4$ or $Pd_2(dba)_3$ were inactive. This method

of the palladium-catalyzed hydrogenolysis has been applied to the regioselective and stereoselective generation of *cis*- and *trans*-fused decalins and hydrindanes.[5]

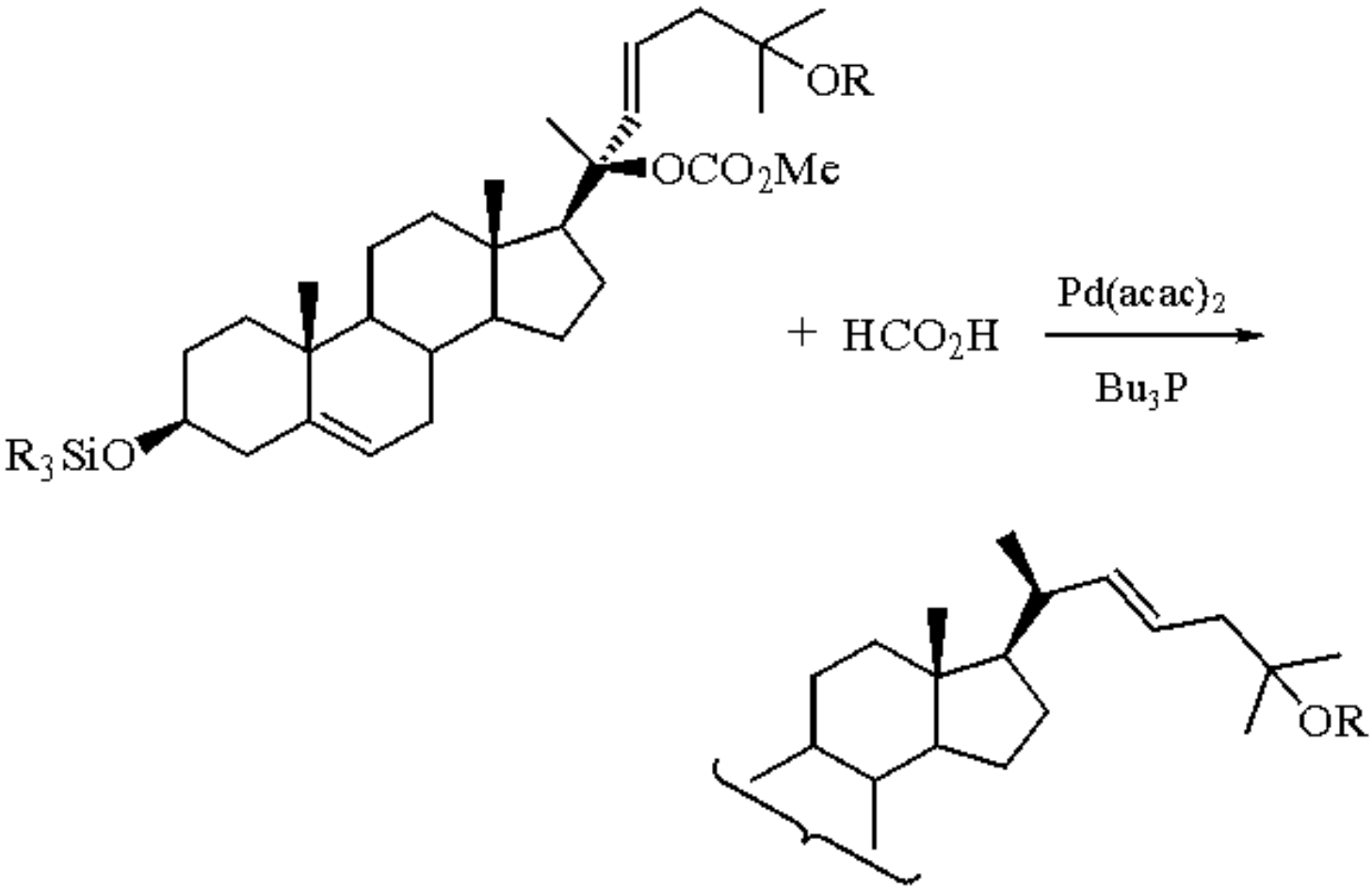

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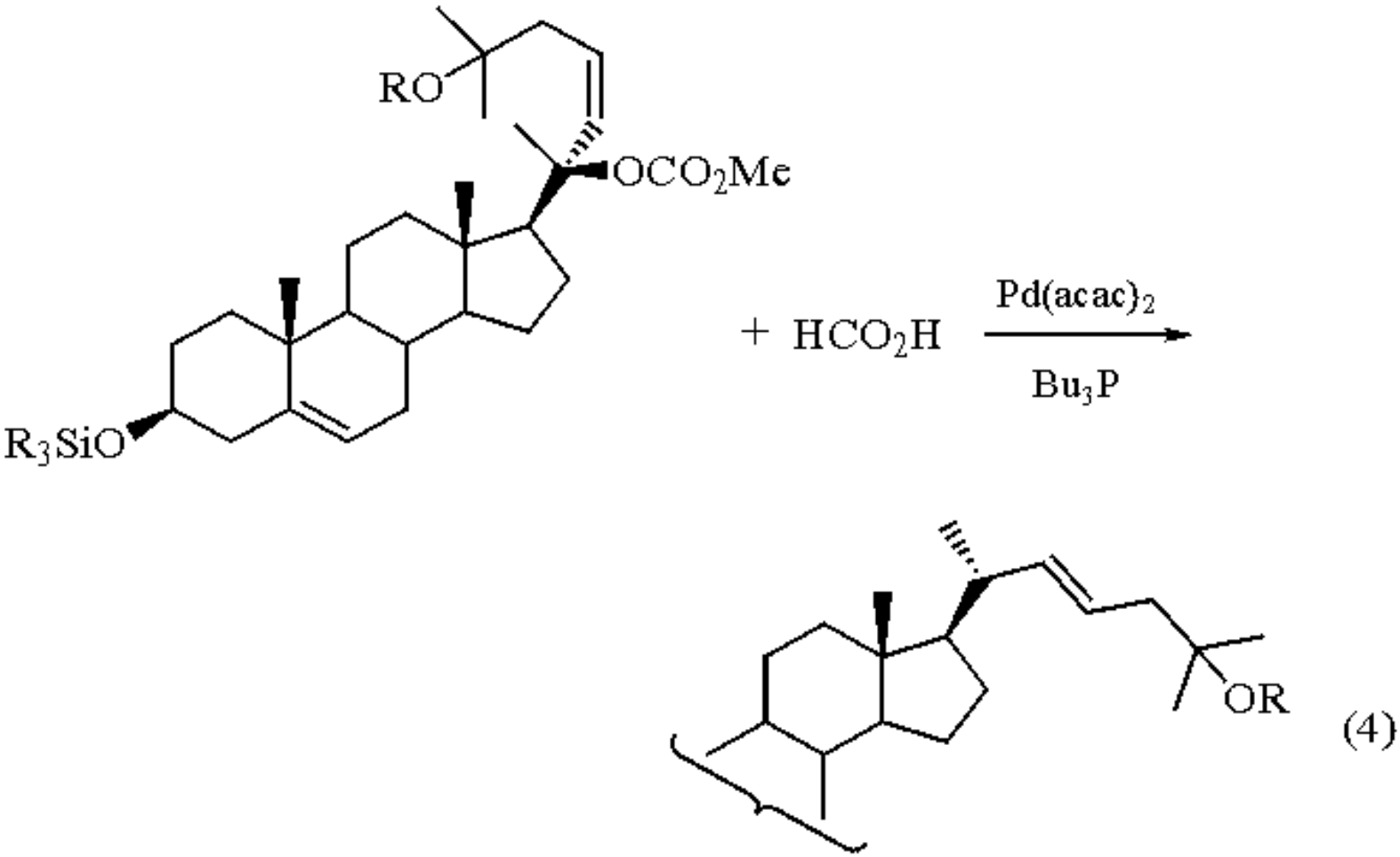

Displacement Reactions of Vinyl Sulfones.

Pd^0 species generated from $Pd(acac)_2$ and a Grignard reagent catalyze the reaction of vinyl sulfones with Grignard reagents. Displacement takes place with ***Methylmagnesium Bromide*** and hydrogenolysis takes place with ***Ethylmagnesium Bromide*** (eq 5).[6,7]

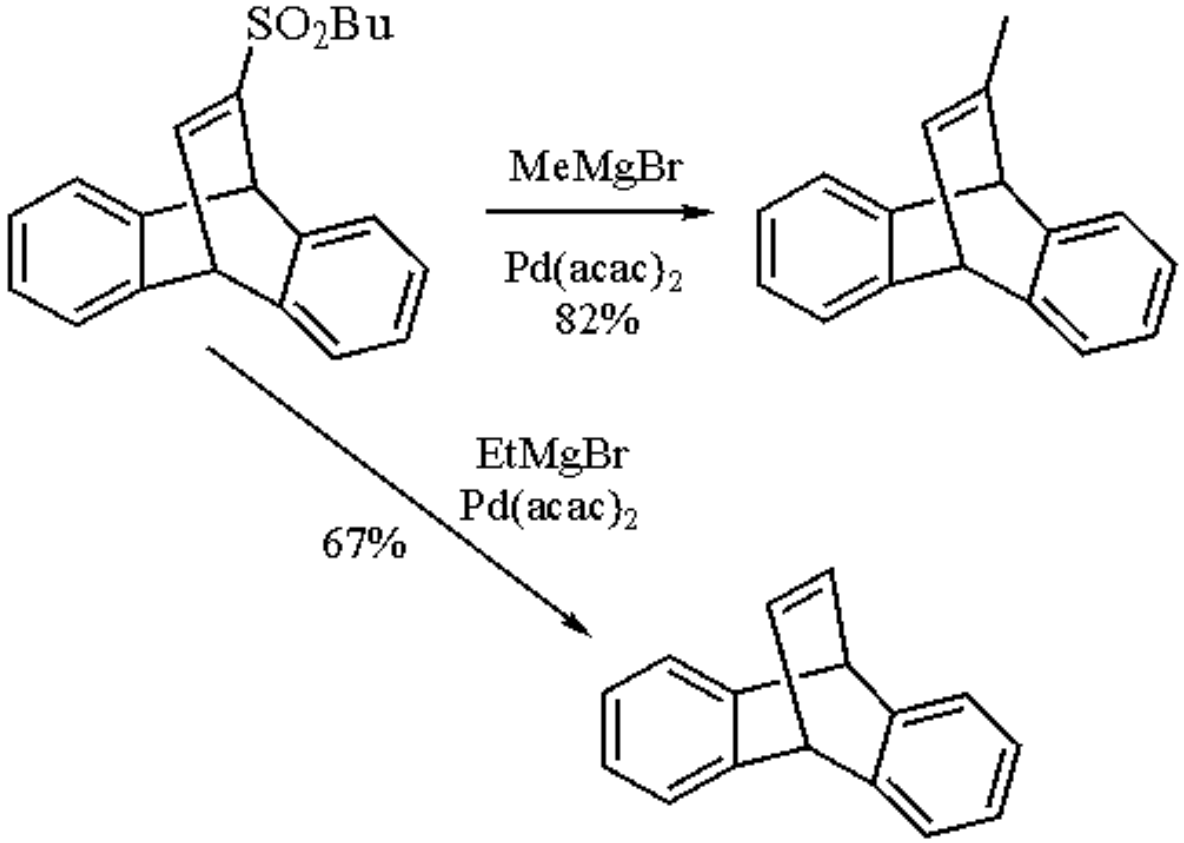

(5)

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Palladium on Barium Sulfate[1]

$Pd/BaSO_4$

[7440-05-3] · Pd · Palladium on Barium Sulfate · (MW 106.42)

(usually supported on $BaSO_4$, or an appropriate form of carbon, when used to catalyze the hydrogenation of acyl chlorides to aldehydes, the Rosenmund reduction;[2] useful catalyst for many other hydrogenations[1b-e])

Alternate Name: Rosenmund catalyst.

Form Supplied in: Pd-on-$BaSO_4$ and Pd-on-C are available commercially or may be prepared.[3]

Handling, Storage, and Precautions: the catalysts may be stored indefinitely in well-sealed containers.[1e] Although the unused catalysts can be exposed to a clean atmosphere, they may ignite organic solvent vapors; heating a Pd-on-C catalyst in a vacuum drying oven at 115 °C for more than 48 h causes it to become extremely pyrophoric.[4] After use, all catalysts are liable to contain adsorbed hydrogen and may ignite when dried. The filtered catalyst should be kept wet and away from combustible vapors or solvents.

Traditional Rosenmund Procedures.

The palladium-catalyzed hydrogenation of an acid chloride to an aldehyde is known as the Rosenmund reduction (eq 1). In the original procedure, hydrogen is bubbled through a heated suspension of the catalyst, $Pd/BaSO_4$, in a xylene or toluene solution of the acyl chloride.[2] The HCl formed is absorbed in water and titrated to monitor the reaction's progress. Although the procedure works well for many acyl chlorides, for others the further reduction of the aldehyde to the alcohol, and the consequential formation of esters, ethers, and hydrocarbons, seriously lowers the yield of the aldehyde.[1] In initial experiments, it was reported that benzoyl chloride was converted almost completely to benzaldehyde; however, repetition of the same experiment, but with all reactants carefully purified, gave none.[5] Seeking possible catalyst modifiers or regulators, it was found that quinoline-sulfur, a crude preparation of thioquinanthrene, was most suitable.[5,6] Other regulators which have been recommended are pure thioquinanthrene, thiourea, and tetramethylthiourea.[5,7] The purity of the solvent, which is used in much larger amounts than any of the reactants or the catalyst, is a key to reproducible reductions.[8,9] Attaining the lowest temperature at which HCl is evolved was reported to optimize the yield of aldehyde.[1a]

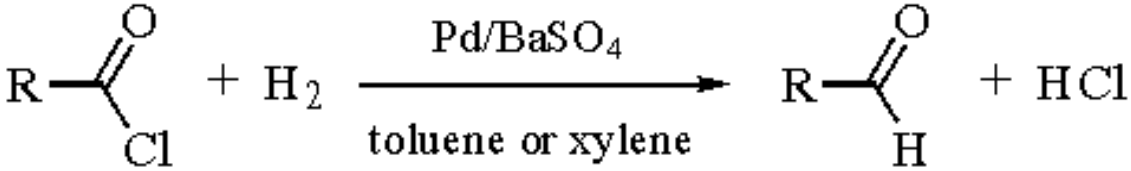

(1)

In a 1948 review, it is claimed that For accomplishing this transformation, RCO_2H -> RCHO, the Rosenmund reduction is probably the most useful method for application to a large number of aldehydes of varied types.[1a] This critical review describes the scope and limitations of the reaction, the experimental conditions, reagents, and procedures and includes tables recording the acid chlorides whose reduction by the Rosenmund method had been reported to November 1947.

Rosenmund described a simple apparatus for performing the reduction.[5] A detailed description of a more elaborate apparatus and procedure used for the hydrogenolysis of β-naphthoyl chloride (0.30 mol) in xylene catalyzed by 5% $Pd/BaSO_4$ and regulated by quinoline-sulfur was given by Hershberg and Cason (eq 2).[10] They recommended that a poison always be added to ensure controlled conditions. The hydrogenolysis of mesitoyl chloride in xylene over unpoisoned $Pd/BaSO_4$ is described in the same volume; vigorous stirring shortens the reaction time by about one third.[11]

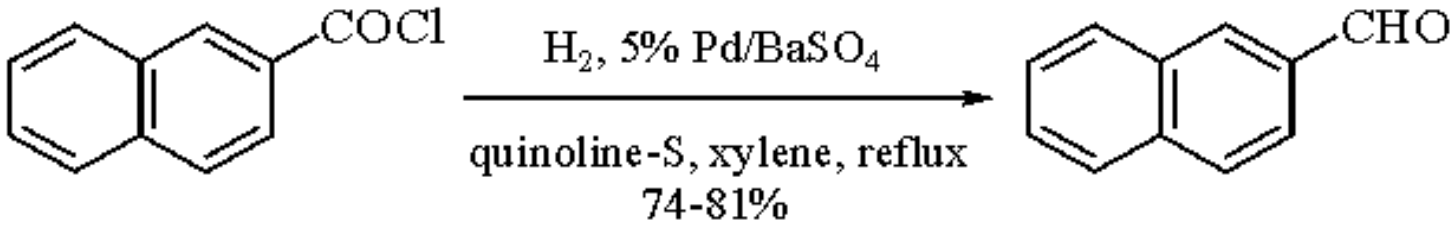

(2)

The omission of catalyst poisons is common and the original Rosenmund procedure[2] has been successful with acid halides containing other functional groups, or condensed benzenoid or heterocyclic systems.[1a] For example, discouraged by attempts to obtain high yields with a variety of metal hydride reducing reagents, Danishefsky et al. found that the original Rosenmund procedure converts the acid chloride (eq 3) in an essentially quantitative yield.[12] The reduction of the related compound with a methyl group proximate to the C(O)Cl group gave only a 49% yield of the aldehyde (eq 4) (however, see below).

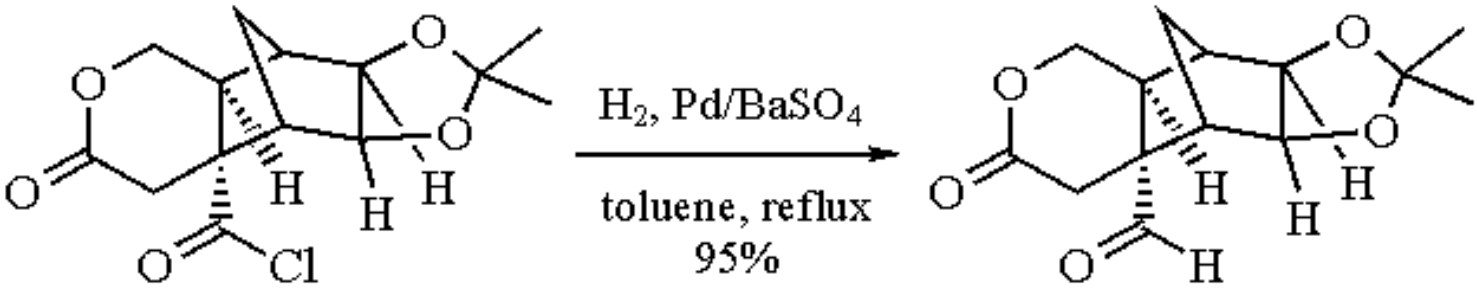

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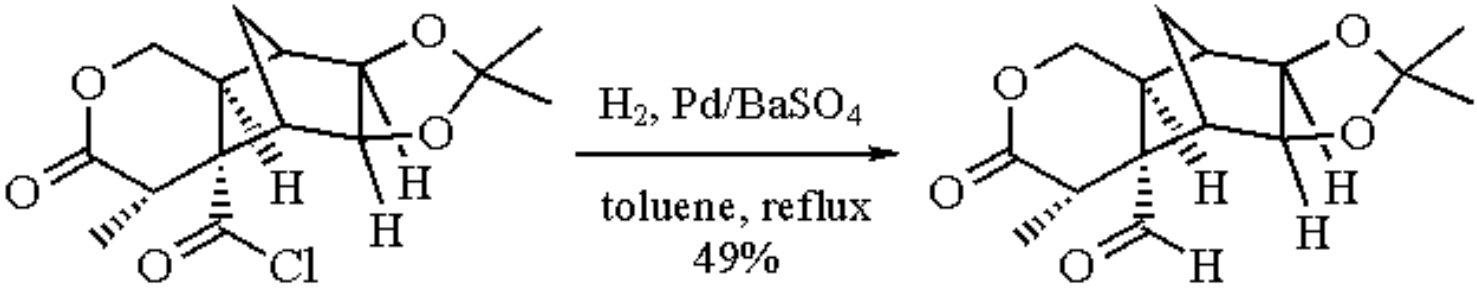

(4)

A procedure for the unpoisoned 10% ***Palladium on Carbon*** catalyzed hydrogenation of α-phthalimido acid chlorides to the aldehydes in benzene at 40 °C has been described.[13] To cause the benzene to reflux at 40 °C, the pressure is lowered with a vacuum pump which is attached to the outlet in a manner which allows the collection and titration of the evolved HCl. This procedure was suited particularly for the preparation of the phthaloyl methionine aldehyde (eq 5) but the (±)-phenylalanine and (±)-alanine derivatives gave yields of 93% and 94% respectively with benzene refluxing at 1 atm. An almost identical low temperature (reduced pressure) procedure was used to hydrogenate a diacid chloride to the dialdehyde in 92-94% yield (eq 6).[14]

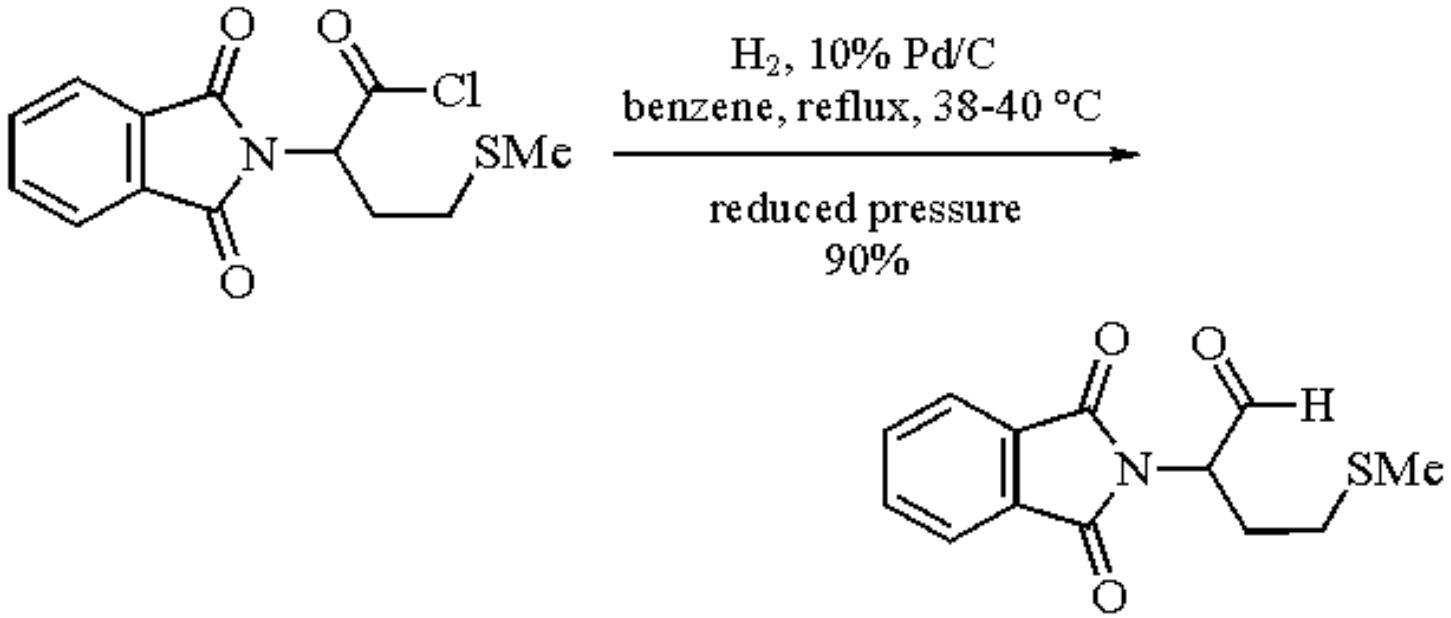

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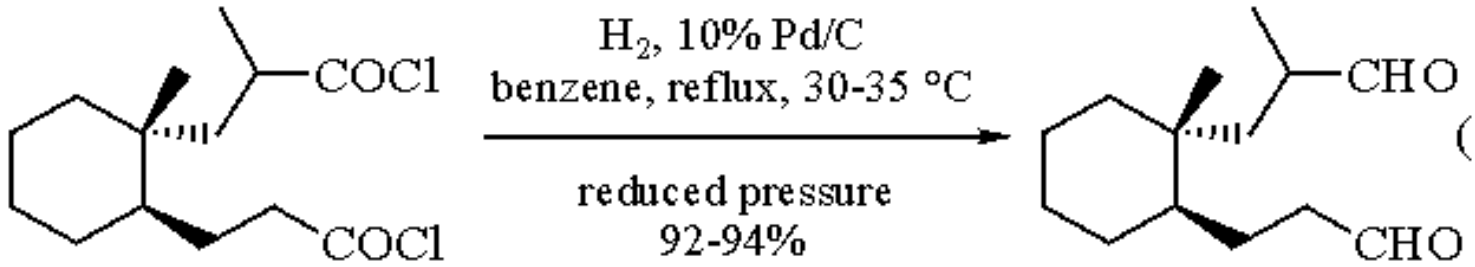

(6)

Rosenmund Reductions within Closed Systems.

To avoid the higher temperature and the hazard of free flowing hydrogen of the classical Rosenmund procedure, particularly for large scale preparations, an autoclave can be used for the Pd/C catalyzed hydrogenolysis of 3,4,5-trimethoxybenzoyl chloride to the aldehyde (yield, 64-83%); the reduction was done at 35-40 °C and H_2 (4 atm) in

toluene containing quinoline-S with anhydrous sodium acetate as HCl adsorber (eq 7).[4,15] The same reaction has been achieved repeatedly in 80-90% yields by the Rosenmund procedure without added regulators and either Pd/$BaSO_4$ or Pd/C catalysts and either xylene or PhOMe as solvent.[1a]

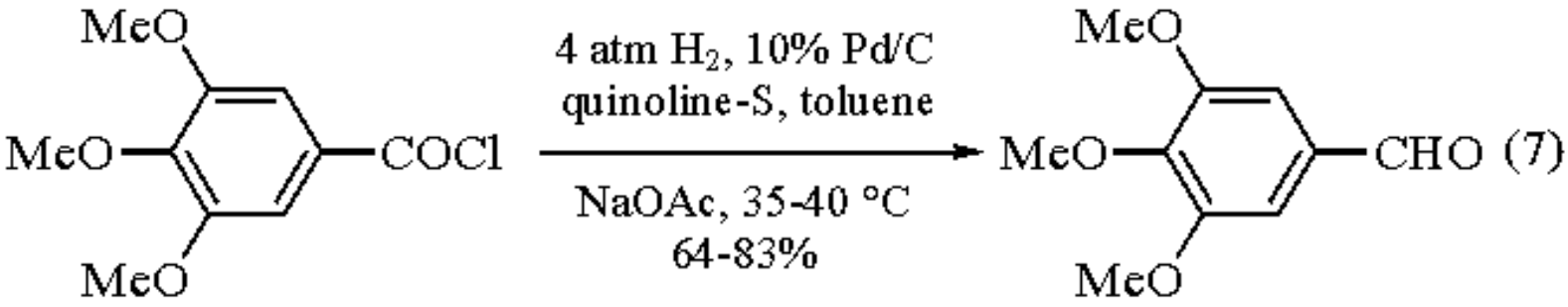

Sakurai and Tanabe were the first to report the use of a closed system for the Pd/$BaSO_4$ catalyzed hydrogenolysis of an acyl halide.[16] The reduction (H_2, 1 atm) was conducted at rt in the presence of a hydrogen chloride acceptor, *N*,*N*-dimethylaniline, and acetone as solvent. *N*-Phthaloyl derivatives of (±)-α-amino acid chlorides have been hydrogenated to the aldehydes using 10% Pd/C in the solvent ethyl acetate (H_2, 3 atm) in the presence of dimethylaniline, with yields of over 90%.[13]

The Sakurai and Tanabe procedure (5% Pd/$BaSO_4$) gave high yields of arachidaldehyde (72%) and stearaldehyde (96%); for convenience, *N*,*N*-dimethylacetamide was used as the acid acceptor to obtain excellent yields of palmitaldehyde (96%) and decanaldehyde (96%).[17] Peters and van Bekkum chose ethyldiisopropylamine as HCl acceptor due to the competitive reduction of *N*,*N*-dimethylaniline, which obscured the end-point (vol H_2) of the hydrogenolysis of the acid chloride.[18] The mild conditions converted the sterically hindered carbonyl chloride function in 1-*t*-butylcyclohexanecarbonyl chloride to the aldehyde (78%), although *t*-butylcyclohexane was the sole product of the original Rosenmund procedure (eq 8). Burgstahler and Weigel also modified the Sakurai and Tanabe procedure by using 2,6-dimethylpyridine in place of *N*,*N*-dimethylaniline and THF as solvent with either Pd/$BaSO_4$ or Pd/C as catalyst to obtain excellent yields of 15 sensitive aliphatic and alicyclic aldehydes such as hexanedial (74%) and (*Z*)-9-octadecenal (96%) (eq 9).[19] The reaction temperature was lowered to 0 °C to convert dehydroabietic acid chloride to the aldehyde (92%) (eq 10).[19]

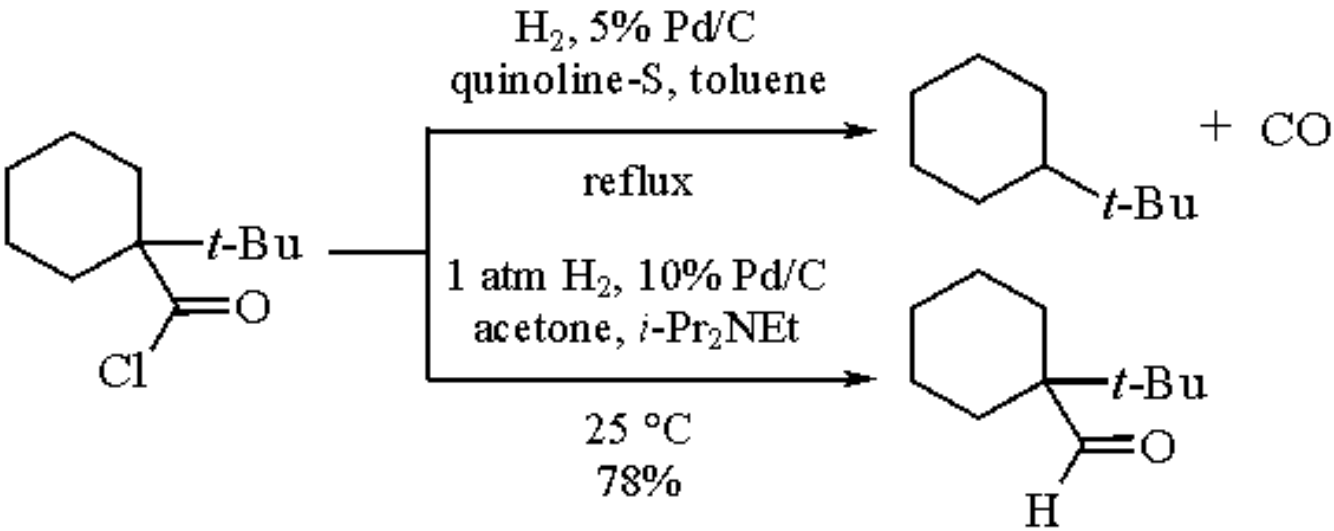

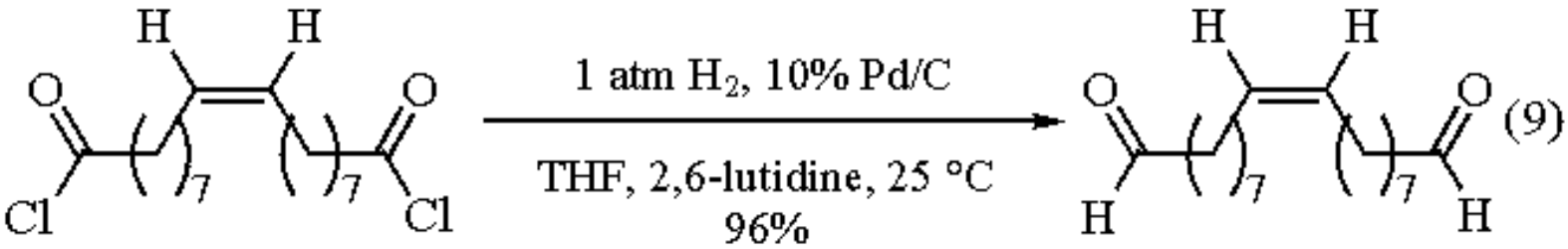

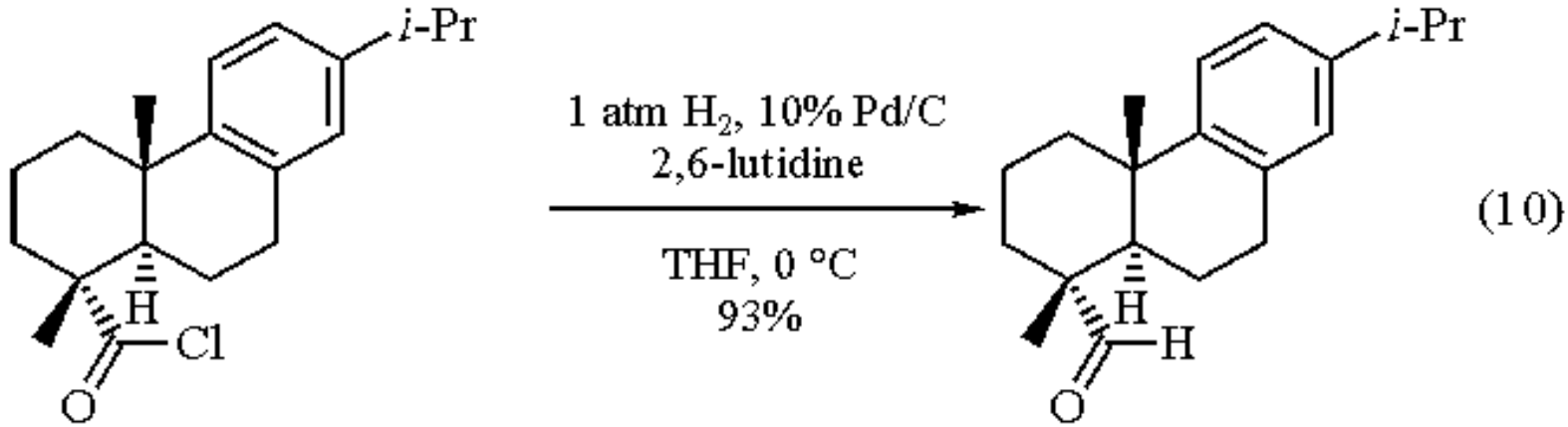

Both aliphatic and aromatic acid chlorides are reduced smoothly at room temperature and atmospheric pressure to aldehydes with 10% Pd/C as catalyst, acetone or ethyl acetate as solvent, and ethyldiisopropylamine as HCl acceptor.[20] The reaction proceeds with high selectivity; over reduction is less than 1%, and nitro and chloro substituents in benzoyl chlorides are unaffected, as is the double bond in cinnamoyl chloride.

Recent Practice.

Some more recent examples show that both the older and the newer procedures are used successfully. As an important step in the preparation of 10-nor-*cis*-α-irone, the classical Rosenmund reduction (H_2, 5% Pd/$BaSO_4$, toluene/reflux) converted the acid chloride (**1**) to the product aldehyde in 93% yield (eq 11).[21]

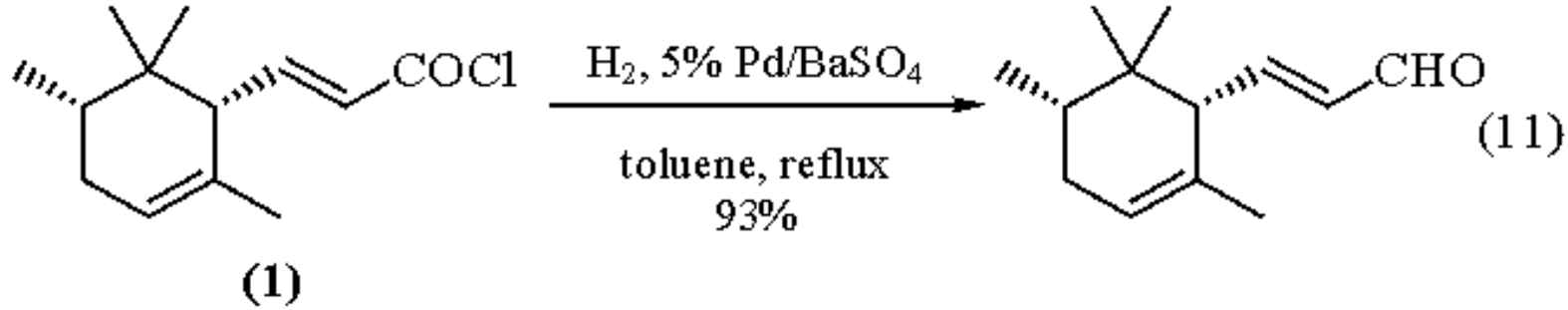

The semialdehyde derivatives of aspartic and glutamic acids have been obtained in good yields and in higher purity than by hydride reductions; acid-sensitive protecting groups are unaffected.[22] The acid chlorides (**2**) and (**3**) (benzyloxycarbonyl (*Z*) derivatives) were converted to the aldehydes using an unpoisoned catalyst (5% Pd/$BaSO_4$, boiling toluene, H_2) (eq 12). The same procedure was used to reduce the acid chloride (**4**), derived from L-alanine, to the aldehyde in 93% yield (eq 13).[23]

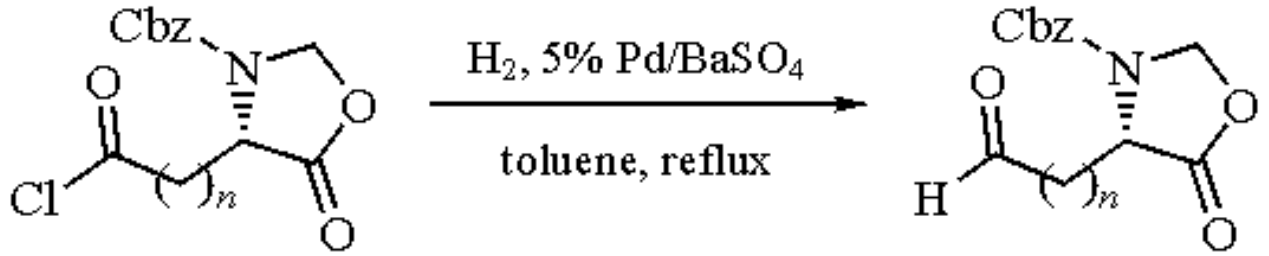

(12)

(2) $n = 1$
(3) $n = 2$

$n = 1$, 87%
$n = 2$, 82%

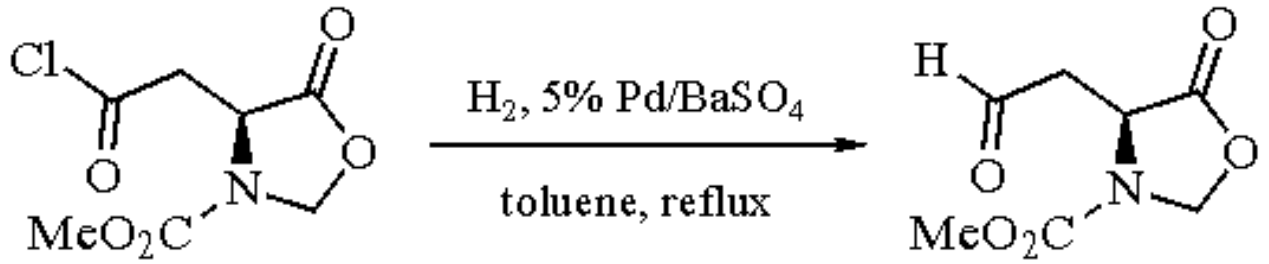

(13)

(4)

To protect the acid labile *t*-butoxycarbonyl protecting group in acid chloride (**5**), the Burgstahler procedure (H_2, 5% Pd/C, 2,6-lutidine, THF, 10-15 °C) converted (**5**) to the aldehyde (eq 14).[19,22]

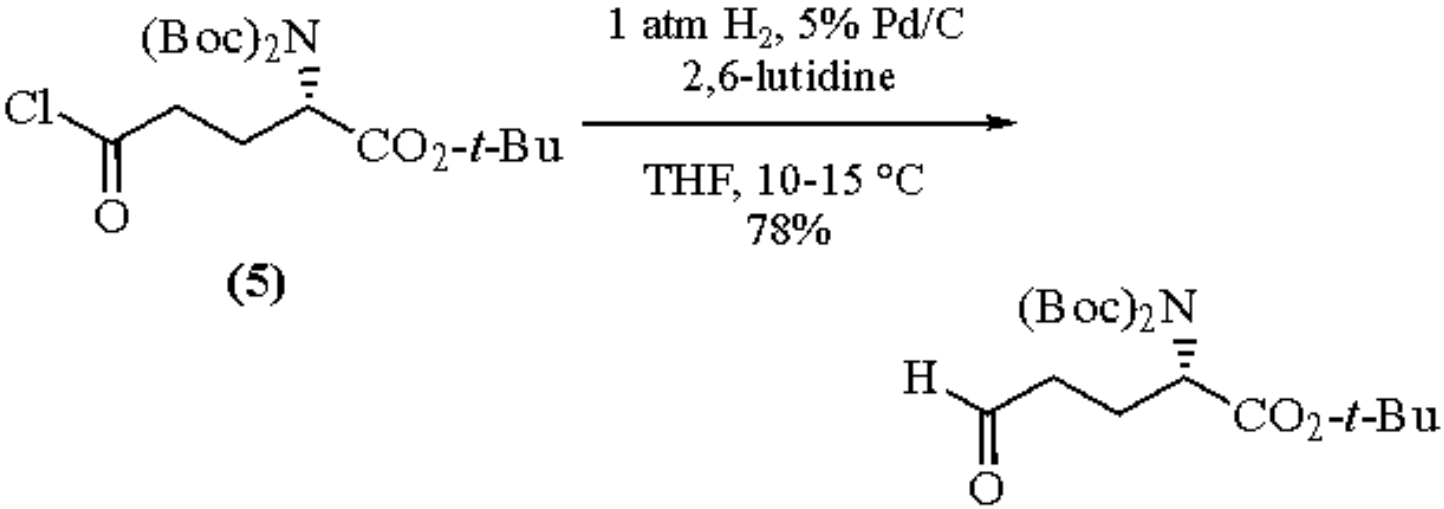

(5)

(14)

The quinoline-sulfur system was used to prepare methyl 4-oxobutanoate from 3-methoxycarbonyl chloride as the first of a three-step synthesis of a series of 5-vinyl γ-lactones.[10,24]

Kinetics and Mechanism of the Rosenmund Reaction.

The kinetics of the amine-modified Rosenmund reduction has been examined in detail.[20] In the absence of the tertiary amine, the hydrogenolysis of 4-*t*-butylbenzoyl chloride proceeds beyond the aldehyde stage to a complex mixture with bis(4-*t*-butylbenzyl) ether as the main product. In the presence of the efficient HCl acceptor zeolite NaA, most of the side reactions (acid catalyzed) are suppressed, but reduction proceeds to 4-*t*-butylbenzyl alcohol. In the presence of the

tertiary amine, the aldehyde is the sole product. However, benzaldehydes subjected to the conditions of the amine-modified reduction are hydrogenated to the alcohols, but more slowly than in the absence of the amine and substantially slower on a catalyst which has been used previously in a hydrogenation of an acid chloride. The nature of the deactivation is a subject of speculation.[20,25]

The tertiary amine not only neutralizes HCl, but also acts as a nucleophile which serves to moderate the reaction and enhance the selectivity by competing with both the acid chloride and the product aldehyde for active sites on the catalyst. A useful analogy is the effect of tertiary amines upon increasing the selectivity of the hydrogenation of alkynes to alkenes on palladium catalysts.[1b,26,27] The solvent also may compete for active sites; for example, the rate constants for the Pd-catalyzed hydrogenation of cyclohexene, corrected for the difference in the solubility of H_2 in the solvents, are smaller in benzene and smaller still in xylene, both commonly used in the Rosenmund reduction, than in saturated hydrocarbons.[28] The presence of nucleophilic groups elsewhere in the acid chloride may also act to moderate the reduction and affect selectivity in the absence of an added catalyst poison.

Aliphatic acid chlorides generally are more easily hydrogenolyzed than are aromatic ones; however, the Peters and van Bekkum paper contains the most direct comparison of relative reactivities for some representative carbonyl chlorides (15 compounds including 10 aromatic).[20] For benzoyl chlorides, electron-donating substituents increase the reaction rate while electron-withdrawing substituents have a retarding effect. The rates of hydrogenation of aroyl chlorides generally are faster in the solvents ethyl acetate or THF than in acetone.

The mechanism of the Rosenmund reduction has been discussed in relation to the characteristic reactions of transition metal complexes.[29] It has been proposed that the acid chloride adds oxidatively to the palladium metal, forming a complex which gives rise to the observed products which depend upon the reaction conditions, e.g. temperature, H_2 pressure, and solvent. Some dissolution of the palladium when heated with an acid chloride at about 100 °C was observed. However, exposing single crystals of palladium to heptanoyl chloride in pentane and H_2 at room temperature for 52 h did not change the (755) crystal surface which had catalyzed the formation of the aldehyde.[25] A means of representing catalytic processes on such crystal surfaces by analogy with the reactions of transition metal complexes has been given for catalytic hydrogenation.[26]

Other Hydrogenations.[1b-e]

$Pd/BaSO_4$ has also been used in the conversion of alkynes to *cis*-alkenes.[30] In some cases, where results of the reduction of alkynes to *cis*-alkenes with Lindlar catalysts (see ***Palladium on Calcium Carbonate (Lead Poisoned)***) are unsatisfactory, the use of $Pd/BaSO_4$ as the catalyst has been effective (eqs 15 and 16).[31]

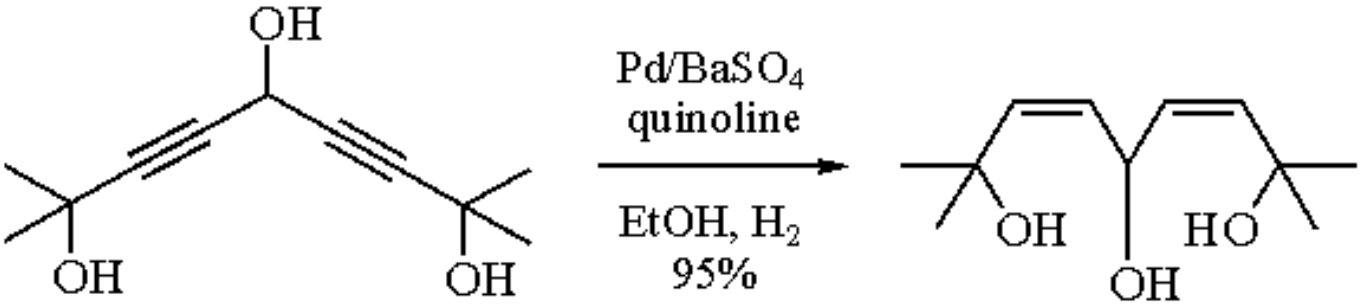

(15)

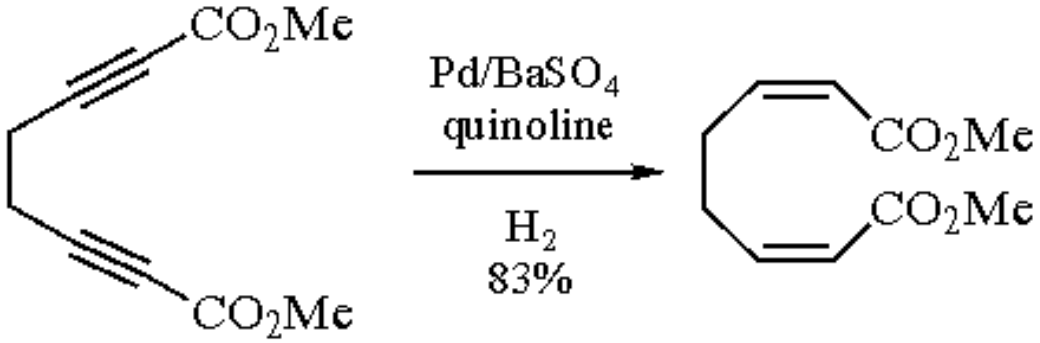

(16)

The reverse has also been observed.[32] Interestingly, the saturation of the trisubstituted alkene in humulinic acid B has also been reported with this catalyst.[33]

Hydrogenolysis of various functional groups has also been reported with Pd/$BaSO_4$. For example, the conversion of vinyl epoxides to homoallylic alcohols,[34] α-bromo-β-mesyluridines to hydrocarbons (eq 17),[35] *N*,*N*-dibenzylamino acids to *N*-benzylamino acids,[36] and the enantioselective mono-dehydrohalogenation of α,α-dichlorobenzazepin-2-one[37] have all been reported.

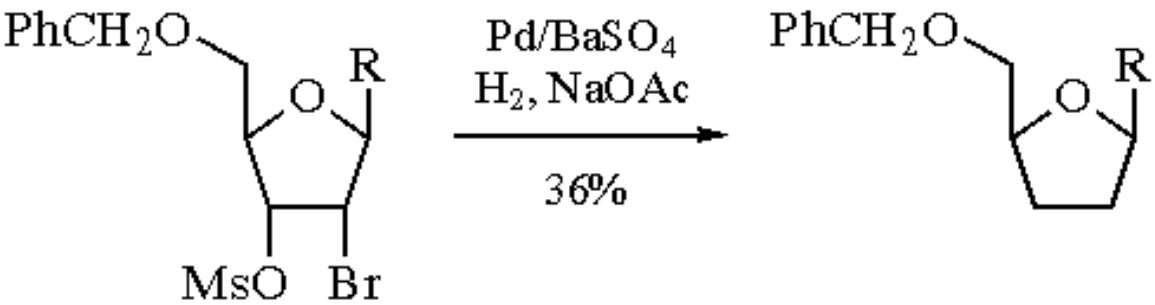

(17)

The maximum % ee observed for α-chlorobenzazepin-2-one was 50%, but surprisingly the method was not effective for other substrates, including α,α-dibromobenzazepin-2-one. Eq 17 also shows the C-O bond of a benzyl ether was not cleaved while the C-O bond of a mesylate and a C-Br bond were both hydrogenolyzed.

Regioselective opening of a 1,2-disubstituted epoxide was observed with this catalyst (eq 18).[38] The benzylic ketone was not reduced or hydrogenolyzed under the reaction conditions.

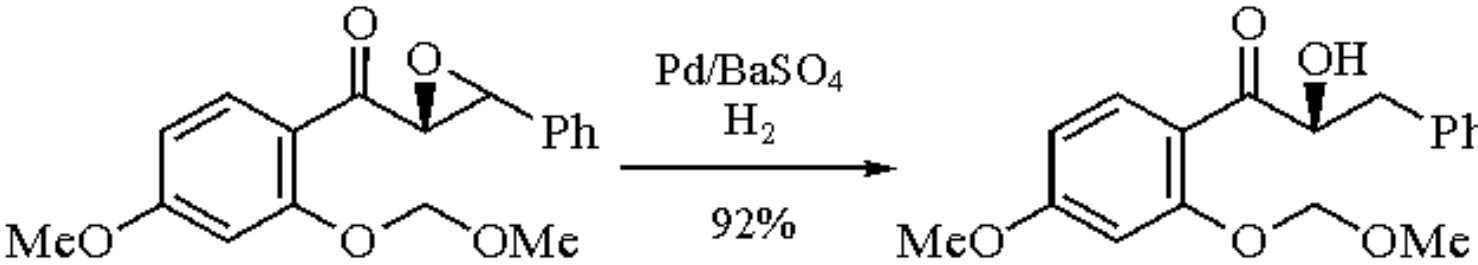

(18)

Related Reagents.

Palladium on Carbon; ***Palladium-Graphite***; ***Palladium on Poly(ethylenimine)***.

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Palladium *t*-Butyl Peroxide Trifluoroacetate

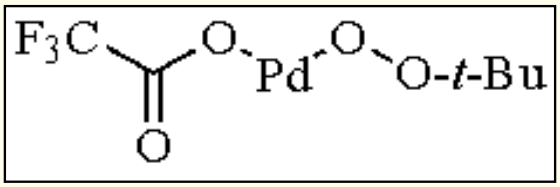

[75123-99-8] · $C_6H_9F_3O_4Pd$ · Palladium *t*-Butyl Peroxide Trifluoroacetate · (MW 308.57)

(oxidizing agent for the selective transformation of terminal alkenes to methyl ketones;[1,2] oxidative ring cleavage of cyclic acetals[5])

Alternate Name: PPT.

Physical Data: yellow crystals, mp 130-150 °C (dec).

Solubility: sol most common organic solvents, e.g. CH_2Cl_2, toluene, THF; destroyed by alcohols through anion exchange.

Analysis of Reagent Purity: IR: ν(O-O) = 855-860 cm^{-1}; $\nu(C{=}O)_{asym}$ = 1615-1630 cm^{-1}; ^1H NMR: δ 1.36-1.41 (*t*-Bu).

Preparative Methods: 1 g ***Palladium(II) Acetate*** is dissolved in 2 mL of ***Trifluoroacetic Acid***, and 10 mL of anhydrous 80% ***t-Butyl Hydroperoxide*** is added to the brown slurry at room temperature. After stirring for ca. 6 h, fine yellow crystals precipitate from the reaction mixture. The solid is filtered, washed repeatedly with pentane, and dried in vacuo; yield 85%.

Handling, Storage, and Precautions: not explosive or shock sensitive, but must be stored in a refrigerator.

Oxidation of Terminal Alkenes to Methyl Ketones.

PPT is a powerful and selective reagent for the oxidation of terminal alkenes to methyl ketones according to eq 1. The reaction is carried out at rt in solvents such as benzene, toluene, or dichloromethane, using a large excess of alkene (alkene/Pd > 5). Alkenes such as 1-hexene, 1-octene, or styrene are selectively converted to 2-hexanone, 2-octanone, and acetophenone, respectively.

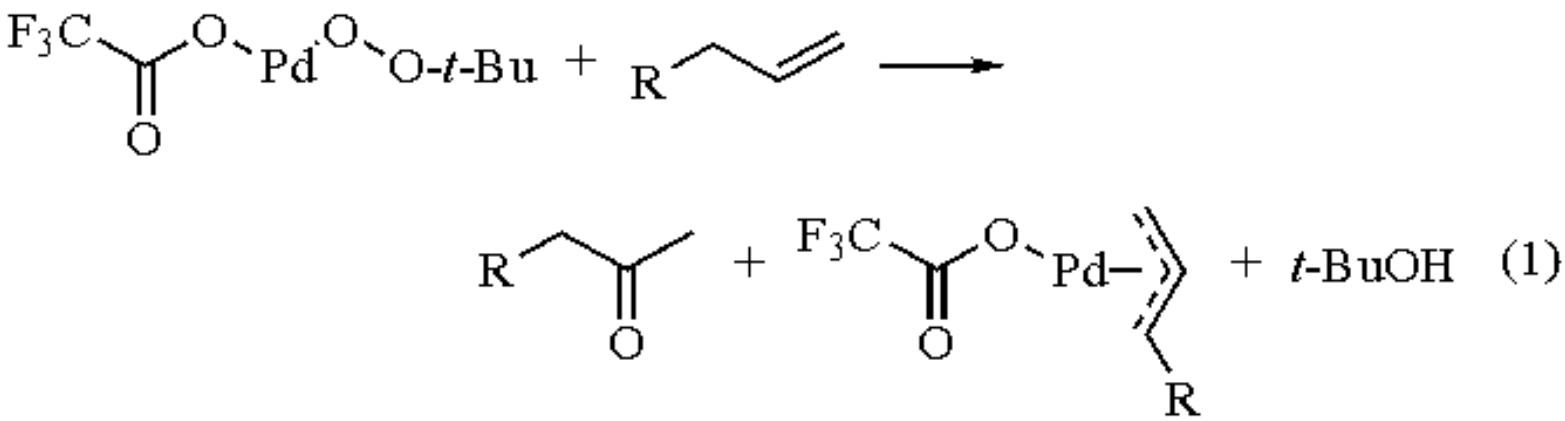

Internal alkenes are not oxidized, but form stable η^3-allyl Pd complexes (eq 2).

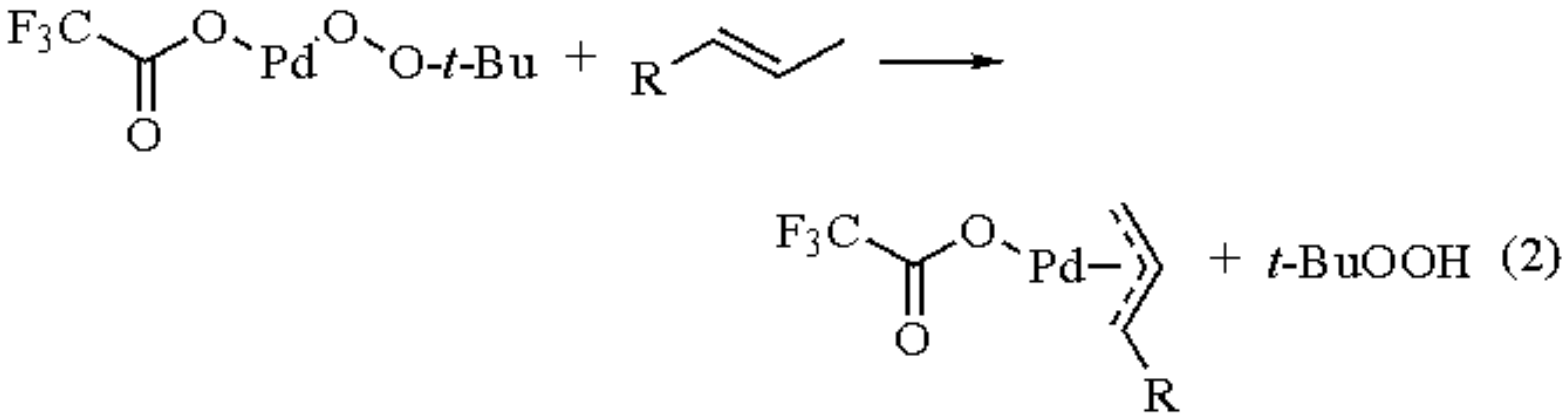

The mechanism of the ketonization of terminal alkenes (eq 3) has been shown to proceed via coordination of the alkene to palladium followed by intramolecular Markovnikov nucleophilic attack of the *t*-BuOO moiety on the coordinated alkene, forming the five-membered peroxometallocycle (pseudocyclic peroxymetalation); this decomposes with a β-hydride migration to form the methyl ketone and the palladium *t*-butoxy complex. The latter can react with excess alkene to give the η^3-allyl complex, or with excess *t*-BuOOH in a catalytic ketonization of terminal alkenes which is less effective than the oxidation by ***Hydrogen Peroxide*** (see below).

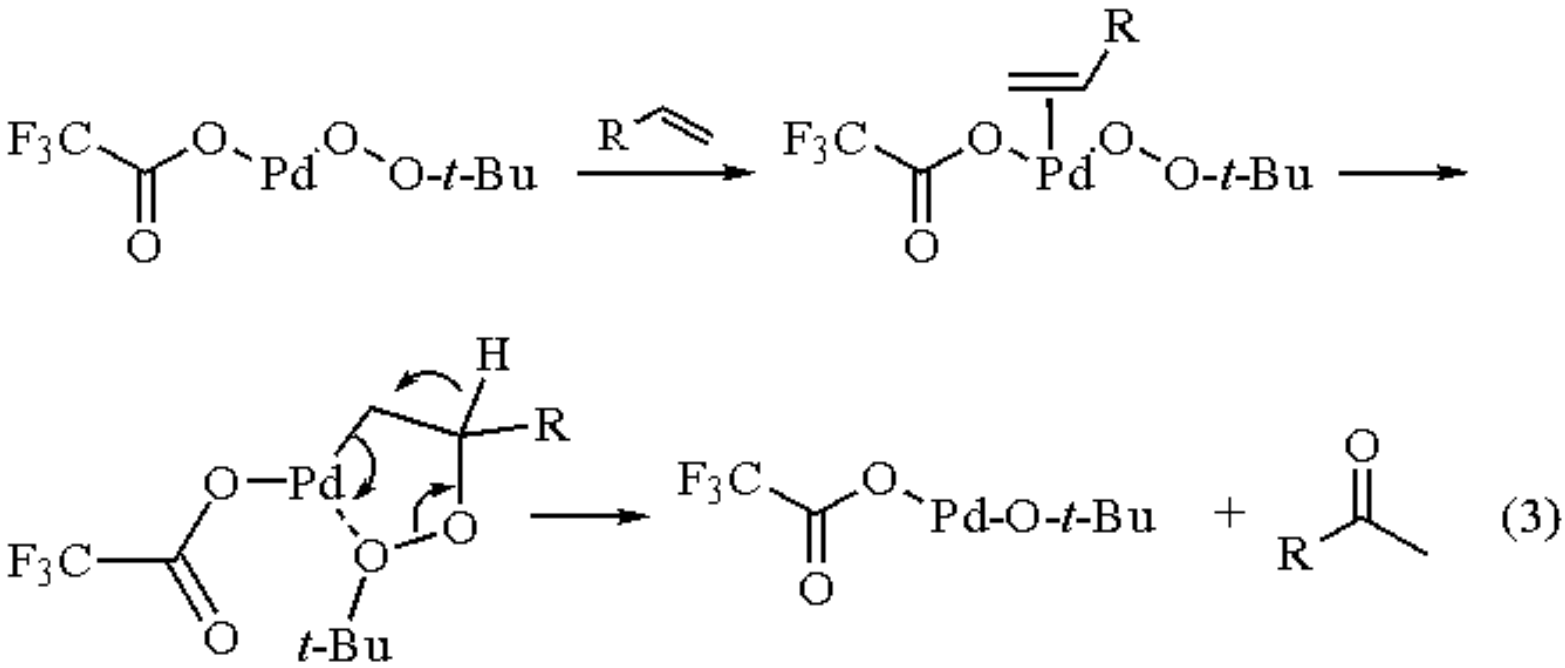

Palladium complexes are powerful catalysts for the selective oxidation of terminal alkenes to methyl ketones. In contrast to the Wacker ***Palladium(II) Chloride-Copper(II) Chloride***-H_2O-O_2 system, this reagent system (eq 4) can be successfully applied to most terminal higher alkenes, does not give chlorinated byproducts, and is not corrosive.

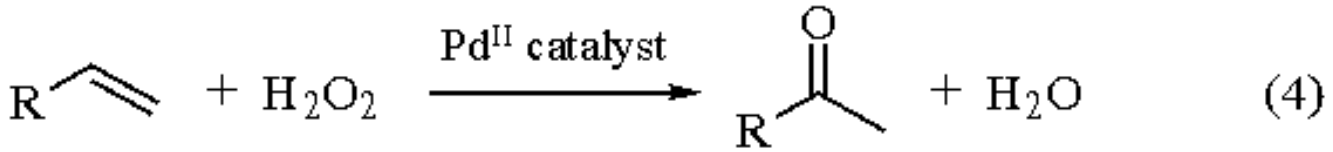

This reaction can be carried out at room to moderate (70 °C) temperature in a two-phase (benzene, toluene, AcOEt, MTBE) or single-phase (*t*-BuOH, AcOH) mixture. Several palladium complexes (particularly $Pd(OAc)_2$) can be used as catalysts for this transformation in concentrations as low as 10^{-4} molar in solution, with turnover numbers higher than 400 mol ketone produced per mol Pd and per hour. The reaction can be applied to most terminal alkenes, e.g. 1-hexene, 1-octene, 1-dodecene, or allyl acetate, and gives the corresponding methyl ketones with conversions and selectivities higher than 80%. Byproducts include mainly the internal isomers of the starting alkenes, and some internal ketones. During the reaction, a Pd-catalyzed parallel decomposition of H_2O_2 occurs, and two equiv or more are often necessary to reach a complete conversion of the substrate.

The mechanism of this reaction (eq 5) has been shown to proceed through a hydroperoxypalladation of the coordinated alkene, similar to that described in eq 3. Labeling studies have shown that the oxygen atom incorporated into the methyl ketone exclusively derives from H_2O_2, not H_2O.[2]

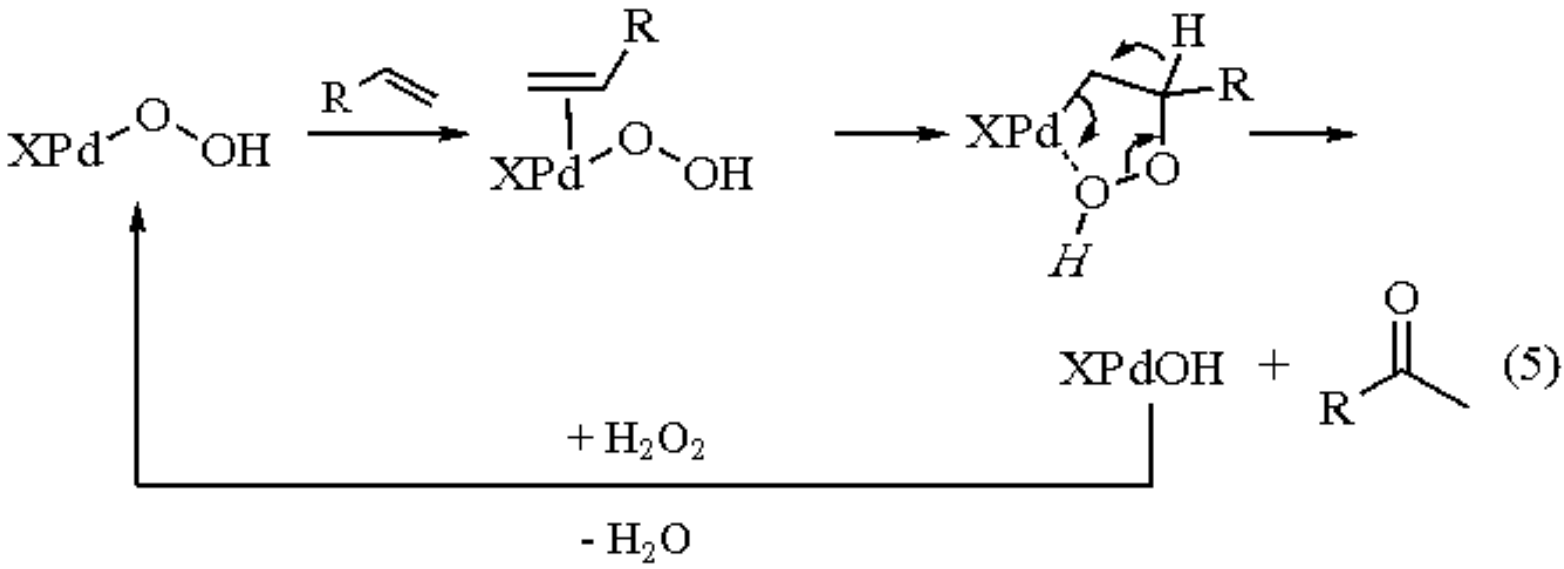

Almost quantitative yields of methyl ketones were obtained in biphasic conditions by adding a terminal alkene (from 1-hexene to 1-octadecene) to a suspension of ***Tetrakis(triphenylphosphine)palladium(0)*** in a 3.2 M aqueous solution of H_2O_2 at 40-80 °C (alkene:Pd = 2000; H_2O_2:alkene = 10). The ketonization is thought to proceed via the formation of an active anionic intermediate $[(Ph_3P)_3Pd(OOH]^-H^+$ which transfers oxygen to the alkene as in eq 5.[3]

A heterogenized reusable Pd complex on layered montmorillonite silylpropylethylenediamine (Figure 1) was shown to exhibit a much higher activity for the selective ketonization of terminal alkene by H_2O_2 (substrate:Pd = 4500; AcOH, 80 °C, with alkenes ranging from 1-hexene to 1-dodecene, styrene, allyl alcohol, and allyl acetate; yields higher than 90%). Consistent activity was found for 4 catalyst recycles.[4]

Oxidative Cleavage of Cyclic Acetals.

The trifluoroacetate catalyzes the oxidative cleavage of cyclic acetals by *t*-butyl hydroperoxide to give diol monoesters. In a typical reaction, the cyclic acetal and two equivalents of *t*-butyl hydroperoxide were mixed with 5 mol % of the catalyst in dry benzene at 50 °C (eqs 6, 7).[5]

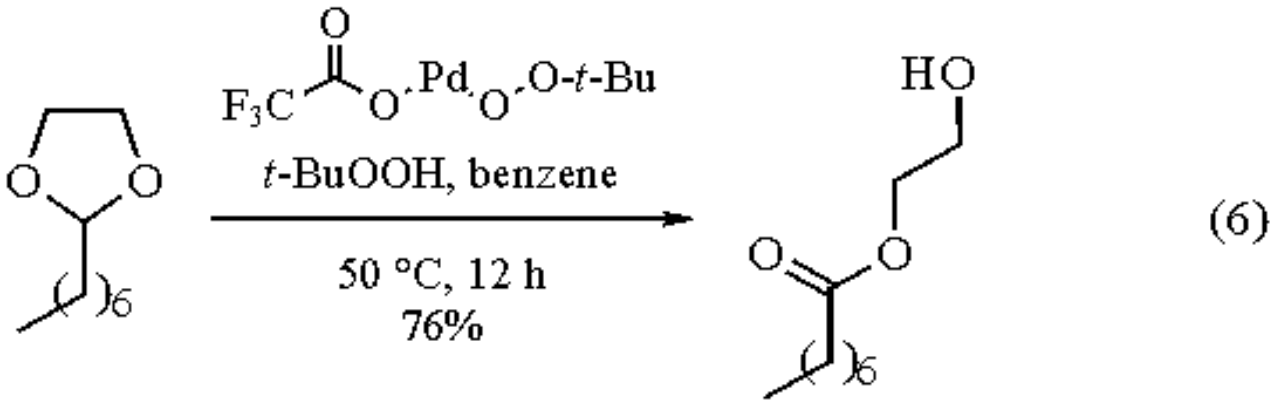

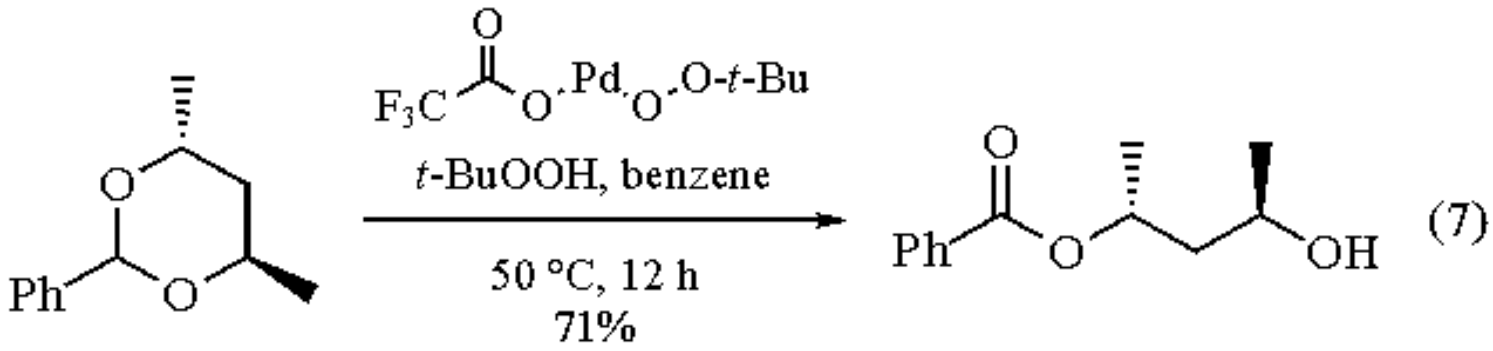

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Palladium on Calcium Carbonate (Lead Poisoned)

$Pd/CaCO_3/Pb$

[7440-05-3] · Pd · Palladium on Calcium Carbonate (Lead Poisoned) · (MW 106.42)

(catalyst used for selective hydrogenation of alkynes to *cis*-alkenes;[1-7] used to reduce azides and nitro compounds to amines;[8] used infrequently for oxidation of aldehydes to acids[10])

Alternate Name: Lindlar catalyst.

Solubility: insol most organic solvents; incompatible with water or acids.

Form Supplied in: dark gray to black powder, typically 5 wt% of palladium.

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds. The reagent is pyrophoric in the presence of solvents. General precautions for handling hydrogenation catalysts should be followed. The catalyst must be suspended in the organic solvent under an atmosphere of N_2. During filtration the filter cake must not be allowed to go dry.

Hydrogenations.

Lead-poisoned palladium on calcium carbonate, also known as Lindlar catalyst, is mainly used for the selective conversion of alkynes to *cis*-alkenes.[1] The catalyst has been used frequently in the presence of an amine. The hydrogenation in most cases stops sharply after one equiv of hydrogen uptake. For example, the reduction of 1,2-epoxydec-4-yne over Lindlar catalyst and quinoline gave (*Z*)-1,2-epoxydec-4-ene in 95% yield. The epoxide was stable under the reaction conditions.[2] Terminal alkynes can be reduced selectively to 1-alkenes. The ease of reduction was established to be 1-alkyne > internal alkyne > 1-alkene.[3] Conjugated enynes can be reduced smoothly to the corresponding dienes with excellent selectivity (eq 1).[4]

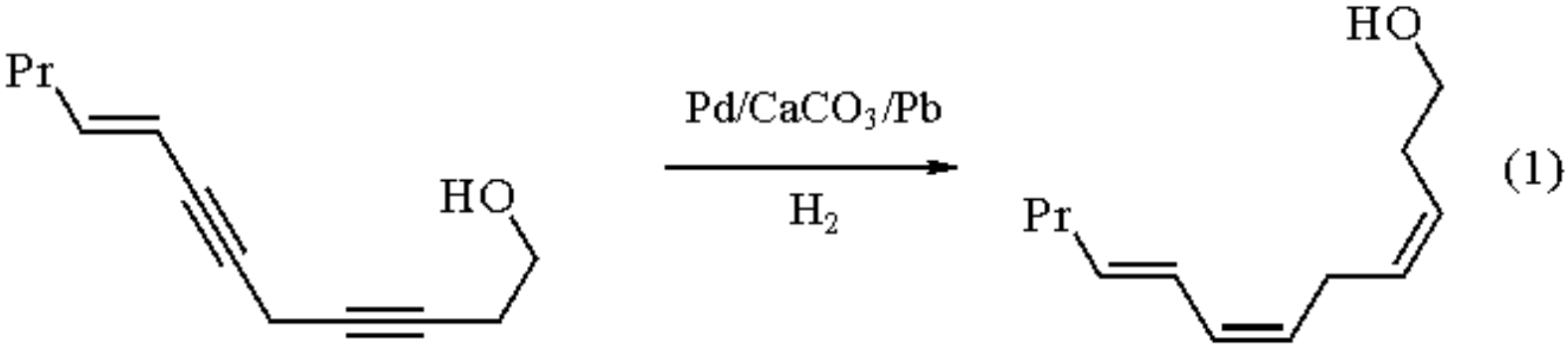

Alkynes in conjugation with one or two carbonyl functions are also reduced smoothly to the alkene. Lactone formation was observed when the hydroxyalkynoic acid shown in eq 2 was hydrogenated.[5]

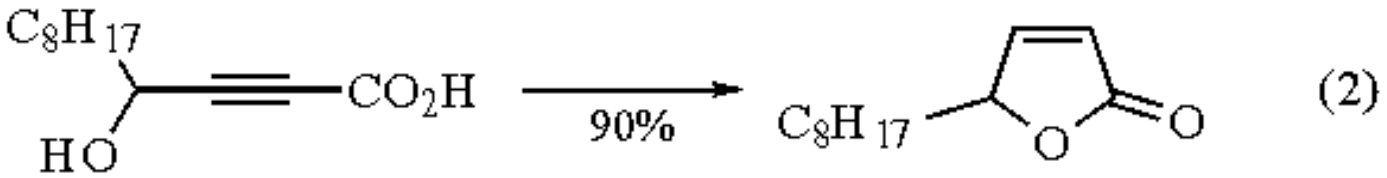

The reduction of 1-octynyldiisopropoxyborane with Lindlar catalyst in 1,4-dioxane with a small amount of pyridine gave a 95:5 (*cis*:*trans*) ratio of vinyl boronates. High selectivity was also observed with a variety of 1-alkynyl-1,3,2-dioxaborinanes under the above optimized reaction conditions.[6] It is important to note that other catalysts, such as ***Palladium on Barium Sulfate***, ***Nickel Boride***, and, more recently, ***Palladium on Poly(ethylenimine)***, have also been used to effect the reduction of alkynes to *cis*-alkenes with excellent results and are sometimes superior to Lindlar catalyst.[7]

Azides are readily hydrogenated to amines with this catalyst. As expected, alkenic groups are stable under the reaction conditions.[8]

Under catalytic transfer hydrogenation conditions, nitrobenzenes and azoxybenzenes are converted to hydrazobenzenes (eq 3).[9]

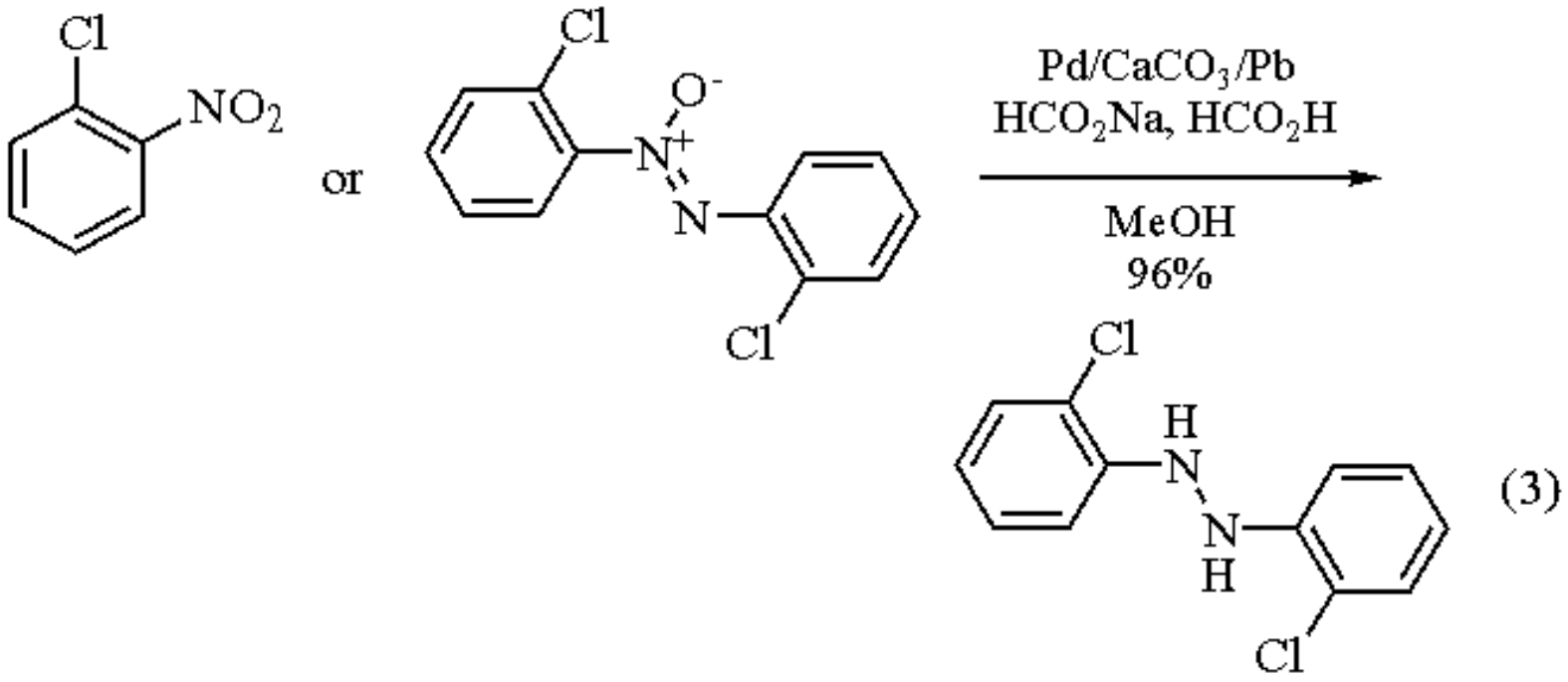

Oxidation.

The catalyst has also been used in oxidation reactions. Methacrolein in MeOH was oxidized to give 93% yield of methyl methacrylate with a selectivity of 95% at 98% conversion.[10]

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Palladium on Carbon

Pd/C

[7440-05-3] · Pd · Palladium on Carbon · (MW 106.42)

(catalyst for hydrogenation of alkenes, alkynes, ketones, nitriles, imines, azides, nitro groups, benzenoid and heterocyclic aromatics; used for hydrogenolysis of cyclopropanes, benzyl derivatives, epoxides, hydrazines, and halides; used to dehydrogenate aromatics and deformylate aldehydes)

Solubility: insol all organic solvents and aqueous acidic media.

Form Supplied in: black powder or pellets containing 0.5-30 wt % of Pd (typically 5 wt %); can be either dry or moist (50 wt % of H_2O).

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds. Pyrophoric in the presence of solvents. General precautions for handling hydrogenation catalysts should be followed. The catalyst must be suspended in the organic solvent under an atmosphere of N_2. During filtration the filter cake must not be allowed to go dry. If a filter aid is necessary, a cellulose-based material should be used if catalyst recovery is desired.

Hydrogenation and Hydrogenolysis: Carbon-Carbon Bonds.

The use of Pd/C for the selective reduction of alkynes to alkenes is generally not satisfactory, but a few examples have been reported. For example, the Pd/C-catalyzed reduction of 3,6-dimethyl-4-octyne-3,6-diol gave the enediol in 98% yield after absorption of 1 mol of H_2.[1] Further reduction gave the diol in 99% yield. Pd on other supports, such as $Pd/CaCO_3$ and $Pd/BaCO_3$, are much more effective for this conversion. Pd/C is usually used for the complete saturation of alkynes and alkenes to their corresponding hydrocarbons.[2] In some instances, isomerization of the double bond during hydrogenation occurs before reduction, which leads to unexpected results. For example, reduction of car-3-ene gave the cycloheptane with Pd/C instead of the expected cyclohexane derivative (eq 1).[3]

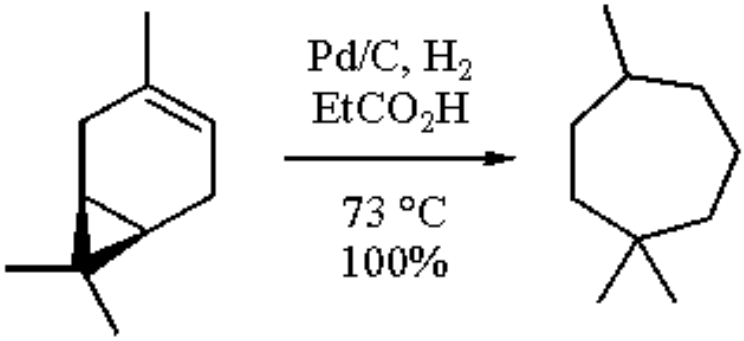

(1)

Isomerization of a double bond from one position to a hydrogenation inaccessible location has also been observed (eq 2).[4]

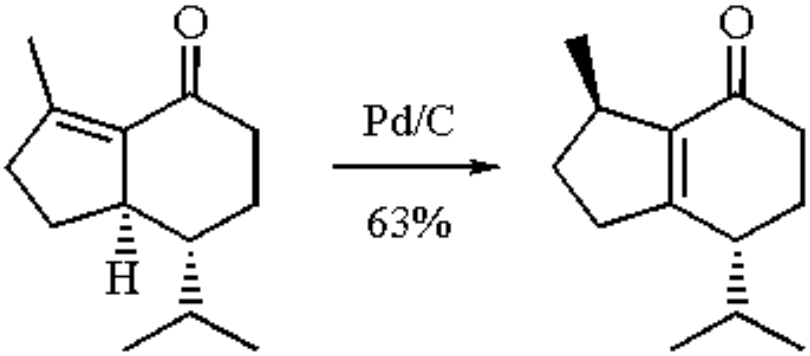

(2)

Next to the reduction of nitro groups, double and triple bonds are generally the next easiest functional groups to undergo hydrogenation. Some less reactive functional groups include ketones,[5] esters,[6] benzyl ethers,[7] epoxides,[8] and N-O bonds.[9] These remain intact under conditions needed to reduce alkenes and alkynes. Under longer reaction times and/or more forcing conditions, some of these functional groups will also be affected. Allylboron compounds can be hydrogenated to the propylboron derivatives, the C-B bond remaining intact (eq 3).[10]

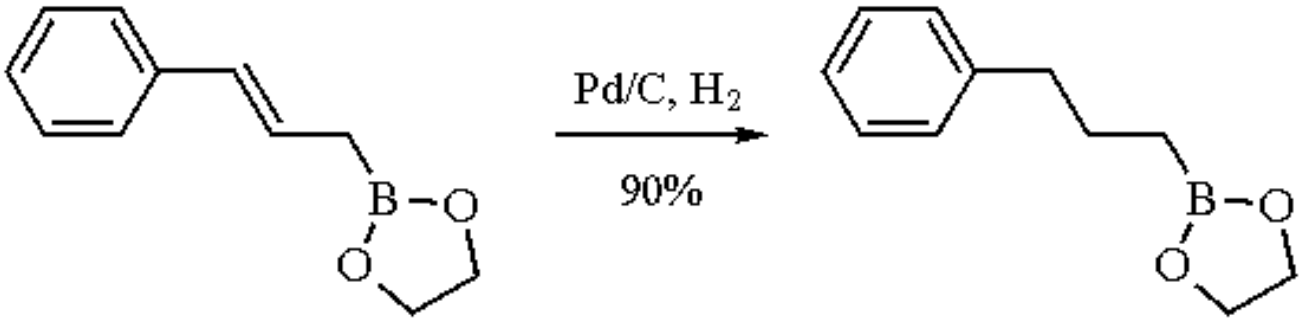

(3)

Treatment of acylated aldonolactones with hydrogen in the presence of Pd/C and triethylamine provided 3-deoxyaldonolactones in excellent yields (eq 4).[11] The α,β-unsaturated intermediate was hydrogenated stereospecifically to give the product. Substituting Pd with Pt catalysts gave the 2-acetoxy hydrogenolyzed product (**1**) instead. Hydrogenolysis of the acetate preceded the double bond hydrogenation.

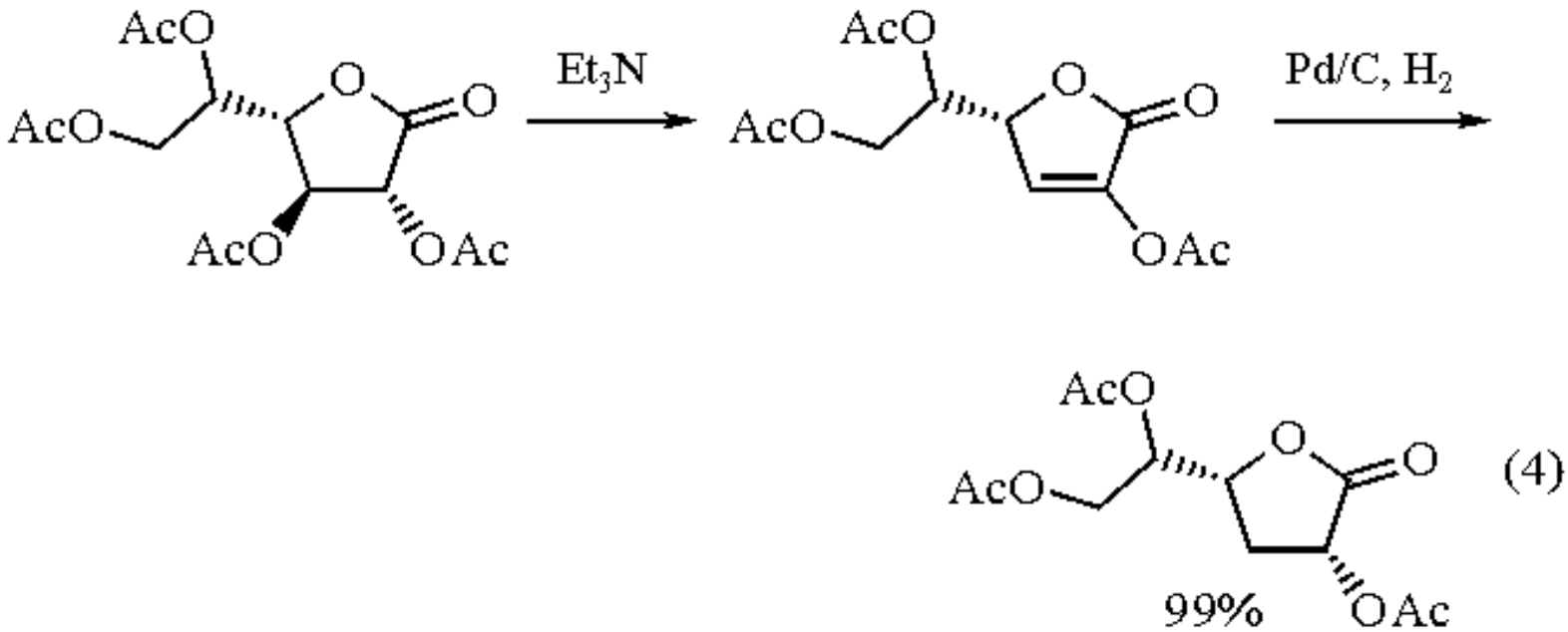

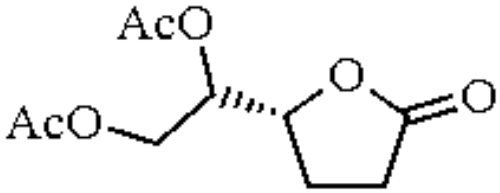

(1)

Hydrogenolysis of C-C bonds using Pd/C is mainly limited to cyclopropane opening. The less substituted and electronically activated bond cleavage is preferred. An example is shown in (eq 5).[12]

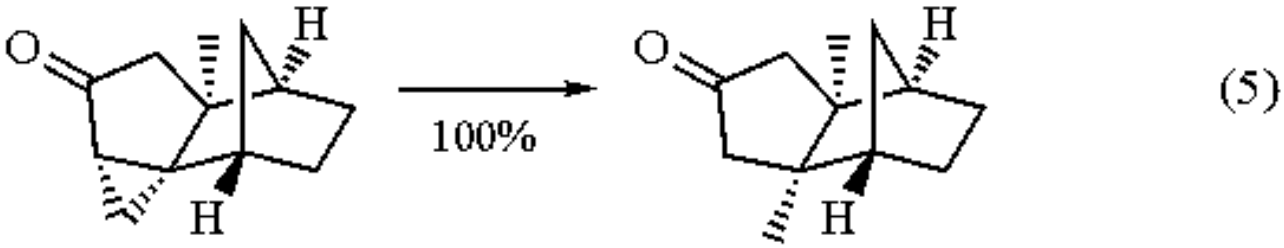

Carbon-Nitrogen Bonds.

The hydrogenation of nitriles to primary amines is best accomplished with Pd/C in acidic media or in the presence of ammonia. In the absence of acid or ammonia, a mixture of primary and secondary amines is observed. This effect was taken advantage of and mixed secondary amines were obtained selectively by the reduction of a nitrile in the presence of a different amine (eq 6).[13] Hydrogenation in aqueous acidic conditions can lead to aldehydes and/or alcohols.[14]

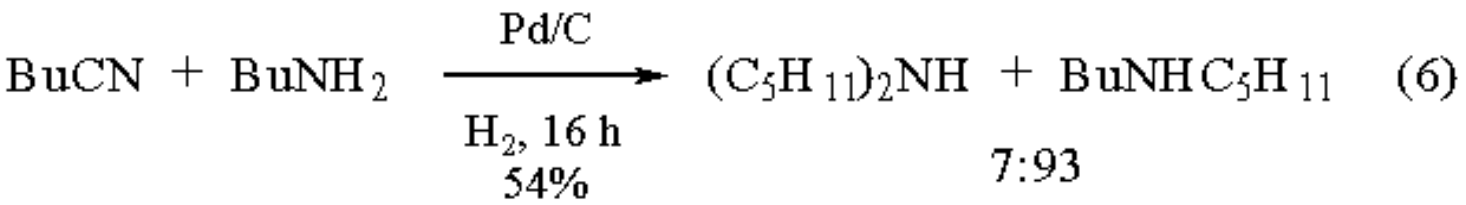

Reductive alkylation is a convenient and efficient way of obtaining secondary and tertiary amines.[15] *N*,*N*-Dimethyl tertiary amines can be obtained from both aromatic and aliphatic primary amines or their precursors. Using α-methylbenzylamine as the chiral auxiliary, highly diastereoselective reduction of the intermediate imine has been observed (eq 7).[16]

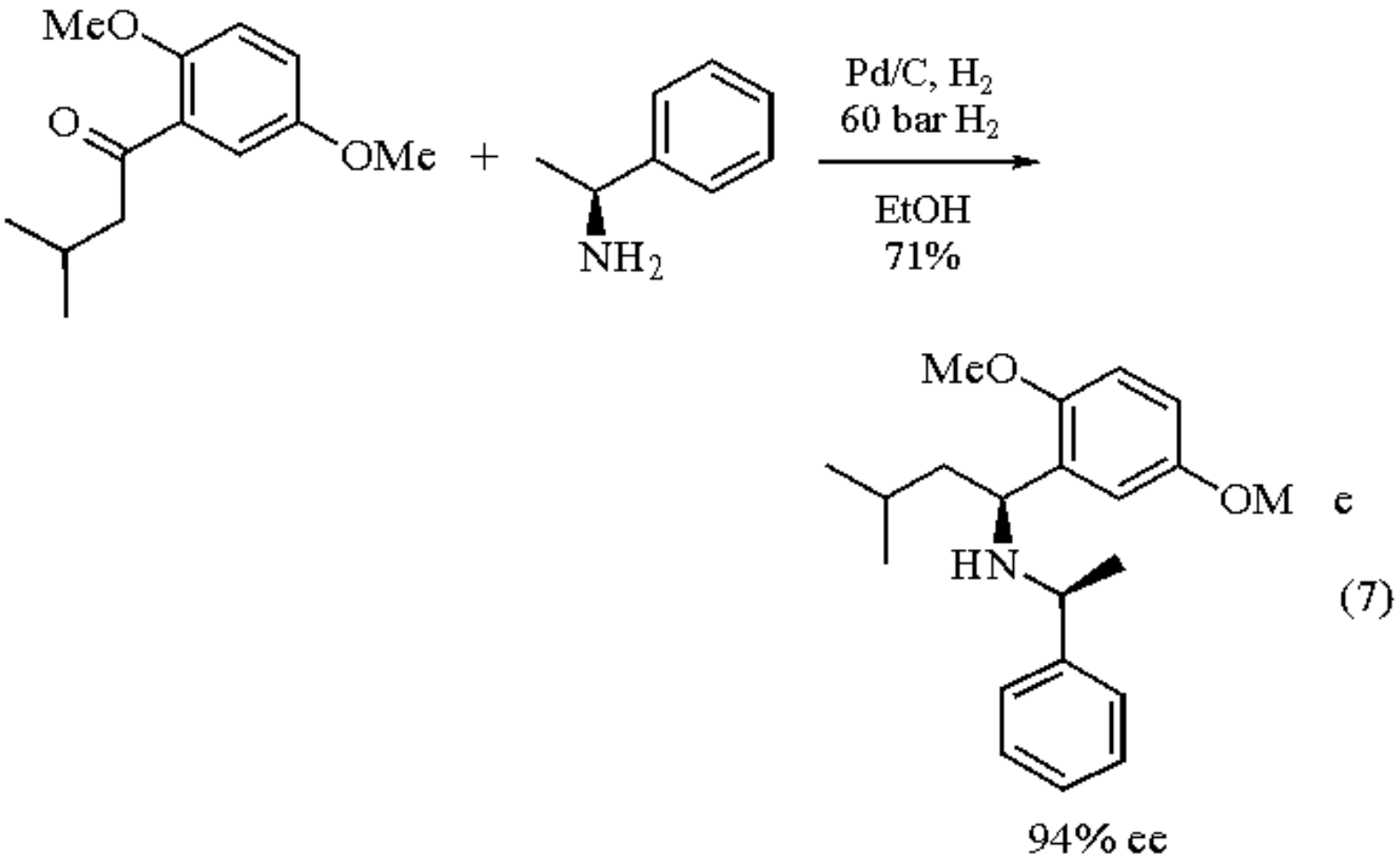

This method also provides a convenient route to nitrogen containing heterocycles. Hydrogenolysis of the Cbz group followed by an in situ reductive alkylation process gave a bicyclic heterocycle (eq 8).[17] The alkene was also reduced.

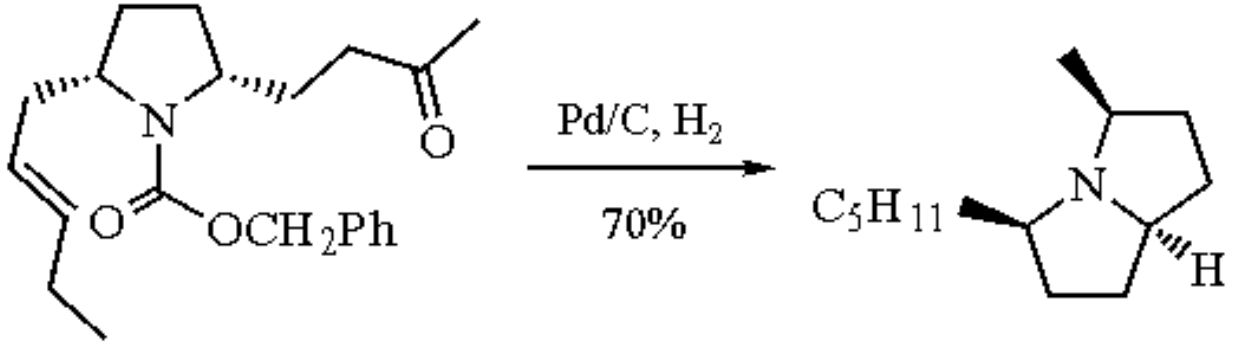

(8)

Other amine precursors, such as azides, can be utilized in the reductive alkylation reaction. For example, a furanose ring was opened and reclosed to form a piperidine ring system (eq 9).[18] A pyranyl azide similarly provided the seven-membered nitrogen heterocycle.

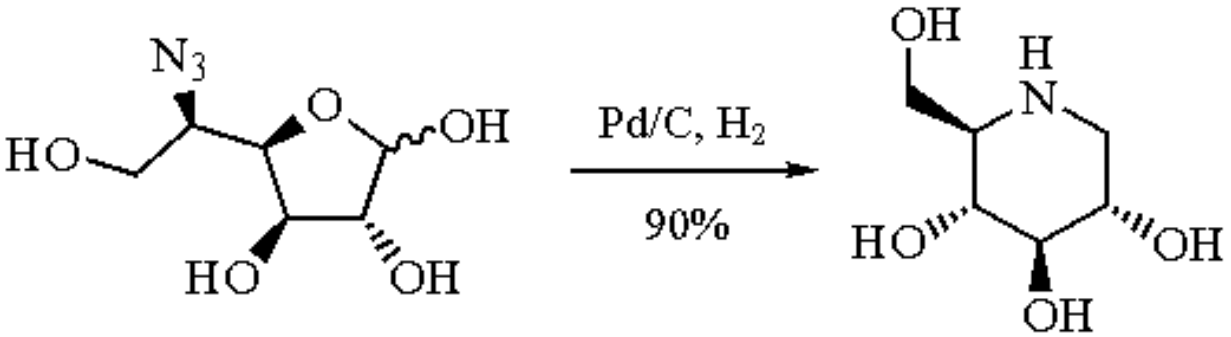

(9)

Similar to nitriles, hydrogenation of oximes is best carried out under acidic conditions to minimize secondary amine formation.[19]

Benzylic amines can be readily hydrogenolyzed to give less alkylated amines.[20] The C-N bond can be cleaved under both transfer hydrogenation[21] and regular hydrogenation conditions.[22] In many cases the newly debenzylated amines can further react, resulting in more structurally complex products (eq 10).[23]

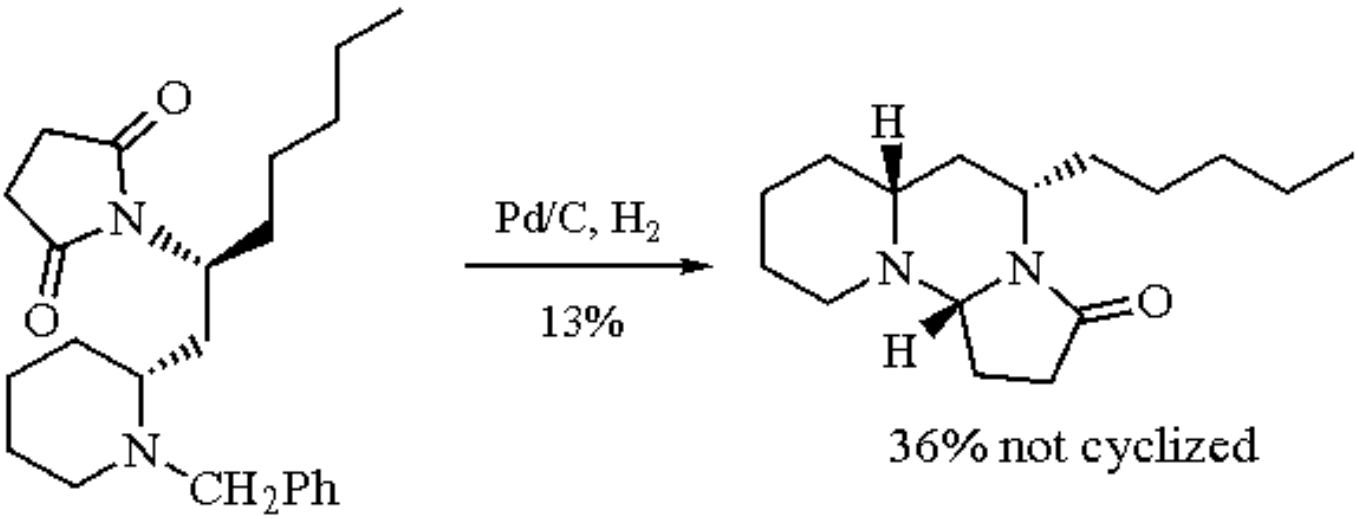

(10)

The heterogeneous catalytic debenzylation of *N*-benzylated amides with Pd/C is generally a difficult process and should not be considered in a synthetic scheme.

Allylamines have also been deallylated using Pd/C catalysis (eq 11).[24]

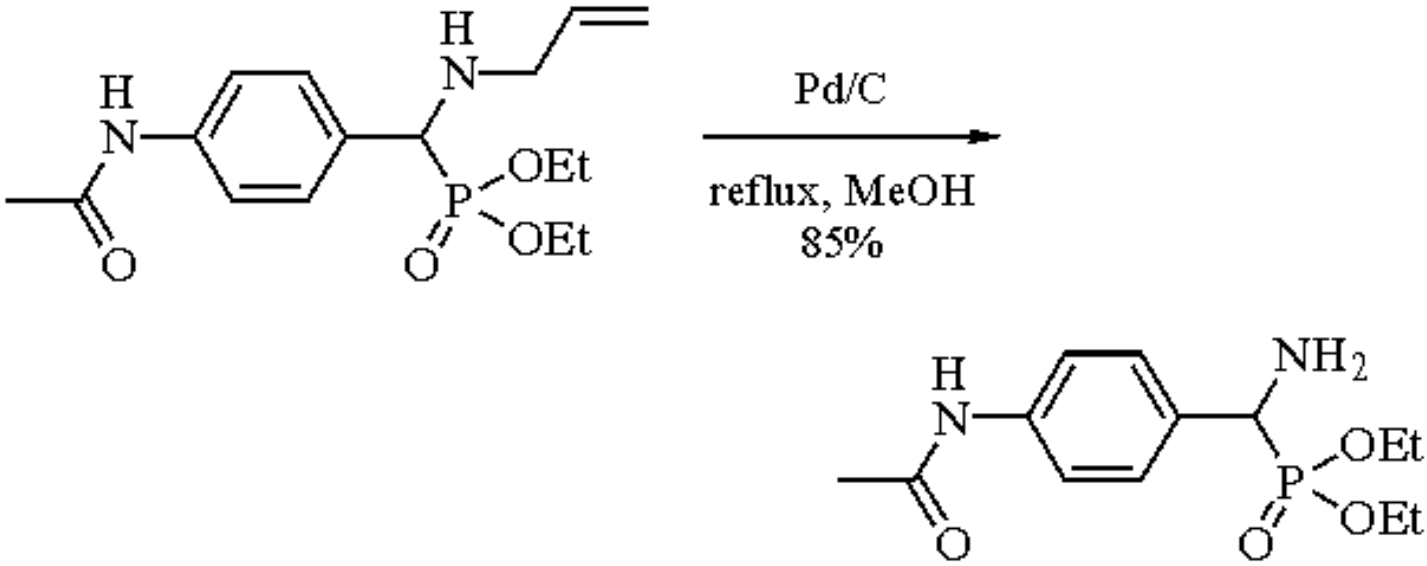

(11)

Aziridines are hydrogenolyzed to give ring-opened amines. In eq 12, the more reactive benzylic C-N bond was cleaved selectively.[25]

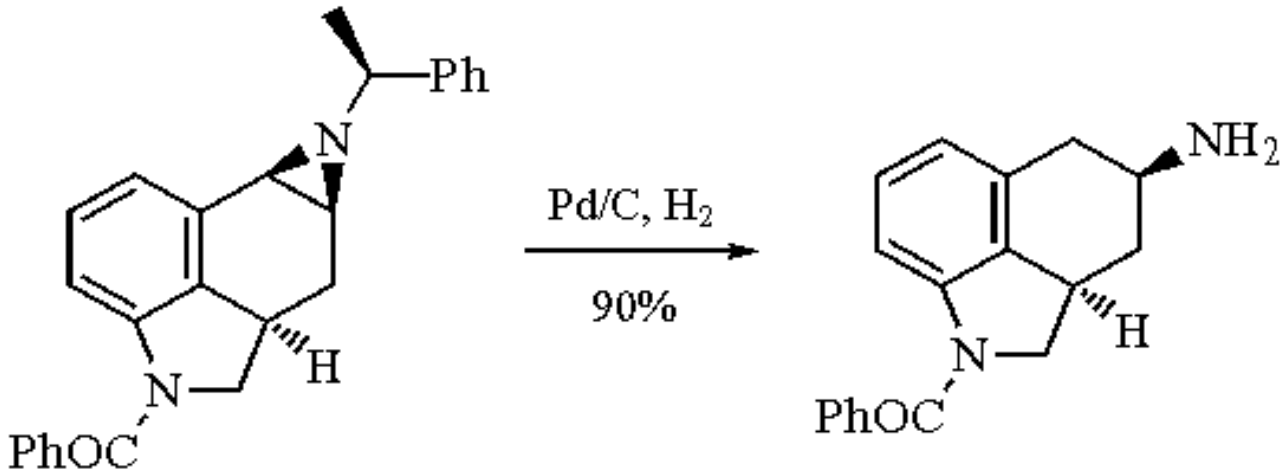

(12)

Carbon-Oxygen Bonds.

Pd/C is best suited for the hydrogenation and hydrogenolysis of benzylic ketones and aldehydes. The reduction of dialkyl ketones to the alcohols is more sluggish and further hydrogenolysis to the alkane is even slower.[26] The hydrogenation of benzylic ketones (aryl alkyl and diaryl ketones) to alcohols is a very facile process with Pd/C.[27] Further hydrogenolysis of the benzylic alcohols to the alkane products can be a major problem with Pd/C catalysts, but can be controlled.[28] In general, aryl ketones and aldehydes can be reduced to alcohols under neutral conditions or in the presence of an amino functional group or an added amine base.[29] In the presence of acids, hydrogenolysis is more prone to occur. Using other catalysts such as ***Platinum on Carbon*** Ru/C, Rh/C and ***Raney Nickel***, is an alternative.

Trifluoromethyl ketones are reduced to alcohols without dehalogenation or further hydrogenolysis.[30] The hydrogenation of a chiral proline derivative provided the α-hydroxyamide product in 77% de and 100% yield (eq

13).[31]

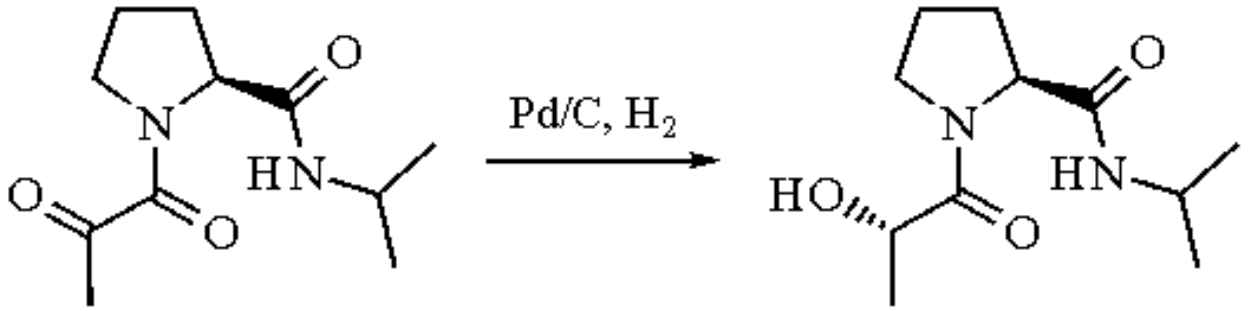

Hydrogenolysis of a benzyl group attached to an oxygen atom is a common step in complex synthetic schemes. Benzyl esters,[32] benzyl carbamates,[33] and benzyl ethers[34] are readily hydrogenolyzed to acids, amines, and alcohols, respectively. *N*-Oxides protected as the benzyl ethers can be deprotected without hydrogenolysis of the N-O bond.[35] Hydrazines protected with benzyloxycarbonyl (Cbz) groups have been deprotected without N-N bond cleavage or the hydrogenolysis of benzylic C-O bonds (eq 14).[36]

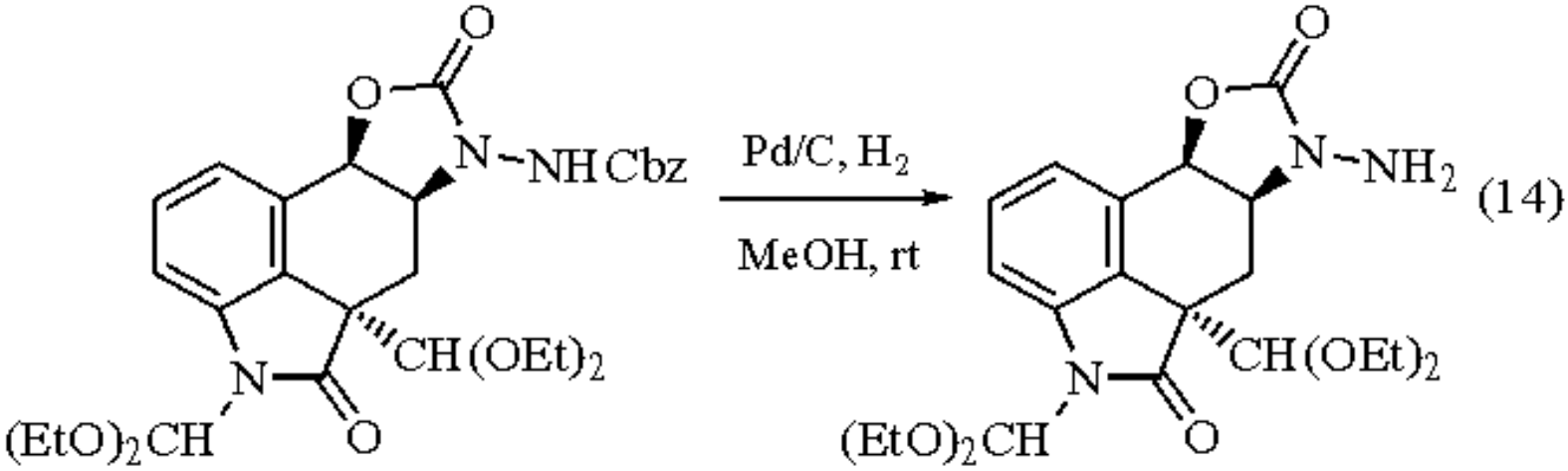

Benzyl carbamates have been transformed into *t*-butyl carbamates under transfer-hydrogenolysis conditions, but high catalyst loading was needed (eq 15).[37] A benzyl ether function survived these reaction conditions but a 1-alkene was saturated.

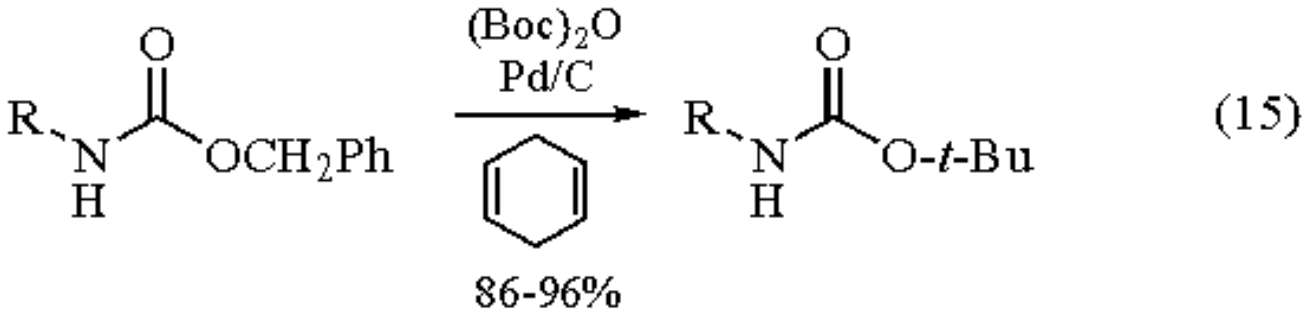

1,2-Diols protected as the acetal of benzaldehyde were deprotected under hydrogenolysis conditions (eq 16).[38]

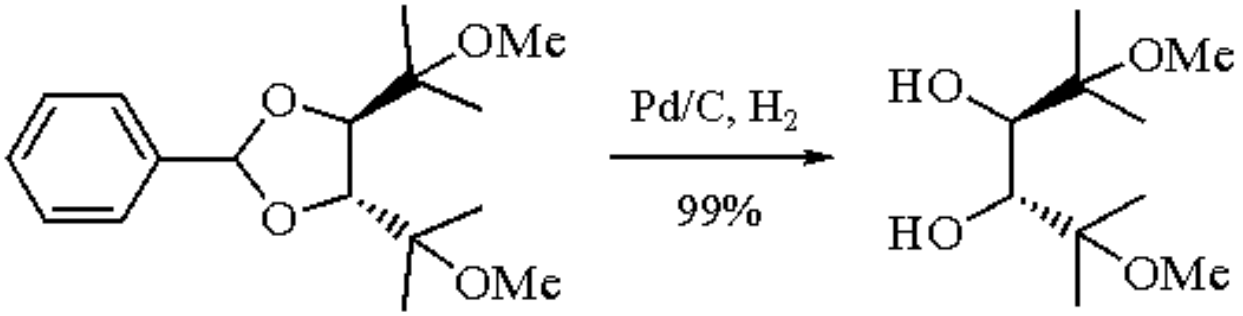

(16)

3-Acyltetronic acids were easily hydrogenolyzed to 3-alkyltetronic acids. Further reduction of the enol was not observed under the reaction conditions (eq 17).[39]

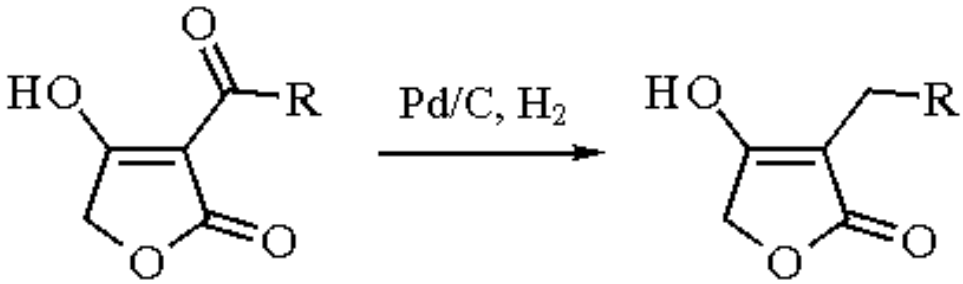

(17)

R = Me 96%
R = CH_2Ph 93%

The C-O bond of epoxides can be hydrogenolyzed to give alcohols. Regioselective epoxide ring opening has been observed in some cases (eq 18).[40]

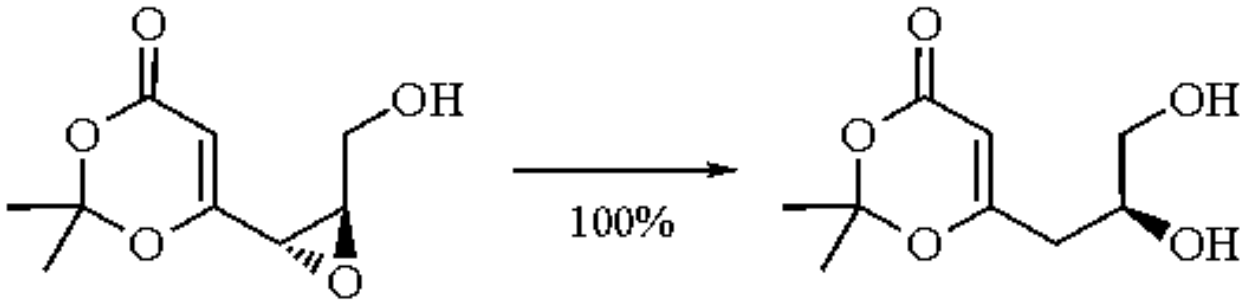

(18)

Nitrogen-Oxygen Bonds.

Both aliphatic and aromatic nitro groups are reduced to the corresponding amines (eq 19).[41] N-O bonds are also readily hydrogenolyzed using Pd/C (eq 20).[42a]

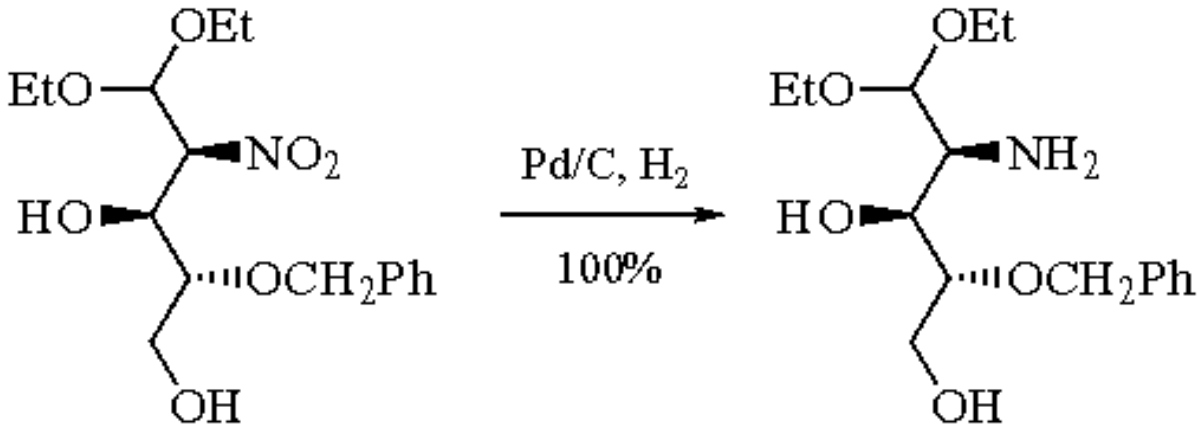

(19)

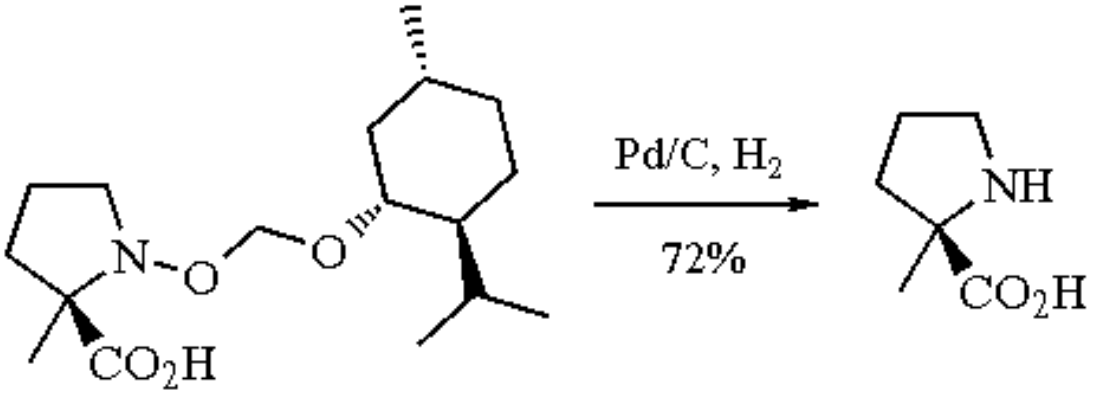

(20)

Carbon-Halogen Bonds.

Aromatic halides (Cl, Br, I) are readily hydrogenolyzed with Pd/C.[43] The reaction generally requires the presence of a base to neutralize the acid formed. In the absence of an acid neutralizer, dehalogenation is slower and may stop short of completion. Vinyl halides are also dehalogenated but concomitant saturation of the alkene can also occur (eq 21).[44a] Defluorination is a very slow process but one case has been reported (eq 22).[45]

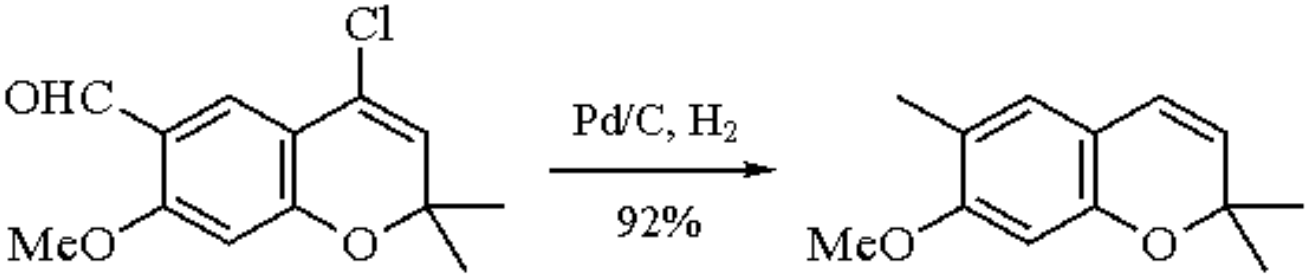

(21)

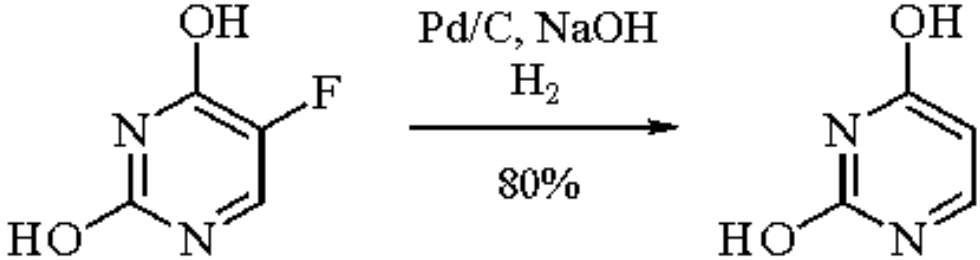

(22)

Selective dehalogenation of acyl halides can also be carried out with Pd/C and H_2 in the presence of an amine base to give aldehydes. This type of dehalogenation is commonly known as Rosenmund reduction (see ***Palladium on Barium Sulfate***).[46]

Nitrogen-Nitrogen Bonds.

Azides[47] and diazo[48] compounds can be reduced over Pd/C to give amines. These groups have also been used as latent amines which, when hydrogenolyzed, can react with amine-sensitive functional groups in the molecule to give other amine products (eq 23).[47c]

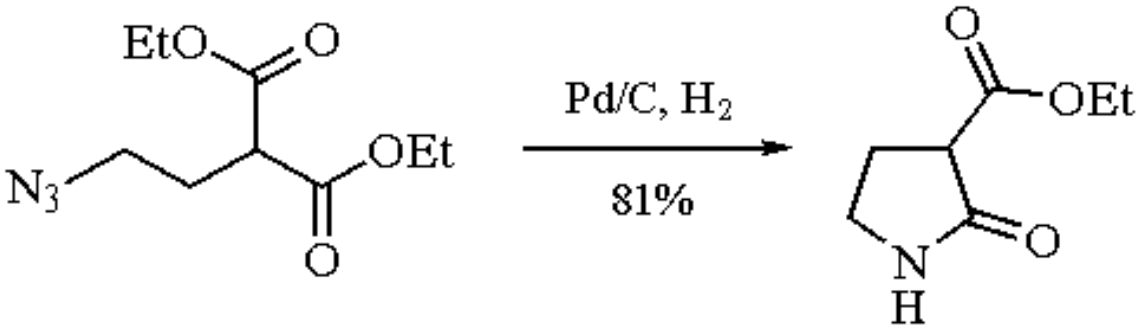

(23)

Carbocyclic and Heterocyclic Aromatics.

Hydrogenation of carbocyclic aromatic compounds can be accomplished with Pd/C under a variety of reaction conditions.[49] The conditions are generally more vigorous than those used with Pt or Rh catalysts.

Pyridine and pyridinium derivatives are hydrogenated readily to give piperidines.[50] Other heterocyclic aromatic ring systems such as furan,[51] benzofuran,[52] thiophene,[53] pyrrole,[54] indole,[55] quinoline,[56] pyrazine,[57] and pyrimidine[58] have also been hydrogenated over Pd/C.

Dehydrogenation.

At high temperatures, Pd/C is an effective dehydrogenation catalyst to provide carbocyclic and heterocyclic aromatic compounds.[59] An enone has been converted to a phenol (eq 24)[59f] and a methoxycyclohexene derivative has provided an anisyl product (eq 25).[59g]

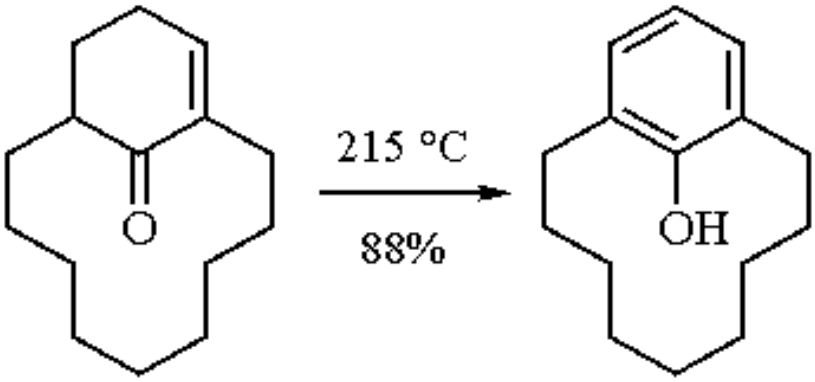

(24)

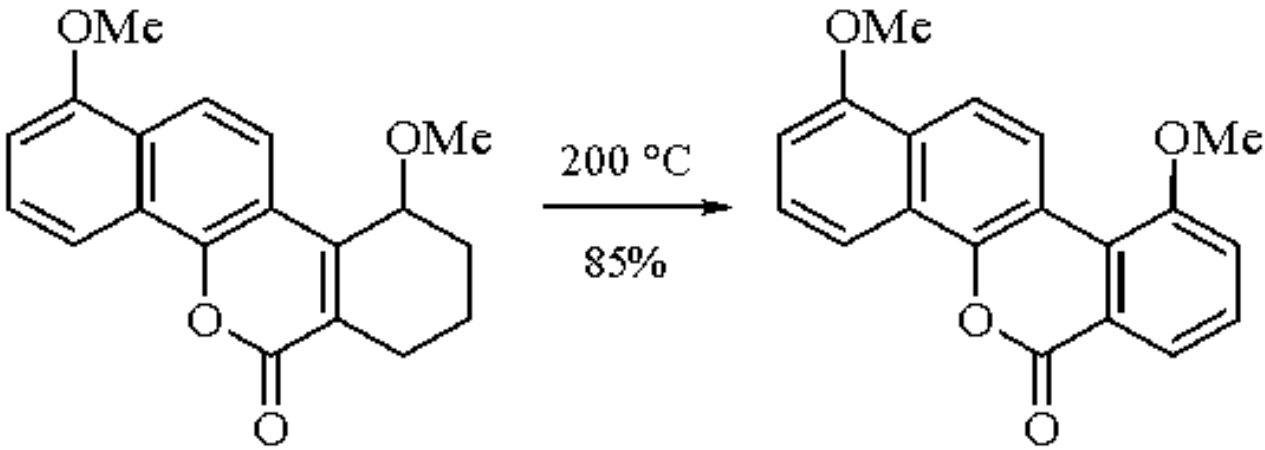

(25)

Miscellaneous Reactions.

Decarbonylations can be carried out under the same conditions used for dehydrogenation (eq 26).[60] In this case, a trisubstituted alkene remained intact.

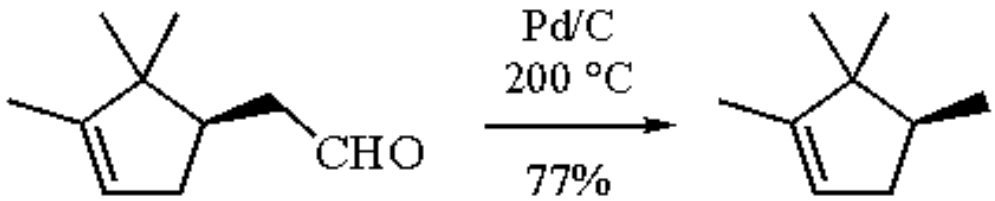

(26)

Reduction of an acylsilane gave an aldehyde without further hydrogenation to the alcohol or the hydrogenolysis of the benzyl ether (eq 27).[61]

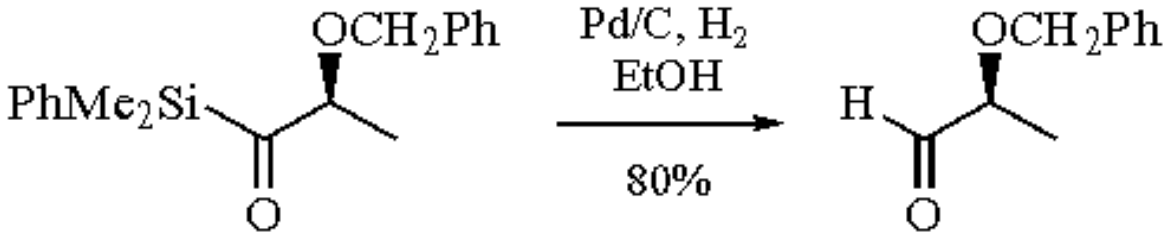

(27)

Pd/C also catalyzed the cycloaddition reaction of an alkyne with a heterocycle to give a tricyclic heteroaromatic compound (eq 28).[62]

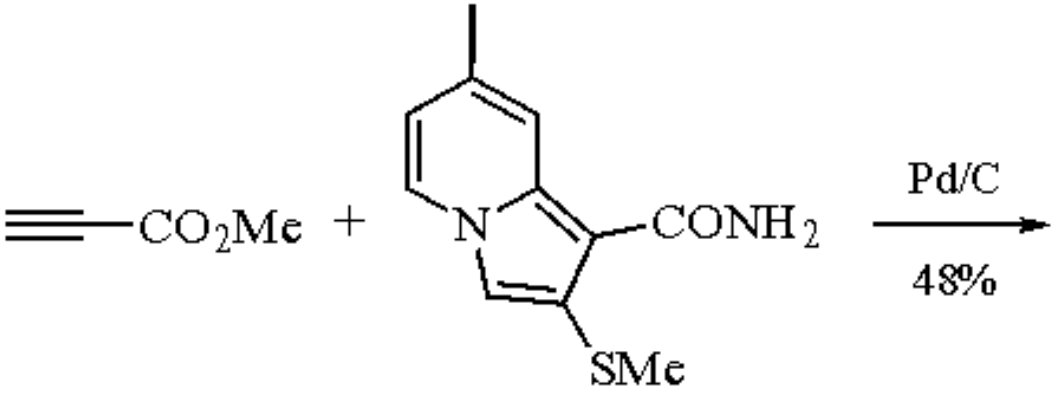

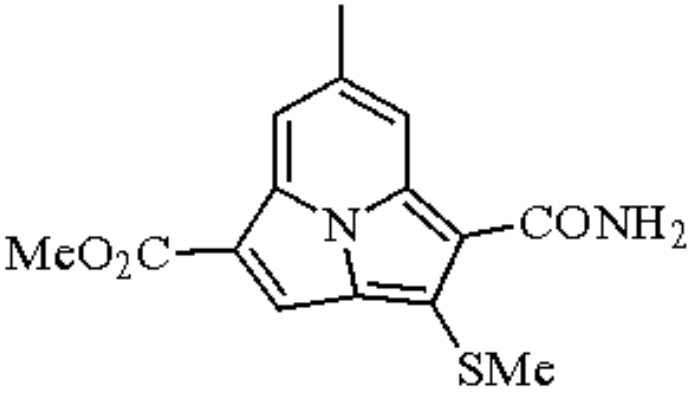

(28)

In conjunction with ***Copper(II) Chloride***, Pd/C catalyzed the biscarbonylation of norbornene derivatives (eq 29).[63] Norbornadiene itself was tetracarbonylated but in only 30% yield.

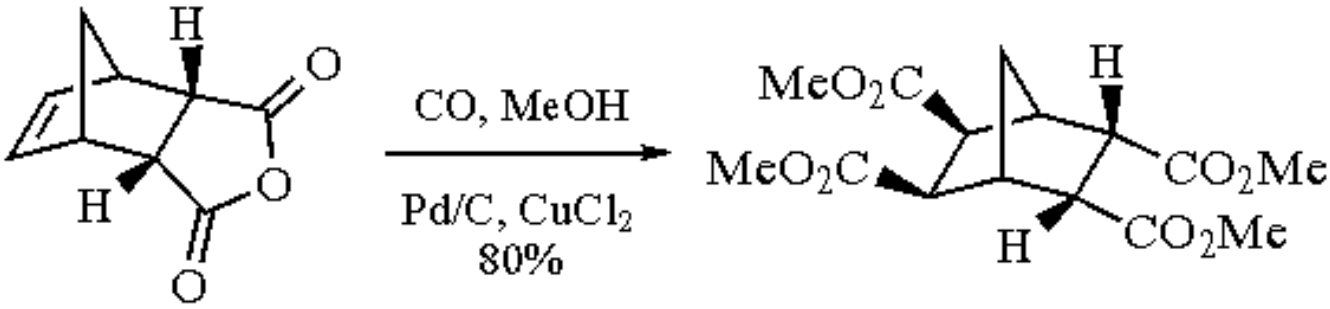

(29)

Related Reagents.

Palladium on Barium Sulfate; ***Palladium(II) Chloride***; ***Palladium(II) Chloride-Copper(II) Chloride***; ***Palladium-Graphite***.

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Palladium(II) Chloride[1]

$PdCl_2$

[7647-10-1] · Cl_2Pd · Palladium(II) Chloride · (MW 177.32)

(used as an oxidizing agent and to a lesser extent as a source of Pd^0 complexes)

Physical Data: mp 678 °C (dec).

Solubility: slightly sol H_2O; sol H_2O in the presence of chloride ion; sol aqueous HCl; sol PhCN, forming $Pd(PhCN)_2Cl_2$; insol organic solvents.

Form Supplied in: commercially available as a rust-colored stable powder or crystalline solid.

Handling, Storage, and Precautions: air stable; not hygroscopic.

General Considerations.

Many of the reactions described below can be accomplished using derivatives of palladium chloride such as ***Potassium Tetrachloropalladate(II)***, ***Disodium Tetrachloropalladate(II)***, ***Bis(benzonitrile)dichloropalladium(II)***, dichlorobis(acetonitrile)palladium, and dichlorobis(triphenylphosphine)palladium. The physical properties of these alternative reagents are described under their separate entries, but their chemistry is included in this article.

Synthetic applications of $PdCl_2$ and its derivatives can be classified into three types: use as oxidizing agents, use as Pd^{II} catalysts, and use as a source of Pd^0 catalysts. Characteristic features of these applications are briefly summarized below.

Use as Oxidizing Agents.

$PdCl_2$ and ***Palladium(II) Acetate*** are representative Pd^{II} salts used for various oxidation reactions, but their uses are different. For example, oxidative reactions of aromatic compounds are possible only with $Pd(OAc)_2$; $PdCl_2$ and its derivatives cannot be used. Oxidation reactions of various substrates with $PdCl_2$ are stoichiometric and Pd^0 is formed after the oxidation. Sometimes, but not always, Pd^0 can be reoxidized in situ to Pd^{II} with proper reoxidizing agents. In such a case, the oxidation reaction can be carried out with a catalytic amount of $PdCl_2$. Examples of reoxidants include $CuCl_2$, CuCl, $Cu(OAc)_2$, MnO_2, HNO_3, benzoquinone, alkyl nitrites, H_2O_2, and organic peroxides. Since solubility of $PdCl_2$ in water and organic solvents is small, the more soluble ***Dilithium Tetrachloropalladate(II)***, Na_2PdCl_4, K_2PdCl_4, and $Pd(PhCN)_2Cl_2$ are sometimes used for similar purposes.

Use as Pd^{II} Catalyst.

$Pd(PhCN)_2Cl_2$ is used as a homogeneous Pd^{II} catalyst for some non-oxidative reactions such as rearrangement reactions.

Use as Source of Pd^0 Catalyst.

Pd^{II} salts are reduced to Pd^0 catalysts with various reducing agents. Although $Pd(OAc)_2$ is more convenient for this purpose than $PdCl_2$ and its derivatives, $PdCl_2$ derivatives are used in many cases. Typically, $Pd(Ph_3P)_2Cl_2$ is reduced to form a Pd^0 phosphine complex.

Oxidations.

Oxidative Reactions of Alkenes.[2]

Oxidative reactions of alkenes can be classified into two types: oxidative substitution and oxidative addition, as shown in eq 1. Here X^- and Y^- represent nucleophiles such as HO^-, RO^-, RCO_2^-, R_2N^- and CO, as well as soft carbon nucleophiles such as active methylene compounds.

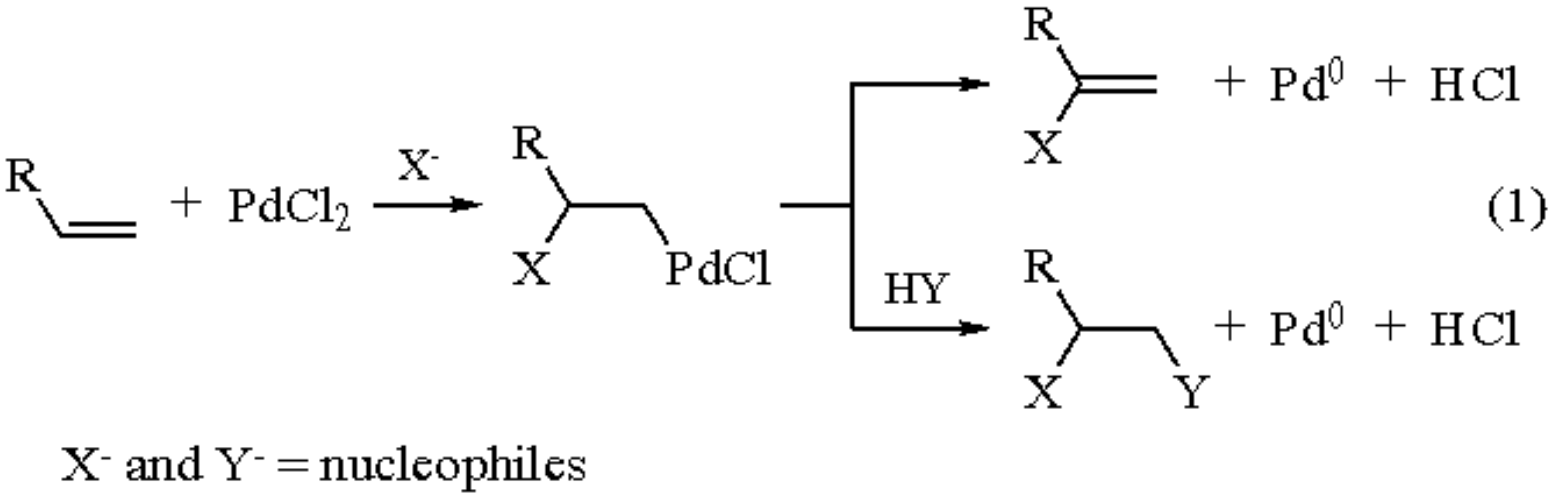

Reaction with Water.[2a,b]

Oxidation of ethylene to acetaldehyde under oxygen atmosphere is an industrial process called the Wacker process. $PdCl_2$ and ***Copper(II) Chloride*** in aqueous HCl are used as the catalysts. As shown by eq 2, the Wacker process comprises three unit reactions; $CuCl_2$ is a unique reoxidant of Pd^0.

$$CH_2{=}CH_2 + H_2O + PdCl_2 \longrightarrow MeCHO + 2\,HCl + Pd^0$$

$$Pd^0 + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl$$

$$2\,CuCl + 2\,HCl + 0.5\,O_2 \longrightarrow 2\,CuCl_2 + 2\,H_2O \qquad (2)$$

$$CH_2{=}CH_2 + 0.5\,O_2 \longrightarrow MeCHO$$

Higher terminal alkenes are also oxidized in organic solvents containing water; DMF is most widely used as the solvent.[3] On a laboratory scale the oxidation can be carried out easily in a way similar to the hydrogenation of alkenes under atmospheric pressure. Instead of Pd black and hydrogen, the oxidation is carried out with $PdCl_2$ and the copper salt under an oxygen atmosphere at room temperature using a similar apparatus. Since the reaction proceeds under mild neutral conditions, many functional groups such as esters, acetals, THP ethers, alcohols, halogens, and amines are tolerated. The ketones obtained by the oxidation are sometimes chlorinated with $CuCl_2$ to give chloro ketones as byproducts. For this reason, nonchlorinating ***Copper(I) Chloride*** is recommended as the reoxidizing agent. This is easily preoxidized to the Cu^{II} state with oxygen.[4] In a laboratory synthesis, a stoichiometric amount of ***1,4-Benzoquinone*** is conveniently used as the reoxidant.

The reaction is a unique method for the one-step synthesis of ketones from alkenes, and allows alkenes to be regarded as masked ketones which are stable to acids, bases, and nucleophiles. Particularly useful is the oxidation of terminal alkenes, which provides methyl ketones (eq 3).[5] As a typical application, the allylation of a ketone, followed by the oxidation, affords a 1,4-diketone. A cyclopentenone can then be prepared by an aldol condensation (eq 4).[5] The annulation method has widespread uses in the synthesis of natural products such as pentalenene,[6] muscone,[7] and coriolin.[8] 1,5-Diketones are prepared by 3-butenylation of a ketone followed by the oxidation. This process has been used to prepare cyclohexenones (eq 5).[5]

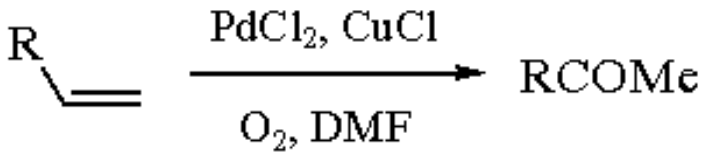

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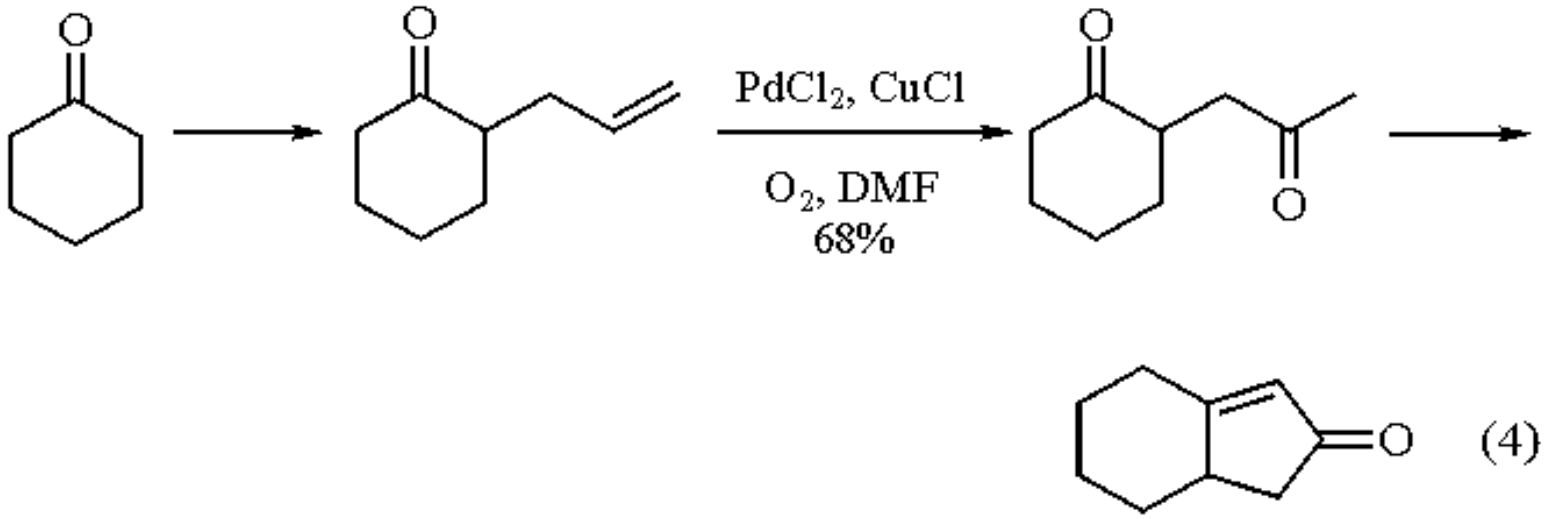

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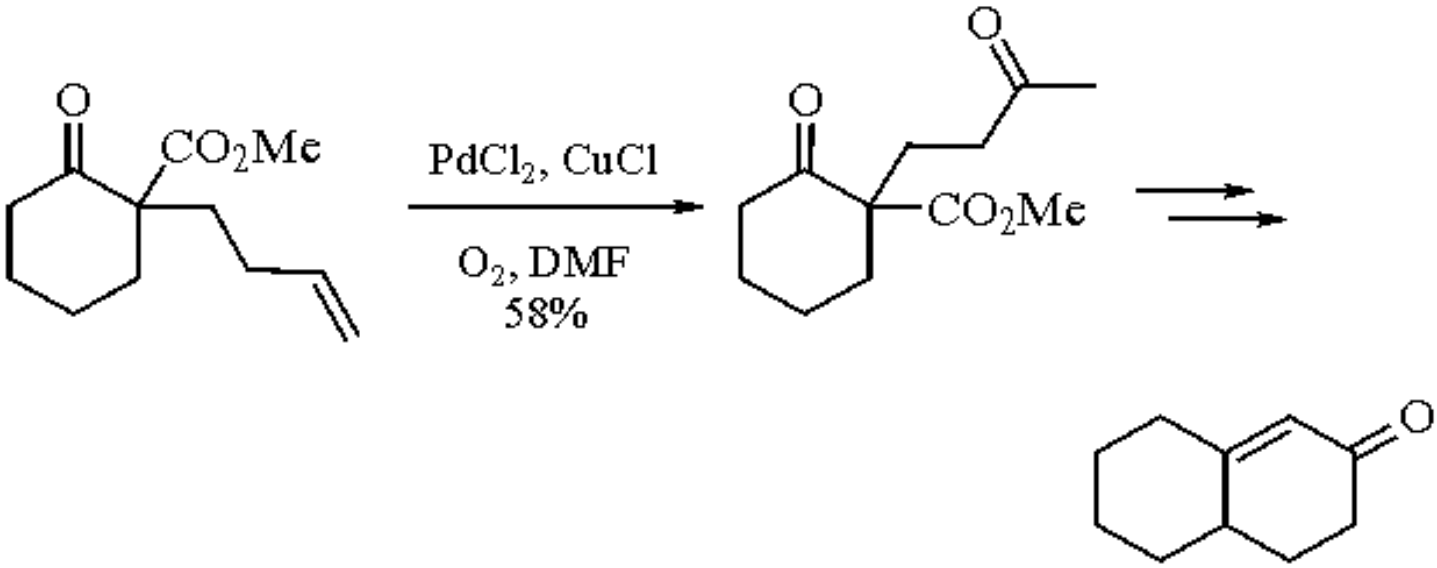

(5)

Simple internal alkenes are difficult to oxidize. However, the regioselective oxidation of internal alkenes takes place in the presence of suitably disposed oxygen functional groups by neighboring group participation. For example, α,β-unsaturated esters are oxidized to β-keto esters using Na_2PdCl_4 as catalyst and ***t-Butyl Hydroperoxide*** as the reoxidant (eq 6).[9] Allylic ethers are oxidized to β-alkoxy ketones which can be converted to α,β-unsaturated ketones for use in annulation reactions (eq 7).[10] Cyclohexene and cyclopentene can not be oxidized under the usual conditions, but are oxidized to cyclohexanone and cyclopentanone under different conditions. For example, chloride-free Pd^{II} salts, prepared from $Pd(OAc)_2$ and $HClO_4$, H_2SO_4, or HBF_4, are active catalysts (eq 8).[11] For additional examples of the Wacker process, see ***Palladium(II) Chloride-Copper(I) Chloride*** and ***Palladium(II) Chloride-Copper(II) Chloride***.

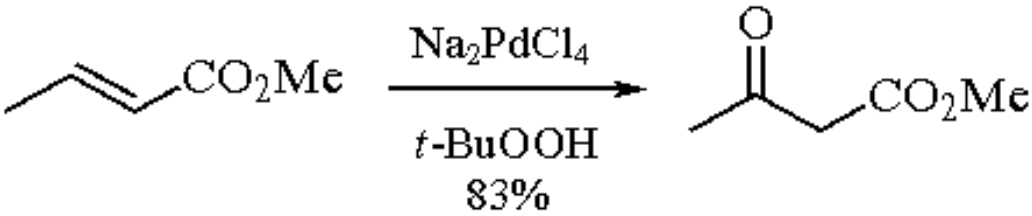

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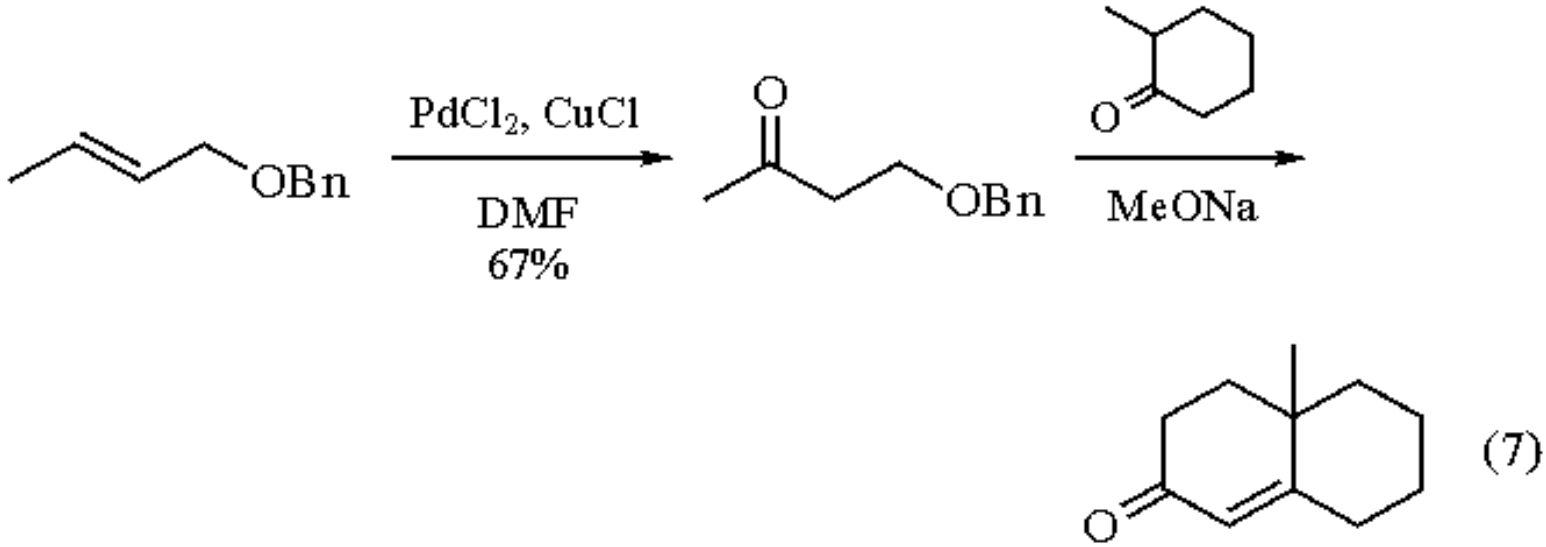

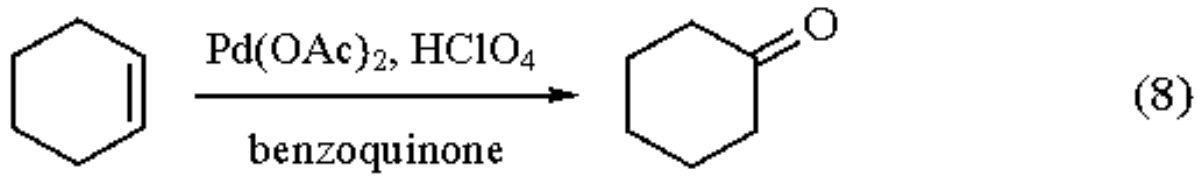

Reaction with Alcohols and Phenols.[2c]

The reaction of alcohols with terminal alkenes affords acetals of ketones (eq 9).[12] An elegant application of the reaction was a brevicomin synthesis (eq 10).[13]

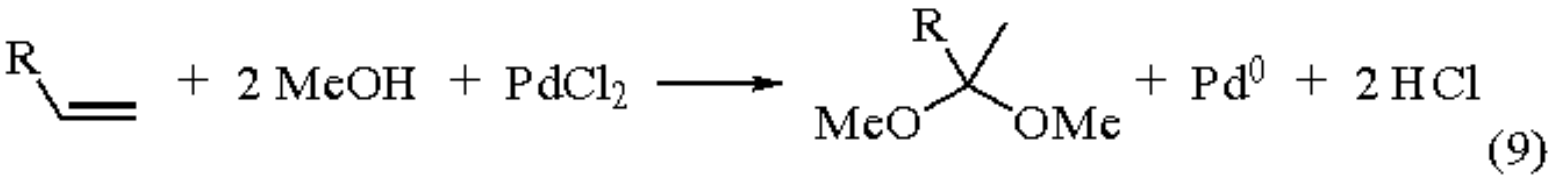

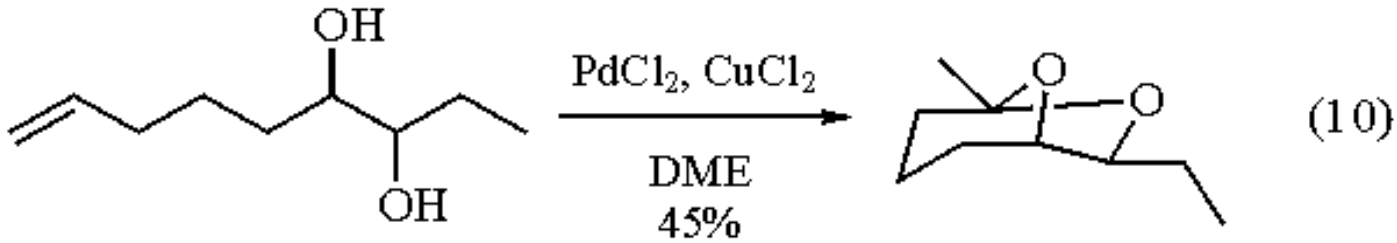

Alkenes with an electron-withdrawing group such as styrene, ***Acrylonitrile***, and acrylate are converted to acetals of the aldehydes rather than the ketones. The reaction of styrene with ethylene glycol affords the cyclic acetal (eq 11).[12a] 3,3-Dimethoxypropionitrile is produced commercially using methyl nitrite as the reoxidant. The nitrite can be regenerated easily by the oxidation of NO with oxygen (eq 12).[14]

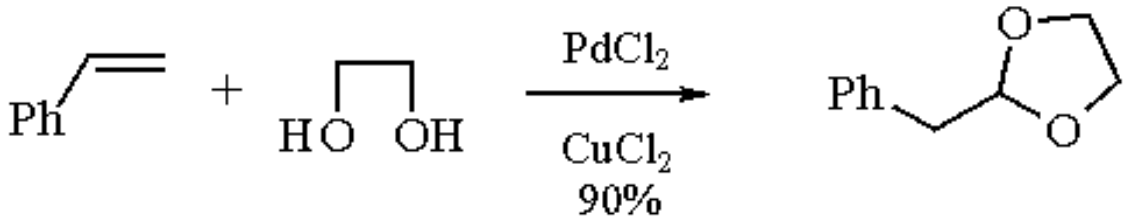

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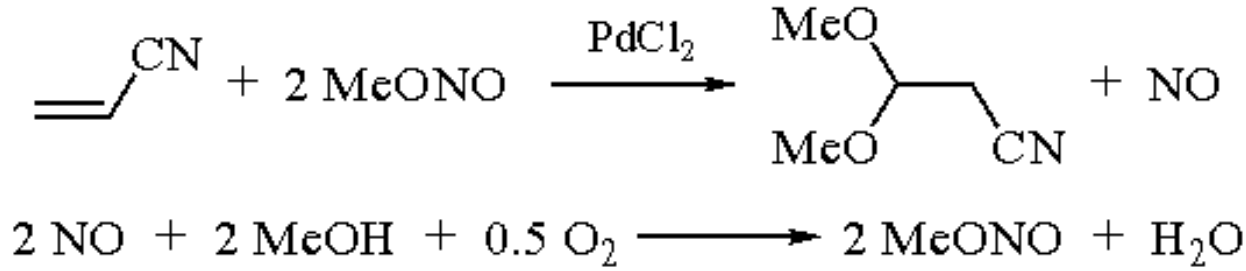

(12)

The intramolecular reaction of phenols or enols affords furans and pyrans (eq 13).[15]

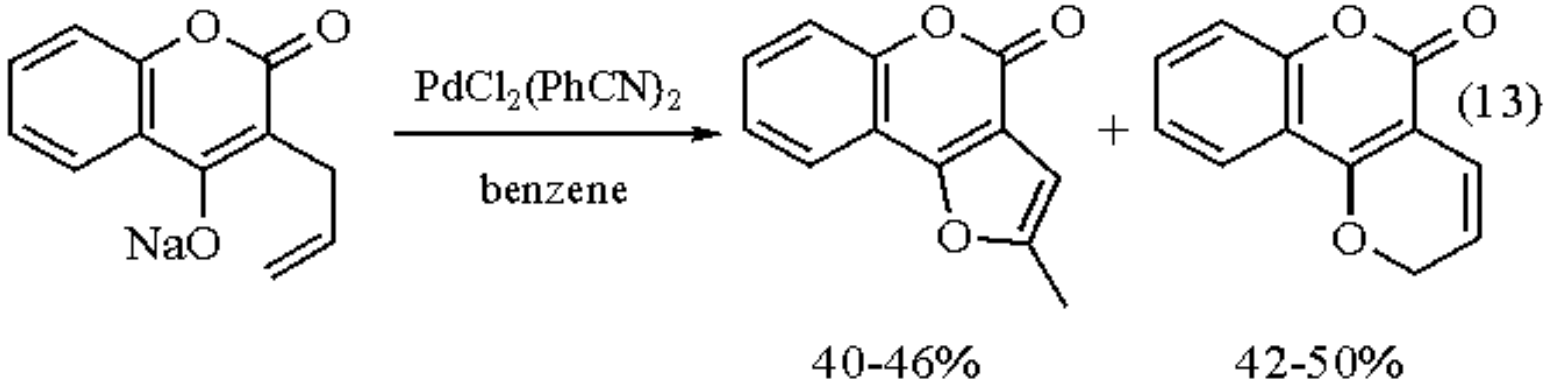

(13)

Reaction with Carboxylic Acids.[2c]

The intramolecular reaction of carboxylic acids with alkenes affords unsaturated lactones (eq 14).[16]

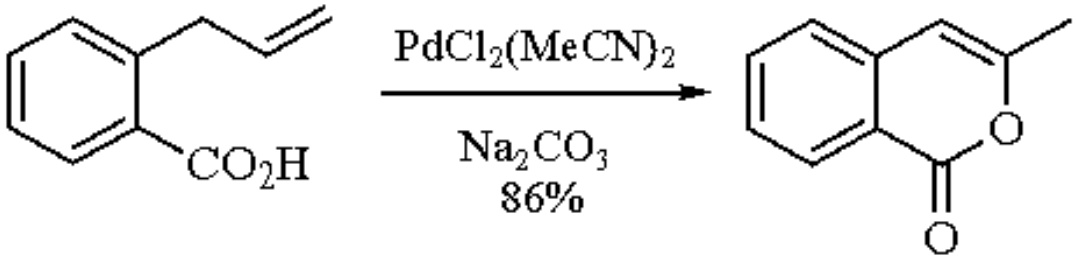

(14)

Reaction with Amines and Amides.[2c]

Reaction of amines with alkenes proceeds most smoothly as an intramolecular version. Amides can be used in the intramolecular reaction to afford various heterocyclic compounds. In the example shown in eq 15, it should be noticed that the Pd^{II} species is regenerated by the β-elimination of OH, rather than the β-hydrogen. For this reason the reaction proceeds catalytically without a Pd^{0} reoxidant.[17]

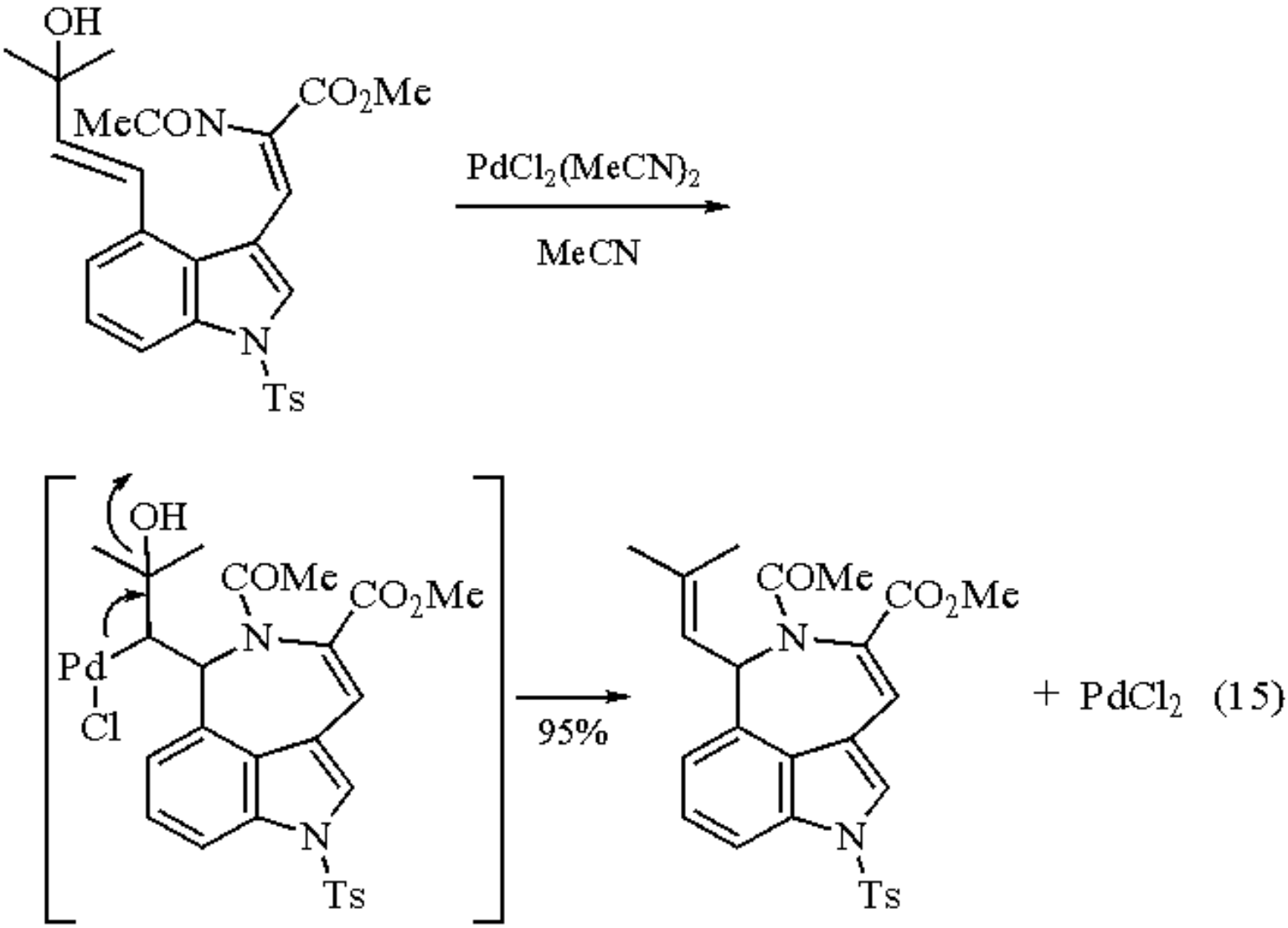

Reaction with Carbon Nucleophiles.

The cyclooctadiene (cod) complex of $PdCl_2$, which is insoluble in organic solvents, reacts in ether with malonate or acetoacetate under mild heterogeneous conditions; facile carbon-carbon bond formation takes place to give a new complex in a quantitative yield. Further intramolecular reaction of the complex with a base affords the cyclopropane derivative. Attack of a second malonate on the complex yields the [3.3.0] system (eq 16).[18] Carbopalladation of the double bond of *N*-vinylcarbamate with acetoacetate at -78 °C, and subsequent carbonylation of the Pd-carbon bond, proceeds smoothly to yield the carbocarbonylation product in 92% yield (eq 17).[19]

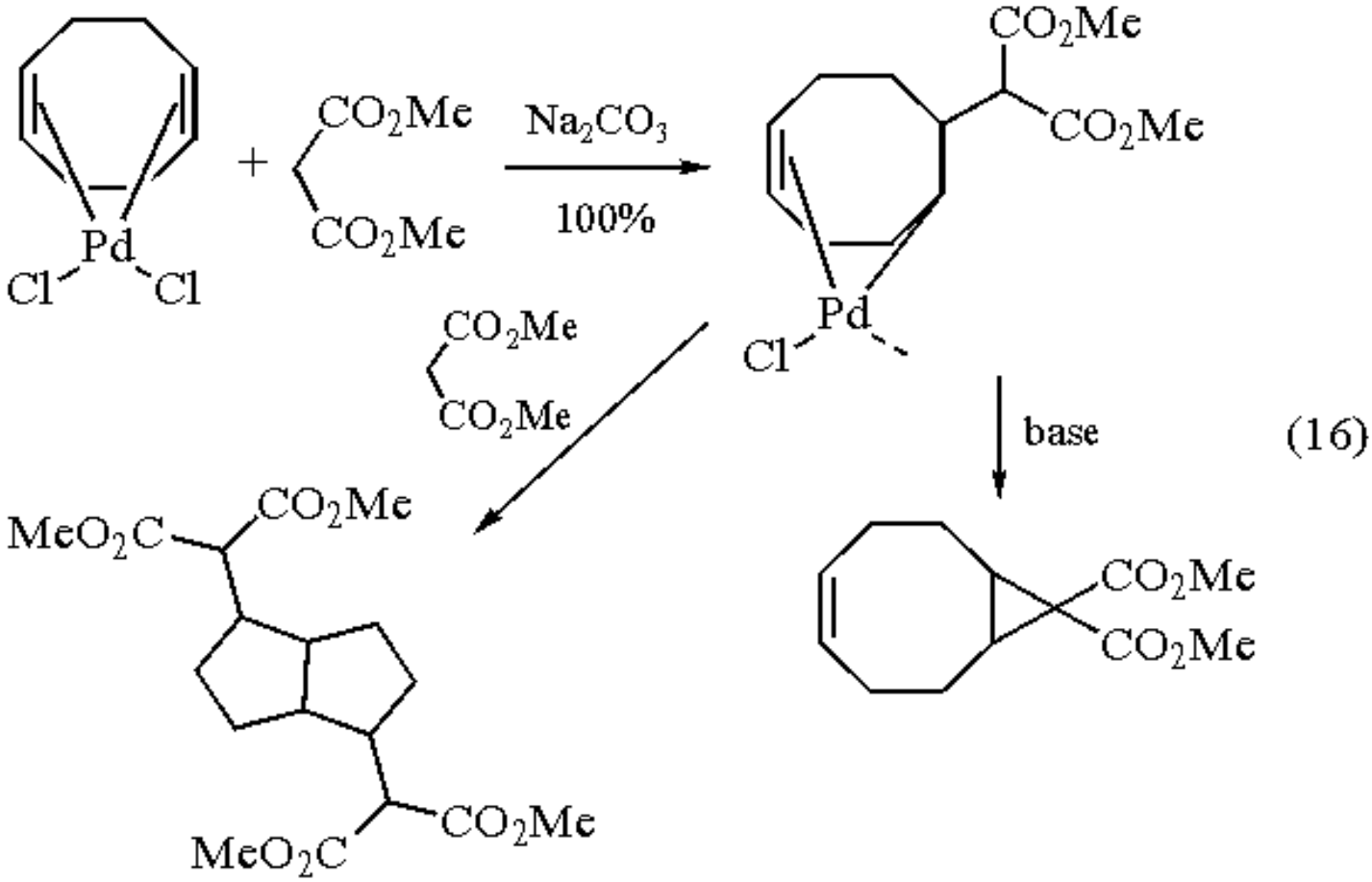

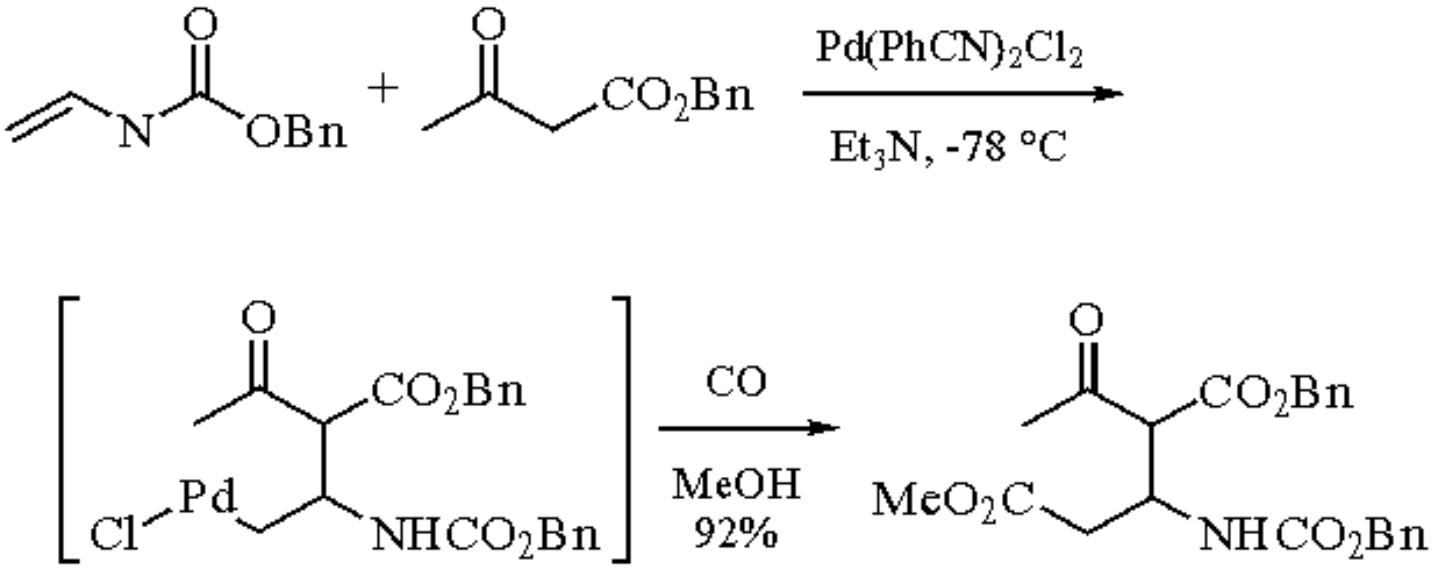

π-Allypalladium Complex Formation.[20]

π-Allylpalladium complexes are prepared by the reaction of alkenes with $PdCl_2$ or its soluble forms under various conditions (eq 18).[21] These π-allylpalladium chloride complexes react with carbon nucleophiles in DMSO as a coordinating solvent to form carbon-carbon bonds.[22] Thus π-allylpalladium complexes are clearly different in chemical reactivity from other organometallic reagents, which normally react with electrophiles (eq 19).

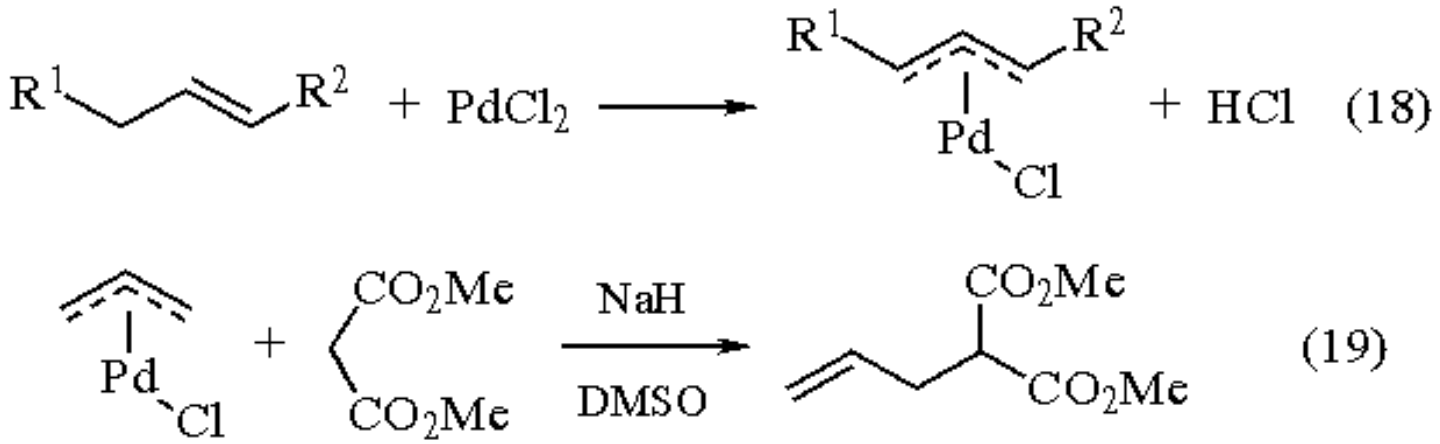

Based on this reaction, allylic alkylation of alkenes is possible. Active methylene compounds, such as malonates and β-keto esters, can be introduced to a steroid skeleton by the reaction of the steroidal π-allylpalladium complex in DMSO (eq 20).[23] The reaction of carbon nucleophiles also proceeds in the presence of an excess of ***Triphenylphosphine*** (eq 21).[24]

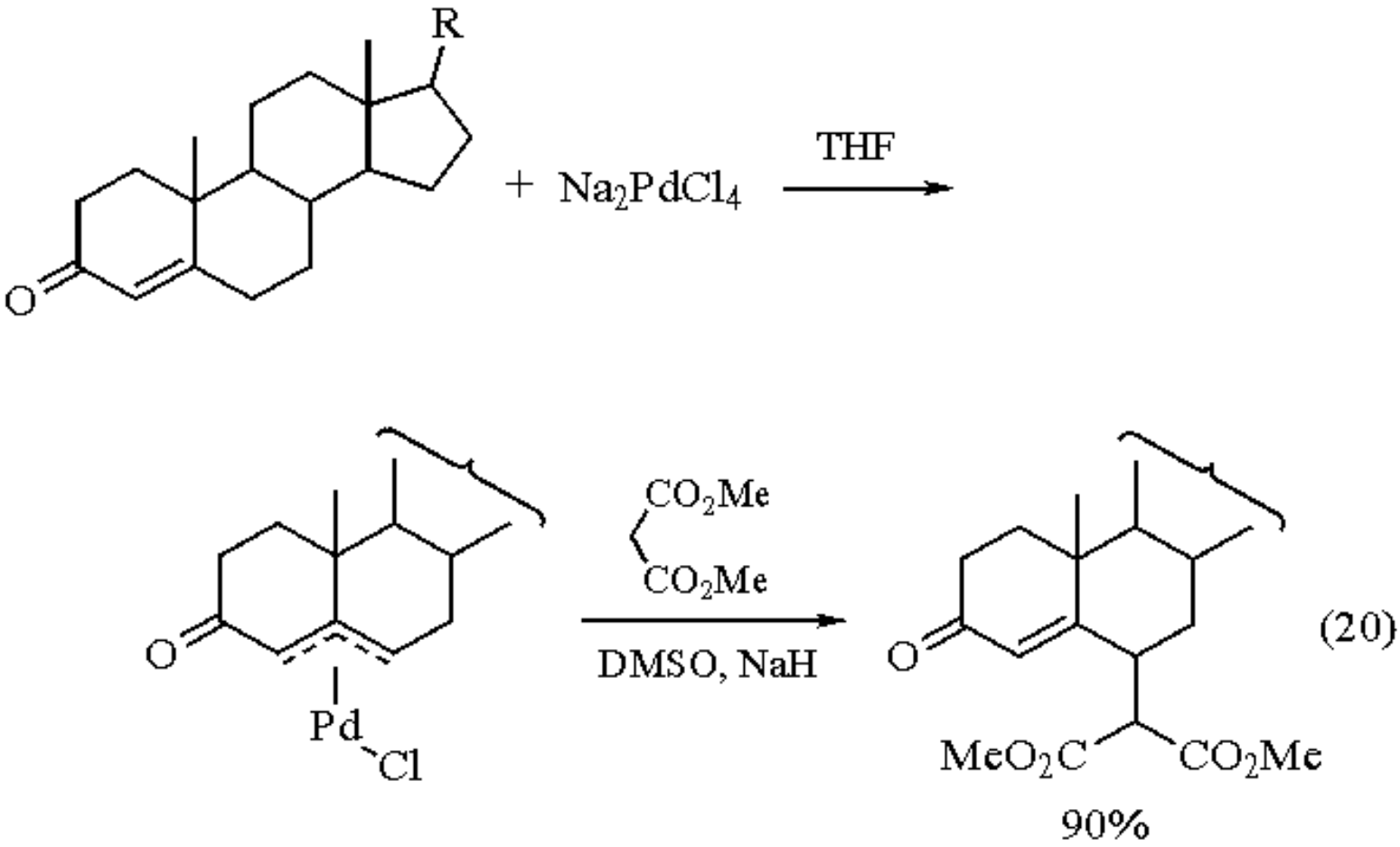

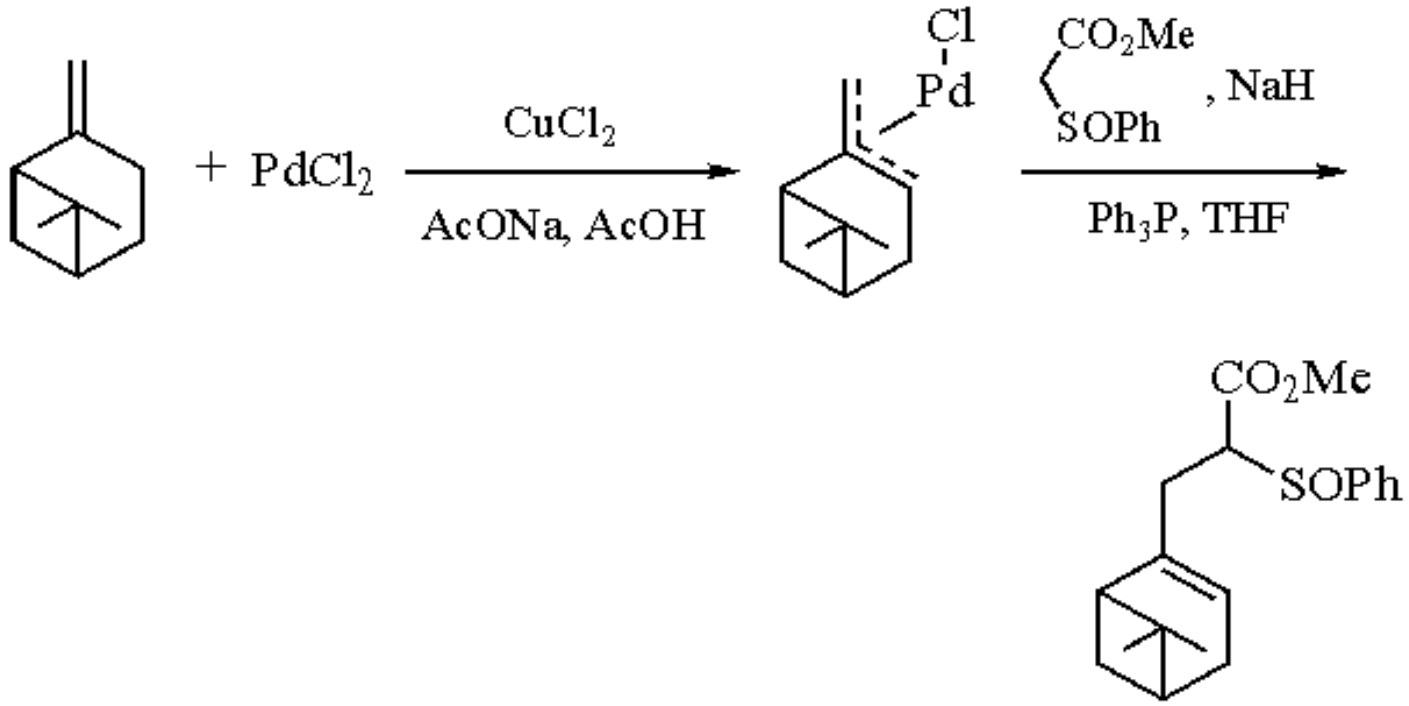

(21)

ortho-Palladation of Aromatic Compounds and Cyclopalladation of Allyl and Homoallyl Compounds.[25]

Azobenzene,[26] *N*,*N*-dimethylbenzylamine,[27] and related aromatic compounds react with Na_2PdCl_4 in ethanol to form stable *ortho*-palladation complexes. These carbon-palladium σ-bonded complexes are useful for the preparation of *ortho*-substituted aromatic compounds by the facile insertion of alkenes, alkynes, and CO. For example, insertion of CO to the azobenzene complex affords 2-aryl-3-indazolone (eq 22),[28] and facile insertion of styrene to the benzylamine complex yields a stilbene derivative (eq 23).[1a,29]

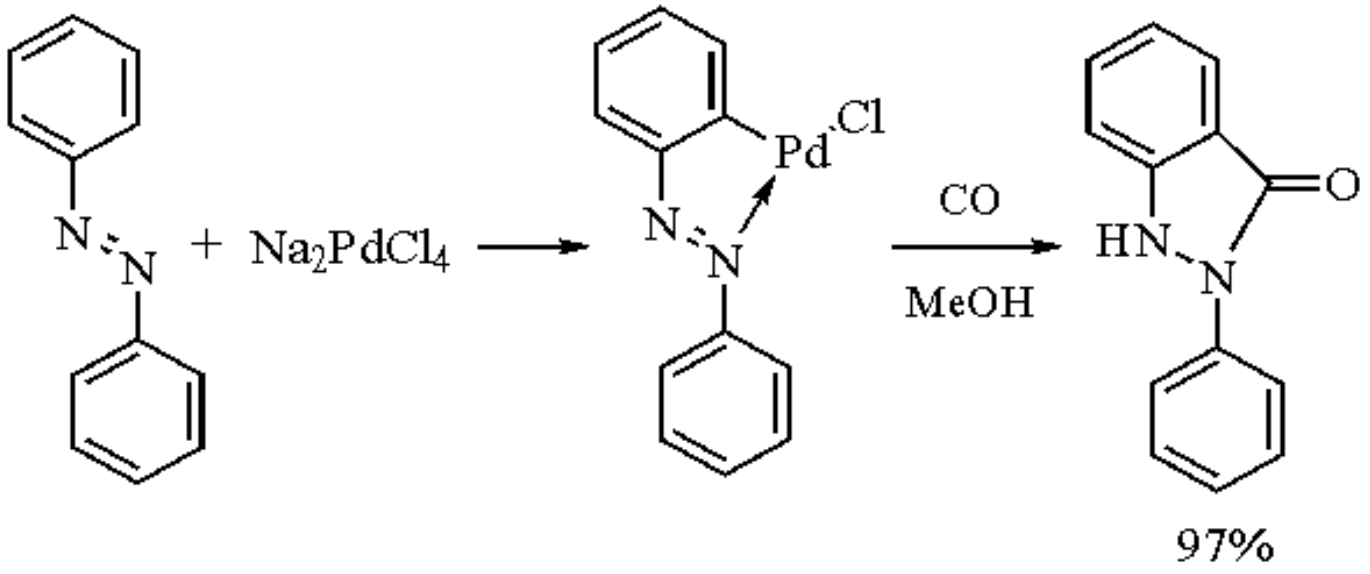

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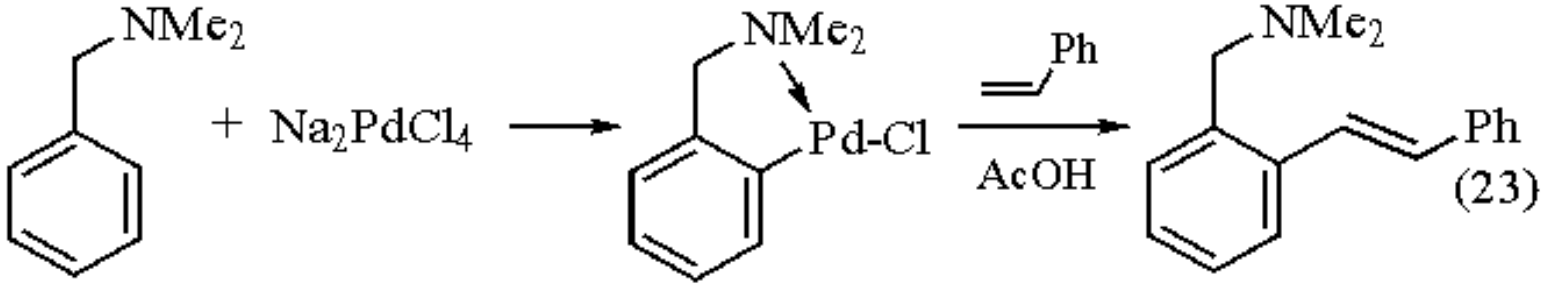

The cyclopalladation of allylic or homoallylic amines and sulfides proceeds due to the chelating effect of N and S atoms, and has been used for functionalization of alkenes. For example, *i*-propyl 3-butenyl sulfide is carbopalladated with methyl cyclopentanecarboxylate and Li_2PdCl_4. Reduction of the chelated complex with ***Sodium Cyanoborohydride*** affords the alkylated keto ester in 96% yield (eq 24).[30] Functionalization of 3-*N*,*N*-dimethylaminocyclopentene for the synthesis of a prostaglandin skeleton has been carried out via a *N*-chelated palladium complex as an intermediate. In the first step, malonate was introduced regio- and stereoselectively by carbopalladation (eq 25).[31] Elimination of a β-hydrogen generated a new cyclopentene, and its oxypalladation with 2-chloroethanol, followed by insertion of 1-octen-3-one and β-elimination, afforded the final product.

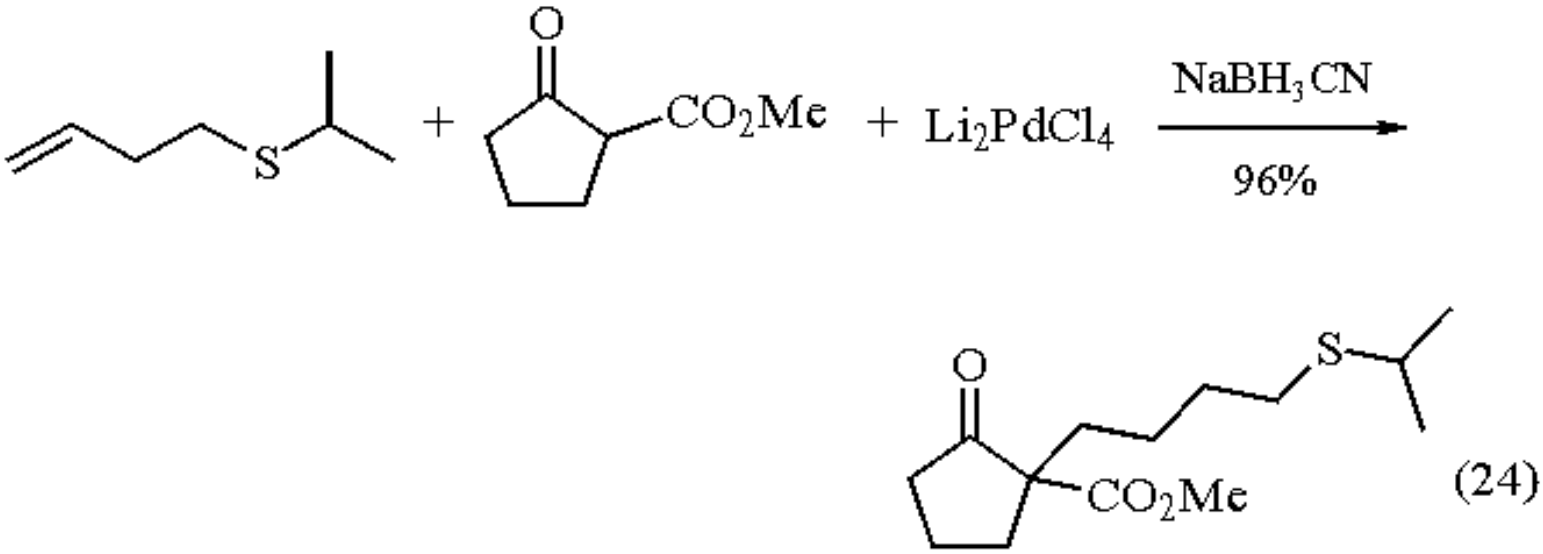

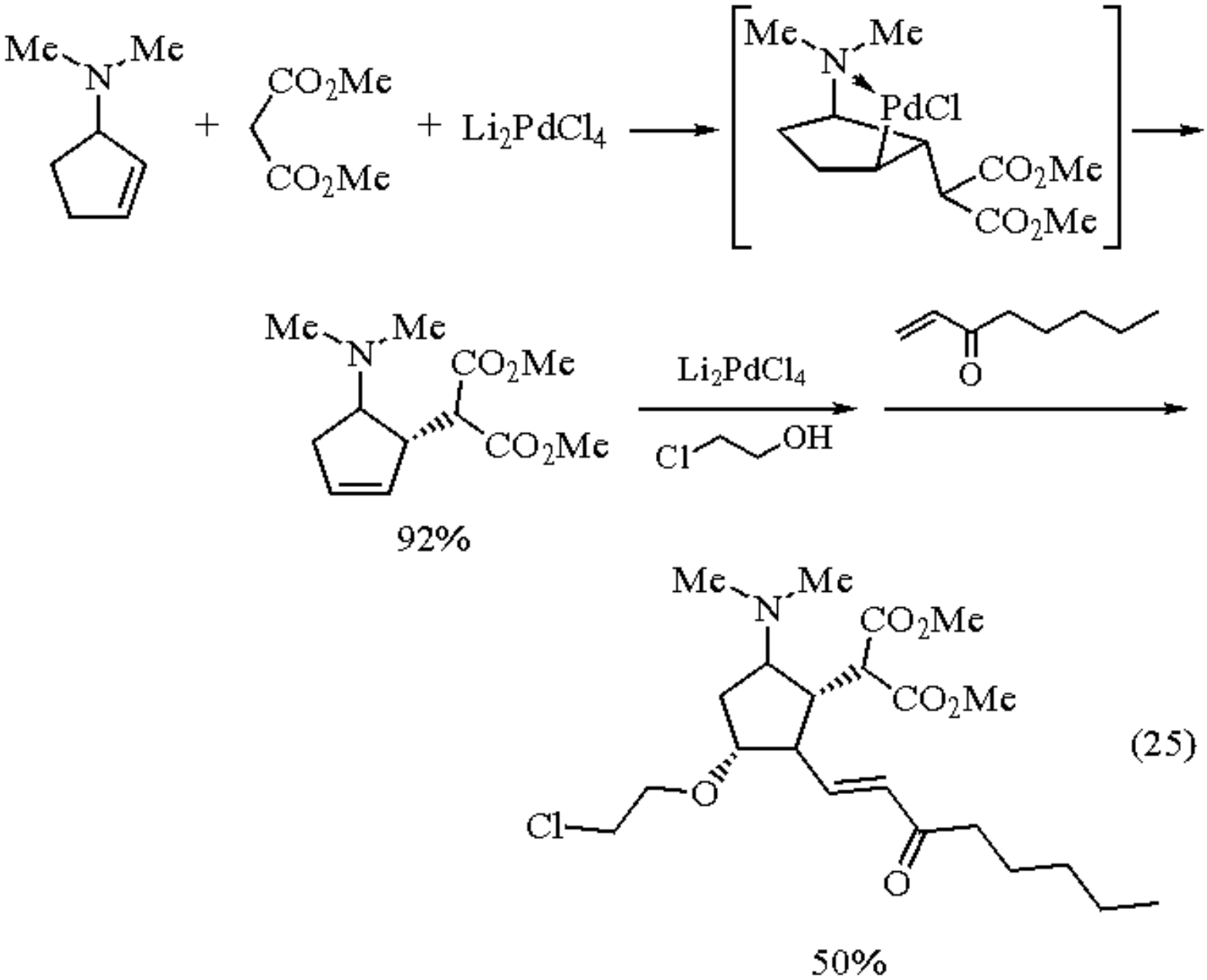

(25)

Oxidative Carbonylation.[32]

Oxidative Carbonylation of Alkenes.

Oxidative carbonylation of alkenes with $PdCl_2$ in benzene affords β-chloroacyl chlorides (eq 26).[33] Oxidative carbonylation of alkenes in alcohol affords α,β-unsaturated esters and β-alkoxy esters by monocarbonylation and succinate derivatives by dicarbonylation (eq 27).[34]

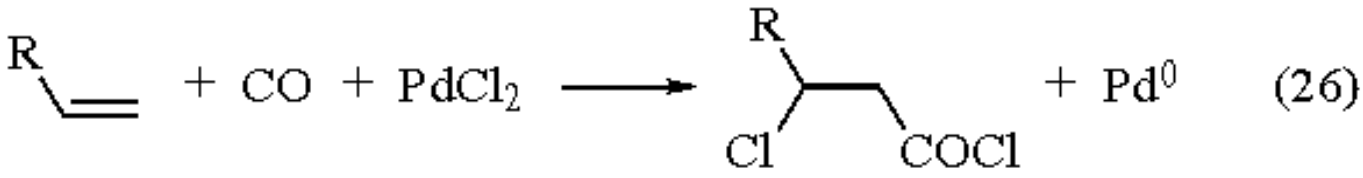

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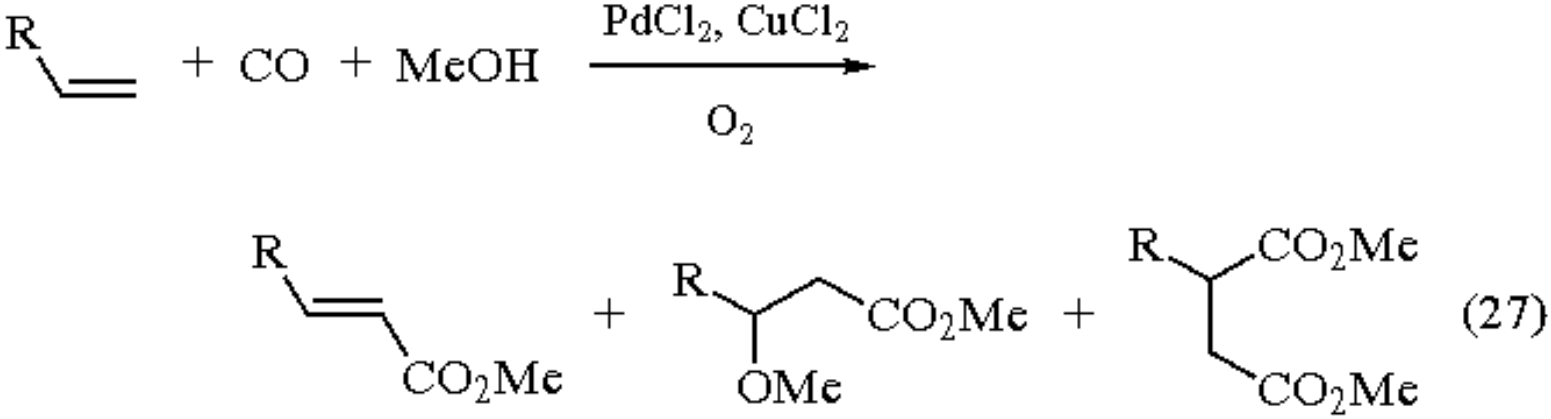

Intramolecular oxycarbonylation and aminocarbonylation are also known. As an example, frenolicin has been synthesized using oxycarbonylation at 1.1 atm of CO as a key step (eq 28).[35] The intramolecular aminopalladation of a carbamate group and subsequent carbonylation of the substituted 3-hydroxy-4-pentenylamine proceeds smoothly in AcOH (eq 29).[36]

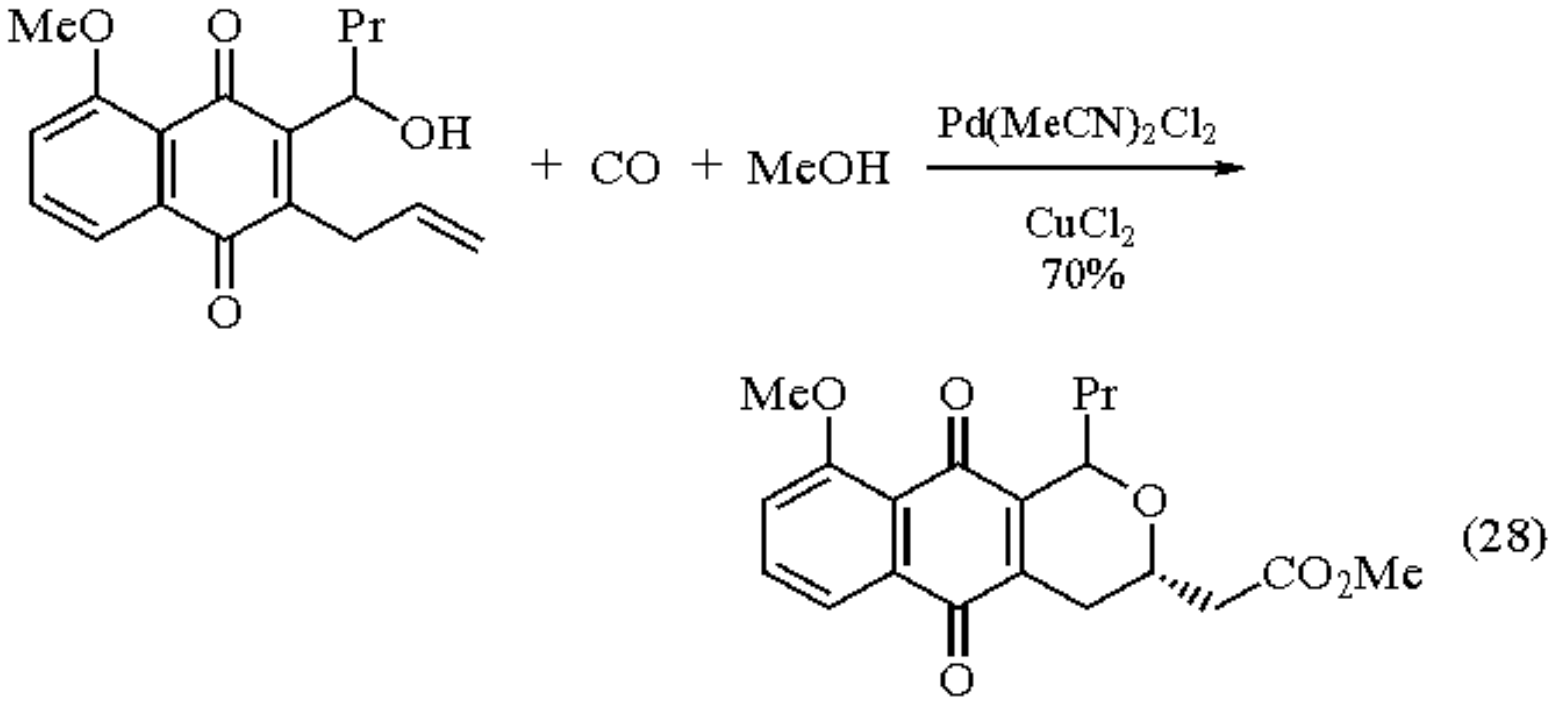

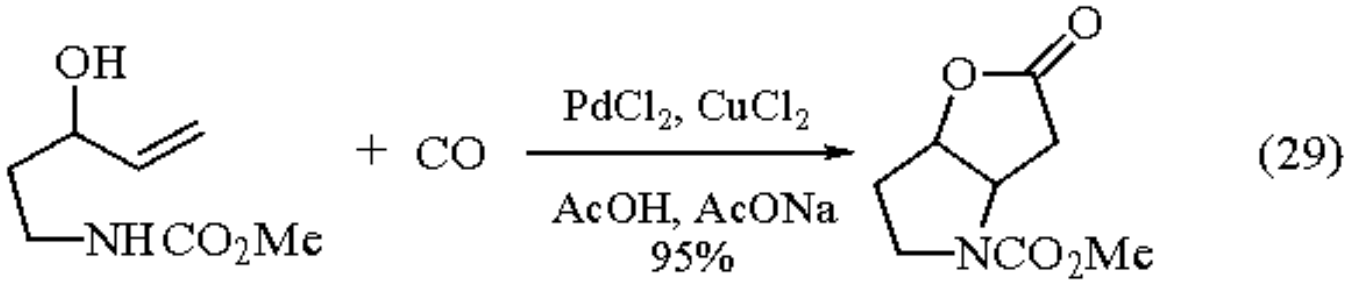

Oxidative Carbonylation of Alkynes.

Terminal alkynes are carbonylated to give acetylenecarboxylates using $PdCl_2$ and $CuCl_2$ as catalysts (eq 30).[37] The

acetylenecarboxylate in a β-lactam has been prepared by this procedure and then converted to a β-keto ester (eq 31).[38]

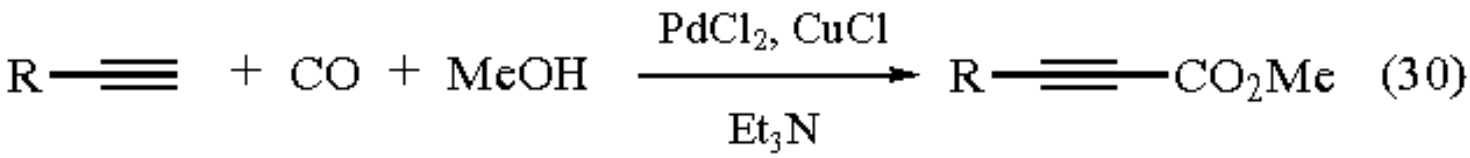

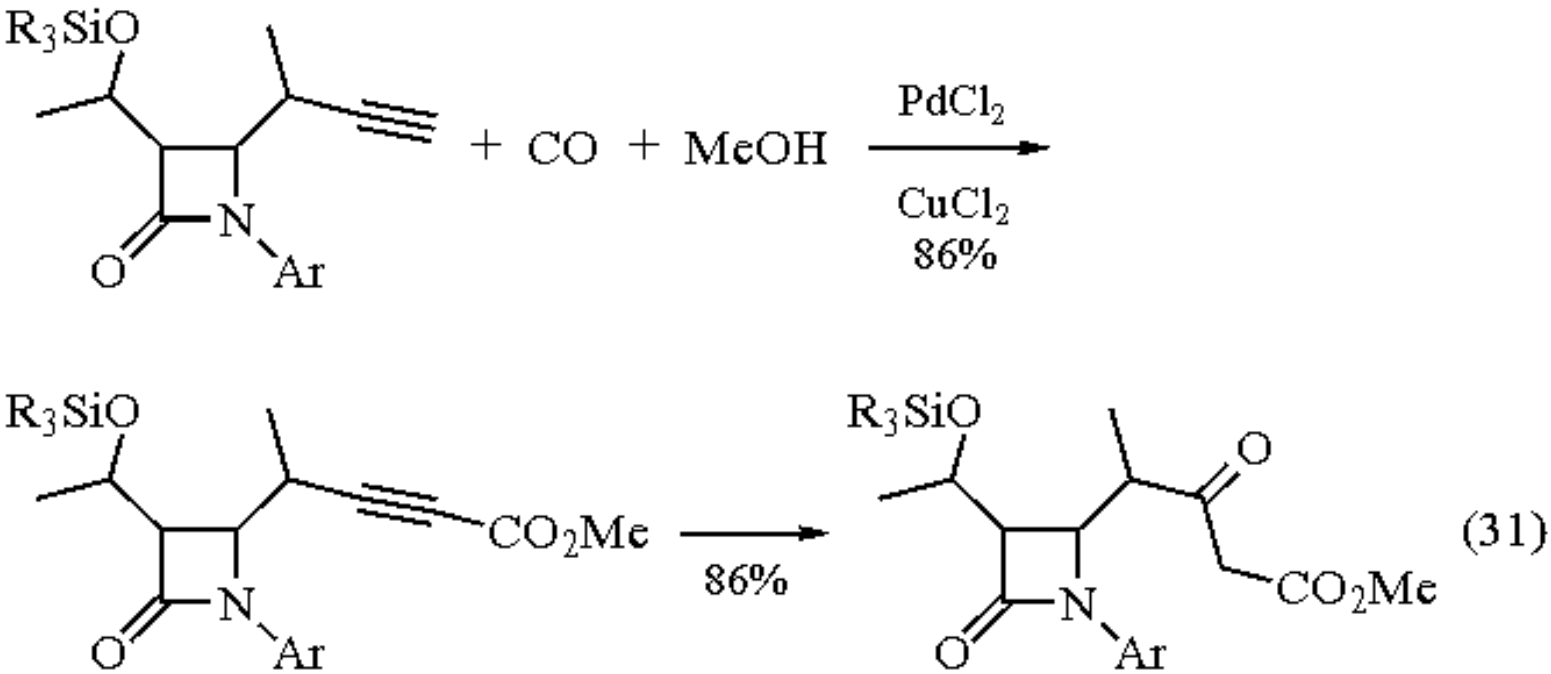

Oxidative dicarbonylation of acetylene with $Pd(PhCN)_2Cl_2$ in benzene affords the chlorides of maleic, fumaric, and muconic acids (eq 32).[39] Methyl muconate is obtained by passing acetylene and oxygen through MeOH containing thiourea and a catalytic amount of $PdCl_2$.[40] The oxidative dicarbonylation of alkynes produces maleate derivatives as a main product using $PdCl_2$ and $CuCl_2$ as catalysts under oxygen in alcohol.[41]

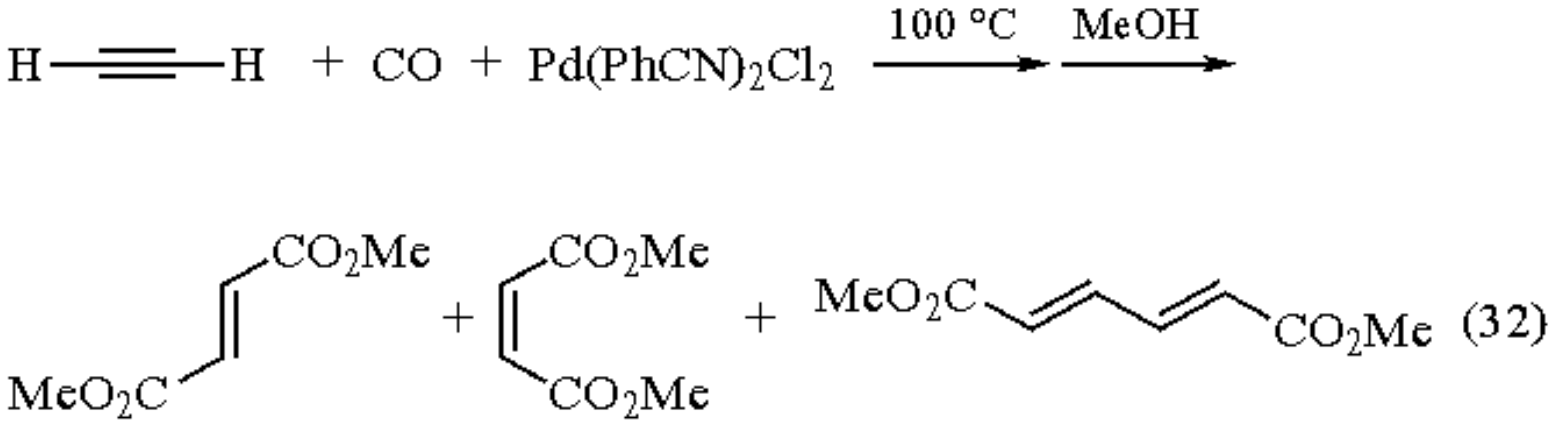

Oxidative Carbonylation of Alcohols.

Oxalates and carbonates are formed by the oxidative carbonylation of alcohols. The reaction can be made catalytic by using $PdCl_2$ and $CuCl_2$ under oxygen in the alcohol.[42] Either oxalate or carbonate is obtained chemoselectively under different conditions (eq 33). Alkyl oxalates are produced commercially using alkyl nitrites as reoxidants (eq 34).[43]

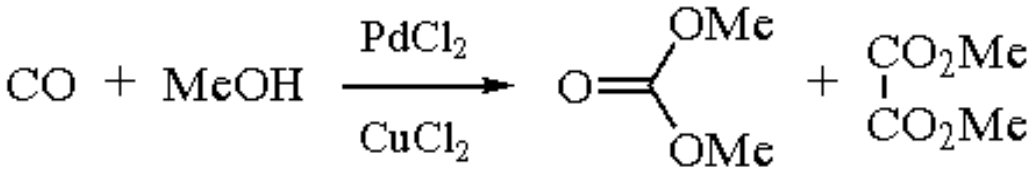

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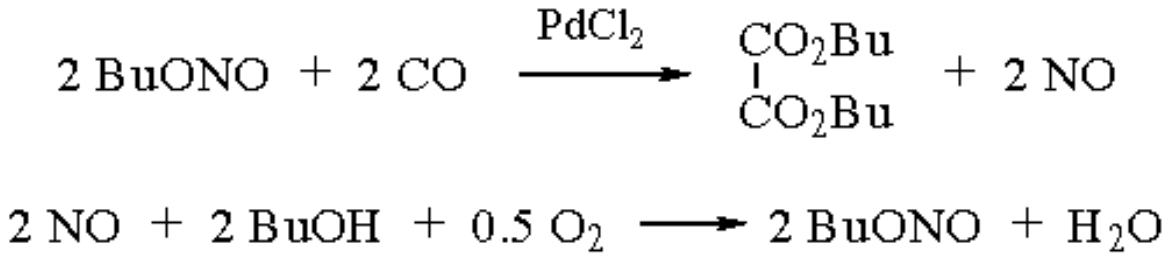

(34)

Reactions via Transmetallation of Organometallic Reagents.

Transmetalation of organometallic compounds of Hg, B, Sn, Si, Tl, etc., with $PdCl_2$ produces the reactive organopalladium species, which undergoes insertion and coupling reactions. Aryl- or alkenylpalladium complexes, generated in situ from aryl- or alkenylmercury compounds, undergo insertion reactions with alkenes;[44,45] an example is shown in eq 35.[46] The arylmercury compound with 1,3-cyclohexadiene and Li_2PdCl_4 generates a π-allylpalladium intermediate, which then attacks the amide group intramolecularly to yield the cyclized product (eq 35).[46] CO insertion produces ketones and esters.[47] The *ortho*-thallation of benzoic acid and subsequent transmetalation with Pd^{II} generates a reactive arylpalladium complex, which reacts with butadiene to give an isocoumarin (eq 36).[48]

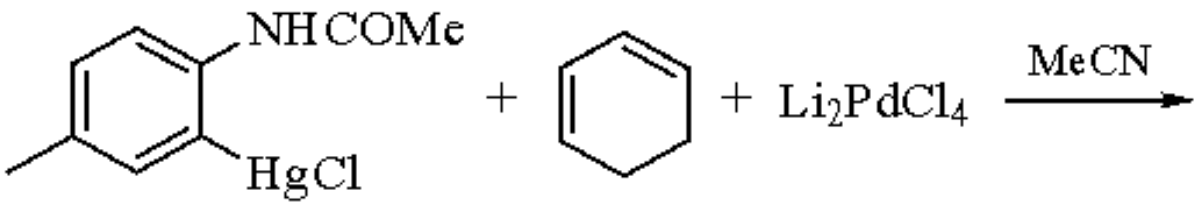

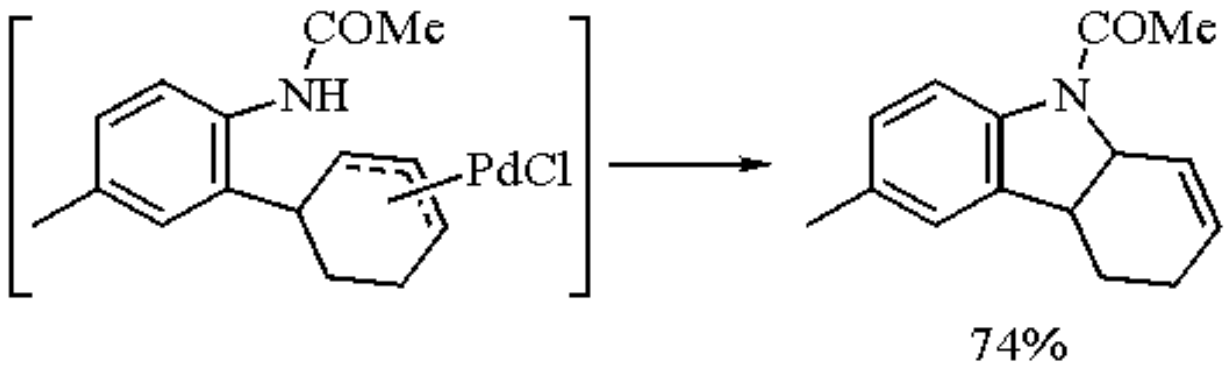

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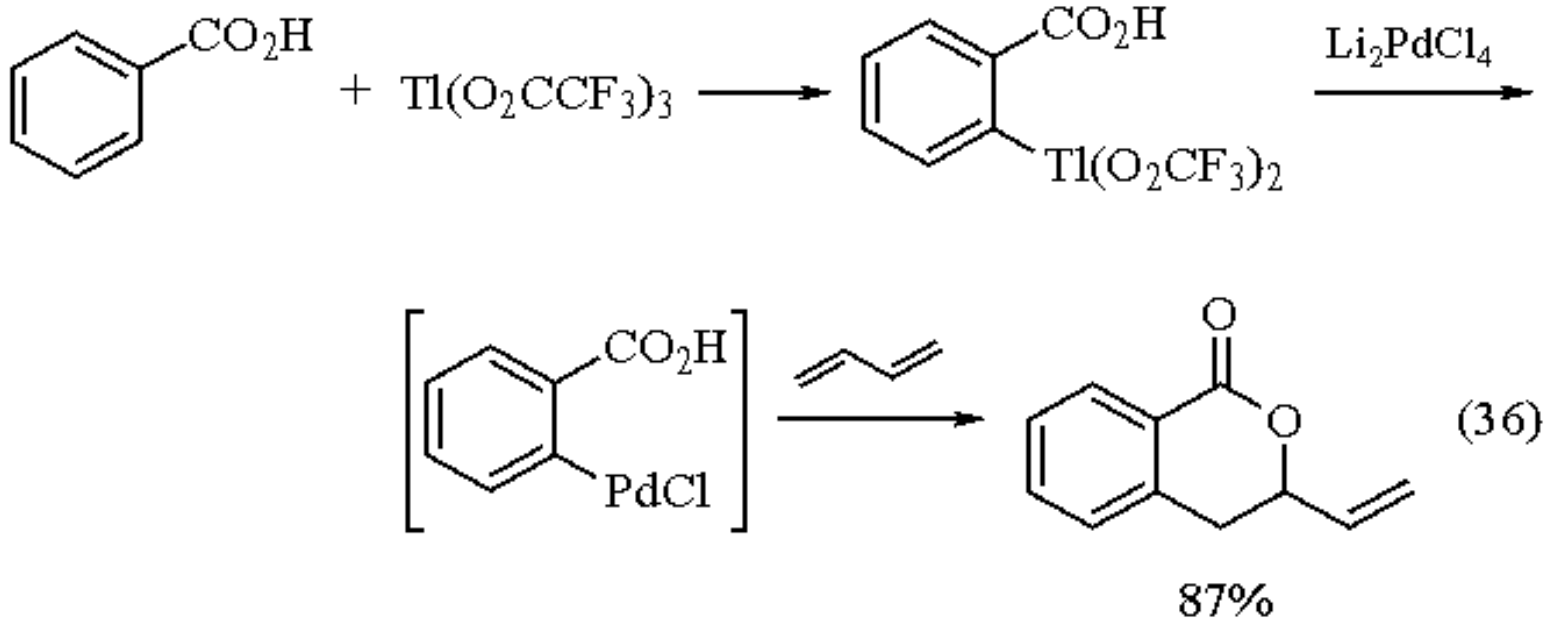

α,β-Unsaturated esters are obtained by the carbonylation of alkenylboranes[49] and alkenyl- or arylpentafluorosilicates (eq 37).[50] Conjugated dienes and diaryls are formed by the coupling of alkenyl- and arylstannanes. The homocoupling of the vinylstannane of benzoquinone is catalyzed by $PdCl_2(PhCN)_2$ with benzoquinone as the reoxidant (eq 38).[51]

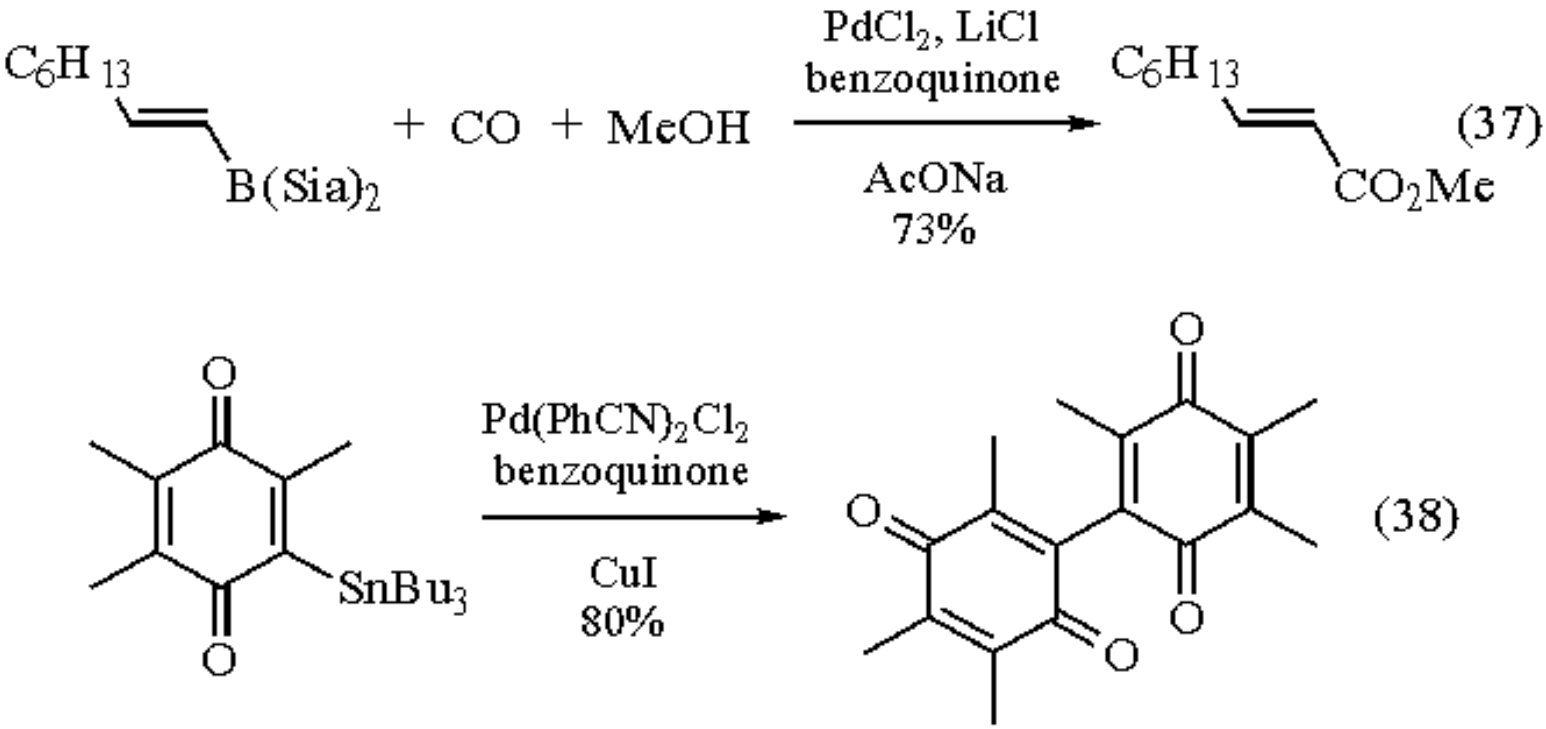

Miscellaneous Oxidation Reactions.

Some oxidative reactions can be carried out only with $Pd(OAc)_2$, but not with $PdCl_2$. However, $Pd(OAc)_2$ can be generated in situ by the reaction of $PdCl_2$ with AcOK or AcONa. The oxidative coupling of aromatic rings is a typical example of a $Pd(OAc)_2$-promoted reaction. The following coupling reaction proceeds by $Pd(OAc)_2$ generated in situ from $PdCl_2$ (eq 39).[52]

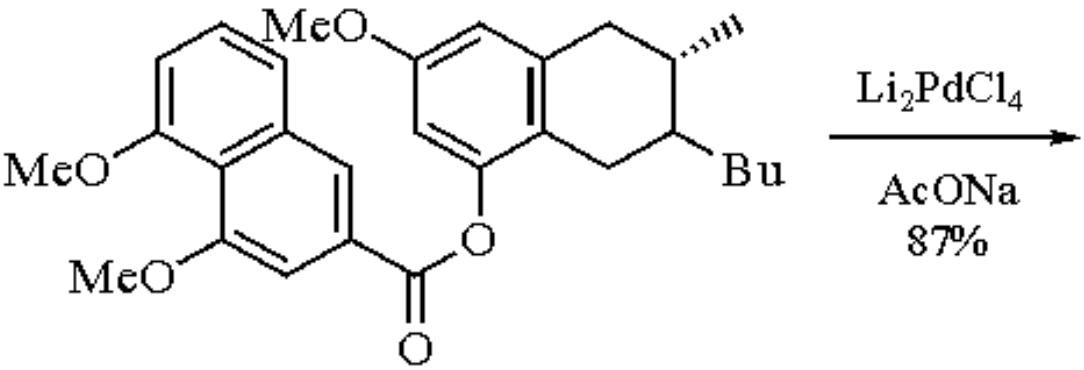

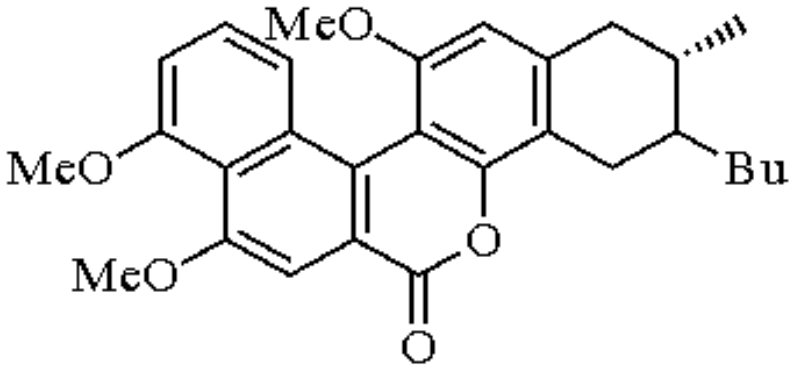

(39)

The following oxidative rearrangement of a propargylic ester proceeds with a catalytic amount of $PdBr_2$ under oxygen. Interestingly, the reoxidation of Pd^0 takes place with oxygen without addition of other reoxidants (eq 40).[53]

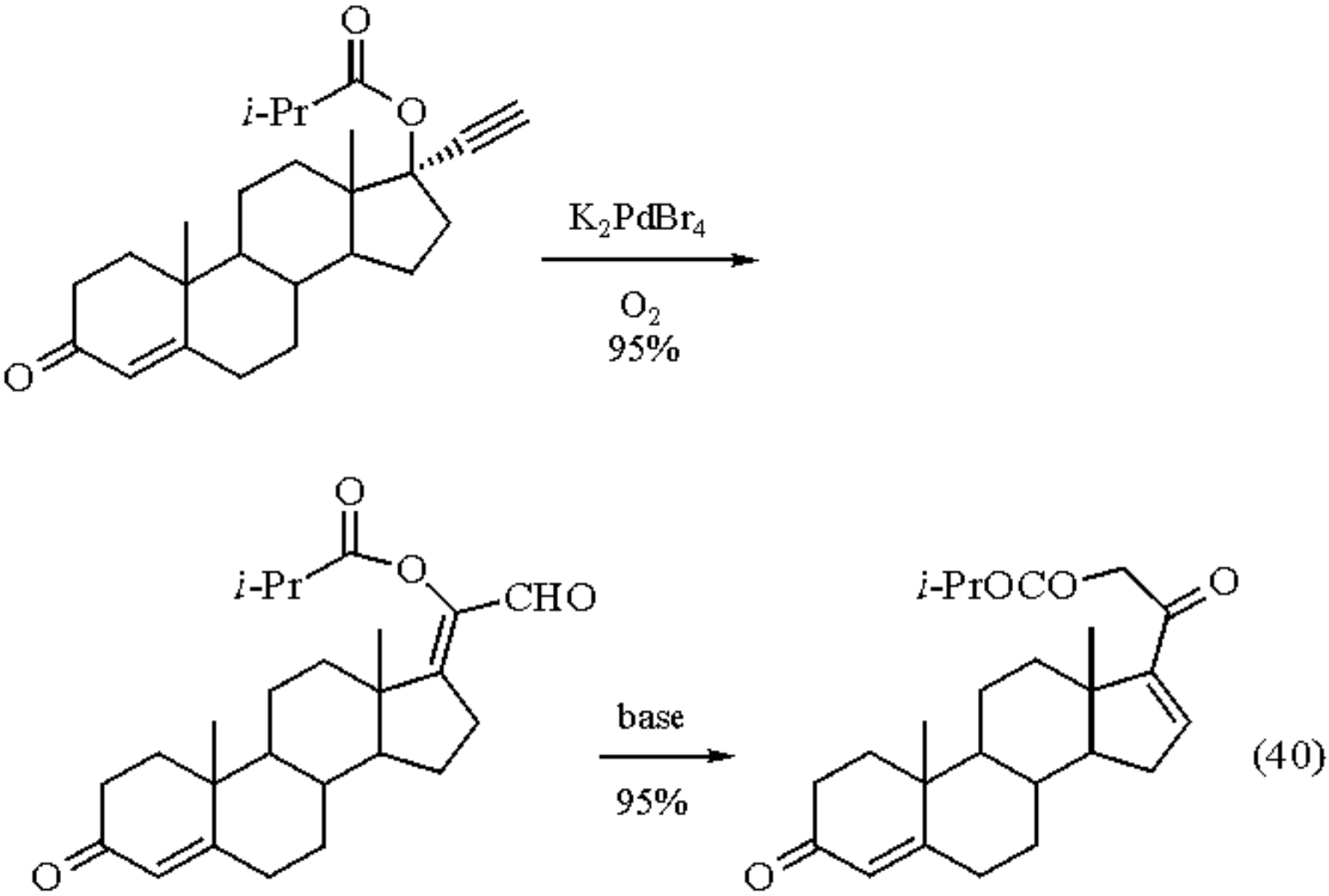

Catalytic Reactions with Pd^{II}.

Exchange Reactions of Vinyl Ethers and Esters.[54]

Vinyl ethers are activated by Pd^{II}. Exchange with other alcohols to give mixtures of acetals and vinyl ethers is catalyzed by $PdCl_2$ (eq 41).[55] This reaction was used as the key step in the total synthesis of rhizobitoxine (eq 42).[56]

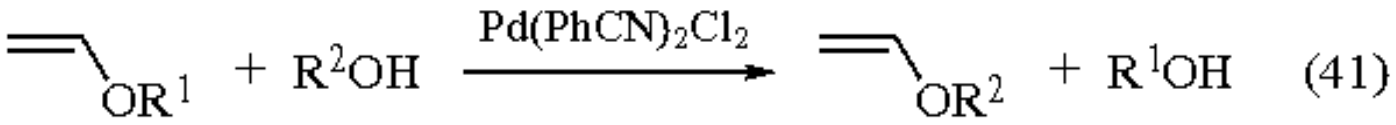

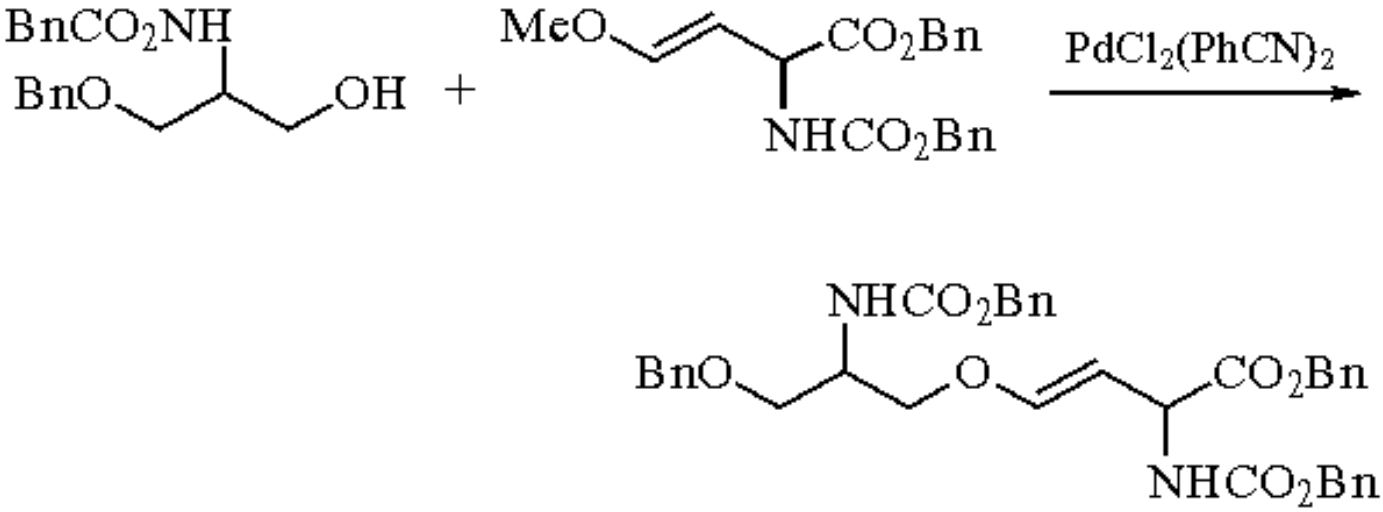

(42)

The exchange reaction of the acid component of vinyl esters with other acids is catalyzed by $PdCl_2$ (eq 43).[54] Thus various vinyl esters are prepared from easily available ***Vinyl Acetate***. As an example, vinyl itaconate is prepared by the reaction of vinyl acetate with itaconic monomethyl ester (eq 44).[57] *N*-Vinyllactams and cyclic imides are prepared by the exchange reaction of lactams and imides with vinyl acetate (eq 45).[58]

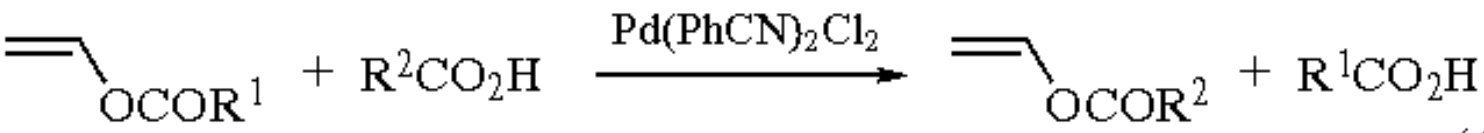

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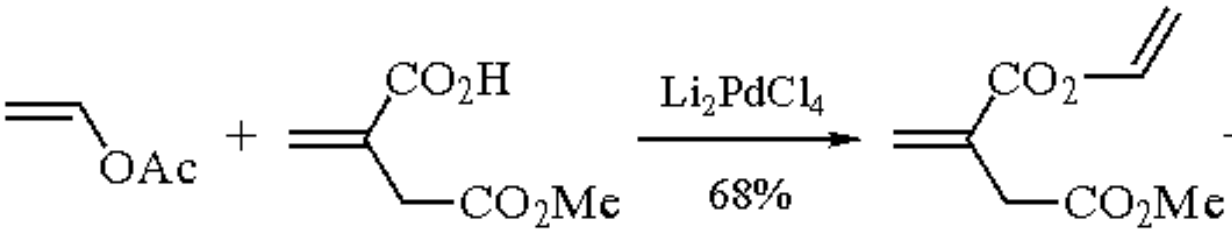

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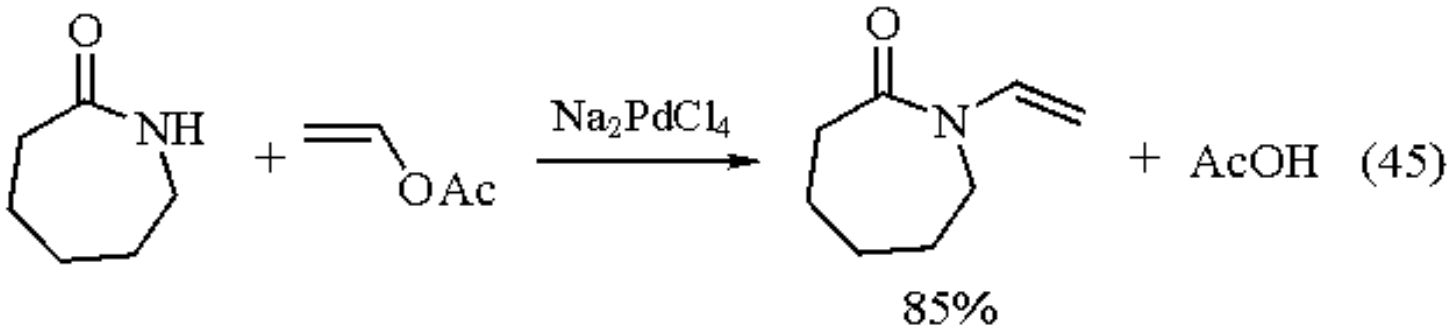

(45)

Pd^{II}-Catalyzed Rearrangement Reactions.

Cope rearrangements are accelerated by catalytic amounts of $Pd(PhCN)_2Cl_2$, such that they proceed at room temperature in benzene or CH_2Cl_2 (eq 46).[59] Successful Pd^{II} catalysis appears to require that atoms 2 and 5 of the substituted 1,5-hexadienes have one H and one nonhydrogen substituent.[60] Oxy-Cope rearrangements proceed at room temperature

using $Pd(PhCN)_2Cl_2$ catalysis (eq 47).[61]

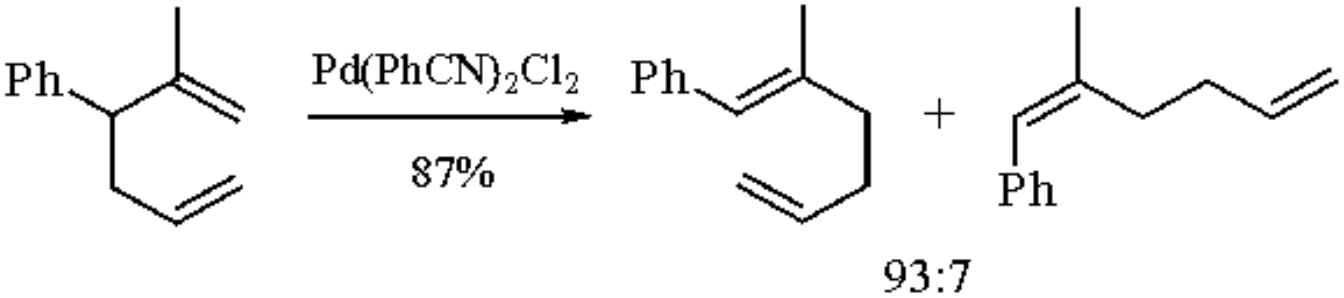

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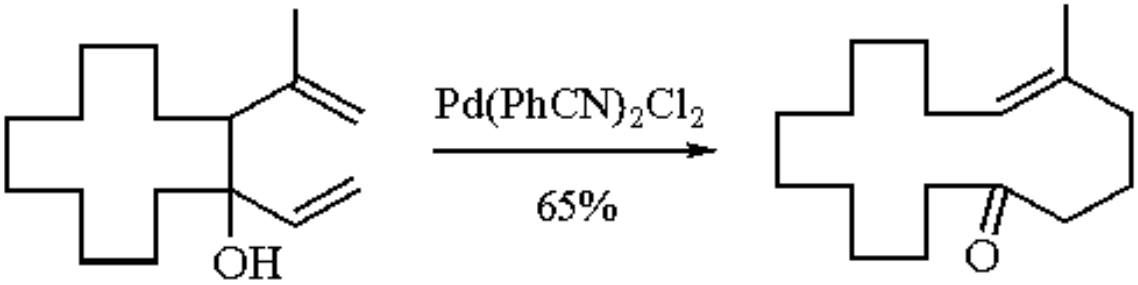

(47)

The $Pd(PhCN)_2Cl_2$ catalyzed Claisen rearrangement of allyl vinyl ethers has been studied to a lesser extent. The Claisen rearrangement shown in eq 48 proceeds smoothly even at room temperature to give the *syn* product with high diastereoselectivity.[62] The Claisen rearrangement of 2-(allylthio)pyrimidin-4-(3*H*)-one affords the *N*-1 allylation product as a main product rather than the *N*-3 allylation product (eq 49).[63]

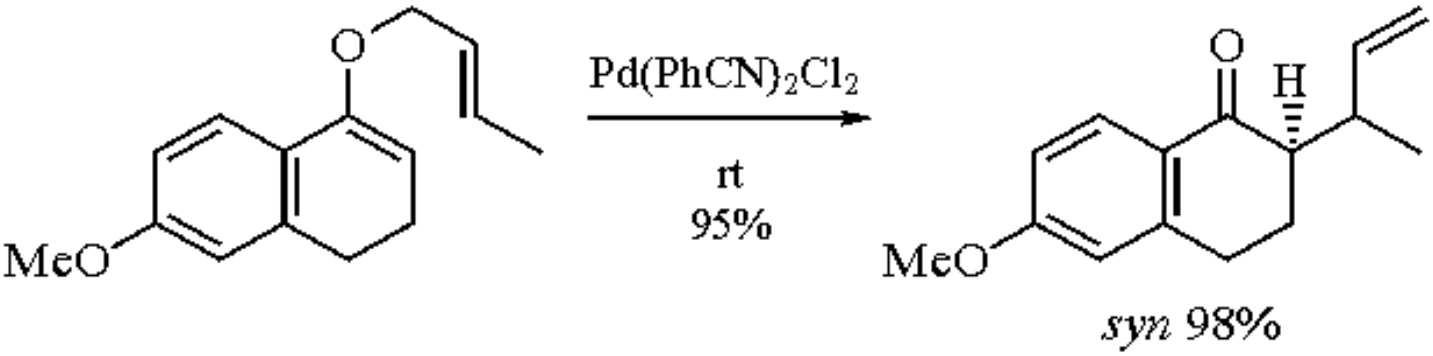

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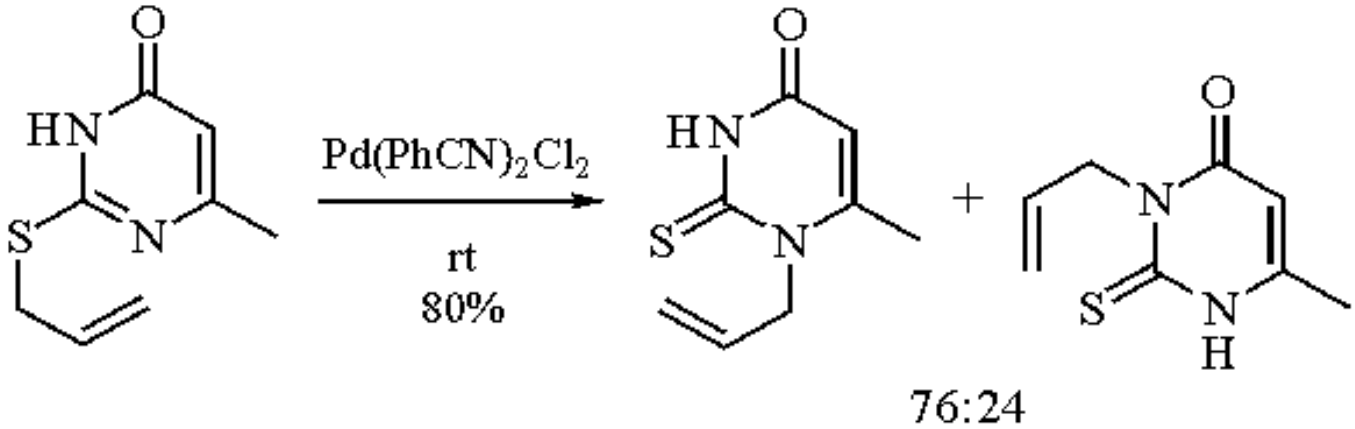

(49)

The rearrangement of allylic esters, a useful reaction, is catalyzed efficiently by Pd^{II}.[64] The allylic rearrangement shown

in eq 50, used in a prostaglandin synthesis, proceeds in one direction irreversibly, yielding the thermodynamically more stable product possibly due to steric reasons.[65] The diacetate of a 1,5-diene-3,4-diol is isomerized to the more stable conjugated diene with complete transfer of chirality (eq 51).[66] The Pd^{II}-catalyzed allylic rearrangement has been explained by an oxypalladation or cyclization-induced rearrangement. It is mechanistically different from rearrangements catalyzed by Pd^0 complexes, which proceed by formation of π-allylpalladium intermediates.

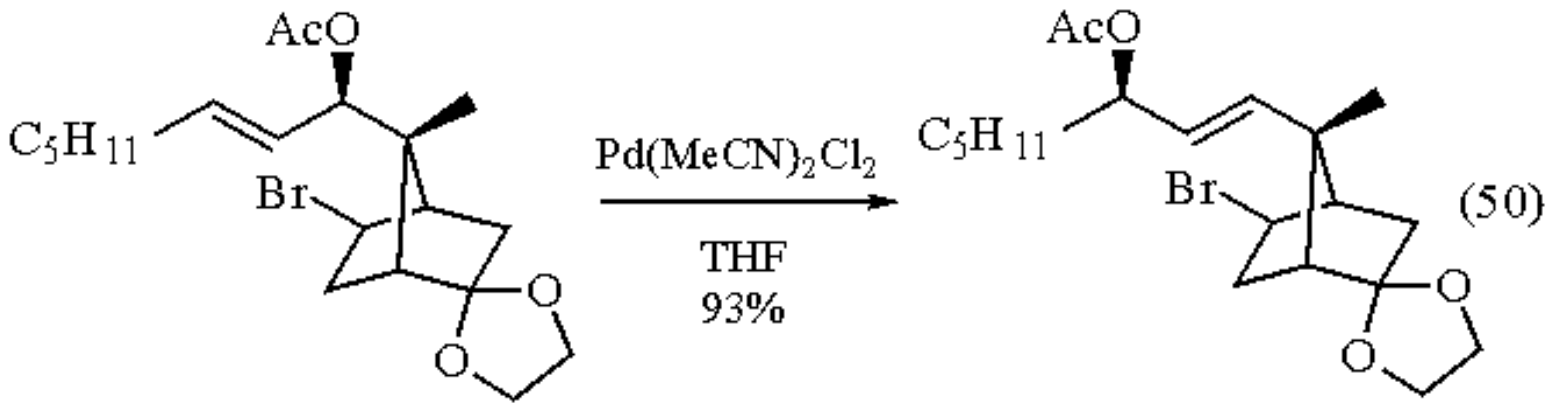

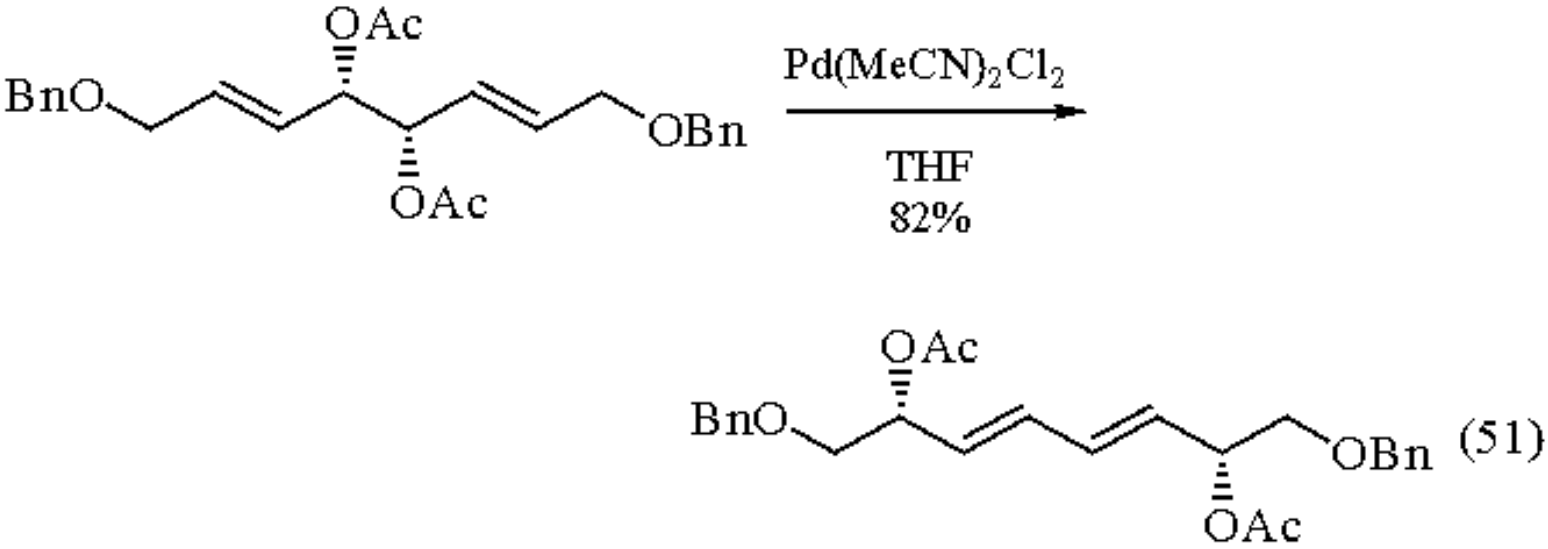

Skeletal rearrangements of some strained compounds, such as bulvalene to bicyclo[4.2.2]deca-2,4,7,9-tetraene,[67] cubane to cuneane,[68] hexamethyl Dewar benzene to hexamethylbenzene (eq 52),[69] and quadricyclane to norbornadiene (eq 53),[70] are catalyzed by derivatives of $PdCl_2$.

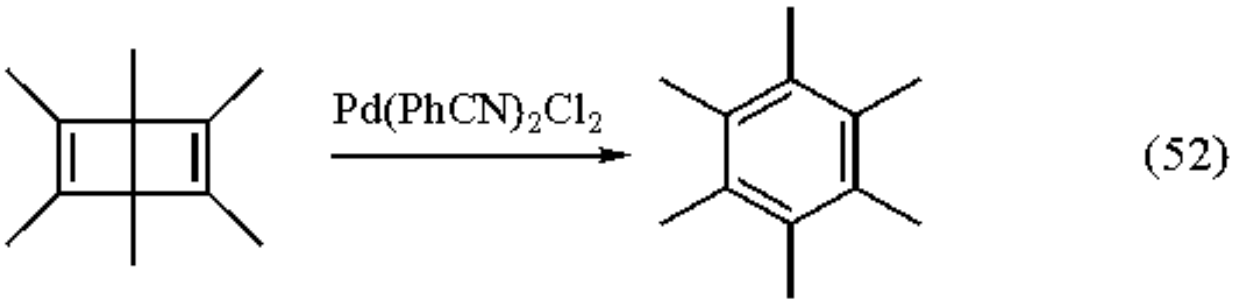

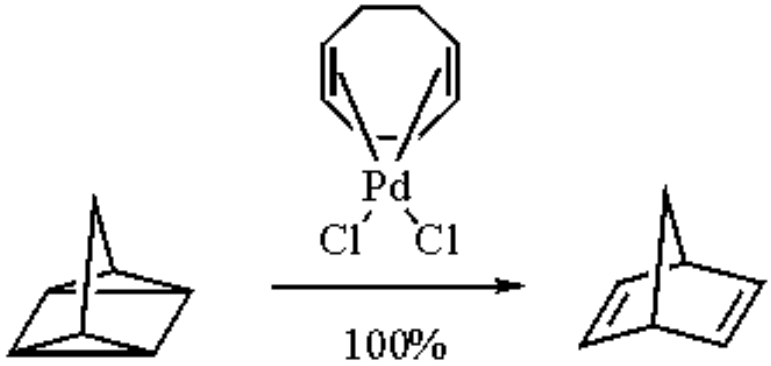

(53)

Intramolecular Reactions of Alkynes with Carboxylic Acids, Alcohols, and Amines.

Addition of carboxylic acids, alcohols, and amines to alkynes via oxypalladation and aminopalladation proceeds with catalysis by Pd^{II} salts. Intramolecular additions are particularly facile.[71] Unsaturated γ-lactones are obtained by the treatment of 3-alkynoic acid and 4-alkynoic acid with $Pd(PhCN)_2Cl_2$ in THF in the presence of Et_3N (eq 54), and δ-lactones are obtained from 5-alkynoic acids.[72] 5-Hydroxyalkynes are converted to the cyclic enol ethers (eq 55).[71] The oxypalladation is a *trans* addition. Thus stereoselective enol ether formation by reaction of the alkynoic alcohol with $Pd(PhCN)_2Cl_2$, followed by reduction with ***Ammonium Formate***, has been applied to the synthesis of prostacyclin (eq 56).[73] Intramolecular addition of amines affords cyclic imines. 3-Alkynylamines are cyclized to 1-pyrrolines while 5-alkynylamines are converted to 2,3,4,5-tetrahydropyridines (eq 57).[74]

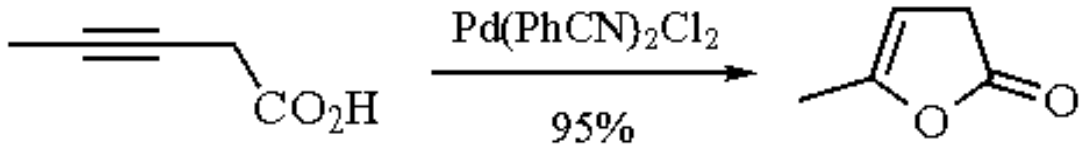

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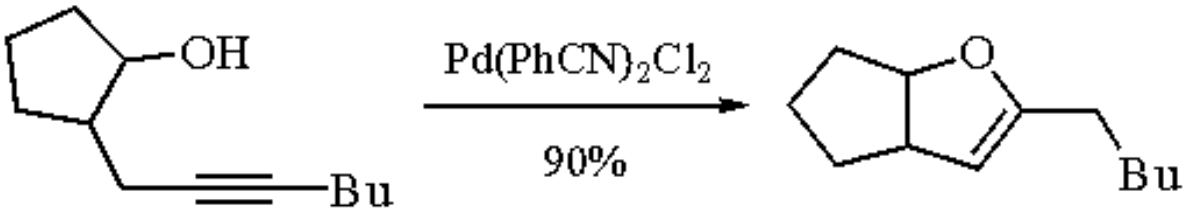

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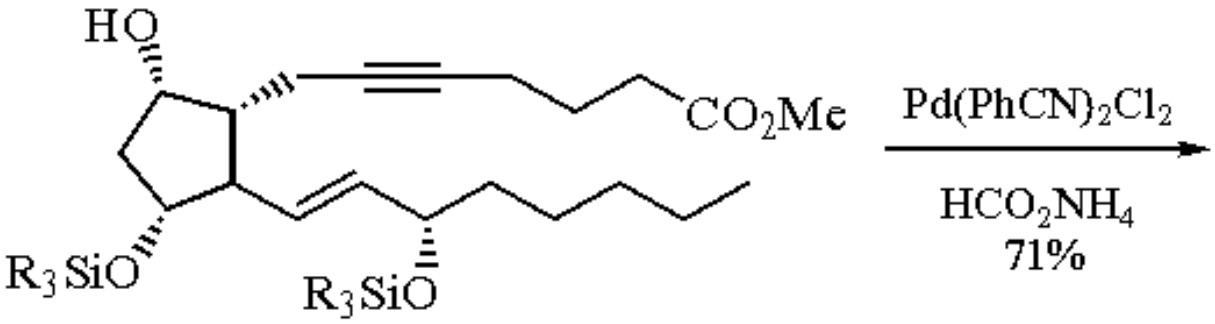

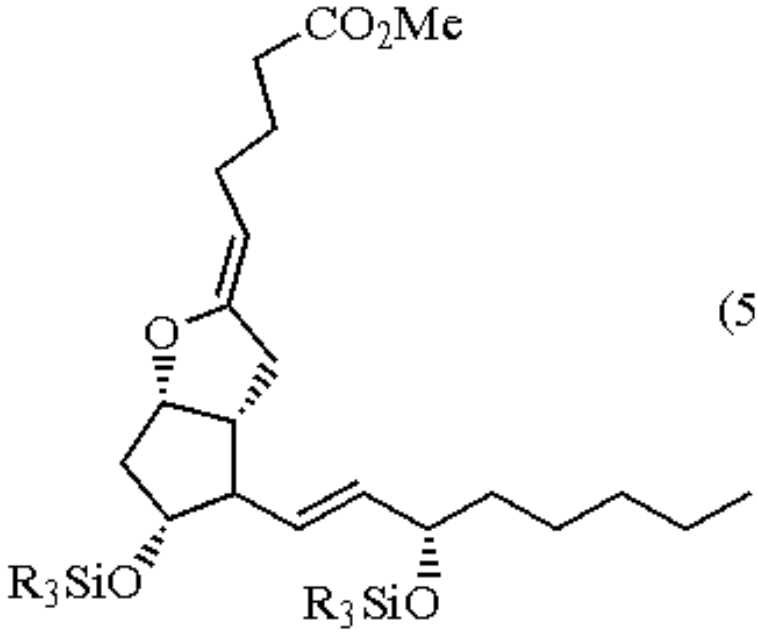

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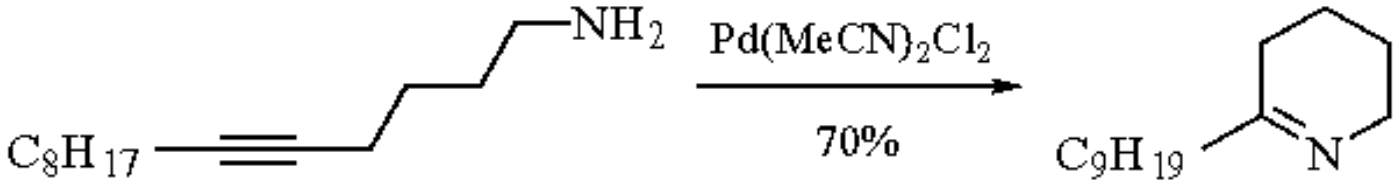

(57)

Simple alkynes cannot be hydrated with a palladium catalyst, but triple bonds are hydrated regioselectively to yield ketones with participation of suitably located carbonyl or hydroxy groups. 1,5-Diketones are prepared by the participation of a 5-keto group (eq 58).[75] 4-Hydroxyalkynes are converted to 4-hydroxy ketones and then oxidized to 1,4-diketones (eq 59).[71]

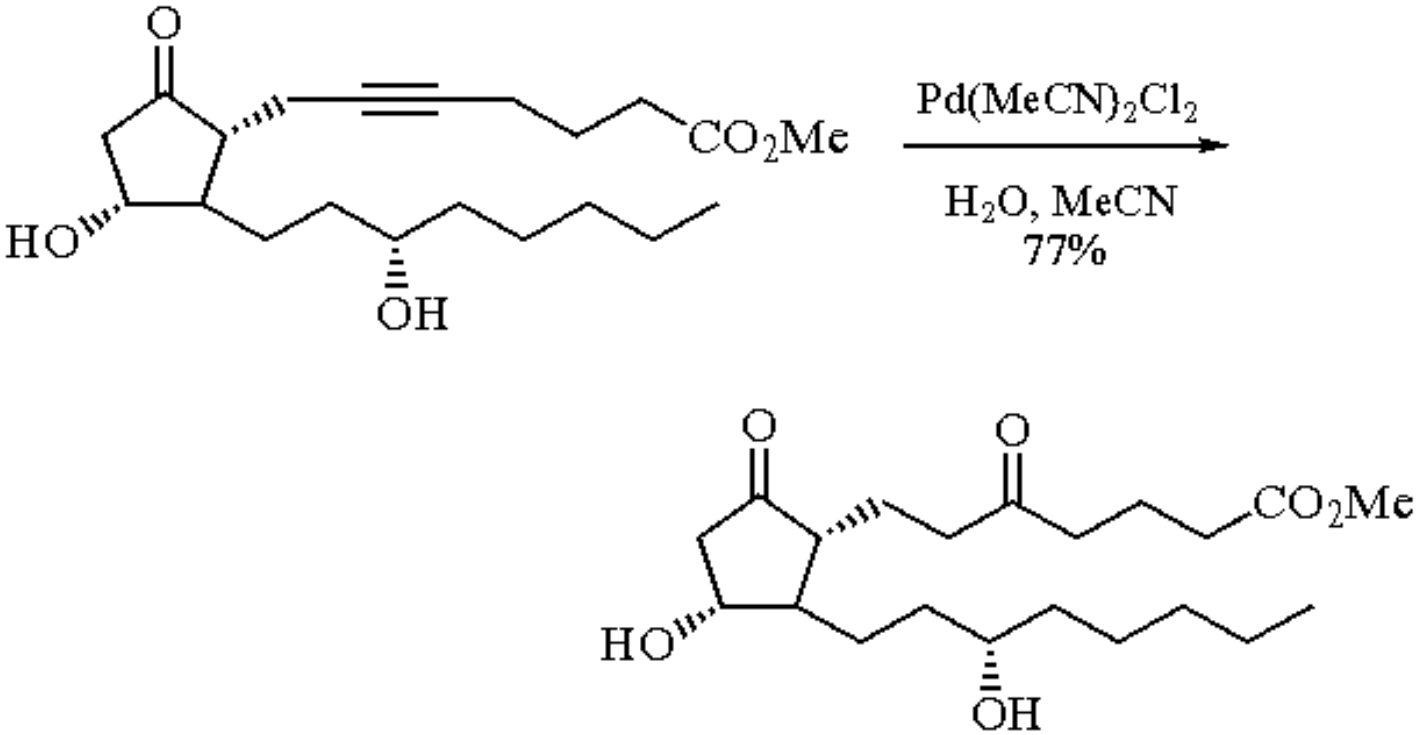

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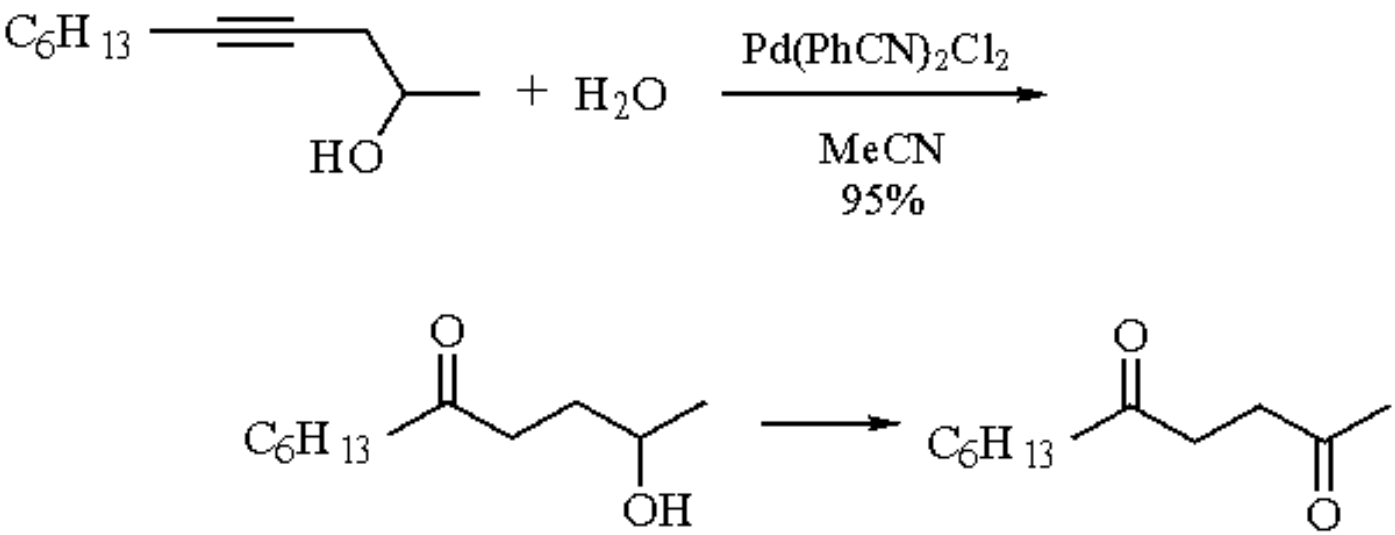

(59)

Cyclopentenone formation by the isomerization of 3-acetoxy-1,4-enynes is catalyzed by $Pd(PhCN)_2Cl_2$ (eq 60).[76]

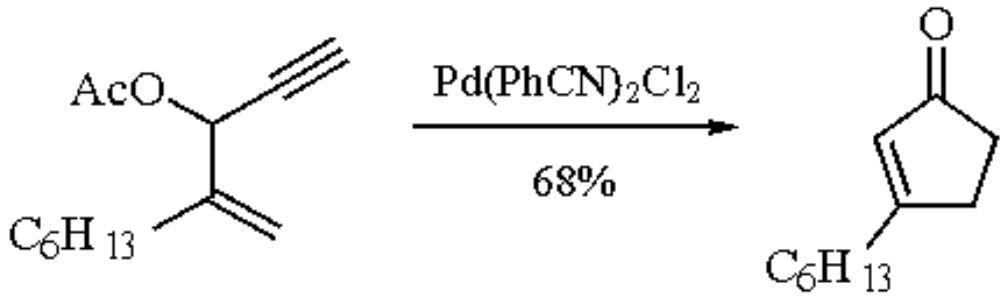

(60)

Generation of Carbenes from Diazo Compounds.

Both $PdCl_2$ and $Pd(OAc)_2$ are used for carbene generation from azo compounds.[77] The cyclopentenone carboxylates have been prepared by intramolecular insertions of the carbenes generated from α-diazo-β-keto esters (eq 61).[78]

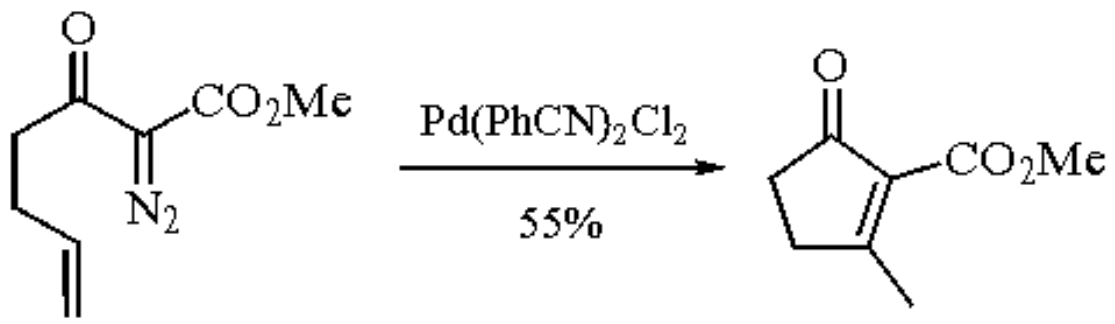

(61)

Generation of Pd^0 catalysts.

Pd^0 catalysts can be generated in situ from Pd^{II} in the presence or absence of phosphine ligands. ***Tetrakis(triphenylphosphine)palladium(0)*** is a commercially available Pd^0 complex used frequently as a catalyst, but it is air unstable. Therefore in situ generation of $Pd^0(Ph_3P)_n$ catalysts by the reduction of Pd^{II} in the presence of Ph_3P is convenient to use. In many cases the in situ reduction to Pd^0 takes place without addition of reducing agents. Alkenes, alcohols, CO, and phosphines, present in the reaction medium, behave as the reducing agent and react with Pd^{II} to give Pd^0. Generation of Pd^0 by reduction of $Pd(OAc)_2$ with phosphines has been reported.[79] Similarly, $PdCl_2$ and its derivatives have been converted to Pd^0 species with phosphines and bases.

$PdCl_2$ itself is used for the carbonylation of an aryl iodide in the presence of a base (eq 62).[80] More frequently, ***Bis(benzonitrile)dichloropalladium(II)*** is used for various Pd^0-catalyzed reactions. The coupling reaction of an acyl chloride with a disilane is catalyzed by Pd^0, generated from $Pd(PhCN)_2Cl_2$ and Ph_3P (eq 63).[81] The intermolecular coupling of a vinylenedistannane with two alkenyl iodides has been carried out using $Pd(PhCN)_2Cl_2$ without addition of Ph_3P in a total synthesis of rapamycin (eq 64).[82]

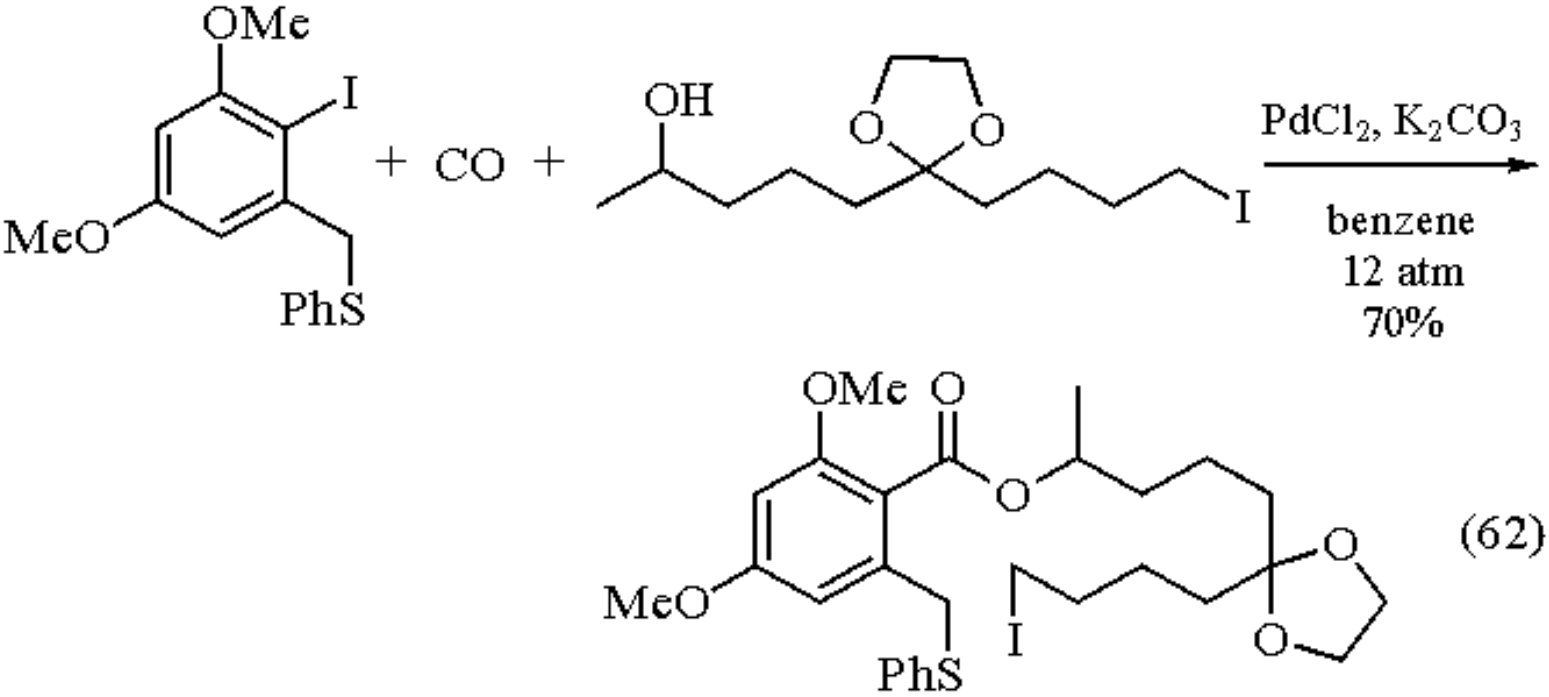
OMe
I
MeO
PhS
+ CO +
OH
O
O
I
PdCl2, K2CO3
benzene
12 atm
70%
OMe
O
O
MeO
PhS
I
O
O

(62)

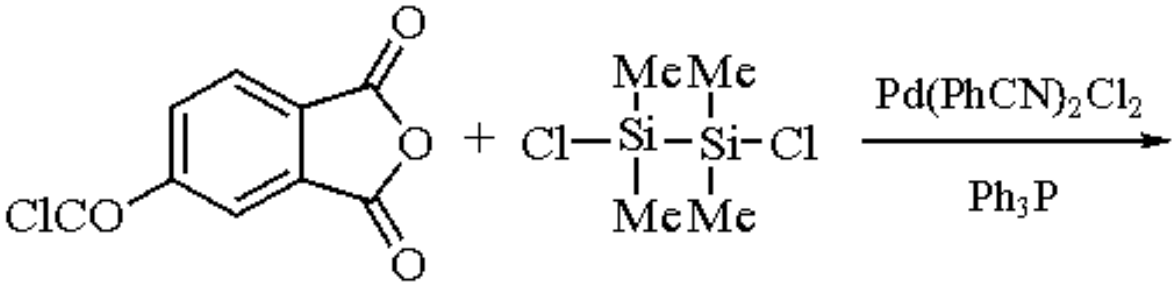
O
O
O
ClCO
+ Cl—Si—Si—Cl
Me Me
Me Me
Pd(PhCN)2Cl2
Ph3P

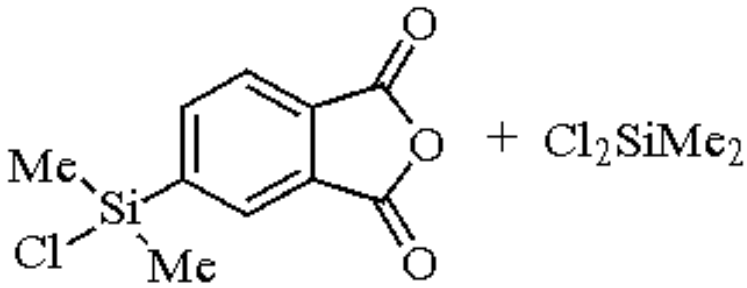
O
O
O
Me
Si
Cl
Me
+ Cl2SiMe2

(63)

83%

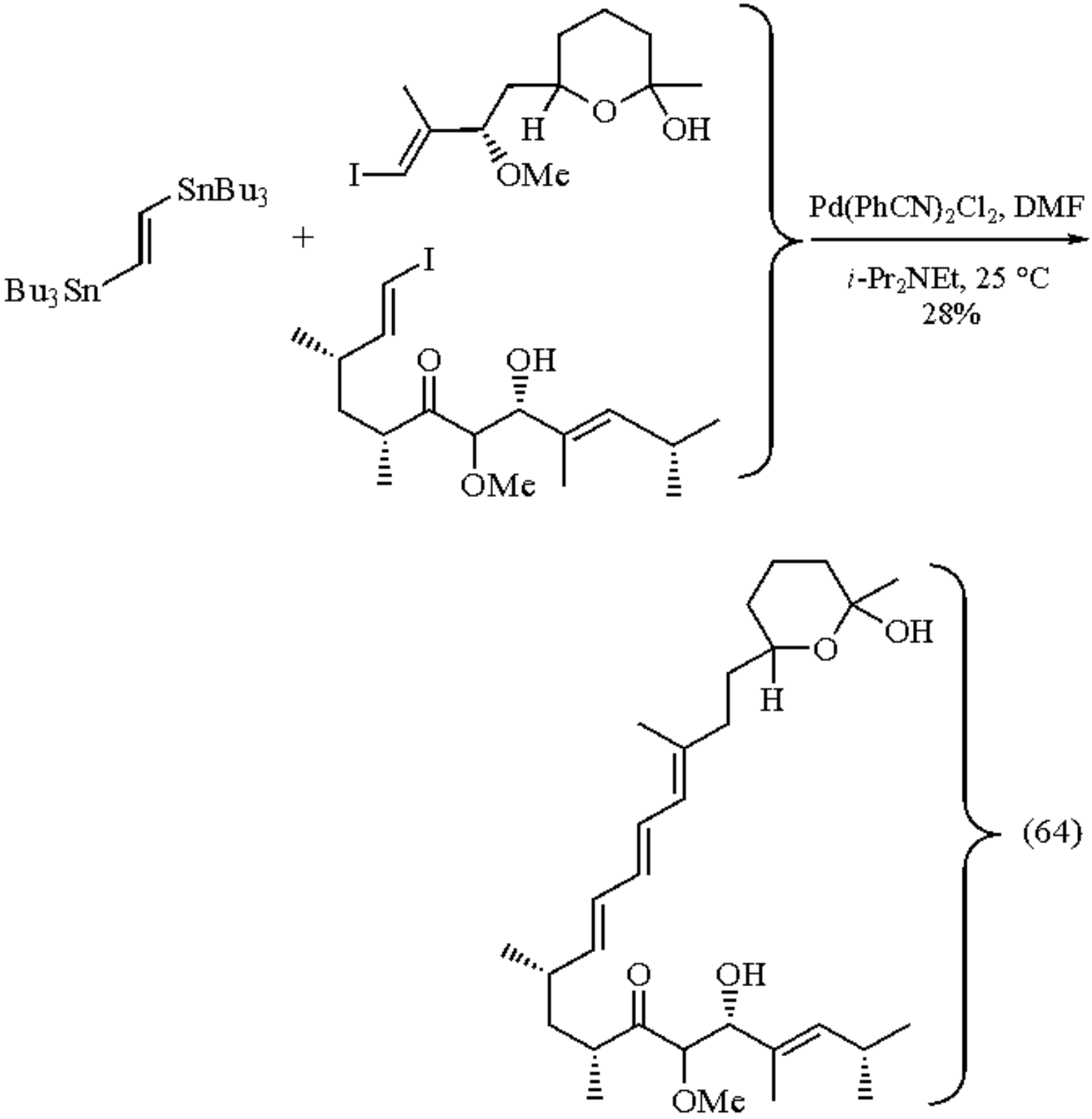

Dichlorobis(triphenylphosphine)palladium is used for Pd^0-catalyzed reactions without adding a reducing agent. For example, the coupling of terminal alkynes with halides is carried out with $Pd(Ph_3P)_2Cl_2$ and ***Copper(I) Iodide*** in the presence of ***Triethylamine*** without addition of a reducing agent. Hexaethynylbenzene is prepared by the coupling of hexabromobenzene with trimethylsilylacetylene (eq 65).[83] Similarly, the carbonylation of cinnamyl acetate, to give

naphthyl acetate, is carried out in the presence of Et_3N (eq 66).[84]

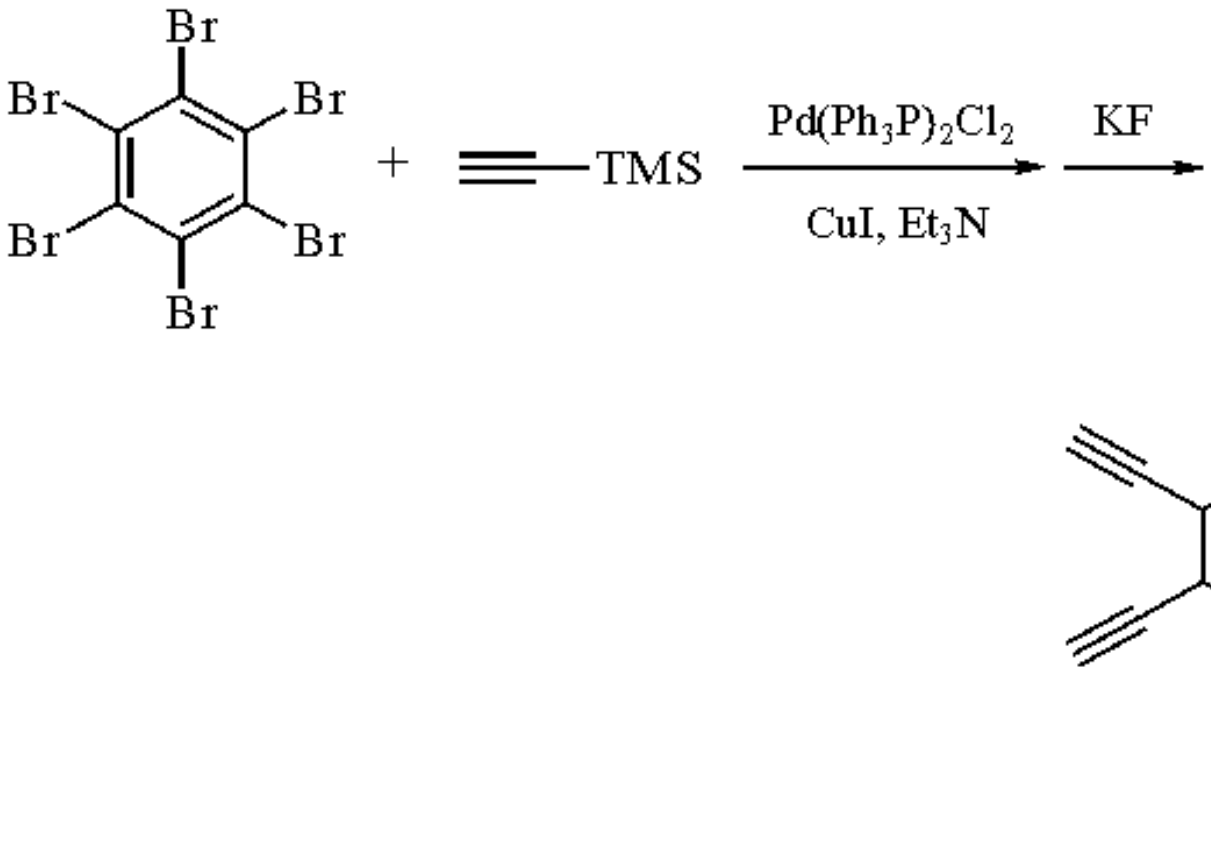

(65)

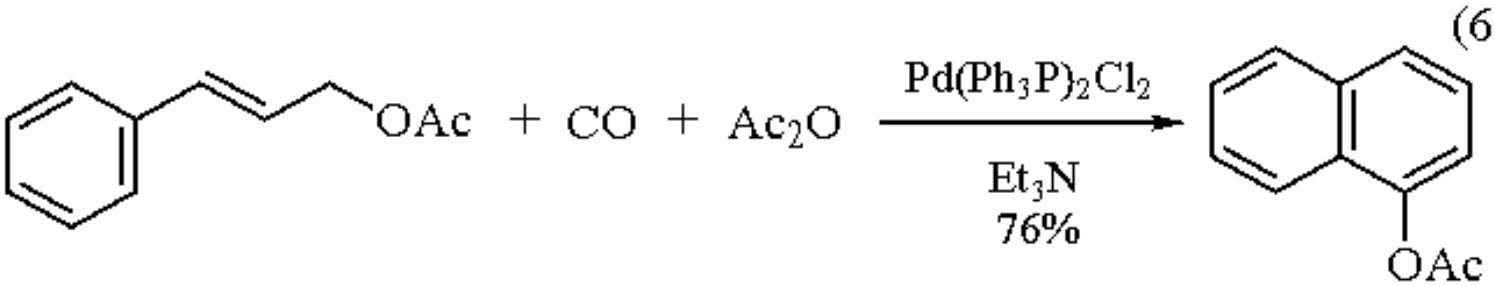

(66)

In some cases, $Pd(Ph_3P)_2Cl_2$ is reduced to Pd^0 in situ with reducing agents such as metal hydrides, and used for Pd^0 catalyzed reactions. For example, $Pd(Ph_3P)_2Cl_2$ is reduced with ***Diisobutylaluminum Hydride*** and used for coupling reactions (eq 67).[85]

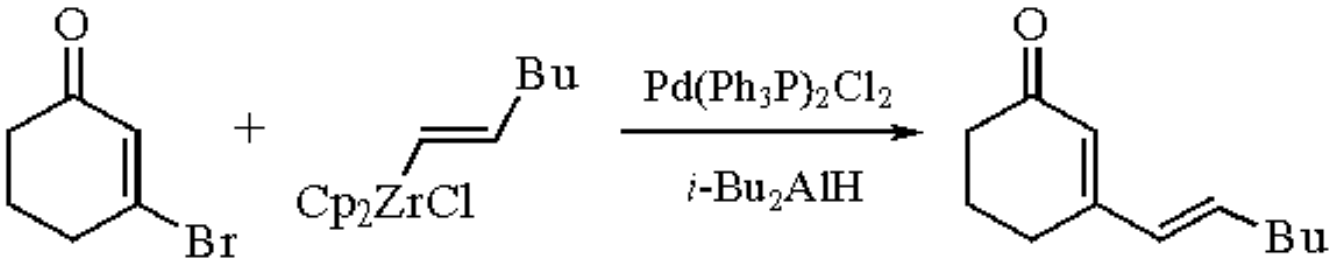

(67)

The carbonylation of alkenes in alcohols to give saturated esters proceeds smoothly with $PdCl_2$ or $Pd(Ph_3P)_2Cl_2$ as a catalyst (eq 68).[86] Alkynes are carbonylated efficiently to give α,β-unsaturated esters with the same catalyst in the

presence of ***Iodomethane*** (eq 69).[87] In some reactions the Pd^0 species generated from $PdCl_2$-Ph_3P and $Pd(OAc)_2$-Ph_3P show different reactivities. For example, in the carbonylation of ***1,3-Butadiene***, 3-pentenoate is obtained with $PdCl_2$-Ph_3P, while 3,8-nonadienoate is obtained with $Pd(OAc)_2$-Ph_3P. The presence of chloride anion in the coordination sphere of palladium gives different catalytic activity (eq 70).[88]

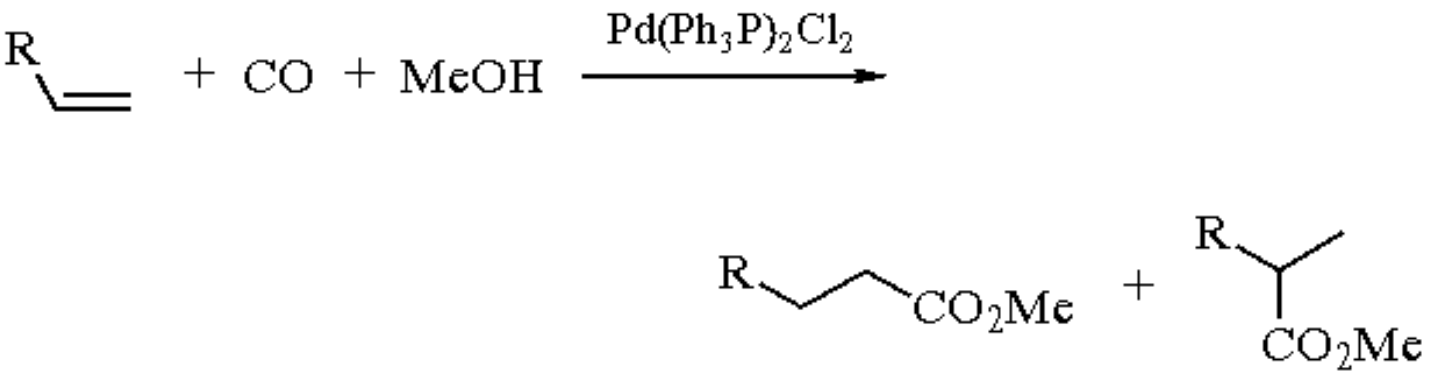

(68)

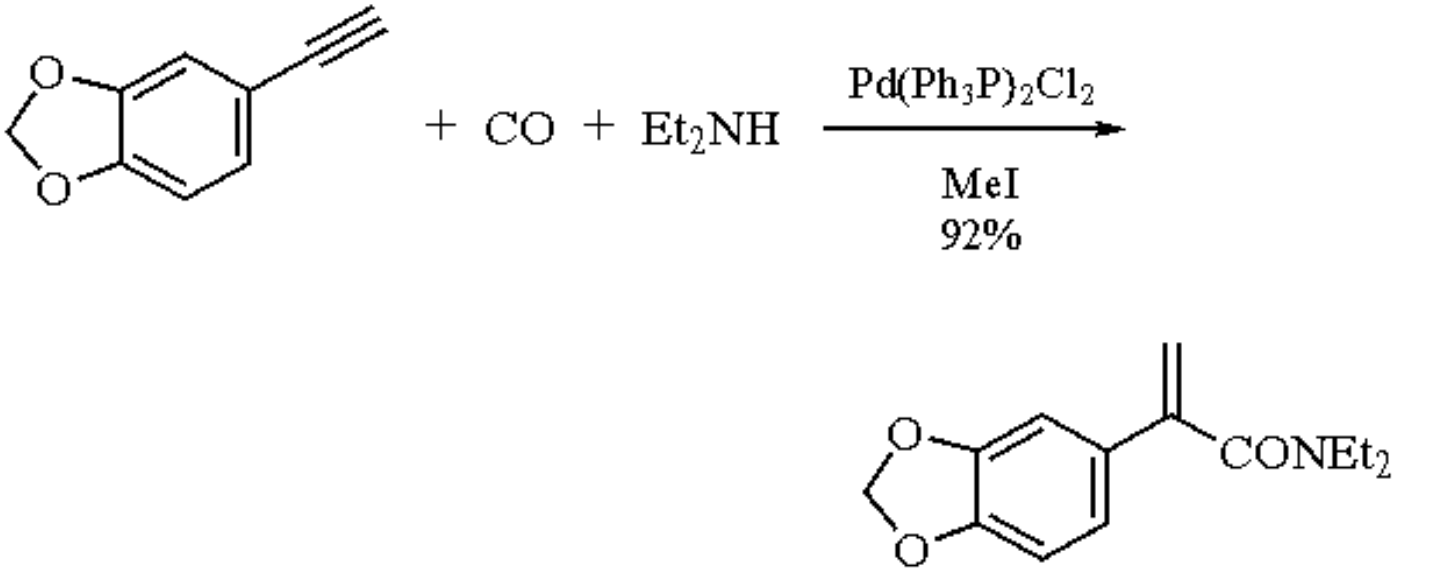

(69)

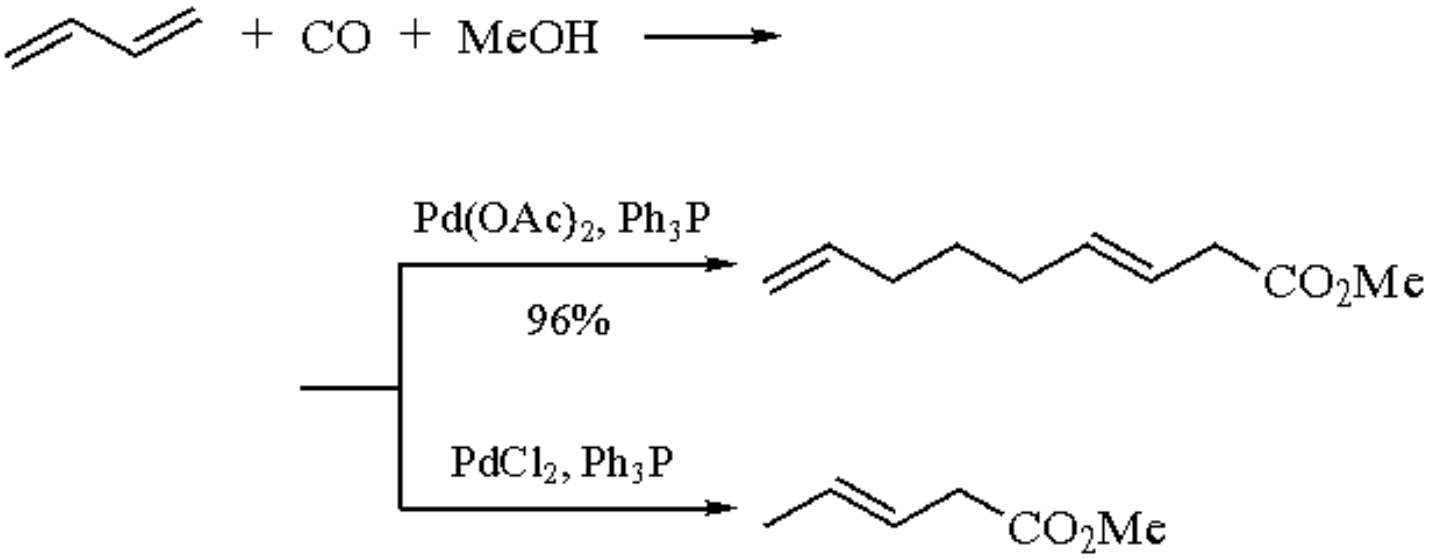

(70)

Related Reagents.

Palladium(II) Chloride-Copper(I) Chloride; ***Palladium(II) Chloride-Copper(II) Chloride***; ***Palladium(II) Chloride-Silver(I) Acetate***.

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Palladium(II) Chloride-Copper(I) Chloride[1]

$PdCl_2$-CuCl

($PdCl_2$)

[7647-10-1] · Cl_2Pd · Palladium(II) Chloride-Copper(I) Chloride · (MW 177.31) (CuCl)

[7758-89-6] · ClCu · Palladium(II) Chloride-Copper(I) Chloride · (MW 99.00)

(oxidation of alkenes[2])

Physical Data: $PdCl_2$, mp 680 °C; CuCl, mp 430 °C.

Solubility: $PdCl_2$ sol water, acetone, alcohol; CuCl insol most solvents.

Form Supplied in: $PdCl_2$, red-brown crystals; CuCl white/pale green powder; both widely available.

Handling, Storage, and Precautions: CuCl is oxygen, moisture, and light sensitive and should be stored in the dark under an inert atmosphere.

Oxidation of Alkenes to Ketones and Aldehydes.

The combination of ***Palladium(II) Chloride*** and ***Copper(I) Chloride*** to oxidize alkenes to ketones and aldehydes is a variant of the well-known Wacker reaction, first used to make acetaldehyde from ethylene.[3] The catalytic reaction comprises three individual steps (eq 1).

$$\begin{array}{l} PdCl_2 + H_2O + CH_2{=}CH_2 \longrightarrow Pd^0 + 2\,HCl + MeCHO \\ Pd^0 + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl \\ 2\,CuCl + 0.5\,O_2 + 2\,HCl \longrightarrow 2\,CuCl_2 + H_2O \\ \hline 0.5\,O_2 + CH_2{=}CH_2 \longrightarrow MeCHO \end{array} \qquad (1)$$

The first step is the Pd^{II}-induced oxidation of the alkene to give aldehyde/ketone and Pd^0. The reduced palladium is reoxidized by ***Copper(II) Chloride*** which in turn is reduced to CuCl. Finally, CuCl is oxidized by O_2 in the presence of HCl to regenerate $CuCl_2$. A variety of other oxidants have been used to reoxidize the palladium, including $CuCl/O_2$ (discussed herein), benzoquinone, $FeCl_3$, H_2O_2, *t*-BuOOH, and heteropoly acids (reactions using $CuCl_2$ or other Pd salts will be referenced occasionally in this article, given the similarity of various systems). $CuCl_2$ is problematic because it produces chlorinated byproducts or otherwise lowers the yields. For this reason, CuCl in combination with O_2 is favored.[4]

The solvent of the original Wacker reaction is water, which causes solubility problems and correspondingly lower rates with higher alkenes. This has been partially resolved by adding surfactants, both ionic and non-ionic,[5] or by using solvents that dissolve both water and the organic substrate to a certain extent such as DMF.[6] Alcohols, however, give acetals. Another problem is double bond isomerization, which is particularly severe in alcohols or acetic acid, but minor in DMF. For these reasons, DMF has become the solvent of choice for the oxidation of alkenes with $PdCl_2/CuCl$.

Terminal alkenes are more reactive than disubstituted alkenes (eq 2),[7] and are generally oxidized with good selectivity to methyl ketones. Aldehydes can also be formed in certain cases as discussed below. Indeed, terminal alkenes, which are easy to synthesize and relatively inert under a variety of conditions, may be considered masked methyl ketones because they are readily oxidized by the existing procedures.[8] They can generally be oxidized selectively in the presence of various functional groups such as internal alkenes, alcohols, ketones, aldehydes, carboxylic acids and esters, ethers, acetals, chlorides, bromides, and sulfones among others, although cyclization reactions can sometimes occur. Alcohols can be oxidized if the reaction conditions become severe, and acetals are somewhat prone to hydrolysis due to the acidic nature of the reaction. Amine-containing substrates can be oxidized provided that the amine is protonated by acid.[9]

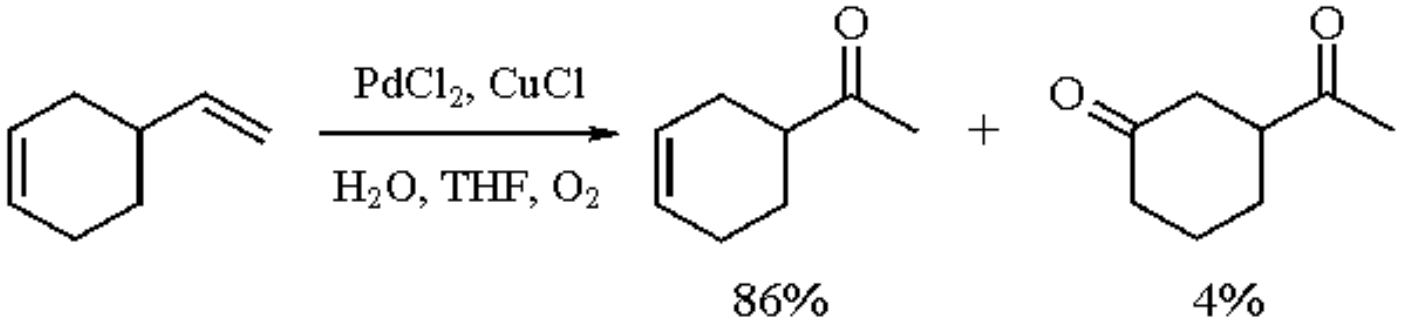

(2)

The reagents can distinguish among several terminal alkenes, with the least sterically hindered being more readily oxidized. For instance, in eq 3 the least hindered double bond required 3 h whereas the more hindered double bond required 36 h (71% overall yield).[2] There are numerous applications of this procedure in natural product synthesis,[10] with some of the more important being the preparation of 1,4-dicarbonyl compounds, cyclopentenones (eq 4), 1,5-dicarbonyl compounds, cyclohexenones (eq 5),[11] and steroids.

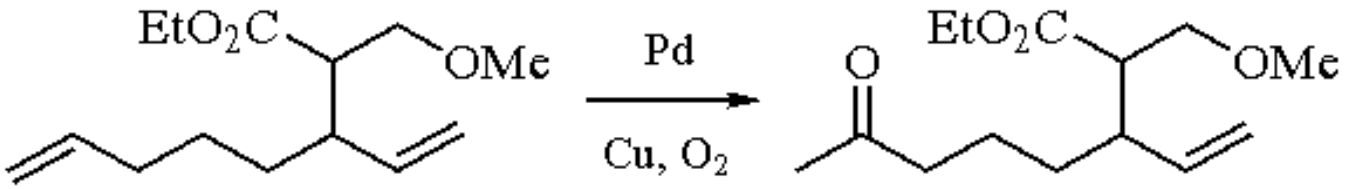

(3)

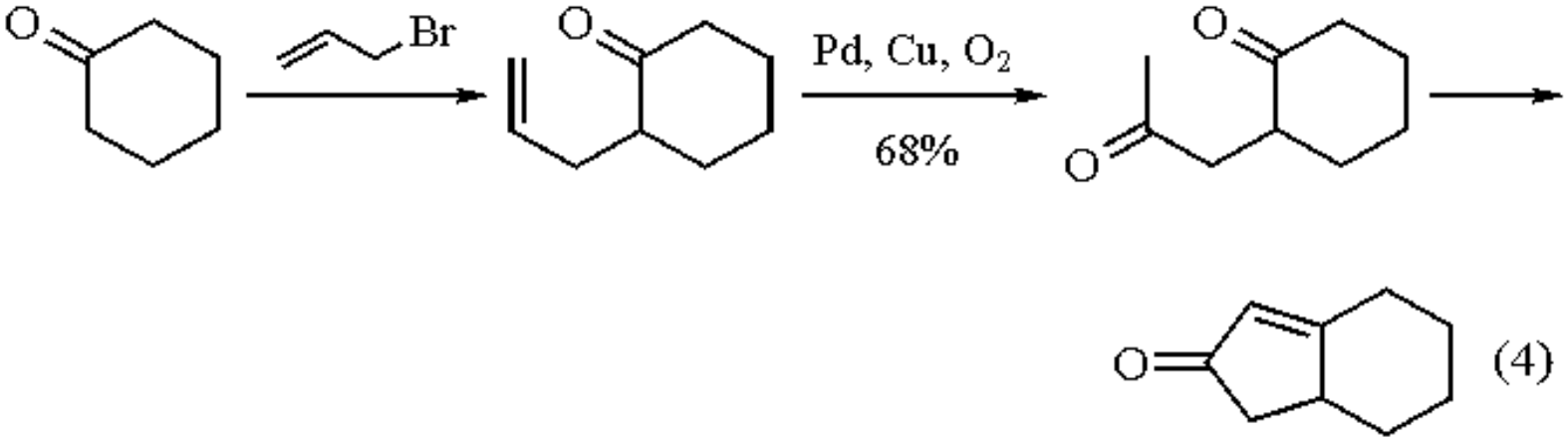

(4)

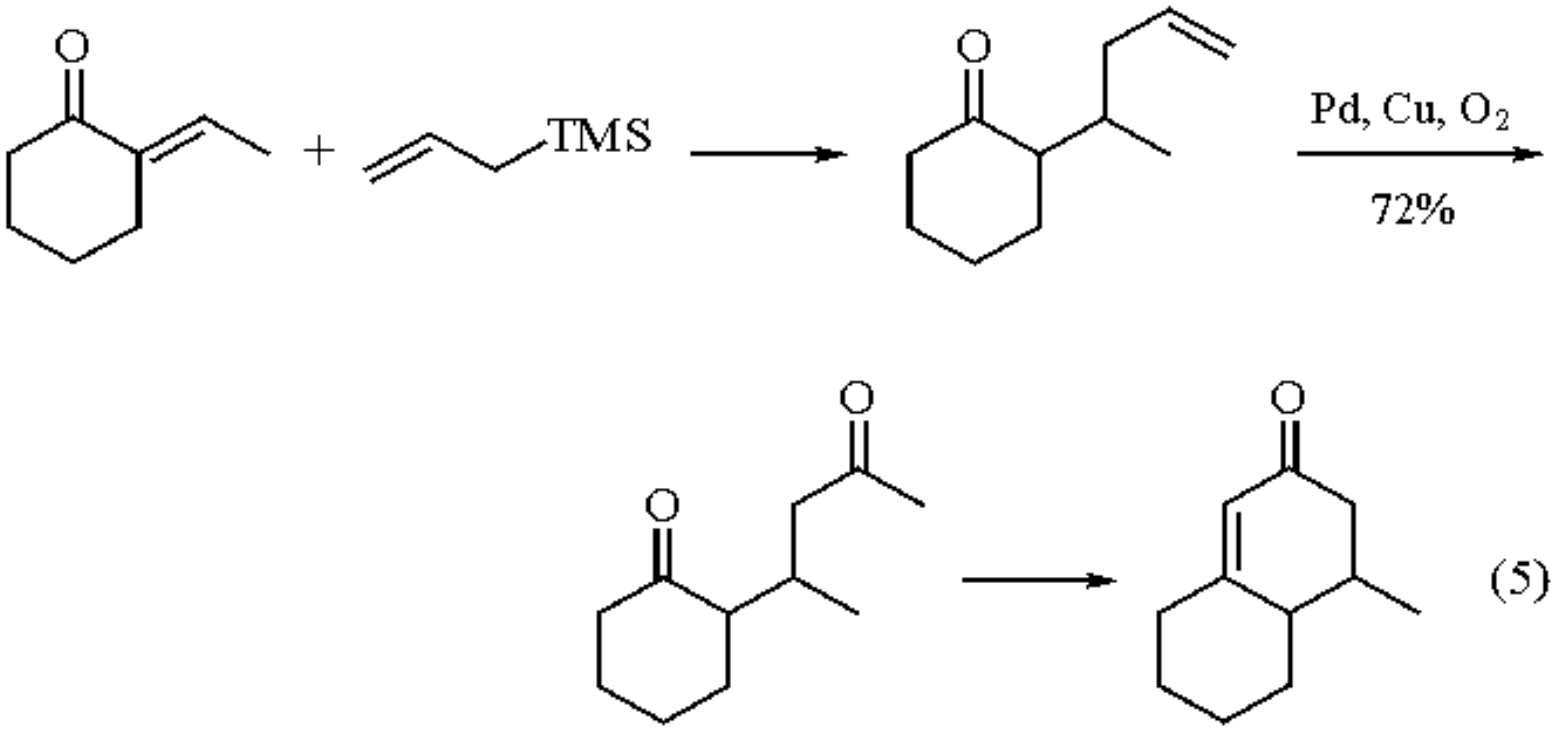

(5)

Aldehydes can sometimes be obtained instead of methyl ketones, if the alkene is conjugated with an electron withdrawing group or if certain remote functionalities are present.[12] The reaction conditions can also influence the ketone/aldehyde selectivity. For instance, the use of *t*-BuOH as solvent,[13] or anhydrous 1,2-dichloroethane and HMPA,[14] can significantly enhance the selectivity toward aldehyde formation.

Alkenes conjugated to carbonyl groups are poorly oxidized by $PdCl_2$/CuCl and better results are obtained with peroxide reoxidants.[15] Benzofurans can be hydrolytically and oxidatively cleaved.[16] Internal alkenes are oxidized much more slowly than terminal alkenes,[17] and are only poorly oxidized with the $PdCl_2$ system unless certain functionality is present. For instance β,γ-unsaturated esters or ketones can be oxidized to the respective ketones in 45-61% yield provided that the reaction is done in aqueous dioxane or THF (π-allyl Pd compounds are formed in DMF).[18] In all cases, only the 1,4-dicarbonyl products were obtained (eq 6).

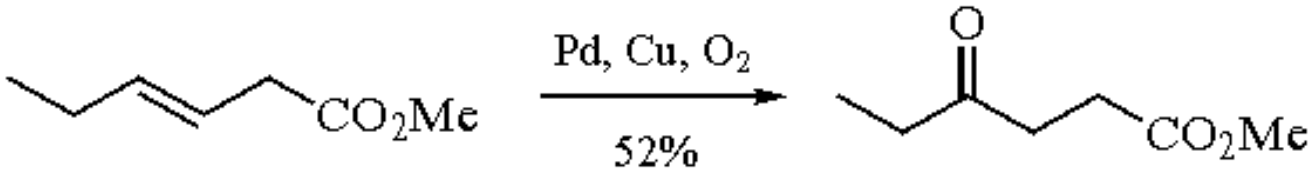

(6)

Similarly, allylic and homoallylic ethers and esters are regioselectively oxidized at the carbon more remote from the functional group (eq 7).[19]

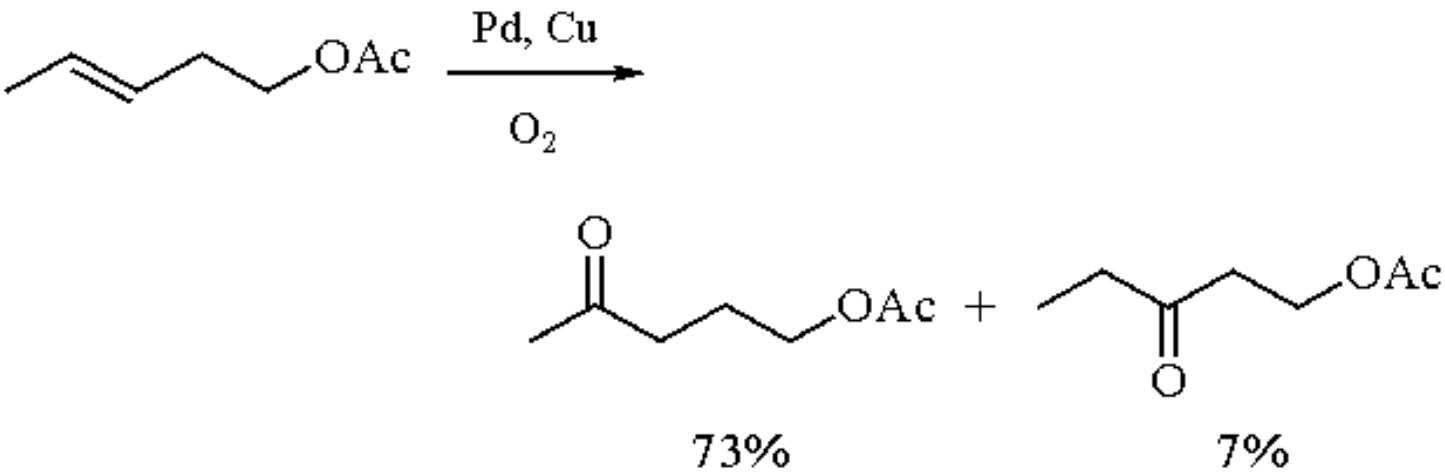

(7)

Oxidation of Alkenes to Acetals.[20]

In alcohol solvents, acetals can be obtained from alkenes, but since an equivalent amount of water is generated under catalytic conditions, often the ketone is ultimately obtained.[21] The yield of acetal is increased by using diol solvents. Electron withdrawing groups conjugated to a terminal double bond[22] or the presence of certain remote functionalities[23] favor oxidation at the terminal carbon. α,β-Unsaturated ketones require the use of Na_2HPO_4 to prevent simple Michael addition of the diol.[22b] The presence of a chiral auxiliary can lead to diastereomeric excesses as high as 95% (eq 8).[24]

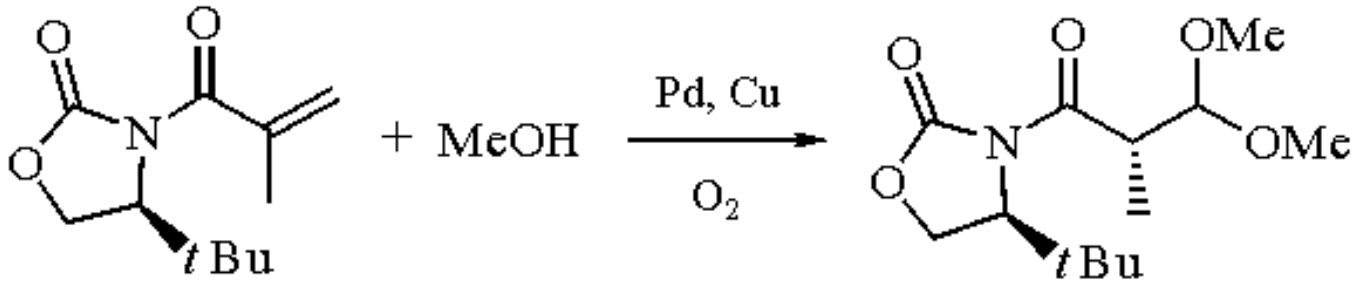

(8)

Cyclization.

Intramolecular oxidative addition of an O-H or N-H bond to an alkene is a useful way to make heterocycles and can be accomplished with a number of Pd catalysts.[20a,25] Specific examples with $PdCl_2$/CuCl (or $CuCl_2$) are given here. Diol alkenes can be cyclized to bicyclic acetals such as brevicomin;[26] intramolecular optical induction can be observed, as in a similar synthesis of frontalin (eq 9).[27]

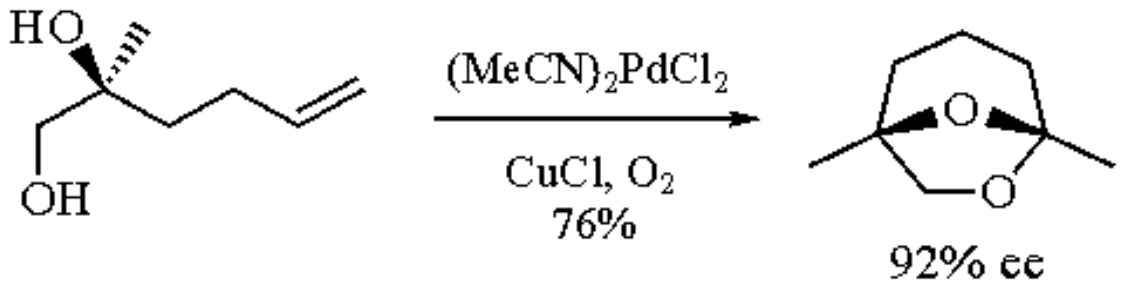

(9)

Aromatic heterocycles such as indoles can be synthesized by cyclizing β-amino alkenes and their toluenesulfonamide derivatives using Pd^{II} catalysts.[28] Acetanilide derivatives, which cyclize poorly with other Pd catalysts,[29] cyclize especially well with $PdCl_2/CuCl/O_2$ in 1,3-propanediol (eq 10).[30] Styryl amides cyclize well under similar conditions (eq 11).[31] Aliphatic amino alkenes, whose basicity interferes with catalytic cyclization, can be cyclized well in the presence of acid.[32]

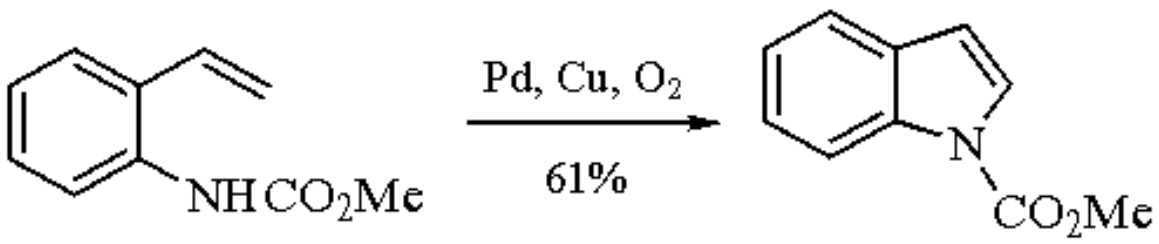

(10)

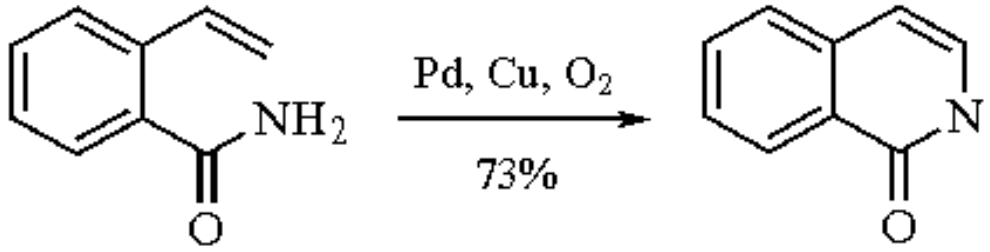

(11)

Related Reagents.

Palladium(II) Acetate; ***Palladium(II) Chloride***; ***Palladium(II) Chloride-Copper(II) Chloride***.

---

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Palladium(II) Chloride-Copper(II) Chloride[1]

$PdCl_2$-$CuCl_2$

($PdCl_2$)

[7647-10-1] · Cl_2Pd · Palladium(II) Chloride-Copper(II) Chloride · (MW 177.32) ($CuCl_2$)

[7447-39-4] · Cl_2Cu · Palladium(II) Chloride-Copper(II) Chloride · (MW 134.45)

(oxidation and carbonylation of alkenes; carbonylation of amines, alcohols)

Physical Data: $PdCl_2$, mp 680 °C; $CuCl_2$, mp 630 °C (dec).

Solubility: $PdCl_2$ sol water, acetone, alcohol; $CuCl_2$ sol water, acetone, alcohol.

Form Supplied in: $PdCl_2$, red-brown crystals; $CuCl_2$, yellow/brown powder; both widely available.

Handling, Storage, and Precautions: $CuCl_2$ is deliquescent and forms the green-blue dihydrate on exposure to moist air.

Oxidation of Alkenes to Ketones, Aldehydes, and Acetals.[2]

Palladium(II) Chloride combined with ***Copper(II) Chloride*** is the catalyst for the Wacker reaction, which was originally used to oxidize ethylene to acetaldehyde.[3] Subsequent work broadened the application to a variety of alkenes. Typically, terminal alkenes yield only methyl ketones.[4] In the presence of alcohols, acetals are obtained.[5] Cyclization reactions can occur with hydroxyalkenes.[6] In general, these reactions can be accomplished more selectively with ***Palladium(II) Chloride-Copper(I) Chloride***.

Hydrocarboxylation/Hydroesterification of Alkenes.

$PdCl_2$/$CuCl_2$ is a useful reagent for hydrocarboxylating alkenes to carboxylic acids (eq 1).[7] The reaction proceeds in good yield and is highly regioselective, favoring the branched carboxylic acid over the linear isomer. Hydroesterification to give the analogous ester occurs equally well, again with the branched isomer predominating (eq 2).[8] With a diol as the alcohol, only the monoester is obtained.[9]

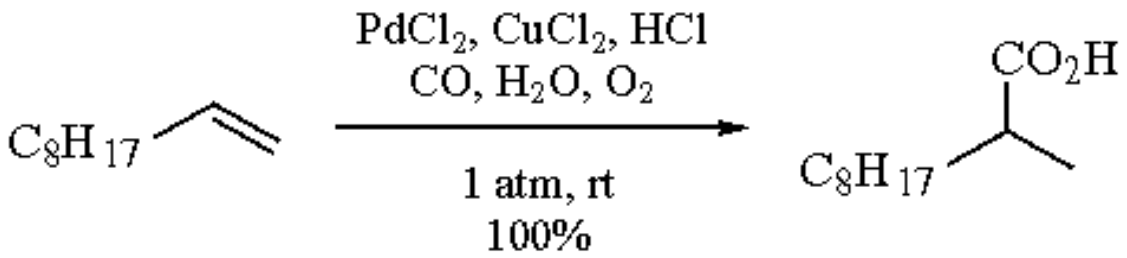

(1)

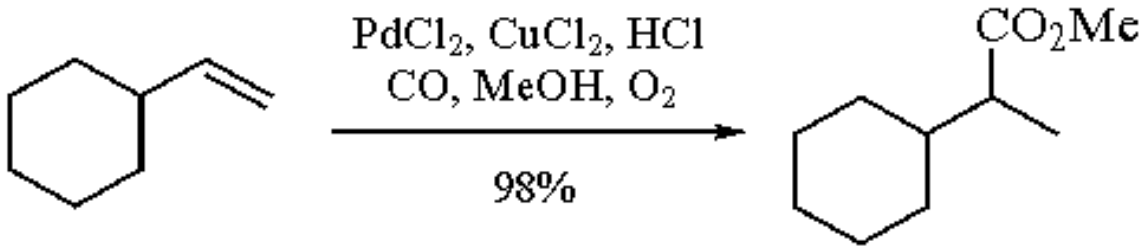

(2)

Internal alkynes are hydroesterified to (*E*)-unsaturated monoesters resulting from *cis* addition (eq 3).[10] However, terminal alkynes are oxidatively carbonylated to give predominantly the (*Z*)-unsaturated diesters (eq 4). Under similar conditions in the presence of base, terminal alkynes can also be non-oxidatively carbonylated to the acetylenecarboxylate ester.[11]

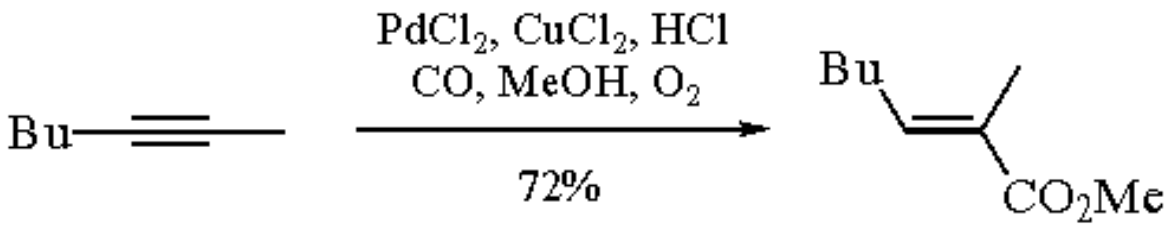

(3)

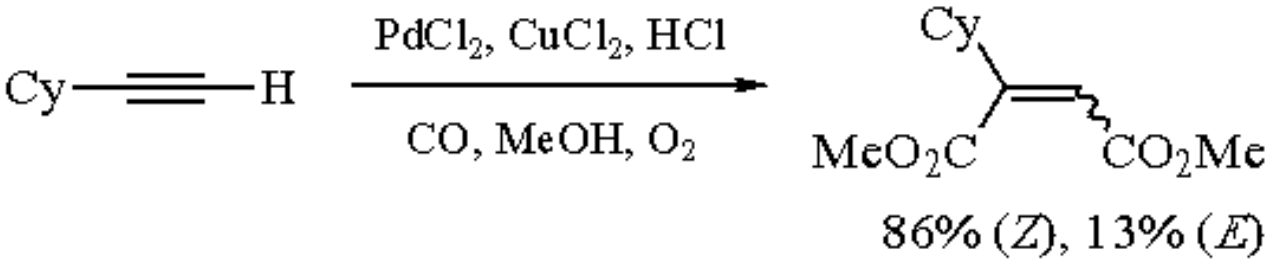

(4)

Hydroxyalkenes will cyclize under similar conditions to give the five- or six-membered ring saturated lactone (eq 5).[12] Chiral additives, especially poly-L-leucine, afford the cyclized lactone with as high as 61% ee.[13]

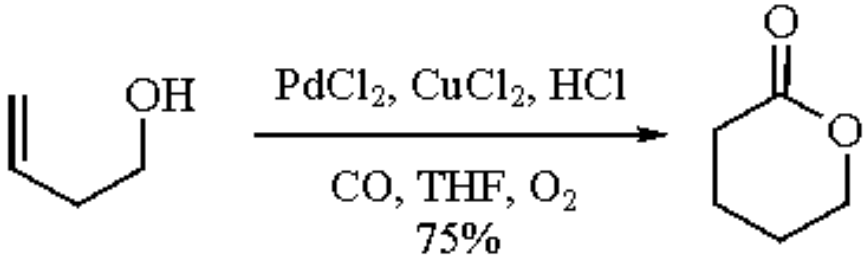

(5)

Oxidative Carbonylation of Alkenes.

In contrast to hydroesterification, oxidative carbonylation (or alkoxycarbonylation) is an oxidation that converts alkenes to vinyl esters, α-alkoxy esters, or diesters depending on the reaction conditions.[14] Typically, $CuCl_2$ is used as a stoichiometric oxidant, because in the presence of oxygen and water (which would be coproduced in the presence of oxygen) the CO can be oxidized to CO_2 and the alkene can be oxidized to the ketone or aldehyde. Linear, terminal alkenes are oxidized to either the alkoxy ester or to the diester, depending on whether base (NaOAc) is present or not (eq 6).[15] The alkoxyester arises from *trans* addition whereas the diester arises from a *cis* addition. The choice of re-oxidant can also control the reaction pathway: $CuCl_2/O_2$ favors the branched alkoxy monoester, whereas $CuCl/O_2$ favors the diester.[16] Oxidative carbonylation can also occur using acetic anhydride solvent with NaCl.[17] Cyclic alkenes give both the *cis*-1,2- and *cis*-1,3-diesters along with a variable amount of *trans*-2-methoxy ester.[15] Allenes are oxidatively carbonylated to the α-alkoxy ester.[18] Butadiene can be dicarbonylated to linear hexenedioate diesters in high yields.[15e] Terminal alkynes are dicarbonylated to maleic anhydride derivatives.[19]

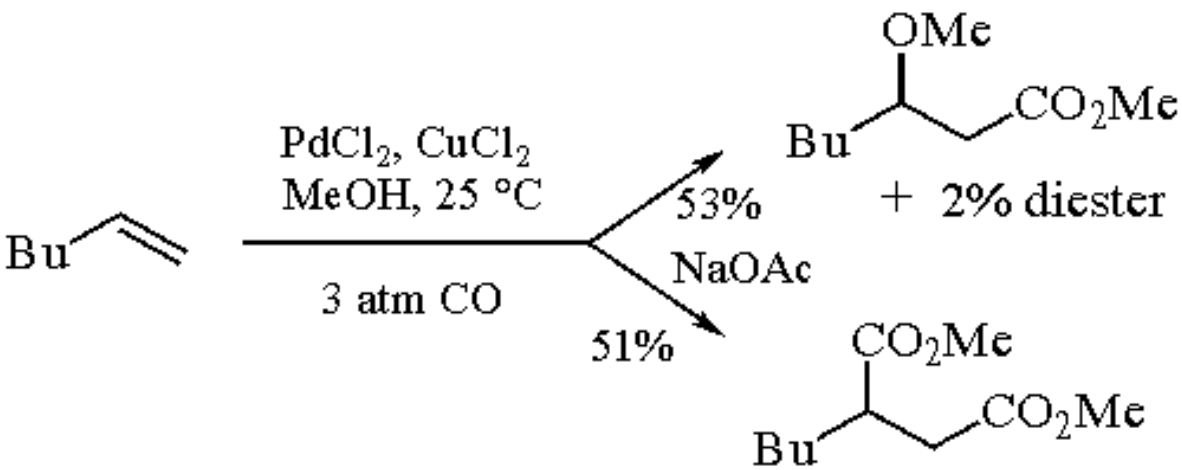

(6)

Cyclization can occur with hydroxyalkenes to give pyran or furan carboxylates;[20] allenes are similarly cyclized.[21] The carbon-oxygen bond tends to form at the more substituted end of the double bond; the geometry of the alkene can also determine the ring size (eq 7).[20] Aminoalkenes cyclize similarly, especially if protected as the carbamates, tosylamides, or ureas.[22] The latter can use both nitrogen atoms to form bicyclic molecules (eq 8).

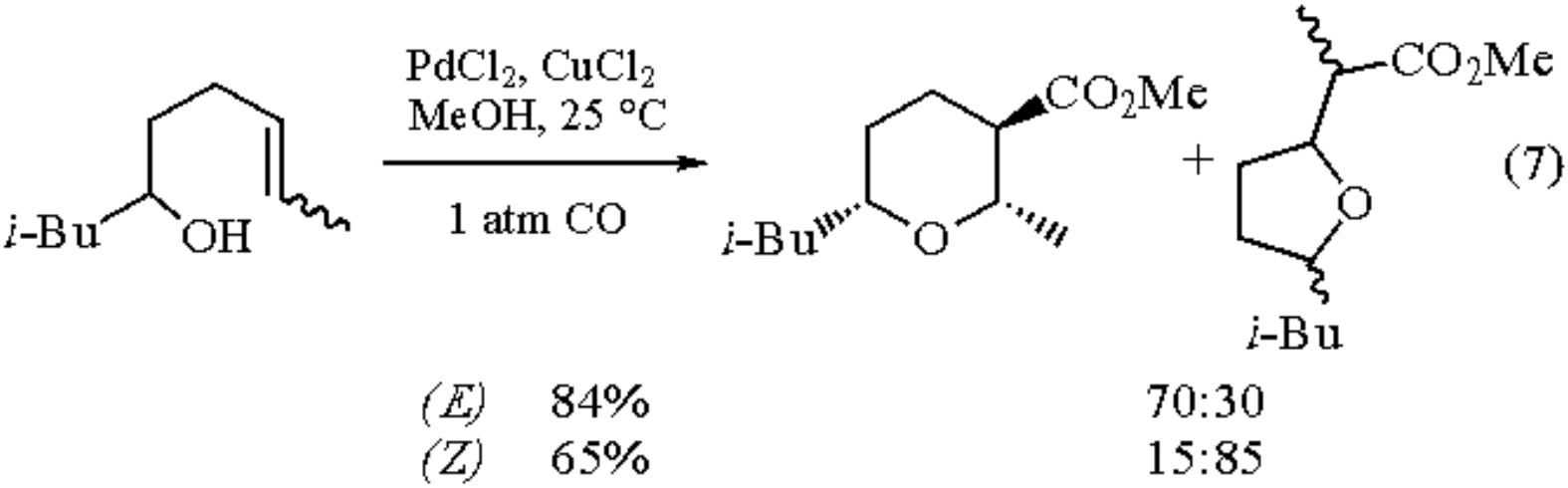

(7)

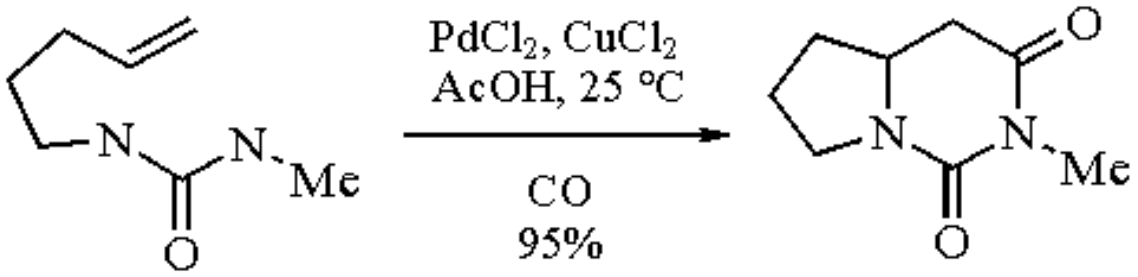

(8)

Bis-carbonylation occurs with homoallylic alcohols (eq 9).[23] The use of CuCl appears to mitigate the need for additives such as epoxides or orthoesters in these reactions.[18] Dihydroxy alkenes can form bicyclic ether-lactones (eq 10).[24] A similar reaction occurs with a carboxylic acid group at the terminus.[25]

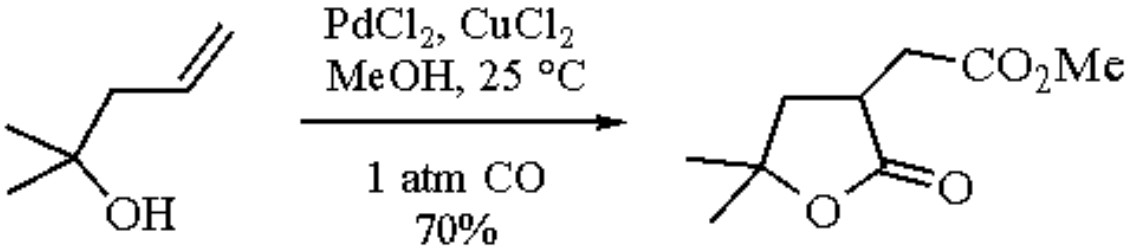

(9)

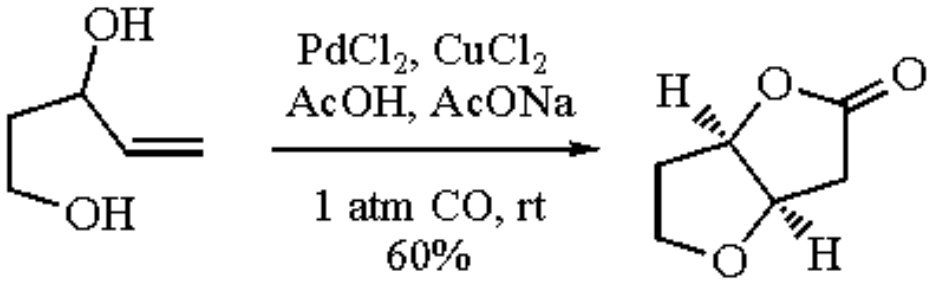

(10)

Oxidative Carbonylation of Heteroatoms.

Amines and alcohols can be oxidatively carbonylated to the carbamate and carbonate esters in alcohol solvents.[26]

Related Reagents.

Palladium(II) Acetate; ***Palladium(II) Chloride***; ***Palladium(II) Chloride-Copper(I) Chloride***.

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Palladium(II) Chloride-Silver(I) Acetate

$PdCl_2$-AgOAc

($PdCl_2$)

[7647-10-1] · Cl_2Pd · Palladium(II) Chloride-Silver(I) Acetate · (MW 177.32) (AgOAc)

[563-63-3] · $C_2H_3AgO_2$ · Palladium(II) Chloride-Silver(I) Acetate · (MW 166.92)

(catalyst system used for the allylic oxidation of alkenes and for altering the regioselectivity of intermolecular Heck reactions of allylic alcohols)

Physical Data: see ***Palladium(II) Chloride*** and ***Silver(I) Acetate***.

Allylic Oxidation.

Treatment of alkenes with palladium chloride (5 mol %), silver acetate (10 mol %), tellurium oxide (5 mol %), and ***t-Butyl Hydroperoxide*** (50 mol %) in acetic acid affords allylic oxidation products.[1] This procedure is especially useful for cyclic alkenes which fail to react with the ***Selenium(IV) Oxide-t-Butyl Hydroperoxide*** system for allylic oxidations (eq 1).

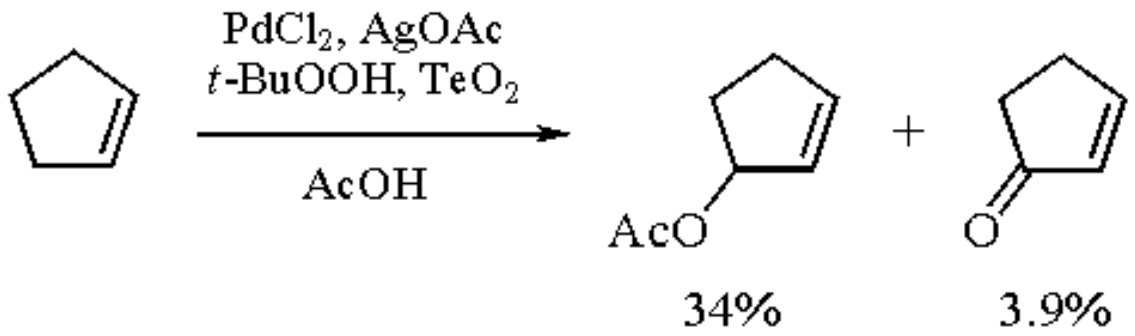

(1)

Two mechanisms appear to be operative depending on substrate structure. The reaction may proceed via either π-allyl palladium complexes[2,3] (best explains compound (**1**), eq 2) or via acetoxypalladation followed by dehydropalladation[4] (best explains compound (**2**), eq 3). The extent of regiocontrol is highly substrate dependent (eqs 2 and 3).

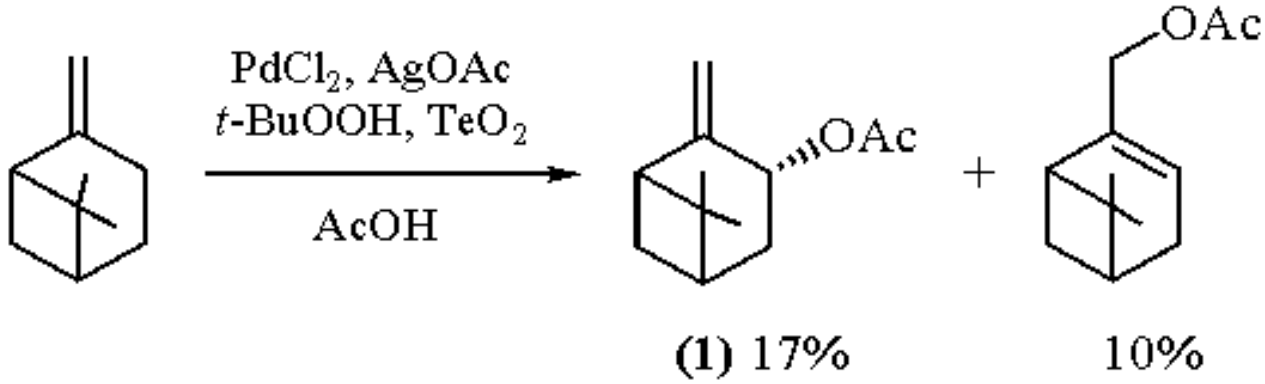

(2)

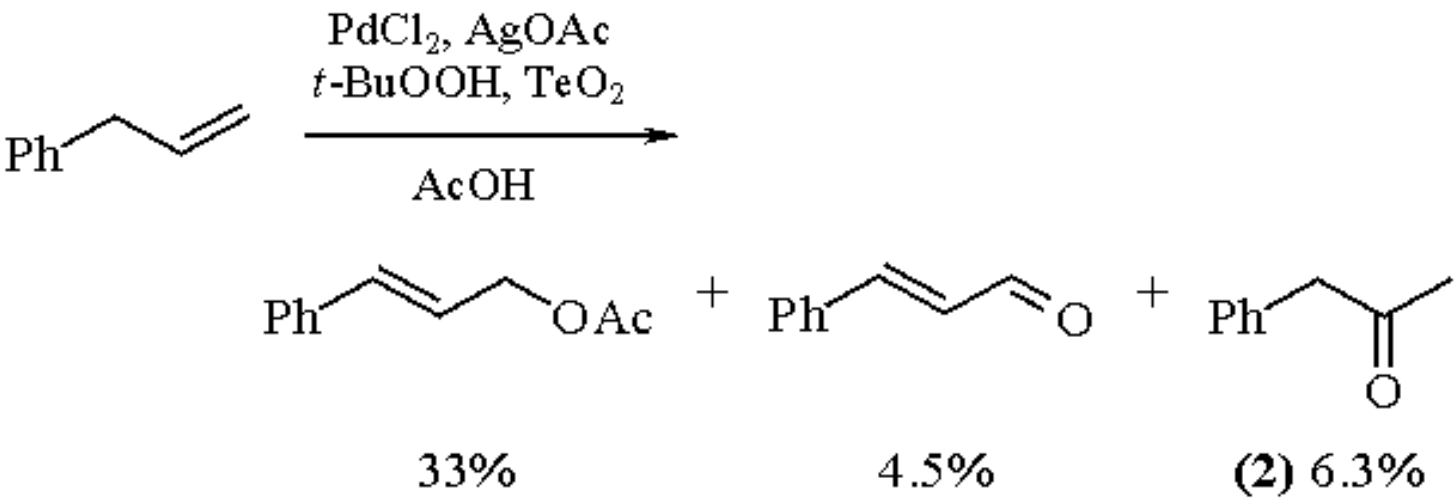

(3)

Intermolecular Heck Reactions.

Closely related to the palladium chloride/silver acetate catalyst system is the use of ***Palladium(II) Acetate***/silver acetate in Heck reactions of aryl and vinyl halides. Silver carbonate is usually equally effective in this process (eqs 4 and 5). The use of silver acetate completely reverses the regioselectivity of β-hydride elimination in Heck reactions of allyl alcohols (eq 4).[5,6]

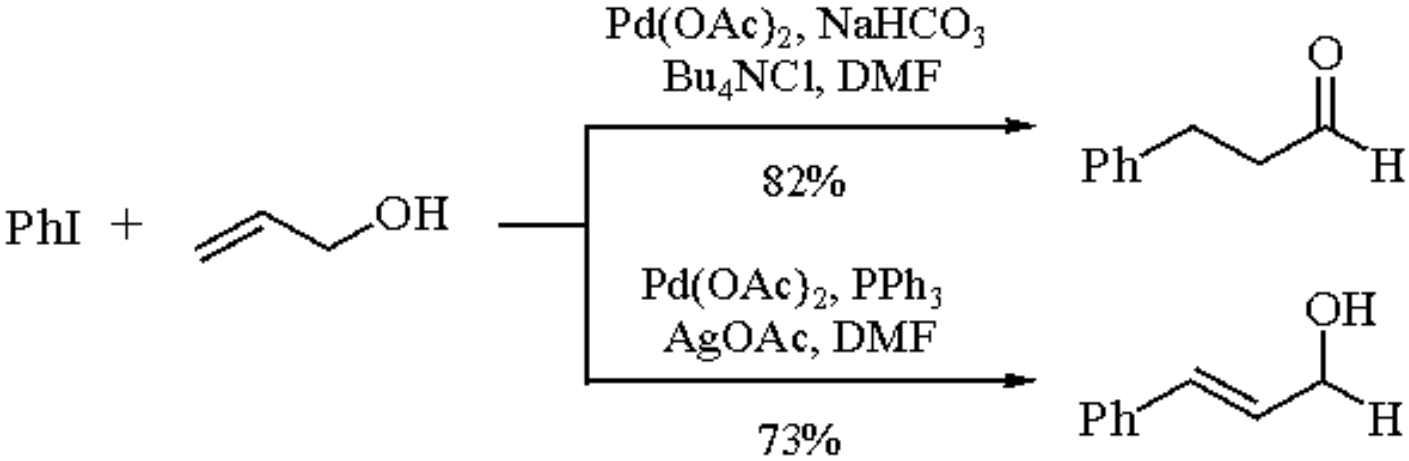

(4)

The stereochemistry of chiral allylic alcohols is maintained in the silver acetate promoted process (eq 5), indicating that reversible β-hydride elimination to the enol does not occur.[7]

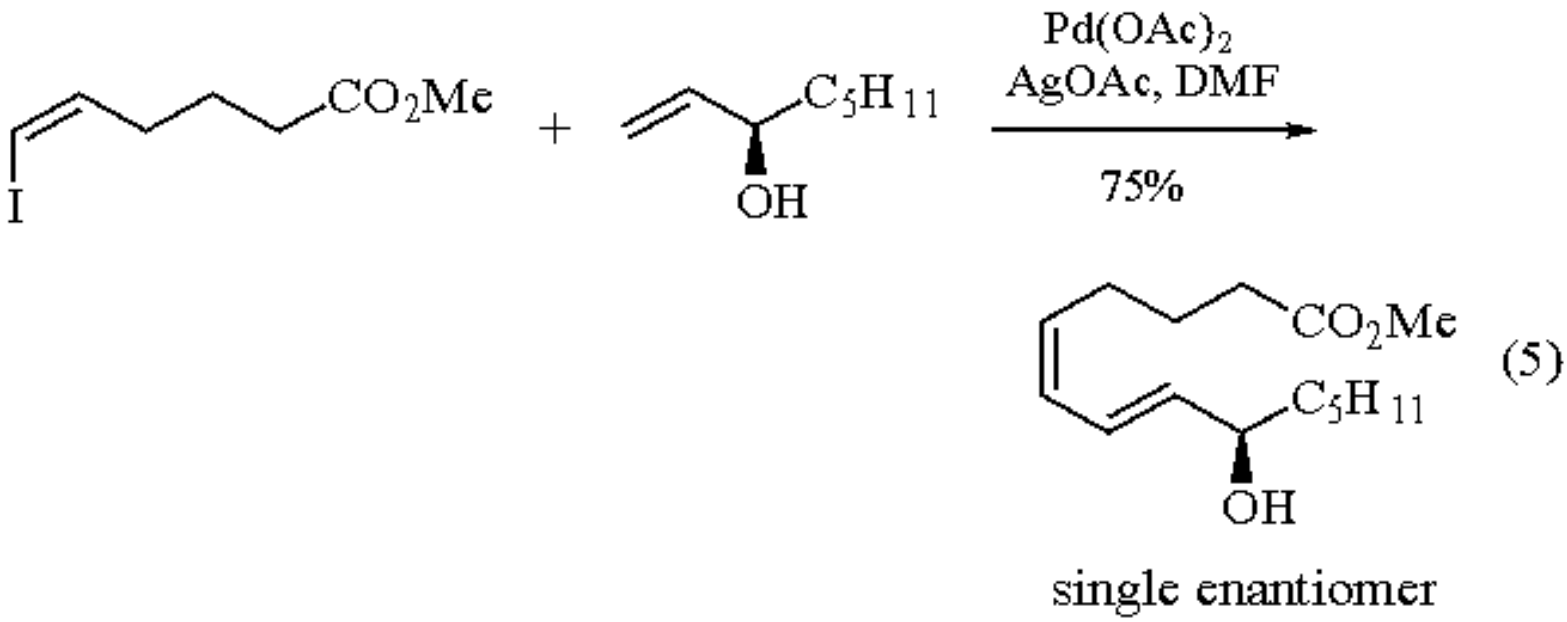

Related Reagents.

Palladium(II) Acetate; ***Silver(I) Carbonate***; ***Silver(I) Phosphate***.

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Palladium-Graphite

Pd-Gr

[59873-73-3] · Pd · Palladium-Graphite · (MW 106.42)

(hydrogenation catalyst for aromatic nitro compounds, alkenes, and alkynes;[1] catalyzes arylation and vinylation of activated double bonds[2,3])

Physical Data: 31-33% Pd by weight.

Form Supplied in: not commercially available.

Preparative Method: by reduction of ***Palladium(II) Chloride*** by ***Potassium-Graphite*** in 1,2-dimethoxyethane at 100 °C.[1]

Handling, Storage, and Precautions: no special handling or storage necessary; the catalyst is stable in air and can be stored for a long time without loss of activity.

Hydrogenation Catalyst.

Palladium-graphite is an effective catalyst for hydrogenation of aromatic nitro compounds to anilines (eq 1) and alkenes to alkanes (eq 2).[1] The results of these investigations indicated that palladium-graphite is an alternative to the more commonly used ***Palladium on Carbon*** catalyst.

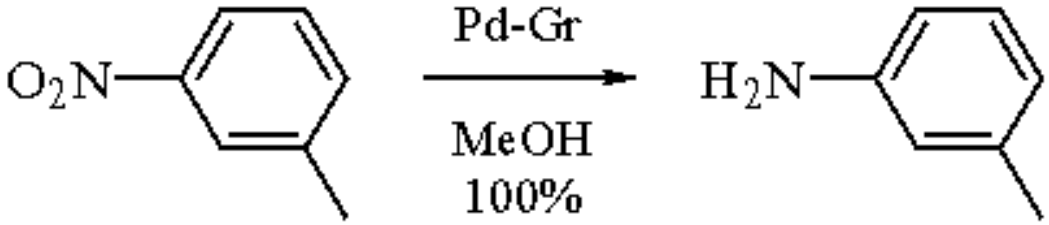

(1)

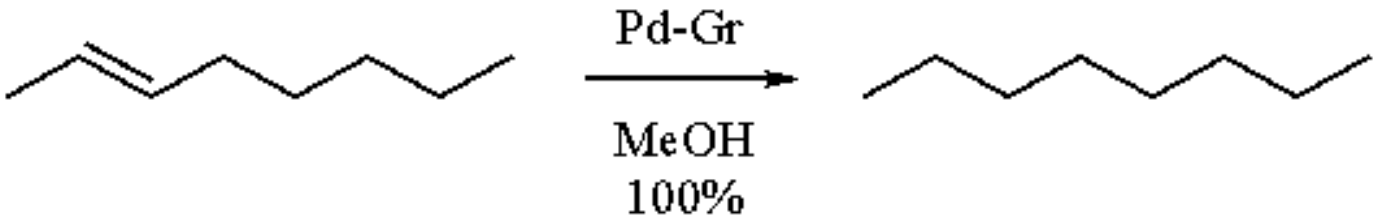

(2)

The catalyst has also been found to be effective in the stereospecific semihydrogenation of mono- and disubstituted alkynes to (*Z*)-alkenes (eqs 3 and 4).[1] Addition of ***1,2-Diaminoethane*** (EDA) is required for this stereospecificity to be achieved. Full hydrogenation is almost completely suppressed and results are comparable to those obtained by Lindlar or P-2 nickel catalysts. In fact, higher specificity is achieved with palladium-graphite compared to palladium on carbon in the presence of ethylenediamine although the rate of hydrogenation is slower.

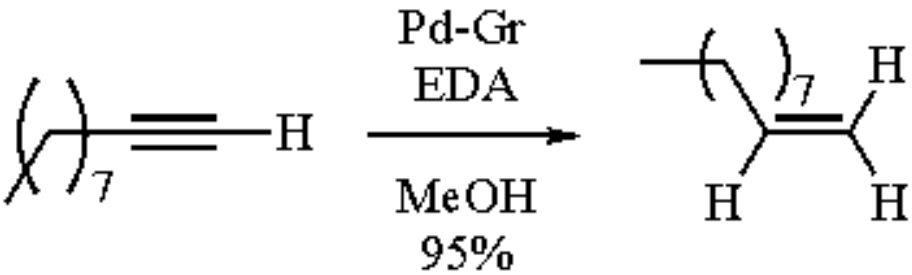

(3)

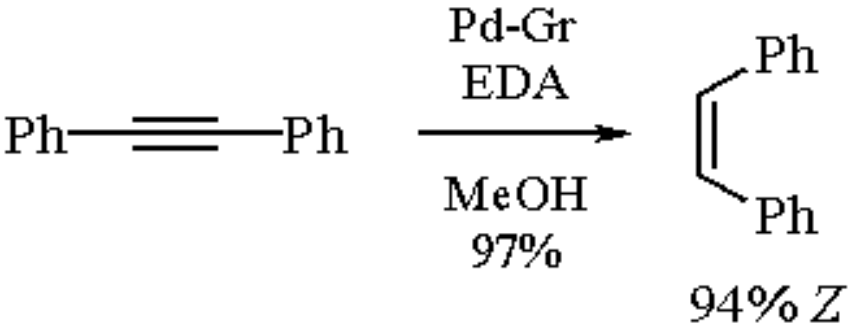

(4)

Arylation and Vinylation of Activated Double Bonds.

Palladium-graphite undergoes oxidative addition into the carbon-halogen bond of aryl and vinyl iodides, which, after reductive elimination, yield the corresponding arylated or allylated compounds.[2] Aryl bromides should not be used as they are not as reactive under these reaction conditions. By using a stoichiometric amount of a tertiary amine to trap the HI, the reaction can be carried out with a catalytic amount of palladium. When monosubstituted alkenes are used, high stereospecificity is achieved, thereby affording substituted (*E*)-alkenes (eqs 5 and 6). The yields are comparable with those reported using other palladium catalysts such as ***Palladium(II) Acetate***.

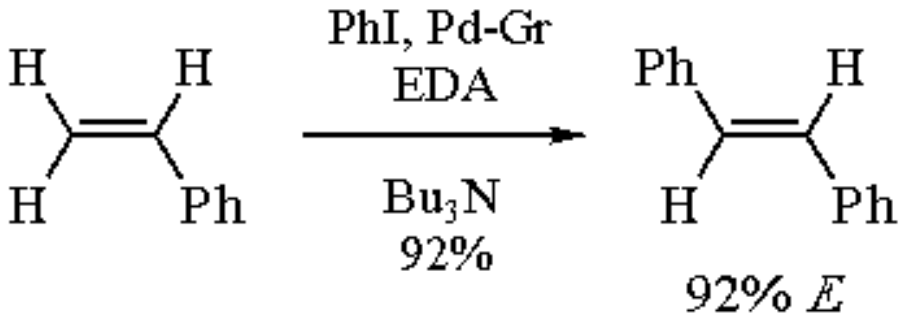

(5)

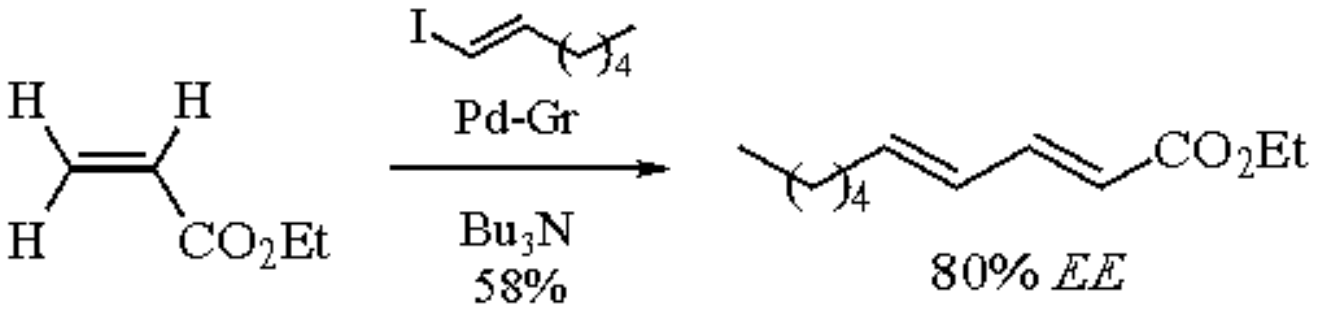

(6)

Substitution reactions of allylic esters are also catalyzed by palladium-graphite.[3] The reaction between allyl acetate and ***Sodium Benzenesulfinate*** in the presence of catalytic amounts of Pd-Gr and ***Triphenylphosphine*** afforded the allyl phenyl sulfone in quantitative yield (eq 7). In fact, the catalyst can be recovered and after ten runs the yield was 93%, showing that the catalyst retains its activity.

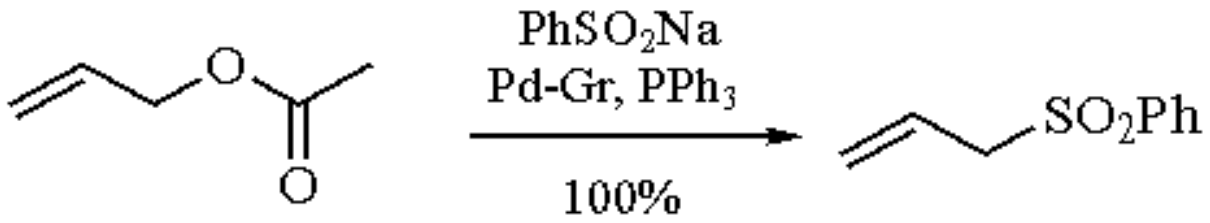

(7)

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Palladium(II) Hydroxide on Carbon

$Pd(OH)_2$

[7440-05-3] · H_2O_2Pd · Palladium(II) Hydroxide · (MW 140.44)

(catalyst for hydrogenolysis of benzyl groups and epoxides; used to reduce nitro compounds to amines and as dehydrogenation reagent)

Alternate Name: Pearlman catalyst.

Solubility: insol all organic solvents.

Form Supplied in: black powder, typically containing 20 wt % of Pd and 10-15 wt % of H_2O.

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds. The reagent is pyrophoric in the presence of solvents. General precautions for handling hydrogenation catalysts should be followed. The catalyst must be suspended in the organic solvent under an atmosphere of N_2. During filtration the filter cake must not be allowed to go dry. If a filter aid is necessary, a cellulose-based material should be used if catalyst recovery is desired.

Hydrogenolysis and Hydrogenation.

Palladium hydroxide on carbon has been used for difficult debenzylations when other supported palladium catalysts were not effective or satisfactory.[1] For example, although *para*- and *meta*-substituted benzyl alcohols were easily hydrogenolyzed with 10% ***Palladium on Carbon***, hydrogenolysis of the *ortho*-substituted substrate was only effective with 20% $Pd(OH)_2/C$ (eq 1).[2] This catalyst also catalyzes hydrogenation and hydrogenolysis of other functional groups.

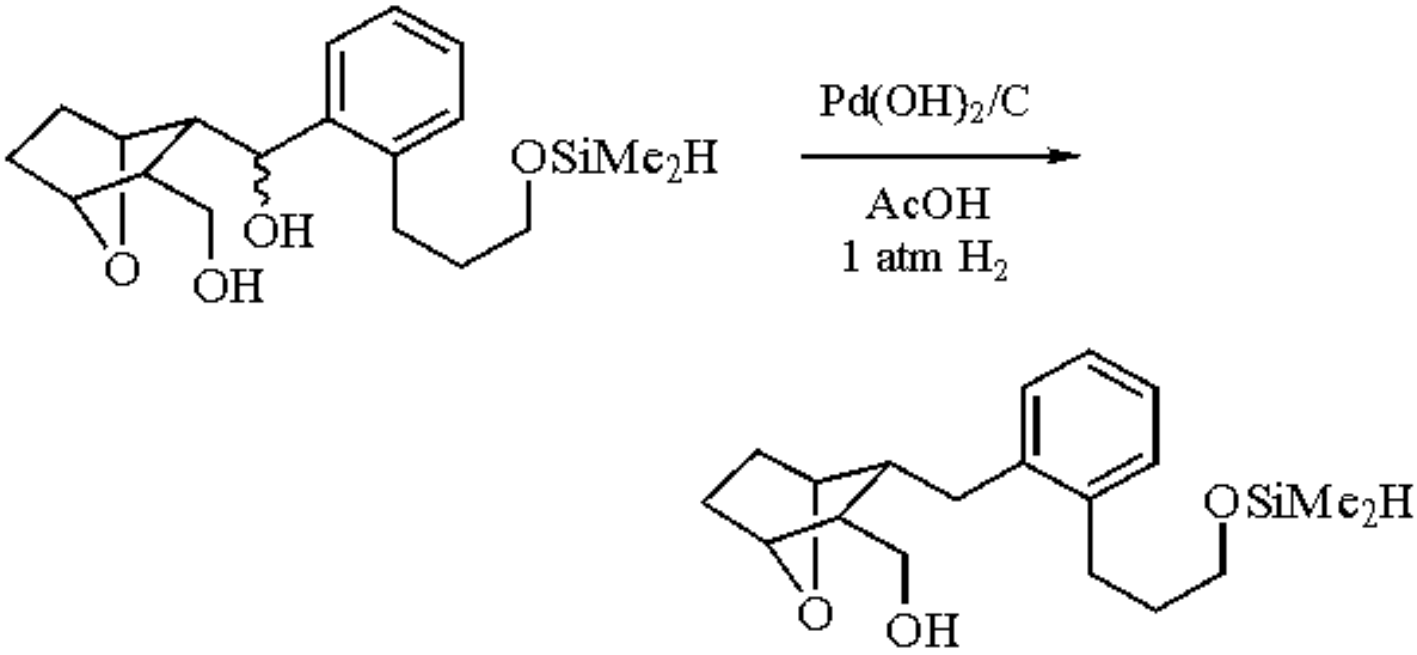

(1)

The transfer hydrogenolysis of a benzyl ether proceeded in high yield without the hydrogenolysis of the chlorine or the hydrogenation of the alkene (eq 2).[3] Evidence showed that an oxidative mechanism, rather than the usual reductive mechanism, might be involved in this case.

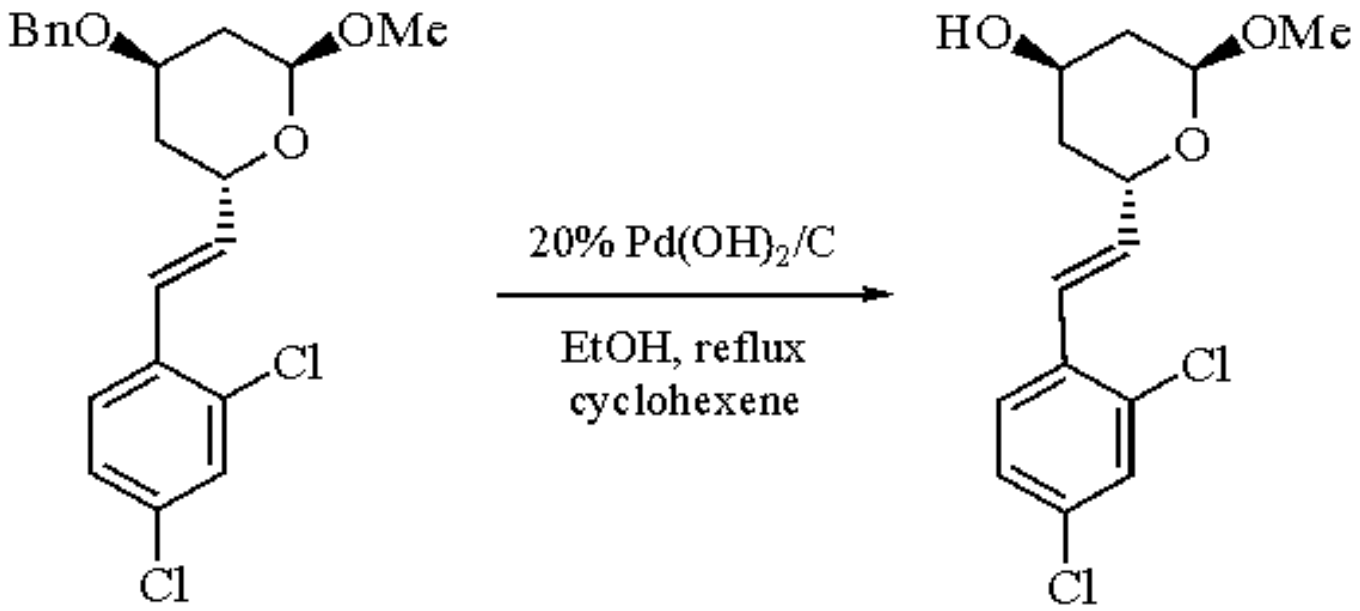

(2)

Deprotection of a benzyl carbamate and concomitant reduction of a double bond with the Pearlman catalyst has provided an amino acid in 82% yield (eq 3).[4]

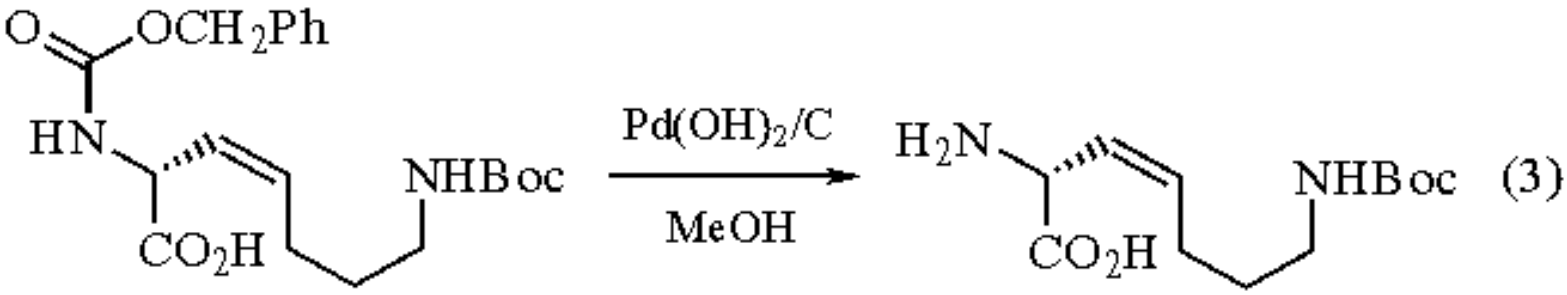

Debenzylations of *N*-benzylated imidazole derivatives are very difficult, but in the case of the imidazole derivative in eq 4, hydrogenolysis proceeded to give 84% yield of the desired product. The N-N bond was not cleaved under the reaction conditions, but the formyl group was hydrogenolyzed (eq 4).[5]

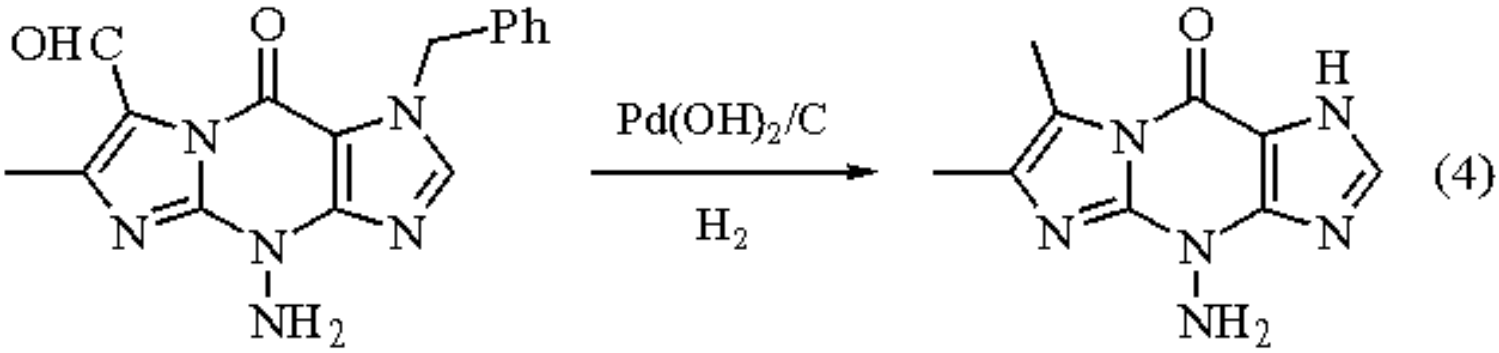

An *N*-protected azete hydrochloride was deprotected in EtOH to provide the azete hydrochloride in 86% yield. The azete ring was stable under the reaction conditions. This intermediate was converted to δ-coniceine in four steps (eq 5).[6]

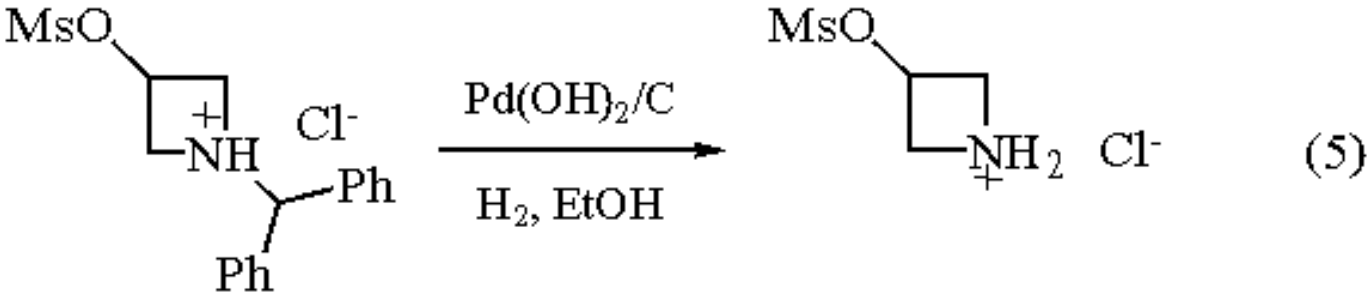

Excellent regioselective opening of an epoxide has been accomplished with the Pearlman catalyst. The epoxide opening with ***Lithium Aluminum Hydride*** (LAH) gave no selectivity and a 50/50 mixture of the triol isomers was obtained. Hydrogenolysis with the Pearlman catalyst gave 99% selectivity. An equivalent weight of catalyst vs. substrate must be used to obtain the excellent 92% yield (eq 6).[7]

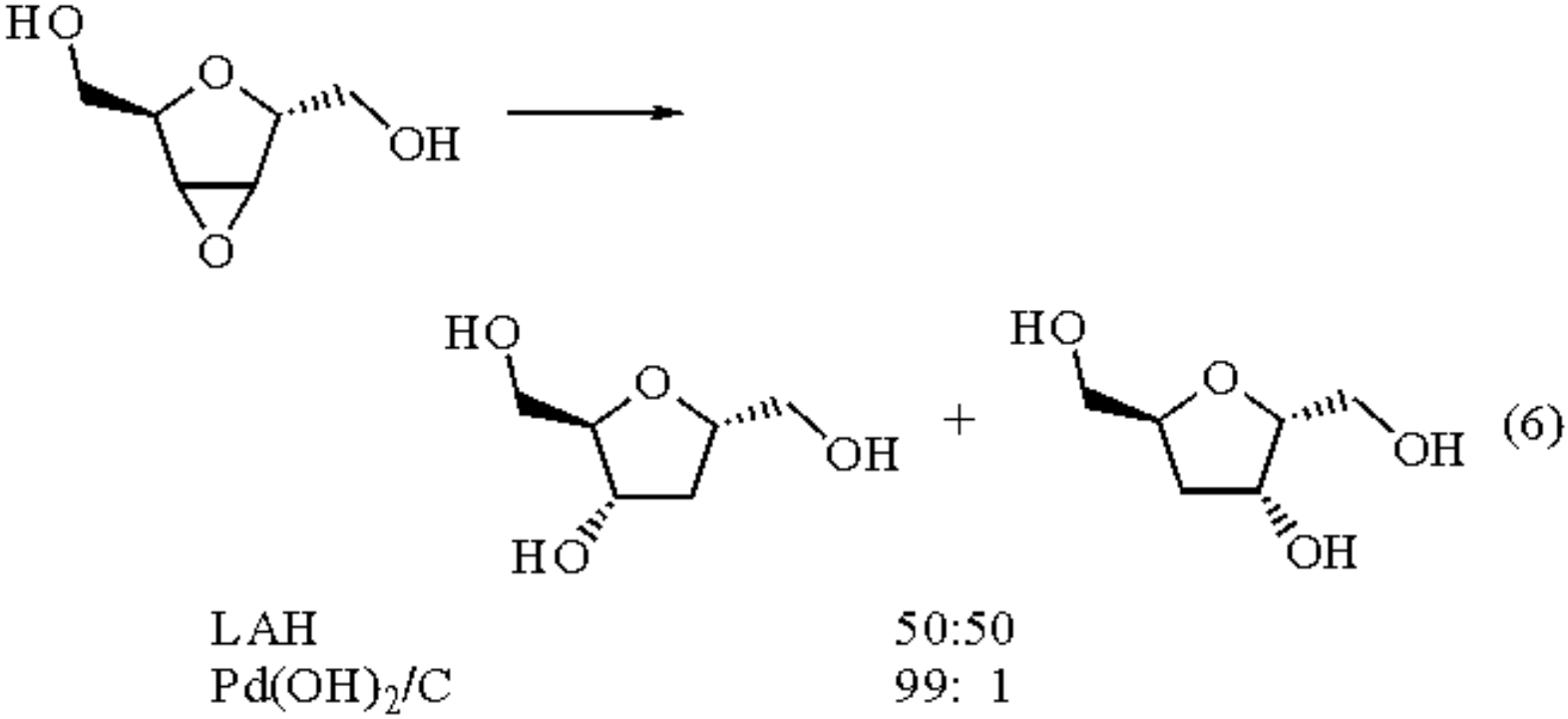

Deuterium studies showed that the ring opening proceeded with inversion of configuration at C-3 to give the deuterated product (**1**). This is a common observation with Pd catalysts.

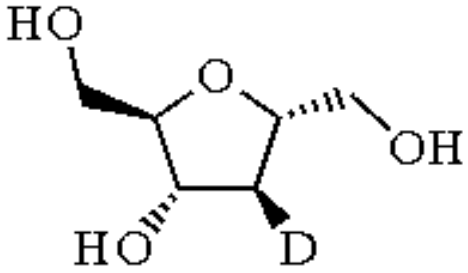

(1)

The reduction of a variety of azides to amines was carried out under transfer hydrogenation conditions with hydrazine and Pearlman catalyst in refluxing MeOH. The yields ranged from 71 to 90%.[8]

An *o*-substituted dinitrostyrene has been reduced in THF/HOAc at 150 psi H_2 and 50 °C to provide an indole in 75% yield. Interestingly, when the H_2 pressure was lowered to atmospheric pressure, the reaction proceeded only to 30% conversion to give an unidentified intermediate (eq 7).[9]

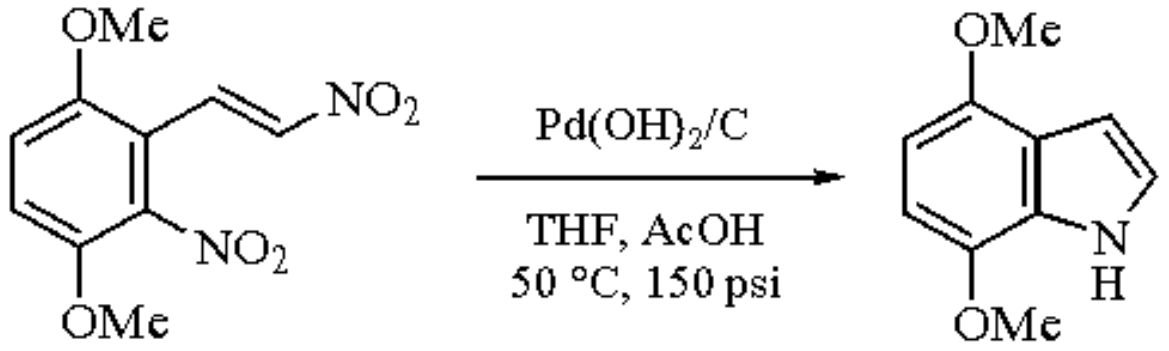

(7)

Dehydrogenation.

The reagent has also been used as a dehydrogenation catalyst. The ketone shown in eq 8 was converted to the enone in 79% yield. *trans*-4-Phenyl-3-buten-2-one was obtained in 50% conversion in toluene from 4-phenylbutan-2-one, but no dehydrogenation was observed with propiophenone, indanone, α-tetralone, or cyclohexanone.[10]

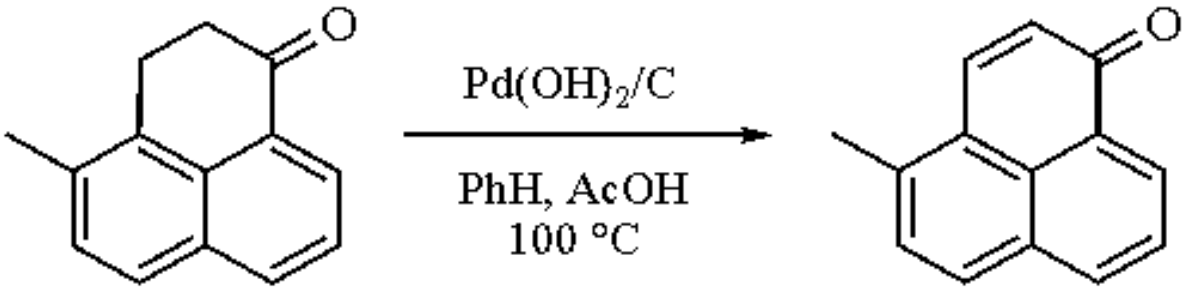

(8)

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Palladium(II) Nitrate

$Pd(NO_3)_2$

[10102-05-3] · N_2O_6Pd · Palladium(II) Nitrate · (MW 230.44)

(catalyst for alkene nitration to glycol dinitrates[1])

Physical Data: no mp (dec).

Solubility: sol nitric acid; sol w/dec. water.

Form Supplied in: brown, deliquescent crystals; probably exists as the dihydrate;[2] commercially available.

Handling, Storage, and Precautions: store under anhydrous conditions, protected from light.

Palladium(II) nitrate is a useful stoichiometric reagent for the nitration of alkenes to glycol dinitrates.[3] The reaction can be made catalytic in the presence of nitric acid and nitrite ion, the latter being necessary to reoxidize the metallic Pd that is formed (eq 1).[1] Alternatively, oxygen can be used to reoxidize the NO_2 coproduct back to nitric acid and water (eq 2). This reaction is most useful for the production of ethylene glycol dinitrate, which is formed in up to 88% selectivity in a 1:1 mixture of dioxane and ***Nitric Acid***. With higher α-alkenes the NO_2 coproduct adds to the alkene at rates that are competitive with oxidation, even in the presence of oxygen, so that the selectivity for dinitrate is reduced to the 40-60% range.

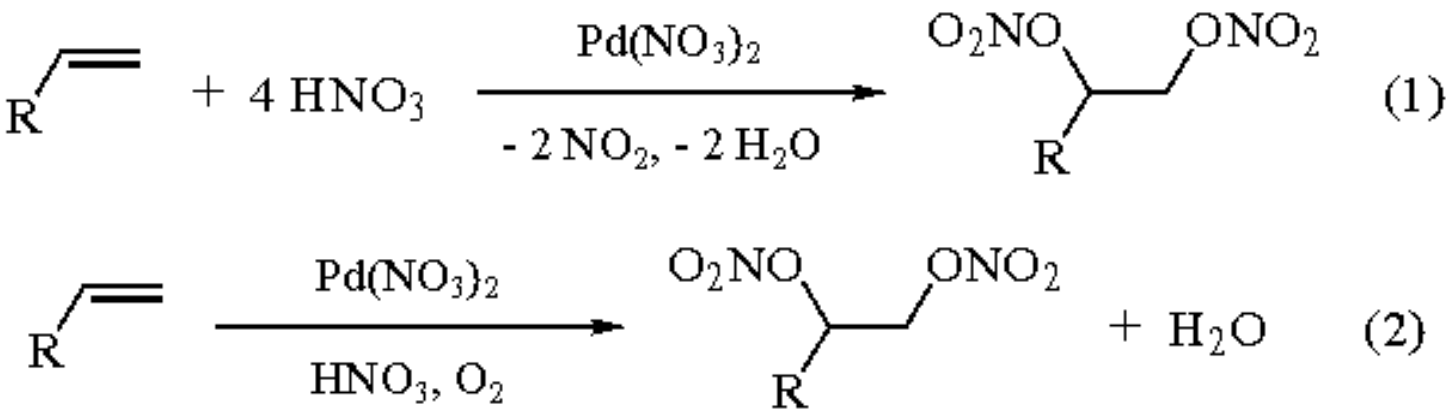

Palladium nitrate can often be substituted for other palladium salts in catalyst mixtures, but the catalyst performance varies with the particular salt chosen. For instance, although $Pd(NO_3)_2$ can be used in Wacker-like oxidation reactions,[4] ***Palladium(II) Chloride*** or related salts often give better results.[5] However, $Pd(NO_3)_2$ is often preferred in

industrial oxidation processes, such as the oxidative coupling of ***Carbon Monoxide*** to give oxalic acid esters (eq 3).[6]

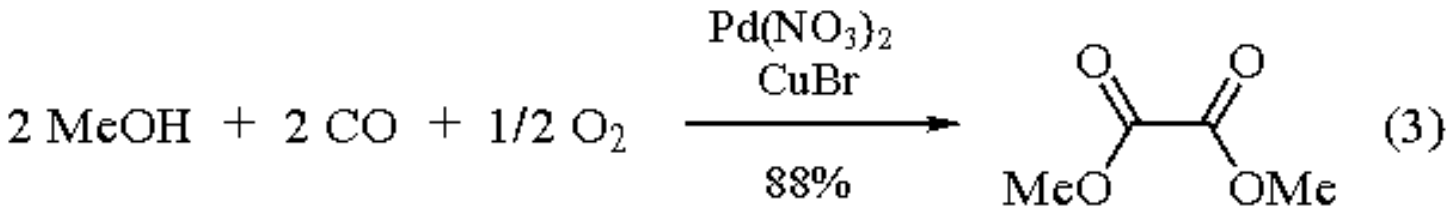

Another example where $Pd(NO_3)_2$ appears to work better than other Pd salts is in the stoichiometric carboxylation of aromatic compounds to give aryl carboxylic acids (eq 4).[7]

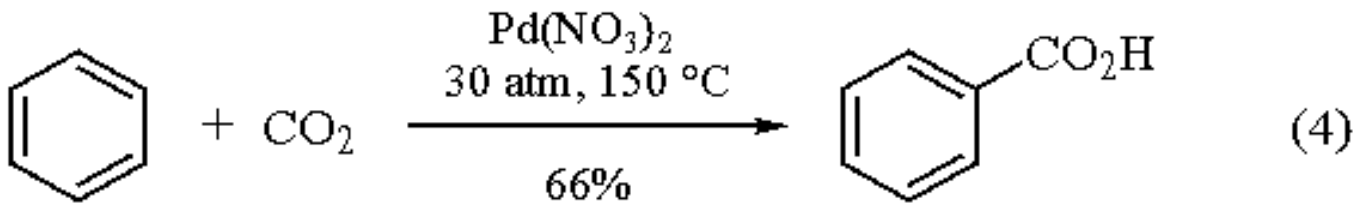

Palladium(II) nitrate can also be used in place of other palladium salts as a precursor to palladium catalysts formed in situ, such as Pd^{II} or Pd^{0} phosphine complexes. One example where only $Pd(NO_3)_2$ works well is in the ***Triphenylphosphine***-promoted dimerization of ***1,3-Butadiene*** with Schiff bases to give divinylpiperidines (eq 5).[8]

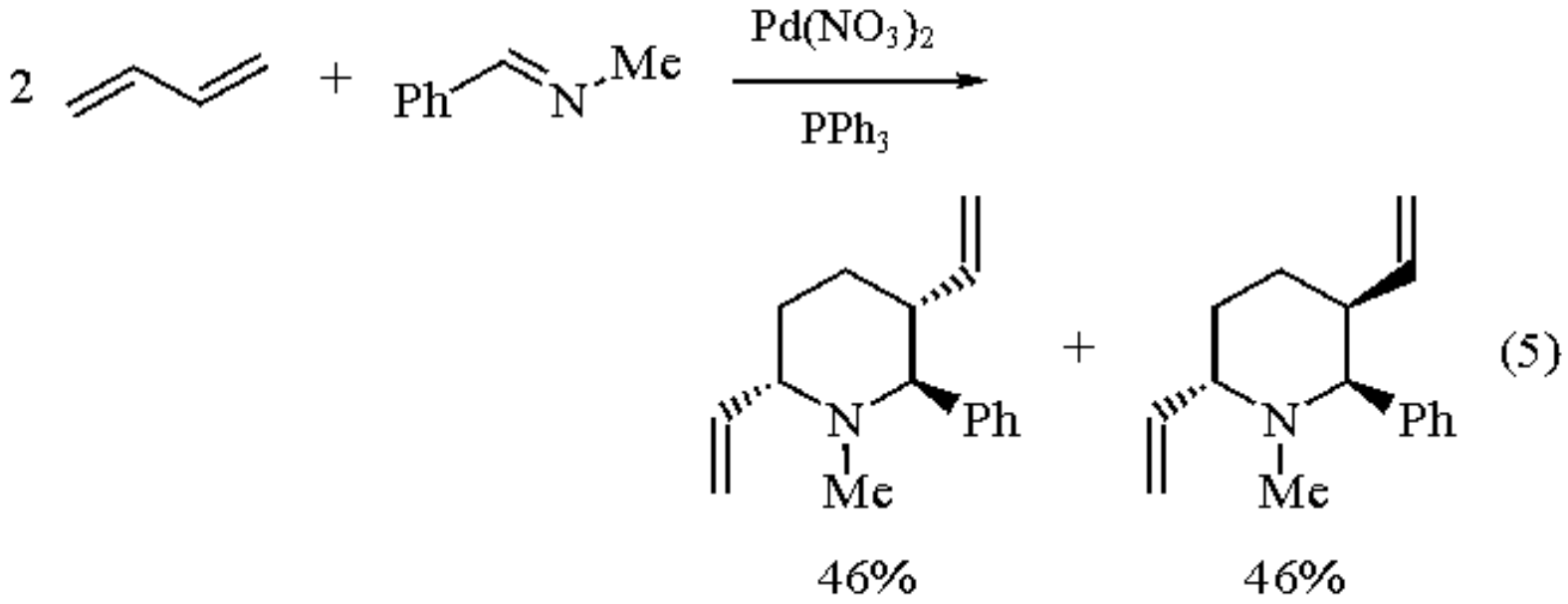

Palladium(II) nitrate is also commonly used as a precursor to supported Pd catalysts.[9]

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1. (a) Likholobov, V. A.; Ermakov, Y. I. *Kinet. Katal.* **1976**, *17*, 123. (b) Likholobov, V. A.; Ermakov, Y. I. *Kinet. Katal.* **1976**, *17*, 133. (c) Likholobov, V. A.; Ermakov, Y. I. *DOK* **1974**, *218*, 848.
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Palladium on Poly(ethylenimine)

Pd/PEI

[7440-05-3] · Pd · Palladium on Poly(ethylenimine) · (MW 106.42)

(catalyst used for the reduction of alkynes to *cis*- or *trans*-alkenes;[1] hydrogenolysis of benzyloxycarbonyl protecting groups on peptides[2])

Solubility: sol many organic solvents except when deposited on a support such as silica gel; insol water and alcohols.

Form Supplied in: commercially available as deposit on a porous silica support.

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: nonpyrophoric and air stable.

Preparation and Properties.

The deposition of Pd on a minimally cross-linked poly(ethyleneimine) polymer has produced a new type of catalyst that features interesting characteristics.[1] The catalyst is very active and also readily recyclable without loss of activity. Unlike Pd on other solid supports, this polymer is soluble in different solvent media and necessitates membrane separation technology for its removal after the desired synthetic conversion is completed. The catalyst is not soluble in water and alcoholic solvents and can be removed by filtration at the end of the reaction.

Hydrogenations.

The catalyst mediates the reduction of 2-pentyne at 20 °C and 0.1 mPa H_2 pressure in 40 min to give *cis*-2-pentene with 98% stereoselectivity. The stereoselectivity and catalyst turnover were cited to be superior to the Lindlar catalyst (***Palladium on Calcium Carbonate (Lead Poisoned)***). By binding benzonitrile to the Pd on the support, a dramatic change in the reduction of 2-pentyne occurred. The

result was the formation of *trans*-2-pentene selectively.[2] The versatility of this catalyst in providing either *cis*- or *trans*-alkenes selectively from alkynes has never been demonstrated by any other heterogeneous catalyst. With formic acid as the hydrogen source, transfer hydrogenolysis of the benzyloxycarbonyl (Cbz) protecting group on polypeptides was readily carried out in a mixture of MeOH and H_2O at rt.[1a] The catalyst used in this case was highly cross linked and was insoluble in the MeOH/H_2O solvent mixture, and removal of the catalyst by a simple filtration was possible.

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Palladium-Triethylamine-Formic Acid

Pd-Et_3N-HCO_2H

(Pd)

[7440-05-3] · Pd · Palladium-Triethylamine-Formic Acid · (MW 106.42) (Et_3N)

[64-18-6] · $C_6H_{15}N$ · Palladium-Triethylamine-Formic Acid · (MW 101.22) (HCO_2H)

[121-44-8] · CH_2O_2 · Palladium-Triethylamine-Formic Acid · (MW 46.03)

(transfer hydrogenation system used with a variety of palladium catalysts for hydrogenation and hydrogenolysis reactions; hydrogenation of alkynes, alkenes, nitro compounds; hydrogenolysis of *N*-benzyl and *O*-benzyl groups; hydrogenolysis of allyic esters and allylic carbonates)

Alternate Name: triethylammonium formate (TEAF).

Physical Data: see ***Palladium on Carbon***, ***Triethylamine***, and ***Formic Acid***.

Solubility: heterogeneous catalyst system.

Hydrogenation and Hydrogenolysis.

Triethylammonium formate, prepared most frequently in situ from triethylamine and formic acid, has been used in conjunction with both heterogeneous and homogeneous palladium catalysts for a variety of chemical transformations. With heterogeneous palladium catalysts, such as palladium on charcoal, both hydrogenation and hydrogenolysis are observed. When used in combination with homogeneous catalysts, hydrogenolysis is mainly observed. Many of these reactions can also be carried out by replacing triethylammonium formate with ***Ammonium Formate*** or hydrogen. The use of a hydrogen transfer agent, such as triethylammonium formate, enables the use of ordinary laboratory glassware and no special hydrogenation equipment is required.

The following reactions have been carried out with heterogeneous palladium catalysts. The reduction of alkynes and conjugated enynes with Pd/C or Pd/$CaCO_3$ catalyst was not stereoselective and gave mixtures of (*E*)- and (*Z*)-dienyl esters along with substantial amounts of over-reduced byproducts. The yields of the dienyl esters ranged from 59 to 84%.[1] A combination of triethylammonium formate and Pd/C was used to reduce alkynes to alkenes or alkanes. Reduction of 3-hexyne was not selective, giving a mixture of 3-hexenes (70%) and hexanes (18%). Diphenylacetylene, on the other hand, gave *cis*-stilbene (93%) with only 2% of bibenzyl. Selective reduction of the double bond in α,β-unsaturated carbonyl compounds, such as citral (91%), crotonaldehyde (81%), 2-cyclopentenone

(83%), methyl crotonate (83%), and methyl cinnamate (86%), provided good yields of the carbonyl compounds.[2]

The facile reduction of aromatic nitro compounds to anilines has been reported and oxindole and benzolactam can be formed directly from *o*-nitrophenylacetic acid and *o*-nitrocinnamic acid, respectively, in 72-75% yields.[3] Some selectivity was observed in the reduction of one nitro group in dinitro aromatic compounds. The best results were observed with 2,4-dinitrotoluene, in which 2-nitro-4-aminotoluene was obtained in 92% yield. The yields of other dinitro compounds ranged from 24 to 77%.[4]

Hydrogenolyses of aryl benzyl ethers and allylic acetates or amines have been reported to give phenols and alkenes, respectively.[5] Hydrogenolysis of aryl halides with triethylammonium formate in the presence of heterogeneous catalysts is another useful synthetic method. Some interesting selectivity was observed when the heterogeneous catalysts were replaced with homogeneous catalysts. For example, reduction of 1-nitro-3-bromobenzene in the presence of 5% Pd/C gave a mixture of nitrobenzene (46%) and aniline (15%). Replacement of the 5% Pd/C with ***Palladium(II) Acetate*** and 2 equiv of tri-*o*-tolylphosphine gave nitrobenzene (81%) and only 2% of aniline. Similarly, the yield of benzonitrile from 4-bromobenzonitrile was improved from 53 to 83% with the homogeneous catalyst.[3]

The homogeneous catalytic system, on the other hand, is also able to deoxygenate phenols via their aryl sulfonates (eq 1).[6] By varying the phosphine ligands, the phenol starting materials could be regenerated and thus the sulfonyl group only acts as a protecting group (eq 2). Similarly, aryl triflates are also hydrogenolyzed in excellent yields (eq 3).[7] Selective hydrogenolysis of the triflates was realized in the presence of alkenes.

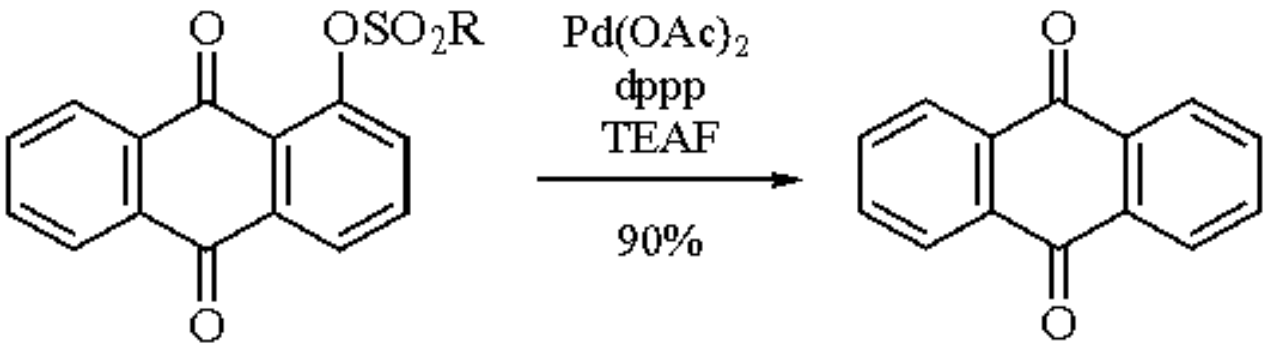

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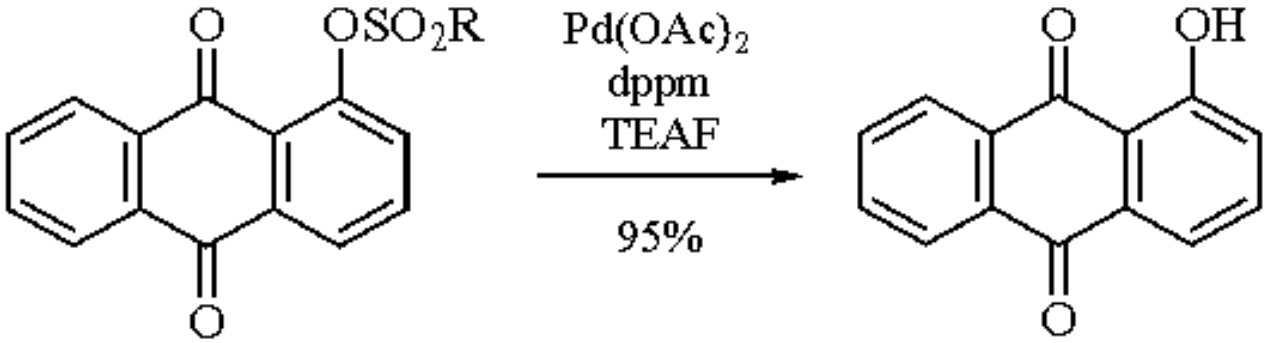

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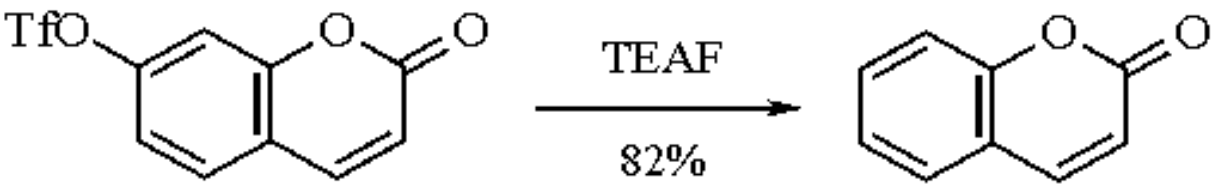

(3)

Allyl esters (eq 4) and carbonates (eq 5) are converted to alkenes under the homogeneous catalysis reaction conditions.[8] The least substituted alkene is formed preferentially.

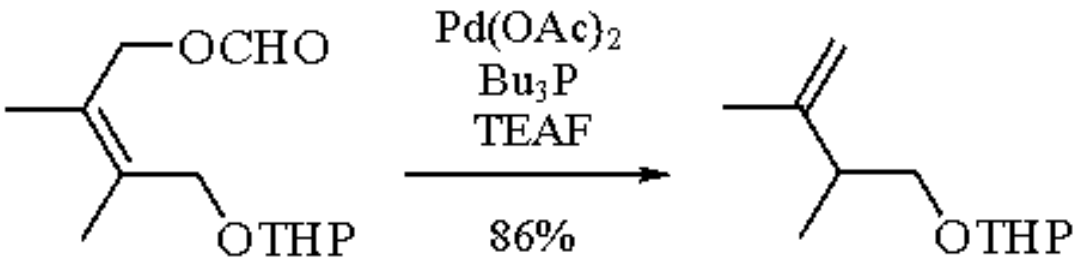

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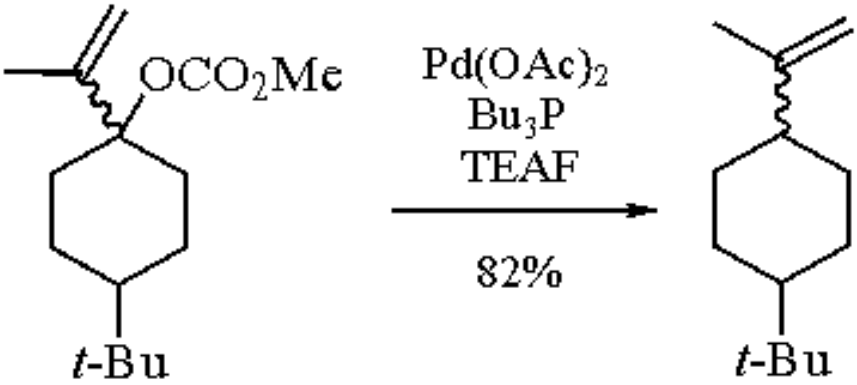

(5)

The Pd-catalyzed Carroll rearrangement of allyl β-ketocarboxylates to give α-allyl ketones was realized in THF (eq 6).[9]

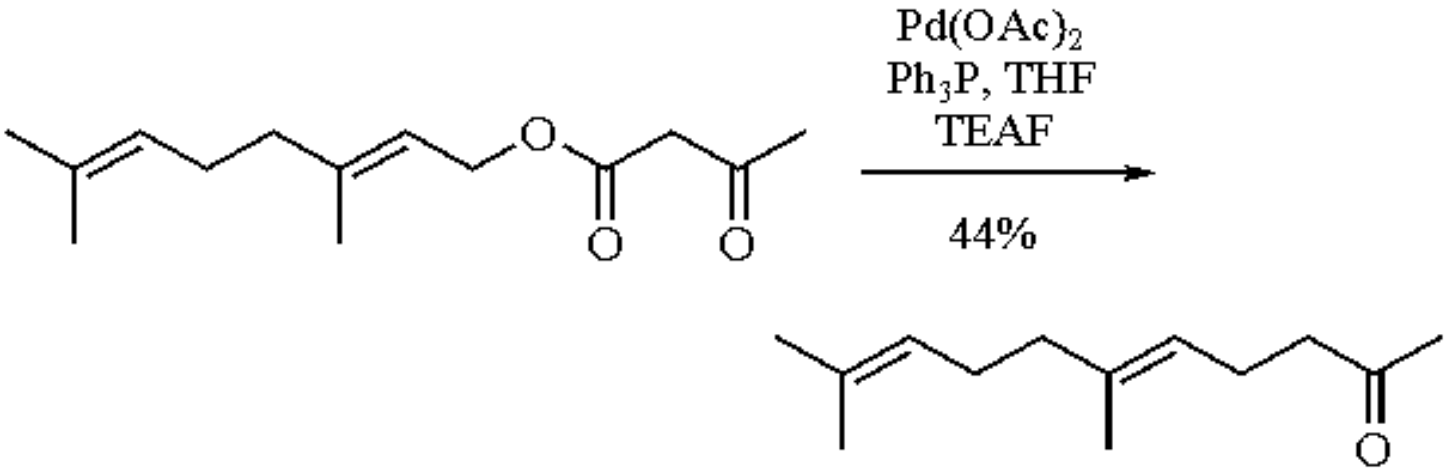

(6)

Switching the solvent to MeCN provided α,β-unsaturated ketones instead (eq 7).[10]

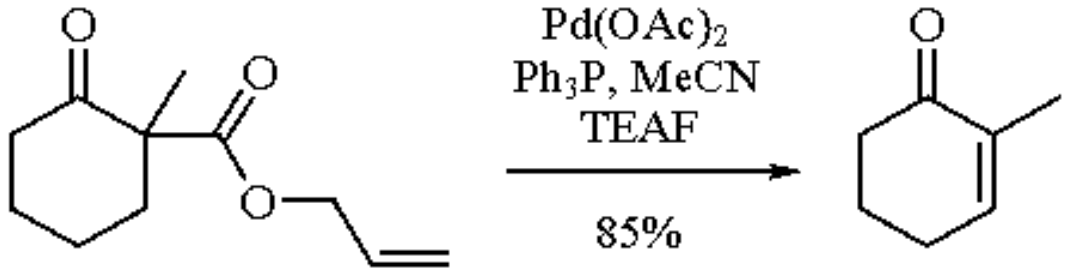

(7)

Allyl β-keto esters can also be hydrogenolyzed to form ketones without allylation (eq 8).[11]

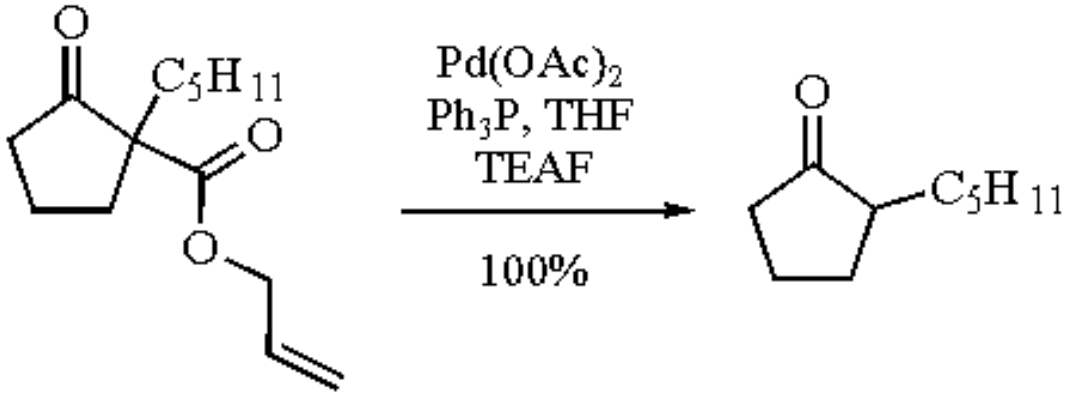

(8)

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2. Cortese, N. A.; Heck, R. F. *JOC* **1978**, *43*, 3985.
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Palladium(II) Trifluoroacetate

$(CF_3CO_2)_2Pd$

[42196-31-6] · $C_4F_6O_4Pd$ · Palladium(II) Trifluoroacetate · (MW 332.46)

(palladium catalyst used in the oxidation of alkenes[3-5] and C-C bond formation[6-8])

Physical Data: mp 210 °C (dec).

Solubility: sol diethyl ether, acetone; insol benzene, chloroform, trifluoroacetic acid.

Form Supplied in: brown powder; commercially available.

Analysis of Reagent Purity: IR: ν 1690, 1435 cm^{-1}.

Preparative Methods: by reaction of ***Palladium(II) Acetate*** with excess ***Trifluoroacetic Acid*** on a steam bath, to yield a brown powder after drying in vacuo.[1] The reagent is also prepared in 89% yield by reaction of ***Palladium(II) Chloride*** with aqueous hydrochloric acid, then 15% sodium hydroxide solution at 85 °C, followed by excess trifluoroacetic acid at 80 °C.[2]

Handling, Storage, and Precautions: stable solid; irritant and hygroscopic.

Oxidation of Alkenes.

Photolysis of oxygenated acetone solutions of allylsilanes with an arylsulfonyl group at the allylic position in the presence of the title reagent (**1**) affords α,β-enals and α,β-enones (eq 1).[3] Palladium(II) trifluoroacetate also catalyzes the oxidation of styrene to acetophenone in the presence of an oxygen atom donor such as a molozonide (**2**) (eq 2).[4]

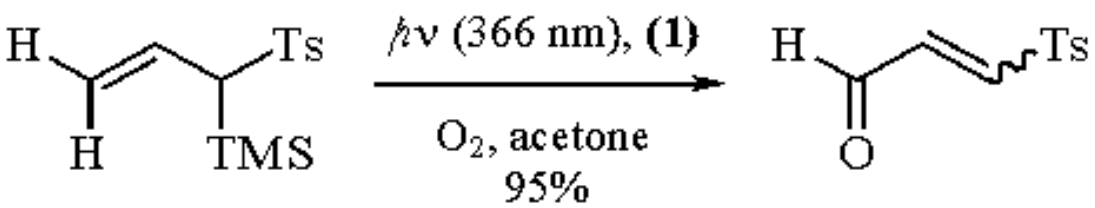

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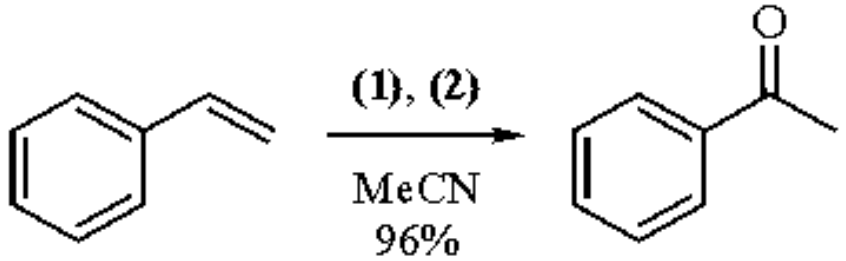

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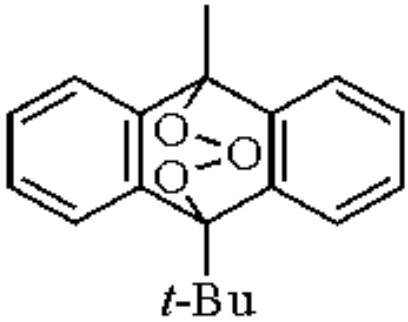

(2)

Allylic Acetoxylations.

The terminal allylic methyl group of geranylacetone is selectively oxidized with a catalytic amount of (**1**), ***1,4-Benzoquinone*** as oxidant, *o*-methoxyacetophenone as added ligand, and acetic acid as solvent (eq 3).[5]

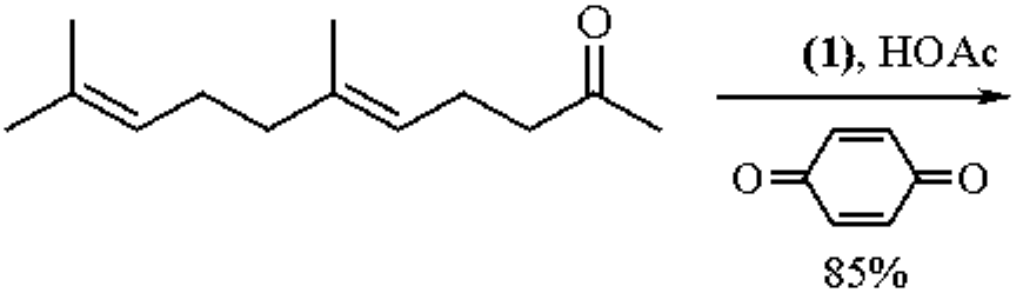

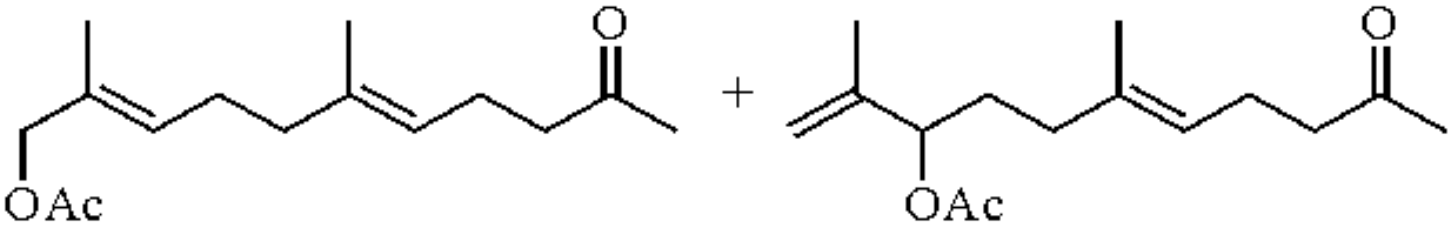

(3)

1.94:1.0

Alkylidenecyclopentenedione Synthesis.

The 4-alkynyl-4-hydroxycyclobutenone ring system rearranges with ring expansion to alkylidenecyclopentenediones in the presence of (**1**) (eq 4).[6] A similar selective ring expansion has provided 2-alkylideneindene-1,3-dione monoacetals (eq 5).[6] In both cases the nonvinylic C-C bond migrates more rapidly.

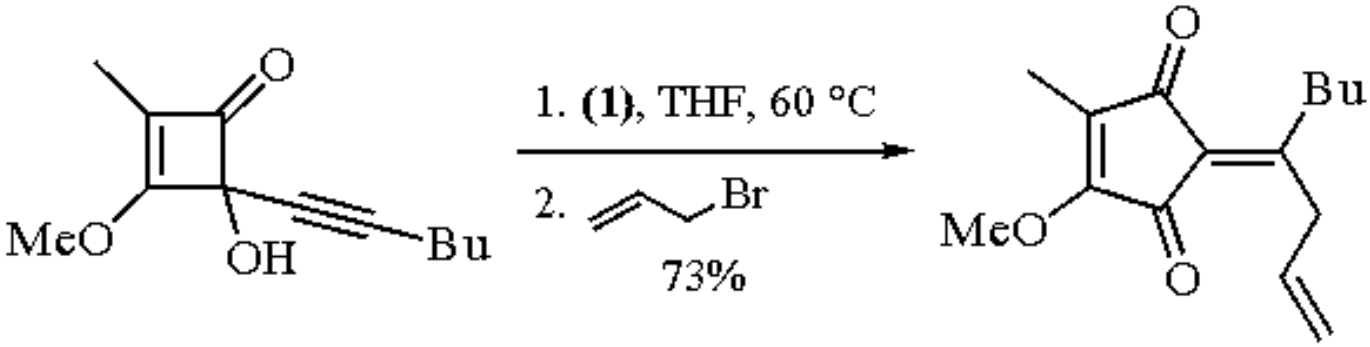

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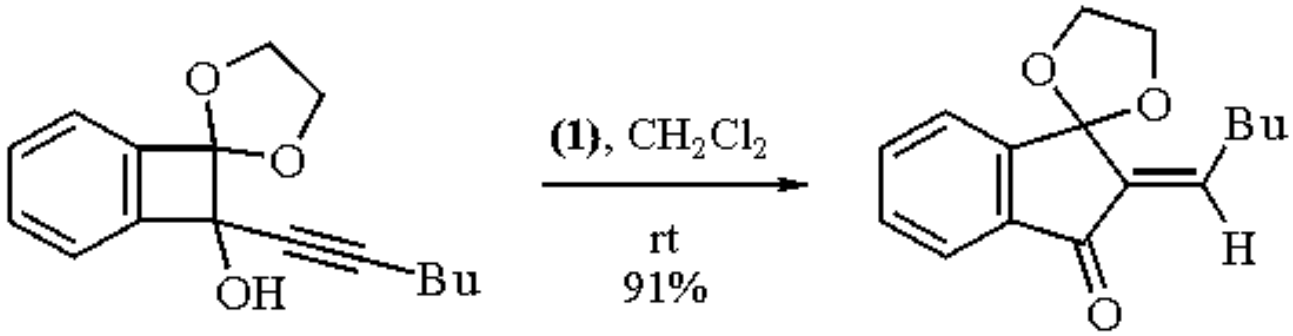

(5)

$(Z):(E) = 36:1$

Tetraene Carbocyclizations.

Cyclization of a tetraene employing a catalytic amount of (**1**) with ***Triphenylphosphine*** as an additive in THF afforded a 73% yield of the cyclized and intramolecularly trapped diene (eq 6).[7]

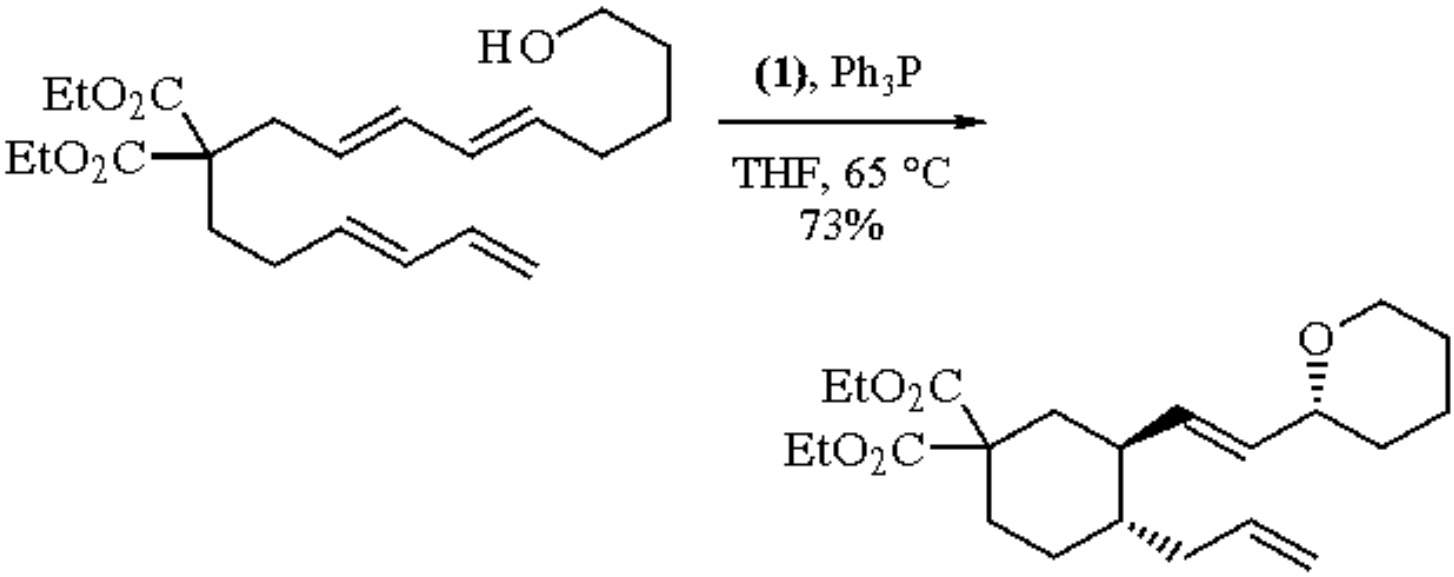

(6)

π-Allyl Palladium Complex.

The dimethyl ester of *N*-(ethoxycarbonyl)kainic acid forms a π-allyl palladium complex upon treatment with (**1**)

followed by conversion to the more stable chloride complex.[2] This π-allyl complex reacts with the anion of *t*-butyl acetoacetate to afford the alkylated product (eq 7).[8]

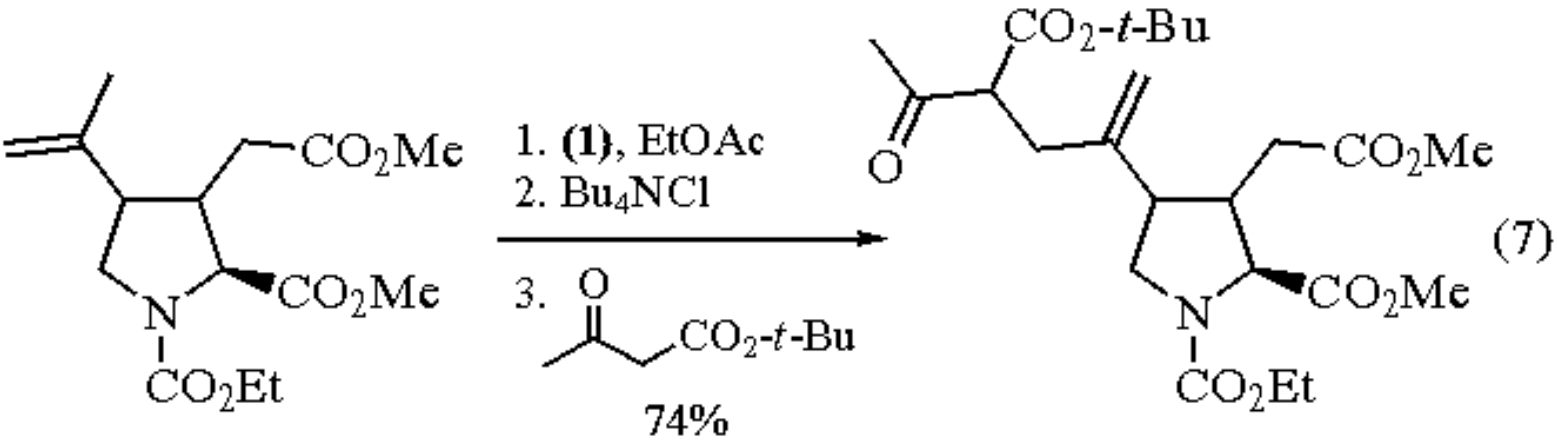

Related Reagents.

Palladium(II) Acetate is similar to palladium(II) trifluoroacetate. Comparable results are obtained in most of the reactions, except acetate is a better nucleophile than trifluoroacetate.

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1. Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Heffer, J. P.; Wilkinson, G. *JCS* **1965**, 3632.
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(*R*)-Pantolactone[1]

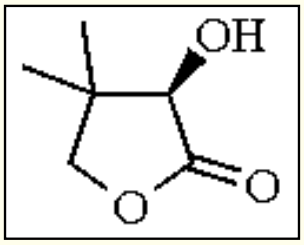

[599-04-2] · $C_6H_{10}O$ · (*R*)-Pantolactone · (MW 130.16)

(effective chiral auxiliary in diastereoselective Diels-Alder reactions,[1] and for diastereoselective addition to ketenes;[2] used as a chiral pool reagent; also used as a covalently bound resolving agent[3])

Alternate Name: (*R*)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone.

Physical Data: mp 92 °C; bp 120-122 °C/15 mmHg; [α]25D -50.7° (*c* 2.05, H_2O).

Solubility: sol water, alcohols, benzene, ether, chlorocarbons, THF.

Form Supplied in: crystalline white solid; commercially available.

Handling, Storage, and Precautions: hygroscopic.

Availability.

Although commercially available via the degradation of pantothenic acid, (*R*)-pantolactone is also conveniently prepared by enantioselective reduction of its corresponding keto lactone employing homogeneous catalysis,[4a-g] or by microbial methods.[5] The (*S*)-enantiomer has been prepared by inversion of the natural product in 90% yield and 97% ee via triflate activation, acetate displacement, and ***Lithium Hydroxide*** hydrolysis.[6] The enantiomers were also prepared by resolution of the racemate with (*R*)- and (*S*)-phenethylamine.[7] A gas chromatographic method exists for ee determination.[8]

Diels-Alder Reactions.

(*R*)-Pantolactone is one of the most effective chiral auxiliaries for preparative scale Diels-Alder additions of simple enoate esters in the presence of Lewis acids (eq 1).[9]

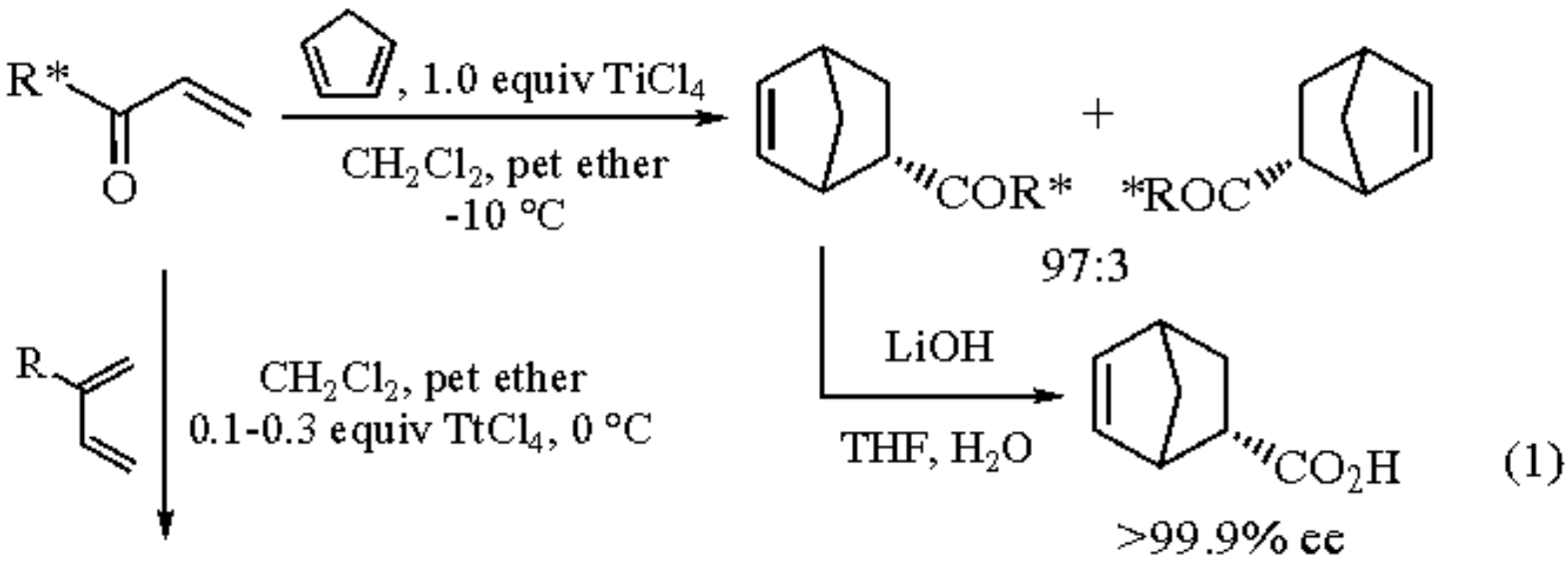

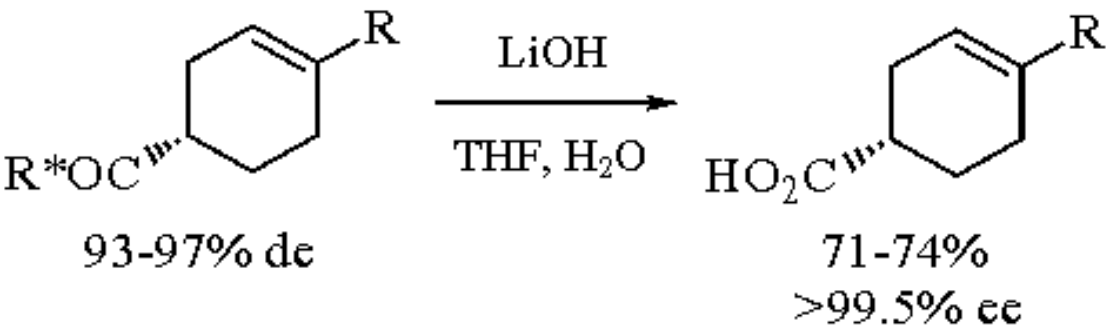

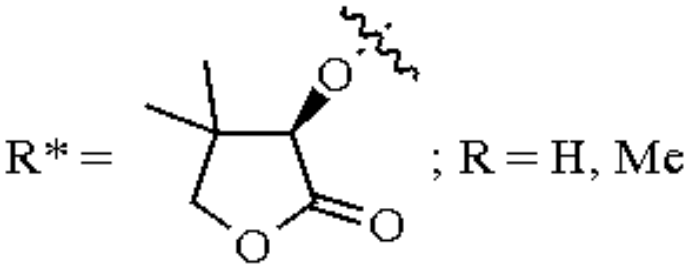

Endo-exo selectivity typically ranges from 20:1 to 45:1 with a maximum of 97.5:2.5 diastereoselection. Preparatively convenient reaction conditions are employed (CH_2Cl_2, CH_2Cl_2/cyclohexane; temp. approx. 0 °C; ca. 0.3 M concentration; and 0.1-1.0 molar equiv of Lewis acid). Products are typically crystalline and brought to high optical purity by recrystallization. Epimerization-free hydrolysis is effected with LiOH in THF/water. This procedure has been successfully applied in a nine-step synthesis of cyclosarkomycin in 17% overall yield (eq 2),[10] and to syntheses of the sandalwood fragrances.[11]

(R)-Pantolactone

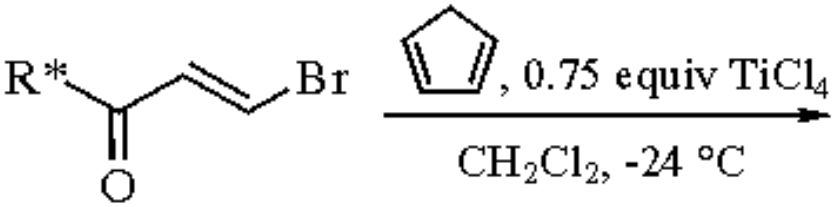

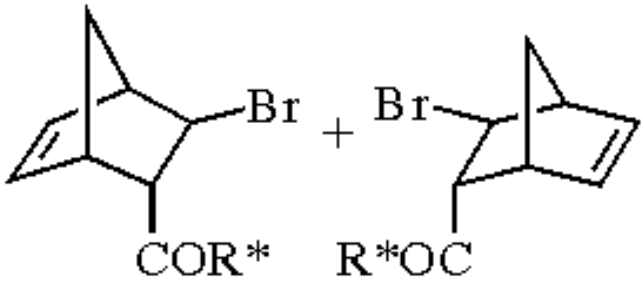

+ *exo* isomers (2)

98:2

78%, >99% ee

Cyclosarkomycin
17% overall yield

The cyclohexane unit of the C(30) stereocenter of the C(18)-C(35) segment of FK-506 was established in excellent yield and de employing the same concept (eq 3).[6]

(R)-Pantolactone

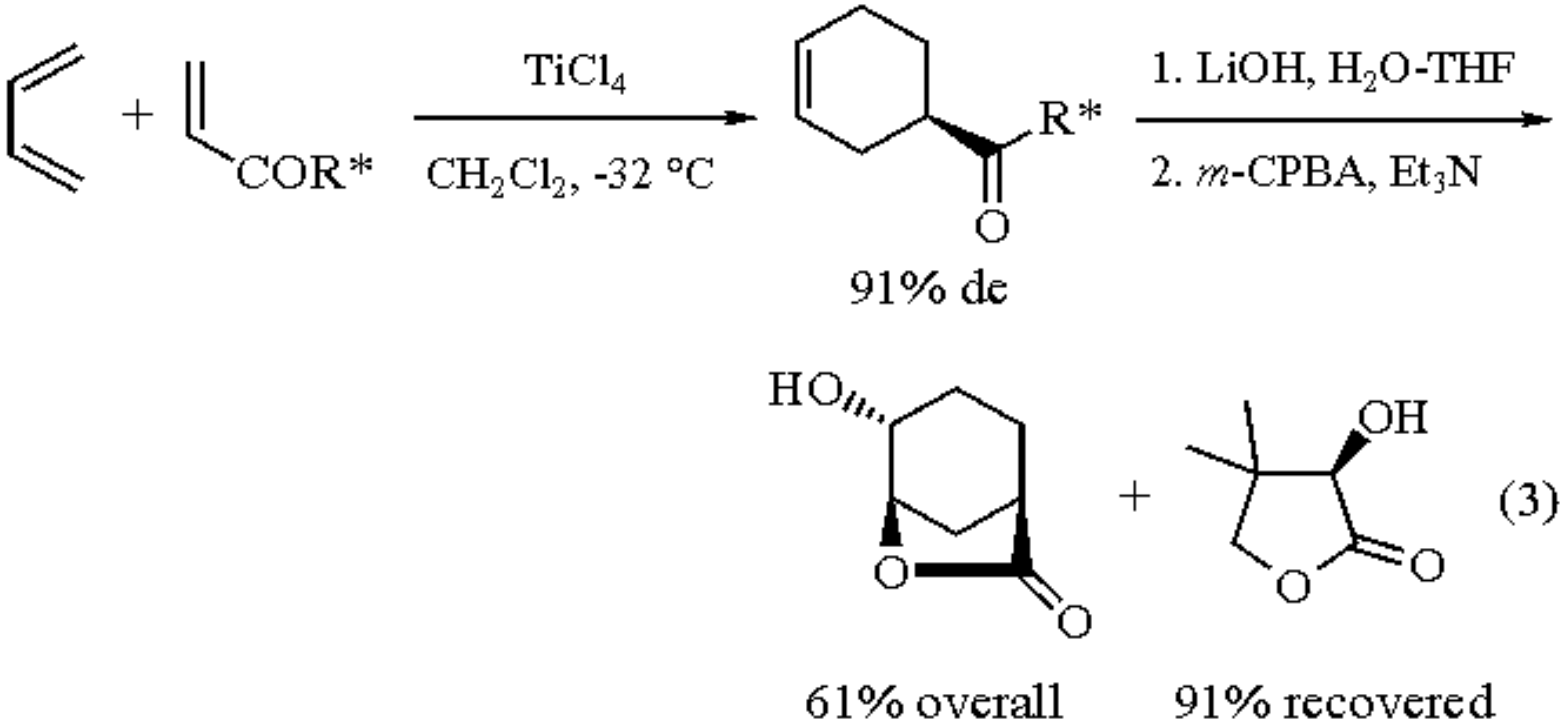

(3)

(*E*)-2-Cyanocinnamates have been similarly used as dienophiles. An *endo-exo* selectivity of 85:15 at a diastereoselectivity of 99:1 was obtained (eqs 4 and 5).[12,13]

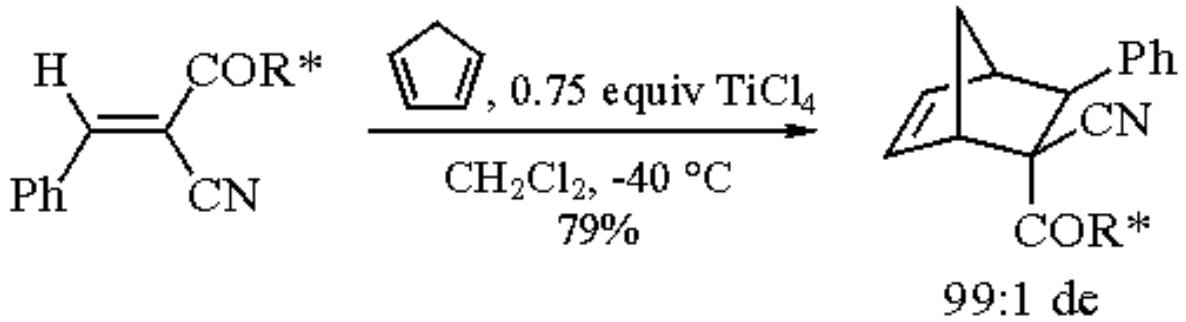

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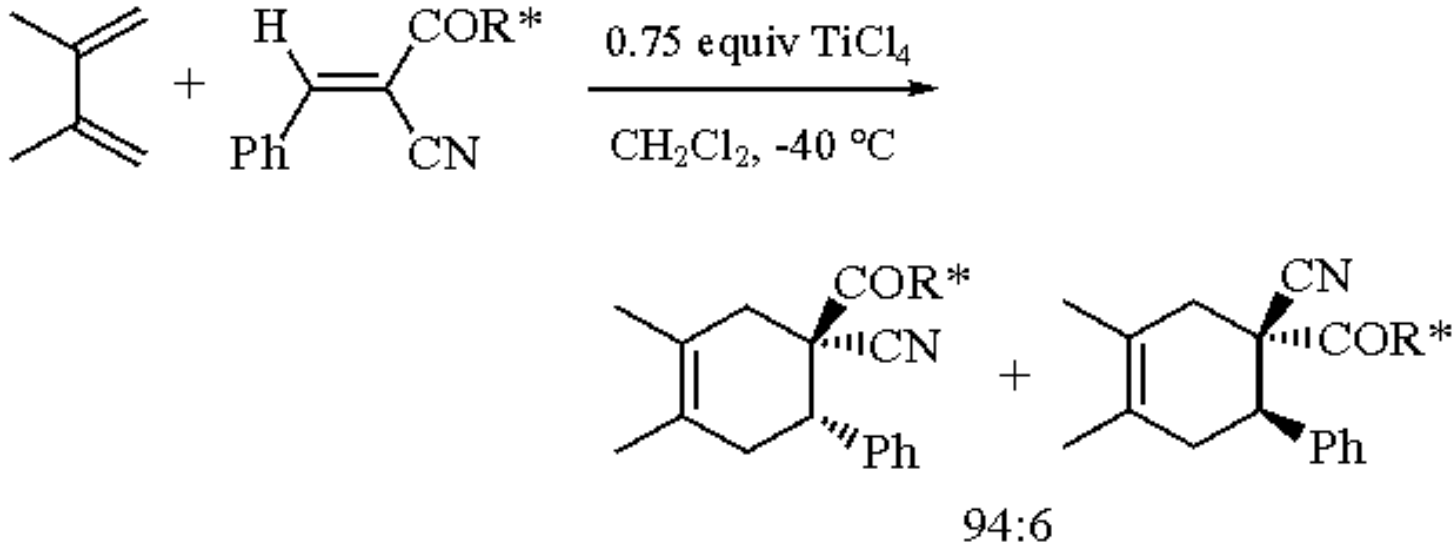

(5)

Further variations in dienophile have been equally successful (eqs 6 and 7),[14] including applications to the Michael

reaction (eq 7)[15] and in the synthesis of a prostaglandin intermediate (eq 8).[16]

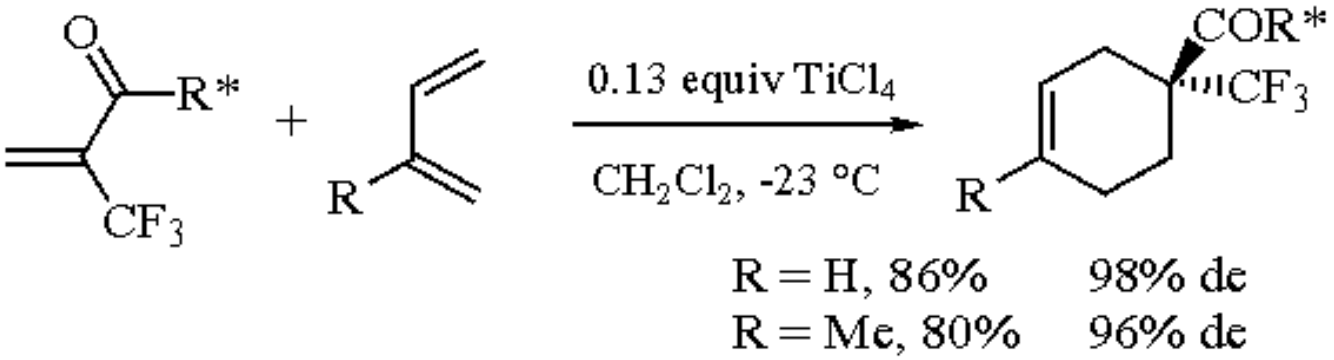

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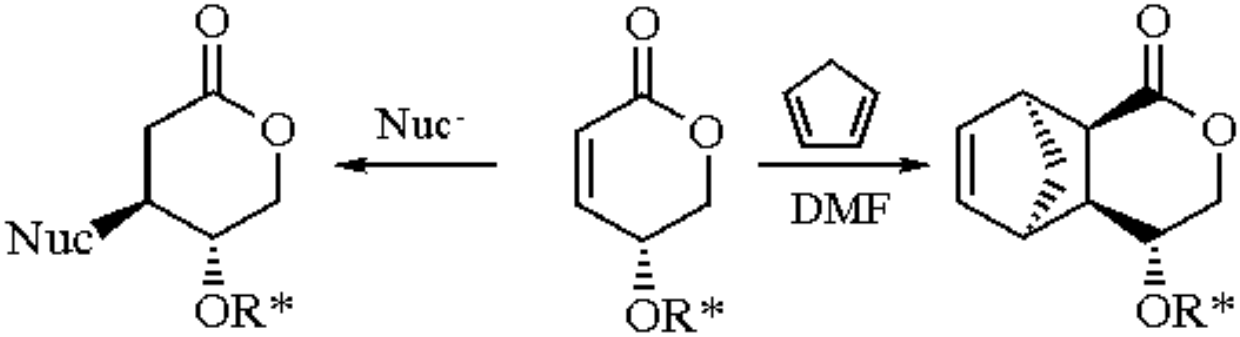

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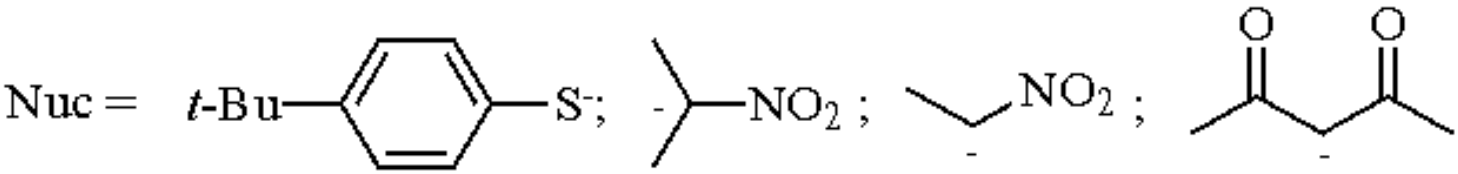

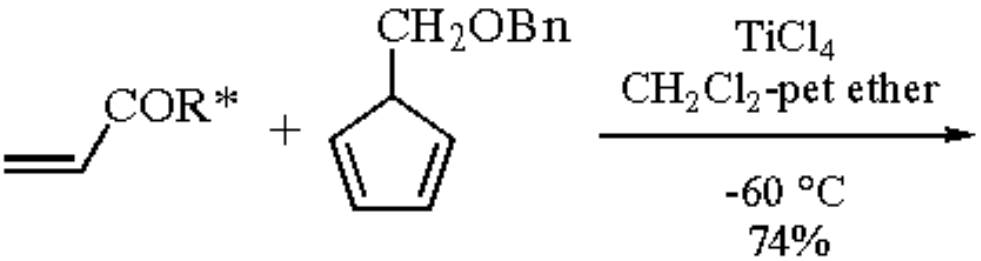

98:2 de

Corey lactone (8)

Ketene Additions.

Reaction of the ketene derived from ibuprofen (Ar = *p*-isobutylphenyl) with (*R*)-pantolactone in the presence of simple tertiary amine bases in apolar solvents yielded a >99% de favoring the (*R*,*R*)-ester (eq 9).[3] The reaction is first order in each component and possesses a pronounced deuterium isotope effect (k_H/k_D &AApprox; 4). The ketene from naproxen (Ar = 2-(6-methoxynaphthyl)) affords a de of 80% under similar conditions.

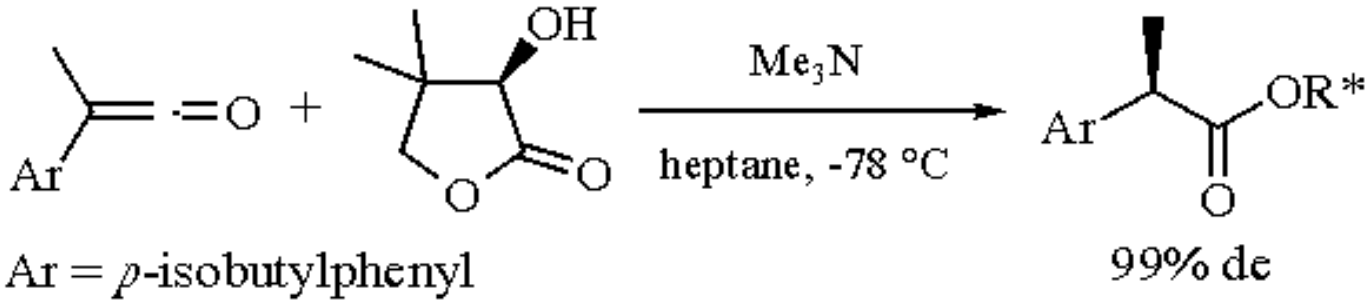

(9)

Extension of this work to a series of bromo- and iodoketenes proceeds with good to excellent de (eq 10).[17] Reaction of the products with azide ion affords a ready entry into amino acid synthesis (eq 11). However, with R = aryl, no selectivity was noted, possibly due to base-mediated epimerization under the reaction conditions.

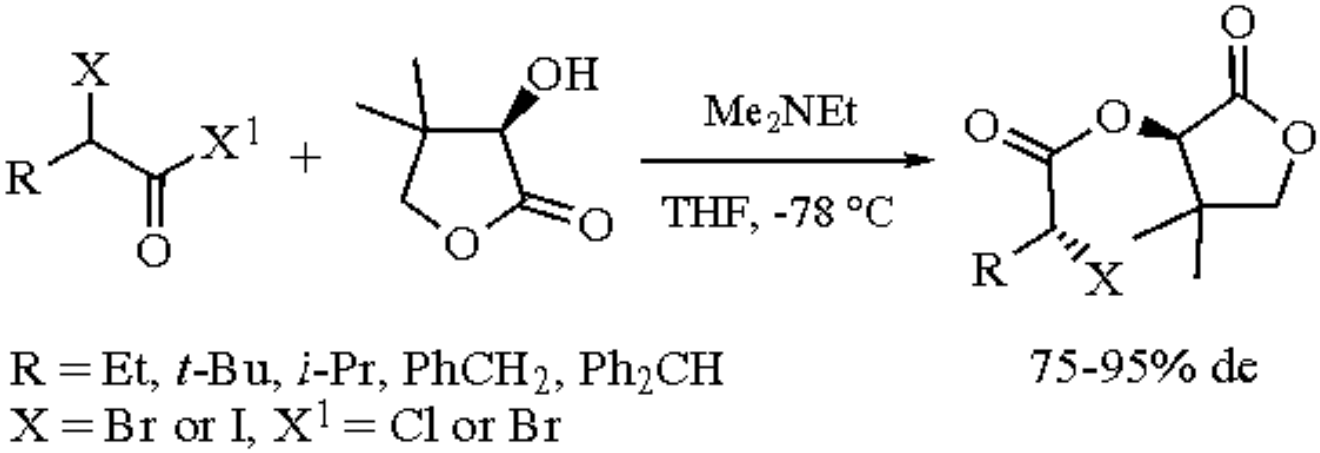

(10)

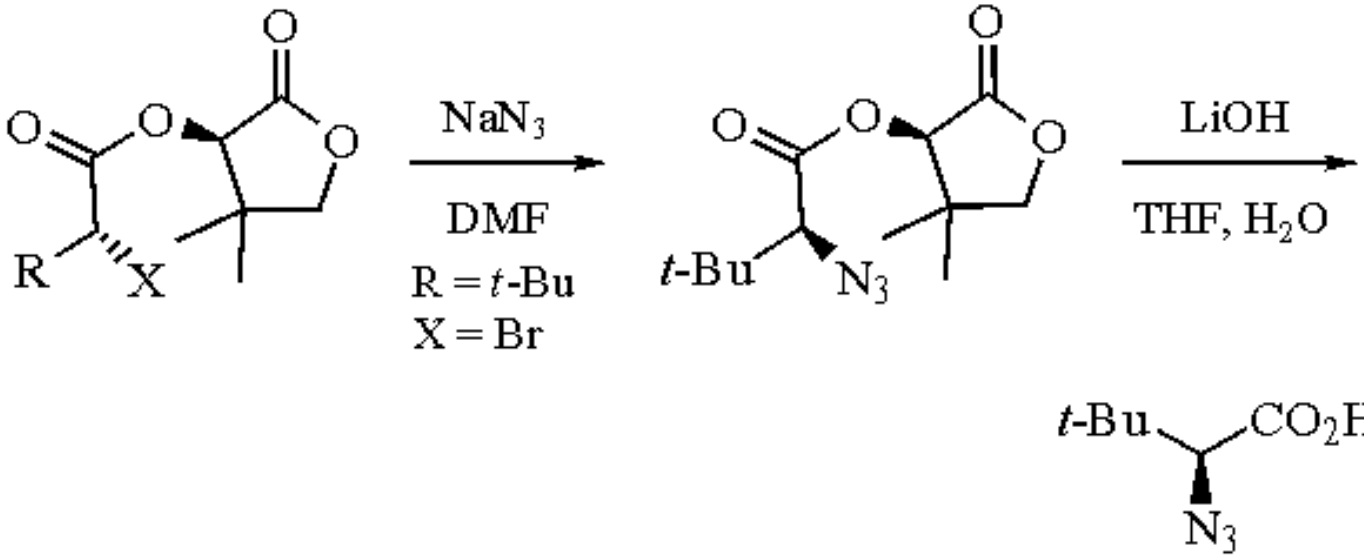

(11)

Chiral Pool Reagent.

(*R*)-Pantolactone has been used as a source of chiral fragments for synthesis. Applications include use in the syntheses of the elfamycins (eq 12)[18] and the bryostatins (eq 13).[19a,b] It has also been used to prepare potentially useful chiral epoxide synthons possessing a quaternary *gem*-dimethyl carbon.[20]

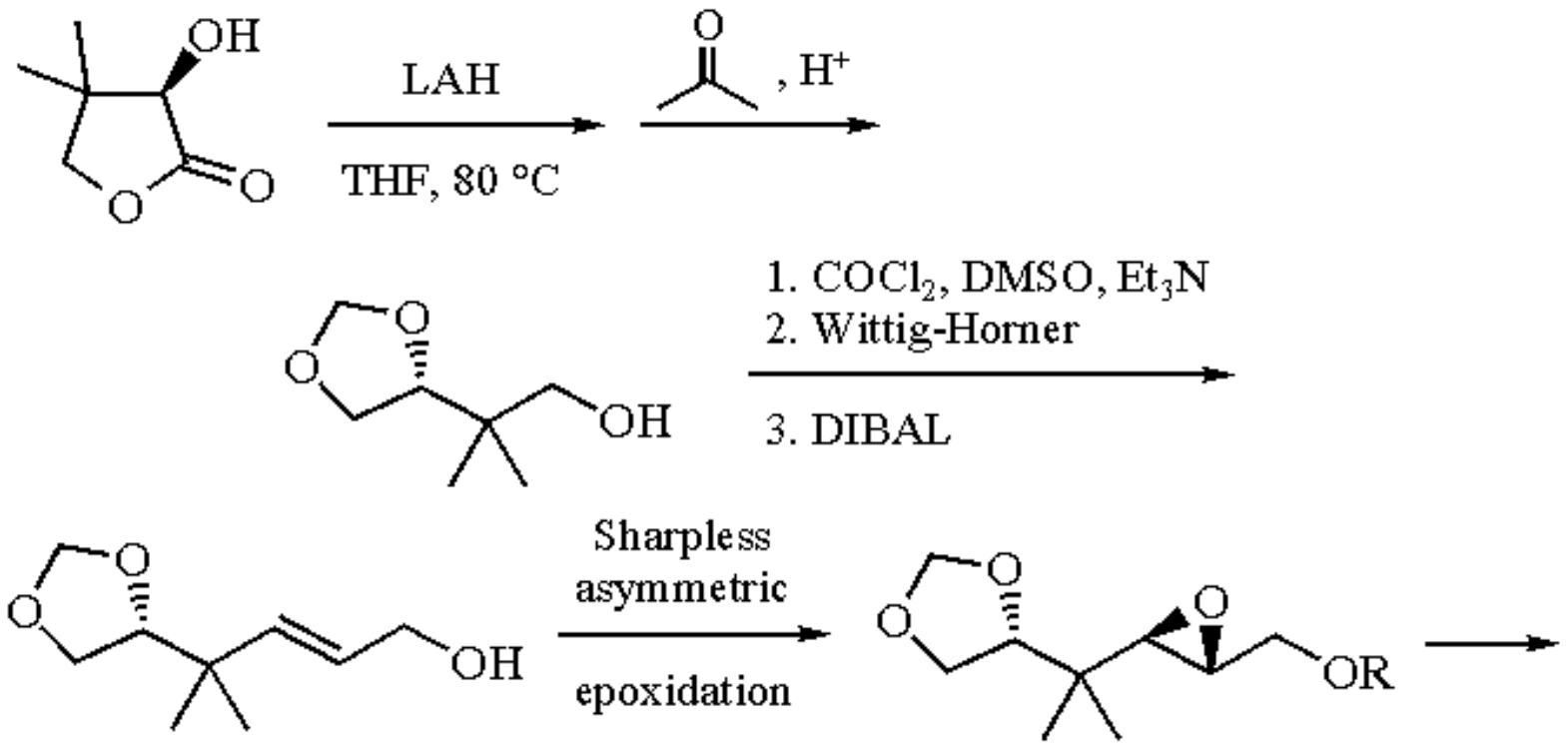

Elfamycins (12)

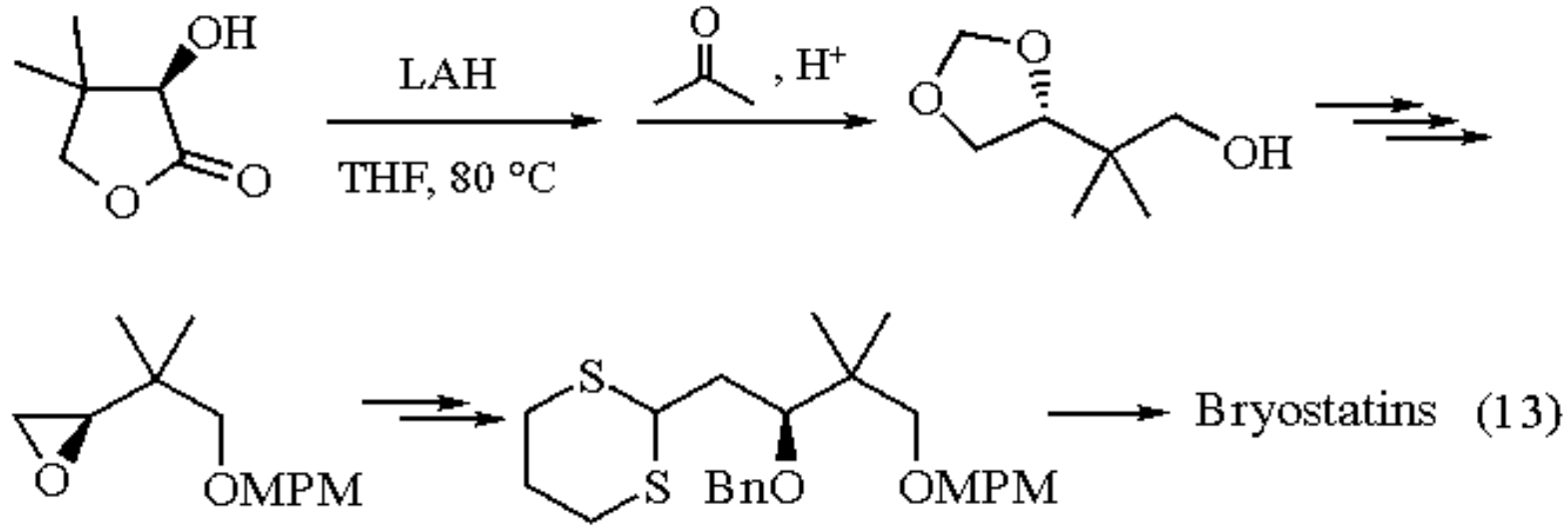

Bryostatins (13)

Miscellaneous Applications.

Only one attempt to use (*R*)-pantolactone as an enantioselective protonating agent for enolates has been reported.[21] A series of structurally diverse chiral alcohols afforded modest ee's with (*R*)-pantolactone affording the largest ee noted for the series. The complexities of attempting a protonation of this sort in the presence of base and under exchanging conditions are discussed. Finally, the lactone has been used to resolve chiral acids by crystallization and chromatographic techniques applied to the (*R*)-pantolactone-derived esters.[3,22,23]

Related Reagents.

(S)-Ethyl Lactate; ***Ethyl Mandelate***; ***3-Hydroxyisoborneol***.

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Paraformaldehyde

$(CH_2O)_n$

[30525-89-4] · CH_2O · Paraformaldehyde · (MW 30.03)

(convenient source of anhydrous monomeric formaldehyde for aldol condensation;[1] electrophilic source of halomethyl[2] and hydroxymethyl groups;[3] convenient source of Mannich reaction intermediates;[4] homologation of alkynes;[5] synthesis of macrocyclic ligands[6])

Physical Data: mp 160-165 °C.

Solubility: sol organic solvents.

Form Supplied in: solid; widely available.

Handling, Storage, and Precautions: generally stable; irritant.

Introduction.

The need to carry out one-carbon homologations during the course of organic syntheses is widespread. Since ***Formaldehyde*** itself is a hygroscopic gas which forms the hydrate easily, the ability to utilize functional equivalents of formaldehyde is quite useful. The proper choice for the synthetic equivalent of a tenuous species like formaldehyde is dictated by the context. Unlike the two other most common precursors, formalin and trioxane, paraformaldehyde is rather easy to handle. It is compatible with most organic systems and displays useful reaction patterns. The polymeric acetal system cleaves easily under acidic conditions and, to a lesser extent, under basic and neutral conditions, to afford one-carbon homologs. On those occasions when a solution of the monomeric formaldehyde is needed, the best approach is the thermal cracking of paraformaldehyde, with the evolved gaseous monomer bubbled into a solution and used immediately.

Reactions with Enolates and Enols.

As the functional equivalent of formaldehyde, paraformaldehyde can afford aldol products, especially under acidic conditions wherein the enol intermediate is generated and conditions lead to unsaturated carbonyl compounds. Methyl ketones undergo reaction (eq 1) with paraformaldehyde to afford the vinyl ketones under acidic conditions.[7] Similar results are obtained with other active hydrogen reactants such as the treatment of methyloxazolines with paraformaldehyde and acid.[8] Under neutral aqueous conditions, multiple aldol reactions with cyclohexanone have been reported (eq 2).[9]

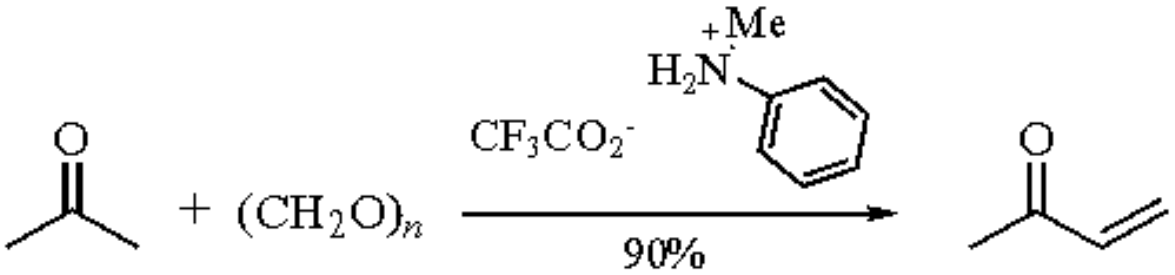

(1)

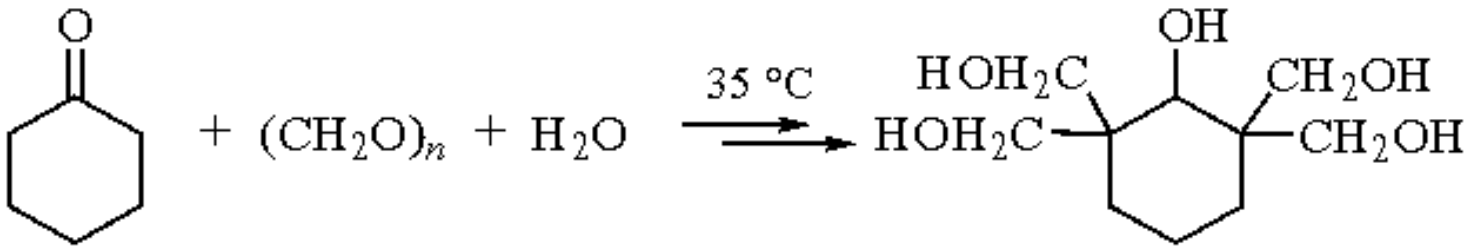

(2)

Noteworthy observations in this particular reaction are the ultimate reduction of the ketone, presumably via a crossed Cannizzaro reaction, and the ability to utilize large excesses of paraformaldehyde without major difficulties. Of course, both phenomena are related to the absence of α-hydrogens and resultant inability of formaldehyde to enolize.

While paraformaldehyde can be effective in enolate chemistry,[10] the more common practice, when condensation onto a preformed enolate is required, is to generate a solution of monomeric formaldehyde through pyrolysis.[1,11] One can isolate the resultant hydroxy ketone (eq 3),[12] or force dehydration through the use of ***Methanesulfonyl Chloride***,[12] or a variety of organometallic agents.[13] The monomer generated in this way also reacts readily with the dianions of carboxylic acids.[14]

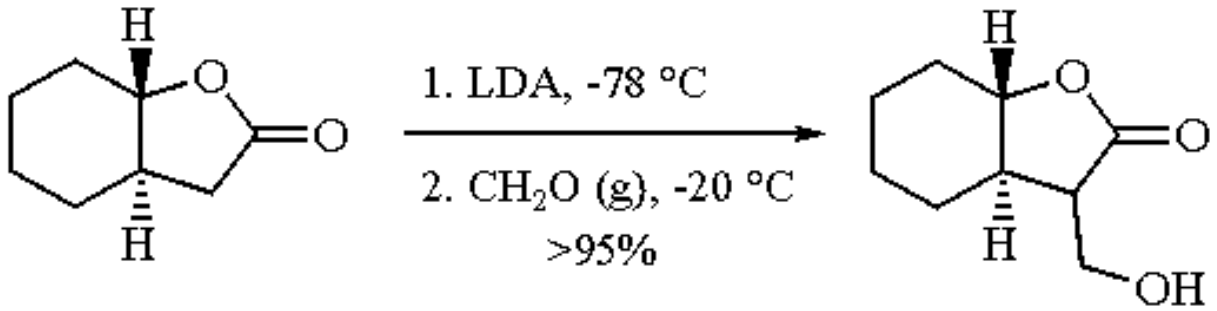

(3)

Halomethyl and Hydroxymethyl Electrophiles.

The chloromethylation of aromatic systems[2] and heteroaromatic compounds[15] can be accomplished using paraformaldehyde, ***Zinc Chloride***, and ***Aluminum Chloride***. Similar chemistry allows bromomethylation of aromatic systems.[16] Halomethyl esters can be obtained from carboxylic acids as well.[17] The hydroxymethylation of anthraquinones has been reviewed[3] and paraformaldehyde can be used for the protection of alcohols as the methoxymethyl group.[18-20]

The Mannich Reaction and other Iminium Ion Reactions.

While the trapping of an iminium ion (generated by the acid-catalyzed reaction of an amine and paraformaldehyde) by enols[4] has been well investigated (eq 4),[21,22] a variety of other nucleophiles are available, such as allylstannanes.[23] Of particular note are those reactions which bring about cyclization. In this context a vinylsilane (eq 5)[24] is effective, as is an alkene (eq 6).[25]

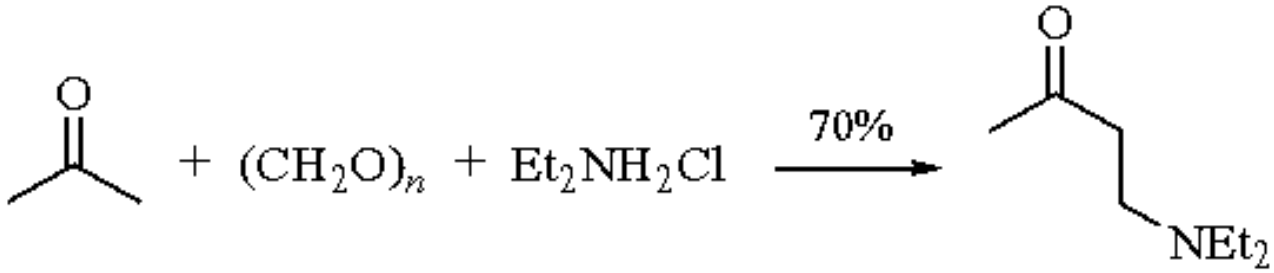

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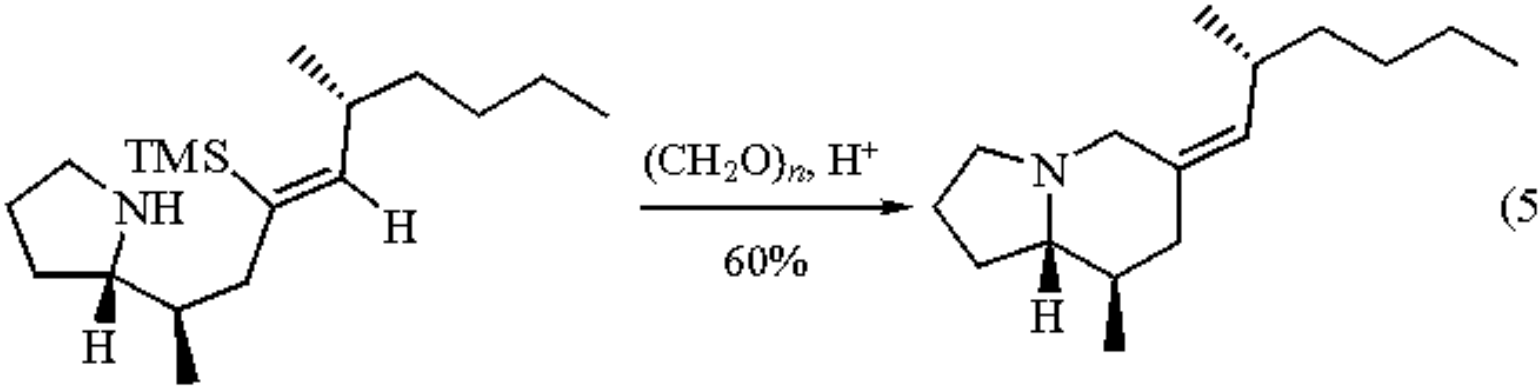

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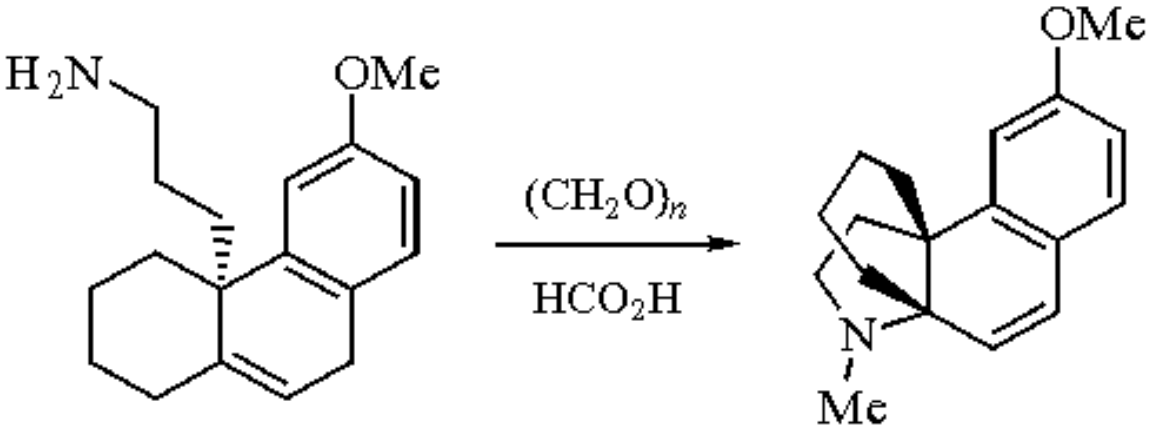

(6)

Homologation of Alkynes.[5]

While the terminal alkyne group is a relatively weak nucleophile, strong Lewis acids can bring about homologation, albeit with some isomerization (eq 7).

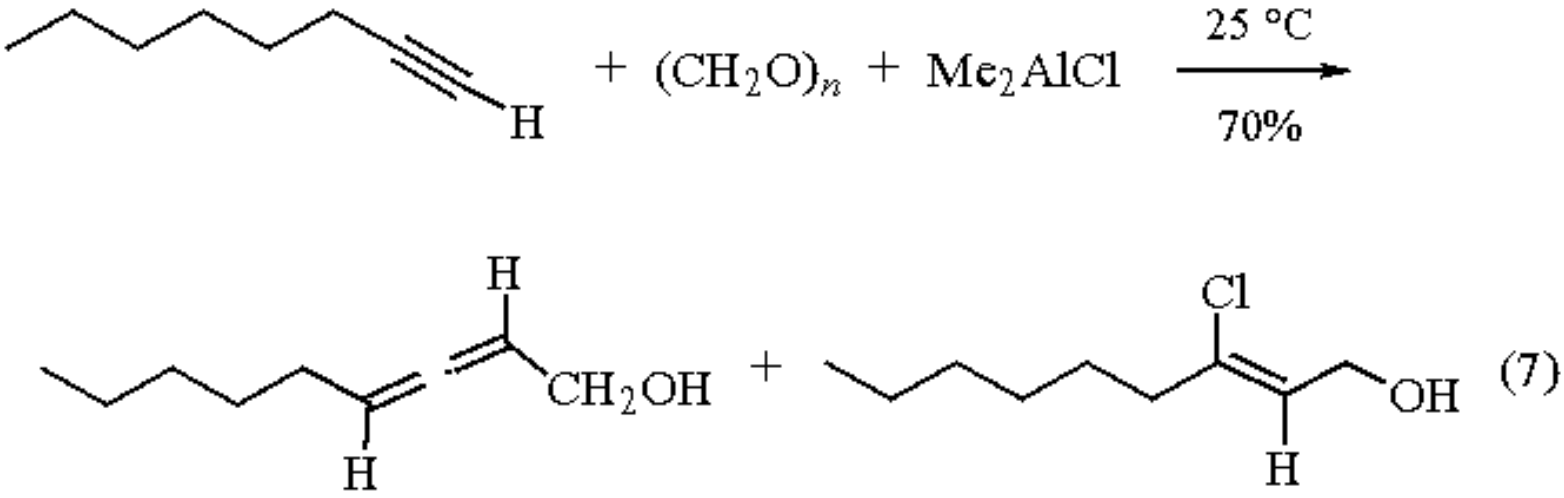

Macrocyclic Ligands.[6]

By making use of template control, aza macrocycles can be formed which act as organometallic ligands and sequestering agents (eq 8).

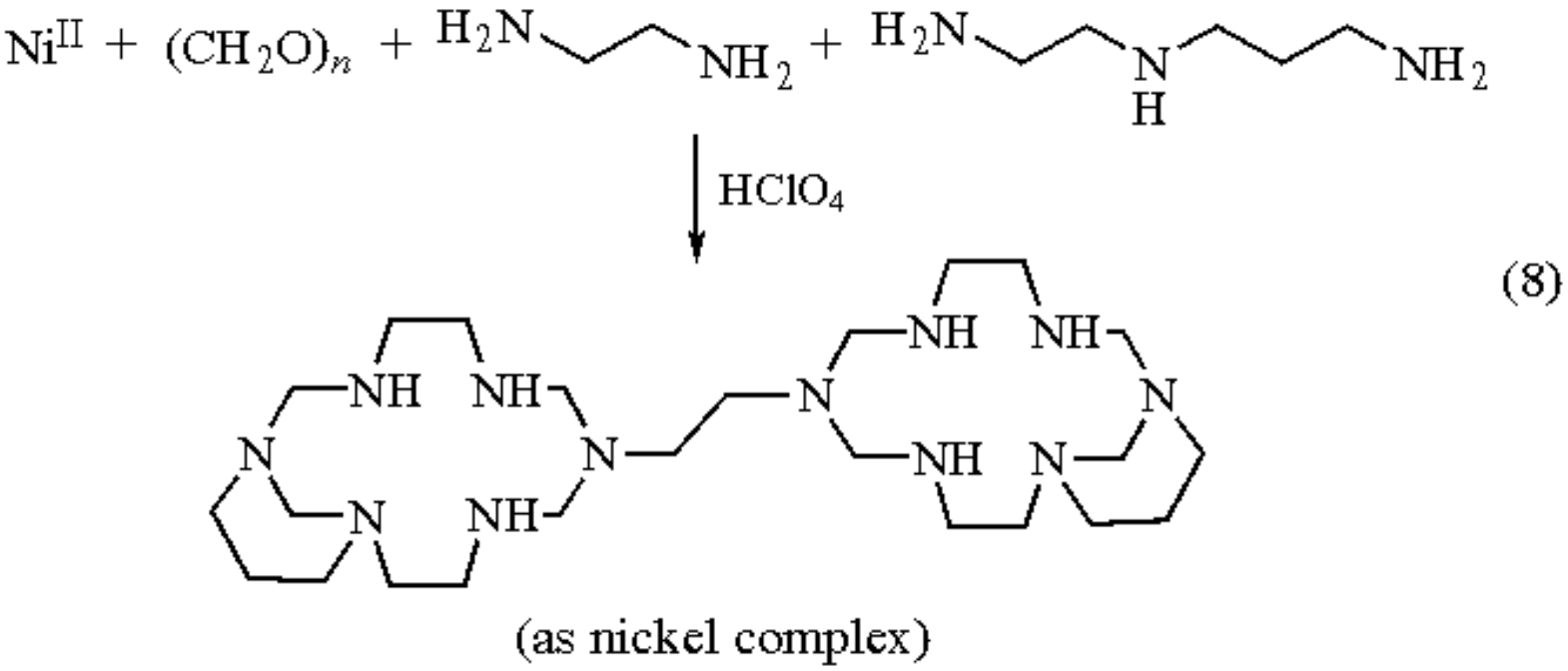

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Pentacarbonyliron[1]

$Fe(CO)_5$

[13463-40-6] · C_5FeO_5 · Pentacarbonyliron · (MW 195.90)

(diene complexation;[4] carbonyl insertion;[62-64] cycloaddition; reduction[96] and deoxygenation)

Physical Data: mp -20 °C; bp 103 °C; fp -15 °C; *d* 1.490 g cm^{-3}; *n* 1.5196; X-ray diffraction studies at -100 °C confirm the trigonal bipyramidal structure of $Fe(CO)_5$.[2]

Solubility: miscible with organic solvents.

Form Supplied in: straw-yellow liquid.

Handling, Storage, and Precautions: $Fe(CO)_5$ is a volatile, flammable, and highly toxic liquid,[3] which does not react with air at room temperature. It has a relatively high vapor pressure (21 mmHg at 20 °C). When $Fe(CO)_5$ is exposed to light, $Fe_2(CO)_9$ impurity slowly accumulates. The monomeric pentacarbonyl complex can be purified by trap-to-trap distillation in a vacuum system, but for routine use this purification step is usually omitted. Use in a fume hood.

Diene Complexation.

Tricarbonyl(η^4-butadiene)iron(0), the first iron-diene complex, was prepared as long ago as 1930 by Reihlen and co-workers, by heating butadiene with $Fe(CO)_5$.[4] Subsequently, substituted derivatives were studied by Pettit's group and by others.[5] The first complex of a cyclic diene, tricarbonyl(η^4-cyclohexadiene)iron(0), became available in 1958.[6] The real breakthrough for the development of synthetic methods sprang from pioneering work with substituted complexes in the cyclic (particularly cyclohexadiene) series in the 1960s and 1970s, by Birch,[7-10] Lewis,[11,12] and co-workers, then of the group of Pearson,[13] work which was initiated by the discovery by Fischer and Fischer in 1960[14] of hydride abstraction from tricarbonyl(η^4-cyclohexadiene)iron(0) to yield an η^5 iron-complexed cyclohexadienyl cation.

A wide range of methods are now available for the preparation of η^4-diene tricarbonyliron complexes, but by far the most common technique remains the direct complexation of free dienes. $Fe(CO)_5$ is less reactive than $Fe_2(CO)_9$ or $Fe_3(CO)_{12}$, but under the right conditions it provides an inexpensive and efficient route to iron-alkene complexes, particularly from the 1,4-cyclohexadienes.

1,4-Diene Complexation.

Thermal Complexation.

Because 1,4-cyclohexadienes are readily available from the metal-ammonia reduction (Birch reduction) of the corresponding aromatic compounds,[15] they have been extensively studied as substrates for direct 1,4-diene complexation, leading to isomerized 1,3-diene complexes. This methodology suffers, however, from the disadvantage that products are often obtained as mixtures of regioisomers. $Fe(CO)_5$ provides a simple, low-cost source of $Fe(CO)_4$ for initial addition to the π-system of a double bond. By recycling the reagents and the uncomplexed ligand, preparations on a 50-60 g scale can be achieved from a series of overnight thermal reactions. The procedure most frequently used, that of Cais and Maoz,[16] modified by Birch,[8] involves heating a cyclohexadiene with pentacarbonyliron in boiling di-*n*-butyl ether. In the extensive literature on the formation of differently functionalized tricarbonyl(1,3-cyclohexadiene)iron complexes from substituted 1,4-cyclohexadienes[8,9,11,12,17,20] (including the tricarbonyliron complexes of a number of dihydroanisic esters,[18] various cyclohexadiene esters,[9,19] and 1-methoxy-2,4-dimethyl-1,4-cyclohexadiene[21]), at present the most useful and representative intermediates for synthetic applications carry methoxy substituents on the diene ligand. For example, 2,5-dihydroanisole (**1**) or 4-methyl-2,5-dihydroanisole (**2**) upon treatment with pentacarbonyliron at elevated temperature afford a mixture of the 1- and 2-OMe substituted complexes (**3**) and (**5**) or (**4**) and (**6**) (eq 1).[7-9,11,12,22]

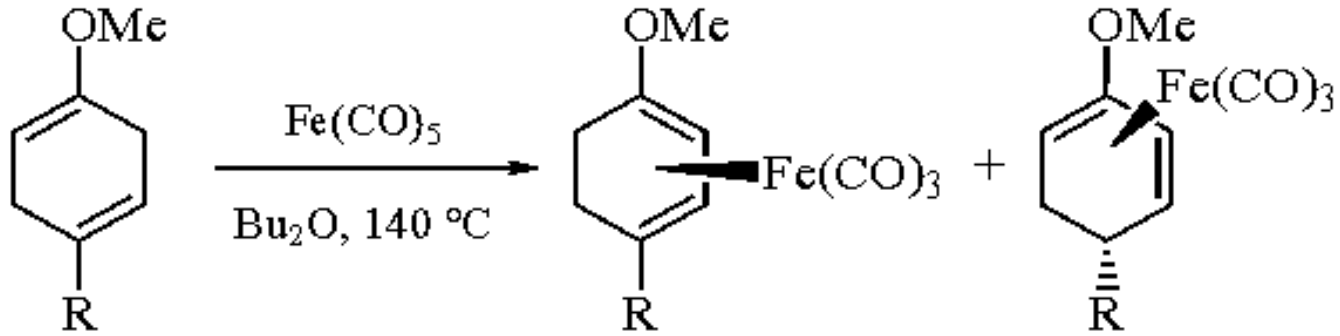

(1) R = H
(2) R = Me

(3) R = H
(4) R = Me

(5) R = H
(6) R = Me

Although 1-methoxy-1,4-cyclohexadiene itself leads to a mixture of the 1- and 2-OMe complexes, bicyclic compounds of substitution type (**7**) do not give the 2-OMe regioisomer, affording instead a mixture of complexes (**8**) and (**9**) in a 1:1 ratio (eq 2).[22,23] In a more unusual case, an amide substituent was present on the 1,4-diene.[24]

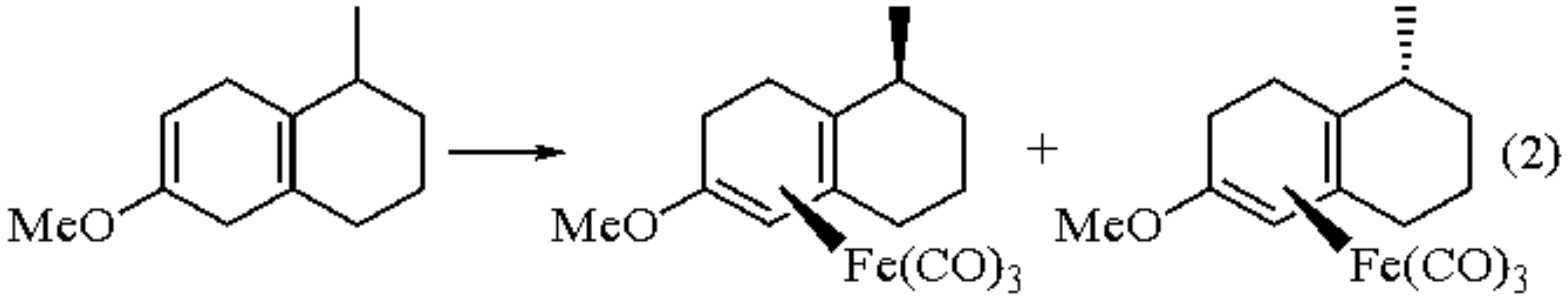

(7) **(8)** 1:1 **(9)**

More extensive rearrangement of the position of unsaturation in α,o-dienes also leads to η^4-diene complexes.[25] In other cases where rearrangement is blocked, homoconjugated dienes can form stable bis(alkene) complexes by thermal

reaction with $Fe(CO)_5$.[26] Isotetralene offers an unusual case where rearrangement to the 1,3-diene is possible, but a 1,4-diene complex is reported.[27]

Photolysis.

Photolysis offers an alternative for the direct conversion of 1,4-dienes into 1,3-diene complexes. In eq 3 the deuterium labeling reveals that isomerization during complexation of the 1,4-diene precursor proceeds by a 1,3-hydrogen transfer.[28]

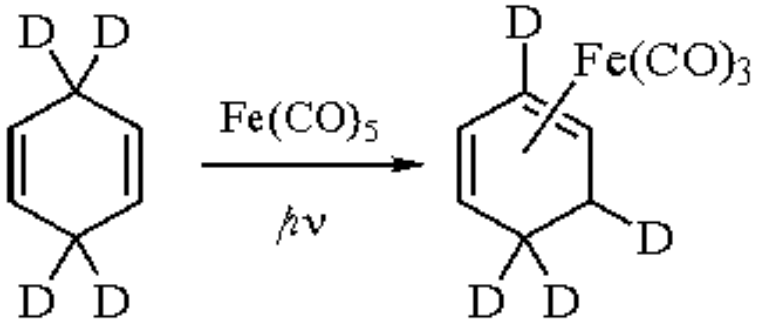

(3)

The direct complexation of 1,4-dienes can form specific stereoisomers. Initial π-complexation occurs before the conjugation step, and the hydrogen atom moves only on the face of the ligand carrying the metal.[29] Unfortunately, a mixture of regioisomers usually results, which may present separation problems. Loss of OMe can also sometimes occur, particularly from some 1,3-dimethoxy-1,4-cyclohexadienes. In these cases, preconjugation of the diene is essential[30] if a dimethoxydiene complex is required. Mixtures of complexes obtained from 1,4-dienes may also be equilibrated[31] to thermodynamic ratios of isomeric complexes, which do not correspond to the equilibrium ratios of the free dienes.[32,33]

1,3-Diene Complexation.

Thermal Complexation.

Low yields and mixed products render some nonconjugated dienes unattractive as precursors for η^4-complexes. For many synthetic applications, cleaner routes are required to form a single defined compound in good yield. A good approach employs a conjugation step prior to complexation.[30] The 1-NR_2 series can usually be conjugated thermally.[33] Equilibration of 1-methoxy-1,4-cyclohexadiene with the 1,3-diene (ca. 75%) using potassium in liquid ammonia as catalyst yields only the 1-OMe substitution pattern on the conjugated isomer.[34] Other conjugation catalysts include bases,[35] Wilkinson's catalyst,[36] Cr derivatives,[29] and charge-transfer complexation reagents such as dichloromaleic anhydride.[37] Frequently, only about 70-80% of the conjugated isomer is present at equilibrium,[38] but the complexation product, if formed under mild conditions, corresponds to the conjugated isomer present. This process of preconjugation followed by complexation, using the usual $Fe(CO)_5$ thermal methodology, has led, for example, to an important key intermediate in the synthesis[39] of limaspermine. The use of azadiene catalysts improves the thermal complexation reaction.[40]

Complexation of dienes with several methyl,[41] alkyl,[42] or methoxy[43] groups is straightforward, but with bulky substituents, rearrangements can lead to the formation of mixtures of products,[44] and care is also needed in the presence

of side-chain leaving groups.[45] Trialkylsilyl-substituted dienes complex well. In the reactions of 2-(trimethylsilyl)-1,3-cyclohexadiene derivatives with excess pentacarbonyliron in refluxing di-*n*-butyl ether,[46] (**10**) gave rise to an 8:2 mixture of (**11**) and its epimer (**12**), with coordination to $Fe(CO)_3$ occurring preferentially on the less hindered face of the 1,3-cyclohexadienyl ring (eq 4).

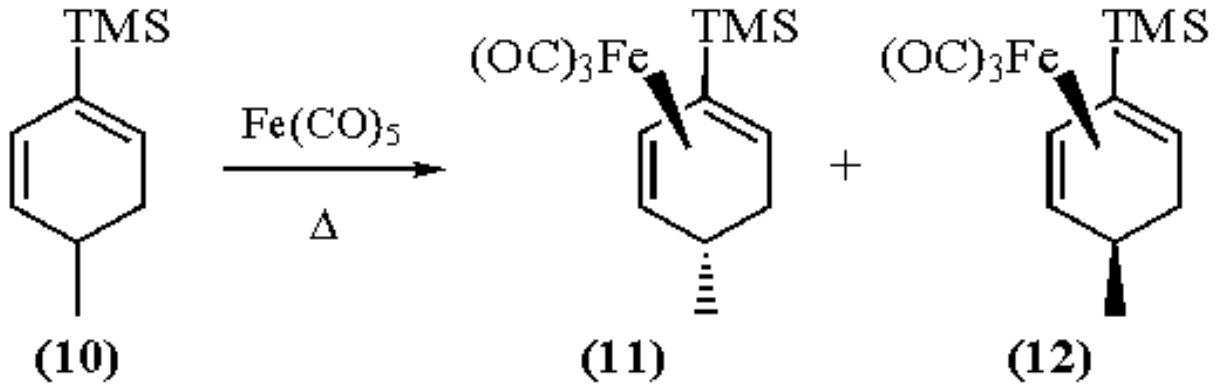

(4)

Photochemical Complexation.

The studies of Birch et al. on the thebaine modification using tricarbonyliron complexes[47,48] exemplify the possibility of complexation of 1,3-dienes by photolysis, and illustrate the potential for iron complexes to ensure control of skeletal rearrangement. Thus, via the initial step of complexation of the methoxycyclohexadiene ring of thebaine (**13**), practically quantitative access to northebaine (**14**) and 14α-substituted thebainone derivatives could be easily obtained with $Fe(CO)_5$ under UV irradiation (eq 5).[47]

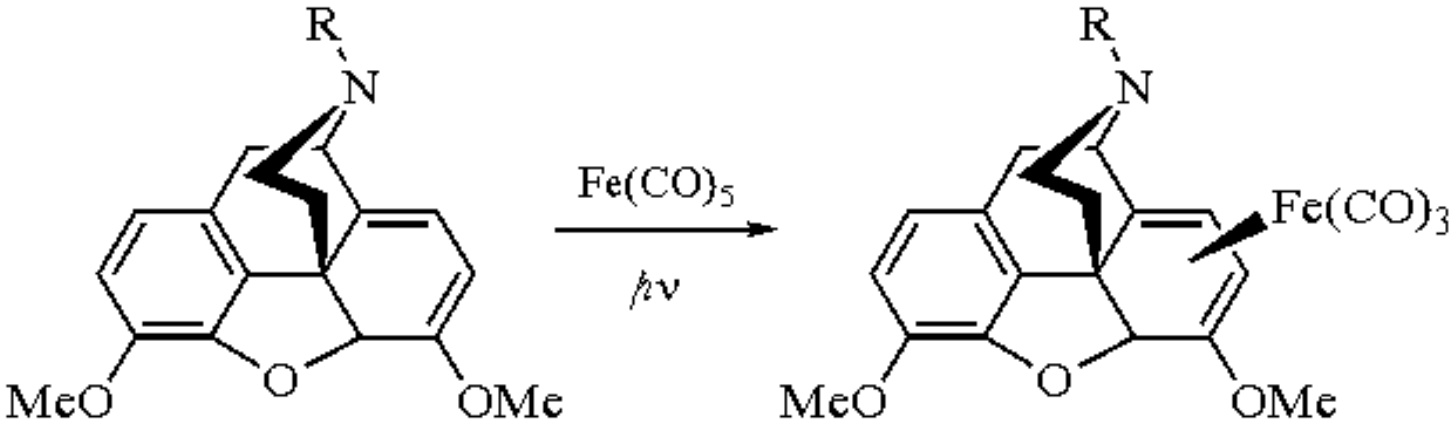

(5)

(13) R = Me
(14) R = H

Thermal and Photochemical Reactions in Other Ring Sizes.

Similar complexation reactions can be performed in seven- and eight-membered rings,[49] but with cyclopentadiene the reaction takes a different course, producing a dimeric cyclopentadienyl complex.[50] Complexation of silyl-substituted cyclopentadienes afforded dinuclear products.[51] In more unsaturated systems, competing reduction processes are possible. Cycloheptatriene reacts with pentacarbonyliron to give a mixture of tricarbonyliron complexes of cycloheptatriene and 1,3-cycloheptadiene.[52] Substituted cycloheptatrienes[53] and cycloheptadienes[54] can also be

complexed. Thermal complexation of divinylpyrrolidines forms exocyclic diene complexes by rearrangement of the location of unsaturation.[55]

Complexation Using $Fe(CO)_5$ and Me_3NO.

Reaction of a conjugated diene with $Fe(CO)_5$ in the presence of ***Trimethylamine N-Oxide*** resulted in the formation of tricarbonyl(1,3-diene)iron complexes. The use of amine oxides, preferably Me_3NO, permits fast reactions even at low temperatures. Reduction of amine oxides by $Fe(CO)_5$ has been described by Alper et al.[56] and, in the case of trimethylamine *N*-oxide, the intermediate compound trimethylaminotetracarbonyliron was isolated (eq 6).[57,58]

$$Fe(CO)_5 + Me_3NO \longrightarrow Me_3N \cdot Fe(CO)_4 + CO_2 \qquad (6)$$

The reverse reaction, namely the known disengagement of the ligand from the (diene)$Fe(CO)_3$ complex, presents no problem because of the lower reaction temperature and the smaller molar ratio of Me_3NO:$Fe(CO)_5$ employed in the complexation procedure.[57] Trimethylaminotetracarbonyliron is attractive as a mild reagent but further generalization is needed.

Acyclic Series.

The first complex in the acyclic series was prepared from butadiene by the thermal method.[4] Heating isoprene and pentacarbonyliron at high temperature, however, is inefficient due to competitive Diels-Alder dimerization. Despite the formation of some bis(diene) iron carbonyl complexes on prolonged irradiation, the photochemical method is superior in this case. Complexation of acyclic dienes by $Fe(CO)_3$ is limited to those that can adopt a cisoid conformation, with the *syn* substitution pattern normally preferred. 2,4-Hexadienoic acid, for example, can be conveniently complexed by a photolytic procedure.[59] Trialkylsilyl-substituted dienes have also been complexed.[60]

Isomerization of Alkenes.

In some cases the positional rearrangement of alkenes affords useful products which are not 1,3-diene complexes. The isomerization of allyl ethers in the presence of $Fe(CO)_5$ under UV irradiation has also been reported.[61]

Ring-Opening Reactions with Carbonyl Insertion.

Cyclopropane rings.

Synthesis of (diene)$Fe(CO)_3$ complexes, and of cyclohexenones, lactones, ketones, or sulfones, can follow from the opening of vinylcyclopropanes with $Fe(CO)_5$ under either thermal or photochemical conditions. Reactions of the vinylcyclopropane (**15**) with $Fe(CO)_5$ under thermal conditions resulted in ring opening with concomitant hydrogen shift to form the diene complex (**16**) (eq 7).[62,63,64]

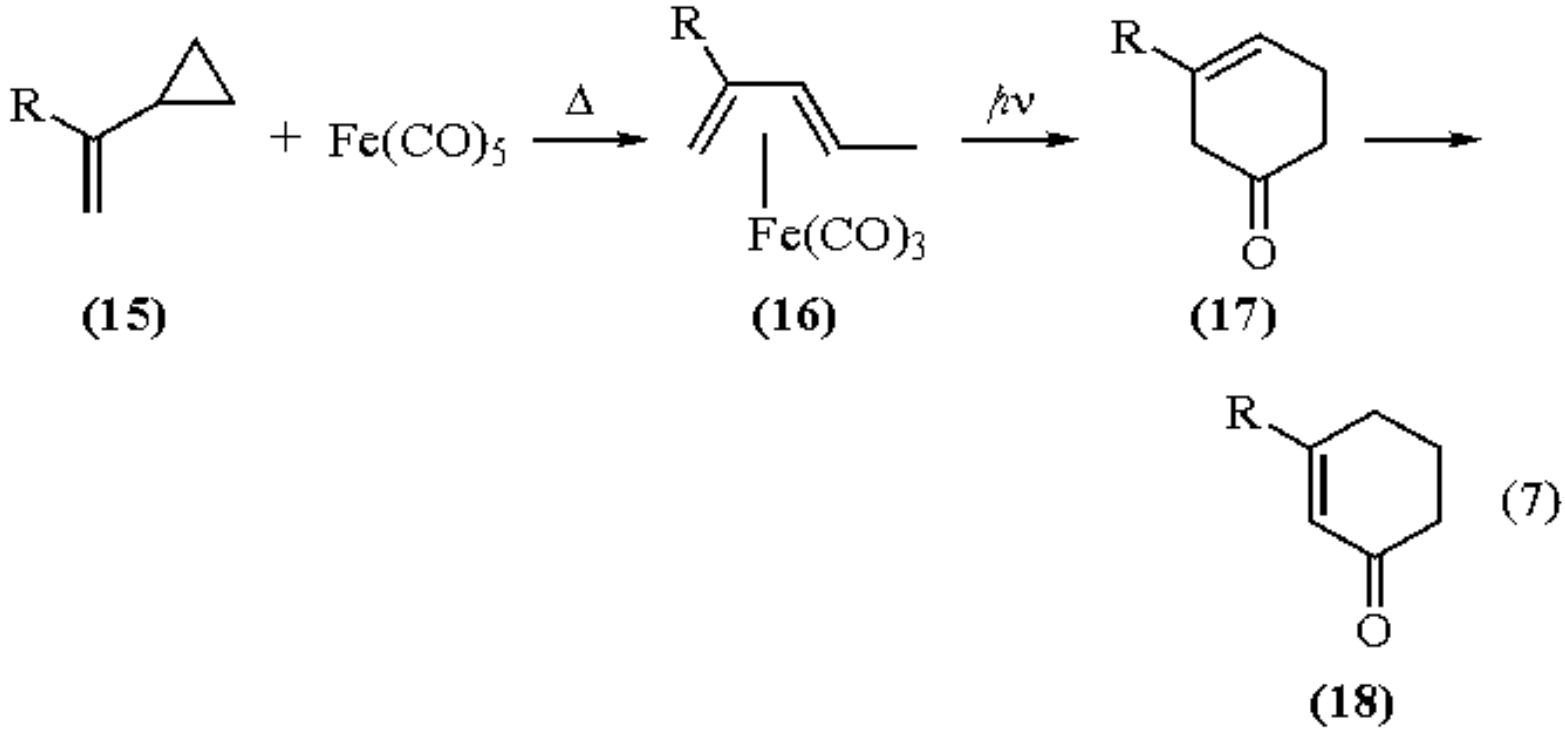

The reaction of (**16**) under photochemical conditions led to (**17**) by ring opening and carbonyl insertion. Conjugation may occur, forming the cyclohexenone (**18**) (eq 7).[65] The expansion of the carbon skeleton of terpene hydrocarbons via carbonylation offers an interesting means to prepare optically active strained ketones (eq 8).[66]

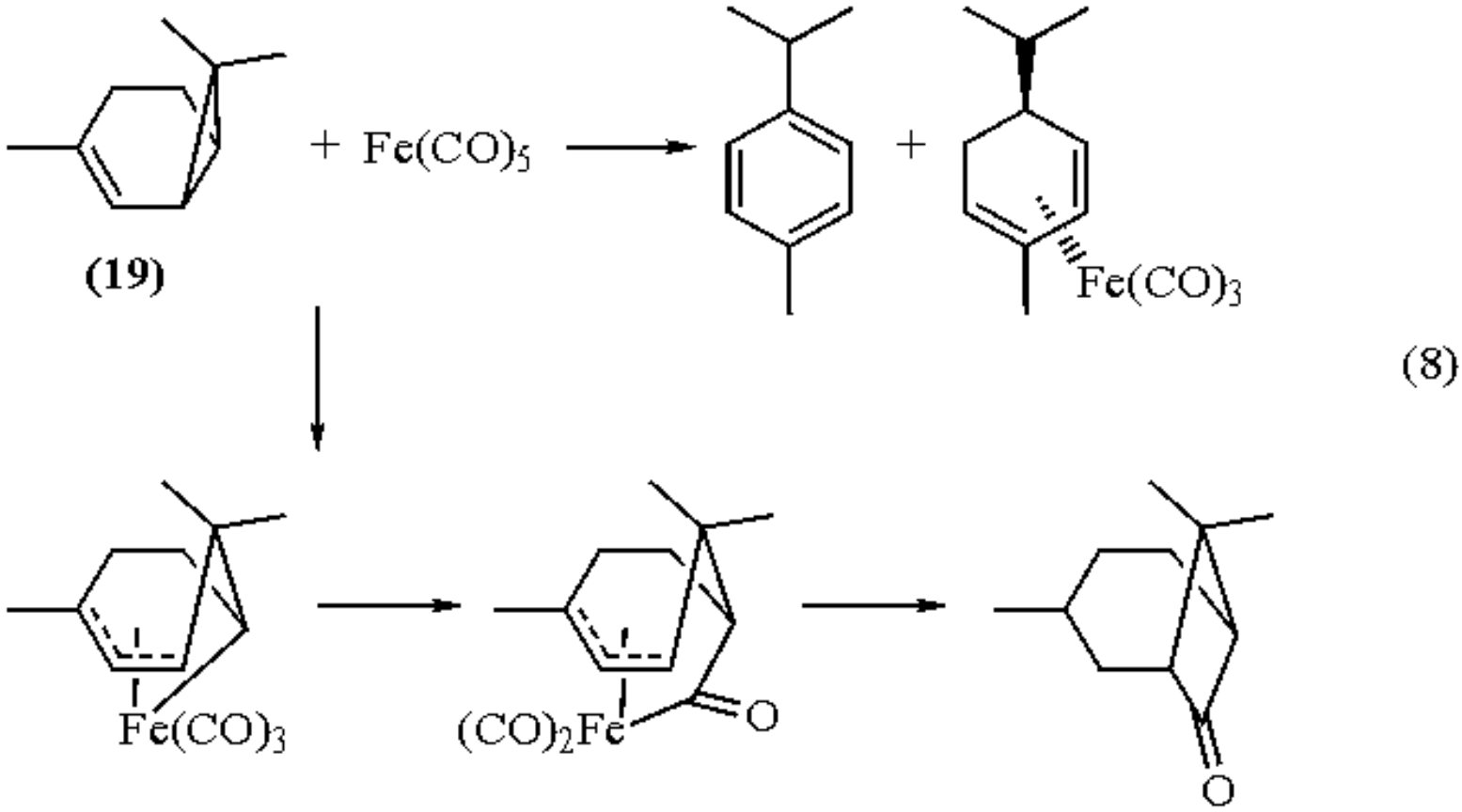

Regiocontrol, however, is a limitation. In the reaction between (+)-2-carene (**19**) and $Fe(CO)_5$, five compounds are

isolated. A recent study[67] improved the reaction with (+)-2-carene and extended the method to (+)-3-carene.

Epoxide Rings.

The synthesis of alcohols, β-lactones, and bicyclic derivatives occurs via a ferralactone complex. Irradiation of α,β-unsaturated epoxides in the presence of $Fe(CO)_5$ yields ferralactone complexes by ring opening and CO insertion (eq 9). For example, the vinyloxirane (**20**) gives the lactone (**21**).[68]

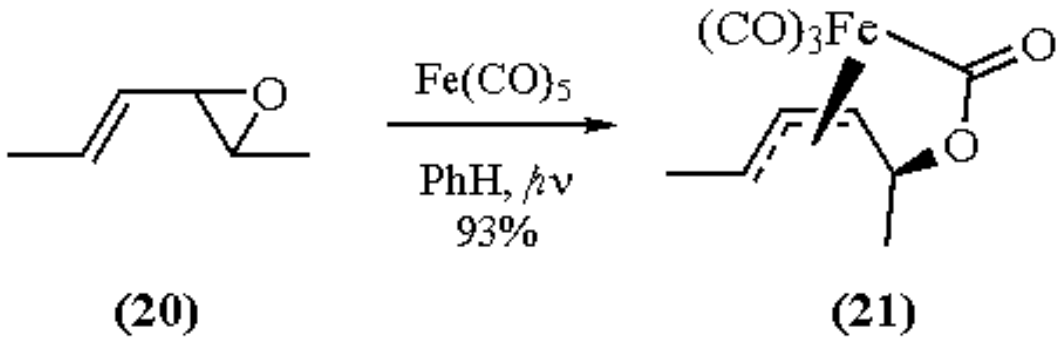

(9)

While the photochemical reaction[69] proceeds stereospecifically, the thermal process between $Fe(CO)_5$ and vinyl epoxides gives mixtures of diastereoisomers. Subsequent treatment of ferralactones with ***Cerium(IV) Ammonium Nitrate*** results predominantly in the formation of β-lactones, with a few exceptions where δ-lactones are obtained.[70]

A thermal treatment of the ferralactone displaces one molecule of CO. The α,β-unsaturated epoxide (**22**) forms the lactone (**23**) after irradiation in the presence of $Fe(CO)_5$, but subsequent heating leads to the formation of the (hydroxycyclohexadiene)$Fe(CO)_3$ complex (**24**) (eq 10).[67]

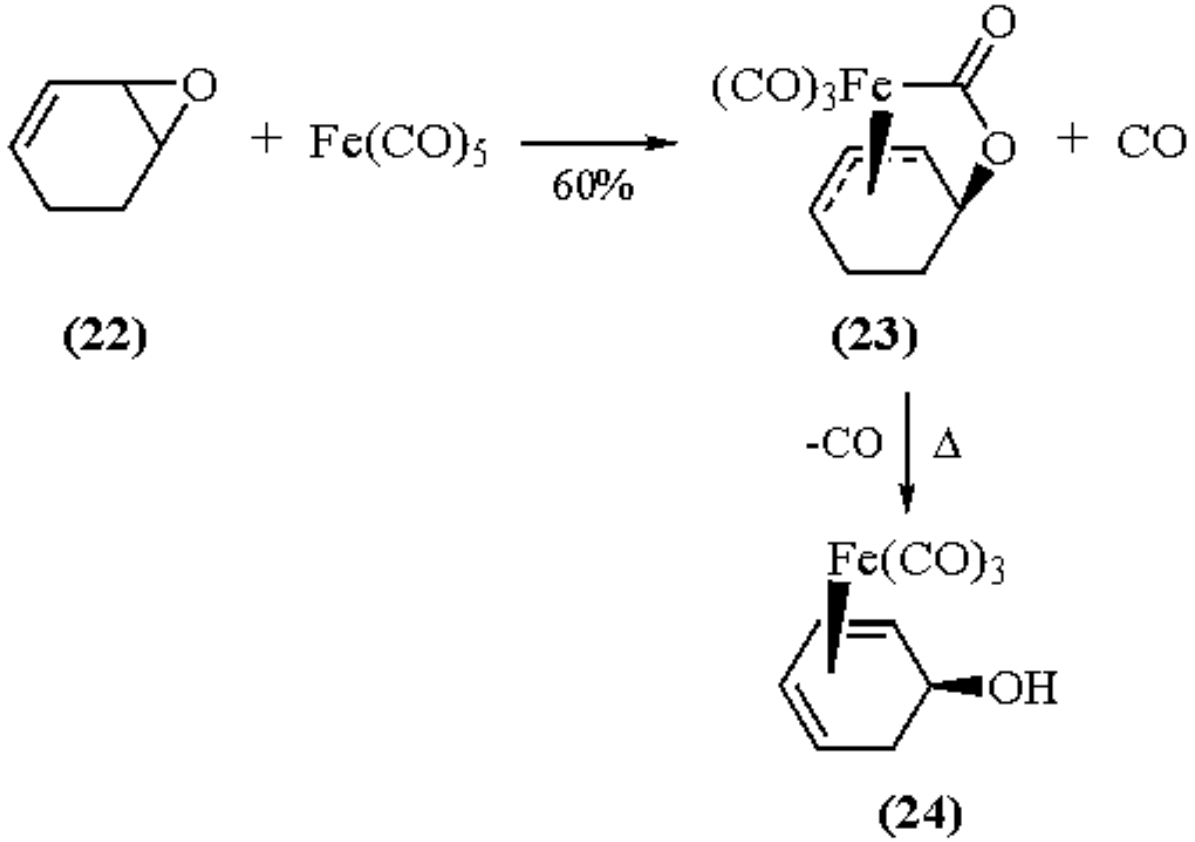

(10)

UV irradiation of 9-oxabicyclo[6.1.0]nona-2,4,6-triene (**25**) (the monoepoxide of cyclooctatetraene) in the presence of $Fe(CO)_5$ promotes an overall 1,2 to 1,4 skeletal rearrangement via the lactone (**26**) and the $Fe(CO)_3$ complex (**27**) to form the $Fe(CO)_3$-$Fe(CO)_4$ complex (**28**). Subsequent decomposition of the bis(iron) complex (**28**) gave the previously unknown 9-oxabicyclo[4.2.1]nona-2,4,7-triene (**29**) (eq 11).[71]

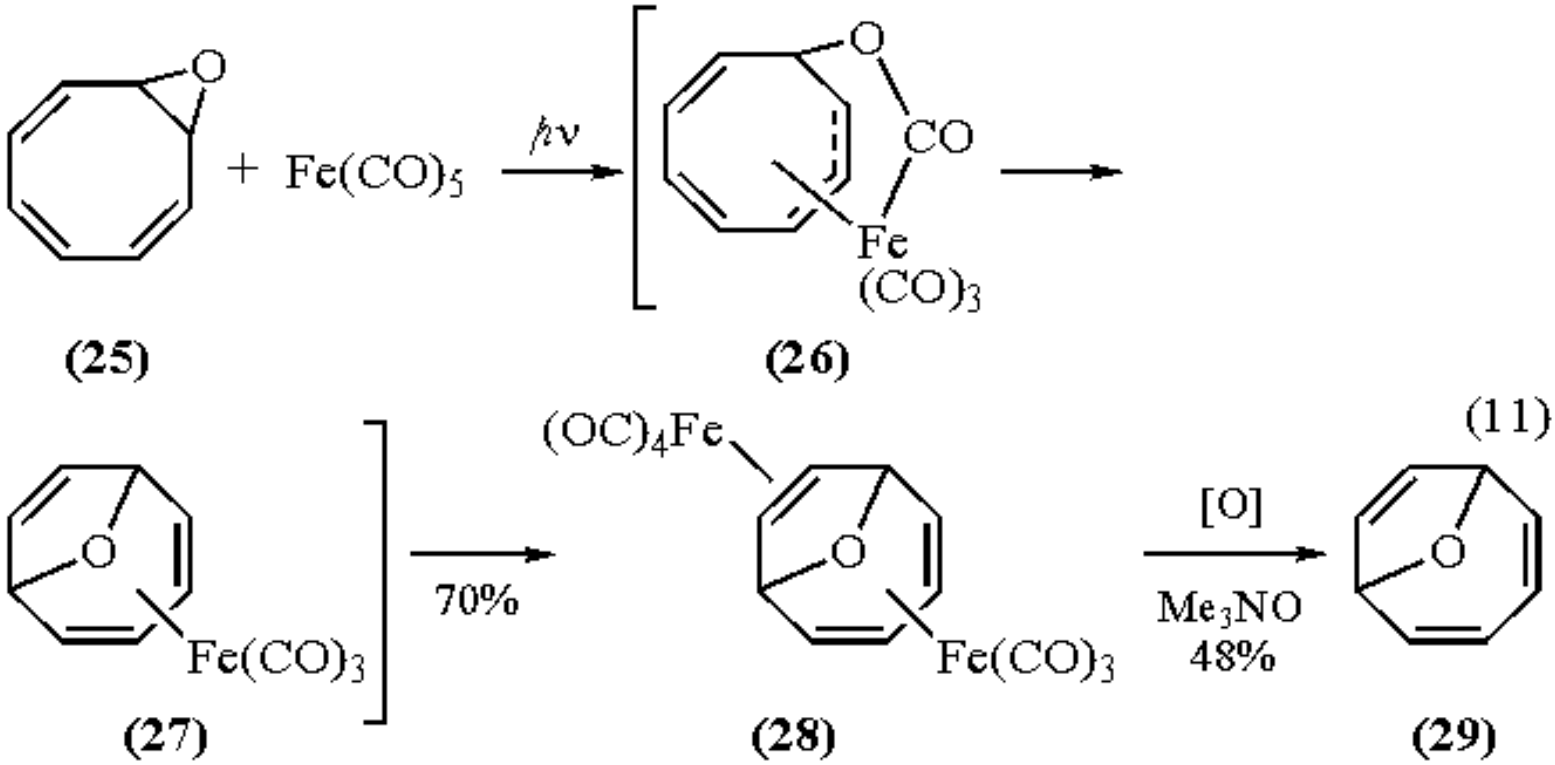

(11)

Carbonylative Ring Expansion.

When either α- or β-pinene (**30**) or (**31**) is heated neat with an equimolar amount of $Fe(CO)_5$ under an initial pressure of 30 psi CO at 160 °C, two ketones (**32**) and (**33**) are obtained, formed by insertion of CO into the cyclobutane ring (eq 12).[72] Both ketones are optically active.

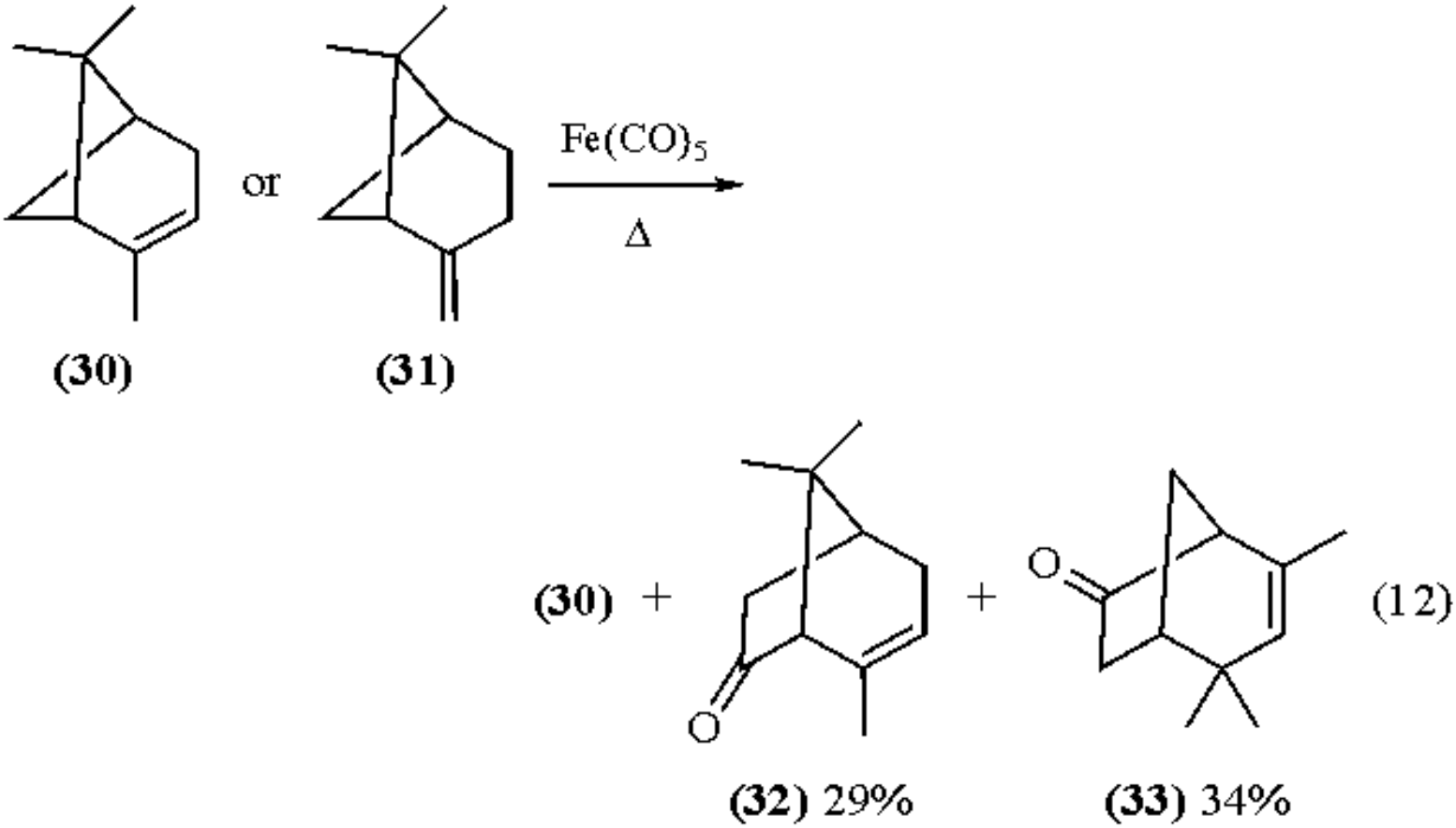

Dehalogenation Reactions.

Coupling of *gem*-Dihalides.

Pentacarbonyliron effects dehalogenative coupling of dichloro- or dibromodiphenylmethane and benzylic *gem*-dihalides to form alkenic compounds in good yields (eq 13).[73]

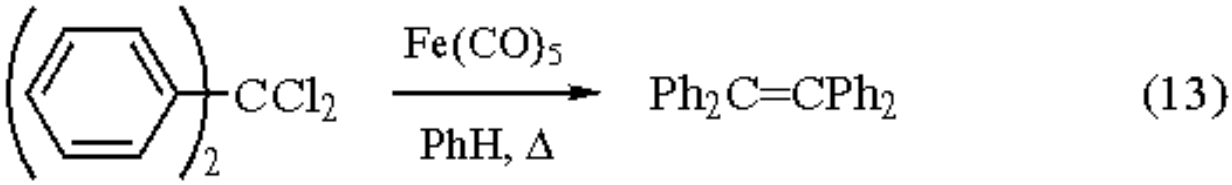

α-Halo Ketones.

Treatment of α-halo ketones (**34**) with $Fe(CO)_5$ was found by Alper to result in formation of coupled 1,4-diketones (**35**) and reduced monoketones (**36**) (eq 14).[74]

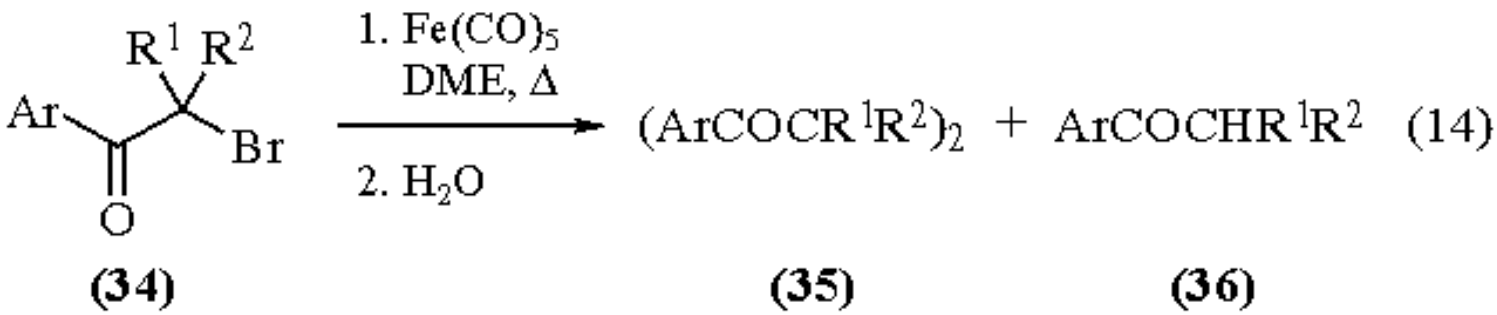

α,α´-Dibromo Ketones and α,α,α´,α´-Tetrabromo Ketones.

Although dehalogenation combined with carbon-carbon bond formation is more commonly performed with ***Nonacarbonyldiiron***, $Fe(CO)_5$ may also be used. The use of a tribromo ketone, followed by a separate reductive dehalogenation step, is illustrated for the synthesis of carbocamphenilone (eq 15), a compound of interest as a skewed glyoxal model.[75]

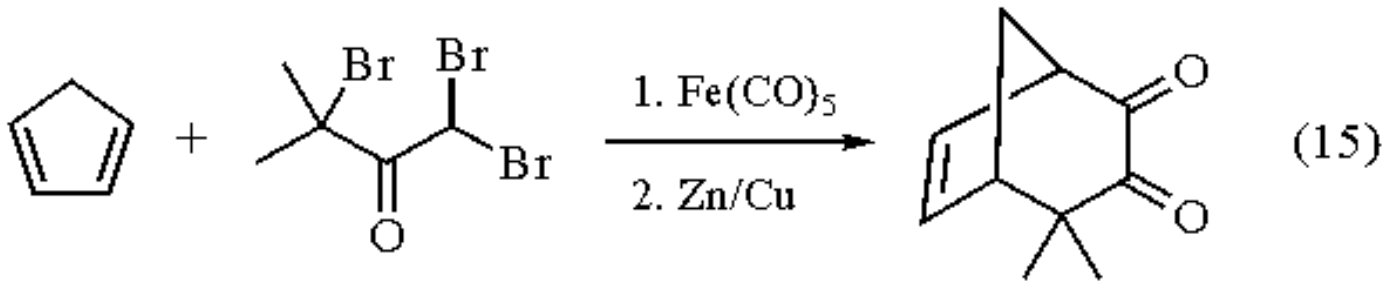

The reaction between the allylic bromide (**37**) and $Fe(CO)_5$ constitutes an alternative method of preparation of tricarbonyl(1,3-cyclohexadiene)iron (**38**) (eq 16).[76] Allylic alcohols react in a similar way (eq 17) under neutral conditions,[77] but in the presence of acid (HBF_4), cationic η^3 iron carbonyl complexes are produced.[78]

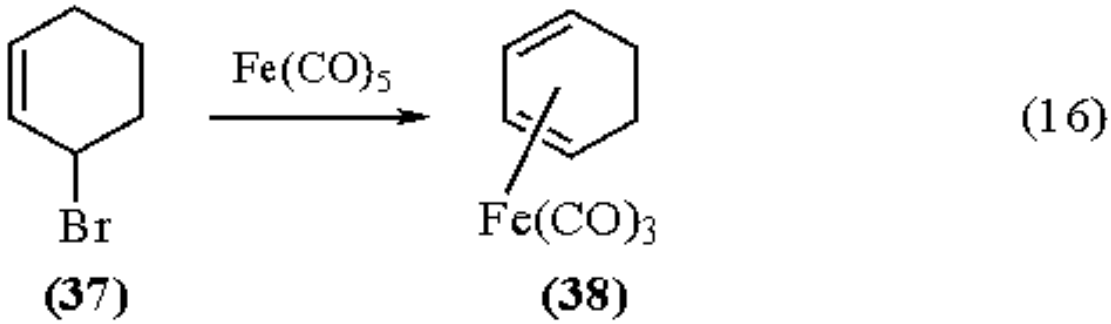

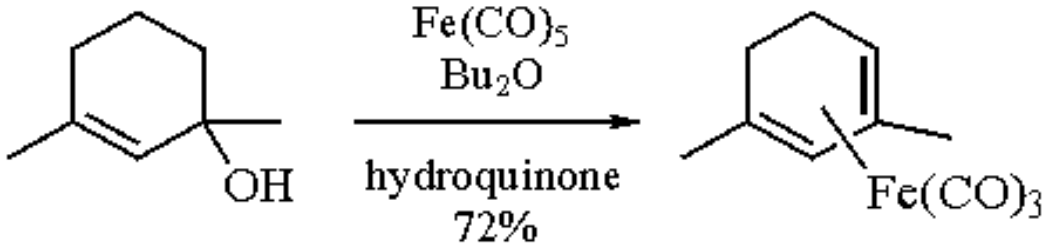

(17)

Benzohydroxamoyl Chlorides.

Benzohydroxamoyl chlorides (**39**) are converted into nitriles (**40**) when refluxed with $Fe(CO)_5$ in THF (eq 18).[79]

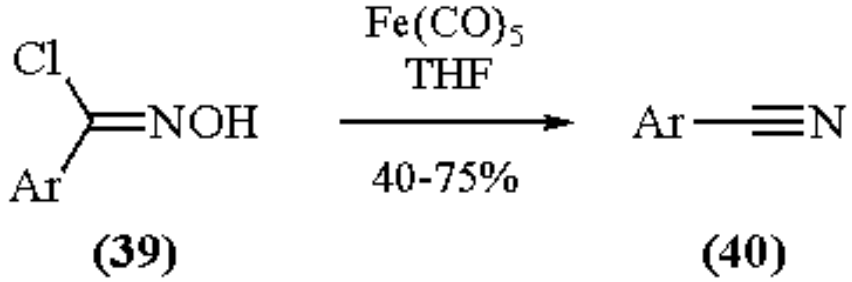

(18)

Dehydration and Dehydrosulfuration Reactions.

Certain amides and thioamides, on treatment with $Fe(CO)_5$, yield nitriles or imines depending on the degree of substitution present (eq 19).[80] Dithioesters, on the other hand, form trinuclear iron carbonyl complexes.[81]

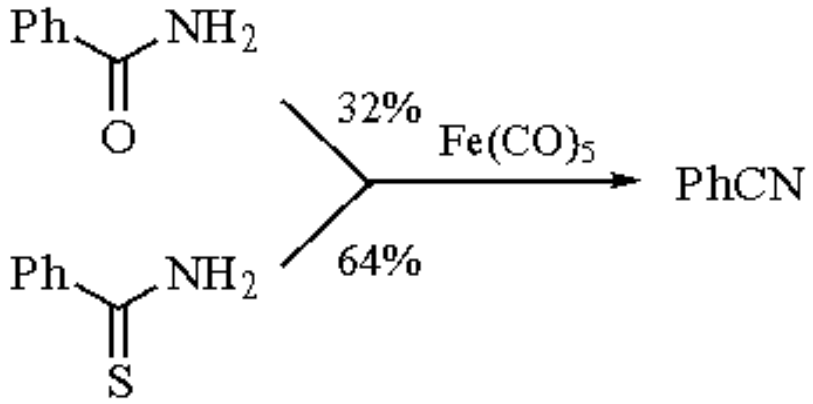

(19)

Reaction with Oximes; Deprotection of Ketones.

Regeneration of protected ketones from their oximes can be achieved by refluxing the oxime in di-*n*-butyl ether with one equiv of $Fe(CO)_5$ and a catalytic amount of a Lewis acid (eq 20).[82]

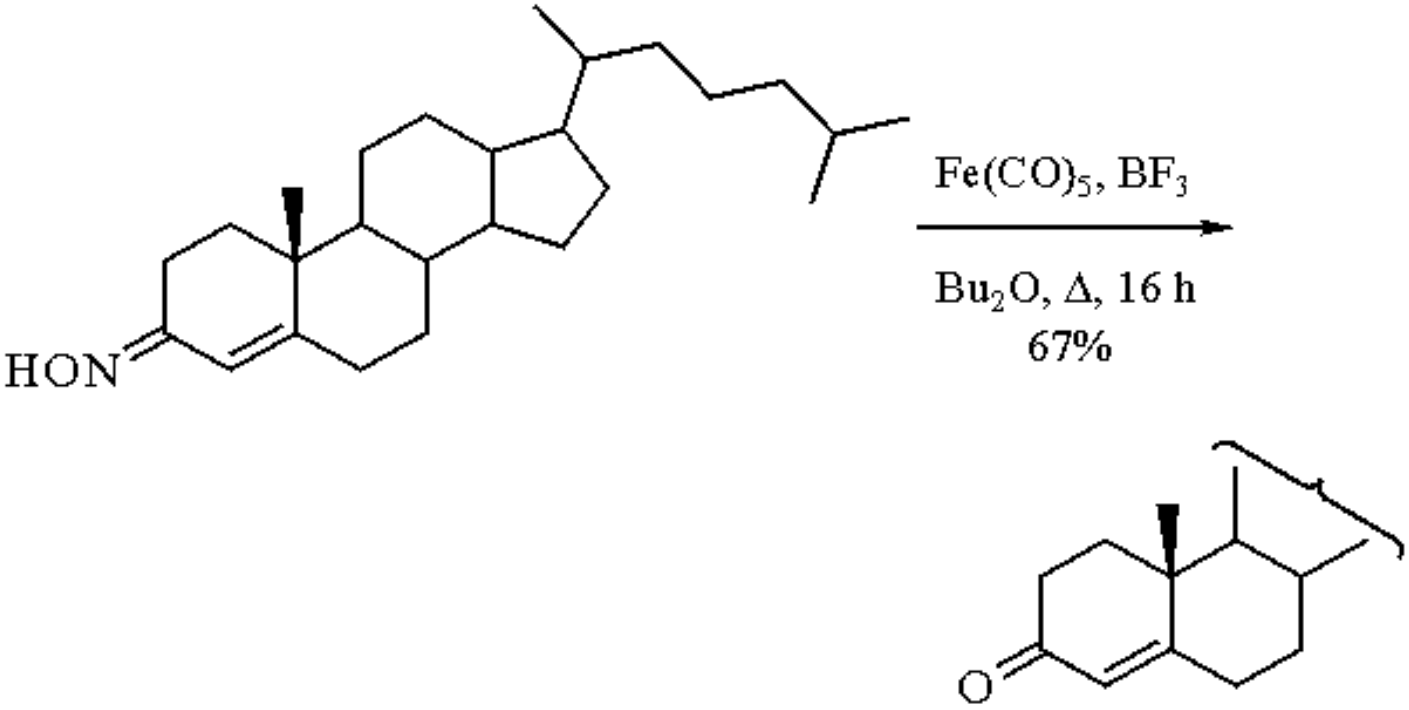

(20)

Other Reactions Occurring with Carbonyl Insertion.

Carbonylation of Benzyl Halides.

Benzyl halides can be converted into phenylacetic acids by reaction with $Fe(CO)_5$.[83] Phase-transfer catalysis is useful in this reaction.[84]

Diazonium Salts.

Carboxylic acids or ketones are obtained from the reaction of diazonium salts with $Fe(CO)_5$, depending on the reaction conditions.[85]

Nucleophiles.

Nucleophiles such as amines (eq 21)[86] and organolithium reagents (eq 22)[87] are also found to react with $Fe(CO)_5$ to give products of CO insertion. Cyclopentadienide, on the other hand, undergoes an unusual tricarbonylation reaction to form a cyclopentadienyl complex with an iron-acyl bridge connecting the metal and the cyclopentadienyl ring (eq 23).[88] The product was isolated by protecting the two OH groups. An aryllithium reagent, in which the aromatic ring is bound to a tricarbonylchromium group, also follows a different reaction path, and bimetallic tetracarbonyliron ferrate derivatives are isolated.[89]

$$RNH_2 + Fe(CO)_5 \longrightarrow RNHCHO$$
$$R_2NH + Fe(CO)_5 \longrightarrow R_2NCHO \qquad (21)$$

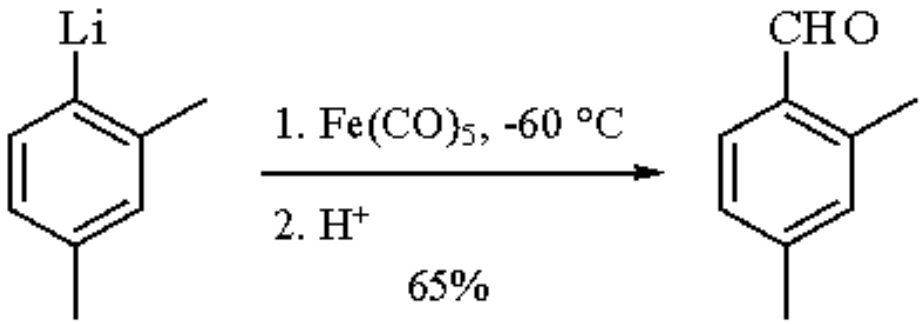

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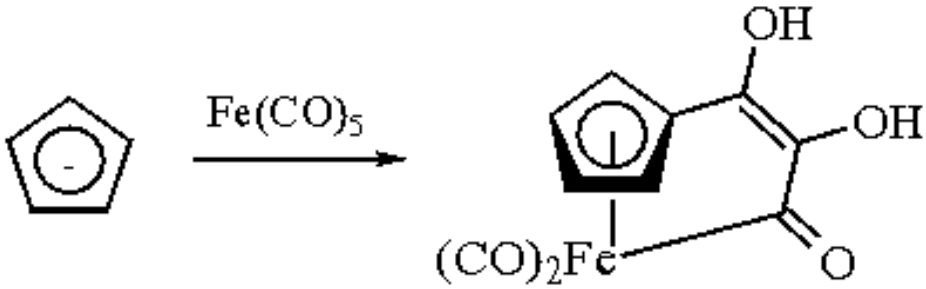

(23)

An arylmethylmalonate derivative, with an *ortho* iodine substituent on the aromatic ring, undergoes a carbonylative cyclization by oxidative addition to the aryl iodide and reaction at the nucleophilic center of the malonate group.[90]

Formylation and Acylation of Pyridine.

Direct formylation and acylation at the β-position of pyridine is possible by reaction with phenyllithium and then with $Fe(CO)_5$. 2-Phenylpyridine is also formed in these reactions.[91]

Formation of *N,N´*-Disubstituted Ureas.

The substituted ureas are prepared in about 50-95% yield by reaction of aryl or alkyl nitro compounds with the MgBr derivative of an amine in the presence of $Fe(CO)_5$ (eq 24).[92]

$$R^1NHMgBr + R^2NO_2 \xrightarrow[2.\ H_2SO_4]{1.\ Fe(CO)_5} R^1NHCONHR^2 \qquad (24)$$

Formation of Carboxylic Esters[93,95] and Ketones.[94]

Grignard reagents can also be converted into esters and ketones by $Fe(CO)_5$ (to supply CO). A cathodic ester synthesis from alcohols and alkyl halides uses carbon monoxide (at 1 atm) and $Fe(CO)_5$ as a catalyst.[95]

Deoxygenation Reactions and Reductions.

Deoxygenation of N-O Bonds.

Deoxygenation of amine oxides has been discussed above (see eq 6); pyridine *N*-oxides provide a further illustration (eq 25).[96]

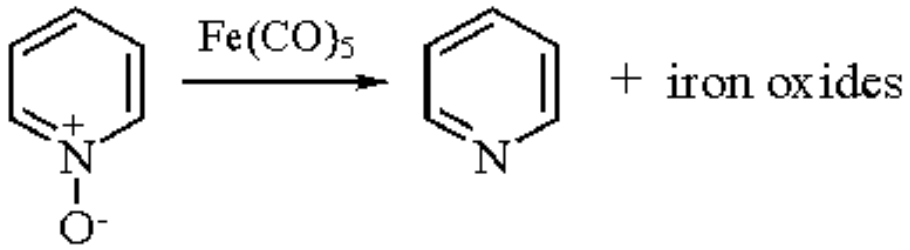

(25)

Nitroso Compounds.

Similar treatment of nitrosobenzene resulted in a 75% yield of azobenzene. Aromatic *N*-nitroso amines have been converted into the secondary amines in 85-92% yields.[97] Under photolytic conditions, azoxyarenes are produced.[98] The choice of solvent is important. Dialkylnitrosoamines afford ureas (eq 26).[97]

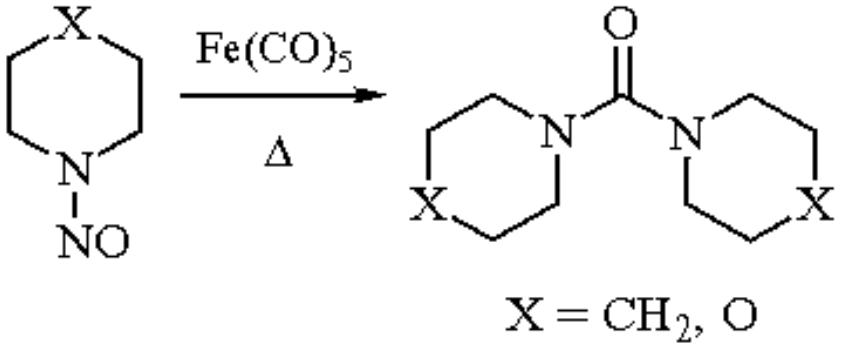

(26)

Aromatic Nitro Compounds.

Indoles are formed[99] by $Fe(CO)_5$ catalyzed deoxygenation of *o*-nitrostyrenes with CO (eq 27).

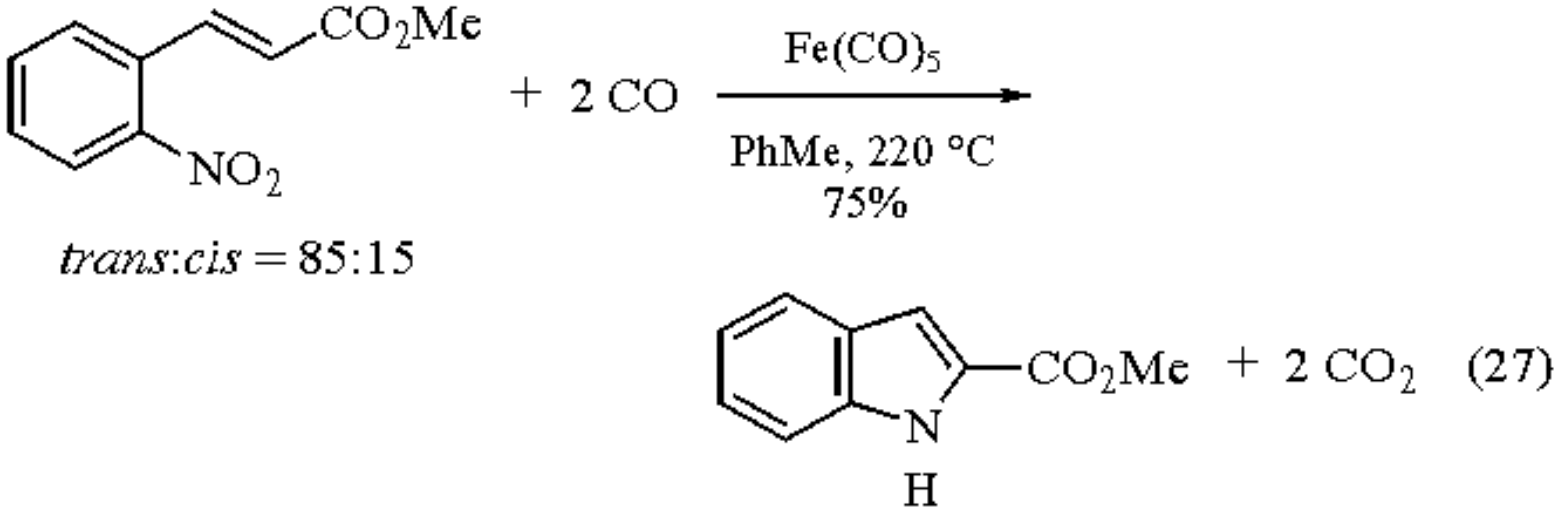

Deoxygenation of Epoxides.

$Fe(CO)_5$ in *N*,*N*-dimethylacetamide or tetramethylurea deoxygenates epoxides (2 h, 145 °C). The reaction is not stereospecific: *trans*-stilbene oxide is converted into both *trans*- (56%) and *cis*-stilbene (22%).[100] Epoxides of 1-alkenes are converted mainly into mixtures of internal alkenes.

Stabilization of Reactive or Unstable Species.

The complex (**42**), formed from the reaction between the dibromoxylene (**41**) and $Fe_2(CO)_9$ or $Na_2Fe(CO)_4$, reacts with $Fe(CO)_5$ to yield the mixture of stereoisomers (**43**) and the complex (**44**) (eq 28).[101] With pentacarbonyliron, however, (**41**) is taken directly on to an indanone by carbonylative cyclization (see above).[102]

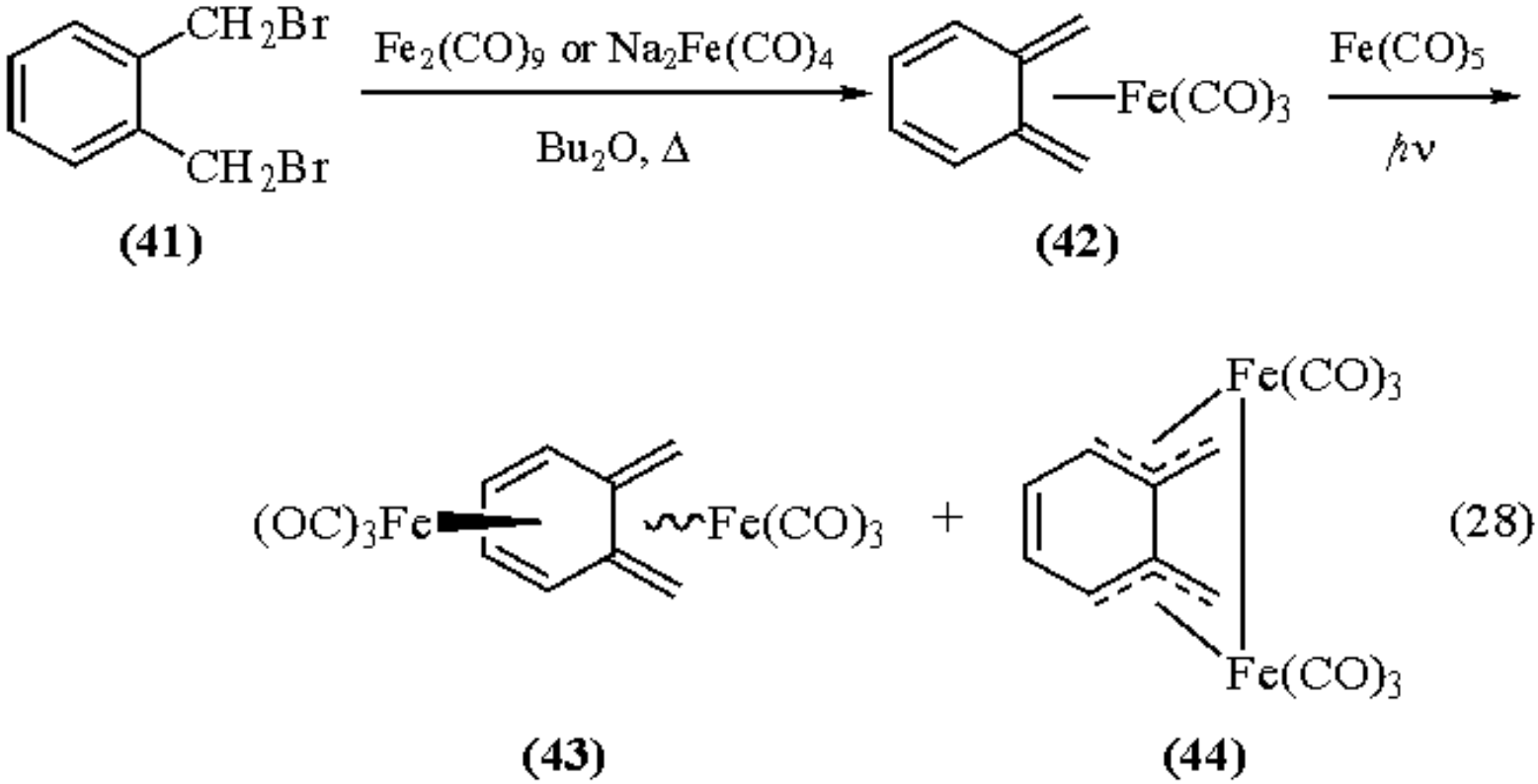

A pentafulvalene has been trapped as a diiron complex using $Fe(CO)_5$.[103] Thiophene dioxide has also been stabilized as its tricarbonyliron complex.[104] The irradiation of α-pyrone (**45**) in the presence of $Fe(CO)_5$ gives cyclobutadiene stabilized by complexation with the $Fe(CO)_3$ moiety (**46**), together with the (α-pyrone)$Fe(CO)_3$ complex (**47**) (eq 29).[105]

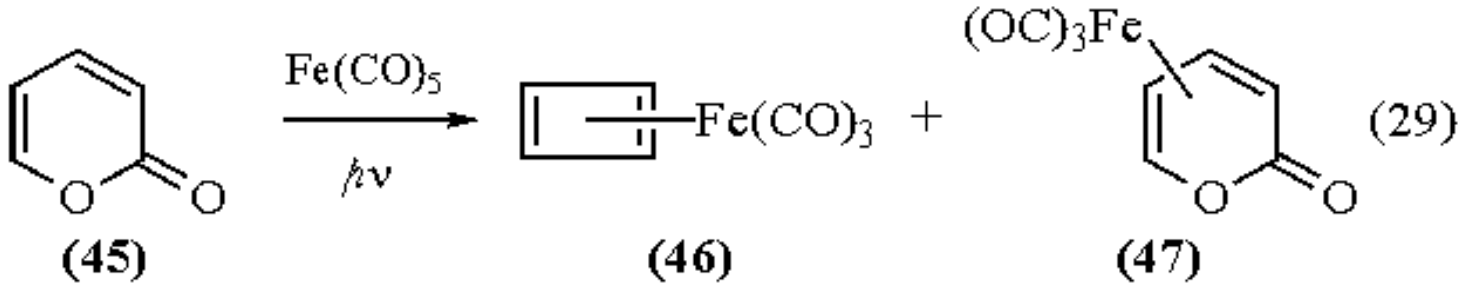

Reactions with Alkynes.

Dimerization.

Two alkynes can be combined to form a cyclobutadiene ligand. The reaction has been reported for a dialkylamino trimethylsilyl-substituted alkyne, and forms a diaminocyclobutadiene complex.[106]

Dimerization with Insertion of One Molecule of CO.

A number of tricarbonyliron complexes of substituted cyclopentadienones have been prepared from alkynes. The

reaction was first described by Jones et al.[107] for $Fe(CO)_5$ and Ph-C&tbond;CH in the presence of $Ni(CO)_4$. A number of other alkynes (PhC_2Me, PhC_2SiMe_3, Me_3SiC_2R, $BrC_6H_4C_2H$, $CF_3C_2CF_3$, PhC_2Ph and α,o-diynes) give cyclopentadienone complexes (eq 30).[108]

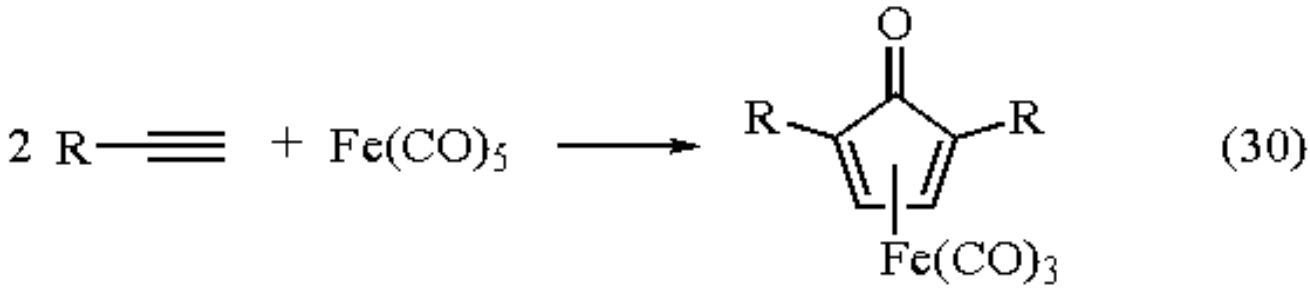

Cyclization of an alkyne to an alkene with carbonyl insertion (analogous to the Pauson-Khand reaction) has also been achieved using pentacarbonyliron.[109]

Dimerization with Insertion of Two Molecules of CO.

By manipulating reaction conditions, formation of benzoquinones can be achieved (eq 31).[110]

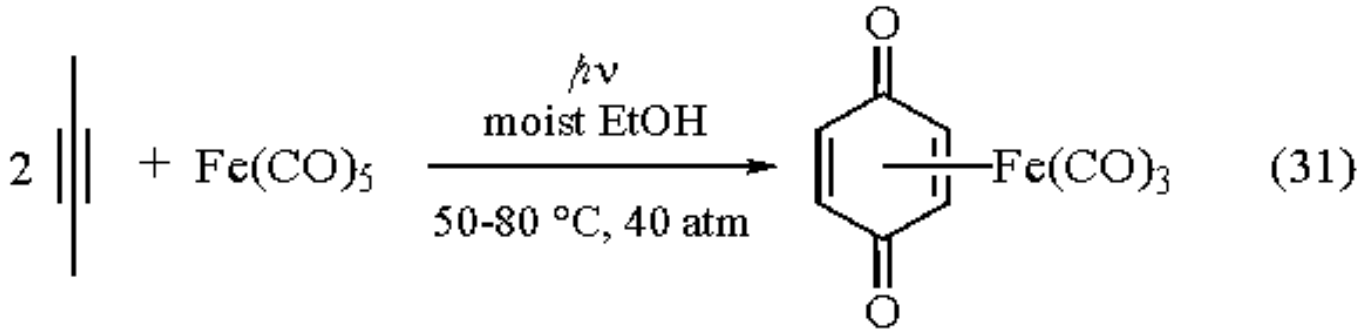

Reaction with Allenes.

A diallene, hexatetraene (eq 32), reacts with $Fe(CO)_5$ with insertion of carbon monoxide to form 2,5-dimethylenecyclopent-3-enone.[111] Allenyl ketones, on the other hand, form dinuclear complexes.[112]

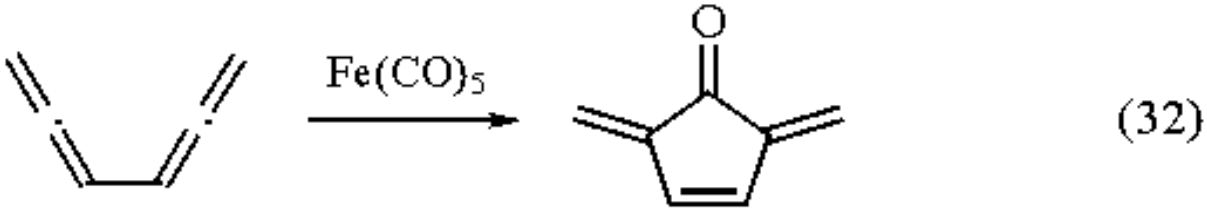

Formation of Naphthoquinones via Iron Metallocycles.

Benzocyclobutenedione (**48**) forms the iron complex (**49**) by irradiation with $Fe(CO)_5$.[113] Complex (**49**) reacts with a

wide variety of alkynes to give naphthoquinones, in yields usually >70% (eq 33).

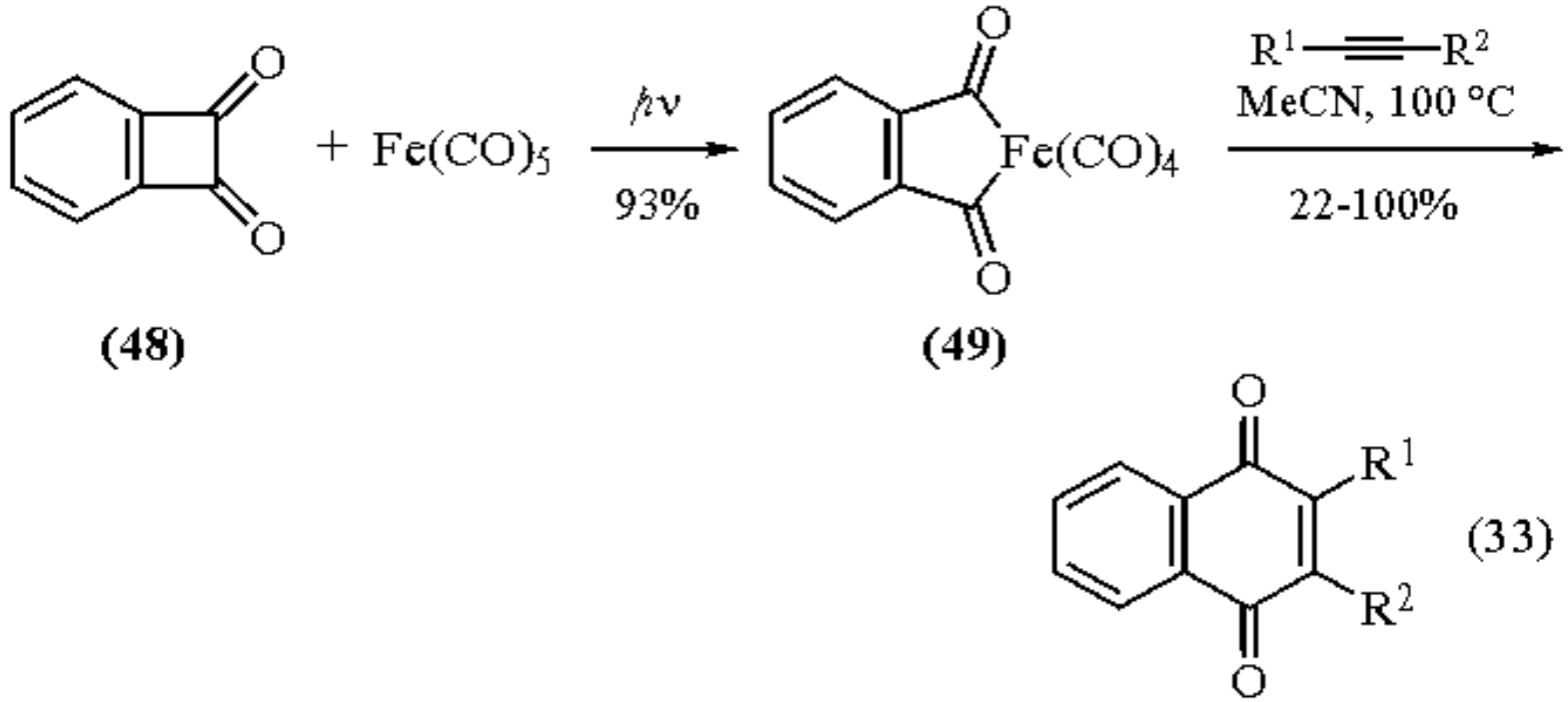

(33)

Trimerization of Benzonitriles.

Benzonitrile is trimerized in good yield by heating with $Fe(CO)_5$ for several hours (eq 34).[114]

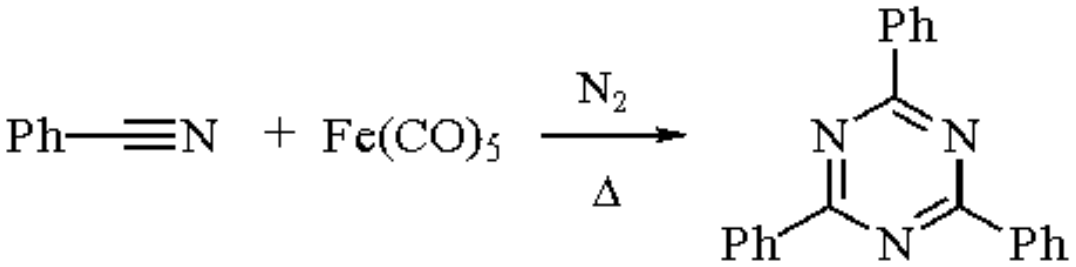

(34)

Formation of Carbodiimides.

Carbodiimides are obtained in ca. 50% yield from the reaction of azides with isocyanides catalyzed by $Fe(CO)_5$.[115]

Anionic Iron Carbonyl Reagents.

The reagent $[HFe(CO)_4]^-$ can be generated in situ from pentacarbonyliron, allowing straightforward, regiocontrolled, hydroxycarboxylation of acrylic acid by $Fe(CO)_5$, $Ca(OH)_2$, and H_2O/*i*-PrOH under 1 atm of CO.[116]

Formation of Iron Carbene Complexes.

$Fe(CO)_5$ is the starting material for the preparation of the tetracarbonyl(ethoxyphenylmethylidene)iron(0) (**50**) (eq 35).[117]

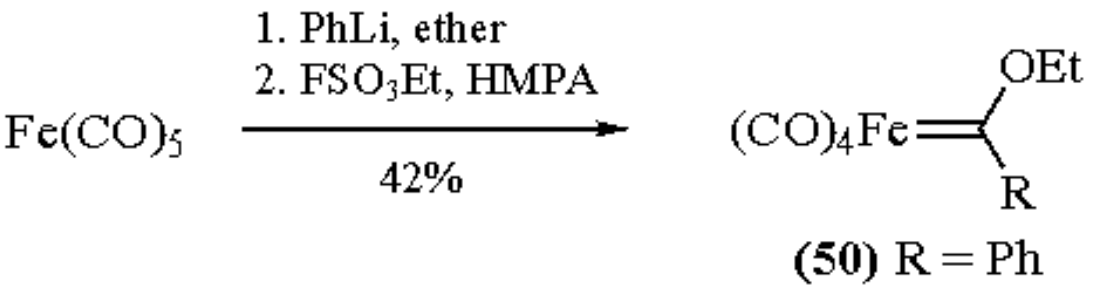

(35)

Iron carbene complexes react with alkynes under CO atmosphere to form (α-pyrone)$Fe(CO)_3$ complexes.[118]

Modified Corey-Winter Alkene Synthesis.

Daub et al.[119] have obtained satisfactory yields by using $Fe(CO)_5$ in an iron-mediated version (eq 36) of the reaction of thionocarbonates with ***Trimethyl Phosphite***, which gives poor yields in the case of thermally labile alkenes.

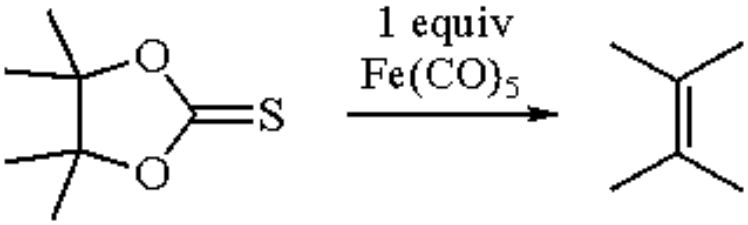

(36)

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Pentacarbonylchloromanganese[1]

$(CO)_5MnCl$

[14100-30-2] · C_5ClMnO_5 · Pentacarbonylchloromanganese · (MW 230.44)

(precursor to reactive carbonyl halide complexes;[2] precatalyst for the oligomerization of benzyl chloride[3])

Physical Data: pale yellow crystals; sublimes at 40 °C/0.1 mmHg.

Solubility: sol CH_2Cl_2; moderately sol benzene, toluene; v sl sol hexane.

Form Supplied in: not commercially available. $(CO)_5MnBr$ is available from commercial sources as orange-yellow crystals.

Analysis of Reagent Purity: IR (CCl_4, cm^{-1}) 2140 (w), 2054 (s), 2021 (vw), 1998 (m).[4] Related compounds: $(CO)_5MnBr$ 2134 (w), 2051 (s), 2020 (vw), 2000 (m); $(CO)_5MnI$ 2127 (w), 2045 (s), 2016 (vw, sh), 2005 (m)

Preparative Methods: (a) treatment of a CH_2Cl_2 solution of ***Decacarbonyldimanganese*** with 30 equiv ***Sulfuryl Chloride*** at rt, followed by evaporation, washing with ethanol, and drying in vacuo, affords pure $(CO)_5MnCl$ in 91% yield (eq 1).[5] (b) a solution of ***Chlorine*** in CCl_4 is added slowly to $Mn_2(CO)_{10}$ in CCl_4 at 0 °C under a dry nitrogen atmosphere. After stirring at room temperature for 4 h, the precipitate is filtered in air, washed with CCl_4, and dried in vacuo. The product is approximately 90% pure, the remainder being $[MnCl(CO)_4]_2$.[1,6,7] (c) A solution of $Mn_2(CO)_{10}$ in CCl_4 irradiated with UV-visible light gives $(CO)_5MnCl$ with high quantum yield; $(CO)_5MnI$ is also available by photolysis in the presence of I_2.[8]

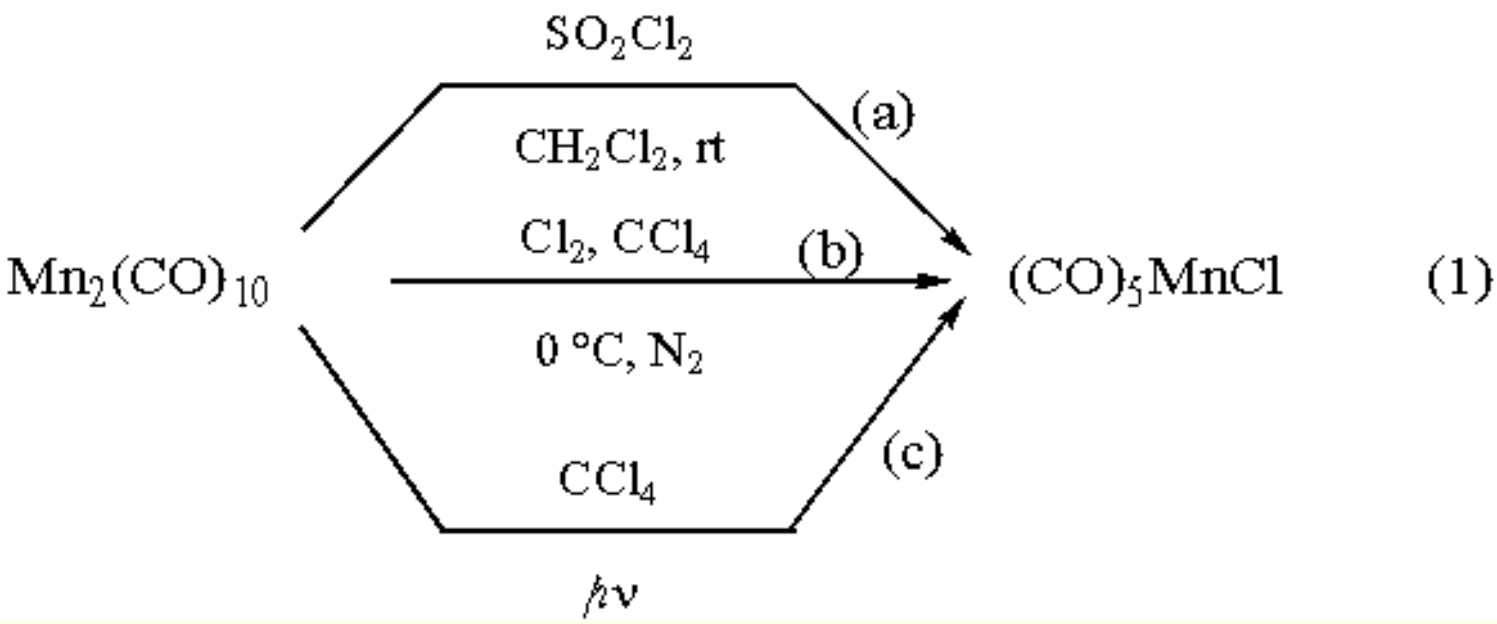

The related compounds $(CO)_5MnBr$ and $(CO)_5MnI$ may be prepared by methods similar to (b).[1] In addition, the iodide may be obtained from $Na[Mn(CO)_5]$ and I_2.[1]

Purification: $(CO)_5MnCl$ (40 °C/0.1 mmHg), $(CO)_5MnBr$ (50 °C/0.05 mmHg), and $(CO)_5MnI$ (50 °C/0.05 mmHg) are purified by sublimation and/or recrystallization from hydrocarbon solvents such as pentane or hexane.

Handling, Storage, and Precautions: light sensitive; dimerizes slowly in solution with loss of CO. The product, $[MnCl(CO)_4]_2$, is readily detected by IR (2104 (m), 2045 (vs), 2012 (s), 1975 (vs)).[9] Pentacarbonylmanganese halides are indefinitely stable when stored as solids in the absence of air at -20 °C. While no information concerning the toxicity of these compounds is available, one should assume that metal carbonyls are highly toxic; since they are volatile solids, extra care should be taken to avoid exposure. Use in a fume hood.

Carbonyl Substitution.

Substitution of a CO ligand with a two-electron donor usually occurs *cis* to the halide (eq 2). The products are configurationally stable. Attacking ligands include monodentate or chelating phosphines and arsines,[2] and silylphosphines, with subsequent hydrolysis of the P-Si bond to afford parent phosphine (P-H) complexes and dinuclear compounds under some conditions.[10]

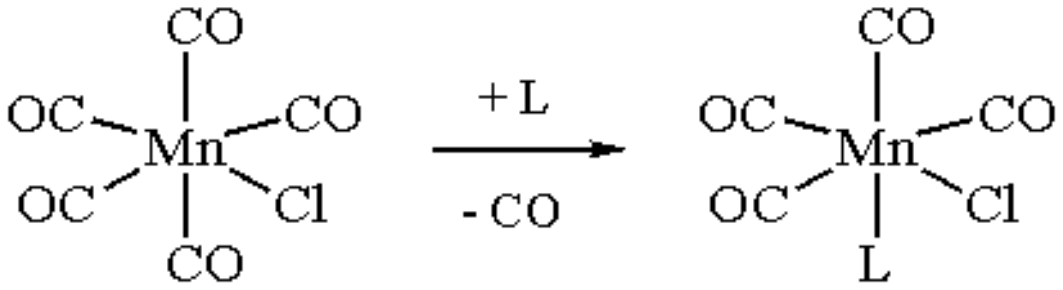

(2)

Halide Substitution.[11]

Treatment with ***Silver(I) Trifluoromethanesulfonate*** affords the labile $Mn(CO)_5(OTf)$ complex, which may be treated by a variety of neutral two-electron donors to give cationic complexes $[(CO)_5Mn\text{-}L](OTf)$ (L = THF, MeCN, PBu_3).[11] The following compounds are available by displacement of both halide and CO ligands: $(\eta^3\text{-allyl})Mn(CO)_4$, from attack of hydroxide ion on coordinated CO followed by loss of CO_2 and alkylation with allyl bromide;[12] $(\eta^5\text{-}C_5Z_4X)Mn(CO)_3$ (Z = H or Cl), from reaction with diazocyclopentadienides with transfer of the halide of the Cp fragment;[7,13] and aminooxy- or dioxycarbene compounds from reaction with oxirane or aziridine and catalytic bromide ion.[14]

Oligomerization of Benzyl Chloride.

When heated at 100 °C with catalytic quantities of $(CO)_5MnCl$ or $(CO)_5MnBr$, benzyl chloride is converted to highly branched oligomers linked at benzylic and aromatic ring sites.[3] An average of 30-50 monomer units are incorporated per oligomer. The analogous rhenium complexes are also active, as are Group 6 carbonyl halides.

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Pentacarbonyl(methoxyphenylcarbene)chromium(0)

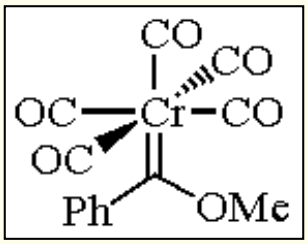

[27436-93-7] · $C_{13}H_8CrO_6$ · Pentacarbonyl(methoxyphenylcarbene)chromium(0) · (MW 312.21)

(metal-carbene complex[1])

Alternate Name: pentacarbonyl[methoxy(phenyl)methylene]chromium.

Physical Data: mp 46 °C.

Solubility: sol THF, ether, benzene, hexane.

Form Supplied in: orange-red crystals; not commercially available.

Preparative Method: prepared from ***Phenyllithium***, ***Hexacarbonylchromium***, and ***Trimethyloxonium Tetrafluoroborate*** according to the procedure of Fischer.[2]

Purification: recrystallized from petroleum ether at -78 °C. Can also be purified by column chromatography on silica gel using pure hexane as the eluent.

Handling, Storage, and Precautions: slightly air sensitive; should be stored in a refrigerator. Chromium compounds display variable toxicity. Care is recommended. Use in a fume hood.

Benzannulation.

Reaction of pentacarbonyl(phenylmethoxycarbene)chromium (**1**) with alkynes leads to *p*-methoxynaphthol derivatives (eq 1).[1] The reaction is tolerant of a variety of substitution patterns on the alkyne. The regiochemistry is such that the larger alkyne substituent preferentially ends up *ortho* to the hydroxy group, and the smaller substituent ends up *ortho* to the methoxy group. The observed regioselectivity is proportional to the size difference of the alkyne substituents. Terminal alkynes react with complete control of regiochemistry (eq 2), but unsymmetrical internal alkynes provide mixtures of products (eq 3).[3] The initially obtained arene complexes (**2**) are not very stable, and are converted to the free arene (**3**) upon exposure to air and light. Treatment of the arene complex with oxidants leads to naphthoquinone (**4**) or naphthoquinone monoacetal derivatives (**5**). In most cases, naphthalene derivatives are the major products from reaction of complex (**1**) and alkynes; however, in some cases other products such as cyclobutenones[4] or furans[5] are significant products in the reaction.

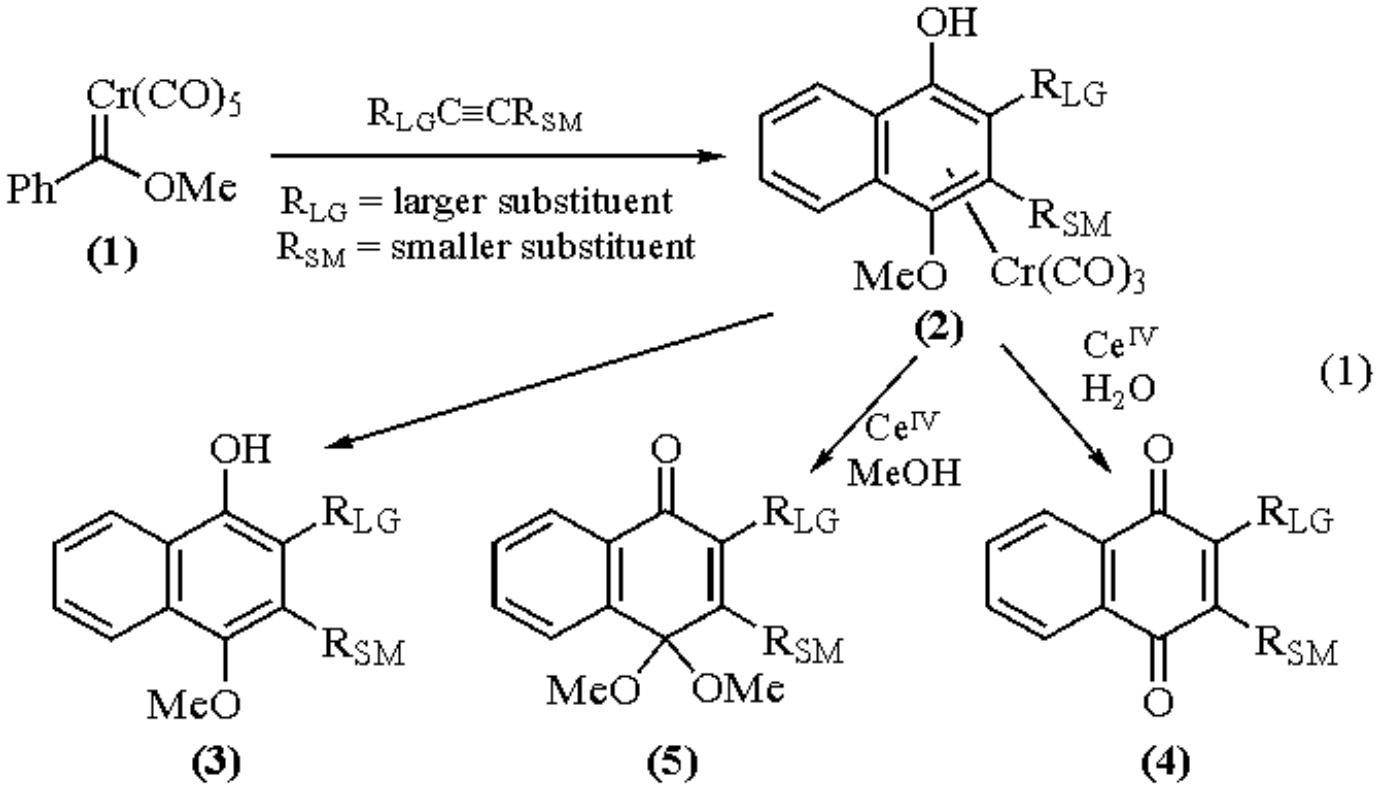

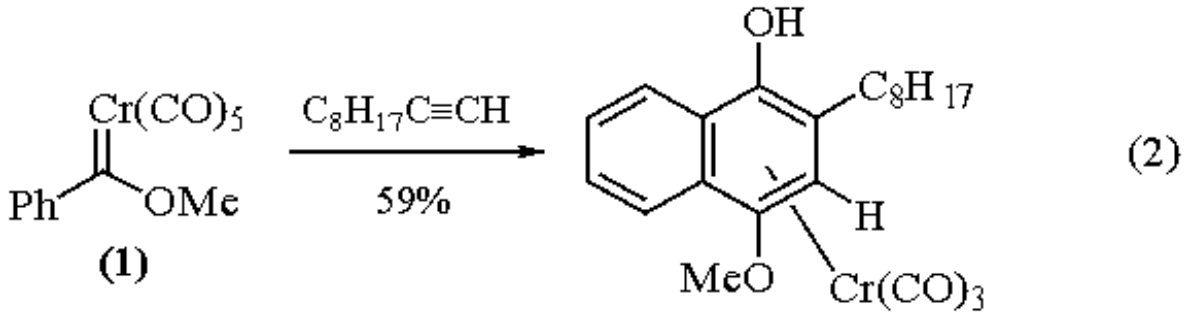

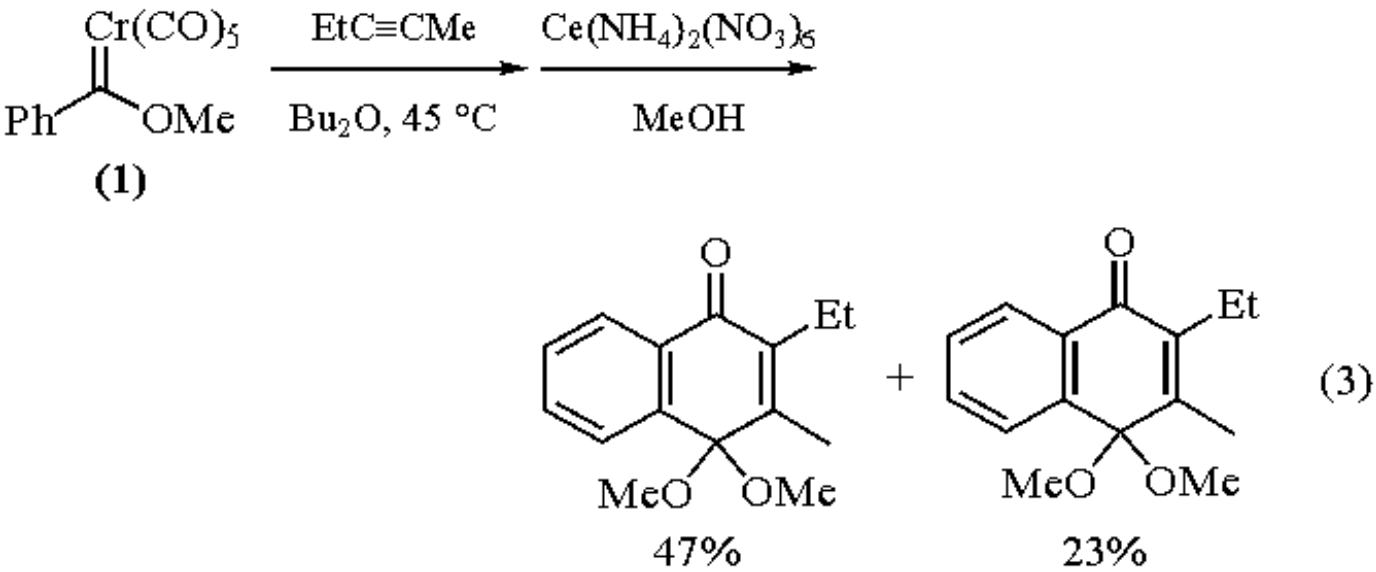

Photochemical Conversion to the Ketene and Subsequent Trapping.

Upon irradiation by UV light, complex (**1**) undergoes conversion to a ketene-metal complex (**7**), which can subsequently be intercepted (eq 4) if the irradiation is performed in the presence of suitable traps. Irradiation of complex (**1**) in the presence of imines leads to β-lactam derivatives (**8**),[6] while treatment with alkenes leads to cyclobutenones (**9**).[7] Compounds (**8**) and (**9**) are produced with excellent control of relative stereochemistry.[8] Irradiation in the presence of alcohols leads to α-hydroxy esters (**10**).[9]

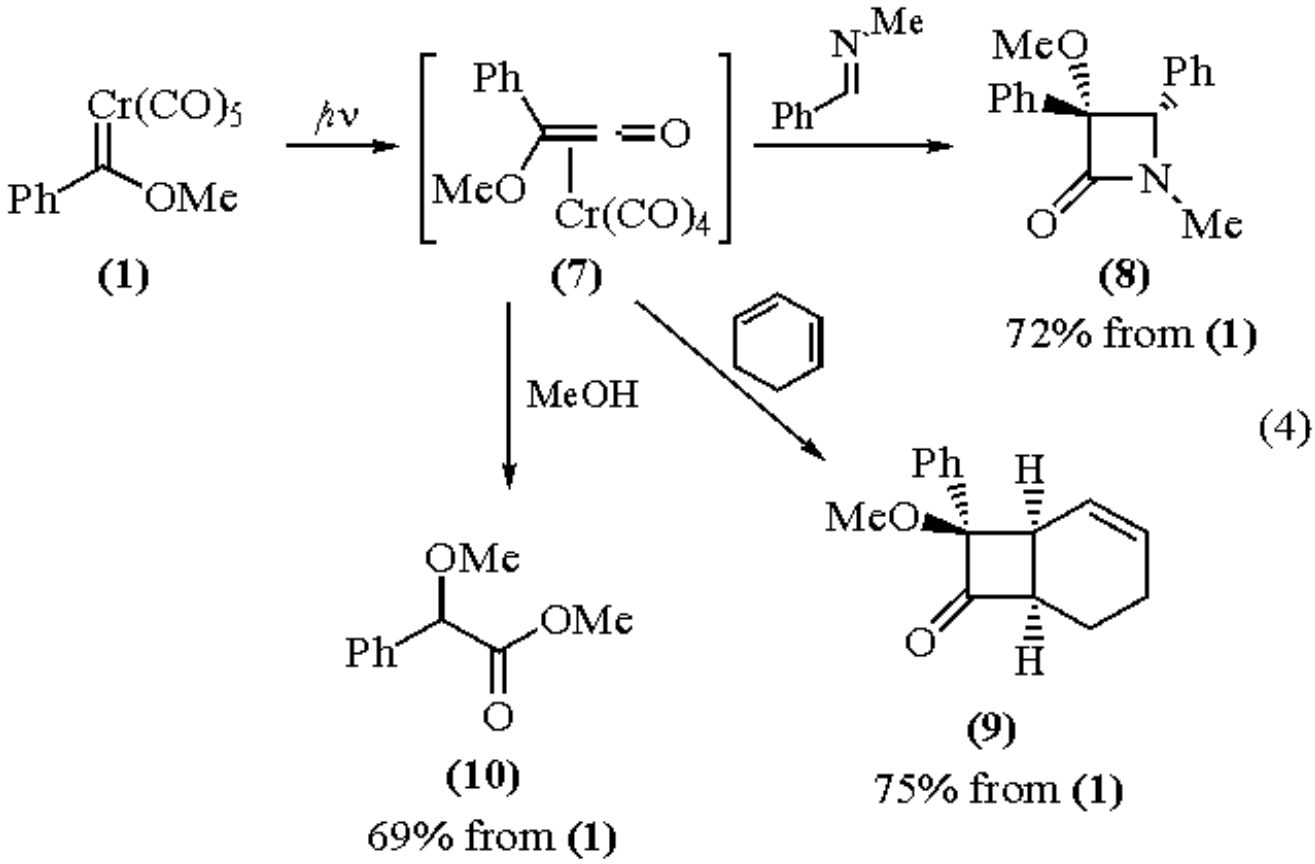

(4)

Cyclopropanation.

Complex (**1**) effects cyclopropanation of selected alkenes (eqs 5-7). The reaction is restricted to highly polarized alkenes such as α,β-unsaturated esters (eqs 5 and 6)[10,11] and enol ethers (eq 7).[12] The cyclopropanation of electron-rich alkenes must be conducted under ***Carbon Monoxide*** pressure; in the absence of CO, alkene metathesis is the major reaction pathway. In the case of dienoic acid esters, cyclopropanation occurs primarily at the 4,5-double bond (eq 6).

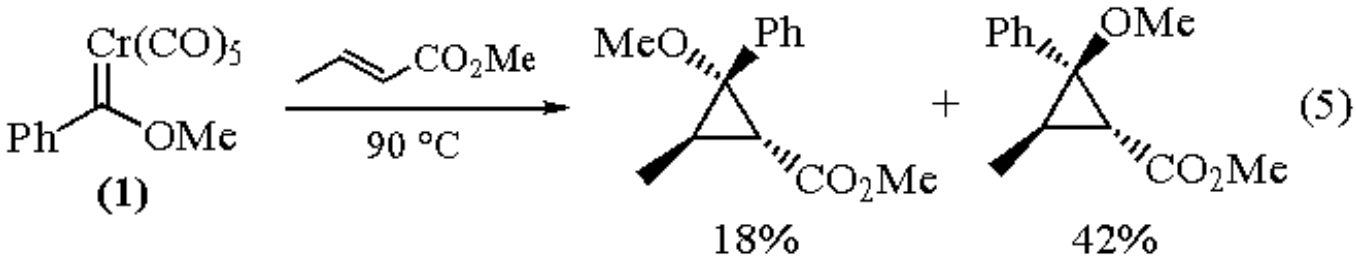

(5)

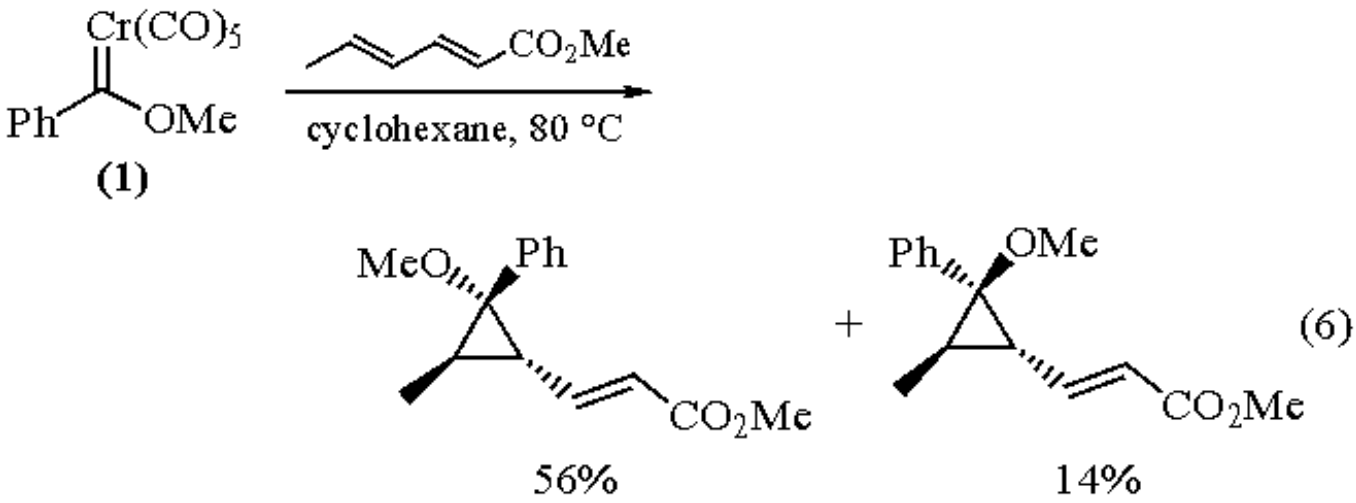

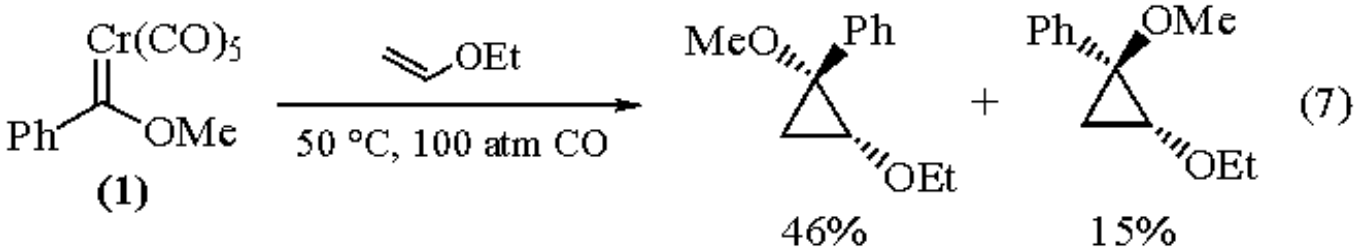

Alkenation.

Treatment of complex (**1**) with sulfur ylides leads to vinylogous carbonate derivatives (eq 8).[13] Similar ylide-type alkenation reactions have been reported for the tungsten analog of complex (**1**),[14] and although not reported, should proceed similarly for the molybdenum complex. Similar transformations using the electronically similar compound methyl benzoate are considerably more difficult.[15]

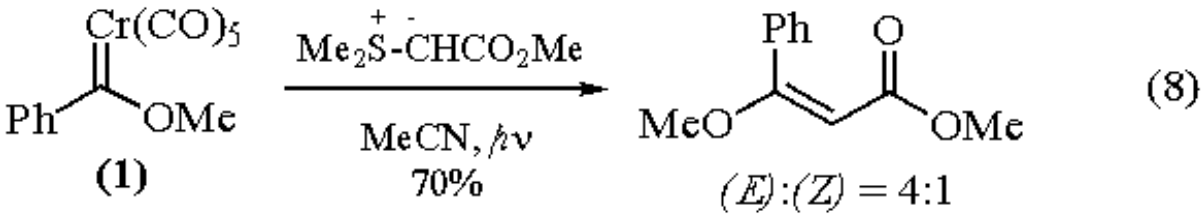

Reaction with Isocyanides.

Treatment of complex (**1**) with isocyanides leads to the ketimine complex (**11**), whose reactivity is best characterized by the zwitterionic structure (**12**) (eq 9).[16] The reactivity of the ketimine complex is very different from that of free ketimines, which are nucleophilic at the α-carbon. This reactivity profile is demonstrated by the addition of methanol (eq 10), which leads to carbene complex (**13**) (this result was obtained using the *ethoxy* analog of complex **1**).[17]

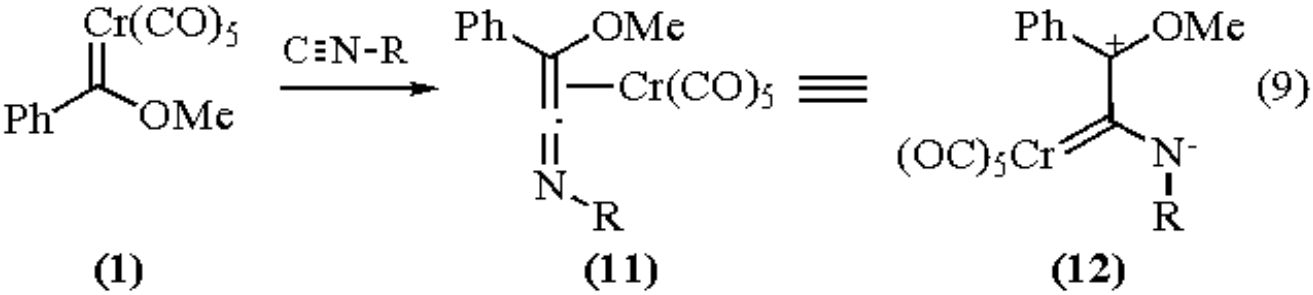

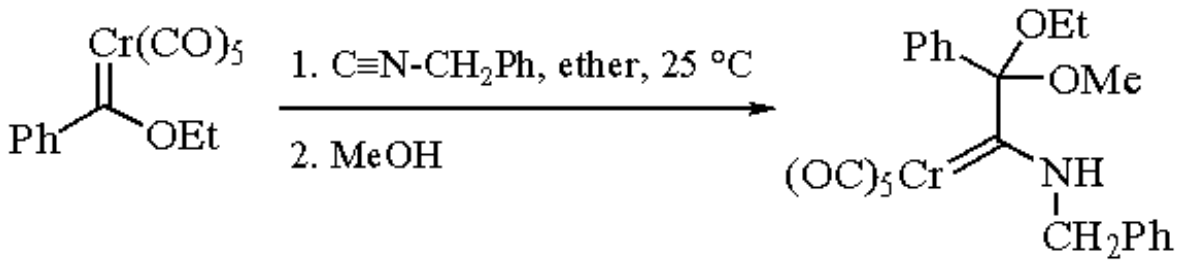

(10)

(1)-Et **(13)**

Insertion into σ-Bonds.

Certain compounds undergo net bond insertion reactions upon treatment with carbene complexes (e.g. complex **1**). Notable classes of compounds undergoing this transformation with complex (**1**) include Group 14 metal hydrides (eq 11)[18] and 1,2-cyclobutenediones.[19] In the latter case, the initial insertion product (**15**) might undergo isomerization to the observed product, alkylidenefuranone (**16**) (eq 12).

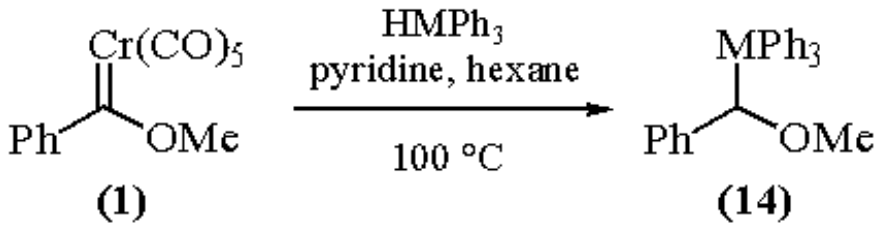

(11)

(1) **(14)**

M = Si, 49%; Ge, 92%; Sn, 53%

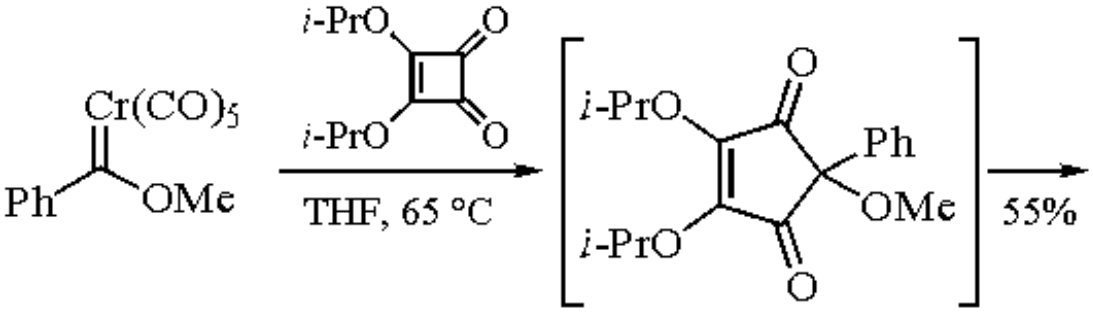

(1) **(15)**

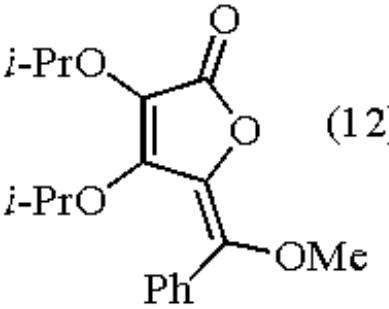

(12)

(16) *(E)*:*(Z)* = 1:1

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Pentacarbonyl(methoxyphenylcarbene)tungsten(0)

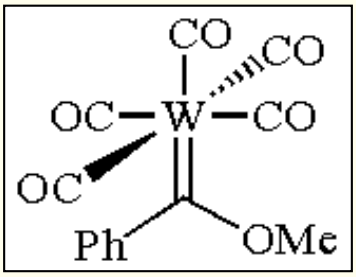

[37823-96-4] · $C_{13}H_8O_6W$ · Pentacarbonyl(methoxyphenylcarbene)tungsten(0) · (MW 444.06)

(metal-carbene complex[1])

Alternate Name: pentacarbonyl[methoxy(phenyl)methylene]tungsten.

Physical Data: mp 59 °C.

Solubility: sol THF, ether, benzene, hexane.

Form Supplied in: orange-red crystals; not commercially available.

Preparative Method: prepared from ***Phenyllithium***, ***Hexacarbonyltungsten***, and ***Trimethyloxonium Tetrafluoroborate*** according to the procedure of Fischer.[2]

Purification: recrystallized from petroleum ether at -78 °C. Can also be purified by column chromatography on silica gel using pure hexane as the eluent.

Handling, Storage, and Precautions: slightly air sensitive; should be stored in a refrigerator.

Alkenation.

Treatment of pentacarbonyl(methoxyphenylcarbene)tungsten (**1**) with Wittig reagents leads to the corresponding enol ether (eq 1),[3a] and pentacarbonyl(triphenylphosphine)tungsten. Alternatively, the same transformation can be effected using diazo compounds (eq 2).[3b] In each case the reaction occurs via nucleophilic attack at the carbene carbon followed by an elimination reaction. Similar transformations using the electronically similar compound methyl benzoate are considerably more difficult.[4]

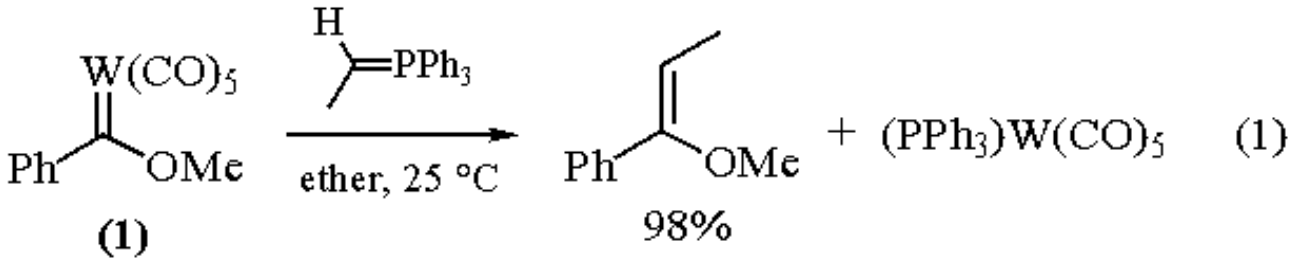

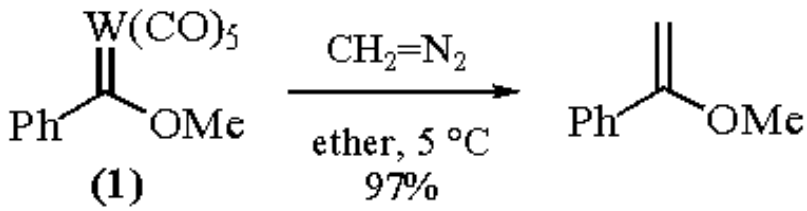

(2)

Reaction with Alkynes.

Treatment of alkynes with (**1**) leads to intermediate vinylcarbene complexes (e.g. **2**),[5] which undergo subsequent transformations (eq 3).[1] The reaction of ***Diphenylacetylene*** with complex (**1**) produces the indene in high yield (eq 4).[6] Treatment of enyne (**3**) with complex (**1**) leads to vinylphenanthrene derivative (**4**) (eq 5).[7] Formation of (**4**) involves alkyne insertion, followed by alkene insertion and alkene metathesis. The chromium analog of complex (**1**) (***Pentacarbonyl(methoxyphenylcarbene)chromium(0)***) has been better studied in its reaction with alkynes.[1]

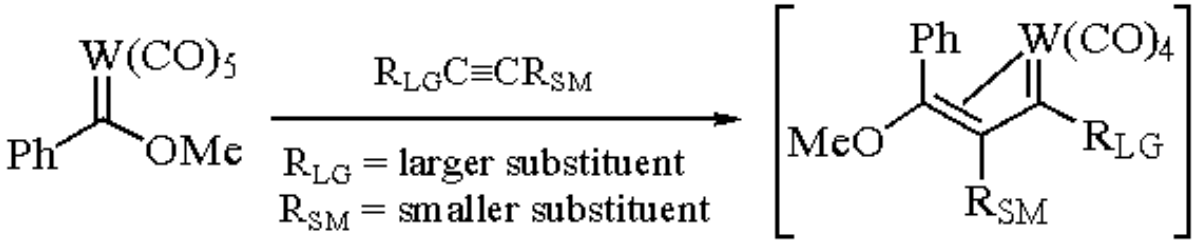

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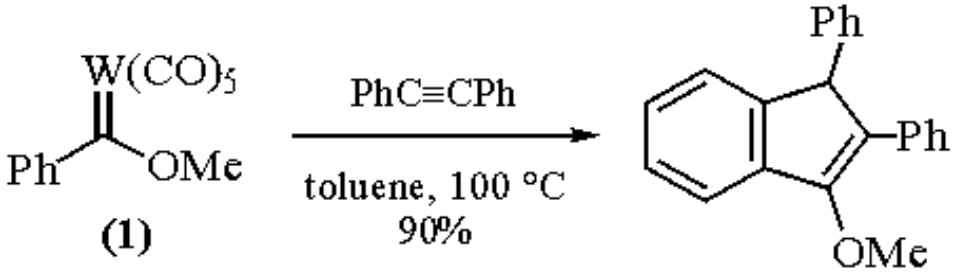

(4)

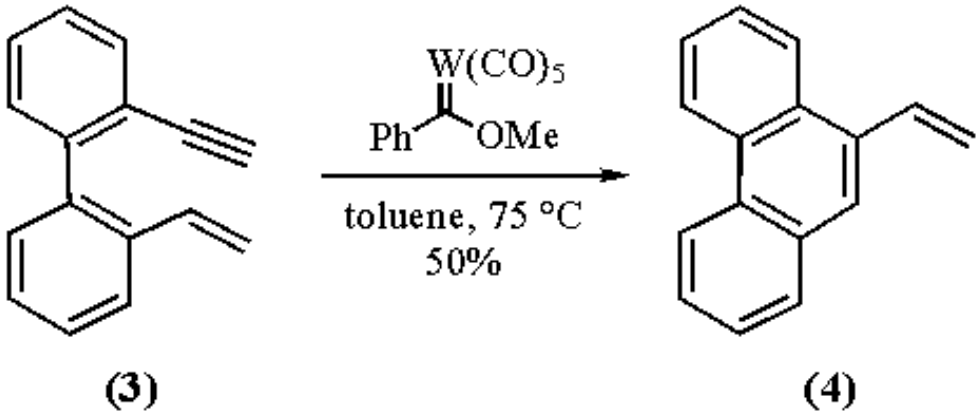

(5)

Reaction with Alkenes.

Pentacarbonyl(methoxyphenylcarbene)tungsten effects cyclopropanation of some alkenes (eqs 6 and 7).[8] The reaction is restricted to highly polarized alkenes such as α,β-unsaturated esters and enol ethers. Cyclopropanation of electron-rich alkenes proceeds through zwitterionic intermediates.[9] Although stereoselectivity is poor, the method does generate highly functionalized cyclopropanes which

Pentacarbonyl(methoxyphenylcarbene)tungsten(0)

would be difficult to prepare by other methods.

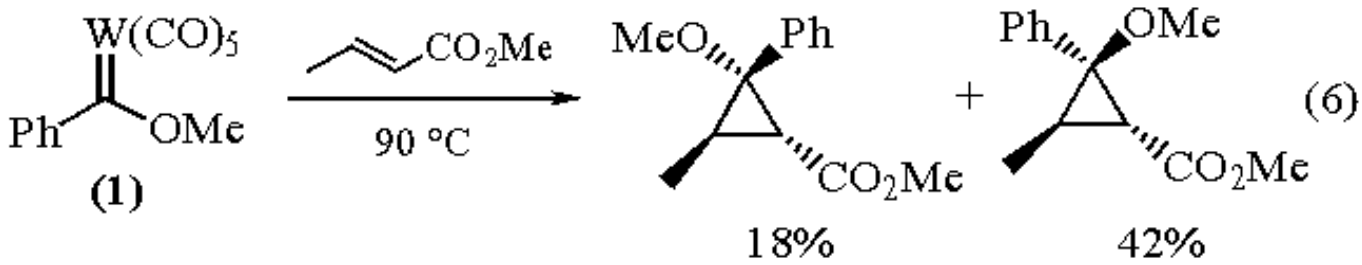

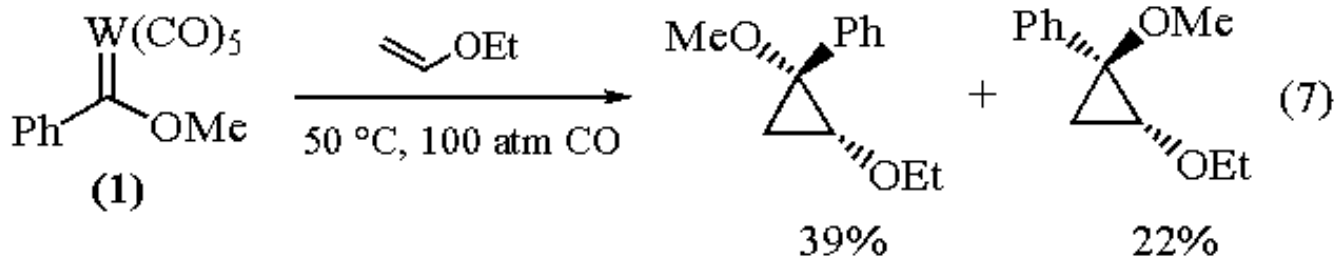

Reaction with Isocyanides.

Treatment of complex (**1**) with isocyanides leads to the ketimine complex (**5**), whose reactivity is best characterized by the zwitterionic structure (**6**) (eq 8).[10] The reactivity of the ketimine complex is very different from that of free ketimines, which are nucleophilic at the α-carbon. This reactivity profile is demonstrated by the cycloaddition reaction in eq 9, which leads to hydantoin (**7**) after oxidative removal of the metal (this result was obtained using the *ethoxy* analog of complex **1**).[11]

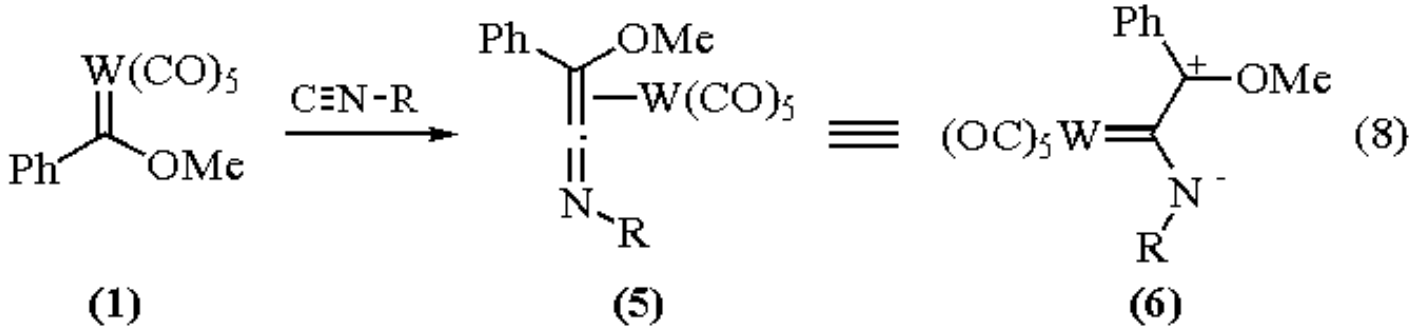

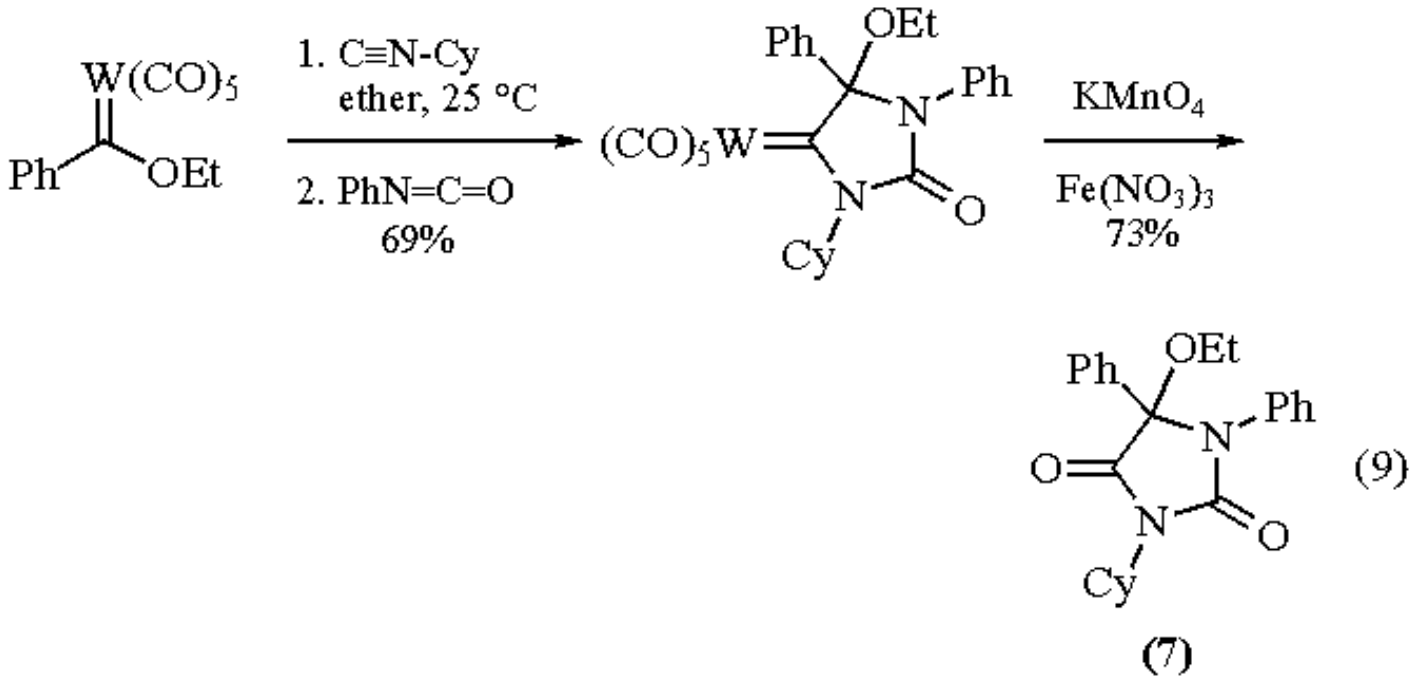

Synthesis of Diaziridines.

Treatment of complex (**1**) with some azo compounds leads to the corresponding diaziridine derivatives (eq 10).[12] The reaction is restricted to electron-deficient azo compounds since electron-rich azo compounds undergo metathesis reactions when treated with complex (**1**).

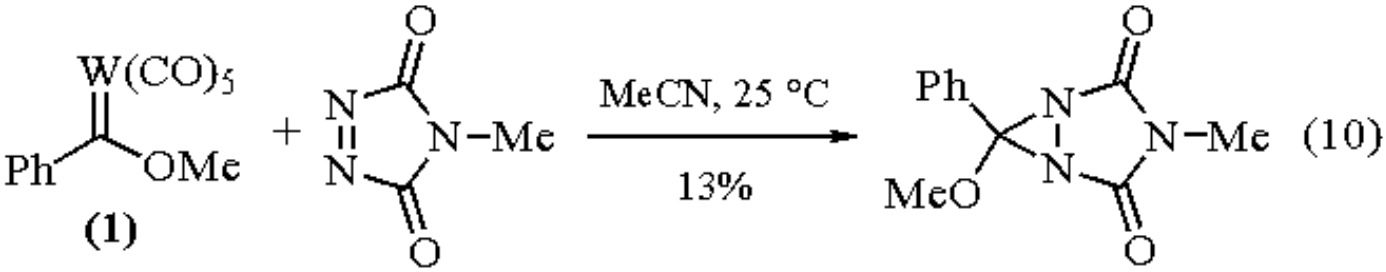

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1. For reviews, see: (a) Wulff, W. D. *COS* **1991**, *5*, 1065. (b) Dötz, K. H. *AG(E)* **1984**, *22*, 587. (c) Casey, C. P. In *Reactive Intermediates*; Jones, M., Jr.; Moss, R. A., Eds.; Wiley: New York, 1985; Vol. 3, p 109.
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James W. Herndon

Pentacarbonylmethylmanganese[1,2]

$(CO)_5MnMe$

[13601-24-6] · $C_6H_3MnO_5$ · Pentacarbonylmethylmanganese · (MW 210.03)

(prototypical reagent for migratory insertion of CO into metal-alkyl bonds;[3,4] can acylate alkenes and alkynes;[2] can cyclometalate keto- and iminoarenes[1,5])

Physical Data: colorless crystals; mp 95 °C; sublimes at 25-40 °C/0.1 mmHg.

Solubility: sol organic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: IR.

Preparative Methods: (a) alkylation of ***Sodium Pentacarbonylmanganate*** under N_2 atmosphere (eq 1).[1,6,7] (b) decarbonylation of pentacarbonylacetylmanganese; not used on a preparative scale, but often the method of choice for synthesis of analogous alkyl- and arylmanganese complexes.

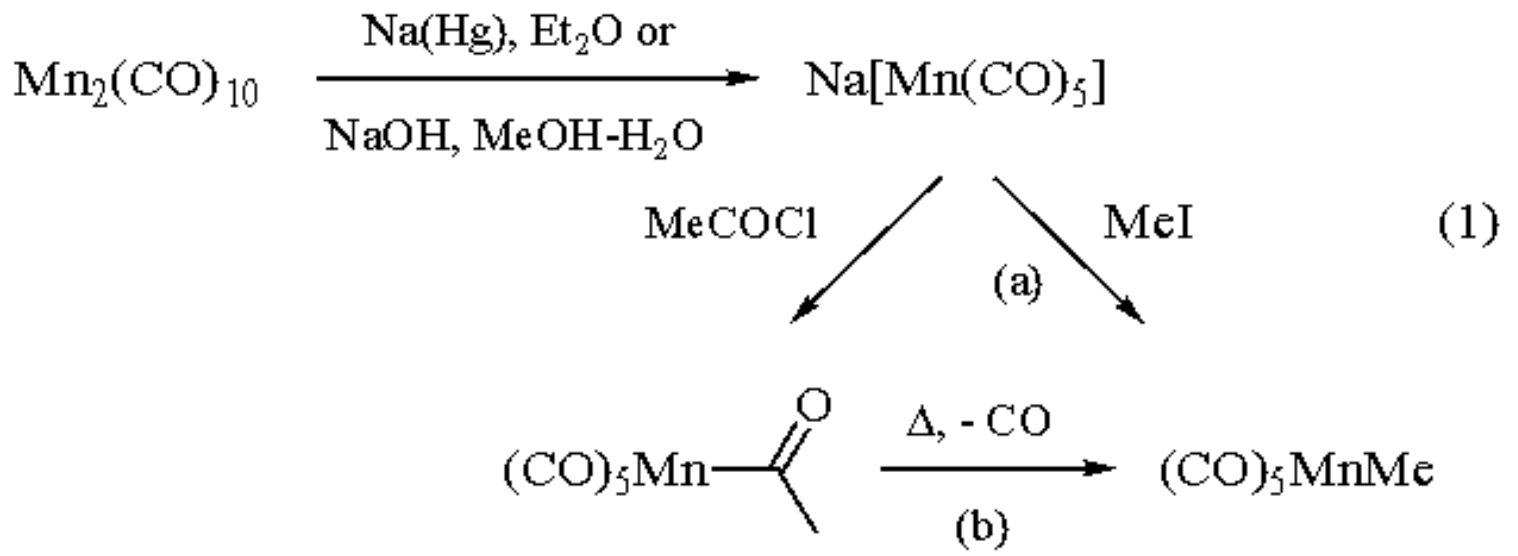

Purification: sublimation (25-40 °C/0.1 mmHg).

Handling, Storage, and Precautions: slightly light sensitive; may be handled in air, but decomposes upon prolonged exposure to oxygen. Indefinitely stable when stored as a solid in the absence of air at -20 °C. While no information concerning this compound is available, one should assume that metal carbonyls are

highly toxic; since this is a volatile solid (vapor pressure ~2 mmHg at 20 °C),[6] extra care should be taken to avoid exposure. Use in a fume hood.

Migratory Insertion Reactions: Alkyl Carbonylation.

$(CO)_5MnMe$ was employed in seminal studies elucidating the mechanism of migratory insertion reactions of alkyl ligands to coordinated CO.[3,4,8-12] Stereochemical and labeling experiments demonstrated (a) that the methyl group migrates to an adjacent CO, opening a *cis* coordination site, and (b) that the coordinatively unsaturated intermediate is a configurationally stable square pyramid in the absence of a coordinating solvent.[4,13] The process is faster in polar solvents than nonpolar ones, consistent with the formation of solvent-bound species,[14,15] although recent flash photolysis experiments suggest the intermediacy of an η^2-coordinated acyl moiety.[16] The migratory insertion step is accelerated by Lewis[17-20] or Brønsted[21] acids. Thermochemical measurements have been reported,[20] and the reaction has been subjected to theoretical analysis.[19,22-26] The Mn-Me bond dissociation energy is 44.7 ± 1 kcal mol^{-1}.[27]

Much of the synthetic chemistry of pentacarbonylmanganese alkyl compounds derives from the trapping of the coordinatively unsaturated acyl intermediate $(CO)_4Mn(COR)$ produced from migratory insertion. Addition of simple donor ligands such as phosphine or CO provide good yields of acyl complexes (eq 2). In addition to the processes outlined below, the following miscellaneous trapping agents have been reported (product type in parentheses): a W&tbond;C triple bond (bridging dinuclear acyl-carbyne complex),[28] various metal hydrides (metal-metal bound dinuclear complexes,[29] including those bearing an η^1-coordinated aldehyde resulting from formylation of the starting alkyl);[30] Ph_2PSiMe_3 (metallacyclic α-silyloxymanganese phosphide complex);[31,32] and chiral and achiral germyl anions, R_3GeLi, or $Mn(CO)_5^-$ (*cis*-tetracarbonylacyl complexes bearing Mn-Ge or Mn-Mn bonds, leading to Fischer carbene compounds).[33-35]

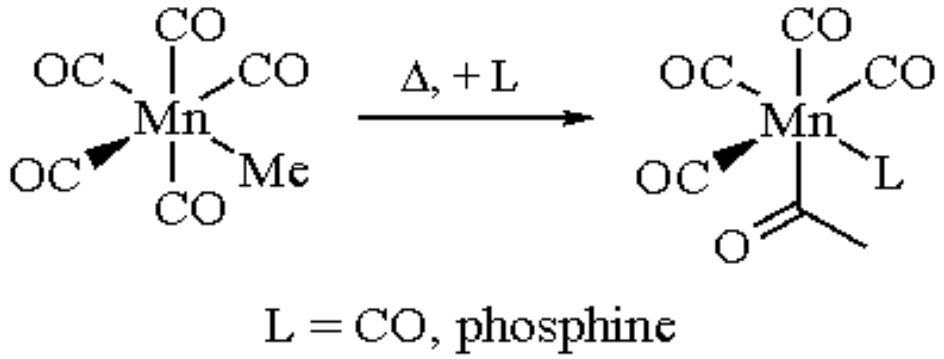

(2)

Hydroacylation of Alkenes and Alkynes: Sequential CO/Alkene or CO/Alkyne Insertion.

Electron-deficient or strained alkenes are metalloacylated by exposure to $(CO)_5Mn$-alkyl complexes under high pressure (2-10 kbar; eq 3).[2,36-40] Alkynes undergo a similar reaction, sometimes at ambient pressure (eq 4).[39,41,42] Advantages include: (1) no β-elimination is observed; (2) multiple insertion of alkenes and alkynes does not occur; (3) addition is regiospecific for terminal (R^2 = H) or trimethylsilyl-substituted ($R^2 = SiMe_3$) alkynes;[41] and (4) demetalation is accomplished under mild oxidative (replacing Mn with H), acidic (Mn -> H), or reductive

conditions.[42,43] Yields are low for sterically hindered alkenes. ^{55}Mn NMR chemical shifts have been used to characterize the products and predict reactivity.[40,42-44] The alkene insertion methodology has been used in the synthesis of spiroacetal systems present in natural products[39,40] and in the elaboration of glycosyl halides.[45]

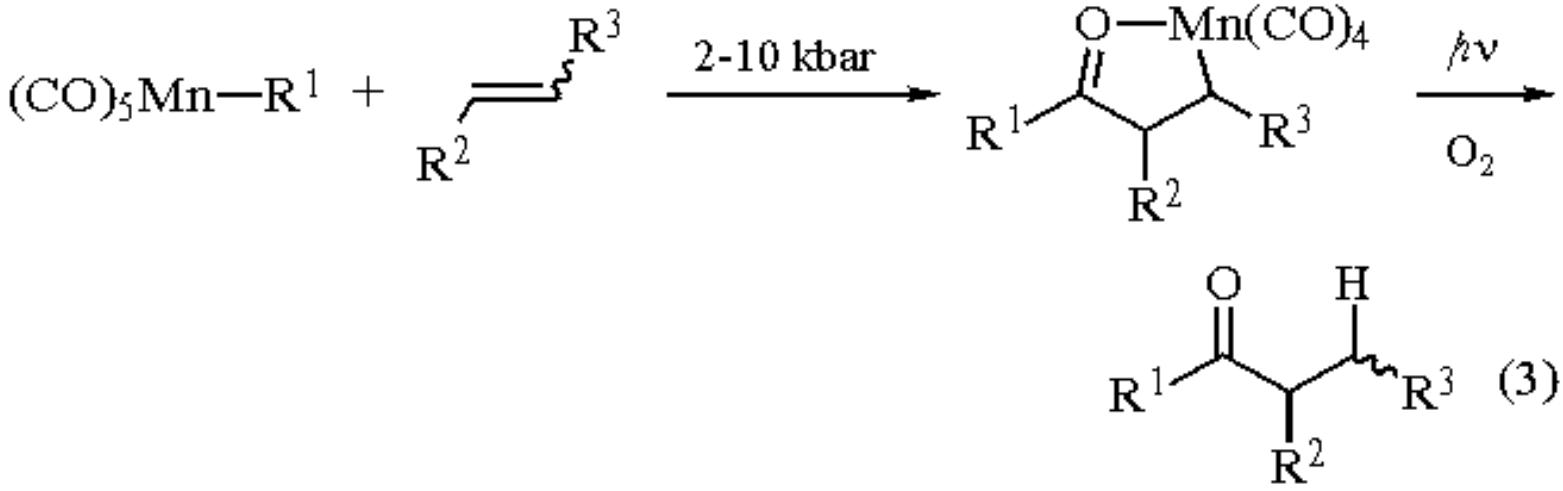

(3)

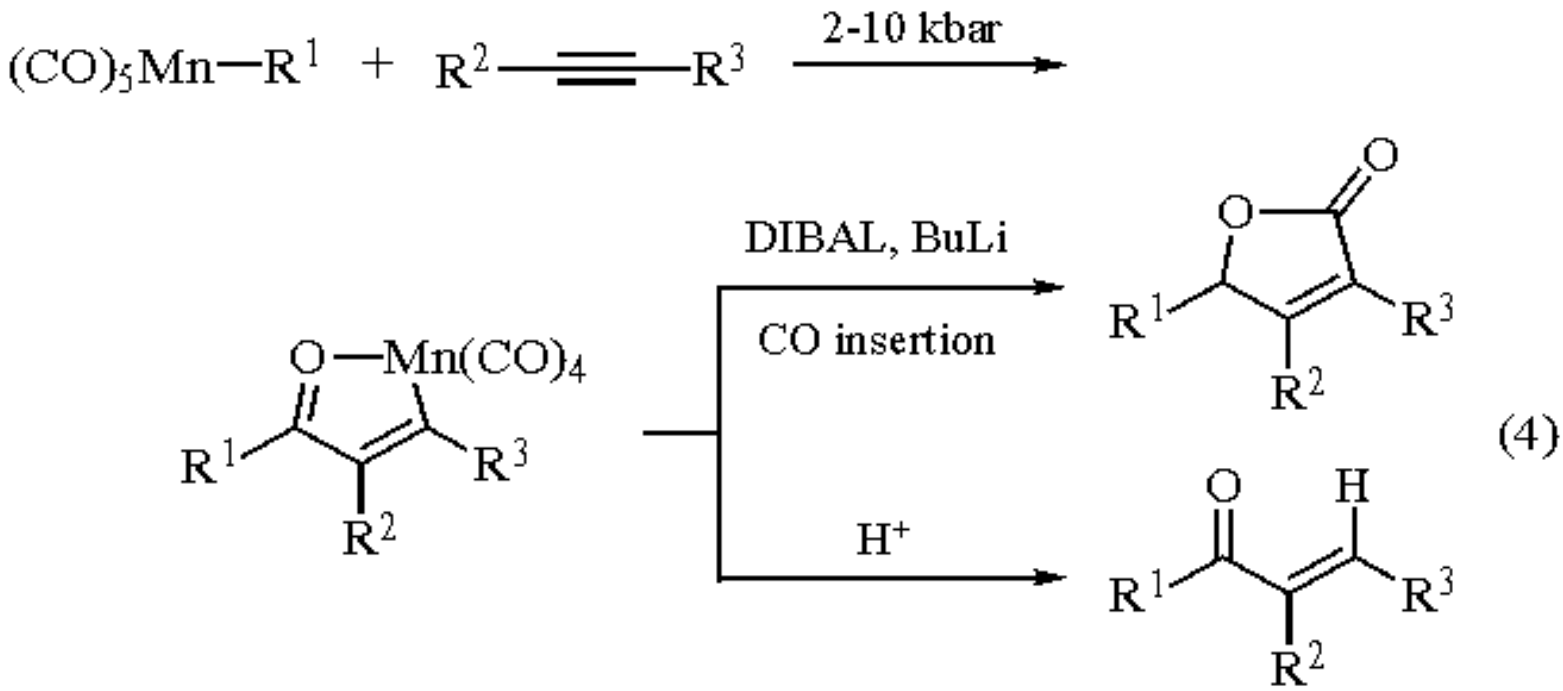

(4)

Cyclometalation.

Aromatic imines and ketones, when treated with $(CO)_5$MnMe, are metalated *ortho* to the directing group with loss of methane and carbon monoxide (eq 5).[5,41,46-48] The same types of cyclometalated ketone are available from $(CO)_5$MnR and ***Diphenylmercury*** (R = alkyl).[48] The products are stable in air and may be purified by column chromatography.

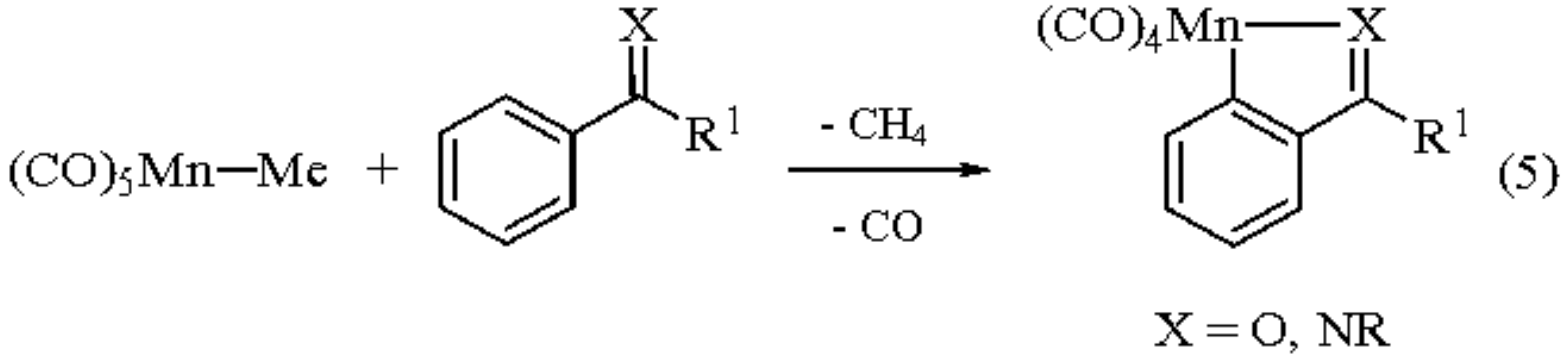

Methyl Transfer.

Reaction with the highly nucleophilic $Fe(CO)_4^{2-}$ dianion results in clean transfer of Me^+ from manganese to iron, giving $MeFe(CO)_4^-$ and $Mn(CO)_5^-$.[49]

Protonolysis.

Alkanes may be liberated from pentacarbonylmanganese alkyls by protonation with strong acids.[50]

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Pentacarbonylphenylmanganese

$(CO)_5MnPh$

[13985-77-8] · $C_{11}H_5MnO_5$ · Pentacarbonylphenylmanganese · (MW 272.10)

(undergoes migratory insertion of CO into metal-aryl bonds;[1] can acylate alkynes and alkenes[2])

Physical Data: white crystals; mp 51-52 °C.

Solubility: sol organic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: IR (CCl_4, cm^{-1}) 2115 (m), 2019 (vs), 1997 (s);[2] (KBr, cm^{-1}) 2126 (w), 2058 (m), 2015 (vs).[3]

Preparative Methods: decarbonylation of $(CO)_5MnCOPh$ by heating under N_2 atmosphere (eq 1), either in situ or after isolation of the acyl complex.[2-5] The complex is also available in 93% yield from irradiation (254 nm) of ***Decacarbonyldimanganese*** and ***Diphenylmercury*** in cyclohexane/THF solvent.[6]

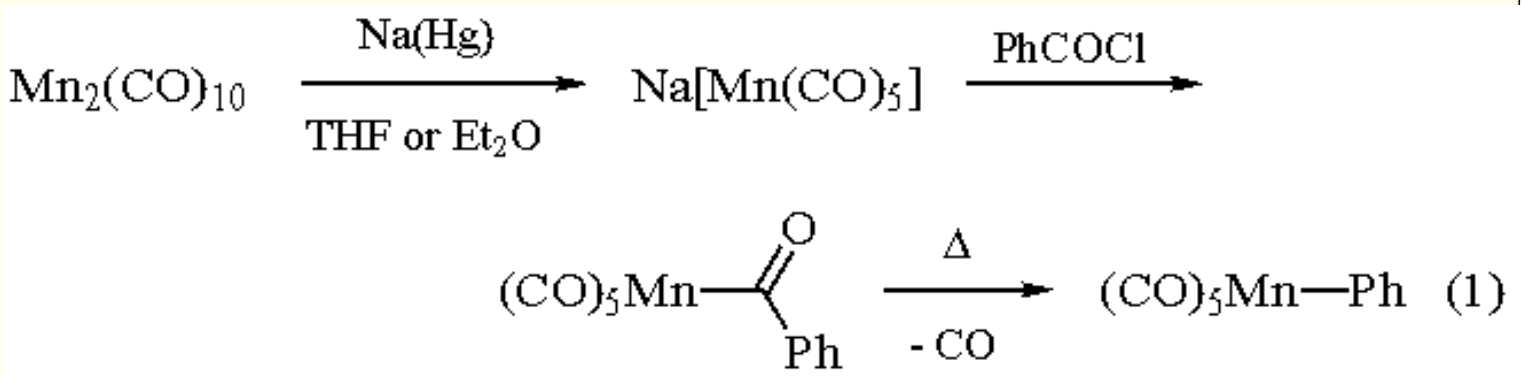

Purification: sublimation (25-40 °C/0.1 mmHg); recrystallization from pentane, hexane, or light petroleum ether; column chromatography on silica gel with hexane. Complexes bearing electron-donating substituents on the aromatic ring (*p*-Me, *p*-OMe) are apparently less stable to chromatography than the parent or electron-deficient (*p*-Cl) compounds.[6]

Handling, Storage, and Precautions: may be handled in air, but decomposes upon prolonged exposure to oxygen. Indefinitely stable when stored as a solid in the absence of air at -20 °C. While no information concerning the toxicity of this compound is available, one should assume that metal carbonyls are highly toxic; since this is a volatile solid (vapor pressure ~2 mmHg at 20 °C), extra care should be taken to avoid exposure. Use in a fume hood.

Migratory Insertion Reactions: Aryl Carbonylation.

Much of the synthetic chemistry of pentacarbonylmanganese aryl compounds derives from the trapping of the coordinatively unsaturated acyl intermediate $(CO)_4Mn(COR)$ produced from migratory insertion. In the absence of added ligand the pentacarbonyl aryl complex is favored, but the addition of simple donor ligands such as phosphine or phosphite provides good yields of *cis*-substituted acyl complexes (eq 2).[1,4,7] The migratory insertion step is assisted by polar solvents.[8] In addition to the processes outlined below, the following miscellaneous trapping agents have been reported (product type in parentheses): Ph_2PSiMe_3 (metallacyclic α-silyloxymanganese phosphide complex);[9,10] chiral and achiral germyl anions, R_3GeLi, or $Mn(CO)_5^-$ (*cis*-tetracarbonylacyl complexes bearing Mn-Ge or Mn-Mn bonds, leading to Fischer carbene compounds).[11-13] Substitution of a *cis*-CO ligand without aryl migratory insertion may be achieved by the addition of *N*-oxides.[7]

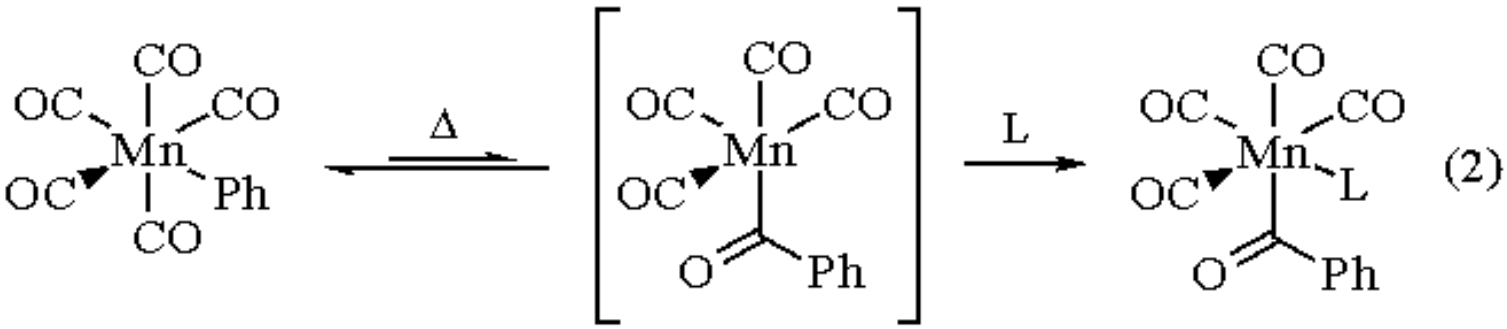

Acylation of Alkenes and Alkynes: Sequential CO/Alkene or CO/Alkyne Insertion.

The interception of coordinatively unsaturated aromatic acyl intermediates with alkenes has been reported for a few cases. Dicyclopentadiene affords β-benzoyl alkyl complexes stabilized by intramolecular coordination of the ketone oxygen.[14] The use of dienes gives rise to η^3-ketoallyl products (eq 3).[15] Under photolytic conditions, CO is ejected and alkene insertion directly into the Mn-Ph bond is observed (eq 4).[16] Interestingly, cycloheptatrienes afford noncarbonylated η^5-pentadienyl products from a similar alkene insertion process upon heating.[17]

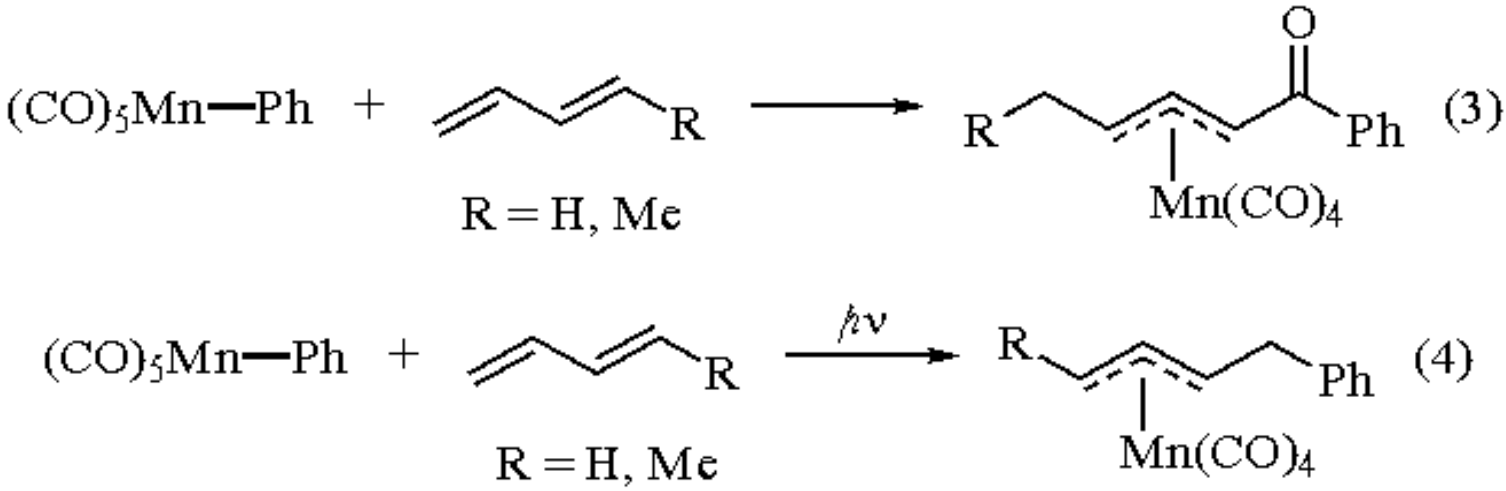

Alkynes are also acylated by $(CO)_5$Mn-aryl complexes, although this reaction has not been used as frequently as the analogous reactions of $(CO)_5$Mn-alkyls (eq 5).[2,18,19] Demetalation is accomplished under mild acidic (replacing Mn with H) or reductive conditions.[2,19,20]

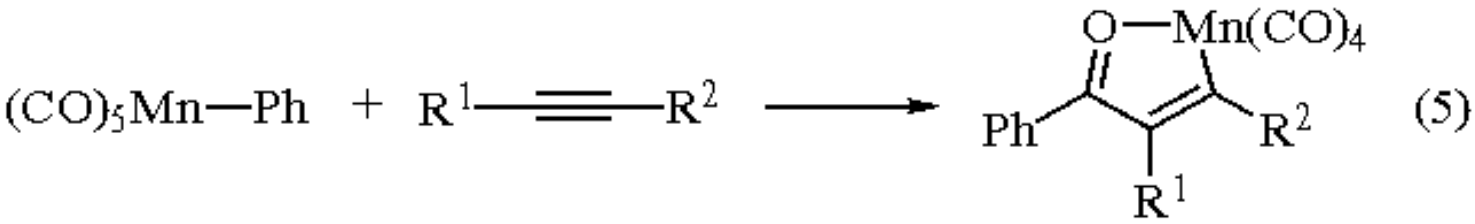

Cyclometalation.

Aromatic imines and ketones, when treated with $(CO)_5$MnPh, are metalated *ortho* to the directing group (see ***Pentacarbonylmethylmanganese***).[21,22] The same type of cyclometalated ketones are available from $(CO)_5$Mn-R and Ph_2Hg (R = alkyl).[6] The products are stable in air and may be purified by column chromatography.

Protonolysis.

Arenes may be liberated from pentacarbonylmanganese alkyls by protonation with strong acids.[23]

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Pentacarbonyl(trimethylsilyl)manganese[1,2]

$(CO)_5MnSiMe_3$

[26500-16-3] · $C_8H_9MnO_5Si$ · Pentacarbonyl(trimethylsilyl)manganese · (MW 268.20)

(carbon-carbon bond formation with strained cyclic ethers by ring opening followed by CO insertion;[1,3] synthesis of enol ethers from acetals;[2] can add to aldehydes and ketones[2]).

Physical Data: white crystals; mp 26.5 °C;[3] 25.6-26.2 °C.[4]

Solubility: sol most organic solvents.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: IR (cyclohexane, cm^{-1}) 2094 (w), 2000 (s), 1993 (vs); NMR (cyclohexane, δ) 0.49 ppm.[4]

Preparative Methods: [3-5] (a) a suspension of $KMn(CO)_5$ in pentane is stirred with ***Bromotrimethylsilane*** for two days at rt to afford $(CO)_5MnSiMe_3$ in 60-80% yield after purification (eq 1);[3] a similar reaction with ***Chlorotrimethylsilane*** gives a lower yield.[4] (b) The desired product is obtained in 70% yield by heating Me_3SiH and ***Decacarbonyldimanganese*** without solvent for 48 h at 132 °C.[4] (c) Heating Me_3SiH and $HMn(CO)_5$ in similar fashion to method (b) provides $(CO)_5MnSiMe_3$ in 23% yield.[4]

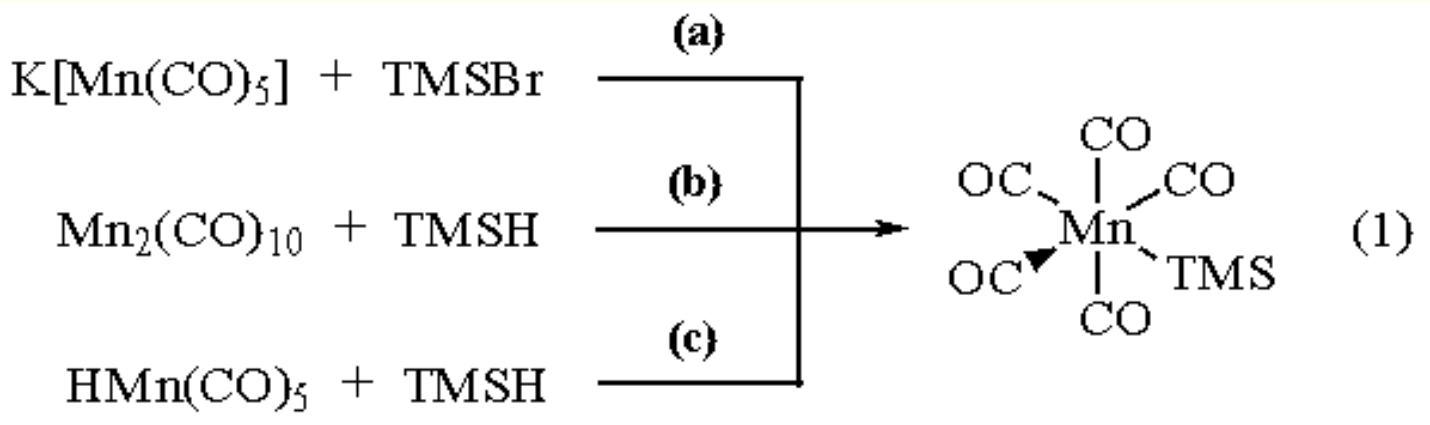

The related compound $(CO)_5MnSi(t\text{-}Bu)Me_2$ is obtained by treating ethereal solutions of $NaMn(CO)_5$ with ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** and is used in situ.[6]

Purification: by sublimation or vacuum line transfer at ambient temperature.

Handling, Storage, and Precautions: the solid may be handled in air; upon prolonged exposure, it oxidizes to a brown material and should therefore be stored under inert atmosphere. Solutions of $(CO)_5MnSiMe_3$ react readily with water, giving $HMn(CO)_5$ and $Me_3SiOSiMe_3$. While no information concerning the toxicity of this compound is available, one should assume that metal carbonyls are highly toxic; since this is a volatile solid, extra care should be taken to avoid exposure. Use in a fume hood.

Ring Opening of Cyclic Ethers.

Much of the chemistry of $(CO)_5$Mn-silyl compounds derives from the apparent heterolysis of the Mn-Si bond, making available a combination of Lewis acidic (SiR_3^+) and nucleophilic ($Mn(CO)_5^-$) moieties. Thus exposure to ***Trimethylamine*** immediately gives the salt $[Me_3N\text{-}SiMe_3]^+[Mn(CO)_5]^-$.[4] More useful examples are provided by the ring opening of strained cyclic ethers to give manganese alkyls in good to excellent yields by treatment with $(CO)_5$Mn-silyl complexes under moderate pressures of CO (eq 2).[1,3,4,7] The insertion is regioselective, with the manganese fragment ending up on the less-hindered carbon (one isomer for epoxides; 10:1 ratio for 2-methyltetrahydrofuran).[6] The reaction mechanism is thought to involve interaction of the ether oxygen with Me_3Si^+, followed by attack of $Mn(CO)_5^-$ on a C-O bond.[4]

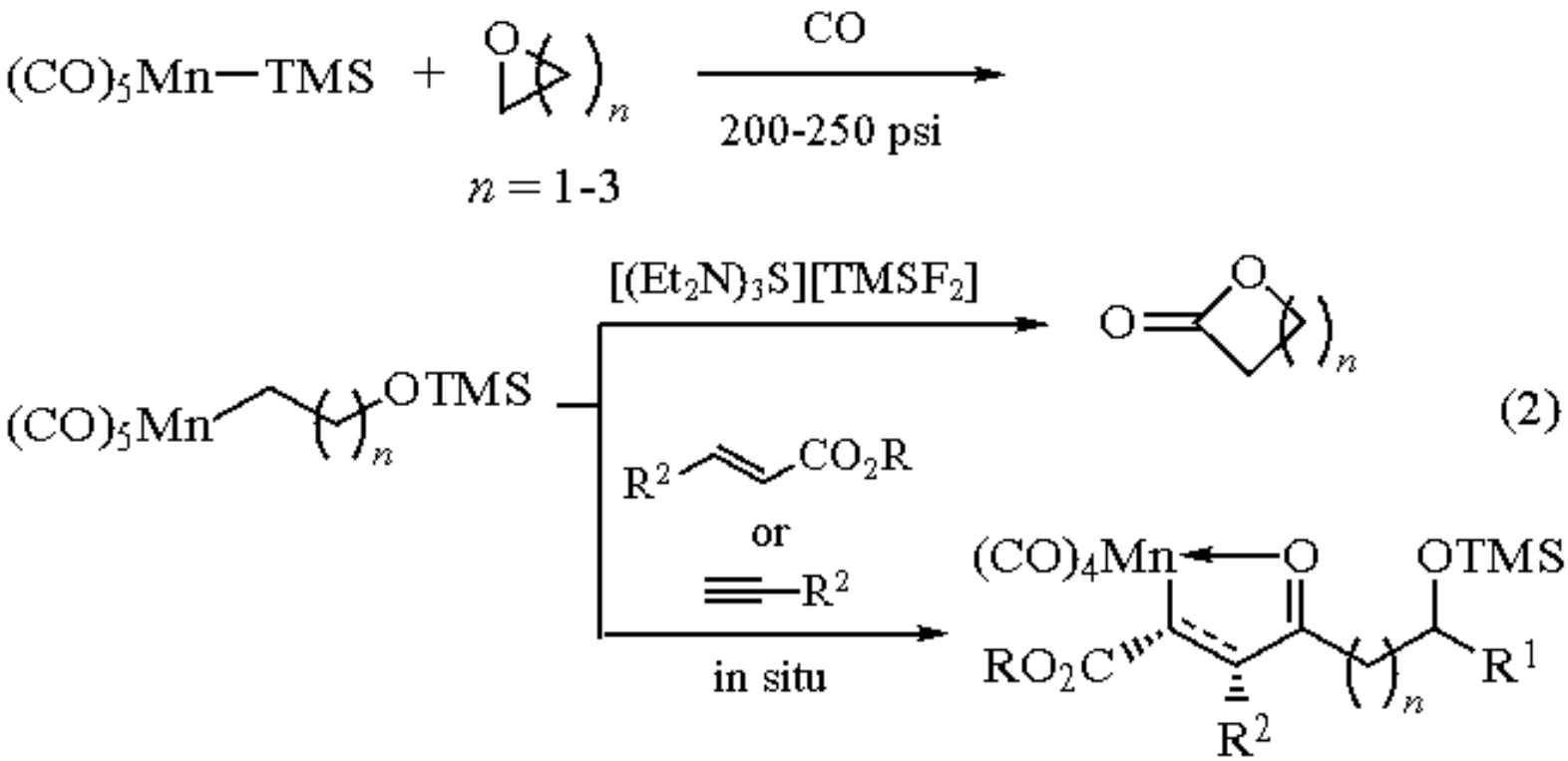

(2)

When performed in the presence of alkynes or activated alkenes, products derived from the sequential insertion of CO and the unsaturated substrate into the Mn-C single bond are obtained in good to excellent yields (eq 2; see ***Pentacarbonylmethylmanganese***).[8] This methodology has been employed in the efficient synthesis of spiroacetal systems.[6,8] Alternatively, carbonylation may be followed by desilylation to produce lactones.[2]

Conversion of Acetals to Vinyl Ethers.

Treatment of acetals with $(CO)_5MnSiMe_3$ under mild conditions affords vinyl ethers (eq 3).[2,9,10] Mixtures of (*E*)- and (*Z*)-isomers are produced under thermodynamic control, consistent with the mechanism shown in eq 3. Related reagents are *cis*-$(CO)_4Fe(SiMe_3)_2$ and $(CO)_4CoSiMe_3$.[2]

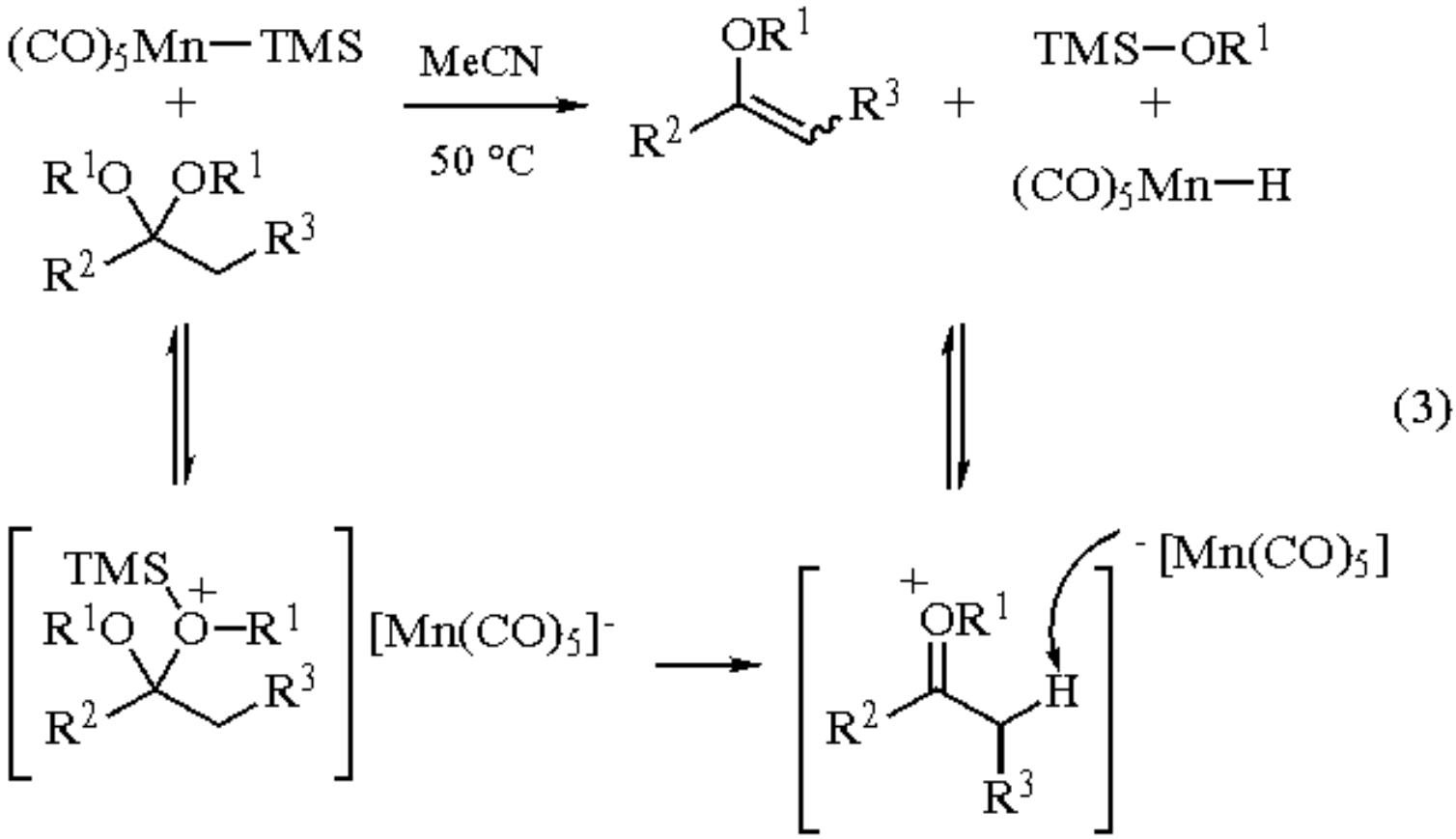

(3)

Reductive Silylation of α-Halocarbonyl Compounds.

Silyl enol ethers and silyl ketene acetals are available from $(CO)_5MnSiMe_3$ and aromatic α-halo ketones or α-halo esters bearing simple aromatic and aliphatic substituents (eqs 4 and 5).[2,11] The tolerance of the reaction to more sensitive functionality has not been explored.

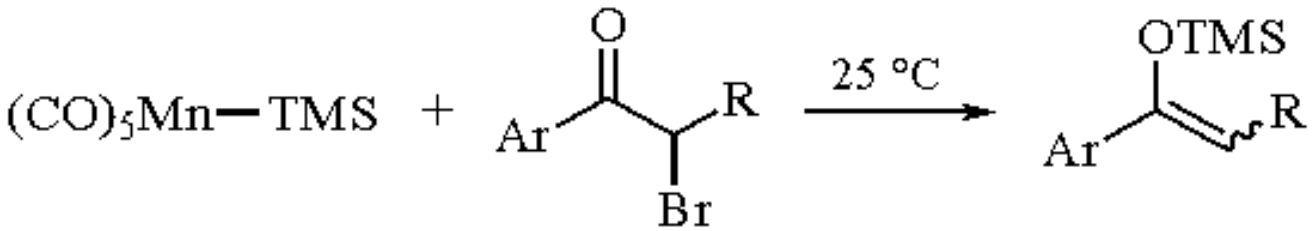

(4)

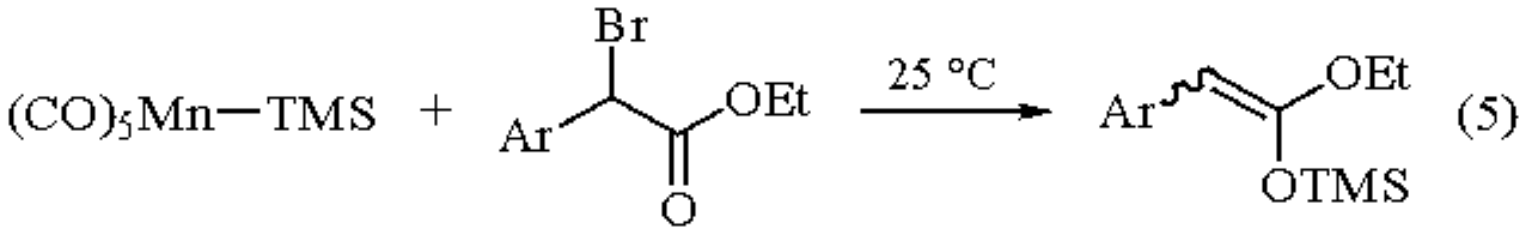

Addition to Aldehydes and Ketones.

The facile addition of $(CO)_5Mn\text{-}SiMe_3$ across the carbonyl of aldehydes and ketones has been observed. The α-siloxymanganese alkyl intermediates may undergo CO insertion under CO pressure to give α-silyloxyacyl complexes, reductive coupling upon heating to give 1,2-diol TMS ethers, or β-hydride elimination to give silyl enol ethers (eq 6).[1,2,7,12] Yields for the first pathway range from 26-72% for a selection of alkyl, aryl, and vinyl aldehydes,[12] and are improved if the reaction is performed in the presence of $(CO)_5MnH$.[1] β-Hydride elimination is rapid for ketones.

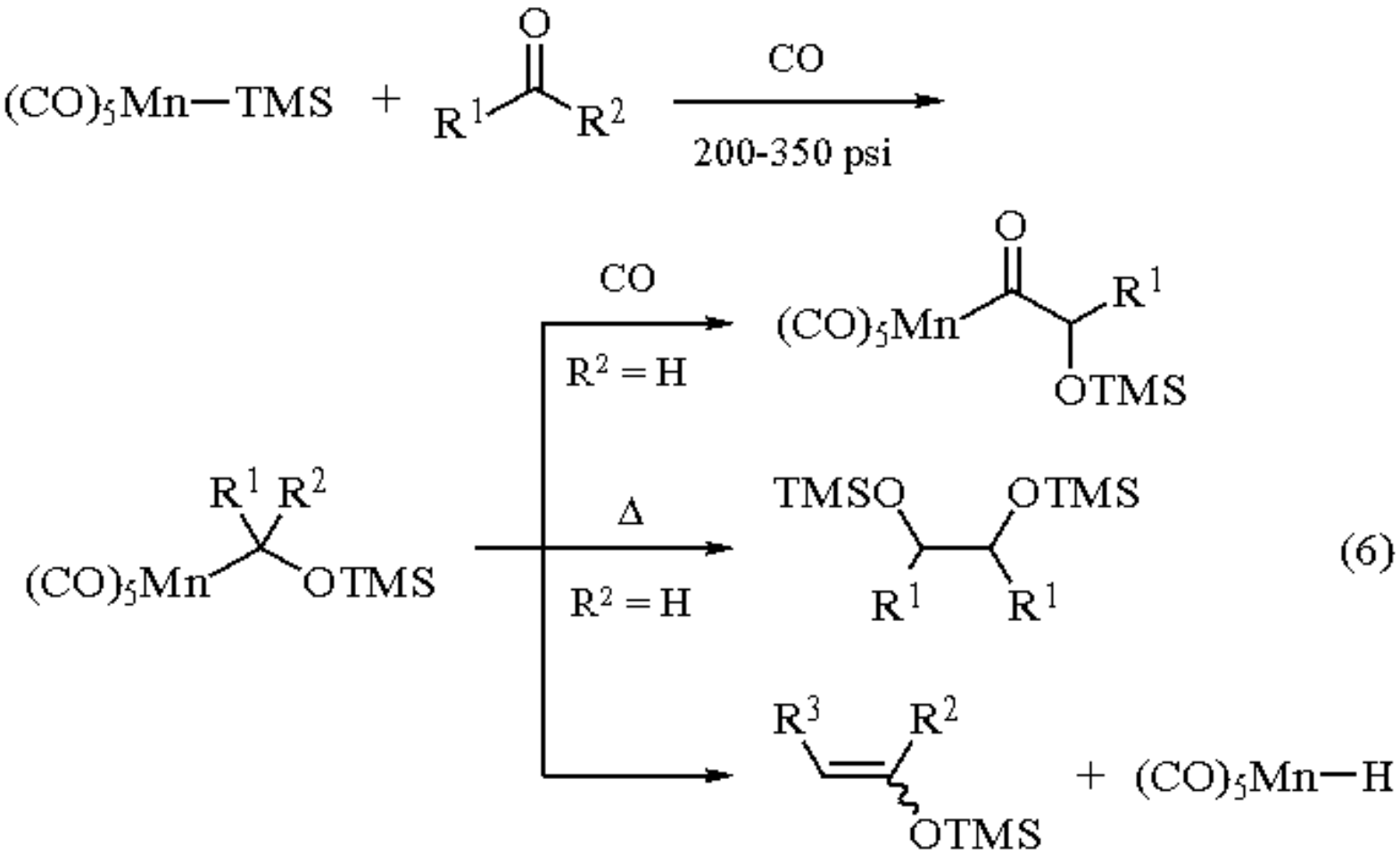

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Pentachlorophenol

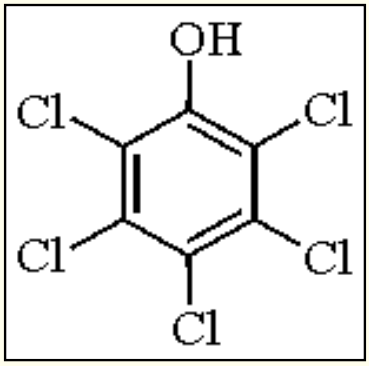

[87-86-5] · C_6HCl_5O · Pentachlorophenol · (MW 266.32)

(coupling reagent in peptide synthesis, to form active esters; a probe in various NQR studies on pentachlorophenol-amine hydrogen bonded complexes;[1] a standard in GC analysis[2]

Physical Data: mp 188-191 °C (anhyd); bp 310 °C; *d* 1.978 g cm^{-3}.

Solubility: sol ether, alcohol, hot benzene, ligroin; insol H_2O.

Form Supplied in: widely commercially available.

Purification: recrystallize from alcohol (monoclinic prisms) or benzene (needles) and vacuum dry.

Handling, Storage, and Precautions: highly toxic and possible teratogen. May be fatal if inhaled, swallowed, or absorbed through the skin. Causes skin and eye irritation and irritation to the mucous lining of respiratory tract. Do not breathe dust; avoid prolonged exposure. Readily absorbed through the skin. Incompatible with strong oxidizing agents, strong bases, acid chlorides, and anhydrides. More basic in organic solvents. Store in a cool dry place. There are concerns as to its environmental chemical effects.[2,3]

Polypeptide Synthesis.

The most important stage in peptide synthesis is the coupling step of one amino acid or peptide to another. Coupling reagents have been proposed following early attempts at coupling because of their inherent convenience. These generally work by peptide bond formation between a carboxyl and an amine component in the presence of a specific condensing or coupling agent. In the late 1950s and early 1960s, considerable effort was made to synthesize polypeptides with a known repeating sequence of amino acids. The problem until then with the more traditional methods[4a,b] (e.g. mixed anhydrides and the ***1,3-Dicyclohexylcarbodiimide*** method) was undesirable side reactions[4] which could lead to early termination of polymerization; in addition, various other methods which avoid this, e.g. thiophenyl and *p*-nitrophenyl esters, may not be used when *N*-protecting groups are removed by catalytic

hydrogenation.[4,5] The use of pentachlorophenyl esters was first fully reported in 1965[6] although there had been brief references to their use before then.[7a,b]

The use of pentachlorophenyl active esters in the synthesis of polypeptides of known repeating amino acid sequence has several advantages:

- 1)Pentachlorophenyl esters work particularly efficiently when coupled with benzyloxycarbonyl and *t*-butyl protecting groups in trifunctional amino acids for polymerization, e.g. a protecting *N*-Cbz group is selectively cleaved by catalytic hydrogenation,[6] leaving pentachlorophenyl and *t*-butyl groups intact. Compare HBr cleavage of the Cbz group which would prevent the use of *t*-butyl groups (*t*-butyl groups are essential when utilizing aspartic or glutamic acids to prevent *trans*-peptidation reactions).
- 2)Pentachlorophenyl esters of both amino acids and peptides tend to be easier to purify since they generally have higher melting points compared to other active esters. This assists in the purification of *C*- or *N*-activated peptide intermediates which must be very pure in polymerization to avoid early termination reactions. Table 1[8] gives some illustrative examples of this, along with melting point values of other active esters for comparison.

Table 1 Peptide Active Esters

Active ester derivative	OC_6Cl_5 mp (°C)	$OC_6H_2Cl_3$ mp (°C)	$OC_6H_4NO_2$ mp (°C)
Cbz-Ala	172-173	104	78
Cbz-Val	144	94	66
Cbz-Gly	185	107-108	128
Cbz-Phe	158	142	126
Cbz-Glu-O-*t*-Bu $NH(CH_2)_2CO_2H$	151	96	56-57

Given these requirements, pentachlorophenyl esters give polypeptides of higher molecular weights than those obtained by other methods, as determined by end-group analysis and viscometry.

Pentachlorophenyl active esters are amongst the most reactive esters, e.g. aminolysis of Cbz-L-phenylalanine pentachlorophenyl ester has a half life of 1.34 min on treatment with benzylamine in dioxane; cf. the half life of the 2,4,5-trichlorophenyl ester which is 4.9 min and the *p*-nitrophenyl ester which is 23.2 min.[8] This short reaction time limits the time available for side reactions to occur during coupling reactions.

The first cited example of pentachlorophenyl esters being utilized was in the synthesis of poly-β-L-aspartic acid.[9] This polymer was required in optically pure form for various chemical, biological, and immunochemical investigations.[10] In summary, the coupling of the amino acid with pentachlorophenol using the DCC method (see below) gives an active ester which polymerizes rapidly in the presence of a tertiary amine to give a poly(amino acid) of higher molecular weight than is obtained using other methods, notably the *p*-nitrophenyl ester.

Another example is the synthesis of poly-β-L- (or -D-) glutamyl-β-alanine[11] (**3**) from the precursor α-*t*-butylglutamyl-β-alanine pentachlorophenyl ester hydrochloride (**2**).

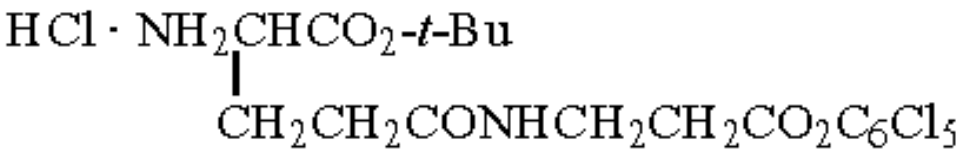

(2)

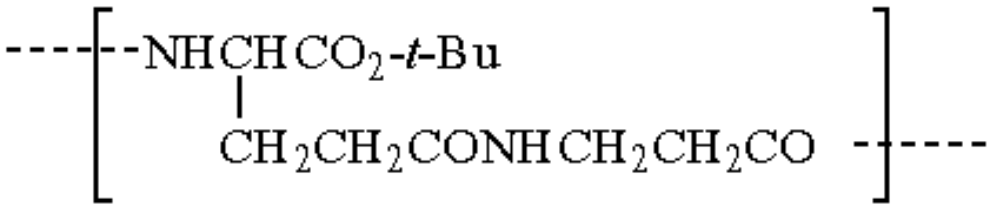

(3) R = *t*-Bu or H

The precursor (**2**) was prepared according to eq 1. *N*-Benzyloxycarbonyl-α-*t*-butylglutamic acid pentachlorophenyl ester was coupled to the methyl ester of β-alanine to give (**4a**). This was hydrolyzed using NaOH to give the free acid (**4b**) which was subsequently coupled to pentachlorophenol with DCC to give *N*-benzyloxycarbonyl-α-*t*-butylglutamyl-β-alanine pentachlorophenyl ester (**4c**; 60% yield, >97% optically pure). The same method was used to prepare the 2,4,5-trichloro- (**4d**) and *p*-nitrophenyl (**4e**) esters for comparison, but the pentachlorophenyl esters immediately proved easier to purify, for the reasons already described.

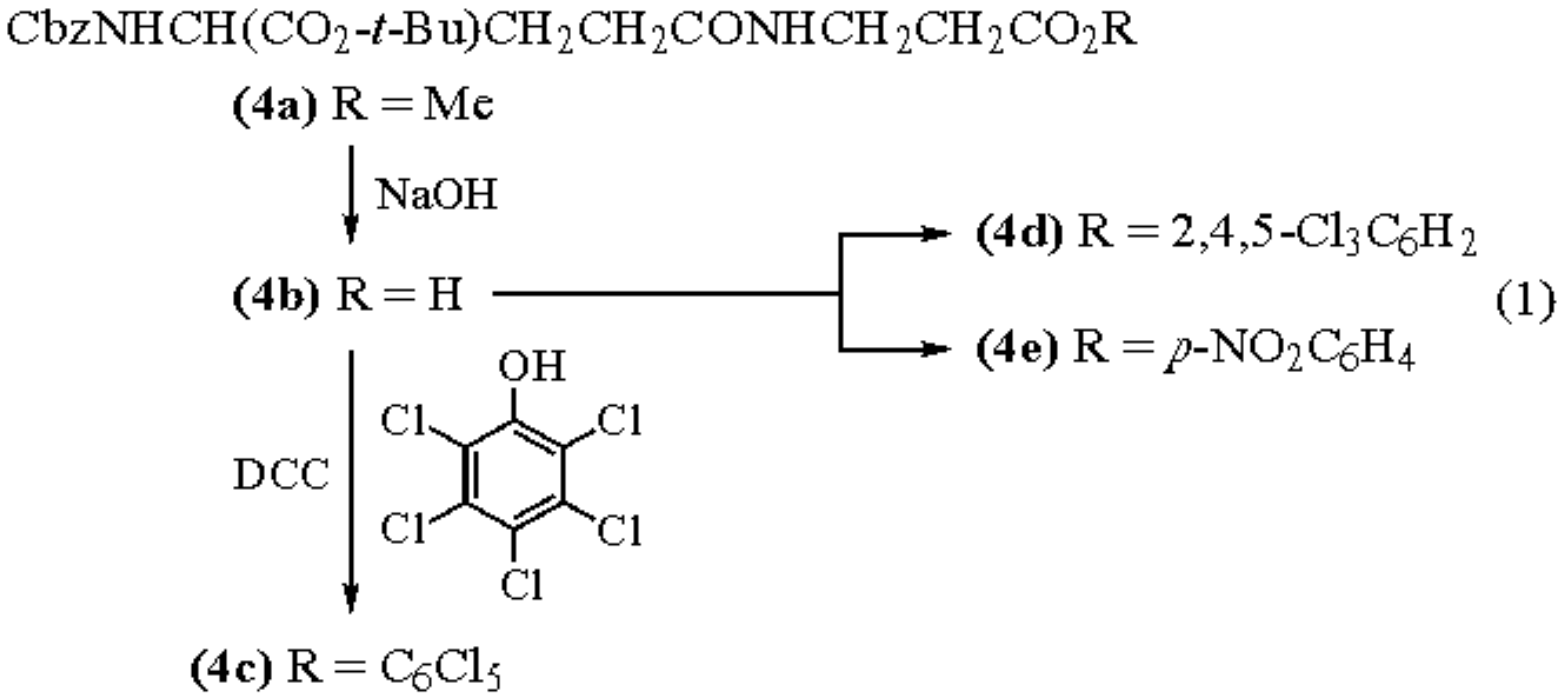

Hydrogenation of (**4c**) using 10% ***Palladium on Carbon*** catalyst in the presence of HCl in methanol gave (**2**) in good yield (59%). Polymerization in DMF with an excess of ***Triethylamine*** at the highest possible concentrations gave (**3**) with *t*-Bu protecting groups which were readily removed with 90% ***Trifluoroacetic Acid*** to give the free polypeptide.

There are many other examples of pentachlorophenyl active esters being used in peptide syntheses similar to those described above, but these will not be described in detail here.[8,12a-f]

Very little by way of modification or variation in pentachlorophenyl active ester coupling procedures has occurred; they have mostly found new applications. There is, however, one exception where a different procedure has been used to prepare pentachlorophenyl esters of *N*-protected amino acids.[13] The pentachlorophenyl di- (**5**) or tri- (**6**) chloroacetates (known plant growth regulators) were prepared and subjected to ester exchange reactions with trialkylammonium salts of acylamino acids (**7**) in DMF, rapidly giving good yields of the desired esters (eq 2).

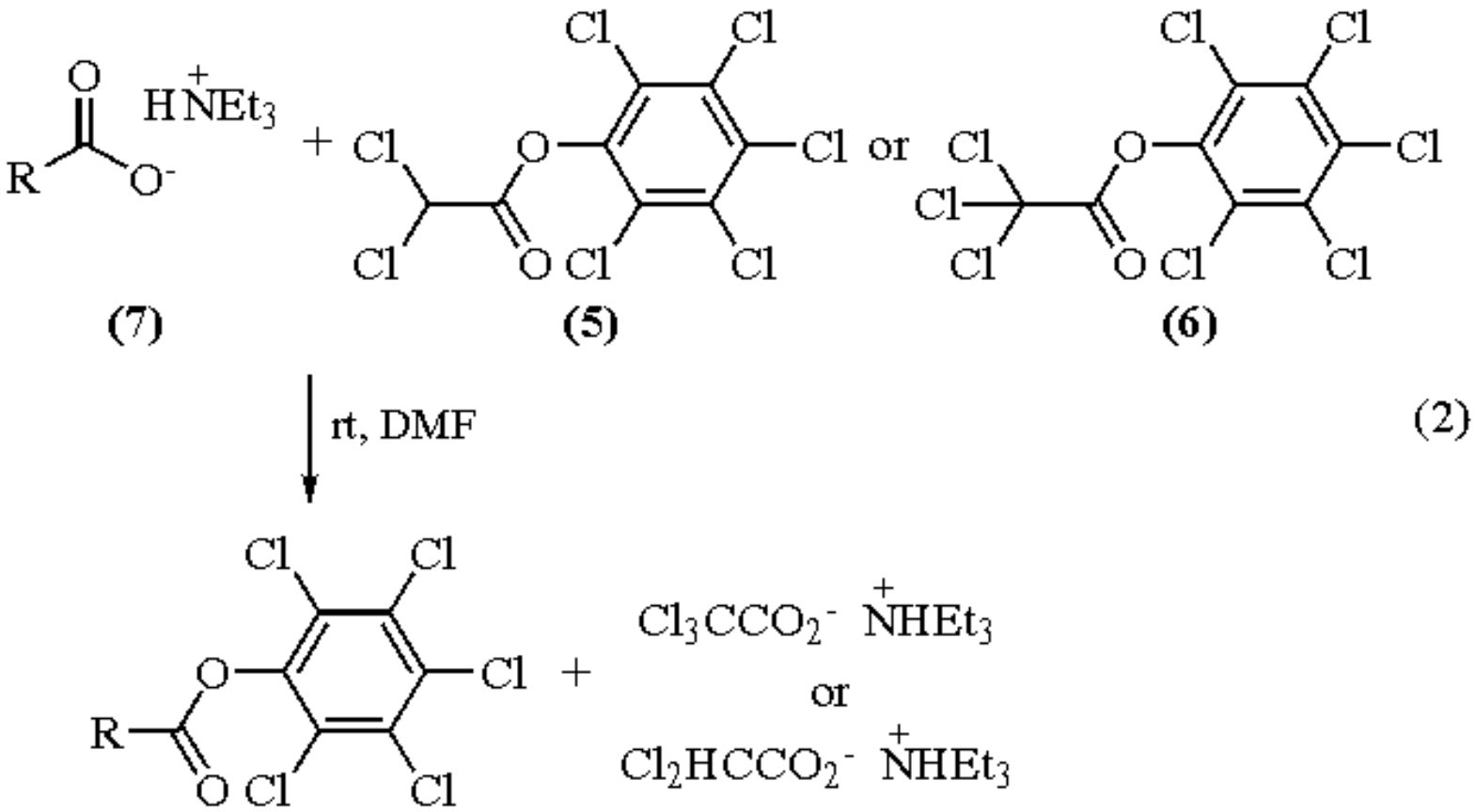

One last novel reaction which may involve pentachlorophenyl esters is the formation of polypeptides and Leuchs' anhydrides from carbamic acid derivatives of *C*-activated amino acids.[14] *C*-Activated *N*-Cbz amino acids (**8**) on catalytic hydrogenation give the carbamic acid derivative (**9**), which cyclizes to the corresponding Leuchs' anhydride (**10**) (eq 3); in some cases this immediately polymerizes to the polypeptide, e.g. the mixed anhydride *N*-Cbz-DL-phenylalanine polymerized to poly-L-phenylalanine via the Leuchs' anhydride.

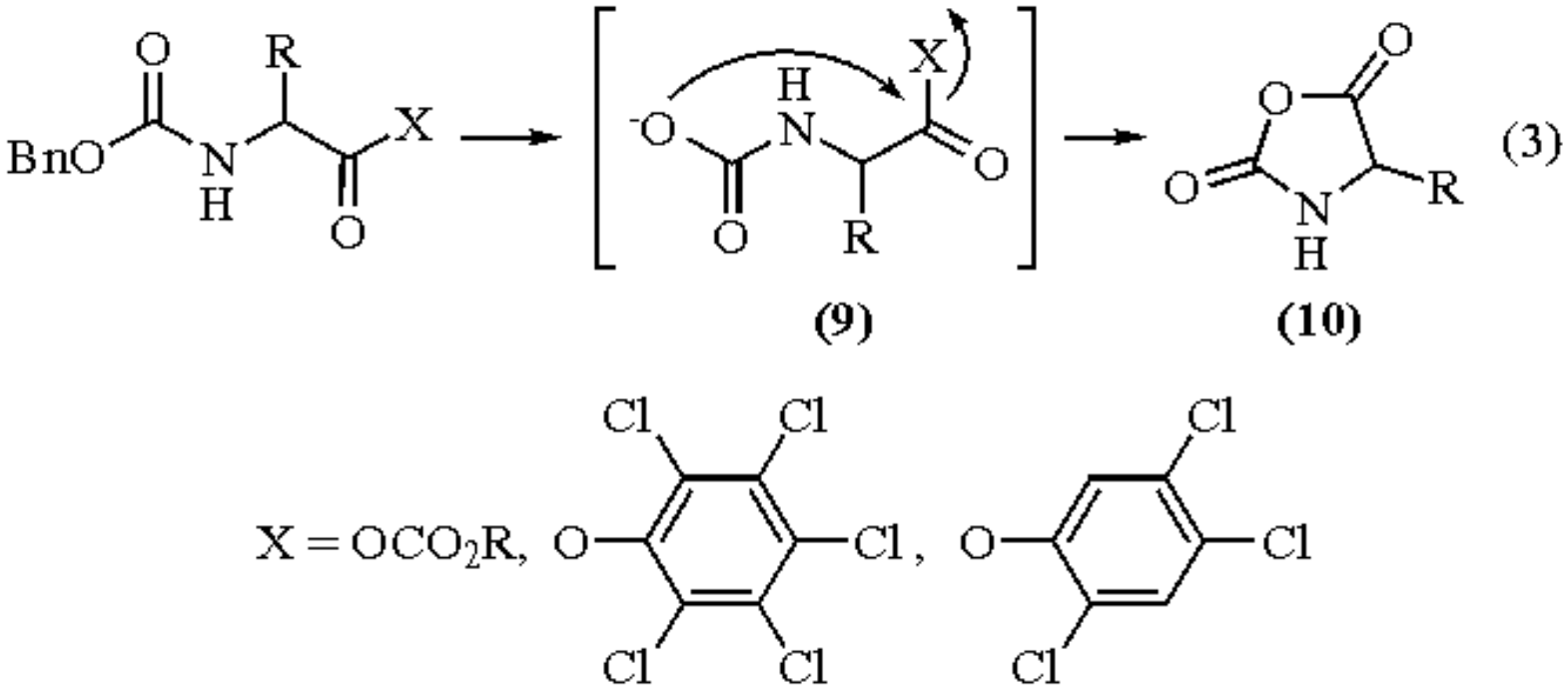

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1,3-Pentadiene

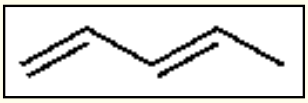

[504-60-9] · C_5H_8 · 1,3-Pentadiene · (MW 68.13) (*cis*)

[1574-41-0] (*trans*)

[2004-70-8]

(widely used diene for Diels-Alder cycloaddition reactions;[1] common ligand in transition metal-pentadienyl complexes[2])

Alternate Name: piperylene.

Physical Data: cis: mp -141 °C; bp 44 °C; *d* 0.691 g cm^{-3}. *trans*: mp -87.5 °C; bp 42 °C; *d* 0.683 g cm^{-3}. Mixture of isomers: bp 42 °C; *d* 0.683 g cm^{-3}.

Solubility: sol alcohol, acetone, ether, benzene, heptane; insol H_2O.

Form Supplied in: widely available as *cis* isomer, *trans* isomer, and as a mixture of isomers.

Purification: colorless liquid distilled from $NaBH_4$; purified by preparative gas chromatography.

Handling, Storage, and Precautions: flammable liquid, irritant.

Diels-Alder Reactions.[1]

The *trans* isomer of piperylene has been widely used in cycloaddition reactions to construct six-membered carbocyclic[3-10] and heterocyclic rings.[11-15] The electron-donating ability of the methyl group causes *trans*-piperylene to be 3-5 times more reactive than ***1,3-Butadiene*** in Diels-Alder reactions with ***Maleic Anhydride*** or ***Tetracyanoethylene*** (TCNE).[3c,4] Unlike *trans*-piperylene, the *cis* isomer is known to be very unreactive except with highly activated dienophiles, and generally undergoes polymerization reactions (eq 1).[3] In reaction with TCNE, *cis*-piperylene has been estimated to be over 10^5 less reactive than the *trans* isomer.[3c] The unfavorable steric interactions between the methyl group and the vinyl hydrogens in the *s-cis* conformation of *cis*-piperylene, required in the transition state for the Diels-Alder, are thought to be responsible for the lower reactivity.[1] Both piperylenes give predominently the *endo* Diels-Alder products.

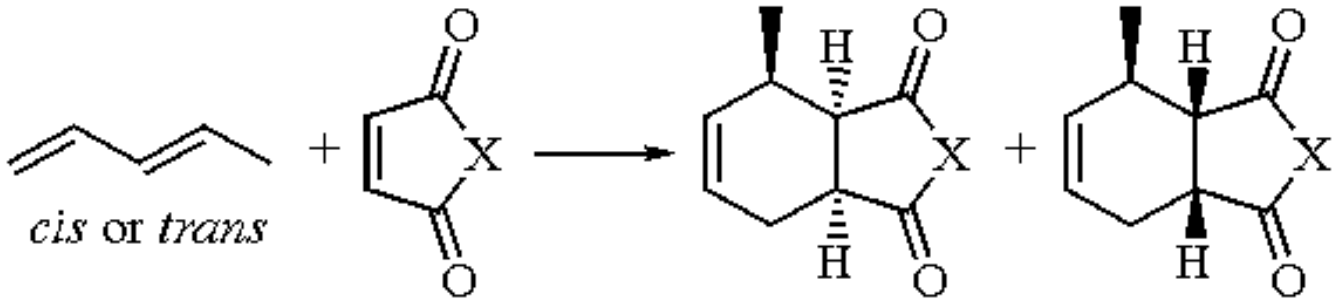

(1)

X = O	PhH, reflux 30 min	100%	-
X = NPh	PhH, reflux 1 h	100%	-
X = NMe	PhMe, reflux 18 h	87%	-

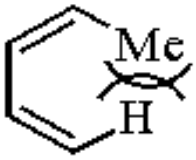

X = O	Ac_2O, 94-100 °C 8 h	-	4%
X = O	CuCl, NH_4Cl 130 °C, 2 h	9%	49%
X = NPh	CuCl, NH_4Cl 130 °C, 13 h	-	35%

As with other unsymmetrical dienes, the Diels-Alder reactions of piperylene obey the *ortho* rule,[1] which predicts that the electron-donating group will be adjacent (*ortho*) to the electron-withdrawing substituent on the dienophile (eq 2).[5] Similar selectivities are observed for ***Acrylonitrile*** and ***Acrolein***.[1,3] In general, the regio- and endoselectivities are higher at lower reaction temperatures and, especially, in the presence of Lewis acids such as ***Aluminum Chloride***.[6]

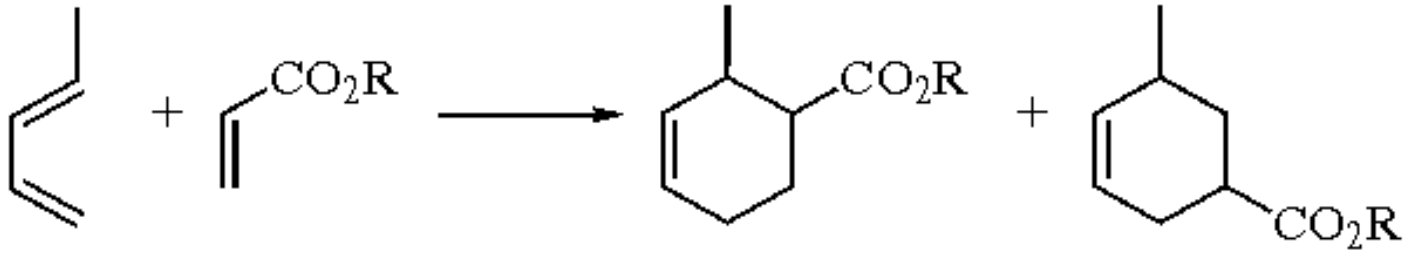

(2)

(1) **(2)**

		(1) (*cis*/*trans*):**(2)** (*cis*/*trans*)
R = H	120 °C, 7 h, 52%	89 (64/36):11 (62/38)
R = Me	120 °C, 6 h, 53%	84 (54/46):16 (66/34)
R = Me	25 °C, 70 d, 39%	90 (57/43):10 (73/27)
R = Me	10-20 °C, $AlCl_3$ (cat), 3 h, 50%	98 (95/5) :2 (mostly *cis*)

The reactions with more complex dienophiles have shown similar regio- and endoselectivities.[6] The cycloadditions between *trans*-1,3-pentadiene and substituted quinones give products with high endoselectivity and with expected regiochemistry based on electronic considerations (eqs 3 and 4).[7,8] A remarkable reversal in regioselectivity was achieved for 2,6-dimethylbenzoquinone by using a Lewis acid for the reaction (eq 4).[8] In the cycloadditions with a substituted 2,5-cyclohexadienone, exclusive addition from the ester face was observed (eq 5).[9] Other examples showing endo-, regio-, and facial selectivity are known (eq 6).[10,6]

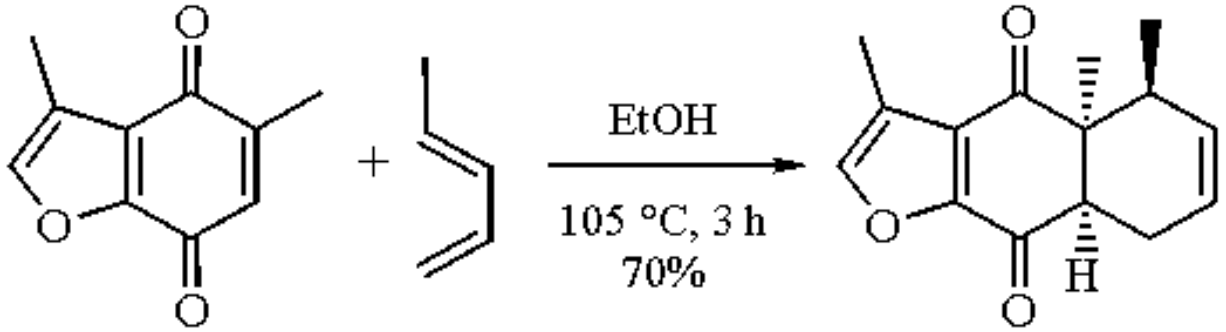

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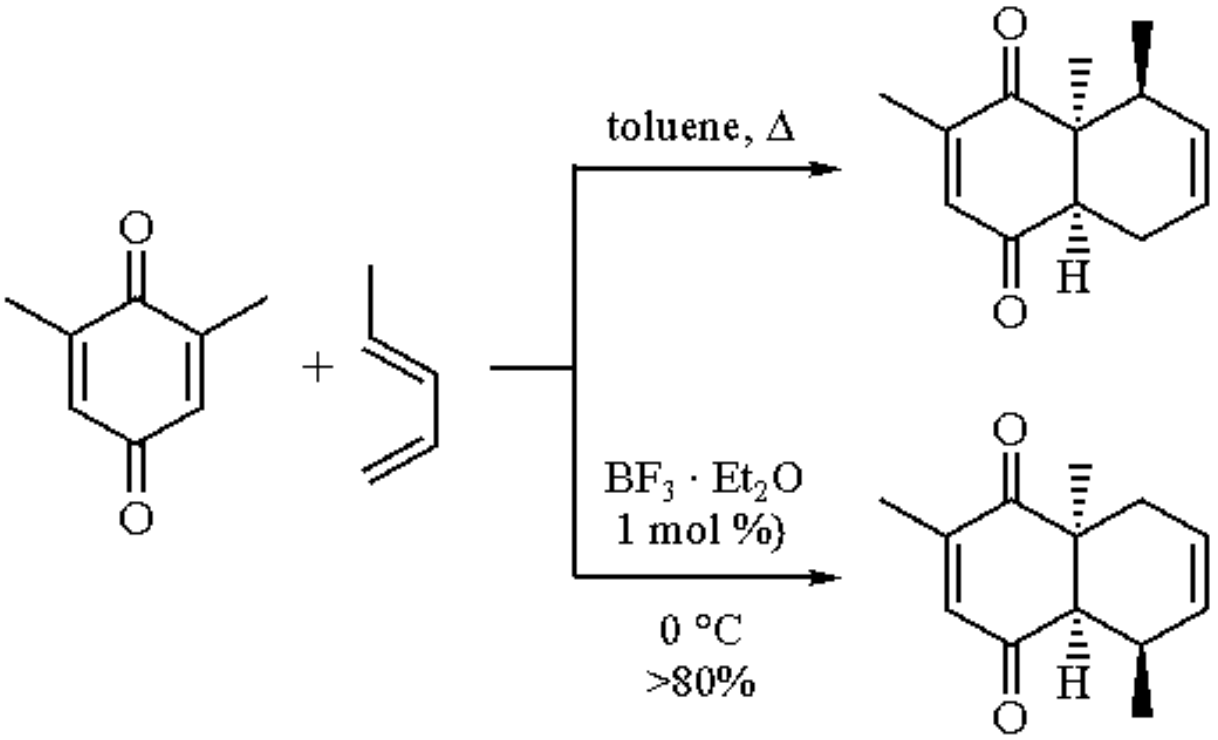

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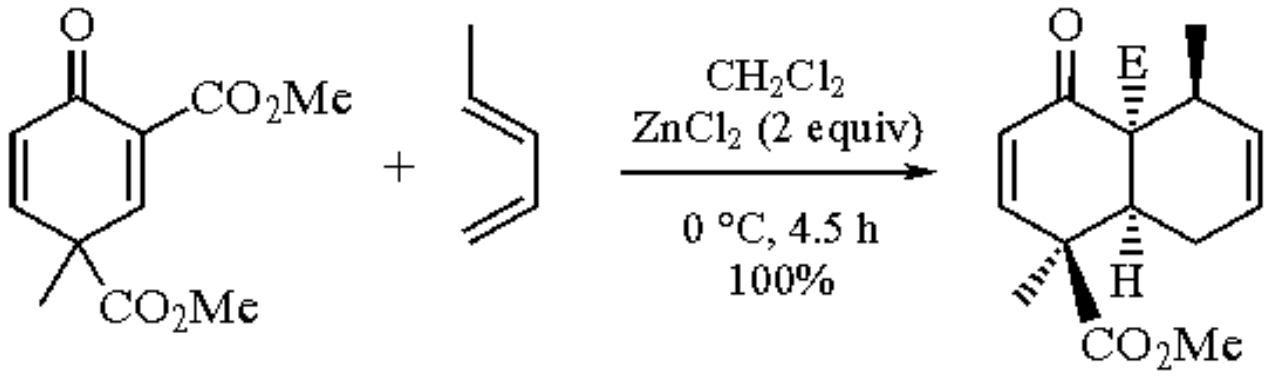

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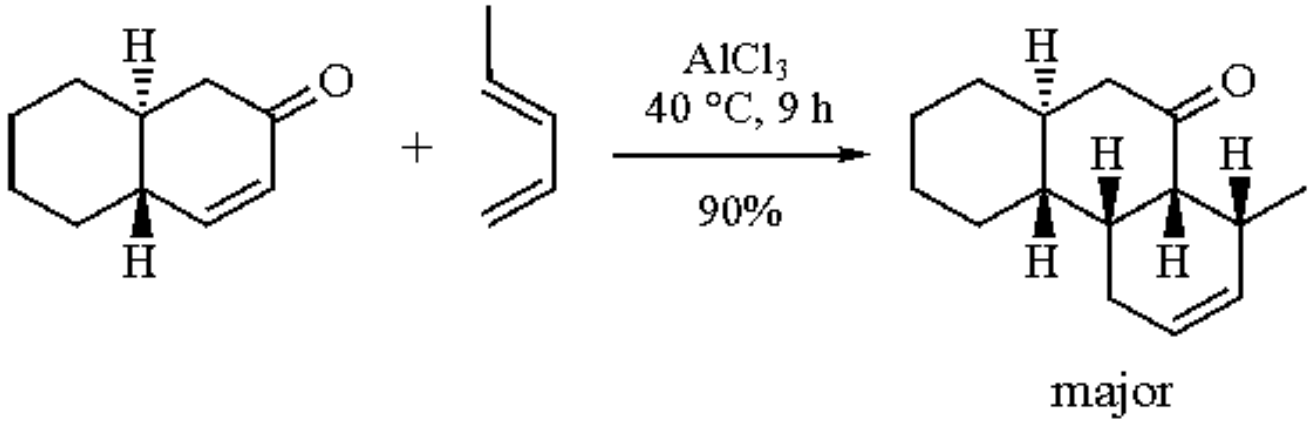

(6)

The use of 1,3-pentadiene in hetero-Diels-Alder reactions is well precedented.[11] It reacts with carbonyls,[12] imines,[13] nitroso groups,[14] and other heterodienophiles[15] to yield the corresponding heterocycles. For example, the in situ generated sulfonyl imine from propanal can be effectively trapped by 1,3-pentadiene in a [4 + 2] cycloaddition reaction (eq 7).[13a]

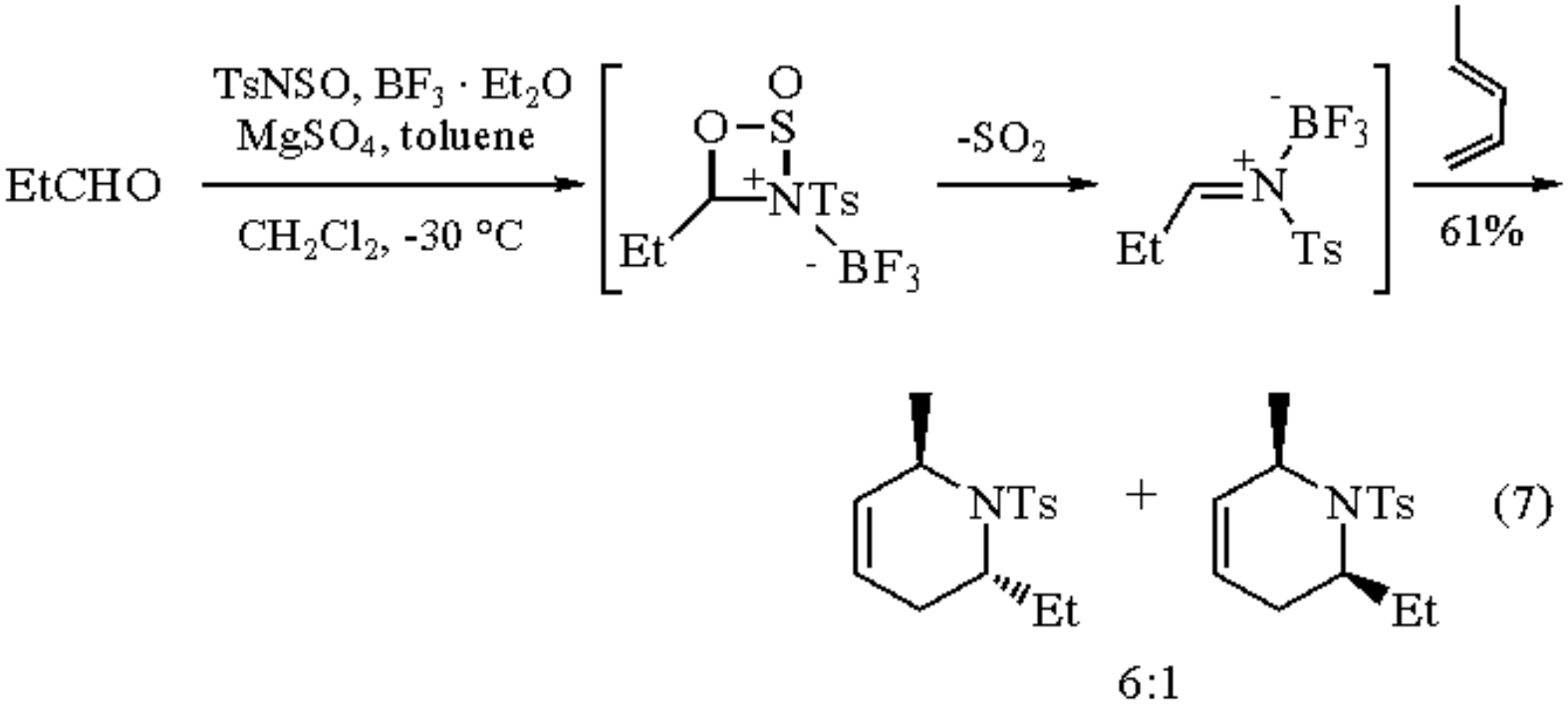

More recently, 1,3-pentadiene has been used in asymmetric Diels-Alder reactions, yielding carbocycloadditions[16] and heterocycloadditions.[13] The asymmetry can be induced by a chiral auxiliary on the dienophile (eq 8)[16a] or by a chiral Lewis acid (eq 9).[17]

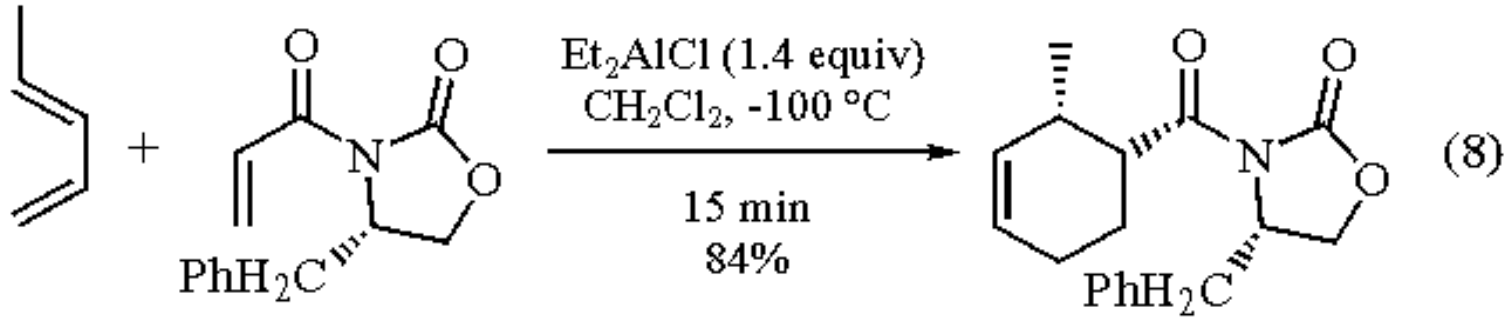

>100:1 diastereoselection

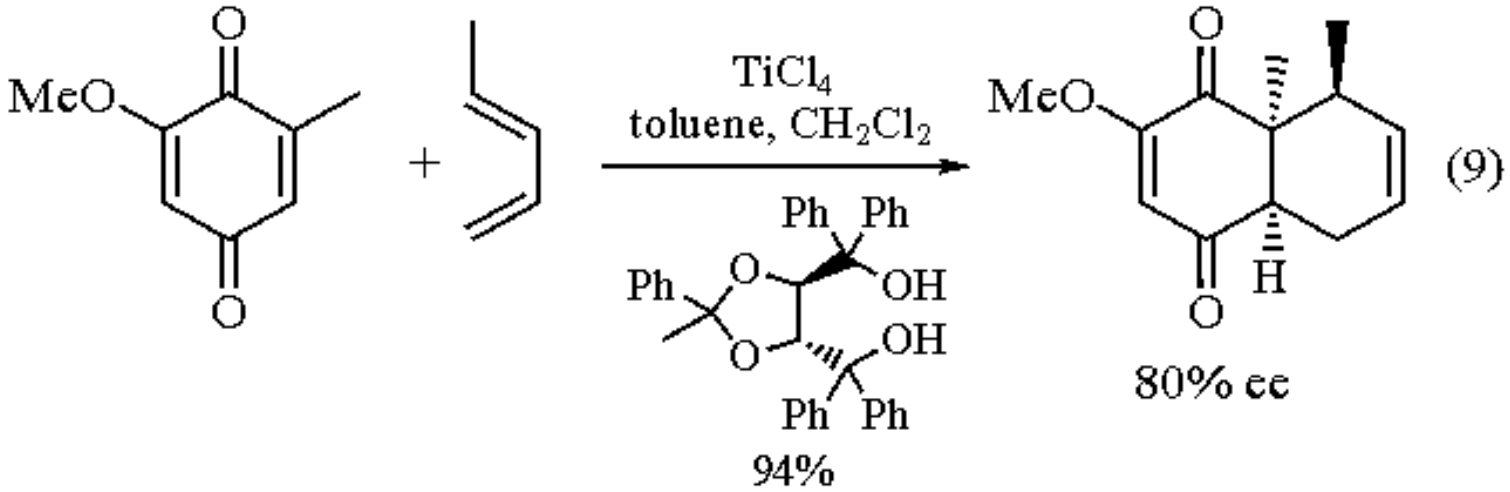

The rhodium(II)-catalyzed decomposition of vinyldiazomethanes in the presence of *cis*- and *trans*-1,3-pentadienes generates cycloheptadienes with complete stereocontrol (eq 10).[18]

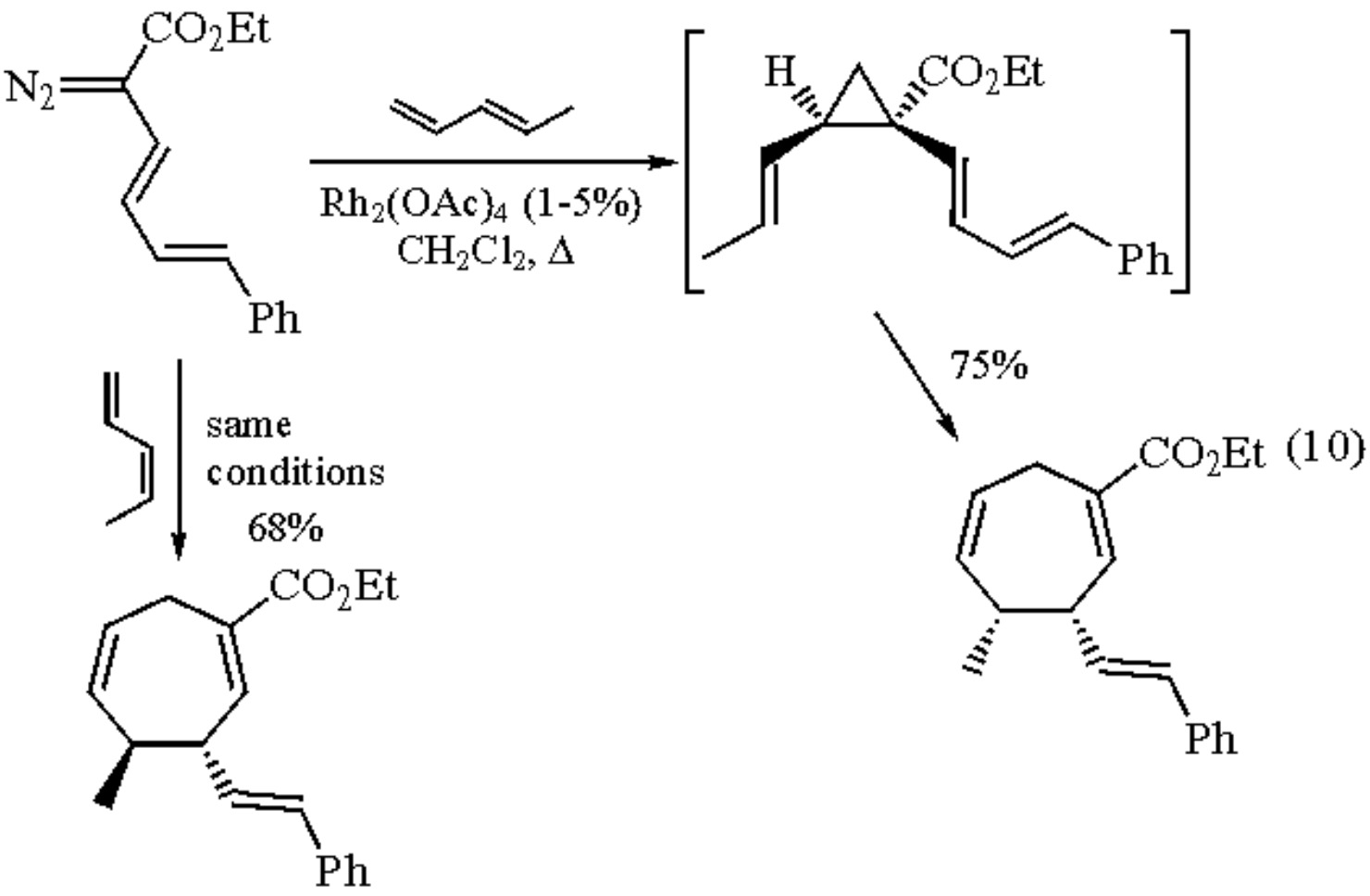

Complexes with Transition Metals.

Many transition metal complexes of 1,3-pentadiene, which coordinates as the pentadienyl ligand, are known. The complexes are generally η^5 (e.g. **3, 4**) or η^3 (e.g. **5-8**).[2] Both modes of coordination are found in compound (**9**).[19]

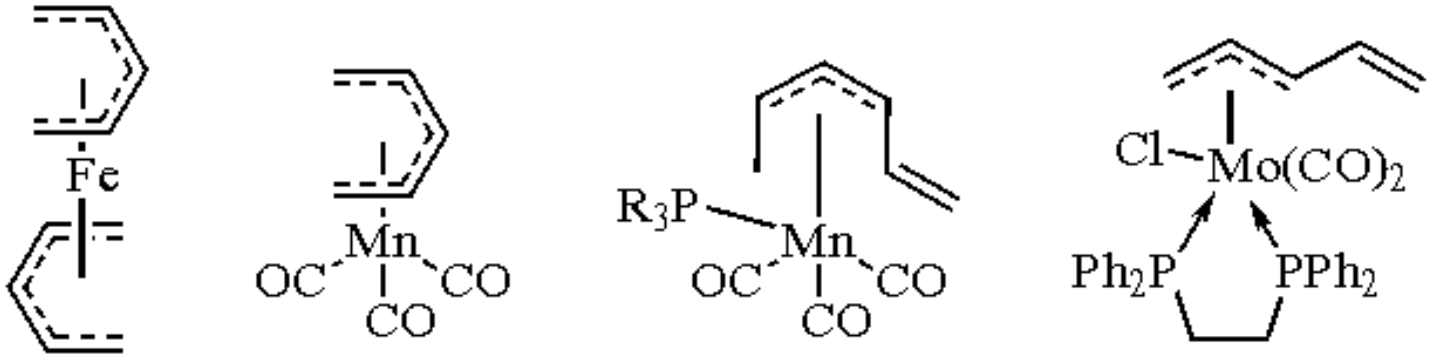

(3) **(4)** **(5)** **(6)**

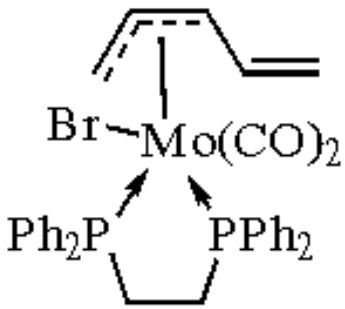

(7)

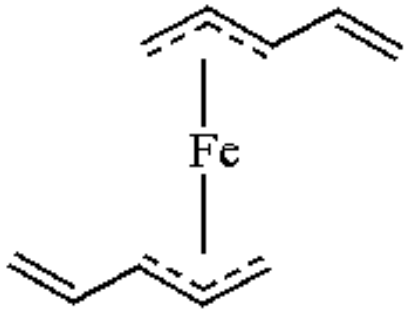

(8)

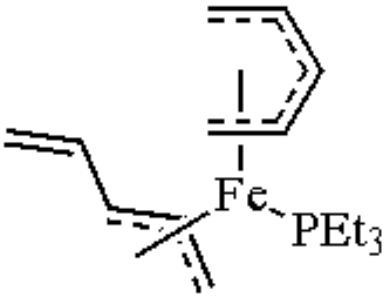

(9)

While the first complex of a pentadienyl ligand, $Fe(C_5H_7)(CO)_3$, was prepared in 1962 by protonation of the neutral Fe(η^4-pentadienyl)$(CO)_3$,[20] until recently there was little indication that pentadienyl complexes might lead to potentially useful carbon-carbon bond-forming reactions. Recent reports have described the addition of nucleophiles to neutral (η^5-pentadienyl)maganese,[21] -iron, or -ruthenium[19] complexes to generate novel (σ,η^3-pentadienyl) complexes (eq 11).[21] Under photochemical conditions, the tricarbonyl(η^5-pentadienyl)manganese complex reacts with conjugated dienes, such as *trans*- or *cis*-piperylenes, in a formal [4 + 5] cycloaddition to give macrocyclic complexes (eq 12).[22]

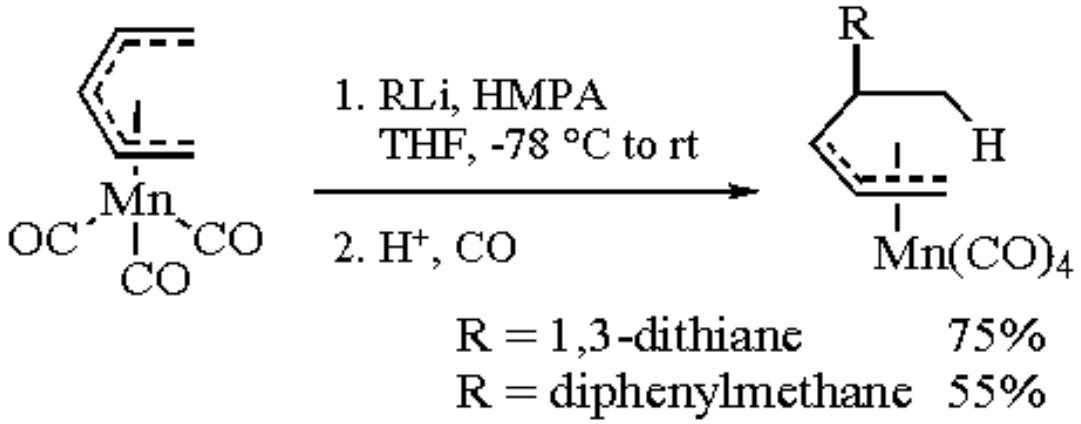

(11)

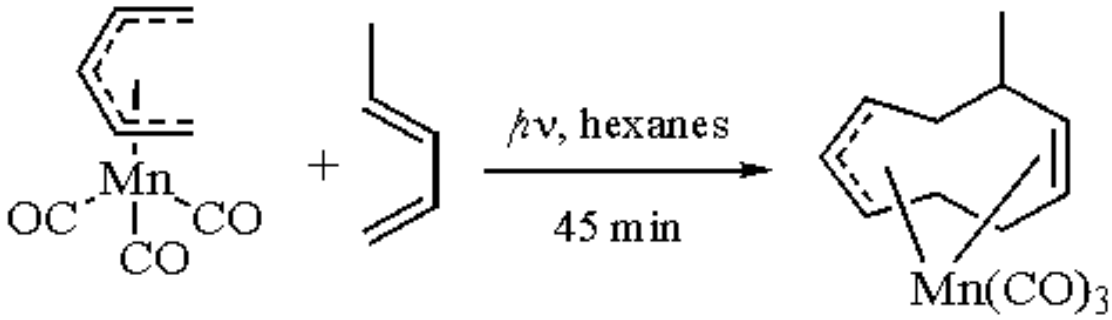

(12)

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Pentadienyllithium[1]

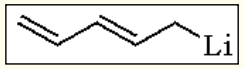

[54962-98-0] · C_5H_7Li · Pentadienyllithium · (MW 74.06)

(pentadienylating agent in substitutions and additions; used to attach pentadienyl groups to other metals and nonmetals)

Physical Data: orange crystals. Solution NMR studies and trapping experiments indicate a predominant planar W shape; pentadienylpotassium prefers a U shape under most conditions and is used when a U shape is desired.[2]

Solubility: usually prepared and used without isolation, in hydrocarbon/ether mixtures.

Preparative Methods: by metalating 1,4-pentadiene with BuLi/THF[3] or Li/amines,[4] or the more readily available ***1,3-Pentadiene*** with Li/amines (best for large scale),[4] or by cleaving alkyl 2,4-pentadienyl ethers with alkyllithiums.[5]

Form Supplied in: prepared in situ and used directly.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas to exclude oxygen and moisture.

Reactions.

Alkylations give mixtures of products from reaction at the central and end carbons.[1] Borylation,[2a,b] silylation,[2c -e,6] and related reactions[6] occur almost exclusively at an end carbon to provide (*E*) derivatives (eq 1; cf. eq 2[2c]). The TMS derivatives thus produced are more selective in their additions to aldehydes and ketones than are the pentadienylmetals.[7] Additions of pentadienyllithium to aldehydes[5] and ketones[8] were found to be reversible, with the product on the left (eq 3) reverting to the thermodynamic product on the right under more vigorous conditions. Pentadienyllithium has been used to make open versions of the well-known cyclopentadienyl transition metal complexes.[1,9]

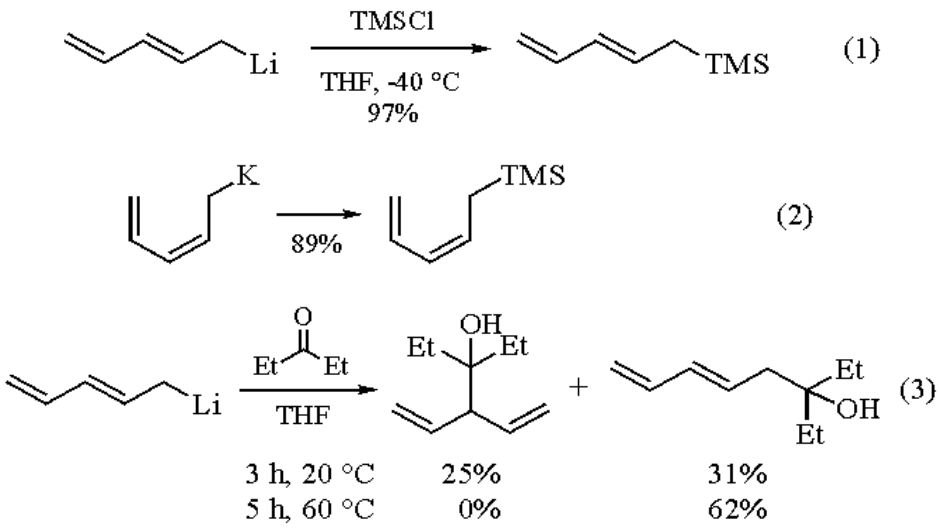

Related Reagents.

Table 1 lists some useful pentadienyllithium derivatives.[1,10-14] See also ***Allyllithium***, ***Allylmagnesium Bromide***, and ***Crotyllithium***.

Table 1 Pentadienyllithium Derivatives

Structure	Name	Molecular formula	Ref.
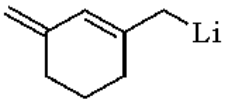	Cyclohexene, 1-lithiomethyl-3-methylene-	$C_8H_{11}Li$	10
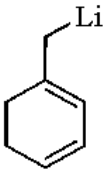	1,3-Cyclohexadiene, 1-lithiomethyl-	C_7H_9Li	10
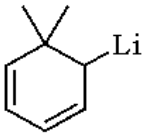	2,4-Cyclohexadienyllithium, 6,6-dimethyl-	$C_8H_{11}Li$	10
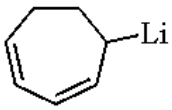	2,4-Cycloheptadienyllithium	C_7H_9Li	11
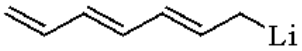	2,4,6-Heptatrienyllithium	C_7H_9Li	11
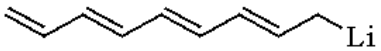	2,4,6,8-Nonatetraenyllithium	$C_9H_{11}Li$	12
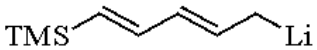	2,4-Pentadienyllithium, 5-trimethylsilyl-	$C_8H_{15}LiSi$	1
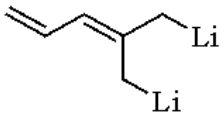	2,4-Pentadienyllithium, 2-lithiomethyl-	$C_6H_8Li_2$	13
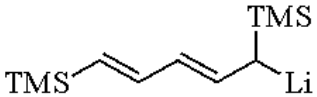	2,4-Pentadienyllithium, 1,5-bis(trimethylsilyl)-	$C_{11}H_{23}LiSi_2$	1
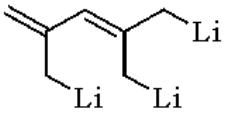	2,4-Pentadienyllithium, 2,4-bis(lithiomethyl)-	$C_7H_9Li_3$	13
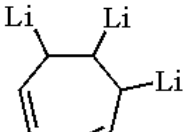	1,3-Cycloheptadiene, 5,6,7-trilithio-	$C_7H_7Li_3$	14

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Pentafluorophenol

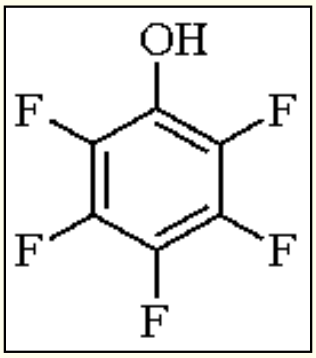

[771-61-9] · C_6HF_5O · Pentafluorophenol · (MW 184.07)

(preparation of pentafluorophenyl active esters for peptide synthesis;[1] formylating agent; preparation of aromatic fluoro derivatives)

Physical Data: white solid, mp 34-36 °C; bp 143 °C; fp >72 °C; n_D 1.4263.

Solubility: sol most organic solvents, particularly aprotic ones.

Form Supplied in: available commercially.

Handling, Storage, and Precautions: toxic and irritant. Harmful if swallowed, inhaled, or absorbed through the skin. Incompatible with strong oxidizing agents, bases, acid chlorides, and anhydrides. Keep away from heat and naked flames: combustible solid/liquid. Store in a cool, dry place.

Use in Peptide Synthesis.

Solution Techniques.

Simple alkyl esters of amino acids (which may be protected) undergo aminolysis at a rate too slow for peptide bond synthesis. Phenyl esters are more reactive and, if electronegative substituents are present on the ring, may undergo aminolysis at rates similar to those of anhydrides. The overriding requirements in peptide bond formation are efficiency and freedom from side reactions. Esters of pentafluorophenol have found wide application in the synthesis of peptides (cf. ***Pentachlorophenol***).[1a-c] Pentafluorophenol (**1**) serves as a coupling reagent, i.e. a compound added to a mixture of carboxyl and amino components to promote condensation. However it is very difficult to find efficient coupling reagents which do not give undesirable side reactions. Kinetic studies have shown the superiority of pentafluorophenyl esters compared to other coupling reagents with respect to speed of coupling (and thus lowering or eliminating undesirable reactions, e.g. α-hydrogen abstraction leading to racemization).[2a,b] Relative rates are OPFP >> OPCP > ONp, corresponding to 111:3.4:1, where PFP = pentafluorophenyl; PCP = pentachlorophenyl; Np = nitrophenyl.

Pentafluorophenyl esters have been used in both solution and solid phase peptide syntheses, the difference being that solid phase synthesis involves linking the peptide to a solid support (see below), whilst solution techniques involve just one phase. There are many examples of pentafluorophenyl esters being used in peptide synthesis,[1a,3a-e] e.g. the peptide sequence *t*-Boc-Phe-Pro-Pro-Phe-Phe-Val-Pro-Pro-Ala-Phe-OMe[3a] and the alkaloid peptide (**2**)[3b] have been synthesized by these methods.

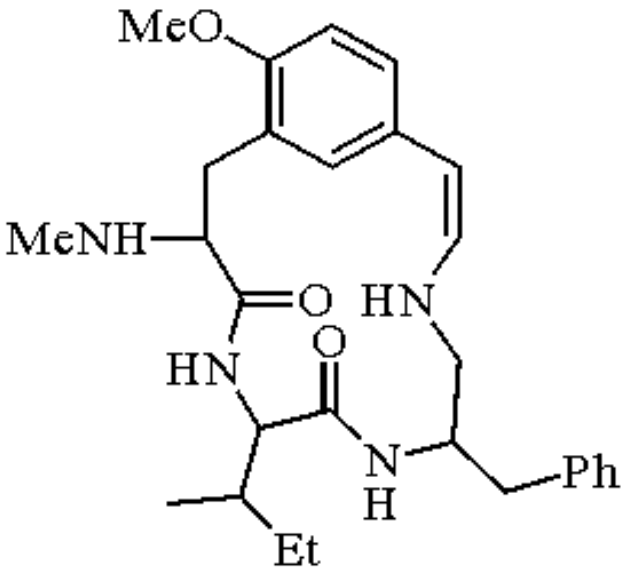

(2)

More recently, the base labile 9-fluorenylmethoxycarbonyl (Fmoc) group has become well established in peptide synthesis for the protection of amino functionalities.[4,5] The problem associated with this group is cleavage of the Fmoc group by the free amino component to be acylated, which results in double acylations. The principal method of avoiding this now is to use the Fmoc group in association with highly reactive pentafluorophenyl esters to greatly increase the rate of coupling compared with the undesirable reactions. Formation of these esters is shown in eq 1.[4]

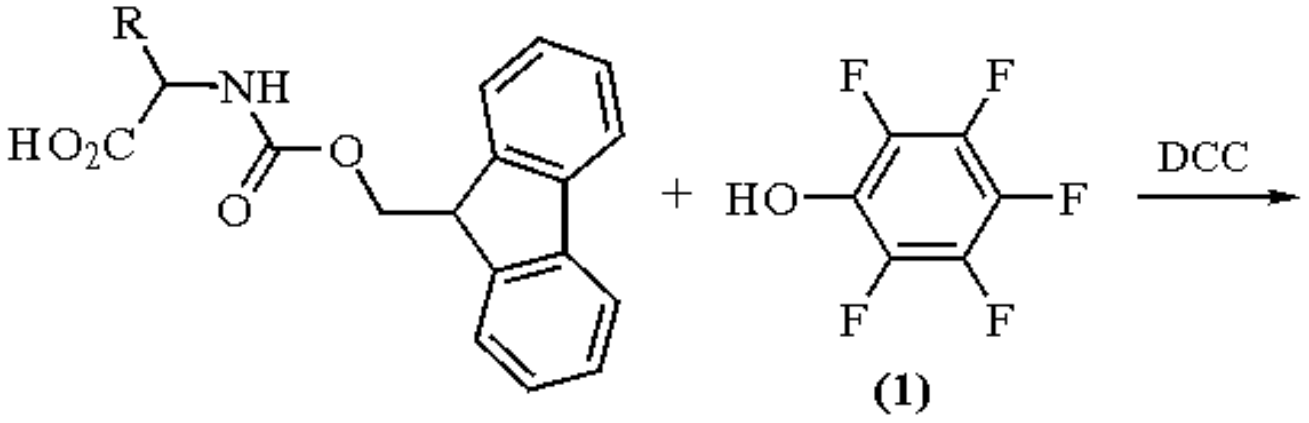

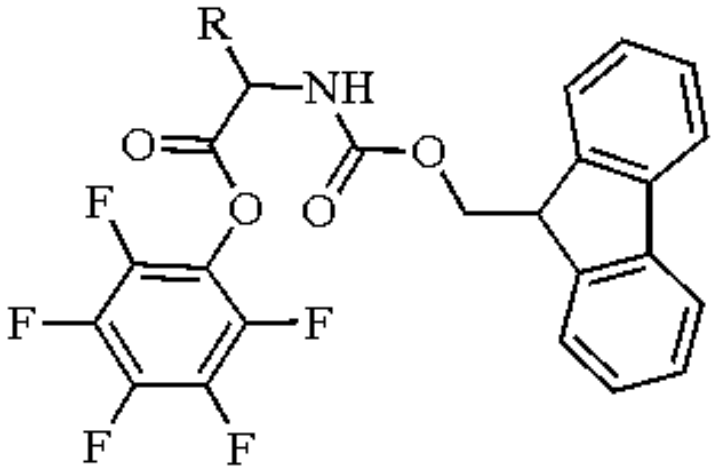

(1)

For example, this methodology was first used in the synthesis of Fmoc-glycyl-L-tryptophyl-L-leucyl-L-aspartyl-L-phenylalaninamide (Fmoc-Gly-Trp-Leu-Asp-Phe-NH_2) with the isolation of all pentafluorophenyl ester intermediates in excellent yields (75-99%); the coupled amino acids were subsequently prepared stepwise, again in very good yields, with the minimum of undesirable side reactions.[4]

This method has since been modified and improved further by utilizing 9-fluorenylmethyl pentafluorophenyl carbonate (eq 2).[5a]

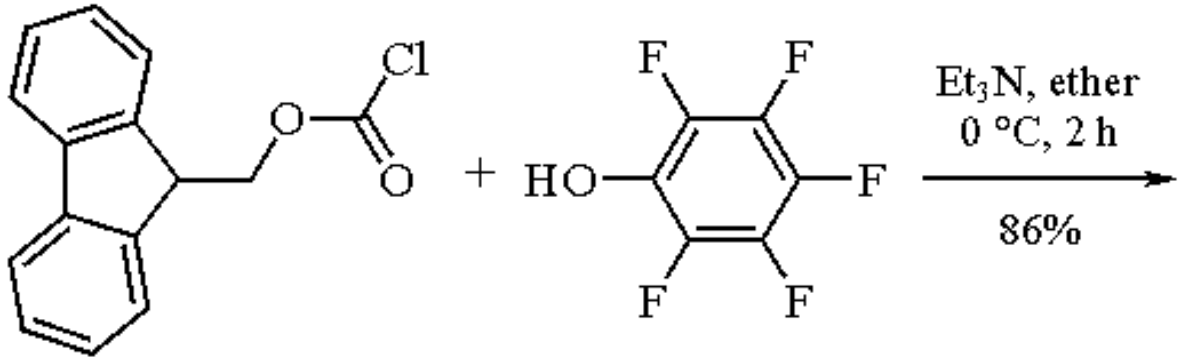

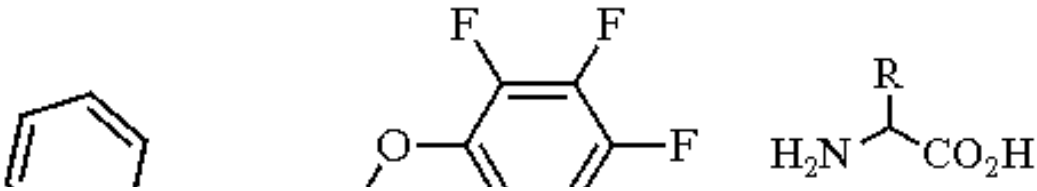

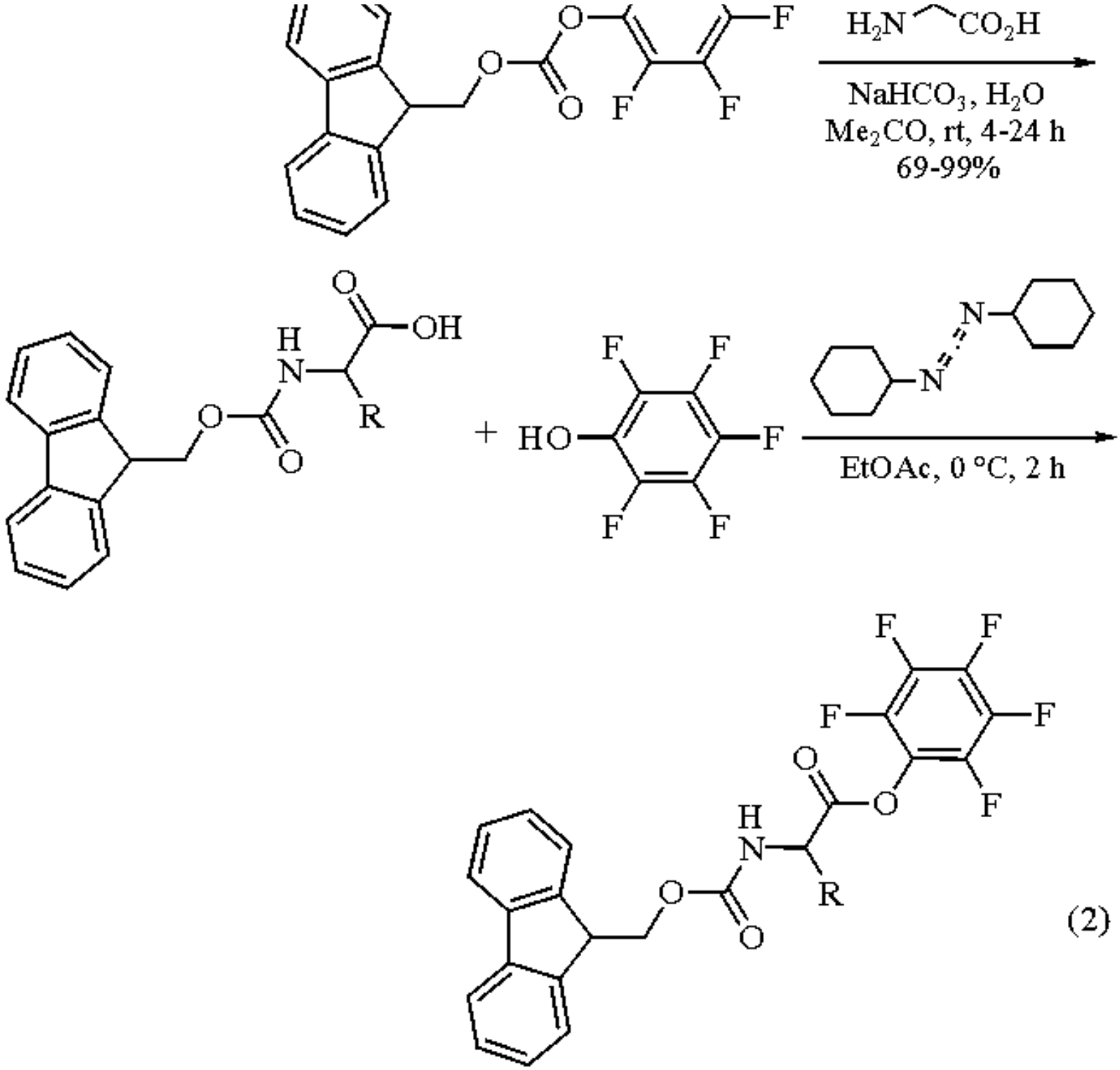

There is a newer alternative method of synthesizing Fmoc-protected pentafluorophenyl ester amino acids employing pentafluorophenyl trifluoroacetate (**3**).[5b]

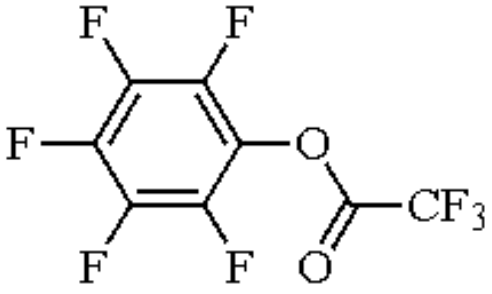

(3)

Table 1 gives some typical examples of the *N*-9-Fluorenylmethoxycarbonyl (Fmoc) amino acids and their pentafluorophenyl (PFP) esters which have been prepared by these methods.[4,6,7] The physical data are in agreement with either preparative method, and with early preparations of these compounds.[4,5a,b]

Table 1 Examples of Fmoc-Protected Amino Acids and their Pentafluorophenyl (PFP) Esters

Amino acid	Fmoc derivative mp (°C)	Fmoc derivative yield (%)	Fmoc amino acid PFP ester mp (°C)	Fmoc amino acid PFP ester yield (%)	Ref.
Gly	171 172	84	158 160	72	4, 6
Ala	141 142	93	173 175	74	4, 6
Leu	151 152	83	113 114	78	4, 6
Val	143 144	90	121 123	77	4, 7
Pro	114 115	82	125 127	89	4, 7
Phe	181 182	86	152 154	90	4, 6
Trp	163 165	89	184 185	85	4, 6
Tyr	98 107	70	152 156	70	4
Ser	90 94	78	124 126	83	4, 7
Ser (*t*-Bu)			67 71	67	4, 7

Solid Phase Peptide Synthesis (SPPS).

Pentafluorophenyl esters have been used in both solution and solid phase peptide synthesis. So far, only solution methods have been considered. The principal of SPPS is incorporation of single amino acid residues into peptide chains built on insoluble polymeric supports. The famous Merrifield paper[8] started the tradition of SPPS using *t*-butoxycarbonyl (Boc) amino acids activated with ***1,3-Dicyclohexylcarbodiimide***, although this has now been superseded with the introduction of the Fmoc group in polystyrene- and polyamide-based SPPS. The theory of SPPS will not be discussed here. Needless to say, the use of pentafluorophenyl esters in SPPS was inevitable and was first reported by Atherton in 1985.[9] Fmoc-amino acid pentafluorophenyl active esters were used in the polyamide solid phase series in polar DMF solutions in the presence of ***1-Hydroxybenzotriazole*** as a catalyst.

The preparation of the decapeptide H-Val-Gln-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH (**4**) will be used as an example of pentafluorophenyl esters in SPPS.[9,10] This is a good example to use since it contains normal, sterically hindered, and functionalized amino acids. All Fmoc-pentafluorophenyl esters were prepared by the method of Kisfaludy and Schön already described.[4,5] Beaded polymethylacrylamide gel resin was used as the solid phase with fivefold excesses of the pentafluorophenyl esters dissolved in a minimum of DMF. The resin was first functionalized with a reference norleucine residue and then with an acid-labile linkage agent (**5**).

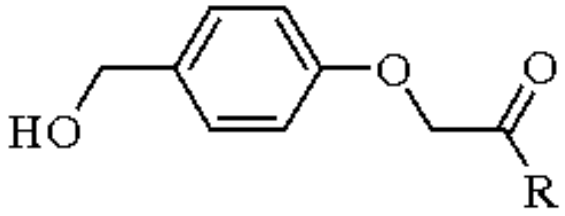

(5) R = 2,4,5-$Cl_3C_6H_2O$

Esterification of the first residue, glycine, to the free OH used the symmetrical anhydride/***4-Dimethylaminopyridine*** procedure.[11] The subsequent peptides were all coupled using standard techniques like those already described above and are fully documented. Slightly varying conditions and catalysts were required for some of the amino acids.[10] After addition of the last amino acid, the final Fmoc group was cleaved and the complete decapeptide detached from the support resin using 95% aqueous ***Trifluoroacetic Acid***. Side chain protecting groups were also cleaved simultaneously. Crude peptide analysis was achieved by HPLC and showed the samples obtained by this method to be extremely pure.

More recently, SPPS has also been employed in glycopeptide synthesis.[12] There is an excellent review of active esters in SPPS, including pentafluorophenyl esters.[13]

A New and Efficient Derivative of Pentafluorophenol.[14]

Pentafluorophenol has found many applications in both solution and solid phase peptide syntheses. Diphenylphosphinic mixed anhydrides are also well known in peptide chemistry. A new and efficient reagent has been prepared from these precursors: pentafluorophenyl diphenylphosphinate (FDPP; **6**) which can be used directly as a coupling reagent without side reactions. FDPP is prepared from mixing equimolar amounts of ***Diphenylphosphinic Chloride***, pentafluorophenol (**1**), and ***Imidazole*** in CH_2Cl_2 at room temperature (eq 3).[14]

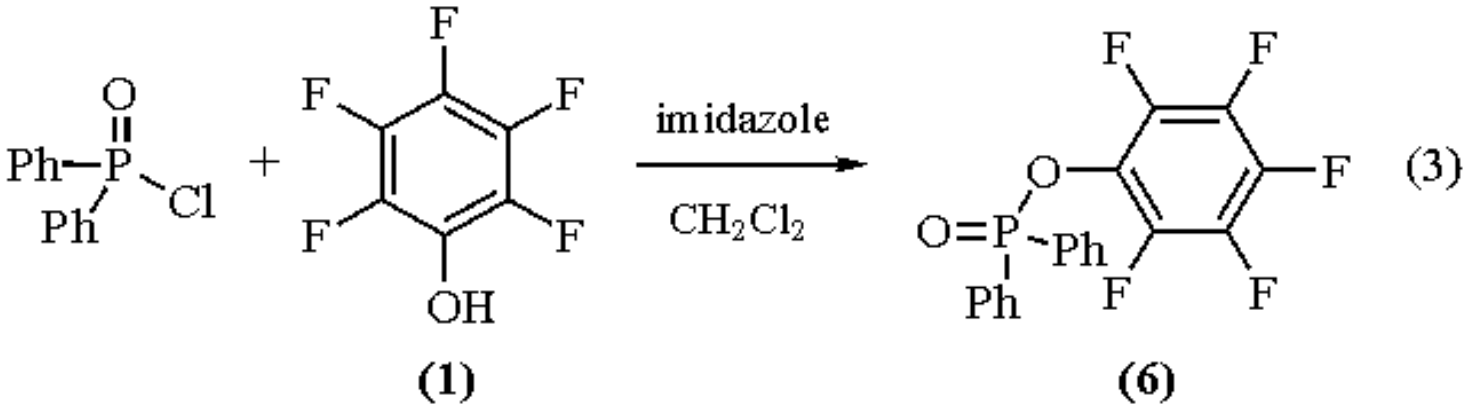

FDPP may be kept refrigerated for several months and is used as an efficient coupling reagent, by simply mixing the carbonyl and amine components with a tertiary amine and FDPP in an organic solvent, of which DMF was found to be the most efficient (eq 4).

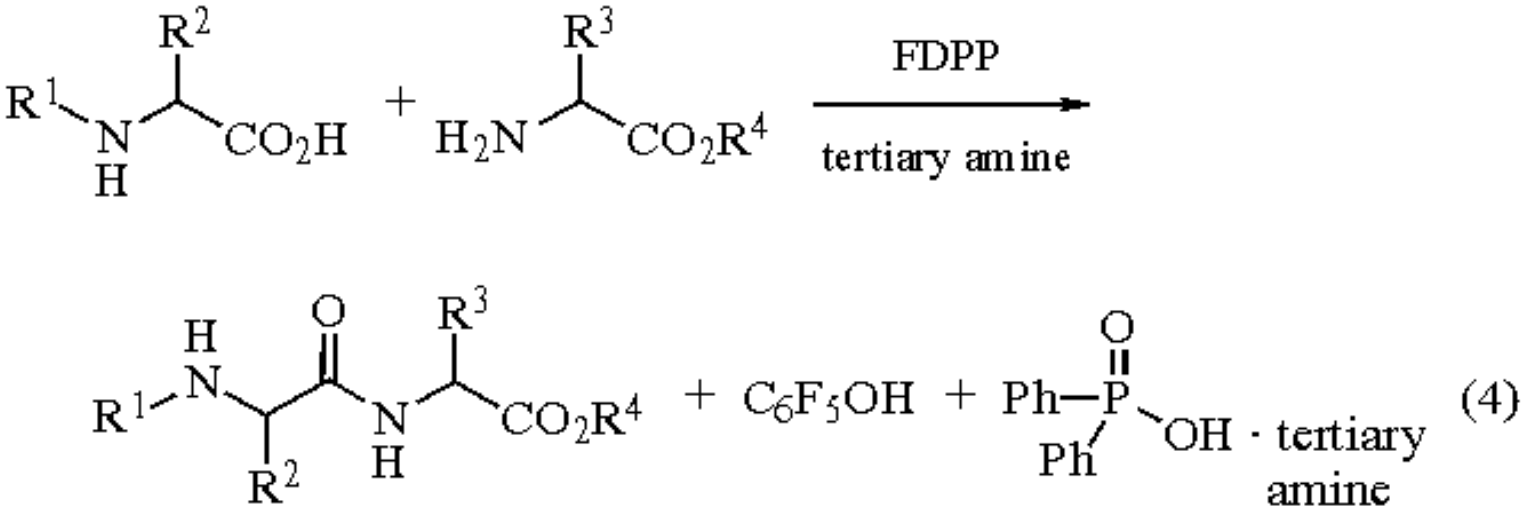

FDPP has been used in both solid and solution peptide syntheses and analysis has shown it to have the lowest rate of racemization of any of the common coupling reagents.[14]

Comparison of Pentafluorophenyl Active Esters with Pentachlorophenyl Esters.[15]

It is interesting to compare these two compounds with respect to active ester formation since they are very closely related and both have been employed in both liquid and solid phase peptide syntheses (see ***Pentachlorophenol***). Pentachlorophenyl esters generally have higher melting points, which can be of advantage if crystallization is difficult or a compound is of low melting point, e.g. for serine and threonine the oily pentafluorophenyl esters are usually replaced by the pentachlorophenyl esters.

As already mentioned, pentafluorophenyl derivatives are much more reactive than pentachlorophenyl ones. The reason for this is still not clear. Many calculations have been performed on the net atomic energies of these esters and show that there is no significant difference between the environment of the electrophilic center in OPFP esters compared to OPCP ones. Analysis of the carbonyl stretching frequencies of these compounds is quite revealing (Table 2), i.e. there is no significant difference in the carbonyl stretching frequencies of these functionalized esters. This, plus additional evidence from MM

calculations and NMR studies, suggests that electronic factors do not play a significant role in determining the reactivity of these esters.

Table 2 IR Stretching Frequencies of Carbonyl Groups in Pentachlorophenyl (OPCP) and Pentafluorophenyl (OPFP) Active Esters[a]

Amino acid	OPCP	OPFP	Δn
Z Gly	1794	1800	6
Boc Val	1782	1788	6
Boc Phe	1784	1790	6
Boc Tyr(*t*-Bu)	1786	1794	8
Z Cys(Bn)	1784	1794	10

[a] In $CHCl_3$; in cm^{-1}.

There is however, an important steric effect, as would be expected given the differing sizes of the halogens involved (van der Waals atomic radii = 1.75 Å for Cl and 1.47 Å for F). X-ray crystal analysis is interesting in that it shows there is no intramolecular interaction in OPFP esters and the structure is an extended conformation. The main interaction is the strong dipole-dipole of a negative fluorine to a positive carbon of another PFP ring in a neighboring molecule. CO...NH interactions appear to be only minor in comparison and the carbonyl group and PFP ring are almost perpendicular. Studies have shown that the same conformation applies whether in solid or solution.

One of the explanations offered for the high reactivity of the OPFP ester is neighboring group participation of an *ortho* fluorine atom in accelerating the collapse of a tetrahedral intermediate transition state, i.e. anchimeric acceleration. This would explain the low solvent effect on aminolysis rates, the high second-order rate constant, and unaffected third-order rate constant. Pentahalogen esters fall midway between quinol-8-yl esters, where there is definite participation, and nitrophenol esters where there is none (from studies on the model system of phenyl acetates and piperidine).[15] The PFP ester shows greater interaction than the PCP ester. There are other possible explanations: this could still be explained in steric terms, or by the high solvation of the leaving group (pentafluorophenol is much more soluble and reactive in aprotic solvents than pentachlorophenol).

Formylation Reactions.[16]

The problem with ***Acetic Formic Anhydride***, the most commonly used formylating agent, is undesirable side reactions, particularly if there are acid sensitive functionalities in the compound. One of the best alternatives is to use pentafluorophenyl formate (**7**), an easily prepared and stable compound which reacts with N-nucleophiles in minutes at

room temperature to yield the *N*-formyl derivative (eq 5) (Table 3). Significantly, no reaction occurs with alcohols, thiols, or sterically hindered amines.

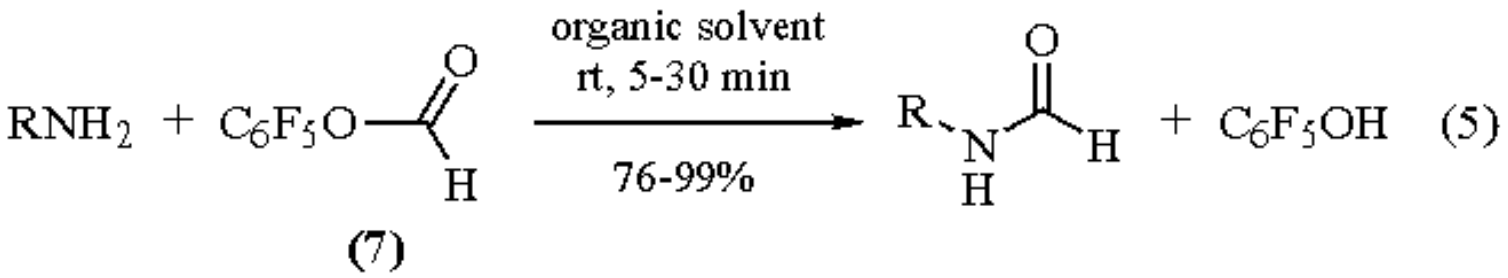

Table 3 Examples of *N*-Formylamines Prepared from Primary Amines and Pentafluorophenyl Esters

Amine	Solvent	Yield (%)	mp (°C)	R_f
Aniline	$CHCl_3$	90	48	0.6[a]
2-Aminobiphenyl	$CHCl_3$	99	67 70	0.6[a]
Benzylamine	$CHCl_3$	90	62 63	0.35[a]
H Met Leu Phe OMe	$CHCl_3$	93	135 136	0.4[b]

[a] Chloroform methanol (9:1). [b] Ethyl acetate.

Preparation of Aromatic Fluoro Derivatives.

Reaction of (**1**) with VF_2, VF_4, ***Vanadyl Trifluoride***, or ***Xenon(II) Fluoride*** in HF, $CFCl_3$, or MeCN at -30 to 20 °C yields mixtures of perfluoro-2,5-cyclohexadien-1-one together with its 2- and 4-pentafluorophenoxy derivatives and/or perfluoro-6-phenoxy-2,4-cyclohexadien-1-one, along with traces of perfluoro-2-cyclohexen-1-one or perfluoro-*p*-benzoquinone. Using ***Antimony(V) Fluoride*** or NbF_4, however, only gives stable complexes or pentafluorophenolates.[17]

Pentafluorophenol (**1**) reacts with ***Phosphorus(V) Chloride*** in the presence of a base, triethylamine or γ-collidine, to yield perfluoropentaphenoxyphosphorane (**8**) plus perfluorotriphenyl phosphate (**9**) and perfluorodiphenyl ether (**10**) (eq 6).[18]

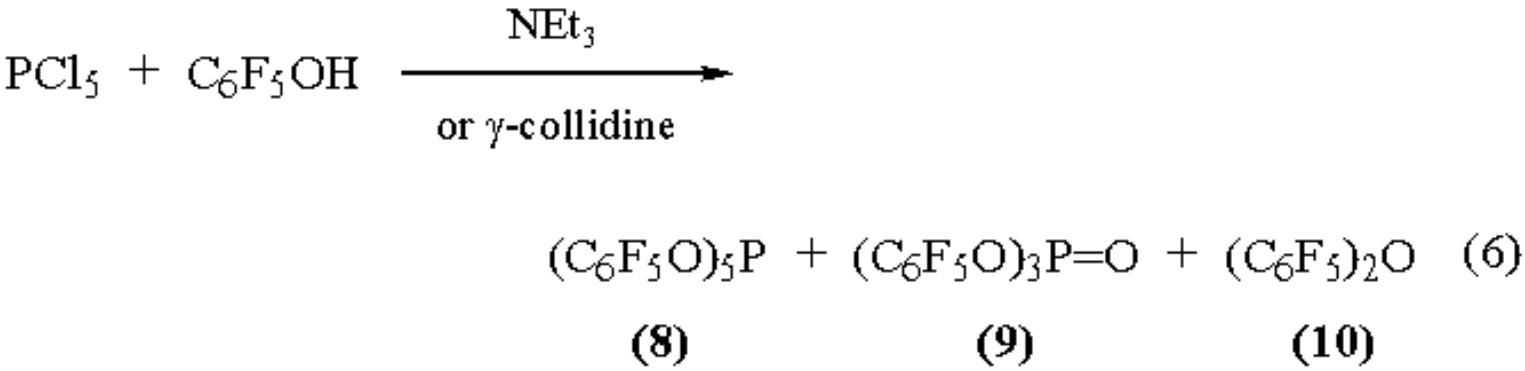

This reaction has also been used to prepare pentafluorothiophenol phosphorus derivatives. These compounds have been utilized in ^{31}P, ^{19}F, and ^{1}H variable temperature NMR studies on intramolecular ligand rearrangement processes in phosphorus compounds.[18]

The preparation and reactions of Polyfluoroaromatics, including pentafluorophenol derivatives, have been studied by various Russian workers, who have also evaluated the pentafluorophenoxy group as a leaving group (eq 7).[19a]

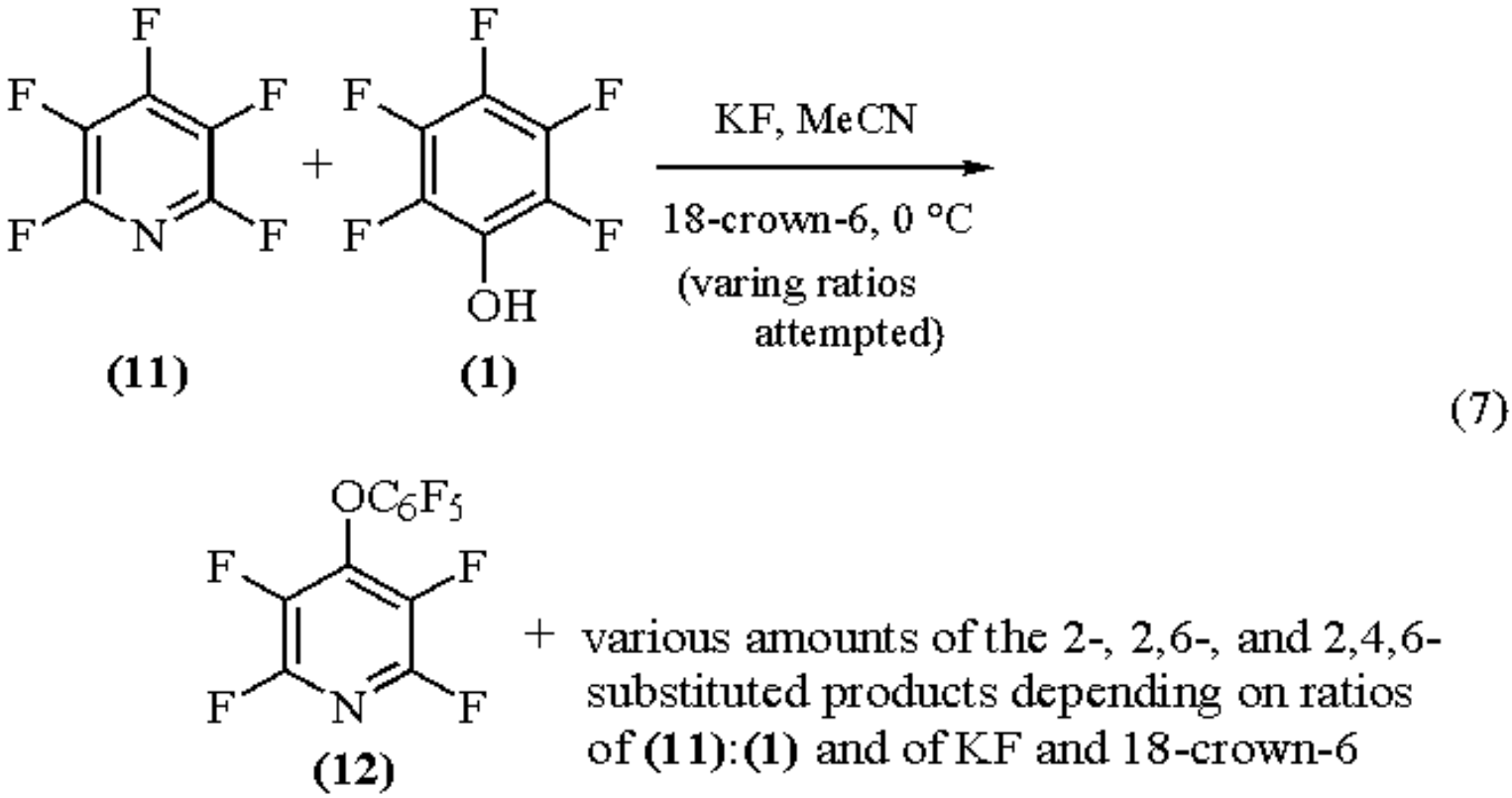

The main product of the reaction was the 4-substituted tetrafluoropyridine, although varying yields of the 2-, 2,6- and 2,4,6-pentafluorophenoxypyridines were obtained depending on the ratios of (**11**):(**1**) and also on the levels of ***Potassium Fluoride***, ***18-Crown-6***, the reaction temperature, and solvent. This reaction has been studied in comparison with 4-$NO_2C_6H_4$ (which is of similar basicity) and in competition with F^- anions.

More recently it has been shown that the substitution reaction of pentafluoropyridine with (**1**) in the presence of ***Cesium Fluoride***/graphite gave much better yields of (**12**), but still with traces of the other products. The catalyst activity was found to increase in the order: NaF < KF < RbF < CsF and was similar for the free fluorides and their graphite-supported analogs.[19b]

1. For examples of early work on pentafluorophenyl esters in peptide synthesis, see: (a) Kisfaludy, L.; Roberts, J. E.; Johnson, R. H.; Mayers, G. L.; Kovacs, J. *JOC* **1970**, *35*, 3563 and references therein. (b) Kisfaludy, L.; Schón, I.; Szirtes, T.; Nyéki, O.; Lów, M. *TL* **1974**, 1785 and references therein. (c) Kovacs, J.; Kisfaludy, L.; Ceprini, M. Q. *JACS* **1967**, *89*, 183.
2. (a) For a kinetic study of coupling rates and competing reactions, see: Gross, E.; Meienhofer, J. In *The Peptides-Analysis, Synthesis and Biology*, 2nd ed.; Academic: New York, 1980; p 519; (b) see also Ref. 1(c).
3. There are many examples of solution peptide synthesis utilizing pentafluorophenyl esters. A few notable examples are cited here: (a) Kisfaludy, L.; Schön, I.; Szirtes, T.; Nyéki, O.; Low, M. *TL* **1974**, 1785. (b) Schmidt, U.; Schanbacher, U. *LA* **1984**, *6*, 1205. See also Ref. 1(a). (c) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Haeusler, J. *LA* **1982**, *12*, 2153. (d) Karel'skii, V. N.; Krysin, E. P.; Antonov, A. A.; Rostovskaya, G. E. *Khim. Prir. Soedin.* **1982**, *1*, 96 (*CA* **1982**, *97*, 92 730s). (e) Polevaya, L. K.; Vegners, R.; Ars, G.; Grinsteine, I.; Cipens, G. *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.* **1981**, *4*, 469 (*CA* **1982**, *96*, 7059s).
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5. (a) Kisfaludy, L.; Schön, I. *S* **1986**, 303. (b) Green, M.; Berman, J. *TL* **1990**, *31*, 5851.
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11. Atherton, E.; Logan, C. J.; Sheppard, R. C. *JCS(P1)* **1981**, 538.
12. For the use of pentafluorophenyl esters in SPPS of glycopeptides, see: Meldal, M.; Jensen, K. J. *CC* **1990**, 483 and references therein.
13. For a review of active esters in SPPS, see: Bodanszky, M.; Bednarek, M. A. *J. Protein Chem.* **1989**, *8*, 461.
14. Chen, S.; Jiecheng, X. *TL* **1991**, *32*, 6711.
15. Kisfaludy, L.; Low, M.; Argay, G.; Czugler, M.; Komives, T.; Sohar, P.; Darvas, F. In *Peptides (Proceedings 14th European Peptide Symposium)*; Loffet, A., Ed.; Editions de l´Université de Bruxelles: Bruxelles, 1976; p 55 and references therein.
16. Kisfaludy, L.; &OOuml;tvos, Jr., L. *S* **1987**, 510.
17. Avramenko, A. A.; Bardin, V. V.; Karelin, A. L.; Krasil'nikov, V. A.; Tushin, P. P.; Furin, G. G.; Yakobson, G. G. *ZOR* **1985**, *21*, 822 (*CA* **1985**, *103*, 141 551n).
18. Denny, D. B.; Denney, D. Z.; Liu L-T. *PS* **1982**, *13*, 1.
19. (a) Aksenov, V. V.; Vlasov, V. M.; Yakobson, G. G. *JFC* **1982**, *20*, 439. (b) Aksenov, V. V.; Vlasov, V. M.; Danilkin, V. I.; Naumova, O. Y.; Rodionov, P. P.; Chertok, V. S.; Shnitko, G. N.; Yakobson, G. G. *IZV* **1984**, *9*, 2158 (*CA* **1985**, *102*, 131 881k).

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1,1,2,3,3-Pentaisopropylguanidine

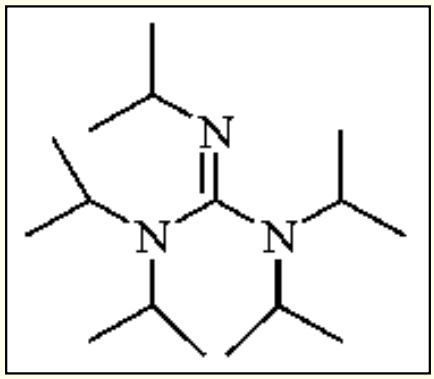

[81236-11-5] · $C_{16}H_{35}N_3$ · 1,1,2,3,3-Pentaisopropylguanidine · (MW 269.54)

(hindered amine base; used in oxidations of ketone hydrazones, and in eliminations of hydrogen iodide and *p*-toluenesulfonic acid)

Preparative Method: the reagent is not commercially available, but is easily prepared in two steps. First, ***Thiophosgene*** is slowly added to ***Diisopropylamine*** to give *N,N,N´,N´*-tetraisopropylthiourea, as a pale yellow liquid, in 44% yield. A Vilsmeier salt is then formed from the reaction of tetraisopropylthiourea with ***Phosgene***, and subsequently treated with isopropylamine to give 1,1,2,3,3-pentaisopropylguanidine (69% yield) as a liquid, bp 60 °C/0.01 mmHg (eq 1).[1] The compound solidifies on storing at -20 °C under argon.

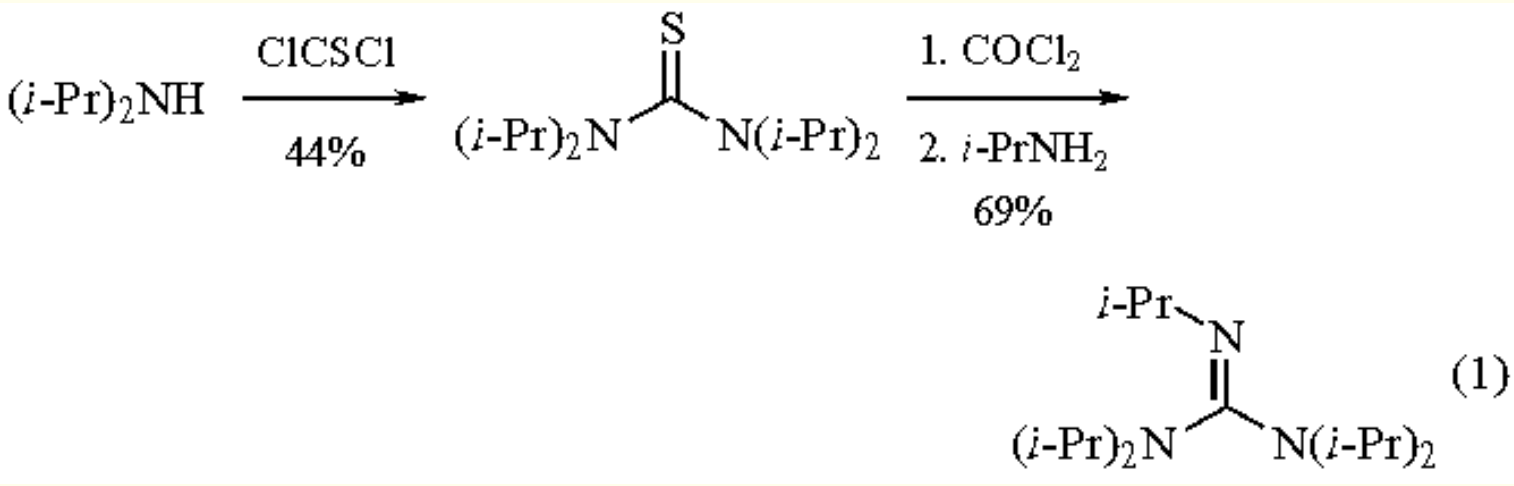

Handling, Storage, and Precautions: Use in a fume hood.

Oxidation of Ketone Hydrazones.

Ketone hydrazones are oxidized to vinyl iodides when treated with ***Iodine*** in the presence of a base. Yields of vinyl iodides improve significantly with the use of strong guanidine bases under anhydrous conditions (eq 2).[2]

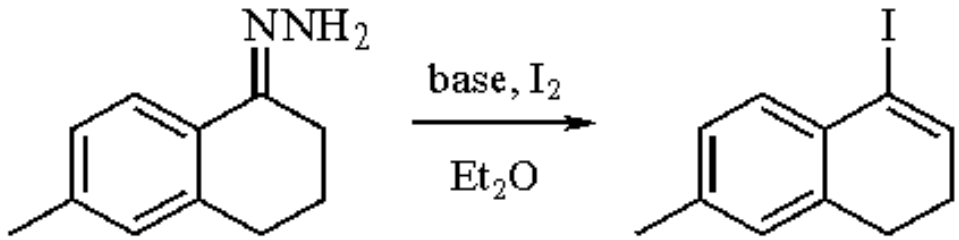

(2)

Conditions	base	Yield (%) vinyl iodide
A	Et_3N	38
A	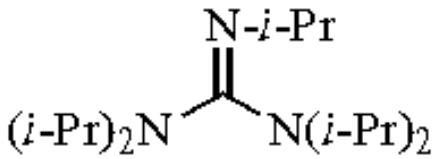	78
B	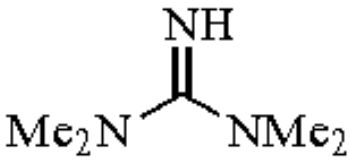	87
B	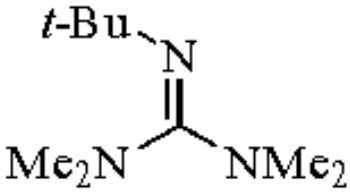	89
A	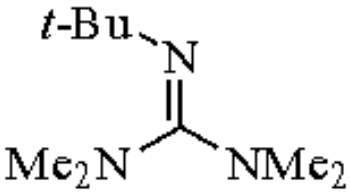	78

A. Normal addition: iodine solution was added to a solution of base and hydrazone at room temperature.
B. Inverse addition: hydrazone solution was added to a mixture of base and iodine.

Eliminations.

The base-induced elimination of hydrogen iodide from β-iodo-α,β-unsaturated ester (**1**) is effected by reaction with

pentaisopropylguanidine in methylene chloride at -35 °C to give alkynic ester (**2**) in 70% yield (eq 3).[3] Likewise, reaction of β-iodo-α,β-unsaturated ester (**3**) with pentaisopropylguanidine in chloroform at -30 °C affords alkynic ester (**4**) in 69% yield (eq 4).[4]

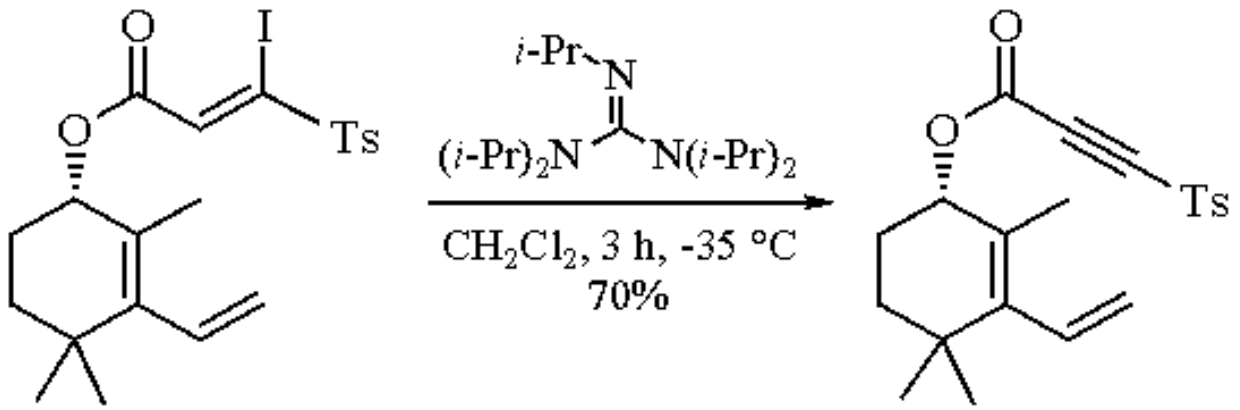

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(1) (2)

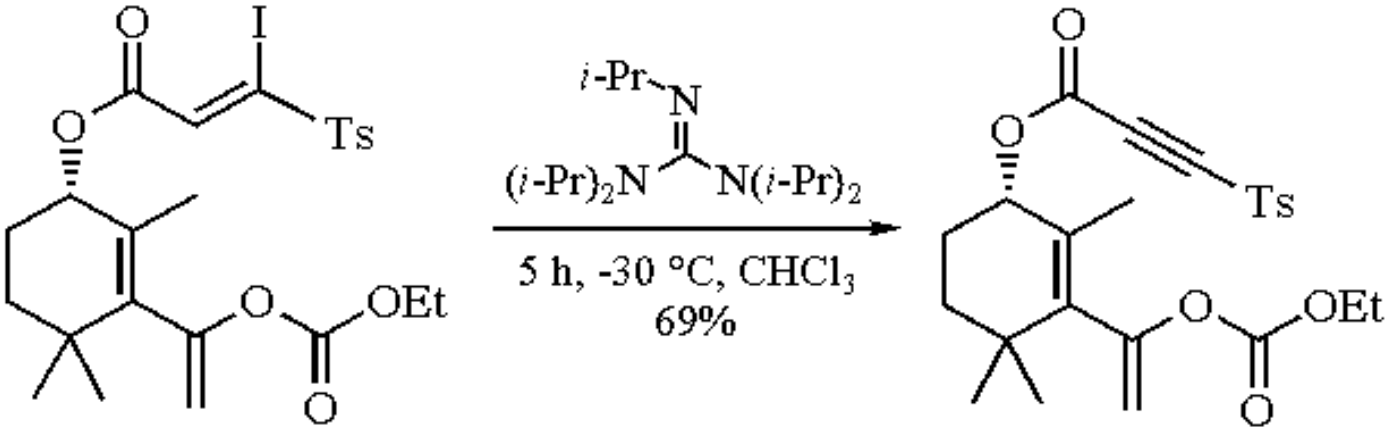

(4)

(3) (4)

Pentaisopropylguanidine is also used in the elimination of sulfonic acids from the corresponding esters to afford alkenes. For example, heating cholestan-3β-yl *p*-toluenesulfonate (**5**) with pentaisopropylguanidine at 120 °C for 26 h gives a mixture of cholest-2-ene (**6**) and cholest-3-ene (**7**) in 85% yield (eq 5).[1] This compares favorably with the literature method involving ***2,4,6-Collidine*** (170 °C, 6 h, 63% yield).[5] The same reaction performed using ***1,5-Diazabicyclo[4.3.0]non-5-ene*** (DBN) only gives 31% of the mixed alkenes but at a lower temperature (80-90 °C).

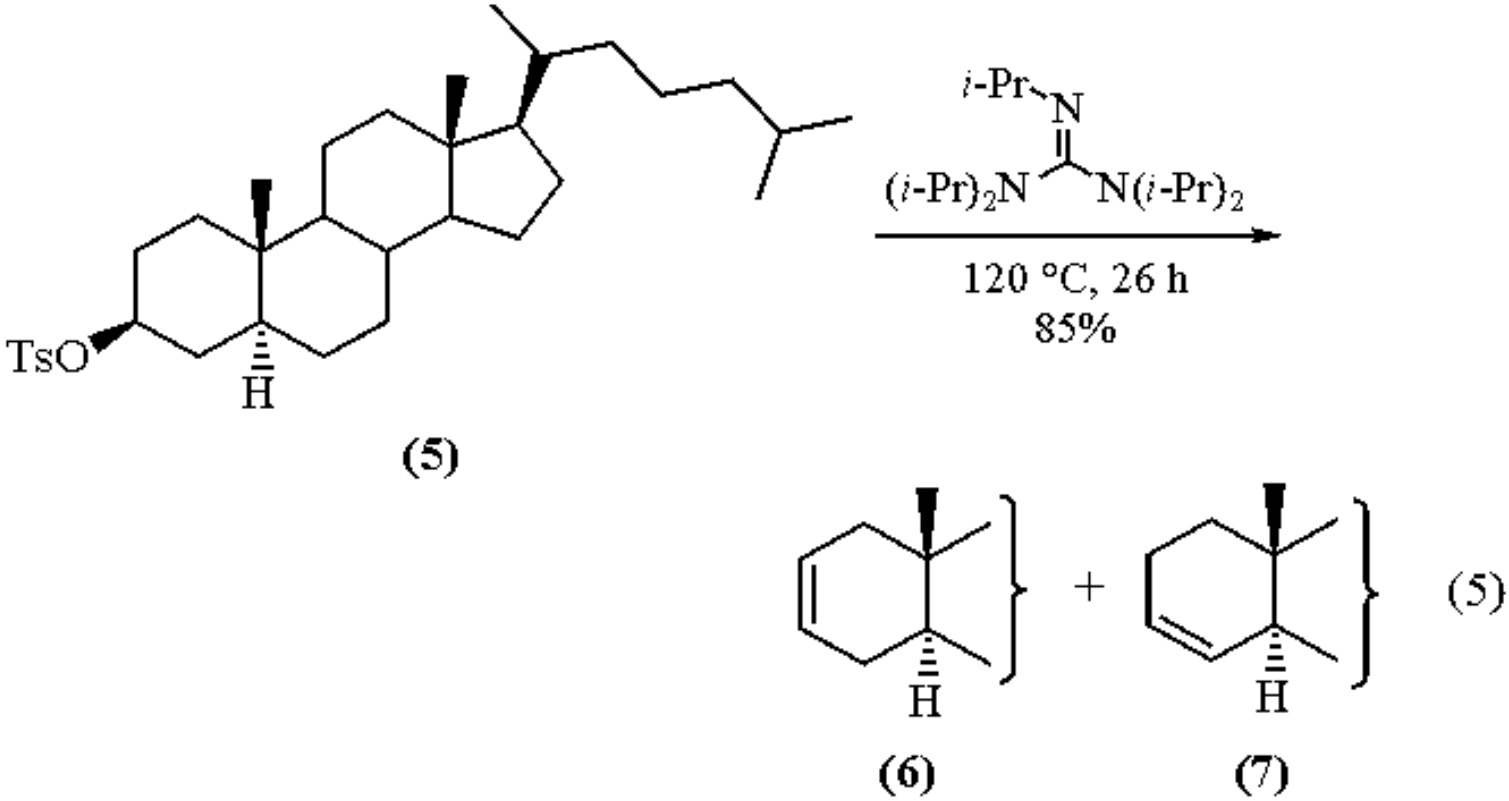

Related Reagents.

1,1,3,3-Tetramethylguanidine.

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N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine

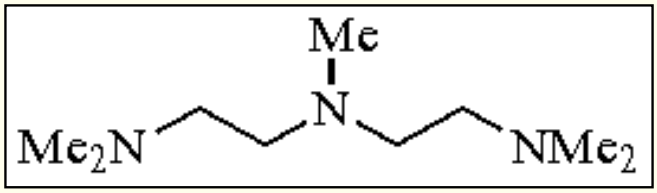

[3030-47-5] · $C_9H_{23}N_3$ · *N,N,N´,N´´,N´´*-Pentamethyldiethylenetriamine · (MW 173.35)

(ligand for lithium which enhances the reactivity of organolithium compounds)

Alternate Names: PMDTA; PMDETA.

Physical Data: mp -20 °C; bp 198 °C; *d* 0.830 g cm^{-3}; n_D 1.4420.

Solubility: sl sol H_2O; sol ethanol, acetone, ethers, alkanes.

Form Supplied in: liquid; widely available. *Drying:* distilled from CaH_2 at 10 mmHg, then stored under N_2 or argon in the absence of moisture and oxygen.

Handling, Storage, and Precautions: use in a fume hood.

N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine forms monomeric complexes with several organolithium compounds[1a-e] in which lithium is tridentately coordinated to PMDTA as determined by ^{13}C NMR (**1a**[1] and **1b**[2]) and X-ray crystallography (**1c**,[3] **1d**,[4] and **1e**[5]) and the interesting chloride-bridged monocation in salt (**2**).[6]

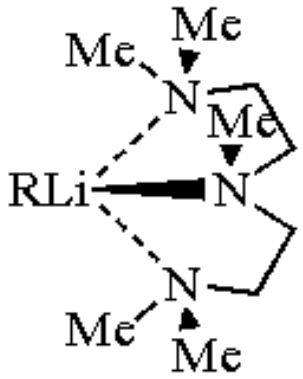

(1)

(PMDTA)Li--Cl--Li(PMDTA)$^+$ LiC(TMS)$_2$

(2)

(1a) R = neopentyl
(1b) R = 2,4,6-tri-*t*-butylphenyl
(1c) R = TMSCH
(1d) R = η^3-allyl
(1e) R = phenyl

Allylamine (**3**) undergoes, in diethyl ether, metalation at the vinyl carbon (to form **4**), whereas in the presence of PMDTA, metalation takes place at the allylic carbon (to form **5**). The dilithium species react with electrophiles (eq 1) in the expected fashion.[7]

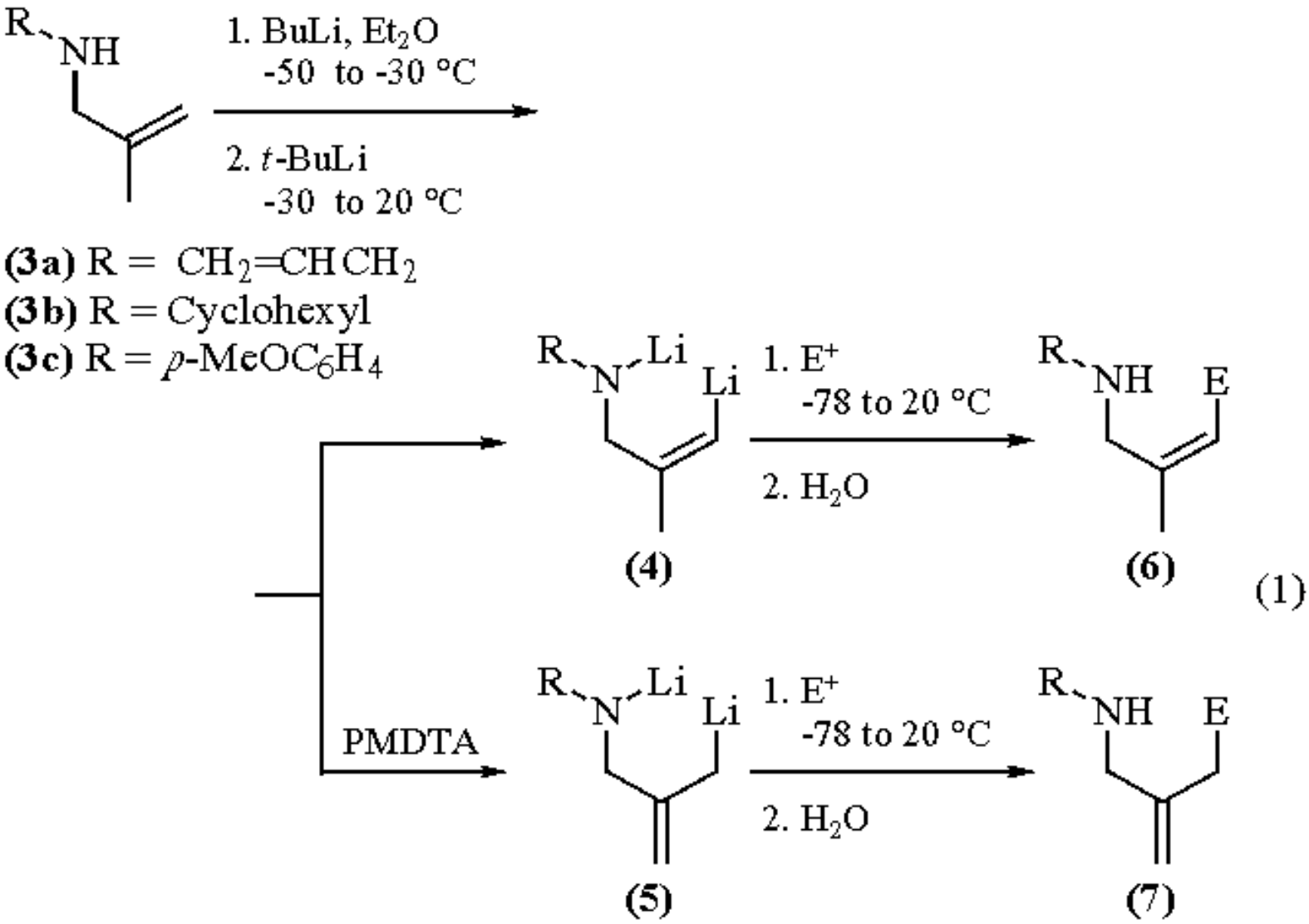

Reagent	E	Et_2O (6c)	PMDTA + Et_2O (7a)	(7b)	(7c)
D_2O	D	92	94	80	65
Bu_3SnCl	Bu_3Sn	90	72	70	63
PhCHO	PhCHOH	78	-	-	57

The metalation of *o*- and *p*-fluoroanisole also shows dramatic changes in regiochemistry (eqs 2 and 3). With PMDTA, complete metalation *ortho* to fluoro was observed; in its absence, metalation occurred *ortho* to the methoxy group.[7]

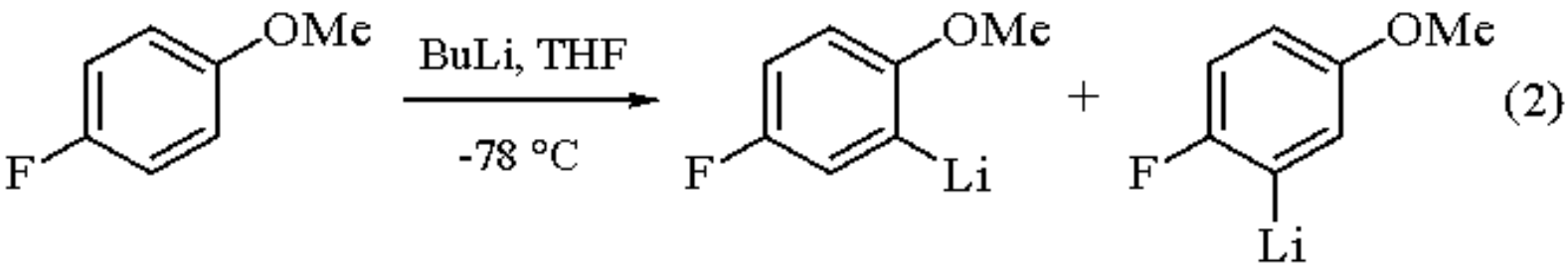

Cosolvent		
none	100:0	50%
PMDTA	0:100	85%

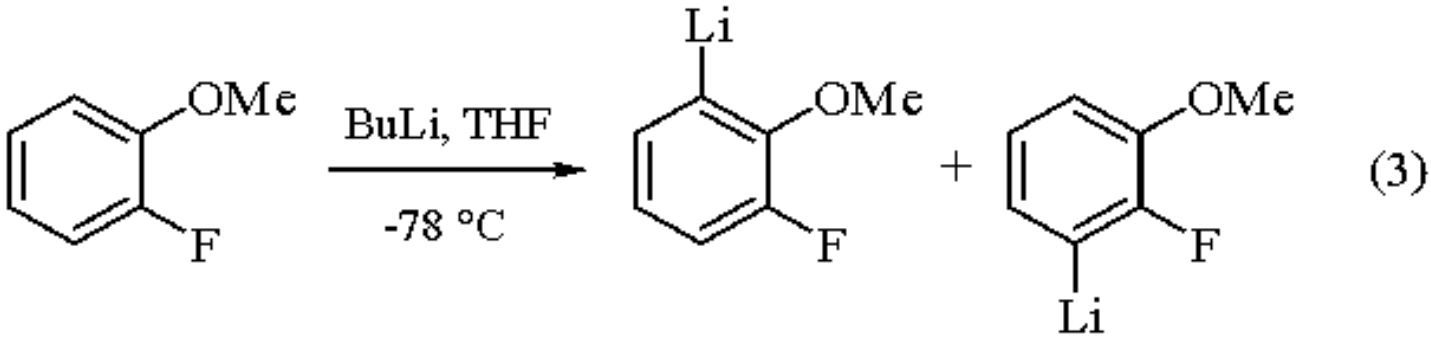

Cosolvent		
none	100:0	50%
PMDTA	0:100	77%

Metalation of PMDTA by *s*-BuLi in cyclohexane at 25 °C yields a mixture of the two lithiomethyl compounds (**8**) and (**9**) in ratio of 98:2, as indicated by NMR and the products of reactions (**10** and **11**) with electrophiles (eq 4).[8] Products (**10**) and (**11**) were not separated.

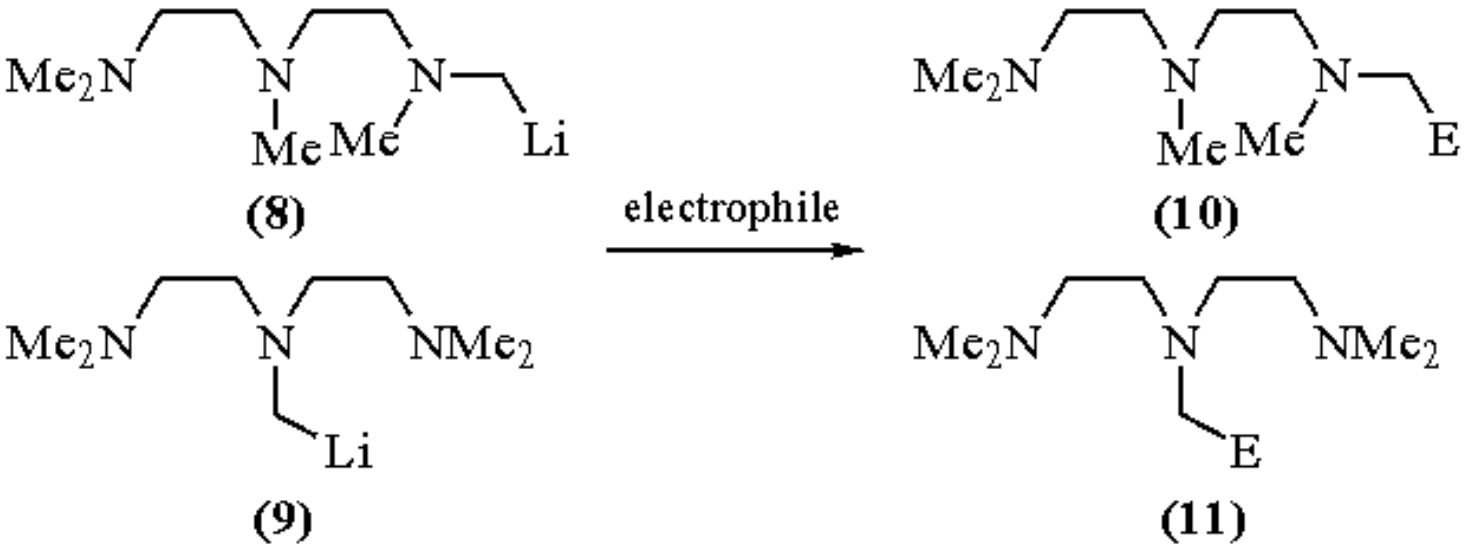

(4)

Electrophile	E
Me_3SnCl	Me_3Sn
PhCHO	PhCHOH

In hydrocarbon and benzene solution, the 1-lithiomethyl derivative of PMDTA, (**8**) has been shown, from NMR studies, to form two monomeric species in which lithium is tridentately coordinated.[9] NMR lineshape analysis reveals Δ*H*&DDagger; for interconversion of the two monomers (A &ibond; B) to be 10.3 ± 1 kcal mol^{-1} with Δ*S*&DDagger; = -27 ± 1 cal K^{-1} mol^{-1}.[9]

A variety of substituted 5-hexen-yllithiums (e.g. **12**) are formed from the corresponding iodides (**13**) by halogen lithium exchange using ***t-Butyllithium***.[10] These compounds cyclize to the cyclopentylmethyllithiums (**14**) on warming to 20 °C in the presence of different lithium ligands such as THF, ***N,N,N´,N´-Tetramethylethylenediamine***, and PMDTA (eq 5).[10] The reaction is totally regiospecific and more stereospecific than the analogous radical-mediated cyclization which forms the same products.

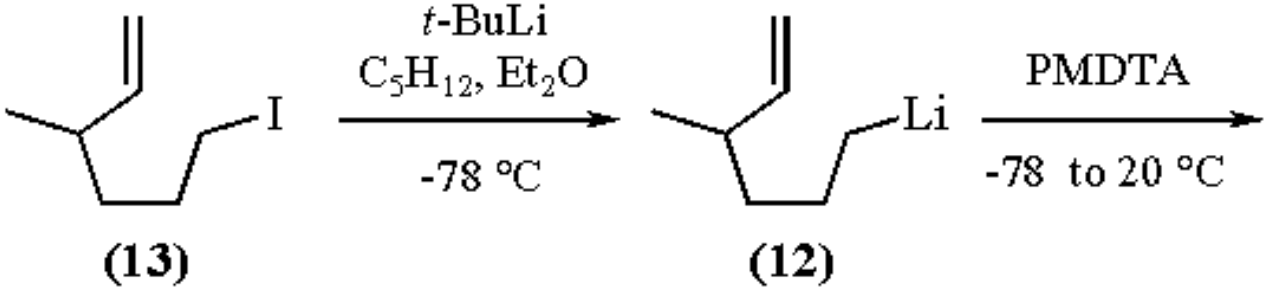

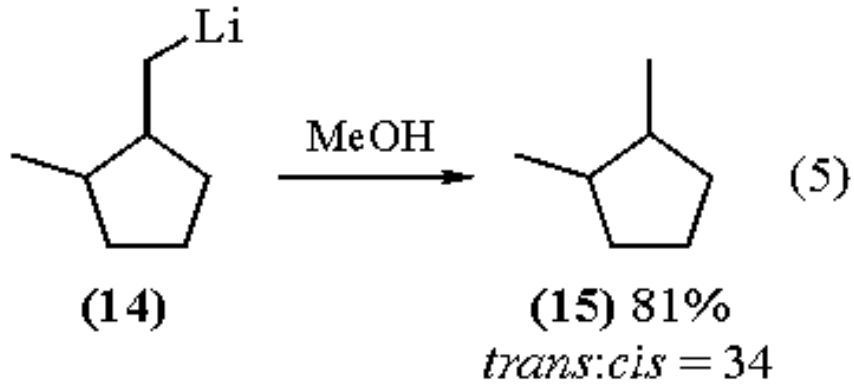

Product distribution from electrogenerated (magnesium anode) nickel(0)-catalyzed ***Carbon Dioxide*** incorporation into α,o-diynes (**16**) is influenced by the nature of the ligands L used (eq 6).[11] With L = PMDTA at 65 °C the ratio of (**17**):(**18**) is 80:20, whereas using TMEDA the ratio is 50:15; with bipy a 5:95 (**17**):(**18**) ratio was obtained.

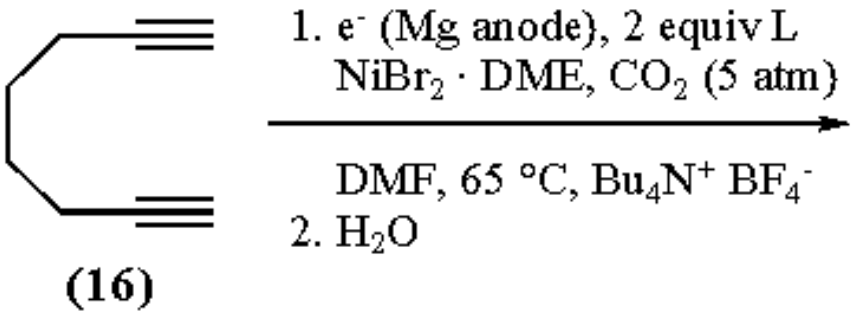

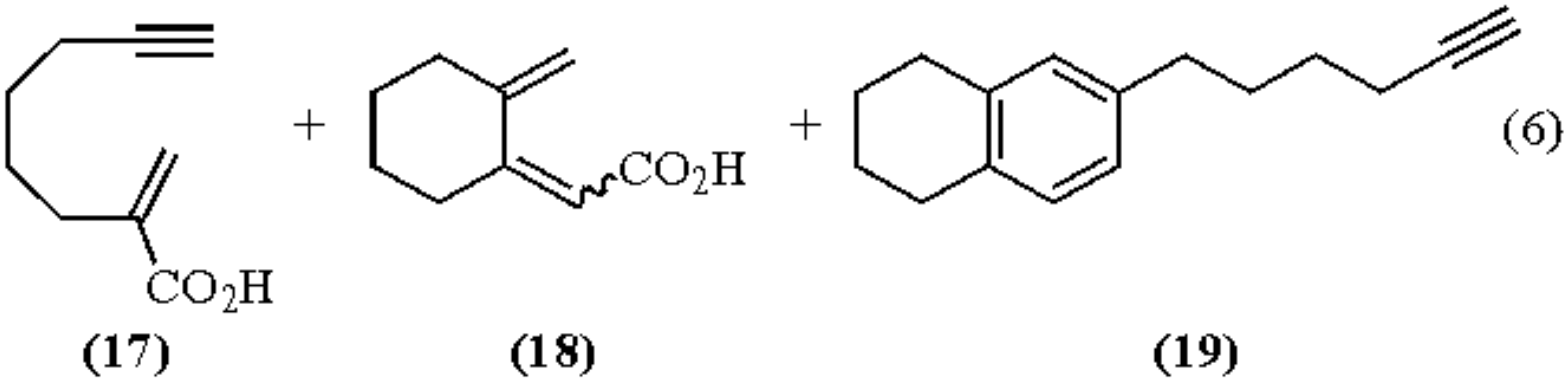

Related Reagents.

N,N´-Dimethylpropyleneurea; ***Hexamethylphosphoric Triamide***; ***N,N,N´,N´-Tetramethylethylenediamine***.

---

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(2*R*,4*R*)-2,4-Pentanediol[1]

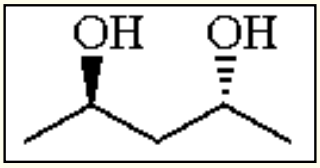

[42075-32-1] · $C_5H_{12}O_2$ · (2*R*,4*R*)-2,4-Pentanediol · (MW 104.17)

(diol used for the preparation of chiral acetals[1])

Physical Data: mp 48-50 °C; bp 111-113 °C/19 mmHg.

Form Supplied in: white solid; widely available.

Preparative Methods: via asymmetric hydrogenation of ***2,4-Pentanedione***.[2] Its enantiomer *[72345-23-4]* is also available by the same method.

Purification: recrystallization from ether.

Handling, Storage, and Precautions: should be stored in a tightly closed container since it is hygroscopic.

Cleavage of Acetals.

Acetals of 2,4-pentanediol are easily prepared from aldehydes via standard procedures (e.g. cat. PPTS, PhH, Dean-Stark removal of H_2O). These acetals have been cleaved with a variety of nucleophiles in the presence of Lewis acids to yield hydroxy ethers with high (typically 90-95% de) diastereoselectivities. Oxidation and β-elimination then provides enantiomerically enriched alcohols (eq 1). Nucleophiles have included allylsilanes to produce homoallylic alcohols,[3] alkynylsilanes to give propargylic alcohols,[4] Me_3SiCN to provide (after hydrolysis) α-hydroxy acids,[5] and enol silyl ethers, α-silyl ketones, or silyl ketene acetals to yield aldol-type products.[6] The same strategy using organometallic reagents/Lewis acid combinations (e.g. $RCu/BF_3.OEt_2$,[7] $RMgX/TiCl_4$,[8] $RLi/TiCl_4$,[8,9] $R_2Zn/TiCl_4$[9]) is a general route to secondary alcohols. Other nucleophile/Lewis acid combinations that have been used include alkynylstannanes/$TiCl_4$[10] and zinc enolates/$TiCl_4$.[11] These acetals have also been used in polyene cyclizations.[3a,12]

(2R,4R)-2,4-Pentanediol

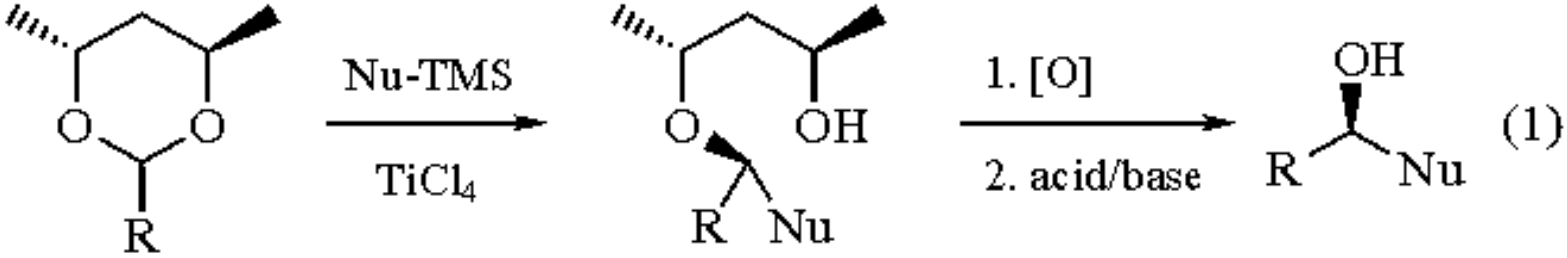

2,4-Pentanediol is often superior to other diols such as 2,3-butanediol for these reactions because of higher distereoselectivities in reactions with nucleophiles and the more facile cleavage of the resulting hydroxy ether by oxidation-β-elimination.[3] Removal of the chiral auxiliary is usually carried out with ***Pyridinium Chlorochromate*** oxidation followed by β-elimination using KOH,[3] K_2CO_3,[13] piperidinium acetate,[6] dibenzylammonium trifluoroacetate,[14] or DBU.[4c] In some cases, 1,3-butanediol is preferred because the final β-elimination may be effected under milder conditions.[14]

A detailed study of the mechanism and origin of stereoselectivity in reactions of allyltrimethylsilane with dioxane acetals has been published.[15]

Reduction of Acetals.

Reductions of acetals of 2,4-pentanediol can provide (after removal of the chiral auxiliary by oxidation and β elimination) secondary alcohols with good enantioselectivity. The choice of reagents dictates the configuration of the final product. Use of ***Dibromoalane*** gives products from selective *syn* cleavage of the acetal while ***Triethylsilane/Titanium(IV) Chloride*** gives the more usual *anti* cleavage products (eq 2).[13]

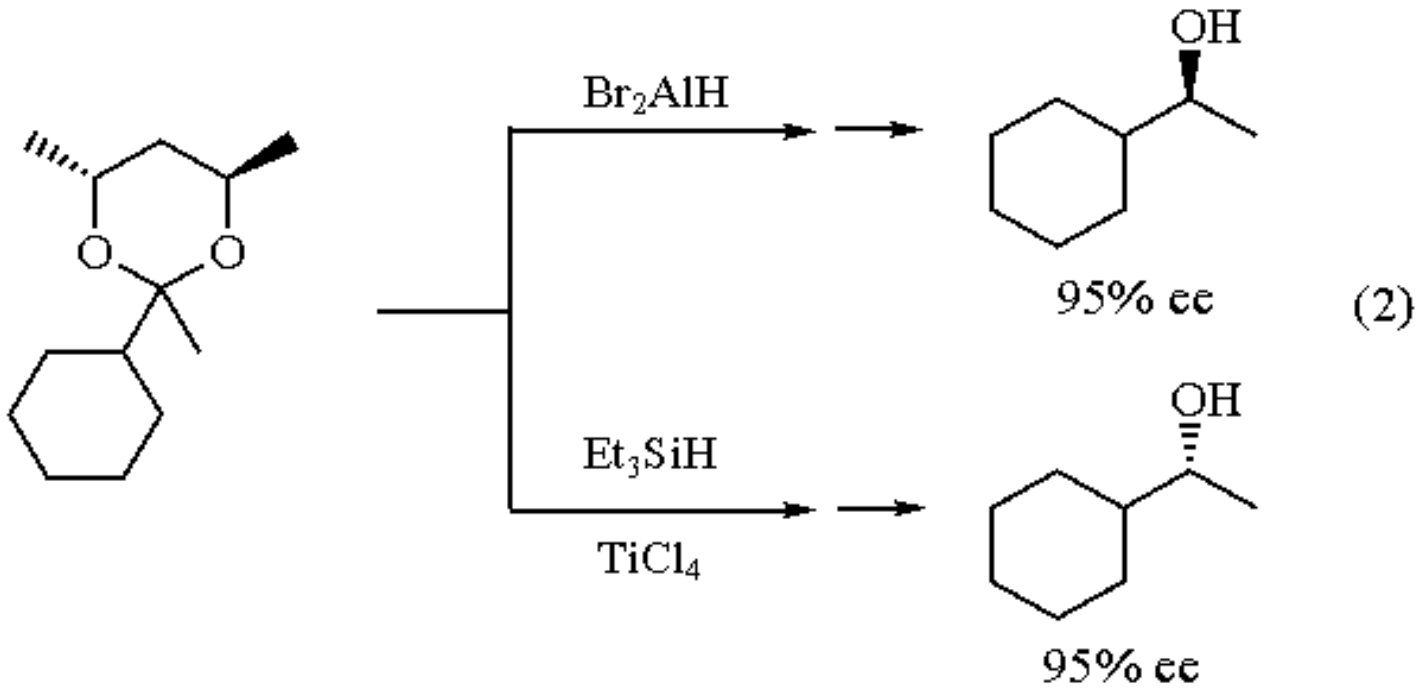

Elimination of Acetals.

Treatment of 2,4-pentanediol acetals of *meso* ketones with ***Triisobutylaluminum*** gives enol ethers with high diastereoselectivities (eq 3).[16]

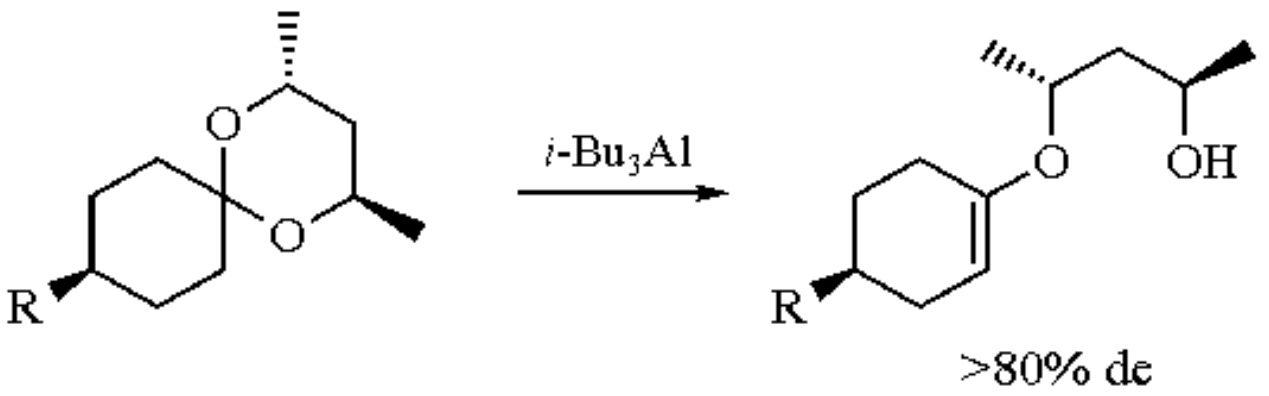

(3)

Acetals as Chiral Auxiliaries.

There have been many applications of acetals of 2,4-pentanediol as chiral auxiliaries to control the diastereoselectivity of reactions on another functional group.[1] Examples include cyclopropanation of alkenyl dioxanes,[17] lithium amide-mediated isomerization of epoxides to allylic alcohols,[18] and addition of dioxane-substituted Grignard reagents[19] or organolithiums[20] to aldehydes.

Other Uses.

Acetals of 2,4-pentanediol have also been prepared in order to determine the enantiomeric purity of aldehydes and ketones by analysis of diastereomers by GC or NMR.[21] ***2,3-Butanediol***[22] is more commonly used for this purpose but has been shown to be less effective in some cases.

---

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2,4-Pentanedione

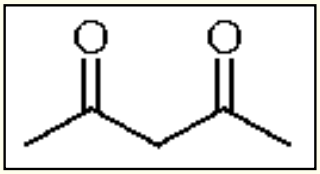

(keto)

[123-54-6] · $C_5H_8O_2$ · 2,4-Pentanedione · (MW 100.13) (enol)

[1522-20-9]

(carbon-carbon condensations involving mono-, di-, and trianions; formation of pyrazoles, isoxazoles, pyrroles, and pyridines; catalysis by metal chelates)

Alternate Names: acetylacetone; acac.

Physical Data: liquid, bp 45 °C/30 mmHg;[26] *d* 0.975 g cm^{-3}. Keto form: mp -23 °C; bp 134-136 °C.[24] Enol form: mp -9 °C.[24]

Solubility: misc organic solvents; sol dil HCl; slightly sol hot H_2O.[24]

Form Supplied in: commercially available liquid, in which the enol form predominates; the keto form predominates in aq soln.

Preparative Methods: conveniently prepared by BF_3-catalyzed reaction of acetone and acetic anhydride, or by reaction of ethyl acetate, acetone, and NaOEt.[25]

Purification: distillation after drying over anhyd K_2CO_3; several other methods are available.[26]

Handling, Storage, and Precautions: moderately toxic; reactions should be conducted in a well-ventilated fume hood.

General Considerations.

2,4-Pentanedione (**1**) is weakly acidic (pK_a &AApprox; 9) and exists as a solvent-dependent tautomeric mixture. The enol form is favored by aprotic organic solvents, being stabilized by internal hydrogen bonding. Reactions of (**1**) involve (i) reactions of electrophiles at the 3-position via the enolate anion (eq 1), (ii) reactions at the terminal methyl

position via the 1,3-dianion (eq 1), (iii) reactions at the terminal position via the 1,3,5-trianion, and (iv) nucleophilic attack on the carbonyl groups, often to form heterocyclic compounds.

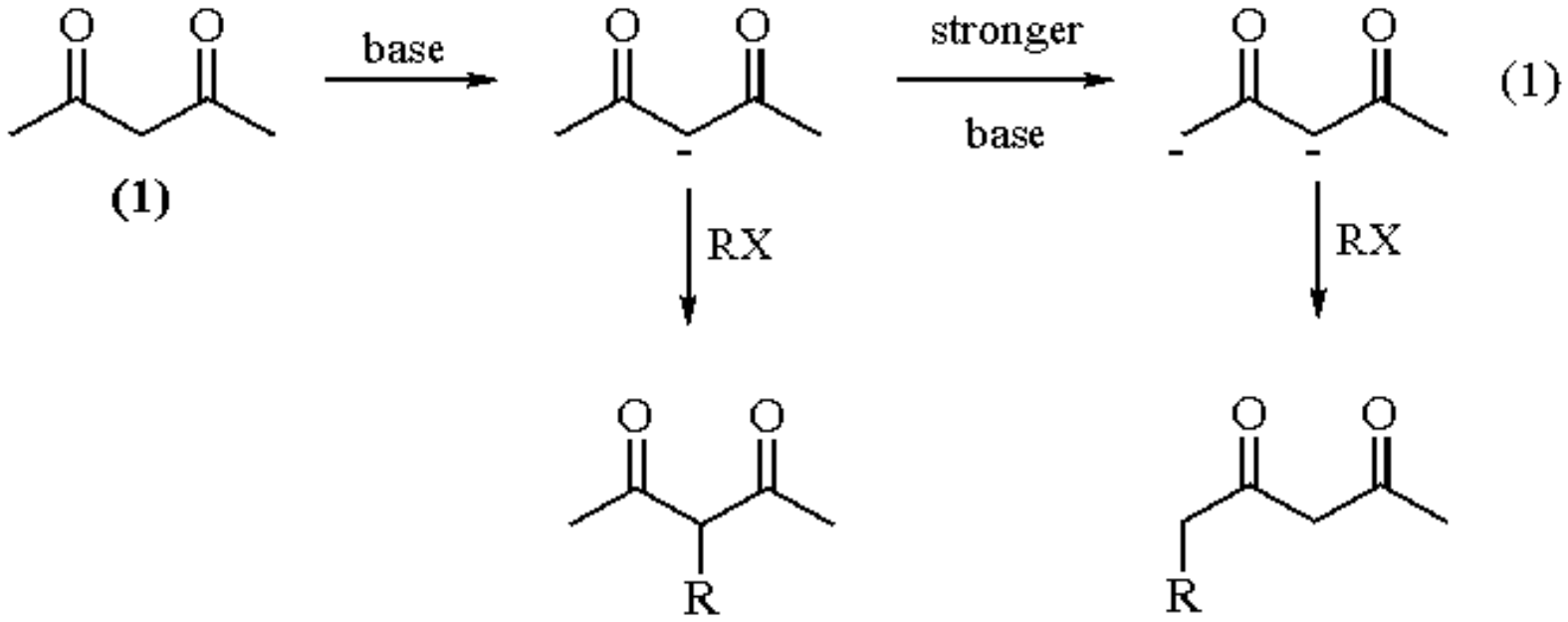

Alkylations of monoanions of (**1**) and homologs can occur on either carbon or oxygen, the site of reaction depending on alkylating agent, counterion, and solvent.[1] Dialkylation can be a serious complication. The highly toxic Tl^{I} chelates were reported to be effective for alkylation,[2] but claims for carbon specificity with alkyl halides other than MeI have been disputed.[3] Preferable counterions for *C*-alkylation include Ni^{II} [4] and R_4N^+.[5] Alkylations carried out with K_2CO_3 in EtOH lead to the corresponding alkylated ketones via retro-Claisen reactions of the alkylated diketone.[6] For arylations, $S_{RN}1$ processes have been observed in a few cases, but the processes are by no means general.[7]

Other widely used reactions[1] involving the monoanions of (**1**) and homologs include conjugate additions (Michael reactions) to α,β-unsaturated compounds,[8] and aldol[9] and Knoevenagel[10] reactions with carbonyl compounds. The Knoevenagel reactions employ secondary amine catalysts and are likely to involve iminium ion and/or enamine intermediates. Enol esters of (**1**) are produced by treatment with acid chlorides in pyridine.[11]

The reagent can be converted to the 1,3-dianion by treatment with alkali amides in liquid ammonia or ***Lithium Diisopropylamide*** in THF.[12] The dianion undergoes reaction exclusively at the 1-position and is markedly more reactive than the monoanion. Reactions of the dianion include alkylation, arylation by benzyne and radical pathways, aldol condensations, conjugate additions, acylations, and carboxylation.[12] Condensations with aliphatic carbonyl compounds subject to ionization are best carried out with dilithio-(**1**). Dianions of higher aliphatic homologs of (**1**) form preferentially at the less-branched sites. Acylations of (**1**) and benzoylacetone by aromatic esters to give 1,3,5-triketones can also be achieved using ***Sodium Hydride*** as the ionizing base; the reactions may not involve dianions.[13] Other types of electrophiles have given fair to poor results in the NaH system. The strongly basic 1,3,5-trianion has been prepared; only limited studies of its reactivity have been made.[14]

Heterocycles.

The difunctionality of 2,4-pentanedione has frequently been used in the synthesis of heterocyclic compounds. Examples include reactions to form pyrazoles, isoxazoles, pyrroles, and pyridines.[15]

Transition Metal Chelates.

Metals form highly crystalline chelated complexes with (**1**), some of which have useful applications as synthetic reagents. ***Copper(II) Acetylacetonate*** modifies the reactivity of carbenes generated from diazo compounds.[16] Reactions appear to involve copper-carbene complexes. For example, it stabilizes benzoylcarbene sufficiently to permit 1,3-dipolar additions and catalyzes intramolecular dimerization of 1,7-bis(diazo)-1,6-heptanediones to cyclohept-2-ene-1,4-diones. ***Tris(acetylacetonato)iron(III)*** catalyzes reductive decyanation of alkyl nitriles by sodium and epoxidations of alkenes by H_2O_2 in MeCN.[17] ***Manganese(III) Acetylacetonate*** oxidizes phenols to dimers without formation of quinones.[18] ***Nickel(II) Acetylacetonate***, a cancer suspect agent, is a highly effective catalyst for addition of β-diketones to Michael acceptors; it catalyzes coupling of aryl Grignard reagents with aryl iodides, and in the Wilke catalytic system ($Ni(acac)_2$-PPh_3-$AlEt_3$) it alters the regiochemistry of some Diels-Alder reactions between dienes.[19,20] The pyridine complex of ***Palladium(II) Acetylacetonate*** is a homogeneous catalyst for reduction of nitrobenzene.[20,21] ***Vanadyl Bis(acetylacetonate)*** catalyzes oxidation by ***t-Butyl Hydroperoxide*** of tertiary amines to *N*-oxides, alkenes to epoxides, and aniline to nitrobenzene.[22] Organoboranes require addition of ***Bis(acetylacetonato)zinc(II)*** to achieve Pd-catalyzed cross-coupling with aryl and benzyl halides.[23] $Zr(acac)_4$ *[17501-44-9]* catalyzes acylation of amines, thiols, and alcohols (primary > phenol > secondary) by 3-acyl-2-oxazolones.[24]

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trans-3-Penten-2-one

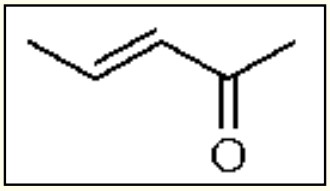

[3102-33-8] · C_5H_8O · *trans*-3-Penten-2-one · (MW 84.13)

(undergoes conjugate addition as in Michael[1-3] and cuprate[4] reactions; reagent for Robinson annulation[5-11] and Diels-Alder[12] reaction)

Physical Data: bp 121.5-124 °C; *d*204 0.8624 g cm^{-3}; *n*25D 1.4329.

Solubility: sol water and all organic solvents.

Form Supplied in: liquid; commercial material is often contaminated with 3-penten-2-ol which is difficult to remove by distillation.

Analysis of Reagent Purity: IR, NMR, and GC.[13]

Preparative Methods: an excellent method[14] involves the Wittig reaction of ***Acetylmethylenetriphenylphosphorane*** and ***Acetaldehyde*** (2.5 mol equiv) in methylene chloride (reflux, 6 h, 76% yield). Another good method[13] proceeds via the ***Aluminum Chloride*** catalyzed addition of ***Acetyl Chloride*** to propene followed by dehydrochlorination.

Purification: fractional distillation.[13,14]

Handling, Storage, and Precautions: best stored in refrigerator; moderately toxic;[15] lachrymator. This reagent should only be handled in a fume hood.

Conjugate Addition Reactions.

Enolates of esters,[1] amides,[2] ketones (eq 1),[1] and organocuprates[4] participate in conjugate addition reactions with *trans*-3-penten-2-one.

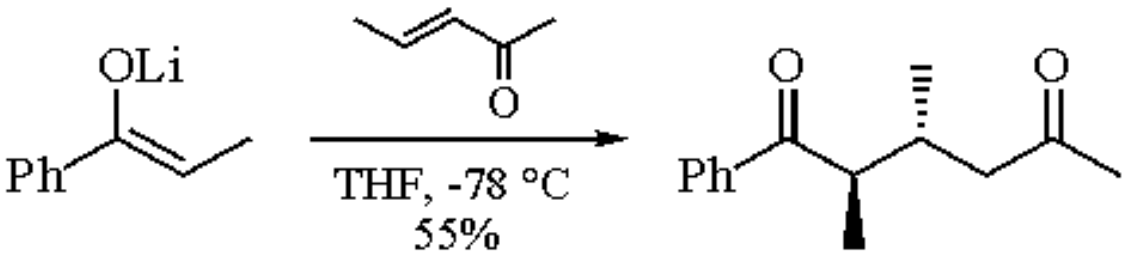

(1)

Basic conditions can be avoided by using the Lewis acid-catalyzed Michael reaction of enol silyl ethers with the reagent (eq 2).[3]

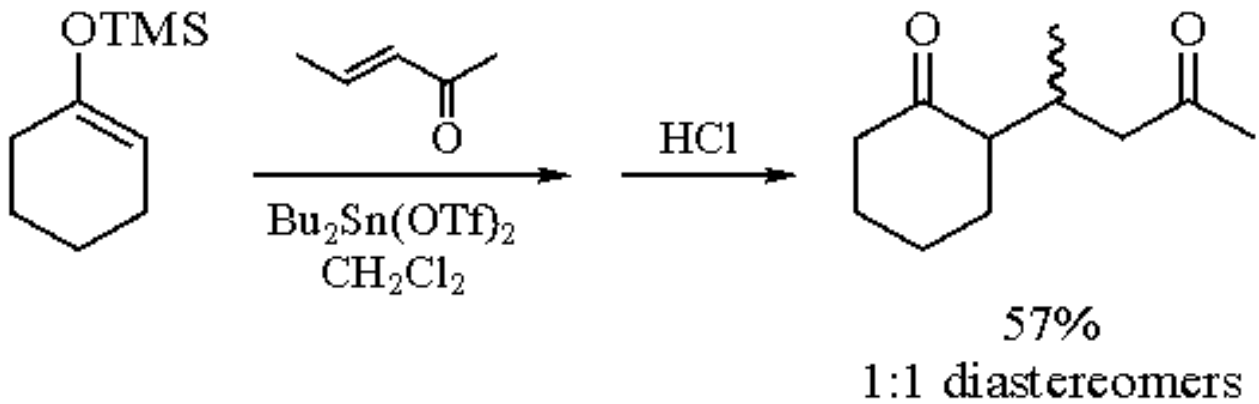

(2)

Robinson Annulation.

An important application of *trans*-3-penten-2-one is in the Robinson annulation reaction,[5-11] which has been widely used for the synthesis of natural products such as eremophilane sesquiterpenes.[5-7] Annulations involving this enone have been involved as key steps (eqs 3 and 4) in the total synthesis of isonootkatone[5] and calarene.[6]

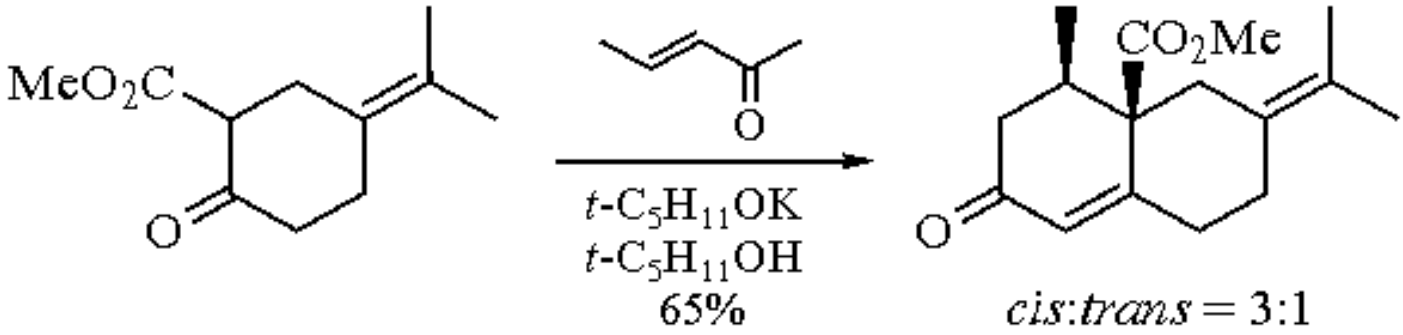

(3)

trans-3-Penten-2-one

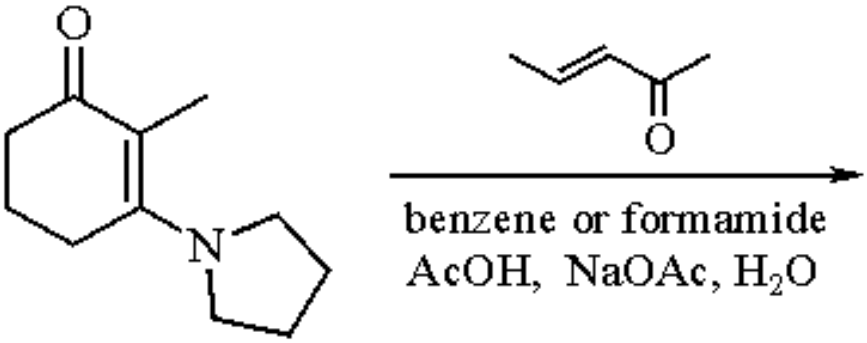

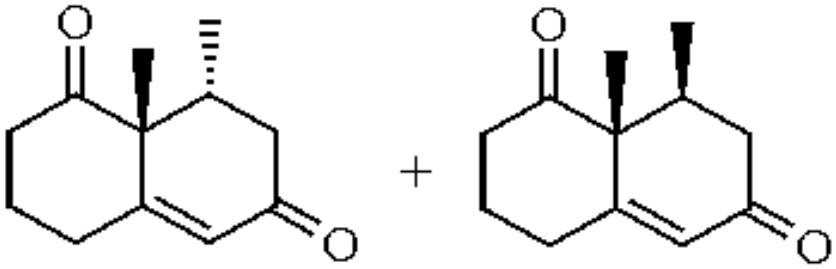

(4)

The steric outcome of these reactions is very dependent on the reaction conditions.[5-9] In eq 4 the use of benzene as solvent gave a 10:1 ratio of the *trans*- and *cis*-dimethyl products while formamide gave a 1:1 ratio. Likewise, reaction of 2-methylcyclohexanone and *trans*-3-penten-2-one using ***Sodium Hydride*** in dioxane gave the *cis*-dimethyl product (eq 5), but DMSO gave the *trans* product.[8] However, other workers reexamined this work and observed somewhat different yields and stereoselectivities.[9]

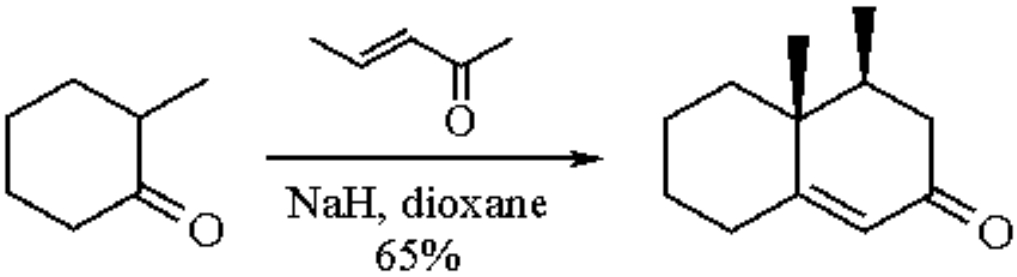

(5)

A variation of the Robinson annulation involves the Lewis acid-catalyzed reaction of a silyl enol ether with the enone (eq 6).[11]

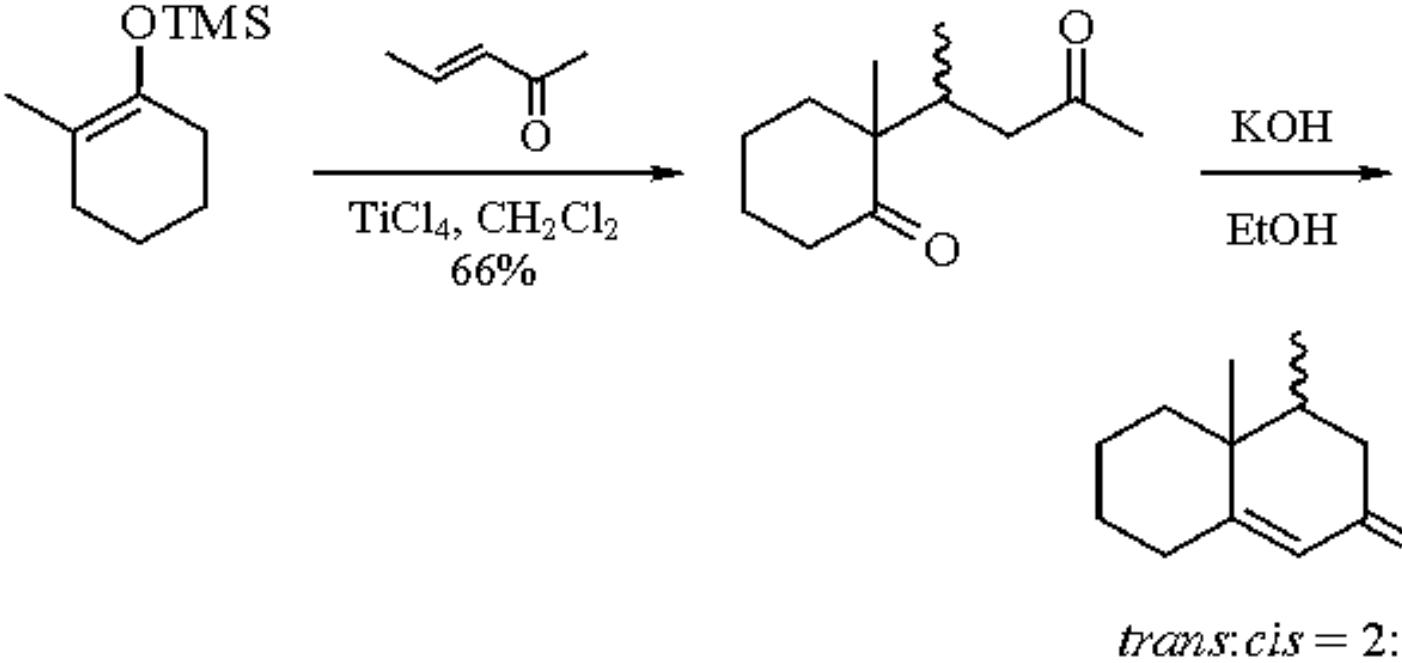

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1-Pentynylcopper(I)[1]

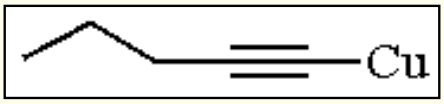

[19093-51-7] · C_5H_7Cu · 1-Pentynylcopper(I) · (MW 130.67)

(coupling agent for delivery of PrC&tbond;C group;[2] formation of mixed lithium cuprates[3])

Physical Data: canary yellow polymeric solid.[4,5]

Solubility: sol pyridine (10^{-5} M, 25 °C); slightly sol ether, THF; insol DMF, water.

Preparative Methods: an aqueous ammoniacal solution of ***Copper(I) Iodide*** is added to 1-pentyne in ethanol, and the resulting precipitate is filtered and washed.[5,6]

Purification: can be dried under vacuum (20 mmHg) at 50 °C; traces of unremoved ammonia impart a greenish-yellow color.[5]

Handling, Storage, and Precautions: all copper(I) acetylides are potentially explosive when dry and should be treated with due caution. Use in a fume hood.

Copper(I) Substitutions.

Mild substitutions of acyl and sulfenyl halides can be accomplished with high efficiency (eqs 1 and 2).[7] Thermolysis is either carried out neat or in acetonitrile solution.

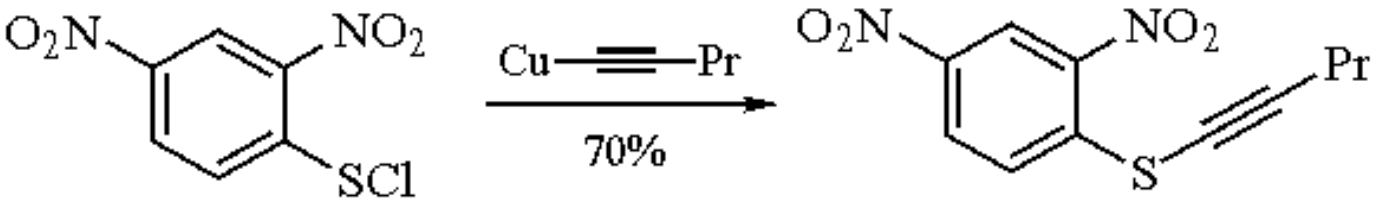

(1)

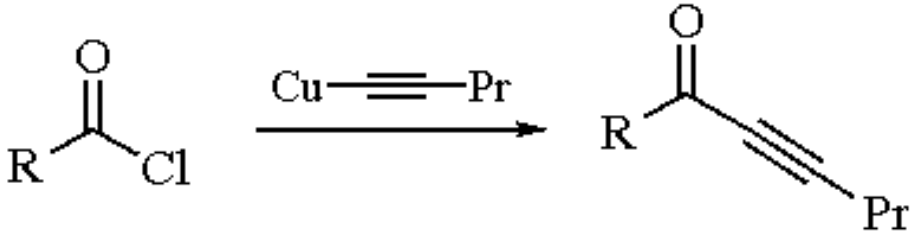

(2)

R = Me 75%
R = $PhCH_2CH_2$ 81%

Halides that are prone to homolytic scission, however, instead of yielding substitution products give rise to acetylenic oxidative coupling products.[7] Addition of pentynylcopper to aryl iodides results in formation of coupled tolanes; *ortho*-amino substituted tolanes can be thermolyzed to give a range of 2-propyl indoles in good yield (eq 3).[2,5,7] The cyclizations, which can be carried out either neat or in refluxing pyridine, cyclohexane or DMF, can be catalyzed by copper(I) iodide or a range of salts including HgI_2, $AgNO_3$, Hg_2Cl_2, $PdCl_2$, and $PtCl_2$.[7]

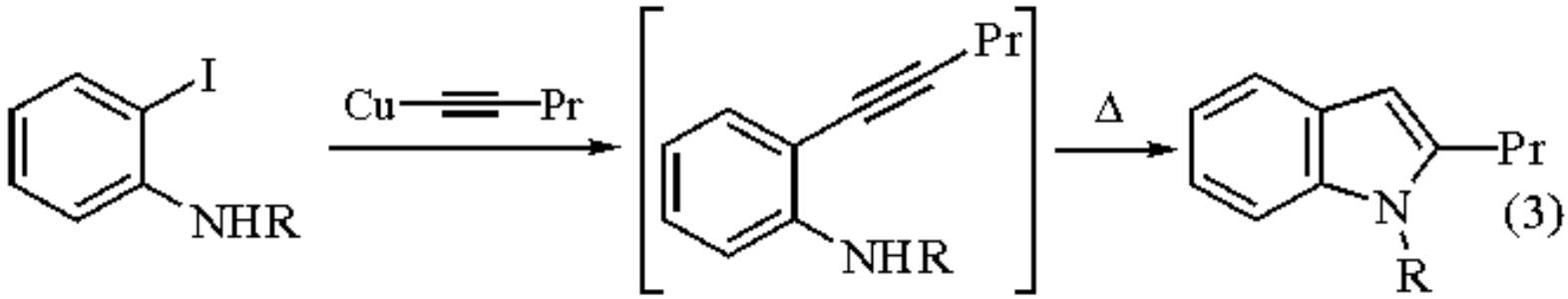

(3)

55-100%

A similar protocol has been used to convert substituted *o*-bromophenols into the corresponding 2-propylbenzofurans (eq 4).[2] In this series it is not possible to isolate the intermediate tolanes.

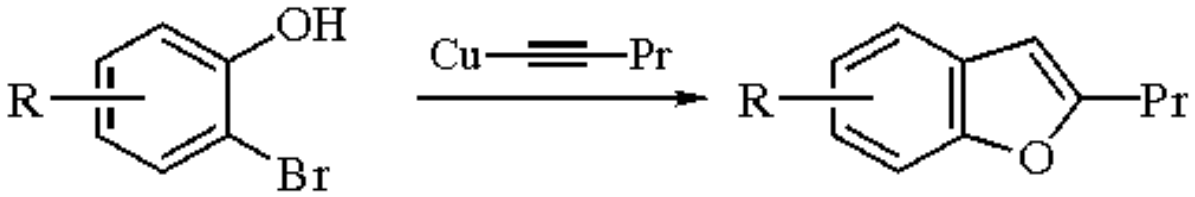

(4)

Intramolecular additions to tolanes can be effected by other groups, including carboxylic acids, yielding isocoumarins and benzylidenephthalides (eq 5). The yields of such bicyclic adducts are very dependent on both the conditions used and ring size. Intramolecular cyclization of the tolane derived from addition to *o*-iodobenzyl alcohol gives a 50% yield of the corresponding dihydrobenzopyran bearing an *n*-propyl substituent. However, reaction of pentynylcopper with *o*-iodophenethyl alcohol results in formation of dihydrobenzofuran and 1-pentyne in 79% yield.[7]

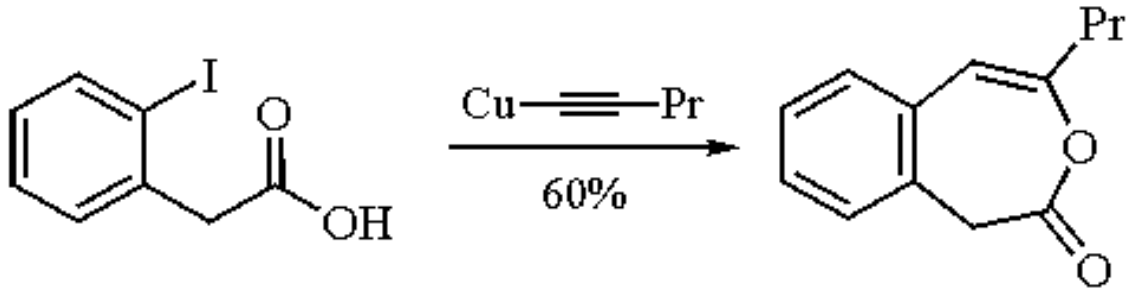

(5)

Pentynylcopper has been employed to effect coupling to acetylenic halides. Treatment with bromoethynyltrimethylsilane in pyridine at room temperature results in a near-quantitative yield of 1-trimethylsilyl-1,3-heptadiyne (eq 6).[8]

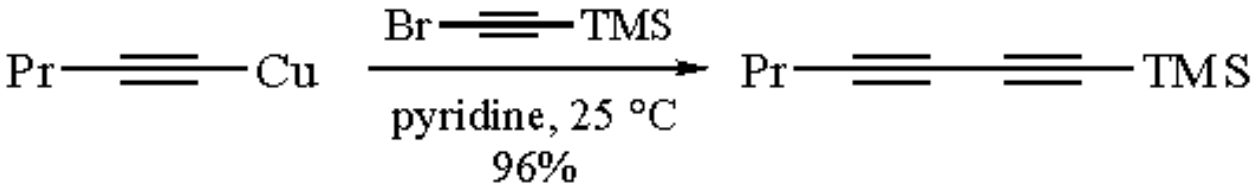

(6)

Mixed Organocuprates.

Mixed organocuprates derived from addition of the copper acetylide to vinyllithium reagents can be used to selectively transfer the vinylic group to a suitable electrophile (eq 7).[9] In this manner the pentynyl group behaves as a nontransferable dummy ligand.[3] The solubility of pentynylcopper in ether and THF is increased on addition of HMPA; thus the complex is more versatile for use in the preparation of mixed lithioorganocuprates for selective ligand transfer (see ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***).[3]

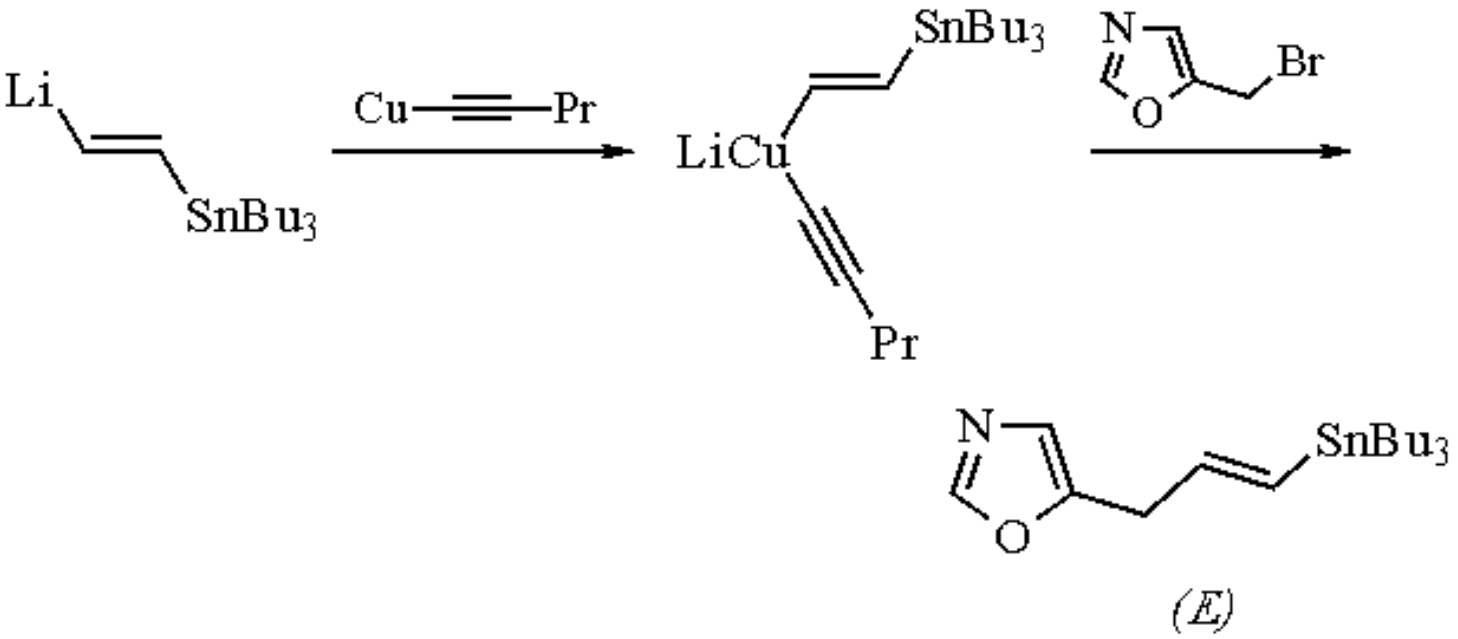

(7)

Dilithium Trialkynylcuprates.

Dilithium tris(1-pentynyl)cuprate, prepared by addition of pentynyllithium to copper iodide, adds to α,β-unsaturated systems with 1,2-chemoselectivity (eq 8).[10] The additions, which are best effected in the presence of HMPA, are effective in cyclohexenone and cyclopentenone systems, and tolerate β-substitution on the enone.[10] As an example of its utility, oxidative rearrangement of the product of addition to 2-allylcyclopent-2-enone gives access to a possible prostaglandin precursor (eq 8).

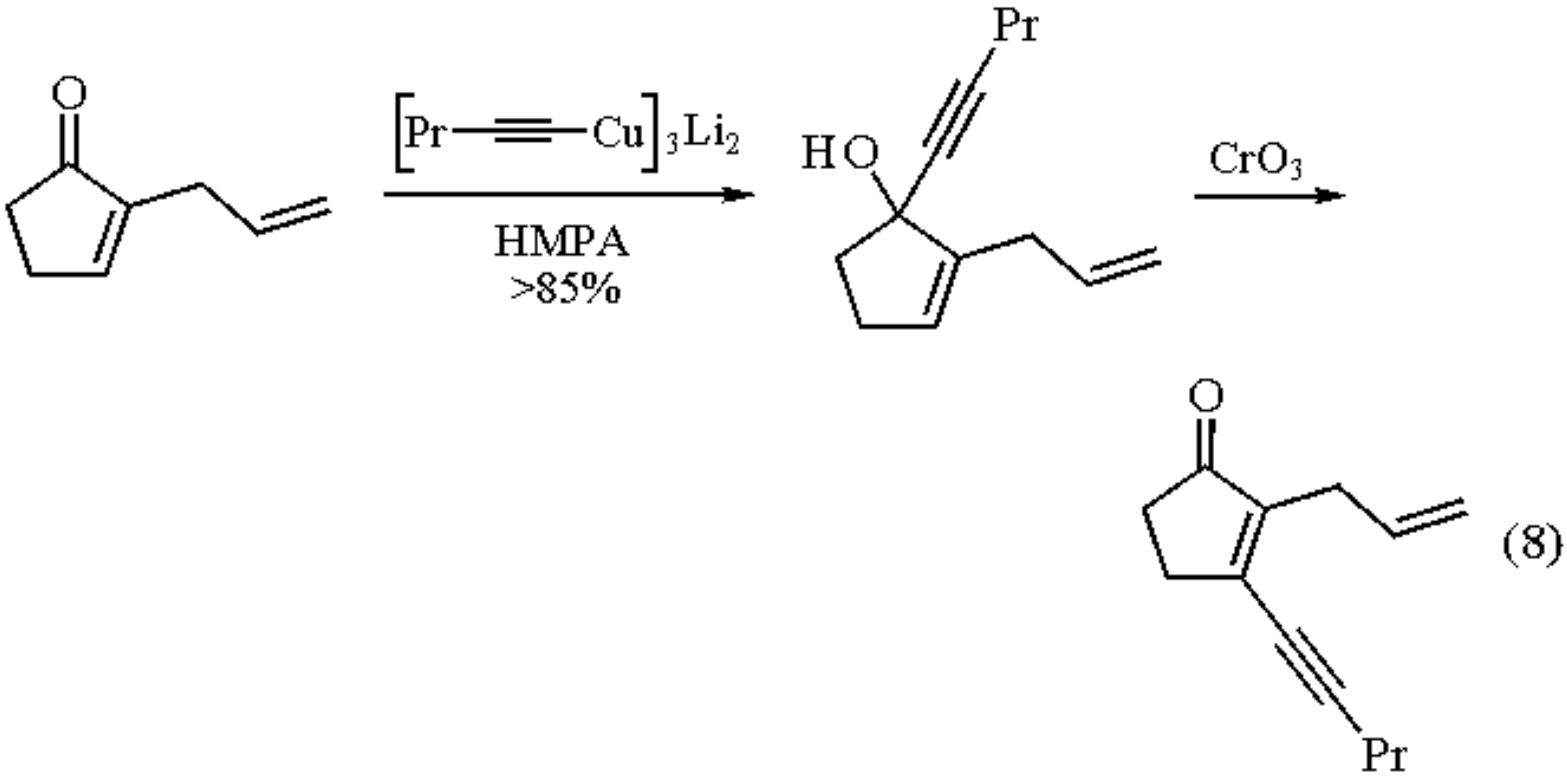

Related Reagents.

Dilithium Tris(1-pentynyl)cuprate; ***1-Hexynylcopper(I)***; ***Lithium (1-Hexynyl)(2-tri-n-butylstannylvinyl)cuprate***; ***Lithium (1-Pentynyl)(2-tri-n-butylstannylvinyl)cuprate***.

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Graham B. Jones & Brant J. Chapman

1-Pentynylcopper(I)-Hexamethylphosphorous Triamide[1]

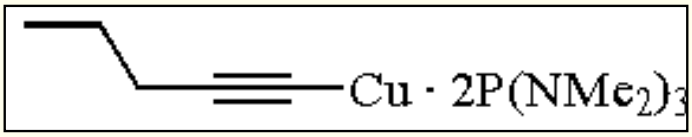

[67840-54-4] · $C_{17}H_{43}CuN_6P_2$ · 1-Pentynylcopper(I)-Hexamethylphosphorous Triamide · (MW 457.15)

(freely soluble, nontransferable dummy ligand employed in mixed lithioorganocuprates[2])

Physical Data: clear solution in ether (also see entries for ***1-Pentynylcopper(I)*** and ***Hexamethylphosphorous Triamide***).

Solubility: sol ether, THF at -78 °C.

Preparative Methods: addition of $P(NMe_2)_3$ (HMPT) to pentynylcopper in ether or THF at 25 °C.[2]

Handling, Storage, and Precautions: all copper(I) acetylides are potentially explosive when dry. Use in a fume hood.

Mixed Organocuprates.

Since initial disclosures by Corey,[2] copper(I) acetylides have found widespread use for the preparation of mixed lithiocuprates R_rR_tCuLi where R_t is a transferable group and R_r is a residual dummy group.[2-13] Copper(I) acetylides can be prepared in pure form and, due to the stabilizing d-π backbonding that exists between copper and alkynes connected by a σ-bond, alkynes represent ideal nontransferable ligands. For preparation of mixed cuprates (R_rR_tCuLi), alkynylcopper species (R_rCu) are combined with appropriate alkyllithium reagents (R_tLi). The relative insolubility of pentynylcopper in ether or THF at low temperature precluded its use for this purpose; however, the bis(HMPT) complex is soluble and reactive to alkyllithium reagents at -80 °C. The HMPT residues are water-soluble, allowing uncomplicated workup after delivery of R_t to the desired electrophile.[2]

Alkyl-Transferable Groups.

The first reported applications of the HMPT complex involved addition of alkyllithiums to the complex, forming in situ mixed lithioorganocuprates which alkylated cyclohexenone in excellent yield and chemoselectivity (eq 1).[2]

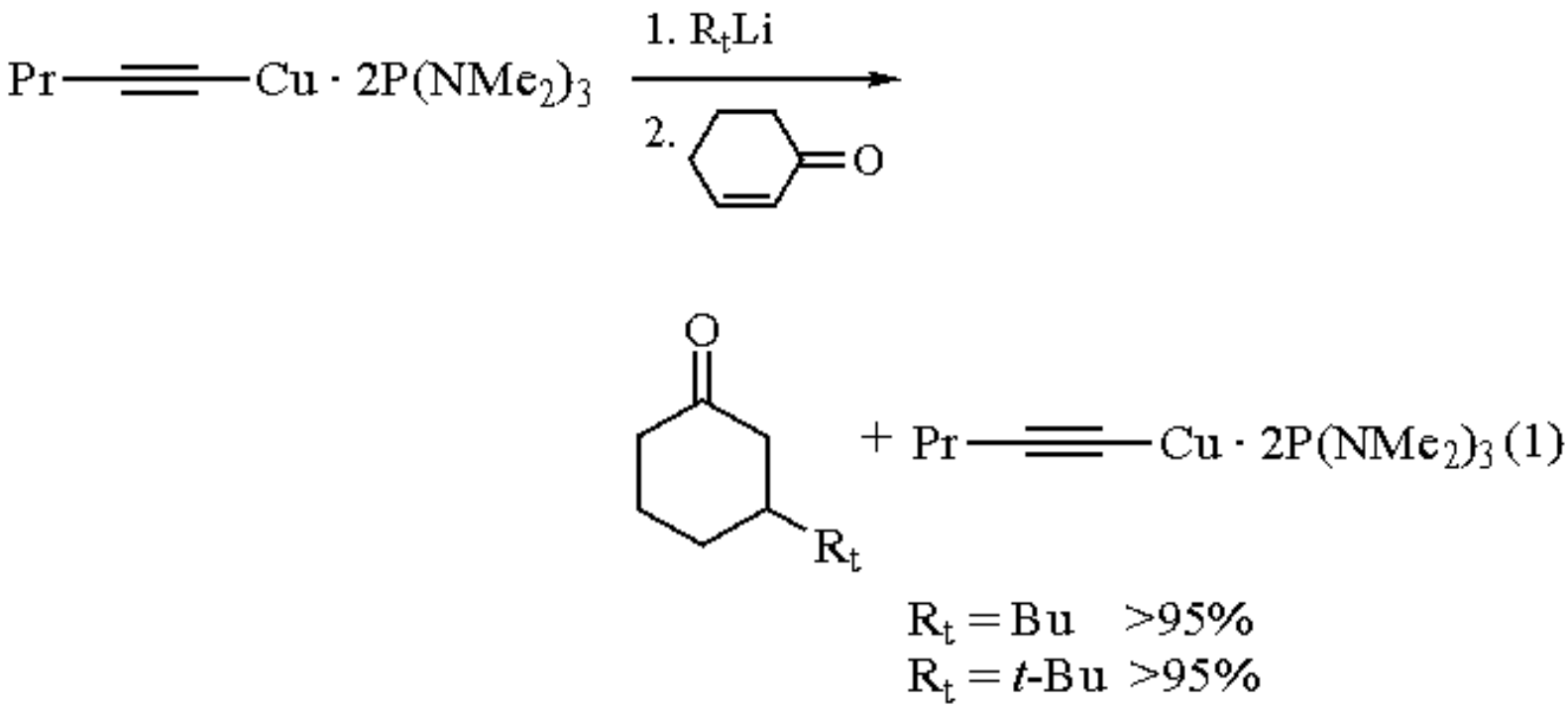

Since this initial report, general application in synthesis has been widespread, reflecting the importance of such transformations[3-5] (see also ***3,3-Dimethyl-1-butynylcopper(I)***, ***1-Hexynylcopper(I)***, and ***(3-Methoxy-3-methyl-1-butynyl)copper(I)***). It has been shown that in situ generation of the R_t group, by way of its lithio derivative using sonication methods, can result in superior yields of 1,4-addition products.[4] A representative example of a complex alkyl R_t is displayed in a synthesis of ceroplastol I (eq 2).[5]

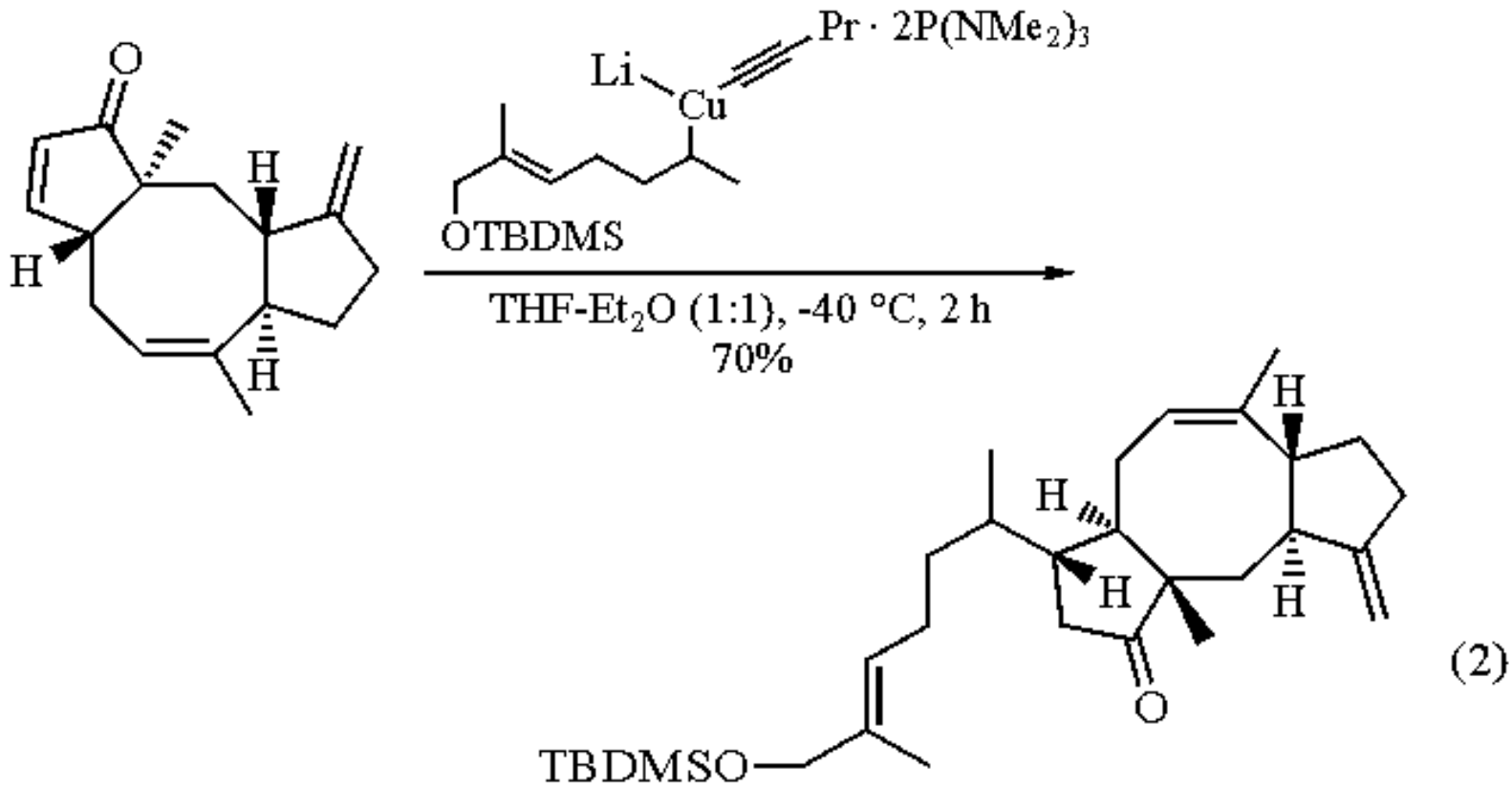

Alkenyl-Transferable Groups.

The numerous applications of this transformation underline its strategic importance in the synthesis of many natural product systems.[6-13] Perhaps the most widely celebrated uses of lithiovinyl-pentynylcuprates have been in the synthesis of prostaglandins and their derivatives.[9-12] Vinylogous organocuprates have also been used to construct the framework of prostaglandin endoperoxides (eq 3),[6] again highlighting chemoselectivity and efficiency. Chemoselectivity has also been observed in the vinylation of alkyl iodides.[7] One-pot conjugate addition-enolate alkylation procedures have been reported, giving moderate yields of the functionalized products (eq 4).[8]

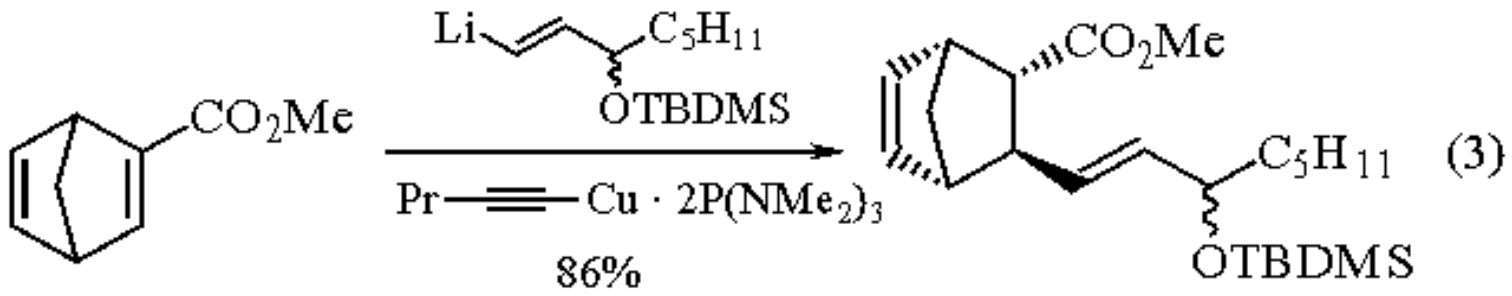

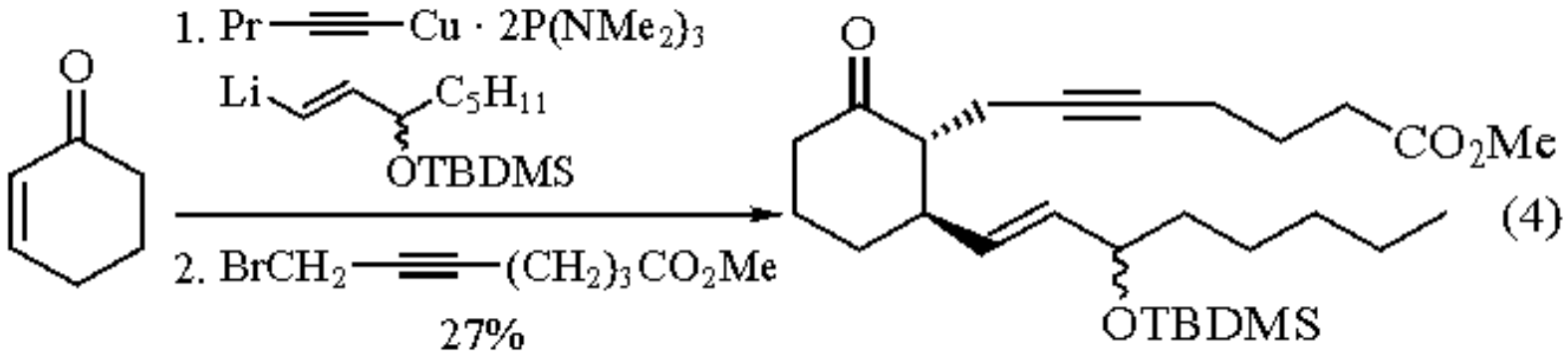

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Peracetic Acid[1]

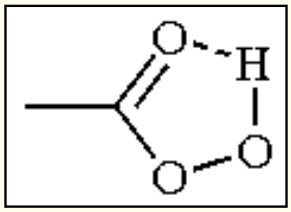

[79-21-0] · $C_2H_4O_3$ · Peracetic Acid · (MW 76.06)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes, sulfides, selenides, and amines)

Alternate Name: peroxyacetic acid.

Physical Data: mp 0 °C; bp 25 °C/12 mmHg; *d* 1.038 g cm^{-3} at 20 °C.

Solubility: sol acetic acid, ethyl acetate, $CHCl_3$, acetone, benzene, CH_2Cl_2, ethylene dichloride, water.

Form Supplied in: 40% solution in acetic acid (*d* 1.15 g cm^{-3}) having approximately the following composition by weight: peracetic acid, 40-42%; H_2O_2, 5%; acetic acid, 40%; H_2SO_4, 1%; water, 13%; diacetyl peroxide, nil; other organic compounds, nil; stabilizer, 0.05%. A solution of the peracid in ethyl acetate is also available commercially.

Analysis of Reagent Purity: assay using iodometry;[2] estimation of diacetyl peroxide.[3]

Preparative Methods: prepared in the laboratory by reacting ***Acetic Acid*** with hydrogen peroxide in the presence of catalytic quantities (1% by weight) of ***Sulfuric Acid***; when 30% H_2O_2 is used the concentration of the peracid reagent obtained is less than 10%.[1a] If a stronger solution of the reagent is required, 70-90% H_2O_2 must be used. Caution: for hazards see ***Hydrogen Peroxide***. ***Hydrogen Peroxide-Urea*** (which is commercially available and is safe to handle) has been used as a substitute for anhydrous hydrogen peroxide.[3] In the preparation of peracetic acid from acetic anhydride and H_2O_2, the dangerously explosive diacetyl peroxide may become the major product if the reaction is not carried out properly.[1a]

Purification: peracetic acid is rarely prepared in pure undiluted form for safety reasons. The commercially available material contains acetic acid, water, H_2O_2, and H_2SO_4. After neutralization of the sulfuric acid, this reagent is satisfactory for most reactions. If water is undesirable, an ethyl acetate solution of the reagent may be used. Details for the preparation of the H_2O_2-free reagent are available.[4]

Handling, Storage, and Precautions: peracetic acid is an explosive compound but is safe to handle at room temperature in organic solutions containing less than 55%. Use in a fume hood. Since peroxides are potentially explosive, a safety shield should generally be used.[5] Peracetic acid can be stored at 0 °C with

essentially no loss of active oxygen and at rt with only negligible losses over several weeks.

General Considerations.

Peracetic acid oxidizes simple alkenes, alkenes carrying a variety of functional groups (such as ethers, alcohols, esters, ketones, and amides), some aromatic compounds, furans, sulfides, and amines. It oxidizes β-lactams in the presence of catalysts. Ketones and aldehydes undergo oxygen insertion reaction (Baeyer-Villiger oxidation).

Epoxidation of Alkenes.

Peracetic acid is a comparatively safe reagent for small-scale reactions. In industry, to avoid the hazards involved in handling large quantities of the reagent, it is prepared in situ. Peracetic acid prepared in this fashion is widely used for epoxidation of vegetable oils and fatty acid esters. To the substrate in acetic acid containing catalytic (1% by weight) quantities of H_2SO_4 maintained around 50 °C is added gradually, with stirring, 50% H_2O_2 at such a rate that there is no buildup in the concentration of H_2O_2. The peracid is consumed as it is formed (eq 1). The addition of H_2O_2 is usually completed in 2 h and then the temperature is raised to and maintained at 60 °C until all the H_2O_2 is consumed (about 3 h). The reaction mixture is diluted with water, at which point the epoxides (being water-insoluble) separate out. The use of hexane during the reaction minimizes epoxide ring opening. Since the catalyst (H_2SO_4) is essential for the speedy formation of peracetic acid, in situ methods can be used for preparing only those epoxides which can tolerate the presence of the acid catalyst. Epoxides of fatty acid esters are obtained in good yields if the reaction temperature and time taken for completion of the reaction are properly controlled.

$$MeCO_2H + H_2O_2 \overset{H^+}{\rightleftharpoons} MeCO_3H + H_2O \qquad (1)$$

Peracetic acid in ethyl acetate is a better reagent for preparing epoxides from alkenes than the reagent in acetic acid since the large quantities of acetic acid in the latter reagent facilitate epoxide ring opening. However, since the reagent in acetic acid is more readily available, it is normally used for epoxidation; the sulfuric acid present in the commercial sample has to be neutralized by adding sodium acetate before the epoxidation. After epoxidizing the alkene with peracetic acid, the reaction mixture is diluted with water. The unreacted peracid, acetic acid, and traces of hydrogen peroxide are removed in the aqueous layer. The separated epoxide is filtered if it is a solid; when the epoxide is a liquid, the organic layer is separated using a small quantity of solvent, if needed. Another method of workup is to remove unreacted peracid and acetic acid through evaporation under reduced pressure.

Epoxidation of terminal alkenes with organic peracids is sluggish since the double bond is not electron rich (eq 2).[6]

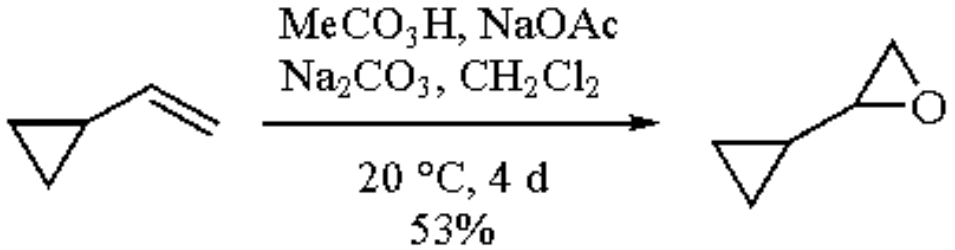

(2)

Adequately substituted acrylic esters furnish epoxides in good yields. Ethyl crotonate has been epoxidized in kg quantities according to eq 3;[7] the workup is simple, involving direct fractionation of the reaction mixture. For the preparation of epoxide (**1**) from ethyl crotonate using ***Trifluoroperacetic Acid***, the yield is 73%.[8] The sensitive allylic epoxide (**2**) has been prepared according to eq 4.[9] This procedure has been applied successfully for the preparation of allylic epoxides from 1,3-cyclopentadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene.

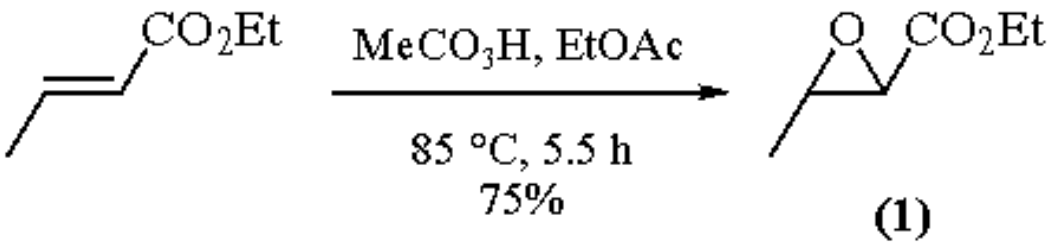

(3)

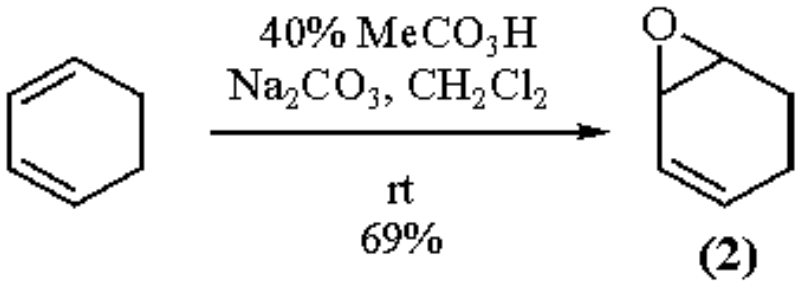

(4)

Epoxidation of the triene (**3**)[2] is regioselective, involving reaction at the tetrasubstituted double bond (eq 5). Epoxidation of (**3**) using ***m-Chloroperbenzoic Acid*** furnishes the monoepoxide in 76% yield.[10] Epoxidation of the diene (**4**) was regio- and stereoselective (eq 6);[11] the more substituted double bond was epoxidized from the less hindered side.

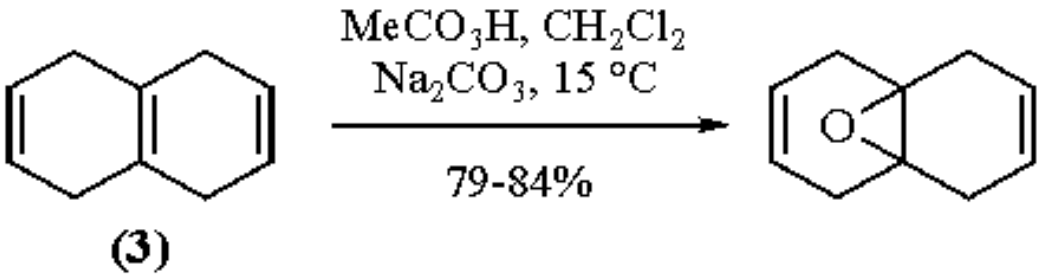

(5)

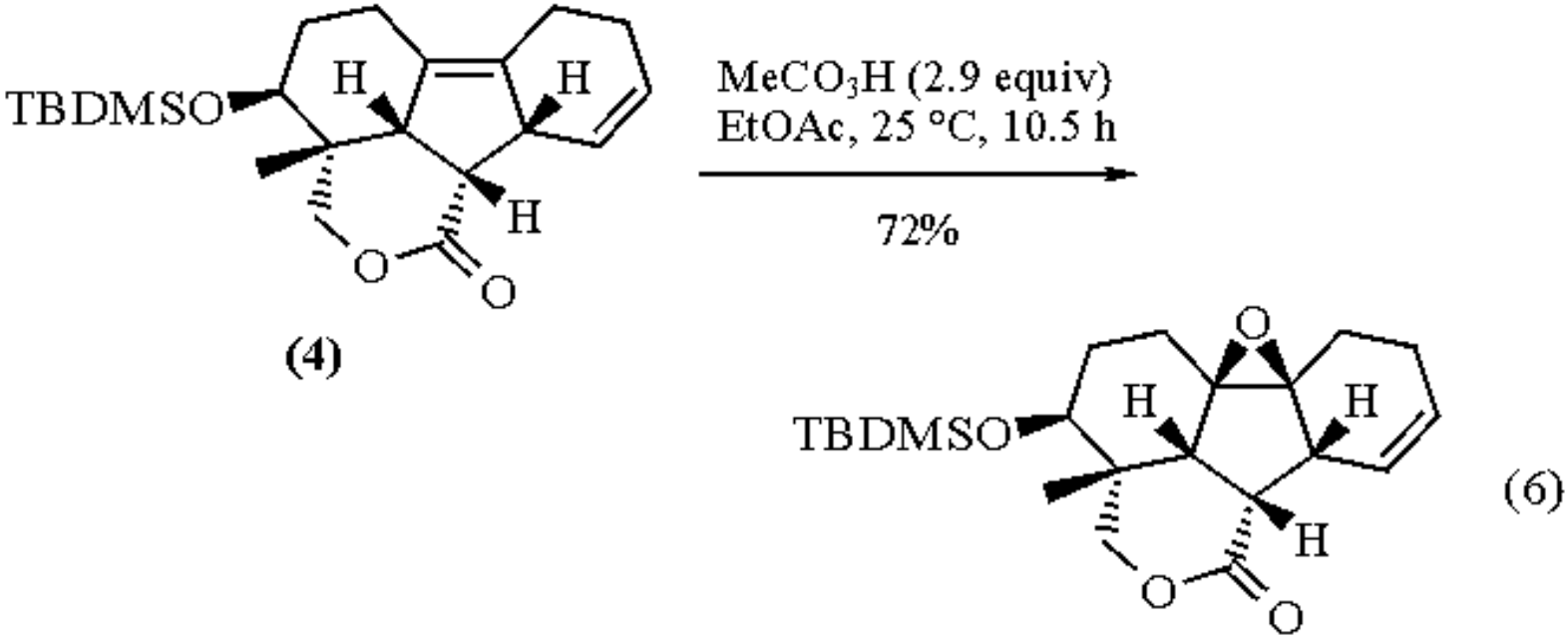

Epoxidation of the unsaturated γ-lactone (**5**) furnished stereoselectively the epoxide (**6**), involving approach of the reagent from the more hindered side of the double bond (eq 7).[12] This selectivity is observed only when acetic acid is the solvent. The selectivity was much less when *m*-CPBA was used.

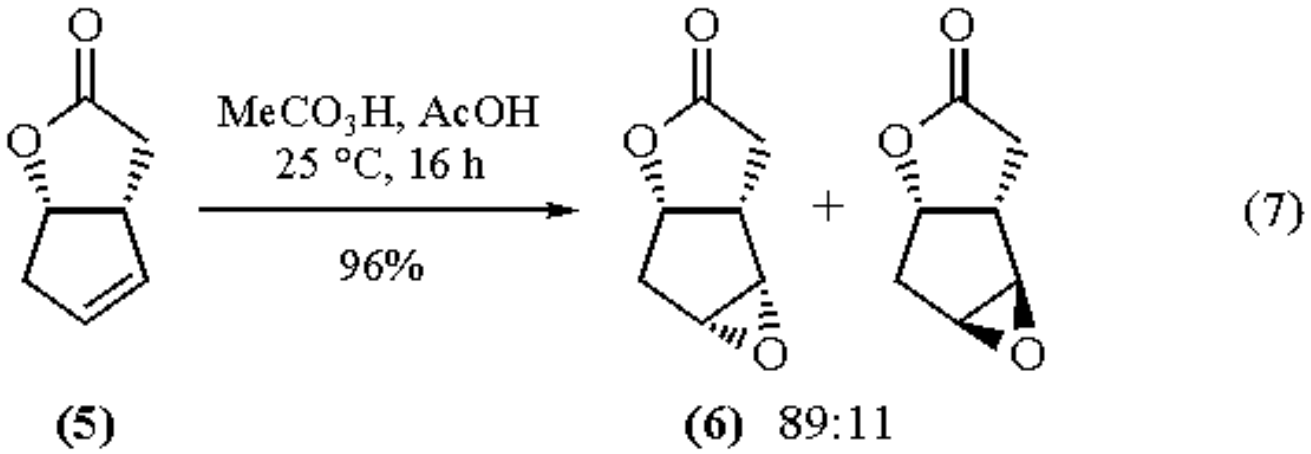

Moderate stereoselectivity is observed during the epoxidation of sterically unbiased 3,3-diarylcyclopentenes; the major product is formed through approach of the electrophile from the side *trans* to the better electron donor (eq 8).[13]

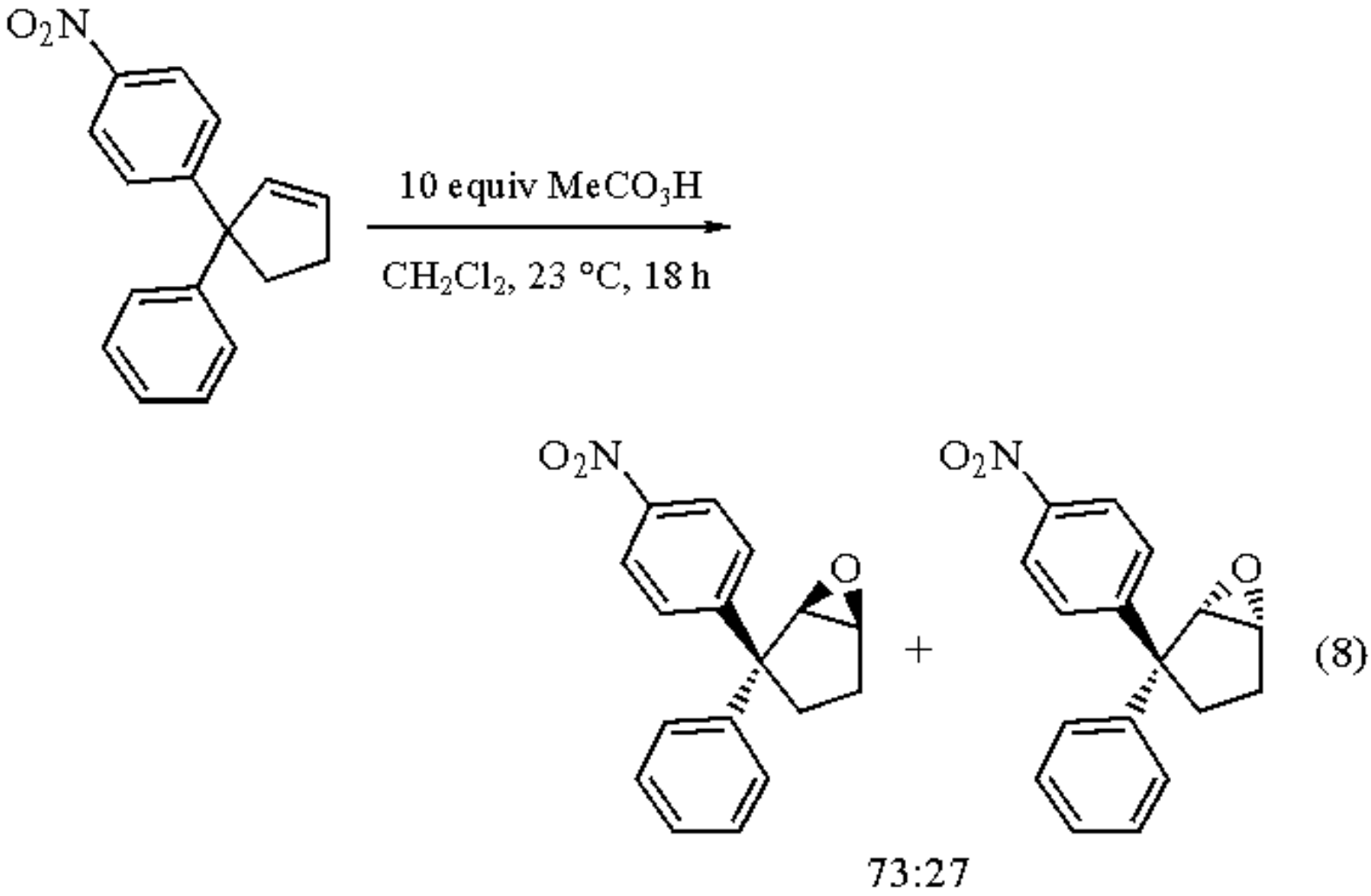

A systematic study of the epoxidation of the acyclic allyl alcohol (**7**) has been carried out, employing several reagents.[14] Epoxidation with peracetic acid generated from urea/H_2O_2 showed small *syn* selectivity (eq 9). *m*-CPBA epoxidation of (**7**) furnished in 87% yield a 40:60 mixture of the epoxy alcohols (**8**) and (**9**).

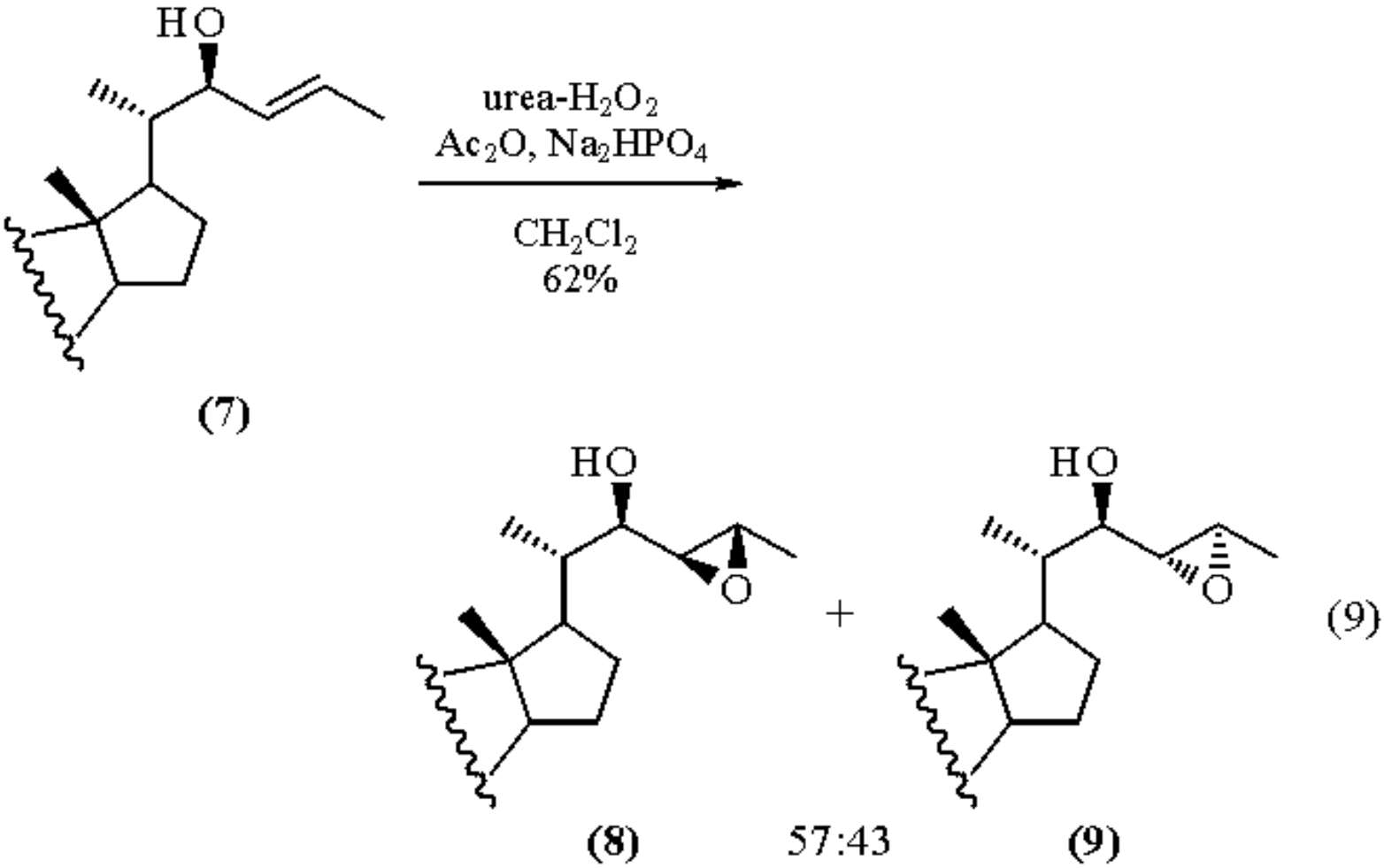

Epoxidation of Alkenes via Peracids Generated In Situ.

Alkenes have been epoxidized by reacting them with peracids generated in situ. The system consisting of molecular oxygen and aldehydes, particularly isobutyraldehyde and ***Pivalaldehyde***, converts various alkenes to epoxides in high yields when they are reacted at 40 °C for 3-6 h (eq 10).[15]

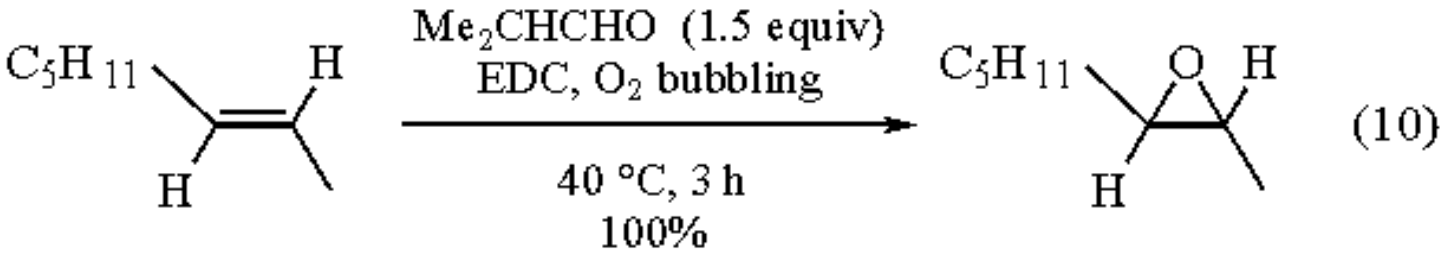

Oxidation of Furans.

2,5-Disubstituted furans are oxidatively cleaved by peracids; for example, see eq 11.[16] *m*-CPBA can also be used for this reaction. Δ^3-Butenolides have been synthesized by oxidizing 2-trimethylsilyl furans with peracetic acid; as in eq 12.[17]

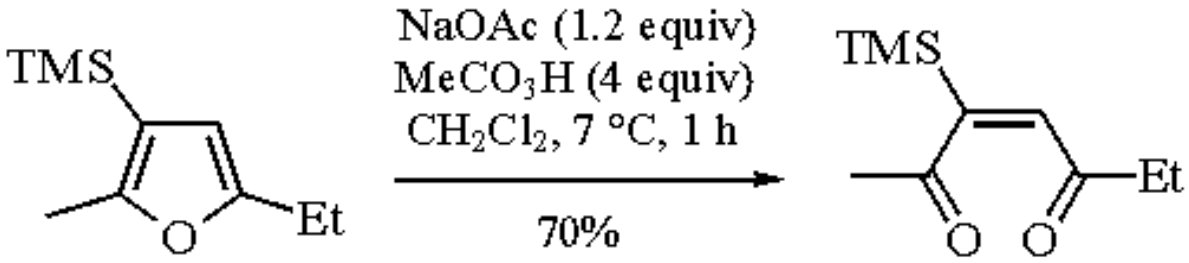

(11)

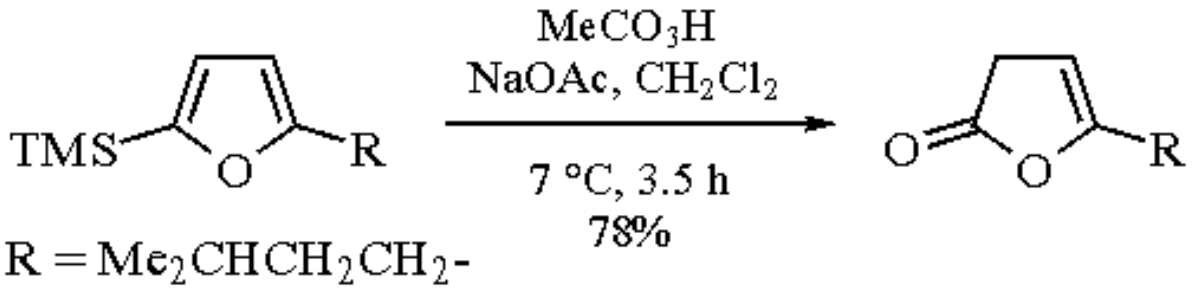

(12)

This reaction does not proceed smoothly when there is a hydroxyl group in the furfuryl position; however, the reaction is facile if the furfuryl OH is blocked. The reaction does not take place if electron-withdrawing groups are present on the furan ring. *m*-CPBA is not a good reagent for this oxidation. An interesting application of this reaction has been published.[18]

Oxidation of Aromatic Compounds.

Suitably substituted aromatic compounds are oxidized efficiently to the quinones by peracetic acid. The quinone (**10**) is obtained in 22% yield by oxidizing naphtho[*b*]cyclobutene.[19] Slow addition of 1,5-dihydroxynaphthalene to excess peracetic acid furnished juglone (**11**) in 46-50% yield.[20]

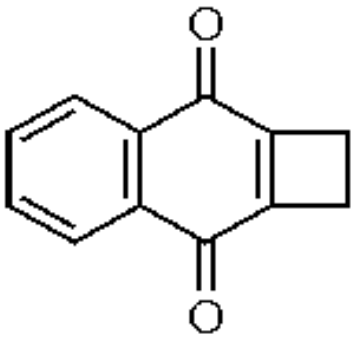

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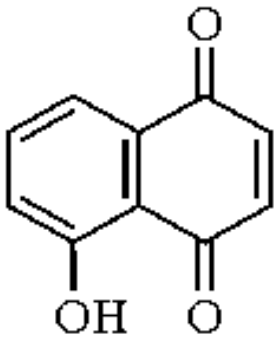

(11)

Baeyer-Villiger Oxidation.

A systematic study of the Baeyer-Villiger reaction of the bicyclic ketone (**12**) has been carried out employing different organic peracids.[21] Selective formation of lactone (**13**) was highest when peracetic acid was used (eq 13). Reaction of (**12**) with *m*-CPBA furnishes a 55:45 mixture of (**13**) and (**14**) in 81% yield.

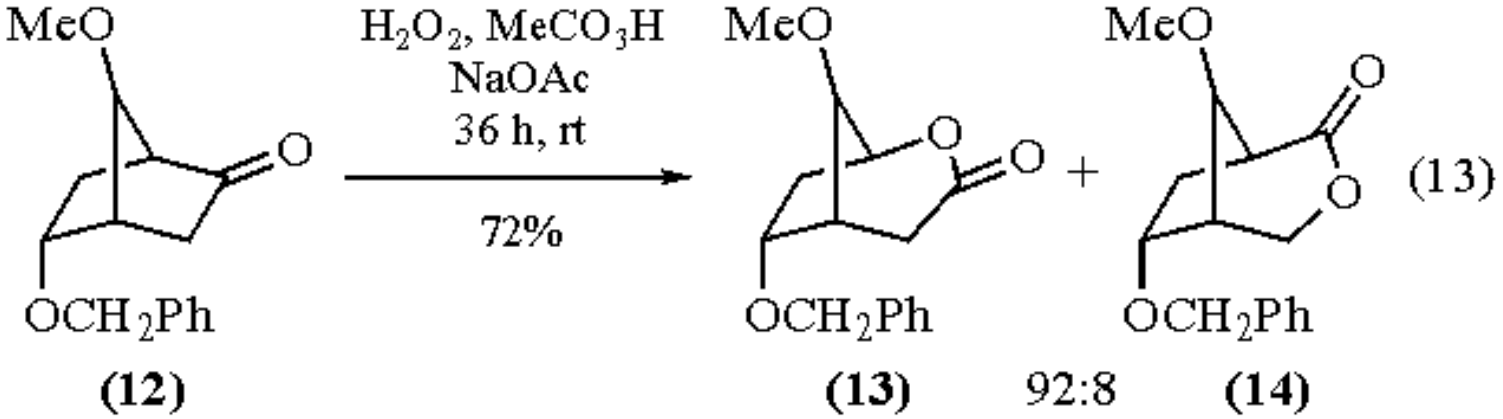

Position-specific Baeyer-Villiger rearrangement has been observed in the reaction of peracetic acid with some polycyclic ketones.[22,23] An ε-lactone, required for the synthesis of erythronolide B, was synthesized in 70% yield through position-specific Baeyer-Villiger rearrangement of a cyclohexanone having substituents on all the ring carbons;[24] the ketone was treated with excess 25% peracetic acid in ethyl acetate for 6 days at 55-58 °C. Peracetic acid oxidation of the keto β-lactam (**15**) furnishes stereoselectively the interesting β-lactam (**16**) (eq 14);[25] the initially formed Baeyer-Villiger reaction product undergoes further reaction. Ketone (**15**) has also been reacted with *m*-CPBA in acetic acid but the selectivity is slightly less, forming (**16**):(**17**) in 10:1 ratio.

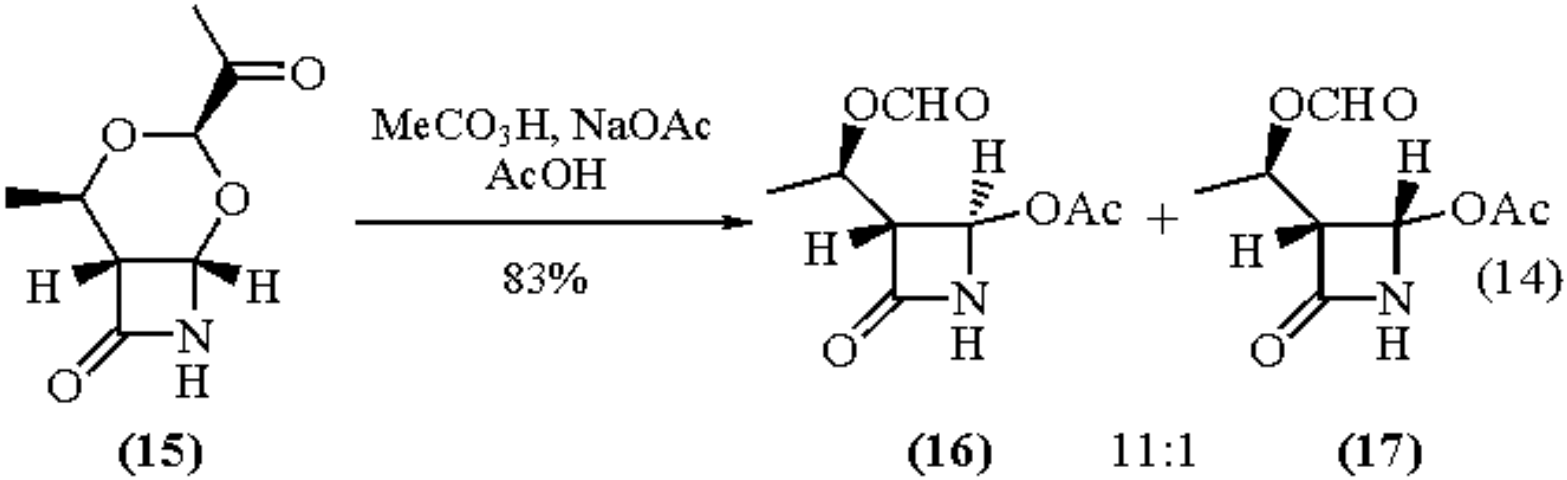

Ruthenium- and Osmium-Catalyzed Oxidations.

α-Ketols have been synthesized by reacting alkenes with peracetic acid in the presence of a ***Ruthenium(III) Chloride*** catalyst.[26] α-Ketol (**19**) was synthesized from the alkene (**18**) chemo- and stereoselectively (eq 15). The two-phase aqueous system is essential for this reaction. Conjugated dienes, allylic azides, and α,β-unsaturated esters have been oxidized with this reagent.

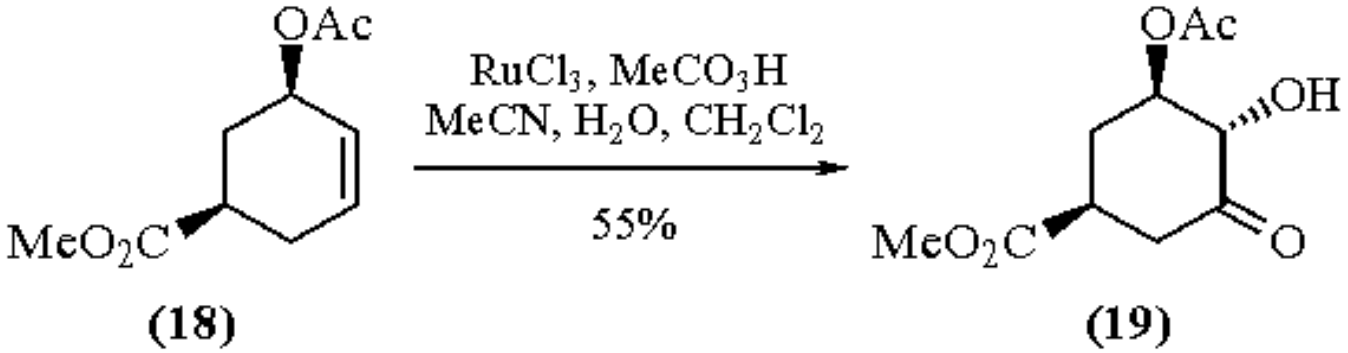

(15)

The methylene group adjacent to the nitrogen of β-lactams has been oxidized with peracetic acid in the presence of a ruthenium catalyst (eq 16).[27] Peracetic acid is the best oxidant for this reaction. Instead of ruthenium, $OsCl_3$ can be used to catalyze the oxidation.[28] The peracetic acid required for the reaction can be generated in situ from acetaldehyde and molecular oxygen (eq 17).[29]

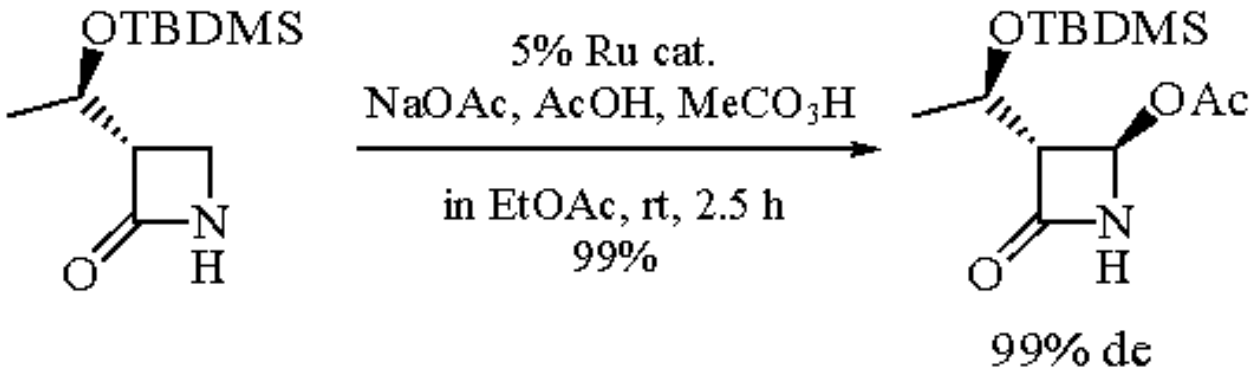

(16)

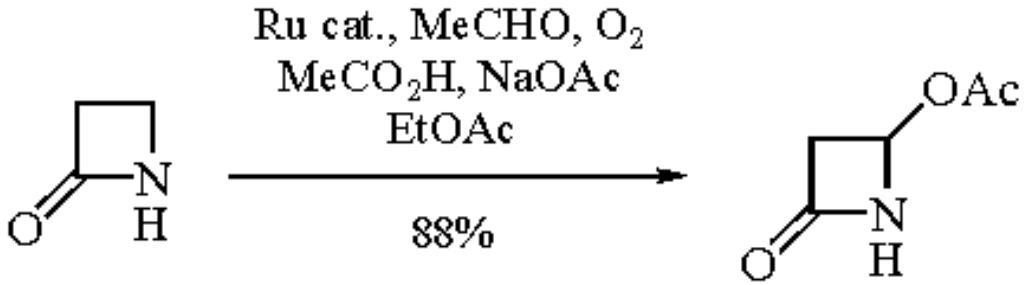

(17)

Other Applications.

Peracetic acid has been used to (a) oxidize primary amines to nitroso compounds,[30] (b) oxidize secondary alcohols to ketones in the presence of a Cr^{VI} ester catalyst (eq 18)[31] or sodium bromide,[32] (c) oxidize sulfenamides to sulfonamides (eq 19),[33] (d) oxidize iodobenzene to iodosobenzene diacetate[34] and iodoxybenzene,[35] and (e) oxidize N-heterocycles such as pyridine to *N*-oxides.[36] α,β-Unsaturated aldehydes (and α,β-unsaturated ketones) do not undergo facile epoxidation with peracetic acid since the double bond is not electron rich. However, the acetals of α,β-unsaturated aldehydes can be oxidized readily (eq 20).[37] For the epoxidation of α,β-unsaturated aldehydes with H_2O_2/base see ***Hydrogen Peroxide***.

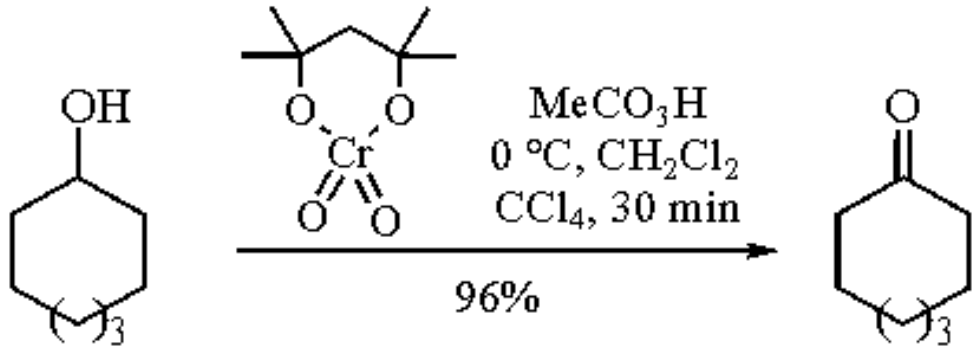

(18)

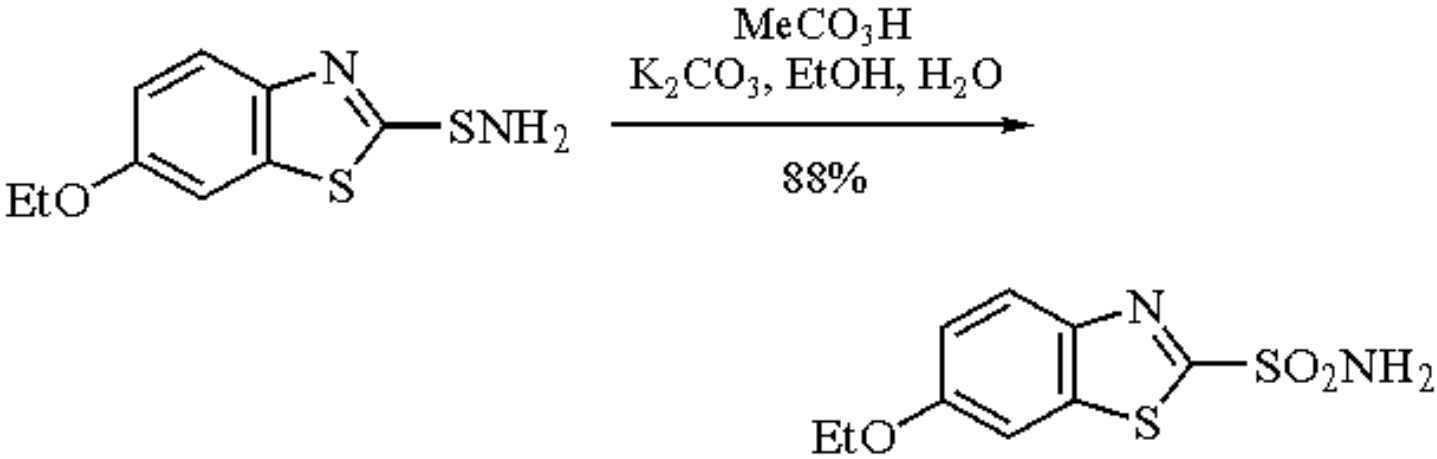

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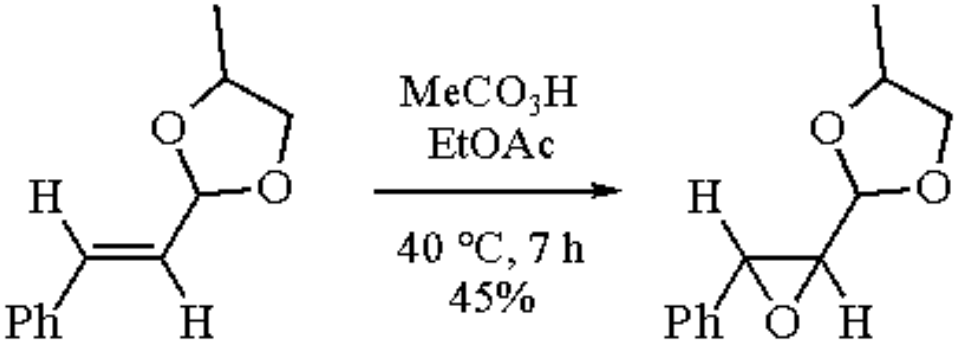

(20)

For industrial applications, peracetic acid is the most widely used organic peracid since it is inexpensive. It is the only commonly used peracid which can be prepared in situ for epoxidation reactions, since the acid catalyst (1% H_2SO_4; eq 1), which can facilitate epoxide ring opening, is used in low concentrations; the accompanying acetic acid, being a weak acid, is not very efficient in epoxide opening. The in situ method is not hazardous. Although the reagent is available commercially, it is also prepared in the laboratory since its preparation is easy, fairly fast, and no solvent is required for isolation. Epoxidation reactions and subsequent workup can be performed with no solvent, or only small quantities of solvent since the peracid and accompanying acetic acid are both water soluble and volatile. It is not essential that the substrate should dissolve in the reagent (peracetic acid-acetic acid).

Related Reagents.

m-Chloroperbenzoic Acid; ***Perbenzoic Acid***.

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Perbenzoic Acid[1]

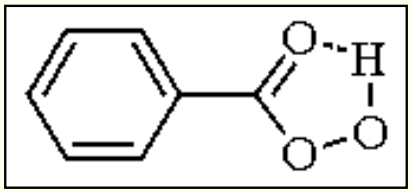

[93-59-4] · $C_7H_6O_3$ · Perbenzoic Acid · (MW 138.13)

(electrophilic reagent capable of delivering oxygen to alkenes,[1] amines,[2] and sulfides[3])

Alternate Name: peroxybenzoic acid; PBA.

Physical Data: mp 41-42 °C.

Solubility: sol $CHCl_3$, CH_2Cl_2, benzene, ethyl acetate, ether; slightly sol water.

Form Supplied in: long white needles, but usually handled in solution; not available commercially.

Analysis of Reagent Purity: iodometric assay.[4,6]

Preparative Methods: ***Sodium Methoxide*** reacts readily with ***Dibenzoyl Peroxide*** (**1**) (eq 1); complete experimental details are available for preparing perbenzoic acid based on this reaction.[4] Alkaline perhydrolysis (HOO^-) of (**1**) in aqueous organic solvents has been employed for preparing PBA in 90% yields.[5] PBA has been prepared in 85-90% yield by adding 70% ***Hydrogen Peroxide*** (**Caution**!) to a suspension of benzoic acid (**2**) in methanesulfonic acid (eq 2).[6] PBA has been prepared in 90% yield by passing oxygen containing catalytic quantities of ozone through a solution of benzaldehyde in ethyl acetate.[7]

$$\underset{\textbf{(1)}}{(PhCO)_2O_2} + MeONa \longrightarrow PhCO_3Na + PhCO_2Me \qquad (1)$$

$$\underset{\textbf{(2)}}{PhCO_2H} + H_2O_2 \overset{H^+}{\rightleftharpoons} PhCO_3H + H_2O \qquad (2)$$

Purification: PBA can be purified by recrystallization at -20 °C from a 3:1 mixture of petroleum ether-diethyl ether.

Handling, Storage, and Precautions: analytically pure PBA can be stored for long periods in a refrigerator without significant loss of active oxygen. Since PBA is a peroxide and potentially explosive, care must be exercised in carrying out the reactions with it; during workup, check for peroxides before evaporating the solvent. This reagent should be handled in a fume hood.

Functional Group Oxidations.

This reagent oxidizes simple alkenes, including alkene substrates incorporating a variety of functional groups (ethers, alcohols, esters, etc.), amines, and sulfides. Ketones undergo oxygen insertion reactions (Baeyer-Villiger oxidation).

Epoxidation of Alkenes.

PBA, like other organic peracids, reacts with alkenes readily under mild conditions to furnish epoxides in good yields (see, for example ***m-Chloroperbenzoic Acid***).[8] Styrene is thus oxidized to styrene oxide (**3**) (eq 3).[9] To PBA (0.33 mol) in 500 mL of $CHCl_3$ is added at 0 °C, with stirring, 0.3 mol of styrene. The reaction mixture is kept at 0 °C for 24 h. Assay of PBA at this stage will show that one equivalent of PBA has been consumed. The reaction mixture is shaken with aq 10% NaOH solution, water, and then dried (Na_2SO_4). The solvent is evaporated and the residue is fractionated using a Vigreux column to furnish the epoxide (**3**) in 70-75% yield.

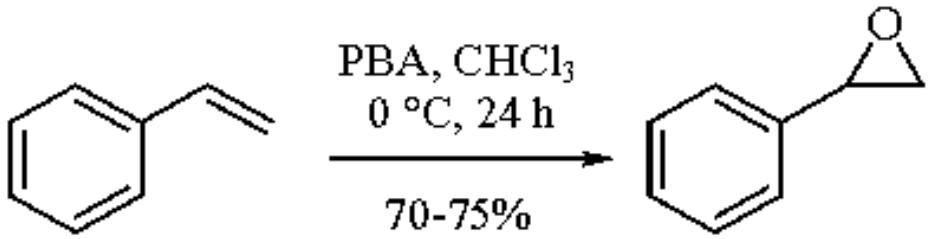

(3)

(3)

Oxidation of the alkene (**4**) furnishes the epoxide (**5**) (eq 4).[10] The disubstituted *cis*-alkene (**6**) gave in quantitative yield the corresponding *cis*-epoxide (**7**).[11] Epoxidation of cycloheptene in $CHCl_3$ (3.2% solution, 48 h, 0 °C) furnished cycloheptene oxide in 78% yield.[12]

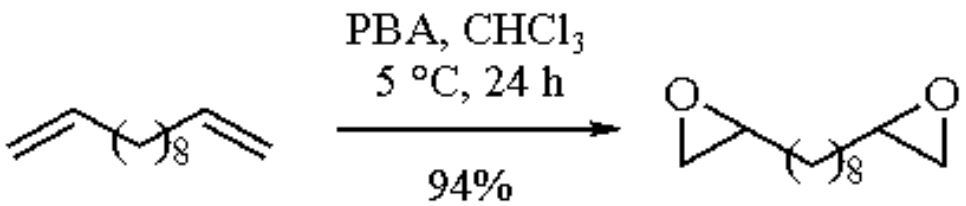

(4)

(4)

(5)

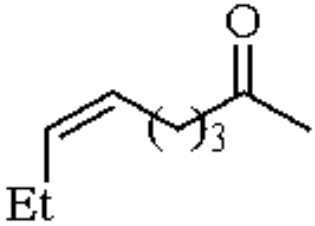

(6)

(7)

Reaction of the diene (**8**), having two trisubstituted double bonds, with 1 equiv of PBA proceeded regio- and stereoselectively to give monoepoxide (**9**) (eq 5).[13]

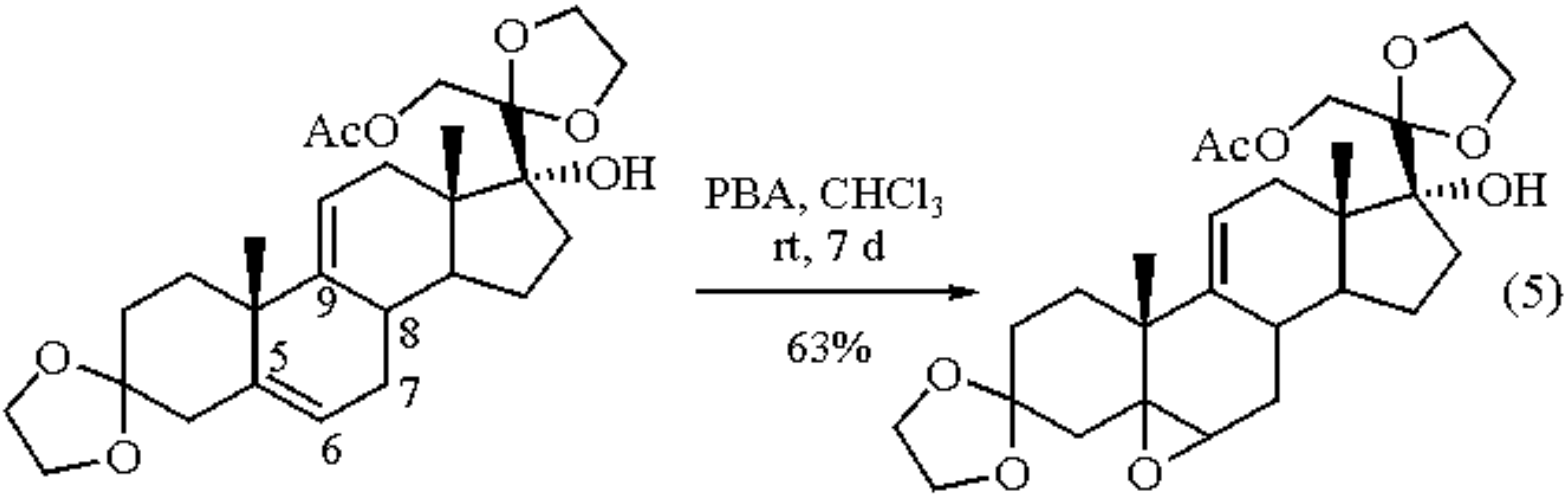

(8) (9)

The benzylic epoxide (**10**) has been obtained in 77% yield by epoxidizing 1-phenylcyclohexene with a $CHCl_3$ solution of PBA at 0 °C.[14] A pure sample of (**10**) was obtained by distilling the crude reaction product over powdered KOH; this epoxide is very sensitive to acids but is stable in basic medium. It has been observed that 7α,8α-epoxides of steroids and triterpenes are stable in basic media but these epoxides are readily cleaved even with traces of acids.[15]

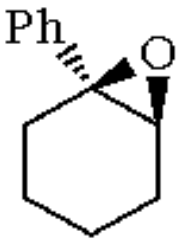

(10)

Epoxidation of the diene (**11**) takes place regioselectively at the tetrasubstituted double bond to furnish the monoepoxide (**12**) in 61% yield.[16] 3β-Acetoxy-8α,9α-epoxyergostane was prepared in 85% yield by epoxidizing the alkene (**13**) using benzene as solvent.[17]

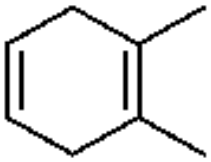

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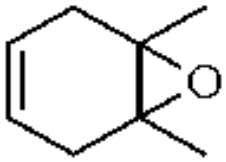

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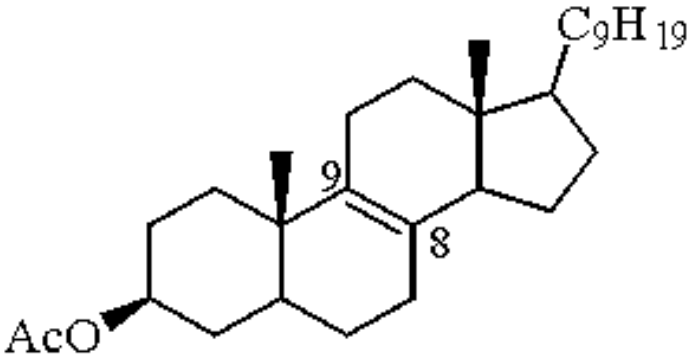

(13)

Epoxidation of 3-acetoxycholest-2-ene (**14**) in $CHCl_3$ solution (-12 °C, 42 h) is stereoselective; the 2α,3α-epoxide is isolated in 80% yield.[18] Epoxidation of the vinyl chloride (**15**) ($CHCl_3$ solution, 12 h, rt) furnished the corresponding chloro epoxide in 68% yield.[19]

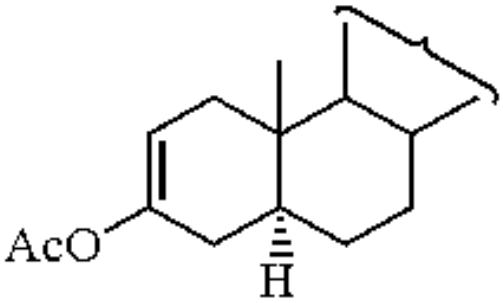

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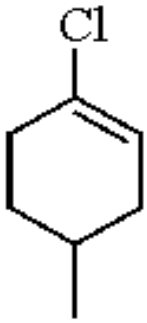

(15)

The sensitive epoxide (**17**) has been prepared from the enol ether (**16**) in 90% yield (eq 6).[20] An ether solution of (**16**) and PBA is allowed to react for 30 s; benzoic acid is removed by passing the reaction mixture rapidly (30 s) through an alumina column.

(6)

(16) (17)

Epoxidation of the α,β-unsaturated ketone pulegone (**18**) (5-10 °C, 24 h) is not stereoselective; a 2:1 mixture of α,β-epoxy ketones (**19**) and (**20**) is obtained in 86% yield.[21]

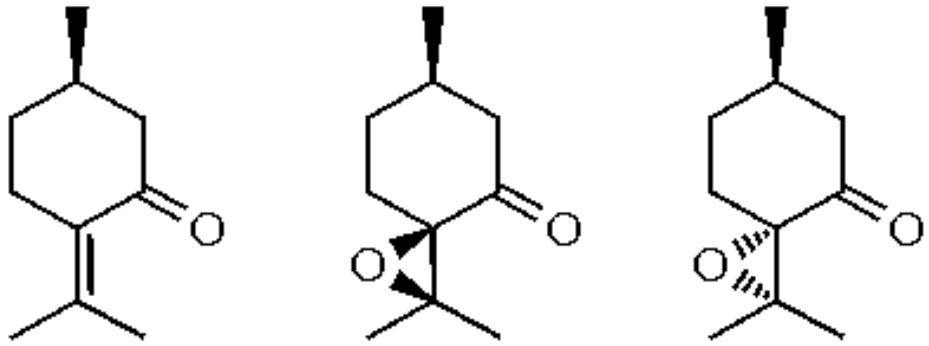

(18) (19) (20)

Hydroxy-directed stereoselective epoxidation has been observed with allylic cyclohexenols (eq 7).[22]

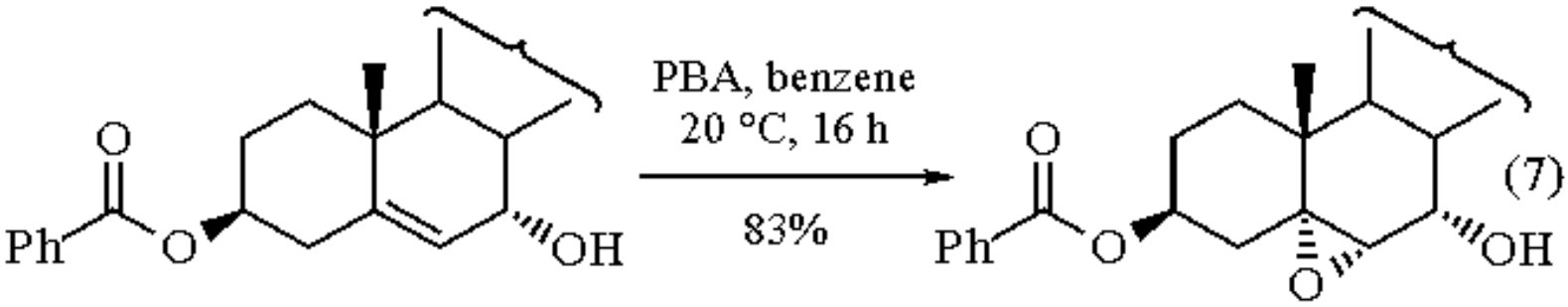

(7)

Baeyer-Villiger Reaction.

Fe_2O_3-catalyzed oxidation of ketones with molecular oxygen in the presence of benzaldehyde at rt gives the lactones efficiently (eq 8).[23] The reacting species may be PBA or the radical $PhCO_3$&bdot;. Baeyer-Villiger reaction of (-)-(**21**) furnishes the ester (-)-(**22**) in 85% yield with retention of configuration.[24]

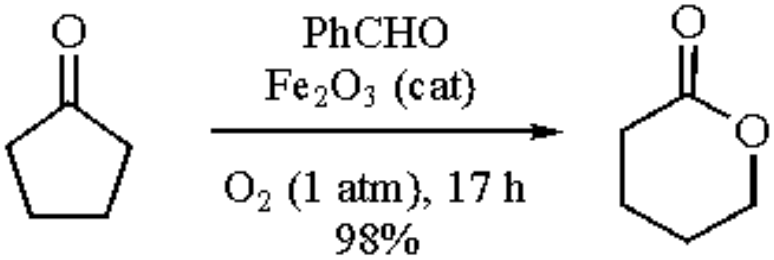

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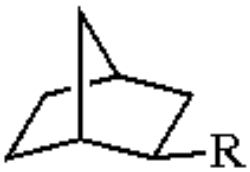

(21) R = COMe
(22) R = OCOMe

Reaction with Compounds Containing Nitrogen and Sulfur.

Aromatic primary amines containing electron-withdrawing groups are oxidized to nitroso compounds.[2] Oxidation of (**23**) thus furnishes the nitroso compound (**24**) in 85% yield. This reaction cannot be carried out with peracetic acid. The oxaziridine (**25**) has been prepared in 56-74% yield by reacting the corresponding aldimine with PBA.[25] Episulfides are oxidized to episulfoxides.[3] The episulfoxide (**26**) has been obtained in 77% yield by oxidizing the episulfide in CH_2Cl_2 at -20 °C.

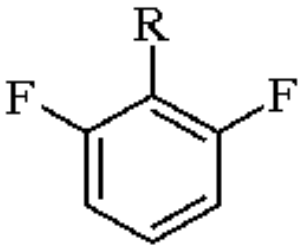

(23) R = NH_2
(24) R = NO

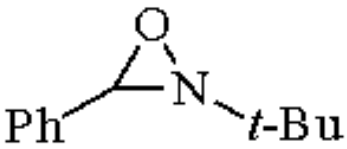

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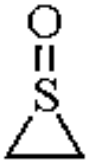

(26)

In the epoxidation of alkenes which are moderately or highly reactive, the yields obtained with PBA are comparable to the yields obtained using ***m-Chloroperbenzoic Acid*** or ***Peracetic Acid***. However, *m*-CPBA and $MeCO_3H$ are available commercially; PBA is not available commercially, but can be prepared conveniently in a short time. For the epoxidation of alkenes which react sluggishly (e.g. α,β-unsaturated esters) *m*-CPBA and ***Trifluoroperacetic Acid*** are preferred.

Related Reagents.

Monoperoxyphthalic Acid.

---

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Perchloryl Fluoride[1]

$FClO_3$

[7616-94-6] · $ClFO_3$ · Perchloryl Fluoride · (MW 102.45)

(electrophilic reagent capable of fluorinating a variety of activated methylene compounds,[1-3] steroids,[1,4-13] and organometallics;[1,14] useful for the formation of covalent aromatic perchlorates[1,15])

Alternate Names: chlorine fluoride oxide; chlorine oxyfluoride.

Physical Data: mp -147.7 °C; bp -46.7 °C; d^{25} 1.412 g cm^{-3} (liq), 0.065 g cm^{-3} (g).[1b,16]

Solubility: sol THF, Me_2O, MeOH, DMF, MeCN, H_2O. Specific solubilities have been measured.[17,18]

Form Supplied in: colorless gas shipped in cylinders under its own vapor pressure[1b] (12 atm at 25 °C).

Analysis of Reagent Purity: assessed in the condensed phase using ^{19}F NMR spectroscopy and in the gas phase using vibrational spectroscopy.[1f]

Preparative Methods: the synthesis of $FClO_3$ involves extremely hazardous materials[1f] and should not be attempted by inexperienced or untrained personnel.

Handling, Storage, and Precautions: mixtures of $FClO_3$ and organic compounds are potentially hazardous because explosions are always possible. Numerous serious accidents involving $FClO_3$, including those resulting in fatalities, have been documented.[1,19] These incidents are normally violent and destructive and occur unexpectedly, e.g. *a mixture of $FClO_3$ and THF exploded violently and without warning at room temperature*.[20] Toxicity, health, and safety information as well as recommendations for selection and use of personal protective equipment can be found in numerous publications.[21] Perchloryl fluoride should only be handled by experienced and thoroughly trained personnel and should only be used in a fume hood.

General Considerations.

Safer alternative reagents are commercially available which perform as well and in many cases better than $FClO_3$ in all of its chemistry, e.g. XeF_2, $(CF_3SO_2)_2NF$, *N*-fluoropyridinium triflate, *N*-fluoropyridinium pyridine heptafluorodiborate, *N*-alkyl-*N*-fluorotoluenesulfonamides, *N*-fluoroquinuclidinium triflate, and *N*-fluorodibenzenesulfonamide. A safer, cost-effective, and easily handled reagent, ***1-(Chloromethyl)-4-fluoro-1,4-***

diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate) (F-TEDA-BF_4), particularly useful for selective fluorination of steroids as well as a wide range of other activated substrates, including methylene and methine carbons,[22,23] has recently become available in commercial quantities.

Perchloryl fluoride was one of the first readily available sources of electrophilic fluorine and, as such, gained immense popularity for selective fluorinations of a wide variety of substrates. However, numerous accidents involving $FClO_3$ and the advent in subsequent years of cleaner and safer-to-use electrophilic fluorination reagents have all but abolished perchloryl fluoride from the synthetic chemist's repertoire. Nevertheless, a short summary of the major synthetic transformations which are possible with $FClO_3$ is given below.

Fluorination of Activated Methylenes.

The acidic hydrogen(s) of a methylene group can be substituted by fluorine with $FClO_3$ providing an equimolar amount of a sufficiently strong base is also used. Selectivity in these reactions does vary, depending on the choice of base and solvent. Thus, the fluorination of diethyl malonate in ethanol (eq 1)[3] yields four different products, whereas in toluene (eq 2),[3] only two products are obtained.

$$H_2C(CO_2Et)_2 \xrightarrow[\text{2. } FClO_3\text{, 10-15 °C}]{\text{1. Na, EtOH}}$$

$$\underset{26.2\%}{F_2C(CO_2Et)_2} + \underset{28.2\%}{HCF(CO_2Et)_2} + \underset{5.2\%}{EtCH(CO_2Et)_2} + \underset{0.5\%}{EtCF(CO_2Et)_2} \quad (1)$$

$$H_2C(CO_2Et)_2 \xrightarrow[\text{2. } FClO_3\text{, 10-15 °C}]{\text{1. Na, toluene}} \underset{29.2\%}{F_2C(CO_2Et)_2} + \underset{41.6\%}{HCF(CO_2Et)_2} \quad (2)$$

Fluorination of Activated Methines.

Perchloryl fluoride can be used in many cases to substitute the proton of an activated methine carbon with fluorine. While the majority of examples come from the steroid literature, some nonsteroidal examples have also been reported, e.g. the fluorination of cyclohexene enol ether (eq 3)[8].

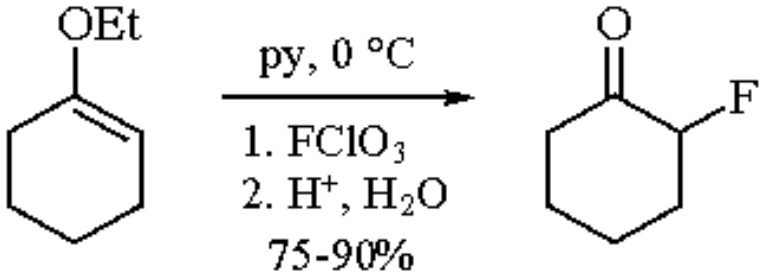

(3)

Fluorination of Activated Steroid Enol Ethers and Esters, Enamines, and Enamides.

Perchloryl fluoride can be used for regioselective incorporation of fluorine at a number of positions on activated steroidal substrates. Thus 2-fluoro steroids can be prepared from their corresponding enol ethers, e.g. 3-ethoxy-5α-cholest-2-ene (eq 4),[8] enamines, e.g. cholest-2-en-3-one pyrrolidylenamine (eq 5),[4] α-hydroxymethylene ketones, e.g. 2,17β-dihydroxyandrostan-3-one (eq 6),[6] and from alkoxalyl enolates,[24-26] e.g. 2-methoxalylhydrocortisone 20-ethylene acetal (eq 7).[25]

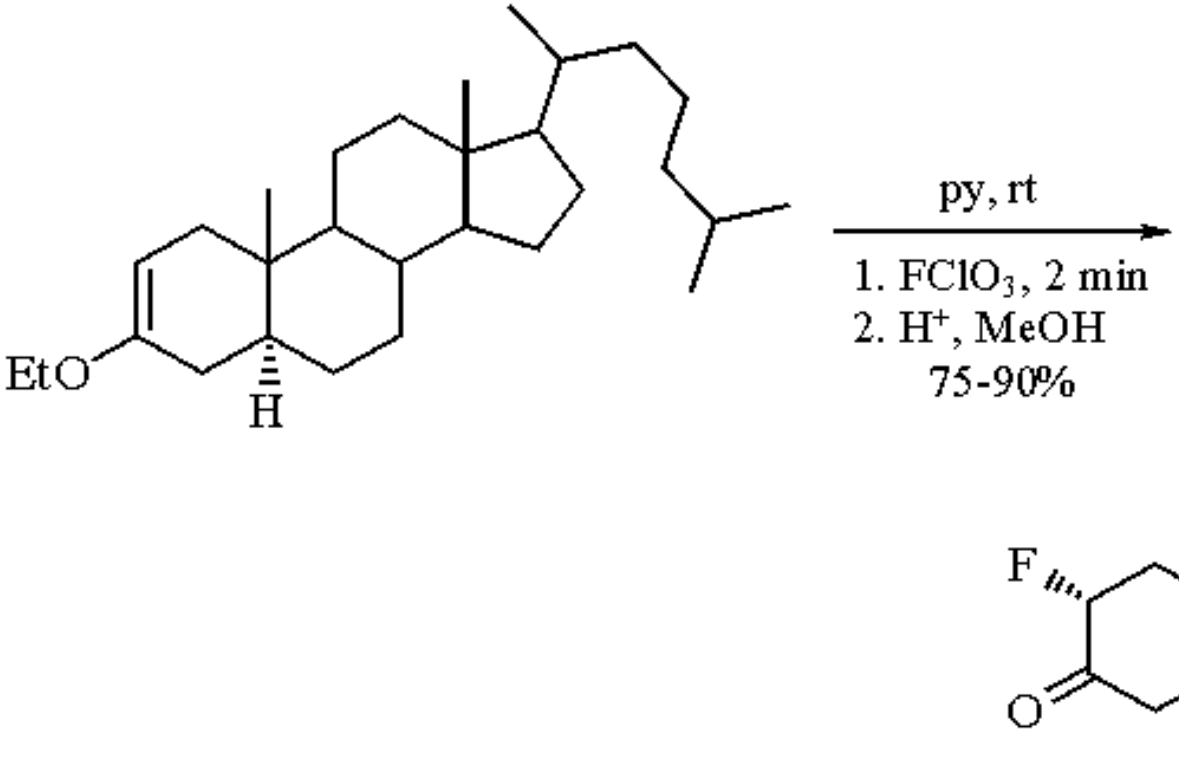

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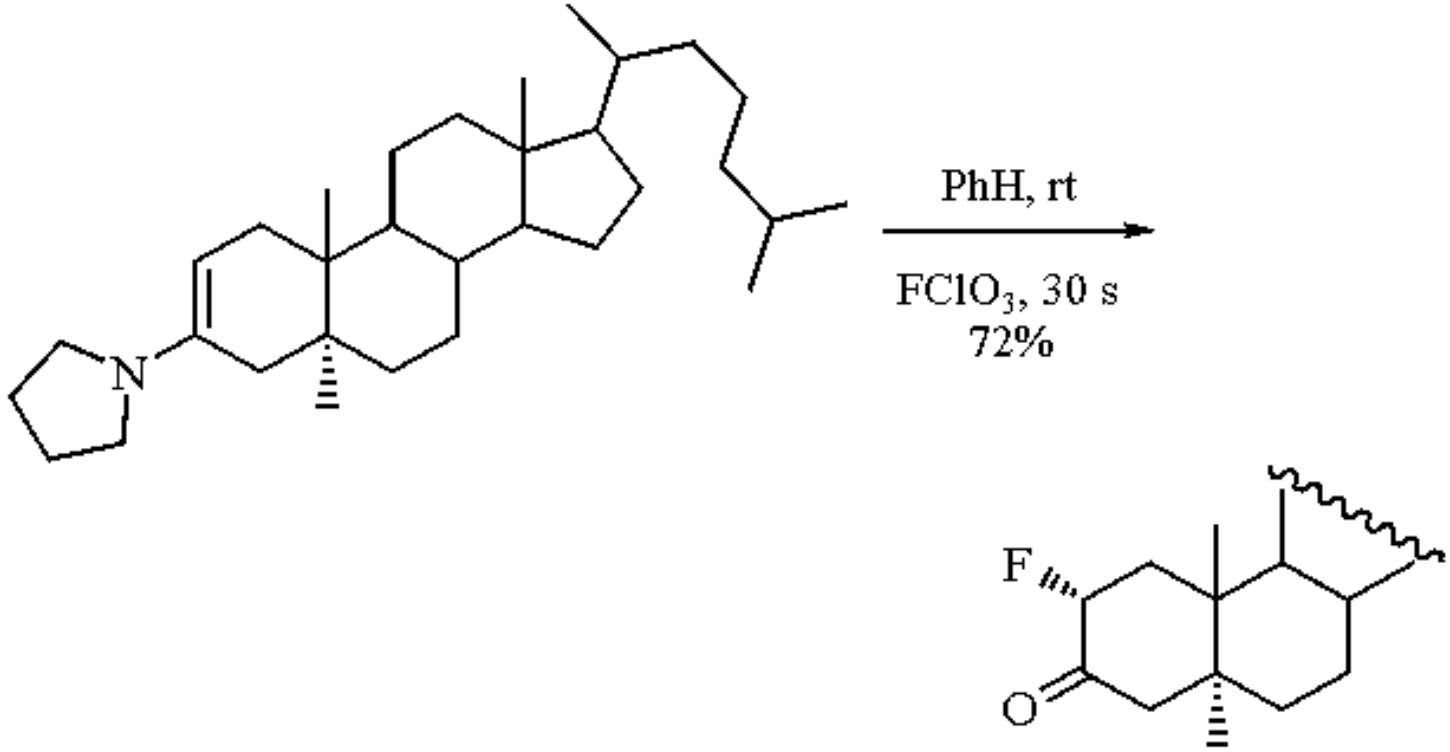
PhH, rt
FClO3, 30 s
72%
N
F
O

(5)

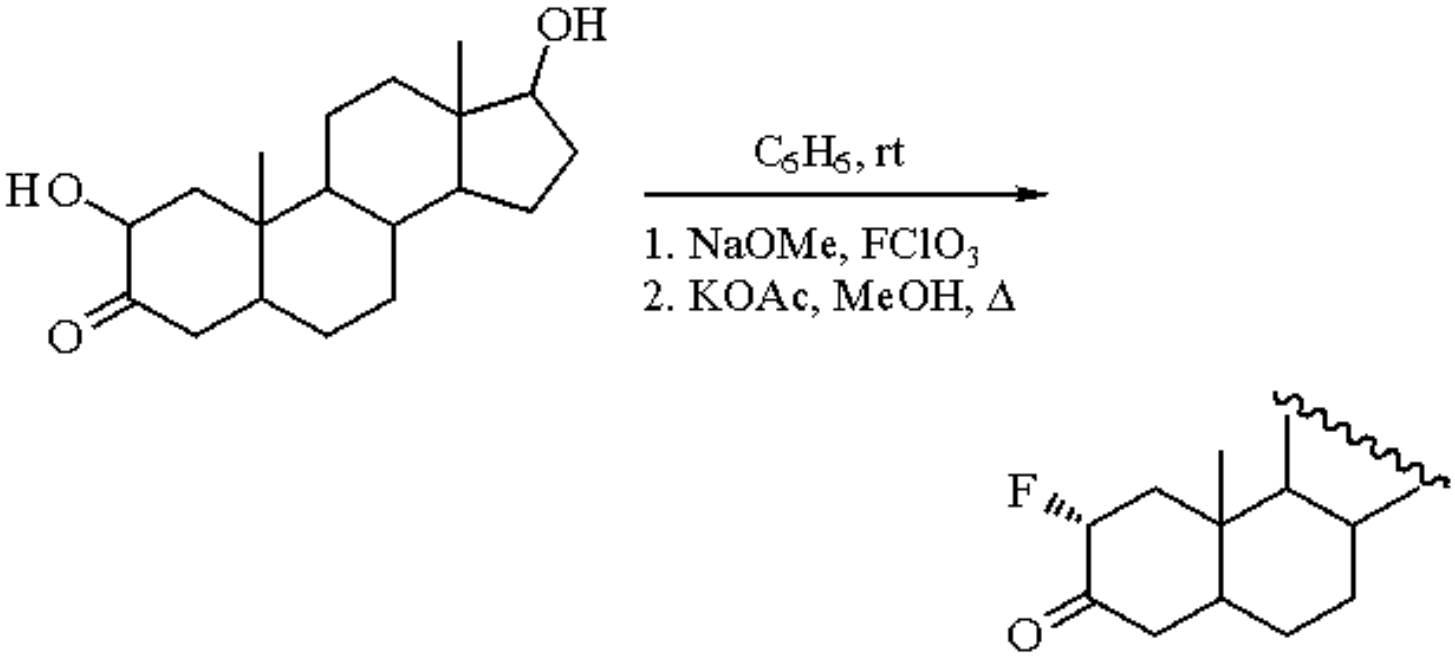
OH
HO
O
C6H6, rt
1. NaOMe, FClO3
2. KOAc, MeOH, Δ
F
O

(6)

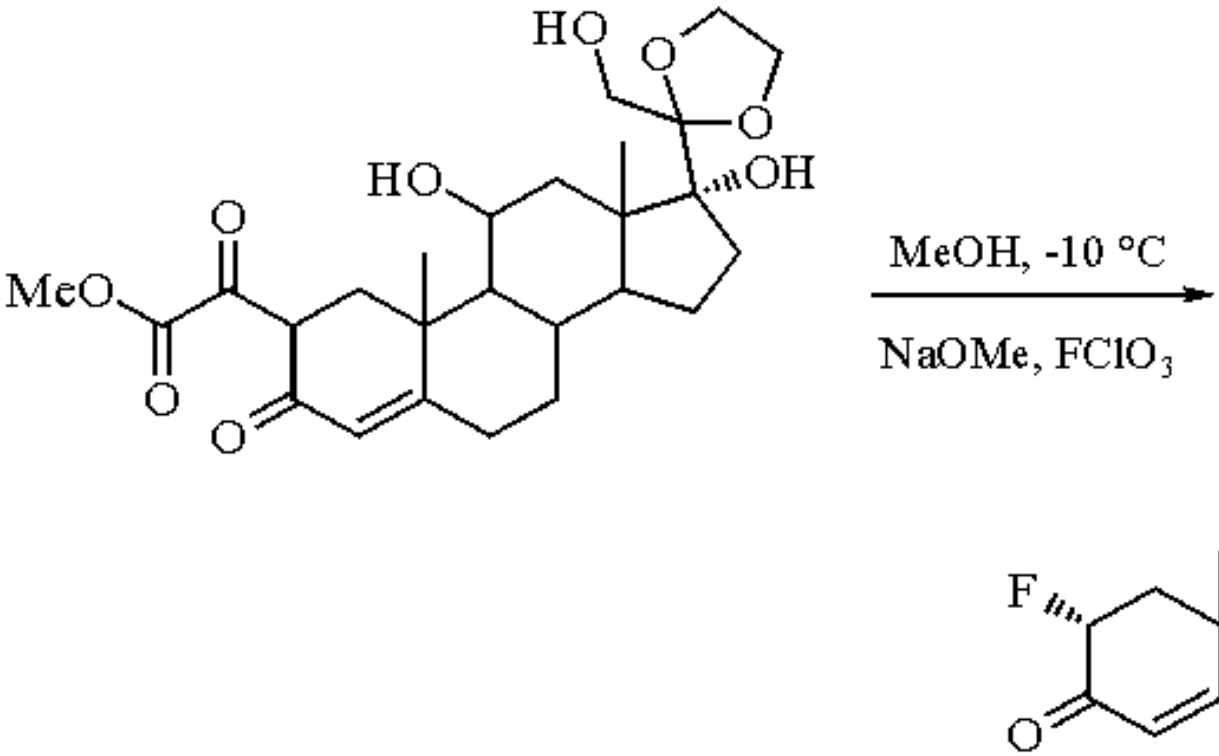

(7)

Perchloryl fluoride and 3-keto steroids conjugated via 3,5-dienes yield different products depending on the functional group at position 3. Thus 21-acetoxy-3-ethoxy-11β-hydroxy-3,5,17(20)-*cis*-pregnatriene, an enol ether, and the analogous enol acetate of progesterone yield 6-fluoro products (eqs 8 and 9),[27,28] respectively, while methyl 11-oxo-3-pyrrolidyl-3,5,17(20)-*cis*-pregnatrien-21-oate, a dienamine, gives the 4,4-difluoro product (eq 10).[27]

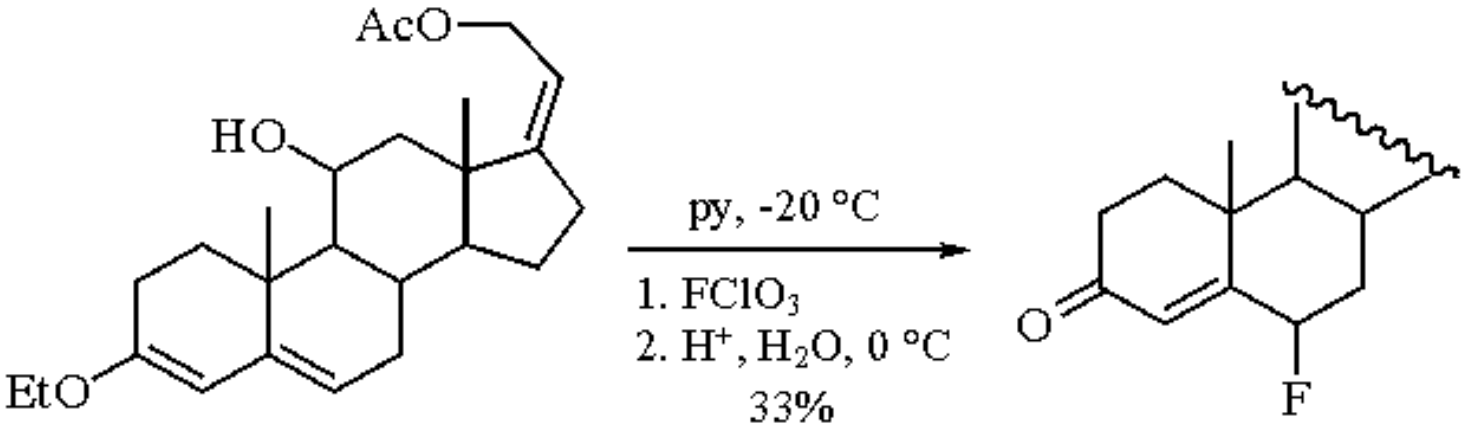

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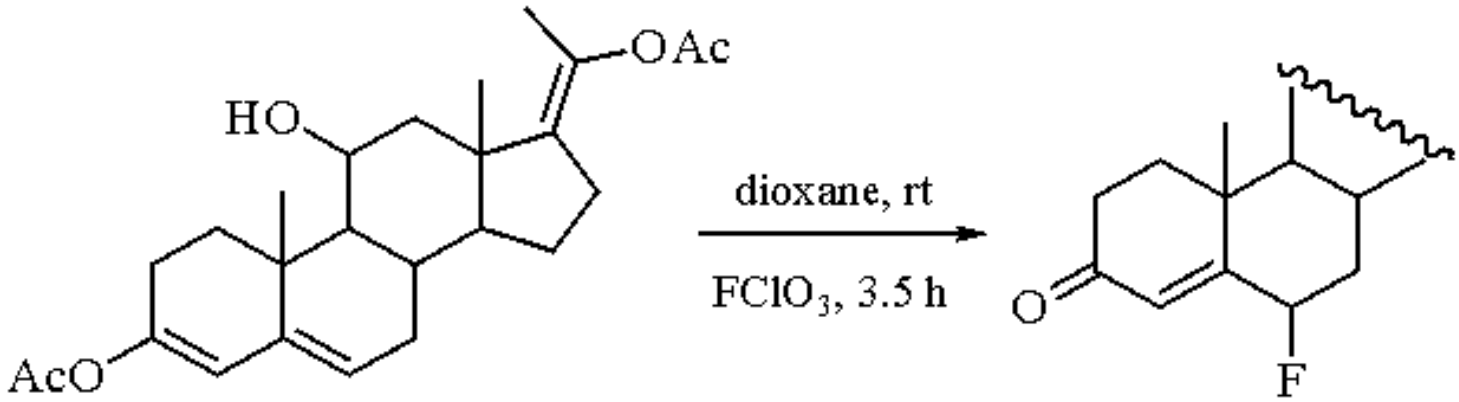

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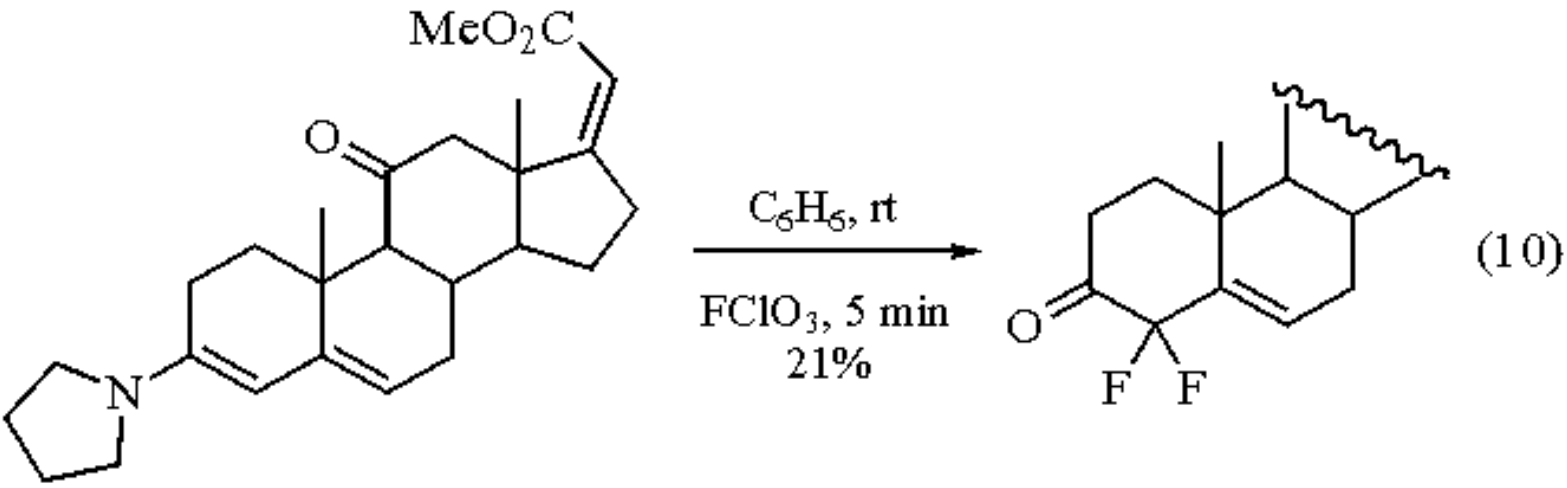

Incorporation of fluorine at the 16-position of steroids using $FClO_3$ requires highly activated substrates such as 16-formylandrost-5-en-17-one[29] and 16-ethoxalylandrost-5-en-17-one.[30] In addition, a noteworthy activating group is found in the 17-amino-Δ^{16}-steroid (enamide) prepared by Beckmann rearrangement of the corresponding 20-keto-Δ^{16}-steroid.[31] Thus treatment of the androstane derivative 3β-acetoxy-17-acetaminoandrosta-5,16-diene, in pyridine, with $FClO_3$ leads to the 16α-fluoro product, 16α-fluoro-3β-acetoxyandrost-5-en-17-one, in 70% yield (eq 11).[31] The same transformation can be accomplished in higher yield using either ***Xenon(II) Fluoride*** (95% yield) or *N*-fluoroquinuclidinium triflate (85% yield).

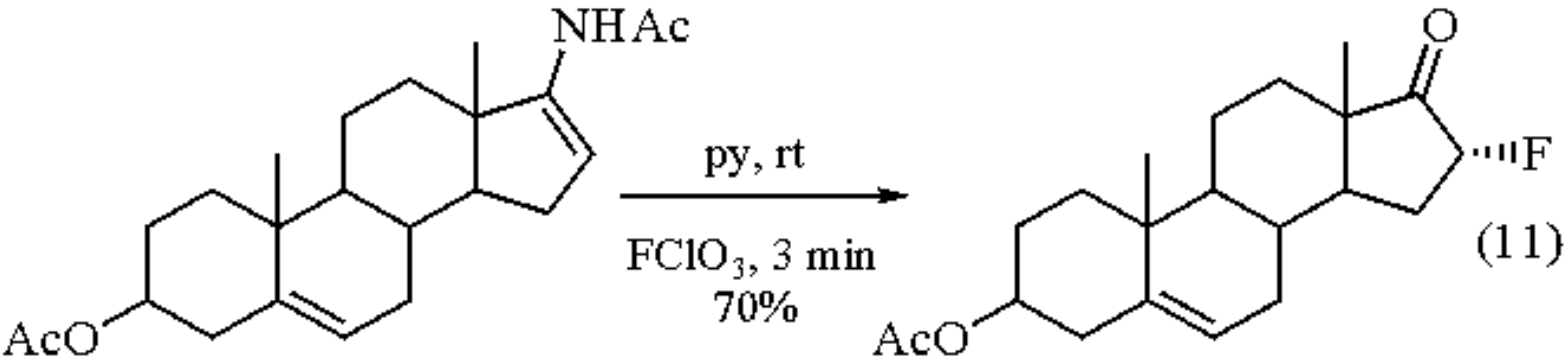

Fluorination of Organometallic Compounds.

Perchloryl fluoride can be used for the fluorination of carbon-metal bonds in ether or THF at low temperature, yielding the monofluoro and, in most cases, protonated derivatives (eqs 12 and 13).[14] This type of reaction has also been applied to the fluorination of organolithium heterocycles.[32]

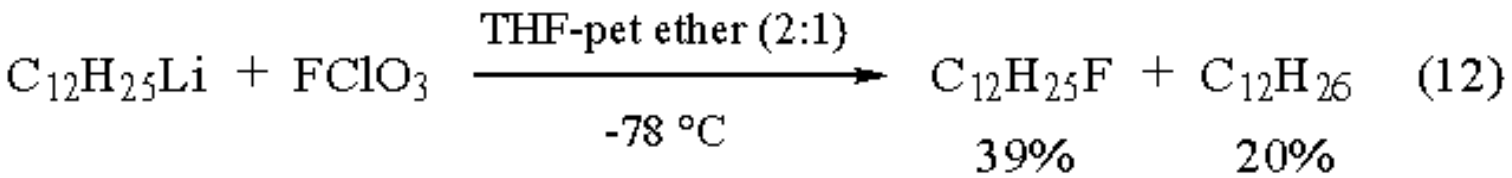

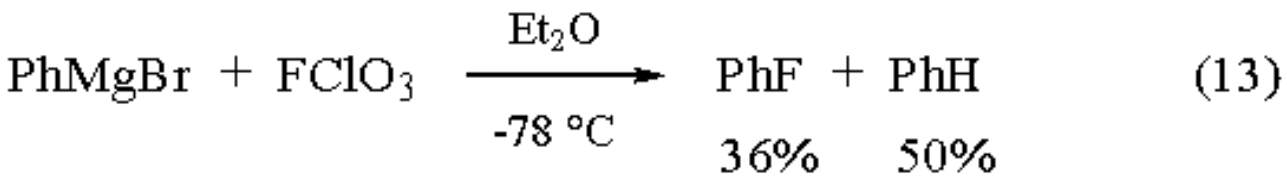

(13)

The fluorinated products in eqs 12 and 13 can be prepared in higher yields under milder conditions using F-TEDA-BF_4.[23]

Perchlorylation of Aromatic Compounds.

A capability unique to perchloryl fluoride is its use for the Friedel-Crafts perchlorylation of activated aromatics (eq 14).[15] This type of electrophilic aromatic substitution can be applied to substituted benzene compounds such as toluene, fluorobenzene, and *p*-xylene, but does not work for deactivated systems such as nitrobenzene. While perchloryl aromatics are resistant to reduction, oxidation, and hydrolysis, they are easily detonated with either heat or shock.[15]

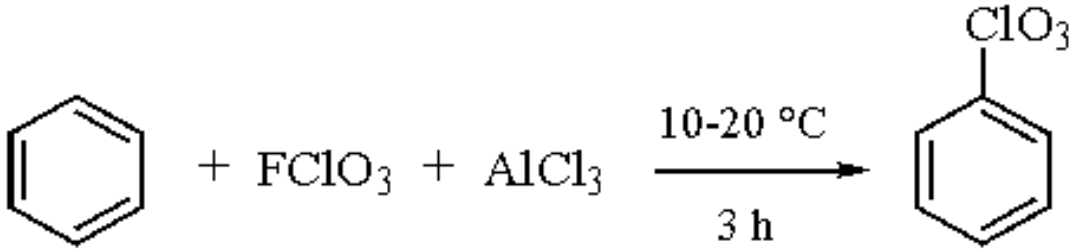

(14)

Other Applications.

Perchloryl fluoride can be used for a number of other applications, including the fluorination of nitro and polynitro hydrocarbons,[20,33-36] the fluorination of steroidal-ring phenols,[37] the *N*-fluorination and *N*-perchlorylation of certain amines,[38] and the oxofluorination of certain alkenes.[39]

Related Reagents.

1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate); ***N-Fluoro-N-t-butyl-p-toluenesulfonamide***; ***N-Fluoro-N-(phenylsulfonyl)benzenesulfonamide***; ***N-Fluoropyridinium Triflate***; ***Xenon(II) Fluoride***.

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T. Robert G. Syvret

Perfluoro-*N*-fluoropiperidine[1]

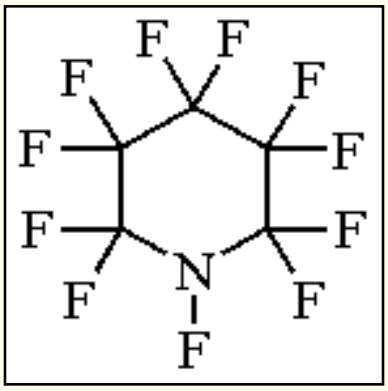

[836-77-1] · $C_5F_{11}N$ · Perfluoro-*N*-fluoropiperidine · (MW 283.06)

(liquid, site-selective, mild electrophilic fluorinating agent for stabilized carbanions[2])

Physical Data: bp 49.5 °C; d^{25} 1.7043 g cm^{-3}; *n*20D 1.2752.

Solubility: sol MeOH, EtOH, Me_2CO, Et_2O, THF, toluene, perfluorocarbons (PFCs); slightly sol $CHCl_3$; insol H_2O; unaffected and insol hot (70 °C) 18% aq HCl or 8% aq NaOH; oxidizes ethanol slowly at 100 °C (EtOH -> acetaldehyde, diethyl ether, diethyl hexafluoroglutarate).[3]

Form Supplied in: colorless liquid (bp 48-50 °C) of ca. 97% purity; inert PFC impurities are *n*- and *i*-C_5F_{12}, perfluoro(*N*-methylpyrrolidine).

Analysis of Reagent Purity: ^{19}F NMR, GC, iodimetric titration (treat with KI in warm Me_2CO/H_2O (9:1 v/v); estimate I_2 with thiosulfate, 1 NF &tbond; 1 I_2).

Preparative Methods: electrochemical fluorination in anhydrous HF (Simons process) of pyridine (8% yield) or 2-fluoropyridine (13%) in specialized metal equipment.[3]

Handling, Storage, and Precautions: this toxic, highly volatile, nonflammable liquid should be stored (preferably at 0-5 °C) in tightly stoppered glass vessels (hydrocarbon or silicone greases are not affected) or in sealed ampoules (PTFE/glass stopcocks). Always cool the reagent before transferring it to reaction vessels to avoid losses by evaporation and toxicity hazards. Transfer, in vacuo, from a storage ampule is desirable. Use in a fume-hood. Take standard precautions to avoid breathing vapor, contact of vapor or liquid with eyes, and liquid or its solution with the skin: avoid contamination of clothing. Beware the high toxicity of perfluoro-1-azacyclohexene,

produced initially (see below) when using the reagent to effect electrophilic fluorinations. Treatment of mixtures of the reagent and its defluorination product with alkaline aq KI converts them to alkali metal salts of hexafluoroglutaric acid.

Undergoes defluorination to perfluoro-1-azacyclohexene ($CF_2(CF_2)_3CF{=}N$) and thence pentafluoropyridine with mild steel at temperatures above 200 °C.[3] (Perfluoro-1-azacyclohexene is best prepared by defluorination of the reagent with triphenylphosphine (-> Ph_3PF_2)).[2,4] The N-F bond is broken homolytically by UV light[5] or pyrolysis in platinum.[3] Stable in Pyrex at rt in Manchester daylight.

Fluorination of Carbanions.

The reagent delivers F^+ to carbon centers in highly stabilized carbanions, e.g. sodium salts of nitroalkanes (eq 1),[2] substituted malonates (eq 2),[2] β-keto esters (eq 3),[2] and tris(alkanesulfonyl)methanes (eq 4).[6] Yields can be increased by adding an alkali metal fluoride or chloride to reaction mixtures to scavenge perfluoro-1-azacyclohexene produced through fluorine transfer from nitrogen to carbon (eq 5).[2] This highly electrophilic imidoyl fluoride competes with the NF reagent for carbanionic species (eq 6),[2] a situation which detracts from the use of perfluoro-*N*-fluoropiperidine with expensive or hard-won substrates; the same situation applies for the analogous NF reagent perfluoro-*N*-fluoromorpholine[7] (noncommercial at present).

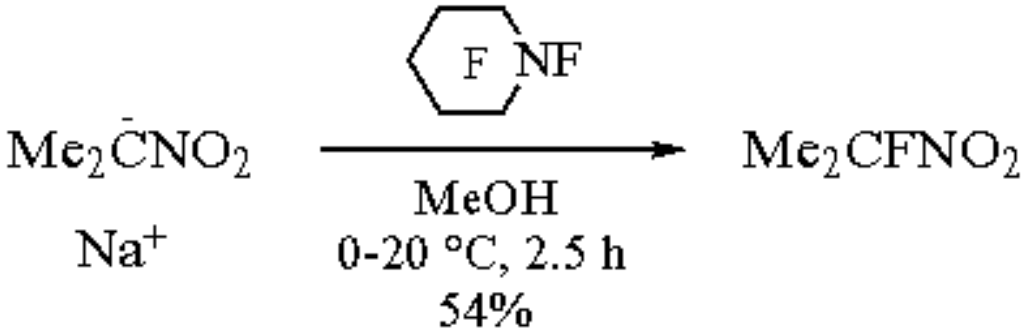

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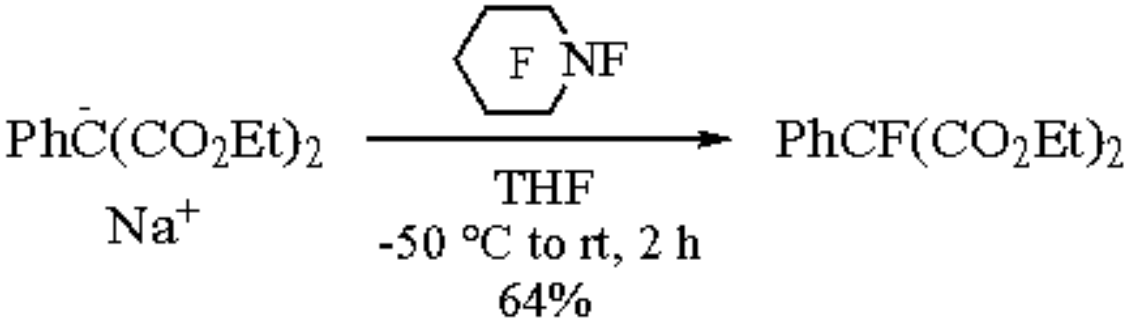

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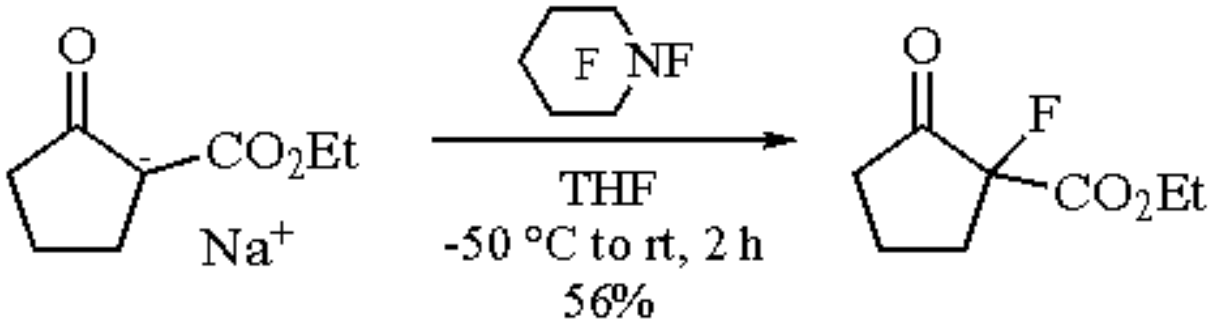

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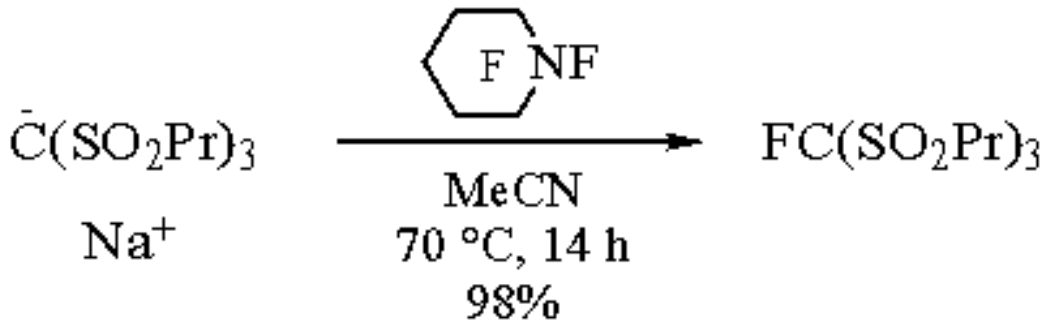

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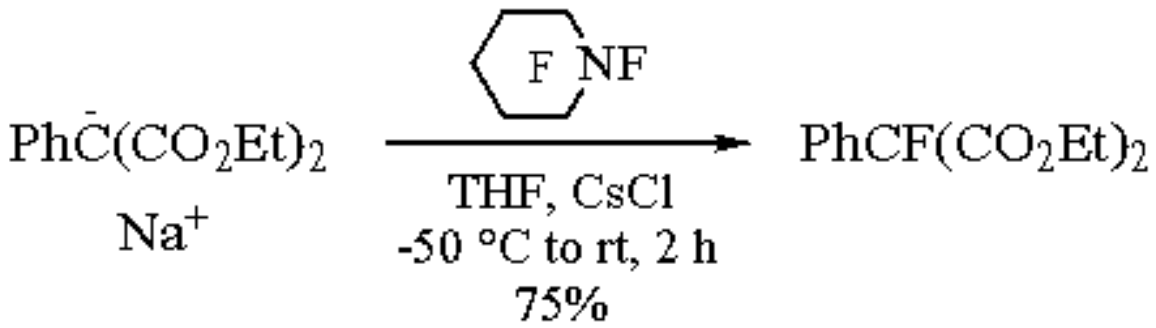

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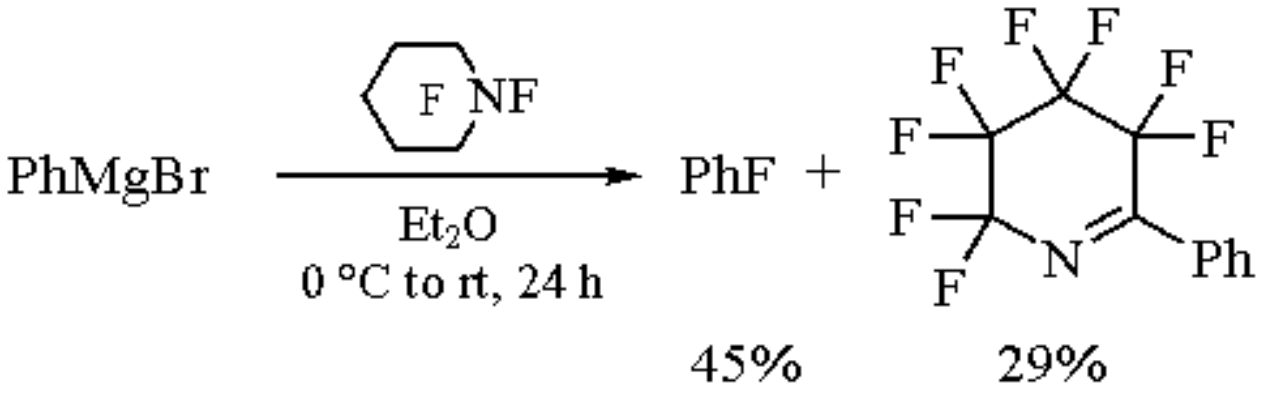

(6)

Perfluoro-*N*-fluoropiperidine (and its 2,6-bis(trifluoromethyl) analog) proved unsatisfactory compared with the hazardous gaseous reagent ***Perchloryl Fluoride*** as a means for effecting site-selective fluorination of tetraethyl methylenebisphosphonate.[8]

Fluorination at Nucleophilic Heteroatom Sites.

The reagent has been used to convert piperidine to *N*-fluoropiperidine (eq 7; exothermic: care!) and triphenylphosphine, -arsine, and -stibine to the corresponding pentavalent difluorides (eq 8).[9] The formation of perfluoro-1-azacyclohexene leads to serious consumption of substrates only in the case of piperidine.

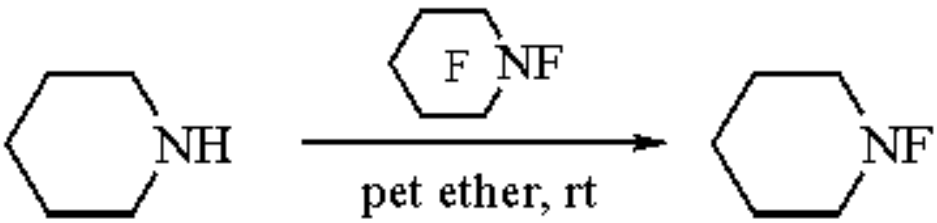

(7)

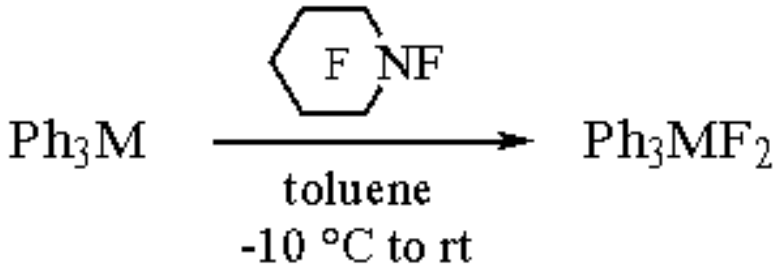

(8)

M = P, 84%; As, 81%; Sb, 69%

Sodium sulfinates smoothly yield sulfonyl fluorides (eqs 9 and 10),[6] although restricted choice of solvent can cause loss of product (eq 10).

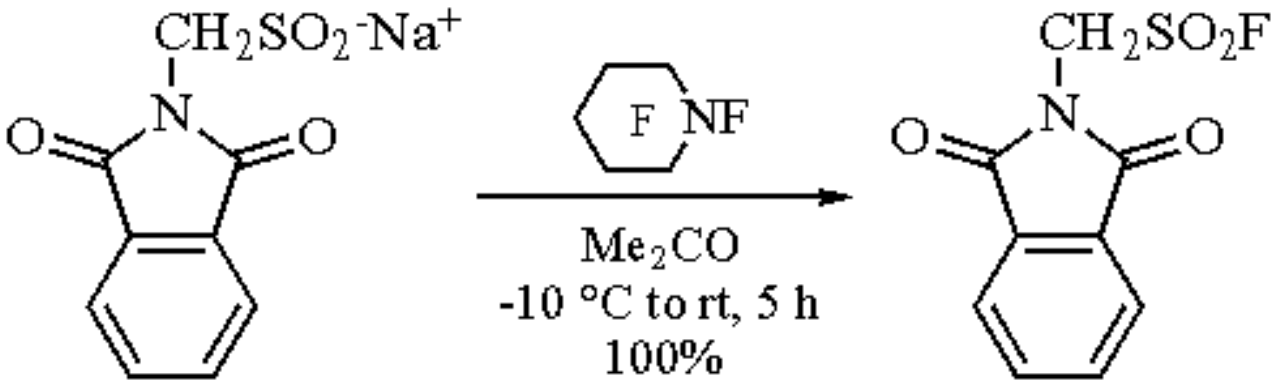

(9)

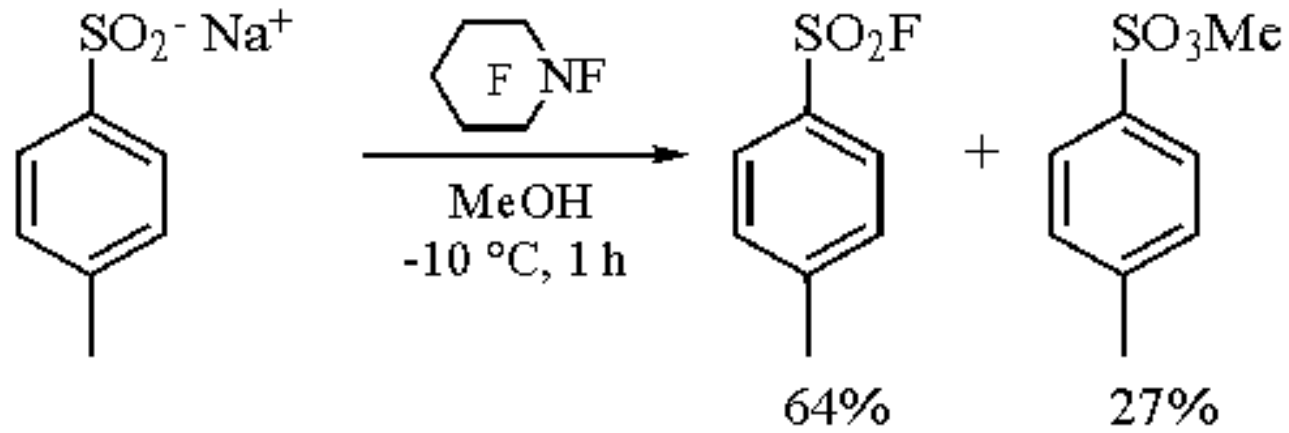

(10)

Fluorination of Electron-Rich Aromatics.

This application has received relatively scant attention (eqs 11 and 12),[10,11] the main objective being to probe the mechanism of F^+ transfer (see a recent discussion of $S_N2(F)$ vs. SET mechanisms for NF and $^+$NF reagents[2,12]). As with carbanions, the formation of the imidoyl fluoride perfluoro-1-azacyclohexene leads to loss of substrate material.

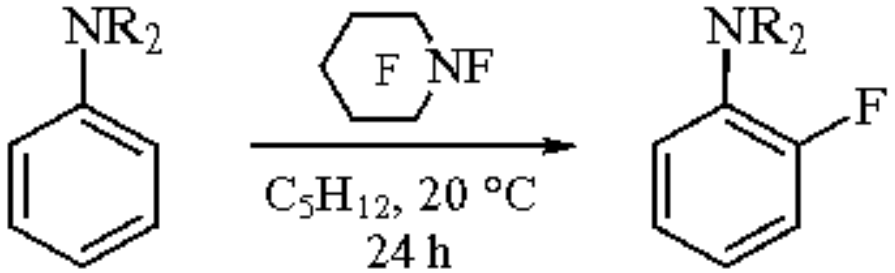

(11)

R = Me, 18% (conv. 88%)
R = Et, 48% (conv. 59%)

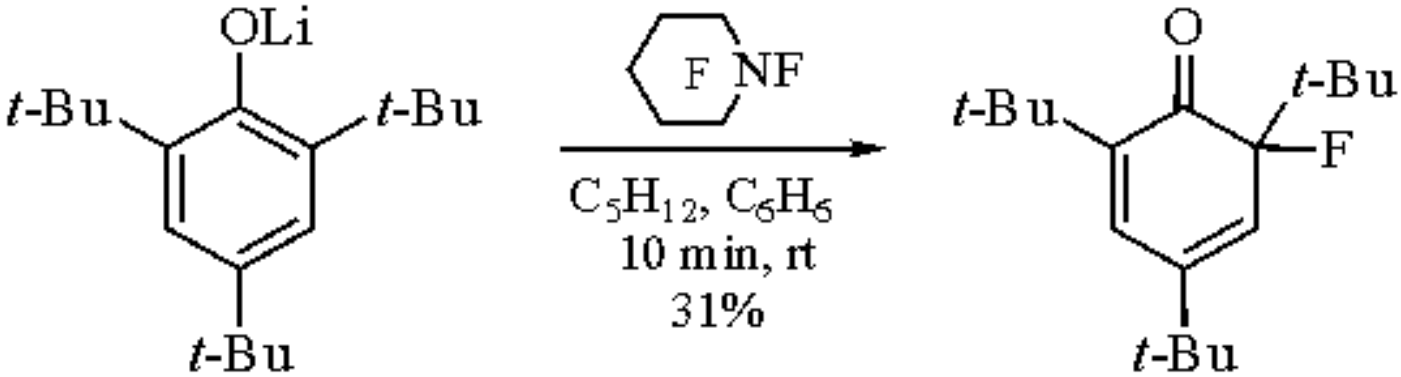

(12)

Utilization.

Although its fluorinating ability was discovered in the early 1960s,[13] perfluoro-*N*-fluoropiperidine has received little attention owing to its low-yield specialized synthesis. The commercial availability of the reagent, coupled with its ease of use and recovery, should lead to far more interest in its applications.

---

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University of Manchester Institute of Science and Technology, UK

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Peroxyacetimidic Acid

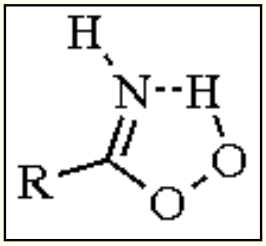

(R = Me)

[64415-45-8] · $C_2H_5NO_2$ · Peroxyacetimidic Acid · (MW 75.08) (R = Ph)

[20996-66-1] · $C_7H_7NO_2$ · Peroxybenzimidic Acid · (MW 137.15)

(oxygen atom transfer that is useful for the epoxidation of alkenes)

Preparative Methods: these reagents are generated in situ by the reaction of 30% aqueous H_2O_2 with either ***Acetonitrile*** or benzonitrile at room temperature.

Alkene Epoxidation.

Although ***Hydrogen Peroxide*** is readily available and relatively inexpensive, it is not a very reactive oxidant. For example, H_2O_2 will not effect the epoxidation of a nonconjugated carbon-carbon double bond. Heterolytic cleavage of the O-O bond in H_2O_2 has a relatively high activation barrier since the hydroxy anion is a poor leaving group. Alkene epoxidation[1] is typically achieved by its reaction with a peroxy acid (**1**) such as ***Peracetic Acid*** or ***m-Chloroperbenzoic Acid*** (*m*-CPBA).[2]

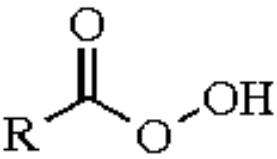

(1)

When the -OOH functional group is placed in conjugation with a carbonyl group, a carboxylate anion is the leaving group upon heterolylic cleavage of the O-O bond. ***Trifluoroperacetic Acid*** (CF_3CO_3H) is a highly reactive epoxidizing reagent since electron-withdrawing groups stabilize the departing carboxylate anion.

The O-O bond in H_2O_2 can also be activated by its conjugative interaction with an imine functionality. One of the

earliest and most useful adaptations of this type of O-O bond activation was accomplished by Payne.[3] The peroxyimidic acid derived from the alkaline hydrogen peroxide/benzonitrile system has been used with steroids[4a] and in the total synthesis of prostaglandin $F_{2\alpha}$.[4b] Hydrogen peroxide reacts with nitriles under controlled pH conditions (~pH 8) to generate a peroxyimidic acid (eq 1). Although peroxyimidic acids (**2**) have not been isolated, they react rapidly with a variety of reducing agents.

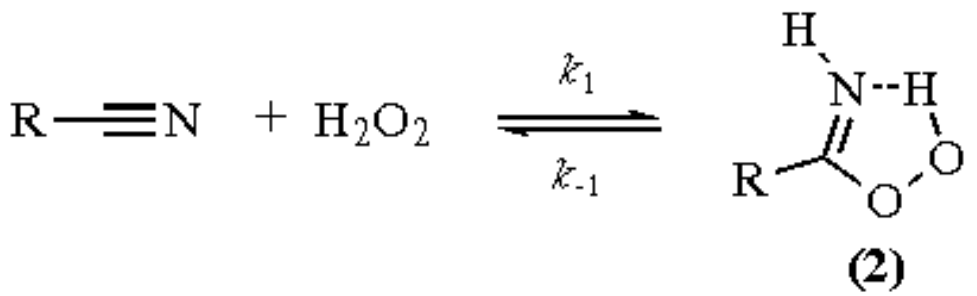

(1)

Acetonitrile, benzonitrile, and ***Trichloroacetonitrile***[3,5a] have been used as coreactants to produce peroxyimidic acids that are highly effective oxidants for the epoxidation of alkenes. This oxidation reaction has the advantage of being useful for both large- and small-scale reactions. For example, the epoxidation of (*Z*)-cyclooctene has been carried out with acetonitrile and H_2O_2 (eq 2) on a 4.4 mol scale to afford (*Z*)-cyclooctene oxide in 60-61% isolated yield.[5b]

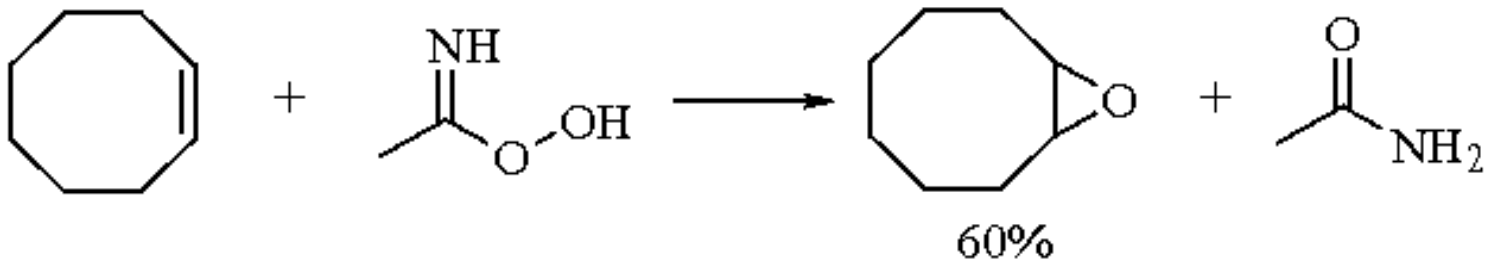

(2)

The epoxidation procedure is usually carried out in methanol solvent using $KHCO_3$ as a buffer. The reaction does not proceed well when sodium bicarbonate is employed and omission of a protic solvent such as methanol results in substantially reduced yields. The rate limiting step appears to be the nucleophilic attack of the alkene on the O-O bond.[6] Formation of the epoxide is an exothermic reaction and caution should be exercised to keep the temperature of the reaction mixture from rising.

Wiberg[7] has investigated the mechanism of the addition of H_2O_2 to a nitrile in the pH range 7-8. At higher pH values the mechanism can change and nucleophilic attack by the anion of (**2**) on H_2O_2 can result in the formation of dioxygen and the corresponding amide.[8] Radical pathways for the decomposition of (**2**) have also been proposed.[9] The epoxidation of aliphatic alkenes with peroxybenzimidic acid (**2**; R = Ph) has been shown to be less selective and have greater steric requirements than a peroxy acid.[10] Differences in the stereoselectivity of diepoxide formation between peroxy acids and peroxyimidic acids have also been noted.[11]

Related Reagents.

O-Ethylperoxycarbonic Acid.

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Peroxyacetyl Nitrate

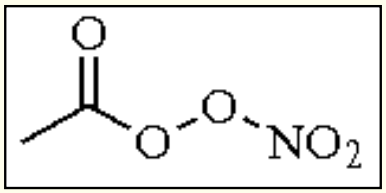

[2278-22-0] · $C_2H_3NO_5$ · Peroxyacetyl Nitrate · (MW 121.06)

(convenient source of acetylperoxy radicals;[1] epoxidizes alkenes;[2] oxidizes aldehydes,[3] thiols and sulfides;[4] acetylates primary amines[5])

Alternate Name: acetyl nitro peroxide; PAN.

Physical Data: mp -48.5 °C; bp 104 °C (extrapolated).

Solubility: sol pentane, benzene, CCl_4, $CHCl_3$, acetone.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: GLC.[6]

Preparative Methods: to a stirred mixture of ***Peracetic Acid*** (5 mmol) and 10-15 mL of dry pentane maintained at -5 to 0 °C is added 90% ***Nitric Acid*** (1 equiv) and ***Sulfur Trioxide*** (30% SO_3 in H_2SO_4, 1 equiv). The reaction mixture is stirred at -5 °C for 3 h and then treated with ice water. The organic layer is dried over $MgSO_4$ at -20 °C. The yield of unpurified PAN in pentane solution is 39%.[1]

Purification: by GLC.[1,6]

Handling, Storage, and Precautions: explosions occur when pure PAN is condensed as a liquid.[7] PAN is thermally unstable above 0 °C.[8] Purified PAN is stored as an N_2-diluted gas at 1000 ppm, 100 psi in gas cylinders at 0 °C.[4,9] Use in a well ventilated fume hood.[10]

General Considerations.

PAN is formed in polluted air by the photochemical action of sunlight on hydrocarbons and nitrogen oxides. It is an eye irritant and it also damages plants. It reacts with biologically important materials such as enzymes. Hence, there is considerable interest in studying its reactions.[7]

PAN is a convenient source of radicals; it decomposes rapidly (t_{12} for decomposition at 25 °C = 30 min) to yield acetylperoxy radicals (**1**) and NO_2 (eq 1).[1]

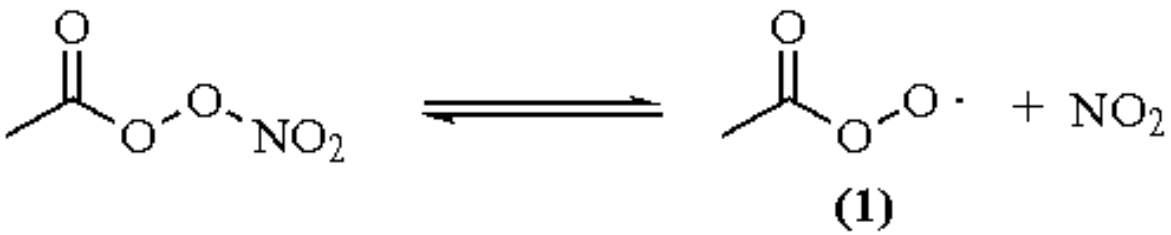

Epoxidation of Alkenes.

Reaction of PAN with alkenes yields epoxides (eq 2).[2] PAN reacts with either *cis*- or *trans*-stilbene to give only (>95%) *trans*-stilbene oxide (eq 3).

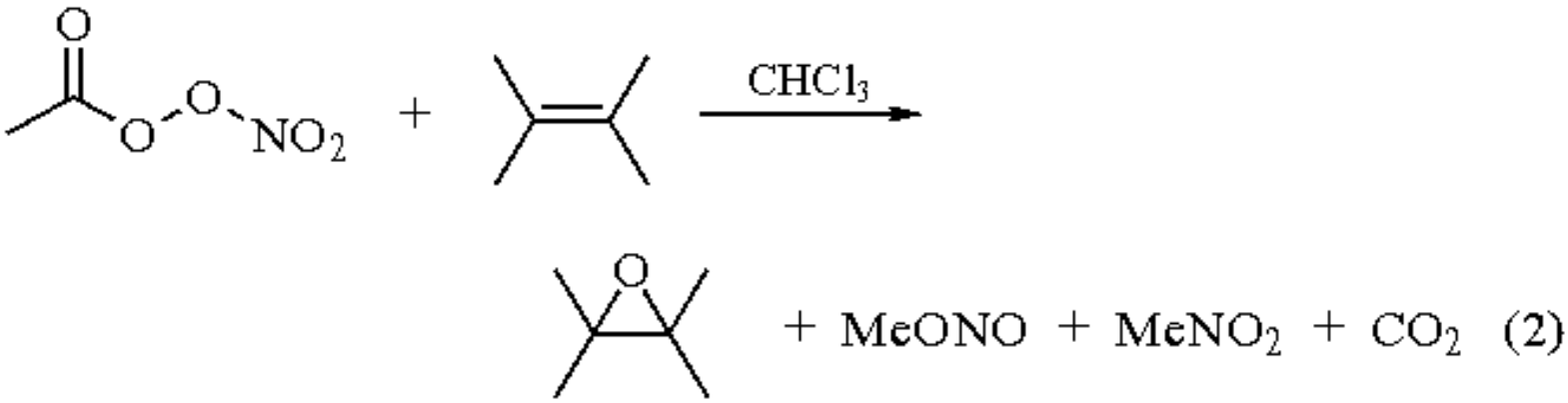

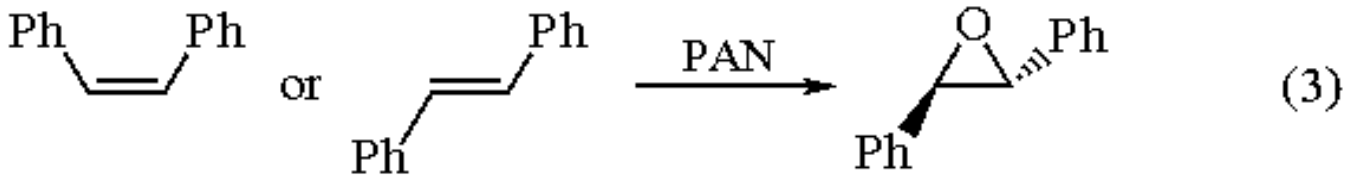

The acid-sensitive acenaphthylene oxide (**2**) has been prepared in 50% yield by epoxidizing acenaphthylene. PAN may find applications in the synthesis of acid sensitive oxides.

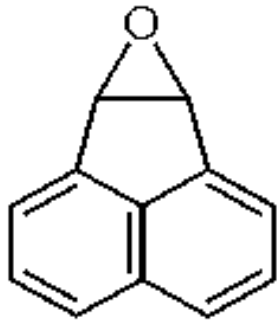

(2)

Oxidation of Aldehydes.

Aldehydes are oxidized by PAN in $CDCl_3$, CCl_4, benzene, or acetone to the corresponding acids in good yield.[3] The reaction proceeds by a radical mechanism. Ketones are not oxidized by PAN.

Acetylation of Primary Amines.

When liquid *n*-propylamine is injected into a solution of PAN (0.5 M in $CDCl_3$), vigorous evolution of oxygen is observed.[5] The reaction is complete in less than 1 min after mixing the reactants; the amide (**3**) is formed (yield >90%).

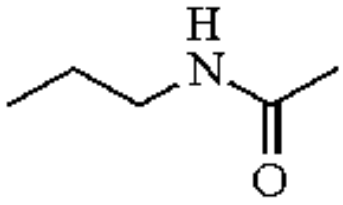

(3)

Action of KOH on PAN.

When 0.4 M KOH in benzene-methanol (9:1) is added to dilute solutions of PAN (0.2-0.3 M in benzene), there is vigorous evolution of oxygen (eq 4).[11] Singlet oxygen, which may be important in oxidations involving PAN, has been shown to be a product of this reaction.

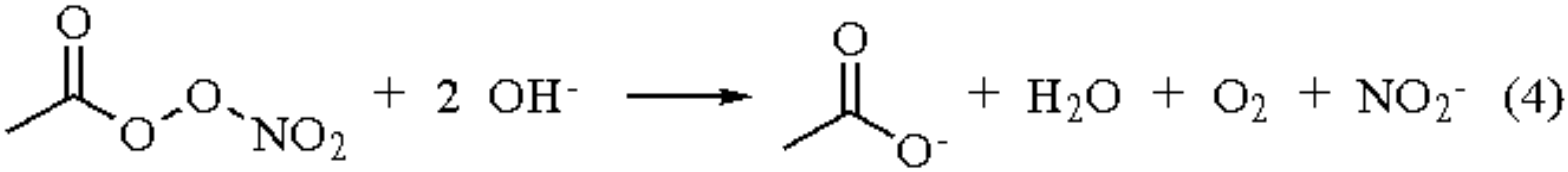

Oxidations at Sulfur Atoms.

Thiols are oxidized by PAN to disulfides; cysteine (**4**) is oxidized to cystine.[4] Sulfides are oxidized to sulfoxides (e.g. methionine (**5**) to methionine sulfoxide). PAN rapidly oxidizes dimethyl sulfide to DMSO (t_{12} <1 min).[2]

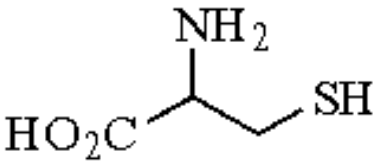

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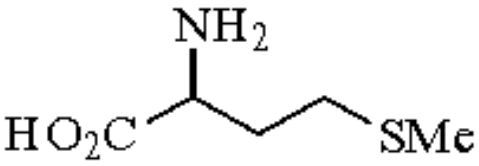

(5)

Considering the hazards involved in handling large quantities of PAN, it is not yet particularly useful in synthetic

organic chemistry. Oxidation reactions presented above can be carried out conveniently and in good yields using ***m-Chloroperbenzoic Acid*** or ***Hydrogen Peroxide***.

---

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Peroxybis(triphenylphosphine)palladium

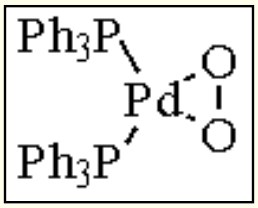

[29933-60-6; 15614-66-1] · $C_{36}H_{30}O_2P_2Pd$ · Peroxybis(triphenylphosphine)palladium · (MW 663.02)

(an oxygen carrier for mild oxidation of alkenes,[1] sulfur compounds,[2] and oximes[3])

Alternate Name: dioxygenbis(triphenylphosphine)palladium.

Physical Data: described as green crystalline solid; mp 105 °C (darkens); 140-143 °C (melts);[4] also described as pale blue powder; mp 100 °C (dec).[5]

Solubility: sol CH_2Cl_2.

Preparative Methods: prepared by bubbling oxygen through a solution of ***Tetrakis(triphenylphosphine)palladium(0)*** in a carbon dioxide-free mixture of CH_2Cl_2 and diethyl ether[4] or benzene,[6] or by bubbling oxygen through a carbon dioxide-free solution of bis(triphenylphosphine)palladium in benzene.[5]

Purification: recrystallization from a 1:1 mixture of CH_2Cl_2 and ether with oxygen bubbling through continuously.[4]

Handling, Storage, and Precautions: the solid and its solutions decompose in a few days to metallic palladium and oxygen or phosphine oxide.

Oxygenation of Alkenes.

Electron-deficient alkenes and α,β-unsaturated carbonyl compounds react with $(PPh_3)_2PdO_2$ to form five-membered ring dioxapalladacycles in high yields below room temperature (eq 1).[1] At temperatures above 25 °C these dioxapalladacycles break down to a ketone and an oxapalladacyclopropane, where the lone carbon in the heterocyclopropane is the carbon of the alkene bearing the electron-withdrawing groups (eq 2).[1] If the dioxapalladacycle is treated with ***Trifluoroacetic Acid***, an epoxide is obtained in high yield and with high stereoselectivity where applicable (eq 2).[1]

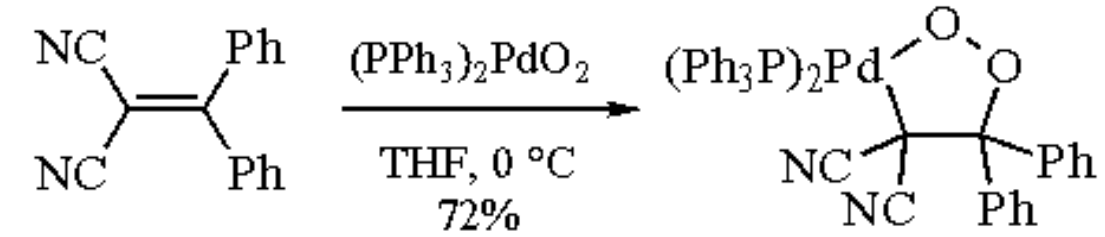

(1)

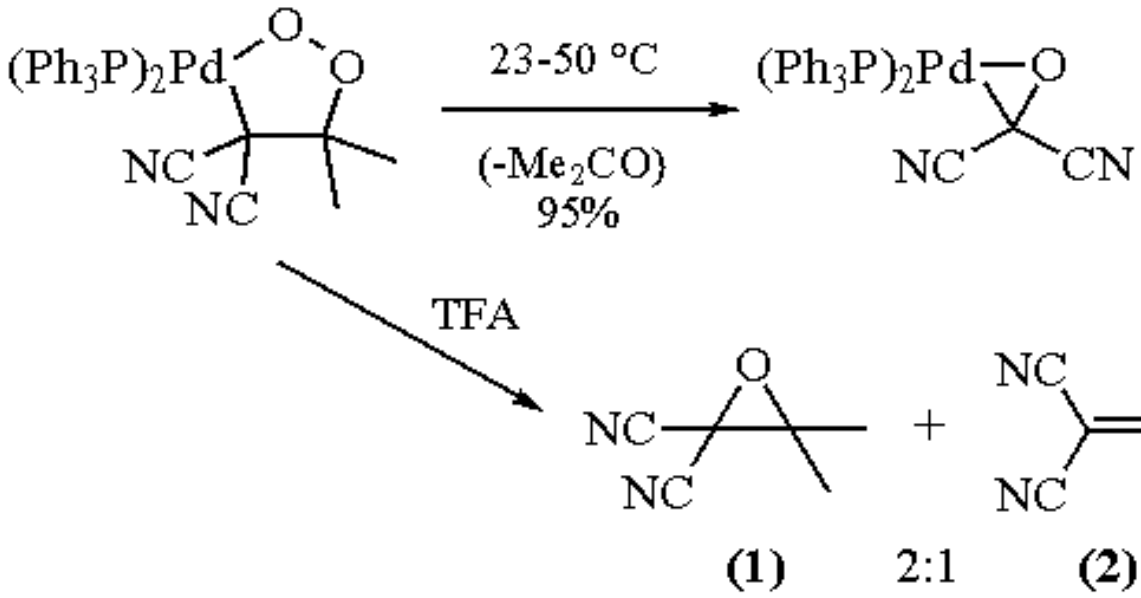

(2)

Electron-rich alkenes are epoxidized by $(PPh_3)_2PdO_2$ only in the presence of acid derivatives (eq 3).[2] The need for the acid derivative has been suggested to imply that a peroxy acid-palladium complex is the active oxidizing agent. The O_2 of $(PPh_3)_2PdO_2$ adds to reactive dienes under thermal or photochemical conditions to give endoperoxides which can break down to diketones.[7] For example, 1,3-diphenylisobenzofuran reacts with $(PPh_3)_2PdO_2$ to give a mixture of endoperoxide and *o*-dibenzoylbenzene (eq 4). 9,10-Diphenylanthracene, however, is unreactive under thermal conditions, but on irradiation gives an endoperoxide which breaks down to *o*-dibenzoylbenzene (eq 5). Photochemical reactions involving $(PPh_3)_2PdO_2$ must avoid the presence of alkyl halides and the use of alkyl halogenated solvents, because zerovalent palladium species that may be present react with aliphatic halides to give $(PPh_3)_2PdX_2$ and the oxygen atoms of the peroxy complex are diverted to the formation of phosphine oxide under these conditions.[8]

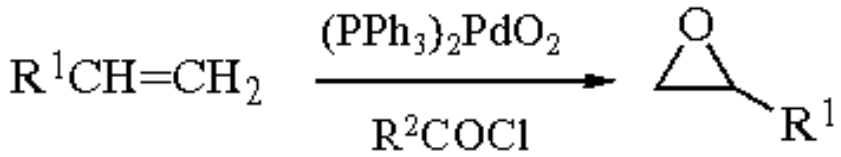

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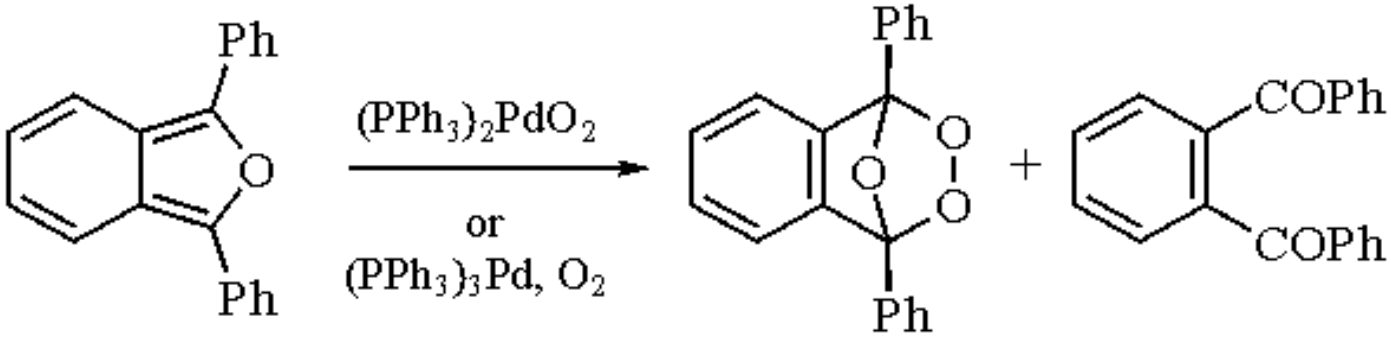

(4)

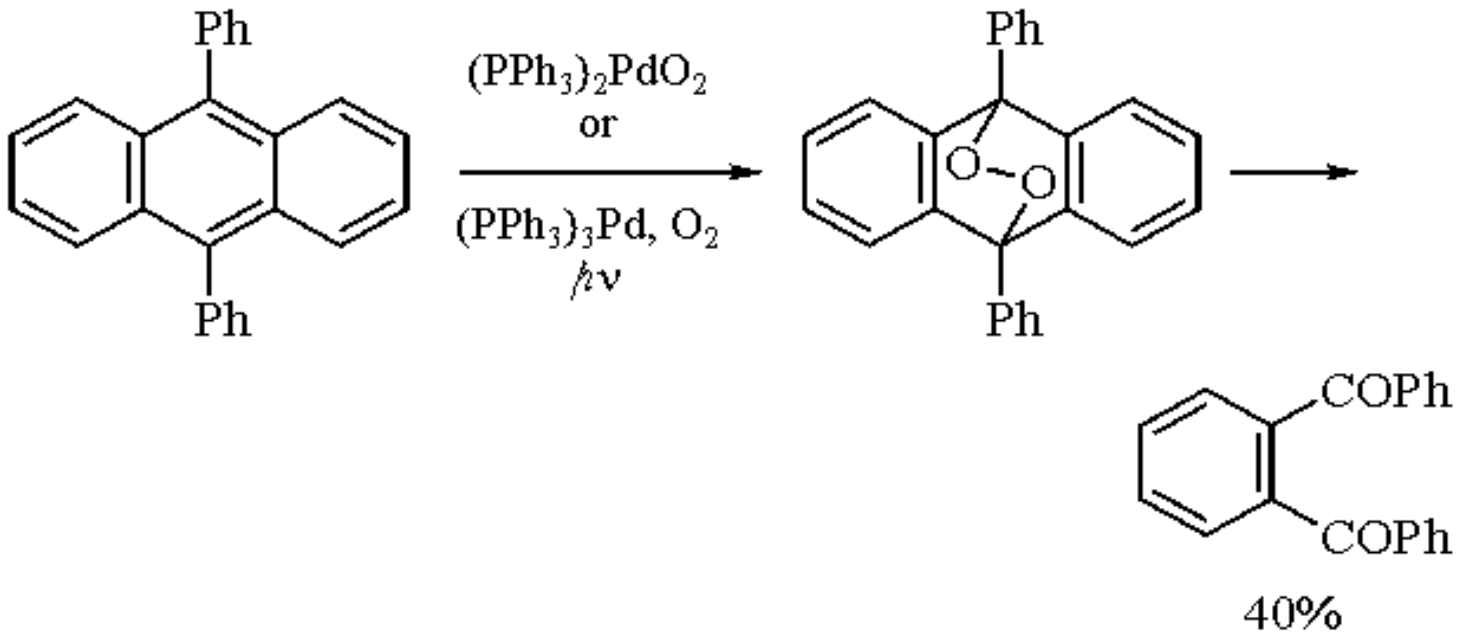

(5)

Other Oxygenation Reactions.

$(PPh_3)_2PdO_2$ effectively converts base- and acid-sensitive ketoximes to ketones (eq 6).[3] In the presence of acid derivatives, sulfides are oxidized to sulfoxides and sulfoxides are oxidized to sulfones in good yield (eq 7).[2]

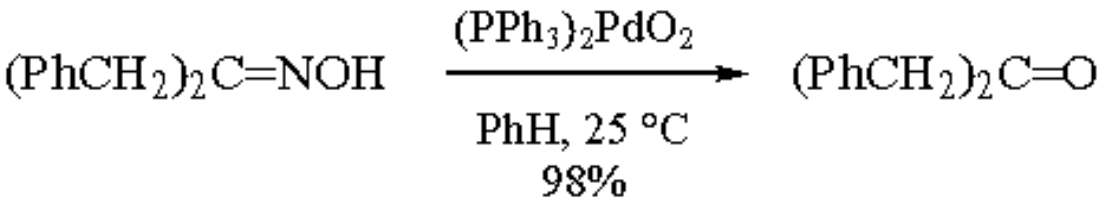

(6)

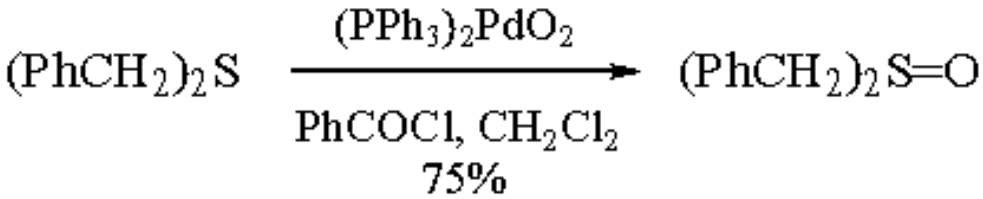

(7)

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Peroxymaleic Acid[1]

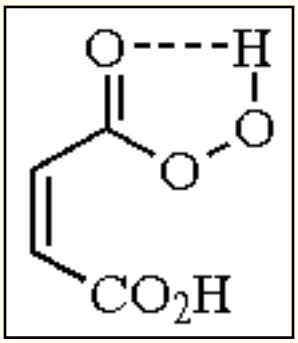

[3851-95-4] · $C_4H_4O_5$ · Peroxymaleic Acid · (MW 132.08)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes and amines[2])

Alternate Names: permaleic acid; PMA.

Solubility: sol CH_2Cl_2, $CHCl_3$ and water.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: assay using iodometry.[3]

Preparative Methods: (a) to a cooled (0 °C) and stirred mixture of 90% ***Hydrogen Peroxide*** (**caution**!) (11.6 g, 0.34 mol) and CH_2Cl_2 (150 mL) is added in one batch 39.2 g (0.4 mol) of freshly crushed ***Maleic Anhydride***. When the major portion of the anhydride has reacted, the reaction mixture is heated to reflux.[2] (b) 0.1 mol of 88% H_2O_2, 0.13 mol of maleic anhydride, $CHCl_3$ (19.5 mL), and DMF (0.5 mL) are stirred at 20 °C for 1.5 h to give the reagent, essentially free from H_2O_2.[4]

Handling, Storage, and Precautions: reasonably stable in CH_2Cl_2 solution, decomposing to the extent of 5% in 6 h at rt. Since peroxy acids are potentially explosive, care is required while carrying out the reactions; during workup, test for peroxides before solvent removal. This reagent should be handled in a fume hood.

Baeyer-Villiger Reaction.

Simple acyclic ketones and cyclic ketones having seven or more carbon atoms in the ring do not undergo facile Baeyer-Villiger reaction with normal peroxy acids like ***m-Chloroperbenzoic Acid***; only PMA and ***Trifluoroperacetic Acid*** (TFPAA) are useful for this reaction. Although PMA is not as powerful an oxidizing agent as TFPAA, its reactivity is adequate. When TFPAA is used, an inorganic buffer reagent has to be added; when PMA is used there is no need for such a buffer reagent.[2]

Baeyer-Villiger reaction of the ketone (**1**) furnishes the ester (**2**) (eq 1).[2] Oxidation of the diketone (**3**) furnishes the lactone (**4**) in 77% yield; the reaction was performed on a 1.0 mol scale.[5] Baeyer-Villiger reaction of the ketone (**5**) furnished in 93% yield the acetate (**6**).[6] Ketone (**7**) gave the acetate (**8**) in 90% yield;[7] this oxidation cannot be carried out with *m*-CPBA.

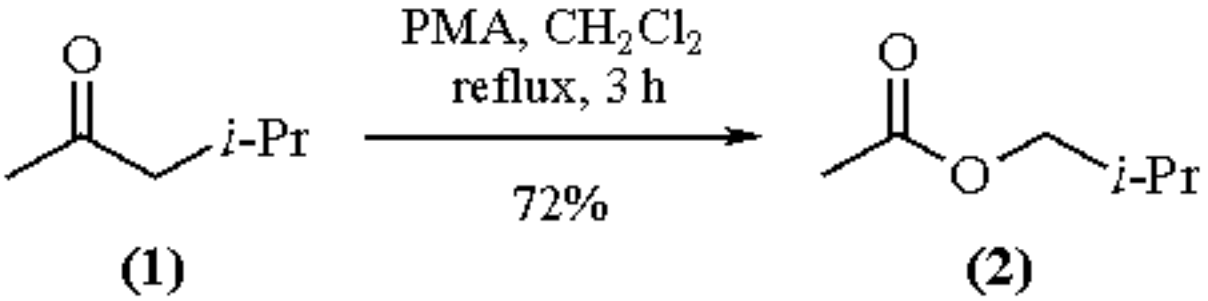

(1)

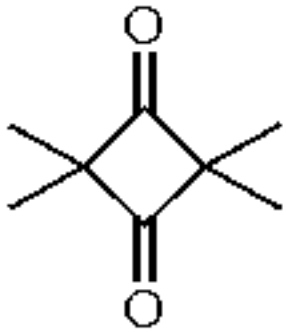

(3)

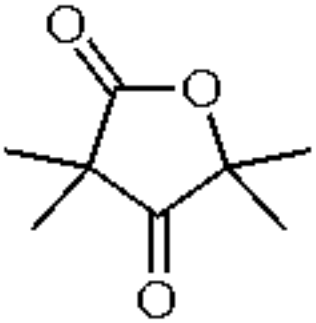

(4)

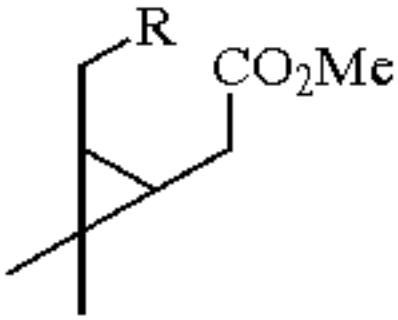

(5) R = COMe

(6) R = OCOMe

(7) R = COMe

(8) R = OCOMe

Cyclododecanone has been oxidized to the lactone (**9**) (eq 2).[8] The reaction has been carried out on the 250 g scale. In this case, PMA satisfactory for the Baeyer-Villiger reaction was prepared with 30% H_2O_2 by using enough ***Acetic Anhydride*** to react with the water present.

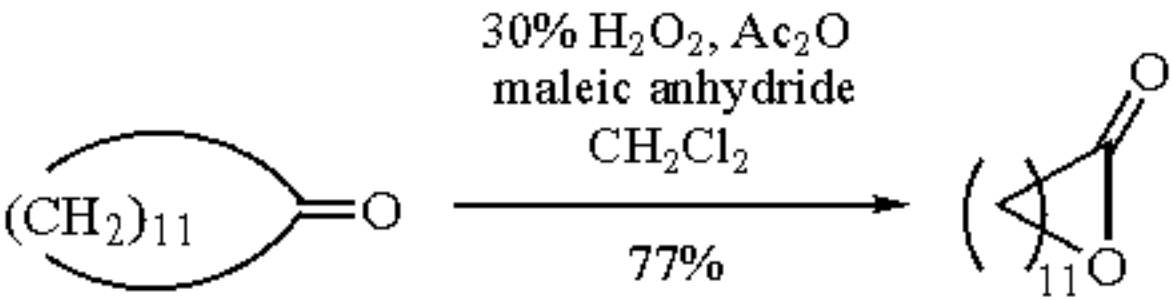

(2)

(9)

It has been observed that reaction of maleic anhydride with 86% H_2O_2 in CH_2Cl_2 is incomplete even at reflux temperature. PMA prepared by method (b) above reacted rapidly (15-30 min) with a slight excess of cyclohexanone at 35-40 °C to provide hexanolide in 90-100% yield.[4]

Oxidation of Nitrogen-Containing Compounds.

Aromatic primary amines (**10**) and (**12**) have been oxidized by PMA to the nitro compounds (**11**)[2] and (**13**)[9] in yields of 40% and 61%, respectively. The nitro compound (**11**) cannot be prepared from (**10**) using TFPAA.[2]

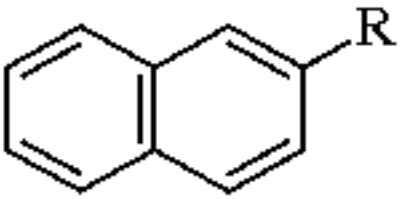

(10) R = NH_2
(11) R = NO_2

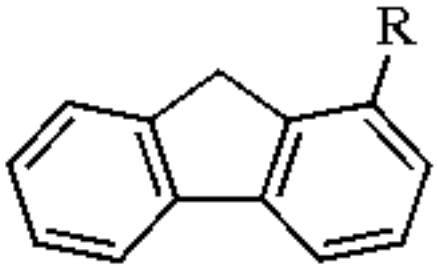

(12) R = NH_2
(13) R = NO_2

Other Applications.

Alkenes which are not electron rich can be epoxidized by PMA; 1-octene and methyl methacrylate have been epoxidized in 80% and 74% yields.[2] Adenine 1-oxide nucleotides have been prepared by oxidation of natural compounds in 75-80% yields with PMA in aqueous solution at neutral pH.[10]

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Peroxydisulfuryl Difluoride[1]

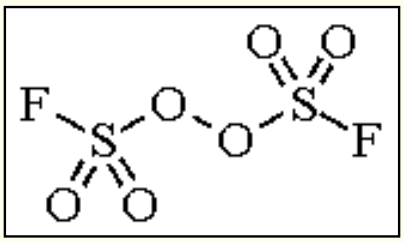

[13709-32-5] · $F_2O_6S_2$ · Peroxydisulfuryl Difluoride · (MW 198.14)

(fluorosulfating agent, capable of halogen[2-7] and hydrogen abstraction[2,8,9] reactions to give esters of fluorosulfuric acid; powerful oxidant[10,11])

Physical Data: bp 67.1 °C; mp -55.4 °C.[1,11,12]

Form Supplied in: colorless liquid with unpleasant odor.

Preparative Methods: can be obtained by the reaction of SO_3 with F_2 in the presence of AgF_2[11] or by electrolysis of fluorosulfuric acid.[12]

Handling, Storage, and Precautions: although the reagent appears to be stable and there are no reports of explosive properties, it should be handled with care. It can ignite organic materials upon contact. It is hydrolyzed by water to give oxygen and fluorosulfuric acid.[12] Use in a fume hood.

Synthesis of Fluorosulfates.

The chemical behavior of $F_2S_2O_6$ is determined by two features of its reactivity: (a) the ability to generate the radical species &bdot;OSO_2F in the reversible dissociation reaction,[2,13] and (b) the high oxidation ability[10,11] and, in particular, the generation of high-valent species containing two fluorosulfate groups.[1] The reagent (**1**) smoothly substitutes halogen atoms (Cl, Br, I) for fluorosulfate groups, probably via transient formation of hypervalent species of type (**2**) (eq 1).[3]

$$\underset{(1)}{RX + FSO_2OOSO_2F} \longrightarrow \underset{(2)}{\left[RX(OSO_2F)_2\right]} \longrightarrow ROSO_2F \quad (1)$$

For example, methyl chloride or bromide reacts with $F_2S_2O_6$ at -25 °C to give methyl fluorosulfate.[2] The reaction is applicable to fluorochlorocarbons (eq 2).[4]

$$CF_2ClCFCl_2 \xrightarrow{F_2S_2O_6} CF_2ClCFClOSO_2F \qquad (2)$$

In the case of perfluoroalkyl iodides the relatively stable hypervalent iodine derivatives of type $R_fI(OSO_2F)_2$ can be isolated; they are also readily transformed into the corresponding fluorosulfates R_fOSO_2F.[5-7]

Perfluoroalkenes react with (**1**) to give *vic*-difluorosulfates,[14 -17] e.g. eq 3.[15]

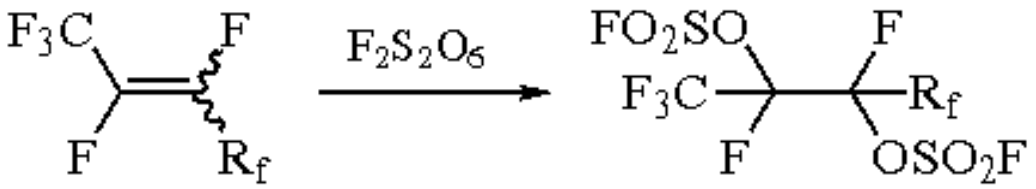

(3)

C_6F_6 also gives a 1,4-addition product and then 1,2,3,4- and 1,2,3,4,5,6-addition products.[18]

Hydrogen Abstraction.

Reactions of (**1**) with a variety of organic compounds such as amines, alcohols, thiols, aromatics, and even saturated hydrocarbons, proceed by hydrogen abstraction and addition of an OSO_2F moiety (R-H -> $ROSO_2F$).[1,2,8,9,19,20] For example, methane gives a mixture of methyl fluorosulfate and methylene difluorosulfate.[20] Methyl fluorosulfate also gives methylene difluorosulfate in reaction with (**1**).[2] Hexafluoropropane[8] and propionic acid[20] react in accordance with eqs 4 and 5.

$$(CF_3)_2CH_2 \xrightarrow{F_2S_2O_6} (CF_3)_2CHOSO_2F \qquad (4)$$

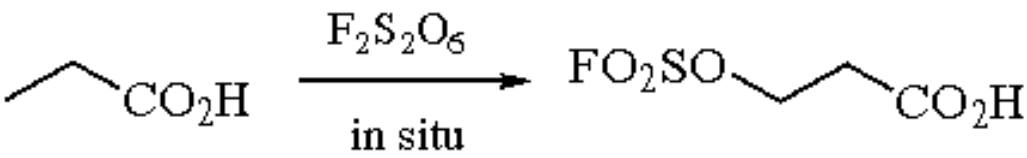

(5)

Hexafluoroacetone imine also reacts with substitution of the imine hydrogen atom (eq 6).[19]

$$(CF_3)_2C{=}NH \xrightarrow{F_2S_2O_6} (CF_3)_2C{=}NOSO_2F + (CF_3)_2C(FO_2SO)-N{=}N-C(OSO_2F)(CF_3)_2 \quad (6)$$

Benzene gives phenyl fluorosulfate[1] and nitrobenzene gives *m*-nitrophenyl fluorosulfate[21], respectively, in reaction with (**1**).

Oxidation.

Peroxide (**1**) is a powerful oxidant and can be used for the oxidation of noble metals (Ag, Au, Re, Pt, Os, Rh) to the salts of fluorosulfuric acid.[10,22] For example, the oxidation of metallic silver by $F_2S_2O_6$ in the presence of $HOSO_2F$ gives $Ag(SO_3F)_2$.[22] Oxidation of organic compounds can produce radicals. For example, the trimer (**3**) of perfluoropropylene reacts with (**1**) to give stable radical (**4**), isolated in analytically pure form (eq 7).[23]

$$\underset{\textbf{(3)}}{[(CF_3)_2CF]_2C{=}CFCF_3} \xrightarrow{F_2S_2O_6} \underset{\textbf{(4)}}{[(CF_3)_2CF]_2C^{\cdot}-CF(OSO_2F)CF_3} \quad (7)$$

Dimethyl ether reacts with (**1**) to give dimethoxyethane as the sole product, presumably via selective dimerization of transient methoxymethyl radicals (eq 8).[24]

$$2\,Me_2O + \underset{\textbf{(1)}}{FSO_2OOSO_2F} \xrightarrow{FSO_3H} MeOCH_2CH_2OMe + 2\,FSO_3H \quad (8)$$

Carbon monooxide is oxidized by (**1**) to CO_2.[3] Nitroso groups in perfluoronitrosoalkanes are either oxidized to nitro groups or undergo substitution by an OSO_2F group.[25]

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Phenacyl Bromide

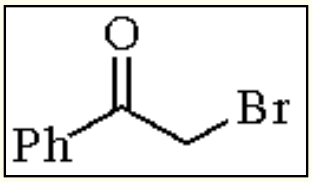

[70-11-1] · C_8H_7BrO · Phenacyl Bromide · (MW 199.05)

(protecting group for acids and phenols;[1] removable by zinc reduction)

Alternate Name: 2-bromoacetophenone.

Physical Data: mp 48-51 °C; bp 135°/18 mmHg.

Solubility: insol H_2O; sol common organic solvents.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: corrosive lachrymator; use in a fume hood.

Carboxylic Acids.

The phenacyl group was introduced[1] as a useful protecting group for carboxylic acids since it is easily attached, stable to a range of conditions, and removable again under conditions which do not affect most other functional groups. The ester is made by S_N2 displacement of phenacyl bromide by the salt of the acid, in water or other solvents, rapidly and in good yields.[2] It has also been made using crown ethers,[3] phase transfer,[4,5] KF catalysis,[6] and with ion-exchange resins loaded with the carboxylate salt.[7] It may be removed again by zinc reduction in glacial or aqueous acetic acid in about an hour at room temperature, affording the acid and acetophenone.[1] The ***Zinc-Acetic Acid*** reduction has been improved by using chelating agents to sequester the formed zinc salts.[8] It has also been expeditiously removed by displacement with thiophenoxide[9] and telluride[5] ions, which do not affect carbonyls. As a variation, the *p*-bromophenacyl esters have been used in the same way and have the advantage of higher melting points and of clear AB patterns in the NMR.

Because of its ease of introduction, high yields, and selectivity, the phenacyl protecting group has found extensive use in peptide synthesis[10] as it is stable to the hydrogenation conditions used to remove benzyl protecting groups and to the acid conditions removing Boc. In general, the phenacyl esters have not caused racemization during amino acid coupling, except for a report of racemization of proline.[11] Phenacyl esters have also been employed to derivatize fatty acid mixtures for chromatographic analysis.[12]

A special feature of the method lies in the opening of lactones that spontaneously reclose. Since esterification of 4-bromophenacyl bromide occurs via S_N2 displacement with the carboxylate anion, from the base-opened lactone, the hydroxy ester can often be isolated, for further reactions on the hydroxyl group. This is illustrated in the conversion of the *trans*-lactone of santonin to its *cis*-lactone diastereomer[13] in eq 1. Conversion in the reverse direction in this case was not effective, however, since alkali on the *cis*-lactone only caused elimination.

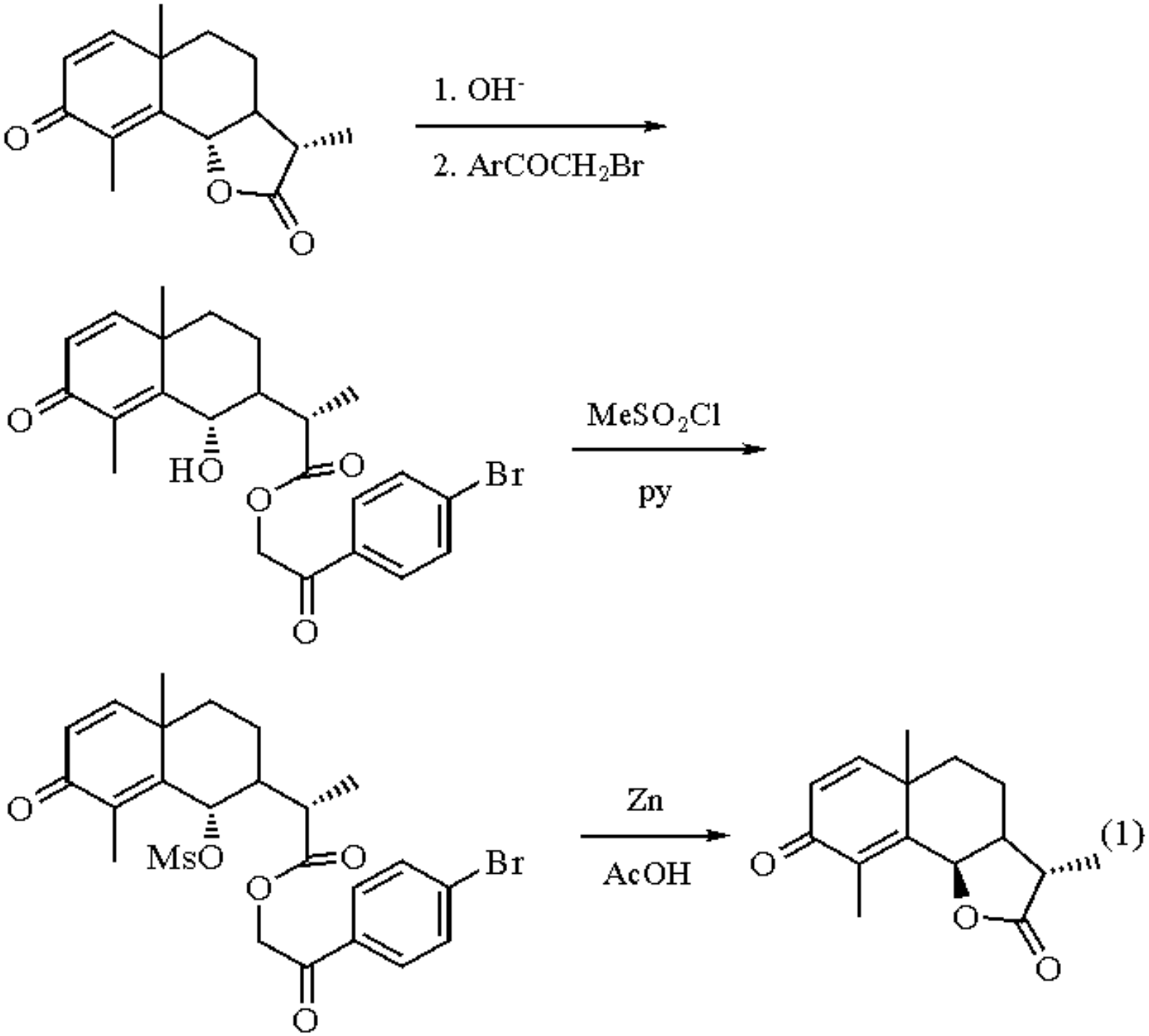

Phenols.

While much used for acids, the phenacyl group has seen less use for phenol protection.[14,15] Commonly made by alkylation of the phenols with K_2CO_3 in refluxing acetone for 1-2 hours, the phenacyl ethers are as easily removed with

zinc.[1] As in peptide synthesis the group is valued for its selectivity, being stable to hydrogenation and the acid conditions used to remove MEM ethers.[15] Under stronger acid conditions, however, the phenacyl ethers are apt to cyclize to benzofurans, as in eq 2.

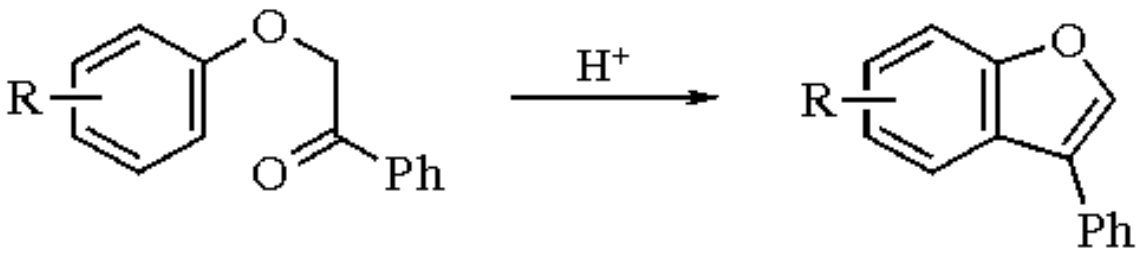

(2)

Amines.

In a variant on the Gabriel synthesis, phenacylsulfonyl amines were made (from phenacylsulfonyl chloride and primary amines) and could be efficiently monoalkylated on nitrogen, then the phenacylsulfonyl group removed as above with zinc and acid, releasing the secondary amine product with SO_2 and acetophenone (eq 3).[16] As protecting groups, these were found to be sensitive to alkali (cleavage to benzoic acid), and in the monoalkylation of the nitrogen, the methylene of phenacylsulfonyl was also alkylated.

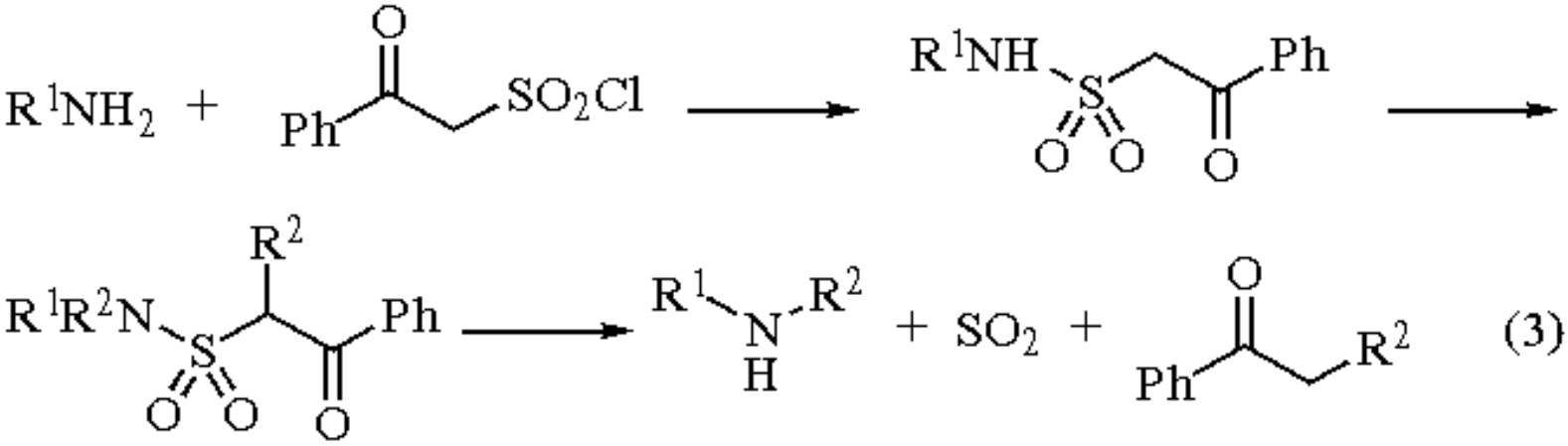

(3)

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Phenoxyacetic Acid

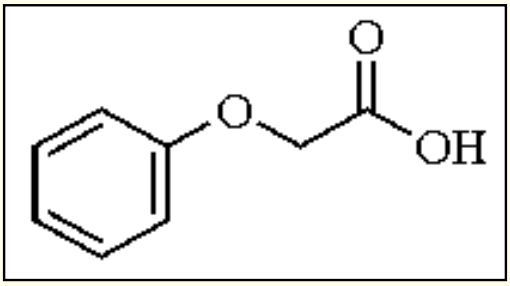

[122-59-8] · $C_8H_8O_3$ · Phenoxyacetic Acid · (MW 152.16) (dilithio dianion)

[67774-23-6] · $C_8H_6Li_2O_3$ · Dilithiophenoxyacetate · (MW 164.02)

(dianion used for α-alkylation,[1] carboxymethylation of organoboranes,[2,3] aldol addition reactions to give α-phenoxy-β-hydroxy acids,[2-5] and phenyl enol ether synthesis;[2,3] phenoxymethylation of quinones;[6] OH and NH protection of nucleosides[7,8])

Physical Data: mp 98-99 °C; pK_a 5.12.

Form Supplied in: commercially available.

Preparative Methods: the title reagent and other substituted aryloxyacetic acids are easily synthesized by a Williamson ether synthesis using a phenol, base, and an α-haloacetic acid derivative.[9]

Purification: recrystallization from H_2O.

General Discussion.

Deprotonation of phenoxyacetic acid by ***Lithium Diisopropylamide*** (LDA) generates dilithiophenoxyacetate that can be alkylated by alkyl halides and carbonyl compounds (eq 1).[1,4]

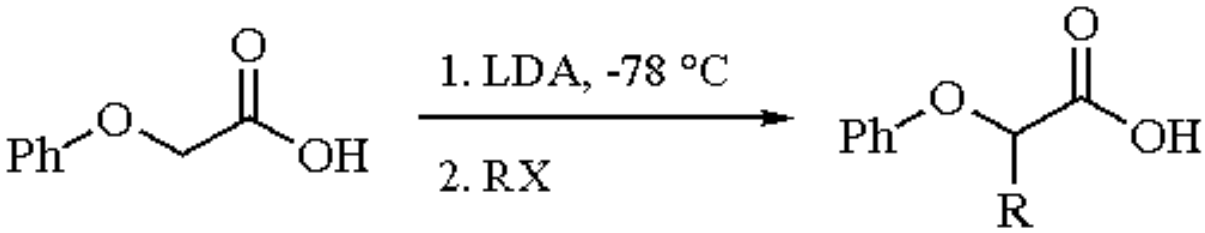

(1)

The dilithio anion formed in the above chemistry is useful as a reagent to carboxymethylate organoboranes (eq 2).[2,3] The yields are poor with very hindered alkyl groups; only a single alkyl group is transferred. ***9-Borabicyclo[3.3.1]nonane*** can be used to maximize the efficiency and yield in terms of transfer of the alkyl group.

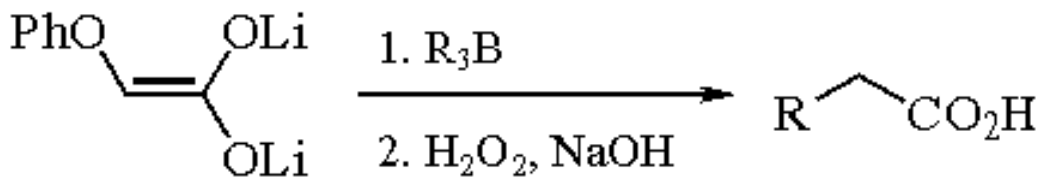

(2)

Reaction of the dianion with carbonyl compounds gives the expected α-phenoxy-β-hydroxy acids.[4,10] The reaction with aldehydes can be stereoselective for the *threo* isomer.[4,5] Subsequent cyclization of the intermediate β-hydroxy acid to the β-lactone then allows for a thermal decarboxylation to provide phenyl enol ethers (eq 3).[10] ***Magnesium Bromide***-catalyzed rearrangement of the β-lactone derived from the dianion and cyclopentanecarbaldehyde provides an entry to *trans*-fused cyclohexane butyrolactones.[4]

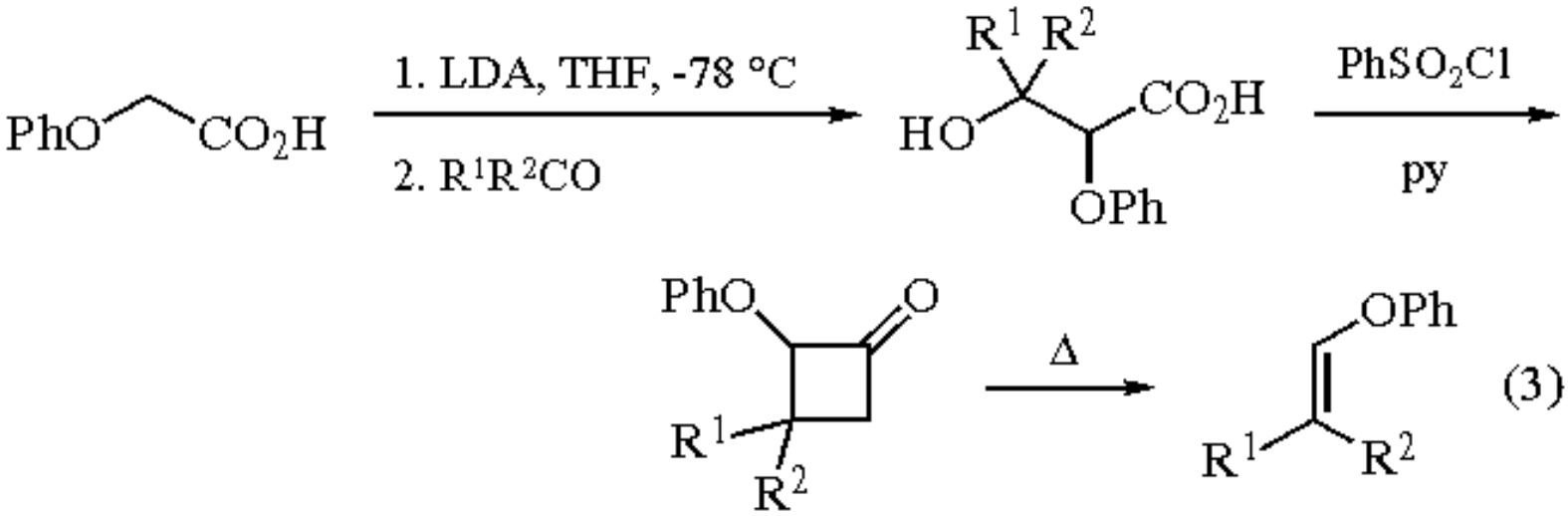

(3)

1,2-Addition occurs in reaction of the dianion with α,β-unsaturated aldehydes and again high stereoselection can be observed.[5]

Decarboxylation of phenoxyacetic acid with ***Ammonium Peroxydisulfate-Silver(I) Nitrate*** in the presence of ***1,4-Benzoquinone*** gives 2-phenoxymethyl-1,4-benzoquinone by a radical alkylation (eq 4).[6]

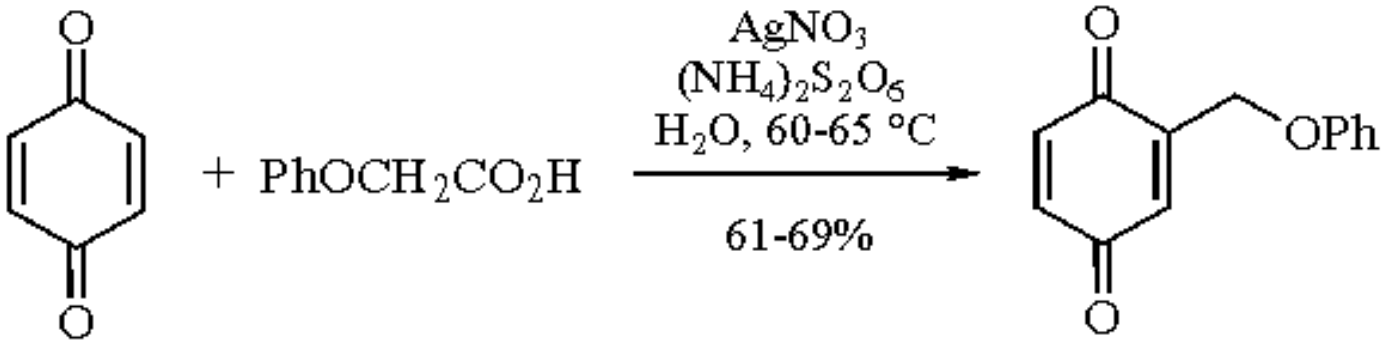

(4)

Phenoxyacetyl derivatives are useful for the protection of hydroxy and amino groups. Phenoxyacetate esters can be

selectively cleaved by aqueous or methanolic ammonia in the presence of simple acetate or benzoate esters.[7] Similarly, phenoxyacetamide derivatives are reportedly useful in nucleotide synthesis.[8] Specifically, the acid chloride of phenoxy acetic acid has been used to protect the exocyclic amino group of purine or pyrimidine nucleic acid bases. The phenoxyacetamide group increases the lipophilicity of the intermediate nucleic acid bases and improves their stability to acid treatment in oligodeoxyribonucleotide synthesis.

Related Reagents.

Dilithioacetate; ***Ethyl Lithioacetate***; ***Ethyl Mandelate***; ***Ethyl Trimethylsilylacetate***; ***Methyl O-Methyllactate***; β-***Propiolactone***; ***Trimethylsilylacetic Acid***.

---

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(2*R*,3*R*)-(*Z*)-*cyclo*-Phenylalanine

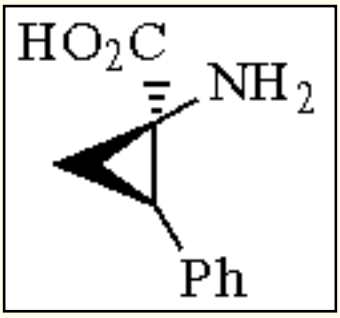

(.HCl)

[110716-95-5] · $C_{10}H_{12}ClNO_2$ · (2*R*,3*R*)-(*Z*)-*cyclo*-Phenylalanine · (MW 213.68)

(reagent for syntheses of conformationally constrained peptidomimetics)

Physical Data: (HCl salt) mp 201 °C (dec); [α]25D +105° (*c* 0.69, H_2O).

Solubility: the compounds of this series closely resemble the parent amino acids; they are sol water, moderately sol lower alcohols, and insol apolar solvents.

Form Supplied in: colorless solid; not currently commercially available on a routine basis.

Analysis of Reagent Purity: chemical purities are accessed by mp and NMR; optical purities are deduced by forming diastereomeric derivatives, or by derivatization and analysis in the presence of chiral NMR shift reagents.

Preparative Methods: substituted 2,3-methanoamino acids are difficult to prepare. Unfortunately, most of the reported syntheses give racemic materials whereas stereochemically pure compounds are required for studies of cyclopropane-based peptidomimetics. The only 2,3-methanologs of protein amino acids prepared in optically active form are (*E*)- and (*Z*)-*cyclo*-Phe[1-4] and -Tyr,[5] all four stereoisomers of *cyclo*-Met,[6] (*Z*)-*cyclo*-Arg[7] and (2*S*,3*S*)-(*Z*)-*cyclo*-Trp,[8] although several routes to enantio-enriched 2,3-methanologs of simple nonproteogenic amino acids have been reported.[9-12] The most practical synthesis of the title compound is that based on a diastereoselective, rhodium-catalyzed cyclopropanation reaction.[3]

Handling, Storage, and Precautions: some compounds in this series are slightly hygroscopic,

but they are otherwise quite stable, and indefinitely so under an inert atmosphere in a freezer. For good results in peptide syntheses these compounds must be used with the same precautions taken for any common amino acid derivative.

Background.[13]

One of the least drastic perturbations of amino acid structure is to link the α- and β-carbons of the side chain with a methylene group, giving 2,3-methanoamino acid analogs (or methanologs, e.g. the cyclopropyl analogs of phenylalanine, *cyclo*-Phe, and of methionine, *cyclo*-Met). Incorporation of a cyclopropane ring locks the side chain substituent *cis* or *trans* to the amino functionality. Designation of the absolute configurations of the two chiral centers completely defines the stereochemistry, whereas (*Z*) and (*E*) nomenclature specifies the diastereomeric, but not the enantiomeric, form. Both systems are shown on the examples in Figure 1, even though it is redundant to specify (*Z*) or (*E*) stereochemistry if the absolute configuration is marked.

These amino acid surrogates have side chains locked *cis* or *trans* to the amino functionality and the cyclopropane ring also restricts rotations about the N-C_α and C_α-CO bonds (i.e. φ and ψ, respectively).[14 -16] A Ramachandran plot[17] for a related compound indicates these conformational restrictions are severe.[14 -16,18,19] Consequently, systematic variations of stereoisomeric 2,3-methanolog substitutions facilitate controlled restrictions on the conformational freedom of peptidomimetics,[20,21] and it is possible to constrain them into molecular orientations that resemble bioactive conformations of the parent peptide. Substitution of a protein amino acid with its 2,3-methanolog therefore can enforce or preclude structural shapes required for various bioactivities. They can also impart considerably enhanced resistance to proteolytic degradation.[22-27] These are the main applications of this class of compounds.

At the present time, 2,3-methanoamino acid analogs can only be viewed as *reagents* in the context of syntheses of peptidomimetics. Consequently, this entry describes only that chemistry related to incorporation of protein amino acid methanologs into peptide sequences.

Incorporation into Peptidomimetics.

Solution phase methods have been used to incorporate *cyclo*-Phe stereoisomers into enkephalin analogs. The mixed anhydride method (*i*-BuOCOCl, ***Isobutyl Chloroformate***) was used as illustrated in Figure 2, which depicts the deprotection/coupling sequence used in the preparation of Tyr-D-Ala-Gly-(*cyclo*-Phe)-Leu-OH. Thus the first step was *N*-Cbz protected *cyclo*-Phe being coupled with Leu-OMe via the mixed anhydride method; the dipeptide so formed was coupled with Cbz-Tyr-D-Ala-Gly-OH after ***Trifluoroacetic Acid*** deprotection.[22] Methyl ester protecting groups were used at the *C*-terminus, and benzyloxycarbonyl (Cbz) protection was employed at the *N*-termini. The Cbz groups were removed by acid deprotection and not hydrogenolysis, since the latter conditions cause extremely facile ring-opening

of methanologs with aromatic substituents connected to the strained ring.[2]

Peptide syntheses have undergone extensive improvements in the decade since the preparations described above were performed.[28,29] A more contemporary approach to syntheses of peptidomimetics using the solid phase Fmoc (9-fluorenylmethoxycarbonyl) approach is illustrated in Figure 3.[23,30] The couplings were performed using Castro's reagent (BOP, ***Benzotriazol-1-yloxytris(dimethylamino)phosphonium Hexafluorophosphate***) in the presence of ***1-Hydroxybenzotriazole*** (HOBt).[31]

Other peptides in the F{*cyclo*-M}RF-NH_2 series have been prepared using a more acid stable resin (MBHA, methoxybenzhydrylamine) and Boc (*t*-butoxycarbonyl) protecting groups, but the Fmoc approach above gives superior yields.[23,30]

---

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Phenyl Azide[1]

PhN_3

[622-37-7] · $C_6H_5N_3$ · Phenyl Azide · (MW 119.14)

(reagent for the synthesis of 4,5-dihydro-1,2,3-triazolines, 1,2,3-triazoles, aziridines, and other heterocycles via 1,3-dipolar cycloaddition with alkenes, alkynes, and other unsaturated functional groups;[2] allows measurement of the degree of strain present in alkenes and alkynes by their relative rates of dipolar cycloaddition;[2a,3,4] converts organoboranes into *N*-alkylanilines;[5] in combination with Lewis or protic acids, produces nitrenium ions or their equivalent, which react as electrophiles at nitrogen or aromatic carbon to produce substituted anilines;[6,7] reagent for the synthesis of 2-hetero-3*H*-azepines by ring expansion;[7,8] related aryl azides undergo the above reactions as well as thermally or photochemically induced intramolecular C-H insertions to produce a variety of nitrogen heterocycles;[7-10] substituted aryl azides are commonly used in photoaffinity labeling;[11] aryl azides act as electrophiles toward carbon, nitrogen, and phosphorus nucleophiles, leading to new N-C, N-N, and N-P bonds.[1,8a,b,9])

Alternate Name: azidobenzene.

Physical Data: bp 49-50 °C/5 mmHg, 66-68 °C/21 mmHg.[12]

Solubility: freely sol common organic solvents; insol water, aqueous acids, and aqueous alkalis.

Form Supplied in: colorless to pale yellow oil; odor resembling benzaldehyde, benzonitrile, or nitrobenzene; not available commercially.

Analysis of Reagent Purity: the concentration of toluene solutions can be determined by an iodometric titration.[13]

Preparative Methods: diazotization of phenylhydrazine.[12,14]

Handling, Storage, and Precautions: phenyl azide is explosive. A blast shield should be used during its purification by distillation, and the temperature should be controlled as recommended.[12,14] The pure substance may be stored in a brown glass bottle in a cool, dark place for up to a month. It is slowly discolored by light. It is often stored and used as a solution in ether or toluene. Doering's procedure results in material that has a longer shelf-life, due to the absence of traces of phenol.[14] This reagent should only be handled in a fume hood.

Cycloaddition Reactions: Formation of Triazolines, Triazoles, Imines, and Aziridines.

The 1,3-dipolar cycloaddition of phenyl azide and other aryl azides with various π-systems is well known.[2] Cycloaddition with alkenes initially produces triazolines, which may be isolated in many cases. However, triazolines are thermally sensitive and are often converted to other products (e.g. triazoles, aziridines, imines, and diazo compounds) under the conditions required for cycloaddition. While simple alkenes undergo sluggish cycloadditions with phenyl azide,[2] strained alkenes can be quite reactive.[2a,3,4] Since the original observations by Alder and Stein,[3] phenyl azide has been used frequently to trap strained and reactive alkenes and alkynes. The relative rate of reaction of aryl azides with alkenes has been used to measure their relative strain energies.[2,4] The reaction of *trans*-cyclooctene with trinitrophenyl azide serves to illustrate the types of products observed in such cycloadditions (eq 1).[4] The initially formed triazoline fragments easily to a zwiterionic intermediate, which undergoes 1,2-shifts to give imines or direct closure to produce aziridines.

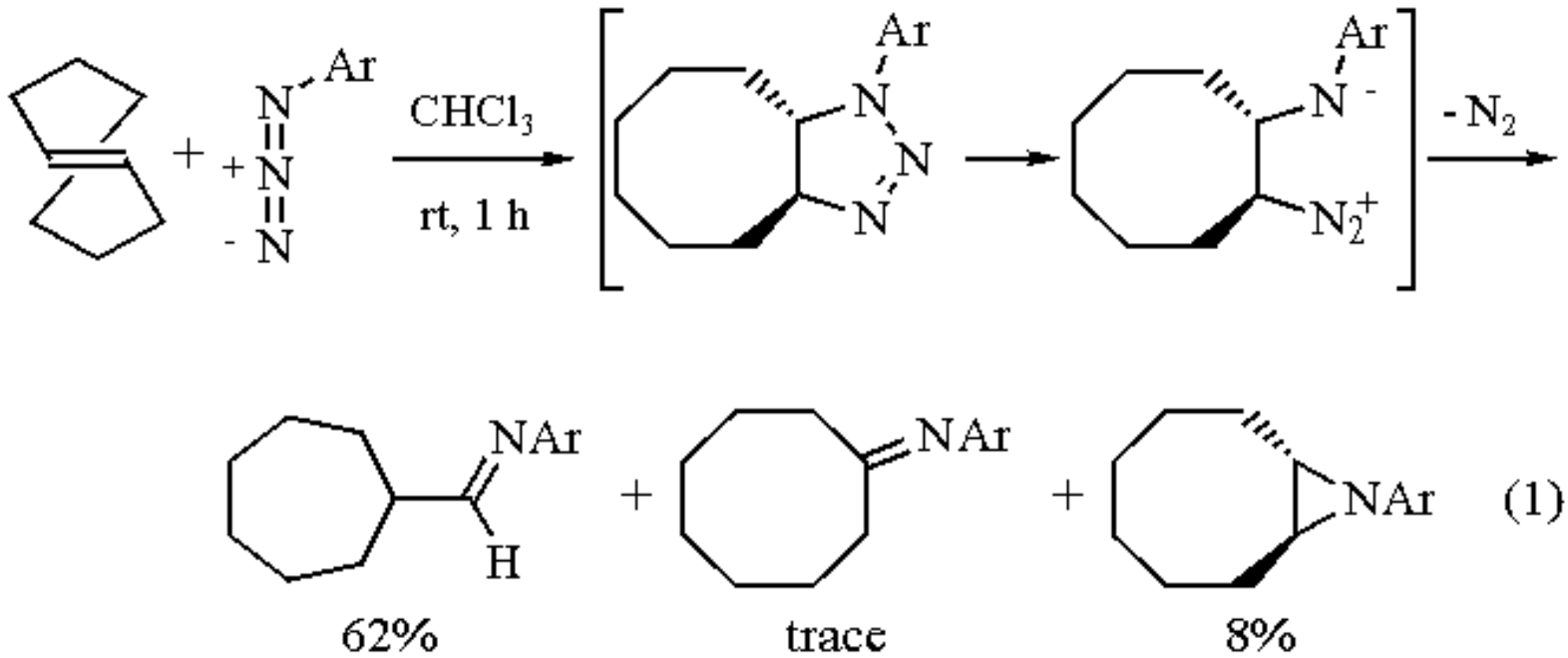

(1)

Conjugated dienes are sufficiently reactive to allow useful cycloadditions.[2a] Simple, unstrained alkenes can be used in intramolecular 1,3-dipolar cycloadditions with aryl azides (eq 2).[2,15]

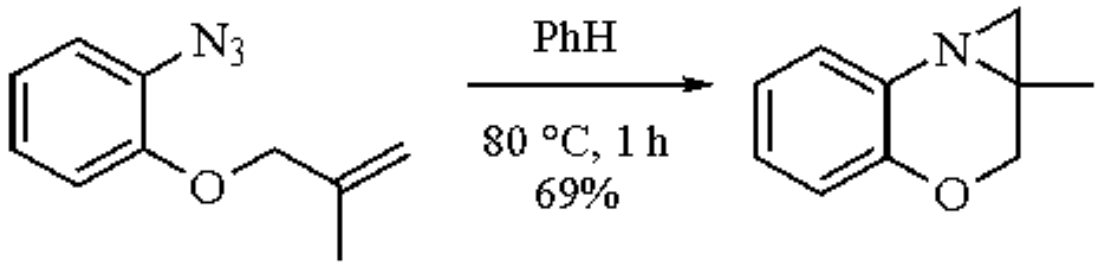

(2)

Electron-poor alkenes and alkynes are excellent dipolarophiles.[2a] Aziridines or diazo compounds may be produced from electron-poor alkenes by fragmentation of the initially formed triazoline intermediate, depending on the exact nature of the electron-withdrawing group and the presence or absence of an adjacent hydrogen on the alkene. Eq 3

illustrates the efficient formation of an aziridine.[16] The triazoline was observed by NMR when the cycloaddition was run at 40 °C. In contrast, the triazoline derived from the cycloaddition of phenyl azide with ***Methyl Acrylate*** was easily transformed to the α-diazoester with base (eq 4).[17] Alternatively, the triazoline could be oxidized to a triazole. Cycloadditions with electron-poor alkynes are also facile, producing triazoles directly. For example, phenyl azide reacts with ***Dimethyl Acetylenedicarboxylate*** to produce a triazole,[18] which was transformed into a bis(hydroxymethyl)triazole derivative for evaluati on as an antineoplastic agent (eq 5).[19]

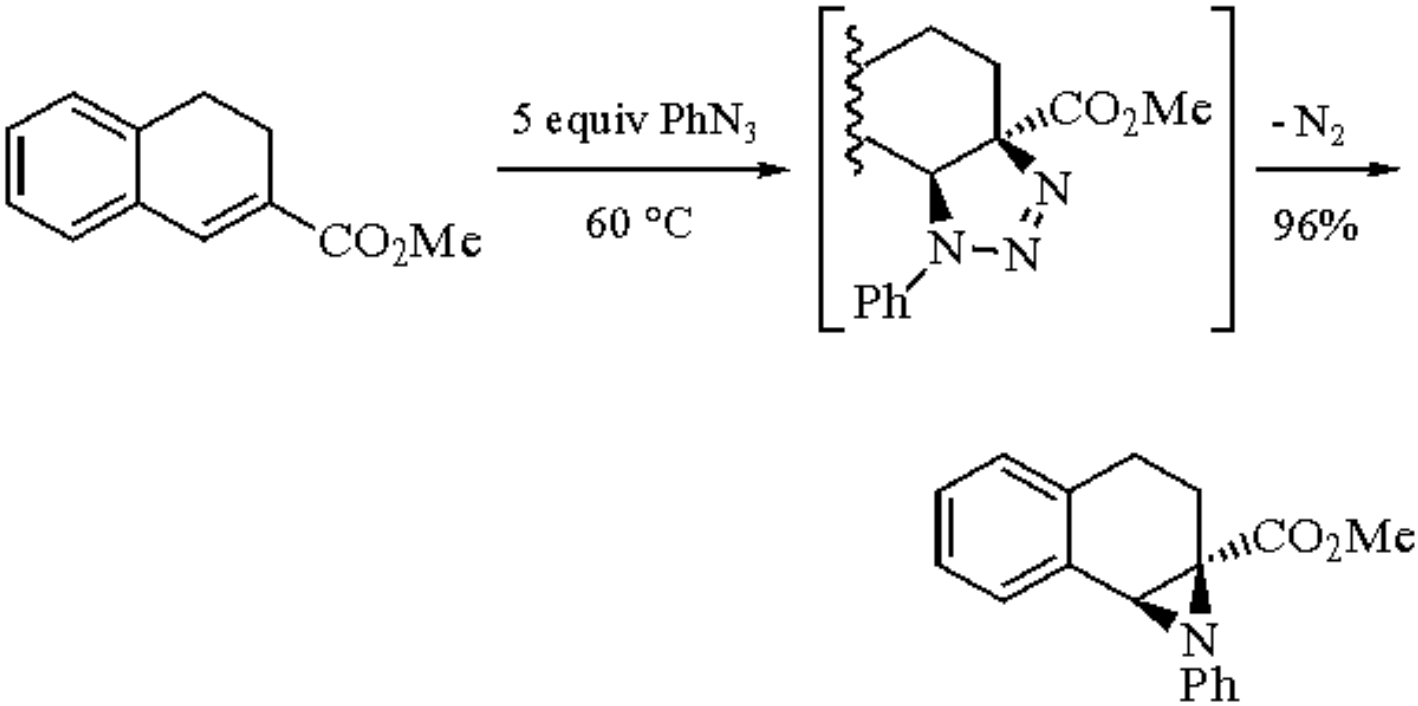

(3)

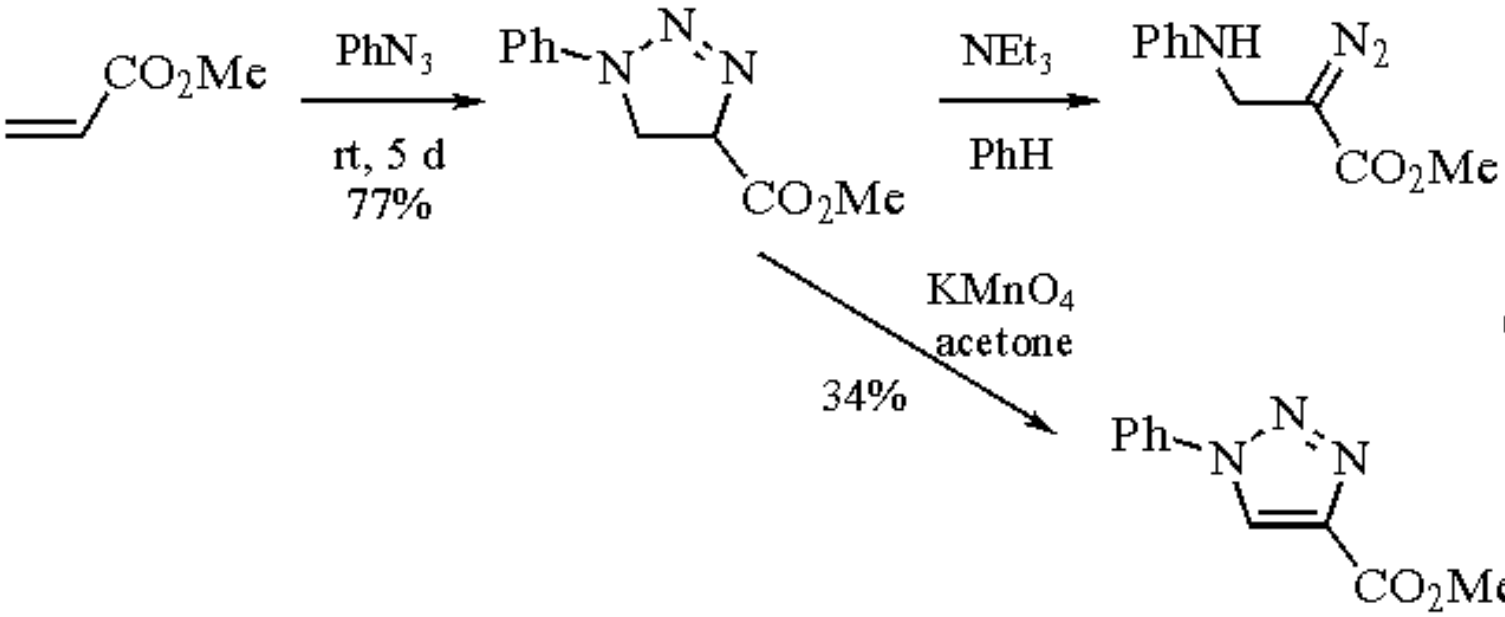

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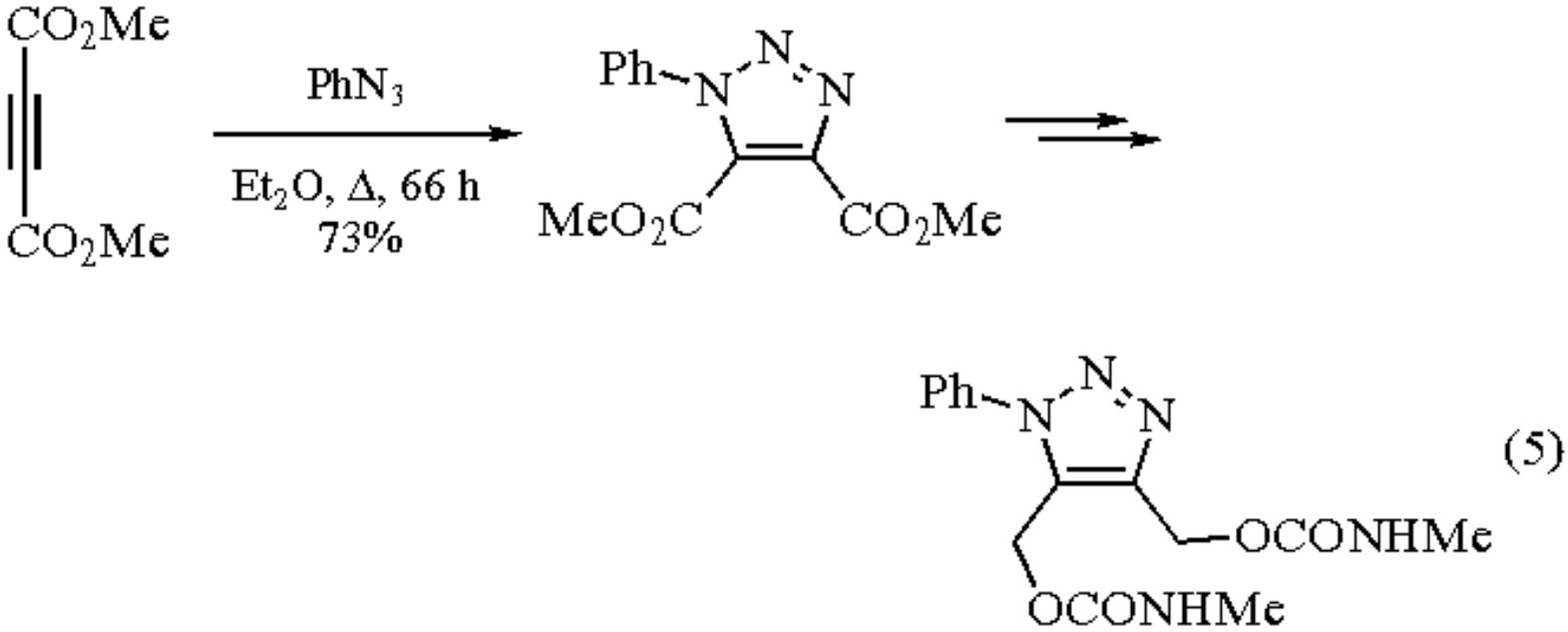

Electron-rich alkenes and alkynes are also reactive dipolarophiles toward aryl azides.[2a] Enol ethers and enamines are particularly useful,[20a] providing an excellent route to 1,2,3-triazoles after loss of the alcohol or amine from the intermediate triazoline (eq 6).[20]

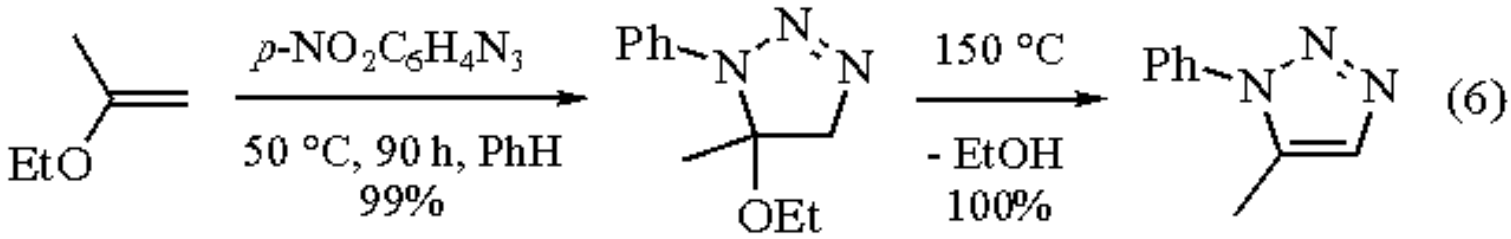

Generation of Nitrenes: C-H Insertion and Aziridination.

The thermal or photochemical decomposition of aryl azides to nitrenes has been an active area of research.[7-10] Singlet nitrenes are produced initially, which may undergo insertion reactions. Triplet nitrenes may be produced by sensitized photolysis of aryl azides or by thermolysis in the presence of certain external agents. Triplet nitrenes often participate in hydrogen atom abstraction reactions. While the thermal and photochemical decomposition of phenyl azide has been well studied, intramolecular reactions of substituted aryl azides are the most synthetically useful. For example, the thermolysis of *o*-azidobiphenyl is an excellent method for the formation of carbazoles (eq 7).[8c,d,21] This reaction is not a direct C-H insertion, since evidence for an intermediate other than the nitrene has been obtained. A likely mechanism is an intramolecular aziridination followed by rearrangement to the carbazole.

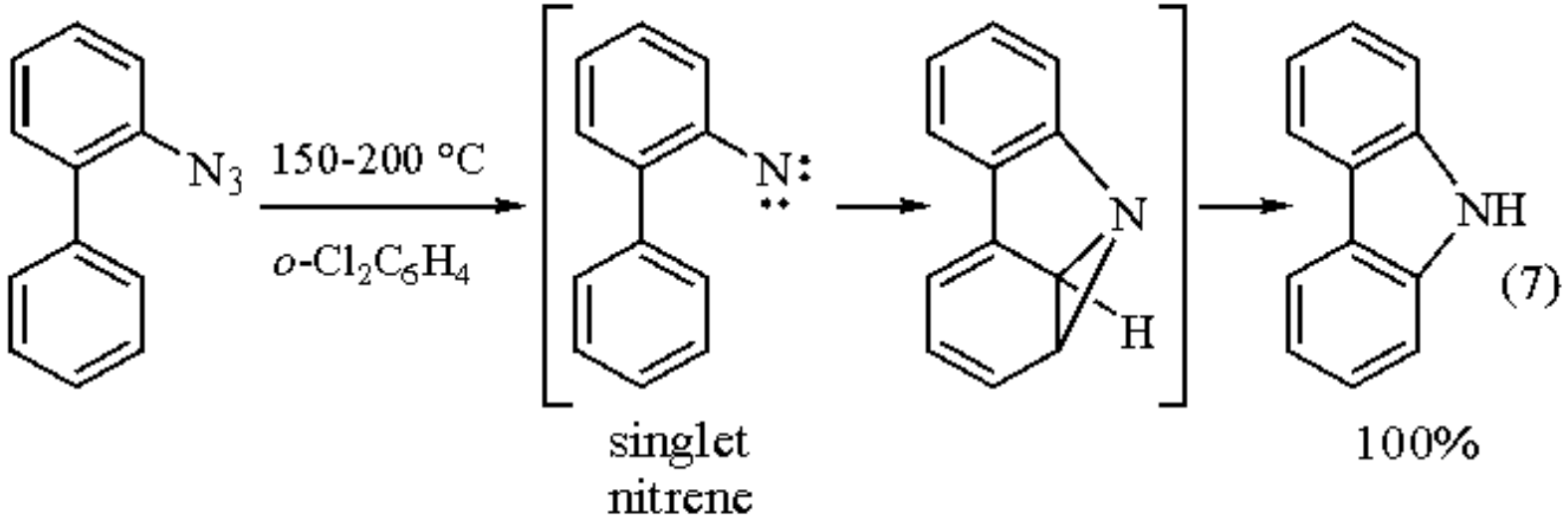

A recent application of aryl azides to natural product synthesis illustrates the complementary chemistry of singlet and triplet nitrenes (eq 8).[22] Thermolysis led to pyridocarbazole formation via a singlet nitrene. Sensitized photolysis led to benzylic C-H insertion, presumably by hydrogen atom abstraction by a triplet nitrene followed by diradical combination. This route was used to make the natural product cystodytin A.

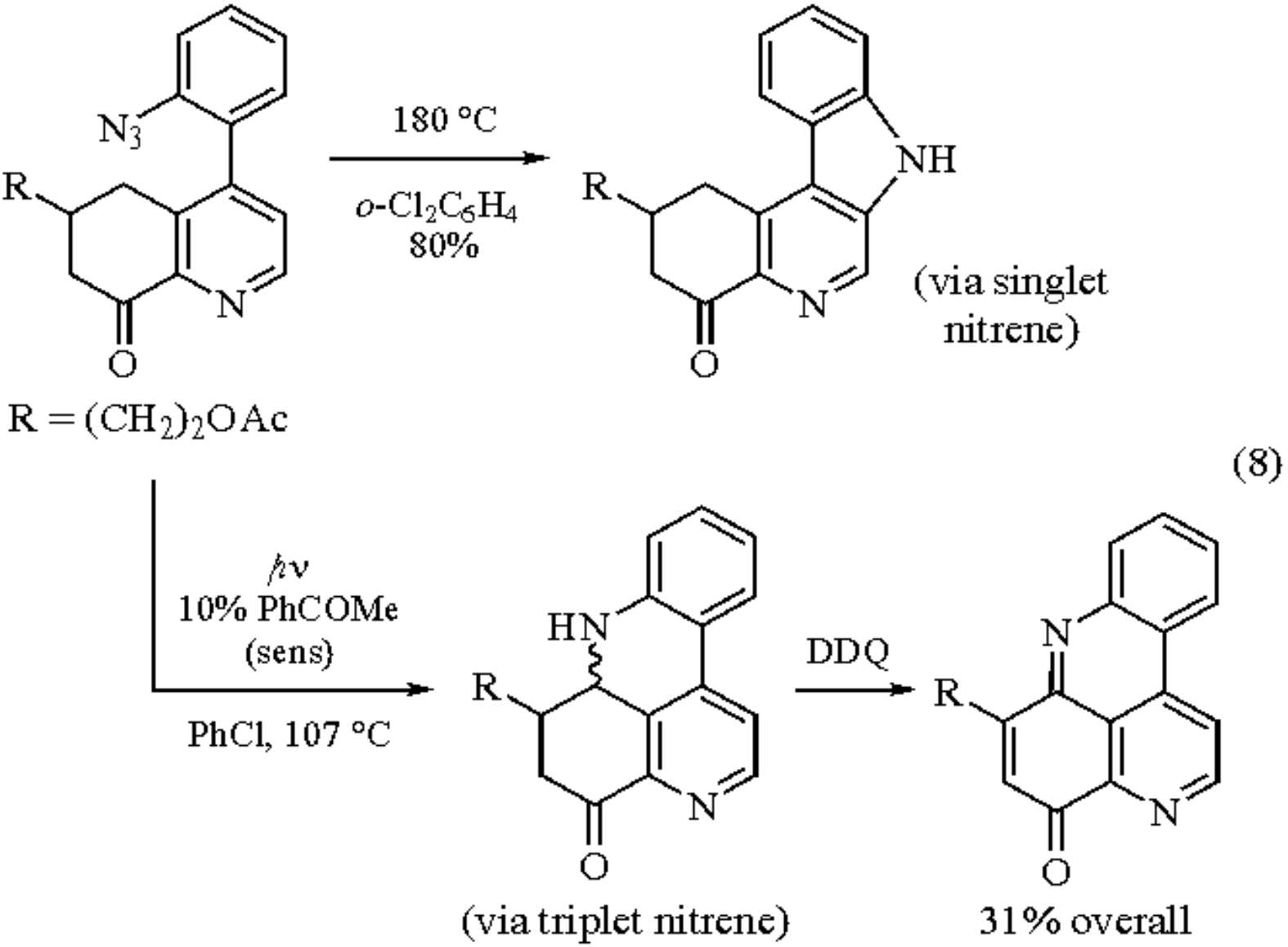

Indoles may be produced by formal C-H insertion of *o*-azidostyrenes (eq 9).[23] If a heteroatom is suitably tethered, reaction with a nitrene may be observed, producing a variety of heterocycles (e.g. eq 10).[24] A wide variety of unsaturated groups in the *ortho* position lead to heterocycle formation, including imines, azo groups, azides, carbonyl groups, amides, imides, and nitro groups.[8a] The photolysis and thermolysis of phenyl azide itself (or of aryl azides with no *ortho* substituents) is complex.[7-10]

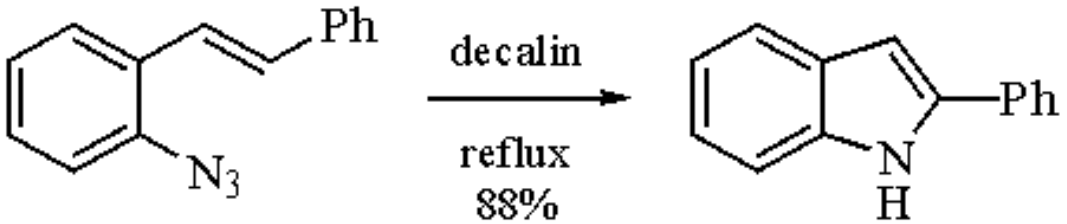

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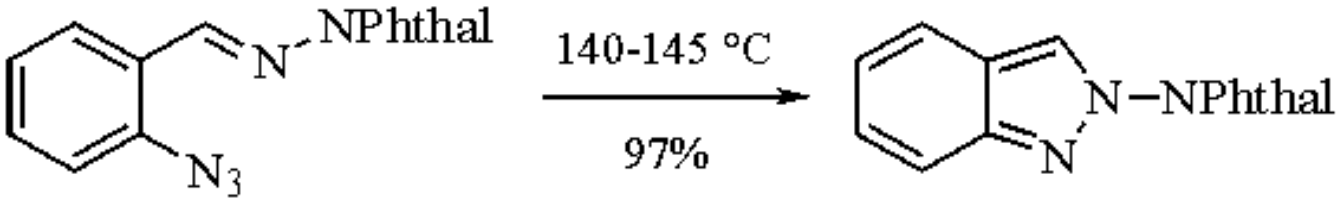

(10)

One useful insertion reaction is the formation of 2-hetero-3*H*-azepines by photolysis of aryl azides in the presence of nucleophiles such as amines and alcohols (eq 11).[25] A proposed mechanism for this reaction is ring expansion of the nitrene to a dehydroazepine followed by nucleophilic addition and tautomerization. Azides are commonly used to generate nitrenes for photoaffinity labeling investigations in biological experiments.[11]

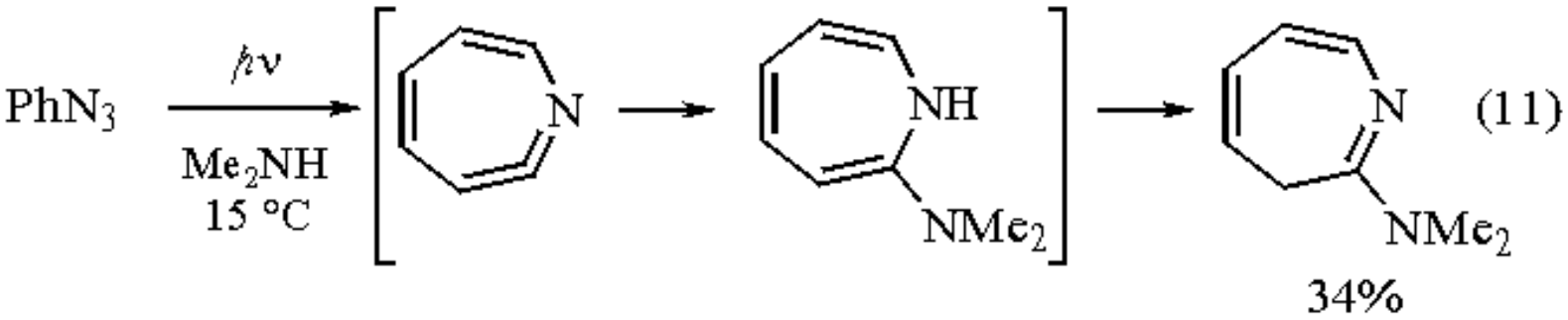

(11)

Reaction with Electrophiles: Nitrenium Ions and Their Equivalents.

Although azides are weak Lewis bases, they may form complexes reversibly with protic acids or Lewis acids. Complexation at the most substituted nitrogen atom is preferred, which generates an electron-deficient nitrogen species which may undergo substitution or deazoniation.[6,7,8a,b,9]

Complexation of trialkylboranes, dialkylchloroboranes, or alkyldichloroboranes with phenyl azide (and other azides) leads to a 1,2-shift of an alkyl group to the electron-deficient nitrogen, producing anilines after hydrolysis (eq 12).[5] Complexation of phenyl azide with ***Aluminum Chloride*** generates an electrophilic reagent which may react with

alkenes to produce aziridines or addition products (eq 13).[26]

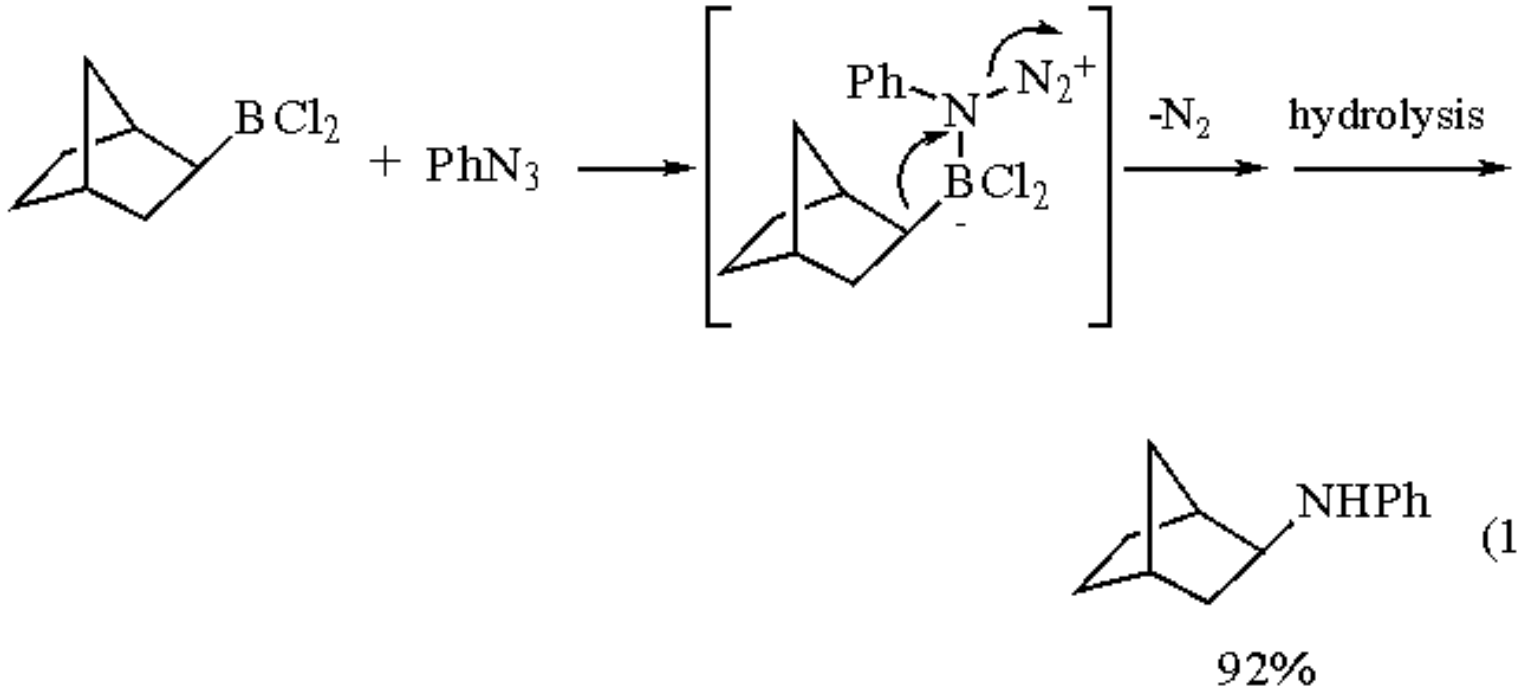

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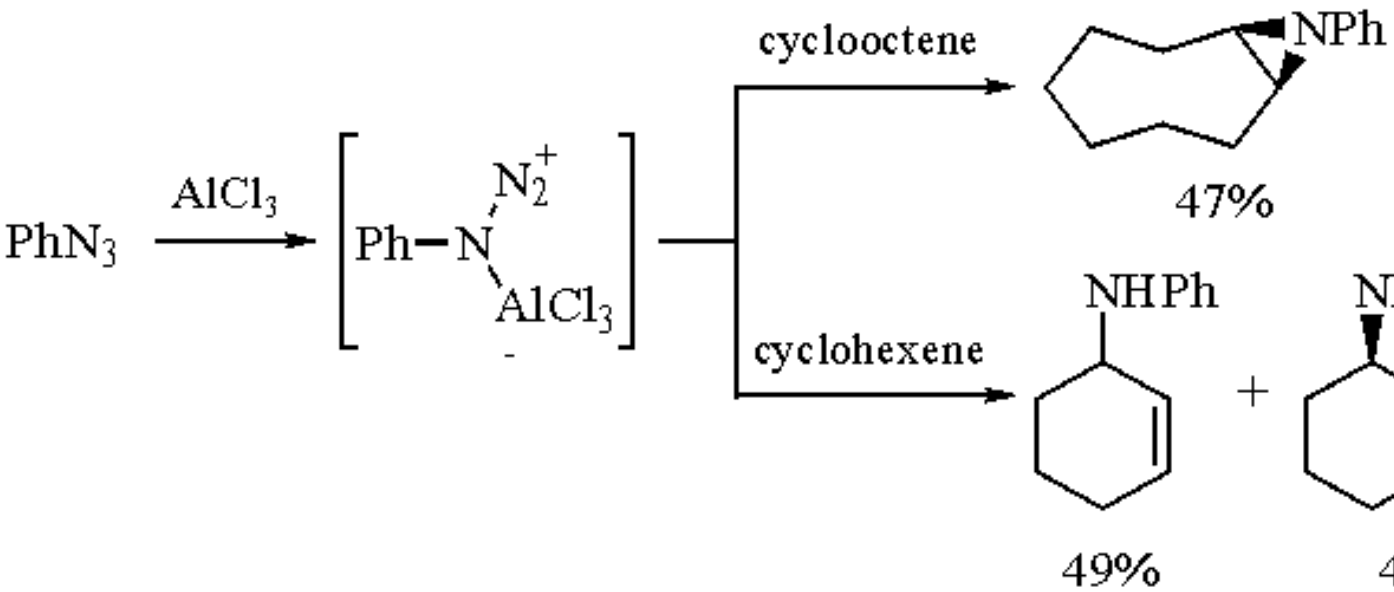

(13)

Protonation of aryl azides with strong acids followed by loss of nitrogen produces nitrenium ions, which are potent electrophiles at both the nitrogen atom and the *ortho* and *para* positions on the arene.[6] Intermolecular reactions with arenes commonly produce diarylamines (eq 14),[27] but *C*-arylation is a competing process.[6] Other nucleophiles, such as sulfides, can be used in intermolecular reactions with nitrenium ions, producing *o*- and *p*-thioanilines.[28] Intramolecular reactions of nitrenium ions with arenes (eq 15)[29] or other nucleophiles (eq 16)[29] are more chemoselective.[6]

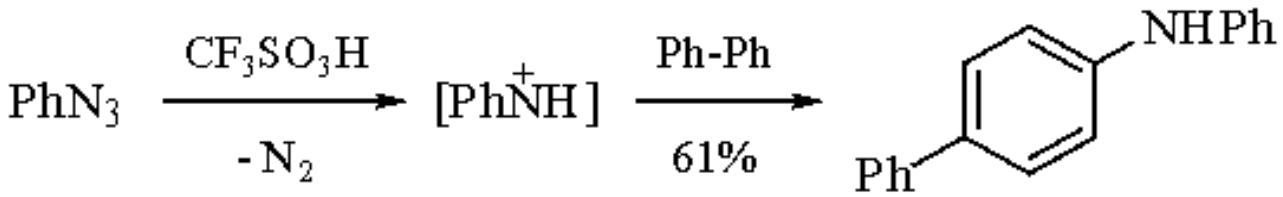

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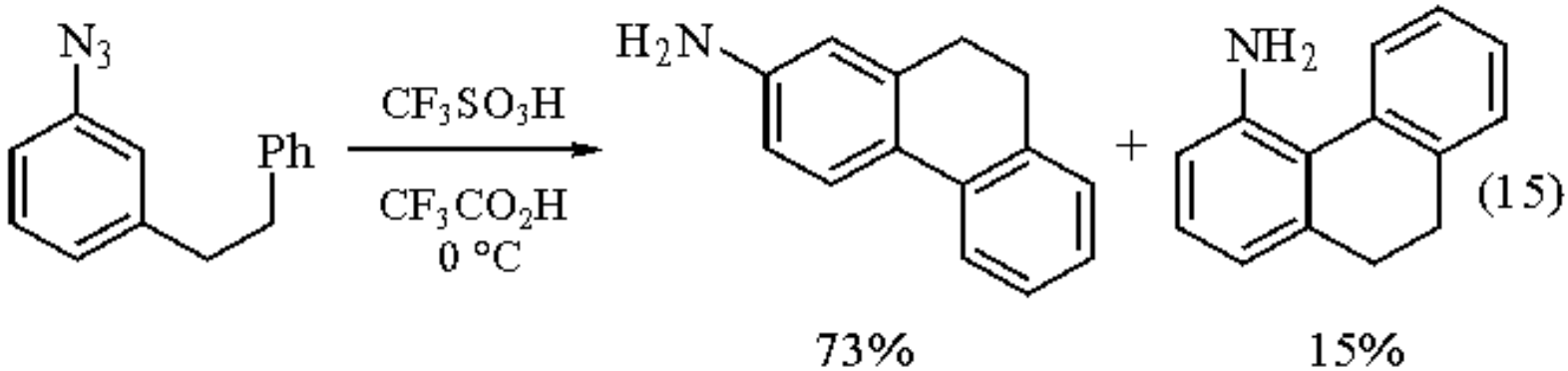

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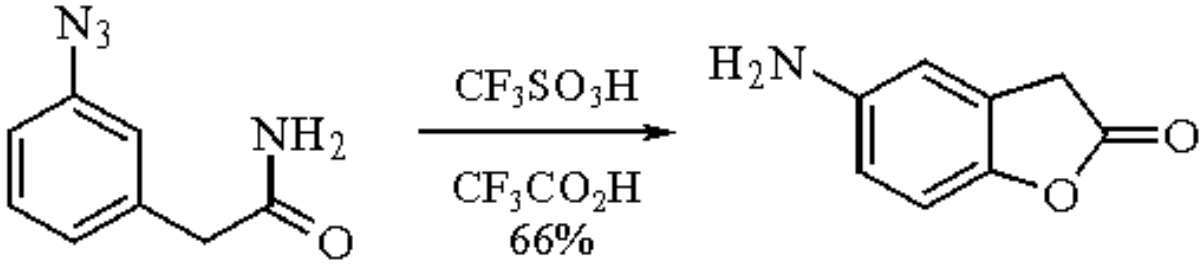

(16)

Reactions with Nucleophiles.

The terminal nitrogen of aryl azides is moderately electrophilic.[1,8a,b,9] Reactions with phosphines (the Staudinger reaction, eq 17),[30,31] cyanide ion (eq 18),[32] organometallic reagents (eq 19),[8a,b,33] and amide anions (eq 20)[34] produce a variety of adducts. The phosphazenes decompose rapidly to iminophosphoranes (eq 17), which are useful for the conversion of carbonyl compounds to imines (the aza-Wittig reaction).[30] The cyanotriazenes (eq 18) are easily decomposed to anilines by alkali.[32] The triazenes derived from organometallic compounds (eq 19) may be converted to anilines by reduction,[33] although there are other azides which better fit this purpose.[8a,b] Dilithiotetrazenes (eq 20) have found use as ligands for transition metals, producing metallacyclotetraazapentadienes.[34] Not shown is the use of metal hydrides to reduce aryl azides.[8a,b]

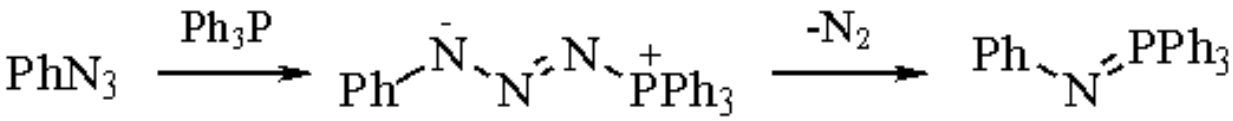

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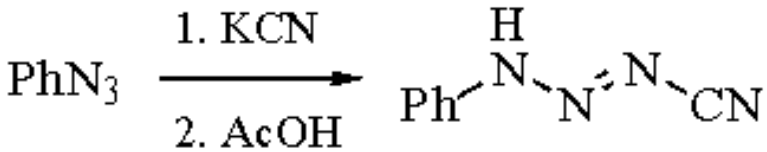

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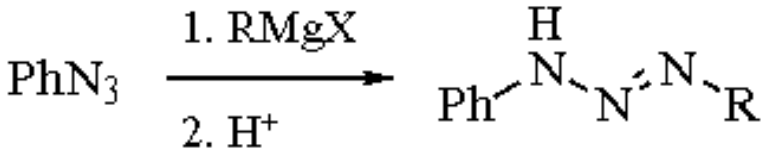

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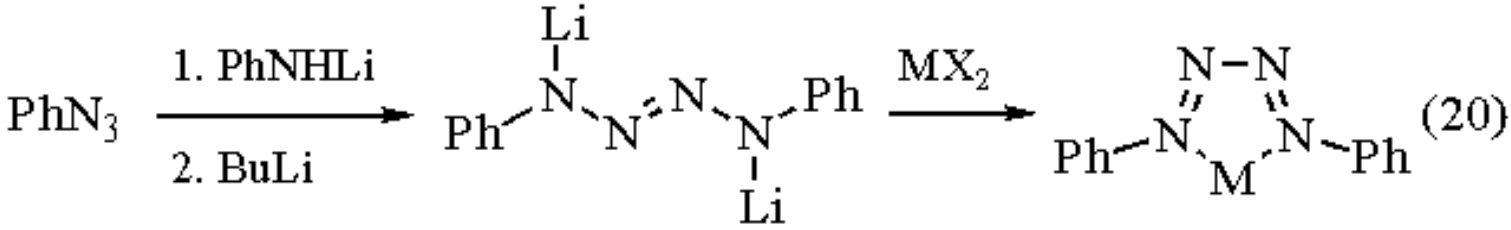

A particularly useful type of nucleophilic addition to azides is their reaction with the anions of active methylene compounds and related nucleophilic carbon species (the Dimroth reaction), leading to 1,2,3-triazoles.[8a,35] An example with phenylacetonitrile is shown in eq 21.[36] Intramolecular reactions of enolates and amide anions (e.g. eq 22) have also been reported, leading to cyclization with nitrogen loss.[37]

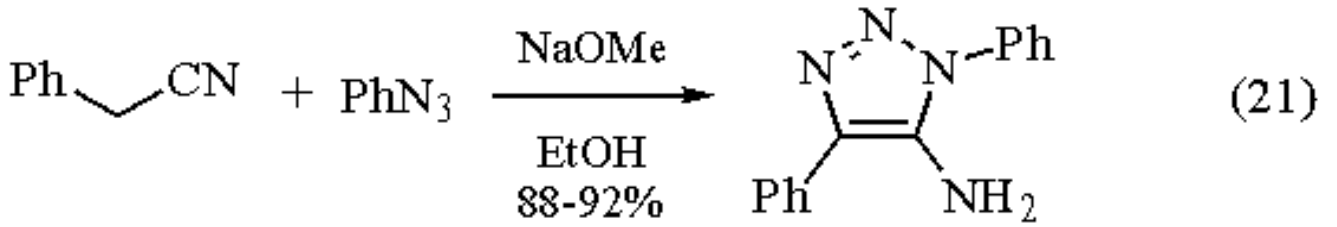

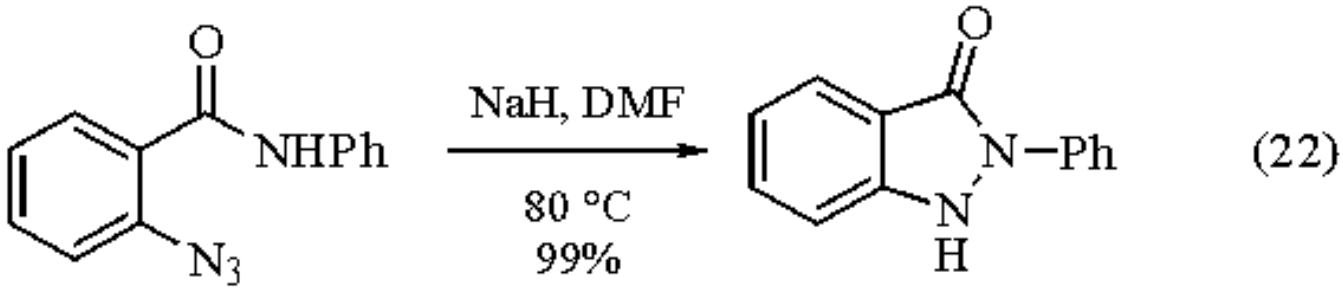

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University of Michigan, Ann Arbor, MI, USA

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Phenyl Benzenethiosulfonate[1]

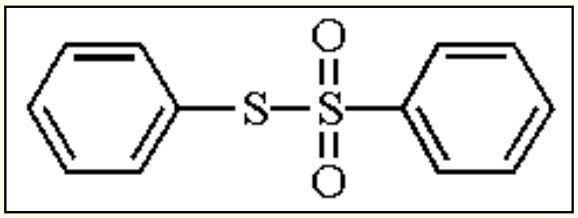

[1212-08-4] · $C_{12}H_{10}O_2S_2$ · Phenyl Benzenethiosulfonate · (MW 250.36)

(sulfenylating agent)

Physical Data: mp 38-42 °C; bp 125 °C/0.01 mmHg.

Form Supplied in: white solid.

Preparative Method: prepared by oxidation of ***Diphenyl Disulfide*** with 30% ***Hydrogen Peroxide*** (72%).[2]

Purification: crystallization from methanol (mp 36-37 °C).[2]

Introduction.

Phenyl benzenethiosulfonate ($PhSSO_2Ph$) is a preferred sulfenylating reagent to ***Methyl Methanethiosulfonate*** and ***Methyl p-Toluenethiosulfonate*** because it possesses higher intrinsic reactivity and because, at times, the latter reagents are not particularly effective, possibly due to the acidity of their methyl and *p*-methyl groups which are activated by the thiosulfonate group.[2] $PhSSO_2Ph$ is also a more reactive sulfenylating agent than the widely used ***Diphenyl Disulfide***, and the reactions are somewhat cleaner and less odoriferous than with PhSSPh. This reactivity difference gives $PhSSO_2Ph$ certain advantages over PhSSPh. For example, it increases the regioselectivity of sulfenylation of 2-methylcyclohexanone (eq 1).[3] This regioselectivity corresponds to the kinetic selectivity in enolate generation.

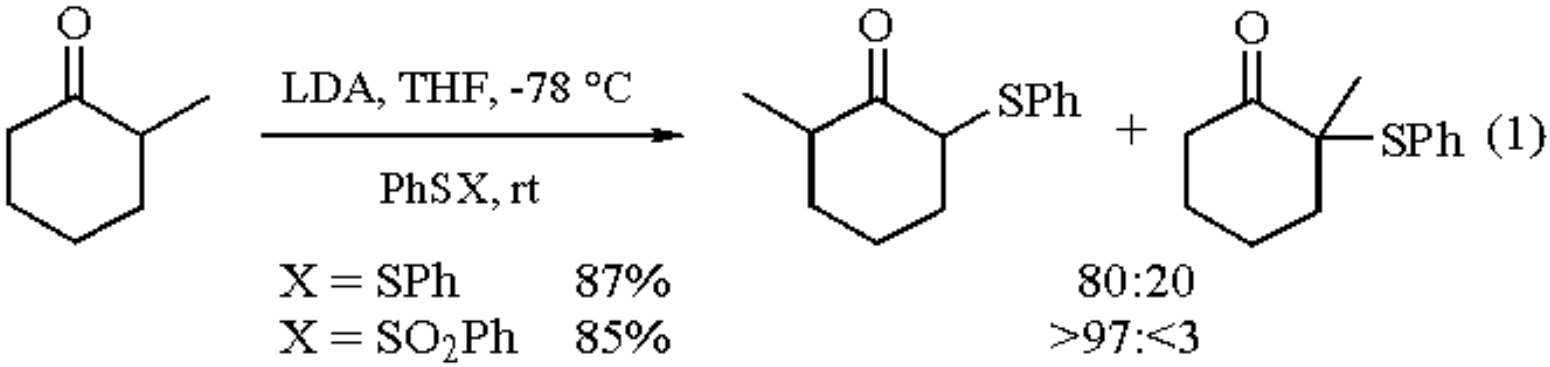

Preparation of 1,2-Diketones via β-Keto Sulfides.[2]

Direct sulfenylation of cyclic ketone enolates with $PhSSO_2Ph$ yields β-keto sulfides which are acetoxylated by ***Lead(IV) Acetate*** in warm benzene. The β-keto acetoxy sulfide represents a monoprotected form of a 1,2-dicarbonyl compound. Oxidation and sulfoxide elimination produce, regiospecifically, the monoenol acetate of the diketone. Treatment with I_2 in MeOH gives the monoacetal. Exposure to basic H_2O_2 leads to the ring-cleaved diacids which can also be obtained directly from the β-keto sulfides upon treatment with basic H_2O_2 (eq 2). Application of this methodology is exemplified by eqs 3 and 4, which show stereo- and regiospecific sulfenylation, respectively.

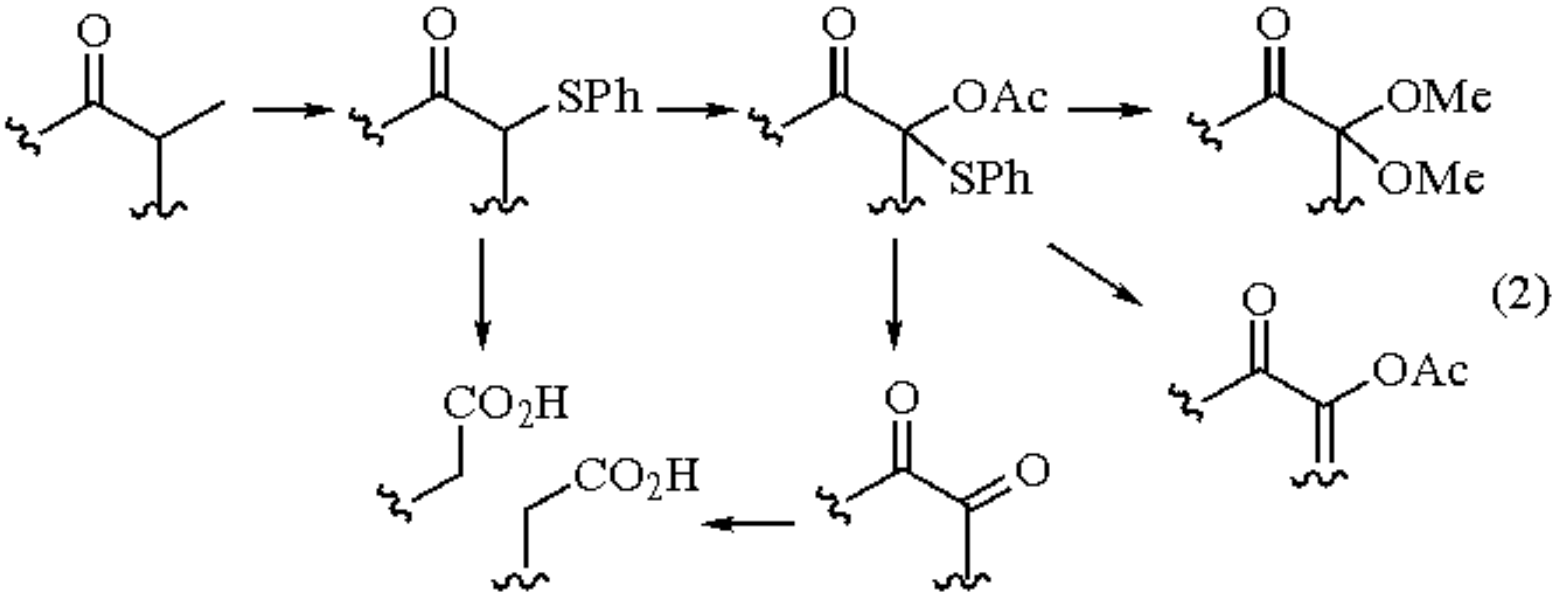

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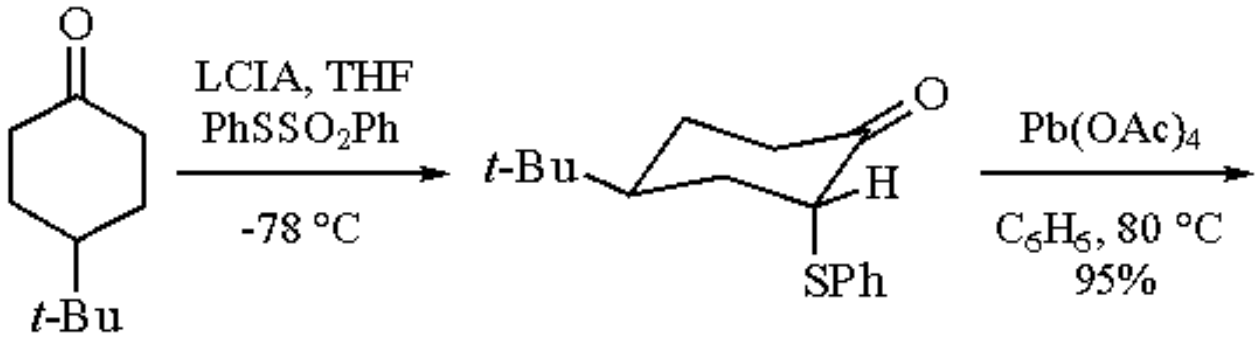

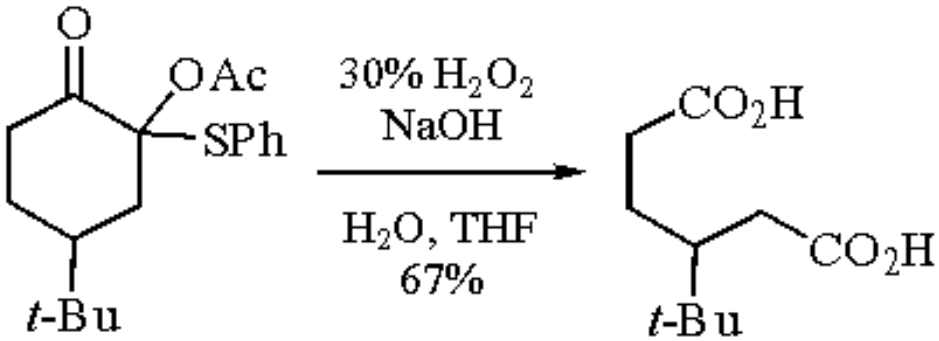

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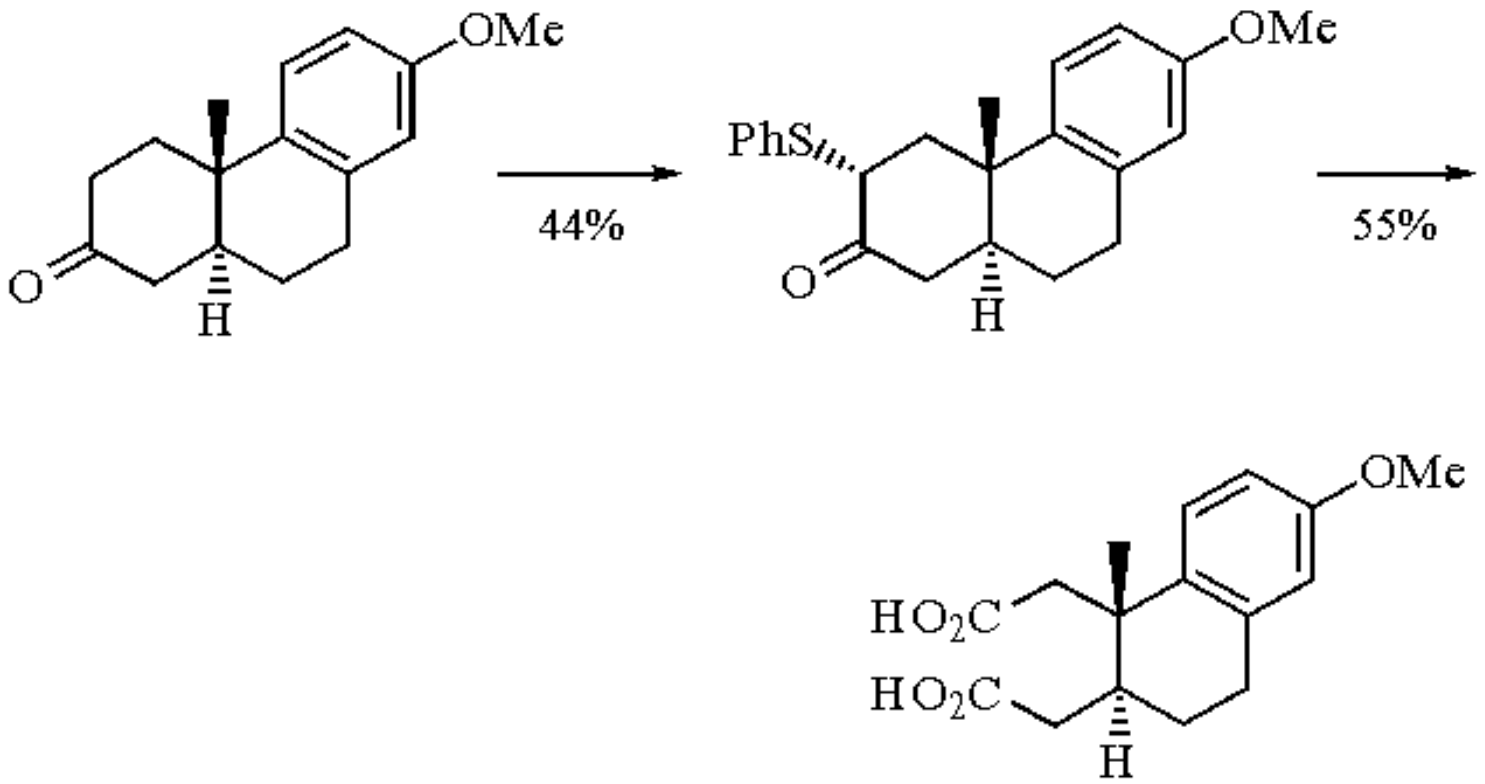

(4)

1,2-Carbonyl Transposition via Bissulfenylation.

Yee and Schultz have modified the above method of Trost to achieve 1,2-carbonyl transposition via bissulfenylation of the lithium enolate generated with ***Lithium 2,2,6,6-Tetramethylpiperidide*** (eq 5).[4] The method has been employed successfully in a total synthesis of a more complex molecule, (±)-lycoramine, in which the carbonyl transposition was accomplished in 64% overall yield.[5]

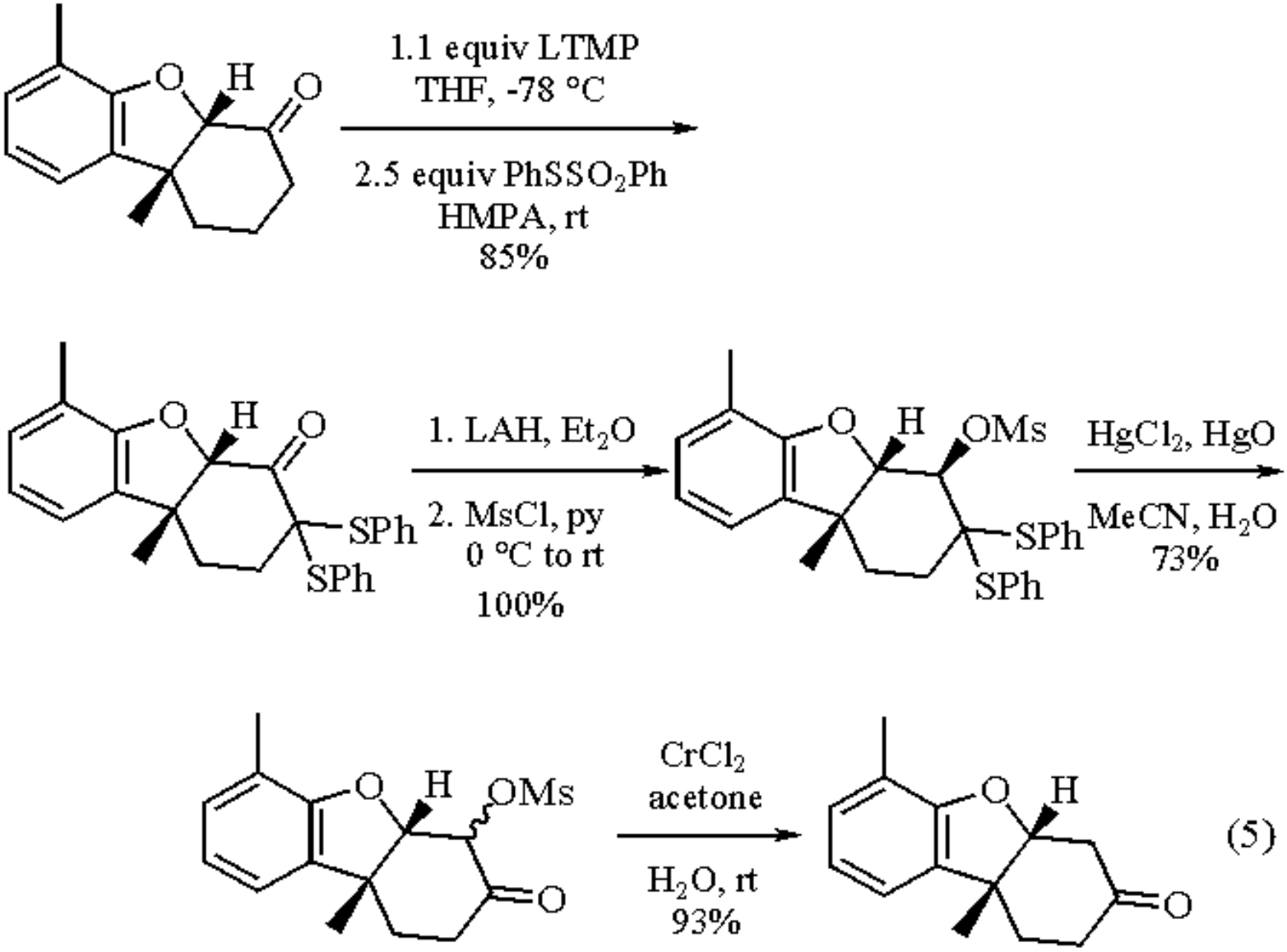

Preparation of 2-(Phenylthio)alkanoic Acids and Esters.

2-(Phenylthio)alkanoic acids and esters are synthesized by successive treatment of substituted malonic esters with ***Sodium Ethoxide*** and $PhSSO_2Ph$, followed by alkaline hydrolysis which causes concurrent decarboxylation (eq 6).[6] Ogura et al. have reported[7] a more convenient method for preparation of 2-(phenylthio)alkanoic esters from the 2-acetylalkanoate (eq 7).

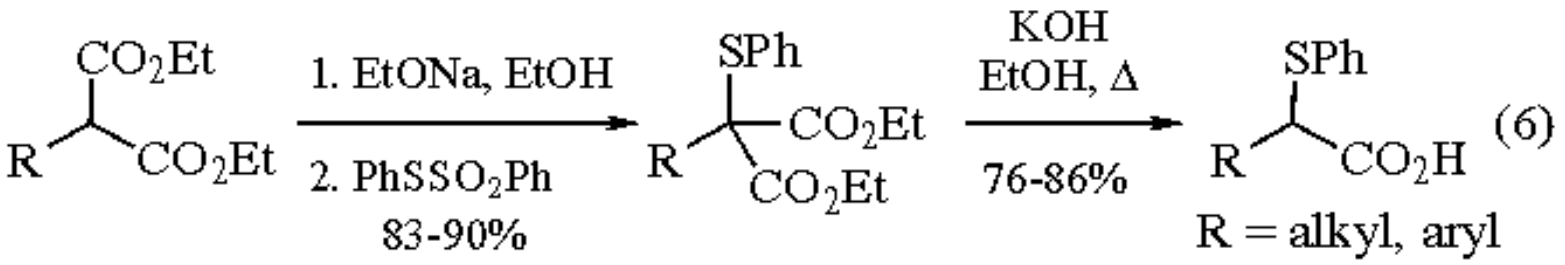

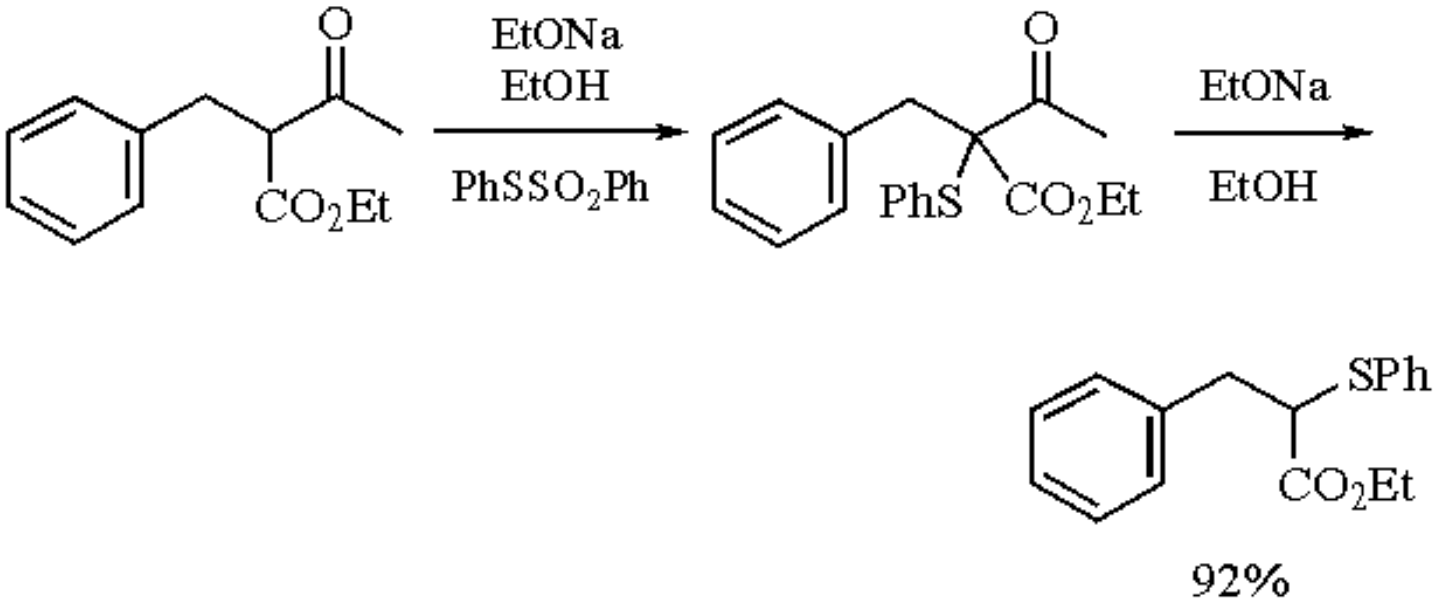

(7)

$PhSSO_2Ph$ can be replaced with PhSSPh as the sulfenylating agent in this transformation, but the reaction with PhSSPh takes much longer. Advantages of the methods described in eqs 6 and 7 over others such as the sulfenylation of alkanoic acids and esters and the alkylation of (phenylthio)acetic acid are: (1) simplicity of the procedure; (2) efficiency and convenience of using an inexpensive base (EtONa) and EtOH as solvent with high product yields; and (3) no bissulfenylation. Moreover, the method described in eq 7 allows direct α-sulfenylation of 2-acetylalkanoates which also contain an additional unprotected keto group (see ***Methyl Methanethiosulfonate***).

Sulfenylated Enolates for Aldol Condensation.

Bissulfenylation followed by monodesulfenylation with a Grignard reagent cleanly provides magnesium enolates of α-phenylthiocarbonyl compounds for aldol condensation (eq 8).[8] The Grignard reagent serves as a nucleophile towards sulfur, not the carbonyl group, to give a clean mixture of the magnesium enolate contaminated only by the byproduct, alkyl phenyl sulfide. In cases where the competitive attack at the carbonyl may become severe, addition of 5 mol % of $CuBr.SMe_2$ (see ***Copper(I) Bromide***) facilitates the chemoselectivity toward sulfur. A related desulfenylation reaction induced by ***Lithium Diisopropylamide*** from a bissulfenylated cyclic imide has also been reported.[9]

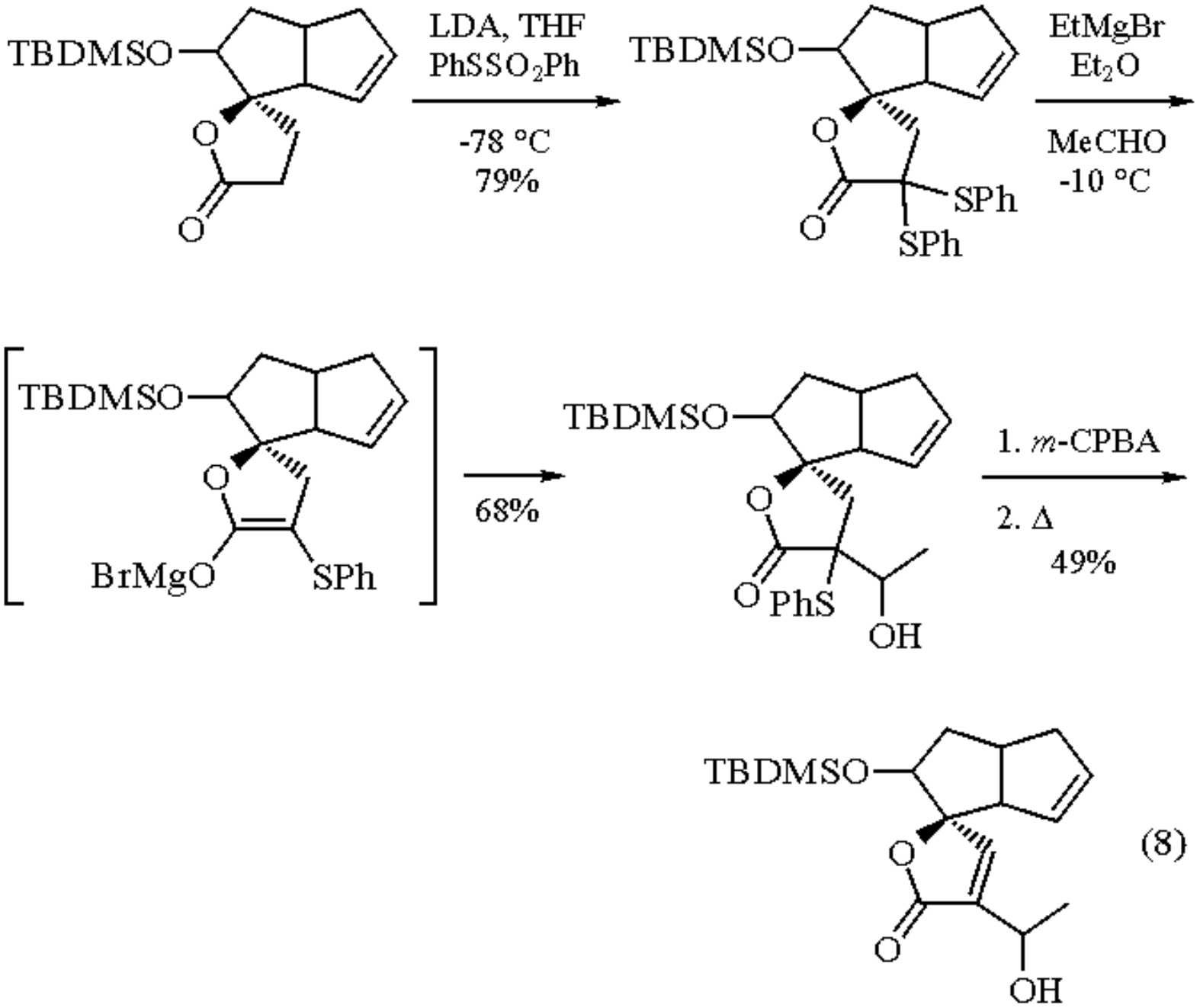

(8)

Dimethyl [(Phenylthio)methyl]phosphonate.

Sulfenylation of dimethyl α-lithiomethylphosphonate with $PhSSO_2Ph$ is a convenient method for synthesis of the title compound. Diethyl ether is a superior solvent to THF in this sulfenylation reaction (eq 9).[10] The method is applicable for the preparation of alkyl- and allylthiomethylphosphonates.

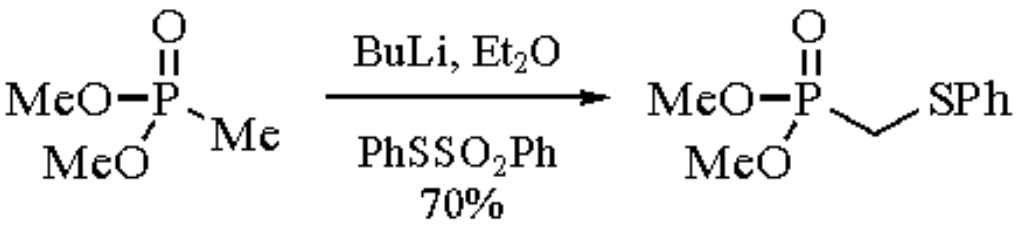

(9)

Formation of Symmetrical or Unsymmetrical Sulfides.

The nucleophilic attack of alkyl- and aryllithiums at the sulfenyl S atom in phenyl benzenethiosulfonate provides a convenient method for the synthesis of both symmetrical and unsymmetrical aromatic sulfides in excellent yields (>90%).[11] The example in eq 10 shows that the reaction is not affected by the steric bulk of the lithiated species.

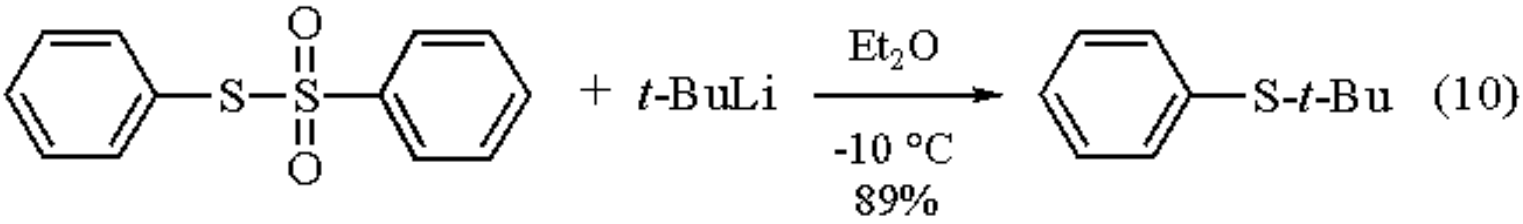

Stereoselective Synthesis of Ethyl (2*E*,4*E*)-Alkadienoates from Ethyl Sulfolane-2-Carboxylate.

α,β;γ,δ-Unsaturated esters are conveniently synthesized with high (*E*,*E*) selectivity from ethyl sulfolane-2-carboxylate through alkylation and oxidation followed by SO_2 extrusion from the 3-sulfolene derivatives resulting from base-induced isomerization.[12] This efficient method has been applied to the synthesis of an insecticidal compound, pellitorine, by simple operations (eq 11).

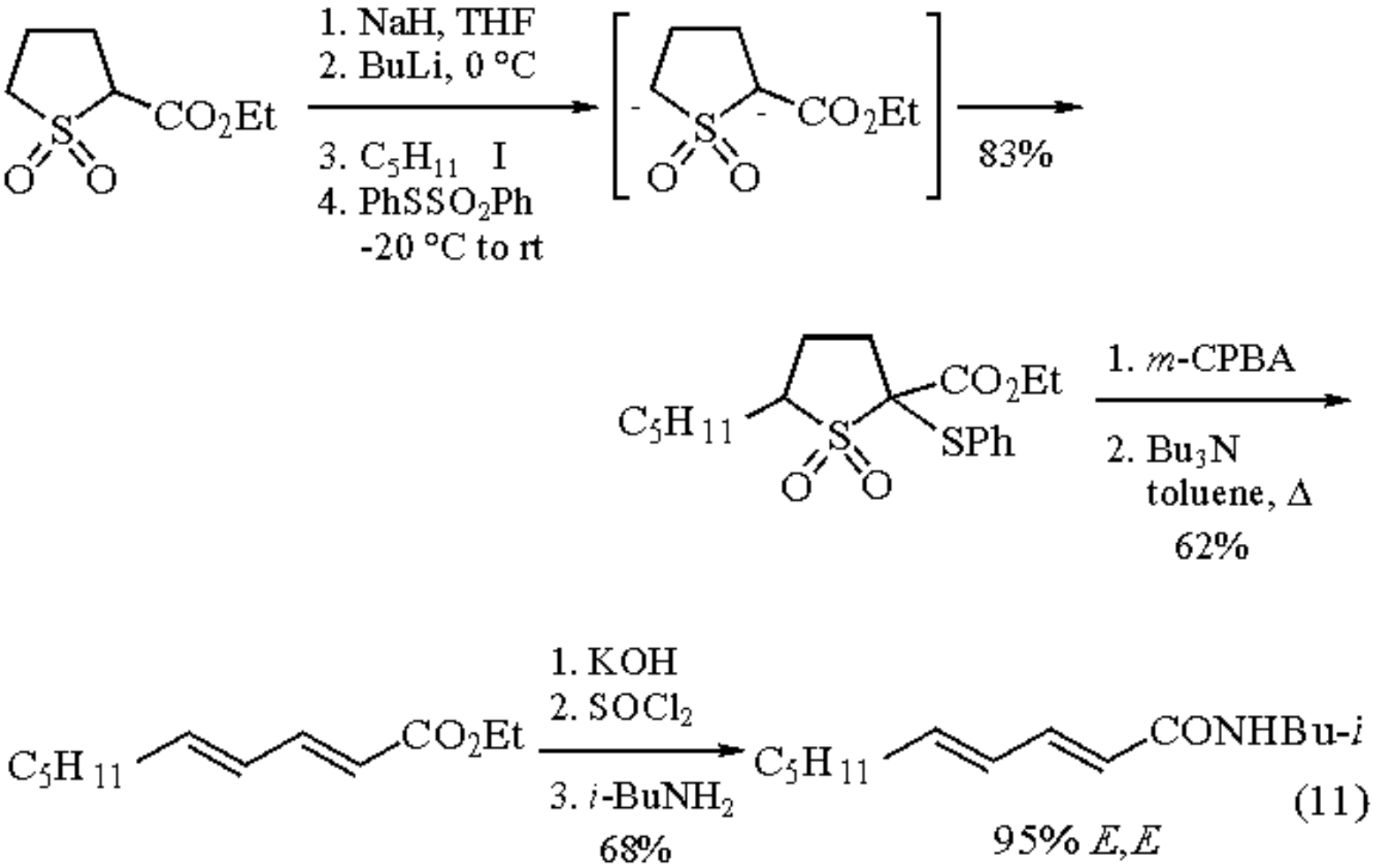

The optimal conditions for general application of this procedure are: (1) RI/$PhSSO_2Ph$ or RBr/PhSCl combination for the alkylation/sulfenylation step and THF as solvent; and (2) ***m-Chloroperbenzoic Acid*** as oxidant of the sulfide formed (critical). Alkyl bromides and alkyl tosylates can also be used in combination with $PhSSO_2Ph$. Secondary alkyl halides, which generally do not react with the α-anion of 3-sulfolene, can also be used with this method.

Regioselective Vinylcarbene Formation and [3 + 2] Cycloaddition under Mild Conditions.

Phenylthio-substituted cyclopropenone acetals undergo highly regioselective vinylcarbene formation below room temperature to permit the thermal [3 + 2] cycloaddition to take place under extremely mild conditions (eq 12).[13] The method is useful for the synthesis of substituted cyclopentenone derivatives.

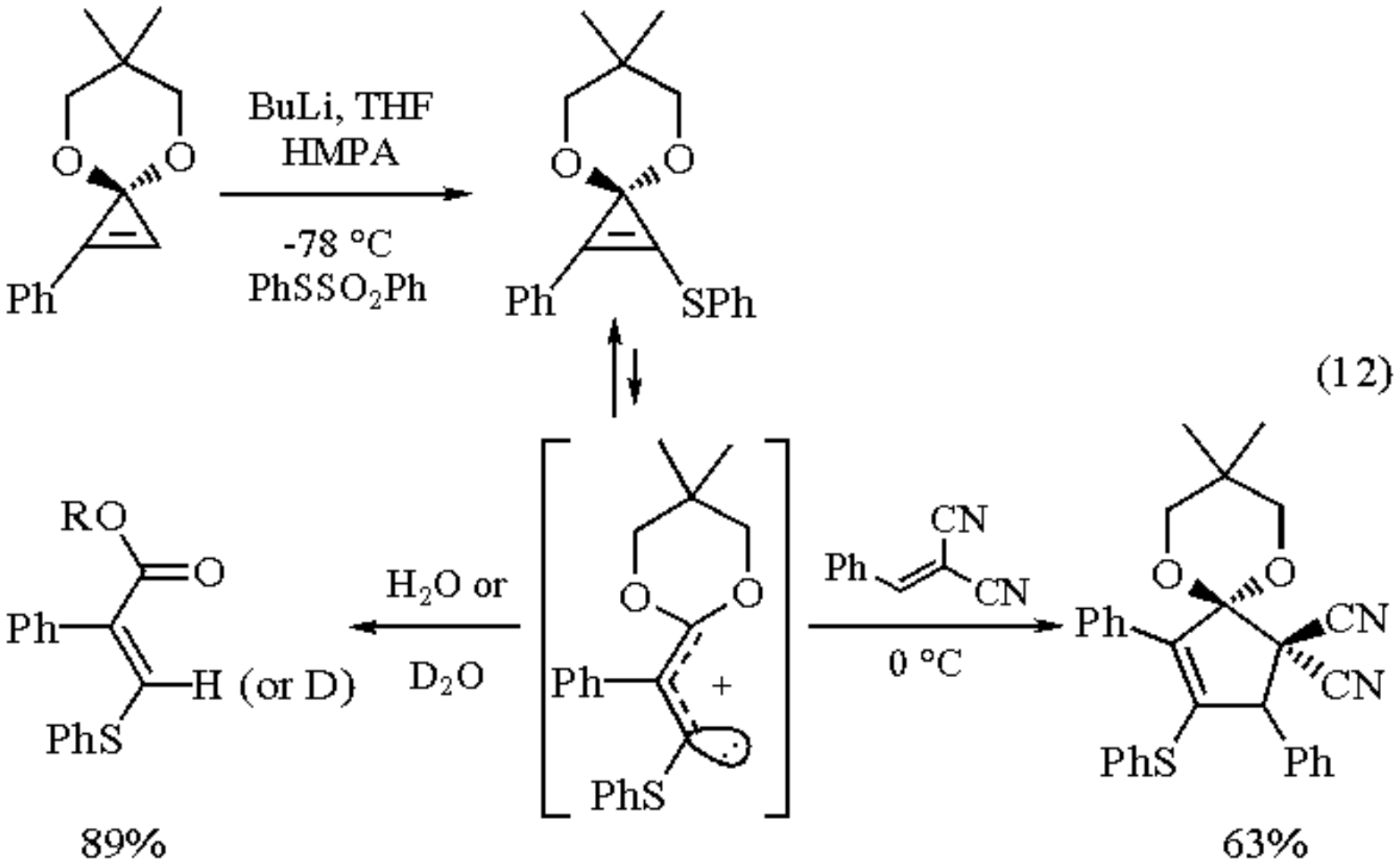

N-Sulfinyloxazolidinones, a New Class of Chiral Sulfinyl Transfer Reagents.[14]

N-Sulfinyloxazolidinone reagents are synthesized either by sulfinylation of the metalated oxazolidinones or by oxidation of the derived *N*-sulfenimides, to afford the diastereomeric *N*-sulfinyloxazolidinones which are readily purified by chromatography (eq 13).

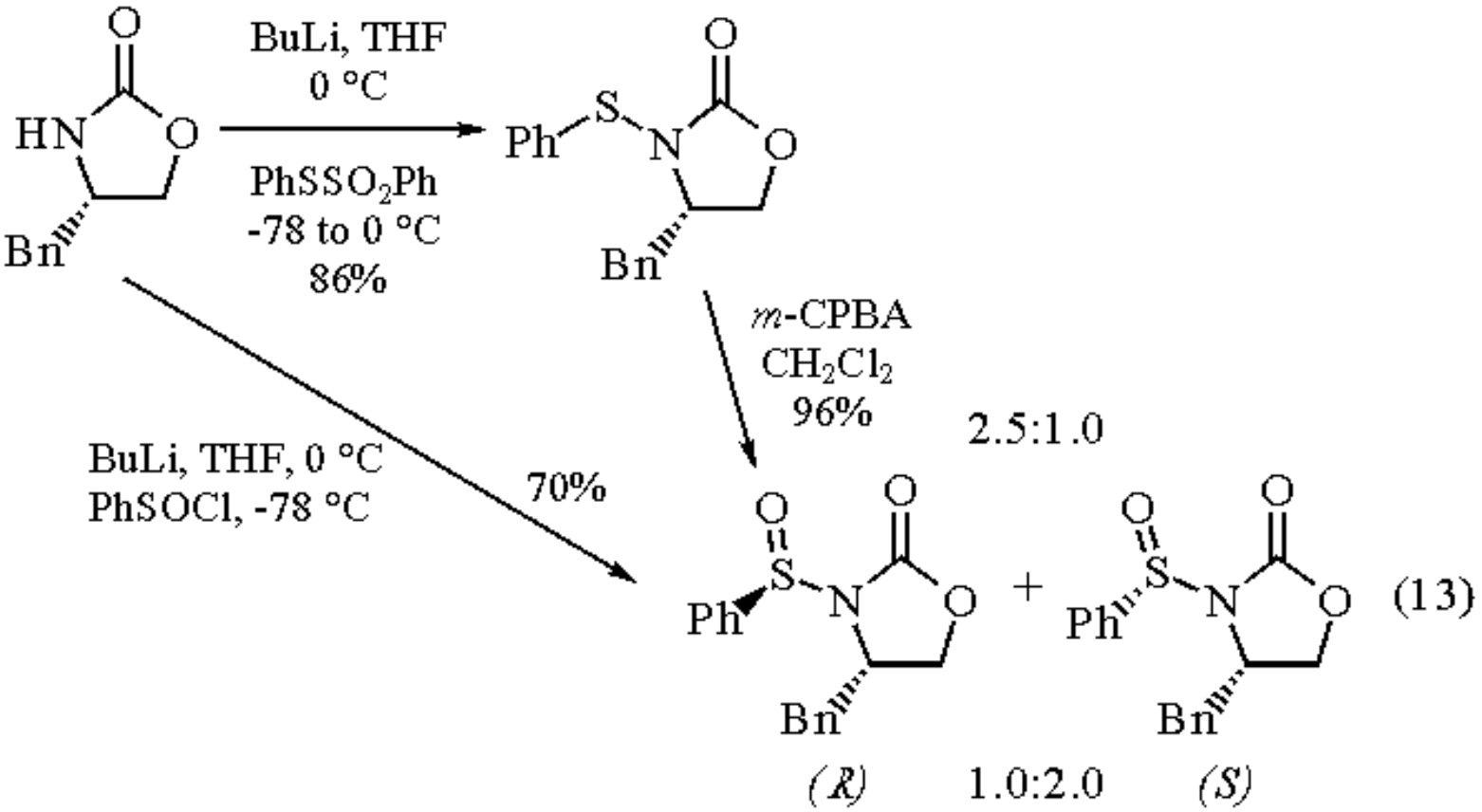

These sulfinylating agents react with a wide range of nucleophiles such as Grignard reagents, enolates, lithium alkoxides, or metalated amides, with inversion of configuration at the sulfur center, to afford chiral sulfoxides, sulfinate esters, and sulfinamides in high yields and enantioselectivities (eq 14). This family of chiral sulfinylating agents is at least 100 times more reactive than the corresponding menthyl sulfinate esters toward Grignard reagents.

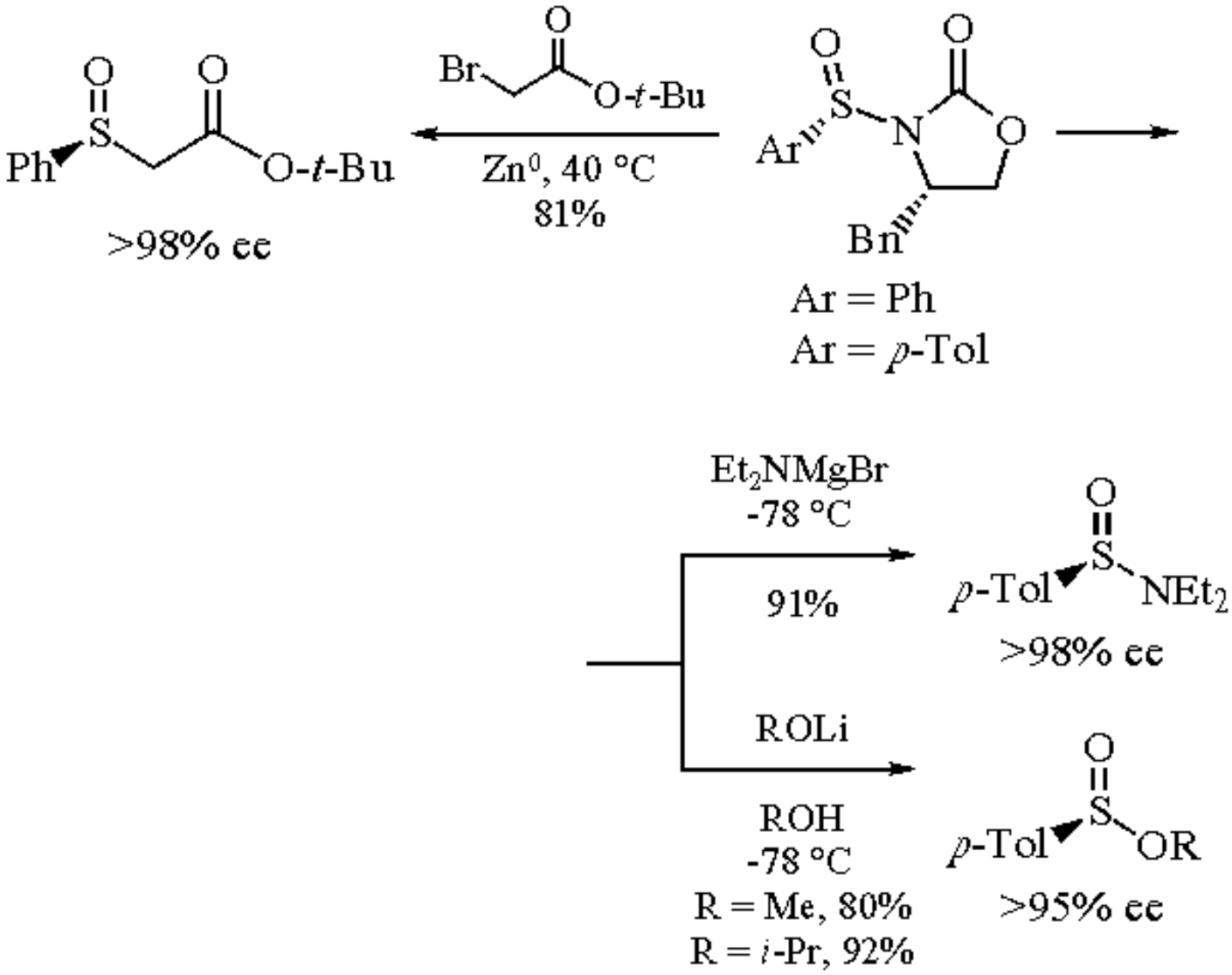

(14)

Related Reagents.

Benzenesulfenyl Chloride; ***Diphenyl Disulfide***.

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Kumiko Takeuchi

Eli Lilly and Company, Indianapolis, IN, USA

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N-Phenylbenzylimine

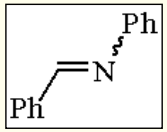

[538-51-2] · $C_{13}H_{11}N$ · *N*-Phenylbenzylimine · (MW 181.25)

(hetero Diels-Alder and cycloaddition reactions; stereospecific β-lactam synthesis; secondary amine and quinoline syntheses)

Alternate Name: N-benzylideneaniline.

Physical Data: mp 52-54 °C; bp 310 °C; fp >110 °C; *d* 1.038 g cm^{-3}. Generally exists in the *trans* form; theoretical studies have shown that the *cis-trans* interconversion occurs by inversion rather than rotation.[1]

Solubility: sol ether, alcohol, chloroform, acetic anhydride, liquid SO_2, NH_3; insol H_2O.

Form Supplied in: commercially available.

Analysis of Reagent Purity: IR.[18]

Purification: recrystallize from CS_2 (pale yellow needles) or dilute alcohol (plates) and vacuum dry.

Handling, Storage, and Precautions: harmful and irritant. Use in a fume hood.

Cycloaddition Reactions.

The initial example of an imino compound participating as a dienophile was reported by Alder in 1943.[2] Whilst full mechanistic details are not known, these [4 + 2] cycloadditions of C=N dienophiles (and also of N=N, N=O and C=O dienophiles) are believed to be $HOMO_{diene}$-$LUMO_{dienophile}$ controlled and concerted pericyclic processes. However, a dipolar mechanistic model is normally sufficient for quantitative predictions as to the regiochemical outcome of these reactions and may even be indicative of dipolar character in a concerted pericyclic transition state. Unless X and Y are very good at stabilizing carbanions, only intermediates (i) and (iii) need to be considered (eq 1). Imino Diels-Alder reactions show excellent *syn* stereoselectivity with respect to the diene component. Krow, however,[3] states that lone pair inversion on the nitrogen in both the imine and product tetrahydropyridine leads to stereochemical ambiguities that are missing in all carbon Diels-Alder reactions. Using a cyclic imine tends to remove this problem.

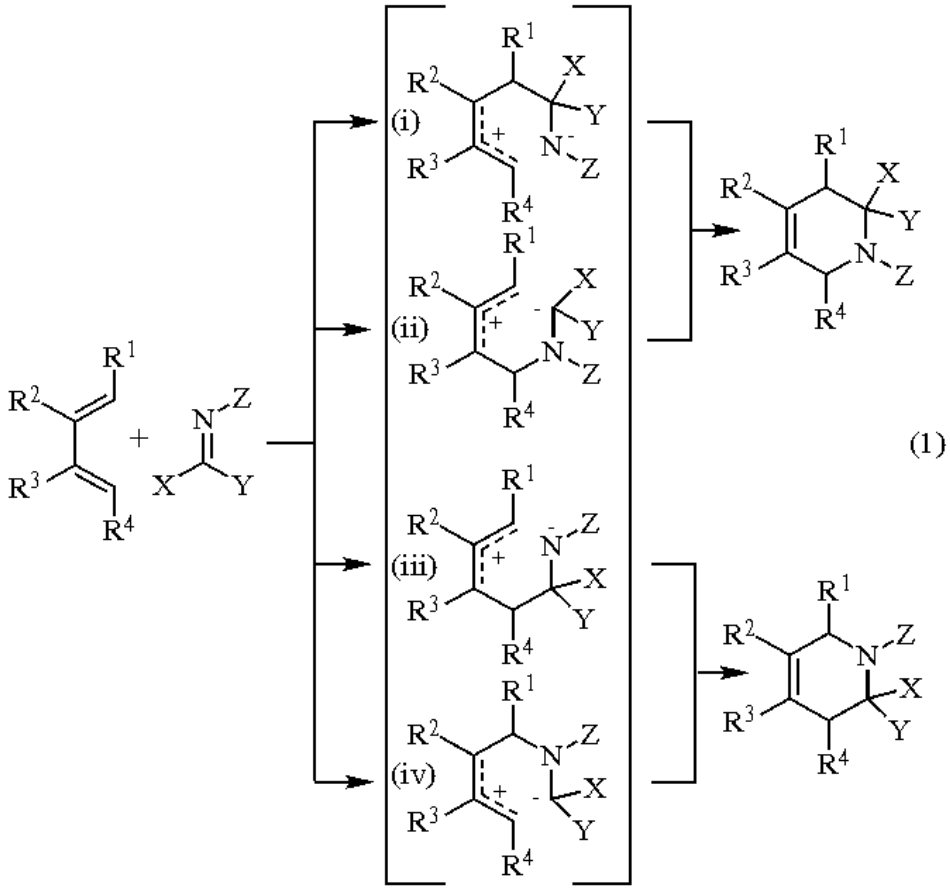

Imine cycloaddition reactions have become generally well known,[4] and there are also examples of iminium salts participating in these reactions.[5] Electron-rich dienes (**3**), in considerable excess, react with imines under the influence of Lewis acids (eq 2).[6,7] Only the one regioisomer (**2**) is detected in the product mixture and this is in keeping with the postulated mechanism in eq 1. The Danishefsky group has done considerable work in this field,[6] with both catalyzed and uncatalyzed reactions and with differing imines and dienes. There are also examples of ***Aluminum Chloride***, dialkylaluminium halides,[8a] ***Boron Trifluoride Etherate***, and ***Zirconium(IV) Chloride*** catalyzing these cycloadditions.[8b] Finally, various studies have been performed on the effects of the nitrogen substituent on the reaction course and heterocycle conformation in these imino Diels-Alder reactions.[8b]

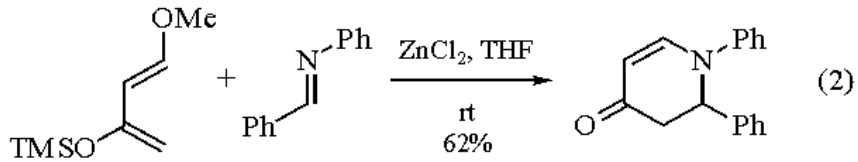

(3) 4.3 equiv **(1)** **(2)**

β-Lactam Synthesis.

Condensation Reactions.

Imines and silyl ketene acetals condense in the presence of a ***Trimethylsilyl Trifluoromethanesulfonate*** (TMSOTf) catalyst to give mainly *anti*-β-amino esters, which can be cyclized to give *trans*-β-lactams (eq 3).[9] Table 1 shows some typical results obtained, mainly using *N*-phenylbenzylimine as the imine (**5**), but another imine is given for comparison.

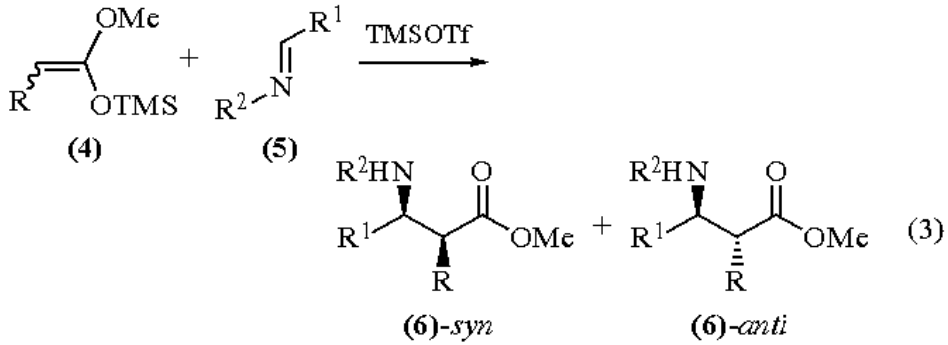

Table 1 Typical Results from Silyl Ketene Acetal Condensation with Imines in the Presence of TMSOTf.[9]

R	(*E*):(*Z*) in (**4**)	R^1	R^2	Solvent	*T* (°C)	(**4**):(**5**)	Yield (%)	*syn*:*anti*
Ph	36:64	Ph	Ph	CH_2Cl_2	- 65	1:1	85	14:86
Me	75:25	Ph	Ph	CH_2Cl_2	- 65	1:1	85	0:100
Ph	36:64	PhCH=CH	*p*-$MeOC_6H_4$	THF	- 65	2:1	78	15:85

All these examples involve an acid-catalyzed condensation between an isomeric mix of silyl ketene acetal and nonenolizable imines. The yields obtained are normally good, with a preference for the *anti*-isomer, irrespective of the starting geometry of the silyl ketene acetal. The isomeric products can be separated by silica gel chromatography. The utility of this reaction is that the *anti*-β-amino esters can be cyclized to the *trans*-β-lactam in excellent yields (eq 4).[9]

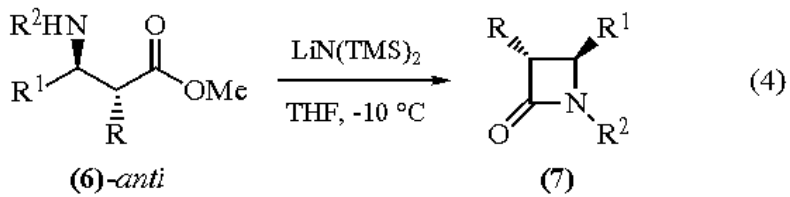

The one well known exception to this is the silyl ketene acetal (**8**) derived from ethyl 3-hydroxybutanoate, which reacts with *N*-phenylbenzylimine with *syn* selectivity and cyclizes to give the *cis*-β-lactam (**9**) (eq 5).[10]

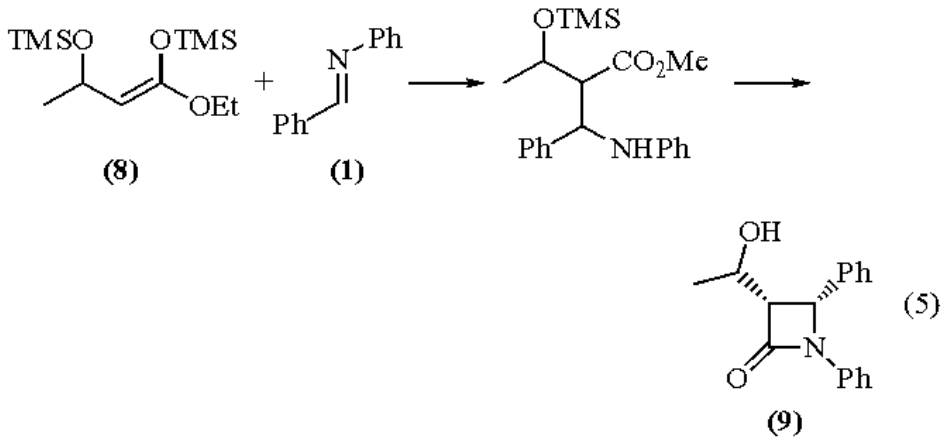

Another group has performed similar reactions to form chiral *trans*-β-lactams with high stereoselectivity using ***Titanium(IV) Chloride*** (eq 6).[11] The silyl ketene acetal (**10**) is derived from (1*S*,2*R*)-*N*-methylephedrine and in the presence of $TiCl_4$ gives the *trans*-β-lactam (**11**) in 79% yield and 95% ee. There are also reports of ***Zinc Iodide*** being used to promote these reactions, with some degree of stereoselectivity.[12]

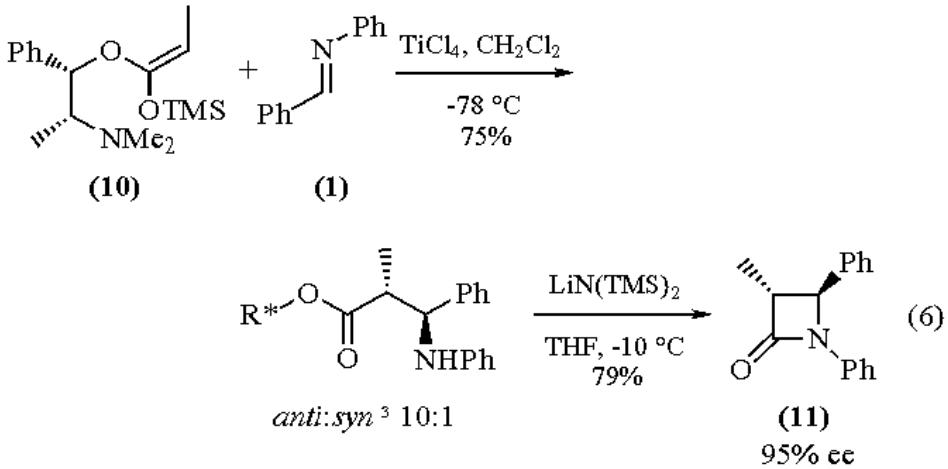

Transition Metal-Mediated.

Simultaneous studies between groups in America and Britain have shown that the condensation of certain transition metal complexes with imines can give unprecedented asymmetric induction (eq 7).[13,14] Previous studies had shown that the enolate (**13**) derived from (**12**) is sufficiently nucleophilic to react with electrophiles, of which readily available imines (from amines and aldehydes/ketones) are a good example, and that the resulting β-aminoacyl complexes are formed stereoselectively. The American group have also shown that the diethylaluminum enolate is also as effective as the lithium enolate, and in some cases leads to greater stereoselectivity, although the yields drop.[14]

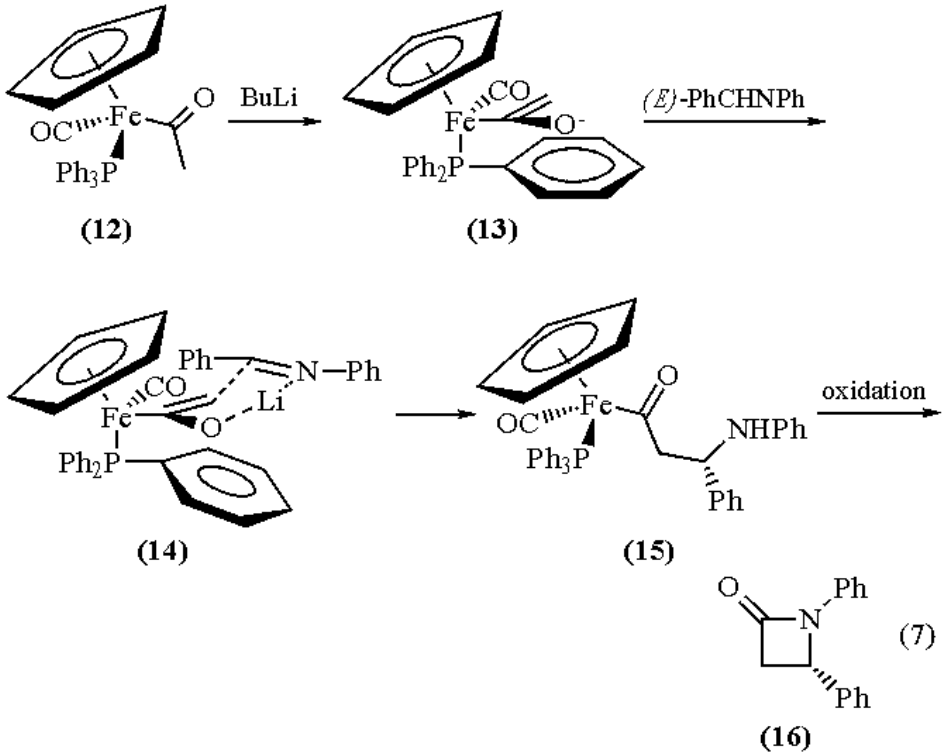

Preparation of Secondary Amines.

The addition of a carbon nucleophile to imines is a useful preparative method for secondary amines.[15] Alkyl organolithiums and Grignard reagents have been used to form secondary amines and considerable attention has been paid to forming allylated derivatives. The general reaction is shown in eq 8 and is an example of an indium-mediated Barbier-type allylation.

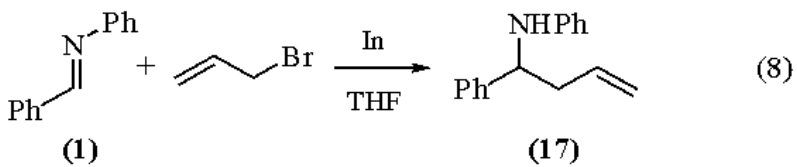

Quinoline Synthesis.

Treatment of *N*-phenylbenzylimine with diisopropyl peroxydicarbonate generates the arylimidoyl radical (**18**) which reacts with 1-alkynes to form 4-alkylquinolines (**19**) (eq 9). This is a useful route to substituted quinolines in high yields.[16] There are other examples of imines being used in annulation reactions with a variety of promoting reagents.[17]

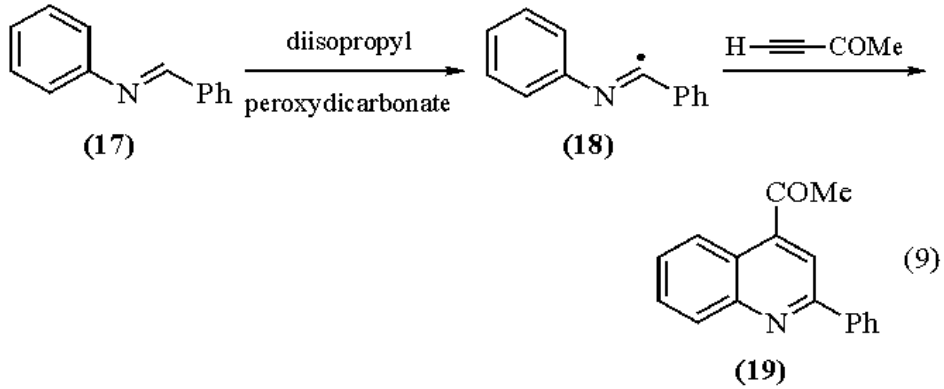

(9)

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Phenylboron Dichloride[1]

$PhBCl_2$

[873-51-8] · $C_6H_5BCl_2$ · Phenylboron Dichloride · (MW 158.82)

(Lewis acidic reagent for ether cleavage and selective condensations; phenylating agent)

Physical Data: mp 7 °C; bp 175 °C; *d* 1.194 g cm^{-3}.

Solubility: dec by water, alcohols, or ethers; sol saturated and halogenated hydrocarbons, aromatic solvents.

Form Supplied in: fuming liquid; widely available.

Preparative Methods: by transmetalation between ***Boron Trichloride*** and Ph_4Sn[2] or ***Phenylmercury(II) Chloride***.[3] Treatment of phenylboronates with boron trichloride in the presence of catalytic ***Iron(III) Chloride*** provides an alternative and efficient process.[4] For large scale preparation, a direct boronation of benzene with boron trichloride and ***Aluminum Chloride*** has been reported.[5]

Handling, Storage, and Precautions: stable under N_2; should be stored in a sealed ampule since it is highly susceptible to air and moisture.

General Discussion.

Phenylboron dichloride has been used in a manner similar to boron trichloride for the cleavage of ethers, but there are no data on their comparative merits.[6] Boron enolates, available by treating ketones with $PhBCl_2$ and ***Diisopropylethylamine*** at -78 °C, undergo highly *syn* selective crossed aldol reaction with aldehydes (eq 1).[7] The formation of the boron enolates is kinetically controlled and produces (*Z*)-enolates stereoselectively. Ketones condense with excess ketene in the presence of 2 equiv of $PhBCl_2$ to give stable cyclic boroles and α,β-unsaturated acid chlorides (eq 2).[8]

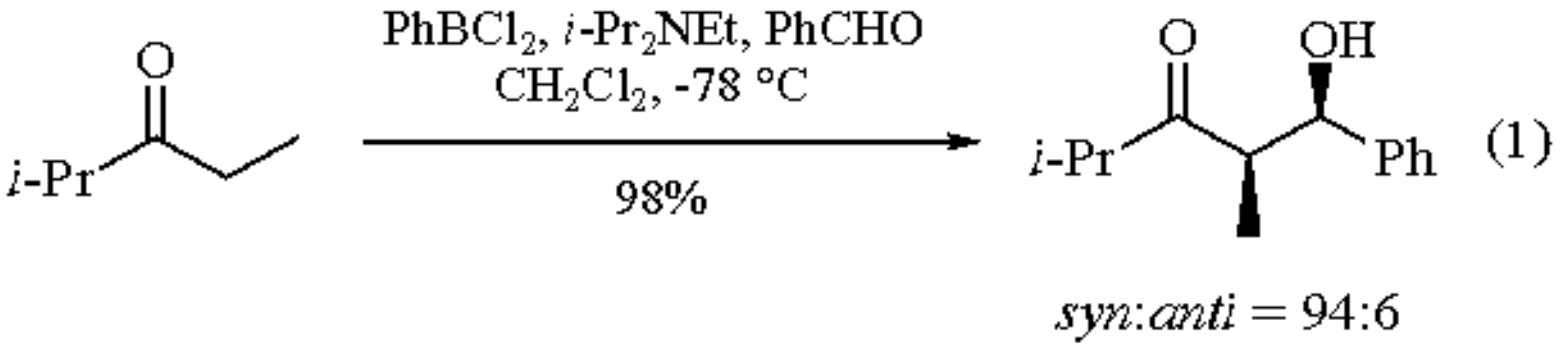

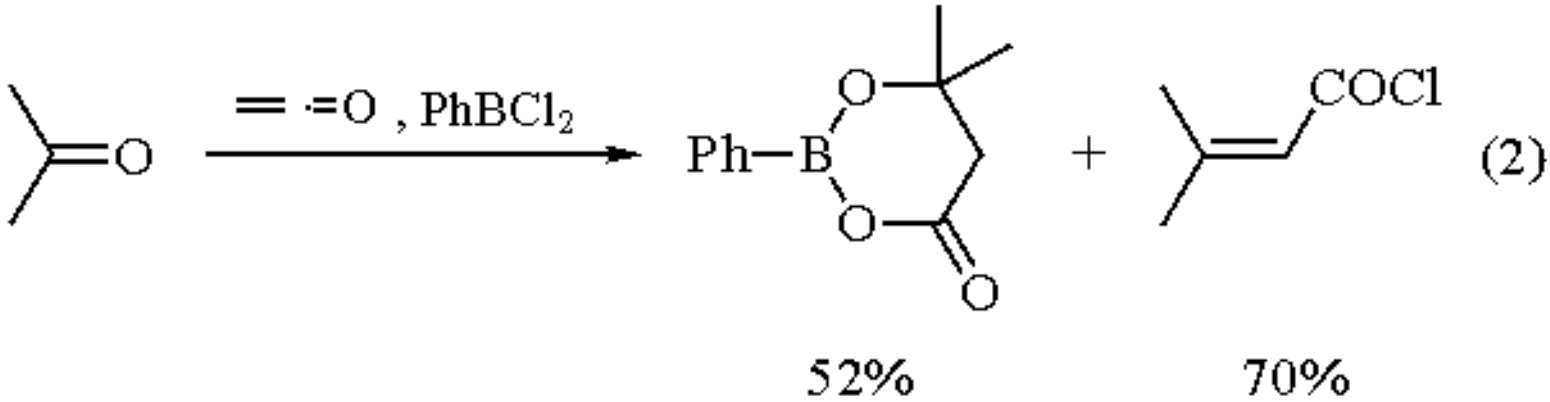

The *ortho*-hydroxyalkylation of anilines is achieved by in situ formation of anilinoboranes which condense with aromatic aldehydes at room temperature (eq 3).[9] The boron atom acts as an efficient template to achieve selective *ortho* substitution via the intermediate (**1**) through a cyclic transition state. The *ortho*-hydroxyalkylation of *N*-alkylanilines and aldehydes may also be performed with BCl_3, but the reaction fails with primary anilines because of competing Schiff base formation.[10]

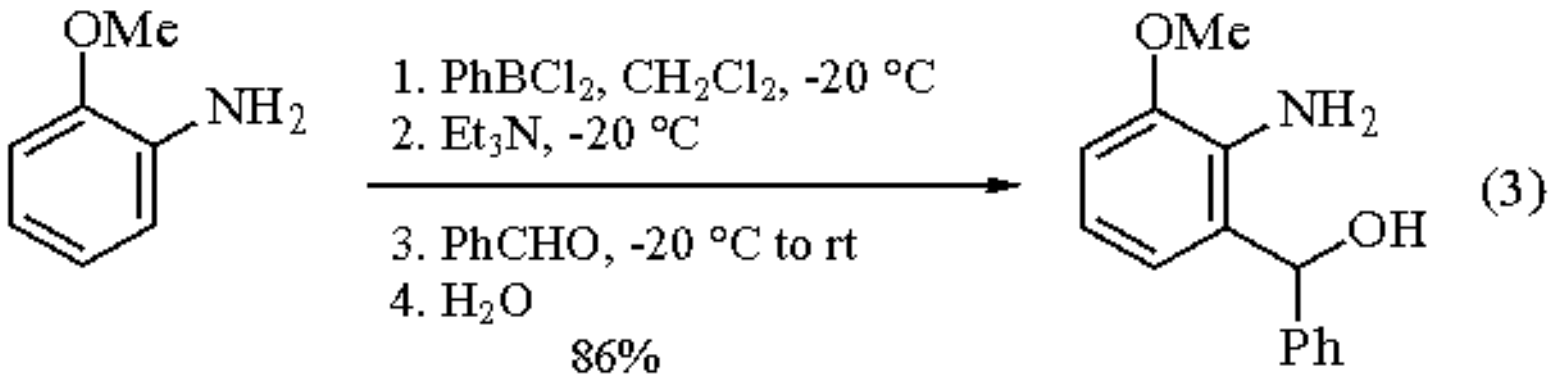

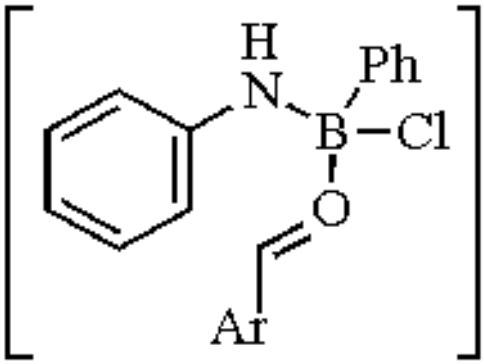

(1)

The reagent is useful for phenylation of azides,[11] e.g. in the stereoselective synthesis of *N*-phenylaziridine (eq 4).[12] Similar reactions of phenylboron dichloride and several other arylboron dichlorides with ***Ethyl Diazoacetate*** at -25 °C provide quantitative yields of ethyl arylacetates (eq 5).[13] The reactions proceed through initial coordination of the azide or diazo group to the boron atom, followed by transfer of the phenyl group from boron to carbon or nitrogen.

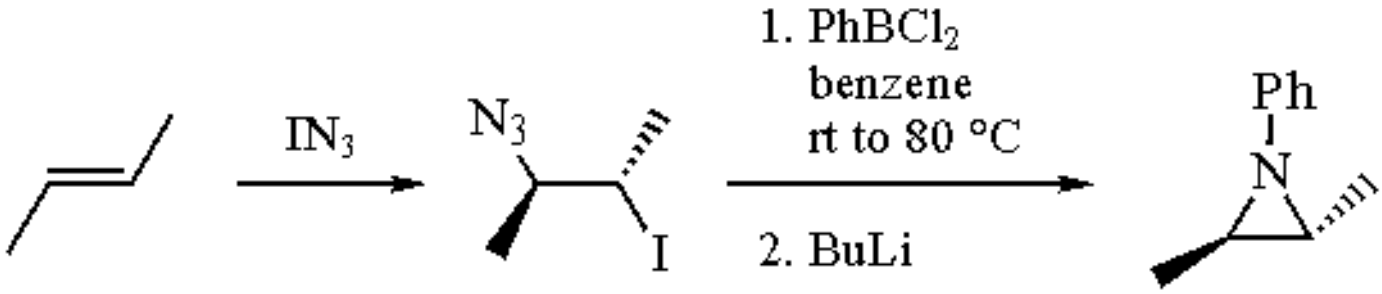

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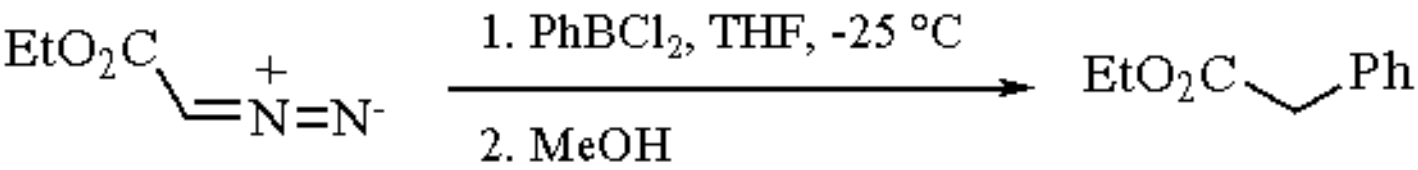

(5)

A variety of phenylboron derivatives have been synthesized via transmetalation with other organometallic compounds, e.g. the transmetalation with Sn provides borepin derivatives (eq 6).[14]

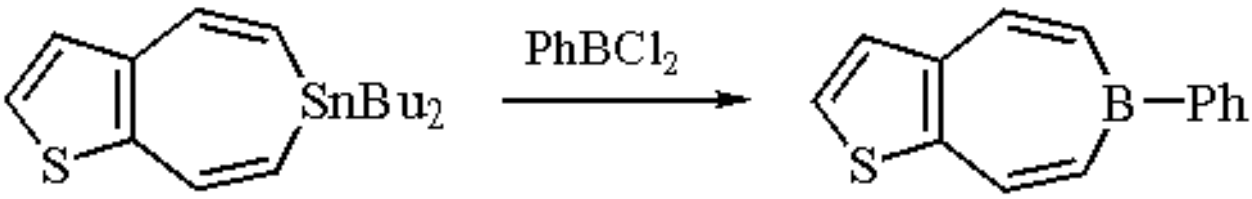

(6)

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N-Phenylcampholylhydroxamic Acid

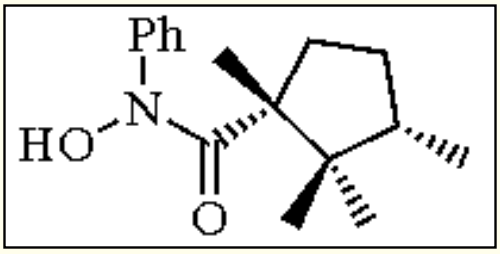

[62668-00-2] · $C_{16}H_{23}NO_2$ · *N*-Phenylcampholylhydroxamic Acid · (MW 261.40)

(chiral ligand in asymmetric epoxidation of allylic alcohols[1])

Solubility: sol toluene, acetonitrile.

Preparative Method: phenylhydroxylamine (2 equiv) is added to a solution of campholyl chloride (1 equiv) in acetonitrile.[1]

Asymmetric Epoxidation.

N-Phenylcampholylhydroxamic acid has been used as a chiral ligand in the transition metal-catalyzed asymmetric epoxidation of allylic alcohols.[1] Three allylic alcohols [geraniol (**1**), (*E*)-α-phenylcinnamyl alcohol (**2**), and 1-hydroxymethyl-2-methylcyclohexene (**3**)] have been oxidized to the corresponding epoxides in the presence of the chiral hydroxamate complex of vanadium. The best asymmetric induction (50% ee) is observed for alcohol (**2**) at -78 °C. Generally, low temperature reactions give higher asymmetric inductions but lower yields. The optimum inductions are attained when a 5:1 ratio of hydroxamic acid and ***Vanadyl Bis(acetylacetonate)*** is used. ***t-Butyl Hydroperoxide*** gives substantially better inductions than ***Cumyl Hydroperoxide***. The asymmetric oxidation is proposed to go through the intermediate (**4**),[1,2] in which the alcohol is coordinated to the metal during the oxygen atom transfer step.

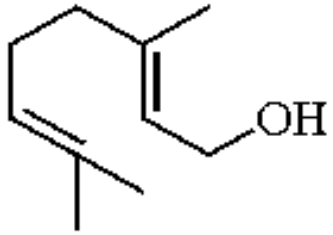

(1)

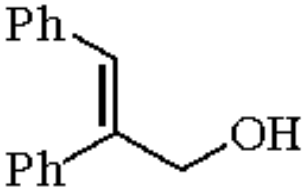

(2)

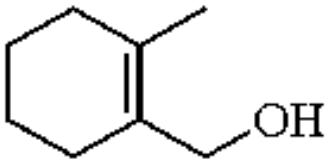

(3)

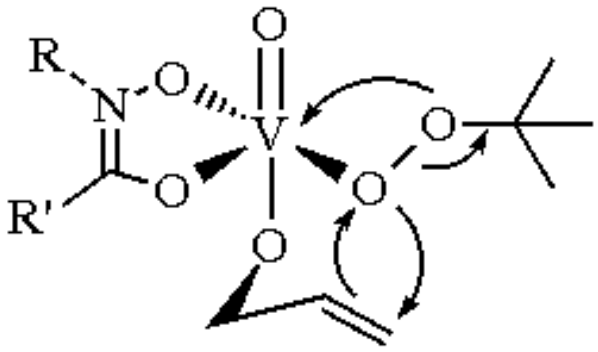

(4)

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Phenyl Chlorothionocarbonate

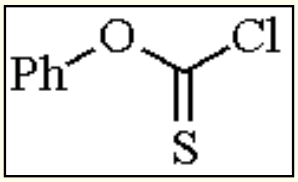

[1005-56-7] · C_7H_5ClOS · Phenyl Chlorothionocarbonate · (MW 172.64)

(forms thionocarbonate ester derivatives of alcohols which can be deoxygenated with tin hydride reagents;[1-5] converts ribonucleosides to 2´-deoxynucleosides;[2] provides allylic thionocarbonates which undergo [3,3]-sigmatropic shifts;[6-9] provides precursors for radical bond-forming reactions;[10,11] reagent for thioacylation[12-16])

Physical Data: bp 81-83 °C/6 mmHg; fp 81 °C; *d* 1.248 g cm^{-3}.

Solubility: sol chloroform, THF.

Form Supplied in: colorless liquid.

Handling, Storage, and Precautions: corrosive; moisture sensitive; should be stored in airtight containers which exclude moisture; incompatible with alcohol solvents.

Deoxygenation of Secondary Alcohols.

Reaction of secondary alcohols with the reagent in the presence of ***Pyridine*** or ***4-Dimethylaminopyridine*** (DMAP) provides thiocarbonate ester derivatives which can be reduced to alkanes using ***Tri-n-butylstannane*** (eq 1).[1] The advantage of this method is the ability to deoxygenate alcohols via radical intermediates and thereby avoid problems associated with ionic reaction conditions (i.e. carbonium ion rearrangements, reduction of other functional groups). This method is particularly useful for the conversion of ribonucleosides to 2´-deoxynucleosides. For example, adenosine can be converted to 2´-deoxyadenosine in 78% overall yield by initial protection of the 3´- and 5´-hydroxyl groups as a cyclic disiloxane, thiocarbonylation, reductive cleavage, and then final deprotection using a fluoride source (eq 2).[2] Treatment of 2´-bromo-3´-phenoxythiocarbonyl nucleosides with tributyltin hydride affords 2´,3´-didehydro-2´,3´-dideoxy nucleosides via radical β-elimination.[3]

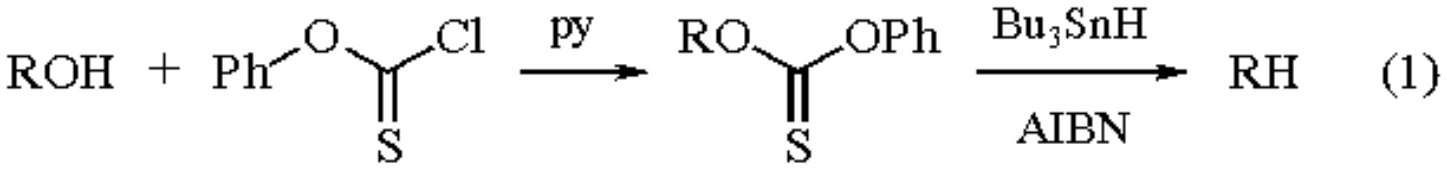

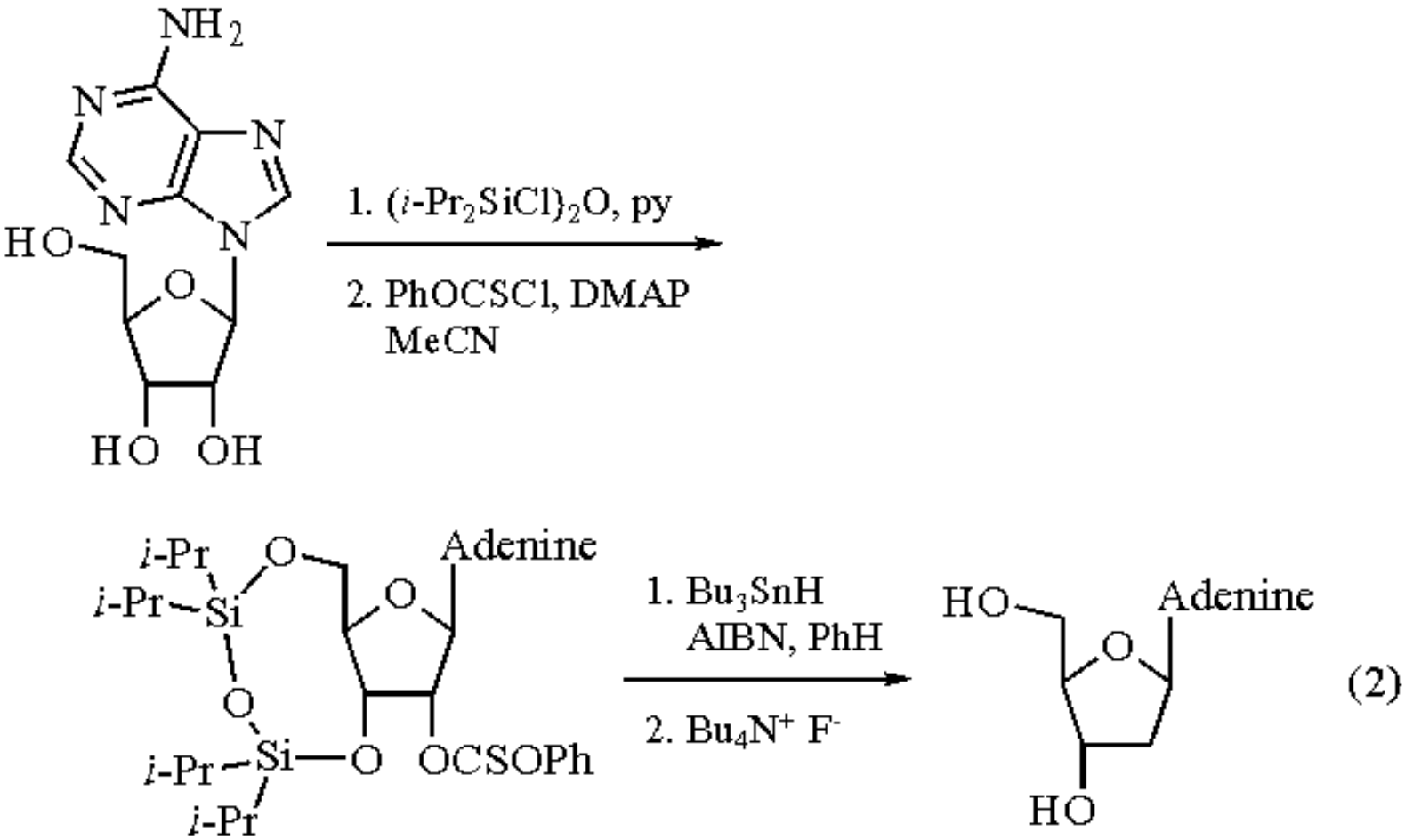

Synthetic intermediates can be selectively deoxygenated without reduction of other functional groups such as esters, ketones, and oxime ethers (eq 3),[4] as well as epoxides, acetate esters, and alkenes.[5]

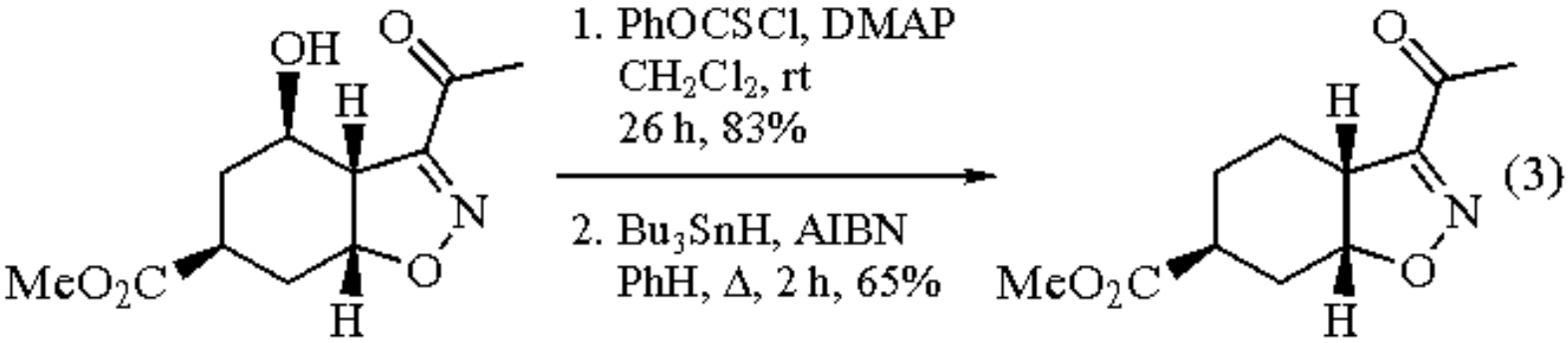

Sigmatropic Rearrangements of Allylic Thionocarbonates.

The reaction of allyl alcohols with aryl chlorothionocarbonates affords *S*-allyl aryl thiocarbonates by [3,3]-sigmatropic rearrangement via the intermediate thionocarbonate esters.[6-9] For example, treatment of 2-methyl-1-penten-3-ol with the reagent in pyridine at -20 °C affords phenyl 2-methyl-2-pentenyl thionocarbonate in 67% yield (*E*:*Z* = 96.5:3.5).[7] This type of rearrangement, coupled with tin hydride mediated reduction of the phenyl thiocarbonate ester product, was used as a key step in the synthesis of isocarbacyclin (eq 4).[8] Rearrangement of cyclic thionocarbonates contained in eight-membered rings or smaller provides two-atom ring enlarged thiocarbonates having (*Z*) double bond geometry (eq 5).[9] Depending on the system, the cyclic thiocarbonates are obtained by either treatment of the diol

monothionocarbonate with base or by reaction of the diol with 1,1´-thiocarbonyldi-2,2´-pyridone. Cyclic thionocarbonates of ring size nine or larger afford ring expanded products with exclusive (*E*) double bond geometry in modest yields.

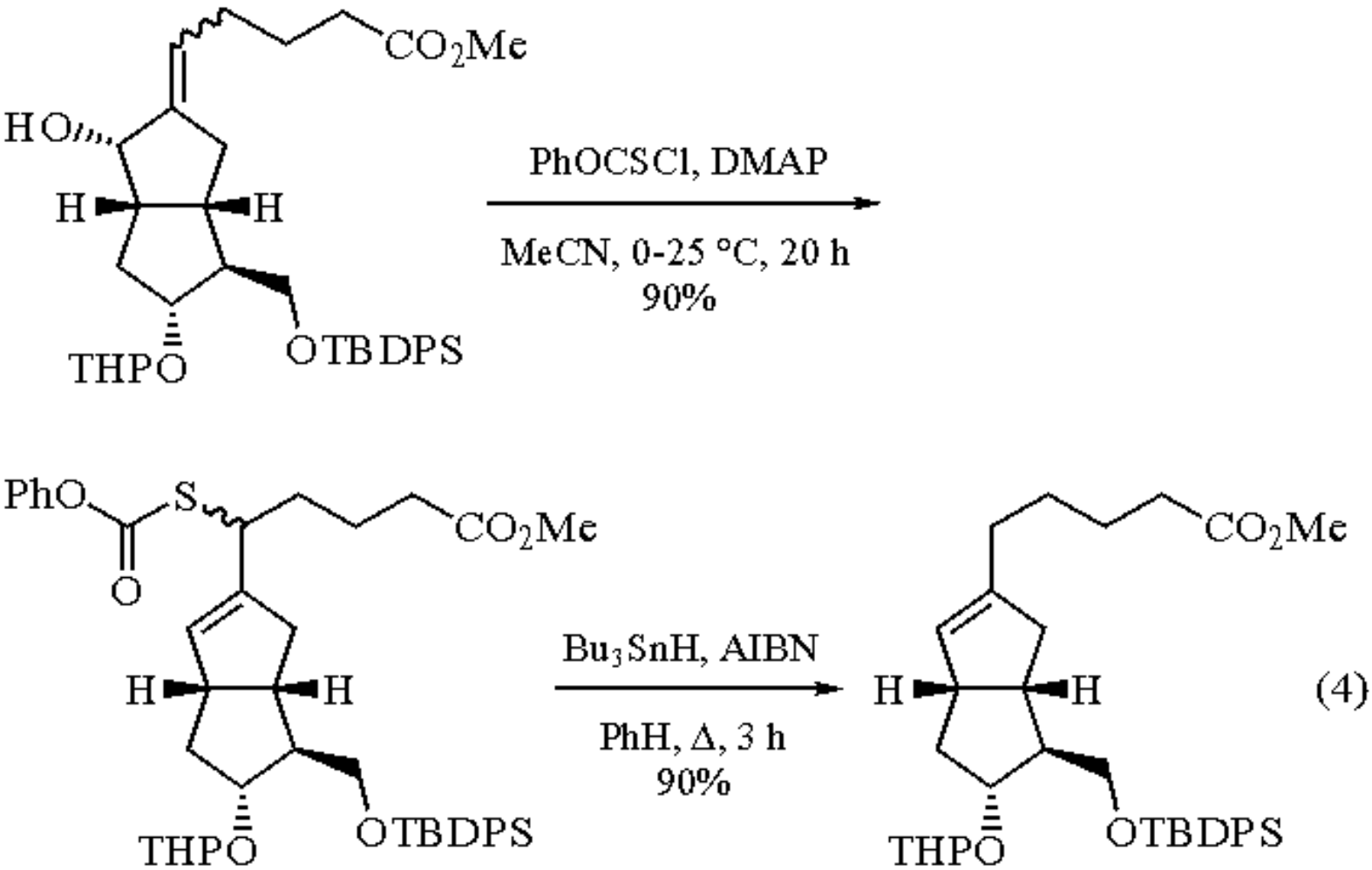

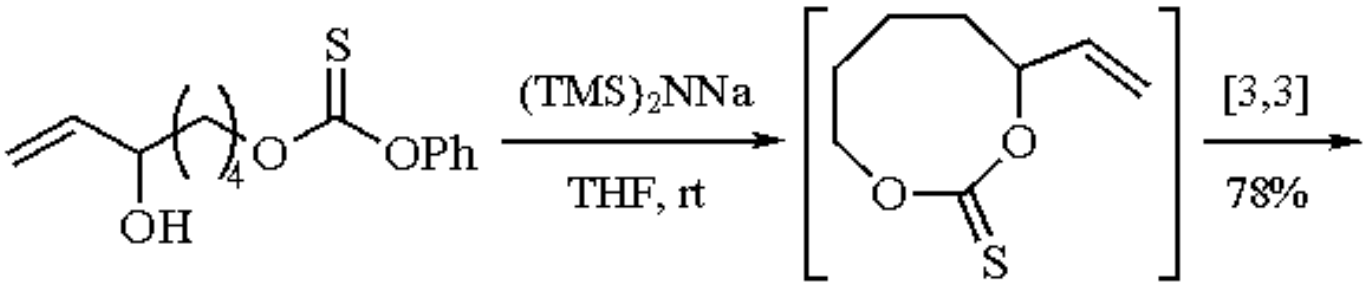

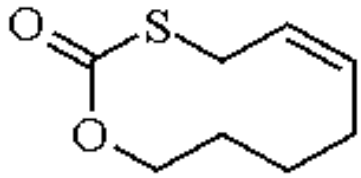

(5)

Radical Coupling and Cyclization Reactions.

Phenyl thionocarbonate esters derived from alcohols serve as efficient precursors for the generation of radical intermediates which can be used for the formation of new carbon-carbon bonds. For example, a 4-thionocarbonate ester derived from L-lyxose undergoes a stereoselective allylation upon photolysis in toluene in the presence of 2.0 equiv of ***Allyltributylstannane*** (eq 6).[10] Photochemical initiation is preferable to chemical initiation using ***Azobisisobutyronitrile*** which results in the formation of side products at the expense of the desired product. The allylation product was used further in a total synthesis of pseudomic acid C.

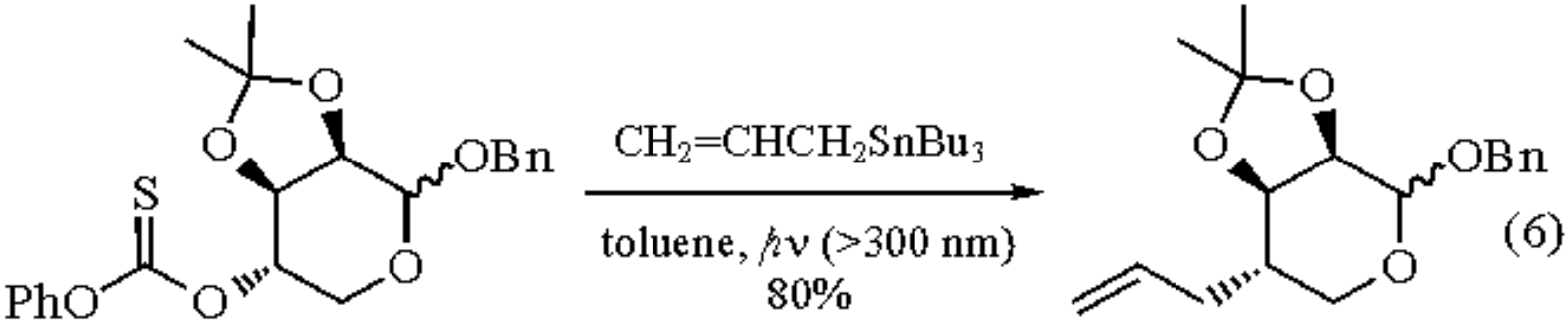

Oxime ethers derived from hydroxy aldehydes, upon conversion to their phenyl thionocarbonate esters, undergo radical cyclizations resulting in the formation of carbocycles.[11] For example, an oxime ether obtained from D-glucose is converted into its phenyl thionocarbonate ester at C-5 and, upon heating in benzene in the presence of tributyltin hydride, affords cyclopentanes in 93% yield as a 62:38 mixture of two diastereomers (eq 7). In general, only low to modest stereoselectivity between the newly formed stereocenters is observed in a number of substrates examined.

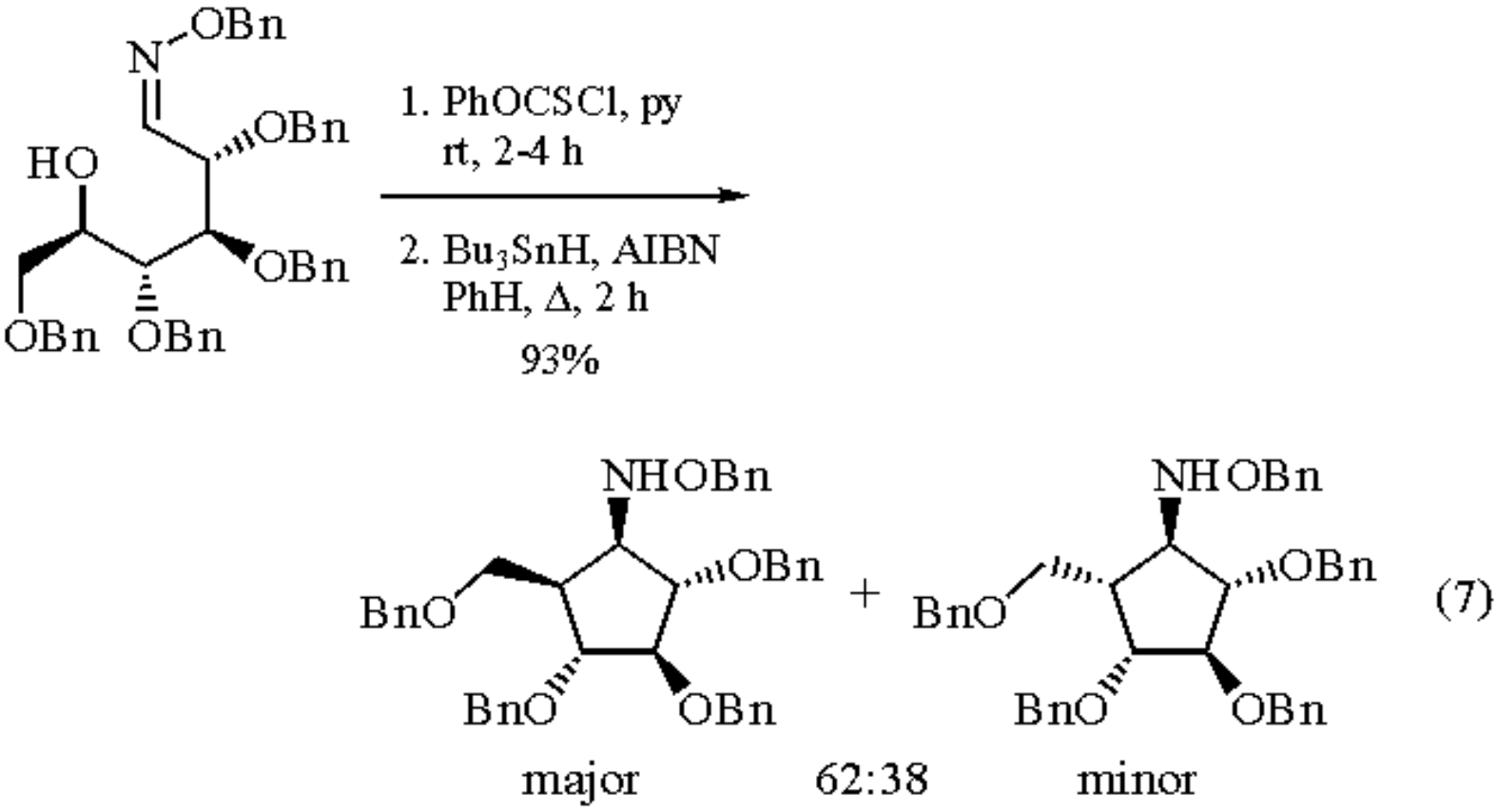

Thioacylation Reagent.

The regioselective thioacylation of unprotected carbohydrates via the agency of ***Di-n-butyltin Oxide*** and the reagent has been investigated.[12] Glycopyranosides having a *cis*-diol arrangement, e.g. galactose, form cyclic thiocarbonates which can be either converted into dihydropyranosides using the Corey elimination procedure or deoxygenated to a mixture of 3- and 4-deoxyglycopyranosides (eq 8). Methyl D-glucopyranoside is monothioacylated with the regioselectivity dependent upon the configuration at the anomeric carbon; the α-epimer gives 83% of 2-thionocarbonate and the β-epimer gives 85% of 6-thionocarbonate. Further treatment with tributyltin hydride affords the corresponding deoxyglucose derivatives in high yield.

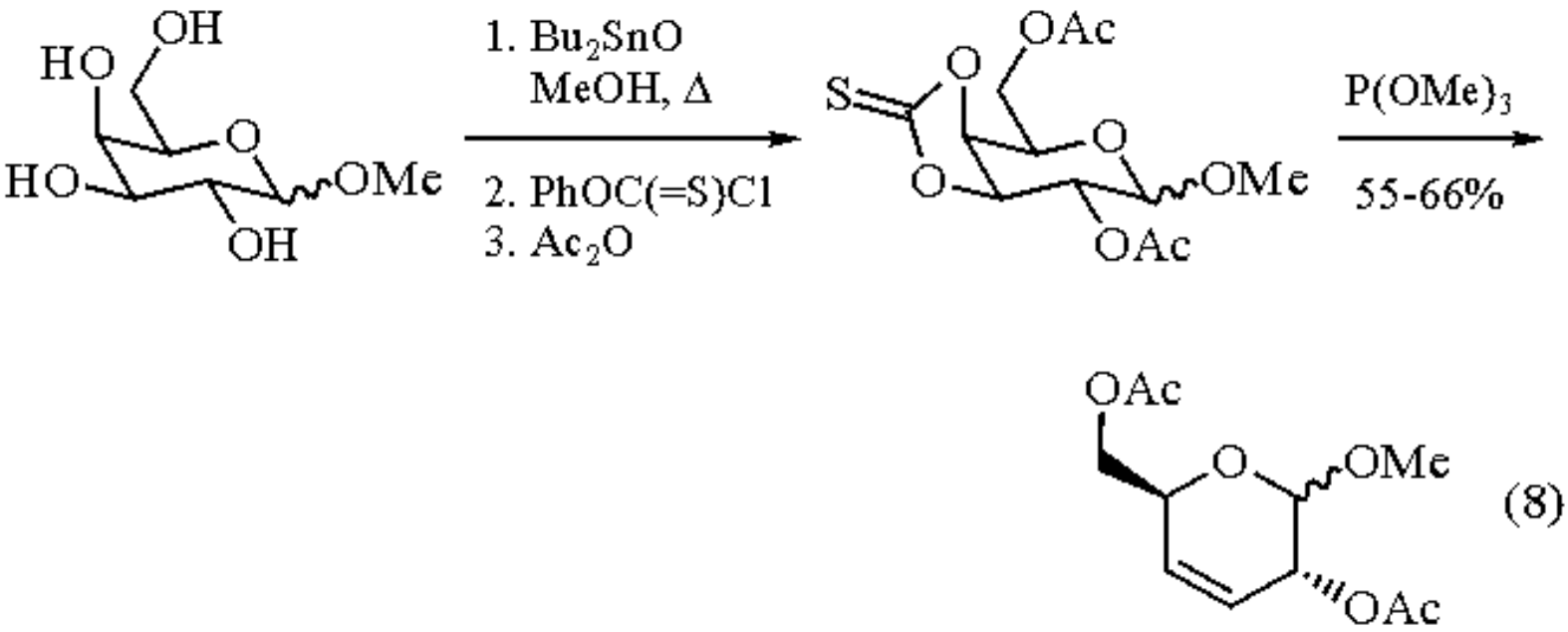

(8)

In a key step leading to a synthesis of saxitoxin, radical fragmentation of a pyrazolidine ring followed by intramolecular thioacylation afforded the ring expanded tetrahydropyrimidine intermediate (eq 9).[13] The thionocarbamate activation of the pyrazolidine *N*-H was found to be necessary to effect the desired transformation.

The intramolecular thioacylation of an ester enolate was used for the synthesis of 2-alkylthiopenem carboxylic acid derivatives.[14] Sequential acylations have led to the synthesis of zwitterionic pyrazole-5-thiones from acyclic precursors,[15] whereas 2-ethoxyoxazolidines react with the reagent to afford the products of *N*-acylation.[16]

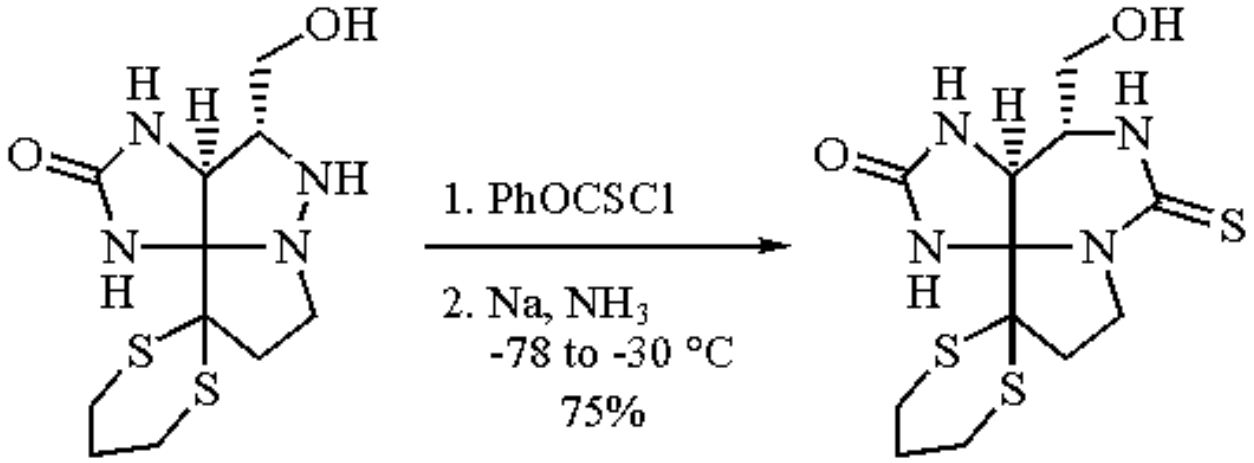

(9)

Heating of *O*-phenyl thionocarbonates of pyrrolidine and piperidine-2-ethanols in acetonitrile gives a ring expanded

azepine or an octahydroazocine accompanied by the pyrrolidine and piperidine *O*-phenyl ethers (eq 10).[17] These products arise via the internal expulsion of carbonyl sulfide, leading to formation of an azetidinium intermediate followed by nucleophilic ring opening with phenoxide ion.

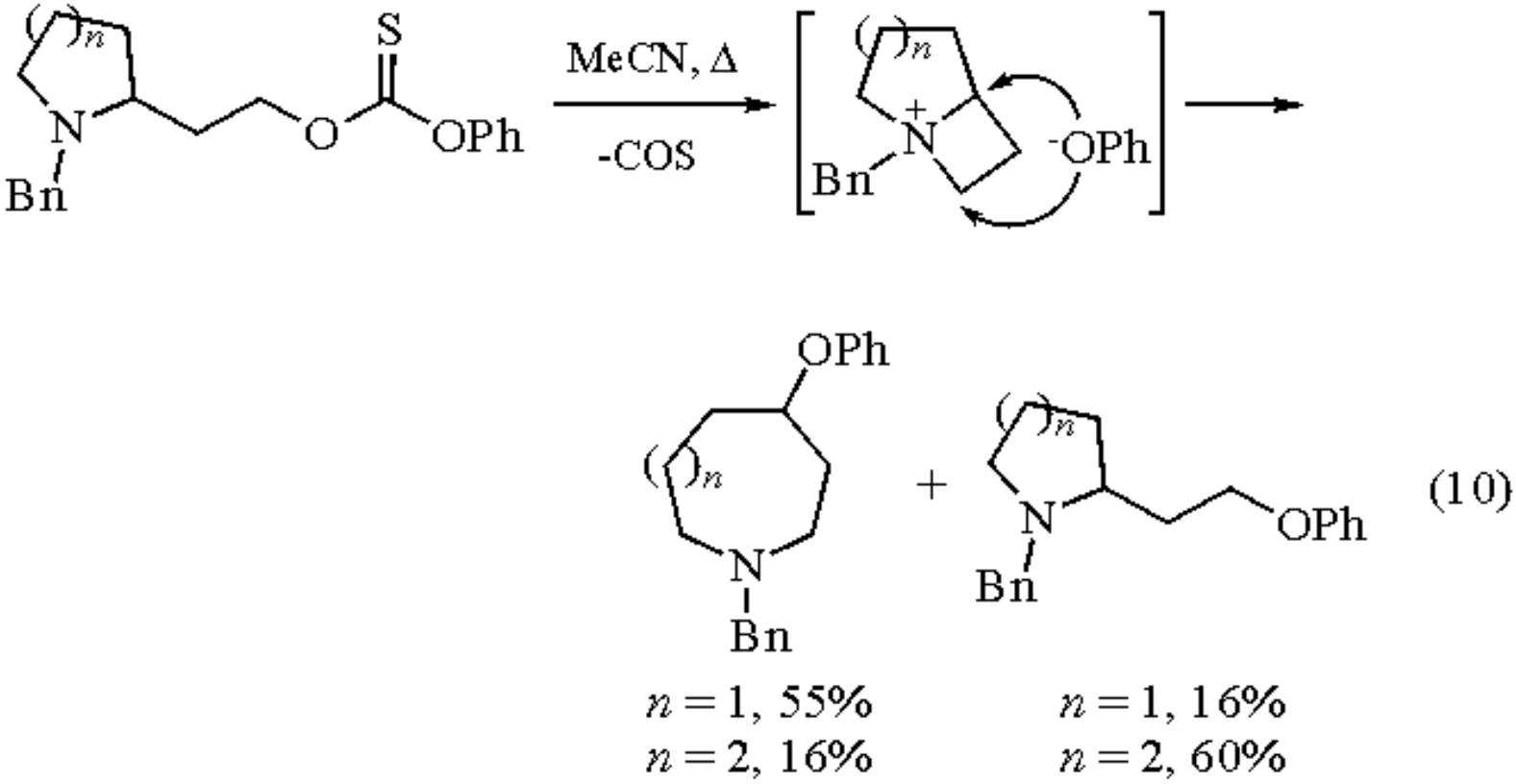

Related Reagents.

Carbon Disulfide; ***RT143-***.

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Phenylcopper[1]

PhCu

[3220-49-3] · C_6H_5Cu · Phenylcopper · (MW 140.66)

(nucleophilic reagent for substitution reactions;[1a,b] selective reagent for conjugate additions;[1a,c,d,2] couples with aryl halides to form biaryls[3])

Alternate Name: copper phenyl.

Physical Data: slightly yellow solid; mp 100 °C (dec).[13]

Solubility: insol ether, tetrahydrofuran.

Preparative Methods: phenylcopper and other arylcopper species are most commonly prepared from equimolar amounts of alkyllithium or Grignard reagent and purified copper(I) halide in ether or THF.[4] Arylcoppers can be prepared from the corresponding aryl halides and highly active zerovalent ***Copper***.[5]

Handling, Storage, and Precautions: decomposes on heating in solution. Hydrolyzed by H_2O.[13] Use in a fume hood.

Nucleophilic Substitutions.

Arylcoppers are suitable nucleophiles for reaction with acid chlorides (to prepare aryl ketones),[5,6] primary alkyl halides,[5a,b] epoxides,[5c] β-lactones (to prepare β-aryl carboxylic acids),[7] and 1,3-dioxolan-4-ones (to prepare protected secondary alcohols).[8] Arylcopper species favor S_N2' substitutions of allylic bromides[9] and propargyl sulfonates.[4d] See also ***Methylcopper***.

Conjugate Additions.

Phenylcopper will add in Michael fashion to conjugated enones,[6] cyanoalkynes,[10] alkynyl sulfoxides,[4c] and alkenyl sulfones.[11] When performed in the presence of ***Chlorotrimethylsilane***[12a,b] or ***Iodotrimethylsilane***,[12b,c] Michael addition of arylcoppers to enones, enals, and enoates is accelerated and 1,4-selectivity (vs. 1,2) is enhanced. Rate and selectivity can also be improved by the presence of ***Dimethyl Sulfide***.[6] See also ***Phenylcopper-Boron Trifluoride Etherate***.

Biaryl Synthesis.

Although arylcoppers are not typically used for the synthesis of unsymmetrical biaryls, a combination of phenylcopper and 2-iodopyridine, or 2-pyridylcopper and an iodoarene, provides 2-arylpyridines in good yield.[4b]

---

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Phenylcopper-Boron Trifluoride Etherate[1]

PhCu + BF_3.OEt_2

(PhCu)

[3220-49-3] · C_6H_5Cu · Phenylcopper-Boron Trifluoride Etherate · (MW 140.66) (BF_3.OEt_2)

[109-63-7] · $C_4H_{10}BF_3O$ · Phenylcopper-Boron Trifluoride Etherate · (MW 141.95)

(selective nucleophilic reagent for substitution reactions[2,3] and conjugate additions[1])

Physical Data: see entries for individual components.

Preparative Method: prepared by the addition of ***Boron Trifluoride Etherate*** to a suspension of ***Phenylcopper*** in diethyl ether or tetrahydrofuran at -70 °C.[2]

Handling, Storage, and Precautions: see entries for individual components. Use in a fume hood.

Nucleophilic Substitutions.

Substitution reactions involving phenylcopper/BF_3 exhibit chemoselectivities, rates, and regioselectivities which are similar to those observed with alkylcopper/BF_3 (see ***Methylcopper-Boron Trifluoride Etherate***). In the presence of ***Tri-n-butylphosphine***, phenylcopper/BF_3 adds to chiral enal acetals in an S_N2' substitution (eq 1). The result, on hydrolysis of the enol ether, is an effective asymmetric conjugate addition to the enal.[4]

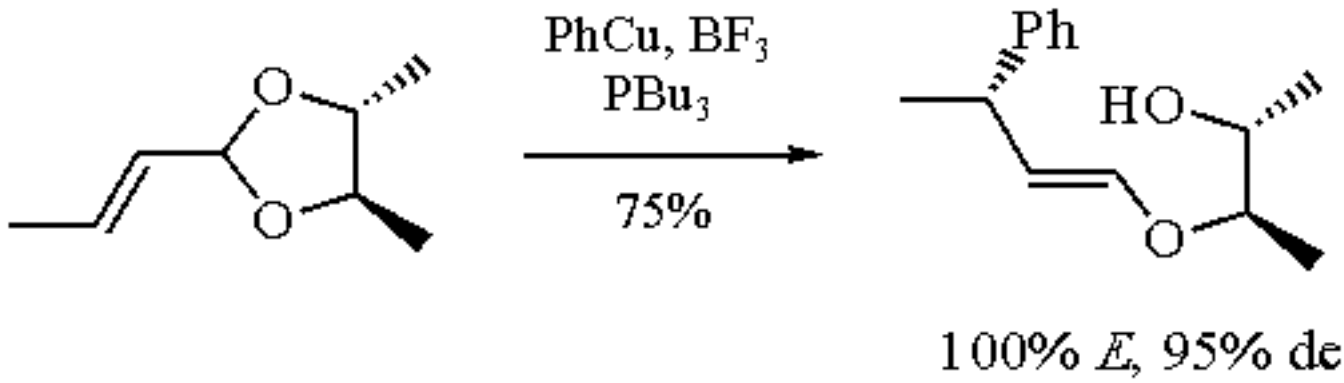

(1)

Conjugate Additions.

Again, the observed chemistry is similar to that observed with alkylcopper/BF_3.

---

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John N. Haseltine

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Phenyldiazomethane[1]

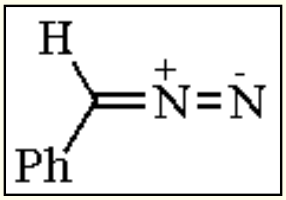

[334-88-3] · $C_7H_6N_2$ · Phenyldiazomethane · (MW 118.15)

(alkylating agent for carboxylic acids and alcohols; synthesis of phenylaziridines and phenylcyclopropanes from imines and alkenes[1])

Physical Data: liquid at room temperature, bp 37-41 °C/1.5 mmHg.

Solubility: sol most organic solvents, including ether, dichloromethane, methanol, acetonitrile.

Preparative Methods: prepared by several methods.[2] The highest yielding and most commonly used method is vacuum pyrolysis of the sodium salt of the tosylhydrazone derived from benzaldehyde.[3] In this preparation, the solid sodium salt is heated in the absence of solvent to a temperature of 220 °C at 0.1 mmHg. The red phenyldiazomethane that is produced is collected in a receiving flask cooled to -50 °C. It is then distilled at reduced pressure below room temperature and is typically used immediately.

Handling, Storage, and Precautions: can be stored at -80 °C for several months; however, storage at -20 °C leads to substantial decomposition after a few weeks. This material is also potentially explosive. For example, a solution which had been allowed to stand at room temperature for an hour underwent violent decomposition a few minutes after exposure to air. Explosions have also been reported when the distillation is carried out at temperatures higher than 30 °C. For these reasons, extreme care must be observed in the synthesis and use of this compound, with all operations being conducted behind a blast shield in a hood. Diazo compounds, as a class, are toxic and irritating and can be sensitizers. They must be used in a well ventilated fume hood and not come in contact with skin. For a description of the hazards associated with this class of compounds, see the handling and storage precautions listed for ***Diazomethane***

Alkylation of Heteroatoms.

As with diazomethane, the most widely used feature of the chemistry of phenyldiazomethane is the alkylation of carboxylic acids. The reaction occurs upon addition of the diazoalkane to the carboxylic acid. The only byproduct is N_2, thus reducing the workup to simple solvent removal. The reaction requires the protonation of the diazoalkane on carbon by the carboxylic acid to give the corresponding benzyl diazonium salt. This then undergoes nucleophilic attack by the carboxylate to give the benzyl ester and N_2. This method has been used to protect carboxylic acids as their benzyl esters. Liberation of the acid can be accomplished by hydrogenolysis, making this a useful reagent for the

protection of carboxylic acids which are base sensitive and cannot tolerate saponification to liberate the acid. This method is compatible with a variety of functional groups such as ketones, amides, alcohols (eq 1),[4] imines, sulfides (eq 2),[5] nitro groups (eq 3),[6] and other nonacidic functional groups.

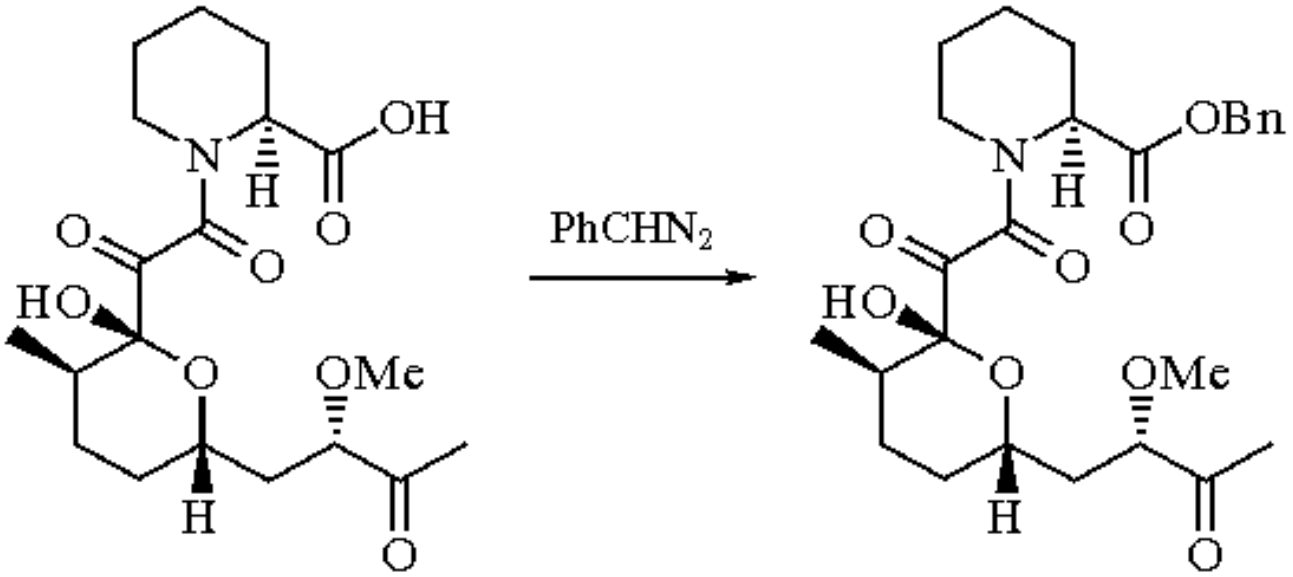

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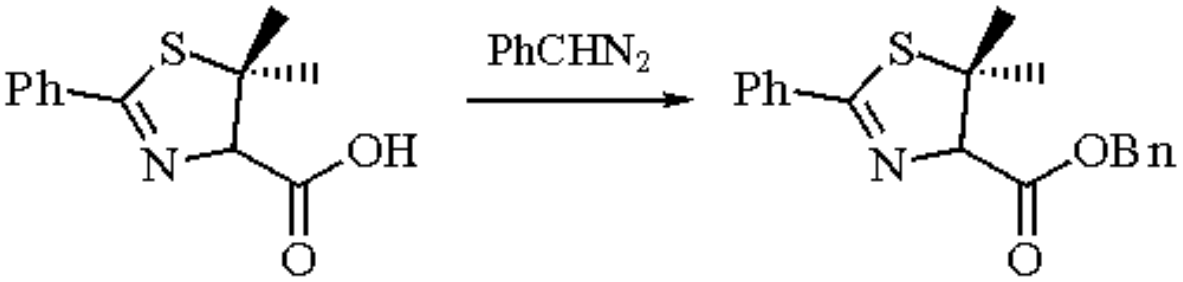

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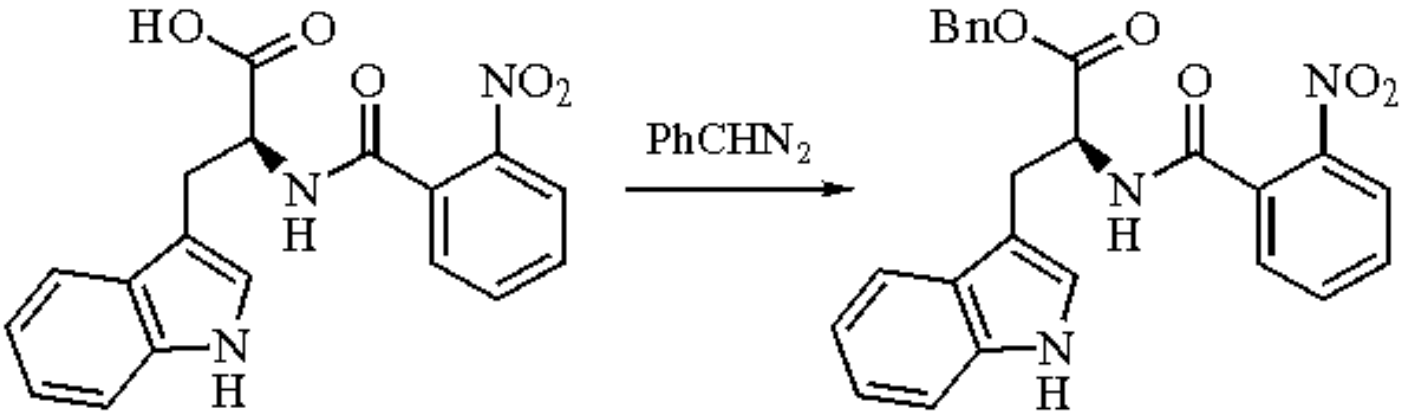

(3)

Other acidic functional groups are also alkylated with phenyldiazomethane. Thus, phosphoric acid esters (eq 4)[7] and isoxazoles (eq 5)[8] readily undergo esterification with phenyldiazomethane. In the case of the isoxazole, a mixture of *N*-alkylated and *O*-alkylated products is observed. As with diazomethane, less acidic functional groups require the addition of a catalyst to promote the reaction. ***Tetrafluoroboric Acid*** is an effective catalyst for the alkylation of alcohols and amines (eqs 6 and 7).[9] Amines react more slowly under these conditions, thus enabling preferential reaction at the hydroxyl group of molecules containing both functional groups. Another catalyst which has been used to benzylate alcohols is ***Tin(II) Chloride***.[10] This reagent is only effective for the monoalkylation of 1,2-diols (the reaction can even be carried out in methanol as a cosolvent) and proceeds in moderate to low yield.

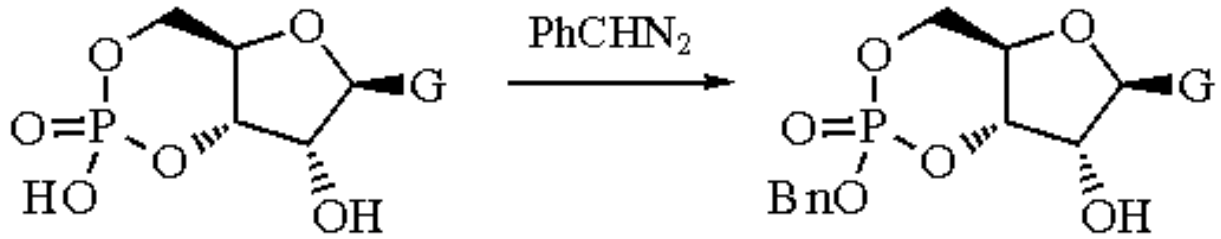

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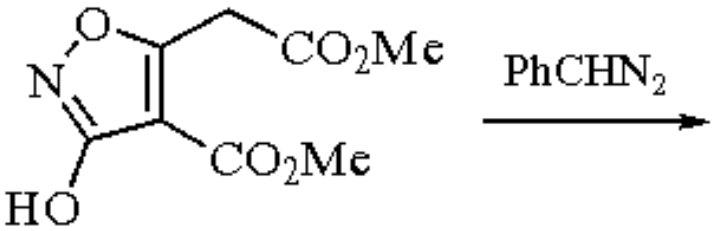

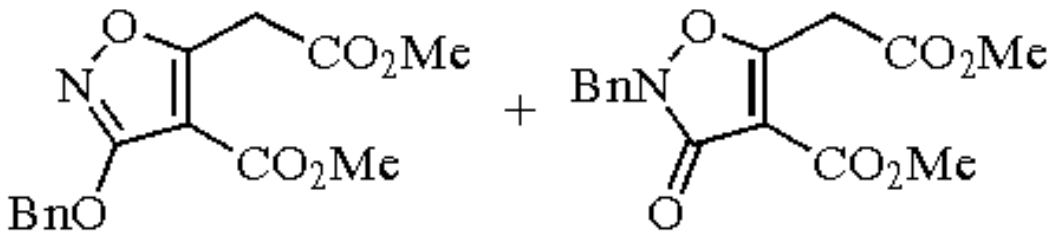

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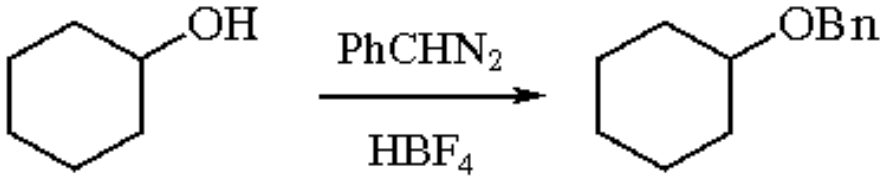

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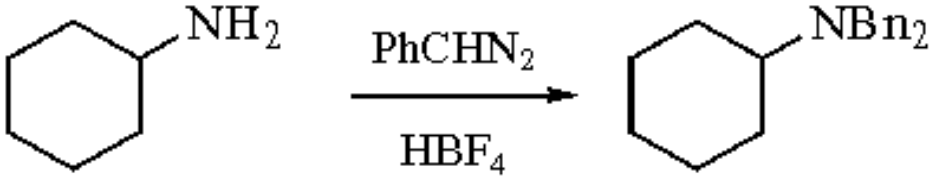

(7)

Cycloadditions.

As with other diazoalkanes, phenyldiazomethane undergoes cycloadditions with alkenes to provide pyrazolines.[11] Upon heating, pyrazolines extrude N_2 and provide the corresponding cyclopropane. In cases where the alkene is substituted with a TMS group, the product pyrazoline can undergo loss of TMS with concomitant extrusion of N_2 to provide the corresponding phenyl substituted β,γ-unsaturated ester (eq 8).[12] This is not a general reaction of diazoalkanes but one which works well only with certain reagents, such as phenyldiazomethane. Phenyldiazomethane has also been used to synthesize cyclopropanes from alkenes. The reaction can be performed photochemically[13] or by using metal complexes such as Rh^{II} or ***Zinc Bromide*** as catalysts.[14] Interestingly, both reactions provide the *cis*-substituted cyclopropanes as the major product (eqs 9 and 10) in varying ratios. The metal-catalyzed reaction using Rh^{II} complexes works well only for very electron rich alkenes such as vinyl ethers, while the method using zinc halides

typically utilizes an excess of the alkene. Finally, aziridines have been synthesized by the addition of phenyldiazomethane to imines in the presence of ***Zinc Iodide***.[15] The yields depend on the structure of the imine and range from poor (9%) to good (74%) with typical values being in the 50% range. This is not a general reaction of diazoalkanes and is not successful with diazomethane, ethyl diazoacetate, diazoacetonitrile, or dimethyl diazomalonate.

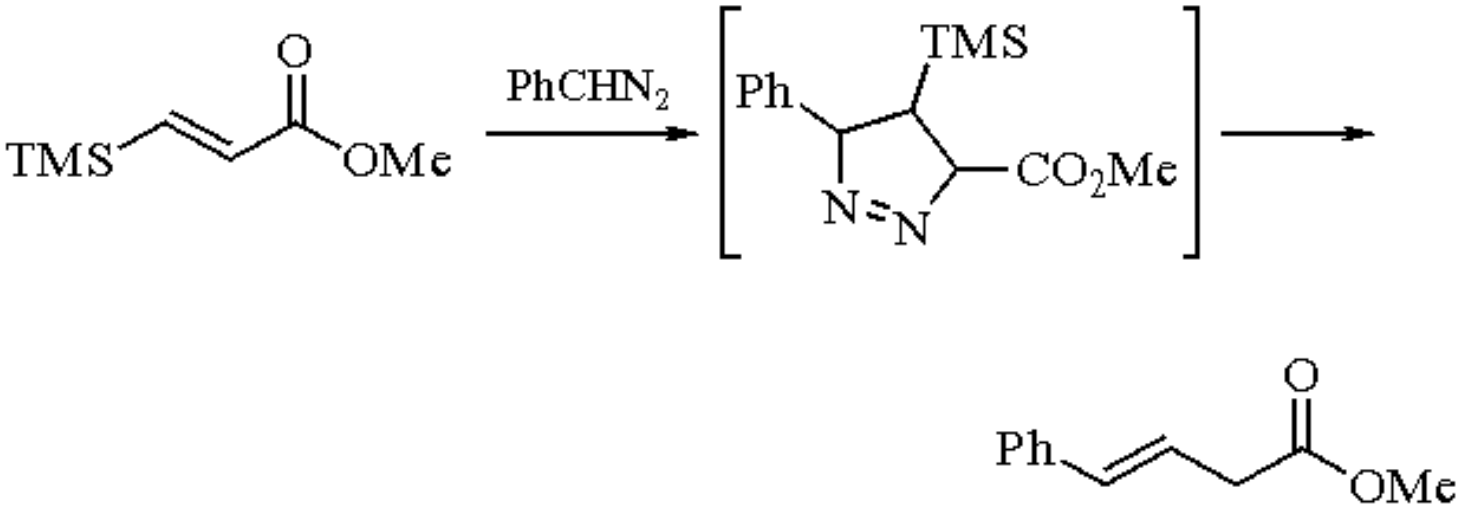

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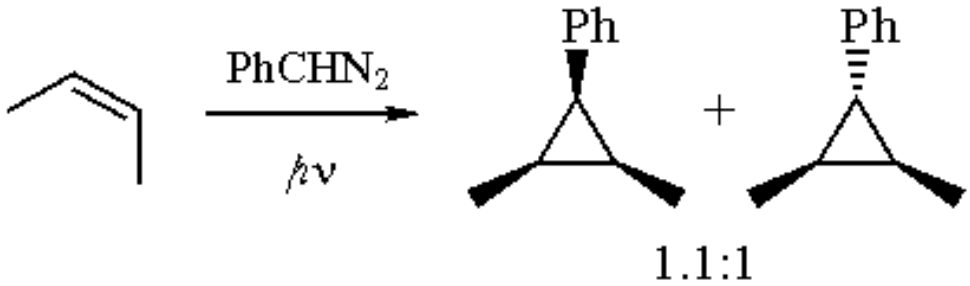

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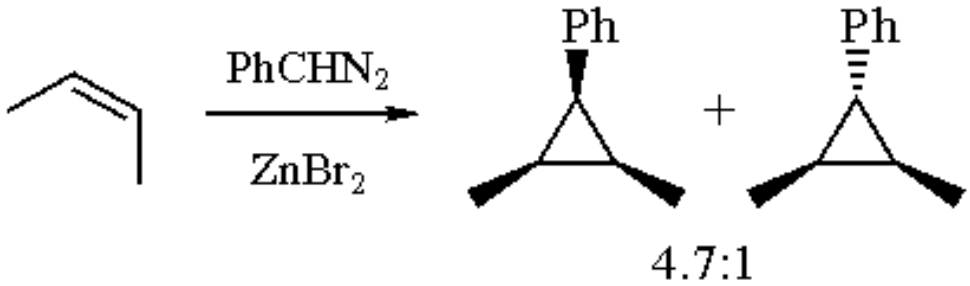

(10)

Homologation.

Phenyldiazomethane has been used in the homologation of aldehydes (eq 11). The reaction requires the addition of ***Lithium Bromide*** and gives good yields with a variety of aldehydes, with the exception of α,β-unsaturated aldehydes. Other lithium halides are not as effective as lithium bromide, and other alkali metals are ineffective.[16]

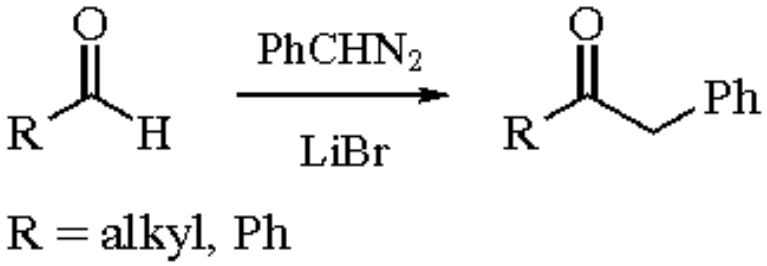

(11)

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5-Phenyl-5*H*-benzophosphindole

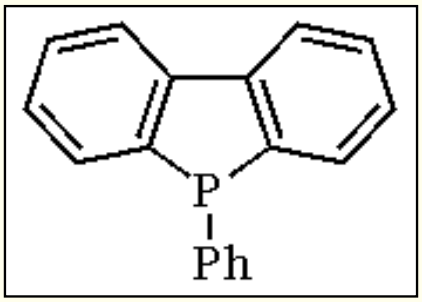

[1088-00-2] · $C_{18}H_{13}P$ · 5-Phenyl-5*H*-benzophosphindole · (MW 260.28)

(synthesis of phosphorus compounds required for Wittig reactions;[1] ring expansion to the dibenzophosphorin system;[2] synthesis of ligands used in asymmetric hydroformylation,[3a-c] hydrosilylation,[4] and hydrogenation[3a,5])

Alternate Name: 5-phenyldibenzophosphole.

Physical Data: mp 95-97 °C.[6]

Solubility: sol THF, benzene.

Form Supplied in: not commercially available.

Preparative Methods: prepared in one step from commercially available tetraphenylphosphonium bromide which has been vacuum dried at 100 °C prior to use.[6] *Drying:* no particular requirements.

Handling, Storage, and Precautions: best kept in an O_2-free container. Slow phosphine oxide formation will occur upon exposure to O_2.

Wittig and Wittig-like Reactions.

Heterolytic C-P bond cleavage of 5-phenyldibenzophosphole (DBP-Ph) with lithium gives lithium dibenzophosphole (DBP-Li). Alkylation of lithium dibenzophosphole with alkyl halides generates the corresponding phosphonium salts. Deprotonation of these phosphonium salts under salt-free conditions (i.e. Na^+ or K^+ derived base) and treatment of the resulting phosphorus ylide with an aldehyde provides *trans*-alkenes predominantly (eq 1).[1] A 5-phenyldibenzophosphole-derived ylide has been used in the synthesis of (+)-dictyopterene C´ for the generation of an intermediate alkene with >99:1 *trans* selectivity.[7]

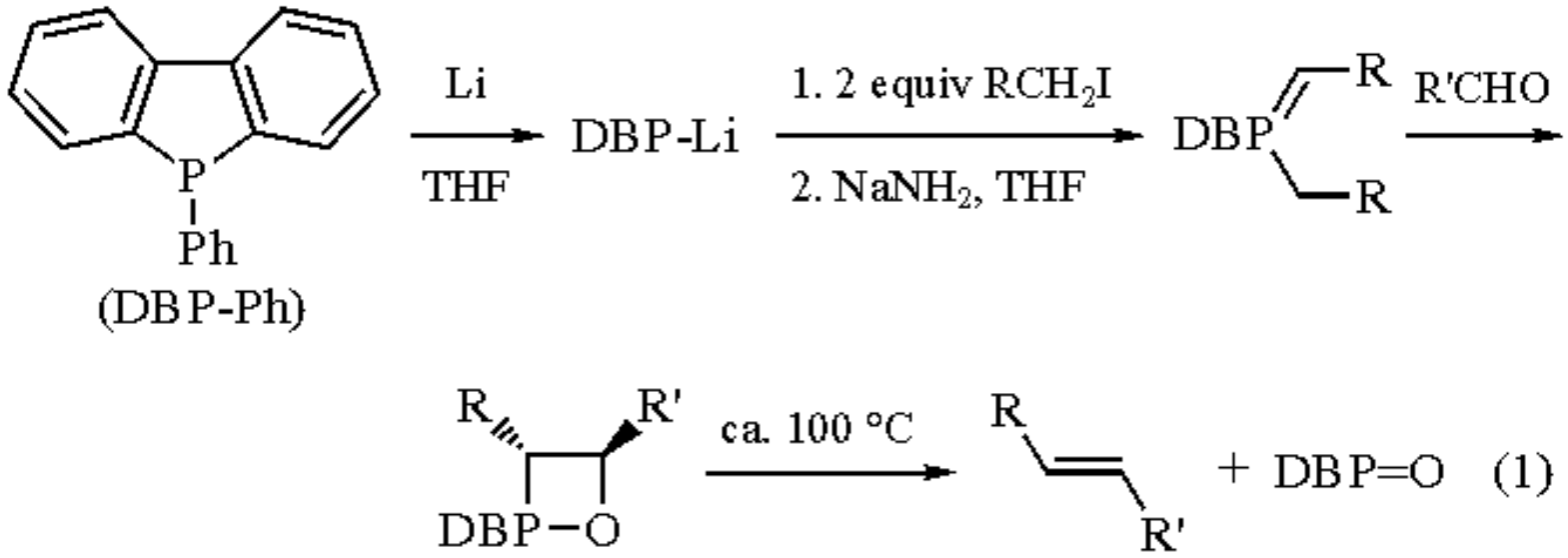

The stability of the intermediate 5-phenyldibenzophosphole-derived oxaphosphetanes has been exploited to show that the only observable intermediates in Wittig reactions are oxaphosphetanes[1] and to demonstrate that betaines are unlikely intermediates in the Wittig reaction.[1c] The reaction of *trans*-stilbene epoxide with DBP-Li (as in eq 1) generates a phosphine oxide.[8] After base treatment of the phosphine oxide, *cis*-stilbene is obtained.

Ring Expansion to Dibenzophosphorin Oxides.

Dibenzophosphorins are obtained after treatment of 5-dibenzophosphole with ***Benzoyl Chloride*** in the presence of ***Triethylamine*** and subsequent hydrolysis (eq 2).[2a,b] A similar reaction occurs with ***Methyl Propiolate***.[2c]

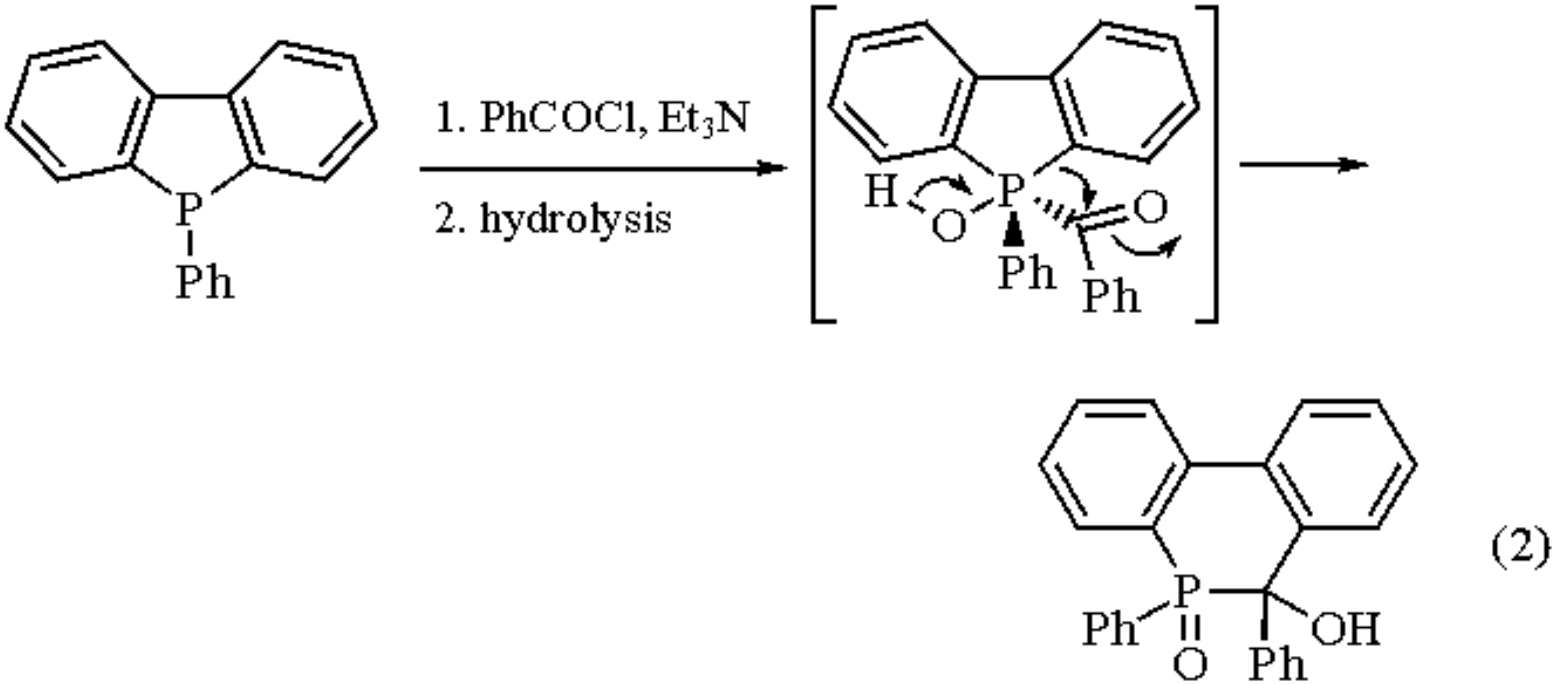

Preparation of Catalysts for Asymmetric Reactions.

5-Phenyldibenzophosphole has been used to prepare bidentate ligands for rhodium[3a] and platinum complexes.[3b-c] Platinum complexes with dibenzophosphole-derived ligands are readily obtained (eq 3), and they can be used as catalysts for the hydroformylation of styrene with high ee's (>95%).[3b] These complexes give the highest ratio of branched to nonbranched aldehydes; however, the conversion is low (eq 4). For rhodium complexes, the 5-phenyldibenzophosphole-based catalysts give the best ee's (40%) in the hydroformylation reaction.[3a]

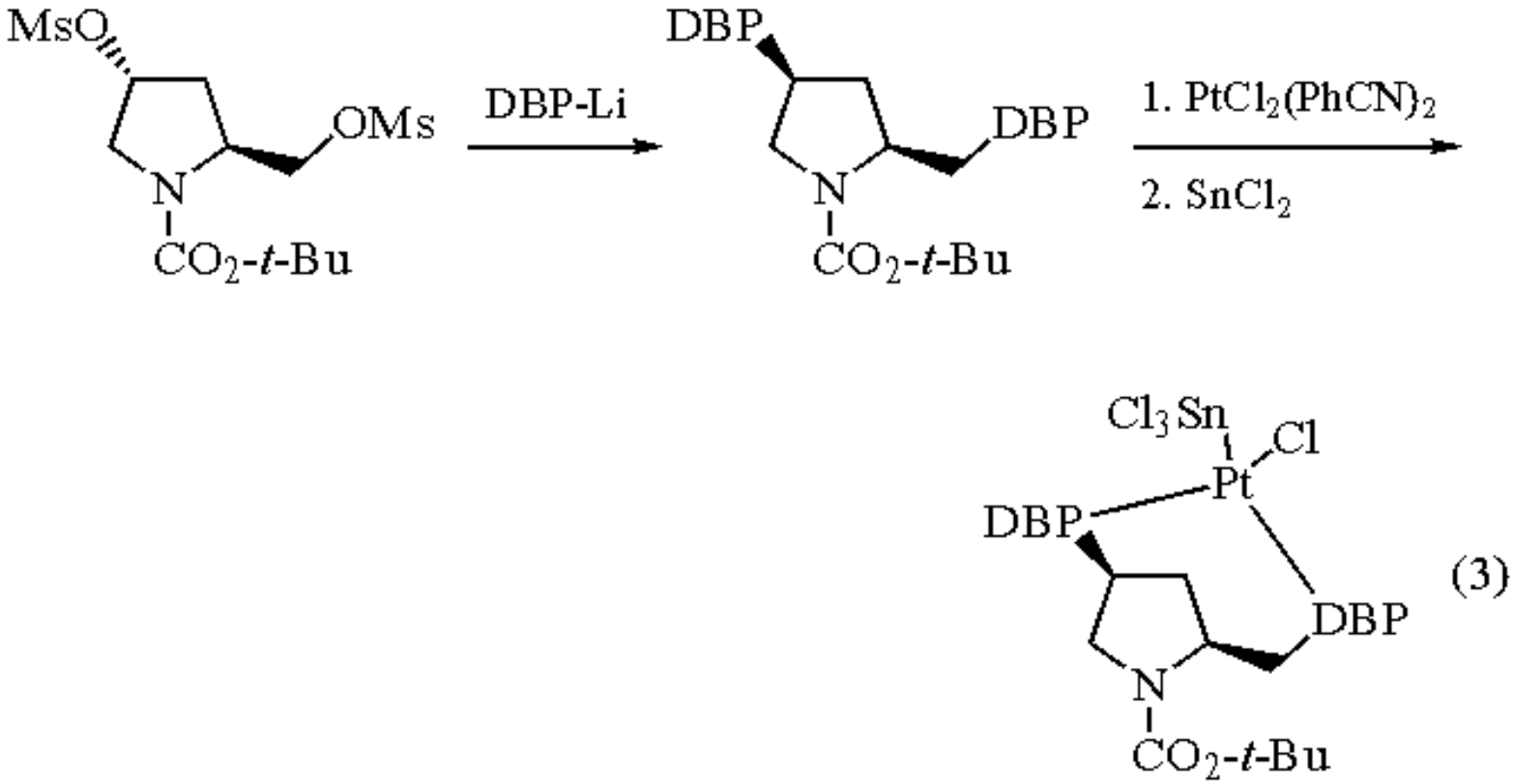

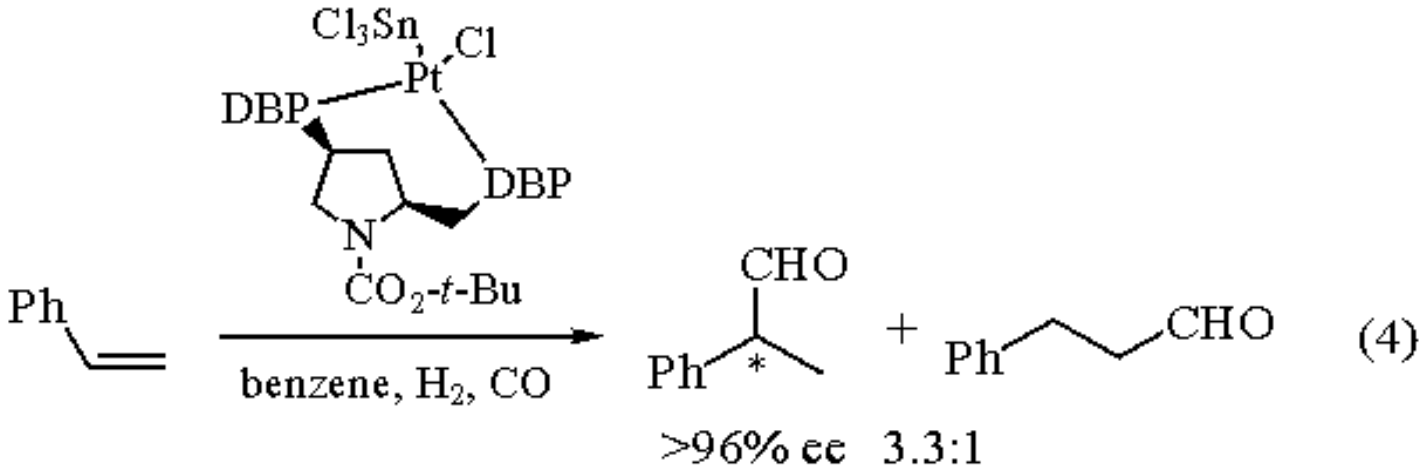

Other alkenes have been hydroformylated with poor to average ee's with similar 5-phenyldibenzophosphole-derived platinum complexes.[3c] A rhodium catalyst with 5-phenyldibenzophosphole ligands does not increase the diastereoselectivity during hydrosilylation of 4-*t*-butylcyclohexanone (eq 5).[4] Hydrogenation of α-acetamidocinnamic acid[3a,5] and 2-phenyl-1-butene[3a] with 5-phenyldibenzophosphole-derived rhodium complexes gives poor ee's (eq 6).

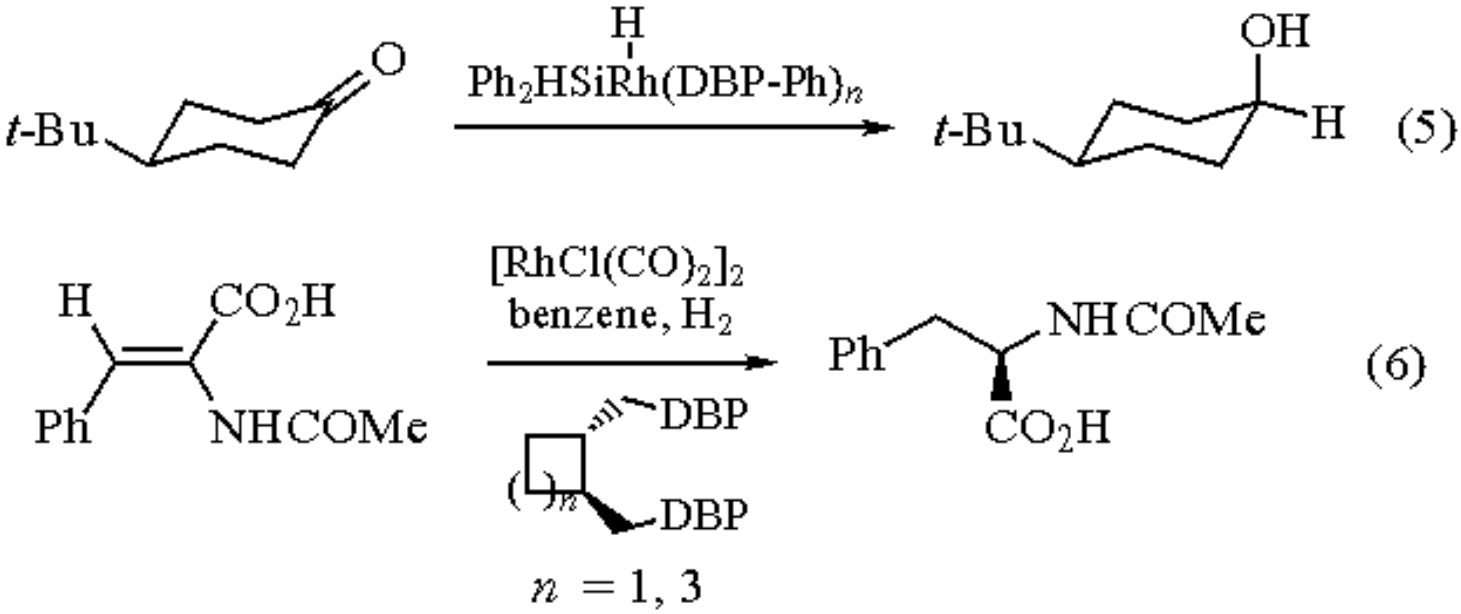

Related Reagents.

Triphenylphosphine.

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1. (a) Vedejs, E.; Marth, C. *TL* **1987**, *28*, 3445. (b) Vedejs, E.; Marth, C. F.; Ruggeri, R. *JACS* **1988**, *110*, 3940. (c) Vedejs, E.; Marth, C. F. *JACS* **1990**, *112*, 3905.
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Phenyl Dichlorophosphate

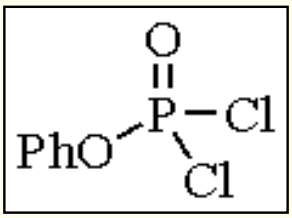

[770-12-7] · $C_6H_5Cl_2O_2P$ · Phenyl Dichlorophosphate · (MW 210.98)

(DMSO activation for Pfitzner-Moffatt oxidation;[1] activation of carboxylic acids for acylation of amine, alcohol, and azide nucleophiles;[4-7] acetal and thioacetal cleavage;[8] phosphorylating agent[10])

Alternate Names: PDCP; phenyl phosphorochloridate.

Physical Data: bp 241-243 °C; *d* 1.412 g cm^{-3}.

Solubility: sol ethyl acetate (50 mg mL^{-1}), most organic solvents.

Form Supplied in: colorless liquid; commercially available.

Purification: redistil under reduced pressure.

Handling, Storage, and Precautions: corrosive; irritant; moisture sensitive; incompatible with strong bases.

Moffatt Oxidation of Alcohols.

The high reactivity of phosphorus-containing compounds towards oxygen functionalities makes them attractive candidates for ***Dimethyl Sulfoxide*** (DMSO) activation in the Pfitzner-Moffatt oxidation of alcohols.[1] Phenyl dichlorophosphate has given better results than other phosphorus-containing compounds such as ***Diphenyl Phosphorochloridate***, ***Diethyl Phosphorochloridate***, ***Phosphorus Oxychloride***, and ***Phosphorus(III) Chloride***.[2] Comparison studies with ***Oxalyl Chloride*** show that the latter is more prone to give chlorine-containing byproducts. The complex (**1**) produced from PDCP and DMSO is believed to be involved as the oxidant for the efficient conversion of primary and secondary alcohols to the corresponding aldehydes and ketones, respectively. A salient feature of the procedure (eq 1) lies in its operational simplicity, low temperatures (20 °C or below), and generally high yields (75-95%).

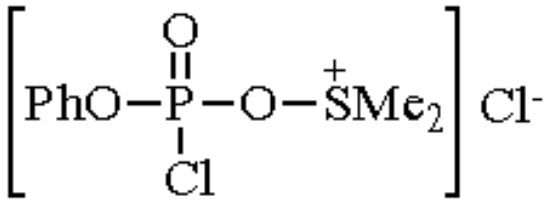

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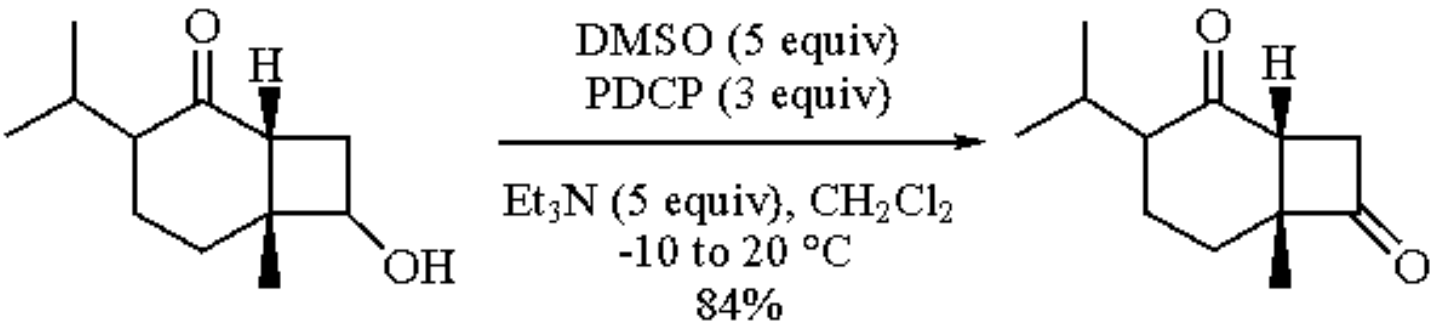

(1)

In the oxidation of 1-octadecanol using Swern conditions, the starting alcohol is recovered intact, whereas octadecanal is formed in 77% yield after 45 min using PDCP. Complex (**1**) has also been used as an oxidant for the conversion of primary and secondary benzylic amines to the corresponding carbonyl compounds (eq 2) in a process that involves formation and subsequent hydrolysis of intermediate imines.[3] The oxidative deamination process is apparently general for benzylic amines and yields are good (57-80%) with one exception, 1-indanone (28%). Nonbenzylic amines failed to give the corresponding carbonyl derivatives under the prescribed conditions.

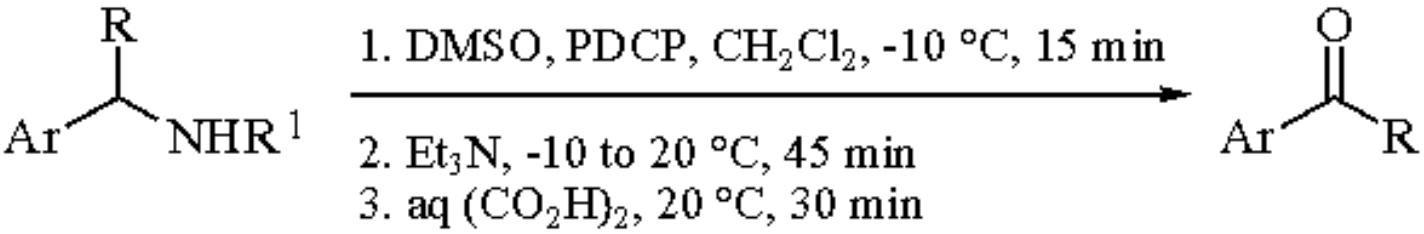

(2)

β-Lactam Formation.

When β-amino acids are treated with equimolar amounts of PDCP in acetonitrile at room temperature for 30-40 h, cyclization proceeds smoothly to give high yields (78-95%) of β-lactams (eq 3).[4]

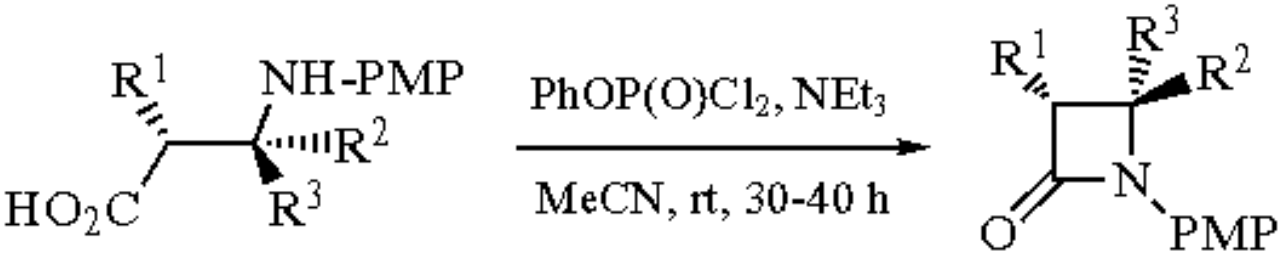

(3)

The reaction works well with both *erythro*- and *threo*-β-amino acids to give the corresponding *cis*- and *trans*-β-

lactams, respectively. Colvin[5] reported an efficient method for the preparation of chiral *cis*-3,4-disubstituted β-lactams (eq 4), based on reaction between imines from homochiral protected lactaldehydes and furfurylamine and PDCP activated carboxylic acid derivatives.

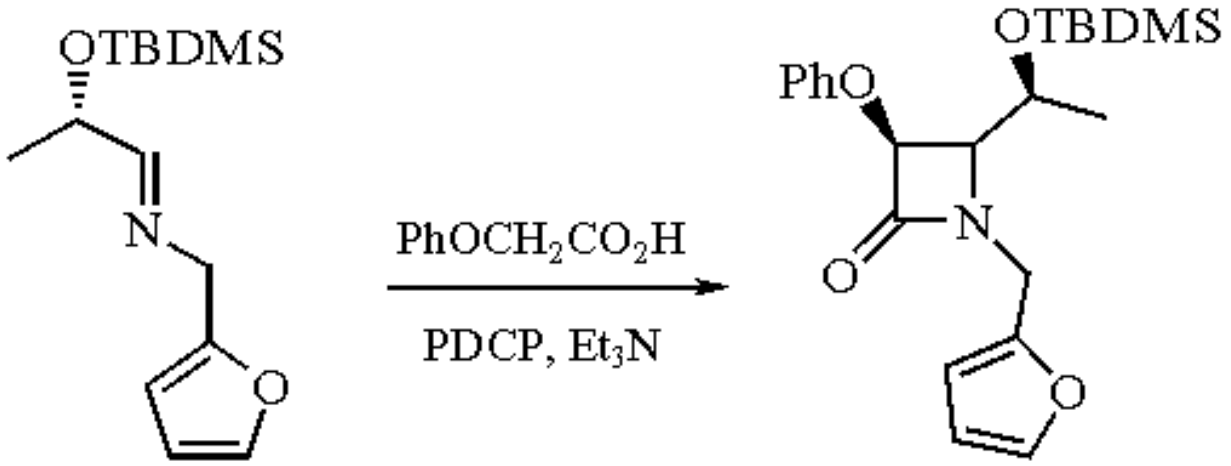

(4)

Esterification.

Activation of carboxylic acids via use of the PDCP/DMF complex is particularly useful for the esterification of substituted malonic acids which easily undergo decarboxylation. For example, the resolution of racemic cyanophthalimido acetic acid (**2**) by reaction with a chiral amine leads to partial or total decarboxylation in basic medium (eq 5). On the other hand, when PDCP and a chiral alcohol such as ***(S)-Ethyl Lactate*** are used, the desired diastereomers are obtained in high yields (90%).[6]

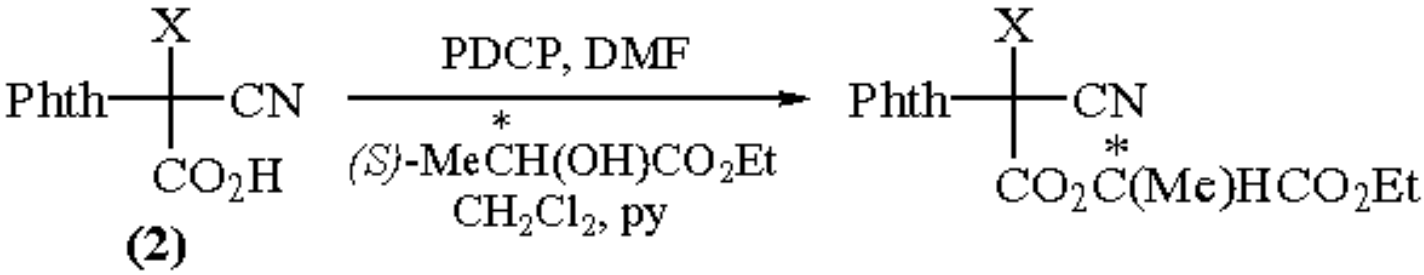

(5)

X = H, Me, OMe
Phth = Phthalimido

Acyl azides have also been prepared by reaction of a carboxylic acid or the potassium salt with PDCP, ***Pyridine***, ***Sodium Azide***, and ***Tetra-n-butylammonium Bromide*** in CH_2Cl_2 at room temperature.[7]

Dethioacetalization.[8]

The combination of PDCP and ***Sodium Iodide*** converts acetals to the corresponding aldehydes or ketones but has little, if any, effect on thioacetals. However, the reagent obtained by addition of DMF converts thioacetals into the corresponding carbonyl compounds at room temperature in 1-17 h in 70-95% yield.

Other Applications.

Primary alcohols are converted to alkyl chlorides by reaction with PDCP at 80 °C. Tertiary alcohols are dehydrated by PDCP to alkenes.[9] PDCP serves as an effective phosphorylating agent in the synthesis of L-glycerylphosphorylethanolamine (**3**),[10] an intermediate in the preparation of α-lecithins and α-cephalins. Cyclic β-diketones have been converted to β-chloro-α,β-enones by reactions with PDCP and LiH in the presence of LiCl (eq 6).[11]

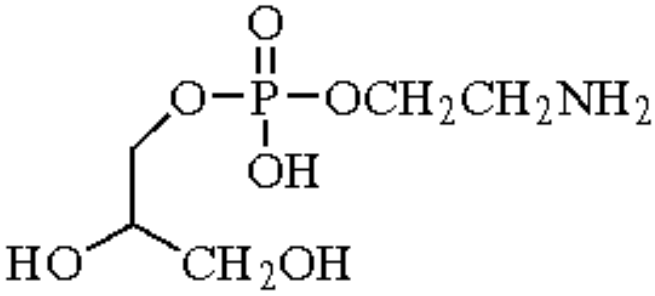

(3)

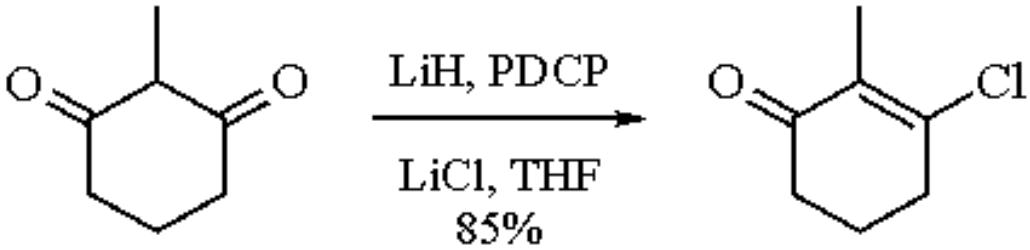

(6)

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Phenyl Dichlorophosphite[1]

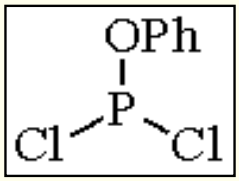

[3426-89-9] · $C_6H_5Cl_2OP$ · Phenyl Dichlorophosphite · (MW 194.98)

(strong phosphorylating agent, used in forming phosphite and phosphate triesters[2] and phospholes;[3] reagent in forming polymers;[4] dehydration of amides[5])

Physical Data: bp 90 °C/11 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: liquid; not commercially available.

Preparative Methods: phenyl dichlorophosphite was first identified in the reaction between ***Phosphorus(III) Chloride*** and phenol (eq 1).[1] However, the yield is low due to formation of side-products, bis- and tris-phosphite esters. Later, phenyl dichlorophosphite was formed in the reaction of phosphorus trichloride and triphenyl phosphite (eq 2), but, again, yields were not particularly high,[8] even when the reaction was later optimized.[9] By introducing $MgCl_2$ into the former reaction and carefully monitoring the reaction by IR spectroscopy, phenyl dichlorophosphite is formed in high yield (eq 3).[10]

$$PCl_3 + PhOH \longrightarrow \underset{25\text{-}50\%}{PhOPCl_2} + (PhO)_2PCl + (PhO)_3P \qquad (1)$$

$$PCl_3 + (PhO)_3P \underset{47\%}{\overset{150\ ^\circ C}{\rightleftharpoons}} PhOPCl_2 \qquad (2)$$

$$PCl_3 + PhOH \xrightarrow[84\%]{MgCl_2} PhOPCl_2 \qquad (3)$$

Purification: redistil under reduced pressure.[6]

Handling, Storage, and Precautions: irritant and moisture sensitive; incompatible with strong oxidizing agents and bases.[7]

Synthesis of Organophosphorus Compounds.

The main use of phenyl dichlorophosphite is in the formation of phosphorus-containing compounds, particularly phosphite triesters (eq 4). These compounds are synthesized by adding alcohols to phenyl dichlorophosphite in the presence of a tertiary amine.[11] However, use of one equivalent of each reagent produces phosphate esters instead (eq 5).[11] Two equivalents of alcohol and base are needed to produce phosphite triesters (eq 4).

$$PhOPCl_2 + 2\,ROH + 2\,Et_3N \xrightarrow[33\%]{} PhOP(OR)_2 \qquad (4)$$

$$PhOPCl_2 + 1\,ROH + 1\,Et_3N \xrightarrow[47\%]{} \text{PhO}\!-\!\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{P}}\!-\!OR \qquad (5)$$

Phosphite triesters carrying three different alkoxy groups are chiral and can be synthesized from phenyl dichlorophosphite under carefully controlled conditions involving the use of a $PtCl_2$ complex (eq 6).[12] The racemic triesters have been resolved via a platinum complex carrying a chiral scalemic ligand.[12]

$$PhOPCl_2 \xrightarrow[\substack{4\text{-}ClC_6H_4OH \\ 51\%}]{\substack{(Z)\text{-}Cl_2Pt(NCPh)_2 \\ 4\text{-}MeC_6H_4OH}} (Z)\text{-}Cl_2Pt[(\pm)\text{-}(4\text{-}MeC_6H_4O)(4\text{-}ClC_6H_4O)POPh \qquad (6)$$

Cyclic phosphorus compounds (phospholes) can be synthesized from phenyl dichlorophosphite with α-hydroxy acids (eq 7),[13] α-amino acids (eq 7),[13] and dilithiated benzyl alcohol (eq 8).[3]

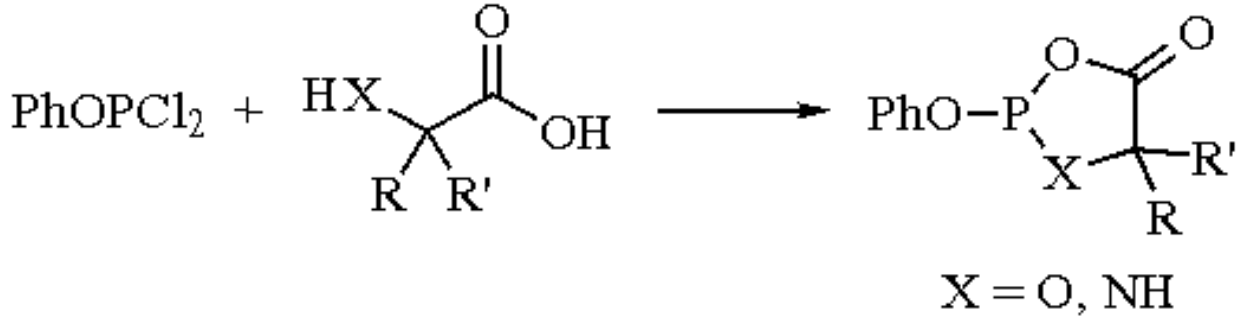

(7)

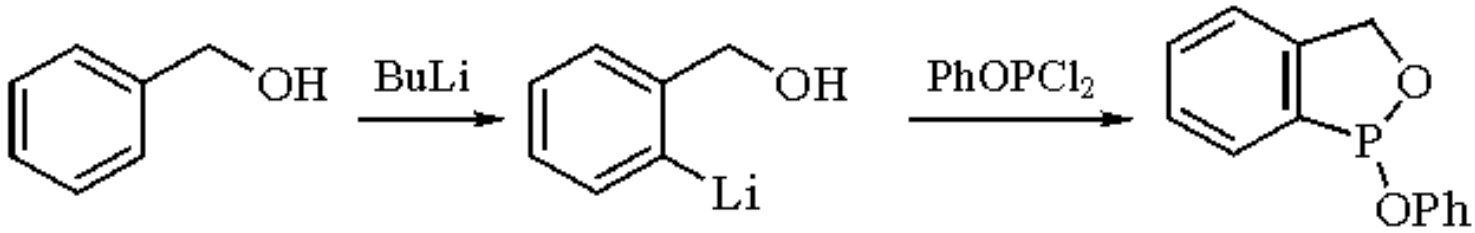

(8)

Phenyl dichlorophosphite can also be used to synthesize organophosphates by preparing the phosphite triester derivative and either oxidizing it to the phosphate triester[14] (when ozone is used, the isolable intermediate, a trioxaphosphetane, decomposes to give singlet oxygen and the phosphate triester[11a]) or alkylating it with an alkyl halide (eq 9).[15]

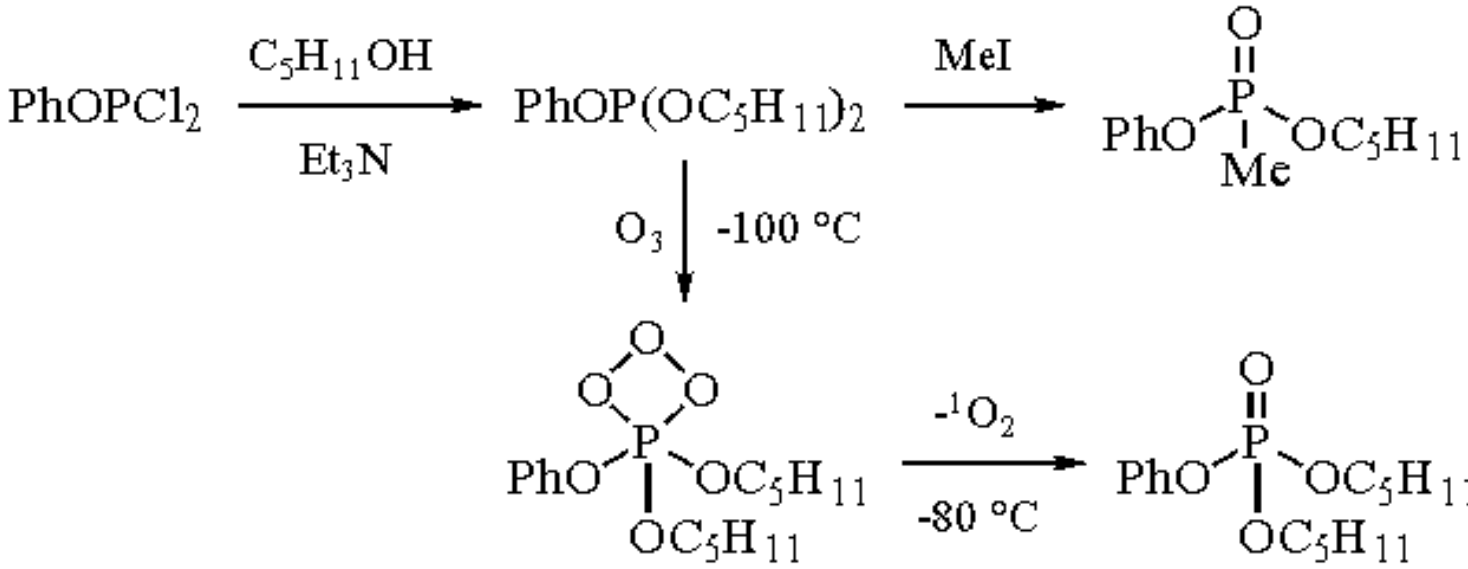

(9)

Phenyl Dichlorophosphite as an Activating Agent.

Phenyl dichlorophosphite has been used in several reactions as an activating agent. Carboxylic acids form symmetrical anhydrides on reaction with phenyl dichlorophosphite;[16] with amines or β-diamines; these form amides[17] or imidazoles,[18] respectively (eq 10). This methodology has been extended to the formation of polyamides/hydrazides from the reaction of diacids with diamines or hydrazines in the presence of phenyl dichlorophosphite.[4]

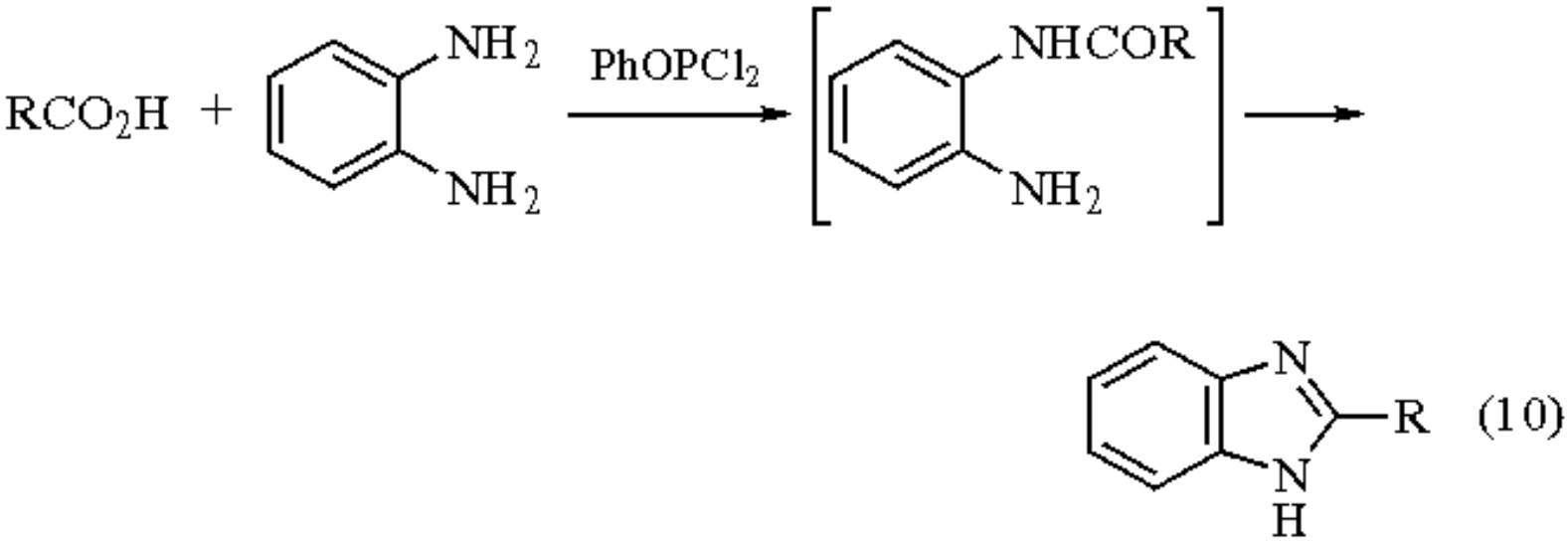

Phenyl Dichlorophosphite as a Dehydrating Agent.

Phenyl dichlorophosphite has also been used with DMF to dehydrate amides to nitriles in high yields (eq 11).[5]

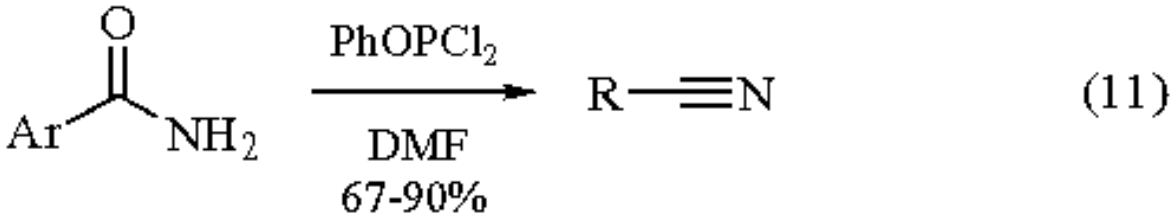

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(Phenyldimethylsilyl)methoxymethyl Chloride

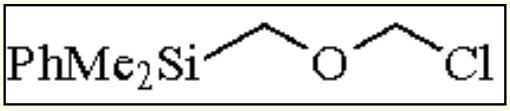

[128784-94-1] · $C_{10}H_{15}ClOSi$ · (Phenyldimethylsilyl)methoxymethyl Chloride · (MW 214.79)

(reagent for the protection of hydroxyl groups[1])

Alternate Name: SMOM-Cl.

Solubility: sol most organic solvents.

Preparative Method: prepared by a three-step sequence starting from (chloromethyl)dimethylphenylsilane. Displacement with NaOAc followed by reduction with ***Lithium Aluminum Hydride*** furnishes $PhMe_2SiCH_2OH$. Subsequent reaction with ***Formaldehyde-Hydrogen Chloride*** provides the crude chloride (>90% pure) which can be used without further purification.

Handling, Storage, and Precautions: although stability and toxicological data for this compound are not available, it is expected to be readily hydrolyzed, toxic, and carcinogenic.

Protection of Hydroxyl Groups.

Hydroxyl groups on sugars may be protected as (phenyldimethylsilyl)methoxymethyl (SMOM) ethers using $PhMe_2SiCH_2OCH_2Cl$ and ***Diisopropylethylamine*** in MeCN (76-91%). Removal of the SMOM group is effected by treatment with ***Peracetic Acid***/KBr in AcOH/NaOAc (82-92%) (eq 1); this presumably proceeds through a Si -> OH conversion[2] and decomposition of the resultant hemiacetal. The SMOM group is stable to hydrogenolysis conditions (H_2, Pd/C), benzylation conditions (NaH, BnBr), fluoride (excess *n*-Bu_4NF in dioxane, 20 °C, 15 h), and base (4 N NaOH, dioxane, MeOH, 20 °C, 8 h). It also survives conditions required to remove an isopropylidene or a trityl group (HOAc, H_2O) (eq 2).

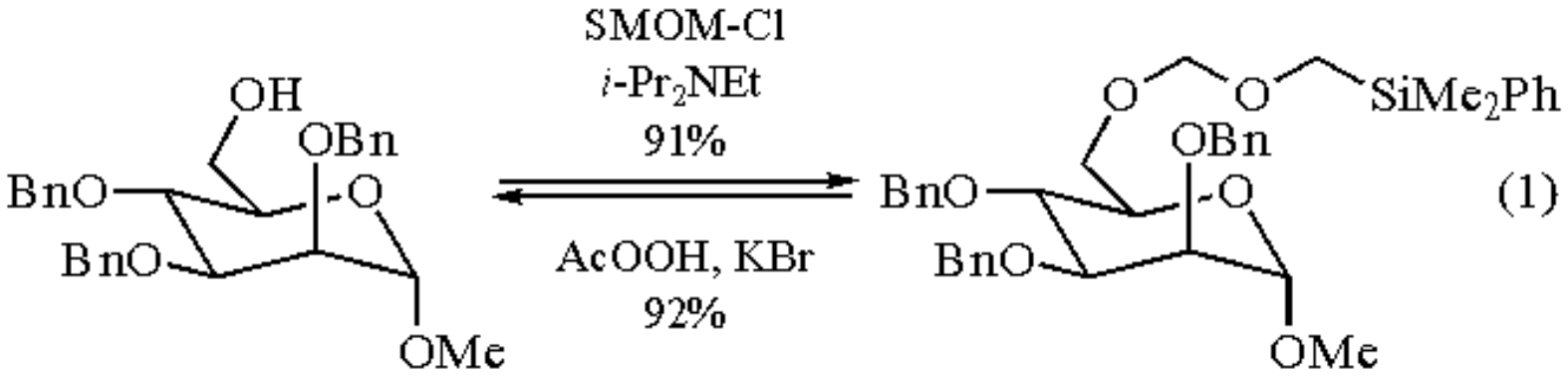

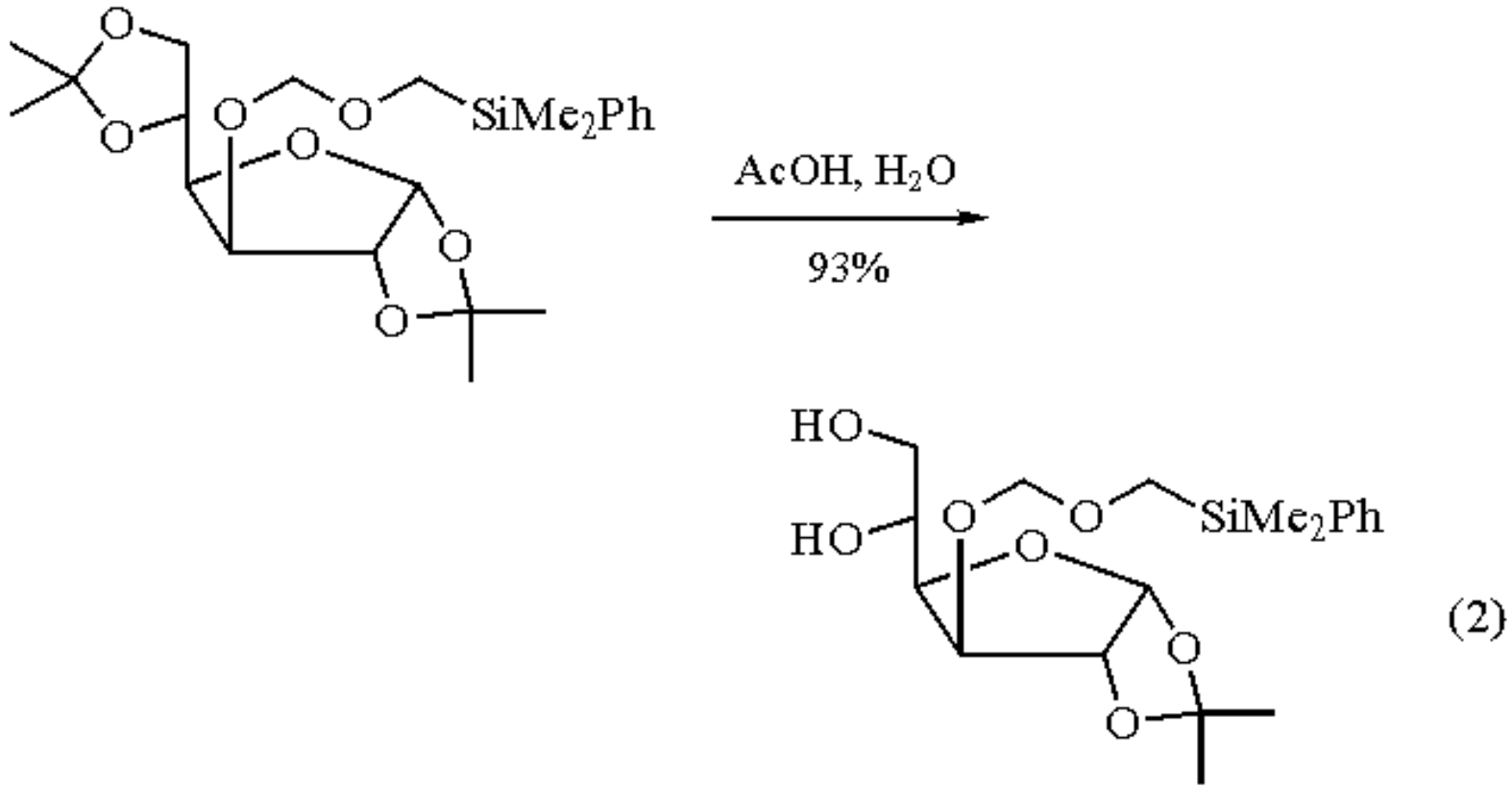

The SMOM group was developed for use in sugar chemistry. It has the advantage of being stable under many reaction conditions including halophilic promoter mediated glycosidation conditions [e.g. $Hg(CN)_2$, $HgBr_2$, MeCN] and being readily removed under mild conditions. It differs from the trimethylsilylethoxymethoxy (SEM) group[3] in its resistance to fluoride cleavage. A closely related function is the phenyldimethylsilyl unit which may be used to protect anomeric hydroxyl groups.[1] It is attached by treatment of a glycosyl halide with phenyldimethylsilylmethanol under glycosidation conditions. It has comparable stability to the SMOM group and is also removed by oxidative cleavage (AcOOH, KBr). ***2-(Trimethylsilyl)ethanol*** has been used in a similar capacity.[4]

Related Reagents.

2-Methoxyethoxymethyl Chloride; ***2-(Trimethylsilyl)ethanol***; ***2-(Trimethylsilyl)ethoxymethyl Chloride***.

---

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1,2-Phenylene Phosphorochloridate

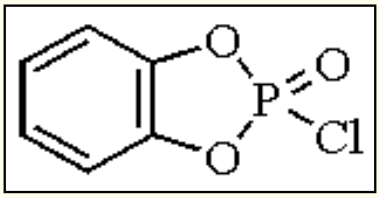

[1449-17-8] · $C_6H_4ClO_3P$ · 1,2-Phenylene Phosphorochloridate · (MW 190.52)

(phosphorylating agent for primary alcohols,[1,2] particularly in nucleoside chemistry[3])

Physical Data: bp 120 °C/9 mmHg; 91 °C/0.9 mmHg.

Solubility: sol most organic solvents; react with alcohols.

Form Supplied in: liquid; commercially available.

Analysis of Reagent Purity: FT-IR.[11]

Preparative Methods: reaction of ***Catechol*** with ***Phosphorus(V) Chloride*** gives the intermediate (**2**) which on warming with ***Acetic Anhydride*** decomposes giving acetyl chloride and 1,2-phenylene phosphorochloridate (**1**) in 88% yield (eq 1).[1]

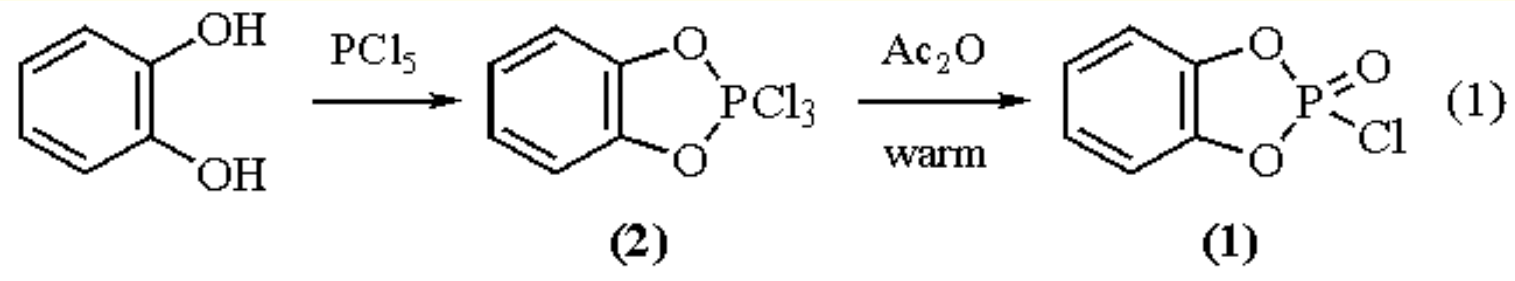

Purification: redistil under reduced pressure.

Handling, Storage, and Precautions: will keep indefinitely in a sealed tube. Harmful and irritant; moisture sensitive. Incompatible with alcohols and water.[4] Use in a fume hood.

Phosphorylation.

1,2-Phenylene phosphorochloridate is a convenient and efficient phosphorylating agent. Reaction with primary alcohols in the presence of base (***Pyridine***) gives the phosphate ester (**3**). This is readily hydrolysed to the *o*-hydroxyphenyl ester

(**4**), which on treatment with ***Bromine*** in neutral aqueous buffer gives the monophosphate ester (**5**) in good yield (eq 2).[2,5]

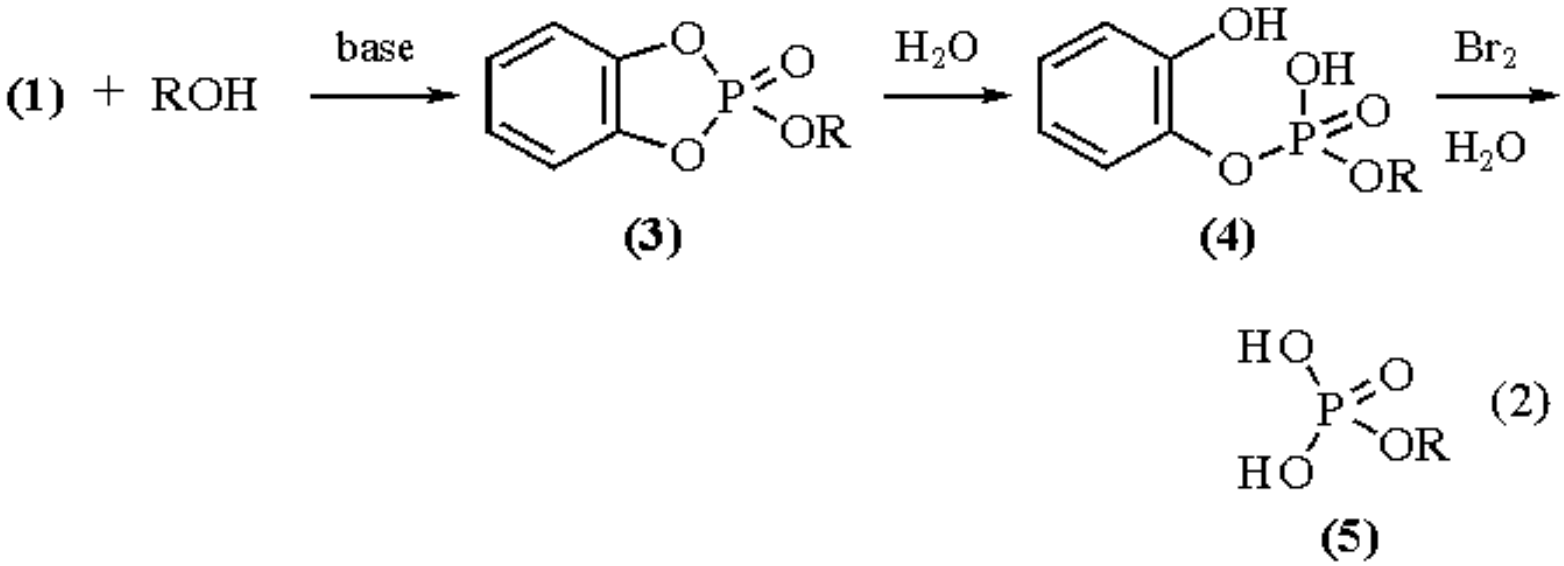

Adams' catalyst[6] has been used as an alternative to bromine in the last step and the use of other oxidative conditions involving periodic acid and ***Lead(IV) Acetate*** has also been reported.[3] Unsaturated alcohols are not compatible with some of the reaction conditions used to cleave (**4**).

The reagent is particularly useful for the phosphorylation of nucleotides (eq 3).[3] Reaction of (**1**) with 2´,3´-*O*-isopropylidene ribonucleosides (**6**) is carried out at room temperature in the presence of ***2,6-Lutidine*** for 3 hours. Addition of water hydrolyses the intermediate phosphotriesters and gives the 5´-*o*-hydroxyphenyl phosphates (**7**) in good yields. This functionality is stable to the acidic conditions required for removal of the isopropylidene group and subsequent treatment with an excess of bromine water gives the 5´-phosphates (**8**) as the sole nucleotide products. For example, with B = adenine, the overall yield for the sequence was 78%.[3] Phosphorylation of a 2´-deoxyribonucleotide using this procedure was successful.[3]

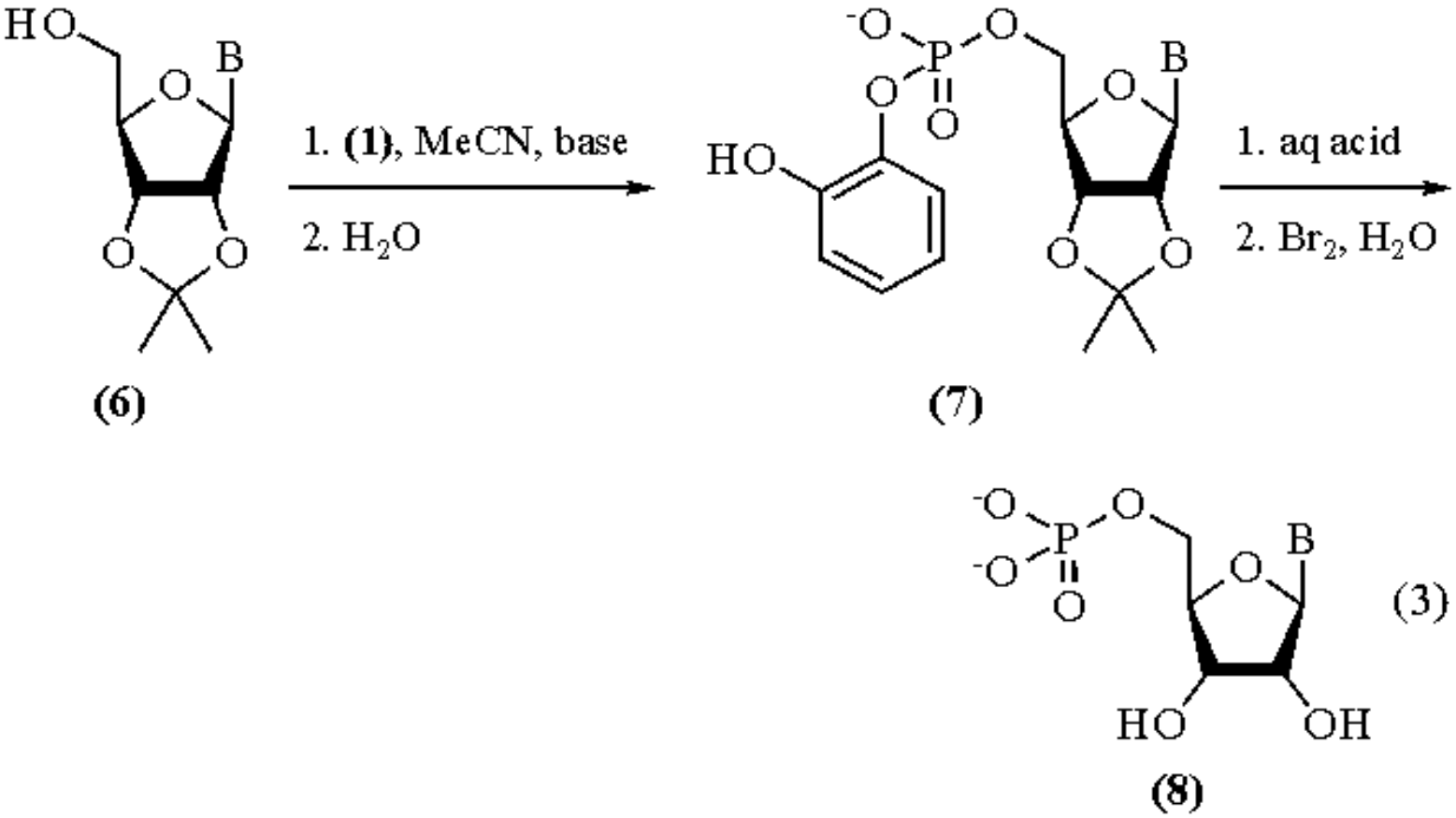

Phosphorylation of Hydrazines.

The reaction of 3-trifluoromethylphenylhydrazine with (**1**) gives the ring-opened monohydrazide (**9**) in 66% yield (eq 4).[7]

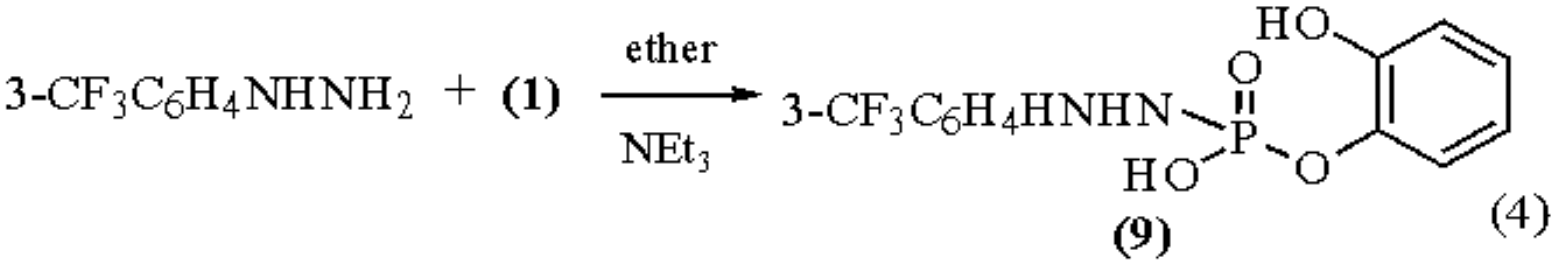

Spirophosphoranes.

Reaction of (**1**) with 1,2-diols, 2-hydroxy acids, or 2-keto acids leads to the formation of spirophosphoranes (**10**) which are in equilibrium with the phosphotriesters (**11**) (eq 5).[8] The use of (**1**) in the synthesis of a hexacovalent phosphate ester has also been reported.[9]

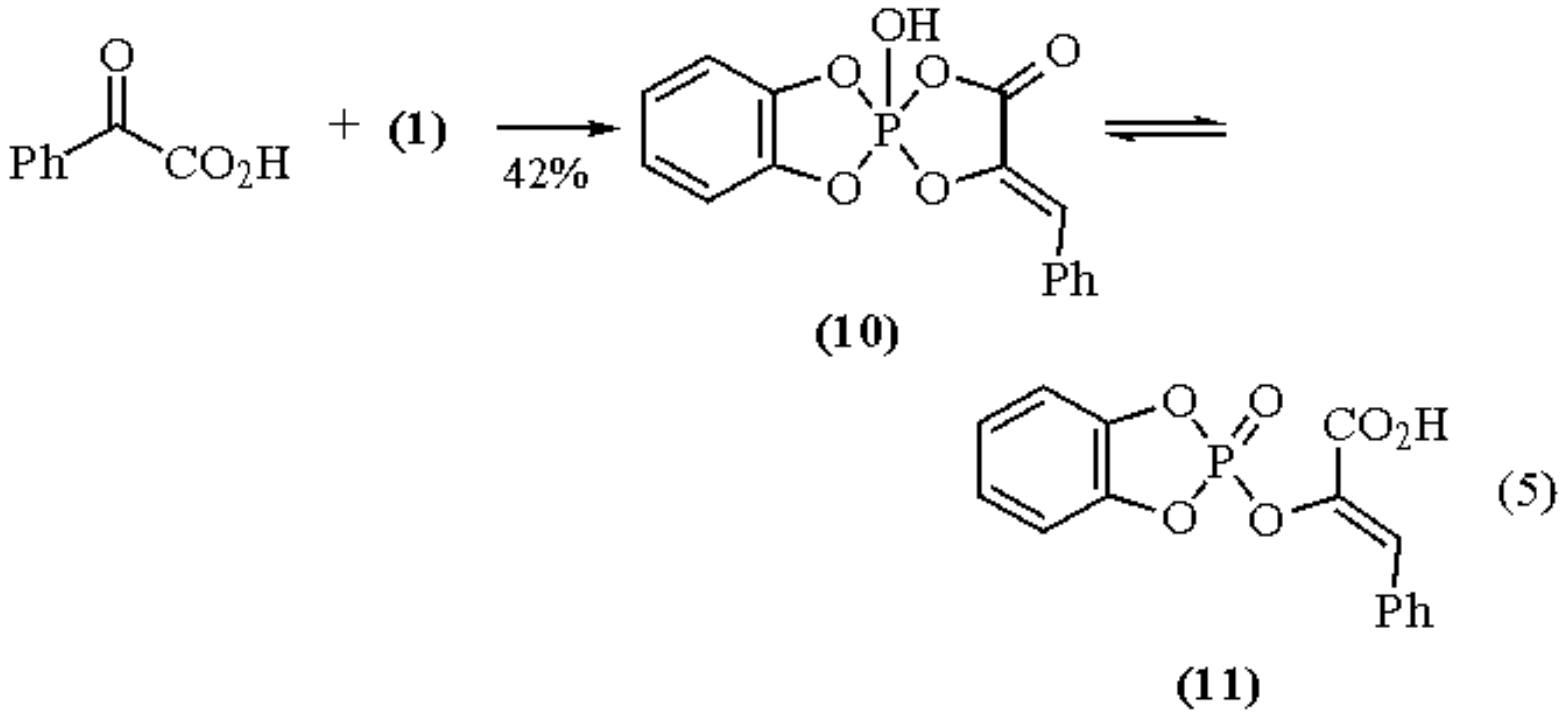

Reaction with Grignard Reagents.

Reaction of (**1**) with a range of aryl Grignard reagents leads to the formation of *o*-hydroxyphenyl phosphinates (**12**) (eq 6).[10]

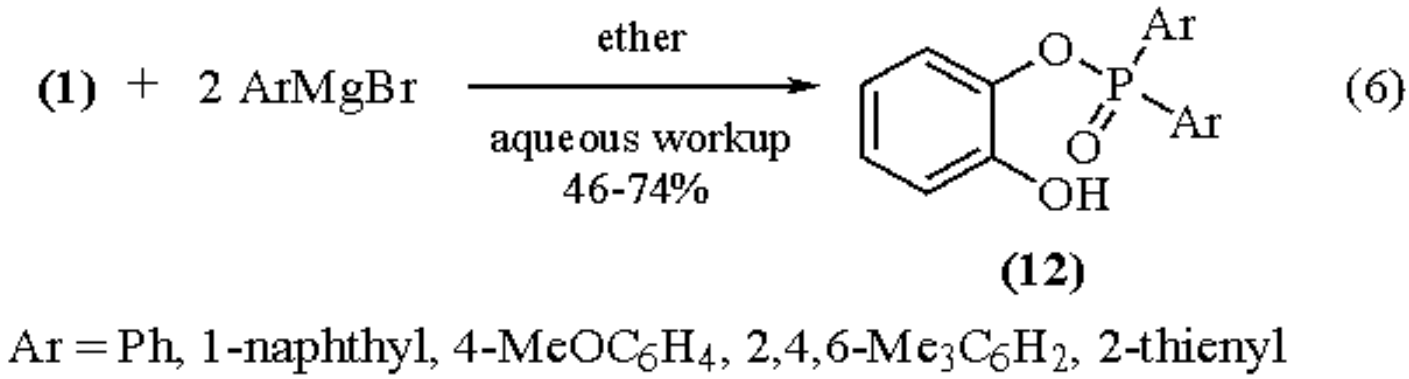

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(*S*)-(-)-5-(α-Phenylethyl)semioxamazide

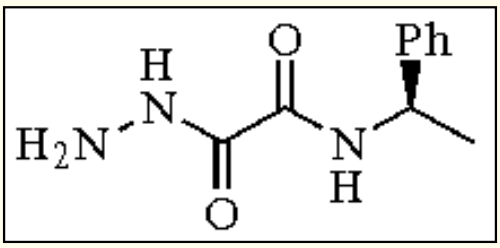

[6152-25-6] · $C_{10}H_{13}N_3O_2$ · (*S*)-(-)-5-(α-Phenylethyl)semioxamazide · (MW 207.26)

(optical resolution of carbonyl compounds[2,3])

Physical Data: $[\alpha]_D$ -103° (*c* 1.0, $CHCl_3$).

Solubility: sol polar aprotic solvents; limited sol hexane, toluene, etc.

Preparative Method: conveniently prepared by sequential addition of (*S*)-(-)-α-phenylethylamine and ***Hydrazine*** to ***Diethyl Oxalate*** (eq 1).[1]

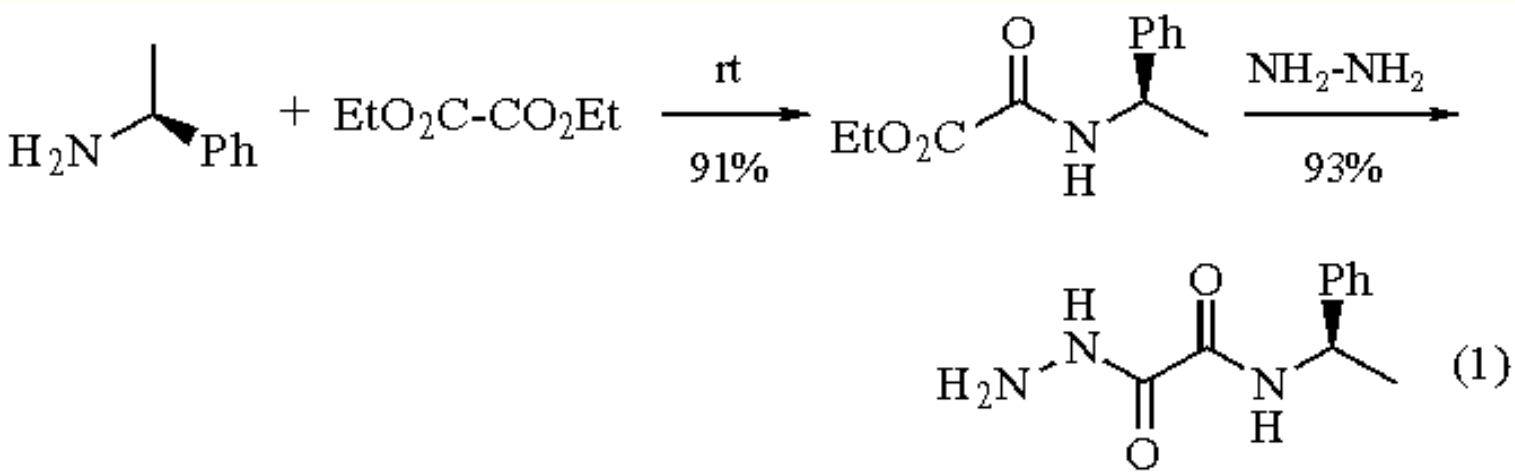

Optical Resolution.

This reagent is commonly used for the optical resolution of various compounds. Racemic spiro[4.4]nonane-1,6-dione was the first compound to be resolved (55% overall yield).[2] The corresponding semioxamazone was obtained in optically active pure form in two or three recrystallizations and hydrolyzed to (-)-(*S*)-spiro[4.4]nonane-1,6-dione in a refluxing methanol-water mixture in the presence of ***Iodine*** (eq 2).

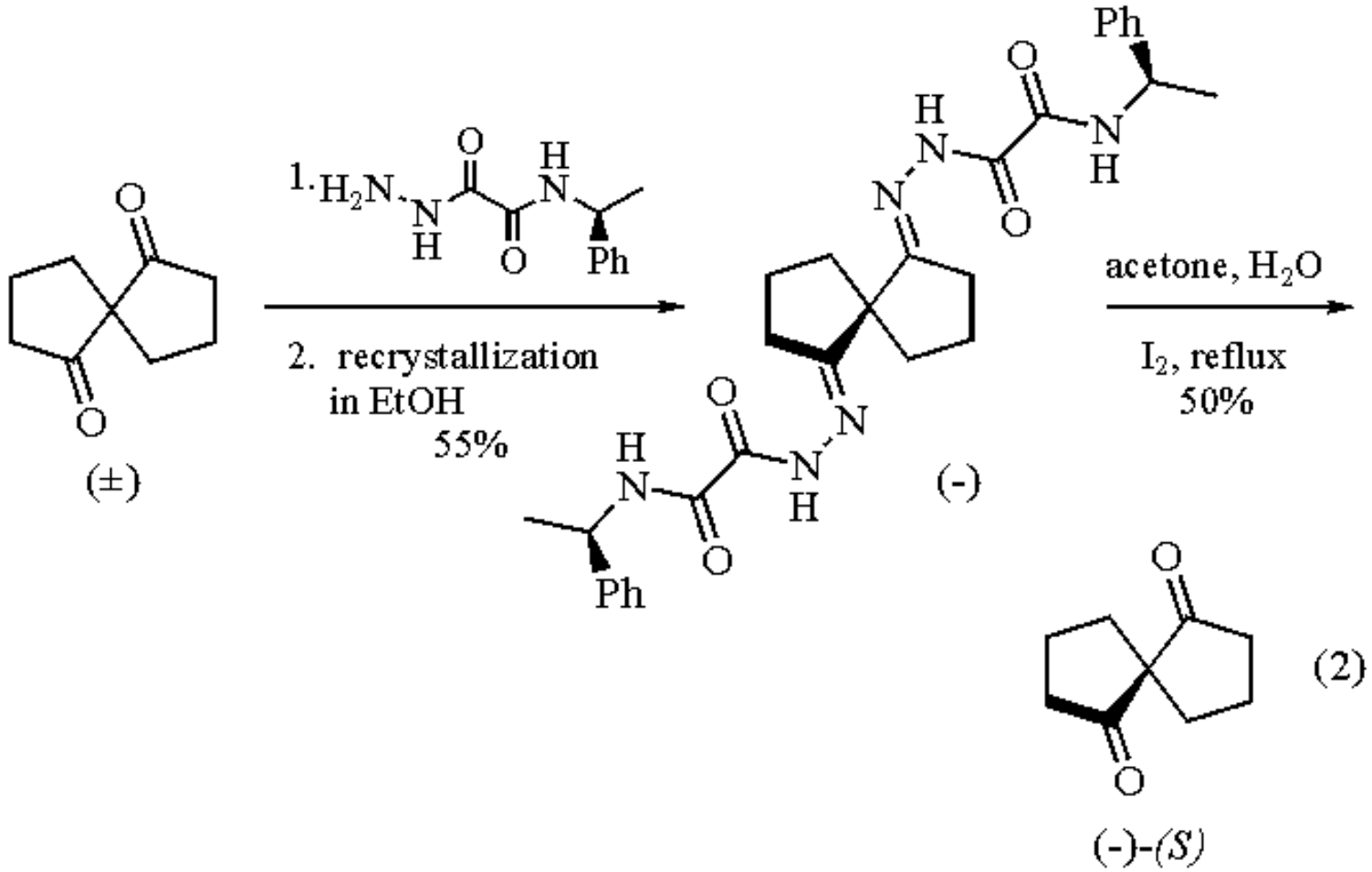

In the field of arene tricarbonyl chromium complexes, racemic aldehydes can be resolved quantitatively by chromatographic separation of the corresponding semioxamazones. The first optical resolution was carried out on the semioxamazone made from the chromium tricarbonyl complex of *o*-anisaldehyde.[3,4] The separation of the diastereomers was done by silica gel chromatography (eq 3). Chromium tricarbonyl complexes of *m*-anisaldehyde,[4] of the trifluoromethyl analog of *o*-anisaldehyde,[5] and of *o*-trimethylsilylbenzaldehyde[6] have also been resolved by the same procedure.

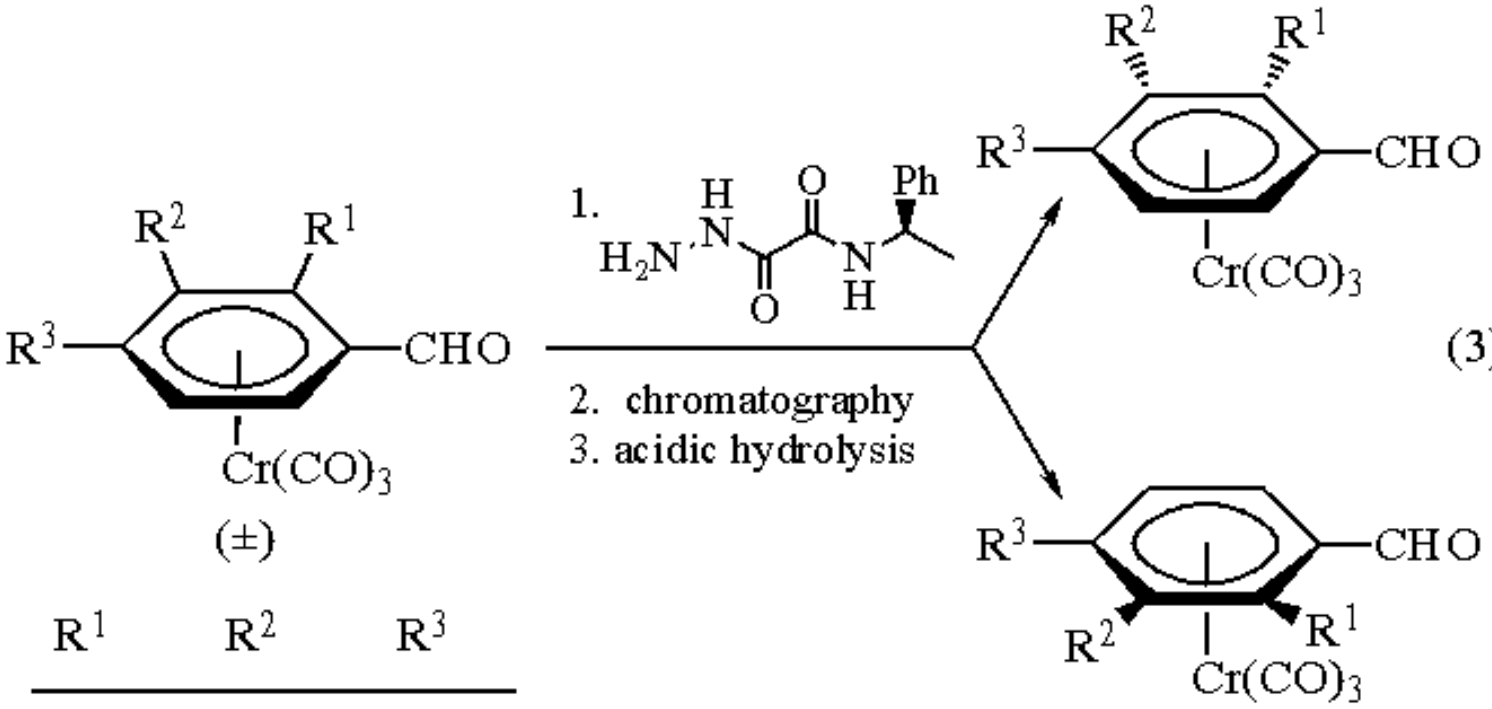

R^1	R^2	R^3
OMe	H	H
H	OMe	H
CF_3	H	H
TMS	H	H
OMe	OMe	H
H	OMe	OMe

The iron tricarbonyl complex of 2-formylbutadiene has been resolved by chromatographic separation of its chiral semioxamazones (eq 4).[7]

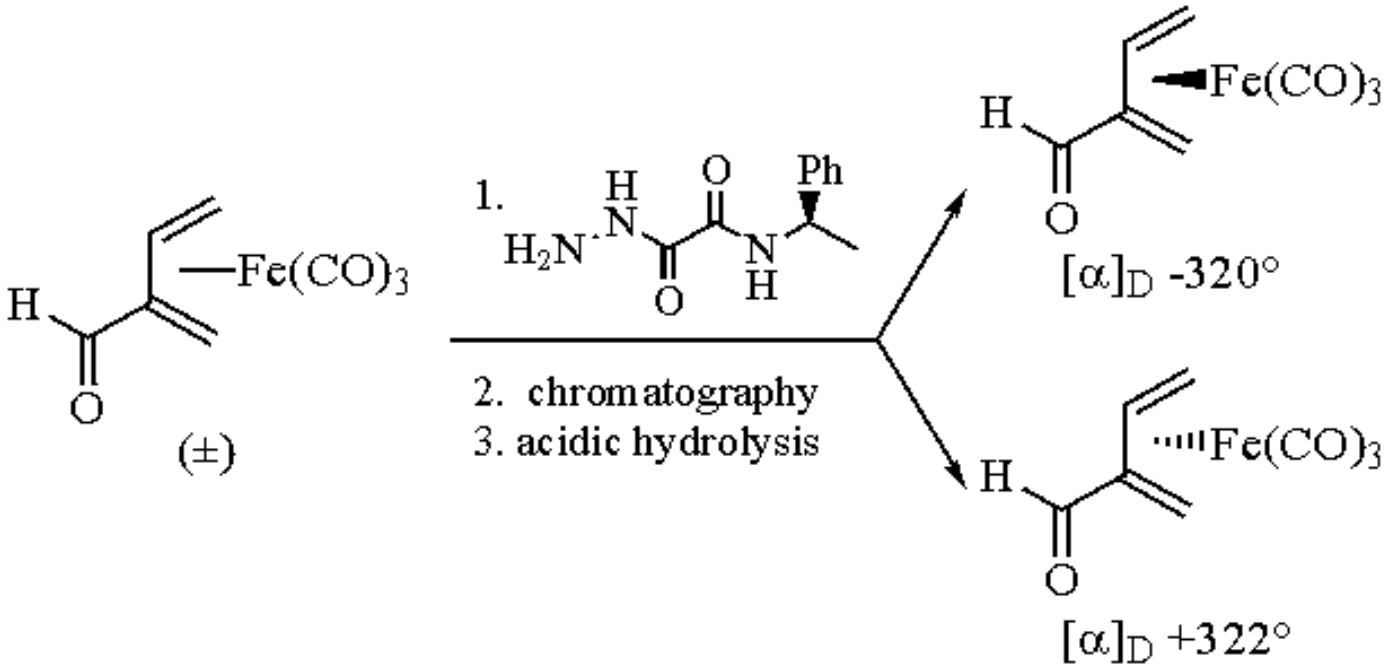

(S)-(-)-5-(alpha-Phenylethyl)semioxamazide

2,3-Dihydro-2-phenyl-4(1*H*)-quinolone has also been resolved by fractional crystallization of the corresponding chiral semioxamazones (eq 5).[8]

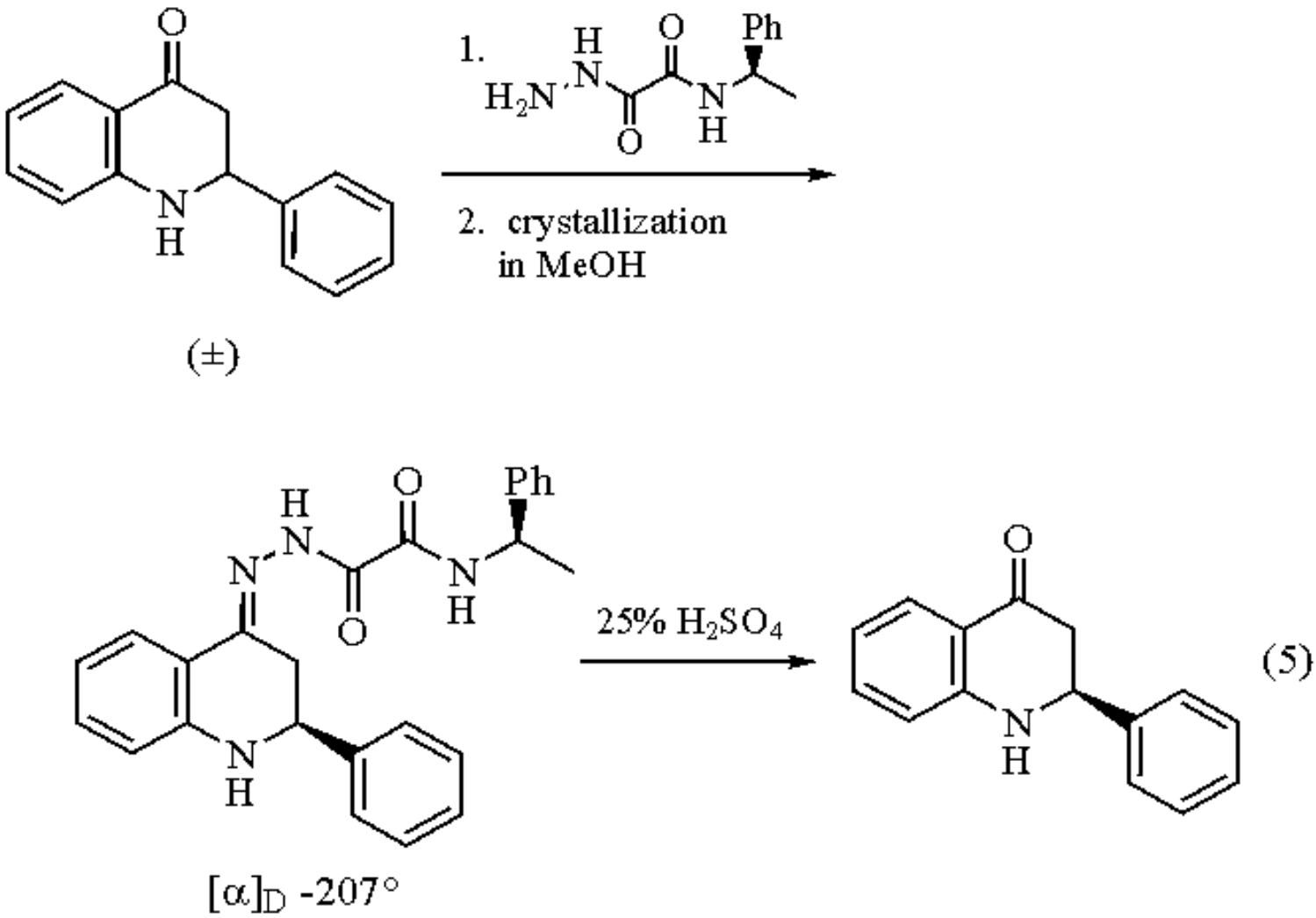

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Phenylethynylcopper(I)[1]

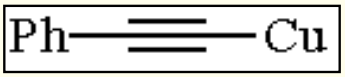

[13146-23-1] · C_8H_5Cu · Phenylethynylcopper(I) · (MW 164.68)

(mild nucleophilic agent for the introduction of the phenylethynyl group,[2] formation of phenylallenes,[3] and Glazer cross-coupling products[4])

Alternate Name: copper(I) phenylacetylide.

Physical Data: bright yellow solid, mp 229 °C;[5a] IR ν(C&tbond;C) 1933 cm^{-1}.[5a] Vibrational spectra have been reported.[5b]

Solubility: sol pyridine, THF, ether, acetonitrile, hot cyclohexane, dioxane; insol water.

Analysis of Reagent Purity: gravimetric analysis of derived salts.[9] Traces of ammonia are reported to impart a green tinge to the solid.

Preparative Methods: (i) phenylacetylene is treated with either ammoniacal ***Copper(II) Sulfate*** and ***Hydroxylamine*** hydrochloride (reductant)[6] or ***Copper(I) Iodide*** in ethanol;[7] (ii) phenylacetylene is lithiated, then treated with copper(I) iodide; (iii) phenylacetylene is treated with ***Copper(I) t-Butoxide***.[8] *Drying:* heat (65 °C) under vacuum.

Handling, Storage, and Precautions: all copper(I) acetylides are potentially explosive in the solid state. Use in a fume hood.

Alkynic Couplings.

Copper(I) phenylacetylide participates in efficient coupling with a range of aryl iodides and bromides to give substituted tolanes[2,6,7,10,11] which, if possessing an *ortho* amino or hydroxy group, can be thermolyzed to yield 2-phenylbenzofurans, -indoles, and -furo[3,2-*b*]pyridines (eq 1).[12] The reactions are usually conducted in refluxing DMF or pyridine (see also ***3-Methyl-3-buten-1-ynylcopper(I)***, ***1-Hexynylcopper(I)***, ***1-Pentynylcopper(I)***).

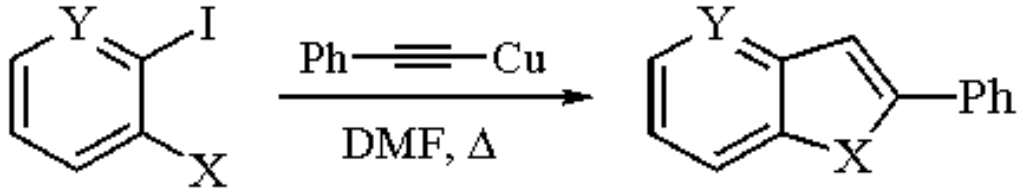

(1)

X = NH_2, Y = CH, 89% X = OH (O), Y = N, 82%
X = NHEt, Y = CH, 50% X = OH (O), Y = CH, 88%

Application of the cross-coupling sequence has been extended to bromo quinones, where milder conditions ensuing from use of a palladium catalyst (eq 2) allow this transformation to proceed with ease and high efficiency (77% yield).[13]

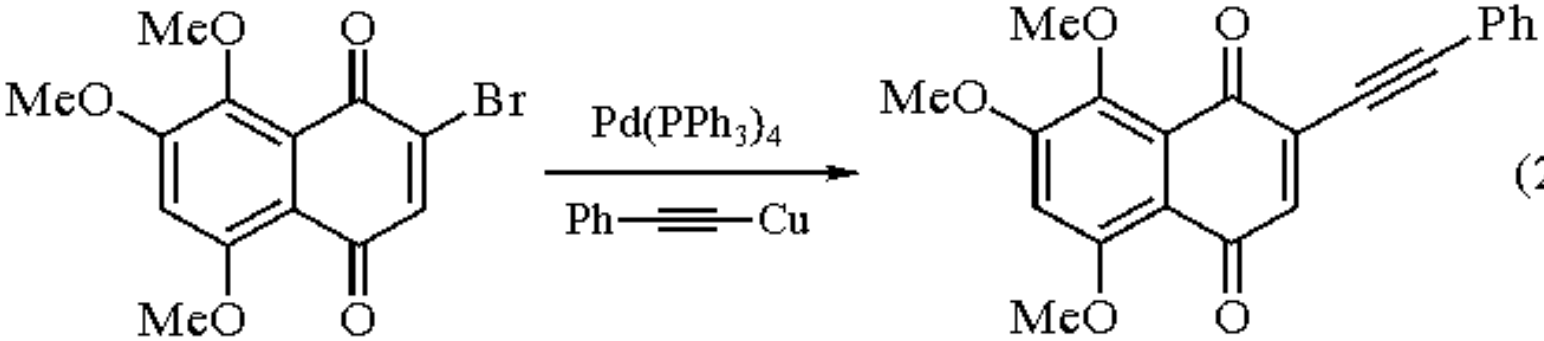

(2)

Coupling to acyl chlorides is reported to be facile (eq 3),[14] allowing direct access to α-alkynones. The couplings are promoted by ***Lithium Iodide***, as lithium chloride was found to be inferior;[14] in some cases addition of ***Hexamethylphosphorous Triamide*** is necessary.[15] This protocol has been applied in the synthesis of natural products.[16] By forming copper(I) phenylacetylide in situ using phenylacetylene and ***Copper(I) Bromide*** in the presence of ***Diisopropylamine***, intermolecular addition to formaldehyde has been demonstrated, giving a potentially versatile route to other substituted allenes (eq 4).[3] Under oxidative conditions, it is possible to couple copper(I) acetylides to form (in this instance) diphenylbutadiyne. The procedure, known as the Glaser coupling, has been reported to proceed either in solution or in the solid state.[4] It is also possible to couple copper(I) phenylacetylide with cyanogen bromide to form phenylpropynenitrile,[17] and with alkylcopper reagents to form disubstituted alkynes.[18] Nucleophilic addition of copper phenylacetylide to organotungsten complexes proceeds with regiocontrol (eq 5), giving ultimate access to enynes.[19]

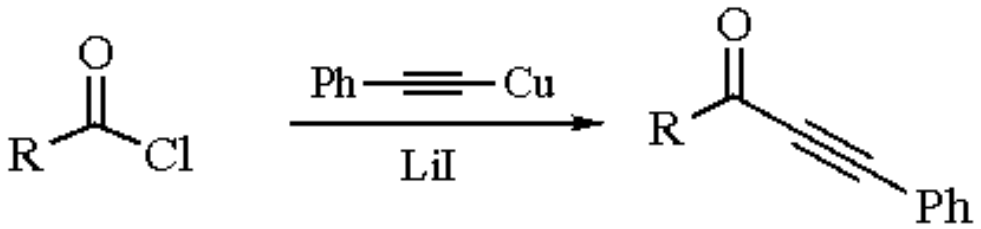

(3)

R = Me, 82%; Ph, 90%

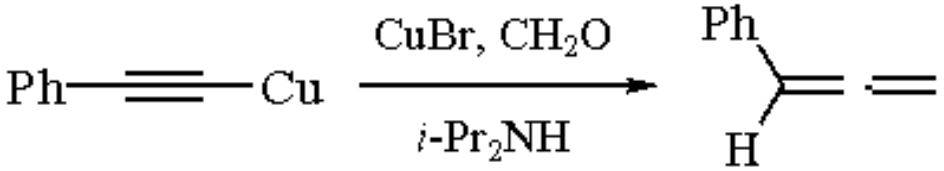

(4)

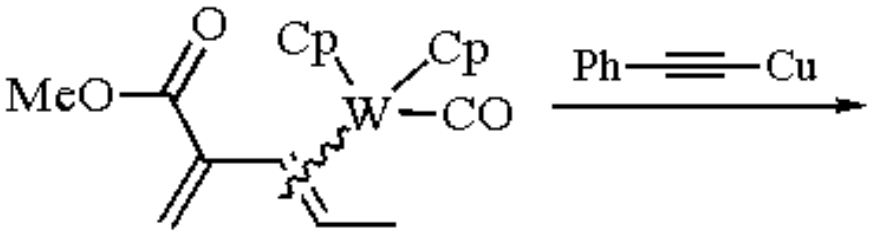

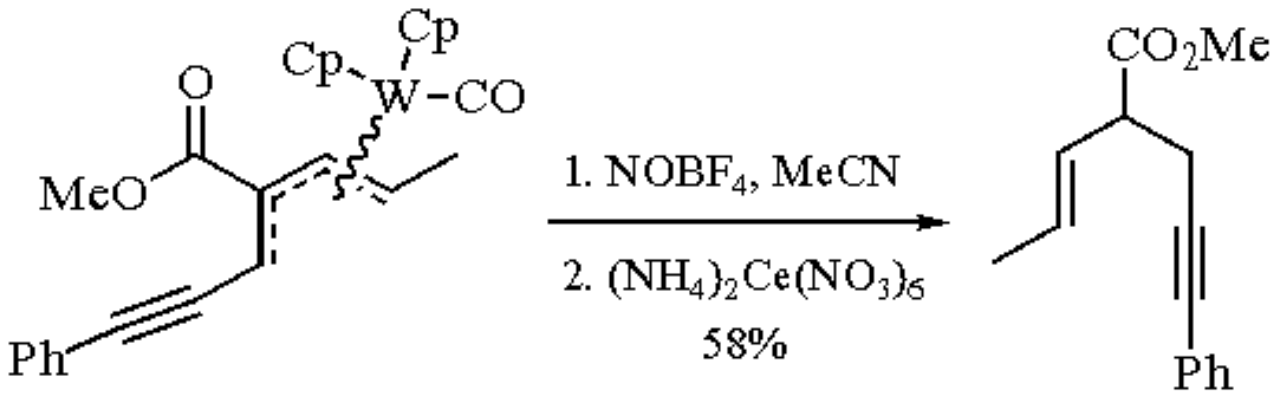

(5)

Other applications of copper(I) phenylacetylide include 2-phenylethynylation of *N*-benzyloxypyridinium salts,[20] [3 + 2] cycloaddition to nitrones (which gives mixtures of azetidin-2-ones: see ***1-Hexynylcopper(I)***),[21] nucleophilic addition to the tetrathiatriazepinium cation,[22] and coupling to activated amines to yield terminal *N*,*N*-dialkylalkynic amines.[23]

Related Reagents.

3,3-Dimethyl-1-butynylcopper(I); ***Phenylethynylcopper(I)-Tris(tributylphosphine)***.

---

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21. For example, see Ding, L. K.; Irwin, W. J. *JCS(P1)* **1976**, 2382.
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Phenylethynylcopper(I)-Tris(tributylphosphine)[1]

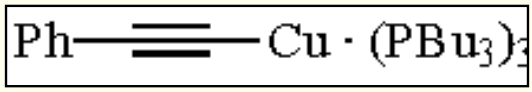

[58659-24-8] · $C_{44}H_{86}CuP_3$ · Phenylethynylcopper(I)-Tris(tributylphosphine) · (MW 771.76)

(carbionic agent for formation of phenylpropiolates;[2] reversible CO_2 uptake carrier[3])

Alternate Name: copper(I) phenylacetylide-tributylphosphine.

Physical Data: prepared in situ.

Solubility: sol THF, pyridine, DMF.

Preparative Method: metalation of phenylacetylene with ***Copper(I) t-Butoxide*** followed by addition of ***Tri-n-butylphosphine*** in THF.[2]

Handling, Storage, and Precautions: all copper(I) acetylides are potentially explosive when dry. Use in a fume hood.

Coupling Agent.

When ***Phenylethynylcopper(I)*** is treated with tributylphosphine in THF and heated to 80 °C, addition to CO_2 can be effected giving, on esterification, methyl phenylpropiolate in moderate yield (eq 1).[2] In the absence of tributylphosphine, the addition does not take place, suggesting that the tributylphosphine may help solubilize and increase the effective nucleophilicity of the copper salt, presumably by dissociating its polymeric form.[4,5] A similar effect is observed with the corresponding ***t-Butyl Isocyanide*** complex, where the yield of carboxylated product increases to 71%.[2]

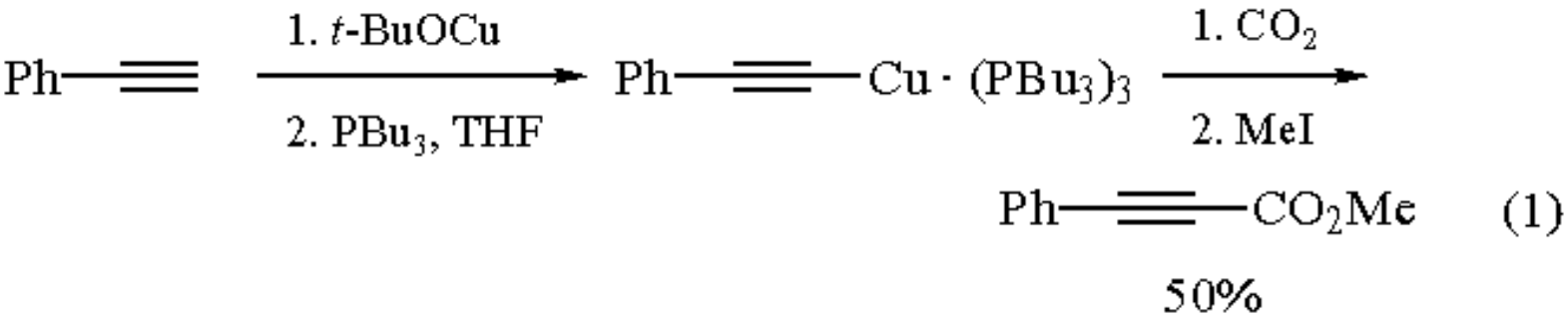

Reversible CO_2 Carrier.

When copper phenylpropiolate is heated to 35 °C in DMF, irreversible decarboxylation ensues, giving copper phenylacetylide. However, when tributylphosphine is added, the decarboxylation is not quantitative, and instead becomes reversible (eq 2).[3] The equilibrium that exists at room temperature can be demonstrated by addition of ***Iodomethane*** as both methyl phenylpropiolate and methylphenylacetylene are isolated. The rate of carboxylation of copper phenylacetylide can be increased by elevating the number of equivalents of tributylphosphine from 1 to 3, but not beyond this, suggesting the species to be coordinatively saturated with three phosphine ligands attached.

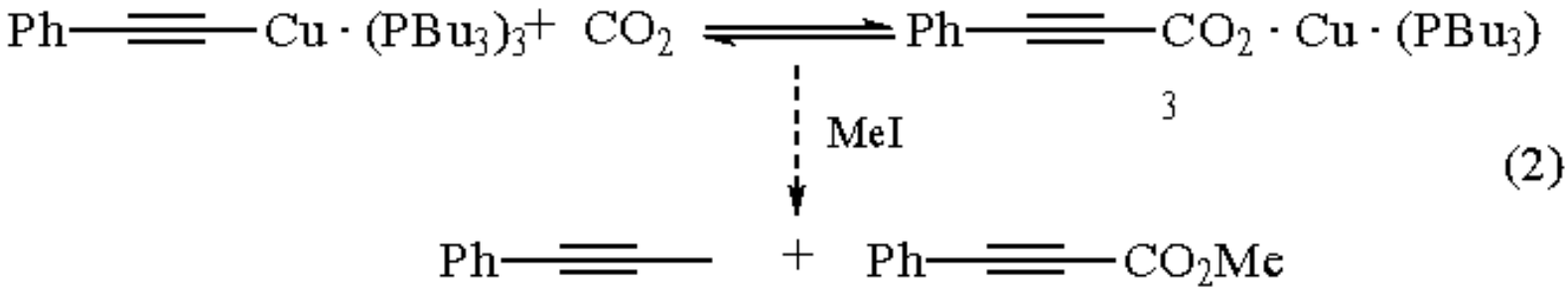

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1. (a) Normant, J. F. *S* **1972**, 63. (b) Sladkov, A. M.; Gol'ding, I. R. *RCR* **1979**, *48*, 868. (c) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (d) *FF* **1977**, *6*, 130.
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Phenylhydrazine[1]

$PhNHNH_2$

[100-63-0] · $C_6H_8N_2$ · Phenylhydrazine · (MW 108.16)

(forms hydrazones with carbonyl compounds;[1,3] useful reagent for the formation of indoles[4-19] and other heterocyclic ring systems[20-27,31])

Physical Data: mp 18-20 °C; bp 238-241 °C, 52-53 °C/0.06 mmHg; *d* 1.098 g cm^{-3}.

Solubility: misc EtOH, Et_2O, $CHCl_3$, benzene; sol dil acids; slightly sol H_2O, petroleum ether.

Form Supplied in: yellow solid or yellow oil.

Preparative Method: from aniline via diazotization, followed by reduction of the resultant benzenediazonium chloride with Na_2SO_3.[2]

Handling, Storage, and Precautions: keep in tightly closed container; protect from light; toxic, possible carcinogen, irritant.

Introduction.

Although $PhNHNH_2$ readily forms hydrazones with ketones and aldehydes, too many of the products thus formed tend to be oils and are difficult to detect visually.[3] For this reason, ***2,4-Dinitrophenylhydrazine*** is, instead, the preferred reagent of choice for making carbonyl derivatives. Phenylhydrazine, however, is very useful in the synthesis of various heterocyclic compounds.

Fischer Indole Synthesis.

Indolization of a phenylhydrazone, in the presence of a catalyst, was first observed by Fischer.[4] Although ***Zinc Chloride*** is the classical reagent of choice for catalyzing these transformations, several other catalysts have since been successfully used.[1b] This method has emerged as a general and powerful method for making indoles (eq 1).[5]

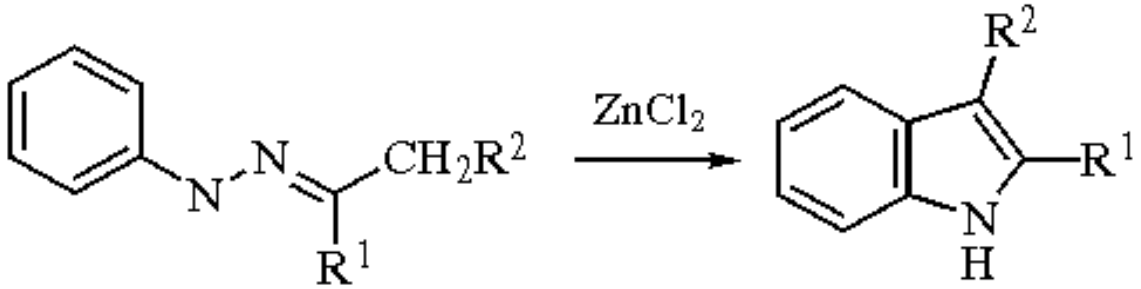

(1)

The generally accepted mechanism for this reaction was originally proposed by Robinson and Robinson.[6] There exists substantial evidence for this mechanism which involves a [3,3] sigmatropic rearrangement as a key step (eq 2).[7-10] The phenylhydrazones are generally not isolated since many of these intermediates either cyclize under mild conditions or decompose upon attempted purification. The phenylhydrazone of cyclohexanone, for instance, is generated and converted into tetrahydrocarbazole in one step by adding phenylhydrazine to a refluxing mixture of the ketone and AcOH (eq 3).[11] A mild, one-step protocol for preparing 2,3-disubstituted indoles in good yields (70-90%) involves treating a solution of a ketone and phenylhydrazine in benzene with ***Phosphorus(III) Chloride*** at room temperature for a few minutes.[12-14] Elaborate polycyclic structures can be rapidly assembled by using this methodology. Indeed, when 4-oxo-1,2,3,4-tetrahydro-β-carboline (**1**) is heated with an excess of phenylhydrazine, the pyridinodiindole (**2**) is readily obtained (eq 4).[15]

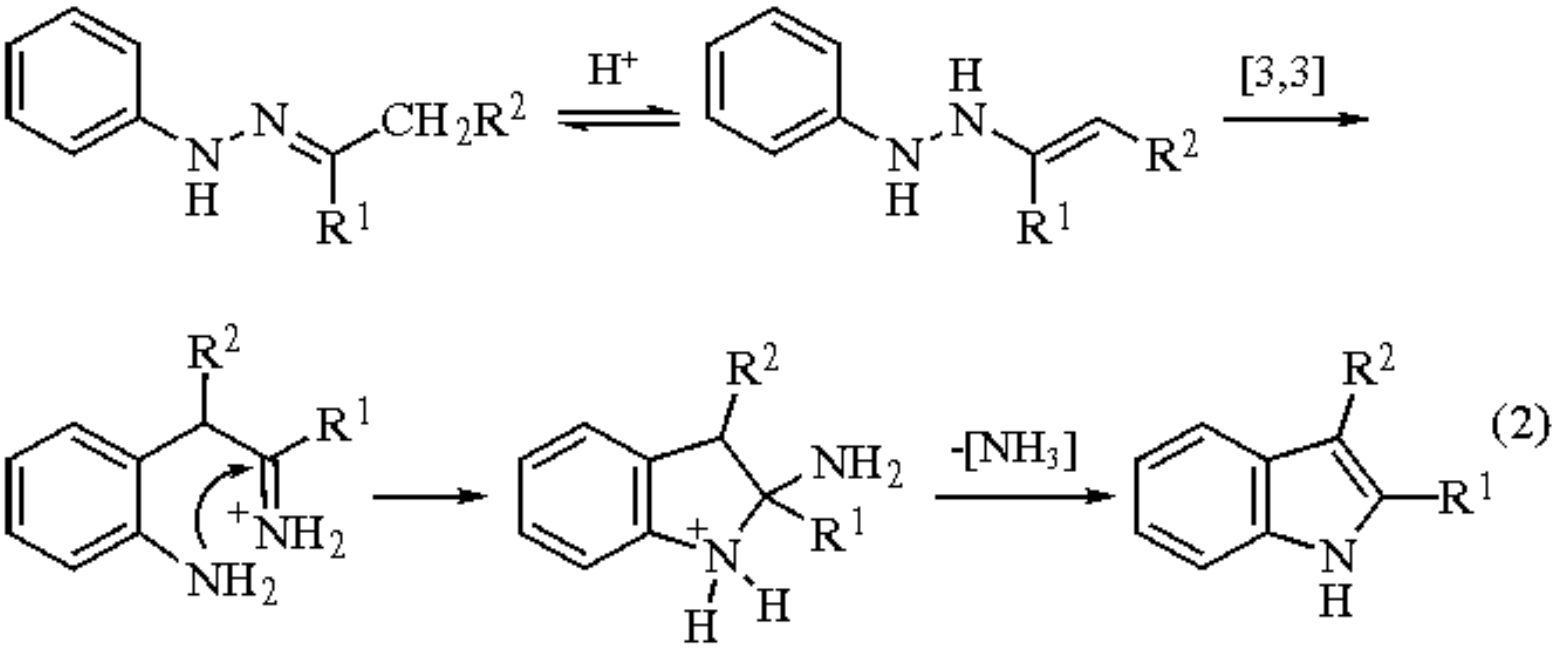

(2)

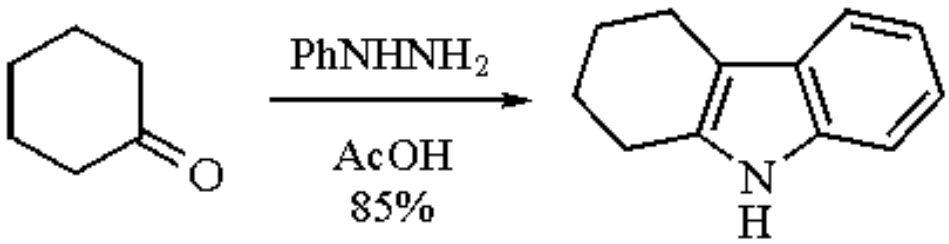

(3)

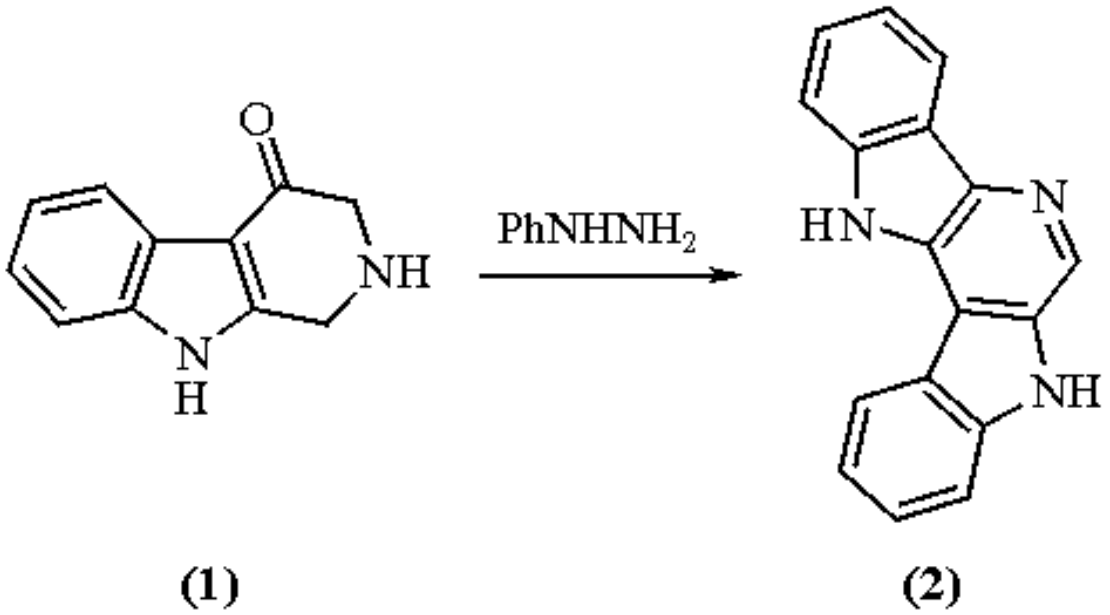

(4)

Use of the bis-Fischer indole synthesis has culminated in the total synthesis of indolo[2,3-*a*]carbazole alkaloids.[16,17] In a variation of the Rubottom oxidation of silyl enol ethers,[18] the Diels-Alder adduct (**3**) is treated with ***m*-Chloroperbenzoic Acid** to presumably provide the dione (**4**), which is then exposed to 2 equiv of phenylhydrazine. Treatment of the osazone (**5**), thus obtained, with ***Trimethylsilyl Polyphosphate*** (PPSE), a mild catalyst, followed by aromatization of the central ring provides *N*-methylarcyriaflavin A (**6**) (eq 5).[16]

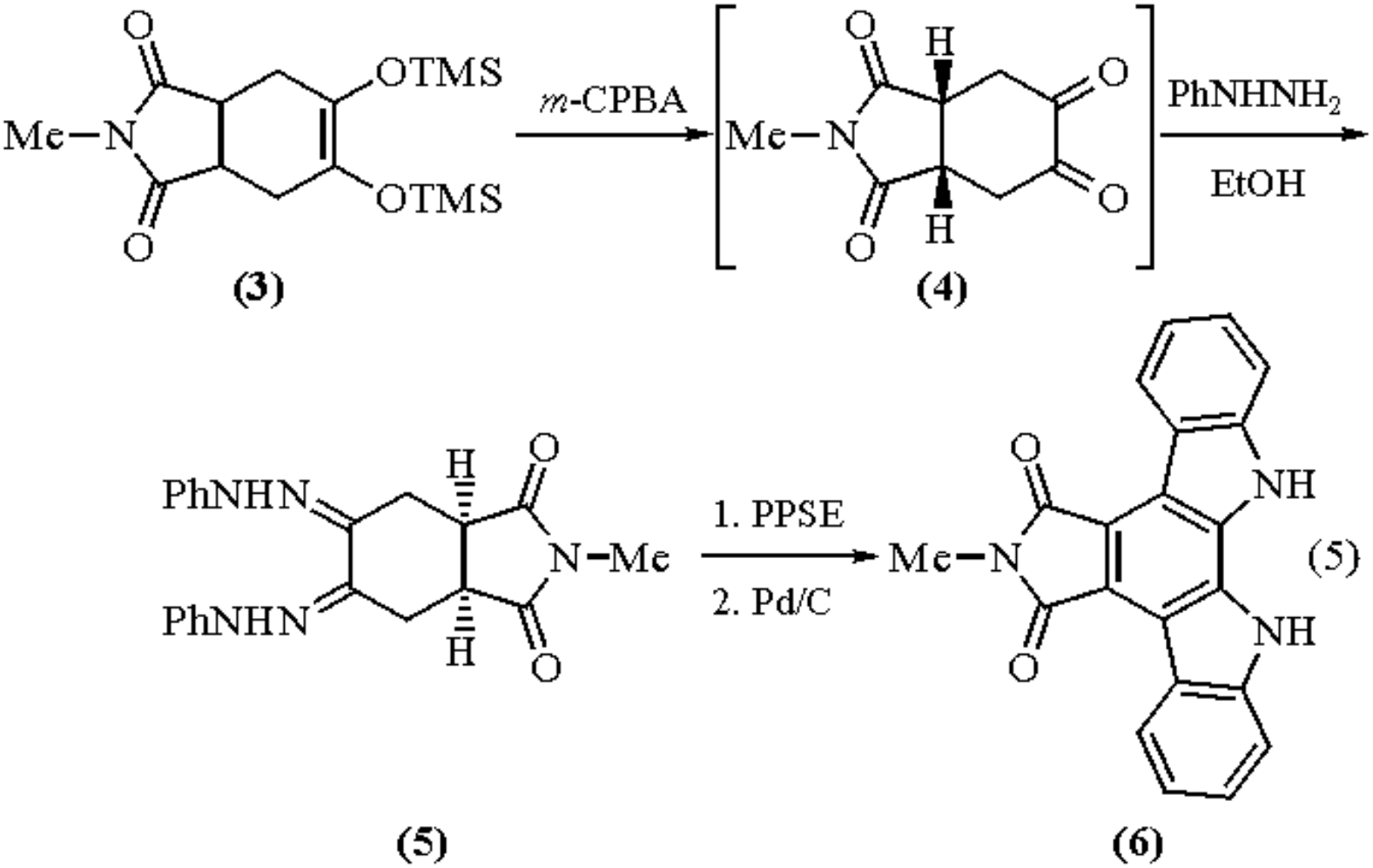

(5)

A variation of the Fischer protocol has been used for the preparation of the dihydropyrrole ring system. Reaction of phenylhydrazine with propionic anhydride (**7**) provides β-propionylphenylhydrazine (**8**) which, upon treatment with ***Calcium Hydride***, loses NH_3 and leads to the formation of 3-methyloxindole (**9**) (eq 6).[19]

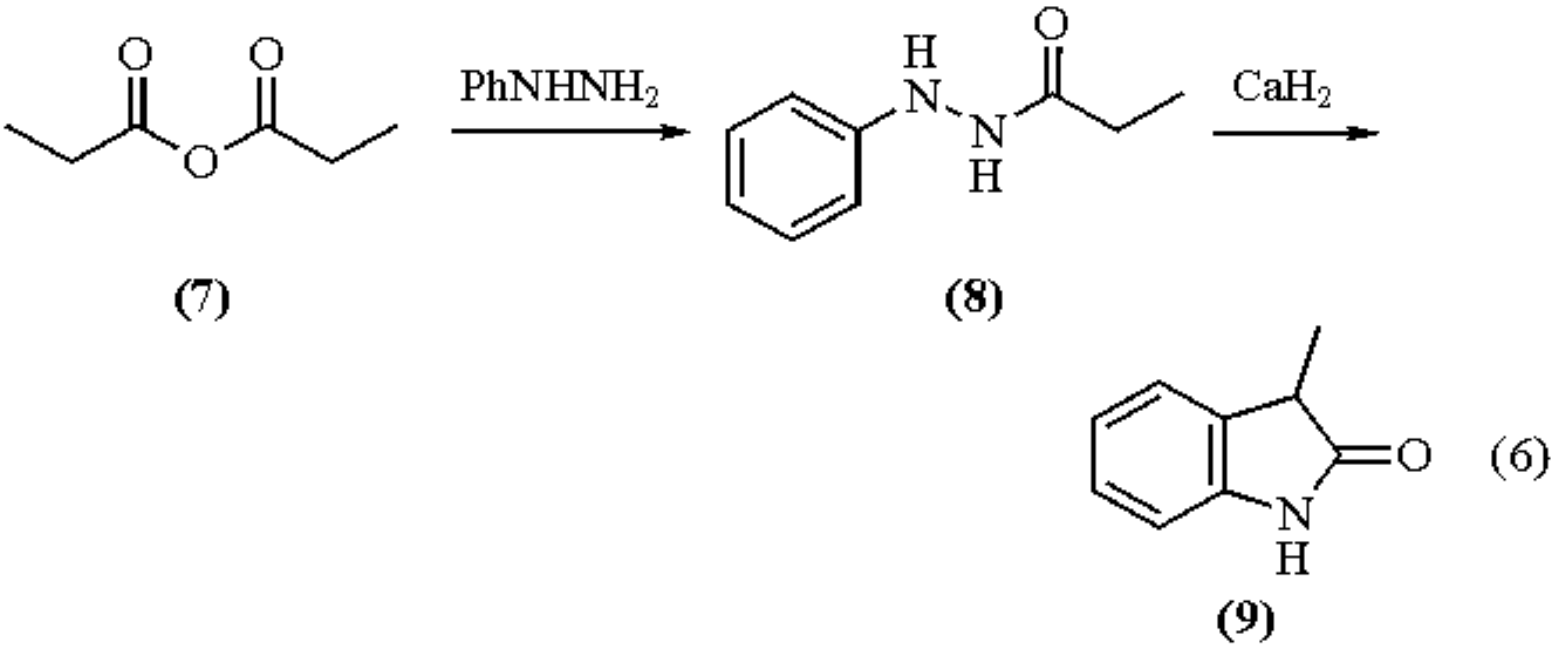

Pyrazoles and Pyrazolines.

Phenylhydrazine has also been used in the synthesis of various five-membered heterocycles.[20] Thermal treatment of 3-acetyl-1,4,5,6-tetrahydropyridine (**10**) with $PhNHNH_2$, under acidic conditions, leads to a 1:1 mixture of isomeric pyrazoles (**11**) and (**12**) (eq 7).[21] The oxidative cyclization of stannylhydrazones (**13**) provides the azocyclopropanes (**14**) in good yields. Whereas the formation of pyrazolines (**15**) is not observed via the direct ring-closure of (**13**), treatment of (**14**) with catalytic amounts of ***Tin(II) Chloride*** in benzene, at refluxing temperature, furnishes the five-membered heterocycles (**15**) in high yields (eq 8).[22]

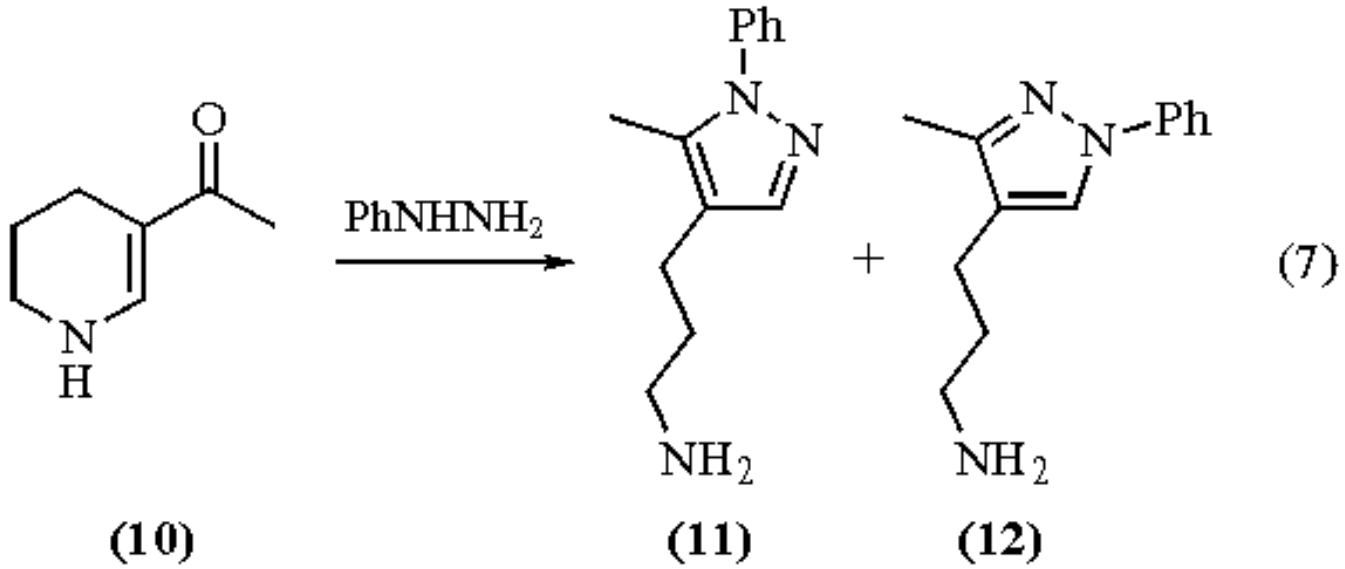

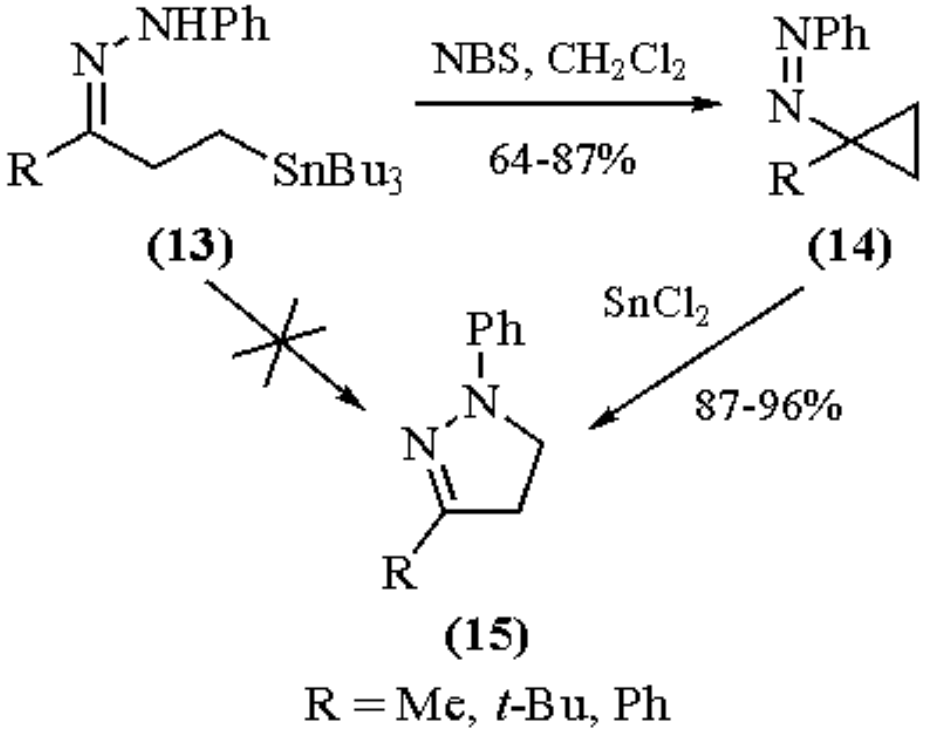

(8)

Synthesis of β-Lactams.

Phenylhydrazones (**16**), when treated with phenoxyketene, give *N*-acylated products (**17**), which do not cycloadd to the ketene. However, *N*-alkylated phenylhydrazones (**18**)[23] undergo [2 + 2] cycloaddition reactions with in situ generated phenoxyketene to provide β-lactams (**19**) (eq 9).[24]

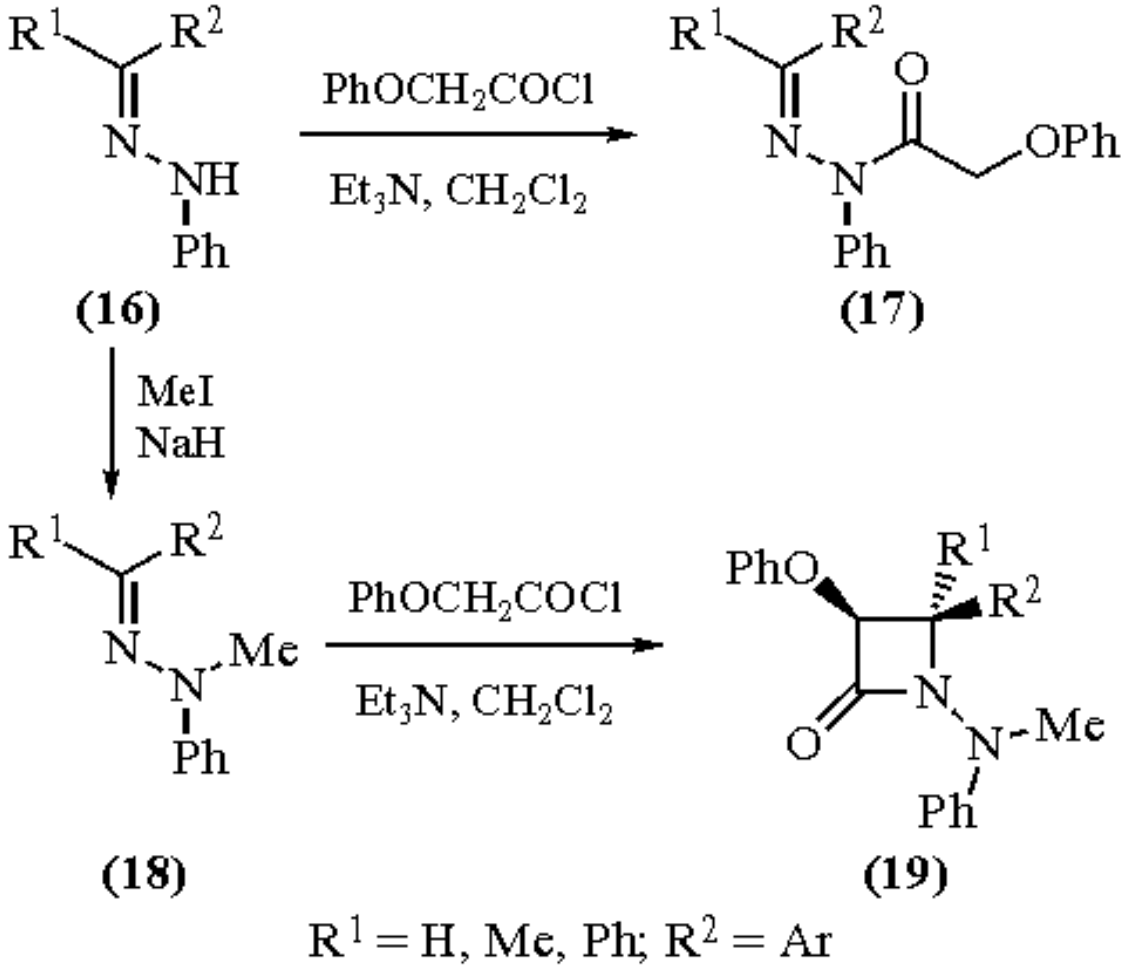

(9)

Synthesis of Piperidines.

Reactions of ***Glutaraldehyde*** and hydrazines, in the presence of benzotriazole, lead to the formation of piperidines (eq 10).[25]

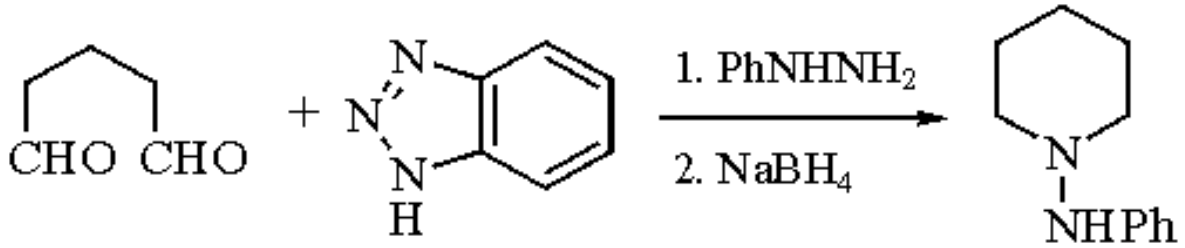

(10)

Reactivity with Heterocumulenes.

Reactions of phenylhydrazones with ***Phenyl Isocyanate***, under thermal conditions, provide triazolidines (eq 11).[26] A 1,3-dipolar reaction between ketone phenylhydrazones and ***Phenyl Isothiocyanate***, in the presence of ***Sodium Hydride*** in DMF, leads to the formation of 4-phenyl-5-phenylimino-1,3,4-thiadiazolidines (eq 12).[27] Reactions using ***Carbon Disulfide***, instead of isothiocyanate, under similar conditions provide 4-phenyl-1,3,4-thiadiazolidine-5-thiones.[27]

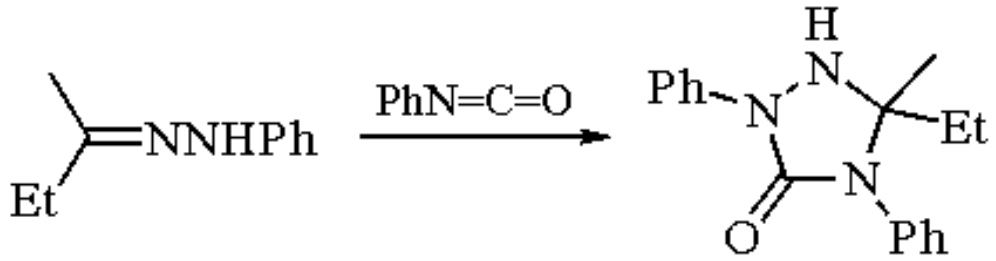

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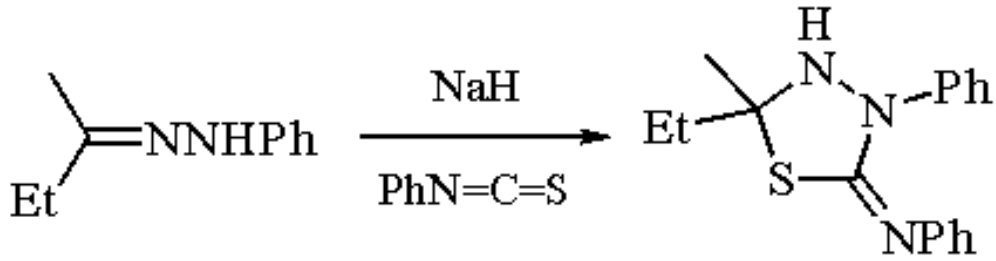

(12)

Generation of Amines.

Phenylhydrazine has been used for the generation and regeneration of different kinds of amines. Reduction of phenylhydrazones has been utilized, for example, in the synthesis of aminophosphonates. The reaction of $PhNHNH_2$ with oxophosphonates (**20**) provides hydrazones (**21**) in almost quantitative yields. Catalytic hydrogenation yields amines (**22**), and the diethylphosphonate moiety in (**22**) can be hydrolyzed to provide 1-aminoalkanephosphonic acids (**24a**) (eq 13).[28] In a variation of the Ing-Manske procedure,[29] where a phthalimide is heated with hydrazine to liberate a primary amine in an exchange reaction, the *N*-protective phthaloyl group of an amino acid or a peptide can be cleaved. Thus refluxing phthaloyl-L-leucine, in the presence of a tertiary amine in EtOH, can be used to access crystalline L-leucine (eq 14).[30]

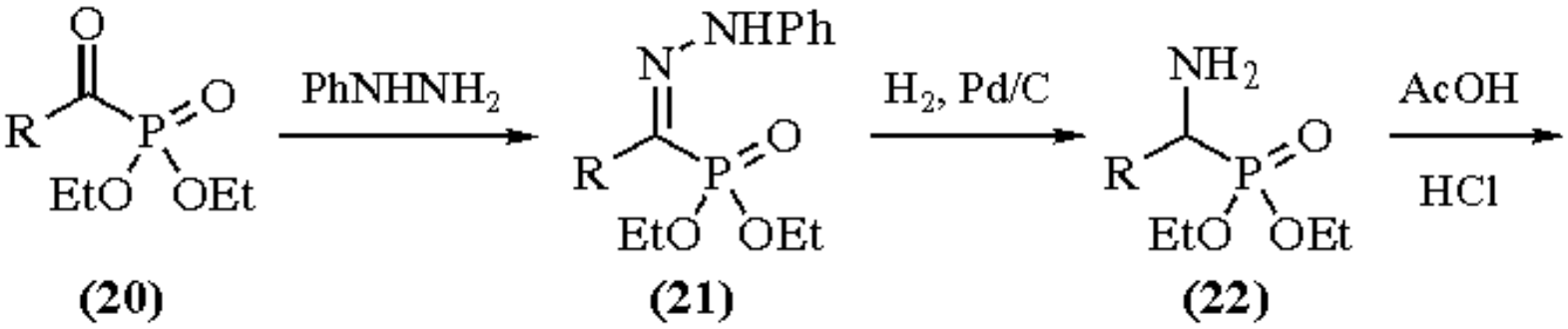

(20) **(21)** **(22)**

R = alkyl, aryl

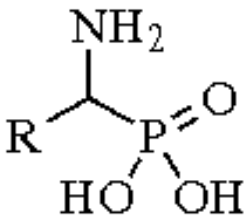

(13)

(23)

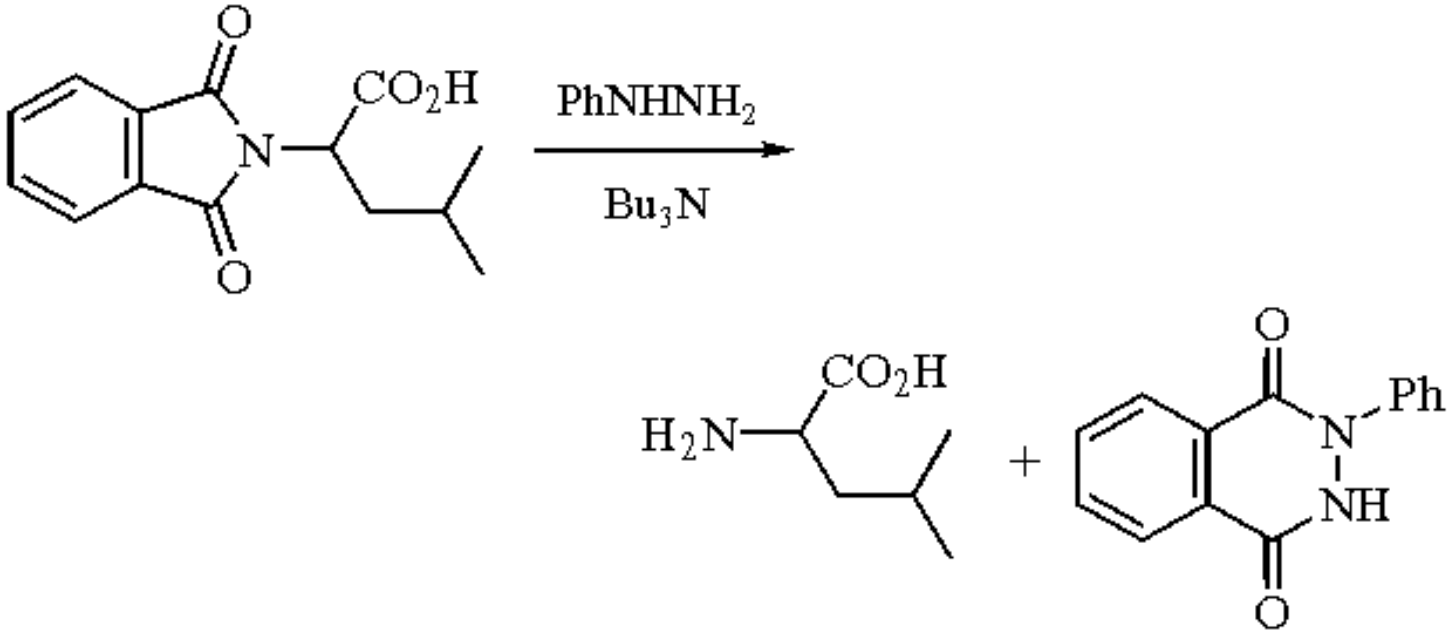

(14)

Synthesis of Quinazolines.

Further utility of phenylhydrazine is apparent in the synthesis of quinazolines. Treatment of methyl anthranilate esters (**24a**) with orthoesters provides *N*-(2-methoxycarbonylphenyl) imidate esters (**24b**). The reaction of these imidate esters with $PhNHNH_2$ leads to the formation of 3-amino-4(3*H*)-quinazolinones (**26**) in a stepwise mechanism, presumably via the intermediate amidrazones (**25**) (eq 15).[31]

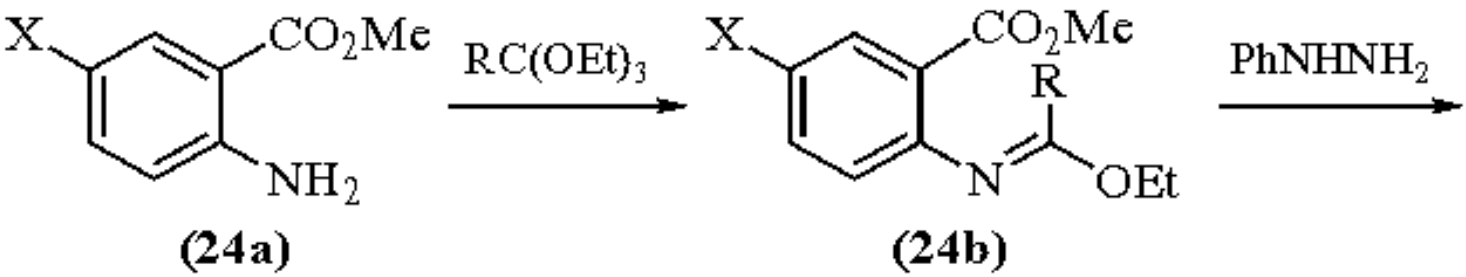

(24a) **(24b)**

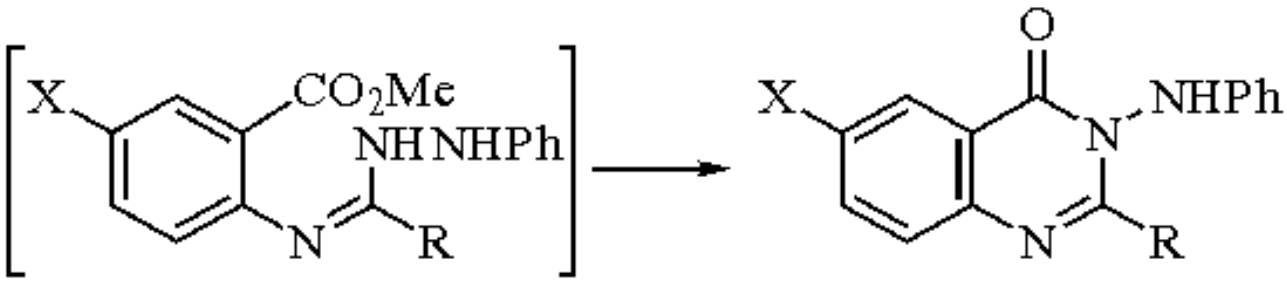

(15)

(25) **(26)**

X = H, Cl, Br; R = Me, Et

Osazones.

Treatment of α-dicarbonyl compounds, α-hydroxy aldehydes and ketones,[32,33] and α-halo ketones[34-36] with $PhNHNH_2$ leads to the formation of osazones (eq 16). Osazones are particularly important in carbohydrate chemistry and have been used in alkaloid synthesis (eq 5). In a reaction of phenacyl chloride (**27**) with $PhNHNH_2$, the yellow crystalline pyridazine derivative (**28**) is rapidly formed and the gradual formation of the osazone (**29**) is also observed. Also produced from this reaction is another compound, a tetrahydropyridazine (**30**). It has been rationalized that the pathway to (**28**) involves the formation of the hydrazone followed by 1,4-elimination of HCl and a subsequent dimerization of the resultant ene-azo intermediate (**31**).[37] It has also been proposed that a retro-Diels-Alder type reaction of (**28**) furnishes the intermediate (**31**), which then participates as the diene in a 1,4-cycloaddition reaction with the osazone (**29**) to provide cyclic (**30**) (eq 17).[38]

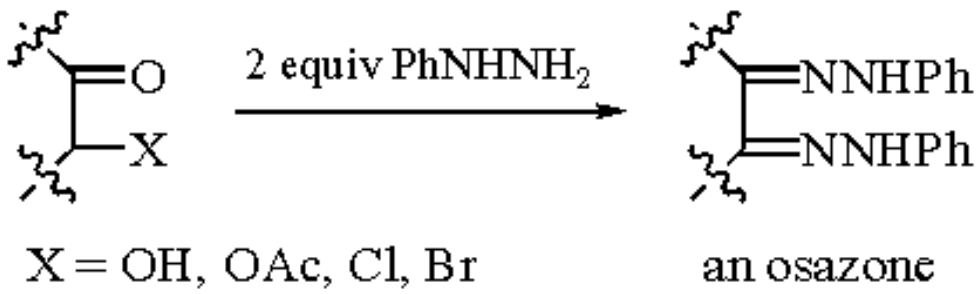

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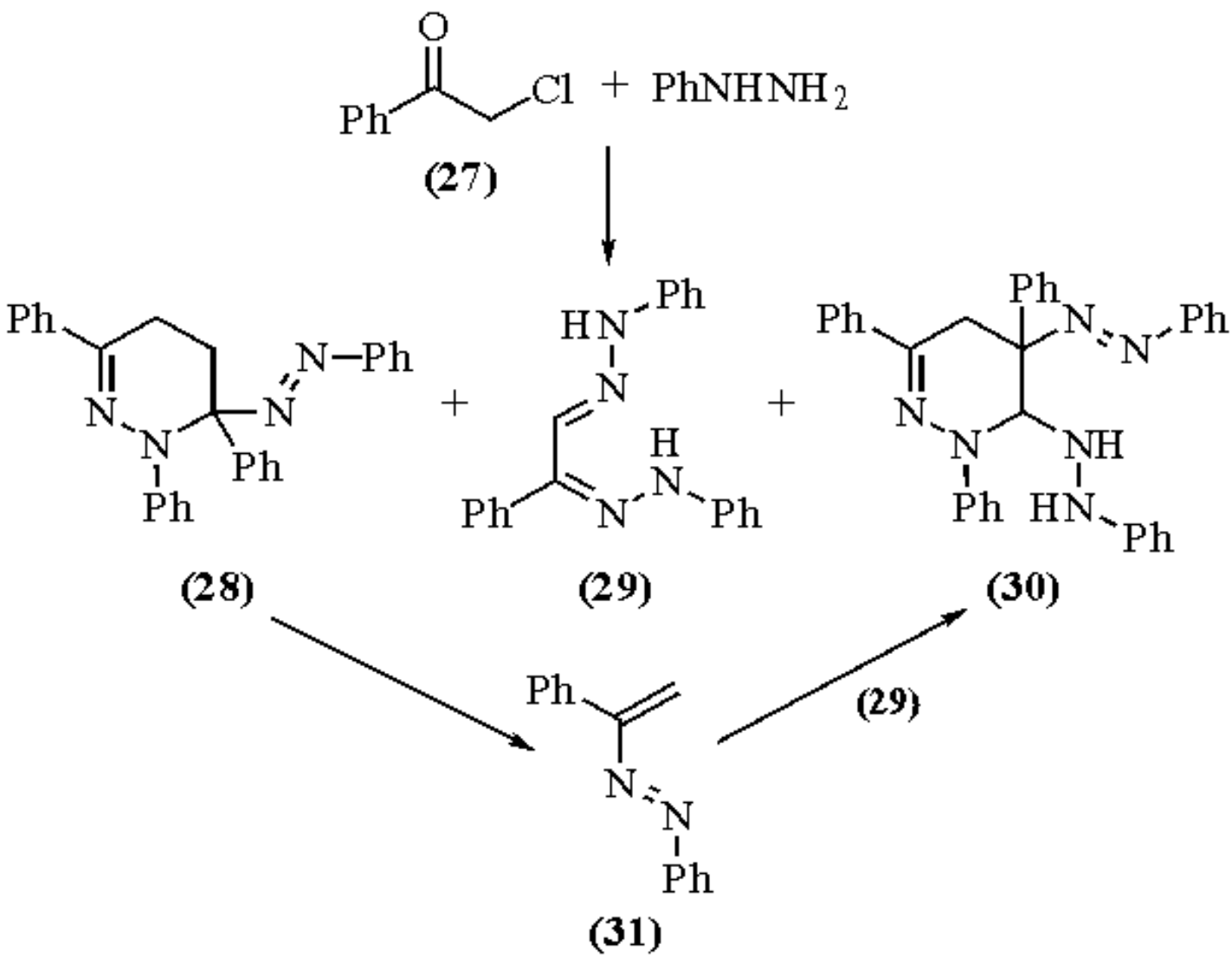

(17)

(31)

Triazolo Compounds.

Hydrazones of acylated heterocycles are widely used as precursors for the preparation of 1,2,4-triazolo compounds.[39,40] Indeed, oxidative cyclizations of arylhydrazones of 2-acylpyridines, in the presence of ***Mercury(II) Acetate*** or ***Lead(IV) Acetate*** (LTA), are efficient means of accessing fused 1,2,4-triazoles and 1,2,3-triazolium systems. A coupling reaction of 2-benzoylpyridine (**32**) with $PhNHNH_2$ provides the (*E*)-isomer of hydrazone (**33**), as established by X-ray structure analysis. An oxidative ring-closure of (**33**) with LTA leads to the formation of the corresponding 1,2,3-triazolium salt (**34**) in high yield (eq 18).[41]

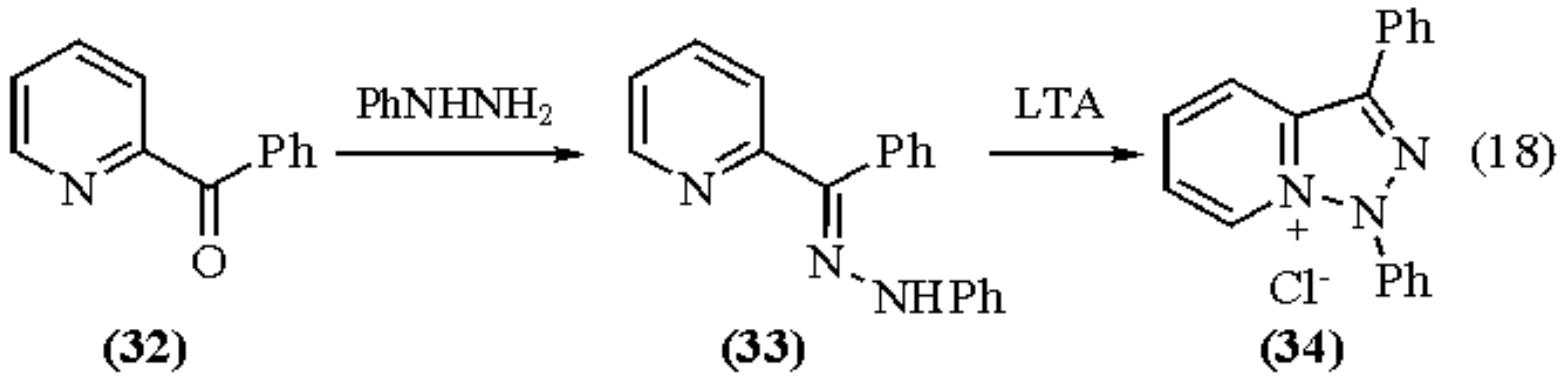

Related Reagents.

N,N-Dimethylhydrazine; ***2,4-Dinitrophenylhydrazine***.

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Phenyliodine(III) Bis(trifluoroacetate)[1]

$(CF_3CO_2)_2IPh$

[2712-78-9] · $C_{10}H_5F_6IO_4$ · Phenyliodine(III) Bis(trifluoroacetate) · (MW 430.05)

(cyclopropyl groups undergo ring opening,[2] alkynes are cleaved,[3] phenols are oxidized to quinones[4-8] and in some cases oxidative intramolecular coupling occurs,[9-13] ketones yield α-hydroxy ketones,[14] certain β-diketones undergo cyclization,[15] Pummerer-type reaction occurs,[16] and deprotective dethioacetalization is an important use[17])

Alternate Names: bis(trifluoroacetoxyiodo)benzene; iodobenzene bis(trifluoroacetate); PIFA; BTI.

Physical Data: mp 121-125 °C.

Solubility: sol CH_2Cl_2, CCl_4, CF_3CH_2OH, $(CF_3)_2CHOH$.

Form Supplied in: white solid; commercially available.

Preparative Method: can be synthesized by reaction of ***(Diacetoxyiodo)benzene*** with ***Trifluoroacetic Acid***.[18]

Handling, Storage, and Precautions: moisture sensitive; irritant.

Bond Cleavage.

1,3-Dehydroadamantane underwent ring-opening with 1,3-addition of $CF_3CO_2^-$ upon reaction with $PhI(OCOCF_3)_2$ (BTI) (eq 1).[2] Alkynes are cleaved upon treatment with three equivalents of BTI.[3] Dibenzyl ether is cleaved to benzaldehyde and benzyl trifluoroacetate (eq 2). Benzylalkyl (or trityl and benzhydryl) ethers react analogously.[19]

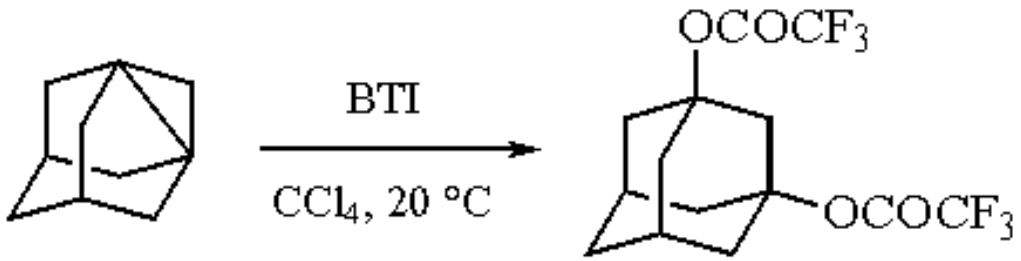

(1)

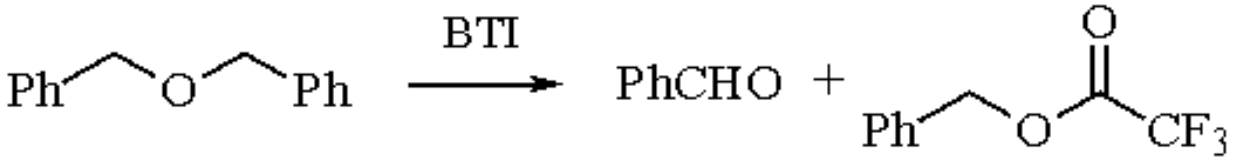

(2)

Oxidation of Phenolic Compounds.

Hydroquinones and catechol derivatives are oxidized to *o*- or *p*-benzoquinones (eq 3).[4-7] In the presence of water, a quinone is formed, while in the presence of methanol the quinone monoacetal is formed (eq 4).[8]

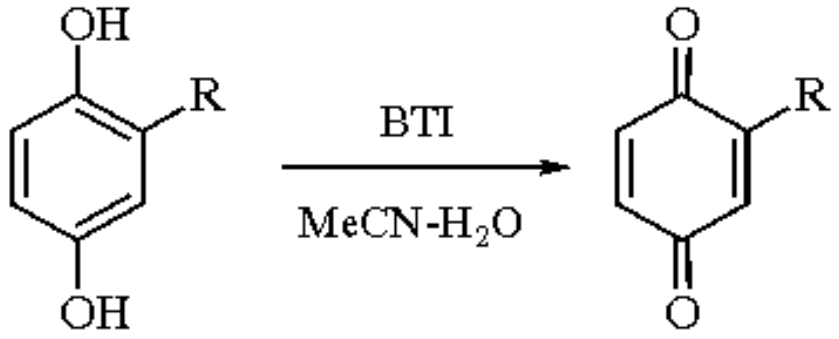

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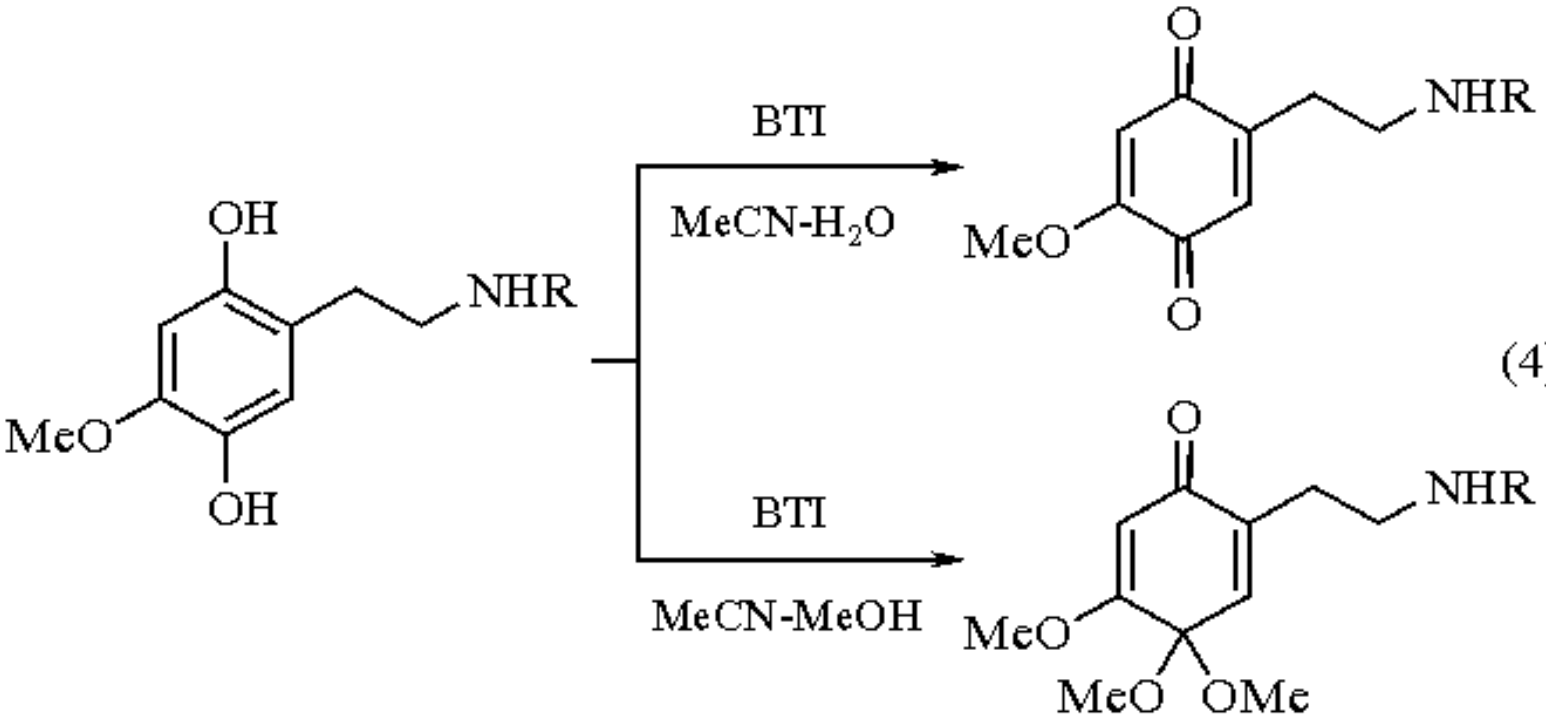

(4)

Intramolecular oxidative cyclization is also an important reaction pathway, as in the case of *N*-acetyltyramines (eq 5),[9] and it has been applied in the syntheses of several natural products. For example, phenolic oxidative coupling with BTI was a key step in the synthesis of 6a-epipretazettine (eq 6).[10]

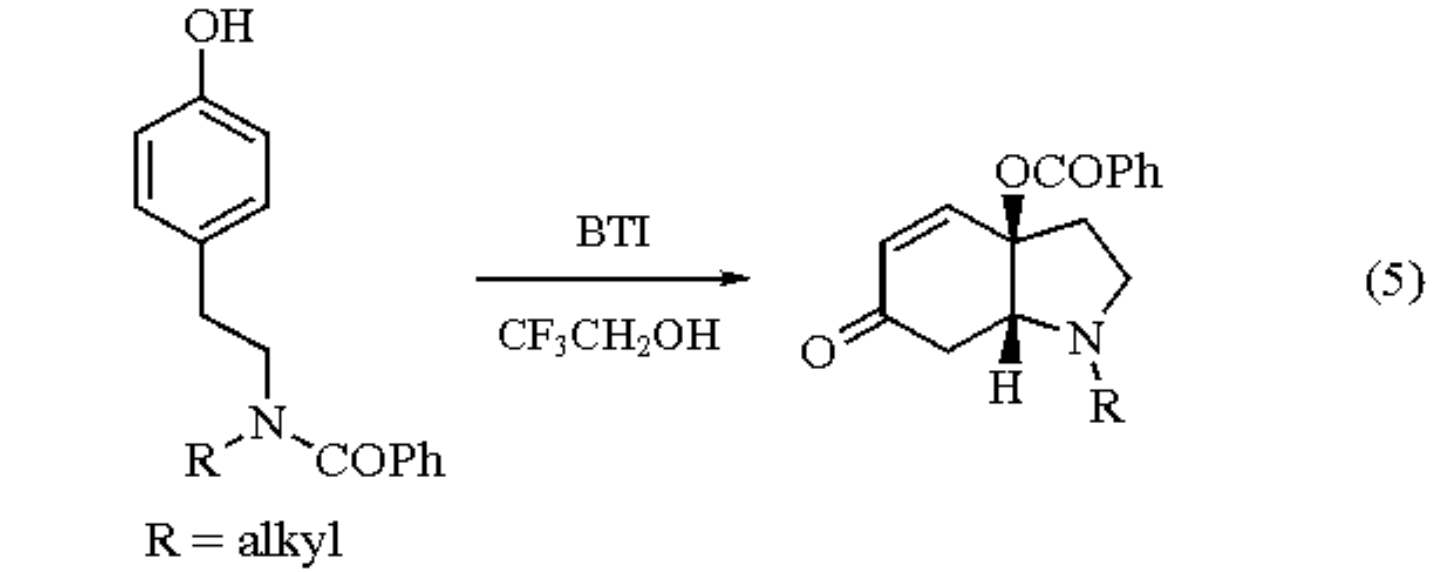

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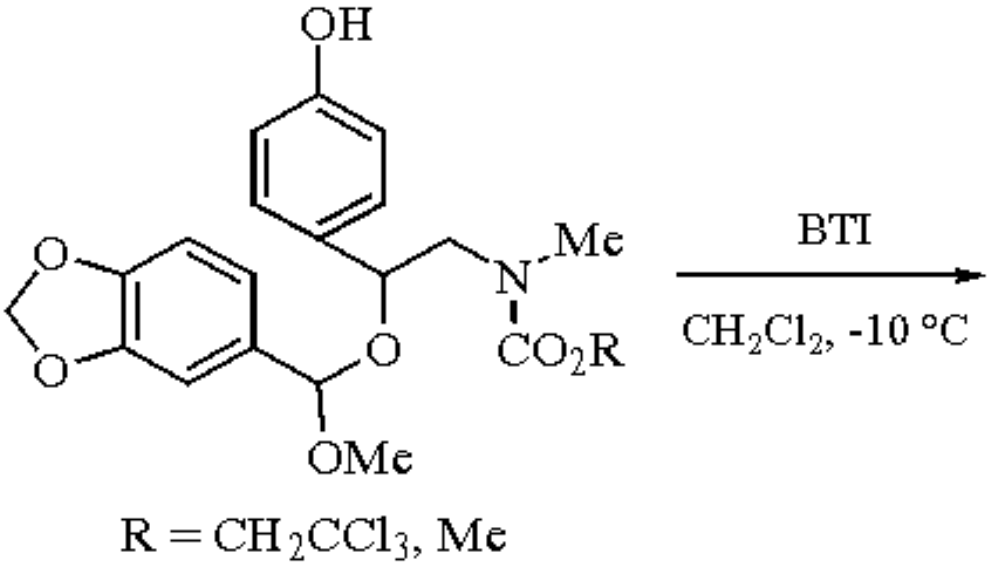

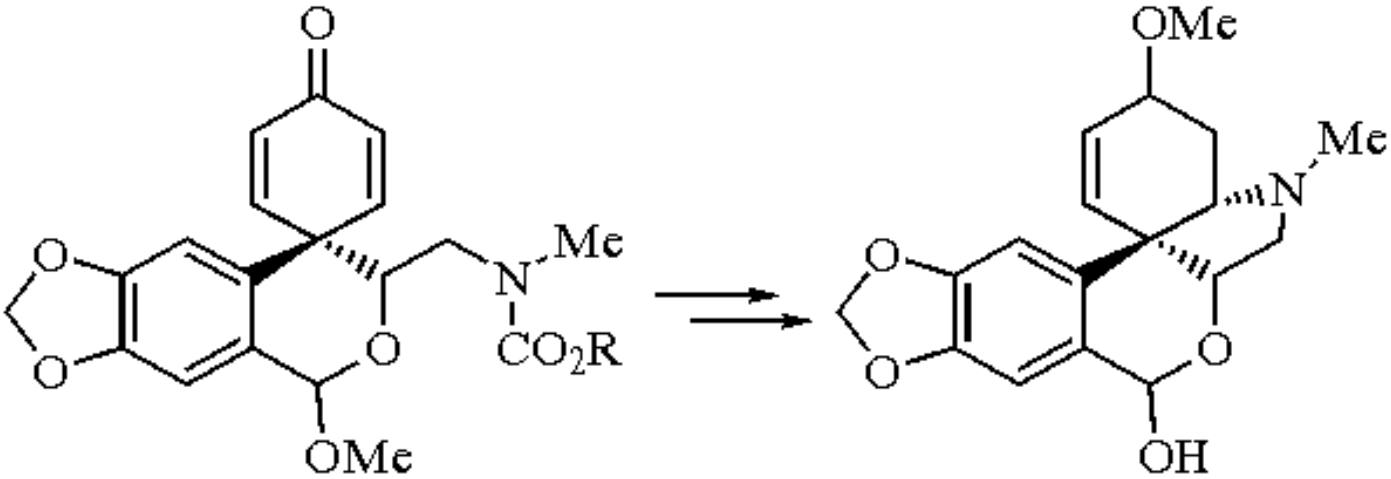

(6)

A similar intramolecular spirodienone formation was observed in a naphthoquinone system (eq 7).[11] An extension of this type of oxidative coupling formed the key step in the synthesis of the marine alkaloid discorhabdin C (eq 8).[12] Intramolecular cyclization has also been used as a key step in a synthetic approach to the natural product aranorosin (eq 9).[13]

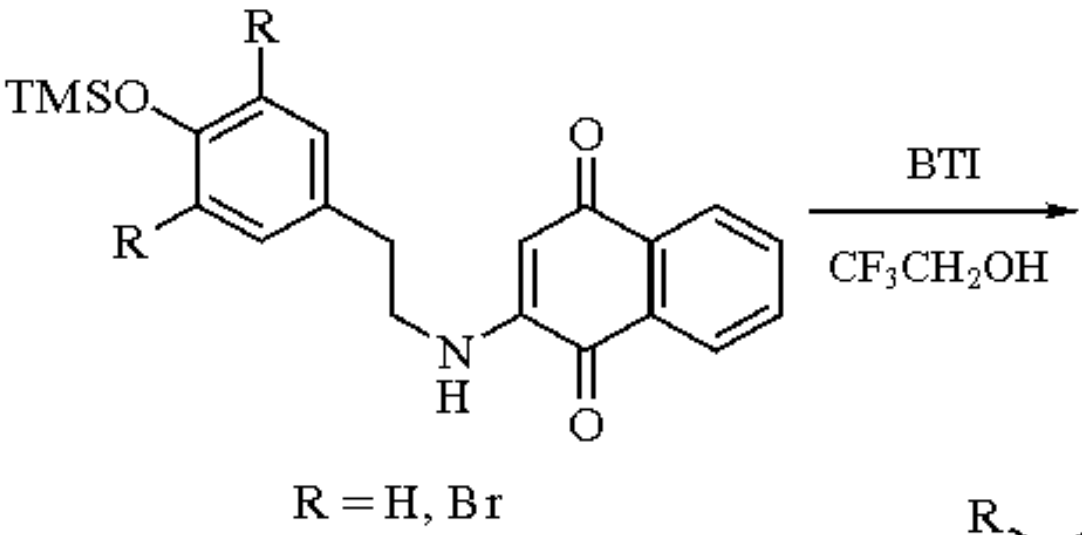

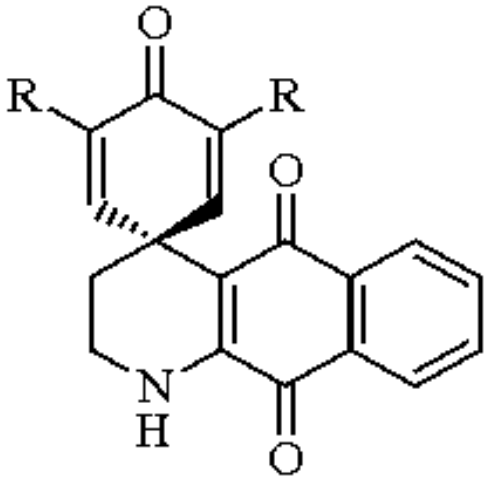

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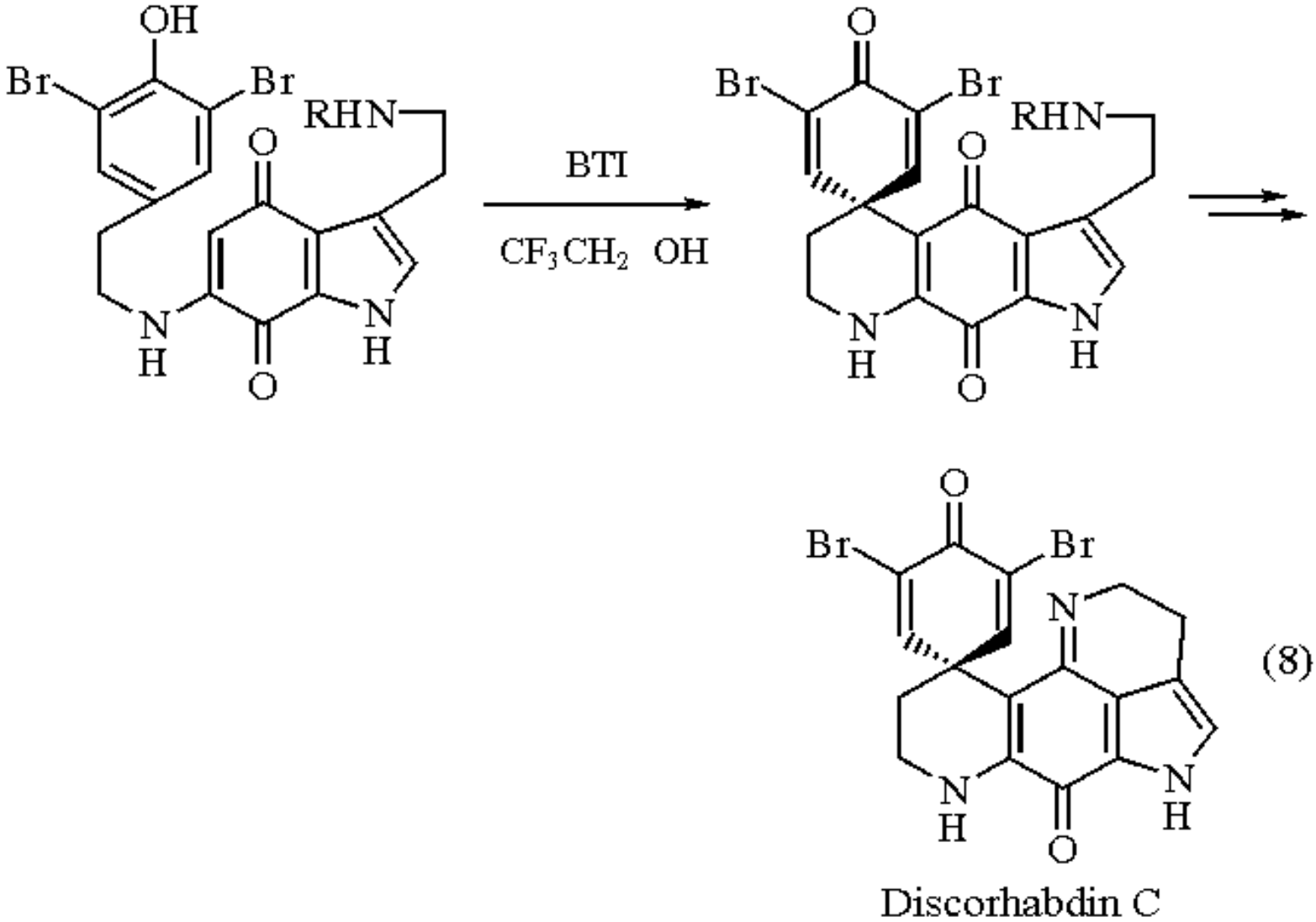

(8)

Discorhabdin C

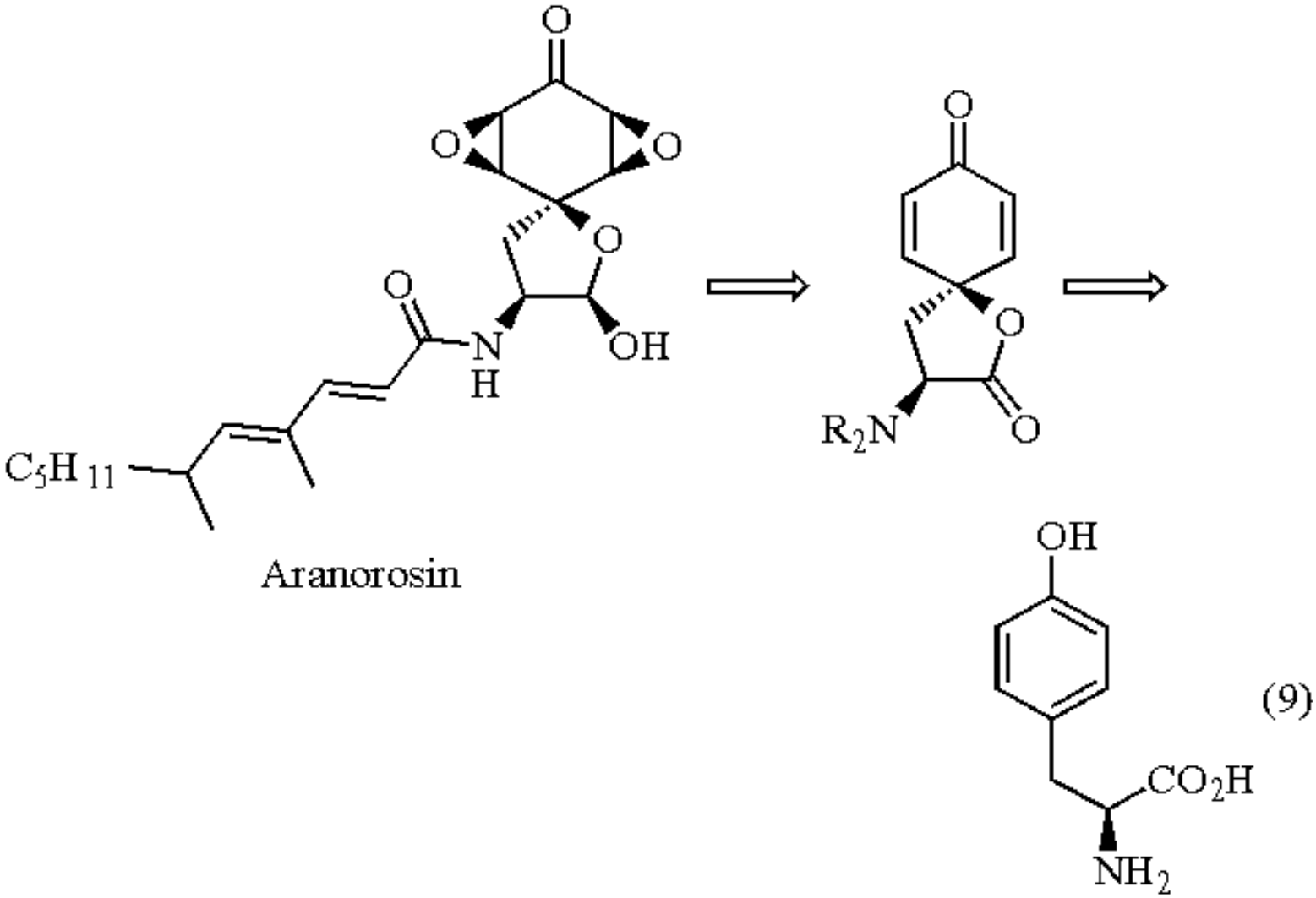

Table 1 illustrates the oxidative cyclization and gives a useful comparison of yields as a function of reagent, solvent, and temperature. All hypervalent iodine oxidations were carried out in acetonitrile or acetonitrile-pyridine (yields in parentheses) at 0 °C.[13]

Table 1 Oxidative Cyclization of 3-(4-Hydroxyphenol)propanoic Acid

Starting material	Reagent	Product	Yield (%)
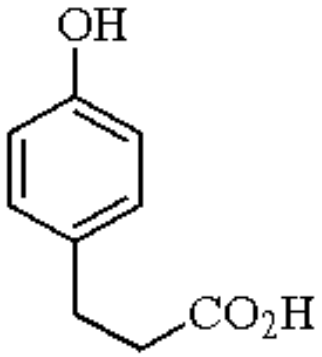			
	$PhI(OCOCF_3)_2$		83 (45-65)
	$PhI(OCOMe)_2$		27 (27)
	$4\text{-}MeC_6H_4I(OCOCF_3)_2$		69 (35)
	$4\text{-}MeC_6H_4I(OCOCF_3)_2$		52 (17)
	$4\text{-}NO_2C_6H_4I(OCOCF_3)_2$		65 (56)
	$1,4\text{-}[I(OCOCF_3)_2]_2C_6H_4$		67 (-)
	$PhI(OH)OTs$		53 (-)

Oxidation of Carbonyl Compounds.

BTI and trifluoroacetic acid in $MeCN/H_2O$ react with aromatic, heteroaromatic, and aliphatic ketones to afford α-hydroxy ketones in moderate to good yields (eq 10).[14] β-Dicarbonyl compounds with α-aralkyl systems can undergo cyclization (eq 11).[15]

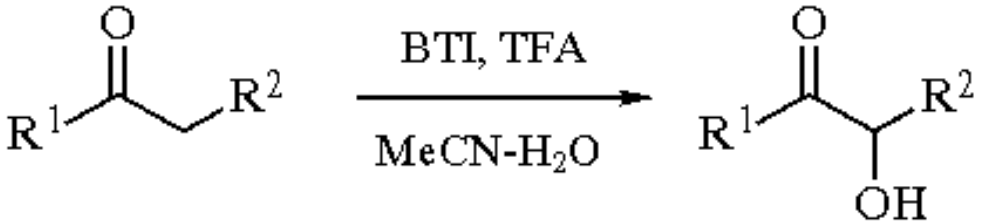

(10)

$R^2 = H$; $R^1 = Ph$, 69%; Tol, 72%; C_5H_{11}, 58%; *p*-FC_6H_4, 67%; *p*-$NO_2C_6H_4$ 29%; furan, 69%; thiophene, 73%; *t*-Bu, 41%; adamantyl, 74%; cyclopropyl, 47%; cyclobutyl, 47%; cyclopentyl, 94%

$R^2 = Me$; $R^1 = Ph$, 36%; *p*-BuC_6H_4, 21%

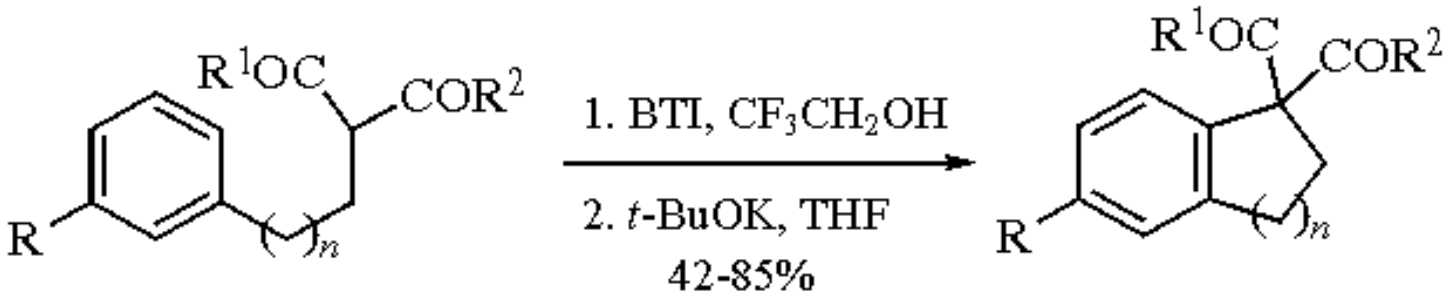

(11)

R = OMe, OTBDMS; R^1 = Me, Et; R^2 = Me, Et, OH, OAc; n = 1, 2

N-[(2-Methylthio)acetyl]-*N*-phenylaniline upon reaction with BTI undergoes Pummerer-type cyclization to yield 3-methylthio-*N*-phenylindol-2(3*H*)-one. This process appears to be a general method of cyclization for appropriate methylthio derivatives (eqs 12-15).[16]

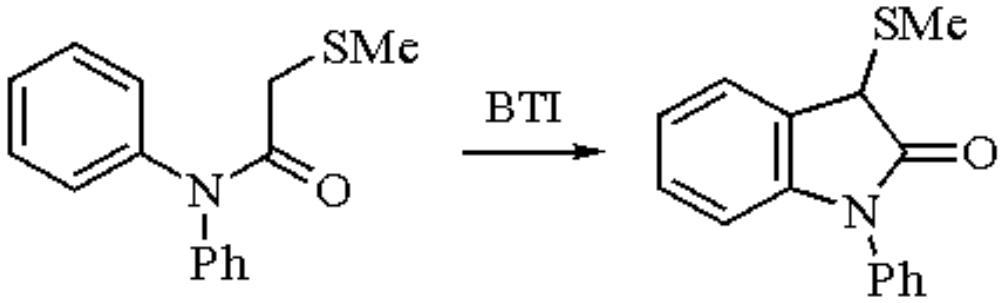

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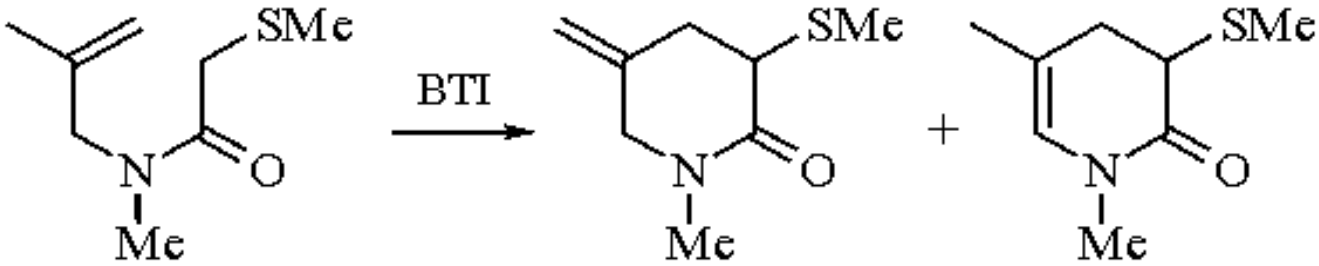

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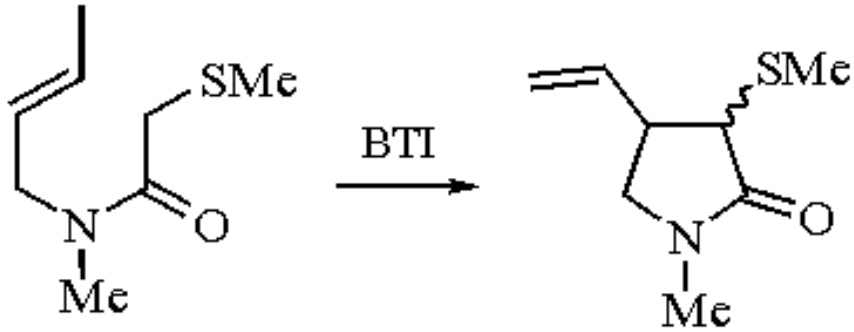

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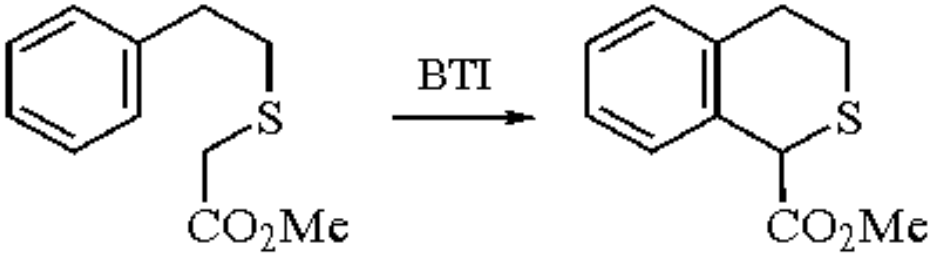

(15)

Dethioacetalization.

BTI is the reagent of choice for dethioacetalization (eq 16).[17] Functional groups, R, such as esters, nitriles, secondary amides, alcohols, halides, alkenes and alkynes, thioesters, and amines are unaffected in this process.

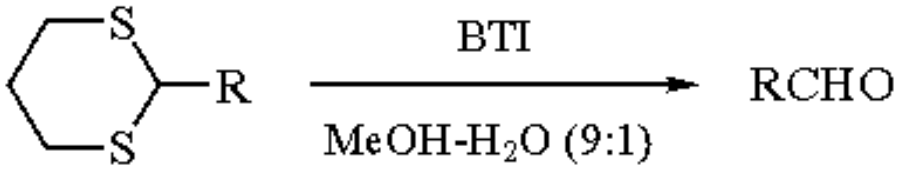

(16)

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Phenyliodine(III) Dichloride

$PhICl_2$

[932-72-9] · $C_6H_5Cl_2I$ · Phenyliodine(III) Dichloride · (MW 274.91)

(selective chlorinating reagent by either radical or ionic mechanisms; reagent for electrophilic chlorination; oxidizing agent)

Alternate Names: phenyliodo dichloride; phenyliodoso chloride; phenylchloroiodonium chloride; dichloroiodobenzene; iododichlorobenzene; iodobenzene dichloride; iodosobenzene dichloride; IBD.

Physical Data: yellow solid; mp 115-120 °C (dec.) from $CHCl_3$; *d* 2.2 g cm^{-3}.

Solubility: sol CCl_4, $CHCl_3$, CH_2Cl_2, $POCl_3$, pyridine; sl sol. Et_2O, pet. ether, CS_2.

Form Supplied in: not commercially available due to lack of stability.

Preparative Methods: by passage of chlorine gas into a solution of iodobenzene in $CHCl_3$ followed by cooling in ice and filtration (87-94%).[1] These recipes specify the use of dry $CHCl_3$ although a later report suggests that ethanol-free solvent is suitable.[2] An alternative preparation is by oxidation of iodobenzene using 5 equiv. of $NaBO_3.4H_2O$ and HCl in MeCN (82%).[3] Some substituted homologs may be obtained by these protocols. Other methods include treatment of iodosylbenzene (PhIO) with Me_3SiCl in CH_2Cl_2[4] and generation in situ by adding sulfuryl chloride to a catalytic amount of PhI.[5,6a] $PhICl_2$ belongs to a useful class of polyvalent iodine reagents, the utility of which in organic synthesis has been reviewed.[6] $PhICl_2$ is a precursor to iodosobenzene, PhIO.[7]

Purification: purity levels can be determined by iodometric titration (typical values: 98-100%).

Handling, Storage, and Precautions: decomposes slowly on standing; corrosive; sensitive to moisture and light; refrigerate and store under nitrogen.

Chlorination of Alkanes.

$PhICl_2$ is widely used as a selective agent for homolytic chlorination of alkanes, alkenes, and alkynes. Radical chain reactions involving PhICl&bdot; as a hydrogen abstracting species or as a chlorine atom donor to multiple bonds were first recognized by Bloomfield in the chlorination of natural rubber.[8] A high selectivity in photochemical chlorination

of branched chain alkanes in iodobenzene solution was subsequently ascribed to the intermediacy of PhICl&bdot;.[9] Using $PhICl_2$ as the chlorinating agent in a photochemically stimulated chlorination of 2,3-dimethylbutane produced the tertiary chloride with <1% of the primary alkyl chloride.[10] High yields of tertiary alkyl chlorides are produced in reactions initiated by traces of $B(C_6H_{13})_3$, possibly in the presence of traces of O_2.[11] Relative reactivities of primary:secondary:tertiary hydrogen atoms in butane and 2,3-dimethylbutane towards PhICl&bdot; are 1:21:368 at 40 °C in CCl_4[12] (vs. 1:3.9:5.1 for Cl&bdot;), although with 1,4-dimethylcyclohexane a tertiary:secondary reactivity of ~10:1 is reported.[13] Towards alkanes substituted with electronegative groups where reactivities are determined by polar effects (e.g. BuCl or PrCN), the isomer distribution of monochlorides is very similar upon photochlorination with Cl_2 or $PhICl_2$. For example, with PrCl at 40 °C in CCl_4 the ratio of 1,1-, 1,2-, and 1,3-dichlorides is 12:58:31 with Cl_2 and 18:48:35 with $PhICl_2$.[12] However, competitive reactions of substituted alkanes indicate a slight difference in overall reactivity using Cl_2 and $PhICl_2$ as the chlorinating agents.[12]

The possibility exists that mixed chains occur for substrates with a low homolytic reactivity, involving both PhICl&bdot; and Cl&bdot; as hydrogen abstracting species. The selectivity of PhICl&bdot; for tertiary attack has been applied in the chlorination of various cholestanyl derivatives, when the major products are derived from attack at the axial hydrogen atoms at the 5α-, 9α-, 14α-, or 17α-positions.[14] In 3α-(trifluoroacetoxy)androsterone the electronegative substituents cause attack to occur nearly exclusively at the 9-position.[15] The remote functionalization of steroids at the 9α-, 14α-, or 17α-positions has been achieved by use of templates which direct the attack of a tethered ArICl&bdot; to the appropriate tertiary position. Thus steroid derivatives with a 3α-substituent (**1a**) yield nearly exclusively chlorine substitutions at C-9 (eq 1), while with (**2**) attack is directed to C-14.[16] The chlorinations are conveniently performed in a relay method by use of a tethered ArI (**1b, 2b, 4**) with $PhICl_2$ or ***Sulfuryl Chloride*** as the source of chlorine.[17] Using this technique with substituent (**1b**) at the 17α-position of 17α-hydroxyprogesterone, a quantitative yield of the 9α-chloride is observed.[18] Template (**3**) at the 3α-position of cholestanol also directs hydrogen abstraction to the C-9 position upon photolysis with $PhICl_2$.[19] With the 3α-substituent (**1b**), tandem radical reactions have also been observed by use of Cl_2 in CBr_4 (to form 9-bromo-3-cholestanol) or in the presence of thiocyanogen (to form the 9-thiocyanate).[20] With the 3α-substituent (**4**), attack of the tethered ArICl&bdot; is directed (>54%) to the axial hydrogen at C-17.[21]

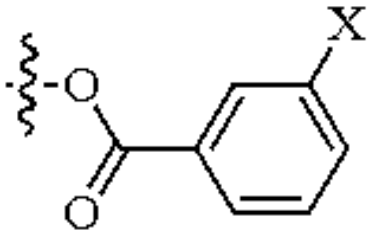

(1a) X = ICl_2
(1b) X = I

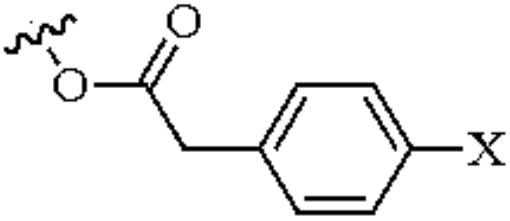

(2a) X = ICl_2
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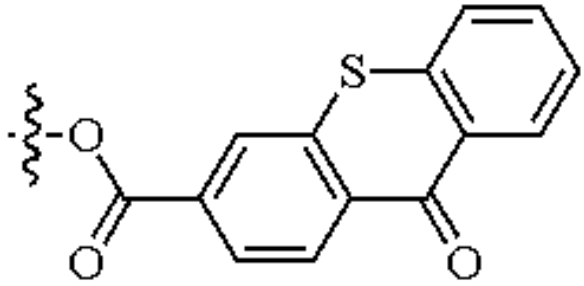

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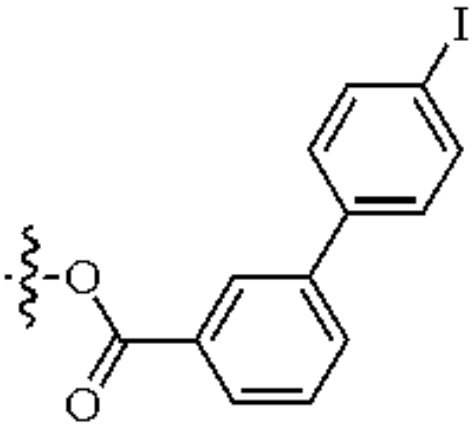

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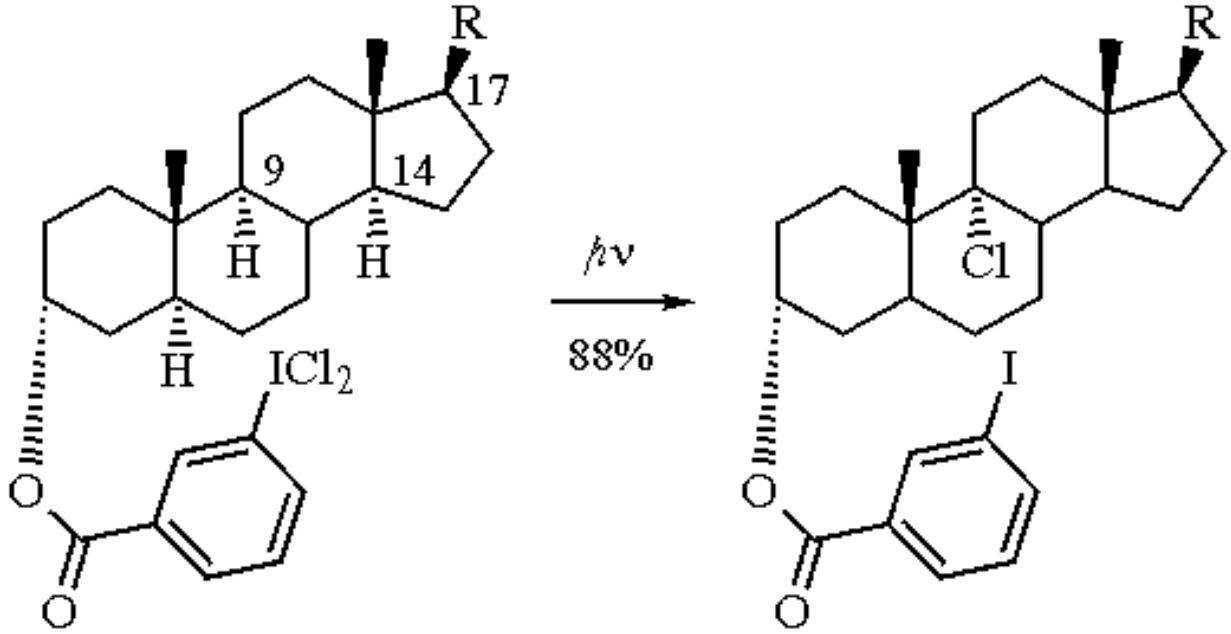

(1)

Chlorination of Alkenes.

In general, chlorinations of alkenes using $PhICl_2$ follow a radical pathway when the reaction is initiated by heat or light; in such cases the stereochemical outcome is much influenced by steric factors.[22] By contrast, ionic mechanisms predominate when no initiation is used or when ***Trifluoroacetic Acid*** is added; Wagner-Meerwein shifts can become important in such cases but are not observed in thermal- or light-induced reactions.[22] $PhICl_2$ has been found to be the most selective of a number of chlorinating reagents in the selective formation of *trans*-1,2-dichlorocyclohexane from cyclohexene (eq 2).[23]

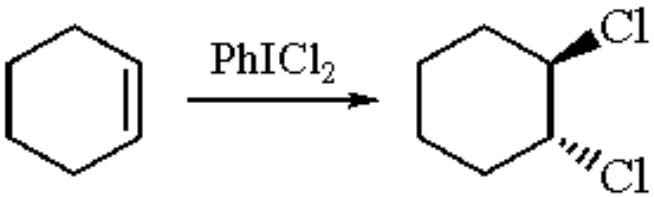

(2)

Similarly, both *p*-dioxene and 1,4-dihydronaphthalene are converted selectively into the corresponding *trans*-1,2-dichloro derivatives.[24] Under radical conditions (i.e. thermally (40-80 °C) or light-induced) norbornene is converted into mixtures of the *exo*-*cis*- and *trans*-dichloro derivatives (eq 3).[25] However, ionic mechanisms appear to operate when the same substrate is treated with $PhICl_2$ in the presence of molecular oxygen, leading to the nortricyclyl chloride (**5**) together with the 2,7-dichloride (**6**).[25] In general, such reactions are much cleaner using $PhICl_2$ than is the case when using other chlorination reagents. The *exo*-*cis*-dichloro acid (**7**) is the major product when the corresponding *endo*-norbornenyl acid is treated with $PhICl_2$.[26]

(5)

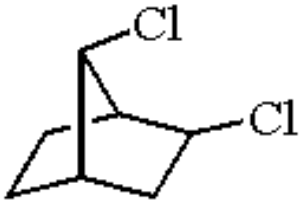

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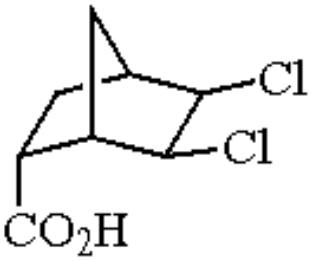

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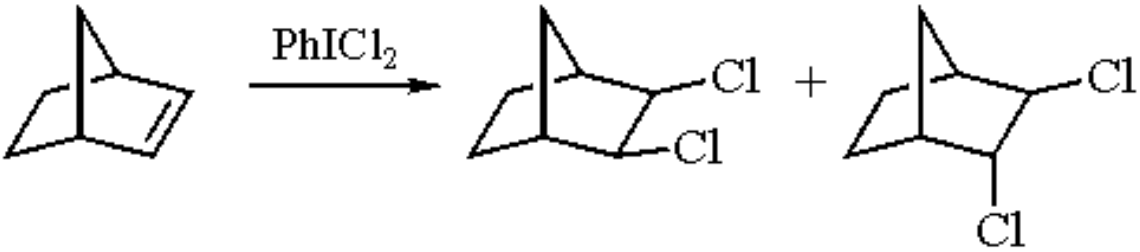

(3)

The selectivity of $PhICl_2$ is further emphasized by its ability to chlorinate a variety of terpenoid alkenes efficiently and without rearrangement.[27] Under strictly anhydrous conditions, $PhICl_2$ in dry $CHCl_3$ converts cholesterol into the 5α,6α-dichloro derivative (eq 4), probably via a cyclic transition state, whereas molecular chlorine gives the 5α,6β-epimer via an ionic mechanism.[28] Under radical conditions, $PhICl_2$ converts acenaphthylene into the *trans*-dichloride whereas molecular chlorine leads to the corresponding *cis*-isomer; both transformations are not especially efficient however.[29] Chlorinations of 1,3-dienes are, in general, not especially useful except in special cases[30] and rearrangements can occur in chlorinations of alkenyl cyclopropanes by $PhICl_2$ (eq 5).[31]

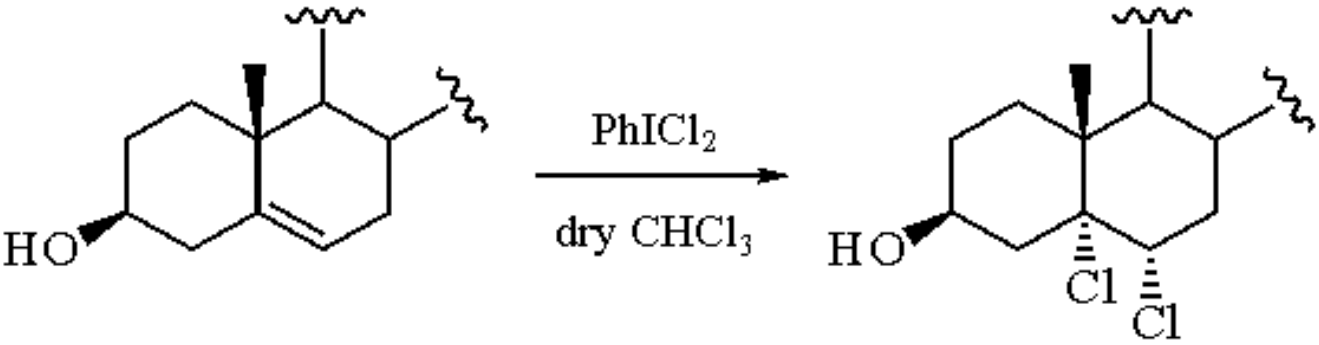

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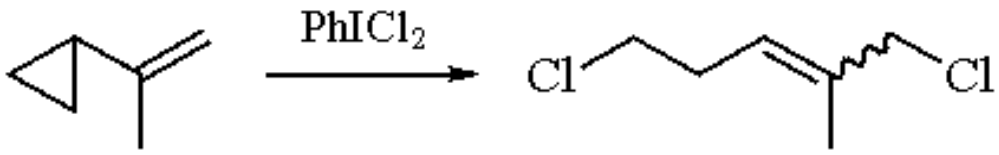

(5)

Chlorinations of Alkynes.

Disubstituted alkynes are chlorinated by $PhICl_2$ under radical conditions ($CHCl_3$, AIBN, reflux) to give mainly (*E*)-dichloroalkenes (eq 6).[32] Depending upon the conditions used, molecular chlorine gives either predominantly the corresponding (*Z*)-isomers or complex mixtures.

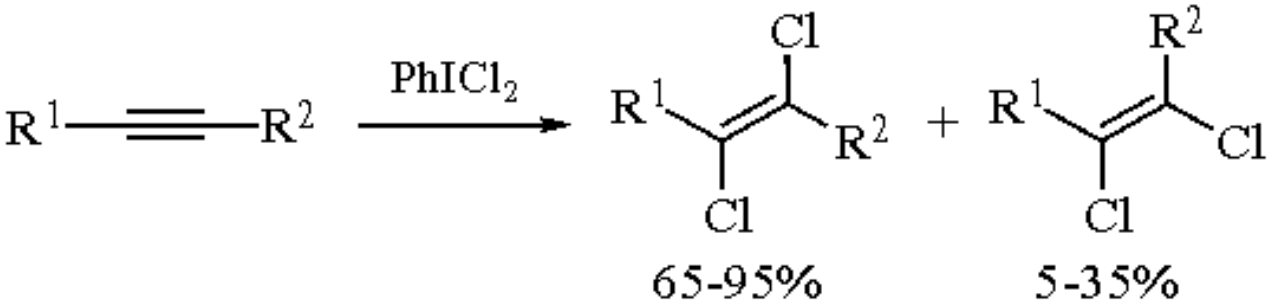

(6)

Electrophilic Substitution.

The chlorination of aromatic systems by $PhICl_2$ is often very efficient. For example, salicylic acid is converted into the 5-chloro derivative in 89% yield (eq 7)[33] and high yields of chlorinated pyrroles[34] and 5-chlorouracils[35] can be similarly obtained.

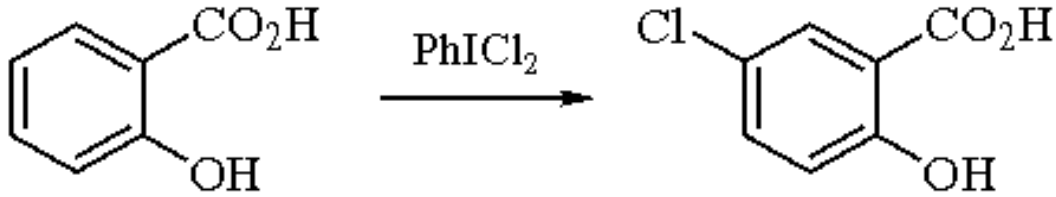

(7)

Other Chlorinations.

α-Chloro ketones can be prepared from the parent ketones or 1,3-diones using $PhICl_2$ under either ionic or radical conditions, although the latter photo-induced method is often more selective.[5] The reagent when prepared in situ from iodobenzene (cat.) and sulfuryl chloride is suitable for these conversions, for which a full recipe is given in a review.[6a] Perchloro-α,α-dichloro ketones have been prepared by treatment of the corresponding perchloro-α-diazo ketones with $PhICl_2$.[36] Similarly, α-chloro ethers can be obtained from the parent compounds using $PhICl_2$; when chlorine is used, α,α-dichloro ethers are generally obtained.[37] Stabilized phosphorylides such as Ph_3PCHCO_2Me are converted into the corresponding α-chloro derivatives upon exposure to $PhICl_2$.[38] In the case of an acylphosphorane, the intermediate α-chlorophosphonium salt can be hydrolyzed by base to give the corresponding α-chloro ketone. Perhaps surprisingly, α-alkoxyphosphoranes from the SCOOPY reaction sequence react with $PhICl_2$ to provide reasonable yields of (*Z*)-vinyl

chlorides (eq 8), whereas reaction with ***N-Chlorosuccinimide*** gives the corresponding (*E*)-isomers.[39]

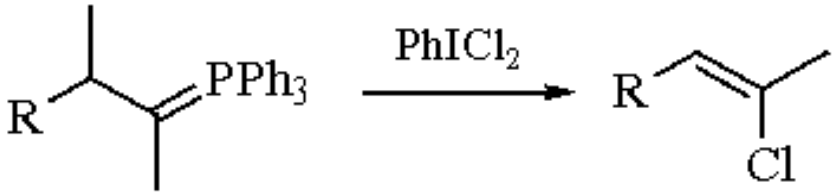

(8)

In similar fashion to the foregoing, aryl aldoximes also undergo α-chlorination by $PhICl_2$; these intermediates are deprotonated in situ to give the corresponding nitrile oxides which are also trapped in situ, leading finally to 60-75% yields of the [1,3]-dipolar adducts (eq 9).[40] By contrast, similar treatment of aryl ketoximes simply results in hydrolysis back to the parent alkaryl ketone.[41] The reaction fails with oximes derived from dialkyl ketones.

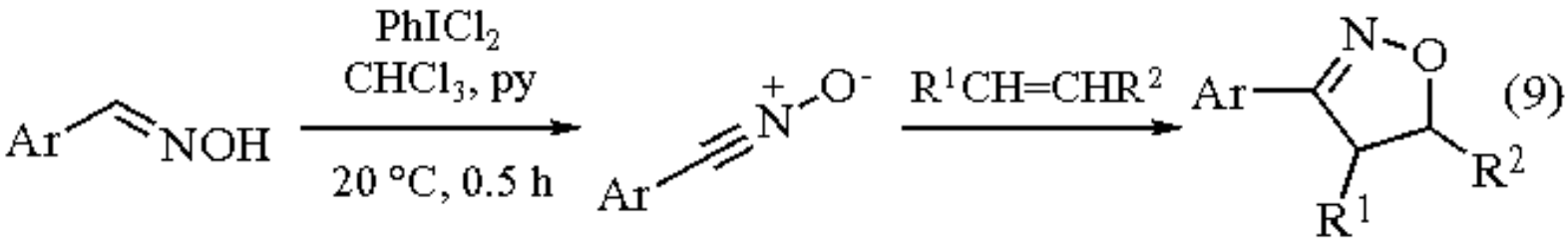

(9)

Remote Functionalization of Steroids.

$PhICl_2$ is a key reagent in a method for the remote functionalization of steroids developed by Breslow and his colleagues. The reaction is a radical relay mechanism in which an aryliodine dichloride is generated in situ from a suitable iodobenzene derivative (e.g. eq 10).[42] A chlorine atom is then transferred to an adjacent tertiary position (the 14-position in the example shown); subsequent elimination of HCl and esterification completes the sequence leading to a Δ^{14}-unsaturated derivative. By varying the length and position of the side chain carrying the iodoaryl function, selective chlorination at both C-9 and C-17 positions can be achieved.[42,43] More recent developments feature a somewhat different mechanism wherein an *S*-chloro species, derived from a similarly tethered heteroaromatic ligand and $PhICl_2$, is a key chain component.[44] Prior to these developments, $PhICl_2$ alone, under photolytic conditions,[45-47] was found to show considerable selectivity for C-9 in suitably designed steroids.[48]

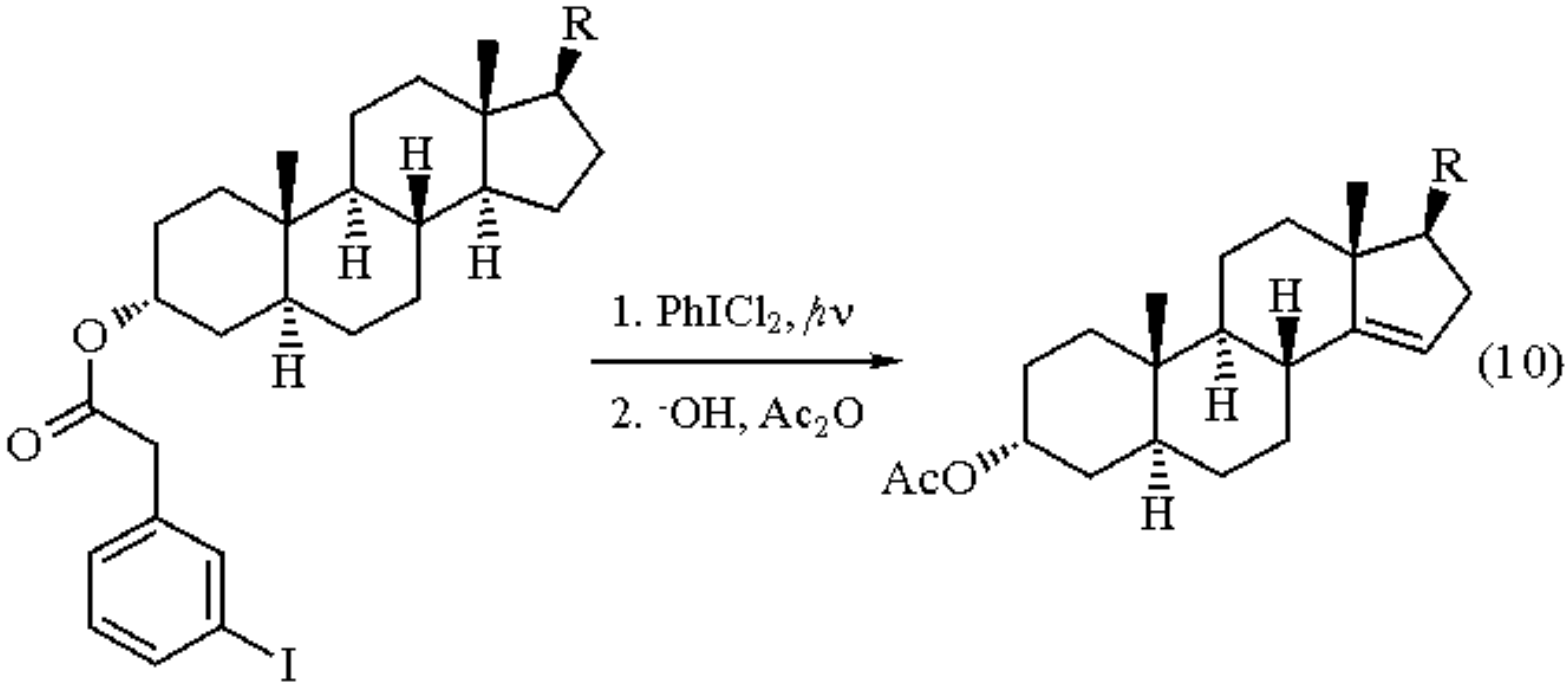

Oxidations of Sulfides and Selenides.

Sulfides[49] and diaryl selenides[6a,50] are rapidly oxidized to the corresponding sulfoxides and selenoxides by $PhICl_2$, which is a more powerful oxidant than metaperiodate in such reactions. Despite this, the reactions can be controlled such that sulfones are not formed. Sulfoxides can also be converted into α-chloro derivatives using $PhICl_2$;[51] it is therefore not surprising that sulfides can be directly transformed into α-chloro sulfoxides (sulfone formation may compete) by lengthier exposure to excess reagent (eq 11),[52] which can also be used to obtain perfluorosulfuryl chlorides from the corresponding sulfinic acids.[53]

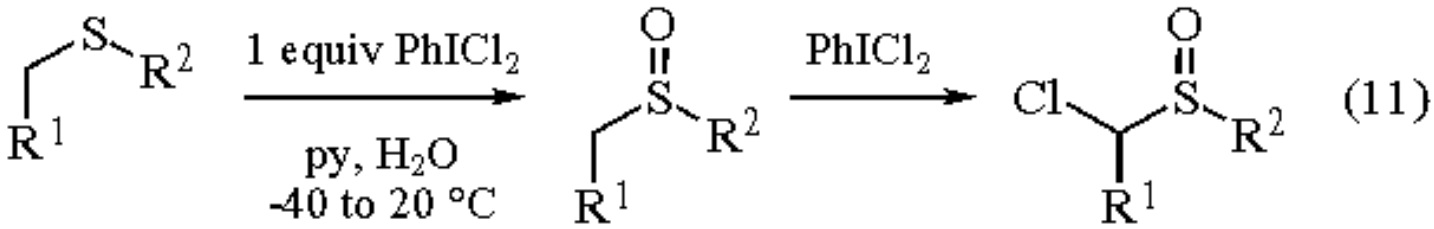

Oxidation of Alcohols.

$PhICl_2$ in the presence of a weak base such as pyridine can be used to oxidize secondary alcohols to ketones (eq 12).[54] The method is not suitable for primary alcohols or diols or to unsaturated substrates due to competing chlorination.[22-32]

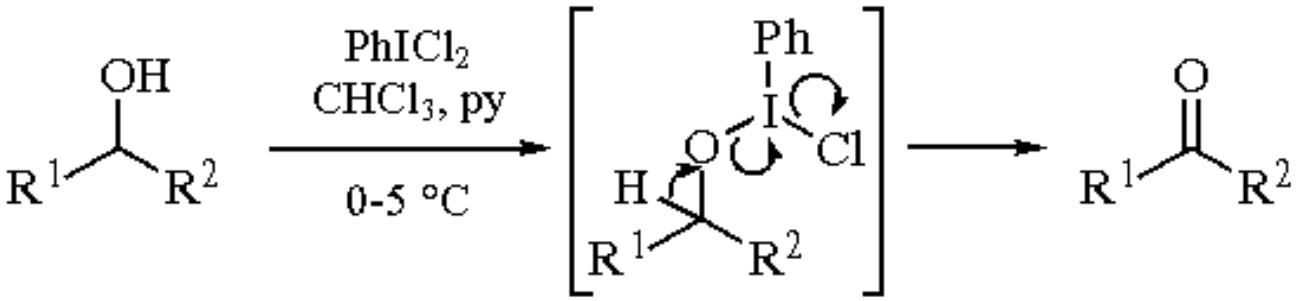

(12)

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Phenyl Isocyanate[1]

PhNCO

[103-71-9] · C_7H_5NO · Phenyl Isocyanate · (MW 119.13)

(organic heterocumulene capable of forming heterocycles via cycloaddition to dipolarophiles;[1a-e] adds nucleophiles producing polyfunctional compounds;[1a,b,f,g] readily inserts into metal-element bonds providing metal-mediated construction of new C-C bond;[1g,h] used as dehydrating agent)

Physical Data: mp -30 °C; bp 55 °C/13 mmHg; *d*19.64 1.10 g cm^{-3}; *n*20D 1.5350.

Solubility: sol ether, alcohol, benzene, toluene, xylene, DMF, MeCN.

Form Supplied in: liquid with acrid odor; purity about 98%.

Analysis of Reagent Purity: GLC.

Purification: addition of Grignard reagent solution and rapid distillation.

Handling, Storage, and Precautions: moisture sensitive; corrosive; highly toxic; irritating to eyes; lachrymator. Use in a fume hood.

Nucleophilic Addition.

Oxygen, nitrogen, sulfur, phosphorus, and carbon nucleophiles add across the C=N bond of phenyl isocyanate (**1**). Due to a high affinity to water, (**1**) is used in ***Triethylamine***-promoted dehydration of primary nitroalkanes to nitrile oxides (Mukaiyama reaction) (eq 1),[2] and of aldoximes[3] and α-hydroximino acids[4] to nitriles. The phenylcarbamic acid formed from (**1**) immediately decomposes with CO_2 evolution. In a similar way, (**1**) reacts with alcohols to produce *N*-phenylurethanes.[1a,b,5] *N*-Phenyl-*O*-arylurethanes can be hydrogenolyzed to give arenes.[5b] Hydroxamic acid azides behave as oxygen nucleophiles toward (**1**) and give 5-phenyloxadiazoles.[6]

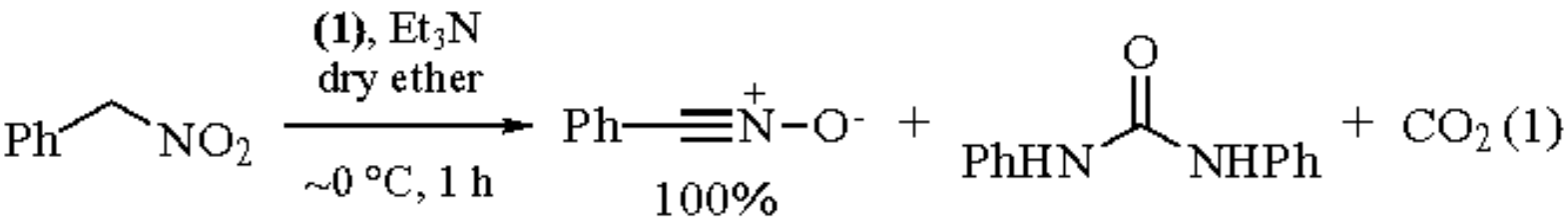

Nitrogen nucleophiles of high basicity (*N*,*N*-acetals, hexahydro-*s*-triazine, iminophosphoranes) are especially active in additions to (**1**),[1a,f,7] while aminoalkylphosphoramidates react regioselectively at the nitrogen of the P-N bond giving carbodiimides (eq 2).[8] Even carboxamides readily react with (**1**) to form uracils after cyclization.[9a] To compensate for the low basicity of tosylamides, their reactions with (**1**), yielding *N*-tosylureas, are carried out in the presence of ***Copper(I) Chloride***.[9b]

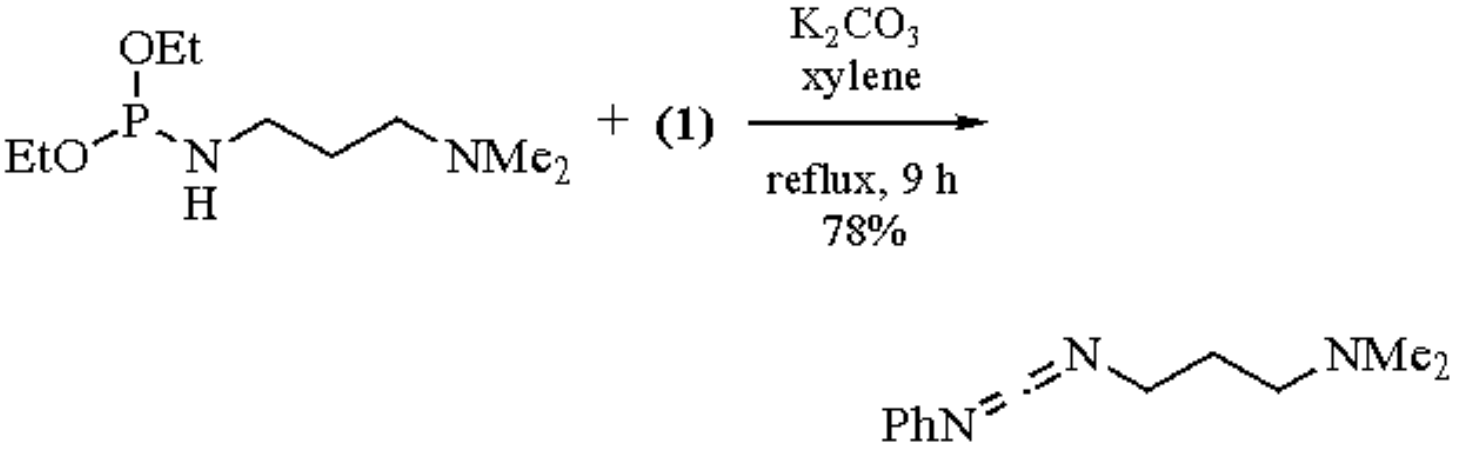

(2)

α,ο-Alkanedithiols react with (**1**) to give biscarbamothioates in good yields.[10] Comparatively weak P-nucleophiles are not very active in additions to (**1**). However, trialkylphosphine-induced dimerization and trimerization of (**1**) does involve intermediate betaine formation due to addition of the phosphorus nucleophile to the isocyano group.[11] Hydride-ion or enolate addition to the isocyanate carbon provides *N*-functionalized *N*-phenylformamido compounds[12] and highly substituted β-keto amides (eq 3),[13] respectively.

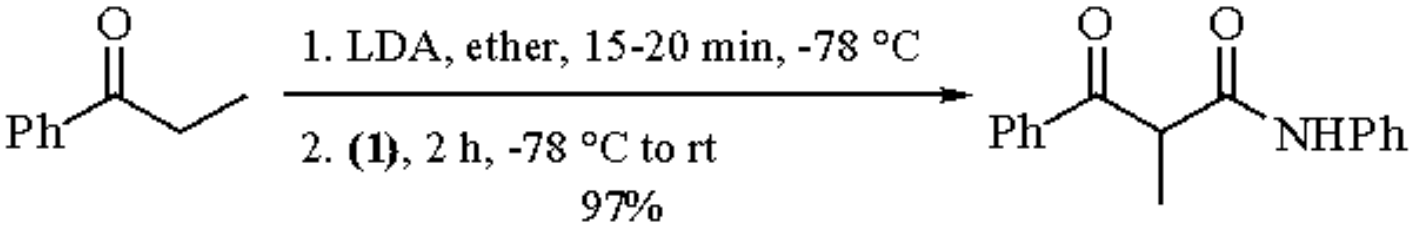

(3)

Aziridines react with (**1**) with ring expansion (eq 4).[14,1f,1g] This is formally a 1,3-dipolar cycloaddition reaction (see below). With more complex bifunctional nucleophiles (silylamines,[15] aminoboranes, and organoboranes[16]) the reactions of (**1**) provide a facile route to polyfunctional organosilicon and organoboron compounds.

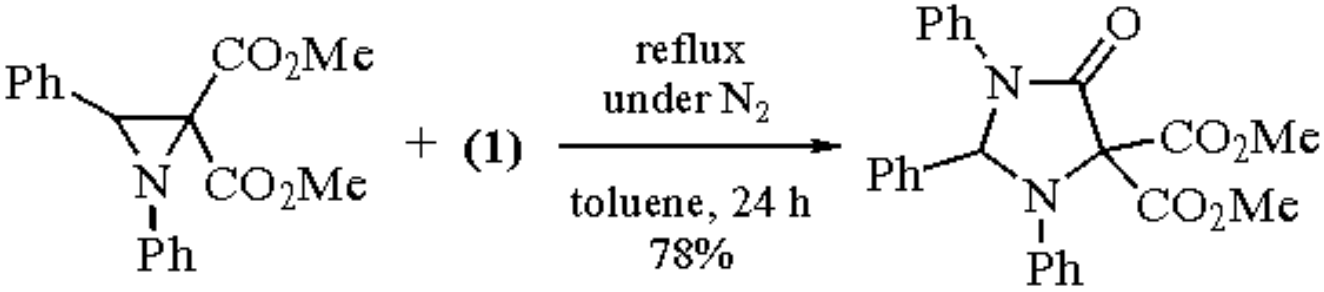

(4)

Cycloaddition.

Phenyl isocyanate undergoes polar cycloaddition reactions with unsaturated substrates to give both heterocycles and

functionalized open-chain compounds. Although both the C=N and C=O double bonds can participate in cycloadditions, usually the process takes place with high regioselectivity across the C=N bond. The structure of cycloadducts and the cycloaddition mode are defined by the nature of the unsaturated substrate and also by the substrate:phenyl isocyanate ratio. Nucleophilic alkenes react with (**1**) to afford unstable [2 + 2] cycloadducts (2-azetidinones), which are readily cleaved to give polyfunctional aliphatic compounds (eq 5).[17]

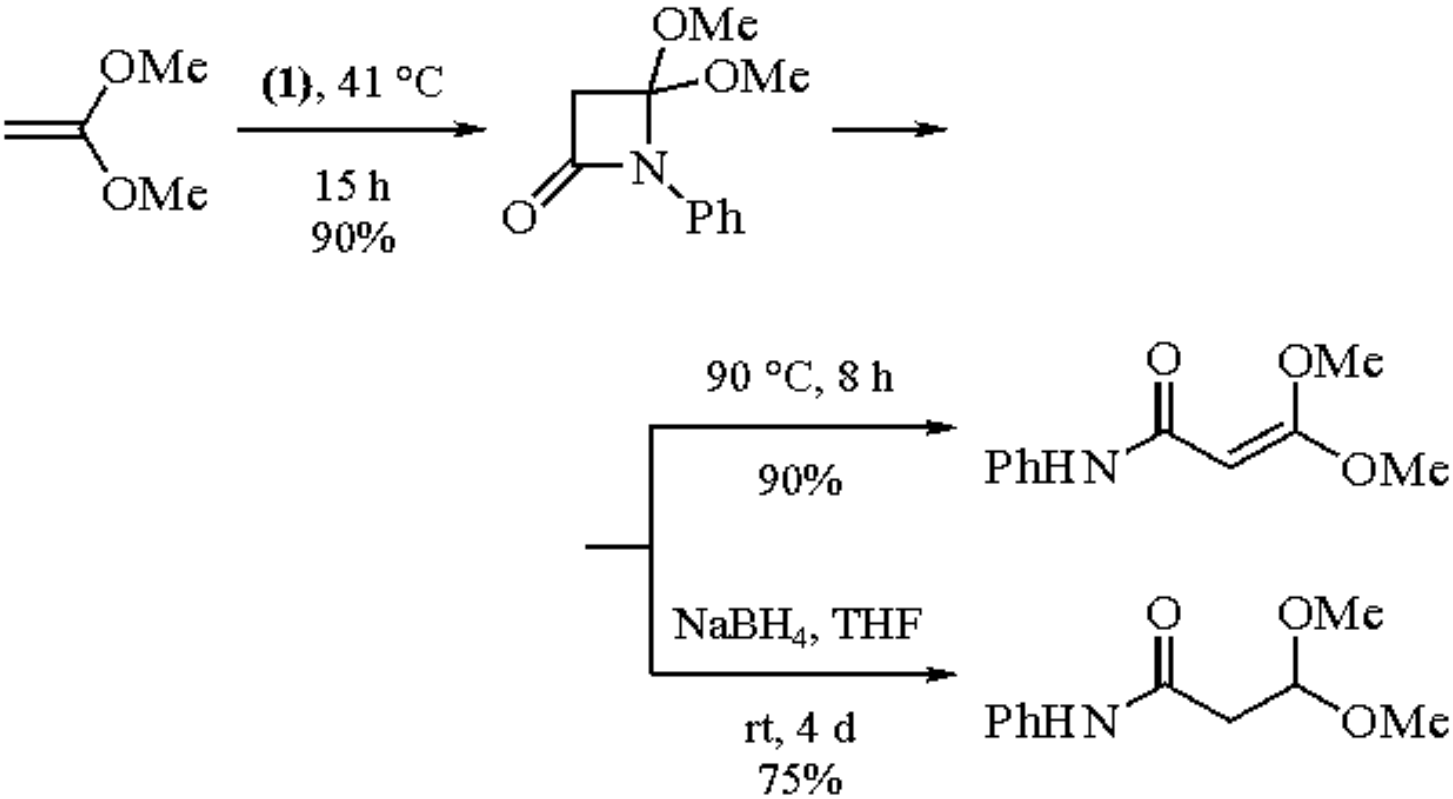

(5)

Reactions of (**1**) with C=N-containing substrates[1d] are sensitive to the nucleophilicity of the C=N double bond. *N*-Alkyl-*N*′-arylcarbodiimides add to (**1**) exclusively at the *N*-alkyl-substituted C=N bond to give 4-arylimino-1,3-diazetidin-2-ones.[18] Six-membered heterocycles can be synthesized from unsaturated substrates and phenyl isocyanate via [2 + 2 + 2′], [2 + 2′ + 2′], or [4 + 2] dipolar cycloaddition reactions. The first two modes are realized due to low stability [2 + 2] adducts which react further (especially at elevated temperature) with an excess of phenyl isocyanate. In a [2 + 2′ + 2′] reaction, ketene *S*,*N*-acetals react with (**1**) (2 equiv reflux in toluene) to afford 1,3-diphenyl-2-pyrimidinones,[19] whereas the [2 + 2 + 2′] route occurs in the reaction with 3*H*-indole (eq 6).[20]

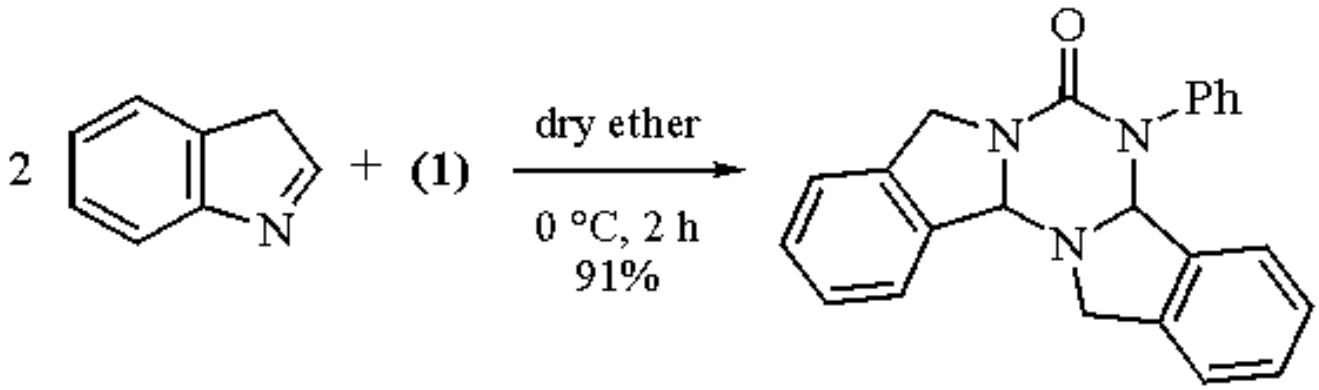

(6)

[4 + 2] Cycloaddition reactions are based on a condensation of (**1**) with a suitable 1,4-dipolar synthon (4-amino-1-

azabutadienes,[21] 1,3-diazabutadienes,[22] 2-aza-1,3-dienes,[23] 1-(triphenylphosphinimido)dienes[24]) and give the corresponding heterocycles (2-imino-1,2-dihydropyrimidines,[21] 5,6-dihydro-1,3,5-triazine-2,4(1*H*,3*H*)-diones,[22] 1,2-dihydropyrimidin-4(3*H*)-ones (eq 7),[23] 2-phenylaminopyridines,[24a] or condensed quinazolines.[24b,c]). Phenyl isocyanate also enters 1,3-dipolar [3 + 2] cycloaddition reactions (with *N*-oxides, 1,2-diimines, 2-imino ketones, azides) to produce five-membered ring heterocycles.[1a,c,e,25]

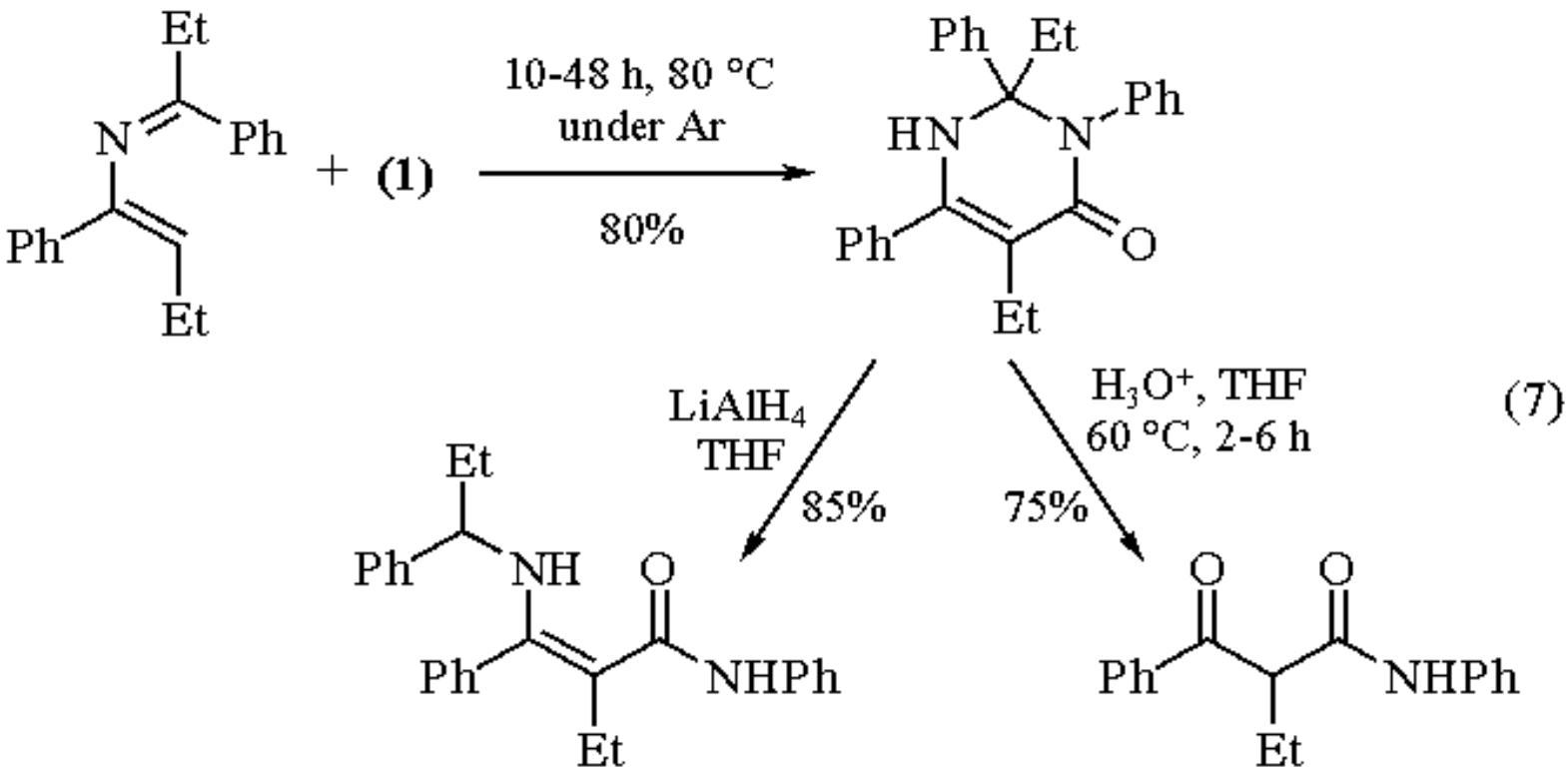

Metal-Promoted C-C Bond Forming Reactions.

The most widely exploited route to new C-C bond formation at the isocyanate carbon is based on insertion of (**1**) into main-group metal-carbon bonds[26] or transition metal-carbon bonds.[27] ***Samarium(II) Iodide***-promoted self-coupling of (**1**) affords *N*,*N*´-diphenyloxamide.[28]

Regiospecific *C*-(*N*-phenylcarbamoylation) reactions of copper and nickel β-keto imine complexes,[29a] phenols (in the *ortho*-position in the presence of ***Boron Trichloride***),[29b] and 5*H*-azepino[1,2-*a*]benzimidazol-7(8*H*)-one at C-6[29c] are examples of electrophilic substitution reactions in which the acidic proton of the substrate or ligand is transferred to the nitrogen atom of phenyl isocyanate.

Numerous coupling reactions of (**1**) with unsaturated substrates are catalyzed by nickel(0) complexes.[1h] These serve as templates providing intermediate formation of nickel azaheterocycles stabilized by strong Ni-N coordination. These heterocycles decompose with formation of unsaturated amides and liberation of coordinated Ni^0 that enables one to employ only a catalytic amount of the Ni^0 source.[1h]

In contrast to 1,1-difluoroalkenes, which produce saturated β,β-difluorocarboxamides with (**1**),[30] alkenes and arylalkenes undergo substitutive *N*-phenylcarbamoylation at the terminal or allylic carbon, yielding the corresponding alkenic carboxamides.[1h,31] 1,3-Pentadiene reacts analogously to form sorbanilide in 250% yield (based on Ni^0) (eq 8).[32] Both acyclic and five-membered carbocyclic amides are formed from 1,5-hexadiene and 1,6-heptadiene (eq 9).[33]

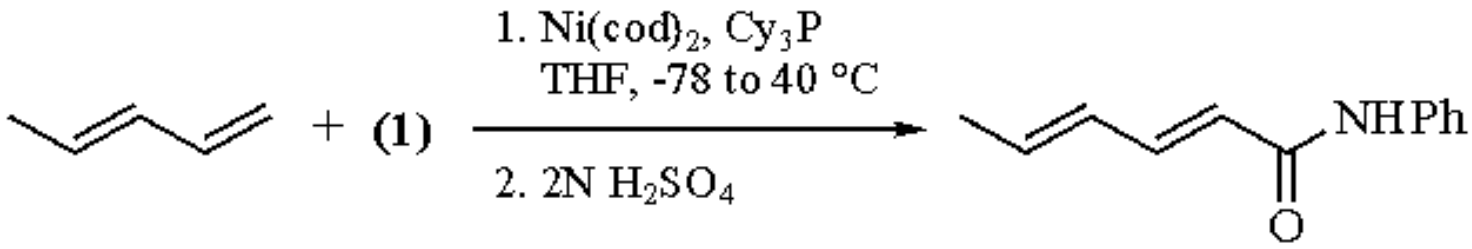

(8)

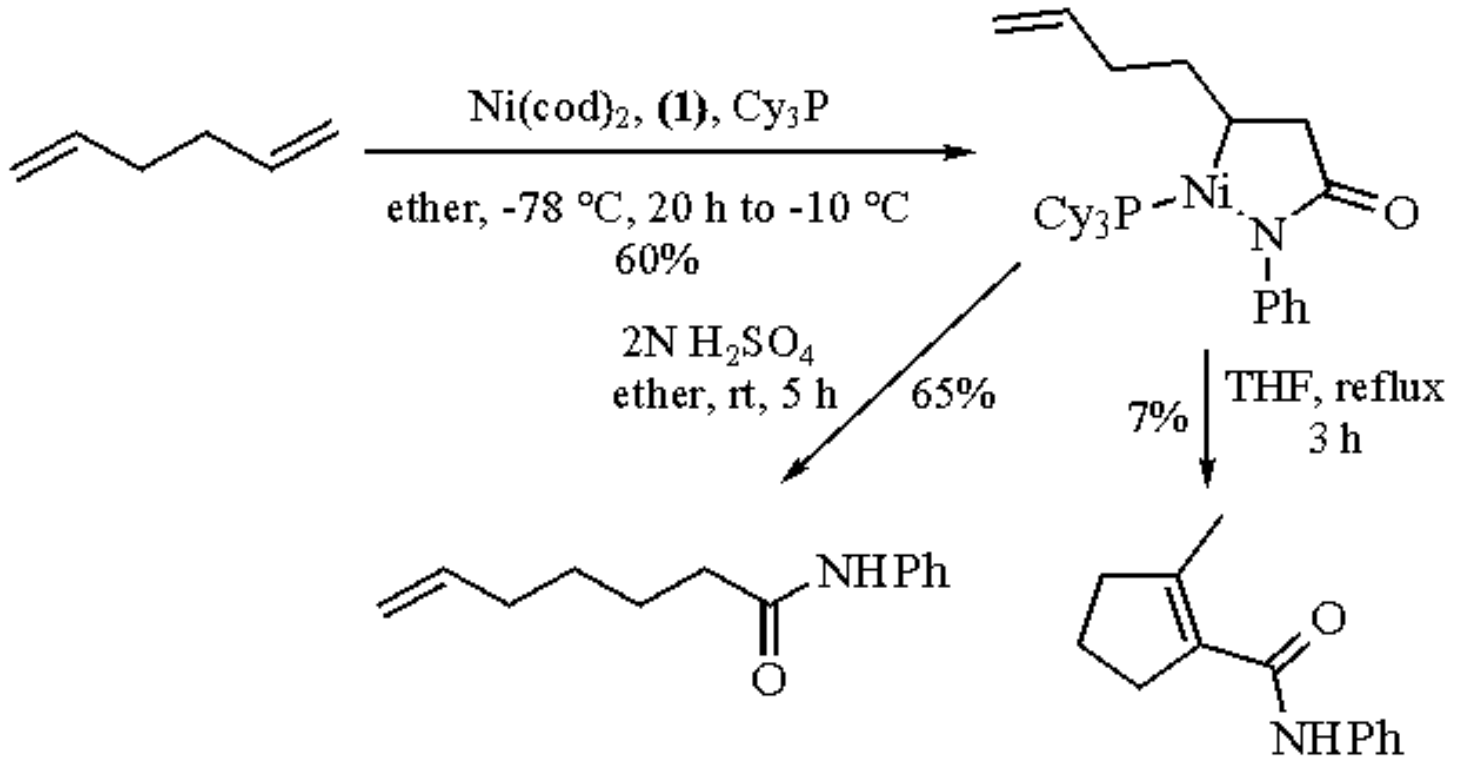

(9)

Nickel(0) complexes[1h] as well as low-valent tantalum complexes[34] promote reductive carbamoylation of alkynes with (**1**) to produce 2-alkenyl- and 2,4-alkadienylcarboxamides (eq 10).[34] [2 + 2 + 2´] Cycloaddition occurs in the presence of basic phosphine ligands under very mild conditions to give 2-pyridones.[1h,35] On the contrary, in ***Pentacarbonyliron***-mediated reactions, [2 + 2´ + 2´] cycloaddition occurs to afford hydantoins (eq 11).[36]

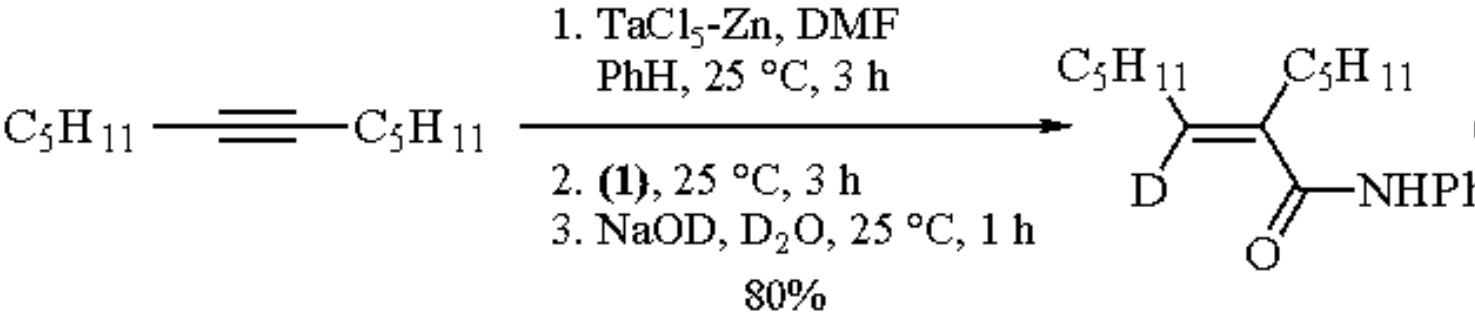

(10)

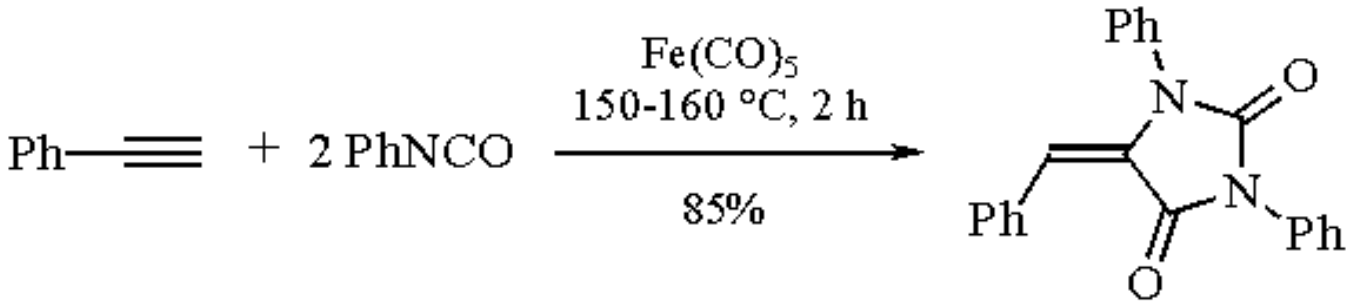

(11)

Strained rings readily undergo ring expansion upon metal-mediated reactions with (**1**). For example, Pd^0 complexes catalyze condensation of (**1**) with vinylcyclopropanes to give 5-vinyl-4-phenylpyrrolidin-2-ones.[37] The direction of ring cleavage of oxiranes with (**1**) depends on the catalyst employed. For example, Sb^V and Pd^0 compounds,[38,39] as well as trialkyltin reagents coordinated by HMPA,[40] affect α-cleavage yielding 4-substituted 3-phenyloxazolidin-2-ones (eq 12), while other organotin reagents afford also the 5-substituted isomers.[41] These heterocycles are masked β-amino alcohols, which are readily liberated on hydrolysis.

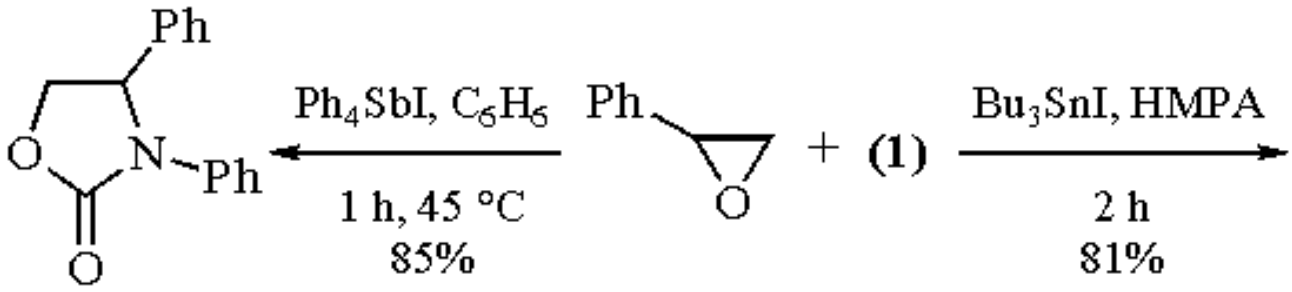

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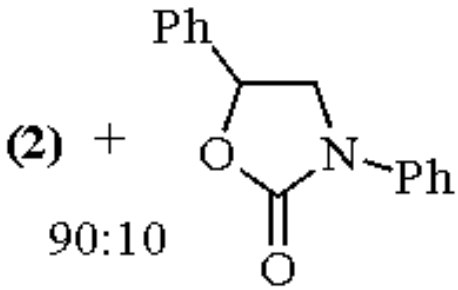

(12)

Related tin-mediated cleavage of four-membered oxetanes, γ-bromo-β-lactones, or β-lactams has been used in facile one-pot syntheses of tetrahydro-1,3-oxazin-2-ones,[42a] 5-(methoxycarbonyl)methyl-3-phenyloxazolidin-2-ones, and 1,3-imidazolidin-2-ones.[42b] ***Tetrakis(triphenylphosphine)palladium(0)***-promoted reaction of propylene carbonates with (**1**)[43] also effectively leads to tetrahydro-1,3-oxazin-2-ones which hydrolyze to the corresponding γ-amino alcohols.

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Emmanuil I. Troyansky

Phenyl Isocyanide[1,2]

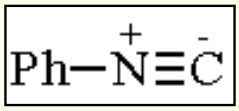

[931-54-4] · C_7H_5N · Phenyl Isocyanide · (MW 103.13)

(synthesis of heterocycles)

Physical Data: bp 54 °C/13 mmHg; *d* 0.98 g cm^{-3}.

Solubility: sol most organic solvents, e.g. methanol, ethanol, ether, toluene, dichloromethane.

Form Supplied in: pure liquid; not commercially available.

Analysis of Reagent Purity: gas chromatography.

Preparative Methods: see Grundmann,[3a] Ugi and Meyr,[3b] and Obrecht et al.[3c]

Handling, Storage, and Precautions: should be used freshly distilled. Foul smelling liquid; should be stored and used in a fume hood. Contaminated equipment should be washed with 5% methanolic sulfuric acid.

Synthesis of Heterocycles.[1,2]

The pharmacologically interesting barbituric acid derivative 6-phenylaminofuro[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione can be synthesized from readily available benzylidene-*N*,*N*´-dimethylbarbituric acid with phenyl isocyanide by Michael-type addition and cyclization with tautomerization (eq 1).[4]

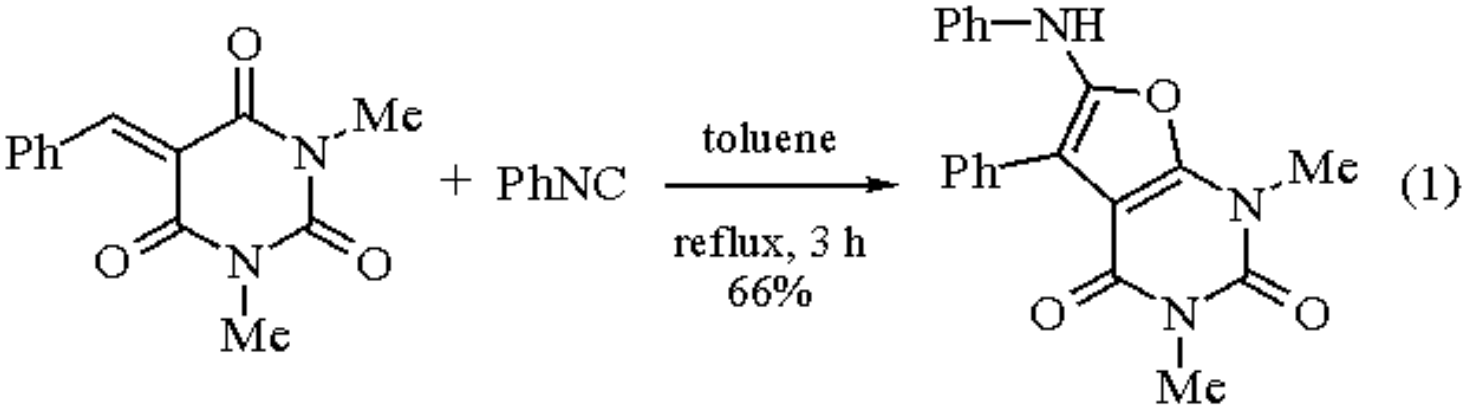

Benzofuran derivatives can be prepared in a general procedure by an Ugi-type reaction from substituted *o*-hydroxybenzaldehydes and isocyanides (eq 2).[5] The reaction of the intermediate iminium compound, from the aldehyde and the ammonium salt, with the isocyanide stops at the addition step of the Ugi reaction. The resulting amino group reacts with another equivalent of the aldehyde, because the phenoxy function, which behaves as an acid equivalent, cannot be cleaved as is usual in the Ugi reaction.

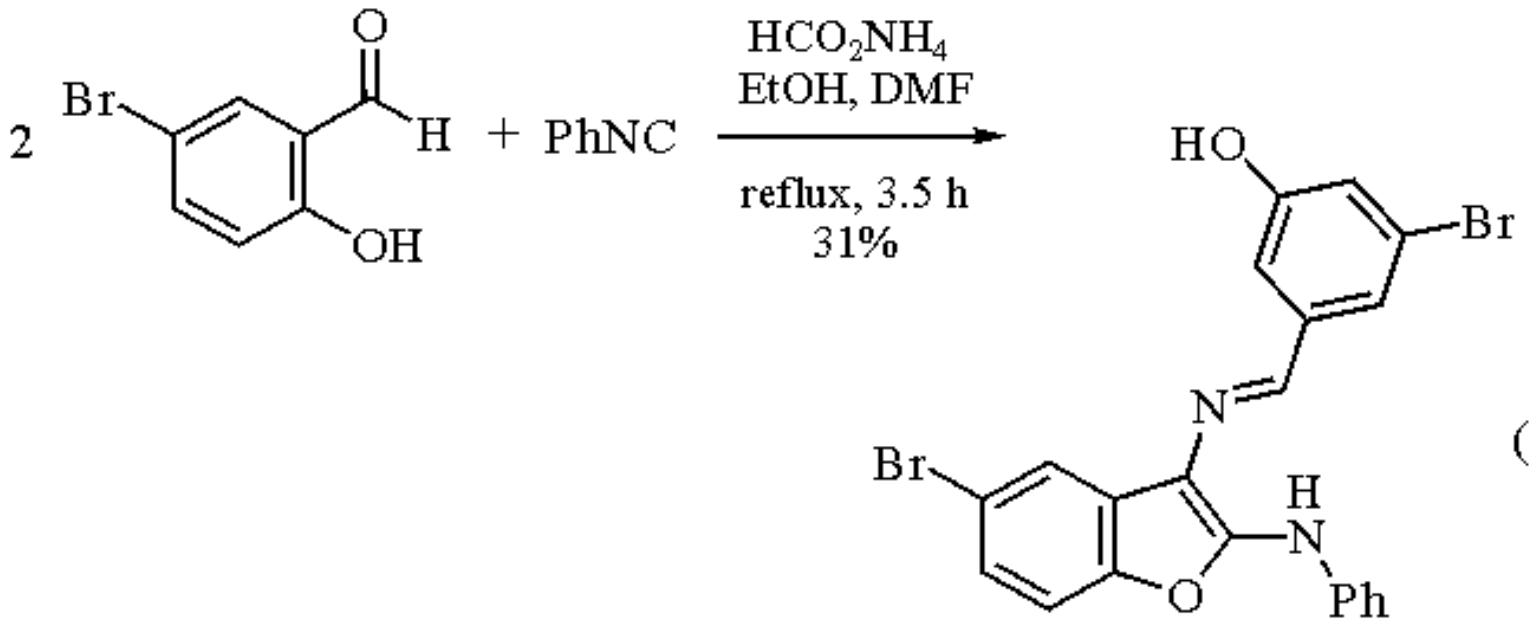

(2)

[4 + 1] Cycloaddition of dimethyl tetrathiooxalate with phenyl isocyanide leads to 2-imino-1,3-dithioles under simple reaction conditions in remarkably high yield (eq 3).[6]

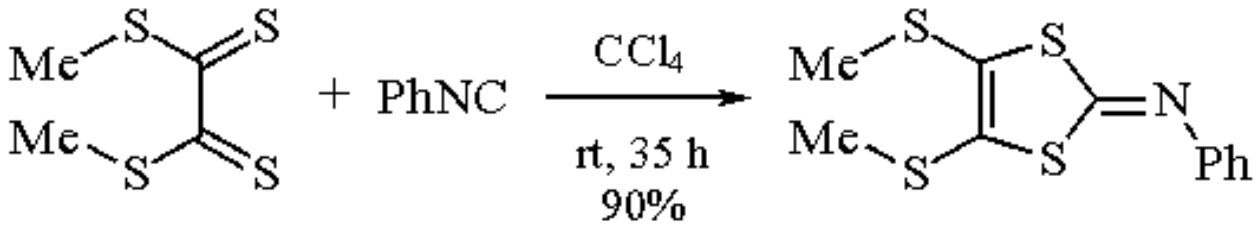

(3)

Another [4 + 1] cycloaddition of kinetically stabilized azetes with phenyl isocyanide affords sterically hindered pyrrole derivatives (eq 4).[7] A simple route to cyclopentane-fused quinolines involves [4 + 1] radical annulation of γ-iodoalkynes with phenyl isocyanide.[8]

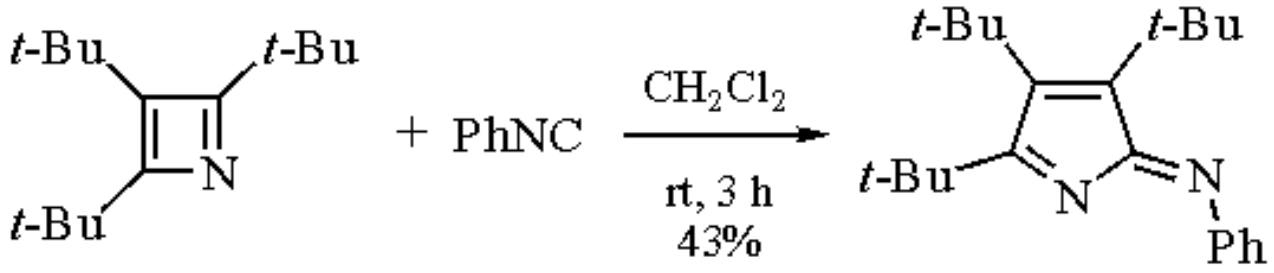

(4)

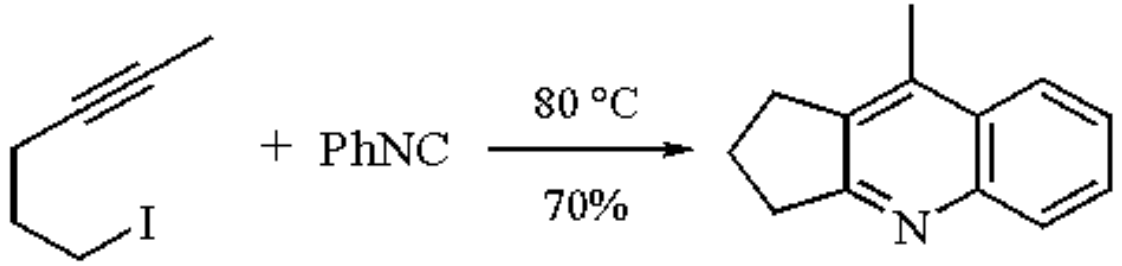

(5)

1,2-Benzo-4-boraimidazolines are available by [4 + 1] cycloaddition of dialkylboryl derivatives with 2-aminopyridine in high yields (eq 6).[9] Another structurally interesting boron heterocycle, namely a borapyrrole derivative, can also be obtained by [4 + 1] cycloaddition and alkyl tautomerization (eq 7).[10]

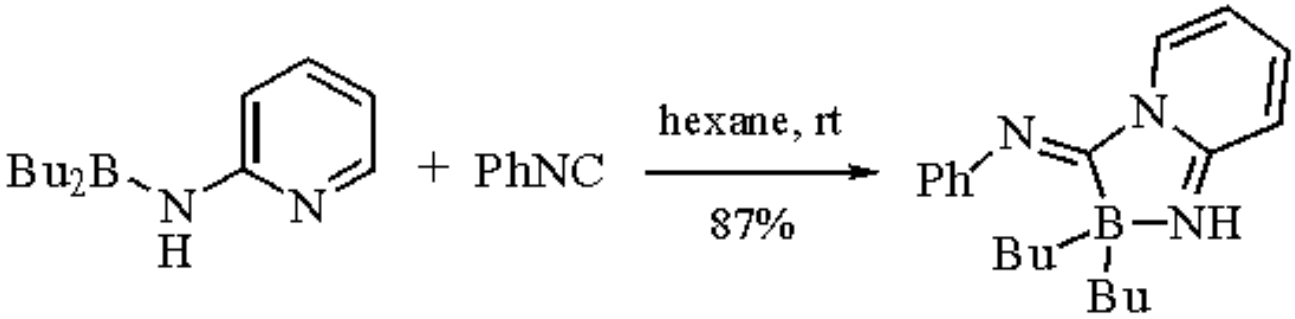

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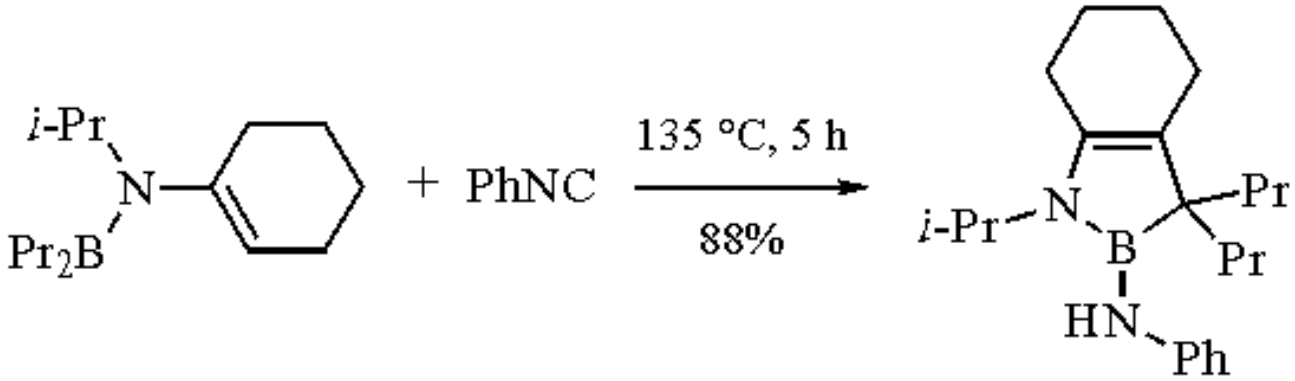

(7)

Phenyl isocyanide is also an effective reagent to form α-(methoxycarbonylamino) amides from α-methoxy urethanes in reasonable yields. As shown in eq 8, a Lewis acid catalyzes formation of the α-methoxycarbonylvalinamide.[11] The insertion of phenyl isocyanide into the C-O bond of *N*-(ethoxymethyl)piperidine gives the α-piperidino acetimidate shown in eq 9.[12]

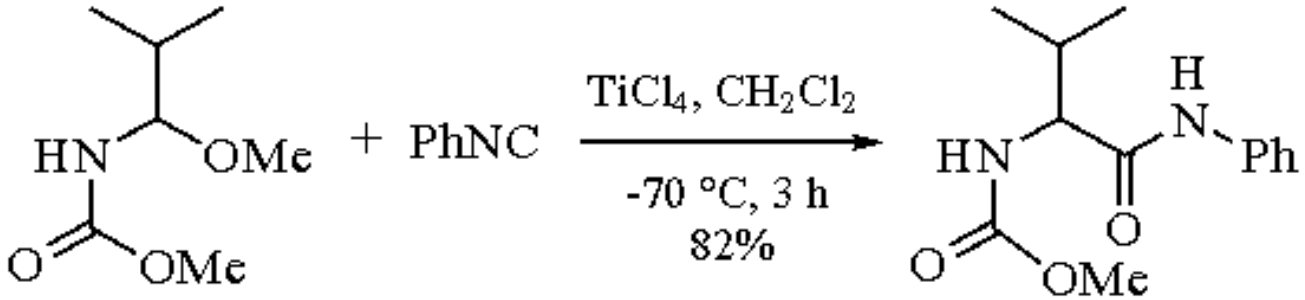

(8)

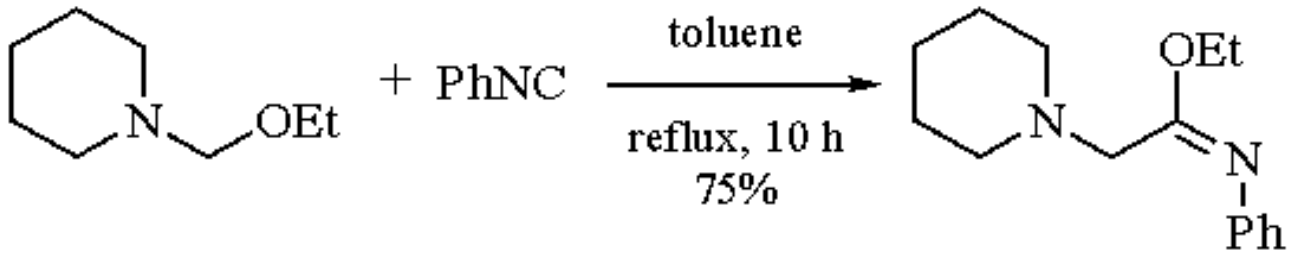

(9)

Syntheses Based on the Passerini Reaction.

Cyclization of levulinic acid[13a] and *o*-formylbenzoic acids[13b] with phenyl isocyanide produces γ-carbamoyl γ-lactones (eqs 10 and 11). The Ugi four-component reaction between cycloalkanones, phenyl isocyanide, and ammonium formate affords α-formylamino *N*-phenylcarboxamides (eq 12).[14]

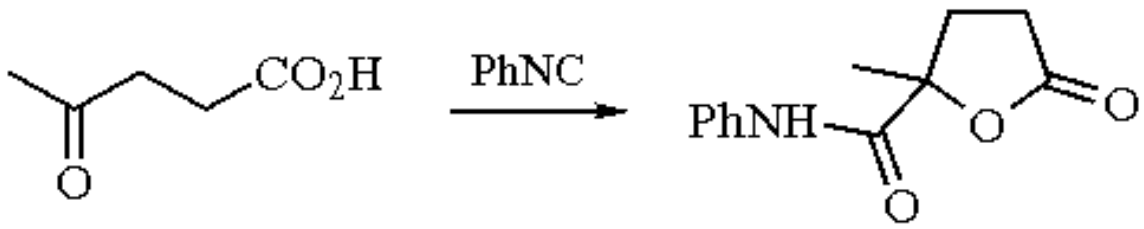

(10)

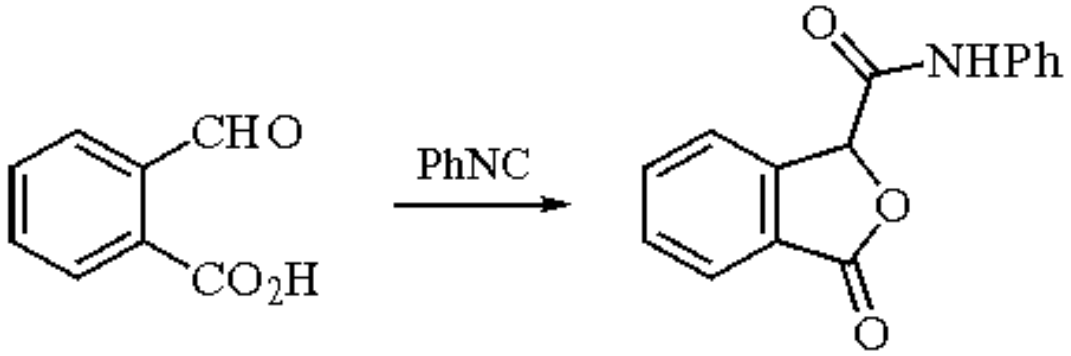

(11)

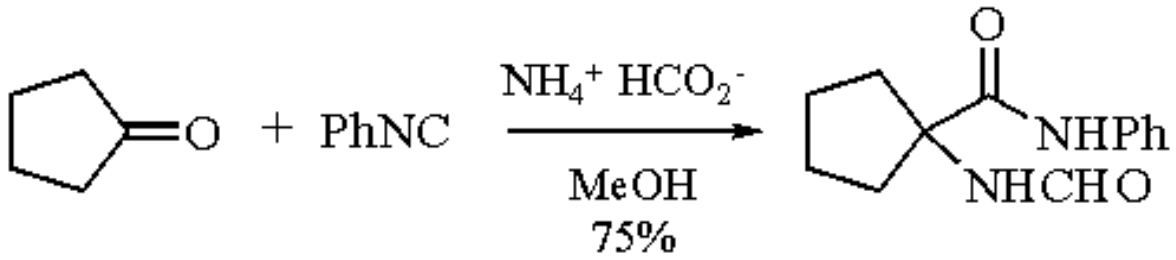

(12)

Other Applications.

Polymerization of isocyanides under the action of Ni^{II} catalysts leads to helical polymethyleneimines (eq 13).[15] Oxidation of phenyl isocyanide by Tl^{I}-catalyzed reaction with dibenzoyl disulfide gives the isothiocyanate in excellent yield (eq 14).[16] Also, the direct oxidation of phenyl isocyanide with elemental selenium gives phenyl isoselenocyanate in high yield (eq 15).[17]

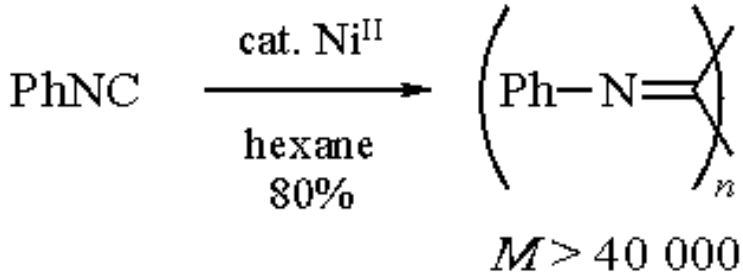

(13)

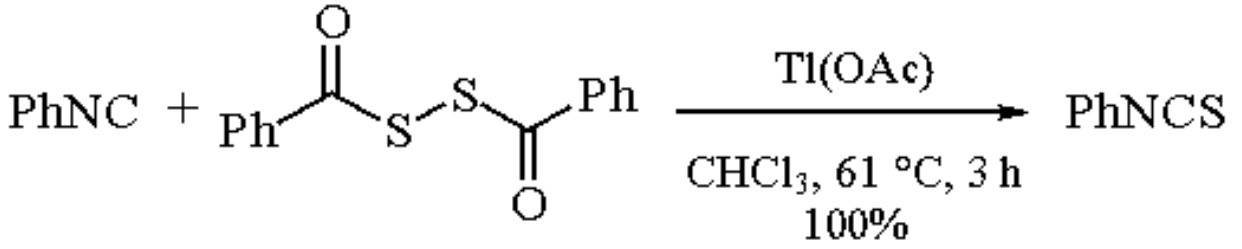

(14)

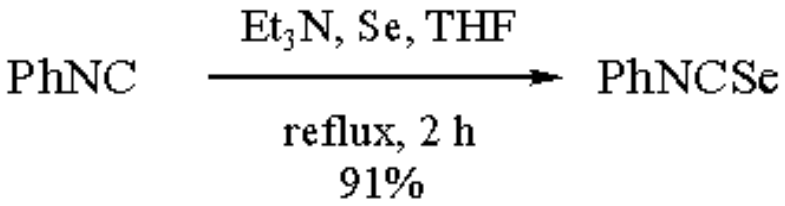

(15)

Related Reagents.

t-Butyl Isocyanide; ***Cyclohexyl Isocyanide***; ***Ethyl Isocyanoacetate***; ***Isocyanomethyllithium***; ***Methyl Isocyanide***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***o-Tolyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***.

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Phenyl Isothiocyanate

Ph-N=C=S

[103-72-0] · C_7H_5NS · Phenyl Isothiocyanate · (MW 135.20)

(Edman degradation of peptides; synthesis of heterocyclic systems)

Physical Data: bp 221 °C; mp -21 °C; *d* 1.1288 g cm^{-3}.

Solubility: insol H_2O; sol alcohol, ether.

Form Supplied in: liquid; widely available.

Handling, Storage, and Precautions: use in a fume hood.

Edman Degradation.

Identification of terminal amino acid residues of peptides can readily be accomplished by an Edman degradation.[1] Treatment of the peptide with phenyl isothiocyanate in pyridine-water (1:1) produces a phenylthiocarbamoyl derivative which, upon exposure to anhydrous ***Hydrogen Chloride*** in nitromethane, rapidly cleaves to form a 3-phenyl-2-thiohydantoin and a peptide with one less amino acid residue. If needed, the free amino acid can be isolated by hydrolysis of the thiohydantoin with ***Barium Hydroxide*** (eq 1).

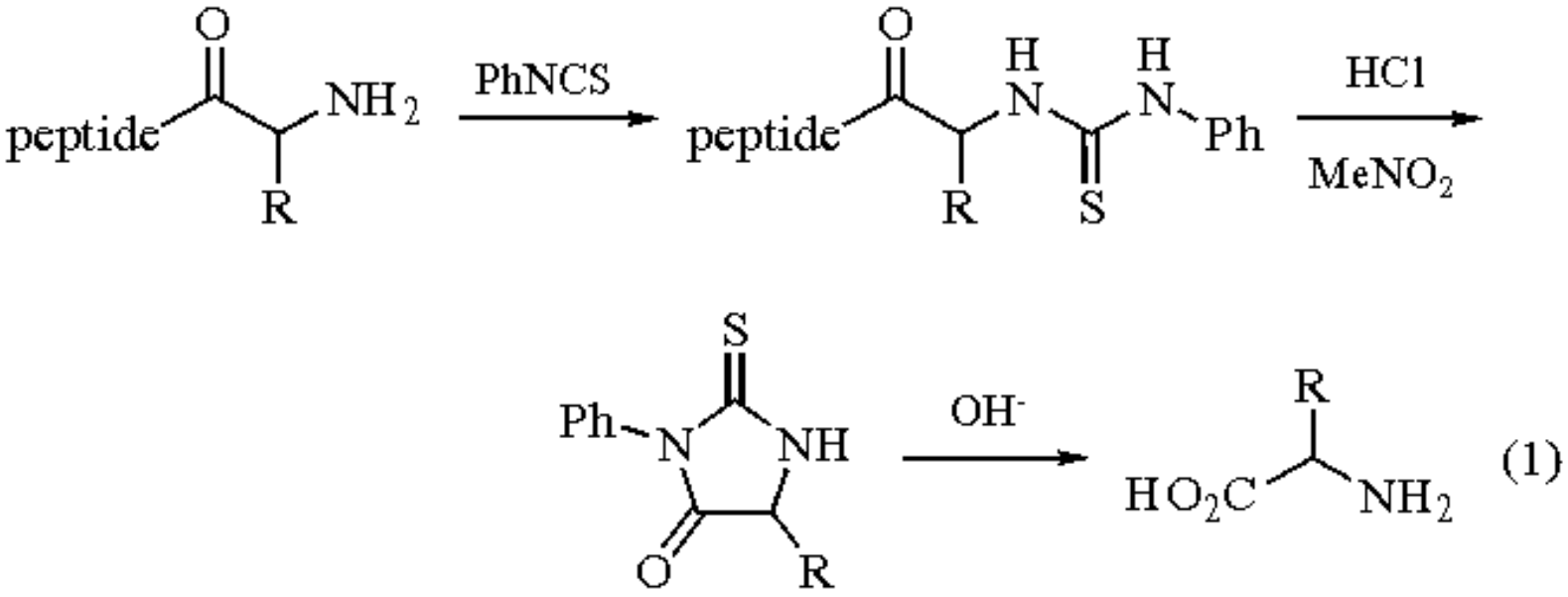

The procedure, which is amenable to complex peptides containing a variety of sensitive functionalities, has been applied to the vancomycin group of antibiotics,[2-4] and was instrumental in the structure elucidation of avoparcin (**1**).[5,6] In this case, the thiohydantoin of the deoxysugar amino acid fragment forms in the first step without a need for acid-catalyzed cyclization.

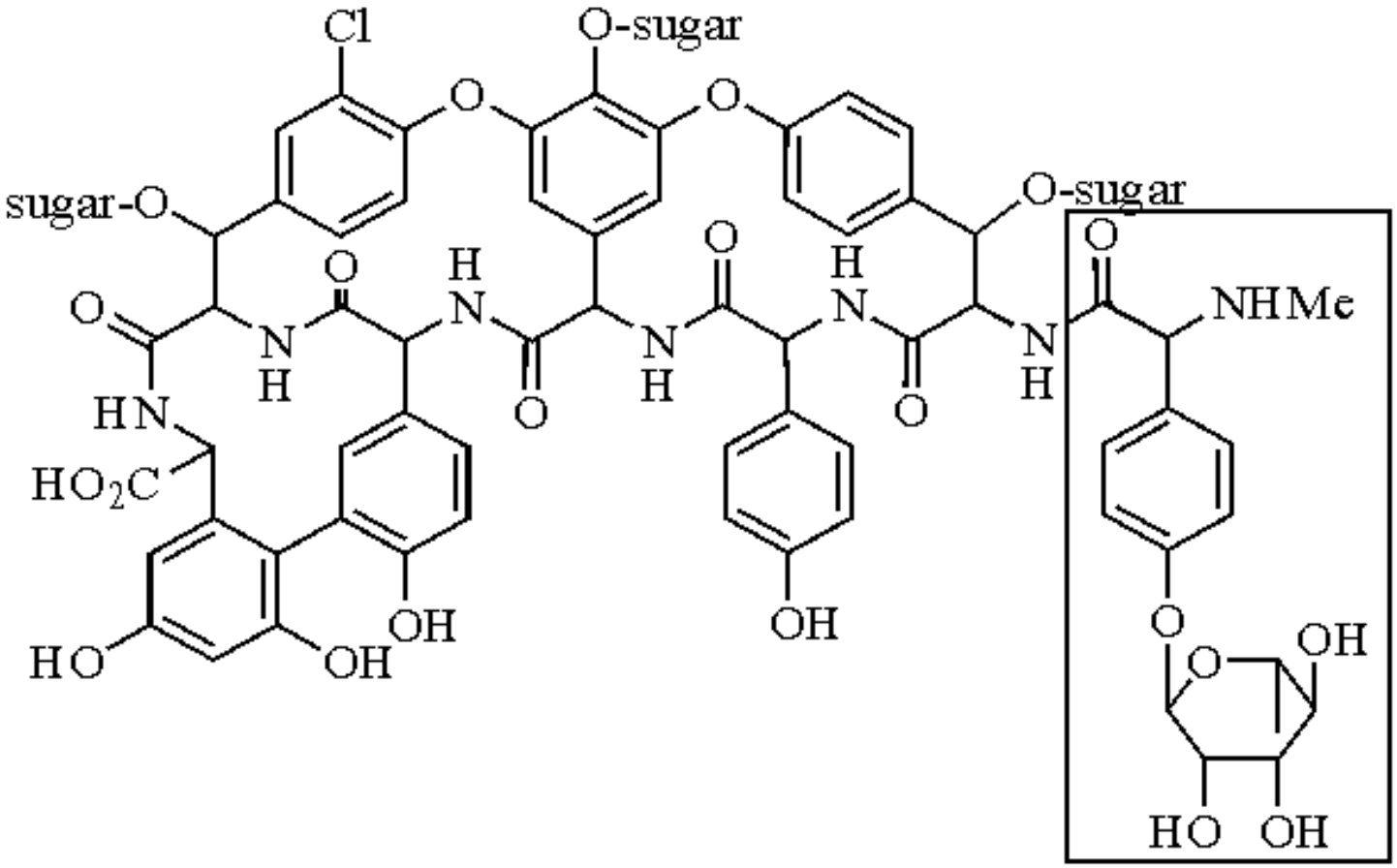

(1)

An interesting method for the resolution of amines involves preparing its amide with L-phenylalanine. Chromatographic separation of the corresponding diastereomers followed by an Edman degradation furnishes either pure enantiomer (eq 2).[7] In this manner, dibenzo[*a*,*d*]cycloalkenimines (**2**)[8] and 3-amino-1-hydroxypyrrolidin-2-one (**3**)[9] have been resolved and evaluated for their *N*-methyl-D-aspartate and glycine antagonist activities, respectively.

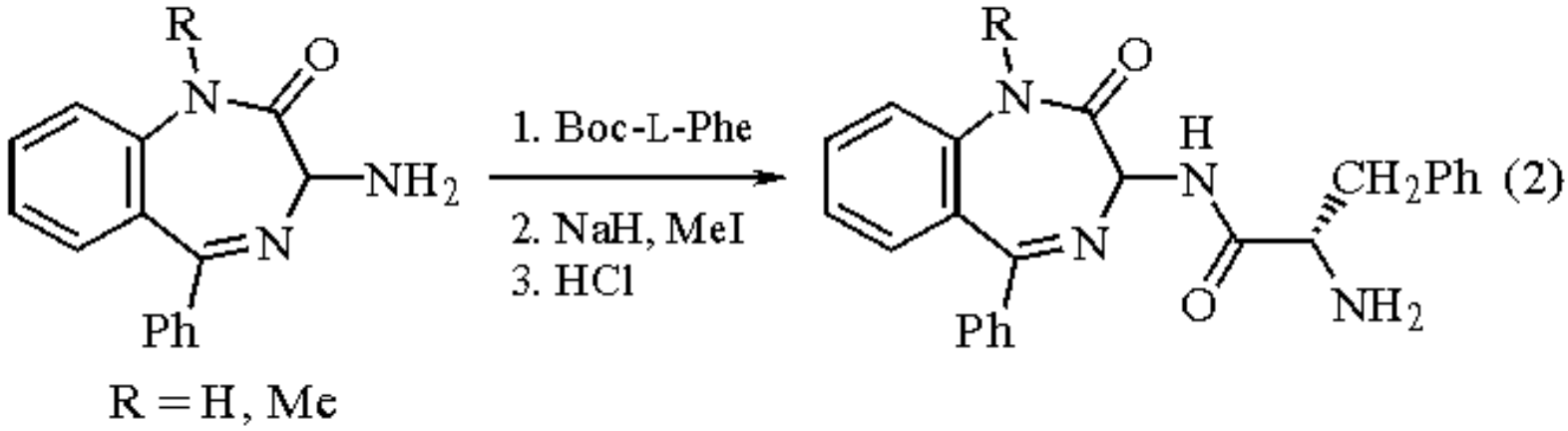

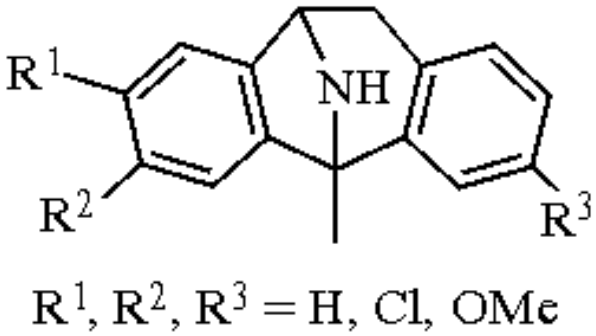

(2)

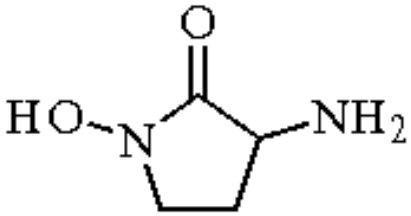

(3)

Cyclization Reactions.

The elements of phenyl isothiocyanate can be incorporated into cyclization motifs to form a variety of heterocyclic systems. For example, treatment of 2-amino-5-chlorobenzhydrol with phenyl isothiocyanate, followed by cyclization of the intermediate thiourea with dilute HCl, produces 6-chloro-3,4-diphenyl-2-thioxo-1,2,3,4-tetrahydroquinazoline in 60% yield (eq 3).[10]

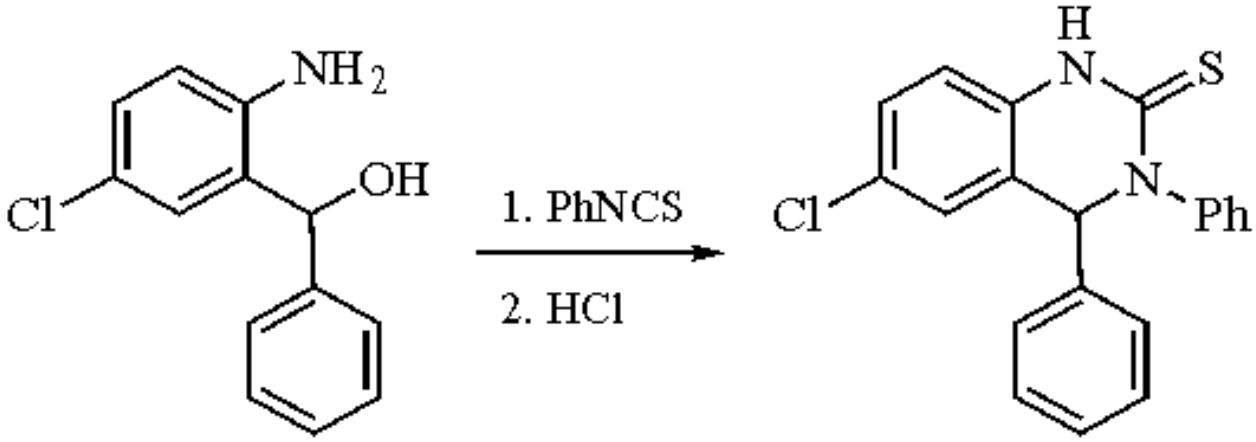

(3)

The core of the penem heterocyclic system can readily be assembled using phenyl isothiocyanate to supply the sulfur and one carbon atom for its five-membered ring. Treatment of a suitable azetidinone with ***Lithium Hexamethyldisilazide*** at -40 °C, followed by phenyl isothiocyanate and acetic anhydride, affords a ketene derivative. Deprotection, chlorinolysis, and hydrolysis produce the 2-phenylaminopenem (eq 4).[11]

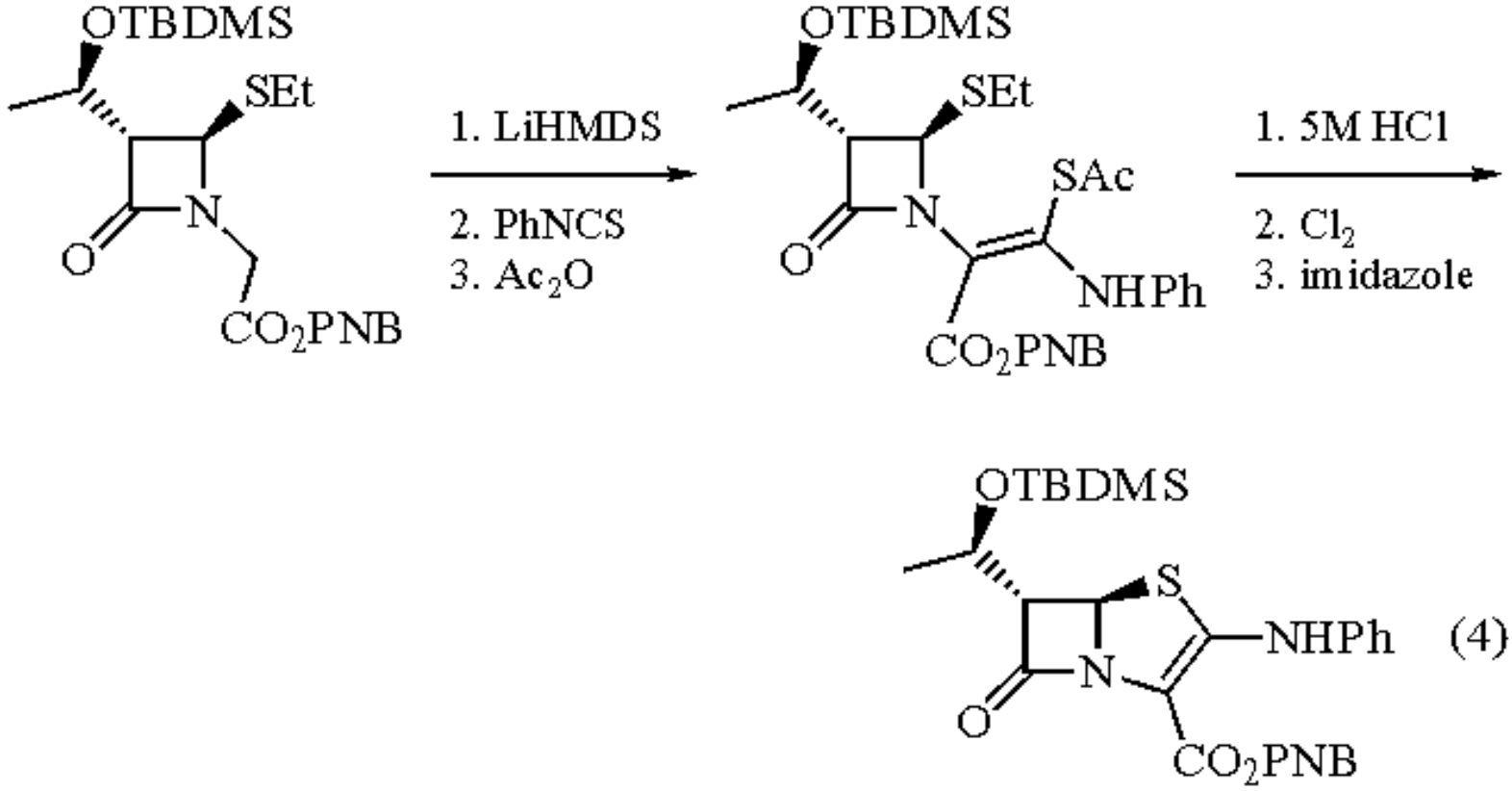

(4)

Dehydration Reactions.

N-Benzoylanthranilic acid, when heated with phenyl isothiocyanate at 160-170 °C in the presence of ***Pyridine*** as a catalyst, gives 2-phenyl-3,1-benzoxazin-4-one in 30% yield (eq 5).[12] Analogously, oxazolones are produced by a phenyl isothiocyanate-mediated cyclodehydration of *N*-acylglycines at 160-170 °C.[13,14] When the reaction is performed in the presence of a salicylaldehyde, 3-*N*-acylaminocoumarins are isolated in yields of 20-68% (eq 6).[15]

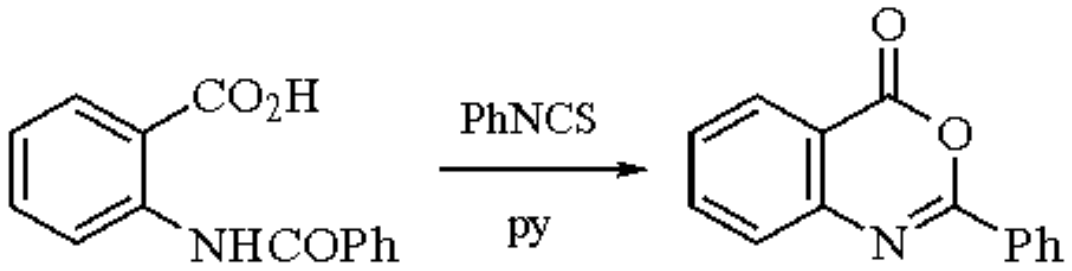

(5)

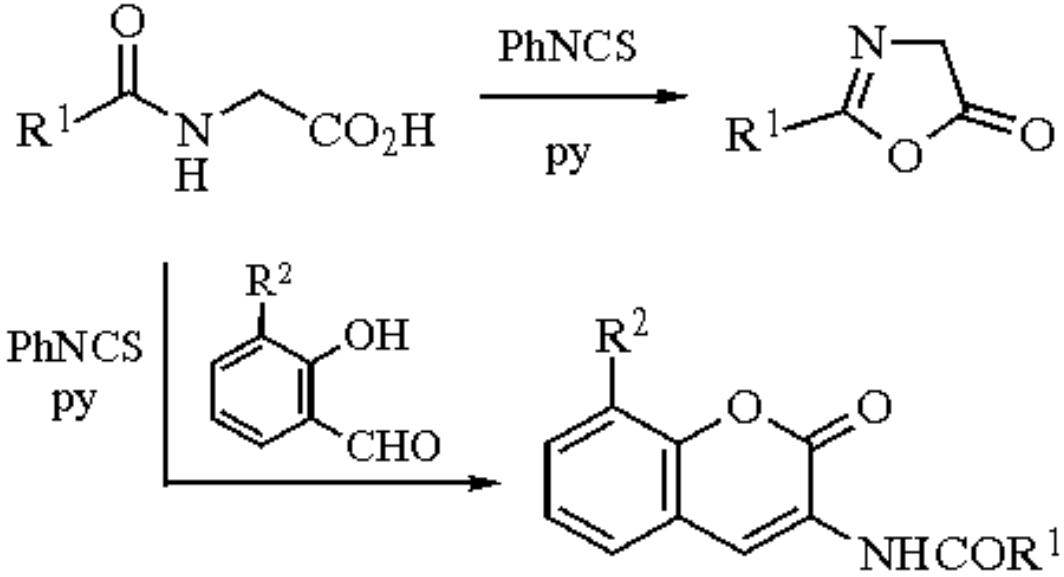

R^1 = Me, Ph, *p*-tolyl
R^2 = H, OH

Related Reagents.

Benzoyl Isothiocyanate; ***Ethoxycarbonyl Isothiocyanate***; ***Iron(III) Thiocyanate***; ***Mercury(II) Thiocyanate***; ***Methyl Isocyanate***; ***Methyl Isothiocyanate***; ***(R)-1-(1-Naphthyl)ethyl Isocyanate***; ***Phenyl Isocyanate***; ***Potassium Thiocyanate***; ***Sodium Thiocyanate***.

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Phenyllithium[1]

PhLi

[591-51-5] · C_6H_5Li · Phenyllithium · (MW 84.05)

(organometallic agent useful as nucleophile for addition and substitution reactions,[1,3-20] and in the preparation of organolithium building blocks via metalation[32] and lithium-metalloid exchange reaction[1])

Physical Data: X-ray structures of the PMDTA-complexed monomer,[2i] the TMEDA-complexed dimer,[2a] the diethyl ether-complexed tetramer,[2b] and the PhLi:LiBr (3:1) mixed tetramer[2b] have been reported. Cryoscopic[2h] and NMR[2c-e] studies have shown that a monomer-dimer equilibrium exists in THF solution and that monomers exist in THF/HMPA[2f] and THF/PMDTA.[2c] PhLi is tetrameric in ether.

Solubility: sol ether solvents; sol hydrocarbon solvents only by the addition of donor solvents/additives such as ether or TMEDA.[2a]

Form Supplied in: commercially available in cyclohexane/ether solution.

Analysis of Reagent Purity: standard titration methods should be used.

Preparative Methods: prepared from phenyl halide (PhCl,[2j] PhBr,[2k,l] PhI[2m]) and lithium metal in ether. Several procedures have been used to prepare solid, salt-free PhLi.[2n-r] The synthesis of ^{13}C-labeled PhLi (*ipso* carbon only) has been described.[2h]

Handling, Storage, and Precautions: moisture and oxygen sensitive. Concentrated solutions are pyrophoric. Ether solutions slowly undergo proton abstraction to generate benzene and should be stored in the freezer.

Addition and Substitution Reactions.

The greatest number of synthetic methodologies using PhLi involve carbon-carbon single bond formation through nucleophilic addition and substitution reactions. PhLi undergoes nucleophilic addition in a 1,2-fashion to a variety of carbonyl containing compounds including ***1,4-Benzoquinone***,[3a,b] cyclobutenediones,[3c] γ-amino enals,[3d] *N*-(alkyl)phthalimides,[3e] optically-active dienone-iron tricarbonyl complexes,[3f] α-silyl ketones[4] (eq 1),[4a] and β-lactams (eq 2).[5] PhLi adds similarly to cumulated carbonyl groups: isocyanates afford amides,[1] ketenes[6] yield enolates (eq 3),[6b] and ***Carbon Dioxide***[7] produces phenyl ketones (eq 4).[7b]

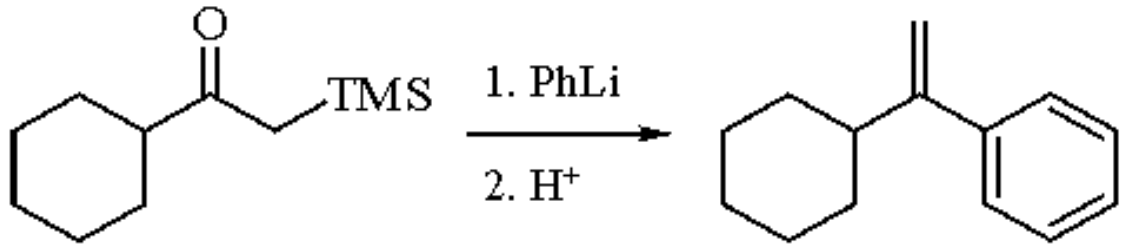

(1)

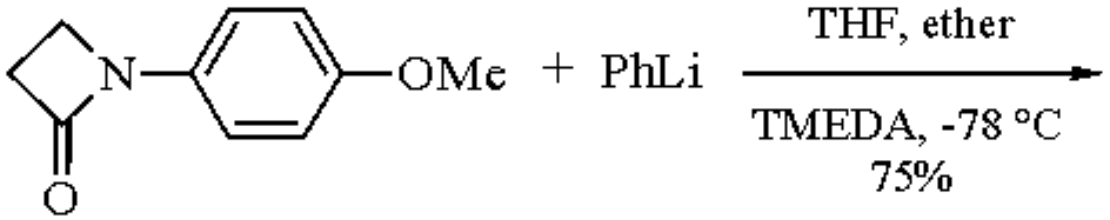

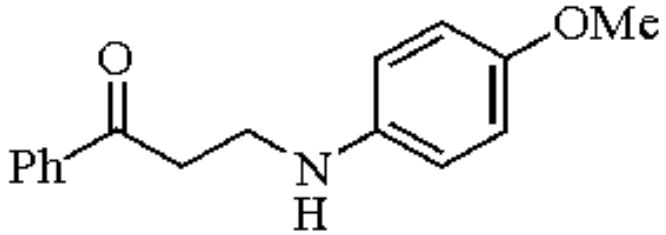

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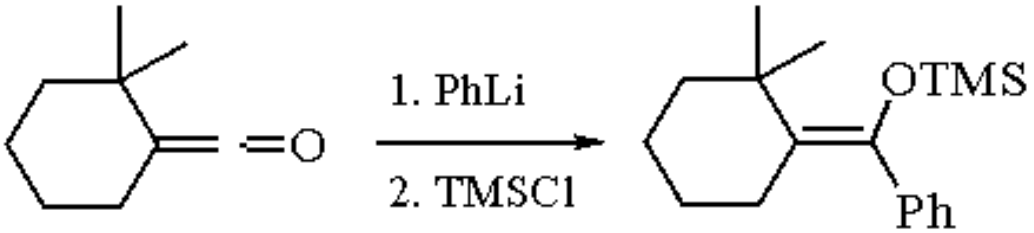

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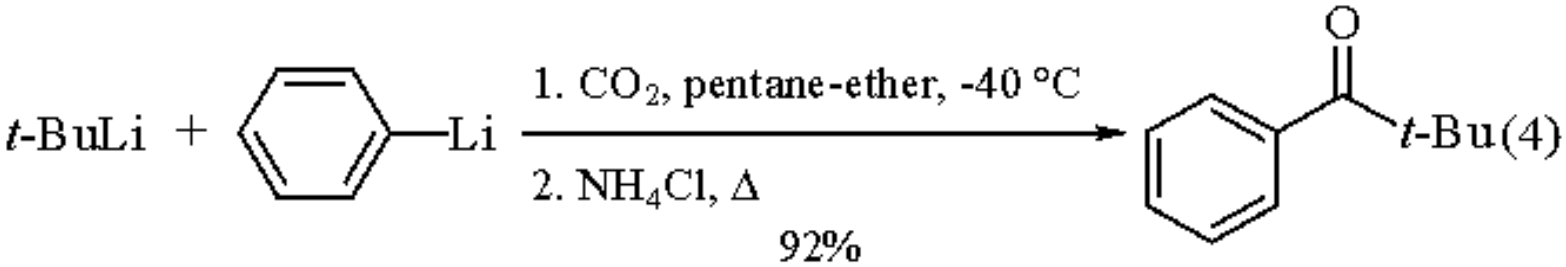

(4)

In general, organolithium compounds preferentially undergo addition to the carbonyl of α,β-unsaturated carbonyl compounds rather than Michael addition. However, conjugate addition is promoted by increased solvent polarity, delocalized organolithium compounds, and lower temperatures which allow for thermodynamic control.[1,9] Conjugate addition of PhLi to vinyl sulfones[8] and α,β-unsaturated esters,[10a] ketones,[10b] and imines[11] has been reported. Thiophilic attack of thiocarbonyl compounds by PhLi has been observed for thioketones,[12] thioketenes (eq 5),[13] and thiocarbonates.[14] Addition of PhLi to carbon-nitrogen double and triple bonds, including the formal carbon-nitrogen double bond of azaaromatic heterocycles such as pyridine[15a] and quinoline,[15b] is general.[15] Arylation of 3,4-dihydro-β-carboline was accomplished by activation with ***Boron Trifluoride Etherate*** (eq 6).[15c] Similarily, the addition of PhLi to 2-isoxazolines[15d] and oxime ethers[15e] in the presence of boron trifluoride has been demonstrated. Addition reactions to nitriles containing no α-hydrogens have been reported to effectively afford ketimines and ketones.[16] Lithium aldimines

have been prepared through the addition of PhLi to isocyanides.[17]

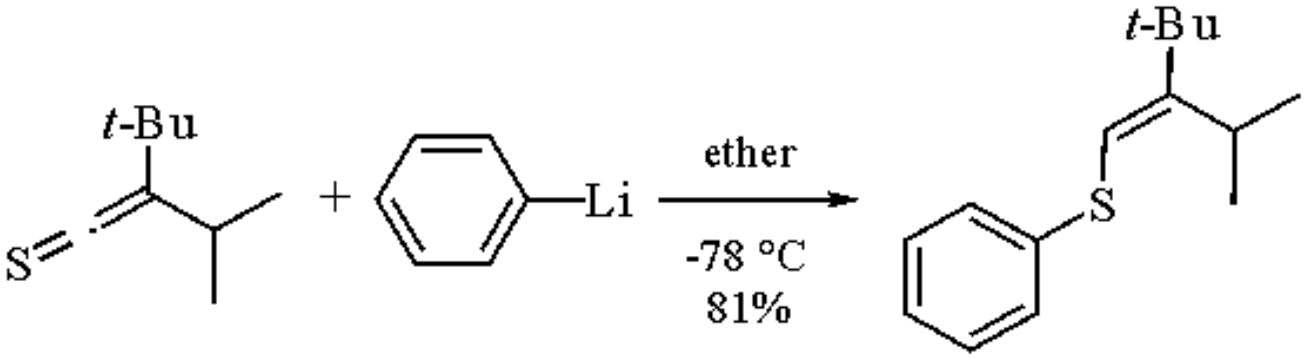

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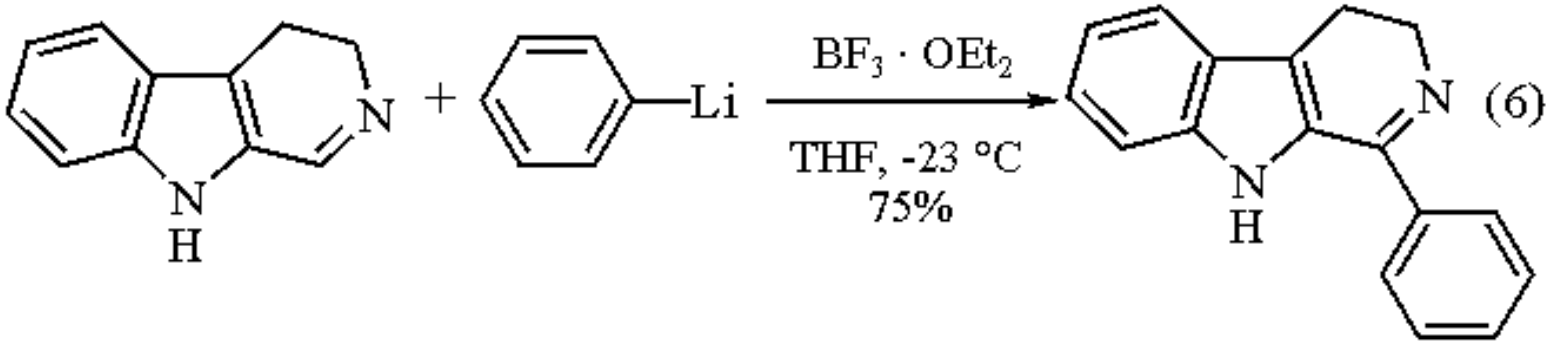

(6)

PhLi undergoes alkylation with primary halides, allylic halides (eq 7),[18a] and benzyl halides.[1a-c,18] Although not nearly as prevalent, displacement of sulfonate has also been reported.[1,19] Nucleophilic ring opening of epoxides with PhLi is general.[20] The reaction of PhLi with α,β-epoxy silanes yields β-hydroxy silanes which subsequently undergo Peterson reaction to afford alkenes (eq 8).[20d] Addition reactions to oxetanes[21a] and substituted aziridines[21b] are known, but have comparatively little utility.

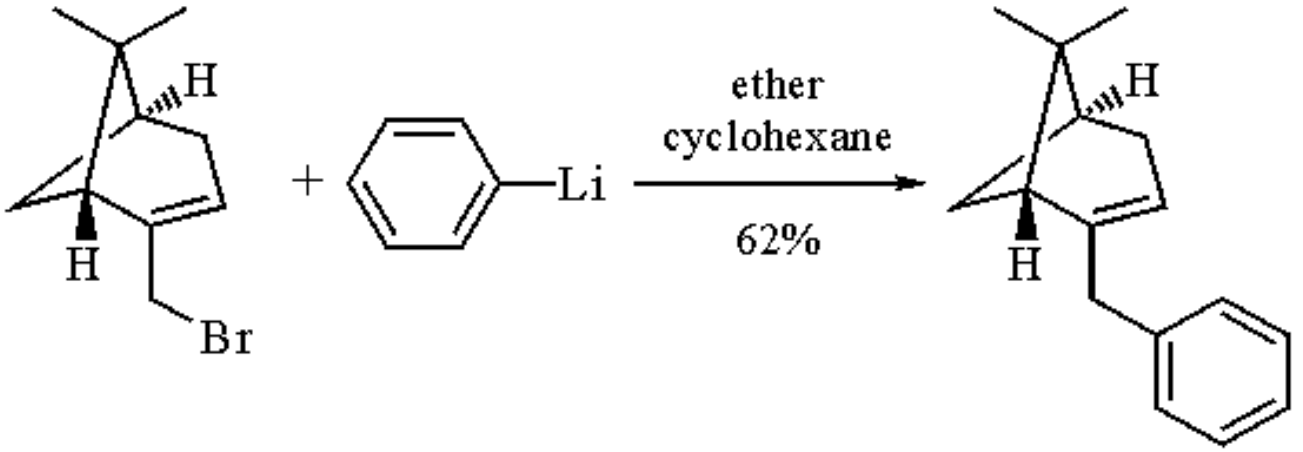

(7)

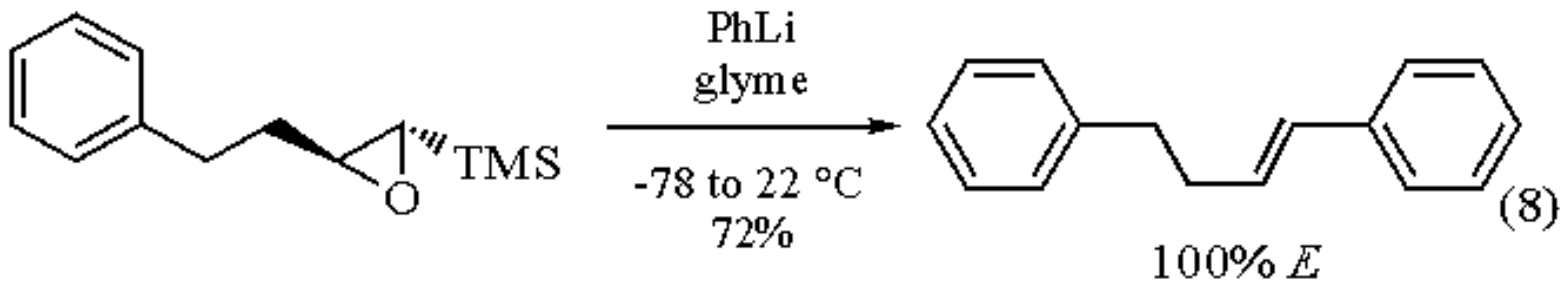

Nucleophilic addition and substitution reactions with PhLi often may be accompanied or followed by other reactions such as lithium-metalloid exchange, enolization, metalation, or carbanionic rearrangements.

Lithium-Metalloid Exchange Reaction.

Phenyllithium undergoes lithium metalloid exchange[1] which is a reversible process with an equilibrium constant that reflects the difference in stability of PhLi and the new organolithium species generated. Mechanistic studies of this reaction abound.[1d,e] Lithium-halogen exchange is most prevalent, although related transmetalations involving selenium,[22] tellurium,[23] tin,[24] and mercury[25] are also common. In general, PhLi/M exchange is characteristically fast (I > Te, Sn > Br > Se > Cl)[1d] even at low temperatures. Exchange rates increase with increased solvent polarity, but are slowed by the presence of lithium salts.[2f,26] PhLi/M exchange reactions have been utilized for the preparation of functionalized aryllithiums (e.g. 4-methoxyphenyllithium,[27a] lithio-nitrobenzenes),[27b,c] substituted benzyllithiums (eq 9),[28] 3-thienyllithium derivatives (eq 10),[29] ***Vinyllithium***,[24c] 2-lithiophosphinines,[30] and other stabilized organolithium reagents which are not readily available by metalation or the reduction of halides. ***Allyllithium*** generated through reaction of PhLi and ***Tetraallylstannane***,[24d,e] can be converted with ***Potassium t-Butoxide*** to the more reactive allylpotassium which subsequently undergoes conjugate addition to vinyl sulfones (eq 11).[31]

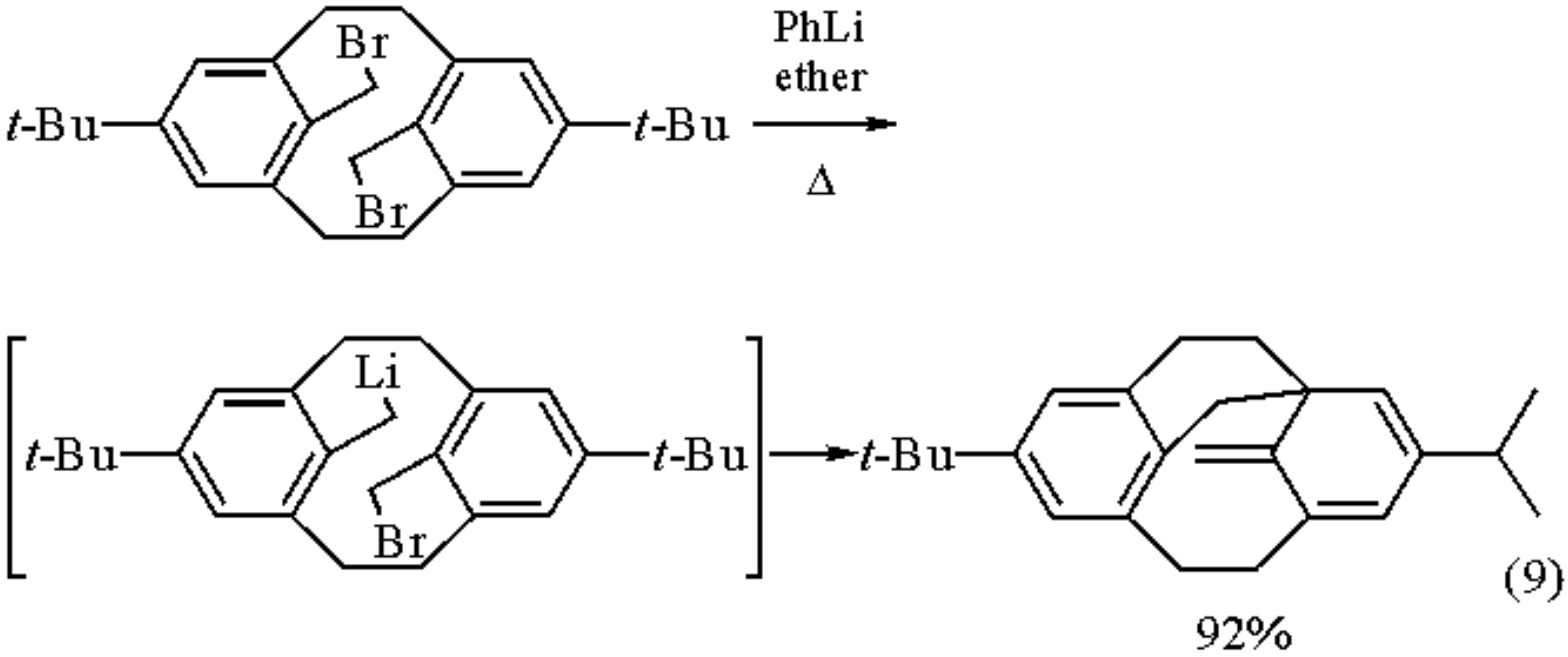

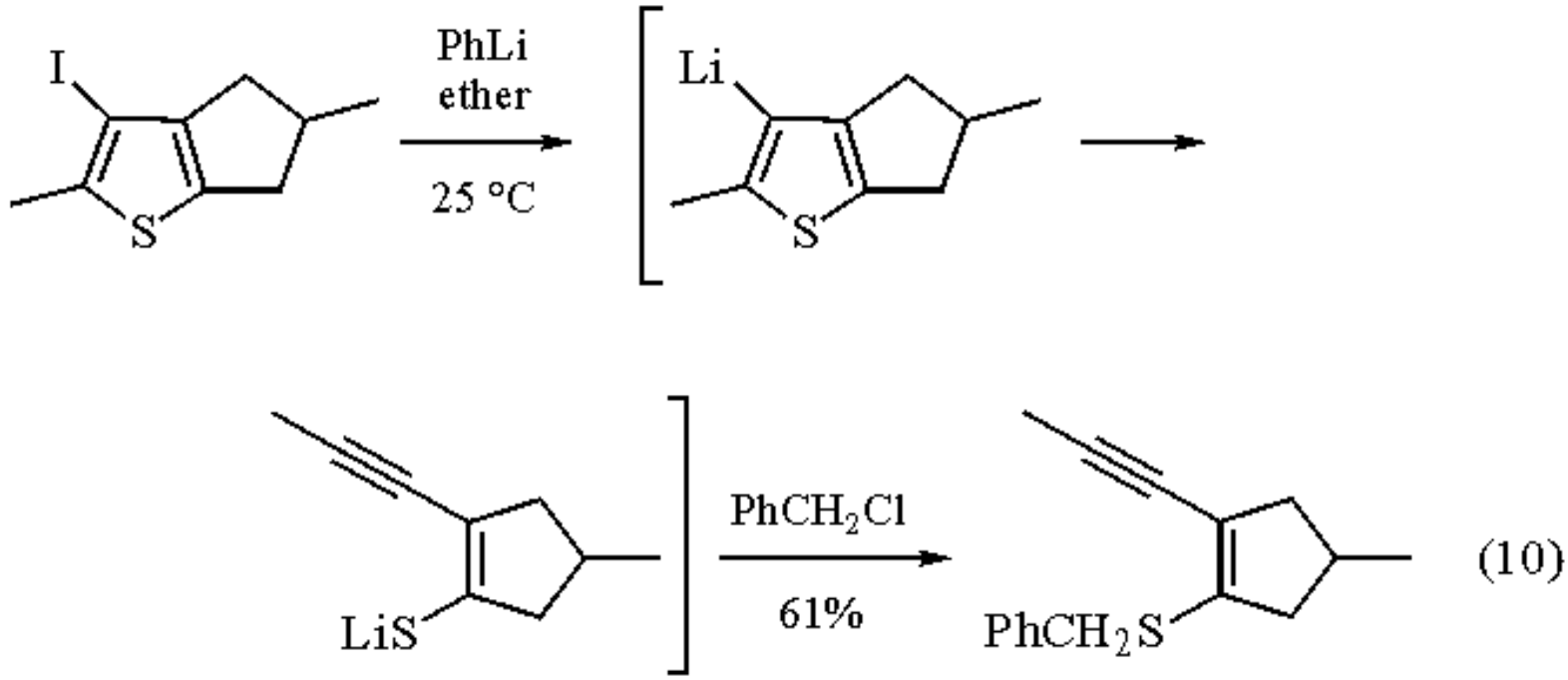

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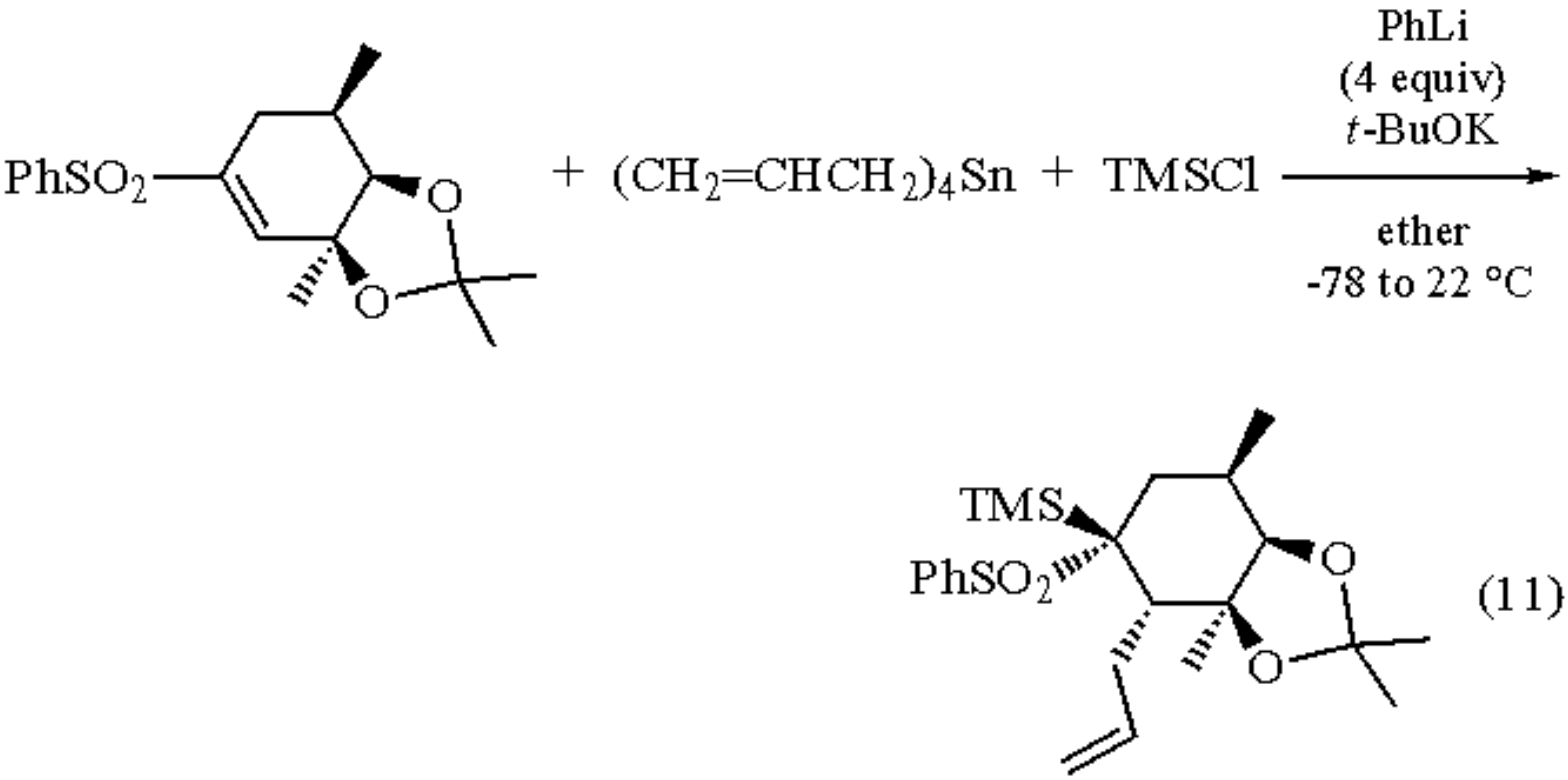

(11)

Lithiation Reactions.[32-36]

Replacement of hydrogen by lithium in an organic compound is perhaps the most versatile method for preparing organolithium compounds. Although not nearly as prevalent as ***n-Butyllithium***, PhLi has been used as a base in heteroatom-facilitated lithiations, lithiations of relatively strong hydrocarbon acids (pK_a of benzene = 43),[37] and in the formation of stabilized anions where a milder reagent is warranted. Thiophenes,[32] sulfones,[8] nitriles,[33] 1,3-dimethoxybenzenes,[34] and α-methylpyridines[35] (eq 12)[35a] have been metalated with PhLi. Reaction of 2 equiv of PhLi

with a β-epoxy sulfone resulted in base-catalyzed β-elimination and subsequent conjugate addition to produce a dianion which was alkylated with ***Iodomethane*** (eq 13).[8] PhLi has been used to deprotonate secondary amines to form lithium amides.[36]

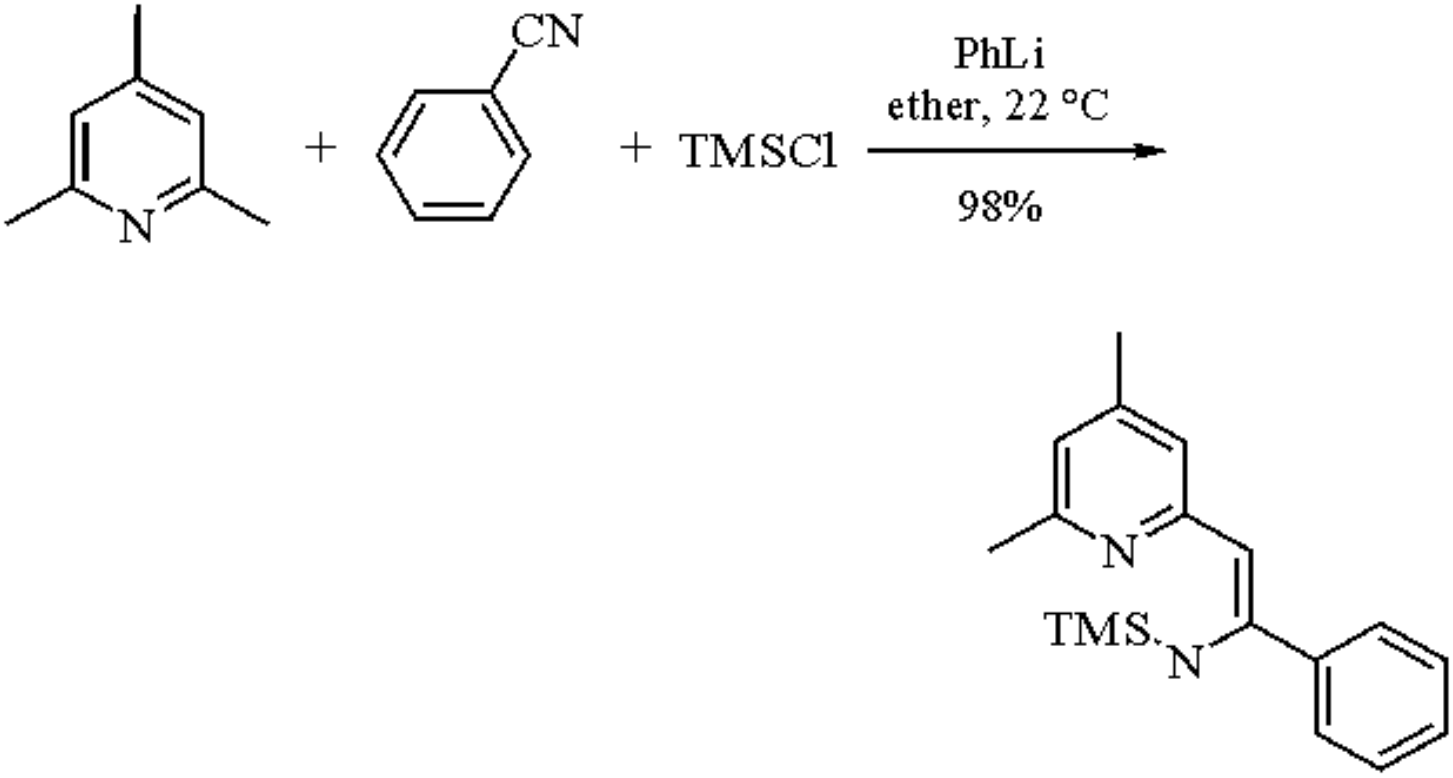

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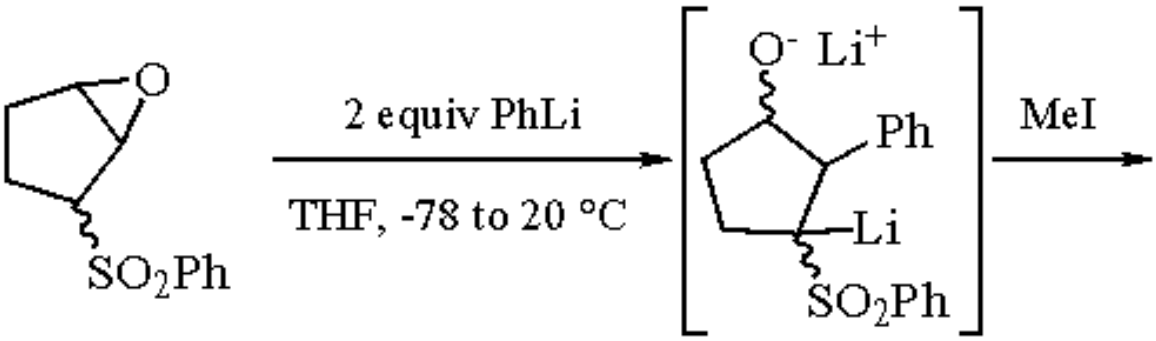

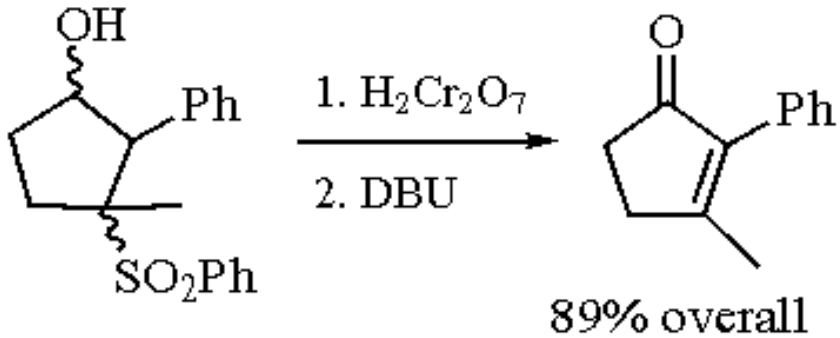

(13)

Related Reagents.

Lithium Diphenylcuprate; ***Lithium Di-p-tolylcuprate***; ***Phenylmagnesium Bromide***.

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Phenylmagnesium Bromide[1]

PhMgX

(X = Br)

[100-58-3] · C_6H_5BrMg · Phenylmagnesium Bromide · (MW 181.32) (X = Cl)

[100-59-4] · C_6H_5ClMg · Phenylmagnesium Chloride · (MW 136.87)

(adds to many unsaturated functional groups; phenyl can displace halide and like groups; functions as a strong base and a Lewis acid[1b-f])

Physical Data: NMR and calorimetric observations indicate that PhMgBr in Et_2O and THF and PhMgCl in THF are actually mixtures of PhMgX, Ph_2Mg, and MgX_2.[2,3] Although PhMgBr and PhMgCl are essentially monomeric in THF, PhMgBr is associated significantly in Et_2O except at low concentrations.[3,4] Solids isolated include $PhMgBr(Et_2O)_2$[5] and $PhMgBr(THF)_2$,[6] both shown by X-ray diffraction studies to have four-coordinate Mg.

Solubility: both sol Et_2O, THF; insol hydrocarbons.

Form Supplied in: solutions of PhMgBr in Et_2O and THF and of PhMgCl in THF and THF/toluene are commercially available.

Analysis of Reagent Purity: see ***Methylmagnesium Bromide***.

Preparative Methods: in spite of their commercial availability, solutions of PhMgBr[8] and PhMgCl[9] are frequently prepared from reaction of a phenyl halide and Mg, usually in Et_2O or THF.[1c,e,7] Preparation of PhMgBr in Et_2O is routine, but the formation of PhMgCl from PhCl and magnesium is difficult to initiate and sustain. By contrast, preparation is generally successful in THF.[9] Use of activated[10] ***Magnesium*** makes possible otherwise difficult preparations, allows the use of lower temperatures which may minimize undesired reactions with other functional groups in the reagent, and allows the use of Et_2O, other less favorable ethers, and hydrocarbons. Stirring Mg under nitrogen is one activation procedure;[11] other effective procedures (chemical treatment of the Mg,[12] preparation of Mg by reduction of salts,[13] use of ethylene bromide as a coreagent during the preparation[14]) can introduce other species.

Handling, Storage, and Precautions: see ***Methylmagnesium Bromide***. Phenyl Grignard reagents do not significantly attack Et_2O or THF at normal reaction temperatures.

Representative Applications.[1b-f]

See also ***Methylmagnesium Bromide***. Phenyl Grignard reagents are used most frequently in reactions that result in attachment of the organic group to an electrophilic carbon atom of the substrate, most often of a carbonyl group, nitrile, or other unsaturated function. The oxazoline function, easily transformed into other functions, facilitates displacement of a methoxyl group (eq 1), probably both by its electronic effects and by coordinating with the Grignard reagent.[15]

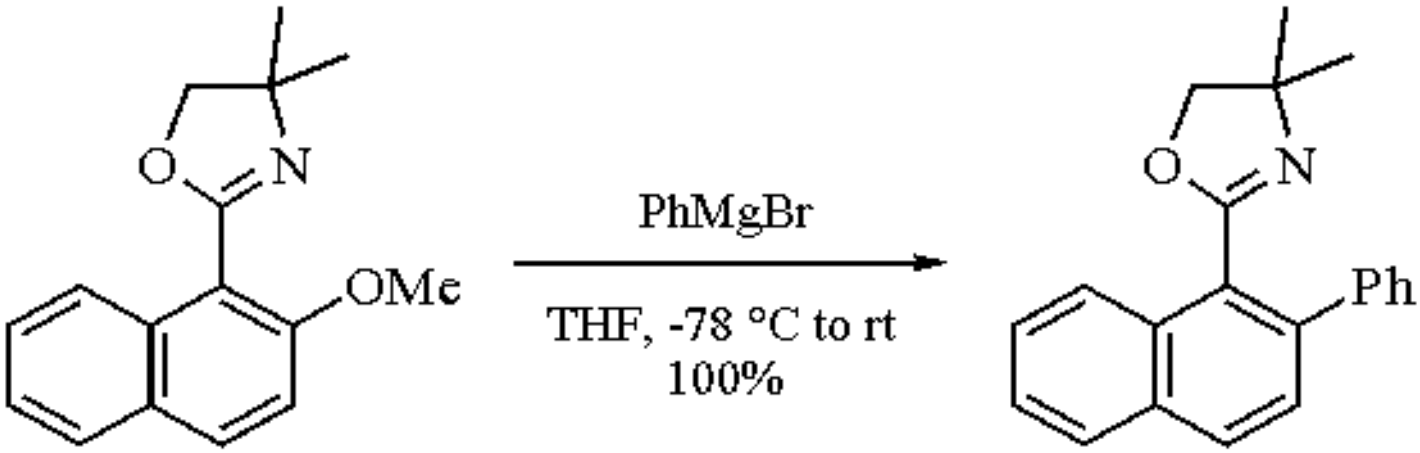

(1)

Related Reagents.

Phenyllithium.

---

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N-Phenylmaleimide

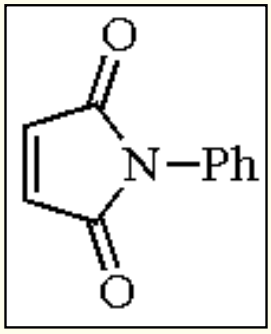

[941-69-5] · $C_{10}H_7NO_2$ · *N*-Phenylmaleimide · (MW 173.18)

(dienophile[2,3] and dipolarophile; Michael acceptor; radical acceptor)

Alternate Name: NPM.

Physical Data: mp 89-90 °C; bp 162-163 °C/12 mmHg.

Solubility: insol H_2O; sol alcohol, ether, benzene.

Form Supplied in: yellow solid; widely available.

Purification: recrystallizaton from benzene/ligroin or from cyclohexane.

Handling, Storage, and Precautions: irritant.

Cycloadditions.

N-Phenylmaleimide is a common dienophile which reacts with a wide variety of dienes. Its advantages relative to other dienophiles are that it gives products in high yield and the Diels-Alder adducts are not susceptible to hydrolysis or retro-Diels-Alder reactions. High *endo* selectivity is usually observed in Diels-Alder reactions with NPM. Exceptionally high *endo* selectivity has been reported with the related *N*-methylmaleimide (NMM) relative to *N*-phenylmaleimide in [4 + 2] reactions with isobenzofuran.[1] Studies which have examined the effect of a stereogenic center adjacent to the diene on the facial selectivity of a Diels-Alder reaction have frequently employed *N*-phenylmaleimide as a representative dienophile.[2,3] Acyclic and cyclic 1,3-dienes containing an allylic stereogenic center have been examined (eqs 1-3). The bromo derivative of NPM, N-*p*-bromophenylmaleimide, has been used to obtain crystalline adducts suitable for single crystal X-ray analysis and unambiguous assignment of stereochemistry.[2c]

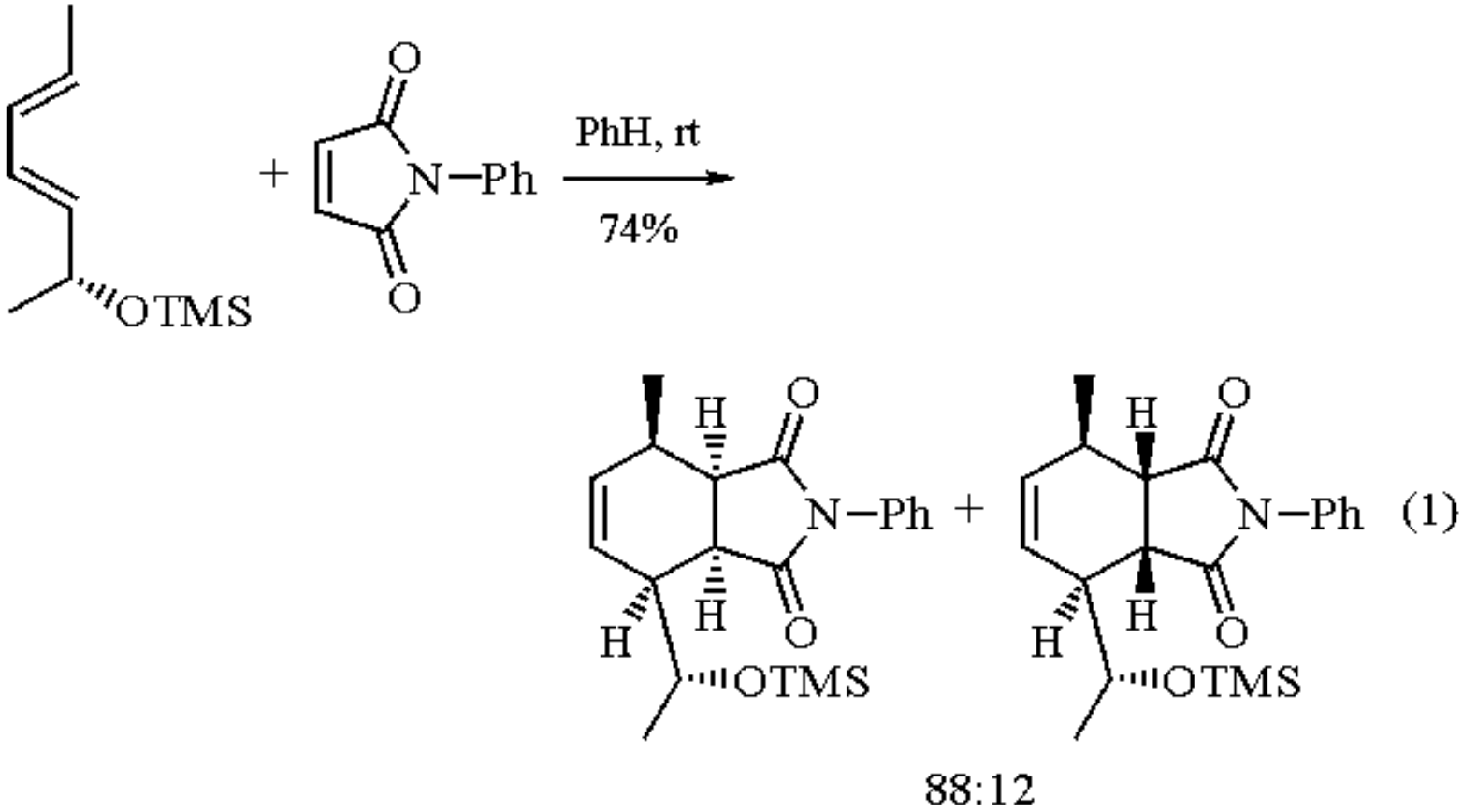
PhH, rt
74%
OTMS
N–Ph
(1)
88:12

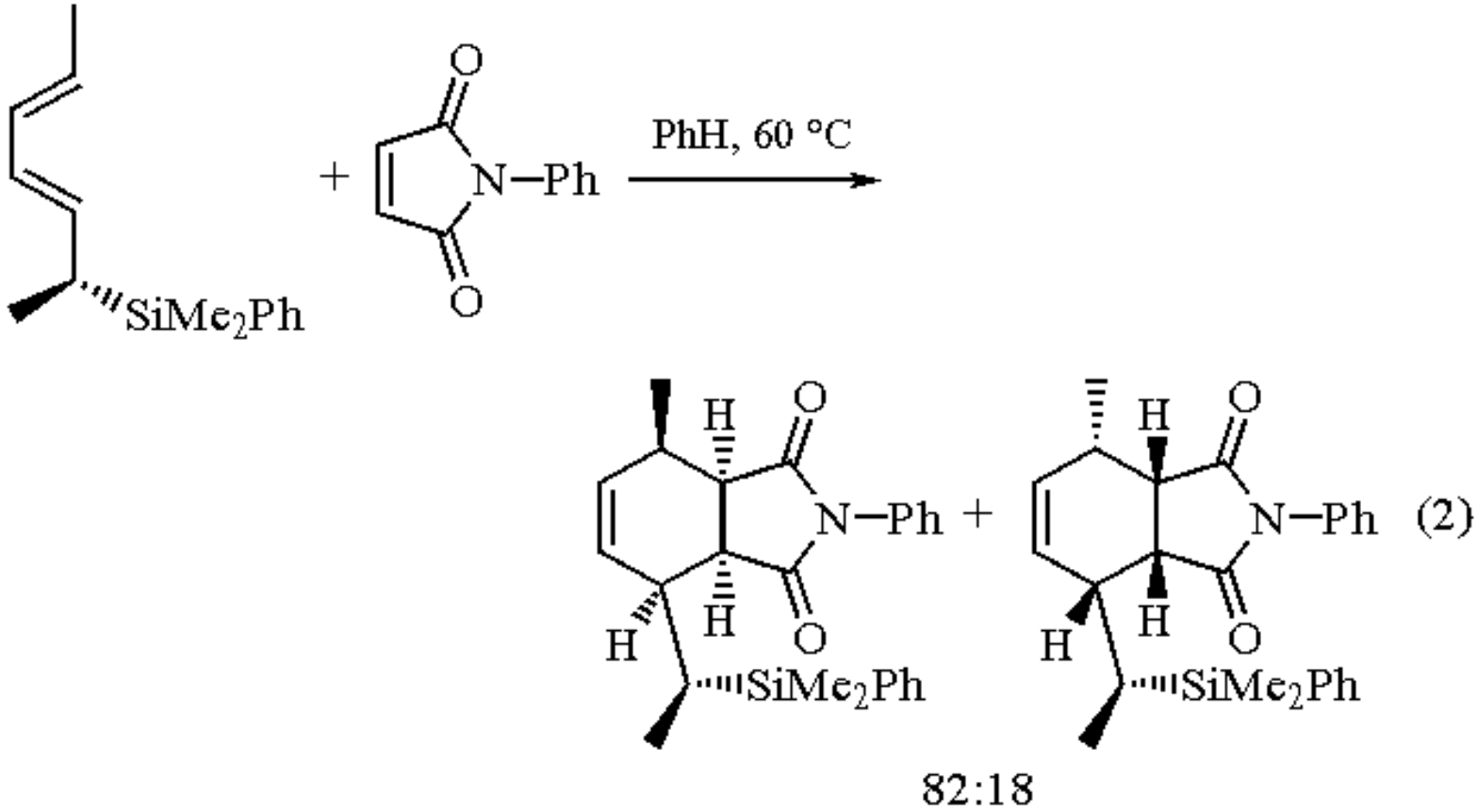
PhH, 60 °C
SiMe2Ph
N–Ph
(2)
82:18

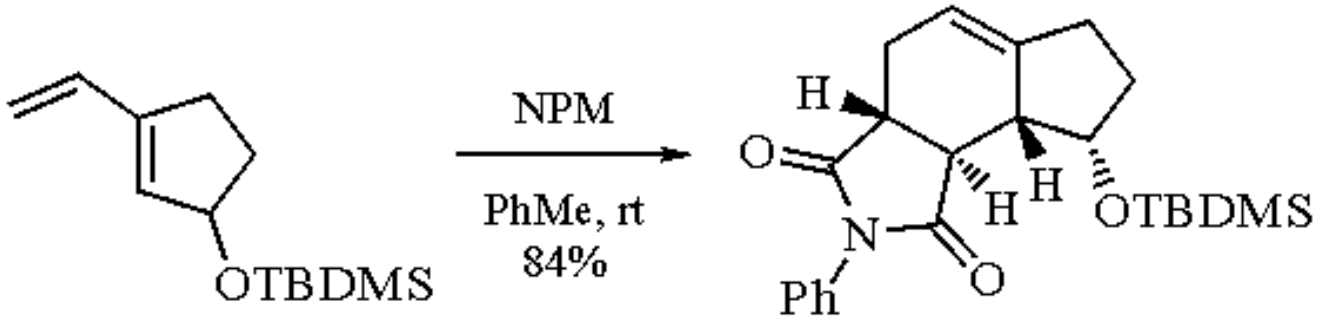

(3)

N-Phenylmaleimide readily reacts with a variety of 1,3-dipoles including azomethine ylides (eqs 4 and 5),[4] carbonyl ylides (eq 6),[5] and nitrones (eq 7).[6] The carbene generated by the photolysis of the sodium salt of a glyconolactone tosylhydrazone has been trapped by NPM to provide a 9:1 mixture of isomeric cyclopropanes (eq 8).[7]

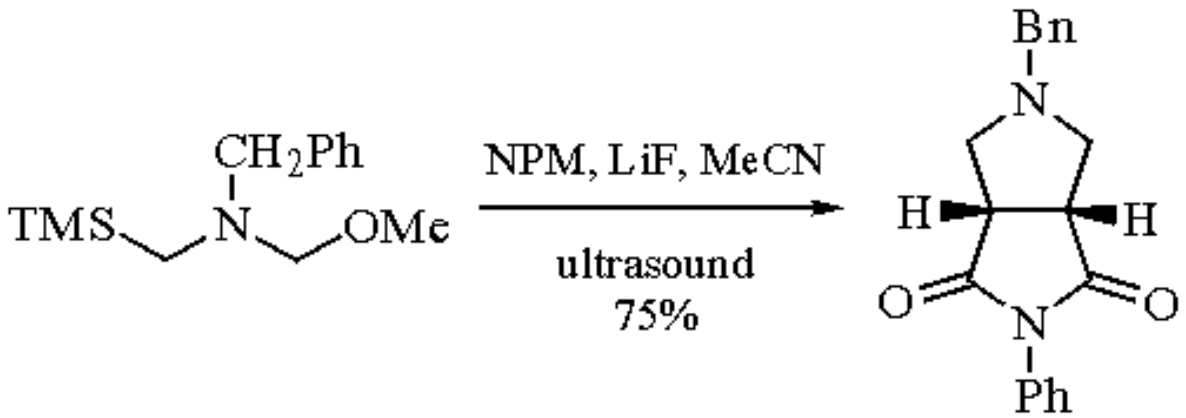

(4)

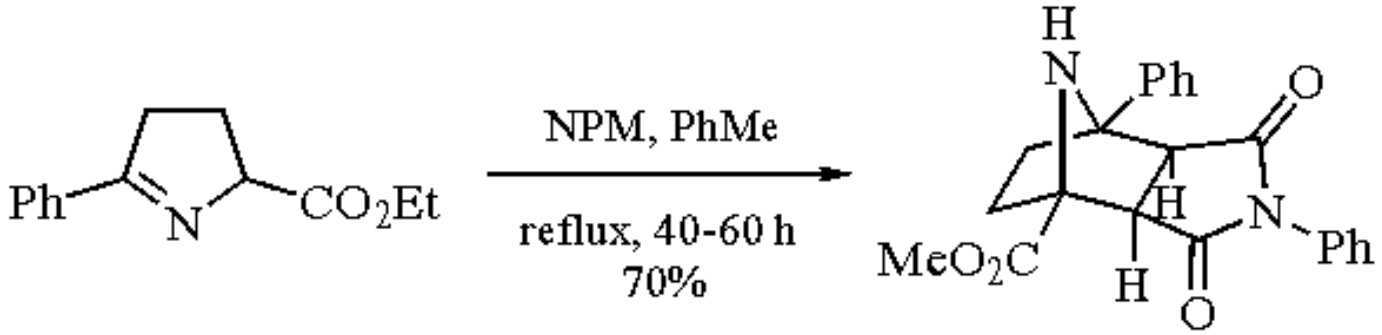

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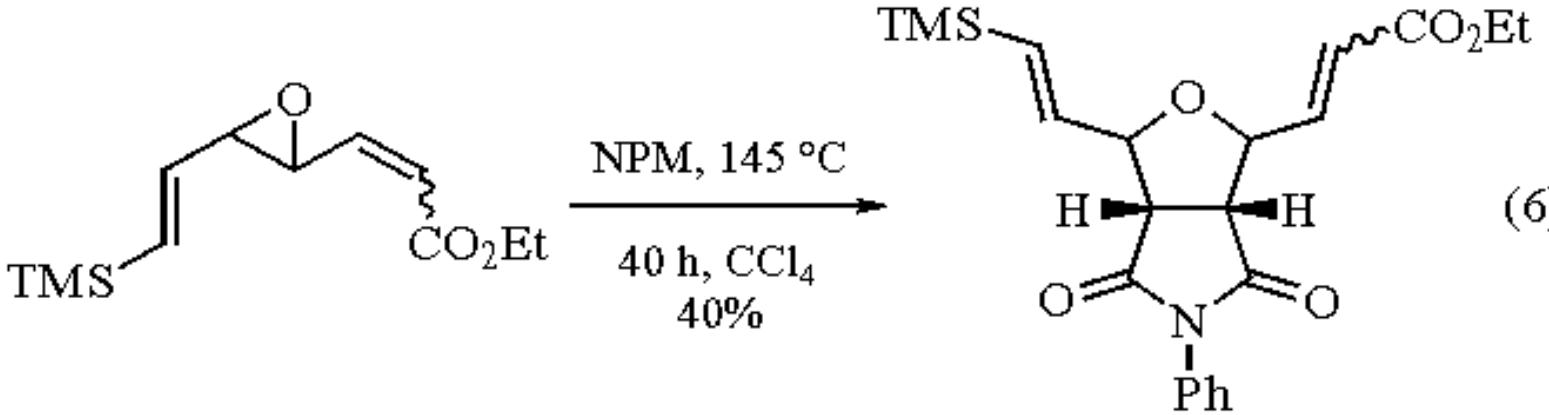

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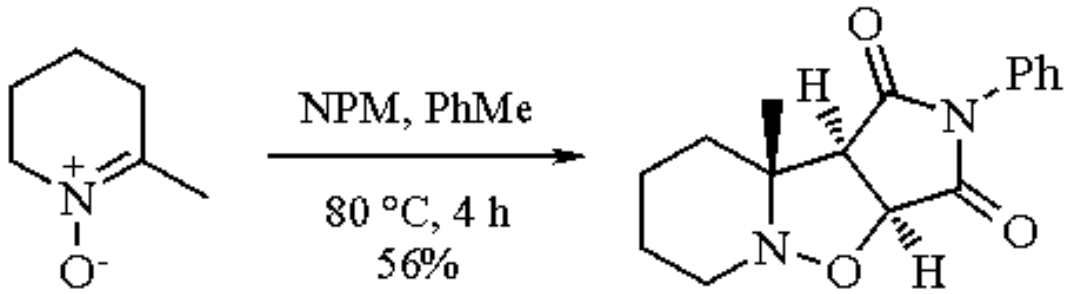

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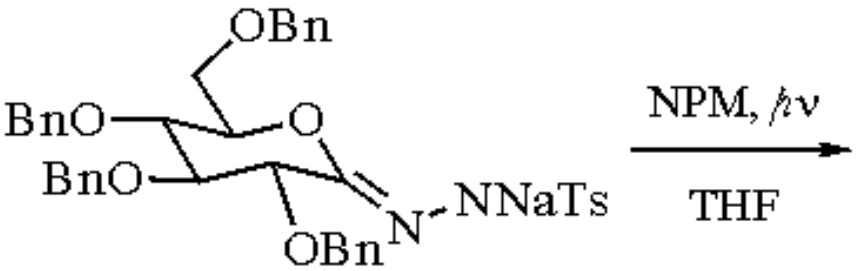

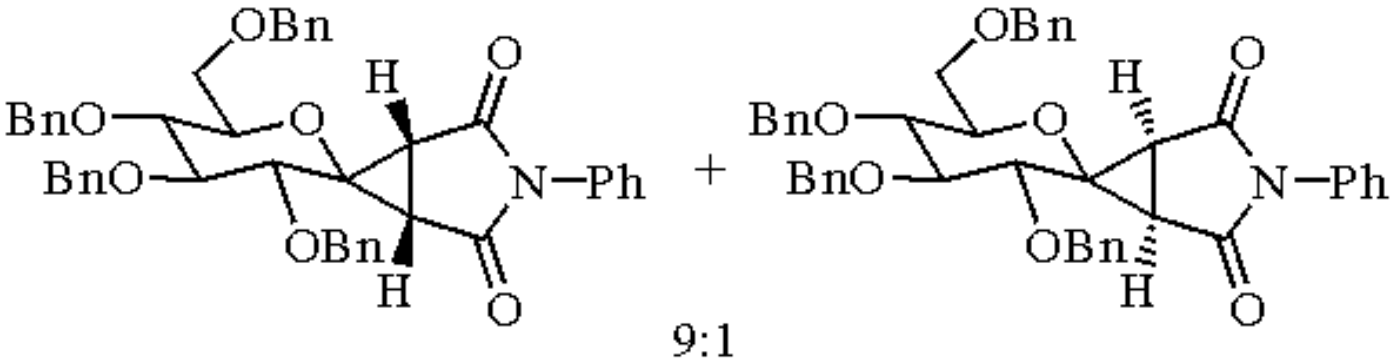

(8)

Miscellaneous.

Substituted amines add in a Michael fashion to *N*-phenyl- and *N*-alkylmaleimides. In this manner, *N*-alkyldaunorubicin derivatives have been prepared in good yield (eq 9).[8] Similarly, ***Tri-n-butylstannane-Azobisisobutyronitrile*** radical additions of glycosyl halides and selenides with *N*-alkylmaleimides provide *C*-glycosyl compounds (eq 10).[9]

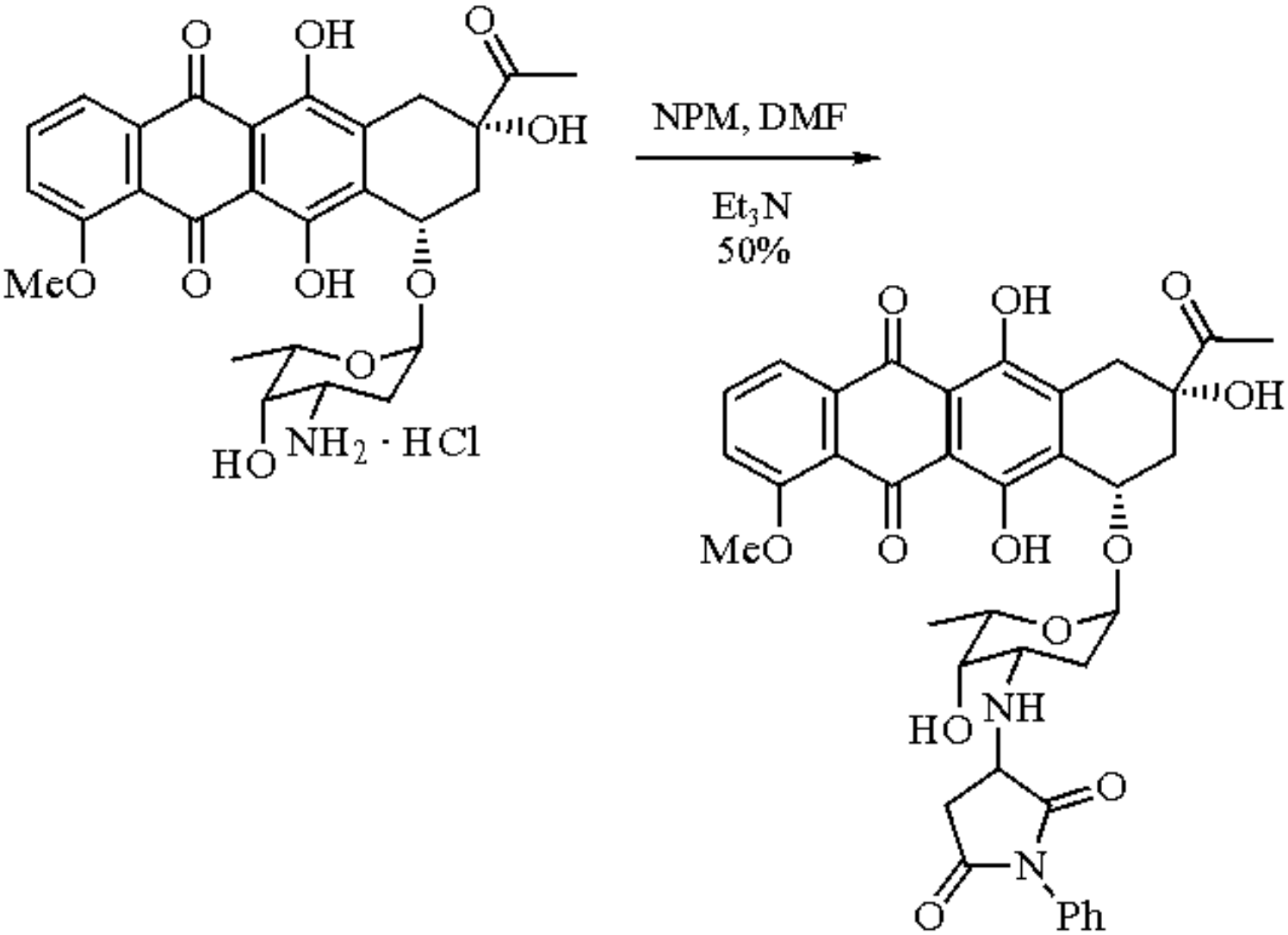

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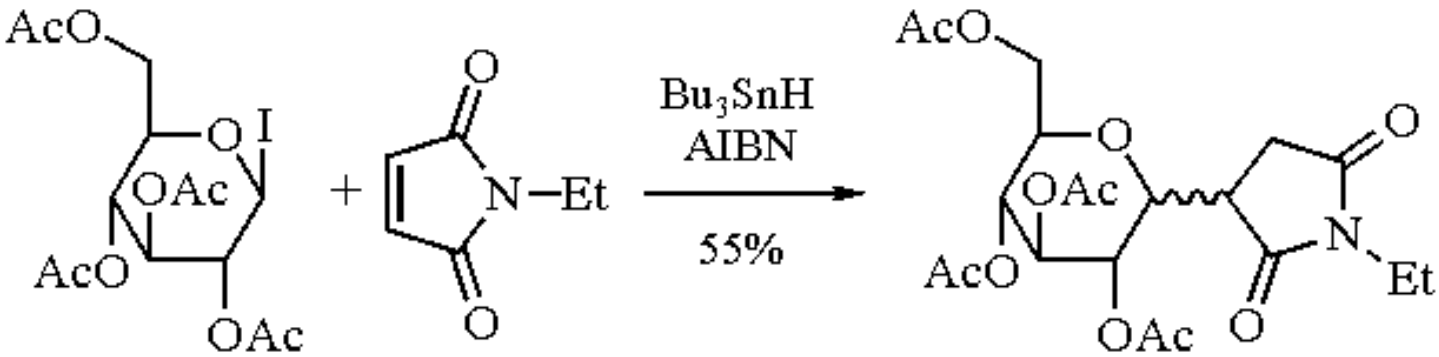

(10)

Related Reagents.

Dimethyl Fumarate.

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(-)-8-Phenylmenthol

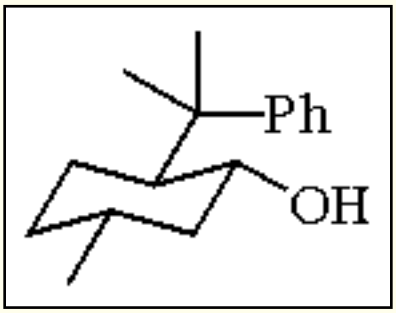

(1*R*,2*S*,5*R*)

[65253-04-5] · $C_{16}H_{24}O$ · (-)-8-Phenylmenthol · (MW 232.37) (1*S*,2*R*,5*R*)

[100101-42-6] (1*S*,2*R*,5*S*)

[57707-91-2]

(chiral auxiliary for asymmetric induction)

Alternate Name: (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexanol.

Physical Data: $[\alpha]_D$ -26° (*c* 2, EtOH); *d* 0.999 g cm^{-3}.

Solubility: sol organic solvents.

Form Supplied in: commercially available as a colorless oil (98%) and as the chloroacetate ester.

Analysis of Reagent Purity: NMR and $[\alpha]_D$.

Preparative Methods: (1*R*,2*S*,5*R*)-(-)-8-phenylmenthol is prepared by the reaction of ***Phenylmagnesium Bromide*** (cat. ***Copper(I) Iodide***) with (+)-pulegone, equilibration of the resulting conjugate addition product, and reduction of the ketone (***Sodium***, isopropanol).[1] The (1*R*,2*S*,5*R*)-isomer is accompanied by the (1*S*,2*R*,5*R*)-isomer and is conveniently separated by recrystallization of the chloroacetate ester.[2] This separation is essential to obtaining high optical yields since it has been shown that the two diastereomers have opposite chiral directing

ability.[3] The preparation of the enantiomeric (1*S*,2*R*,5*S*)-(+)-8-phenylmenthol from (+)-pulegone has been reported.[4]

Handling, Storage, and Precautions: no special precautions are necessary other than those used for combustible organic compounds.

Chiral Auxiliary for Asymmetric Induction.

Numerous derivatives of (-)-8-phenylmenthol have been utilized for asymmetric induction studies. These include inter-[5] and intramolecular[6] Diels-Alder reactions, dihydroxylations,[7] and intramolecular ene reactions[8] of α,β-unsaturated 8-phenylmenthol esters. These reactions usually proceed in moderate to good yield with high diastereofacial selectivity. α-Keto esters of 8-phenylmenthol (see ***8-Phenylmenthyl Pyruvate***) have been used for asymmetric addition to the keto group,[9] as well as for asymmetric [2 + 2] photoadditions[10] and nucleophilic alkylation.[11] Ene reactions of α-imino esters of 8-phenylmenthol with alkenes provide a direct route to α-amino acids of high optical purity.[12]

Vinyl and butadienyl ethers of 8-phenylmenthol have been prepared and the diastereofacial selectivity of nitrone[13] and Diels-Alder[14] cycloadditions, respectively, have been evaluated. α-Anions of 8-phenylmenthol esters also show significant diastereofacial selectivity in aldol condensations[15] and enantioselective alkene formation by reaction of achiral ketones with 8-phenylmenthyl phosphonoacetate gives de up to 90%.[16]

Related Reagents.

8-Phenylmenthyl Crotonate; ***8-Phenylmenthyl Pyruvate***.

---

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8-Phenylmenthyl Acrylate

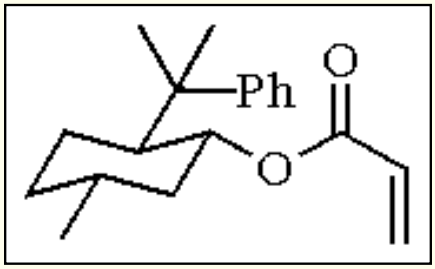

[72526-00-2] · $C_{19}H_{26}O_2$ · 8-Phenylmenthyl Acrylate · (MW 286.45)

(reagent used in asymmetric synthesis for cycloadditions and conjugate additions)

Alternate Name: (1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl acrylate.

Solubility: sol CH_2Cl_2, toluene, most organic solvents.

Analysis of Reagent Purity: ^{1}H and ^{13}C NMR.[1] $[\alpha]_D$ +16.21° (*c* 1.68, CH_2Cl_2).[2]

Preparative Method: prepared by the reaction of ***(-)-8-Phenylmenthol***, acryloyl chloride, ***Triethylamine***, and ***4-Dimethylaminopyridine*** in CH_2Cl_2 at 0 °C. Following an aqueous workup, the compound is purified by chromatography on silica gel.[1]

Handling, Storage, and Precautions: acrylates are prone to polymerization and are best stored below room temperature under N_2.

[4 + 2] Cycloadditions.

The asymmetric Diels-Alder reaction[3] of phenylmenthyl acrylate with 5-benzyloxymethylcyclopentadiene in the presence of ***Aluminum Chloride*** produces an 89% yield of the *endo* cycloadduct (eq 1), accompanied by 7% of the *exo* adduct. This provides a useful intermediate for the preparation of various prostaglandins.[2] The ***Tin(IV) Chloride*** and ***Titanium(IV) Chloride*** catalyzed reactions with ***Cyclopentadiene*** deliver a mixture of *endo* and *exo* adducts in 89% de, and 90% de, respectively (eq 2). The $TiCl_4$ reaction gives an 89:11 *endo*:*exo* ratio, while the $SnCl_4$ reaction gives an 84:16 *endo*:*exo* ratio. From a practical point of view, the titanium and tin catalysts are the best of the various Lewis acids surveyed.[4] The use of $TiCl_4$ is also the most effective for the reaction of the acrylate with ***1,3-Butadiene*** (eq 3).[5] The increased asymmetric induction over the simpler menthyl acrylate is attributed to the shielding of the C(α)-*re* face of the dienophile by the phenyl ring.[6]

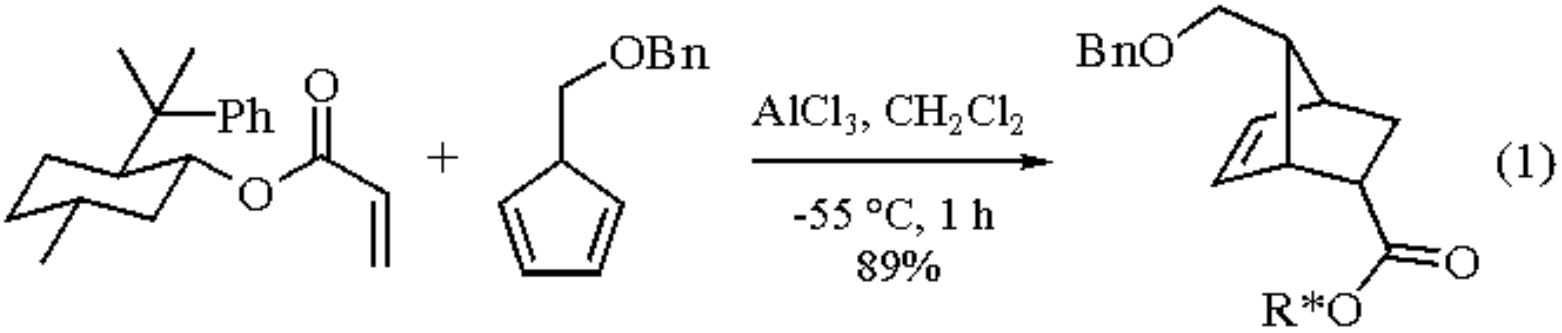

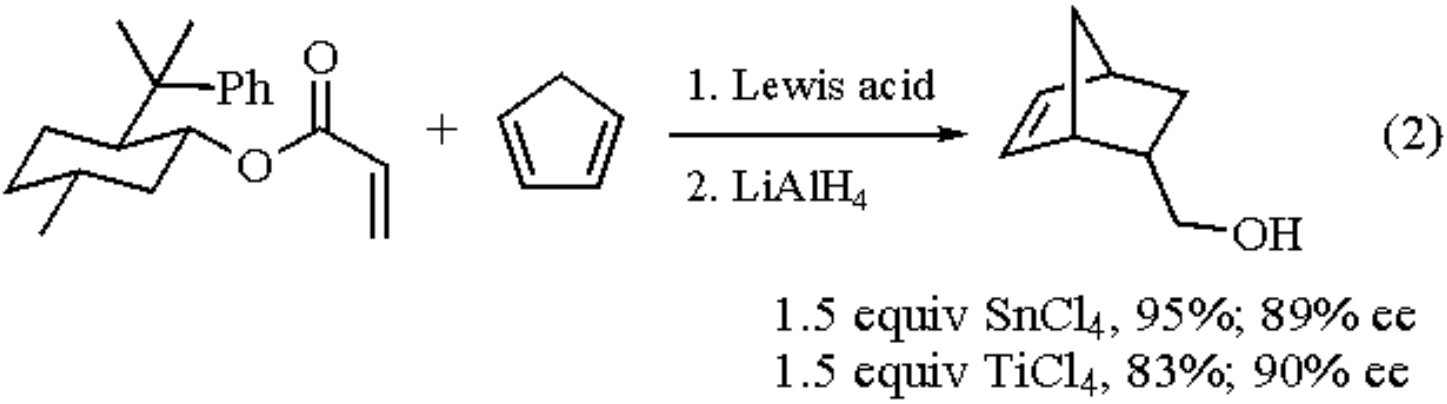

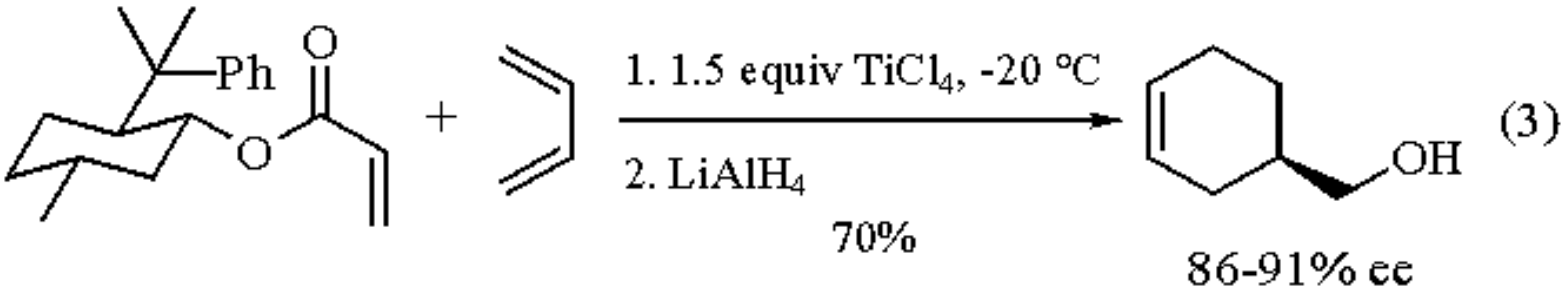

1,3-Dipolar Cycloadditions.

The asymmetric induction for a 1,3-dipolar cycloaddition of phenylmenthyl acrylate is not as good as in the [4 + 2] cycloadditions. The thermal decomposition of diazofluorene in the presence of the acrylate produces the spirocyclopropane in 96% yield, but with only a 20% de (eq 4).[7]

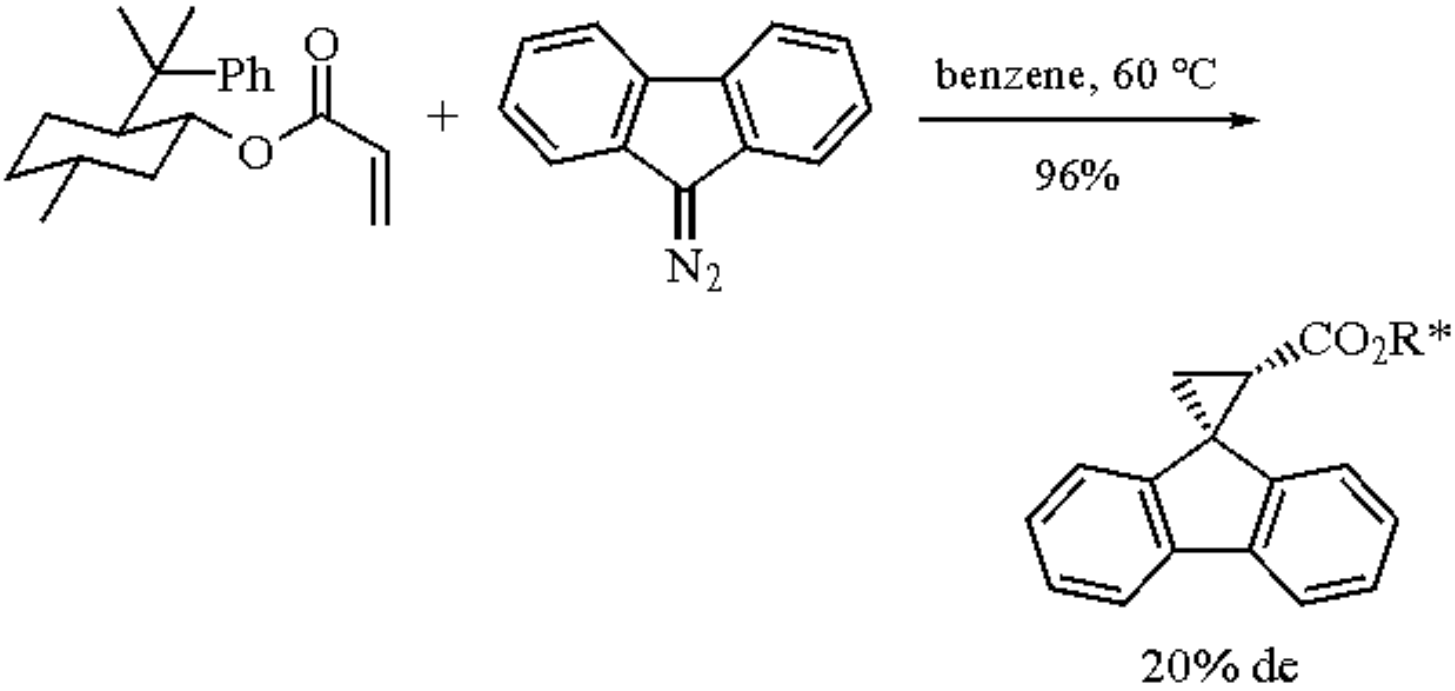

(4)

Conjugate Additions.

The reaction of this acrylate derivative with lithium *t*-butyl hydroperoxide (generated from anhydrous ***t-Butyl Hydroperoxide*** and ***n-Butyllithium***) in THF leads to the corresponding epoxide (eq 5) in 95% yield with a de of 40%.[8]

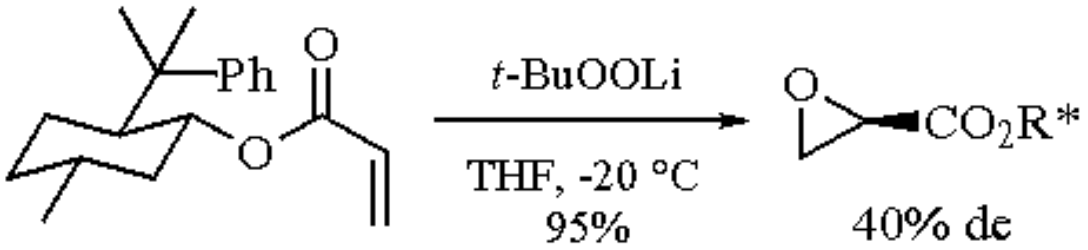

(5)

In an asymmetric approach to the bicyclo[2.2.2]octane ring system, a double Michael addition has been employed using phenylmenthyl acrylate as the initial Michael acceptor. The condensation of the dienolate, generated with ***Lithium Diisopropylamide***, reacts with the acrylate to afford the bicyclo[2.2.2]octane derivative (eq 6). The de for the reaction is only 50%; however, it is highly *endo* selective (>95%).[9]

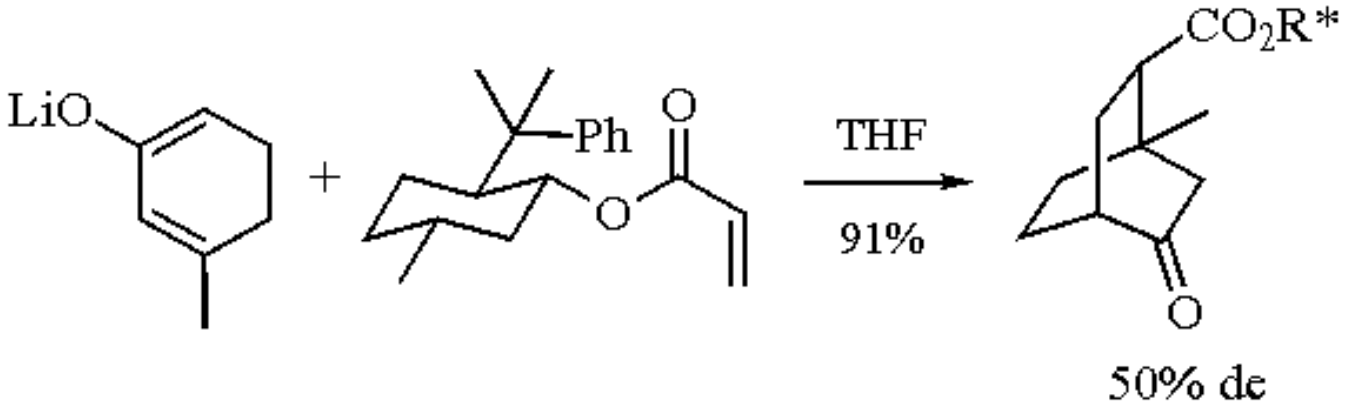

(6)

A Lewis acid-mediated two-fold asymmetric Michael addition allows access to *cis*-decalin derivatives. The reaction of the trimethylsilylenol ether of acetylcyclohexene with phenylmenthyl acrylate in the presence of ***Diethylaluminum Chloride*** (eq 7) yields the decalone in 64% yield (70% de). This has been shown not to be a Diels-Alder reaction. If the reaction is worked-up early, the initial Michael adduct can be isolated.[10]

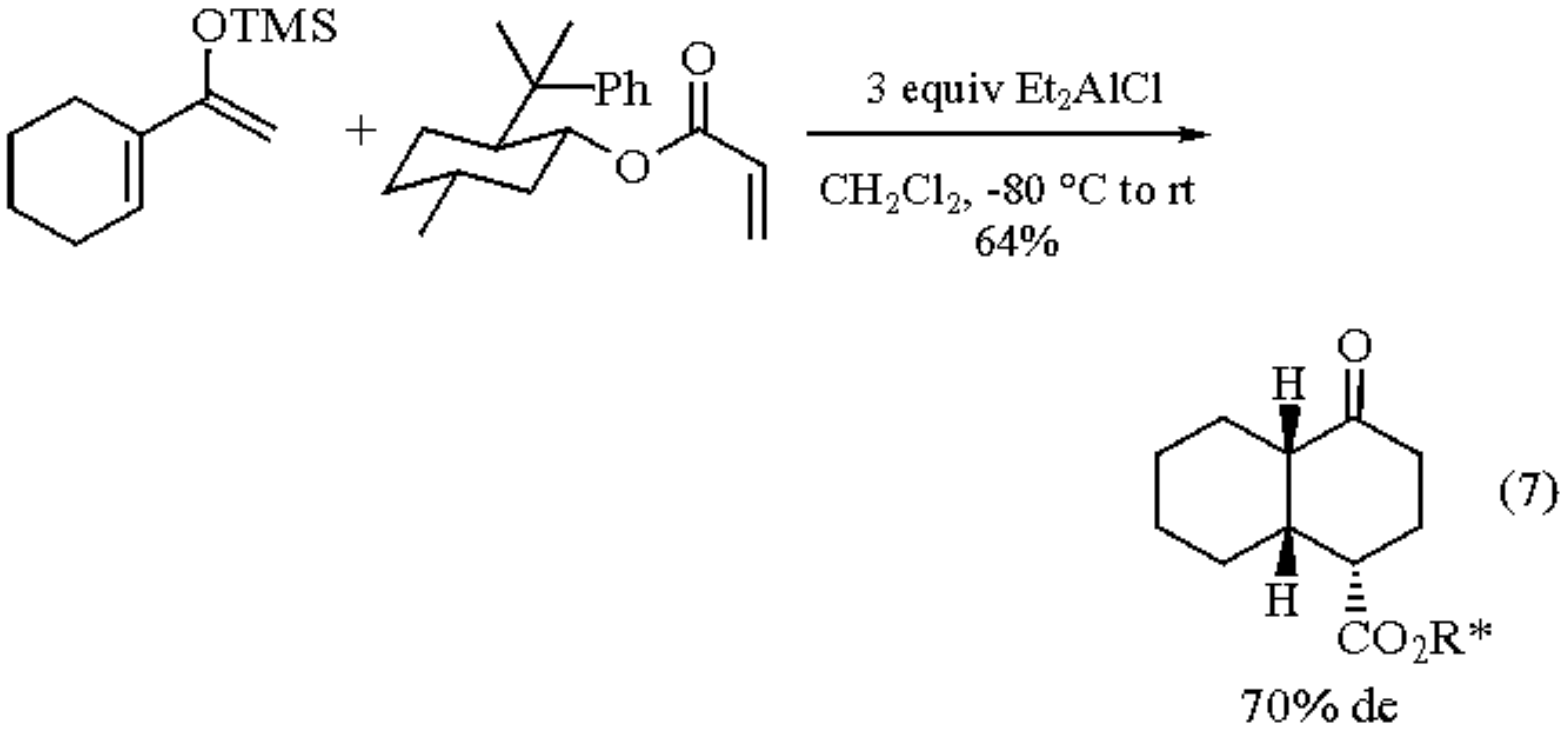

(7)

Phenylmenthyl acrylate has been used as a component in an asymmetric Baylis-Hillman reaction. Treatment of the acrylate with ***1,4-Diazabicyclo[2.2.2]octane*** and benzaldehyde at 8 kbar of pressure delivers the α-(hydroxyalkyl)acrylate (eq 8). The product obtained has an 86% de. Menthyl acrylate is superior to the phenylmenthyl acrylate in this particular application.[11] In a radical-mediated addition, phenylmenthyl acrylate gives rise to the α-pyridyl sulfide in 68% yield (eq 9).[12] The final product is isolated with a 56% de.

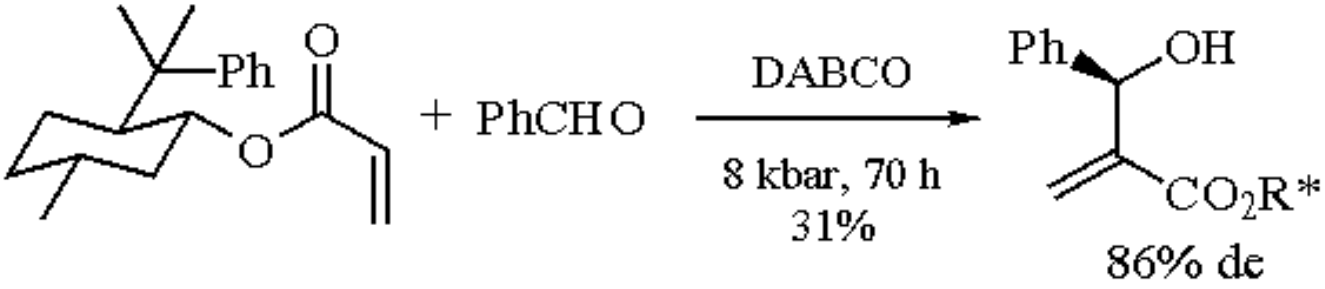

(8)

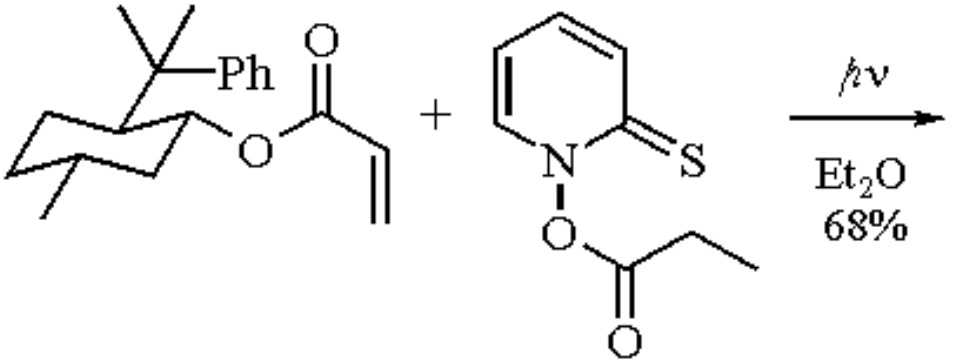

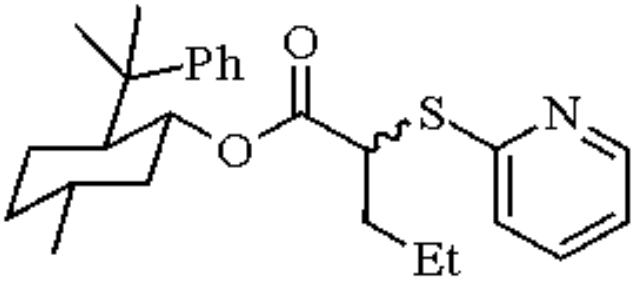

(9)

56% de

Miscellaneous.

The acrylate provides a synthon for the preparation of ***8-Phenylmenthyl Glyoxylate***, which is useful for asymmetric ene reactions.[1] Thus ozonolysis and removal of the water of hydration produces the glyoxylate in 89% yield (eq 10).

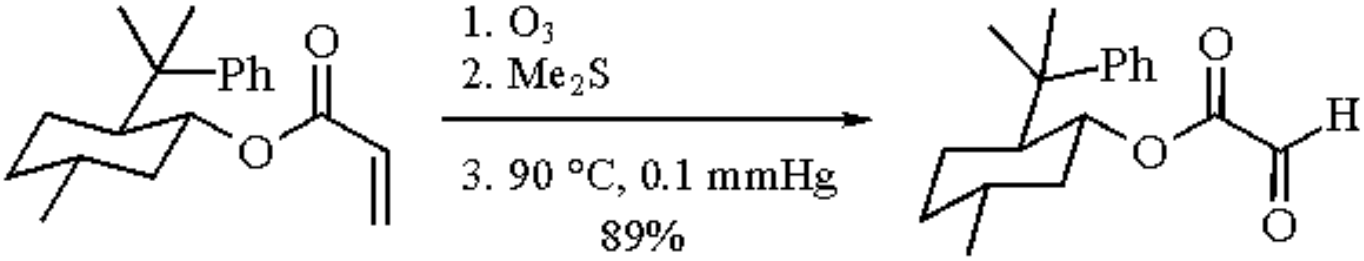

(10)

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8-Phenylmenthyl Crotonate

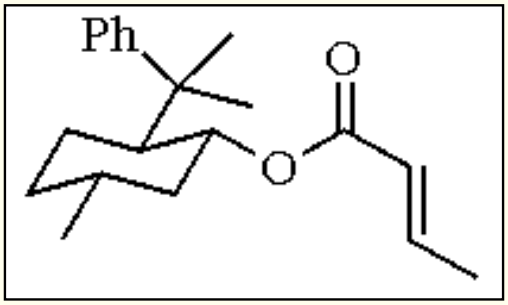

[81002-19-9] · $C_{20}H_{26}O_2$ · 8-Phenylmenthyl Crotonate · (MW 300.46)

(chiral ester for asymmetric induction)

Alternate Name: (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl crotonate.

Solubility: sol organic solvents.

Form Supplied in: not commercially available.

Preparative Methods: isolated as an oil from the esterification of ***(-)-8-Phenylmenthol*** with 2-butenoic acid (DCC, DMAP, CH_2Cl_2).[1]

Analysis of Reagent Purity: NMR[2] and $[\alpha]_D$.

Handling, Storage, and Precautions: no special precautions are necessary other than those used for combustible organic compounds.

General Discussion.

Reaction of the crotyl ester of (-)-8-phenylmenthol with organocopper reagents in the presence of ***Boron Trifluoride*** gives good chemical yields and >99% de of the 1,4-addition product where addition has taken place from the *re* face (eq 1).[1] Extension of this methodology to the 8-phenylmenthyl *cis*-butenoate gives significantly lower de.[1] Epoxidation of 8-phenylmenthyl crotonate with ***t-Butyl Hydroperoxide-n-Butyllithium*** gives 50% de.[2] Chiral β-amino esters of 8-phenylmenthol have been prepared in 50-60% de by the addition of amines to the *re* face of 8-phenylmenthyl crotonate under 14-15 kbar pressures (eq 2). Much higher (75 to >99%) de is obtained using 8-(β-naphthyl)menthol crotonate. The β-amino esters obtained are of the proper configuration for conversion to biologically active β-lactams.[3]

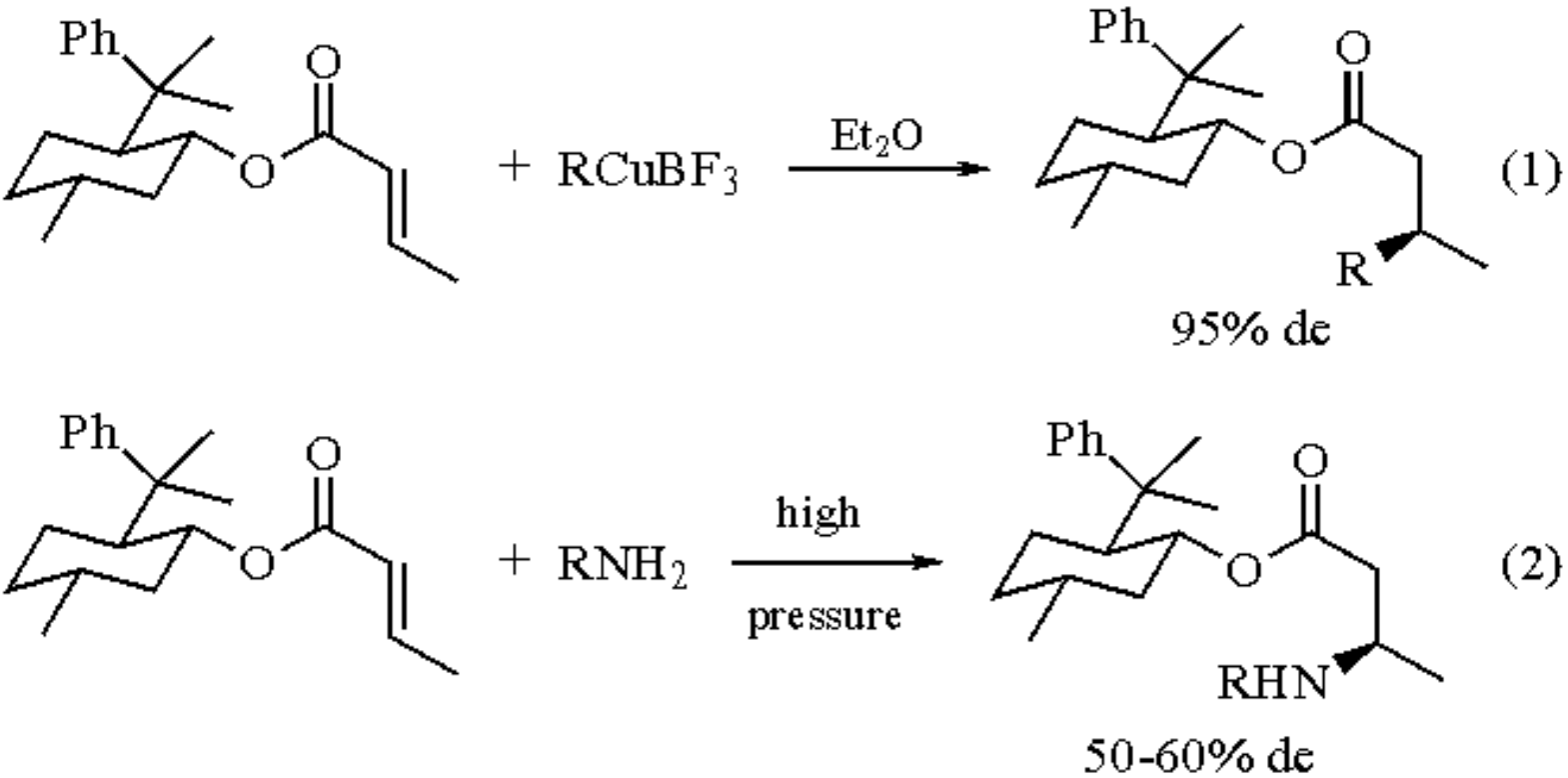

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8-Phenylmenthyl Glyoxylate[1]

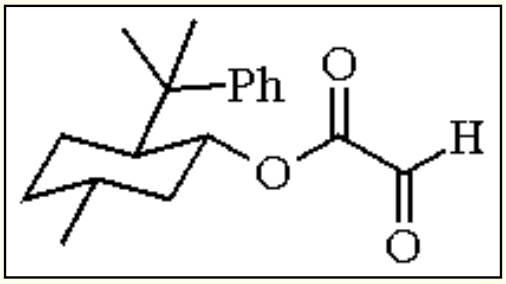

[129444-92-4] · $C_{18}H_{24}O_3$ · 8-Phenylmenthyl Glyoxylate · (MW 288.42)

(two-carbon unit utilized as a versatile chiral reagent in ene reactions,[2] Diels-Alder reactions,[3] various nucleophilic additions,[4] and aromatic substitutions.[5])

Physical Data: bp 135-140 °C/0.3 mmHg; [α]20589 -169° (*c* 0.51, benzene).[6]

Solubility: sol most common organic solvents.

Preparative Methods: ozonolysis of ***8-Phenylmenthyl Acrylate***, NaOAc-catalyzed elimination of nitrite ion from nitrate esters, and direct esterification with glyoxylic acid.[7]

Handling, Storage, and Precautions: heating the glyoxylate monohydrate to 90 °C/0.1 mmHg for 4.5 h or distillation provides material which is sufficiently anhydrous for most practical applications. Due to its tendency to form a monohydrate and/or polymerize, 8-phenylmenthyl glyoxylate should be stored under nitrogen in the refrigerator.

Ene Reactions.

Lewis acid (***Tin(IV) Chloride*** or ***Titanium(IV) Chloride***) catalyzed ene reactions of the glyoxylate esters of 8-phenylmenthol and 2-*epi*,*ent*-8-phenylmenthol, as well as *trans*-2-phenylcyclohexanol, with terminal, monosubstituted alkenes proceed with excellent levels of stereocontrol (eq 1).[8] The phenyl group presumably forms a π-complex with the aldehyde-Lewis acid complex thereby blocking one face of the dicarbonyl, rendering the opposite face accessible to incoming reagents. This has been demonstrated through the systematic study of the effect of auxiliary structure on asymmetric induction in the glyoxylate-ene reaction, as well as by photophysical studies involving a family of α-carbonyl esters of 8-phenylmenthol.[7,9] The ene reactions of glyoxylates with nonterminal alkenes proceed with a high level of relative asymmetric induction to give the (*S*)-configuration at the newly created stereocenter with 8-phenylmenthol and the (*R*)-configuration with *trans*-2-phenylcyclohexanol. The reaction of 8-phenylmenthyl glyoxylate with *trans*-2-butene produces a 93:7 mixture of diastereomers at C-3 in 85% yield; introduction of a TMS group into *trans*-2-butene increases the *anti*-selectivity up to ~100% (eq 2).[8f,g] Double bond isomerization in the

substrate under the reaction conditions, as well as contamination of halogen adducts in the products, point to a cationic mechanism for these ene reactions.[8e]

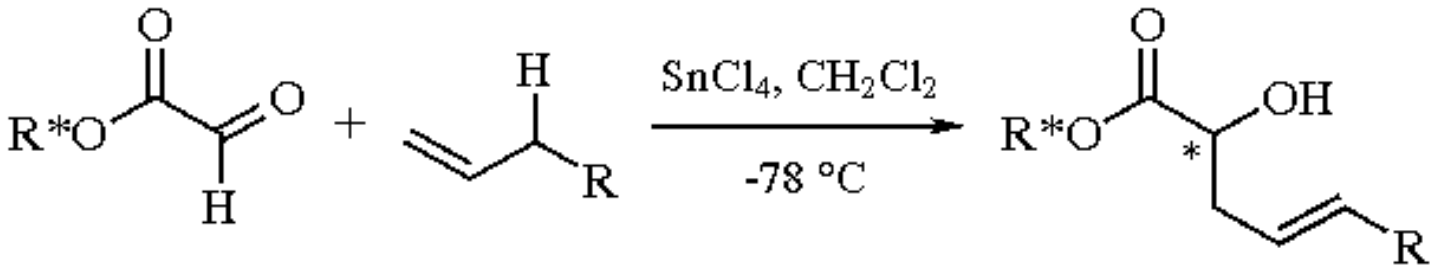

(1)

R* = 8-phenylmenthyl, >99.8% de *(S)*
2-*epi*, *ent*-8-phenylmenthyl, >99.8% de *(R)*
trans-2-phenylcyclohexyl, >97% de *(R)*

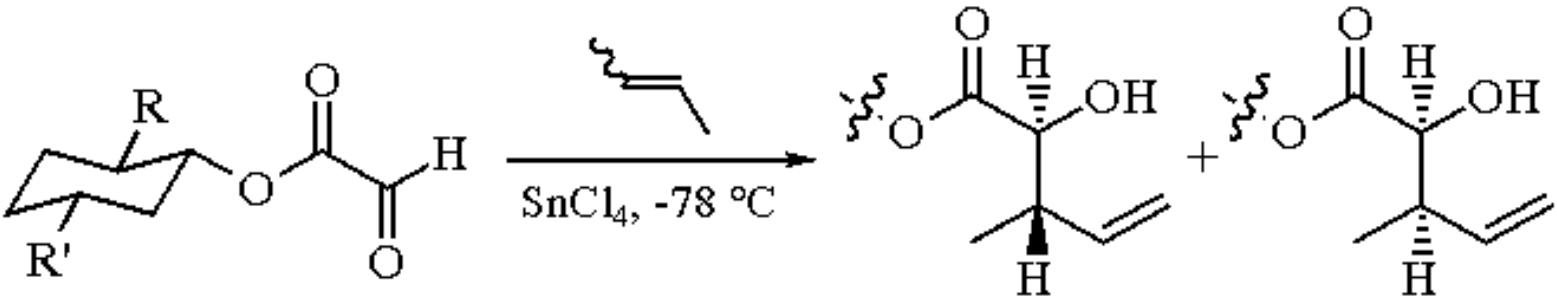

anti *syn* (2)

R = CMe_2Ph	*cis*	8:1
R' = Me	*trans*	15:1

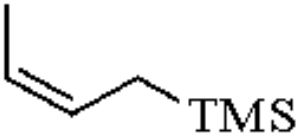

1:15

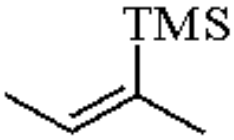

100:0

R = Ph	*cis*	6:1
R' = Me	*trans*	1.6:1

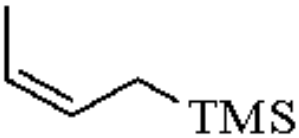

1:2.5

The asymmetric glyoxylate-ene reactions have been exploited in the total synthesis of (-)-specionin, which involves

asymmetric desymmetrization of a prochiral diene (eq 3), and (-)-xylomollin, which involves an efficient kinetic resolution of a racemic diene (eq 4).[10a-c]

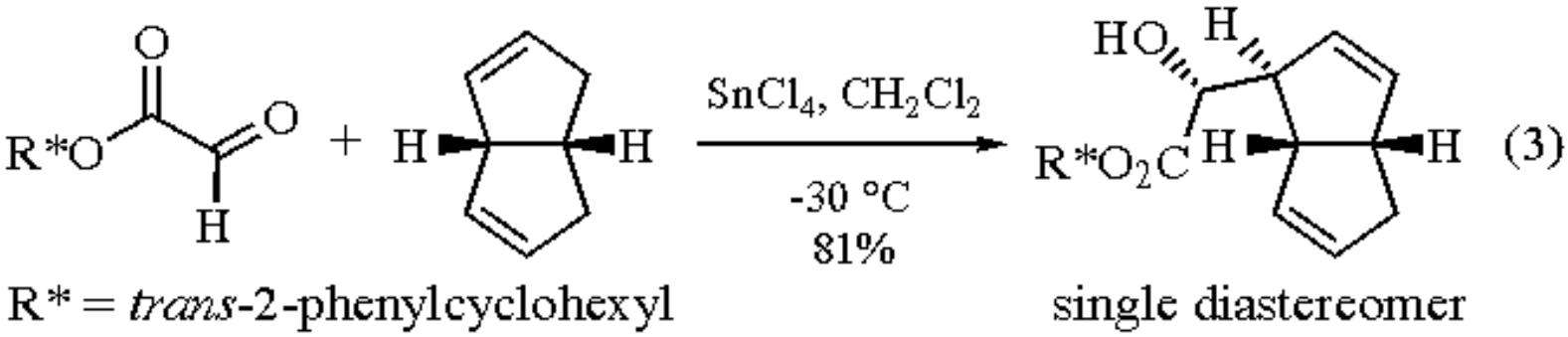

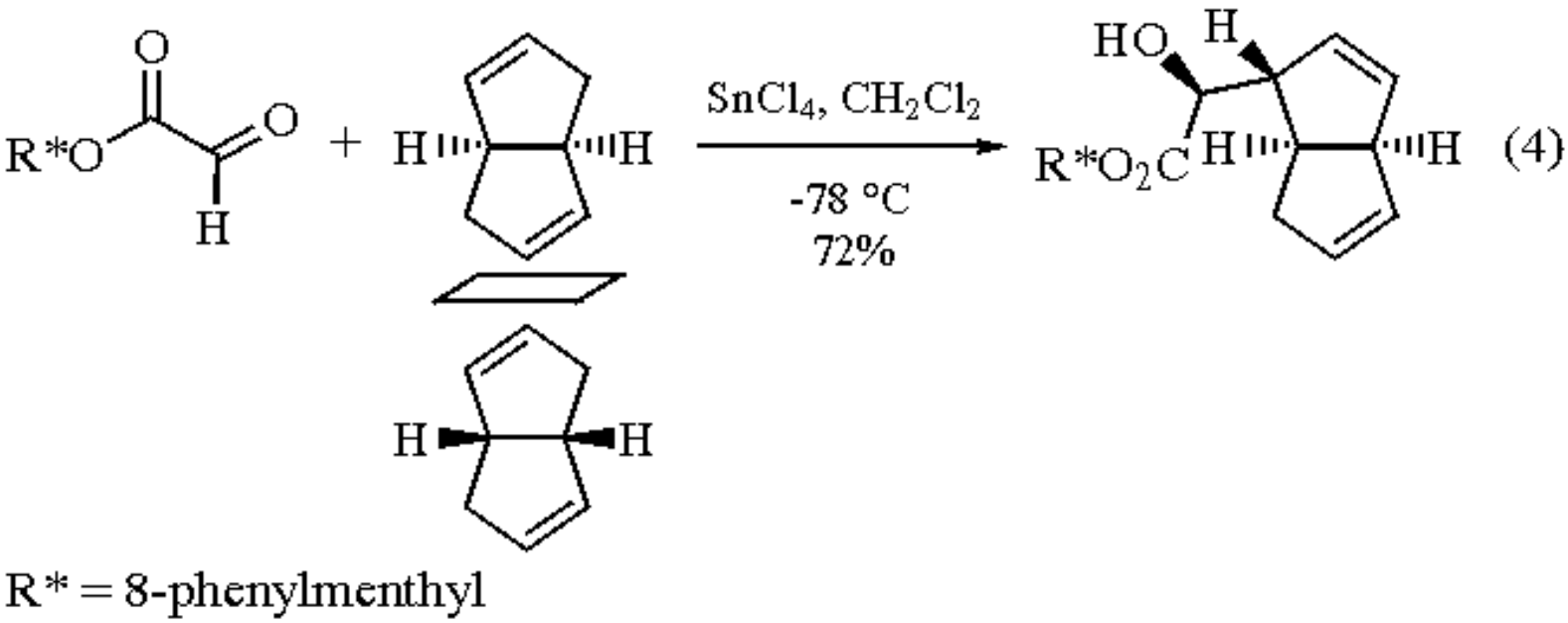

Nucleophilic Additions.

A variety of nucleophiles have been added to 8-phenylmenthyl (and *trans*-2-phenylcyclohexyl) glyoxylates with high levels of asymmetric induction. These include organomagnesium[4] and organotin reagents,[11] as well as nitroalkane anions (eq 5).[12] Other applications of 8-phenylmenthyl glyoxylate include asymmetric hetero-Diels-Alder reactions to produce chiral dihydropyran derivatives[3] and *o*-hydroxylation of phenols producing the corresponding chiral 2-hydroxymandelic acid derivatives.[5] α-Imino esters derived from 8-phenylmenthyl glyoxylate undergo nucleophilic additions[13] as well as ene reactions[14] to produce nonproteinogenic α-amino acid derivatives.

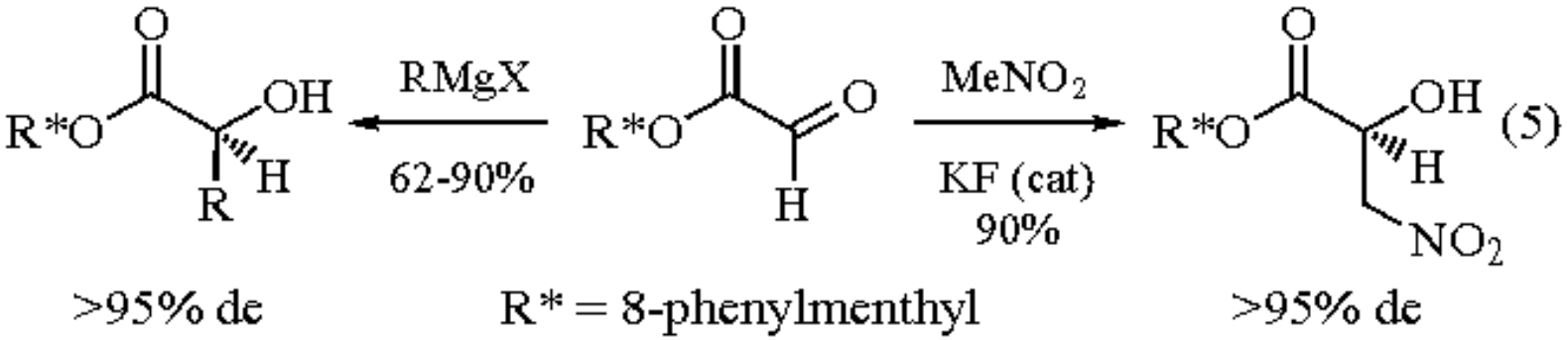

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8-Phenylmenthyl Pyruvate

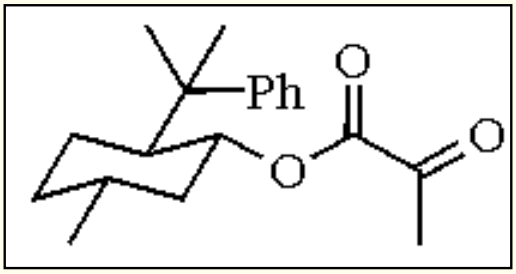

(1*R*,2*S*,5*R*)

[88292-41-5] · $C_{19}H_{26}O_3$ · 8-Phenylmenthyl Pyruvate · (MW 302.45) (1*S*,2*R*,5*R*)

[100101-44-8]

(chiral ester for asymmetric induction)

Alternate Name: (1*R*,2*S*,5*R*)-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexyl pyruvate.

Solubility: sol organic solvents.

Form Supplied in: not commercially available.

Preparative Method: isolated as an oil from the acid-catalyzed esterification of ***(-)-8-Phenylmenthol*** with pyruvic acid.[1]

Handling, Storage, and Precautions: susceptible to hydrate formation on exposure to moisture. No other special precautions other than those for combustible organic compounds are necessary.

Chiral α-Hydroxy Acids.

Grignard reagents add to the pyruvate ester of (-)-8-phenylmenthol from the *si*-face to afford the *S*-α-hydroxy esters (eq 1).[2] Chelation of the pyruvate with magnesium ensures the *s-cis* conformation and is required for high diastereoselectivity.[1] The high degree of diastereoselectivity is attributed to a favorable FMO interaction of the pyruvate with the phenyl moiety.[3] The corresponding *R*-α-hydroxy ester is available by reversing the order of bond formation starting with 8-phenylmenthyl glyoxylate.[4]

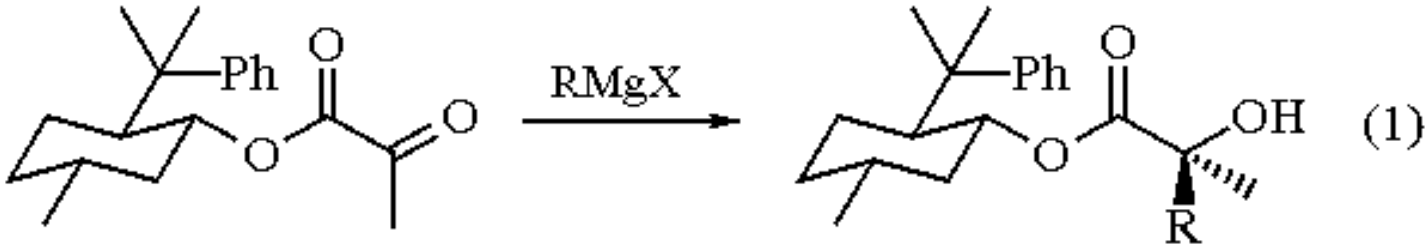

Reduction of 8-phenylmenthyl pyruvate with ***Potassium Triisopropoxyborohydride*** in THF gives 90% de of the (*R*)-lactate ester (eq 2), but other reducing reagents show little selectivity.[2] The stereochemical outcome of this reduction is explained as occurring in the *s-trans* conformation of the pyruvate.

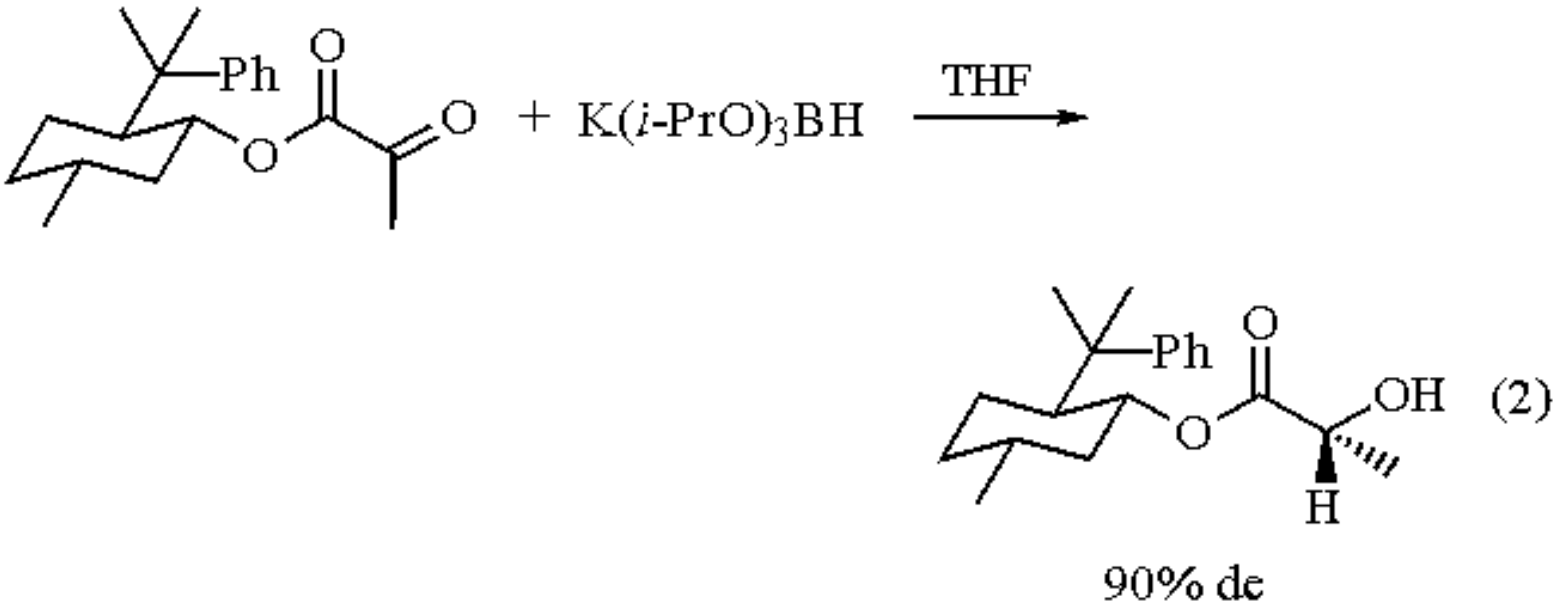

Tin(IV) Chloride-catalyzed ene reaction of the pyruvate ester of (-)-8-phenylmenthol with 1-hexene gives a single diastereomer of the unsaturated (*S*)-α-hydroxy ester (de > 90%) (eq 3).[2] Similarly, tin(IV) chloride-catalyzed ene reactions of 8-phenylmenthyl glyoxylates afford unsaturated secondary alcohols with 93-98% de of the (*S*) configuration.[5]

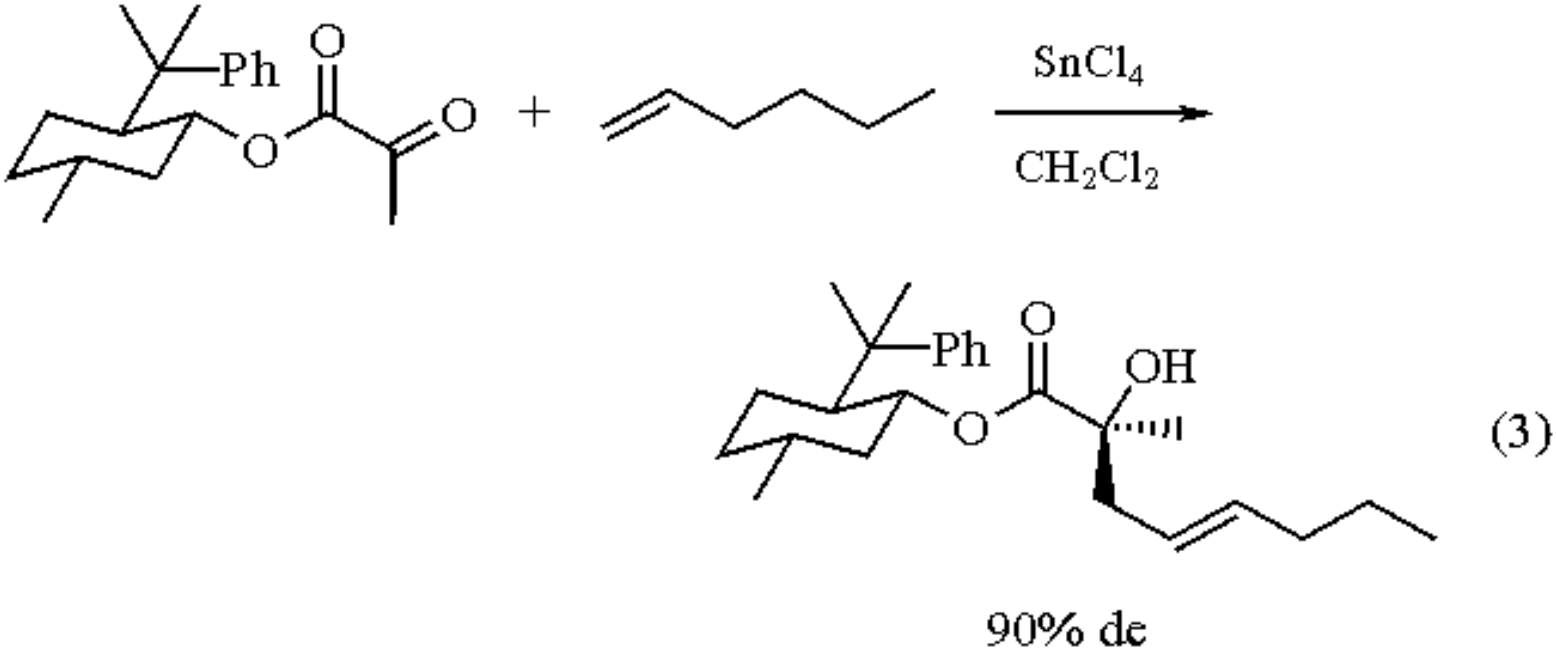

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Phenylmercury(II) Chloride[1]

PhHgCl

[100-56-1] · C_6H_5ClHg · Phenylmercury(II) Chloride · (MW 313.15)

(phenylating agent for allylic halides[3] and alkenes;[4-8] converts primary and secondary allylic alcohols into 3-phenyl alcohols and 3-phenyl aldehydes;[9] reacts with carbon monoxide to give ketone[10-13])

Physical Data: mp 250-252 °C. ^{1}H NMR:[16,17] δ (DMSO, ppm) H_o 7.46 ($^3J_{H_o\text{-}Hg}$ = +203 Hz); H_m 7.37 ($^4J_{H_m\text{-}Hg}$ = +49 Hz); H_p 7.46. ^{13}C NMR:[18,19] δ (DMF + $(CD_3)_2CO$ (20%) at 340 K (ppm)) C_α 150.5, ($^1J_{Hg\text{-}C}$ = 2530 Hz), C_β 136.4 ($^2J_{Hg\text{-}C}$ = 117 Hz); C_γ 128.0 ($^3J_{Hg\text{-}C}$ = 205 Hz); C_δ 127.9 ($^4J_{Hg\text{-}C}$ = 35 Hz). ^{199}Hg NMR:[18] (CH_2Cl_2) -1192, ($(CD_3)_2SO$) -1182 ppm. MS:[20] mass of ions observed: $C_6H_5HgCl^+$&bdot;, $C_6H_5Hg^+$, $HgCl^+$. IR: ν(Hg-Cl) 331-332 cm^{-1}.[15]

Solubility: sparingly sol H_2O; sol C_6H_6, ether, pyridine; slightly sol hot ethanol.[2]

Form Supplied in: white satiny leaflets; stable in air; widely available.

Preparative Methods: by mercuration of benzene[21] with ***Mercury(II) Chloride*** (eq 1) or red ***Mercury(II) Oxide***.

$$\mathrm{PhH} + \mathrm{HgCl_2} \rightleftharpoons [\mathrm{PhH}\quad \mathrm{HgCl_2} \rightleftharpoons \mathrm{H\overset{+}{P}hHgCl} + \mathrm{Cl^-}] \rightleftharpoons \mathrm{PhHgCl} + \mathrm{HCl} \qquad (1)$$

Copper or ***Copper(I) Chloride***[22] promotes facile displacement of nitrogen from double salts of ***Benzenediazonium Chloride*** and mercury(II) chloride in good yield (eq 2).

$$\mathrm{PhN_2Cl} + \mathrm{HgCl_2} \xrightarrow{\mathrm{HCl}} [\mathrm{PhN_2ClHgCl_2}] \xrightarrow{2\ \mathrm{Cu}} \mathrm{PhHgCl} + 2\ \mathrm{CuCl} + \mathrm{N_2} \qquad (2)$$

Phenylmercury(II) chloride can also be prepared by the Peters reaction[23] involving mercury(II) chloride and sulfinic acid (eq 3), by the decomposition of the phenyl-tin bond in $PhSn(alkyl)_3$ with mercury(II) chloride (eq 4),[24] by mixing equimolar mercury(II) chloride and ***Diphenylmercury*** (eq 5),[25] or by photolysis of diphenylmercury in CCl_4 (eq 6).[26]

$$PhSO_2H + HgCl_2 \longrightarrow PhHgCl + SO_2 + HCl \quad (3)$$

$$PhSnR_3 + HgCl_2 \longrightarrow PhHgCl + ClSnR_3 \quad (4)$$

$$Ph_2Hg + HgCl_2 \longrightarrow 2\ PhHgCl \quad (5)$$

$$Ph_2Hg + CCl_4 \xrightarrow{h\nu,\ 100\ °C} PhHgCl + PhCl + C_2Cl_6 \quad (6)$$

In PhHgCl the Ph-Hg bond is less polar than the Hg-Cl bond. The Ph-Hg bond is weak and undergoes homolytic cleavage.

Handling, Storage, and Precautions: highly toxic irritant; LD_{50} orally in rats 60 mg kg^{-1}. Use in a fume hood.

Coupling Reactions.

PhHgCl undergoes dimerization[27] to biphenyl in the presence of 10% ***Palladium(II) Chloride*** and an excess of copper in pyridine solution at 115 °C. The disadvantage of using copper, pyridine, and a high temperature is overcome by replacing the catalyst by 0.5% $[ClRh(CO_2)_2]_2$ (eq 7).[28]

$$2\ PhHgCl \xrightarrow[4\ LiCl,\ HMPA,\ 24\ h,\ 80\ °C]{0.5\%\ [ClRh(CO_2)_2]_2} PhPh + HgCl_2 + Hg^0 \quad (7)$$

PhHgCl undergoes disproportionation on halogenation[29] (eq 8) and when heated in sulfolane with sulfur gives diphenyl sulfide (eq 9).[30]

$$PhHgCl + Cl_2 \longrightarrow PhCl + HgCl_2 \quad (8)$$

$$2\ PhHgCl \xrightarrow[140\text{-}180\ °C]{S_8} PhSSPh \quad (9)$$

PhHgCl undergoes oxidation to phenol[31] by first treating it with ***Borane-Tetrahydrofuran*** and then oxidizing the resulting phenylborane with alkaline ***Hydrogen Peroxide*** (eq 10). It also undergoes transmetalation with borane halide to give aryl borates (eq 11).[32]

$$\mathrm{PhHgCl} \xrightarrow{\mathrm{BH_3}} \mathrm{PhBH_2} \xrightarrow[\mathrm{NaOH}]{\mathrm{H_2O_2}} \mathrm{PhOH} \qquad (10)$$

$$\mathrm{PhHgCl} + \mathrm{BCl_3} \longrightarrow \mathrm{PhBCl_2} + \mathrm{HgCl_2} \qquad (11)$$

Replacement of Counterion.

The chloro group is replaced easily on treatment with $LiCCl_2CH_3$ in THF or with acidic hydrocarbon under basic conditions (eqs 12-14).[33] Replacement of the chloro group by acetate, nitrate, sulfate or perchlorate may be effected using silver salts[34] or Group 14 metals[35] (e.g. Ge or Sn) (eqs 15 and 16).

$$\mathrm{PhHgCl} + \mathrm{LiCCl_2Me} \xrightarrow[\mathrm{THF}]{-100\ ^\circ\mathrm{C}} \mathrm{PhHgCCl_2Me} \qquad (12)$$

$$\mathrm{PhHgCl} + \mathrm{PhF} \xrightarrow{^-\mathrm{OH}} \mathrm{Ph_2Hg} + \mathrm{HCl} \qquad (13)$$

$$\mathrm{PhHgCl} + \mathrm{CHCl_3} \xrightarrow{t\text{-BuOK}} \mathrm{PhHgCCl_3} + \mathrm{HCl} \qquad (14)$$

$$\mathrm{PhHgCl} + \mathrm{AgOAc} \longrightarrow \mathrm{PhHgOAc} + \mathrm{AgCl} \qquad (15)$$

$$\mathrm{PhHgCl} + \mathrm{Bu_3MSPh} \longrightarrow \mathrm{PhHgSPh} + \mathrm{Bu_3MCl} \qquad (16)$$

$$\mathrm{M = Ge\ or\ Sn}$$

Nucleophilic Phenylation.

PhHgCl couples with allylic halides in the presence of a catalytic amount of $PdCl_2$/***Lithium Chloride*** to give allylbenzene (eq 17). The yields are better when the catalyst used is a mixture of 10-30% ($PdCl_2$/LiCl) and 10-30% ***Copper(II) Chloride*** (yield 31-87%).[3] The reaction proceeds at below rt with the transposition of the double bond of the allylic chloride.

$$\mathrm{PhHgCl} + \mathrm{CH_2{=}CHCHClMe} \xrightarrow[\mathrm{CuCl_2}]{\mathrm{LiCl} + \mathrm{PdCl_2}} \mathrm{PhCH_2CH{=}CHMe} \qquad (17)$$

Alkenes undergo a $PdCl_2$-catalyzed addition-elimination reaction with PhHgCl in a wide variety of polar organic solvents and in the presence of O_2 and H_2O to give vinylic hydrogen-substituted products (eqs 18 and 19).[4,5]

$$\mathrm{PhHgCl} \xrightarrow{\mathrm{PdCl_2}} \mathrm{PhPdCl} \xrightarrow{\mathrm{CH_2{=}CHY}} [\mathrm{PhCH_2CH(PdCl)Y}] \longrightarrow \mathrm{PhCH{=}CHY} + \mathrm{HPdCl} \quad (18)$$

$$\mathrm{HPdCl} \longrightarrow \mathrm{HCl} + \mathrm{Pd^0} \quad (19)$$

The direction of addition of PhPdCl is determined more by steric effects than electronic effects, the PdCl adding to the carbon with least hydrogens.[6,7] HPdCl elimination can occur in more than one direction, leading to mixtures of regioisomers as well as stereoisomers. The reaction can be catalytic in palladium if a reoxidant such as $CuCl_2$ is added. When the catalyst $PdCl_2$ is used along with 2M $CuCl_2$, 2-phenylalkyl chlorides are produced instead.[8] The reaction is valuable for the synthesis of 1-halocarbonyl compounds (eqs 20 and 21).

$$\mathrm{PhHgCl} + \mathrm{CH_2{=}CHR} \xrightarrow{\mathrm{CuCl_2,\ PdCl_2}} \mathrm{PhCH_2CHClR} \quad (20)$$

$$\mathrm{PhHgCl} + \mathrm{CH_2{=}CHCHO} \xrightarrow{\mathrm{CuCl_2,\ PdCl_2}} \mathrm{PhCH_2CHClCHO} \quad (21)$$

The reaction of primary and secondary allylic alcohols takes an entirely different course and produces 3-phenyl aldehydes and ketones, respectively (eq 22).[9] The reaction of enol esters provides 2-phenyl aldehydes and ketones.[36]

$$\mathrm{PhHgCl} + \mathrm{CH_2{=}CHCH_2OH} \xrightarrow[\mathrm{MeCN}]{\mathrm{LiCl,\ PdCl_2}} \mathrm{PhCH_2CH_2CHO} \quad (22)$$

PhHgCl with conjugated dienes in the presence of $LiCl/PdCl_2$ gives a π-allyl palladium compound (**1**)[37] by palladium hydride rearrangement. The π-allyl palladium compound on decomposition with a tertiary or secondary amine gives a phenylated diene or phenylated secondary amine,[38] respectively.

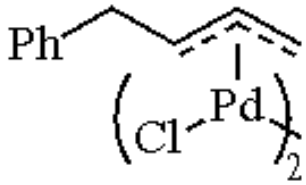

(1)

Direct carbonylation of PhHgCl by CO requires high temperature and pressure.[10-13] $PdCl_2$ promotes carbonylation to give PhCOCl in MeCN (eq 23), esters in alcohol, and anhydride in the presence of PdOAc.

$$\mathrm{PhHgCl} + \mathrm{CO} \xrightarrow[\mathrm{MeCN}]{\mathrm{PdCl_2}} \mathrm{PhCOCl} \qquad (23)$$

PhHgCl reacts with CO under pressure (50 psi) in the presence of $PdCl_2$ to give Ph_2CO.[39] Rhodium(I) and rhodium(III) complexes give better yields at atmospheric pressure. Reaction with ***Tetracarbonylnickel***[40] gives considerably higher yields of Ph_2CO.

PhHgCl undergoes acylation to give the corresponding ketones (eq 24).[41] Ketenes also react with PhHgCl to give ketones (eq 25).[42,43]

$$\mathrm{PhHgCl} + \mathrm{ClCOR} \longrightarrow \mathrm{PhCOR} + \mathrm{HgCl_2} \qquad (24)$$

$$\mathrm{PhHgCl} + \mathrm{CH_2{=}C{=}O} \longrightarrow \mathrm{CH_2{=}C(Ph)OHgCl} \xrightarrow{\mathrm{H^+}} \mathrm{MeCOPh} \qquad (25)$$

PhHgCl forms weak complexes with bidentate ligands. The latter undergo complete or partial disproportionation in boiling benzene solution (eq 26).[44,45]

$$\mathrm{PhHgCl} + 2\,\mathrm{L} \longrightarrow \mathrm{PhHgClL_2} \xrightarrow[\Delta]{\mathrm{C_6H_6}} \mathrm{Ph_2HgL} + \mathrm{LHgCl_2} \qquad (26)$$

$$\mathrm{PhHgClL_2} \longrightarrow \mathrm{PhHgCl} + \mathrm{L_2}$$

L_2 = phen, bipy

Related Reagents.

Phenylthallium Bis(trifluoroacetate).

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4-Phenyloxazole[1,2]

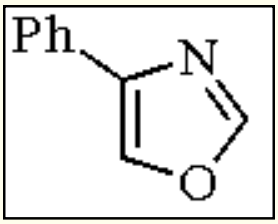

[20662-89-9] · C_9H_7NO · 4-Phenyloxazole · (MW 145.17)

(Diels-Alder reaction with alkynes leads to 3,4-disubstituted furans[3] and with alkenes leads to 2-phenylpyridines;[4] the *N*-methylide derivative leads to 3-pyrrole esters[5])

Physical Data: mp 6 °C; bp 220-222 °C, 60-61 °C/0.1 mmHg; λ_{max} 243 nm (ε 17 420).[6]

Preparative Methods: two different approaches have been described (eqs 1 and 2).[7,8] Four detailed experimentals have been published for the phenacyl bromide route, including a multikilo preparation.[7c]

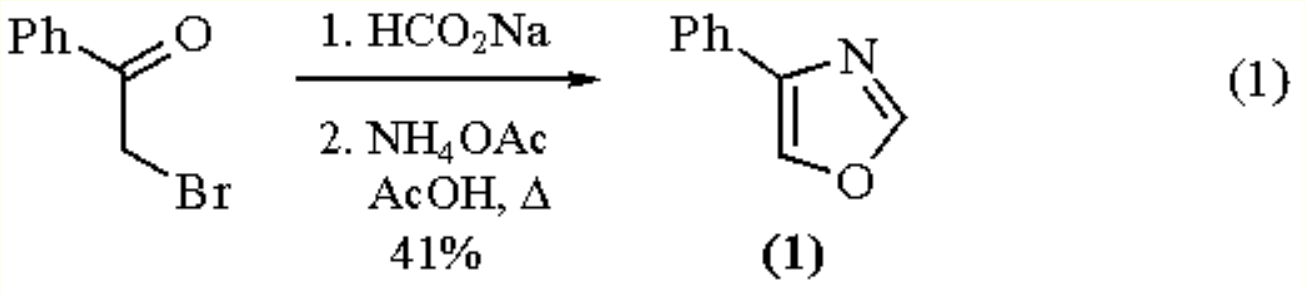

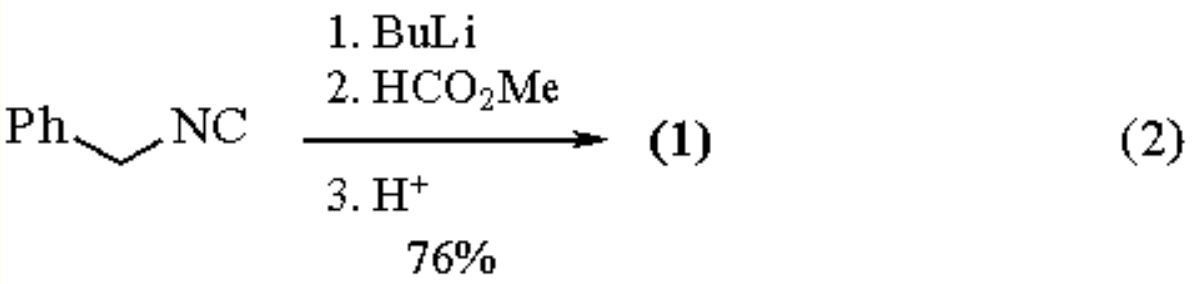

General Discussion.

4-Phenyloxazole (**1**) undergoes Diels-Alder reactions with activated[3a,b] and unactivated[3c-e] alkynes. The

cycloadduct (eq 3) is unstable to the reaction temperatures and undergoes a retro-Diels-Alder reaction with expulsion of benzonitrile, forming a 3-mono- or 3,4-disubstituted furan in good to excellent yield (eqs 4 and 5).

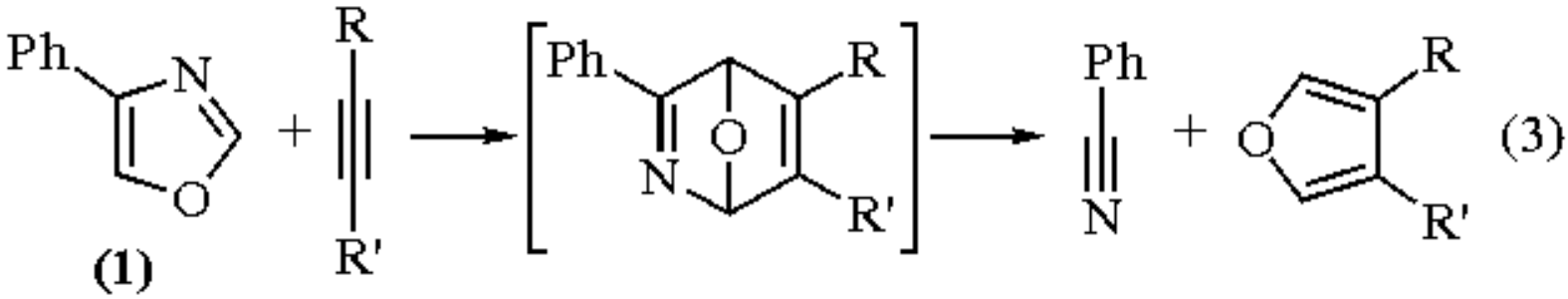

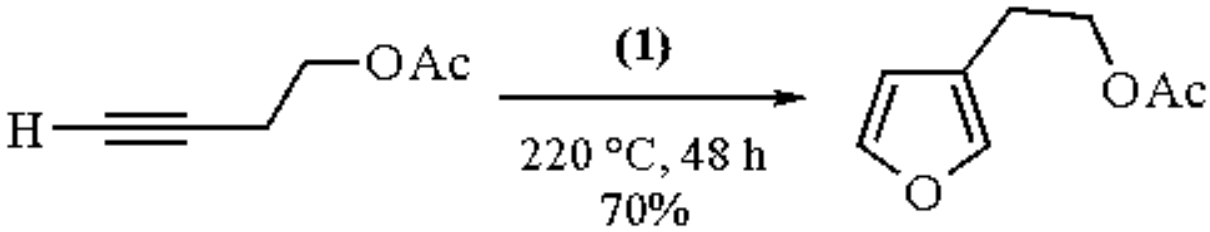

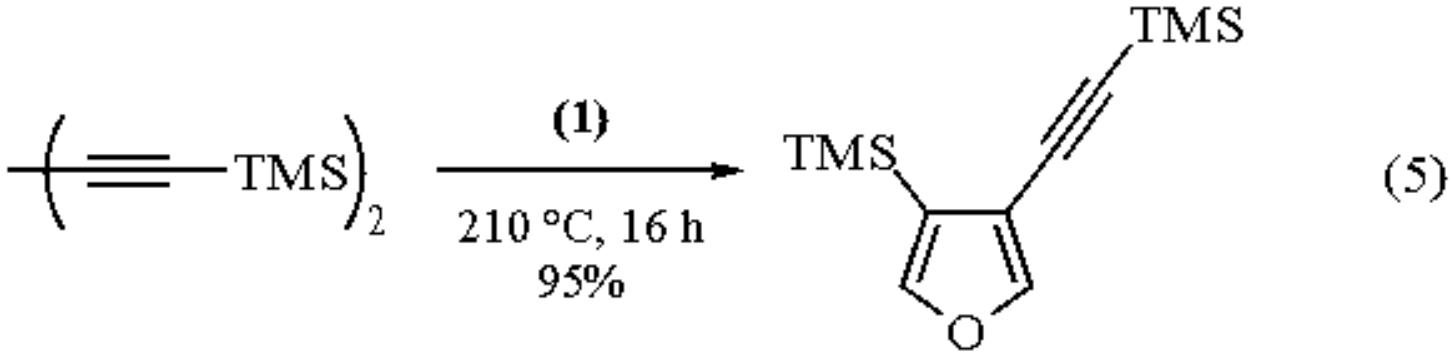

Alkenes also undergo a Diels-Alder reaction with (**1**), and with reactive dienophiles the initial adduct (e.g. (**2**), largely *endo*) can be isolated (eq 6).[4] Adduct (**2**) dehydrates with traces of acid to yield pyridines (eq 7).

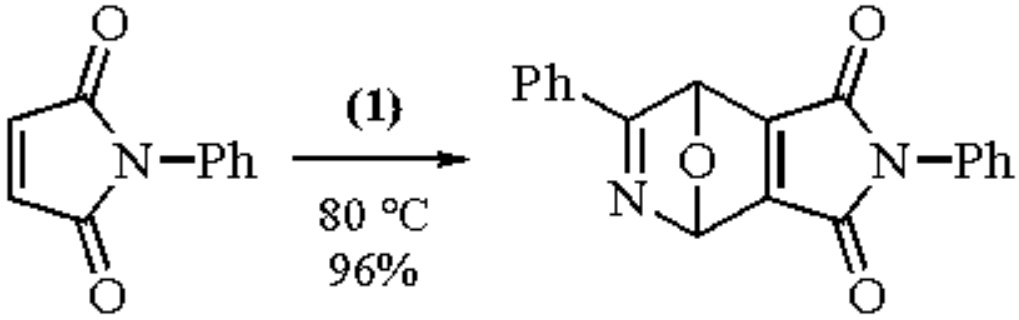

(**2**)

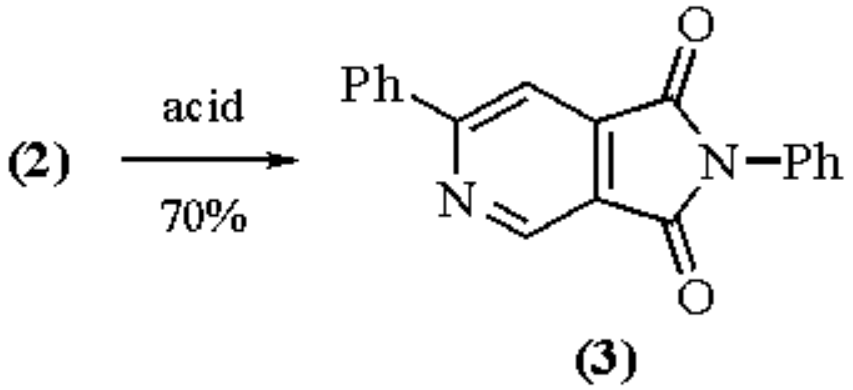

(7)

Trimethylsilylmethyl Trifluoromethanesulfonate readily *N*-alkylates (**1**) (eq 8) and the resulting salt, on treatment with fluoride, generates ylide (**4**). When (**4**) is generated in the presence of an alkynic ester, an unstable cycloadduct is formed that fragments to give pyrroles such as (**5**) (eq 9).[5]

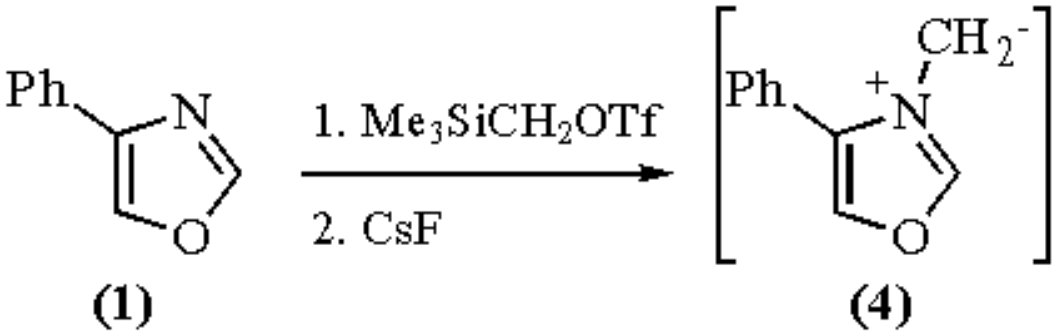

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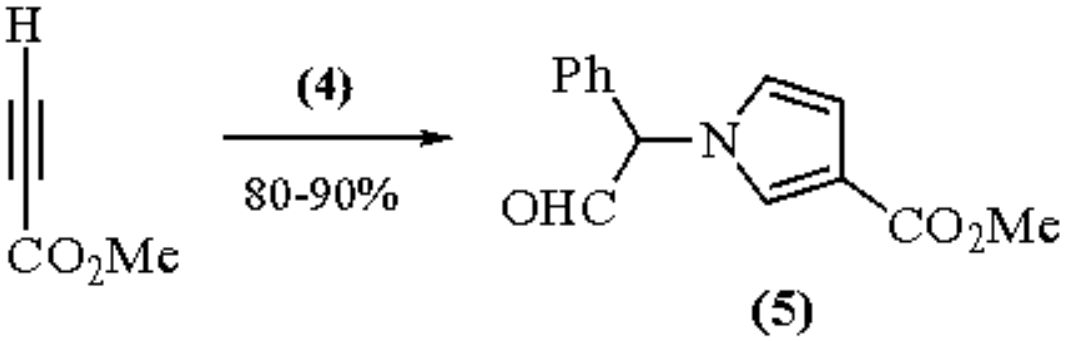

(9)

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Phenylpalladium Acetate[1]

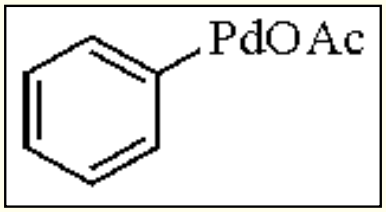

[35742-60-0] · $C_8H_8O_2Pd$ · Phenylpalladium Acetate · (MW 228.58)

(used for the phenylation of alkenes)

Solubility: sol acetonitrile, methanol, acetic acid, THF, benzene, chloroform, monoglyme, and diglyme.

Preparative Methods: (1) from PhN(NO)COMe (1 mmol) and ***Bis(dibenzylideneacetone)palladium(0)*** (0.2 mmol) in acetonitrile at 40 °C for 2 h;[2] (2) from $SbPh_3$ or ***Triphenylphosphine*** (0.5 mmol) and ***Palladium(II) Acetate*** (0.5 mmol) under the same conditions;[2] (3) from PhHg(OAc) (10 mmol) and $Pd(OAc)_2$ (10 mmol) in 1:1 acetone-water (200 mL) at 30 °C for 2 h.[3]

Handling, Storage, and Precautions: very reactive and unstable, and is therefore formed in situ. Decomposition gives palladium metal which should be retained for recycling.

Phenylation of Alkenes.

The reagent is used for the stereospecific phenylation of alkenes. Only the *trans* product is formed. In contrast to traditional methods, the solvent exhibits only a small terminal vs. internal directing effect. The tendency of electron-withdrawing groups on the double bond to favor terminal substitution is reduced. In reaction with methylstyrene, PhPdCl and PhPdBr give some hydroxyphenylated products, whereas PhPd(OAc) gives only phenylated products.[3] The stereo- and regiochemistry have also been studied with propene and other alkenes.[4]

Recently, the reaction of alkenylsilanes has been studied (eqs 1 and 2).[2] The reaction was stereospecific with inversion of the relative disposition of alkene substituents. In contrast, $[PhPd]BF_4$ gave nonspecific aryldesilylation products.

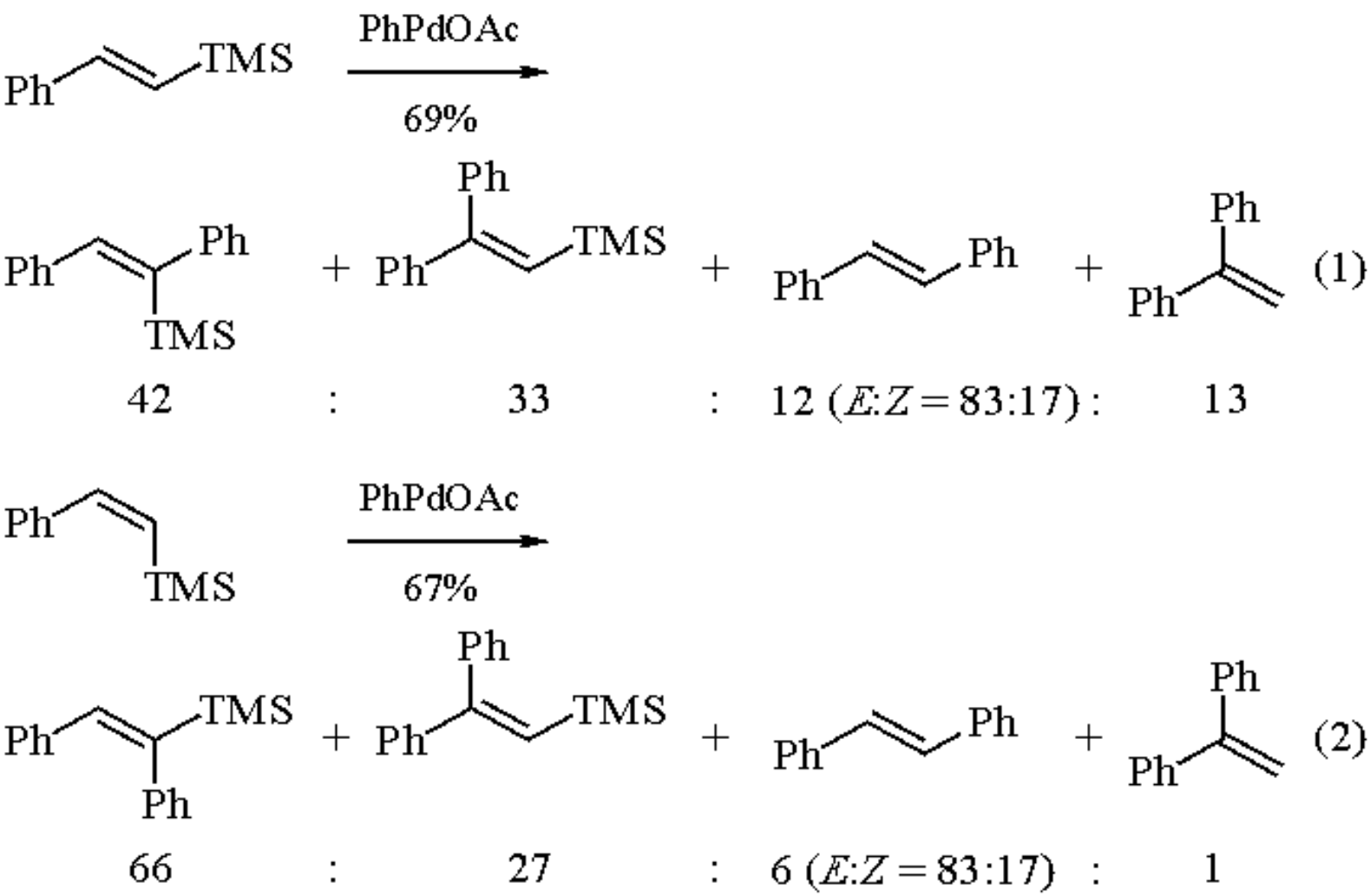

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Phenyl *N*-Phenylphosphoramidochloridate

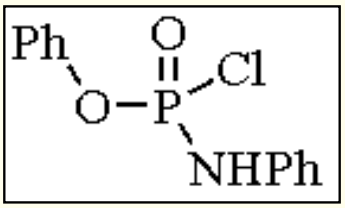

[51766-21-3] · $C_{12}H_{11}ClNO_2P$ · Phenyl *N*-Phenylphosphoramidochloridate · (MW 267.66)

(phosphorylating agent in oligonucleotide synthesis via the phosphotriester approach; for the conversion of acids to their symmetrical anhydrides and for the coupling of acids and amines to give amides; two important derivatives are also considered)

Physical Data: mp 132-134 °C.

Solubility: sol org solvents, e.g. acetone, dichloromethane.

Form Supplied in: white solid; widely available commercially.

Analysis of Reagent Purity: FT-IR;[22] R_f (pure) = 0.63 (chloroform-acetone (5:1) on silica). *Drying:* is moisture sensitive; dry in vacuo (<=10^{-2} mmHg) over P_2O_5 at rt.

Preparative Methods: obtainable from phenyl phosphorodichloridate (**2**) and aniline (eq 1).[1]

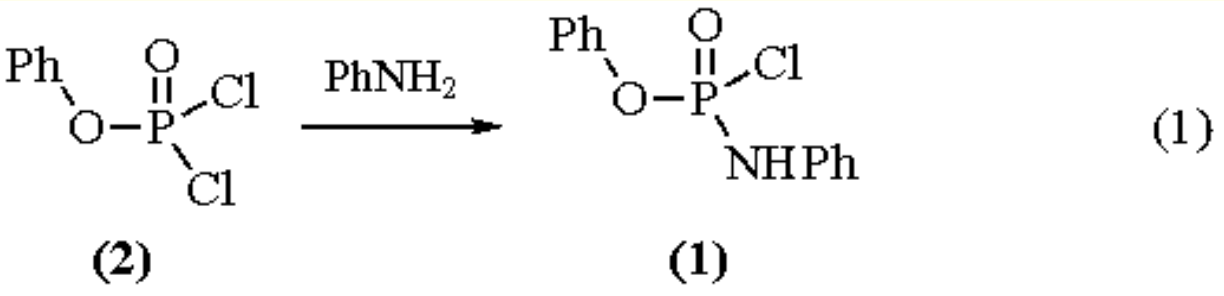

Handling, Storage, and Precautions: irritant and moisture sensitive. May be harmful by inhalation (irritating to mucous membranes and upper respiratory tract), ingestion, or skin absorption. Incompatible with strong oxidizing agents and strong bases.

Phosphorylating Agent.

Phenyl *N*-phenylphosphoramidochloridate (**1**) reacts readily at 0 °C in dry pyridine with equimolar amounts of a

corresponding alcohol or phenol to give the *O*-alkyl-*O*-phenyl-*N*-phenylphosphoramides (eq 2).[2]

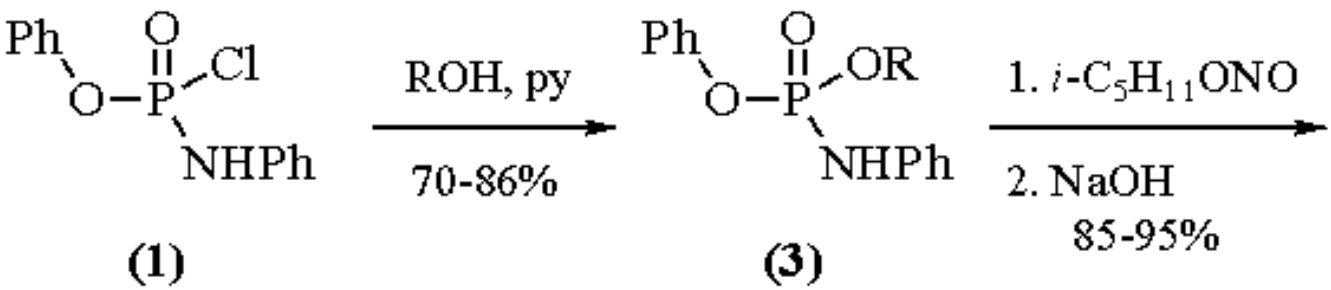

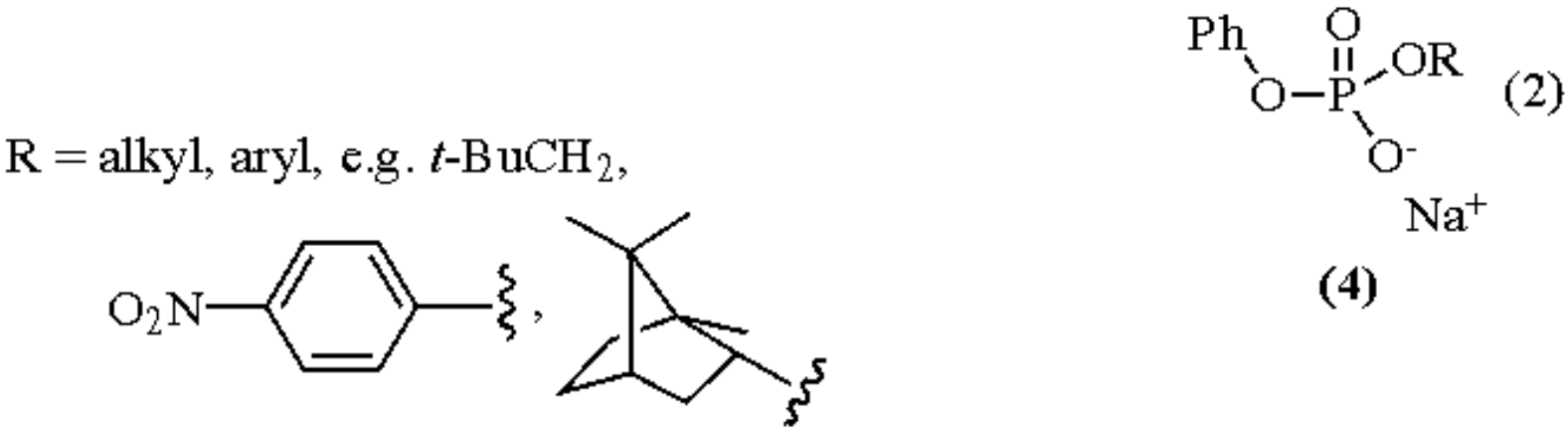

The compound (**3**) is a useful intermediate for the synthesis of mixed diesters of phosphoric acid (**4**). There are several methods of cleaving the N-P bond, of which the method of Ikehara is the most convenient.[3] Reaction of (**3**) with a 40 molar excess of 3-methylbutyl nitrite in acetic acid-pyridine (1:1 v/v) is successful in removing the aniline protecting group from the phosphoryl moiety in almost quantitative yields, giving the *O*-alkyl/aryl-*O*-phenyl hydrogen phosphate.

Given the good yields and simplicity of the process, this procedure has been used to prepare intermediates for oligonucleotide synthesis, e.g. in the synthesis of 5´-*O*-monomethoxytritylthymidine 3´-phenylphosphate (**7**) (eq 3). Phosphorylation of 5´-*O*-monomethoxytritylthymidine (**5**) gave the protected nucleoside phosphate (**6**) in 98% yield which, after removal of the aniline protecting group and workup, gave the pyridinium salt in 85% yield.

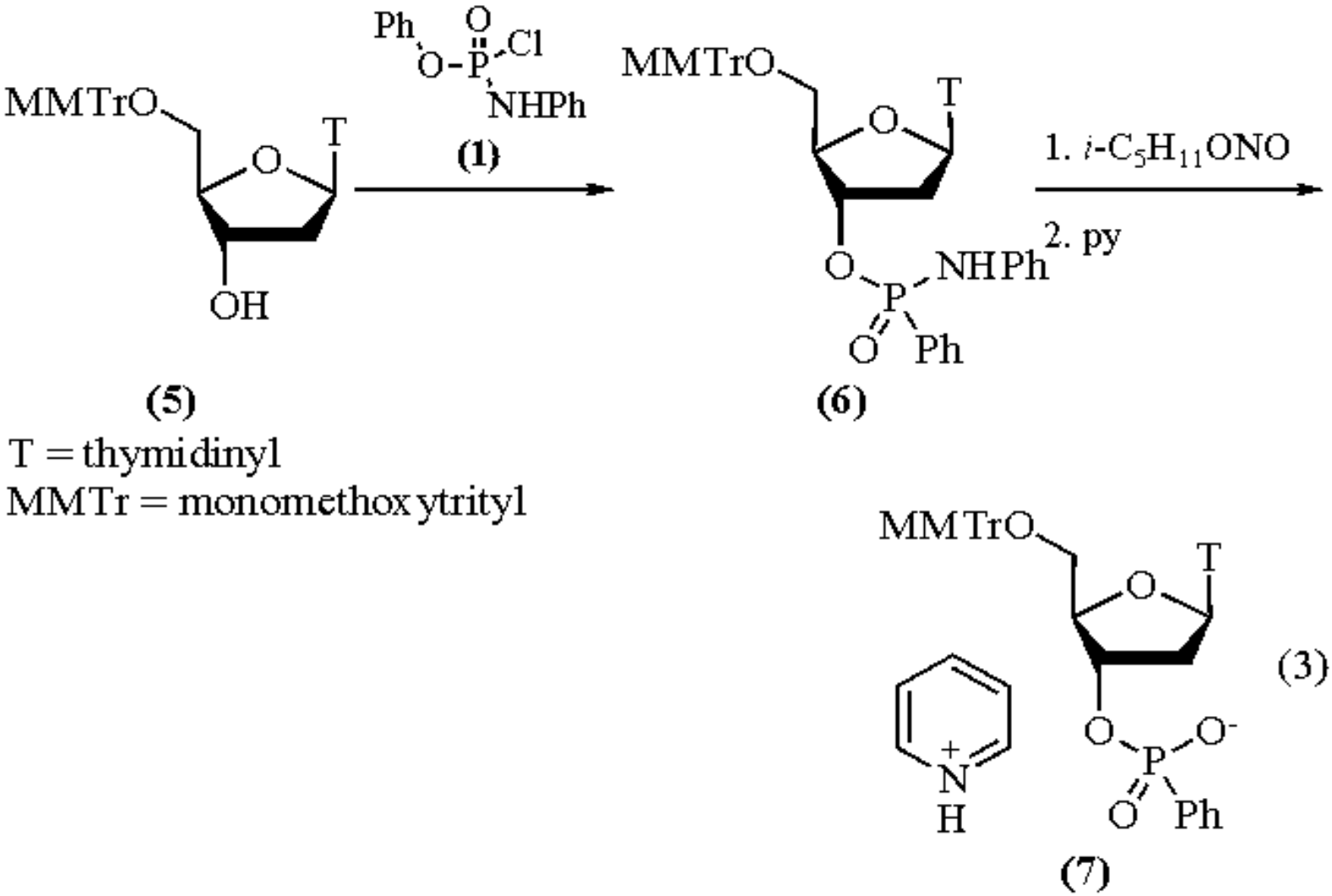

This chemistry has additionally been utilized in the preparation of nucleoside phosphorothioates.[4] Reaction of (**6**) with NaH to remove the *P*-anilido group followed by CS_2 gave the corresponding 5´-monomethoxytritylthymidine 3´-*O*-phenylphosphorothioate (as a mixture of diastereomers, **8**) which was converted to the *S*-methyl ester (**9**) (eq 4). Owing to the chiral nature of pentavalent phosphorus, the compound (**9**) could exist as a mixture of diastereomers; however, the above reaction was the first example of an asymmetric synthesis of a phosphorothioate. There are now more examples of stereospecific synthesis of nucleoside derivatives utilizing this type of chemistry.[5]

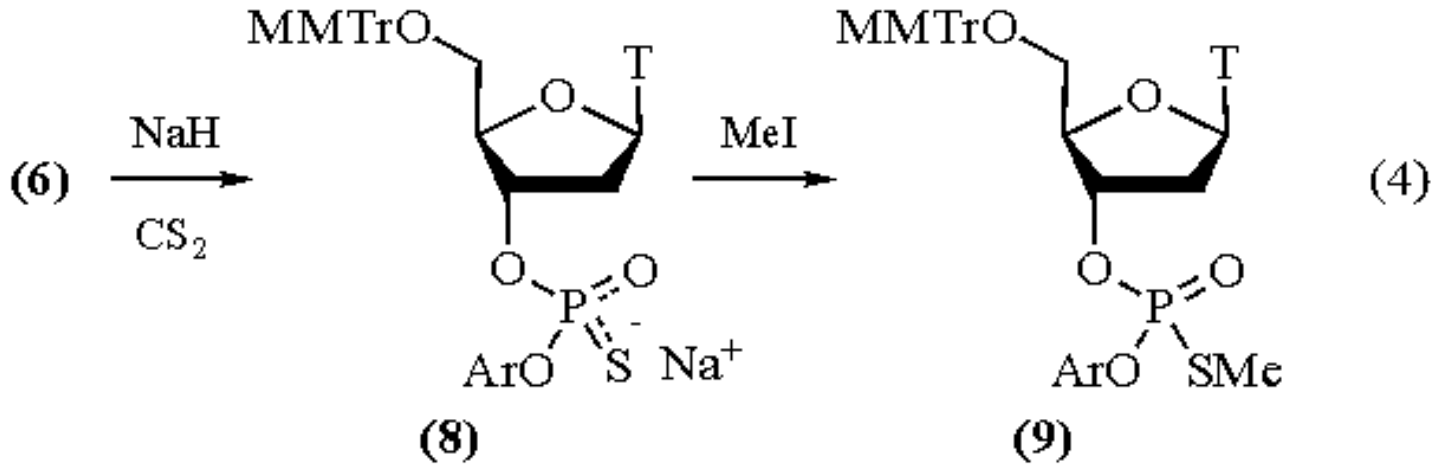

There are numerous reviews on phosphorylation methods in biological molecules, some of which include aryl phosphoramidochloridates.[6]

Activation of Carboxylic Acids.

Formation of Symmetrical Anhydrides.

Symmetrical carboxylic anhydrides are useful reagents for peptide or amide synthesis.[7,8] Unfortunately, most methods require transformation of the acid first into the acid chloride or the use of condensation agents, e.g. ***1,3-Dicyclohexylcarbodiimide*** (DCC), which can lead to separation problems of the product anhydride from the hydrated derivatives of the condensation reagents. The use of ***Thionyl Chloride***/***Pyridine*** to form the acid chloride is often complicated by racemization with amino acid derivatives.

However, carboxylic acids are converted almost quantitatively to their corresponding symmetrical anhydride by treatment with 1 equiv of ***Triethylamine*** or ***1-Ethylpiperidine*** and 0.5 equiv of phenyl *N*-phenylphosphoramidochloridate (or ***Diphenyl Phosphorochloridate***) in acetone or dichloromethane, with the product anhydride (**10**) being obtained by filtration or from evaporation of the solvent after washing with water.[9] The resulting crude products are very nearly pure and the phenyl *N*-phenylphosphoramidochloridate can be regenerated as the aqueous solutions yield the phosphoramidic acid on acidification, which can be converted to (**1**) by reaction with ***Phosphorus(V) Chloride***. The proposed pathway for this is through the mixed anhydride (**11**), which then reacts with a second molecule of acid. The only limitation of this method is the reaction of some of the anhydrides with water, e.g. as observed with trichloroacetic acid.

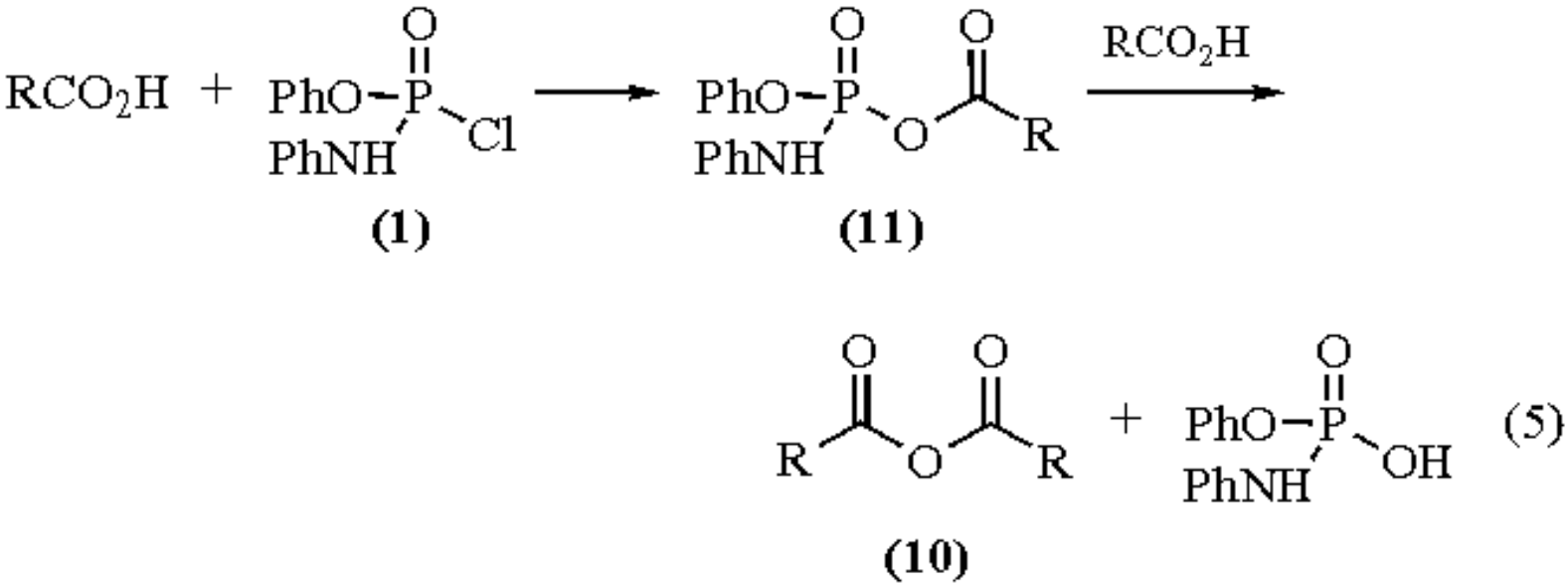

The Synthesis of Polyanhydrides by Dehydrative Coupling.

The synthesis of polyanhydrides was first reported in 1909[10] and led on to a series of aliphatic polyanhydrides being prepared in the 1930s, as potential materials for the textile industry. One method for the formation of such polyanhydrides, particularly where sensitive monomers are involved, is to find suitably powerful dehydrating agents that function in mild reaction conditions. Organophosphorus compounds appear to be one such group of compounds. Phenyl *N*-phenylphosphoramidochloridate was found to be one of the most successful dehydrating agents.[11] The

proposed mechanism of polyanhydride formation is shown in eq 6.

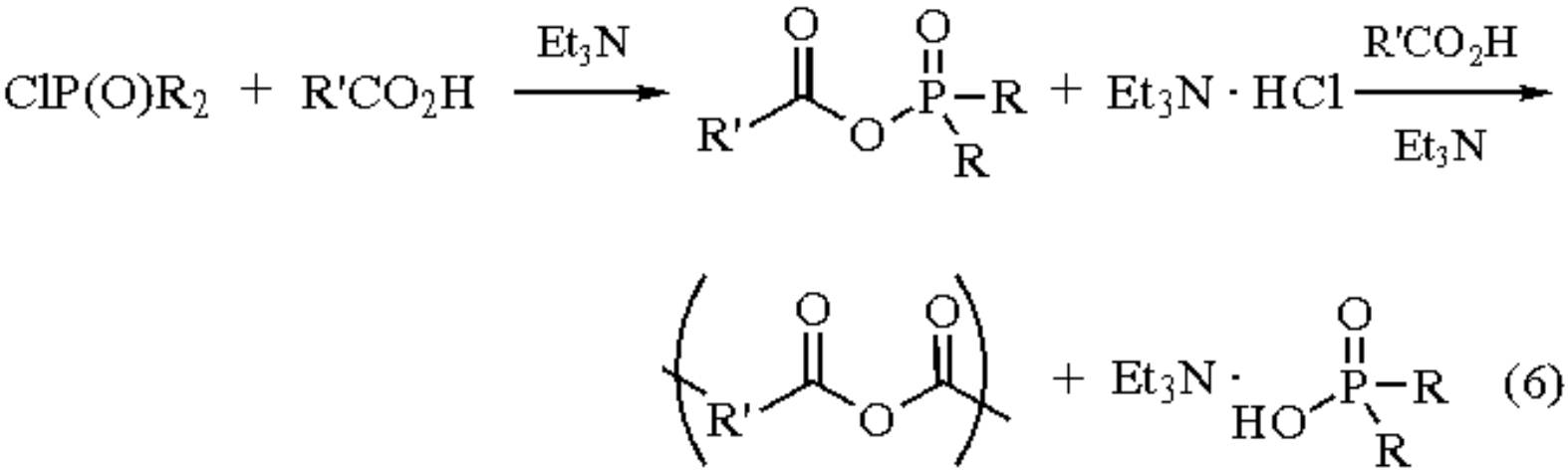

Formation of Carboxamides.

There are many reagents for the conversion of carboxylic acids to carboxamides.[8,12-14] Activating agents such as DCC[15] can lead to purification problems, whilst involvement of the acid chloride can lead to racemization; there are also examples using phosphorus containing reagents, e.g. ***Diethyl Phosphorocyanidate***,[13,16] but again these reagents only react well in certain systems. Other methods involve long reaction times, high temperatures, or low yields.

However, the use of phenyl *N*-phenylphosphoramidochloridate as a condensing agent for carboxylic acids and amines yields carboxamides in a one-step method (eq 7).[17] The amide (**12**) is prepared from the carboxylic acid, 2 equiv of triethylamine, 1 equiv of amine, and 1 equiv of reagent (**1**) and isolated by filtration or evaporation of solvent and washing with water. Once again, a mixed anhydride intermediate (**13**) is presumed, which results from nucleophilic attack by the carboxylate anion on the phosphorus atom with elimination of a chloride ion; a further nucleophilic attack by the amine on the carbonyl group of (**13**) and breakdown of the complex yields the amide (**12**) and phenyl *N*-phenylphosphoramidate (**14**) which can be recycled to (**1**) by reaction with phosphorus pentachloride.

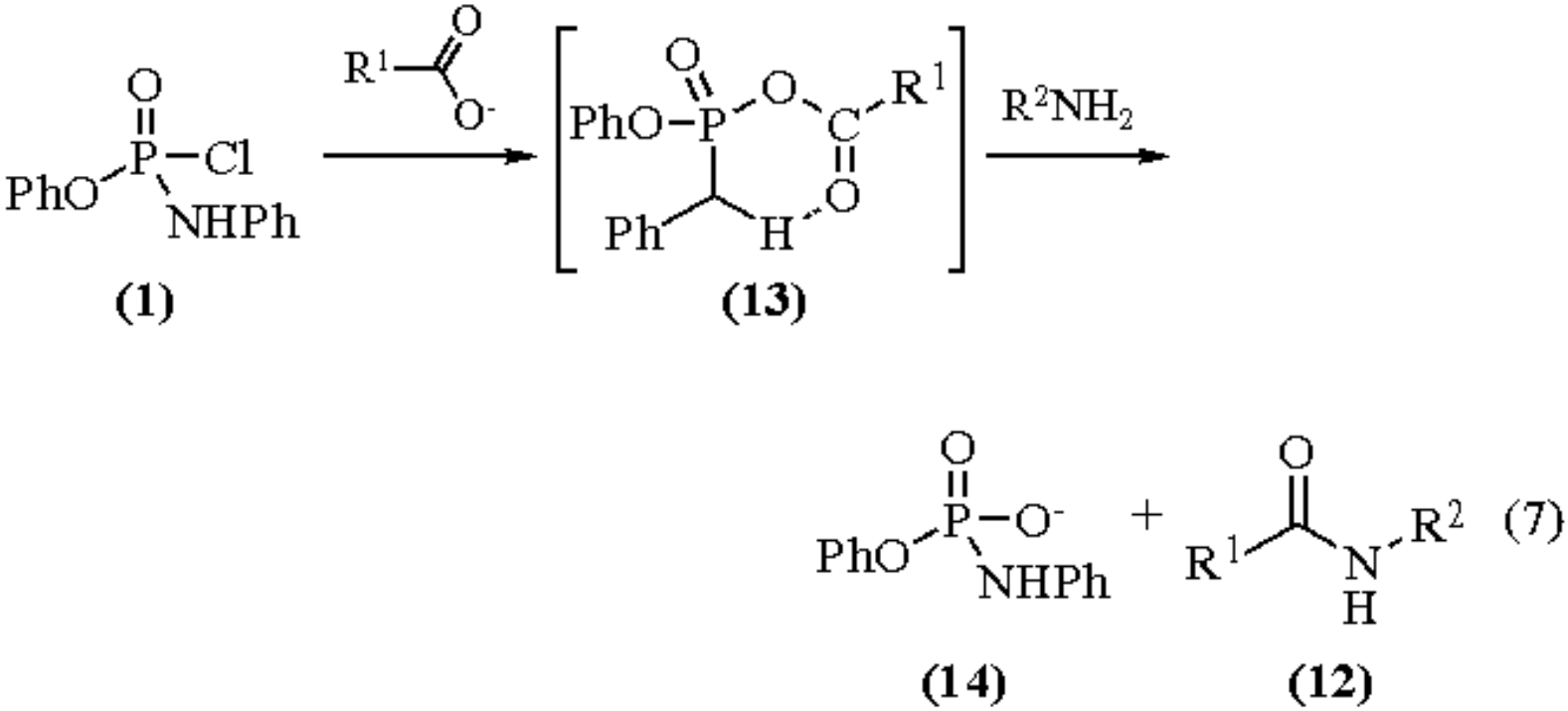

A distinct order of reactivity is observed in these reactions with (**1**): carboxylate anion &egt; aliphatic amines >> aromatic amines. This has led to slight variations in the practical procedures for preparing the amides but these are well documented in the literature.[17] The first route involves a one-step procedure; the second involves reaction of (**1**) with the carboxylate anion and subsequent treatment with the amine and is the preferred method for converting alkanamines to the amides since the first one-step method produces large amounts of phenyl phosphorodiamidates as well as the amide, by nucleophilic attack of (**1**) by the amine. The final method prevents the formation of phenyl phosphorodiamidates as the carboxylic acid first reacts with 0.5 equiv of (**1**) to form its anhydride, which is then converted to the amide in almost quantitative yield (this is largely utilizing the anhydride-formation chemistry described above) (eq 8).

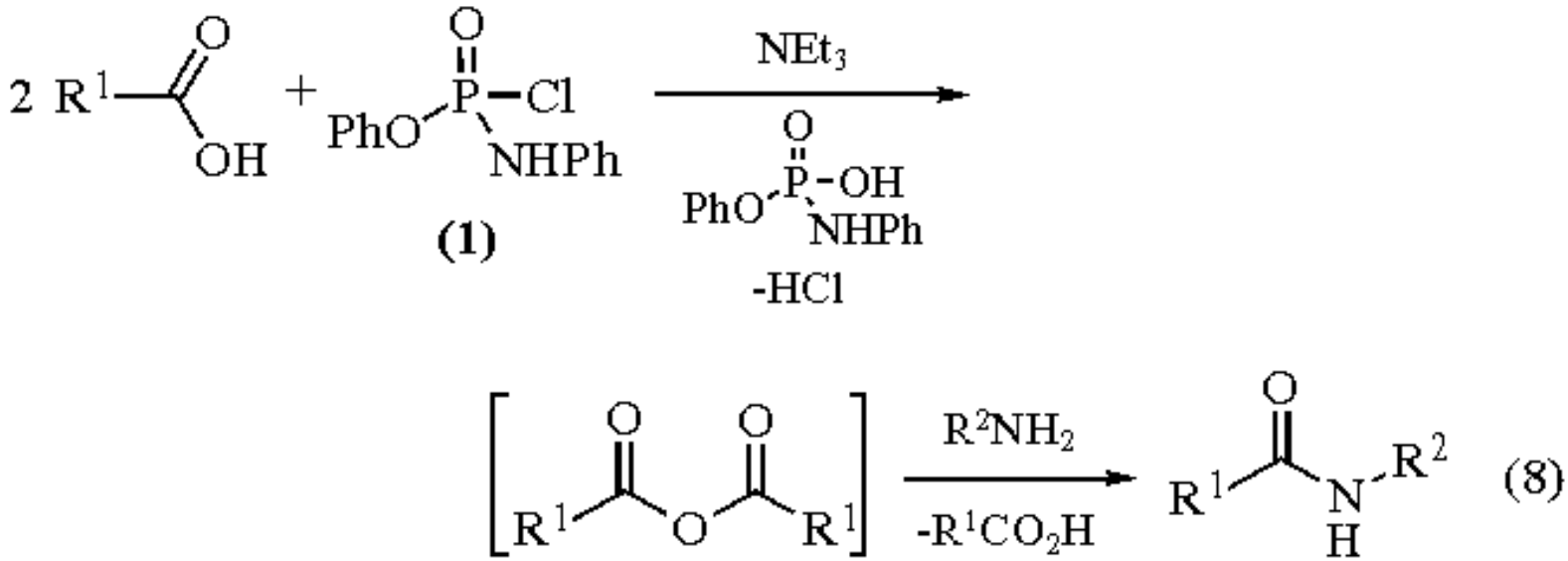

Generally, phenyl *N*-phenylphosphoramidochloridate and other very similar related organophosphorus reagents e.g. phosphorus oxychloride, phenyl dichlorophosphate, diphenylchlorophosphate and *N,N´*-bis(2-oxo-3-oxazolinyl)phosphorodiamidic chloride have been utilised in recent years not only to form symmetrical carboxylic acid

anhydrides but also in esterification and thiol esterification reactions; although phenyl *N*-phenylphosphoramidochloridate is not so efficient for the latter two reactions compared to its analogs but is probably the best choice for forming the anhydride.[18]

Two Important Derivatives of Phenyl *N*-Phenylphosphoramidochloridate.

Phenyl *N*-Phenylphosphoramidoazidate.

This compound (**15**) is a white solid, which is easily prepared from (**1**) (eq 9).[19] It is obtained in excellent yields and is unusual for an organophosphorus compound in that it shows little sensitivity to moisture at room temperature for several months.

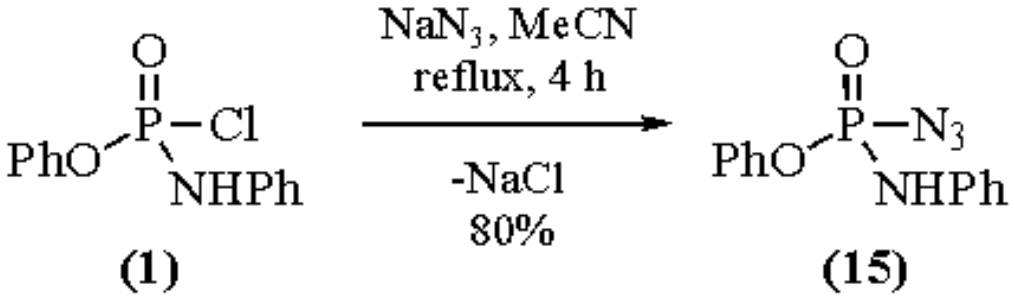

(9)

It is an excellent reagent for the preparation of *N*,*N*′-diarylureas. Reaction of a carboxylic acid, primary amine, and (**15**) in acetonitrile leads to the disubstituted urea (**16**) (eq 10). There is an additional competing reaction to the formation of the diarylurea: formation of phenyl *N*-phenylphosphorodiamidates, involving nucleophilic attack of the carboxylate ion and the alkylamine on the phosphorus atom of phenyl *N*-phenylphosphoramidoazidate. This work has been fully reviewed.[20]

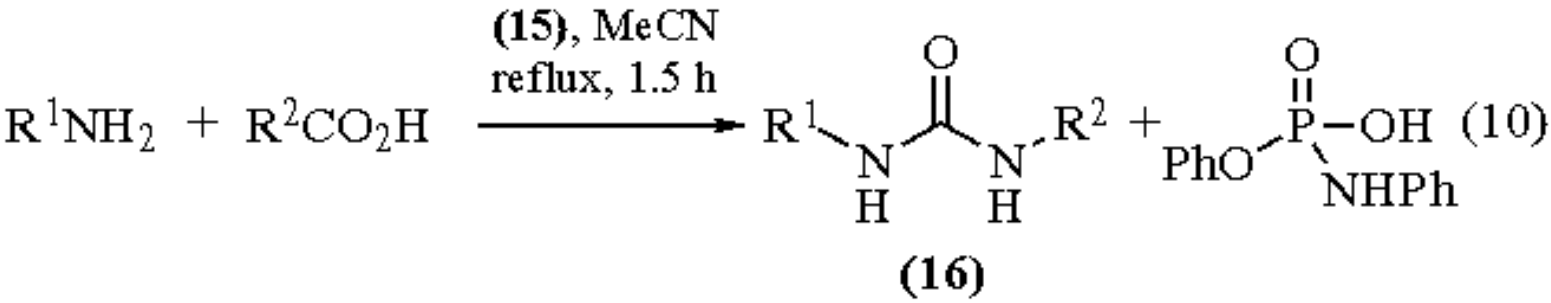

(10)

Phenyl *N*-Methyl-*N*-phenylphosphoramidochloridate.

Like (**1**), phenyl *N*-methyl-*N*-phenylphosphoramidochloridate (**17**) reacts under analogous conditions to give anhydrides and carboxamides (see above). However, phenyl *N*-methyl-*N*-phenylphosphoramidochloridate undergoes one additional reaction which is not observed to any significant degree in (**1**). It is used for the conversion of imines to α-substituted β-lactams (eq 11).[21] The reaction is believed not to work for (**1**) as it requires an excess of triethylamine in the presence of a less nucleophilic imine, which is unfavorable to a mixed anhydride intermediate. The proposed pathway for this reaction is shown in eq 11, and has been performed on a wide variety of imines, proceeding in good

yields (44-78%).

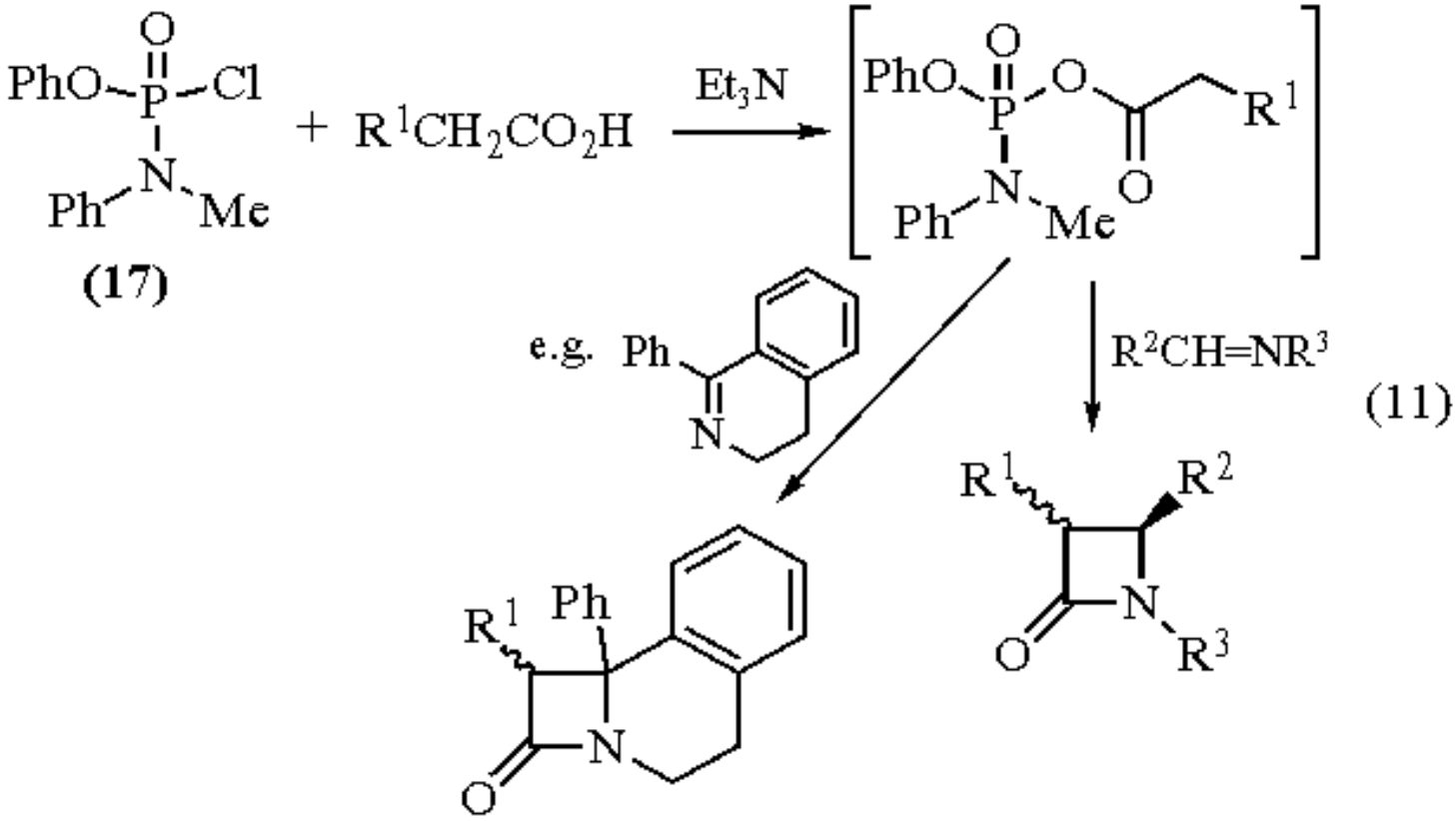

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Phenyl Phosphorodi(1-imidazolate)

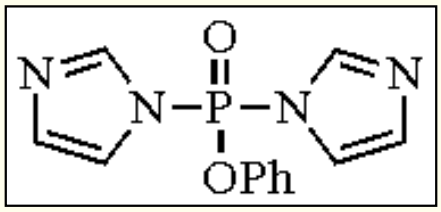

[15706-68-0] · $C_{12}H_{11}N_4O_2P$ · Phenyl Phosphorodi(1-imidazolate) · (MW 274.24)

(used in phosphorylation,[1] as a peptide coupling reagent,[1] and in the dehydration of aldoximes to nitriles[2])

Alternate Name: phenyl diimidazol-1-ylphosphinate.

Physical Data: an exceedingly hygroscopic white solid, mp 96-97 °C[2] (mp 90-92 °C also reported[1]).

Solubility: sol acetonitrile, dioxane, THF; relatively insol benzene, ether.

Form Supplied in: not commercially available.

Preparative Methods: this reagent was first prepared in 81% yield by reaction of 4 equiv of imidazole with 1 equiv of phenyl phosphorodichloridate in benzene at 60 °C.[4] The use of 2 equiv of imidazole and 2 equiv of triethylamine as base has been reported to give a yield of 98% of (**1**) (eq 1).[2]

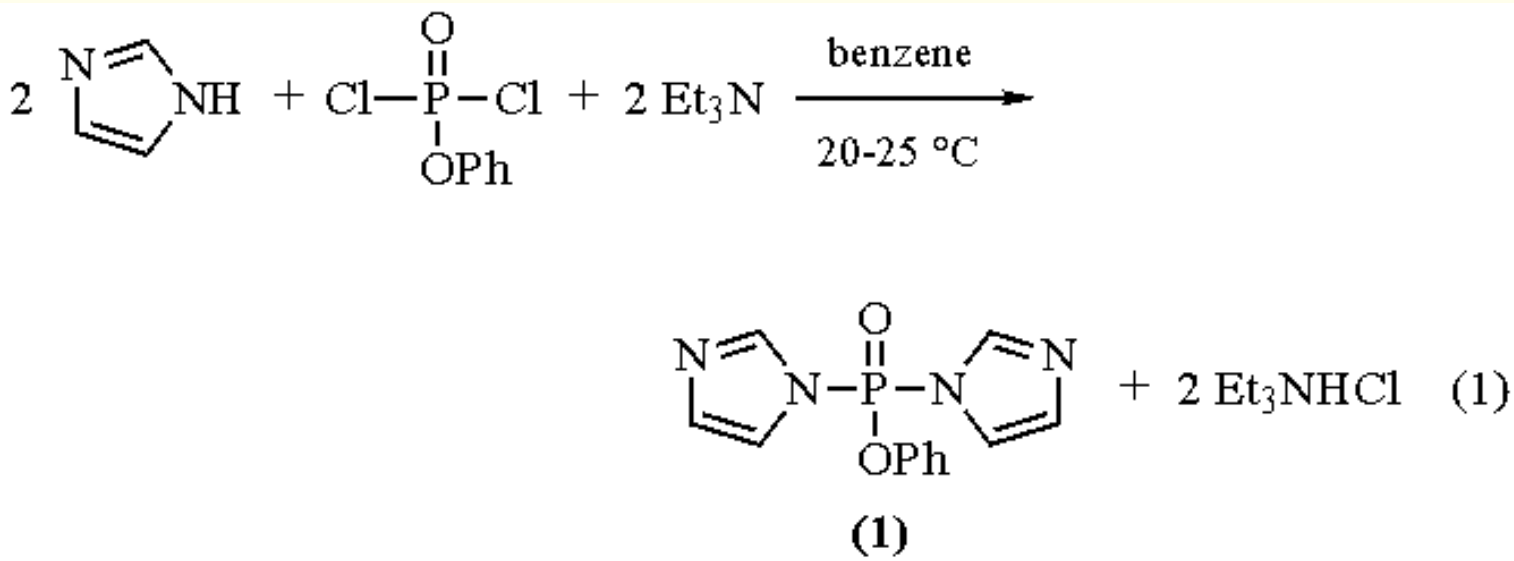

Purification: recrystallization from benzene, filtration under a water-free atmosphere, and drying under vacuum.

Handling, Storage, and Precautions: owing to its hygroscopic nature, exclusion of moisture in handling and use is essential; should be stored in a sealed tube at -20 °C.[3]

Phosphorylation.

The title reagent (**1**) reacts with amines, alcohols, and water to give amides and esters of phenyl phosphate (eqs 2-4).[1] The monoimidazole derivatives are formed rapidly with a much slower reaction to give the disubstitution products.[1]

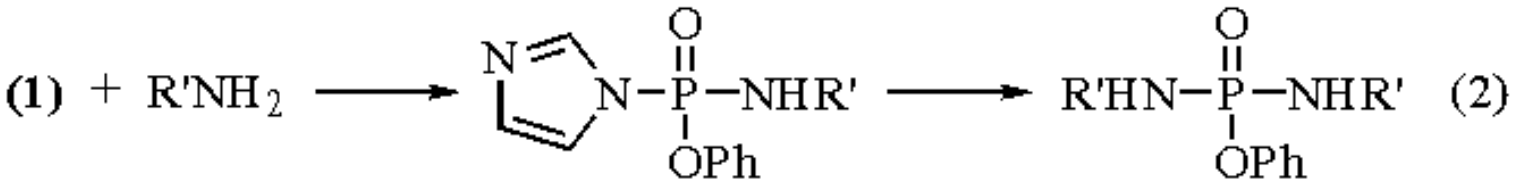

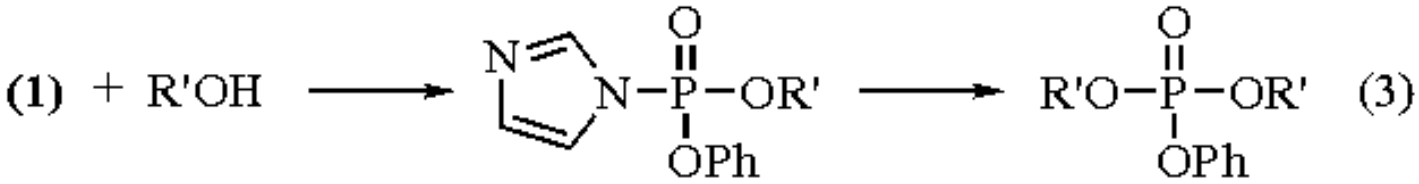

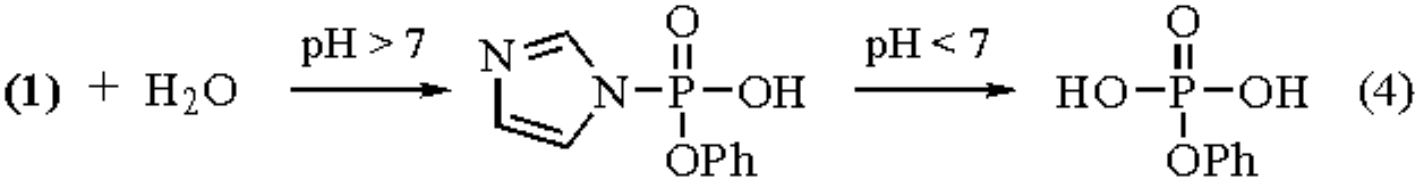

This behavior can be used to synthesize mixed diphosphates by treatment with a small excess of alcohol followed by hydrolysis of the monoimidazole derivative. In this manner the monophenyl ester of 2´,3´-isopropylideneadenosine 5´-phosphate (**2**) has been synthesized in 53.5% yield (eq 5).[1]

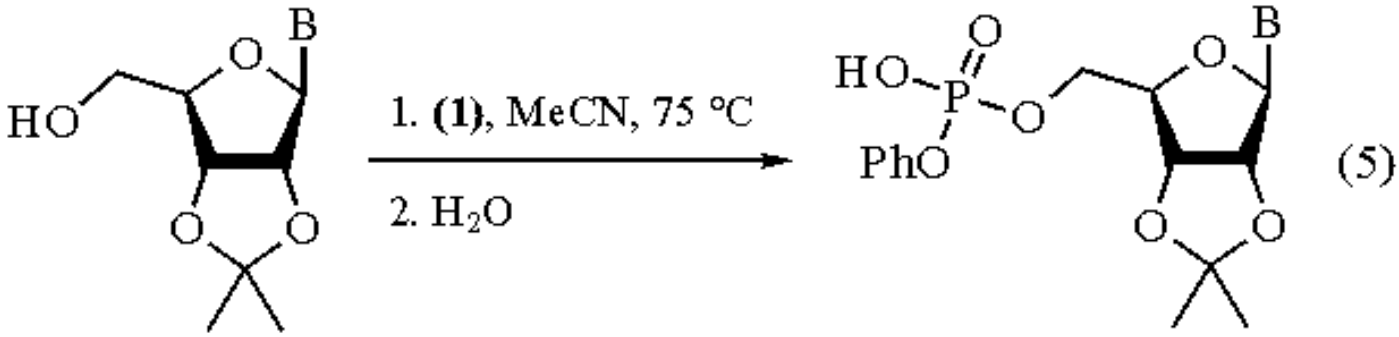

B = adenine

(**2**)

Peptide Synthesis.

Reagent (**1**) has been used as a coupling reagent in the synthesis of benzyloxycarbonylalanylalanine (**3**).[1] Initial treatment of benzyloxycarbonylalanine with (**1**) in acetonitrile at 45 °C for 12 h followed by reaction with an excess of an aqueous solution (pH 8-9) of alanine gave the protected dipeptide in 85% yield (eq 6). No reference to the stereochemistry of the starting materials or product was made.

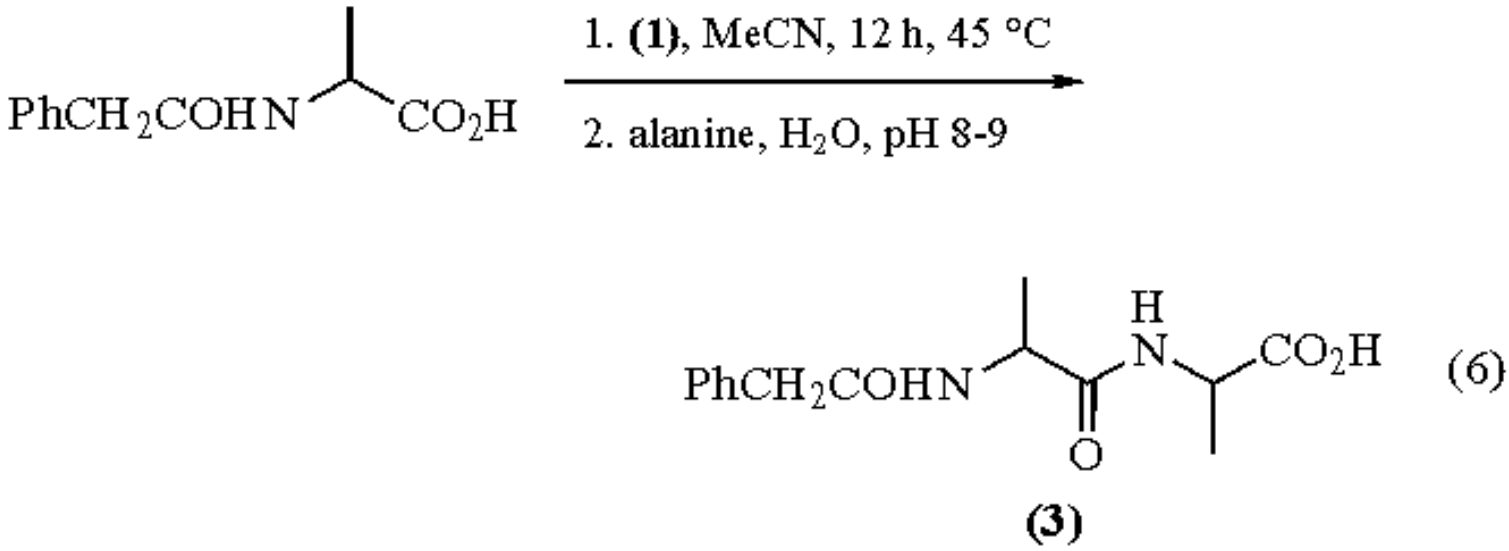

Acylimidazolides have been isolated from the reaction of (**1**) with carboxylic acids[1] and may be involved in the above reaction.

Dehydration of Aldoximes to Nitriles.

Reagent (**1**) has been shown to be excellent for the dehydration of aldoximes of both aromatic and aliphatic aldehydes.[2] This is accomplished by reacting the aldoxime with (**1**) in dioxane at 20 °C for 20 h (eq 7).[2]

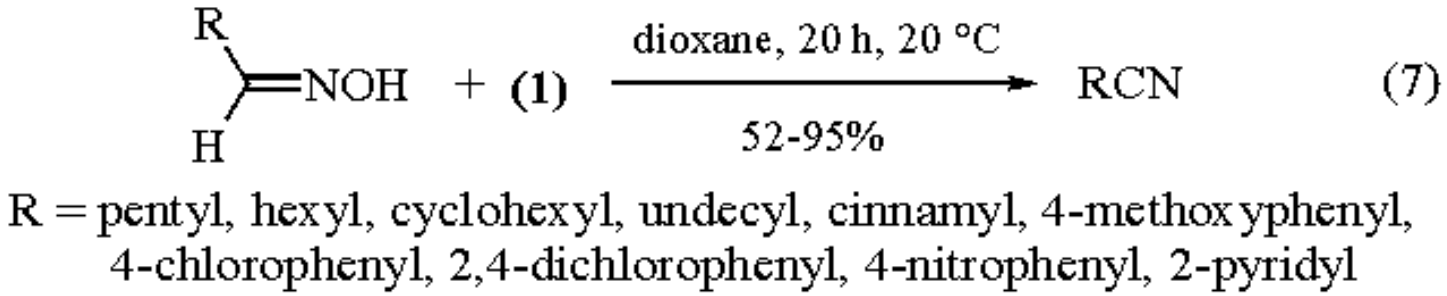

Reagent (**1**) is superior in terms of yield to a variety of phosphorochloridates, including ***Phosphorus Oxychloride***. For example, in the case of 2-pyridyl aldoxime, with (**1**) a yield of 52% was obtained, whereas with phosphorus oxychloride the yield was 33% and with phenyl phosphorodichloridate the yield was 47%.[2] The reaction is thought to proceed via an intermediate formed by *O*-phosphorylation of the aldoxime.[2] The use of spin-labeled versions of (**1**) has been explored, in which the phenyl is replaced with the 2,2,6,6-tetramethylpiperidyl *N*-oxide group.[3,5]

---

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Keith Jones

(*S*)-(+)-1-Phenyl-2-propylamine[1,2]

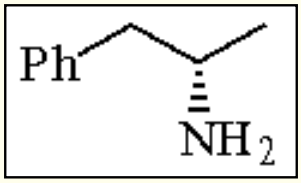

[51-64-9] · $C_9H_{13}N$ · (*S*)-(+)-1-Phenyl-2-propylamine · (MW 135.23)

(chiral reagent for the resolution of racemic acids and aldehydes; chiral directing group for the enantioselective conjugate addition of ketones)

Alternate Names: (+)-amphetamine; *d*-amphetamine; dexamphetamine; dextroamphetamine.

Physical Data: bp 200-203 °C; *d* 0.913 g cm^{-3}; [α]19D +38° (benzene); mp (HCl salt) 154-155 °C.[3]

Solubility: readily sol all common organic solvents and acids; slightly sol water.

Form Supplied in: the free base (**1**) is a colorless liquid. A number of salts of (**1**) and its enantiomer (including the hydrochloride and sulfate) are commercially available.

Preparative Methods: enantiomerically pure (**1**) can be obtained by resolution of racemic (**1**) with (+)-tartaric acid.[4] Several highly stereospecific syntheses have been described.[5]

Analysis of Reagent Purity: enantiomeric and chemical purity of the reagent can be assayed by GC or HPLC analysis of its ***(S)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid*** amide.[3,6]

Handling, Storage, and Precautions: the reagent is a central stimulant and should be handled with gloves in a well-ventilated hood. Both the free base and its salts are stable at room temperature for extended periods of time.

Reagent for the Resolution of Carboxylic Acids.

Reagent (**1**) and its enantiomer have been used, although not as extensively as the more common ***(S)-α-Methylbenzylamine***, as resolving agents for carboxylic acids via fractional crystallization of the corresponding diastereomeric salts.[7] Examples of acids resolved this way include (**2**)-(**6**).[8-10] Additional examples, such as mandelic, hydratopic, and α-aryloxypropionic acids, can be found in the literature.[11,12]

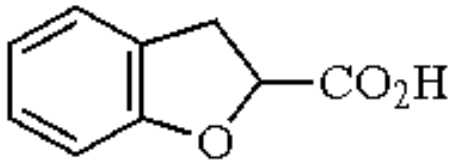

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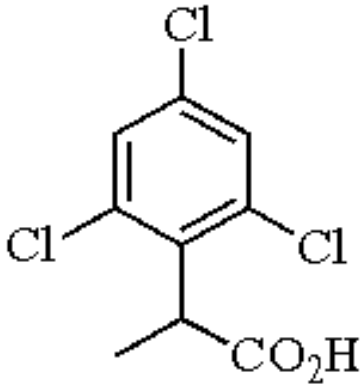

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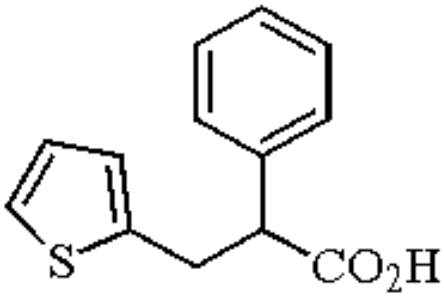

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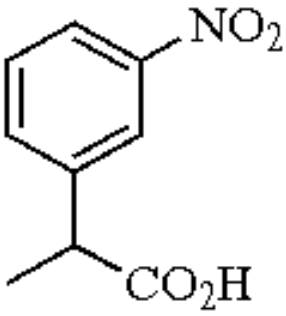

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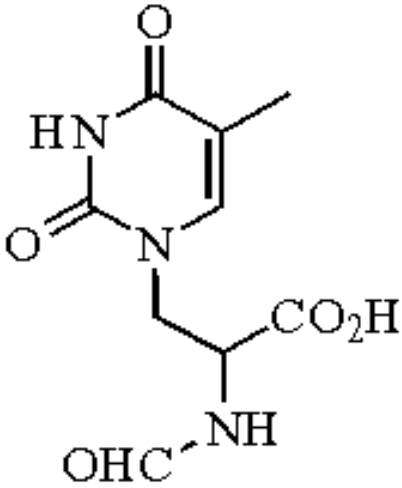

(6)

Resolution of Asymmetric Aldehydes.

The resolution of the aldehyde-containing natural product (±)-gossypol has been accomplished by chromatographic separation of (**7**), the diastereomeric condensation product between (**1**) and gossypol hexaacetate.[13] Other chiral primary amines commonly used for the resolution of aldehydes and ketones by physical separation of diastereomeric imines include 2-amino-1-butanol, α-methylbenzylamine, and Betti's base (**8**).[14,15]

(S)-(+)-1-Phenyl-2-propylamine

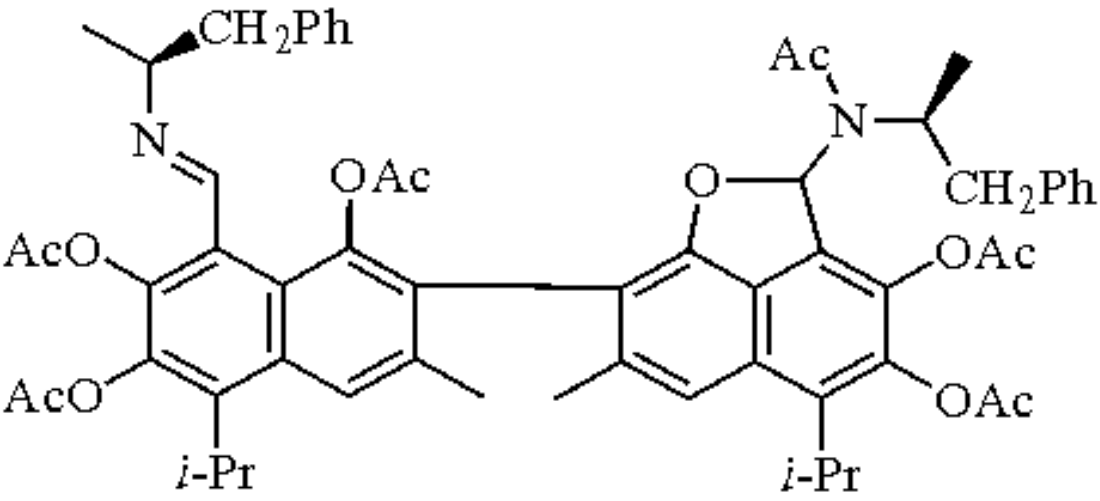

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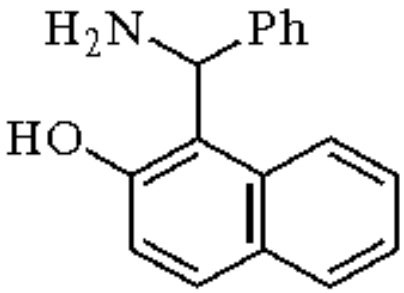

(8)

Stereoselective Synthesis of Biaryl Compounds.

The best known application of (**1**) to the asymmetric oxidative coupling of phenolic compounds is the copper(II)-catalyzed synthesis of 1,1´-binaphthyl-2,2´-diol in greater than 95% ee (eq 1).[16,17]

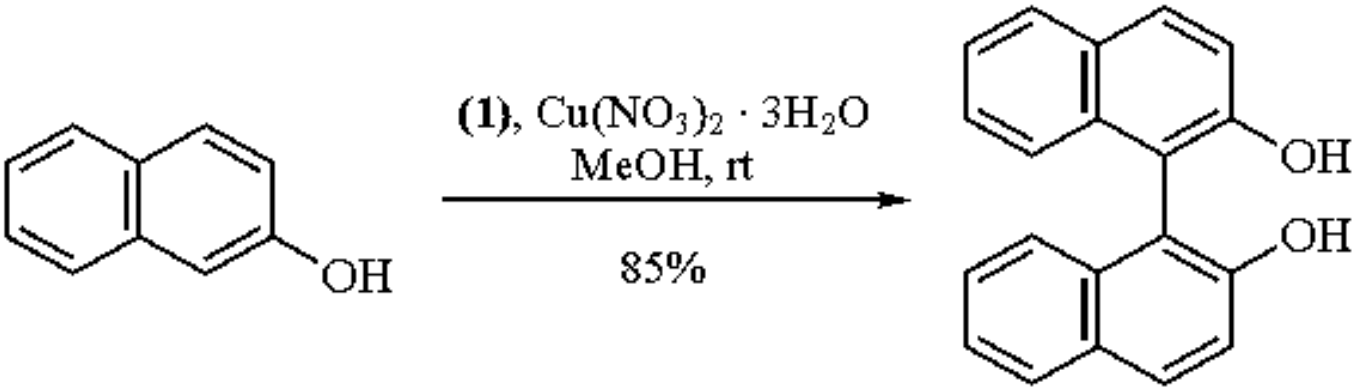

(1)

>95% ee

Enantioselective Conjugate Additions.

The use of chiral imines for the enantioselective conjugate addition of carbonyl compounds to α,β-unsaturated systems is well established, mostly with imines derived from α-methylbenzylamine.[18-20] Recently, (**1**) has been used to effect the Michael addition of a 4-piperidone to acrylonitrile and methyl acrylate (eq 2).[21]

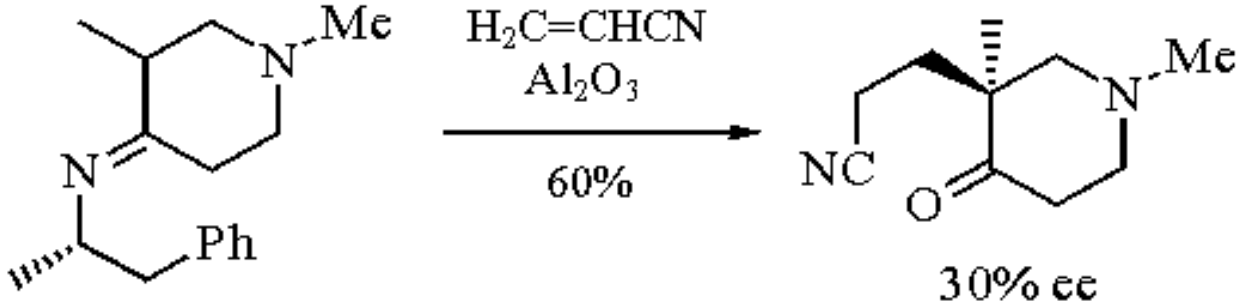

(2)

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Juan C. Jaen

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Phenylselenium Trichloride

$PhSeCl_3$

[42572-42-9] · $C_6H_5Cl_3Se$ · Phenylselenium Trichloride · (MW 261.43)

(for introduction of unsaturation into organic molecules by hydrolytic selenoxide elimination; chlorinating agent)

Alternate Name: benzeneselenenyl trichloride.

Physical Data: mp 133-134 °C (dec).

Solubility: insol ether, hexanes, carbon disulfide; sol DMSO, acetonitrile; slightly sol chloroform, methylene chloride.

Form Supplied in: pale yellow solid; not widely available.

Preparative Methods: conveniently prepared on a large scale by chlorination of ***Diphenyl Diselenide*** with ***Sulfuryl Chloride*** (eq 1).[1]

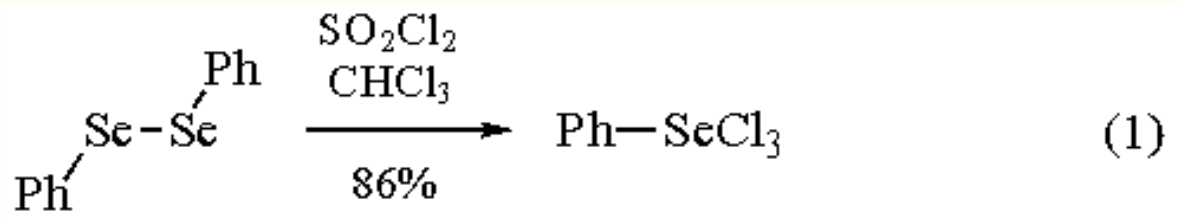

Handling, Storage, and Precautions: unstable under normal laboratory conditions. However, if the freshly prepared material is rapidly dried and kept in a freezer (-20 °C), it can be stored and used for several months without any visible decomposition. Organoselenium compounds are reputed to be toxic. Use in a fume hood.

Hydrolytic Selenoxide Elimination.

Phenylselenium trichloride readily introduces a $PhSeCl_2$ group into the α-position of ketonic substrates with loss of HCl (eq 2).[1,2] The resulting selenium(IV) dichlorides are crystalline and easy to purify. Upon mild hydrolysis (aq $NaHCO_3$), the $SeCl_2$ group is hydrolyzed to the corresponding selenoxide, which undergoes the usual thermal elimination reaction to give an enone (eq 2). Thus, phenylselenium trichloride is complementary to ***Benzeneseleninic Acid*** and ***Benzeneseleninyl Chloride*** for the introduction of unsaturation into organic molecules via direct selenation

with selenium(IV) compounds.

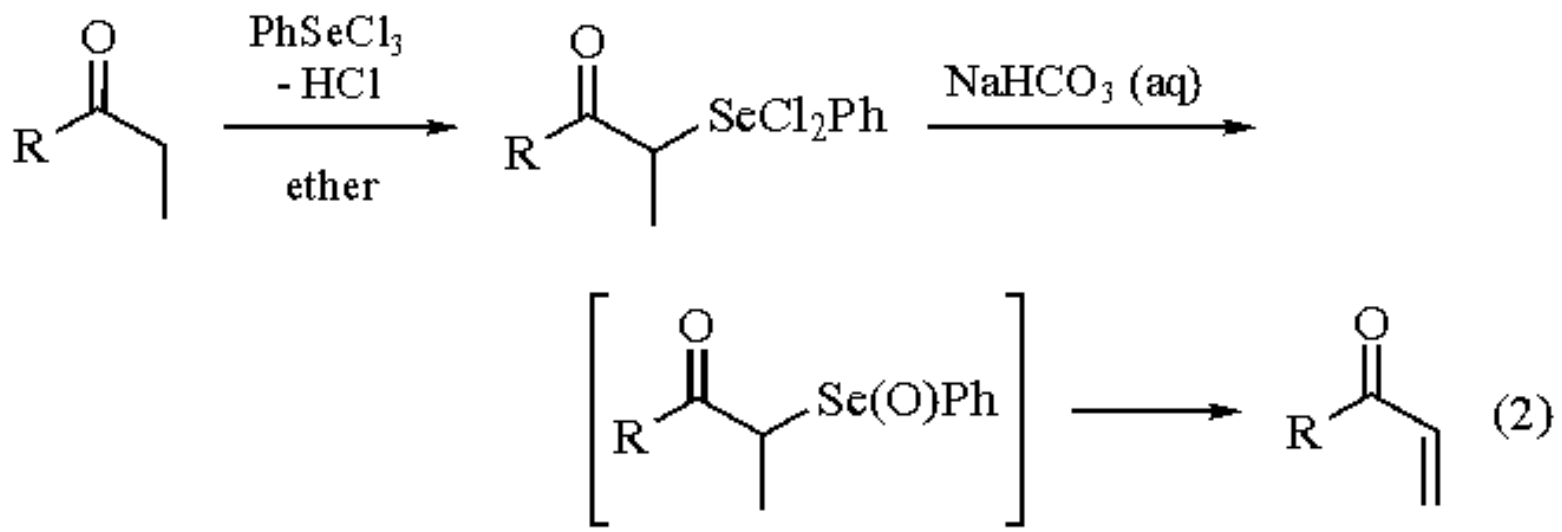

For the preparation of certain enones, the hydrolytic selenoxide elimination reaction has definite advantages (easier operation and purification, higher overall yields) compared to methodology relying on introduction of divalent selenium[3] (see ***Benzeneselenenyl Bromide***, ***Benzeneselenenyl Chloride***, and ***2-Pyridineselenenyl Bromide***) followed by oxidation-elimination. To some extent, depending on the substrate, phenylselenium trichloride acts as a chlorinating agent towards ketones.[1] The benzeneselenenyl chloride formed in this process reacts readily with ketones to give an α-phenylselenenyl ketone (eq 3). For efficient utilization of the selenium reagent it is therefore desirable to use an excess (50-100%) of the ketone and to treat the reaction mixture with sulfuryl chloride to convert the α-phenylselenenyl ketone formed to the desired selenium(IV) dichloride (eq 3).

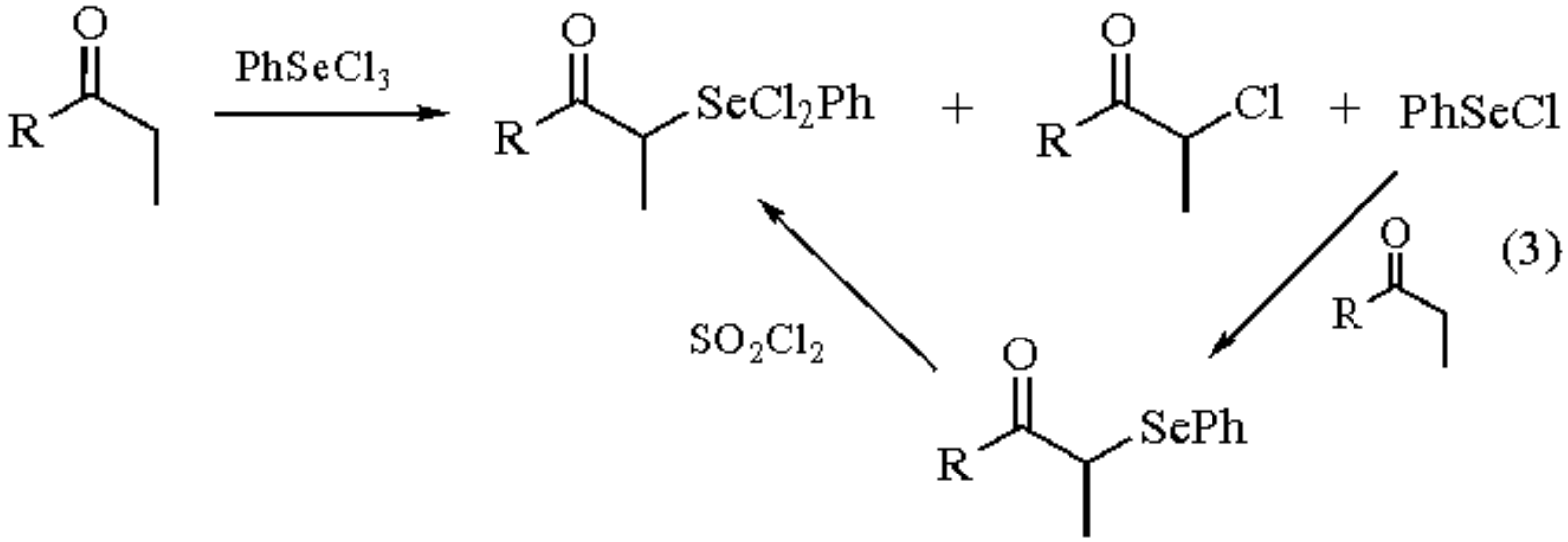

Unfortunately, the reaction of phenylselenium trichloride with unsymmetrical ketones usually shows a poor regioselectivity.[1] Thus ethyl methyl ketone afforded a 57:43 mixture of methyl- and methylene-substituted products (**1**) and (**2**). For this reason, the hydrolytic variation of the selenoxide elimination reaction is best suited for the conversion of symmetrical ketones or aryl alkyl ketones to their corresponding enones (eq 4).

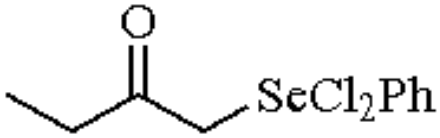

(1)

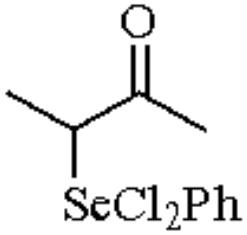

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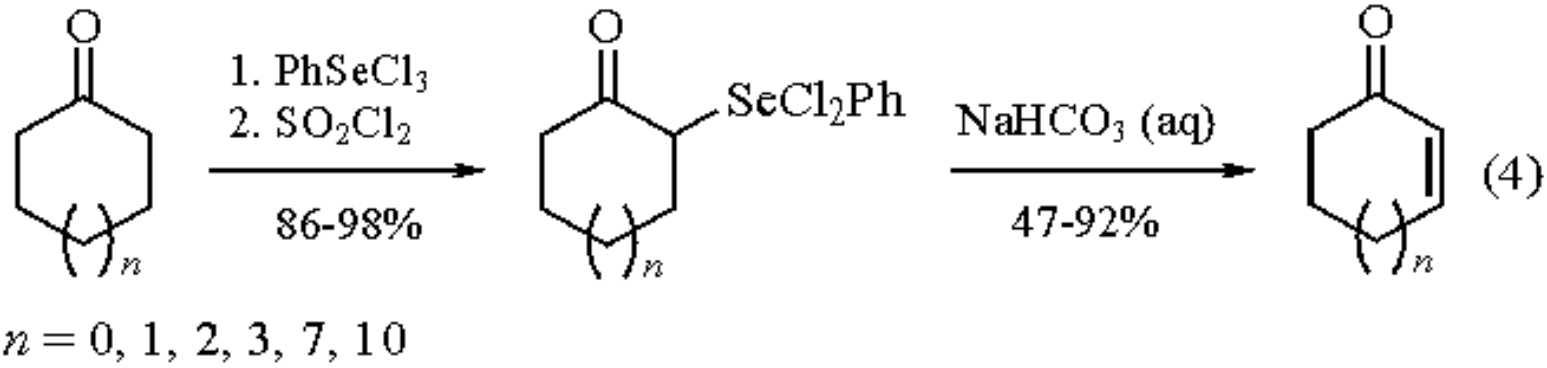

(4)

The chlorination of divalent organoselenium compounds, followed by hydrolysis to effect selenoxide elimination, has been used as an alternative to other methods of oxidation-elimination. In this way, 2-chloro-1-alkenes[4] and allylic and vinylic acetates[5] were successfully prepared.

Phenylselenium trichloride undergoes a stereospecific *anti* addition to alkenic compounds to give (β-chloroalkyl)phenylselenium dichlorides.[6] The regiochemistry of addition is highly substrate dependent. Whereas styrene affords only the Markovnikov addition product, 1-butene produces an 81:19 mixture of anti-Markovnikov and Markovnikov products. The presence of an oxygen substituent (acyloxy or aryloxy group) in the allylic position of the alkene causes addition of $PhSeCl_3$ to occur anti-Markovnikov (eq 5). When the addition products are submitted to the usual conditions for hydrolytic selenoxide elimination, allylic and/or vinylic chlorides are formed. Chloroselenation products derived from alkenes containing a directing allylic substituent show a high preference for elimination away from the oxygen substituent to afford an (*E*/*Z*) mixture of vinylic chlorides (eq 5). Other alkenes, including cyclic ones, afford mixtures of allylic and vinylic chlorides in varying proportions. Symmetrical alkenes without allylic hydrogens are converted to vinylic chlorides with retention of the alkene geometry.

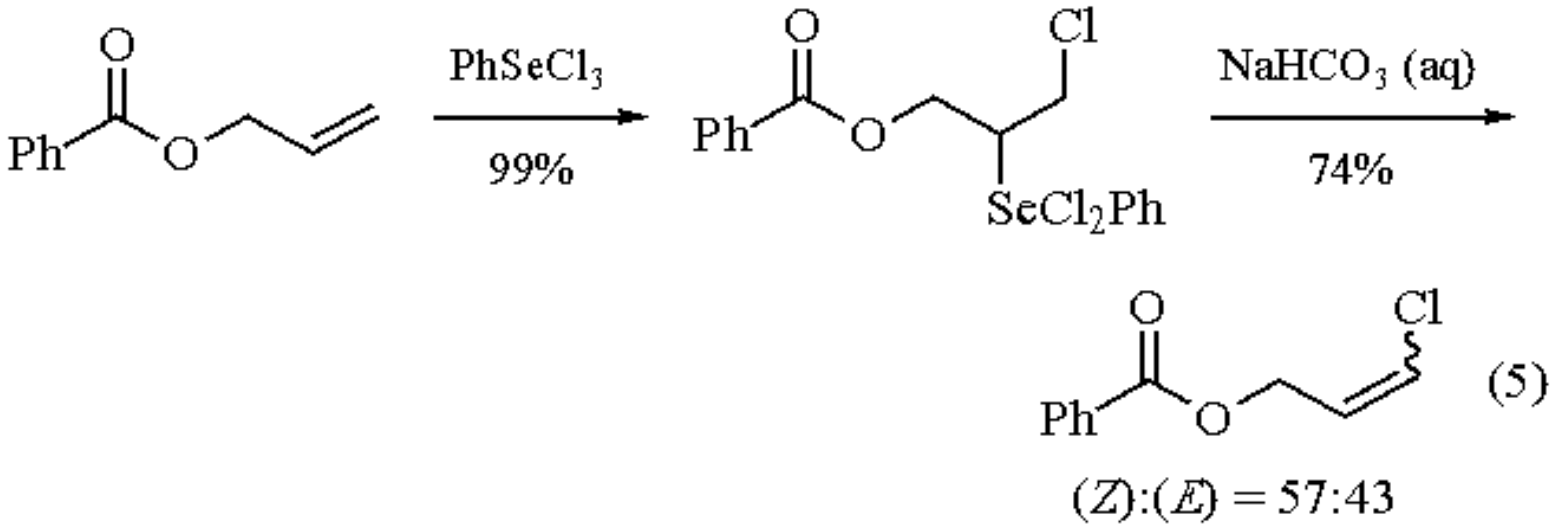

Chlorinating Agent.

Selenium(IV) dichlorides (**3**), prepared from $PhSeCl_3$ and methyl ketones, undergo a Pummerer-like reaction[7] when treated with ***Pyridine*** in methylene chloride (eq 6).[8] The resulting α-chloro-α-phenylselenenyl ketones (**4**) can be chlorinated on selenium and the Pummerer reaction repeated to afford α,α-dichloro-α-phenylselenenyl ketones. The chlorinating properties of phenylselenium trichloride have also been used in the preparation of mono-, di-, tri-, and tetrachlorinated porphyrins.[9]

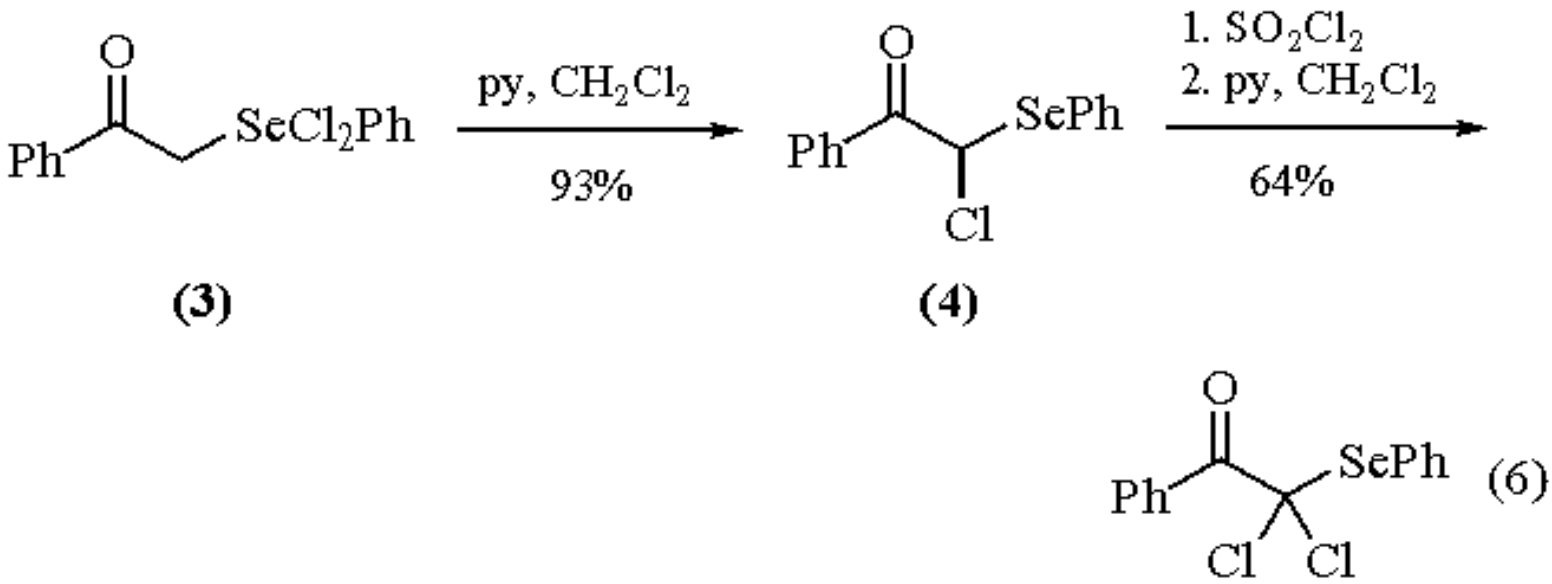

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(Phenylseleno)acetaldehyde

$PhSeCH_2CHO$

[71338-48-2] · C_8H_8OSe · (Phenylseleno)acetaldehyde · (MW 199.12)

(vinyl cation equivalent[1-6] and reagent for two-carbon homologation[7])

Physical Data: bp 110 °C/0.5 mmHg;[1] 57 °C/0.01 mmHg.[7]

Solubility: sol common organic solvents; insol water.[7]

Preparative Methods: reaction of ***Ethyl Vinyl Ether*** with ***Benzeneselenenyl Bromide***, followed by hydrolysis;[1,7] phenylselenenylation of ***Acetaldehyde***;[8] reaction of ***Vinyl Acetate*** with ***Benzeneselenenyl Chloride***.[9]

Handling, Storage, and Precautions: best kept in refrigerator and protected from light. Old material should be redistilled before use.[10]

Vinyl Cation Equivalent.

(Phenylseleno)acetaldehyde serves as a vinyl cation equivalent.[1-6] Aldol condensation with ketones gives keto hydroxy selenides that are convertible, by treatment with ***Methanesulfonyl Chloride*** and ***Triethylamine***, into α-vinyl ketones (eq 1).[2]

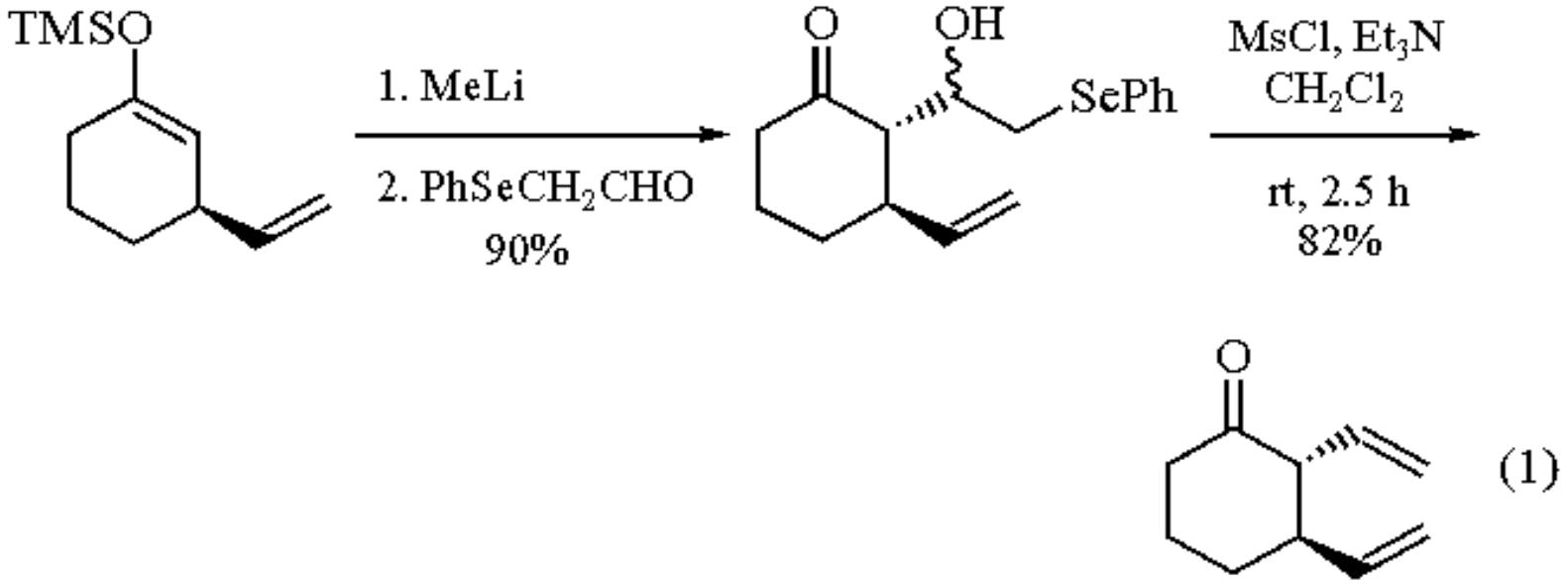

The aliphatic reagent (methylseleno)acetaldehyde appears to be less efficient as a vinyl cation equivalent.[2] The latent vinyl group can also be released by successive action of ***Trifluoroacetic Anhydride***/triethylamine and ***Trimethyl Phosphite*** (eq 2).[1] Similar transformations to that shown in eq 1 can be effected with dicarbonyl(cyclopentadienyl)(ethyl vinyl ether)iron tetrafluoroborate[11] or (*t*-butyldimethylsilyl)acetaldehyde.[12]

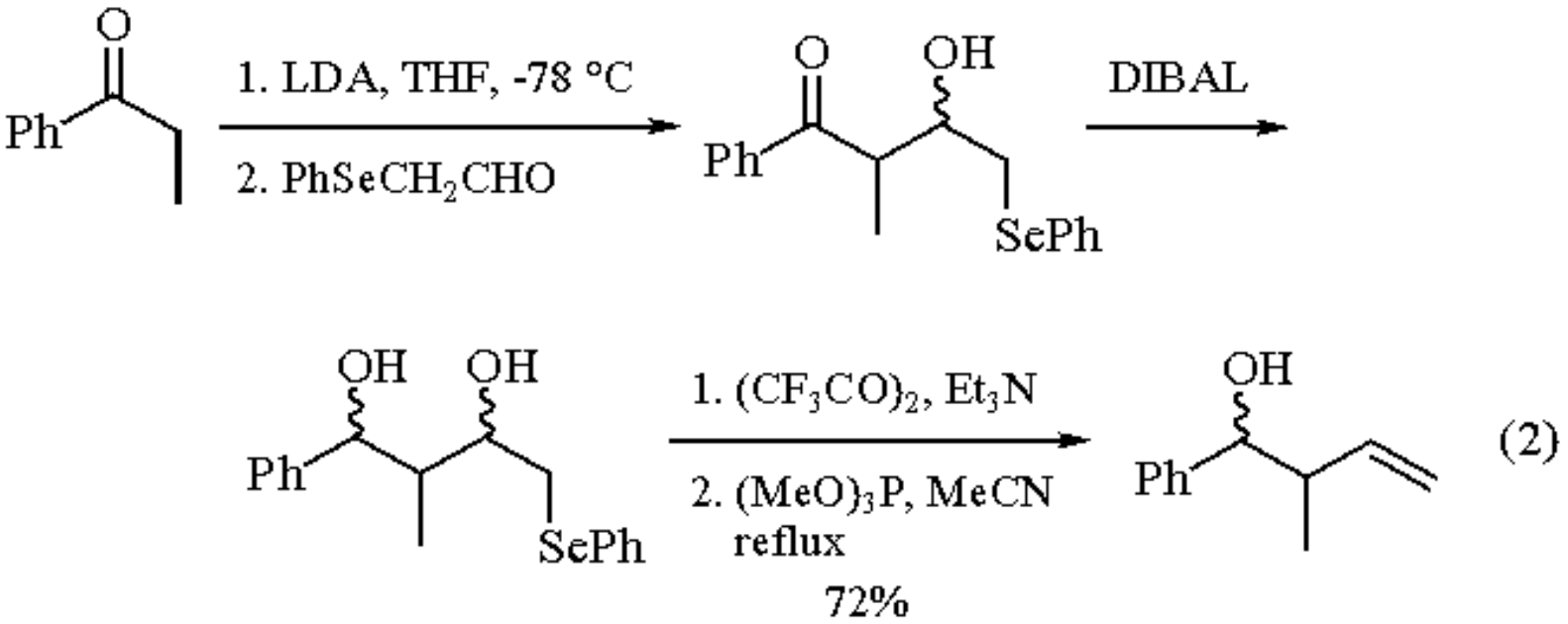

Two-Carbon Homologation.

Grignard reagents can be converted into (phenylseleno) ketones by reaction with (phenylseleno)acetaldehyde, followed by oxidation of the resulting alcohol (eq 3).[7,13] It should be noted, however, that oxidation of hydroxy selenides can be problematic.[14]

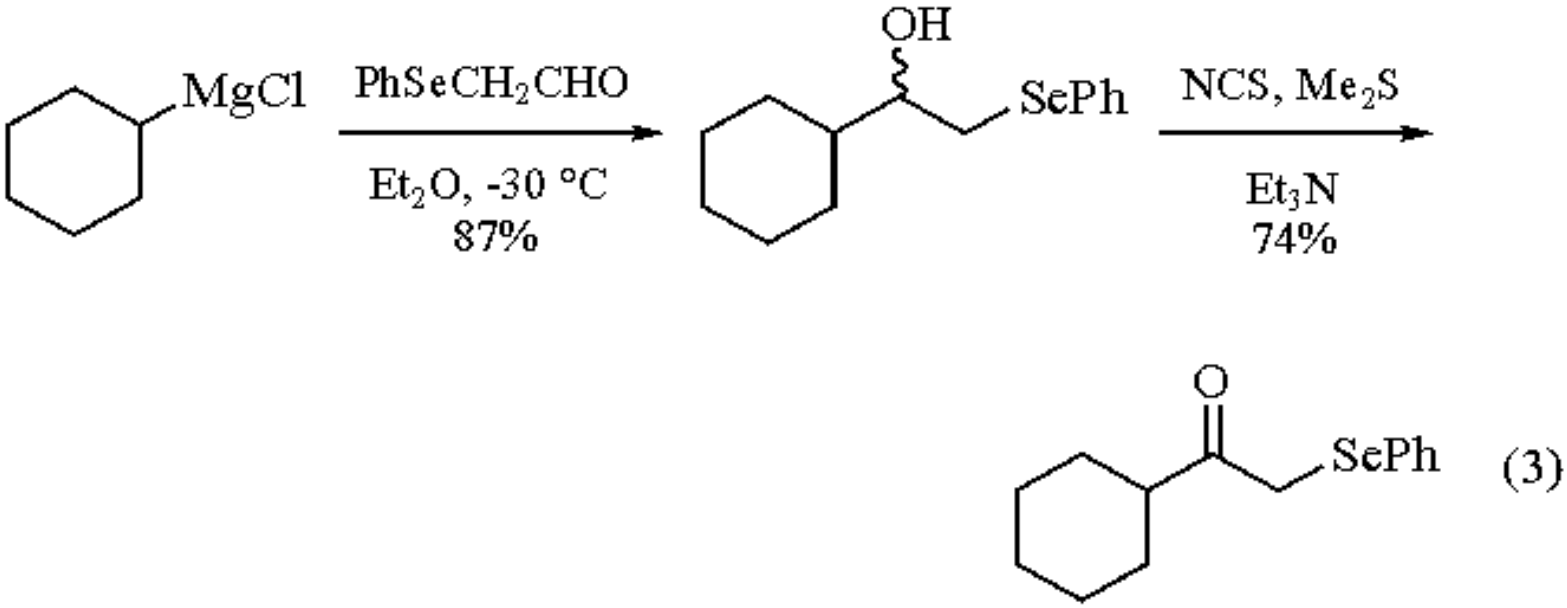

Use in Radical Chemistry.[15,16]

Hydroxy selenides, made using (phenylseleno)acetaldehyde, have been used in radical cyclizations (eqs 4 and 5). The example of eq 4 involves initial use of the reagent in an aldol condensation; in eq 5 the aldehyde is first used to form an iminium species which, on reduction with ***Sodium Cyanoborohydride***, affords the substrate for radical cyclization.

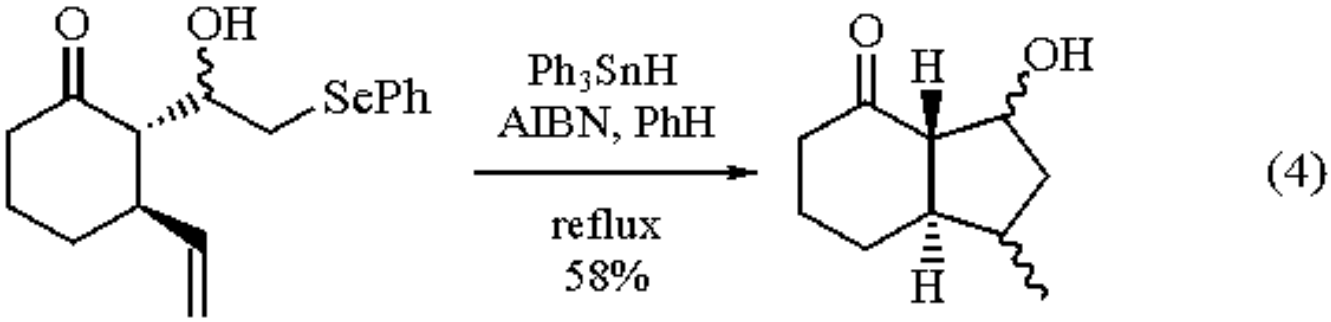

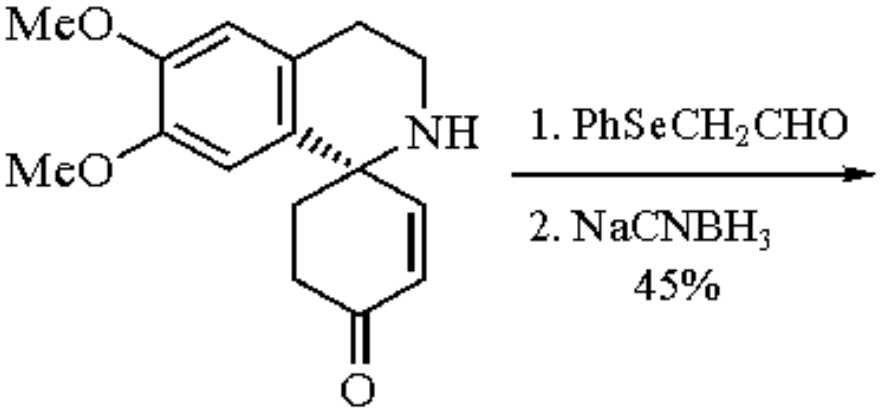

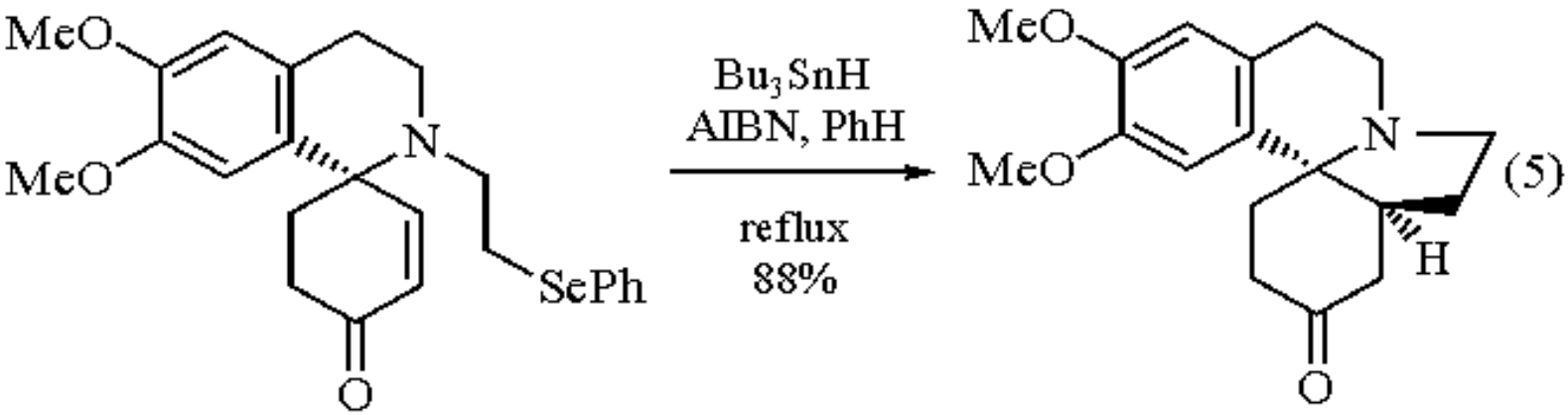

Formation of Allylic Selenides.

Wittig[17] and related[8a,18] alkenations give allylic selenides when applied to (phenylseleno)acetaldehyde (eqs 6 and 7).

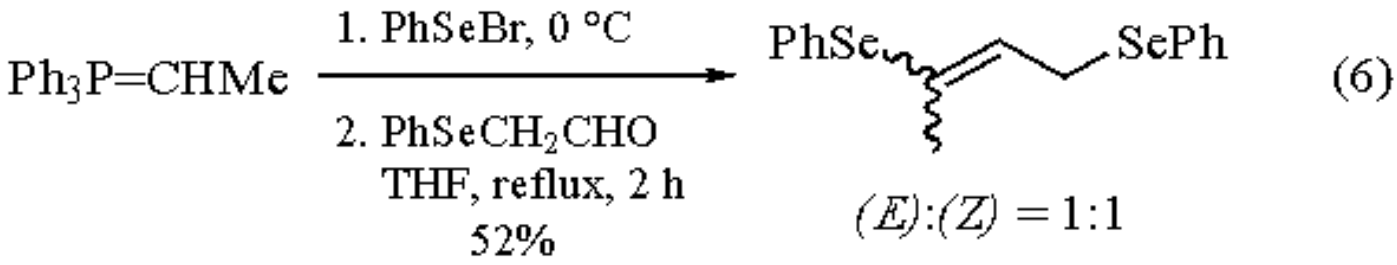

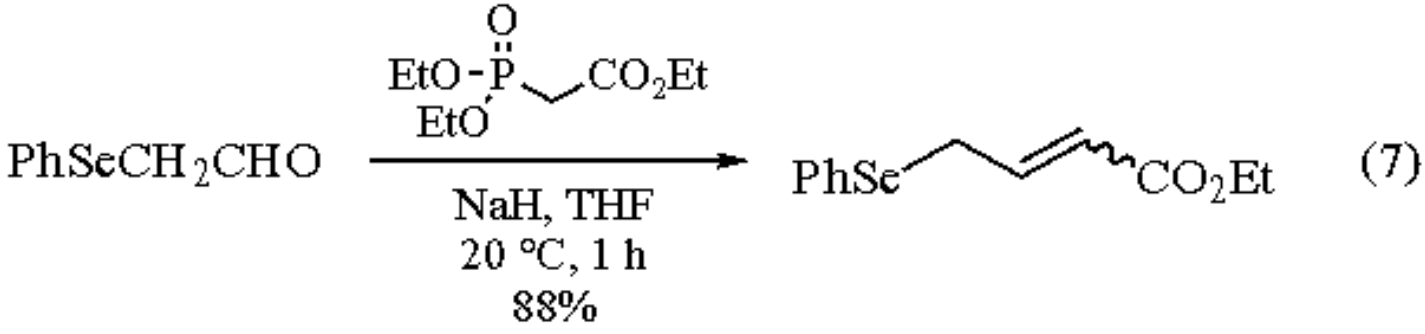

Related Reagents.

Phenylsulfinylethylene.

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(Phenylseleno)acetic Acid

$PhSeCH_2CO_2H$

[17893-46-8] · $C_8H_8O_2Se$ · (Phenylseleno)acetic Acid · (MW 215.12)

(dianion reacts with electrophiles, such as aldehydes[1] and epoxides;[2,3] especially useful for the preparation of 2(5*H*)-furanones)

Physical Data: white prisms, mp 35.5-36.5 °C (from 5% ether/hexane).[1] IR,[1,4] ^{1}H NMR,[1,4] and ^{13}C NMR[5] spectra have been reported. The pK_a (25 °C) has been calculated to be 3.75.[6]

Solubility: sol THF, ether, and alcohol; crystallizes from hexane.

Preparative Methods: the best methods involve the displacement of a halogen atom from an α-haloacetic acid molecule by a phenylselenide moiety. The selenide anion can be obtained by reduction of ***Diphenyl Diselenide*** (eqs 1 and 2)[1,4] or from ***Benzeneselenol*** in basic medium (eq 3).[4]

$$Ph_2Se_2 \xrightarrow[\text{2. } ClCH_2CO_2H]{\text{1. } NaBH_4,\ EtOH} PhSeCH_2CO_2H \qquad (1)$$

$$Ph_2Se_2 \xrightarrow[\text{2. } ICH_2CO_2^-\ \text{3. } HCl]{\text{1. } NaBH_4} PhSeCH_2CO_2H \qquad (2)$$

$$PhSeH + ClCH_2CO_2Na \xrightarrow{NaOH} PhSeCH_2CO_2H \qquad (3)$$

The best yield is described from benzeneselenol through a thallium(I) benzeneselenolate intermediate (eq 4).[4] This method has also been applied to the preparation of 2-phenylselenopropanoic acid.

$$PhSeH \xrightarrow{PhOTl} PhSeTl \xrightarrow{BrCH_2CO_2H} PhSeCH_2CO_2H \qquad (4)$$

Handling, Storage, and Precautions: may be kept in crystalline form in the refrigerator for several months.

Use in a fume hood.

Synthesis of Alkenes.

The dianion of α-phenylselenoacetic acid, usually prepared by deprotonation with ***Lithium Diisopropylamide***, may be employed as a Wittig reagent equivalent for the synthesis of alkenes from aldehydes (eq 5).[1] The reductive elimination of PhSeOH proceeds with high *anti* stereospecificity under very mild conditions compatible with virtually all functionalities.

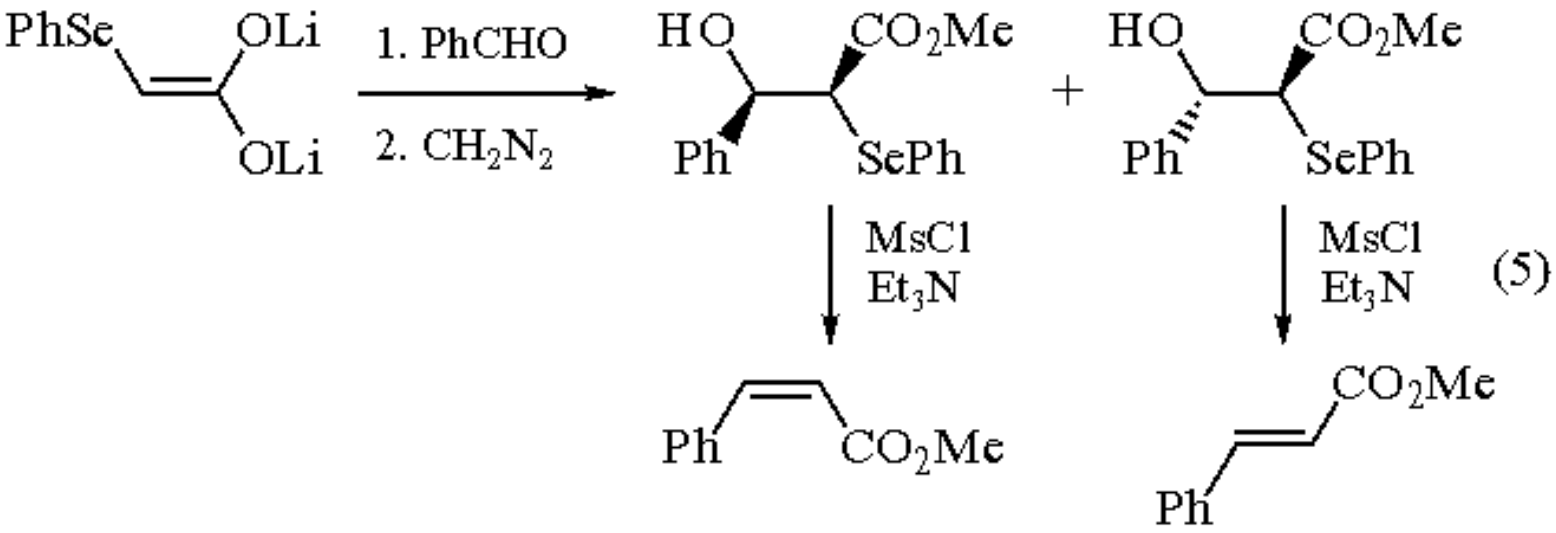

Synthesis of α,β-Unsaturated Esters and Lactones.

The reaction of the dianion of α-phenylselenoacetic acid with epoxides leads to γ-hydroxy acids, which can be dehydrated either with ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride***[2] or under acidic conditions;[3] the oxidation of the α-phenylselenolactone and subsequent pyrolysis of the selenoxide yields 2(5*H*)-furanones, i.e. α,β-butenolides (eq 6).

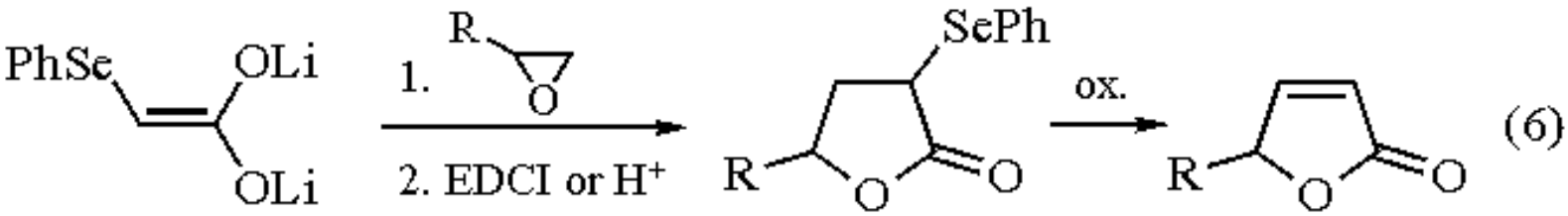

Although a similar route has been described using ***(Phenylthio)acetic Acid***,[7] the selenium pathway allows the pyrolysis step to take place in milder conditions. An additional advantage is the possibility of carrying out the oxidation in the presence of other oxidizable heteroatoms such as nitrogen or sulfur (eq 7).[3]

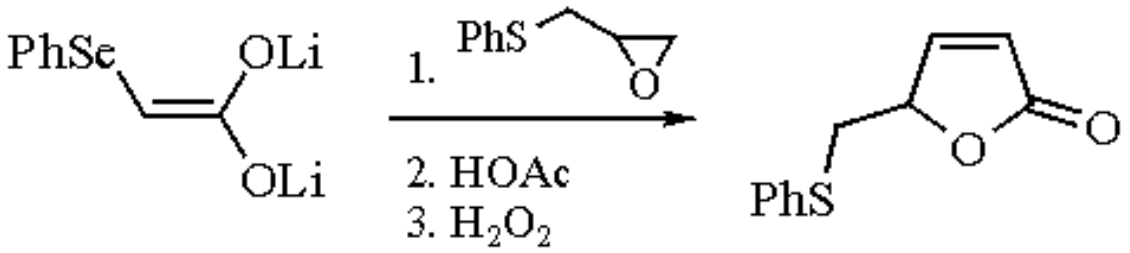

(7)

When optically pure epoxides are used as the starting electrophiles, no loss of the sense of chirality has been observed.[2] Therefore the method has been successfully applied to the synthesis of various natural products, including mevinic acids,[8] ionomycin,[9,10] and cladospolide A.[11] In this last case an α,β-unsaturated ester was prepared instead of a lactone (eq 8).

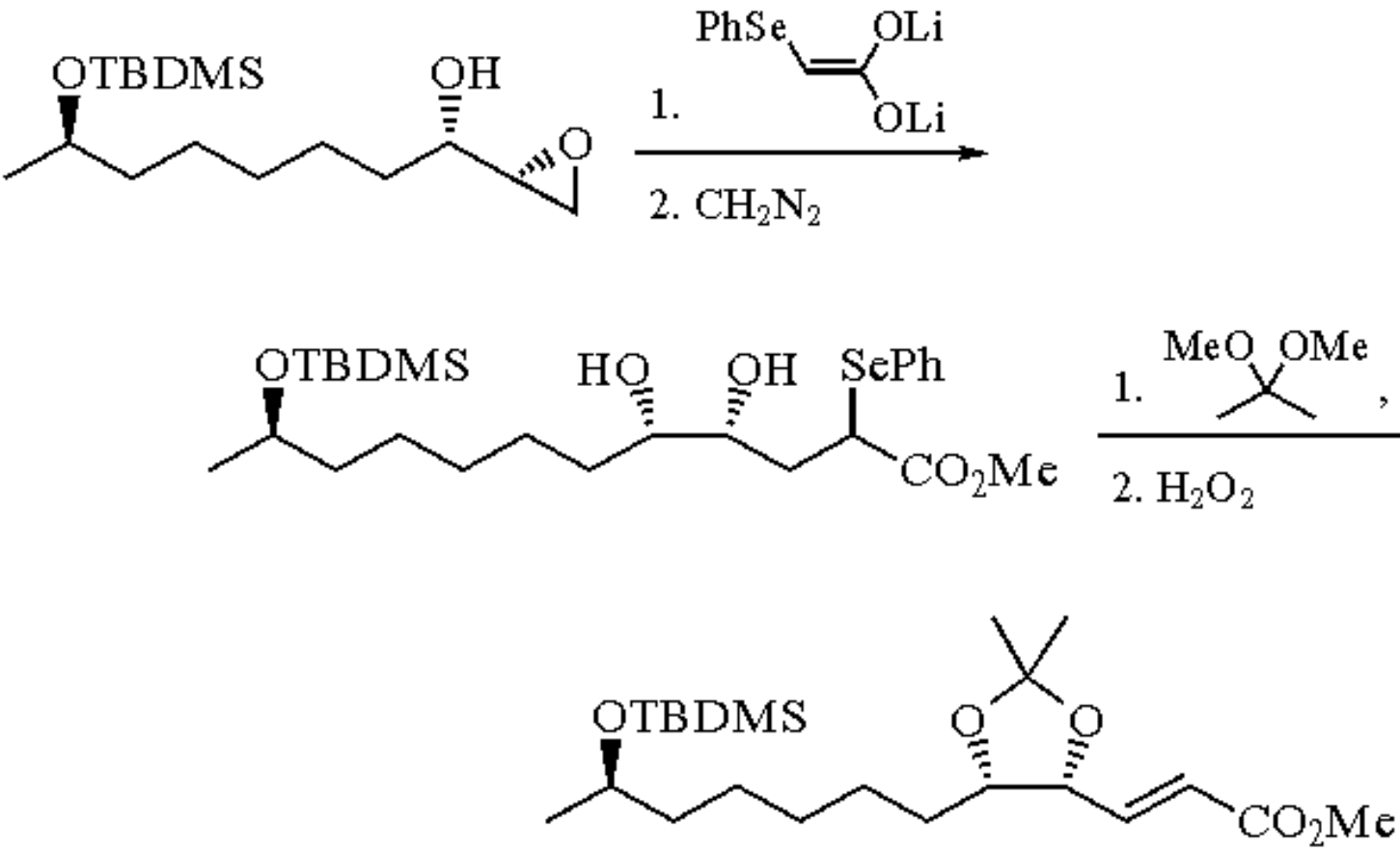

(8)

Related Reagents.

2-Phenylselenopropanoic acid[4,12] has been used as a masked acrylate unit in a crucial step of the synthesis of frullanolide (eq 9).[13] In that example an allylic halide acted as the electrophile and the elimination of the selenoxide resulted in the formation of the exocyclic double bond. Interestingly, in an analogous situation, sulfoxides led exclusively to the formation of an endocyclic double bond (eq 10).[7] See also ***(Phenylthio)acetic Acid***.

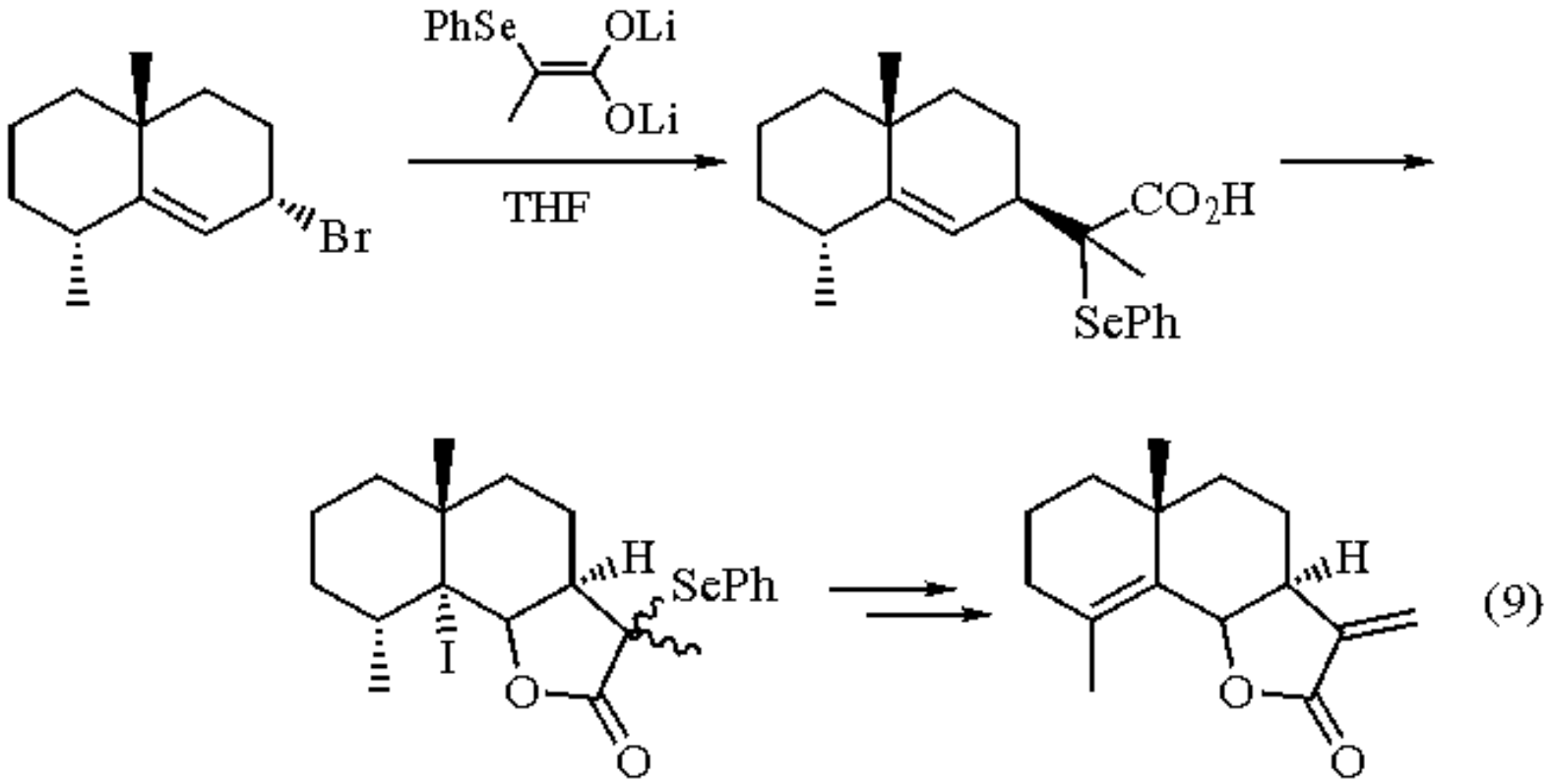

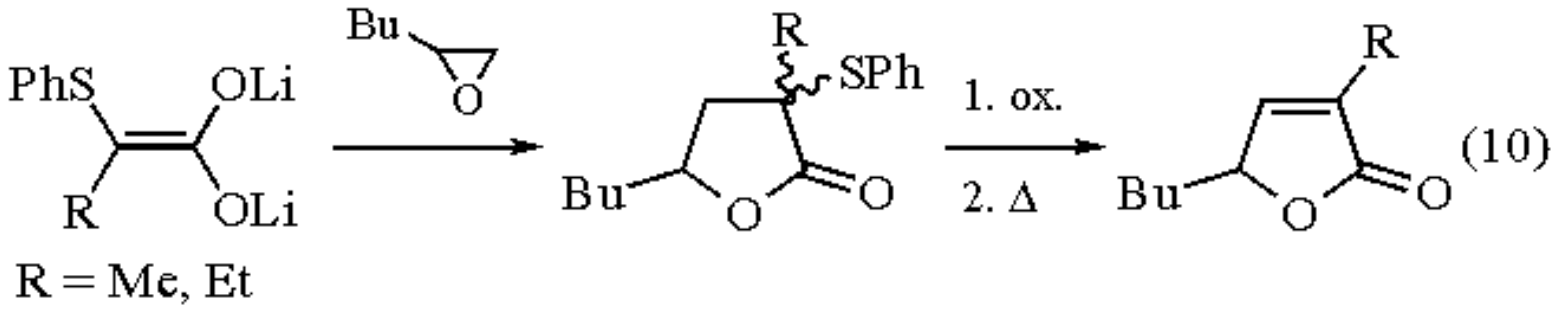

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Josep Font & Marta Figueredo

9-Phenylseleno-9-borabicyclo[3.3.1]nonane[1]

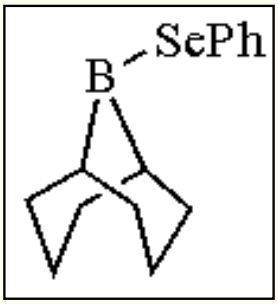

[94348-51-3] · $C_{14}H_{19}BSe$ · 9-Phenylseleno-9-borabicyclo[3.3.1]nonane · (MW 277.10)

(reagent for nucleophilic phenylselenylation of enones)

Preparative Methods: stock solutions of this reagent can be prepared by heating equimolar amounts of ***Benzeneselenol*** and ***9-Borabicyclo[3.3.1]nonane*** in toluene at 60 °C for 5 h. Stock solutions are stable indefinitely when stored at -20 °C in the dark.[1]

Handling, Storage, and Precautions: use in a fume hood.

Crossed Aldol Condensations.

This reagent has been found to add to a variety of cyclic and acyclic α,β-unsaturated ketones to give the corresponding β-phenylselenoboron enolates. These species condense in situ with aldehydes to provide the corresponding unsaturated aldol adducts and aldol acetates after oxidative workup and acetylation (eq 1).[1] It was subsequently found that dimethyl(phenylseleno)aluminum[2] was, in general, a superior reagent for effecting this[3] and related[2] transformations. In this connection, the latter reagent would appear more effective than dimethyl(phenylthio)aluminum.[4]

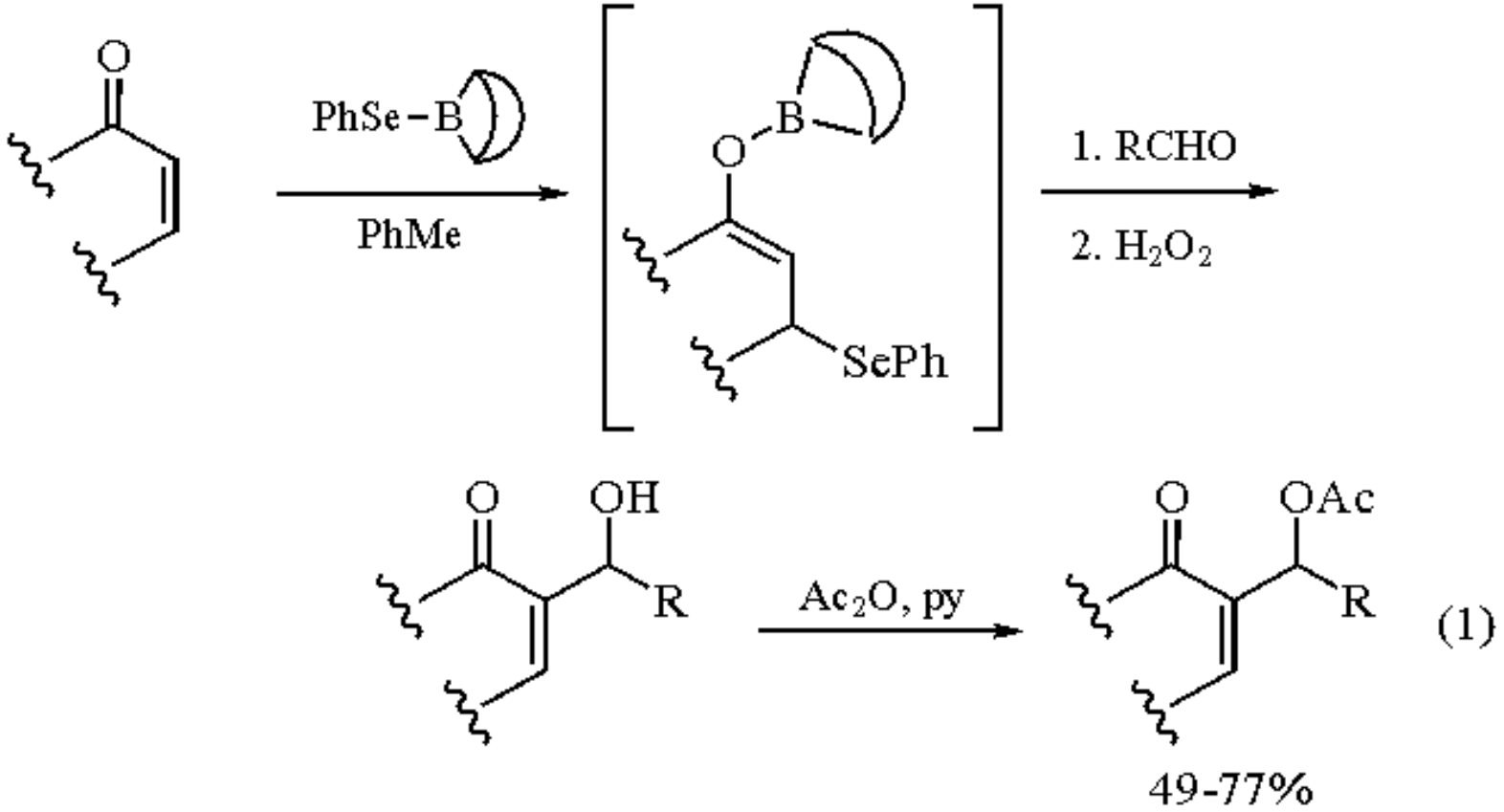

Related Reagents.

Diisobutylaluminum Phenyl Selenide; ***Dimethylaluminum Methylselenolate***; ***Phenyl Trimethylsilyl Selenide***; ***Tris(phenylseleno)borane***.

---

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Phenylselenocopper(I)

PhSeCu

[41962-55-4] · C_6H_5CuSe · Phenylselenocopper(I) · (MW 219.62)

(source of nucleophilic phenylselenide for preparation of lithium alkylphenylselenocuprates and organophosphinecopper(I) phenylselenolate complexes)

Physical Data: mp 150 °C (dec).

Solubility: partially sol cold THF.

Preparative Methods: phenylselenocopper can be prepared by two different procedures (eq 1). In the more straightforward procedure, ***Benzeneselenol*** is reacted with copper(I) oxide in ethanol at reflux to yield PhSeCu as a yellow or brown precipitate in 94% yield.[1] Similarly, uncharacterized $(PhSeCu)_n$ has been prepared from benzeneselenol and ***Copper(II) Acetate*** (2:1) in methanol.[2] A second type of preparation involves reaction of $Bu_2Sn(SePh)_2$ with copper(II) nitrate in methanol;[3] an observed byproduct in this reaction is PhSeSePh. The tin reagent is obtained from PhSeH by reaction with Bu_2SnCl_2. PhSeCu has also been prepared by direct electrochemical oxidation of ***Diphenyl Diselenide***.[6]

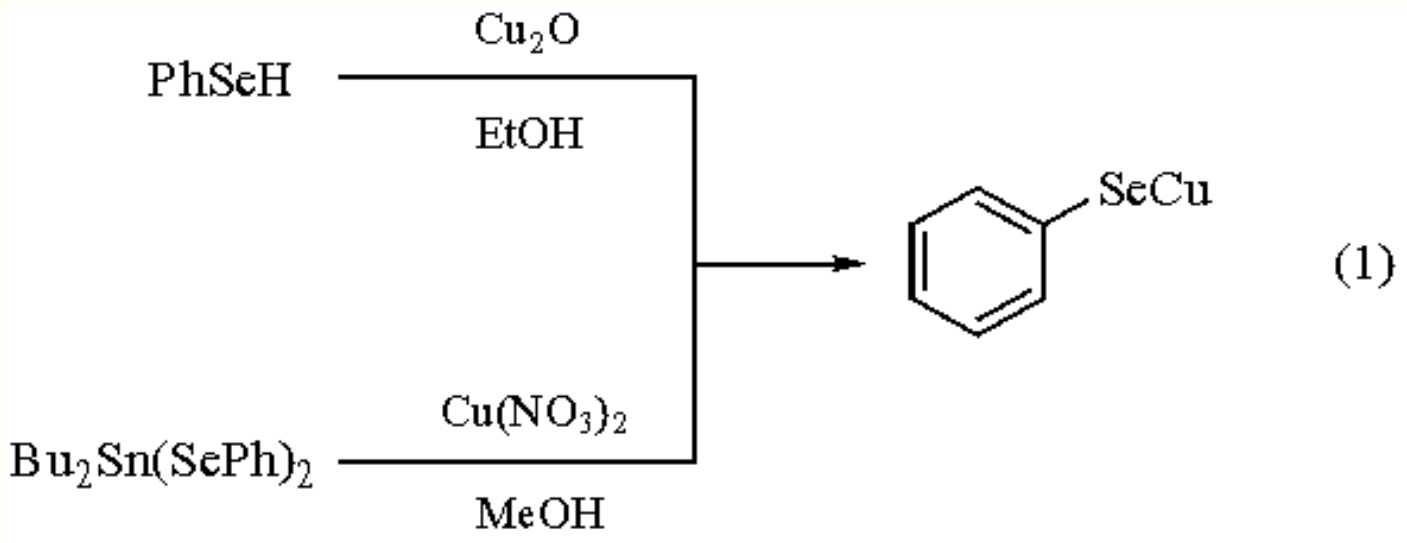

Handling, Storage, and Precautions: selenium reagents should always be used in a fume hood.

Cuprate Reagents.

Lithium alkyl(phenylseleno)cuprates, which are reacted with alkylseleno-substituted vinyl sulfones to effect stereoselective alkylation at the selenium-bearing carbon (eq 2), are prepared by the reaction of PhSeCu with the requisite alkyllithium in THF at 0 °C.[1b] The cuprates are generated in situ and then treated with the sulfone and warmed to rt.[1b,4] Interestingly, these cuprates have afforded superior yields to the traditional cyano and thiophenyl mixed cuprates; the latter reagents also added in a conjugate fashion to give saturated products. Alkyl groups which have been coupled in good yield are Me, *i*-Pr, *n*-Bu, *s*-Bu, *t*-Bu, and 3-pentyl (67-97%).

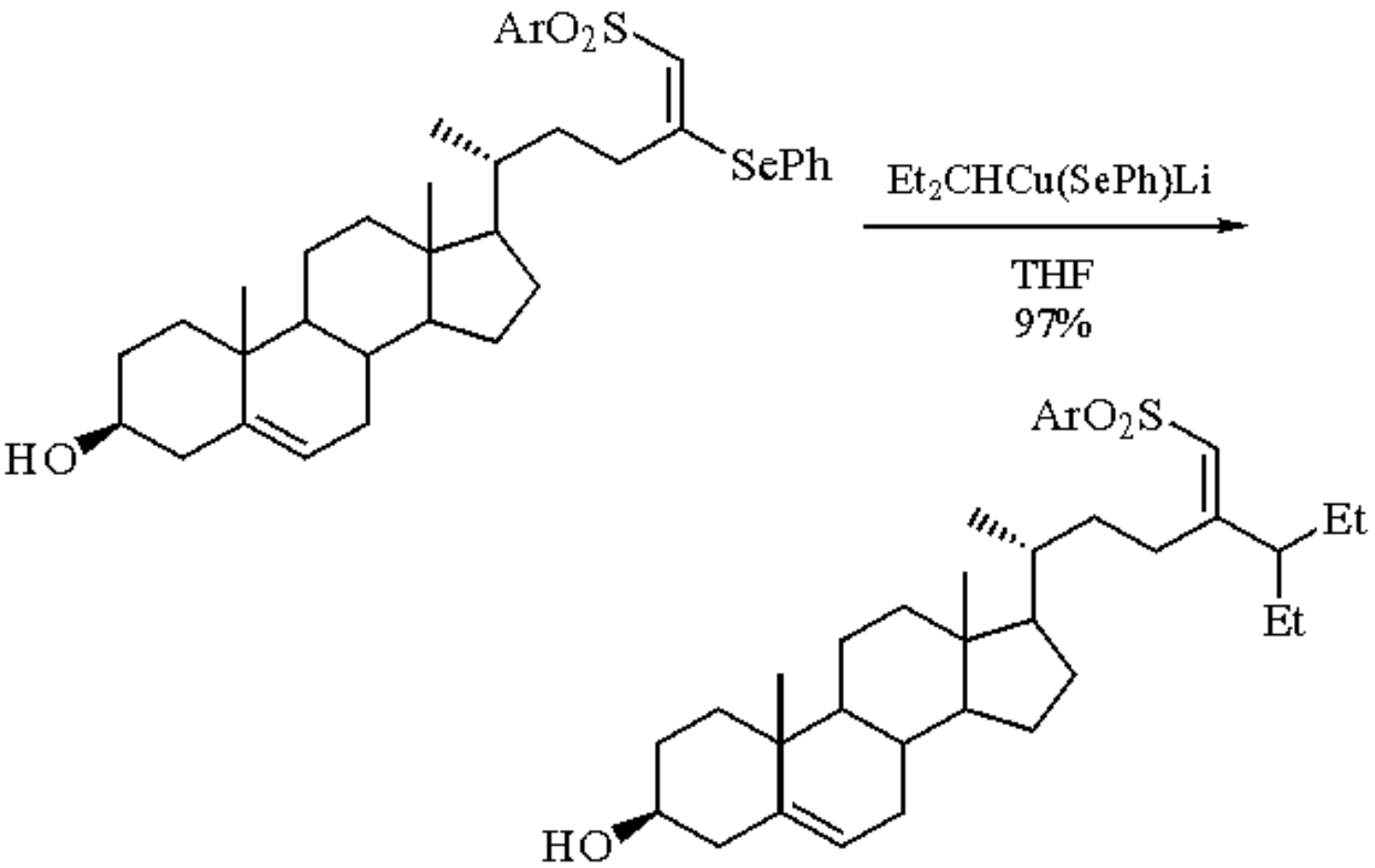

(2)

Organophosphine Complexes.

A cyclohexylphosphinecopper(I) phenylselenolate complex has been synthesized from $(PhSeCu)_n$ to study its 1:1 adduct formation and subsequent stability with SO_2 (eq 3).[5] Addition of solid tricyclohexylphosphine to an acetonitrile suspension of $(PhSeCu)_n$ followed by stirring for 30 min yields the precipitated complex.

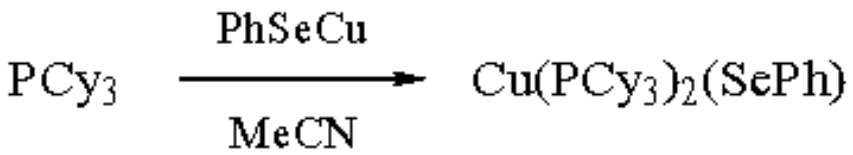

(3)

Related Reagents.

Phenylthiocopper(I).

1. (a) Osuka, A.; Ohmasa, N.; Suzuki, H. *S* **1982**, 857. (b) Back, T. G.; Collins, S.; Law, K.-W. *TL* **1984**, *25*, 1689.
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Phenyl Selenocyanate[1]

PhSeCN

[2179-79-5] · C_7H_5NSe · Phenyl Selenocyanate · (MW 182.09)

(a specific source of nucleophilic[2-5] and electrophilic selenium species[6-8])

Physical Data: light yellow oil; bp 125 °C/16 mmHg, 118 °C/11 mmHg,[9] 104 °C/4 mmHg.[10]

Solubility: sol organic solvents such as THF, dichloromethane, and acetonitrile.

Analysis of Reagent Purity: spectral data (IR, NMR)[10] and physical constants (bp, TLC).

Preparative Methods: diazotization of aniline followed by treatment with ***Potassium Selenocyanate*** in buffer solution containing sodium acetate;[9,11] condensation reaction of ***Benzeneselenenyl Chloride*** with ***Cyanotrimethylsilane*** in dry THF or in dry dichloromethane, giving phenyl selenocyanate in almost quantitative yield.[10]

Purification: the product obtained by above methods contains a slight amount of ***Diphenyl Diselenide*** as impurity, which is usually not troublesome in its application to organic reactions. Pure phenyl selenocyanate can be obtained by fractional distillation or silica gel column chromatography.

Handling, Storage, and Precautions: highly toxic and unpleasant smell. Use in a fume hood.

Nucleophilic Reactions.

Phenyl selenocyanate quantitatively generates a nucleophilic selenium species ($PhSe^-$ equivalent) upon treatment with ***Sodium Borohydride***,[11] which reacts with primary alkyl bromides[11] and mesylates[12] to form alkyl phenyl selenides (see also ***Diphenyl Diselenide*** and ***o-Nitrophenyl Selenocyanate***). A more useful aspect of phenyl selenocyanate is its reactions with electrophilic substrates in the presence of ***Tri-n-butylphosphine***. For example, primary[2] and secondary[2,3] alcohols can be directly converted into the corresponding alkyl phenyl selenides by the reaction with phenyl selenocyanate (eq 1). Yields are somewhat lower for secondary alcohols. Aldehydes react with phenyl selenocyanate to produce cyanoselenenylation adducts in good yields (eq 2), while ketones give rearranged products in only modest yields.[4] Carboxylic acids react with phenyl selenocyanate to form selenol esters in high yields (eq 3).[5]

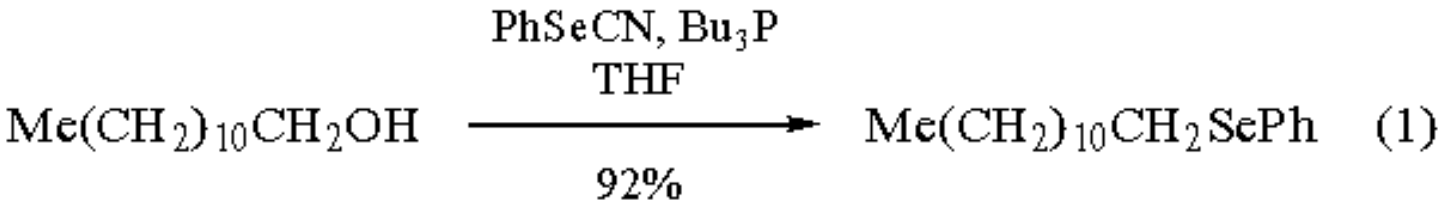

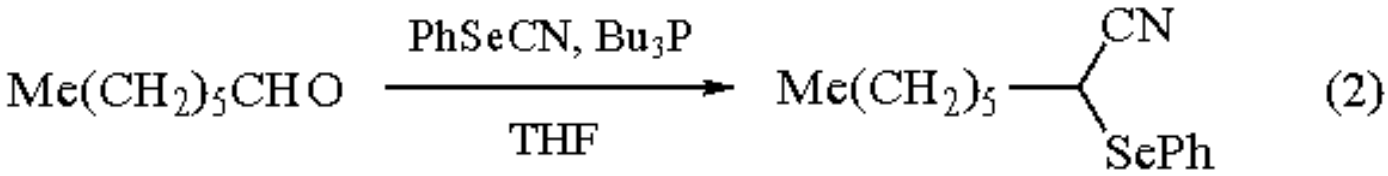

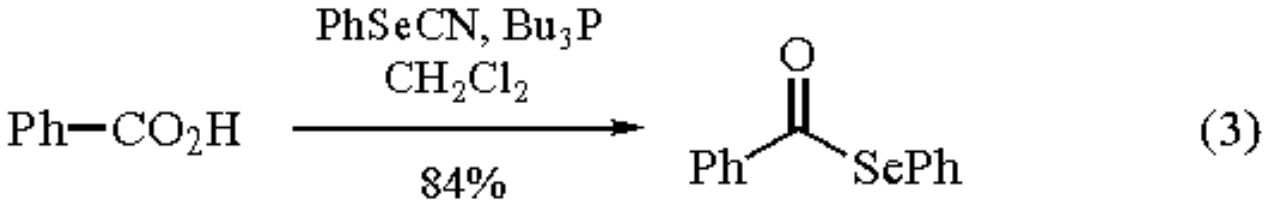

Electrophilic Reactions.

Highly reactive alkenes, such as ketene acetals[13] and enamines,[14] react with phenyl selenocyanate in ethanol to form cyanoselenenylation products regioselectively, which can be converted into β,γ-unsaturated nitriles and α,β-unsaturated aminonitriles,[1] respectively (eqs 4 and 5). Simple alkenes react with phenyl selenocyanate in the presence of Lewis acids. For example, in the presence of ***Copper(II) Chloride*** or ***Copper(II) Bromide*** or in the presence of ***Nickel(II) Chloride*** or ***Nickel(II) Bromide***, phenyl selenocyanate reacts with alkenes in methanol or phenol to produce electrophilic selenium adducts in high yields (eq 6).[6] With dienes in acetonitrile, 1:2 adducts having a cyclic ether skeleton are produced (eq 7).[7] In the presence of ***Tin(IV) Chloride***, phenyl selenocyanate reacts with simple alkenes to form cyanoselenenylation products (eq 8).[8]

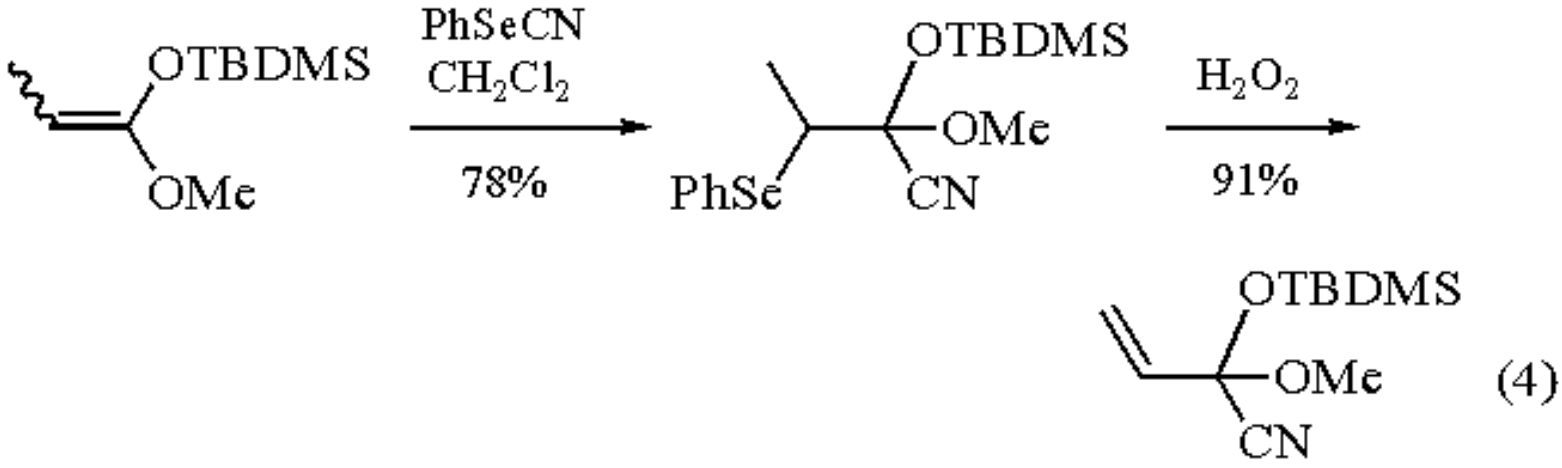

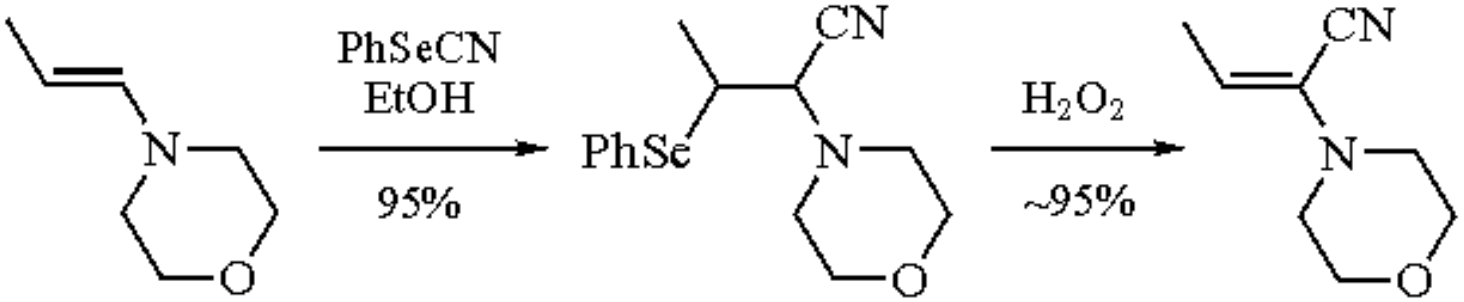

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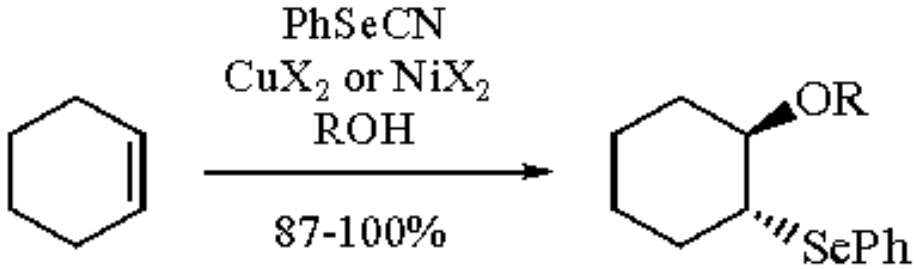

(6)

X = Cl or Br; R = Me or Ph

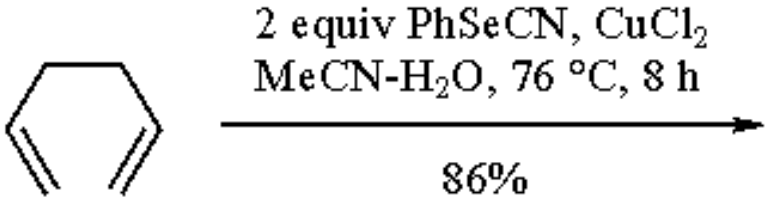

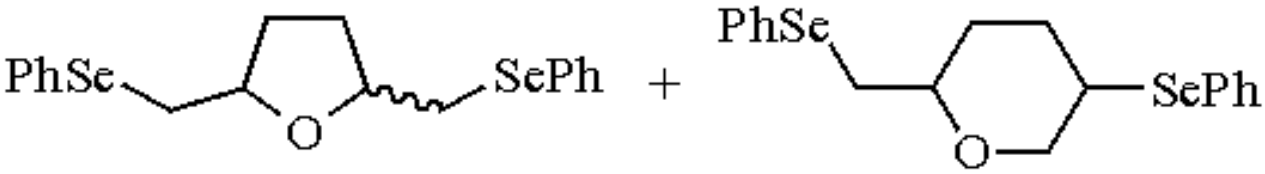

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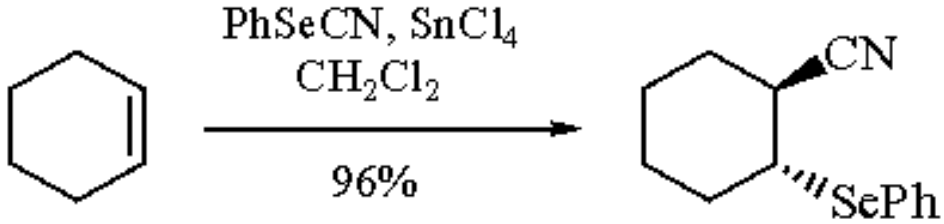

(8)

Related Reagents.

Benzeneselenenyl Chloride; ***Diphenyl Diselenide***; ***o-Nitrophenyl Selenocyanate***; ***Phenylselenium Trichloride***; ***Phenyl Selenocyanate-Copper(II) Chloride***.

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Phenyl Selenocyanate-Copper(II) Chloride

PhSeCN-$CuCl_2$

(PhSeCN)

[2179-79-5] · C_7H_5NSe · Phenyl Selenocyanate-Copper(II) Chloride · (MW 182.09) ($CuCl_2$)

[7447-39-4] · Cl_2Cu · Phenyl Selenocyanate-Copper(II) Chloride · (MW 134.45)

(oxyselenates alkenes, dienes, and α,β-unsaturated aldehydes with regio- and stereoselectivity; forms cyclic ethers)

Physical Data: see ***Phenyl Selenocyanate*** and ***Copper(II) Chloride***.

Form Supplied in: both components are commercially available.

Preparative Methods: the reagent is prepared as needed. PhSeCN can be made[5] from phenyldiazonium salts and commercially available KSeCN or, particularly for small-scale experiments, from the available reagents PhSeCl and Me_3SiCN.[6,7]

Handling, Storage, and Precautions: selenium reagents are highly toxic and corrosive. All reactions should be conducted in a well-ventilated fume hood.

General Discussion.

Phenyl selenocyanate in alcohols, wet THF, or acetic acid/chloroform reacts, in the presence of copper(II) or -(I) chloride, on the C=C double bond of alkenes[1] and dienes[2,3] and produces β-alkoxy-, β-hydroxy-, and β-acetoxyalkyl phenyl selenides and cyclic ethers in good yields. The reaction is best achieved (1-10 h) at 65 °C with stoichiometric amounts of the copper salts. Although it still proceeds at lower temperature (25 °C) and with smaller amounts of catalyst (down to 0.025 mol equiv), it becomes particularly slow. It does not occur in the absence of copper salts or when a pyridine-$CuCl_2$ complex is used.[1] It has nevertheless been reported[4] that this reaction can be catalyzed by copper-loaded polymers, but the yields are lower.

This reaction has been successfully carried out on terminal, alicyclic, and cyclic α,β-disubstituted alkenes as well as on vinyl acetate, α,β-unsaturated aldehydes (eq 1), and their dimethyl acetals.[1] The two latter compounds provide, on reaction in methanol, the same β-methoxy-β´-dimethoxyalkyl phenyl selenide. Oxyselenation does not occur with compounds possessing electron-withdrawing groups attached to the C=C double bonds, such as methyl vinyl ketone, methyl acrylate, and acrylonitrile.[1] Successful reaction of α,β-unsaturated aldehydes is probably due to the

intermediate formation of the corresponding α,β-unsaturated acetal.[1]

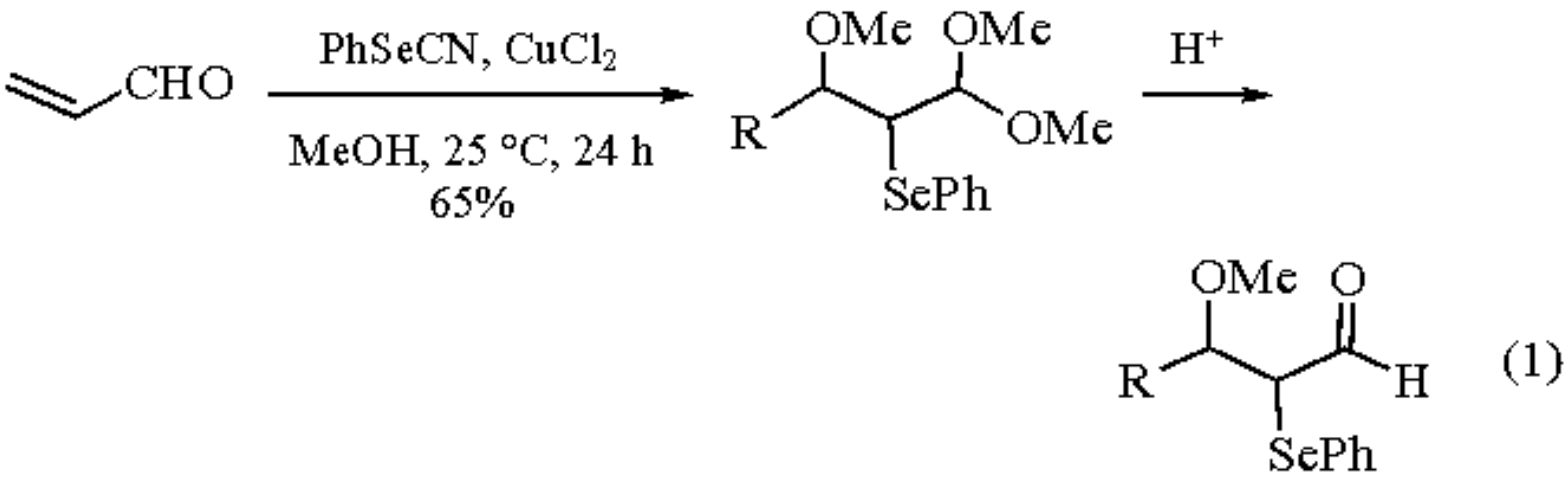

The oxyselenation is regioselective, the phenylseleno group being introduced at the least substituted carbon of styrene, vinyl acetate, and 1-hexene (eq 2).[1] In the last case the highest ratio of primary alkyl selenide is achieved, presumably under thermodynamic control, when the reaction is performed at higher temperature and for a longer time. The selectivity is reversed with acrolein, allowing the synthesis of α-phenylseleno-β-methoxy aldehydes (eq 1).[1]

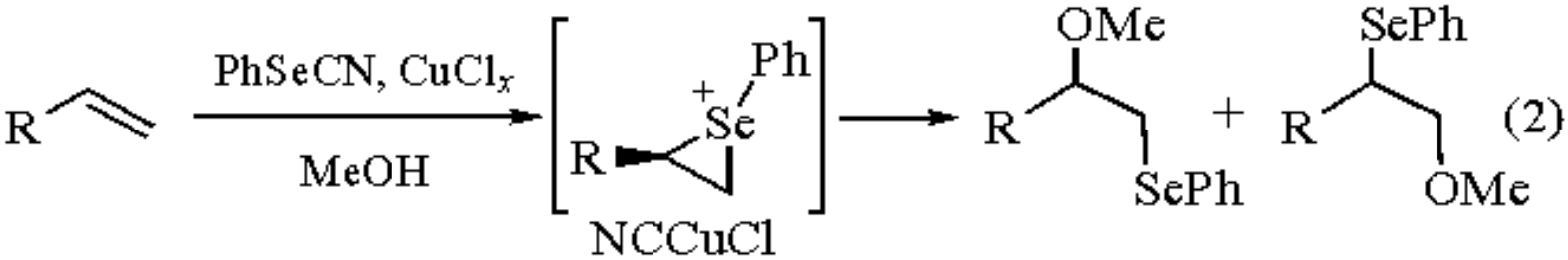

R	Conditions	Yield (ratio)
Hexyl	$CuCl_2$, 25 °C, 15 h	88% (83:13)
Ph	$CuCl_2$, 25 °C, 7 h	87% (100:0)
AcO	CuCl, 25 °C, 12 h	74% (100:0)

The reaction is stereoselective and occurs via *anti* addition (eq 3) except with crotonaldehyde. The intermediate formation of a seleniiranium ion might account for the reported regio- and stereoselectivity. The lower reactivity of the unsaturated aldehydes and the possible (*Z*/*E*) isomerization prior to oxyselenation might be responsible for the lower stereocontrol.

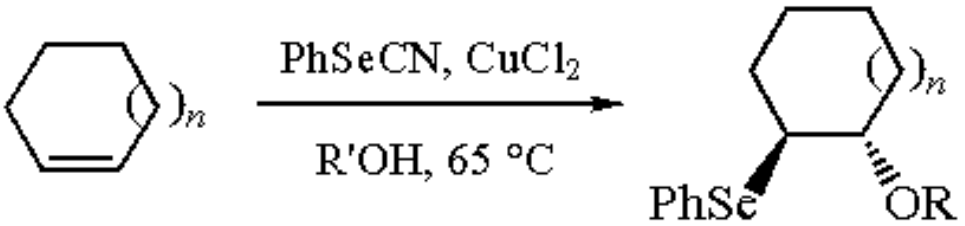

(3)

$n = 0\text{-}2$	MeOH, 3-5 h	66-100%	R = Me
$n = 1$	*i*-PrOH, 0.5 h	88%	R = *i*-Pr
$n = 1$	AcOH-$CHCl_3$, 5 h	80%	R = Ac
$n = 1$	H_2O-THF (5:2), 19 h	45%	R = H

Reaction of *cis,cis*-1,5-cyclooctadiene with phenyl selenocyanate-copper(II) chloride in alcohols, aq THF, or acetonitrile produces[2,3] a mixture of [3.3.1] and [4.2.1] bicyclic ethers in good yields (eq 4).

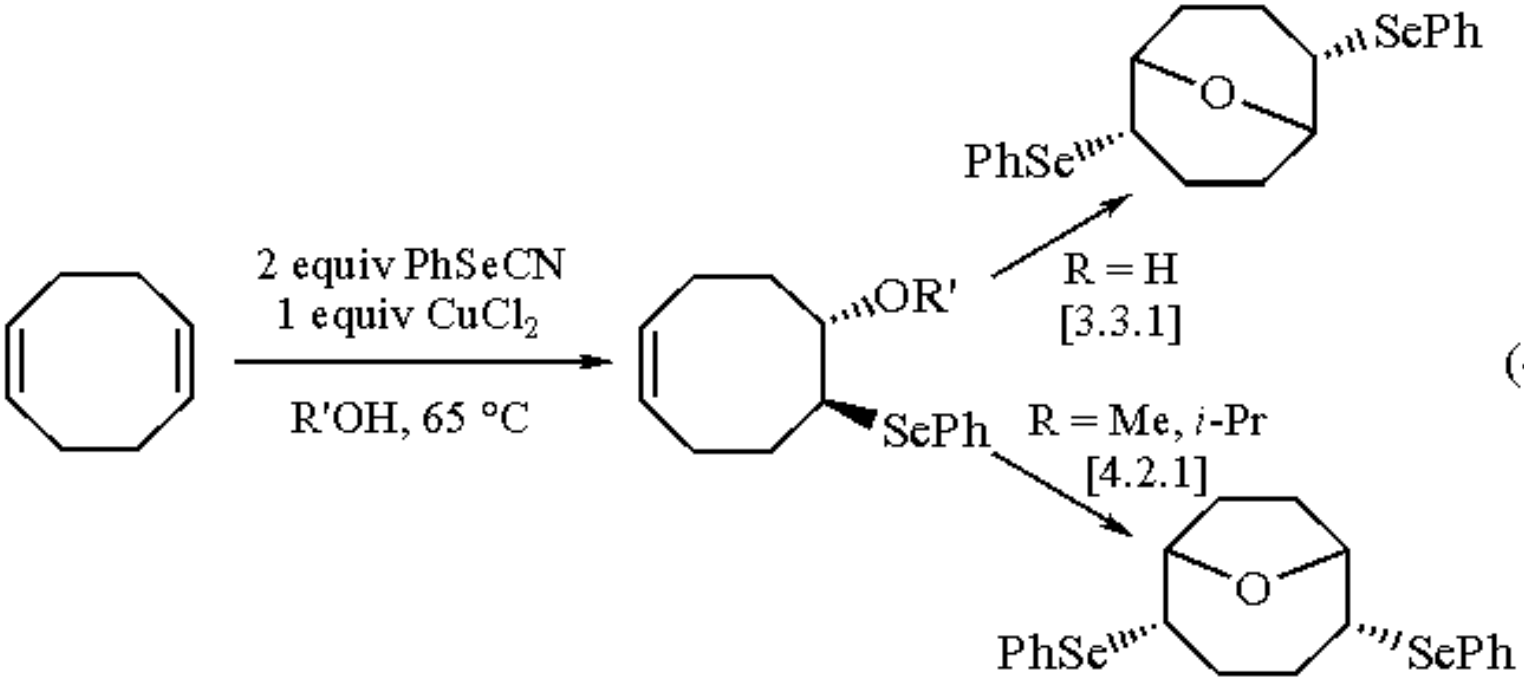

(4)

Solvent	Ratio [3.3.1]:[4.2.1]
MeOH	95:5
i-PrOH	82:18
t-BuOH	38:62
THF-H_2O	0:100

The isomer ratio depends upon the solvent used; a suitable choice of solvent results in a more selective formation of each isomer (eq 4). Synthesis of the [3.3.1] ethers is best achieved in methanol; aq THF provides the other isomer. The

intermediate formation of a β-hydroxyalkyl selenide, rather than the corresponding ether, proved to be responsible for the result observed in aq THF. The PhSeCN-$CuCl_2$ monitored oxyselenation reaction has been successfully applied to other dienes such as 1,5-hexadiene, diallyl ether, and diallyl sulfide (eq 5).

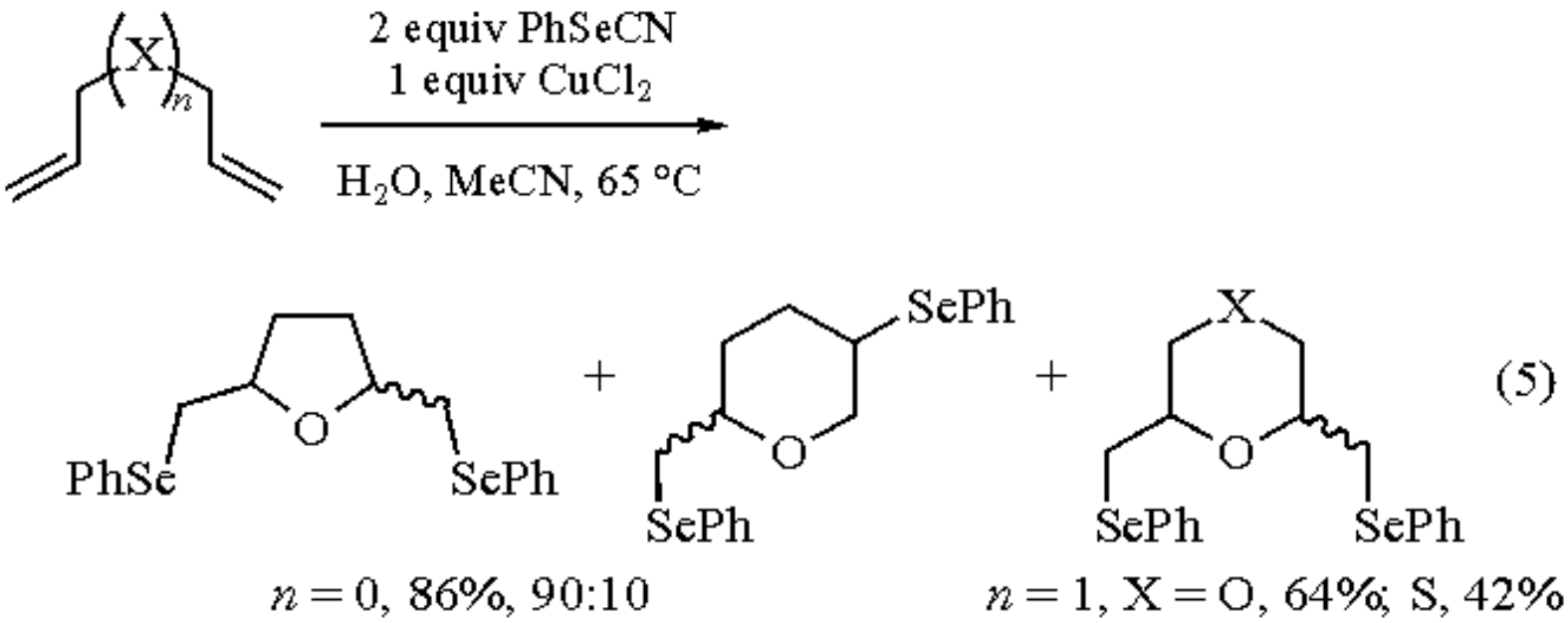

Related Reagents.

Copper(II) Chloride; ***o-Nitrophenyl Selenocyanate***; ***Phenyl Selenocyanate***.

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Phenylselenomethyllithium[1a-i]

$PhSeCH_2Li$

[22859-62-7] · C_7H_7LiSe · Phenylselenomethyllithium · (MW 177.04)

(nucleophilic introduction of phenylselenomethyl group; used for one-carbon homologation of alkyl halides, conversion of aldehydes to terminal epoxides, oxetanes, and tetrahydrofurans; synthesis of terminal alkenes from alkyl halides or carbonyl compounds)

Solubility: sol THF-pentane or ether-pentane.

Preparative Methods: [1a,1d-1f,5] has been prepared by (i) metalation of methyl phenyl selenide with lithium amides or butyllithium-TMEDA,[3,6] (ii) halogen-metal exchange from bromomethyl phenyl selenide and butyllithium,[7] or (iii) Se-Li exchange from bis(phenylseleno)methane and ***n-Butyllithium*** (THF, -78 °C, method of choice).[1b,2,3] The same reaction can be achieved in ether but requires the use of the more reactive ***s-Butyllithium***.[8]

Handling, Storage, and Precautions: stable at 0 °C in THF for more than 10 h,[2,3] but products resulting from its decomposition have been trapped in some cases at lower temperature even after a few minutes. Phenylselenomethyllithium seems to be in equilibrium with lithium benzeneselenolate and methylene.[4] Use in a fume hood.

General Discussion.

Phenylselenomethyllithium reacts with alkyl halides to produce alkyl phenyl selenides,[2,3] epoxides and oxetanes[4] to produce 3-hydroxy- and 4-hydroxyalkyl phenyl selenides, respectively, and aldehydes and ketones to produce 2-hydroxyalkyl phenyl selenides.[2,3,6-13]

Alkylation has been successfully achieved with ***Iodomethane***, primary alkyl halides, and terminal epoxides. In the latter two cases the presence of HMPA minimizes the products resulting from substitution of the electrophiles by lithium phenylselenolate (5% instead of 40%).[4]

Phenylselenomethyllithium adds to hindered or enolizable carbonyl compounds such as 2,2,6,6-tetramethylcyclohexanone or deoxybenzoin.[13] Phenylselenomethyllithium mainly produces the alcohol resulting from equatorial attack on reaction with 4-*t*-butylcyclohexanone (THF, -78 °C, axial:equatorial alcohol = 85:15).[11] It adds on the carbonyl group of enones if the reaction is carried out in THF and 1,4 in THF/HMPA.[1,14-17] The latter conditions have been successfully used to produce a valuable intermediate in the synthesis of (+)-pederin from an α,β-unsaturated

lactone.[15,16]

Phenylselenomethyllithium is a valuable reagent for homologation.[1b] Phenylselenoalkanes, prepared by alkylation of phenylselenomethyllithium, can be transformed to alkanes by reduction with ***Raney Nickel***,[18] ***Lithium-Ethylamine***[18] or, more conveniently, by ***Tri-n-butylstannane*** or ***Triphenylstannane*** (eq 1).[19]

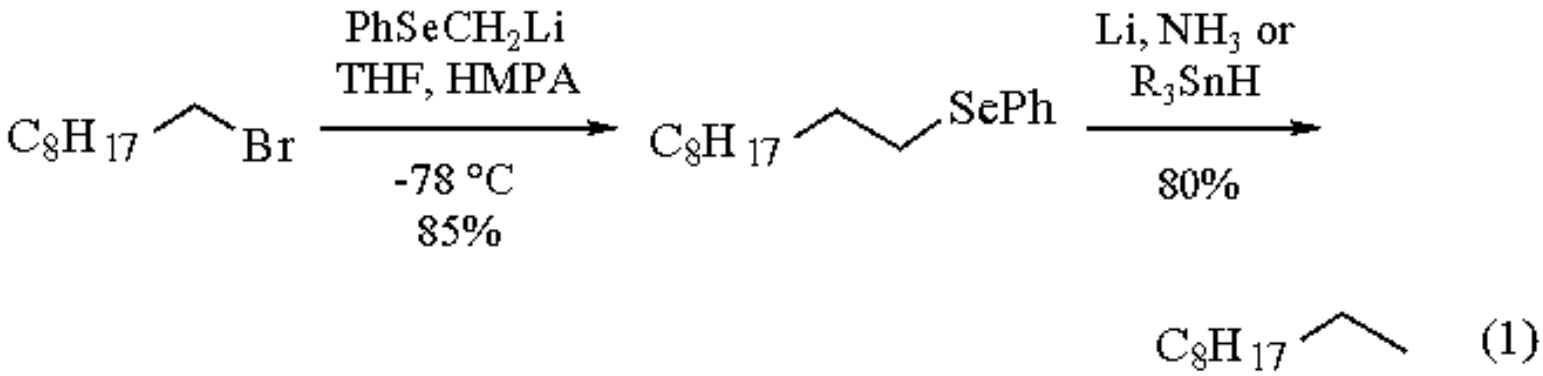

(1)

The phenylseleno group can be replaced by iodide.[20] The reaction proceeds through a selenonium salt, works with functionalized alkyl phenyl selenides such as 3-(hydroxy)nonyl phenyl selenide (eq 2),[4] and allows the one-carbon homologation of primary alkyl halides.[20] A wider range of nucleophiles (I^-, Br^-, Cl^-, OH^-, N_3^-, MeOH,[21,22] PhS^-, CN^-) can be used[23] if the selenide is oxidized to a selenone (eq 3).[24] In the transformations reported (eqs 2 and 3), phenylselenomethyllithium has played alternatively the role of $LiCH_2X$ (X = halogen), $LiCH_2N_3$, $LiCH_2OH$, $LiCH_2OMe$, $LiCH_2SPh$, and $LiCH_2CN$, respectively.

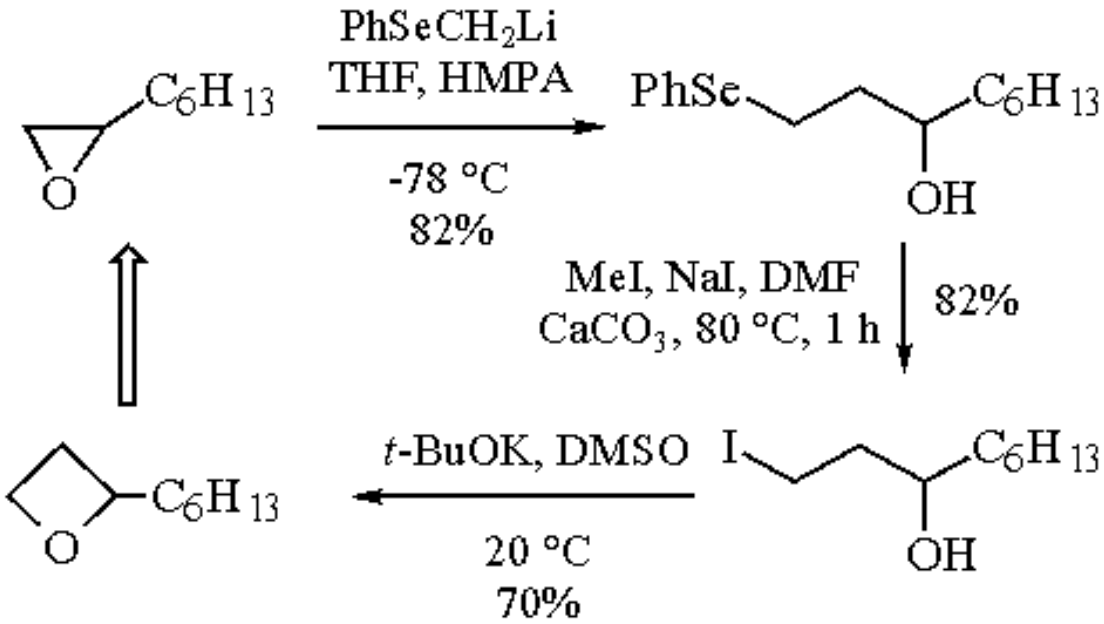

(2)

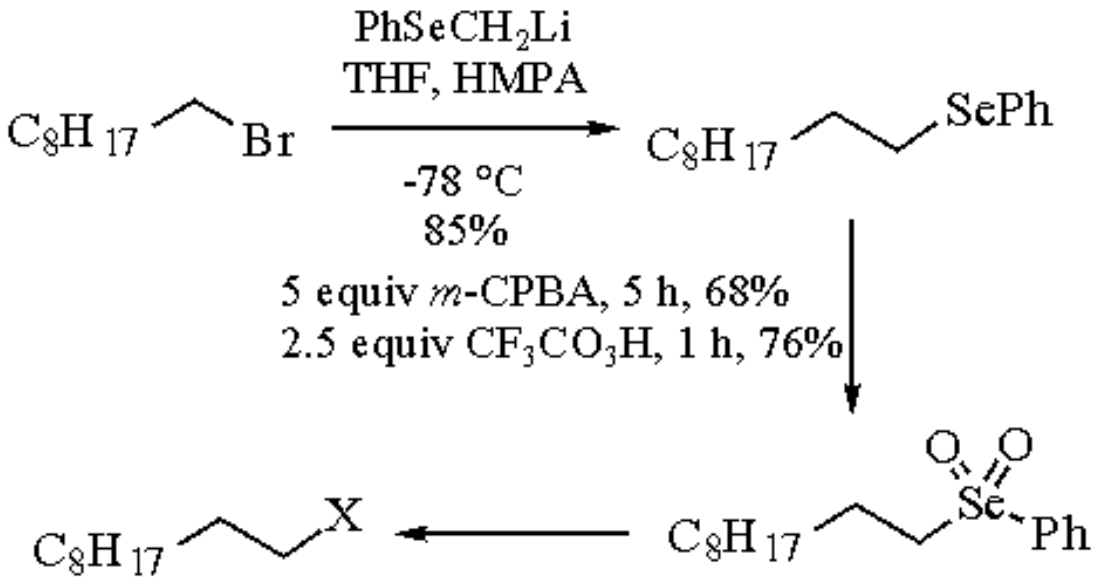

(3)

X = I (2 equiv NaI, 20 °C, 1 h, 97%)
X = Br (1.5 equiv $MgBr_2$ or EtMgBr, 20 °C, 1 h, 77%)
X = Cl (1.5 equiv BuMgCl, 20 °C, 1 h, 51%)
X = N_3 (5 equiv NaN_3, 20 °C, 0.7 h, 93%)
X = OH (H_2O, 80 °C, 1.25 h, 95% or KOH, 80 °C, 22 h, 76%)
X = OMe (1.1 equiv MeONa, 20 °C, 3 h, 73%)
X = SPh (1.1 equiv PhSNa, 20 °C, 3 h, 94%)
X = CN (2 equiv KCN, 75 °C, 2 h, 66%)

Primary alkyl selenides are converted to 1-alkenes on oxidation to the selenoxide with ***Hydrogen Peroxide***,[25] ***Sodium Periodate***,[25] or ***t-Butyl Hydroperoxide***,[26] or by treatment with methyl fluorosulfonate and base-catalyzed elimination of the selenonium intermediate (eq 4).[27]

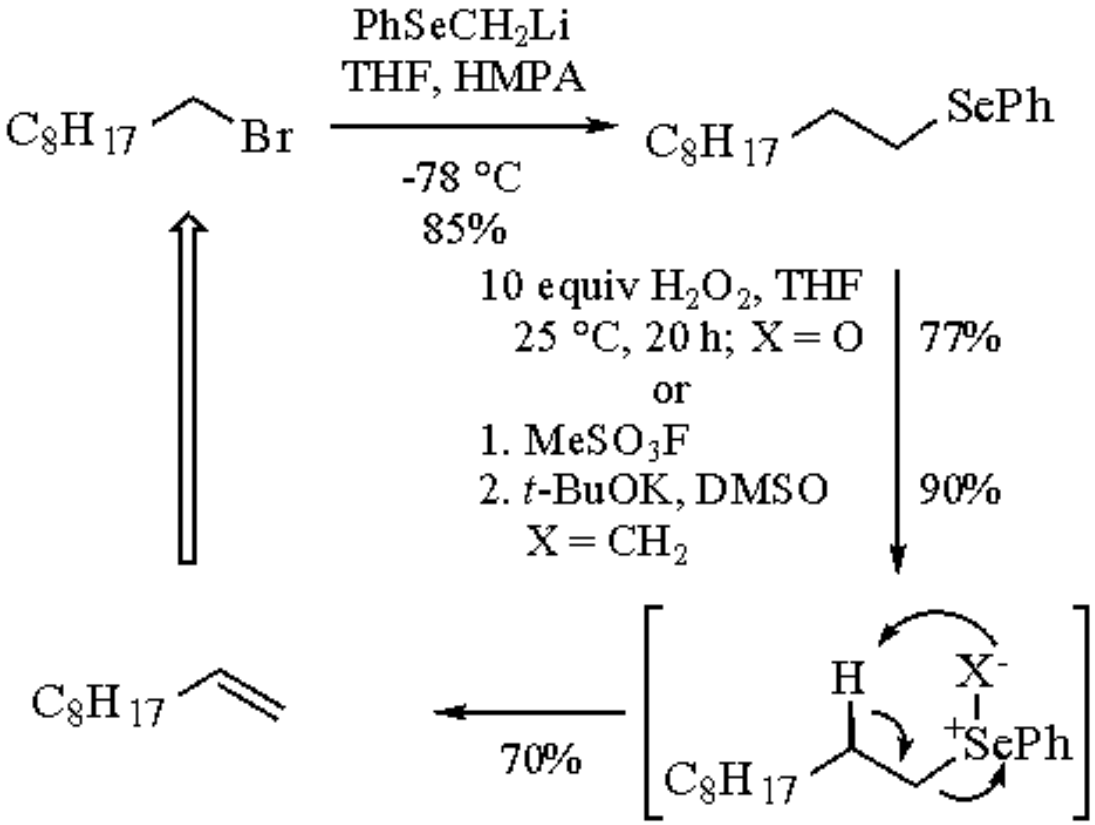

(4)

2-Hydroxyalkyl phenyl selenides, easily prepared from phenylselenomethyllithium and carbonyl compounds, are valuable precursors for the following.

Terminal Epoxides.[10,13,28,29]

Activation of the selenium moiety can be achieved by formation of selenonium salts (eq 5), oxidation to selenone (***m-Chloroperbenzoic Acid***, CH_2Cl_2, 20 °C)[10] or treatment with thallium(I) ethoxide in chloroform, which produces a dichlorocarbene intermediate (eq 6)[30]

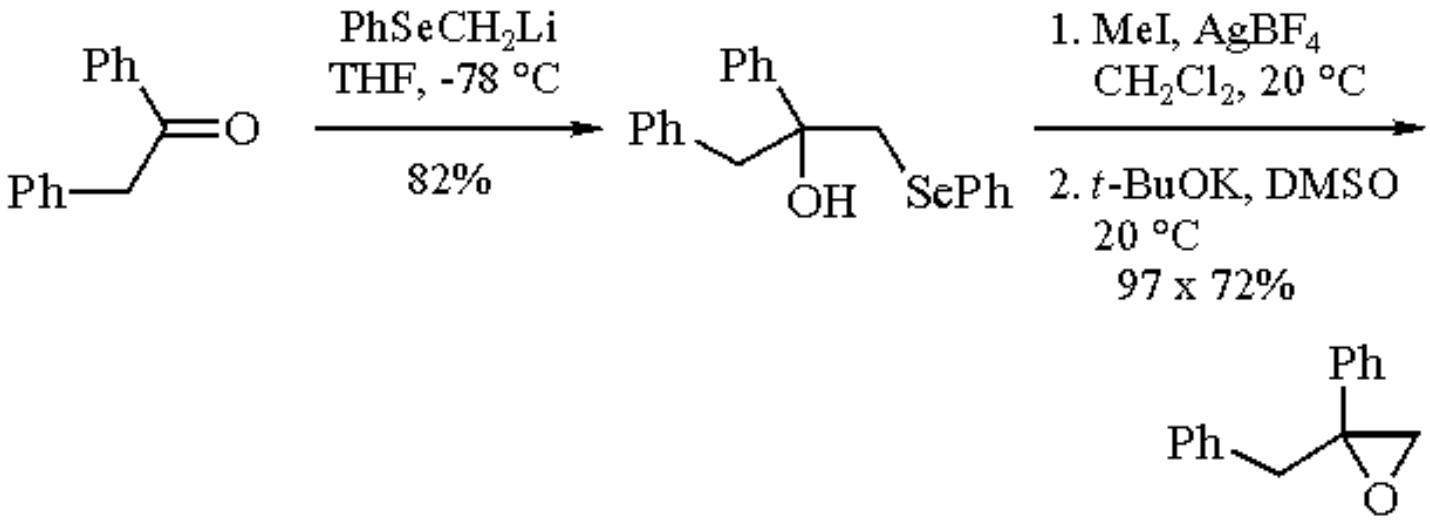

(5)

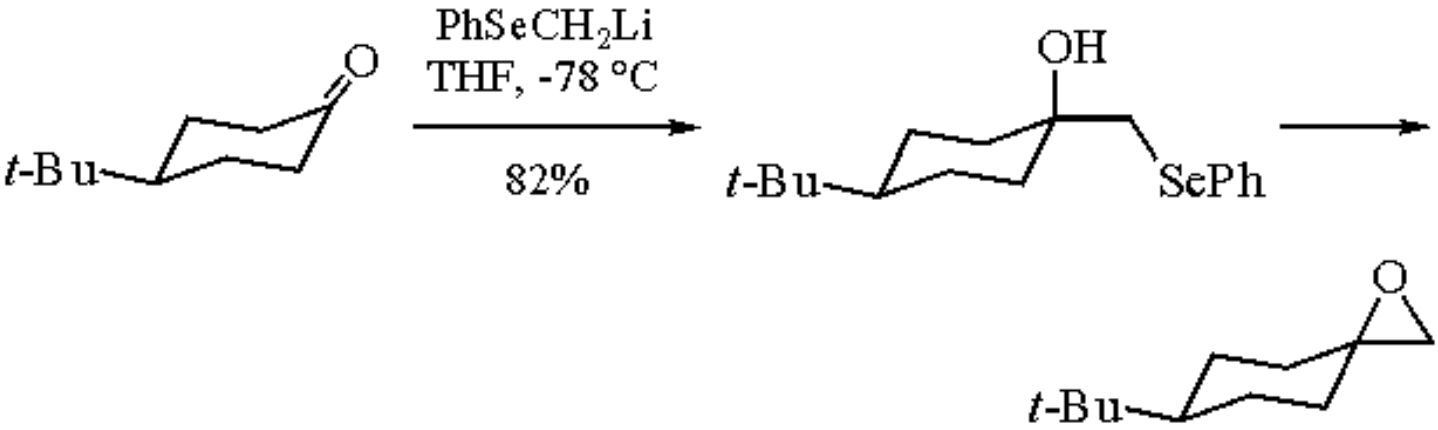

(6)

1. *m*-CPBA, CH_2Cl_2, 20 °C, 4 h; 2. aq K_2CO_3, 20 °C, 0.5 h 44%
5.5 equiv TlOEt, $CHCl_3$, 20 °C, 24 h 80%

Terminal Alkenes.[12]

This reaction, which probably involves the intermediate formation of a seleniranium ion, is best achieved with ***Methanesulfonyl Chloride*** in the presence of ***Triethylamine***[6,12] or with ***p-Toluenesulfonic Acid*** (eq 7).[31]

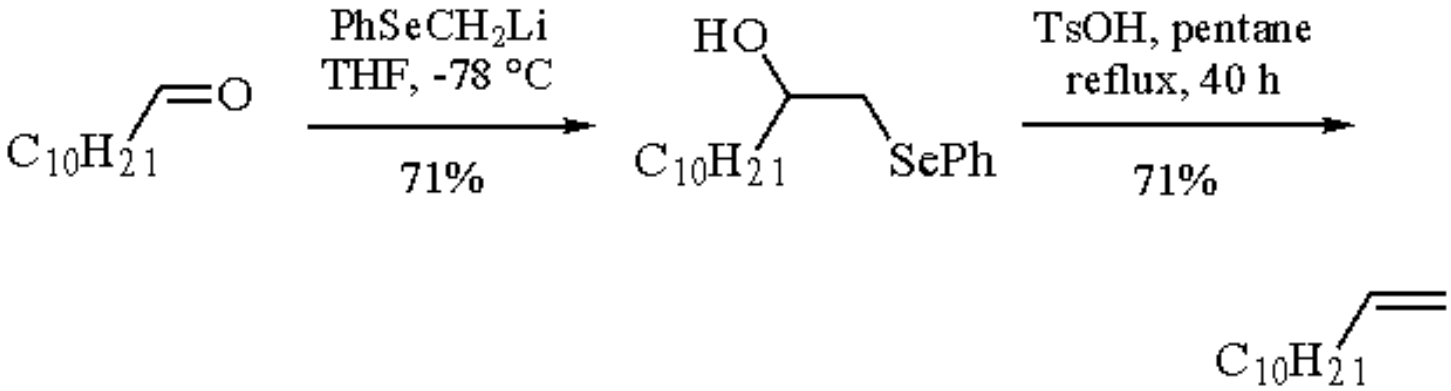

(7)

Ketones.

Ketones, resulting from the rearrangement of the intermediate 2-hydroxyalkyl selenones, are obtained on reaction of 2-hydroxyalkyl selenides derived from aromatic ketones with *m*-CPBA (eq 8).[10,28] Extension of this reaction to 1-phenyl-2-(phenylseleno)ethanol affords methyl phenylacetate in very good yield (86%) resulting from oxidation of the phenylacetaldehyde intermediate by the excess of *m*-CPBA used (3-5 equiv, MeOH, reflux, 3 h, eq 9).[32]

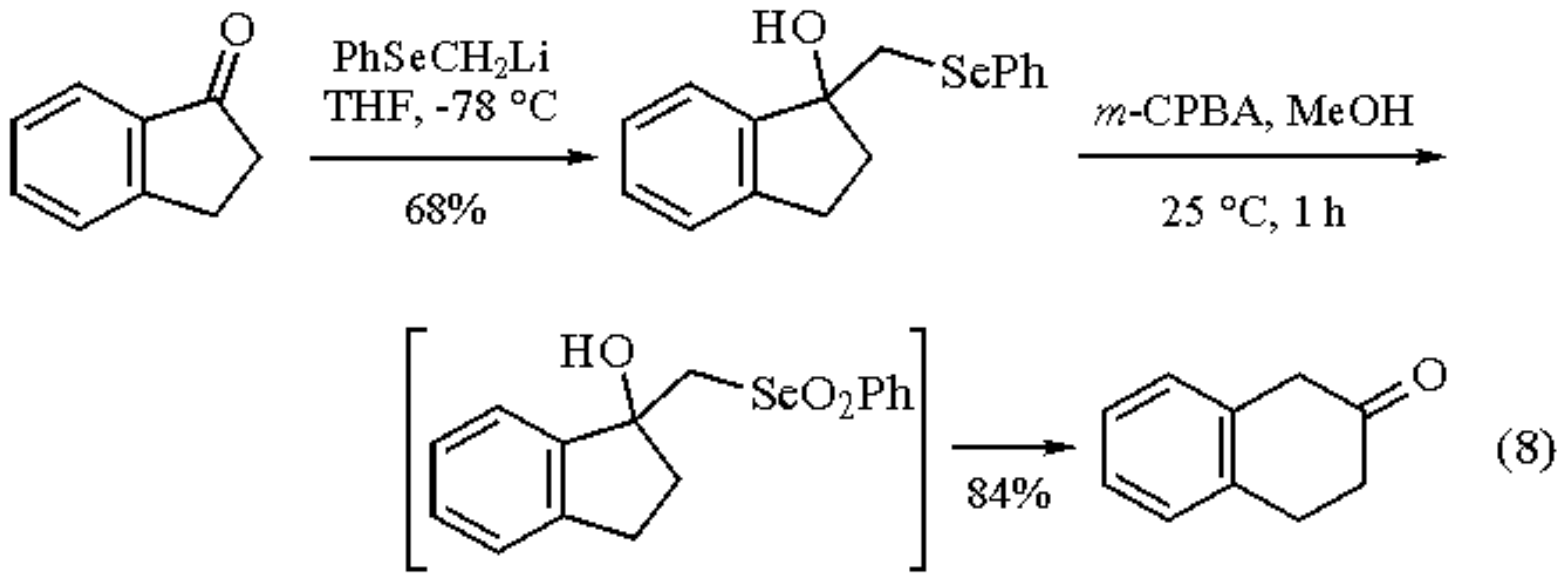

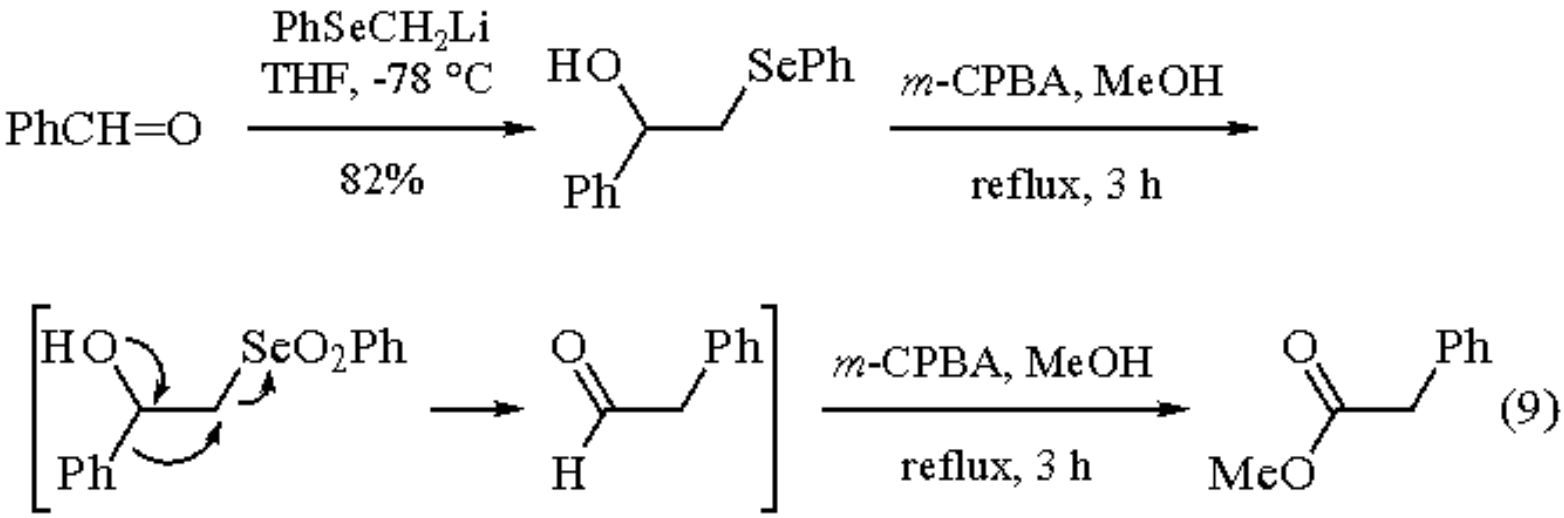

The processes reported above allow the synthesis of terminal epoxides and alkenes from a carbonyl compound in a way similar to that involving methylenesulfuranes and methylenetriphenylphosphorane. Phenylselenomethyllithium has the advantage that terminal epoxides and alkenes derived from hindered or enolizable carbonyl compounds, which are unavailable from ylides, can be prepared.[1g]

3-Hydroxyalkyl and 4-hydroxyalkyl phenyl selenides are available from phenylselenomethyllithium and terminal epoxides or oxetanes. They have been transformed to oxetanes (eq 2) and to tetrahydrofurans.[4] The whole process allows the stepwise homologation of carbonyl compounds to epoxides, oxetanes, and tetrahydrofurans.[4]

Phenylselenomethyllithium is the first member of the series of α-selenoalkyllithiums. These can be prepared on reaction of butyllithiums with selenoacetals, which are readily available from carbonyl compounds and phenyl- or methylselenols. The reactions reported above can be advantageously extended to the higher homologs of selenides, but some further examples must be given (eqs 10-12).[1a,1c,1e-i,33] The synthesis of the most strained or hindered alkenes is best achieved from methylseleno derivatives using ***Phosphorus(III) Iodide*** as reagent.[1g,34] Methylseleno derivatives are also more appropriate for the synthesis of epoxides.[1g,29,34] In such cases best results are obtained by using the two-step sequence involving the intermediate formation of β-hydroxyalkylselenonium salts. This allows the synthesis of the whole range of epoxides including those derived from α,β-unsaturated or hindered carbonyl compounds as well as those derived from selenoalkyllithiums bearing two alkyl groups on their carbanionic center. The latter compounds cannot be

produced using the dichlorocarbene method since pinacol-type rearrangement leads instead to a ketone.[35-38]

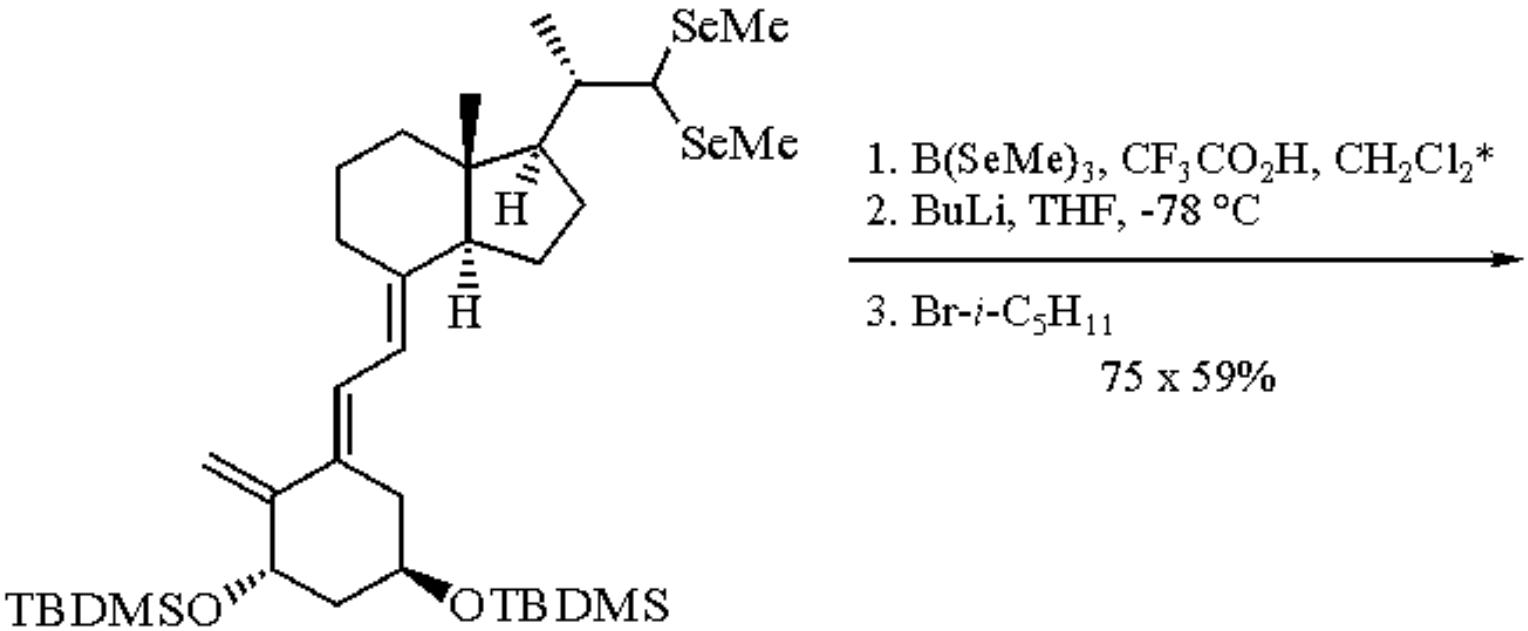

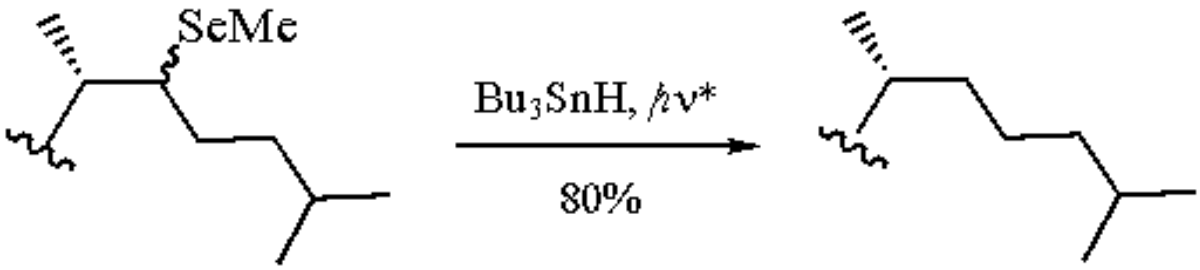

(10)

* carried out on the diene-SO_2 adduct

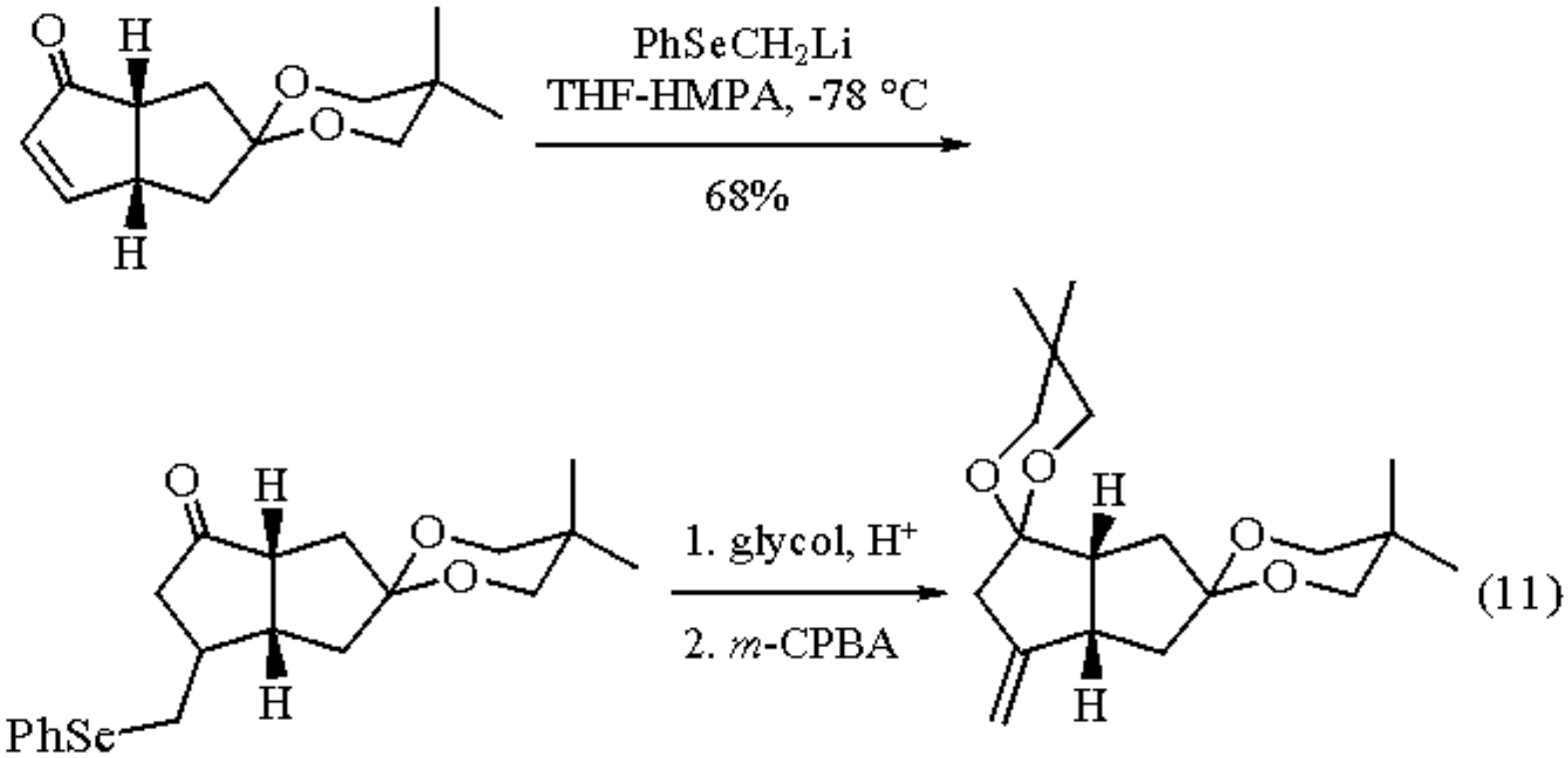

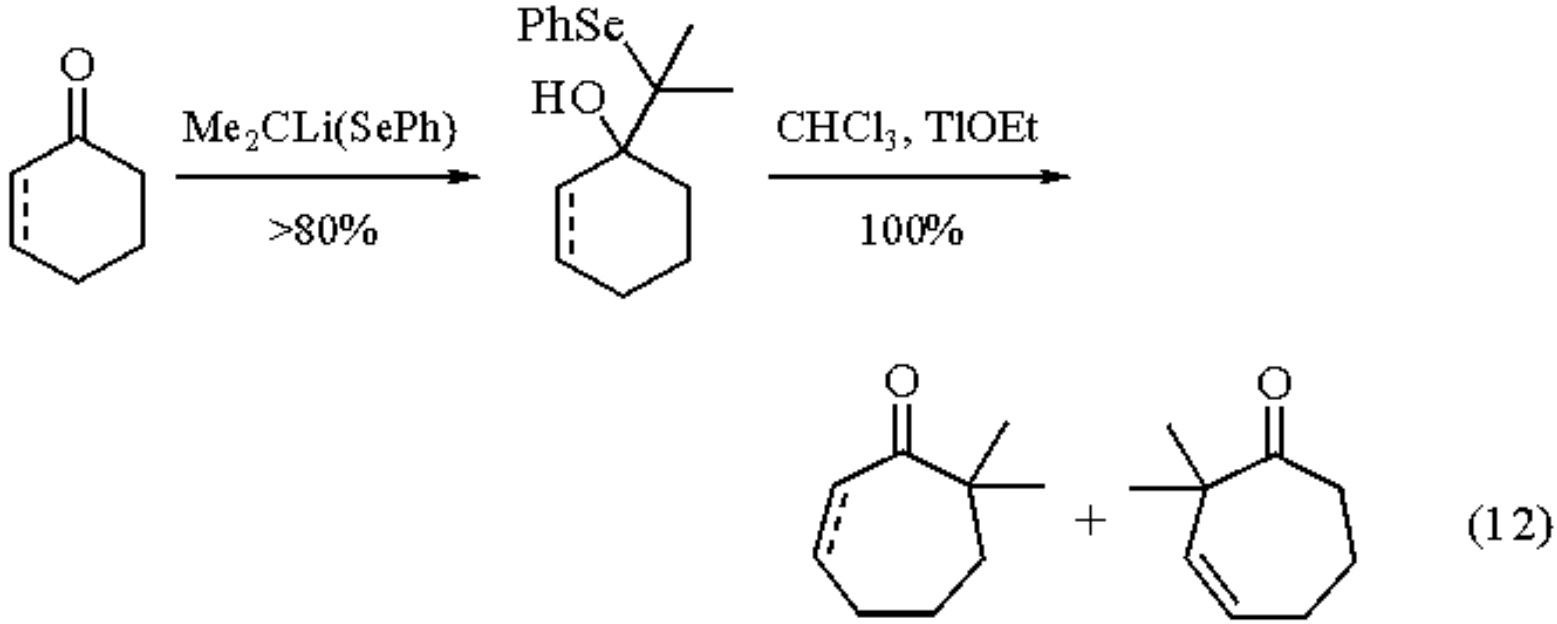

from cyclohexanone	100%	-
from cyclohexenone	92%	8%

Related Reagents.

Bis(phenylthio)methane; ***Dibromomethane-Zinc-Titanium(IV) Chloride***; ***Methylenetriphenylphosphorane***; ***Phenylthiomethyllithium***.

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Phenyl(seleno)phosphonic Dichloride[1]

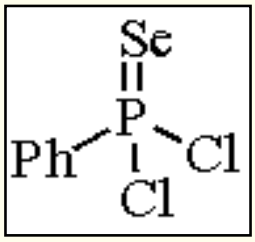

[39078-30-3] · $C_6H_5Cl_2PSe$ · Phenyl(seleno)phosphonic Dichloride · (MW 257.94)

(reagent for effecting oxygen-selenium exchange reactions of polarized carbonyl groups;[1] exchanges O for Se in some O-heterocycles[1])

Physical Data: bp 60 °C/0.01 mmHg; suffers progressive decomposition into $PhPCl_2$ and Se on being heated.

Solubility: sol most inert solvents; most useful are xylene, toluene, benzene, dichloromethane.

Preparative Methods: $PhPCl_2$ is treated at ambient temperature with ca. 6 mol % ***Aluminum Chloride*** under dry N_2 followed by ***Selenium*** powder. The resulting $PhP(Se)Cl_2$ is distilled in a good vacuum.[2] More convenient is to heat $PhPCl_2$ with a 20 mol % excess of powdered black Se at 170-175 °C under dry N_2 for 40 min.[1] The $PhP(Se)Cl_2$, which is formed quantitatively, is cooled and dissolved in dry xylene. The mixture is filtered through a glass frit to remove the excess Se and sufficient additional xylene is added to give a 2 M solution. Other inert solvents may be used in place of xylene.

Handling, Storage, and Precautions: $PhP(Se)Cl_2$, alone or in solution, is sensitive to moisture. Solutions of $PhP(Se)Cl_2$ should be stored in dark bottles which are tightly closed by crown or screw caps fitted with a septum. Required volumes are transferred by means of graduated syringes. For best results, $PhP(Se)Cl_2$ and solutions thereof should be used within 2-3 days after preparation. Reactions involving prolonged times should be carried out in a dry inert atmosphere.

Oxygen-Selenium Exchange Reactions.

Various types of carbonyl compounds in which the carbonyl group is highly polarized undergo O-Se exchange reactions with $PhP(Se)Cl_2$. The carbonyl substrate is allowed to react with an aliquot of a 2 M solution of $PhP(Se)Cl_2$ in xylene, either with or without addition of more xylene or a different inert solvent. Tertiary amides of aliphatic[1], aromatic[1], and electron-rich heterocyclic carboxylic acids[3] are converted into the corresponding selenocarboxamides (eqs 1-4), and *N*-substituted lactams yield the corresponding *N*-substituted selenolactams (eq 5).[1]

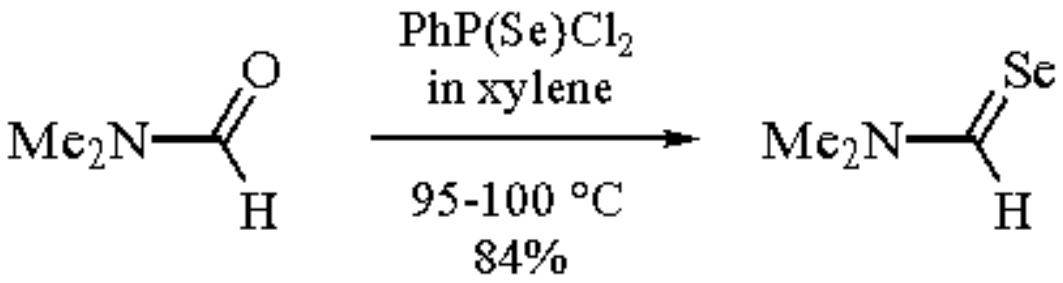

(1)

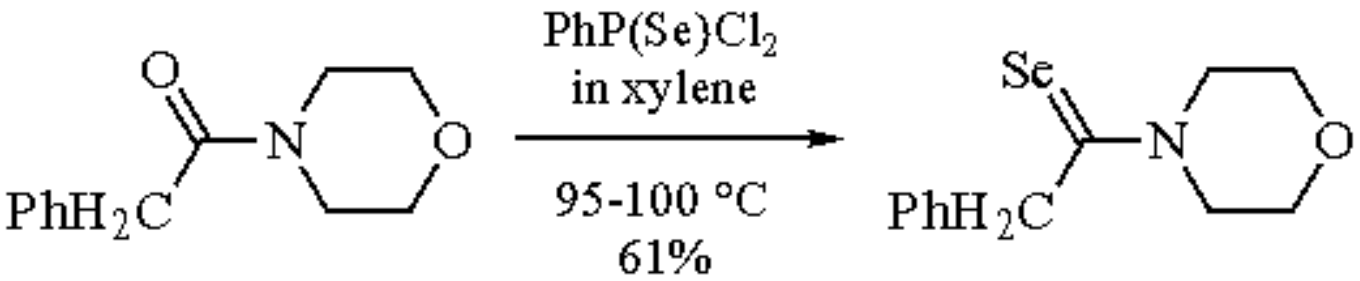

(2)

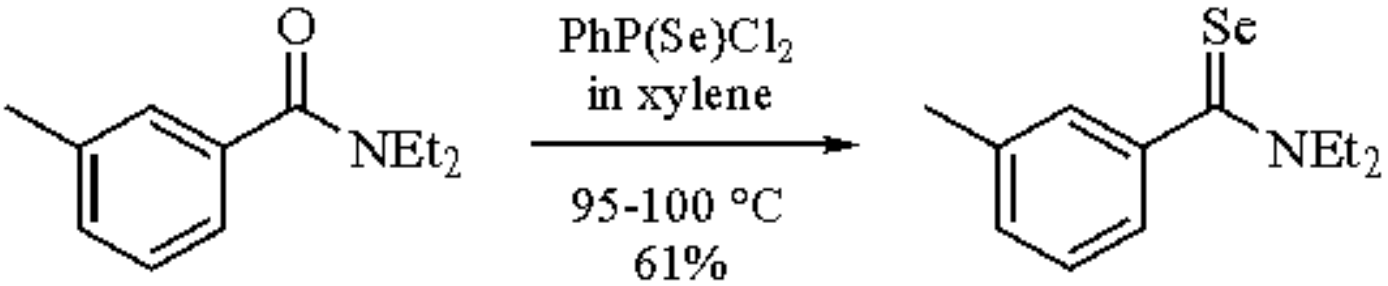

(3)

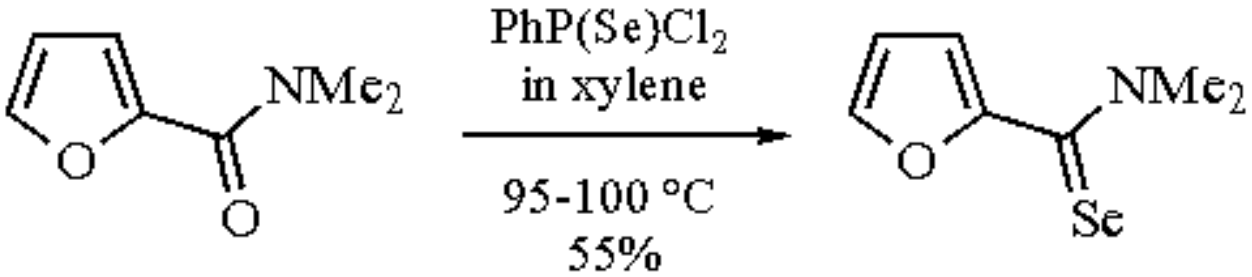

(4)

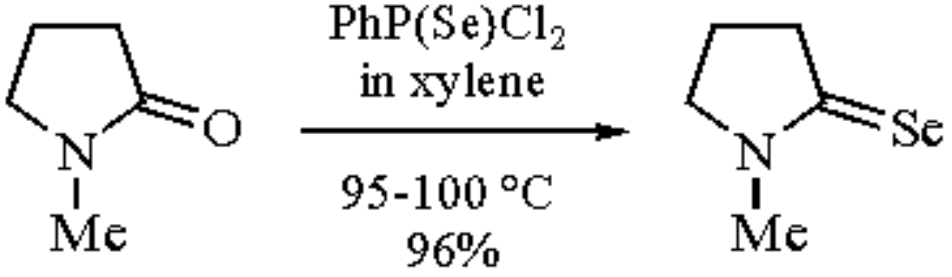

(5)

A recommended workup procedure for small-scale (<25 mmol) reactions is to add chromatographic alumina (activity I-II) to the reaction solution, transfer the resulting slurry to a column of alumina (activity II-III), and elute. Unreacted $PhP(Se)Cl_2$ and its reaction product $PhP(O)Cl_2$ are retained on the basic column.

Indolizine-1- and 3-carbaldehydes are converted into the corresponding indolizineselenocarbaldehydes at room temperature (eq 6).[1] In one case a 1,2-dithiol-3-one was converted into the corresponding 1,2-dithiol-3-selone (eq 7).[1]

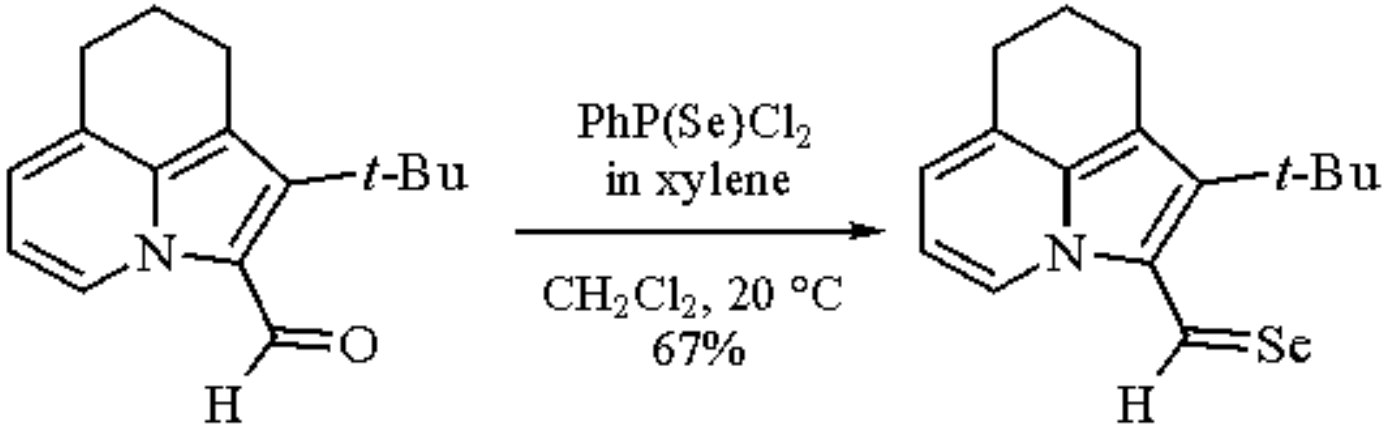

(6)

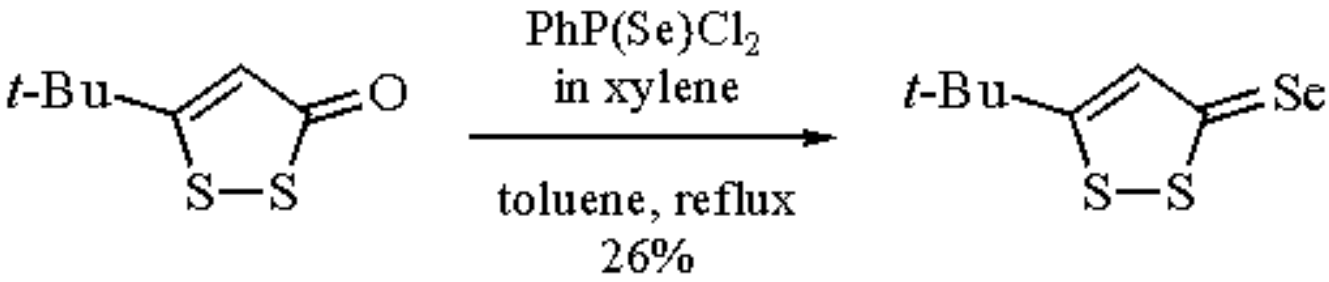

(7)

Conversion of Oxygen Heterocycles into Selenium Heterocycles.

1-Oxa-6,6aλ^4-dithiapentalenes and 6-oxa-6aλ^4-thia-1,2-diazapentalenes, which are masked carbonyl compounds, react at room temperature with $PhP(Se)Cl_2$ in the presence of ***Triethylamine*** to give the corresponding Se-containing heterocycles (eqs 8 and 9).[1] The Et_3N suppresses acid-catalyzed side-reactions

of the substrates.

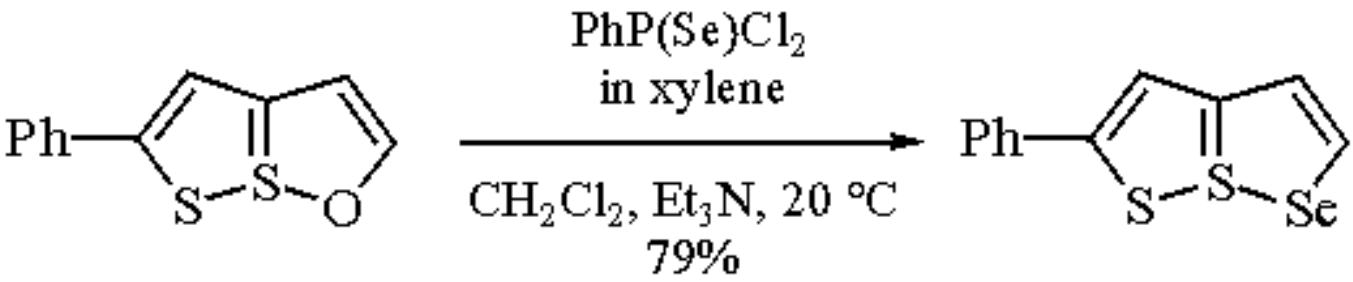

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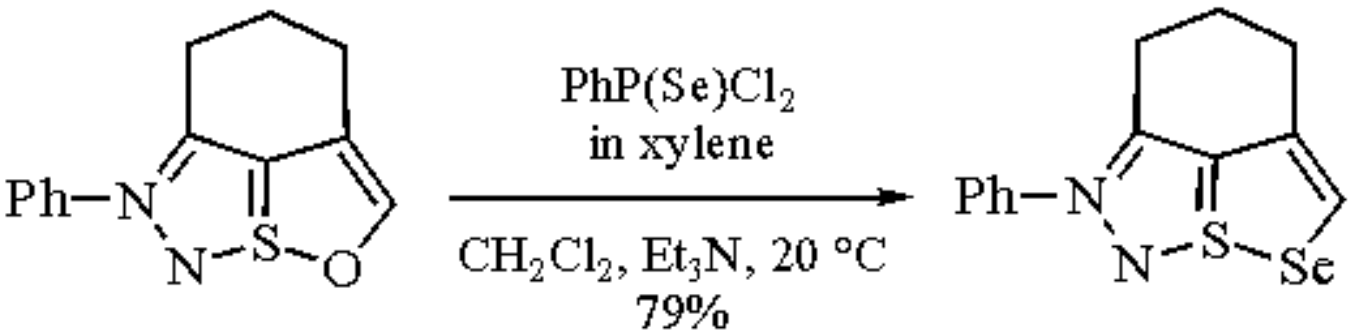

(9)

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N-Phenylselenophthalimide[1]

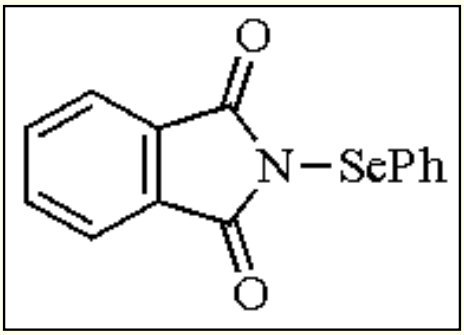

[71098-88-9] · $C_{14}H_9NO_2Se$ · *N*-Phenylselenophthalimide · (MW 302.20)

(reagent for electrophilic phenylselenenylation of alkenes, dienes, enols, and other nucleophiles)

Alternate Name: NPSP.

Physical Data: mp 171-175 °C (dec).

Form Supplied in: colorless solid.

Preparative Methods: prepared in 87% yield by the reaction of ***Benzeneselenenyl Chloride*** with potassium ***Phthalimide*** in hexane.[1]

Handling, Storage, and Precautions: indefinitely stable when stored at -20 °C in the dark. Use in a fume hood.

Selenenylation.

N-Phenylselenophthalimide is a very mild reagent for electrophilic selenenylation and reacts with a wide variety of organic substrates to provide products bearing the PhSe group. The generalized stepwise conversion of an alkene to a functionalized selenide with this reagent is shown in eq 1.

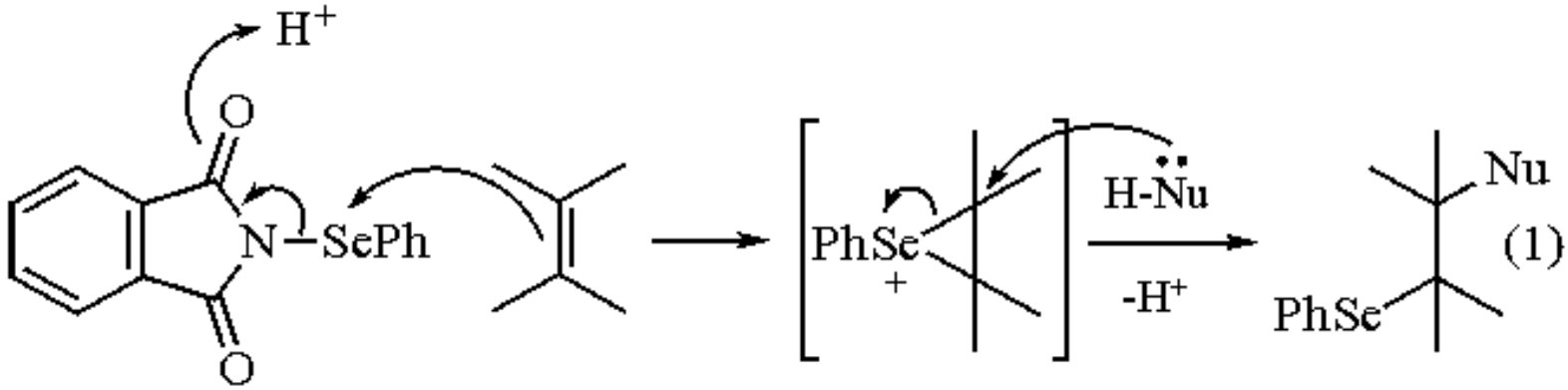

Various alkenes have been found to react in the intermolecular sense with nucleophiles in condensation reactions mediated by NPSP. Representative examples are given in eqs 2 and 3.[1-3]

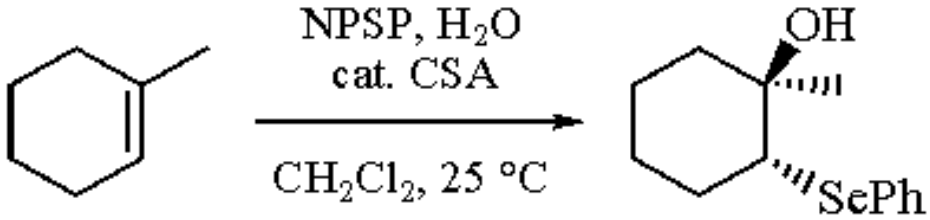

(2)

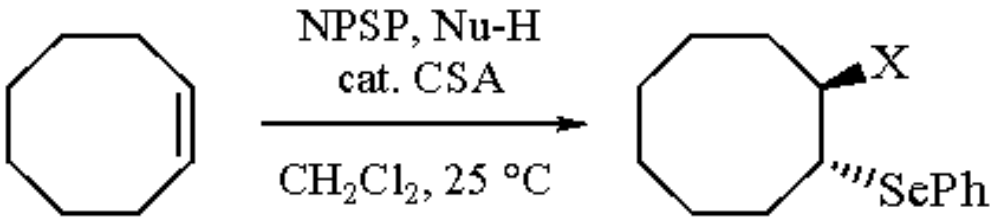

(3)

Nu = HO; X = OH	90%
Nu = OMe; X = OMe	97%
Nu = F; X = F	80%

Dialkenes react with NPSP in the presence of water in a closely related manner to provide cyclic ethers with the net incorporation of two PhSe moieties (eq 4).[3]

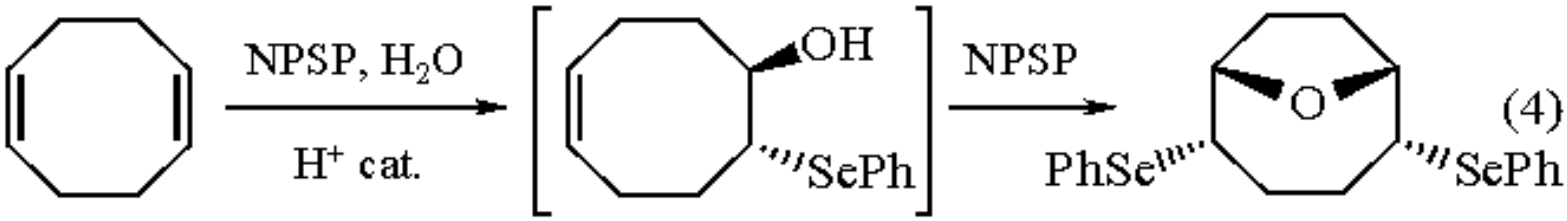

(4)

NPSP is a very efficient reagent for effecting the cyclization of unsaturated substrates containing internal nucleophiles and has been used for macrocyclizations (eqs 5-10)[3] as well as cyclizations of homogeranic acid derivatives.[4] In addition, NPSP has been used to effect annulations leading to carbohydrates.[5]

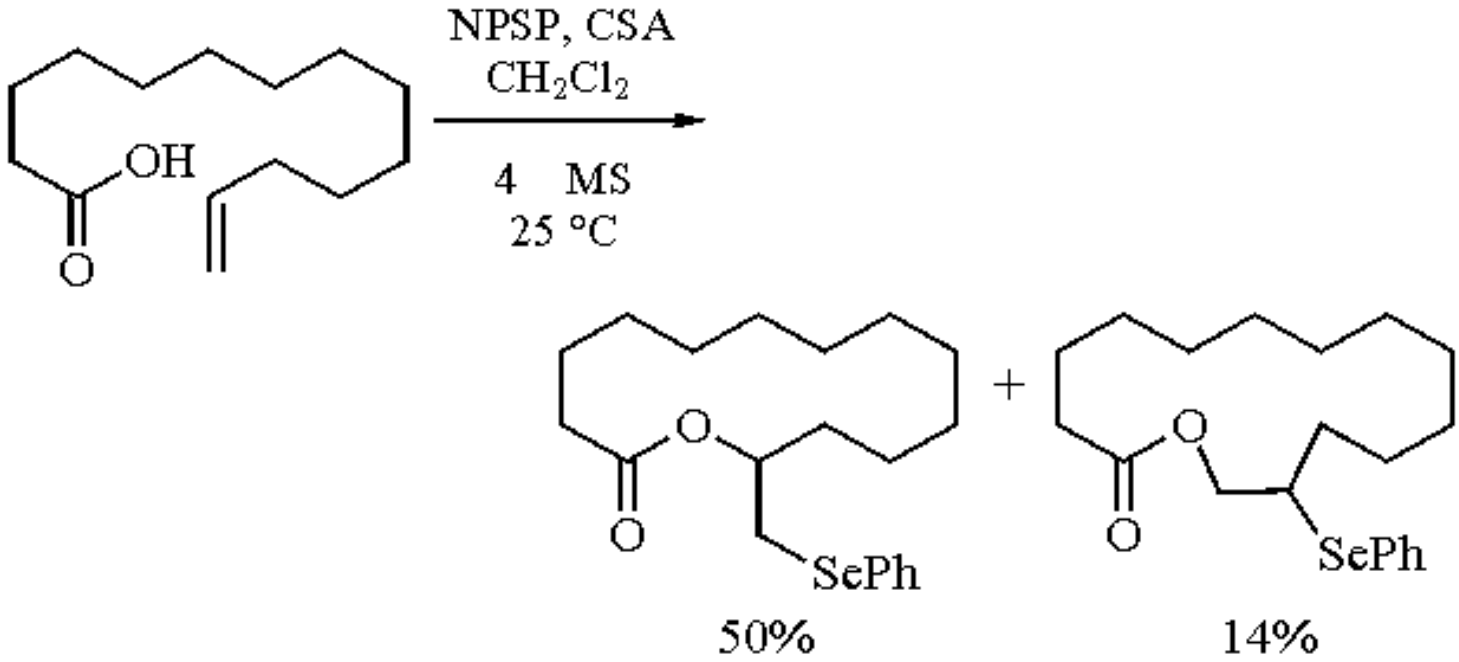
NPSP, CSA
CH_2Cl_2
4 MS
25 °C
OH
O
O
O
SePh
+
O
O
SePh
50%
14%

(5)

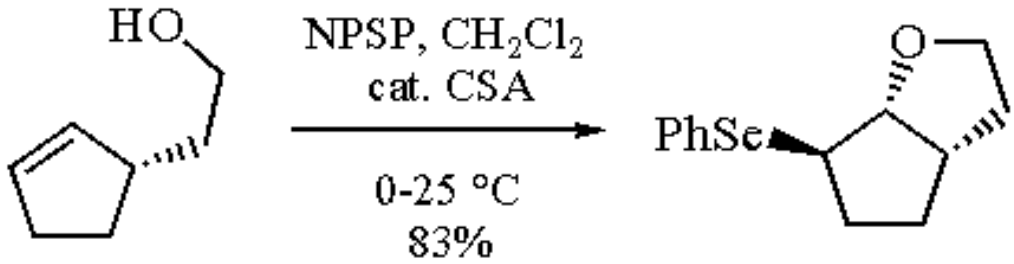
HO
NPSP, CH_2Cl_2
cat. CSA
0-25 °C
83%
O
PhSe

(6)

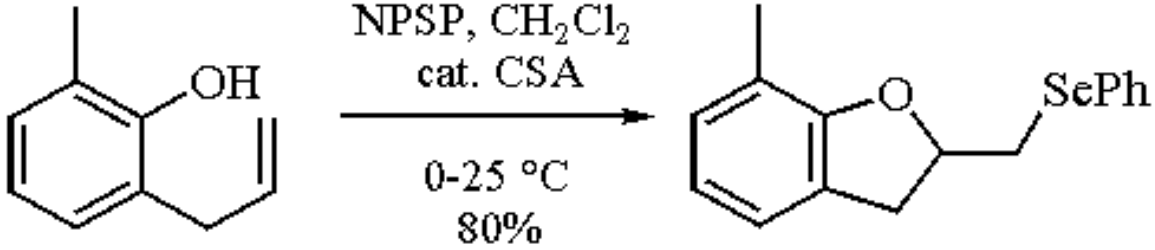
OH
NPSP, CH_2Cl_2
cat. CSA
0-25 °C
80%
O
SePh

(7)

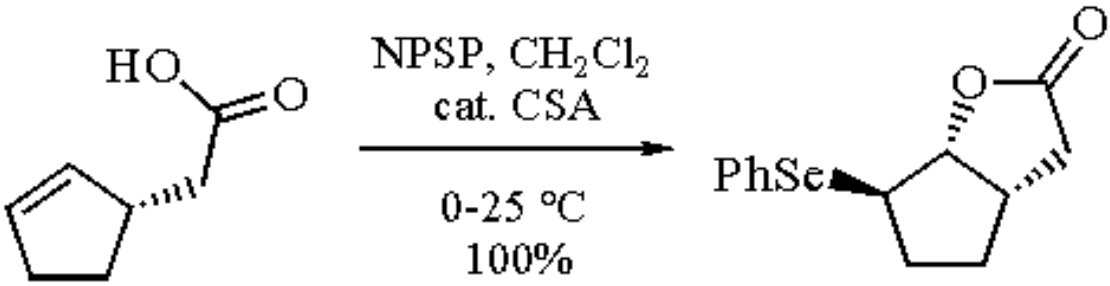
HO
O
NPSP, CH_2Cl_2
cat. CSA
0-25 °C
100%
O
O
PhSe

(8)

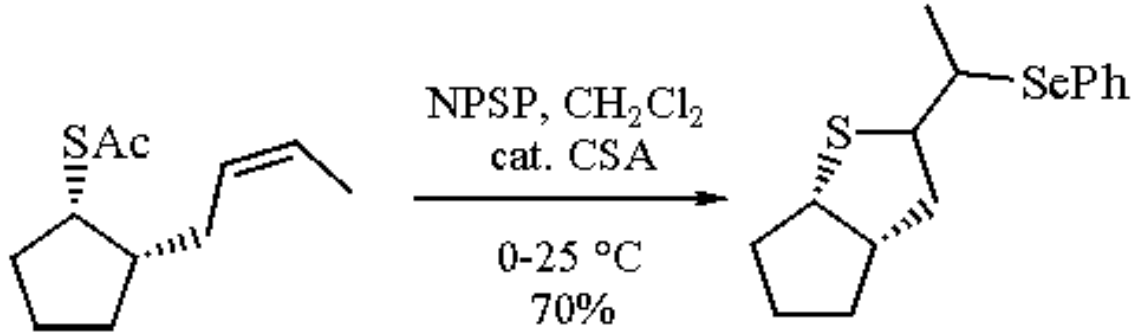

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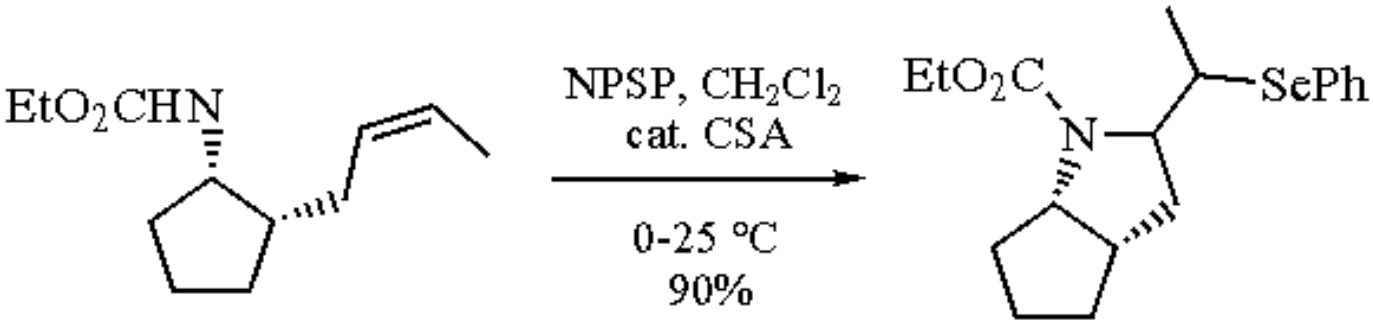

(10)

In several instances the use of NPSP has been found advantageous when compared to the more classical reagents ***Benzeneselenenyl Bromide*** or ***Benzeneselenenyl Chloride***. In this connection the latter reagents have been reported to be useful for the selenenylative cyclization of unsaturated alcohols,[6] carboxylic acids,[7] thio compounds,[8] and urethanes.[9]

Selenolactonization of alkynoic acids also proceeds efficiently in the presence of NPSP (eq 11).[10]

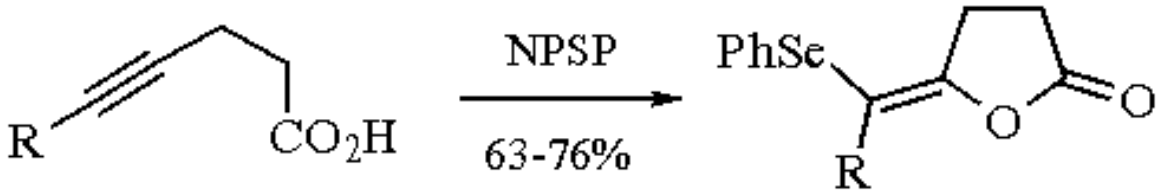

(11)

In addition, suitably disposed β-keto ester moieties can be induced to stereoselectively cyclize onto alkenes in the presence of NPSP (eq 12).[11]

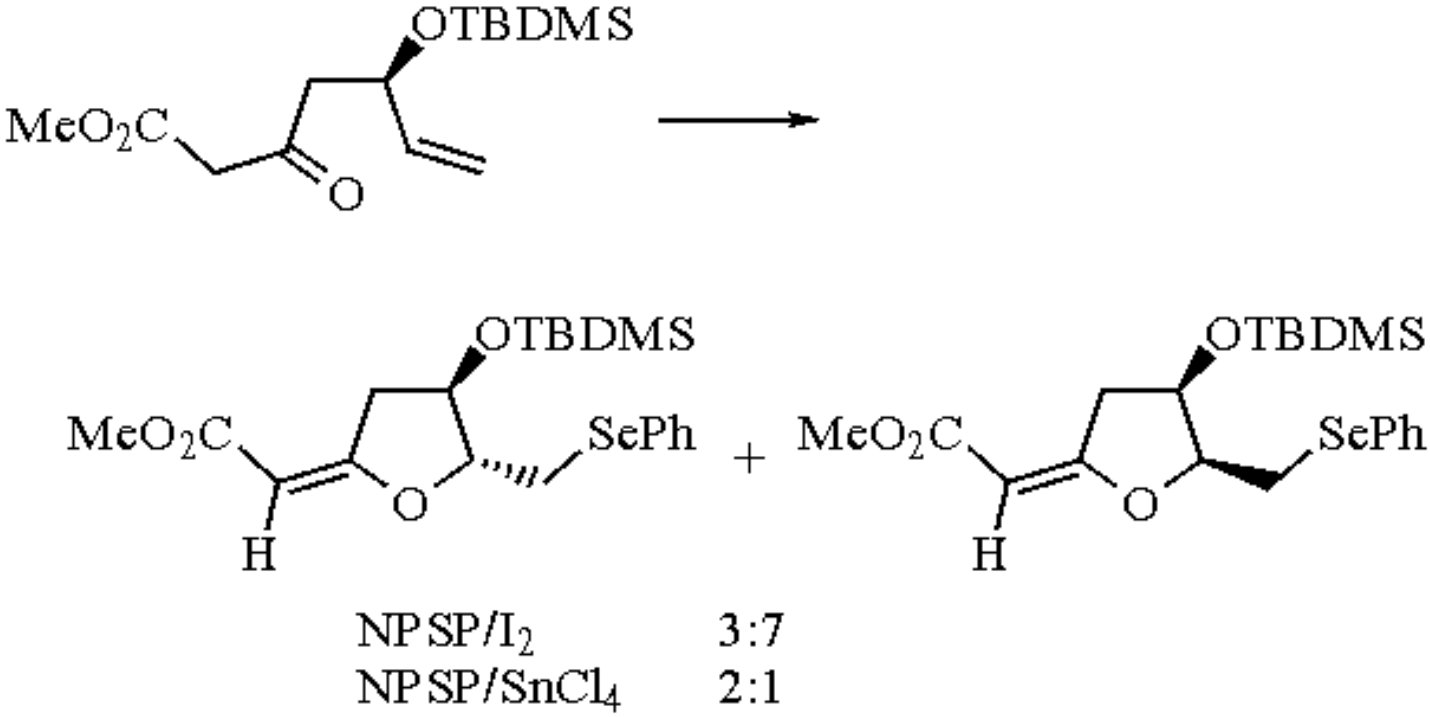

(12)

Heterocyclizations leading to oxazolidine derivatives have been reported to proceed efficiently via the selenenylation of alkenyl amides by NPSP (eq 13).[12] Danishefsky and collaborators have reported an interesting phenylselenenylation-radical functionalization sequence using NPSP[13] and have also used this reagent in the synthesis of mitomycin congeners.[14]

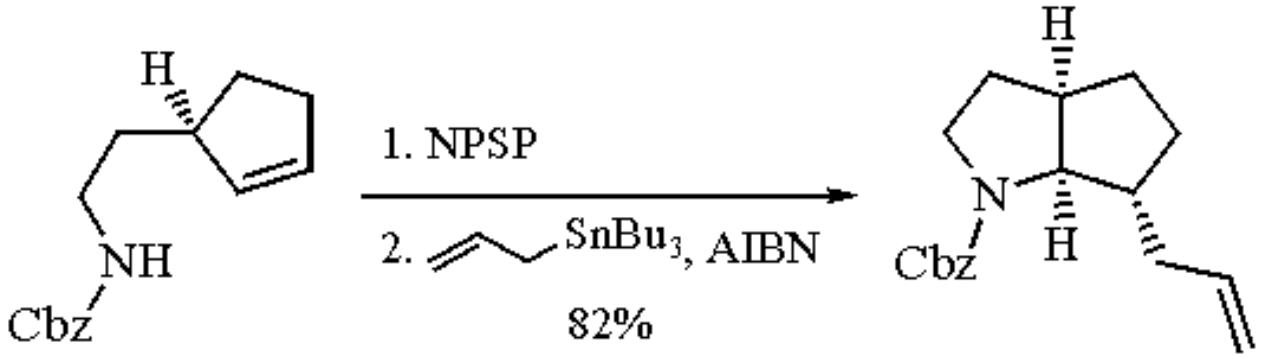

(13)

Ley and co-workers have published extensively on the use of NPSP in the presence of Lewis acids to effect carbocyclizations (e.g. eq 14).[15] In addition, these authors have utilized NPSP for the synthesis of spiroacetals.[16] For the majority of the preceding transformations, NPSP has been found the superior reagent both in terms of chemical efficiency as well as the mild nature of the reaction conditions that are typically employed.[17]

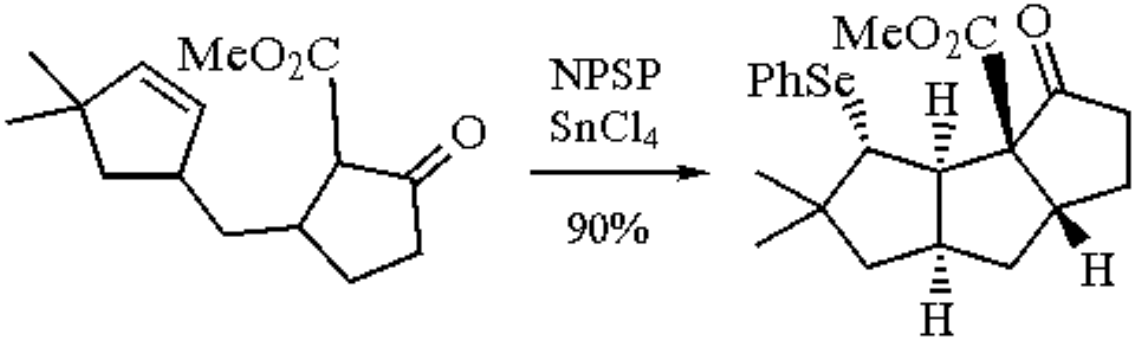

(14)

Alcohols and carboxylic acids have been found to condense with NPSP in the presence of ***Tri-n-butylphosphine*** to provide the corresponding selenoethers (eq 15) and acyl phenyl selenides (eq 16), respectively.[18-20]

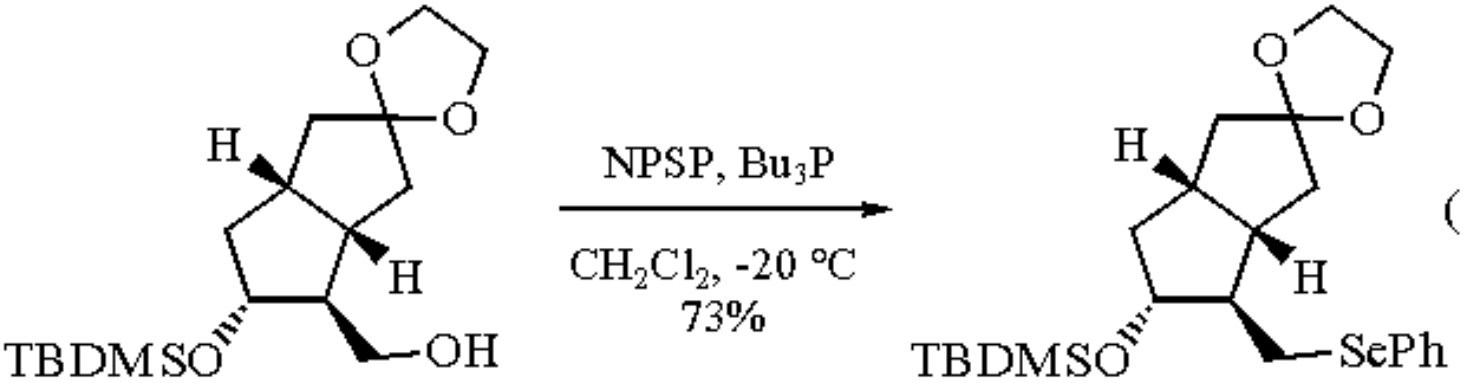

(15)

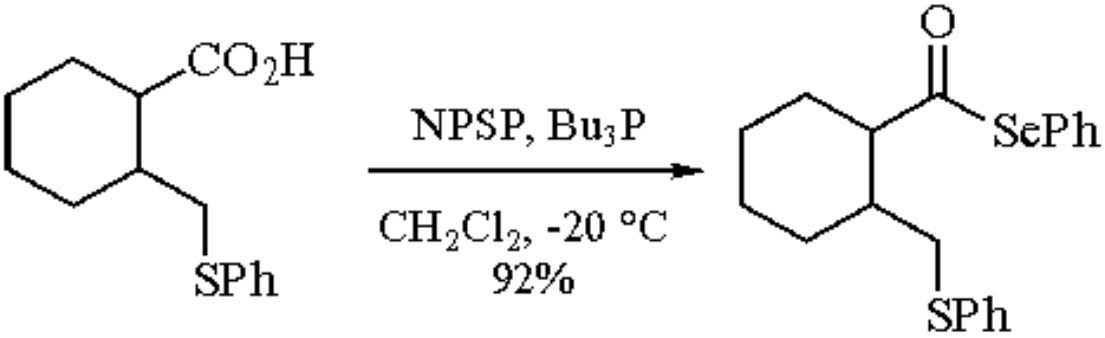

(16)

Sequential hydrozirconation-phenylselenenylation of conjugated enynes has provided a convenient route to stereodefined dienyl selenides (eq 17).[21]

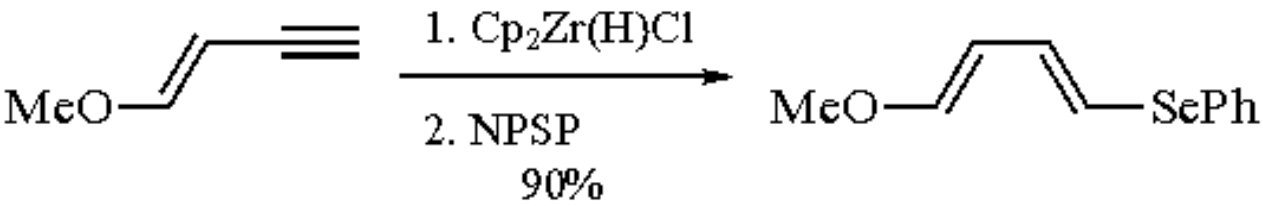

(17)

Related Reagents.

Benzeneselenenyl Bromide; ***Benzeneselenenyl Chloride***; ***Benzeneselenenyl Trifluoromethanesulfonate***;

Benzenesulfenyl Chloride; ***N,N-Diethylbenzeneselenenamide***; ***2-Pyridineselenenyl Bromide***.

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21. Fryzuk, M. D.; Bates, G. S.; Stone, C. *JOC* **1991**, *56*, 7201.

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Phenylsilane-Cesium Fluoride

$PhSiH_3$-CsF

($PhSiH_3$)

[694-53-1] · C_6H_8Si · Phenylsilane-Cesium Fluoride · (MW 108.23) (CsF)

[13400-13-0] · CsF · Phenylsilane-Cesium Fluoride · (MW 151.91)

(mild nucleophilic non-Lewis acidic hydride donor[1] used under aprotic conditions)

Physical Data: phenylsilane: bp 120 °C; *d* 0.877 g cm^{-3}. Cesium fluoride: mp 683 °C.

Solubility: phenylsilane: sol THF, MeCN. Cesium fluoride: sol H_2O; slightly sol THF, MeCN.

Form Supplied in: phenylsilane is a clear liquid; cesium fluoride is a white solid; both widely available.
Drying: anhydrous cesium fluoride is prepared by flame drying under vacuum, taking care not to fuse the salt.

Handling, Storage, and Precautions: no particular requirements.

4-Oxazoline Formation.

The $PhSiH_3$-***Cesium Fluoride*** reagent[1,2] is a nonnucleophilic hydride donor without Lewis acid character with characteristics similar to the ***Diphenylsilane-Cesium Fluoride***,[2] α-$NaphSiH_3$-CsF,[2] and $(RO)_3SiH$-CsF[2] reagents on which it is based. In aprotic solvents, it has been used to reduce 4-oxazolium salts to 4-oxazolines.[1] The 4-oxazolines open at -40 °C to azomethine ylides, which are trapped with dipolarophiles to give 3-pyrrolines (**2**) (eq 1). For isolation purposes the 3-pyrrolines are oxidized to pyrroles (**3**). The mildness of the reagent allows for the selective reduction of the oxazolium salt without further reduction of the 4-oxazoline, azomethine ylide, or dipolarophile which are present at different stages of the reaction. Of the reducing agents tried for (**1**), $PhSiH_3$ gave the highest yield (95%), although Ph_2SiH_2 (93%) worked nearly as well.[1b] Other reducing agents gave much poorer yields. Propiolates, acrylates, ***N-Phenylmaleimide***, and vinyl sulfone dipolarophiles have been used in this [3 + 2] cycloaddition without dipolarophile reduction.

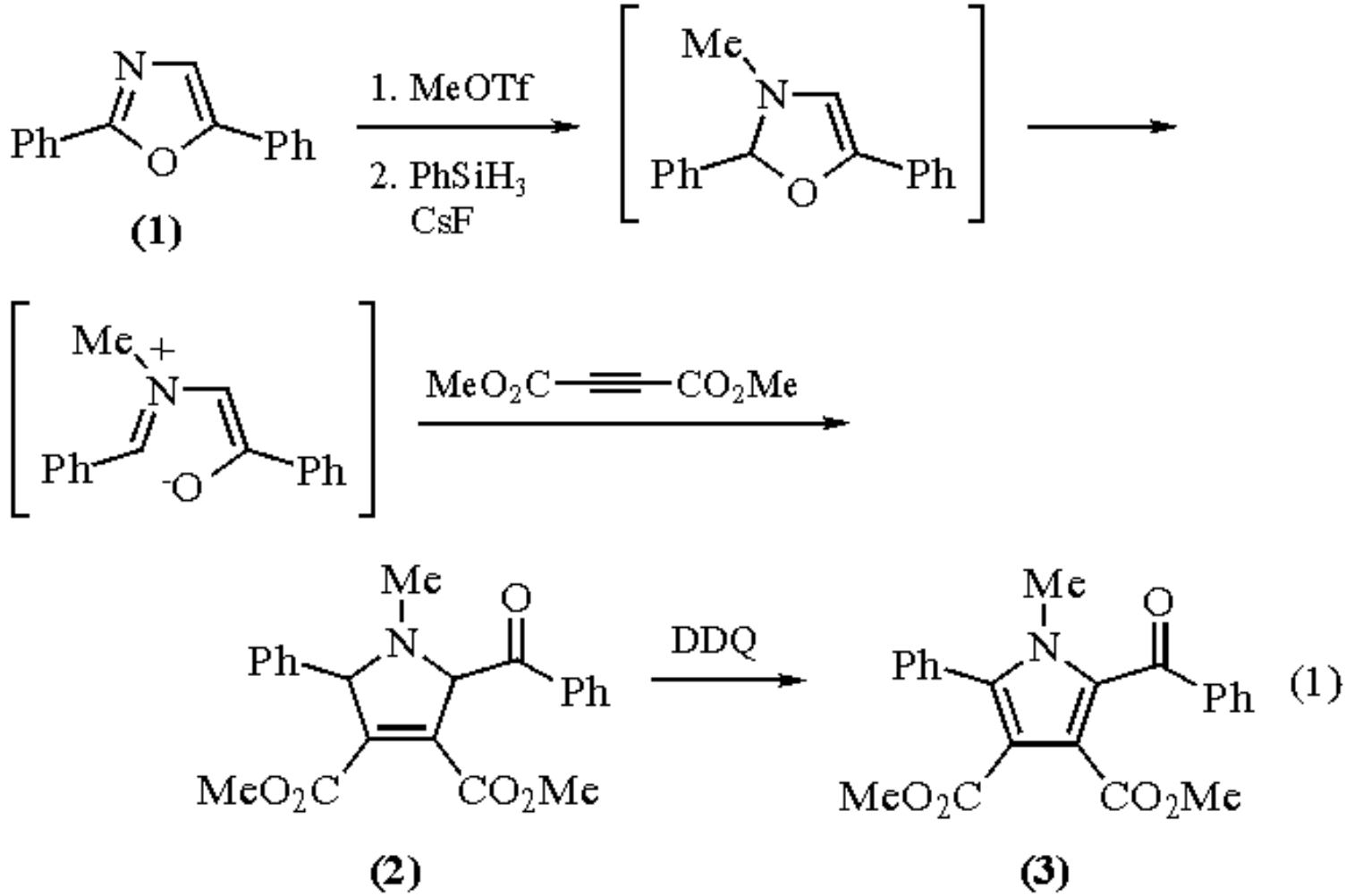

Dipolarophiles such as ***Ethyl Acrylate*** exhibit regiochemical preference for *meta* acyl or carboxyl groups (eq 2).[1] With one exception (entry 6), all cases are consistent with FMO approximation in which the largest dipole HOMO coefficient is at the acceptor-substituted carbon (Table 1).[1b]

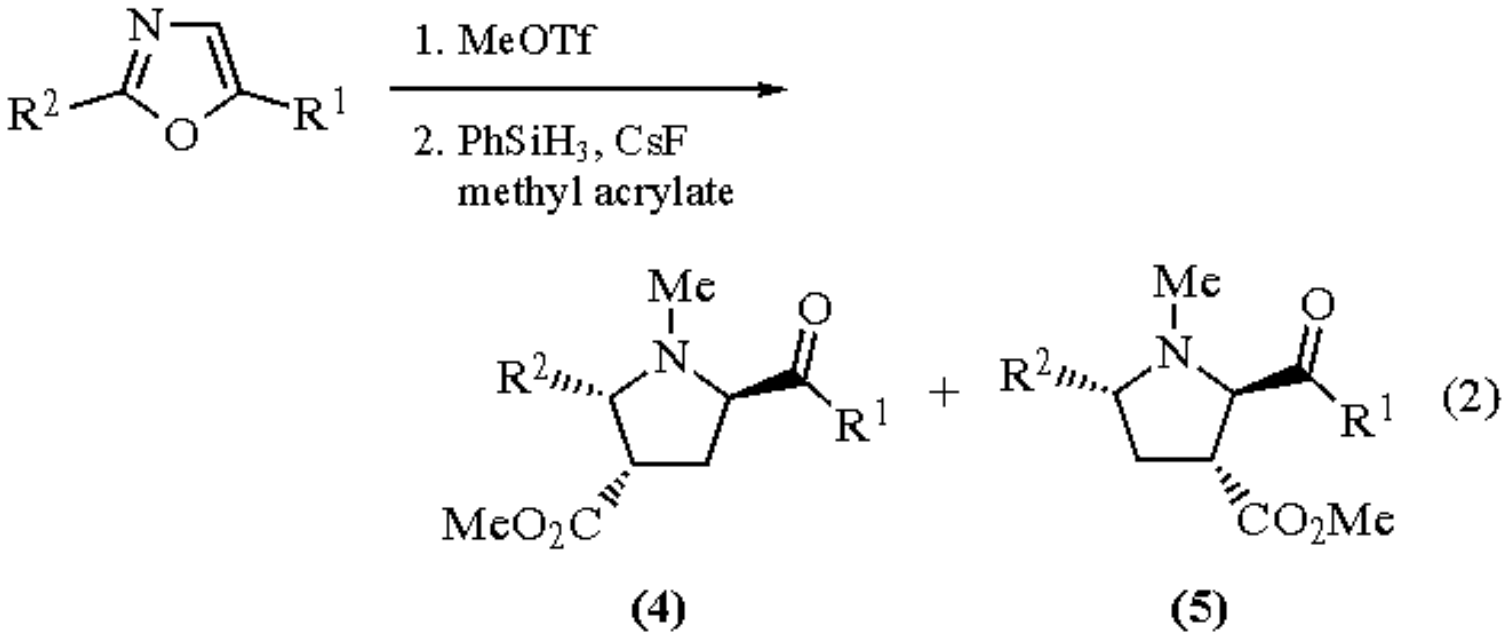

Table 1 Regiochemistry of Acrylate Trapping (eq 2)

Entry	Group		Isolated yield (%)	
	R^1	R^2	(**4**)	(**5**)
1	Ph	Ph	55	9
2	Ph	OEt	63	10
3	Ph	Me	87	0
4	Me	Ph	40	20
5	Me	OEt	61	0
6	H	Ph	0	67
7	H	OEt	47	0
8	Ph	H	57	0

A comparison of methods to generate azomethine ylides via 4-oxazoline ring opening vs. aziridine thermolysis has shown that the oxazoline method can produce the same azomethine dipole under kinetic control as the aziridine method under thermodynamic control.[3] Since the 4-oxazoline method allows improved regiochemical selectivity in many cases, the synthesis of 4-oxazolines from $PhSiH_3$-CsF-induced reduction of oxazolium salts possesses greater potential for azomethine ylide applications in stereocontrolled synthesis.

Intramolecular trapping of an azomethine ylide generated from an oxazolium salt has been accomplished (eq 3).[4] This approach allows a new entry into the mitosene skeleton.

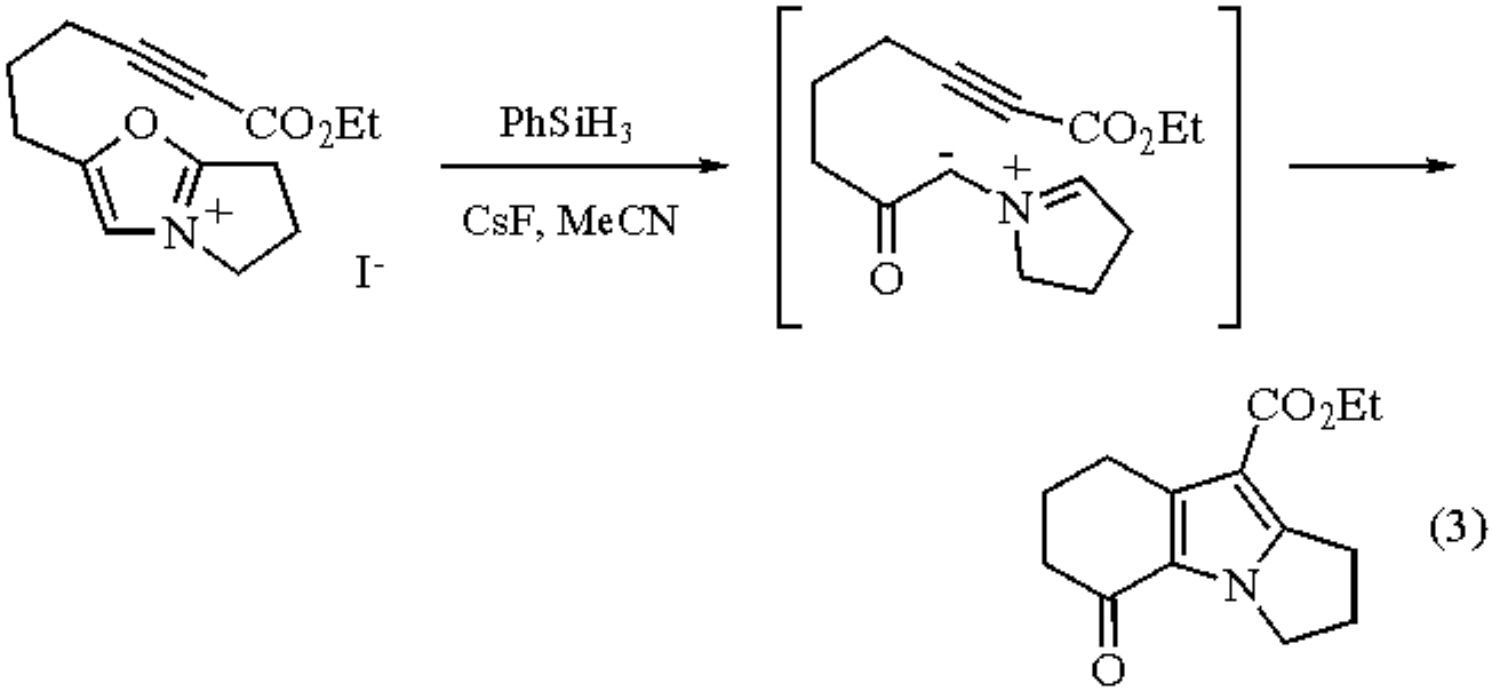

Related Reagents.

Diphenylsilane-Cesium Fluoride.

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1. (a) Vedejs, E.; Grissom, J. W. *JACS* **1986**, *108*, 6433. (b) Vedejs, E.; Grissom, J. W. *JACS* **1988**, *110*, 3238.
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4. Vedejs, E.; Piotrowski, D. W. *JOC* **1993**, *58*, 1341.

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Phenylsodium[1]

PhNa

[1623-99-0] · C_6H_5Na · Phenylsodium · (MW 100.10)

(reagent for metalation;[1a,b] nucleophilic addition and substitution;[1b,c] initiator of anionic polymerization[2])

Physical Data: amorphous, infusible solid.

Solubility: insol hydrocarbons and reacts with ethers; can be solubilized as complexes, e.g. with ***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine***.[3] Also forms more soluble complexes, but with modified reactivity, with phenyllithium, diphenylmagnesium, and magnesium 2-ethoxyethoxide.[4]

Preparative Methods: usually by reaction of chlorobenzene with ***Sodium*** dispersion; also by metalation of benzene with alkylsodium compounds (e.g. as a one-pot process by reaction of 1-chloropentane with sodium dispersion in benzene); by reaction of ***Phenyllithium*** with sodium *t*-butoxide;[3] and by transmetalation of ***Diphenylmercury***, e.g. with sodium.[5]

Purification: the reagent is normally prepared and used in situ. Its composition, and therefore its properties, may depend on the method of preparation.

Handling, Storage, and Precautions: reacts explosively with air and violently with water; hydrolysis gives benzene (carcinogen) and sodium hydroxide (corrosive). It must be handled in an inert atmosphere under strictly anhydrous conditions.

Metalation.

Despite a considerable amount of early work,[1a] phenylsodium has been underutilized as a reagent for metalation. While it is probably less superbasic than, for example, butylpotassium, it is certainly more basic than most organolithium compounds. For example, reaction of phenylsodium with acetophenone results in enolate formation and nucleophilic addition in a ratio of 2:1, whereas with ***Phenyllithium*** the ratio is 1:23.[6] Some examples of its use, chosen with the emphasis on reactions where it differs from organolithium compounds, are shown in the following equations.

Eq 1 represents a convenient synthesis of benzylsodium, via the preparation of phenylsodium in situ in toluene.[7] Toluene is metalated by ***n-Butyllithium*** only in the presence of e.g. ***N,N,N´,N´-Tetramethylethylenediamine***.

$$PhCl \xrightarrow[\text{toluene}]{Na} PhCH_2Na \qquad (1)$$

In contrast to eq 2,[8] reaction of benzyldimethylamine with butyllithium leads mainly to *ortho* metalation.

$$PhCH_2NMe_2 \xrightarrow{PhNa} PhCH(Na)NMe_2 \qquad (2)$$

Both 2- and 4-alkylpyridines may be metalated with phenylsodium as an alternative to ***Sodium Amide*** or organolithium compounds (eq 3).[9]

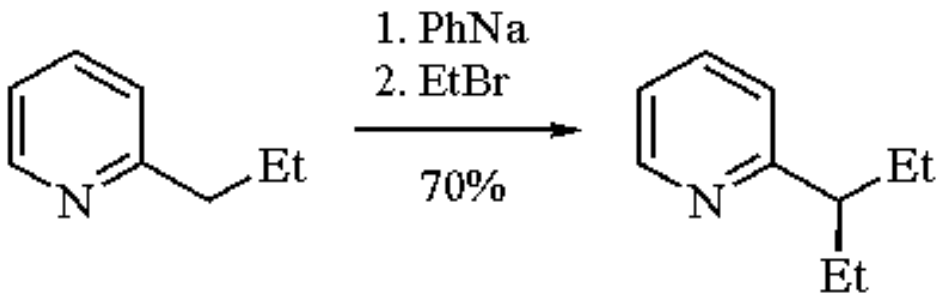

(3)

Nucleophilic Addition and Substitution.

Phenylsodium resembles phenyllithium in its reactions with carbonyl compounds (including α,β-unsaturated carbonyl compounds, where 1,2-addition predominates), ***Carbon Dioxide***, ***Iodomethane***, oxirane (***Ethylene Oxide***), etc.,[1b,c] but generally offers no significant advantage (except possibly cost). Indeed, its higher basicity may be a disadvantage when the substrate contains α-hydrogens, as in its reaction with acetophenone noted above.

A less routine example involves both nucleophilic ring-opening and addition to a carbon-nitrogen double bond (eq 4).[10] In this case also, phenyllithium gave a similar yield of phenol, though a lower yield of the sulfonamide.

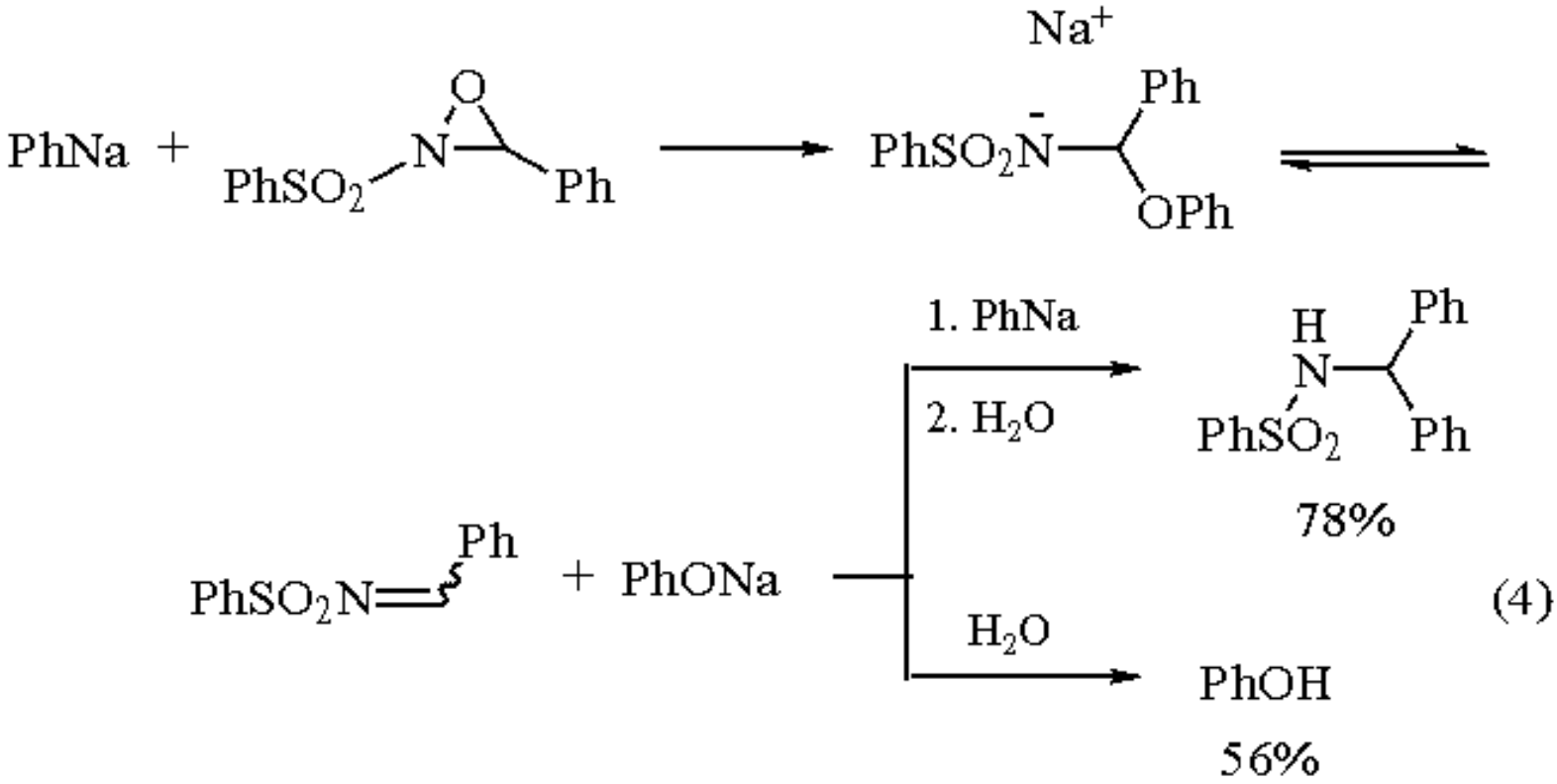

Initiation of Polymerization.

Early studies on the polymerization of dienes and styrene initiated by phenylsodium[2] have not been extensively followed up or exploited, although various patents listed in *Chem. Abstr.* include the use of phenylsodium.

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10. Davis, F. A.; Wei, J.; Sheppard, A. C.; Gubernick, S. *TL* **1987**, *28*, 5115.

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Phenylsulfinylethylene[1]

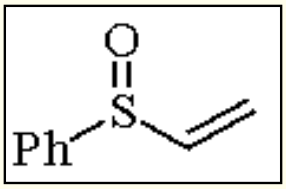

[20451-53-0] · C_8H_8OS · Phenylsulfinylethylene · (MW 152.23) (±)

[88180-53-4] (*S*)

[89299-86-4] (*R*)

[89299-86-5]

(acetylene equivalent in Diels-Alder, dipolar cycloaddition, and Michael reactions; can be deprotonated to the unsaturated α-sulfinyl carbanion; undergoes additive Pummerer reactions)

Physical Data: bp 93-95 °C/0.2 mmHg; *n*20D 1.5865; *d* 1.139 g cm^{-3}; (*S*)-(-): [α]20D -376° (*c* 1.0, MeOH).

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: racemic reagent can be prepared from dibromoethane in one pot by substitution with thiophenolate and elimination of HBr (50-65%), followed by oxidation (68-70%).[2] The preparation of optically active phenylsulfinylethylene has been reported in a few instances only. It is noted, however, that optically active sulfoxides can be prepared by reaction of a carbanion with chiral arylsulfinates derived from menthol[3a] or glucose,[3b] or *N*-sulfinyloxazolidinones of norephedrine or phenylalanine,[3c,d] or by sequential arylation-vinylation of sulfites derived from lactic acid[3e] or aminosulfites derived from ephedrine (99+% ee).[3f] Alternatively, they can be prepared by enantioselective oxidation of sulfides with Sharpless-type reagents,[3g,h] oxaziridines,[3i] and by microbial oxidation.[3j] Finally, resolution is possible via cocrystallization with 1,1´-binaphthol[3k,1] or by chiral HPLC.[3m]

Purification: enantiomeric purity can be determined by ^{1}H NMR using chiral solvating agents.[3n]

Handling, Storage, and Precautions: as with most optically active sulfoxides, optically active phenylsulfinylethylene racemizes in the presence of acids. Use in a fume hood.

Diels-Alder Reactions.

One use of phenylsulfinylethylene is as an acetylene equivalent in Diels-Alder reactions.[4] Indeed, it is the only reagent of this type able to lose the activating functionality (phenylsulfenic acid) spontaneously after the cycloaddition.[5] The examples in eqs 1 and 2 are representative.[5,6]

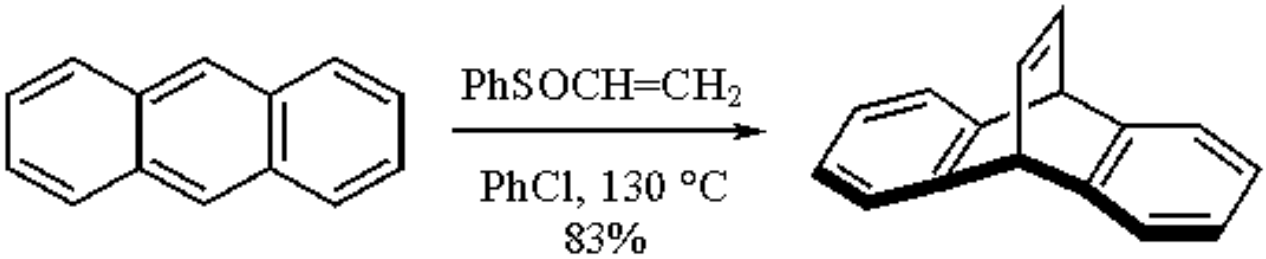

(1)

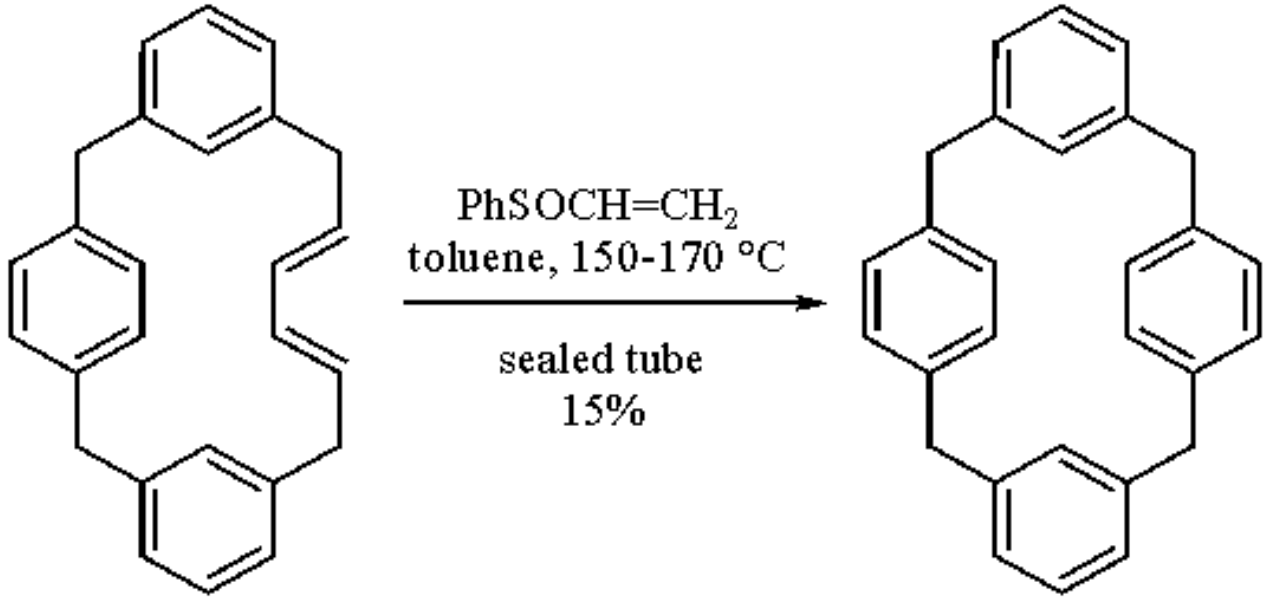

(2)

In most cases the reaction conditions needed for cycloaddition also cause desulfinylation of the adducts, but sometimes the primary cycloadduct can be isolated and subjected to different transformations. For example, adducts can be alkylated[7a] or transformed into a ketone (eq 3).[7b] In such cases, phenylsulfinylethylene can be considered an equivalent of allene or ketene in [4 + 2] cycloadditions. It is notable that phenylsulfinylethylene will react with deactivated dienes as cyclopentadienones,[8a] pyrones (eq 4),[8b] and thiophene dioxides (eq 5).[9]

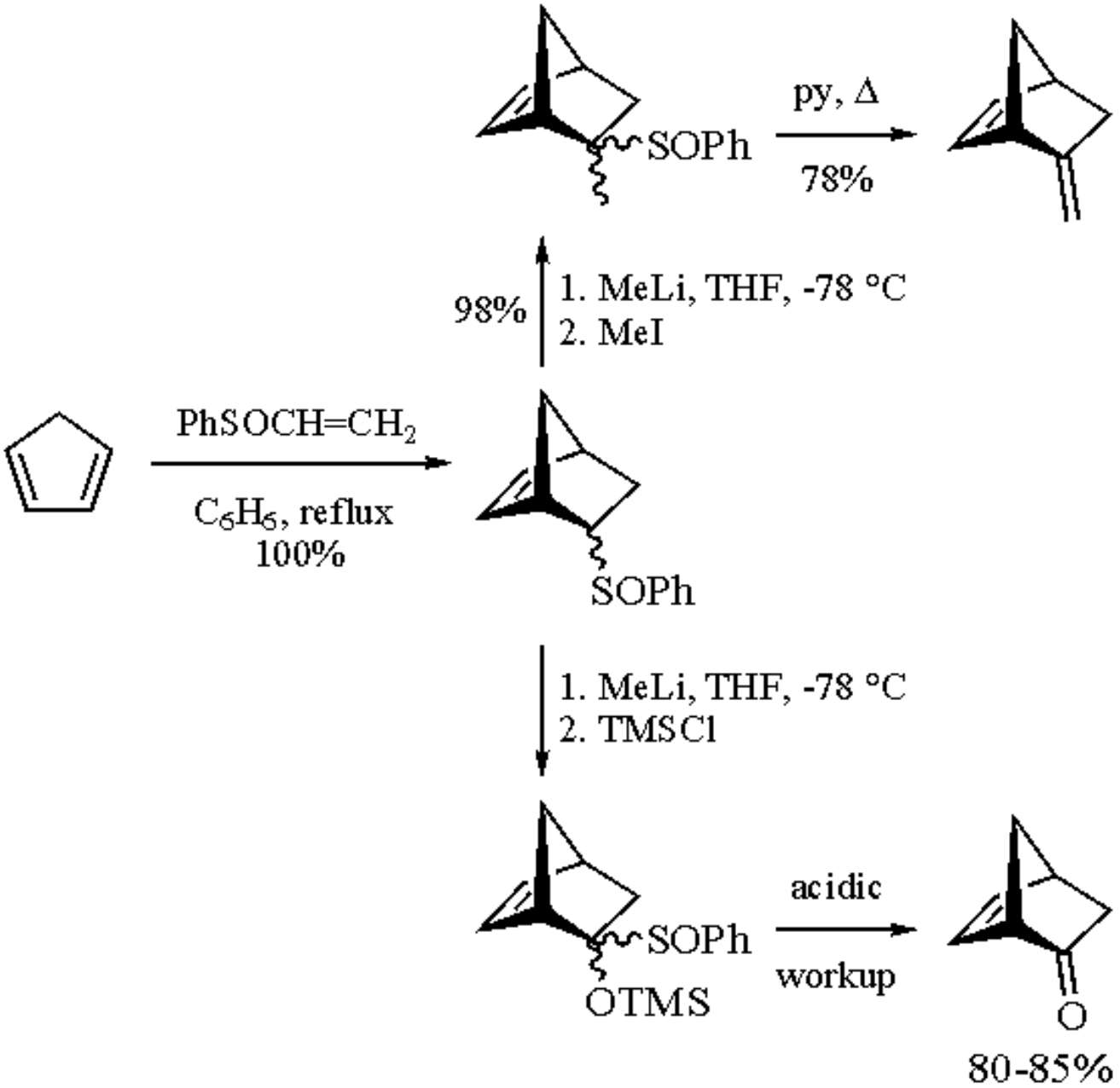
SOPh
py, Δ
78%
98%
1. MeLi, THF, -78 °C
2. MeI
PhSOCH=CH2
C6H6, reflux
100%
SOPh
1. MeLi, THF, -78 °C
2. TMSCl
SOPh
OTMS
acidic
workup
O
80-85%

(3)

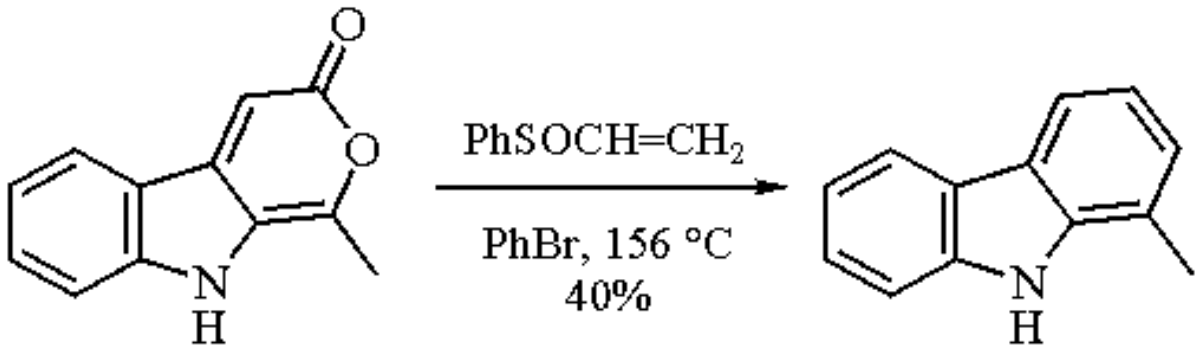
O
O
N
H
PhSOCH=CH2
PhBr, 156 °C
40%
N
H

(4)

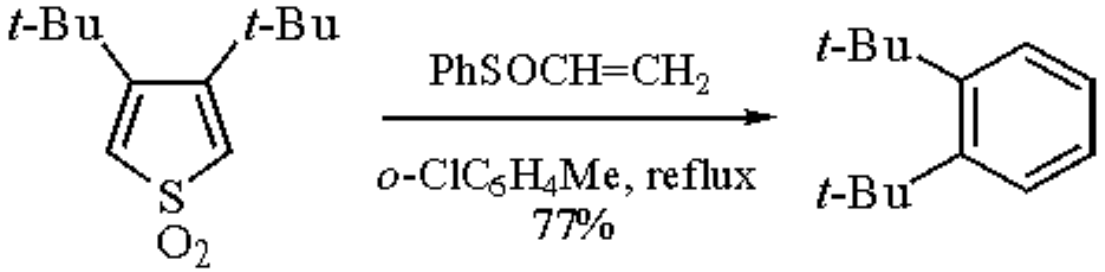

(5)

A close relative of the title reagent, optically active tolylsulfinylethylene (*[36832-47-0]*; (±) *[110455-66-8]*; (*R*) *[54828-68-1]*; (*S*) *[27328-17-2]*), adds to cyclopentadiene with modest *endo-exo* and face selectivity.[10] The stereochemistry of addition favors the *endo-syn* adduct (eq 6).[7] The selectivity is improved if the sulfoxide is transformed into the oxysulfonium salt by alkylation with Meerwein reagent. In this case the product is the *endo-anti* adduct, but treatment with sodium hydroxide regenerates the sulfoxide with inversion of configuration, so that products identical to the cycloaddition of tolylsulfinylethylene itself are obtained.[11a] The method has been used to prepare the Corey prostaglandin intermediate (eq 7).[11b]

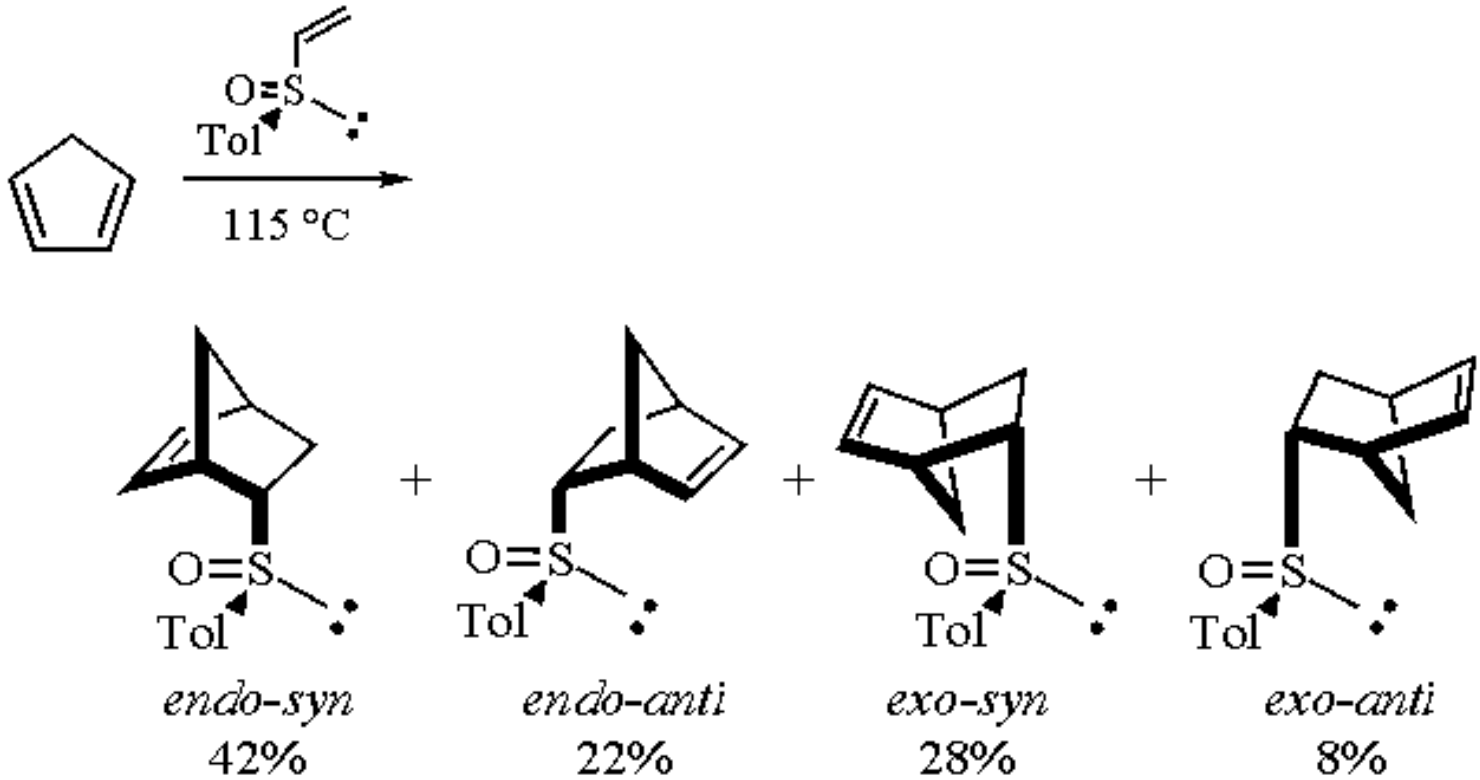

(6)

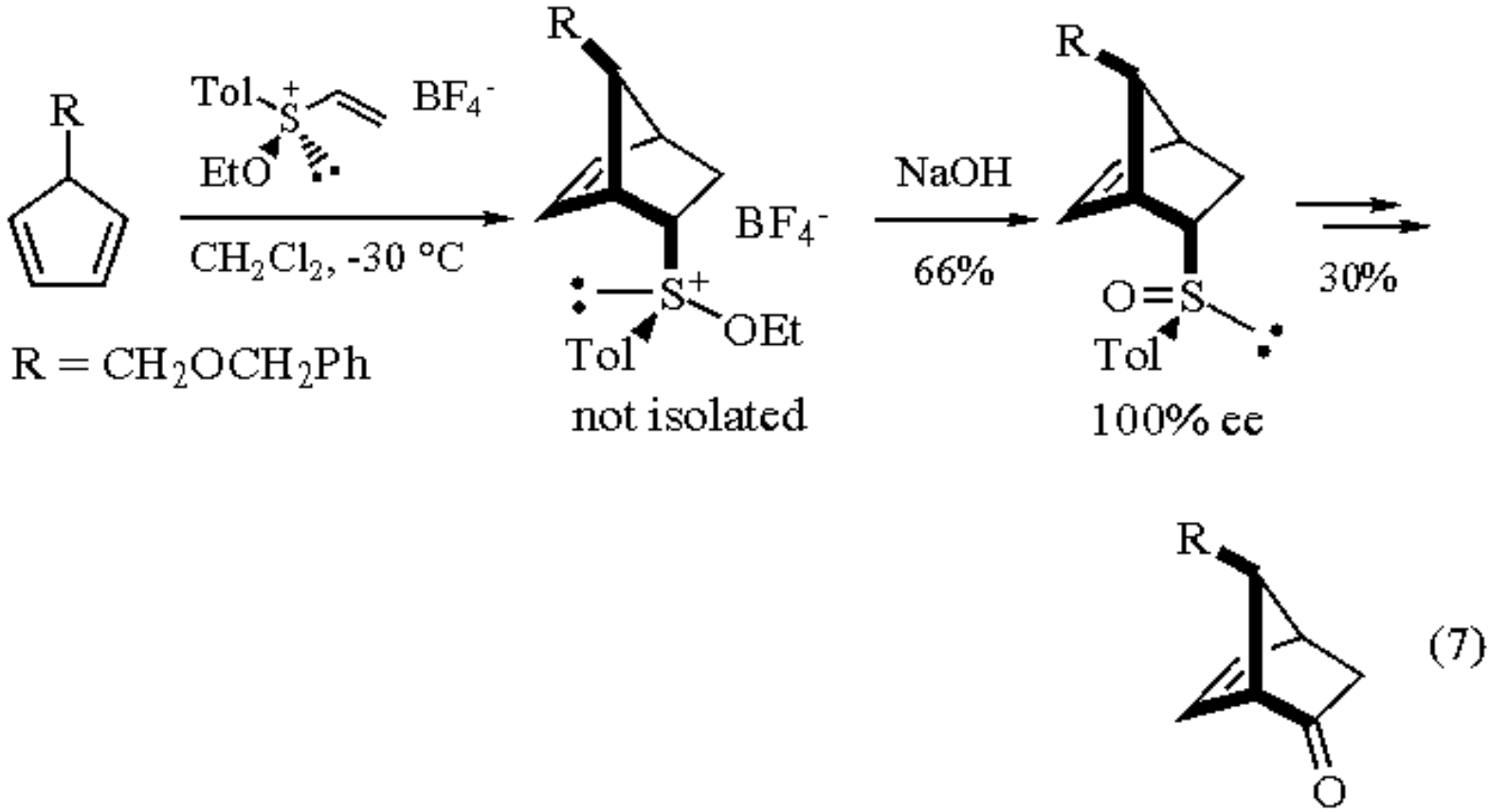

Dipolar Cycloadditions.

In view of the mild conditions of elimination, phenylsulfinylethylene can be used in the synthesis of heterocycles. For example, α- and β-nicotyrines[12a] and indolizines[12b] have been prepared using phenylsulfinylethylene as a dipolarophile. In asymmetric synthesis, the adducts formed between enantiomerically pure tolylsulfinylethylene and nitrones have been converted to optically active amino alcohols (eq 8),[13a] and with 1-methyl-3-oxidopyridinium to enantiomerically pure 2α-tropanol (eq 9).[13b]

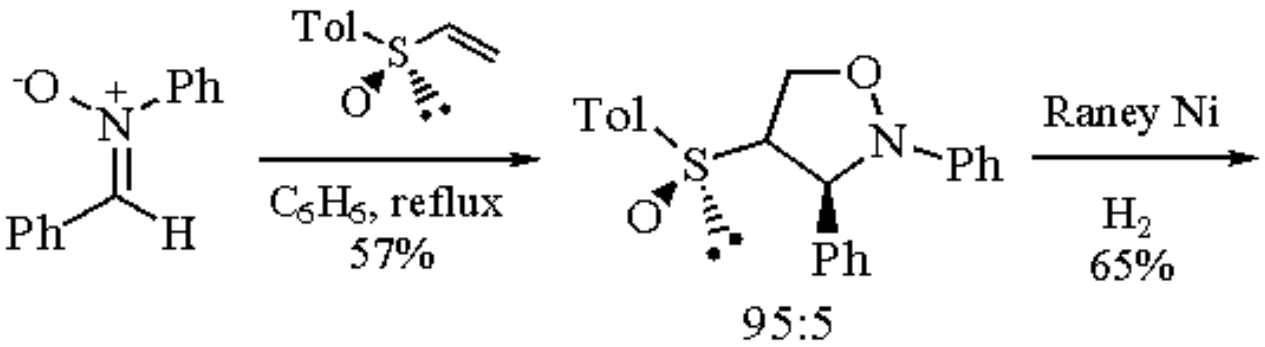

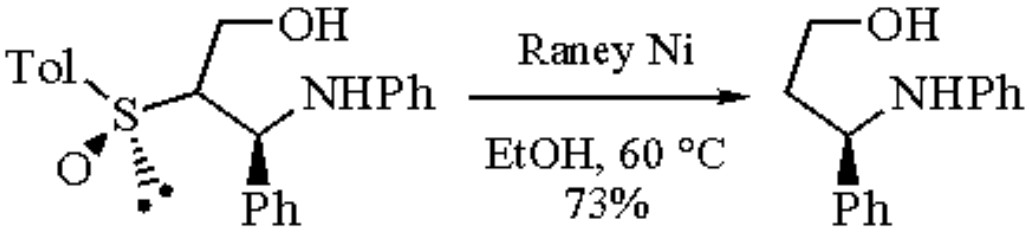

(8)

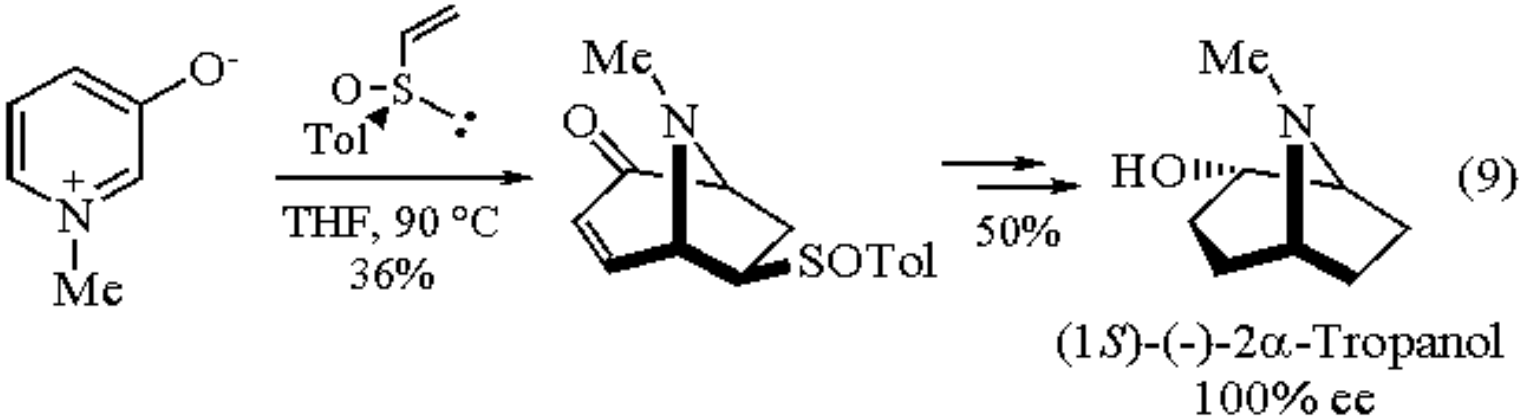

(9)

Michael Additions.

Phenylsulfinylethylene can react as a Michael acceptor, as illustrated in eqs 10 and 11.[14a,b] In these instances the adducts have been subjected to the Pummerer reaction,[15] but adducts can be simply heated to obtain the alkene. In the latter case, phenylsulfinylethylene functions as a vinyl cation equivalent.[14c] In one case the vinyl sulfoxide has been shown to cyclize to a cyclobutane (eq 12).[16]

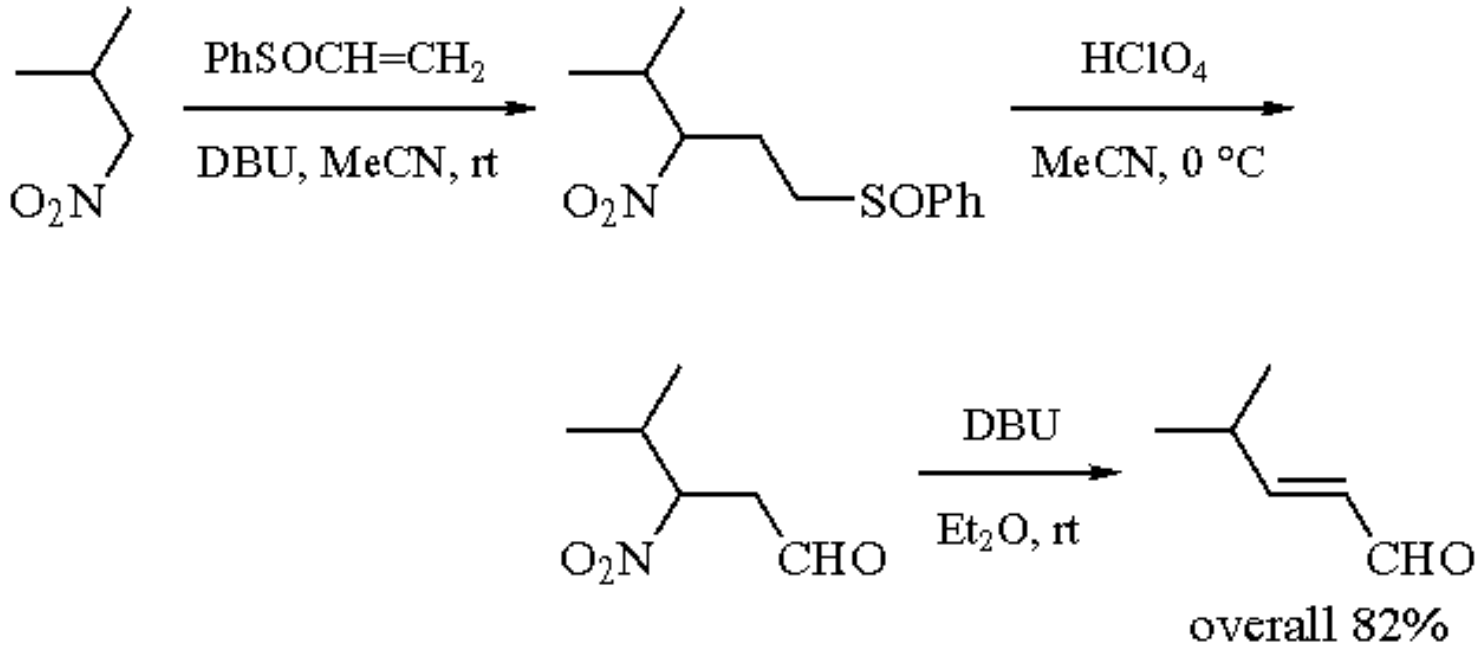

(10)

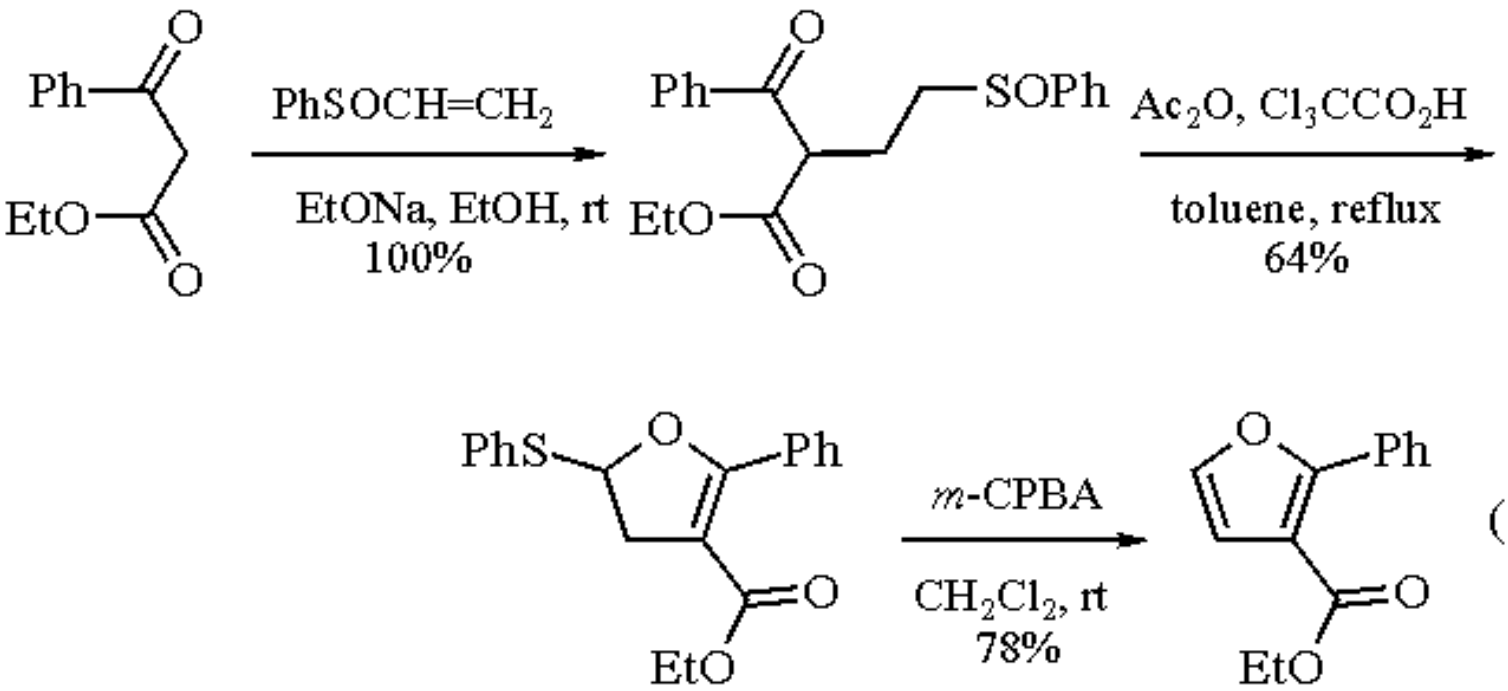

(11)

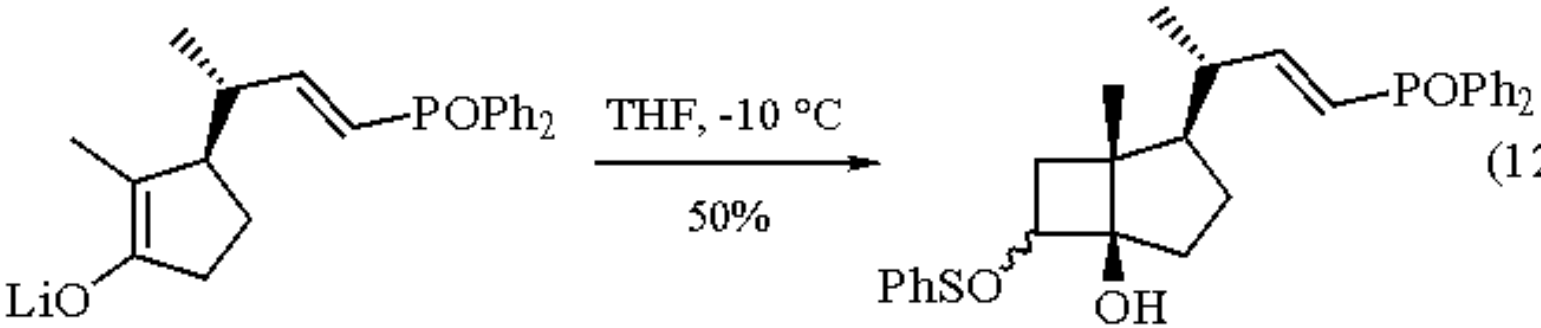

(12)

Pummerer Reactions.[15]

Phenylsulfinylethylene reacts with ***Isopropenyl Acetate*** and catalytic ***p-Toluenesulfonic Acid*** to give phenylthioacetaldehyde via a presumed 3,3-sigmatropic shift (eq 13).[17a] ***Thionyl Chloride***,[17b] ***Trifluoroacetic Anhydride***,[17c] and ***Dichloroketene***[17d] also react with the title reagent in additive-type Pummerer reactions. Pummerer-ene reactions occur in the presence of alkenes with formation of the products shown in eq 14.[18]

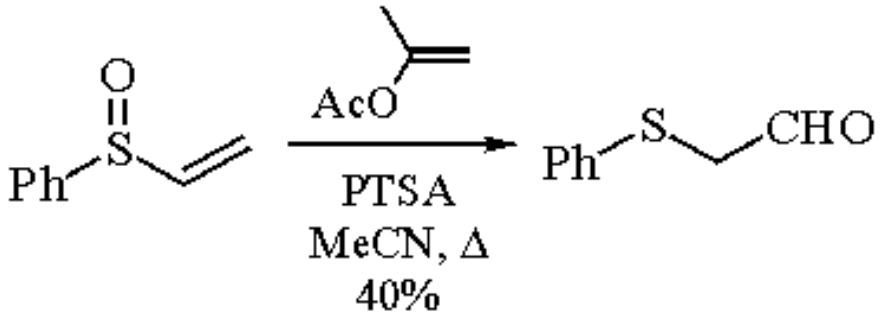

(13)

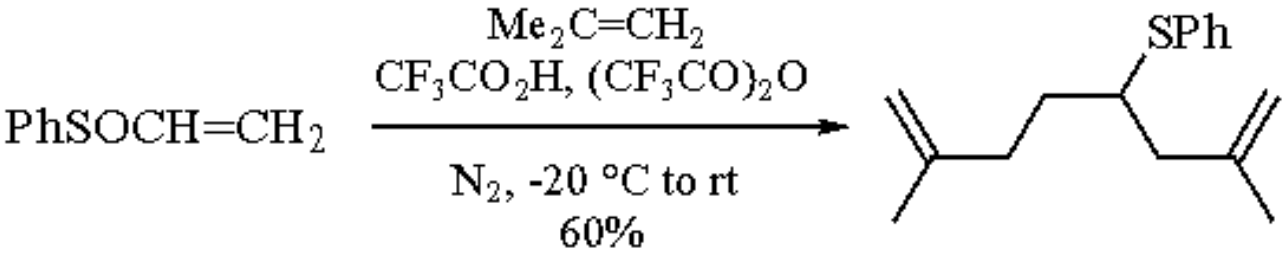

(14)

Reactions as Acids.

Strong bases such as ***Lithium Diisopropylamide*** deprotonate phenylsulfinylethylene to give the vinylic α-sulfinyl carbanion;[19] the latter adds to aldehydes and ketones, e.g. with *o*-acetylphenols it affords 4-substituted chromans (eq 15).[20]

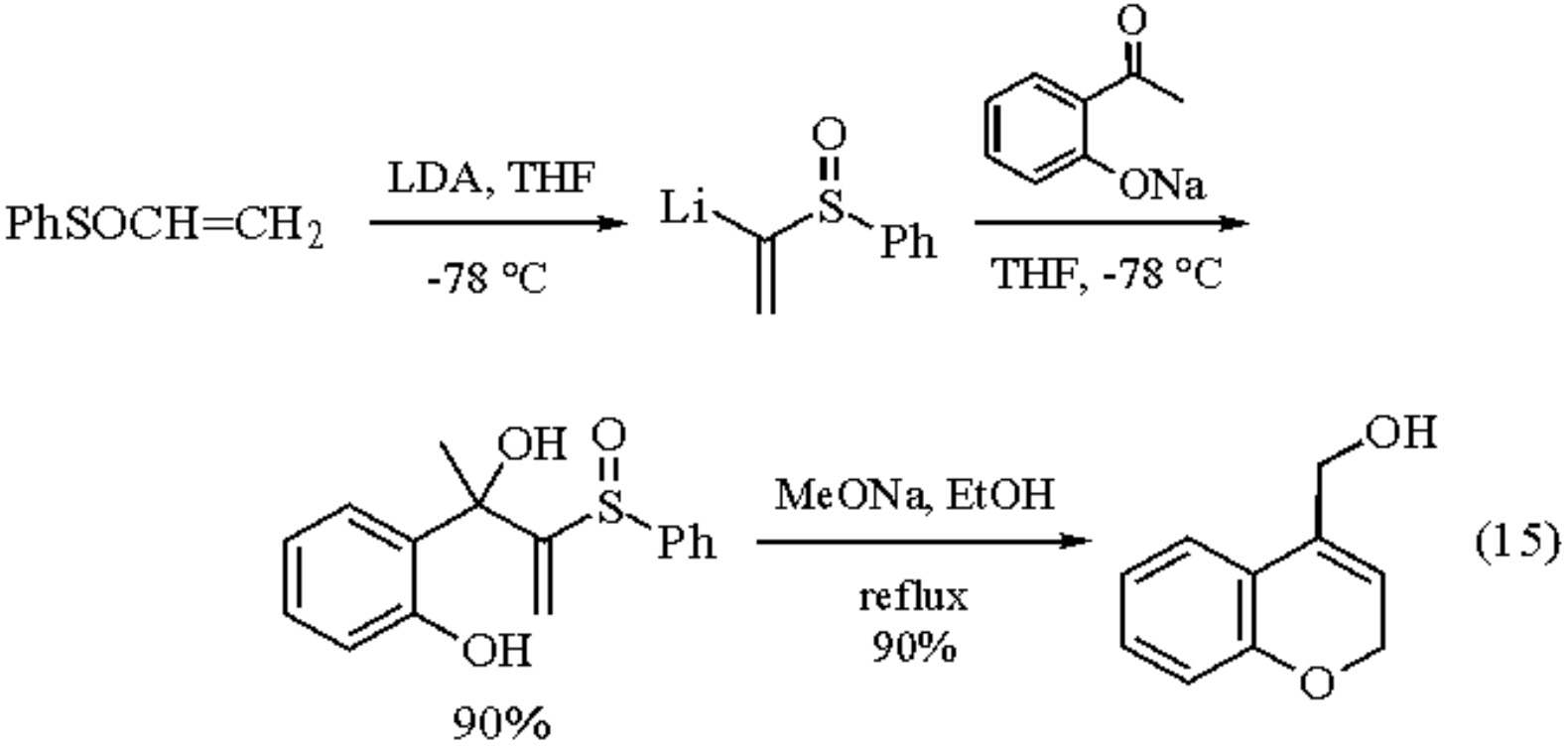

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Phenylsulfonylacetylene[1]

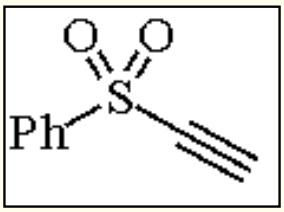

[32501-94-3] · $C_8H_6O_2S$ · Phenylsulfonylacetylene · (MW 166.21)

(acetylene equivalent in cycloaddition reactions;[2] powerful Michael acceptor;[1b] precursor to substituted alkynes[3])

Alternate Name: ethynyl phenyl sulfone.

Physical Data: oil; bp 103-105 °C/0.01 mmHg. The 4-methyl derivative, *p*-TolSO_2C&tbond;CH *[13894-21-8]*, is a solid; mp 75 °C (from 95:5 hexane/ethyl acetate).

Solubility: sol common organic solvents.

Preparative Methods: a convenient preparation of the title reagent and *p*-TolSO_2C&tbond;CH involves $AlCl_3$-mediated substitution of one trimethylsilyl group from ***Bis(trimethylsilyl)acetylene*** by an arylsulfonyl chloride followed by hydrolysis.[4] Older procedures involve oxidation of the corresponding ethynyl thioethers,[5a,b] diazotization of 4-arylsulfonyl-5-aminoisoxazoles,[5c] dehydrobromination of (*Z*)- and (*E*)-bromovinyl phenyl sulfone with fluoride ion,[5d] and oxidative elimination of β-(phenylseleno) vinyl sulfones.[5e]

Handling, Storage, and Precautions: store tightly closed and refrigerated, possibly under an inert gas. Use in a fume hood.

Cycloaddition Reactions.

Phenylsulfonylacetylene undergoes Diels-Alder addition to a number of dienes including 2,3-dimethylbutadiene, cyclopentadiene, and anthracene (eq 1).[2a] The resulting adducts can be reductively desulfonylated to the corresponding 1,4-dienes using ***Sodium Amalgam*** in buffered (NaH_2PO_4) methanol, ***Samarium(II) Iodide*** in HMPA (eq 2),[2b] or tin reagents.[2c] This reaction sequence makes arylsulfonylacetylenes equivalent to acetylene in cycloaddition reactions.[6] The same sequence carried out on the adducts of tolyl trimethylsilylethynyl sulfone (TolSO_2-C&tbond;C-TMS) leads to the formal adducts of trimethylsilylacetylene,[7a] itself a poor dienophile.[7b] The mildness of the reaction conditions allows the synthesis of otherwise inaccessible molecules. 7-Azanorbornadiene (eq 3)[8] and [4]-peristylane (eq 4)[9] are

examples.

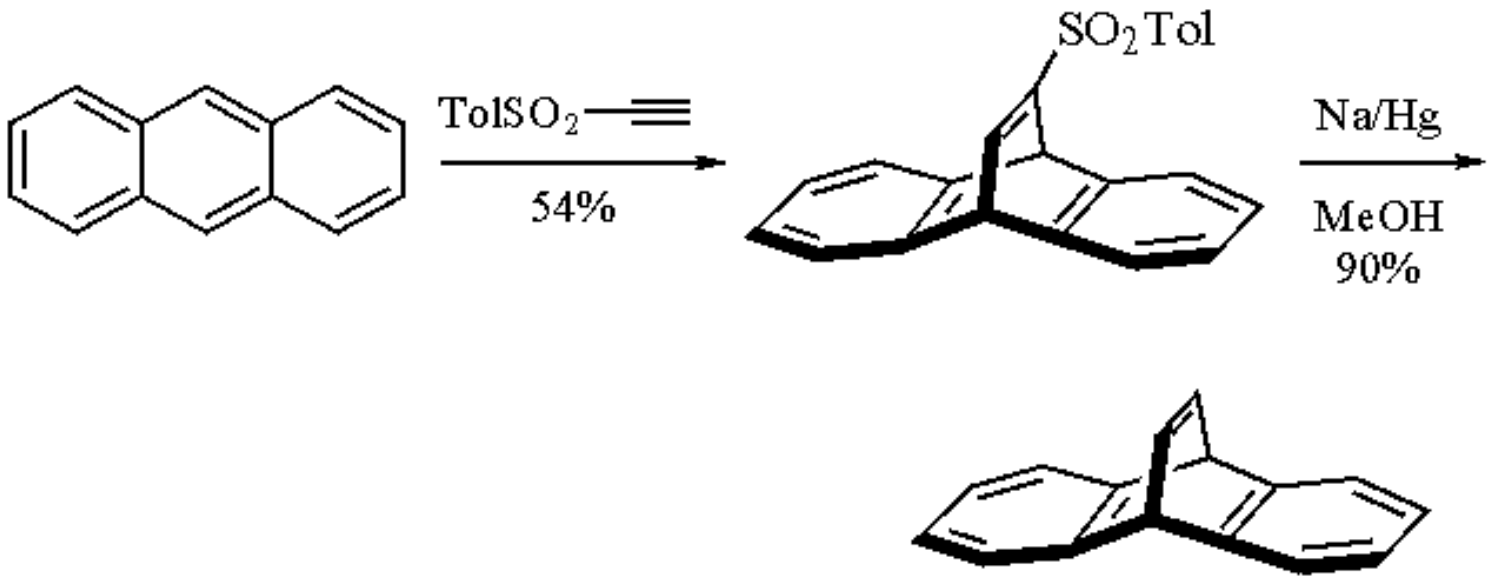

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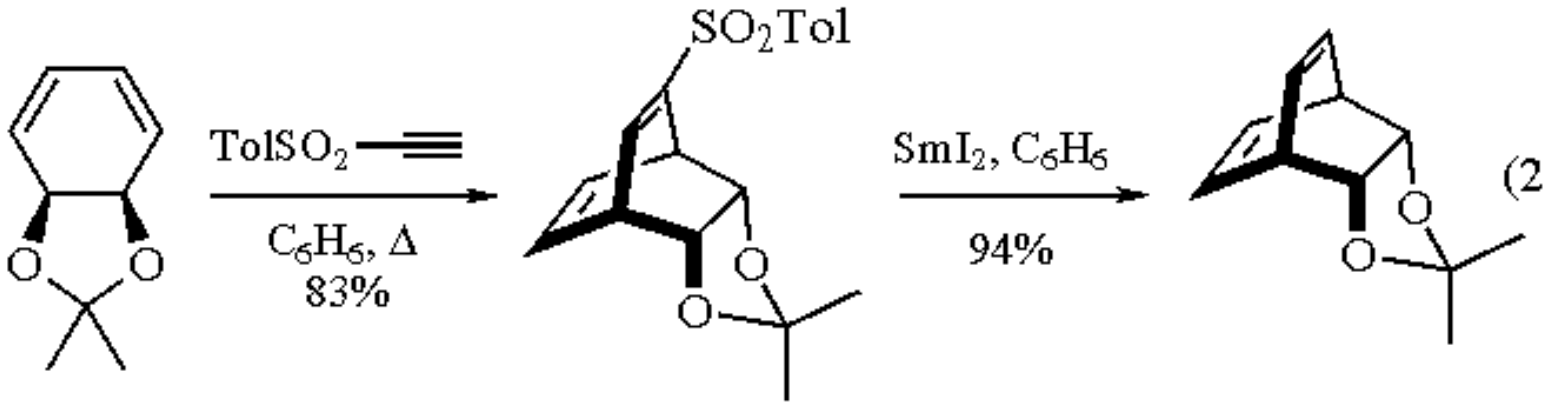

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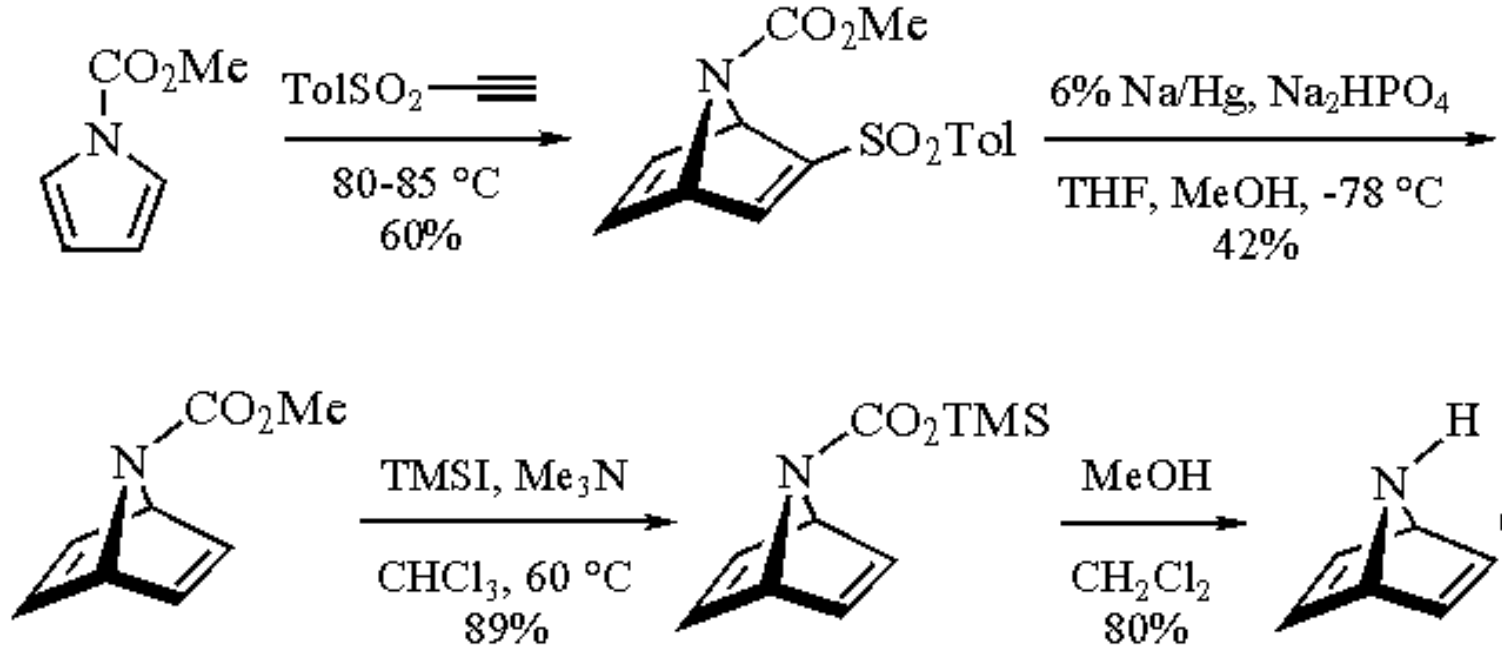

(3)

(4)

Tolylsulfonylacetylene gives ene reactions with appropriate alkenes under ***Ethylaluminum Dichloride*** catalysis (eq 5).[10] In dipolar cycloadditions, arylsulfonylalkynes react with nitrile oxides and nitrile imines to give 4-arylsulfonyl-substituted isoxazoles[11a] and diazoalkanes (eq 6).[11b] They also react with sydnones[11a] to give 4-arylsulfonyl-substituted pyrazoles. In general, the regiochemistry of addition is opposite to that observed with ***Phenylsulfonylethylene***. 4-Chloro-substituted pyridine *N*-oxides and pyridinium-*N*-dicyanomethylides give furopyridines[11c] and indolizines.[11d] Cycloaddition reactions have also been reported with ynamines. With these reagents the products are substituted furans (eq 7).[12]

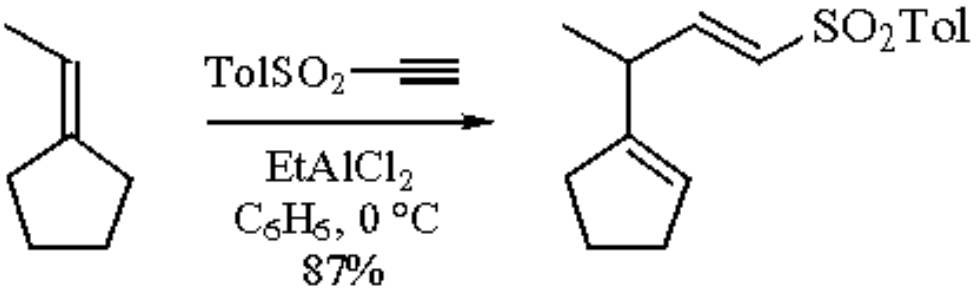

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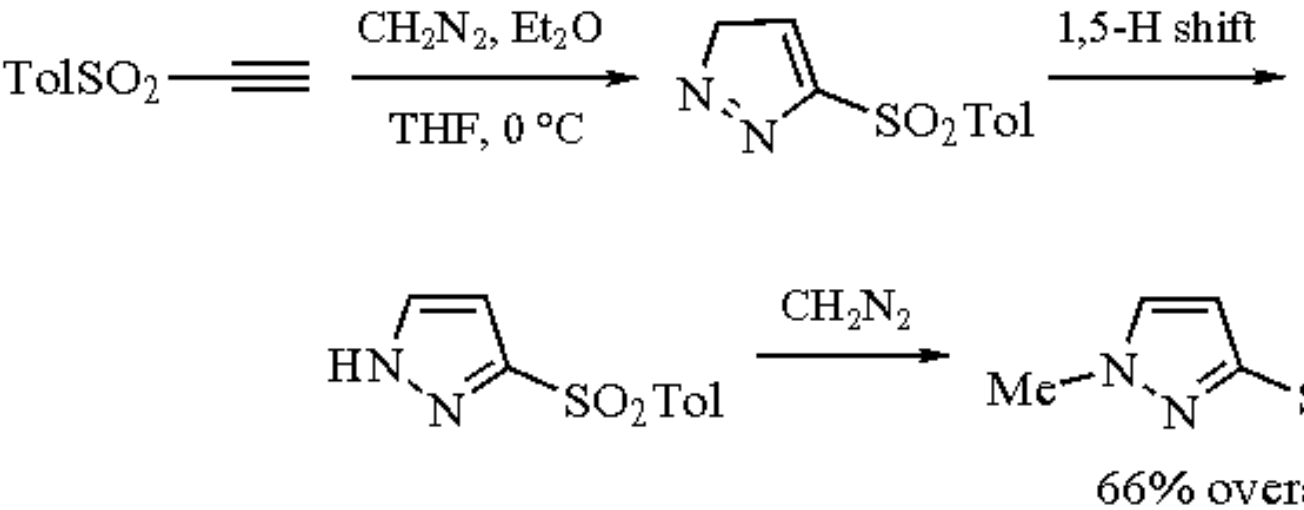

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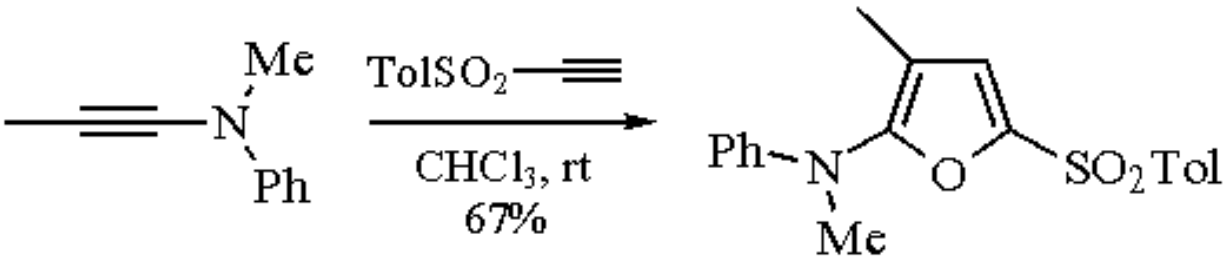

(7)

Nucleophilic Additions.

Arylsulfonylalkynes display powerful Michael acceptor properties. Examples of addition include heteroatomic nucleophiles such as amines,[13] hydroxylamines,[14] alkoxides,[15] thiols,[16,17] and boranes.[18] The stereochemistry of addition depends on the nucleophile and on the solvent and can be controlled to some extent to obtain the (*Z*) or (*E*) adduct. For example, 10-mercaptoisoborneol adds to phenylsulfonylacetylene in acetonitrile in a *trans* fashion (eq 8), affording the corresponding (*Z*) adduct in high yield.[17] The latter was oxidized by ***m-Chloroperbenzoic Acid*** to one diastereomerically pure sulfoxide that proved to be an efficient chiral dienophile.[17] Strong carbon nucleophiles such as malonate anions[19] and cuprates (eq 9)[20] also add to phenylsulfonylacetylene in a Michael fashion with good *syn* stereoselectivity depending upon the reaction conditions. Poorer nucleophiles such as organolithium and Grignard reagents can give the substitution of the phenylsulfonyl group via an electron transfer process (eq 10).[3] A similar substitution occurs with the tin amide of pyrrole that permits direct stannylation of tolylsulfonylacetylene to $TolSO_2$-C&tbond;C-$SnEt_3$ in quantitative yield.[21]

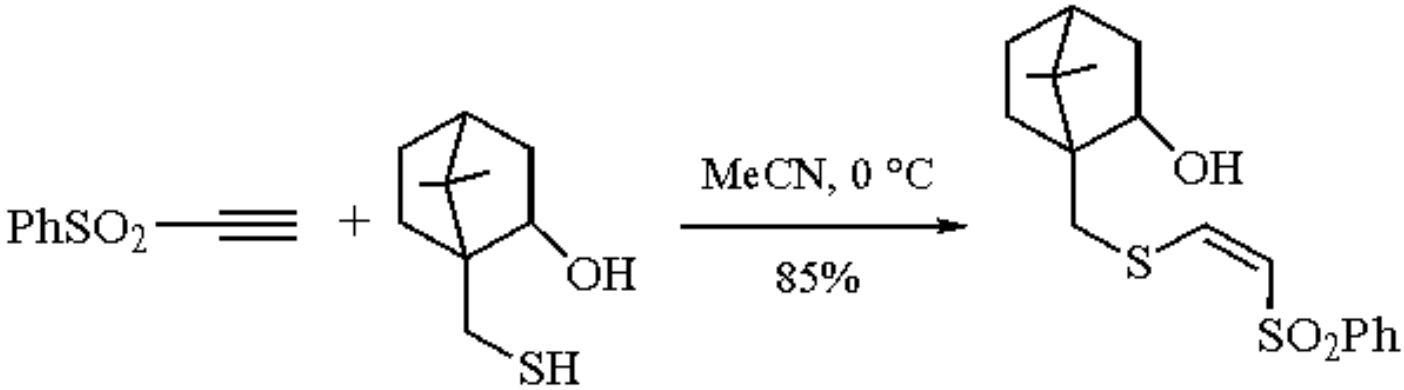

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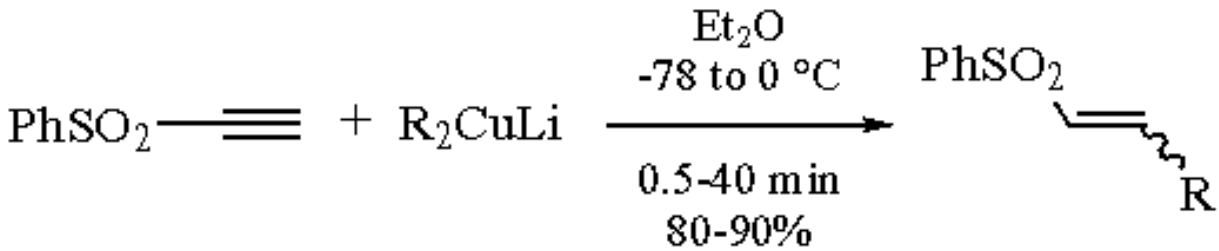

(9)

R = Me, Ph, Bu

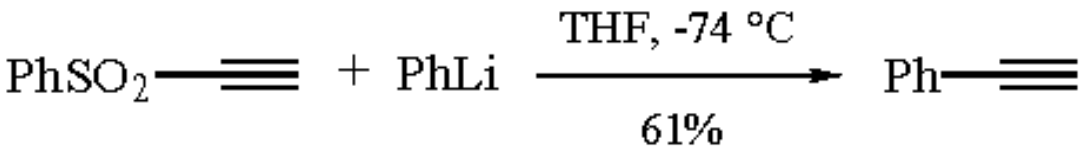

(10)

Radical Additions.

The ***Hexabutyldistannane***-promoted radical addition of alkyl iodides to phenylsulfonylacetylene (tertiary > secondary > primary) is a method to prepare (*Z*) adducts of α-iodo-β-alkyl-vinyl sulfones (eq 11).[22a] ***Triethylborane*** can replace hexabutyldistannane in such reactions.[22b] Functionalized vinylcyclopentenes, as mixture of

stereoisomers, can be obtained from vinylcyclopropanes and the title reagent by a radical reaction initiated by phenylthio radicals (eq 12).[23]

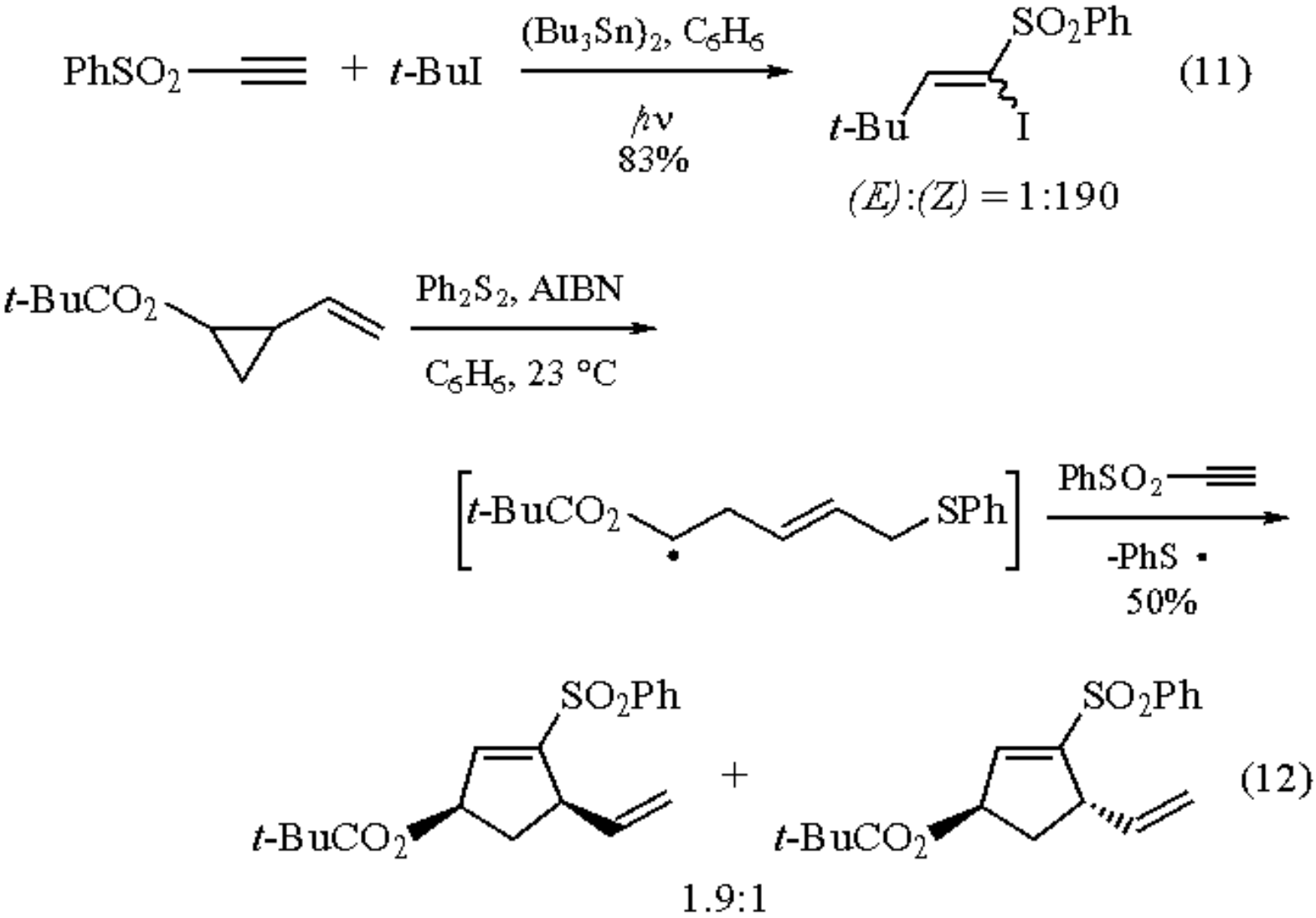

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Phenylsulfonylallene[1]

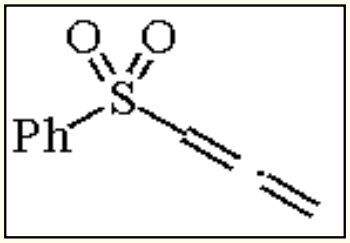

[2525-42-0] · $C_9H_8O_2S$ · Phenylsulfonylallene · (MW 180.24)

(Michael acceptor;[2] dienophile;[3] dipolarophile;[4] [2 + 2] cycloadditions[5])

Alternate Name: 1-phenylsulfonyl-1,2-propadiene.

Physical Data: mp 44-45 °C (isopropyl ether-light petroleum).[6]

Analysis of Reagent Purity: can be distinguished from the isomeric alkynes by NMR: allene resonances, 5.46 (d, 2H) and 6.30 (t, 1H) in $CDCl_3$.

Preparative Methods: prepared via oxidation of the corresponding thioether[2] or by reaction of ***Propargyl Alcohol*** with phenylsulfinyl chloride in high yield.[6] In the latter case the product arises from a 2,3-sigmatropic shift of the intermediate sulfinate ester. It can be also obtained from the reaction of the isomeric alkynes, 1- and 3-phenylsulfonylpropyne, with bases.[7a]

General Discussion.

The title reagent (or the compound tolylsulfonylallene *[17534-15-5]*) is thermodynamically more stable than either of the two related isomeric alkynes (**1**) or (**2**) and thus can be obtained from these under a variety of reaction conditions, among which the most practical appears to be elution over basic alumina.[2] When exposed to a basic reagent, (**1**) or (**2**) first isomerize to the corresponding allene.

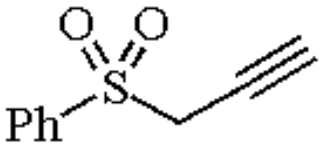

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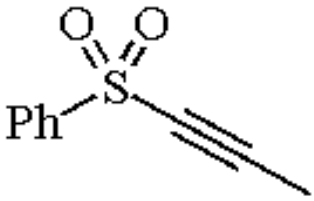

(2)

Sulfur, oxygen, and nitrogen nucleophiles react at the central carbon atom of the allene to produce an alkene that is normally the kinetic product, which isomerizes to the thermodynamically more stable alkene, the *trans*-2-substituted 1-phenylsulfonylpropene (eq 1).[2]

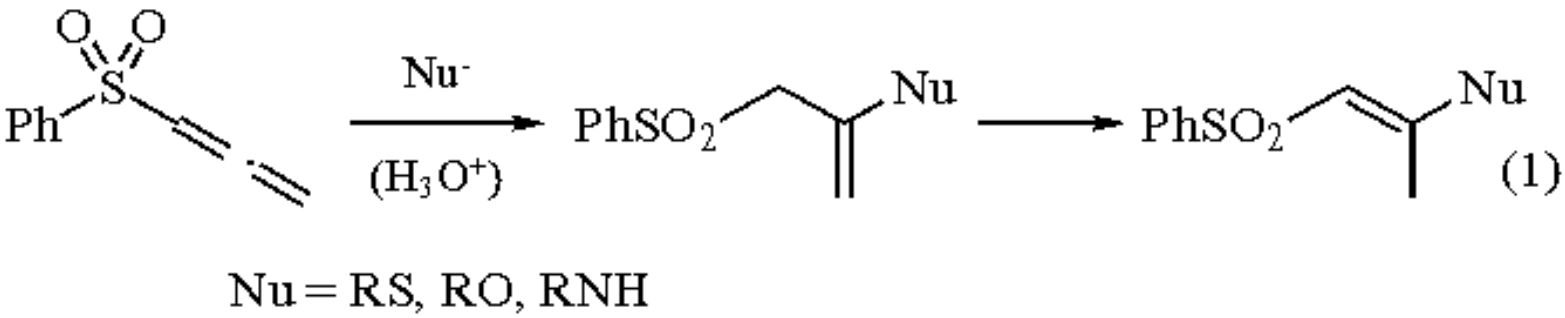

(-)-Ephedrine reacts with the allene to give the enamine that cyclizes stereospecifically to the 1,3-oxazolidine (eq 2).[7] Allyl oxides[8a] and the conjugated bases of hydroxylamines[8b] give adducts that undergo carbanionic Claisen rearrangement. In the example shown in eq 3, this sequence has been used for the synthesis of 2-substituted indoles. Carbon nucleophiles also give addition products at the central carbon atom that eventually isomerize to the more stable isomer. A case in point is the addition of dimethyl malonate (eq 4).[9] The reaction with bis(phenylsulfonyl)methane in the presence of traces of base affords the expected Michael-type adduct in only 6%. The major product in this case was the isomeric adduct shown (eq 4). It was demonstrated that the latter product forms via an initial addition of the phenylsulfonyl anion present in traces in the reaction mixture.[9]

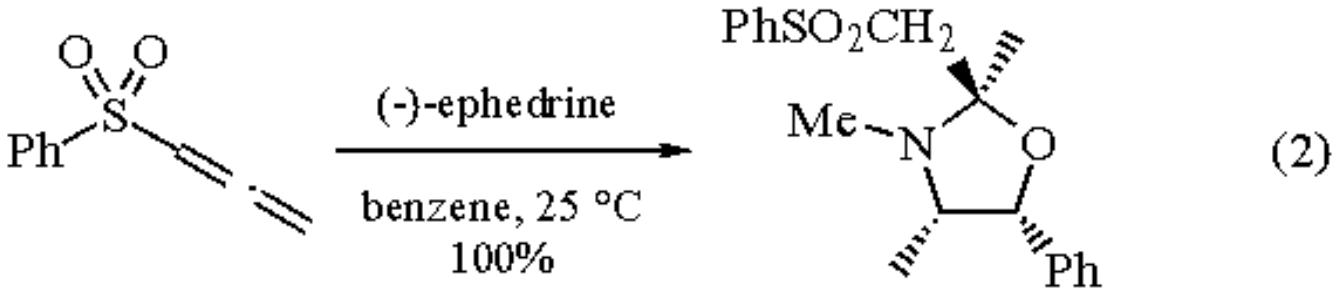

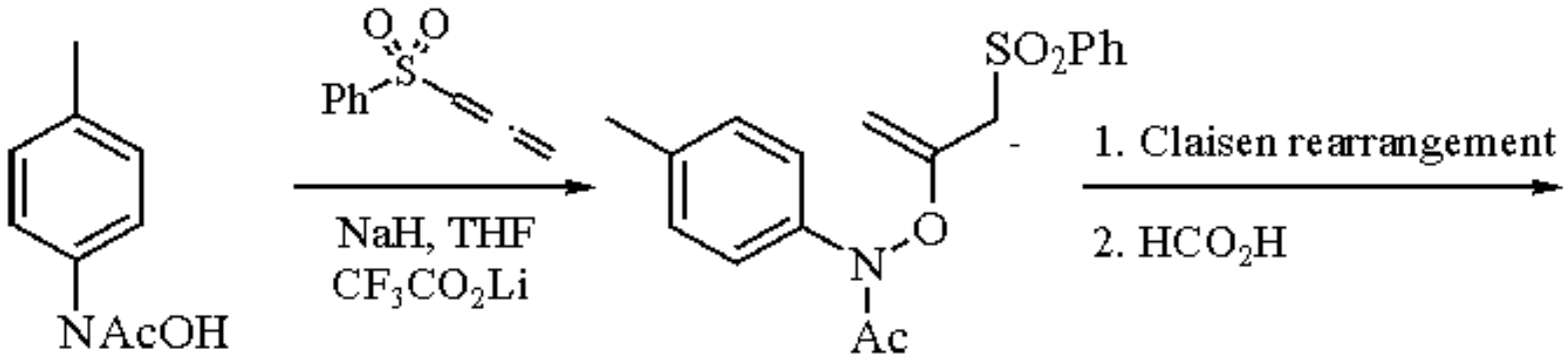
NAcOH
Ph
NaH, THF
CF_3CO_2Li
SO_2Ph
N
O
Ac
1. Claisen rearrangement
2. HCO_2H

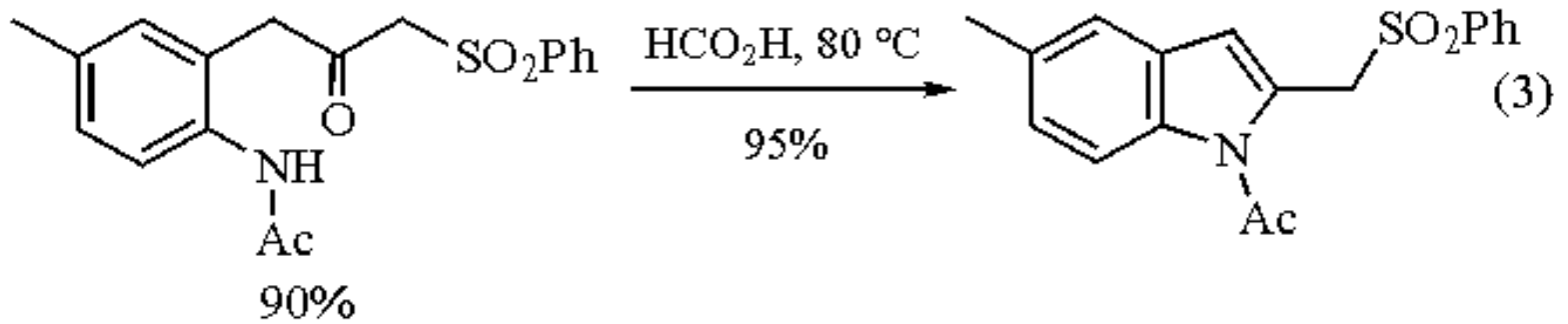
SO_2Ph
O
NH
Ac
90%
HCO_2H, 80 °C
95%
N
Ac

(3)

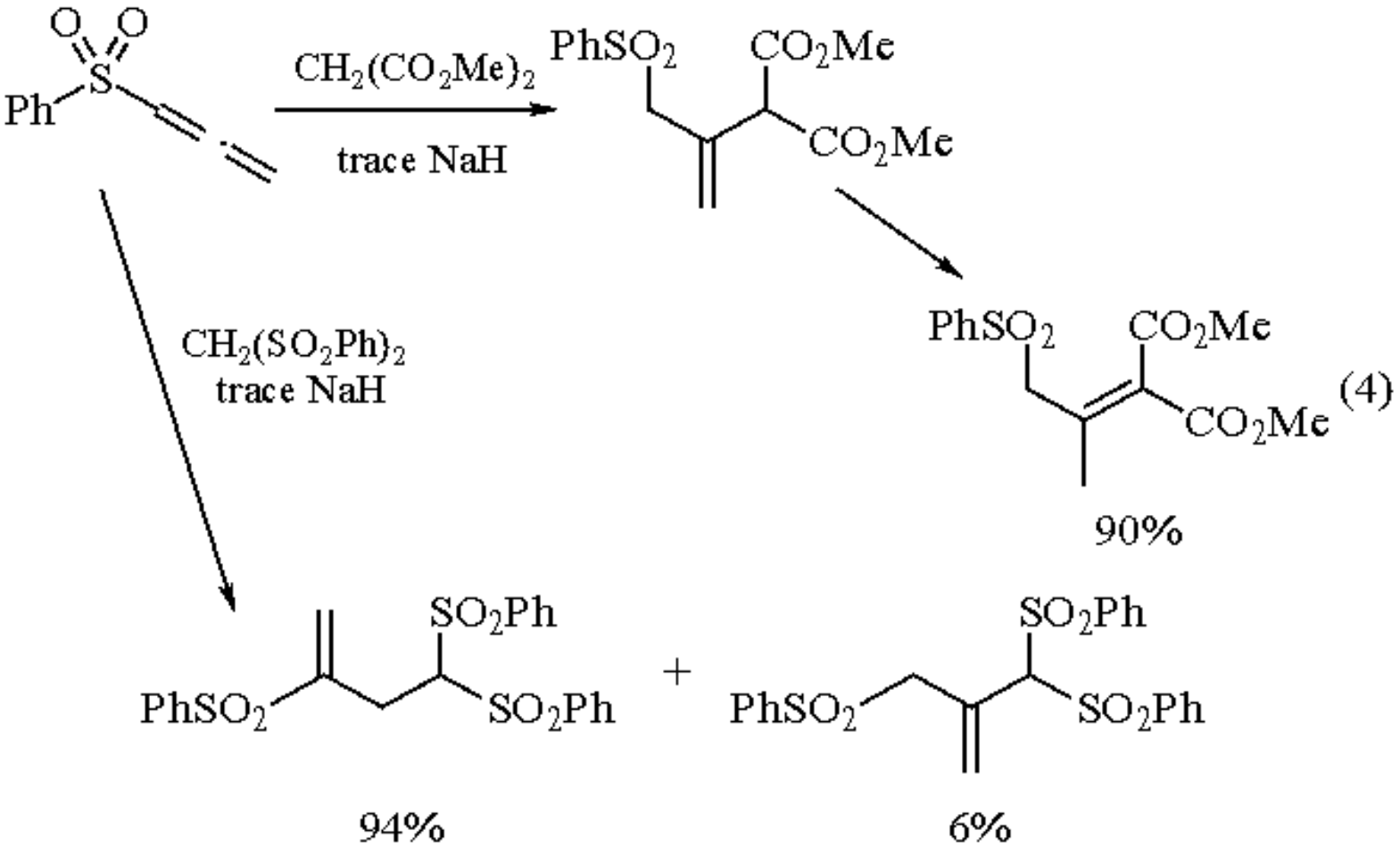
Ph
$CH_2(CO_2Me)_2$
trace NaH
$PhSO_2$
CO_2Me
CO_2Me
90%
$CH_2(SO_2Ph)_2$
trace NaH
SO_2Ph
$PhSO_2$
SO_2Ph
94%
+
6%

(4)

The intermediate α-sulfonyl carbanion generated in the Michael addition can be trapped with electrophilic alkenes, eventually leading to functionalized five-membered rings (eq 5).[9] The reaction with enamines of cyclic ketones (acyclic enamines give [2 + 2] cycloadducts)[5] produces adducts that can be transformed in a simple way into dienes (eq 6).[10]

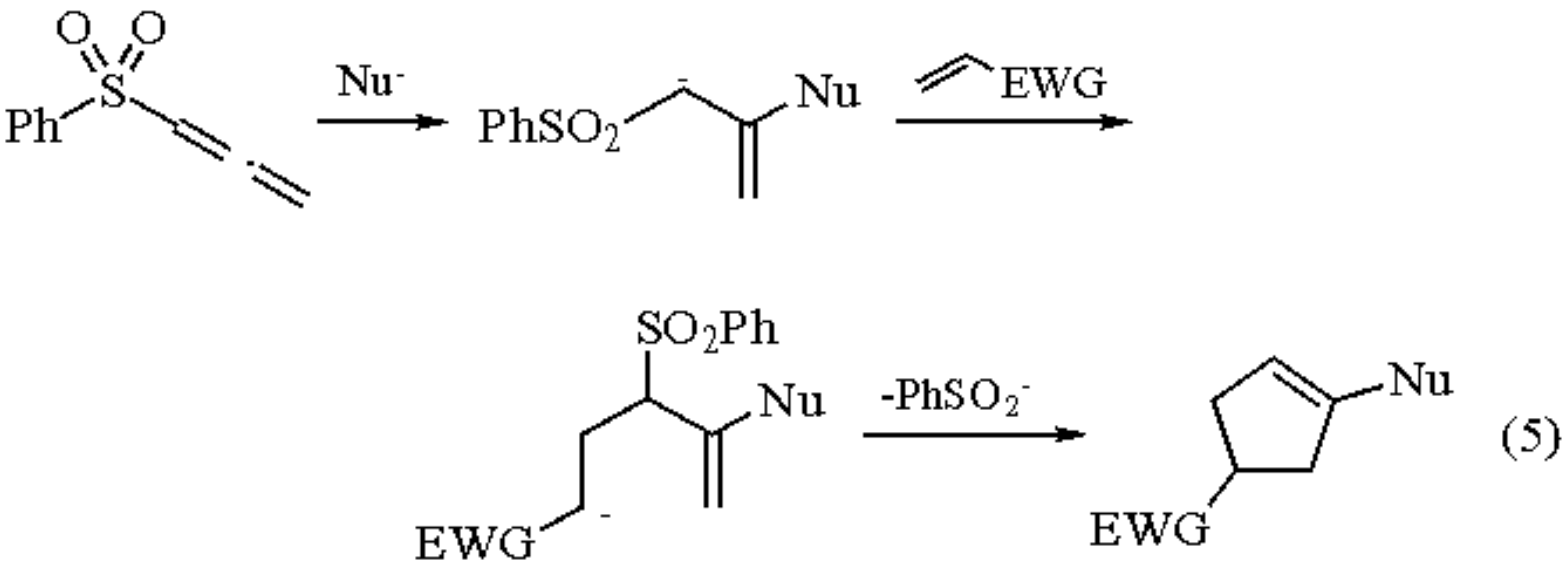

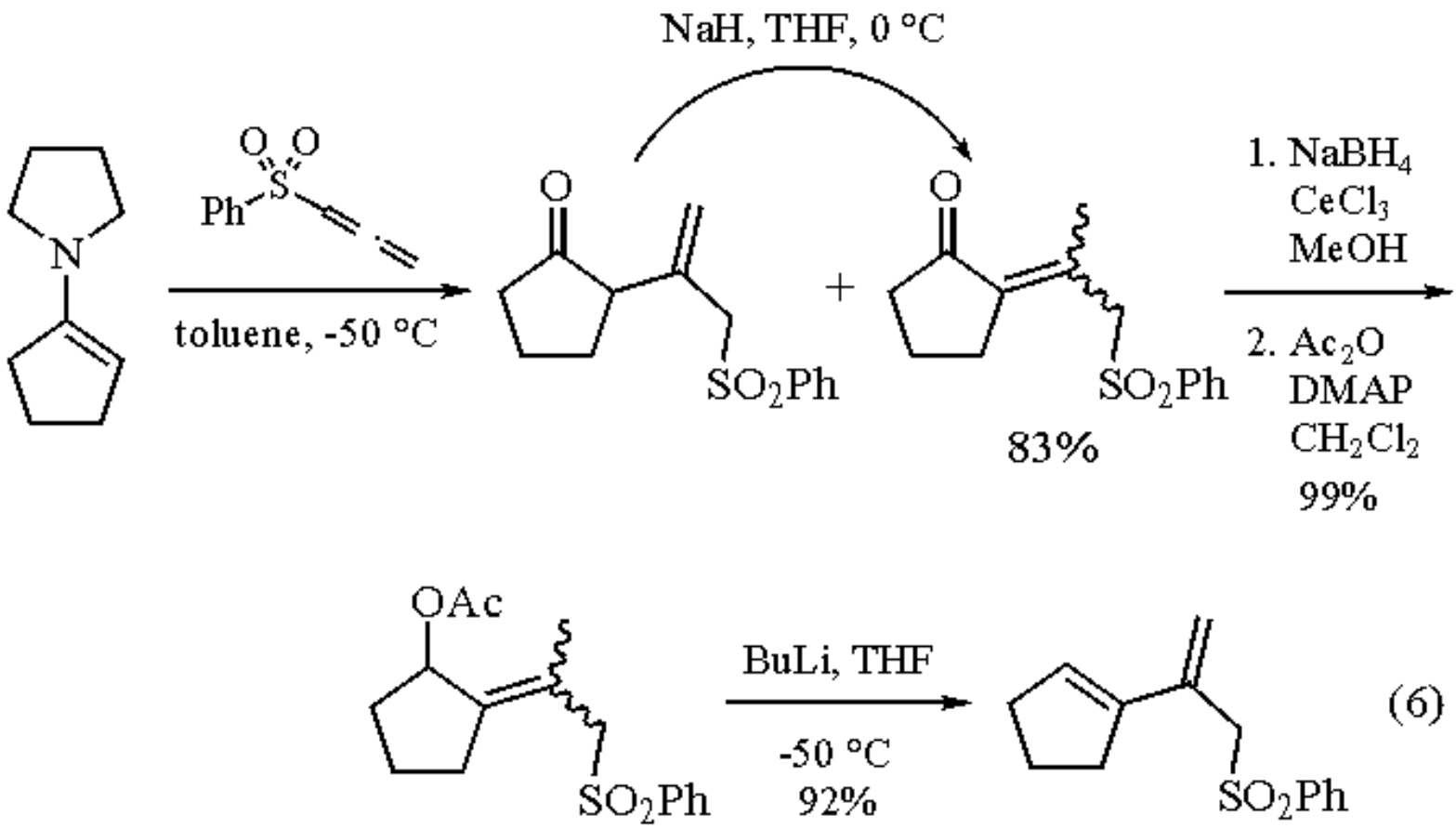

The title reagent, because of its markedly lowered LUMO energy level compared with allene, displays rich cycloaddition chemistry and can be used as the synthetic equivalent of the parent allene after reductive desulfonylation of the adducts.

Diels-Alder reactivity occurs with reactive cyclic dienes such as cyclopentadienes or activated electron-rich acyclic 1,3-

dienes.[3] With cyclic dienes it furnishes mixtures of *endo* and *exo* adducts of which the *endo* form usually predominates. The adducts can be subjected to desulfonylation to mimic the addition of allene[3b] or transformed with bases into α-sulfonyl anions that can be reacted with electrophiles to give a variety of products that can eventually lead to trienes (eq 7).[3b] The adduct with furan, upon hydrogenation, provides a simple entry into substituted cyclohexenols (eq 8).[3c] Higher order cycloadditions occur with tropone and derivatives (eq 9).[3b]

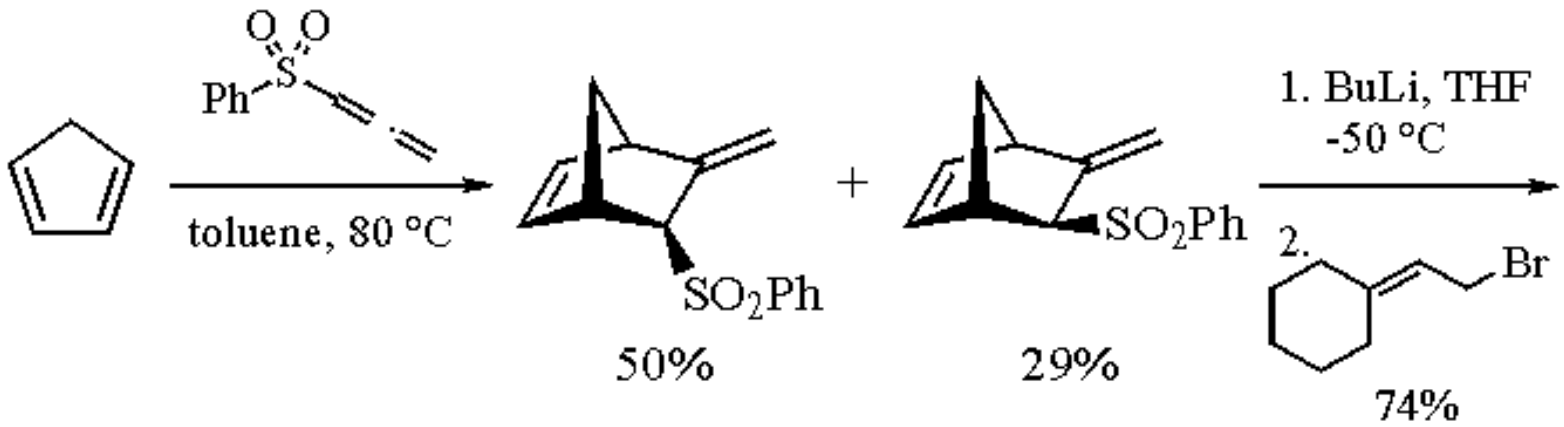

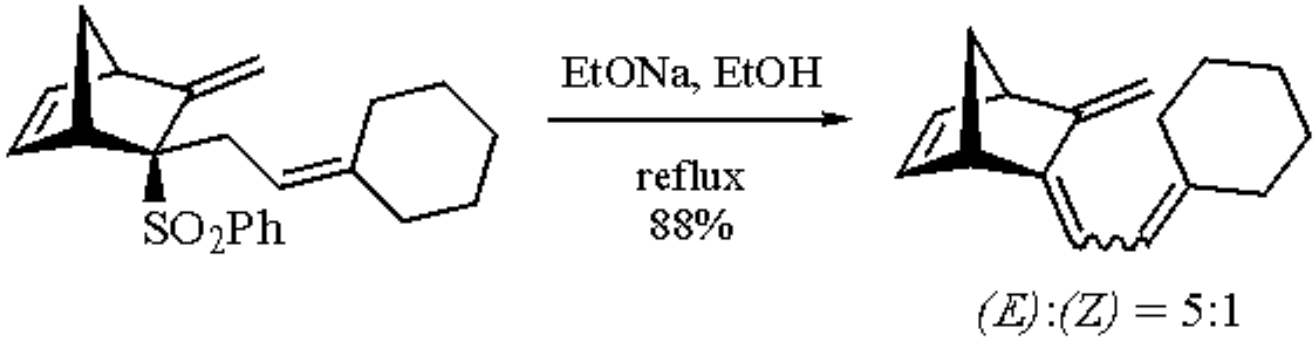

(7)

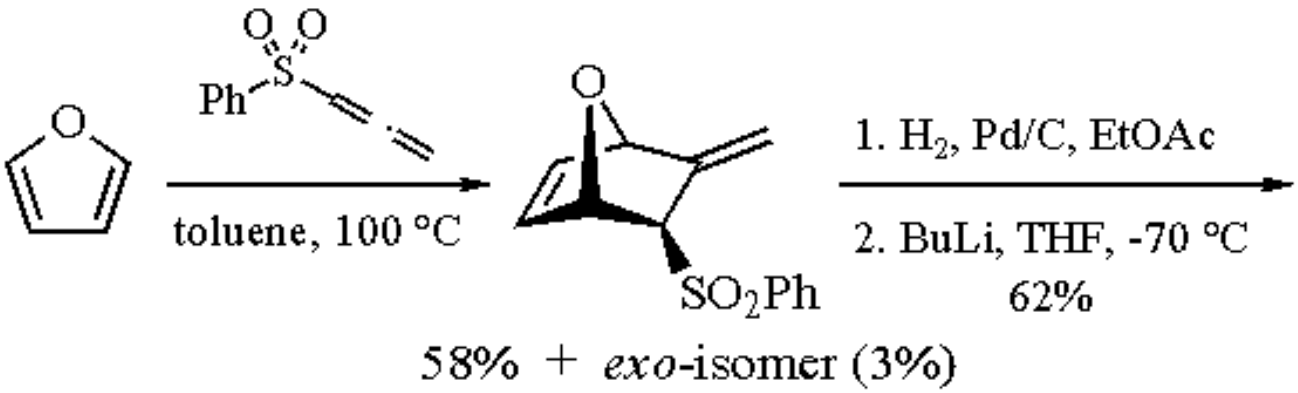

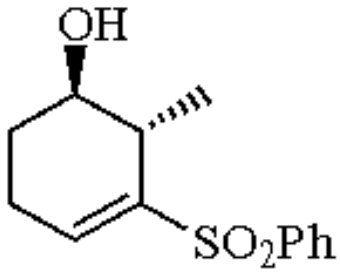

(8)

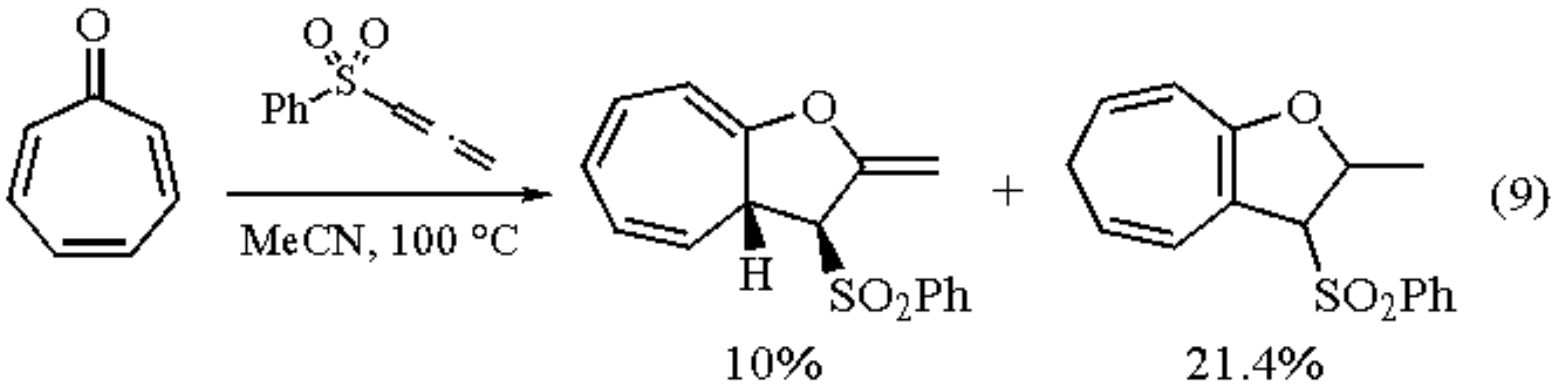

[2 + 2] Cycloadditions with enamines of acyclic ketones and some alkenes give cyclobutanes.[5] In the latter case, the cycloaddition was proved to be catalyzed by ***Ethylaluminum Dichloride*** (eq 10).[5b] This is one of the rare cases in which a sulfonyl-substituted alkene has been shown to be activated by a Lewis acid.

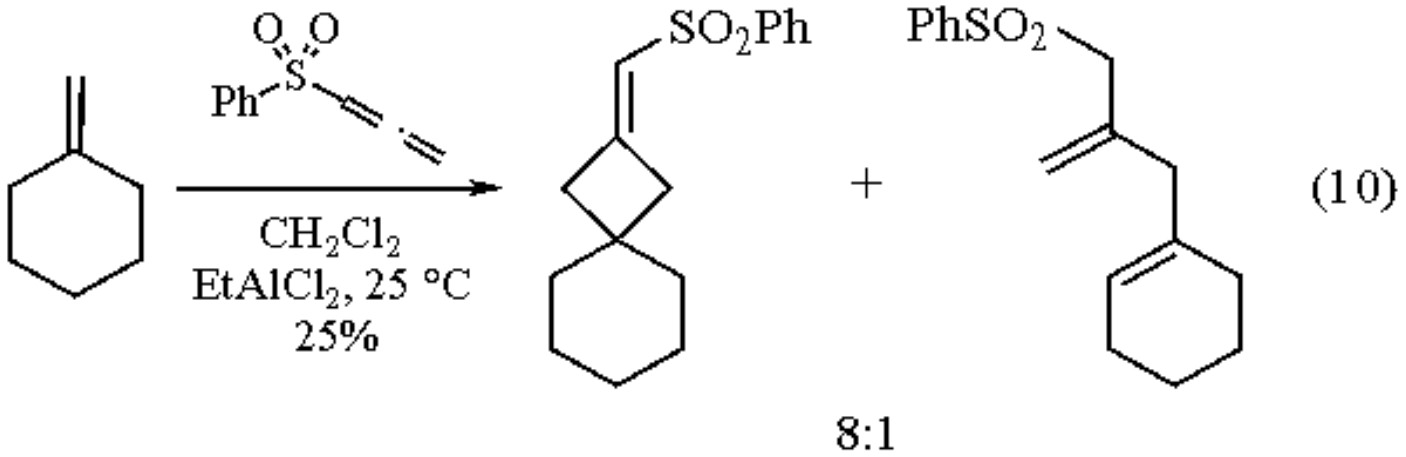

The large field of dipolar cycloadditions include reaction with diazoalkanes,[11] nitrones,[12] and nitrile oxides[13] among others.[14] The reactive site is always the double bond α to the phenylsulfonyl group,[4] at variance with the lower oxidized molecules (i.e. phenylthio- and phenylsulfinylallene). Among the several examples of dipolar cycloadditions of the title reagent, those worth mentioning are the preparation of benzazepines with *N*-phenyl-substituted nitrones (eq 11)[12b,c] and of α,β-unsaturated carbonyl compounds with alkyl-substituted ones (eq 11).[12d]

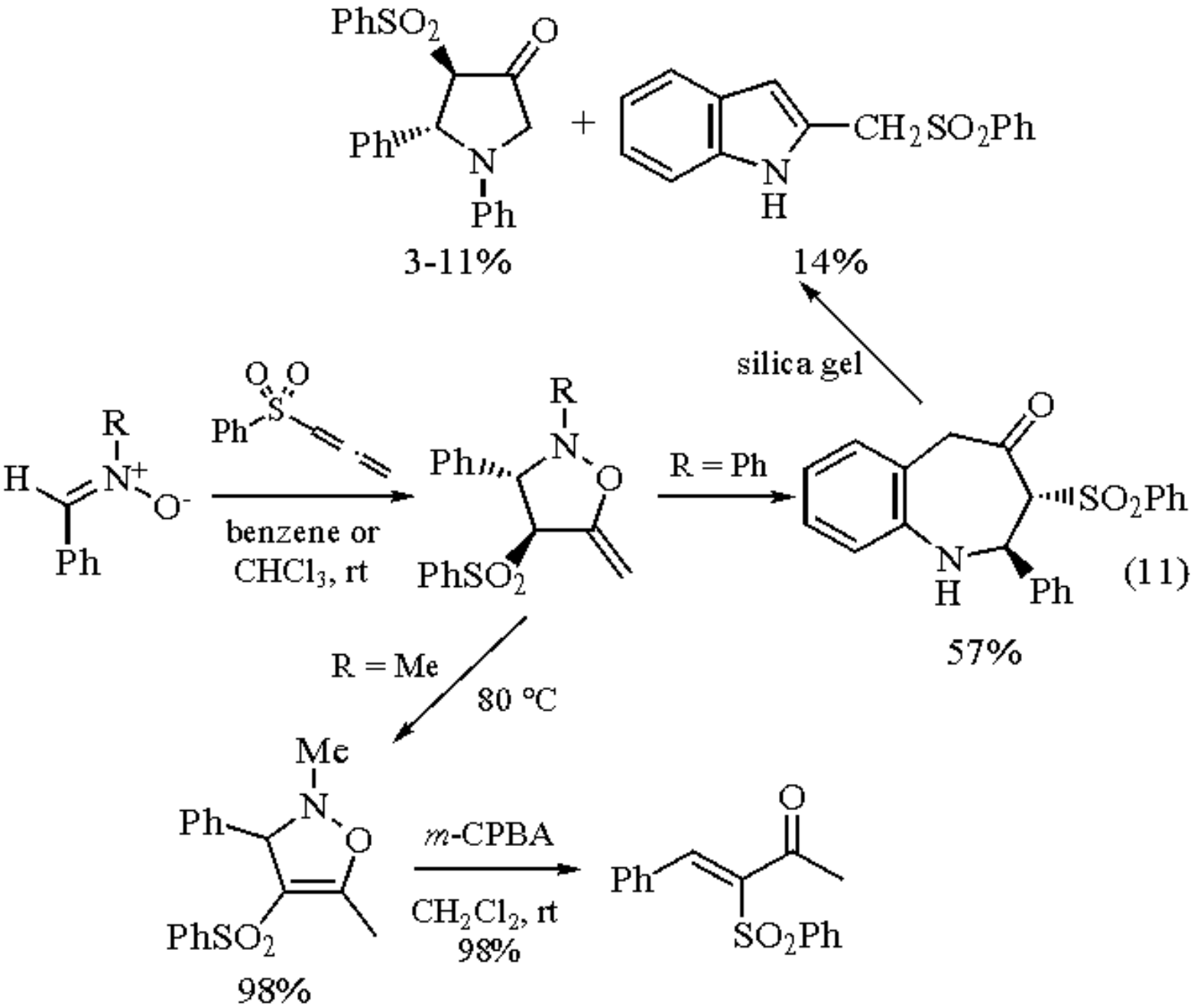

Electrophilic addition of bromine or iodine to phenylsulfonylallene gives 2,3-dihalo-1-phenylsulfonyl-1-propenes, which display a rich chemistry.[15a,b] An example is reported (eq 12).[15a] Similarly useful are the adducts of thiophenol, $PhSO_2CH_2C(SPh)=CH_2$,[15c] and phenylsulfinic acid, $PhSO_2CH_2C(SO_2Ph)=CH_2$.[15d]

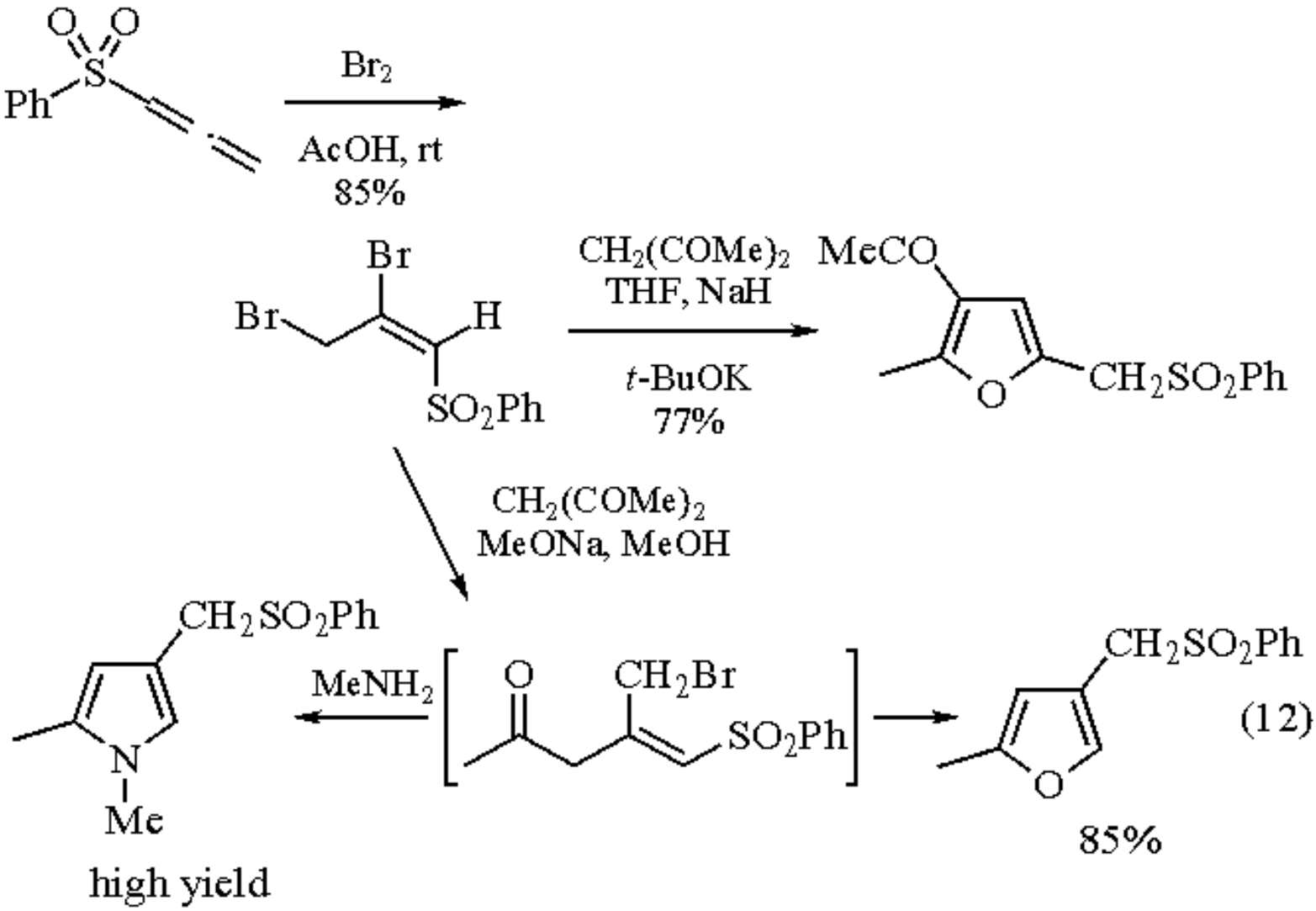

Related Reagents.

1-Methoxy-1,2-propadiene.

---

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8. (a) Denmark, S. E.; Harmata, M. A.; White, K. S. *JOC* **1987**, *52*, 4031. (b) Blechert, S. *HCA* **1985**, *68*, 1835.
9. (a) Padwa, A.; Yeske, P. E. *JACS* **1988**, *110*, 1617. (b) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D.; McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *JOC* **1991**, *56*, 3556. (c) Padwa, A.; Yeske, P. E. *JOC* **1991**, *56*, 6386.

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12. (a) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *JOC* **1988**, *53*, 2238. (b) Parpani, P.; Zecchi, G. *JOC* **1987**, *52*, 1417. (c) Padwa, A.; Kline, D. N.; Norman, B. H. *JOC* **1989**, *54*, 810. (d) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. *JOC* **1989**, *54*, 2862.
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15. (a) Padwa, A.; Murphree, S. S.; Yeske, P. E. *JOC* **1990**, *55*, 4241. (b) Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. L.; Murphree, S. S.; Yeske, P. E. *JOC* **1992**, *57*, 1161. (c) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *JOC* **1990**, *55*, 955. (d) Padwa, A.; Murphree, S. S.; Yeske, P. E. *TL* **1990**, *31*, 2983.

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4-Phenylsulfonyl-2-butanone Ethylene Acetal

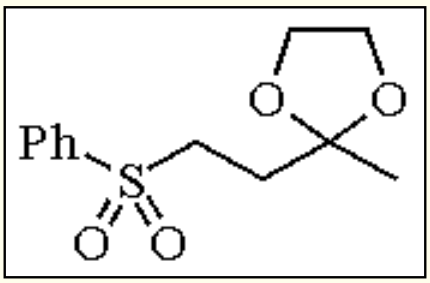

[56161-54-7] · $C_{12}H_{16}O_4S$ · 4-Phenylsulfonyl-2-butanone Ethylene Acetal · (MW 256.35)

(a reagent for synthesizing various derivatives of 2-alkanones)

Alternate Name: PSB-EA.

Physical Data: colorless crystals; mp 33-34 °C or 41-42 °C.[1,2]

Preparative Method: by the Michael addition of benzenesulfinic acid (see ***Sodium Azide***) to 3-buten-2-one followed by acetalization with ethylene glycol.[1,2]

Synthesis of 2-Alkanones and 3-Alken-2-one.

Monoalkylation of 4-phenylsulfonyl-2-butanone ethylene acetal (**1**) takes place at the position α to the phenylsulfonyl group on successive treatment with ***n-Butyllithium*** and then with an alkyl halide (or tosylate). Deprotection of the acetal group and subsequent elimination of the benzenesulfinic acid moiety with a base transforms the monoalkylation product to the corresponding 3-alken-2-one (eq 1).[1,3] A 2-alkanone is obtainable from the monoalkylation product by reductive desulfurization and subsequent acidic deprotection (eq 2).[2-5]

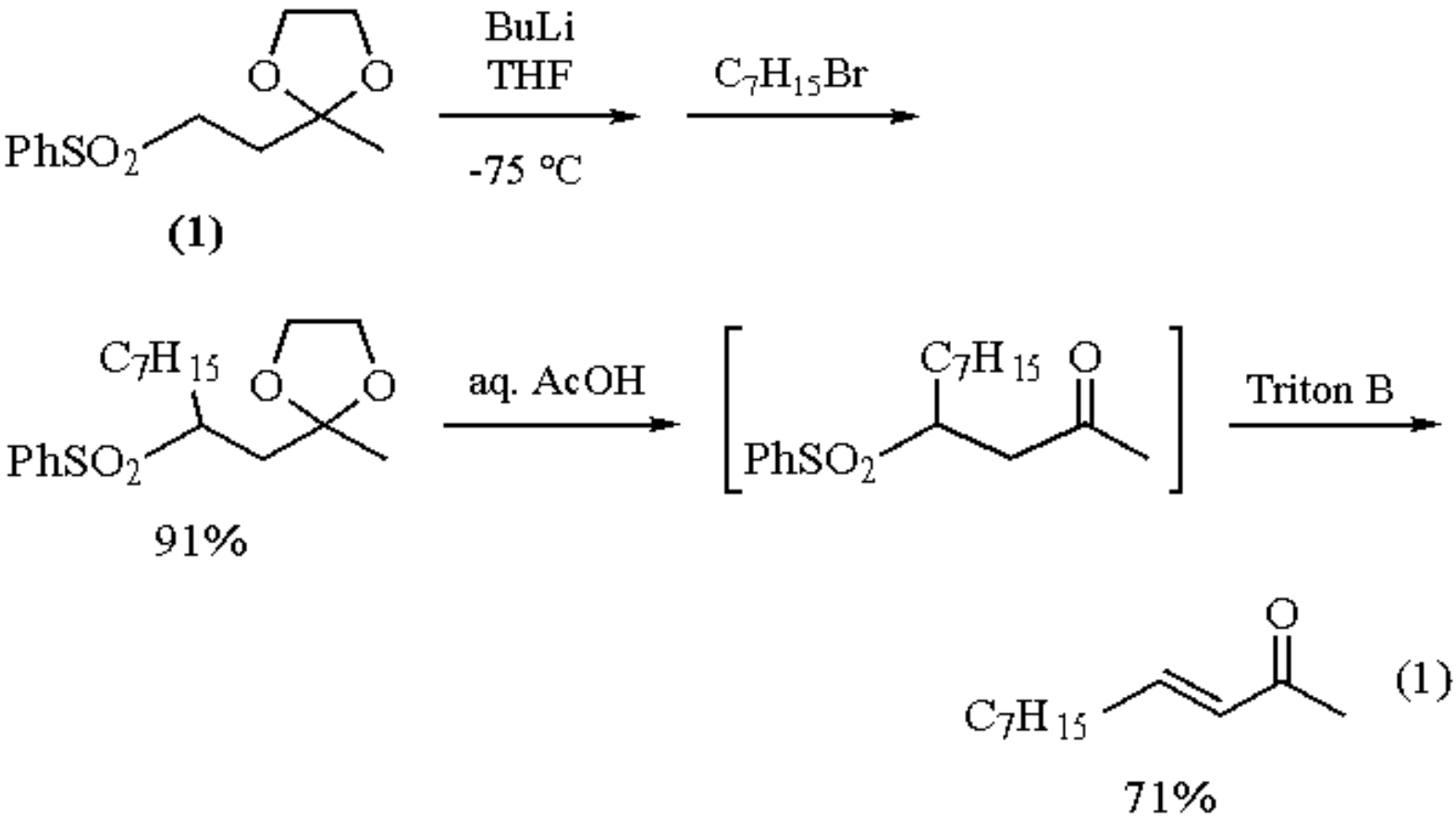

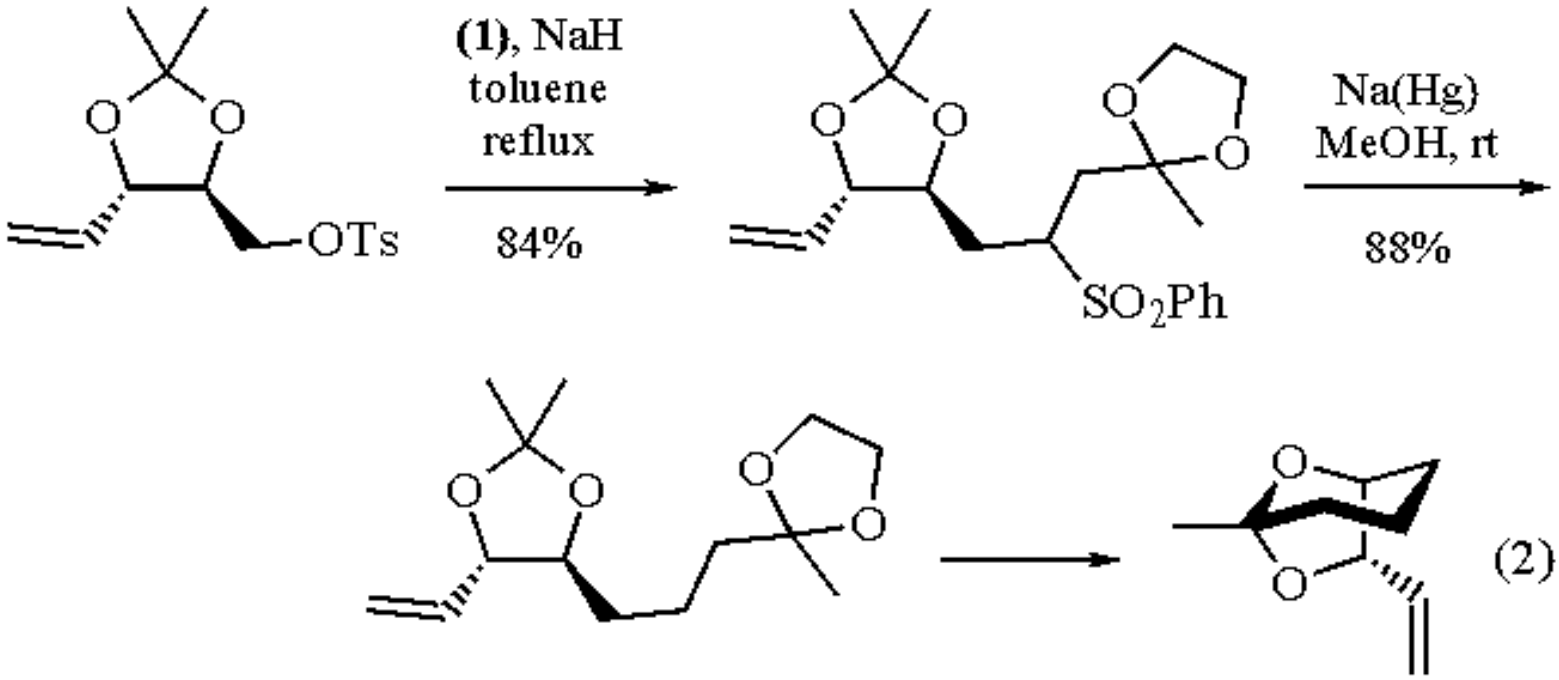

Alkane-2,5-dione Synthesis.

On treatment with *n*-BuLi and an acyl chloride, (**1**) affords an α-acylated product, which easily undergoes reductive desulfurization with ***Aluminum Amalgam*** or ***Sodium Amalgam***. Deprotection forms an alkane-2,5-dione (eq 3).[6,7]

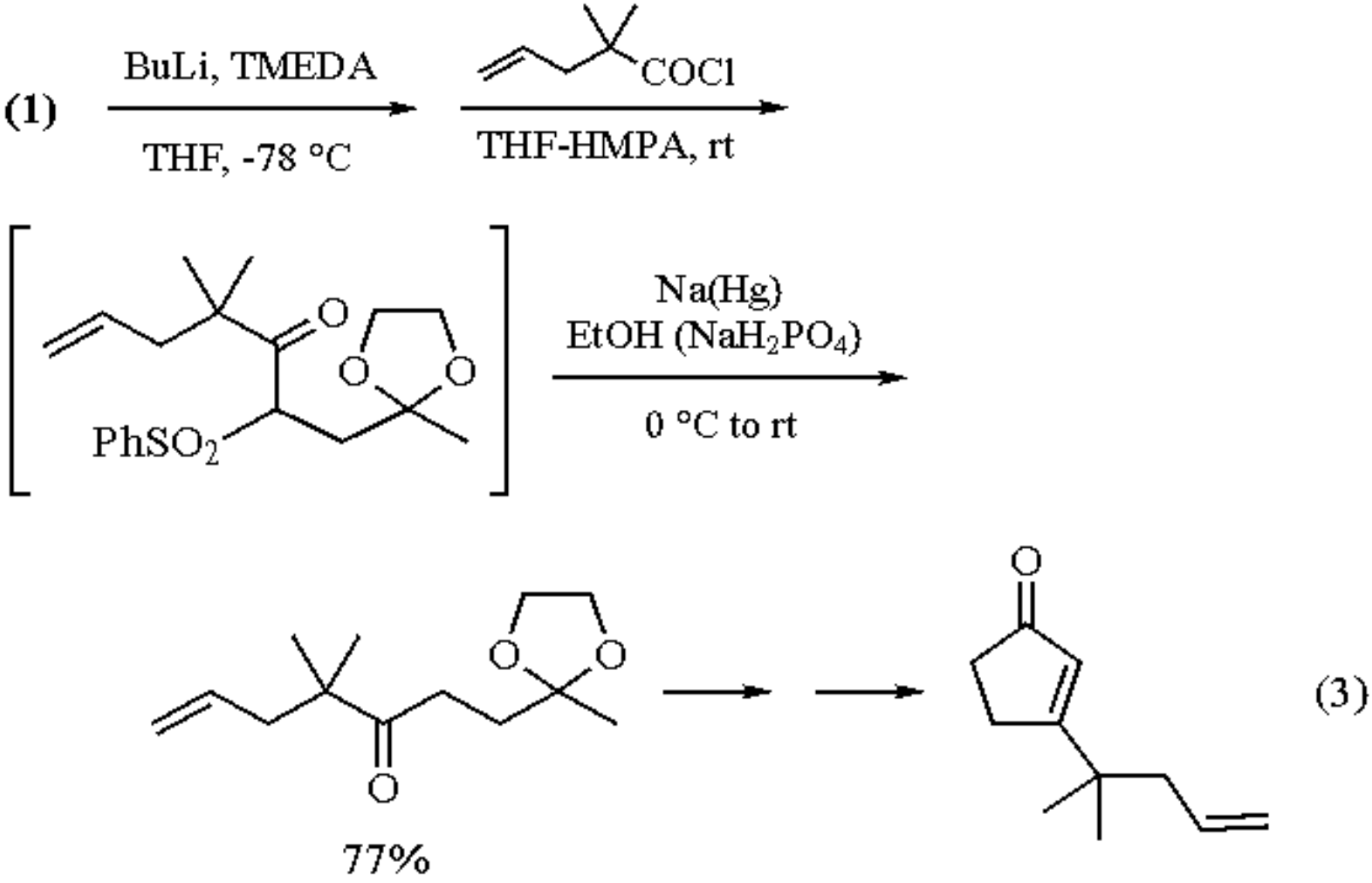

Synthesis of 6-Hydroxy-2-alkanones.

The lithio derivative of (**1**) reacts with a terminal epoxide to give a ring-opened product. Acidic deprotection of the product forms 6-hydroxy-2-alkanone which cyclizes to give a δ-lactol (eq 4).[8]

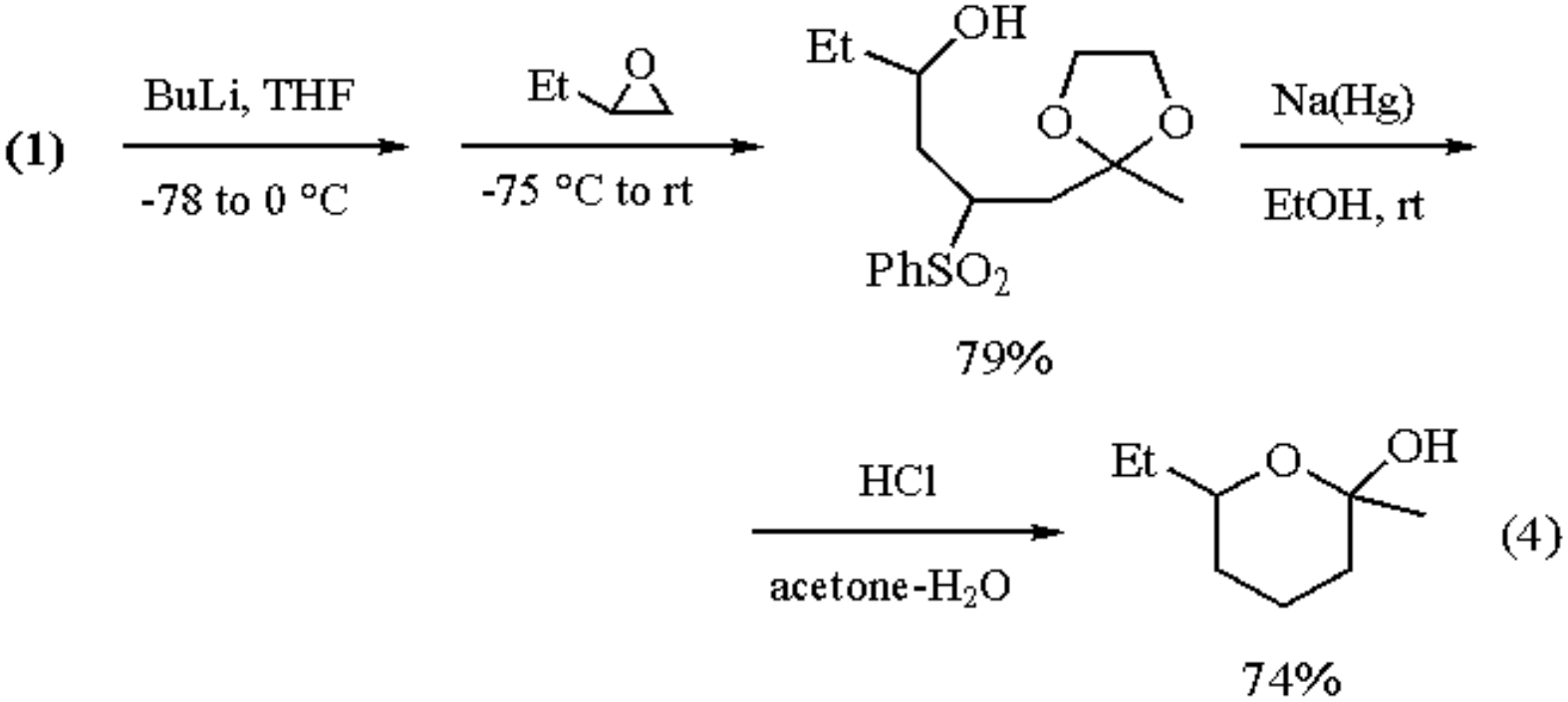

Related Reagents.

3-(Phenylsulfonyl)propanal Ethylene Acetal.

---

1. Kondo, K.; Tunemoto, D. *TL* **1975**, 1007.
2. Wershofen, S.; Classen, A.; Scharf, H. D. *LA* **1989**, 9.
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5. Wershofen, S.; Scharf, H. D. *S* **1988**, 854.
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8. Kondo, K.; Saito, E.; Tunemoto, D. *TL* **1975**, 2275.

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4-Phenylsulfonyl-3-buten-2-one[1]

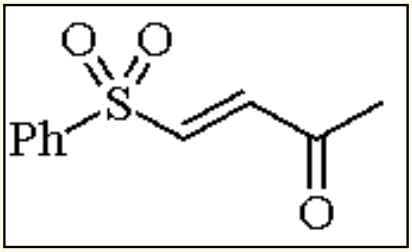

[21860-46-8] · $C_{10}H_{10}O_3S$ · 4-Phenylsulfonyl-3-buten-2-one · (MW 210.27)

(methyl vinyl ketone equivalent which does not undergo polymerization; dienophile)

Physical Data: needles, mp 61-62 °C.

Solubility: insol water; sparingly sol pentane, hexane; sol most other organic solvents.

Preparative Methods: from ***Methyl Vinyl Ketone*** and ***Thiophenol*** in chloroform followed by treatment with ***N-Chlorosuccinimide*** and base-catalyzed dehydrochlorination to give the 4-phenylthiobut-3-en-2-one,[2] oxidation of which with ***m-Chloroperbenzoic Acid*** in ether gives a mixture of geometric isomers of the sulfone.[3] ***Sodium Benzenesulfinate*** and ***(E)-4-Chloro-3-buten-2-one*** in methanol give the (*E*) isomer only.[4] Other preparations are from acetylaldehyde dimethyl acetal[5] and phenylsulfonylmethyl *p*-tolyl sulfoxide and propionaldehyde.[6]

Purification: recrystallization from ether/pentane.[3,4]

Handling, Storage, and Precautions: no special precautions are required although storage at 4 °C or lower will prolong its shelf-life. It is also recommended to protect from light as isomerization to the (*Z*) isomer takes place.

Reactions with Nucleophiles.

Like 4-chlorobut-3-en-2-one, the sulfone serves as an effective methyl vinyl ketone equivalent in the conjugate addition of lithiated carbanions under aprotic conditions.[4,7] In an addition-elimination sequence the sulfonyl group is less reactive than the chlorine and sometimes leads to addition only to give sulfone products.[8] When elimination is desired under very mild conditions, then the related 4-sulfinylbut-3-en-2-one is a preferred reagent.[8] For example, the latter reagent undergoes conjugate addition with heteronucleophiles such as ***Furan*** and pyrroles in the presence of ***p-Toluenesulfonic Acid*** to form ketovinyl derivatives[8] and a double conjugate addition with diimines under neutral conditions to afford 2-acetonyl-1,2-dihydropyrimidines (eq 1).[5]

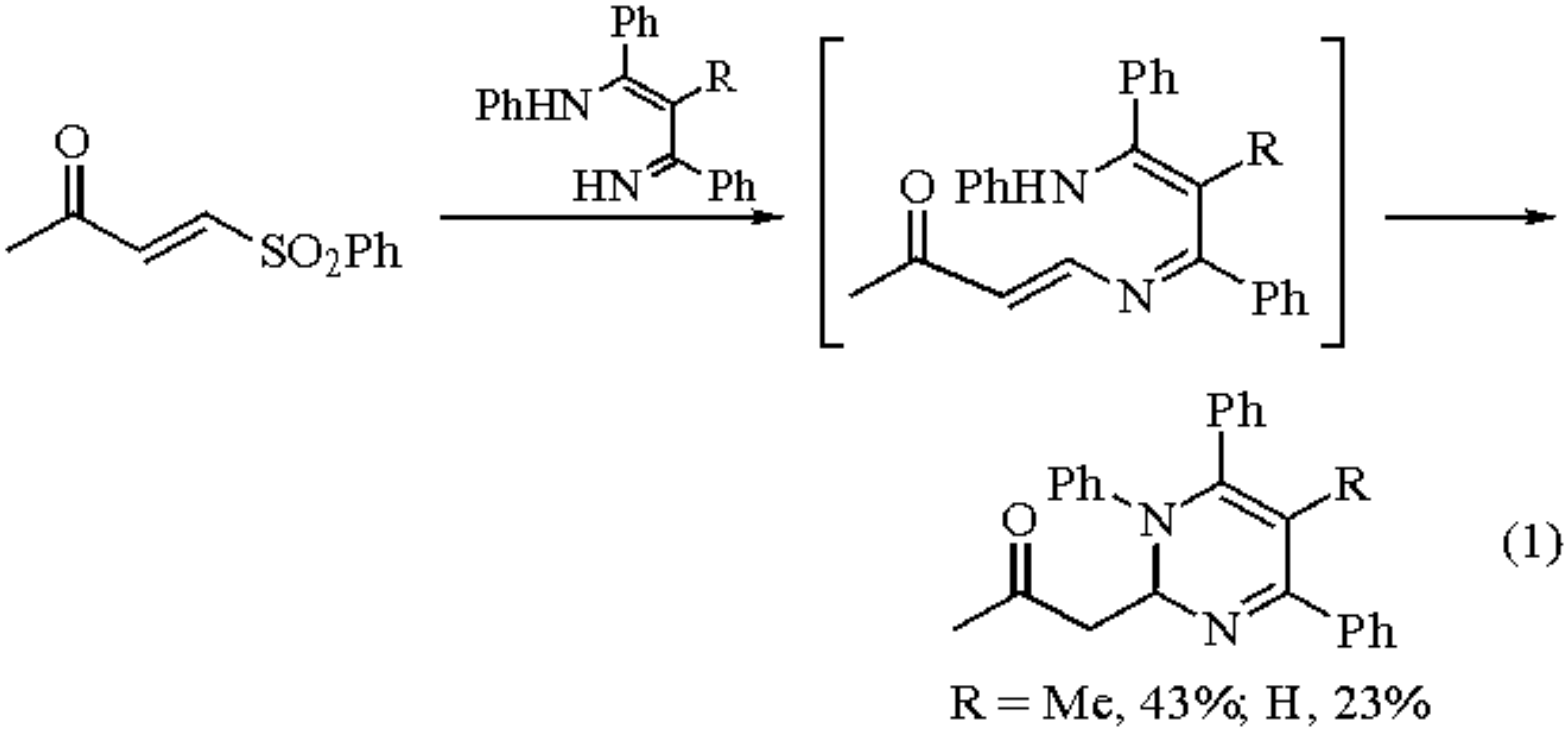

4-Phenylsulfonylbut-3-en-2-one as a Dienophile.

With two electron-withdrawing substituents the sulfone has an electron-deficient double bond and as such is a good dienophile. Under solvent-free conditions it reacts rapidly and cleanly with relatively inactive dienes. For example, when 4-phenylsulfonylbutenone and cyclohexadiene are adsorbed on silica, adduct formation proceeds in nearly quantitative yield after 35 h at room temperature.[9] However, stereoselectivity is poor, giving an *endo*:*exo* ratio of 5:6. When more reactive dienes are employed such as furan and 1-methoxycyclohexa-1,3-diene, selectivity for the *endo* adduct increases to 8:1 and 12:1, respectively. Elimination of the sulfonyl group by the use of ***Sodium Ethoxide*** is facile, affording the corresponding alkenes in very high yields. Thus the sulfone functions as an α,β-alkynic ketone equivalent (eq 2).

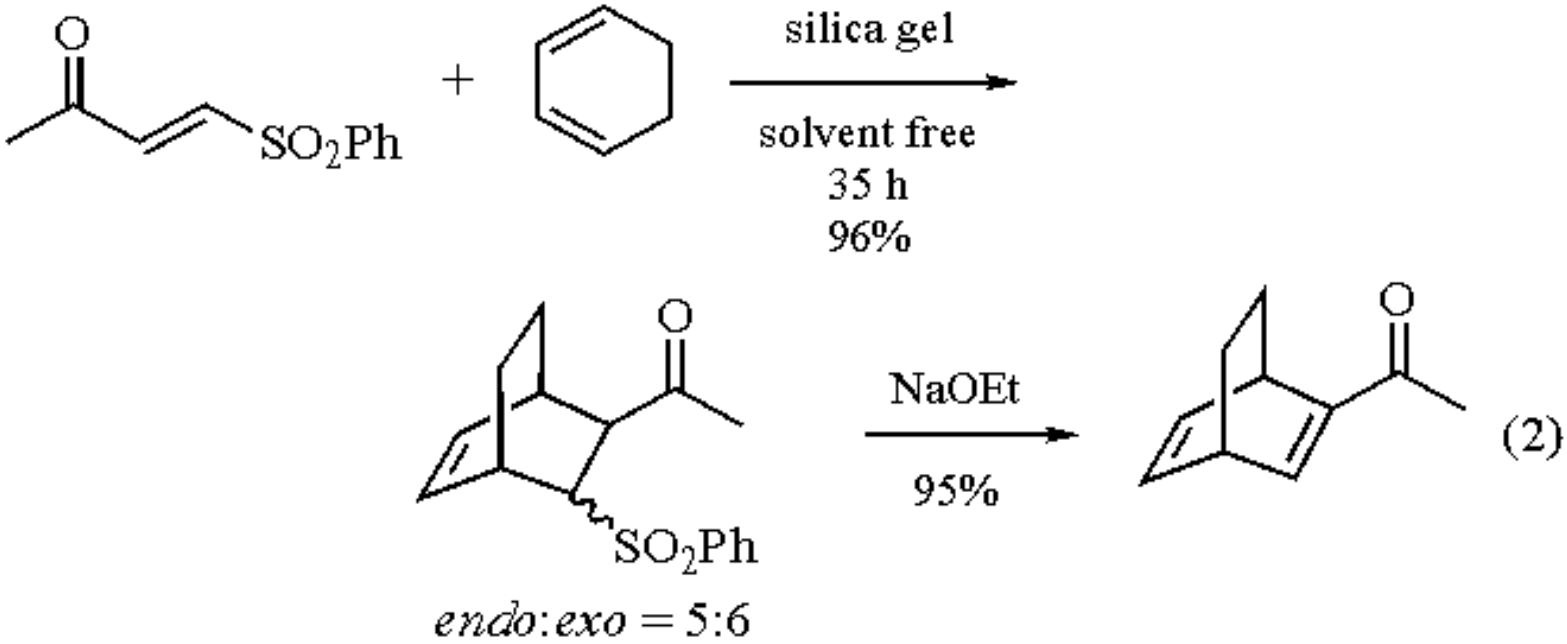

1. (a) Kochetkov, N. K.; Kudryashov, L. J.; Gottich, B. P. *T* **1961**, *12*, 63. (b) For a general discussion on vinyl substitution see Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Patai, S., Ed.; Interscience: London, 1964; Chapter 8, pp 525-546.
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9. Leon, F. M.; Carretero, J. C. *TL* **1991**, *32*, 5405.

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N-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine[1]

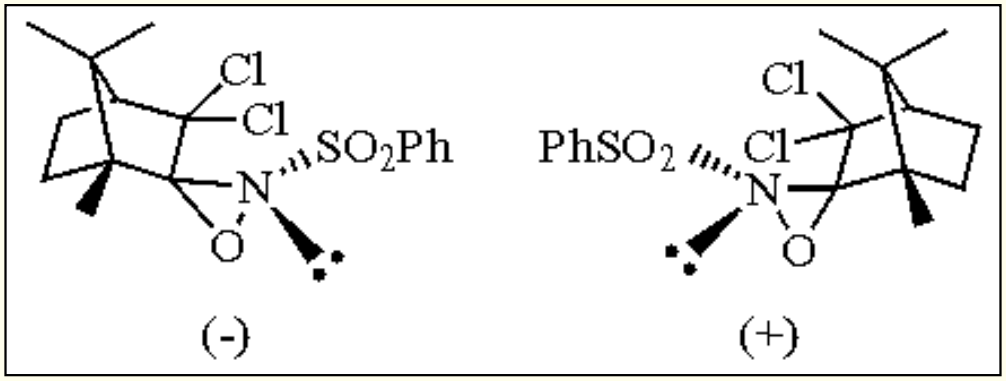

(-)

[22270-28-4] · $C_{16}H_{19}Cl_2NO_3S$ · *N*-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine · (MW 376.33) (+)

[138874-52-9]

(asymmetric oxidizing reagent for the enantioselective oxidation of sulfides to sulfoxides,[1] selenides to selenoxides,[2] and sulfenimines to sulfinimines[3])

Physical Data: mp 121-122 °C; (3´*S*,2*R*)-(-) [α]20D -159° (*c* 4.2, $CHCl_3$); (3´*R*,2*S*)-(+) [α]20D +157° (*c* 4.1, $CHCl_3$).

Solubility: insol H_2O; sol CH_2Cl_2, $CHCl_3$, THF, alcohols; sparingly sol CCl_4.

Form Supplied in: white solid.

Analysis of Reagent Purity: by mp and specific rotation determination.

Preparative Methods: the (-)-oxaziridine (**1**) is prepared from (1*R*)-(+)-camphor by condensation with benzenesulfonamide/$TiCl_4$ (eq 1). The chlorine atoms are introduced via the sulfonimine azaenolate by treatment with ***Sodium Hexamethyldisilazide*** and ***N-Chlorosuccinimide*** or preferably with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** and 1,3-dichloro-5,5-dimethylhydantoin.[4,5] Although oxidation of the dichlorosulfonimine (**2**) requires >95% ***m-Chloroperbenzoic Acid*** and 4-5 days for completion, the oxidation can be carried out on a multigram scale (>60 g). Higher yields of (**1**) are obtained when (**2**) is dissolved in a minimum of the CH_2Cl_2 solvent. The antipode, (+)-(**1**), is similarly available from (1*S*)-(-)-camphor.

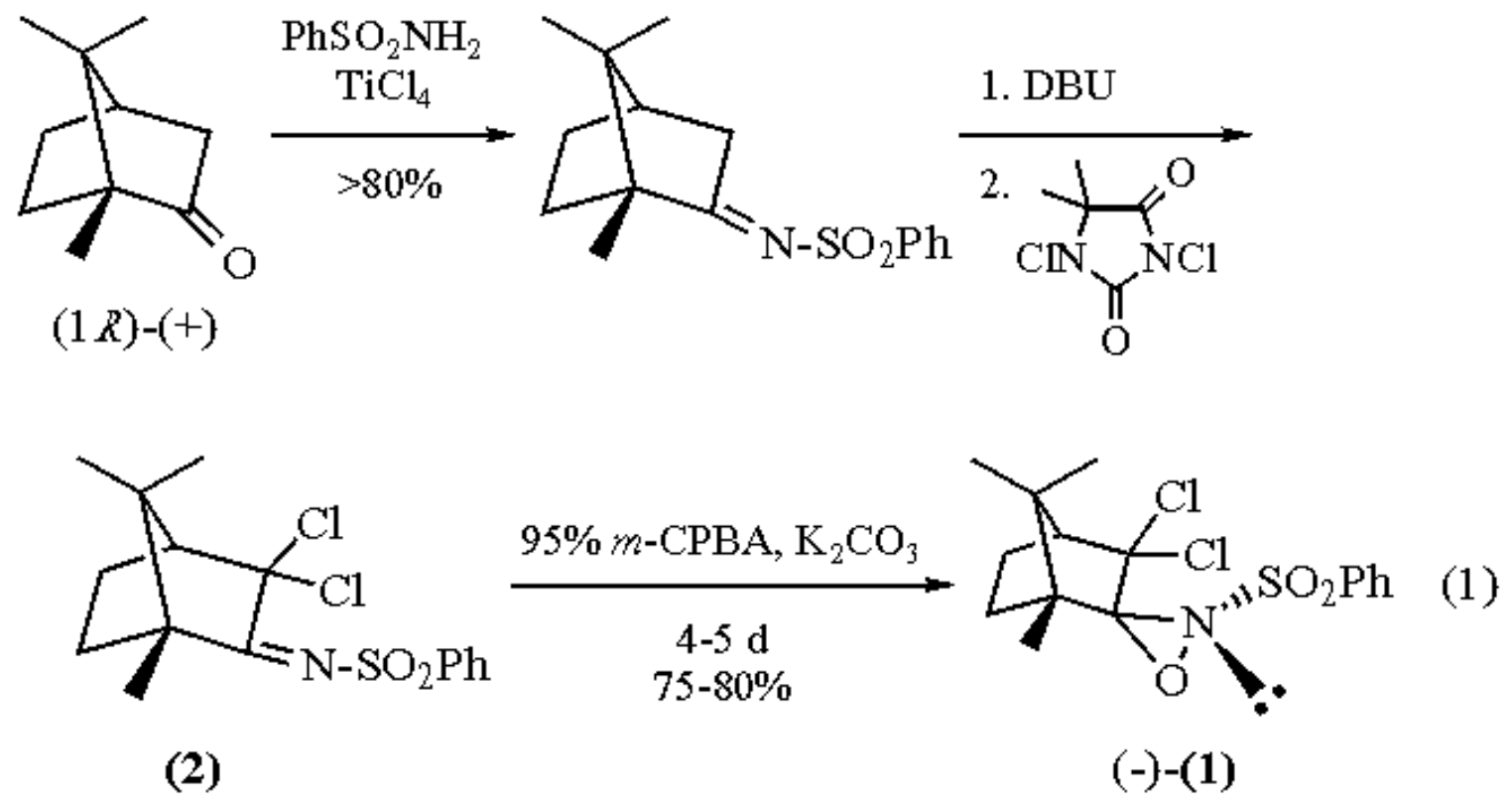

In contrast to 2-(phenylsulfonyl)-3-phenyloxaziridine, this less reactive reagent does not epoxidize alkenes or oxidize amines to amine oxides.

Purification: flash chromatography.

Handling, Storage, and Precautions: store at room temperature.

Asymmetric Oxidation of Sulfides to Sulfoxides.

Enantiopure sulfoxides are important as auxiliaries in the asymmetric construction of C-C bonds.[6] The reaction of an organometallic reagent with a diastereomerically pure ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***, the Andersen synthesis, is the method most often employed for the preparation of nonracemic sulfoxides.[7,8] However, this methodology is limited in the synthesis of highly functionalized sulfoxides as well as certain dialkyl sulfoxides. Alternatively, enantiomerically enriched sulfoxides are available via the asymmetric oxidation of prochiral sulfides to sulfoxides using Kagan's modification of the Sharpless reagent, synthetically useful (>90% ee) only for aryl methyl sulfides (Ar-S-Me)[9] or the more general *N*-sulfonyloxaziridines (**1**).[1]

The asymmetric oxidation of sulfides to the sulfoxides by (-)-(**1**) is carried out at rt in nonpolar solvents (eq 2). Oxidations are generally complete within 1-6 h, although sulfides having electron-withdrawing or sterically demanding groups may require up to 48 h for completion. In these examples, heating to ca. 65 °C increases the rate of oxidation without significantly lowering the ee value. The sulfoxides and the sulfonimines (**2**) are isolated by TLC in >90% yield, with the latter being recycled. The highest enantioselectivities are observed for oxidations in low dielectric solvents such as CCl_4 and for those sulfides (R_L-S-R_S) where the difference in size of the R_L and R_S groups is large, e.g. R_L = aryl or *t*-butyl and R_S = CH_2R. Both enantiomeric sulfoxides are available by choice of the appropriate reagent because the configuration of the oxaziridine three-membered ring controls the absolute stereochemistry of the product, e.g. (-)-(**1**) gives (*S*)-sulfoxides while (+)-(**1**) gives

(*R*)-sulfoxides (eq 2). The molecular recognition is predictable in terms of minimization of nonbonded steric interactions in the transition state. Examples are given in Table 1.[1,8c,10]

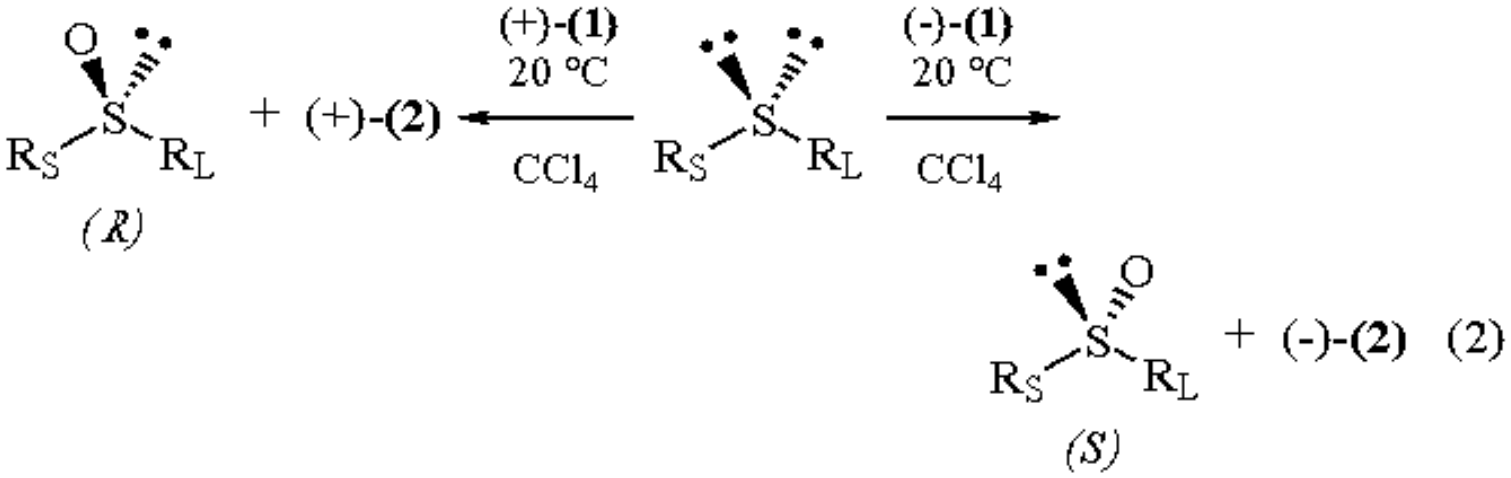

Table 1 Asymmetric Oxidation of Sulfides to Sulfoxides[a] using (+)- and (-)- **(1)**[1]

Sulfide	Oxaziridine	% ee (config.)	Yield (%)	Time (h)
p-Tol-S-Me	(-)- **(1)**	>95 (*S*)	95	1
p-Tol-S-Bu	(-)- **(1)**	91 (*S*)	90	3
	(+)-**(1)**	91 (*R*)	90	3
p-Tol-S-- *i*-Pr	(-)- **(1)**	66 (*S*)	95	6
p-Tol-S-Bn	(-)- **(1)**	94 (*S*)	95	3
Ph-S-cyclopropyl	(-)- **(1)**	92 (*S*)	90	18
t-Bu-S-Me	(-)- **(1)**	94 (*S*)	90	18
	(+)-**(1)**	94 (*S*)	90	18
t-Bu-S-Bn	(+)-**(1)**	91 (*S*)	80	48
	(+)-**(1)** (65 °C)	85 (*S*)	80	1
Bn-S-Me	(-)- **(1)**	13 (*S*)	94	3
Ph-S-CH=CH $_2$	(-)- **(1)**	85 (*S*)	60	48
Ph-S-CH $_2$CO$_2$Me	(-)- **(1)**	94 (*S*)	65	48
Ph-S-CH $_2$CN	(-)- **(1)**	>95 (*S*)	45	48

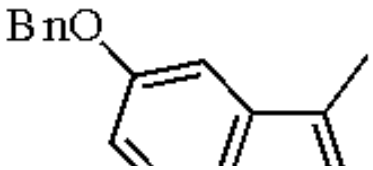

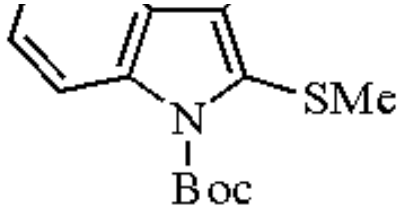	(-)-(**1**)	86 (*S*)	84	96[8c]
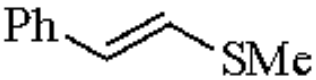	(-)-(**1**)	42 (*S*)	87	18[10]
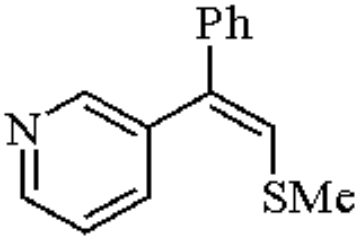	(-)-(**1**)	64 (*S*)	87	6[10]

[a] At rt in CCl_4.

Asymmetric oxidation of 2,3-epoxy sulfides with (-)-(**1**), double stereodifferentiation, gives 2,3-epoxy sulfoxide diastereoisomers (eq 3).[11] Lower de values were observed for the other epoxy sulfide enantiomer. The modified Sharpless reagent gave better de values (5.1:1) with the methyl sulfides.

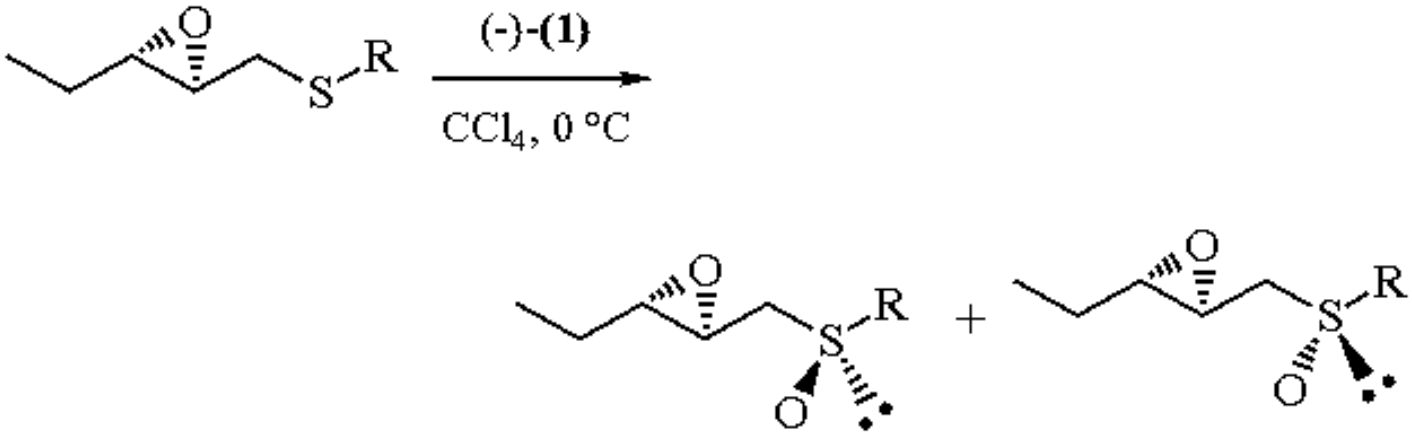

R = Ph	13:1	65%
R = Me	1.5:1	85%

Asymmetric Oxidation of Selenides to Selenoxides.

The difficulty in preparing optically active selenoxides is that they are configurationally unstable, forming achiral hydrates, $ArSe(OH)_2R$, with trace amounts of water.[12] Enantioselective oxidation of alkyl aryl selenides by (-)-(**1**), because of its aprotic nature, gives the selenoxides in 91% to >95% ee (eq 4). Oxidations are carried out as before (eq 2) except that moisture and trace amounts of acids in the solvents need to be rigorously excluded. The optically active selenoxides (Ar = 2,4,6-triisopropylphenyl) can be isolated by chromatography on basic alumina, but with some racemization (85-87% ee).[12]

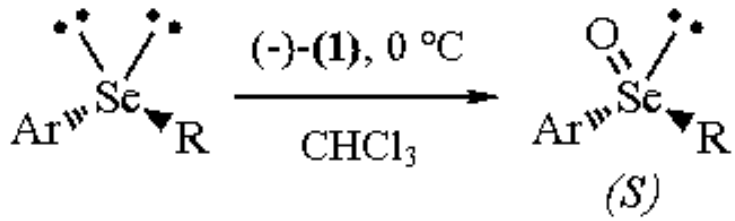

(4)

Ar = Ph, 2,4,6-*i*-$Pr_3C_6H_2$; R = Me, Et, $CH_2C_6H_4OMe$-*p*

Asymmetric oxidation of allylic selenides gives allylic alcohols via a [2,3]-sigmatropic selenoxide-selenate rearrangement (eq 5).[2] In both oxidations, eqs 4 and 5, the configuration at the selenoxide is that predicted based on the sulfoxide model.

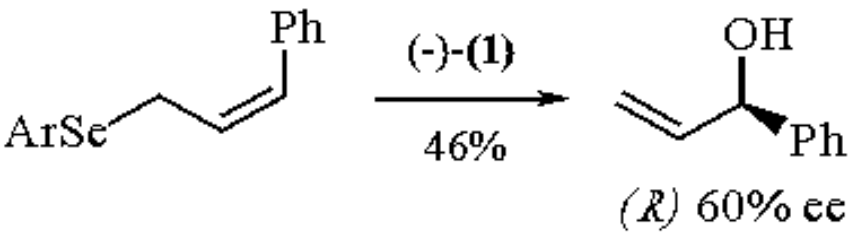

(5)

Ar = 2,4,6-*i*-$Pr_3C_6H_2$

Aryl vinyl selenides (**3**) are oxidized by (-)-(**1**) to selenoxide intermediates which undergo elimination to chiral allenic sulfones (eq 6).[12] Somewhat better ee values were observed using the modified Sharpless reagent (up to 38% ee). Asymmetric oxidation of cyclohexyl selenides by oxaziridine (-)-(**1**) give axially chiral cyclohexylidene derivatives in up to 83% ee (eq 7).[13]

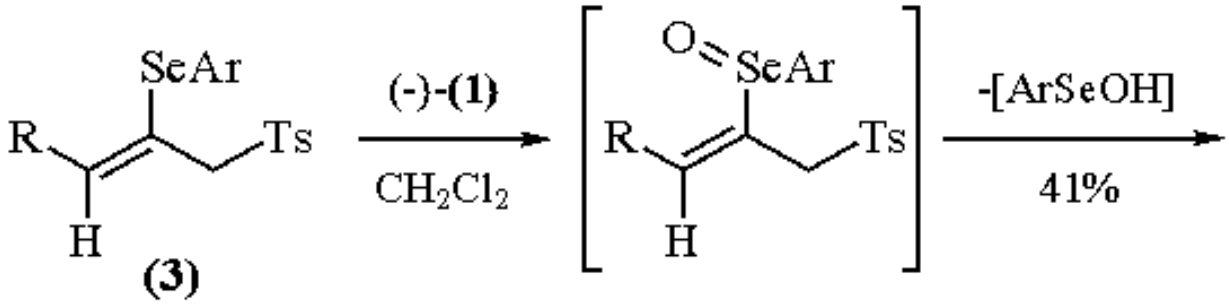

R = Pr, Ar = *o*-$O_2NC_6H_4$

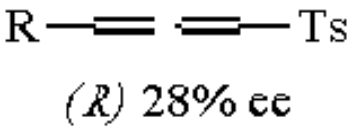

(6)

(*R*) 28% ee

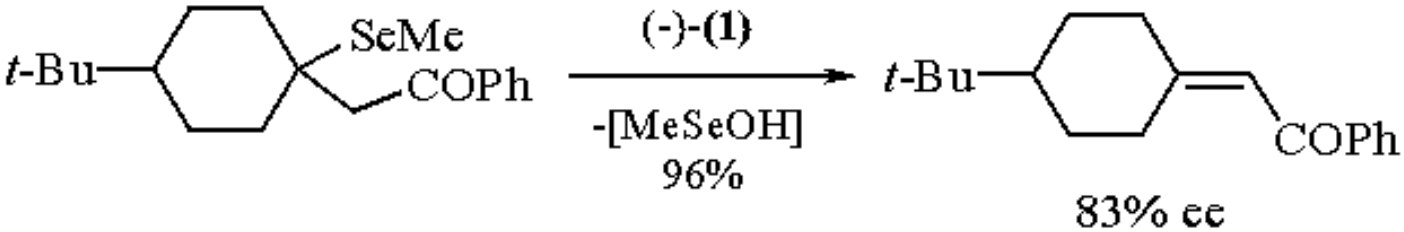

(7)

83% ee

Asymmetric Oxidation of Sulfenimines to Sulfinimines.

Enantiopure sulfinimines are ammonia imine synthons useful in the asymmetric synthesis of amines and β-amino acid derivatives.[3,14,15] Sulfinimines unavailable via the Andersen synthesis (R = H)[14,15] are prepared by asymmetric oxidation of the sulfenimines, ArS-N=C(R)PhX, with (+)-(**1**) or (-)-(**1**) at -20 to 20 °C in CCl_4 (eq 8).[3] Crystallization improves the ee to >95%. The sulfoxide chiral recognition model correctly predicts the configuration of the product.

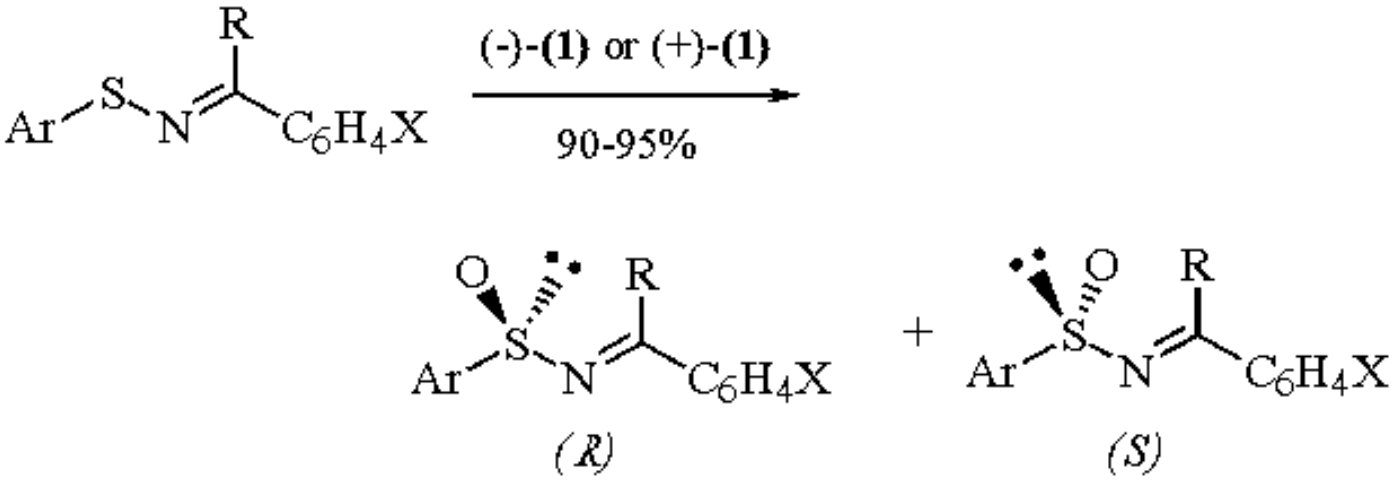

(8)

Ar = Ph, R = X = H	(-)-(**1**) 88% ee (*R*)
Ar = Ph, R = X = H	(+)-(**1**) 88% ee (*S*)
Ar = *p*-Tolyl, R = Me, X = H	(-)-(**1**) 87% ee (*R*)

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Franklin A. Davis

Phenylsulfonylethylene[1]

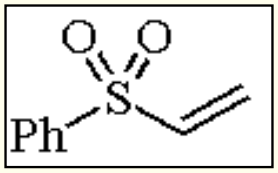

[5535-48-8] · $C_8H_8O_2S$ · Phenylsulfonylethylene · (MW 168.23)

(Michael acceptor;[2] equivalent to ethylene,[3] terminal alkenes,[3] and ketene[4] in cycloaddition reactions; adds radicals;[5] precursor to α-substituted vinyl sulfones[6])

Alternate Name: phenyl vinyl sulfone.

Physical Data: mp 67-69 °C.

Solubility: sol common organic solvents.

Form Supplied in: colorless solid; commercially available.

Preparative Methods: usually prepared by ***Hydrogen Peroxide*** oxidation of ***Phenyl Vinyl Sulfide***. The latter can be prepared by nucleophilic substitution of one mole of phenylthiolate with one mole of dibromoethylene and elimination,[7] or by other methods.[8]

Handling, Storage, and Precautions: good alkylating agent; should be handled with care. Use in a fume hood.

Nucleophilic Additions.

Phenylsulfonylethylene is a powerful Michael acceptor. It readily adds heteroatomic nucleophiles such as amines,[9] alkoxides,[10] and thiolates.[11] Amines and especially thiolates can be reverted back to the sulfonylethylene and nucleophile under mildly basic conditions, thus providing a method for protection of these functional groups.[11,12] The reaction with hydroperoxides and hydrogen peroxide in basic media may be controlled to give either the epoxide or the Michael addition product.[13]

Stabilized carbon nucleophiles add readily to phenyl vinyl sulfone and examples abound. As one example, a step in the synthesis of the biologically active natural product (+)-brefeldin A can be cited (eq 1).[14] The base is usually a nonnucleophilic amine but the reaction can also be carried out under solid-liquid phase-transfer catalysis.[15] In general, the Michael addition of phenylsulfonylethylene provides a method for two-carbon chain elongation.

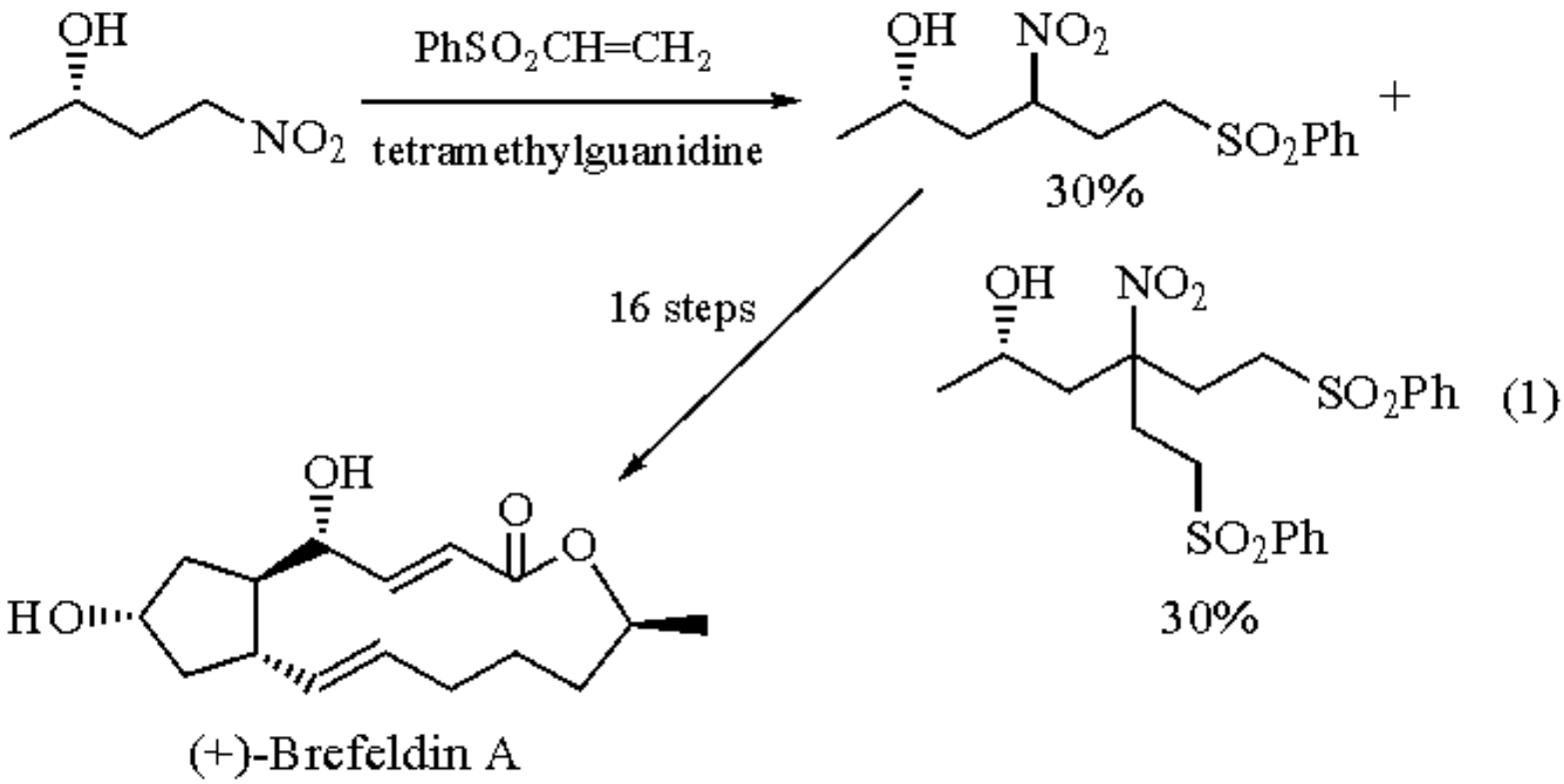

Nucleophilic nonstabilized carbanions, as Grignard or lithium reagents, can add to vinyl sulfones.[16] The direct addition can be complicated by polymerization arising from deprotonation of the α-vinyl proton and self-condensation.[6] Addition of the more nucleophilic organocuprates is more efficient (eq 2),[17a] but is not always devoid of problems.[17b]

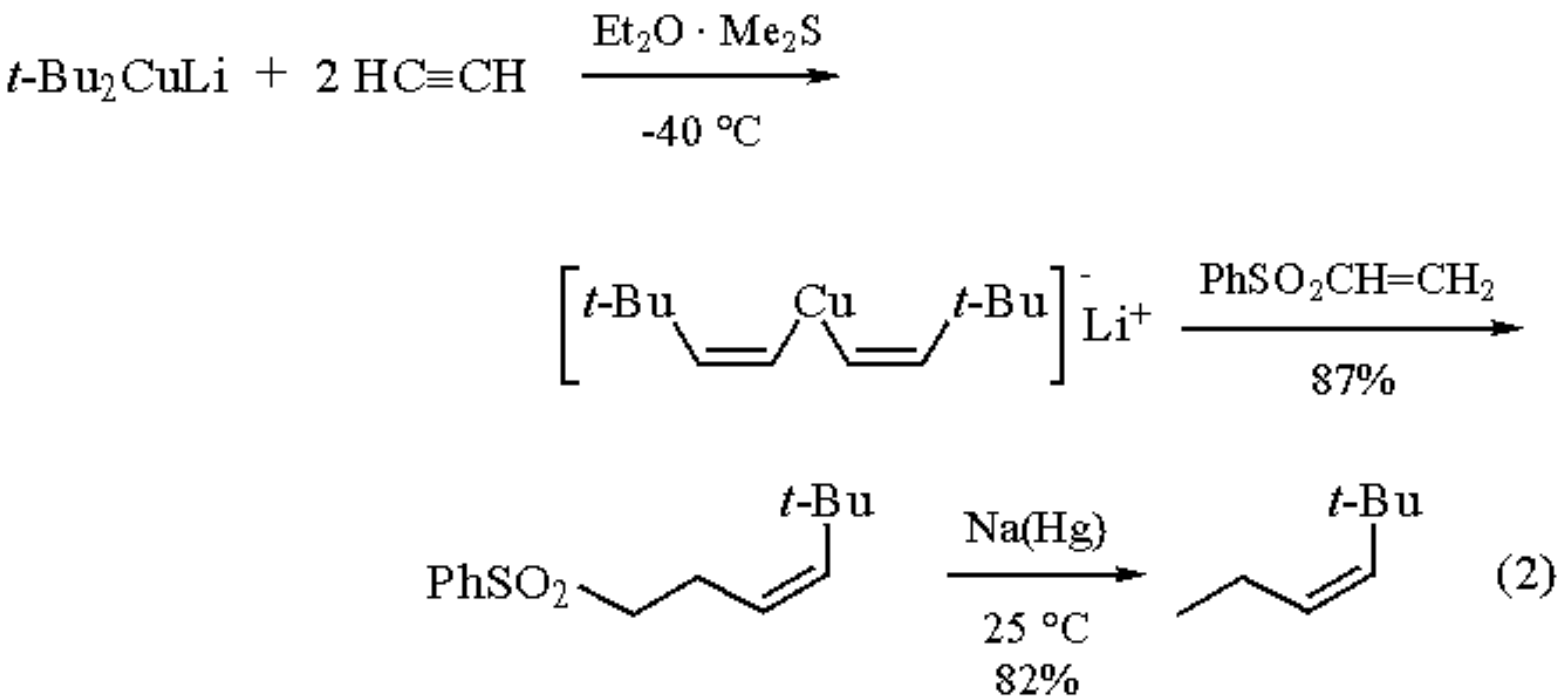

The enolate of cyclohexenone reacts with phenylsulfonylethylene in the presence of HMPA to give tricyclic derivatives in a single synthetic step (eq 3).[18] A method for α-alkylation of α,β-enones involves the addition of α,β-enones to phenylsulfonylethylene under ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** catalysis at high temperature (eq 4).[19] In this case, phenylsulfonylethylene functions as the electrophile in a Baylis-Hillman-type reaction.[20]

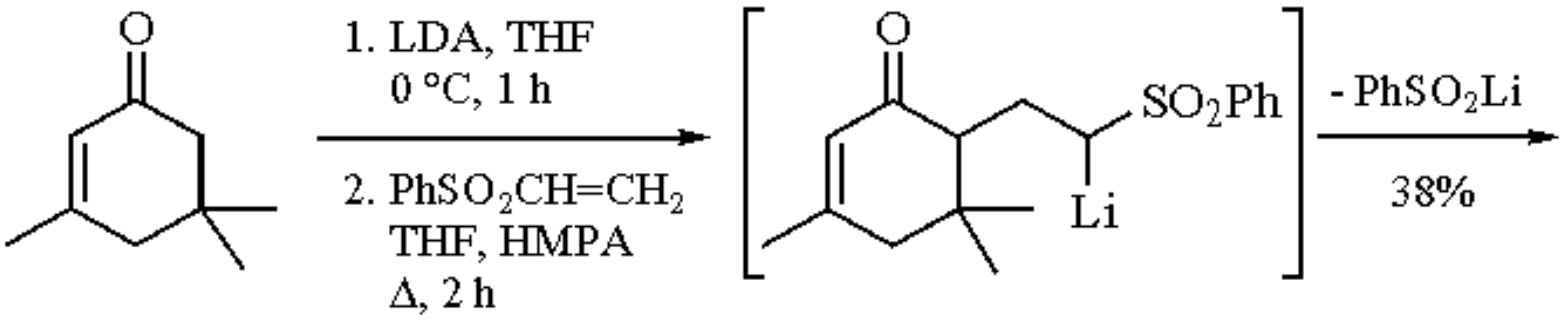

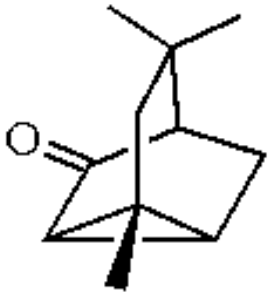

(3)

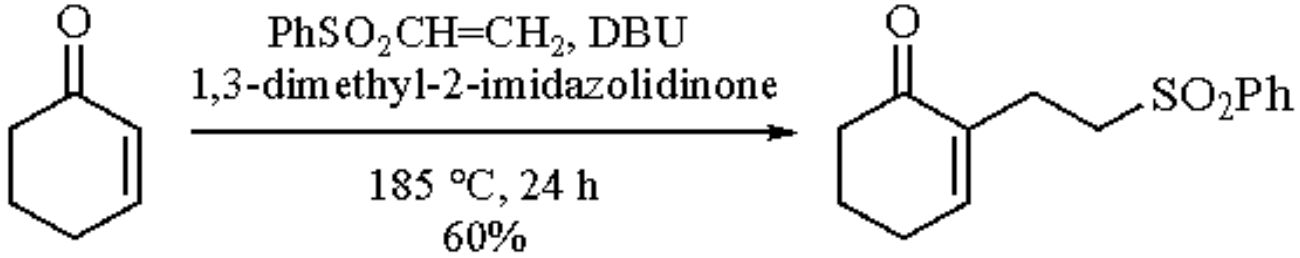

(4)

Neutral carbon nucleophiles such as enamines give [2 + 2] cycloadducts that can be isolated[21] or hydrolyzed to the keto sulfones.[22] Chiral imines react with phenylsulfonylethylene to lead, after hydrolysis, to substituted ketones in high yield with high regio- and enantioselectivity (eq 5).[23a] Enamino esters are far less reactive than imines and activation by high pressure is necessary.[23b]

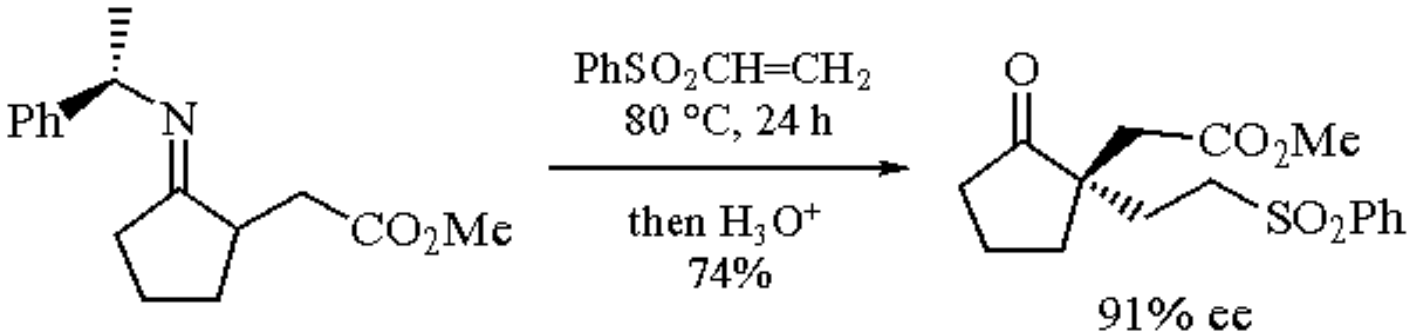

(5)

The Stetter reaction is an unusual type of Michael addition. It involves a mechanism that resembles the benzoin condensation where the aldehydic carbon functions as the nucleophile. It makes available γ-keto sulfones, and hence 1,4-diketones, by a thiazolium salt-catalyzed addition (eq 6).[24]

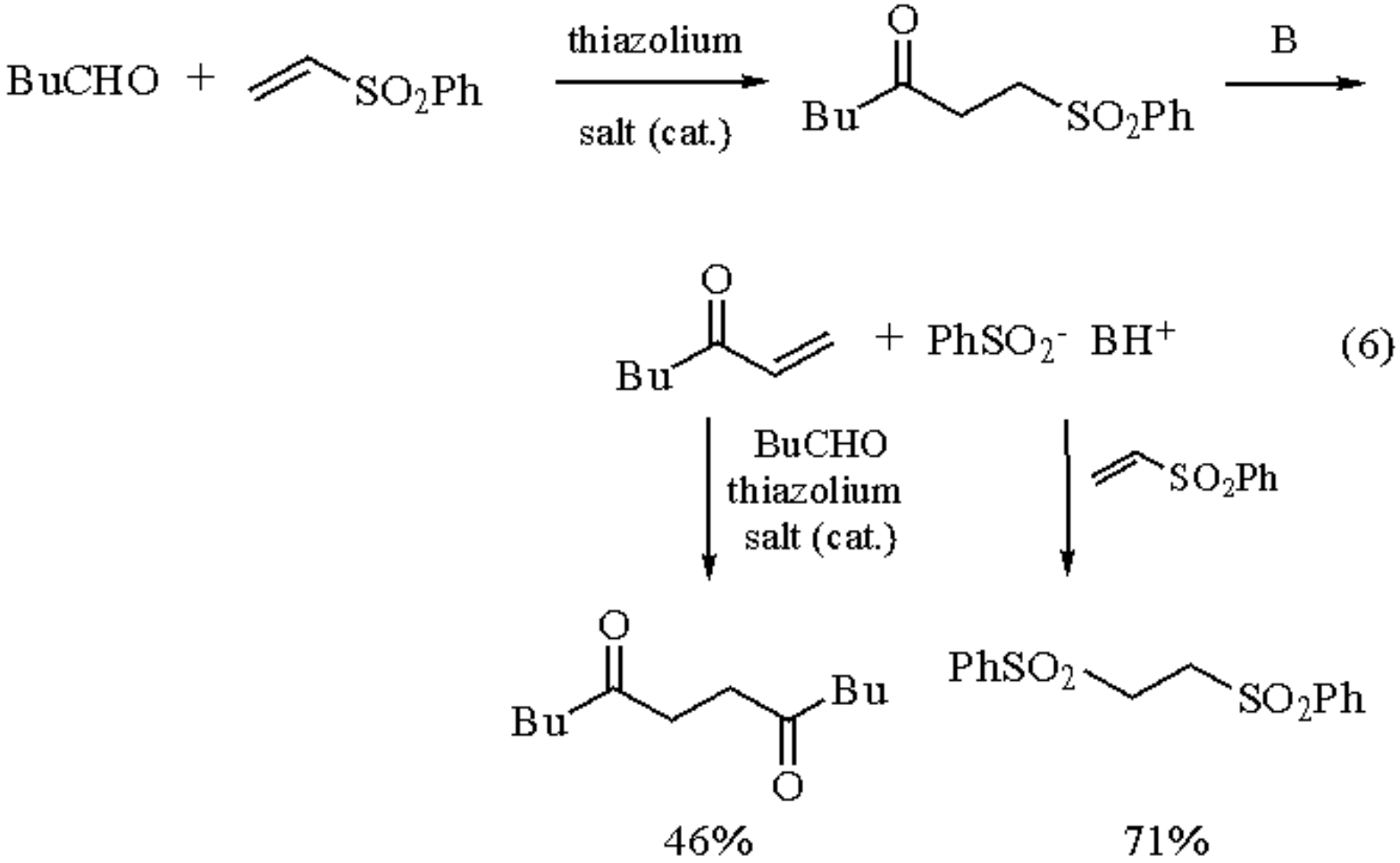

Diels-Alder Cycloadditions.[1c]

Phenylsulfonylethylene enters into [4 + 2] π cycloadditions as a relatively reactive dienophile, usually with modest to high regioselectivity. The reactivity is such to allow addition to most dienes,[3,25] either symmetrical as cyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethylbutadiene, and anthracene, or nonsymmetrical as isoprene, myrcene, 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene), 1,5,5´-trimethylcyclopentadiene,[25b] 1-methoxy-1,3-cyclohexadiene, steroids,[25e] and many others.[25] Studies on the stereoselectivity of addition to norbornyl- and norbornenyl-fused cyclopentadienes (eq 7)[26a] as well as *anti,anti*-2,3-diethylenenorbornane and -norbornene,[27a] or other similar systems,[27b] in comparison with those observed using other dienophiles have been reported.

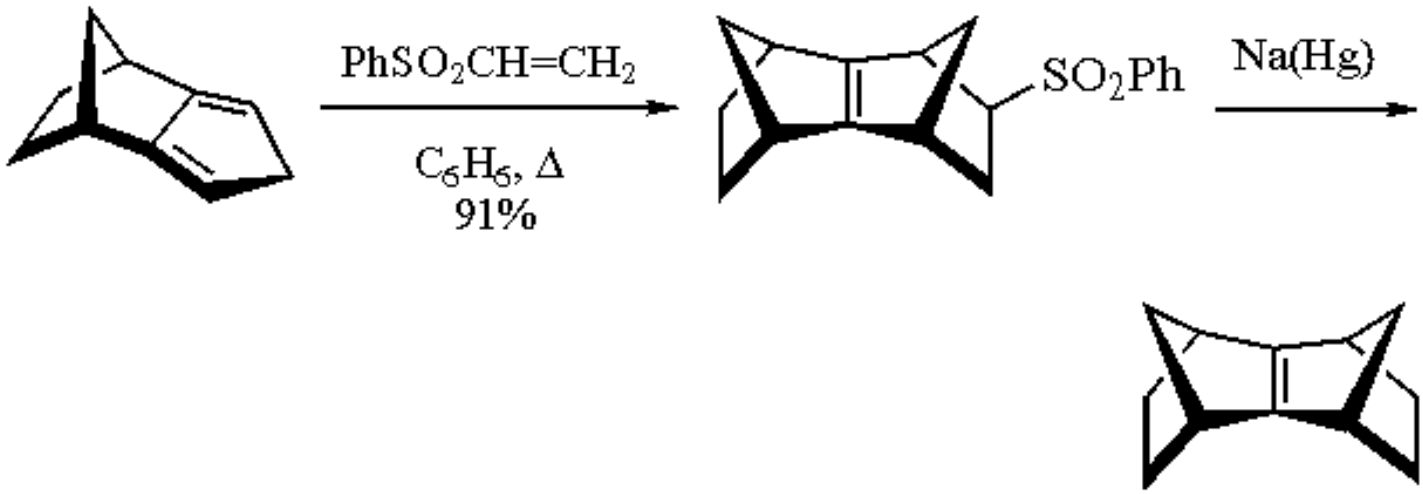

(7)

The sulfonyl group can be replaced with hydrogen by reductive desulfonylation with ***Sodium Amalgam*** or ***Samarium(II) Iodide*** in HMPA.[28] In these cases the cycloaddition-reduction sequence equals the cycloaddition of ethylene, as in the example of eq 7. Since the adducts can be alkylated prior to desulfonylation, phenylsulfonylethylene can be viewed also as an equivalent of terminal alkenes in cycloaddition reactions[3] (eq 8).[29] Thermal or base-induced elimination of benzenesulfinic acid from the adducts makes phenylsulfonylethylene equivalent to acetylene in cycloaddition reactions. This thermal reaction, however, seldom occurs in acceptable yields[30] and the base-induced β-elimination occurs only when a relatively acidic proton at the β-carbon is available.

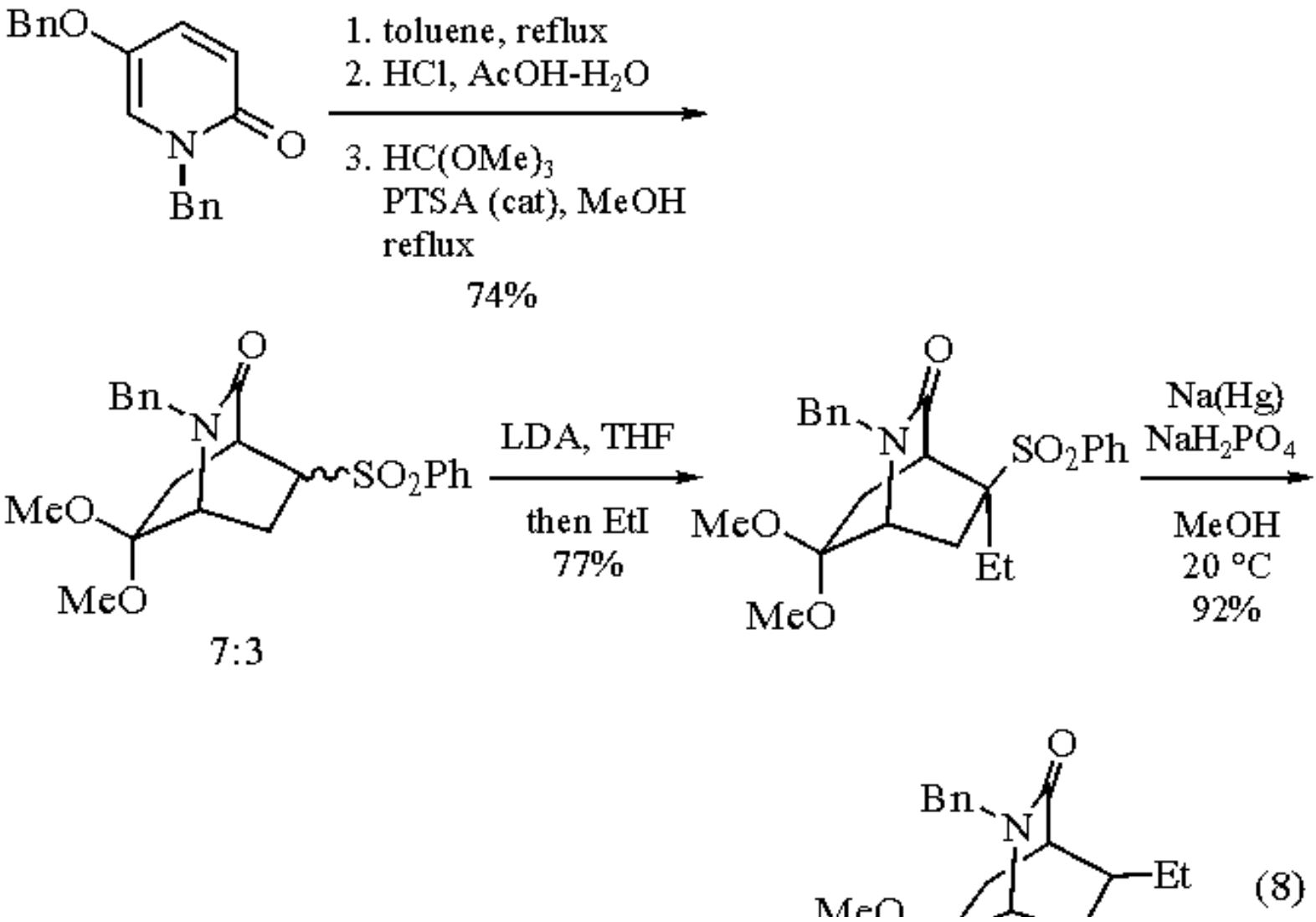

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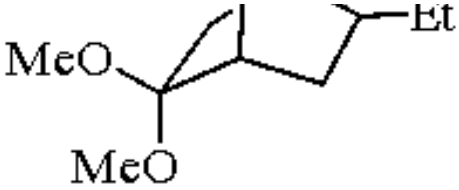

(8)

Cycloaddition to 1-methoxy-3-trimethylsilyloxy-1,3-butadiene followed by direct acetalization provides an adduct that undergoes regiospecific γ-alkylation. This process has been applied in a synthesis of zingiberenol as described in eq 9.[31] Phenylsulfonylethylene efficiently traps 1,3-diradicals generated by extrusion of nitrogen (eq 10). During this research an efficient oxidative desulfonylation of the resulting adducts with the molybdenum complex ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** (MoOPH) was developed so that phenylsulfonylethylene can be also used as a ketene equivalent in cycloadditions (eq 10).[4]

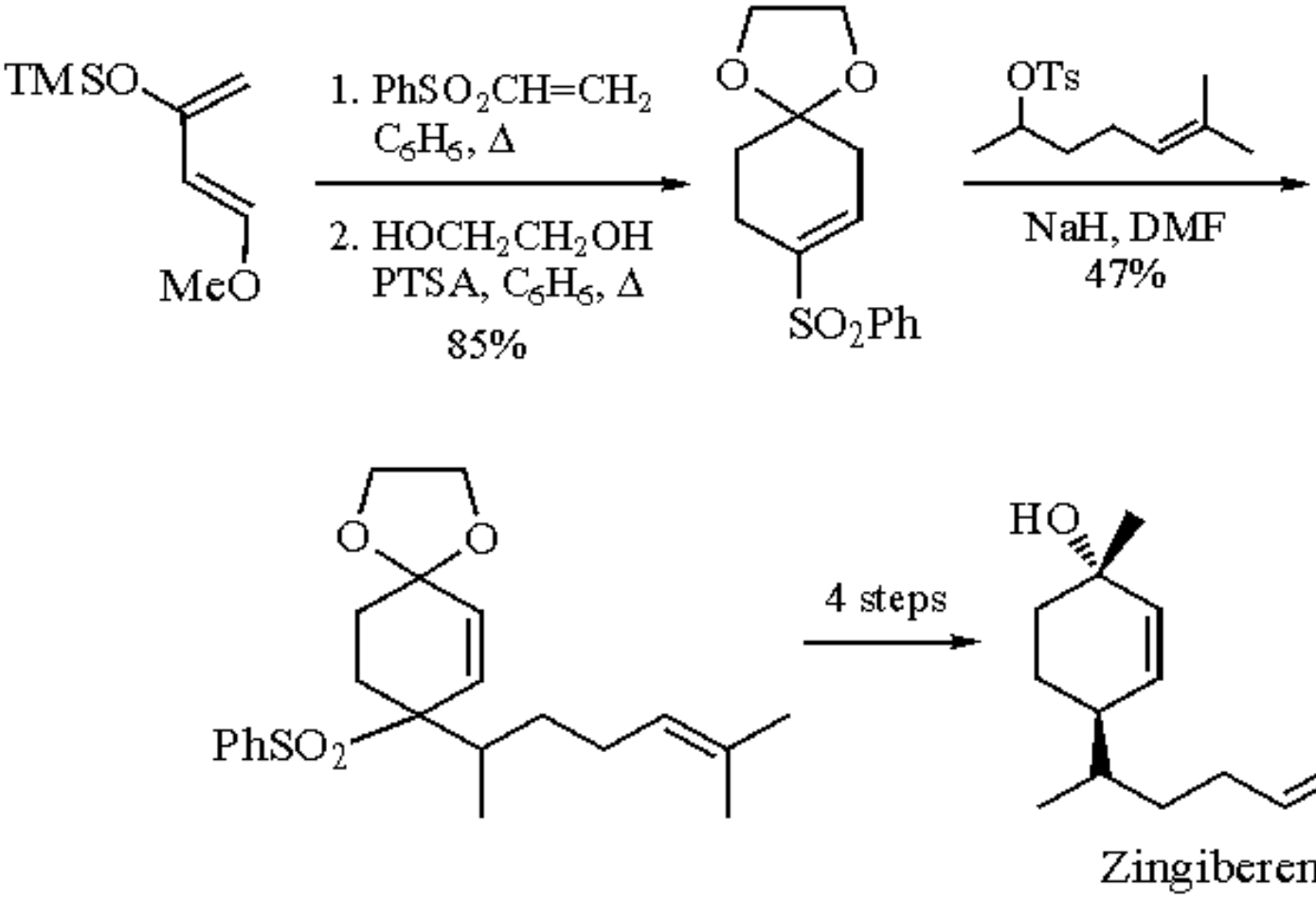

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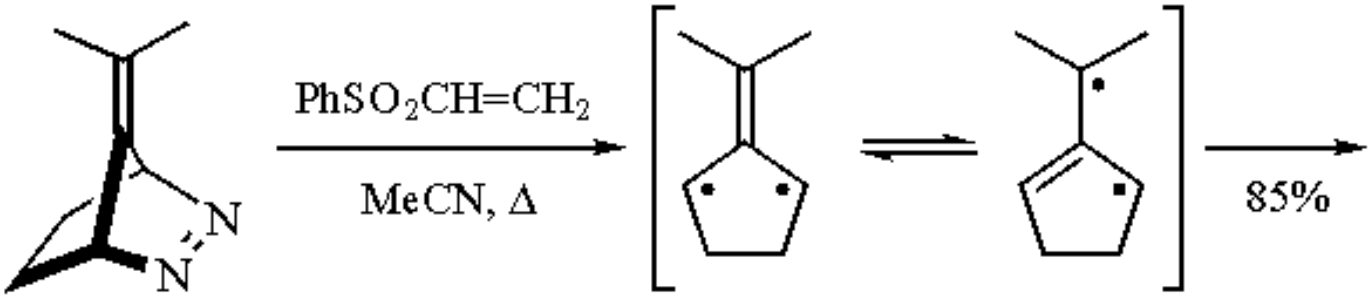

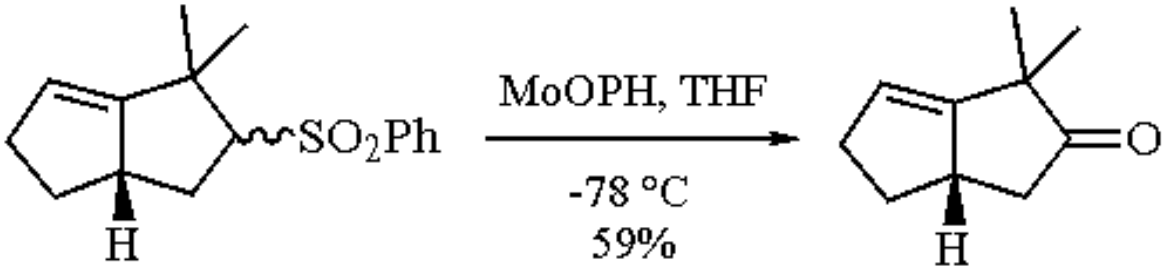

(10)

Dipolar Cycloadditions.

Pyrazoles are synthesized in excellent yield by reaction of diazomethanes with phenylsulfonylethylene or other α,β-unsaturated sulfones.[32] Nitrile oxides react with phenyl vinyl sulfone with high selectivity to give the 5-phenylsulfonylisoxazoline as the sole or predominant product (eq 11).[32] 1-Methyl-3-oxidopyridinium affords regio- and stereoselectively an adduct that can be transformed into 2α- and 2β-tropanols (eq 12).[33]

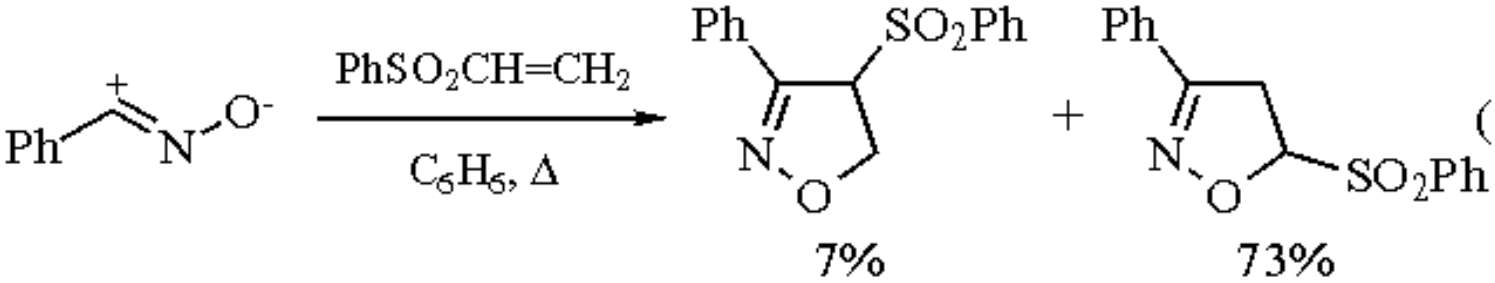

(11)

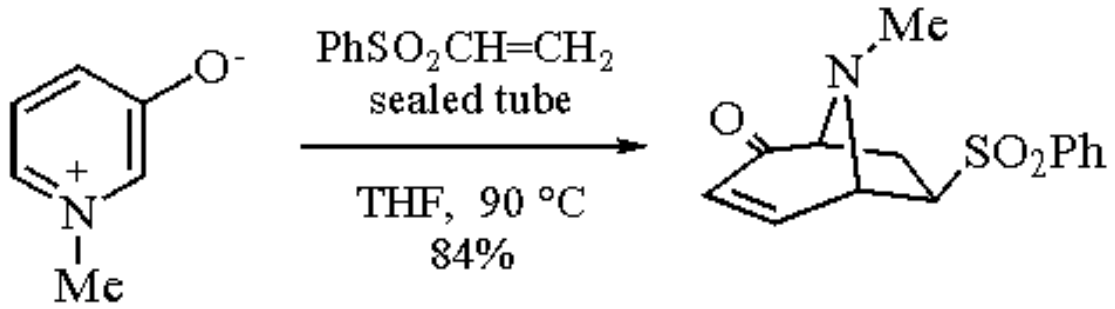

(12)

Oximes undergo tandem Michael addition dipolar cycloaddition to give isoxazolidine derivatives. In this reaction the nitrones generated by the Michael addition are trapped by an external dipolarophile such as *N*-methylmaleimide (eq 13),[34a] or intramolecularly if an alkene is available (eq 14).[34b] A somewhat similar reactivity is displayed by pyridinium or isoquinolinium methylides.[34c]

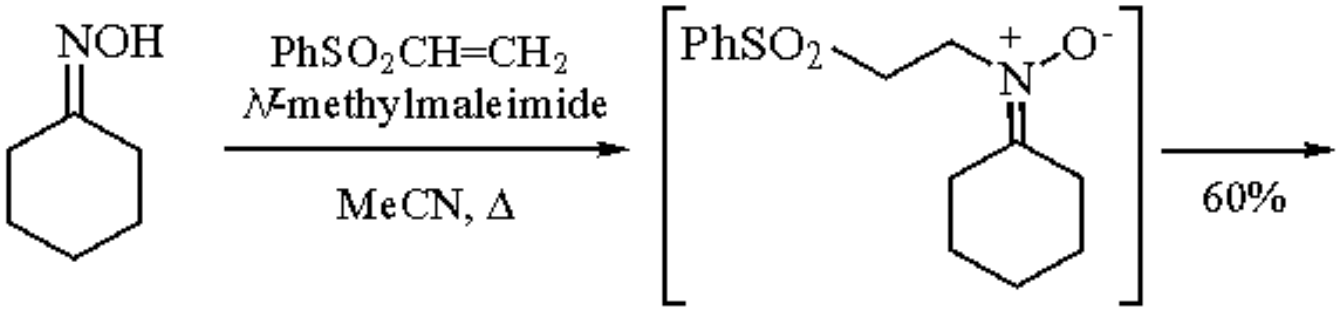

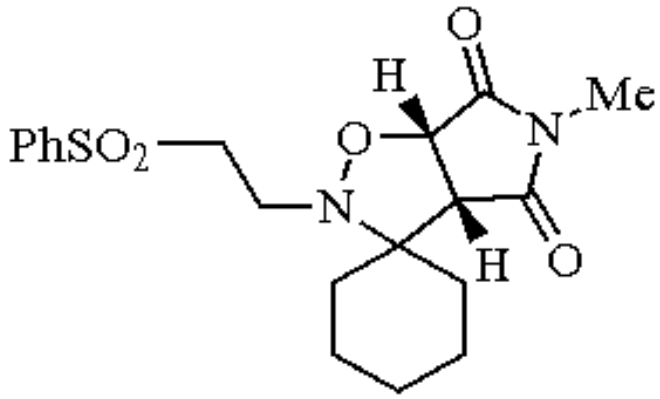

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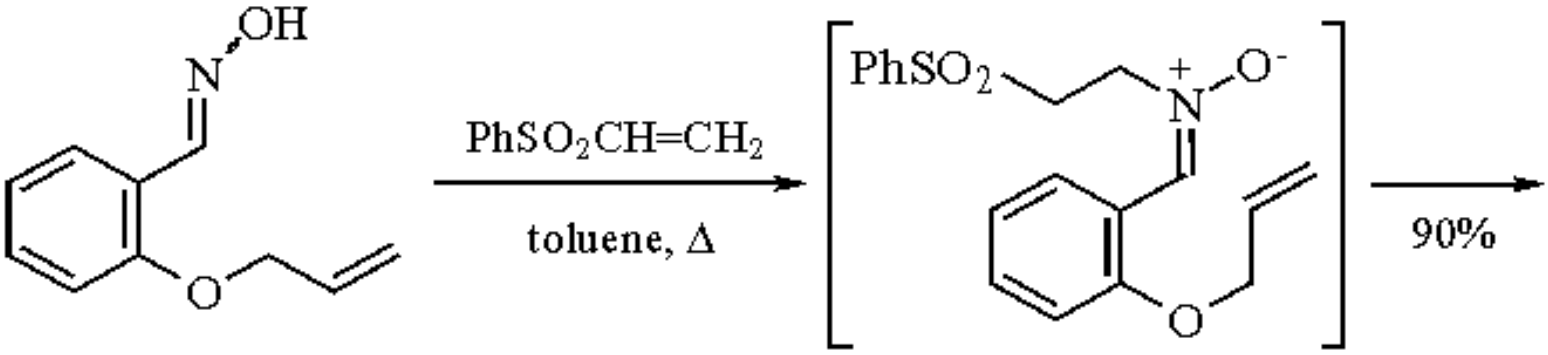

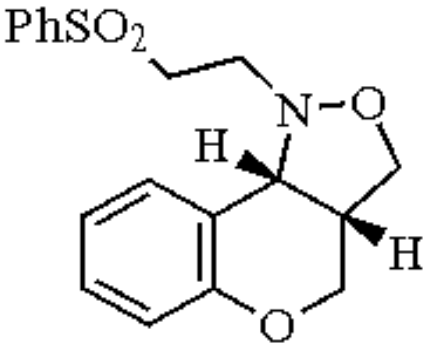

(14)

Radical Additions.[5]

Alkyl radicals derived from decarboxylation of carboxylic acids by the Barton method add to phenylsulfonylethylene.[35] The adducts undergo a wide variety of transformations including conversion to a two-carbon homologous carboxylic

acid or to substituted vinyl sulfones. The conversion of the adducts into hydrocarbons, ketones, and other functional groups is also possible. An example of an application to the synthesis of substituted 2-azetidinones from tartaric acid is shown in eq 15.[36] Multiple radical additions occur when the carboxylic acid possesses accessible double bonds, as in eq 16.[37] The adduct incorporates stereoselectively (three out of four stereogenic centers) two molecules of phenylsulfonylethylene.

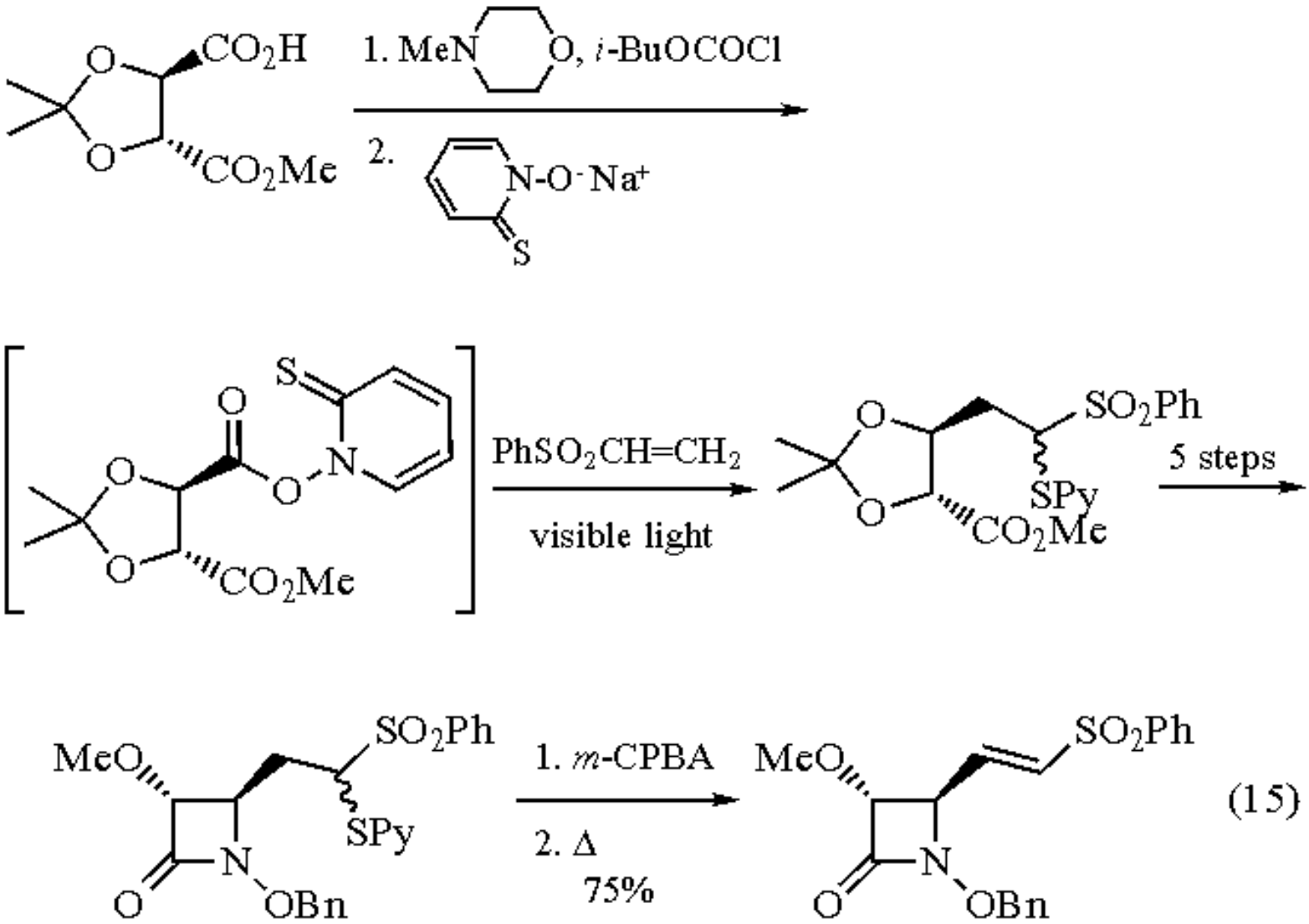

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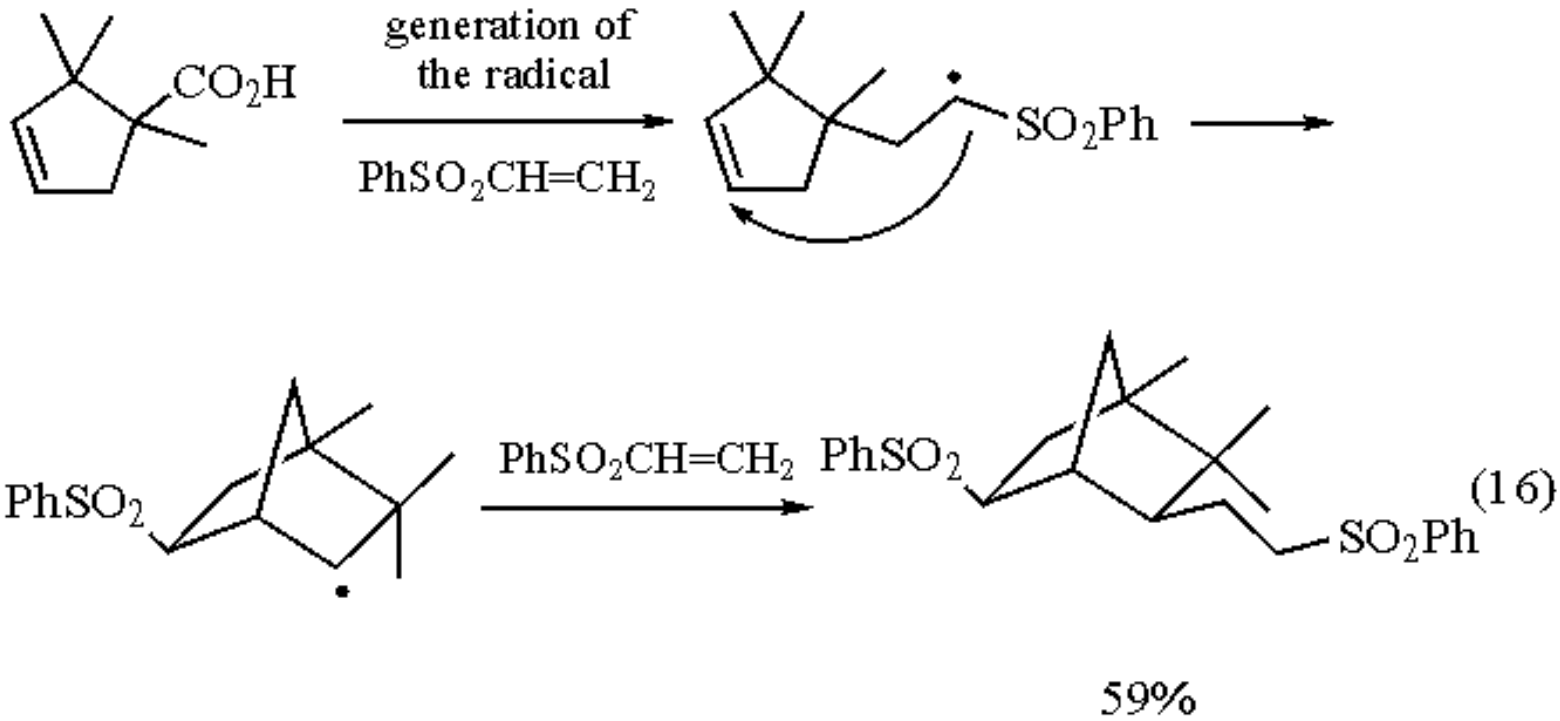

Radicals generated by other means also add to phenylsulfonylethylene.[38]

α-Substituted Vinyl Sulfones via Direct Lithiation or Baylis-Hillman and Related Reactions.

The direct alkylation of the vinyl anion of phenylsulfonylethylene is made difficult by a rapid polymerization due to self-condensation of the vinyl anion with the reagent itself.[6] Indirect methods to overcome this problem are available. These engage in protection of the double bond by means of secondary amines (eq 17)[6b] or trimethylsilyl compounds.[39] With aldehydes as electrophiles, the Baylis-Hillman reaction[20] is possible (eq 18).[40] The allylic alcohols produced can be subjected to numerous transformations; for example, (*E*)-selective dehydration to give 1,3-alkadienes (eq 18)[41a] or modified Jones oxidation to α-methylene-β-keto sulfones.[41b]

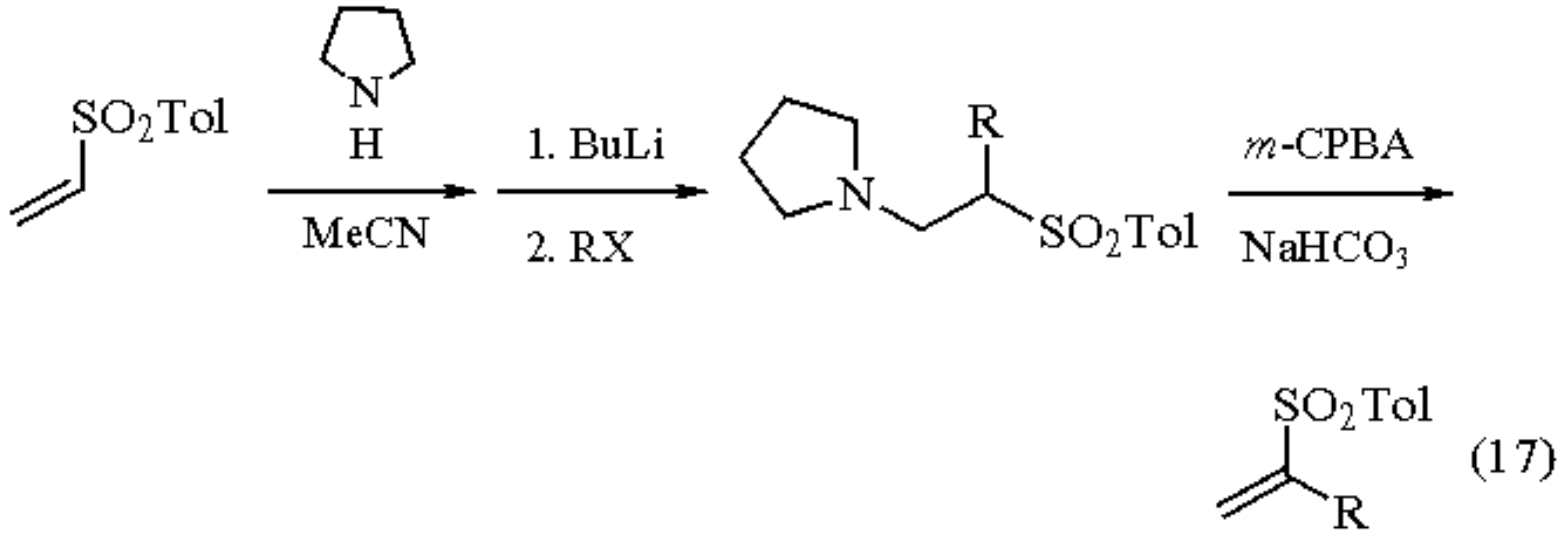

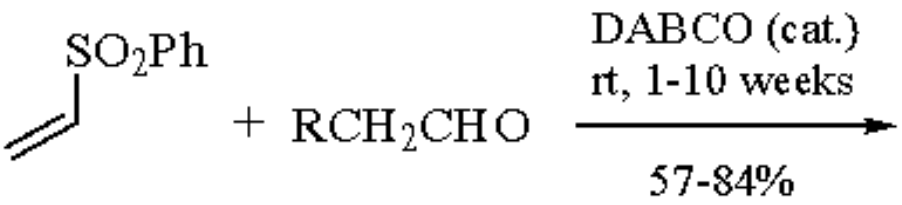

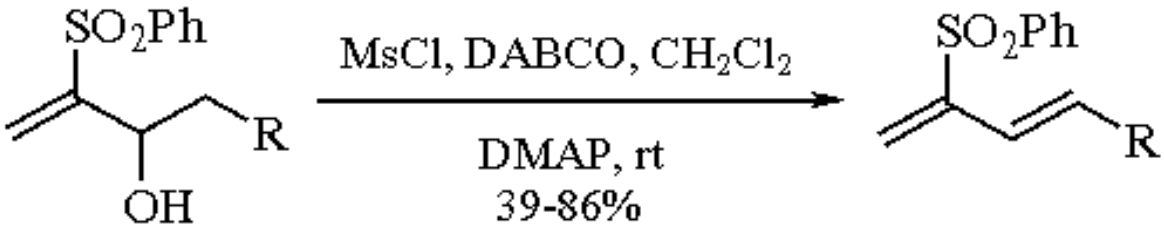

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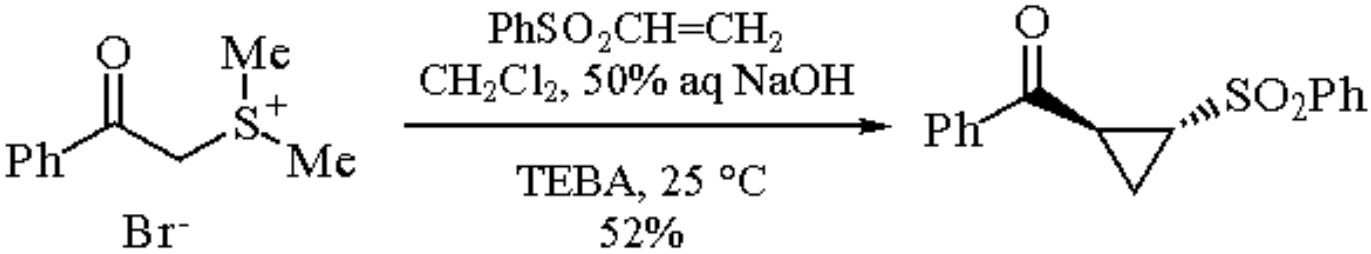

(19)

Other Reactions.

Phenylsulfonylethylenes are dimerized by low cathodic currents to give *trans*-1,2-substituted cyclobutanes.[42] Carbonyl-stabilized sulfur ylides give cyclopropanes (eq 19).[43] Finally, the hydroformylation catalyzed by a rhodium complex gives mostly the branched-chain aldehyde $PhSO_2CH(CHO)Me$.[44]

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α-Phenylsulfonylethyllithium

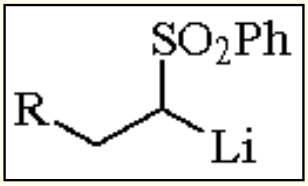

(R = H)

[69291-71-0] · $C_8H_9LiO_2S$ · α-Phenylsulfonylethyllithium · (MW 176.18)

(versatile stabilized carbon nucleophile for forming C-C, C=C, and C&tbond;C bonds with a wide range of carbon and heteroatom electrophiles[1-3])

Physical Data: pK_a in DMSO 31.0.

Solubility: sol THF, Et_2O.

Preparative Methods: prepared in situ as needed by metalation of ethyl phenyl sulfone with ***n-Butyllithium*** or ***Lithium Diisopropylamide***.

Handling, Storage, and Precautions: moisture sensitive; handle under nitrogen or argon.

General Considerations.

The sulfone group is perhaps second only to the carbonyl group in its versatility and utility. It serves the dual role of C-H activator and leaving group under a wide range of conditions,[1] thereby enabling creation of up to three C-C bonds from a single functional group. Alkyl aryl sulfones have a pK_a of ca. 31 and are therefore quantitatively deprotonated by strong bases such as ***n-Butyllithium***, ***Lithium Diisopropylamide***, or Grignard reagents. The resultant colored carbanions (yellow or red-orange)[4] are usually stable at rt. It is also possible to form an α,α-dianion which reacts with even relatively poor electrophiles.[5] In the following discussion, α-phenylsulfonylethyllithium serves as a paradigm for the class of a^1d^1 reagents represented by $ArSO_2$-CH(M)R.

α-Phenylsulfonylethyllithiums as Donors.

α-Arylsulfonylalkyllithiums react with all the typical carbon electrophiles to form a C-C bond in generally good yield; some indication of the scope of the procedure can be gleaned from eqs 1-9. For example, alkylation with primary alkyl bromides (or iodides; eq 1),[6] tosylates (eq 2),[7] or triflates[8] occurs even when there is an α-branch in the chain. In the case of sluggish reactions, additives such as ***Hexamethylphosphoric Triamide*** or ***N,N,N´,N´-***

Tetramethylethylenediamine can be added to accelerate alkylation.

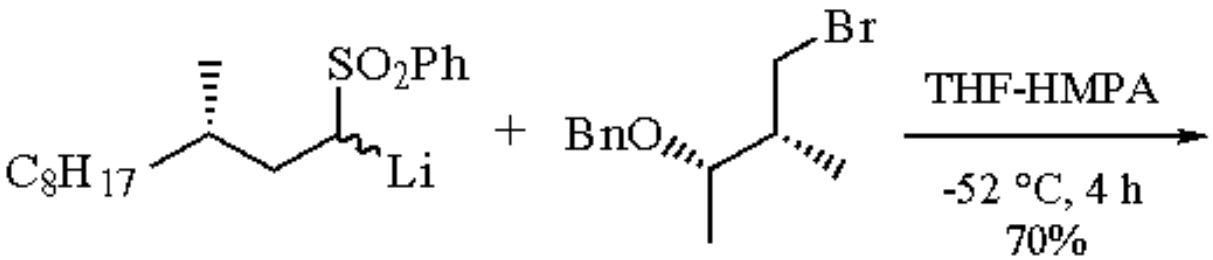

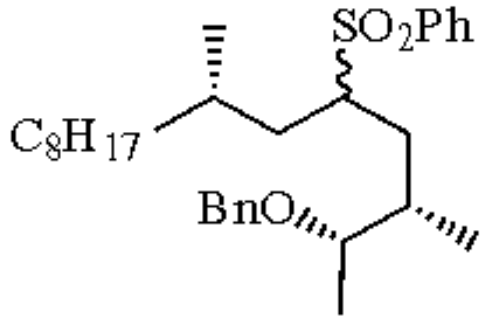

(1)

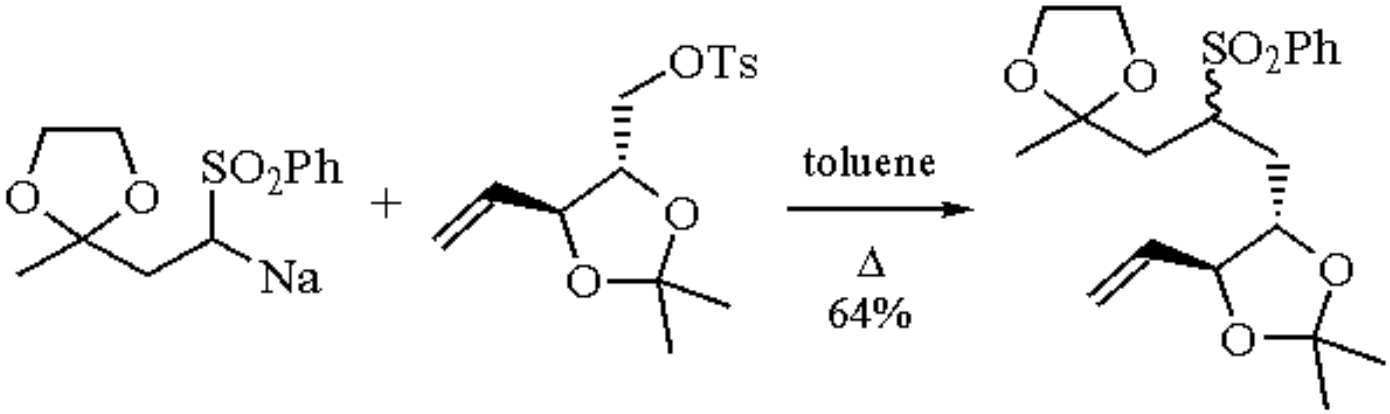

(2)

The reaction of sulfonyl carbanions with halocarbenoids (see ***Tribromomethyllithium***) gives a 1,1-dibromoalkene or a 1-bromoalkene (eq 3).[9] The reaction probably does not involve a carbene intermediate.

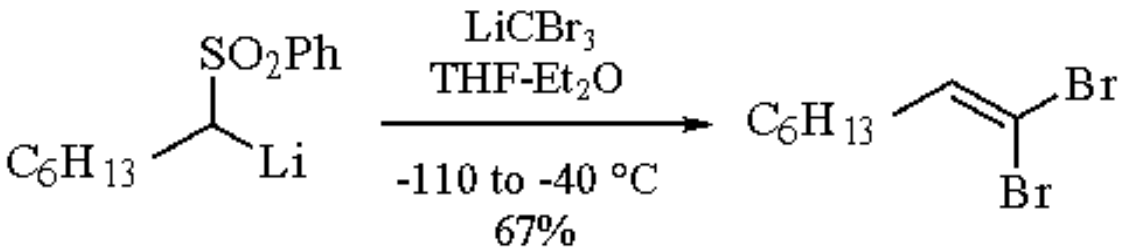

(3)

Terminal epoxides react slowly with sulfonyl carbanions such as the homoenolate equivalent (**1**) (eq 4).[10] With disubstituted epoxides and cyclic epoxides the reactions are slower still. For example, reaction of the lithio derivative of ethyl phenyl sulfone with cyclopentene oxide occurs in excellent yield (98%) after 10 h reflux in toluene.[11] It has been reported that, in some cases, the addition of a Lewis acid (***Magnesium Bromide***,[12] ***Boron Trifluoride Etherate***,[13,14] ***Titanium Tetraisopropoxide***,[15] MeOAl(i-Bu)$_2$[16]) or HMPA[17] improves the yield dramatically.

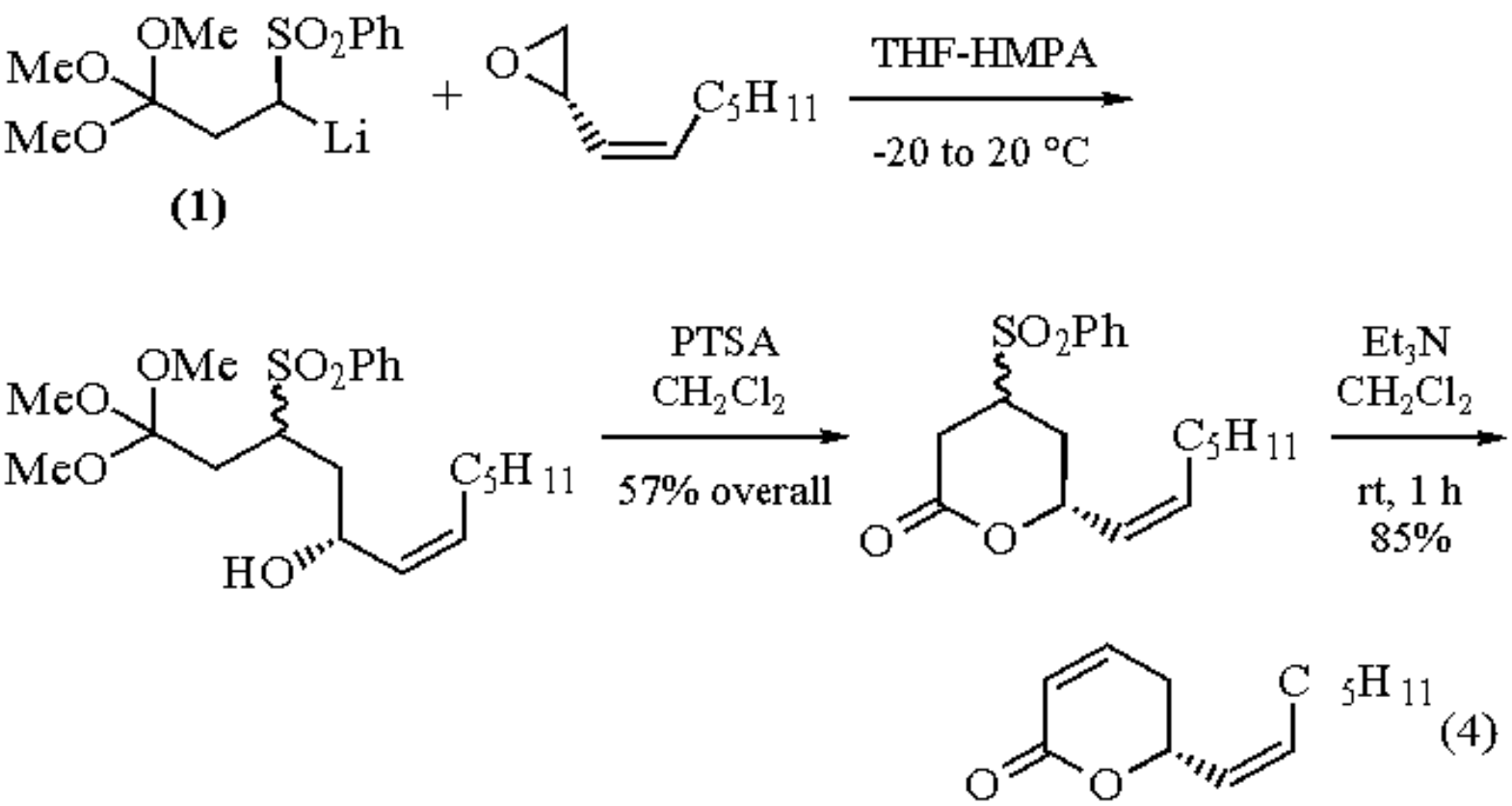

(4)

In the presence of HMPA, the homoenolate equivalent (**1**) underwent conjugate addition to cyclohexenone. In the absence of HMPA, a mixture of 1,2- and 1,4-adducts was obtained (eq 5).[18,19]

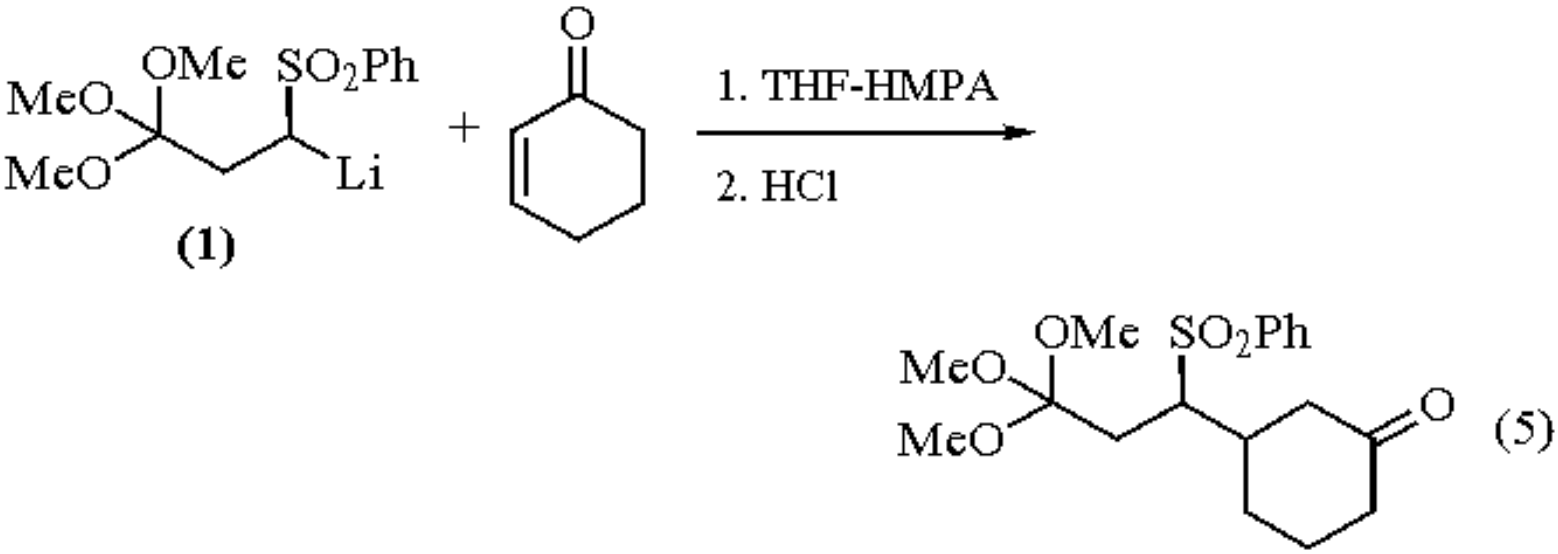

(5)

The addition of metalated sulfones to aldehydes is reversible and in simple cases the reaction displays modest selectivity for the *erythro* isomer (eq 6).[20] The reverse reaction is favored when the adducts are sterically compressed (e.g. ketone adducts) or when the sulfone anion is stabilized by conjugation (i.e. allylic or benzylic sulfones) or proximate heteroatoms. However, in unfavorable cases the position of the equilibrium can be tuned by varying the metal. For example, the lithio sulfone (**2**) did not give a stable adduct with aldehyde (**4**) but the ate complex derived from the lithio derivative and BF_3 gave the desired adduct (**5**) (eq 7).[21]

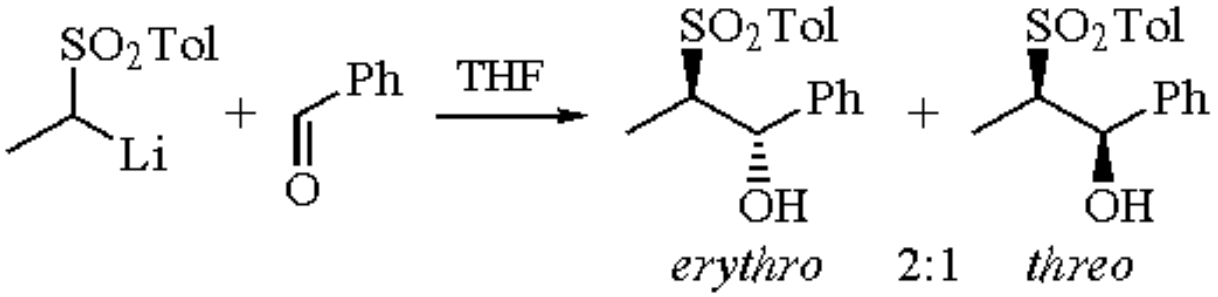

(6)

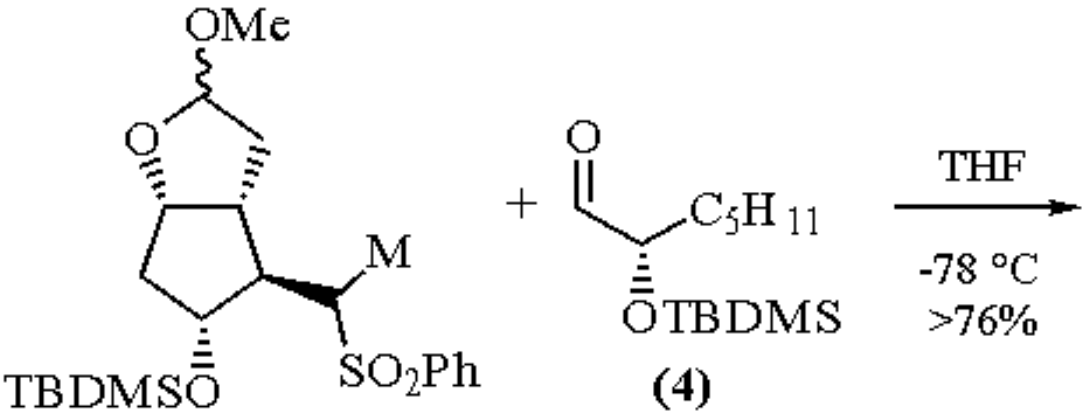

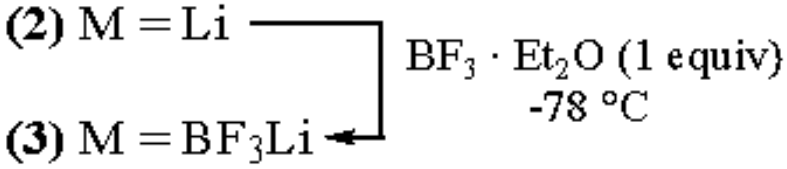

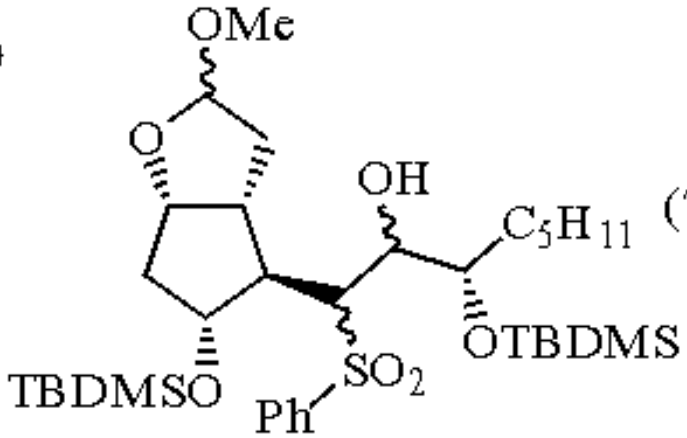

(5)

(7)

α-Phenylsulfonylethyllithium adds to acylsilanes to give an adduct which undergoes a Brook rearrangement with subsequent loss of benzenesulfinate anion. The product of the reaction is an enol silane (eq 8).[22]

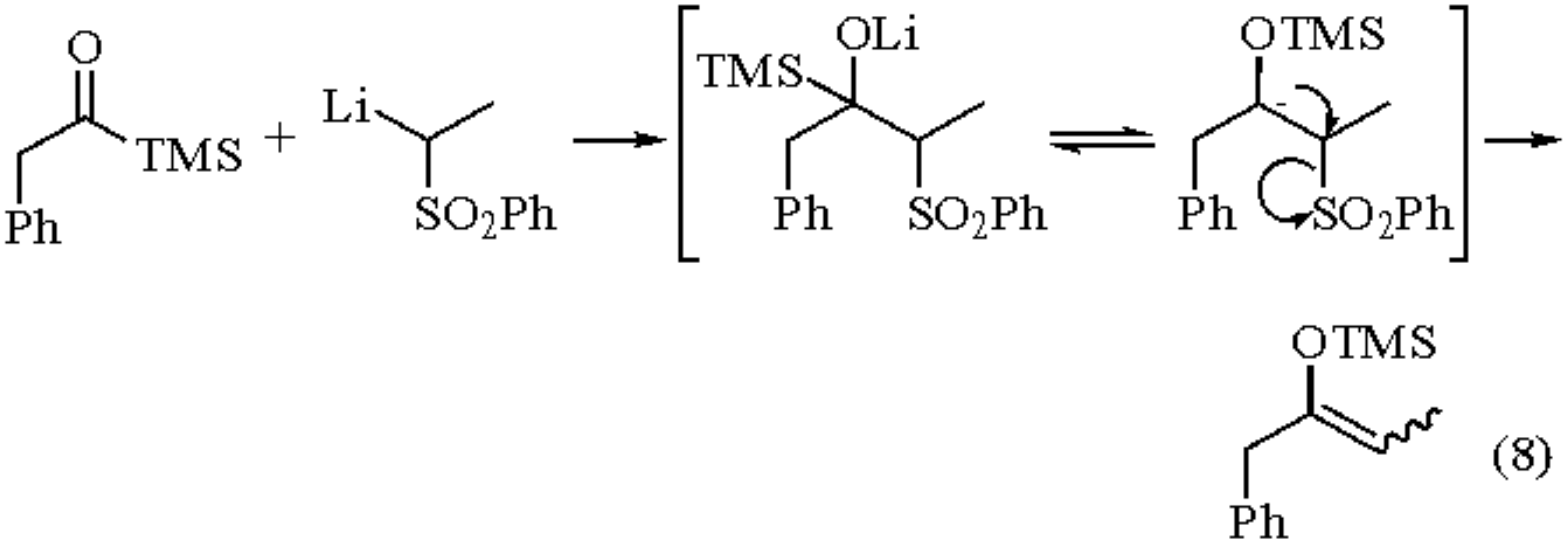

(8)

Reaction of the metalated sulfones with esters,[23,24] lactones,[25,26] amides and carbonates[27] leads to the corresponding β-keto sulfone (eq 9).[23] The β-keto sulfones thus formed display chemistry reminiscent of β-keto esters in their enhanced acidity and tendency to undergo *C*- and *O*-alkylation and acylation.

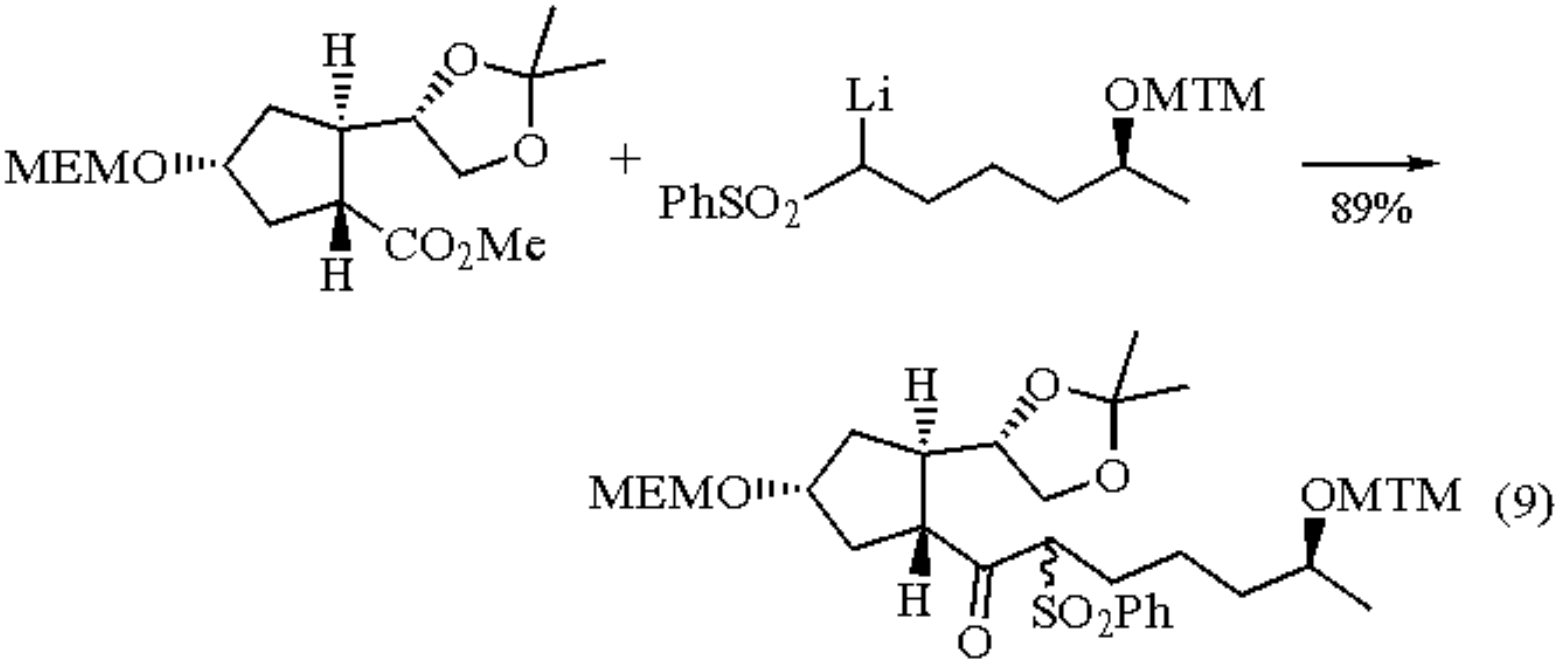

(9)

Aryl Sulfones as Acceptors: Desulfonylation Reactions.

The sulfone group is a powerful electron acceptor which can be cleaved under a wide range of conditions. We have already seen that mild base will cause elimination of benzenesulfinate from β-arylsulfonyl-substituted carbonyl derivatives (eq 5). α-Arylsulfonyl-substituted carbonyl derivatives undergo reductive desulfonylation[28] under very mild conditions using ***Aluminum Amalgam*** (eq 10),[29] but in the absence of carbonyl activation, reductive cleavage of the sulfone group requires much stronger reducing agents such as ***Sodium Amalgam*** in MeOH buffered with Na_2HPO_4,[30] ***Sodium-Ammonia***,[31] ***Magnesium*** in refluxing MeOH,[32] or ***Samarium(II) Iodide*** in THF-HMPA.[33]

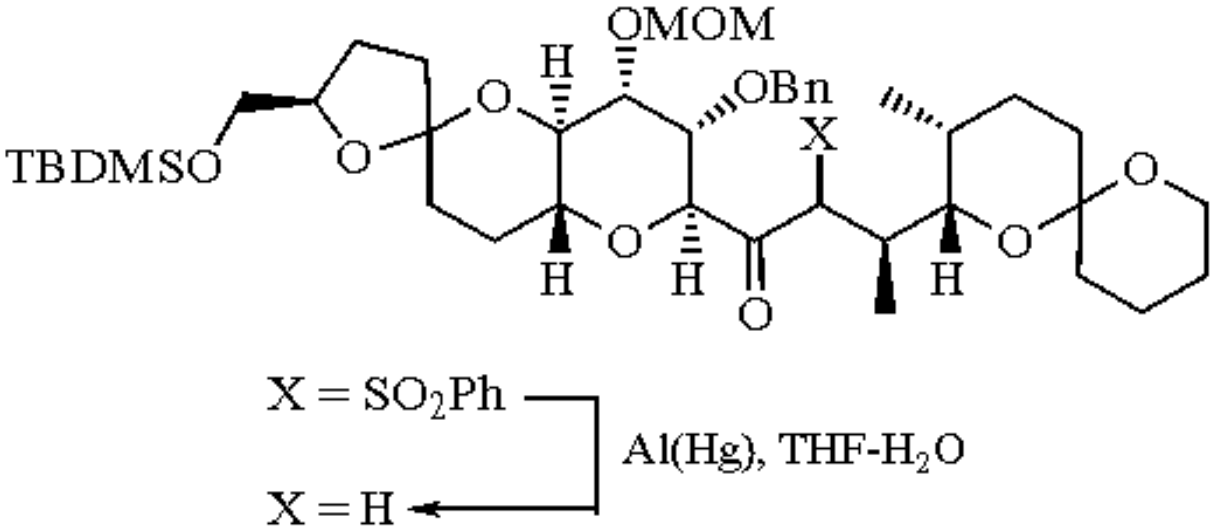

(10)

The Julia Alkenation and Related Reactions.

In 1973, Julia and Paris[34] reported a new connective and regioselective alkene synthesis (eq 10) based on the reductive elimination of β-acyloxy sulfones. The Julia alkenation is now one of the principal methods for fragment linkage in complex natural product synthesis.[35,36] Mono-, di-, tri-, and tetrasubstituted alkenes can be prepared in moderate to good yield, depending on the substrate. The three-step sequence, illustrated in eq 11, entails (a) condensation of a metalated sulfone with an aldehyde or ketone, (b) *O*-functionalization of the adduct as the acetate, benzoate, or mesylate (to prevent retroaldolization), and (c) reductive elimination using 6% Na(Hg) in THF-MeOH (3:1) at -20 °C.[37] In favorable cases, step (b) can be omitted and the reductive elimination performed on a β-hydroxy sulfone intermediate. Potential problems attending each step have been summarized.[35]

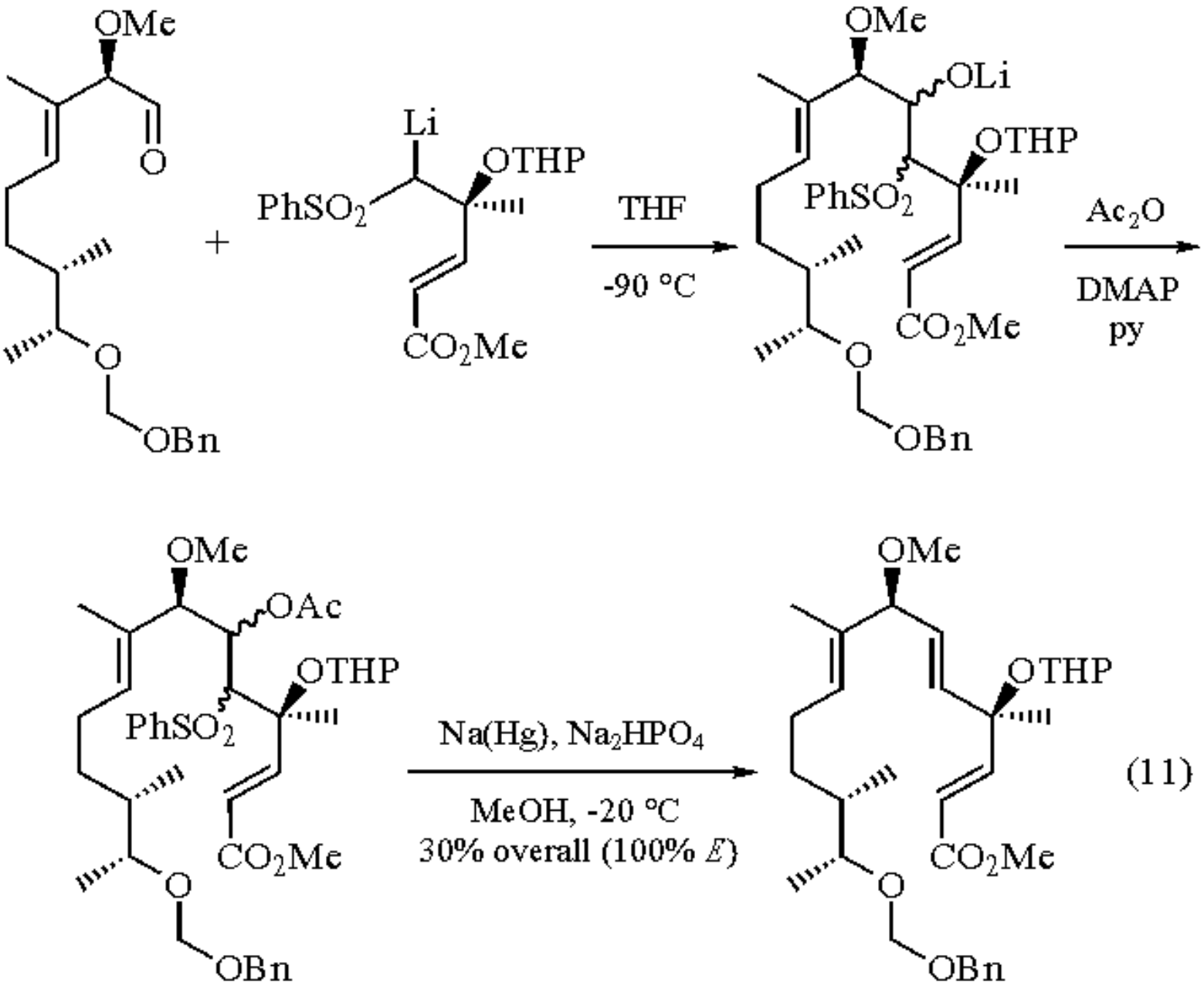

(11)

A detailed investigation of the scope and stereochemistry of the reductive elimination leading to 1,2-disubstituted alkenes revealed high *trans* stereoselectivity which is *independent* of the stereochemistry of the β-acyloxy sulfone adducts.[37,38] Furthermore, the stereoselectivity increases with increasing steric congestion about the nascent alkene and maximum yields and rate are observed for the formation of conjugated dienes and trienes. The Julia procedure has also been adapted to the synthesis of alkynes (eq 12).[39,40]

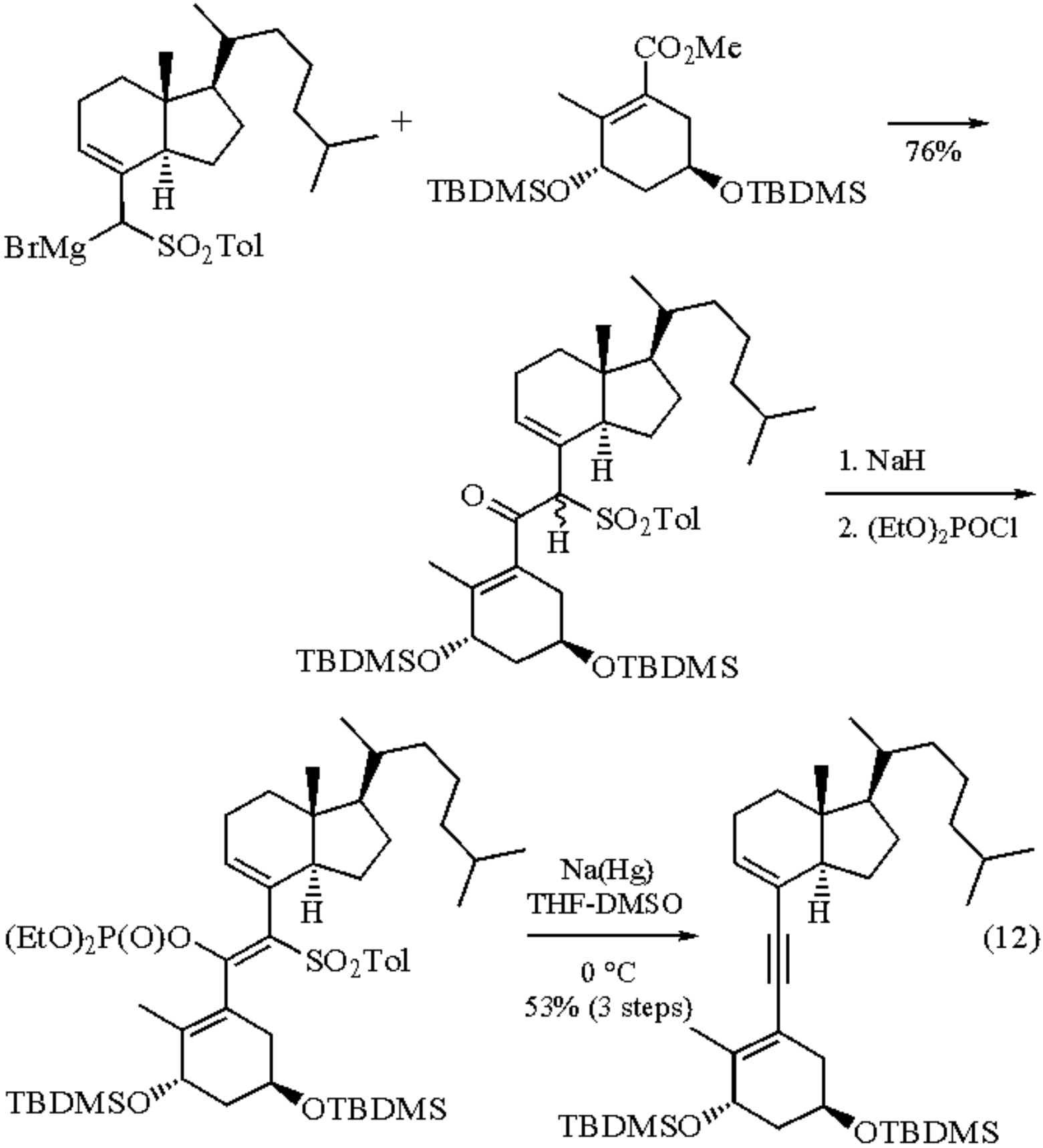

There are two further variants of the Julia alkenation which deserve wider recognition. Both methods surmount the inherent limitation in scale of the reductive elimination step imposed by the use of Na(Hg). The first method involves a radical-induced elimination of thiocarbonyl derivatives of β-hydroxy sulfones,[41] as illustrated in eq 13.[42]

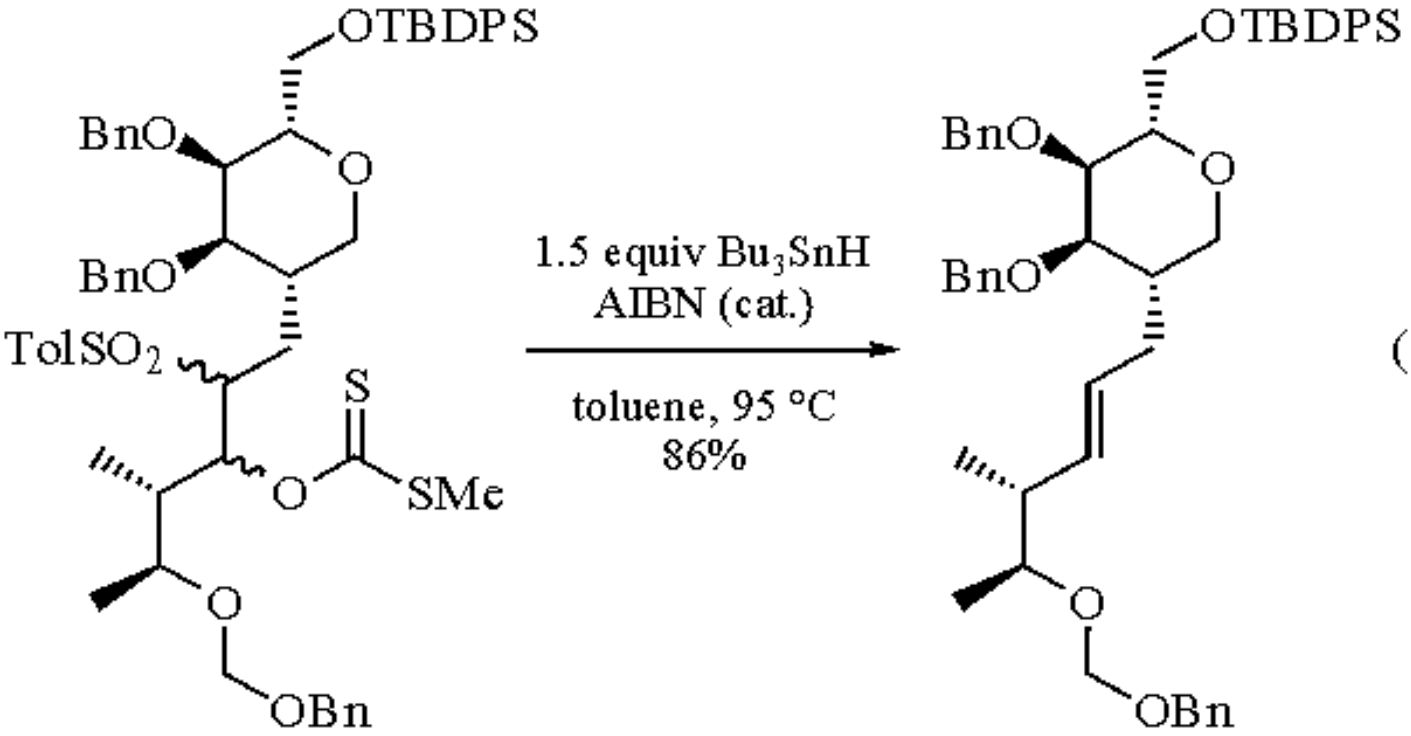

(13)

The second recent variant, developed by Julia and co-workers, avoids reductive elimination altogether and provides a remarkable one-pot connective synthesis of alkenes.[43] The procedure, illustrated in eq 14, involves condensation of an aldehyde or ketone with a lithiated benzothiazolyl alkyl sulfone to give an adduct which first cyclizes and then fragments with extrusion of sulfur dioxide, benzothiazolone (which then tautomerizes to 2-hydroxybenzothiazole), and the alkene. Generally a mixture of (*E*)- and (*Z*)-alkenes is obtained, but in sterically hindered substrates the (*E*) isomer can be obtained selectively. The same reaction has been observed with the pyridinyl sulfone analogs, in which case the separable β-hydroxy sulfone intermediates undergo stereospecific *anti* elimination to the corresponding alkene.

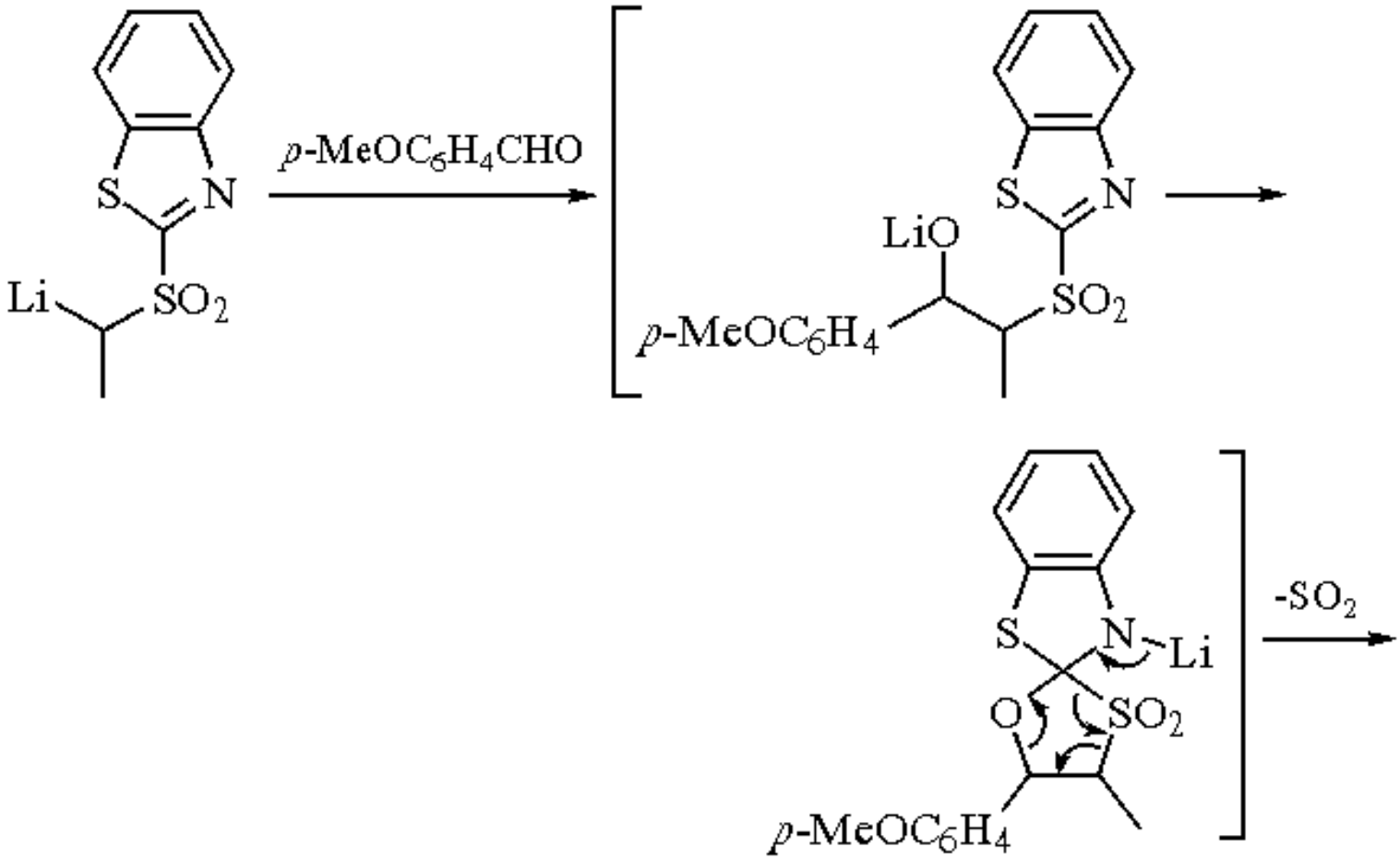

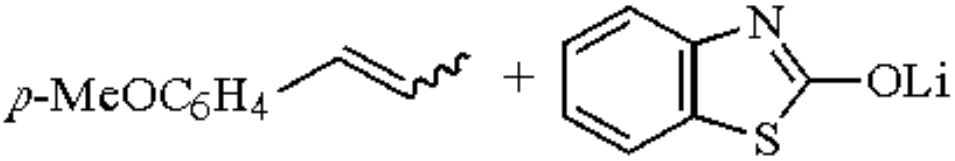

54%, (*E*):(*Z*) = 98:2 (14)

Alternative Desulfonylation/C-C Bond-Forming Procedures.

The foregoing discussion has focussed on reductive methods for removing sulfones and, in the case of the Julia alkenation, desulfonylation is accompanied by the formation of a new C-C bond. Another method which accomplishes desulfonylation with the concomitant construction of a C=C bond entails fluoride-induced elimination of β-silyl sulfones (see ***(2-Phenylsulfonylethyl)trimethylsilane***).

Allylic sulfones undergo S_N2' displacement by cyanocuprates with high *syn* stereoselectivity (eq 15).[44] Stabilized enolates also displace allylic arylsulfonyl groups in the presence of Pd^0 or Ni^0 catalysts.[45]

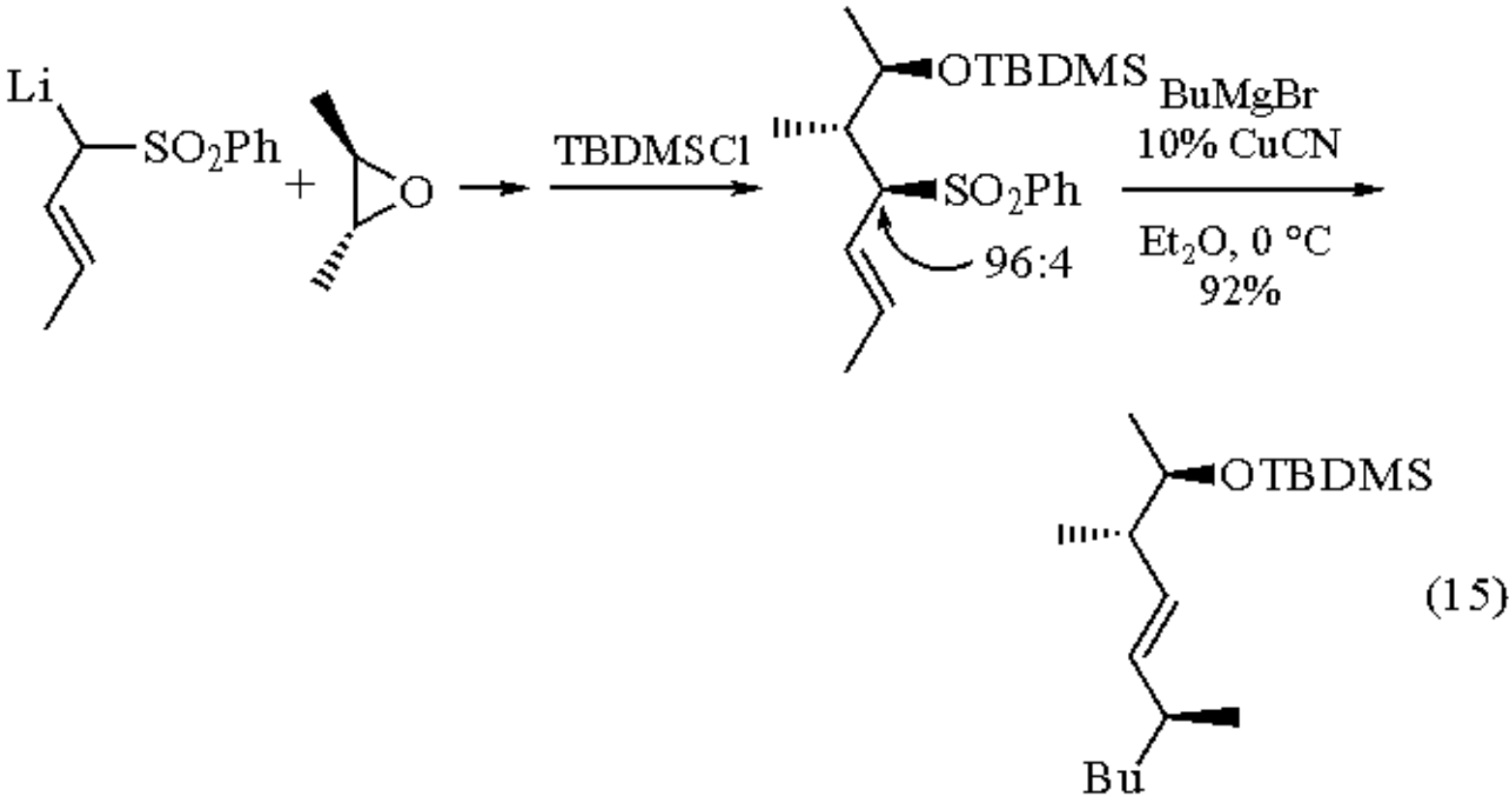

(15)

Allylic and tertiary alkyl sulfones can also participate in electrophilic cyclizations in the presence of ***Aluminum Chloride*** (Friedel-Crafts reaction; eq 16).[46]

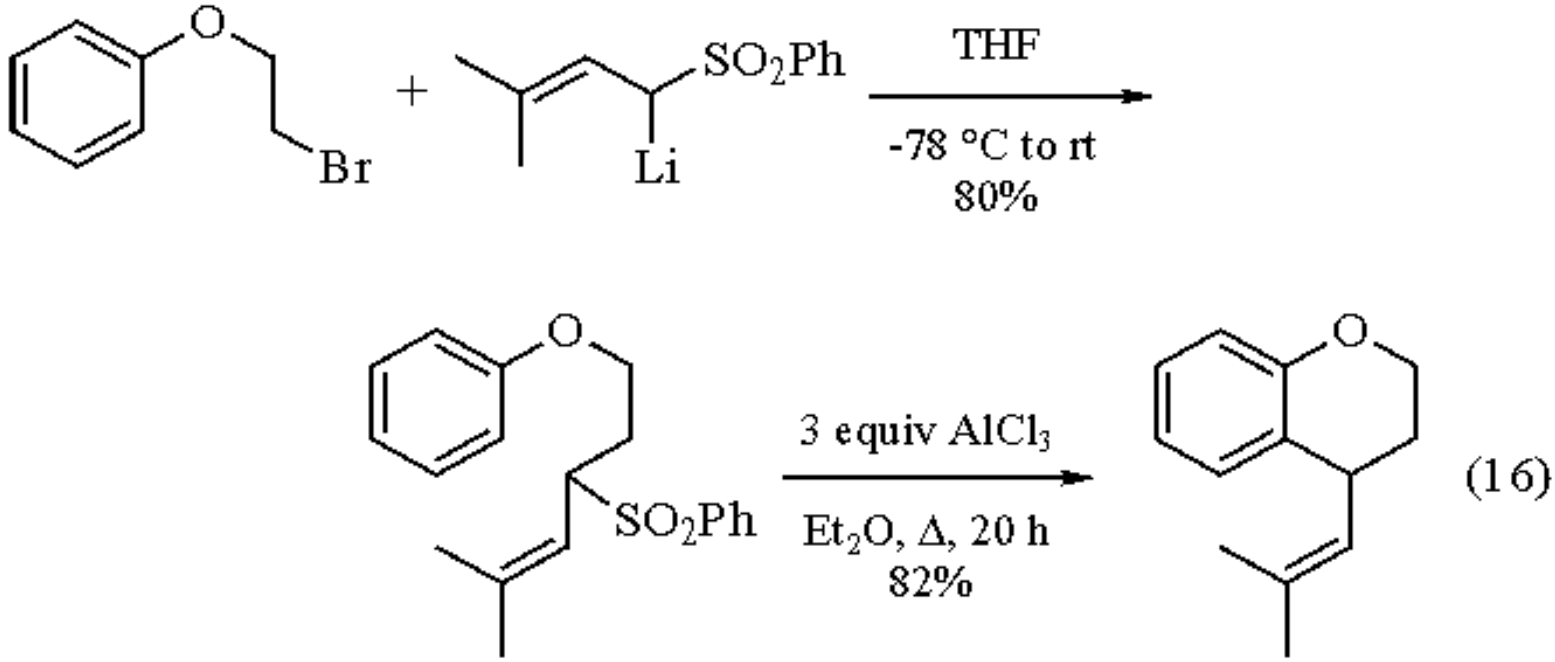

(16)

Base-catalyzed elimination of β-acetoxy sulfones is highly stereoselective, leading to (*E*)-alkenyl sulfones which undergo transition metal-catalyzed coupling with Grignard reagents with retention of configuration to provide a stereoselective synthesis of trisubstituted alkenes.[47] Either ***Nickel(II) Acetylacetonate***, ***Tris(acetylacetonato)iron(III)***, or ***Iron(III) Chloride*** can be used as the catalyst (eq 17).[48]

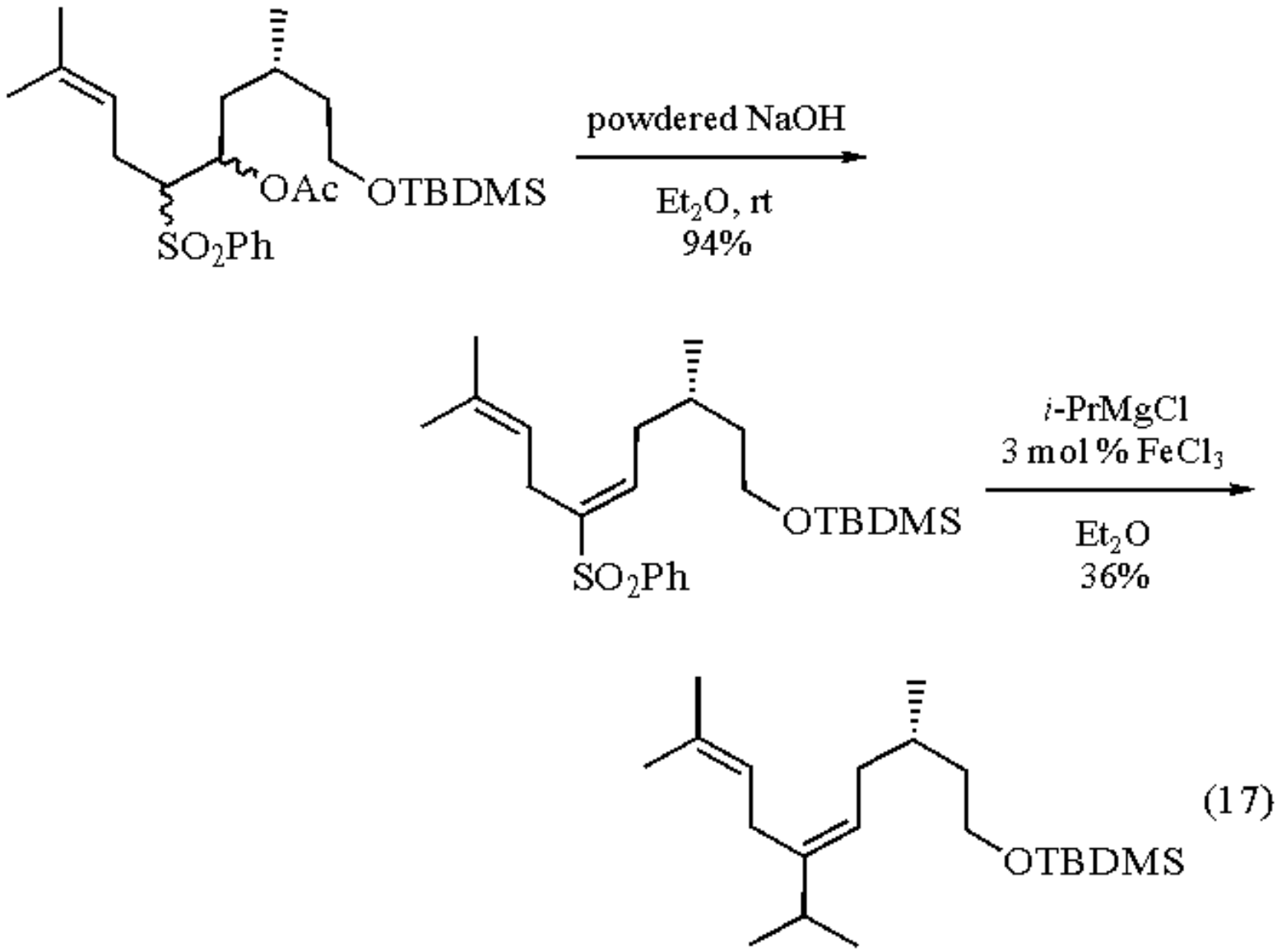

Oxidative Desulfonylation of Arylsulfonylalkyllithiums.

Aryloxysulfonylalkyllithiums can be converted to ketones in one pot by reaction with ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)***,[49] ***Bis(trimethylsilyl) Peroxide***,[50] or ***Chlorodimethoxyborane/m-Chloroperbenzoic Acid***.[51]

Related Reagents.

Methyl Phenyl Sulfone; ***4-Phenylsulfonyl-2-butanone Ethylene Acetal***; ***3-(Phenylsulfonyl)propanal Ethylene Acetal***.

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Georges Hareau & Philip Kocienski

(2-Phenylsulfonylethyl)trimethylsilane

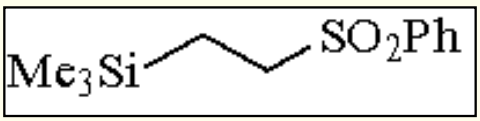

[73476-18-3] · $C_{11}H_{18}O_2SSi$ · (2-Phenylsulfonylethyl)trimethylsilane · (MW 242.45)

(reagent for the synthesis of mono- and 1,1-disubstituted alkenes via sulfone metalation, alkylation, and fluoride-induced elimination[1])

Physical Data: mp 52 °C.

Solubility: sol all common ethereal, halocarbon, and hydrocarbon solvents.

Form Supplied in: solid; commercially available.

Preparative Methods: (2-phenylsulfonylethyl)trimethylsilane (**2**) is prepared by radical addition of ***Thiophenol*** to ***Vinyltrimethylsilane*** to give (2-phenylthioethyl)trimethylsilane (**1**), which is then oxidized with ***Hydrogen Peroxide*** (eq 1).[2,3]

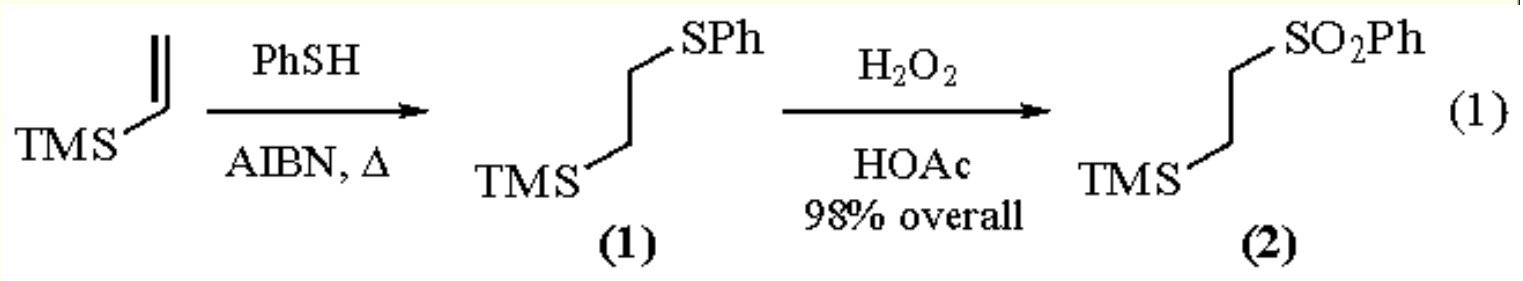

General Considerations.

A sequence involving metalation, alkylation, and fluoride-induced elimination of benzenesulfinate allows the conversion of (**2**) to a terminal alkene. An analogous sequence involving a double alkylation of (**2**) provides a 1,1-disubstituted alkene (eq 2).[4,5] The lithio derivative of (**2**) has also been used to prepare cyclopropylidene derivatives,[6] homoallylic alcohols,[7] and allyl silanes via the Julia alkenation.[3]

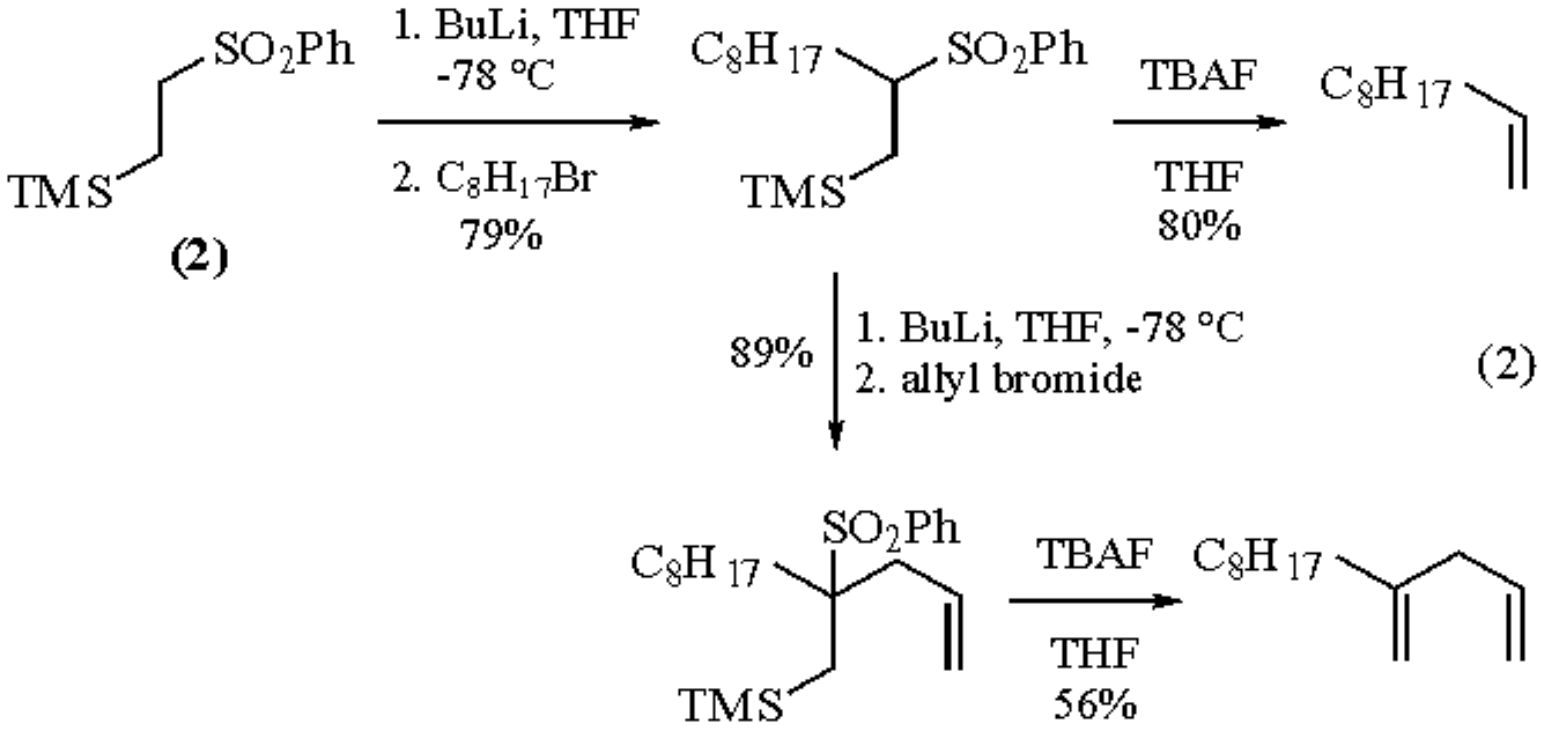

Alternative Routes to Substituted (2-Phenylsulfonylethyl)trimethylsilanes.

Although the fluoride-induced elimination is a reliable and efficient method for synthesizing alkenes, the requisite silyl sulfone precursors are often better prepared by methods which avoid the use of (**2**). For example, eq 3 illustrates an alternative synthesis of 2,2-dialkyl-2-(phenylsulfonylethyl)trimethylsilanes involving alkylation of a lithio sulfone with ***(Iodomethyl)trimethylsilane***.[8,9]

(2-Phenylsulfonylethyl)trimethylsilane

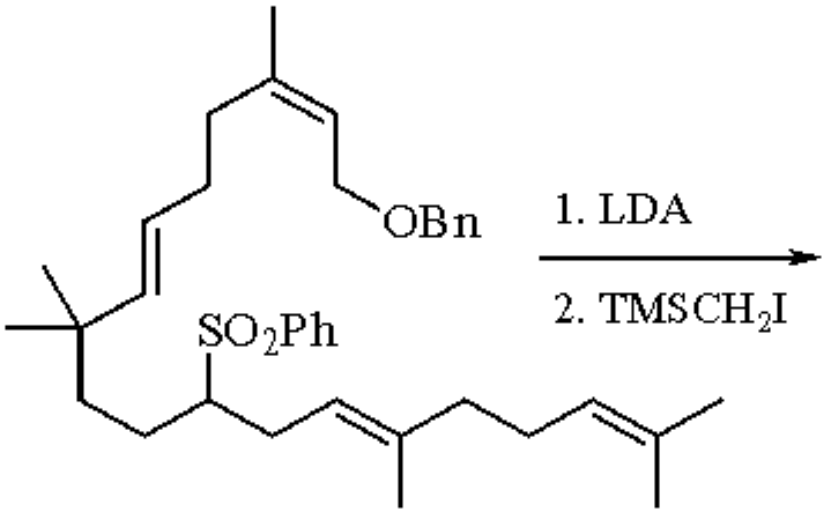

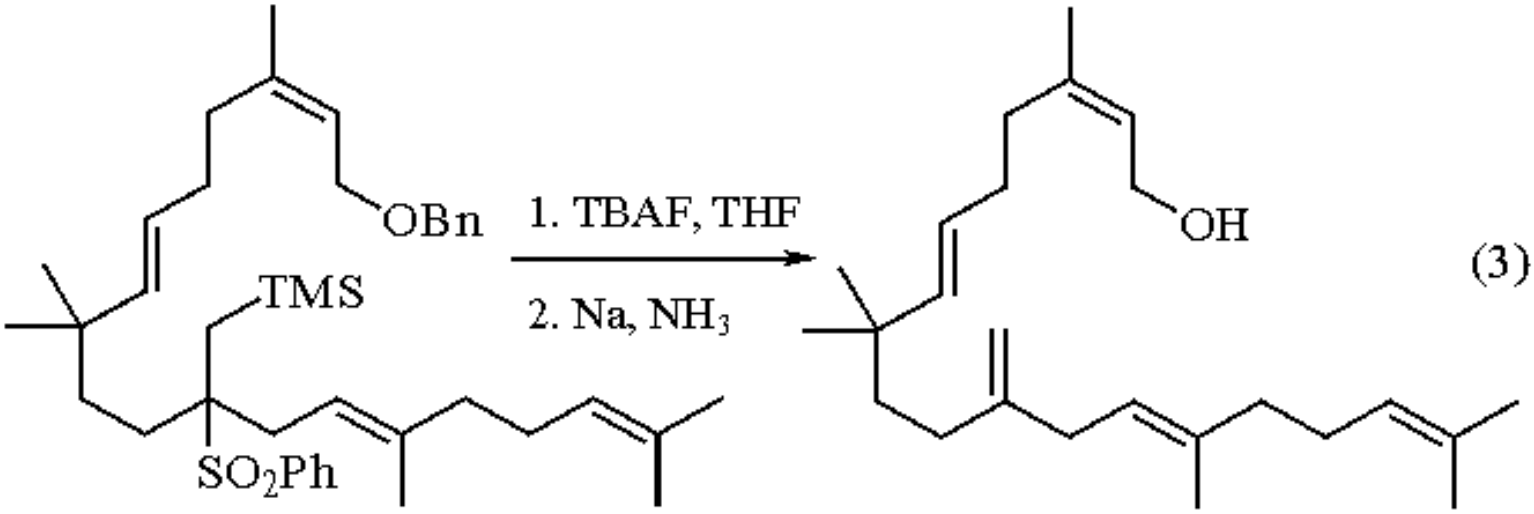

(3)

2-(Phenylsulfonylvinyl)trimethylsilane (**3**) is a useful acetylene equivalent for use in Diels-Alder reactions (eq 4).[10,11]

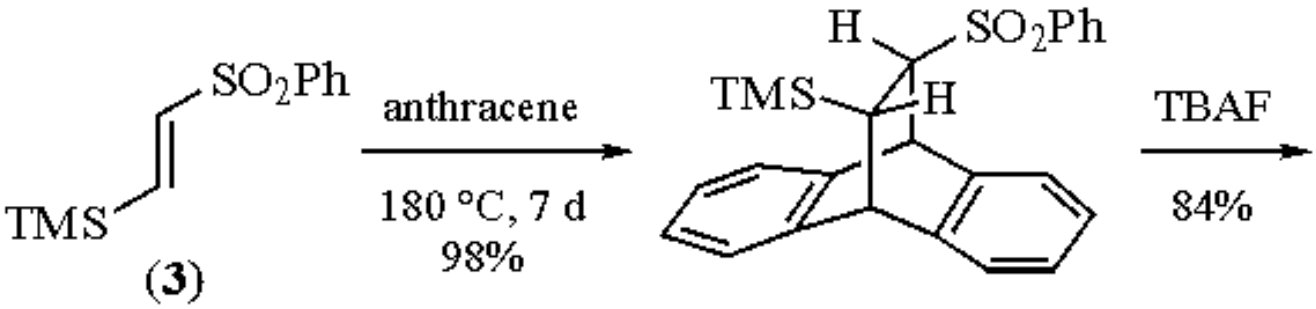

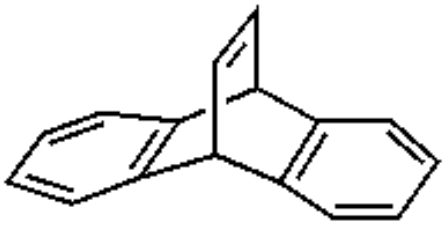

(4)

(2-Phenylsulfonylethyl)trimethylsilane

Phenylsulfonylethylene derivatives undergo conjugate addition reactions. Thus (**3**) reacts with unsaturated Grignard reagents and organocuprates,[12] while the substituted sulfone (**5**) undergoes conjugate addition by the enolate derivative (**4**) to give a bicyclomycin intermediate (eq 5).[13]

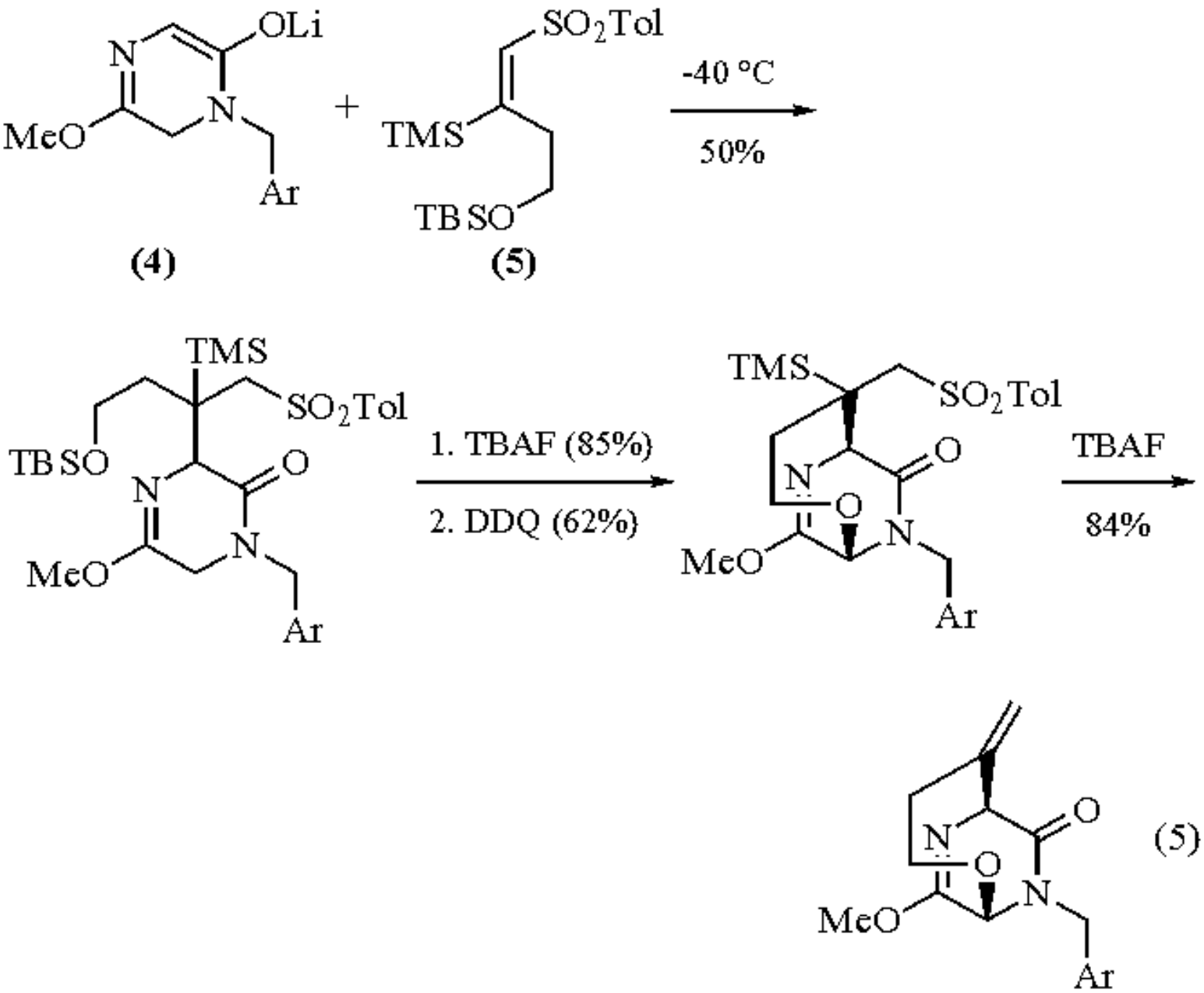

Related Reagents.

1,1-Bis(phenylsulfonyl)ethylene; ***Phenylsulfonylethylene***; ***α-Phenylsulfonylethyllithium***; ***1-Phenylsulfonyl-2-(trimethylsilyl)acetylene***; ***(E)-1-Phenylsulfonyl-2-trimethylsilylethylene***; ***Phenylsulfonyl(trimethylsilyl)methane***.

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Phenylsulfonylnitromethane

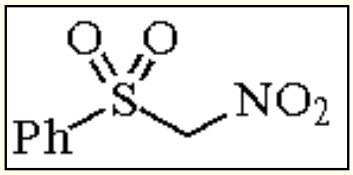

[21272-85-5] · $C_7H_7NO_4S$ · Phenylsulfonylnitromethane · (MW 201.22)

(precursor for α-nitro sulfones;[1] precursor for phenylsulfonylnitrile oxide for 1,3-dipolar cycloadditions[2])

Physical Data: mp 78-79 °C; pK_a 5.69 (MeOH-H_2O, 50:50).[3]

Solubility: insol water; sol CH_2Cl_2, hot alcohol. Sodium salt (**1**) sparingly sol DMSO but not THF; lithium salt (**2**) sol THF.

Form Supplied in: white crystalline solid.

Analysis of Reagent Purity: analytical TLC (CH_2Cl_2 elution) should give one spot, R_f 0.35; a possible impurity is 1,3-bis(phenylsulfonyl)-1,3-dinitropropane, R_f 0.1, which can be removed by sublimation.

Preparative Methods: ***Nitromethane***, ***Sodium Benzenesulfinate***, and ***Iodine*** are added sequentially to a cold (0-5 °C) DMF solution of ***Sodium Methoxide***. The reagent can be converted to $NaO_2N{=}CHSO_2Ph$ (**1**) and $LiO_2N{=}CHSO_2Ph$ (**2**) using NaOMe and LiOMe, respectively.[1]

Handling, Storage, and Precautions: indefinitely stable; the nitronate salts (**1**) and (**2**) can be stored dry without decomposition for several weeks but, *like all nitronate salts, they are explosive*: (2) *vigorously decomposes above 150 °C*.

Alkylation Reactions.

The reagent can be *C*-monoalkylated via its nitronate salts (**1**) and (**2**). α-Nitro sulfones were obtained by reaction of (**1**) with a variety of benzyl halides and primary alkyl iodides (eq 1).[1,4] α-Nitro sulfones were similarly obtained by reaction of (**2**) with allylic acetates in the presence of Pd^0 catalysts (eqs 2 and 3).[1,5] High regioselectivity for the less hindered carbon of the π-allylpalladium intermediate was typically observed. Displacement of the acetate usually occurs with net retention.[6]

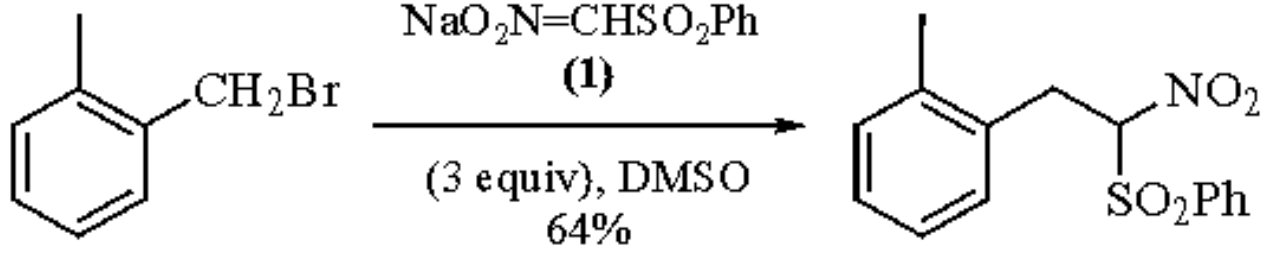

(1)

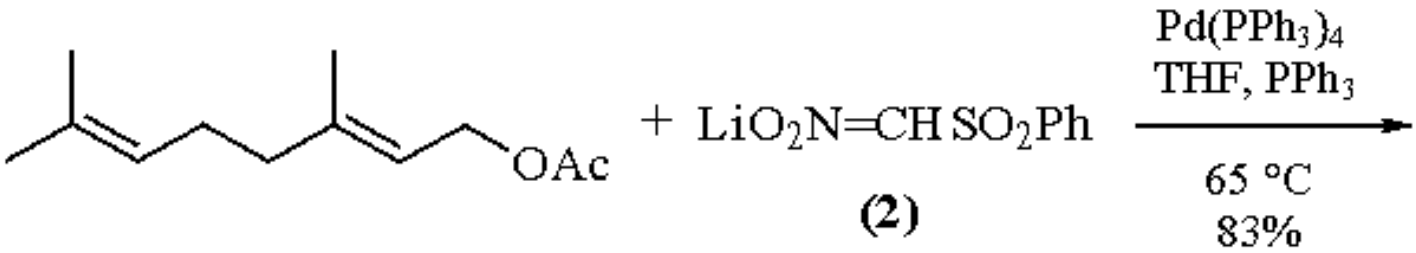

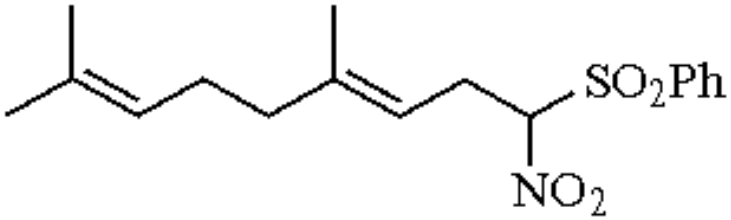

(2)

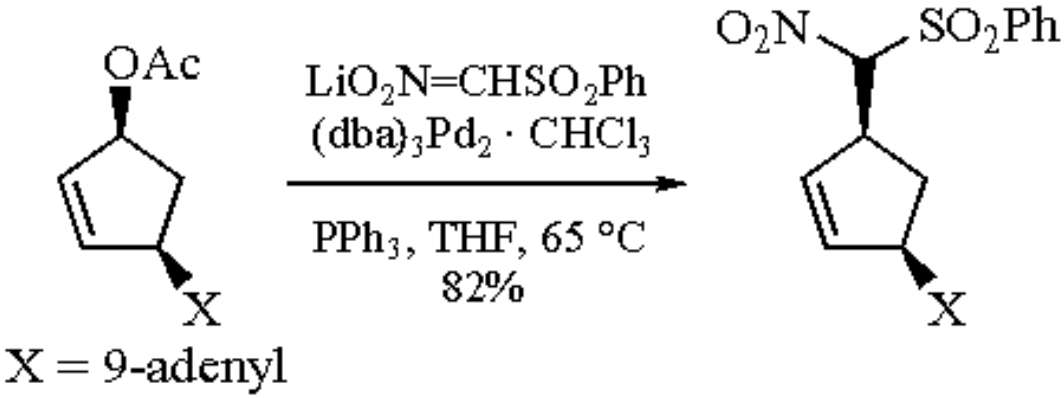

(3)

C,*C*-Dialkylates were not formed in the alkylation reactions owing to congestion at the monoalkylated α-nitro sulfone center. However, internal *O*-alkylation can occur,[1,7] subsequent to *C*-alkylation, affording cyclic nitronic esters (eq 4) which can be deoxygenated to provide 3-phenylsulfonyl-4,5-dihydroisoxazoles. The reagent has also been used to prepare α-nitro sulfones by Michael addition to 3-buten-2-one.[4a] α-Nitro sulfones can be converted to carboxylic acids,[1,5] desulfonated nitro compounds,[1,4a,8] and nitriles.[1]

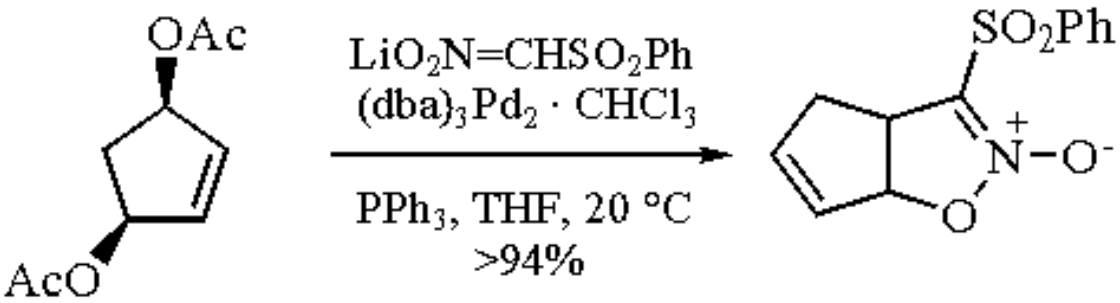

(4)

Cycloaddition Reactions.

The reagent is used to make three precursors for generation of the 1,3-dipole benzenesulfonyl cyanide *N*-oxide ($PhSO_2C$&tbond;+N-O^-). The first precursor, *N*-hydroxy-1-phenylsulfonylmethanimidoyl bromide (**3**), is obtained from the reagent by sequential bromination, methylation, and mild thermolysis (eq 5).[2a] Bromooxime (**3**) is preferred because it gives the nitrile oxide most cleanly.

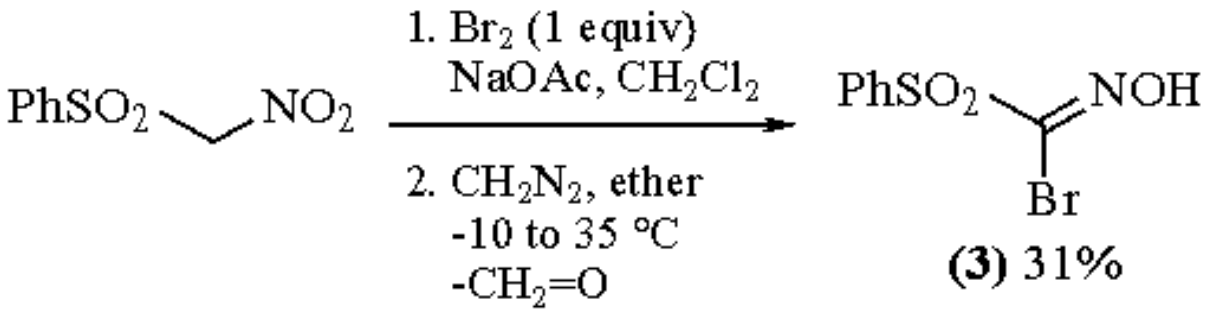

(5)

However, nitronic ester (**4**), *which has been known to explode*, is a more easily obtained precursor: the reagent is simply methylated using diazomethane.[2b,10] The reagent also reacts with nitric acid to provide bis(phenylsulfonyl)furazan 2-oxide (**5**), which is a third nitrile oxide precursor.[9,2c]

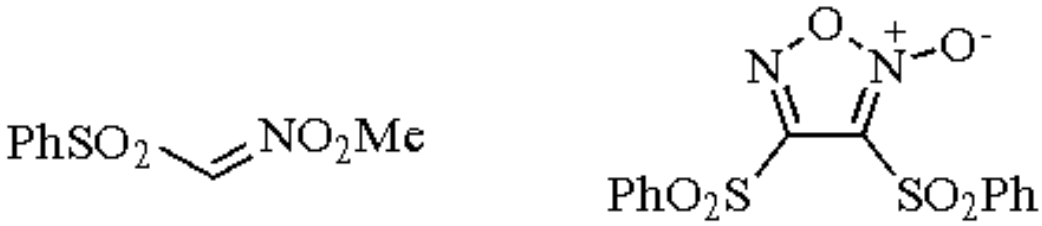

(4) (5)

Any of these precursors, for example (**3**), can be used to generate the nitrile oxide which then reacts in situ with a wide variety of alkenes to give 3-phenylsulfonyl-4,5-dihydroisoxazoles (eq 6).[2,10,11]

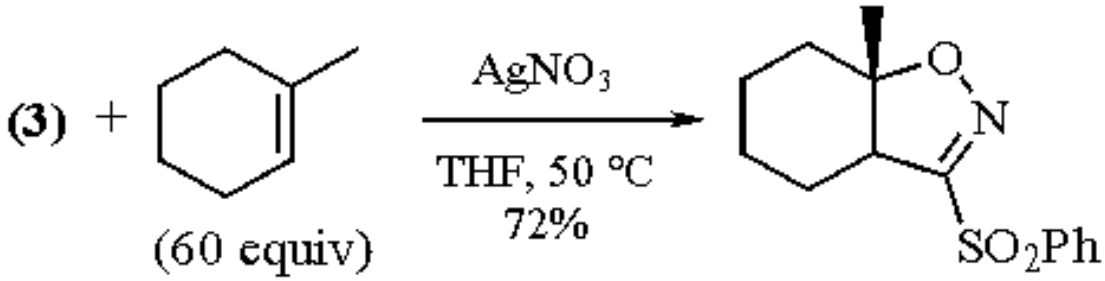

(6)

The alkene configuration is retained in the dihydroisoxazole and regioselectivity is high for monosubstituted, *gem*-disubstituted, and trisubstituted alkenes. Conditions for generation of the nitrile oxide vary: (**3**) requires mild base[2a] or ***Silver(I) Nitrate***,[2b] while nitronic ester (**4**) requires strong base[2b] or strong acid,[12] and (**5**) requires heating (140 °C).[2c] The phenylsulfonyl group of the dihydroisoxazoles can be replaced using a variety of nucleophiles including organolithium reagents and sodium methoxide.[13,7] Reductive cleavage using 2% ***Sodium Amalgam***[14] or

Hexacarbonylmolybdenum[7] affords *cis*-β-hydroxynitriles, and this is the most general route to these compounds (eq 7).

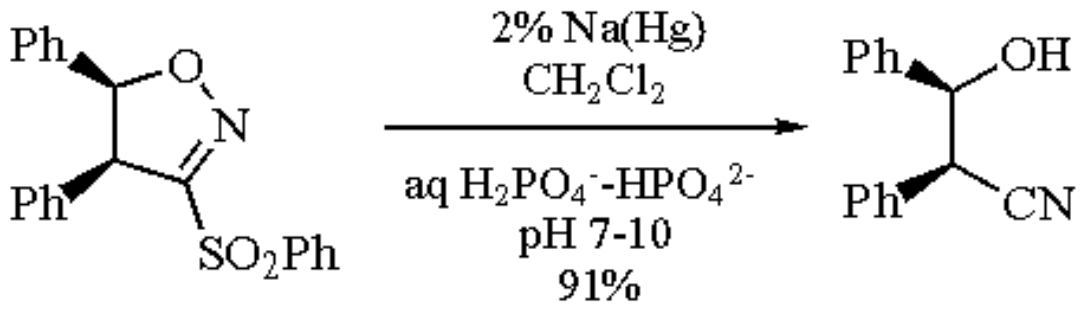

(7)

Related Reagents.

(Phenylthio)nitromethane.

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(*E,E*)-*N*-Phenylsulfonyl-4-phenyl-1-aza-1,3-butadiene[1]

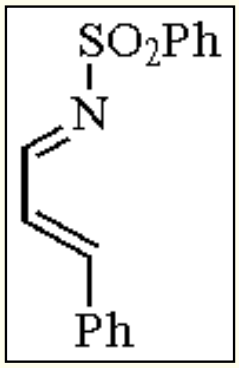

[118922-13-7] · $C_{15}H_{13}NO_2S$ · (*E,E*)-*N*-Phenylsulfonyl-4-phenyl-1-aza-1,3-butadiene · (MW 271.36)

(electron-deficient acyclic 1-azadiene capable of participation in inverse electron demand Diels-Alder reactions with electron-rich dienophiles[2a])

Alternate Name: (*E,E*)-*N*-(3-phenyl-2-propenylidene)benzenesulfonamide.

Physical Data: mp 107-109 °C.

Solubility: sol CH_2Cl_2, C_6H_6.

Form Supplied in: pale yellow solid.

Preparative Methods: a solution of cinnamaldehyde in toluene (0.10 M) is treated with benzenesulfonamide (1.1 equiv) and $MgSO_4$ (2 g $mmol^{-1}$) and the reaction mixture is stirred at reflux for 120 h. The reaction mixture is cooled to 25 °C, the $MgSO_4$ is removed by filtration, and the filtrate is concentrated in vacuo. Flash chromatography (SiO_2, 15% EtOAc/hexane eluent) gives the title reagent (typical yield 50%).[2]

Additional general methods for the synthesis of *N*-sulfonylimines based on the in situ generation of *O*-sulfinate derivatives of oximes employing sulfinyl chlorides (phenyl- and methylsulfinyl chloride)[2a,3-8] or sulfonyl cyanides (*p*-toluenesulfonyl cyanide)[2b] and their subsequent rt rearrangement have been detailed.

Handling, Storage, and Precautions: stable at room temperature but susceptible to hydrolysis and must be stored free of moisture.

Cycloaddition Reactions.

Stable, electron-deficient *N*-(phenylsulfonyl)-1-aza-1,3-butadiene is one of a series of α,β-unsaturated *N*-benzenesulfonyl imines capable of participation in regio- and *endo*-selective inverse electron demand Diels-Alder reactions with a range of electron-rich dienophiles employed in the diastereoselective preparation of substituted *N*-benzenesulfonyl-1,2,3,4-tetrahydropyridines (eq 1).[2a,3]

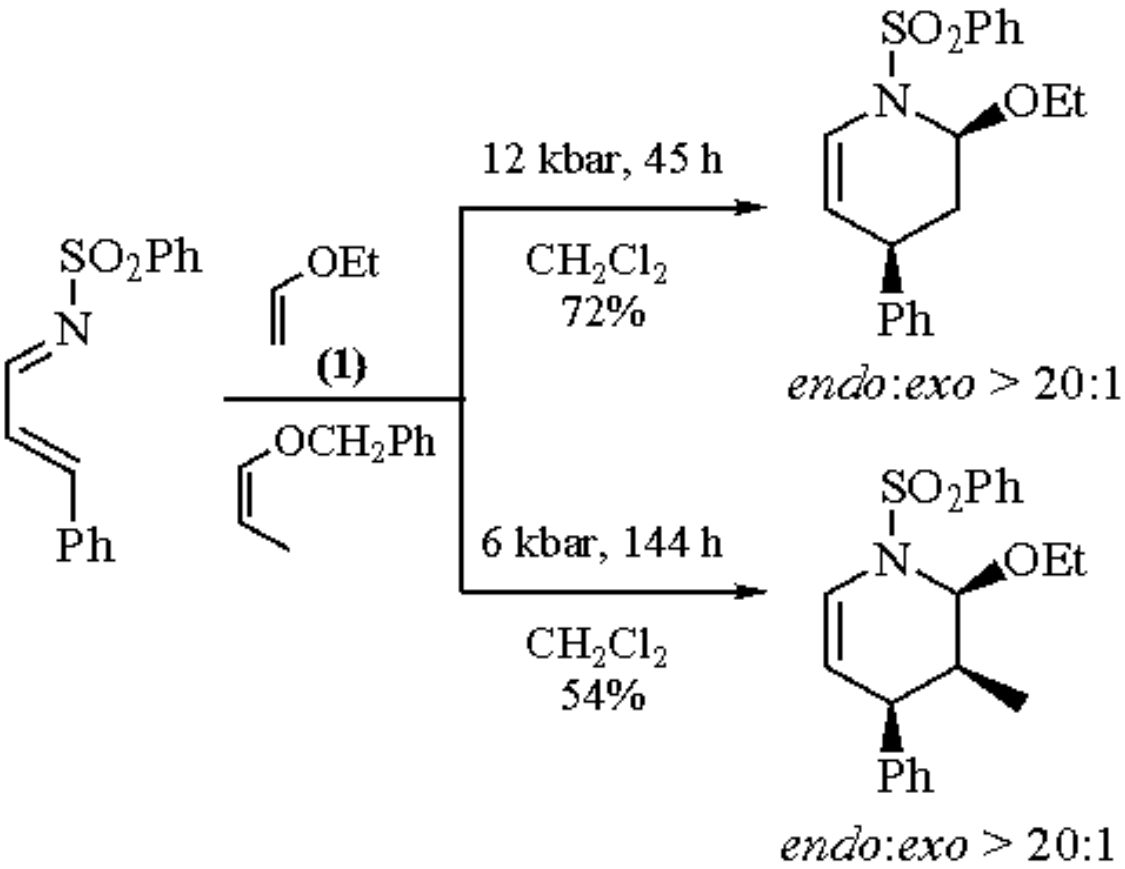

(1)

N-Benzenesulfonyl aldimines have been shown to be more reactive than *N*-benzenesulfonyl ketimines (eq 2),[1,2a,3] and the complementary addition of a C-3 or the noncomplementary addition of C-2 and C-4 electron-withdrawing substituents substantially accelerate the Diels-Alder reaction and maintain the expected cycloaddition regioselectivity and exceptionally high *endo* diastereoselectivity (eqs 3-5).[2a,3-5]

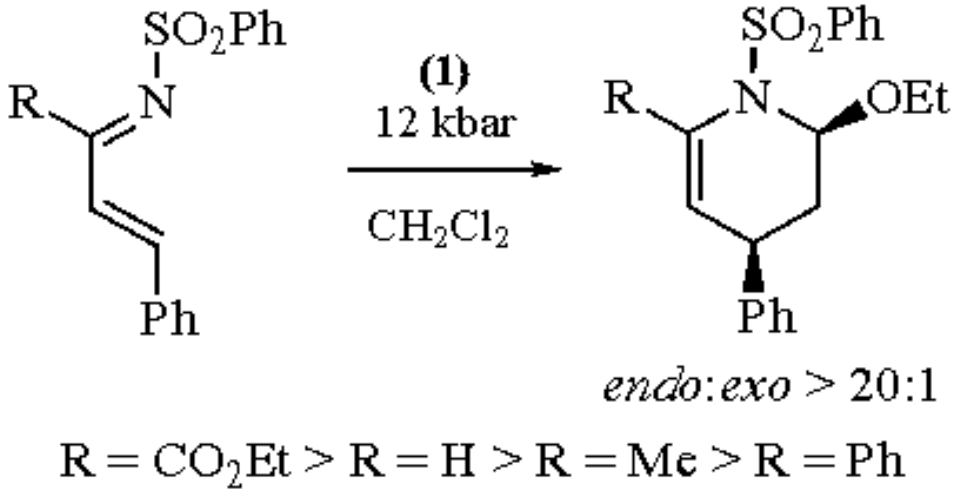

(2)

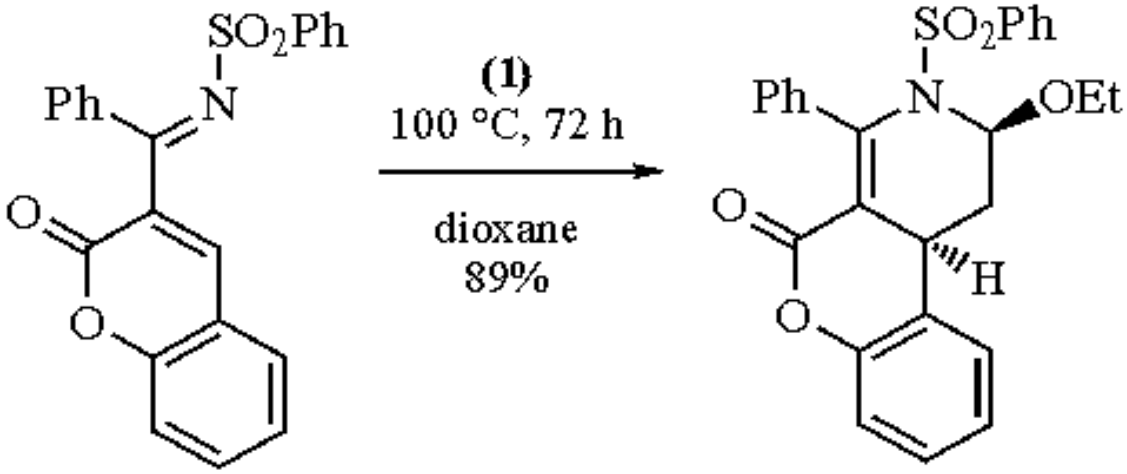

(3)

endo:*exo* > 20:1

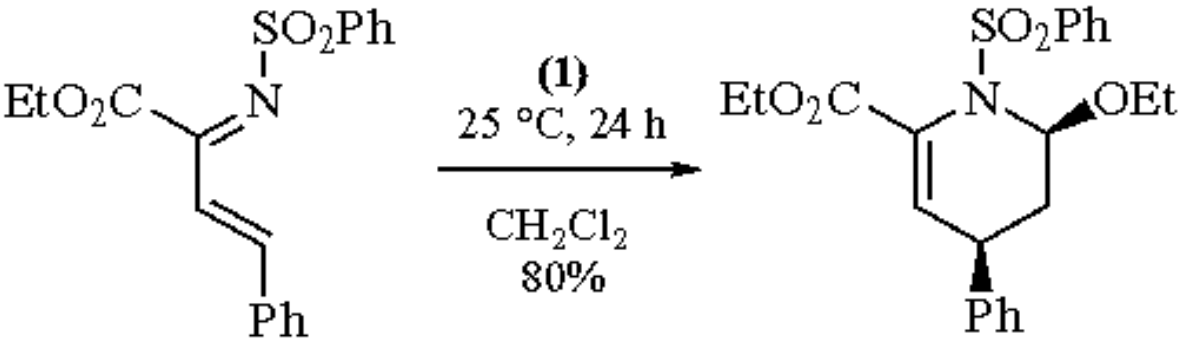

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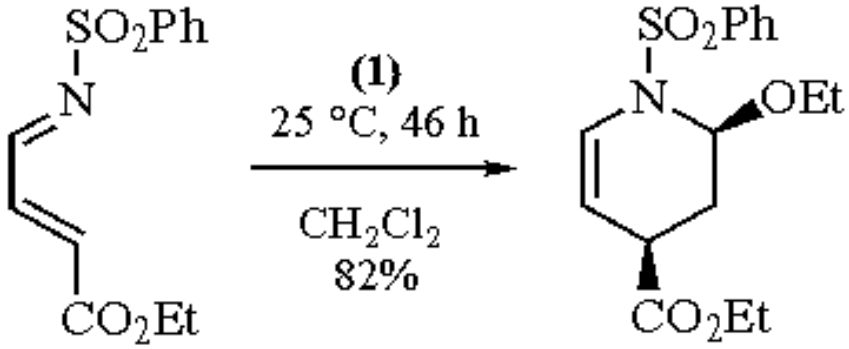

(5)

endo:*exo* > 20:1

Synthetic procedures for preparation of highly substituted or highly functionalized pyridines based on the [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes have been developed and their applications in the total syntheses of fredericamycin A (**2**) (eq 6)[6] and streptonigrone (**3**) (eq 7)[7] have been described. The intramolecular [4 + 2] cycloaddition reactions of *N*-sulfonyl-1-aza-1,3-butadienes have been detailed.[8]

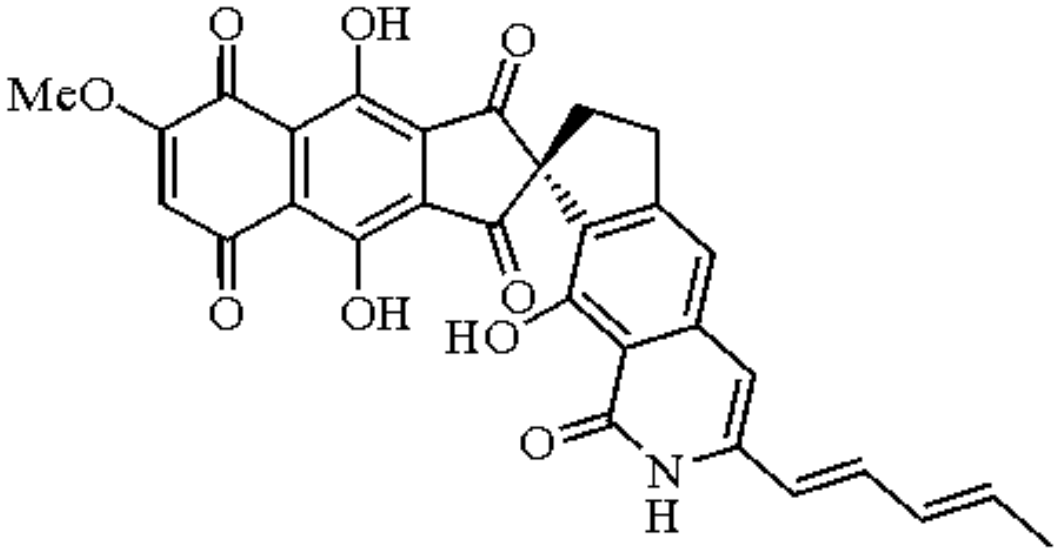

(2) Fredericamycin A

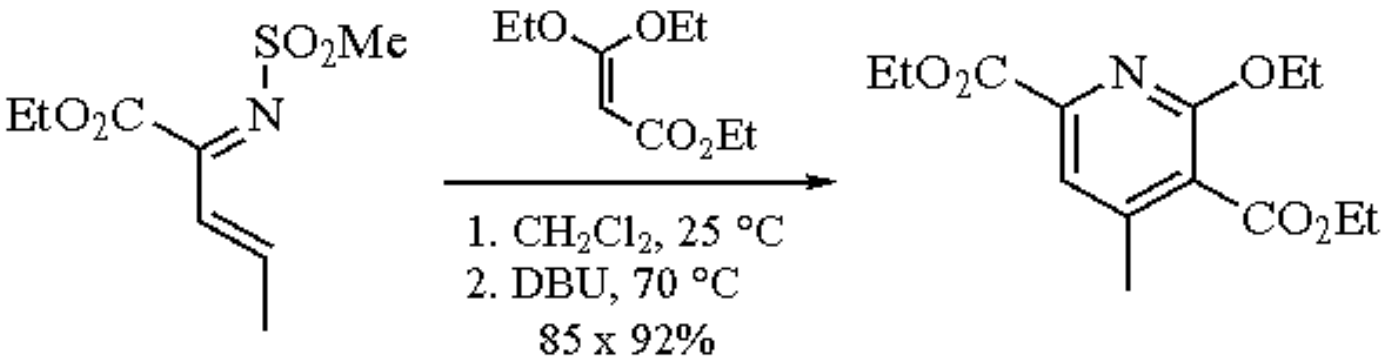

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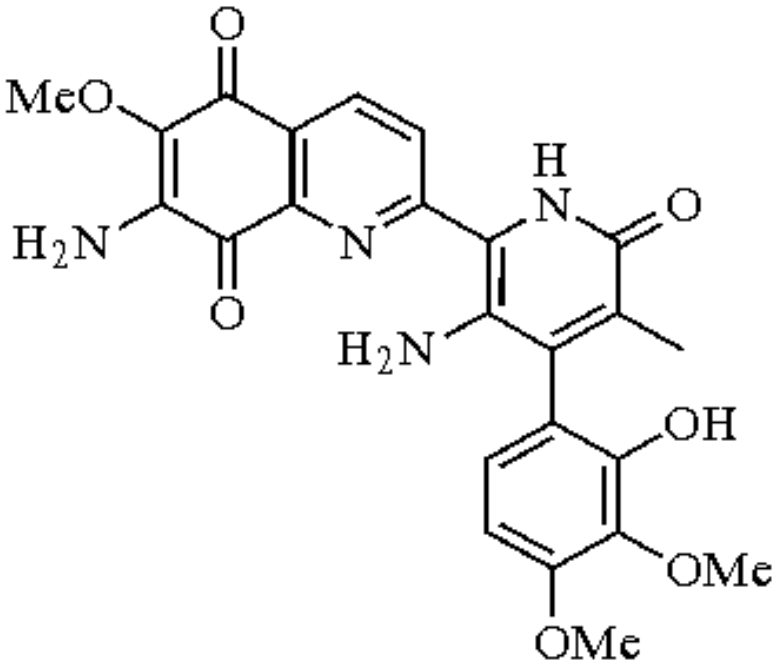

(3) Streptonigrone

(E,E)-N-Phenylsulfonyl-4-phenyl-1-aza-1,3-butadiene

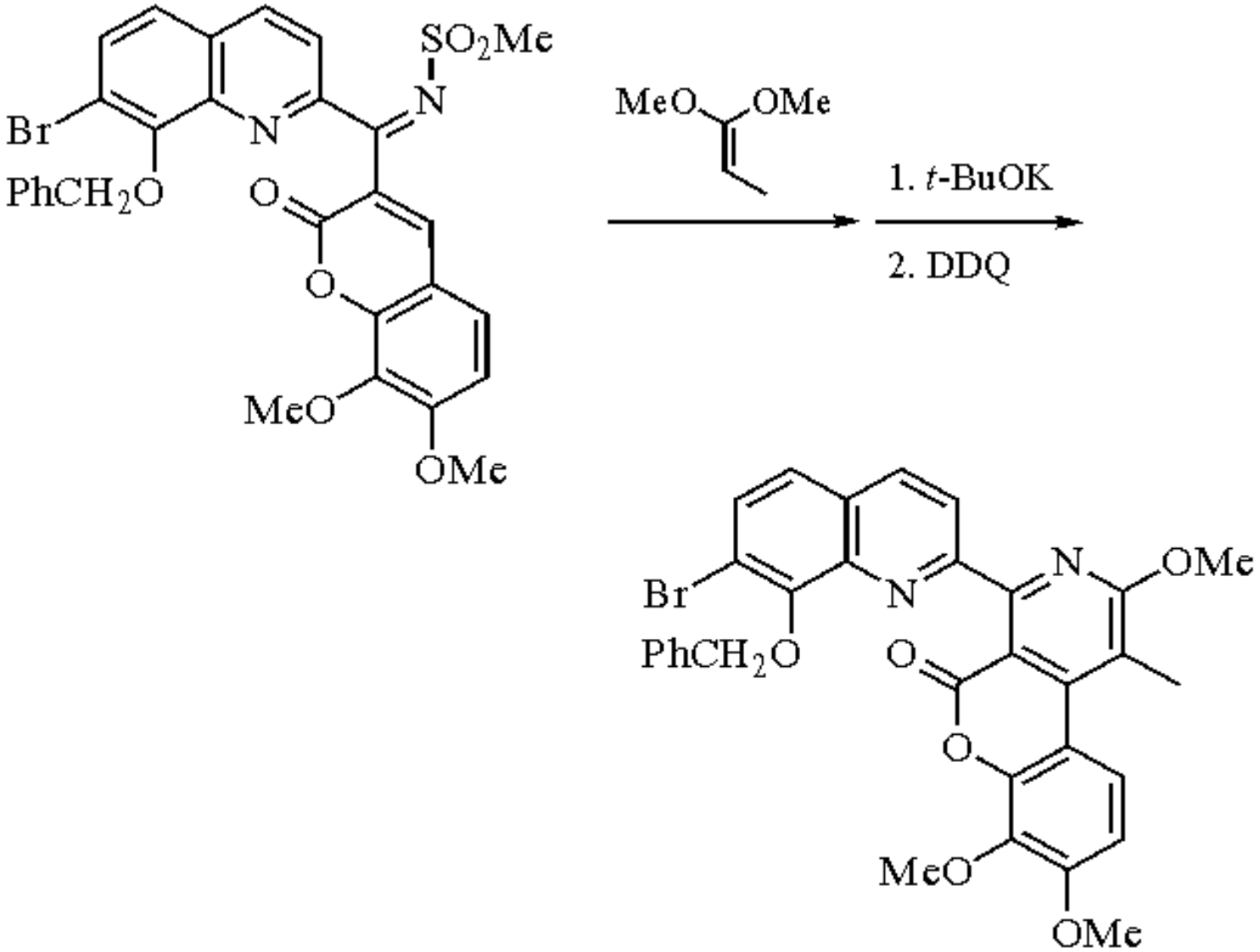

(7)

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Dale L. Boger & Minsheng Zhang

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(±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine[1]

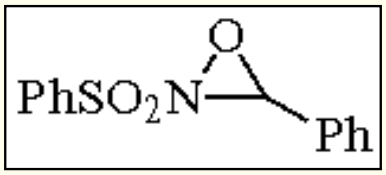

[63160-13-4] · $C_{13}H_{11}NO_3S$ · (±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine · (MW 261.32)

(neutral, aprotic, electrophilic oxidizing agent for the chemoselective oxidation of many nucleophilic substrates[1])

Physical Data: mp 95-95.5 °C.

Solubility: sol CH_2Cl_2, $CHCl_3$, THF; insol hexane, pentane, water.

Form Supplied in: white solid.

Analysis of Reagent Purity: ^{1}H NMR analysis and mp determination.

Preparative Methods: the title reagent (**1**) can be readily prepared on a 100 g scale in 88% yield via oxidation of *N*-benzylidenebenzenesulfonamide with buffered ***m-Chloroperbenzoic Acid***[2] or more conveniently with ***Potassium Monoperoxysulfate*** (Oxone).[3] This Baeyer-Villiger type of oxidation of sulfonimine affords only the *trans*-oxaziridine. A number of other (±)-*trans*-2-(arylsulfonyl)-3-aryloxaziridines (**2**) can also be prepared by these methods.[2,3]

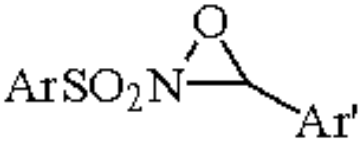

(2a) Ar = Ph, Ar' = $C_6H_4NO_2$-*p*
(2b) Ar = C_6H_4Me-*p*, Ar' = $C_6H_4NO_2$-*p*
(2c) Ar = C_6H_4Cl-*p*, Ar' = C_6H_4Cl-*p*

Purification: recrystallization from ethyl acetate-pentane.[2]

Handling, Storage, and Precautions: can be stored in a brown bottle in the refrigerator for years without noticeable decomposition. Storage at rt for long periods of time, however, is potentially hazardous.[2] The

nitro-substituted oxaziridines (**2**) are more thermally stable and are recommended for reactions at elevated temperatures.

Oxidation of Organosulfur Compounds.

(±)-*trans*-2-(Arylsulfonyl)-3-aryloxaziridines oxidize a variety of sulfides to sulfoxides without over-oxidation to sulfones, even in the presence of excess oxidant.[1a,4] However, longer reaction times (>20 h) can produce sulfones.[4] An example is the oxidation of mustard to the sulfoxide in less than 2 min by *trans*-2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**2a**) (eq 1).[5] In contrast to *m*-CPBA or Oxone, oxaziridine-mediated oxidation of alkynyl phenyl sulfides at 60 °C gives none of the corresponding sulfone (eq 2).[6] The oxidation of sulfides has been developed in a catalytic manner.[7] Disulfides are usually oxidized to thiosulfinates which are difficult to obtain using acidic oxidants such as *m*-CPBA (eq 3).[8] Enantiopure *N*-sulfonyloxaziridines afford enantiomerically enriched sulfoxides and thiosulfinates.[9]

$$(ClCH_2CH_2)_2S + \textbf{(2a)} \xrightarrow{CHCl_3} (ClCH_2CH_2)_2SO + (ClCH_2CH_2)_2SO_2 \quad (1)$$

100:0

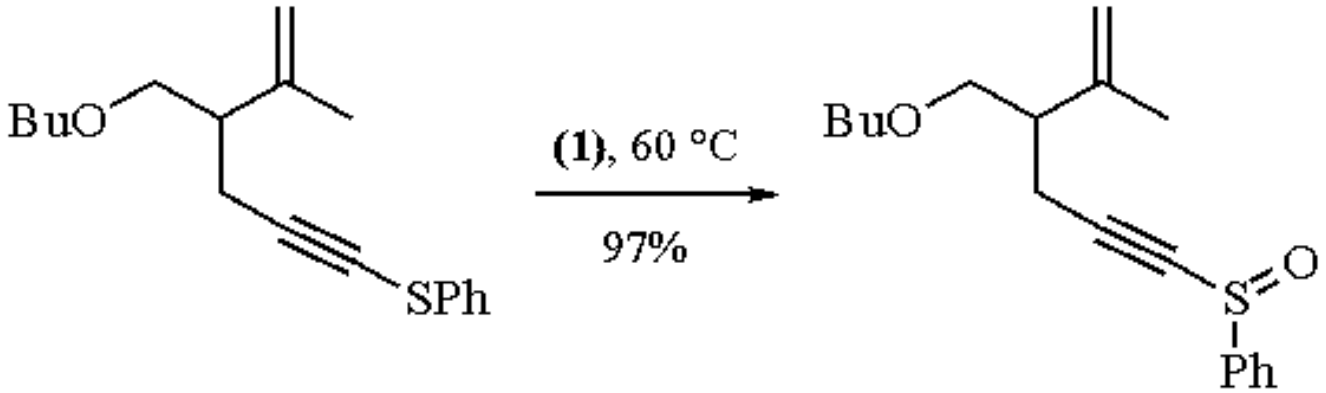

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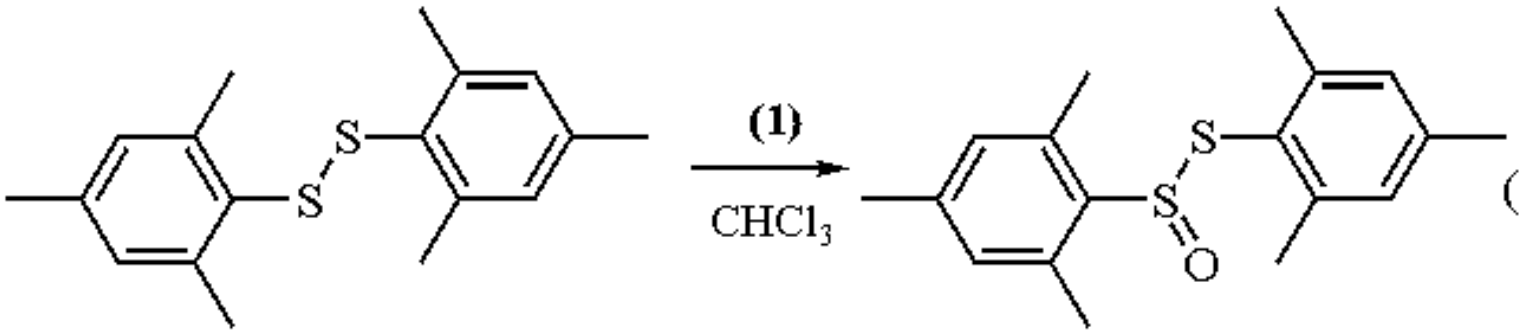

(3)

Thiols are oxidized to sulfenic acids (**3**) which can then be trapped by alkynes to give vinyl sulfoxides (**4**). In the

absence of the trapping agent, the initial sulfenic acid (**3**) is usually further oxidized to a sulfinic acid (**5**) due to the α-effect (eq 4).[10] 2-Mercaptopyridine, however, gives rise to the disulfide (eq 5).[11] Silyl sulfides (silyl ether of thiols), afford silyl sulfinates regardless of the stoichiometry of the reaction (eq 6).[12] Oxidation of thiones gives thione *S*-oxides which may undergo desulfurization to ketones (eq 7).[13] By the oxidation of the corresponding thiones with oxaziridine (**2b**), thiocamphor *S*-oxide (**6**) and thiofenchone *S*-oxide (**7**) are prepared in 91% and 76% yield, respectively.[13] Reaction of phosphorothionate with (**2a**) yields the phosphate (eq 8).[14]

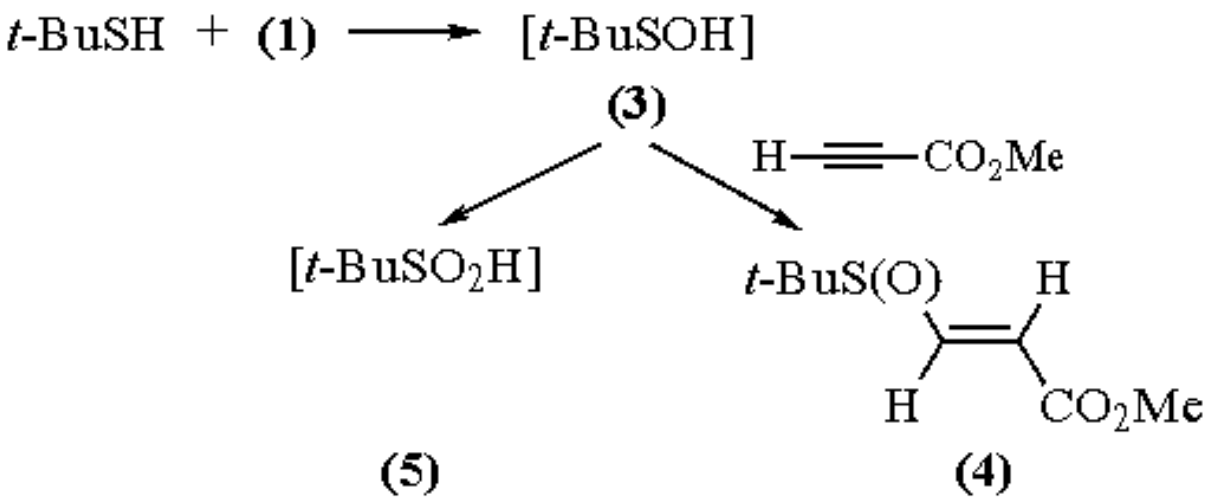

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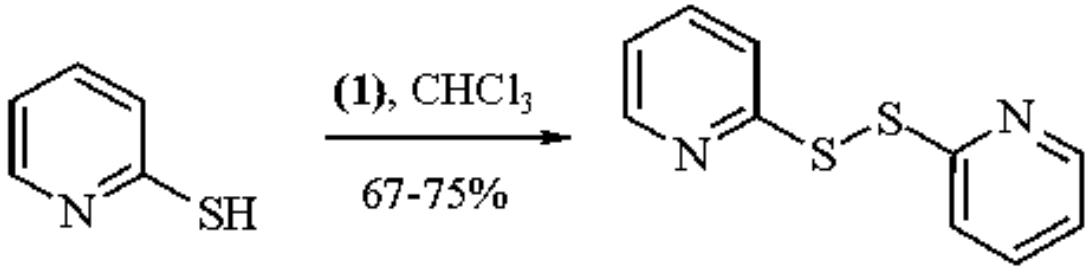

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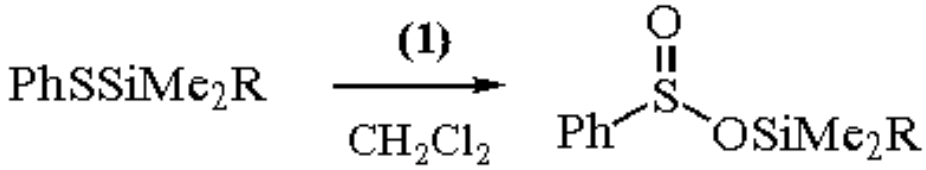

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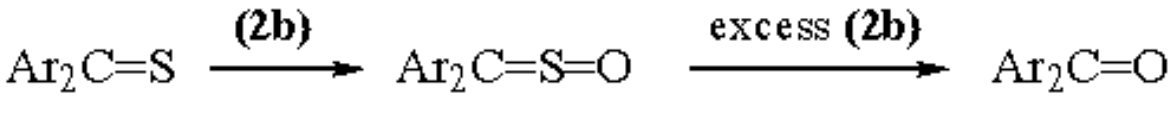

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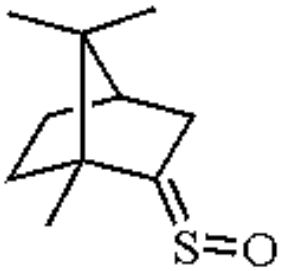

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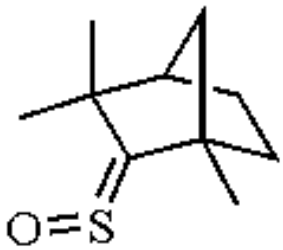

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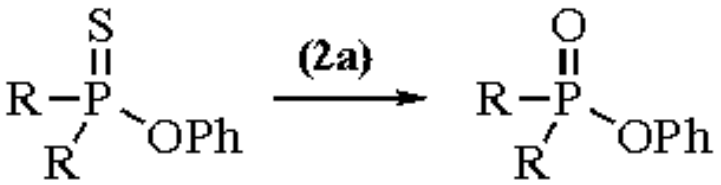

(8)

Oxidation of Organoselenium Compounds.

Selenides, like sulfides, are quantitatively oxidized to selenoxides without overoxidation.[1a,15] The resulting selenoxides may undergo [2,3]-sigmatropic rearrangement to allylic alcohols or β-elimination to alkenes (eq 9).[1a,16] The reaction can be run in the presence of a number of other functional groups such as aldehyde,[17] alkene,[18] and sulfide.[16] Compared to ***Hydrogen Peroxide*** or *m*-CPBA, improved yields are reported using oxaziridine (**2a**).[19] Oxaziridine-mediated selenide oxidations in the presence of pyridine have been used to suppress side products of the selenoxide elimination.[15] Diphenyl diselenide gives benzeneseleninic anhydride (eq 10).[17]

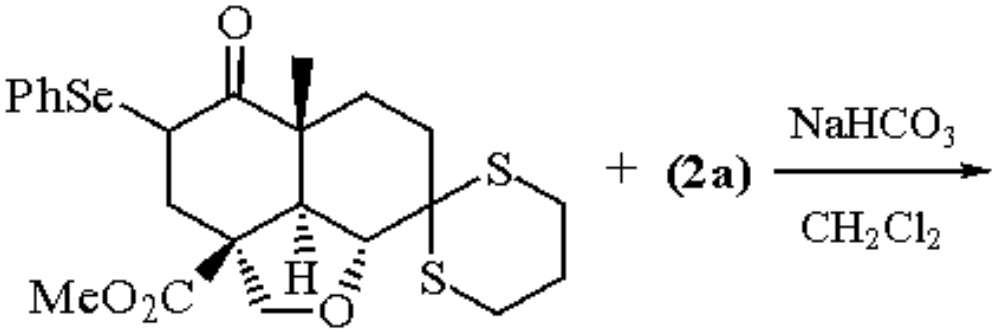

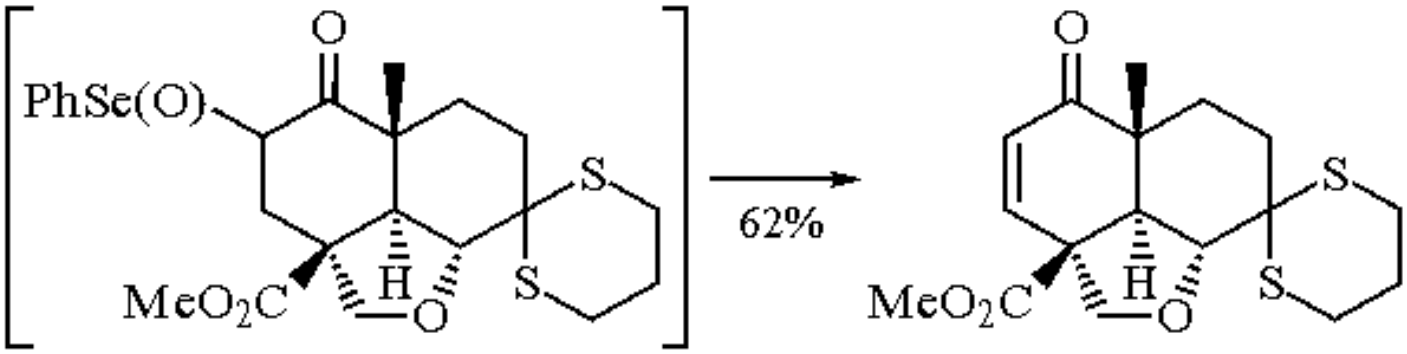

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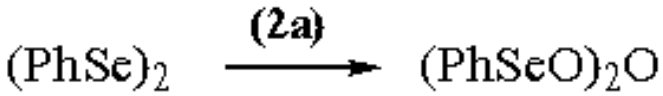

(10)

Oxidation of Organonitrogen and Organophosphorus Compounds.

Tertiary amines react with (**1**) to yield amine oxides (eq 11).[1a,20] Oxidation of secondary amines with one equiv of (**1**) affords the hydroxylamine (eq 12),[21] while excess oxaziridine gives rise to nitrones.[20] Aliphatic primary amines give,

(+/-)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine

on oxidation, nitroso compounds (eq 13).[20] Although pyridine is not reactive towards oxaziridines,[20] imines are oxidized to nitrones (eq 14).[22] With (**2b**), 1,3,2-λ^3-oxazaphospholanes gave 1,3,2-λ^5-oxazaphospholanes (eq 15).[23]

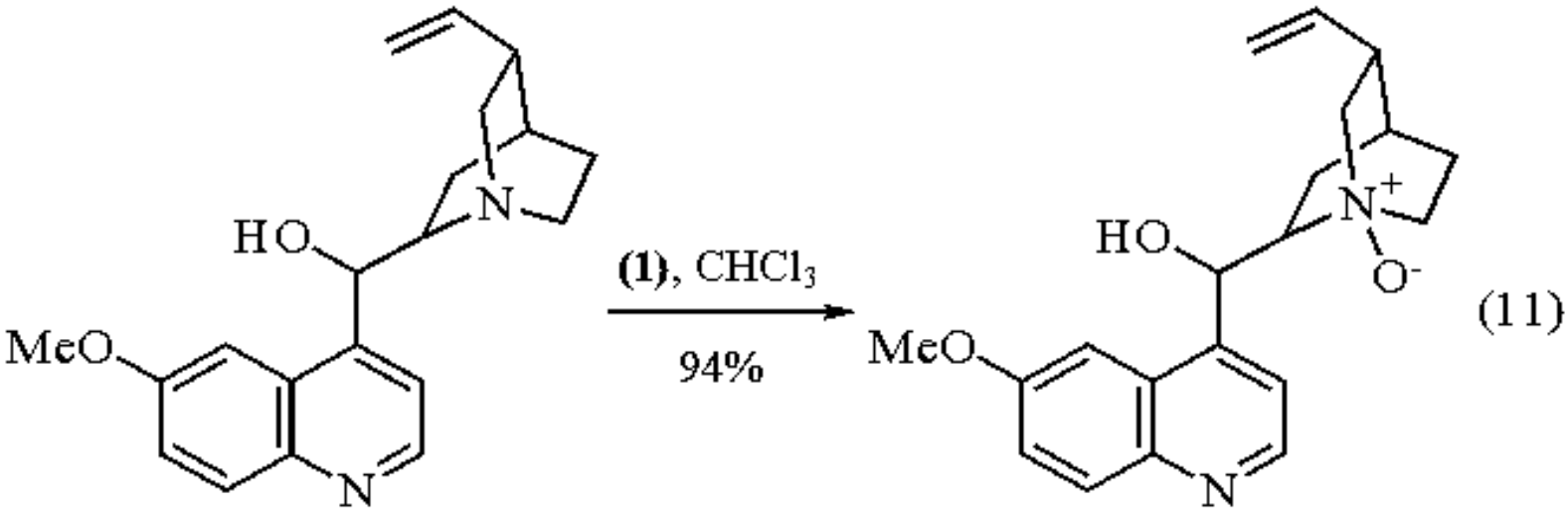

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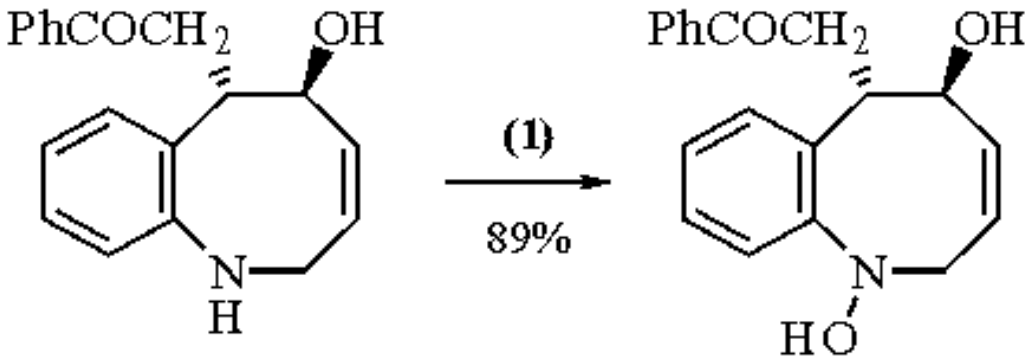

(12)

$$RNH_2 + \textbf{(1)} \longrightarrow RN{=}O \qquad (13)$$

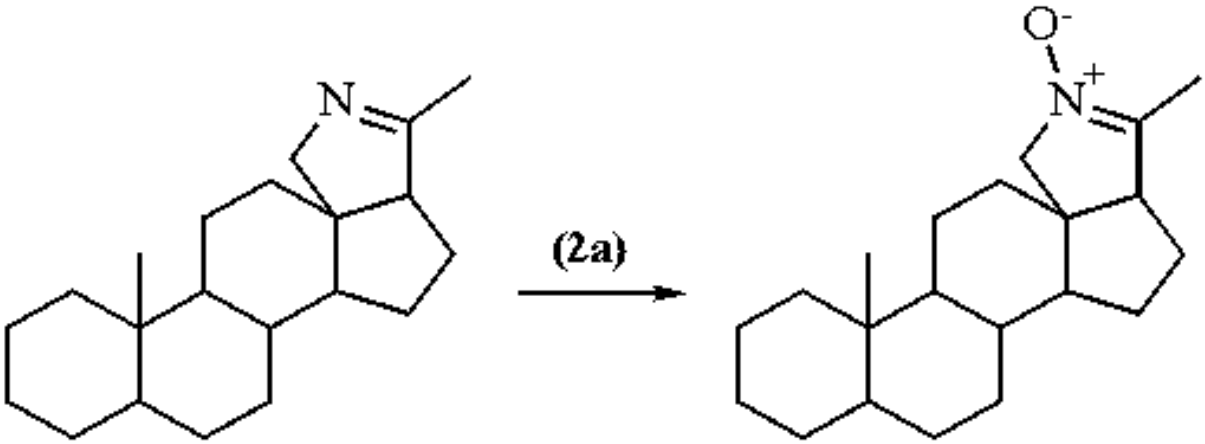

(14)

(+/-)-trans-2-(Phenylsulfonyl)-3-phenyloxaziridine

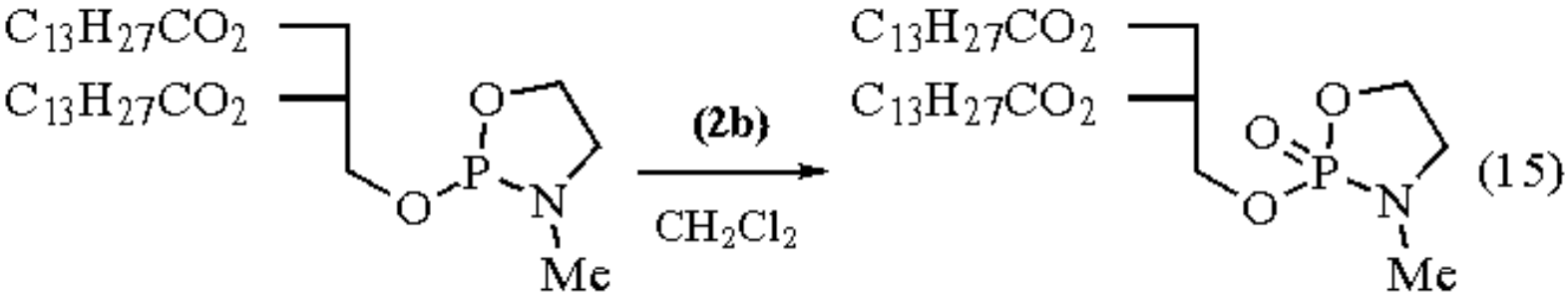

Oxidation of Carbon-Carbon Double Bonds and Aromatic Hydrocarbons.

Like peroxy acids, *N*-sulfonyloxaziridines epoxidize alkenes in a *syn* stereospecific manner, but the epoxidation is slower requiring higher temperature (e.g. 60 °C) for satisfactory yields.[1a,24] For this reason, the more thermally stable *p*-nitrophenyl oxaziridine (**2a**) is recommended. The neutral and aprotic *N*-sulfonyloxaziridine oxidizing reagents can be used to prepare acid-sensitive epoxides. For example, epoxidation of indene with (**2a**) gave the acid-sensitive indene oxide in 63% yield (eq 16).[24] Usually, electron-deficient alkenes are not epoxidized by *N*-sulfonyloxaziridines; however, isoxazoline (**8**) gave epoxides (**9**) and (**10**) in 36% yield on heating with (**2a**) (eq 17).[25] In general, more nucleophilic substrates such as sulfides, amines, selenides, etc., can be oxidized in the presence of C=C double bonds (e.g. eq 2). Alkynes, on the other hand, are not oxidized by *N*-sulfonyloxaziridines such as (**2**).

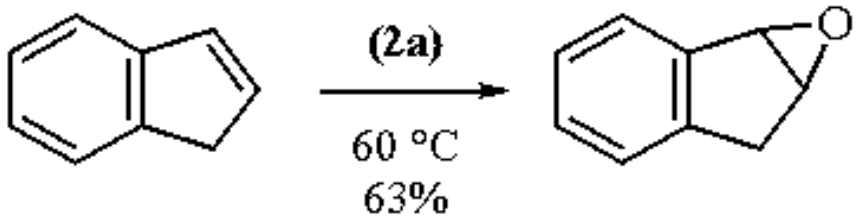

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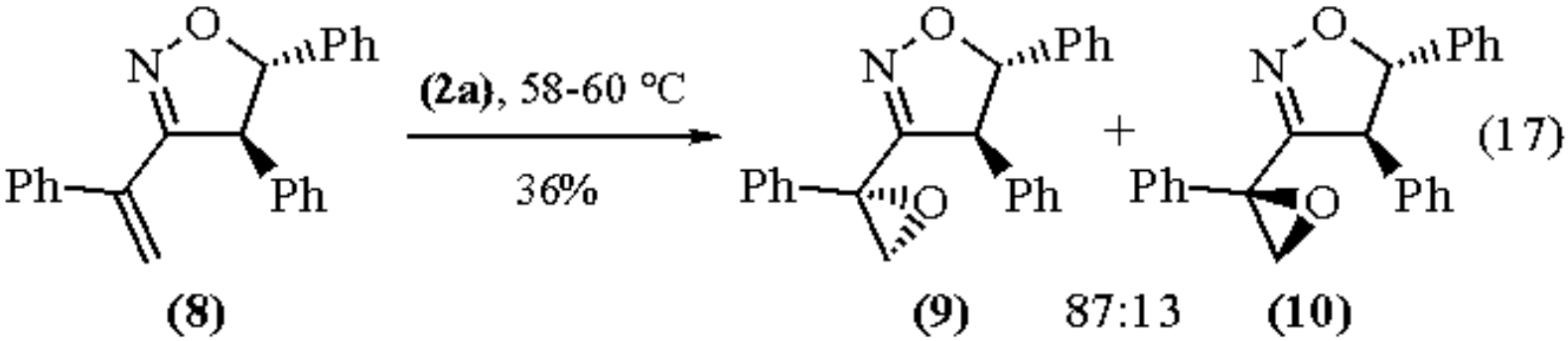

(17)

Oxidation of silyl enol ethers followed by acid hydrolysis gives α-hydroxy carbonyl compounds.[1a,26] The aprotic nature of *N*-sulfonyloxaziridines makes possible the isolation of the α-siloxy epoxide intermediate in high yield (eq 18).[26] α-Hydroxy ketones of high enantiomeric purity (&egt;98% ee) can be prepared via the oxidation of chiral silyl enol ethers (eq 19).[27]

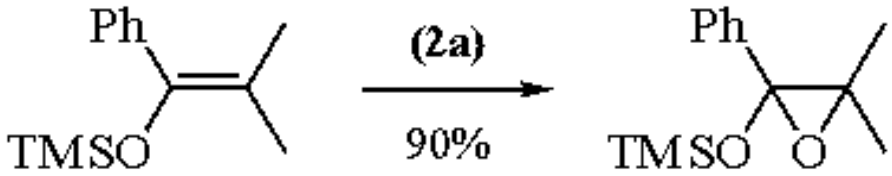

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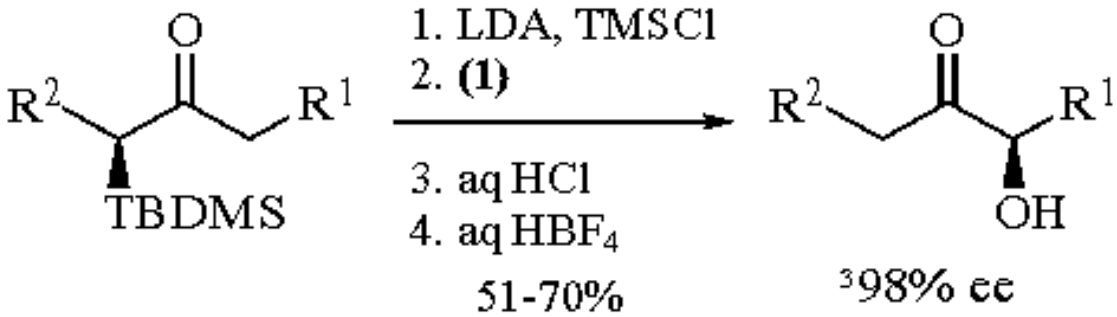

(19)

Disubstituted enamines are rapidly oxidized to α-amino ketones, while tertiary enamines give, after hydrolysis, α-hydroxy ketones (eq 20).[1a,28] Oxidation of bicyclic enamines with (**1**) followed by reduction of the iminium ion with ***Sodium Borohydride*** affords the β-amino alcohol (eq 21).[29] Reaction of diene carboxylic acid with oxaziridine (**1**) is reported to give a diastereomeric mixture of hydroxy lactones (eq 22).[30] Heating anisole with *N*-sulfonyloxaziridine (**2a**) gives a mixture of 2- and 4-methoxyphenols.[31]

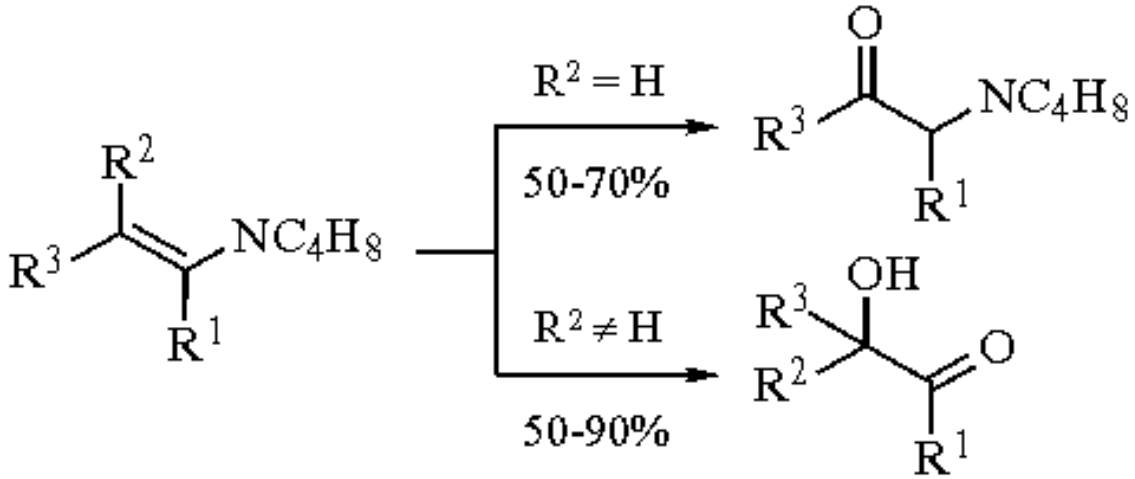

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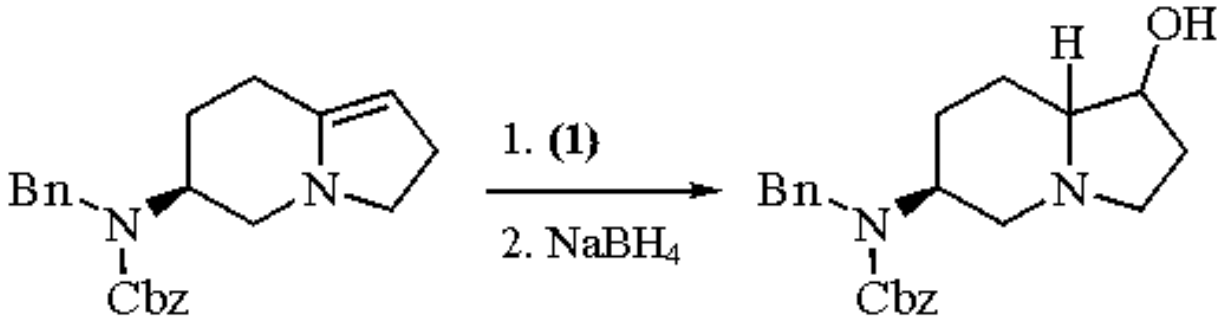

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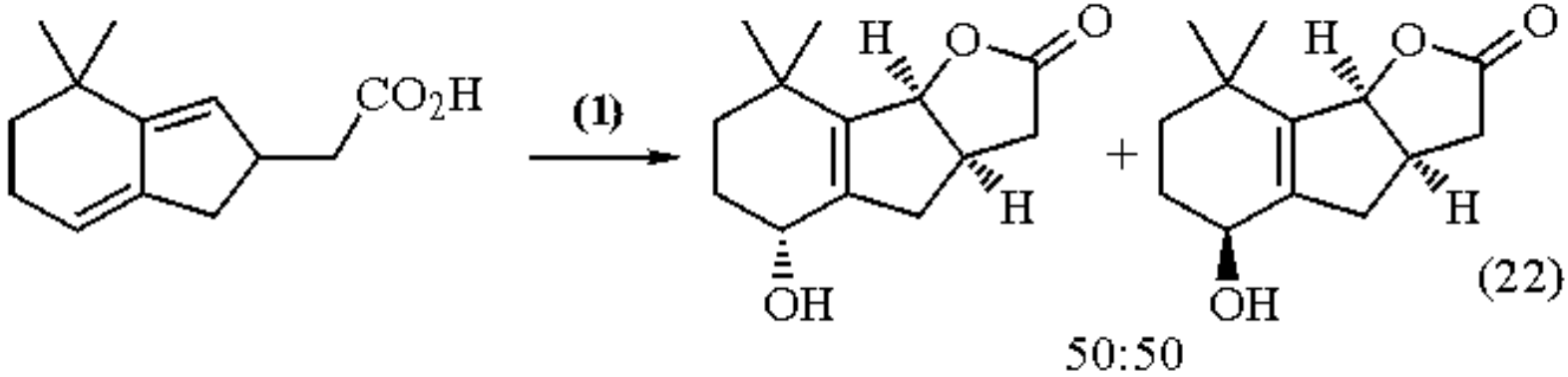

Oxidation of Carbanions and Organometallic Compounds.

Lithium and Grignard (RM) reagents react instantaneously with *N*-sulfonyloxaziridines to give alcohols and phenols (eq 23).[1a,32] Yields are comparable to those obtained using alternative oxidants such as O_2, *t*-BuOOLi, ***Bis(trimethylsilyl) Peroxide***, and ***Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)*** (MoOPH). The oxaziridine reagent is particularly recommended for substrates having certain sensitive functionality. Bishydroxylation is also possible with (**1**) (eq 24).[33] Oxidation of phosphorus ylides (Wittig reagents) with (**1**) gives *trans*-alkenes or ketones depending on the structure of the phosphoranes (eq 25).[34] Bis-ylides dimerize to cycloalkadienes.[34] Reaction of dimethyloxosulfoniummethylide with (**1**) results in the formation of azetidines (eq 26).[35] Unsymmetrical α-diketones are prepared in good yield by oxidation of the carbanions derived from α-sulfonyl ketones with oxaziridine (**2c**) (eq 27).[36]

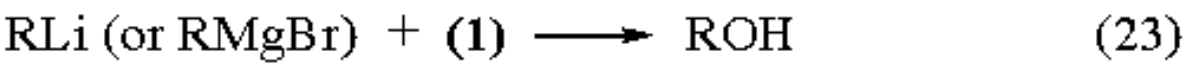

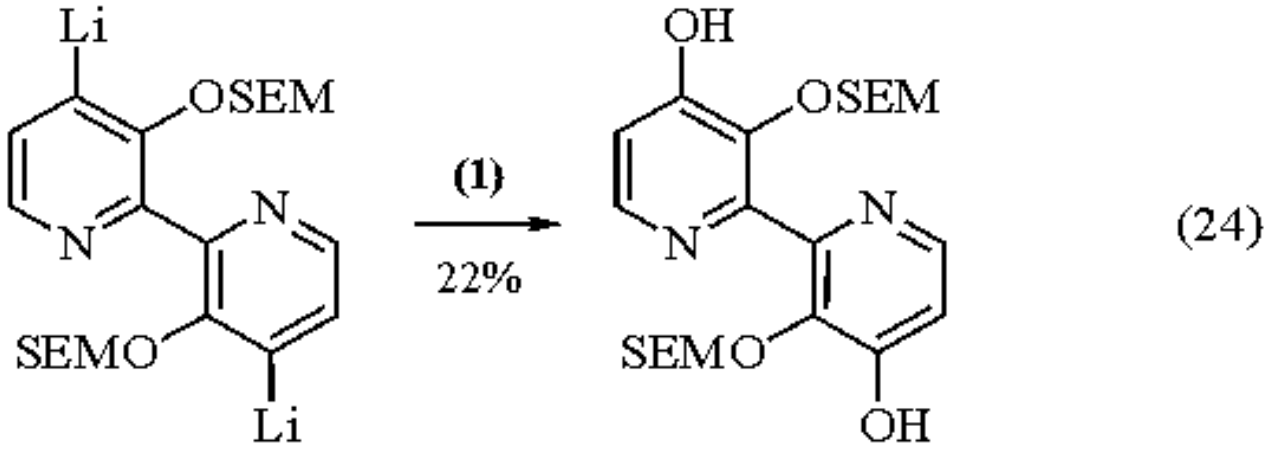

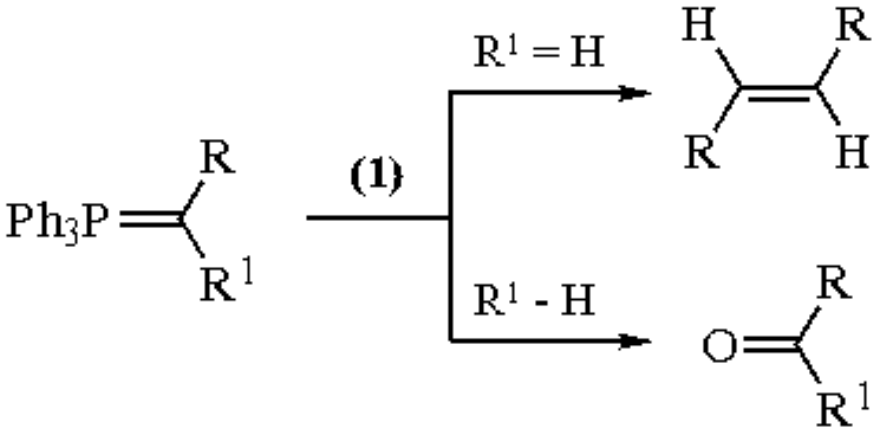

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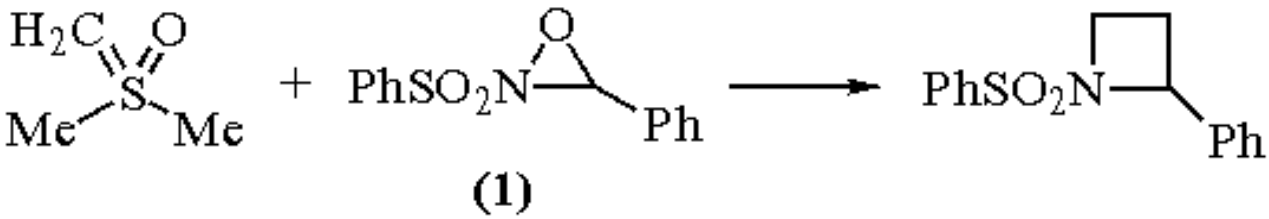

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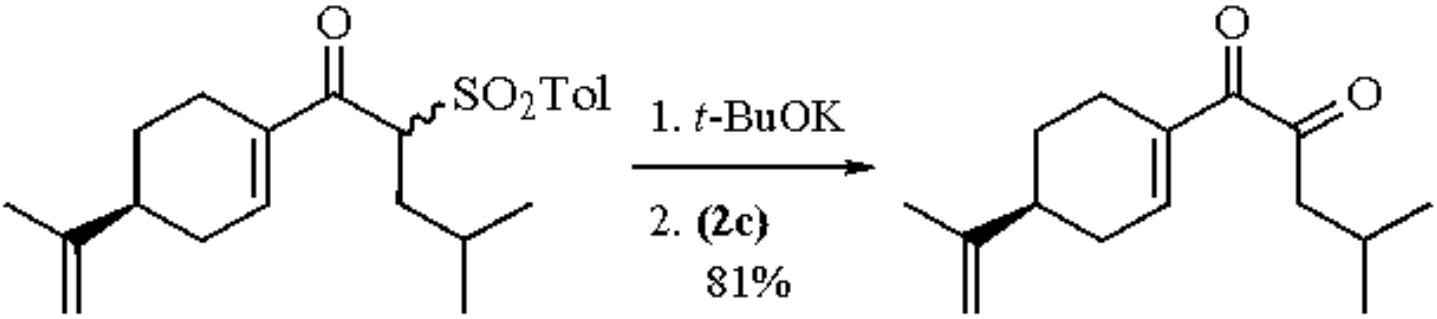

(27)

2-(Arylsulfonyl)-3-aryloxaziridines oxidize a variety of metal enolates to the corresponding α-hydroxy carbonyl compounds (eq 28).[1,37,38] Unlike MoOPH and molecular oxygen, over-oxidation is not a problem with these reagents.[1,39] With chiral enolates, the oxidation takes place from the least hindered face of the enolate.[1,40] α-Hydroxy ketones, aldehydes, and carboxylic acid derivatives of high enantiomeric purity are available using chiral auxiliaries (eqs 29 and 30).[1,41,42]

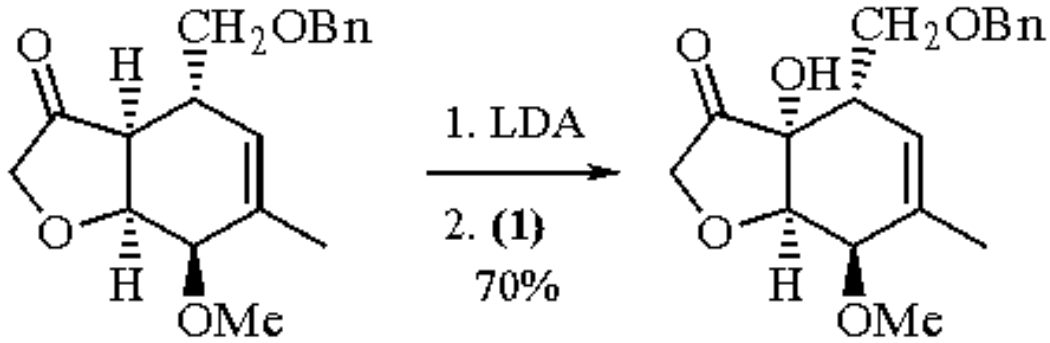

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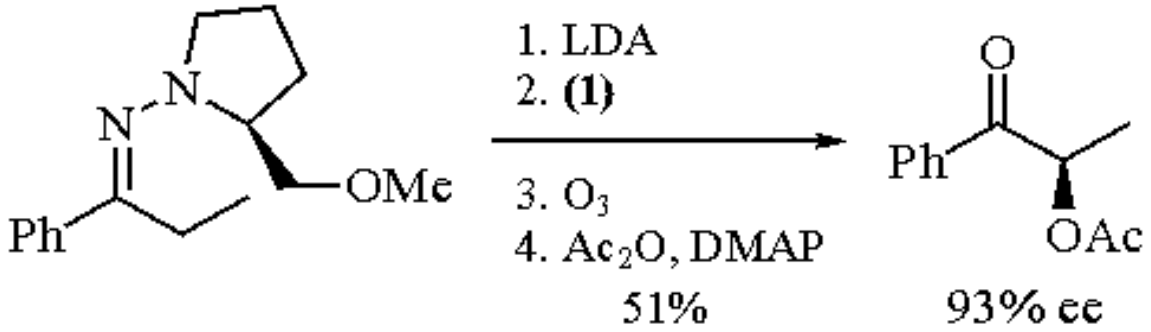

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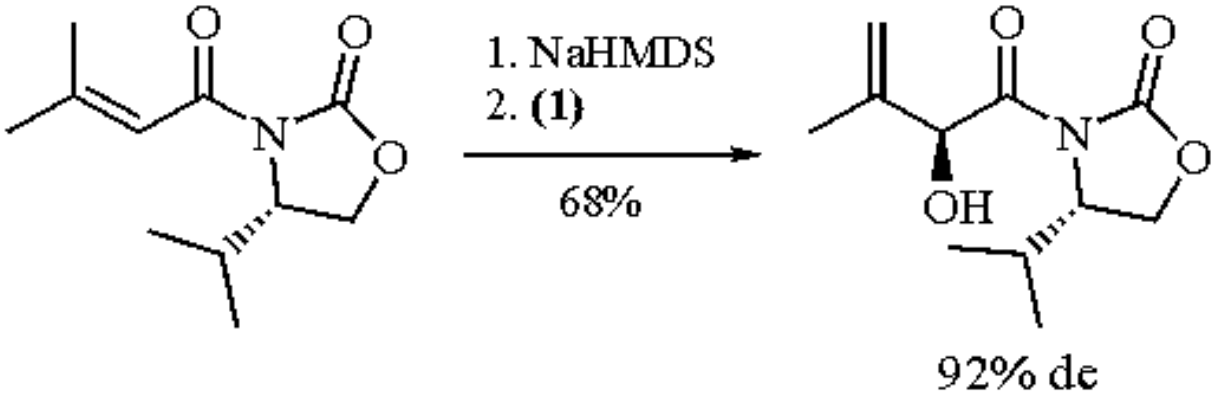

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3-(Phenylsulfonyl)propanal Ethylene Acetal

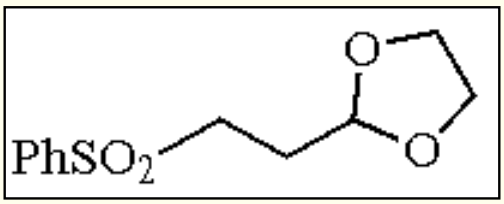

[56161-51-4] · $C_{11}H_{14}O_4S$ · 3-(Phenylsulfonyl)propanal Ethylene Acetal · (MW 242.32)

(synthetic reagent for 2-alkenals, 4-oxoalkanals, and 5-hydroxyalkanals)

Physical Data: mp 62-63 °C or 67-68 °C.[1,2]

Form Supplied in: colorless crystals.

Preparative Methods: by oxidation of 3-(phenylthio)propanal ethylene glycol[1] or by reaction of ***Sodium Benzenesulfinate*** with 3-bromopropanal ethylene acetal.[2]

Synthesis of Alkanals.

Monoalkylation of 3-(phenylsulfonyl)propanal ethylene acetal (**1**) takes place at the position α to the phenylsulfonyl group on successive treatment with ***n-Butyllithium*** and then with an alkyl halide. Deprotection of the acetal group and subsequent elimination of benzenesulfinic acid with a base produces the corresponding 2-alkenal (eq 1).[1]

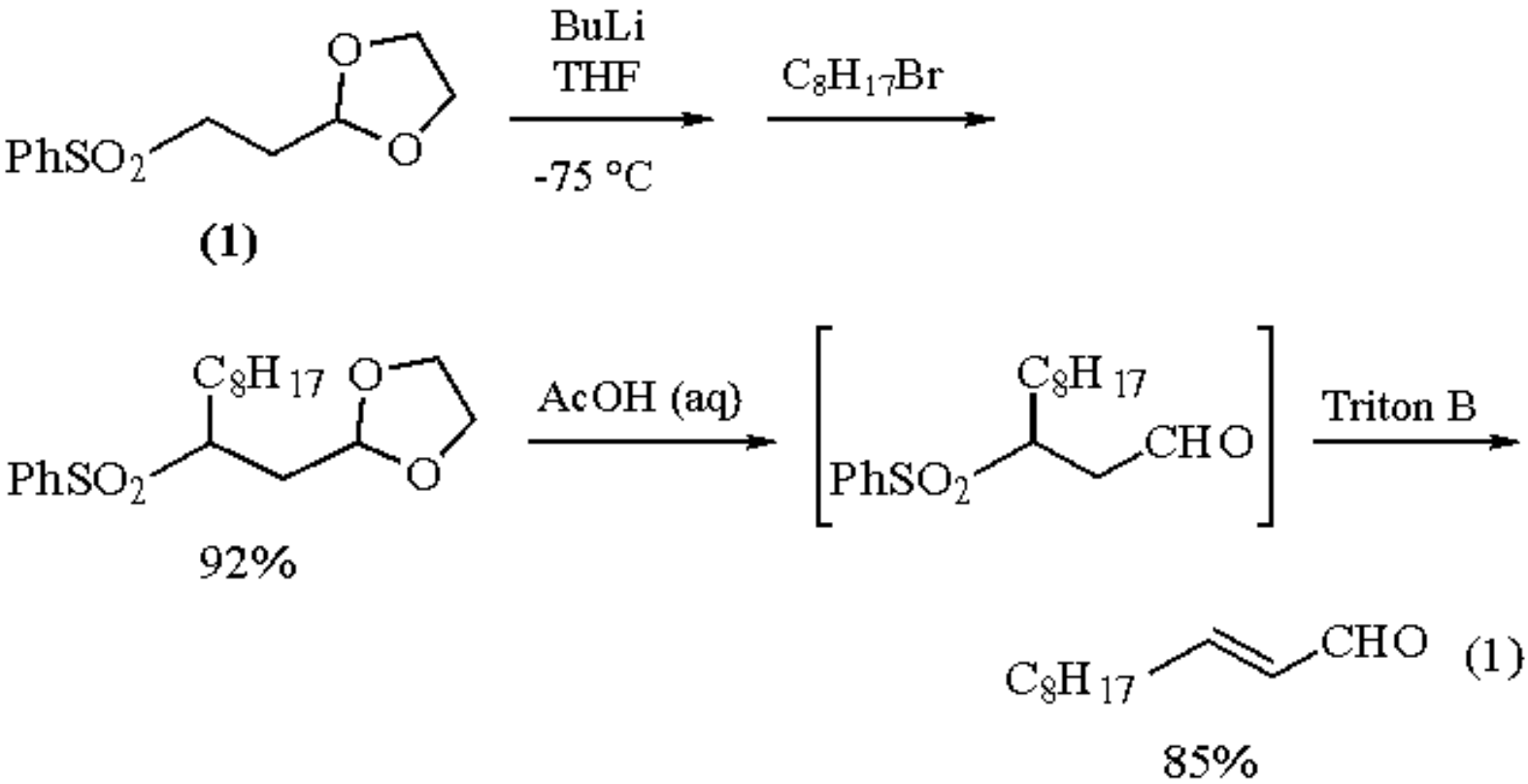

A second alkylation is also possible by treatment with alkyl iodide and *n*-BuLi. Acidic deprotection of the dialkylated product gives the corresponding 2-alkenal (eq 2).[1]

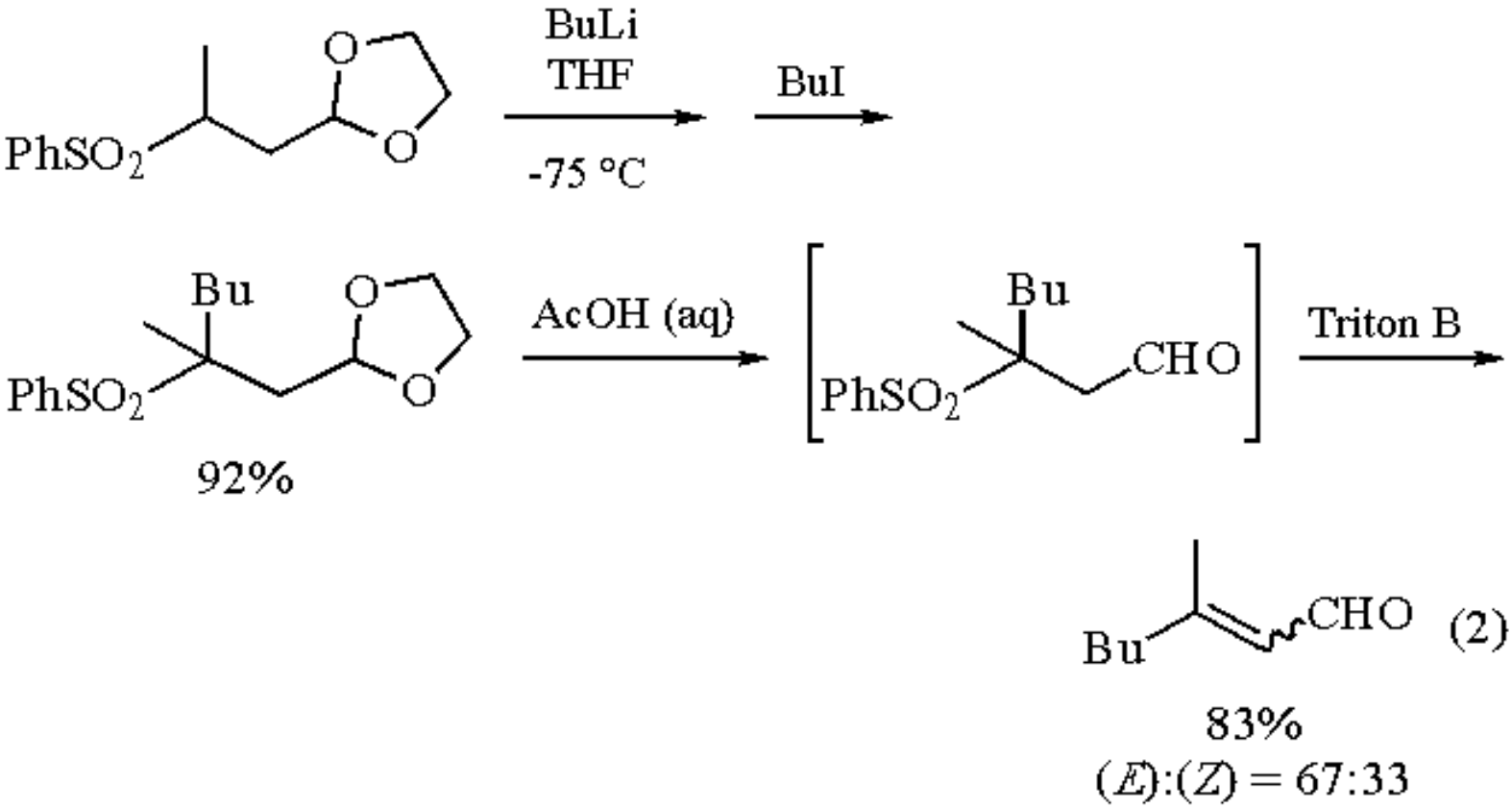

4-Oxoalkanal Synthesis.

The lithio derivative of (**1**) can be acylated with a methyl ester to afford an acylated product which easily undergoes reductive desulfurization with ***Aluminum Amalgam*** or ***Sodium Amalgam*** to produce a 4-oxoalkanal ethylene acetal, an important synthetic precursor (eq 3).[3,4]

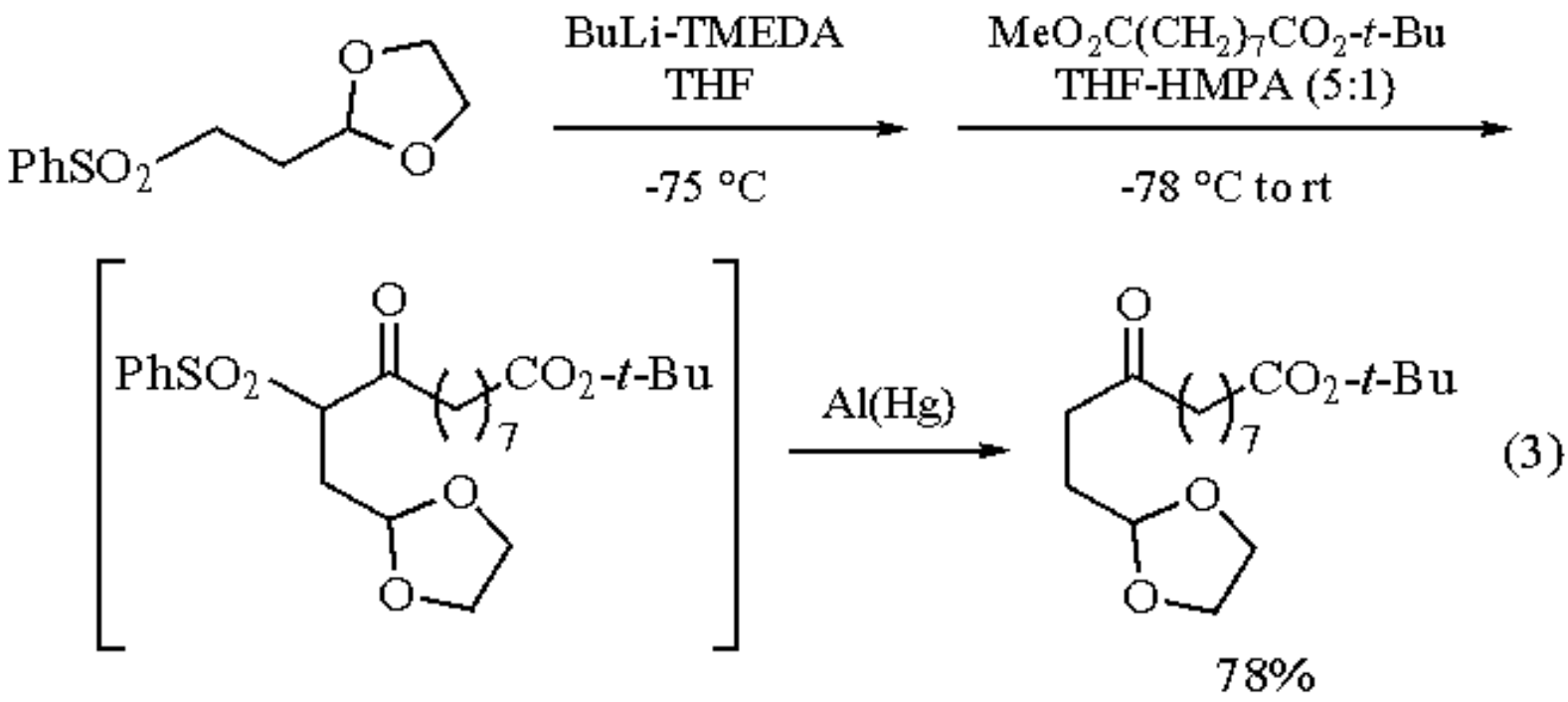

(3)

Synthesis of 5-Hydroxyalkanals.

The lithio derivative of (**1**) reacts with terminal epoxides to give ring-opened products. Reductive desulfurization followed by acidic deprotection forms 5-hydroxyalkanal, which cyclizes to give a δ-lactol (eq 4).[5]

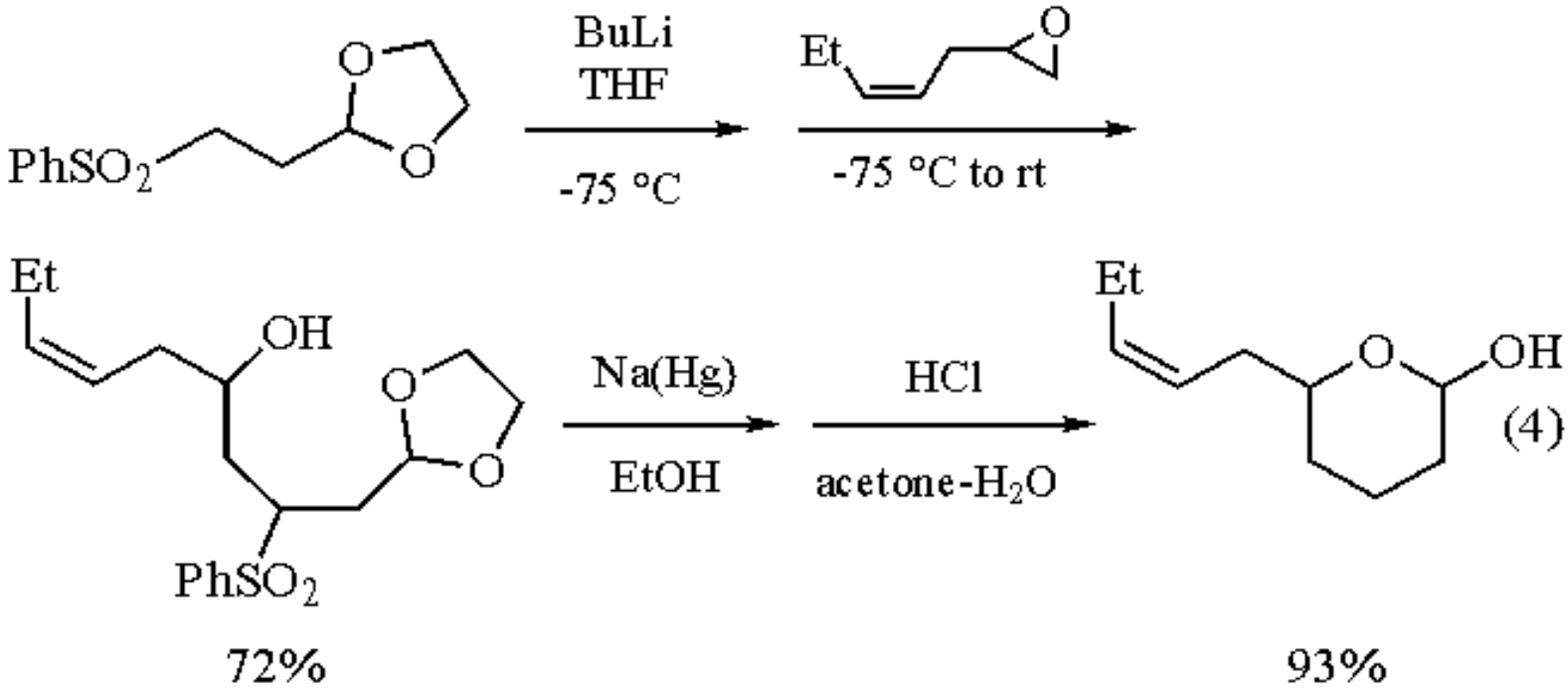

(4)

Multiple Bond Formation.

Lithiated (**1**) adds to aldehydes. After acetylation, treatment of the adduct with ***Potassium t-Butoxide*** causes elimination of benzenesulfinic acid and acetic acid to form an acetal having a triple bond or a conjugated double bond, depending on circumstances (eqs 5 and 6).[6,7]

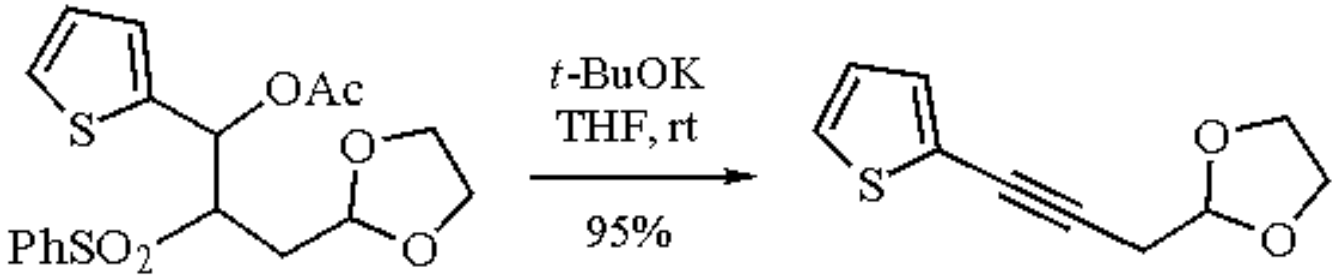

(5)

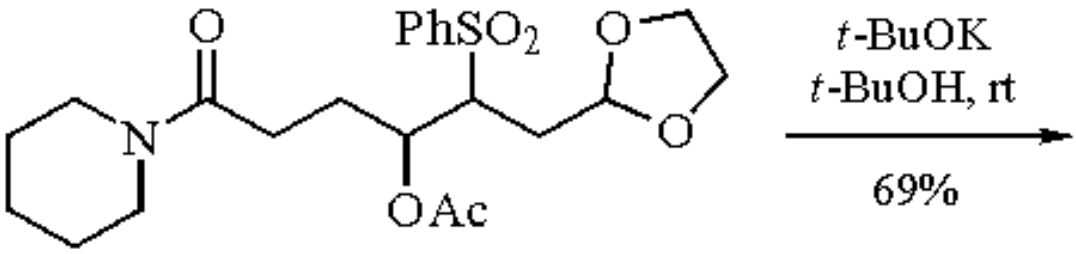

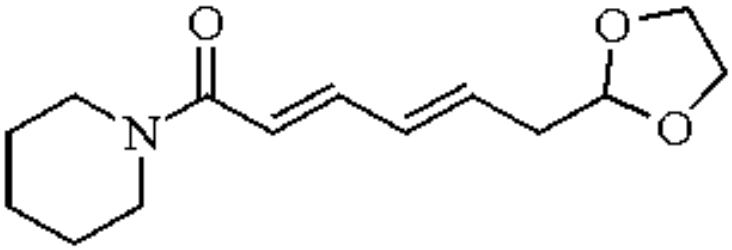

(6)

Related Reagents.

4-Phenylsulfonyl-2-butanone Ethylene Acetal.

---

1. Kondo, K.; Tunemoto, D. *TL* **1975**, 1007.
2. Gaoni, Y.; Tomazic, A.; Potgieter, E. *JOC* **1985**, *50*, 2943.
3. Kondo, K.; Tunemoto, D. *TL* **1975**, 1397.
4. Menicagli, R.; Wis, M. L.; Lardicci, L.; Botteghi, C.; Caccia, G. *JCS(P1)* **1979**, 847.
5. Kondo, K.; Saito, E.; Tunemoto, D. *TL* **1975**, 2275.
6. Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *JACS* **1984**, *106*, 3670.
7. Mandai, T.; Moriyama, T.; Tsujimoto, K.; Kawada, M.; Otera, J. *TL* **1986**, *27*, 603.

Katsuyuki Ogura

1-Phenylsulfonyl-1*H*-tetrazole

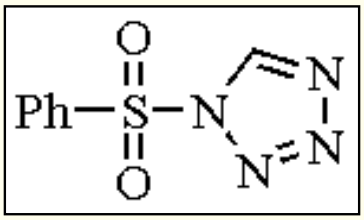

[59128-90-4] · $C_7H_6N_4O_2S$ · 1-Phenylsulfonyl-1*H*-tetrazole · (MW 210.24)

(coupling reagent for oligonucleotide solution synthesis using the phosphotriester method[1-4])

Physical Data: mp 86-92 °C.

Solubility: insol H_2O; sol pyridine, CH_2Cl_2; reacts slowly with H_2O and protic solvents.

Form Supplied in: white crystals; not available from commercial sources.

Analysis of Reagent Purity: prior to use, the purity should be determined by mp.

Preparative Method: by reaction of ***Benzenesulfonyl Chloride*** (1 equiv) and tetrazole (1 equiv) in the presence of ***Triethylamine*** (1 equiv) in dioxane at 5 °C for 2 h. A crystalline product was obtained after dissolving the crude material in benzene, shaking with silica gel, filtering, and evaporating in vacuo to dryness.

Handling, Storage, and Precautions: the dry solid should be stored in a desiccator with drierite at 4 °C. The material decomposes completely after 20 days at 25 °C, and it should be used immediately following preparation. **Cation**: Avoid contact with metals and metal salts, since tetrazole may form explosive metal salts. Contact with strong oxidizers or strong heat may cause fire or explosion.

1-Phenylsulfonyl-1*H*-tetrazole (**1**) has been used as a condensing reagent in deoxyoligonucleotide solution synthesis by the phosphotriester method.[1-3] It activates 5´-dimethoxytrityl (DMT) deoxynucleoside 3´-(*p*-chorophenyl) phosphates in anhydrous pyridine, allowing the coupling reaction with 5´-hydroxy nucleoside in 30 min at 25 °C, yielding the corresponding *p*-chlorophenyl phosphate dimer in 74% yield. This reaction has been extended for the preparation of oligodeoxynucleotides containing up to 12 bases with coupling times in the range of 30-120 min at 25 °C (eq 1). Couplings mediated by (**1**) occur more rapidly than with the corresponding 2,4,6-trimethyl and 2,4,6-triisopropyl analogs and no sulfonation at the 5´-hydroxy group has been observed.[1,3]

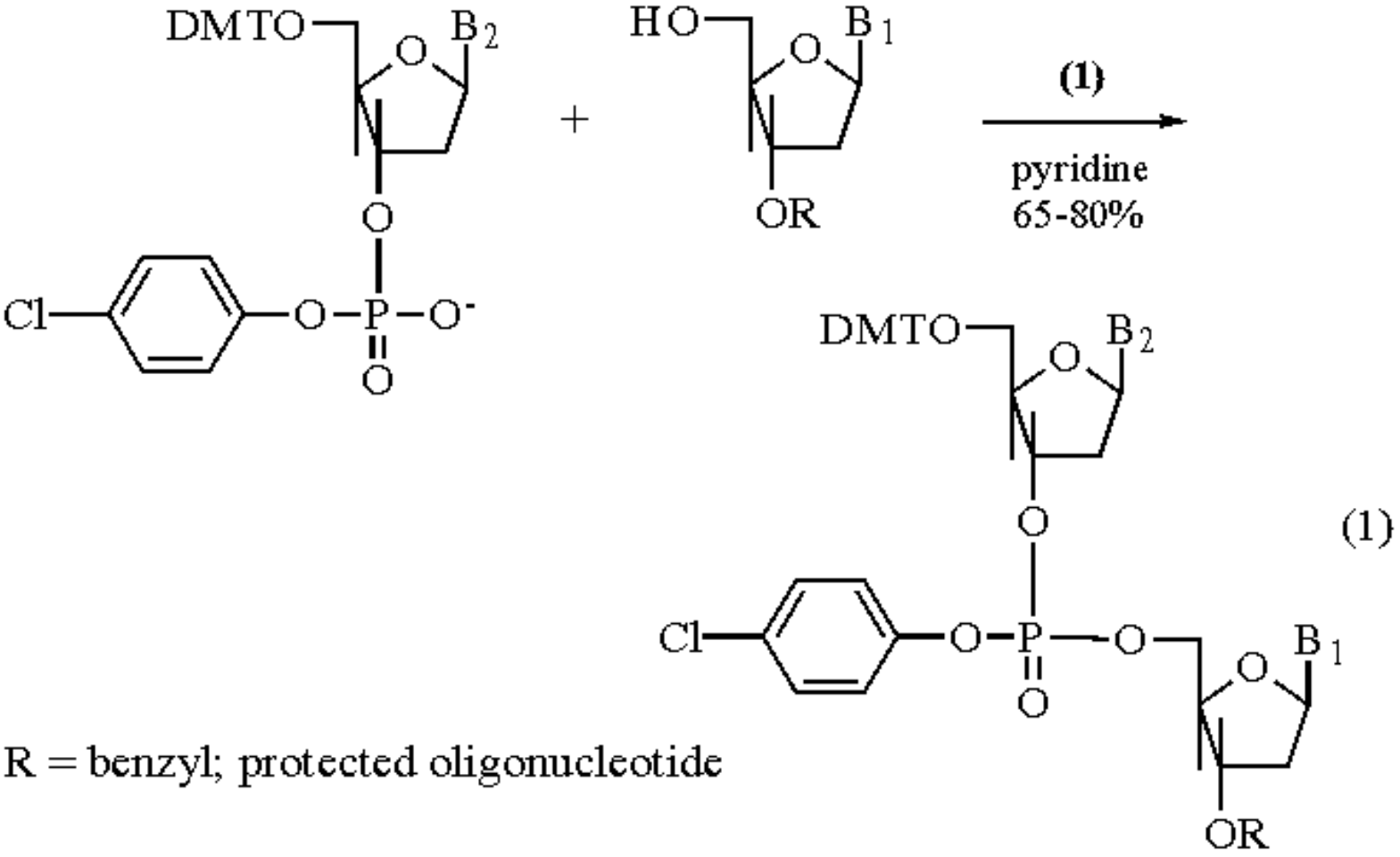

Furthermore, (**1**) has been used in anhydrous pyridine for 24 h at 25 °C for the preparation of a ribonucleotide dimer in 60% yield (eq 2).

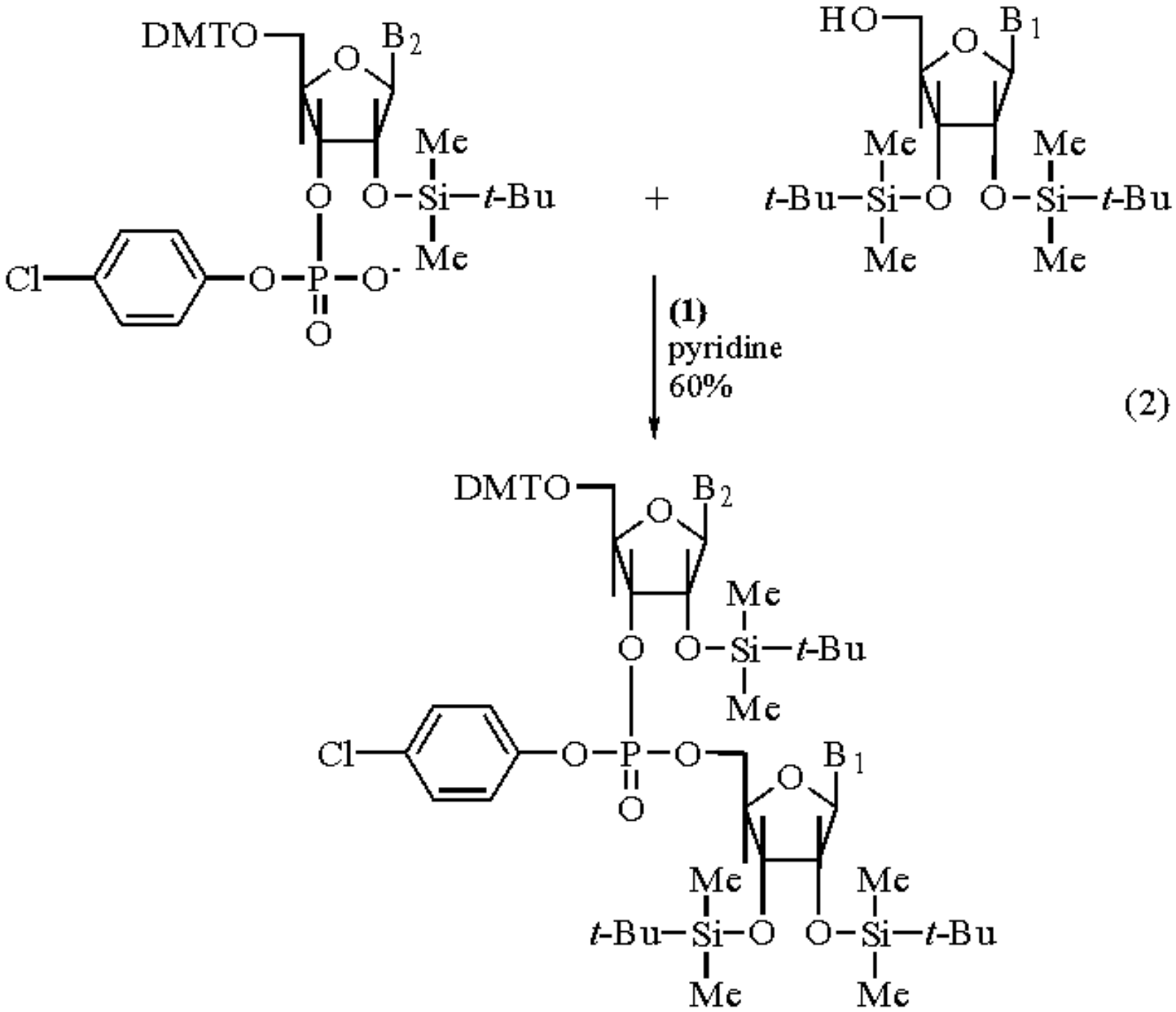

Although (**1**) has not been used in solid-phase oligonucleotide synthesis, another more stable arylsulfonyl derivative, 1-(mesitylsulfonyl)-3-nitro-1,2,4-triazole (MSNT),[5,6] is commonly used in that strategy by the phosphotriester approach.[7]

---

1. Stawinski, J.; Hozumi, T.; Narang, S. A. *CJC* **1976**, *54*, 670.
2. Stawinski, J.; Hozumi, T.; Narang, S. A.; Bahl, C. P.; Wu, R. *Nucleic Acids Res.* **1977**, *4*, 353.
3. Narang, S. A.; Stawinski, J. U.S. Patent 4 059 592 1977 (*CA* **1978**, *88*, 191 349v).
4. Ogilvie, K. K.; Pon, R. T. *Nucleic Acids Res.* **1980**, *8*, 2105.
5. Reese, C. B.; Abasawa, A. *TL* **1980**, *21*, 2265.
6. Tan, Z. K.; Ikuta, S.; Huang, T.; Dugaiczyk, A.; Itakura, K. *Cold Spring Harbor Symp. Quant. Biol.* **1982**, *47*, 383 (*CA* **1983**, *99*, 22 773a).

7. Itakura, K.; Rossi, J. J.; Wallace, R. B. *Annu. Rev. Biochem.* **1984**, *53*, 323.

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1-Phenylsulfonyl-2-(trimethylsilyl)acetylene[1]

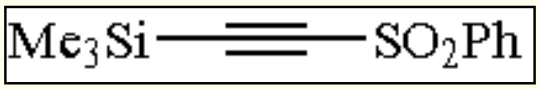

[32501-93-2] · $C_{11}H_{14}O_2SSi$ · 1-Phenylsulfonyl-2-(trimethylsilyl)acetylene · (MW 238.41)

(reagent for preparation of α-vinyl carbonyls, and for use in cycloadditions and preparation of *cis*- and *trans*-vinyl sulfones)

Physical Data: mp 68-70 °C.

Solubility: sol most organic solvents.

Form Supplied in: colorless hygroscopic crystals.

Handling, Storage, and Precautions: very sensitive to alkaline or acidic conditions.

Addition Reactions.

Enolates of 1,3-dicarbonyl compounds add smoothly to the title reagent (**1**) to provide mainly the *cis*-vinyl sulfones (**2**). These are reduced by treatment with ***Aluminum Amalgam*** to give vinyl ketones (**3**) (eq 1).[2] Similarly, addition of organocuprates leads to the *cis*-vinyl sulfones (**4**) (eq 2).[1]

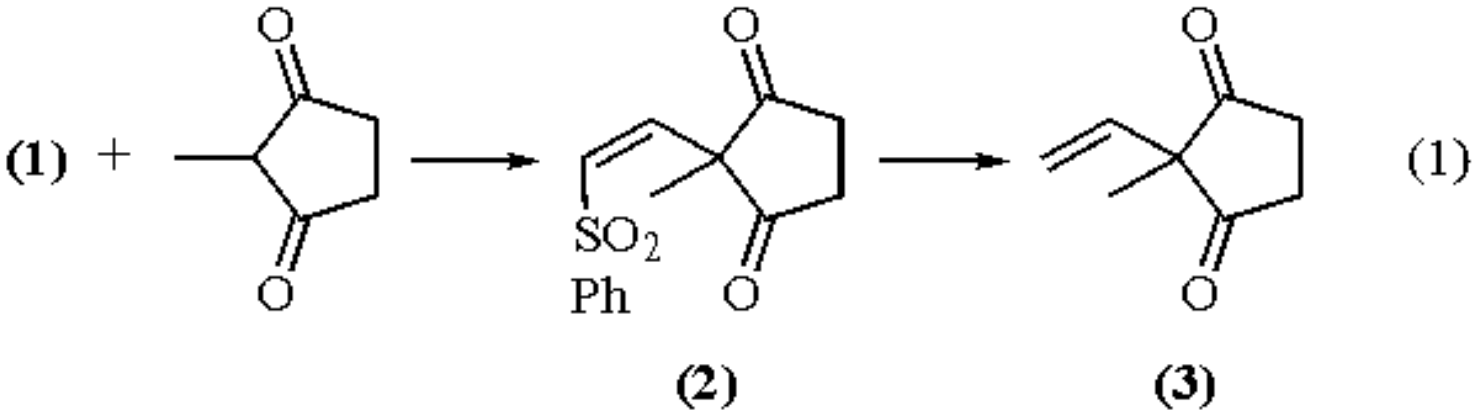

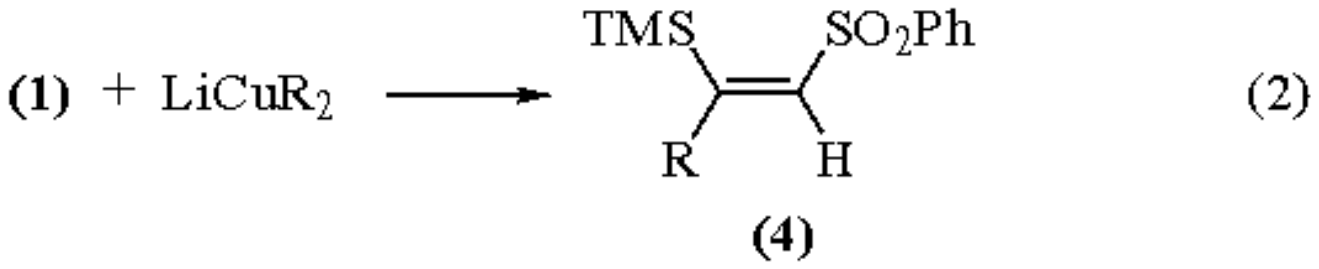

Reduction of (**1**) with hydrogen and palladium in pyridine gives the *cis*-vinyl sulfone, while in the absence of pyridine the *trans* isomer is obtained.[3] These products may also be obtained by reduction with ***Diisobutylaluminum Hydride***, giving the *trans* isomer, or treatment with ***Bis(1,5-cyclooctadiene)nickel(0)*** to produce the *cis* isomer.[1] These vinyl sulfones have been used as acetylene equivalents in a variety of organometallic addition reactions, as well as in cycloaddition reactions.[1,3,4]

Cycloaddition Reactions.

Cycloaddition of (**1**) with ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene*** (Danishefsky's diene) (**5**) has been reported to yield the phenol (**6**) (eq 3), which may be further elaborated to a variety of products.[5] (**1**) has also been used in reactions with azide (**7**) to produce the triazole (**8**) (eq 4).[6]

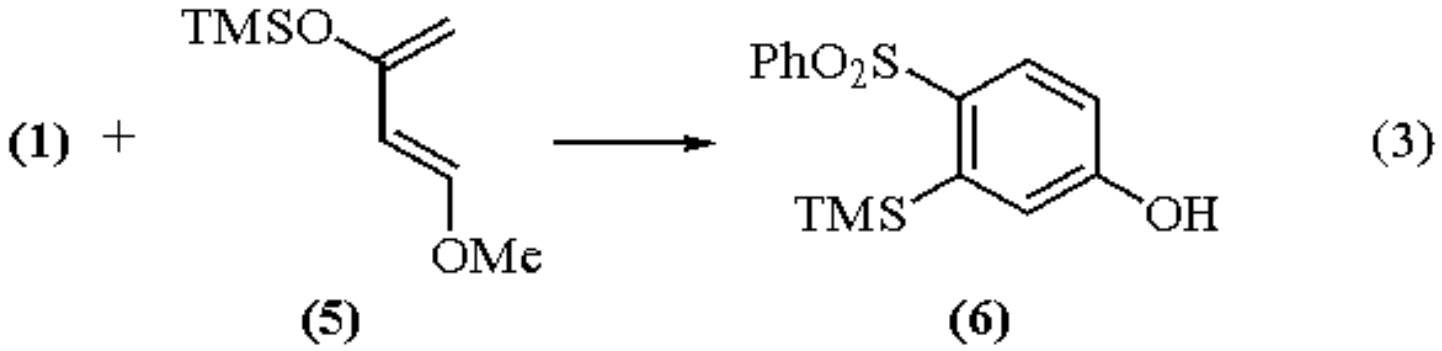

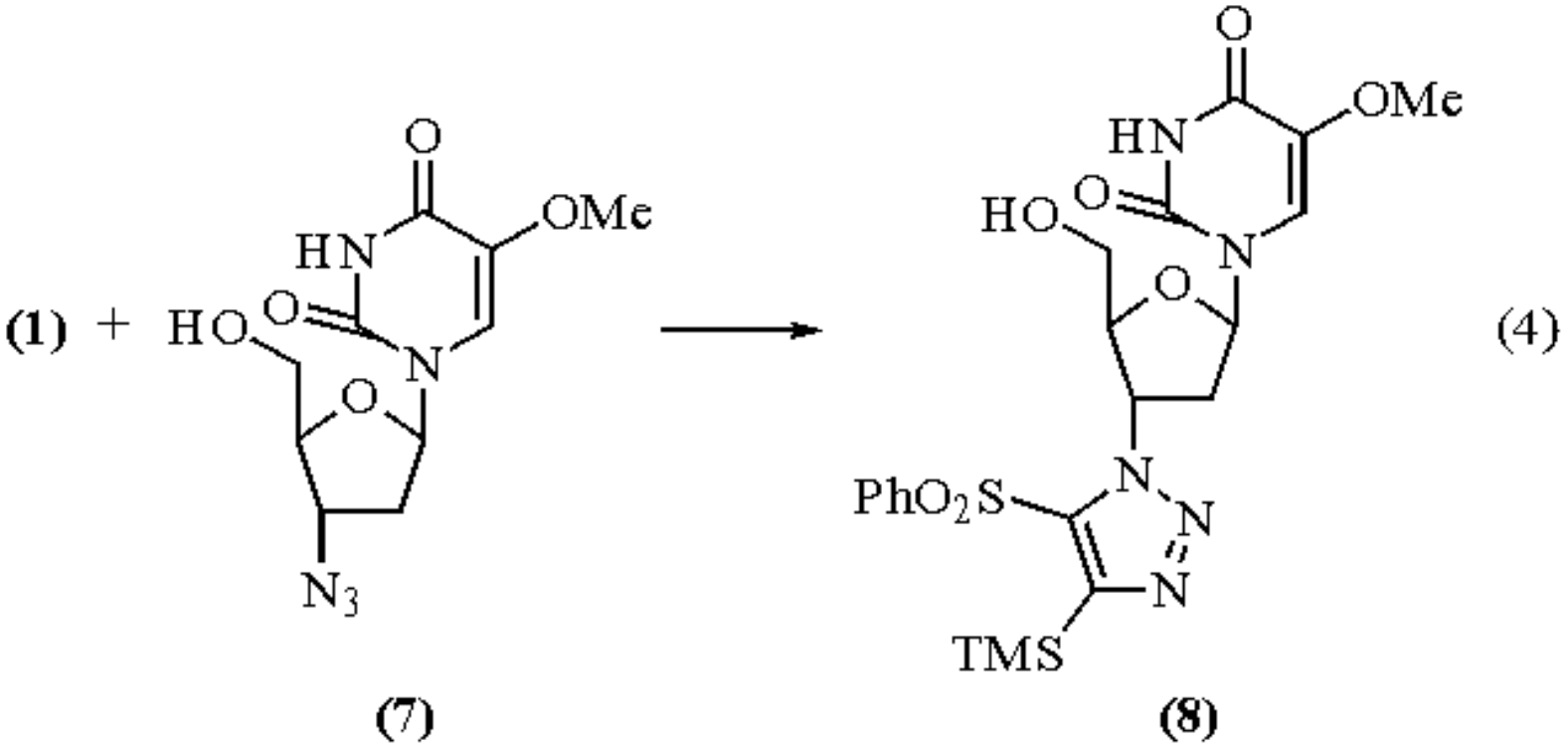

Related Reagents.

***Ethyl* β*-Phenylsulfonylpropiolate*; *Ethynyl p-Tolyl Sulfone*.**

---

1. Eisch, J. J.; Behrooz, M.; Dua, S. K. *JOM* **1985**, *285*, 121.
2. (a) Ohnuma, T.; Hata, N.; Fujiwara, H.; Ban, Y. *JOC* **1982**, *47*, 4713. (b) Ohnuma, T.; Hata, N.; Miyachi, N.; Wakamatsu, T.; Ban, Y. *TL* **1986**, *27*, 219. (c) Sawada, S.; Nakayama, T.; Esaki, N.; Tanaka, H.; Soda, K.; Hill, R. K. *JOC* **1986**, *51*, 3384.
3. Paquette, L. A.; Williams, R. V. *TL* **1981**, *22*, 4643.
4. Carr, R. V.; Williams, R. V.; Paquette, L. A. *JOC* **1983**, *48*, 4976.
5. Kloek, J. A. *JOC* **1981**, *46*, 1951.
6. Habich, D.; Barth, W. *H* **1989**, *29*, 2083.

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The Upjohn Company, Kalamazoo, MI, USA

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(*E*)-1-Phenylsulfonyl-2-trimethylsilylethylene[1]

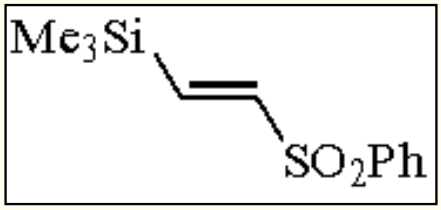

[64489-06-1] · $C_{11}H_{16}O_2SSi$ · (*E*)-1-Phenylsulfonyl-2-trimethylsilylethylene · (MW 240.43)

(dienophile equivalent to a variety of alkynes in Diels-Alder cycloadditions;[2] used to prepare α-substituted allylsilanes[3])

Physical Data: mp 59-60 °C (petroleum ether).[4]

Solubility: sol common organic solvents.

Form Supplied in: colorless solid; not commercially available.

Preparative Methods: prepared by hydrogenation of the corresponding readily available acetylene in 48% yield (this method is also amenable to the synthesis of the deutero derivative)[2] or by phenylsulfonyl chloride addition to trimethylsilylethylene (78%) followed by ***Triethylamine***-mediated dehydrochlorination (97%);[2] selenosulfonation, followed by ***Hydrogen Peroxide*** oxidation, can also be used (84%);[5] an alternative method of preparation involves dehydrochlorination of 1-phenylsulfonyl-1-chloro-2-trimethylsilylethane ($PhSO_2CHClCH_2SiMe_3$) with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (quantitative);[4] can also be prepared by treating the lithium salt of the anion of methylthiomethyl phenyl sulfone ($PhSO_2CH_2SMe$) with ***(Iodomethyl)trimethylsilane*** to give $PhSO_2CH(SMe)CH_2SiMe_3$, followed by oxidation to the sulfoxide and elimination of methanesulfenic acid (60%).[3b]

Handling, Storage, and Precautions: potential alkylating agent; use in a fume hood.

Cycloadditions.

The dienophilic properties of (*E*)-phenylsulfonyl-2-trimethylsilylethylene allow the preparation of adducts with reactive dienes such as ***Cyclopentadiene*** and anthracene.[2] The adducts are smoothly converted to alkenes upon treatment with fluoride ion, establishing the equivalence of the title reagent to ***Acetylene***. Alkylation of the α-sulfonyl carbanion can precede the elimination such that synthetic equivalents to HC&tbond;CH, HC&tbond;CD, and RC&tbond;CH are available. The use of this reagent is highlighted by the synthesis of several functionalized dibenzobarrelenes (eq 1).[2] The

equivalency to DC&tbond;CD and RC&tbond;CD is illustrated by the preparation of deuterated derivatives.

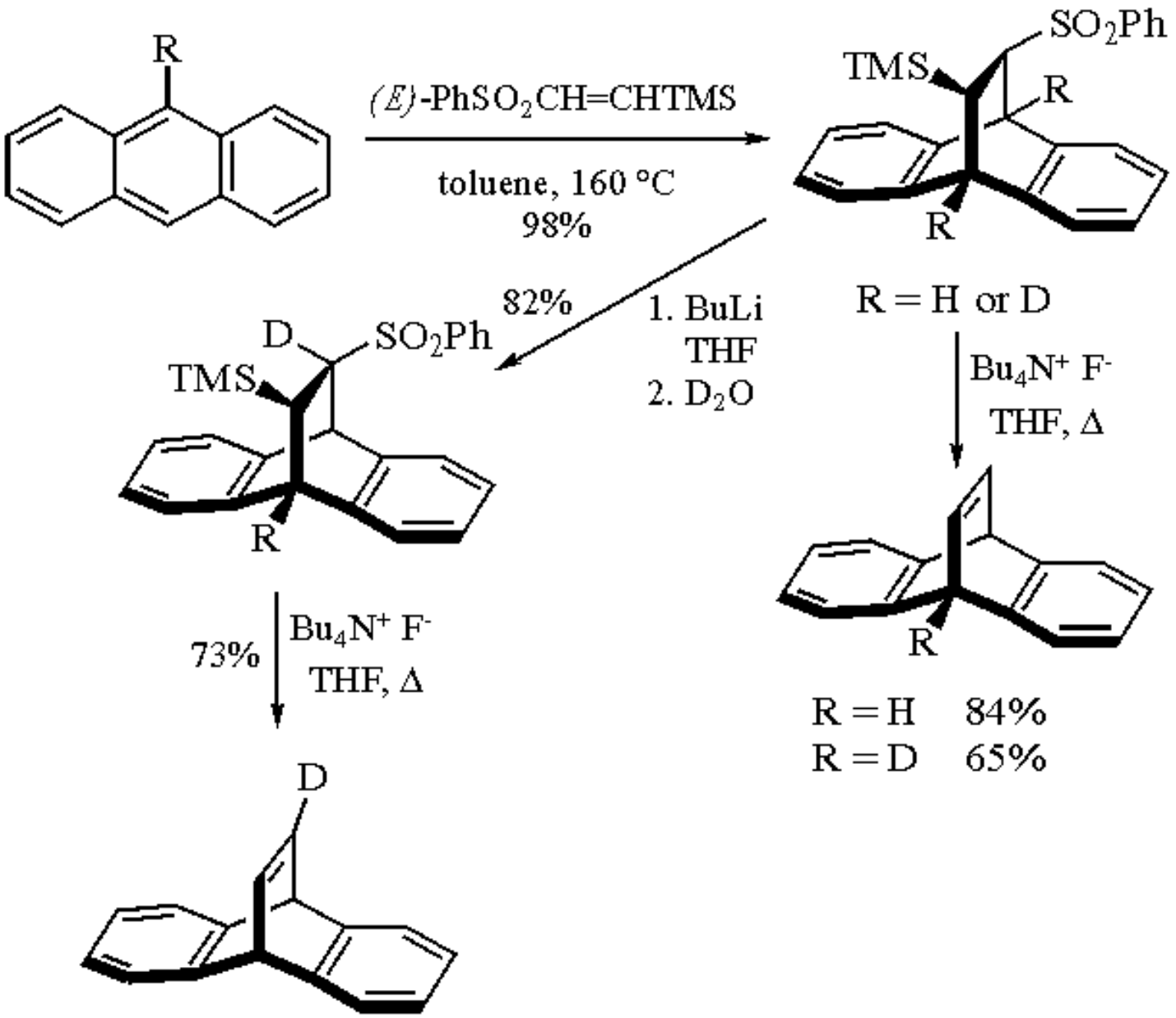

(1)

The somewhat low reactivity of (*E*)-phenylsulfonyl-2-trimethylsilylethylene in Diels-Alder reactions is probably due to steric hindrance exerted by both substituents and by the poor activation imparted by the silyl group. This drawback is partially offset by the effective elimination to the alkene performed under very mild conditions with fluoride ion. The low dienophilic reactivity of the title reagent is evident in the reaction with isodicyclopentadiene, for which it was demonstrated that only the isomer arising from the [1,5]-hydrogen sigmatropic shift was captured by dienophiles of low reactivity. Highly reactive dienophiles react with the symmetric structure, which is obviously a less reactive diene (eq 2).[6]

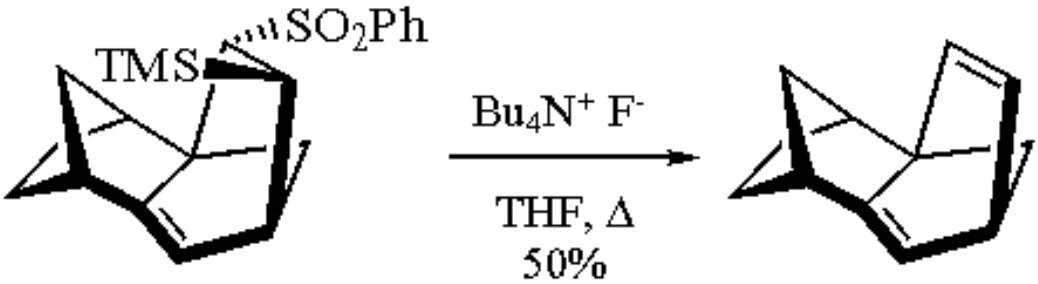

(2)

Addition Reactions.

The utility of (*E*)-phenylsulfonyl-2-trimethylsilylethylene in the synthesis of α-substituted allylsilanes[3] is exemplified in eq 3 for γ-hydroxyvinylsilanes,[3a] and in eq 4 in the preparation of isoprenoid structures.[3b] In these reactions the reagent functions as a Michael acceptor, but α-lithiation may compete with less nucleophilic bases such as butyllithium.[3b]

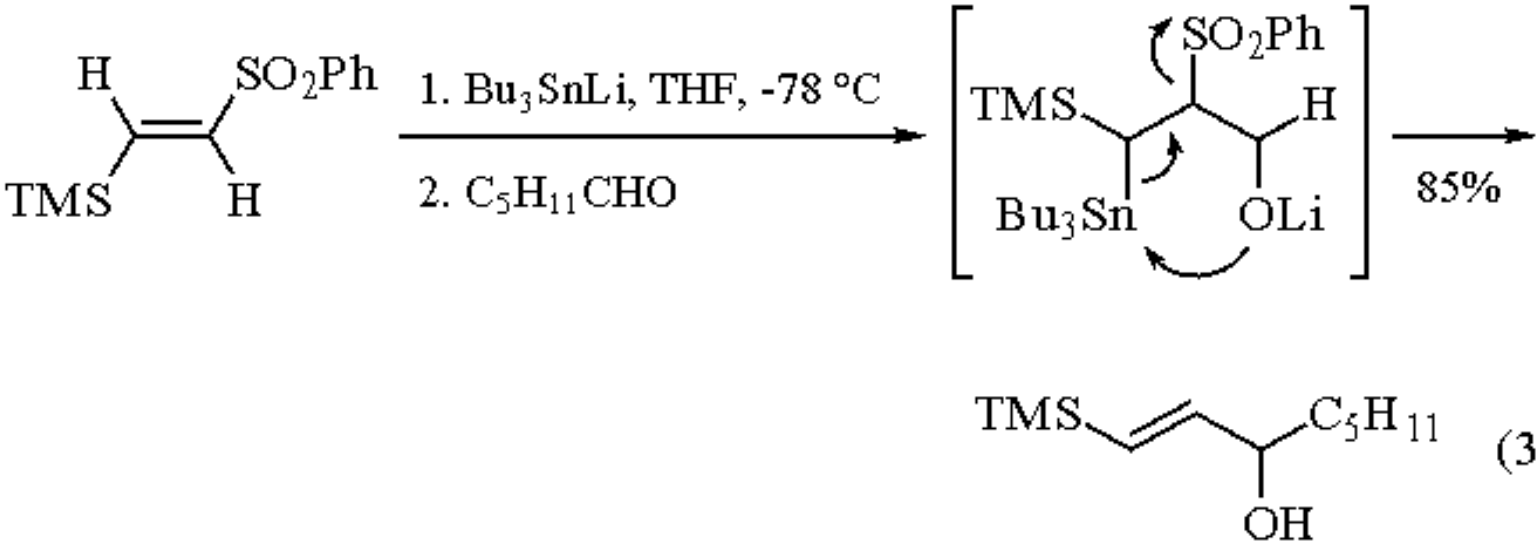

(3)

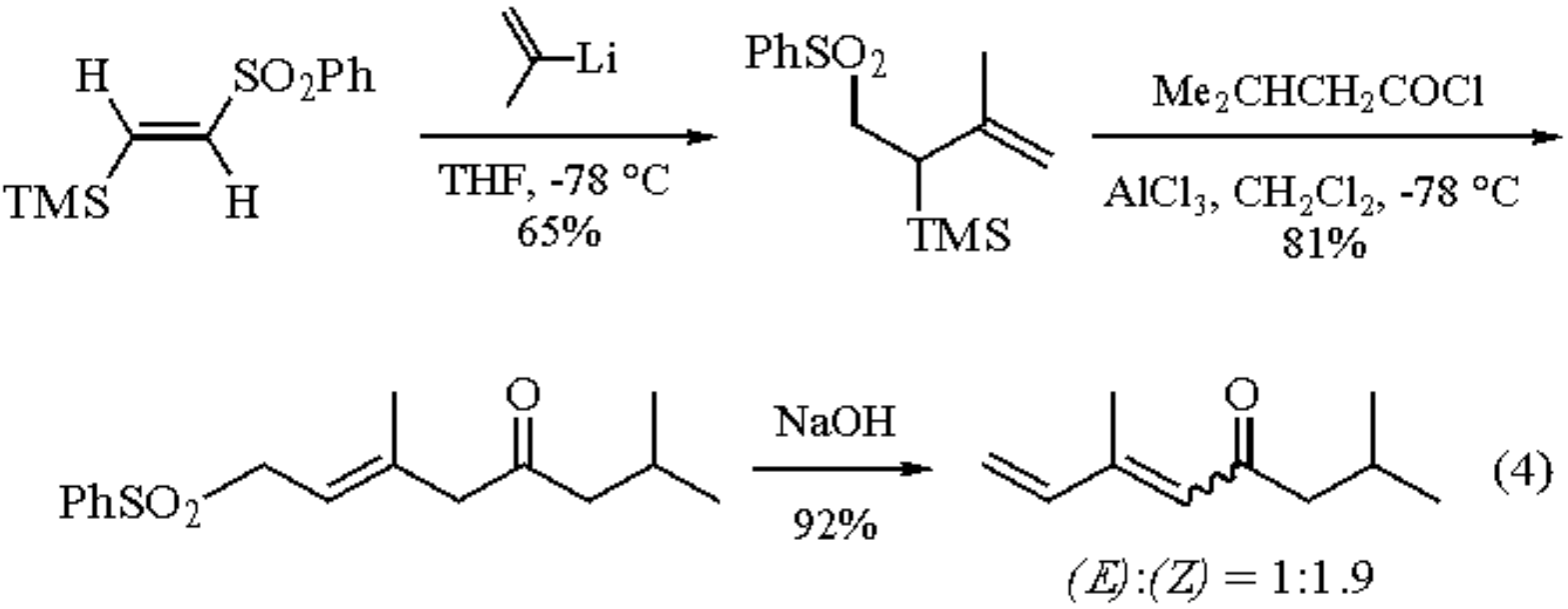

The availability of analogous reagents bearing different atoms in the place of silicon, such as tin,[3] boron,[7a] and chlorine[7b] as well as the alkynic homologs, is notable.[8] Finally, the sulfide related to the title reagent merits mention.[9]

---

1. Block, E.; Aslam, M. *T* **1988**, *44*, 281.
2. (a) Paquette, L. A.; Williams, R. V. *TL* **1981**, *22*, 4643. (b) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. *JOC* **1983**, *48*, 4976. (c) Paquette, L. A.; Bay, E. *JACS* **1984**, *106*, 6693.
3. (a) Ochiai, M.; Ukita, T.; Fujita, E. *TL* **1983**, *24*, 4025. (b) Ochiai, M.; Kenzo, S.; Fujita, E.; Tada, S. *CPB* **1983**, *31*, 3346. (c) Ochiai, M.; Kenzo, S.; Fujita, E. *CPB* **1984**, *32*, 3686.
4. Hsiao, C.-N.; Shechter, H. *JOC* **1988**, *53*, 2688.
5. (a) Paquette, L. A.; Crouse, G. D. *JOC* **1983**, *48*, 141. (b) Lin, H.-S.; Coghlan, M. J.; Paquette, L. A. *OS* **1988**, *67*, 157.
6. Paquette, L. A.; Williams, R. V.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *JOC* **1982**, *47*, 4566.
7. (a) Martinez-Fresneda, P.; Vaultier, M. *TL* **1989**, *30*, 2929. (b) Montanari, F. *G* **1956**, *86*, 406.
8. (a) Williams, R. V.; Sung, C.-L. A. *CC* **1987**, 590. (b) Padwa, A.; Wannamaker, M. W. *CC* **1987**, 1742. (c) Djeghaba, Z.; Jousseaume, B.; Ratier, M.; Duboudin, J.-G. *JOM* **1986**, *304*, 115.
9. Magnus, P.; Quagliato, D. *JOC* **1985**, *50*, 1621.

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Phenylsulfonyl(trimethylsilyl)methane[1]

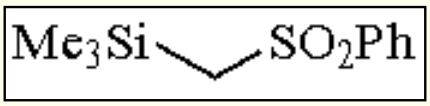

[17872-92-3] · $C_{10}H_{16}O_2SSi$ · Phenylsulfonyl(trimethylsilyl)methane · (MW 228.42)

(the lithio anion reacts with carbonyl compounds to afford vinyl sulfones[2] via a modified Peterson alkenation procedure;[3] double alkylation, reduction, and sila-Pummerer rearrangement provides ketones[4])

Alternate Name: phenyl trimethylsilylmethyl sulfone.

Physical Data: mp 28-30 °C; bp 121 °C/0.01 mmHg.

Solubility: readily sol THF, DME, ether.

Form Supplied in: white solid; widely available.

Preparative Method: can be readily prepared via several routes,[5] of which the most suitable for large-scale preparation involves the reaction of sodium thiophenolate with ***(Chloromethyl)trimethylsilane***, the sulfide obtained then being oxidized to the sulfone with buffered ***Peracetic Acid***.[6]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: store under an inert atmosphere at 0-4 °C.

Preparation of Vinyl Sulfones from Carbonyl Compounds.

The Peterson alkenation reaction provides a useful method for the preparation of alkenes.[3] The scope of the reaction can be expanded to give α-heterosubstituted alkenes by the use of α-heteroatom-substituted carbanions. The lithio anion generated from the title reagent (**1**) reacts with carbonyl compounds to give the corresponding vinyl sulfones via a modified Peterson alkenation procedure (eq 1).[2,5,7,8] Both aldehydes and ketones are suitable substrates, although complications can arise when enolizable ketones are employed.[5] The solvent has a marked effect on the reaction, with the highest yields being obtained with DME.[5]

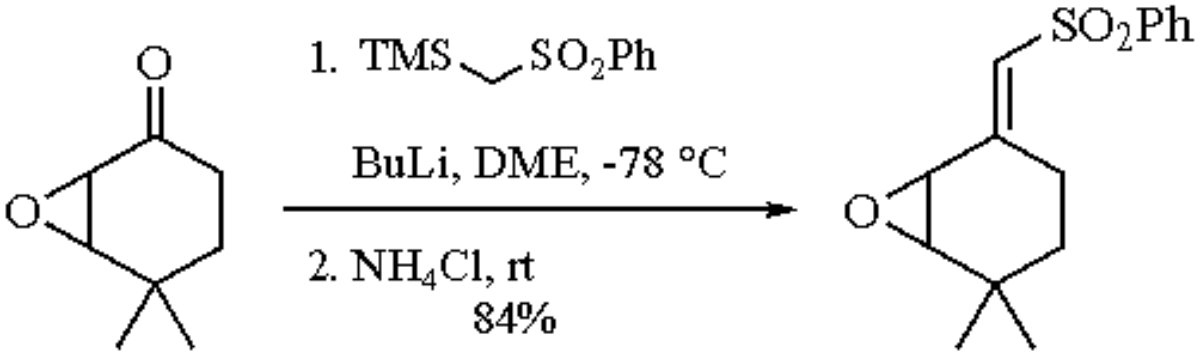

(1)

(*E*):(*Z*) = 1:1

The reaction can tolerate a wide range of functionality, including ethers, esters, and epoxides. The vinyl sulfones are generally obtained as mixtures of (*E*) and (*Z*) isomers, although the degree of selectivity is highly substrate dependent.[5,9] The aldehyde (**2**) was converted to the corresponding vinyl sulfone as a single (*E*) isomer in 96% yield. The vinyl sulfone obtained is an intermediate in the total synthesis of the antifeedant ajugarin I (eq 2).[10]

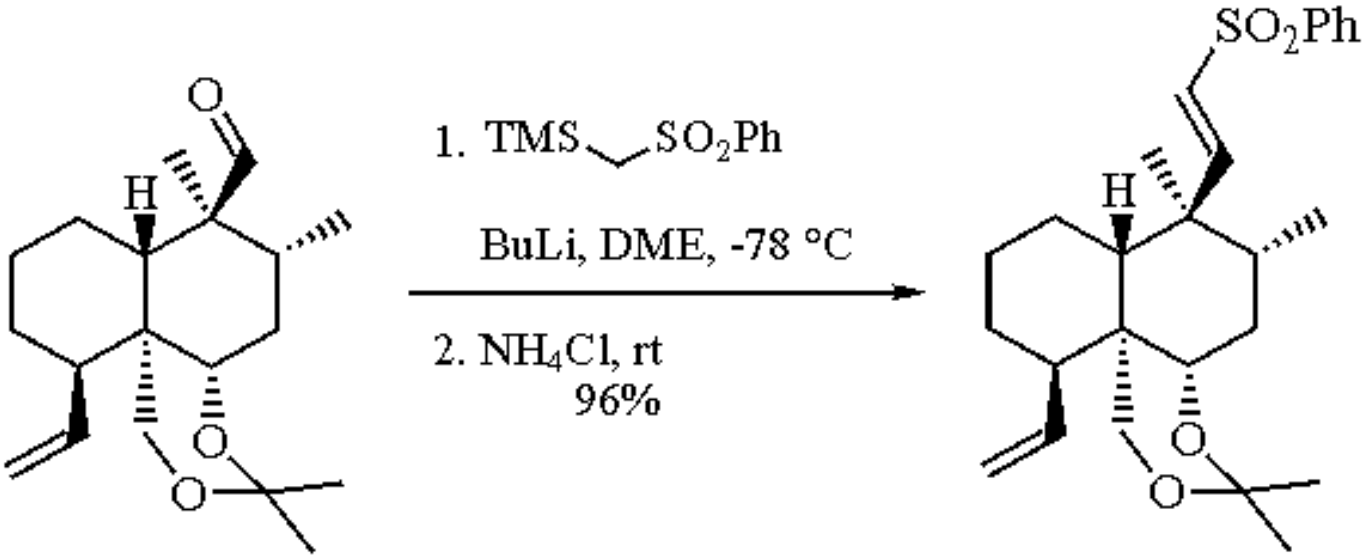

(2)

(2)

The use of ether as solvent allows the trapping of the intermediate alkoxide by acetylation.[5] The β-acetoxy-α-silyl sulfone (**3**), isolated from the reaction of benzaldehyde and the lithium anion of (**1**) followed by trapping with ***Acetic Anhydride*** (eq 3), was shown by NMR to be a single diastereoisomer. However, attempted stereospecific elimination was found to give mixtures of (*E*)- and (*Z*)-sulfones.[5]

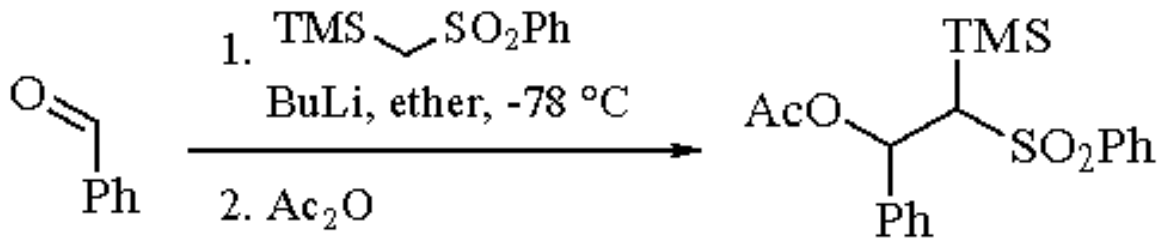

(3)

(3)

Greater (*E*) stereoselectivity can be achieved in the preparation of vinyl sulfones from carbonyl compounds by the use of the related α-sulfonylphosphonates.[11]

Preparation of Ketones via Dialkylation, Reduction, and Sila-Pummerer Rearrangement.

α-Silyl sulfides undergo sila-Pummerer rearrangement to provide aldehydes and ketones.[12] Access to the ketones is inhibited by the difficulty in deprotonating and hence alkylating the α-silyl sulfides. The α-silyl sulfone (**1**) is readily deprotonated with ***n-Butyllithium*** and subsequent alkylation with an alkyl halide proceeds smoothly.[13] The process can be repeated a second time to provide dialkylated α-silyl sulfones (eq 4).[4]

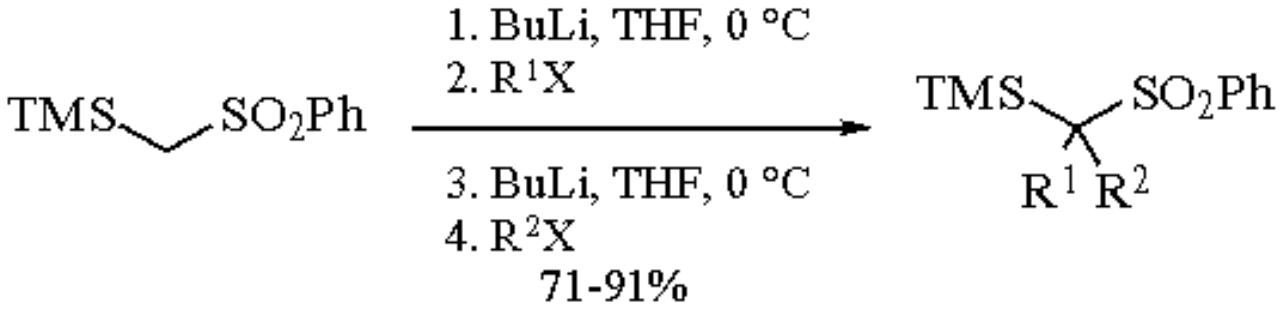

(4)

The lithio anion is formed in THF at 0 °C and can be alkylated with a range of simple alkyl and alkenyl halides. The α-silyl sulfones thus obtained are then reduced with either ***Diisobutylaluminum Hydride*** or ***Lithium Aluminum Hydride*** to give α-silyl sulfides capable of undergoing the sila-Pummerer rearrangement.[4]

Other Applications.

α-Silyl sulfone (**1**) can be doubly deprotonated by the use of a second equivalent of *n*-BuLi.[14] Reaction of the dianion (**4**) with ***Dichlorotitanium Diisopropoxide*** prior to reaction with benzaldehyde provides the α-silylvinyl sulfone (eq 5). The α-silylvinyl sulfone is obtained in good yield as a 2:1 mixture of (*E*) and (*Z*) isomers.[14a]

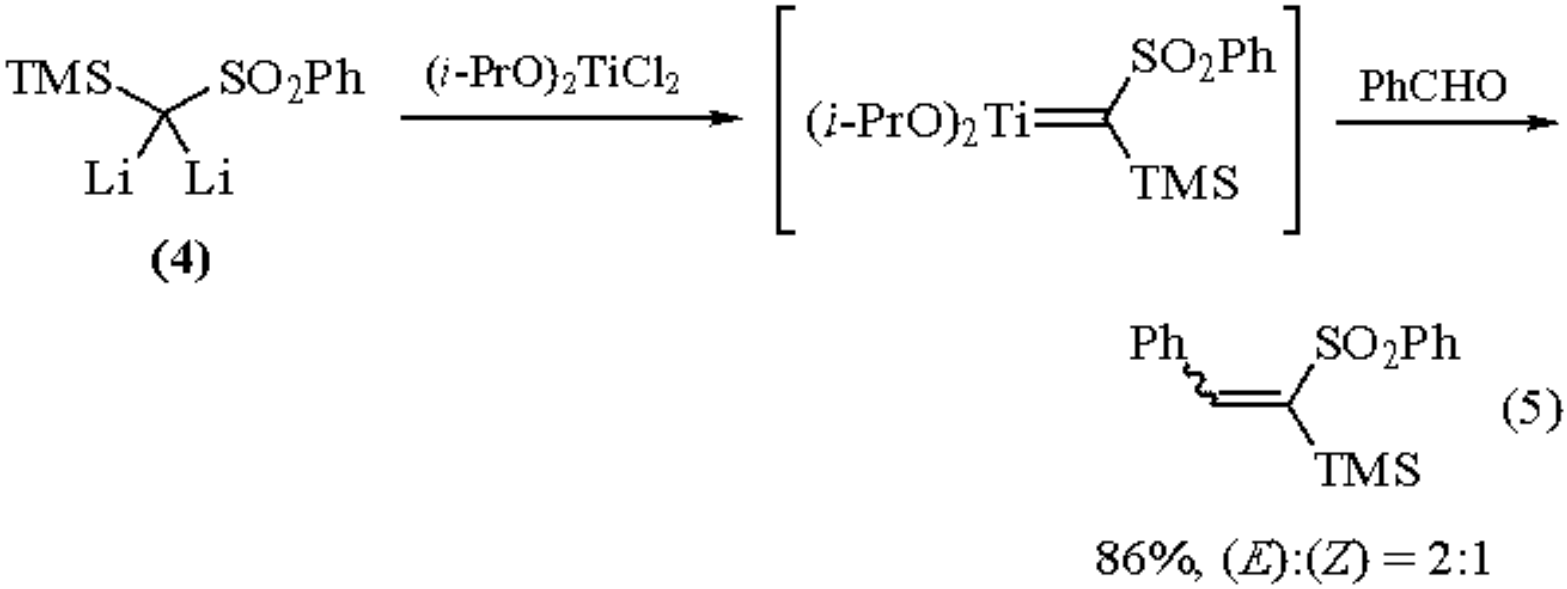

The lithio anion of (**1**) also reacts with simple amides to provide 2-aminovinyl sulfones.[15] Deprotonation is performed with ***Lithium Diisopropylamide*** at -70 °C in THF, and the resultant 2-aminovinyl sulfones are obtained in moderate to good yields with excellent (*E*) selectivity.

---

1. For a comprehensive review of the Peterson alkenation see: Ager, D. J. *OR* **1990**, *38*, 1.
2. Ley, S. V.; Simpkins, N. S. *CC* **1983**, 1281.
3. Peterson, D. J. *JOC* **1968**, *33*, 780.
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1-Phenyl-2-tetrazoline-5-thione

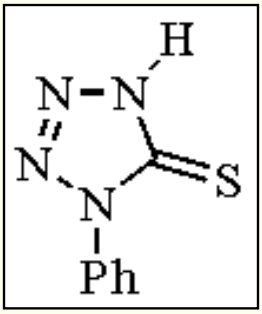

[86-93-1] · $C_7H_6N_4S$ · 1-Phenyl-2-tetrazoline-5-thione · (MW 178.24) (Na salt)

[15052-19-4]

(in combination with isocyanides, activates carboxylate for lactonization,[1] peptide formation;[2] source of nucleophilic sulfur[3])

Physical Data: mp 150 °C (dec).

Solubility: sol organic solvents.

Form Supplied in: red solid; widely available.

Handling, Storage, and Precautions: store in dark.

Introduction.

While this reagent has a wide variety of applications of great value to the photographic industry, it is also a synthetic reagent of some utility. These applications relate to activation of the carboxylate group, introduction of nucleophilic sulfur, and as a heterocyclic building block.

Reaction with Isocyanides.

Treatment of the reagent with ***t-Butyl Isocyanide*** affords an intermediate of the nature indicated (eq 1). Subsequent reaction with a carboxylic acid at -40 °C gives an equilibrium mixture of compounds (eq 2) in which the carbonyl group is activated toward nucleophilic substitution. This intermediate can be effectively utilized in two ways.

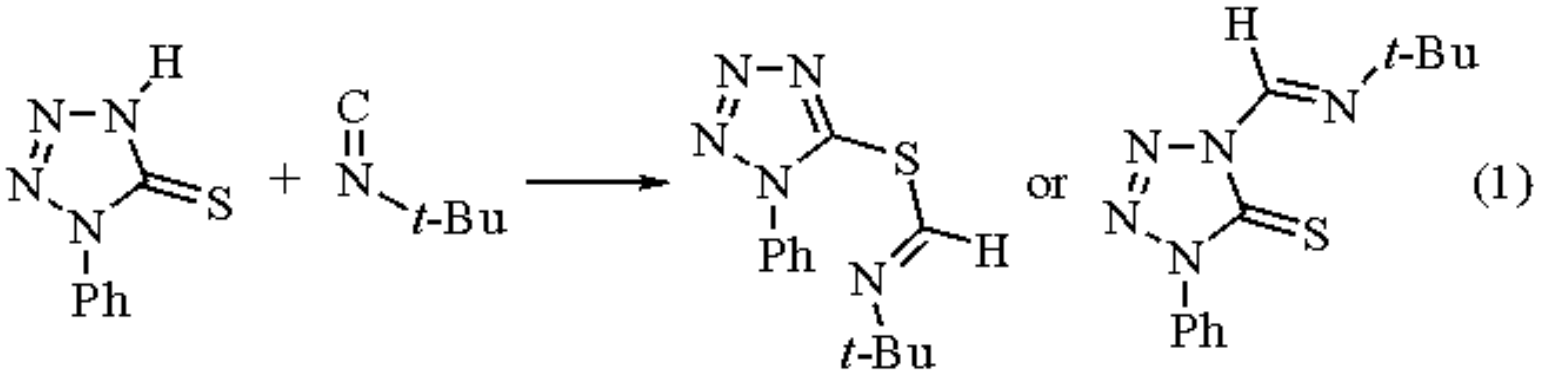

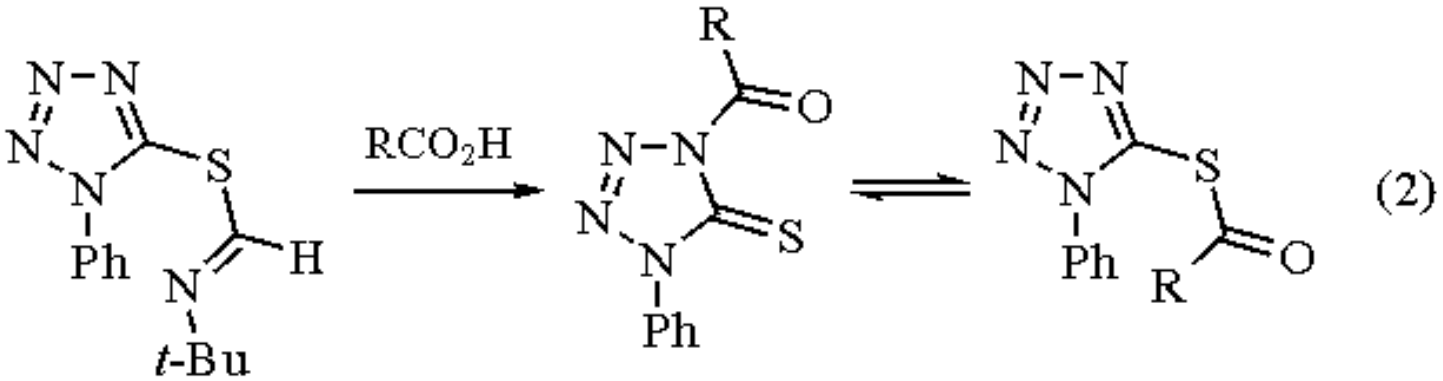

Lactone Formation.

Long-chain hydroxy acids can, by this method, be converted into lactones (eq 3).[1] Of note is the observation that even macrocyclic lactones can be formed in high yields without high dilution or other catalysts.

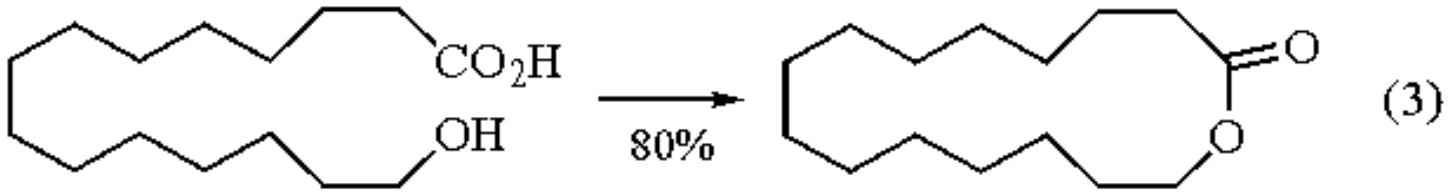

Peptide Formation.

Amino acids can be coupled to form amides using this technology.[2] A nitrogen-protected amino acid is activated and allowed to react with a carboxylate-protected amino acid, thus forming the peptide linkage. The reagent can be recovered unchanged at the end of either of these sequences.

Sulfur Nucleophile.

The nucleophilic nature of the sulfur in 1-phenyl-2-tetrazoline-5-thione can be utilized for the introduction of sulfur into organic compounds. Thus Mitsunobu reaction of a protected sugar with the reagent affords the substituted sugar (eq 4).[3]

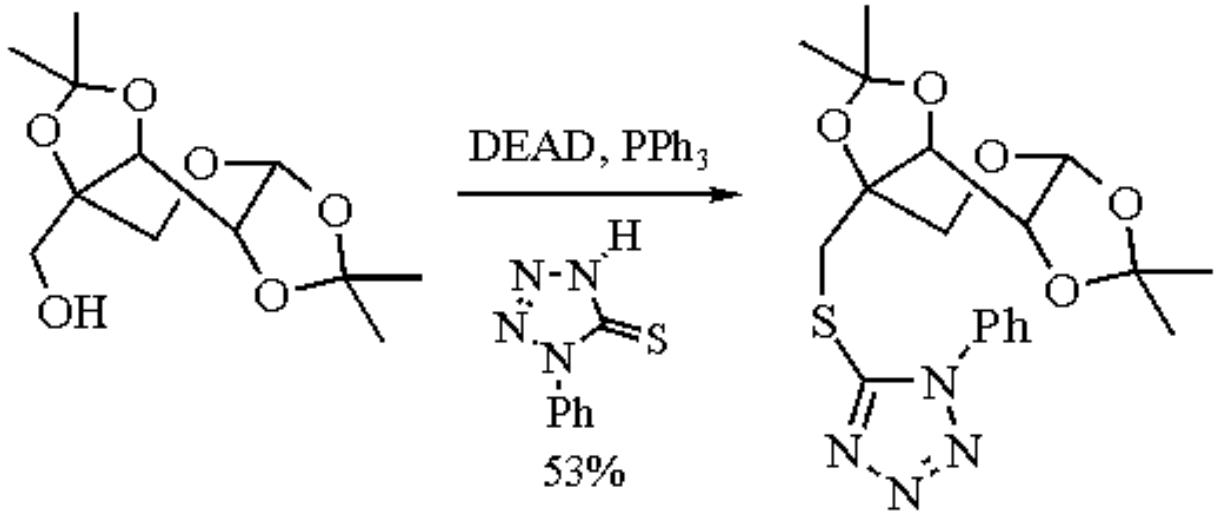

(4)

In a similar fashion, substitution of a cephalosporin could be achieved (eq 5).[4]

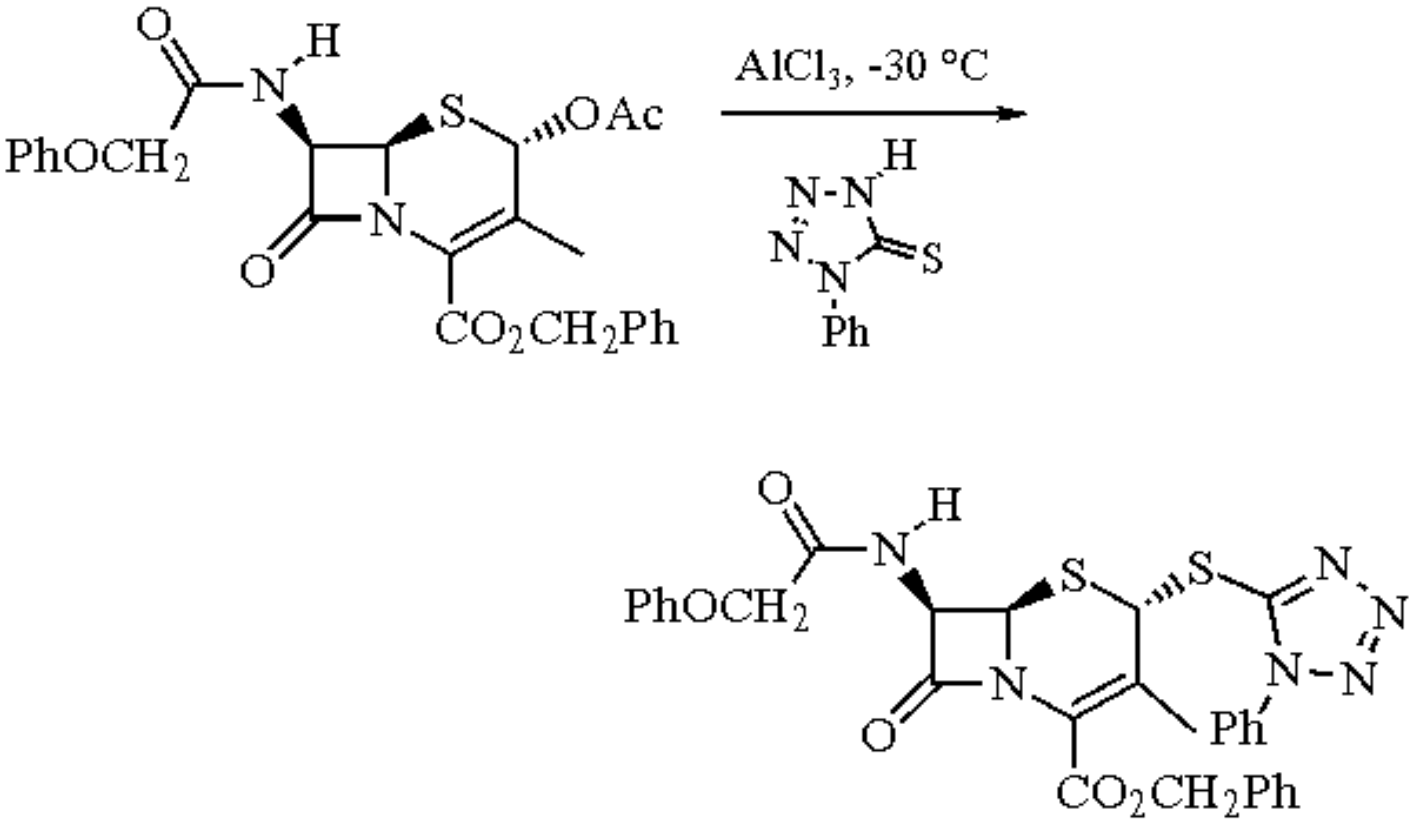

(5)

Alkylation at nitrogen (or redirected to nitrogen) affords the substituted tetrazolinethione. Under photolysis conditions, such compounds undergo loss of sulfur and nitrogen to afford the carbodiimide (eq 6),[5] subsequent hydrolysis providing the urea.

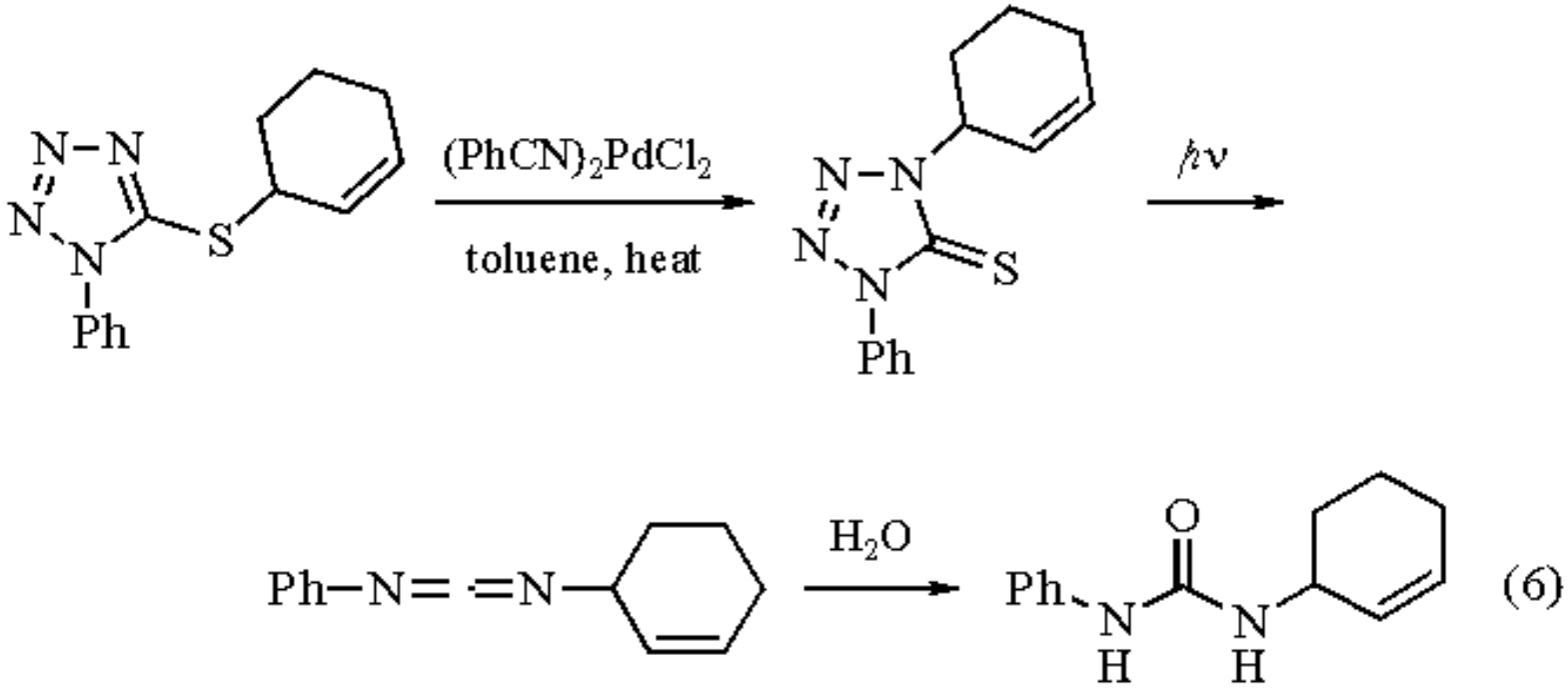

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Phenylthallium Bis(trifluoroacetate)[1]

$PhTl(OCOCF_3)_2$

[23586-54-1] · $C_{10}H_5F_6O_4Tl$ · Phenylthallium Bis(trifluoroacetate) · (MW 507.53)

(reagent for preparation of substituted benzenes)

Physical Data: mp 184-189 °C

Solubility: sol MeOH, EtOH, MeCN, THF, DMSO.

Form Supplied in: colorless crystalline solid. *Drying:* in vacuo over sodium hydroxide.

Preparative Method: readily prepared from benzene.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic (cumulative toxicity) to inhalation, skin contact, and ingestion; extreme caution should be used when handling these materials; use in a fume hood.

General Discussion.

Phenylthallium bis(trifluoroacetate) is a readily accessed and versatile reagent for conversion into a wide variety of other aromatic compounds. Uses for this reagent flourished once the straightforward route to aryl bistrifluoroacetates (treatment of the aromatic compound with a solution of ***Thallium(III) Trifluoroacetate*** (TTFA) in TFA) was published in 1969.[2] The preparation of phenylthallium bis(trichloroacetate) has also been described. This reagent undergoes iodination, chlorination, nitrile formation, selenation, nitration, coupling, and palladium-catalyzed alkenation in good yield.[3] A more recent modification[4] allows the replacement of a trimethylsilyl group with thallium bis(trifluoroacetate) (eq 1).

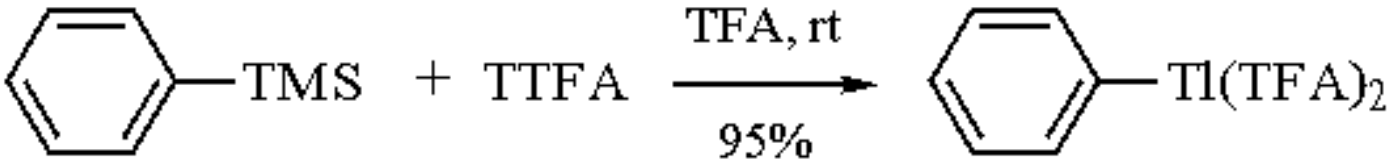

(1)

Phenylthallium bis(trifluoroacetate) can be subsequently converted into numerous aromatic compounds, often without isolation of the bis(trifluoroacetate) salt. Transformation into aryl iodides is readily accomplished (eq 2)[5] with rapid replacement of the thallium by iodine in high yield.

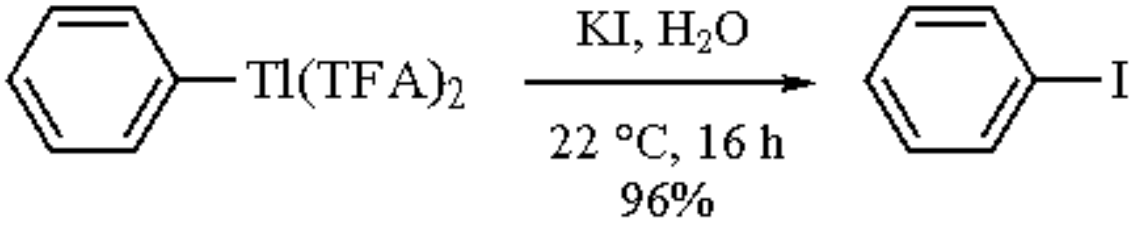

(2)

A method for the preparation of *m*-iodonitrobenzene from phenylthallium bis(trifluoroacetate) has been developed (eq 3).[6] This simple method, noteworthy for its regiospecificity, avoids the often circuitous route of dinitration, mono-reduction to the amine, diazotization, and iodination.

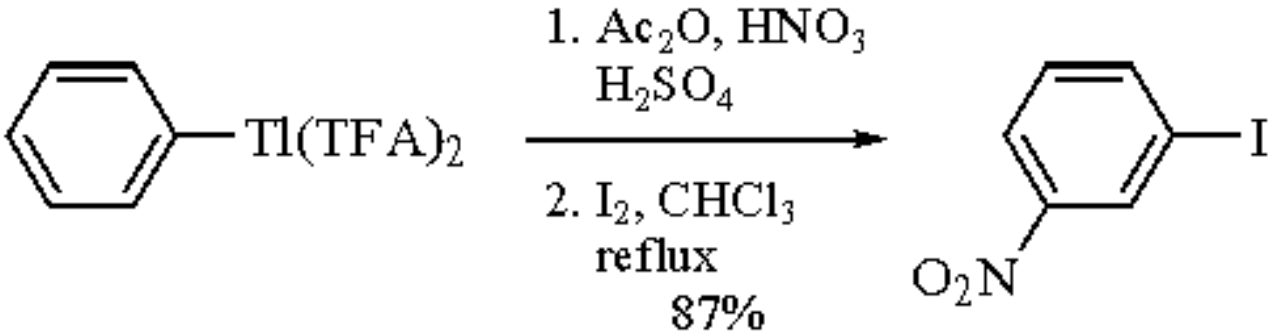

(3)

Preparation of aryl nitroso and nitrile compounds from arylthallium salts has also been reported. In the case of nitrosation, a one-pot reaction of the arylthallium bis(trifluoroacetate) with *n*-propyl nitrite and HCl at rt in chloroform leads directly to the *para*-substituted nitroso compound.[7] For the preparation of aryl nitriles, a variety of nitrile-delivery reagents have been examined (***Potassium Cyanide***,[8] $Cu(CN)_2$,[9a] ***Copper(I) Cyanide***[9]) under varying conditions (photolysis in aqueous solution,[8] pyridine,[9a] or acetonitrile[9] reflux). The reaction of the aryl bis(trifluoroacetate) with copper(I) cyanide in acetonitrile gives the most reliable results in moderate to good yields, and is quite general (eq 4).[9b]

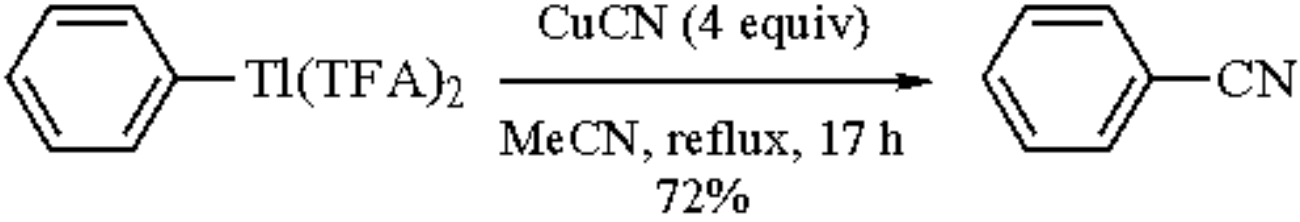

(4)

Phenols are also readily accessed by this methodology. In an interesting illustration of both boron and thallium chemistry, it was found that treatment of phenylthallium bis(trifluoroacetate) with ***Diborane*** yields ***Dihydroxy(phenyl)borane***, which can be oxidized under standard conditions to give phenol (eq 5).[10]

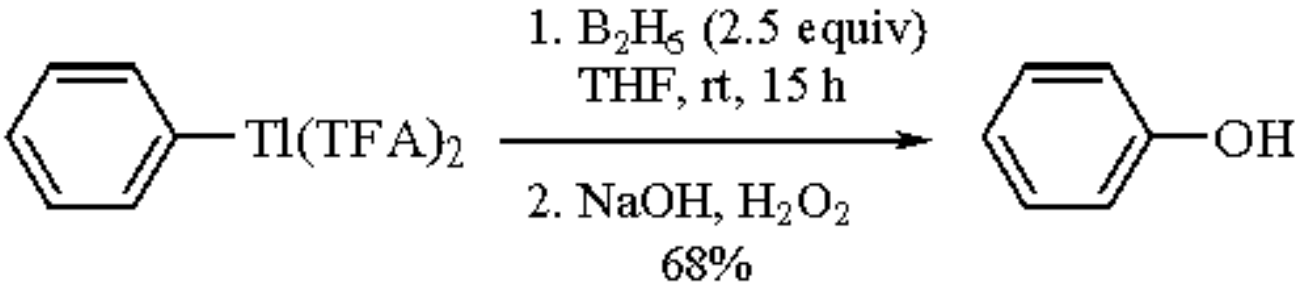

(5)

Conversions of phenylthallium bis(trifluoroacetate) into thiocyanates, selenium compounds, and unsymmetric sulfones have also been described.[11] All these transformations are carried out by heating the arylthallium salt with the appropriate reagent in dioxane. Copper(II) is critical to the success of these transformations, which proceed in moderate yield.

Carbonylation of phenylthallium bis(trifluoroacetate) has also been successfully demonstrated, providing methyl benzoate.[12]

In yet another demonstration of the synthetic utility of arylthallium bis(trifluoroacetates), the preparation of unsymmetrical biphenyl compounds has been developed (eq 6).[13] Capture of the aryl radical by the solvent (benzene) leads to the product. Attempts to extend this methodology by the use of pyridine as solvent were unsuccessful. Use has been made of arylthallium reagents in a ***Palladium(II) Chloride***-catalyzed preparation of symmetrical biaryls in yields ranging from 12 to 75% (eq 7).[14]

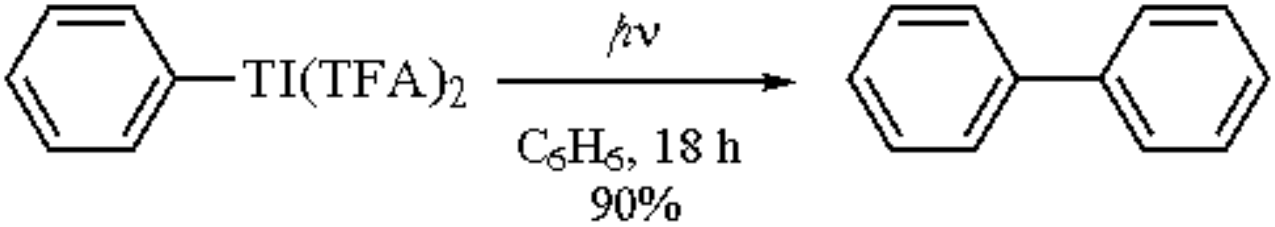

(6)

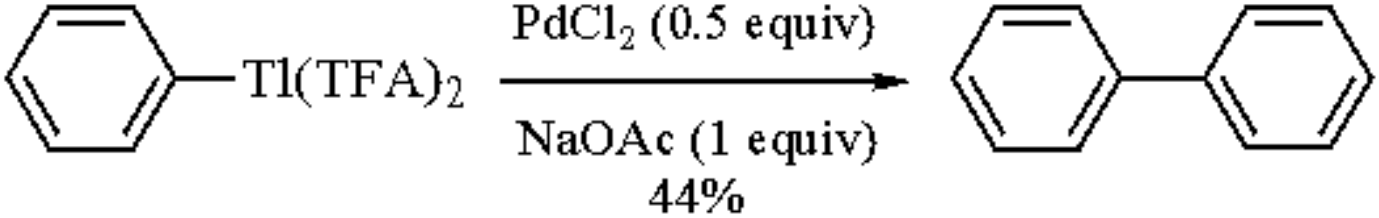

(7)

Related Reagents.

Thallium(I) Bromide; ***Thallium(III) Trifluoroacetate***; ***Thallium(III) Trifluoroacetate--Palladium(II) Acetate***.

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(Phenylthio)acetic Acid

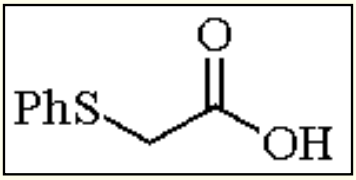

[103-04-8] · $C_8H_8O_2S$ · (Phenylthio)acetic Acid · (MW 168.23)

(preparation of various PhS-containing compounds, such as 3- or 4-hydroxy-2-(phenylthio)alkanoic acids, 4-oxo-2-(phenylthio)alkanoic acids, and α-phenylthio-β-lactams)

Alternate Name: PTAA.

Physical Data: mp 61-62 °C,[1] 62-63 °C;[2] pK_a 3.02 × 10^{-4} (0 °C), 2.76 × 10^{-4} (25 °C).

Form Supplied in: colorless crystals; commercially available.

Preparative Methods: by the substitution reaction of sodium chloroacetate with sodium benzenethiolate, or by the treatment of bromoacetic acid with thallium(I) benzenethiolate.[2]

Derivation of Various PhS Compounds.

(Phenylthio)acetic acid is a synthetic precursor for a variety of PhS-containing compounds such as $PhSCH_2N{=}C{=}O$,[3] $PhSCH_2CON{=}C{=}S$,[3] $PhSCH_2CO_2Me$,[4] $PhSCH_2NO_2$,[5,6] $MeCH{=}C(NO_2)SPh$,[5,6] $PhSCHClCO_2H$,[7] $PhSCH_2Cl$,[7] and 2-(phenylthio)methyl-1-oxazolidine derivatives.[8]

PTAA generates a dianion by the action of 2 equiv of ***n-Butyllithium*** or ***Lithium Diisopropylamide***. The C-anion site of the PTAA dianion is more reactive than the C-anion of methyl (phenylthio)acetate. Treatment of the dianion with alkyl halide gives a monoalkylated product (eq 1).[9-11] Reaction of the dianion with a carboxylic ester accompanied by decarboxylation provides a useful method for introduction of the $PhSCH_2$ moiety (eq 2).[12] Introduction of PTAA into a furan ring has also been achieved by means of [3,3]-sigmatropic rearrangement (eq 3).[13]

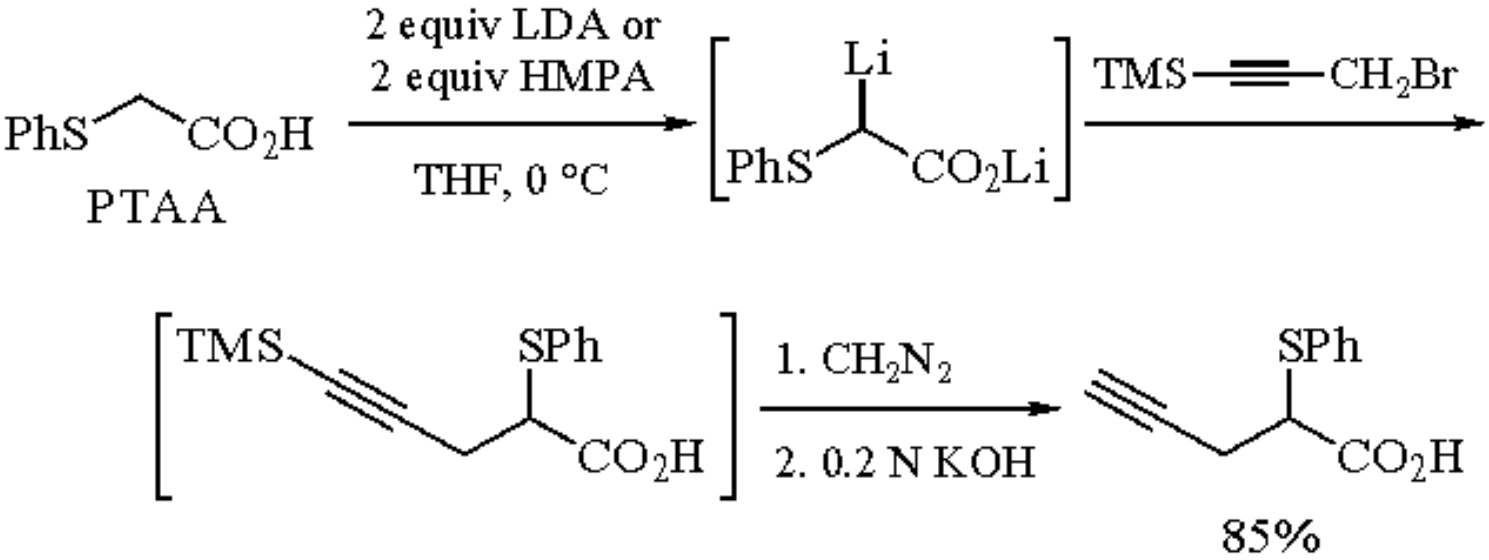
PhS
CO2H
PTAA
2 equiv LDA or
2 equiv HMPA
THF, 0 °C
Li
PhS
CO2Li
TMS
CH2Br
TMS
SPh
CO2H
1. CH2N2
2. 0.2 N KOH
SPh
CO2H
85%

(1)

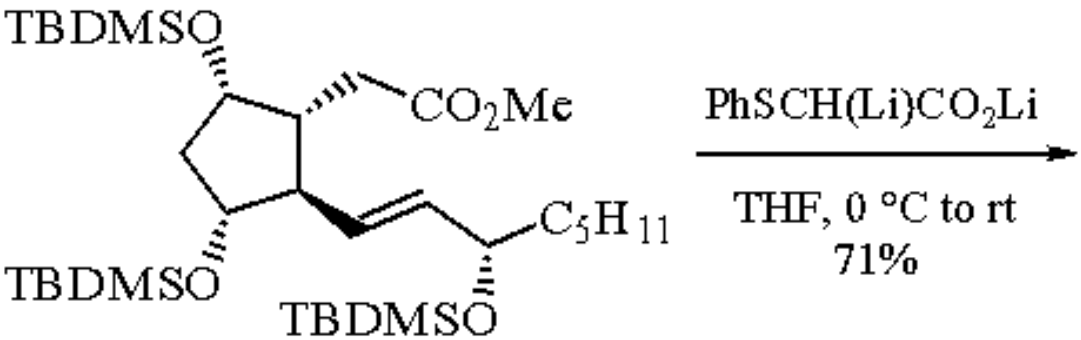
TBDMSO
CO2Me
C5H11
TBDMSO
TBDMSO
PhSCH(Li)CO2Li
THF, 0 °C to rt
71%

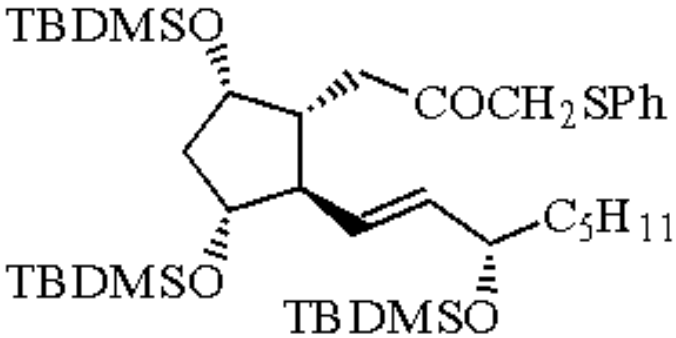
TBDMSO
COCH2SPh
C5H11
TBDMSO
TBDMSO

(2)

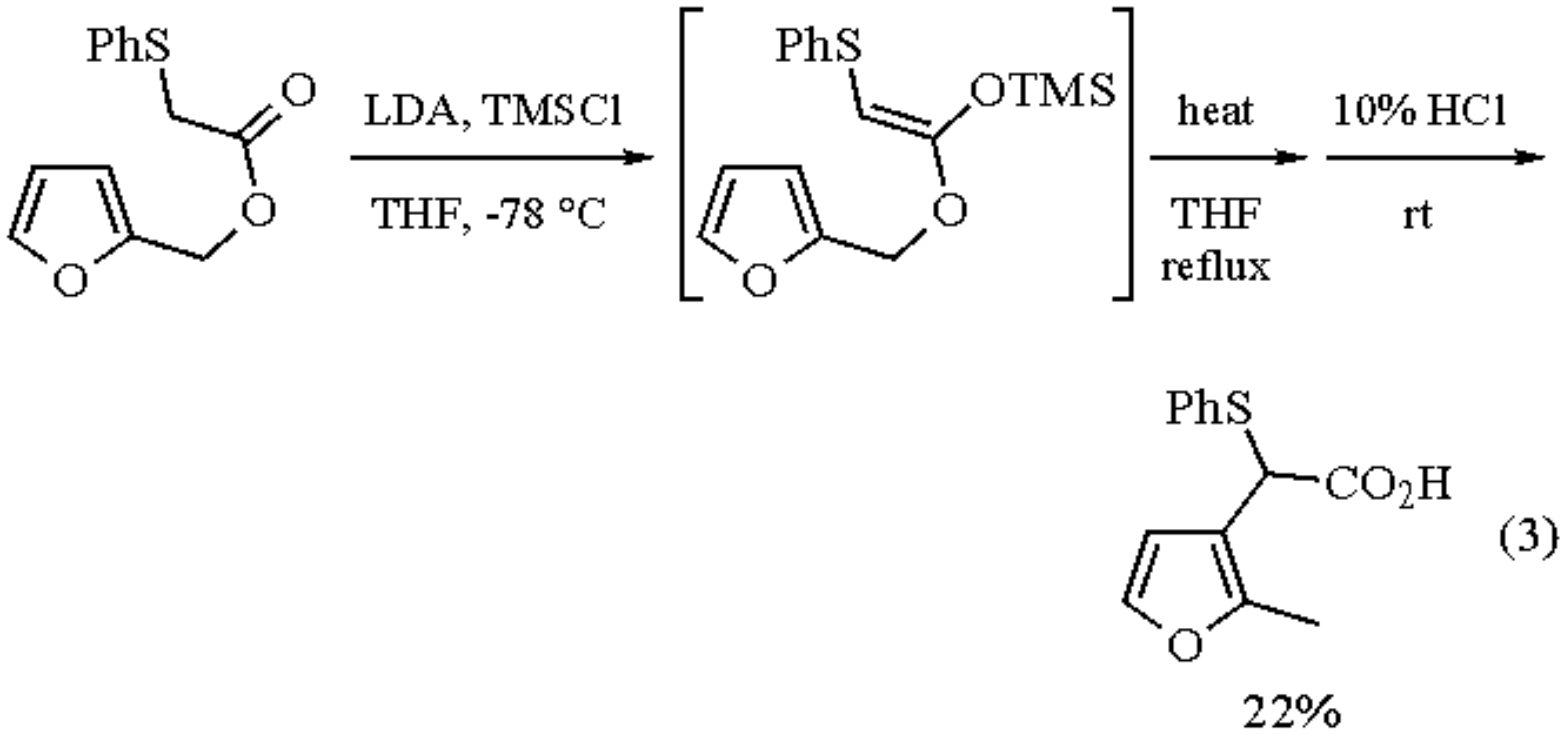

(3)

Synthesis of 4-Hydroxy-2-(phenylthio)alkanoic Acids.

The dianion of PTAA reacts with a terminal epoxide to give a ring-opened product, 4-hydroxy-2-(phenylthio)alkanoic acid, which can be transformed into the corresponding γ-lactone (eq 4),[14] α,β-unsaturated γ-lactones (eq 5),[15] or 4-hydroxy-2-alkanoic ester.[16]

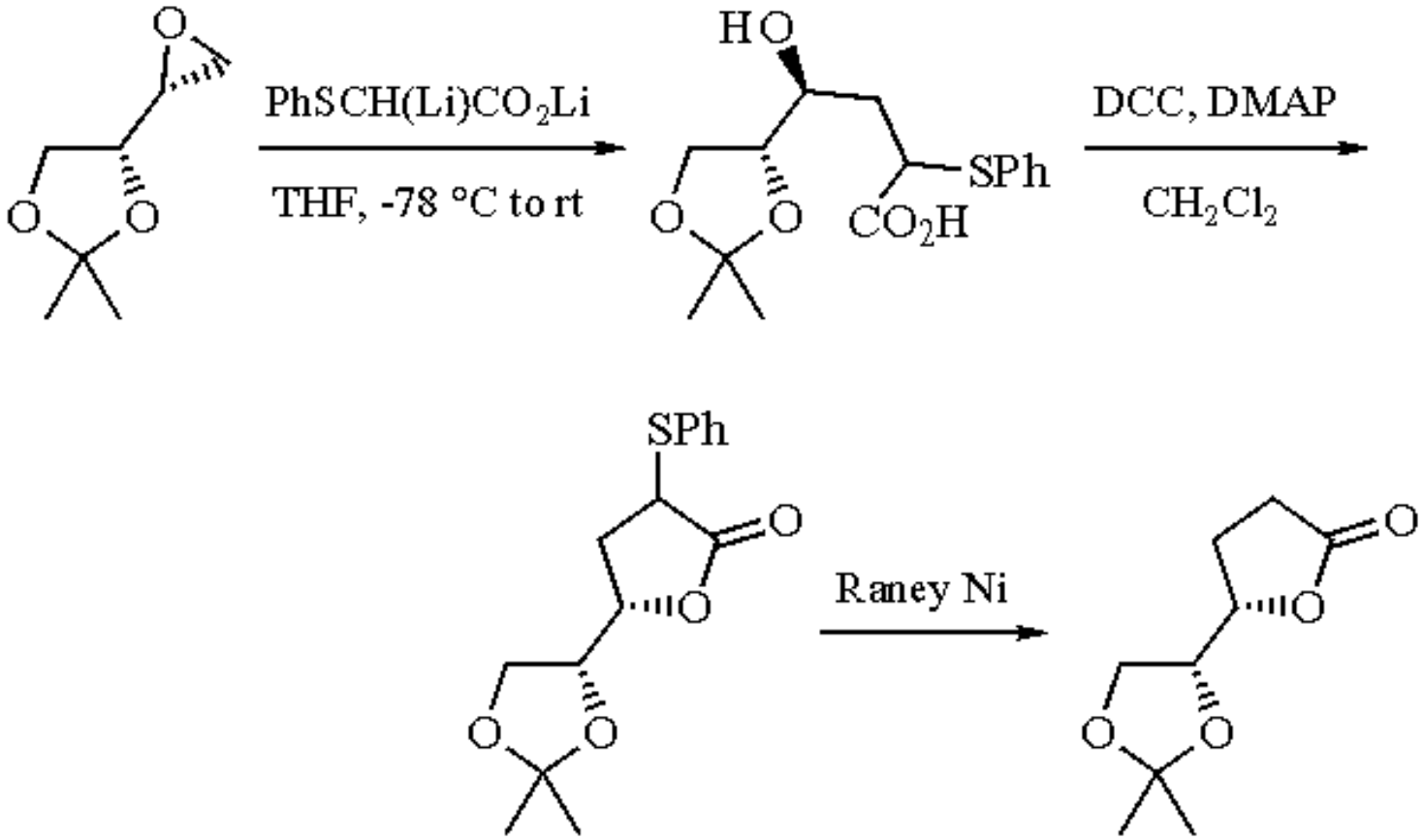
PhSCH(Li)CO2Li
THF, -78 °C to rt
DCC, DMAP
CH2Cl2
HO
SPh
CO2H
SPh
Raney Ni

(4)

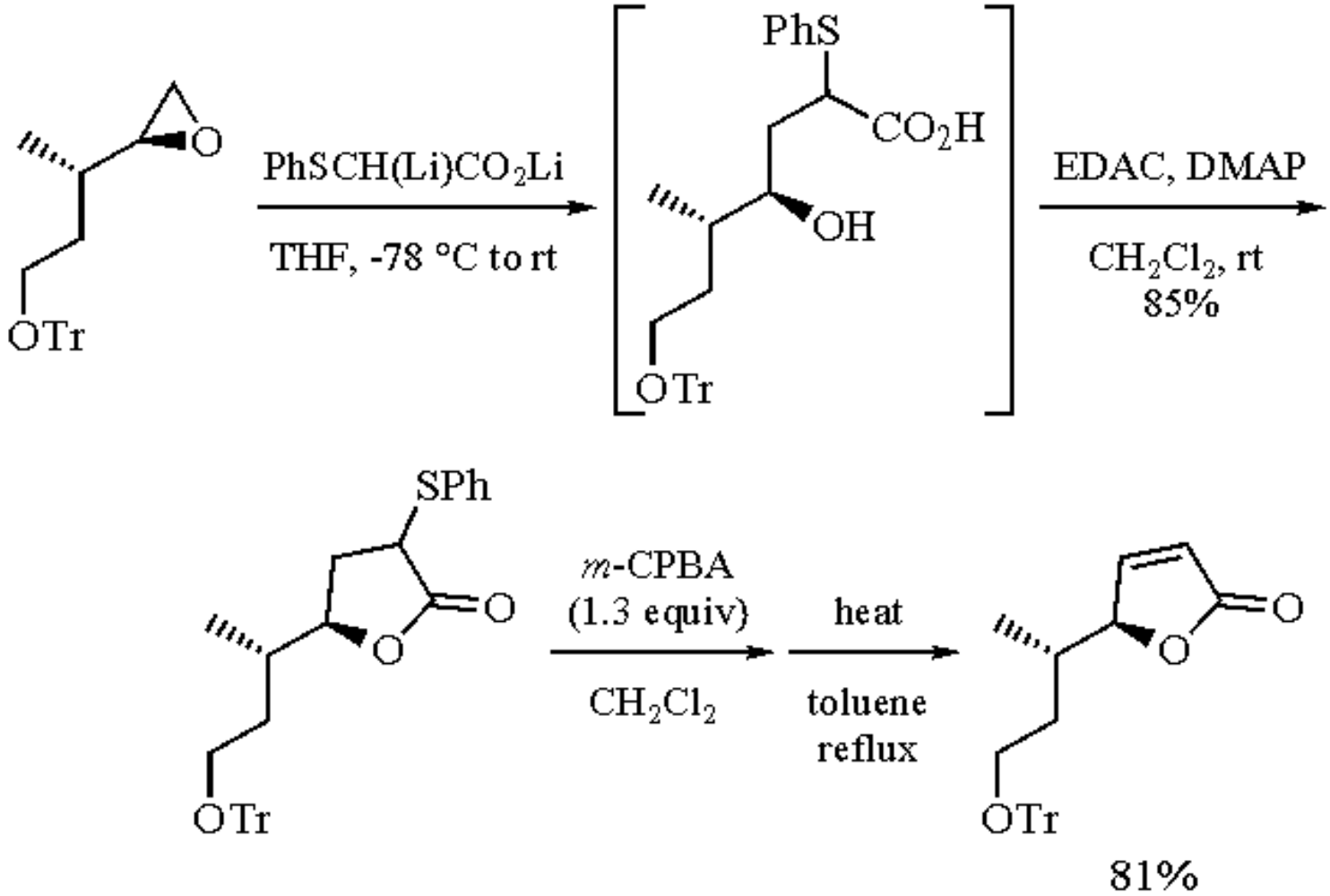
PhSCH(Li)CO2Li
THF, -78 °C to rt
PhS
CO2H
OH
OTr
EDAC, DMAP
CH2Cl2, rt
85%
SPh
m-CPBA
(1.3 equiv)
CH2Cl2
heat
toluene
reflux
81%

(5)

Synthesis of 3-Hydroxy-2-(phenylthio)alkanoic Acids.

The dianion of PTAA adds to aldehydes and ketones, leading to 3-hydroxy-2-(phenylthio)alkanoic acids.[17,18] These can be converted to the corresponding β-lactones which, on treatment with ***Magnesium Bromide***, give the β-phenylthio-γ-lactone (eq 6) or α-phenylthio β,γ-unsaturated carboxylic acid (eq 7).[18]

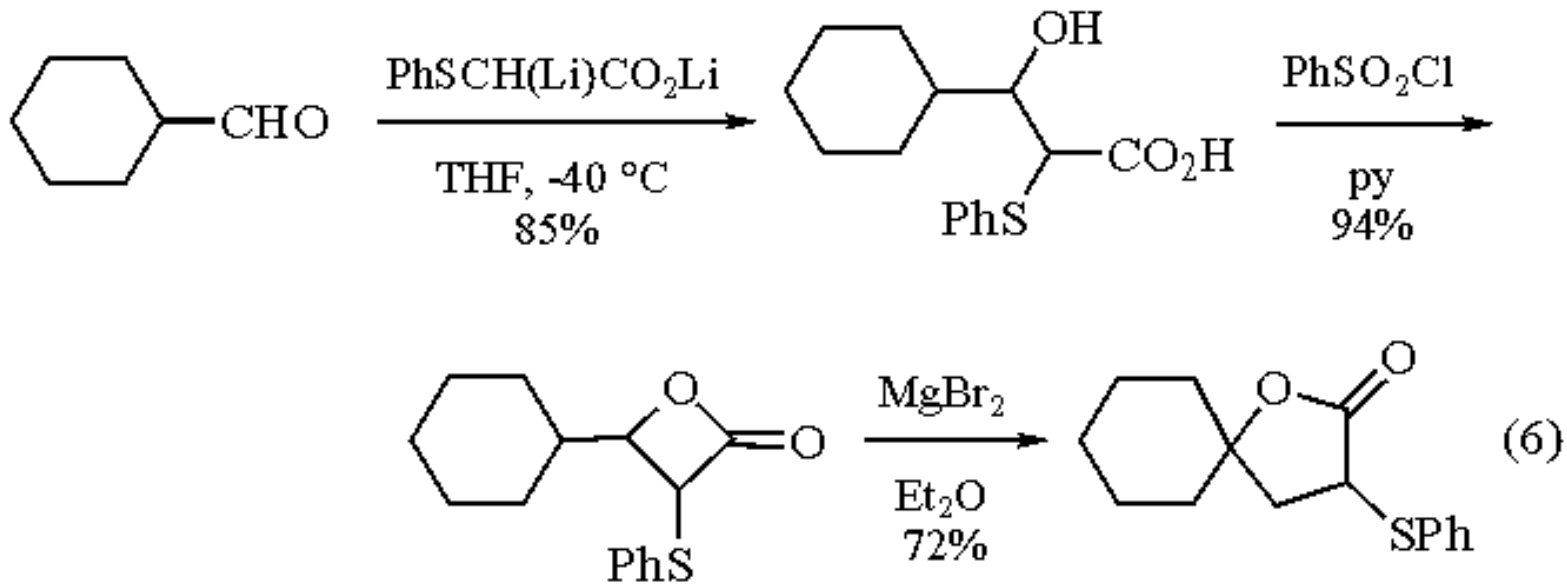

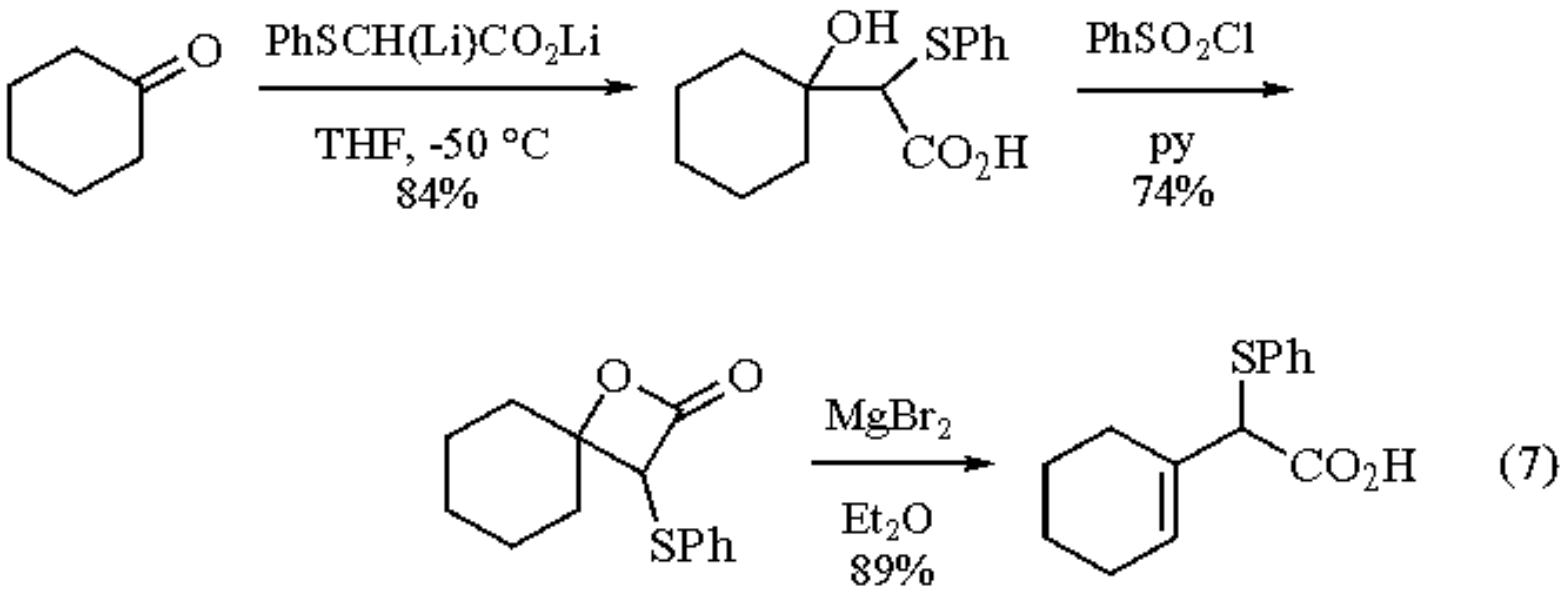

4-Oxo-2-(phenylthio)alkanoic Acid Synthesis.

The dianion of PTAA adds to nitroalkenes, and subsequent acid hydrolysis yields 4-oxo-2-(phenylthio)alkanoic acids, synthetic intermediates of the corresponding 4-hydroxy-2-(phenylthio)alkanoic acids (eq 8).[19]

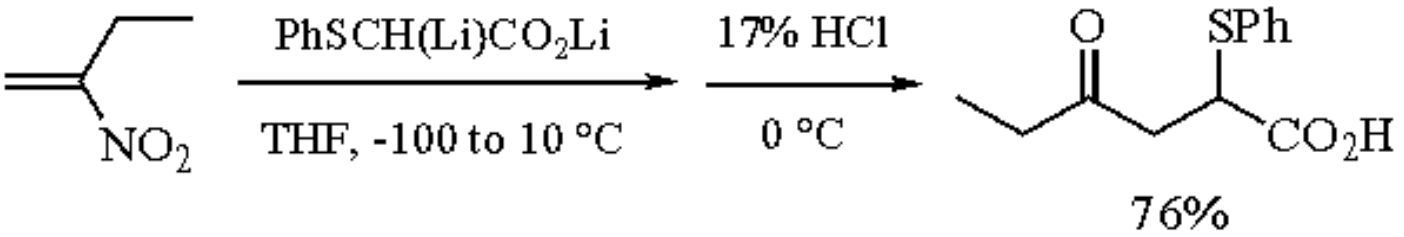

(8)

Synthesis of Cyclic Compounds.

PTAA has two reactive sites, the carboxy group and the active methylene group, providing a useful method for constructing various cyclic compounds (eqs 9 and 10).[20-22] Activation of the carboxy group of PTAA and subsequent treatment with a base in the presence of an imine gives an α-phenylthio-β-lactam (eq 11).[23]

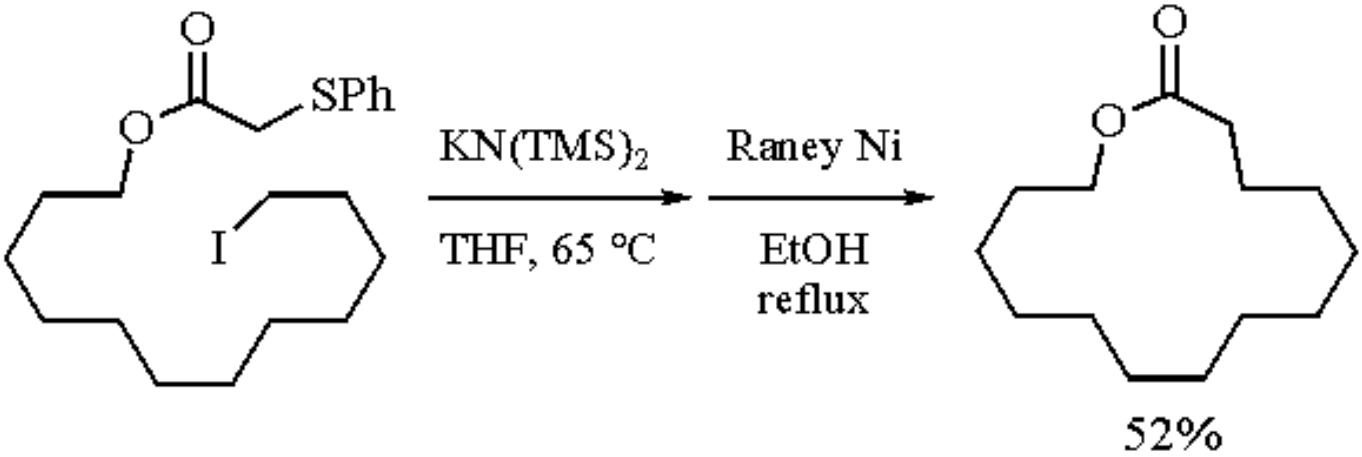

(9)

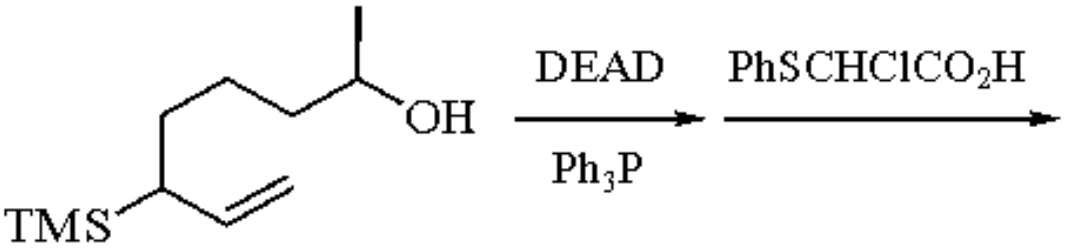

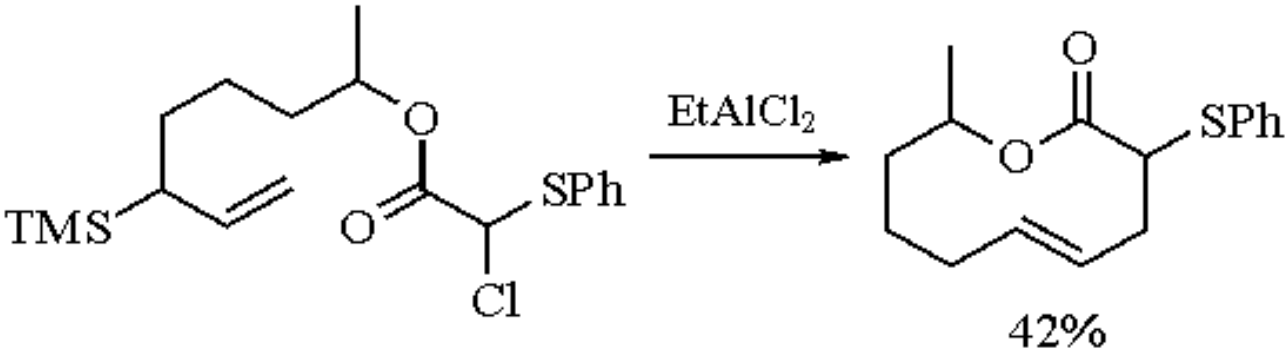

(10)

(Phenylthio)acetic Acid

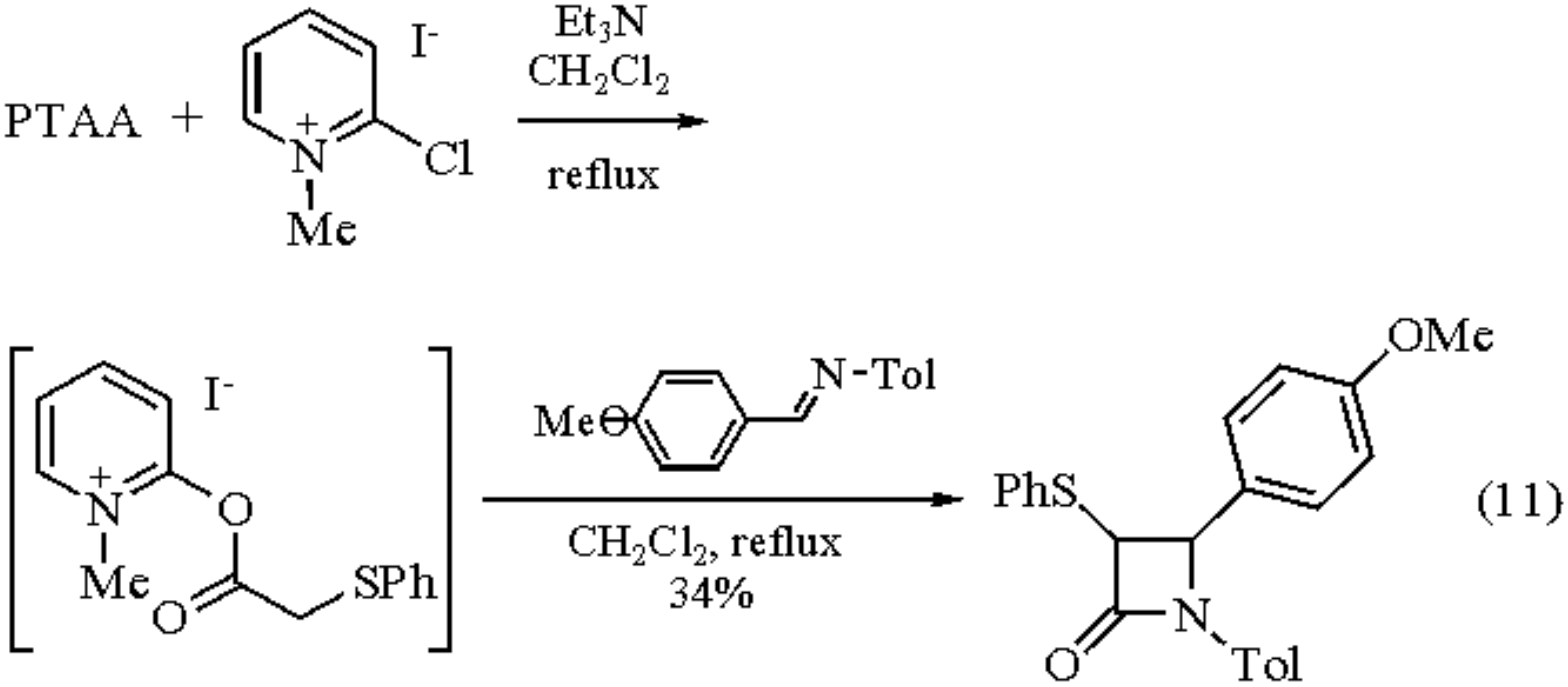

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Phenylthioacetylene

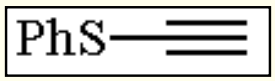

[6228-98-4] · C_8H_6S · Phenylthioacetylene · (MW 134.21)

(synthesis of phenylthioalkynes;[1] synthesis of phenyl thiolesters;[1a] synthesis of vinyl sulfides;[1b,1d,2] synthesis of carbonyl compounds[3])

Physical Data: bp 48-50 °C/1.5 mmHg, 86-88 °C/14 mmHg; *d* 1.084 g cm^{-3}.

Solubility: sol organic solvents.

Form Supplied in: pale yellow to dark brown-green liquid.

Analysis of Reagent Purity: gas chromatography; ^1H NMR.

Preparative Methods: stepwise elimination of HBr from the dibromide obtained by bromination of ***Phenyl Vinyl Sulfide*** (eqs 1 and 2).[4]

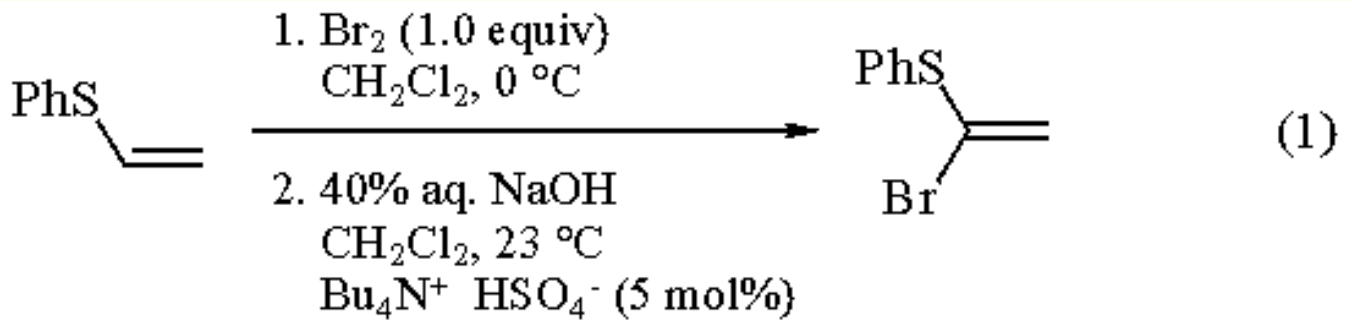

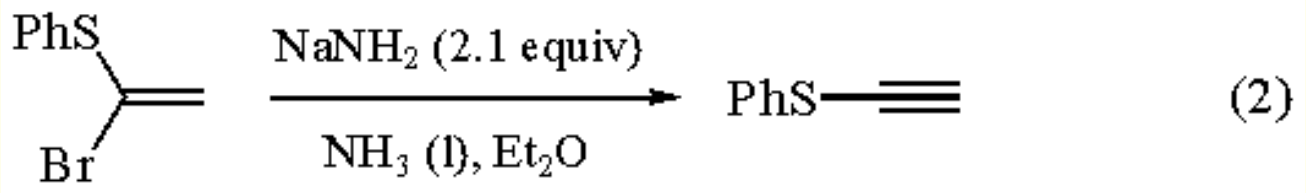

This procedure is recommended due to problems encountered with the reproducibility of the one-pot dehydrobromination of phenylthio-1,2-dibromoethane.[5] Phenylthioacetylene has also been prepared by elimination of thiophenol from *cis*-1,2-bis(phenylthio)ethylene,[6] dehydrobromination of the *cis* isomer of ***(E)-1-Bromo-2-phenylthioethylene***,[7] LDA-induced double elimination of ethanol from bromoacetaldehyde diethyl acetal,[8] and reaction of ***Lithium (Trimethylsilyl)acetylide*** with either

phenylsulfinyl chloride[9] or the relatively expensive ***Phenyl Benzenethiosulfonate***[1b,1d,10] and subsequent desilylation.

Purification: distillation at reduced pressure.

Handling, Storage, and Precautions: use in a fume hood; use immediately after distillation for best results (pale yellow); turns dark brown-green upon storage at -10 °C (freezer) and is stable for a few months under these conditions; methyl phenyl sulfide can act as a stabilizer, and the reagent shows no tendency to darken in its presence.[6b]

Phenylthioalkynes.

A large variety of phenylthio-substituted alkynes can be conveniently prepared via the reactions of phenylthioacetylene metalated derivatives (eqs 3-5);[1] this strategy is more flexible than the one based on nucleophilic substitution of a terminal alkali-metal acetylide with ***Phenyl Benzenethiosulfonate***,[1b,1d,10] ***Benzenesulfinyl Chloride***,[9] or ***Diphenyl Disulfide***.[11]

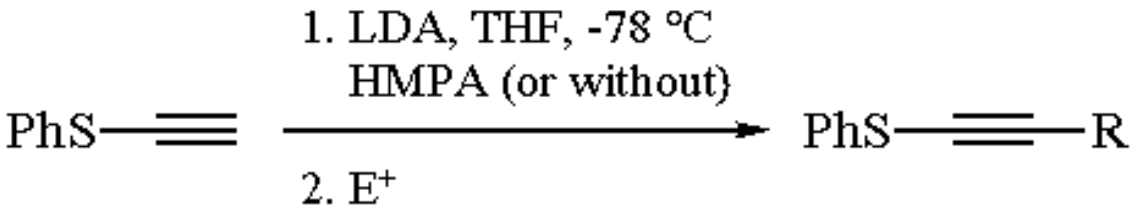

(3)

R = CH_2OH, $CH_2OTBDMS$, Me, Bu, TMS, $CH(OH)CH_2OTBDMS$, CO_2Me, $C(O)CH_2OTBDMS$, $CH_2OCH_2C(O)N(OMe)Me$

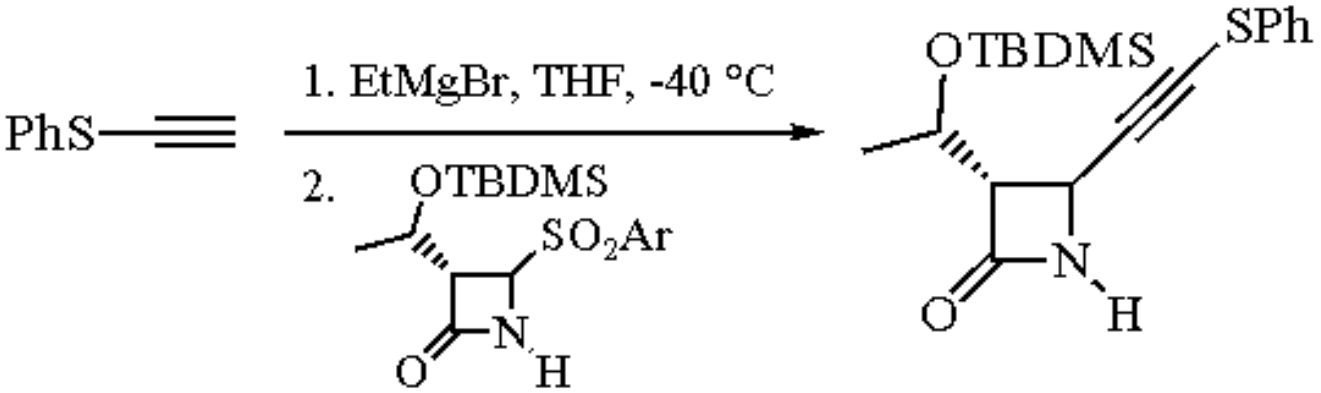

(4)

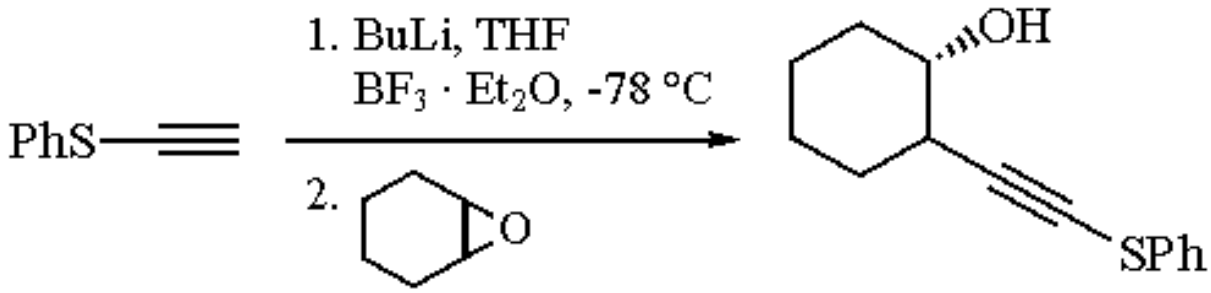

(5)

In addition to serving as precursors to vinyl sulfides, phenylthioalkynes can be hydrolyzed to phenyl thiolesters (eq 6).

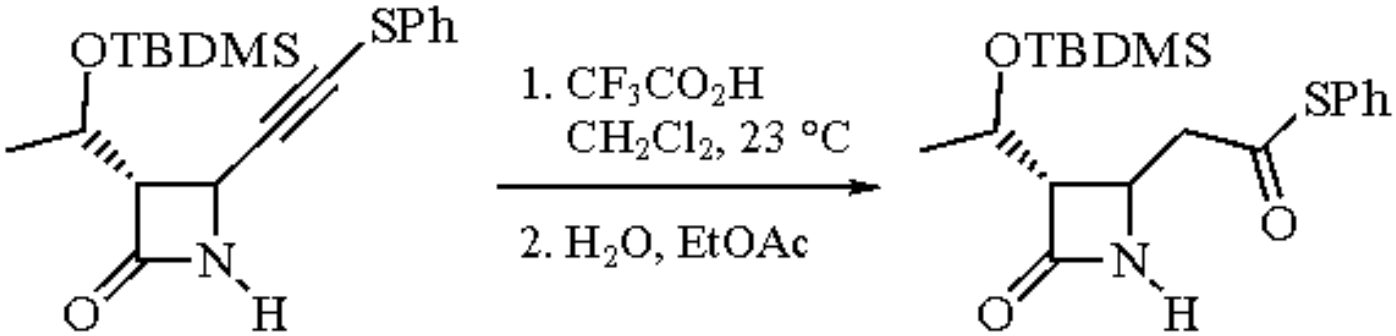

(6)

Vinyl Sulfides.

Regio- and stereoselective syntheses of functionalized vinyl sulfides[2] from phenylthioalkynes are accomplished by palladium(0)-catalyzed hydrostannation (eq 7),[1b] hydroboration,[12] treatment with low-valent tantalum,[13] stannylcupration,[5] or carbocupration.[14]

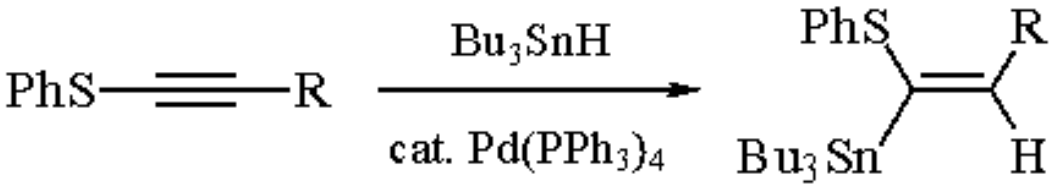

(7)

R = CH_2OH, $CH_2OTBDMS$, Me, Bu, TMS, $CH(OH)CH_2OTBDMS$, CO_2Me, $C(O)CH_2OTBDMS$, $CH_2OCH_2C(O)N(OMe)Me$, Ph

Vinyl sulfides have been shown to be very useful intermediates in organic synthesis, not only as carbonyl-masking moieties[3] but also in a variety of other transformations[15] including the nickel(0)-catalyzed cross-coupling reactions with alkyl, aryl, and alkenyl Grignard reagents.[16] The important role of the phenylthio group (and its higher oxidation states) in activating and directing alkenes in cycloaddition reactions has been reviewed.[17] The synthesis of the hexacarbonyldicobalt complex[18] and the polymerization of phenylthioacetylene[19] have also been described.

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Phenylthiobis(trimethylsilyl)methane[1]

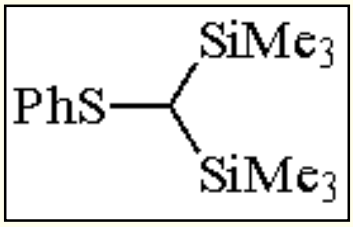

[62761-90-4] · $C_{13}H_{24}SSi_2$ · Phenylthiobis(trimethylsilyl)methane · (MW 268.62)

(formation of vinylsilanes and as a methoxycarbonyl anion equivalent)

Physical Data: bp 88 °C/0.16 mmHg.

Solubility: sol most common organic solvents.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Method: synthesized from phenylthiotrimethylsilylmethane.[2]

Handling, Storage, and Precautions: use in a fume hood.

Vinylsilane Preparation.

The most general utility of the title reagent (**1**) involves Peterson alkenation reactions. Deprotonation of this reagent, followed by addition to carbonyl-containing substrates, affords phenylthiovinylsilanes (eq 1).[3]

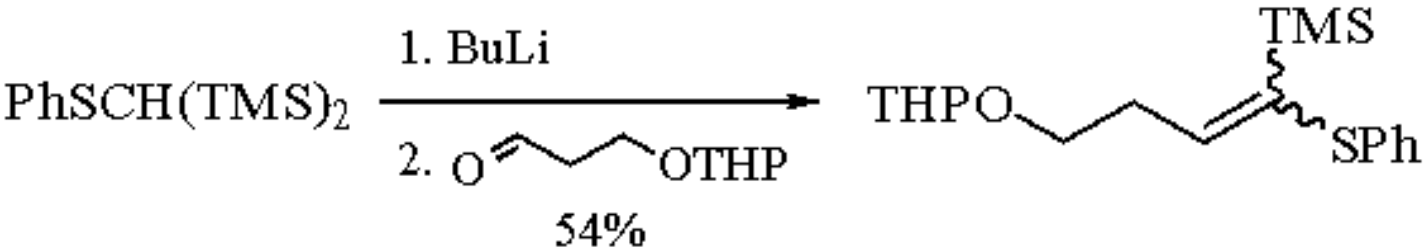

(1)

The reduction of the carbon-sulfur bond in (**1**) with ***Lithium Naphthalenide*** also produces an alkenation reagent (eq 2).[4] This protocol is limited, however, to use with nonenolizable ketones and aldehydes.

Lithiobis(trimethylsilyl)methane, the active intermediate in this reaction, can also be produced through the deprotonation of ***Bis(trimethylsilyl)methane***.

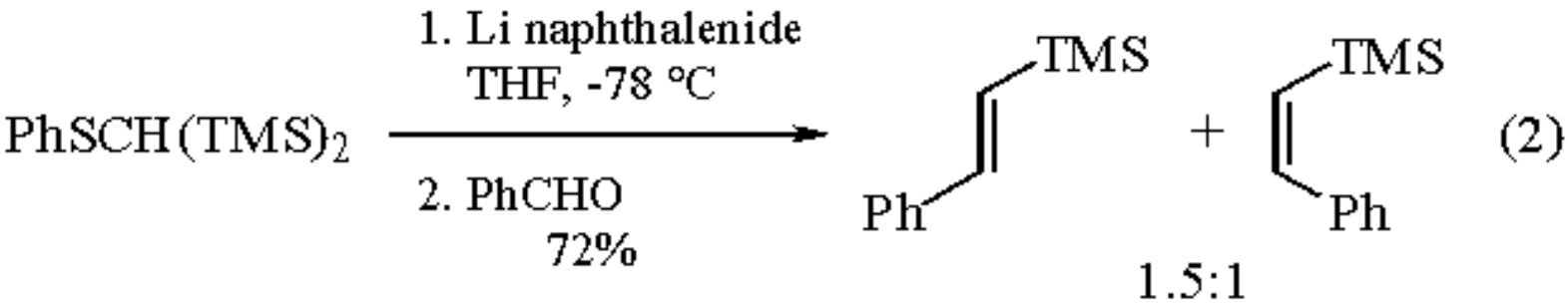

When (**1**) is treated with a fluoride source, a mild alkenation reagent is produced (eq 3).[5] The efficient transformation of enolizable ketones and aldehydes under these conditions, as opposed to the lithium naphthalenide reduction process, aptly demonstrates this fact.

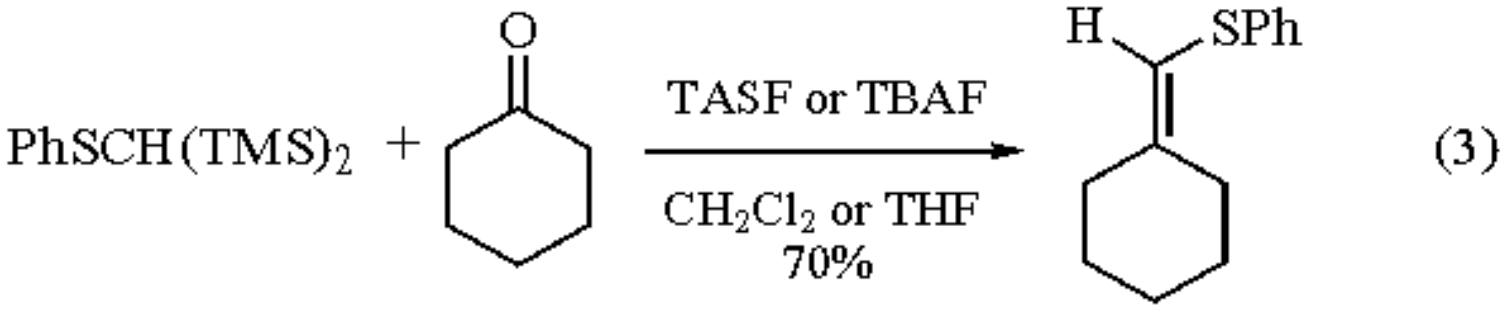

Conjugate Addition.

The lithium anion of (**1**) adds exclusively in Michael fashion to cyclohexenone (eq 4).[6] In comparison, lithiobis(phenylthio)methane predominantly adds to the carbonyl, providing a 2:1 mixture of the possible regioisomers. As with many other 1,4-conjugate additions, substitution at the alkene terminus alters the reaction regioselectivity (eq 5).[6]

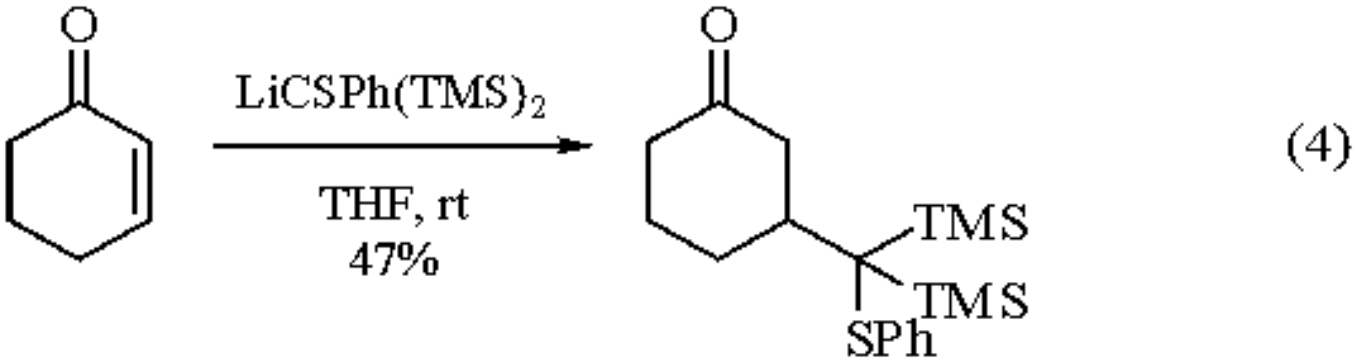

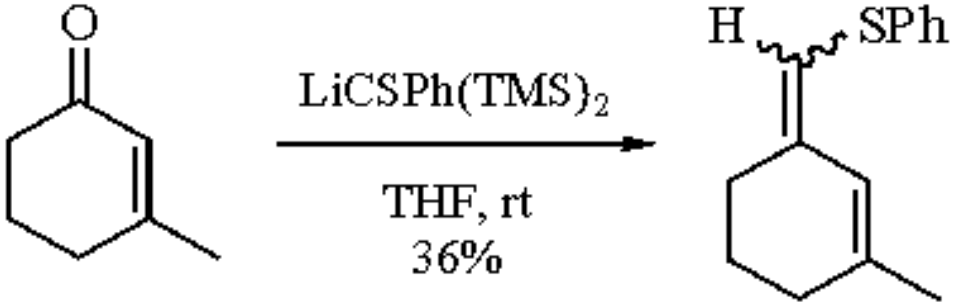

(5)

Homo-Peterson Alkenation.

Styrene oxide reacts with lithiophenylthiobis(trimethylsilyl)methane to afford cyclopropane-containing products (eq 6).[7] This reaction is limited, due to the complexity of its mechanism: the alkenation reagent must serve to generate both alkenic and carbenic species. For this reason, only styrene oxide and trimethylsilyloxirane undergo this transformation.

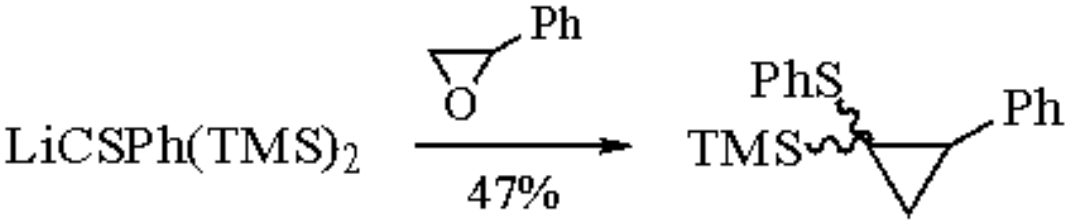

(6)

Methoxycarbonyl Anion Equivalent.

The alkylation of lithiophenylthiobis(trimethylsilyl)methane with an alkyl halide, followed by electrochemical oxidation of the resulting thiobis(silane), provides a homologated methyl ester (eq 7).[8] The electrochemical oxidation, due to its mild nature, can be tolerated by a wide variety of functional groups.

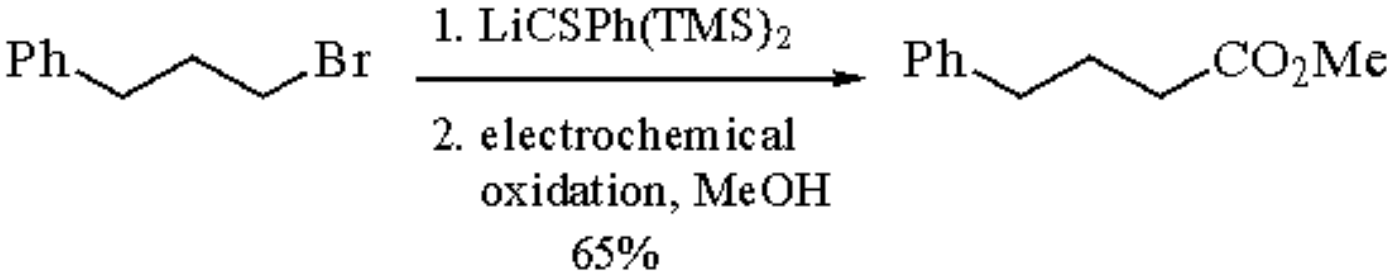

(7)

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1. For a review of organosulfur-silicon compounds, see: Block, E.; Aslam, M. *T* **1988**, *44*, 281.
2. Grobel, B.-T.; Seebach, D. *CB* **1977**, *110*, 852.
3. Hart, D. J.; Tsai, Y.-M. *JACS* **1984**, *106*, 8209.
4. Ager, D. J. *JOC* **1984**, *49*, 168.
5. Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Ganboa, I.; Cossio, F. P.; Lecea, B.; Lopez, C. *JOC* **1990**, *55*,

2498.
6. Ager, D. J.; East, M. B. *JOC* **1986**, *51*, 3983.
7. Schaumann, E.; Friese, C. *TL* **1989**, *30*, 7033.
8. Yoshida, J.; Matsunaga. S.; Murata, T.; Isoe, S. *T* **1991**, *47*, 615.

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Phenylthiocopper(I)

PhSCu

[1192-40-1] · C_6H_5CuS · Phenylthiocopper(I) · (MW 172.71)

(source of nucleophilic phenyl sulfide for preparation of lithium alkyl(phenylthio)cuprates and organophosphinecopper(I) phenylthiolate complexes)

Physical Data: mp 280 °C (dec).

Solubility: sol cold THF.

Form Supplied in: yellow solid; widely available.

Preparative Methods: one method is to treat ***Thiophenol*** with ***Copper(I) Oxide*** in ethanol at reflux to give phenylthiocopper as a yellow suspension (eq 1).[1-3]

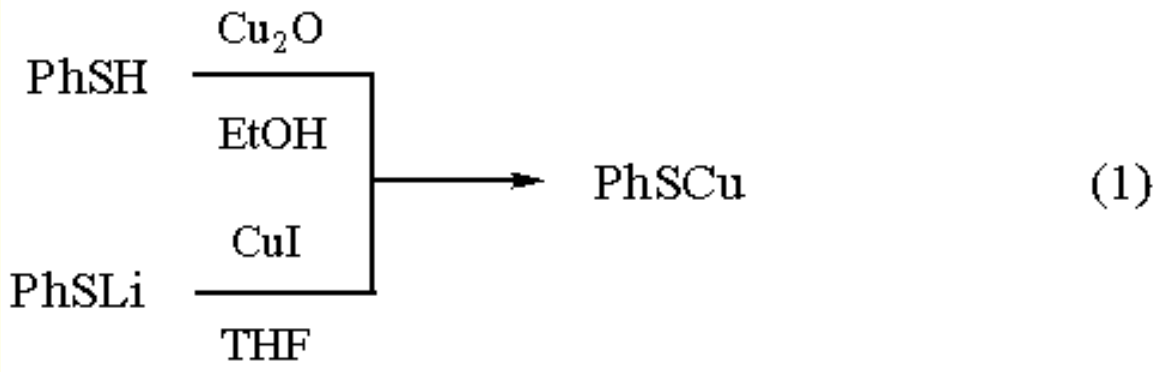

Alternatively, lithiation of thiophenol and quenching with ***Copper(I) Iodide*** affords a yellow solution, which is typically reacted in situ with organometallic reagents.[4]

Handling, Storage, and Precautions: use in a fume hood (stench).

Cuprate Reagents.

Lithium alkyl(phenylthio)cuprates, prepared by the addition of alkyllithiums to phenylthiocopper, are highly reactive reagents which effect selective alkyl group transfers (eq 2).[5] These cuprates have been employed in a singular approach to various cyclohexenone annulation products via α-acetone Gilman reagent addition to

cyclohexenecarboxylate (eq 3).[6] Michael additions of these copper reagents have also provided the regioselective alkylation of octahydroisoquinolines utilizing Grignard precursors (eq 4),[7] and 3-spiroannulation of cyclohexenones via an organobis(cuprate) (eq 5).[8] An example of a vinylcuprate addition to an alkyl iodide in the synthesis of graveolide has been reported (eq 6).[9]

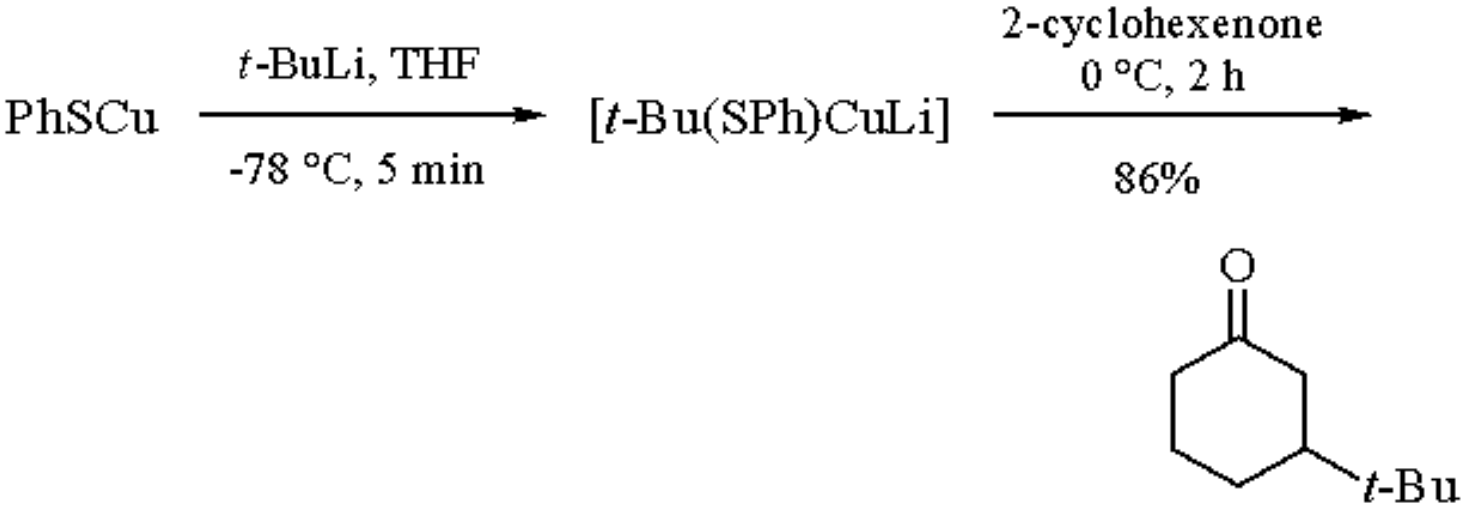

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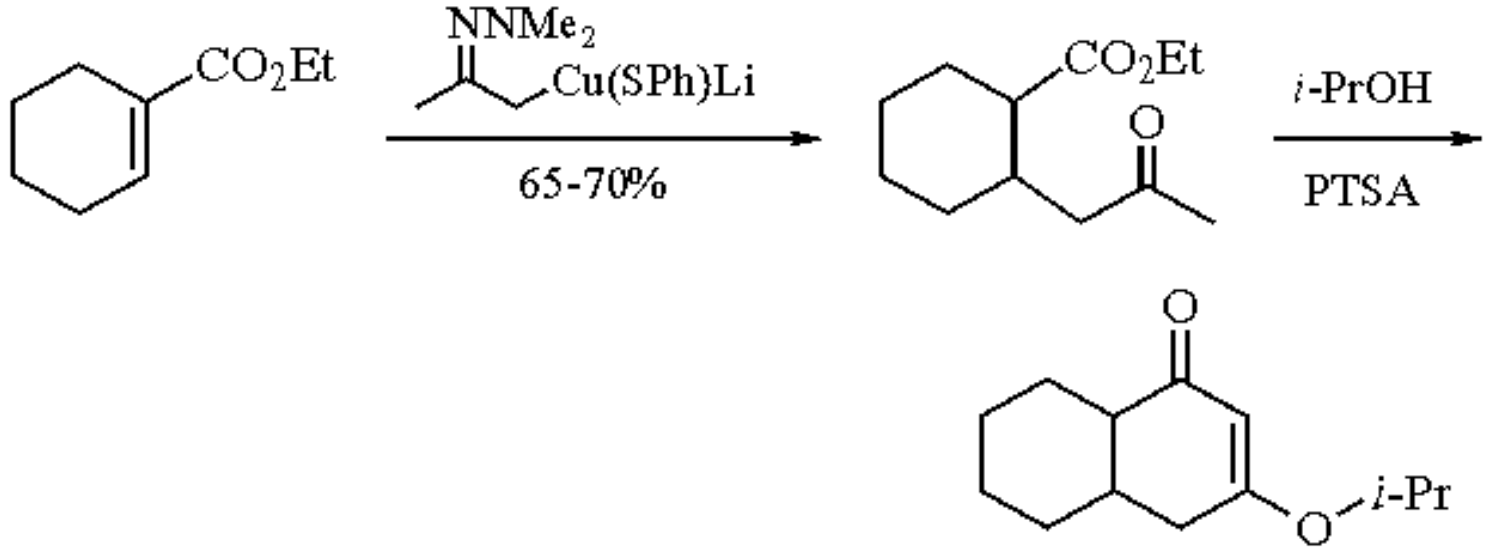

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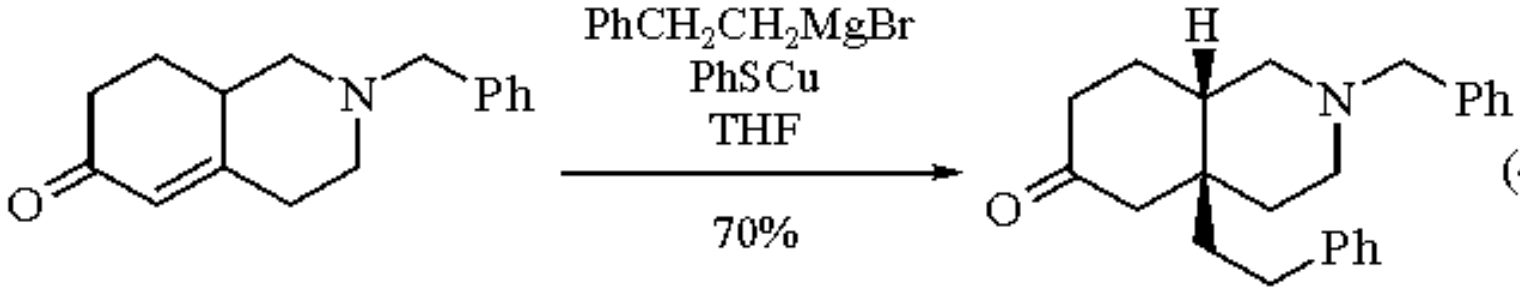

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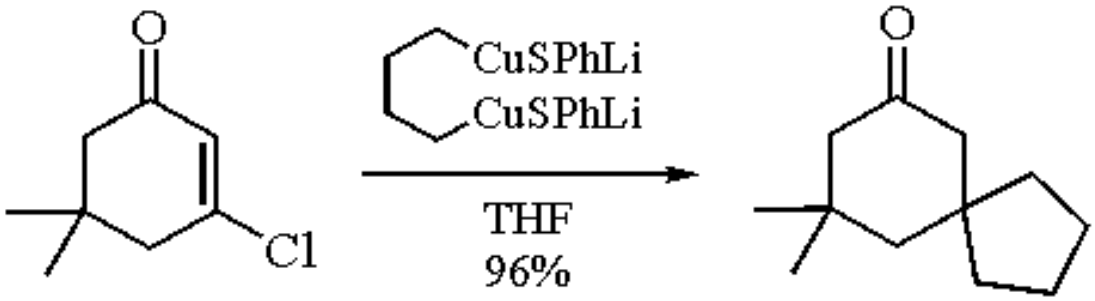

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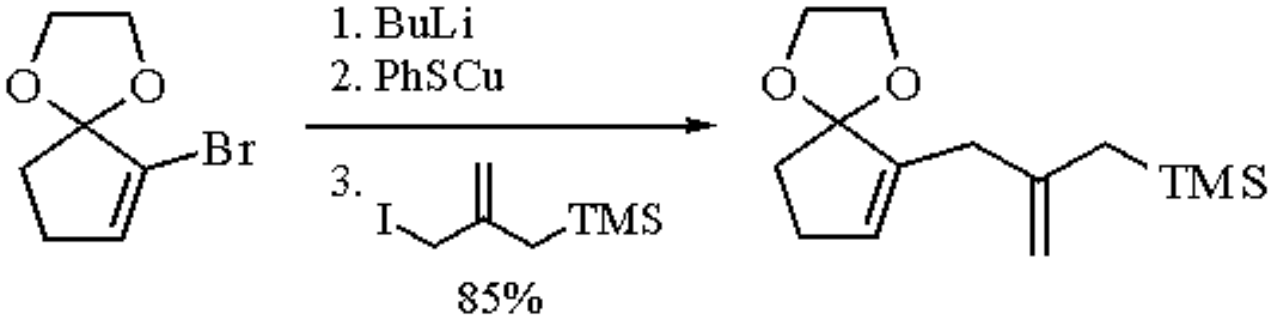

(6)

Miscellaneous.

Phenylthiocopper has been employed in displacement reactions of activated aryl bromides to give aryl phenyl sulfides (eq 7).[10] Reports of similar reactions of vinyl bromide derivatives have been published.[11] Organophosphinecopper(I) thiophenoxide complexes have been isolated by reaction of trialkylphosphines with PhSCu (eq 8).[12] When treated with liquid ***Sulfur Dioxide***, these complexes have formed sulfur dioxide adducts. Other applications of phenylthiocopper include thiophenolatocopper coating of Pt, Mo, and CdS,[13] and formation of thiol esters upon reaction with acid chlorides.[14]

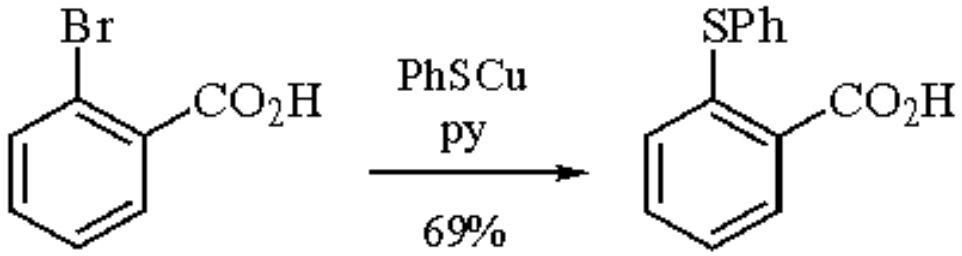

(7)

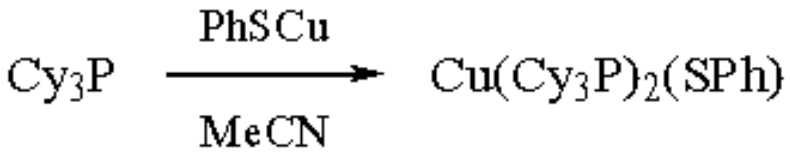

(8)

Related Reagents.

Lithium Cyclopropyl(phenylthio)cuprate; ***Lithium Methyl(phenylthio)cuprate***; ***Lithium Phenylthio(trimethylstannyl)cuprate***; ***Phenylselenocopper(I)***.

1. Adams, R.; Reifschneider, W.; Nair, M. D. *Croat. Chem. Acta* **1957**, *29*, 277.
2. Adams, R.; Reifschneider, W.; Ferretti, A. *OS* **1962**, *42*, 22; *OSC* **1973**, *5*, 107.
3. Posner, G. H.; Brunelle, D. J.; Sinoway, L. *S* **1974**, 662.
4. Posner, G. H.; Whitten, C. E. *OS* **1976**, *55*, 122; *OSC* **1988**, *6*, 248.
5. Posner, G. H.; Whitten, C. E.; Sterling, J. J. *JACS* **1973**, *95*, 7788.
6. Corey, E. J.; Boger, D. L. *TL* **1978**, 4597.
7. Bartmann, W.; Guntrum, E.; Urbach, H.; Wunner, J. *SC* **1988**, *18*, 711.
8. Wender, P. A.; White, A. W. *JACS* **1988**, *110*, 2218.
9. Majetich, G.; Song, J.; Leigh, A. J.-S.; Condon, S. M. *JOC* **1993**, *58*, 1030.
10. Arhart, R. J.; Martin, J. C. *JACS* **1972**, *94*, 4997.
11. Adams, R.; Ferretti, A. *JACS* **1959**, *81*, 4927.
12. Eller, P. G.; Kubas, G. J. *JACS* **1977**, *99*, 4346.
13. Reeves, J. H.; Cocivera, M. *CC* **1982**, 1003.
14. Reissig, H.-U.; Scherer, B. *TL* **1980**, *21*, 4259.

William J. Hoekstra

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Phenylthiocyclopropane[1a,1c]

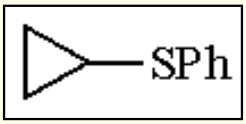

[14633-54-6] · $C_9H_{10}S$ · Phenylthiocyclopropane · (MW 150.26)

(a particularly valuable building block able to transfer a three-carbon unit to various organic molecules, allowing the synthesis of cyclobutanones from aldehydes or ketones)

Alternate Name: cyclopropyl phenyl sulfide.

Physical Data: bp 51-52 °C/0.1 mmHg or 62-63 °C/1 mmHg.[2]

Preparative Methods: easily prepared from 1-phenylthio-3-chloropropane (itself obtained on reaction of 1-bromo-3-chloropropane and phenylthiolates) and ***Potassium Amide*** in liquid ammonia (eq 1).[3]

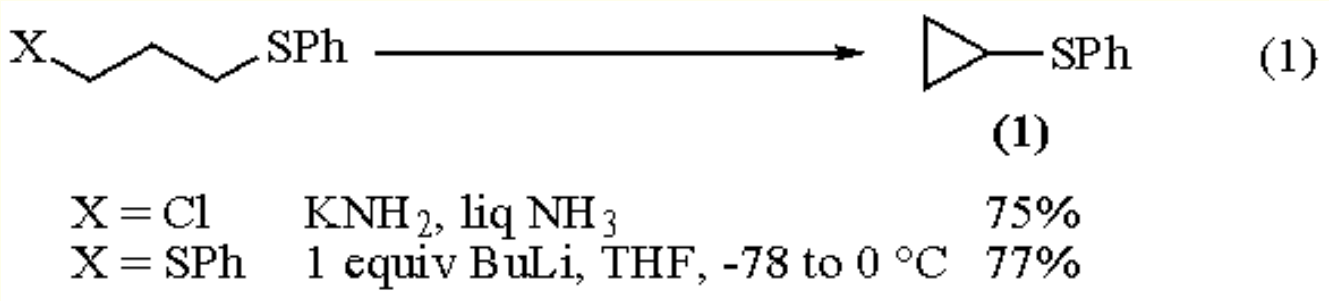

1,3-Bis(phenylthio)propane reacts with ***n-Butyllithium*** in THF to produce the title reagent (**1**) on reaction with only 1 equiv *n*-Buli, or 1-lithio-1-phenylthiocyclopropane (**2**) if 2 equiv are used (eq 2).[4,5]

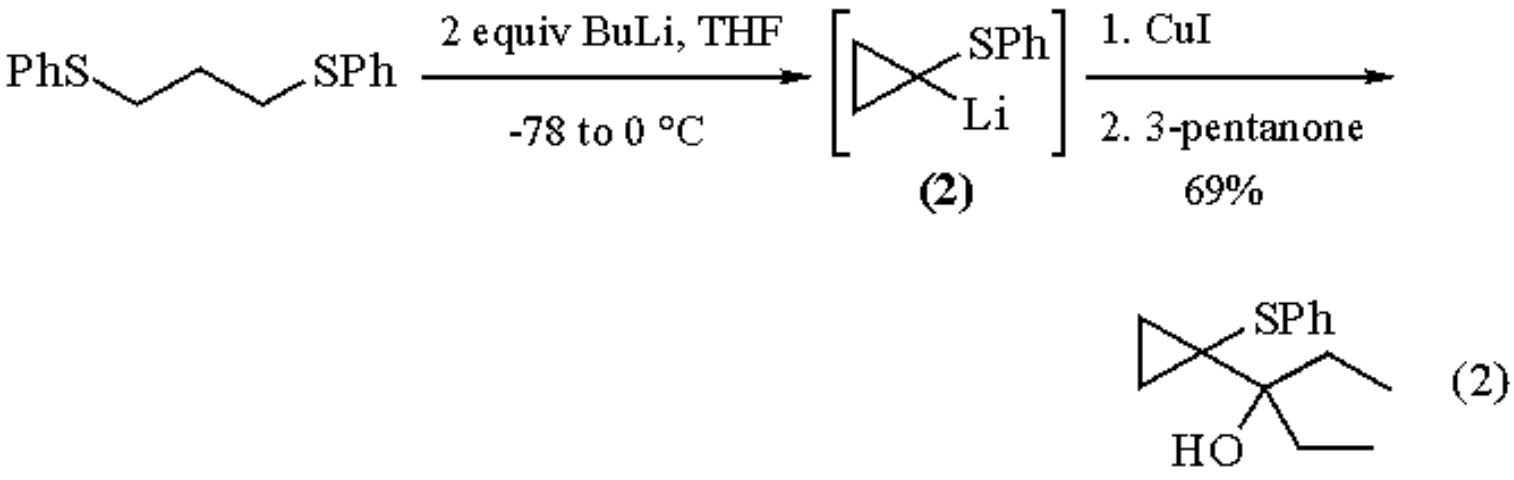

(2)

(**1**) has also been synthesized from 3-tributylstannylpropanal (available from tributylstannyllithium and ***Acrolein***) and trimethylsilyl phenyl sulfide in the presence of ***Titanium(IV) Chloride*** as acid catalyst (eq 3),[6] and on

substitution of (i) ***Cyclopropyllithium*** with ***Diphenyl Disulfide*** (eq 4), (ii) cyclopropyl bromide with potassium benzenethiolate (eq 5)[7] or (iii) 1,1-dibromocyclopropane,[8] also with benzenethiolates, and by reduction of α-bromocyclopropyl phenyl sulfide with sodium methanethiolate (eq 6).[9] In addition, cyclopropyl phenyl sulfoxide can be reduced to (**1**) in more than 70% yield with ***Chlorotrimethylstannane***-benzenethiol (eq 7).[10]

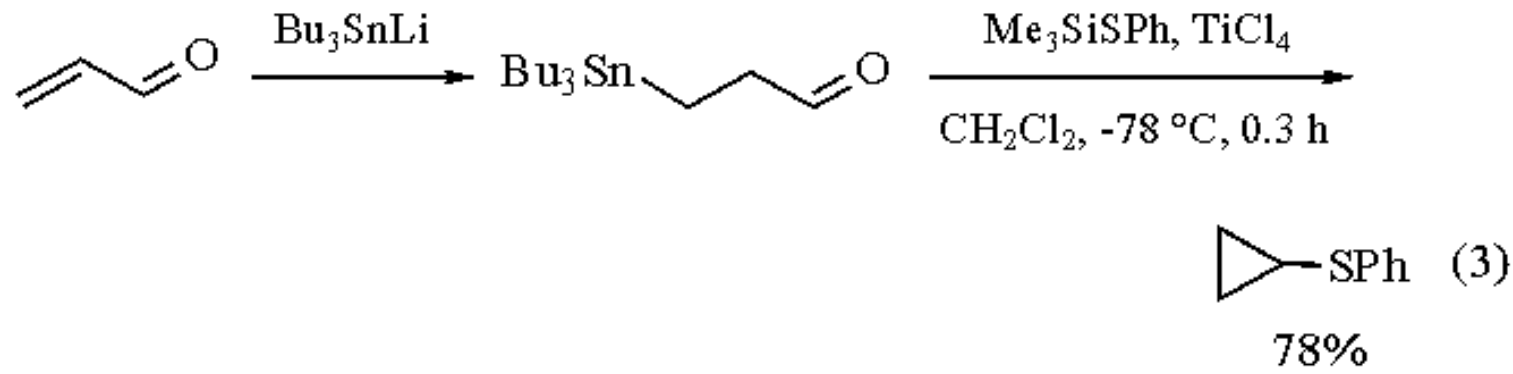

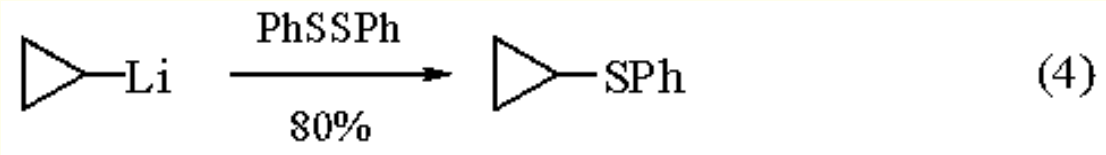

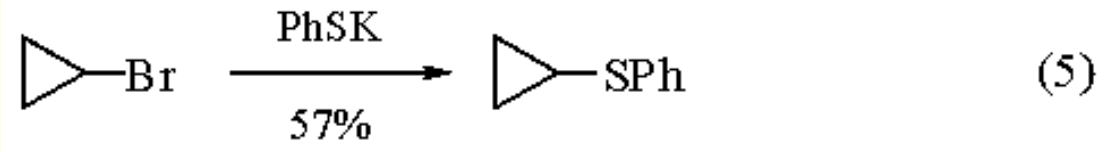

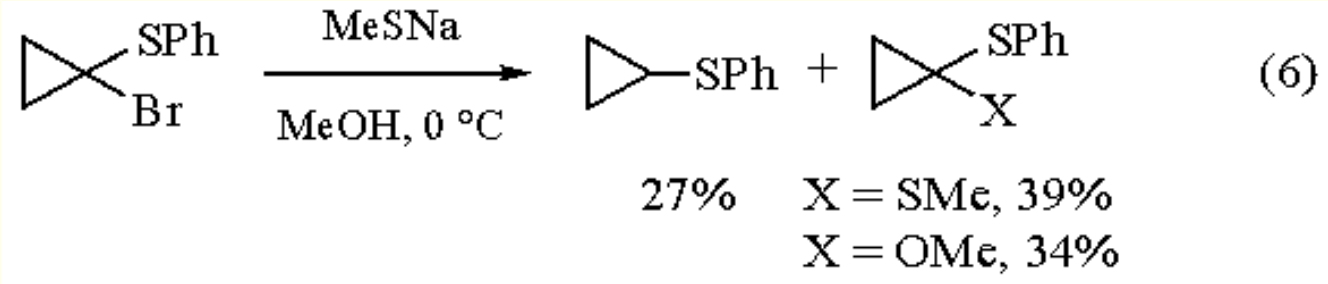

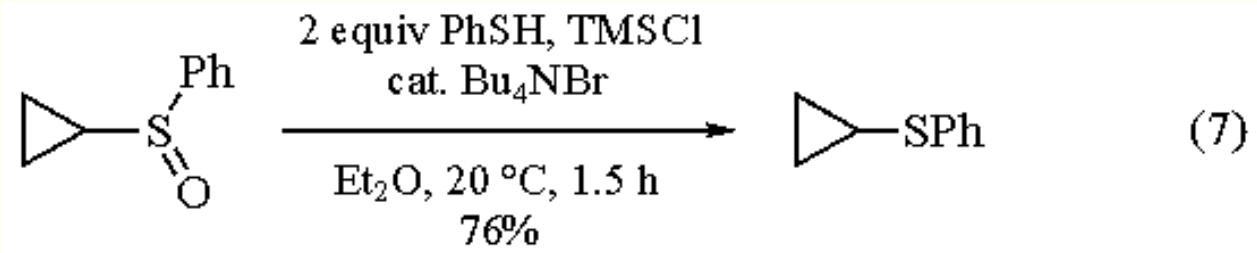

Handling, Storage, and Precautions: use in a fume hood.

Reactions of Phenylthiocyclopropane.

The reactions of (**1**) are those typical of sulfides. Oxidation or alkylation can occur at the sulfur, whereas halogenation or

metalation can occur on the cyclopropane ring at the carbon bearing the phenylthio group. The latter reaction, which produces phenylthiocyclopropyllithium, is the one most frequently used in organic synthesis. (**1**) also reacts with ***Hydrogen Chloride*** and ***Hydrogen Bromide*** to produce thiophenol,[11] and higher homologs provide ethyl ketones in reasonably good yields (eq 8).[12]

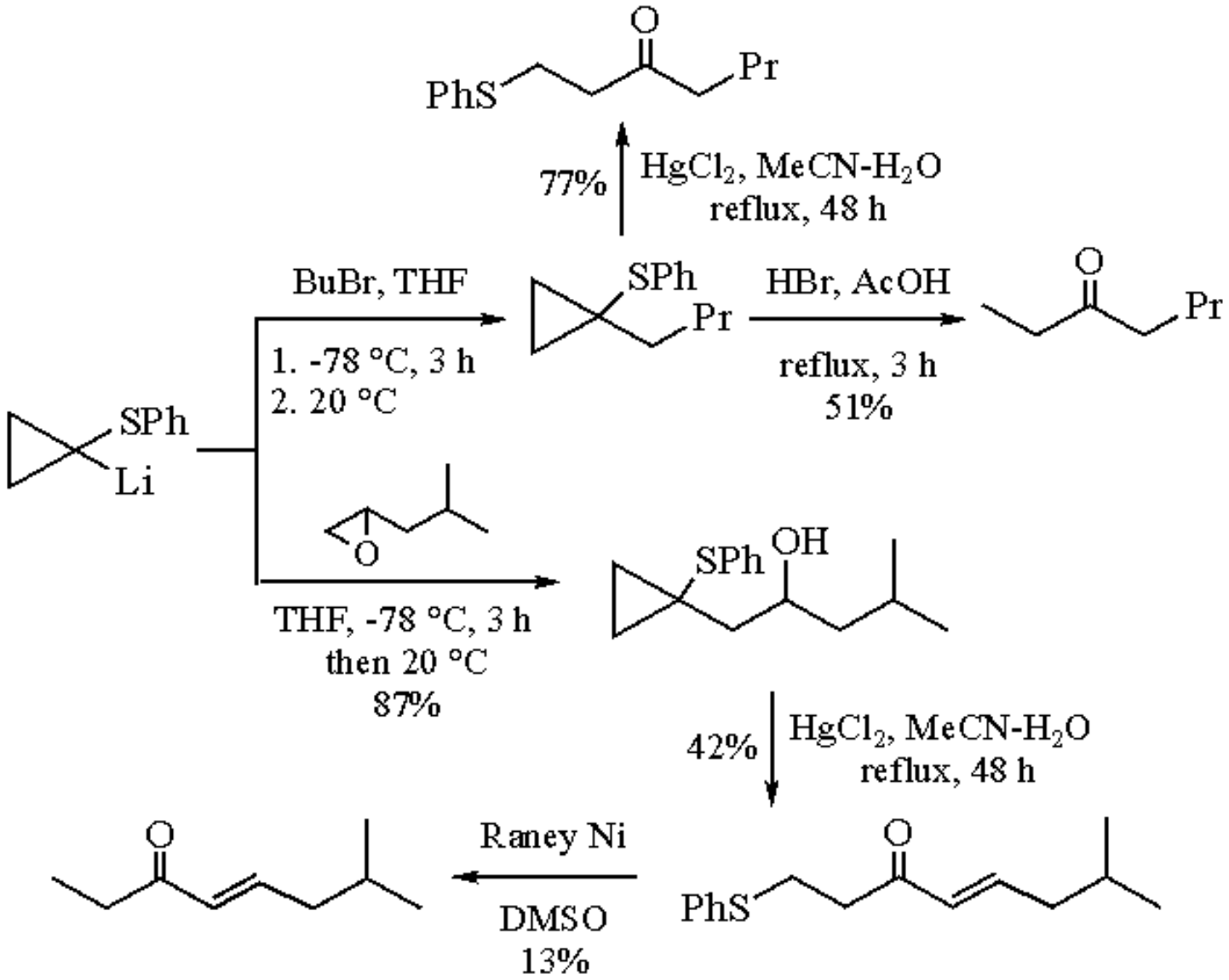

(8)

Oxidation and Alkylation of Phenylthiocyclopropane.

Oxidation of (**1**) to the corresponding sulfoxide, sulfone, and sulfoximine is easily achieved. However, the best synthetic route to the sulfone involves the cyclization of 3-halopropyl phenyl sulfone on reaction with bases.[3] Oxidation to the sulfoxide has been typically carried out with peroxy acids or ***Sodium Periodate*** (eq 9, route a).[13-15] Asymmetric oxidation of (**1**) has been efficiently carried out by Holland[14] using the fungus *Mortierella isabellina* ((*R*)-cyclopropyl phenyl sulfoxide, 58% yield, ee 66%) or better by Kagan[16] using the modified Sharpless method (***Titanium Tetraisopropoxide*** (+)-diethyl tartrate, H_2O, ***t-Butyl Hydroperoxide***, CH_2Cl_2, -20 °C, 24 h, (*R*)-cyclopropyl phenyl sulfoxide, 73% yield, ee 95%) or by Davis[17,18] using (-)-α,α-dichlorocamphorsulfonyloxaziridine (CCl_4, 20 °C, 18 h, (*S*)-cyclopropyl phenyl sulfoxide, 90% yield, ee 92%).

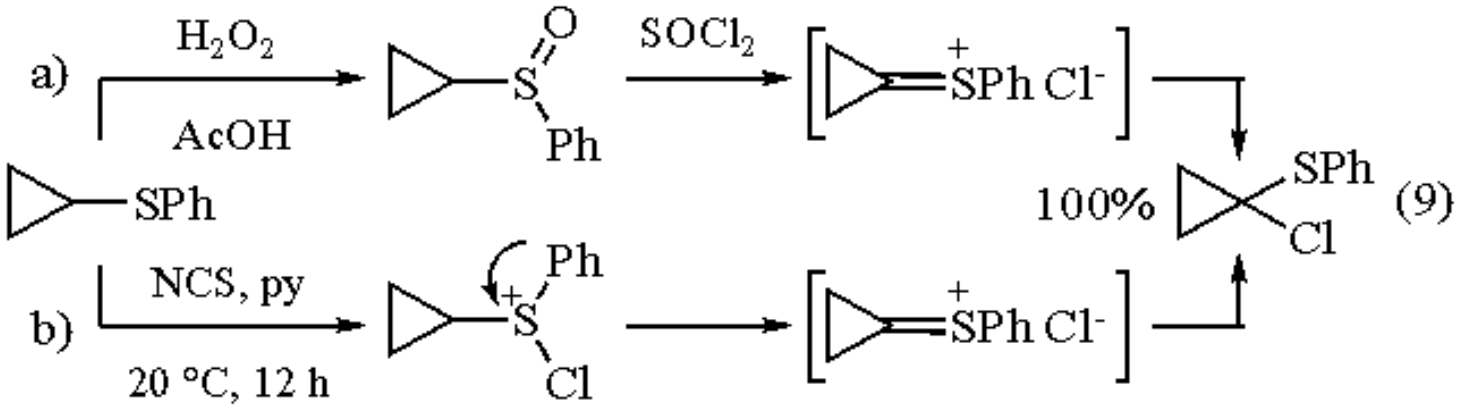

Acid-catalyzed addition of (**1**) to ***1,4-Benzoquinone***, followed by methylation of the resulting dihydroxysulfonium salt with ***Diazomethane*** affords the corresponding diarylcyclopropylsulfonium salt in reasonably good yield (eq 10).[19] Otherwise the synthesis of ***Cyclopropyldiphenylsulfonium Tetrafluoroborate***, a valuable precursor of the corresponding cyclopropylide, is best achieved by cyclization in basic media of 3-chloro-1-propyldiphenylsulfonium tetrafluoroborate.[20] The synthesis of the related (dimethylamino)cyclopropylsulfonium tetrafluoroborate has been carried out from cyclopropyl phenyl sulfoxide by a sequence which involves reaction with ***Hydrazoic Acid*** (eq 11).[13]

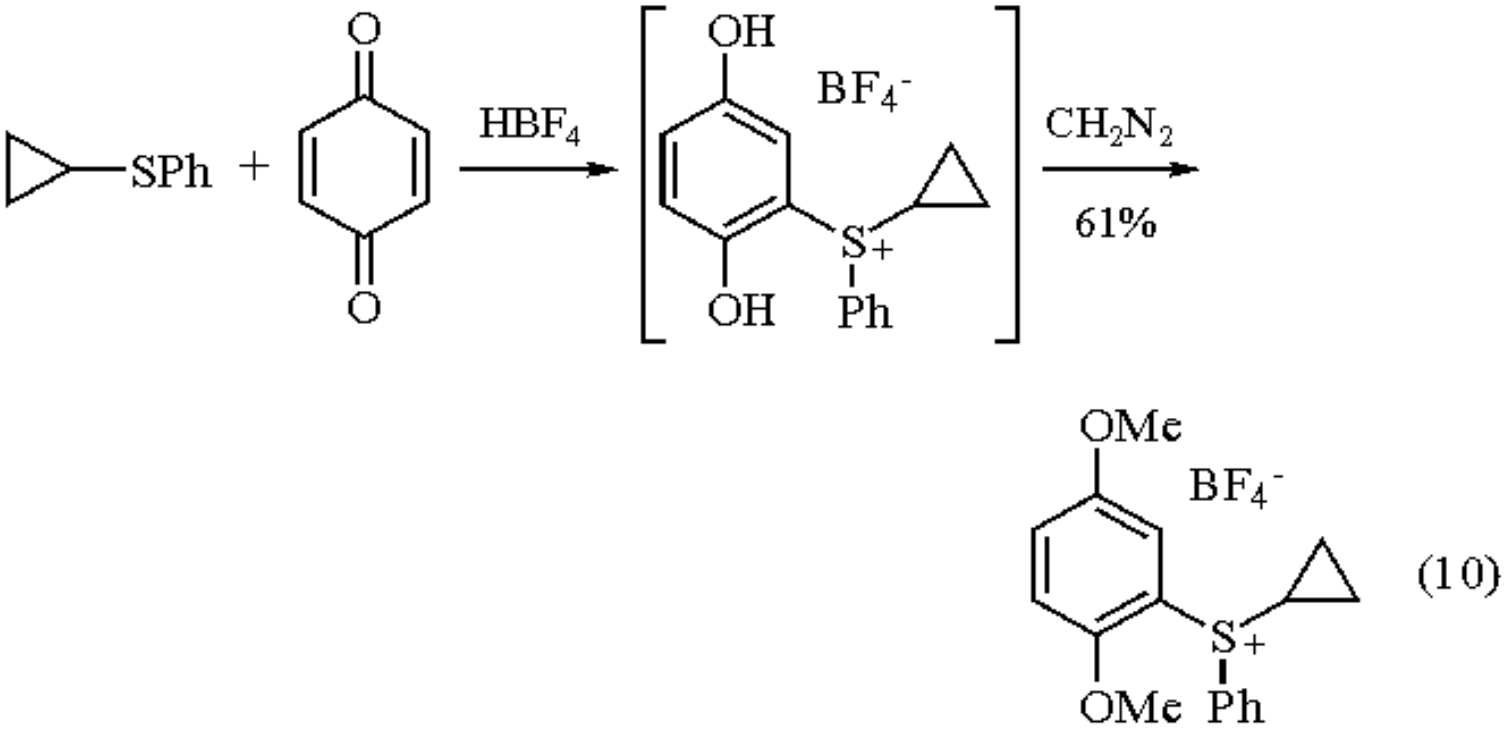

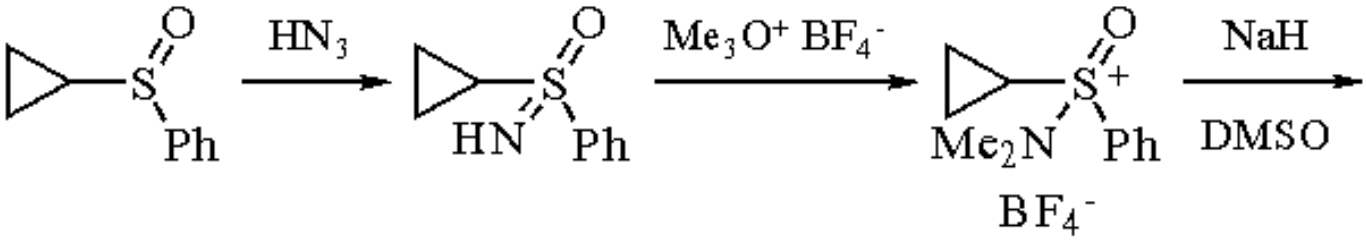

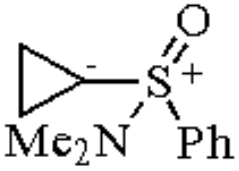

(11)

(**1**) reacts with ***N-Chlorosuccinimide*** (1.2 equiv NCS, pyridine, benzene, 20 °C, 12 h) to produce 1-chloro(phenylthio)cyclopropane in quantitative yield (eq 9, route b).[15,21] Similar results are obtained from cyclopropyl phenyl sulfoxide and ***Thionyl Chloride*** (1.2 equiv $SOCl_2$, CH_2Cl_2, 20 °C, 2 h) or ***Sulfuryl Chloride*** in the presence of pyridine (eq 9, route a).[15,21] It is remarkable that ring-opened products are not found in these reactions, since solvolysis of 1-chloro(phenylthio)cyclopropane affords some allylic derivatives. These chlorinations may proceed via the initial formation of chlorosulfonium salts, which then decompose affording the α-chloro sulfides through an ylide-ylidene ion-pair intermediate as in the Pummerer reaction, rather than involving a free carbonium ion.[15,21]

The synthesis of 1-iodo(phenylthio)cyclopropane has been achieved by metalation of (**1**) with ***n-Butyllithium*** and subsequent reaction with iodine (eq 12).[22] This compound is a valuable precursor of 1-methoxy(phenylthio)cyclopropane and of 1-lithio-1-methoxycyclopropane.[22,23] 1-Methoxy(phenylthio)cyclopropane has also been synthesized from cyclopropyl phenyl sulfoxide via a sequence of reactions which involve the intermediate formation of the corresponding methoxysulfonium salt and its rearrangement (of Pummerer type) on reaction with sodium methoxide in methanol (eq 13).[24]

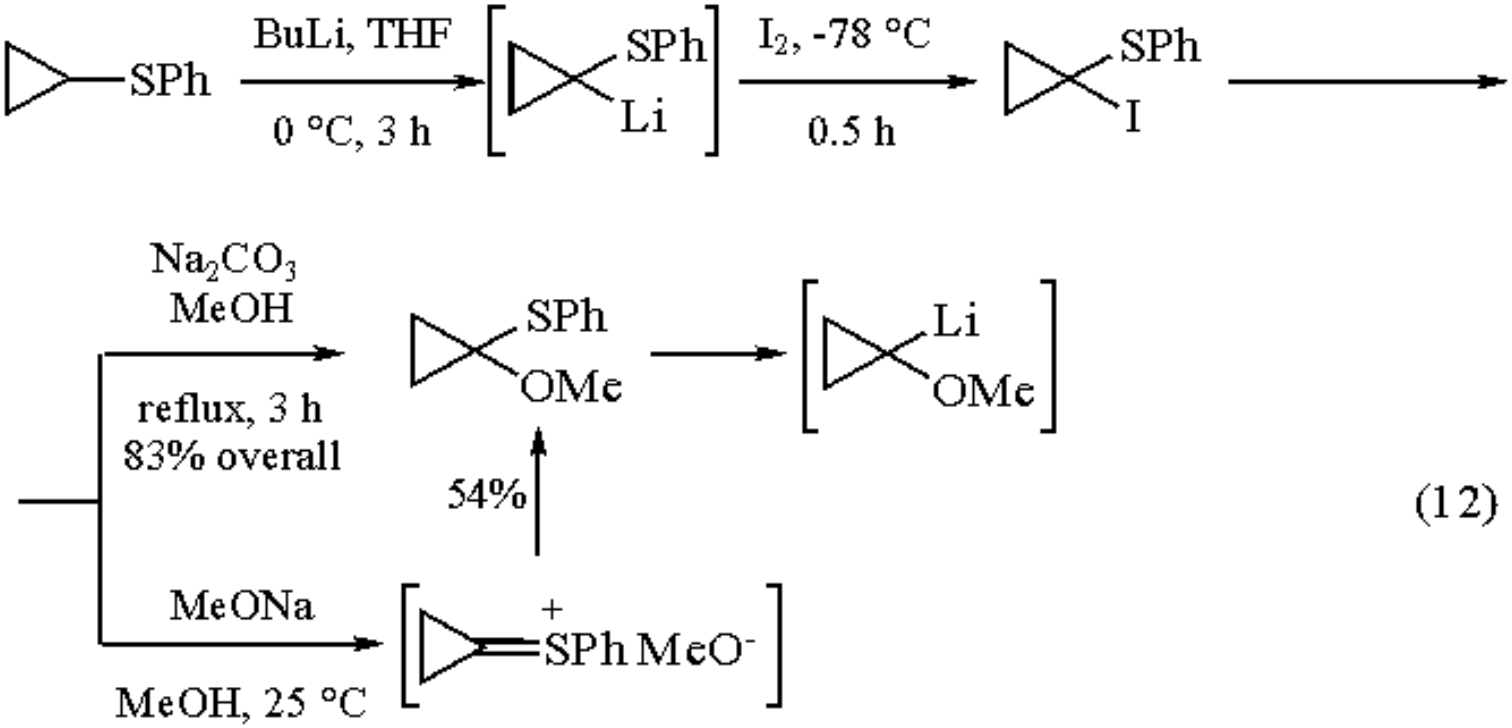

(12)

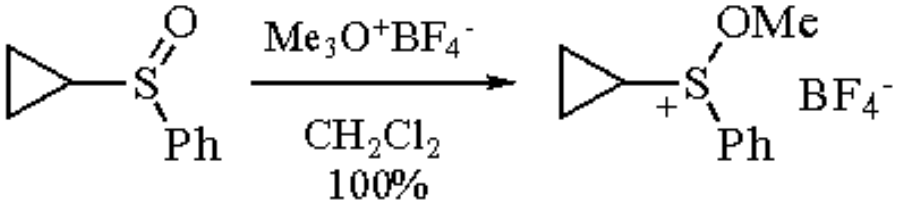

(13)

Reactions involving 1-Lithio-1-phenylthiocyclopropane (2).

This compound is easily synthesized according to the Trost procedure by metalation of (**1**) with *n*-butyllithium (1 equiv, THF, 0 °C, 2 h, 20 °C, 2 h, >90% yield) (eq 12).[1a,25-28] (**2**) is the only α-thio carbanion bearing two alkyl substituents to be generated by hydrogen-metal exchange.[29] It has been alternatively generated[4,5] from 1,3-bis(phenylthio)propane and 2 equiv *n*-butyllithium in THF (-78 to 0 °C, >85% yield, eq 2), or by reductive lithiation of 1,1,3-tris(phenylthio)propane[30] and of 1,1-bis(phenylthio)cyclopropane[31] using ***Methyllithium-N,N,N´,N´-Tetramethylethylenediamine*** or 1-(dimethylamino)naphthalenide, respectively.

(**2**) is a useful reagent in the preparation of:

- 1)cyclobutanones,[1a,26-28,32-35] including cyclobutanone itself (eq 14),[26] the α-vinyl[1a,27,28,32,35-39] and α-aryl[40] analogs, α-(1-phenylthiocyclopropyl)cyclobutanones,[41] γ-ketocyclobutanones,[42] 2-alkyl(or aryl)-1,1-bis(phenylthio)cyclobutanes (eq 15),[43] 1-phenylthiocyclobutenes (eq 15),[28,32,44] 3-alkyl(or aryl)-2-(phenylthio)-1,3-butadienes (eq 15),[43] cyclobutanes,[32,44] annulated cyclopentanones[45] cyclohexen-3-ols,[38] γ,δ-cyclooctenones,[36]
- 2)alkylidenecyclopropanes (eq 16),[46] allylidenecyclopropanes (eq 17),[47] γ-keto sulfides (eq 8),[12] ethyl ketones (eq 8),[12] γ-methoxycarbonyl-1,1-bis(phenylthio)acetals,[35] vinyl sulfides (eq 18),[48] 1-methoxy-1-(phenylthio)cyclopropane (eq 13),[22] and 1-trimethylsilyl-1-(phenylthio)cyclopropane,[31,49] as well as 1-lithio-1-methoxycyclopropane (eq 12) and 1-lithio-1-trimethylsilylcyclopropane.[49]

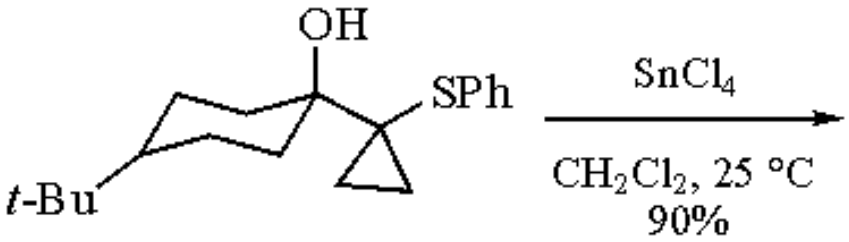

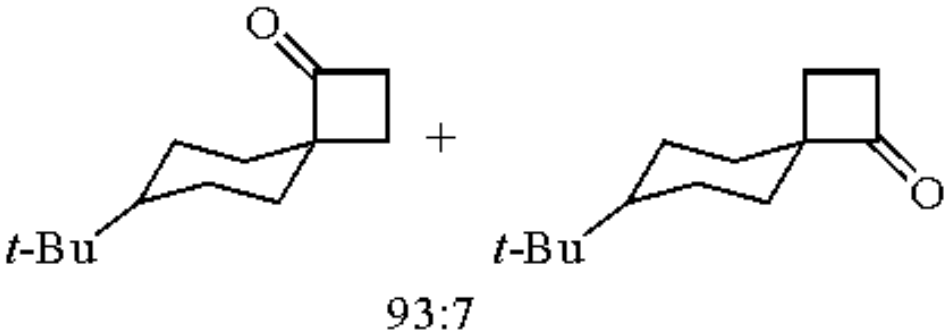

(14)

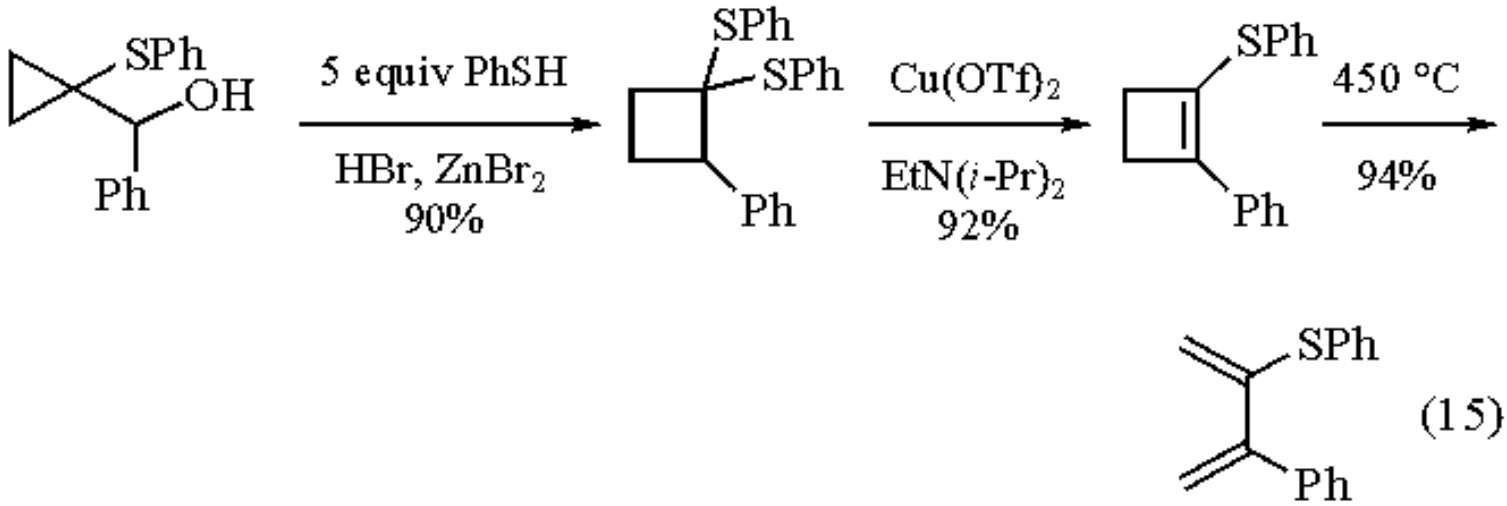
SPh
OH
Ph
5 equiv PhSH
HBr, ZnBr2
90%
SPh
SPh
Ph
Cu(OTf)2
EtN(i-Pr)2
92%
SPh
Ph
450 °C
94%
SPh
Ph

(15)

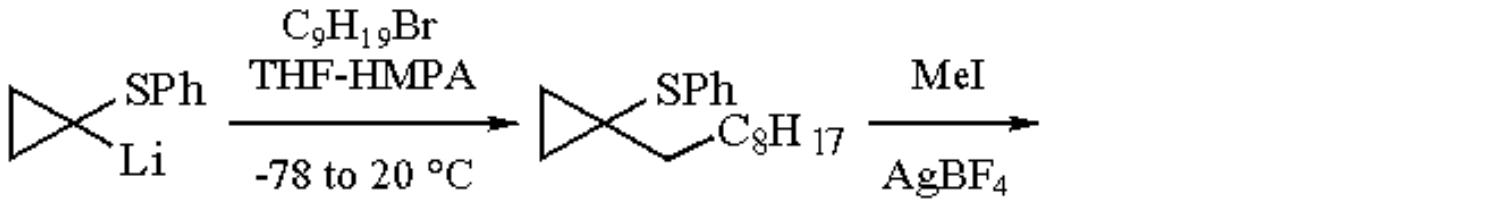
SPh
Li
C9H19Br
THF-HMPA
-78 to 20 °C
SPh
C8H17
MeI
AgBF4

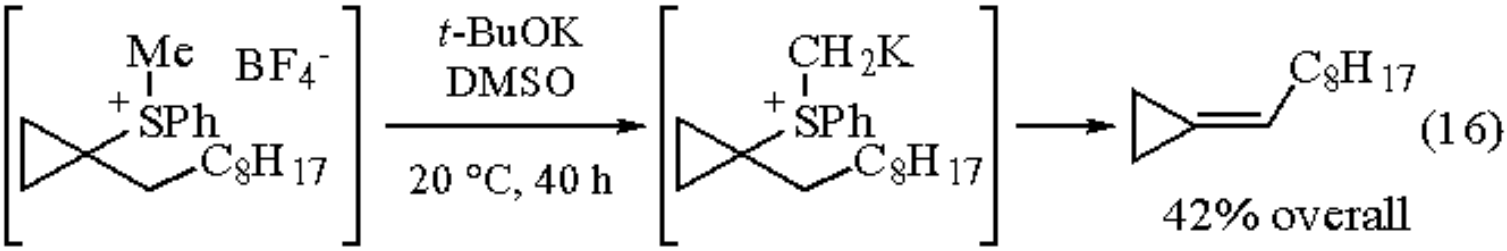
Me
BF4-
+SPh
C8H17
t-BuOK
DMSO
20 °C, 40 h
CH2K
+SPh
C8H17
C8H17
42% overall

(16)

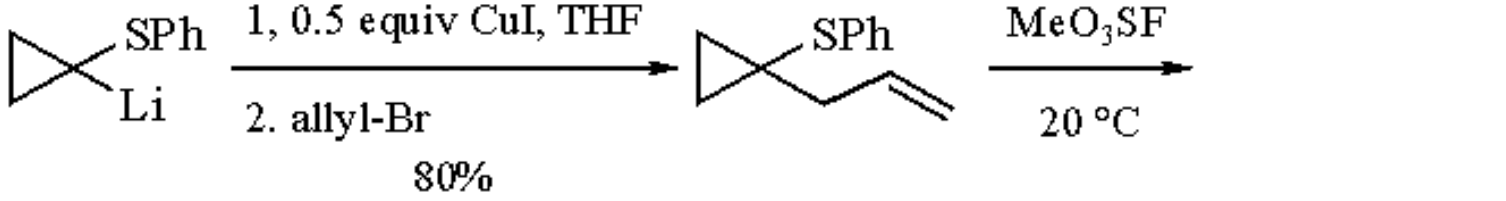
SPh
Li
1, 0.5 equiv CuI, THF
2. allyl-Br
80%
SPh
MeO3SF
20 °C

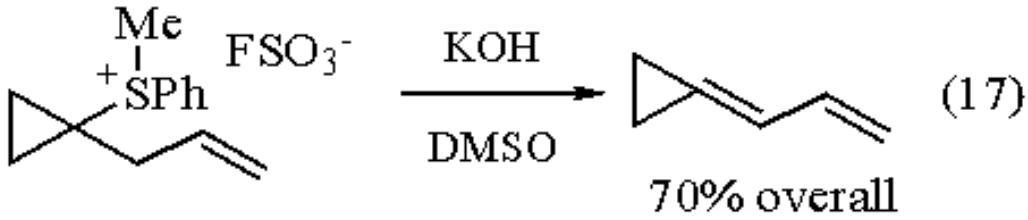
Me
+SPh
FSO3-
KOH
DMSO
70% overall

(17)

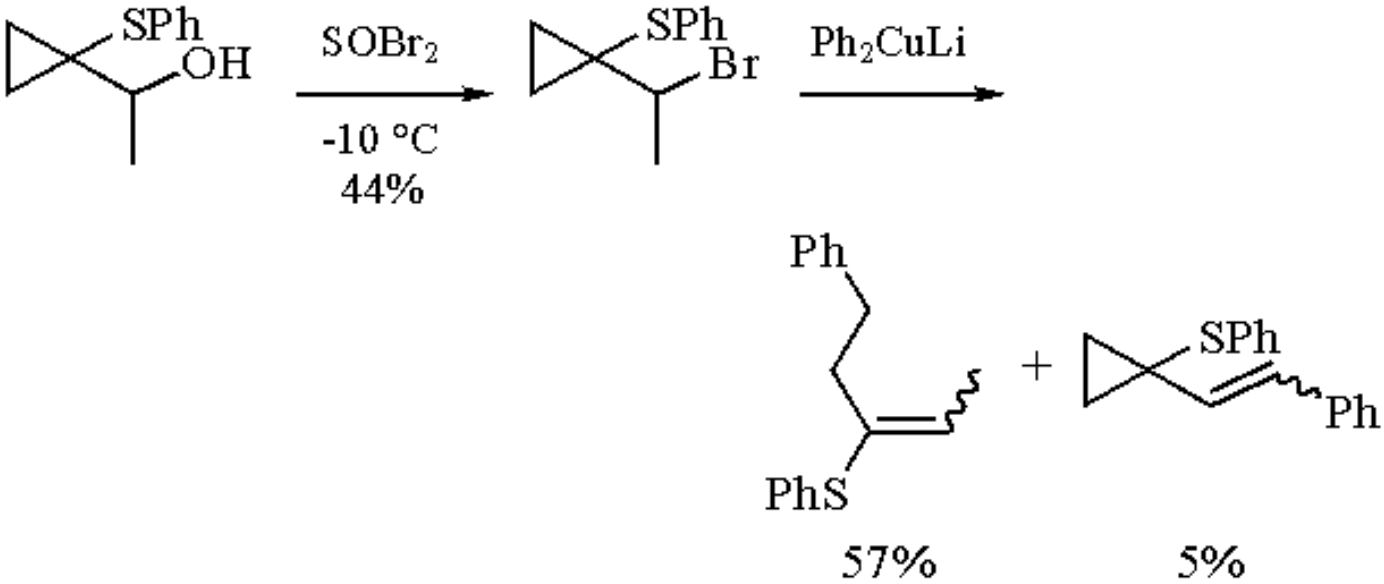

(18)

1-Lithio-1-phenylthiocyclopropane reacts with many electrophiles. In reactions where lithium phenylthiolate is formed (from cyclopropanone thioacetal or from 1,3-bis(phenylthio)propane), ***Copper(I) Iodide*** is used to scavenge the thiolate to improve yields of alkylated or hydroxyalkylated derivatives.[5,31]

Very high yields of β-hydroxyalkyl sulfides are obtained from saturated aldehydes and ketones,[1a,4,5,25-28,32,34,40,43,44,50] including ***Formaldehyde*** (80% yield)[26] and hindered or quite enolizable ketones such as tetramethylcyclohexanone (92% yield)[25,27] or trispiro[3.1.3.1.3.1]pentadecane-1,5,10-trione (54% yield) (eq 19).[44] The reaction occurs regioselectively on the carbonyl group of α,β-unsaturated aldehydes and ketones,[1a,25,27,32,37-39,45,51] including 2-hydroxymethylene ketones,[42] and proceeds stereoselectively with 4-*t*-butylcyclohexanone to produce almost exclusively the alcohol resulting from an equatorial attack (THF, 0 °C, 98% yield, 99:1 ratio of stereoisomers, eq 14).[28] With α-selenoaldehydes, (**2**) leads predominantly to the stereoisomer of β-hydoxyalkyl selenide predicted on the basis of Cram's rules.[41,52]

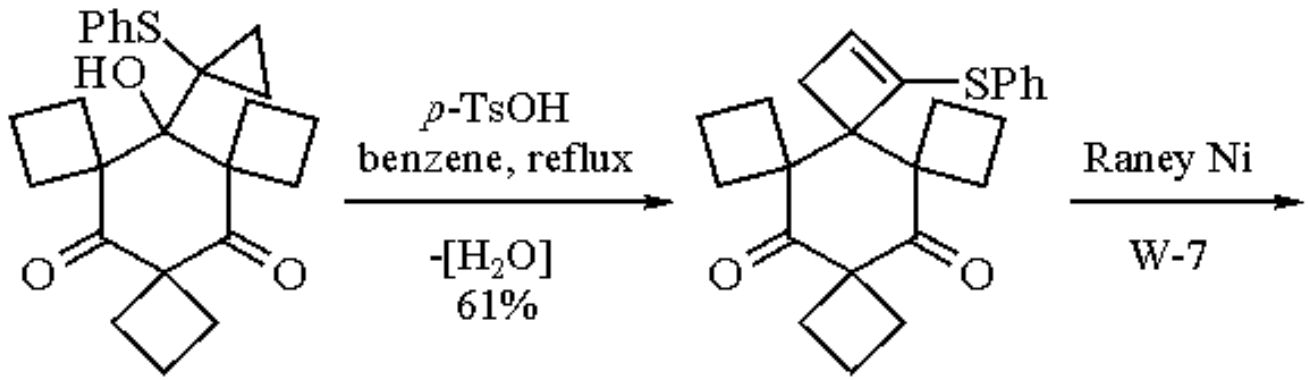

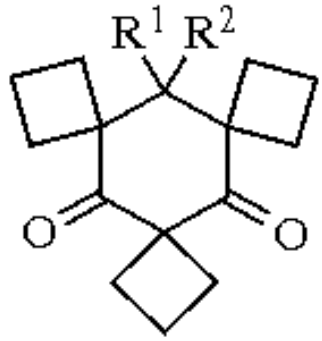

(19)

$R^1, R^2 = CH_2$ 60%
$R^1 = Me, R^2 = Et$ 40%

Alkylation of 1-phenylthiocyclopropyllithium takes place in good yield with primary alkyl bromides and iodides but not with secondary alkyl halides (eq 8).[12,31,46] With ***Benzyl Bromide***, however, halogen-metal exchange occurs, leading to bibenzyl and 1-bromocyclopropyl phenyl sulfide.[12] Allylation works successfully if copper(I) iodide (0.5 equiv) is present and the reaction is carried out at low temperature (eq 15).[47,53] (**2**) adds to epoxides to form 1-(β-hydroxy)cyclopropyl phenyl sulfides (eq 8).[12] Excellent regioselectivity of attack occurs at the less hindered primary carbon of 1,2-epoxybutane, and even with cyclohexene oxide a high yield of adduct is obtained.[12] Reaction with ***Chlorotrimethylsilane***, ***Iodine***, esters, or DMF and carbonic anhydride leads to 1-trimethylsilyl(phenylthio)cyclopropane (Me_3SiCl, 88% yield),[31,49] 1-iodo(phenylthio)cyclopropane (eq 12),[22] 1-alkoyl-1-(phenylthio)cyclopropanes (80% yield),[38,41] and 1-(phenylthio)cyclopropanecarboxylic acid (55% yield),[41] respectively.

Thus 1-phenylthiocyclopropylcarbinols are valuable precursors of cyclobutanones.[1a,26-28,32-40,42] The rearrangement takes place in the presence of an acid catalyst. The more general and vigorous conditions involve the use of ***Tin(IV) Chloride*** in methylene chloride (eq 14).[32] Protic acids with a nonnucleophilic anion, such as 48% aqueous ***Tetrafluoroboric Acid***, work nicely with β-hydroxy sulfides derived from sterically unhindered ketones, but increasing steric hindrance led to no reaction.[32] The reaction has also been performed with ***p-Toluenesulfonic Acid*** in wet benzene[32] or tetralin.[26] These conditions require heating and are particularly useful for the adducts derived from saturated aldehydes.[32] They have been used for the synthesis of the parent cyclobutanone[26] (70-120 °C in the presence of ***Mercury(II) Chloride*** as a thiol trap). The rearrangement is stereoselective.[28,32,33] For example, the β-hydroxyalkyl sulfide derived from 4-*t*-butylcyclohexanone shown in eq 14 leads selectively to the cyclobutanone arising from axial migration[1a,28,32] and allows the introduction of the substituted carbon-carbonyl bond on the sterically less crowded face. The stereochemical outcome of this process is complementary to the one which involves cyclopropylidenediphenylsulfurane[20] and introduces instead the carbon-carbonyl bond on the more sterically hindered face.[32]

1-Phenylthiocyclopropylcarbinols produce cyclobutanone enol thioethers on reaction with anhydrous *p*-toluenesulfonic acid

in refluxing benzene (eq 19) or more efficiently with the Burgess reagent ((carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester).[32] Alternatively, reaction of 1-phenylthiocyclopropylcarbinols derived from aldehydes with excess of thiophenol (5 equiv) in the presence of 48% hydrobromic acid-zinc bromide affords cyclobutanone phenylthio acetals (eq 15).[43] Their further reaction with copper triflate and Hünig's base produces very good yields of cyclobutanone enol thioethers[43] precursors of 2-(phenylthio)-1,3-butadienes (eq 15).[32,43]

1-Alkyl- and 1-allylcyclopropyl phenyl sulfides are efficiently converted to alkylidenecyclopropanes[46] and allylidenecyclopropanes (eqs 16 and 17),[47] respectively on methylation to the corresponding sulfonium salt followed by reaction with a base. The reaction is expected to occur via the intermediate formation of a sulfur ylide of the type described in eq 12.[46] Otherwise 1-alkylcyclopropyl phenyl sulfides afford[12] ethyl ketones on reaction with hydrobromic acid-acetic acid, and β-keto sulfides on reaction with mercury(II) chloride (see eq 8).

Related Reagents.

Cyclopropyldiphenylsulfonium Tetrafluoroborate; ***Cyclopropyllithium***; ***1-Lithio-1-methoxycyclopropane***.

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Phenylthiomethyllithium

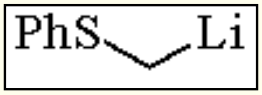

[13307-75-0] · C_7H_7LiS · Phenylthiomethyllithium · (MW 130.15)

(nucleophilic organolithium reagent useful for addition to ketones, aldehydes, esters; synthesis of alkenes, epoxides, cyclopentenones, allylic sulfides, γ-phenylthioenones, α-phenylthiofurans and butenolides, and (phenylthiomethyl)trimethylsilane)

Preparative Methods: by the treatment of methyl phenyl sulfide with ***n-Butyllithium*** in ether (reflux, 15 h),[1] or in THF containing 1 equiv of DABCO (eq 1, 0 °C, 45 min).[2]

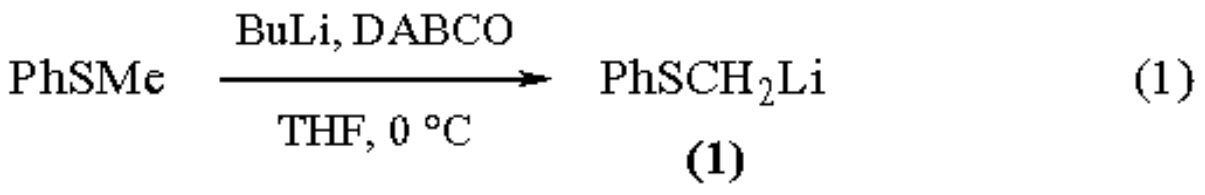

Handling, Storage, and Precautions: is generated in situ, under anhydrous conditions, in an inert atmosphere, and used shortly after preparation; as *n*-BuLi is employed, the precautions for preparation and use would mirror those of *n*-BuLi and related reactive organometallic reagents.

Alkene Synthesis.

Phenylthiomethyllithium (**1**) is a versatile reagent for the preparation of alkenes from ketones, and is particularly useful when the carbonyl compound is susceptible to base-catalyzed epimerization.[3-5] Addition of (**1**) to ketones followed by aqueous quench gives rise to β-hydroxy sulfides (which are not generally isolated).[2] Conversion to a β-thioester is accomplished by successive treatment with butyllithium and an acylating agent (typically ***Benzoyl Chloride*** or ***Acetic Anhydride***).[6,7] Alternatively, the lithium alkoxide produced by the addition of (**1**) to the ketone can be trapped in situ with ***Benzoic Anhydride*** to afford the β-benzoyloxy sulfide.[6] ***Lithium Amide*** or ***Sodium Naphthalenide*** reduction affords exocyclic methylene compounds in good to high yields,[6,7] even in the case of hindered ketones (eq 2).[8]

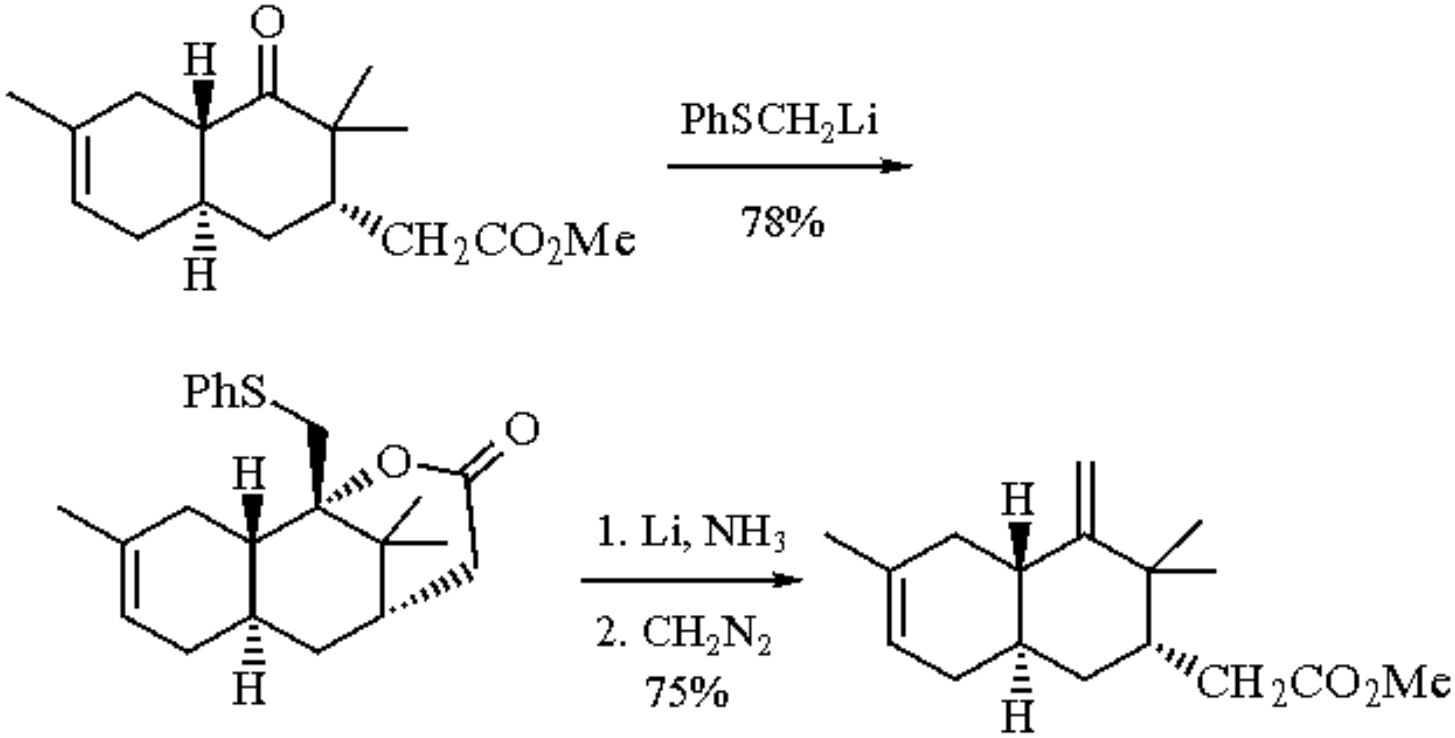

(2)

Alternatively, in the case of β-benzoyloxy sulfides derived from ketones, the reduction to methylene compounds may be accomplished by the use of low-valent titanium compounds (prepared by treating pyridine solutions of ***Titanium(IV) Chloride*** with ***Zinc*** metal)[9] or with ***Titanium*** metal.[10] In a further extension, the reduction of the intermediate β-hydroxy sulfides formed from both ketones and aldehydes may be reduced with titanium tetrachloride-***Lithium Aluminum Hydride*** to provide the methylene compounds in high yields.[11]

Epoxide Synthesis.

Epoxides are produced when the intermediate β-hydroxy sulfides, from the addition reaction of (**1**), are alkylated (for example, with ***Triethyloxonium Tetrafluoroborate*** or its trimethyl analog) and treated with aqueous base (eq 3).[12a] The overall yields for the three-step process are high and compare favorably to the one-step methylene transfer accomplished by sulfur ylides, a reaction that is sometimes hindered by steric interference and proton abstraction. Vinyl epoxides can be prepared by the addition of (**1**) to an α,β-unsaturated aldehyde to give a vinylphenylthiomethylcarbinol, which is alkylated with triethyloxonium tetrafluoroborate, followed by base-catalyzed (***Sodium Hydride***) epoxide closure (eq 4).[12b]

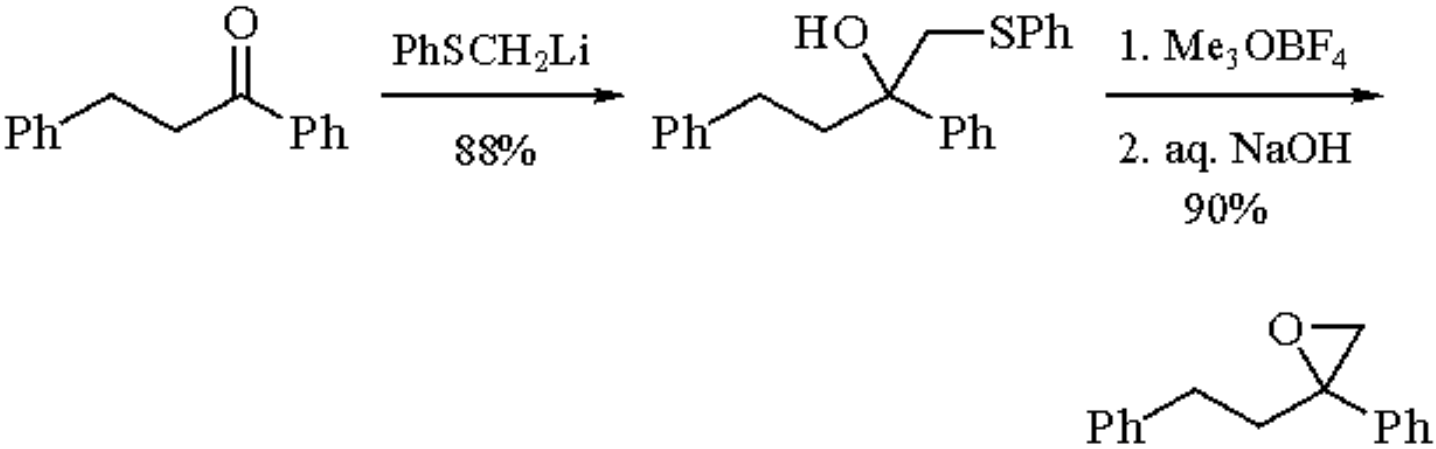

(3)

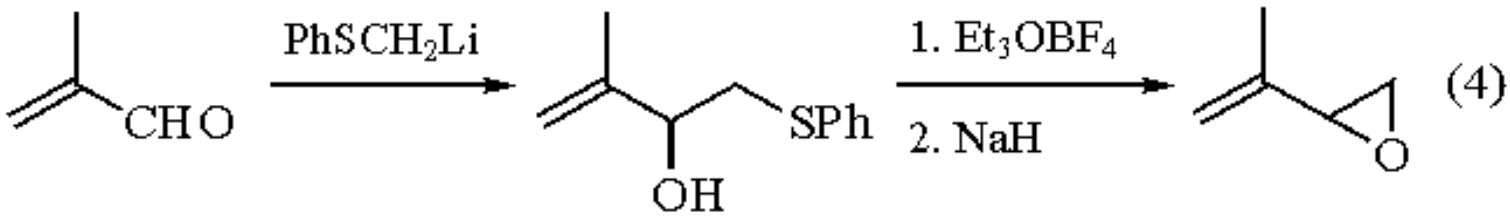

Cyclopentenone Synthesis.

The reagent (**1**) has also found use in the synthesis of cyclopentenones. The addition of (**1**) to α-chloro-β,γ-unsaturated esters has been demonstrated to lead directly to 5-phenylthio-2-cyclopentenones (eq 5).[13]

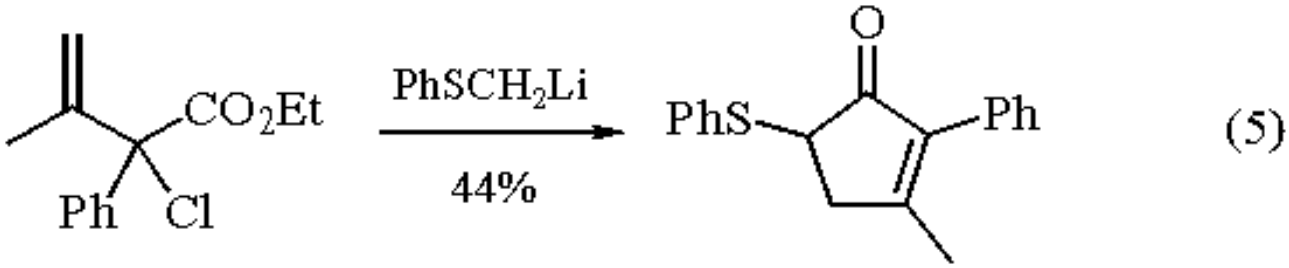

Allylic Sulfides, γ-Phenylthio-α,β-unsaturated Ketones.

The reagent (**1**) adds smoothly to cyclic ketones (ring sizes 5-10, 12, 15) and the resultant tertiary alcohols can be readily dehydrated to furnish allylic sulfides (eq 6).[14] The addition of (**1**) to an α,β-unsaturated ketone affords the related tertiary allylic alcohol, which gives a γ-phenylthio-α,β-unsaturated ketone on treatment with ***Pyridinium Chlorochromate*** on silica gel and ultrasound (eq 7).[15]

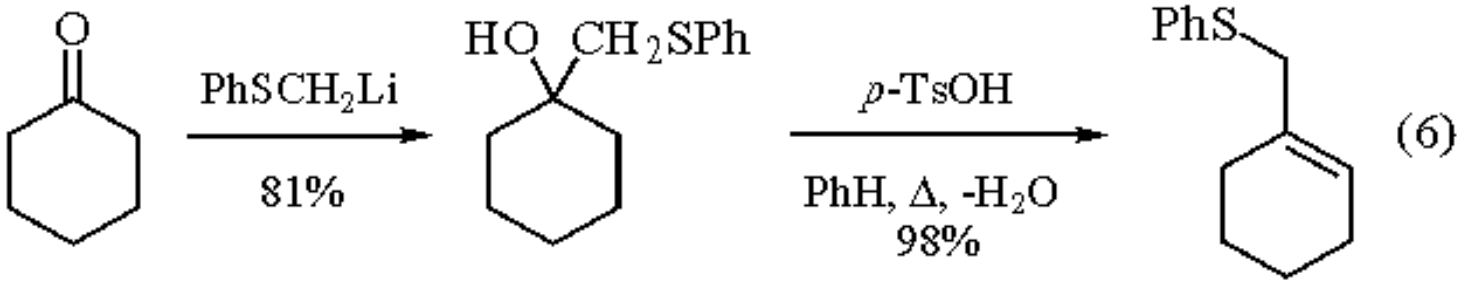

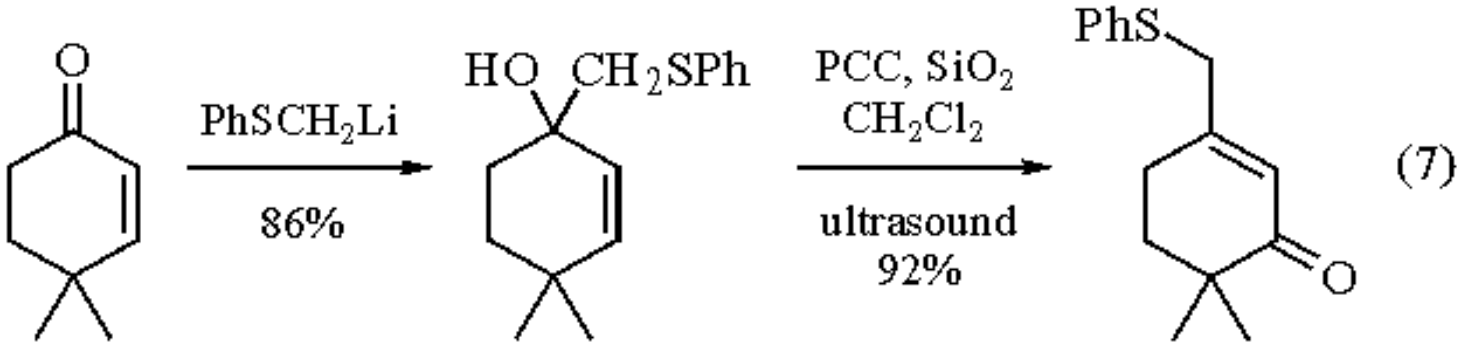

Phenylthiofuran and Butenolide Synthesis.

The reagent (**1**) has been utilized for phenylthiofuran and butenolide formation in the synthesis of the sesquiterpene (±)-colorata-4(13),8-dienolide (**2**).[16] (**1**) was added to an α-butylthiomethylene ketone, to afford an α,β-unsaturated aldehyde after hydrolysis (eq 8). The hydrolysis reaction to provide the conjugated aldehyde required 4 weeks at 20 °C, in order to prevent double bond isomerization. Oxidation (***Sodium Periodate***) and treatment with acetic anhydride and heat led to the desired α-phenylthiofuran in 70% yield.

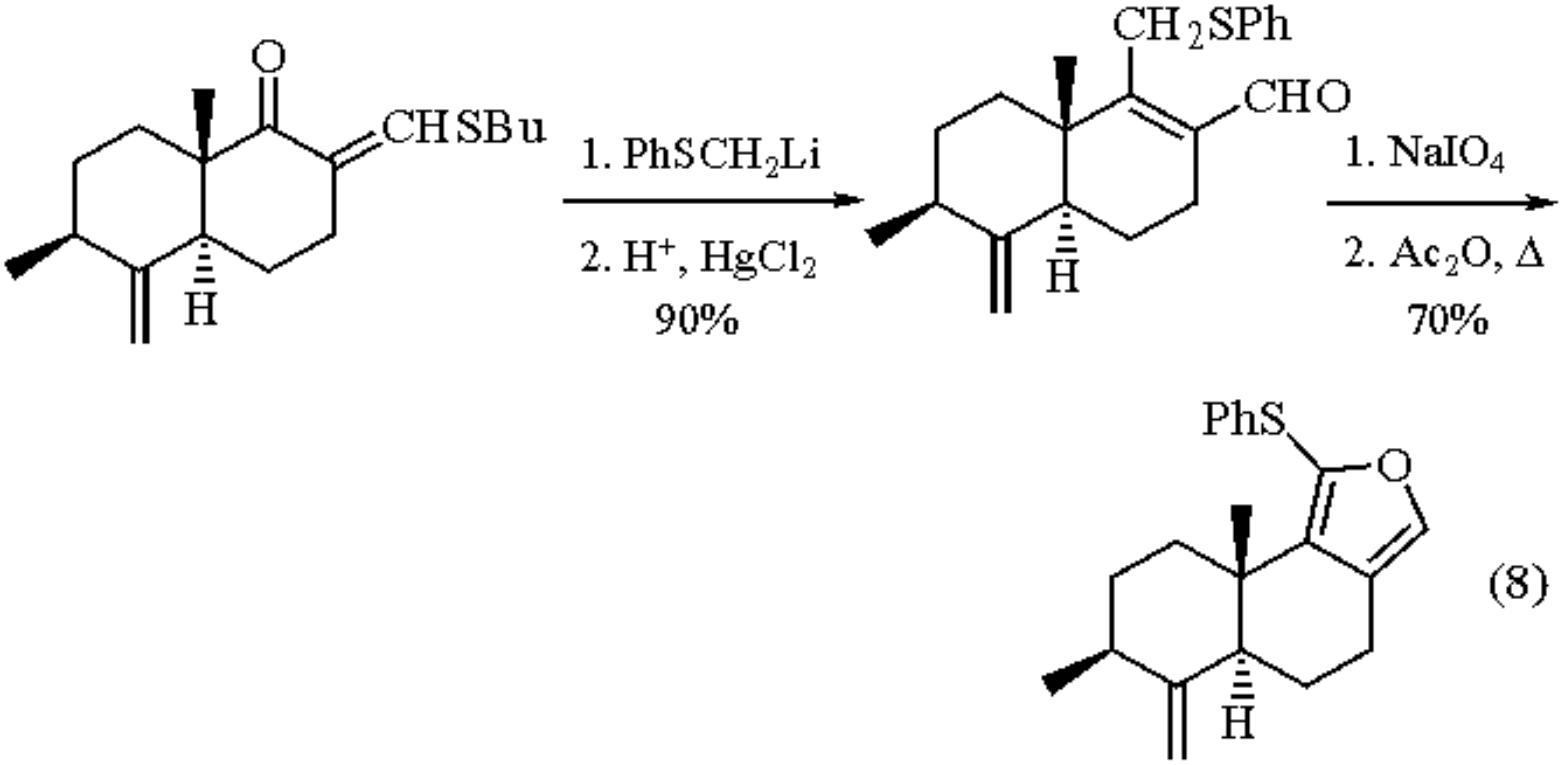

(8)

The conversion of the phenylthiofuran to the target butenolide was again complicated by long exposure times to acid and ***Mercury(II) Chloride*** (1 week) to avoid double bond isomerization and give the butenolide (**2**) in 60% yield (eq 9).

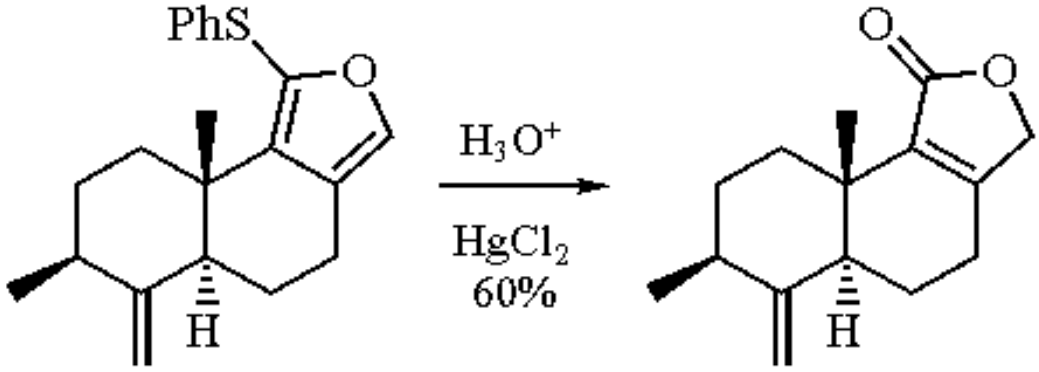

(9)

(**2**)

Phenylthiomethyltrimethylsilane.

(**1**), produced by the Gilman method,[1] readily reacts with ***Chlorotrimethylsilane*** to give ***(Phenylthiomethyl)trimethylsilane*** (eq 10).[17]

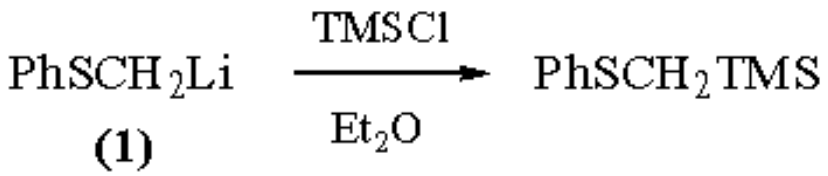

(10)

Related Reactions.

Nucleophilic phenylthiomethyl equivalents have been prepared from phenylthiomethyltrimethylsilane[18] and ***Chloromethyl Phenyl Sulfide***.[19] Phenylthiomethyltrimethylsilane can be treated with ***Tetra-n-butylammonium Fluoride*** (eq 11, path 1)[18a] or ***Potassium t-Butoxide*** (eq 11, path 2)[18b] to furnish species which will add to ketones. Phenylthiomethyltrimethylsilane has also seen use in the synthesis of aldehydes,[17] alcohols,[17] ketones,[20] and alkenes,[21] in conjugate additions to cycloalkenones,[21] and in the preparation of chloro(phenylthio)methyltrimethylsilane.[22] Phenylthiochloromethane produces a reactive organometallic species when treated with ***Samarium(II) Iodide*** and a ketone (eq 12).[19] These mild conditions permit the use of readily enolized ketones as substrates for phenylthiomethyl addition.

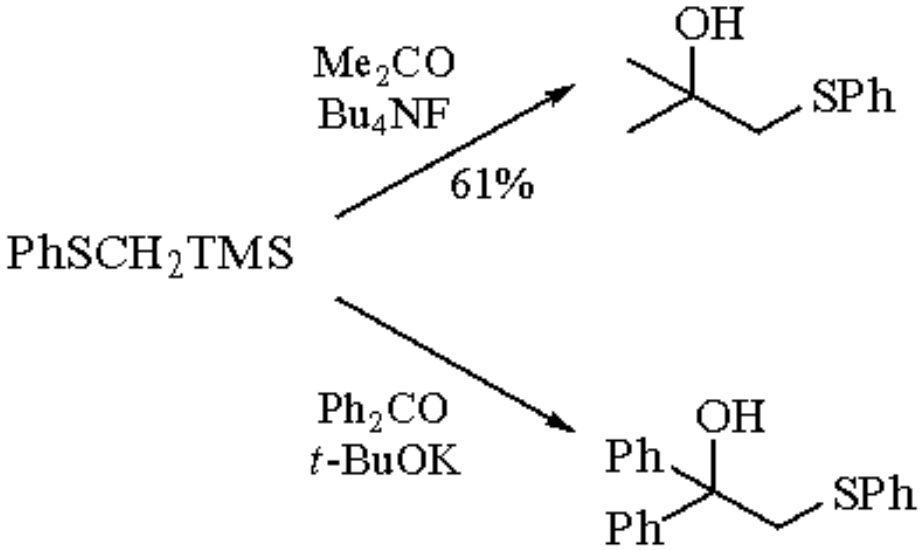

(11)

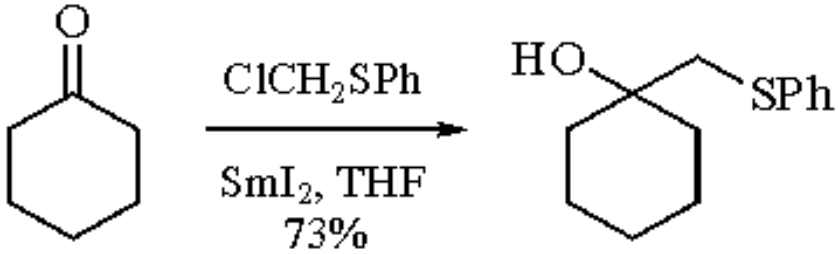

(12)

Methyl phenyl sulfide can be treated with 2.2 equiv of *n*-butyllithium-TMEDA to generate a dianion which can be efficiently reacted with a range of electrophiles (eq 13).[23] Attempts to alkylate the dianion sequentially with two different electrophiles have not been very successful.

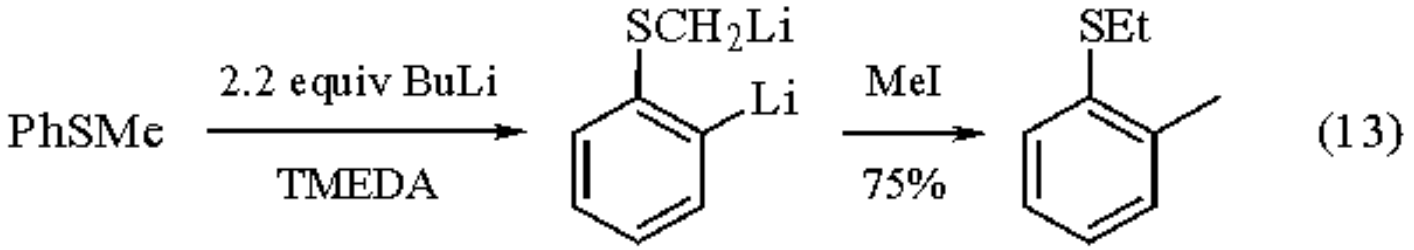

1-Phenylthio-1-lithioethane is prepared from 1,1-bisphenylthioethane by reductive cleavage with lithium naphthalenide (eq 14).[17] The 1-phenylthio-1-lithioethane thus produced is then captured with chlorotrimethylsilane in 90% yield (eq 14).

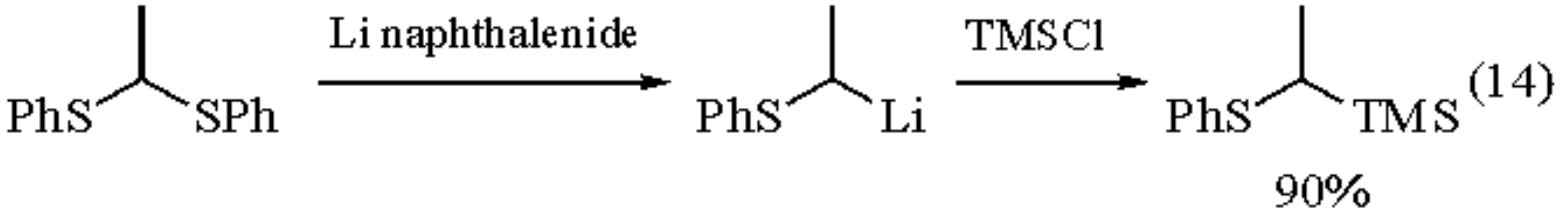

Related Reagents.

Bis(phenylthio)methane; ***Dibromomethane-Zinc-Titanium(IV) Chloride***; ***S,S-Dimethyl-N-(p-toluenesulfonyl)sulfoximine***; ***2-Lithio-1,3-dithiane***; ***Methylenetriphenylphosphorane***; ***Phenylselenomethyllithium***.

---

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(Phenylthiomethyl)trimethylsilane

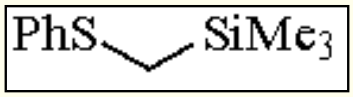

[17873-08-4] · $C_{10}H_{16}SSi$ · (Phenylthiomethyl)trimethylsilane · (MW 196.42)

(lithio derivative is a one-carbon homologating agent leading to aldehydes via sila-Pummerer rearrangement,[1] vinyl sulfides via Peterson alkenation,[2] and vinylsilanes from silyl epoxides[3])

Physical Data: bp 158-159 °C/52 mmHg; d^{20} 0.967 g cm^{-3}; *n*20D 1.5390.

Solubility: sol most common organic solvents.

Form Supplied in: oil; commercially available.

Analysis of Reagent Purity: by GC or ^{1}H NMR analysis.

Preparative Methods: by reaction of ***Phenylthiomethyllithium*** with ***Chlorotrimethylsilane***.[4]

Purification: by distillation under reduced pressure.

Handling, Storage, and Precautions: irritant; foul smelling; use in a fume hood.

Formylation Reactions.

Metalation of the title reagent (**1**) with ***n-Butyllithium*** gives the fairly stable anion phenylthio(trimethylsilyl)methyllithium (**2**), which is a formyl anion equivalent as illustrated by the sequence in eq 1.[1] Anion (**2**) reacts with primary alkyl bromides and iodides to yield 1-phenylthio-1-trimethylsilylalkanes (**3**) in high yields. These intermediates are easily oxidized by ***m-Chloroperbenzoic Acid*** to the corresponding sulfoxides. Subsequent heating promotes a sila-Pummerer rearrangement[5] to produce aldehydes after hydrolysis.[1] Reagent (**1**) is superior to ***1,3-Dithiane*** for the synthesis of aldehydes from alkyl halides, in view of the greater ease of hydrolysis of (**3**). Application of this procedure to the synthesis of unsymmetrical ketones has also been reported.[6]

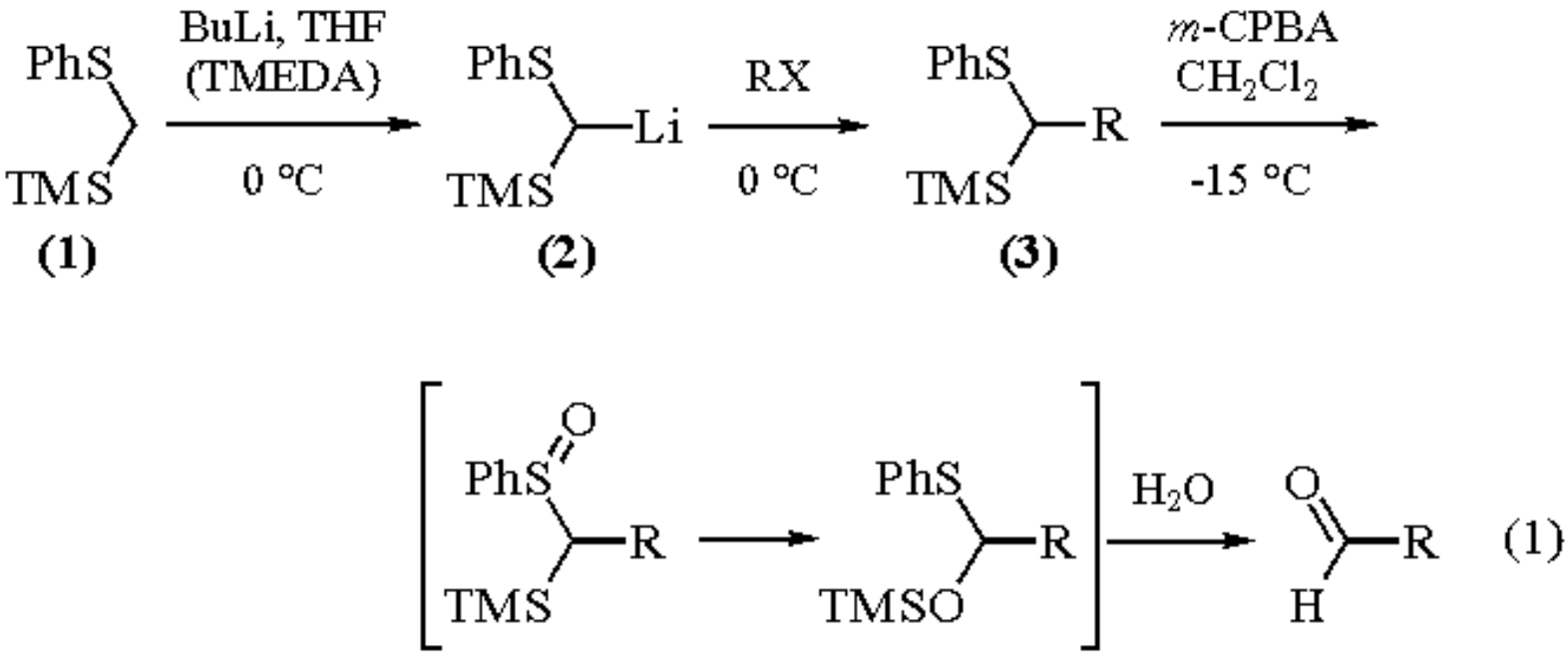

The ***Zinc Bromide*** catalyzed alkylation of enol silanes by α-halo-α-(phenylthio)methyltrimethylsilanes (eq 2) provides an efficient method for electrophilic formylation (i.e. an umpolung of the transformation in eq 1) which is useful for the synthesis of β-ketoaldehydes.[7] The sequence can also be diverted for the synthesis of β-trimethylsilylenones (eq 2).[8]

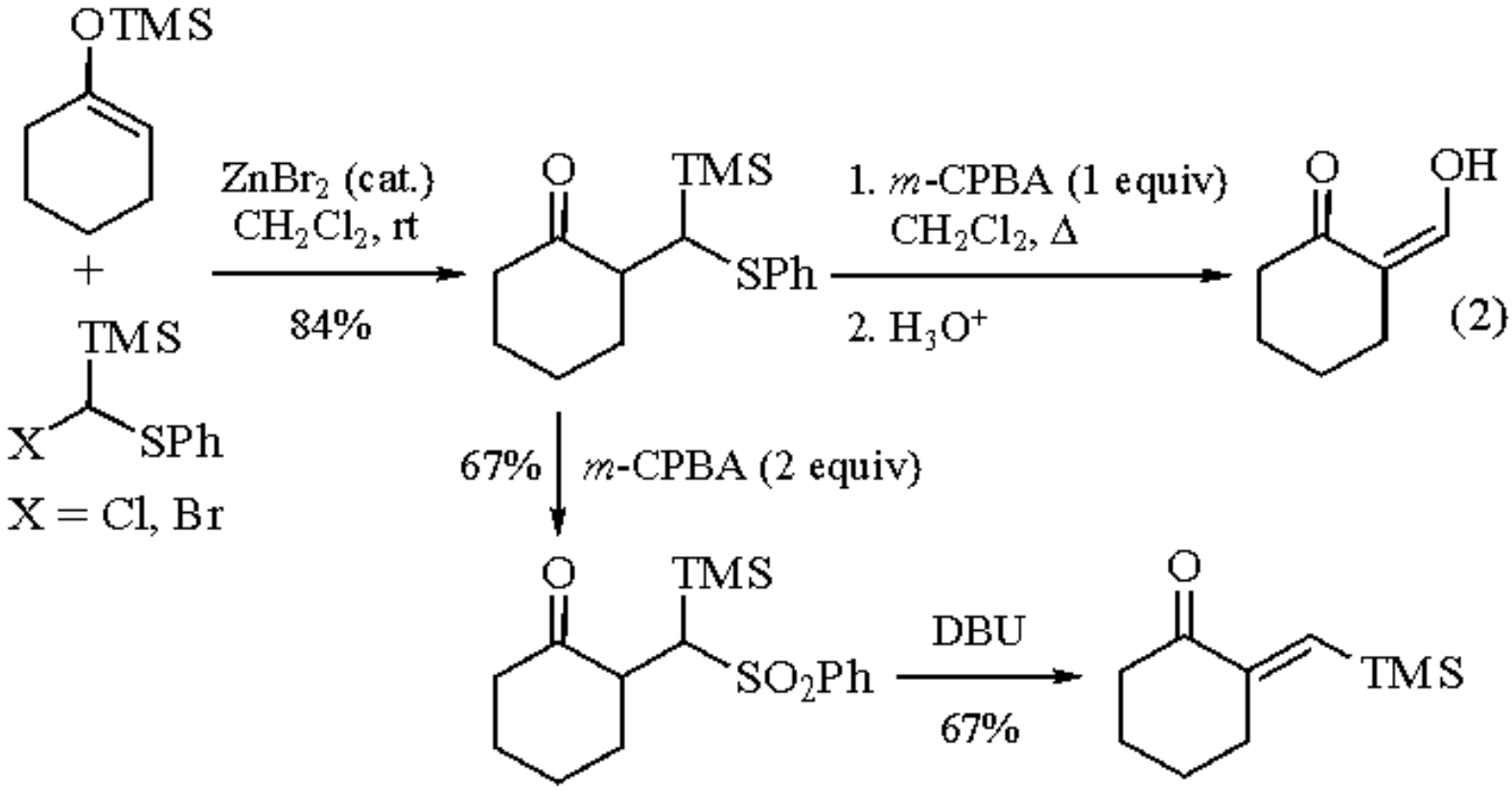

Phenylthiobis(trimethylsilyl)methane (**4**), prepared by the reaction of (**2**) with Me_3SiCl, serves as a synthetic equivalent of $LiCO_2Me$.[9] Metalation of (**4**) with BuLi in the presence of ***N,N,N´,N´-Tetramethylethylenediamine*** gives phenylthiobis(trimethylsilyl)methyllithium (**5**); subsequent alkylation and electrochemical oxidation achieves chain homologation to form an ester (eq 3). Alternatively, alkylation of (**5**) with a terminal oxirane followed by

cycloelimination in situ generates 1-phenylthio-1-trimethylsilylcyclopropanes.[10] Anion (**2**) itself reacts with oxiranes to give adducts which can also be converted to 1-phenylthio-1-trimethylsilylcyclopropanes, but two intermediary steps are required to accomplish cycloelimination (eq 4).[11]

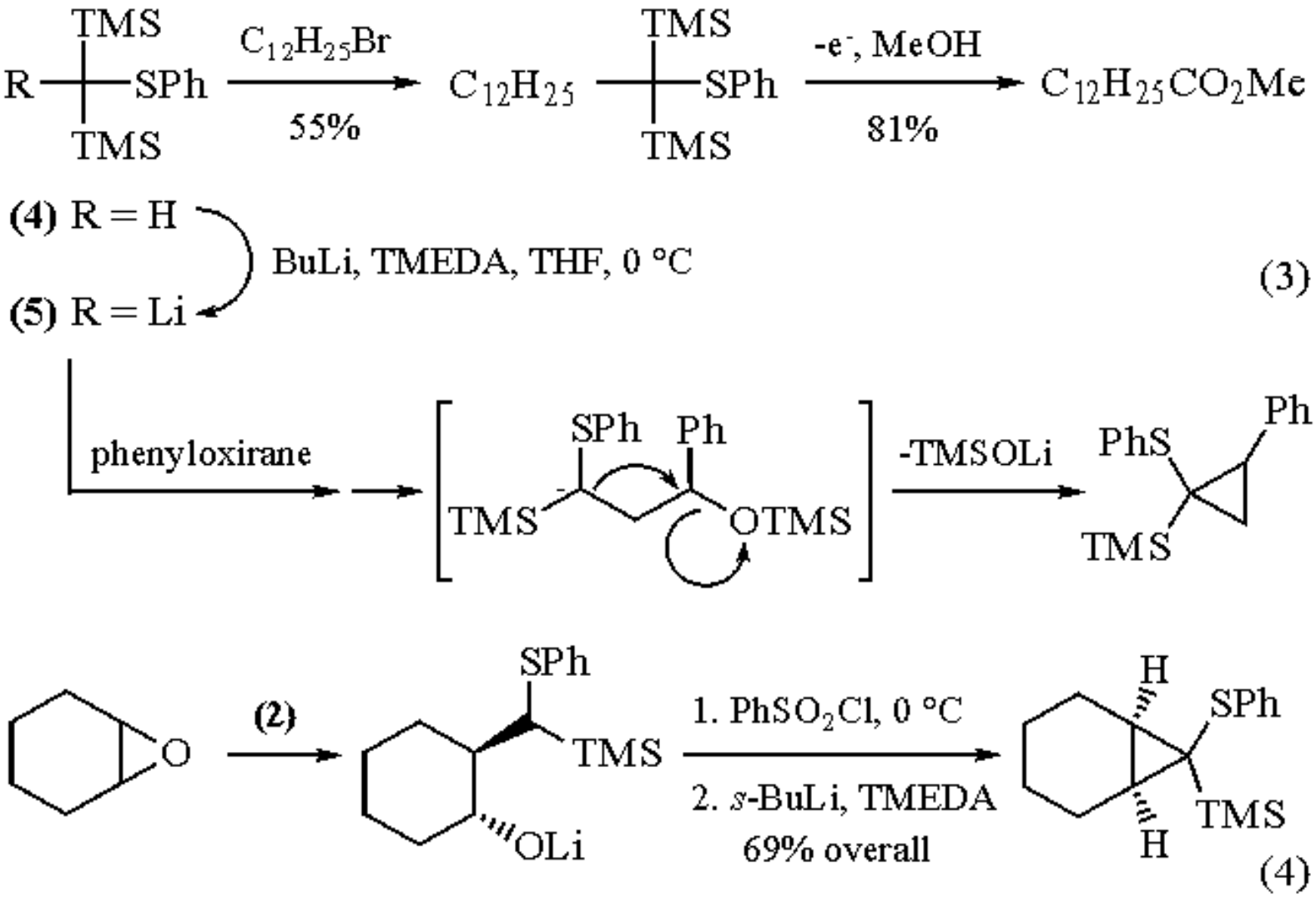

Synthesis of Vinyl Sulfides.[2]

Anion (**2**) adds to aldehydes, ketones, and enones, in the last-named case in either 1,2- or 1,4-manner depending on the reaction conditions.[12] In the case of 1,2-addition the β-hydroxysilane adduct usually cannot be isolated owing to rapid elimination (Peterson alkenation) to vinyl sulfides (eq 5), which can be hydrolyzed to the corresponding aldehydes.[2] The vinyl sulfides are not formed stereoselectively unless there are proximate bulky substituents.[13] Peterson alkenation products have also been observed in the reaction of (**2**) with amides, ureas, and carbonates.[14]

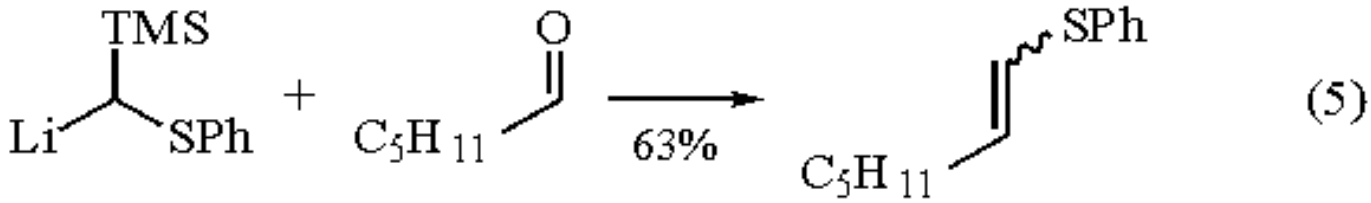

(Phenylthiomethyl)trimethylsilane

The reaction of (**2**) with esters provides α-phenylthio-α-trimethylsilyl ketones, which can be easily converted to α-phenylthio ketones (eq 6).[15] β-Hydroxy sulfides are obtained from the reaction of (**1**) with carbonyl compounds in the presence of a catalytic amount of fluoride ion (eq 7).[16]

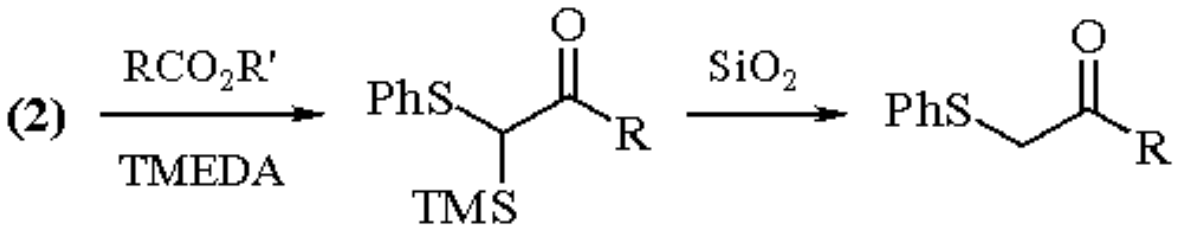

(6)

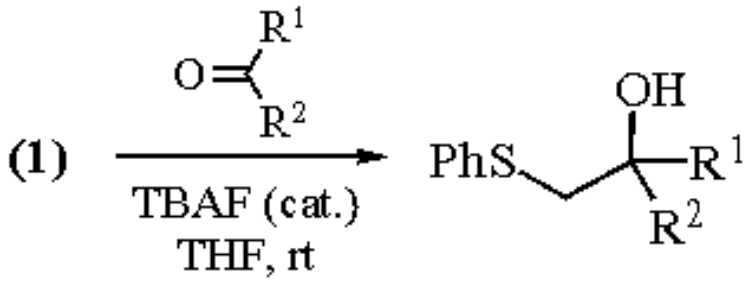

(7)

Synthesis of Vinylsilanes.[3]

Lithiated reagent (**2**) reacts with α-trimethylsilyloxiranes to yield vinylsilanes (eq 8). The reaction involves nucleophilic opening of the oxirane ring by (**2**), followed by 1,2-elimination of a silyl and a phenylthio group.[3]

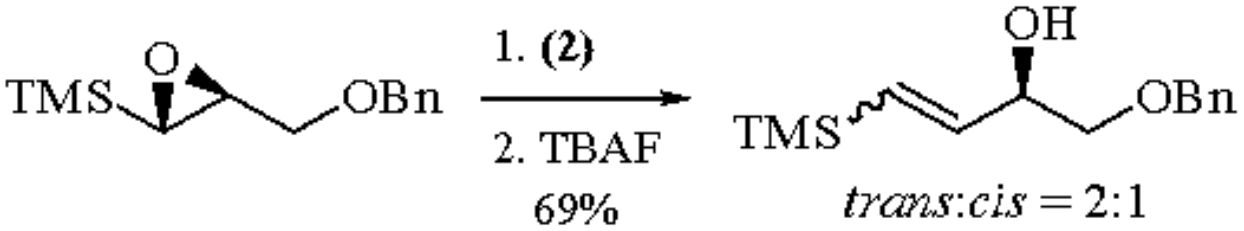

(8)

Vinylsilanes are also prepared from (**2**) as illustrated in eq 9.[17] Treatment of (**2**) with ***Bis(trimethylsilyl) Peroxide*** provides (**6**) which reacts with phosphonium ylides in the presence of ***Tetra-n-butylammonium Fluoride*** to give mixtures of vinylsilanes favoring the (*Z*)-isomer.

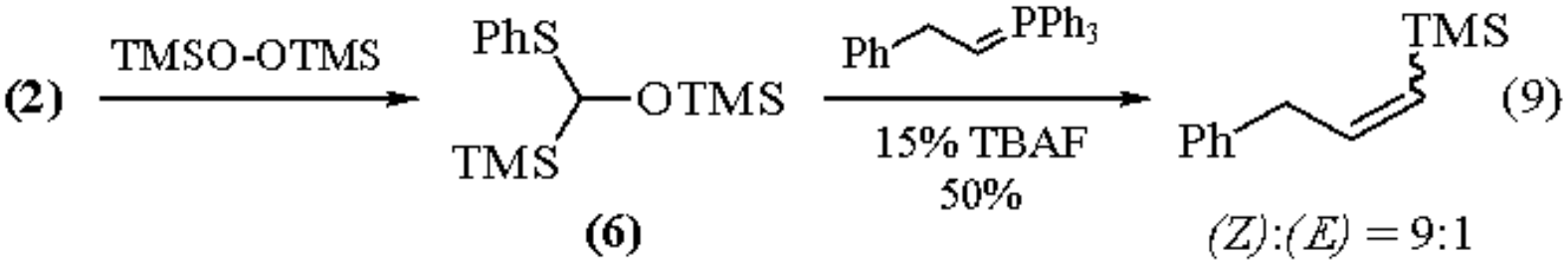

(9)

Other Reactions.

In addition to haloalkanes, carbonyl derivatives, and oxiranes, anion (**2**) reacts with a wide range of other electrophiles including ***N-Chlorosuccinimide***,[18] ***Chlorotrimethylsilane***,[8] Bu_3SnCl,[15] ***Diphenyl Disulfide***, and ***Benzenesulfenyl Chloride***,[15] and trialkylboranes.[19]

Related Reagents.

Methoxy(phenylthio)(trimethylsilyl)methane (**7**) is prepared by metalation-silylation of phenylthiomethyl methyl ether.[20] [Methoxy(phenylthio)(trimethylsilyl)methyl]lithium (**8**), prepared from (**7**) by metalation with ***s-Butyllithium*** in the presence of TMEDA, undergoes clean and efficient Peterson alkenation with aldehydes to give (*E*)-ketene-*O*,*S*-acetals stereoselectively, which can then be hydrolyzed to thioesters (eq 10).[21]

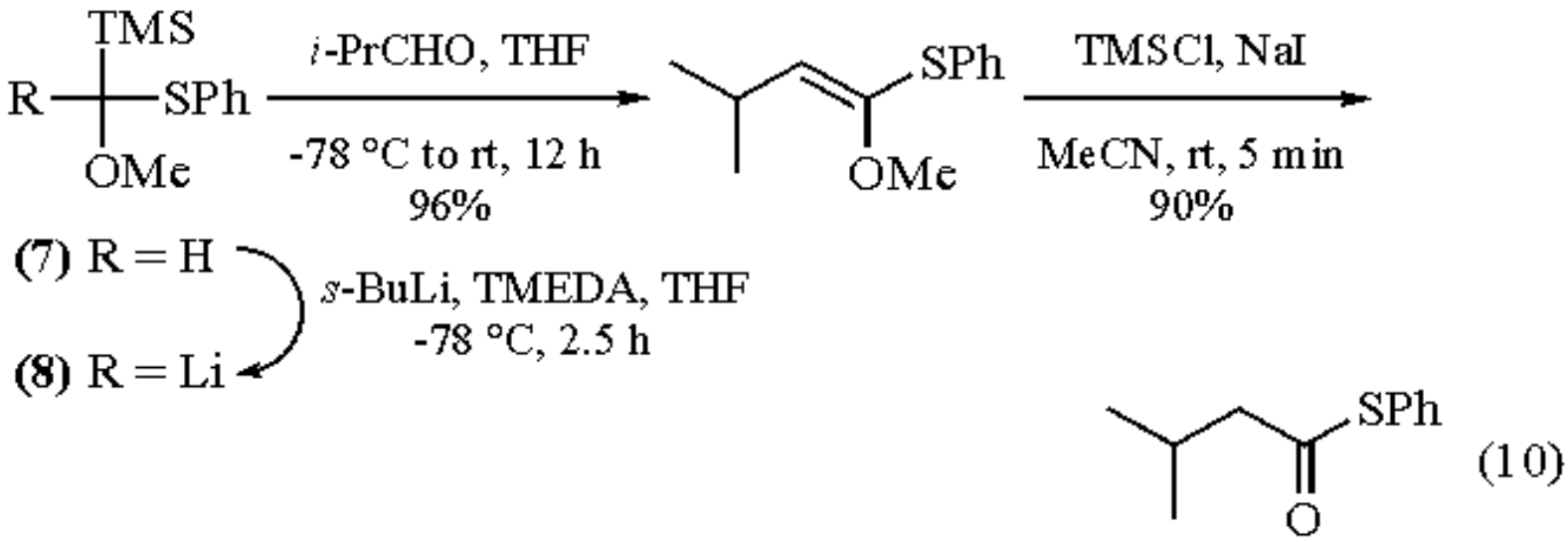

The selenium analog of (**2**) is prepared by deprotonation of (phenylselenomethyl)trimethylsilane with ***Lithium Diisopropylamide*** or ***Lithium 2,2,6,6-Tetramethylpiperidide*** (eq 11). The anion (**9**) thus formed can be alkylated in good yields, and the alkylated product can be oxidized to the corresponding selenoxide at low temperature, but selenoxide elimination leading to a vinylsilane competes with the sila-Pummerer rearrangement.[22,23]

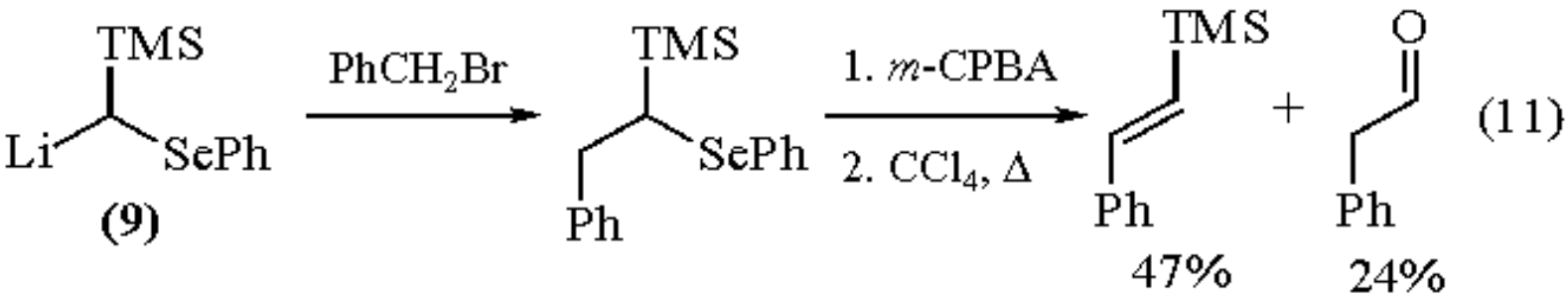

See also ***2-Lithio-1,3-dithiane***, ***Phenylthiomethyllithium***, and ***Bis(phenylthio)methane***.

---

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(Phenylthio)nitromethane[1]

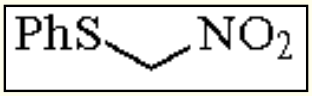

[60595-16-6] · $C_7H_7NO_2S$ · (Phenylthio)nitromethane · (MW 169.22)

(precursor for 1-nitro-1-phenylthioalkenes,[2] furans,[3] bicyclic β-lactams,[4] and amino acids[5])

Alternate Name: nitro(phenylthio)methane

Physical Data: bp 85-95 °C/0.05 mmHg;[6] *n*23D 1.5785;[7] pK_a (DMSO) 11.9.[7]

Solubility: insol cold H_2O; sol CH_2Cl_2, benzene, THF.

Analysis of Reagent Purity: ^{1}H NMR: 5.45 (s, 2H) and 7.25-7.5 ppm (m, 5H).[6]

Preparative Method: most conveniently prepared by reaction of the sodium salt of ***Nitromethane*** with ***Benzenesulfenyl Chloride***.[6,8]

Handling, Storage, and Precautions: may be stored essentially unchanged in a freezer at -25 °C; unpleasant odor; best handled in a well-ventilated hood; any spillage may be cleaned up with commercial bleach.

Nitroalkene Synthesis.

Henry reaction of (phenylthio)nitromethane with aldehydes followed by dehydration has been used to prepare (*Z*)-1-nitro-1-phenylthioalkenes.[2-5] ***Potassium t-Butoxide***-catalyzed addition and dehydration via mesylation (eq 1), or direct condensation catalyzed by piperidinium acetate (eq 2),[9] are the methods of choice. Henry reaction can be also carried out by reaction of the nitroalkene dianion with aldehydes.[8,10,11] The adducts of cyclic ketones and (phenylthio)nitromethane undergo ring expansion to provide 2-(phenylthio)cycloalkanones on ***Aluminum Chloride***-mediated denitration.[11]

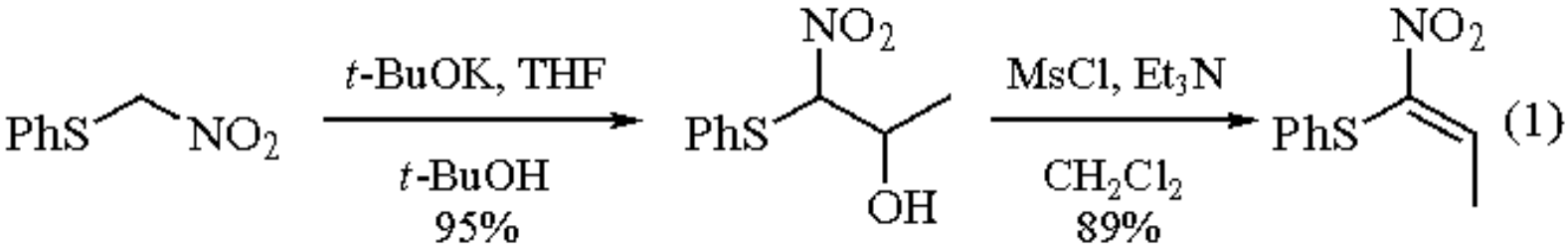

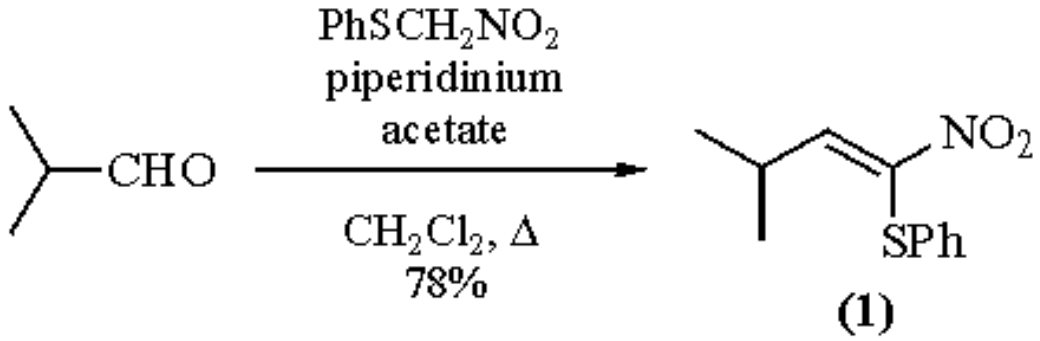

(2)

1-Nitro-1-phenylthioalkenes (**1**), on reaction with ***t-Butyl Hydroperoxide***, are converted into epoxides and these species react with nucleophiles (halide salts, ***Boron Trifluoride Etherate***, ***Trifluoroacetic Acid***, MsOH) to provide α-substituted phenylthio esters (eq 3).[9] Alternatively, Michael addition of nucleophiles (alkoxides, $Phth^-$, Ts^-, malonate) to 1-nitro-1-phenylthioalkenes and ozonolysis of the intermediate nitronate gave similar adducts (eq 4), including α-amino and α-hydroxy acid derivatives.[2]

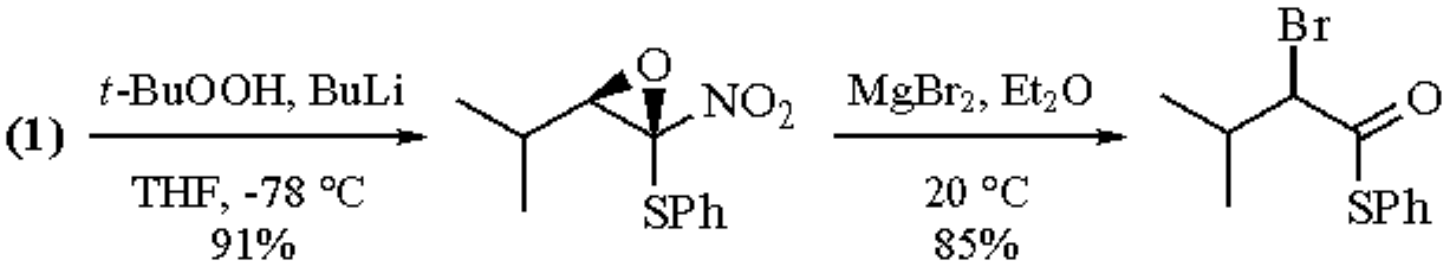

(3)

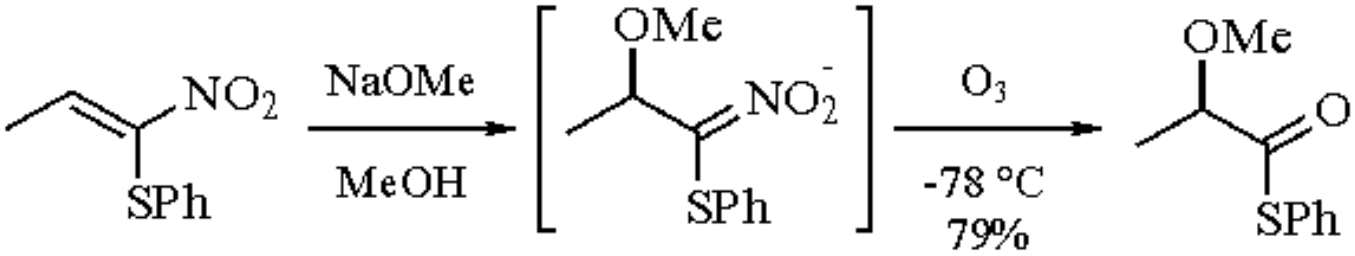

(4)

(Phenylthio)nitromethane is useful in polyoxin synthesis.[5,12] A ribose nitroalkene (**2**), derived from (phenylthio)nitromethane and the corresponding aldehyde (93%), was found to react with opposite stereochemical biases with potassium trimethylsilanoate (eq 5) and ***Phthalimide*** (eq 6) followed by ozonolysis. The hydroxy acid (eq 5) was further transformed into polyoxin C.

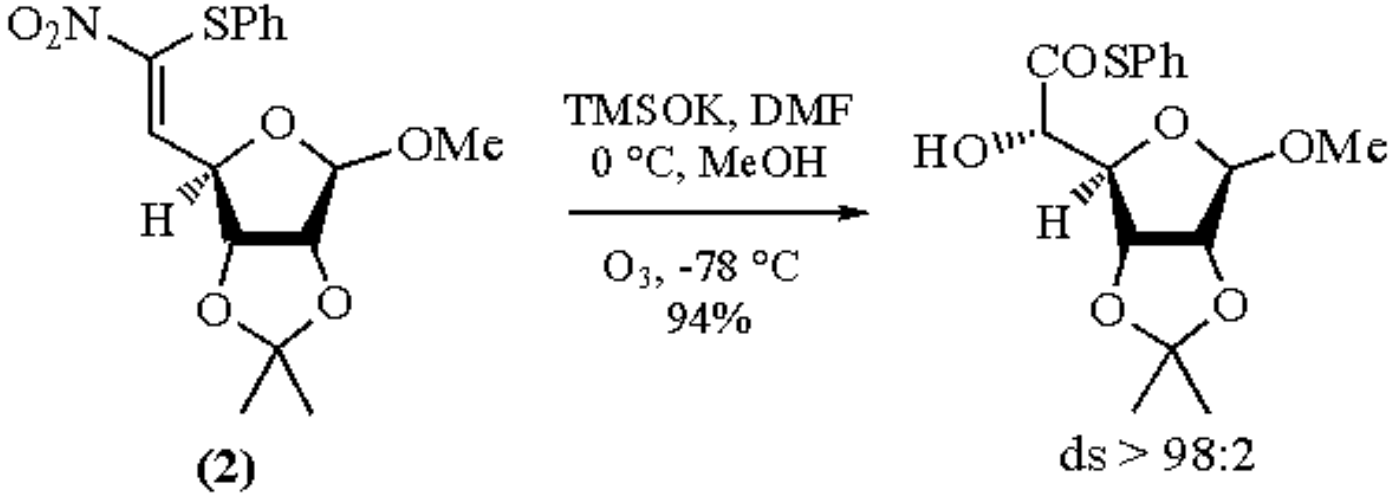

(5)

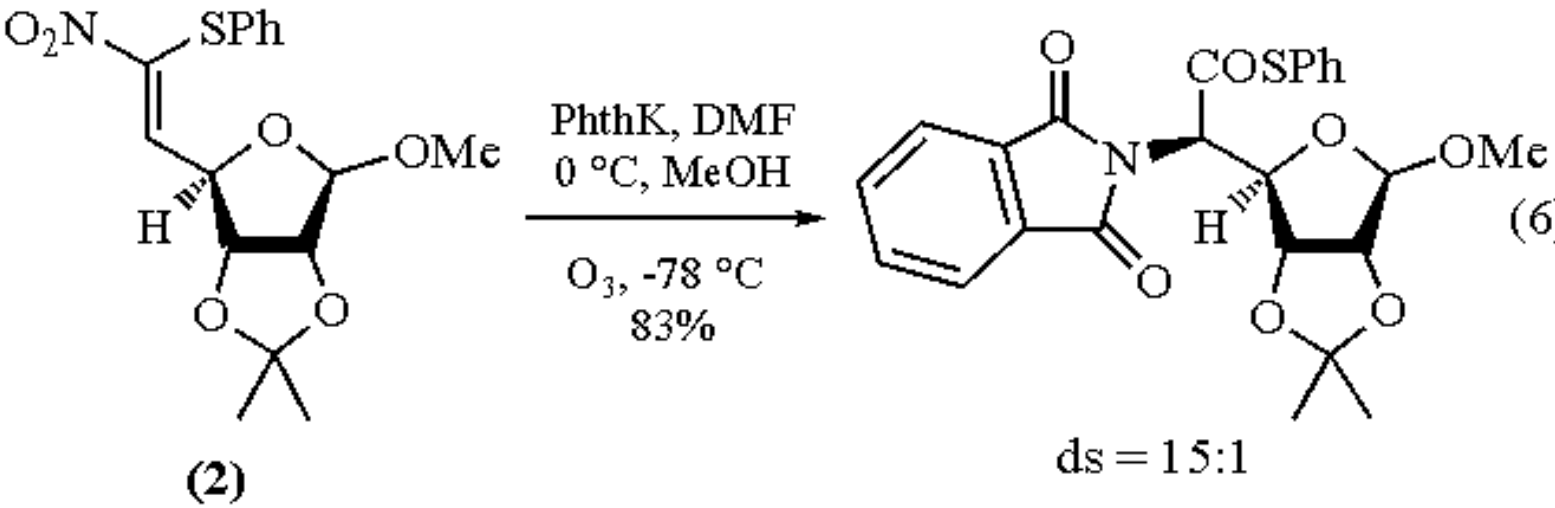

(6)

Synthesis of Heterocycles.

1-Nitro-1-phenylthiopropene is an excellent reagent for the synthesis of furanoterpenoids.[3,13] Condensation with β-diketones and sulfoxide elimination gave ligularone and isoligularone, respectively (eq 7). The methods were also used to prepare curzerenone, epicurzerenone, and pyrocurzerenone.

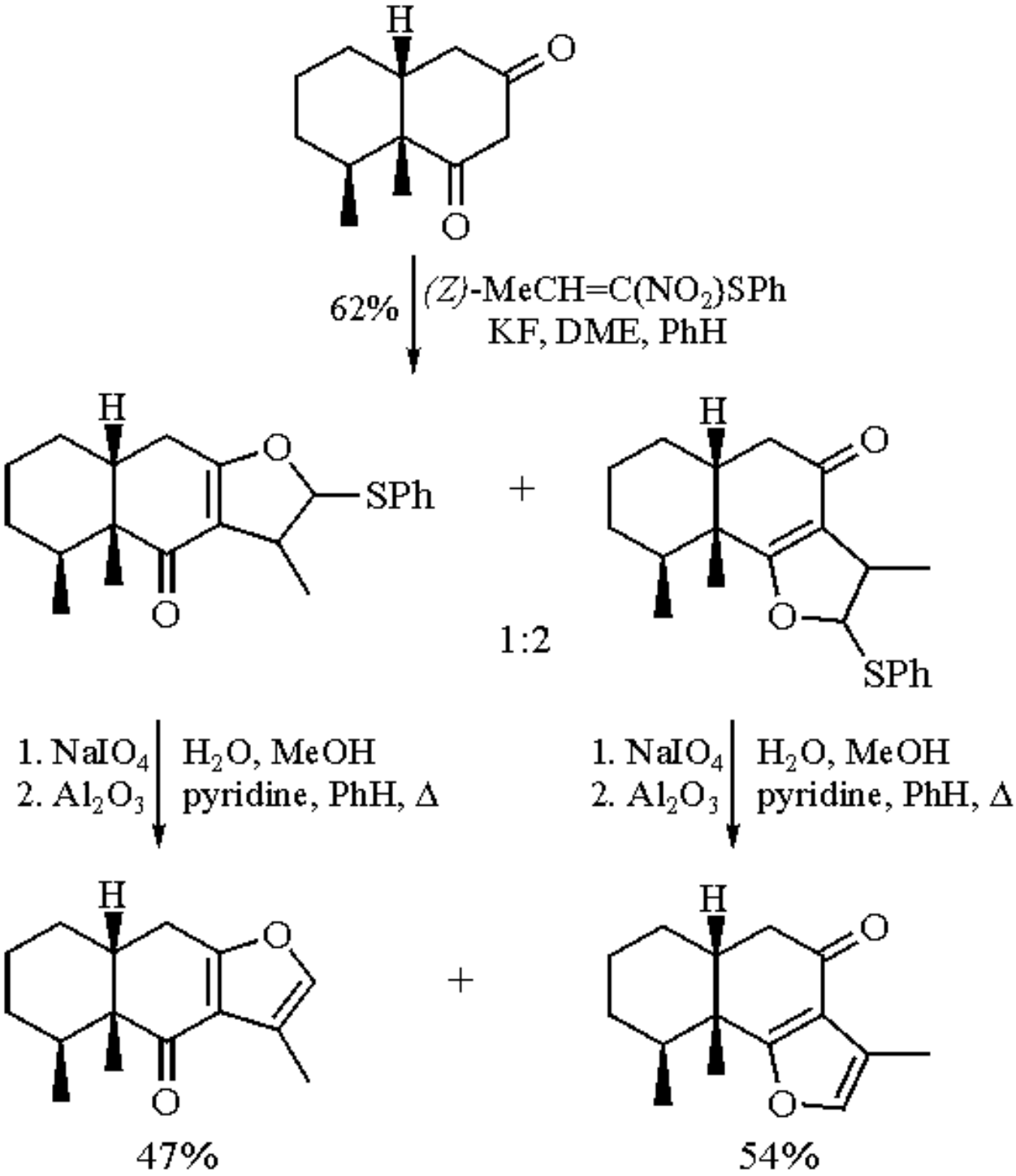

(7)

Nitroalkenes derived from β-lactam aldehydes may be converted into diverse bicyclic β-lactams via intramolecular Michael addition and ozonolysis (eq 8). The method is appropriate for penam, carbapenam, carbacephem, and oxapenam arrays.[4] In some cases, (benzyloxy)nitromethane is a superior reagent.[14] This Michael addition-oxidation strategy is also useful for the synthesis of tetrahydrofuran (eq 9) and -pyran systems.[15]

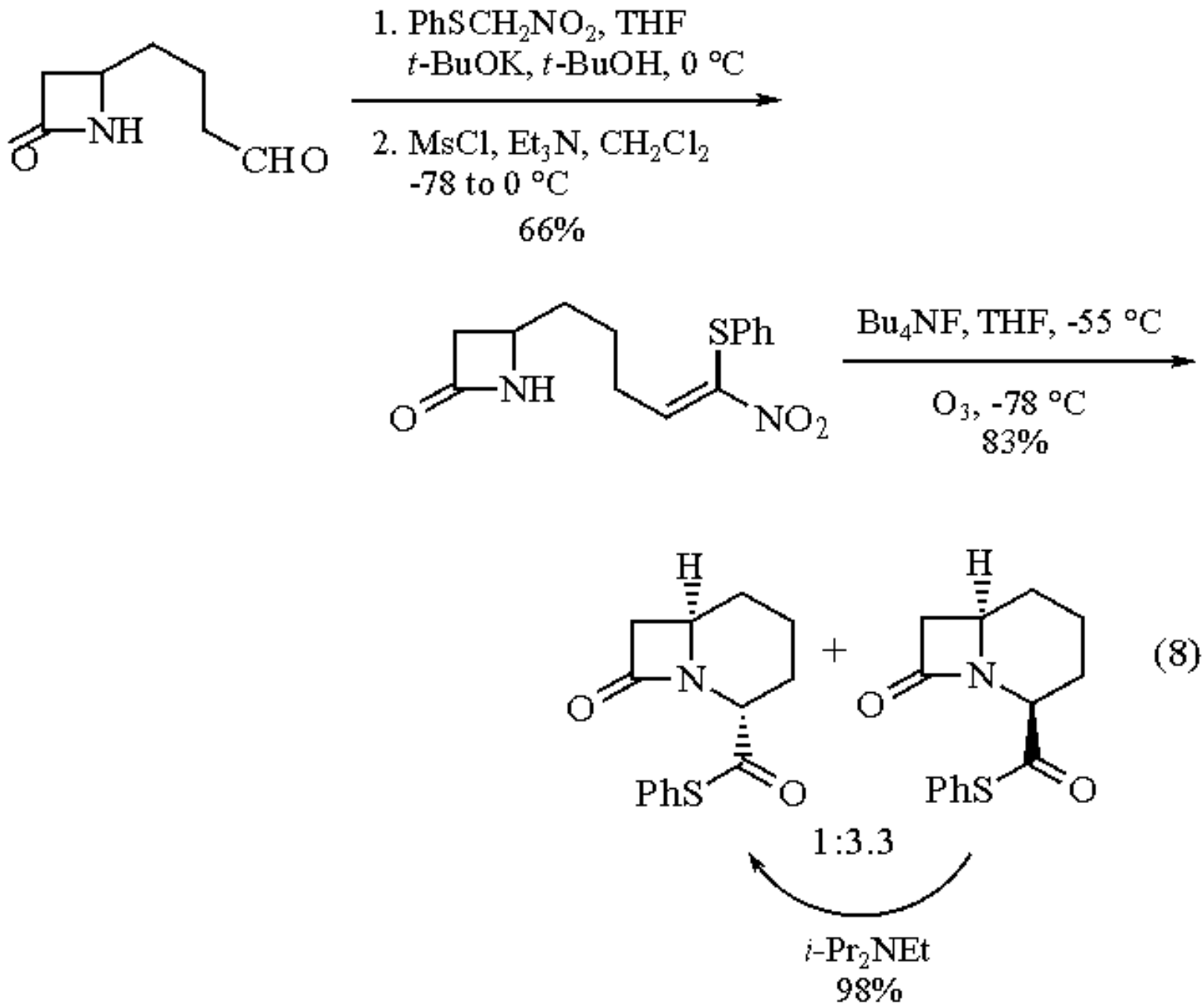
1. PhSCH2NO2, THF
t-BuOK, t-BuOH, 0 °C
2. MsCl, Et3N, CH2Cl2
-78 to 0 °C
66%
NH
O
CHO
SPh
NO2
Bu4NF, THF, -55 °C
O3, -78 °C
83%
H
N
PhS
1:3.3
i-Pr2NEt
98%

(8)

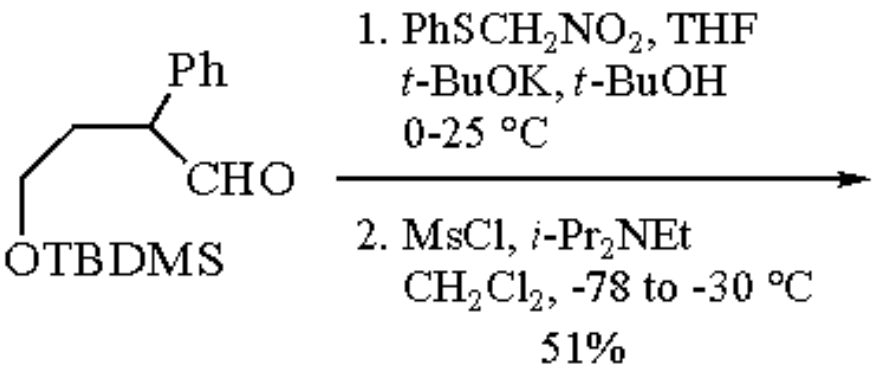

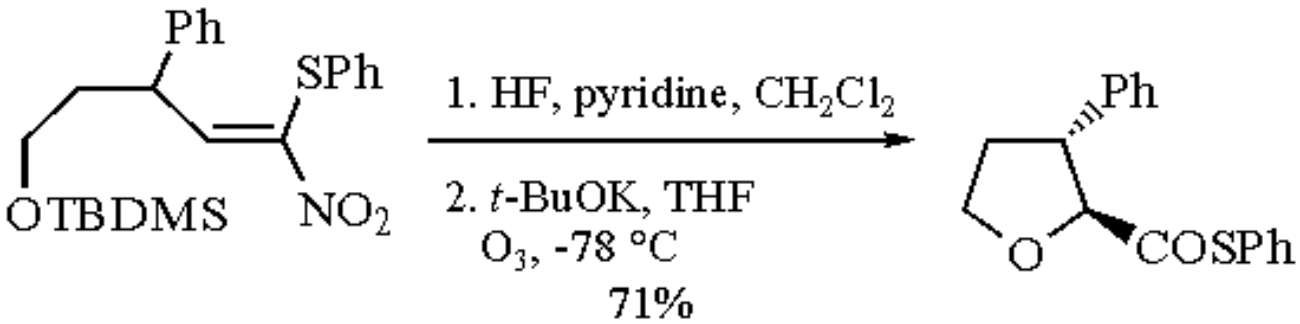

(9)

(Phenylthio)nitromethane has been dehydrated and the resultant phenylthionitrile oxide trapped with alkenes to provide isoxazolines (eq 10).[16] These compounds are convenient precursors for 3-(phenylsulfonyl)isoxazolines (see ***Phenylsulfonylnitromethane***) and β-hydroxy ketones. The cycloaddition-ring contraction of ynamines with 1-nitro-1-phenylthioalkenes has been used to prepare cyclic nitrones (eq 11).[17]

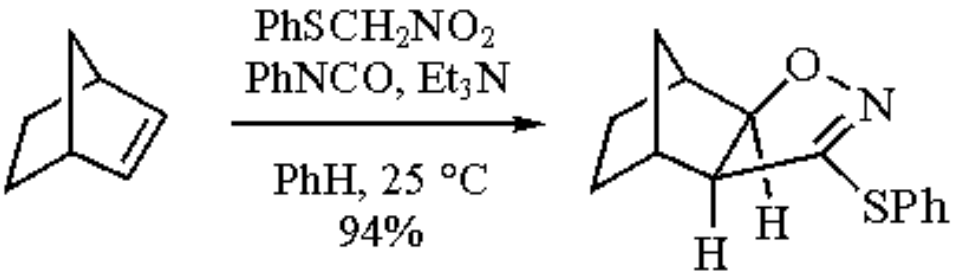

(10)

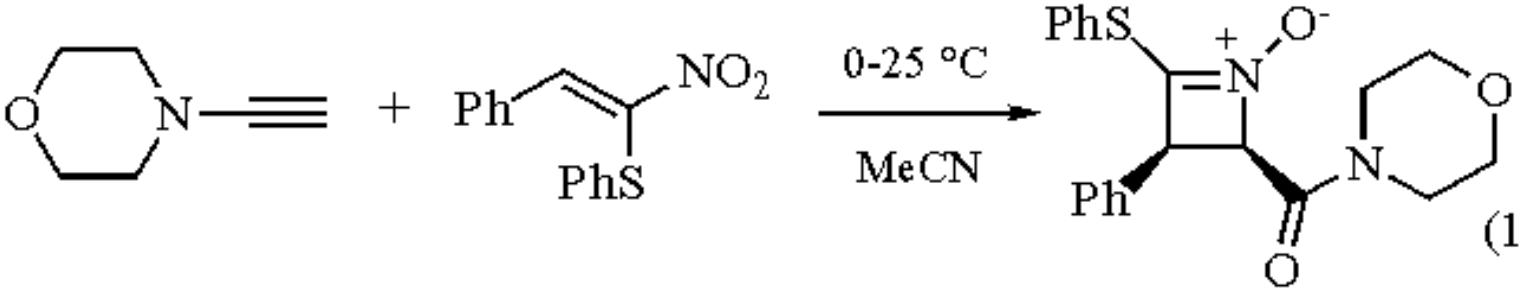

(11)

The Michael addition of (phenylthio)nitromethane to a steroidal enone and nitro displacement (eq 12) has been employed in the stereoselective 16-methylation of corticosteroids.[18]

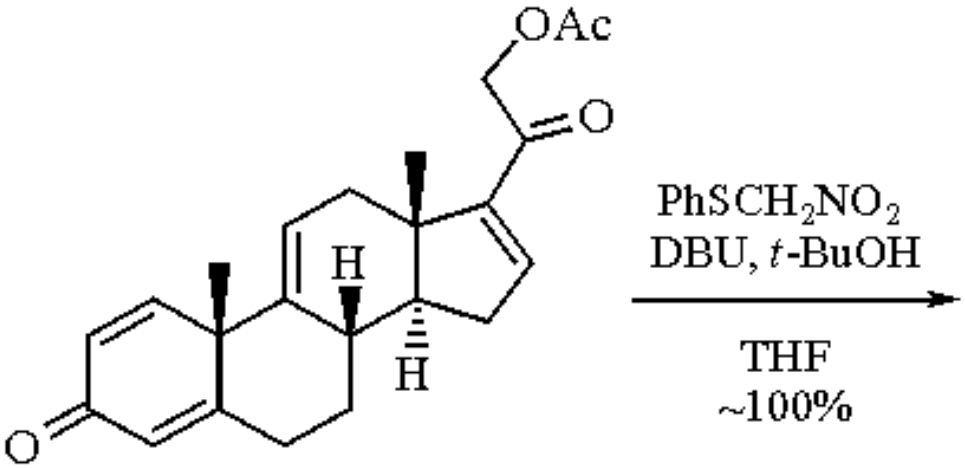

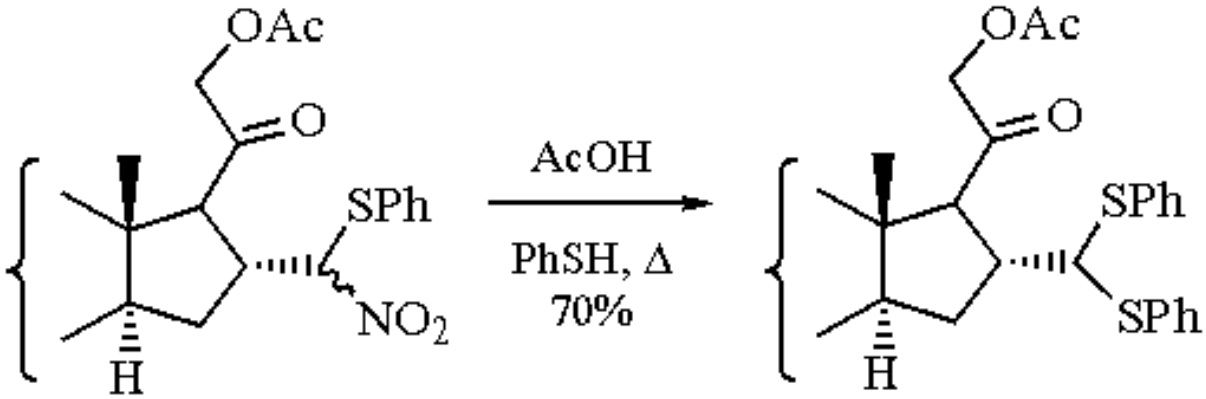

(12)

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13. (a) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Tennen Yuki Kago Butsu Toronki Koen Yoshishu* **1978**, *21*, 472 (*CA* **1979**, *90*, 168 757j). (b) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *JOC* **1984**, *49*, 3728. (c) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *CL* **1981**, 593; **1979**, 163.
14. (a) Barrett, A. G. M.; Cheng, M.-C.; Spilling, C. D.; Taylor, S. J. *JOC* **1989**, *54*, 992. (b) Barrett, A. G. M.; Cheng,

M.-C.; Sakdarat, S.; Spilling, C. D.; Taylor, S. J. *TL* **1989**, *30*, 2349. (c) Barrett, A. G. M.; Sakdarat, S. *JOC* **1990**, *55*, 5110.
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N-Phenylthiophthalimide[1]

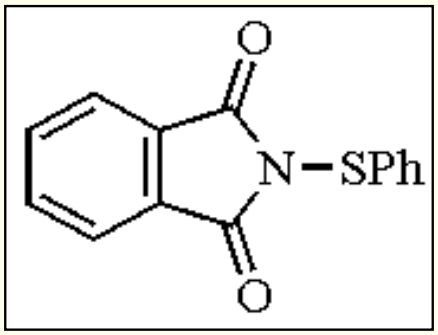

[14204-27-4] · $C_{14}H_9NO_2S$ · *N*-Phenylthiophthalimide · (MW 255.31)

(mild sulfenylating reagent)

Physical Data: mp 160-161 °C; colorless solid.

Preparative Method: by reaction of ***Benzenesulfenyl Chloride*** with ***Phthalimide*** in the presence of ***Triethylamine***.[1]

General Discussion.

N-Phenylthiophthalimide has been shown to be a mild sulfenylating reagent that is useful for a range of synthetic applications. This reagent reacts with amines[2] and thiols[3] to give the corresponding sulfenyl amines and disulfides respectively (eq 1).

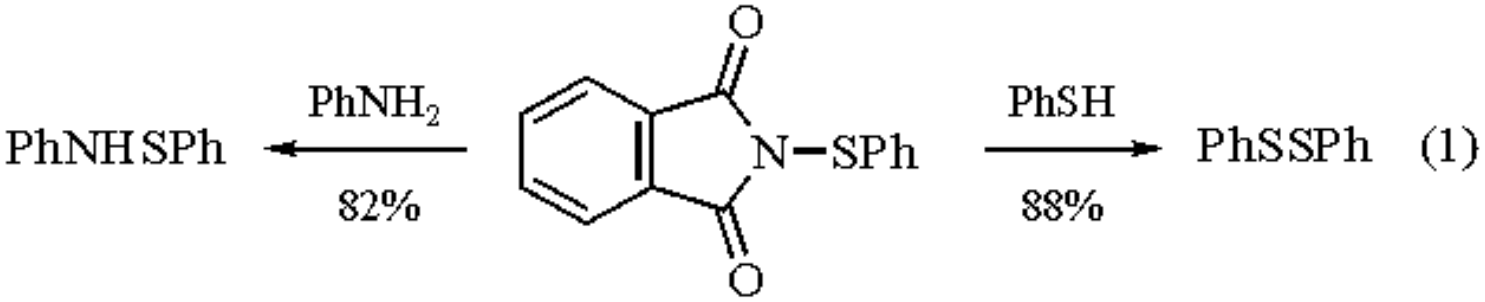

Upon reaction with Grignard reagents or organolithium compounds, mixed sulfides are formed (eq 2).[4]

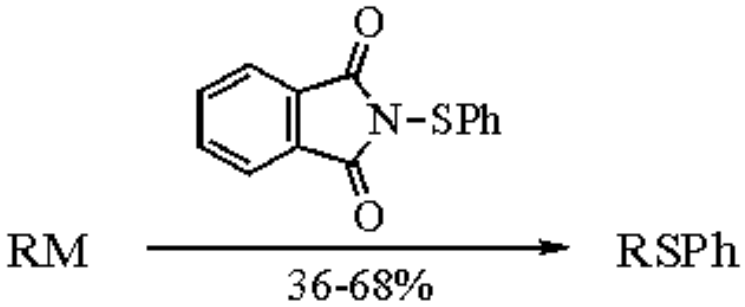

(2)

M = MgBr, Li

Activated carbonyl compounds can be cleanly bis-sulfenylated by this reagent in the presence of Et_3N (eq 3).[5]

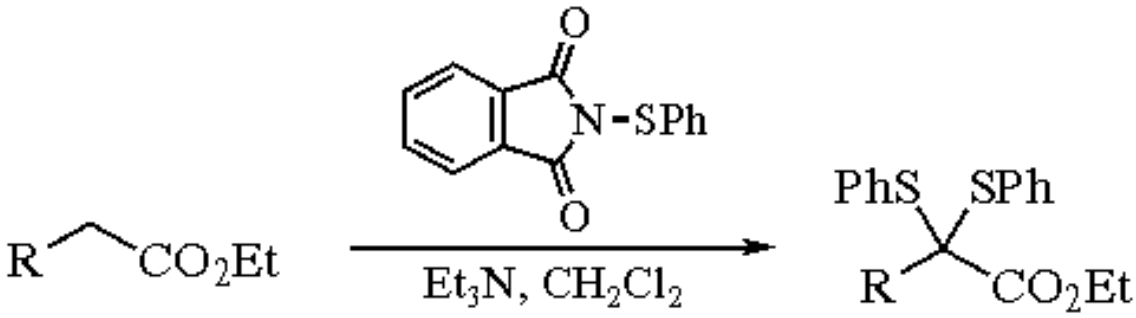

(3)

R = CO_2Et, 94%; MeCO, 93%

Bis-sulfenylation of γ-butyrolactone, as well as of cyclic ketones, has been achieved with this reagent via the corresponding lithium enolates.[6] This reaction has been utilized in an efficient synthesis of 3-substituted 2-buten-4-olides (eq 4).

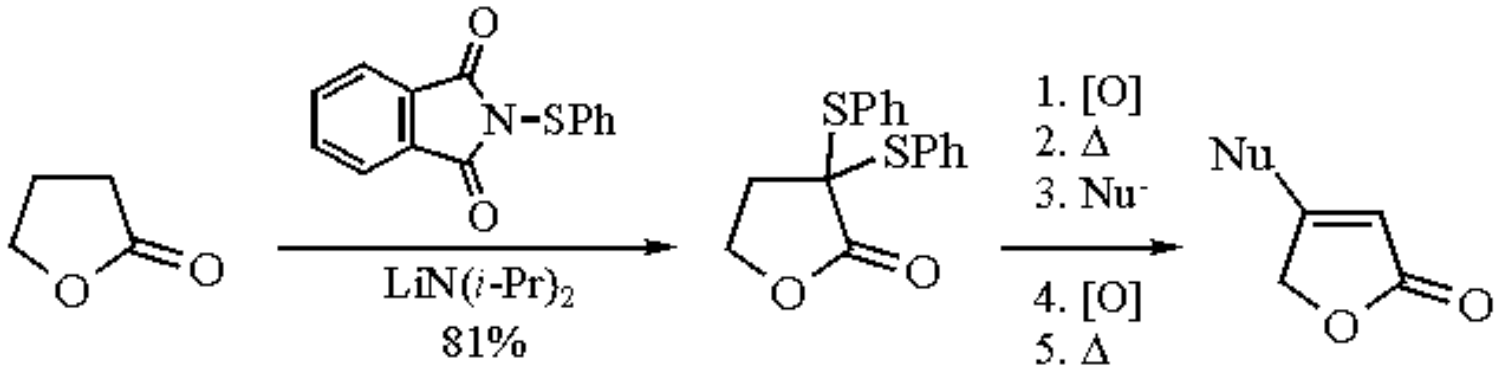

(4)

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(Phenylthio)trimethylsilane

$PhSSiMe_3$

[4551-15-9] · $C_9H_{14}SSi$ · (Phenylthio)trimethylsilane · (MW 182.39)

(selective carbonyl protection;[1,2] preparation of thioesters;[3] cleavage of ethers[4])

Physical Data: bp 93-99 °C/12 mmHg; *d* 0.967 g cm^{-3}.

Solubility: sol organic solvents; incompatible with strong acids and strong oxidizing agents.

Preparative Method: commercially available, but can be prepared.[5]

Handling, Storage, and Precautions: moisture sensitive; use in a fume hood.

Thioacetalization.

In the presence of an acid catalyst (***Zinc Iodide***, ***Aluminum Chloride***, anhyd ***Hydrogen Chloride***, ***Titanium(IV) Chloride***), (phenylthio)trimethylsilane reacts with aldehydes and ketones at rt or below to form the corresponding thioacetals (eqs 1 and 2).[1,2,6] With α,β-unsaturated aldehydes and ketones, initiation of the reaction with ***Potassium Cyanide-18-Crown-6*** leads to exclusive formation of the 1,4-addition product (eq 3).[1]

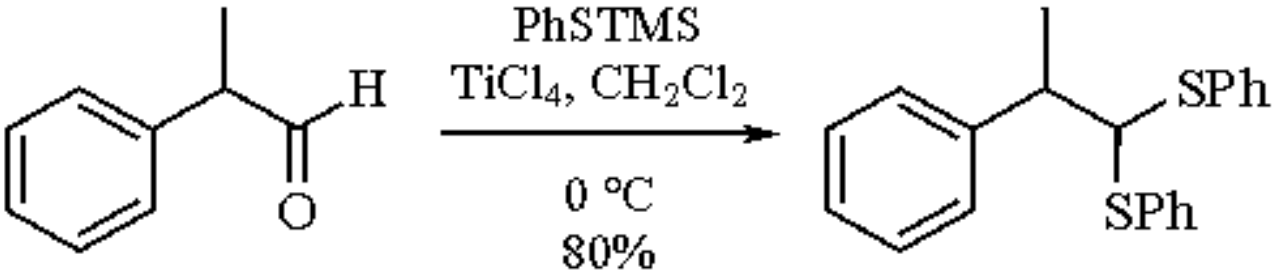

(1)

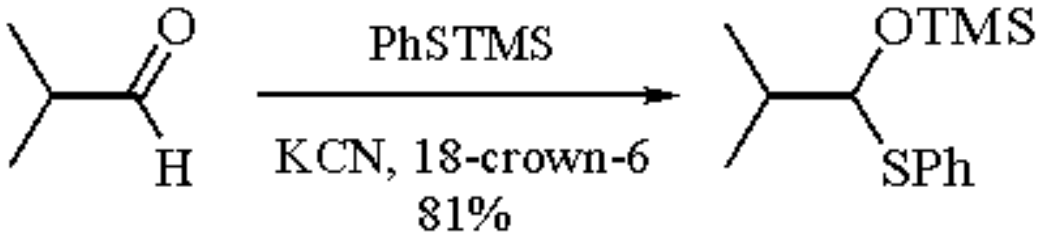

(2)

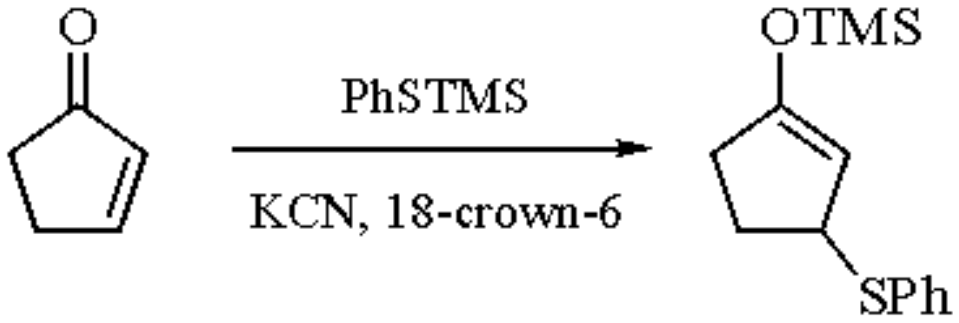

(3)

Cleavage of Ethers.

Methyl and benzyl ethers can be readily cleaved under mild conditions (eq 4).[4] The reagent also effects the stepwise and selective dealkylation of phosphotriesters.[7]

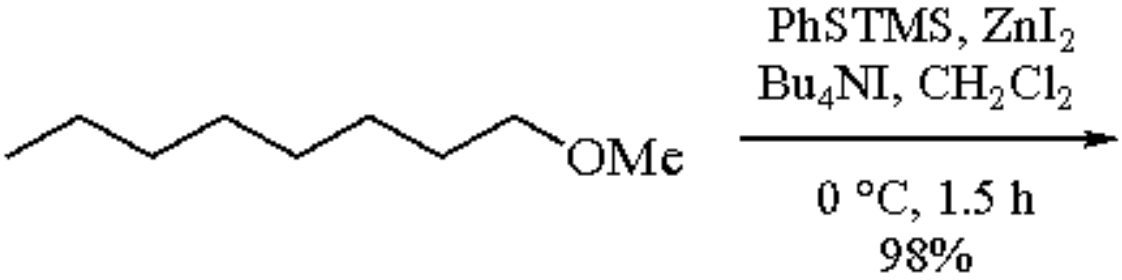

(4)

Miscellaneous Transformations.

(Phenylthio)trimethylsilane effects the direct conversion of glycosides into 1-thioglycosides,[8,9] esters into thioesters,[3] epoxides into β-(trimethylsilyloxy) thioethers and β-hydroxy ethers (eq 5),[10] sulfoxides into sulfides,[11] chalcone-derived acetals into α-alkoxy-α,β-unsaturated nitriles,[12] and silyl enol ethers into vinyl sulfides (eq 6).[13] The $AlCl_3$-catalyzed reaction of (phenylthio)trimethylsilane with electrophilic cyclopropanes leads to the formation of ring-opened products (eq 7).[14]

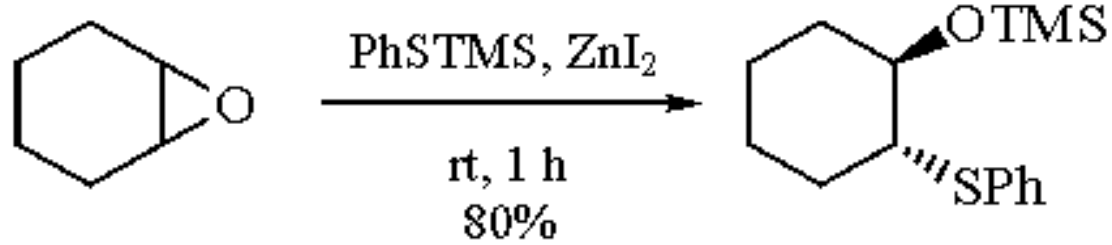

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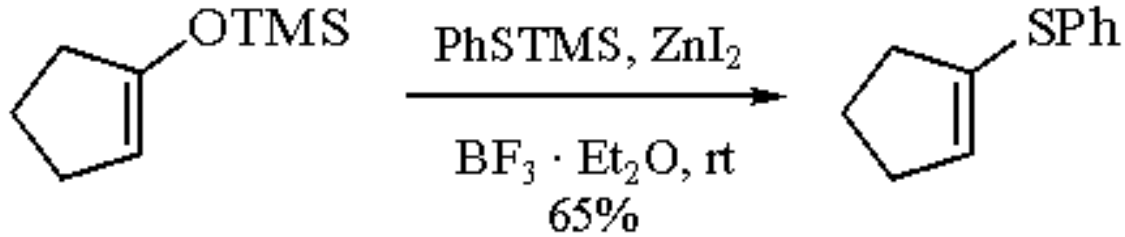

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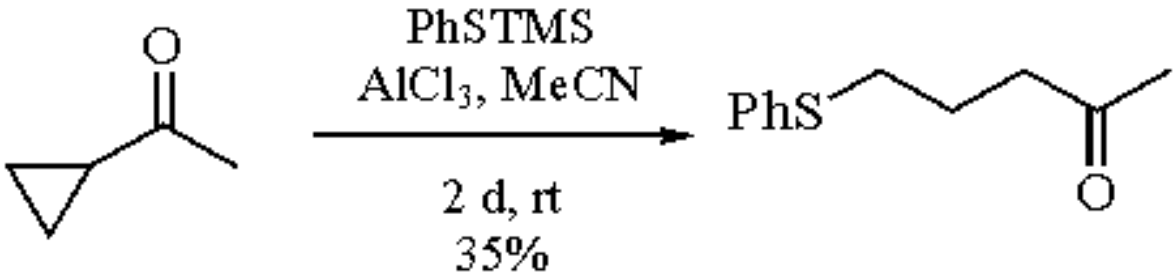

(7)

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1-(Phenylthio)-1-(trimethylsilyl)cyclopropane[1]

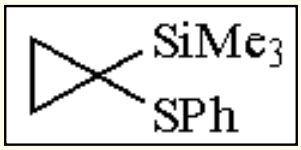

[74379-74-1] · $C_{12}H_{18}SSi$ · 1-(Phenylthio)-1-(trimethylsilyl)cyclopropane · (MW 222.46)

(Peterson alkenation;[1] cyclobutane synthesis[2] and cyclopentane[3] annulation via 1-lithio-1-(trimethylsilyl)cyclopropane)

Physical Data: bp 64 °C/0.1 mmHg; *d* 0.991 g cm^{-3}.

Form Supplied in: liquid; commercially available.

Analysis of Reagent Purity: FT-IR;[1c] also by NMR, IR, and mass spectrometry.[1b]

Preparative Methods: by reductive lithiation of 1,1-bis(phenylthio)cyclopropane followed by trimethylsilylation with ***Chlorotrimethylsilane***.[4,5]

Purification: by distillation.[1b]

Handling, Storage, and Precautions: use in a fume hood.

Peterson Alkenation.

1-Lithio-1-(trimethylsilyl)cyclopropane, derived from 1-phenylthio-1-(trimethylsilyl)cyclopropane by reductive lithiation with ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN), condenses with aldehydes to give carbinols which are converted to alkylidenecyclopropanes under Peterson alkenation conditions (eq 1).[1]

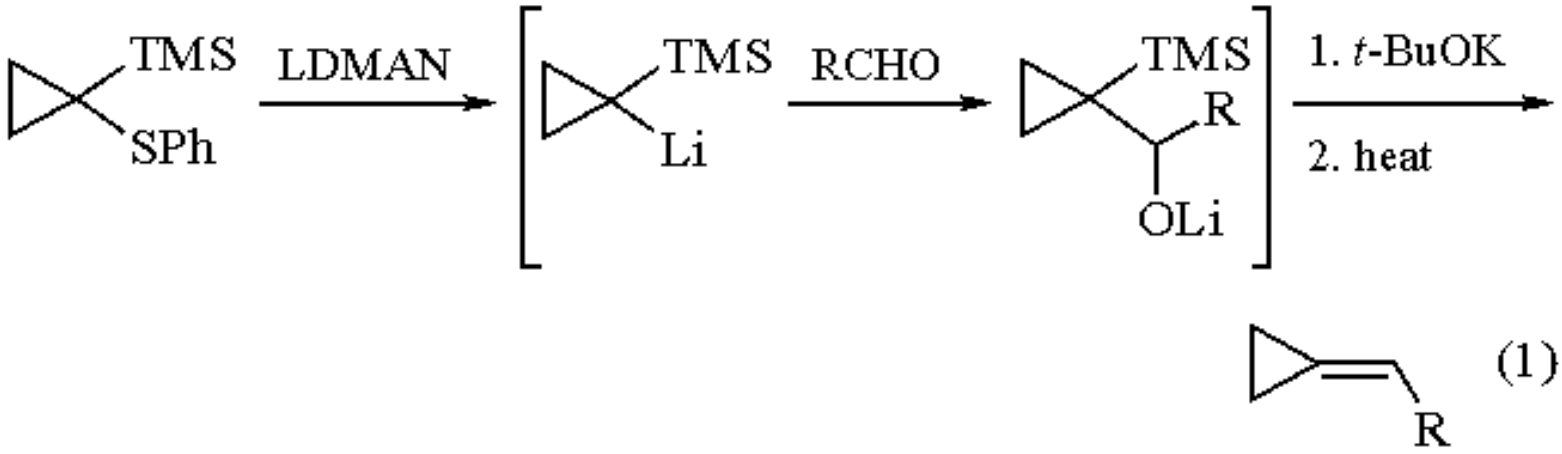

Synthesis of Cyclobutanes.

m-Chloroperbenzoic Acid oxidation of 1-phenylthio-1-(trimethylsilyl)cyclopropane furnishes a sulfoxide which could undergo thermal sila-Pummerer rearrangement to give the masked cyclopropanone 1-(phenylthio)-1-trimethylsiloxy)cyclopropane (eq 2).[2a]

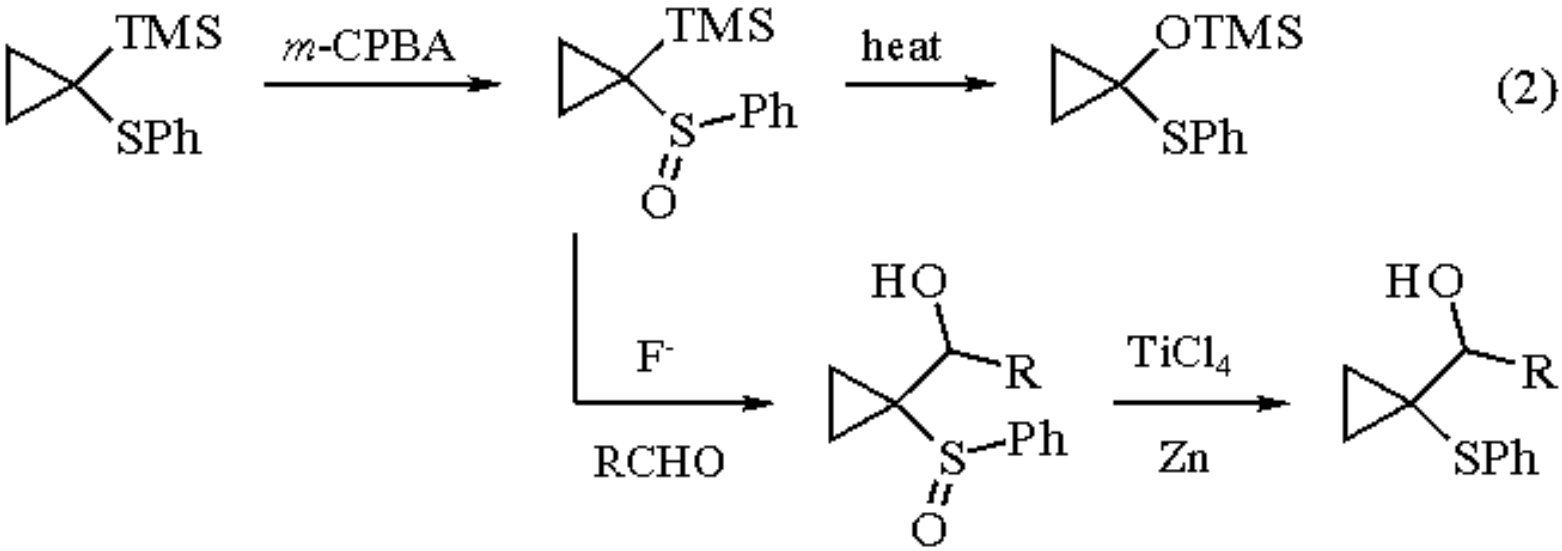

Alternative treatment of the sulfoxide with aldehydes in the presence of ***Tetra-n-butylammonium Fluoride*** gives the phenylsulfinylcarbinol and thence the phenylthiocarbinol following reduction. The two last-named compounds are intermediates in the synthesis of cyclobutanones and cyclobutenes, respectively (eqs 3 and 4).[2b,2c,2e]

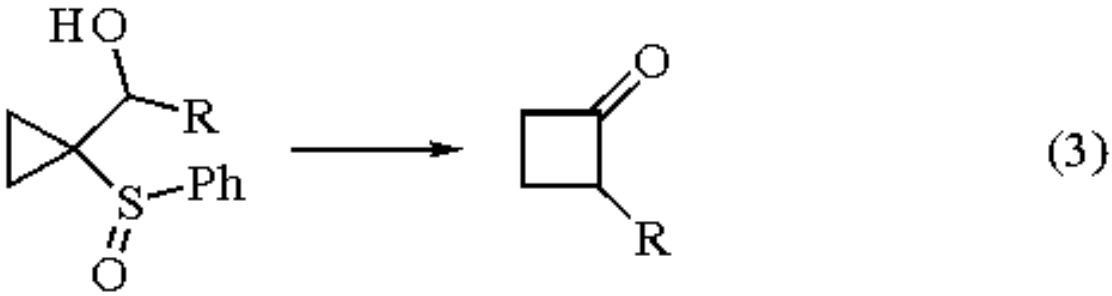

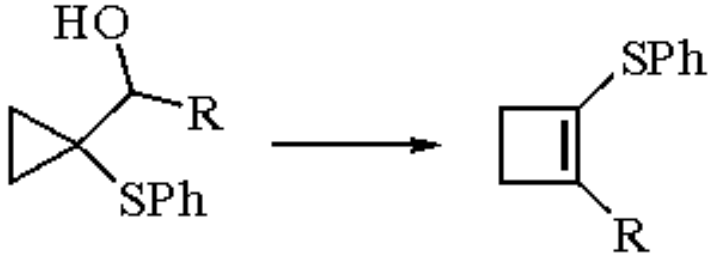

(4)

Cyclopentane Annulation.

Condensation of 1-lithio-1-(trimethylsilyl)cyclopropane with ketones gives vinylcyclopropane intermediates, which upon pyrolysis undergo vinylcyclopropane rearrangement to give annulated cyclopentene derivatives (eq 5).[3]

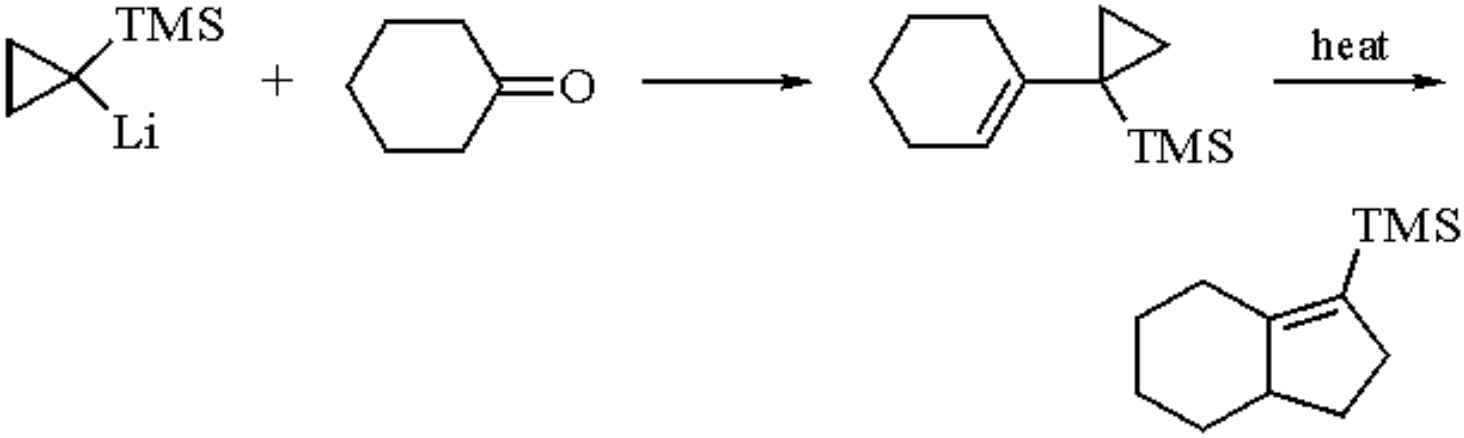

(5)

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5. Paquette, L. A.; Horn, K. A.; Wells, G. J. *TL* **1982**, *23*, 259.

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1-Phenylthio-1-trimethylsilylethylene

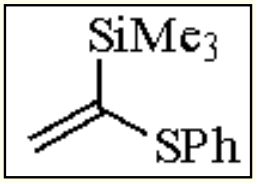

[62762-20-3] · $C_{11}H_{16}SSi$ · 1-Phenylthio-1-trimethylsilylethylene · (MW 208.43)

(a reagent for C_2 homologation and a Michael acceptor)

Physical Data: colorless liquid; bp 130-134 °C/15 mmHg;[1] IR,[1,2] ^{1}H NMR,[1] and MS data[1] are available.

Solubility: very sol most organic solvents.

Preparative Methods: by lithiation of ***Phenyl Vinyl Sulfide*** with ***Lithium Diisopropylamide***, followed by silylation,[1,2] or the base-induced elimination of 2-chloro-1-trimethylsilyl-1-phenylthioethane,[2] or the lithiation of ethyl phenyl sulfoxide with LDA followed by silylation,[3] or the Pd-catalyzed coupling reactions of trimethylstannyl phenyl sulfide with 1-bromo-1-trimethylsilylethylene.[4]

Handling, Storage, and Precautions: use in a fume hood.

Addition of Organolithiums.

Organolithiums undergo smooth additions to 1-phenylthio-1-trimethylsilylethylene at low temperature. The resulting adduct anions are stabilized by two anion-stabilizing substituents, phenylthio and trimethylsilyl. They can be quenched with a variety of electrophiles. Sulfines are formed by treatment with ***Sulfur Dioxide*** (eq 1),[5] phenyl 1-silylalkyl sulfides by hydrolytic quenching with NH_4Cl,[1] alkanals by oxidation with ***m-Chloroperbenzoic Acid*** and subsequent rearrangement reaction (eq 2),[6,7] phenyl silylalkyl sulfides by alkylation with a variety of alkylating agents,[8] and vinyl sulfides by condensation with aldehydes.[8]

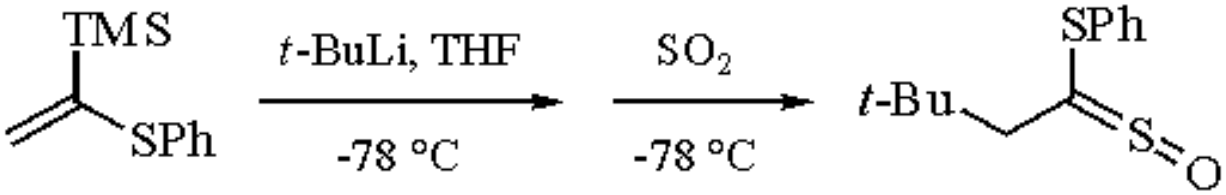

(1)

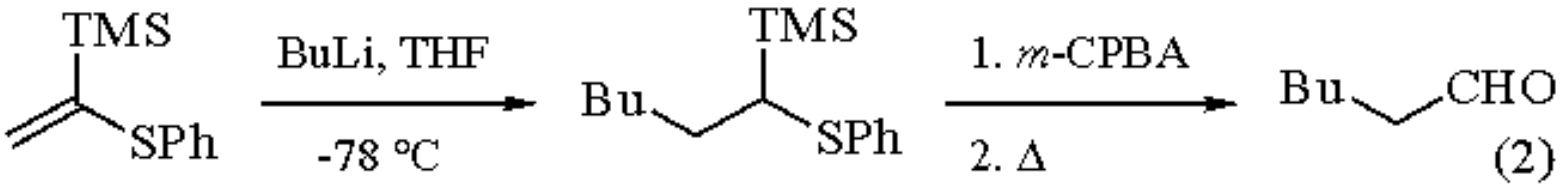

Cyclopentenone Synthesis.

When activated with Lewis acid catalysts or silver ion, 1-phenylthio-1-trimethylsilylethylene reacts with α,β-unsaturated acid chlorides at a low temperature in CH_2Cl_2.[2,9] The cation intermediates undergo a silicon-directed Nazarov cyclization to give 3-phenylthio-substituted cyclopentenone derivatives (eq 3). The phenylthio moiety at the β-position of cyclopentenones can be effectively utilized for the introduction of an alkyl substituent by addition/elimination.

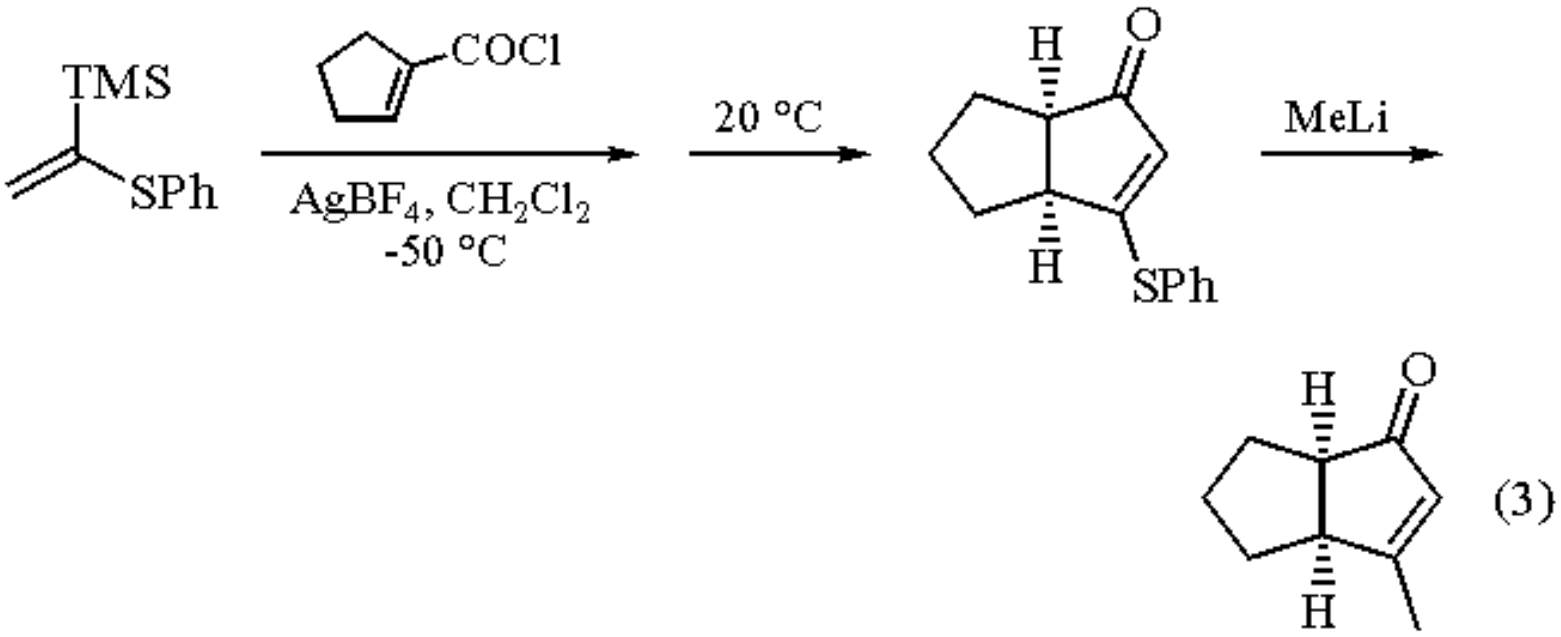

Cyclopropanation.

Although the adduct anions formed by addition of organolithiums to 1-phenylthio-1-trimethylsilylethylene have high stability at low temperature, at higher temperatures (0 °C) in THF the anions may react with another molecule of 1-phenylthio-1-trimethylsilylethylene. The final anions undergo intramolecular alkylation under the reaction conditions to give cyclopropane derivatives in high yields (eq 4).[10] Employment of sulfur-stabilized anions as donor molecules is even more effective (eq 5).[11]

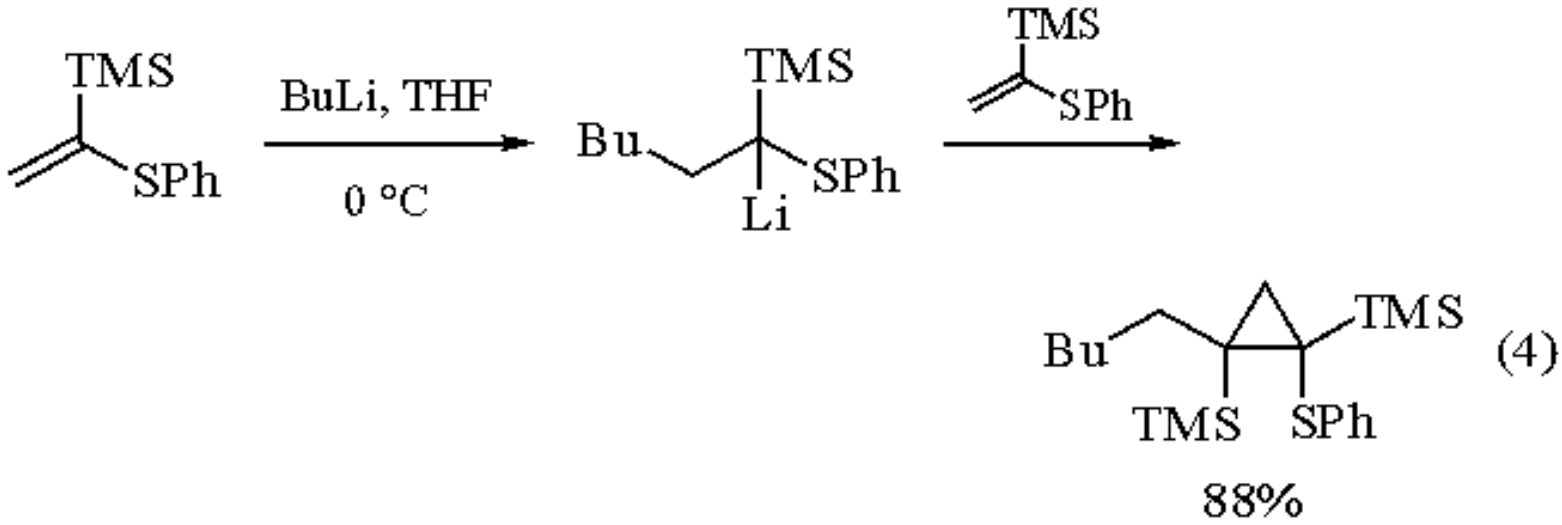

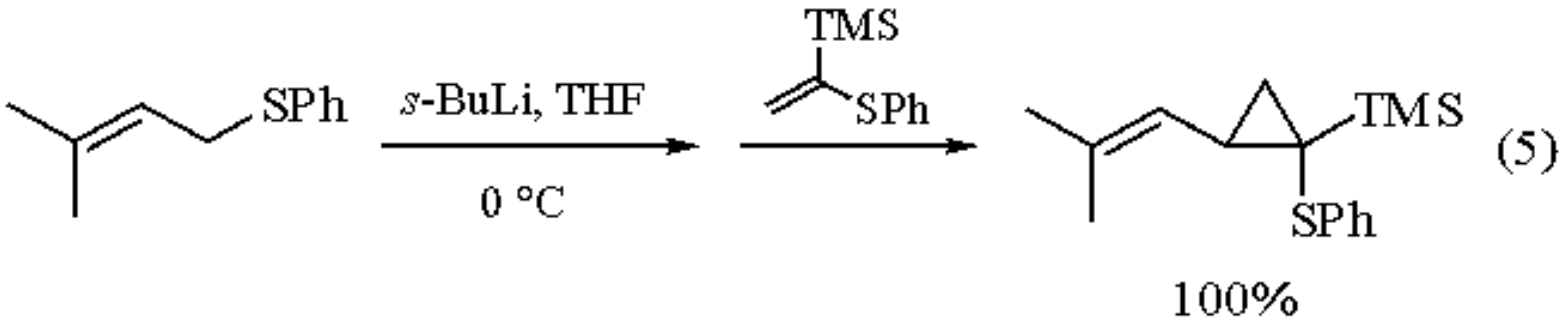

Cyclohexanone Annulation.

The benzyllithium intermediates formed by metalation of *o*-toluamide derivatives with LDA at -78 °C react with 1-trimethylsilyl-1-phenylthioethylene. The resulting adduct anions undergo intramolecular cyclization on to the adjacent amide moiety to provide a convenient route for cyclohexanone annulation (eq 6).[12]

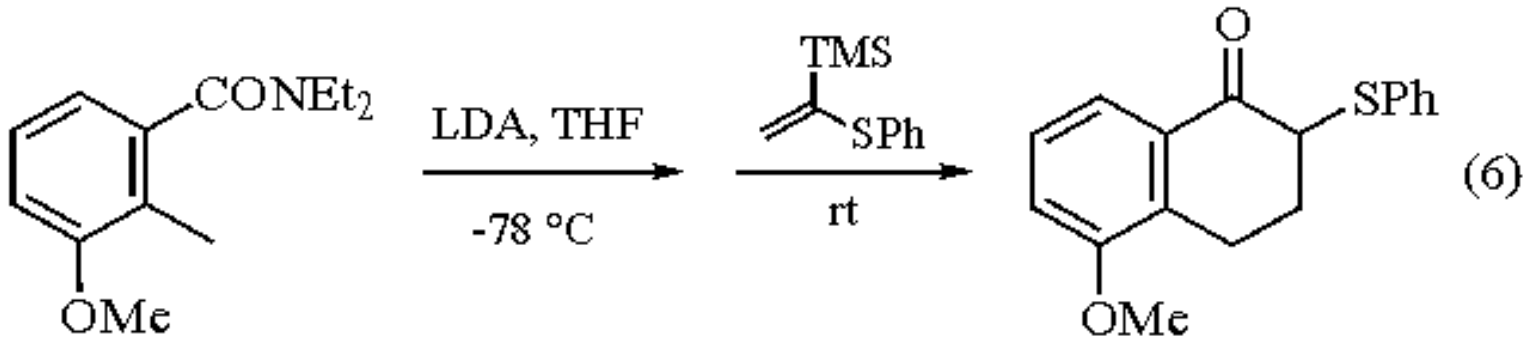

Analogous Reagents.

1-Phenylsulfinyl-1-trimethylsilylethylene (**1**)[2] and 1-phenylsulfonyl-1-trimethylsilylethylene (**2**) are used as synthetic analogs of 1-phenylthio-1-trimethylsilylethylene. The sulfoxide (**1**) is an electron-deficient alkene so it is a highly reactive dienophile in Diels-Alder reactions. The cycloadduct with ***Cyclopentadiene*** undergoes the sila-Pummerer rearrangement to a thioacetal, which is then hydrolyzed to the ketone (eq 7).[6] By this sequence, (**1**) becomes a useful

synthetic equivalent of ketene. The sulfone (**2**) works as an excellent acceptor molecule for the Michael addition reactions using the aryllithium donors generated by the directed lithiation of *o*-chloroarenes. The adducts then undergo intramolecular cyclizations by the aid of metal amides to offer an excellent entry to benzocyclobutene derivatives.[13]

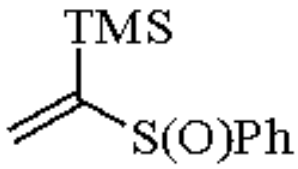

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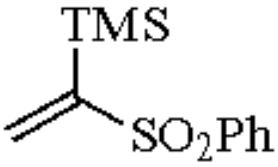

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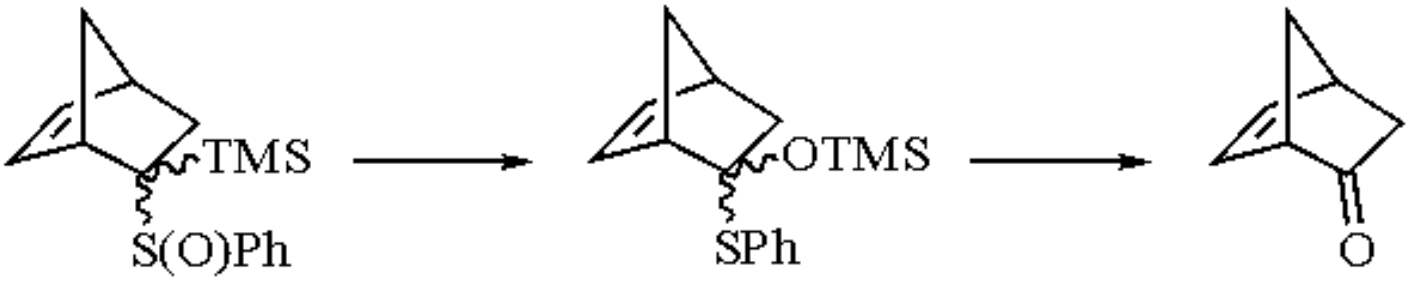

(7)

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2-(Phenylthio)-2-(trimethylsilyl)propane[1]

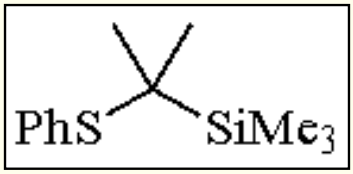

[89656-96-2] · $C_{12}H_{20}SSi$ · 2-(Phenylthio)-2-(trimethylsilyl)propane · (MW 224.48)

(Peterson alkenation[1] and preparation of ketones via 2-lithio-2-(trimethylsilyl)propane[2,3])

Physical Data: bp 70-80 °C/0.6 mmHg.

Preparative Method: by reductive lithiation of 2,2-bis(phenylthio)propane followed by trimethylsilylation with ***Chlorotrimethylsilane***.[2,3]

Purification: by flash chromatography and by Kugelrohr distillation.[3]

Handling, Storage, and Precautions: use in a fume hood.

Synthesis of Dienes via Peterson Alkenation.

Reductive lithiation of 2-(phenylthio)-2-(trimethylsilyl)propane with ***Lithium 1-(Dimethylamino)naphthalenide*** (LDMAN) furnishes 2-lithio-2-(trimethylsilyl)propane, which is an intermediate for Peterson alkenation. The specific example in eq 1 features silicon-directed diene synthesis.[1]

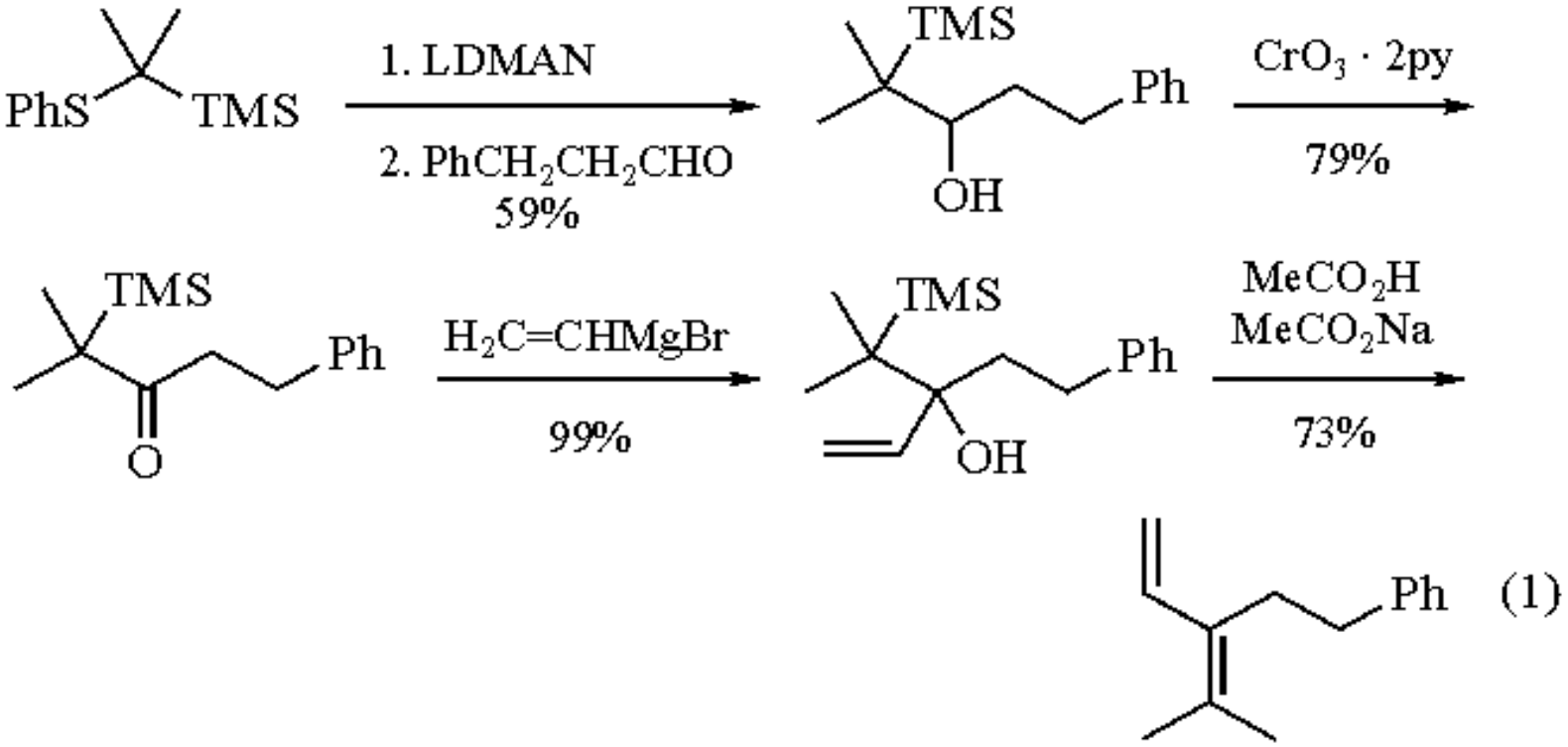

Synthesis of Ketones.

m-Chloroperbenzoic Acid oxidizes 2-(phenylthio)-2-(trimethylsilyl)propane to the sulfone, which is then converted to the ketone via sila-Pummerer rearrangement (eq 2).[3]

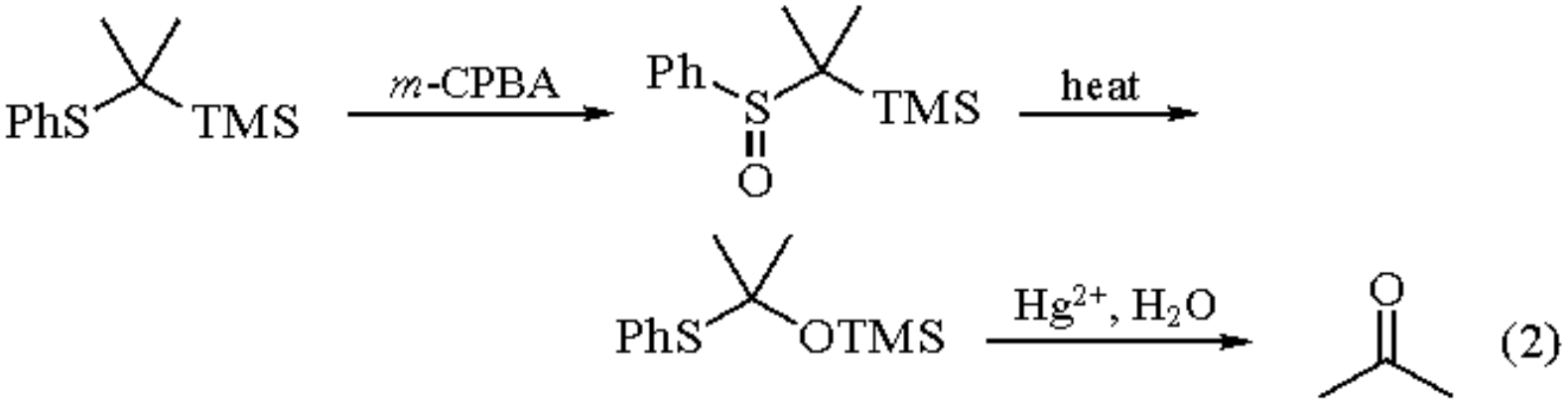

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Se-Phenyl *p*-Tolueneselenosulfonate[1]

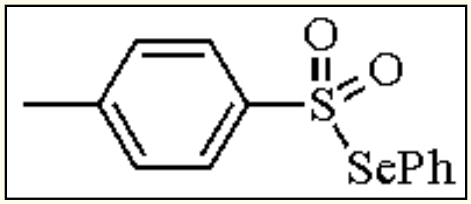

[68819-94-3] · $C_{13}H_{12}O_2SSe$ · *Se*-Phenyl *p*-Tolueneselenosulfonate · (MW 311.28)

(undergoes 1,2-additions to alkenes, allenes, dienes, and alkynes, affording various unsaturated sulfones after selenoxide elimination or sigmatropic rearrangement[1])

Physical Data: mp 79.5-80 °C.

Solubility: sol chloroform, dichloromethane, THF, benzene.

Form Supplied in: yellow, crystalline, odorless solid.

Preparative Methods: add ***p-Toluenesulfonylhydrazide*** in methanol dropwise to an equimolar amount of ***Benzeneseleninic Acid*** in methanol at 0 °C; cool at -5 °C overnight, filter the highly pure crystalline selenosulfonate (96% yield);[2] alternatively, use 2 equiv ***p-Toluenesulfinic Acid*** instead of *p*-toluenesulfonylhydrazide;[3] *Se*-phenyl benzeneselenosulfonate is prepared in the same way and can be employed similarly for most purposes.

Purification: recrystallization from methanol.

Handling, Storage, and Precautions: routine handling is possible; for prolonged storage, keep in the dark at 0 °C; probably toxic. Use in a fume hood.

Selenosulfonation of Alkenes, Allenes, and Dienes.

The selenosulfonate adds stereospecifically (*anti*) and regioselectively (Markovnikov) to alkenes in the presence of ***Boron Trifluoride Etherate*** to afford 1,2-adducts (eq 1).[4] The addition can also be effected by a nonstereospecific radical process, initiated thermally in the presence of ***Azobisisobutyronitrile*** (AIBN), or photochemically, to give anti-Markovnikov products (eq 2).[3,4] These processes are known as selenosulfonations.[4] Selenoxide *syn* elimination of the adducts can be effected with ***m-Chloroperbenzoic Acid*** (*m*-CPBA) or ***Hydrogen Peroxide***, and affords high yields of the corresponding vinyl sulfones.

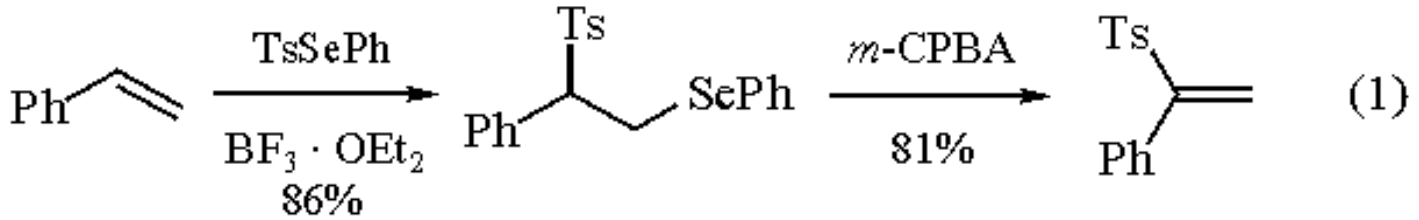

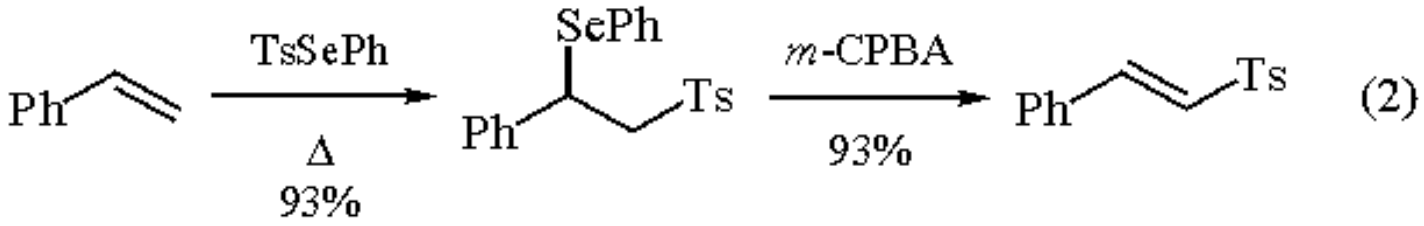

Allenes undergo radical selenosulfonation with regioselective incorporation of the sulfonyl moiety at the central carbon atom, producing 2-sulfonyl allylic alcohols after oxidation and [2,3]-sigmatropic rearrangement (eq 3).[5] Conjugated dienes react with the selenosulfonate in the presence of Lewis acids to afford chiefly the corresponding 1,2-adducts, in turn producing 2-sulfonyl-1,3-dienes after selenoxide elimination (eq 4),[4,6] while 1,6-dienes are converted into cyclopentanes by radical cyclization.[7]

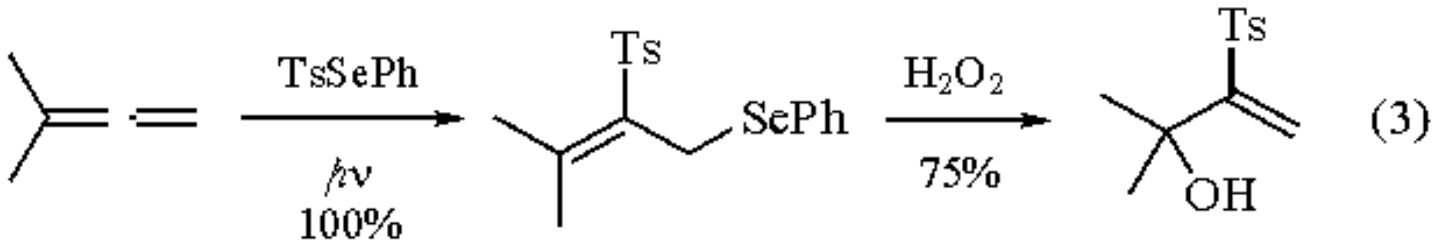

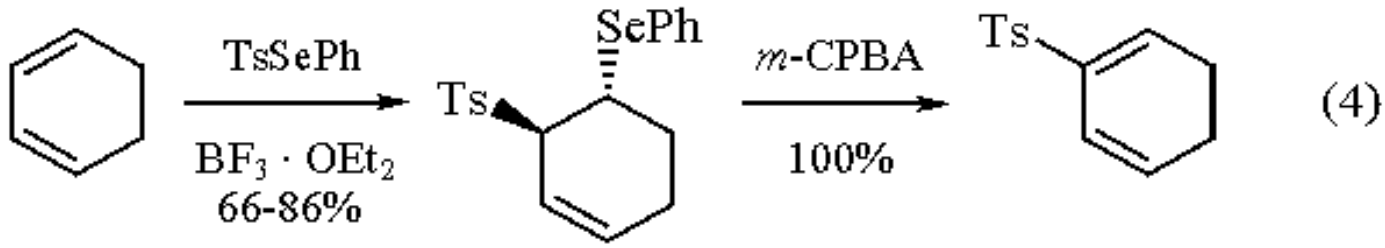

Selenosulfonation of Alkynes.

The radical selenosulfonations of alkynes proceed in a stereo- and regioselective manner to give the products of *anti* addition and anti-Markovnikov orientation in generally high yield.[8] Subsequent selenoxide eliminations produce alkynic sulfones from terminal alkynes (eq 5) and allenic sulfones from internal ones (eq 6). Moreover, the initial adducts can be alkylated in the α-position and isomerized to the corresponding allylic sulfones under base-catalyzed conditions, thereby also providing access to allenic sulfones from terminal alkynes (eq 7).[9] The adducts or their selenoxides also react with various nucleophiles by addition-elimination or elimination-addition processes to give the products of overall substitution of the selenium residue (eq 8). Possible nucleophiles include organocuprates, alcohols, amines, cyanide, active methylene compounds, dithianes, and propargylic anions.[8a,10] When such reactions are employed in conjunction with reductive desulfonylation, the overall transformation renders alkynes the synthetic equivalents of vinyl cations.

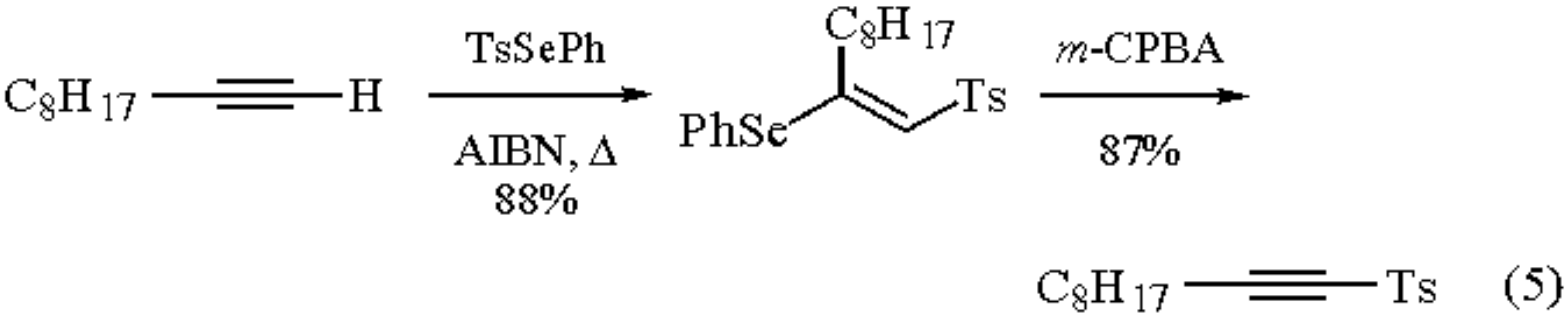

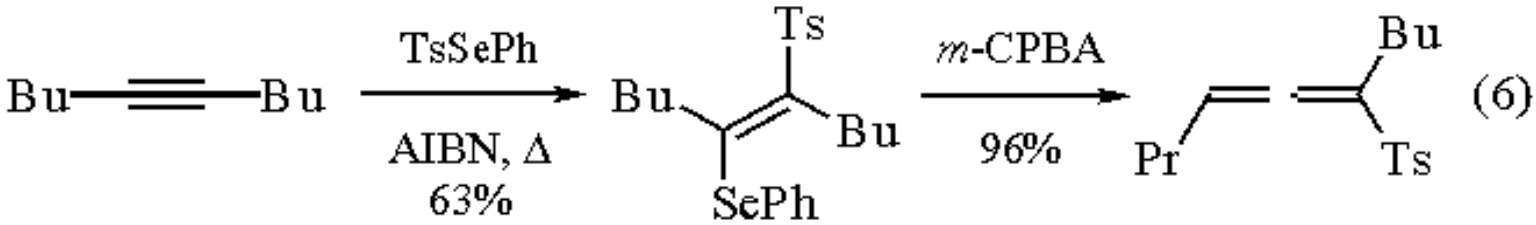

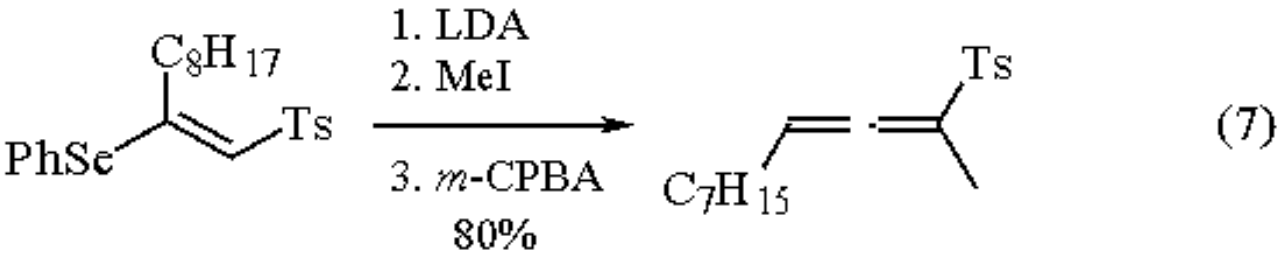

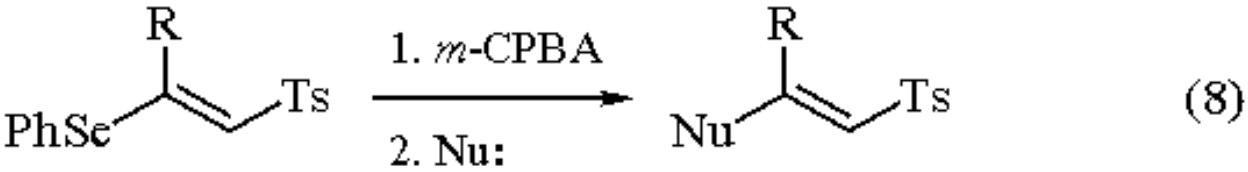

Enynes with terminal alkyne moieties cleanly afford the products of 1,2-addition to the triple bond (eq 9), but more highly substituted derivatives and those containing terminal alkene groups give more complex mixtures containing the products of addition to the double bond, as well as 1,4-adducts.[11] Products such as the example in eq 9 smoothly generate allenic alcohols after oxidation and [2,3]-sigmatropic rearrangement. ***1,4-Dichloro-2-butyne*** can be employed as an enyne equivalent, since reductive dehalogenation generates an additional unit of unsaturation. The resulting 2,3-adduct can be used to prepare 3-substituted 2-sulfonyl-1,3-dienes,[11] as shown in eq 10.

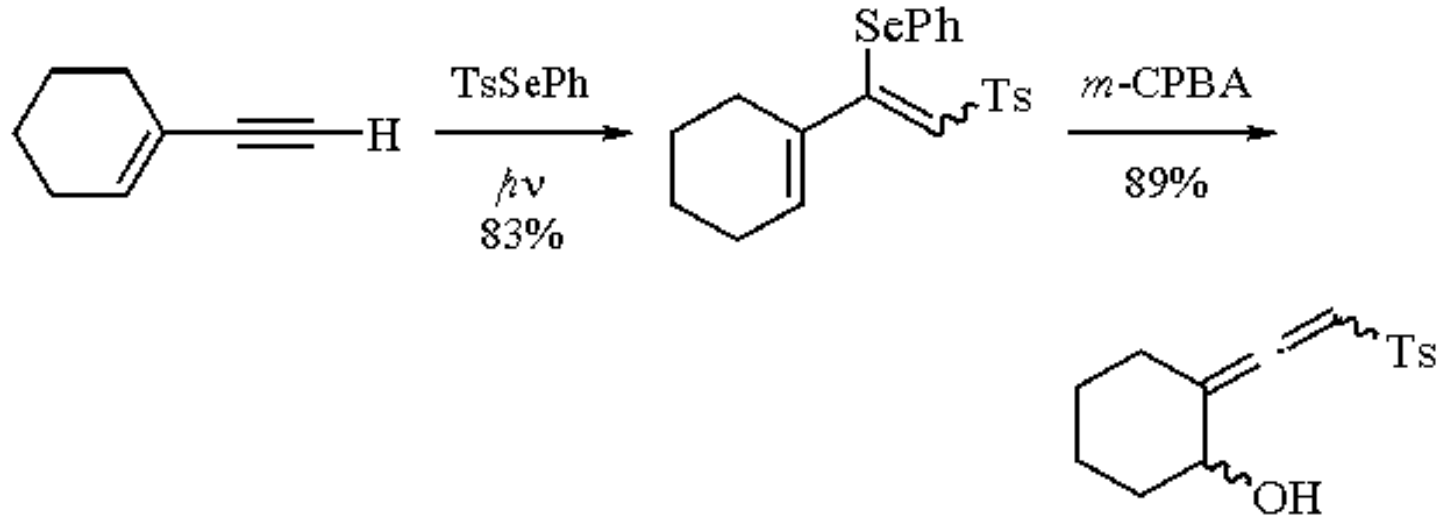

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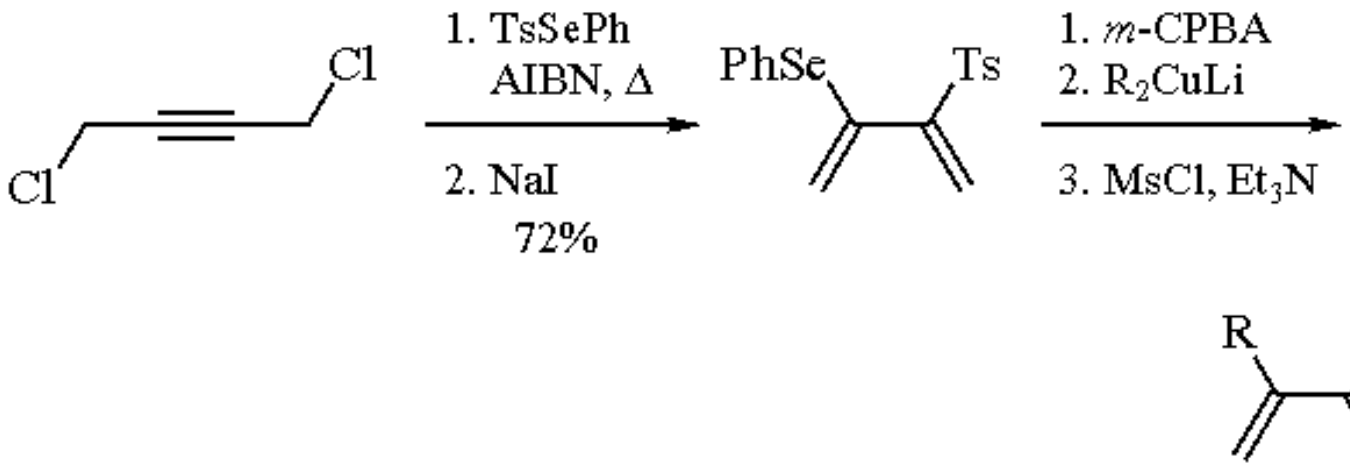

(10)

Selenosulfonation of Unsaturated Cyclopropanes.

The radical selenosulfonation of vinylcyclopropanes is accompanied by ring-opening to give 1,5-addition products that afford 1-sulfonyl-2,4-dienes by selenoxide elimination (eq 11).[12] Similar ring-opening is observed in cyclopropylidenes, whereas cyclopropylacetylene undergoes mainly 1,2-addition and provides the corresponding alkynic sulfone after selenoxide elimination (eq 12).[12]

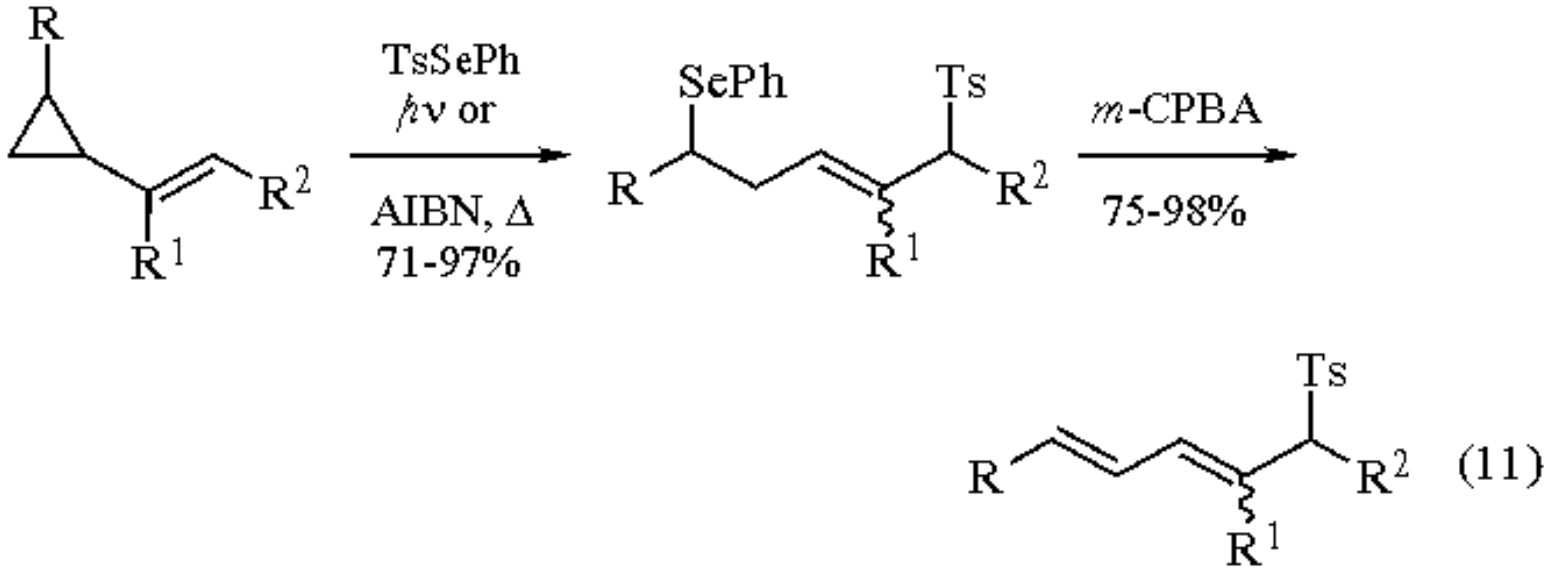

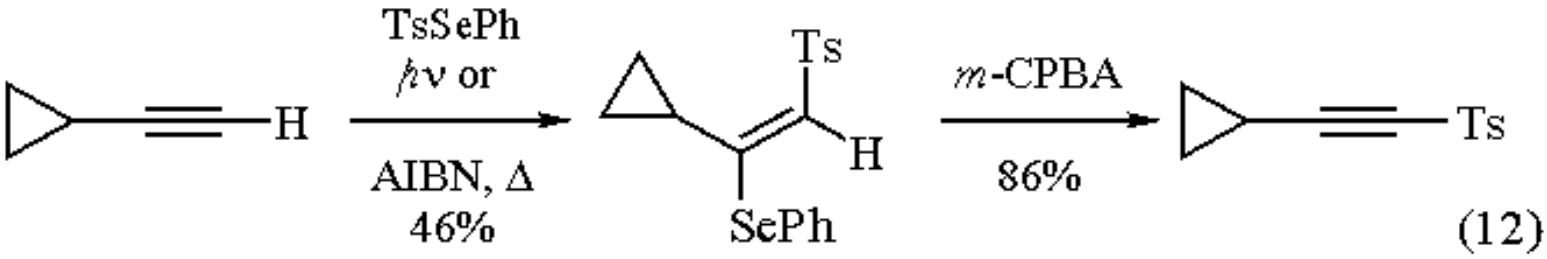

Related Reagents.

Benzeneselenenyl Bromide; ***Benzeneselenenyl Chloride***; ***Benzeneselenenyl Trifluoromethanesulfonate***; ***Diphenyl Diselenide***; ***N-Phenylselenophthalimide***.

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(*R*)-(+)-Phenyl (*p*-Toluenesulfinyl)acetate

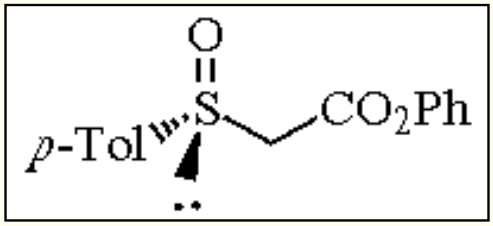

[75340-59-9] · $C_{15}H_{14}O_3S$ · (*R*)-(+)-Phenyl (*p*-Toluenesulfinyl)acetate · (MW 274.36)

(asymmetric aldol-type condensations[1])

Physical Data: $[\alpha]_D$ +87° ($CHCl_3$, *c* 0.95).

Preparative Methods: conveniently prepared by deprotonation of (*R*)-(+)-*p*-tolyl methyl sulfoxide and treatment of the resulting sulfinyl carbanion with phenyl chloroformate (eq 1).[1]

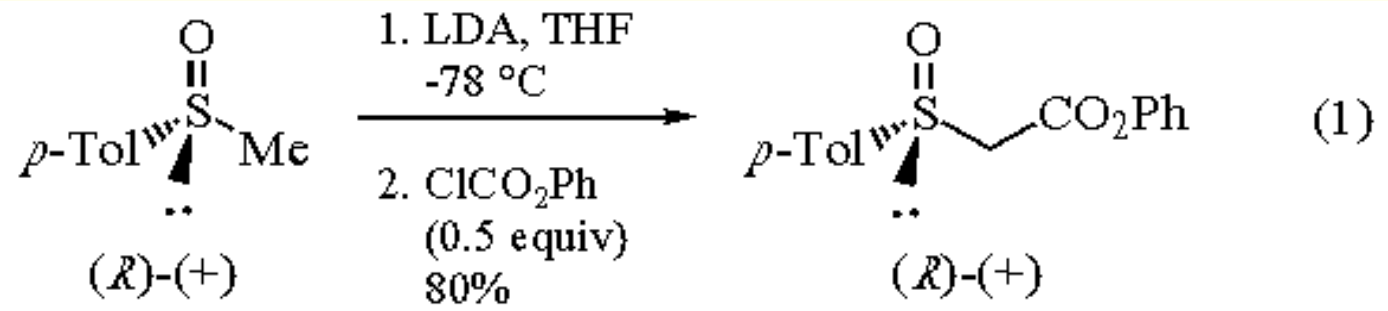

(1)

Asymmetric oxidation of phenyl (*p*-toluenesulfinyl)acetate with bovine serum albumin (BSA) gave a poor ee (eq 2).[2]

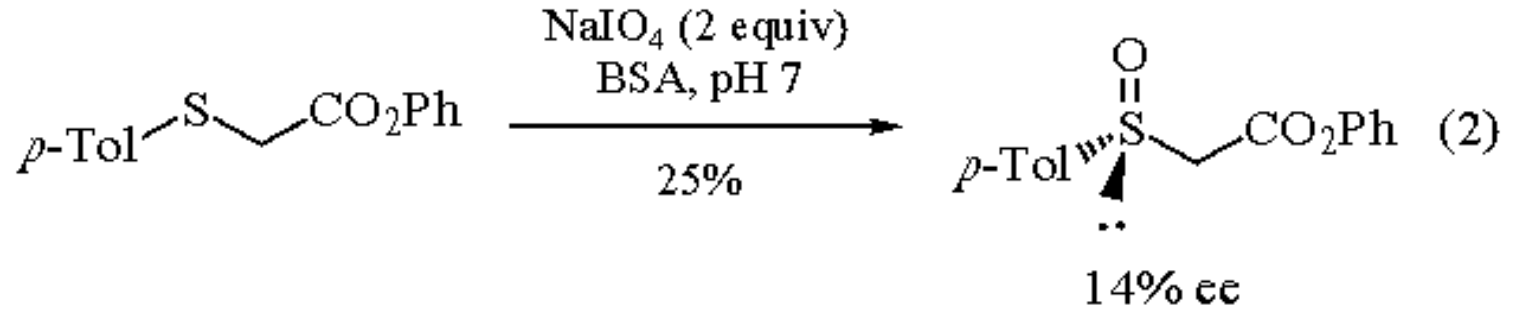

(2)

General Discussion.

Aldol-type condensation of the magnesium enolate of (*R*)-(+)-phenyl (*p*-toluenesulfinyl)acetate, prepared with *t*-butylmagnesium bromide, with the aldehyde precursor of maytansine afforded, after desulfurization with ***Aluminum Amalgam***, the desired 4,5-unsaturated 3-(*S*)-hydroxy ester in high yield and high diastereoselectivity (eq 3).[1]

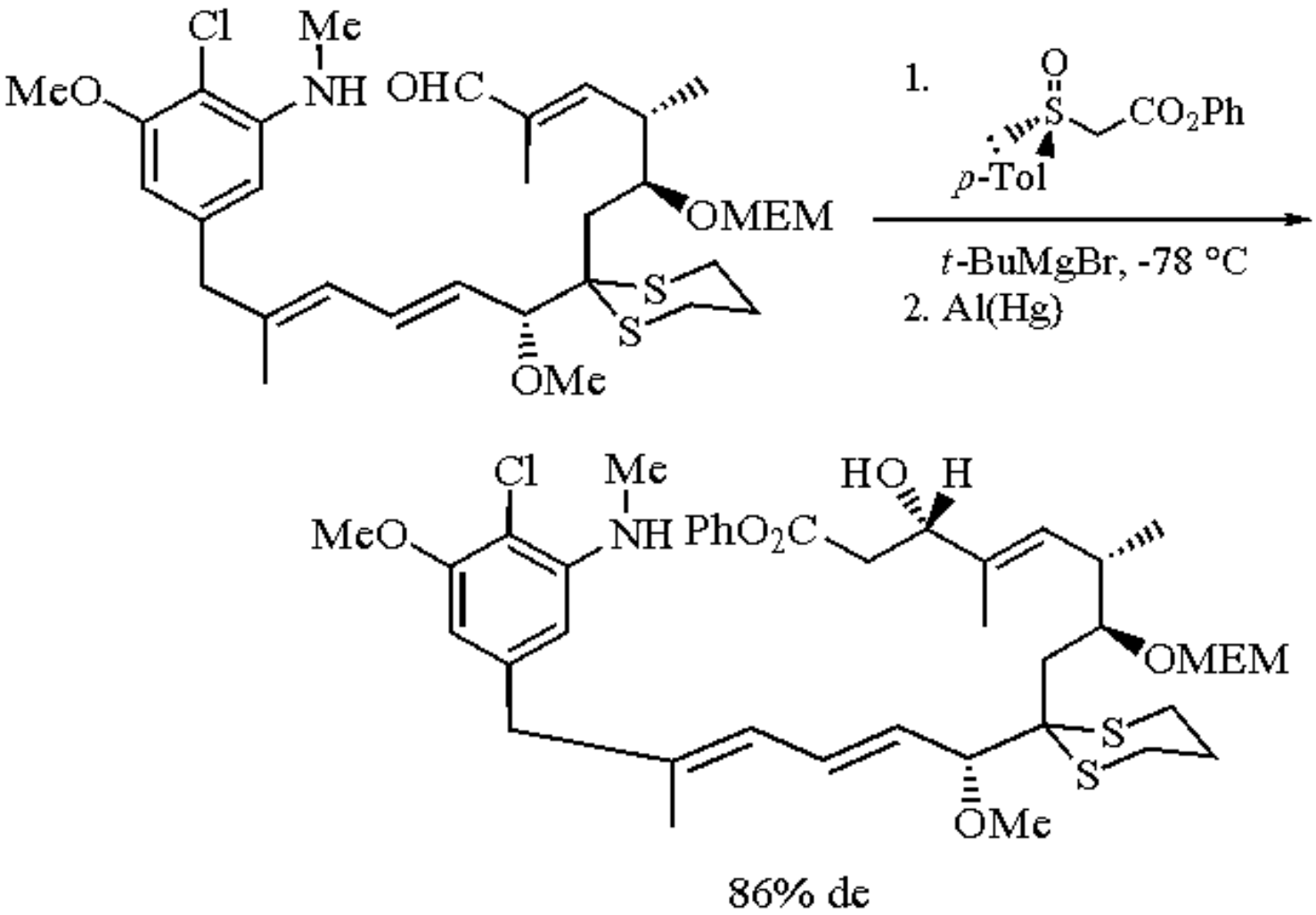

(3)

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University Louis Pasteur, Strasbourg, France

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4-Phenyl-1,2,4-triazoline-3,5-dione[1]

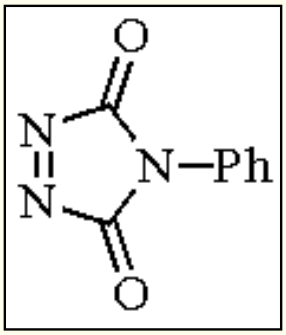

[4233-33-4] · $C_8H_5N_3O_2$ · 4-Phenyl-1,2,4-triazoline-3,5-dione · (MW 175.16)

(highly reactive dienophile and enophile)

Alternate Names: PTAD; *N*-phenyl-1,2,4-triazoline-3,5-dione.

Physical Data: mp 179 °C (dec).[2]

Form Supplied in: PTAD and 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) *[13274-43-6]*) are widely available commercially.

Preparative Methods: there are several reported preparations,[2-9] particularly for the in situ preparation.

Handling, Storage, and Precautions: normal precautions against exposure to moisture and air; reacts with alcohols and water.

Diels-Alder Cycloaddition Reactions.

4-Substituted 1,2,4-triazoline-3,5-diones (e.g. PTAD and MTAD) are exceptionally reactive dienophiles and are more reactive than good dienophiles such as ***Maleic Anhydride***, ***N-Phenylmaleimide***, ***Diethyl Azodicarboxylate***, and ***Dimethyl Acetylenedicarboxylate***. For example (eq 1), PTAD reacts rapidly with ***Cyclopentadiene*** without a catalyst at -78 °C and with ***1,3-Butadiene*** at -50 °C.[10-12]

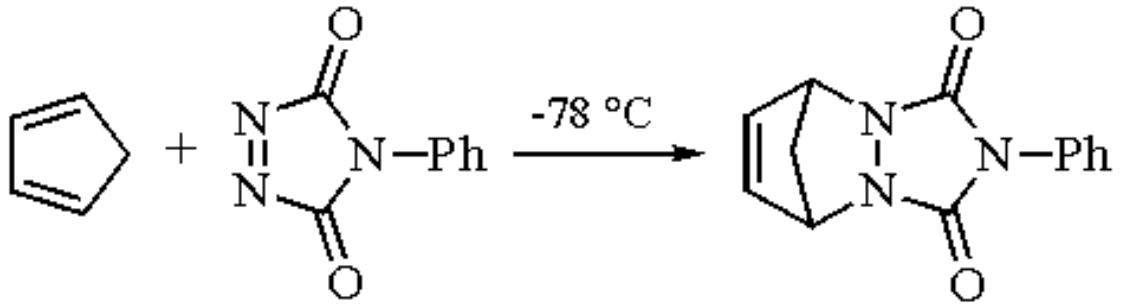

(1)

Given the facility with which PTAD undergoes [4 + 2] cycloaddition, mechanistic aspects of its reaction have been extensively studied,[13,14] and PTAD has become the classic reagent for probing the reactivity of weak Diels-Alder dienes. For example (eq 2), ***1,3,5-Cycloheptatriene*** reacts via its norcaradiene isomer to afford the PTAD [4 + 2] cycloadduct.[15-17] Cyclooctatetraene,[18] styrenes,[19] and 2-vinylindoles[20] also undergo [4 + 2] cycloaddition with PTAD.

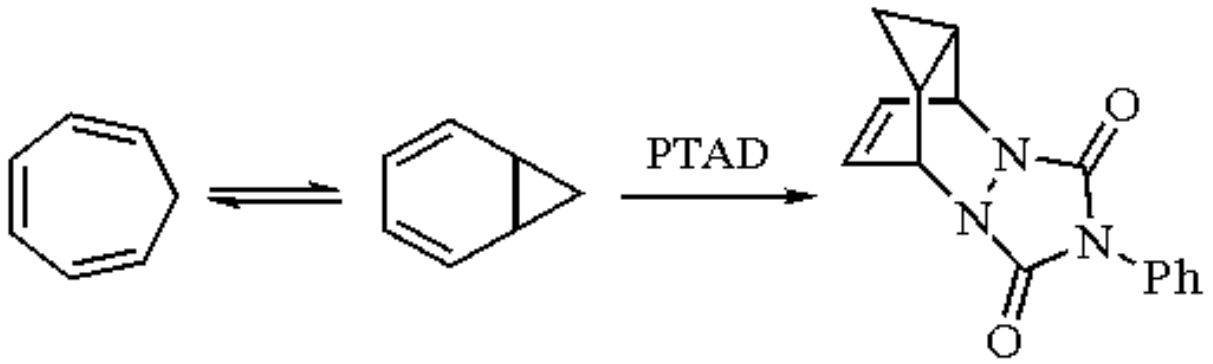

(2)

The synthetic utility of PTAD [4 + 2] cycloadducts has been relatively modest. The cycloadducts have been used in the synthesis of certain piperazic acids.[21] The PTAD group can be removed from the cycloadduct by treatment with ***Lithium Aluminum Hydride***,[22] ***Potassium Carbonate*** in DMSO,[23] refluxing ***1,1,3,3-Tetramethylguanidine***,[24] and ***Potassium Hydroxide*** in 95% ethanol.[9] Thus PTAD can be considered as a protecting group for 1,3-dienes. For example (eq 3), Barton and co-workers[9] reported that ergosterol reacts with PTAD in near-quantitative yield and the diene can be regenerated from the cycloadduct by treatment with 2.1 N KOH in 95% ethanol (1.5 h, 65 °C, 98%).

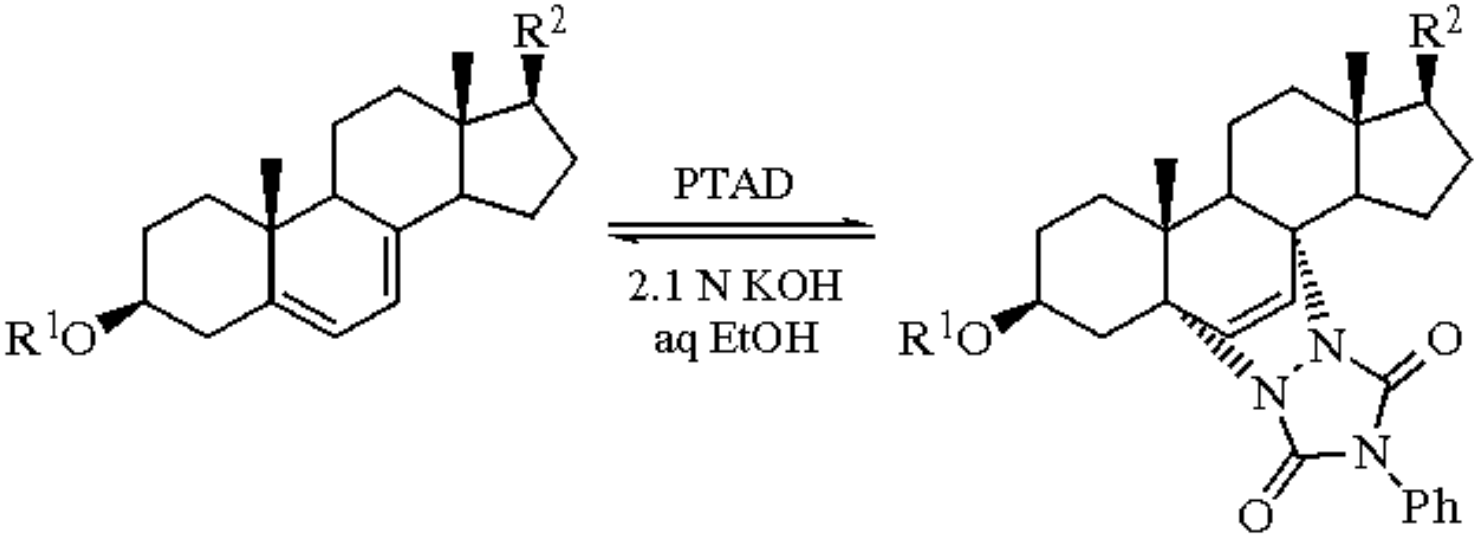

(3)

PTAD cycloadducts can be converted to the corresponding azoalkanes via hydrolysis and subsequent oxidation, and in

some cases this offers advantages over the use of diethyl azodicarboxylate. For example, Adam and co-workers[25] reported the preparation of the bicyclic azoalkane shown in eq 4 in good yield from the PTAD cycloadduct. More commonly PTAD [4 + 2] cycloadducts have found use as a tool for structure elucidation via classical chemical reactivity,[26,27] crystallographic,[19,28-30] or mass spectral analysis.[31,32]

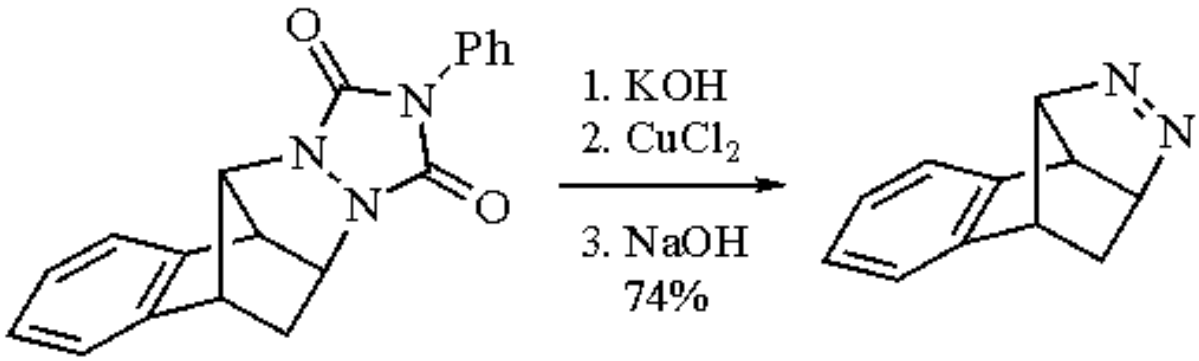

(4)

Ene Reactions.

PTAD and other 4-substituted 1,2,4-triazoline-3,5-diones are exceptionally reactive enophiles, PTAD reportedly being some 10^4 times more reactive than diethyl azodicarboxylate in the reaction with cyclohexene (eq 5).[33,34] The ene reactions of PTAD with alkenes[35-39] and enones[40,41] have been the subject of several mechanistic investigations.

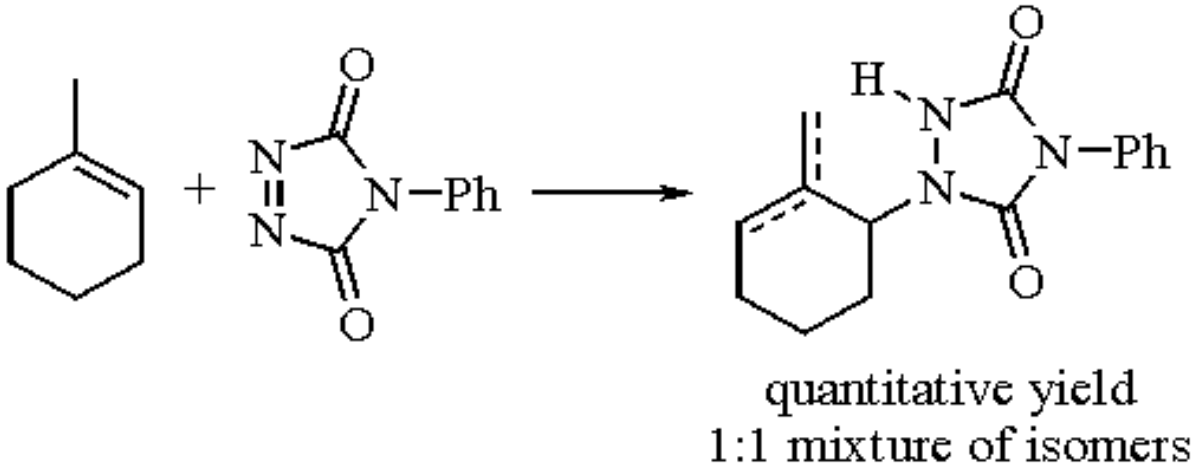

(5)

PTAD reacts with β-diketones and β-keto esters to afford novel 1:1 and 2:1 adducts, perhaps via an ene pathway involving the enol form of the β-dicarbonyl compound. For example (eq 6), PTAD reacts with ***2,4-Pentanedione*** to give the 2:1 adduct in 95% yield.[42]

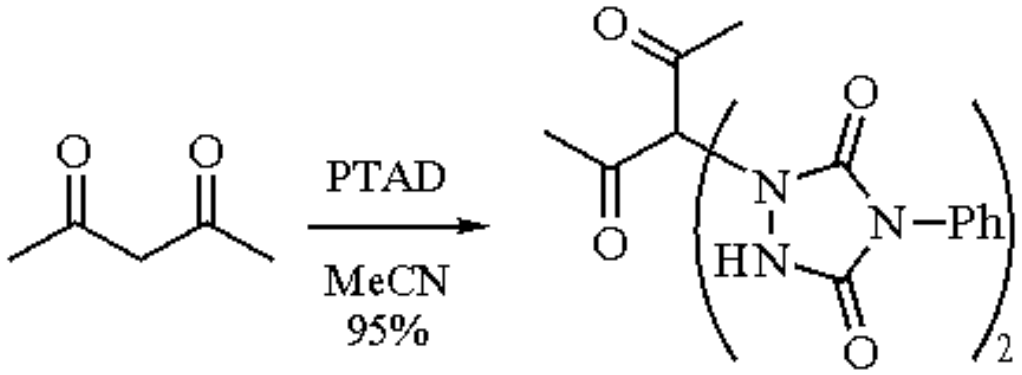

(6)

The reactions of allylsilanes,[43-45] -germanes,[45] and -stannanes[46] with PTAD partition between ene and metallo-ene pathways. For example, the allylsilane[43] in eq 7 undergoes ene reaction with PTAD to afford the adduct in 95% yield, while the allylstannane[46] in eq 8 undergoes predominantly metallo-ene reaction with PTAD. Silyl enol ethers and PTAD condense with *O*- to *N*-silyl transfer to afford α-amino ketone derivatives.[47] PTAD can participate in the relatively rare acyl-ene reaction.[48]

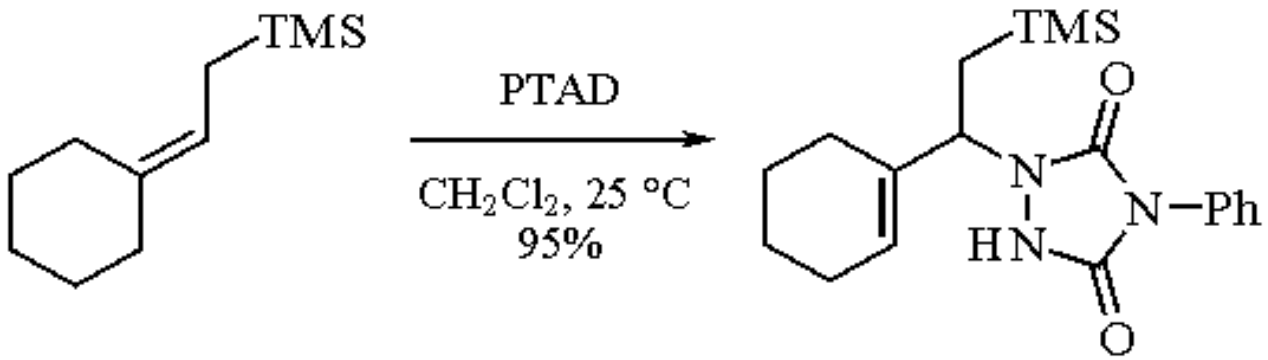

(7)

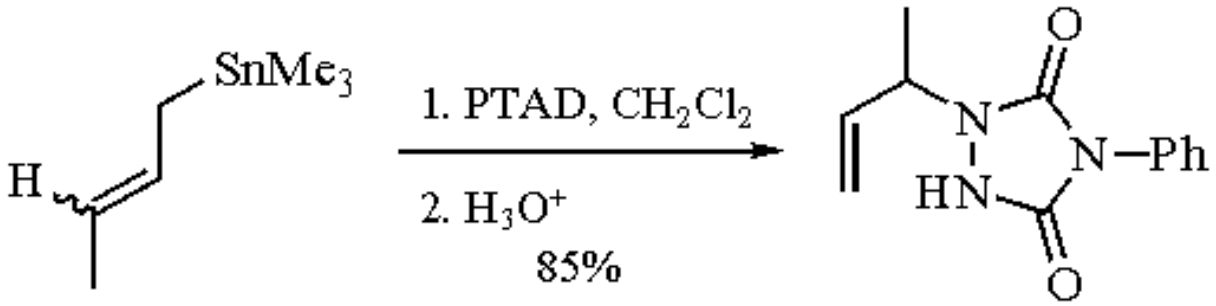

(8)

Miscellaneous Reactions.

PTAD has been used as an efficient trap for certain reactive intermediates, including radical species[49] and disilirane.[50] PTAD can effect the oxidation of certain alcohols[51] and sulfides[52] and MTAD has been employed for the mild oxidation of a hydrazine to the corresponding diazene.[52b] PTAD reacts with electron-rich alkenes or aromatic rings to give dipolar intermediates,[53-55] and with ***Ethyl Diazoacetate*** to afford the unusual cycloadduct shown in eq 9.[56,57]

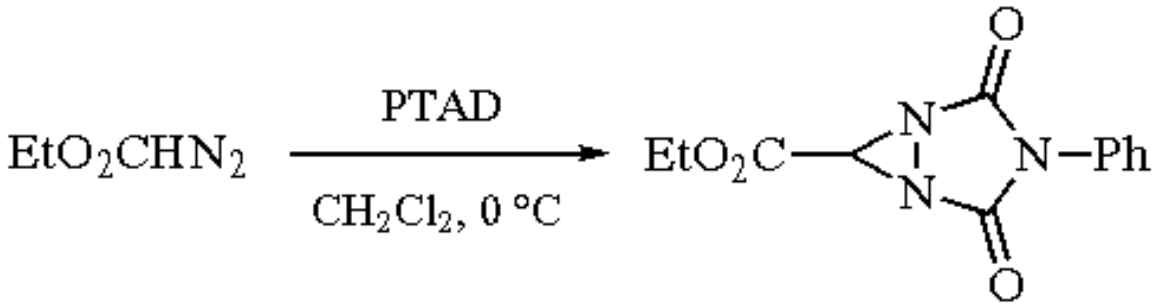

(9)

PTAD undergoes [2 + 2] cycloaddition with ***Diphenylketene***[58] and certain alkenes.[59,60] Strained ring systems often undergo unusual cycloaddition modes with PTAD. For example, the strained bicycloalkene in eq 10 affords the rearranged urazole in 95% yield,[61,62] and the alkenylidenecyclopropane shown in eq 11 affords the bicyclic structure.[63,64]

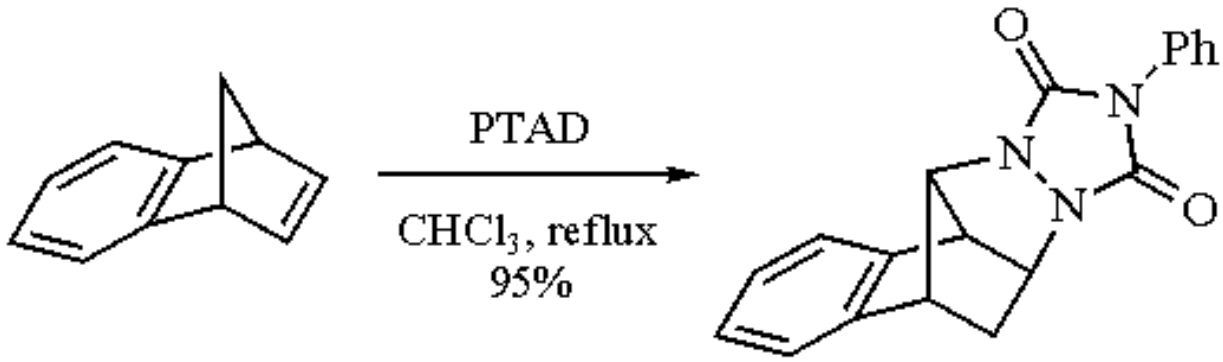

(10)

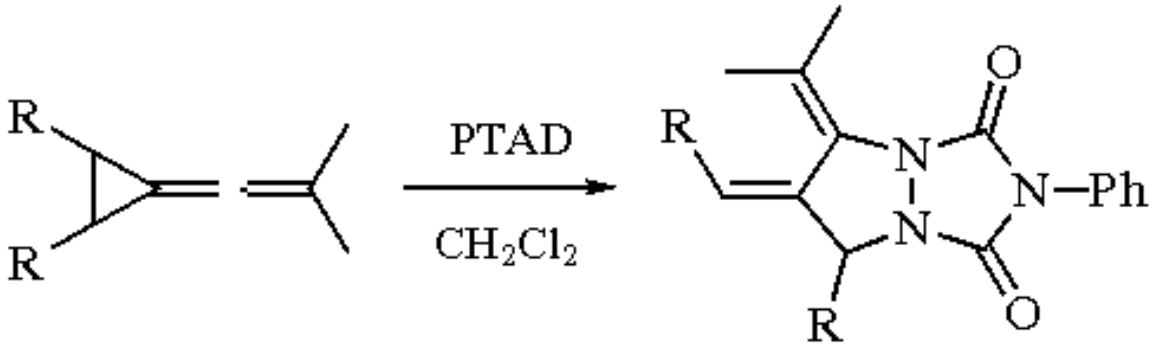

(11)

Related Reagents.

Diethyl Azodicarboxylate.

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Phenyl(tribromomethyl)mercury[1]

$PhHgCBr_3$

[3294-60-8] · $C_7H_5Br_3Hg$ · Phenyl(tribromomethyl)mercury · (MW 529.41)

(precursor for the generation of dibromocarbene under neutral conditions)

Physical Data: mp 119-120 °C (dec).

Form Supplied in: commercially available.

Preparative Method: readily prepared from ***Phenylmercury(II) Chloride*** and ***Bromoform*** using ***Potassium t-Butoxide*** in THF.[2]

Handling, Storage, and Precautions: highly toxic; should be handled in an efficient fume cupboard with caution. Best stored as a solid below 5 °C.

General Discussion.

Phenyl(tribromomethyl)mercury is a source of dibromocarbene and as such has been employed in cyclopropanation and insertion reactions.[1] The carbene is generated by gently heating phenyl(tribromomethyl)mercury in a hydrocarbon solvent (often benzene).[3] The mild reaction conditions make this a good method for the generation of dibromocarbene under neutral conditions.

The most widespread application of phenyl(tribromomethyl)mercury has been in the dibromocyclopropanation of alkenes. The mechanism of this and related reactions has been studied in some detail and it has been proposed that they proceed via a free carbene intermediate.[4] The reagent has proven particularly useful for the dibromocyclopropanation of base-sensitive systems and of relatively unreactive alkenes.[1] For example, vinyl chlorides[5] and monosubstituted alkenes[6] can be successfully transformed to the corresponding cyclopropanes using this methodology (eqs 1 and 2). Cyclopropane (**1**) was produced in only 7% yield using a more conventional method ($HCBr_3$/*t*-BuOK) to generate the dibromocarbene.

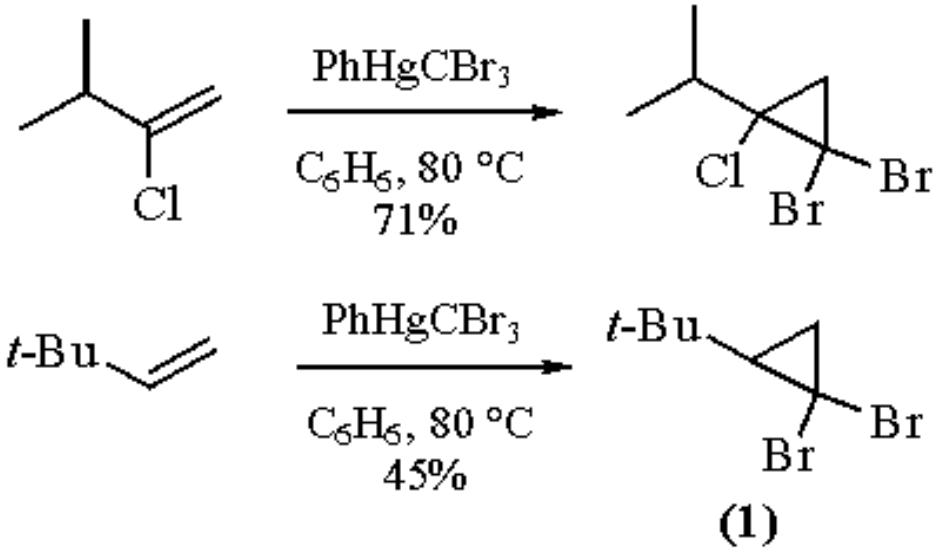

(1)

(2)

This method for preparing cyclopropanes is highly chemoselective and tolerates a wide range of functional groups. Notable exceptions are alcohols, amines, and carboxylic acids, which undergo competitive insertion reactions.[1] The mildness of this reagent is well illustrated by the conversion of tricyclic ketone (**2**) into (**3**) in near quantitative yield (eq 3).[7,8] This reaction is also stereospecific, with attack of the carbene occurring on the least hindered side of the double bond.

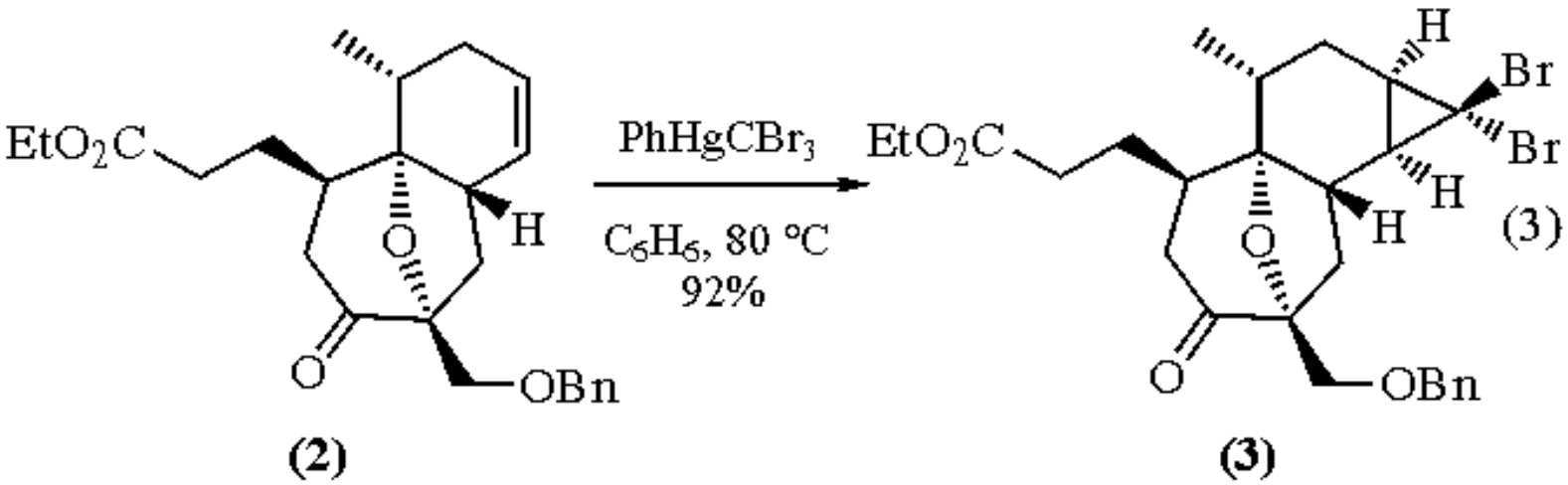

(2) (3)

Systems containing several double bonds can be regioselectively cyclopropanated at the most nucleophilic position. For example, treatment of costunolide (**4**) with phenyl(tribromomethyl)mercury in refluxing benzene produces (**5**) as the sole carbene addition product (eq 4).[9] It has been speculated that the Lewis acidity of the organomercury reagent is responsible for the competitive formation of the undesired cyclocostunolide (**6**).

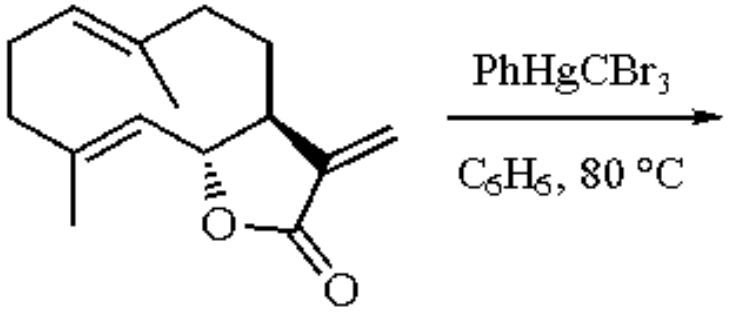

(4)

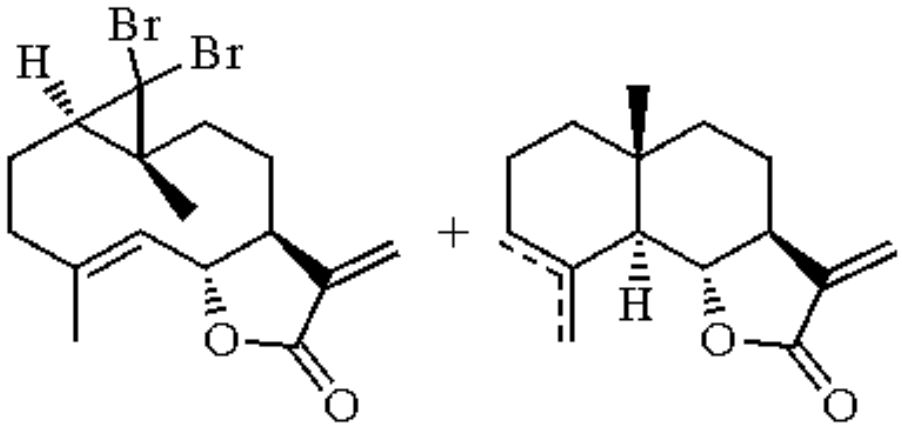

(5) 34% (6) 57% (4)

Phenyl(bromodichloromethyl)mercury has been prepared in a fashion similar to phenyl(tribromomethyl)mercury.[2] Thermal decomposition of this reagent occurs via loss of phenylmercury(II) bromide, producing dichlorocarbene as the only carbene intermediate.[10] Phenyl(bromodichloromethyl)mercury has been utilized in the dichlorocyclopropanation of unreactive[11] and base-sensitive alkenes (eqs 5 and 6).[12] Dichloromethyl esters can readily be prepared from the corresponding carboxylic acids using this reagent by insertion of the carbene into the OH bond.[13]

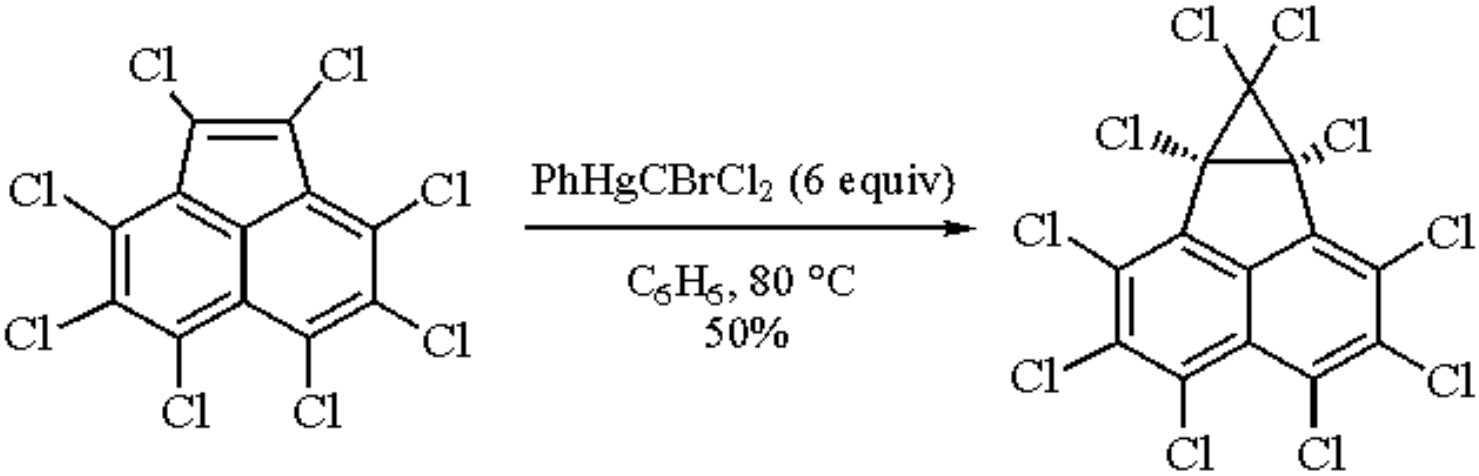

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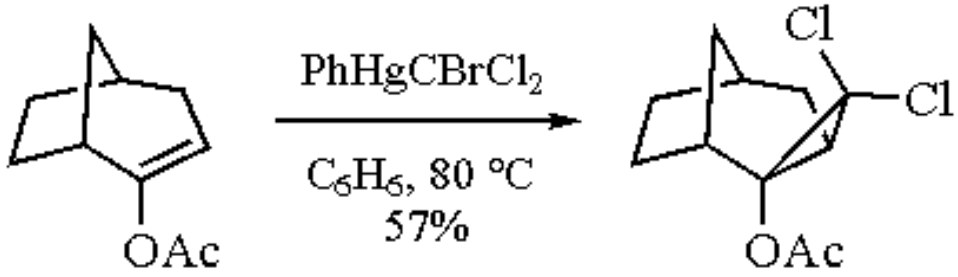

(6)

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Phenyl(trichloromethyl)mercury[1]

$PhHgCCl_3$

[3294-57-3] · $C_7H_5Cl_3Hg$ · Phenyl(trichloromethyl)mercury · (MW 396.06)

(transfers **:**CCl_2 to many unsaturated systems, to heteroatoms, and to several σ-bonds)

Physical Data: mp 117-118 °C.

Solubility: sol ether, benzene, chloroform.

Form Supplied in: colorless solid; commercially available.

Preparative Methods: prepared from PhHgBr either by reaction with ***Potassium t-Butoxide-Chloroform*** in benzene at 10 °C in 66% yield,[2] or by treatment with ***Sodium Methoxide-Ethyl Trichloroacetate*** in 62% yield.[3] ***Phenylmercury(II) Chloride*** furnishes $PhHgCCl_3$ by reaction with ***Sodium Trichloroacetate*** in refluxing DME (65%).[4] A two-phase approach from PhHgCl and $CHCl_3$ using aqueous ***Sodium Hydroxide-Potassium Fluoride*** and small amounts of ***Benzyltriethylammonium Chloride*** furnishes $PhHgCCl_3$ in 72% yield.[5]

Purification: recrystallization from chloroform.

Handling, Storage, and Precautions: flame-dried glassware and an atmosphere of dry nitrogen are used for the reactions. Organomercury(II) compounds should be carefully handled and skin contact and inhalation should be particularly avoided. All reactions must be conducted in a well-ventilated fume hood. The reagent is light sensitive and should be stored under nitrogen at 4 °C.

Cyclopropanation of Alkenes.

A wide and representative set of alkenes react with $PhHgCCl_3$ to afford *gem*-dihalocyclopropanes in good yield (eq 1).[6] Reactions are carried out under nitrogen, using dry benzene as solvent, and can be easily monitored by TLC analysis. When all the starting mercurial has been consumed, PhHgCl is filtered off, the solvent and the excess alkene are removed in vacuo, and the resulting cyclopropanes are generally purified by distillation. The simplicity of product isolation represents an important synthetic advantage of this procedure.

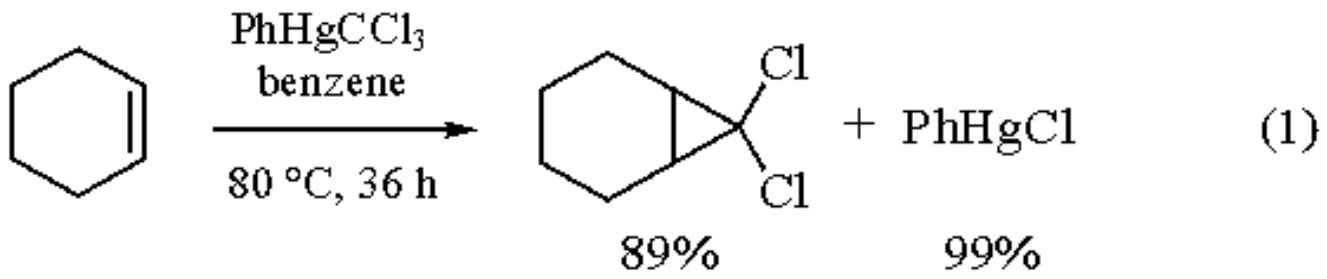

A distinctive feature of $PhHgCCl_3$ as a cyclopropanating reagent is that it reacts with alkenes that are electron-poor (eq 2).[6] In contrast, attempts to cyclopropanate tetrachloroethylene using *t*-BuOK-$CHCl_3$ or thermal decomposition of Cl_3CCO_2Na give only modest (less than 10%) yields of hexachlorocyclopropane.[7]

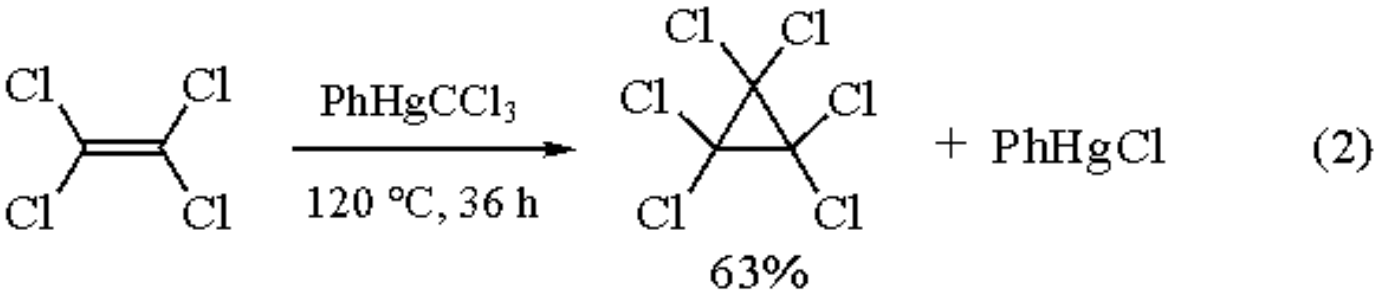

$PhHgCCl_3$ competes well in several aspects with $PhHgCCl_2Br$ as a **:**CCl_2 transfer reagent for *gem*-dichlorocyclopropanation of alkenes; in particular, the former is a cheaper reagent and is more easily prepared. Conversely, the latter behaves as a milder source of **:**CCl_2, requiring shorter reaction times that enhance its synthetic potential.[6]

A simple modification of the experimental protocol, involving addition of ***Sodium Iodide***, has been developed. It decreases either the reaction time or the reaction temperature of the cyclopropanation with respect to that required when using α-haloorganomercurials.[8] Following this procedure, *trans*-stilbene smoothly undergoes cyclopropanation in high yield (eq 3).[9]

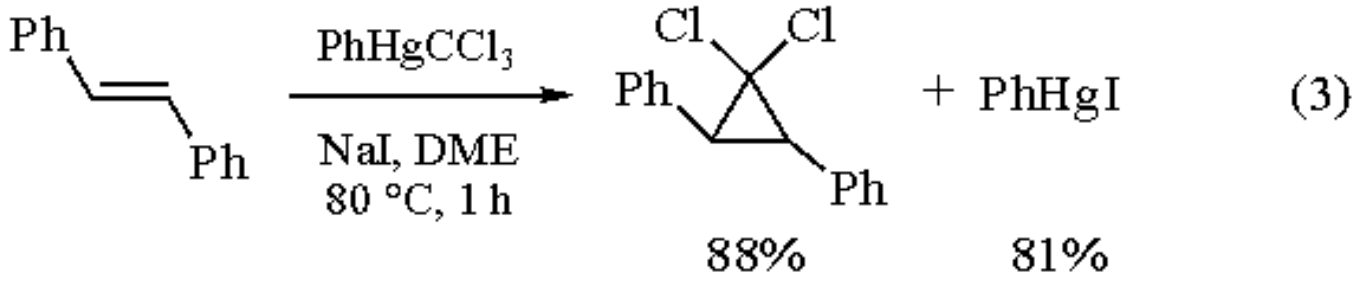

Using the above-mentioned conditions, cyclohexene is cyclopropanated (3 h, 85 °C) in 91% yield, while the cyclopropane derivative is formed in only 15% yield in the absence of NaI. Interestingly, the NaI method allows cyclopropanation by $PhHgCCl_3$ to take place at rt (eq 4).[9]

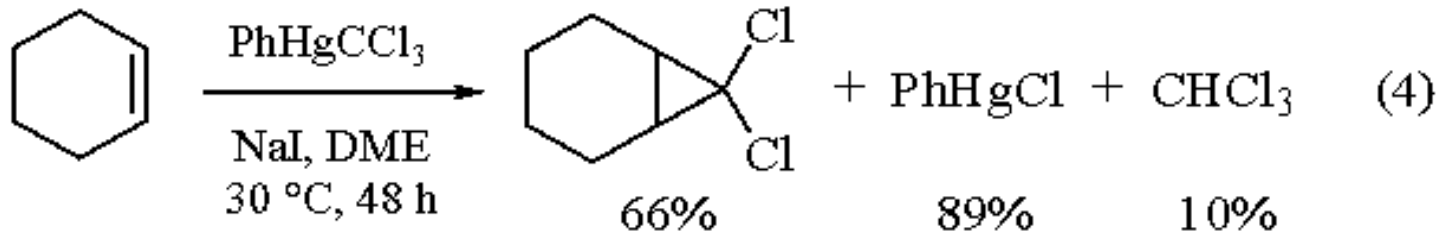

The activating effect of added NaI has been interpreted in terms of iodide attack at mercury and concomitant displacement of $^{-}CCl_3$, which generates in turn the dihalocarbene species ($^{-}CX_3$ -> **:**CX_2 + X^{-}). Consistent with that assumption, the reaction of NaI with equimolecular amounts of $PhHgCCl_3$ in dry acetone at 25 °C yields products that arise from ketone trapping by CCl_3^{-}.[9] The NaI-based procedure has some limitations. It reacts sluggishly with alkenes like tetrachloroethylene, reputed to be quite unreactive towards **:**CCl_2. Also, in good agreement with the electrophilic nature of the intermediate, the observed trend of alkene reactivity in this process ($R_2C{=}CR_2$ > $R_2C{=}CHR$ > $R_2C{=}CH_2$ > $RCH{=}CHR$ > $RCH{=}CH_2$)[9] matches well with that observed for the reactivity of carbenes generated by thermal treatment of Cl_3CCO_2Na in DME.

A major advantage of $PhHgCCl_3$ in *gem*-dichlorocyclopropanation reactions is realized when dealing with base-sensitive alkenes. In these cases, conventional carbene generation by treatment of chloroform with strong bases does not afford significant cyclopropane formation.[6] Many examples are known, and several synthetic applications have been reported. For example, 2-vinyl-4,4,6,6-tetramethyl-1,3,2-dioxaborinane is cleanly cyclopropanated with $PhHgCCl_3$ (eq 5);[10] cyclopropanation of this compound through thermal decomposition of Cl_3CCO_2Na as a source of **:**CCl_2 gives the desired cyclopropane in only 4% yield.[10]

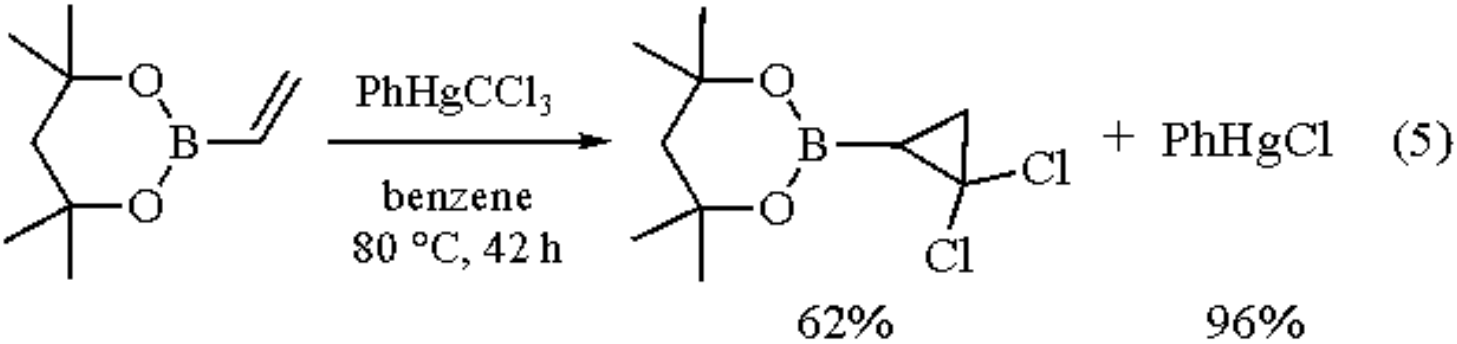

Diketene is also smoothly *gem*-dichlorocyclopropanated by $PhHgCCl_3$ (eq 6).[11] Interestingly, further reactions on the resulting dichlorocyclopropanespirolactone do not induce opening of the three-membered ring, in contrast with the behavior of the cyclopropanation product obtained by reaction of diketene with α-diazo ketones.[11]

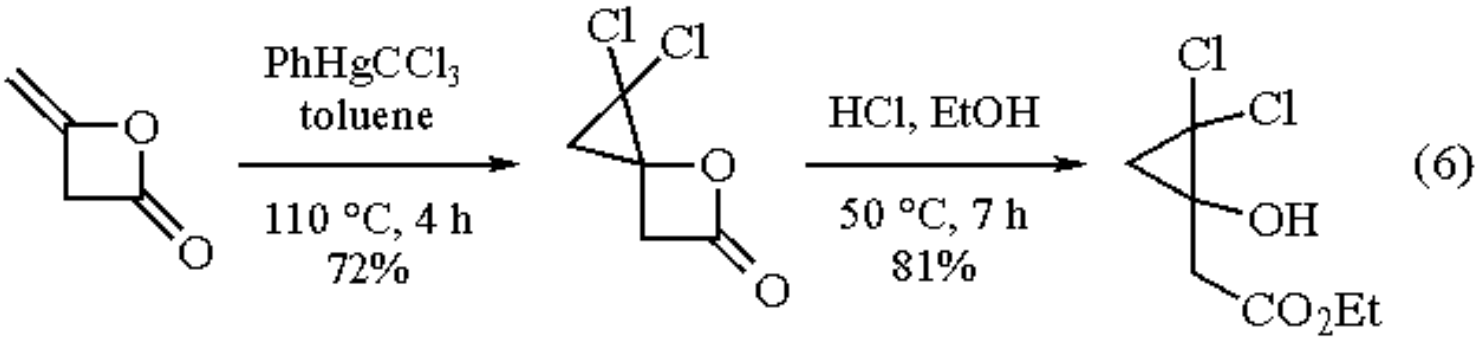

Vinyl Acetate, a base-sensitive compound that cannot be cyclopropanated by traditional methods, reacts readily with trihalomercurial reagents,[6] forming *gem*-dichlorocyclopropanes which are useful synthons leading to pyrazole rings (eq 7).[12]

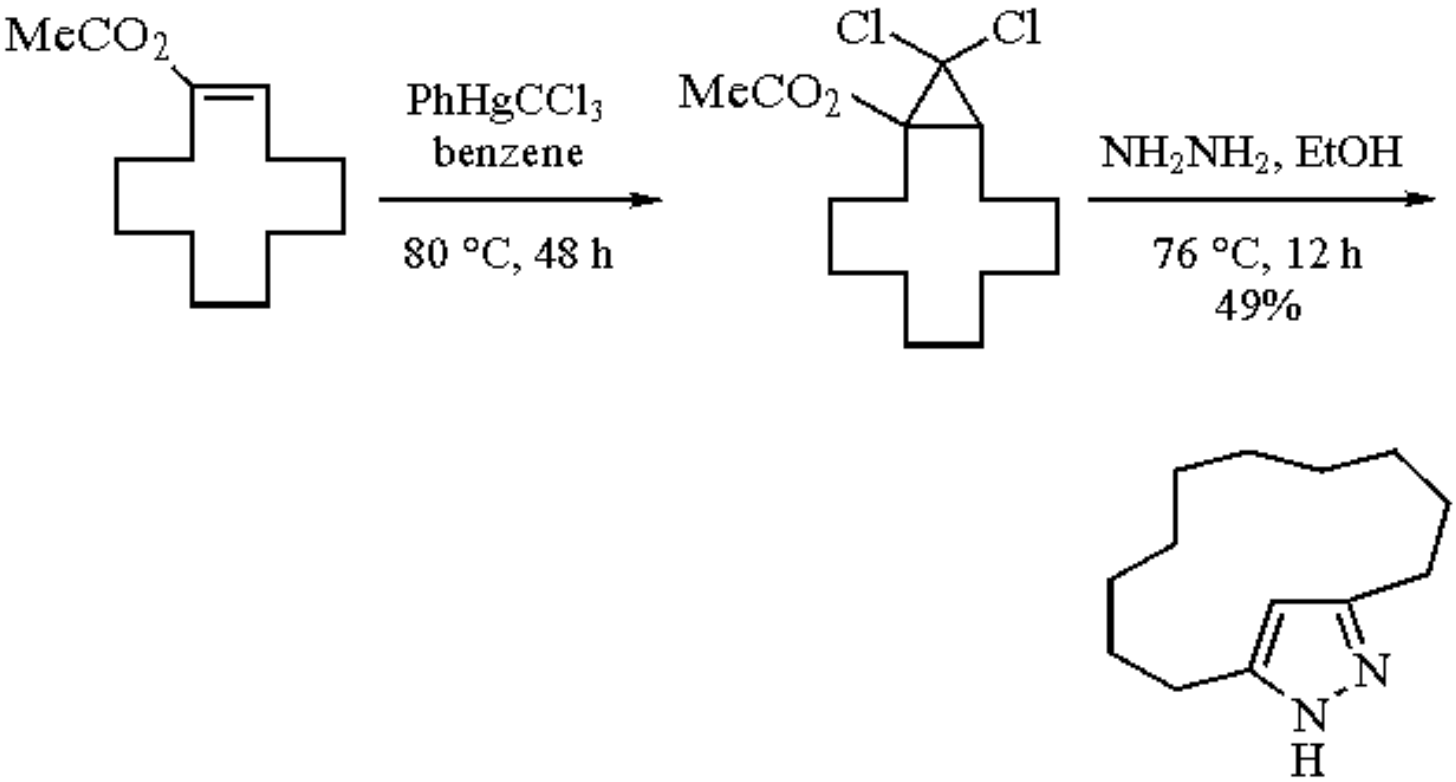

(7)

In this respect, if the size of the cycloalkenyl acetate is reduced then the yield of metacyclophane goes down, and the 1,2-function becomes significant. Treatment of cyclohexenyl acetate with $PhHgCCl_3$ and further reaction of the resulting *gem*-dichlorocyclopropane with ***Hydrazine*** yields exclusively 4,5,6,7-tetrahydroindazole (1,2-ring fusion) in 40% yield.[13] 2-Aminopyrimidines are also accessible by treating the α,α-dichlorocyclopropyl acetates with ***Guanidine*** (eq 8).[14]

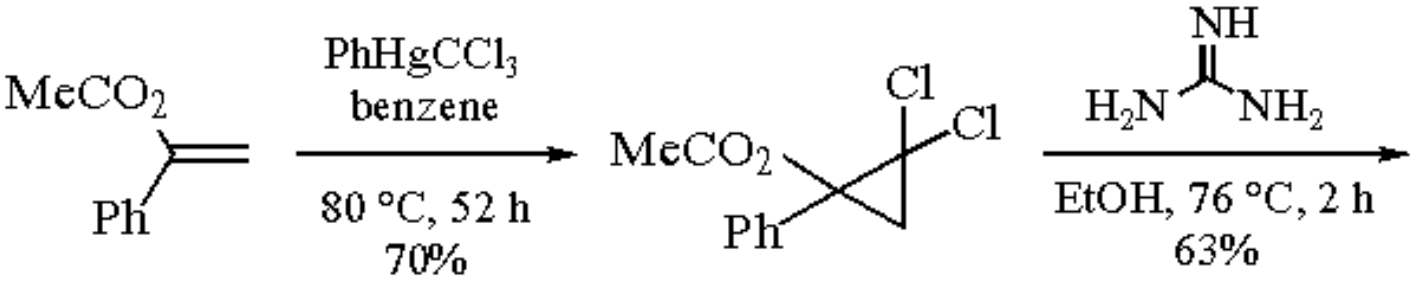

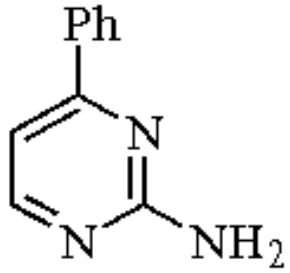

(8)

Similarly, the enol acetate function of steroids reacts with $PhHgCCl_3$ to give the corresponding cyclopropane derivatives; these are useful compounds for furnishing new skeletal rearrangements through ring-expansion reactions in basic media (eq 9).[15]

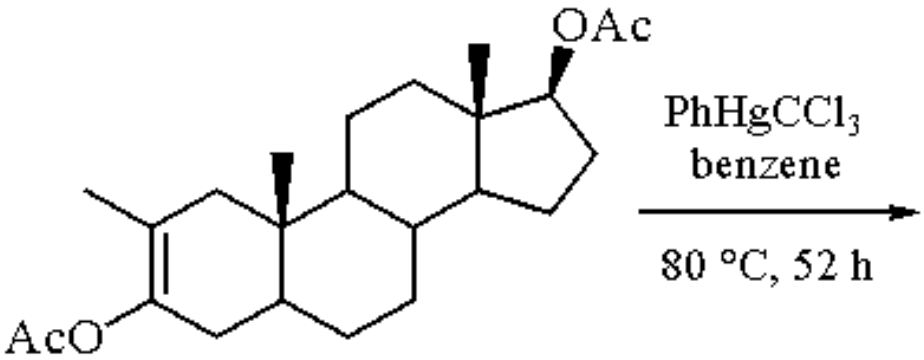

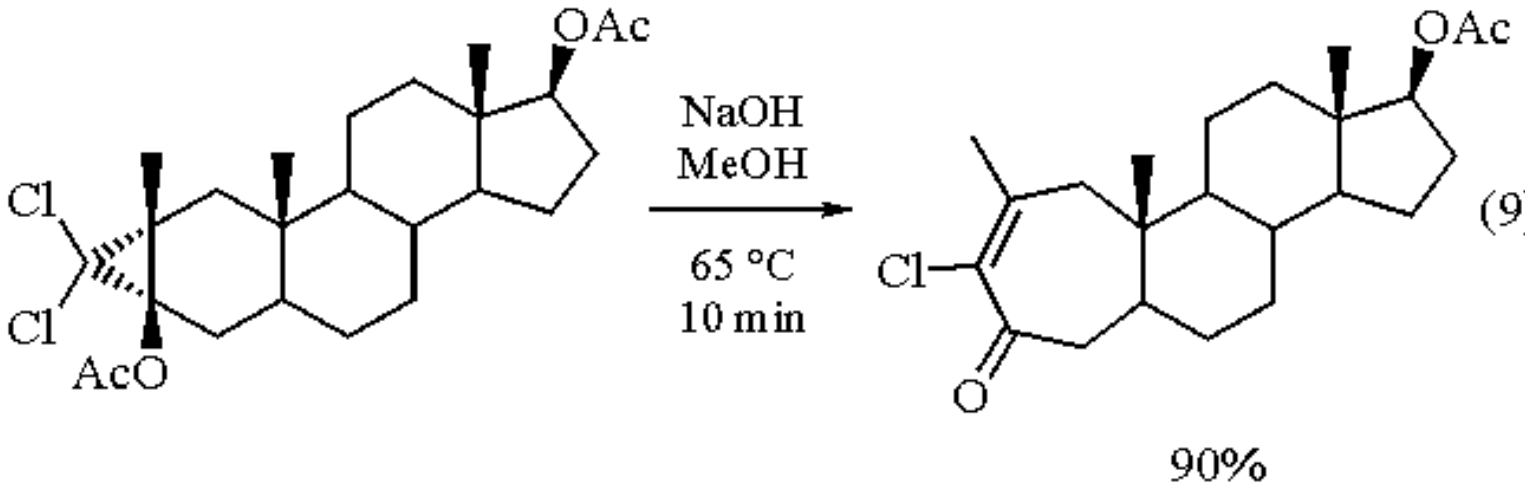

(9)

Depending on the strain of the system, ring-opening processes take place spontaneously under the reaction conditions,

as illustrated in eq 10.[16]

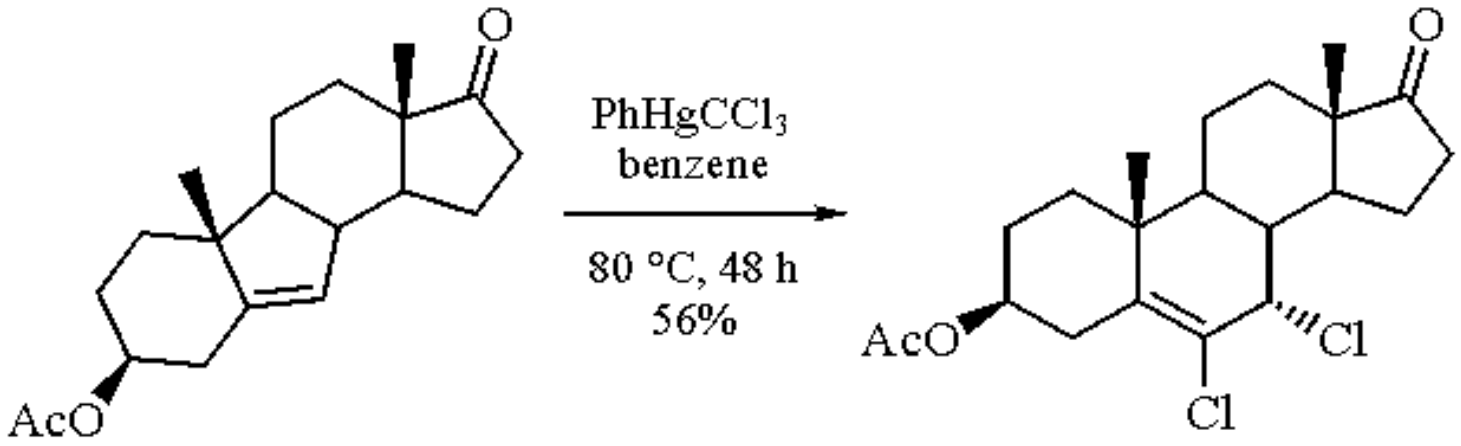

(10)

Carbene transfer from $PhHgCCl_3$ to 5-enyl acetate steroids occurs from the less-hindered side, the so-called α-face.[17] Thus the stereochemical outcome is generally opposite to that observed when using the Simmons-Smith procedure, suggesting that precoordination of the reagent does not occur.[17]

The cyclopropane derived from norbornene and $PhHgCCl_3$ also undergoes spontaneous ring expansion under the reaction conditions, affording 3,4-dichlorobicyclo[3.2.1]oct-2-ene.[18] This sequence, cyclopropanation/thermal ring expansion, has been successfully applied to cyclophane synthesis by starting from substituted indenes[19] and indoles.[20] Recently, cyclopropanation of alkenes has been used for the preparation of 1*H*-cyclopropa[*a*]naphthalene in a multistep sequence (eq 11).[21]

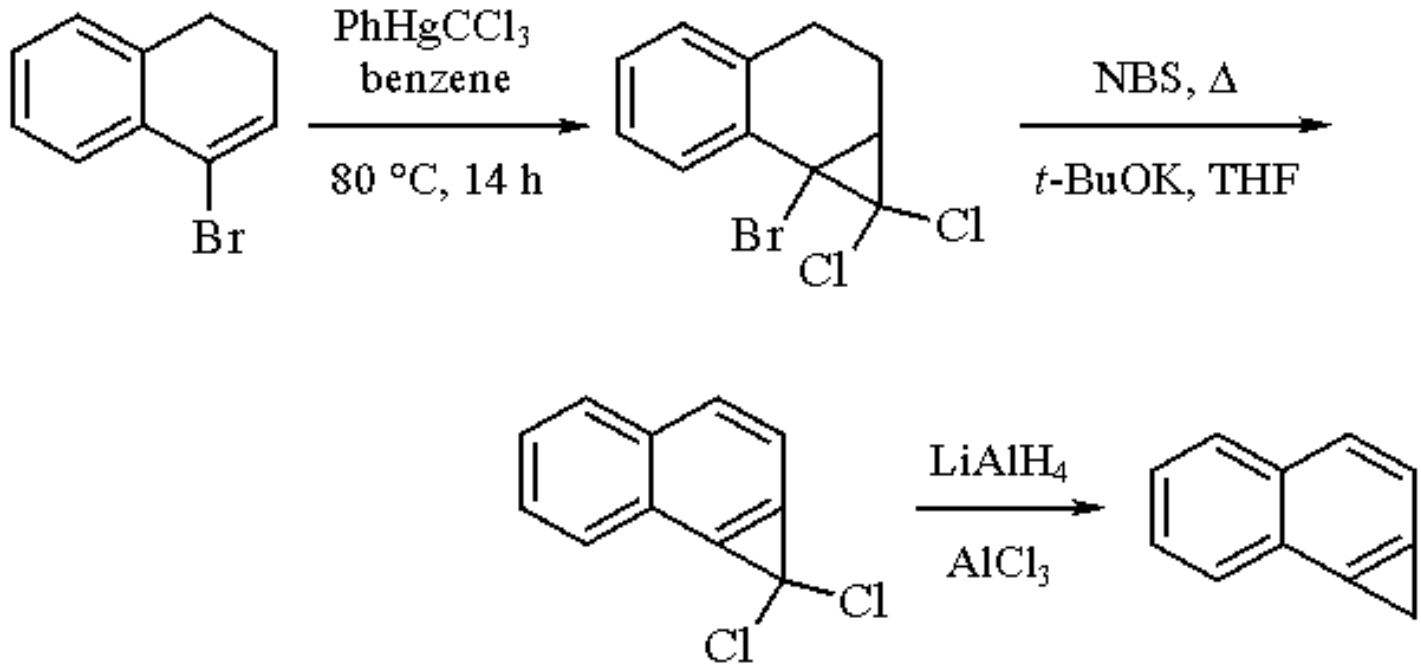

(11)

In short, the merit of $PhHgCCl_3$ as a **:**CCl_2 transfer reagent to cyclopropanate alkenes is derived from experimental facts; namely, the carbene is generated under neutral conditions at moderate reaction temperatures. The absence of side reactions clearly underlines the aforementioned comments. The accepted mechanism for the thermally induced cyclopropanation of alkenes with $PhHgCCl_3$ involves carbene generation from the α-halo organomercurial in the rate limiting step, followed by fast trapping of **:**CCl_2 by the alkene. The body of knowledge derived from the above

described reactions supports this assumption. Of special relevance in this context is the easy cyclopropanation of vinyl acetates that clearly rules out participation of the trichloromethyl anion; in fact, all attempts to cyclopropanate this base-sensitive alkene using *t*-BuOK-$CHCl_3$ as carbene source were unsuccessful. Indirect evidence is provided by kinetic studies of related processes using $PhHgCCl_2Br$ as the carbene precursor.[22] Further support for the proposed mechanism is obtained from gas-phase pyrolysis studies on $PhHgCCl_3$,[23] and subsequent characterization of the thermally generated carbene by matrix isolation techniques.[24]

Reaction with Methoxynaphthalene.

$PhHgCCl_3$ adds to the C-3-C-4 double bond of 1-methoxynaphthalene to give, after ring expansion under the reaction conditions, 5-chloro-2,3-benzotropone (eq 12),[25] a structure which was initially misassigned.[25a]

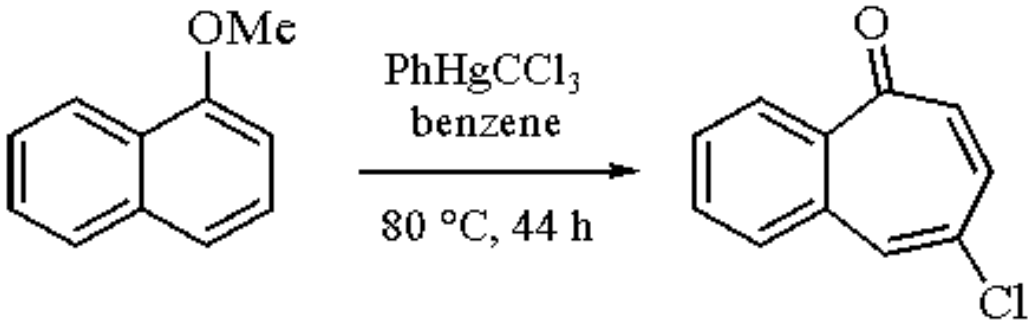

(12)

Reaction with Diiodoacetylene.

The addition of *gem*-dichlorocarbene (generated from $PhHgCCl_2Br$) to different alkynes has been described.[26] On this ground, some of the products of the reaction mixture obtained from $PhHgCCl_3$ and IC&tbond;CI were mechanistically interpreted to arise from initial addition of dichlorocarbene to the diiodoacetylene. Using a 2:1 ratio of $PhHgCCl_3$/IC&tbond;CI, 1-iodo-3,3,3-trichloropropyne and tetrachlorocyclopropene were formed as the major components of the reaction mixture (eq 13).[27]

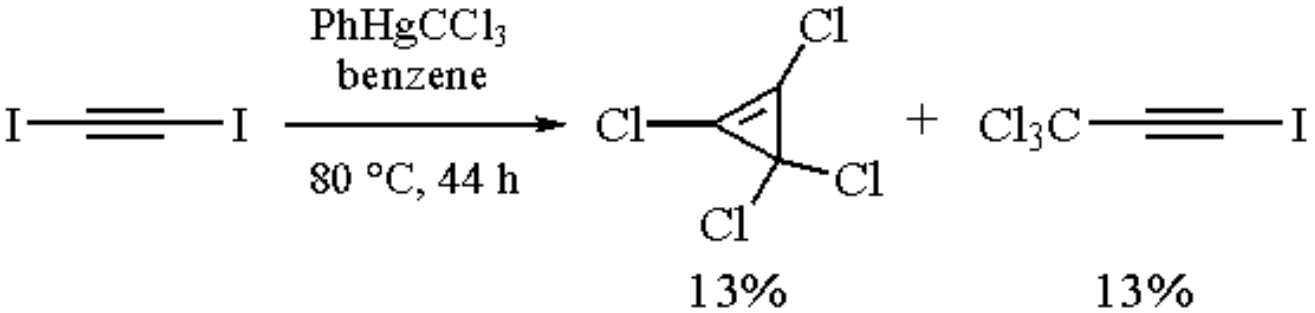

(13)

Reaction with 1,3-Dienes.

1,1,2,2,3,3-Hexamethyl-4,5-bis(methylene)cyclopentane is an interesting 1,3-diene to check whether 1,4-addition is a feasible reaction path for a given transformation. Its reaction with $PhHgCCl_3$ shows clearly that this possibility is a true alternative for a singlet carbene (eq 14).[28]

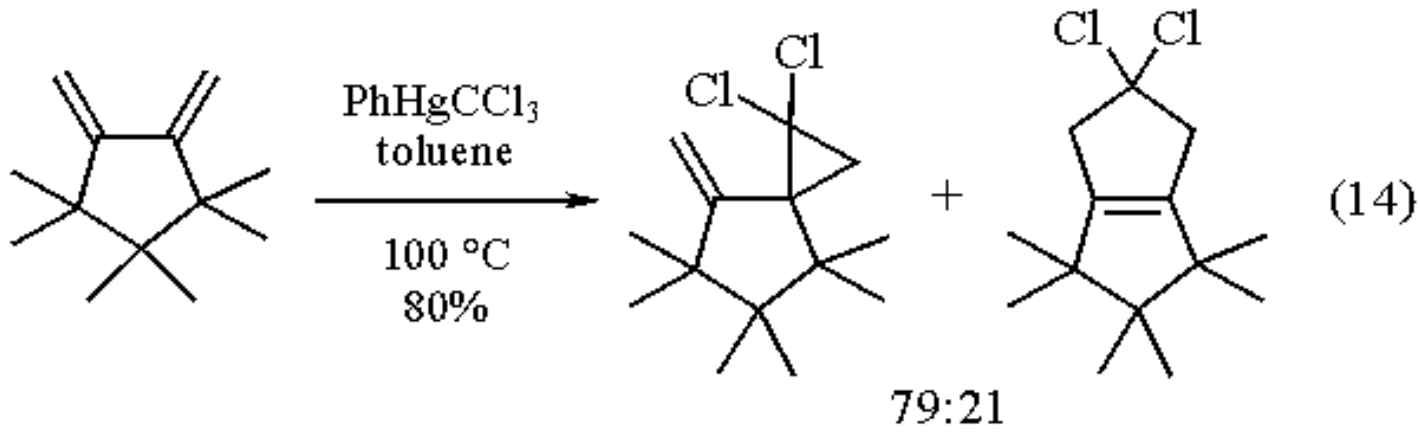

Reaction with Nitrogen- and Other Heteroatom-Substituted Compounds.

Tertiary amines react with $PhHgCCl_3$ in boiling benzene; for instance, Et_3N gives EtCl, PhHgCl, and *N*,*N*-diethyltrichlorovinylamine ($Et_2NCCl{=}CCl_2$) in low yield.[29] Short reaction times have been noticed, suggesting an initial nucleophilic substitution reaction on mercury by the amine and $^{-}CCl_3$ displacement. Subsequent decomposition reactions would eventually lead to the nitrogen ylide (Et_3N^{+}-CCl_2-$^{-}CCl_2$) from which reaction products will be formed.[29] These findings are consistent with the interesting behavior shown by several allylamines towards $PhHgCCl_3$ (eq 15).[30] The yield of cyclopropane increases as the nucleophilic character of the nitrogen decreases. For more nucleophilic nitrogen atoms, competitive enamine formation could be the major pathway.

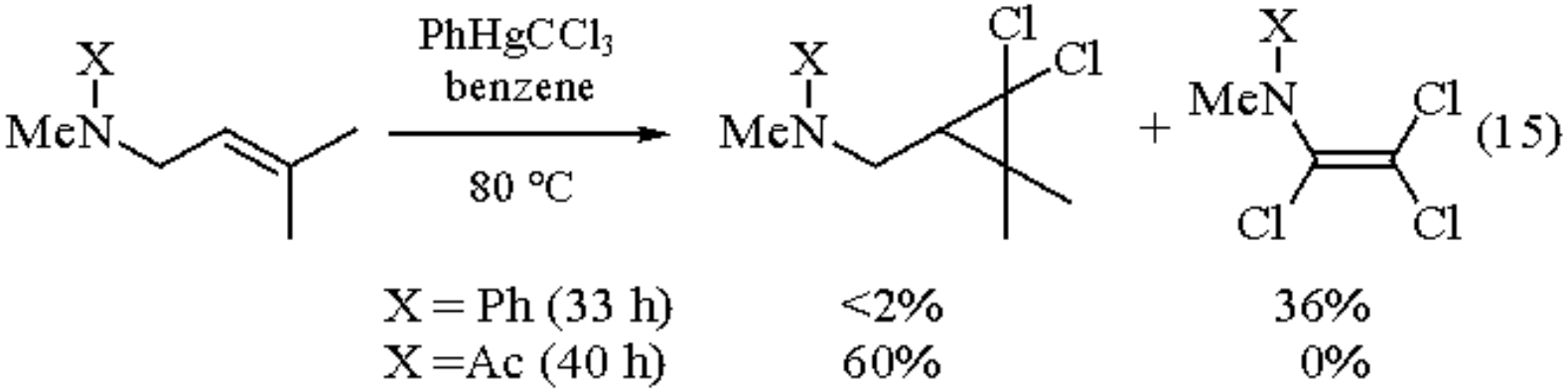

The reaction of *N*,*N*-dimethylaniline with $PhHgCCl_3$ has also been described.[31] In this case, a novel class of compound is formed via electrophilic substitution on the starting amine, along with the expected products arising from an attack on nitrogen. Thermal reaction of $PhHgCCl_3$ with the C=N double bond should offer a simple entry to aziridines. However, its synthetic utility is severely limited due to the presence of PhHgCl, formed in the reaction.[32] To overcome this, cyclopropanation was attempted in the presence of NaI.[9] Although remarkable examples have been recorded (eq 16), the procedure lacks generality since the PhHgI formed catalyzes aziridine ring opening at rt.[32]

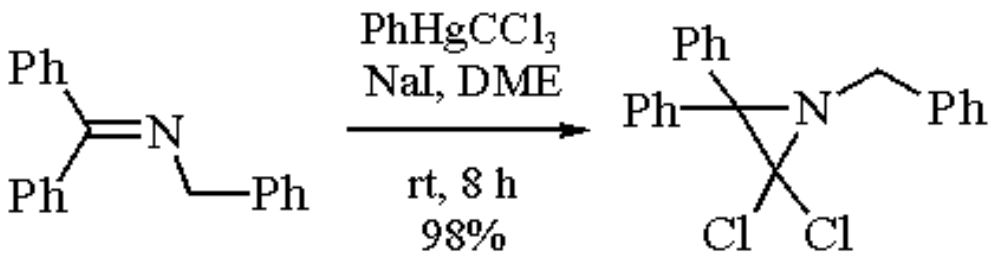

(16)

The C=N function of azirines reacts with $PhHgCCl_3$, giving ring-opened products (eq 17).[33] A minor byproduct, identified as the corresponding *N*-vinylaziridine, results from further attack of **:**CCl_2 on the C=N rather than the C=C bond of the azadiene.[33]

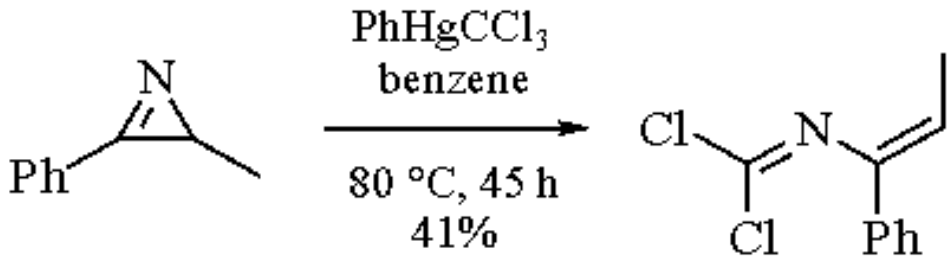

(17)

The reaction of oxygen-containing compounds with **:**CCl_2 generated from α-halo organomercurials ($PhHgXCCl_2$) is known, but most of the work deals with $PhHgCCl_2Br$ (reactions with ROH,[34] RCO_2H,[35] RCHO,[36] and RCOR[37] have been studied). $PhHgCCl_3$ attack at oxygen of the carbonyl group of several unsaturated steroidal ketones triggers skeletal rearrangements, and subsequent aromatization of the A ring.[38] $PhHgCCl_3$ is reported to deoxygenate pyridine *N*-oxides by carbene attack onto the oxygen atom to afford deoxygenated products.[39]

With respect to sulfur-containing substrates, sulfoximines react with $PhHgCCl_3$ to furnish sulfur ylides in modest yields via nitrogen displacement.[40] Of synthetic interest is the reaction of penams with $PhHgCCl_3$, offering a nonbasic approach to the corresponding azetidinones via thiazolidine ring opening (eq 18).[41] For these substrates, addition of NaI not only permits the use of milder reaction conditions, but results in a different type of product formation,[41b] probably due to $^-CCl_3$ acting as a base.

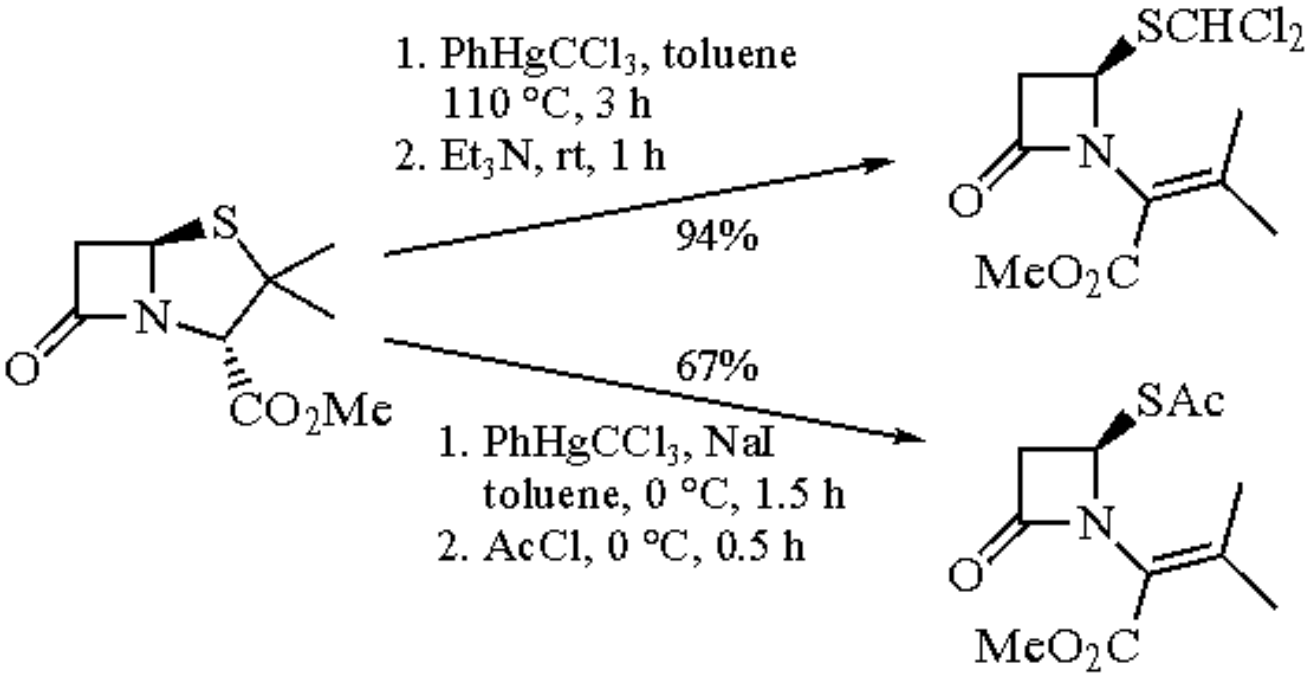

(18)

Insertion Reactions.

$PhHgCCl_3$ easily inserts **:**CCl_2 into the Si-H bond.[42] In this respect, good yields of insertion product are obtained with silanes having bulky groups (eq 19).[42a] In contrast, carbenes generated following the *t*-BuOK-$CHCl_3$ protocol fail to react with these silicon compounds. Optically active silanes have been used to study the mechanism.[43] Since retention of configuration is mainly observed,[43a] the insertion process is seen to take place through a three-centered transition state.[43b]

$$t\text{-}Bu_3SiH \xrightarrow[120\ ^\circ C]{PhHgCCl_3} \underset{55\%}{t\text{-}Bu_3SiCHCl_2} + PhHgCl \qquad (19)$$

Insertion of **:**CCl_2, generated by thermal treatment of $PhHgCCl_3$, into C-H bonds usually does not compete with the addition to C=C bonds in typical alkenes, although some examples have been described in steroidal systems.[17] Several examples of insertion into Si-Br and Ge-Cl bonds are also known for $PhHgCCl_3$.[44]

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José Barluenga, Miguel Tomás & José M. González

Phenyltrichlorotungsten[1]

$PhWCl_3$

[54161-21-6] · $C_6H_5Cl_3W$ · Phenyltrichlorotungsten · (MW 367.31)

(transition metal catalyst for the alkene metathesis reaction)

Physical Data: brown crystalline solid; diamagnetic; mp >108 °C (dec).

Solubility: slightly sol toluene, diethyl ether.

Preparative Method: from the reaction of ***Tungsten(VI) Chloride*** with 2 equiv of Ph_4Sn in refluxing pentane.

Handling, Storage, and Precautions: highly air sensitive; reacts vigorously with water or alcohols to liberate benzene.

Alkene Metathesis.[2]

Phenyltrichlorotungsten in combination with ***Aluminum Chloride*** is one of a large number of transition metal catalysts[3] for the alkene metathesis reaction (eq 1). The mechanism has been extensively studied.[4]

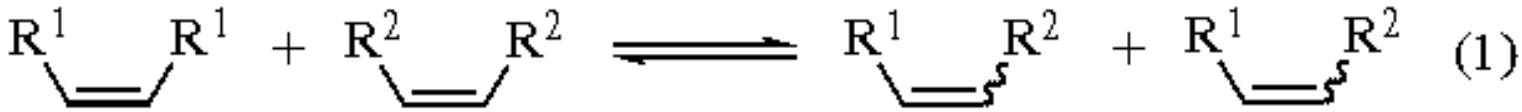

The phenyltrichlorotungsten-aluminum chloride catalyst is extremely air sensitive and must be prepared in oxygen-free conditions. Typically, phenyltrichlorotungsten (1 mmol) is added to a centrifuge tube fitted with a rubber septum containing aluminum chloride (1 mmol) in an inert atmosphere of nitrogen. Oxygen-free chlorobenzene (25 mL) is then added and the mixture is shaken for 0.5 h and centrifuged. The supernatant liquid contains the active catalyst. Reaction of 1,7-octadiene with the above catalyst for ca. 21 h gives cyclohexene and ethylene (eq 2).[5]

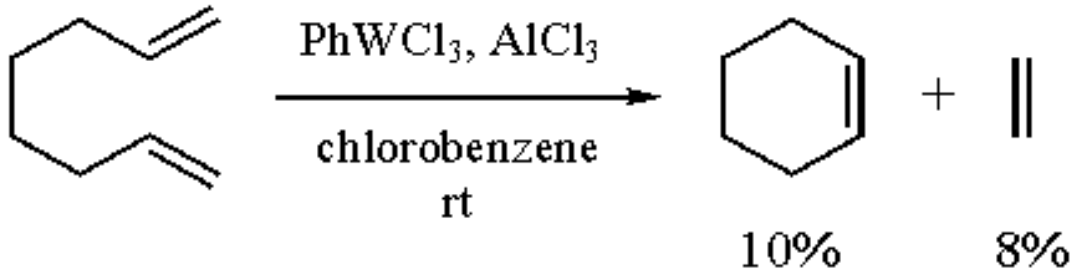

(2)

In general, although cyclobutanes are not products from the alkene metathesis reaction, Gassman and Johnson[6] have found that treatment of a strained diene, 11,12-bis(trifluoromethyl)-(*i*,*o*)-bicyclo[8.2.2]tetradeca-11,13-diene, with the above catalyst for 5 min results in equilibration with the corresponding, less strained, cyclobutane derivative (eq 3). Both 2,3-bis(trifluoromethyl)bicyclo[2.2.1]hepta-2,5-diene and 2,3-bis(trifluoromethyl)bicyclo[2.2.2]octa-2,5-diene, are unreactive under these conditions; however, the reverse reactions are readily achieved (eqs 4 and 5).

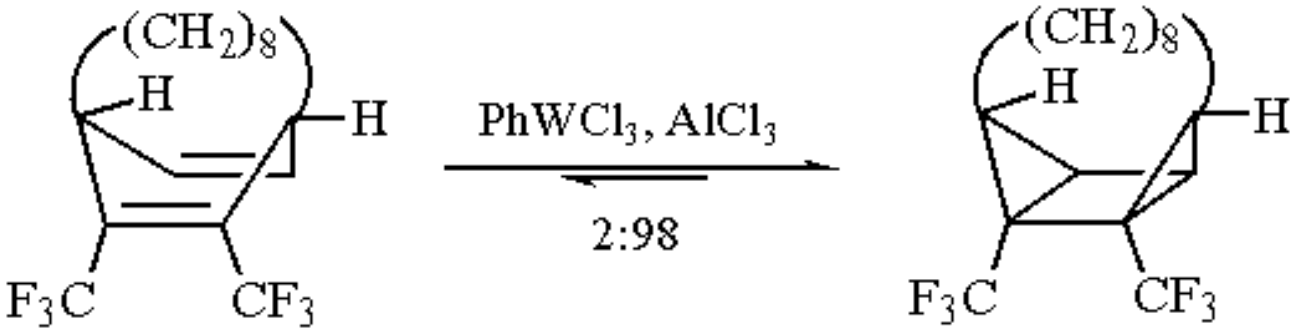

(3)

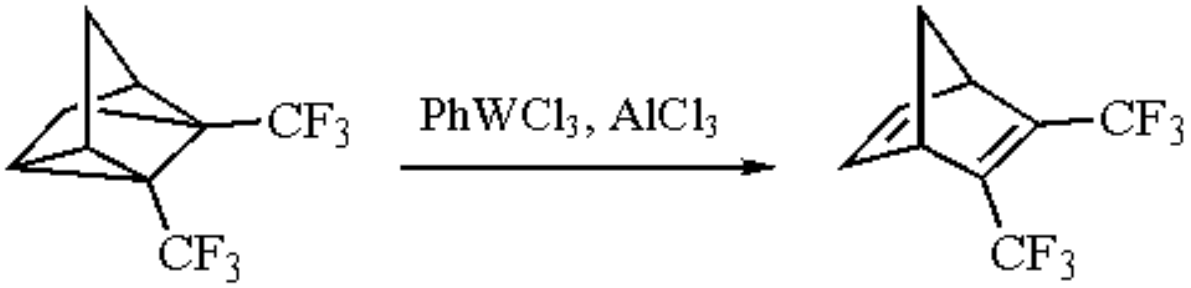

(4)

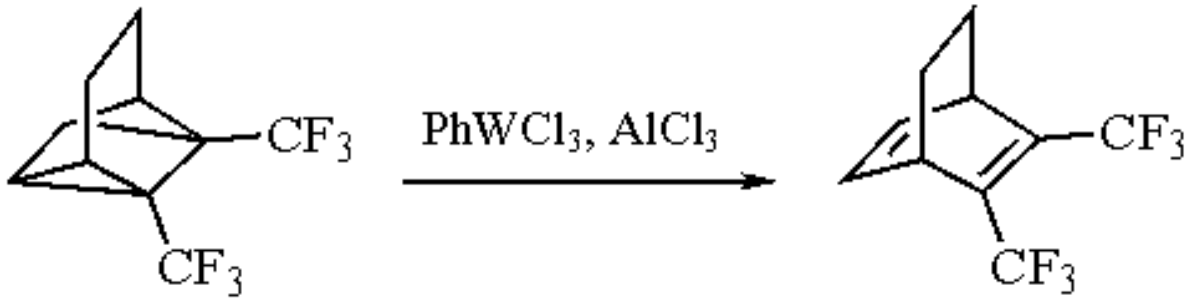

(5)

Retro-Carbene Additions.

Treatment of 1-alkylcyclopropanes with a catalytic quantity of phenyltrichlorotungsten-aluminum chloride in a

sealed Carius tube at rt in dimethyl ether-chlorobenzene (5:1) results principally in the formation of the corresponding 1-alkene through loss of a methylene fragment (eq 6). Similar treatment of bicyclo[2.1.0]pentane with $PhWCl_3/EtAlCl_2$ gives cyclobutene (eq 7).[7]

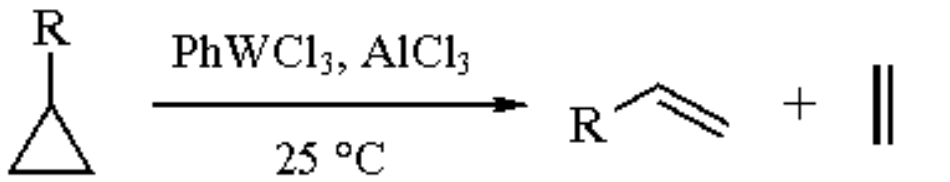

(6)

R = Et	83%	11%
R = Bu	80%	9%
R = *i*-Pr	72%	10%

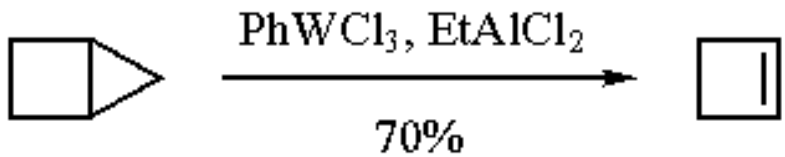

(7)

Cyclopropane-Alkene Cross Metathesis.

Treatment of a mixture of ethylcyclopropane and ethyl acrylate with catalytic phenyltrichlorotungsten-aluminum trichloride results in the formation of ethyl cyclopropanecarboxylate in low yield (eq 8). By using ***Ethylaluminum Dichloride*** rather than aluminum trichloride, the yield is slightly improved.[8]

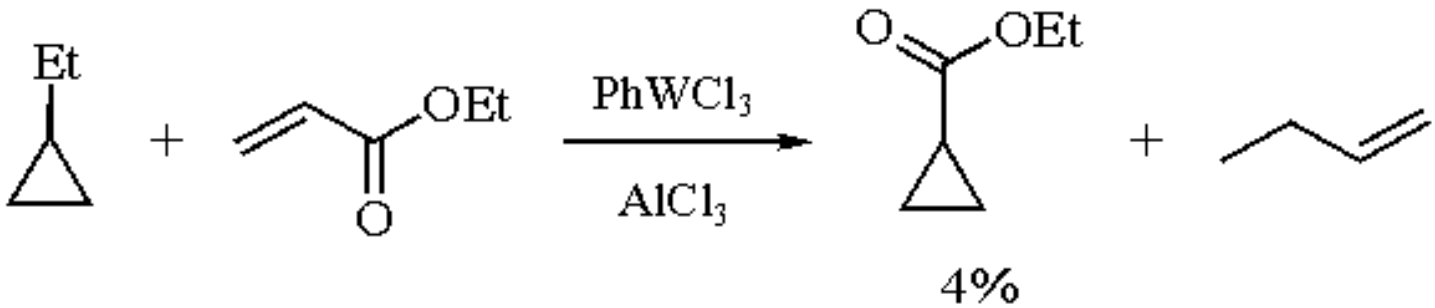

(8)

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N-Phenyltrifluoromethanesulfonimide[1]

$(CF_3SO_2)_2NPh$

[37595-74-7] · $C_8H_5F_6NO_4S_2$ · *N*-Phenyltrifluoromethanesulfonimide · (MW 357.28)

(mild triflating agent[2] for amine protection;[3,4] vinyl triflate formation from thermodynamic[2] and kinetic enolates[5] generated by deprotonation, conjugate reduction,[6,7] or conjugate addition;[7] formation of aryl triflates[2])

Alternate Names: N-phenyltriflimide; Hendrickson-McMurray reagent.[6]

Physical Data: mp 101-103 °C (Aldrich), 93-94 °C.[2]

Form Supplied in: white solid; widely available.

Preparative Methods: prepared in 92% yield from the reaction of aniline with 2 equiv each of ***Trifluoromethanesulfonic Anhydride*** and ***Triethylamine*** in CH_2Cl_2 at -78 °C.[2]

Handling, Storage, and Precautions: nonhygroscopic and extremely stable.

Utility and Selectivity with Amines and Alcohols.

The trifluoromethanesulfonyl group provides for effective protection of primary and secondary amines[4] and the monoalkylation of secondary trifluoromethanesulfonamides.[3] These substrates are typically formed by the reaction of the amine with ***Trifluoromethanesulfonic Anhydride*** (triflic anhydride, Tf_2O). As a less reactive triflating reagent, *N*-phenyltrifluoromethanesulfonimide[2] (Tf_2NPh) is more convenient to use and provides higher selectivity than that encountered with triflic anydride. Triflates of secondary aliphatic amines are easily isolated from the byproduct phenyltriflamide by carbonate extraction[3] and Tf_2NPh does not react with aromatic secondary amines under similar or more vigorous conditions.[3] This selectivity is also observed in selective triflation of primary over secondary alcohols, allowing selective dehydration in a series of dipeptides (eq 1).[9]

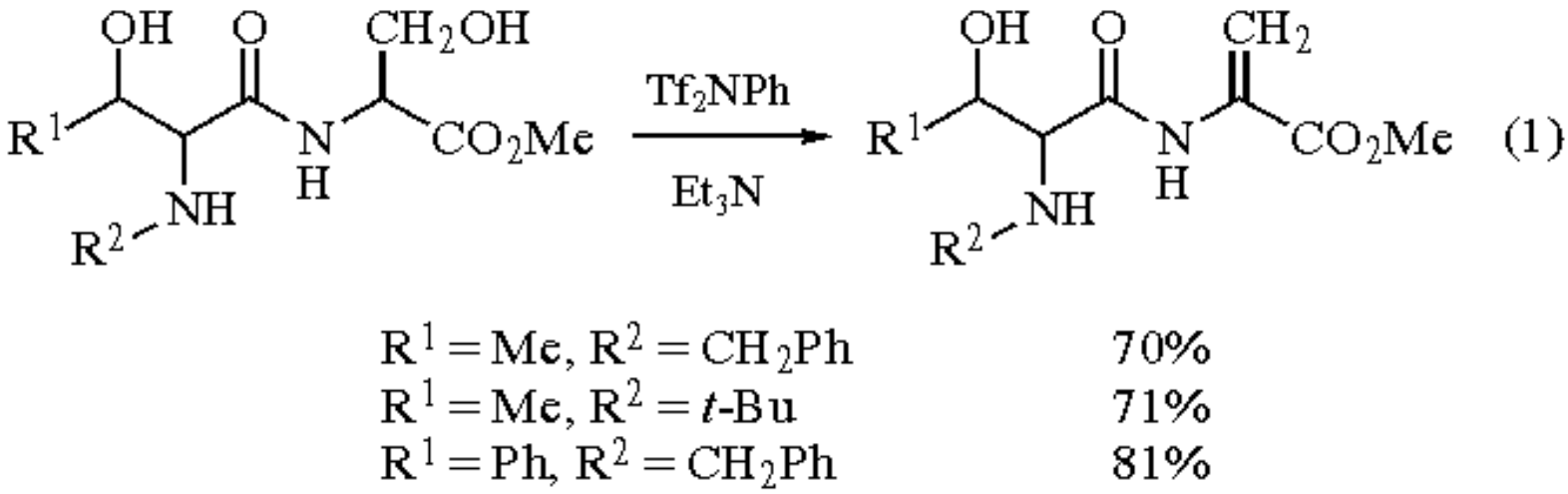

Formation of Enol Trifluoromethanesulfonates (Enol Triflates).

Kinetic or thermodynamic enolate formation, through reaction of unsymmetrical ketones with properly selected strong bases, followed by treatment with Tf_2NPh provides regioselective formation of vinyl triflates[7,8,10,11] in good to excellent yields (eq 2). Minor discrepancies to these generalities have been documented, but appear to be substrate (eq 3)[12,13] or base dependent (eq 4).[13] This sequence surpasses the triflic anhydride/base protocol (which provides predominantly thermodynamic products) both in regiocontrol and material yield and has led to preparation of enol triflates where triflic anhydride fails (eq 5).[7,14-16] Enol triflates of symmetrical and unidirectionally enolizable ketones[13,14,17-20] are produced in typically higher yield by trapping with Tf_2NPh compared with Tf_2O[7,16] or (trifluoromethylsulfonyl)imidazole[14,17] and enolates of five- to seven-membered lactones have been isolated as their trifluoromethanesulfonyl ketene acetals (eq 6).[21]

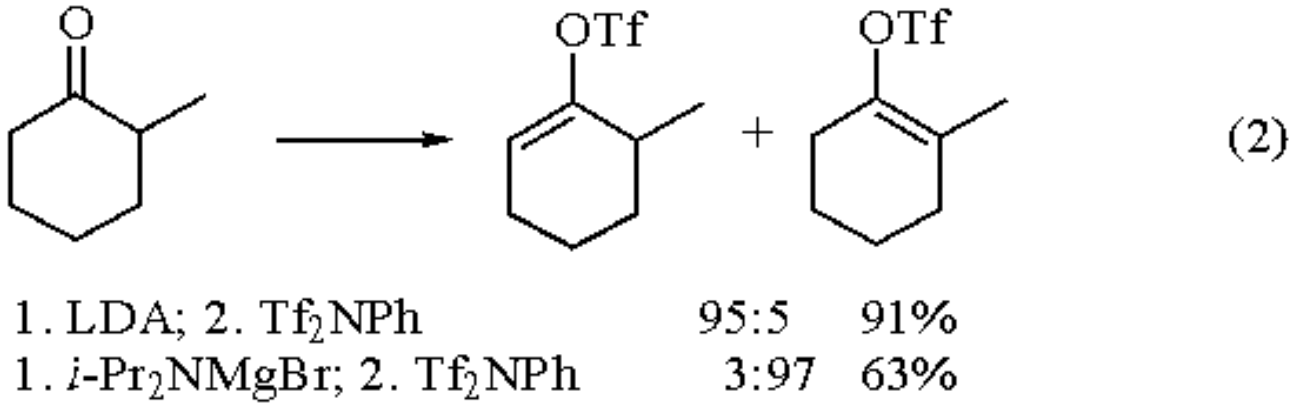

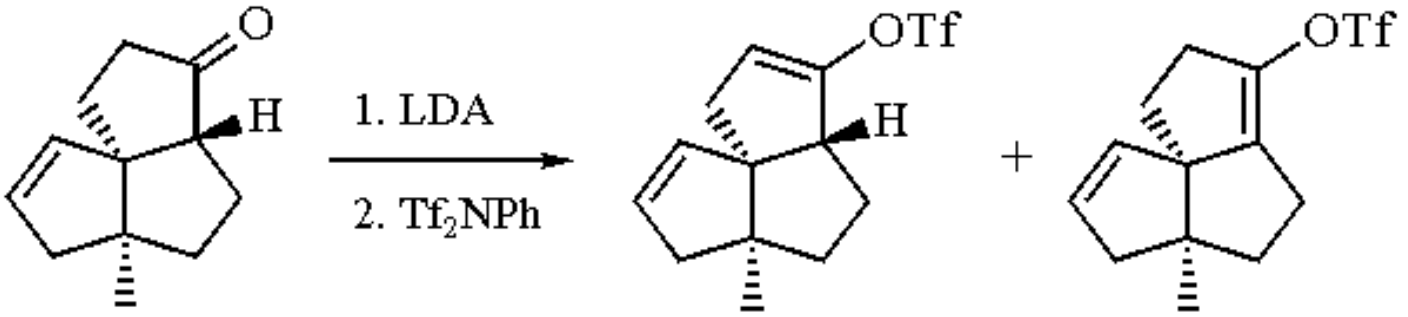

(3)

9:1

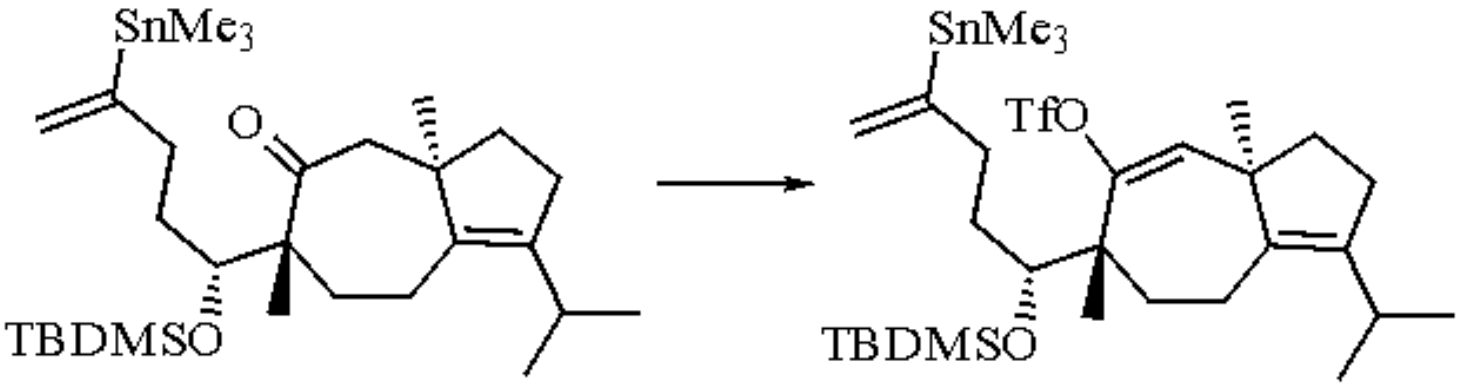

(4)

1. LDA; 2. Tf_2NPh — No reaction

1. $KN(TMS)_2$; 2. Tf_2NPh — >74%

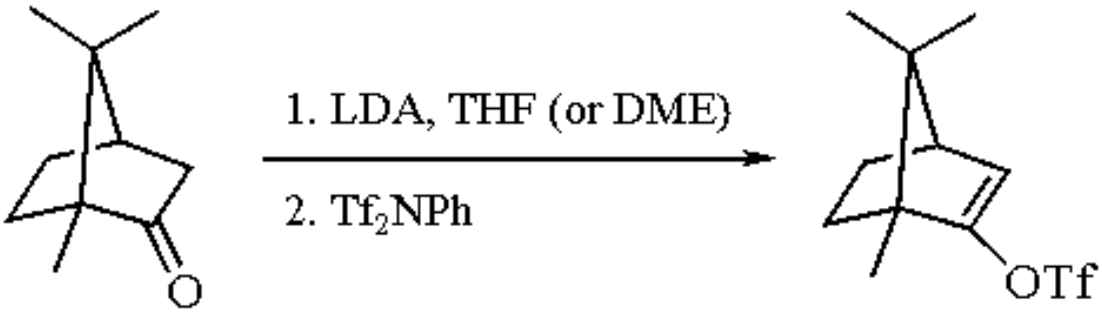

(5)

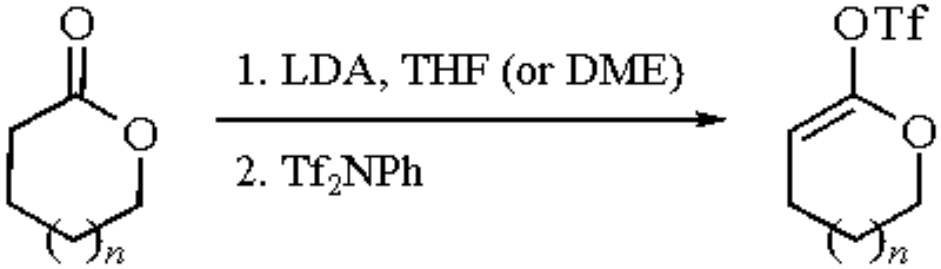

(6)

$n = 1$ — 75%

$n = 2$ — 89%

Regiospecific Generation of Enol Triflates.

A variety of enolate generation methods followed by exposure to Tf_2NPh provides regiospecific vinyl triflates. Regiospecific enolates generated from conjugate reduction of enones with ***Lithium***[7,22] in liquid ***Ammonia***, from pure silyl enol ethers with ***Methyllithium***,[6] and by conjugate addition of dialkylcuprate reagents to enones[6,23] are all successfully trapped by Tf_2NPh. *N*-Phenyltriflimide efficiently captures regiospecific enolates generated from conjugate reduction of cyclopentenones[6] and cyclohexenones[6,24] with ***Lithium Tri-s-butylborohydride*** (eqs 7 and 8), with the exception of sterically encumbered substrates.[6] *N*-Phenyltriflimide has become a widely utilized reagent for the conversion of phenols to aryl triflates. Optimal yields[2] and chemoselectivity[2,25] allow aryl triflate formation in the presence of amines, alcohols, or carboxylates[2] and on relatively sensitive substrates.[25]

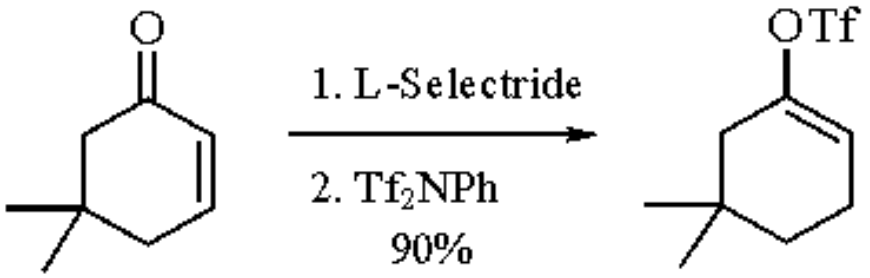

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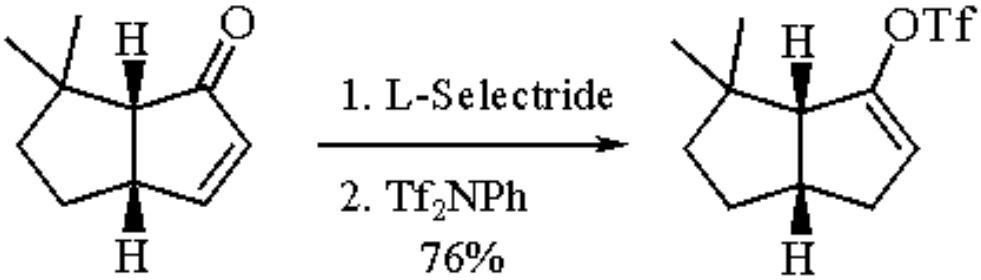

(8)

Utility of Enol and Aryl Triflates.

Enol triflates have been utilized for the generation of vinyl cations and carbenes,[26] and the transient 1,2,3-cyclohexatriene.[27] Enol triflates and trifluoromethanesulfonyl ketene acetals[21] undergo coupling with diorganocuprate reagents to give alkenes and substituted enol ethers, respectively. Palladium-catalyzed coupling and carbonylation reactions of enol and aryl triflates with organostannanes, alkenes, and alkynes abound in the literature.[14]

Other Applications.

A selected number of primary and secondary saturated triflones are available from the reaction of the respective alkyllithium or dialkylcuprate reagent with *N*-phenyltriflimide.[28]

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N-Phenyltrimethylacetimidoyl Chloride[1]

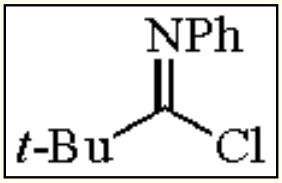

[50993-08-3] · $C_{11}H_{14}ClN$ · *N*-Phenyltrimethylacetimidoyl Chloride · (MW 195.71)

(strong iminating agent, used in forming imines[2] and amidines,[3] and in peptide synthesis[1,4])

Physical Data: bp 112 °C/13 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: liquid; must be synthesized.

Preparative Method: the amide precursor (**1**) is treated with a chlorinating agent such as ***Phosphorus(V) Chloride***[1] or ***Thionyl Chloride***[3] (eq 1).

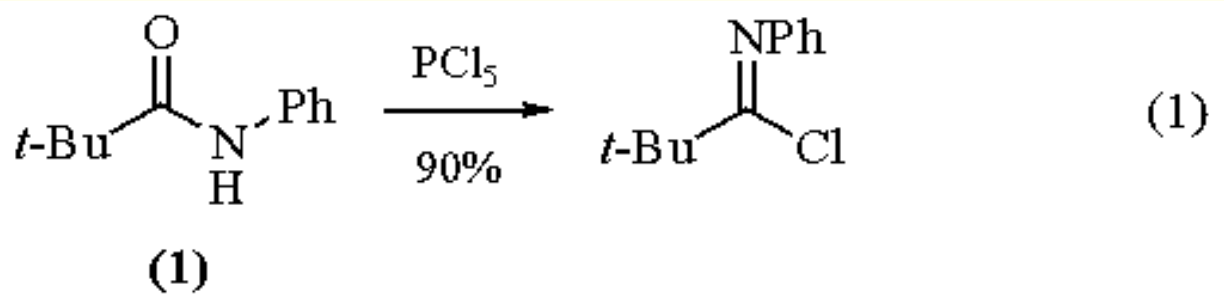

Purification: redistill under reduced pressure.[5]

Handling, Storage, and Precautions: irritant and moisture sensitive. Incompatible with strong bases (see Aldrich safety index for trimethylacetyl chloride).[6]

Addition-Elimination Reactions.

Most reactions of *N*-phenyltrimethylacetimidoyl chloride involve an addition-elimination reaction (similar to the reactions of the oxa analogs, the acid chlorides) with a C-,[7] O-,[1] N-,[8] P-,[9] or As-centered[10] nucleophile. However, the imine products (**2**) can isomerize, the double bond shifting to give enamine derivatives (**3**) (eq 2).

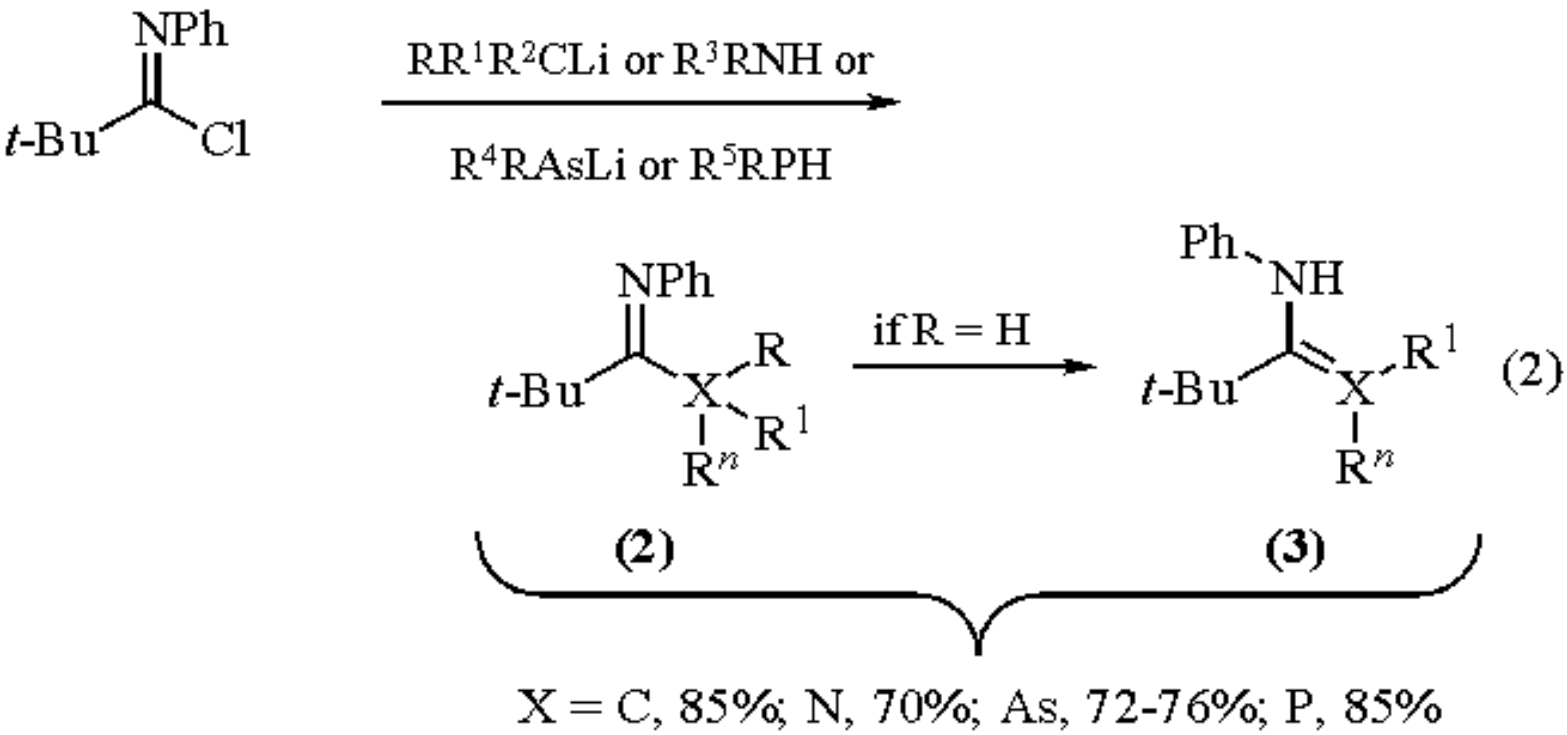

Cyclizations.

Several N-, P-, and As-containing heterocyclic compounds have been synthesized using *N*-phenyltrimethylacetimidoyl chloride (eq 3).[11,12]

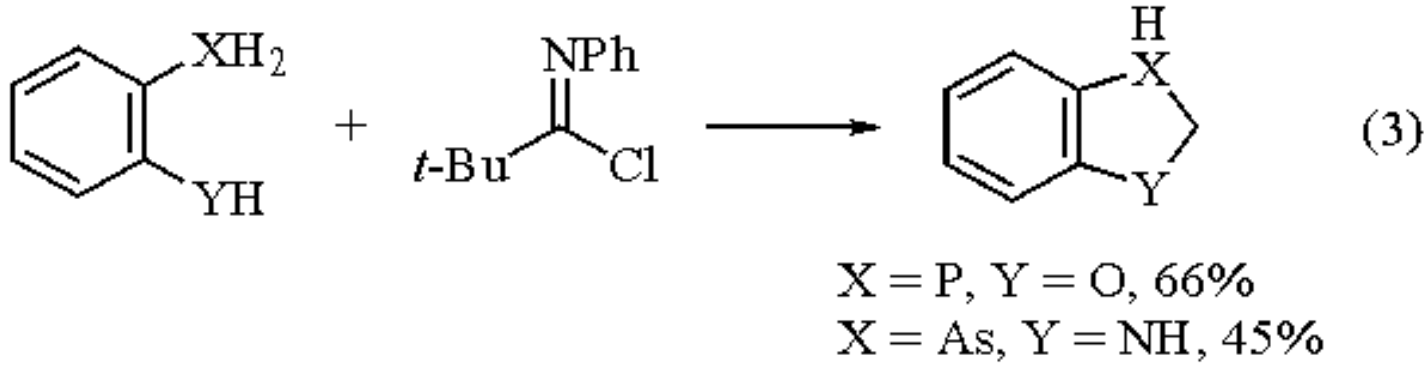

Peptide Synthesis.

N-Phenyltrimethylacetimidoyl chloride was initially used to activate the carboxylic acid group on *N*-tosylalanine (**4**) to form peptide links with amines (eq 4).[1]

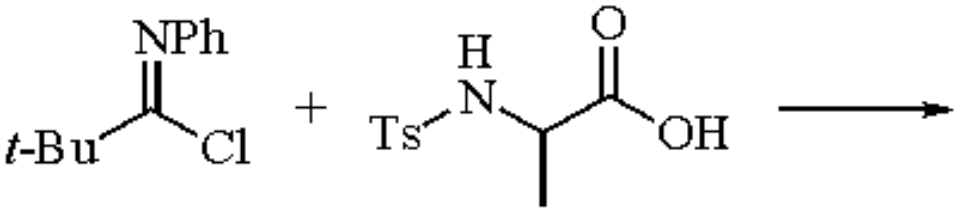

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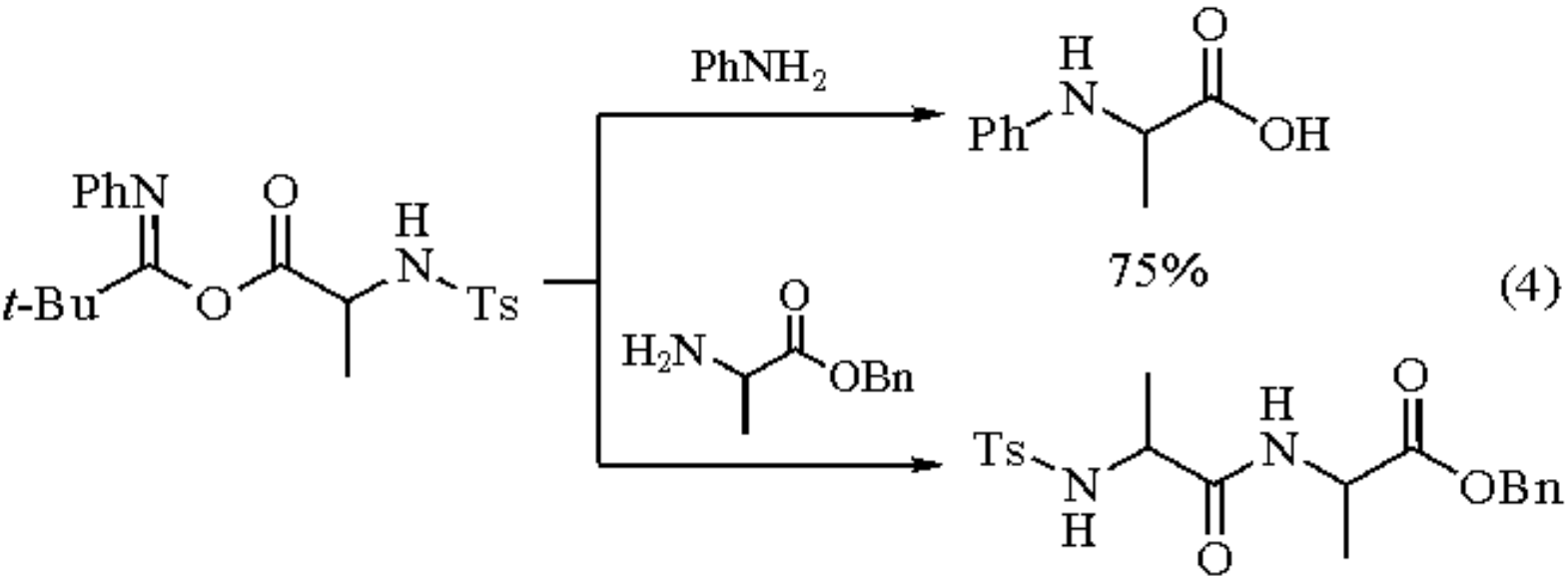

(4)

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Phenyltrimethylammonium Perbromide

$Ph^{+}NMe_3\ Br_3^{-}$

[4207-56-1] · $C_9H_{14}Br_3N$ · Phenyltrimethylammonium Perbromide · (MW 375.94)

(α-bromination of acetals;[1-5] selective bromination of ketones;[1,6] oxidation of tosylhydrazones to tosylazoalkenes[7])

Alternate Names: phenyltrimethylammonium tribromide; PTAB; PTT.

Physical Data: mp 115.5-116.5 °C.

Solubility: very sol THF, CH_2Cl_2; sol acetic acid.

Form Supplied in: orange crystals; widely available.

Preparative Methods: prepared in situ by reaction of equimolar amounts of phenyltrimethylammonium bromide and ***Bromine*** in THF (eq 1).[5,6,8] The stable reagent, suitable for storage, is prepared by quaternization of *N*,*N*-dimethylphenylamine with ***Dimethyl Sulfate*** in toluene, followed by bromination with bromine in aqueous hydrogen bromide (eq 2).[6]

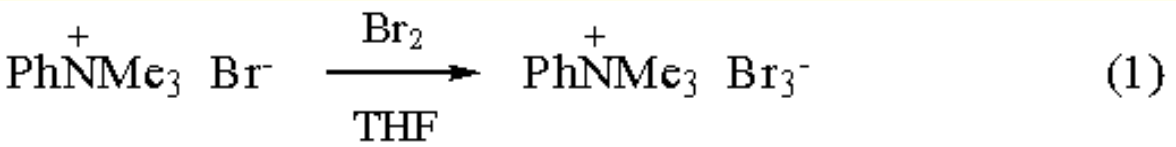

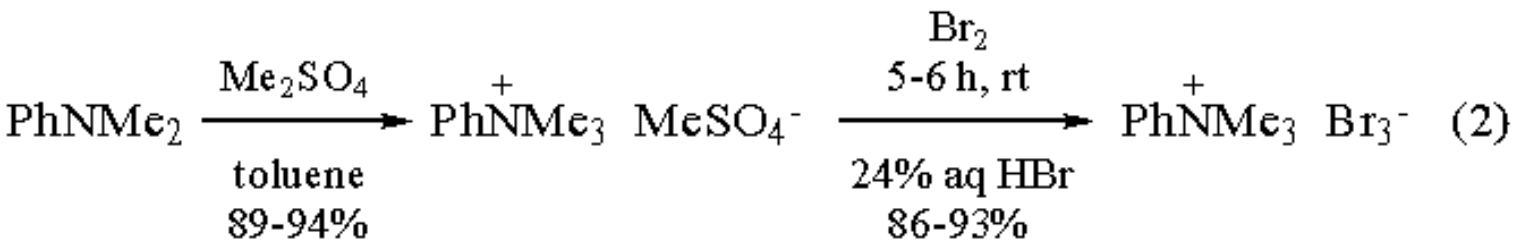

Handling, Storage, and Precautions: the reagent is highly stable but should be protected from moisture as it is slightly hygroscopic. For some applications, phenyltrimethylammonium perbromide must be strictly anhydrous in order to achieve maximum selectivity.

Introduction.

Phenyltrimethylammonium perbromide has the same properties as ***Pyridinium Hydrobromide Perbromide*** without the disadvantages.[1]

α-Bromination of Acetals.

This reagent is widely used for the α-bromination of ethylene acetal derivatives of ketones. Phenyltrimethylammonium perbromide in THF converts 3β-acetoxy-20-ethylenedioxypregna-5,16-diene into 3β-acetoxy-20-oxo-21-bromopregna-5,16-diene;[1] various other ethylene acetals have been transformed into the corresponding brominated acetals, which are readily hydrolyzed to α-bromo ketones (eqs 3 and 4).[1-3,5]

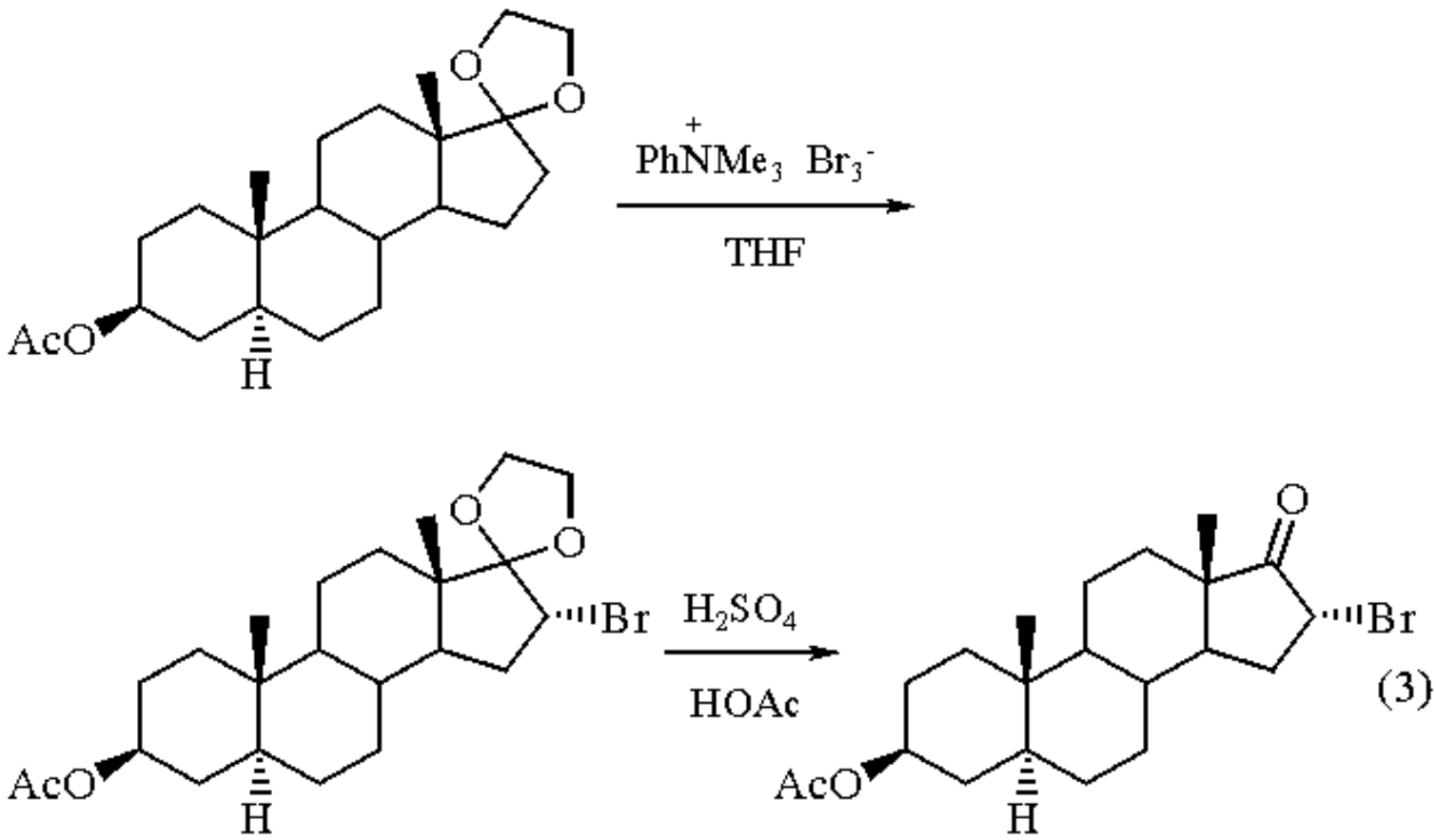

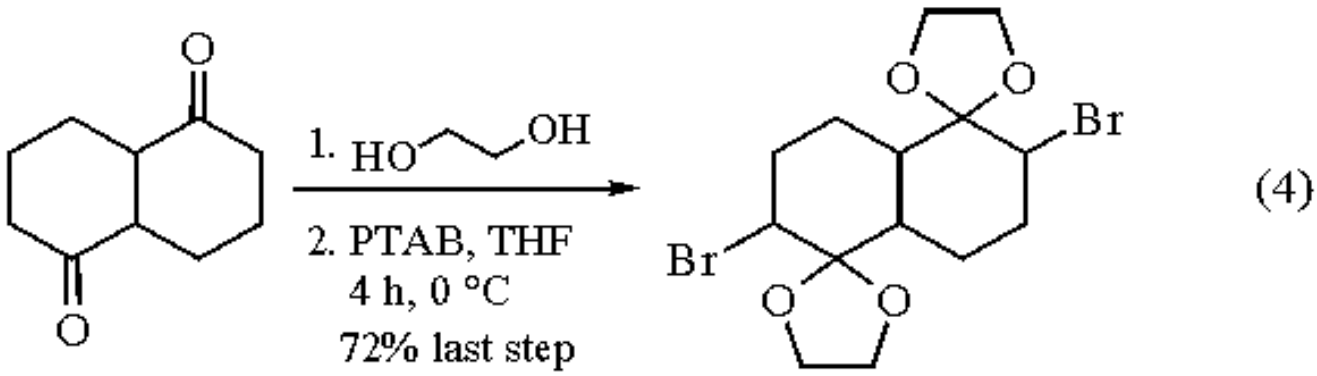

This conversion has also been performed as a one-pot procedure starting with a ketone, ethylene glycol, and PTAB in THF (eq 5).[4] Anhydrous THF is important to the selectivity of this process because of the stability of Br_3^- in this solvent. Moreover, THF acts as a buffer by reacting with liberated HBr, and is therefore very useful for reactions of substrates

bearing acid-sensitive functions.

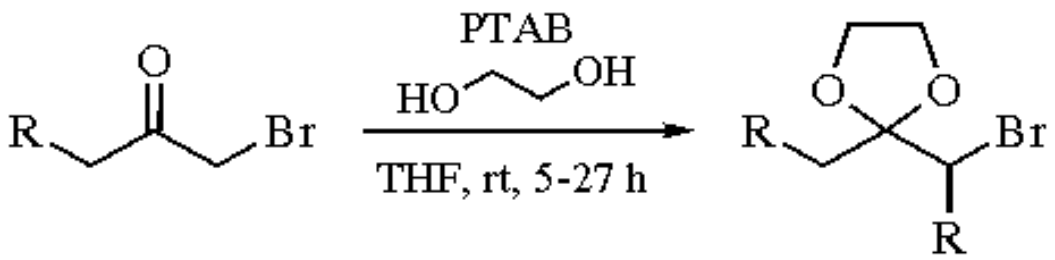

(5)

R = H, 90%; Me, 89%; R,R = $(CH_2)_2$, 68%; $(CH_2)_3$, 89%

Selective Bromination of Ketones.

Ketones are selectively monobrominated at the α-position with PTAB in anhydrous THF. Small amounts of water can greatly retard the rate of bromination and can result in decreased selectivity. α-Monobromination of methyl aryl ketones with PTAB occurs smoothly, and α,α-dibromination is also possible (eq 6).[6]

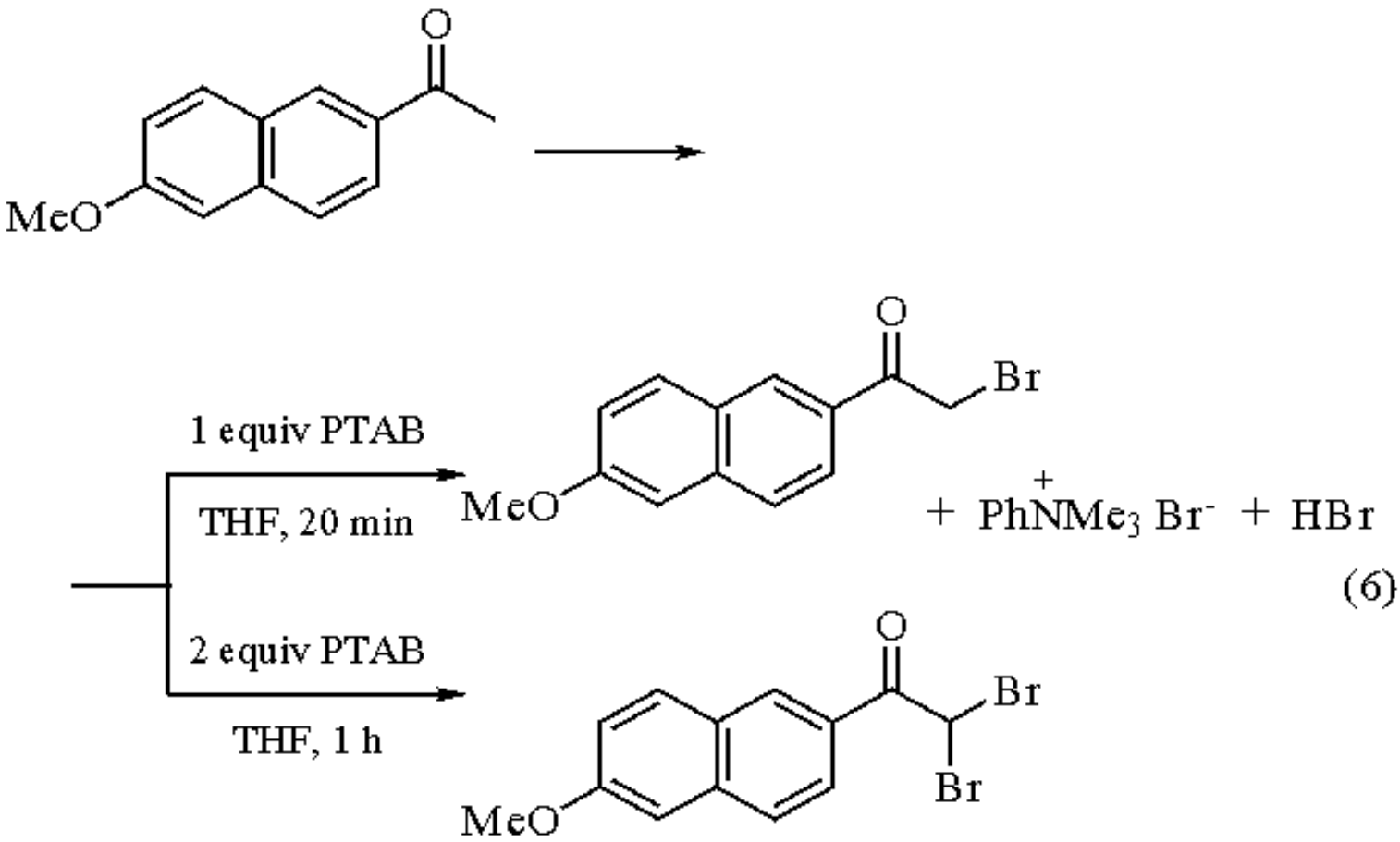

(6)

α-Bromo ketones have been selectively obtained in substrates containing carbon-carbon double bonds[3] and cyclopropane rings.[9-11] Thus *trans*-dihydroaristolone can be α-brominated and dehydrobrominated to (±)-aristolone (eq 7), a sesquiterpene from *Aristolochia debilis*,[9] while methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate has been α-brominated and further converted into methyl *cis*-chamic ester (eq 8).[10] α-Bromination of cyclic ketones with PTAB has been used for the construction of *anti*-bishomoquinone[12] and triasteranedione[13] from cyclooctane-1,5-dione and bicyclo[3.3.1]nonane-3,7-dione, respectively (eqs 9 and 10).

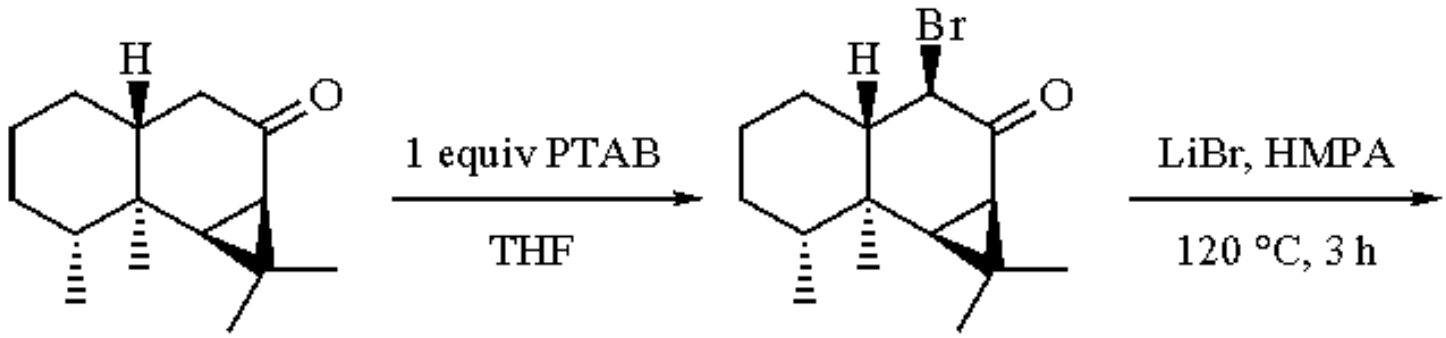

trans-Dihydroaristolone

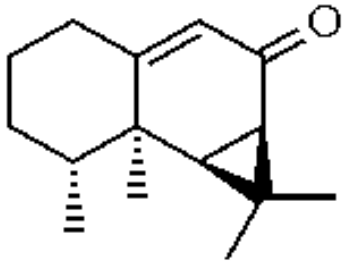

(7)

(±)-Aristolone

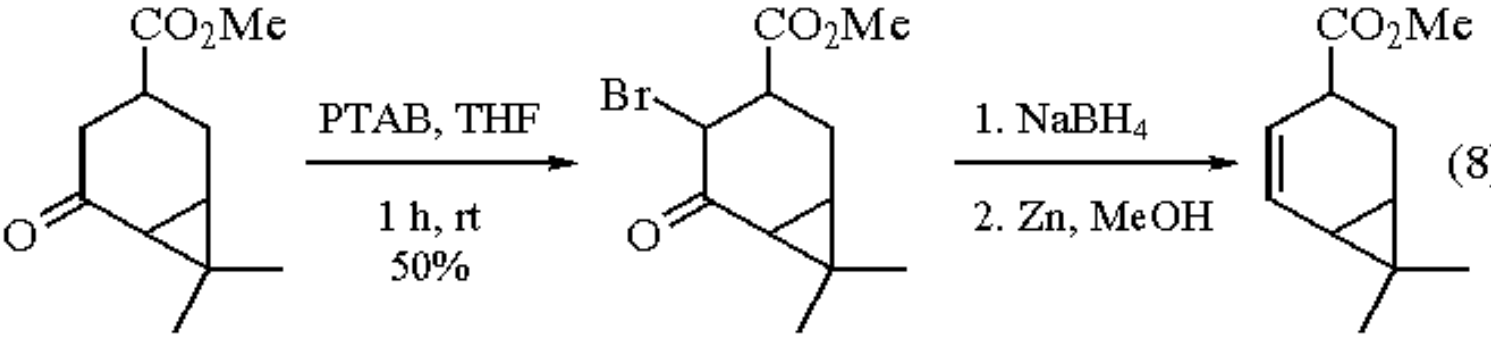

(8)

Methyl *cis*-chamic ester

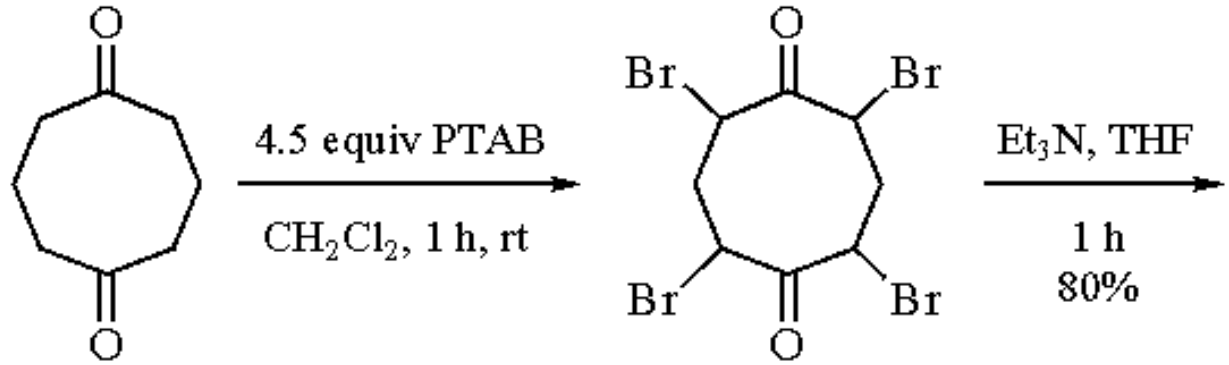

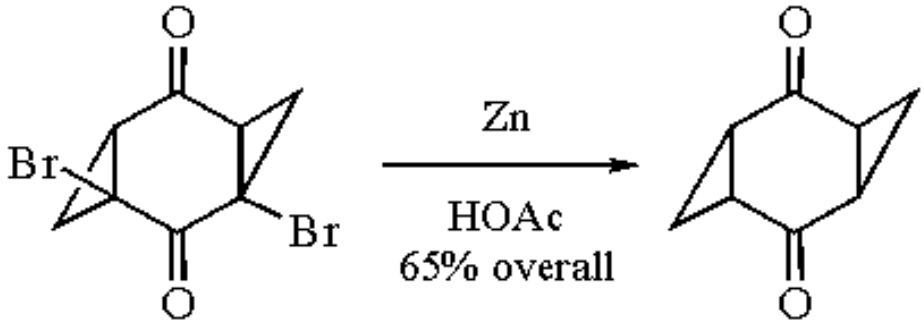

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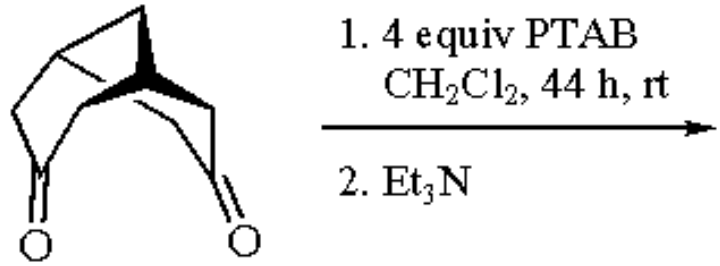

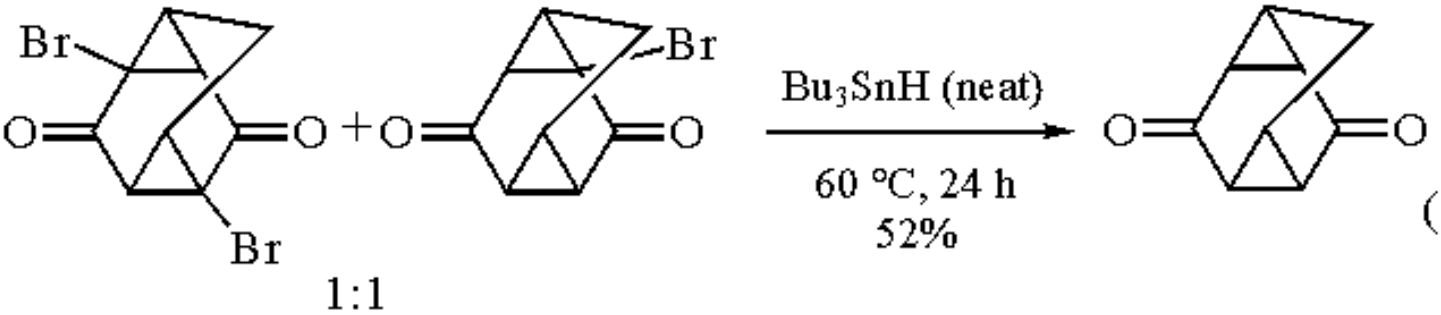

(10)

Oxidation of Tosylhydrazones into Tosylazoalkenes.

Tosylazoalkenes are obtained from the reaction of tosylhydrazones and PTAB, followed by treatment with base (eq 11).[7,14] The reaction fails with bromine and *N*-bromosuccinimide.[14]

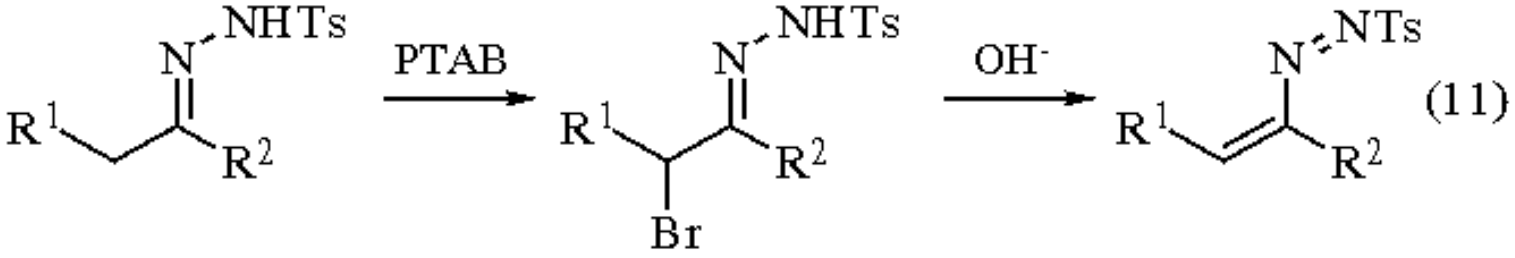

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Phenyl Trimethylsilyl Selenide

$PhSeSiMe_3$

[33861-17-5] · $C_9H_{14}SeSi$ · Phenyl Trimethylsilyl Selenide · (MW 229.28)

(synthesis of benzeneselenol;[1a] introduction of the phenylseleno function into a variety of oxygen-containing compounds[2-4,6])

Physical Data: bp 92-93 °C/5 mmHg. ^1H NMR ($CDCl_3$) δ 0.35 (Me_3Si); ^{13}C NMR ($CDCl_3$) δ 1.49 (Me_3Si).

Solubility: sol benzene, Et_2O, THF, MeCN.

Preparative Methods: conveniently prepared by the reduction of ***Diphenyl Diselenide*** with ***Sodium*** in THF, followed by silylation of thus formed PhSeNa with ***Chlorotrimethylsilane***.[1a,b] In a small scale reaction, silylation of PhSeLi, which can be prepared in situ from metallic ***Selenium*** and ***Phenyllithium*** in THF, is alternatively utilized.[1c]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: although phenyl trimethylsilyl selenide isolated as a colorless liquid is somewhat sensitive to atmospheric moisture, it can be handled conveniently using syringe techniques and can be stored indefinitely under dry nitrogen (or argon). Use in a fume hood.

Reaction with Aldehydes and Ketones.

Phenyl trimethylsilyl selenide does not react with carbonyl compounds at 25 °C or on heating. However, use of ***Aluminum Chloride*** as catalyst results in selective formation of selenoacetals, whereas the copresence of zinc halide in place of $AlCl_3$ leads to *O*-(trimethylsilyl) monoselenoacetals,[2a-d] which can be utilized as α-siloxy radical precursors (eq 1).[2e]

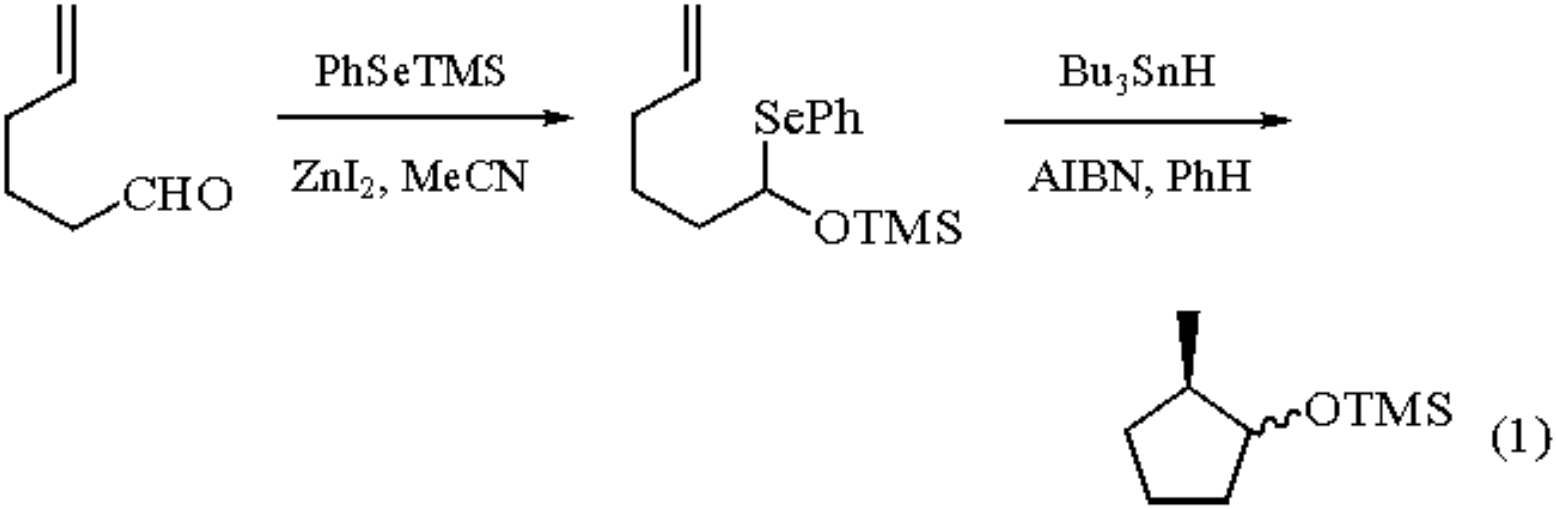

Reaction with Acetates and Lactones.

In the presence of a catalytic amount of ***Zinc Iodide***, alkyl acetates and lactones react with phenyl trimethylsilyl selenide to afford alkyl phenyl selenides and o-(phenylseleno)carboxylic acids, respectively (eq 2).[3]

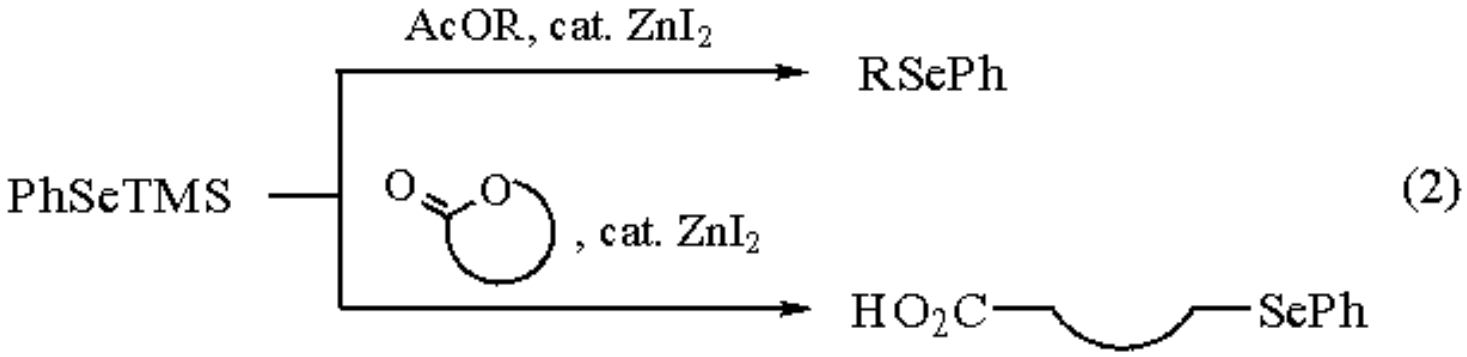

Reaction with α,β-Unsaturated Carbonyl Compounds.

Conjugate addition of phenyl trimethylsilyl selenide to α,β-unsaturated aldehydes and ketones has been attained by using ***Triphenylphosphine***,[2c] ***Zinc Chloride***,[2c] or ***Trimethylsilyl Trifluoromethanesulfonate***[4] as the catalyst. Combination of this reaction with selenoxide elimination[5] provides a one-pot procedure for α-alkoxyalkylation of α,β-unsaturated ketones (eq 3).

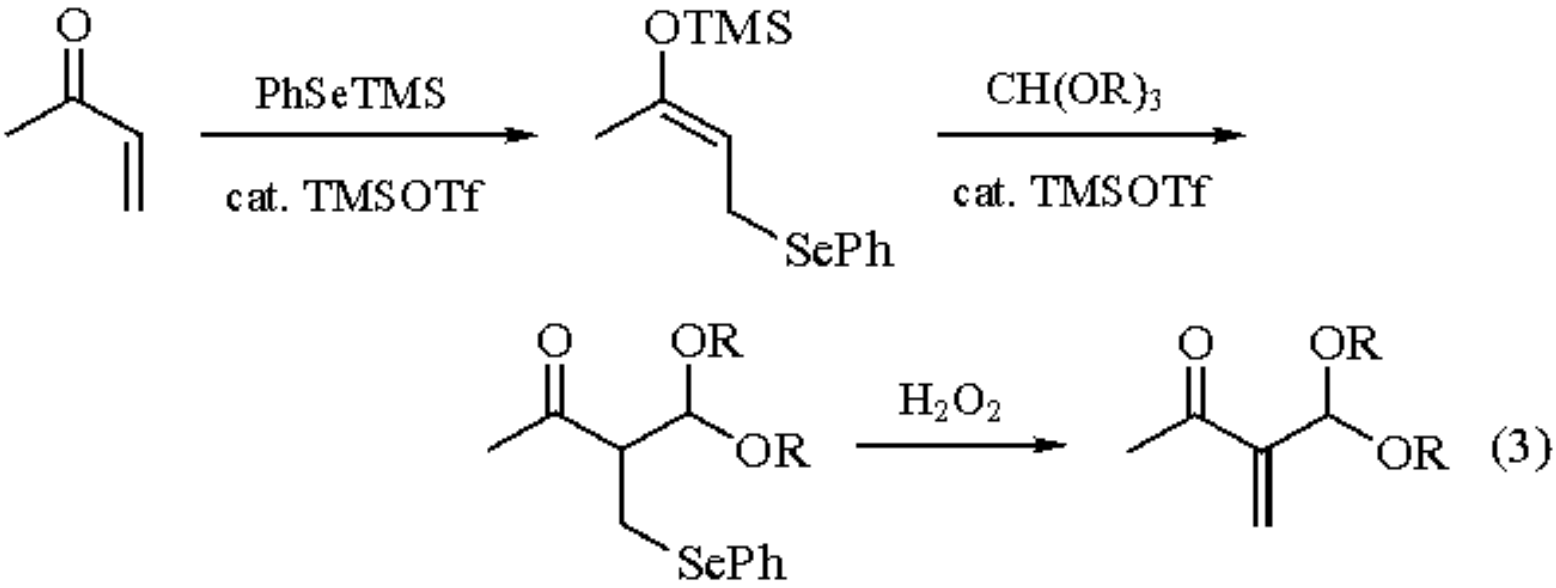

Reaction with Cyclic Ethers.

Ring opening of epoxides, oxetanes, and tetrahydrofurans with phenyl trimethylsilyl selenide takes place in the presence of ZnI_2 to provide β-, γ-, and δ-siloxyalkyl phenyl selenides, respectively, in good yields (eq 4).[6]

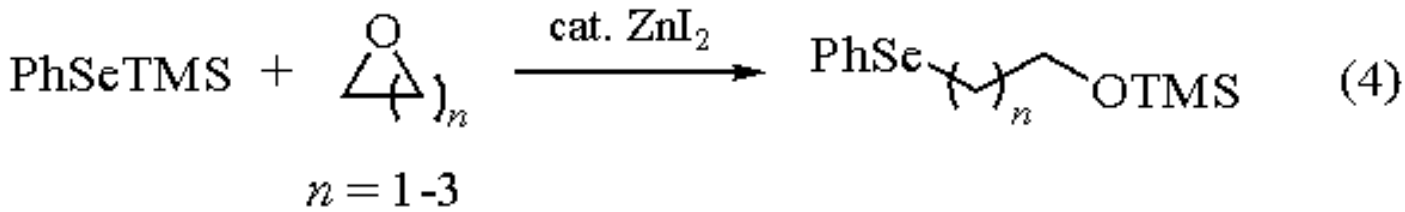

Miscellaneous.

Introduction of a phenylseleno function into organic molecules has also been attained by the reaction of phenyl trimethylsilyl selenide with organic halides.[7] Palladium-catalyzed addition of $PhSeSiMe_3$ to arylacetylenes takes place regio- and stereoselectively to give β-silyl substituted vinylic selenides (eq 5).[8] $PhSeSiMe_3$ serves as a mild reducing agent for deoxygenation of sulfoxides, selenoxides, and telluroxides.[9]

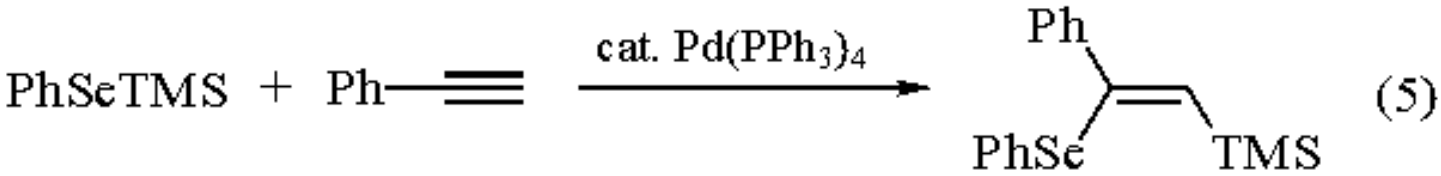

Phenyl Trimethylsilyl Telluride.

$PhTeSiMe_3$ is synthesized by the reaction of Me_3SiCl with PhTeLi,[10a] PhTeNa,[10b] or PhTeMgBr,[10c] and is purified by distillation (bp 77-79 °C/2 mmHg). It can be stored as a 2.5 M hexane solution in a Schlenk flask. Like

$PhSeSiMe_3$, $PhTeSiMe_3$ reacts with cyclic ethers and lactones to give ring-opened products.[10b] Upon treatment with MeOH, benzenetellurol is formed in situ.[10d]

Related Reagents.

Benzeneselenol; ***Bis(trimethylsilyl) Selenide***.

---

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10. (a) Drake, J. E.; Hemmings, R. T. *IC* **1980**, *19*, 1879. (b) Sasaki, K.; Aso, Y.; Otsubo, T.; Ogura, F. *TL* **1985**, *26*, 453. (c) Jones, C. H. W.; Sharma, R. D. *JOM* **1984**, *268*, 113. (d) Ohira, N.; Aso, Y.; Otsubo, T.; Ogura, F. *CL* **1984**, 853.

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Phenyl Trimethylsilyl Sulfide

$PhSSiMe_3$

[4551-15-9] · $C_9H_{14}SSi$ · Phenyl Trimethylsilyl Sulfide · (MW 182.39)

(hemithioacetal formation;[1] ether deprotection[9])

Physical Data: bp 72 °C/8 mmHg; *d* 0.963 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: liquid; commercially available.

Analysis of Reagent Purity: GC.

Handling, Storage, and Precautions: flammable liquid; moisture sensitive; avoid inhalation and body contact; use in a fume hood.

Hemithioacetal Formation.

The reaction of phenyl trimethylsilyl sulfide with aldehydes or acetals under base or acid catalysis affords the corresponding hemithioacetals in moderate to high yields (eq 1). Omission of the catalyst results in longer reaction times, harsher reaction conditions, and substantially reduced yields (eq 2).[1,2] This method has been used extensively to convert carbohydrates into versatile coupling reagents (eq 3).[3-5]

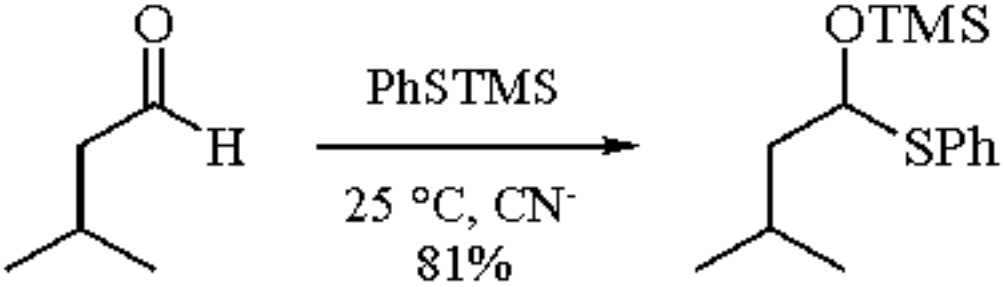

(1)

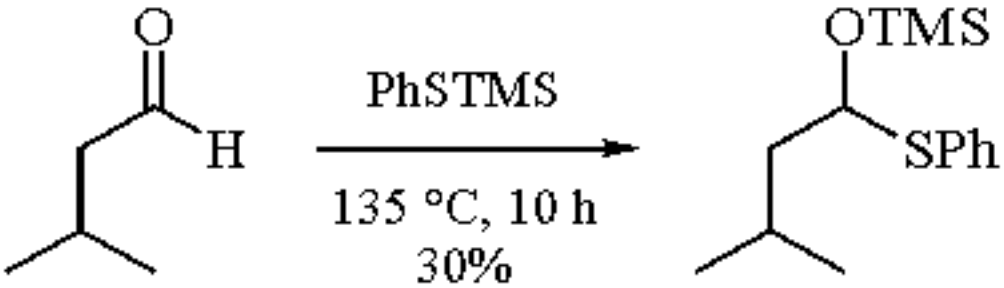

(2)

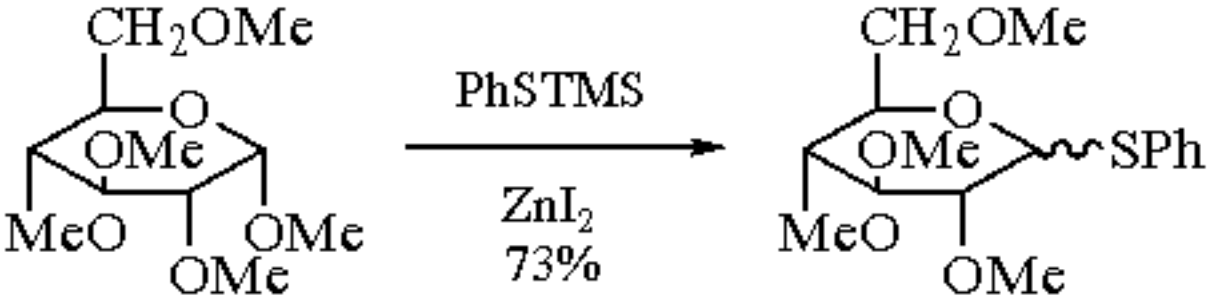

(3)

Conjugate Additions.

Under nucleophilic catalysis, phenyl trimethylsilyl sulfide adds to α,β-unsaturated aldehydes, ketones, and esters exclusively in 1,4-fashion (eq 4).[1,6,7] As with the addition to saturated carbonyl systems, reactions carried out in the absence of cyanide, thiolate, or fluoride require elevated reaction temperatures and extended reaction times. This process allows the mild protection of enones and enals as well as the production of highly functionalized, silicon-containing synthetic building blocks (eq 5).[8]

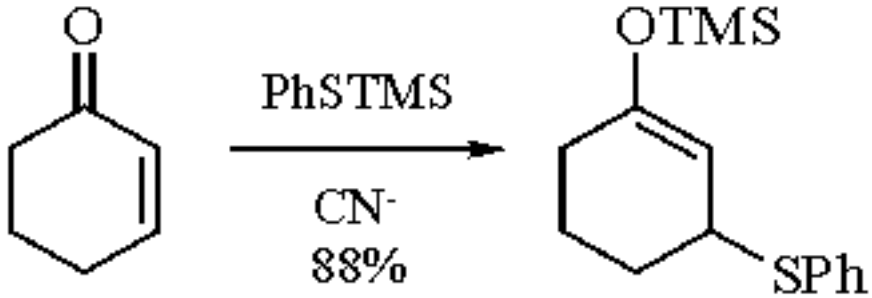

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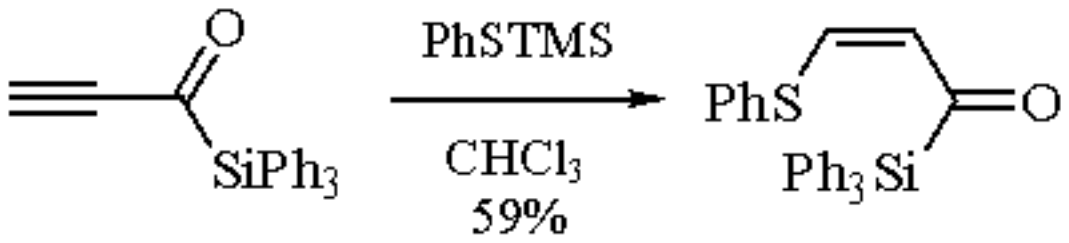

(5)

Nucleophilic Displacements.

Phenyl trimethylsilyl sulfide reacts with a large variety of ethers to afford the corresponding alcohols or silylated alcohols. Methyl and benzyl ethers are mildly and efficiently deprotected upon treatment with the reagent and a Lewis acid (eq 6).[9] When exposed to the same reaction conditions, epoxides are opened to afford vicinal hydroxy thiophenolates (eq 7).[10] Dioxaphospholanes also react in this fashion, providing functionalized silyl ethers upon expulsion of triphenylphosphine oxide (eq 8).[11]

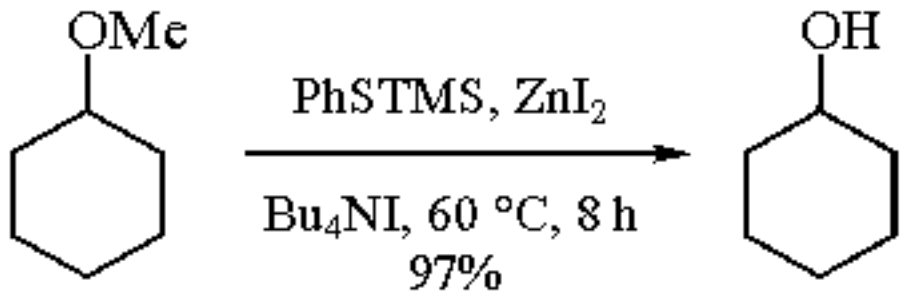

(6)

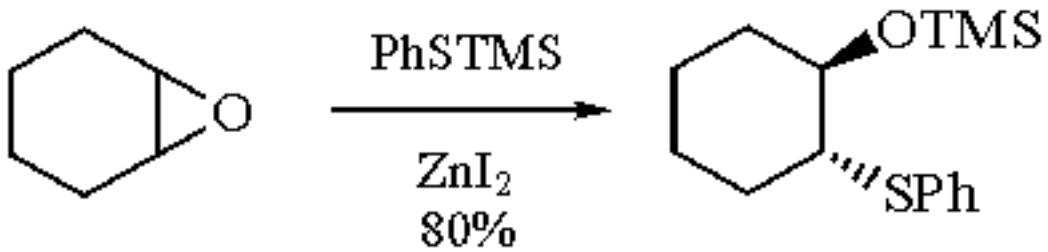

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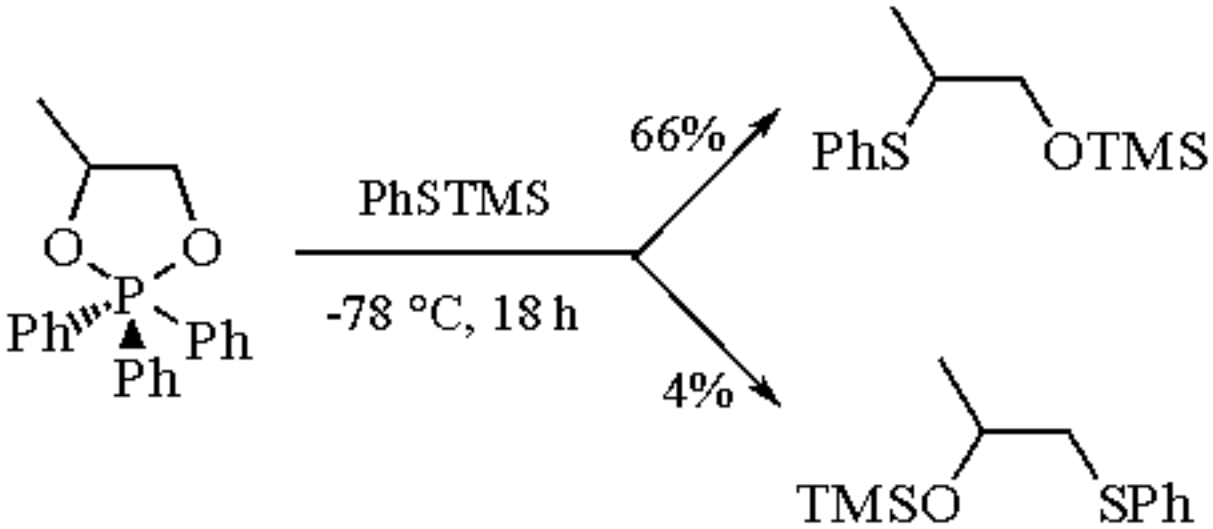

(8)

Preparation of Thiohydroxamate Esters.

Thiohydroxamate esters result when primary nitro compounds are sequentially treated with ***n-Butyllithium*** and phenyl trimethylsilyl sulfide (eq 9).[12] This method is milder and involves fewer transformations than more traditional methods (i.e. reaction of hydroximic acid chlorides with thiols).

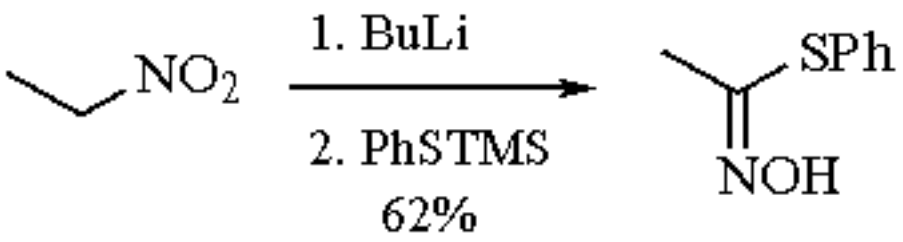

(9)

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Phenyl Vinyl Sulfide

$PhSCH{=}CH_2$

[1822-73-7] · C_8H_8S · Phenyl Vinyl Sulfide · (MW 136.23)

(deprotonation gives 1-phenylthiovinyllithium,[1] an acyl anion equivalent which reacts with electrophiles; utilized as a probe in [4 + 2],[2,3] [3 + 2],[4] and [2 + 5][5] cycloaddition reactions; serves as a Diels-Alder dienophile synthetic equivalent of ethylene, acetylene, and ketene)

Physical Data: bp 94-95 °C/25 mmHg; *d* 1.042 g cm^{-3}.

Form Supplied in: liquid; widely available.

Preparative Methods: recent preparative methods include: the reaction of ***Ethylene*** with ***Thiophenol*** and ***N-Chlorosuccinimide*** to give the β-chloroethyl sulfide followed by dehydrohalogenation with ***1,8-Diazabicyclo[5.4.0]undec-7-ene***;[6] reaction of acetaldehyde diphenyl dithioacetal with ***Copper(I) Trifluoromethanesulfonate***;[7] reaction of ***Phenylmagnesium Bromide*** with 2-chloroethyl thiocyanate followed by dehydrohalogenation with ***Potassium t-Butoxide***;[8] phenylthiolate addition to ***1,2-Dibromoethane*** followed by dehydrohalogenation with ***Potassium Hydroxide*** under phase transfer catalysis;[9] reaction of acetaldehyde diphenyl dithioacetal with ***Benzenesulfenyl Chloride*** followed by dehydrohalogenation with ***Diisopropylethylamine***;[10] and as a recoverable byproduct of the reaction of 1,3-oxathiolanes with benzyne.[11]

Handling, Storage, and Precautions: stench; it is imperative that phenyl vinyl sulfide be used in a well-ventilated fume hood.

1-Phenylthiovinyllithium.[1]

This reagent has been prepared by metalation of phenyl vinyl sulfide with ***Lithium Diisopropylamide*** in THF/HMPA[12] or as a slurry in hexanes[13] or with ***n-Butyllithium/N,N,N´,N´-Tetramethylethylenediamine***[14] or ***Lithium 2,2,6,6-Tetramethylpiperidide***/TMEDA,[15] providing specific lithiation in the α-position (eq 1).[1] Under these conditions, alkyllithium addition[16] is suppressed. 1-Phenylthiovinyllithium reacts with a variety of electrophiles (eq 2)[13,16,17] to give substituted phenyl vinyl sulfides, useful compounds in their own right. This vinyllithium species undergoes addition reactions with alkyl halides[15,18] to give substituted phenyl vinyl sulfides, which under hydrolytic conditions with aqueous Brønsted[12,14] or Lewis[12,14] acids provide the corresponding ketones. Hence, 1-phenylthiovinyllithium belongs to the acyl anion equivalent class of umpolung reagents.

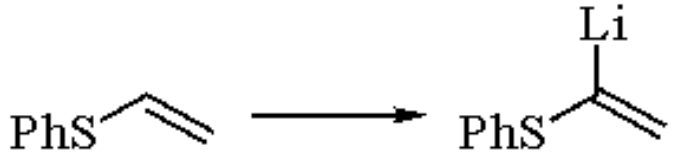

(1)

LDA, THF-HMPA, -60 °C
LDA, hexanes (slurry)
BuLi-TMEDA (1:1), THF, -90 °C
LTMP-TMEDA

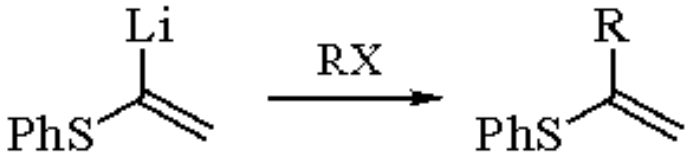

(2)

RX = TMSCl	R = TMS	97%
RX = MeSSMe	R = SMe	61%
RX = PhSSPh	R = SPh	59%
RX = PhSeBr	R = SePh	84%
RX = Bu_3SnCl	R = $SnBu_3$	87%

Aldehydes react with 1-phenylthiovinyllithium to give 2-phenylthioallylic alcohols (eq 3),[12,14] which have been converted to vinyl ketones[14] and 1,4-diketones.[12] Addition of 1-phenylthiovinyllithium to ketones has provided valuable substrates for the study of [3,3]-sigmatropic rearrangements of divinylcyclobutanols[19] and tandem cationic aza-Cope rearrangement-Mannich cyclization reactions.[20]

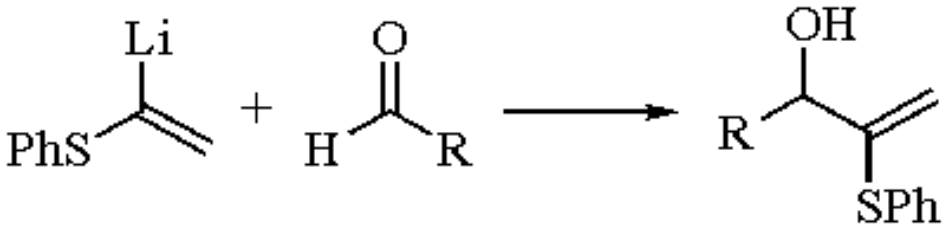

(3)

R = C_5H_{11}	76%
R = C_6H_{13}	81%

Utility in [4 + 2], [3 + 2], and [2 + 2] Cycloadditions.

The electron richness and half-wave potential of the double bond in phenyl vinyl sulfide have been used to advantage in reverse-electron demand and cationic radical[2] Diels-Alder reactions. Phenyl vinyl sulfide reacts with tropone regiospecifically to provide bicyclo[3.2.2]nonadienone systems (eq 4),[21] reacts with pyrone sulfoxide[22] with high

diastereoselectivity under high pressure (eq 5), has trapped the transient [1,5]-sigmatropic shift isomer of isodicyclopentanediene,[3] and undergoes photosensitized electron transfer (PET) initiated cycloaddition[23] with dienes to give Diels-Alder products (eq 6). The resulting sulfides of these adducts have been cleaved to the corresponding alkanes,[3] oxidized to the sulfoxides followed by thermolysis to give the corresponding alkenes,[22] and oxidized to the sulfones followed by α-hydroxylation to give the corresponding ketones.[23] Thus phenyl vinyl sulfide can represent Diels-Alder dienophile equivalents of ethylene, acetylene, and ketene.

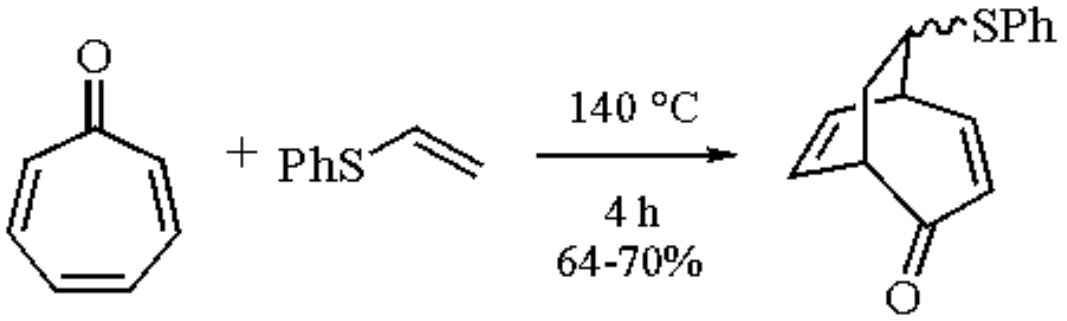

(4)

1.5:1 epimeric ratio

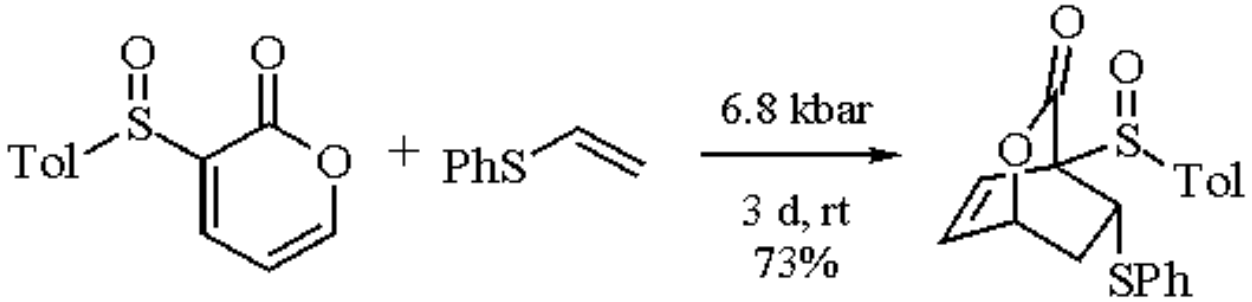

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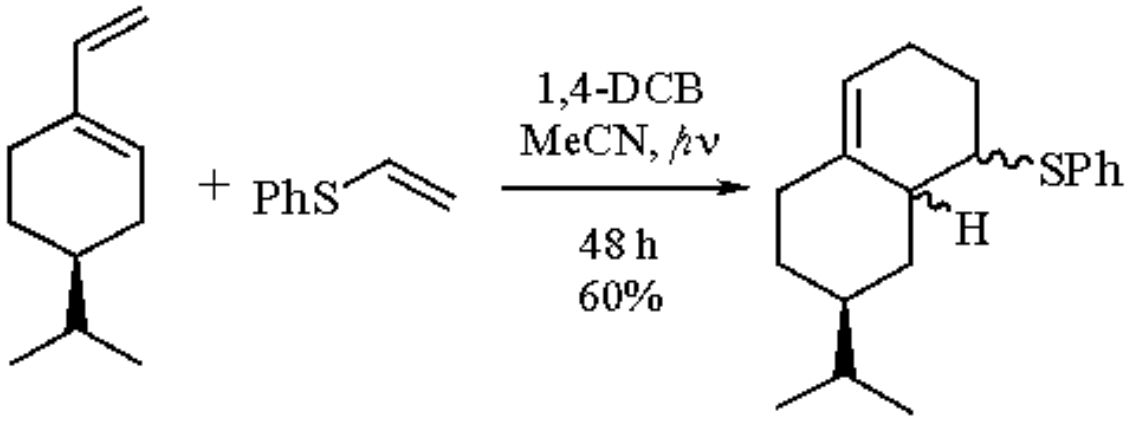

(6)

1,4-DCB = 1,4-dicyanobenzene

Phenyl vinyl sulfide participates in 1,3-dipolar cycloadditions with 2-azaallyl anions, generated from *N*-(tributylstannyl)methanimines and *n*-BuLi, to provide substituted pyrrolidines (eq 7)[4] and highly stabilized isoquinolium methylides,[24] and also undergoes thiyl-radical catalyzed chain cyclizations to give methylenecyclopentanes.[25] ***Tetracyanoethylene*** undergoes spontaneous [2 + 2] cycloaddition with phenyl vinyl sulfide[5,26] and oxetanes are derived from ***Boron Trifluoride Etherate*** catalyzed reaction of sugar-derived aldehydes with electron-rich alkenes (eq 8).[27]

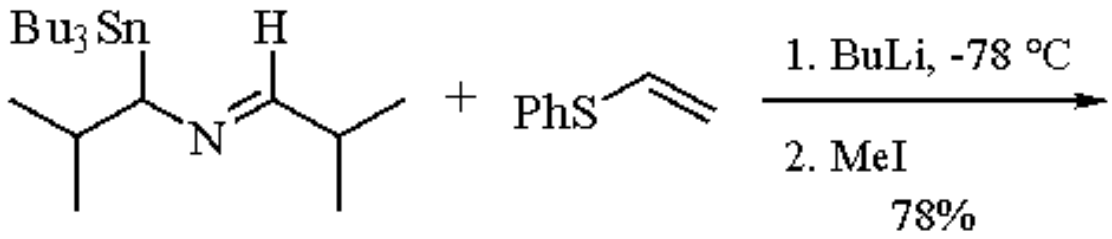

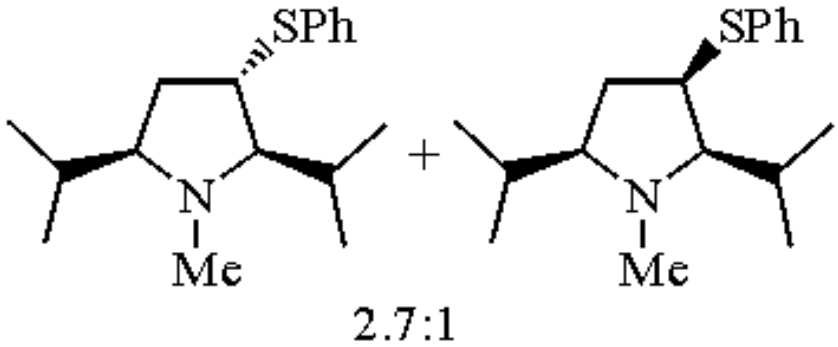

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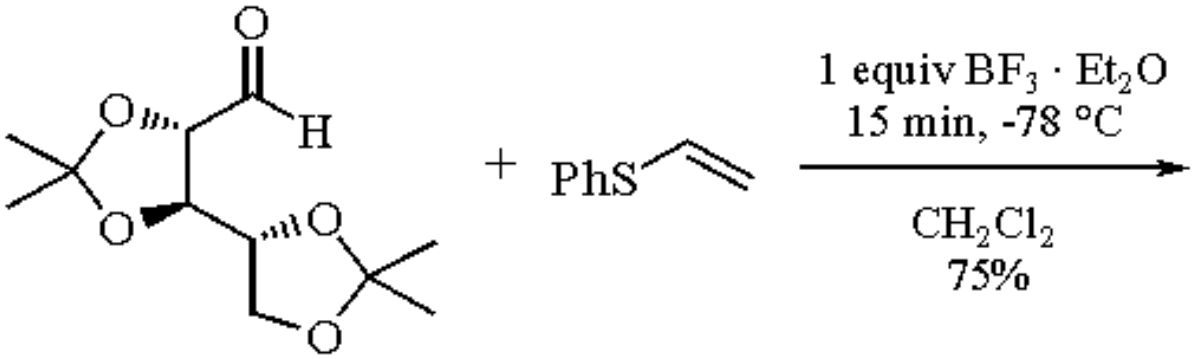

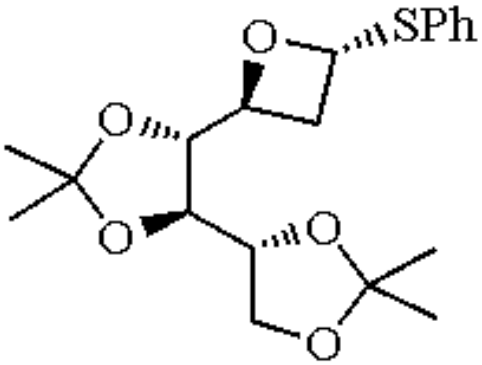

(8)

Other Applications.

Phenyl vinyl sulfides exhibit higher selectivity and better yields than enol acetates and enol ethers in palladium catalyzed Heck-like reactions with aryl halides.[28] Phenyl vinyl sulfide has been transformed into ***Phenylthioacetylene*** via a bromination-bis(dehydrobromination) sequence,[29] converted to the *S*-vinyl sulfilimine, and utilized as an acetaldehyde enolonium ion equivalent ($^{+}CH_2CHO$),[30] and utilized as a sensitive substrate for examination of novel hydrosilylation,[31] diimide reduction,[32] and asymmetric oxidation to the corresponding sulfoxide.[33,34]

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S-Phenyl-*S*-vinyl-*N*-(*p*-toluenesulfonyl)sulfilimine[1]

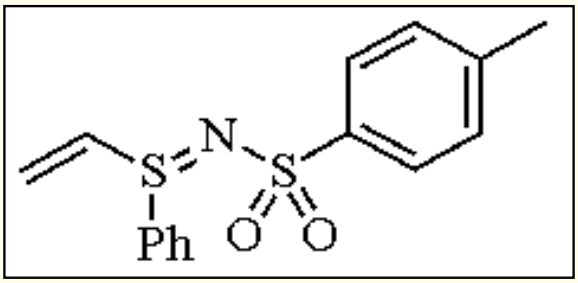

[56692-06-9] · $C_{15}H_{15}NO_2S_2$ · *S*-Phenyl-*S*-vinyl-*N*-(*p*-toluenesulfonyl)sulfilimine · (MW 305.45)

(vinylation;[1,2] cyclopropanation;[3] hetero-ring construction[4])

Physical Data: mp 111-113 °C.

Solubility: insol H_2O; sol EtOH, MeOH, acetone, chloroform, other common polar organic solvents.

Preparative Method: the title reagent (**1**) is prepared via sulfimination of 2-chloroethyl phenyl sulfide[5] followed by dehydrochlorination.[6] The sulfimination is carried out as follows. A solution of the sulfide (10 mmol) in CH_2Cl_2 (70 mL) and a solution of ***Chloramine-T*** trihydrate (11 mmol) and tetrabutylammonium chloride (0.2 mmol) in water (70 mL) are vigorously stirred at 40 °C for 4 h. The resulting *S*-(2-chloroethyl)-*S*-phenyl-*N*-tosylsulfilimine (**2**) is recrystallized from CH_2Cl_2-Et_2O. The yield is almost quantitative (mp 101-103 °C).[5] The dehydrochlorination is carried out as follows. A solution of (**2**) (10 mmol) in benzene (100 mL) and a solution of NaOH (10.5 mmol) and tetrabutylammonium bromide (0.05 mmol) in water (50 mL) are vigorously stirred at rt overnight. The crude product is recrystallized from CH_2Cl_2-Et_2O. The yield of (**1**) is almost quantitative (mp 111-113 °C).[6]

Handling, Storage, and Precautions: stable and storable at rt in a sealed bottle. Use in a fume hood.

Vinylation.[1,2]

Sulfilimine (**1**) undergoes Michael-type addition with various protic nucleophiles (RZH) such as alcohols, thiols, amines, and amides. The reactions of (**1**) with an excess of RZH in the presence of ***Sodium Hydride*** in THF are carried out at rt for several hours to 1 day to give the corresponding adducts in high yields. The amount of NaH used depends on the basicity of attacking nucleophile. The basicity of the intermediate carbanion formed is estimated to be between those of alcohols and amines. When alcohols and thiols are used as RZH, the addition reactions proceed in the presence of catalytic amounts of NaH (eqs 1-3), while the reactions of (**1**) with amines require equimolar amounts of NaH. The

adducts obtained decompose at higher temperature (ca. 20-30 °C) than their melting points to give vinyl compounds in almost pure form (eq 4).[1]

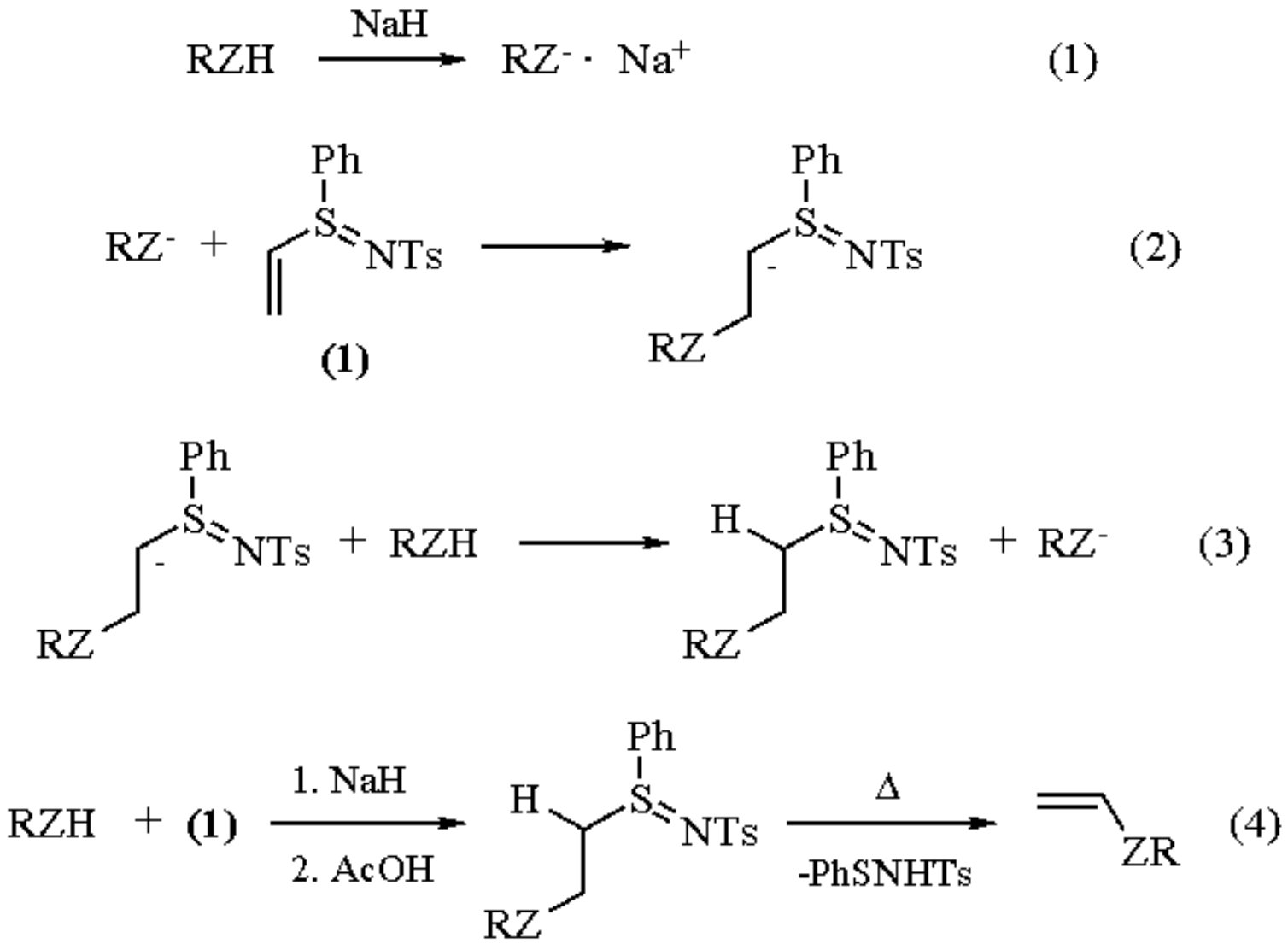

Similarly, allyl vinyl ethers[2a] and alkynyl vinyl ethers[2b] can be obtained from the addition reactions between (**1**) and allyl or alkynyl alcohols followed by the thermal decomposition of the adducts (eqs 5 and 6). The times required for completion of the addition reaction are about 24 h for primary alcohols in THF and for secondary and tertiary ones used as cosolvents. Under these conditions the corresponding vinyl ethers can be obtained from allyl, methallyl, crotyl, and 1-methylallyl alcohols in high overall yields (>80%). Alkynyl vinyl ethers are also formed efficiently.

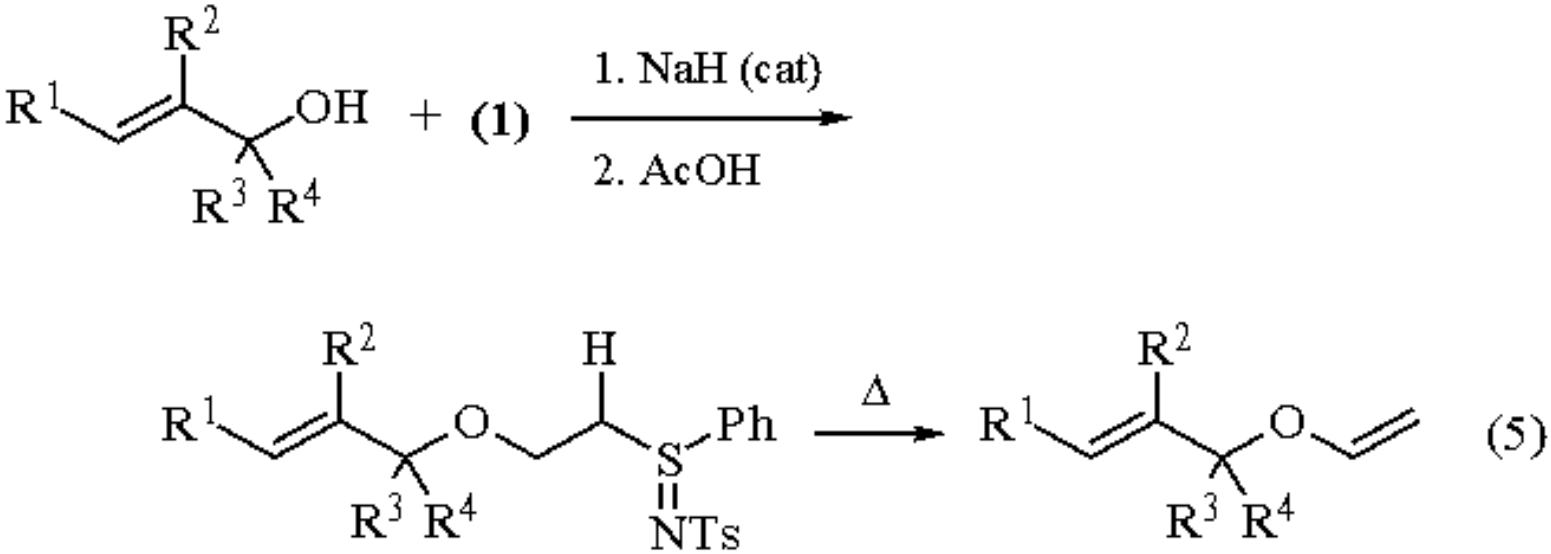

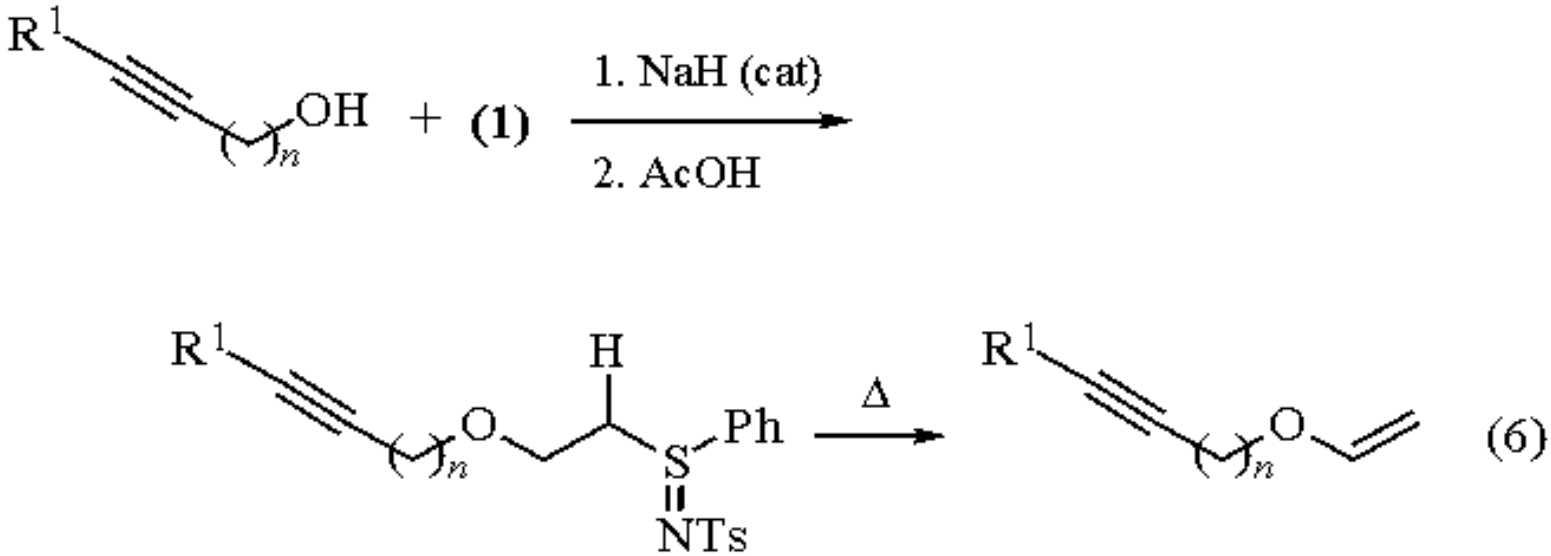

Cyclopropanation.[3]

When the sulfilimine (**1**) is allowed to react with diprotic nucleophiles (RZH_2) in the presence of equimolar amounts of NaH, cyclic compounds incorporating the vinyl carbons are produced. When the compounds RZH_2 are active methylene compounds, cyclopropane derivatives are obtained (eq 7). The addition is carried out at rt for 24 h and then the cyclization at 35-40 °C for 4 h. In this way, the corresponding cyclopropanes are formed from dibenzoylmethane, anthrone, and fluorene in 60-77% yields.

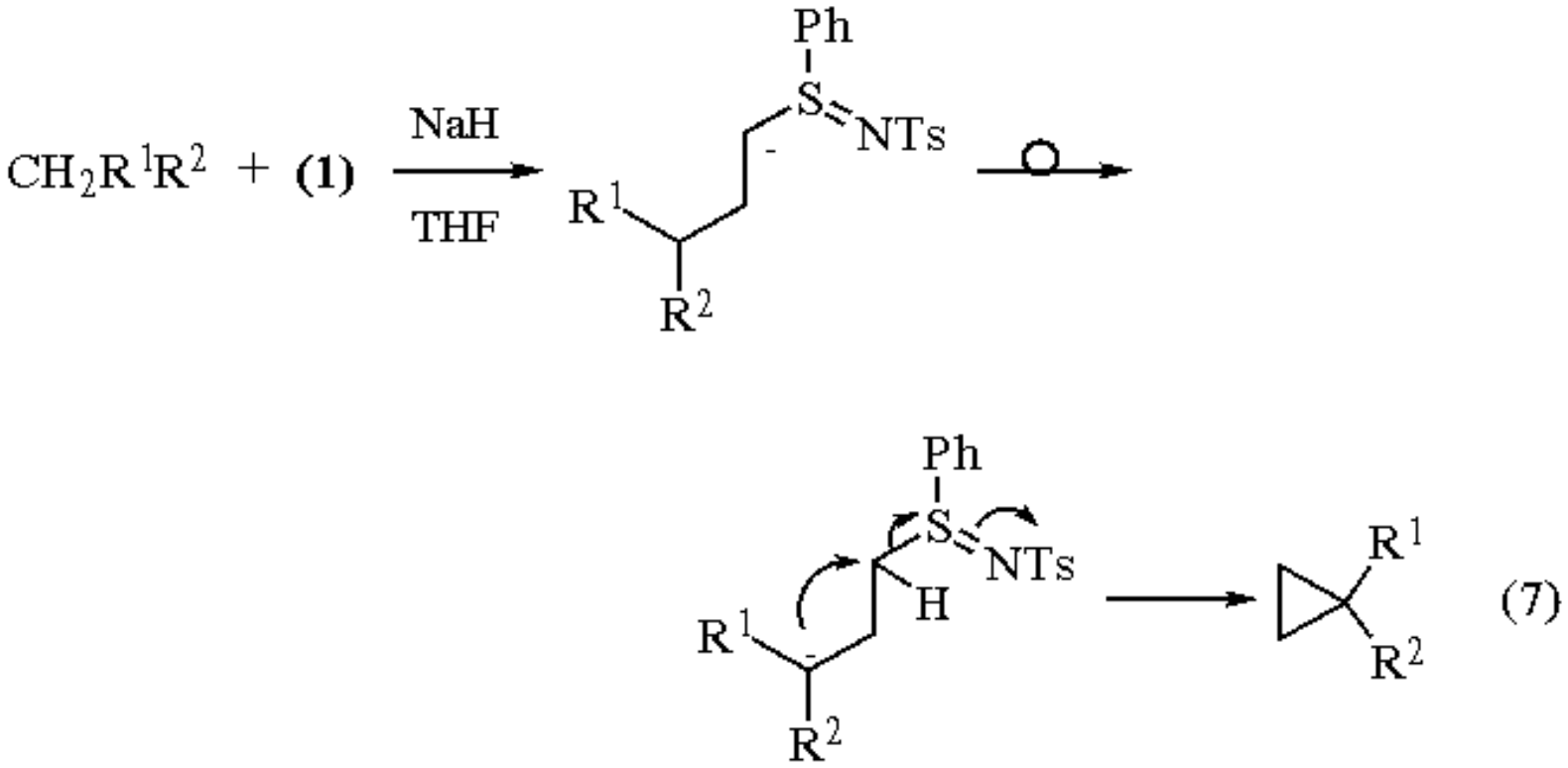

Hetero-ring Construction.[4]

Amides, as diprotic nucleophiles RZH_2, react with (**1**) in THF to give 2-substituted oxazolines (eq 8). The addition is carried out at rt for 24 h and then the cyclization at 40 °C for 5 h. The yields of 2-aryloxazolines (ca. 70%) are superior to those of the alkyl analogs.

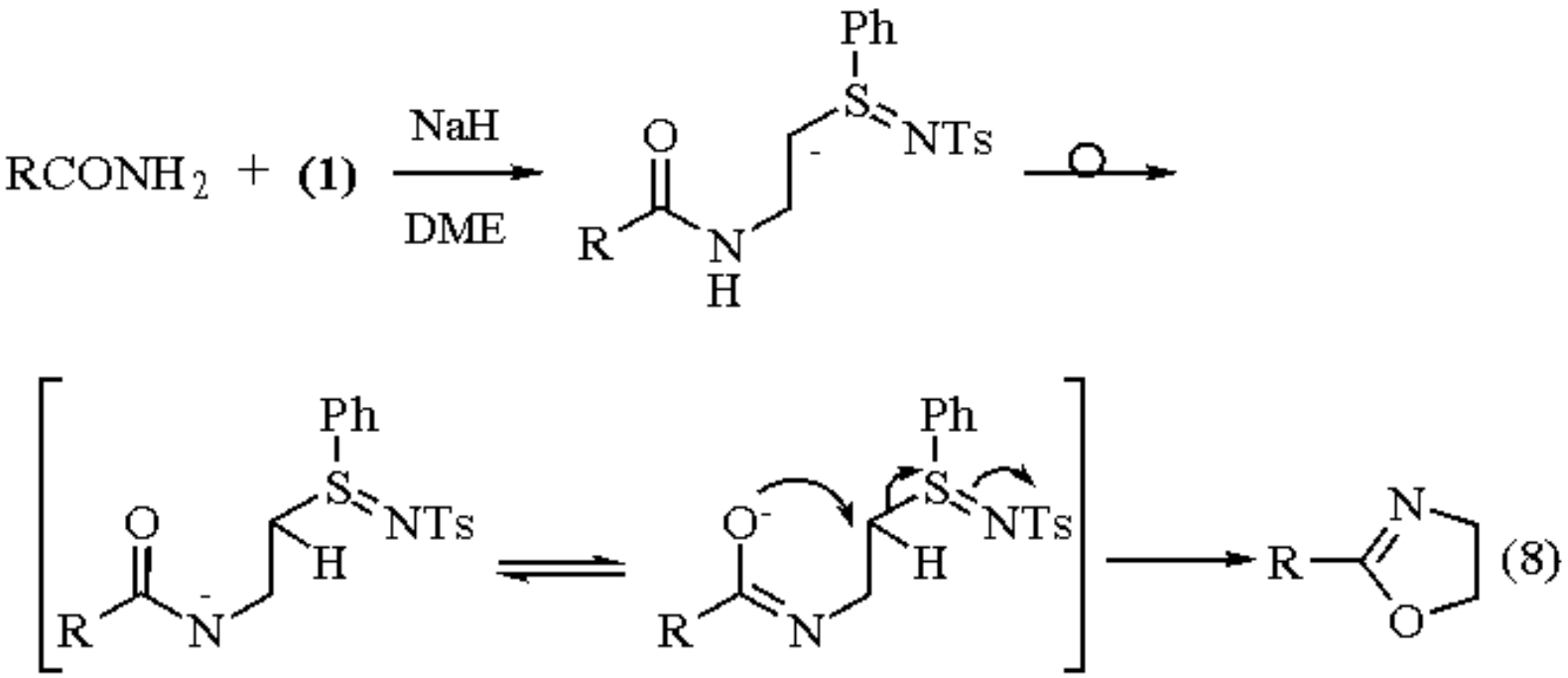

Miscellaneous.

The reaction of (**1**) with ***Methyllithium*** in THF gives mainly a polymer,[7] whereas the reactions with Grignard reagents (R = Ph, *p*-Tol, Et, *i*-Pr) give 2-substituted phenyl vinyl sulfides in 45-76% yields via addition and elimination of the tosylamino group (eq 9).[7]

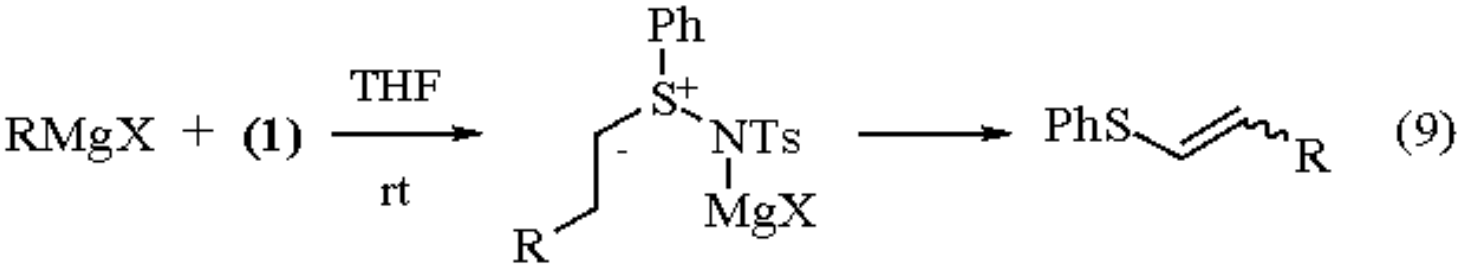

Related Reagents.

S,S-Dimethyl-N-(p-toluenesulfonyl)sulfilimine; ***S,S-Diphenylsulfilimine***; ***Ethyl Vinyl Ether***; ***Phenyl Vinyl Sulfide***; ***p-Tolyl Vinyl Sulfoxide***; ***Vinyl Acetate***.

---

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Phenylzinc Chloride

PhZnCl

[28557-00-8] · C_6H_5ClZn · Phenylzinc Chloride · (MW 177.95)

(phenyl coupling reagent in the presence of palladium(0) or copper(I) complexes)

Solubility: sol ether, THF; reacts rapidly with H_2O and protic solvents.

Preparative Methods: usually prepared by transmetalation of ***Phenylmagnesium Bromide*** with ***Zinc Chloride***.[1] Related arylzinc halides can either be prepared by the direct insertion of zinc,[2] by a transmetalation from the corresponding aryllithium,[3] or electrochemically.[4] Diarylzincs have been generated under Barbier conditions.[5]

Handling, Storage, and Precautions: reacts with oxygen; should be handled and stored under an inert atmosphere in the absence of moisture.

Palladium- and Nickel-Catalyzed Reactions.

Although arylzinc halides display a low reactivity toward many organic electrophiles, the use of late transition metal (Ni, Pd) complexes allows cross-coupling reactions to be performed with a variety of electrophiles. In pioneering work by Negishi,[1,6] the coupling of phenylzinc chloride with various aromatic, allenic, and alkenyl[7] iodides or bromides in the presence of 1-5 mol % of a Pd^0 catalyst provides a unique preparation of polyfunctionalized unsaturated molecules (eqs 1 and 2).[8,9] Cross coupling with alkenyl triflates is also possible (eq 3).[10]

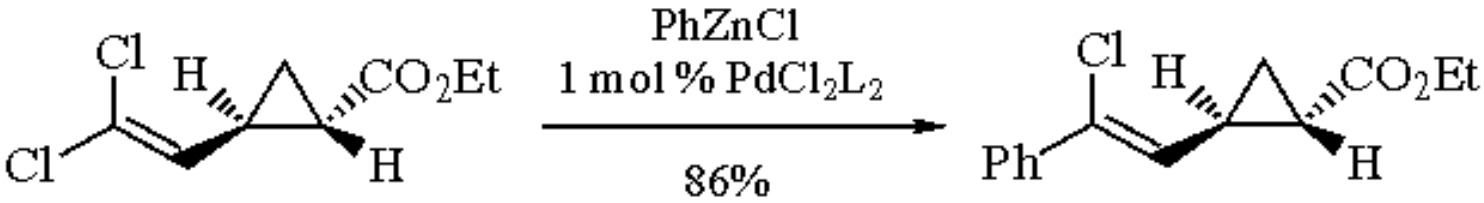

(1)

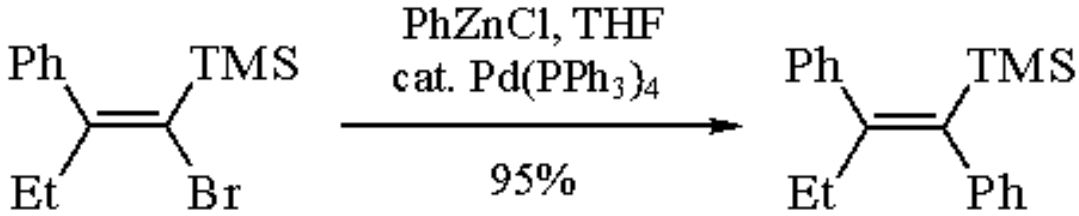

(2)

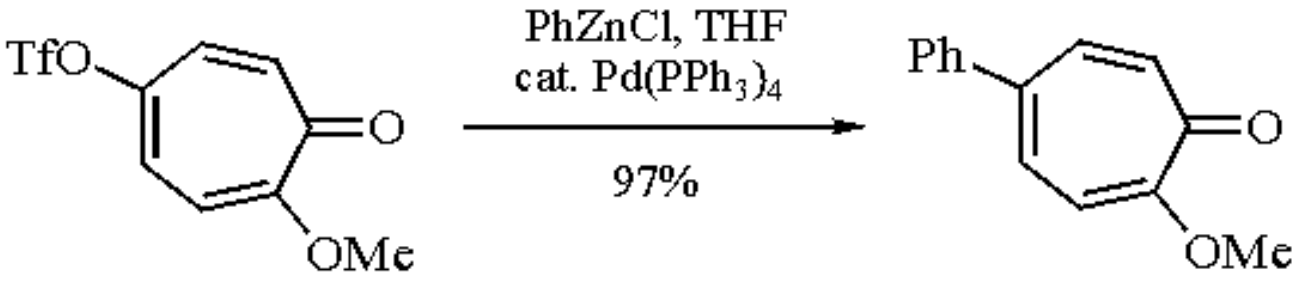

(3)

The Pd-catalyzed reaction of phenylzinc chloride with acid chlorides gives an efficient preparation of various types of ketones (eq 4).[11] The Ni-catalyzed coupling of α-bromo nitriles and esters furnishes the arylated carbonyl derivatives in satisfactory yields.[12] The Pd-catalyzed substitution with allylic acetates proceeds at the more hindered position of the allylic system, whereas the substitution reaction with stabilized nucleophiles occurs at the less hindered position (eq 5).[13] Also, contrary to the reaction with stabilized nucleophiles, the substitution with phenylzinc chloride always proceeds with formal inversion (eq 6).[14] 1-Vinylcyclopropyl tosylate reacts with high regioselectivity with phenylzinc chloride.[15] An intramolecular carbopalladation of alkynes triggered by an oxidative addition of a phenylpalladium complex to aromatic iodides provides an interesting synthesis of various cyclic systems (eq 7).[16] Finally, diphenylzinc undergoes a 1,4-addition to unsaturated aldehydes and ketones in the presence of a nickel catalyst.[5]

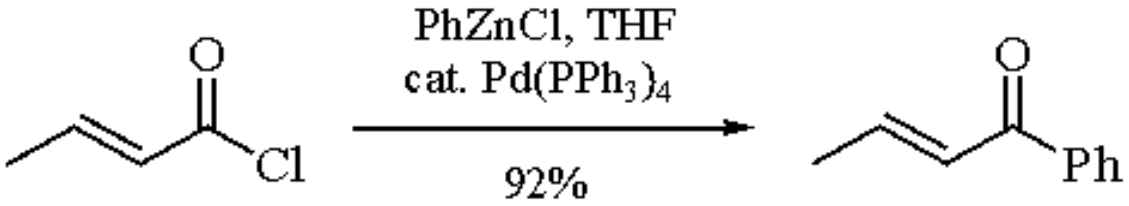

(4)

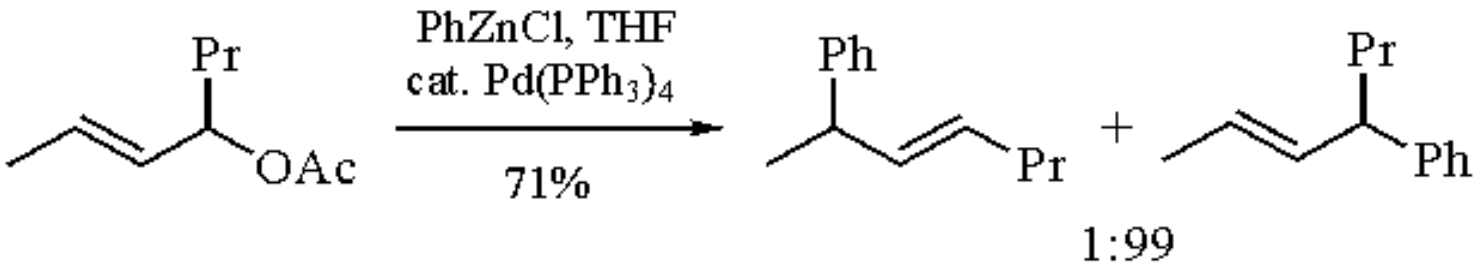

(5)

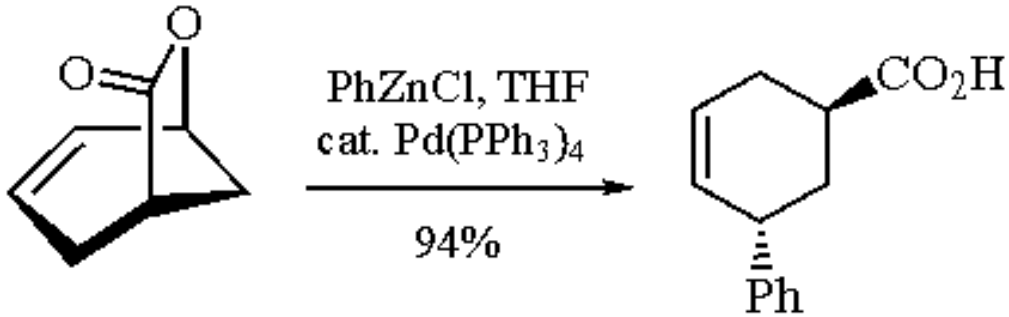

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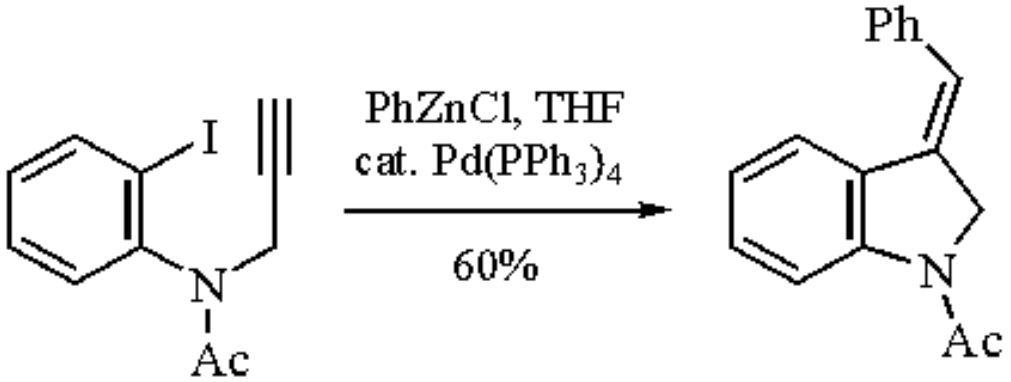

(7)

Copper-Mediated Reactions.

Transmetalation of phenylzinc halides to the corresponding copper reagents allows the reaction with allylic halides, enones, and acid chlorides in satisfactory yields (eq 8).[2]

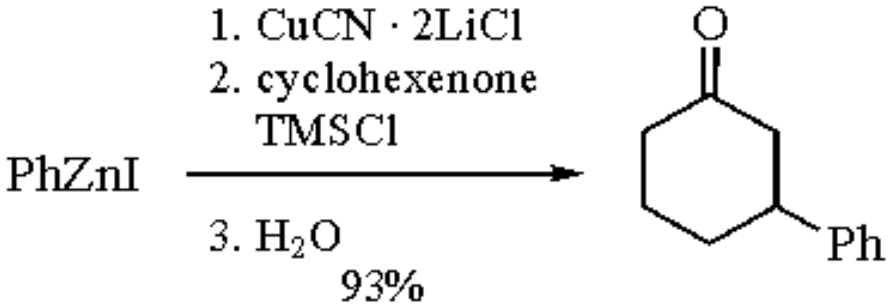

(8)

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Phosgene[1]

$COCl_2$

[75-44-5] · CCl_2O · Phosgene · (MW 98.91)

(chlorinating agent;[2] carbonylating agent; dehydrating agent;[1] with DMF forms a chloromethyleniminium salt, used in formylation reactions[3])

Alternate Name: carbonyl chloride.

Physical Data: mp -118 °C; bp 8.3 °C; *d* 1.381 g cm^{-3}.

Solubility: slightly sol H_2O (dec); sol toluene, chloroform.

Form Supplied in: liquefied gas in cylinders; solution in toluene.

Purification: chlorine is an impurity which can be detected by bubbling through mercury (gives discoloration) and removed by bubbling through two wash bottles containing cottonseed oil.

Handling, Storage, and Precautions: highly toxic gas; avoid contact or inhalation; there may be a delay of several hours before symptoms of exposure develop (pulmonary edema); keep container tightly closed and well-ventilated; excess phosgene should be vented into a water-fed scrubbing tower. Use in a fume hood.

Reactions with Carboxylic Acids, Alcohols, and Amines.

Phosgene reacts with carboxylic acids to give anhydrides, with liberation of carbon dioxide.[4] This has been used to activate acids to attack from nucleophiles, e.g. in esterification,[5] lactonization,[6] and thiolation.[7] For example, acids can be protected as 3-butenyl esters using phosgene and ***Pyridine***,[5] followed by addition of 3-buten-1-ol (eq 1).

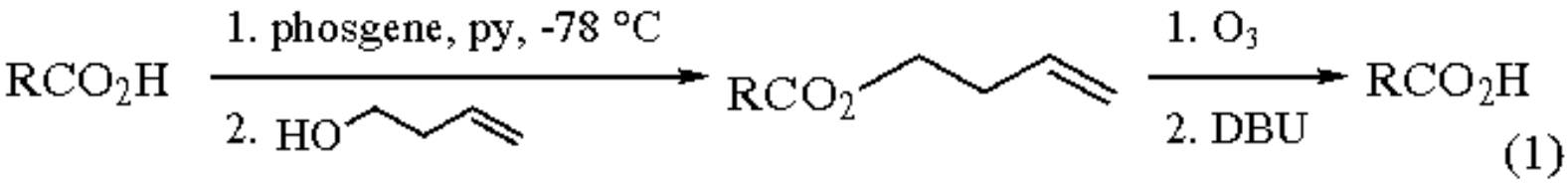

(1)

The ester is removed under mild conditions by ozonolysis and β-elimination of the resulting aldehyde. In contrast, reaction with acids in the presence of a variety of catalysts (including ***Imidazole***, ***1,8-Diazabicyclo[5.4.0]undec-7-ene***,

and ***1,3-Dicyclohexylcarbodiimide***) cleanly affords the corresponding acid chloride.[2] ***N,N-Dimethylformamide*** has also been used as a catalyst (eq 2).[8]

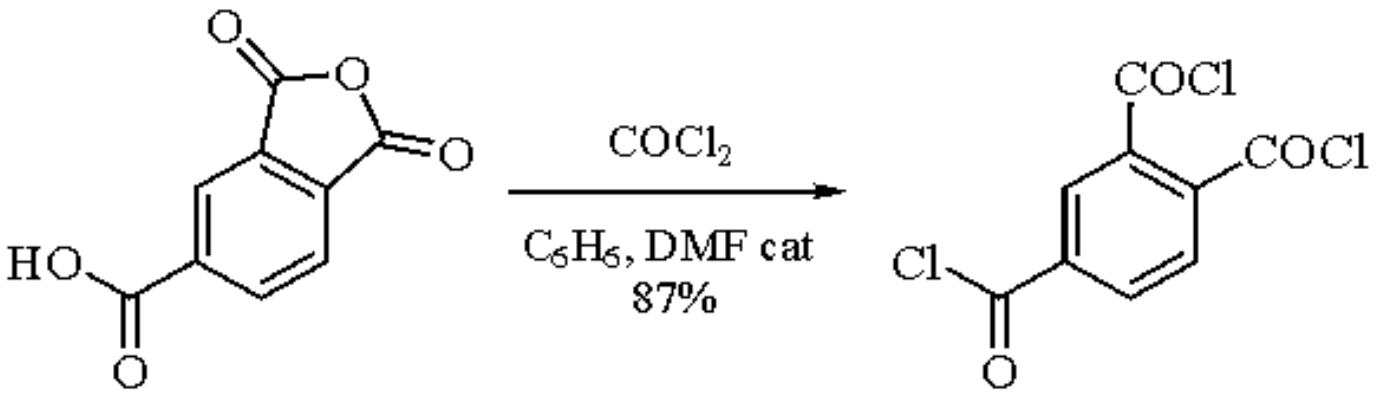

(2)

Phosgene reacts with alcohols to give chloroformates,[9,1b] and with secondary amines to give chloroformamides[10] (it reacts preferentially with the latter).[11] The formation of a chloroformate is the first step in the Barton oxidation of primary alcohols to aldehydes,[12] which is followed by complex formation with ***Dimethyl Sulfoxide*** and elimination by base (eq 3),[12b] a mechanism closely related to that of the Swern and Moffatt oxidations.[13]

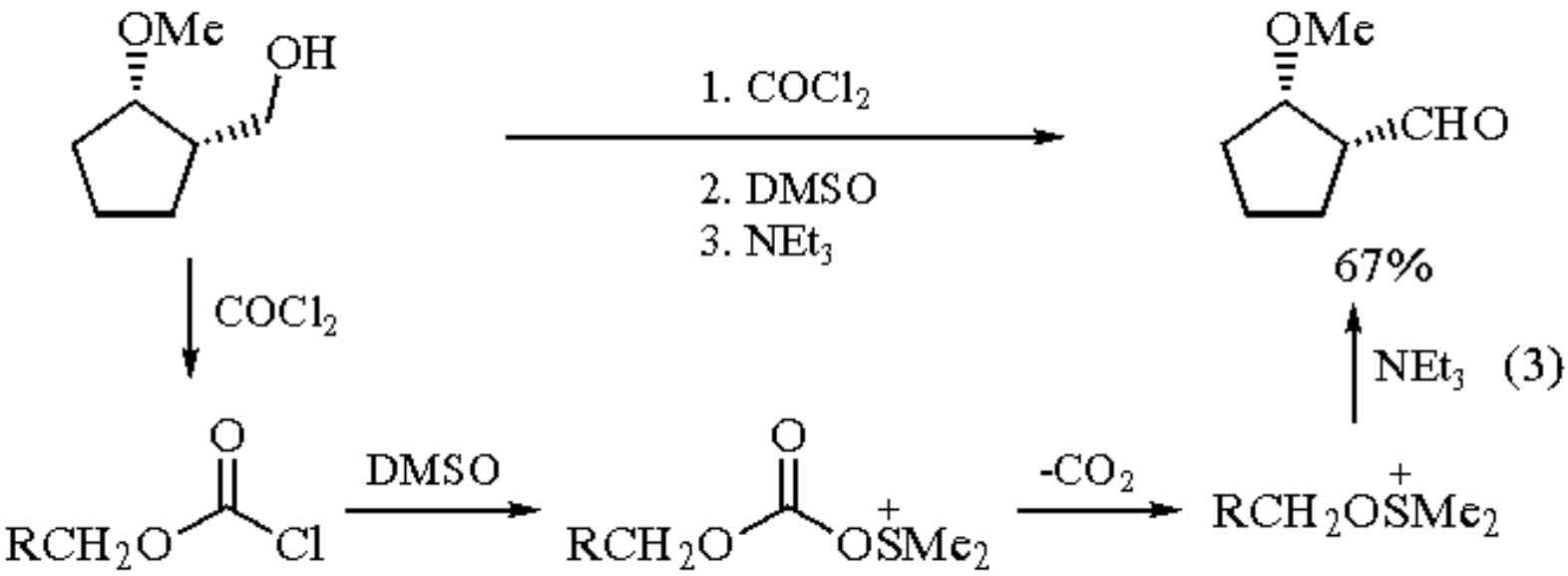

(3)

There are many examples of further displacement of the chloroformate in an intramolecular or intermolecular sense by suitably disposed second nucleophiles (e.g. hydroxy, amino, thio, or acid groups), resulting in carbonates (eq 4),[14] ureas (eq 5),[15] carbamates,[11,16] dithiocarbonates (eq 6),[17] etc.

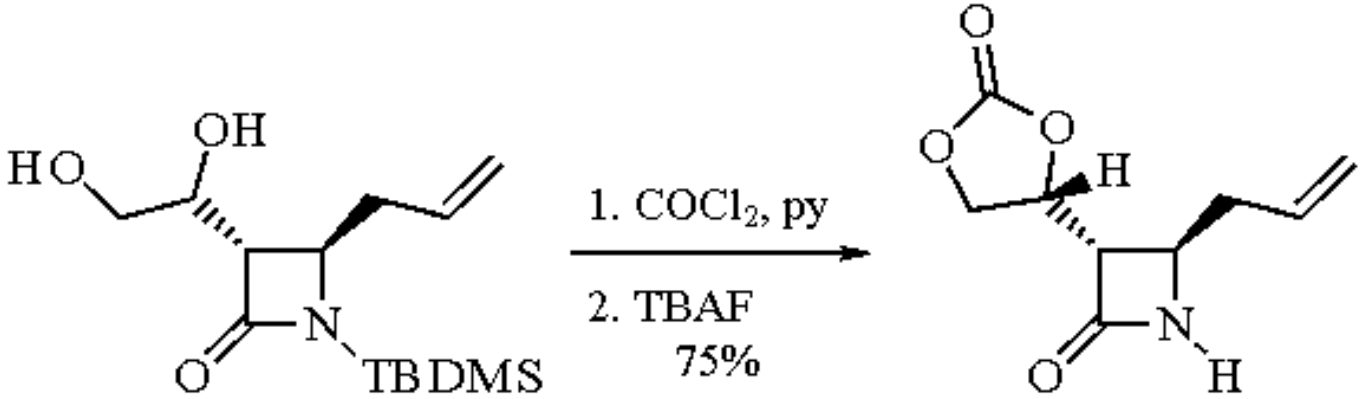

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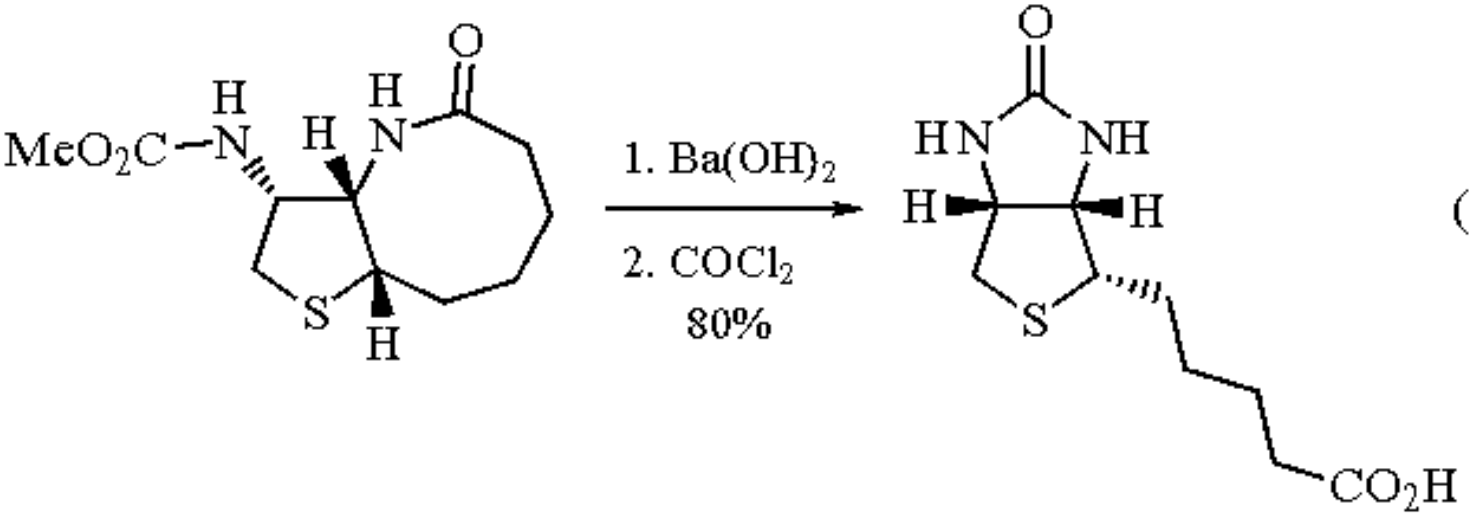

(5)

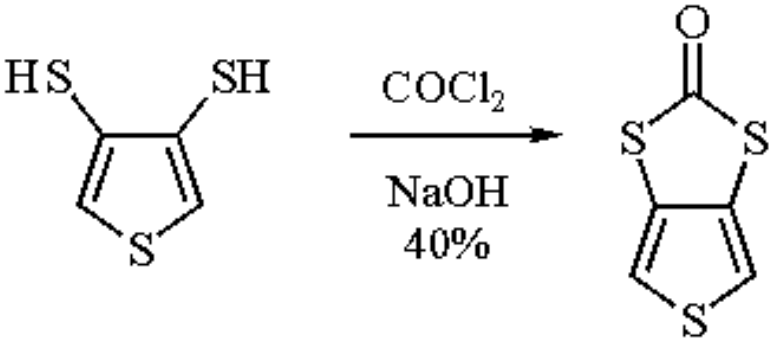

(6)

The reaction of phosgene with primary amines initially forms chloroformamides which on heating above 50 °C eliminate HCl to give isocyanates. This useful reaction constitutes a general method for isocyanate synthesis (eq 7).[18]

$$RNH_2 + COCl_2 \longrightarrow RNHCOCl \xrightarrow{-HCl} RN{=}C{=}O \qquad (7)$$

With tertiary amines, phosgene-amine complexes can be formed.[1a] Warming results in decomposition to an *N*,*N*-dialkylchloroformamide by elimination of alkyl chloride.[19] This has been utilized for the mild and high yielding deprotection of *N*-methyl amines (eq 8).[20] α-Chloroethyl chloroformate, prepared from phosgene and ***Acetaldehyde***, has also been used for this purpose.[21]

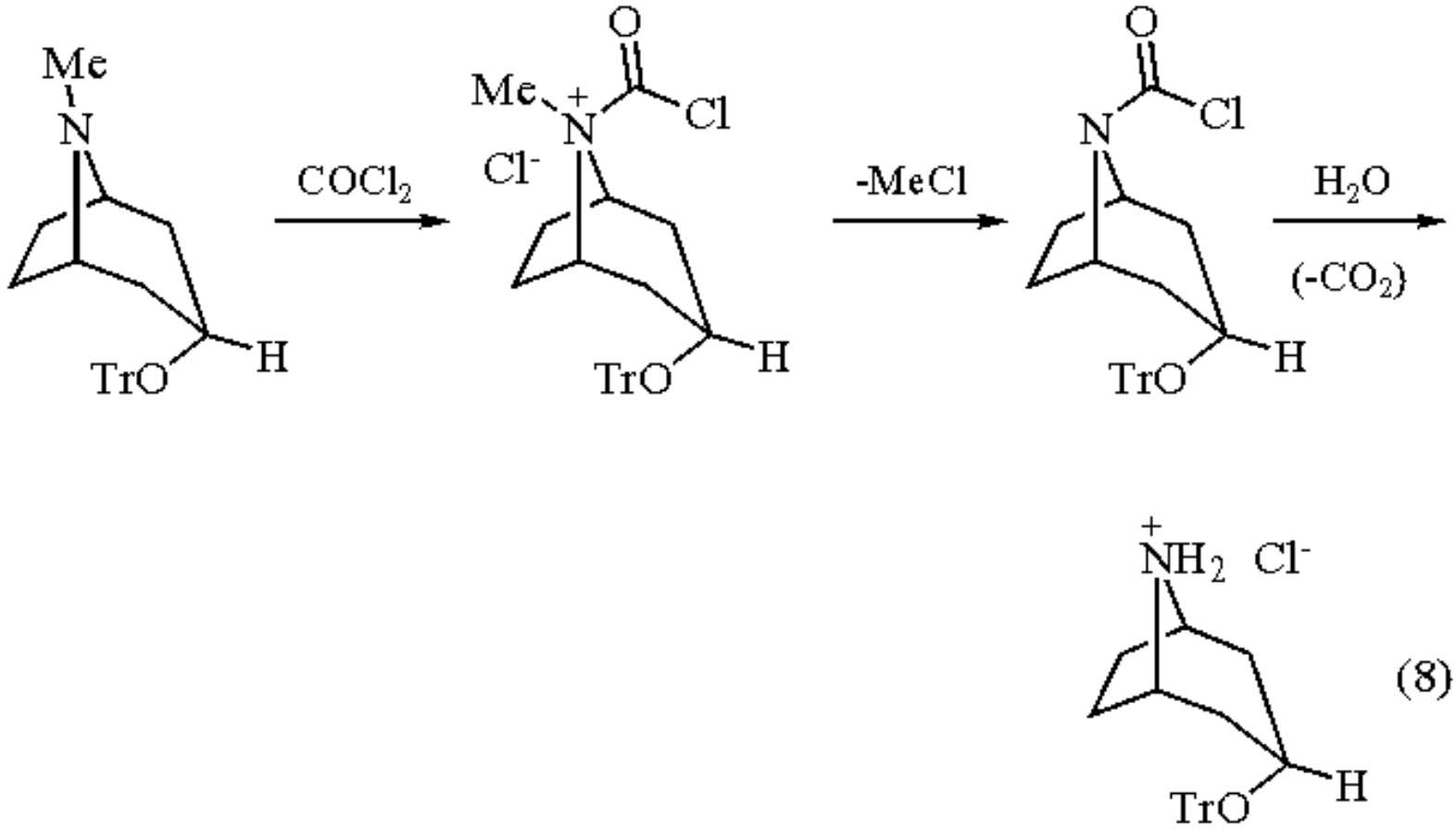

(8)

Reactions with Amides and Thioamides.

The action of phosgene on amides (and thioamides) initially gives dehydration to a chloromethyleneiminium chloride (eq 9). Primary amides react further, losing HCl to form nitriles in the presence of a base such as pyridine[22] (this can also be accomplished by the Vilsmeier-Haack reagent generated using phosgene - see below). Secondary formamides are converted to isocyanides in the presence of ***Triethylamine*** or pyridine (eq 10).[23] *N*-Formyl enamines also form isocyanides (eq 11);[24] ***1,4-Diazabicyclo[2.2.2]octane*** is claimed to be a more efficient base due to the avoidance of azeotrope formation with the low boiling vinyl isocyanide products. Other secondary amides lose HCl to give imidoyl chlorides, which can undergo further reaction, e.g. to form pyrroles (eq 12)[25] and oxazolones (eq 13).[26]

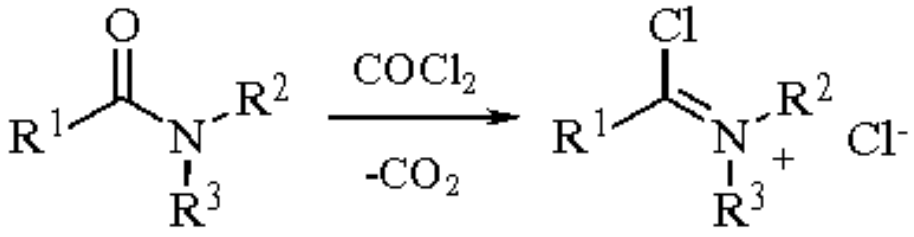

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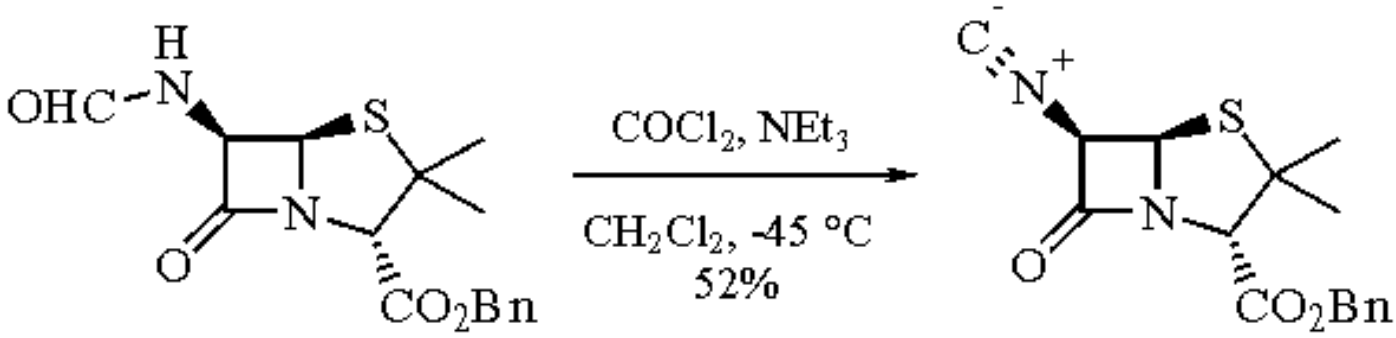
OHC
H
N
S
N
O
CO2Bn
COCl2, NEt3
CH2Cl2, -45 °C
52%
C
N
+
S
N
O
CO2Bn

(10)

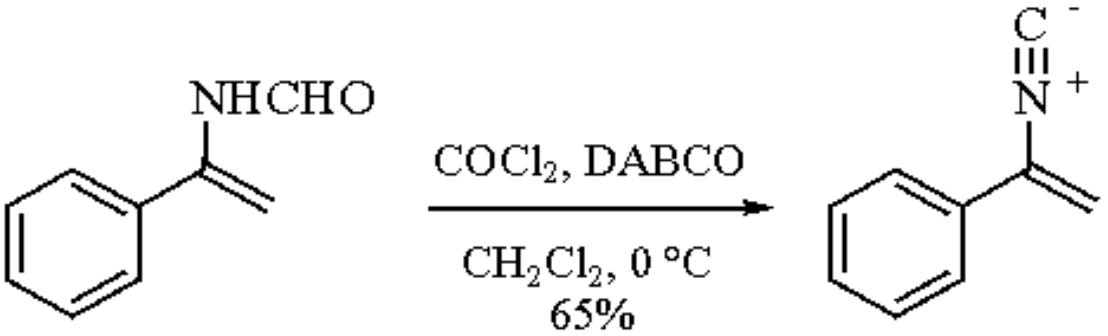
NHCHO
COCl2, DABCO
CH2Cl2, 0 °C
65%
C
N
+

(11)

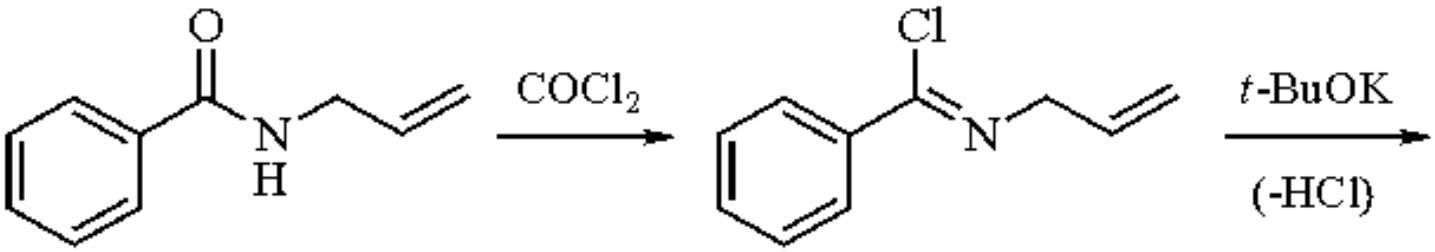
O
N
H
COCl2
Cl
N
t-BuOK
(-HCl)

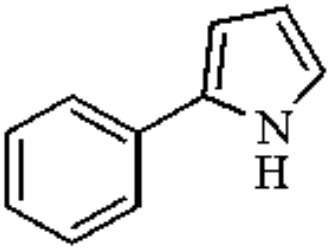
N
H

86%

(12)

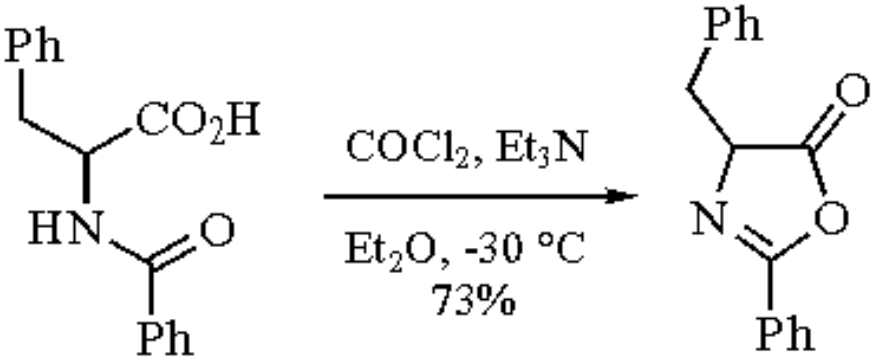
Ph
CO2H
HN
O
Ph
COCl2, Et3N
Et2O, -30 °C
73%
Ph
O
N
O
Ph

(13)

Secondary thioureas can be dehydrated to carbodiimides (eq 14).[27]

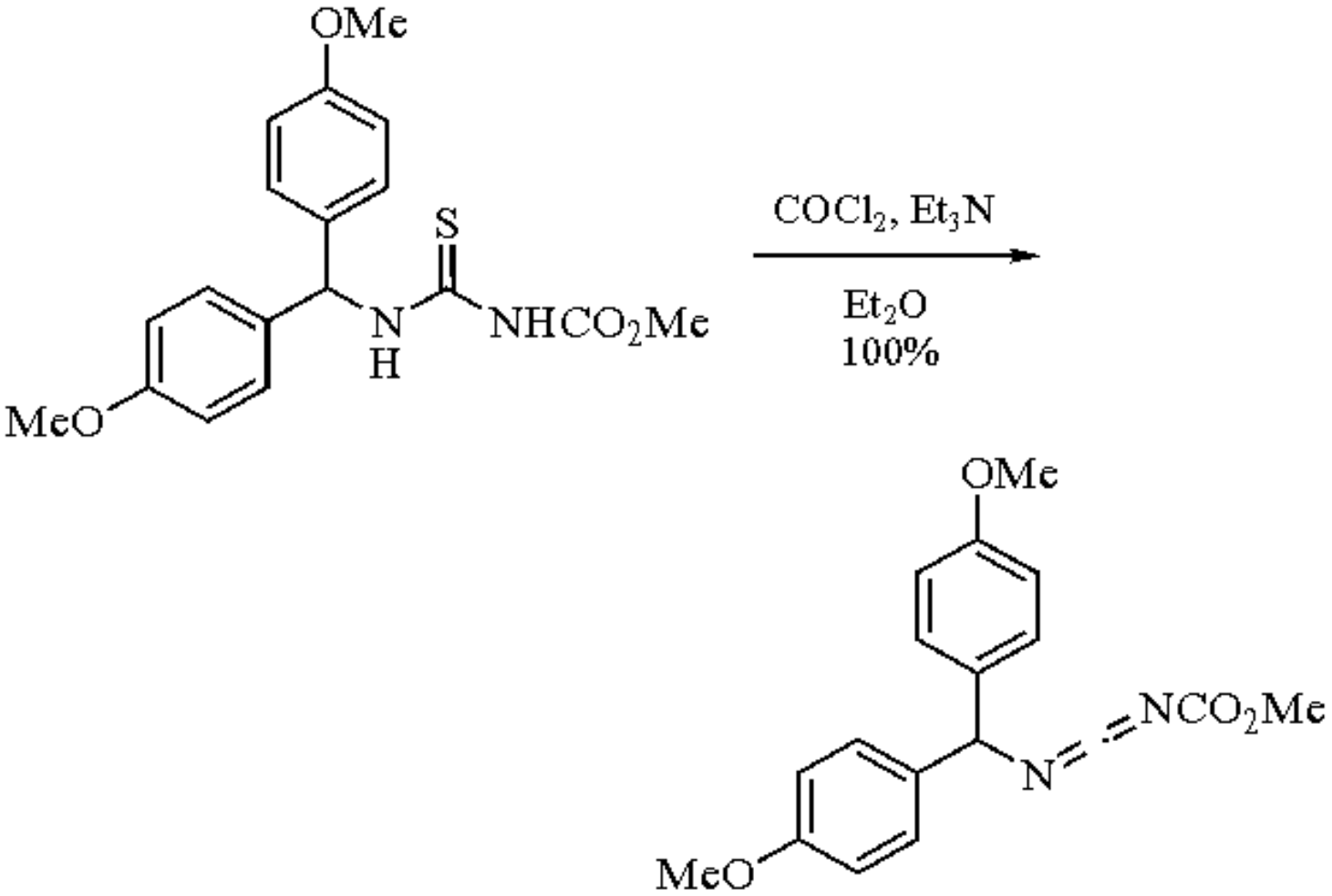

(14)

Tertiary amides give stable chloromethyleneiminium chlorides. A particularly important example is the complex formed between phosgene and DMF (known as the Vilsmeier-Haack reagent), which is a versatile formylating agent.[3] An identical or equivalent species can be generated with ***Oxalyl Chloride***, ***Thionyl Chloride***, or ***Phosphorus Oxychloride***, and these are perhaps preferred in view of phosgene's toxicity. However, the Vilsmeier reagent generated from phosgene is claimed to be a more efficient reagent for the dehydration of primary amides to nitriles.[28]

Tertiary amides (and thioamides)[29] with an α-proton react instead to give chloro enamines.[30] These can undergo nucleophilic substitution (eq 15).[30,31] Chloro enamines are also intermediates in synthetically useful dehydrogenation reactions, using ***Pyridine N-Oxide*** or DMSO as oxidant (eq 16).[32] Tertiary ureas and thioureas form related adducts which have been utilized in the synthesis of hindered guanidine bases by further reaction with amines (eq 17).[33]

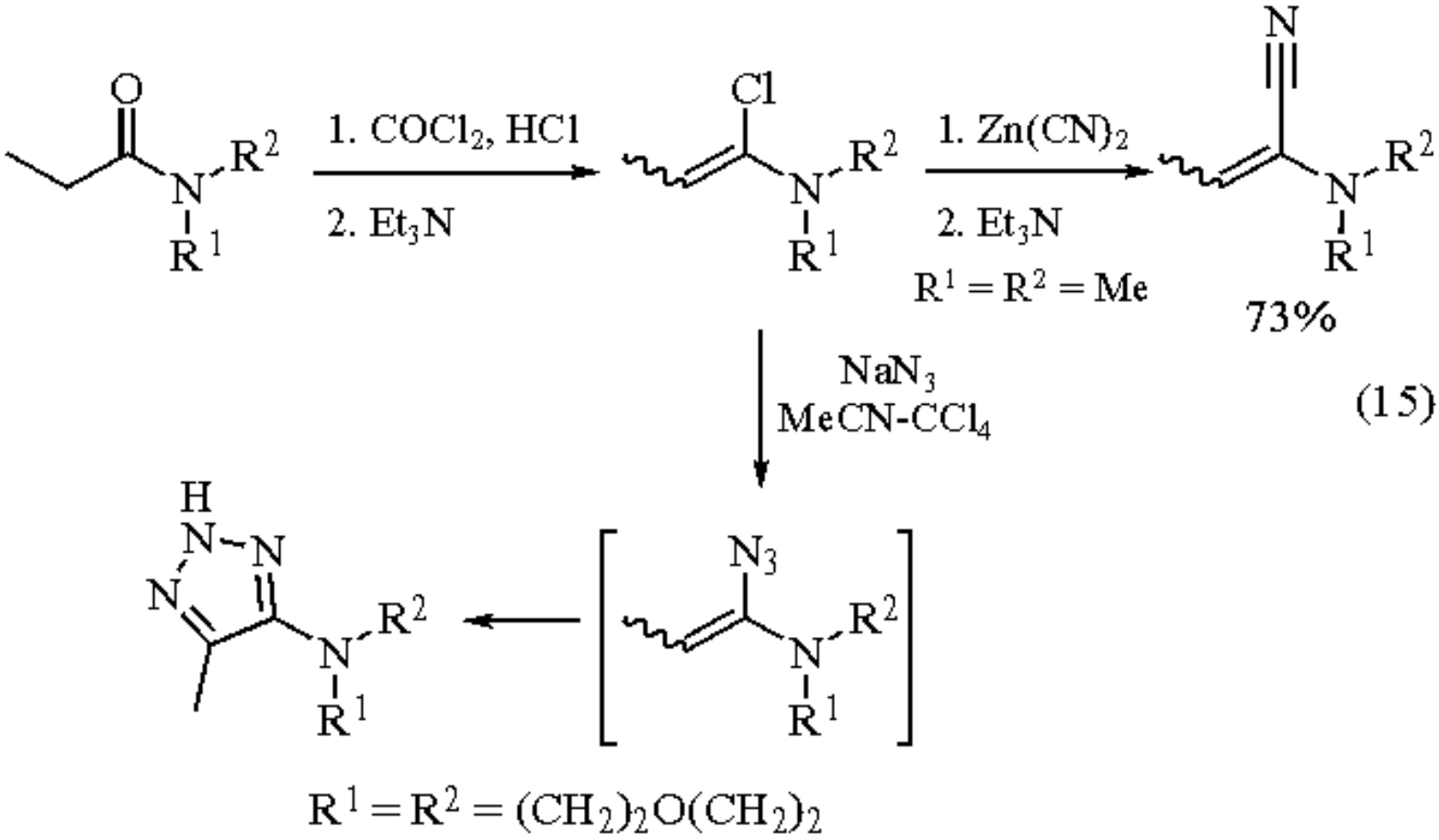

(15)

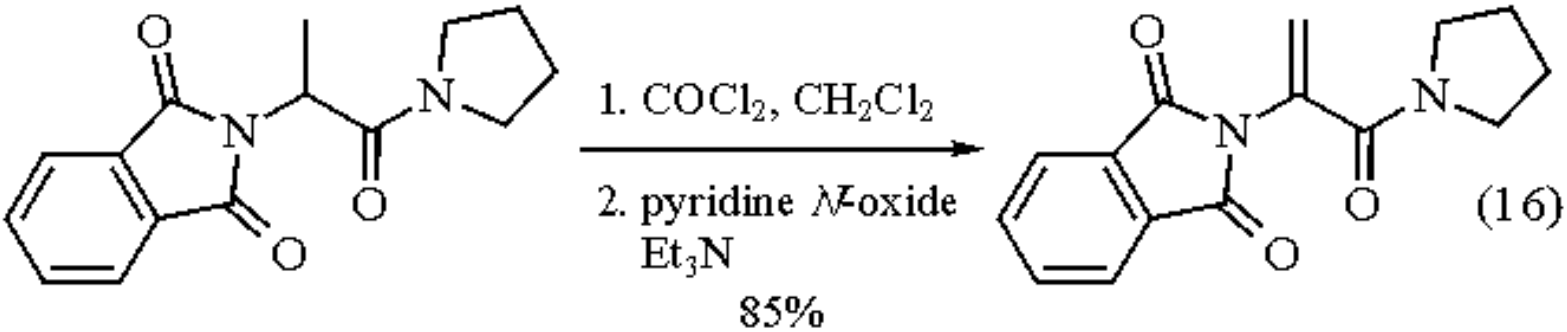

(16)

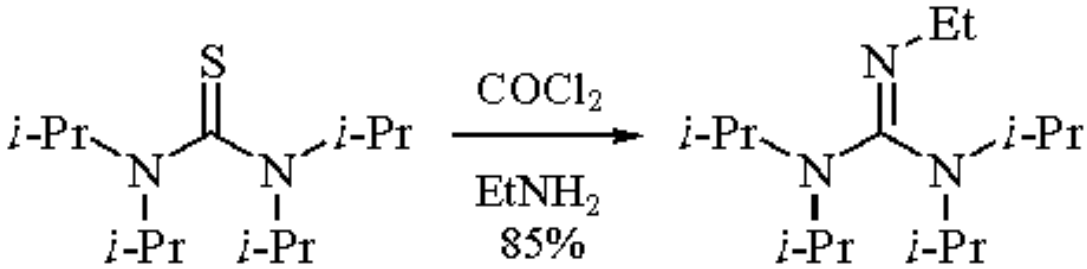

(17)

Phosgene Equivalents.

In recent years, ***Bis(trichloromethyl) Carbonate*** (triphosgene) has been introduced as a crystalline phosgene source;[34] similarly, ***Trichloromethyl Chloroformate*** (diphosgene) has been used as a liquid equivalent[35] (bp 128 °C, d_{15} 1.65 g mL^{-1}). They have the advantages of much easier manipulation (particularly for small-scale work), safer transport and

storage, and they are less susceptible to hydrolysis. Triphosgene has so far been shown to perform several reactions undergone by phosgene itself, e.g. carbonylation[36] and Barton oxidation.[37] Diphosgene generates phosgene slowly at elevated temperatures, or rapidly in the presence of a charcoal catalyst;[38] it is also effective in several of the reactions of phosgene, including *N*-carboxyanhydride formation[38] and the conversion of amino alcohols to oxazolidinones,[39] where it has been recommended for large-scale use.

Related Reagents.

Dimethyl Sulfoxide-Phosgene.

---

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Phosphazene Base P_4-*t*-Bu

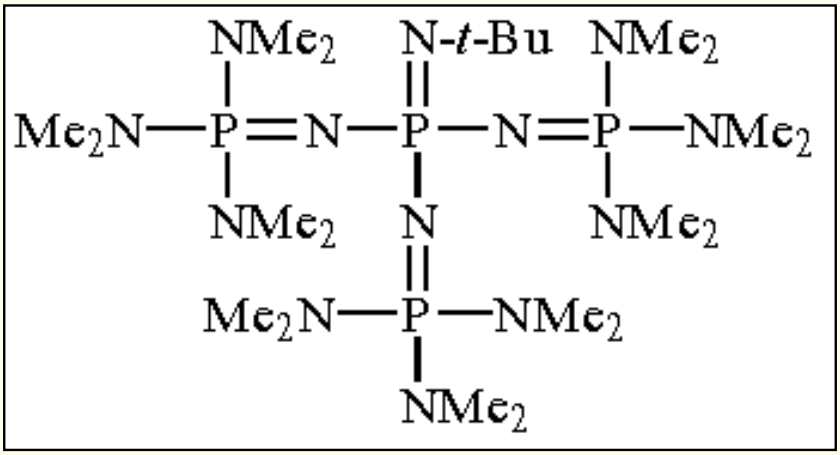

[111324-04-0] · $C_{22}H_{63}N_{13}P_4$ · Phosphazene Base P_4-*t*-Bu · (MW 633.86)

(extremely strong, highly hindered, kinetically highly active base;[1] generates exceptionally nucleophilic naked carbanions from a wide range of carbon acids;[2] the very low Lewis acidity of the cation suppresses side reactions commonly observed with metal organyls, e.g. aldol and ester condensations[3] and β-eliminations[4])

Alternate Name: 3-*t*-butylimino-1,1,1,5,5,5-hexakis(dimethylamino)-3-{[tris(dimethylamino)phosphoranylidene]amino}-1λ^5,3λ^5,5λ^5-1,4-triphosphazadiene.

Physical Data: mp ca. 207 °C (dec); pK_{BH^+} 30.1.[5]

Solubility: very sol THF, ether, hexane, benzene, toluene; sol with protonation in protic solvents, MeCN; reacts rapidly with all types of haloalkanes except fluoroalkanes.

Form Supplied in: 1 M solution in hexane; commercially available.

Analysis of Reagent Purity: NMR in benzene-d_6. ^{1}H NMR: δ 1.83 (s, 9 H), 2.73 (d, *J* = 10 Hz, 54 H); ^{13}C NMR: δ 35.6 (br d, *J* &AApprox; 13 Hz), 38.08 (d, *J* = 4 Hz), 51.31 (d, *J* = 5.5 Hz); ^{31}P NMR: δ -24.44 (q, *J* = 20 Hz), 5.74 (br m).

Purification: all water-soluble salts of P_4-*t*-Bu can be converted to the HBF_4 salt by precipitation from aqueous solution with $NaBF_4$. Water-insoluble salts are first converted to the chloride by means of a column charged with strongly basic anion exchange resin (Cl^- form, MeOH). P_4-*t*-Bu.HBF_4 is recrystallized from aqueous ethylamine and dried in vacuo at 60 °C. 2.35 g (60 mmol) of potassium metal and 5 mg of $Fe(NO_3)_3.9H_2O$ are added to 50 mL of anhydrous NH_3(l) with stirring (glass-covered stirring bar) under N_2 and the solution kept at ca. -40 °C until the color turns to gray and evolution of H_2 ceases. A

solution of 21.6 g (30.0 mmol) of P_4-*t*-Bu.HBF_4 in 50 mL of THF is added and the mixture stirred at -40 °C for another 15 min. After evaporation of solvents in vacuo, the residue is extracted with 60 mL of hexane (caution! KNH_2 is pyrophoric), rigorously protecting from moisture. The solvent is removed at reduced pressure, affording up to 18.3 g (96%) of the crystalline base. P_4-*t*-Bu can be sublimed at 160 °C/10^{-3} mmHg, but protic impurities are not removed thereby.

For most applications, P_4-*t*-Bu must be strictly anhydrous, but water content is not readily detected by NMR. The following procedure has proven to be effective in the elimination of small amounts of protic impurities: to a 0.5 M solution of the base in hexane or heptane, ethyl bromide (at least 3 mol per mol of H_2O) is added. After 0.5 h at rt, diethyl ether and excess ethyl bromide (bp 31 °C) are removed by evaporating part of the solvent in vacuo, the precipitated hydrobromide salt of the base is filtered off, the solvent is removed completely in vacuo, and the residue is dried in a high vacuum.

Handling, Storage, and Precautions: P_4-*t*-Bu is extremely hygroscopic and must be stored and handled so as to rigorously exclude moisture. It is thermally stable up to ca. 120 °C, extremely resistant towards (basic) hydrolysis, and likewise insensitive to dry oxygen.

Alkylations of Carbanions.

P_4-*t*-Bu is a member of a novel class of kinetically highly active uncharged bases,[1,2,6-8] with pK_{BH^+} values ranging from 13[5,6] to ca. 34;[1,2,5,7,8] among the strongest of these phosphazene bases, it is the most readily available.[1] In the presence of alkylating agents, in situ alkylation of low acidic substrates in concentrated (ca. 0.5 M) THF solution is generally extremely rapid on (gradual) addition of P_4-*t*-Bu at -100 °C to -78 °C. Due to the high solubilizing power of phosphazene bases, solubility problems are scarce. Separation of products from salts of the base is easily achieved, e.g. by direct precipitation of its halide salts with diethyl ether or benzene, by extraction (CH_2Cl_2) or precipitation ($NaBF_4$) of salts from aqueous solution, or by filtration over silica gel. The very low Lewis acidity of the huge cation contrasts sharply with the characteristics of lithium amide bases. Thus Lewis acid-catalyzed side reactions, e.g. aldol or ester condensations in alkylations of enolates, are effectively suppressed; even β-lactones are easily mono-[2] or peralkylated (eq 1).[8] In cases where the corresponding lithium organyls decompose entirely via β-alkoxide elimination,[4,9] naked enolates of β-alkoxy esters undergo clean alkylation.

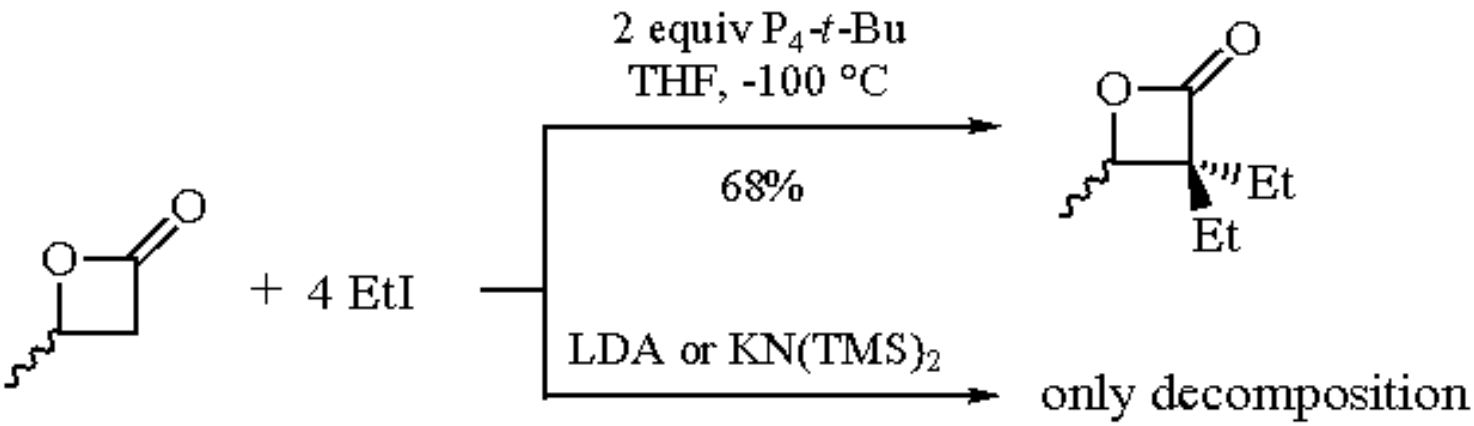

(1)

Using more hindered bases like P_4-*t*-Oct[2,7,10] (*t*-Oct = 1,1,3,3-tetramethylbutyl) enhances the selectivity for monoalkylation considerably (eq 2).[2] This tendency also holds for selective monoalkylation of secondary carbon centers.[8] Even sterically congested quaternary centers are formed with great ease (eq 3).[4]

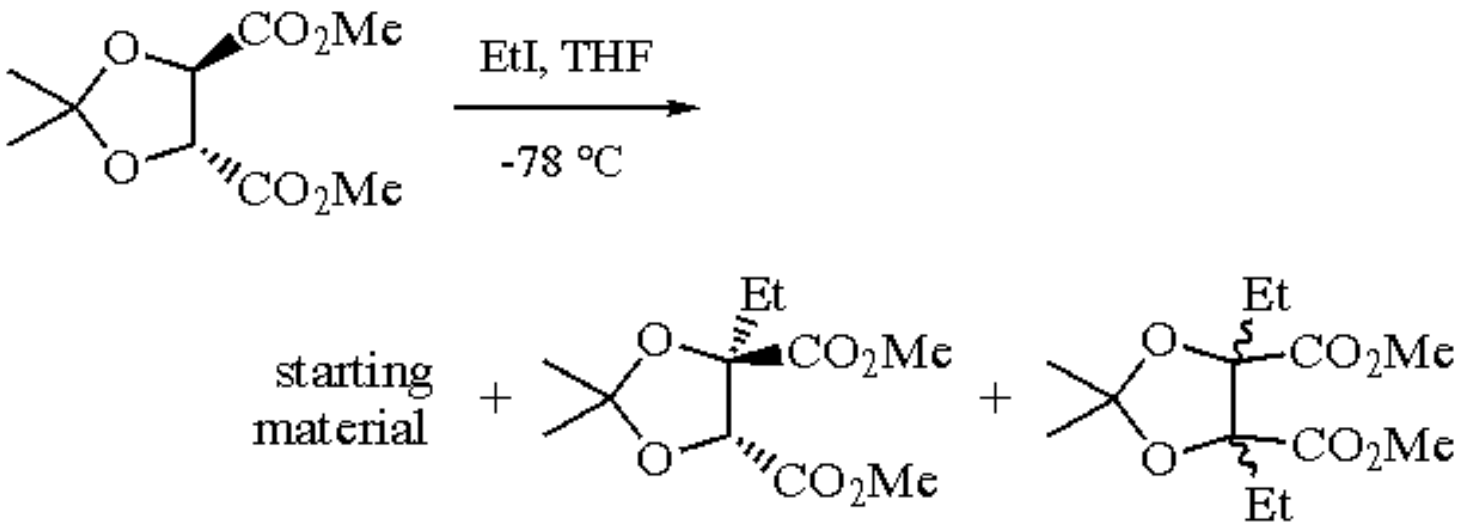

(2)

	starting material		
P_4-*t*-Bu	28%	41%, 97% de	14%
P_4-*t*-Oct	9%	71%, 98% de	8%
LDA, HMPA		no alkylation product	
K[N(TMS)$_2$]		no alkylation product	

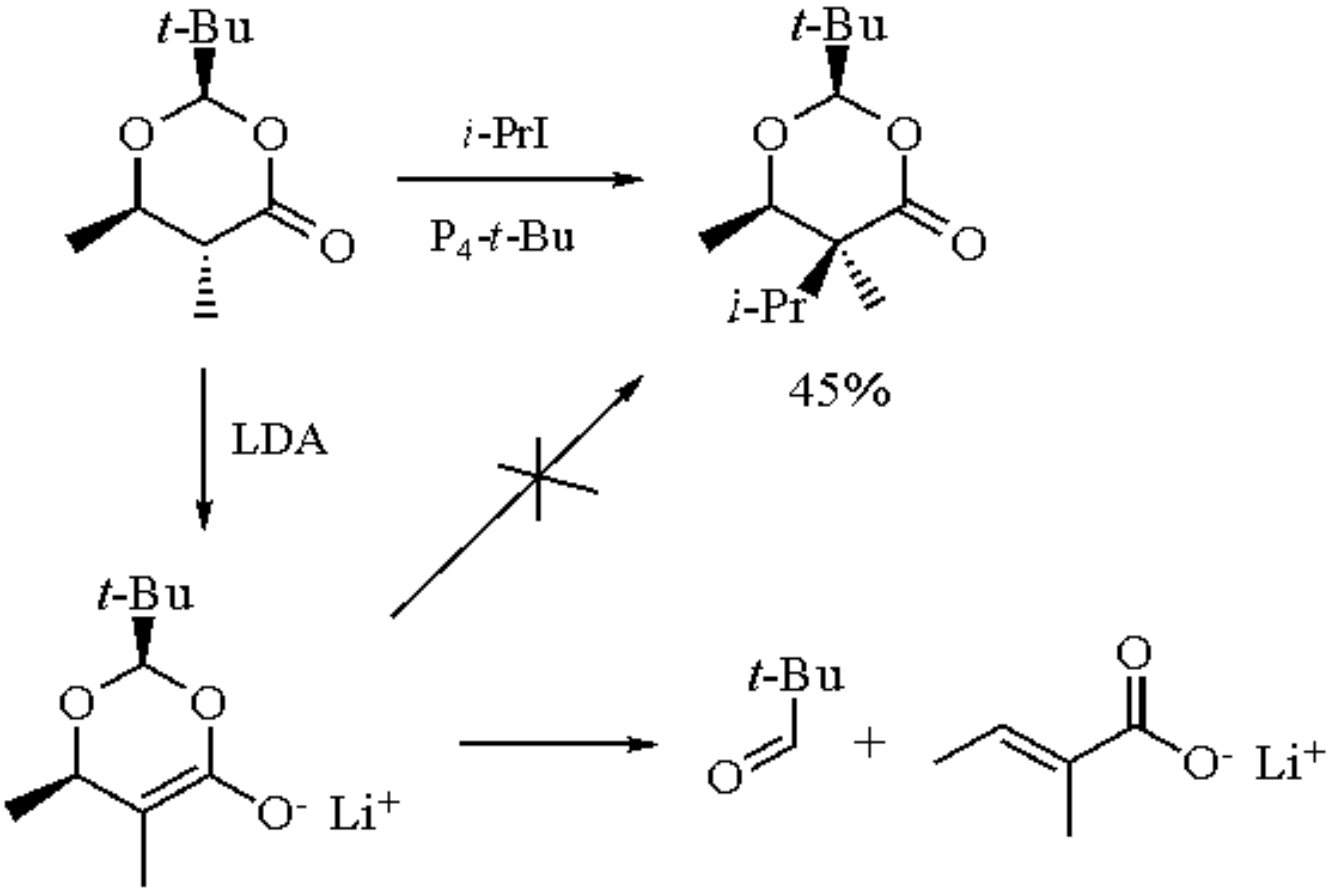

(3)

Alkylation of nitriles is not complicated by Thorpe condensation, as observed with ***Lithium Diisopropylamide*** as base. Alkylation of 1,2-dinitriles with no elimination of hydrocyanic acid (eq 4)[8] is achieved in high yield.

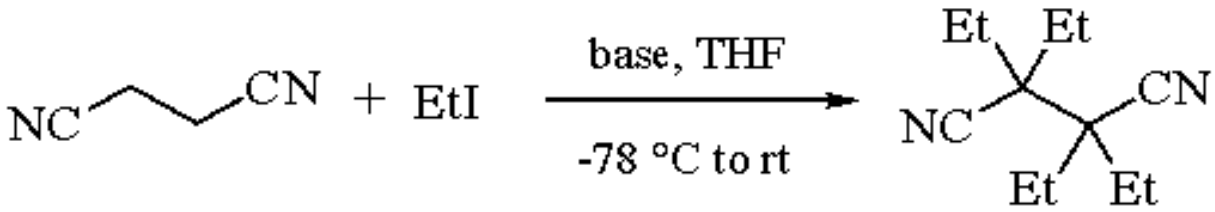

(4)

P_4-*t*-Bu	98%
LDA	0.5%
LDA, HMPA	15%
$KN(TMS)_2$	2%

Alkylation of Nitrogen Acids.

N-Perbenzylation of rather insoluble *N*-Boc-protected or cyclic peptides leads to easily soluble, fully protected derivatives.[11] Occasionally, regioselective *C*-alkylation of glycine or sarcosine subunits is also observed (eq 5).

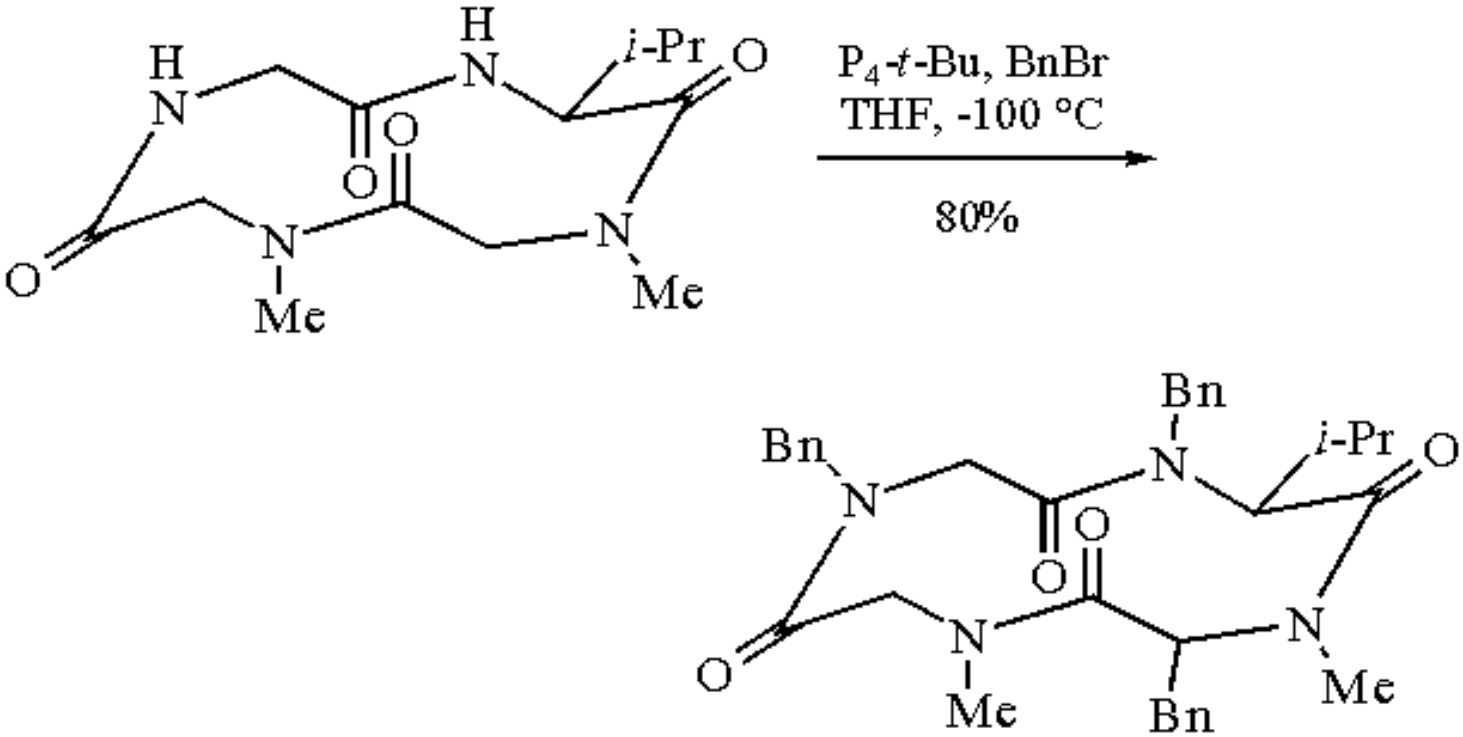

(5)

Anionic Polymerization.

Polymerization of methyl methacrylate occurs in the presence of P_4-*t*-Bu. Using ethyl acetate as initiator in THF at

elevated temperatures, high molecular weights and narrow molecular weight distributions are achieved,[3] back-biting by ester condensation[12] being effectively suppressed. Presumably due to lack of chelate control by the cation, the stereochemistry differs from that of polymerizations with metal organyls, syndiotactic diads being favored (eq 6).

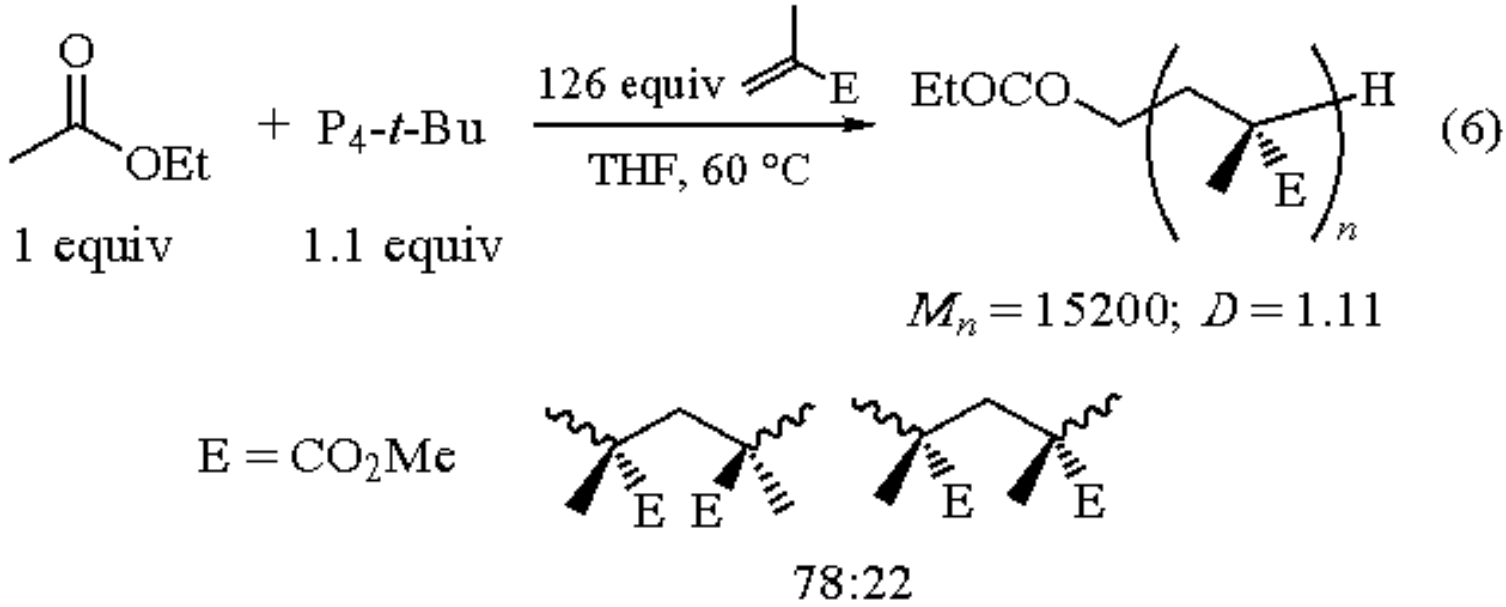

Other Applications.

The high steric hindrance of P_4-*t*-Bu enables the formation of isomerically pure 1-alkenes from primary halides at rt in almost quantitative yield.[1] The simplicity of the NMR spectra, the UV transparency (end absorption below 230 nm), and the simplicity of handling recommends P_4-*t*-Bu and other phosphazene bases for obtaining spectroscopic data of highly basic or unstable naked anions.[13]

Related Commercially Available Bases.

A number of other phosphazene bases are commercially available. P_1-*t*-Oct (**1**), P_1-*t*-Bu (**2**), BEMP (**3**), BEMP bound to a Merrifield polymer, and BTPP (**4**)[10] are hindered bases, suitable for *O*-alkylation of carbohydrates[6,14] and cyanohydrins,[6] *N*-alkylation of nucleosides[6] and carbamates,[15] *C*-alkylation of alkyl malonic esters,[6] *O*-tosylation of amino alcohols,[16] and aldol condensations;[17] reactions with these bases are often considerably more selective than with metal bases.

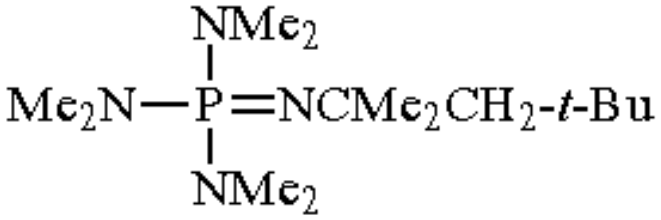

(1)
P_1-*t*-Oct
$pK_{BH}^{+} = 14.0$

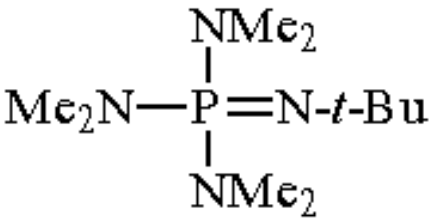

(2)
P_1-*t*-Bu
$pK_{BH}^{+} = 14.4$

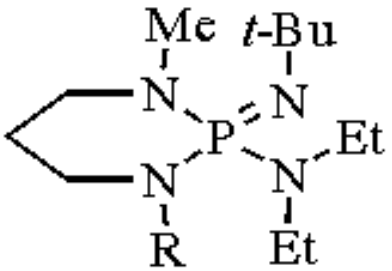

(3)
R = Me: BEMP
$pK_{BH}^{+} = 15.1$

R = H_2C-(P)

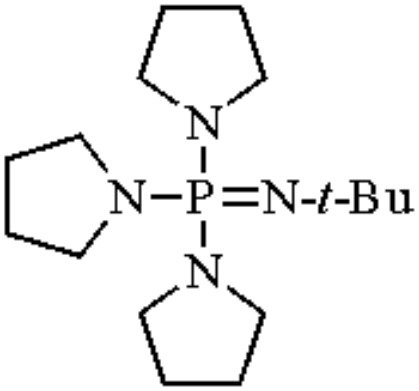

(4)
BTPP
$pK_{BH}^{+} = 15.8$

N-Alkylation of phthalimide (Gabriel synthesis) occurs in homogeneous acetonitrile solution at rt.[18] In contrast to DBU or guanidines, all phosphazene bases are highly resistant towards basic hydrolysis, thus representing easy-to-recover catalysts for the basic hydrolysis of sensitive esters in a relatively apolar medium (eq 7).[19]

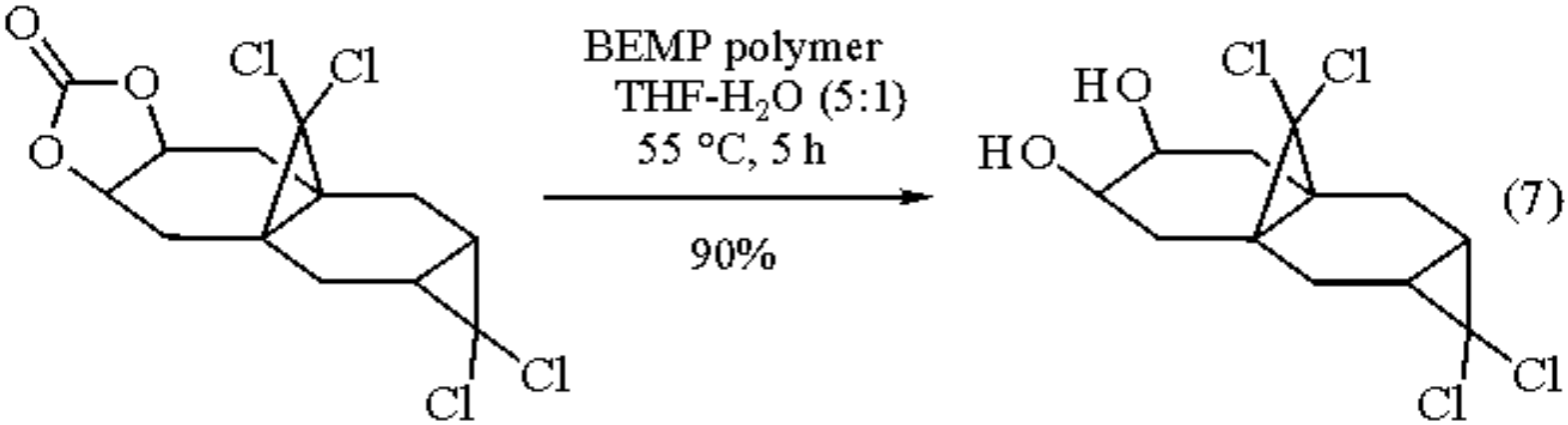

(7)

P_2-Et (**5**)[10,20] is only a moderately hindered base (pK_{BH^+} = 20.2),[5] suitable for E2 elimination reactions of secondary halides, which is ca. 4 orders of magnitude more reactive and less easily alkylated than DBU (pK_{BH^+} = 11.8).[5]

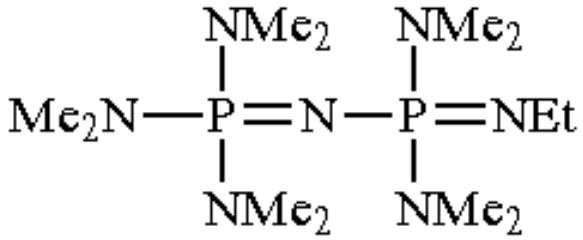

(5)

Related Reagents.

1,1,1,3,3,3-Hexakis(dimethylamino)-1λ^5,3λ^5-diphosphazenium Fluoride.

---

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Phosphoric Acid

H_3PO_4

[7664-38-2] · H_3O_4P · Phosphoric Acid · (MW 98.00)

(acid catalyst; dehydrating agent; phosphorylating agent[1])

Physical Data: mp 41 °C; bp 158 °C.

Solubility: sol water, formic acid, acetic acid.

Form Supplied in: commercially available; low melting white solid or colorless liquid.

Analysis of Reagent Purity: titration.

Preparative Method: anhydrous H_3PO_4 can be prepared by dissolving P_2O_5 in 85% H_3PO_4.

Purification: dry at 150 °C. At temperatures above 200 °C, monomeric H_3PO_4 changes to oligomeric metaphosphoric acid.

Handling, Storage, and Precautions: corrosive.

Introduction.

Phosphoric acid is a strong, nonoxidizing acid that is available in a number of different forms. Anhydrous, monomeric H_3PO_4 (orthophosphoric acid) is a low melting solid that can be purchased commercially or prepared by adding P_2O_5 to commercial 85% aqueous H_3PO_4. This combination has been used to iodinate alcohols, cleave ethers, and hydroiodinate alkenes, in addition to a variety of uses listed below.[2] Metaphosphoric acid [*37267-86-0*] is an oligomeric form, also commercially available.[3]

Hydrolysis of Imines, Amides, and Nitriles.

The hydrolysis of imines,[4] amides, and nitriles to carboxylic acids (eq 1) using H_3PO_4 is a time-honored technique.[5] There are numerous methods for accomplishing this transformation.[6]

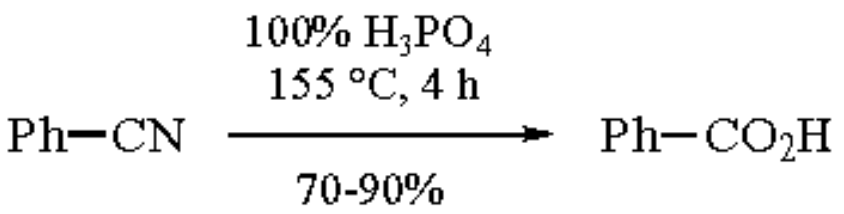

(1)

Preparation of Phosphates.[1]

Phosphate mono- and dialkyl esters have been prepared from phosphoric acid (see also ***Phosphorus Oxychloride***). Treatment of (**1**) with H_3PO_4 at rt provides the corresponding phosphate in good yield (eq 2).[7] At high temperatures, diesterification can occur (eq 3).[8]

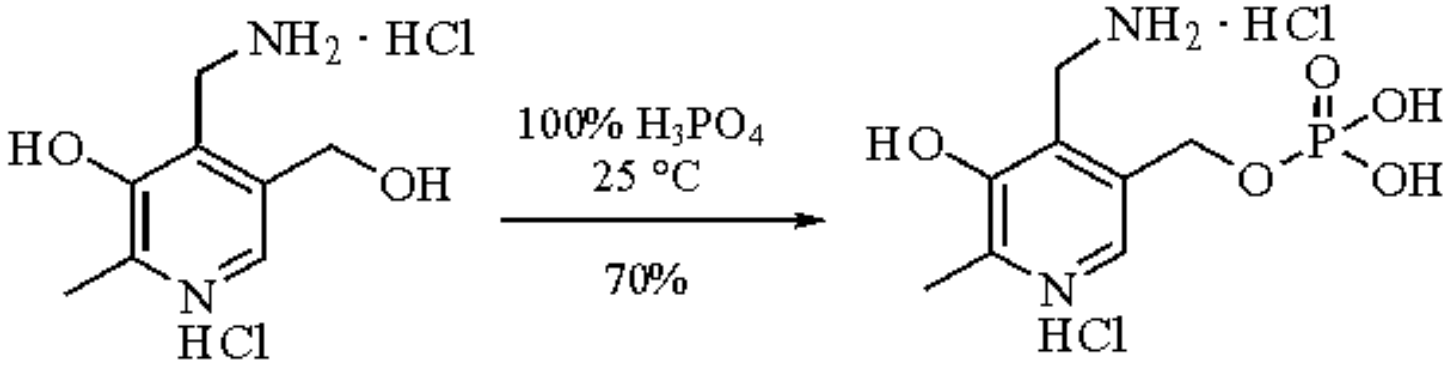

(1) (2)

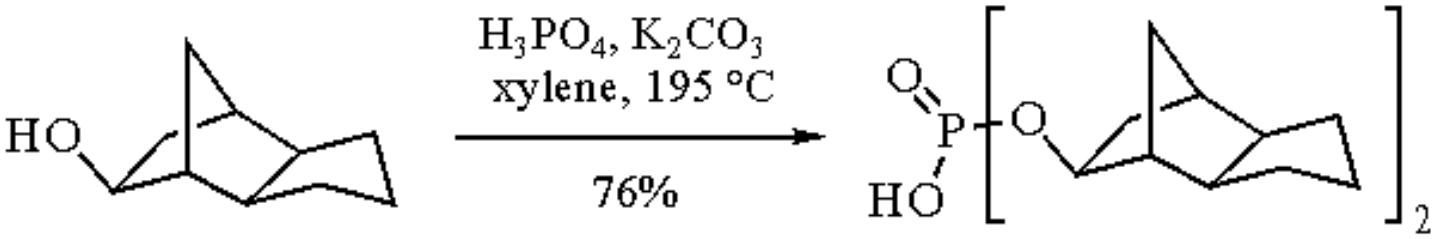

(3)

An effective, large-scale synthesis of diammonium acetylphosphate has been developed, and involves direct acylation of H_3PO_4. Either ketene[9] or acetic anhydride[10] (eq 4) can be used in this process.

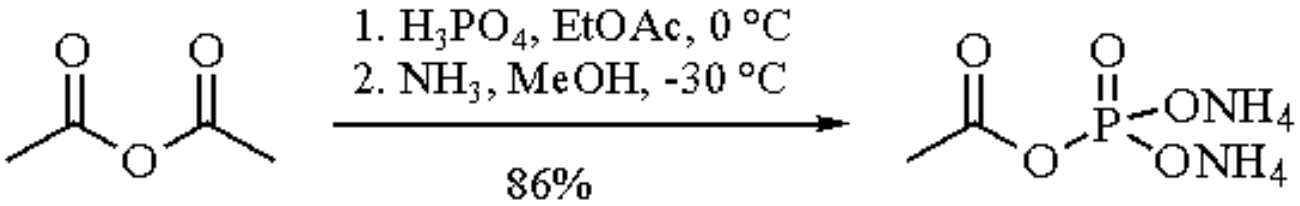

(4)

Acid Cyclization Catalyst.

A common use for H_3PO_4, as a solution in water, a liquid acid, or in anhydrous form, is as an acid cyclization catalyst. Cyclization of cross-conjugated ketones in H_3PO_4/formic acid leads to 2,3-dialkylcyclopentenones (eq 5)

rather than the 3,4-dialkyl products expected of the Nazarov cyclization.[11] This result is obtained when either the ketone or the corresponding ethylene acetal is used as starting material. Similar results are obtained using HBr/HOAc, although, in these examples, some of the 3,4-dialkyl products are obtained as well.

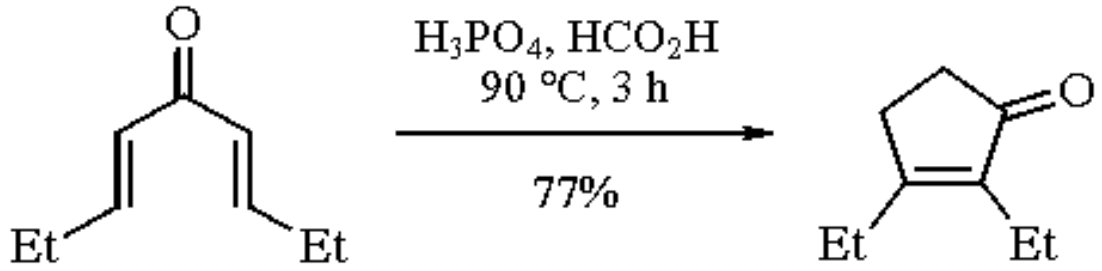

(5)

An intermolecular example of an alkene-cation addition reaction provides access to chromenes through isoprenylation of a phenol (eq 6).[12]

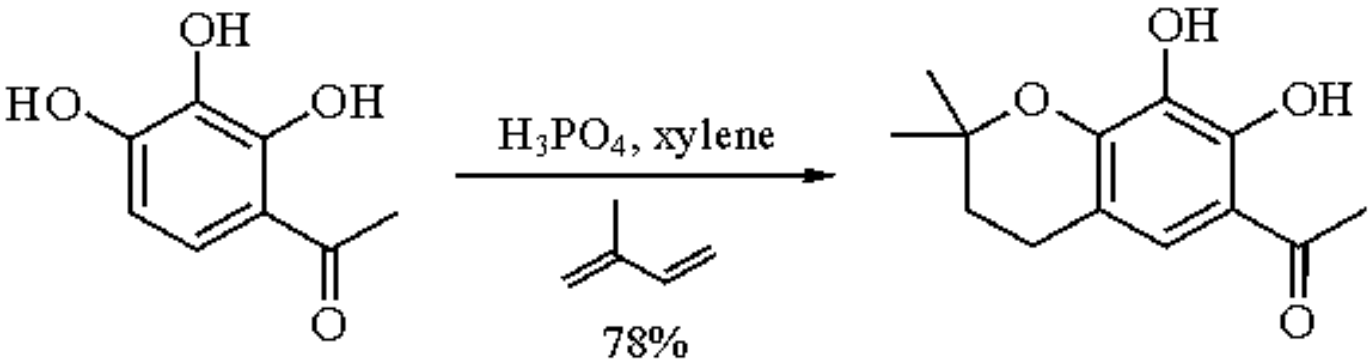

(6)

Cyclization of (**2**) in phosphoric acid results in an azabicyclononane (eq 7).[13]

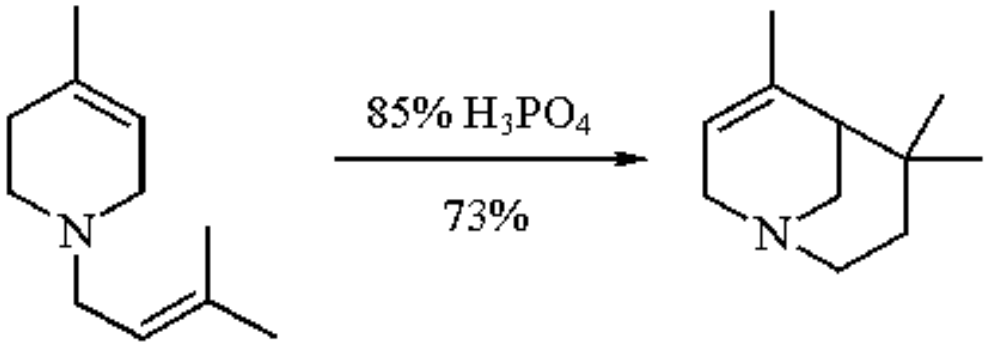

(7)

(2)

Phosphoric acid-mediated condensation of indole derivatives with ketones provides access to 3-substituted indoles (eq 8).[14]

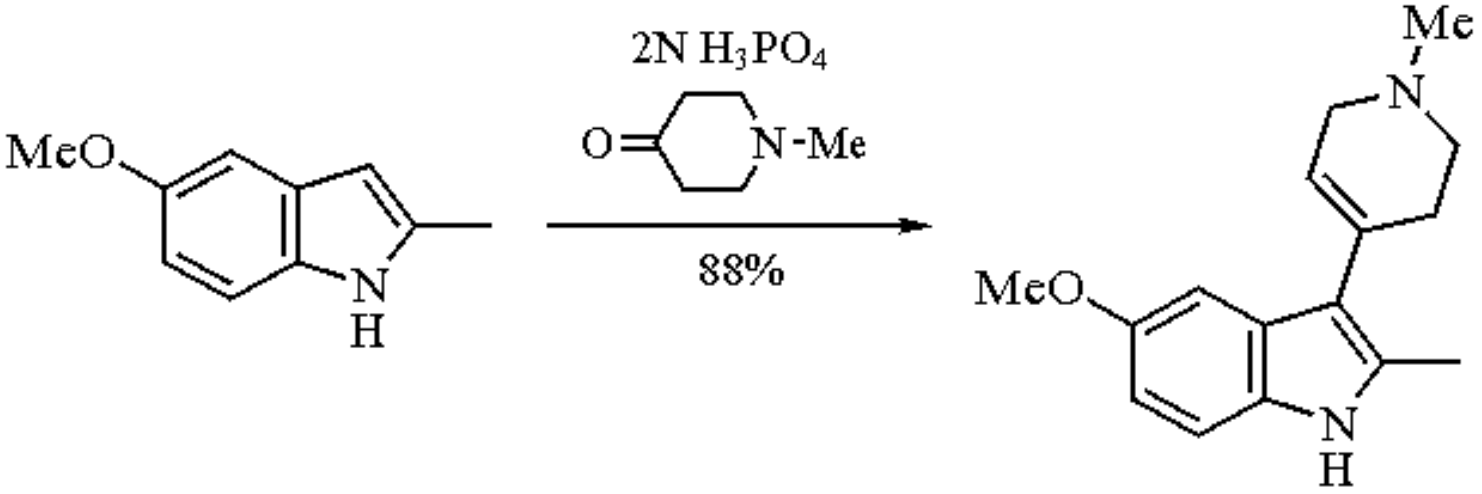

(8)

Cyclization of enol acetates (eq 9), δ,ε-unsaturated aldehydes,[15] and ketene dithioacetals (eq 10) can also be accomplished by heating in H_3PO_4. The cyclization of (**3**) results in dithiopyridines by way of an intramolecular Ritter reaction followed by a 1,3-methylthio shift. Lewis acids, ***Boron Trifluoride Etherate*** in particular, lead to simple dehydration.[16]

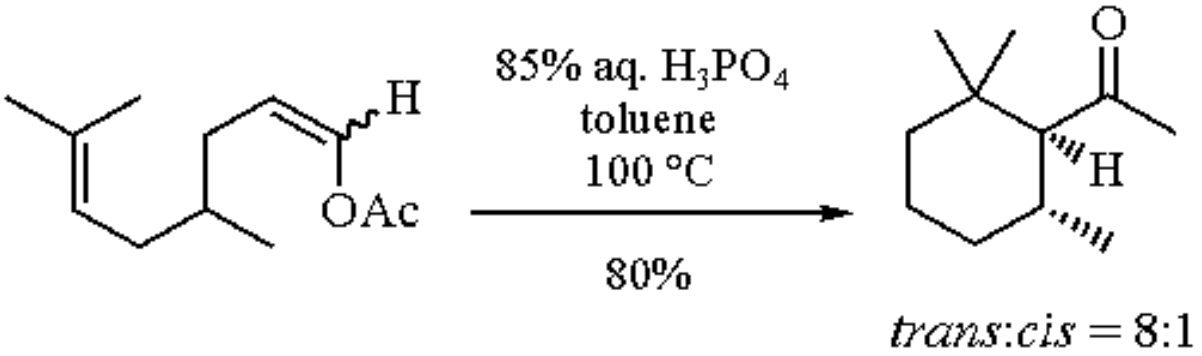

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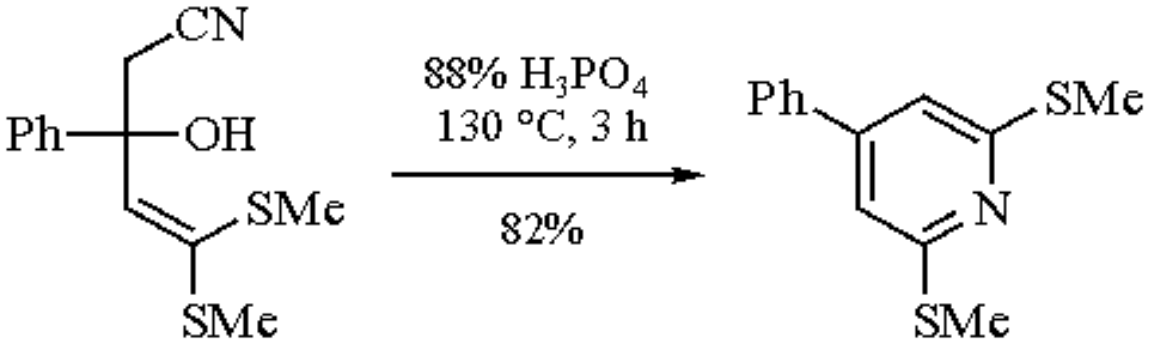

(10)

(3)

Debenzylation.

Treatment of (**4**), an *N*-benzyl derivative of biotin, with anhydrous H_3PO_4 and phenol at elevated temperature leads to debenzylation (eq 11).[17] This reaction provides a nonreductive route to deprotection of the urea while not attacking the unsaturated ester.

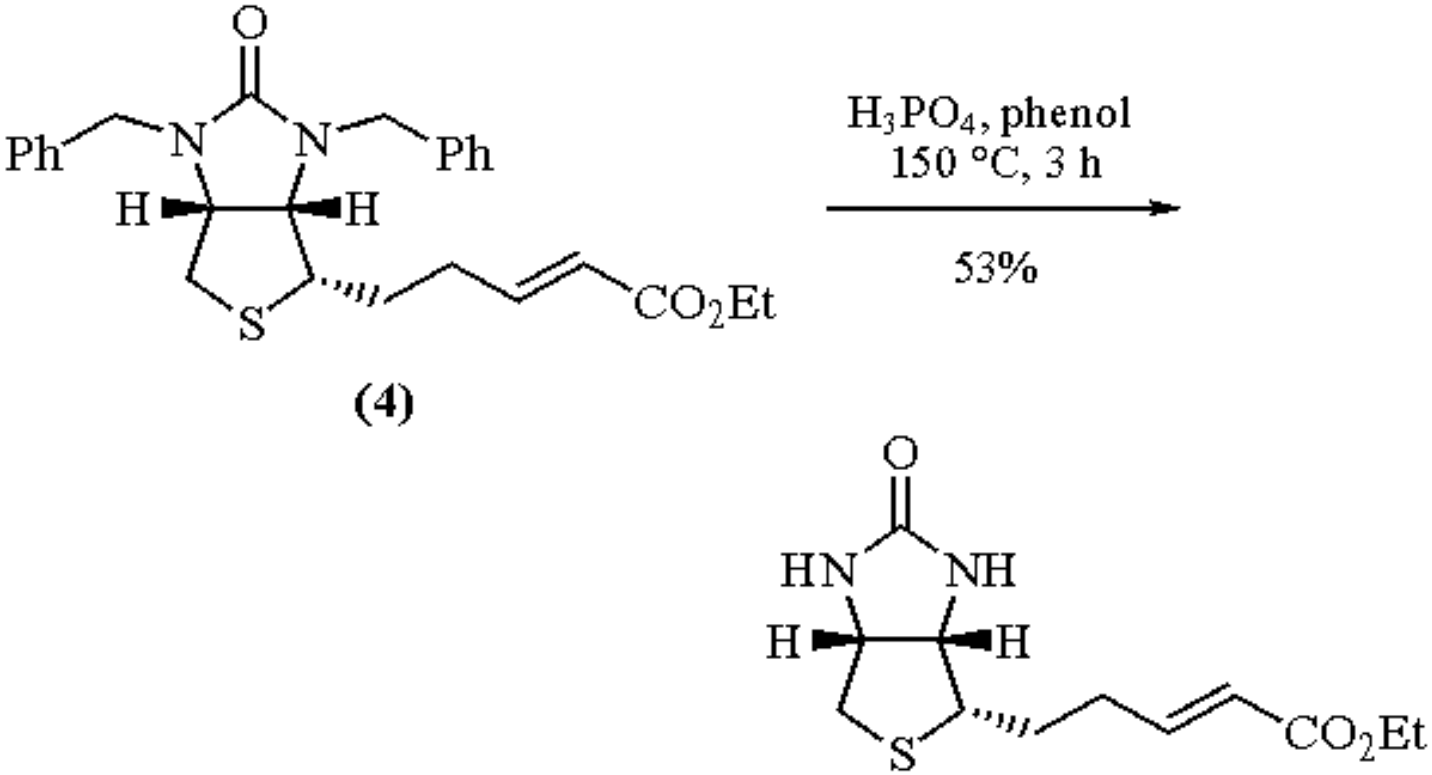

Related Reagents.

Phosphorus(V) Oxide-Phosphoric Acid; ***Phosphorus Oxychloride***; ***Polyphosphoric Acid***; ***Sulfuric Acid***.

---

1. *MOC* **1982**, *E2*, 491.
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Mark S. Meier

Phosphorus(III) Bromide

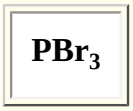

[7789-60-8] · Br_3P · Phosphorus(III) Bromide · (MW 270.67)

(brominating agent for conversion of alcohols to bromides)

Alternate Name: phosphorus tribromide.

Physical Data: mp 41.5 °C; bp 168-170 °C/725 mmHg; *d* 2.85 g cm^{-3}.

Solubility: sol acetone, CH_2Cl_2, CS_2.

Form Supplied in: widely available as liquid and 1.0 M solution in CH_2Cl_2.

Preparative Method: from ***Bromine*** and red phosphorus.[1]

Purification: generally used without purification; can be distilled under N_2 at atmospheric pressure.

Handling, Storage, and Precautions: corrosive. The colorless, fuming liquid has a very penetrating odor. It has a vapor pressure of 10 mmHg at 48 °C. The reagent is stable if kept dry, but reacts violently with water. It is extremely destructive to tissue of mucous membranes, upper respiratory tract, eyes, and skin. This reagent should only be used in a fume hood.

Conversion of Alcohols to Bromides.

The conversion of alcohols (ROH) into bromides (RBr) using PBr_3 is very general. Reaction conditions for this transformation are quite varied. Each of the bromine atoms in the reagent is available for reaction with an alcohol. The reagent can be used to prepare chiral bromides from chiral alcohols (eq 1).[2] It is generally important to carry out the conversion under relatively mild conditions (between 4 °C and rt). Addition of HBr at the end of workup increases both the optical purity and the isolated yield. An example is provided by eq 2. A polyhydroxylic compound has been converted to a polybrominated product (eq 3).[3]

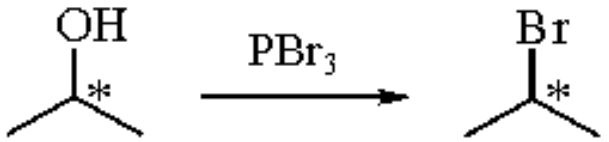

(1)

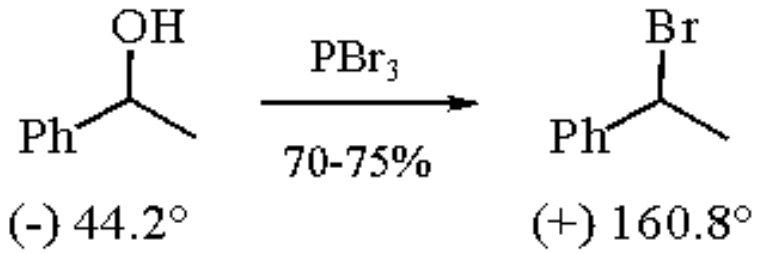

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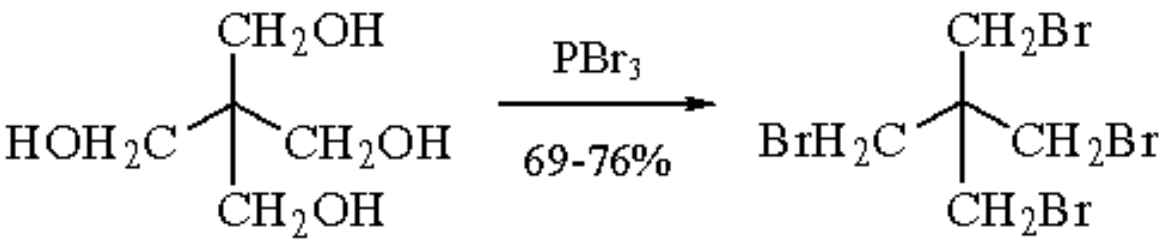

(3)

Bromination of Allylic Alcohols.

The reaction of an allylic alcohol with PBr_3 in ether at 0 °C leads to both stereoselective and regioselective replacement of the hydroxy group by bromine.[4] Examples of this transformation are given in eqs 4 and 5.[5,6] The latter example shows that the reaction can be run in the presence of significant unsaturation. There are many examples of similar reactions.[7]

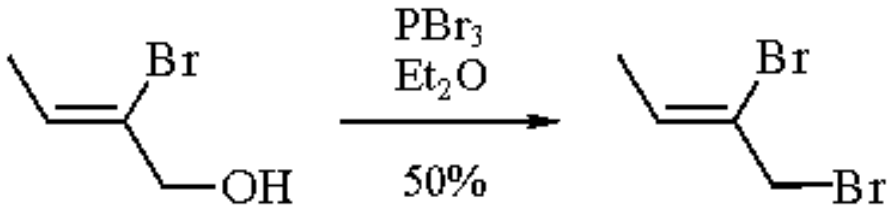

(4)

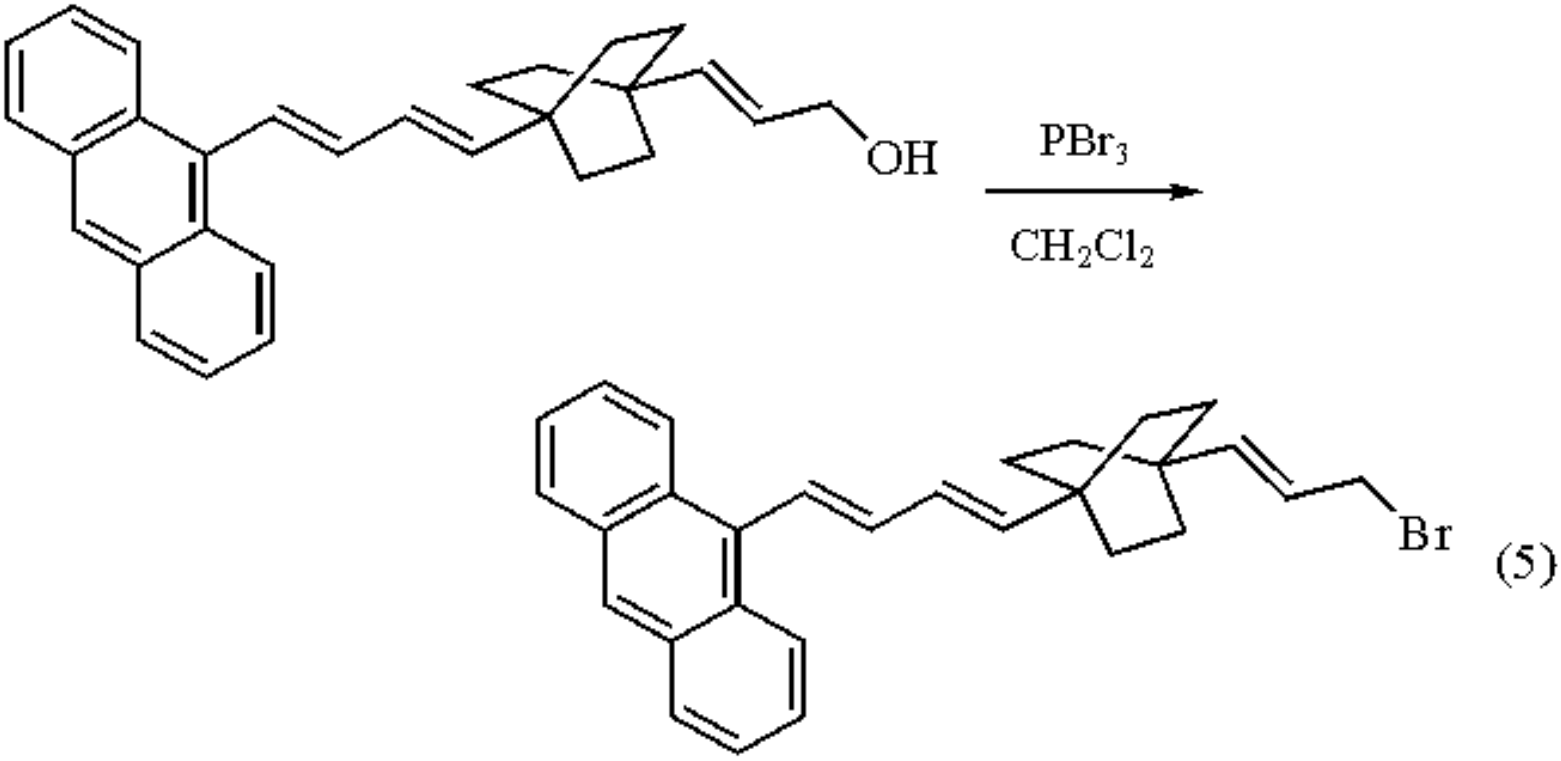

Silverstein[8] followed an older procedure[9] that results in rearrangement of a secondary allylic alcohol to a terminal bromide (eq 6). In a similar fashion, the conversion of propargylic alcohols to allenyl bromides has been noted (eq 7).[10]

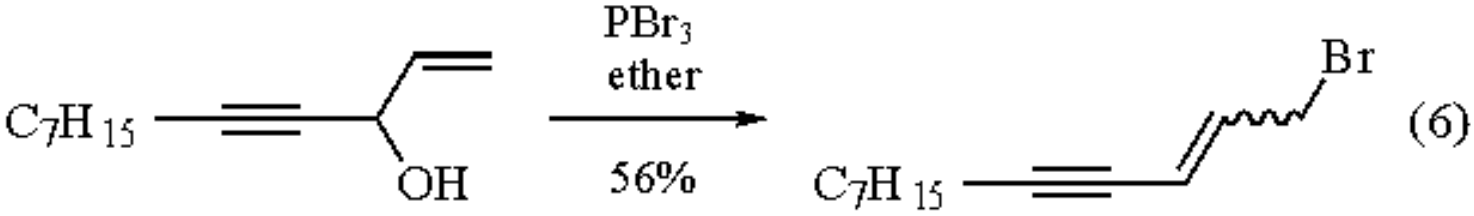

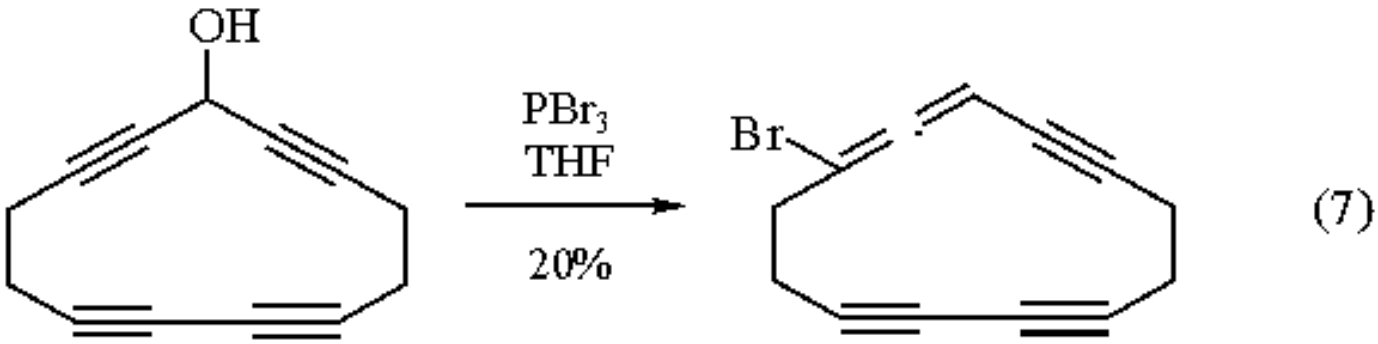

Remote π-bond participation provides important stereochemical control in the reaction. Heathcock (eq 8)[11] has reported retention of stereochemistry due to π-bond participation, in contrast to a similar system without the π-system (eq 9).[12]

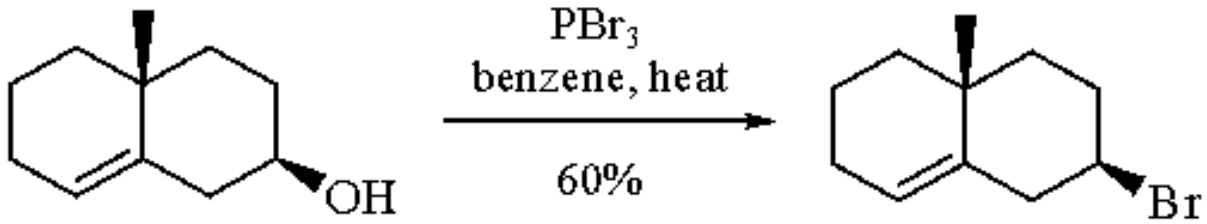

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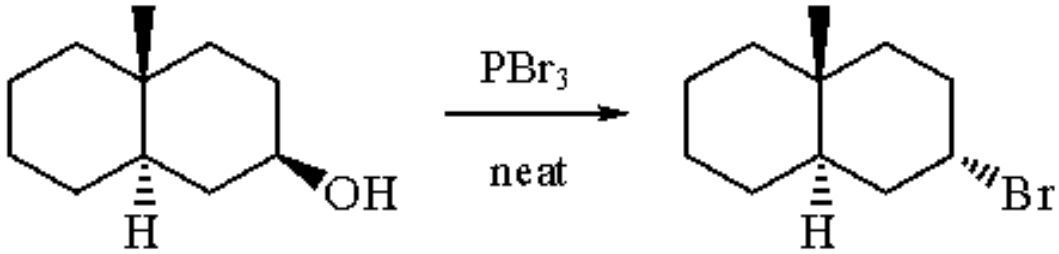

(9)

The reagent will convert an alcohol to a bromide in the presence of an ether (eq 10).[13] Acetals are also stable to the bromination procedure,[14] although an interesting reaction of a cyclopropanone acetal has been reported (eq 11).[15]

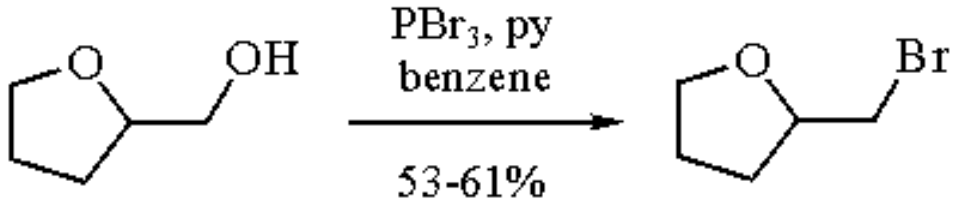

(10)

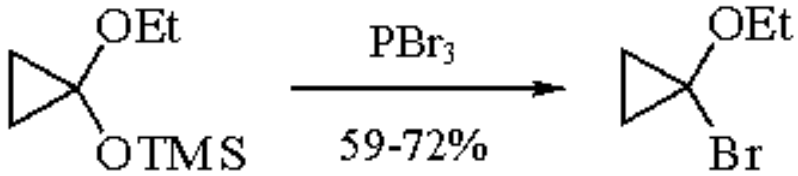

(11)

Use for Alkene Preparation.

Replacement of two alcohol groups by bromine, followed by zinc dehalogenation, provides an interesting alkene synthesis methodology (eq 12).[16] The preparation of 1,3,5-hexatriene is readily accomplished via a PBr_3 step (eq 13).[17] In the presence of DMF, PBr_3 has been used to eliminate a hindered diallylic tertiary alcohol (eq 14).[18] See also ***Phosphorus(III) Bromide-Copper(I) Bromide-Zinc***.

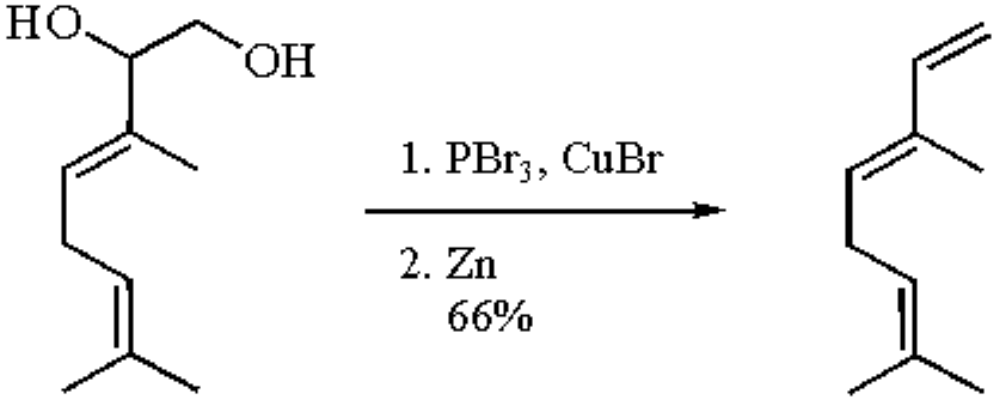

(12)

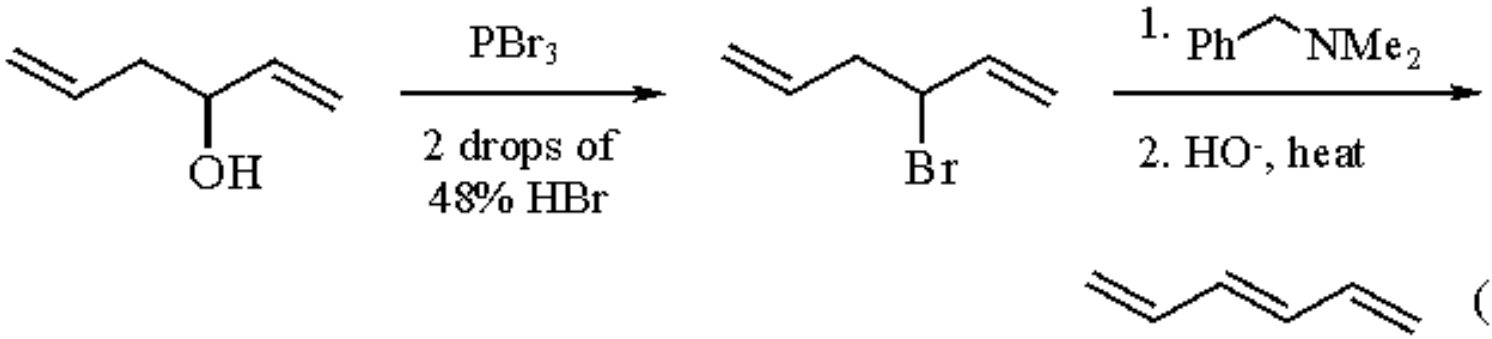

(13)

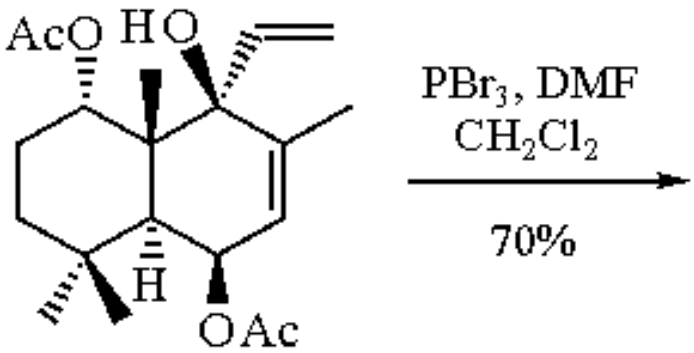

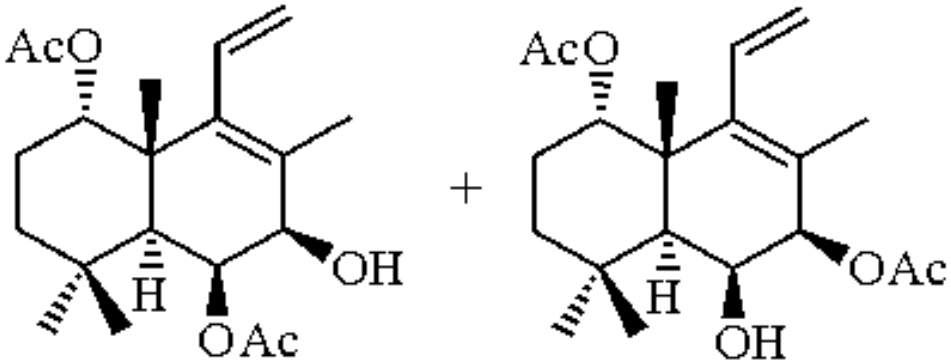

(14)

Other Reactions.

A simple one-step preparation of 2-bromo-2,3-dihydro-1,3,4,2-oxadiazaphospholes has been reported (eq 15).[19] An interesting preparation of 1,5-dibromopentane from piperidine is available (eq 16).[20]

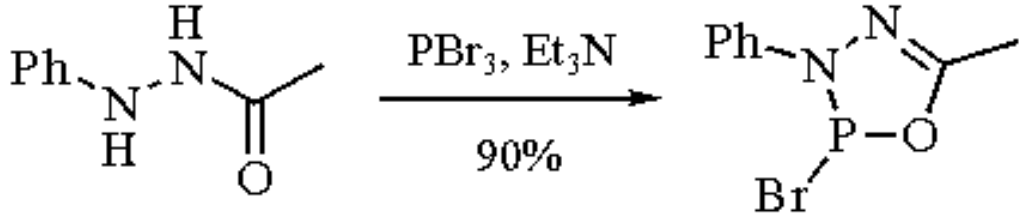

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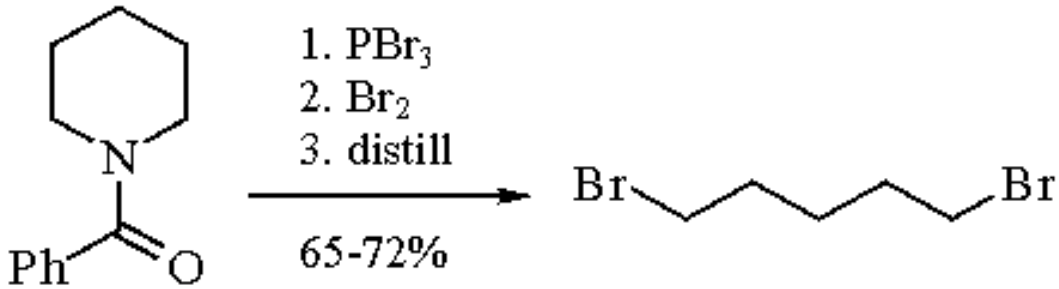

(16)

Related Reagents.

A number of related reagents have been used for the conversion of alcohols to bromides. Other reagents for this purpose covered in this encyclopedia include ***Hydrogen Bromide***, ***Triphenylphosphine Dibromide***, ***Triphenylphosphine-Carbon Tetrabromide***, ***Bromine-Triphenyl Phosphite***, and ***1,2-Bis(diphenylphosphino)ethane Tetrabromide***.

---

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2. Hutchins, R. O.; Masilamani, D.; Maryanoff, C. A. *JOC* **1976**, *41*, 1071.
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4. Corey, E. J.; Kirst, H. A.; Katzenellenbogen, J. A. *JACS* **1970**, *92*, 6314.
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7. See, for example: (a) Marshall, J. A.; Faubl, H.; Warne, T. M., Jr. *CC* **1967**, 753. (b) Piers, E.; Britton, R. W.; deWaal, W. *TL* **1969**, 1251. (c) Mori, K. *T* **1974**, *30*, 3807. (d) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *CB* **1976**, *109*, 1942. (e) Mori, K.; Tominaga, M.; Matsui, M. *T* **1975**, *31*, 1846. (f) Gonzales, A. G.; Martin, J. D.; Melian, M. A. *TL* **1976**, 2279.
8. Silverstein, R. M.; Rodin, J. O.; Burkholder, W. E.; Gorman, J. E. *Science* **1967**, *157*, 85.
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10. Leznoff, C. C.; Sondheimer, F. *JACS* **1968**, *90*, 731.
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Phosphorus(V) Bromide

PBr_5

[7789-69-7] · Br_5P · Phosphorus(V) Bromide · (MW 430.47)

(bromination agent for conversion of alcohols to bromides)

Alternate Name: phosphorus pentabromide.

Physical Data: mp 179-181 °C; *The Merck Index* (11th ed.) reports dec above 100 °C.

Solubility: sol CS_2, CCl_4.

Form Supplied in: yellow solid; commercially available.

Preparative Method: from ***Bromine*** and ***Phosphorus(III) Bromide***,[1] with which it is in equilibrium.

Handling, Storage, and Precautions: corrosive and highly toxic; stable if kept dry, but reacts violently with water; store under N_2 at rt; use in a fume hood.

Conversion of Alcohols to Bromides.

The conversion of alcohols (ROH) into bromides (RBr) using PBr_5 would appear to be quite general for alcohols; however, the literature does not report many examples of this reaction. Eliel[2] reported that PBr_5 is better able to convert 4-*t*-butylcyclohexanol to 4-*t*-butylbromocyclohexane than ***Phosphorus(III) Bromide*** (eq 1).

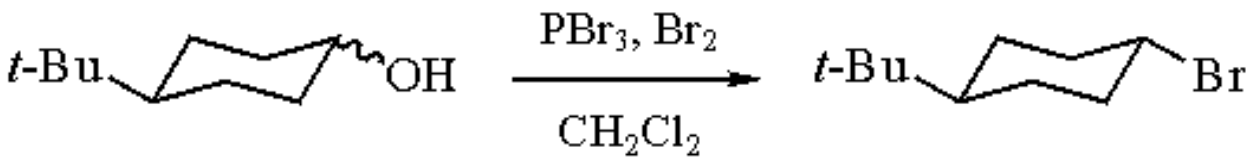

(1)

In the steroid series, D-ring enlargement accompanies reaction of a secondary alcohol with PBr_5 (eq 2).[3] It should be noted that reaction of ***Phosphorus(V) Chloride*** with this same substrate gave direct replacement of the OH with Cl with inversion of configuration.[4] Rearrangement and addition of bromine across a double bond has been noted in the reaction with a propargyl alcohol derivative (eq 3).[5]

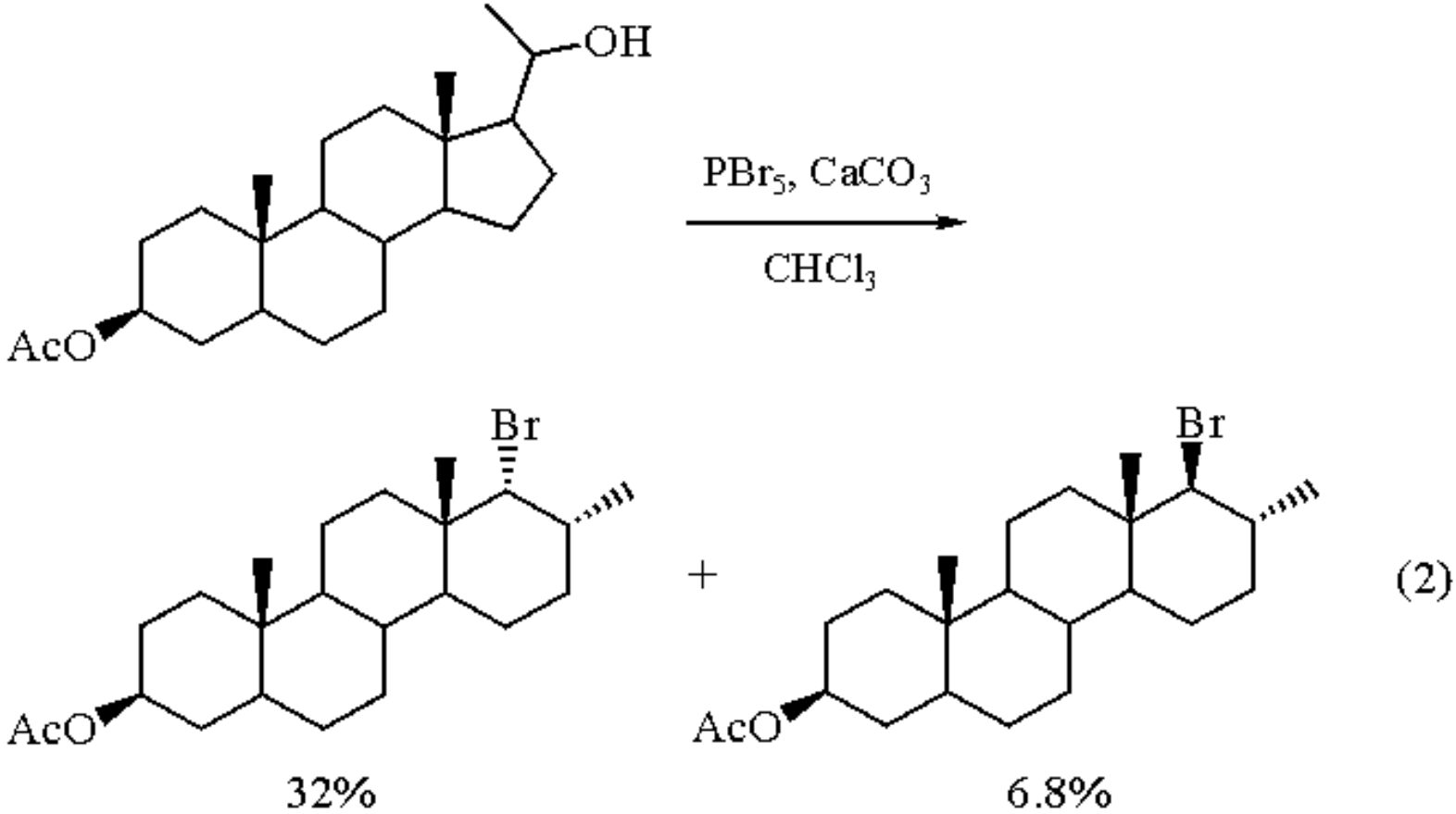

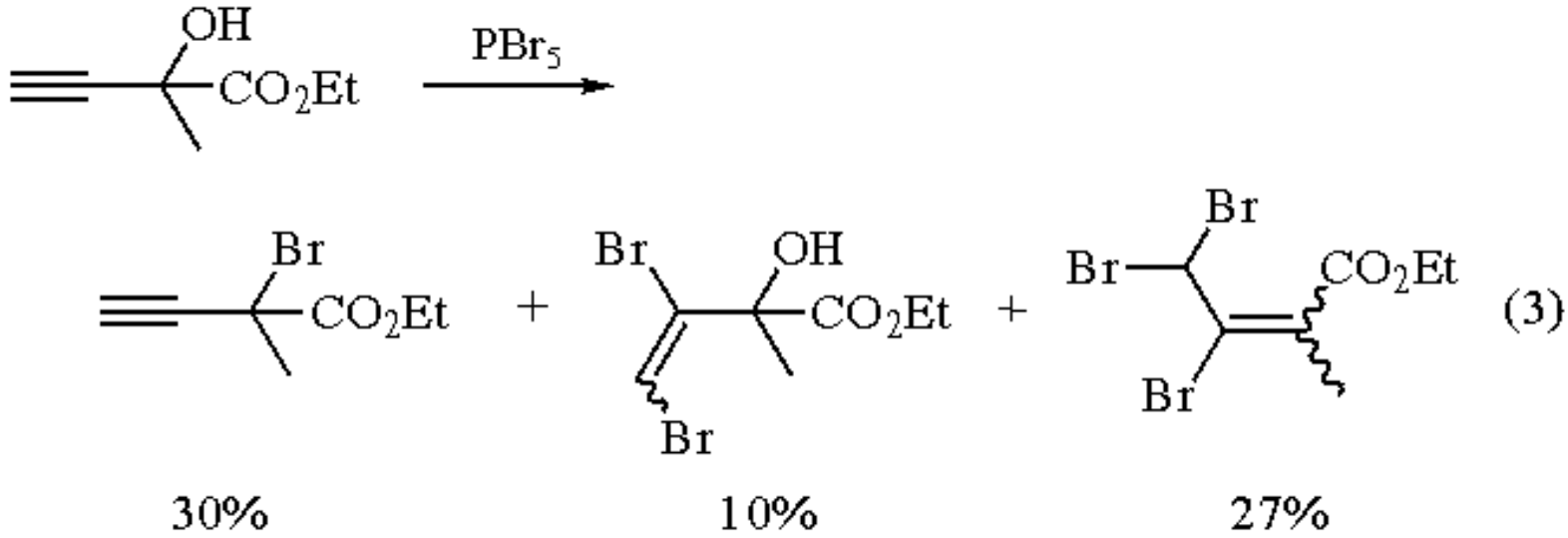

Cleavage of Ethers.

PBr_5 has been used to cleave diisopropyl ether to isopropyl bromide.[5]

Reaction with Ketones.

A regioselective dibromination of a diketone has been reported (eq 4).[6]

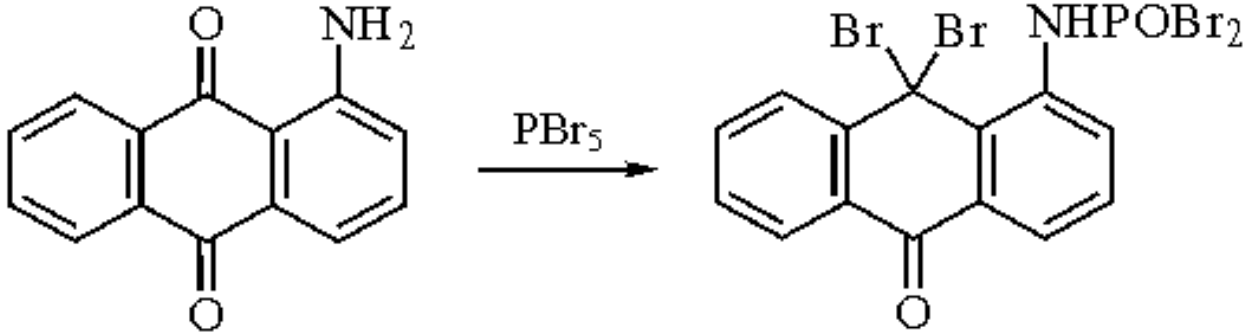

(4)

Related Reagents.

Many related reagents are available for the conversion of alcohols to bromides (see ***Phosphorus(III) Bromide*** and related reagents cited therein).

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Phosphorus(III) Bromide-Copper(I) Bromide-Zinc

PBr_3-Cu_2Br_2-Zn

(PBr_3)

[7789-60-8] · Br_3P · Phosphorus(III) Bromide-Copper(I) Bromide-Zinc · (MW 270.67) (Cu_2Br_2)

[7787-70-4] · Br_2Cu_2 · Phosphorus(III) Bromide-Copper(I) Bromide-Zinc · (MW 286.90) (Zn)

[7440-66-6] · Zn · Phosphorus(III) Bromide-Copper(I) Bromide-Zinc · (MW 65.39)

(conversion of enediols into 1,3-dienes)

Physical Data: see entries for ***Phosphorus(III) Bromide***, ***Copper(I) Bromide***, and ***Zinc***.

General Discussion.

Transformation of 3-ene-1,2-diols into 1,3-dienes can be accomplished in the presence of PBr_3 and Cu_2Br_2, followed by addition of excess Zn powder.[1,2] Excess Cu_2Br_2 (2.5 equiv) is utilized for the best results. It is thought that the Cu_2Br_2 facilitates both bromination and debromination to afford the conjugated dienes. Treatment of the reaction with zinc should be monitored carefully, since longer reaction times can cause cyclization induced by the ***Zinc Bromide*** and reduce yields of the desired alkenes. A variety of dienes can be produced by this method. Overall, allylic alcohols can be transformed into 1,3-dienes (eq 1). First, the allylic alcohol is epoxidized using the Sharpless epoxidation procedure, followed by protection of the alcohol as the silyl ether. Conversion of the epoxy silyl ether into the 3-ene-1,2-diol can be accomplished by treatment with ***Diethylaluminum 2,2,6,6-Tetramethylpiperidide*** (DATMP). Deoxygenation using PBr_3-Cu_2Br_2-Zn gives moderate yields of the diene. Deoxygenation using other standard methods gives low yields of alkene products. Geraniol can likewise be converted to the corresponding 1,3-diene (eq 2), and cyclic enediols can also be deoxygenated to afford cyclic dienes (eq 3).

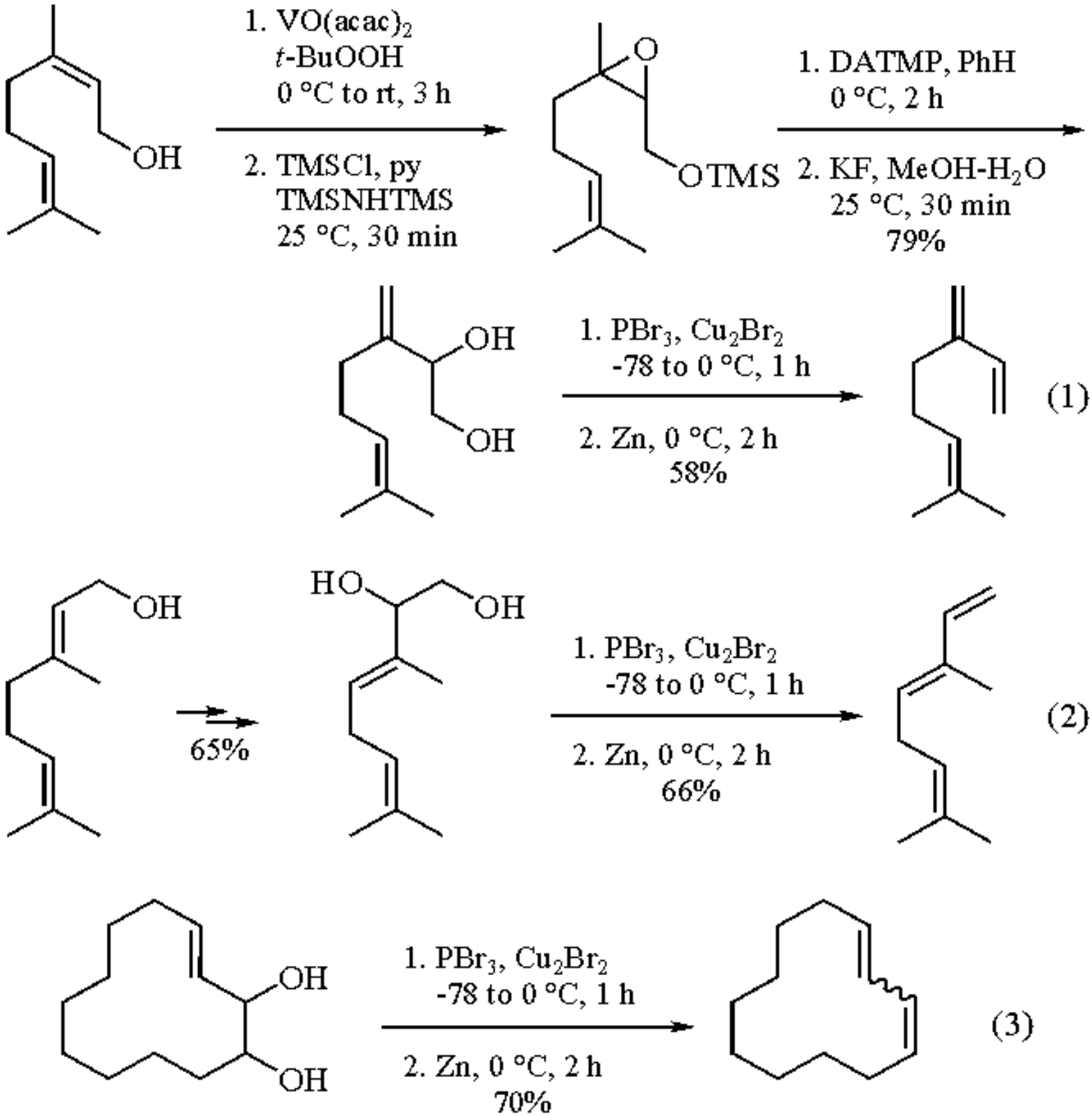

Related Reagents.

Chlorodiphenylphosphine; ***Potassium Hexachlorotungstate(IV)***.

---

1. Tanaka, S.; Yasuda, A.; Yamamoto, H.; Nozaki, H. *JACS* **1975**, *97*, 3252.
2. Yasuda, A.; Tanaka, S.; Yamamoto, H.; Nozaki, H. *BCJ* **1979**, *52*, 1752.

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Phosphorus(III) Chloride[1]

PCl_3

[7719-12-2] · Cl_3P · Phosphorus(III) Chloride · (MW 137.32)

(reactive chlorinating agent;[1,2] strong oxo, aza, thio, and dienophilicity; reactive with organometallics and metal salts; phosphorus source for metal ion ligand synthesis[28])

Alternate Name: phosphorus trichloride.

Physical Data: mp -112 °C; bp 76 °C; *d* 1.586 g cm^{-3}.

Solubility: sol benzene, $CHCl_3$, CH_2Cl_2 ether, CS_2; dec in water or alcohols.

Form Supplied in: water-white liquid; widely available.

Purification: generally used as received without further purification. To purify, heat under reflux to expel dissolved hydrogen chloride, then distill at atmospheric pressure under N_2. Further purification is possible by vacuum fractionation several times through a -45 °C trap into a -78 °C receiver.

Handling, Storage, and Precautions: the liquid is highly toxic by ingestion and slightly toxic by single dermal applications. Inhalation can cause delayed, massive, acute pulmonary edema and death. Contact with water will be violent and result in sufficient gas evolution to rupture closed or inadequately vented containers. Acids produced by contact with water can evolve hydrogen on contact with metals. This reagent must be used in a fume hood.

Chlorinations.

Alcohols, aldehydes, ketones, and carboxylic acids have been chlorinated with PCl_3. The alternative phosphorochloridites, $SOCl_2$, HCl, PCl_5, Ph_3PCl_2, Ph_3P-hexachloroacetone, Ph_3P-CCl_4, and NCS-SEt_2,[1,2] have been used to convert alcohols to chlorides. Aldehydes and ketones are converted to phosphites by PCl_3. Conversion of a carboxylic acid to the acid chloride has been accomplished using PCl_3, PCl_5, $POCl_3$, and $SOCl_2$. In some cases, these reactions tend to be sluggish and substrate, solvent, and temperature dependent. Modified phosphorus halides, i.e. 2,2,2-trichloro-1,3,2-benzodioxaphospholes or Ph_3PCl_2, are superior phosphorus reagents for acid chloride formation.[1] Carboxylic acids are α-brominated with a combination of PCl_3 and Br_2.[3] Imidoyl halides, generated from amides, thioamides, or hydroxamic acid derivatives with PCl_3, are valuable synthetic intermediates and provide

access to a wide range of heterocycles, e.g. quinazolinones and oxadiazoles.[4]

Preparation of Phosphites.

Alcohols, diols, and phenols are readily converted to phosphites. Analogous reactions are seen with thiols[1] and amines.[5] Diaryl phenols react to form medium-sized heterocyclic ring systems (eq 1).[6]

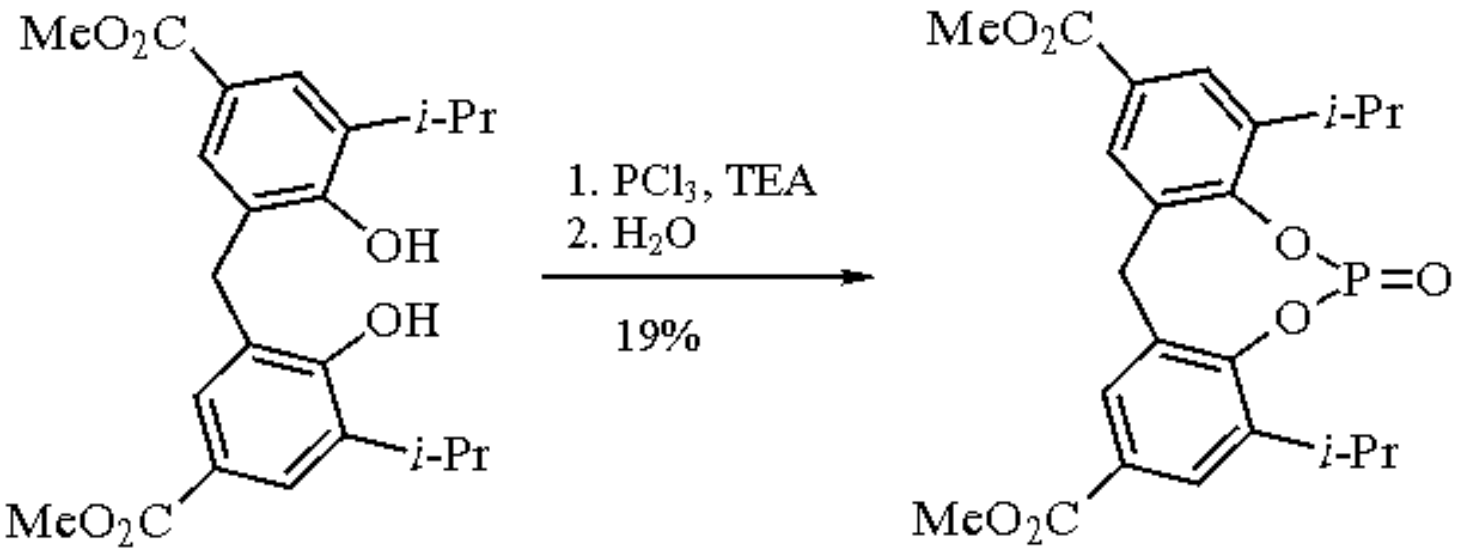

(1)

Dihydroxyarenes yield dioxaphospholes with PCl_3.[7] A special subclass of phosphite reactions are phosphitylations. Dichlorophosphite derived from PCl_3 and an alcohol, epoxide, or $P(OMe)_3$ are common phosphitylation reagents. Replacement of the alcohol by an amine leads to dialkylaminodichlorophosphites and subsequent phosphoramidation of the substrate.[8] Direct phosphitylation with PCl_3 is useful with sterically hindered axial hydroxy functions which fail to phosphorylate with other reagents (eq 2).[9]

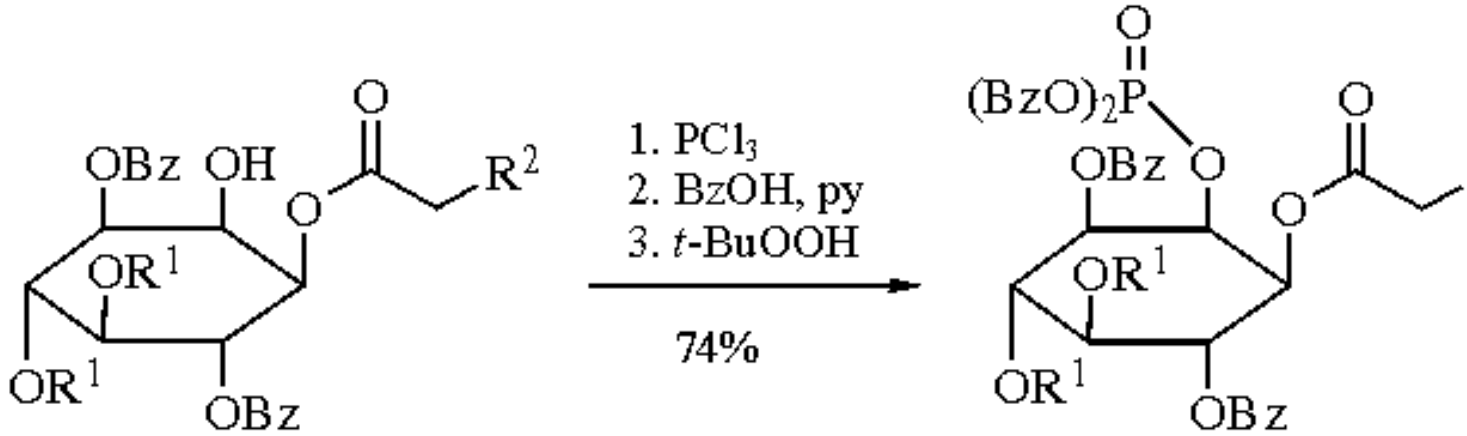

(2)

$R^1 = 4\text{-}MeOC_6H_4CO$, $R^2 = 1\text{-menthol}$

Oxidations.

Oxidation of PCl_3 with ozone,[10] diazomethane/chlorine,[11] or oxygen/ethylene,[12] produces $POCl_3$ or, in the latter two cases, phosphate esters.

Deoxygenations.

Sulfoxides,[13] amine *N*-oxides,[14] and hydroxy amides[15] are readily reduced with PCl_3 to the corresponding sulfides, amines, and amides. Alternative sulfoxide reducing agents include AcCl, RCOCl, I^-, Sn^{2+}, Fe^{2+}, $SiHCl_3$, $Si_2H_2Cl_2$, $LiAlH_4$, $NaBH_4/CoCl_2$, $BHCl_2$ (aliphatic >> aryl), Rh/H_2, $Pd/C/H_2$, $Fe(CO)_5$, $TiCl_3$, TMSI, TMSBr, I_2, and $PhSiMe_3$. The presence of active hydrogens will complicate attempts to reduce amine *N*-oxides. Amine *N*-oxides can also be reduced using H_2SO_3, Raney Ni, $Pd/C/H_2$, and R_3P (R = alkyl or aryl).

Amines.

Reaction of PCl_3 with quaternary ammonium salts yields phosphaindolizines and thiazolodiazaphospholes.[16] Imines produce phosphonates[17] whereas hydrazones are converted to pyrazoles, indoles, and nitriles.[18] Nitrones undergo rearrangement to secondary or tertiary amides[19] and primary alkylnitro compounds are reduced to nitriles (eq 3).[20] Diazonium salts are transformed to phosphonic acids.[21]

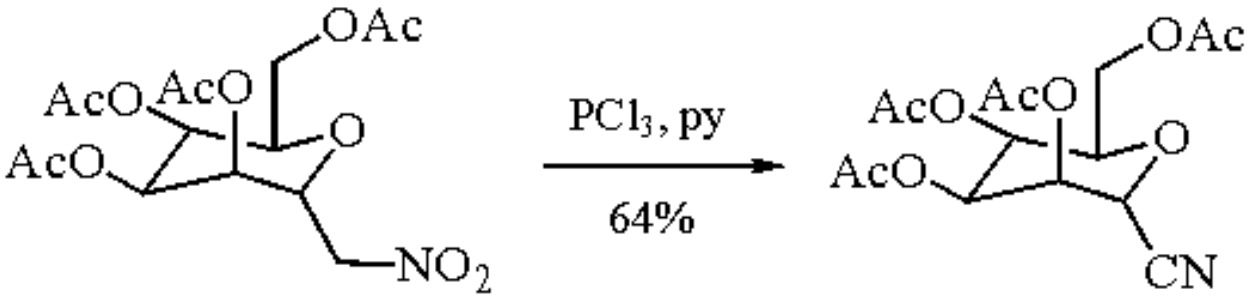

(3)

Reaction with Organometallic Compounds.

Organomagnesium (eq 4),[22,23] lithium,[24] and other main group metals[25] readily undergo ligand transfer with PCl_3 to form mono-, di-, or trialkyl(aryl) phosphines. A subclass of reactions include ***Aluminum Chloride***-assisted transformations to form phosphetanes (eq 5).[26]

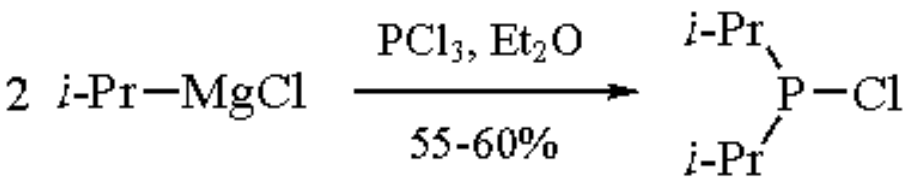

(4)

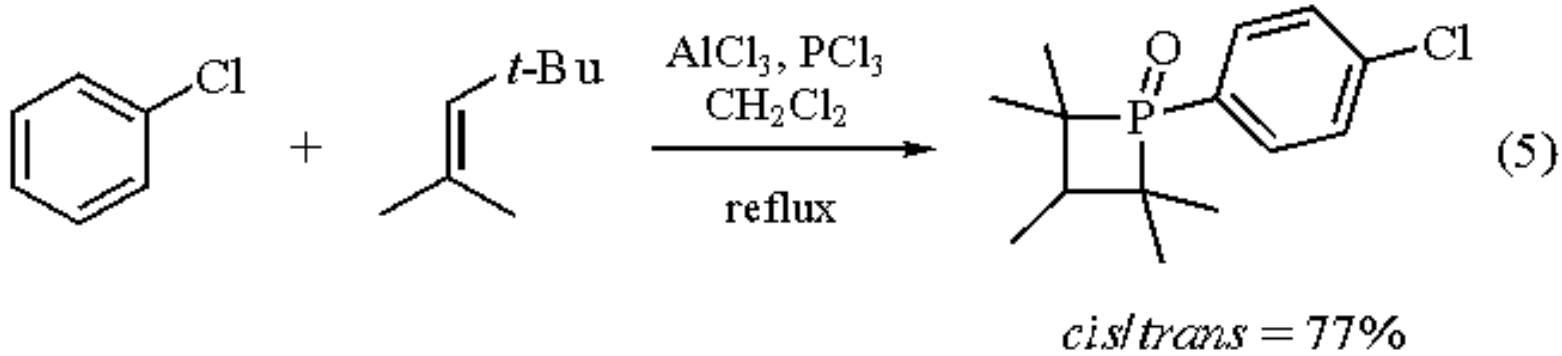

Enols and Ketene Silyl Acetals.

Reaction of a silyl enol ether with PCl_3/***Zinc Chloride*** leads to the formation of dichlorophosphine addition products (see also ***Phosphorus(III) Chloride-Zinc(II) Chloride***). Ketene silyl acetals react directly with PCl_3 under very mild conditions to form similar addition products (eq 6).[27]

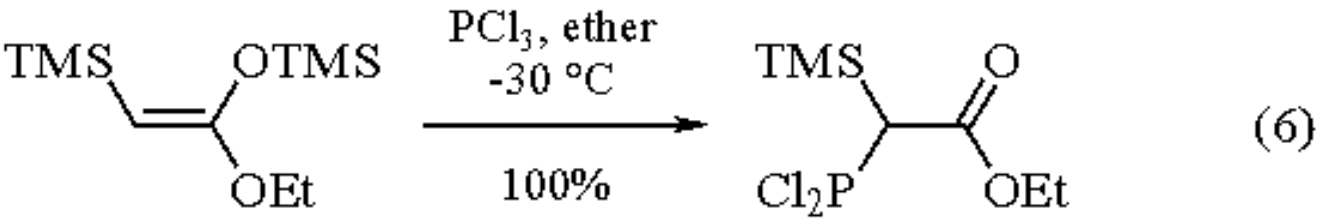

Ligands.

Synthesis of some phosphorus-containing ligand molecules have utilized PCl_3 as a key reagent for introduction of the phosphorus atom.[28]

Related Reagents.

Acetyl Chloride; ***Bromotrimethylsilane***; ***N-Chlorosuccinimide-Dimethyl Sulfide***; ***Dichloroborane Diethyl Etherate***; ***Hydrogen Chloride***; ***Iodine***; ***Iodotrimethylsilane***; ***Lithium Aluminum Hydride***; ***Pentacarbonyliron***; ***Phosphorus(V) Chloride***; ***Phosphorus Oxychloride***; ***Sodium Borohydride***; ***Thionyl Chloride***; ***Titanium(III) Chloride***; ***Trichlorosilane***; ***Triphenylphosphine Dichloride***; ***Triphenylphosphine-Hexachloroacetone***.

---

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26. (a) Lochschmidt, S.; Mathey, F.; Schmidpeter, A. *TL* **1986**, *27*, 2635. (b) Yao, E.; Szewczyk, J.; Quin, L. D. *S* **1987**, 265.
27. Pellon, P.; Hamelin, J. *TL* **1986**, *27*, 5611.
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Phosphorus(V) Chloride[1]

PCl_5

[10026-13-8] · Cl_5P · Phosphorus(V) Chloride · (MW 208.22)

(chlorination of alcohols,[2] carboxylic acids,[3] amides,[4] aldehydes, ketones, and enols; Bischler-Napieralski synthesis of 3,4-dihydroisoquinolines;[5] Beckmann rearrangement of oximes[6])

Alternate Name: phosphorus pentachloride.

Physical Data: mp 179-181 °C (sublimes); *d* 1.6 g cm^{-3}.

Solubility: sol CS_2, CCl_4. Typical solvents for reactions which use PCl_5 are CCl_4, $CHCl_3$, CH_2Cl_2, hexane, decane, benzene, toluene, and diethyl ether.

Form Supplied in: white to pale yellow solid; widely available. In the solid state, PCl_5 exists in the ionic form, $[PCl_4]^+$ $[PCl_6]^-$.

Purification: by vacuum sublimation.[7]

Handling, Storage, and Precautions: reacts with moisture to liberate hydrochloric acid and phosphoric acids. It is extremely corrosive to the skin, eyes, and mucous membranes. It should be stored in a dry area in containers impervious to moisture and resistant to corrosion. Laboratory quantities may be stored in polyethylene bags placed within glass containers. This reagent should be used in a fume hood.

Chlorides from Alcohols and Phenols.

Alcohols are converted to alkyl chlorides with the formation of 1 equiv of HCl and $POCl_3$ by the action of PCl_5.[2] The stability of the substrate and product to acidic reaction conditions and the ease by which the product can be separated from the reaction byproducts greatly influences the suitability of PCl_5 for this functional group transformation. Depending upon the structure of the alcohol, dehydration to form an alkene[8] or rearrangement[9] may be significant competing processes. The conversion of the 3-hydroxymethyl cephalosporin to the 3-chloromethyl derivative[10] shown in eq 1 illustrates the use of PCl_5 for the chlorination of a primary alcohol with a substrate of considerable functional complexity and lability.

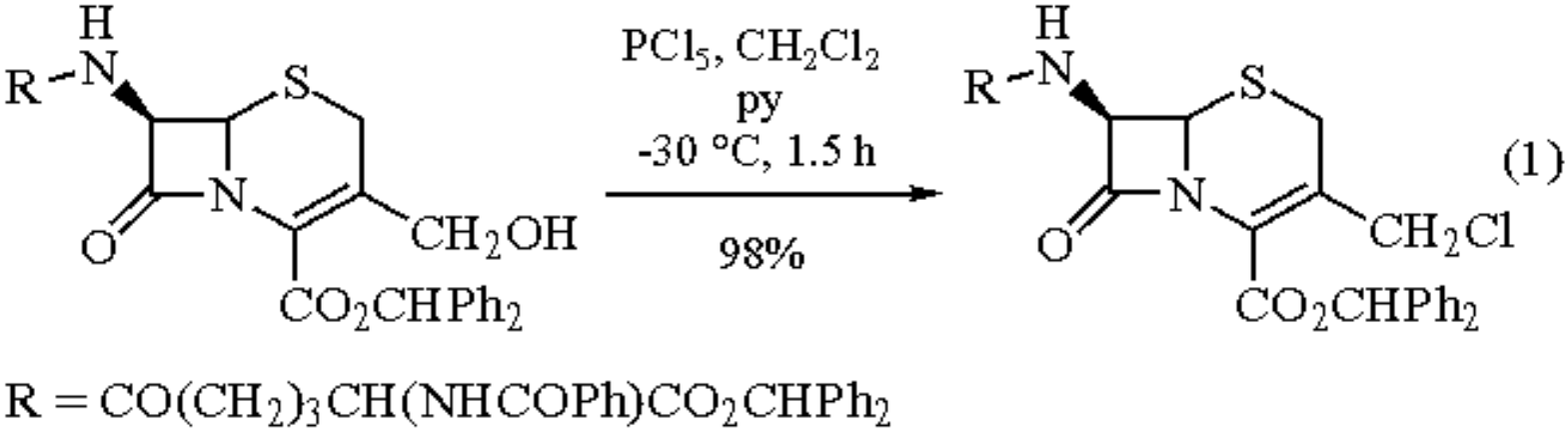

In select cases, secondary alcohols undergo chlorination with inversion of configuration upon reaction with PCl_5 (eq 2).[11]

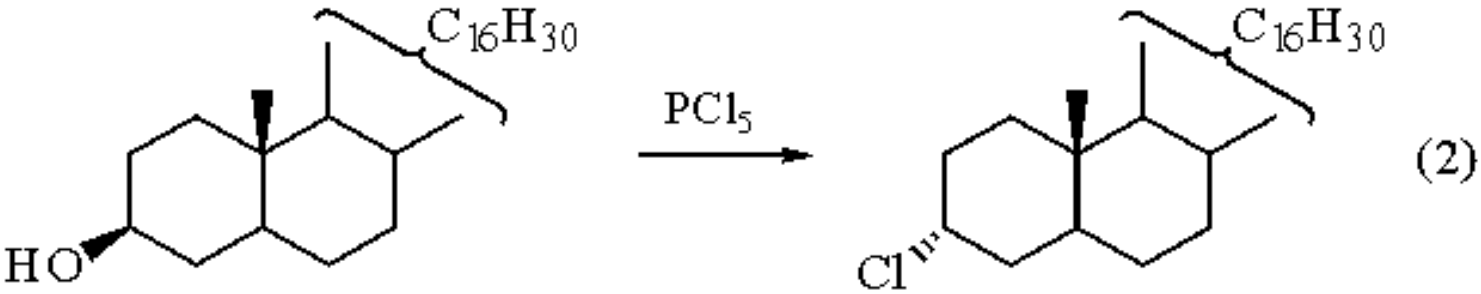

Tertiary alcohols are converted to tertiary chlorides under mild conditions with retention of configuration, presumably through an S_N1, tight ion-pair mechanism (eq 3).[12] The reactions are complete within minutes of mixing the tertiary alcohol with PCl_5 in $CHCl_3$ or ether at 0 °C in the presence of calcium carbonate. Chlorination of 1,1,1-trifluoro-2-(trifluoromethyl)-3-butyn-2-ol with PCl_5 leads to 1-chloro-3,3-bis(trifluoromethyl)allene (eq 4).[13] This tertiary alcohol is unreactive towards $SOCl_2$, $POCl_3$, PCl_3, concd. HCl, and $POCl_3$/pyridine. Phenols substituted with strong electron-withdrawing groups can be converted to aryl chlorides with PCl_5.[14]

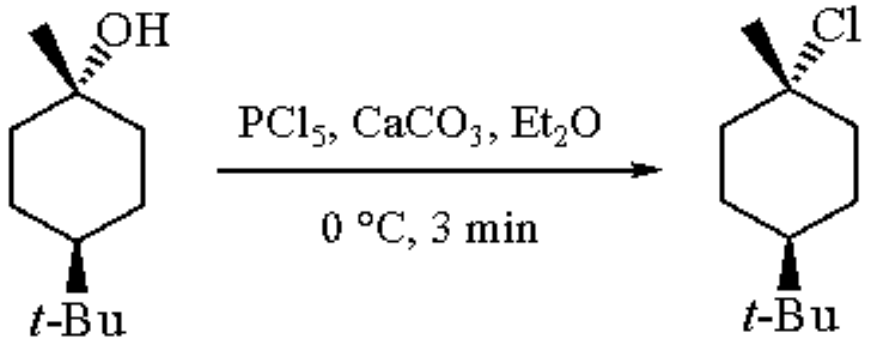

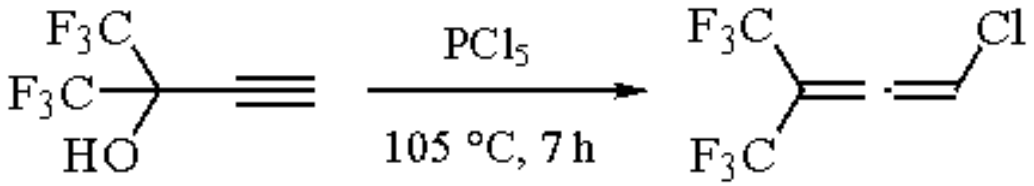

A polymer-supported form of PCl_5 has been developed by slurrying PCl_5 with Amberlite IRA 93 resin in CCl_4.[15] The resulting resin is effective for the chlorination of primary and secondary alcohols in yields of 70-98%. Some elimination products are observed with secondary alcohols. The reaction may be conducted in hydrocarbon, ether, or halogenated hydrocarbon solvents. The phosphorus byproducts are retained on the resin and separated from the product by filtration. Regeneration of the resin is possible by washing with aqueous acid and base. Acid-sensitive substrates are susceptible to degradation.

Carboxylic Acid Chlorides from Acids.

PCl_5 may be employed for the conversion of carboxylic acids to their acid chlorides.[16] Typically, the acid is combined with PCl_5 either neat[17] or in solvents such as ether[18] or benzene.[19] The use of PCl_5 is most convenient when the product can be isolated by direct crystallization[20] or distillation[21] from the crude reaction mixture. In some cases, aqueous workups may be employed to remove acidic byproducts without significant hydrolysis.[22] Because of the difficulties associated with separating the acid chloride from the byproduct $POCl_3$, the use of PCl_5 for this functional group transformation has largely been supplanted by $SOCl_2$, $COCl_2$, or $(COCl)_2$,[23] particularly in conjunction with catalytic amounts of DMF.[24] The polymer-supported form of PCl_5,[15] described above for the chlorination of alcohols, also converts carboxylic acids to the corresponding acid chlorides in 48-91% yields.

Nitriles from Amides.

Primary amides are dehydrated to afford nitriles upon heating with PCl_5.[4a-e] Due to the severity of the reaction conditions, substrates of limited functional complexity are tolerated. The reactions are generally conducted either neat[25] or with $POCl_3$[26] as a solvent. This method is useful for products which can be isolated by distillation from the crude reaction mixture. Secondary amides, most notably *N*-alkylbenzamides, when subjected to PCl_5 may undergo the von Braun degradation to produce a benzonitrile and an alkyl chloride.[27]

Chloromethyleneiminium Chlorides and Imidoyl Chlorides from Amides, Oximes, Hydroxamic Acids, and Ureas.

Tertiary amides react with PCl_5 to afford chloromethyleneiminium chlorides,[4d,g-i] whereas secondary amides afford imidoyl chlorides.[4d-f,j] In each case, $POCl_3$ and HCl are generated as reaction byproducts. The amide chlorides and imidoyl chlorides are frequently used as intermediates for subsequent chemical transformation and are not isolated. When desired, isolation has been accomplished by either distillation or crystallization. In choosing PCl_5 as a reagent for this transformation, consideration must be given to the acid lability and reactivity of the substrate. Depending upon the substrate and reaction conditions, the formation of imidoyl chlorides by the action of PCl_5 may be accompanied by further reaction to produce a nitrile and alkyl chloride via the von Braun degradation.[27] α-Chlorination can be a problem if excess PCl_5 is used, and self-condensation can occur at elevated temperatures if an α-CH is present in the imidoyl chloride.[4g] The presence of a strong electron-withdrawing group α to the amide carbonyl can influence the course of the chlorination of an amide with PCl_5, as seen by the formation of the diazadiphosphetidine (eq 5) when *N*-methyltrifluoroacetamide is reacted with PCl_5.[28]

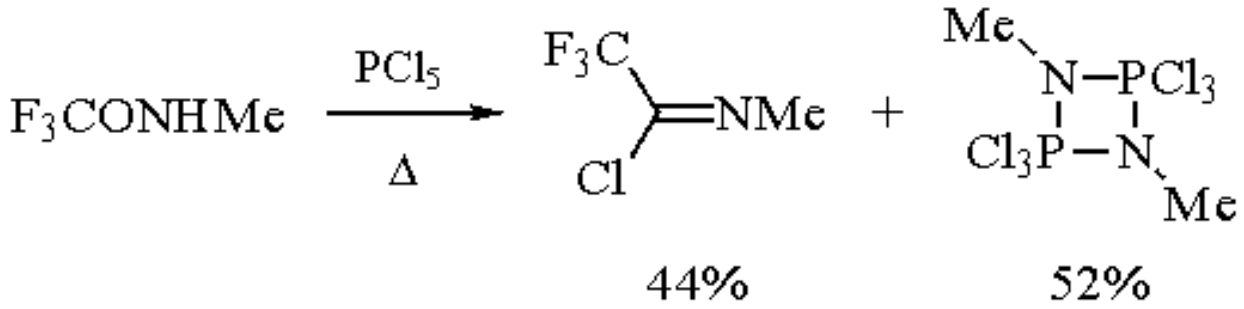

(5)

A highly practical example of the reaction of PCl_5 with a tertiary amide is the synthesis of ***Dimethylchloromethyleneammonium Chloride***, the Vilsmeier reagent. This salt is obtained in 88% yield by the careful addition of PCl_5 to ***N,N-Dimethylformamide*** while allowing the reaction to exotherm to 100 °C followed by cooling to 0 °C, filtration, and washing.[29] The Vilsmeier reagent is useful for the chlorination of alcohols and acids.

PCl_5 has found considerable application for the removal of amide side chains[30] in the industrial scale manufacture of semisynthetic cephalosporins[31] and penicillins.[32] The intermediate imidoyl chlorides, produced by the action of PCl_5 on a secondary amide, are converted to imino ethers upon the introduction of an alcohol to the reaction mixture. The imino ethers undergo further reaction to afford the deprotected C(7)-amino cephalosporin or C(6)-amino penicillin.[33]

Iminium and imidoyl chlorides have a prominent position as intermediates for the synthesis of heterocyclic compounds. In this regard, PCl_5 has found extensive application. Imidoyl chlorides derived from the treatment of *N*-(2-phenylethyl)carboxamides with PCl_5 can undergo Bischler-Napieralski cyclization[5] to form 3,4-dihydroisoquinolines (eq 6).[34] In addition to PCl_5, this cyclization has been effected with P_2O_5, $POCl_3$, $POCl_3$ in refluxing xylene or decalin, P_2O_5 in pyridine, and polyphosphoric acid. *N,N´*-Disubstituted oxamides (eq 7)[35] and the imines or hydrazones of α-acylamino ketones (eq 8)[36] react with PCl_5 to form imidoyl chlorides which undergo subsequent intramolecular cyclization to produce imidazoles.

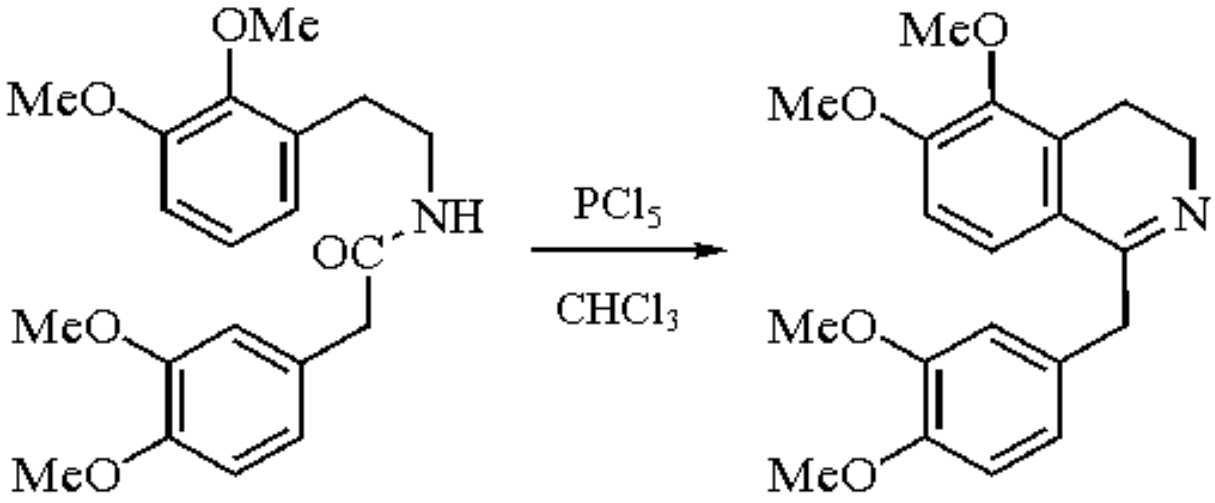

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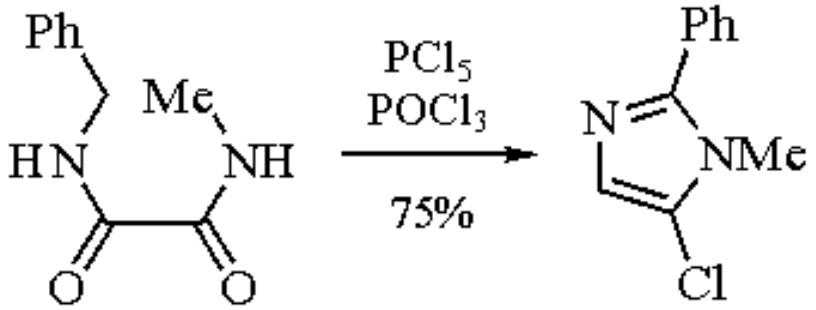

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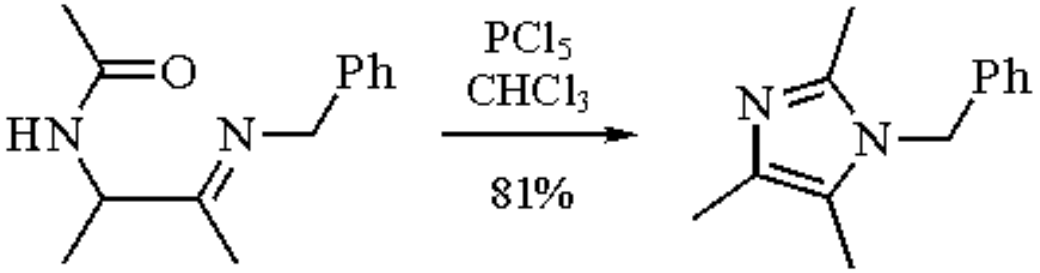

(8)

The reaction of oximes with PCl_5 can lead to imidoyl chlorides via Beckmann rearrangement.[6] The reaction is frequently conducted in ether at or below ambient temperature. Aromatic, hydrocarbon, and halogenated hydrocarbon solvents are also used. The oxime of 4-phenyl-3-methyl-3-buten-2-one undergoes Beckmann rearrangement within 5 to 15 min upon treatment with PCl_5 in decalin at 0 °C to give an imidoyl chloride.[37] Subsequent treatment with P_2O_5 at reflux affords 1,3-dimethylisoquinoline (eq 9). 2-(Oximino)indan-1-ones afford 1,3-dichloroisoquinolines when subjected to 1 equiv of PCl_5 in $POCl_3$ followed by treatment with anhydrous HCl and then a second equiv of PCl_5 (eq 10).[38] Treatment of an oxime which contains an α-alkoxy, α-alkylthio, or α-alkylamino group with PCl_5 can lead to second-order Beckmann rearrangement,[39] as exemplified in eq 11.[40]

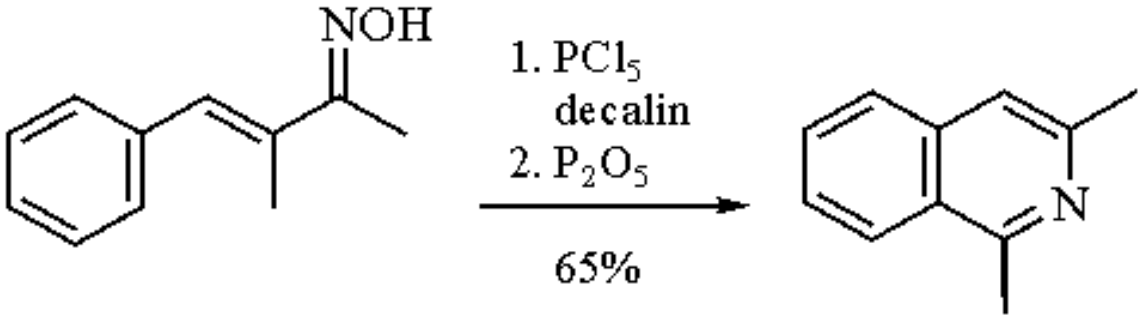

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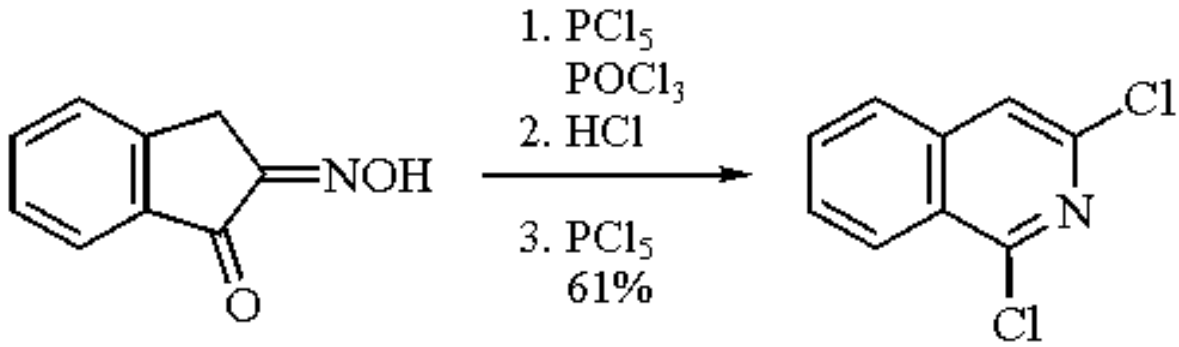

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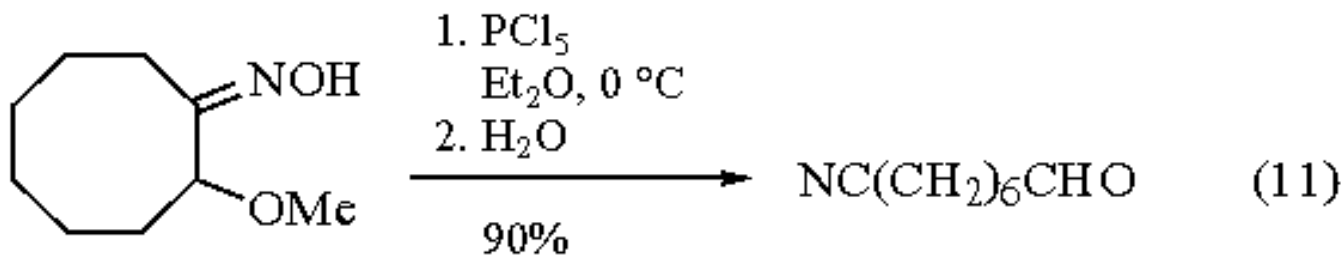

The reaction of alkylbenzohydroxamates with PCl_5 in ether offers a general preparative method for the synthesis of *O*-alkylbenzohydroximoyl chlorides.[41] Ketenimines[42] can be derived by the treatment of secondary amides bearing a single α-CH with PCl_5 followed by dehydrohalogenation with triethylamine.[43] Alkoxycarbonylimidoyl chlorides are obtained by the reaction of the esters of *N*-acylcarbamic acids with PCl_5.[44] *N,N´*-Dialkylureas in which the alkyl groups are primary react with PCl_5 to form 1,3-diaza-2-P^V-phosphetidinones, whereas chloroformamidinium chlorides are produced when the alkyl groups are secondary.[45] *N*-Alkyl-*N*-nitrosamides undergo rearrangement to the corresponding *N*-alkyloxamides via an intermediate *N*-nitrosochloroiminium chloride upon reaction with PCl_5.[46]

gem-Dichlorides from Ketones, Aldehydes, and Esters.

Ketones and aldehydes may be converted into *gem*-dichlorides by the action of PCl_5.[47] Formate esters[48] and esters with strong electron-withdrawing groups α to the carbonyl[47] react with PCl_5 to give the corresponding *gem*-dichlorides. Conversions have been effected either neat,[49] or with PCl_3,[50] $POCl_3$,[51] or halogenated hydrocarbons[52] as solvents. The reaction rate and product distribution are influenced by the solvent employed.[52a,b] Polar solvents, such as nitromethane and acetonitrile, greatly retard the reaction. The presence of an α-CH group can lead to the formation of vinyl chlorides as frequent byproducts.[52a,53] Perhaloacetones are resistant to chlorination with PCl_5 under the typical conditions employed for this conversion; however, the *gem*-dichlorides can be obtained in modest yields upon heating at 275-300 °C in an autoclave.[54]

Vinyl Chlorides from Enols.

PCl_5 reacts with the enolic form of enolizable cyclic[55] and acyclic[56] carbonyls to form vinyl chlorides. A side-reaction encountered with esters has been formation of the acid chloride, in which case reesterification during the reaction workup affords improved yields (eq 12).[55] Hydroxypyridines,[57] hydroxyquinolines,[58] and hydroxyisoquinolines[38] are converted to chloropyridines, chloroquinolines, and chloroisoquinolines by the action of PCl_5.

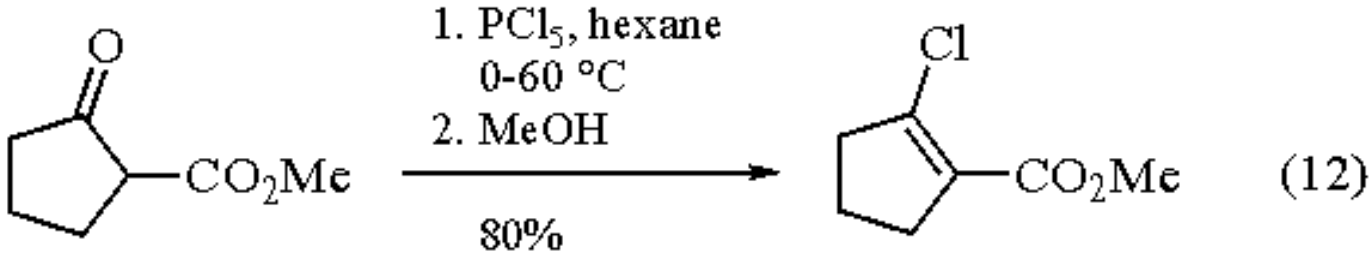

Other Applications.

Alkanes,[59] arylalkanes,[59a] heteroaromatics,[60] and alkenes[59,61] have been chlorinated with PCl_5 to afford chloro alkanes, chloro aromatics and *vic*-dichlorides. The use of PCl_5 as a catalyst for the chlorination of alkanes, cycloalkanes, and arylalkanes has been reported.[62] Secondary nitriles are α-chlorinated when subjected to PCl_5 either neat[63] or in an inert solvent such as CCl_4 or $CHCl_3$.[64] Anhydrides are converted to diacid chlorides by the action of PCl_5.[65] Sulfonyl and sulfamoyl chlorides may be prepared by heating the corresponding acid[66] or acid salt[67] either neat or in an inert solvent with PCl_5. PCl_5 has been used to deoxygenate *N*-oxides,[68] hydroxylamines,[69] and sulfoxides.[70] Hydroxylamines in which the α-carbon is tertiary can undergo the Stieglitz rearrangement to afford imines when treated with PCl_5.[71] Highly fluorinated carbinols bearing an α-CH, which prove resistant to the action of $SOCl_2$, SO_2Cl_2, HCl, and $ZnCl_2$, are converted to alkenes by the action of PCl_5.[72] Cyclic acetals of α-keto acids, when reacted with PCl_5 in CH_2Cl_2, afford esters of halohydrins.[73] Glyoxal bis-acetals are converted to 1,2-dichloro-1,2-dialkoxyethanes by the action of PCl_5.[74] This has been developed into a procedure for the synthesis of alkynic diethers.[75] Imines have been converted into amides upon heating with PCl_5, either neat or in a solvent such as xylene, followed by treatment with water.[76] A method has been developed for the synthesis of alkyl chlorides by the reaction of PCl_5 with the alkyl salicylates.[77] The yields are higher in several cases for this procedure when compared to other methods for the chlorination of alcohols; however, synthesis of the alkyl salicylate is required.

Related Reagents.

Oxalyl Chloride; ***Phosphorus(III) Chloride***; ***Phosphorus(V) Oxide***; ***Phosphorus Oxychloride***; ***Thionyl Chloride***; ***Triphenylphosphine-Carbon Tetrachloride***; ***Triphenylphosphine Dichloride***; ***Dimethylchloromethyleneammonium Chloride***.

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Phosphorus(III) Chloride-Zinc(II) Chloride

PCl_3-$ZnCl_2$

(PCl_3)

[7719-12-2] · Cl_3P · Phosphorus(III) Chloride-Zinc(II) Chloride · (MW 137.32) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Phosphorus(III) Chloride-Zinc(II) Chloride · (MW 136.29)

(preparation of aminodiphosphonic acids,[1] trialkylphosphines,[2] and arylphosphonic acids;[3] conversion of alcohols to alkyl chlorides[4])

Physical Data: see entries for ***Phosphorus(III) Chloride*** and ***Zinc Chloride***.

Handling, Storage, and Precautions: freshly fused $ZnCl_2$ is used in most cases.

Phosphorylation.

PCl_3 and $ZnCl_2$ can be used to prepare phosphonic acids and trisubstituted phosphines. Aminodiphosphonic acids can be formed by the reaction of nitriles and PCl_3 in the presence of a Lewis acid. In particular, HCN can be converted to (aminomethylene)diphosphonic acid by reaction of PCl_3 and $ZnCl_2$ (eq 1).[1] A proton source such as HCl is required.

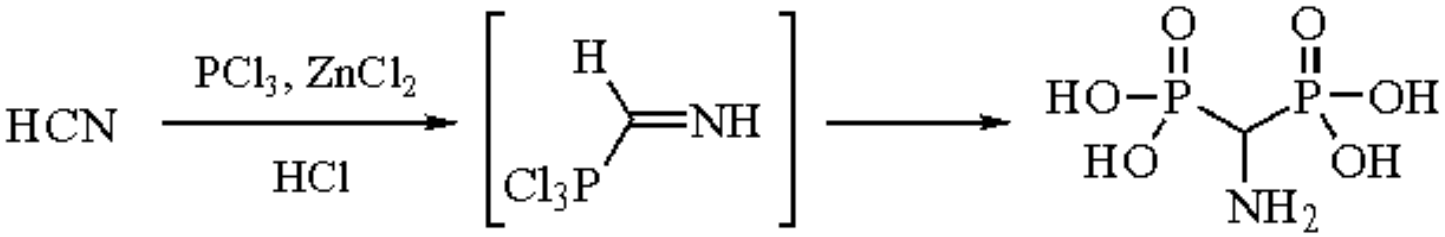

(1)

Arylphosphonic acids and diarylphosphonic acids can also be obtained by reacting diazonium salts with PCl_3.[5] Although diazonium tetrafluoroborates are most often used, because of their stability and ease of isolation, diazonium chlorozincates (zinc chloride double salts of diazonium chlorides) can be used to prepare the arylphosphonic acids. Thus diazonium chlorozincate is reacted with PCl_3 in the presence of Cu^I to afford the arylphosphonium salt. Arylphosphonic acids are formed after aqueous workup (eq 2).[3] Use of diazonium chlorozincates does not offer any advantages over use of the tetrafluoroborate salts.

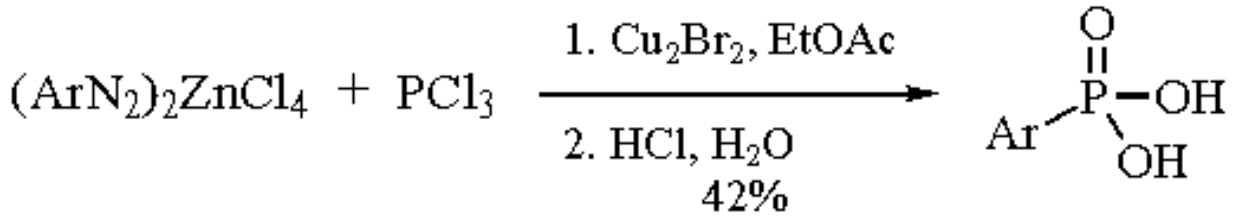

(2)

Tertiary phosphines can be prepared by the Friedel-Crafts reaction of aromatic compounds with PCl_3 in the presence of $ZnCl_2$. When 3 equiv of aromatic compound are utilized, triarylphosphines are produced.[6] However, if 1 equiv of aromatic compound is used, the aryldichlorophosphine is formed. These aryldichlorophosphines can be hydrolyzed to give arylphosphonous acids, or reacted with 2 equiv of Grignard reagent to give unsymmetrical trisubstituted phosphines (eq 3).[2]

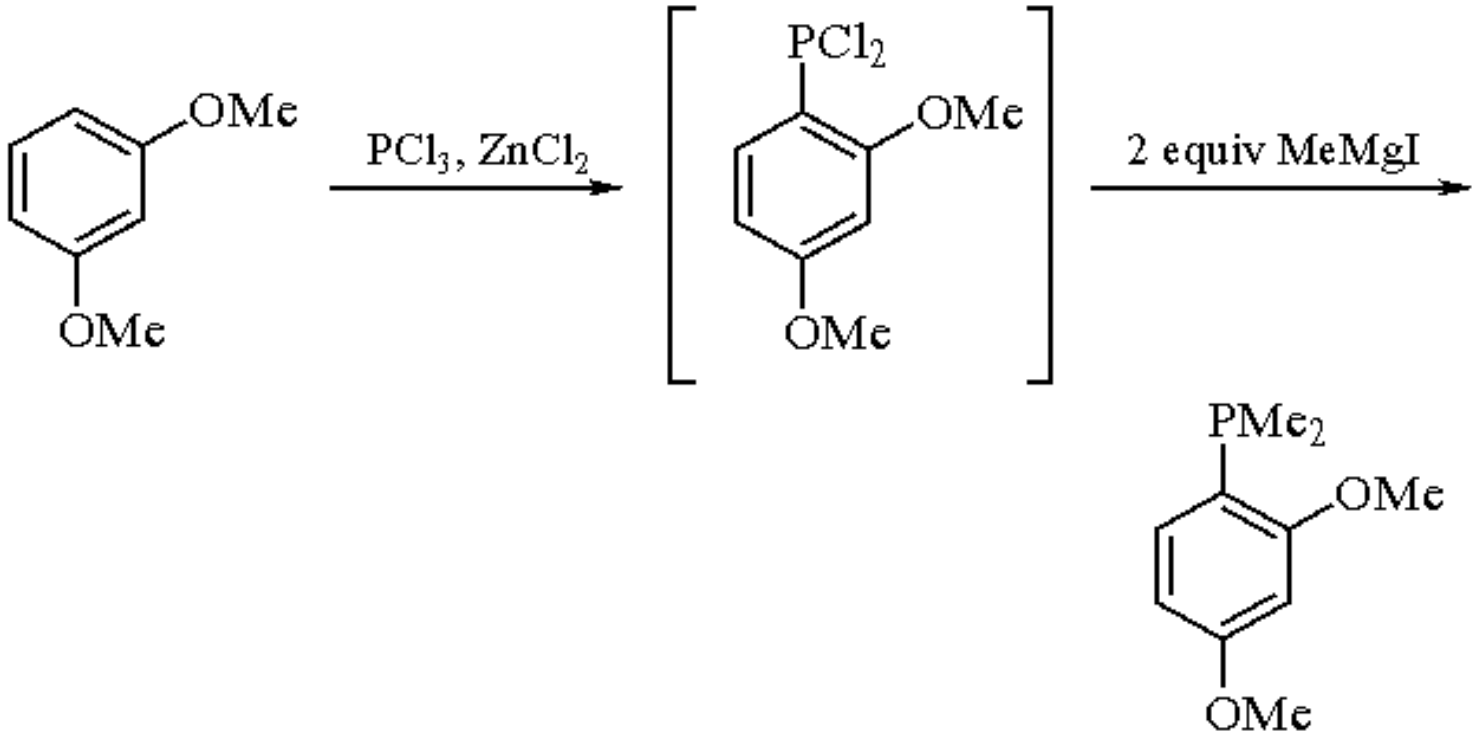

(3)

Chlorination.

Conversion of an alcohol to an alkyl chloride can also be accomplished with PCl_3 and $ZnCl_2$. Although this transformation is usually attained from simple alcohols with a number of reagents including $POCl_3$, conversion of *O*,*O*-diethyl *S*-(hydroxymethyl) phosphorodithioate to the chloromethyl phosphorodithioate is not successful when $POCl_3$ is used, and only dehydration occurs. Conversion of the hydroxymethyl to the chloromethyl phosphorodithioate can be accomplished in good yield (eq 4) by reaction of the alcohol with PCl_3 followed by addition of a catalytic amount of anhydrous $ZnCl_2$.[4] Other Lewis acid catalysts such as $SnCl_4$ are not as effective. Use of PCl_5 in inert solvents also gives chlorinated products.

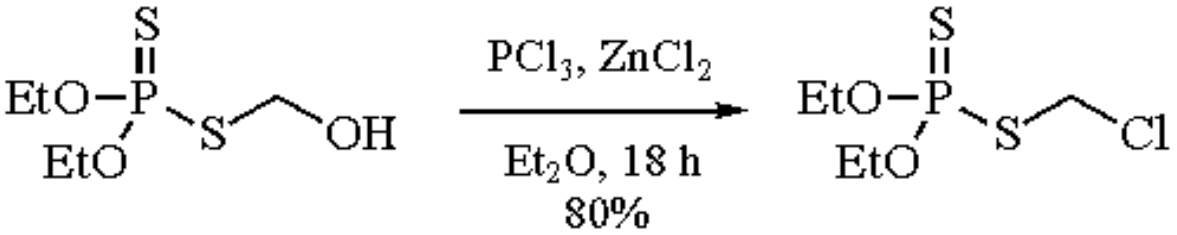

(4)

Related Reagents.

Phosphorus(V) Chloride; ***Phosphorus Oxychloride***.

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Phosphorus(III) Iodide

[13455-01-1] · I_3P · Phosphorus(III) Iodide · (MW 411.67)

(conversion of alcohols to iodides; deoxygenation of epoxides to alkenes; reduction of sulfoxides, selenoxides, selenones, ozonides, and α-halo ketones; elimination of β-hydroxy sulfides, dithioacetals, and orthothioesters or their selenium counterparts to form alkenes; conversion of aldoximes and nitro compounds to nitriles; cleavage of dimethyl acetals; water-soluble phosphorus byproducts are usually formed)

Alternate Name: phosphorus triiodide.

Physical Data: mp 61 °C.

Solubility: very sol CS_2; reacts with protic solvents.

Form Supplied in: red solid; widely available commercially.

Handling, Storage, and Precautions: commercial samples are generally suitable for use without purification; store under an inert atmosphere.

Conversion of Alcohols to Iodides.

PI_3 is a classic reagent for the conversion of iodides to alcohols. For example, cetyl alcohol is converted to 1-iodohexadecane in 85% yield by treatment with PI_3 (neat).[1] More recently, Krief and co-workers[2] found that a cyclopropyl carbinol (eq 1) is cleanly converted to the iodide with ring opening upon treatment with PI_3 (Et_3N, CH_2Cl_2, 0 °C, 0.5 h, 73%). ***Diphosphorus Tetraiodide***, a commercially available phosphorus halide which is in equilibrium with PI_3 in solution, is a more commonly employed reagent for the conversion of alcohols to iodides and effects many of the same transformations as PI_3.[3] See also ***Triphenylphosphine-Iodine*** for the conversion of alcohols to iodides.

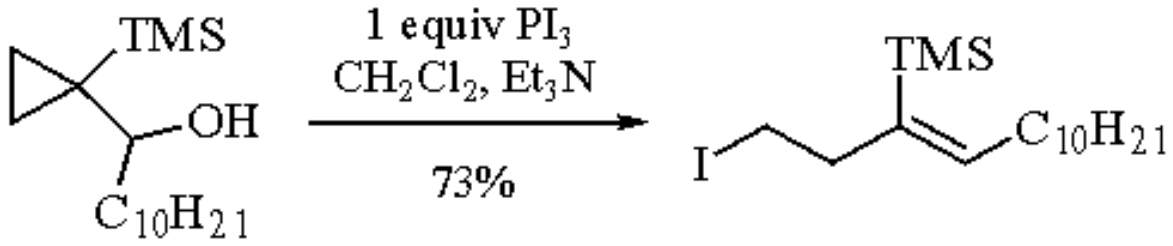

(1)

Deoxygenations and Reductions.

PI_3 has found use as a deoxygenating and reducing agent. Epoxides are stereospecifically deoxygenated to the corresponding alkenes in good yield and with retention of configuration. For example, the *cis*- and *trans*-epoxides shown in eq 2 are converted (CS_2, 20 °C, 6-8 h) to *cis*- and *trans*-9-octadecene in 83 and 90% yields, respectively.[4] Diphosphorus tetraiodide (P_2I_4) and ***Iodotrimethylsilane*** (TMSI) give similar results. A number of other methods for epoxide deoxygenation have been developed.[5]

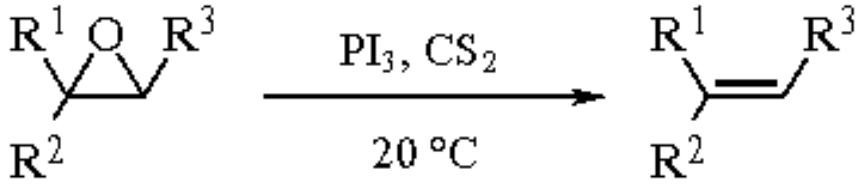

(2)

(a) $R^1, R^3 = (CH_2)_7Me$; $R^2 = H$; 83%
(b) $R^1 = H$; $R^2, R^3 = (CH_2)_7Me$; 90%

A variety of methods for the reduction of sulfoxides to sulfides are available.[6] PI_3 rapidly reduces aryl alkyl and dialkyl sulfoxides and selenoxides, usually at -78 °C (eq 3).[7] For example, treatment of ethyl phenyl sulfoxide with 1 equiv of PI_3 (CH_2Cl_2, -78 °C, 15 min) affords ethyl phenyl sulfide in 91% yield. Others have successfully employed this procedure.[8,9] Dialkyl sulfoxides generally react in somewhat lower yield. A phenyl vinyl sulfoxide (eq 3, entry c) requires ambient temperatures to react. Selenoxides behave similarly, and P_2I_4 can usually be used in place of PI_3.[10] Treatment of decyl phenyl selenone with PI_3 (CH_2Cl_2, 0 °C, 30 min) affords a mixture of the reduced product, decyl phenyl selenide (69%), and the substitution product, *n*-decyl iodide.[11]

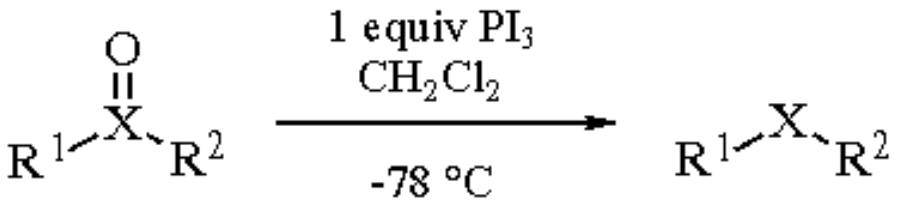

(3)

(a) X = S; R^1 = Ph; R^2 = Et; 91%
(b) X = S; R^1, R^2 = Pr; 71%
(c) X = S; R^1 = Ph; R^2 = CH=CHC_5H_{11}; 75%
(d) X = Se; R^1 = Ph; R^2 = $C_{10}H_{21}$; 93%
(e) X = Se; R^1 = Me; R^2 = CH(Me)C_6H_{13}; 87%

PI_3 can be used for the efficient reduction of an ozonide, as illustrated by the formation of the cyclopropanecarbaldehyde in eq 4.[12,13] An advantage over the traditional ***Triphenylphosphine*** reduction is the formation of water-soluble phosphorus byproducts from PI_3. It should be noted, however, that PI_3 is reported to react with certain aldehydes.[14]

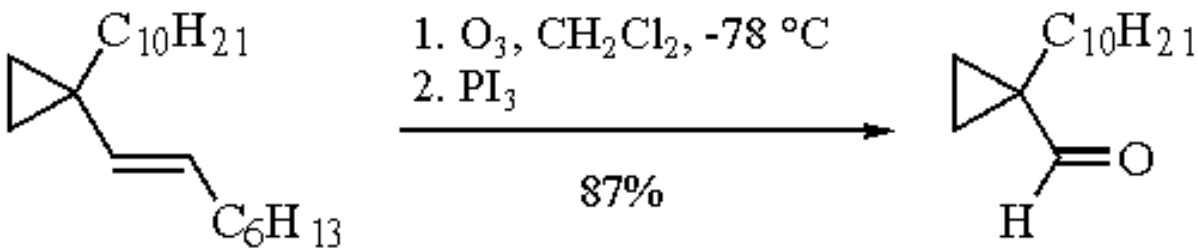

(4)

PI_3 is reported to dehalogenate α-bromo and α-iodo ketones.[15] For example, as shown in eq 5, 1-iodo-2-dodecanone is reduced to 2-dodecanone by PI_3 in CH_2Cl_2 (25 °C, 1 h, 89%). 1-Bromo-2-octanone affords 2-octanone in 75% yield (25 °C, 4.5 h). This PI_3 reduction can be coupled with the regioselective opening of terminal epoxides by TMSI and alcohol oxidation for a three-step transformation of a terminal epoxide to a methyl ketone.[15,16] P_2I_4,[15] triphenylphosphine,[17] ***1,3-Dimethyl-2-phenylbenzimidazoline***,[18] $PhSiH_3/Mo^0$,[19] ***Samarium(II) Iodide***,[20] ***Zinc-Acetic Acid***,[21] ***Iron-Graphite***,[22] ***Tri-n-butylstannane***,[23] ***Sodium O,O-Diethyl Phosphorotelluroate***,[24] lithium 2-thiophenetellurolates,[25] and a wide variety of other reagents[26,27] can also be used for the reduction of α-halo carbonyl compounds.

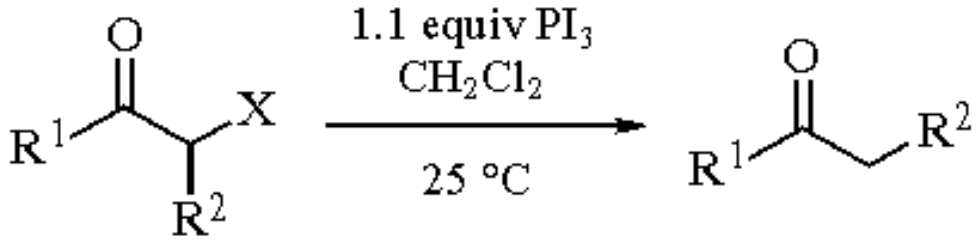

(5)

$R^1 = C_{10}H_{21}$, $R^2 = H$, $X = I$; 89%
$R^1 = C_6H_{13}$, $R^2 = H$, $X = Br$; 75%
$R^1, R^2 = C_8H_{17}$, $X = I$; 97%

Elimination Reactions.

PI_3 or P_2I_4 effects the stereospecific *anti*-elimination of β-hydroxy sulfides to alkenes.[28] For example (eq 6), treatment of the *anti*-β-hydroxy sulfide with PI_3 (CH_2Cl_2-Et_3N, 50 °C, 1.5 h) affords (*E*)-9-octadecene (93% yield). Treatment of the *syn*-isomer affords (*Z*)-9-octadecene (93% yield, *Z*:*E* = 94:6). Trisubstituted, but apparently not tetrasubstituted, alkenes can also be formed from the appropriately substituted β-hydroxy sulfides using these reagents. Similarly, β-hydroxy selenides undergo elimination to the corresponding alkenes. With these latter substrates, certain tetrasubstituted alkenes are accessible.[29] ***Methanesulfonyl Chloride***/Et_3N[30] and *N*-ethyl-2-fluoropyridinium tetrafluoroborate/lithium iodide[31] are alternative reagents.

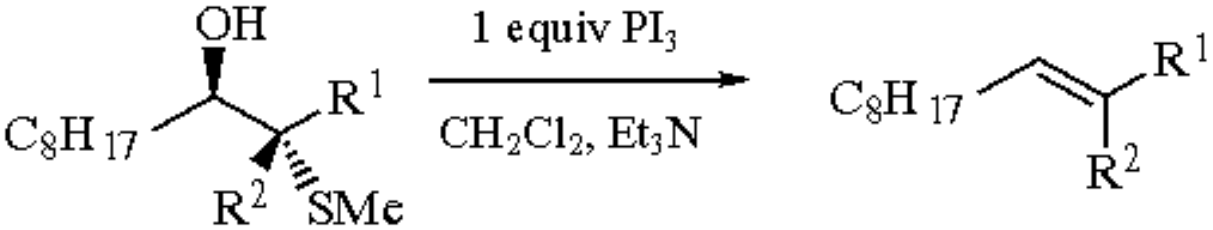

(6)

anti; $R^1 = C_8H_{17}$, $R^2 = H$ (*E*) isomer, 93%
syn; $R^1 = H$, $R^2 = C_8H_{17}$ (*Z*) isomer, 90%

Vinyl sulfides and ketene dithioacetals[32] are available via treatment of β-hydroxy thioacetals and β-hydroxy orthothioesters with PI_3 or P_2I_4.[33] For example (eq 7), treatment of the β-hydroxy orthothioester (entry a) with PI_3 (CH_2Cl_2-Et_3N, 0 °C, 0.5 h) affords the thioketene acetal (**1**) in 69% yield. With certain substitution patterns the rearranged product (**2**) competes (e.g. entry b) or is the predominant product (e.g. entry c). The rearrangement is less of a problem with the corresponding β-hydroxy orthoselenoester (i.e. entry c vs. entry d). ***Thionyl Chloride*** is also a useful reagent in some cases.

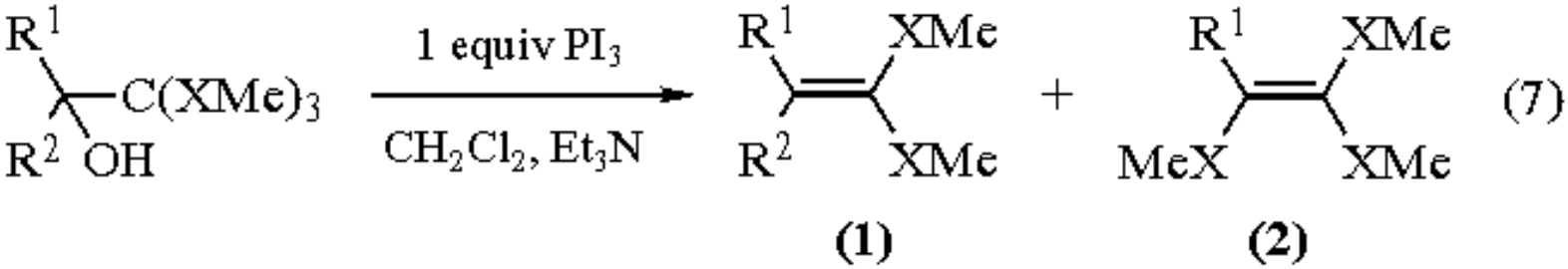

(a) $R^1 = c\text{-}C_3H_5$, $R^2 = Me$, X = S (1):(2) = 69: 0
(b) $R^1 = C_5H_{11}$, $R^2 = H$, X = S (1):(2) = 63:13
(c) $R^1 = Ph$, $R^2 = H$, X = S (1):(2) = 7:68
(d) $R^1 = Ph$, $R^2 = H$, X = Se (1):(2) = 86: 0

Vinyl sulfides and ketene thioacetals[32] are also available via treatment of thioacetals and orthothioesters with PI_3 or P_2I_4 (eqs 8 and 9).[34] The corresponding seleno analogs are similarly available. For example (eq 8), treatment of the trimethyl orthoselenoester with PI_3 (CH_2Cl_2-Et_3N, 20 °C, 1 h) affords the ketene selenoacetal in 90% yield. ***Tin(IV) Chloride*** or ***Titanium(IV) Chloride*** in combination with ***Diisopropylamine*** is also effective for the transformation of orthothioesters and orthoselenoesters to ketene acetal derivatives.[35] ***Copper(I) Trifluoromethanesulfonate***,[36] ***Mercury(II) Trifluoroacetate***/***Lithium Carbonate***,[37] and ***Benzenesulfenyl Chloride***[38] are useful reagents for the conversion of dithioacetals to vinyl sulfides.

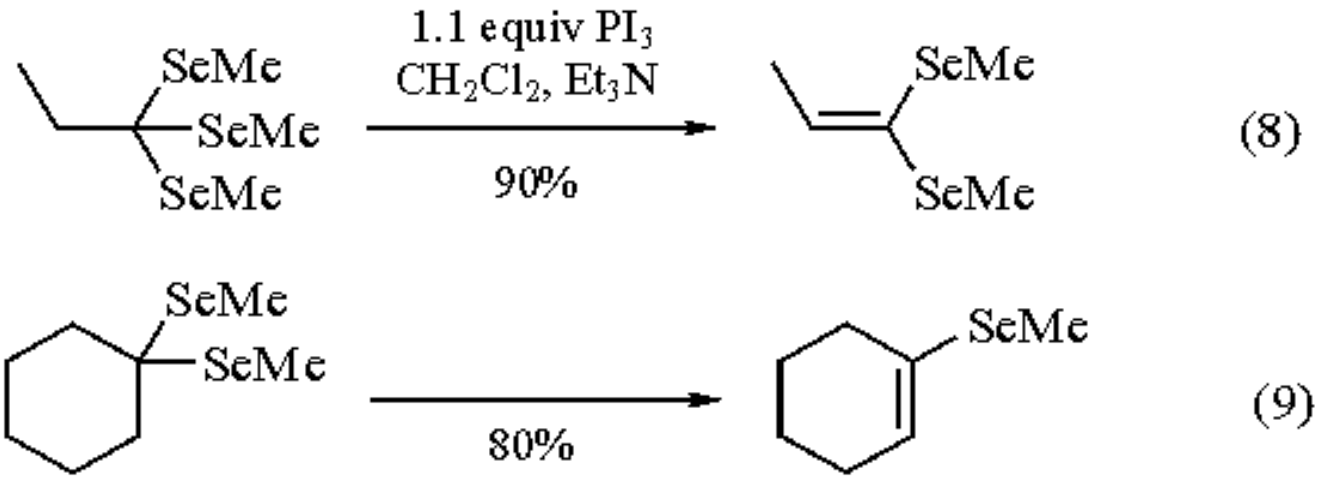

In the presence of ***Triethylamine***, PI_3[7] or P_2I_4[10] effects the conversion of aldehyde oximes or primary nitro compounds to nitriles. For example, treatment of the aldoxime derived from phenylacetaldehyde with 1 equiv of PI_3 (CH_2Cl_2-Et_3N, 25 °C, 15 min) affords benzyl cyanide in 83% yield (eq 10). Similarly, treatment of 1-nitrodecane with 2 equiv of PI_3 (CH_2Cl_2-Et_3N, 25 °C, 15 min) affords 1-cyanononane (82%) (eq 11). Other reagents for the direct conversion of primary nitro compounds to nitriles include $Sn(SPh)_4$/Ph_3P/DEAD,[39] TMSI,[40] ***Sulfur Dioxide***/Et_3N,[41] and ***Phosphorus(III) Chloride***.[42]

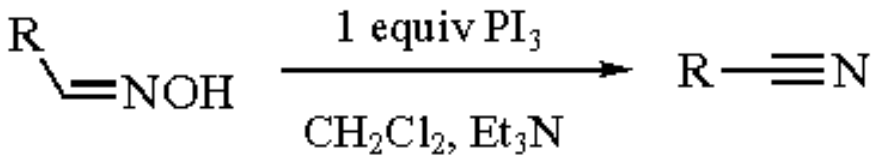

(10)

$R = PhCH_2$, 83%
$R = C_{10}H_{21}$, 85%

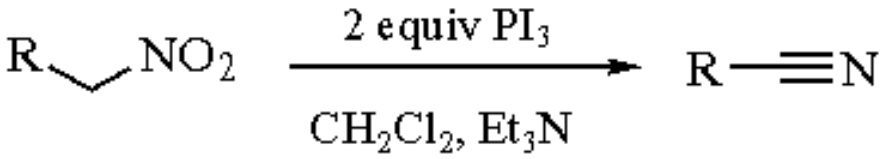

(11)

$R = C_9H_{19}$, 82%

Miscellaneous Transformations.

PI_3 has been used for the cleavage of dimethyl acetals under nonaqueous conditions.[43] For example (eq 12), treatment of the dimethyl acetal derived from 2-decanone with PI_3 (CH_2Cl_2, 20 °C, 15 min; aq workup) affords the ketone in 85% yield. Alternative nonaqueous acetal cleavage reagents include P_2I_4,[43] TMSI,[44,45] ***Diiodosilane***,[46] $TiCl_4$/***Lithium Iodide***,[47] ***Bromodimethylborane*** or bromodiphenylborane,[48] and ***Samarium(III) Chloride***/***Chlorotrimethylsilane***.[49]

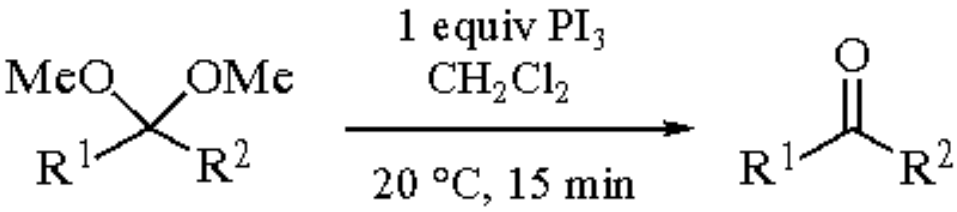

(12)

(a) $R^1 = C_9H_{19}$, $R^2 = Me$, 85%
(b) $R^1 = C_8H_{17}$, $R^2 = H$, 57%

PI_3 is a useful ***Hydrogen Iodide*** precursor in the silica- and alumina-mediated additions of HI to alkenes.[50,51] PI_3 has also found use as a source of electrophilic phosphorus in the synthesis of novel organophosphorus compounds (e.g. $(CF_3)_3P$[52]) and novel phosphorus-containing organometallic compounds.[53]

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Phosphorus(V) Oxide

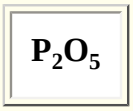

(P_2O_5)

[1314-56-3] · O_5P_2 · Phosphorus(V) Oxide · (MW 141.94) (P_4O_{10})

[16752-60-6] · $O_{10}P_4$ · Phosphorus(V) Oxide · (MW 283.88)

(dehydrating agent for acids and amides;[1] cyclization catalyst)

Alternate Names: phosphorus pentoxide; phosphoric anhydride.

Physical Data: mp 569 °C; sublimes at 250 °C under vacuum.

Solubility: sol H_2SO_4, $MeSO_3H$.

Form Supplied in: white powder; commercially available from many sources.

Preparative Method: prepared by combustion of phosphorus in dry air.

Purification: generally used without further purification; can be sublimed under vacuum.

Handling, Storage, and Precautions: corrosive! Reacts violently with water, releasing H_3PO_4 and heat.

Dehydration of Amides to Nitriles.

Dehydration of amides with P_2O_5 is one of many methods for the synthesis of nitriles.[2] Distillation of an unsubstituted amide from an excess of P_2O_5 leads to good yields of the nitrile (eq 1).[3,4] In many cases the reaction is carried out in the absence of solvents, although suitably high-boiling solvents can be used. These conditions are not compatible with many common functional groups, and this transformation can be achieved by other reagents,[5] including ***Thionyl Chloride*** and ***Phosphorus Oxychloride***.

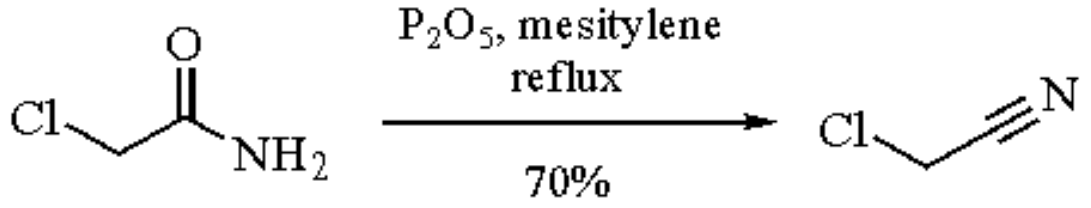

(1)

Amides can be made by treatment of silyl esters with P_2O_5, followed by treatment with ***Hexamethyldisilazane***.[6] Some *N*-substituted amides convert to ketene imines upon treatment with P_2O_5 (eq 2).[7]

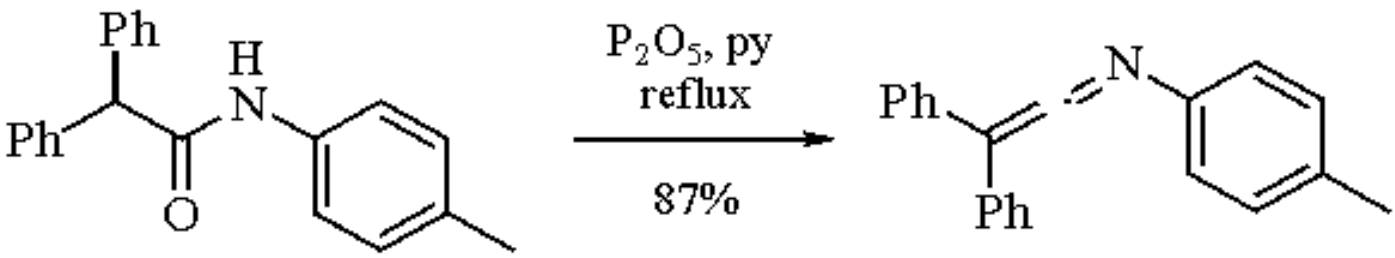

(2)

Formation of Anhydrides.

Dehydration of carboxylic acids with P_2O_5 is an effective method for the preparation of carboxylic anhydrides (eq 3). Acids have been converted to anhydrides with silica gel-supported P_2O_5, marketed as Sicapent by Merck.[8] Similar results are obtained by heating a suspension of a carboxylic acid with a powdered mixture of P_2O_5, $CuSO_4$, and Na_2SO_4 in a primary alcohol. This gives the ester in 60-80% yields.[9]

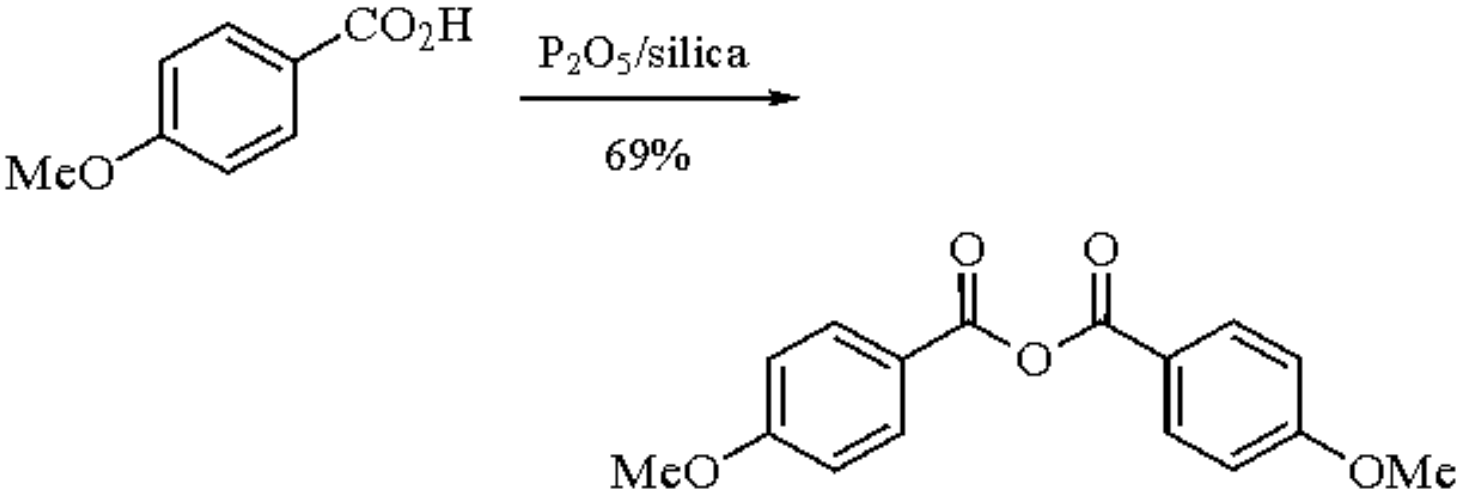

(3)

Cyclization Catalyst.

A 10% by weight (approximately saturated) solution of P_2O_5 in ***Methanesulfonic Acid*** (Eaton's reagent) has been used as an effective replacement for ***Polyphosphoric Acid*** (PPA) as an acid cyclization catalyst. Advantages to this reagent include the ease of stirring $MeSO_3H$ solutions relative to PPA and the greater solubility of many organic compounds in $MeSO_3H$ relative to PPA. Yields are comparable to or better than those obtained with PPA in Beckmann rearrangements (eq 4).[10] The combination of P_2O_5 and methanesulfonic acid is an efficient catalyst for

acid/alkene cycloadditions (eq 5).[11] See also ***Phosphorus(V) Oxide-Methanesulfonic Acid***.

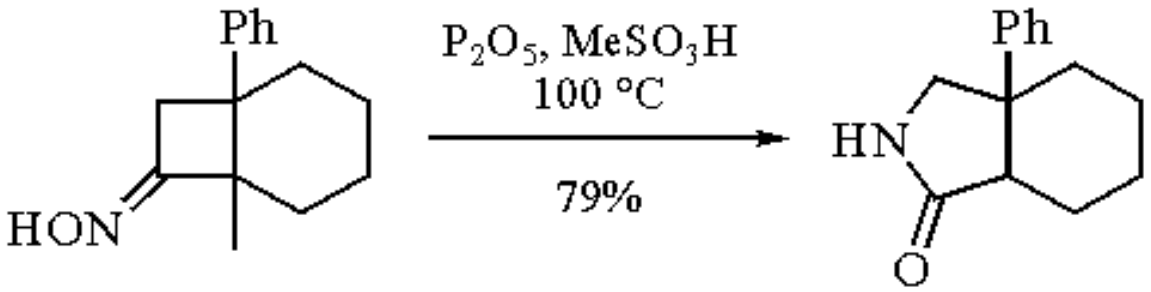

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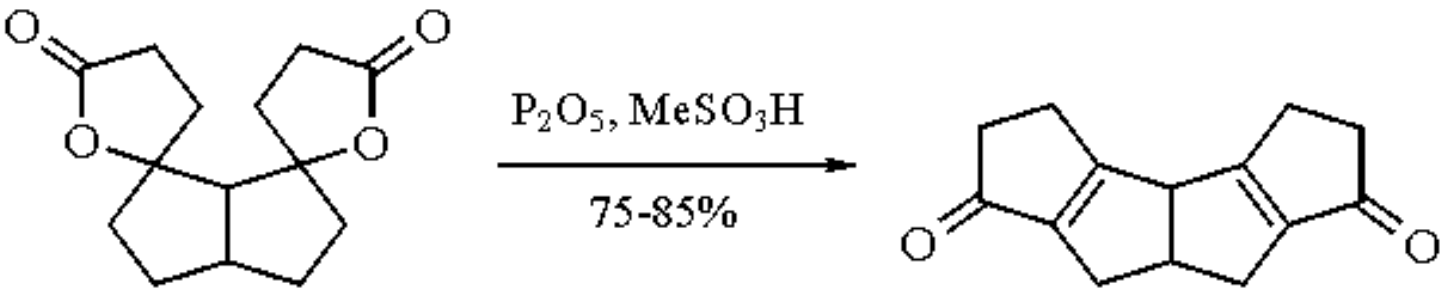

(5)

This mixture is a particularly useful catalyst in the synthesis of 2-substituted indole derivatives via the Fischer indole reaction of asymmetrical ketones (eq 6).[12] Other catalysts (PPA, H_2SO_4/MeOH, PPSE, Amberlyst 15) give lower regioselectivity. Decomposition of the starting material can be minimized by dilution of the P_2O_5/$MeSO_3H$ mixture with CH_2Cl_2. Treatment of (**1**) with P_2O_5 at high temperature results in cyclization to produce 7-deazahypoxanthines (eq 7).[13]

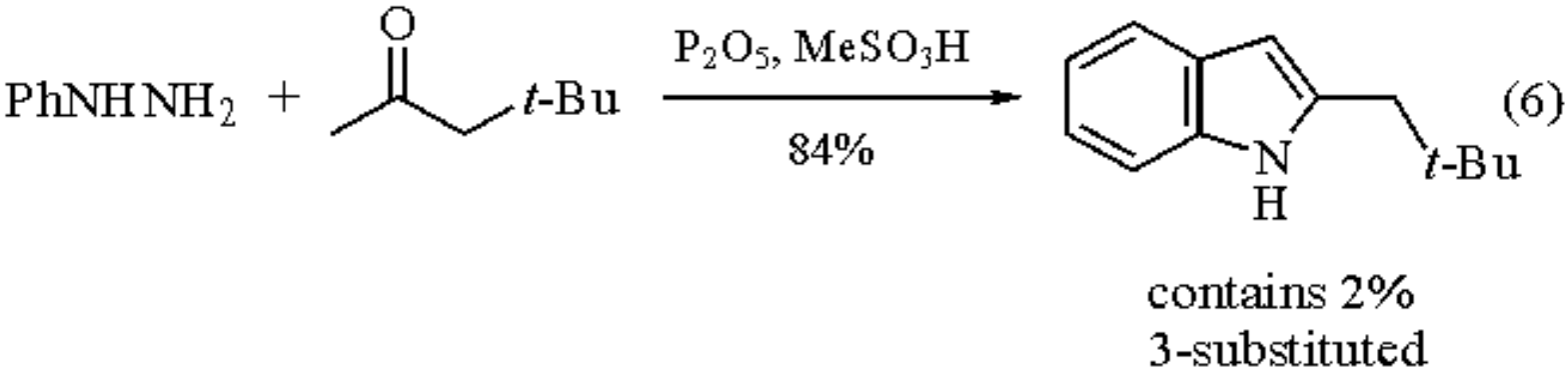

(6)

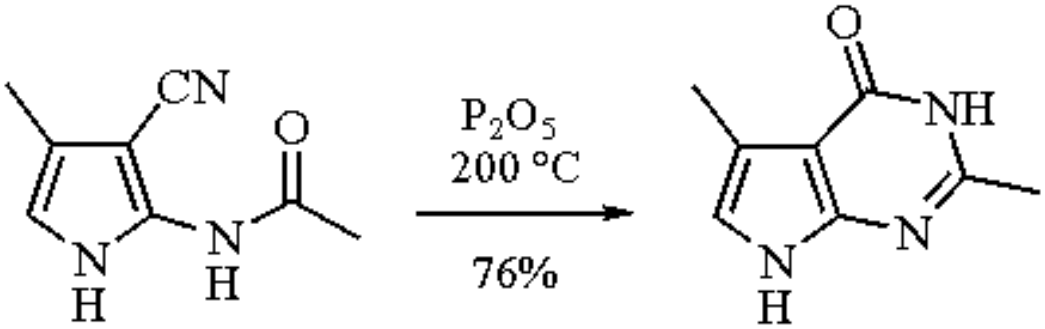

(7)

(1)

Condensing Agent.

Heating a mixture of P_2O_5, a primary or secondary amine (often using the amine as solvent), and a heterocyclic ketone or alcohol is a general route to substituted adenines (eq 8),[14,15] purines,[16,17] and pyrimidines.[18] Cyclization and ketone/amine condensations can often be combined in the one-pot transformations of 4,5-disubstituted imidazoles to substituted adenines (eqs 9 and 10).[19]

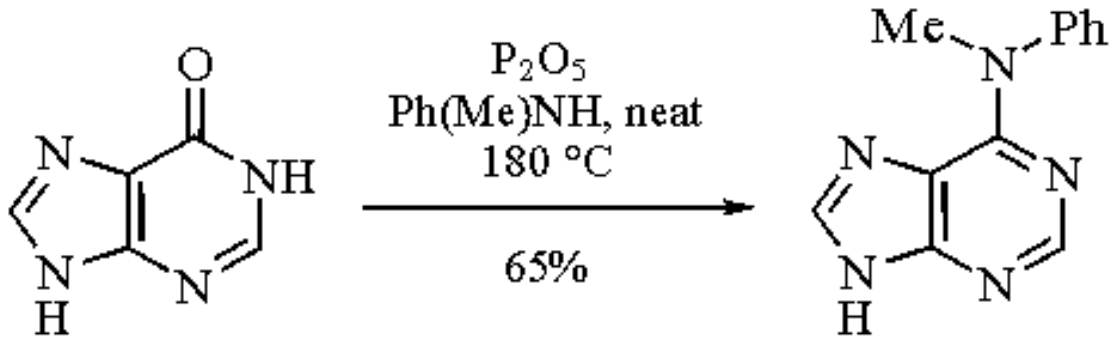

(8)

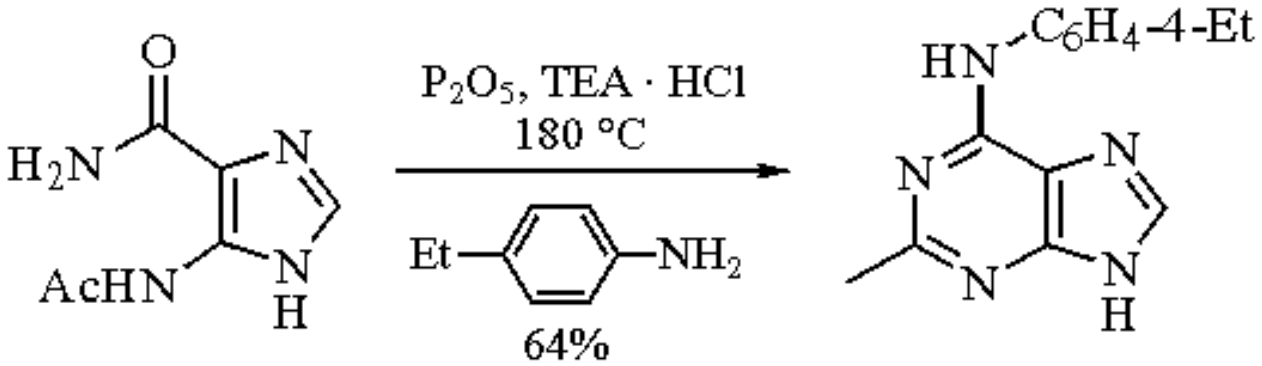

(9)

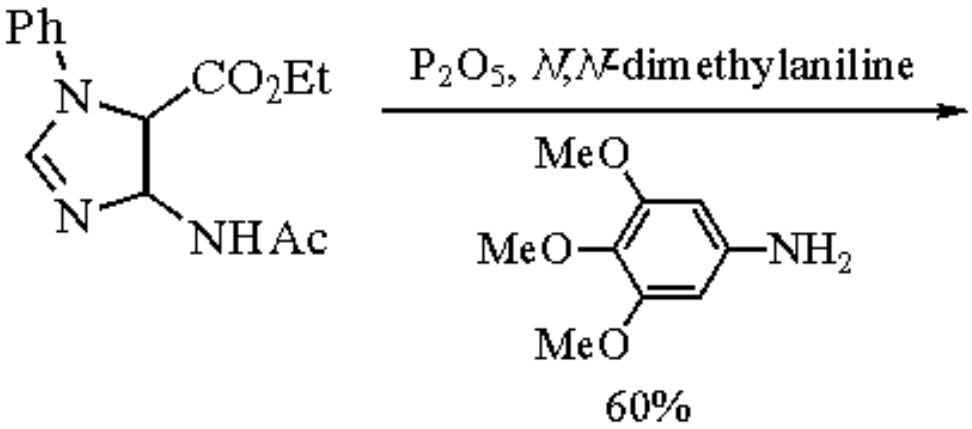

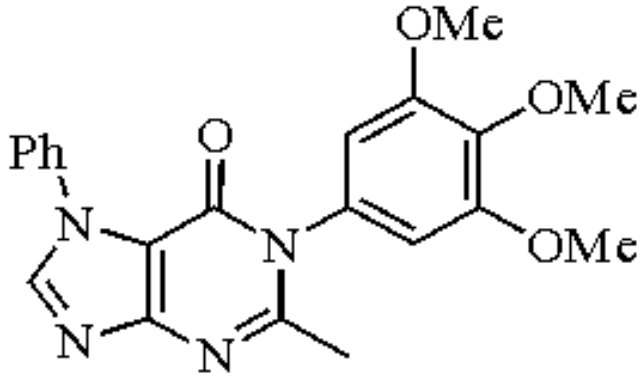

(10)

Cyclodehydrations.

The Pictet-Gams modification of the Bischler-Napieralski reaction is an important method for the preparation of isoquinolines.[19] This reaction relies on the dehydration of molecules such as (**2**) with P_2O_5 at high temperature (eq 11).[20] Lower temperatures lead to oxazoles, which can be converted to the isoquinolines by heating to 196 °C.

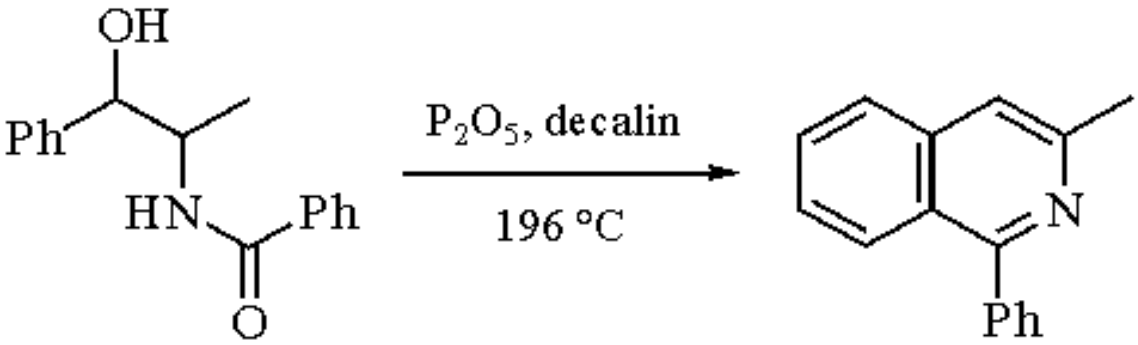

(2)

(11)

Trimethylsilyl Polyphosphate.

Heating a mixture of P_2O_5 with ***Hexamethyldisiloxane*** results in the formation of ***Trimethylsilyl Polyphosphate*** (PPSE), an organic soluble, aprotic alternative to PPE or PPA.[21] This reagent has proven useful for Beckmann rearrangements (eq 12),[21-23] and for generation and cyclization of nitrilium ions.[24]

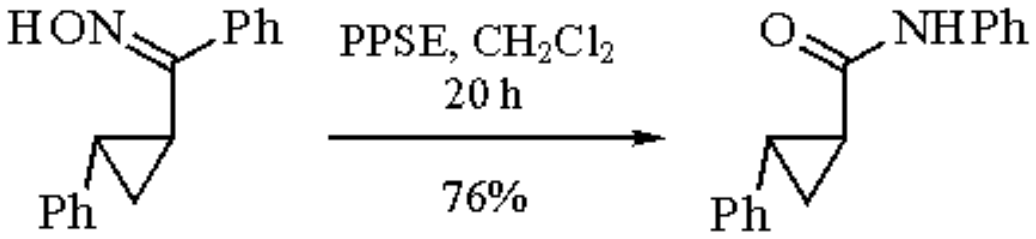

(12)

Formamidines.

Condensation of formanilides with secondary amines in the presence of P_2O_5 produces formamidines in good yield (eq 13).[25] The reaction is compatible with electron-rich and electron-deficient arenes, but is limited to secondary amines.

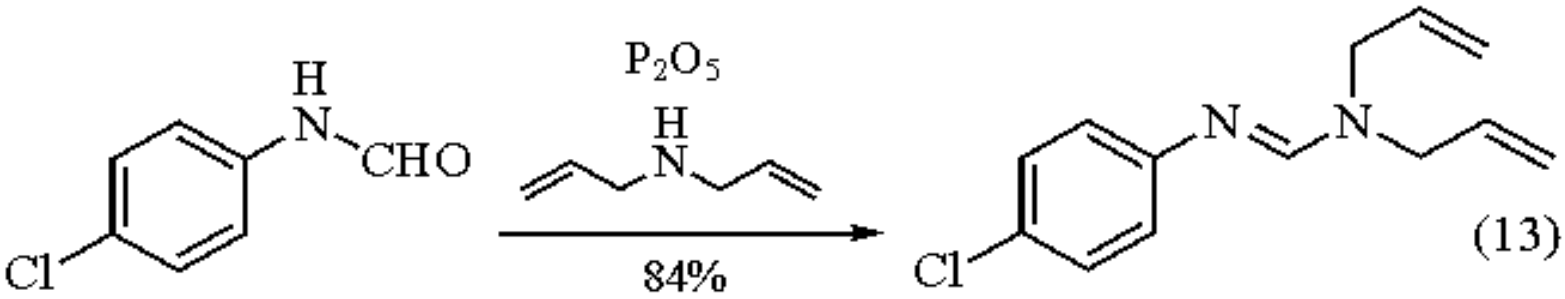

(13)

Related Reagents.

Dimethyl Sulfoxide-Phosphorus Pentoxide; ***Phosphorus(V) Oxide-Methanesulfonic Acid***; ***Phosphorus(V) Oxide-Phosphoric Acid***.

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Phosphorus(V) Oxide-Methanesulfonic Acid[1]

P_2O_5-$MeSO_3H$

[39394-84-8] · $CH_4O_8P_2S$ · Phosphorus(V) Oxide-Methanesulfonic Acid · (MW 238.06) (P_2O_5)

[1314-56-3] · O_5P_2 · Phosphorus(V) Oxide-Methanesulfonic Acid · (MW 141.94) ($MeSO_3H$)

[75-75-2] · CH_4O_3S · Phosphorus(V) Oxide-Methanesulfonic Acid · (MW 96.12)

(acidic dehydrating agent used in cycloalkenone synthesis,[1] Friedel-Crafts reactions,[1] the Fischer indole synthesis,[2] the Beckmann rearrangement,[1] and other dehydrations; an alternative to polyphosphoric acid[1])

Alternate Name: Eaton's reagent.

Physical Data: 7.5 wt% solution: bp 122 °C/1 mmHg; *d* 1.500 g cm^{-3}.

Solubility: sol ether, alcohol, MeCN, CH_2Cl_2; insol toluene, hexane.[2,3]

Form Supplied in: 7.5 wt% solution is commercially available.

Preparative Method: prepared[1] by adding ***Phosphorus(V) Oxide*** (P_2O_5, 36 g) in one portion to ***Methanesulfonic Acid*** (360 g) and stirring at rt[3] until the P_2O_5 dissolves.[4] Although Eaton recommends the use of freshly distilled methanesulfonic acid to allow for a clean workup and good yields,[1] others report using the acid as purchased.[5,6]

Handling, Storage, and Precautions: Eaton's reagent is toxic and corrosive. Direct contact with this reagent should be avoided. The solution begins to yellow upon standing for long periods of time; however, this does not appear to affect the viability of the reagent.[1] Use in a fume hood.

Reagent Description.

The reagent was conceived as an alternative to the widely used, but often inconvenient, ***Polyphosphoric Acid*** (PPA) (see also ***Polyphosphate Ester***, PPE).[1] Eaton's reagent successfully addresses the drawbacks of PPA's physical properties. It is much less viscous, and is, therefore, easier to stir. Organic compounds are generally soluble in Eaton's

reagent, and the hydrolytic workup is less tedious.[1] Reactions are run at ambient or slightly elevated temperatures. Standard aqueous workup is easy and clean. Eaton recommends quenching the reaction with water; quenching in ice may cause methanesulfonic anhydride to precipitate and be extracted into the organic layer; quenching in aqueous base may cause extensive foaming.[1] In addition to its ease of handling, yields obtained with Eaton's reagent compare favorably with those obtained with PPA.[7] Few modifications of Eaton's original procedure have appeared. A 1:5 by weight ratio has been reported to be as effective as a 1:10 ratio.[8] It has been noted that, to avoid polymer formation, only the minimum amount of reagent needed to effect condensation should be used.[9] The nature of the reagent has not been rigorously determined. It appears that the reactive or catalytic species may vary by reaction. In certain acid-catalyzed reactions, P_2O_5 has been found to be superfluous.[10]

Cycloalkenones.

$P_2O_5/MeSO_3H$ is used as a reagent in several reactions leading to cycloalkenones. First described in Eaton's original paper, the lactone-to-cyclopentenone rearrangement (eq 1)[1] has since found wide use.[11]

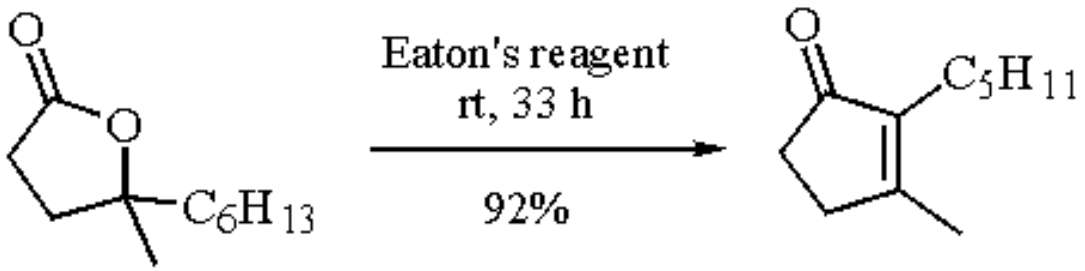

(1)

In a related reaction, readily available nitroalkanoic acids cyclize to form cyclopentenones (eq 2).[12] As illustrated in eq 3,[13a] vinylcyclobutanones undergo acyl migration to produce either cyclopentenones or cyclohexenones.[13]

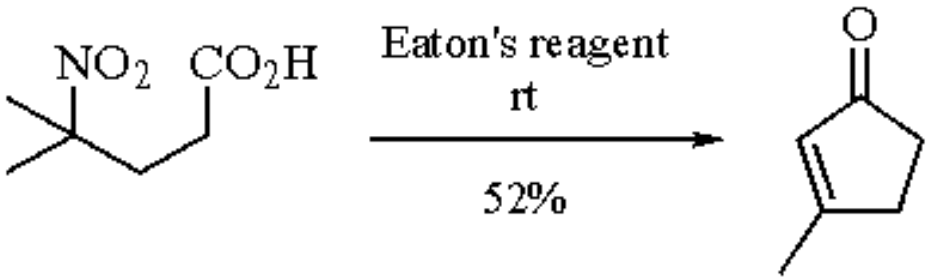

(2)

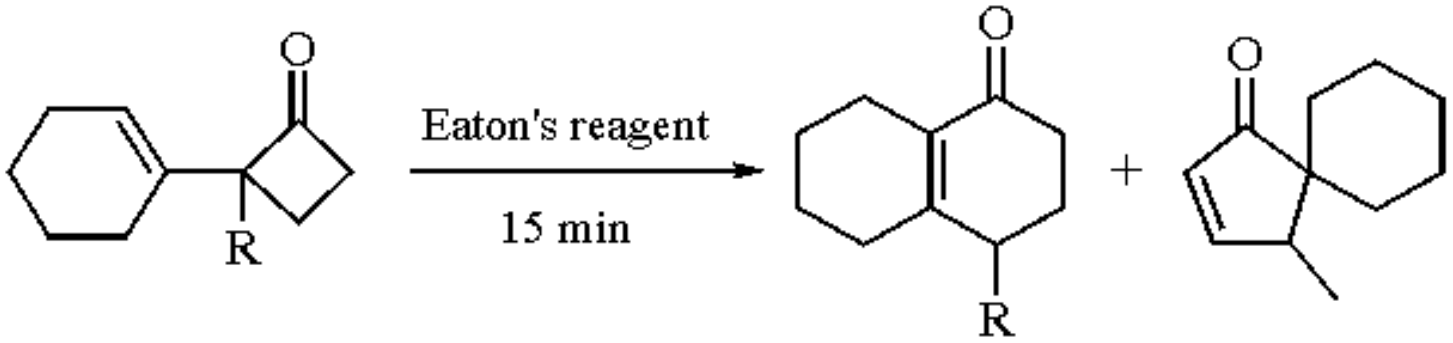

(3)

R = H	65%	0%
R = Me	13%	51%

Vinylcyclopentenones have undergone the Nazarov cyclization in good yield in the presence of Eaton's reagent (eq 4).[14] However, other reagents may be more generally useful, since there are reports of Eaton's reagent not providing optimal results in this reaction.[15]

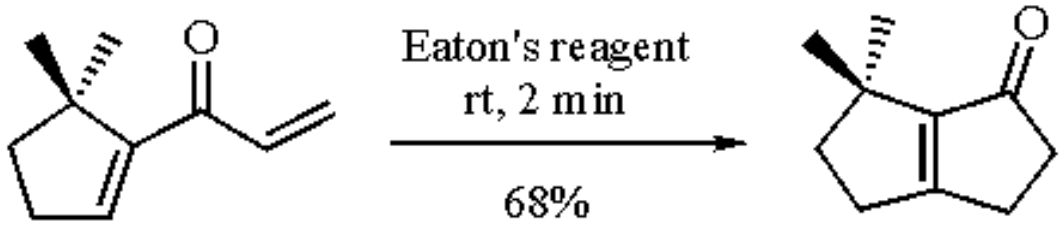

(4)

Friedel-Crafts Acylations of Aromatic Rings.

Eaton's reagent has been used widely and very effectively[16a] to catalyze Friedel-Crafts acylations.[16] One of the few potential drawbacks is the deprotection of an aryl ether. The examples shown below compare the utility of Eaton's reagent vs. PPA with regard to this deprotection problem. In eq 5, although the cyclization proceeds with an undesired protecting group exchange, the cyclization fails in PPA.[17] Deprotection of an aryl methyl ether is avoided by using Eaton's reagent in place of PPA in one case (eq 6),[18] but not in another.[19] Intramolecular Friedel-Crafts acylations have been observed to occur without the addition of P_2O_5.[10] A comparative study found this observation to be generally applicable to intramolecular acylations, but not intermolecular acylations.[10b,20]

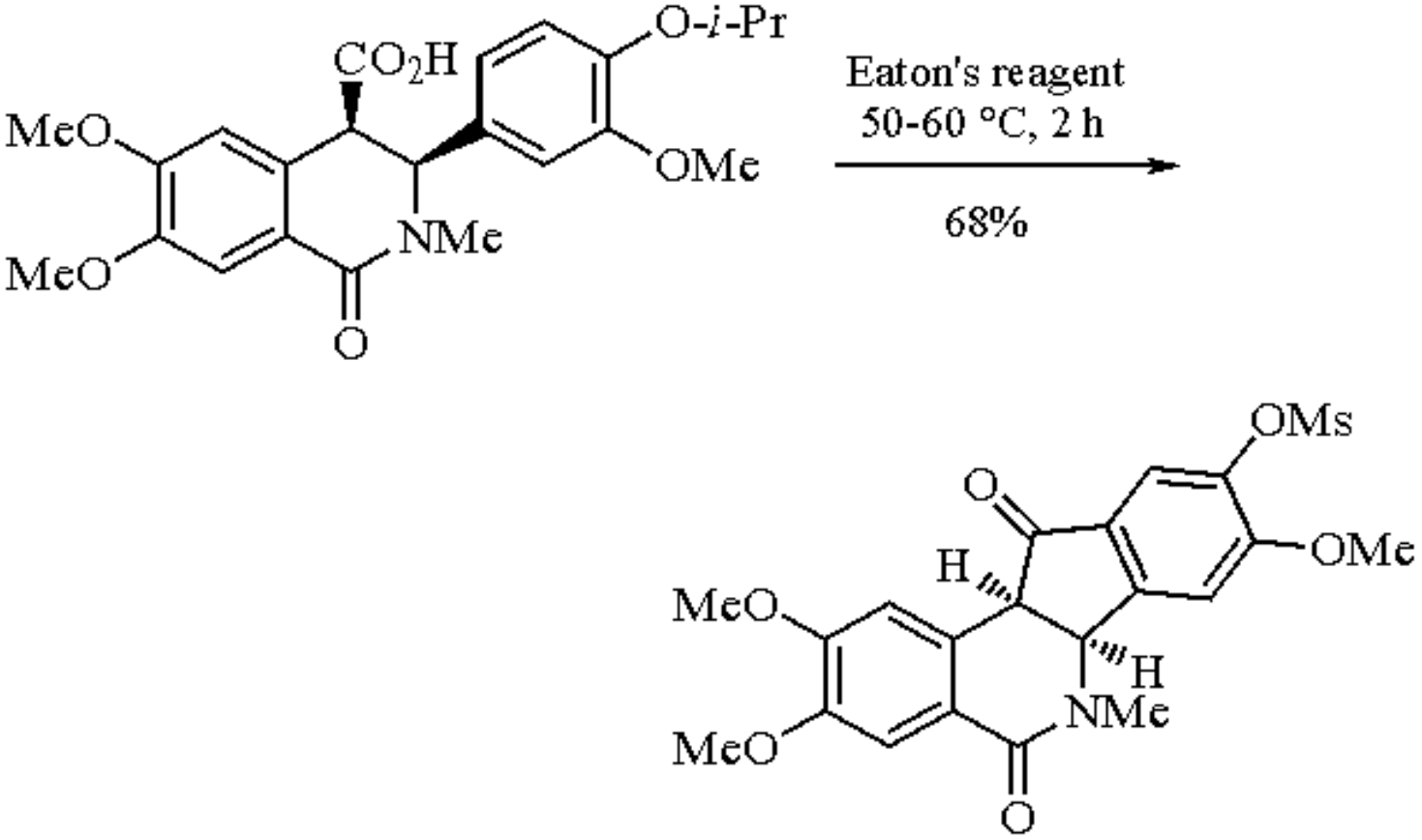

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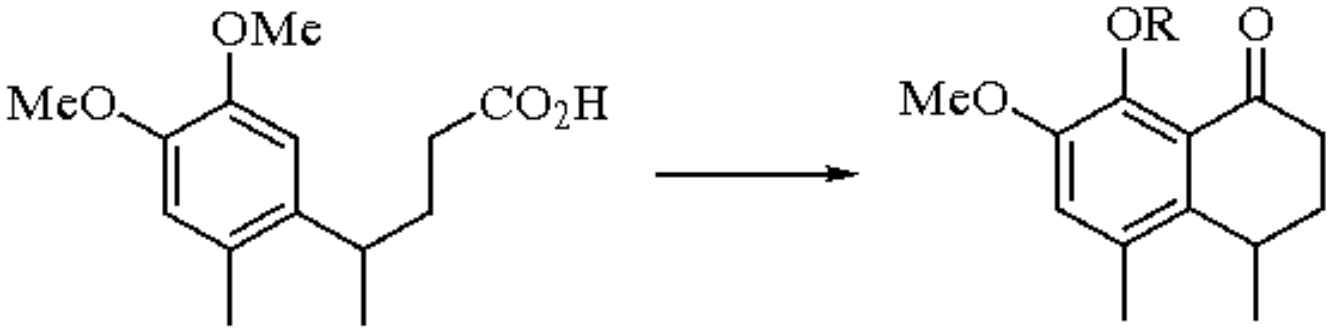

(6)

Eaton's reagent R = Me, 70%
PPA R = H, 28%

Friedel-Crafts Alkylations.

$P_2O_5/MeSO_3H$ compares favorably with other reagents in the Friedel-Crafts alkylation reaction.[21] Mechanistic aspects of this reaction have been discussed.[21b] Eq 7 shows an alkene-initiated alkylation that provides (+)-*O*-methylpodocarpate selectively.[22]

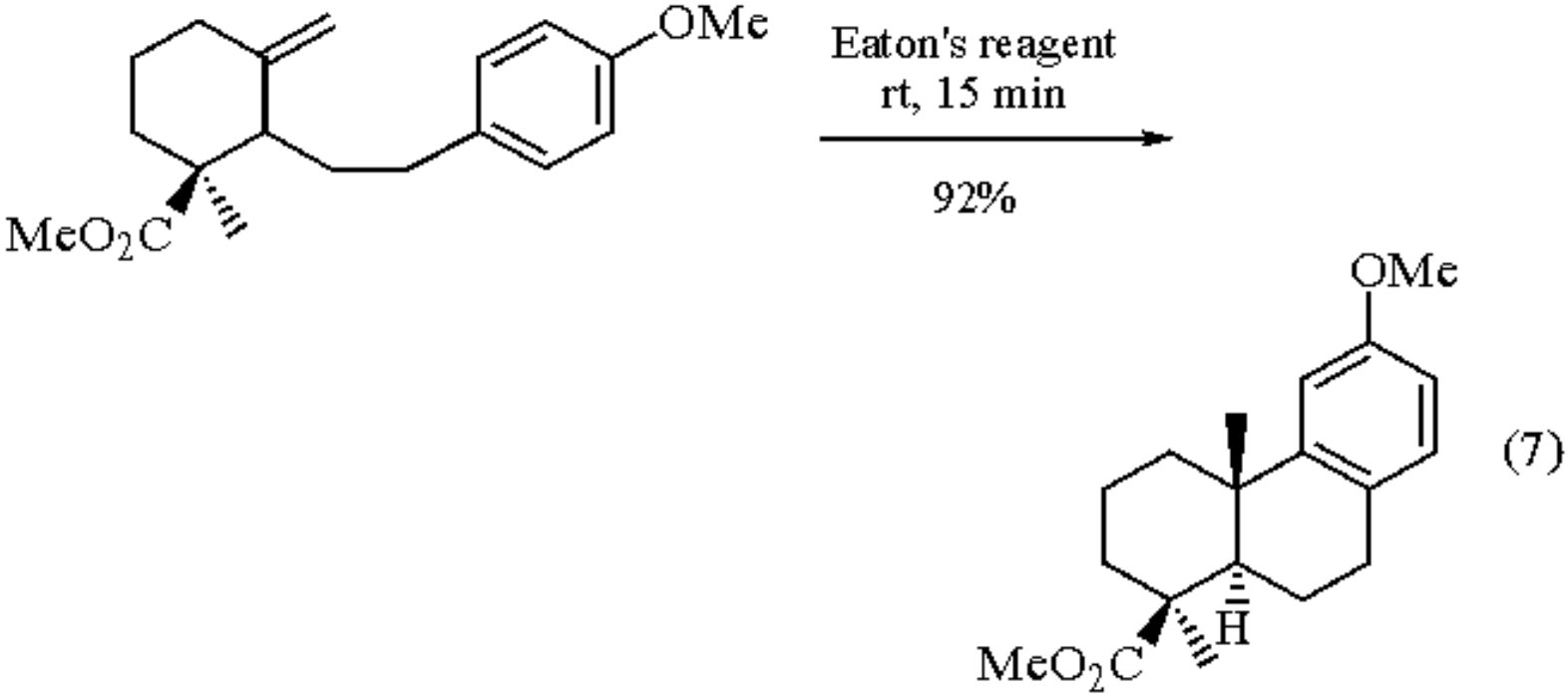

Dehydration.

Alcohols have been dehydrated to alkenes with Eaton's reagent (eq 8).[23] In a formal dehydration, a cyclopentenone has been transformed into a diene (eq 9).[24]

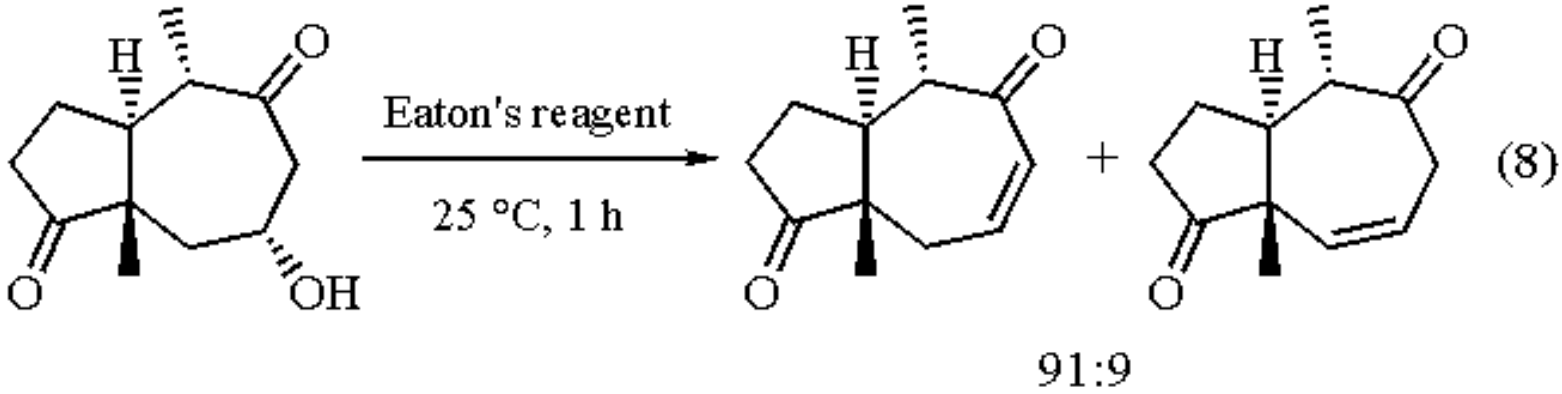

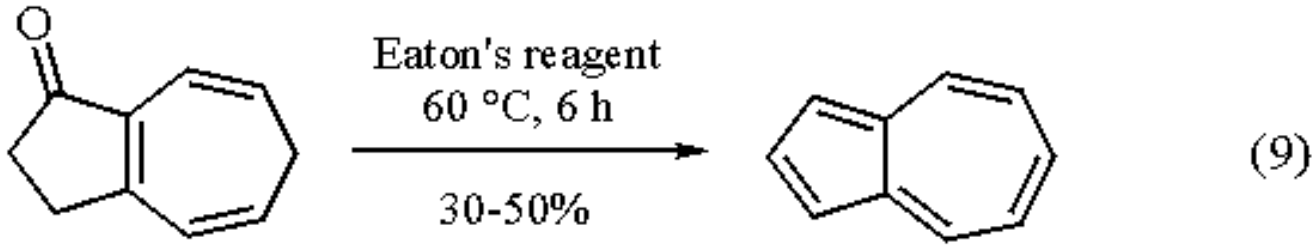

Fischer Indole Synthesis.

The use of Eaton's reagent as the acid catalyst in the Fischer indole reaction results in unprecedented regiocontrol

favoring 2-substituted indoles (eq 10).[2] In cases where the harshness of the reagent results in low yields of indoles, dilution of the reaction mixture in sulfolane or CH_2Cl_2 attenuates the problem. Mechanistic studies indicate that the catalytic species, in this reaction, is $MeSO_3H$. The role of P_2O_5 is to act as a drying agent. Further experiments indicate that for the Friedel-Crafts acylation this is not the case; a mixed anhydride is the catalytic species.[2]

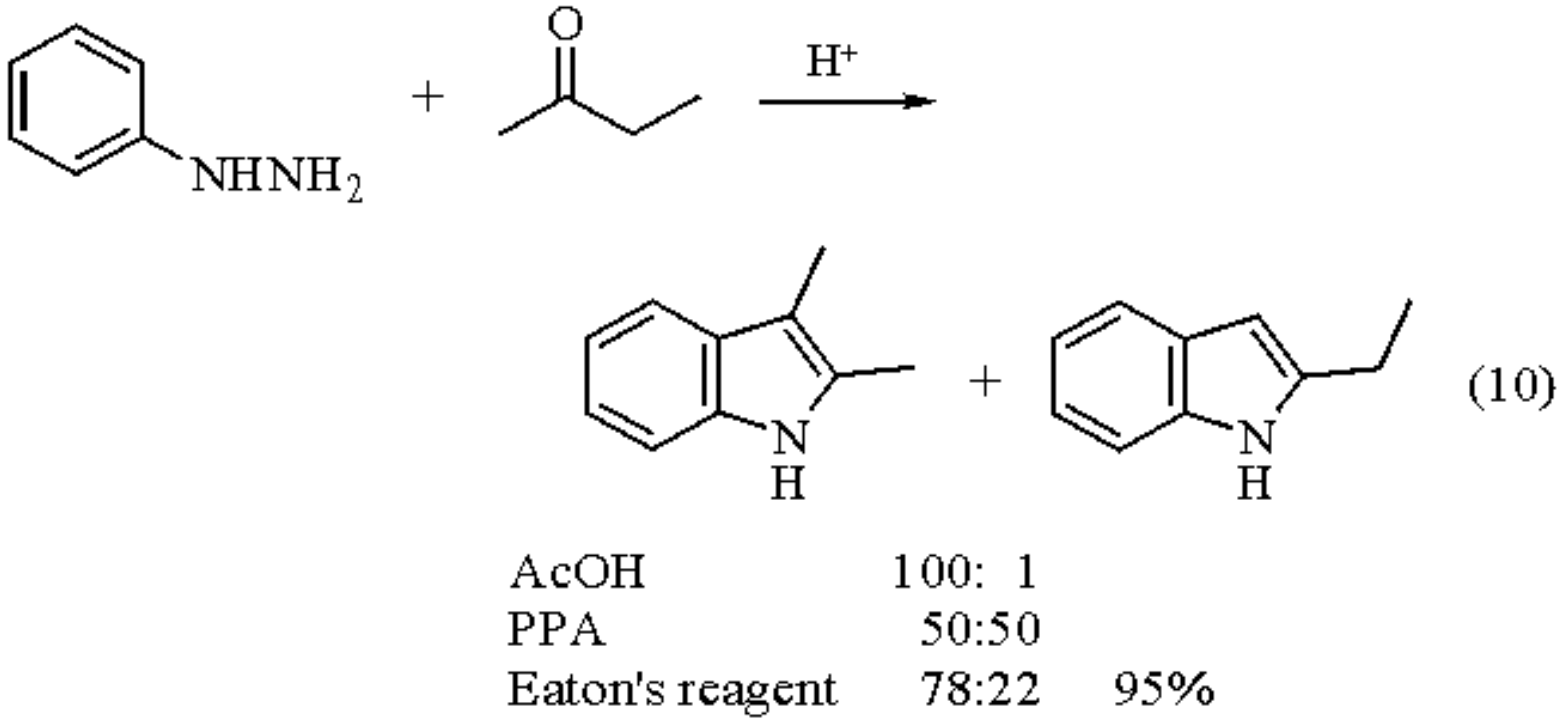

Heterocycle Preparation.

Various heterocycles have been prepared through $P_2O_5/MeSO_3H$-mediated cyclizations. Condensation, and subsequent dehydration, of aminothiophenol and the appropriate acid provides benzothiazoles (eq 11).[25]

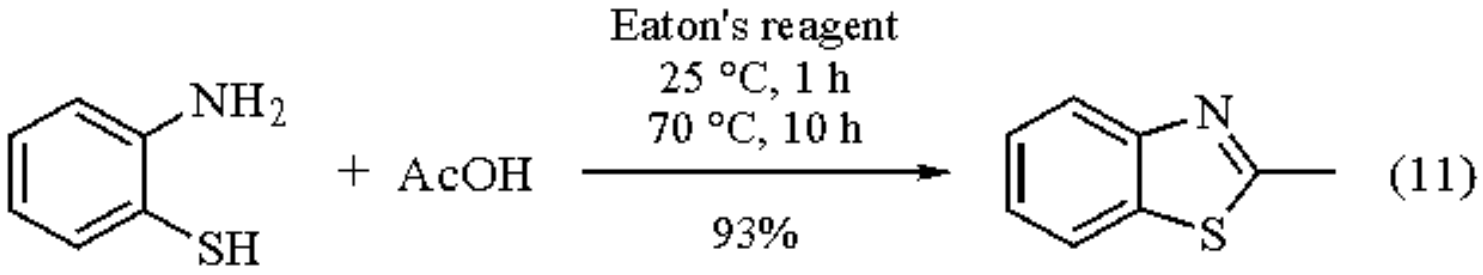

Oxadiazoles can be prepared from diacylhydrazines (eq 12).[26] Furans are formed from the cyclodehydration of a phenolic ketone (eq 13).[27]

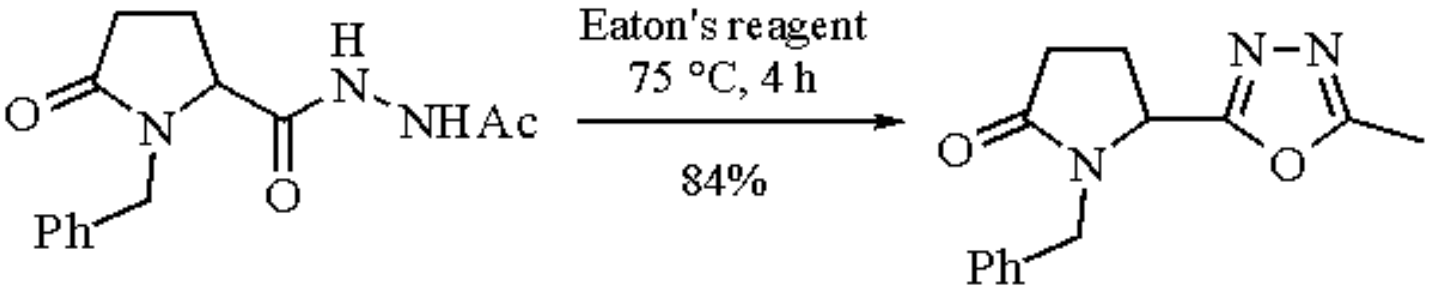

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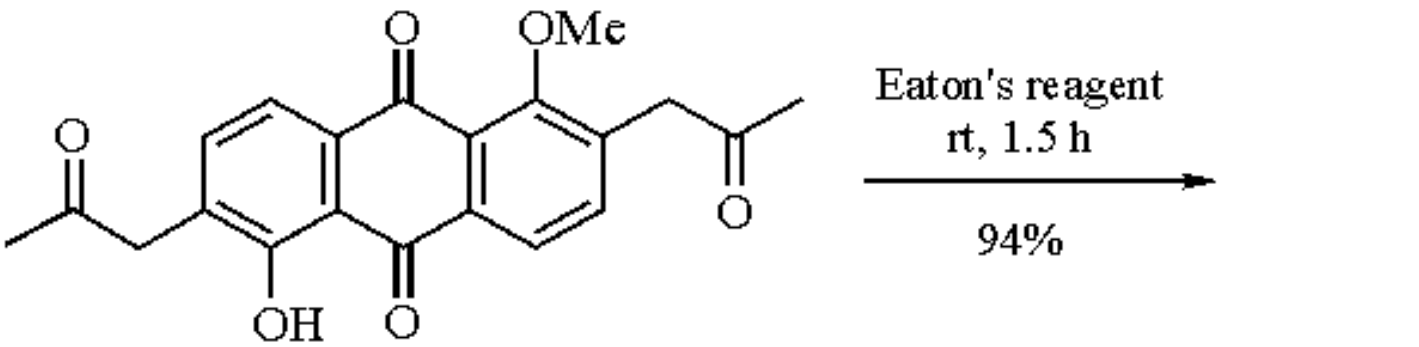

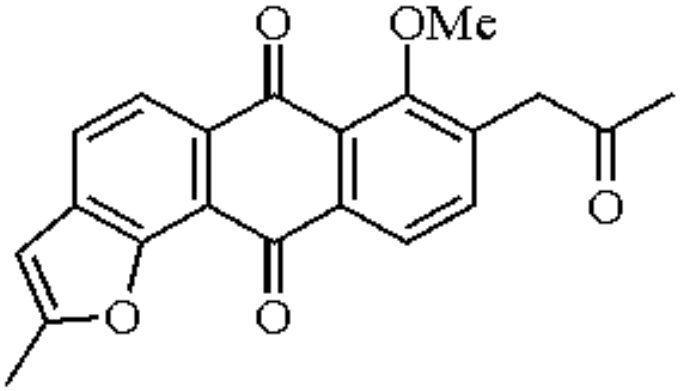

(13)

Butenolides have been prepared by cyclization of keto esters (eq 14)[28] or by elimination of H_2O from a preformed hydroxy butenolide (eq 15).[29]

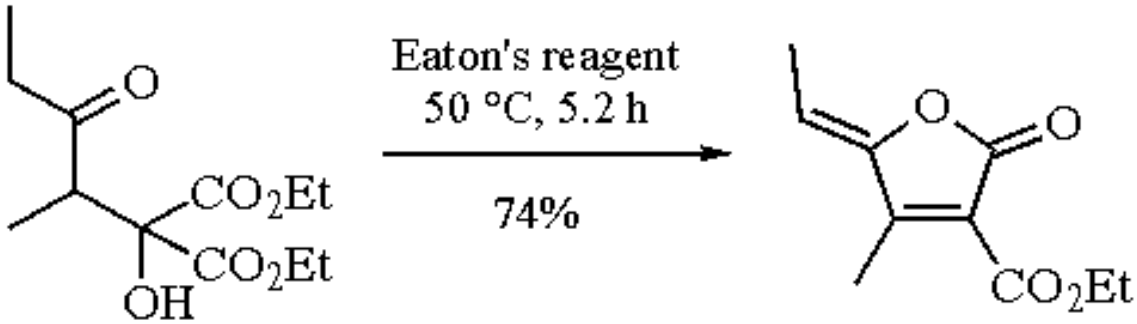

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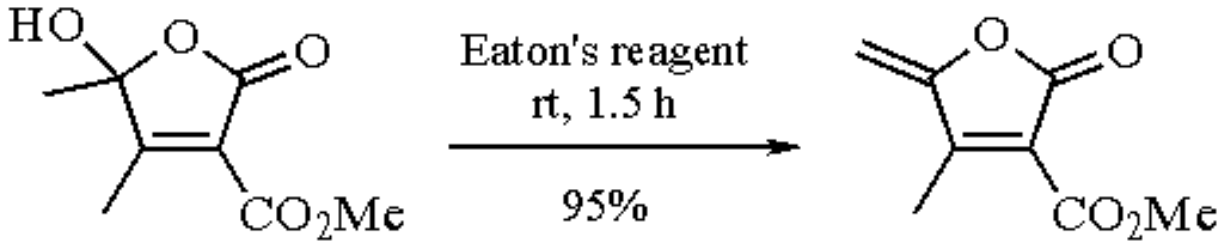

(15)

Yields in the synthesis of thiadiazolo[3,2-*a*]pyrimidin-5-ones have been greatly improved by using Eaton's reagent in the place of PPA (eq 16).[8b]

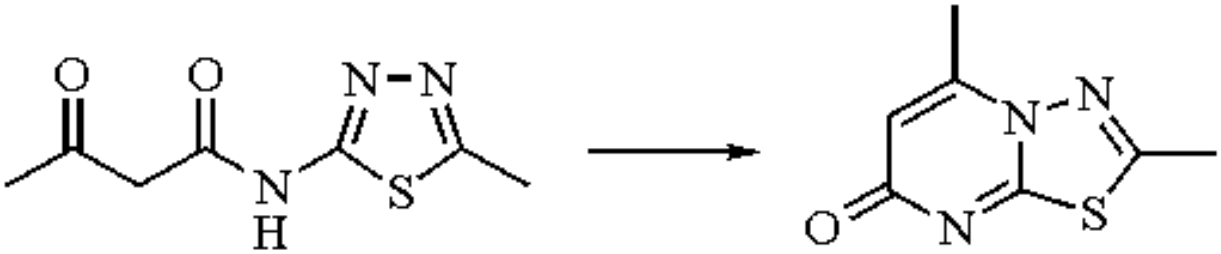

(16)

P_2O_5, $MeSO_3H$; 1:5	87%
PPA	18%

Eaton's reagent is superior to PPA in the addition of an amide across a double bond (eq 17).[30] In another synthesis of lactams, 3-alkenamides reacted stereoselectively with benzaldehyde to provide lactams containing three contiguous stereogenic centers (eq 18).[31]

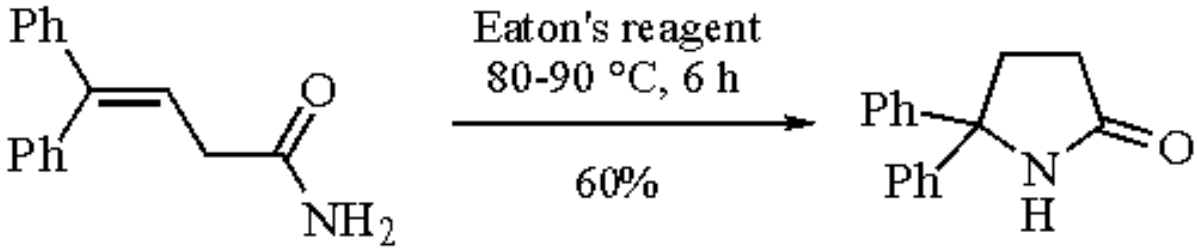

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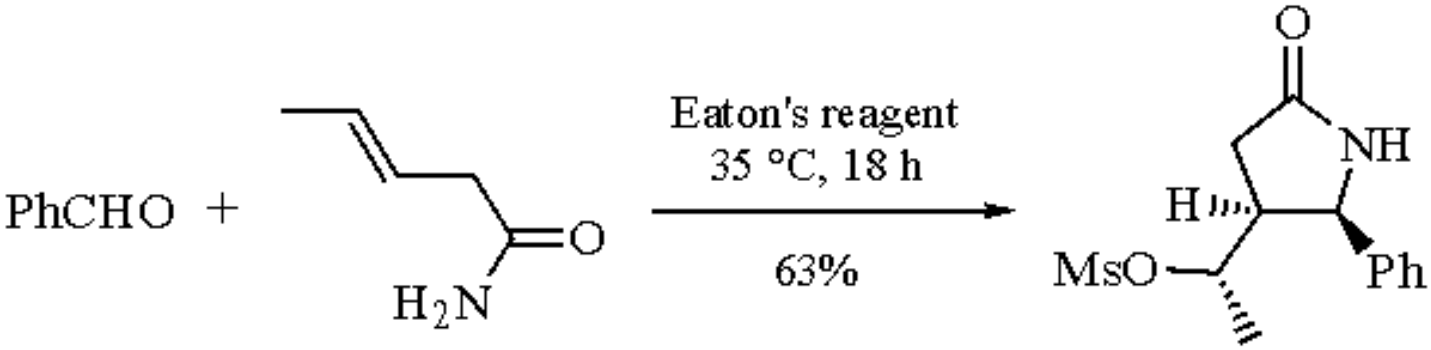

(18)

Beckmann Rearrangement.

Eaton's disclosure of $P_2O_5/MeSO_3H$ as an alternative to PPA compared the two reagents' ability to effect the

Beckmann rearrangement.[1] Eaton's reagent has been reported to be superior to other reagents at inducing stereospecific rearrangement of the (*E*)- and (*Z*)-oximes of phenylacetone.[4] However, this is not a general finding. Rearrangement of the oxime in eq 19 does not provide the product expected from an *anti*-migration process.[32]

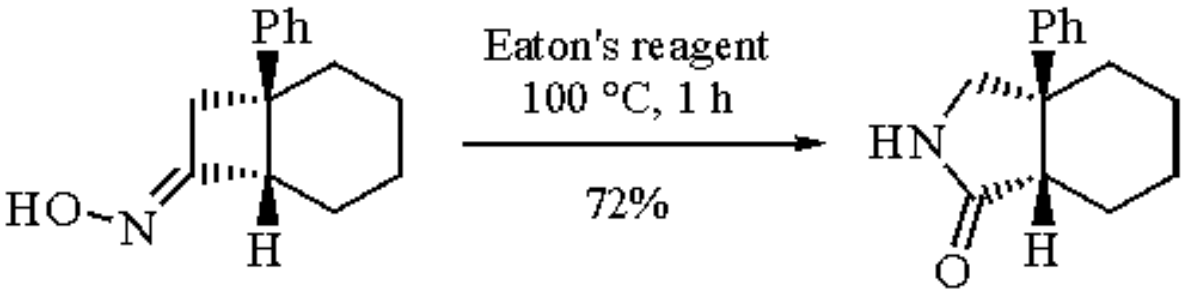

(19)

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1. Eaton, P. E.; Carlson, G. R.; Lee, J. T. *JOC* **1973**, *38*, 4071.
2. This paper reports that in the preparation of 2-substituted indoles Eaton's reagent is superior to PPA, H_2SO_4, and PPSE: Zhao, D.; Hughes, D. L.; Bender, D. R.; DeMarco, A. M.; Reider, P. J. *JOC* **1991**, *56*, 3001.
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7. Examples of exceptions: (a) PPA is superior to either Eaton's reagent or H_2SO_4 in a Friedel-Crafts acylation: Hormi, O. E. O.; Moisio, M. R.; Sund, B. C. *JOC* **1987**, *52*, 5272. (b) PPA is superior to Eaton's reagent, $BF_3.OEt_2$, HCO_2H, $ZnCl_2$, CF_3CO_2H, *p*-TsOH, and H_2SO_4 in a Friedel-Crafts alkylation: Maskill, H. *JCS(P1)* **1987**, 1739. (c) PPA is superior to Eaton's reagent or $CF_3CO_2H/(CF_3CO)_2O/BF_3.OEt_2$ in a Friedel-Crafts acylation: Hands, D.; Marley, H.; Skittrall, S. J.; Wright, S. H. B.; Verhoeven, T. R. *JHC* **1986**, *23*, 1333. (d) PPA is superior to Eaton's reagent in a Friedel-Crafts acylation: Bosch, J.; Rubiralta, M.; Domingo, A.; Bolos, J.; Linares, A.; Minguillon, C.; Amat, M.; Bonjoch, J. *JOC* **1985**, *50*, 1516. (e) PPA is superior to Eaton's reagent or PPE in a Friedel-Crafts acylation: Jilek, J.; Holubek, J.; Svatek, E.; Schlanger, J.; Pomykacek, J.; Protiva, M. *CCC* **1985**, *50*, 519. (f) In a Friedel-Crafts acylation, where PPA or Eaton's reagent fails to give satisfactory results, the corresponding acid chloride is cyclized using $AlCl_3$: Barco, A.; Benetti, S.; Pollini, G. P. *OPP* **1976**, *8*, 7.
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13. (a) Matz, J. R.; Cohen, T. *TL* **1981**, *22*, 2459. (b) For a related ring expansion of 1-alkenylcyclopropanols to cyclopentenones, see: Barnier, J.-P.; Karkour, B.; Salaun, J. *CC* **1985**, 1270.

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15. (a) This paper reports obtaining Nazarov cyclization products in 8-10% yield with either Eaton's reagent or $FeCl_3$. A silicon assisted Nazarov was also explored: Cheney, D. L.; Paquette, L. A. *JOC* **1989**, *54*, 3334. (b) PPA is superior to Eaton's reagent or methanesulfonic acid in effecting cyclization of 1,1´-dicyclopentenyl ketone: Eaton, P. E.; Giordano, C.; Schloemer, G.; Vogel, U. *JOC* **1976**, *41*, 2238. (c) Many other reagents including HCO_2H/H_3PO_4, HCl, H_2SO_4, $SnCl_4$, and TsOH have been used in this type of Nazarov cyclization. For a review of the Nazarov cyclization, see: Santelli-Rouvier, C.; Santelli, M. *S* **1983**, 429.
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Phosphorus(V) Oxide-Phosphoric Acid

P_2O_5-H_3PO_4

(P_2O_5)

[1314-56-3] · O_5P_2 · Phosphorus(V) Oxide-Phosphoric Acid · (MW 141.94) (H_3PO_4)

[7664-38-2] · H_3O_4P · Phosphorus(V) Oxide-Phosphoric Acid · (MW 98.00)

(moderately strong mineral acid with a range of dehydrating properties; used for cyclizations and phosphorylations)

Physical Data: hygroscopic; viscous to highly viscous; colorless or light amber; specific gravity is dependent upon the concentration of the reagent, 2.060 at 83% phosphorus pentoxide content (see below).

Solubility: dissolution in any protic solvent will result in *violent* solvolysis of the reagent; dissolution in polar aprotic solvents can result in dehydration or destruction of the solvent; these reagents are not soluble in and do not react with nonpolar organics such as toluene or hexane.

Preparative Methods: best carried out by heating P_2O_5 with 85% H_3PO_4. A solution which is theoretically 76% P_2O_5 (see below) is obtained when 3*x* g of ***Phosphorus(V) Oxide*** is mixed with 4*x* g of 85% orthophosphoric acid. This mixture is heated and stirred until complete dissolution occurs.[1] When concentrations over 83% are desired, polyphosphoric acid (PPA) is used to dissolve the P_2O_5. A concentration of 86% P_2O_5 (super polyphosphoric acid) is reported to be useful in reactions which fail when PPA is used.[2] Preparation of super polyphosphoric acid is accomplished by mechanically stirring *x* g of P_2O_5 and 5*x* g of PPA while heating to 170-180 °C for 1 h. The reagent is kept warm while the substrate is added to avoid the extremely viscous mixture which results upon cooling to rt. Workup is accomplished by pouring the hot mixture onto ice.

Handling, Storage, and Precautions: when diluting P_2O_5 or any partially hydrolyzed derivative, care must be taken to avoid spattering caused by the exothermic hydrolysis. PPA has the ability to burn mucous membranes immediately and unprotected skin with time. Other than its corrosive nature, it has low inherent toxicity. Use in a fume hood.

Description of the Reagent.

P_2O_5/H_3PO_4 is not a discrete molecular entity, but can be considered to be any mixture which results from partial hydration of P_2O_5. The resulting solution is a complex mixture of phosphoric acids, which consists of

orthophosphoric acid and linear phosphoric acid chains. In order to avoid discussion of this complicated equilibrium, these mixtures are described empirically by stating the weight percent of the solution as if it were simply a solution of P_2O_5 in water. When the theoretical weight percent of P_2O_5 reaches 83%, the resulting mixture is commonly known as ***Polyphosphoric Acid*** (PPA). As the weight percent of P_2O_5 goes above 83%, longer chain phosphoric acids begin to predominate until at 89% P_2O_5 the mixture is 87% hypolyphosphoric acid (greater than 14 phosphoric acid units).

Cyclizations.

In work directed toward the synthesis of jasmone, the utility of a PPA/P_2O_5 (86% P_2O_5) mixture was first evidenced when a lactone was converted into a cyclic ketone (eq 1).[3]

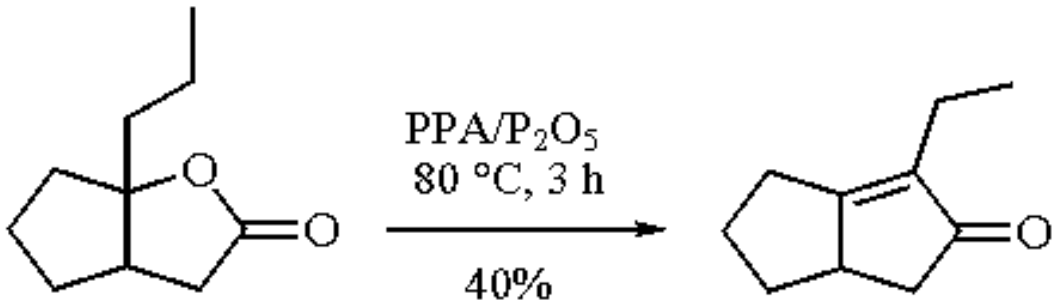

(1)

The term super polyphosphoric acid was first coined when 86% P_2O_5 successfully effected the Pomeranz-Fritsch cyclization even though the resulting isoquinoline is sterically congested (eq 2).[2] Super PPA was also used to effect a Bischler-Napieralski cyclization to obtain isoquinolines in higher than normal yields (eq 3).[2] Some confusion exists about this report since *N*-formylphenethylamines should yield dihydroisoquinolines and not the tetrahydroisoquinolines reported.[4] It would appear that reduction of the intermediate dihydroisoquinoline was inadvertently omitted. In an efficient synthesis of a benzindolone (6-methoxy-Uhle's ketone), use of super PPA improved the low yield route which utilized normal PPA (eq 4).[5] In an attempt to develop methodology to convert methylcyclohexenones into indolones and pyrroloazepinediones, cyclization of a pyrrolo acid was found to proceed in 85% yield using super PPA while normal PPA gave poor yields (eq 5).[6]

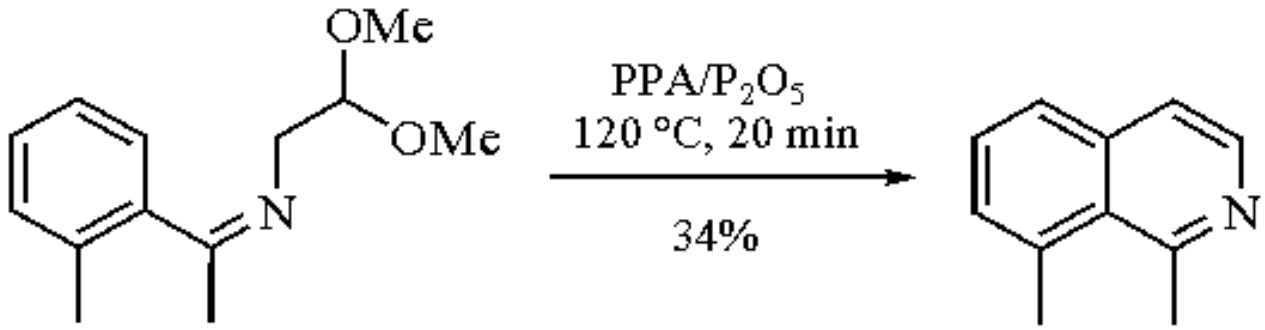

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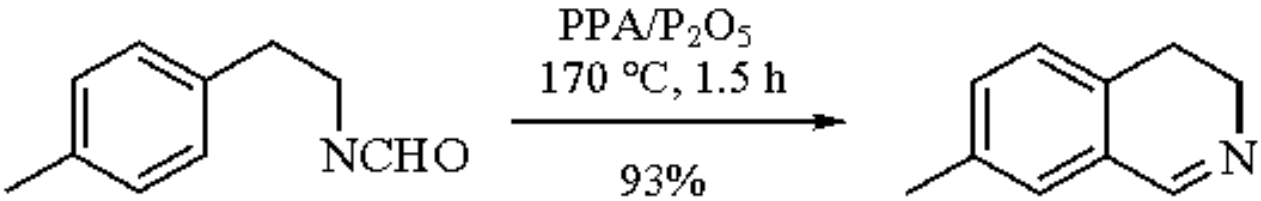

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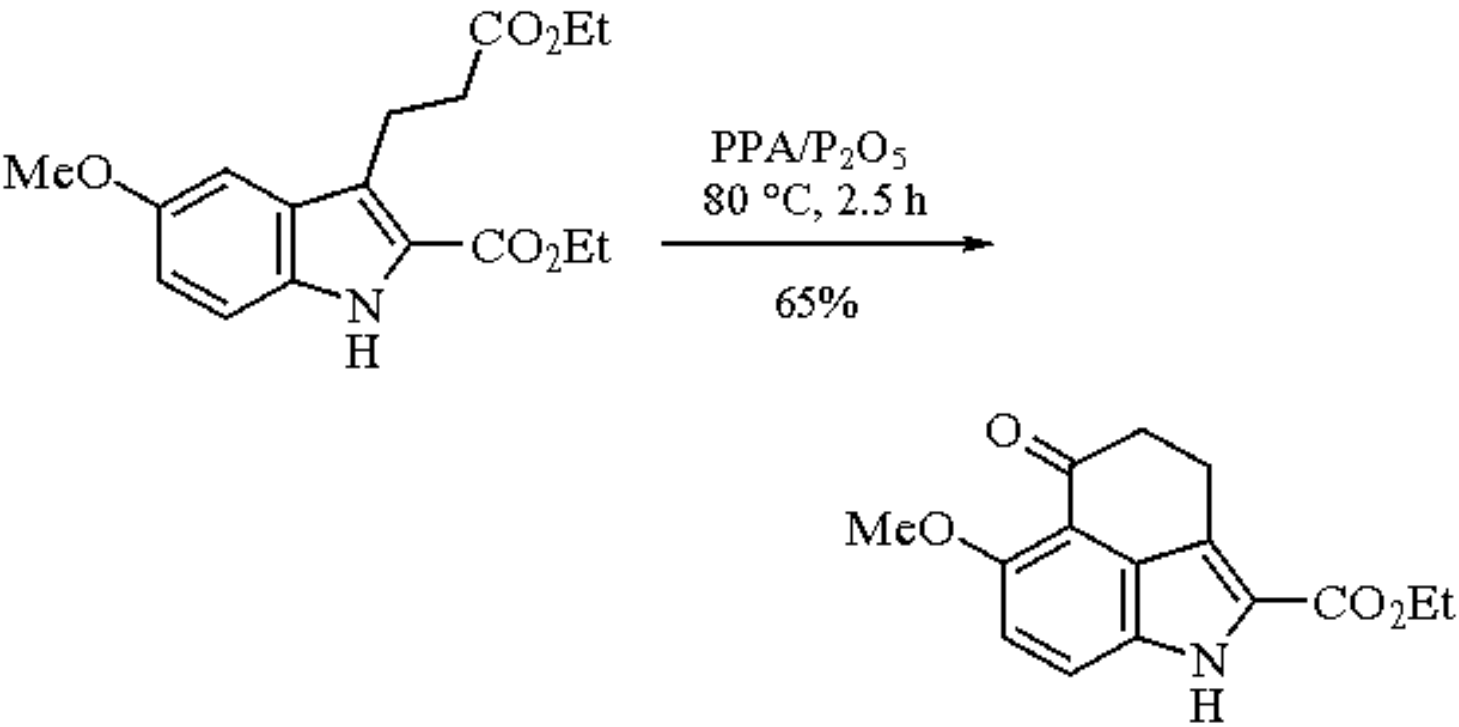

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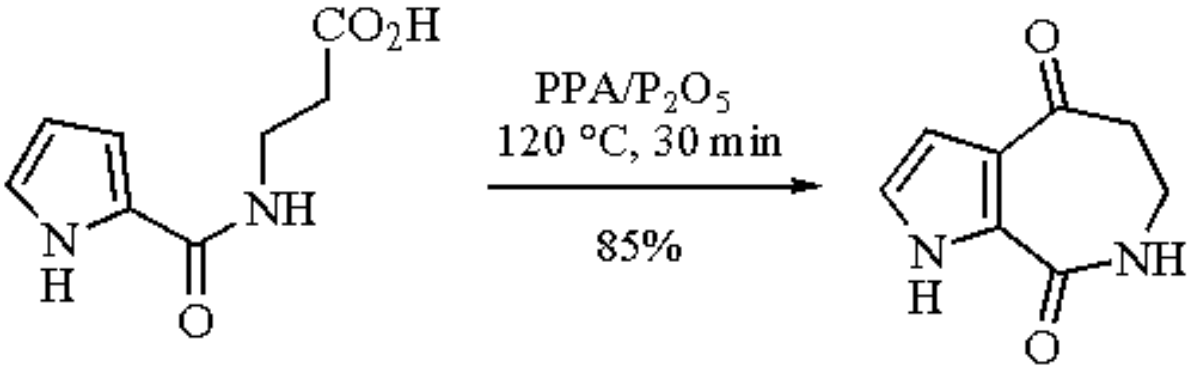

(5)

Phosphorylations.

A mixture of P_2O_5 and H_3PO_4 (78% P_2O_5) was used to phosphorylate proteins in the first reported use of this reagent.[1] This methodology was applied to small molecules in the synthesis of pyridoxal phosphate (eq 6).[7]

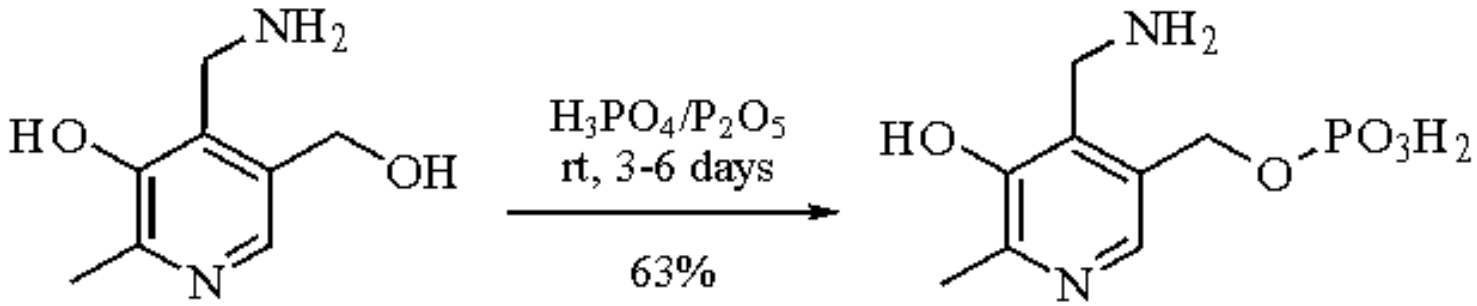

(6)

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Phosphorus Oxychloride

$POCl_3$

[10025-87-3] · Cl_3OP · Phosphorus Oxychloride · (MW 153.32)

(formylation of aromatic rings[1,2] (Vilsmeier-Haack reaction); phosphorylating agent;[3] dehydrating agent for amides; halogenation of alcohols, phenols, and heterocycles)

Alternate Name: phosphoryl chloride.

Physical Data: mp 1 °C; bp 106 °C; *d* 1.675 g cm^{-3}; *n* 1.461.

Solubility: sol THF, MeCN, CH_2Cl_2, many other solvents.

Form Supplied in: colorless, fuming liquid; commercially available.

Purification: by distillation in vacuo.[4]

Handling, Storage, and Precautions: toxic and corrosive; reacts vigorously with alcohols and water, liberating HCl, phosphoric acid, and heat. Protect from water. Use in a fume hood.

Chloromethyleneiminium Ions.[5-8]

Phosphorus oxychloride (**1**) is a strong Lewis acid that is widely used in synthesis. Of particular importance are reactions of (**1**) with substituted amides, most often ***N,N-Dimethylformamide*** or dimethylacetamide (DMA). These reactions lead to the formation of chloromethyleneiminium salts (**2**) (eq 1). These salts (Vilsmeier reagents, see ***Dimethylchloromethyleneammonium Chloride***) are highly versatile intermediates[6] and are involved in numerous important reactions, including the Vilsmeier-Haack[2,6] and Bischler-Napieralski[9] reactions. Formation of (**2**) can be achieved using ***Thionyl Chloride*** or ***Phosgene***, although there have been reports of differences in reactivity between $POCl_3$/DMF, $SOCl_2$/DMF, and $COCl_2$/DMF systems.[7,10,11]

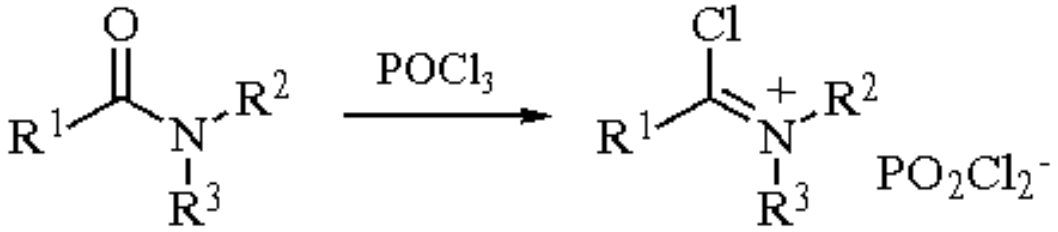

(1)

(2)

Formylation of Aromatic Rings.[2,5,6,8,11]

The Vilsmeier reagent attacks electron-rich aromatic systems to form arylmethyleneiminium ions which liberate a formylated aromatic compound upon hydrolysis (eq 2). Thio- and selenoaldehydes can be prepared by hydrolysis in the presence of ***Sodium Hydrogen Sulfide***[6,12] or ***Sodium Hydrogen Selenide***.[13] A wide range of aromatic systems[6,11] can be formylated in this fashion, including benzene derivatives, polyaromatic hydrocarbons (eq 3), and azulene.[11] Substitution occurs at relatively electron-rich positions.

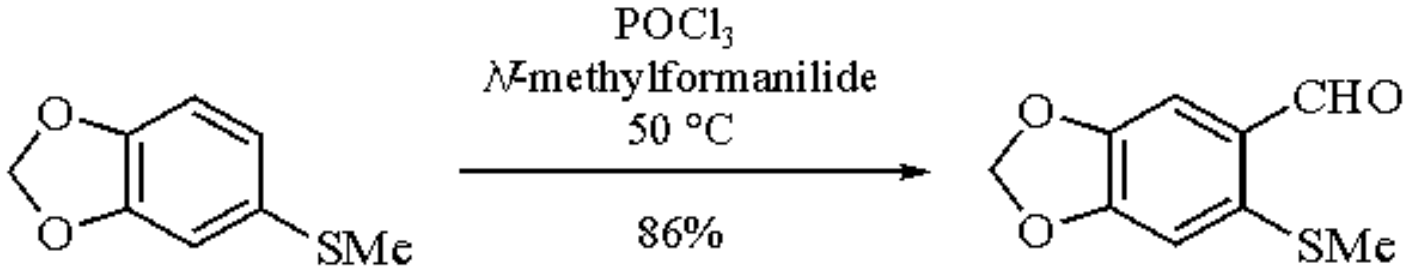

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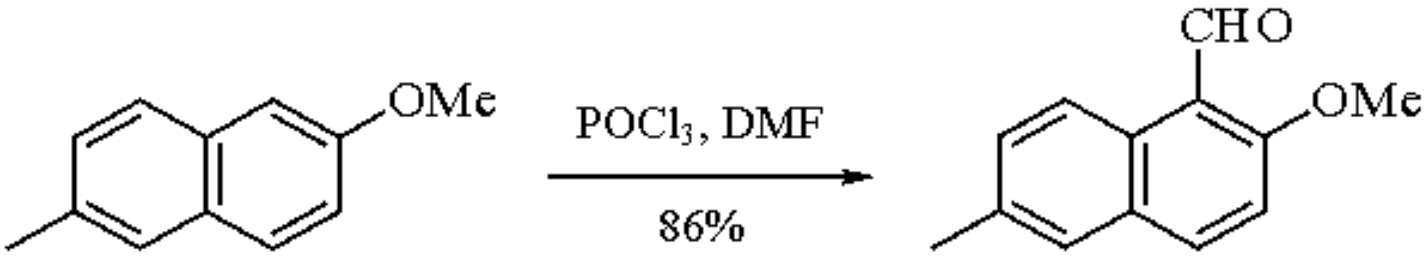

(3)

Formylation of Heterocycles.[6,11,14]

Many heterocycles are readily formylated by $POCl_3$/DMF, including pyrroles, thiophenes, furans, indoles, quinolines, pteridines, and purines.[6] Reaction at the 2- and 5-positions of pyrroles, furans, and thiophenes is preferred, and indoles undergo attack at the 3-position (eq 4).[6]

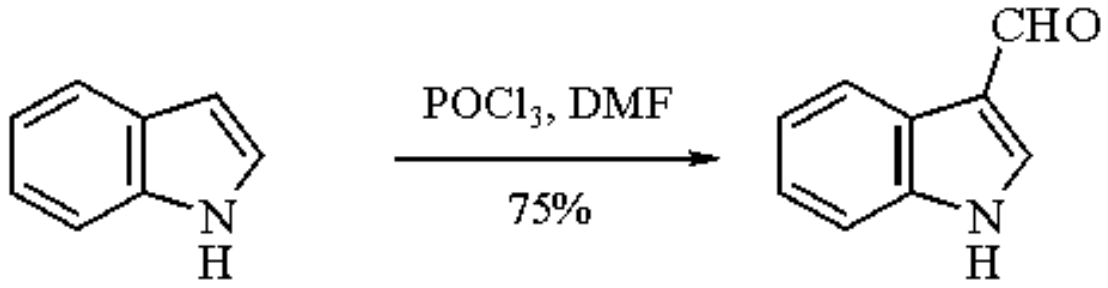

(4)

Formylation of Alkenes.[10,11]

Both activated and unactivated alkenes undergo electrophilic attack by (**2**).[5] Reaction at terminal positions is preferred.[6] Styrene derivatives give cinnamaldehydes; enamines[6] and aryl polyenes[15,16] react at terminal positions (eq 5).

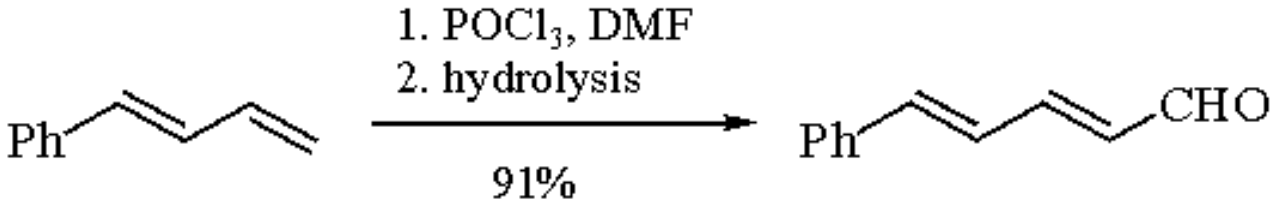

(5)

Bischler-Napieralski Reaction.

A widely used method for cyclization of *N*-β-phenylethyl amides to form dihydroisoquinolines and isoquinolines (eq 6)[17-19] is the Bischler-Napieralski reaction.[9] A nitrilium ion intermediate has been implicated in this reaction.[20,21]

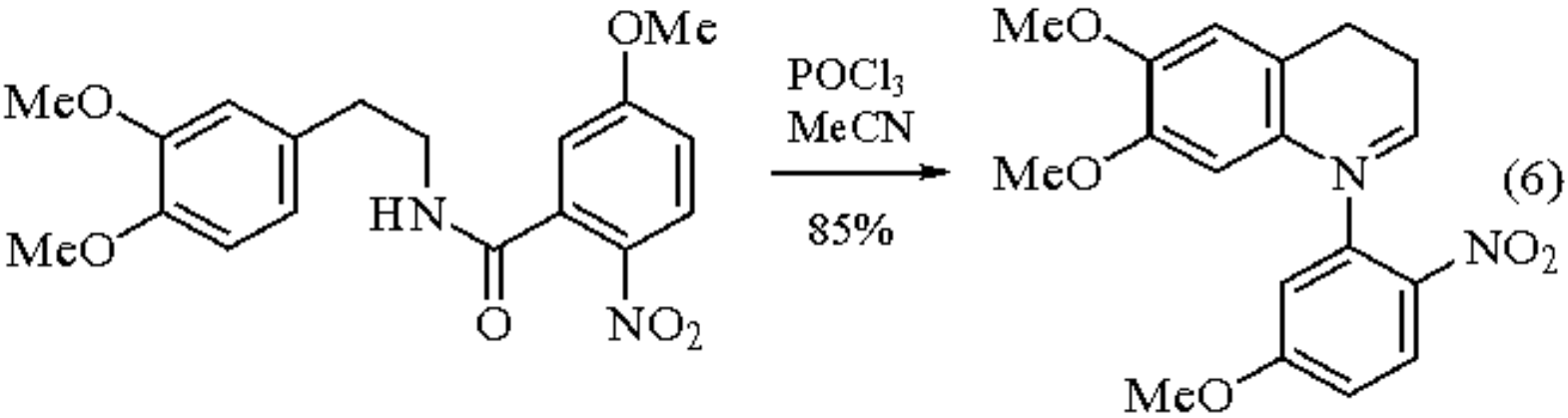

(6)

Fragmentation of the nitrilium ion interferes with the cyclization[20,21] of 1,2-diphenylethane derivatives, leading to formation of stilbenes rather than cyclization products. This problem has been overcome by using ***Oxalyl Chloride*** instead of (**1**).[22] Fragmentation (von Braun reaction or retro-Ritter reaction) occurs whenever a highly stable cation can be formed, such as benzyl[20] or *t*-butyl (eq 7).[21,23,24]

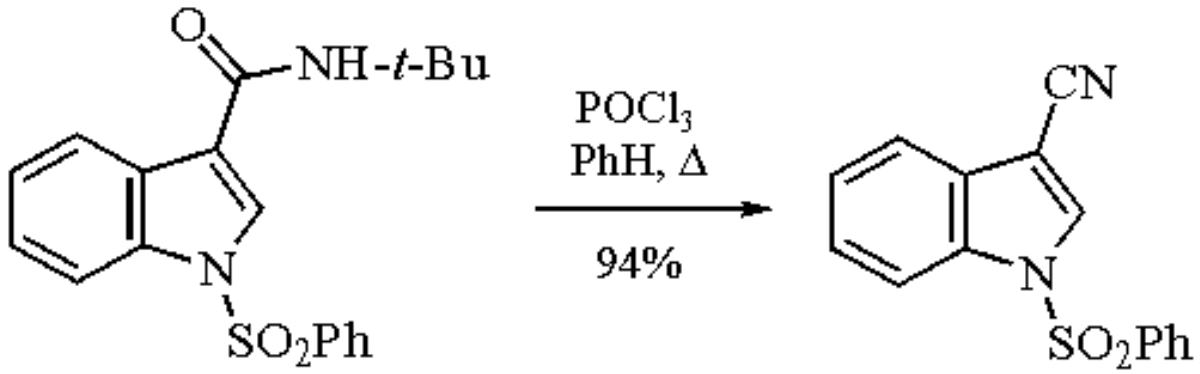

(7)

Treatment of tertiary amides with $POCl_3$/DMF (**2**) results in formation of β-dimethylamino α,β-unsaturated amides. The highly electrophilic iminium ion (**3**) is formed in this reaction, and in the presence of an alkene this undergoes cyclization (eq 8).[14,25]

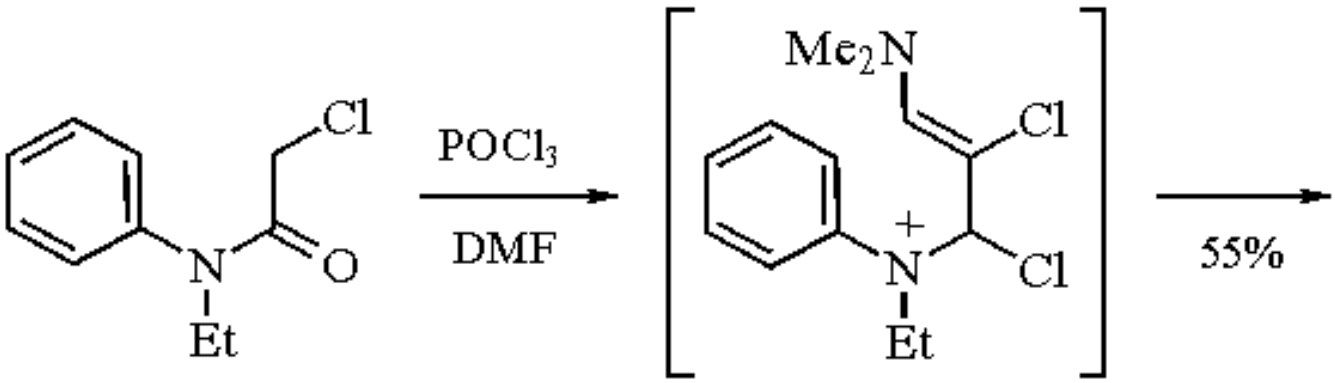

(3)

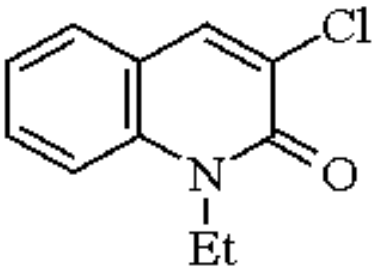

(8)

Excess $POCl_3$ and DMF can lead to formylation of the initial heterocycle (eq 9). A series of α-substituted acrylonitriles has been prepared by dehydration of α,β-unsaturated amides (eq 10). $POCl_3$/DMF and $SOCl_2$/DMF give comparable results.[26]

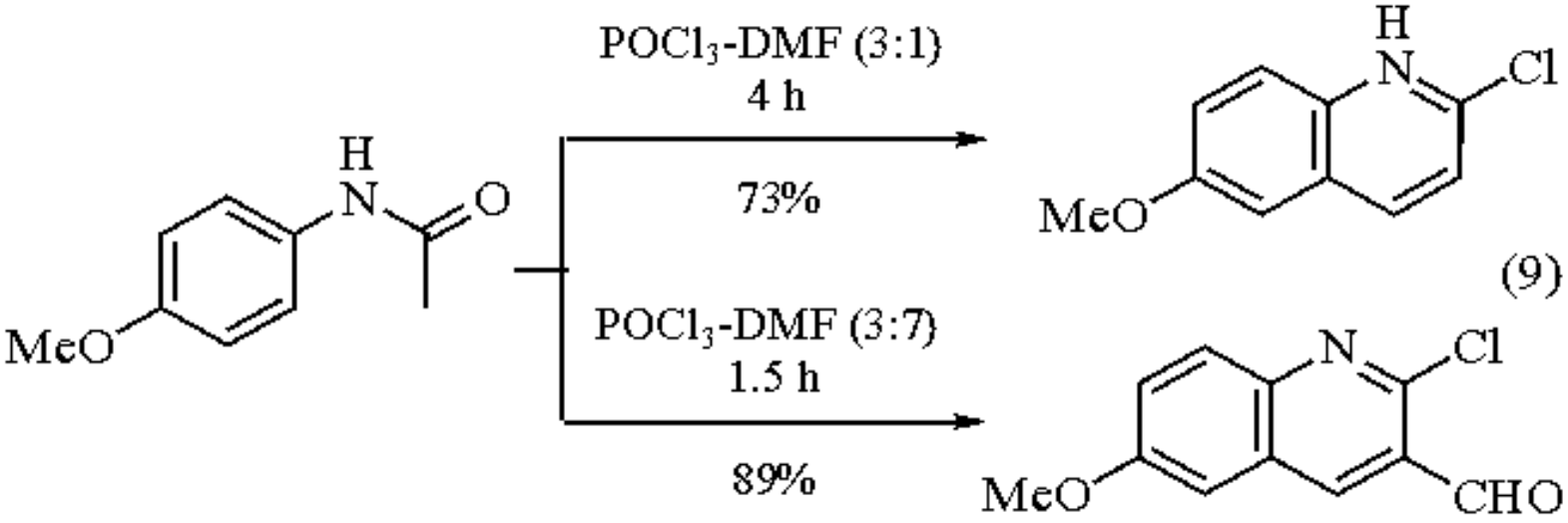

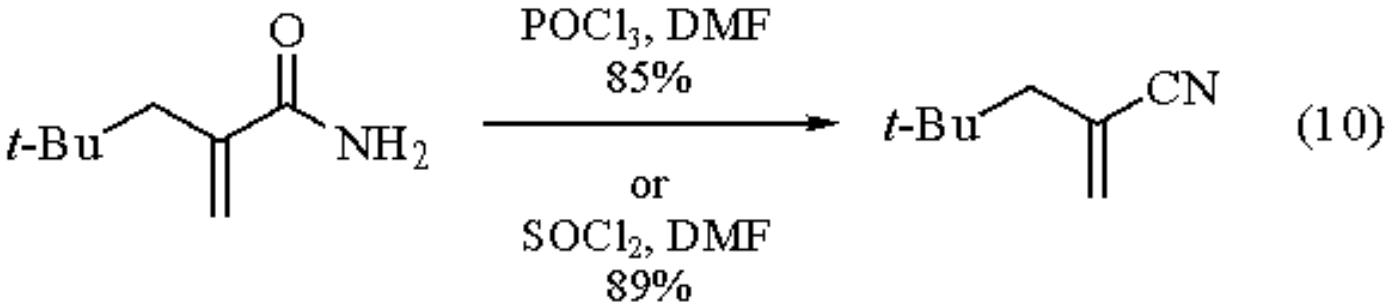

Chloroaldehydes from Carbonyl Compounds.[7]

The enol tautomers of ketones react with $POCl_3$/DMF to form β-chloroacrolein derivatives (eq 11). The regiochemistry is determined both by the stability of the enol as well as by steric factors. Nonsymmetrical ketones often give a mixture of regioisomers, and most ketones produce a mixture of (*E*) and (*Z*) isomers of the product.[27] Aldehydes will undergo this type of reaction, although there are relatively few reports.

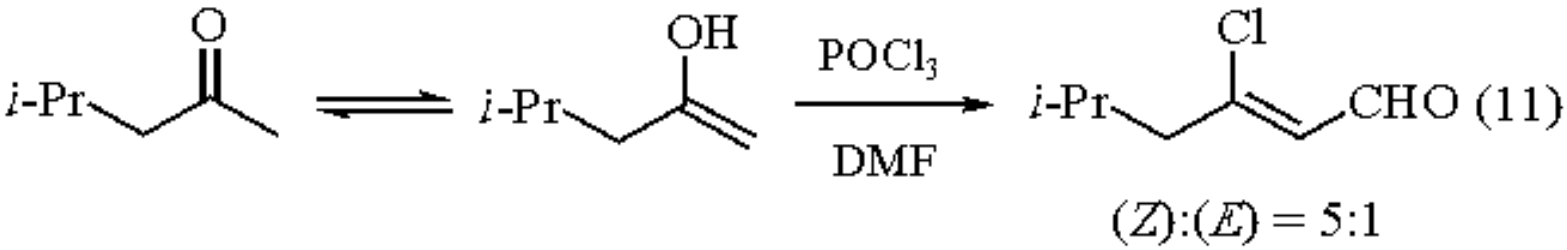

Reaction of $POCl_3$/DMF with carboxylic acids results in vinamidinium ions (eq 12).[28,29] These ions react with a variety of nucleophiles to produce pyrazoles, oxazoles, pyrimidines, diazepines, quinolines, quinolizines, and vinylogous sulfonamides.[30]

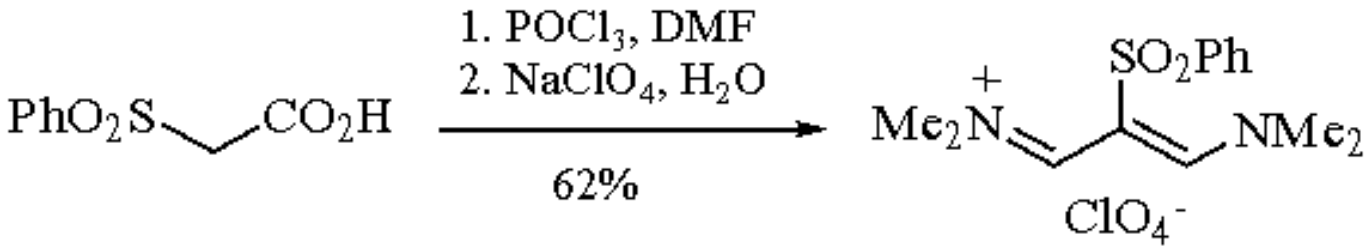

(12)

The Vilsmeier reagent (**2**) reacts with Grignard reagents as well as with alkylzinc and alkylaluminum reagents to form tertiary amines.[31] It also reacts with heteroatom nucleophiles, including thiols,[32] alcohols, and amines,[8] as well as with nucleophilic amines containing other functional groups.[5,33,34] Aromatic alcohols react with $POCl_3$/DMF to form aryl formates in 50-80% yield,[35] but aliphatic alcohols are more efficiently formylated with ***Benzoyl Chloride***/DMF.[36] Homoallylic alcohols such as (**4**) produce biphenyls in 30-98% yield[16] through initial dehydration[6] (eq 13) followed by electrophilic attack on the resulting aryl diene.

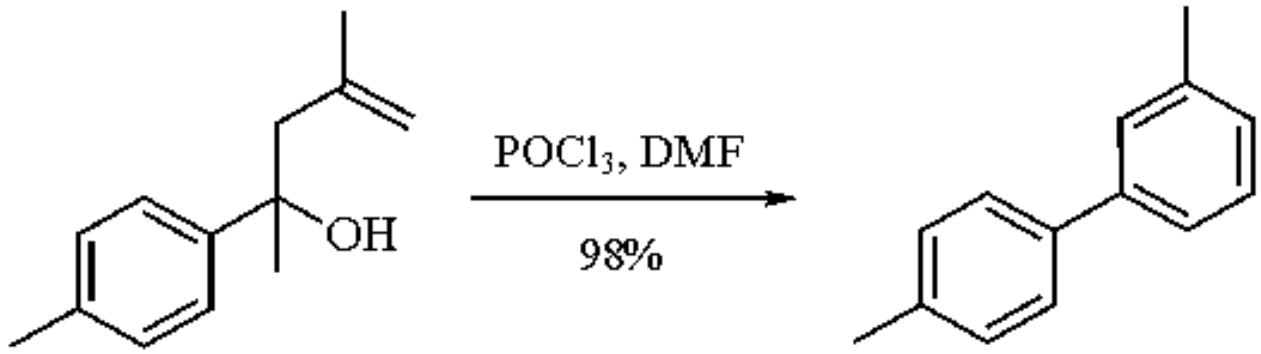

(13)

(**4**)

Halogenation of Alcohols.

The combination of $POCl_3$ and DMF can be used to halogenate primary, secondary, and tertiary aliphatic alcohols (eq 14),[37] whereas the reaction of primary alcohols and $POCl_3$ without DMF or DMA will generally lead to the formation of trialkyl phosphates.

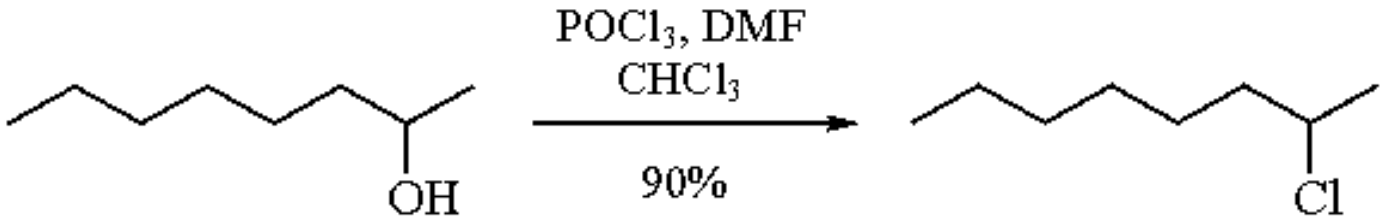

(14)

A comparison of $POCl_3$ with SO_2Cl_2, PCl_3, MsCl, and $SOCl_2$ indicated that optimum conditions for the conversion of (**5**) to (**6**) (eq 15) are 1.1 equiv $POCl_3$ in DMF at 0 °C.[38]

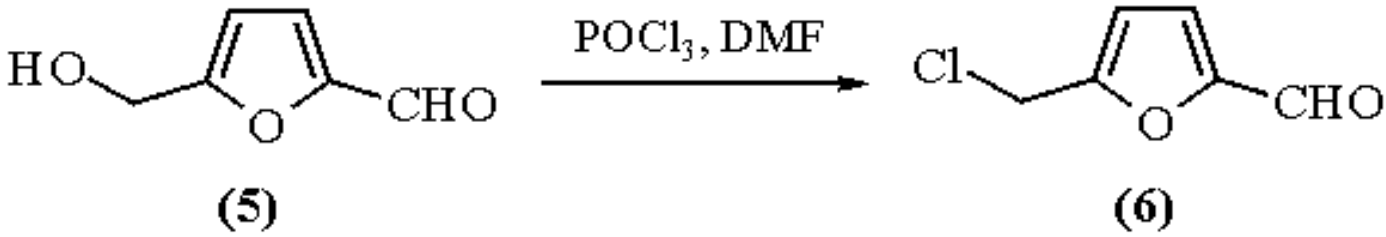

(15)

Halogenation of Heterocycles.

Phosphorus oxychloride is widely used in the chlorination of heterocycles. In general, heterocyclic ketones (eq 16) or alcohols (eq 17) react readily with (**1**), including pteridines,[39] purines,[40,41] and others.

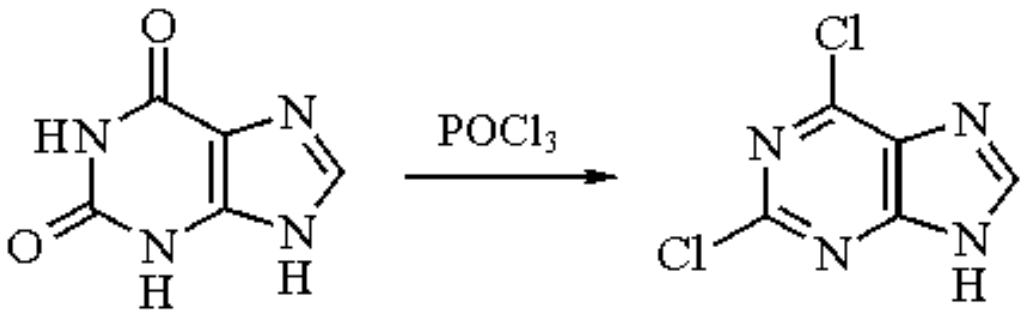

(16)

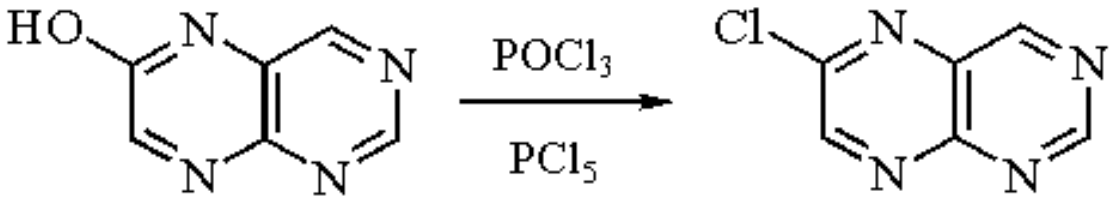

(17)

In the chlorination of the isoxazole (**7**), it was noted that freshly distilled $POCl_3$ is ineffective but that an older sample leads to the formation of the chloride (**8**). Further investigation showed that a mixture of $POCl_3$, acid (H_3PO_4), and an additional chloride source (pyridinium chloride) leads to reliable conversion of (**7**) to (**8**) (eq 18).[42]

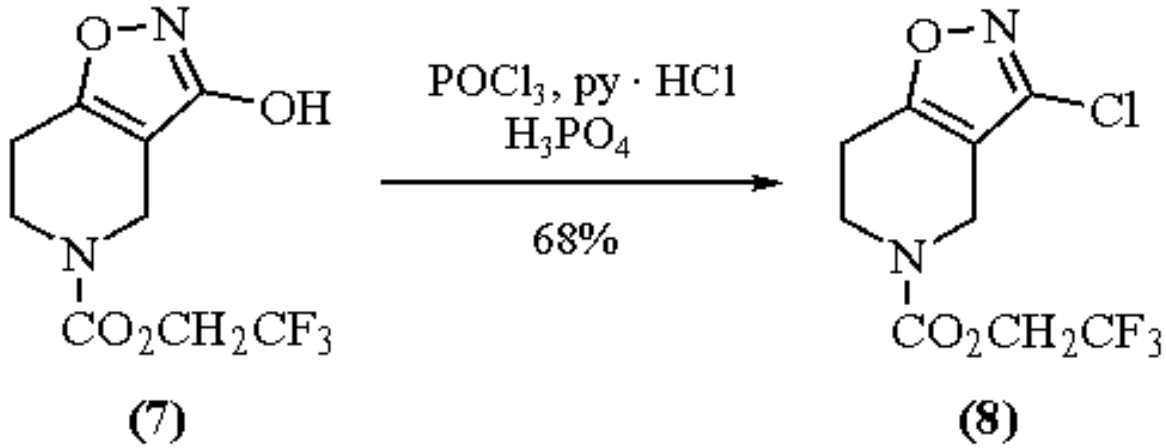

(18)

Phosphorylation.[3,43]

Phosphorus oxychloride reacts with alcohols, amines, and thiols, resulting in phosphorylation of these functional groups. Trimethyl phosphate is a particularly effective solvent,[44] and tertiary amine bases are generally used as well. Treatment of primary alcohols with $POCl_3$ results in the formation of phosphonyl dichloride intermediates which, in the presence of excess alcohol, convert to symmetrical trialkyl phosphates.[10] It is generally possible to isolate aryl phosphorodichloridates when a two-fold excess of (**1**) is used and $AlCl_3$, KCl, or pyridine is used as a catalyst.[45,46] Secondary and tertiary alcohols tend to form alkyl chlorides and phosphoric acid.

Phosphorus oxychloride is very useful in the preparation of nucleoside 5´-phosphates (eq 19) given appropriate mixtures of $POCl_3$, pyridine, and water.[44,47] The primary hydroxy (5´) is sufficiently reactive for there to be minimal formation of cyclic phosphates at the 2,3-positions of nucleosides. The intermediate phosphorodichloridate can be converted to the corresponding triphosphate by treatment with inorganic phosphate in a convenient one-pot fashion.

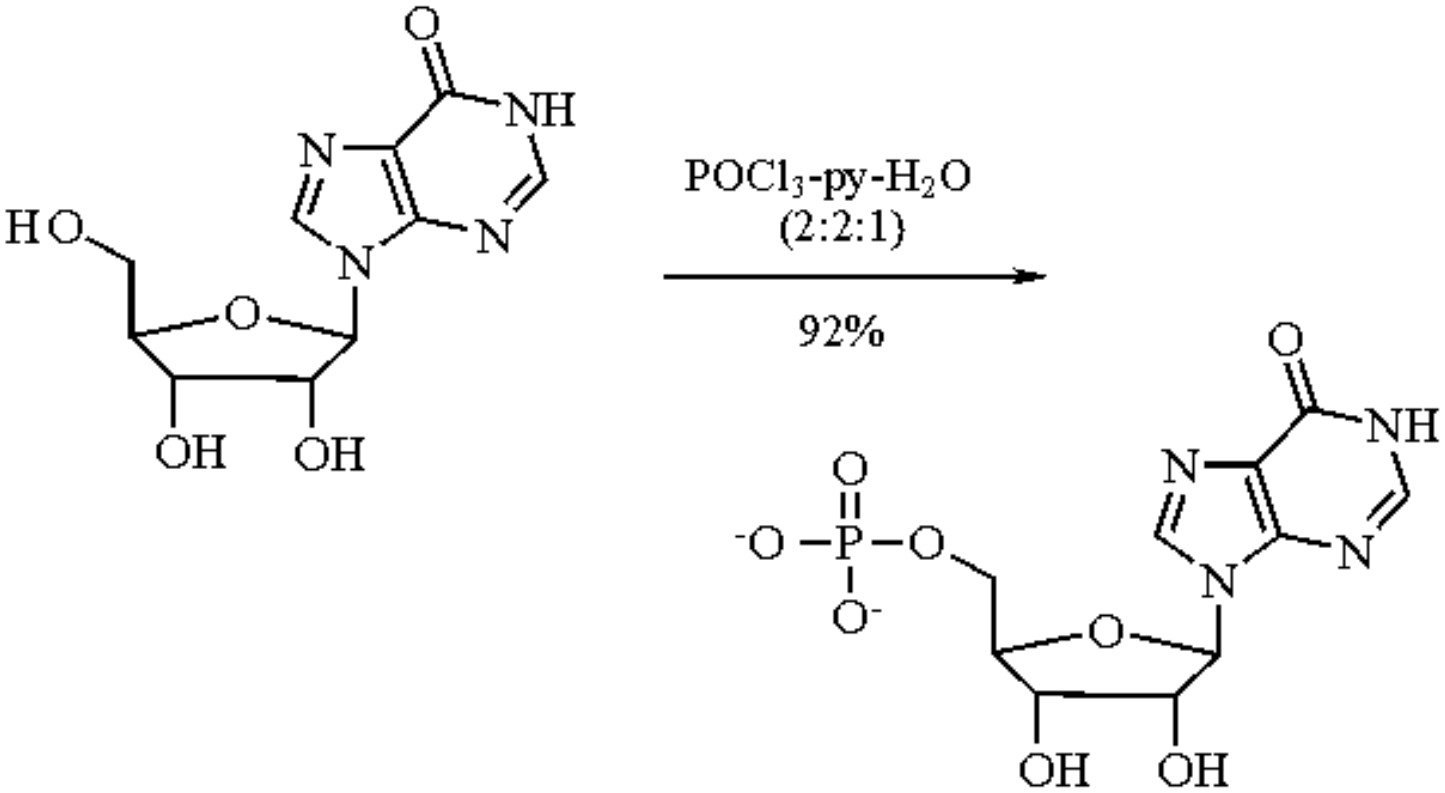

(19)

Under anhydrous conditions, $POCl_3$ can be used to produce cyclic dialkyl phosphonyl chlorides from diols, and these can be hydrolyzed with water to the cyclic phosphates or with an alcohol to trialkyl phosphates. Treatment of forskolin (**9**) with $POCl_3$ leads to the formation of the cyclic phosphoryl chloride (**10**) in 55% yield as a mixture of two stereoisomers at phosphorus (eq 20).[48] A comparison of several phosphorylating agents showed that $POCl_3$, $(MeOC_6H_4)_2POCl$, and 2-chloro-2-oxo-1,3,2-dioxaphospholane all give the analogous products in virtually identical yield.[48]

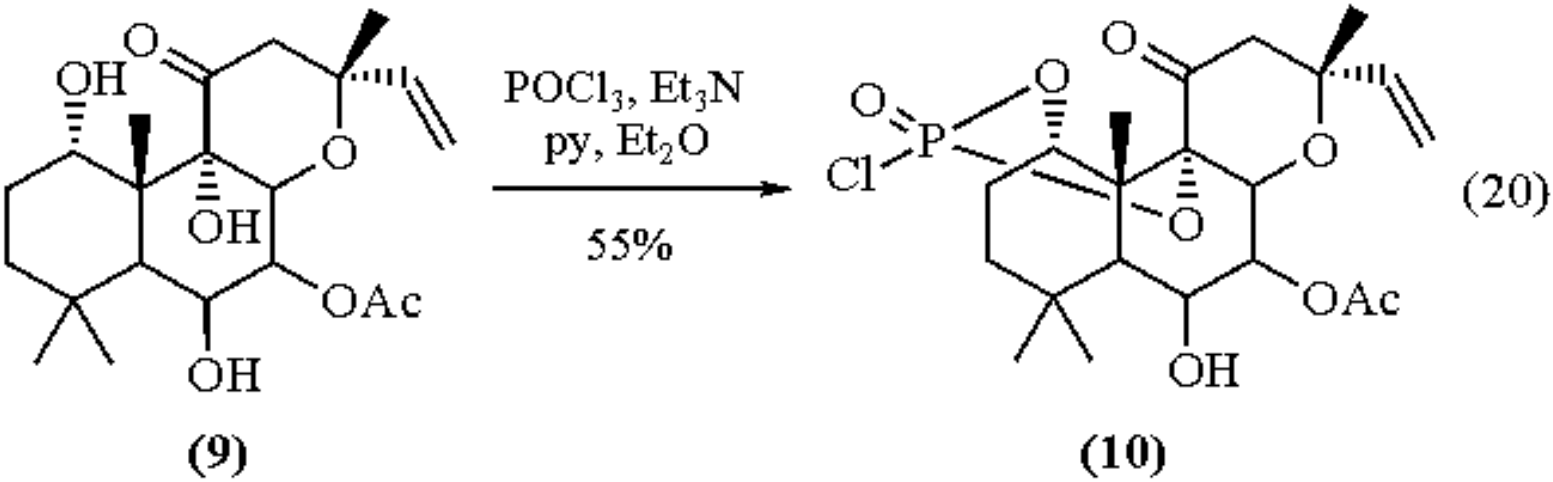

Similar results can be obtained with primary amines,[49] although it is possible to obtain diamidophosphorochloridates by reaction of $POCl_3$ with substoichiometric amounts of amine.[50] Phosphorus oxychloride reacts more readily with primary amines than with primary alcohols, so that it is possible to prepare phosphoramides.[51] Alkoxides, however, react more rapidly than amines so it is possible to phosphorylate hydroxyls in the presence of amines. Again, like the reaction of $POCl_3$ with diols, diamines react with $POCl_3$ to form diazaphospholidines (eq 21).[52]

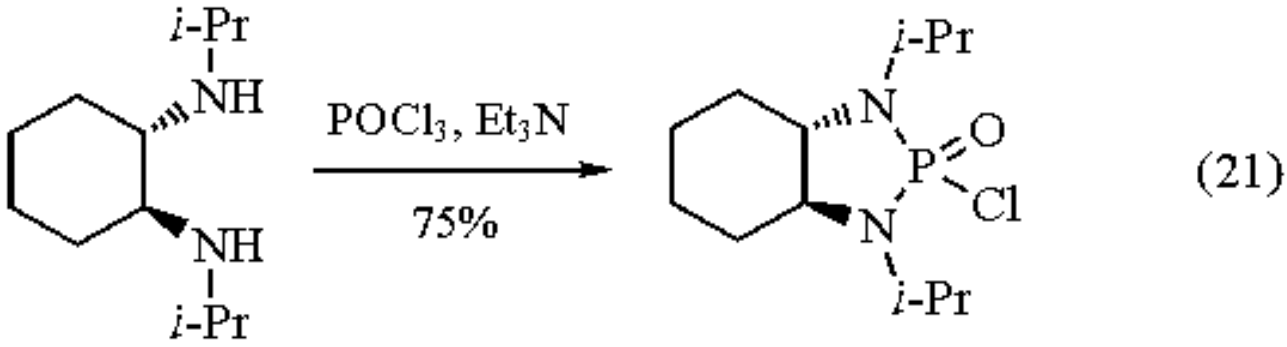

Carboxylic anhydrides can be prepared by treatment of carboxylic acids with $POCl_3$,[32] allowing the formation of both esters[32] and amides, although other methods are more common.[53] Dichloroacetyl chloride produces dichloroketene when treated with $POCl_3$ and ***Zinc/Copper Couple***.[54]

Dehydration of Amides.

Unsubstituted amides undergo dehydration upon treatment with $POCl_3$. This reaction can also be performed with P_2O_5, $SOCl_2$, or other reagents, and in a study of racemization at the α-position it was determined that dehydration with $POCl_3$ leads to more (albeit little) epimerization than dehydration with P_2O_5 or $SOCl_2$ (eq 22).[55]

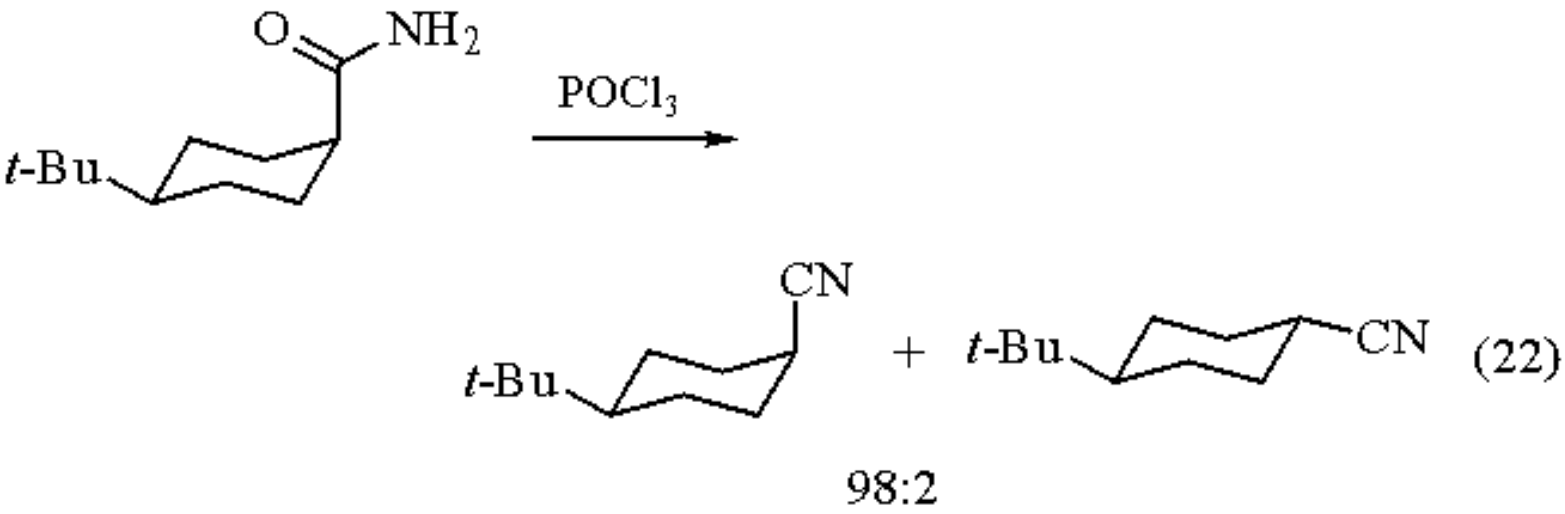

Dehydration of alkyl and aryl *N*-formyl compounds with $POCl_3$ is one of the more general routes to alkyl and aryl isocyanides (eq 23).[56-59] A base, typically an amine base or ***Potassium t-Butoxide***, is also required. The method is simple and effective, although less useful for small, volatile isocyanides than other techniques.[60] The Bischler-Napieralski reaction can occur preferentially to isocyanide formation.[17]

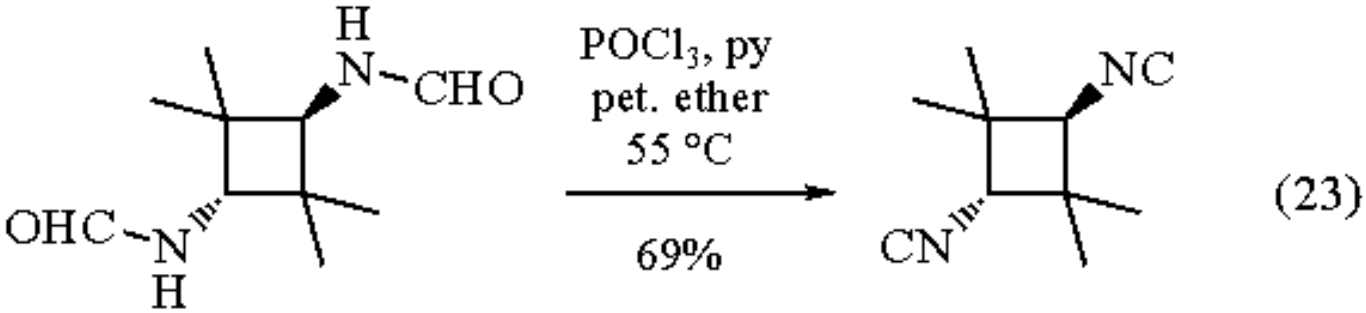

Dehydration of Alcohols.

The combination of $POCl_3$ and ***Pyridine*** is an effective dehydrating agent for alcohols (eq 24)[61] and cyanohydrins.[62] The stereochemistry of elimination is *anti*, although the regioselectivity is often not high, particularly for tertiary alcohols.[63]

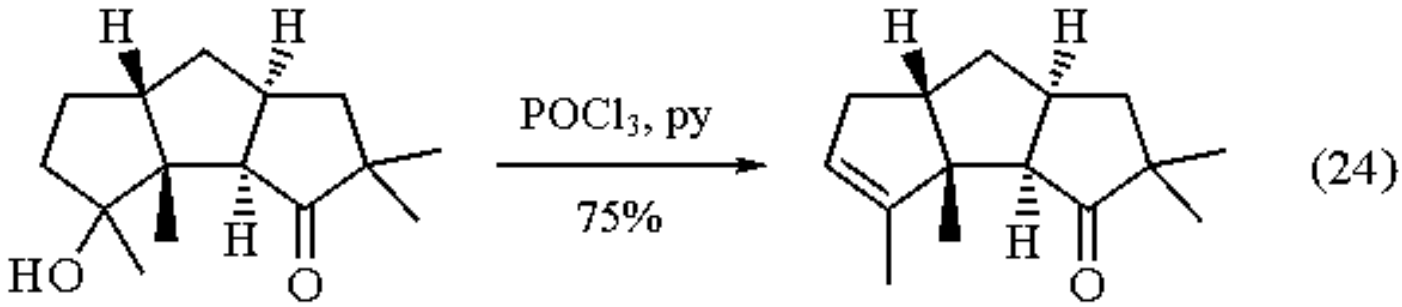

The combination of phosphorus oxychloride and ***Tin(II) Chloride*** reduces halohydrins to alkenes (eq 25). The elimination proceeds in an *anti* fashion.[64]

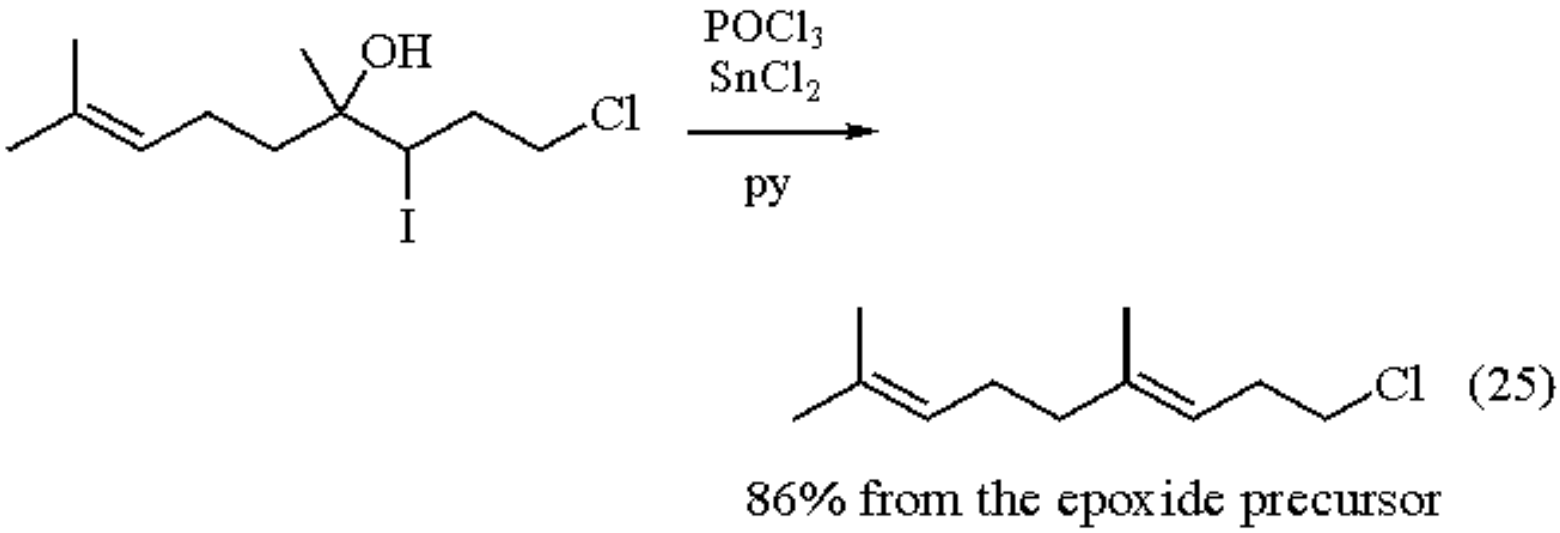

Beckmann Rearrangement.

Treatment of ketoximes with $POCl_3$ induces Beckmann rearrangement to form amides (eq 26).[65] Numerous other Lewis acids can be used for this transformation.[66,67]

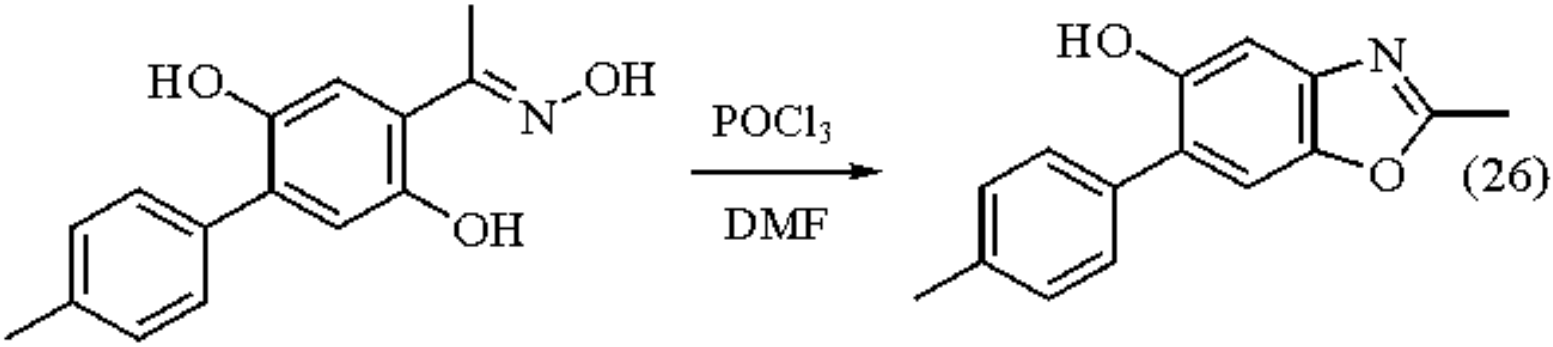

Related Reagents.

Bis(trichloromethyl) Carbonate; ***Phosphorus(V) Oxide***; ***Phosphorus Oxychloride-Zinc(II) Chloride***; ***Thionyl Chloride***; ***p-Tolyl Vinyl Sulfoxide***; ***Trichloromethyl Chloroformate***.

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Phosphorus Oxychloride-Zinc(II) Chloride

$POCl_3$-$ZnCl_2$

($POCl_3$)

[10025-87-3] · Cl_3OP · Phosphorus Oxychloride-Zinc(II) Chloride · (MW 153.32) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Phosphorus Oxychloride-Zinc(II) Chloride · (MW 136.29)

(powerful Lewis Acid used in Friedel-Crafts reactions to prepare xanthones,[1] benzophenones,[2] coumarins,[3] and chromanones;[4] phosphorylation of alcohols[5])

Physical Data: see entries for ***Phosphorus Oxychloride*** and ***Zinc Chloride***.

Handling, Storage, and Precautions: in most cases, freshly fused $ZnCl_2$ must be used for the best results. See ***Phosphorus Oxychloride*** for potential hazards.

Friedel-Crafts Reactions.

Phosphorus oxychloride and zinc(II) chloride combined are used as a catalyst[6] in Friedel-Crafts reactions. Hydroxyxanthones can be prepared by reaction of *o*-hydroxybenzoic acid and hydroxybenzenes in the presence of $POCl_3$ and $ZnCl_2$ (eq 1).[1] Although hydroxybenzophenones are also isolated by this method, they can be converted to xanthones by heating to 200 °C. A variety of hydroxyxanthones[7,8] and methoxyxanthones,[9] as well as benzophenones,[2] can be prepared in this manner.

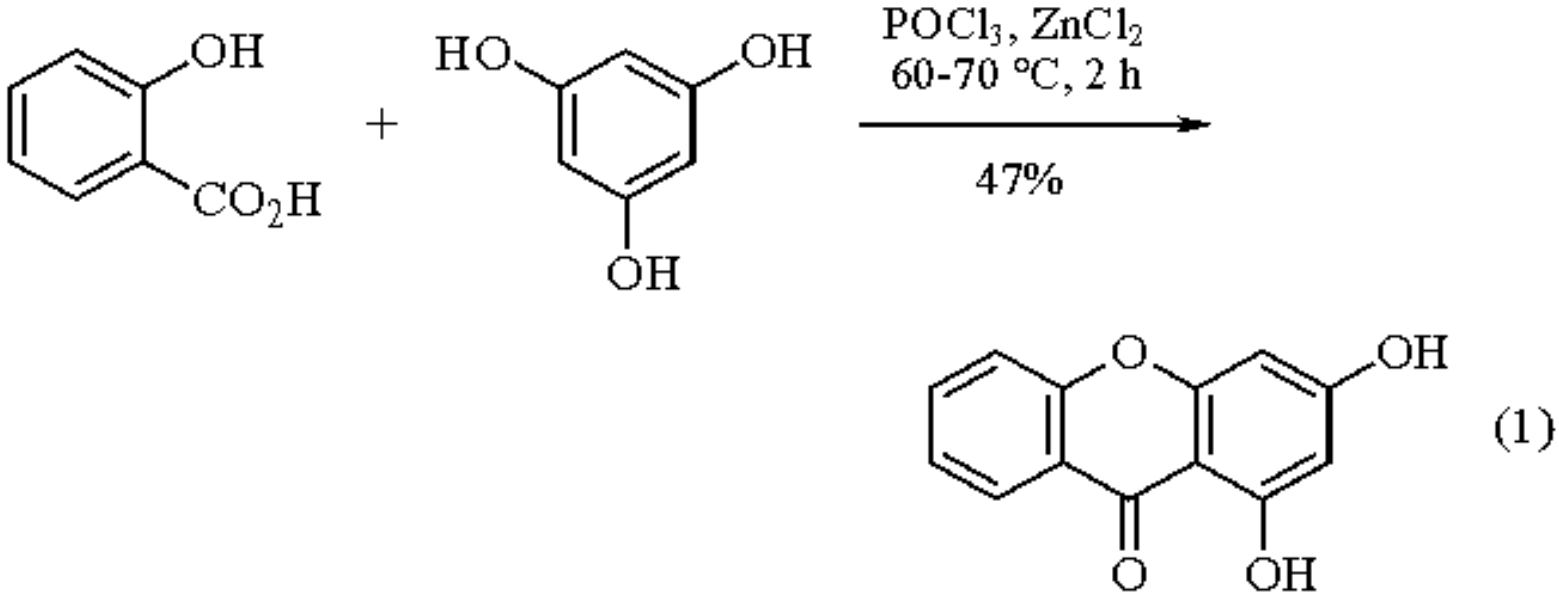

In a similar fashion, the Friedel-Crafts reaction of phenol and malonic acid in the presence of $POCl_3$ and $ZnCl_2$ gives 4-hydroxycoumarin (eq 2).[3] Neither $POCl_3$ nor $ZnCl_2$ are effective alone. Additionally, the use of $AlCl_3$ instead of $ZnCl_2$ is not effective. Other coumarins can also be prepared in a similar manner.[10,11]

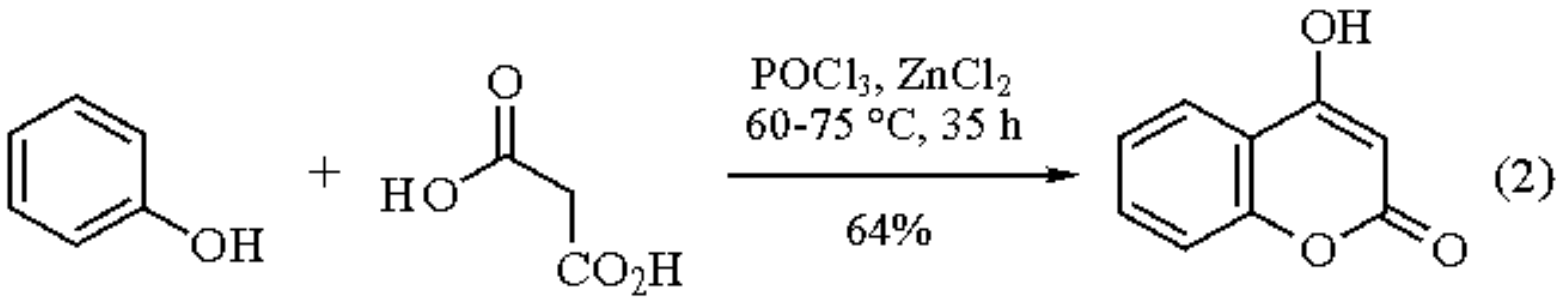

Phosphorus oxychloride and $ZnCl_2$ can also be employed to prepare chromanones from hydroxybenzenes and 3,3-dimethylacrylic acid in one step (eq 3).[4]

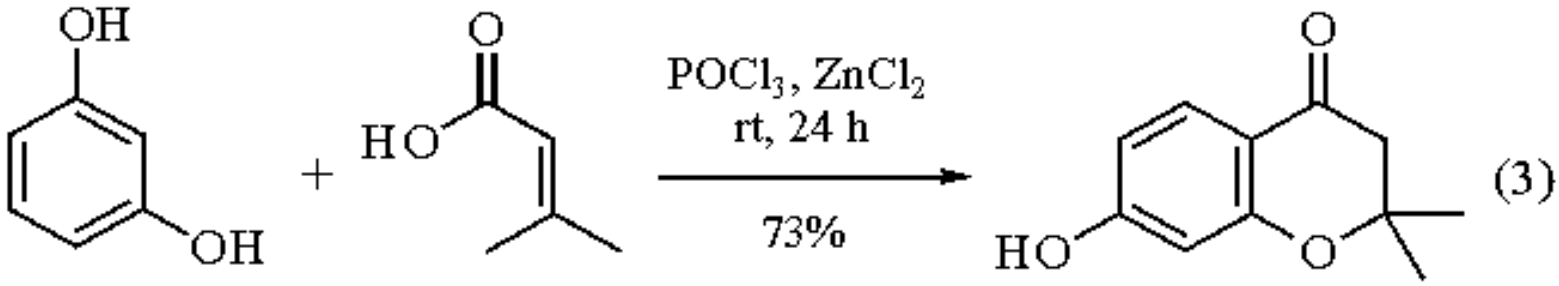

Phosphorylation of Alcohols.

The phosphorylation of alcohols with $POCl_3$ and $ZnCl_2$ can also be accomplished. Simple alcohols,[12] as well as fluorinated alcohols (eq 4),[5] when added in excess to $POCl_3$ and $ZnCl_2$, form phosphates readily.

$$\underset{(3.4\text{-}6\ \text{equiv})}{CF_3CO_2H} \xrightarrow{POCl_3,\ ZnCl_2} (CF_3CH_2O)_3PO \qquad (4)$$

Related Reagents.

Phosphorus(III) Chloride; ***Phosphorus(V) Chloride***; ***Phosphorus Oxychloride***.

---

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Phosphorus(V) Sulfide[1]

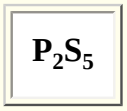

[1314-80-3] · P_2S_5 · Phosphorus(V) Sulfide · (MW 222.29) (P_4S_{10})

[15857-57-5] · P_4S_{10} · Phosphorus(V) Sulfide · (MW 444.58)

(thiating agent for many different types of compounds;[1,2] can activate carboxylic acids and alcohols;[3] deoxygenating agent;[4] dehydrating agent;[5] can undergo electrophilic aromatic substitution at phosphorus[6])

Alternate Name: phosphorus pentasulfide.

Physical Data: mp 286-290 °C; bp 514 °C; *d* 2.09 g cm^{-3}.

Solubility: sol CS_2 (0.2 g/100 g) and aq soln of alkali hydroxides; modestly sol ethers, aromatics, tertiary amines, chlorinated solvents, MeCN; reacts with DMSO, primary and secondary amines, alcohols, and neutral or acidic H_2O.

Form Supplied in: exists as P_4S_{10}; light yellow crystalline solid; widely available.

Analysis of Reagent Purity: melting point, IR.[7]

Handling, Storage, and Precautions: a highly flammable solid which decomposes in the presence of moisture (including moist air) to form the toxic gas H_2S and H_3PO_4. It is harmful if inhaled or absorbed through the skin. This reagent should be handled with care in a fume hood in the absence of moisture and oxygen.

Use as a Thiating Agent.

Phosphorus pentasulfide accompanied by a base such as pyridine[8] or $NaHCO_3$ (Scheeren's reagent)[9] has been extensively used as a thiating agent for the conversion of amides,[2,10] ketones,[11] aldehydes,[12] esters,[13] *S*-substituted thioesters,[14] phosphinates,[15] and acid chlorides[16] to thioamides, thiones, thioaldehydes, thioesters, dithioesters, phosphothionates, and thioketenes, respectively. Due to milder reaction conditions, higher yields, and ease of handling, Lawesson's reagent (***2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-Disulfide***) is usually the preferred reagent for these conversions.[13,17] Nevertheless, P_2S_5 accompanied by other agents such as Na_2CO_3/CF_3SO_3Me,[10] ultrasound,[18] alkyllithiums,[19] or Et_3N[20] have been reported to be just as effective and in some

cases more cost efficient than Lawesson's reagent. When used in excess, P_2S_5 has also been shown to convert esters to dithioesters in high yield (eq 1).[20b] Since the substitution of oxygen by sulfur has been reported to be sensitive to steric effects, the least hindered carbonyl compound will react first when given a choice (eq 2).[21]

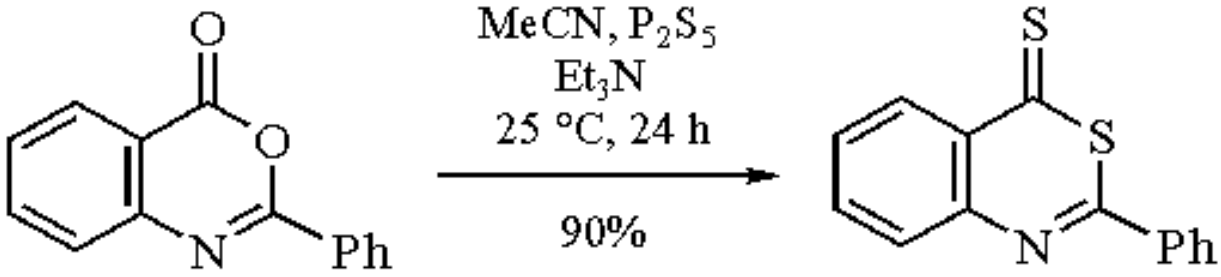

(1)

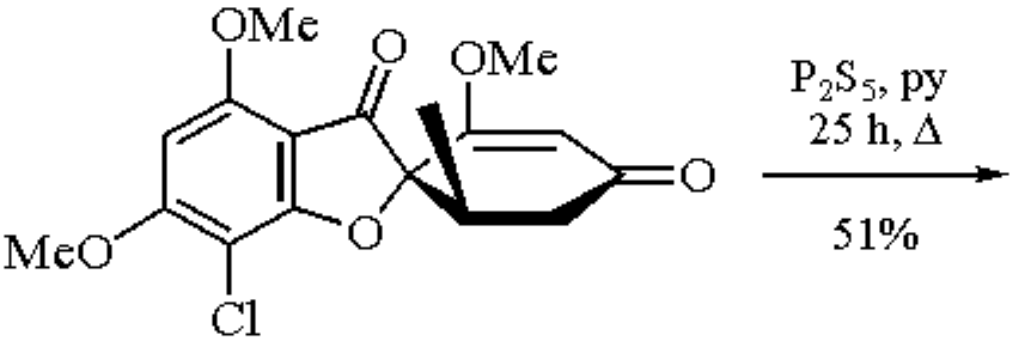

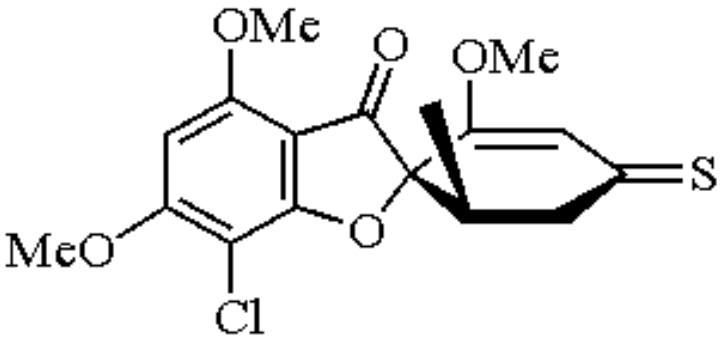

(2)

The presence of other functional groups during these conversions can lead to tandem reactions. The reaction of this reagent with 1,4-dicarbonyl compounds results in the formation of thiophenes (eq 3)[22] or mesoionic thieno[3,4-*f*]benzo[*c*]thiophenes (eq 4).[23] On the other hand, 1,3-dicarbonyl compounds give way to different sets of heterocycles depending on the solvent and temperature (eqs 5, 6).[24,25] The presence of a nucleophilic amine elsewhere in the molecule can lead to further reactions as well (eqs 7, 8).[26,27]

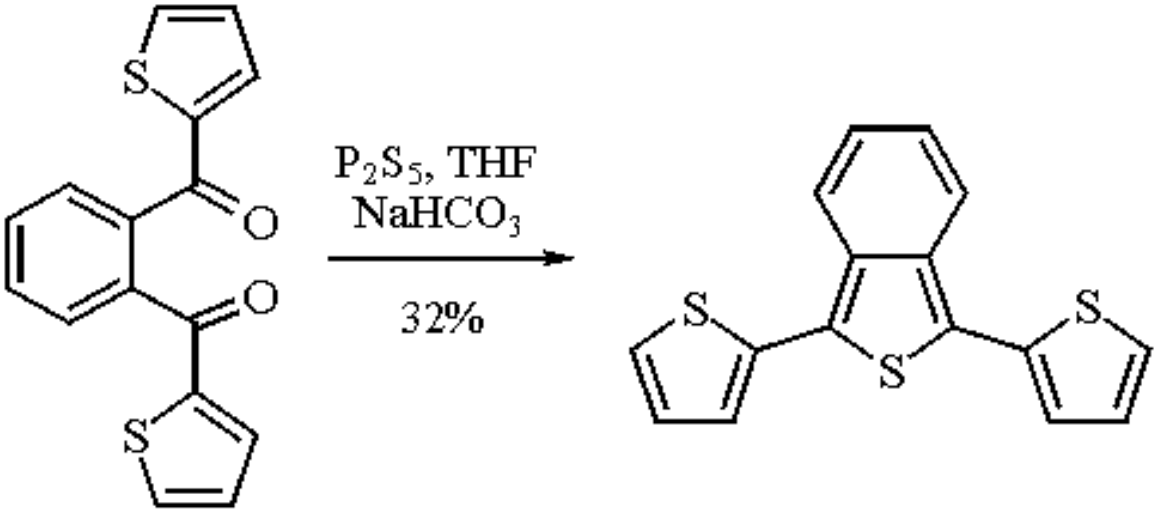
S
O
O
S
P_2S_5, THF
$NaHCO_3$
32%
S
S
S

(3)

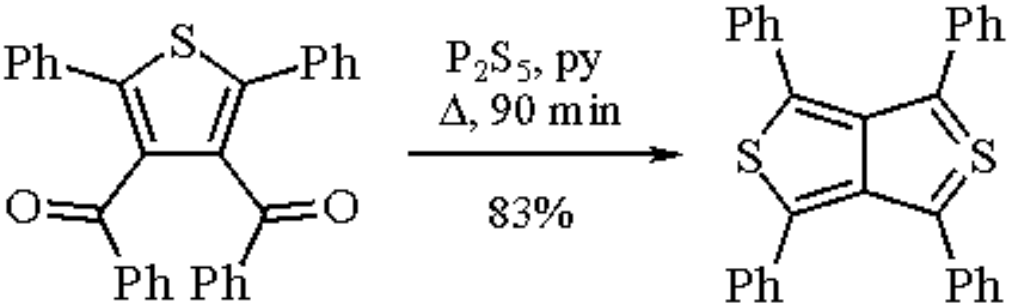
Ph
S
Ph
O
O
Ph Ph
P_2S_5, py
Δ, 90 min
83%
Ph
Ph
S
S
Ph
Ph

(4)

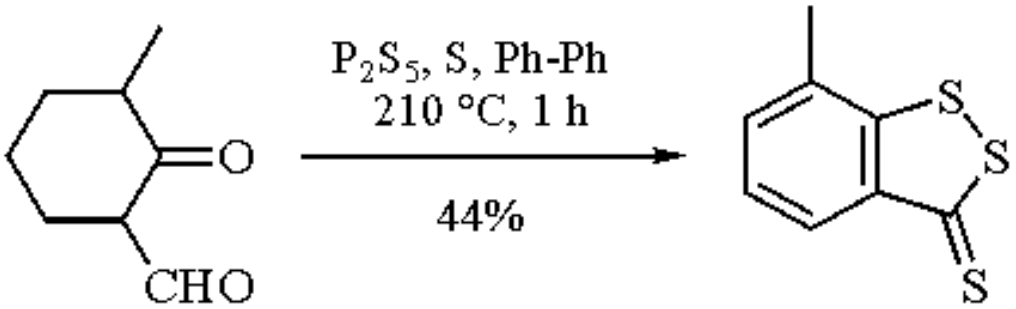
O
CHO
P_2S_5, S, Ph-Ph
210 °C, 1 h
44%
S
S
S

(5)

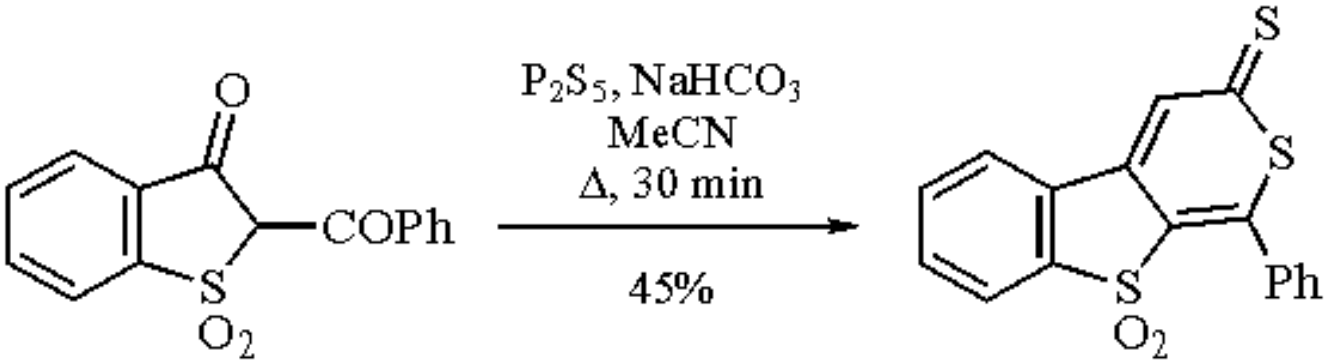
O
COPh
S
O_2
P_2S_5, $NaHCO_3$
MeCN
Δ, 30 min
45%
S
S
S
Ph
O_2

(6)

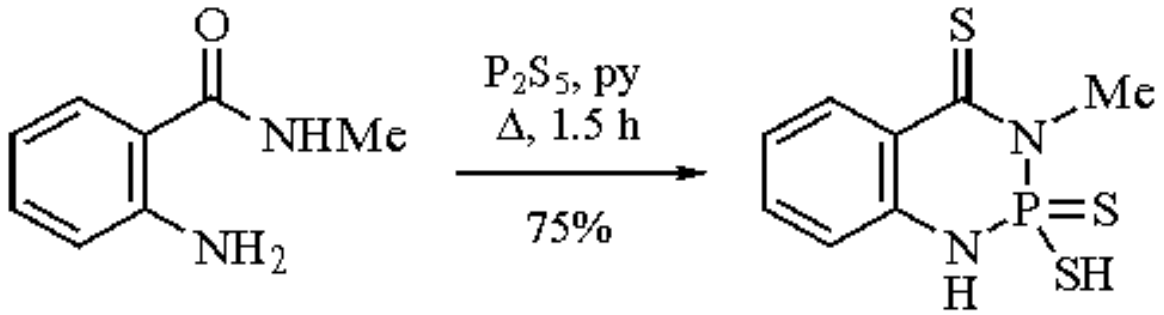

(7)

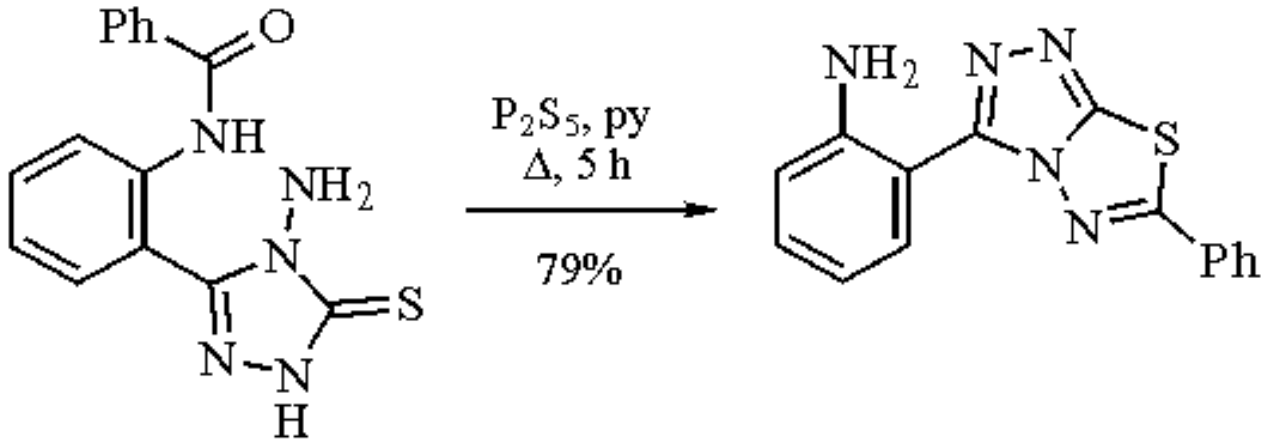

(8)

Some advantage has also been taken of the enhanced nucleophilic character of thiocarbonyl compounds. Strategically placed leaving groups can thus lead to sulfur-containing heterocycles from thioaldehydes (eq 9),[12] thioamides (eqs 10, 11),[28,29] and vinylogous thiocarboxylic acids (eq 12).[30]

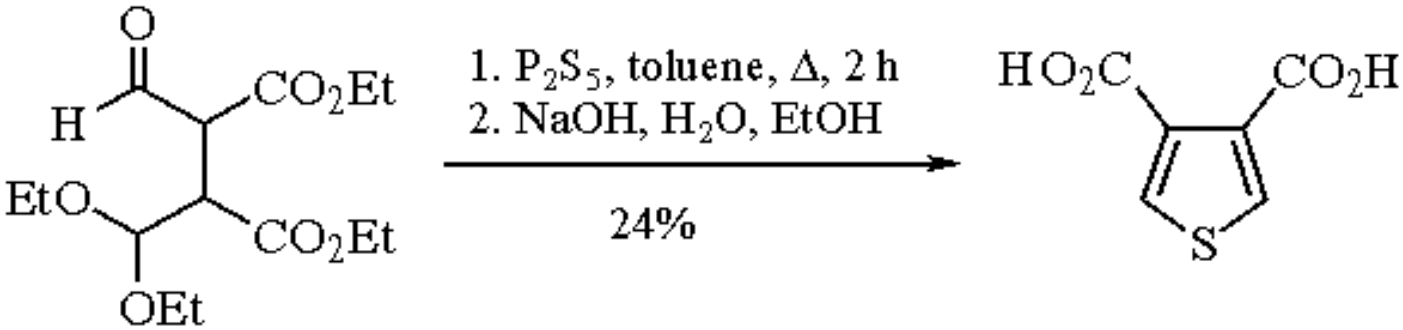

(9)

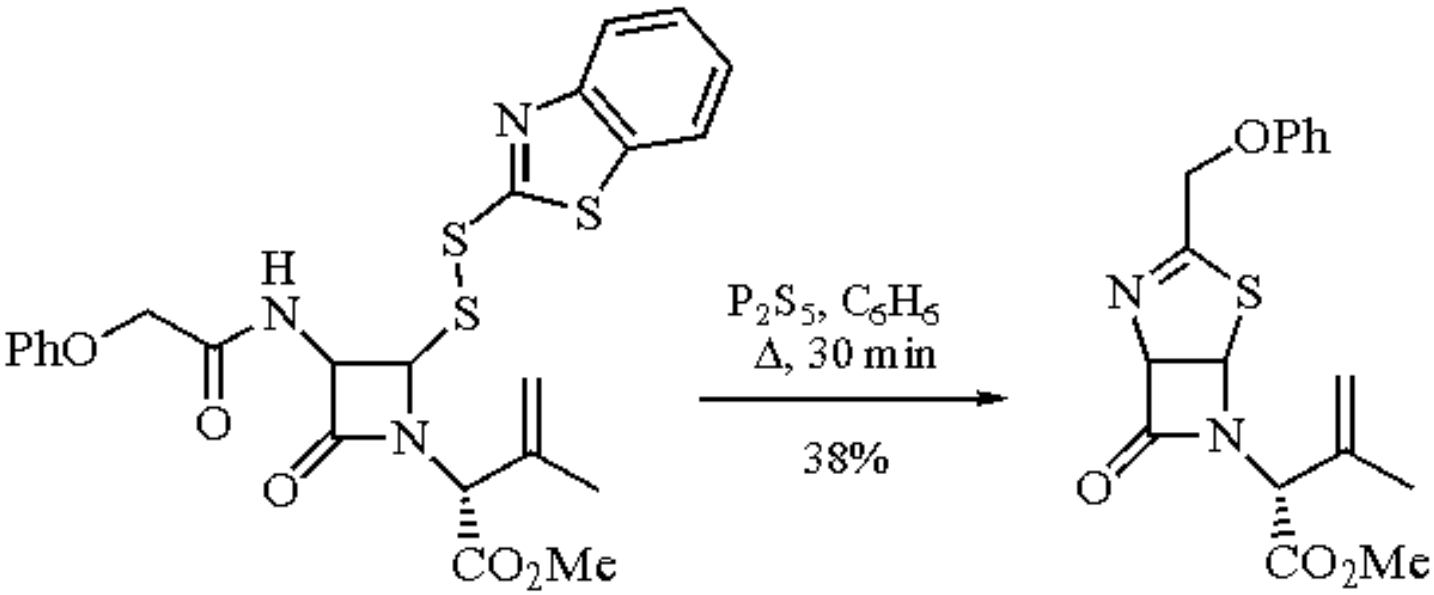

(10)

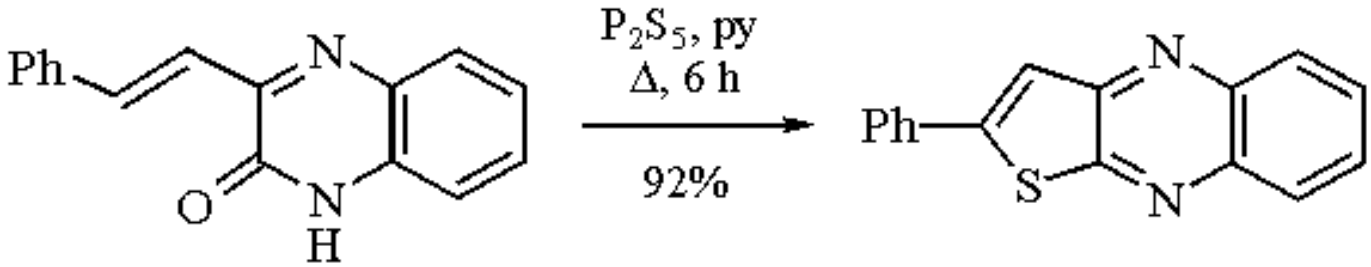

(11)

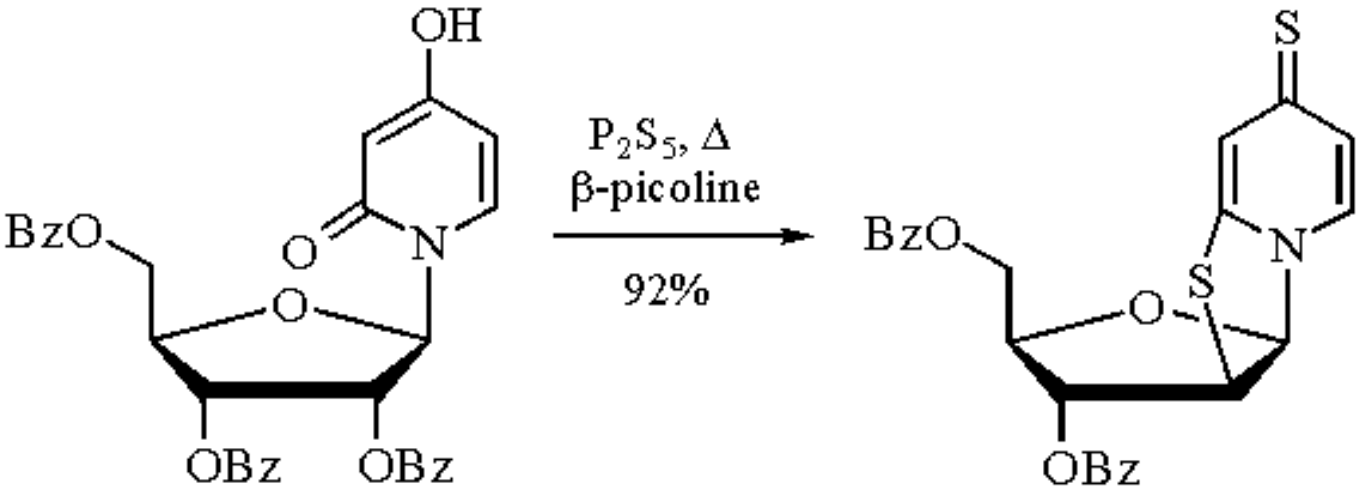

(12)

In some cases, the conversion of a carbonyl to a thiocarbonyl promotes other reactions as well. When acyclic enones are converted to α,β-unsaturated thiones, for example, a [4 + 2] cycloaddition has been observed (eq 13).[31]

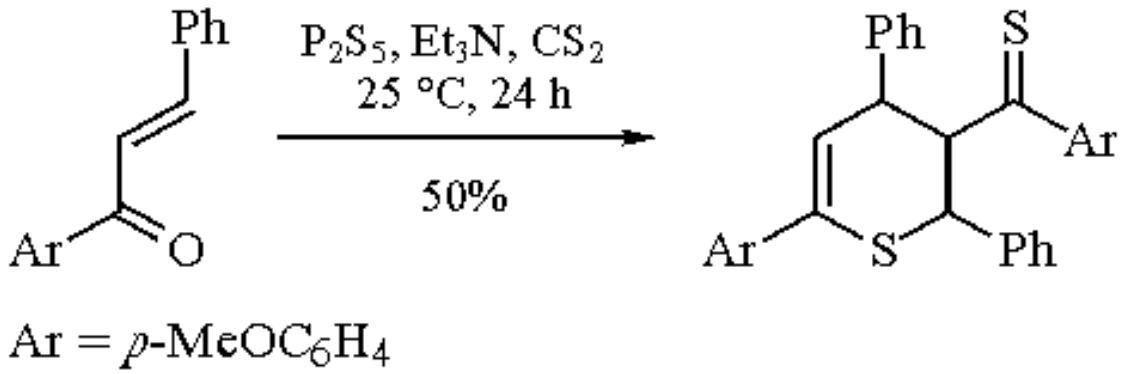

(13)

The conversion of a furan to a thiophene under the aegis of P_2S_5 has also been reported.[5]

Activation of Acids and Alcohols.

Similar to other pentavalent phosphorus compounds, P_2S_5 activates the free hydroxyls of carboxylic acids or alcohols to become good leaving groups. When this activation is done in the presence of another nucleophile, substitution reactions can occur (eq 14).[31] Although P_2S_5/Cl_2 has been used to substitute primary alcohols with chlorides,[3] other reagents appear to be superior for such transformations.

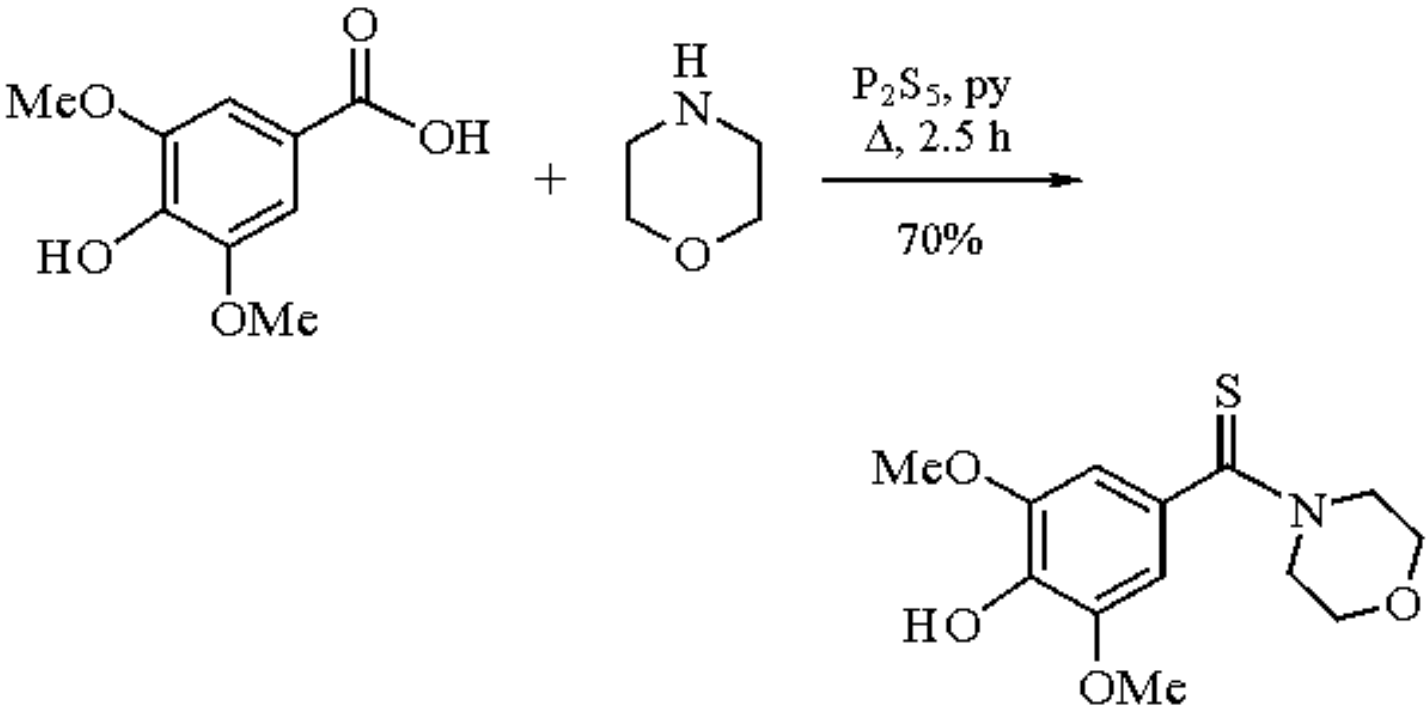

(14)

Use as a Deoxygenating Agent.

P_2S_5 is one of the most mild and selective reagents for the conversion of sulfoxides to sulfides.[4] This reduction will take place selectively without affecting functional groups such as esters, amides (eq 15),[32] or ketones.[33] Interestingly, sulfones are also unreactive under these conditions.[34] Moreover, this reagent can be used for the reduction of sulfilimines to sulfides (eq 16),[35] sulfonic acids to polysulfides,[36] and sulfines to thiones.[37]

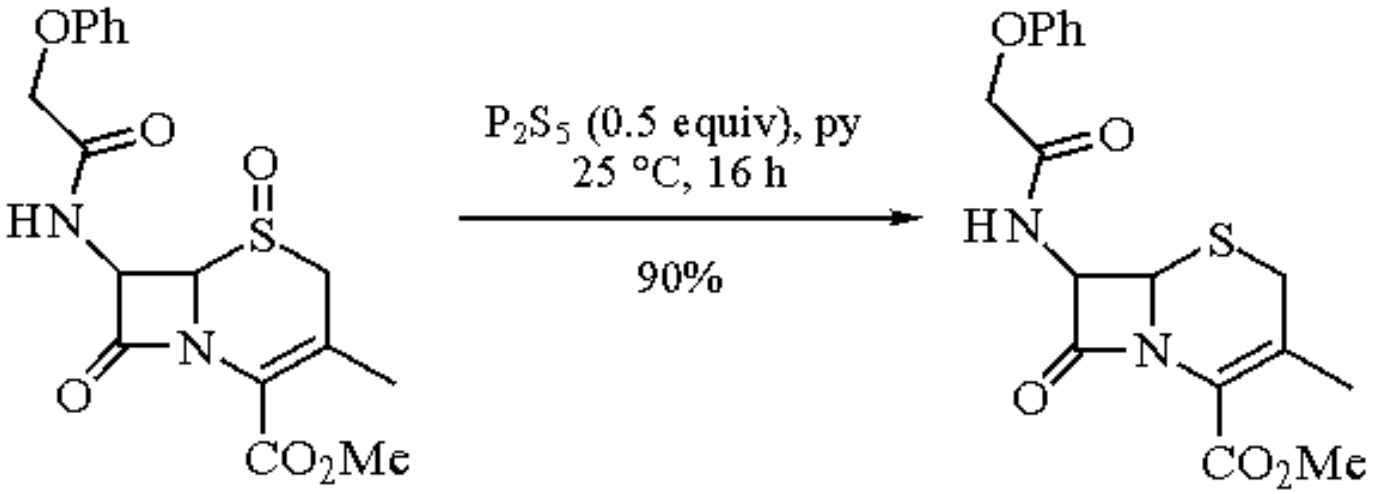

(15)

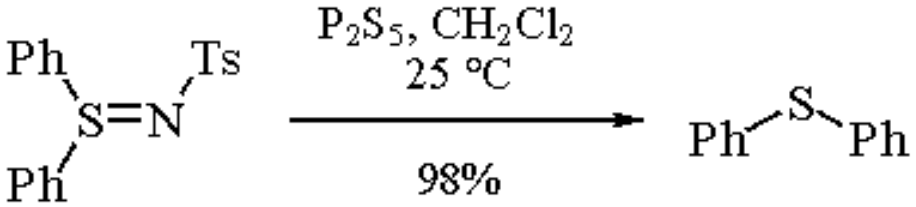

(16)

Use as a Dehydrating Agent.

Surprisingly little use of P_2S_5 as a dehydrating agent has been reported. The aromatization of furan Diels-Alder adducts (eq 17)[5] using P_2S_5 in CS_2 has been reported to be far superior than either HCl/HOAc[38] or polyphosphoric acid.[5]

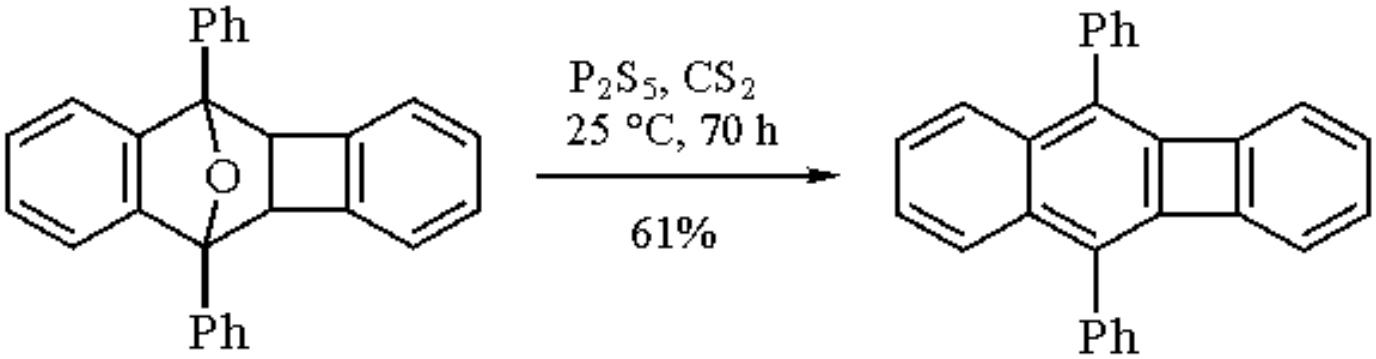

(17)

Use in Electrophilic Aromatic Substitution Reactions.

The formation of Lawesson's reagent from P_2S_5 and anisole (eq 18)[39] is an example of an electrophilic aromatic substitution reaction with this reagent. The addition of ***Aluminum Chloride*** facilitates the ability of P_2S_5 to undergo electrophilic aromatic substitution reactions (eq 19).[6]

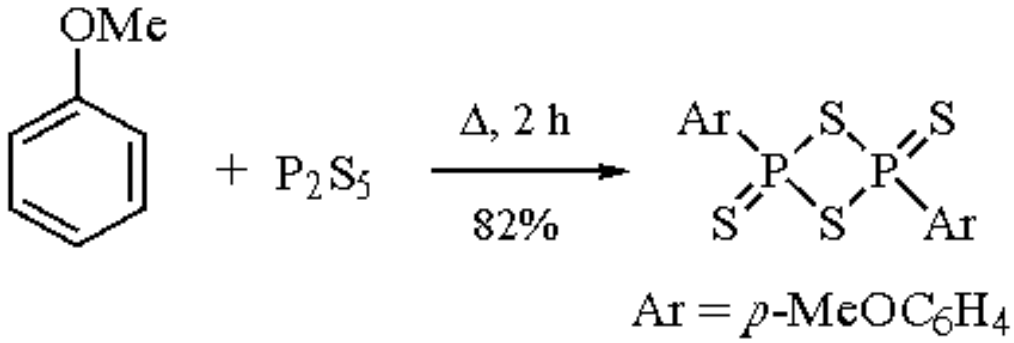

(18)

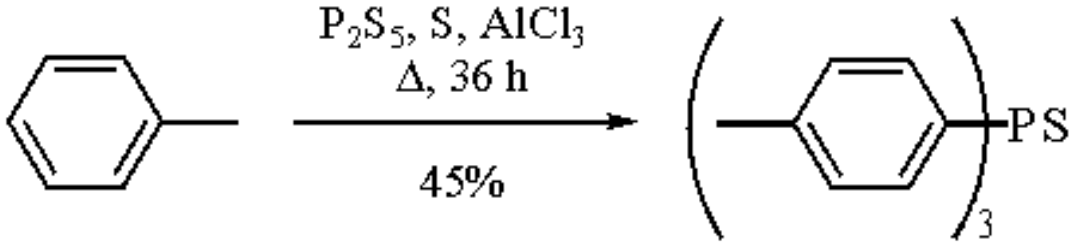

(19)

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Phthalimide[1]

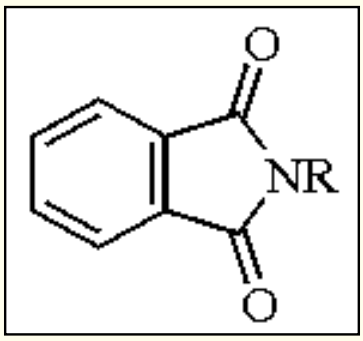

(**1**; R = H)

[85-41-6] · $C_8H_5NO_2$ · Phthalimide · (MW 147.14) (**2**; R = K)

[1074-82-4] · $C_8H_4KNO_2$ · Potassium Phthalimide · (MW 185.23)

(reagent for preparation of primary amines and amino compounds via Gabriel synthesis;[2] building block for synthesis of heterocyclic compounds)

Physical Data: (**1**) mp 238 °C; bp 366 °C; *d* 1.47 g cm^{-3}; dipole moment 2.91 D (dioxane; 30 °C); pK_a 9.90 (H_2O; 25 °C). (**2**) mp >300 °C.

Solubility: (**1**) sol boiling AcOH, H_2O (0.036 g/100 mL at 25 °C; 0.4 g/100 mL at bp), ethanol (5 g/100 mL at bp); insol benzene, ligroin. (**2**) sol H_2O, DMF; insol ethanol, ether.

Form Supplied in: both are white solids.

Handling, Storage, and Precautions: (**2**) may be harmful by inhalation, ingestion, or skin absorption. May cause irritation. Moisture sensitive. Use in a fume hood.

Reactions at the Nitrogen Atom.

A widely used method for the preparation of primary amines comprises reaction of a halo compound with potassium phthalimide and subsequent hydrolysis of the *N*-substituted phthalimide; this method is commonly referred to as the Gabriel synthesis (eq 1).[2]

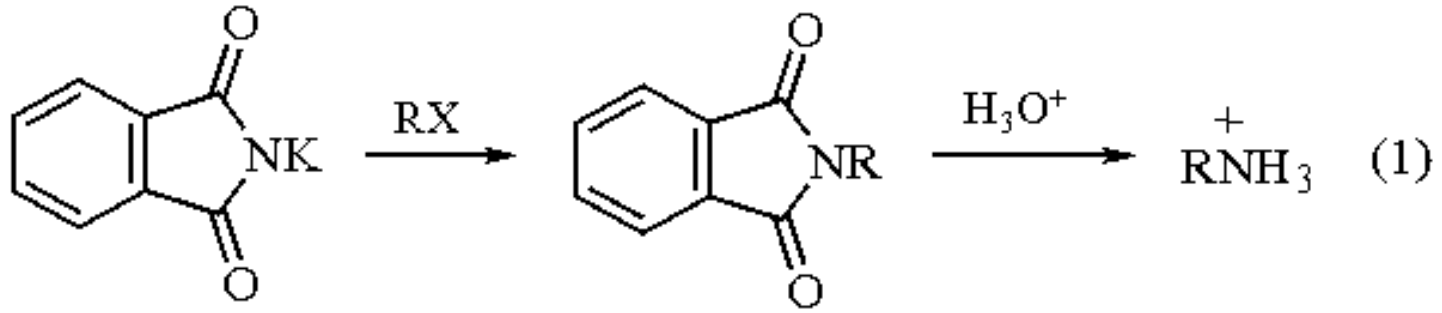

Gabriel Synthesis. First Step: Formation of *N*-Alkylphthalimide.

In the original method of conducting the reaction, potassium phthalimide and the alkyl halide are heated without solvent, or in the presence of a high-boiling, nonpolar solvent (e.g. xylene). Because potassium phthalimide is insoluble under these conditions, the long periods of heating required at relatively high temperatures (150-240 °C) result in lowered yields and impure products (eq 2).[3] Alkyl sulfonates have been used as an alternative for organic halides.[4] Later it was found that DMF, in which potassium phthalimide is appreciably soluble, is an excellent solvent for the alkylation, which often starts at rt and is completed within minutes for the more reactive halides (eq 3).[5]

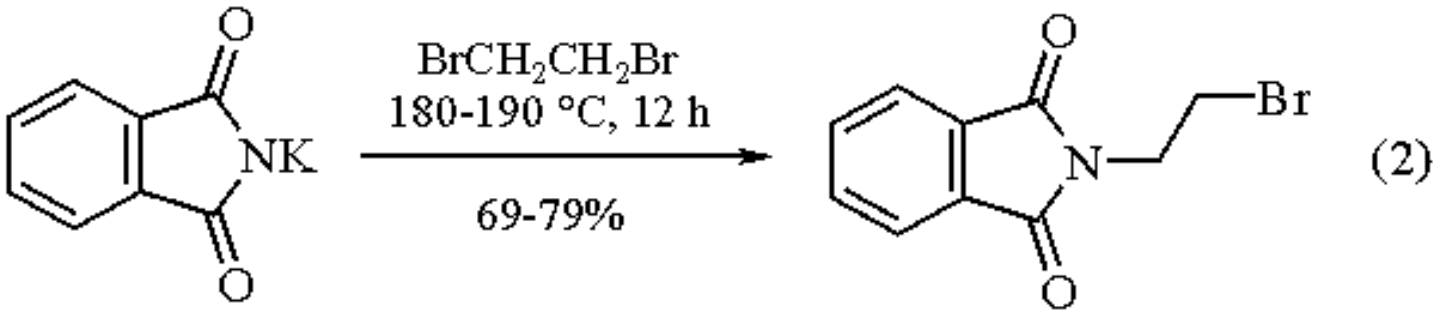

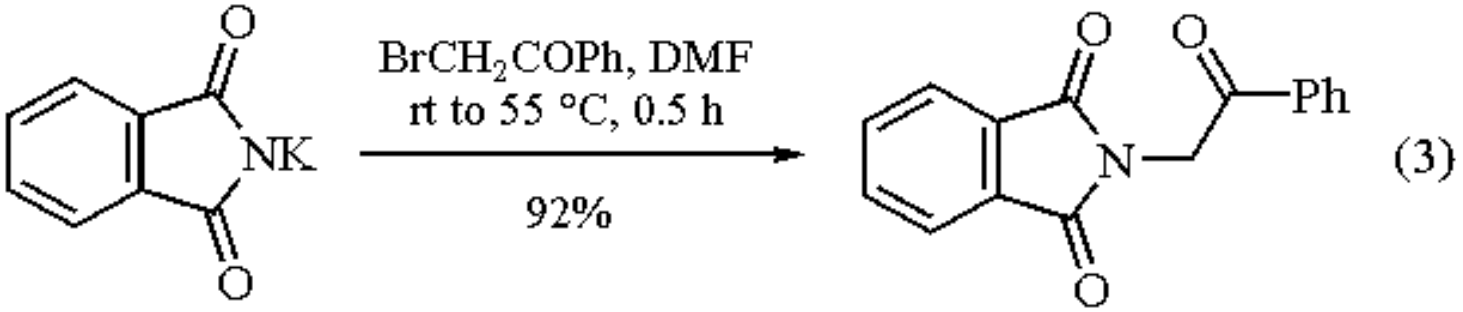

Another convenient procedure for alkylation of the potassium salt with alkyl halides or methanesulfonates, in solvents like benzene or toluene, makes use of solid-liquid phase-transfer catalysis by quaternary phosphonium[6] or ammonium[7] salts or ***18-Crown-6***[8] (eqs 4 and 5).[6,7b] In the case of the phosphonium salt, even 2-octyl derivatives have been obtained in high yield.

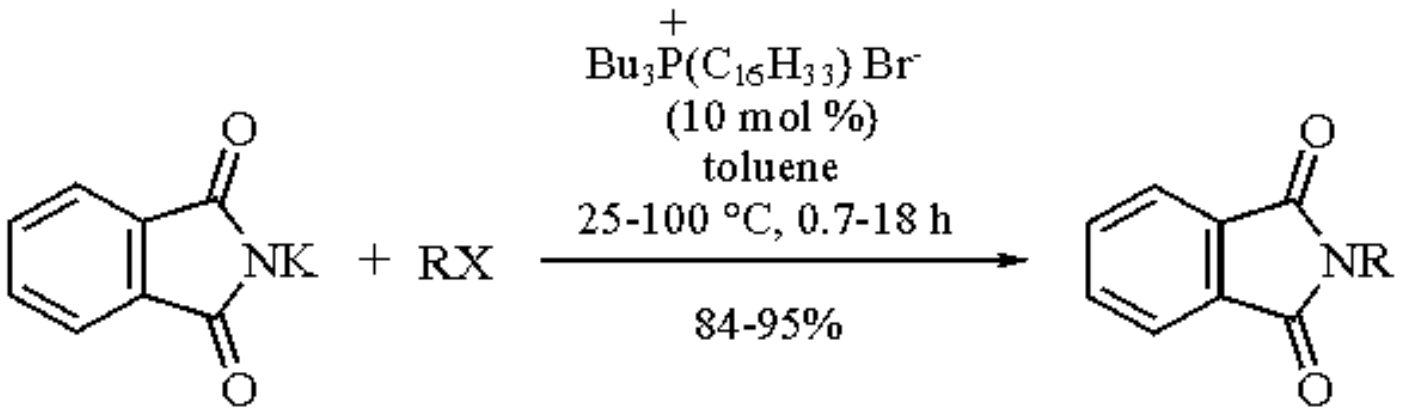

(4)

X = Cl, Br, I, Ms
R = primary alkyl, 2-octyl

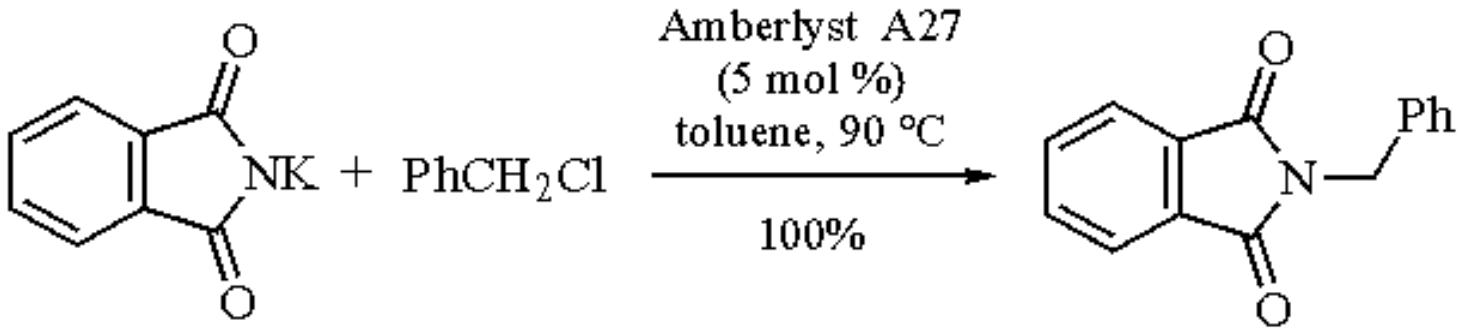

(5)

The Gabriel synthesis can be extended to include aromatic and vinylic halides. Under appropriate conditions, the copper-catalyzed nucleophilic substitution with the potassium salt is effective with a wide range of aryl bromides or iodides, which may contain either electron-withdrawing or electron-donating substituents. The polar effect of the substituents is small, and the reaction is strongly subject to steric inhibition (eq 6).[9] Similar reaction conditions have been used for vinylic bromides RCH=CHBr (R = H, alkyl, aryl).[10] Copper(II) oxide has been used for condensing phthalimide with aryl or ferrocenyl halides.[11]

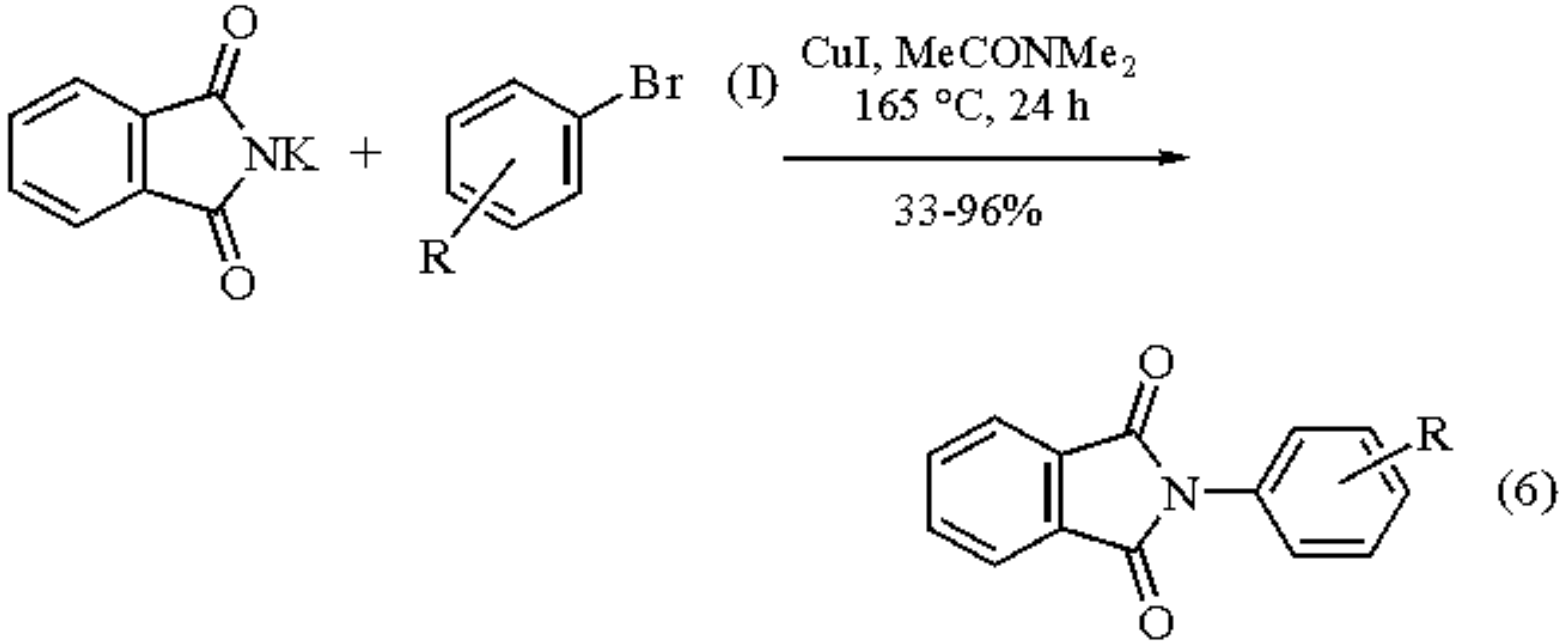

Gabriel Synthesis. Second Step: Formation of the Primary Amine.

Hydrolysis of the *N*-substituted phthalimides is usually carried out by refluxing in 20% hydrochloric acid[2] (eq 7).[2b] In certain cases, concentrated hydrochloric acid at temperatures up to 200 °C (sealed tube) may be necessary. Other acids, such as HBr, HI, and H_2SO_4, have also been used. Alkaline hydrolysis of the *N*-substituted phthalimides (e.g. 10% KOH or NaOH) is not commonly used.

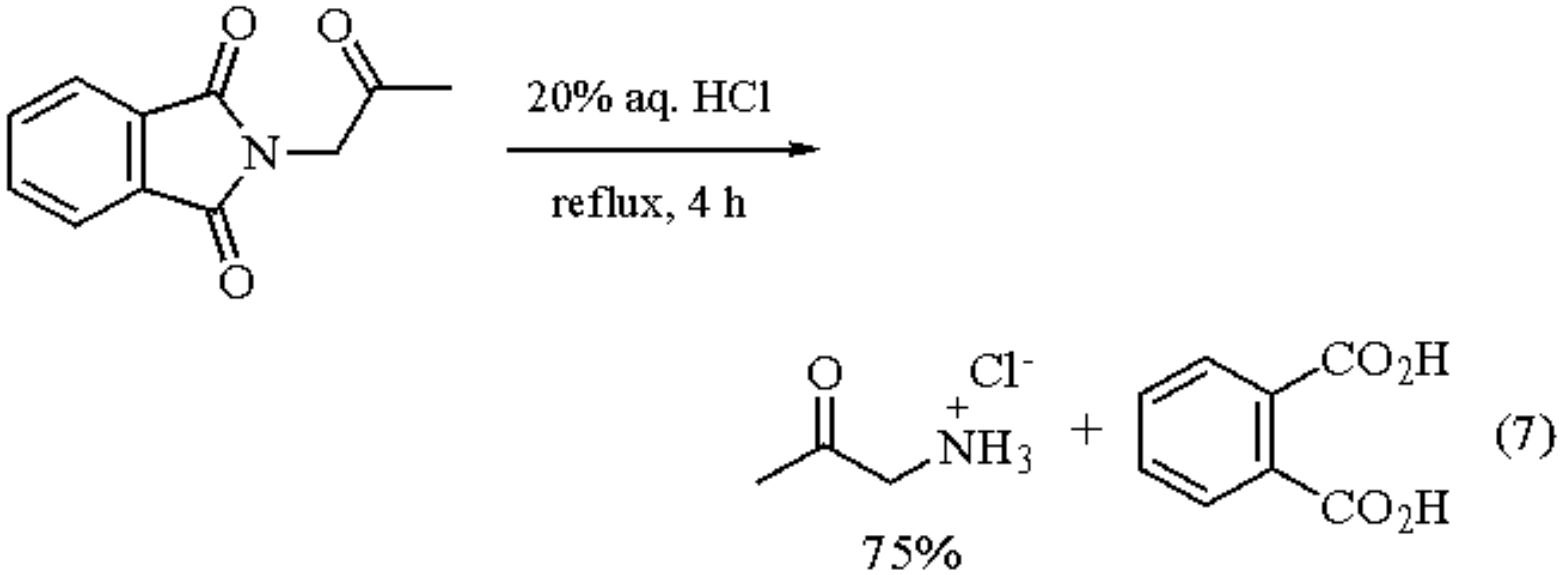

Mild cleavage with ***Hydrazine***[12] is the method of choice for *N*-substituted phthalimides not containing functional groups like halogen, aldehyde, or ketone that react with hydrazine. Usually the phthalimide compound is refluxed in ethanol with an equivalent amount of hydrazine hydrate. Upon removal of the ethanol, the residue is heated with hydrochloric acid. The phthalyl hydrazide is filtered off, leaving a solution of the amine hydrochloride (eq 8).

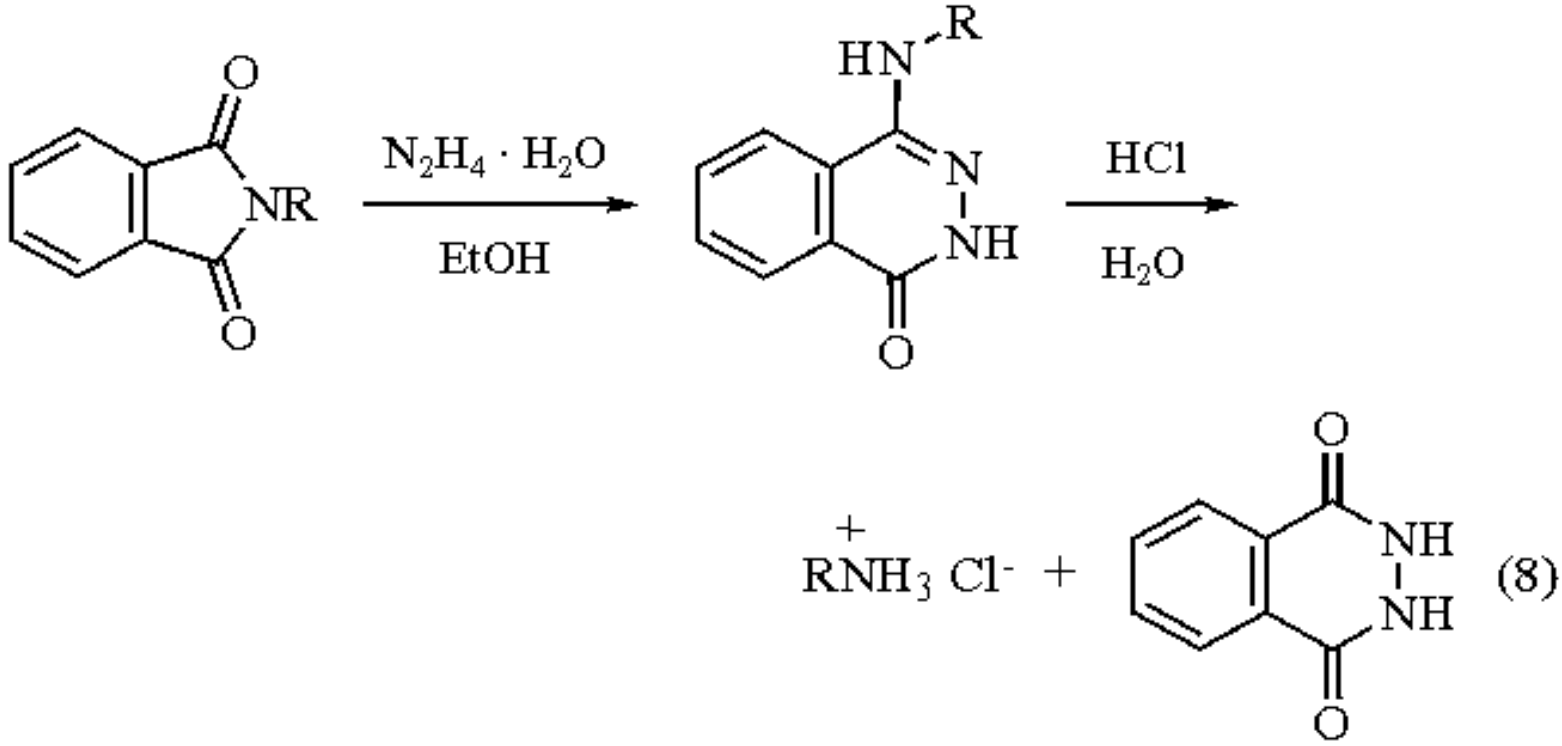

The primary amines may also be liberated by reactions with 40% aqueous methylamine,[13a] *n*-pentylamine,[13b] ***Sodium Borohydride***-2-propanol followed by acetic acid,[13c] and ***Sodium Sulfide*** in aqueous THF or acetone.[13d]

Miscellaneous Alkylations.

A mild alternative for the above-described reaction of potassium phthalimide and alkyl halides is the direct coupling of phthalimide with alcohols under Mitsunobu's conditions.[14a] The advantage of this method is that a primary or secondary alcohol is activated in situ by using ***Triphenylphosphine*** and $RO_2CN{=}NCO_2R$, and then reacts (with inversion of configuration) with phthalimide under aprotic conditions at rt or below (eq 9).[14b]

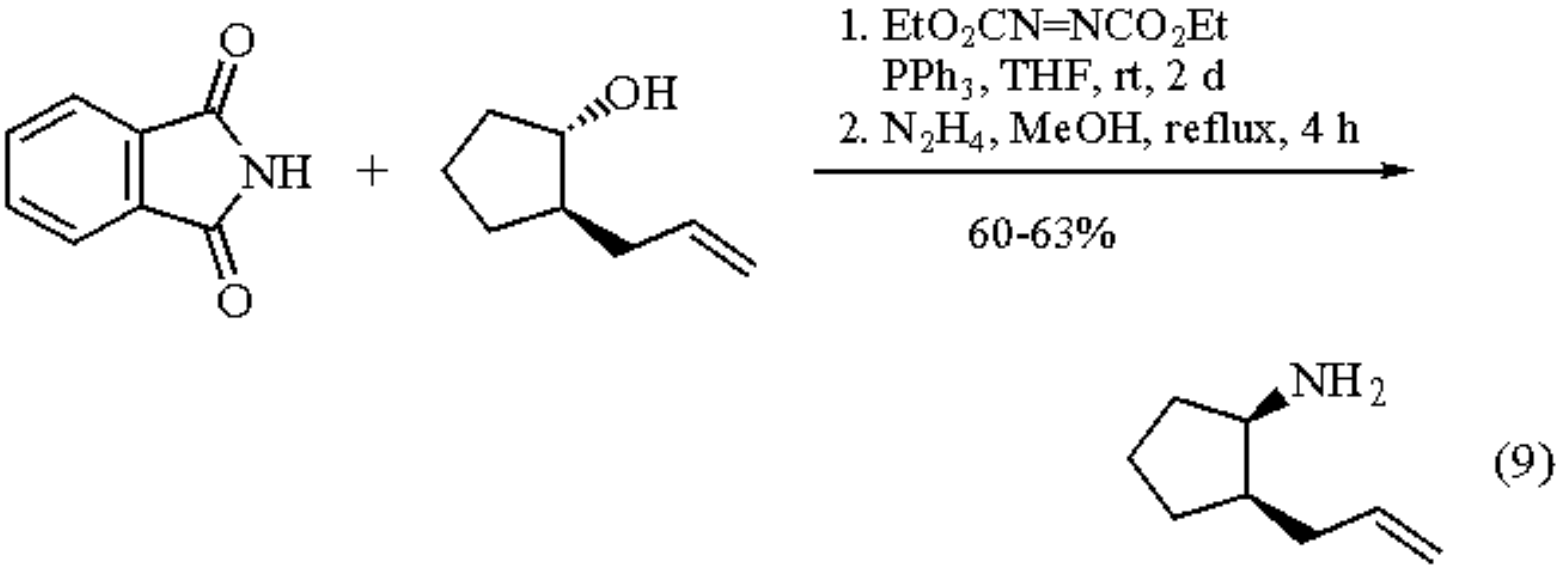

N-Alkylations through base-catalyzed conjugate additions to acrylonitrile[15] and acrolein or its methyl congeners[16] are

known. The smooth reaction of phthalimide and aqueous ***Formaldehyde*** leads to the *N*-hydroxymethylimide (eq 10),[17] which can be used in the acid-catalyzed amidomethylation[17] of aromatic compounds (Tscherniac-Einhorn reaction) or, upon conversion into the *N*-halomethyl derivative, in the amidomethylation of aliphatic nucleophiles. Unfortunately, higher aldehydes do not undergo this reaction with phthalimide. The α-haloalkyl derivatives can be prepared, however, via the α-chloroalkyl phenyl sulfide as an aldehyde equivalent (eq 11).[18]

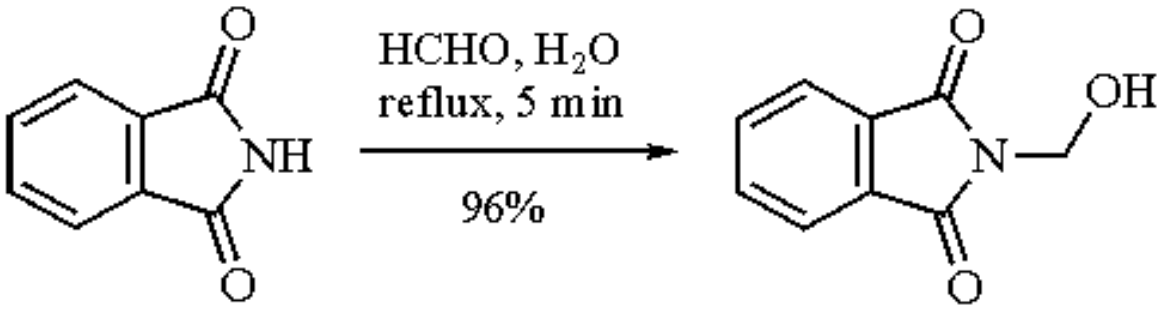

(10)

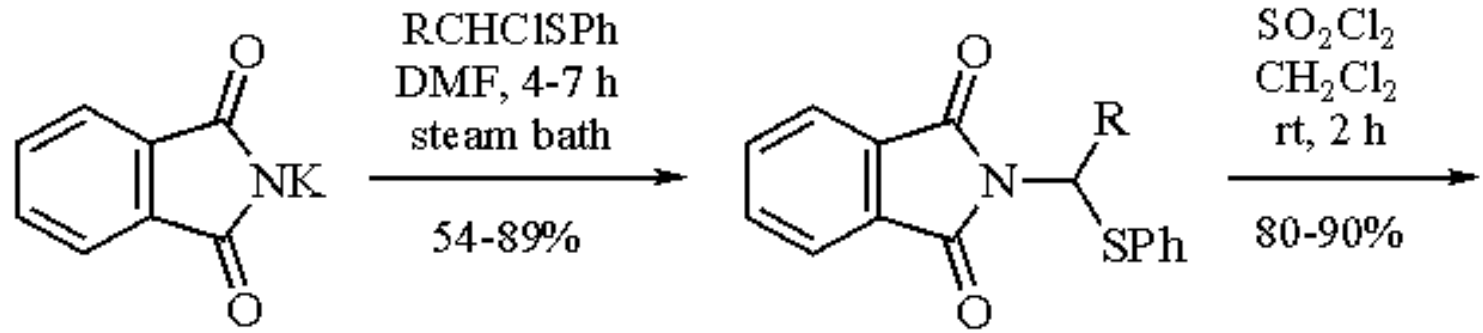

R = H, Me, Ph

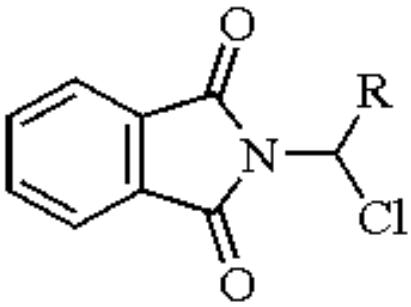

(11)

Epoxides can be used to alkylate phthalimide. Ethyl glycidate, for instance, reacts with phthalimide in the presence of a catalytic amount of base to give exclusively the β-substitution product (eq 12).[19]

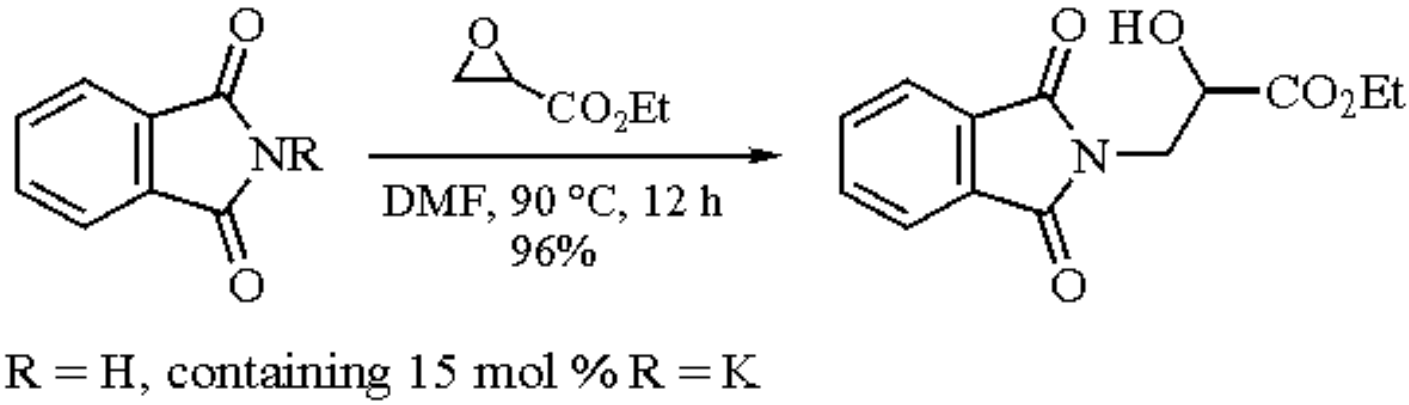

A highly stereoselective route to (*E*)-allylamines has been developed via *N*-alkylation of sodium phthalimide with vinyltri-*n*-butylphosphonium bromide in the presence of an aldehyde, leading to the allylic phthalimide with high (*E*) stereoselectivity (71-100%), which upon subsequent hydrazinolysis gives the desired amine (eq 13).[20] Use of the vinyltriphenylphosphonium salt (Schweizer reaction) gives predominantly the (*Z*)-isomer.

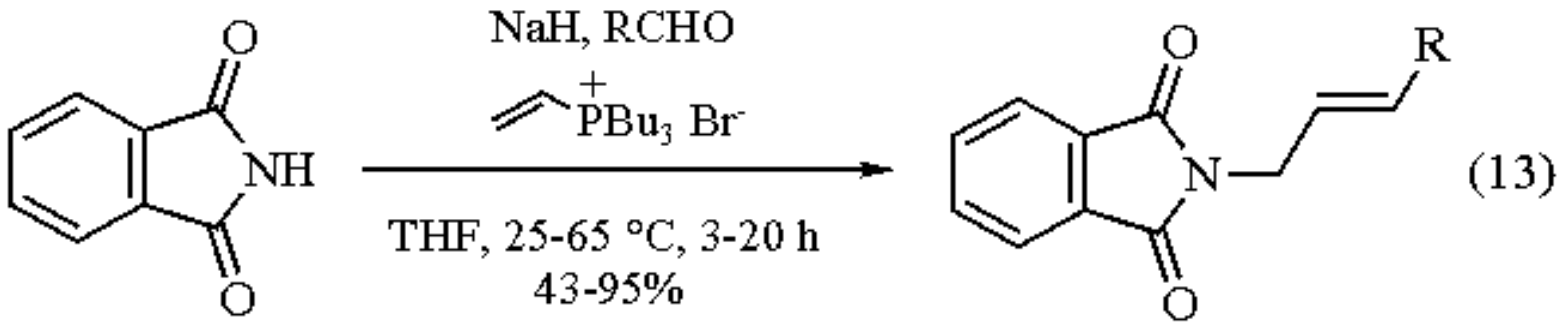

Reactions at the Carbonyl Group.

Though intermolecular Wittig reactions of phthalimide are known, yields are usually poor and rather severe conditions (refluxing xylene for 20 h) are required.[21] Certain tandem reactions, consisting of an *N*-alkylation followed by an intramolecular Wittig-type condensation, lead to fused heterocyclic compounds in high yield. Ring opening of an activated cyclopropane derivative with potassium phthalimide, and Wittig reaction of the intermediary stabilized ylide at the imide carbonyl function, affords the pyrrolo[2,1-*a*]isoindole derivative (eq 14).[22]

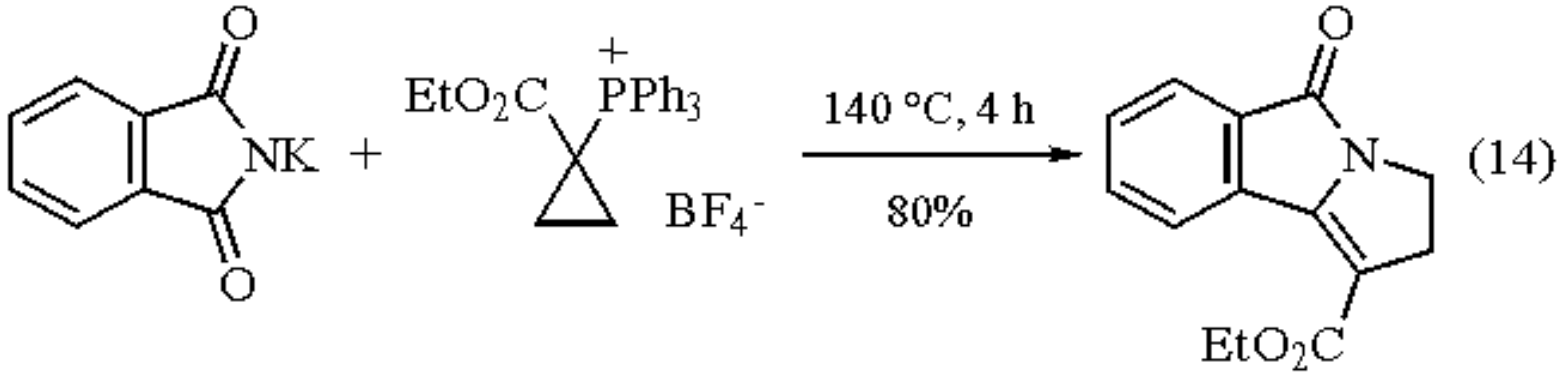

Reaction of sodium phthalimide with 2 equiv of triethyl 2-phosphonoacrylate provides the pyrido[2,1-*a*]isoindole derivative (eq 15).[23] Apparently the carbanion formed upon addition of the first equivalent of the vinylphosphonate

does not undergo the intramolecular Wittig-Horner type reaction to the strained four-membered ring. Upon addition of the intermediary carbanion to a second molecule of the vinylphosphonate, formation of the six-membered ring readily occurs.

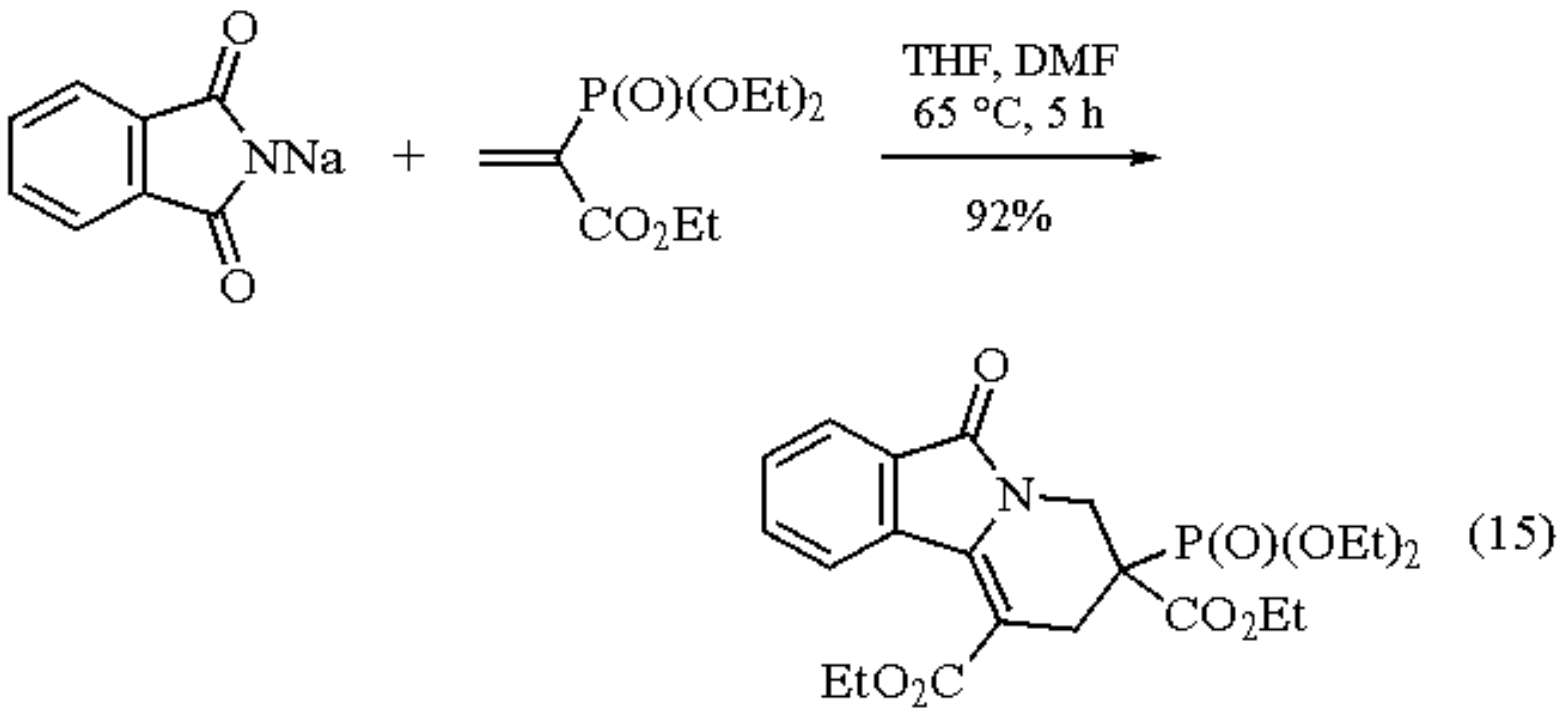

Related Reagents.

Benzophenone Imine; ***Isocyanic Acid***; ***Glutarimide***; ***Hexamethylenetetramine***; ***Sodium Azide***; ***Succinimide***.

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Phthalimidosulfenyl Chloride[1]

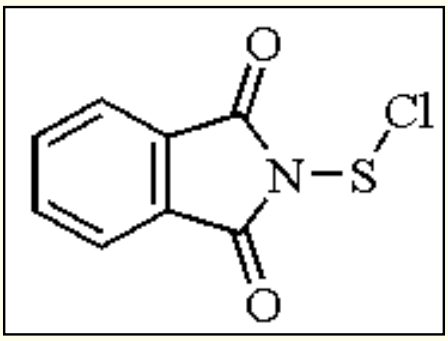

[54974-07-1] · $C_8H_4ClNO_2S$ · Phthalimidosulfenyl Chloride · (MW 213.65)

(reacts as a pseudohalogen;[1] synthetic equivalent of inaccessible sulfenyl chlorides;[2-4] adds across double and triple bonds;[2,3,5] reagent for the formation of episulfides;[6] reacts with ketones to give β-keto sulfides[7])

Alternate Names: phthalimide-*N*-sulfenyl chloride; 1,3-dihydro-1,3-dioxo-2*H*-isoindole-2-sulfenyl chloride; *N*-(chlorothio)phthalimide.

Physical Data: mp 115-117 °C.

Solubility: sol chlorobenzene, benzene, CH_2Cl_2, MeOH; insol pentane.

Form Supplied in: yellow crystals; not commercially available.

Preparative Method: prepared by treatment of potassium phthalimide with S_2Cl_2 to form the disulfide which is then cleaved with chlorine in warm chloroform.[1]

Purification: recrystallization from methanol.

Handling, Storage, and Precautions: can be stored at 0 °C for several months.

Addition to Alkynes.

Phthalimidosulfenyl chloride adds to unsymmetrically substituted alkynes, via a thiirenium ion, to give regioisomeric mixtures of (*E*)-β-chlorovinyl sulfenamides arising predominantly from anti-Markovnikov addition (eq 1).[2,3]

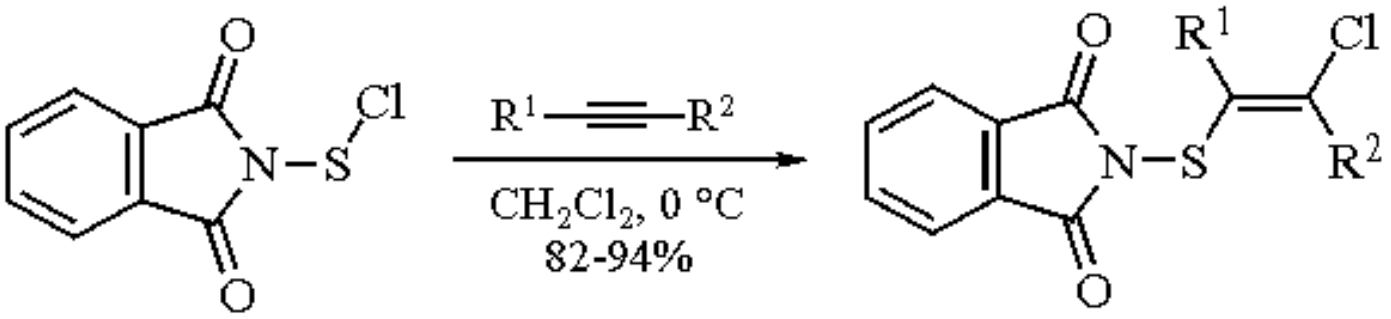

(1)

Alkynes	Adducts anti-M:M
$R^1 = Bu$, $R^2 = H$	89:11
$R^1 = t\text{-}Bu$, $R^2 = H$	100:0
$R^1 = Ph$, $R^2 = H$	85:15
$R^1 = Me$, $R^2 = Ph$	100:0

The sulfur-nitrogen bond of the alkyne adduct enhances this reagent's usefulness since the sulfenamide products are mild sulfur electrophiles, useful for the introduction of sulfur-substituted residues into organic molecules. The phthalimido group has been displaced with various nucleophiles such as carbanions,[2-4,8,9] amines,[2-4,10] thiols,[11] and alcohols;[12] the regio- and stereochemical integrity of the double bond is maintained during such displacements. This suggests that phthalimidosulfenyl chloride may be considered a synthetic equivalent of synthetically inaccessible sulfenyl chlorides such as *t*-butylsulfenyl chloride and *N*,*N*-bis(trimethylsilyl)aminosulfenyl chloride (eq 2).[2-4]

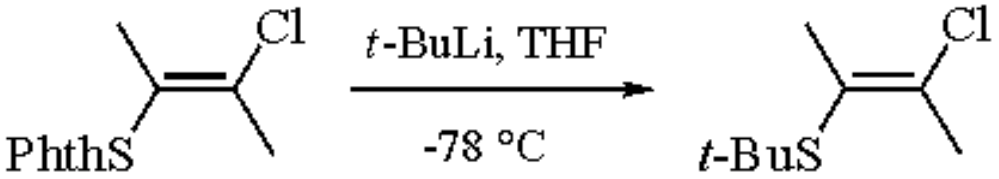

(2)

Reaction of the alkyne adducts with aluminum and boron hydride reagents such as ***Lithium Aluminum Hydride***, ***Sodium Borohydride***, or ***Lithium Triethylborohydride***, however, leads to the formation of unexpected thiirane derivatives (eq 3).[13] These can be desulfurized to give divinyl sulfides.

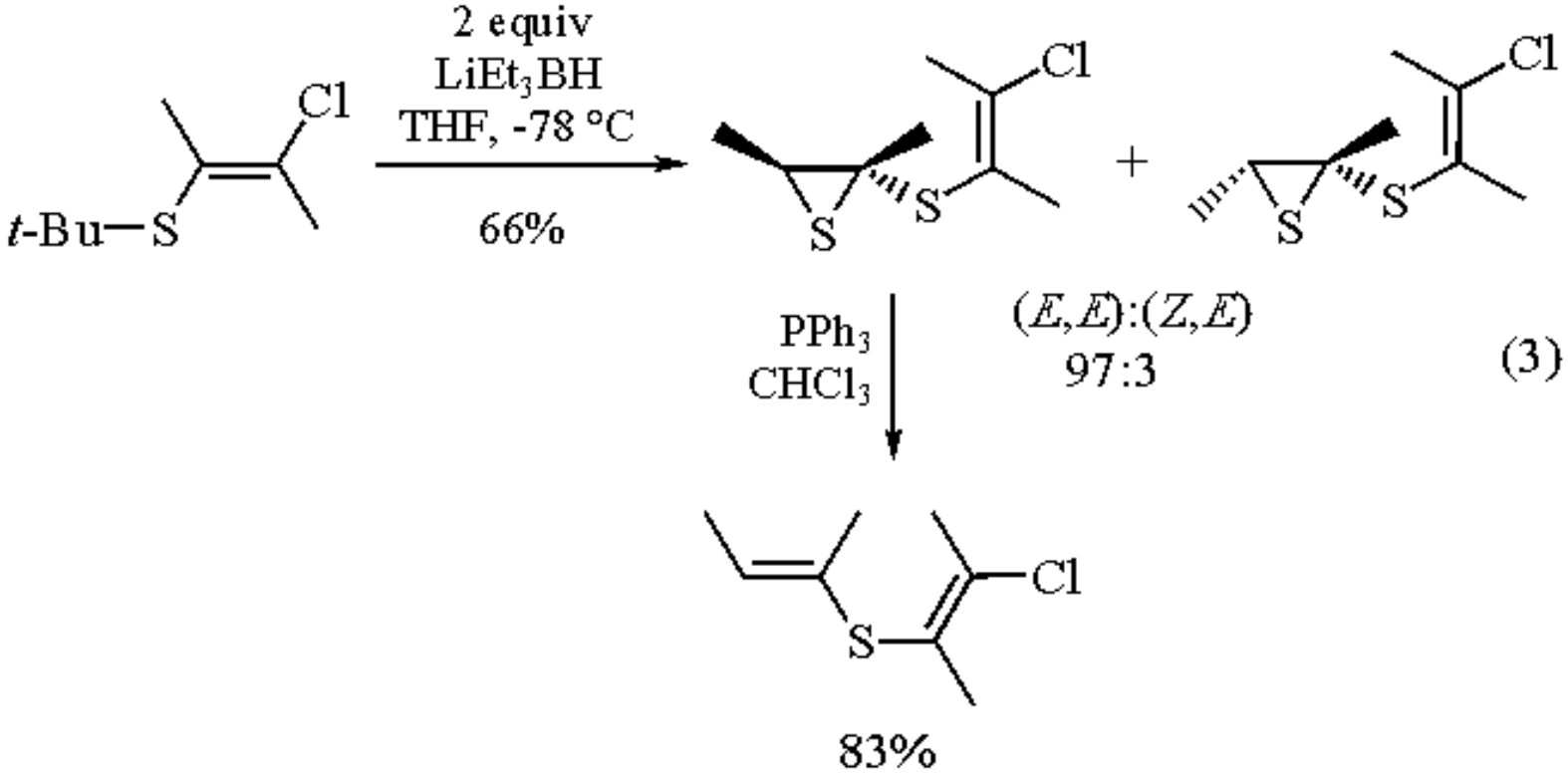

Addition to Alkenes.

Phthalimidosulfenyl chloride can be added to alkenes to yield α-chloro thioethers[5] which, after treatment with lithium aluminum hydride, produce episulfides (eq 4).[6] Sodium borohydride is unsuccessful in transforming the alkene adduct to the episulfide. The alkene addition is stereospecifically *trans* and proceeds through a thiiranium ion intermediate, the opening of which is governed predominantly by steric factors and usually gives a predominance of the anti-Markovnikov addition product.[14] As in the addition of phthalimidosulfenyl chloride to alkynes, the phthalimido group can also be displaced with nucleophiles.[4]

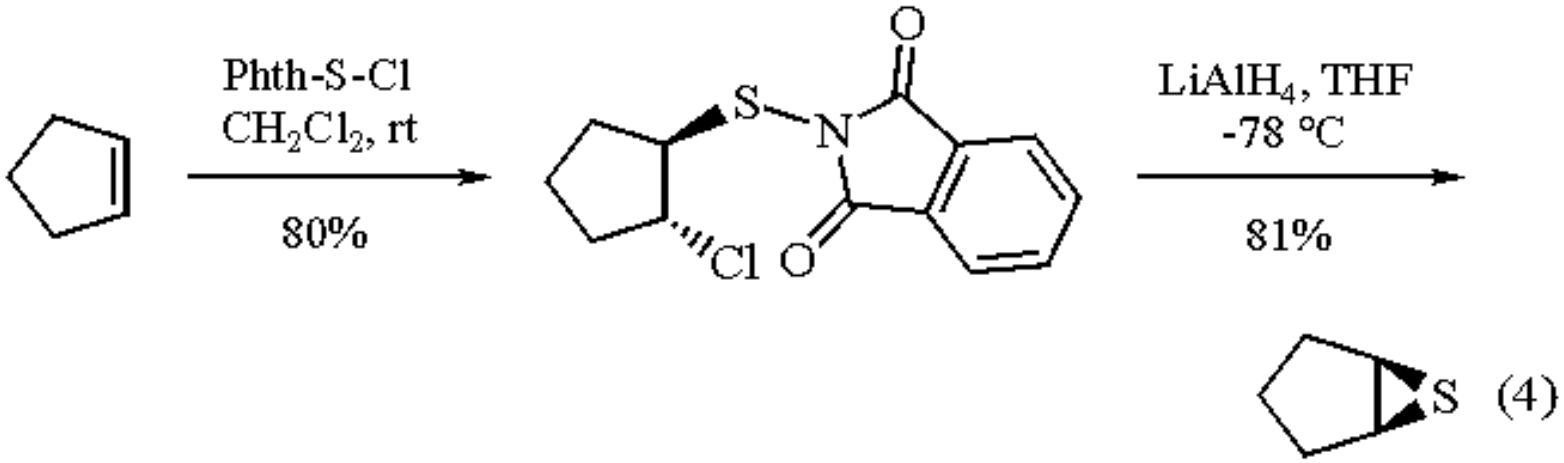

Reaction with Enolizable Carbonyl Compounds.

Good yields of β-keto thioadducts can be obtained from the reaction of phthalimidosulfenyl chloride with ketones at

0 °C using the required carbonyl compound as solvent (eq 5).[5,7] β-Diketones and β-keto esters also react in this manner.[7]

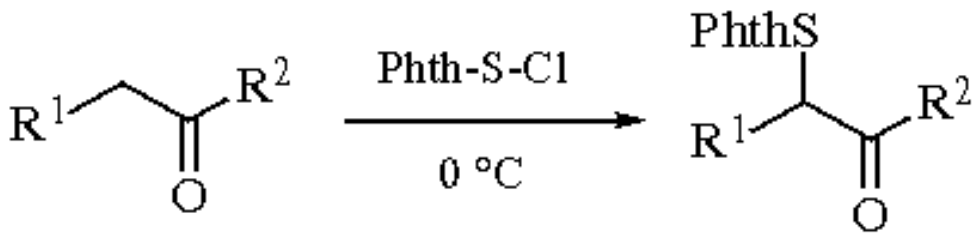

(5)

R^1	R^2	% yield
H	Me	85
H	Ph	71
Me	Ph	87

In contrast, cyclohexanone does not react under the above conditions. The corresponding adduct can be formed by reaction of the trimethylsilyl enol ether with phthalimidosulfenyl chloride (eq 6).[7]

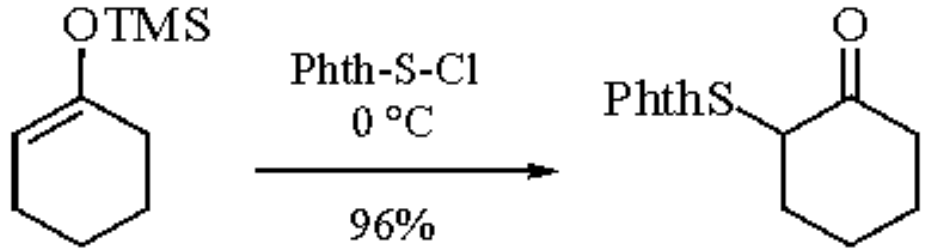

(6)

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Phthaloylbis(triphenylphosphine)cobalt Chloride[1]

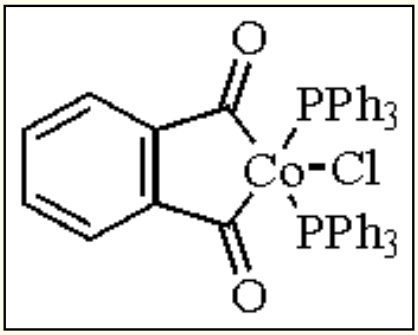

[75895-97-5] · $C_{44}H_{34}ClCoO_2P_2$ · Phthaloylbis(triphenylphosphine)cobalt Chloride · (MW 751.10)

(complex which reacts with alkynes to give naphthoquinones;[1-3] precursor to other phthaloyl complexes which react with alkynes more readily to give naphthoquinones[4,5])

Physical Data: mp 245-246 °C.

Solubility: sol CH_2Cl_2; slightly sol MeCN.

Form Supplied in: brick red solid; not commercially available.

Analysis of Reagent Purity: ^{1}H NMR, IR, microanalysis.

Preparative Method: reaction of benzocyclobutenedione with ***Chlorotris(triphenylphosphine)cobalt*** in chlorobenzene for 24 h at 40 °C.[3,6]

Purification: crystallization from dichloroethane-hexane.

Handling, Storage, and Precautions: the pure complex should be stored in solid form in a sealed container at reasonable ambient temperatures. Quality may deteriorate over time when exposed to air.

Direct Synthesis of Naphthoquinones.

Phthaloyl transition metal complexes can be used in the synthesis of naphthoquinones according to the following scheme: first, an alkyne must coordinate to a free site on a coordinatively unsaturated metal center; secondly, the alkyne must insert into the metal-carbonyl bond; and thirdly, the metal must reductively eliminate to give the naphthoquinone (eq 1).

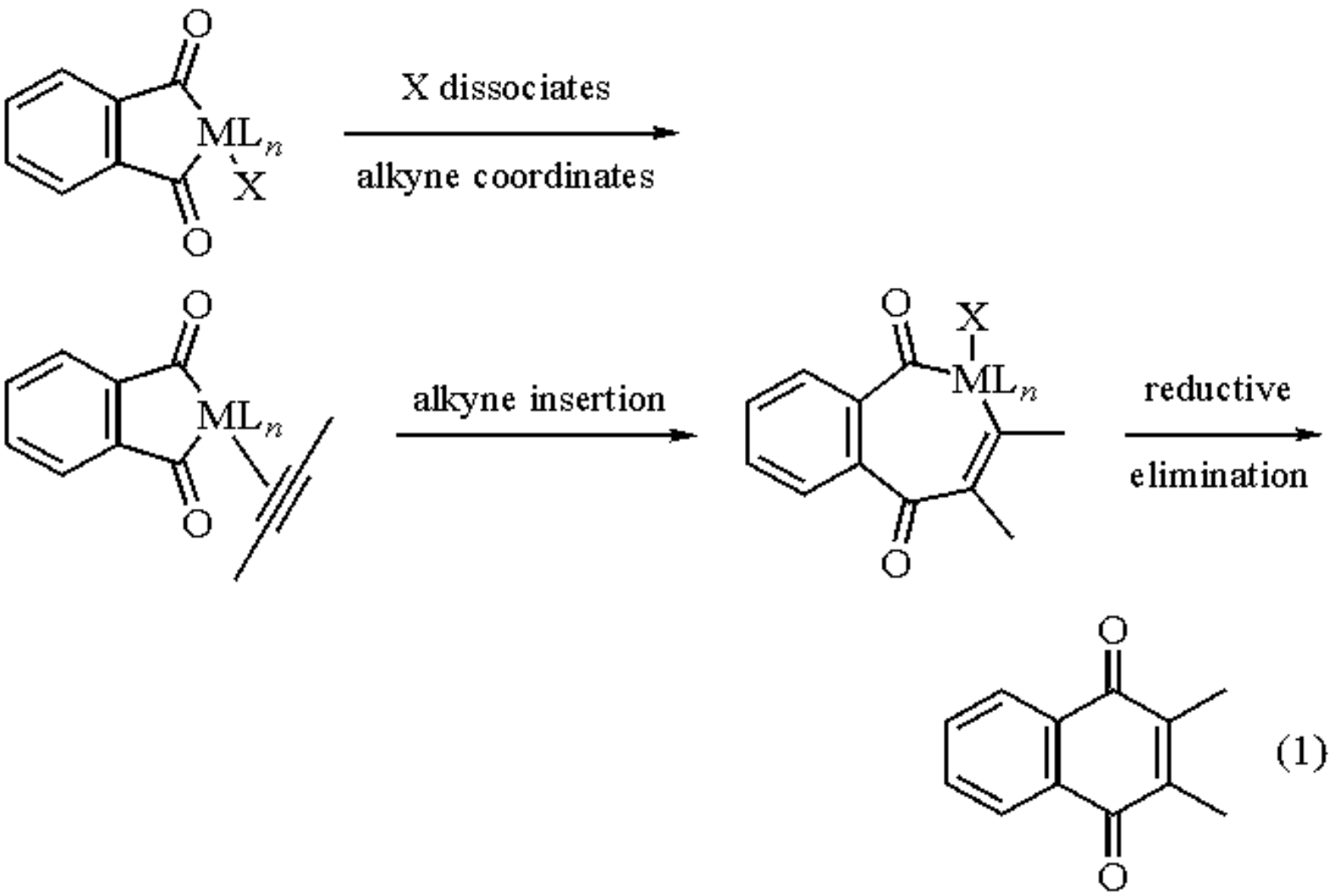

This particular complex will not react with alkynes unless activated by &egt;2 equiv of ***Silver(I) Tetrafluoroborate***; then it will react with a wide variety of alkynes to give naphthoquinones (eq 2).

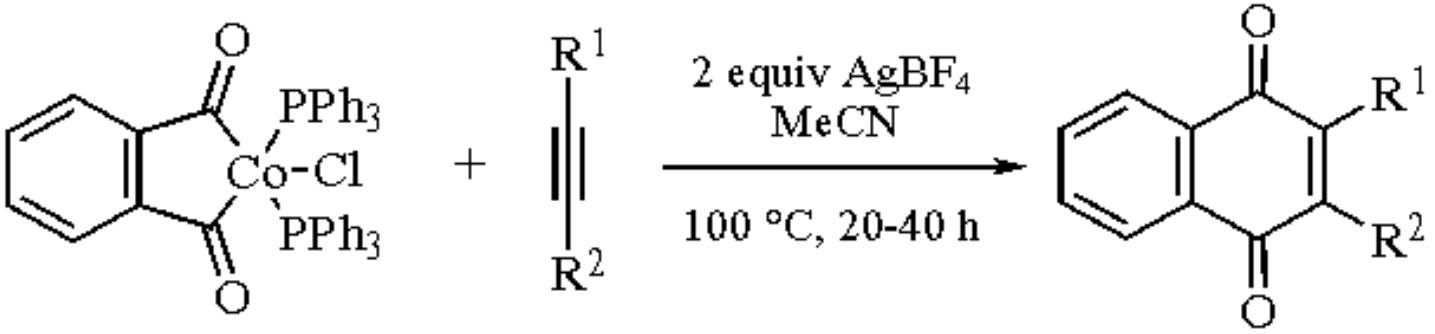

(2)

R^1	R^2	Yield (%)
Me	Me	73
Et	Et	90
Ph	Ph	68
Ph	Me	78
Bu	H	65
Ph	H	57
t-Bu	Me	72
Et	allyl	80
EtO	Et	89
Bu	TMS	68
Ph	$(CH_2)_2OH$	27
Me	CO_2Et	0
Et	COMe	0

Complexes of this type are prepared by the insertion of $CoCl(PPh_3)_3$ into cyclobutenediones,[1,3,6] a preparation which is found to occur quite generally (eq 3).

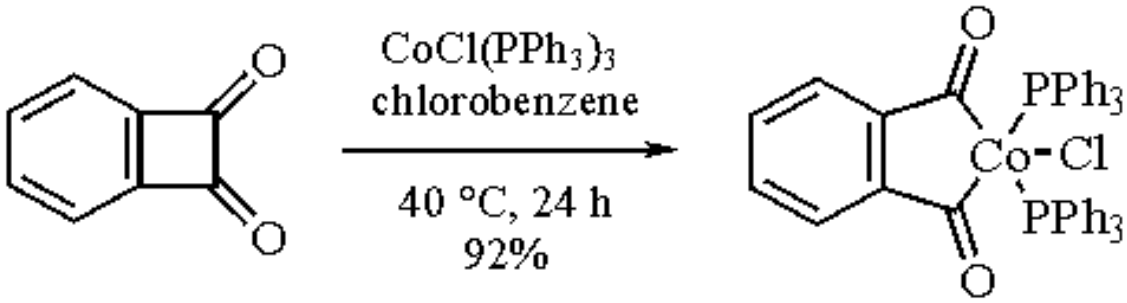

(3)

The overall potential of this synthetic strategy was demonstrated in the synthesis of the natural product (±)-nanaomycin A (eq 4).[7] In this scheme, the alkyne was linked via a tether to control the regiochemistry of the alkyne addition.

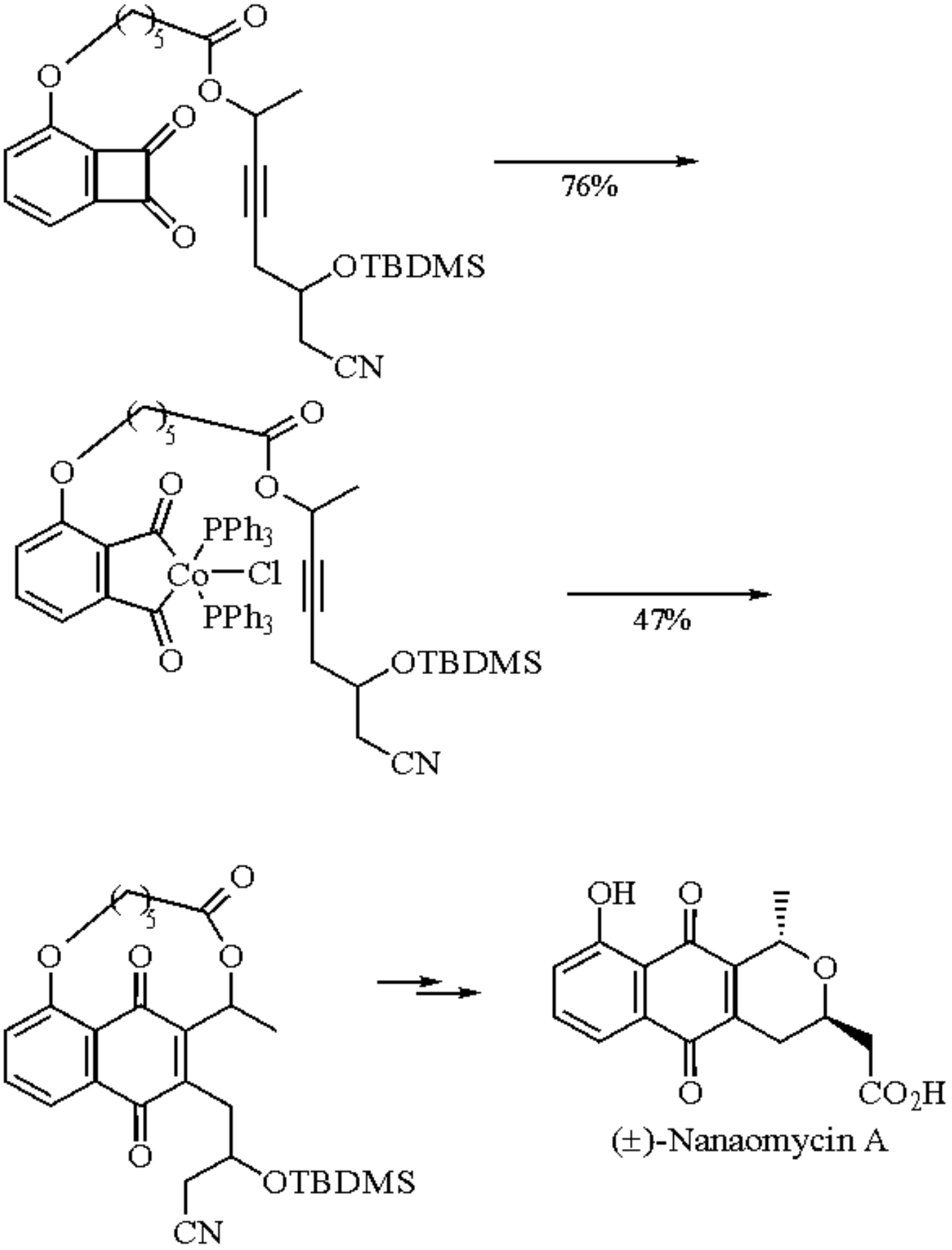

(4)

Precursor to More Reactive Phthaloyl Complexes.

With the method described above, terminal alkynes generally show reduced yields, silyl alkynes are sensitive to desilylation, some alkynes containing heteroatoms require more than 2 equiv of $AgBF_4$, and alkynes containing propargyl ethers or acetals give no naphthoquinone product.[2,3] $AgBF_4$ aids in the ionization of the Co-Cl bond and it complexes with free phosphine ligands to keep an open axial coordination site on cobalt, which seems to be necessary for the quinone-forming reaction (see eq 1).[4,5] By reacting this complex with only one equiv of $AgBF_4$, in the mildly coordinating solvent ***Acetonitrile*** (AN), a somewhat stable cationic cobalt complex is obtained.[4] Although this species cannot be crystallized, it reacts with alkynes to give naphthoquinones. Reaction of this cation with ***1,2-Bis(diphenylphosphino)ethane*** (diphos) affords a very stable diphos cation complex (eq 5).[4] This diphos cation (BF_4^- salt) is crystalline and can be stored in a closed container indefinitely.

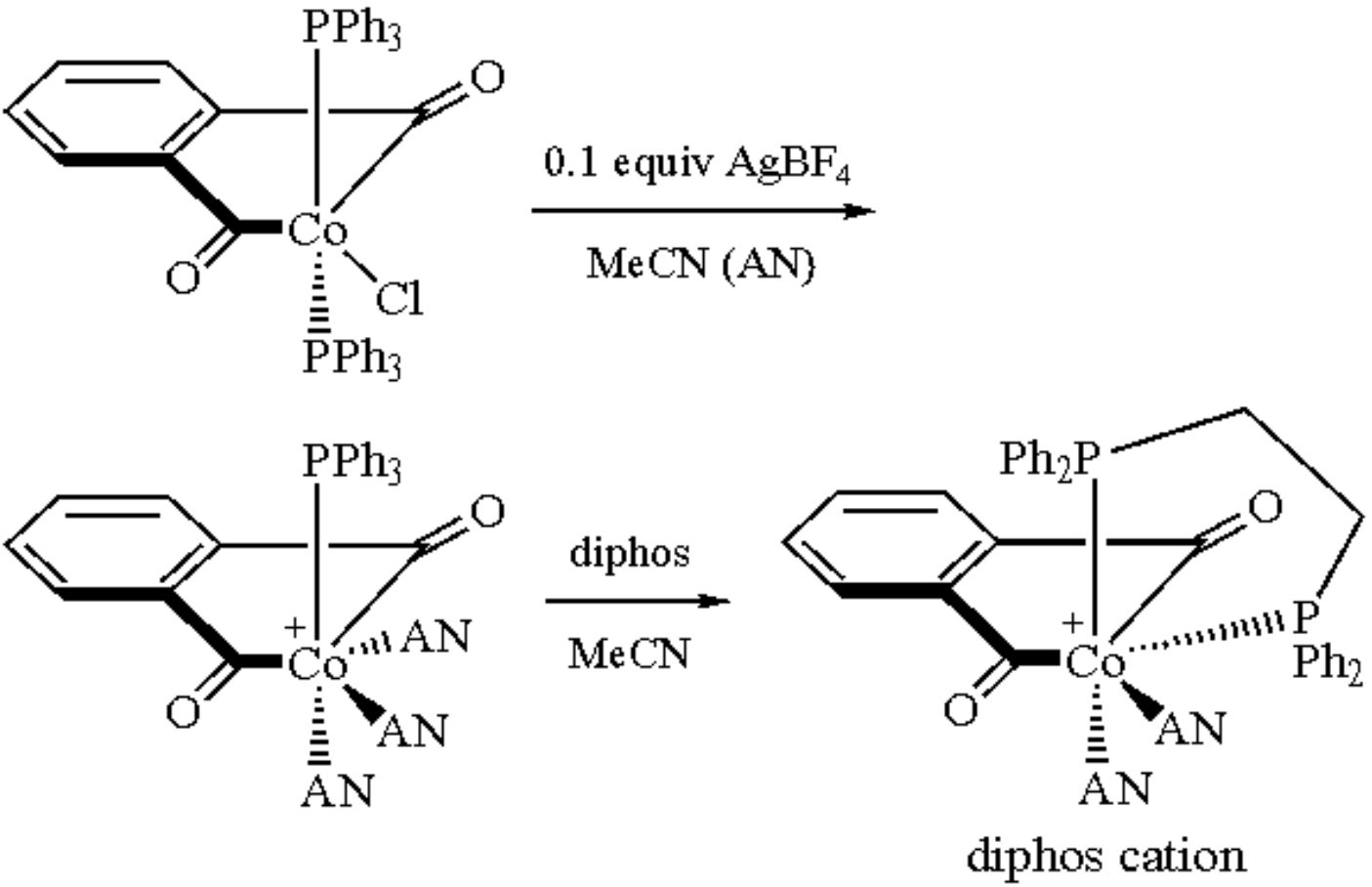

(5)

The diphos cation complex is quite reactive with alkynes, giving naphthoquinones (eq 6). This method is simpler than the $AgBF_4$-mediated reaction of phthaloylbis(triphenylphosphine)cobalt chloride with alkynes because it does not have the complications associated with the use of $AgBF_4$ (use of a hygroscopic reagent and sensitivity of alkynes to Ag^+).

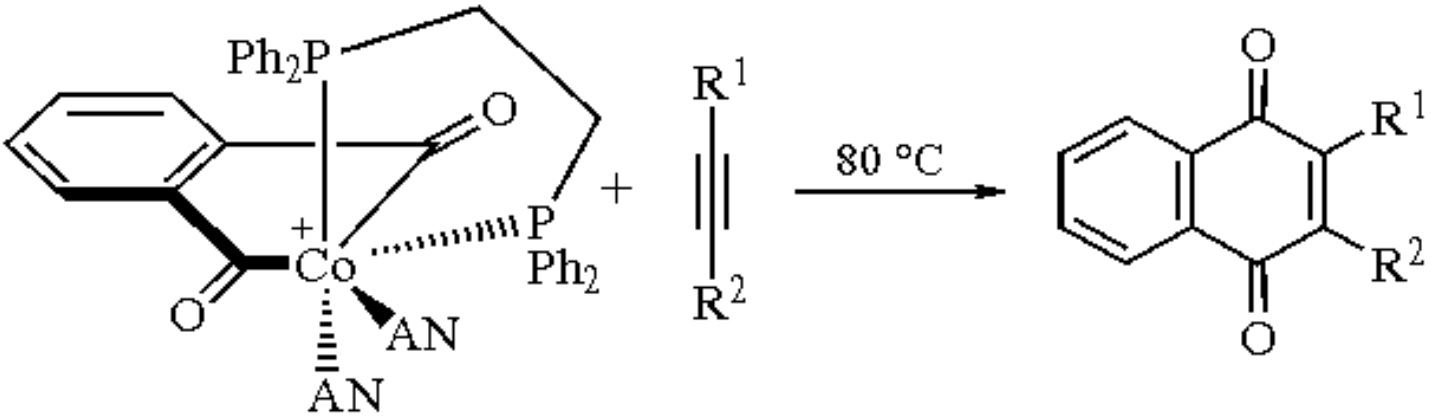

(6)

diphos cation

R^1	R^2	Time (h)	Yield (%)
H	Bu	2	90
Et	Et	2	85
TMS	Bu	4	86
Me	CH_2OEt	2	63
Me	$CH(OEt)_2$	2	51
Et	$(CH_2)_2OTHP$	2	73

The fact that the diphos ligand cannot occupy both axial sites on cobalt allows the labile MeCN ligand to occupy an axial site, which is necessary for coordination of the incoming alkyne.[3-5] In further studies it was found that phthaloylbis(triphenylphosphine)cobalt chloride reacts with 1.1 equiv of dimethylglyoxime (dmg) in pyridine to give phthaloyl(dmg)(pyridine)cobalt chloride. The dmg ligand in cobalt complexes is known to prefer chelating in an equatorial sense; this allows both axial sites to be occupied by more labile ligands (pyridine and chloride) (eq 7).[3-5]

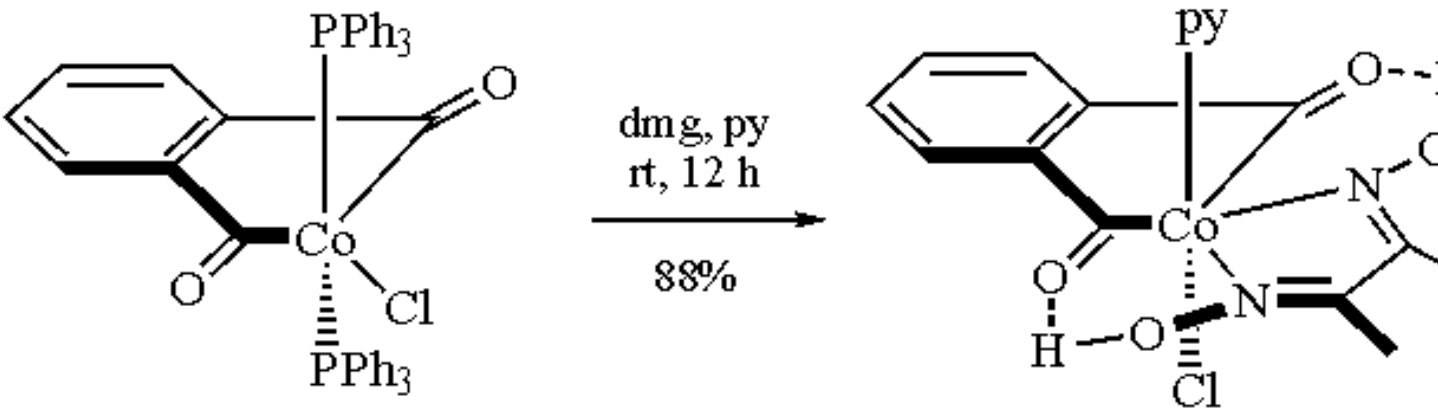

(7)

This dmg complex is the most useful of the cobalt complexes derived from phthaloylbis(triphenylphosphine)cobalt chloride since it reacts with the widest variety of alkynes, both electron rich and electron deficient. In contrast to phthaloylbis(triphenylphosphine)cobalt chloride, phthaloyl(dmg)(pyridine)cobalt chloride reacts with alkynes under relatively mild thermal conditions with no need for $AgBF_4$. For example, 1.5 equiv of 3-hexyne in 1,2-dichloroethane

heated at 80 °C for 18 h gives a 77% yield of 2,3-diethyl-1,4-naphthoquinone. Lewis acidic additives enhance the rate of the reaction of the dmg complex. $AgBF_4$ works well, but the most generally useful Lewis acid catalysts are ***Cobalt(II) Chloride***, which significantly enhances the rate of quinone formation at 80 °C, and ***Tin(IV) Chloride***, which actually gives good quinone yields from many alkynes at rt (eq 8).

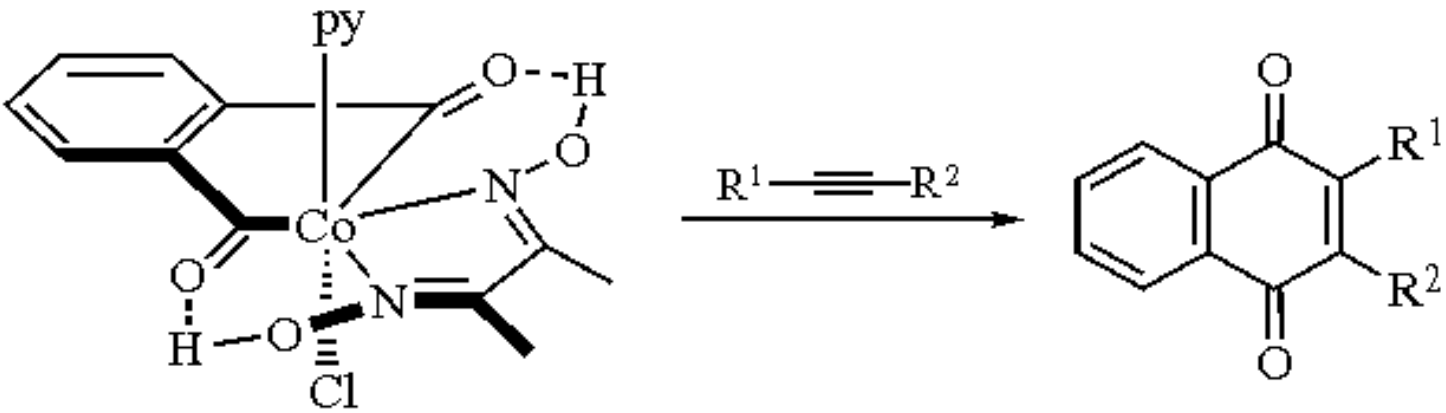

(8)

		Isolated yield (%)	
		$CoCl_2 \cdot 6H_2O$	$SnCl_4$
R^1	R^2	80 °C, 8 h	rt, 7 h
Bu	H	87	80
Et	Et	86	83
Me	CO_2Et	99	80
Et	OEt	85	0
Me	*t*-Bu	72	-
Me	$CH_2N(COMe)Ph$	70	-

General Considerations.

Naphthoquinones can be prepared from a wide variety of alkynes with the methods outlined above. This approach also works for a variety of cyclobutenediones, giving rise to many substituted benzoquinones[1,3,8-10] as well as substituted naphthoquinones.[3,5,7] Much work has been done investigating the regioselectivity of the alkyne additions in cases where the phthaloyl and maleoyl ligands are unsymmetrical.[3,7-9] In particular, the dmg -cobalt complexes show good regioselectivity in the alkyne additions.[8,9] In using this approach to prepare quinone-containing molecules, the key considerations are: (1) is the necessary cyclobutenedione available? and (2) can the regiospecificity of the alkyne addition be controlled sufficiently? Recent advances in the preparation of cyclobutenediones,[11-18] coupled with the information from reported regiochemical studies, will provide strong guidance in the preparation of some complicated structures containing a quinone nucleus.

Related Reagents.

Carbonyl(cyclopentadienyl)(phthaloyl)cobalt.

---

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Phthaloyl Dichloride[1]

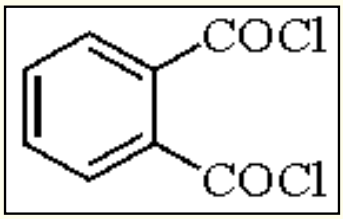

[88-95-9] · $C_8H_4Cl_2O_2$ · Phthaloyl Dichloride · (MW 203.02)

(converts carboxylic acids to acid chlorides;[2] phthaloyl protecting group for amines;[3] useful Friedel-Crafts synthon[4])

Physical Data: mp 15-16 °C; bp 281 °C, 131-133 °C/9-10 mmHg; *d* 1.409 g cm^{-3}.

Solubility: sol CH_2Cl_2, THF, sulfolane, nitrobenzene.

Form Supplied in: liquid; commercially available; phthalic anhydride is an impurity.

Handling, Storage, and Precautions: store in the absence of moisture; corrosive, handle with gloves in a fume hood.

Conversion of Acids and Esters to Acid Chlorides.

Phthaloyl dichloride has been used for the conversion of acids into acid chlorides,[2] and anhydrides into bis-acid chlorides (eq 1).[5]

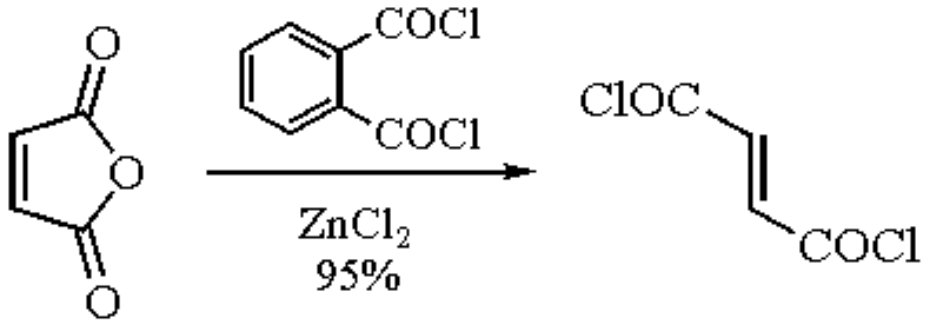

(1)

It is particularly suited to the preparation of fairly volatile acid chlorides which can be simply distilled out of the reaction mixture, though a greater range of chlorides can be prepared than with lower boiling ***Benzoyl Chloride***. ***Zinc Chloride*** has been used as a catalyst. Phthaloyl dichloride has been used in a two-pot sequence for the in situ generation

of acetyl chloride from ***Carbon Dioxide***, using catalytic ***N,N-Dimethylformamide***.[6] In the presence of ***Chlorosulfonic Acid***, it performs the useful conversion of ethyl esters into acid chlorides (eq 2).[7]

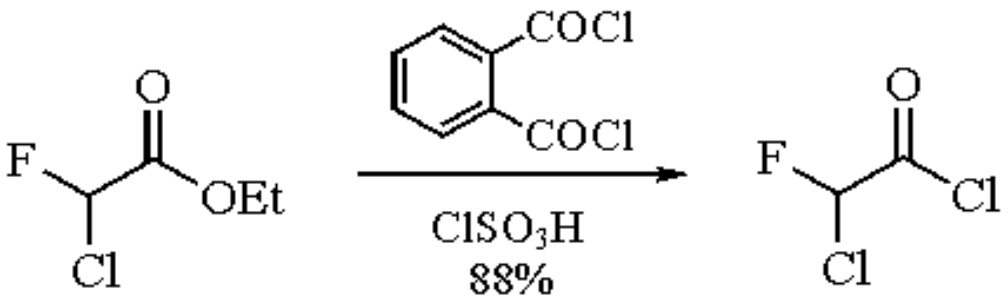

(2)

Protection of Amines.

Amines can be protected with the phthaloyl group using phthaloyl dichloride and ***4-Dimethylaminopyridine*** or ***Pyridine***.[3] This method may offer an advantage over more usual procedures, e.g. phthalic anhydride, in hindered cases.

Friedel-Crafts Reactions.

Though not strictly acting as a reagent, phthaloyl dichloride undergoes Friedel-Crafts acylation of hydroquinones to give 1,4-dihydroxyanthraquinones, the ring system of the daunomycin antitumour family (eq 3).[4]

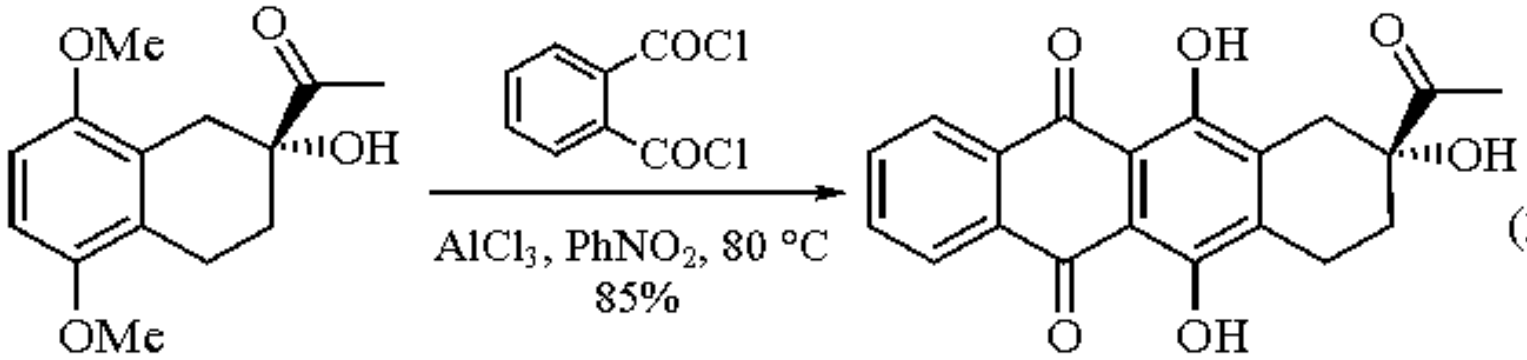

(3)

Miscellaneous.

Aromatic nitro groups have been reported to undergo displacement with fluorine using ***Potassium Fluoride*** as the fluoride source (eq 4). Phthaloyl dichloride was found to be an effective trapping agent for K_2O, formed by the decomposition of KNO_2, by conversion to phthalic anhydride.[8]

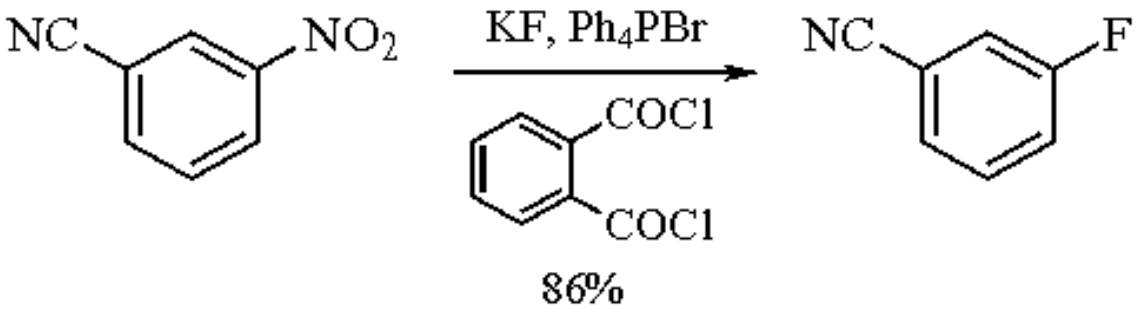

(4)

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4-Picolyl Chloride Hydrochloride

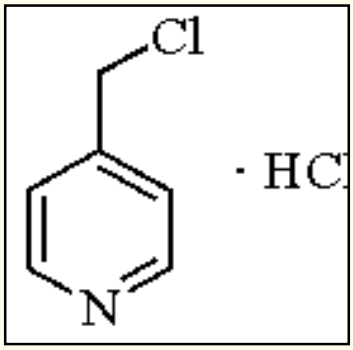

[1822-51-1] · $C_6H_7Cl_2N$ · 4-Picolyl Chloride Hydrochloride · (MW 164.04)

(protection of alcohols,[1,2] phenols,[3] thiols,[3,4] and carboxylic acids[5])

Alternate Name: 4-(chloromethyl)pyridine hydrochloride.

Physical Data: mp 160-163 °C.

Solubility: sol H_2O, EtOH; insol CH_2Cl_2, acetone.

Form Supplied in: white or off-white crystalline solid; available from several commercial sources.

Handling, Storage, and Precautions: the free base is reported to be unstable,[1] and should be generated shortly before use.

Protection Reagent.

Alcohols (eq 1)[1,2] (including hydroxy-containing amino acid derivatives),[2] phenols,[3] carboxylic acids (eq 2),[5] and thiols (eq 3)[3,4] have all been alkylated by this reagent (**1**). Esters (**2**) are also available from the respective acids by ***1,3-Dicyclohexylcarbodiimide*** coupling with 4-pyridylmethanol in CH_2Cl_2[5] in comparable yield.

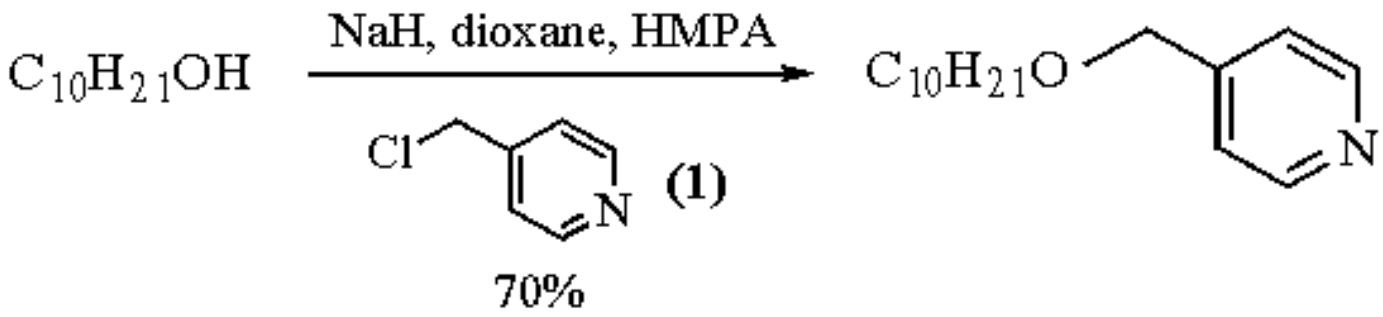

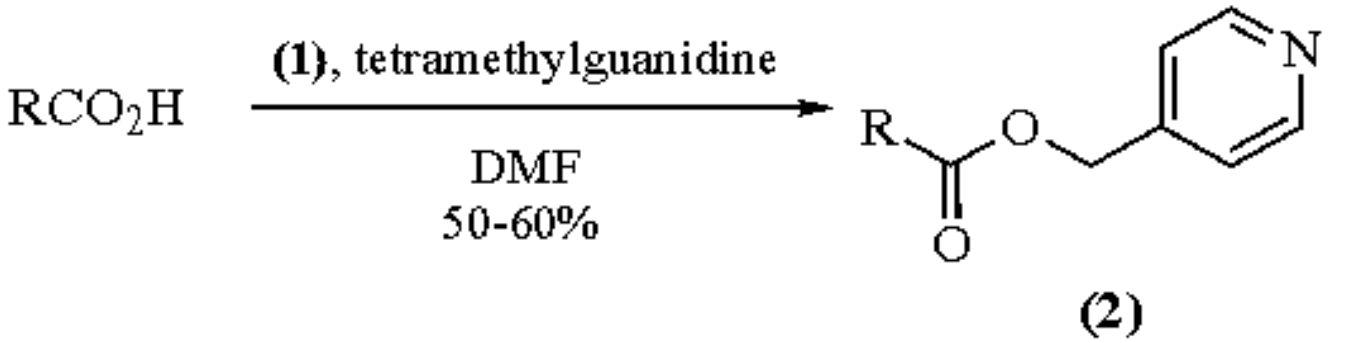

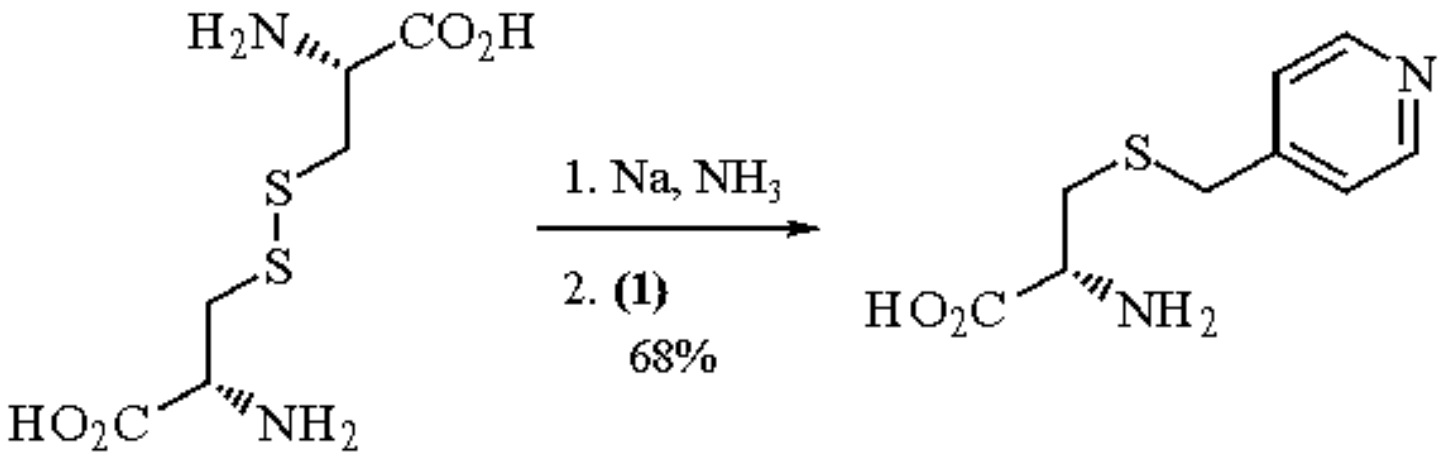

Dihydric alcohols such as (**3**) are preferentially alkylated on the primary OH, but (**4**) yields a mixture of dialkylated and both monoalkylated products.[1]

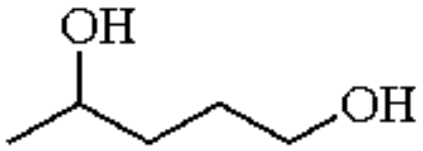

(3)

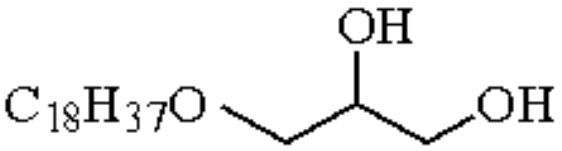

(4)

The protected materials have been of particular value in peptide chemistry. Cleavage[5] of esters (**2**) takes place not only under the more obvious aqueous alkali or catalytic hydrogenation conditions, but also with ***Sodium-Ammonia*** or by electrolytic reduction at a mercury cathode. The protected alcohols,[1,2] phenols,[3] and thiols[3,4] are similarly deprotectable by electrolysis.

The use of 2-[1] and 3-picolyl[2] ethers in such cases has also been investigated, and an *N*-protecting group, (4-picolyloxy)carbonyl,[6] has also been described. The increased polarity of these picolyl-containing materials, relative to the more typical benzylic protecting groups, can appreciably assist in their purification.[2] Nevertheless, these protecting groups remain outside the mainstream of peptide chemistry, probably due to the greater familiarity and availability of, for example, the benzyl- or *t*-butyl-based groups, and the fact that the Na/NH_3 or electrolytic deprotection of the 4-picolyl group is likely to be incompatible with these. In this regard, the use of 2-(2´- or 4´-pyridyl)ethyl protecting groups[7] (Pyoc carbamates,[7a] Pet esters,[7b,7c]), likely to impart similar polarity, but deprotectable cleanly in the presence of these other common functionalities, appears distinctly advantageous.

---

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Pinacol (Chloromethyl)boronate[1]

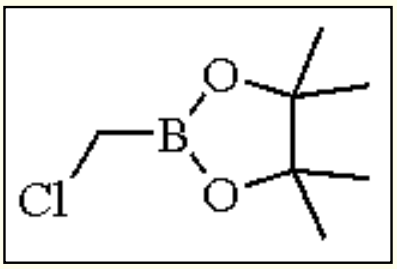

[83622-42-8] · $C_7H_{14}BClO_2$ · Pinacol (Chloromethyl)boronate · (MW 176.45)

(precursor to allylic boronic esters for stereoselective reactions with aldehydes to form homoallylic alcohols;[2] precursor to heterosubstituted methylboronates[1])

Alternate Name: 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

Physical Data: bp 81 °C/14 mmHg; ^{1}H NMR δ 1.22 (s, C*H*$_3$), 2.77 (s, C*H*$_2$Cl).[3]

Preparative Method: addition of BuLi to stirred $ClCH_2Br$ and $B(OMe)_3$ in THF at -78 °C followed by Me_3SiCl yields $ClCH_2B(OMe)_2$, which is transesterified with pinacol.[4]

Handling, Storage, and Precautions: (halomethyl)boronic esters are lachrymators and must be handled in a fume hood. As usual with reactive alkyl halides, skin contact should be avoided.

Reagent Preparation.

The first efficient preparation of (chloromethyl)boronic esters was via reduction of (dichloromethyl)boronic esters with ***Tri-n-butylstannane***.[3]

The most economical route to pinacol (chloromethyl)boronate (**1**) is the addition of ***n-Butyllithium*** to a vigorously stirred solution of bromochloromethane and ***Trimethyl Borate*** in THF cooled with a dry ice-acetone bath. After quenching with ***Chlorotrimethylsilane***, the product is treated with pinacol and distilled (73-85%) (eq 1).[4]

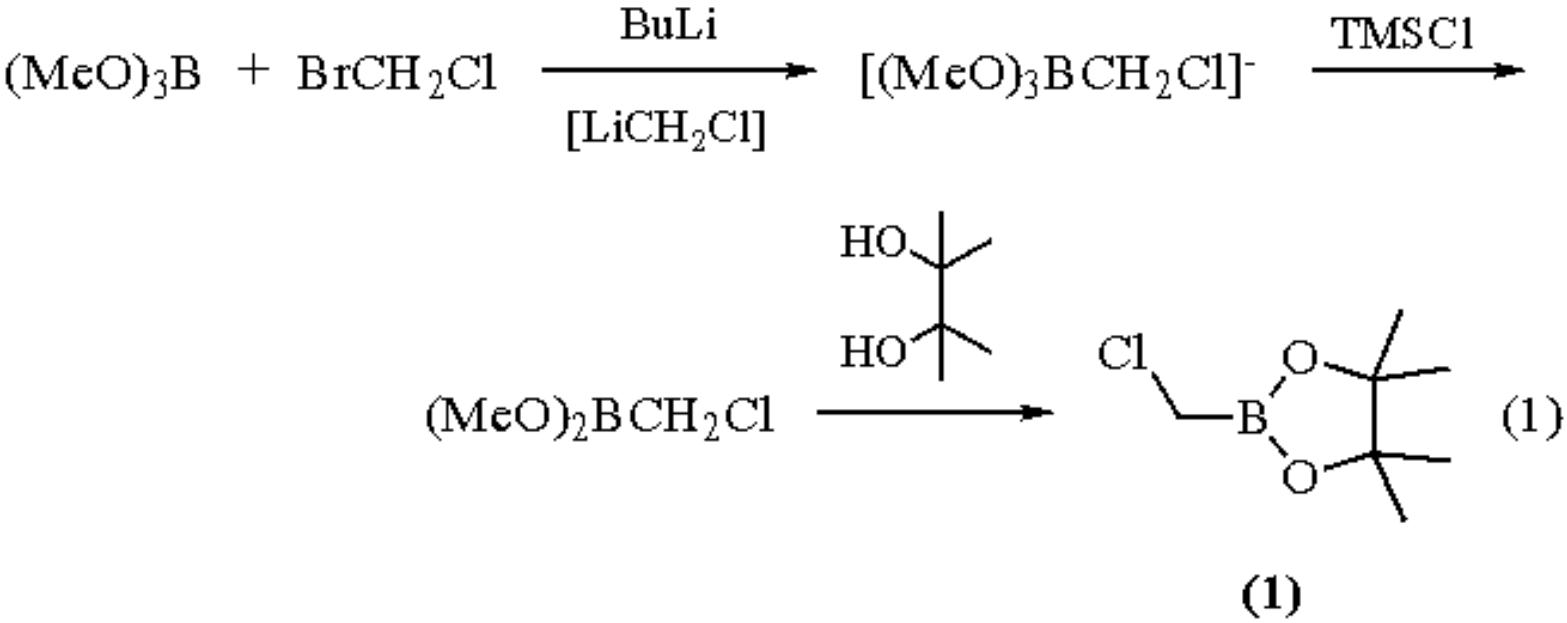

Diisopropyl (chloromethyl)boronate has been made via a similar route from ***Chloroiodomethane***, ***Triisopropyl Borate***, and butyllithium, followed by quenching with ethereal HCl and distillation (84%).[5] Yields have been higher with ICH_2Cl than with $BrCH_2Cl$ in our laboratory. The diisopropyl ester is easily transesterified with a variety of diols.[1,6]

An especially convenient preparation of diisopropyl (bromomethyl)boronate has been reported recently.[7] ***Dibromomethane*** is used in place of chloroiodomethane in the foregoing procedure, there is no halide exchange during workup, and 85% yields are routinely obtained on a 2-mol scale.

For some purposes, especially reactions with enolates, pinacol (chloromethyl)boronate (**1**) is not reactive enough in S_N2 displacements.[5,8] The chloride is easily displaced by ***Sodium Iodide*** in acetone to produce pinacol (iodomethyl)boronate.[3] It remains to be investigated how the bromo analog will compare in reactivity with the chloro and iodo compounds.

Allylic Boronic Esters.

A major use of pinacol (chloromethyl)boronate (**1**) and related compounds has been for the synthesis of allylic boronic esters (**2**),[2] which react diastereoselectively with aldehydes to form homoallylic alcohols. The configuration of the double bond is retained in the synthesis (eq 2),[2] and the required alkenylmetallic reagents are often easily prepared in high isomeric purity, for example, via organocopper chemistry.[9]

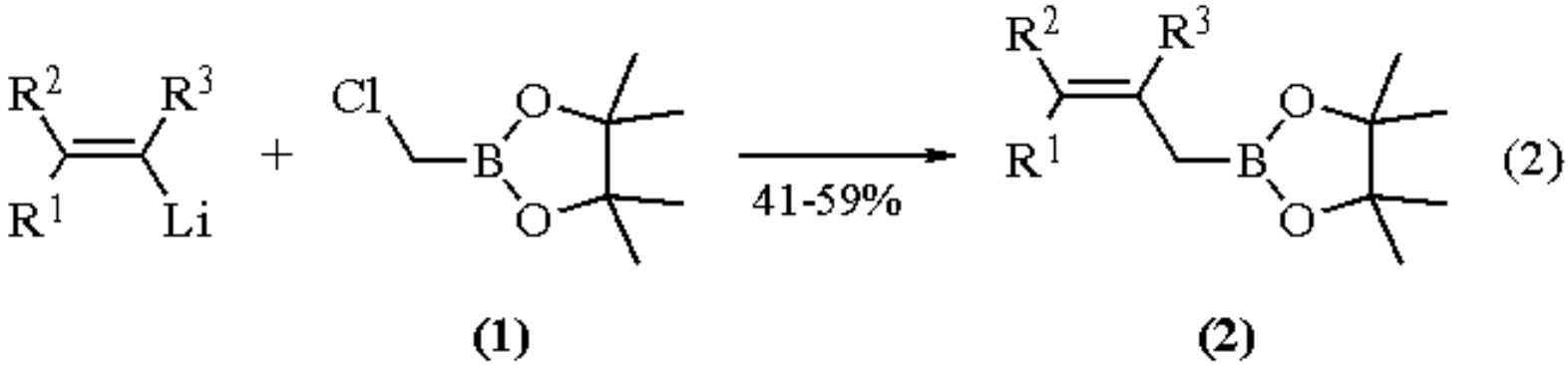

$R^1, R^3 = H, R^2 = Me$ or $THPOCH_2$; $R^1, R^2 = H, R^3 = Me$ or $C(OEt)_3$;
$R^1 = H$ or $Me, R^2 = H, R^3 = Me$; alkene = 1-cyclohexenyl;
$R^3 = H, R^1 = Me$ or $Bu, R^2 = Bu$ or Me

Major byproducts limiting yields in the synthesis of (*Z*)-allylic boronic esters (**3**) were found to include alkenylboronic ester (**4**) and alkene (**5**) (eq 3).[10,11] When (*Z*)-1-propenylmagnesium bromide was used in place of the lithium reagent, formation of alkenylboronic ester (**4**) was reduced below 1%.[11] When (*E*)-1-lithiopropene was used, the (*E*) analog of (**4**) was not a problem. However, either of the simple crotylboronates was more efficiently prepared via reaction of lithiated (*Z*)- or (*E*)-2-butene with $FB(OMe)_2$.[11]

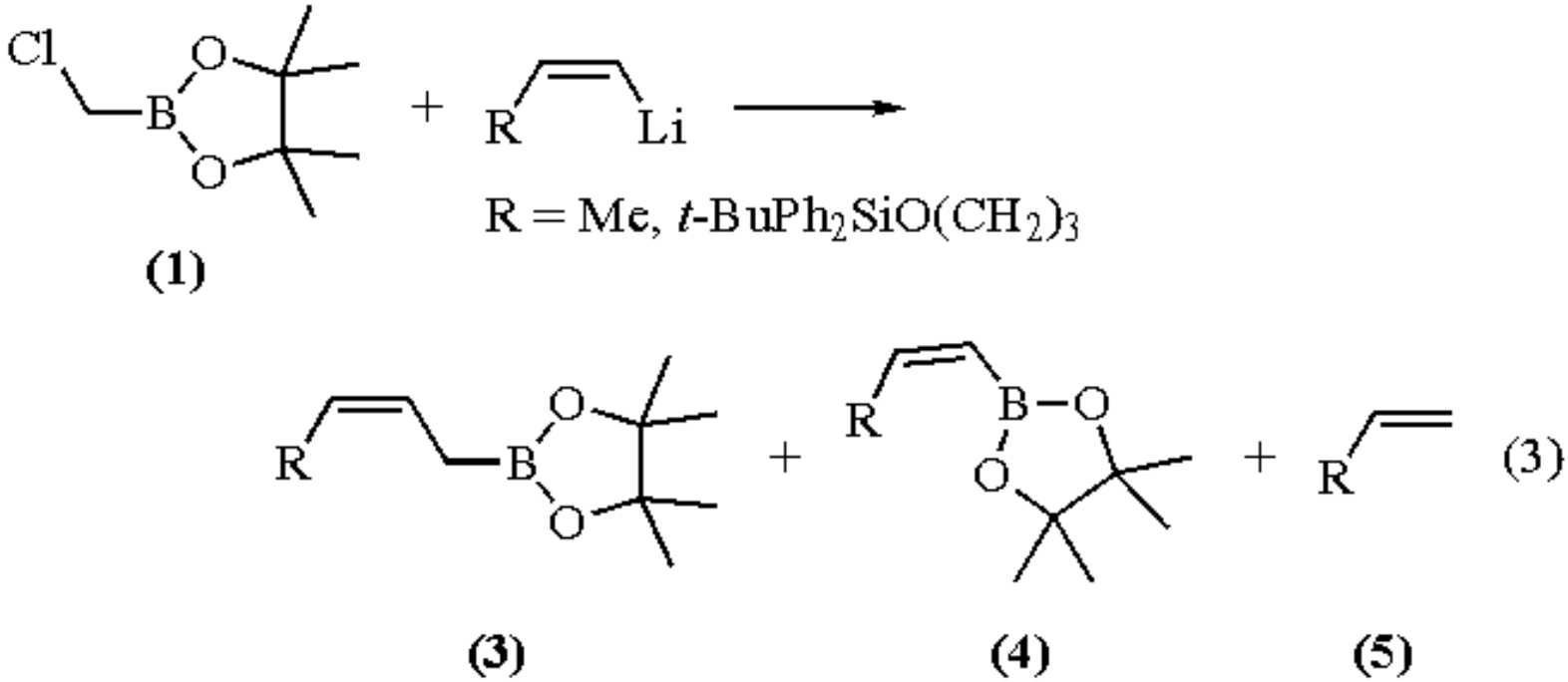

Reaction With Enolates.

Pinacol (iodomethyl)boronate (**6**) reacts with ester, ketone, or amide enolates to form γ-boryl carbonyl compounds (eqs 4 and 5).[4,8] The iodo boronic ester (**6**) has been found superior to the less reactive chloro compound (**1**) for this purpose. Intramolecular interaction of the boron atom with the carbonyl oxygen provides stereocontrol in subsequent reactions of the products.[4]

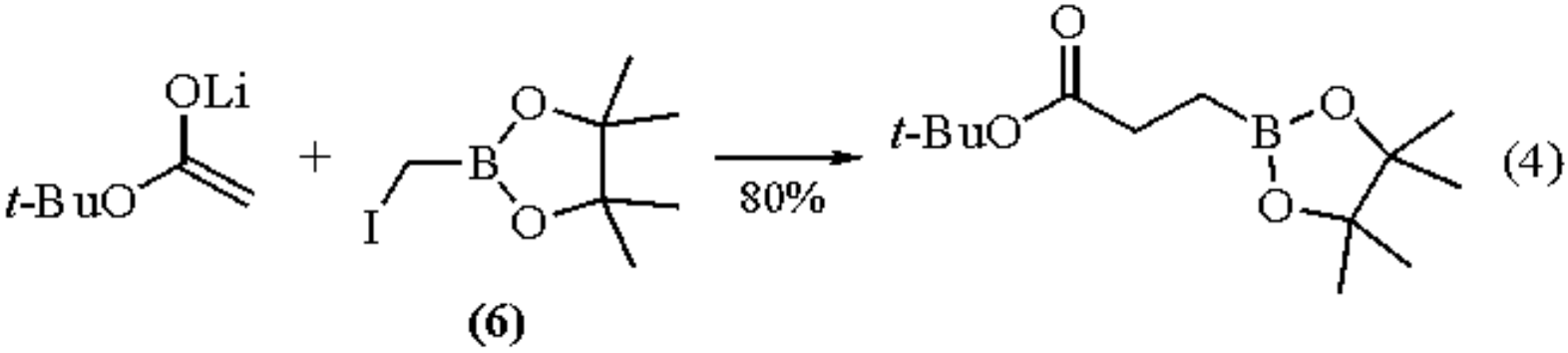

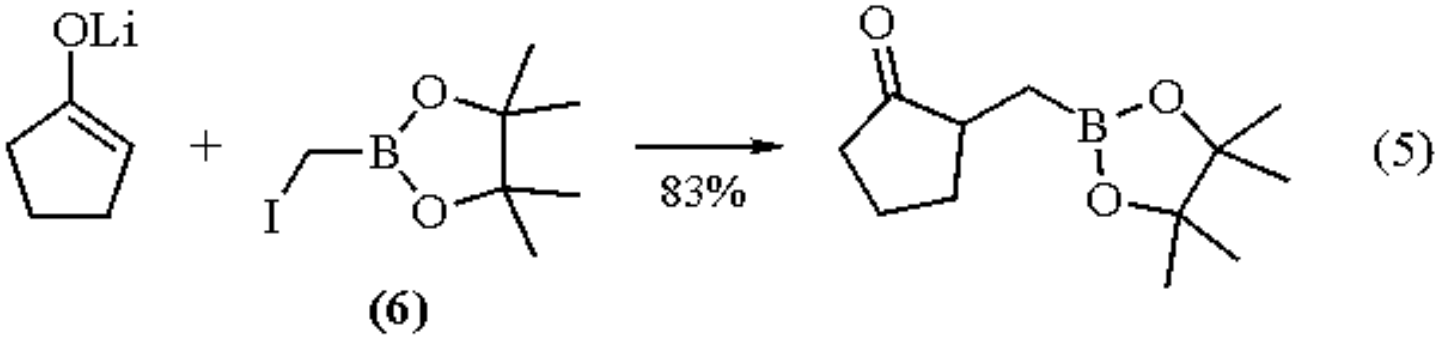

Dibutyl (iodomethyl)boronate and pinacol (chloromethyl)boronate (**1**) alkylate malonic ester anions.[12] Pinacol (iodomethyl)boronate (**6**) also alkylates secondary and tertiary amines.[13]

Zinc Derivative.

Pinacol (iodomethyl)boronate (**6**) reacts with activated zinc to form the zinc reagent (**7**).[14] The zinc reagent is in turn converted to a cuprate, which reacts with electrophiles, for example as illustrated in eq 6.[14]

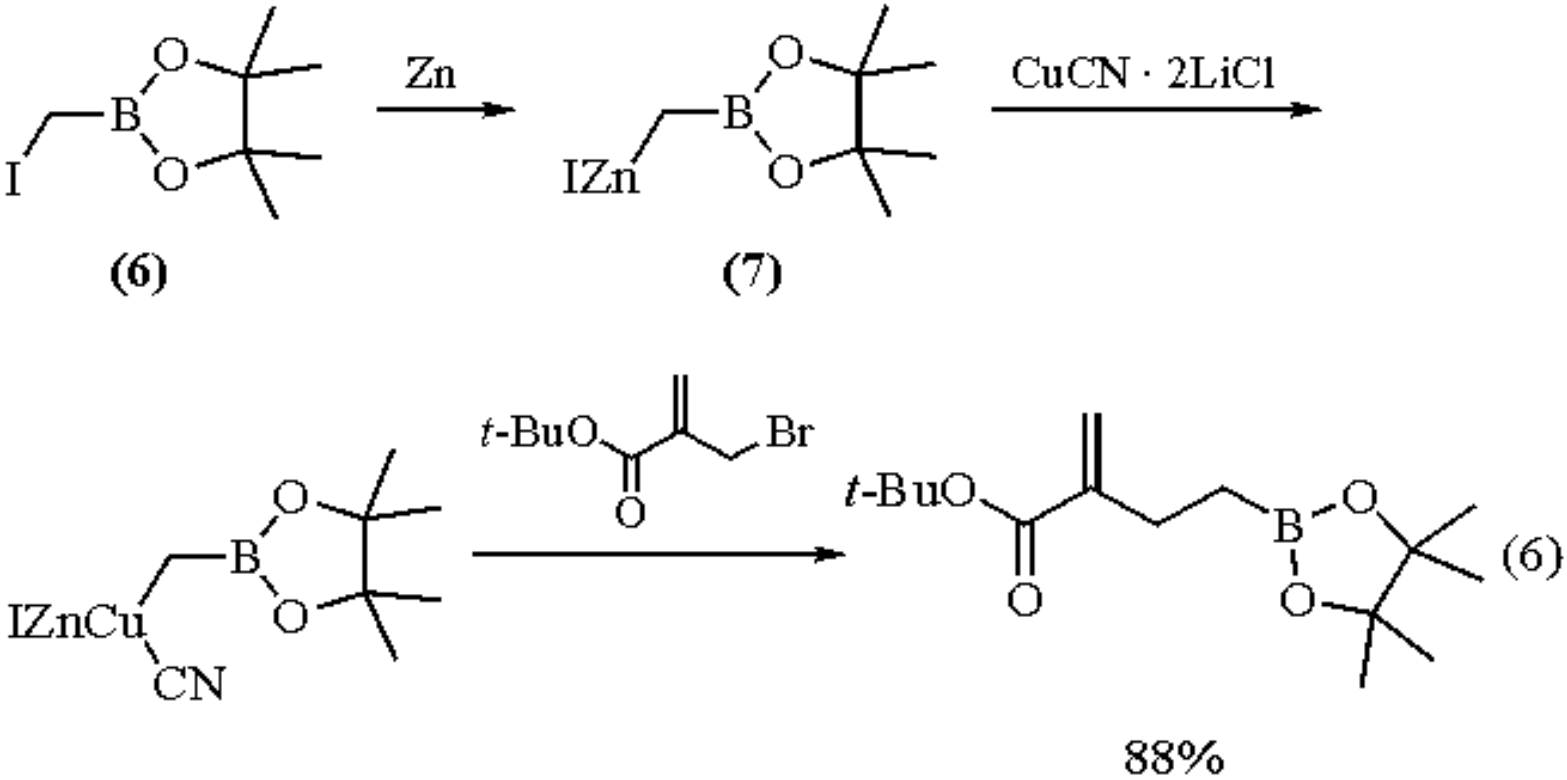

Homologs and Related Reagents.

α-Haloalkylboronic esters constitute a broadly useful class of reagents for making C-C bond connections with organometallics, especially for asymmetric synthesis[1] (see also ***Diisopropyl (Dichloromethyl)boronate***).

α,α-Disubstituted allylic boronic esters are readily prepared from pinacol (1-bromo-1-methylethyl)boronate (**8**) and alkenyllithiums (eq 7).[11]

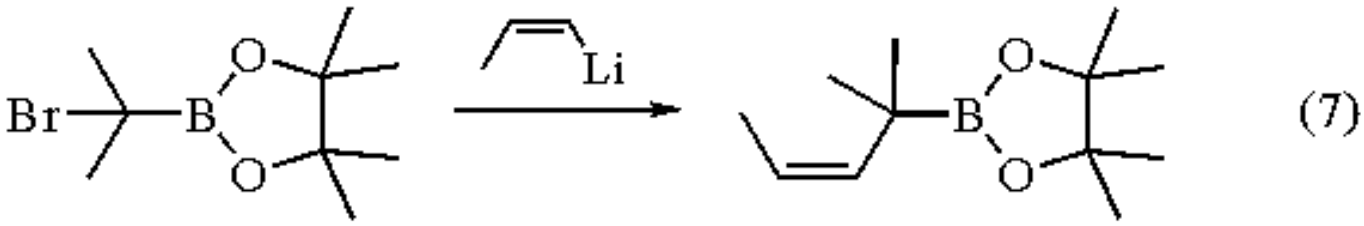

α-Bromoalkyl boronic esters react diastereoselectively with *t*-butyl lithiopropionate (eq 8).[15] Diastereomeric excesses were 88-96%, enantiomeric excesses >98% (R = *i*-Pr, Bu).

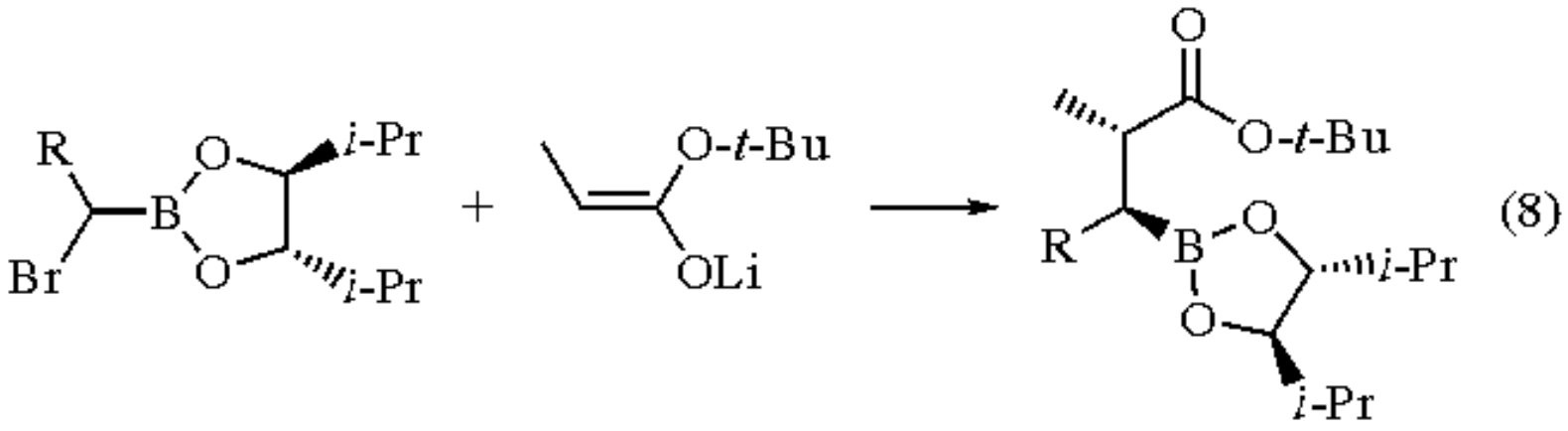

1. (a) Matteson, D. S. *ACR* **1988**, *21*, 294. (b) Matteson, D. S. *CRV* **1989**, *89*, 1535. (c) Matteson, D. S. *T* **1989**, *45*, 1859. (d) Matteson, D. S. *The Chemistry of the Metal-Carbon Bond*; Hartley, F.; Patai, S., Eds; Wiley: New York, 1987; Vol. 4, pp 307-409.
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B-3-Pinanyl-9-borabicyclo[3.3.1]nonane

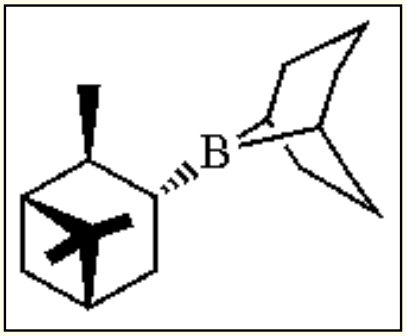

(*R*)

[173624-47-2] · $C_{18}H_{31}B$ · *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane · (MW 258.30) (*S*)

[42371-63-1]

(asymmetric reducing agent which is particularly effective for aldehydes[1] and alkynic ketones[2])

Alternate Name: Alpine-Borane®.

Solubility: sol most organic solvents.

Form Supplied in: 0.5 M solution in THF. (*R*)-Alpine-Borane is prepared from (+)-α-pinene, and (*S*)-Alpine-Borane from (-)-α-pinene. High purity α-pinene is available commercially.

Preparative Methods: readily prepared by hydroboration of either (+)- or (-)-α-pinene[4] with ***9-Borabicyclo[3.3.1]nonane*** (9-BBN) (eq 1).

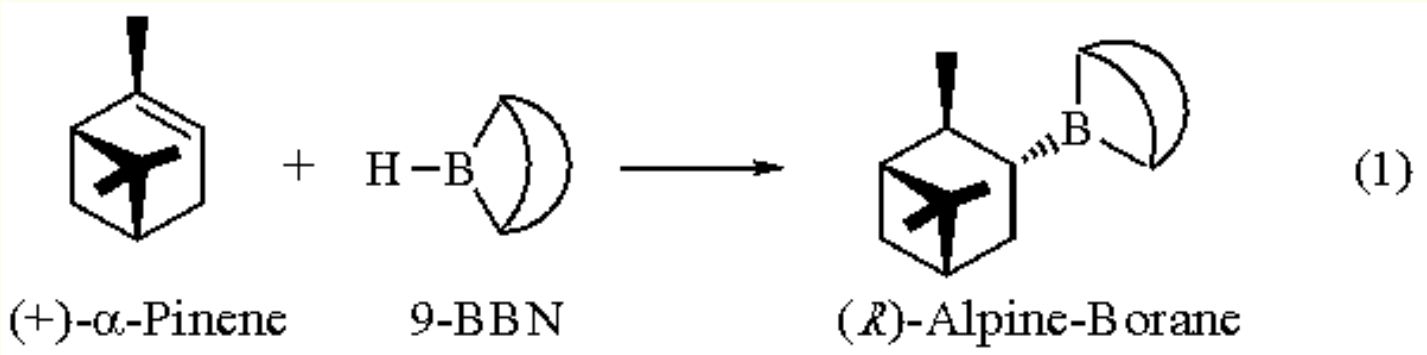

Since the neat reagent is most effective, the solvent is usually removed before reduction of the ketone. Brown has reported a synthesis using neat α-pinene and solid 9-BBN.[5] The deuterium- or tritium-labeled compound may be prepared by hydroboration with labeled 9-BBN.[6] Alternatively *B*-methoxy-9-BBN may

be reduced with $LiAlD_4$ (see ***Lithium Aluminum Hydride***) in the presence of α-pinene.[7,8]

Handling, Storage, and Precautions: organoboranes are spontaneously flammable in air and must be handled under an inert atmosphere. They are generally stable to moisture. Alpine-Borane can slowly undergo dehydroboration.[3] Use in a fume hood.

Reduction of Aldehydes.

Stereospecificially labeled primary alcohols are useful in biochemical and physical organic studies. Such compounds may be prepared by enzymatic reduction of a labeled aldehyde using yeast.[9] However, isolation of the product is often tedious. Alpine-Borane greatly simplifies the process and provides compounds of high enantiomeric purity. It is the most efficient reagent available for reduction of aldehydes. The limiting factor is often the enantiomeric purity of the starting α-pinene. Either enantiomer of the labeled primary alcohol may be obtained by using either (+)- or (-)-α-pinene or by placing the label either on the aldehyde or on the reducing agent (eq 2).

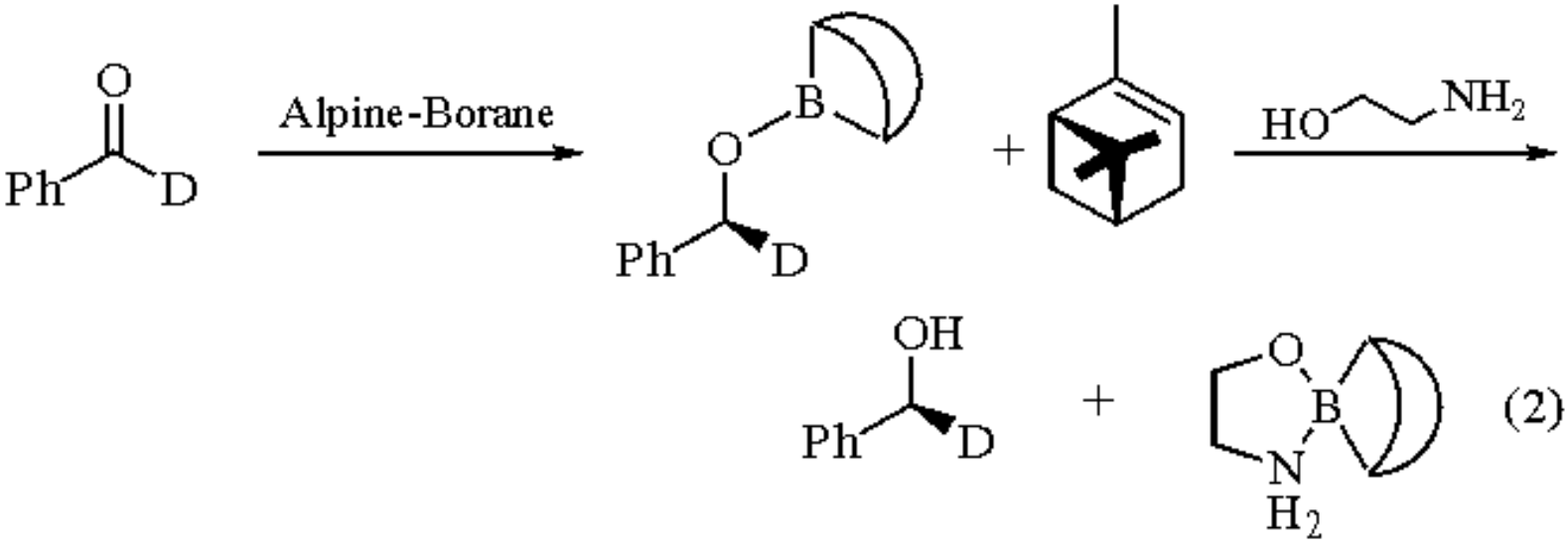

The reduction is bimolecular and thus the rate is dependent on concentration. Running the reaction neat provides the fastest rates. Usually an excess of Alpine-Borane is used to insure that the reaction does not become excessively slow at the end of the reduction. The excess organoborane may be destroyed by addition of an aldehyde such as ***Acetaldehyde***. The resulting alkoxy-9-BBN may be treated with ***Ethanolamine*** to liberate the alcohol and precipitate the majority of the 9-BBN. Any remaining borane impurities may be removed by oxidation with basic ***Hydrogen Peroxide***.

The absolute configuration of the product may be predicted by using a simple six-membered ring transition state model (structures **1** and **2**). In this model the predicted transition state resembles a boat cyclohexane with the small group occupying an axial-like position.

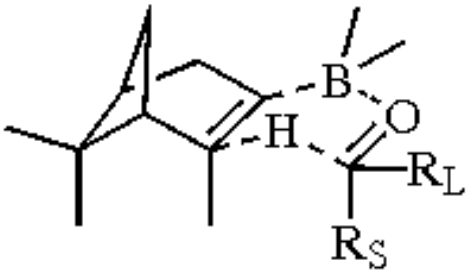

(1) favored

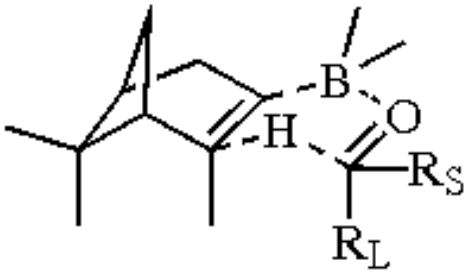

(2) disfavored

Alkynic Ketones.

The reagent is very sensitive to the steric requirements of the carbonyl group. Ketones are reduced at considerably slower rates than aldehydes.[10] Alkynic ketones are reduced at somewhat slower rates than aldehydes, but generally proceed at 25 °C. An alkynic ketone may be reduced in the presence of a methyl ketone (eq 3).

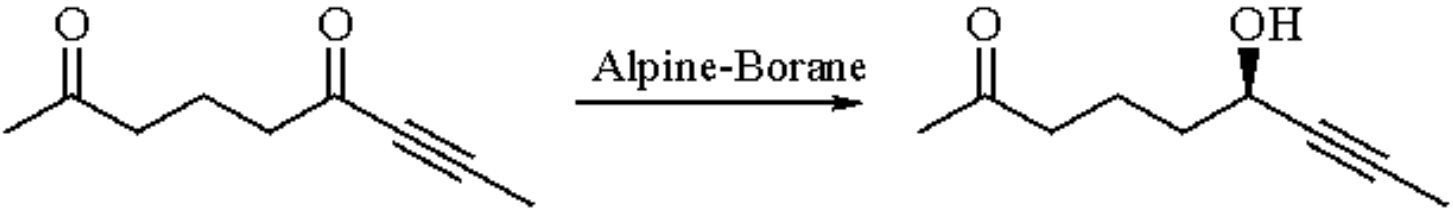

(3)

Aromatic, *n*-alkyl, and branched alkyl alkynic ketones are effectively reduced (eq 4).

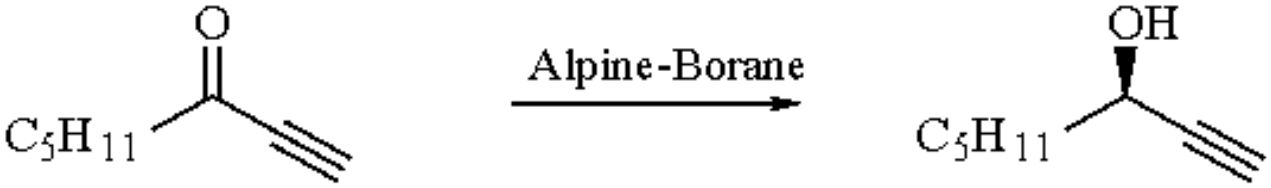

(4)

90-100% ee

Methyl alkynic ketones are reduced with slightly lower efficiency and *t*-butyl alkynic ketones are reduced very slowly. In the latter case, dehydroboration of Alpine-Borane to give 9-BBN competes with the rate of reduction and the liberated 9-BBN reduces the ketone to give products of lower enantiomeric purity. This problem may be overcome by using high pressure[11] or by using *B*-10-*cis*-myrtanyl-9-BBN (eqs 5 and 6).[12]

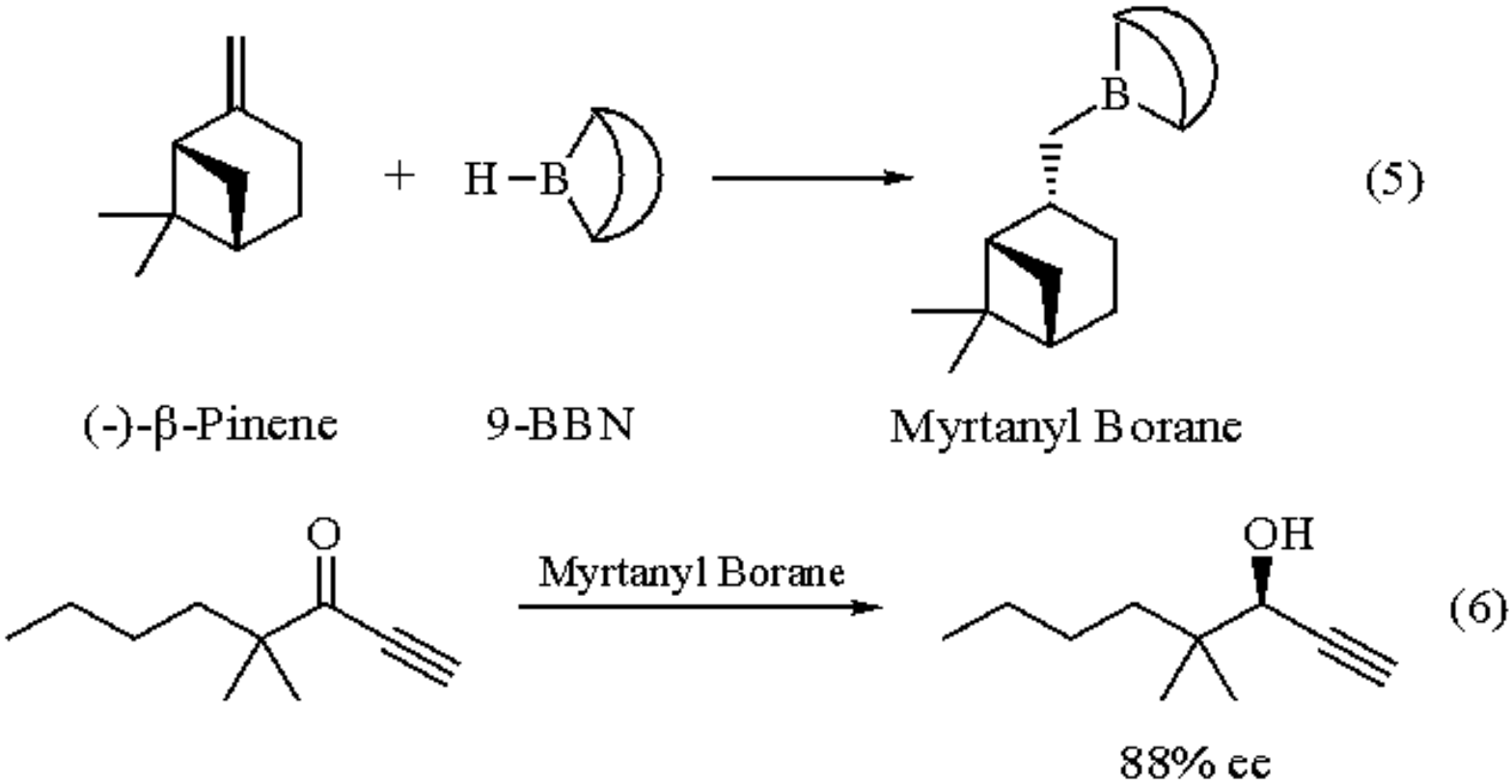

α-Keto Esters.

In general, electron-withdrawing groups enhance the rate of reduction of ketones with Alpine-Borane. Thus α-keto esters are generally good substrates for reduction. Methyl pyruvate is reduced within 4 h at rt with neat Alpine-Borane.[13] The use of *t*-butyl pyruvate increases the efficiency (eq 7).

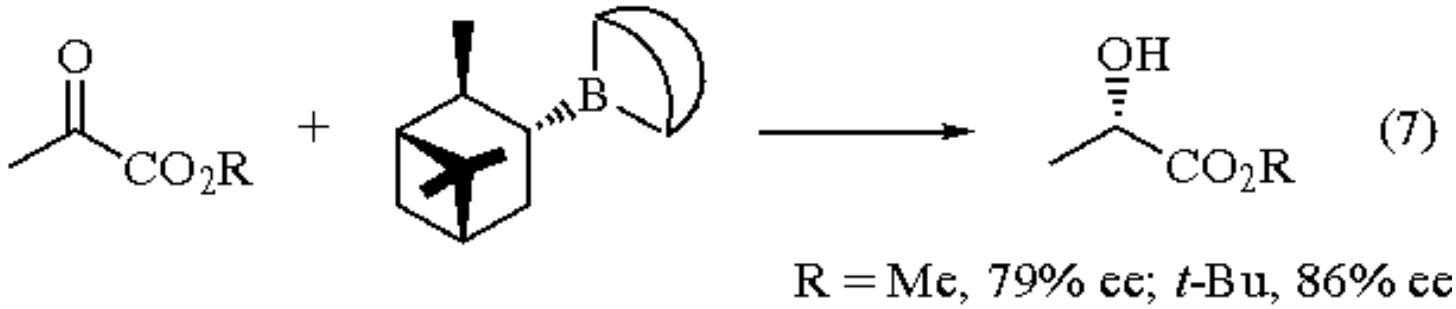

Methyl, *n*-alkyl, and isobutyl behave as small groups in the transition state model for reduction, while isopropyl or aromatic groups behave as large groups (eq 8).

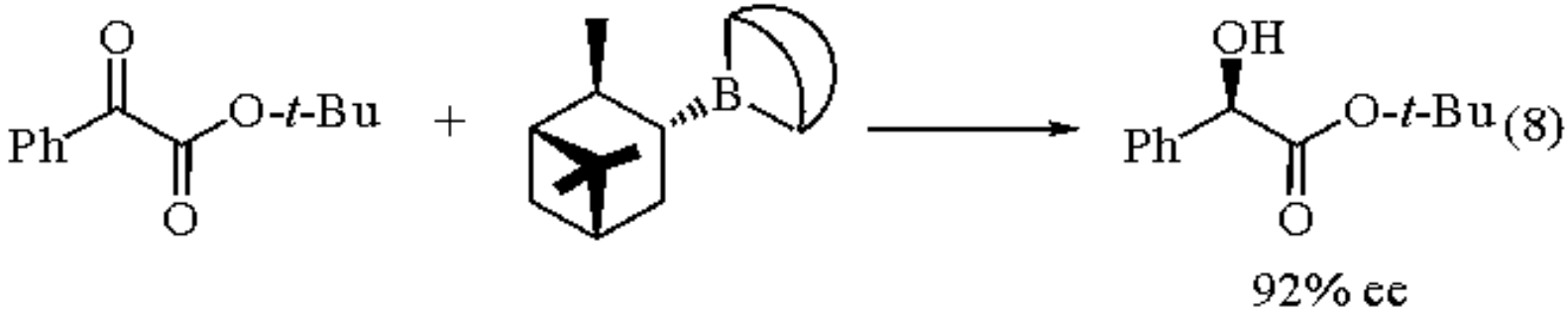

Other Ketones.

Ketones such as acetophenone are reduced rather slowly by THF solutions of Alpine-Borane (eq 9). A competing dehydroboration process leads to reduction via 9-BBN (eq 10).

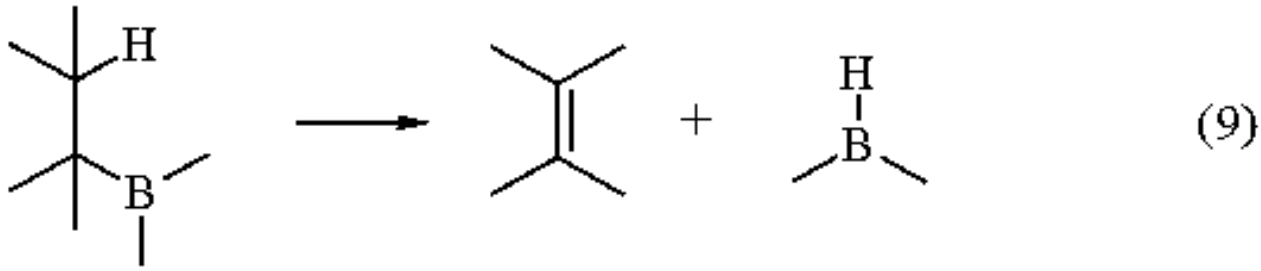

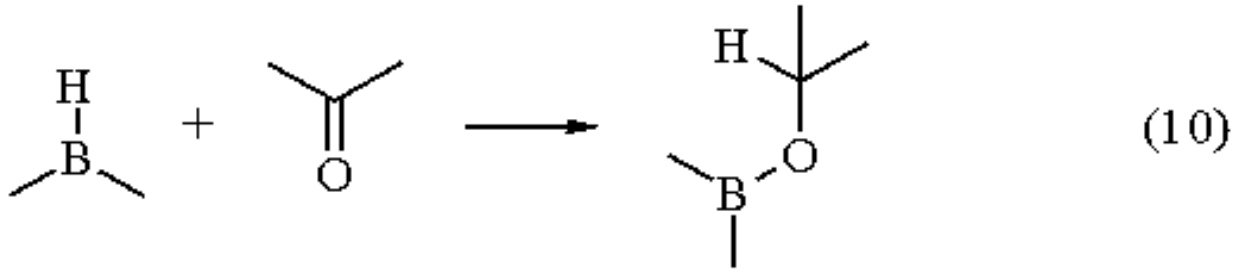

At 65 °C, Alpine-Borane undergoes 50% dehydroboration in 500 min.[3] At rt there is approximately 1-2% dehydroboration per day. Running the reaction neat increases the rate of the favorable bimolecular reduction.[5] Alternatively, high pressure may be used to increase the rate of the bimolecular process and retard the rate of the dehydroboration reaction (eq 11).[11]

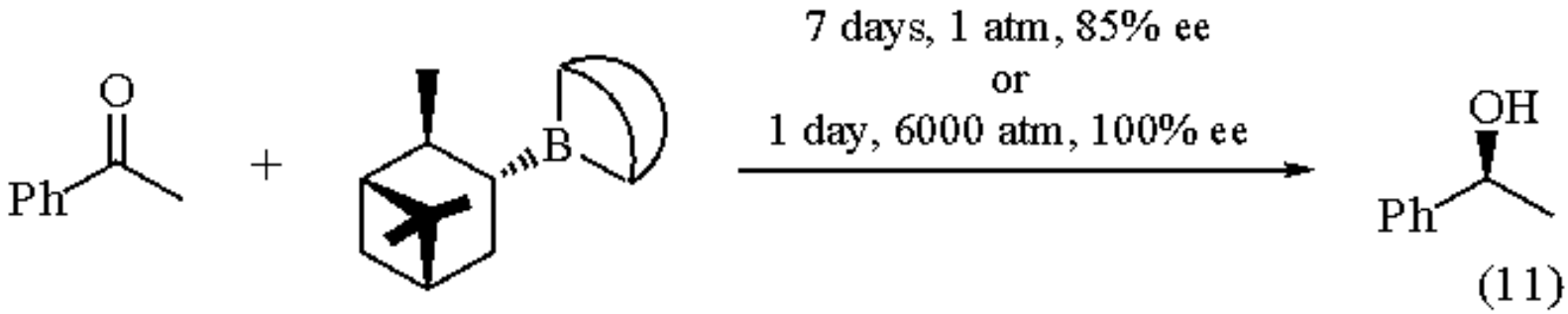

The simple steric model for the transition state may be used to predict the absolute configuration of the product. The

related reagent ***(+)-B-Chlorodiisopinocampheylborane*** reduces ketones with greater ease and efficiency (eq 12).[14]

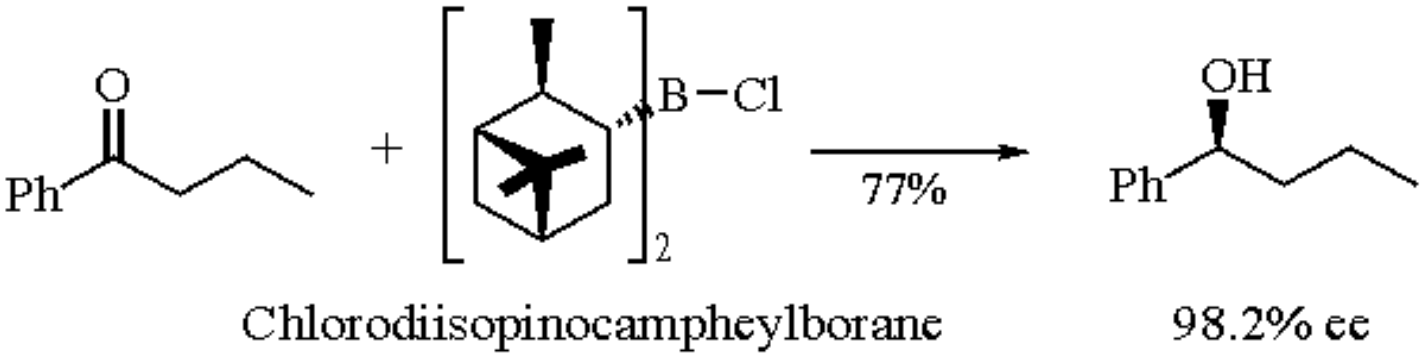

(12)

Related Reagents.

2-[2-[(Benzyloxy)ethyl]-6,6-dimethylbicyclo[3.3.1]-3-nonyl]-9-borabicyclo[3.3.1]nonane.

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2. (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *JACS* **1980**, *102*, 867. (b) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R.; Tsai, D. J-S.; Cardin, D. B. *T* **1984**, *40*, 1371. (c) Midland, M. M; Graham, R. S. *OS* **1984**, *63*, 57. (d) Midland, M. M.; Graham, R. S. *OSC* **1990**, *7*, 402. (e) Midland, M. M. *CRV* **1989**, *89*, 1553.
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14. Brown, H. C., Chandrasekharan, J.; Ramachandran, P. V. *JACS* **1988**, *110*, 1539.

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Piperidine[1]

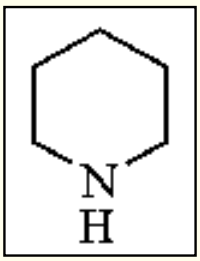

[110-89-4] · $C_5H_{11}N$ · Piperidine · (MW 85.17)

(secondary amine base;[1] condensation catalyst for aldol,[4] Knoevenagel,[3] and Michael condensations;[20] thiophile for mediation of sulfoxide-sulfenate rearrangement;[13] reagent for enamine formation and utilization[22])

Physical Data: mp -9 °C; bp 106 °C; *d* 0.862 g cm^{-3}; secondary amine base of pK_a 11.12.

Solubility: miscible with water; sol common organic solvents (alcohol, benzene, chloroform).

Form Supplied in: liquid (99%). *Drying:* by treatment with standard drying agents, e.g. CaH_2, BaO, sodium metal, P_2O_5, or KOH.

Purification: distillation may be carried out directly from CaH_2, P_2O_5, or sodium.[2]

Handling, Storage, and Precautions: toxic either by absorption through the skin or by breathing. It is highly flammable, with a flash point of 16 °C. Use in a fume hood.

Condensation Catalyst.

Piperidine has had wide usage as a catalyst for aldol condensations, particularly cyclization processes. It is typically also the catalyst of choice, usually in combination with a carboxylic acid, for condensations of relatively acidic carbonyl compounds with aldehydes and ketones: the Knoevenagel condensation.[3] Michael addition of 2-methylcyclohexane-1,3-dione to methyl vinyl ketone in the presence of potassium hydroxide affords a triketone which upon treatment with piperidine[4] (or ***Pyrrolidine***) cyclizes to produce the Wieland-Miescher ketone (eq 1).[5]

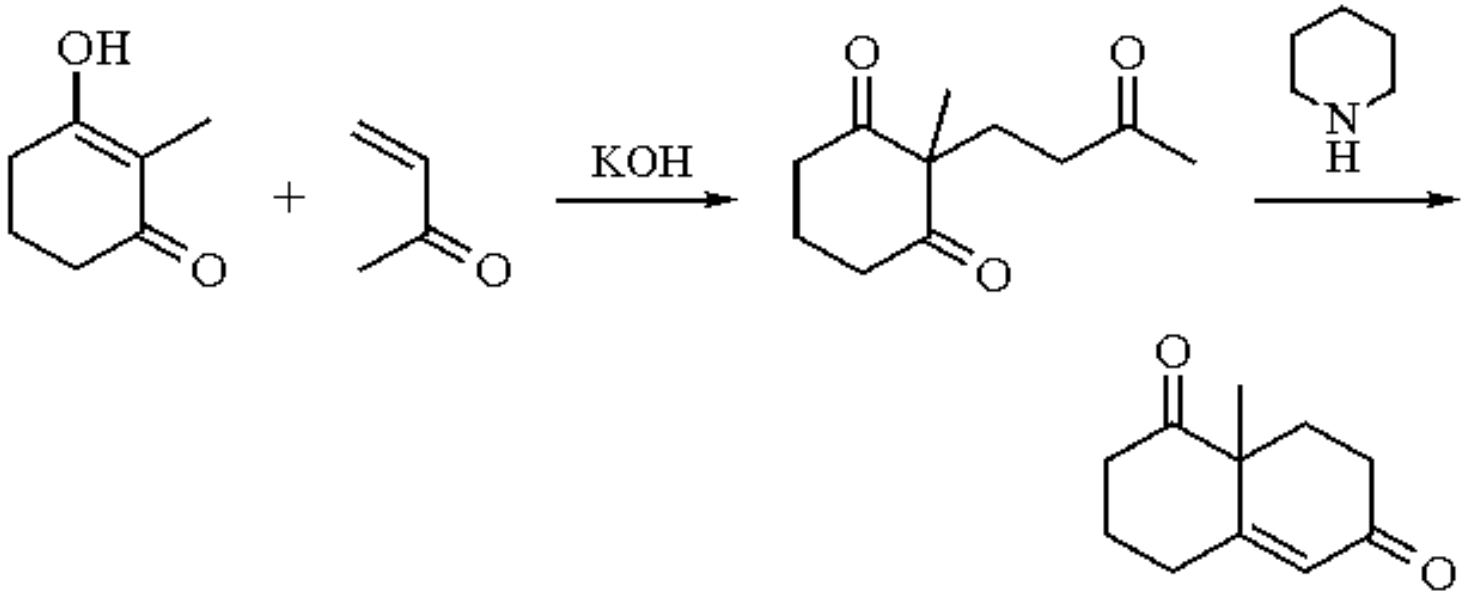

(1)

The particular choice of secondary amine catalyst and acid copartner has been noted to affect the chemoselectivity, and by extension the regioselectivity, of dialdehyde cyclization. Thus piperidine-***Acetic Acid*** mediates the closure of dialdehyde (**1**) to enals (**2**) and (**3**) in a ratio of 19:1 (eq 2).[6] The combination of ***Morpholine*** and camphoric acid affords a 1:25 ratio of the two cyclization products. Similar ratios were observed with related dialdehyde substrates.

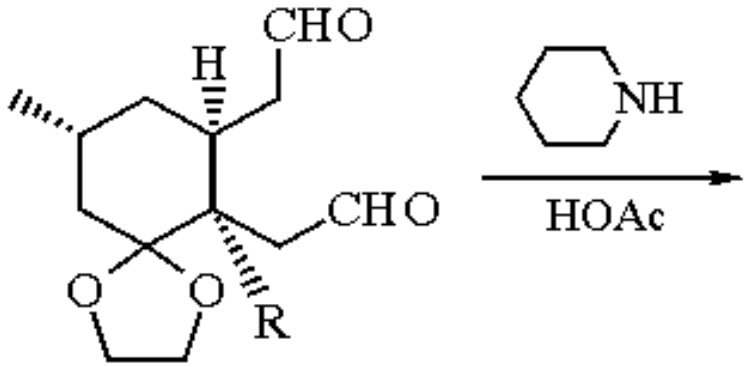

(1)

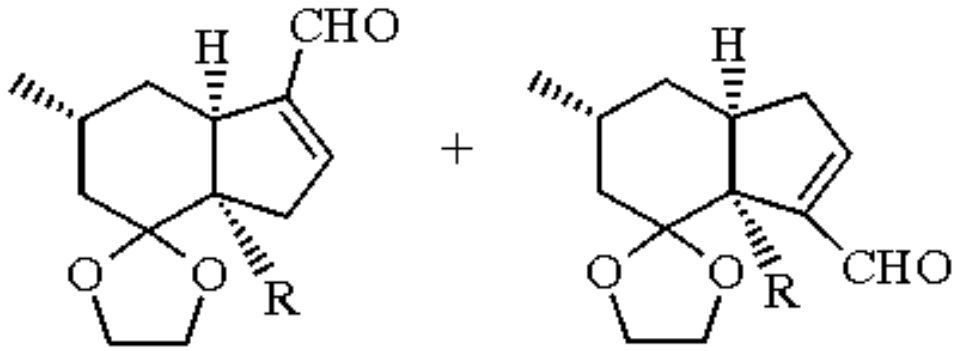

(2)

(2) **(3)**

Piperidine in protonated form and accompanied by a carboxylate counterion is, as noted, the reagent of choice for classical Knoevenagel condensation.[3] Typical among these are condensations of malonic esters and acetoacetic esters

with aromatic aldehydes (eq 3),[7] aliphatic aldehydes (eq 4),[8] and ketones (eq 5).[9]

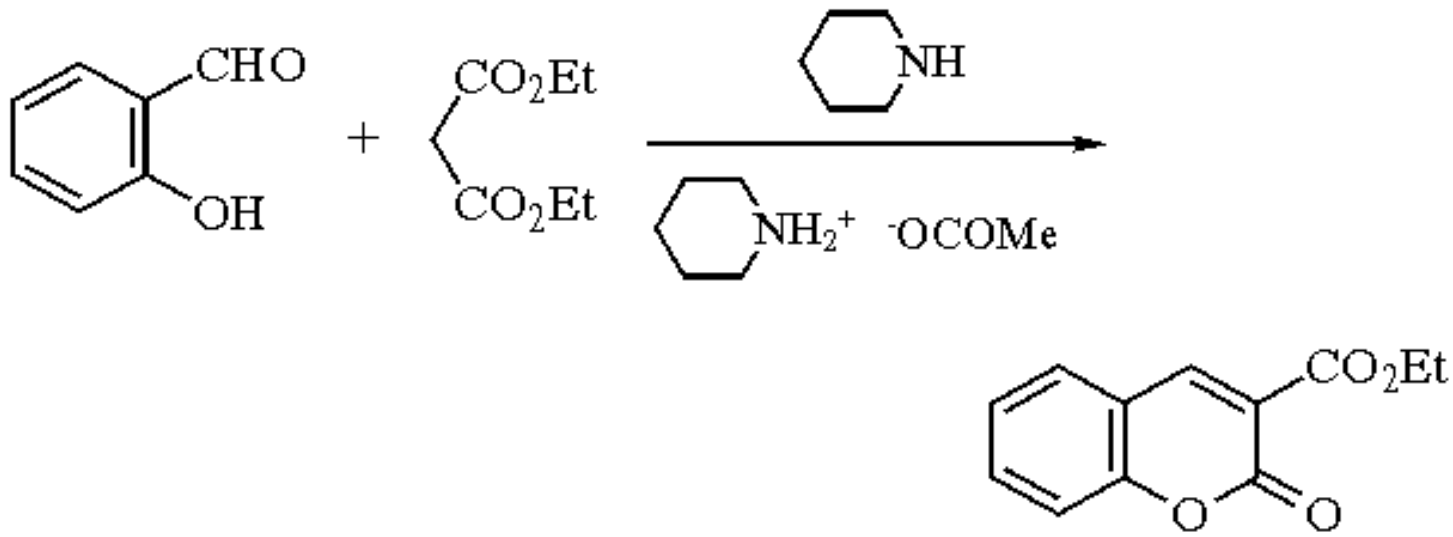

(3)

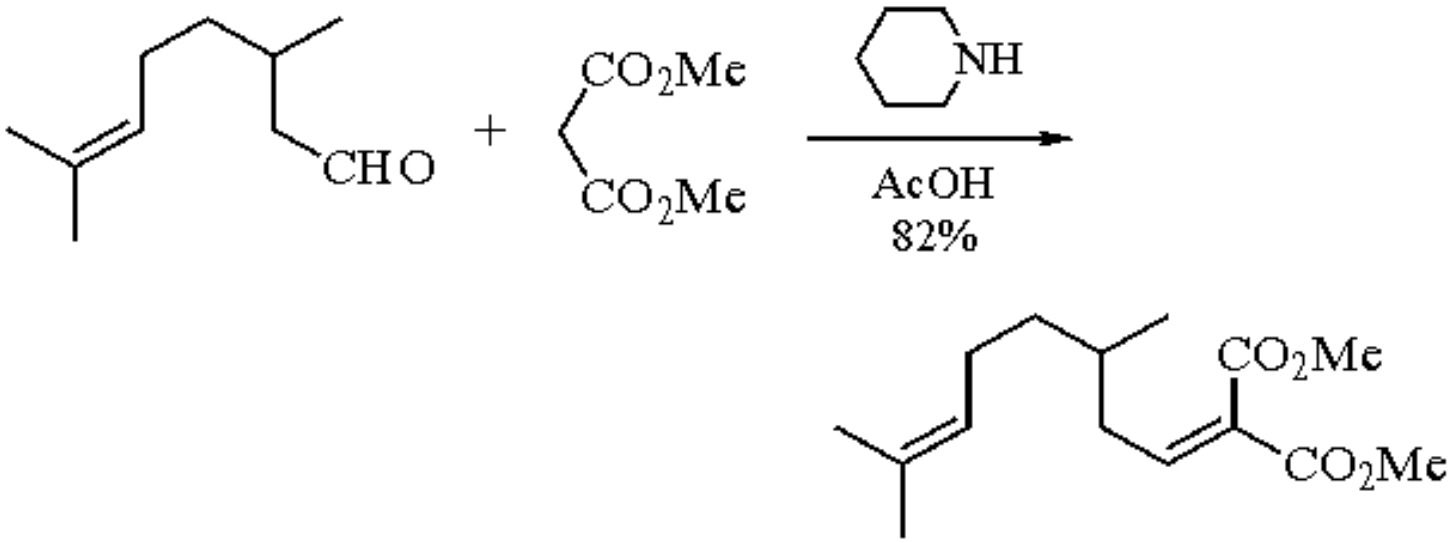

(4)

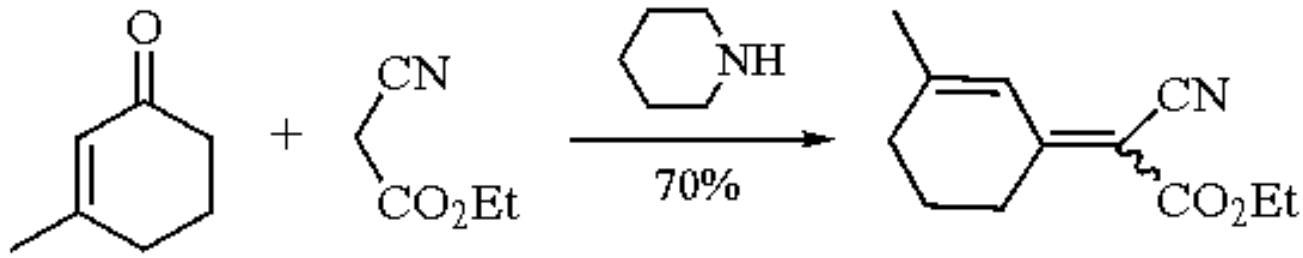

(5)

The entire Robinson annulation sequence for preparing substituted cyclohexenones has also been carried out with piperidine itself as the catalyst for both the Michael and the aldol steps (eq 6).[10-12] In these cases, only a catalytic quantity of piperidine is employed and deethoxycarbonylation of an intermediate β-hydroxycyclohexanone is achieved by heating of the initial reaction products to 100 °C.

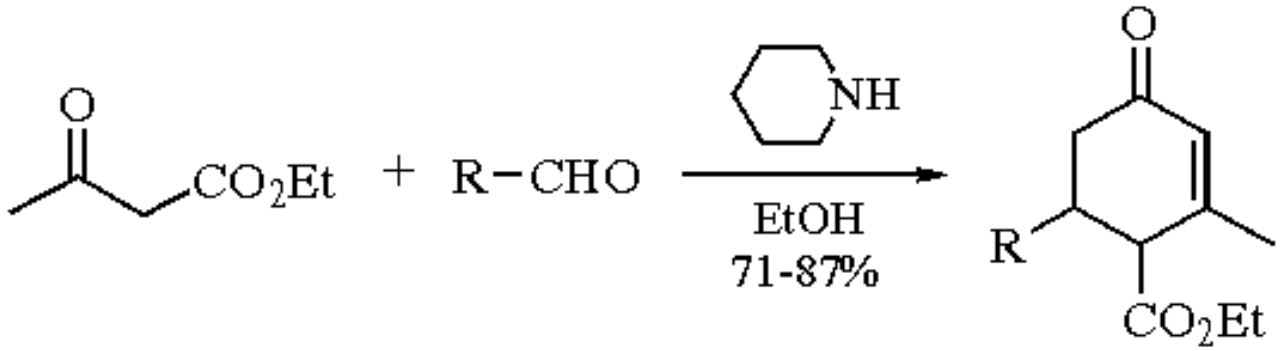

(6)

R = Me, Et, Pr, Bu, C_5H_{11}, C_6H_{13}

Piperidine also serves as an effective thiophile and has been used as both the condensation catalyst and the oxygen-sulfur bond cleavage reagent in Knoevenagel/sulfoxide-sulfenate rearrangement sequences,[13-17] leading to γ-hydroxy-α,β-unsaturated nitriles (eq 7), esters, and sulfones.

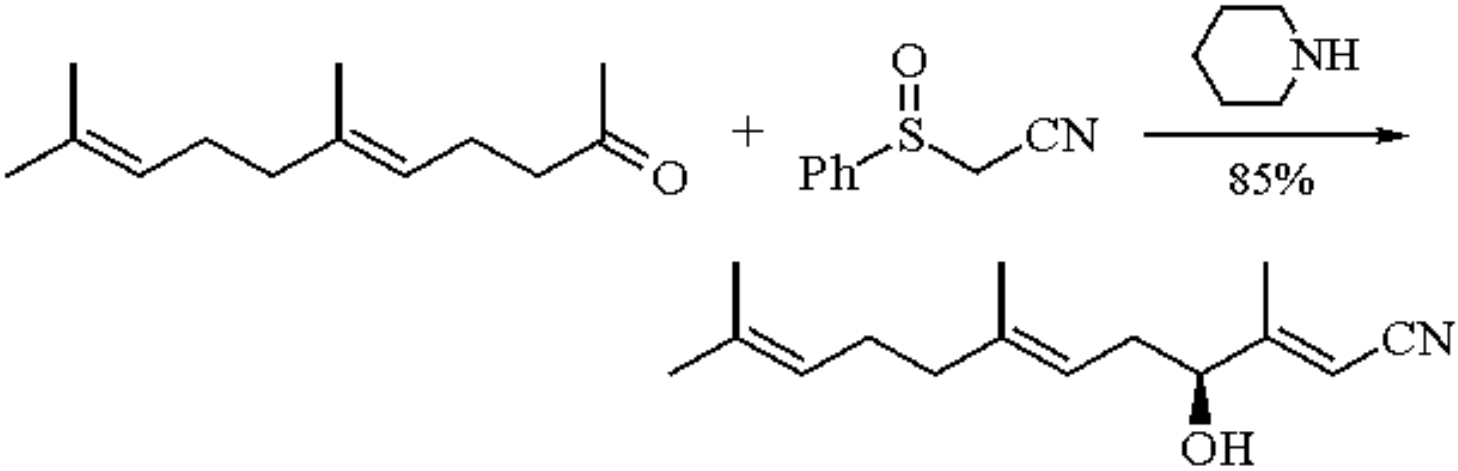

(7)

In many of these cases of piperidine catalysis, the amine presumably acts not only as a simple base for deprotonating relatively acidic β-dicarbonyl compounds but in two other critical and important ways.[18] First, piperidine, particularly when used in conjunction with a carboxylic acid, serves to convert aldehydes and ketones to their electrophilically more reactive iminium derivatives, and second, through the formation of enamines from the donor components of condensation reactions, it effects the conversion of the initial carbonyl compound into a reactive nucleophilic center. Illustrative of the role of piperidine as an imine/enamine-forming agent rather than as a simple base is the selective cleavage of a bis-β-alkoxycarbonyl system (eq 8).[19] Only the less-hindered carbonyl suffers β-elimination, indicating that the cleavage is initiated by enamine formation rather than by simple proton removal. The product is stable to the reaction conditions.

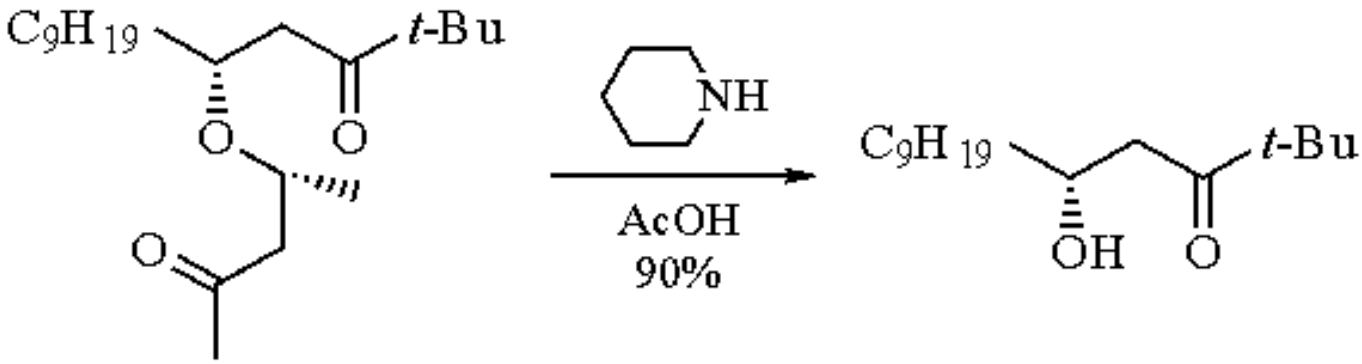

(8)

Piperidine catalyzes Michael addition reactions by both carbon[20] and heteroatom[21] nucleophiles (eqs 9 and 10).

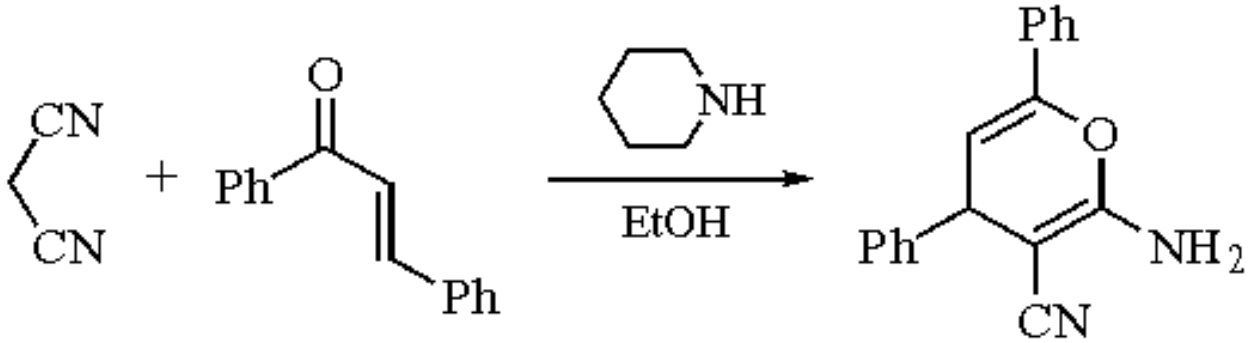

(9)

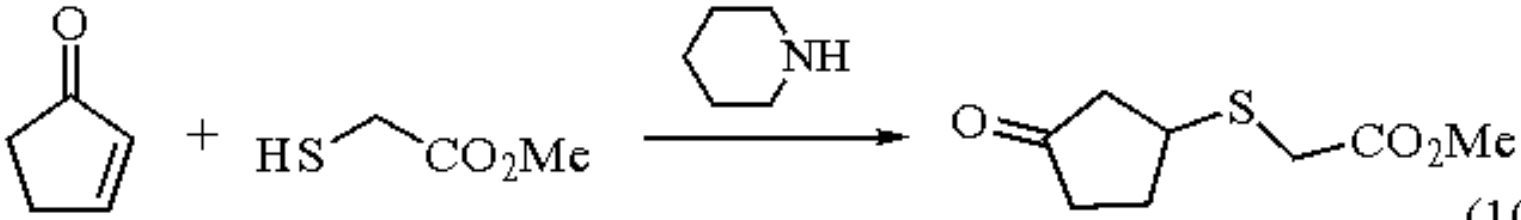

(10)

Enamine Formation.

Piperidine forms enamines more slowly than does pyrrolidine. The enamines have no particular synthetic advantages over the corresponding pyrrolidine or morpholine derivatives and have seen limited utilization. The piperidine enamines of cycloalkyl carbaldehydes are useful for the preparation of spiro bicyclic unsaturated ketones (eq 11).[22]

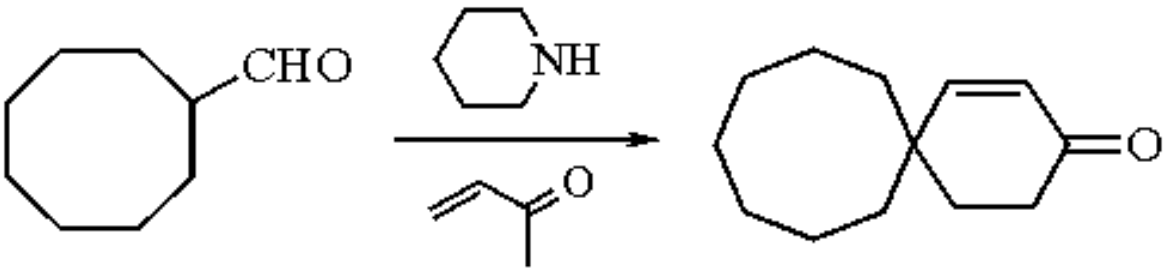

(11)

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Pivalaldehyde

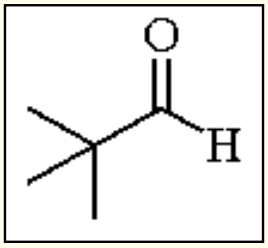

[630-19-3] · $C_5H_{10}O$ · Pivalaldehyde · (MW 86.15)

(sterically demanding electrophile;[1] coreagent in molecular oxygen oxidations; production of reagents for enantioselective synthesis[2])

Alternate Names: 2,2-dimethylpropanal; trimethylacetaldehyde.

Physical Data: mp 6 °C; bp 77-78 °C; *d* 0.793 g cm^{-3}.

Solubility: sol alcohol, ether.

Form Supplied in: colorless liquid.

Preparative Methods: the most accepted preparative method is the reaction of ***t-Butylmagnesium Chloride*** with ***Methyl Formate***.[3] Recently, the use of ***N,N-Dimethylformamide*** as the formylating reagent has been studied,[4] as well as the direct reaction of ***t-Butyllithium*** with ***Carbon Dioxide*** and metal hydrides.[5]

Sterically Demanding Electrophile.

The unique structural characteristics of this reagent include the most sterically demanding, and highly symmetric, simple alkyl group[1] adjacent to a reactive electrophilic center, and the absence of acidic protons on the carbon atom adjacent to the carbonyl functionality. These attributes have made pivalaldehyde a standard reagent in the study of carbanion reactivity, with intensified use in the more recent era of stereoselective synthesis. Thus the oxonium ion generated from pivalaldehyde reacts with the expected high degree of stereoselectivity (eq 1).[6] Likewise, in the reaction of boron enolates derived from α-carbonyl radicals (eq 2),[7] pivalaldehyde consistently affords the highest *erythro*:*threo* selectivity (0:100) with no loss of chemical yield compared to other aldehydes.

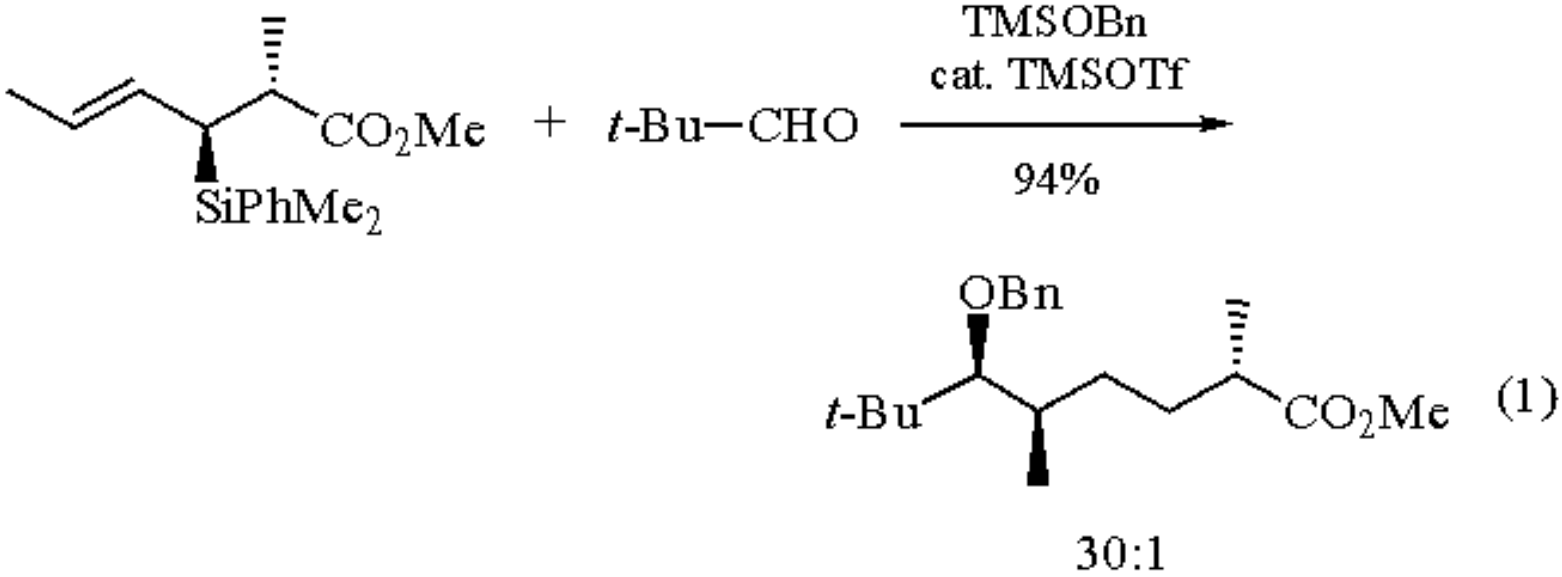

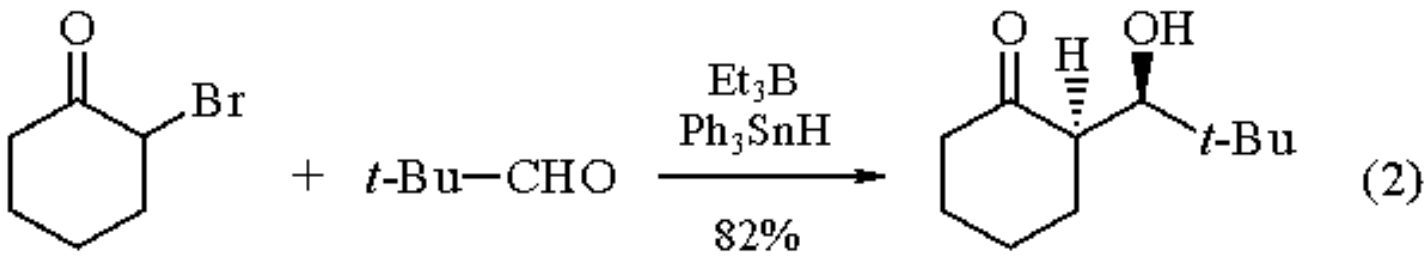

However, there are numerous examples in the literature to indicate that the steric bulk of the *t*-butyl group can severely deactivate the electrophilicity of the aldehyde functionality, resulting in drastically reduced yields. The suggestion that pivalaldehyde is a nonchelating aldehyde, and therefore a poor participant in reactions which progress through chelation of the electrophile prior to C-C bond formation, seems to be reasonable given the experimental results. The reactions of this aldehyde with the lithium anions of amides (eq 3)[8] and esters,[9] the intermolecular pinacol cross-coupling reaction using vanadium(II) reagents (eq 4),[10] and the addition of vinylzinc reagents (eq 5)[11] all suffer severely reduced yields and, in the latter case, significantly reduced stereoselectivity in the C-C bond forming event.

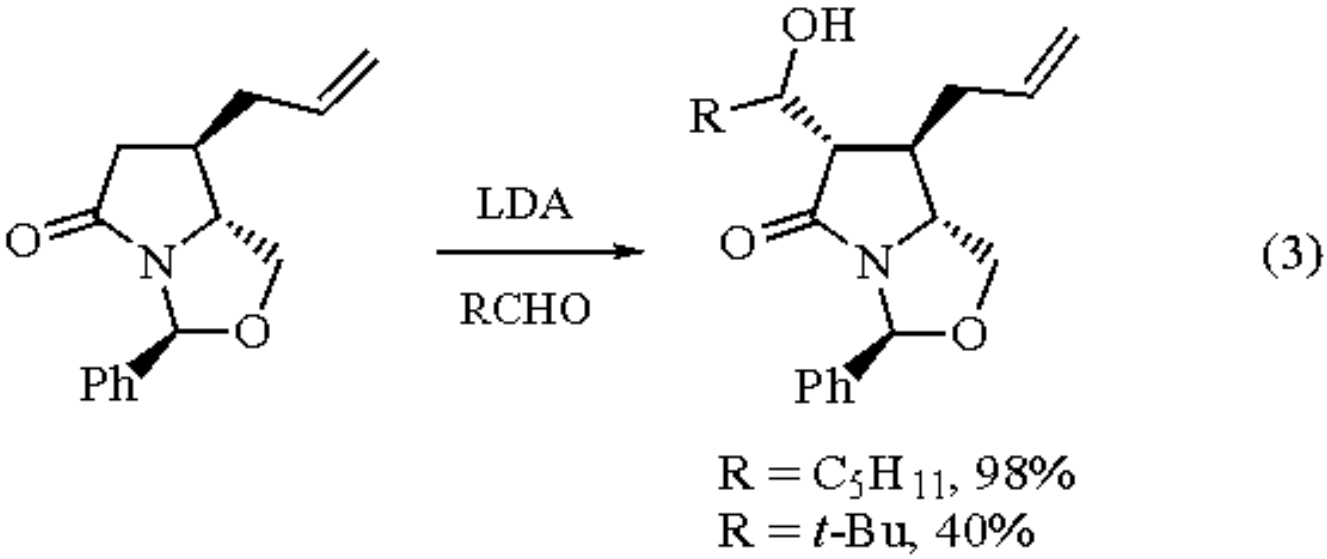

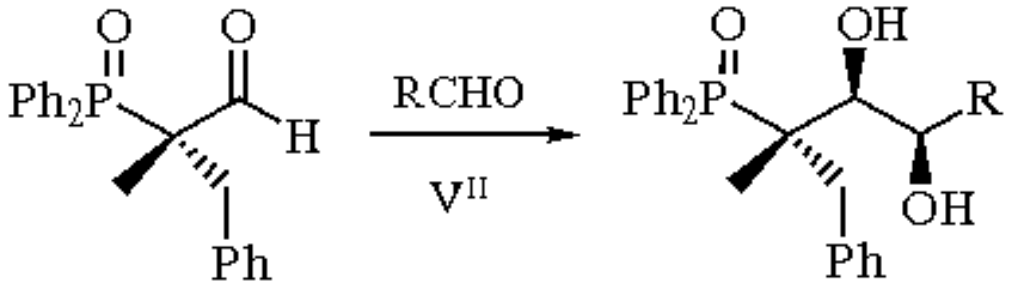

(4)

R = PhCH2CH2, 89%; 43:1 ds
R = *t*-Bu, 32%; >45:1 ds

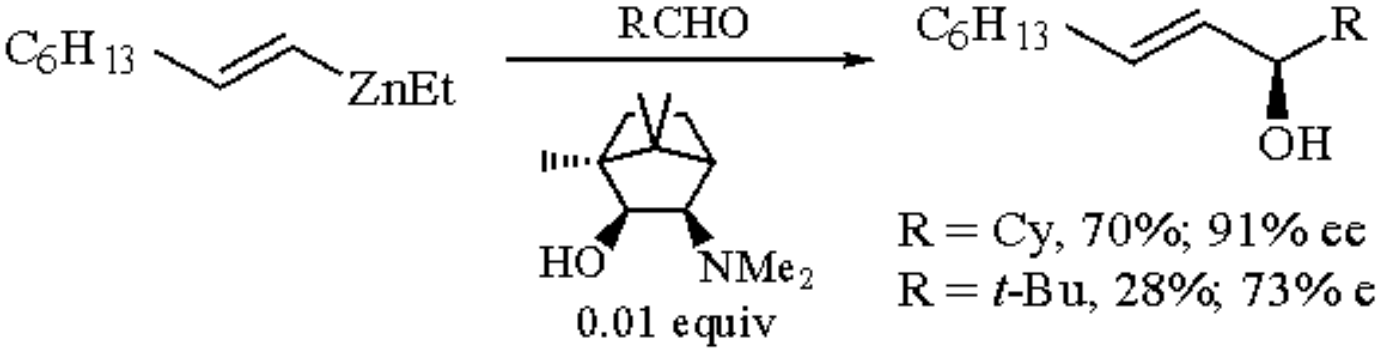

(5)

R = Cy, 70%; 91% ee
R = *t*-Bu, 28%; 73% ee

Coreagent in Molecular Oxygen Oxidations.

Pivalaldehyde has been shown to be one of several aldehydes that function as effective reductants in the oxidation of alkenes to epoxides by molecular oxygen. In the process, which is most often metal catalyzed, the aldehyde is oxidized to the corresponding carboxylic acid. At least two different mechanisms appear to be operating. In the nickel(II)-catalyzed case,[12,13] the oxidation occurs through a singlet oxygen-type species.[14] The reaction is characterized by the loss of stereochemistry in the oxidation of both *cis*- and *trans*-2-butene.[13] In addition, the epoxidation of cholesteryl benzoate affords a 31:69 mixture of stereoisomers, with the β-isomer as the major component. This result is opposite to those from more traditional expoxidation reagents (***m-Chloroperbenzoic Acid***, MMPP), which afford the α-epoxide as the major product. Pivalaldehyde is not an effective reductant in the nickel(II)-catalyzed Baeyer-Villiger oxidation of ketones,[15] but is the most effective aldehyde in the manganese(III)-catalyzed enantioselective epoxidation of 1,2-dihydronaphthalene by oxygen in the presence of various enantiomerically pure salen ligands (eq 6).[16] Similar results have been obtained by Jacobsen[17,18] and Katsuki[19] using ***Iodosylbenzene*** or ***Sodium Hypochlorite*** as oxidant.

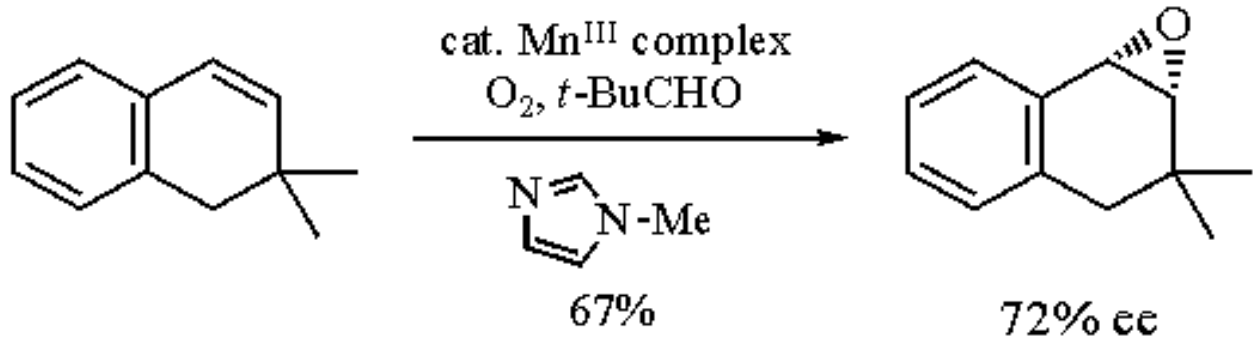

(6)

Epoxidations can also be effected without the use of metal catalysts.[20] In this case it appears as if peroxy acids (formed by oxygen interacting with pivalaldehyde) are the ultimate oxidizing agent. Pivalaldehyde is the most effective aldehyde of those studied in this reaction, which show the usual profile of reactivity and selectivity expected for a peroxy acid oxidation (eq 7).

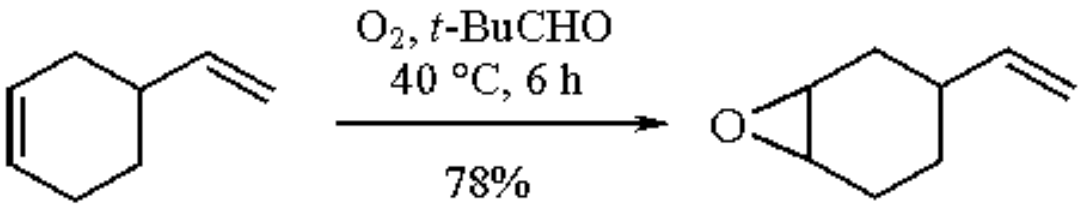

(7)

Reagents for Enantioselective Synthesis.

A large body of work has been accumulated since the mid-1980s which employs the *t*-butyl group of pivalaldehyde as a sterically demanding presence for enantioselective synthesis. The transformation of 4-hydroxyproline to α-methyl-4-hydroxyproline (eq 8)[21,22] in enantiomerically pure form presents both the concept and practice of the self-reproduction of chirality[23] technique, in which substituted α-amino acids are obtained without the use of external chiral auxiliaries. Pivalaldehyde has been employed almost exclusively in the cyclization event, with a small amount of work having been done with benzaldehyde.

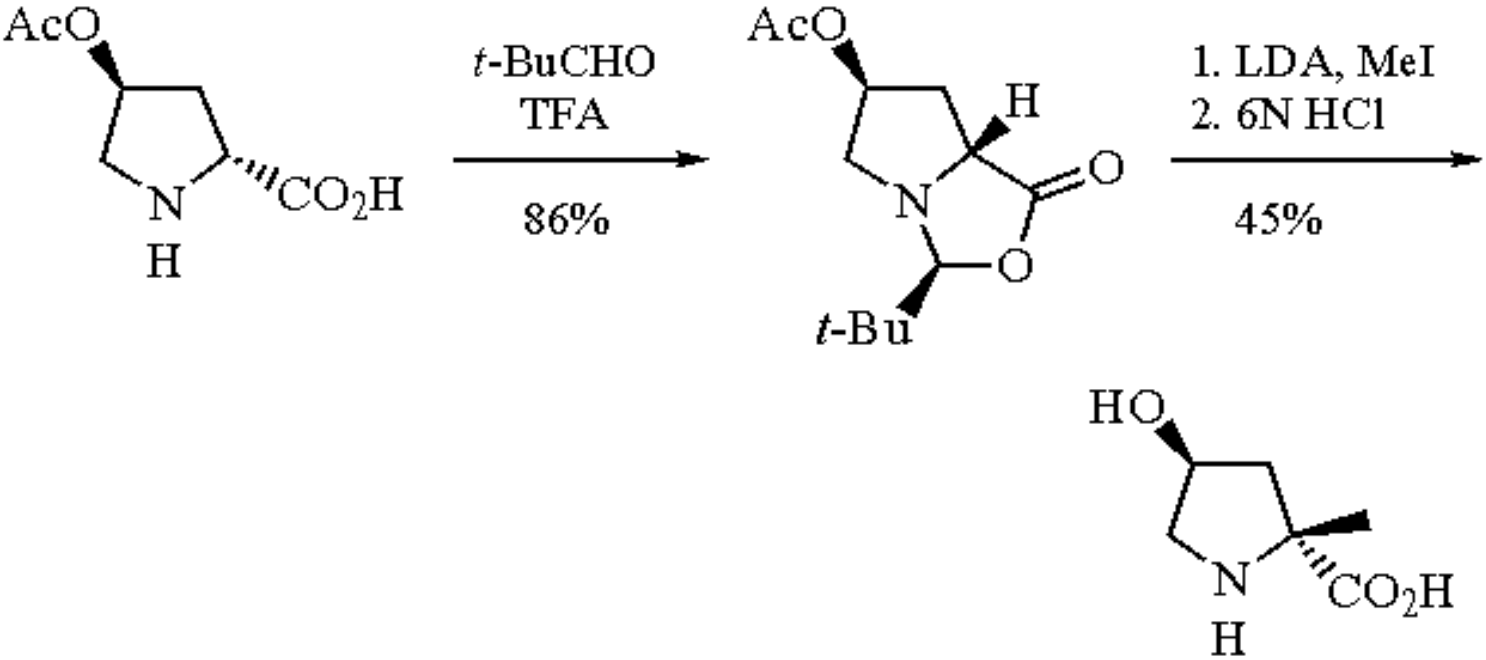

(8)

Analogous transformations have been performed on heterocycles prepared from alanine,[24-26] valine,[24,25] methionine,[24,25] cysteine,[27] phenylglycine,[24] phenylalanine,[24,25] aspartic acid,[28] glutamic acid,[28] serine,[29-31] and 2-azetidinecarboxylic acid.[32] The list is not exhaustive. All have involved the formation of five-membered *N*,*O*-(oxazolidinone) or *N*,*N*-acetals (imidazolidinone), or both, from cyclization with pivalaldehyde. The *N*,*N*-acetals arise from cyclization of the corresponding amino acid *N*-methylamide. Diastereoselection in the cyclization event varies from 0 to 100%. Reactions of the heterocyclic anions with other alkylating reagents (beyond methyl iodide), aldehydes, ketones, heteroelectrophiles, and Michael acceptors are described. Dipeptide derivatives have also been synthesized.[33] A complete discussion of the structures of the heterocycles and the factors controlling the

diastereoselectivity of the anion reactions has been published.[34] It is argued that in certain cases the high diastereoselectivity is not a direct result of steric effects dictated by the *t*-butyl substituent. Rather, it arises from torsional effects exemplified by significant pyramidalization at the trigonal centers in the molecules.[35]

A more general approach to amino acids begins from the corresponding cyclized glycine heterocycle. The enantiomers of the imidazolidinone have been prepared from the degradation of other amino acids,[36] resolution of the racemic mixture with mandelic acids,[37] and by asymmetric synthesis employing α-methylbenzylamine.[38] The corresponding oxazolidinone can be chromatographically resolved.[39] The imidazolidinone can function as both a nucleophilic (eq 9) and electrophilic glycine equivalent (eq 10),[40] similar to molecules developed by other researchers,[41] while the products from oxazolidinone nucleophile reactions are claimed to be more easily isolated.[42]

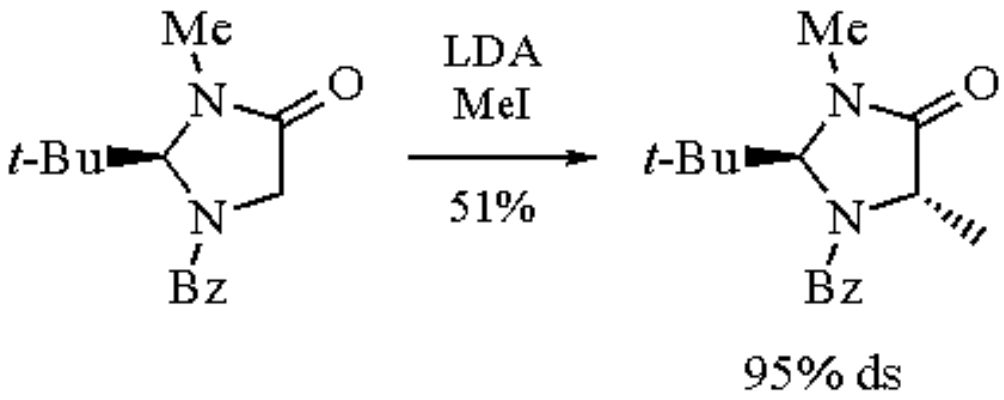

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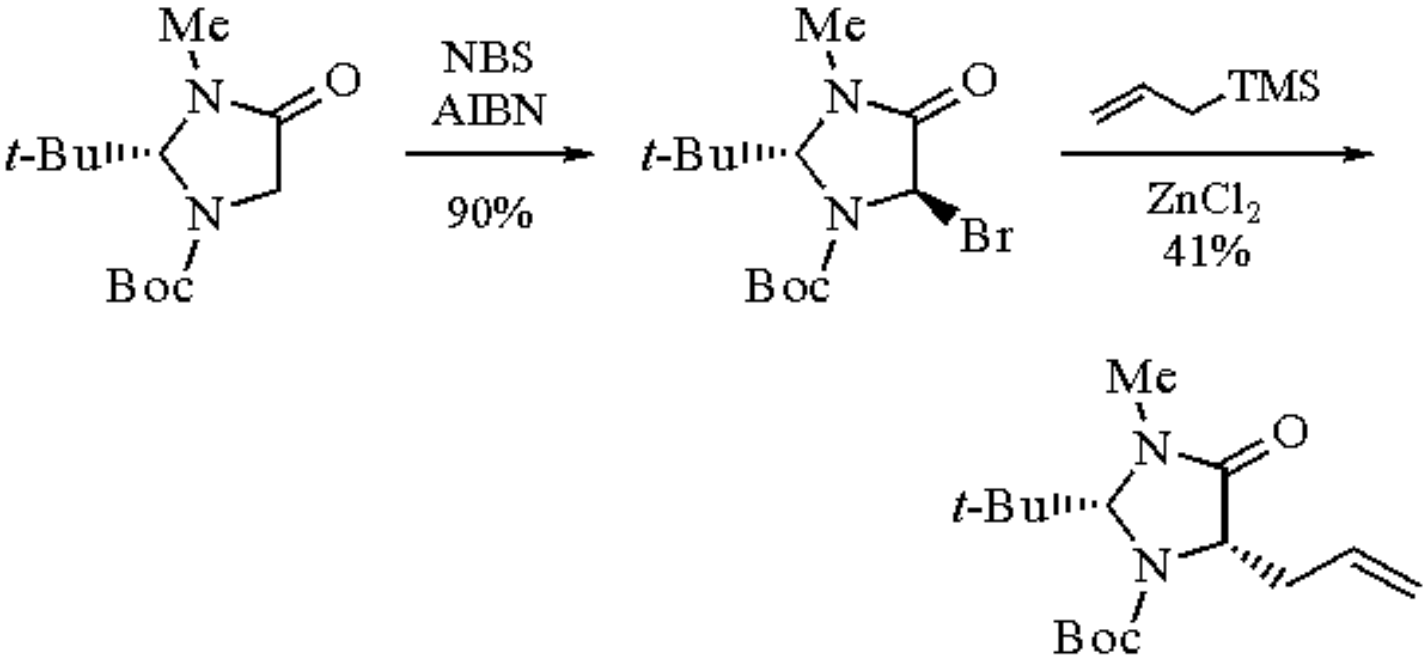

(10)

The utility of these chiral building blocks is extended by the formation of unsaturated derivatives. Cyclic dehydroalanine molecules[43] function as radical[44] and nucleophile[45] acceptors (eq 11). Internal alkenes are prepared[46,47] and reacted[48-50] with a wide variety of reagents, offering additional entries into enantiomerically pure compounds with chirality centers bearing oxygen, nitrogen, and/or sulfur.

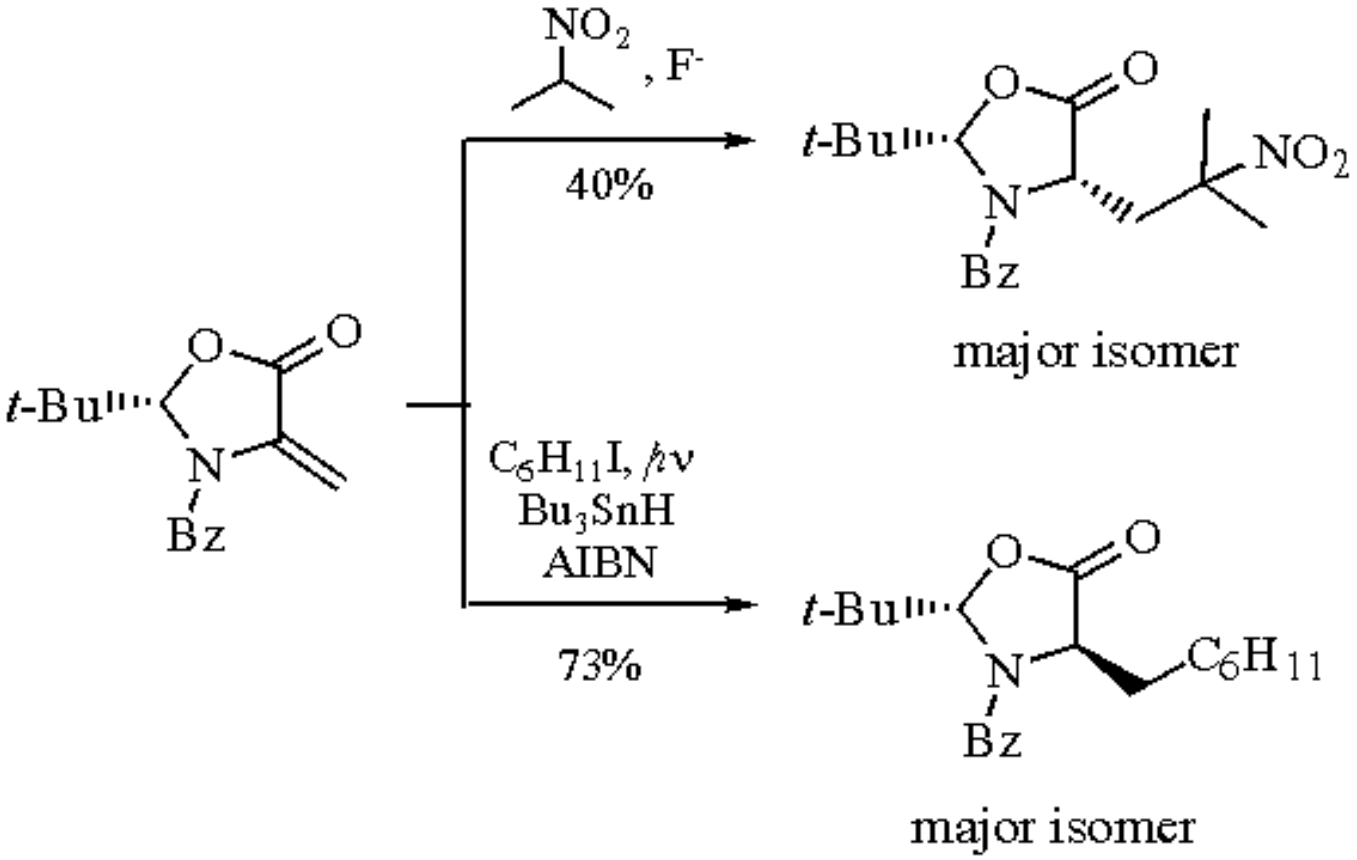

(11)

More recent work has focused on β-amino acid synthesis through pyrimidinone structures, again prepared by this reagent in a cyclization reaction. Enantiomerically pure dihydro- and perhydropyrimidinones can be obtained directly from asparagine[51,52] or 3-aminobutanoic acid.[53] Alternatively, racemic perhydropyrimidinones arise from β-alanine,[54] and the enantiomers have been separated by chromatographic resolution.[39] These compounds all exhibit axial *t*-butyl groups,[34,55] and selectivity is dictated by steric effects. An unusual palladium-catalyzed arylation reaction leads to β-aryl-β-amino acids in enantiomerically pure form (eq 12). A mechanism has been presented.[55]

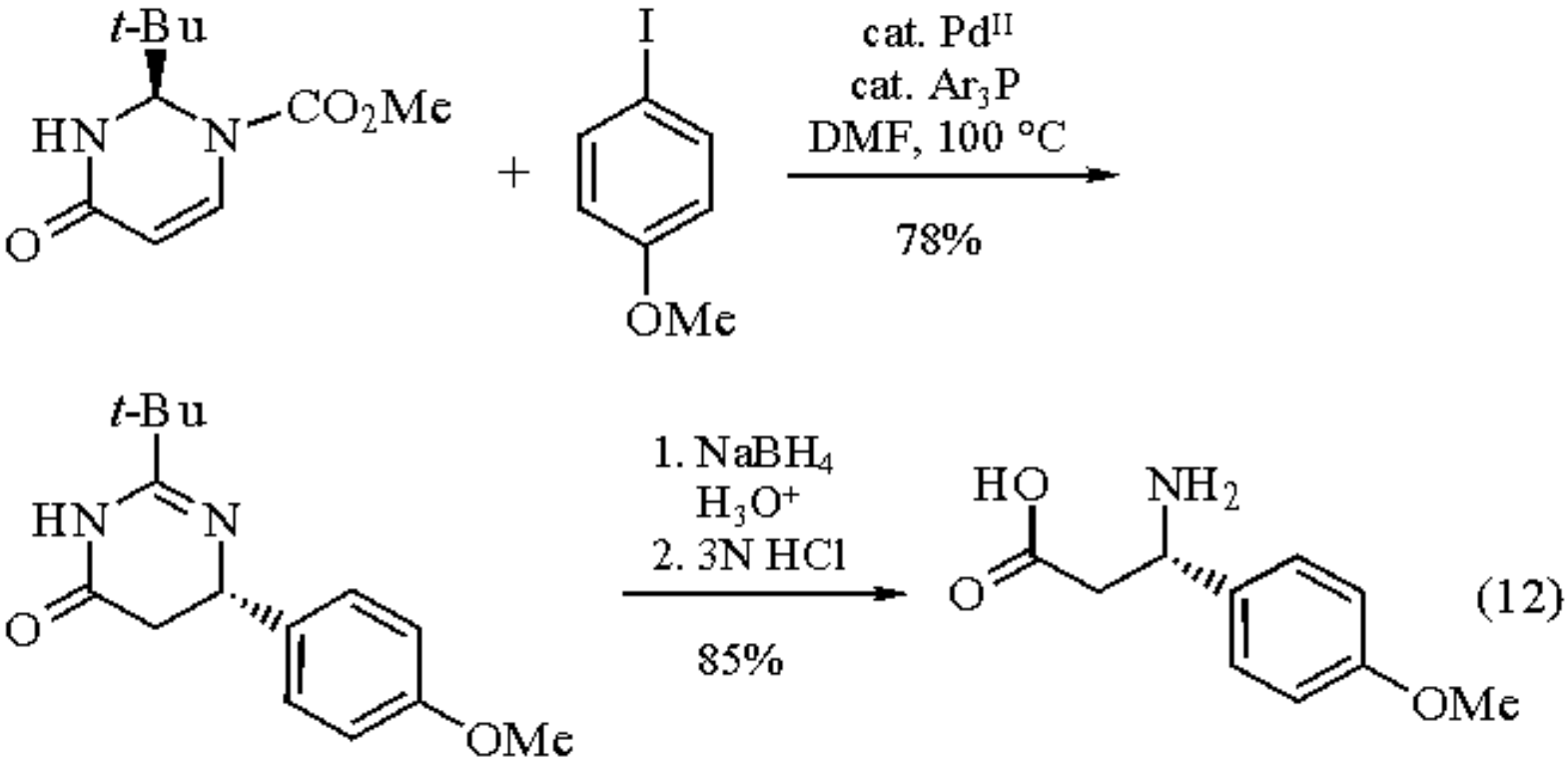

Parallel strategies have been developed with dioxolanones,[56] dioxoanones, and dioxinones[57,58] (*O*,*O*-acetals), leading to a variety of enantiomerically pure oxygen-containing products via the pivalaldehyde-derived stereogenic center. While a wide variety of β-hydroxy carboxylic acids have been employed as starting materials,[59,60] the bulk of the work has been performed on dioxanones and derivatives originating from (*R*)- or (*S*)-β-hydroxybutyric acid. As in the case of the *N*,*O*-acetals, diastereoselectivity in the cyclization event is quite variable, with best success in the formation of bicyclic structures.[60] Transacetalization with mild acid appears promising.[61] Although the *t*-butyl substituent on the six-membered ring heterocycles is in an equatorial environment, these systems nonetheless exhibit high stereocontrol in many different reactions. It has been suggested that torsional effects are responsible.[62] Other explanations have been made.[63] Both nucleophilic (enolates and dienolates[64]) and electrophilic (bromides[65] and both endo-[66] and exocyclic[67] enoates) six-membered ring heterocycles have been prepared and reacted to afford a wide range of products. An interesting example is the production of chiral tris(hydroxymethyl)methane derivatives (eq 13).[68]

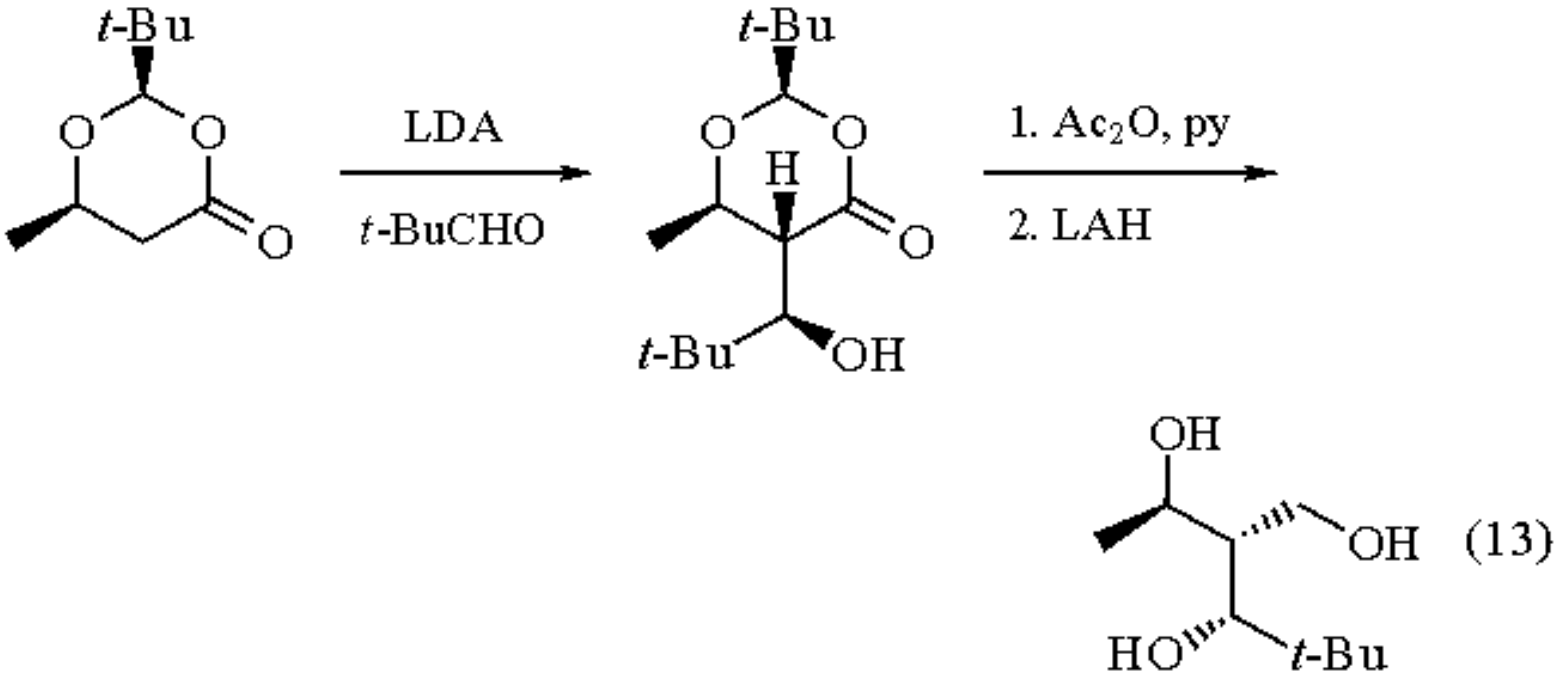

Dioxolanones derived from pivalaldehyde cyclization have been employed in Diels-Alder reactions as captodative dienophiles.[69-71] The corresponding heterocycle with a cyclohexanecarbaldehyde-generated stereogenic center gives somewhat inferior diastereoselectivity in the formation of *exo* cycloaddition products.[72]

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Pivalic Acid

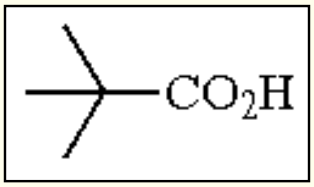

[75-98-9] · $C_5H_{10}O_2$ · Pivalic Acid · (MW 102.15)

(hindered Brønsted acid)

Alternate Names: 2,2-dimethylpropanoic acid; trimethylacetic acid.

Physical Data: mp 35.5 °C; bp 163.8 °C, 78 °C/20 mmHg, 72 °C/0.1 mmHg; pK_a 5.04 (25 °C).[1]

Solubility: sol EtOH, ether, H_2O (2.5 g 100 mL^{-1} at 25 °C).[1]

Form Supplied in: crystalline solid (needles). The sodium salt hydrate is also available.

Preparative Methods: from the bromoform reaction on pinacolone or from *t*-butyl chloride, ***Magnesium***, and ***Carbon Dioxide***; recent improvements involve the reaction of *t*-BuCl, ***Lithium***, and magnesium 2-ethoxyethoxide.[14]

Purification: fractionally distilled in vacuo; recrystallized from benzene.[15]

Handling, Storage, and Precautions: corrosive and can cause burns; it should be treated with the same precautions as ***Acetic Acid***.

Acid Catalyst for Asymmetric Reductions.

Investigations into the use of asymmetrically modified ***Raney Nickel*** for asymmetric hydrogenations have revealed that the use of pivalic acid as catalyst often provides superior optical yields. In a study of the reduction of 2-octanone to 2-octanol over tartaric acid-***Sodium Bromide***-modified Raney nickel, use of a THF/carboxylic acid mixture as the reaction medium resulted in a substantial increase in the optical yield; pivalic acid gave the highest optical yield.[2] In subsequent studies,[3,4] the reduction of a variety of methyl ketones via catalytic hydrogenation over modified Raney nickel in the presence of pivalic acid provided the corresponding (*S*)-RCH(OH)Me compounds in optical yields of 63-80%.

Acid Catalyst for Rearrangements.

When guaiacol and triethyl orthoacrylate were reacted in refluxing benzene using ***Propionic Acid*** as a catalyst, only 50% of the desired Claisen rearrangement/ring closure product was obtained, due to esterification of the catalyst. Use of the more hindered pivalic acid furnished the desired product in quantitative yield (eq 1);[5] see also Sato et al.[6] and Dorsey et al.[7]

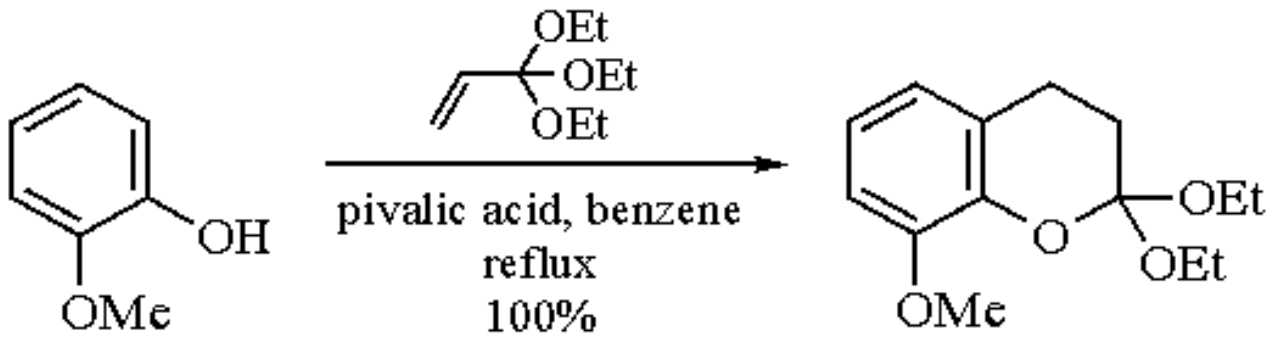

(1)

Regioselective Protonation of Enolates.

In a study of the regioselectivity of protonation of allenyl enolates, pivalic acid demonstrated superior selectivity; in the example shown (eq 2),[8] allene (**1**), resulting from protonation at C-2, was formed exclusively when the intermediate enolate was quenched with pivalic acid at -80 °C.[8,9]

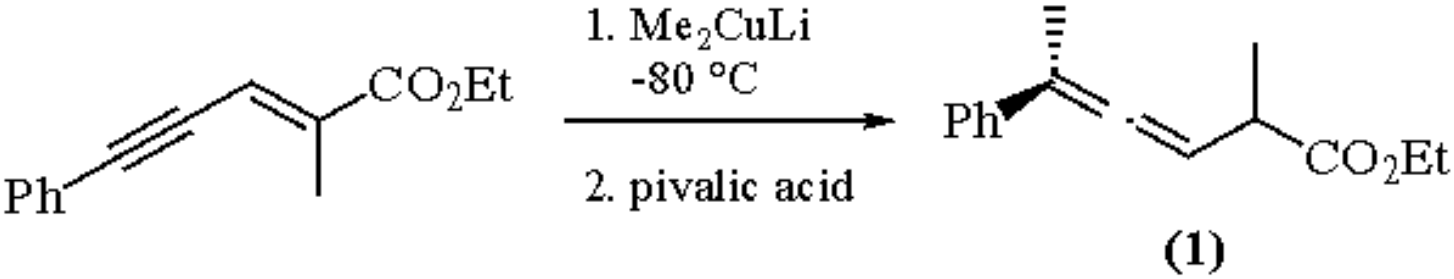

(2)

Generation of *t*-Butyl Radicals via Oxidative Decarboxylation.

Silver-catalyzed decarboxylation of carboxylic acids by persulfate generates alkyl radicals, which have been used for homolytic alkylation of aromatic bases. Pivalic acid is a source of *t*-butyl radicals in this process. 2-*t*-Butylquinoline is formed regioselectively by this method (eq 3);[10] 6-*t*-butylnicotine has been prepared in a similar way.[11]

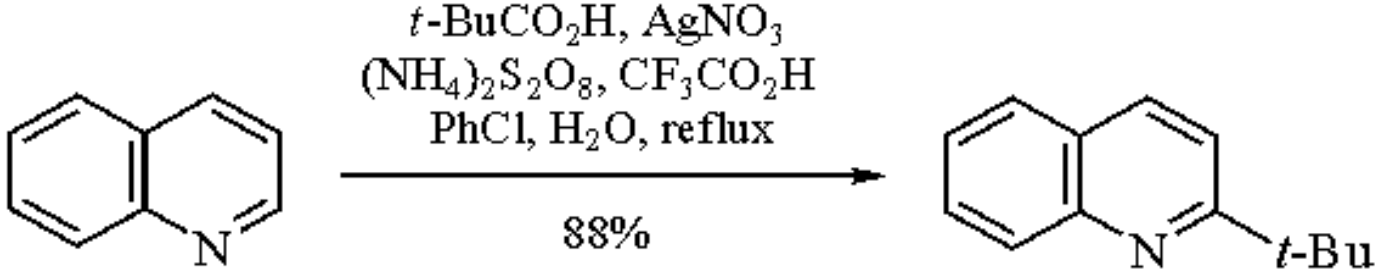

(3)

Preparation of 2-*t*-Butylpyrimidines.

2-*t*-Butylpyrimidines are precursors for 2-*t*-butylpyrimidinyl thiophosphates, which are active insecticides. Syntheses of these compounds from butyldiamines and pivalic acid have recently been described.[12,13]

Related Reagents.

Acetic Acid; ***Hydrochloric Acid***; ***Propionic Acid***; ***p-Toluenesulfonic Acid***; ***Trifluoroacetic Acid***; ***2,4,6-Trimethylbenzoic Acid***.

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Platinum on Alumina

Pt/Al_2O_3

[7440-06-4] · Pt · Platinum on Alumina · (MW 195.08)

(catalyst for the hydrogenation of many functional groups;[1-8] used to prepare aromatic compounds by dehydrogenation[9,10])

Solubility: insol all organic solvents.

Form Supplied in: typically supplied as 0.5-5 wt % of Pt on alumina, but higher metal content may be custom made; dark brown to black powder or pellets.

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air, but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds; Pyrophoric in the presence of solvents; general precautions for handling hydrogenation catalysts should be followed; the catalyst must be suspended in the organic solvent under an atmosphere of N_2; during filtration the filter cake must not be allowed to go dry.

Hydrogenation.

The use of Pt/Al_2O_3 is not as widespread as ***Platinum on Carbon*** or ***Platinum(IV) Oxide***, but like the latter two reagents, Pt/Al_2O_3 has been used for certain selective reactions, including hydrogenation and dehydrogenation reactions. The use of Pt/Al_2O_3 for the reduction of a diene to a *trans*-decalin was shown to give the highest selectivity (eq 1).[1]

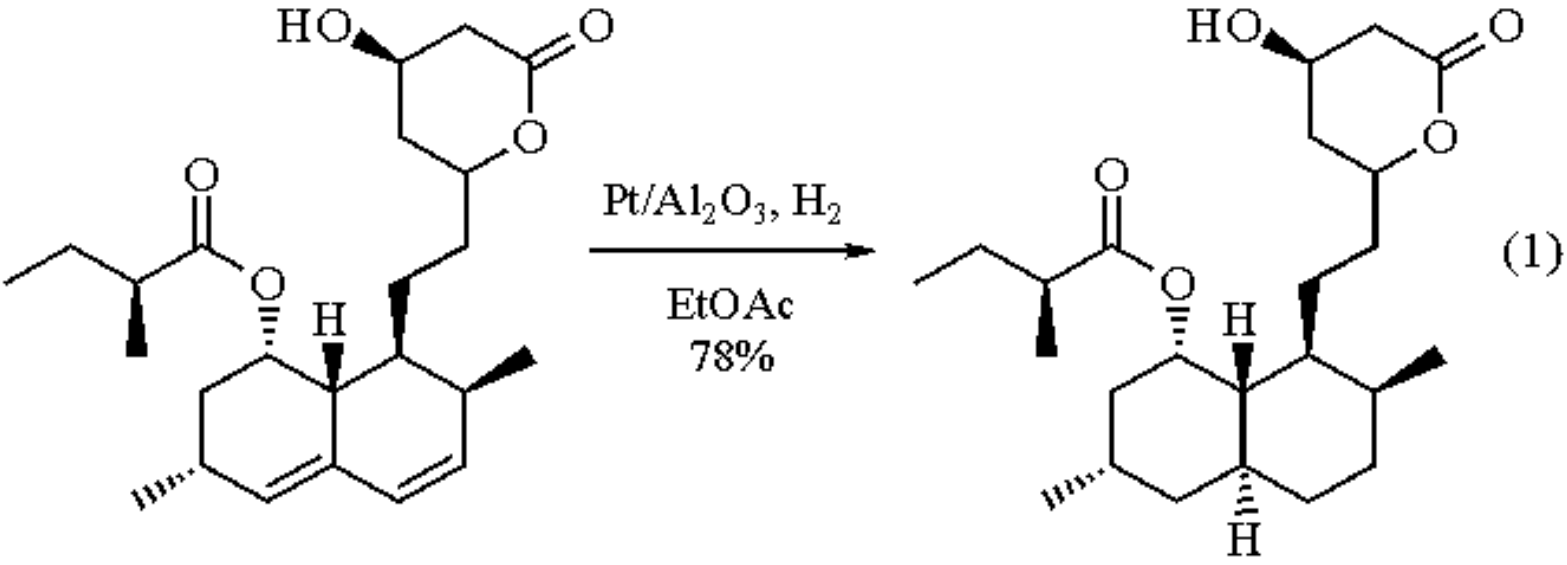

The formation of residual monoenes and the *cis* product was minimized with this catalyst. Pt/Al_2O_3 was also used in the reduction of an α,β-unsaturated enone to an alcohol (eq 2).[2] The stereochemical course of this reduction was attributed to an alumina-alcohol interaction.

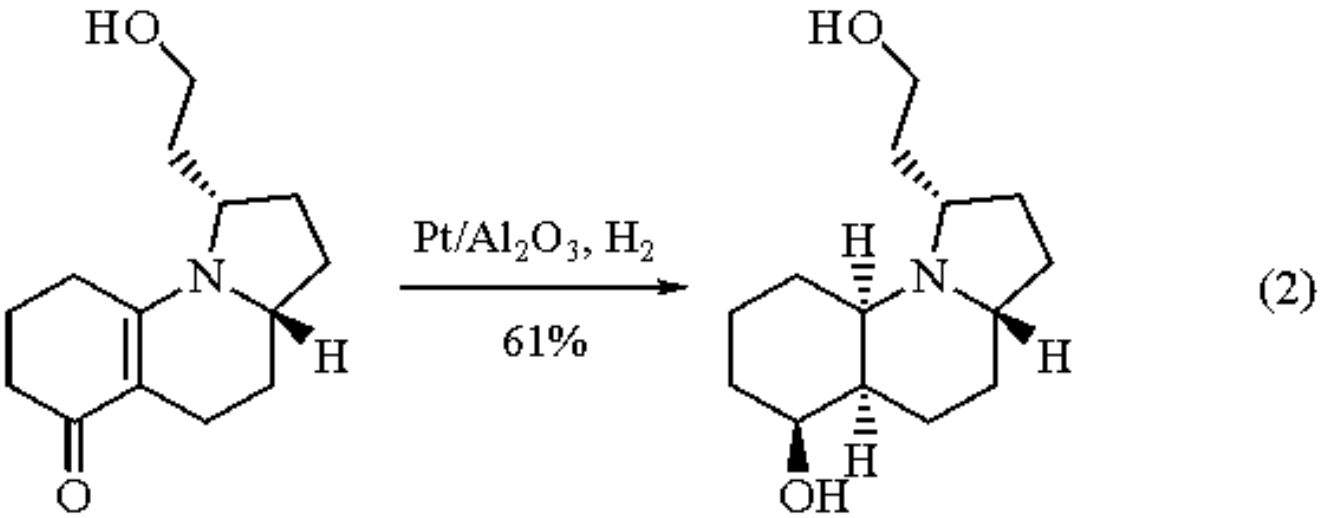

A tetrasubstituted enamine has been hydrogenated to the amine in good yield with no hydrogenolysis of the *N*-benzyl group using Pt/Al_2O_3 (eq 3).[3] Similar to other Pt catalysts, hydrogenolysis is not common with this catalyst.

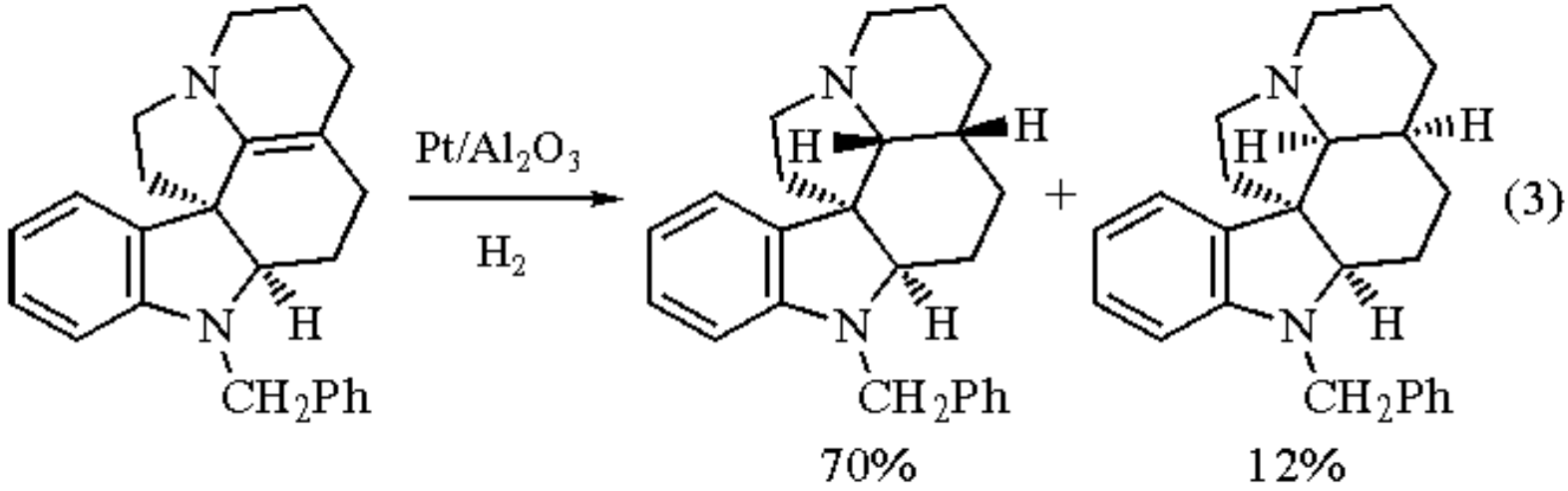

A *cis*-1,2-diamine has been obtained using Pt/Al_2O_3 as the hydrogenation catalyst (eq 4).[4] The allylic pyrrolidine directed the hydrogenation to give the *cis* product.

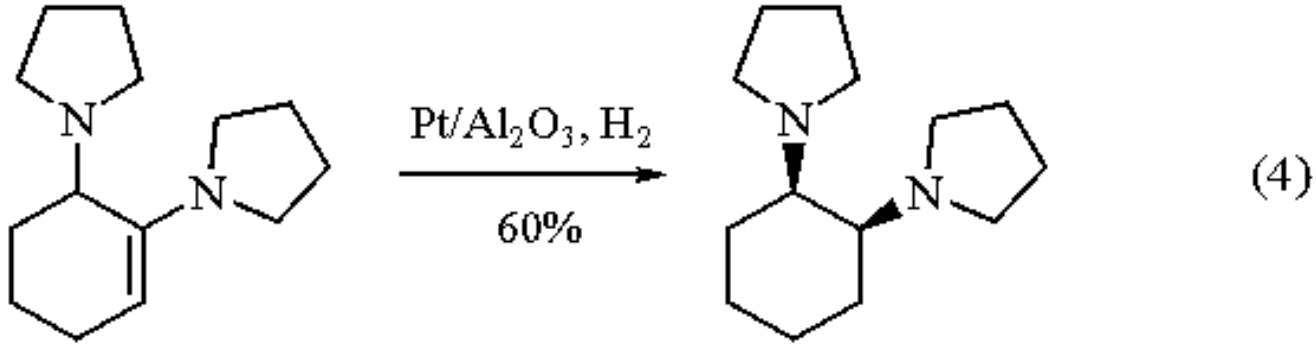

Heterocyclic ring reductions have been reported and quinoline is reduced selectively at the pyridine ring.[5] Even with a 2,4-disubstituted quinoline, only reduction of the substituted pyridine ring in the quinoline system occurred when ***Carbon Disulfide*** was used as a poison. Without the poison the selectivity was only 88% (eq 5). Acridine and indole can also be hydrogenated exclusively in the heterocyclic ring.

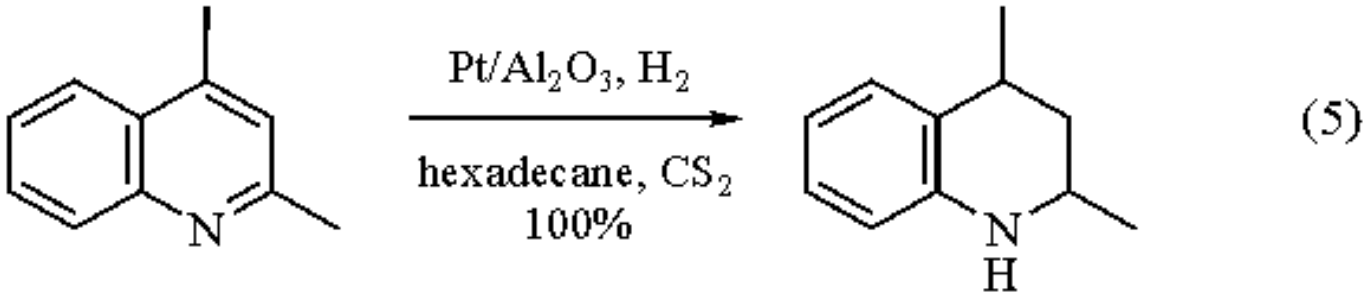

Halogenation.

Pt/Al_2O_3 has been used to catalyze the formation of halogenated compounds. Chlorination of methane with chlorine has been catalyzed by Pt/Al_2O_3 to give ***Chloromethane*** with 99% selectivity. The minor product (1%) was dichloromethane.[6] Another halogenation reaction involving Pt/Al_2O_3 is the decarboxylation of aryl fluoroformates at high catalyst loading and temperature to give acyl fluorides (eq 6).[7]

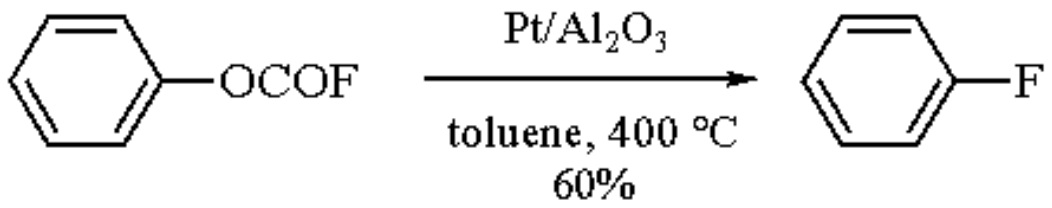

(6)

Dehydrogenation.

Dehydrogenation in the presence of Pt/Al_2O_3 has given various heterocyclic aromatics and hydrocarbon derivatives. Cyclohexane, cyclohexene, cyclohexylamine, and cyclohexanol have been aromatized to give benzene in 100% yield. Toluene has been obtained from methylcyclohexane, 1-methylcyclohexene, 2-methylcyclohexanone, and 3-methylcyclohexanone. Decalin and tetralin produced naphthalene in quantitative yield. *N*-Methylpyrrolidine gave *N*-methylpyrrole in 81% yield.[8] Pyridine derivatives have been obtained from dihydropyrans with NH_3 in the presence of Pt/Al_2O_3 (eq 7).[9]

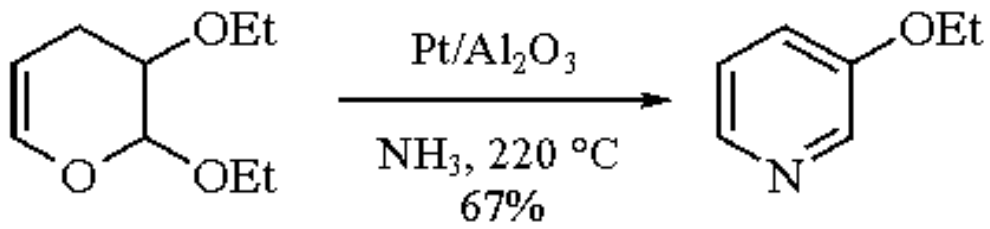

(7)

The last C-C bond coupling in the preparation of dodecahedrane was effected with Pt/Al_2O_3 mixed with a reactive Ti^0 metal.[10] Other substituted dodecahedranes were also prepared via this method.

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Platinum on Carbon

Pt/C

[7440-06-4] · Pt · Platinum on Carbon · (MW 195.08)

(catalyst used for the hydrogenation of alkenes,[1,2] alkynes,[1] nitro groups,[4,5] ketones,[13,14] aromatics;[17] used for hydrogenolysis of cyclopropanes;[3] catalyzes oxidation of alcohols[19])

Solubility: insol all organic solvents and aqueous acidic and basic media.

Form Supplied in: black powder and pellets containing 0.5-10 wt % of Pt (typically 5 wt %); can be either dry or moist (50 wt % of H_2O).

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds; pyrophoric in the presence of solvents; general precautions for handling hydrogenation catalysts should be followed; the catalyst must be suspended in the organic solvent under an atmosphere of N_2; during filtration the filter cake must not be allowed to go dry; if a filter aid is necessary, a cellulose-based material should be used if catalyst recovery is desired.

Hydrogenations.

In many instances where ***Platinum(IV) Oxide*** is used, Pt/C can be a less expensive substitute. Pt/C is a widely used catalyst for many applications. The reduction of alkenes and alkynes can be carried out under mild conditions. Alkenes can be hydrogenated in the presence of terminal alkynes if the latter are protected with a trialkylsilyl group. Without protection the selectivity is not satisfactory (eq 1).[1]

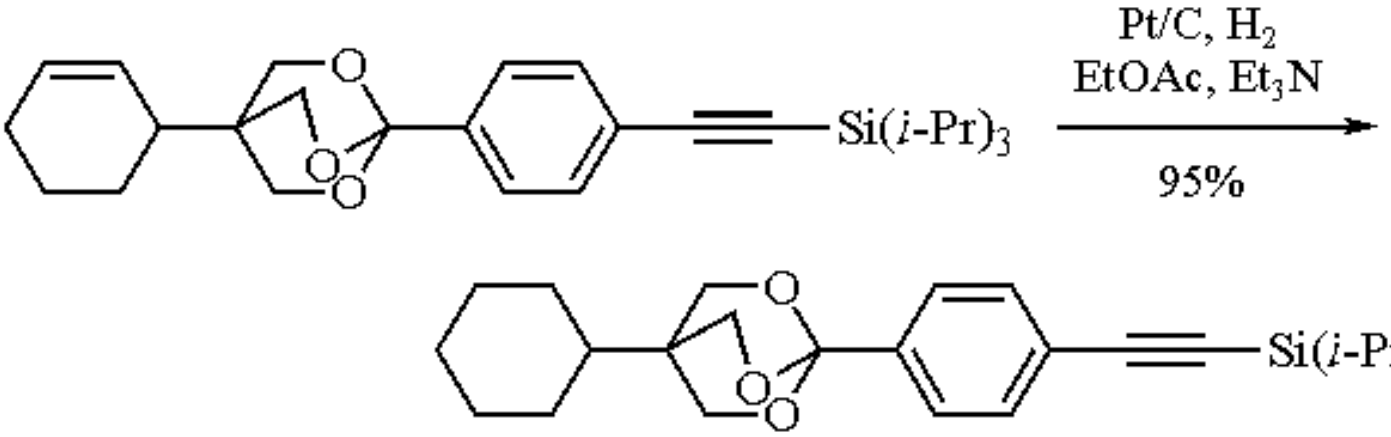

(1)

The diastereoselective reduction of an enamino ketone with Pt/C under acidic conditions is shown in eq 2. This reaction provided the (*SSR-R*) diastereomer in 63% yield plus 15-18% of the (*RRS-R*) diastereomer and other byproducts. After acid-catalyzed lactonization, the desired lactone was conveniently isolated in 57% yield. This intermediate was used in a total synthesis of (+)-thienamycin (eq 2).[2]

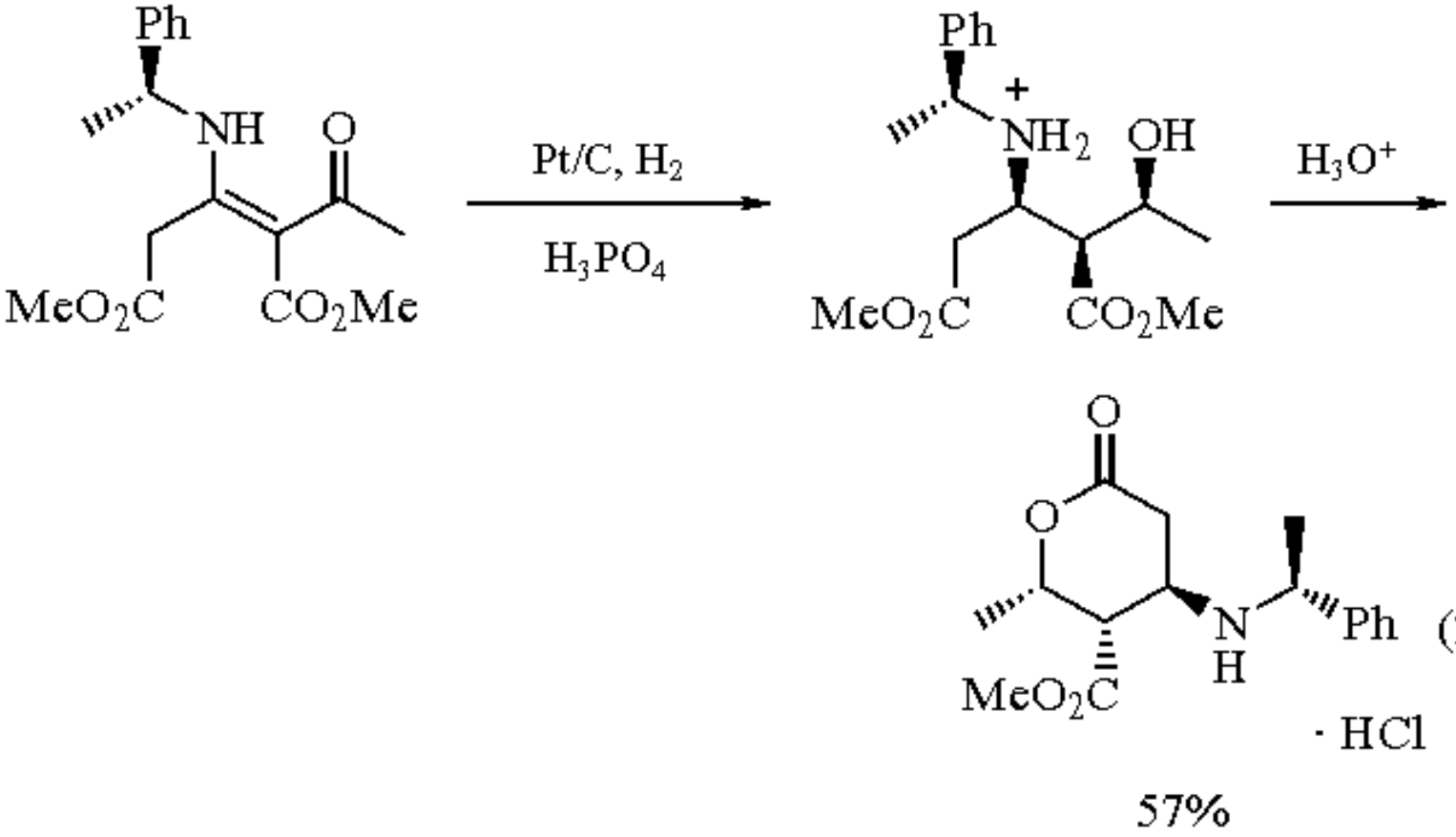

(2)

Hydrogenolysis of cyclopropanes has been accomplished with this catalyst at high temperatures. The example in eq 3 shows the resilience of a cyclobutane to these reaction conditions.[3]

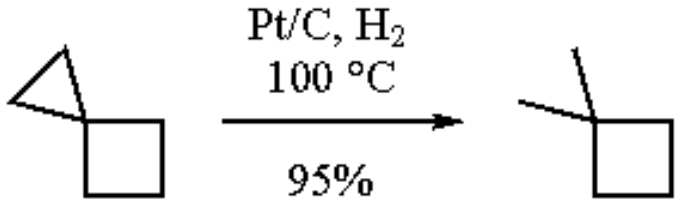

(3)

The reduction of a nitro group in the presence of an aryl bromide (or chloride) can be accomplished using this catalyst. Aryl fluorides are generally stable to all catalysts. In many instances the amine products undergo further cyclization reactions to form a variety of heterocyclic compounds. The bromide was hydrogenolyzed when Pd/C was used under similar conditions (eq 4).[4]

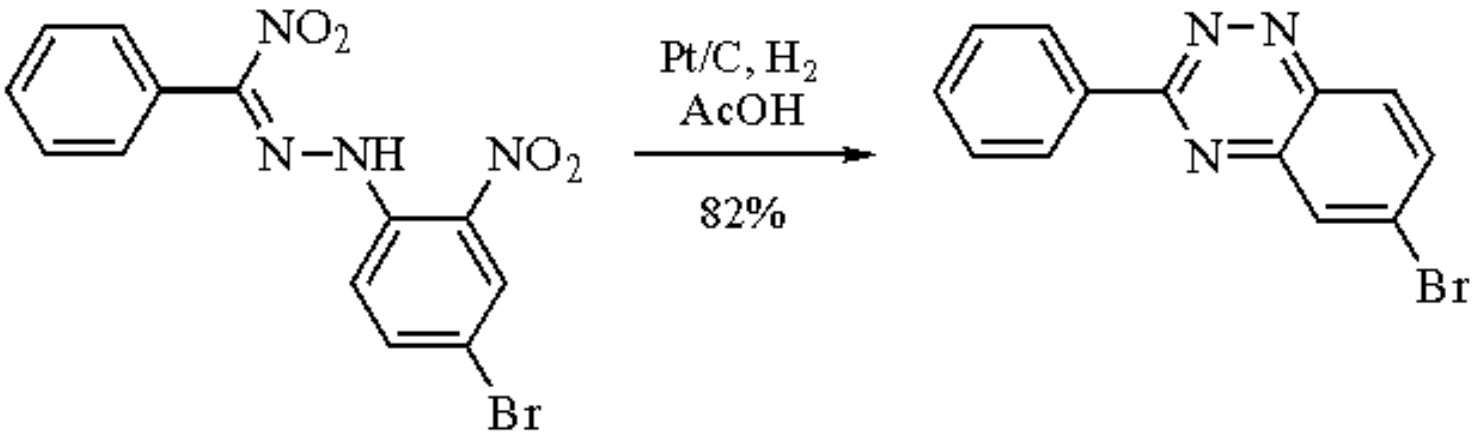

(4)

Varying the pH of the media has been shown to affect the product outcome in a reduction of a nitro amino acid. A 1-hydroxycarbostyril derivative was obtained under acidic conditions, whereas a lactam was produced under basic conditions (eq 5).[5]

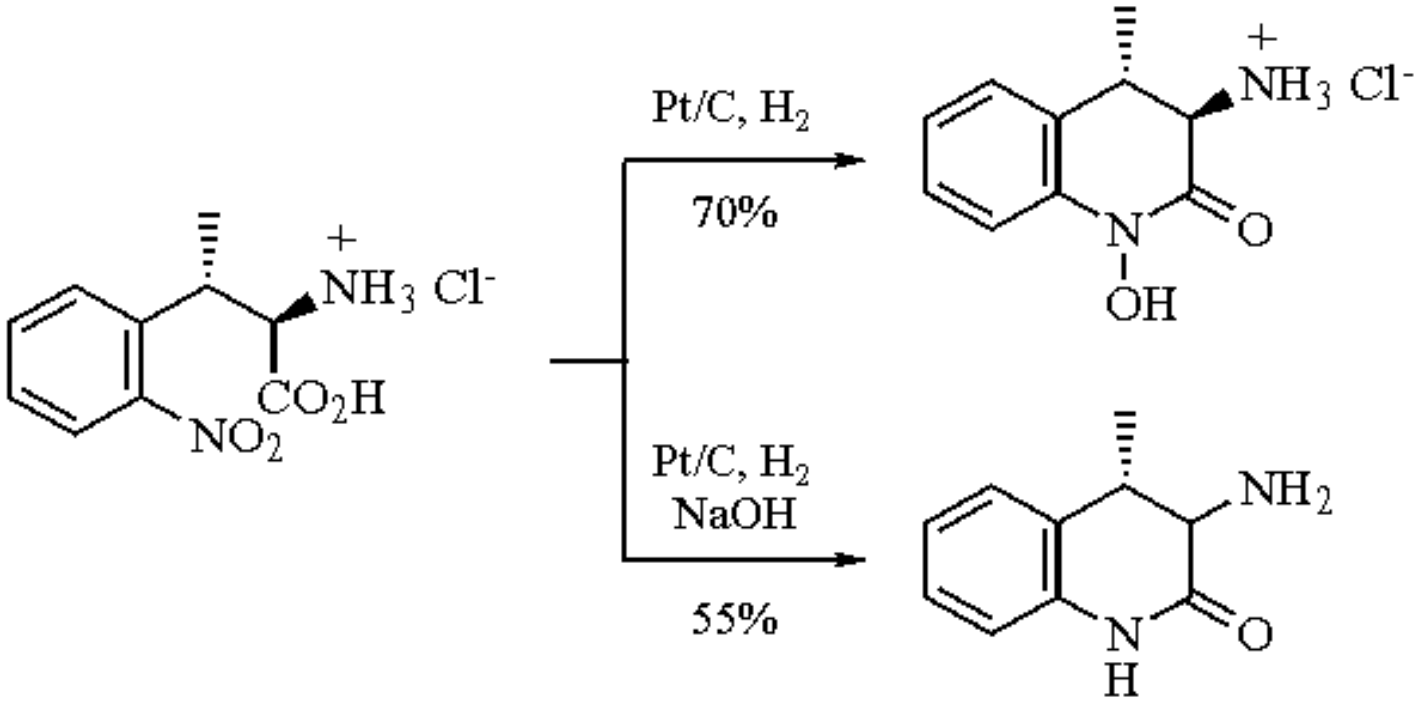

(5)

Reduction of aliphatic nitriles under neutral conditions in the presence of Pt/C gave trialkylamines with high

selectivity.[6] With aromatic nitriles, dibenzylamines were obtained.[7] This can be used to advantage in the preparation of unsymmetrical amines. Thus the reduction of a nitrile, in the presence of a different amine provided the unsymmetrical dialkylamine with greater than 95% selectivity.[8] If the desired product is the primary amine, acidic conditions should be used.

Imines can be reduced selectively in the presence of aryl bromide and chloride and hydrazine functions using Pt/C.[9] Reductive amination between a ketone and an amine or amine precursor proceeds to give a good yield of dialkylamine.[10] Amines can also be formed from the reduction of azides and hydrazines.[9b,11] Hydrogenolysis of C-N σ-bonds with Pt/C is uncommon, but not unknown. For example, hydrogenolysis of decahydro-1,8-naphthyridines in the presence of this catalyst gave 3-(γ-aminopropyl)piperidines (eq 6).[12]

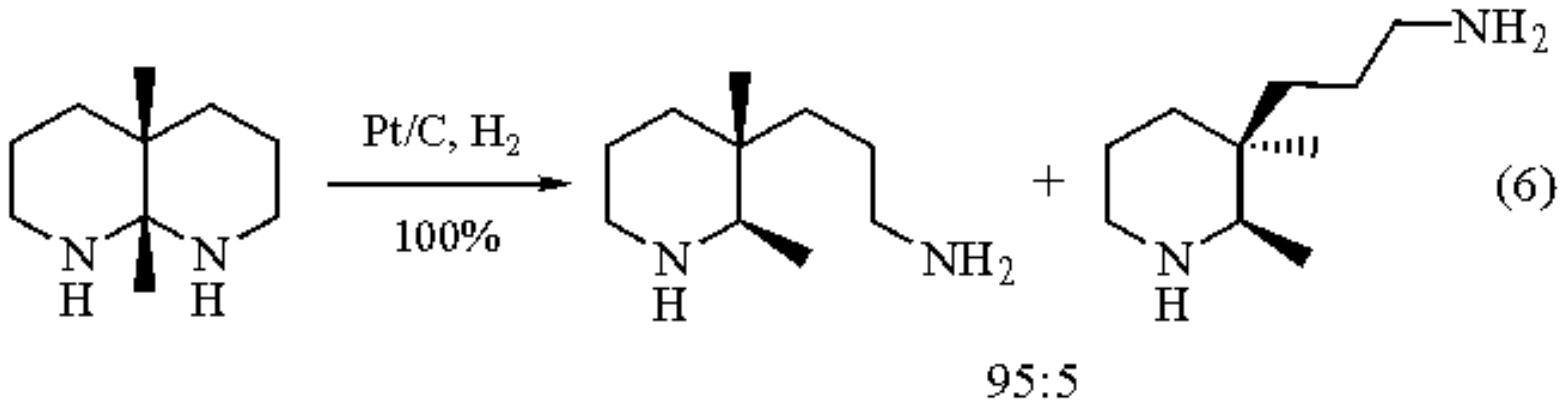

(6)

Pt catalysts are used for the reduction of ketones to minimize hydrogenolysis, especially in the case of aromatic ketones. The solvents used for ketone reduction are important. In the case of ***Ethyl Acetoacetate***, the Pt/C-catalyzed hydrogenation in water gave 12% hydrogenolyzed product, but no hydrogenolysis was observed in THF. The hydrogenolysis side reaction in water can be completely suppressed by the addition of a small amount of zinc acetate.[13] Under acidic conditions, dialkyl ketones have been hydrogenolyzed to the hydrocarbon products, but these conditions are impractical for acid-sensitive substrates. The conversion of ketones to the corresponding enol phosphates followed by hydrogenolysis over Pt/C is a mild and efficient route for the overall removal of an oxygen (eq 7).[14]

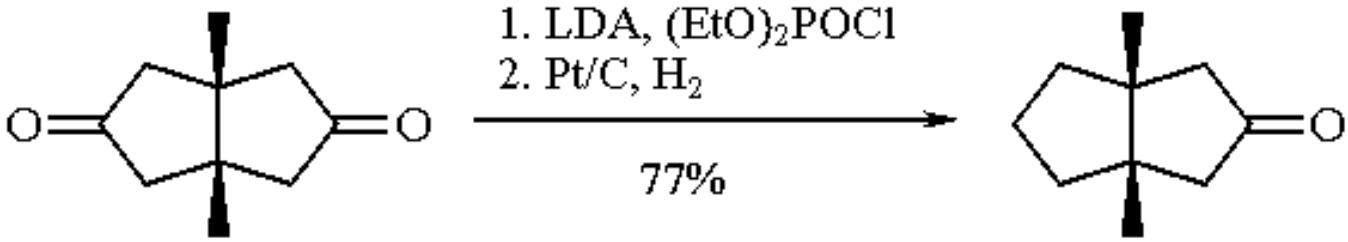

(7)

O-Acetyl sugar lactones have been cleanly converted to the corresponding 2,3-dideoxy sugar derivatives under mild conditions with Pt/C. A trialkylamine base was necessary for the hydrogenolysis to proceed. The mechanism may involve the alkenic intermediates (**1**) and (**2**) (eq 8). This procedure is only applicable to lactones since no deacetylated product was observed with aliphatic and cyclohexyl enol acetates (**3**) and (**4**).[15]

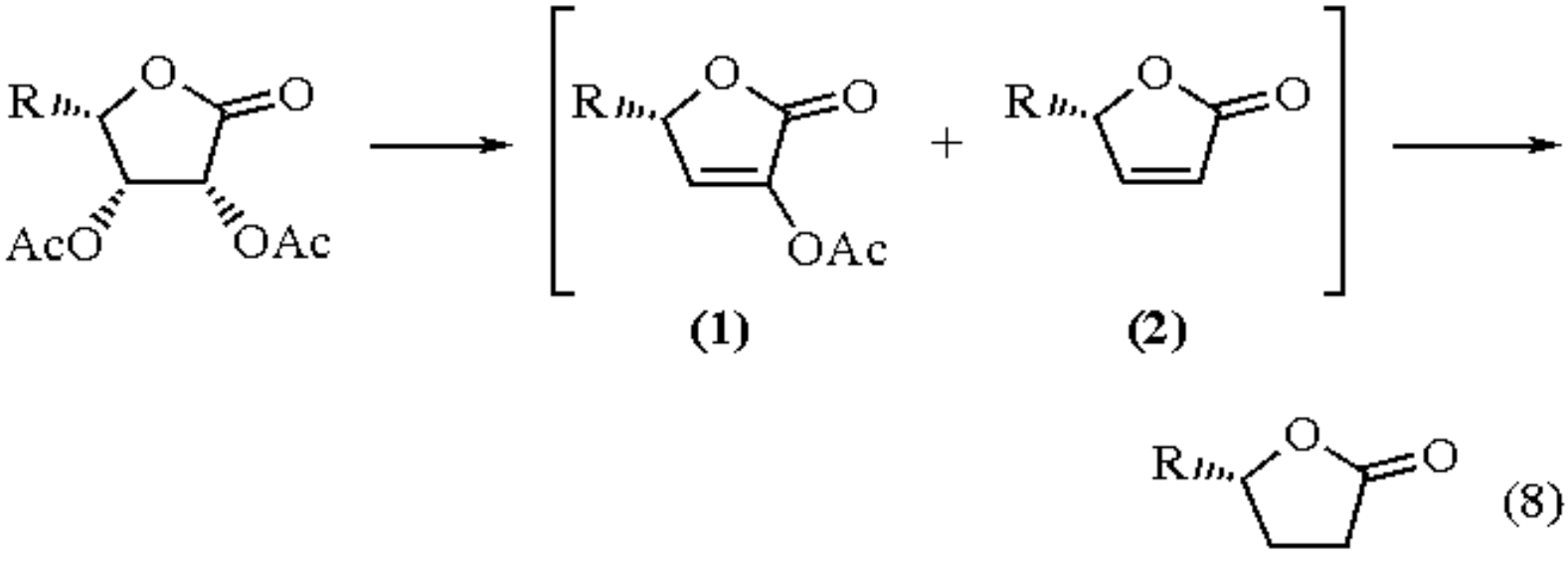

$R = \begin{cases} OAc \\ OAc \end{cases}$ 99%

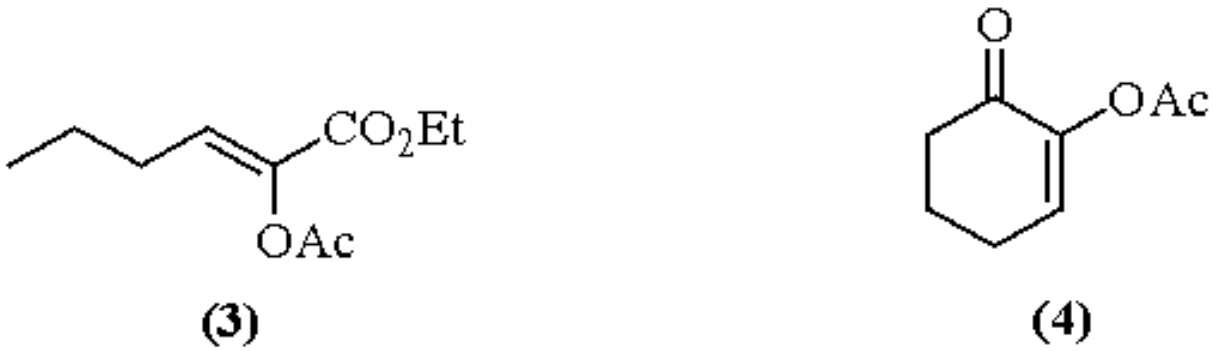

The Pt/C-catalyzed hydrogenation of 4,4-difluorocyclohexadienone provided β-fluorophenol in 90% yield. The dienone had been prepared from phenol via an oxidative fluorination method.[16]

Although Pt/C has been used for the hydrogenation of aromatic rings, PtO_2 is usually the catalyst of choice. High selectivity (>95% *cis*) was observed in the hydrogenation of pyrroles at atmospheric pressure and rt. Under these conditions, both the phenyl ring and the benzyl ether remained intact (eq 9).[17]

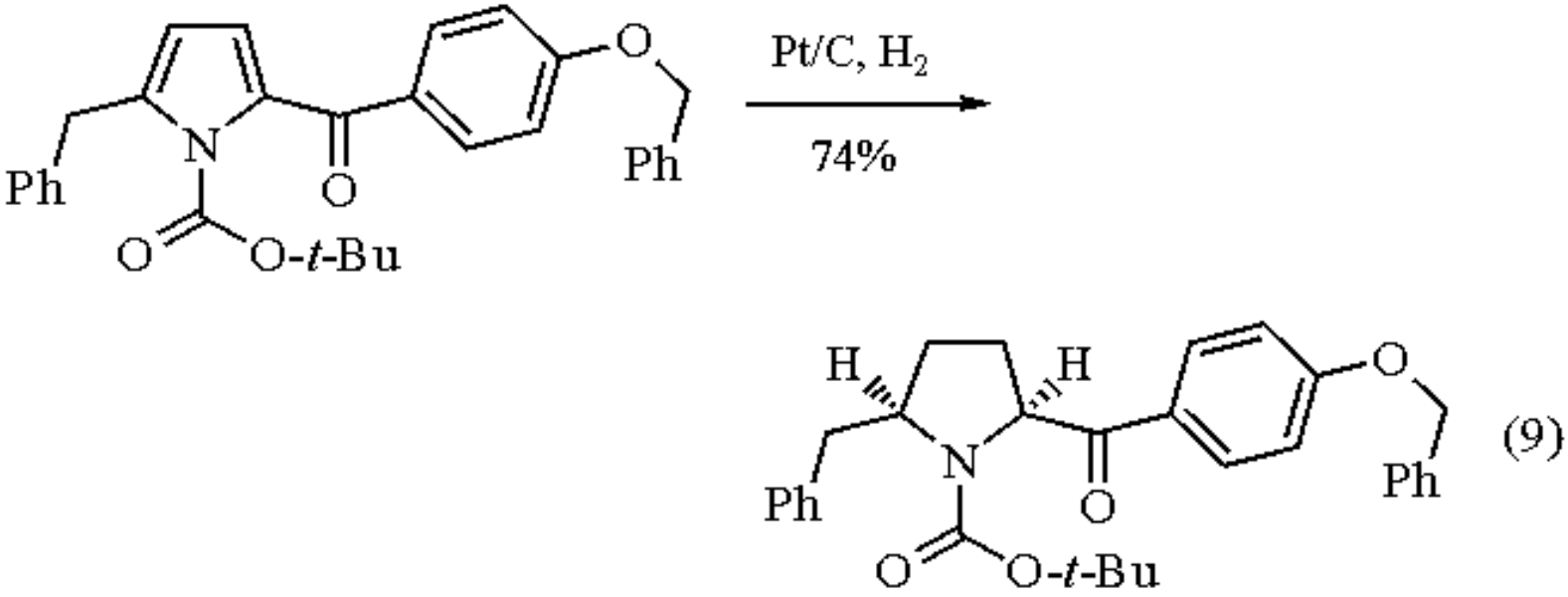

Pt/C is an effective catalyst for dehydrogenation of reducing sugars under basic conditions. For example, glucose was oxidized to the carboxylic acid in excellent yield (eq 10).[18]

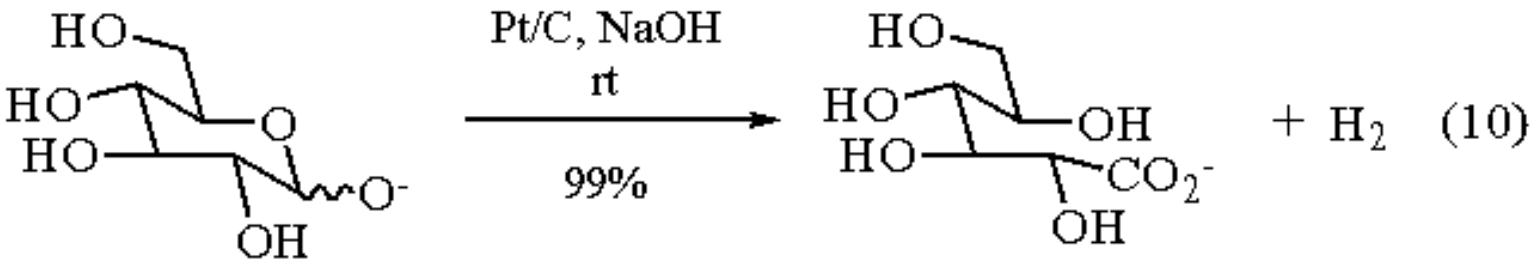

The mild reaction conditions under which reducing sugars are dehydrogenated with Pt/C also makes them good transfer hydrogenation agents. For example, fructose has been reduced to a mixture of glucitol and mannitol (0.77:1) in the presence of glucose and Pt/C.

The selective oxidation of benzylic alcohols to aldehydes by oxygen and Pt/C in the presence of ***Cerium(III) Chloride*** and $Bi_2(SO_4)_3$ cocatalysts has been reported. The selectivity to the aldehyde was excellent. Without the cocatalysts, carboxylic acids were obtained (eq 11).[19]

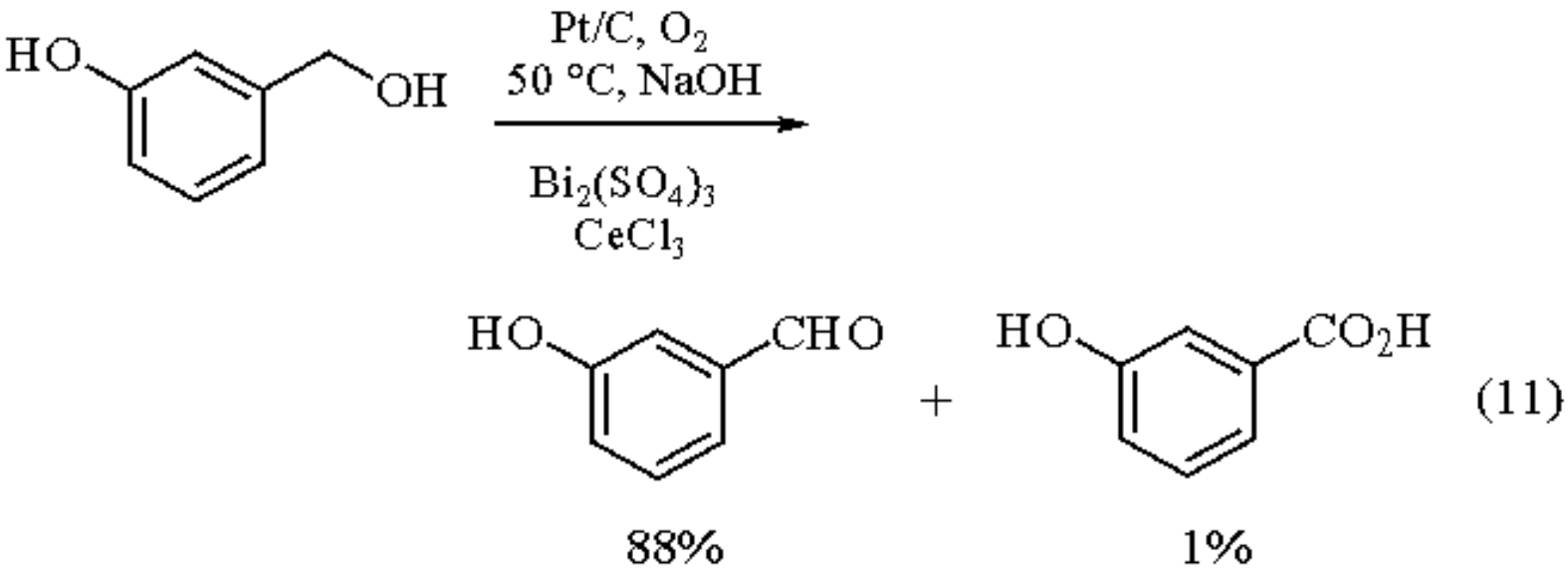

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Merck & Co., Rahway, NJ, USA

Platinum(IV) Oxide

PtO_2

[1314-15-4] · O_2Pt · Platinum(IV) Oxide · (MW 227.08)

(catalyst for hydrogenation of various functional groups with minimal hydrogenolysis problems; used as dehydrogenation catalyst; used for selective oxidation of primary alcohols)

Alternate Name: Adams' catalyst.

Solubility: insol most organic solvents.

Form Supplied in: dark brown solid, usually hydrated with 2 or more mol of H_2O.

Analysis of Reagent Purity: elemental analysis.

Handling, Storage, and Precautions: no precaution is necessary with the oxide, but after exposure to H_2 the Pt black must be handled as a pyrophoric reagent; the general precautions for handling hydrogenation catalysts should be followed; during filtration the filter cake must not be allowed to go dry; if a filter aid is necessary, a cellulose-based material should be used if catalyst recovery is desired.

Hydrogenations and Hydrogenolysis.

Platinum oxide has been used to catalyze the hydrogenation and hydrogenolysis of many functional groups. It has also found use in dehydrogenation and oxidation reactions. PtO_2 is not an active catalyst, but in the presence of H_2 the oxide is reduced to Pt black which is the active form. Pt black can also be made via other procedures.[1] A more recent method for the preparation of Pt black via the reduction of chloroplatinic acid or PtO_2 with ***Sodium Borohydride*** gives a catalyst with slightly increased activity.[2] Unlike the reaction between $NaBH_4$ and ***Nickel(II) Acetate***, which generates ***Nickel Boride*** (Ni_2B),[3] the reaction with Pt gives only pure Pt black. This catalyst, which is generally prepared in situ and used without isolation, was shown to be slightly more active than the Pt black generated from PtO_2 and H_2 in the reduction of 1-octene.

The reduction of alkenes, catalyzed by PtO_2, has been carried out in acidic, neutral, and basic conditions and, in some cases, different results are observed. In the example shown in eqs 1 and 2, stereoselective hydrogenation of a double bond to give the *cis*- or the *trans*-fused product was effected with PtO_2 in either acidic or neutral media.[4] With certain alkenic compounds, PtO_2 acted as an isomerization catalyst and no reduction occurred (eq 3).[5] Isomerization followed

by hydrogenation to give a *cis-trans* mixture of dimethylcyclopentanes has also been observed (eq 4).[6] The normally expected product is the *cis* isomer.

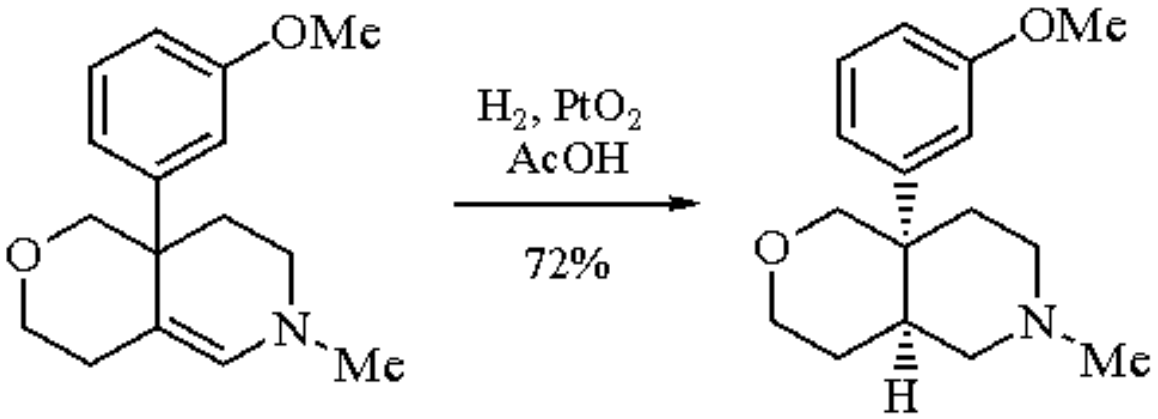

(1)

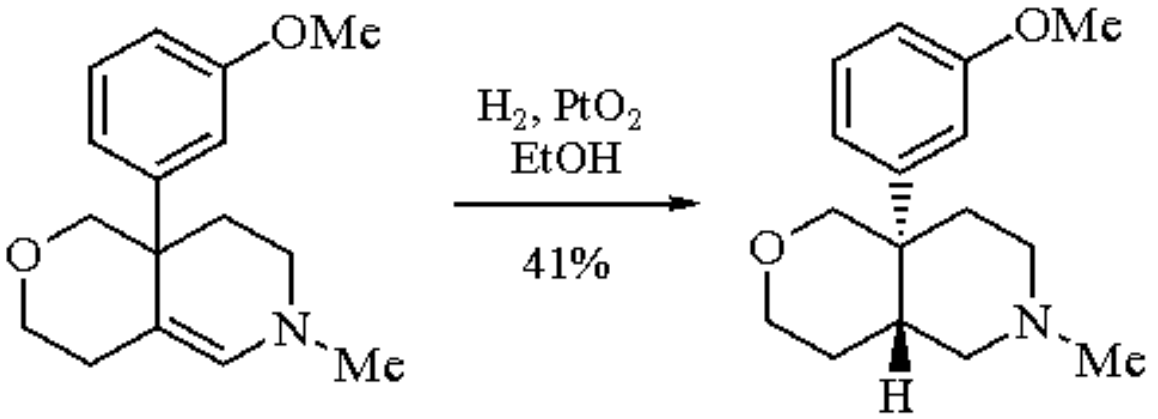

(2)

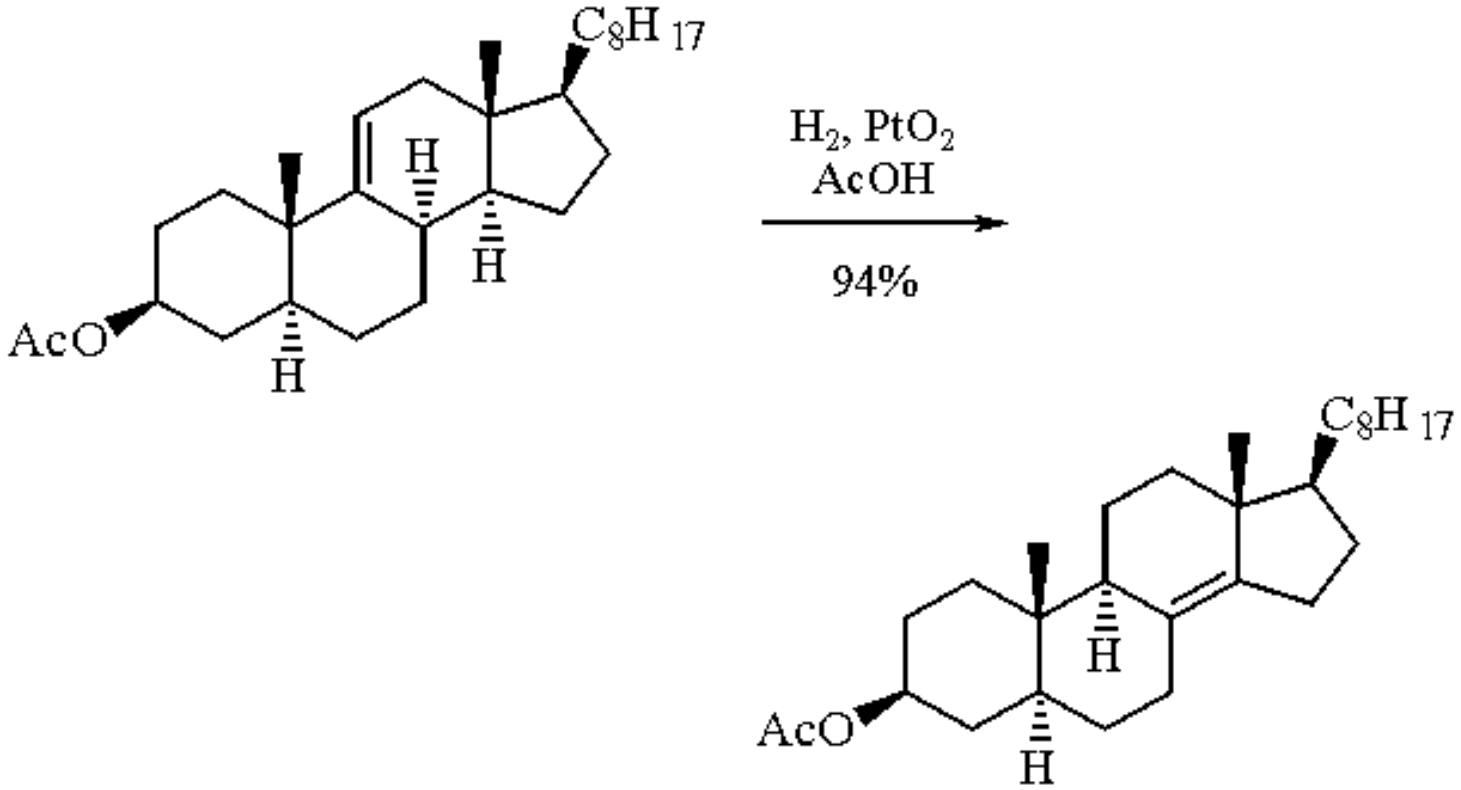

(3)

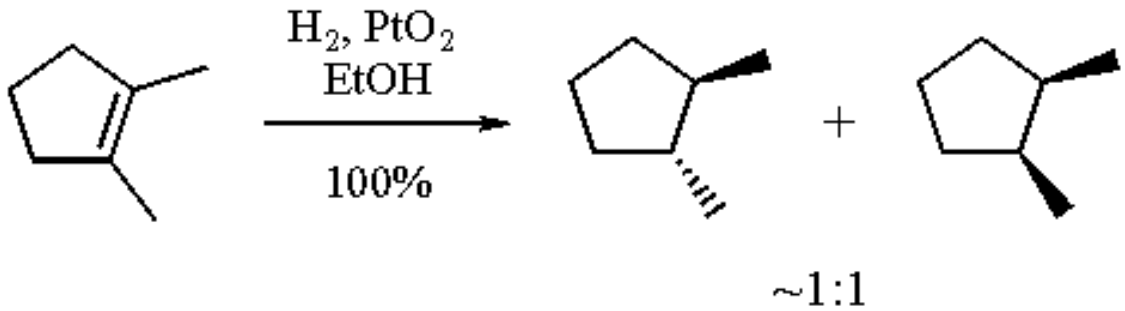

(4)

PtO_2 is generally not a satisfactory catalyst for the reduction of alkynes to alkenes. Even when the reaction is stopped after 1 equiv of H_2 is absorbed, a substantial amount of alkane has already been formed,[7] but a number of exceptions have been reported.[8] Lindlar catalyst (***Palladium on Calcium Carbonate (Lead Poisoned)***), ***Palladium on Barium Sulfate***, nickel boride (P-2Ni), and ***Palladium on Poly(ethylenimine)*** are better catalysts for this task.

Amines can be obtained by reduction of several functional groups. Nitro compounds are readily hydrogenated to amines under PtO_2 catalysis. The reduction of a benzylated nitro compound gave the aniline without loss of the benzyl ether functions (eq 5). Use of Pd/C gave the hydrogenolyzed product (eq 6).[9] In general, Pt catalysts are used in place of Pd catalysts when hydrogenolysis is to be minimized.

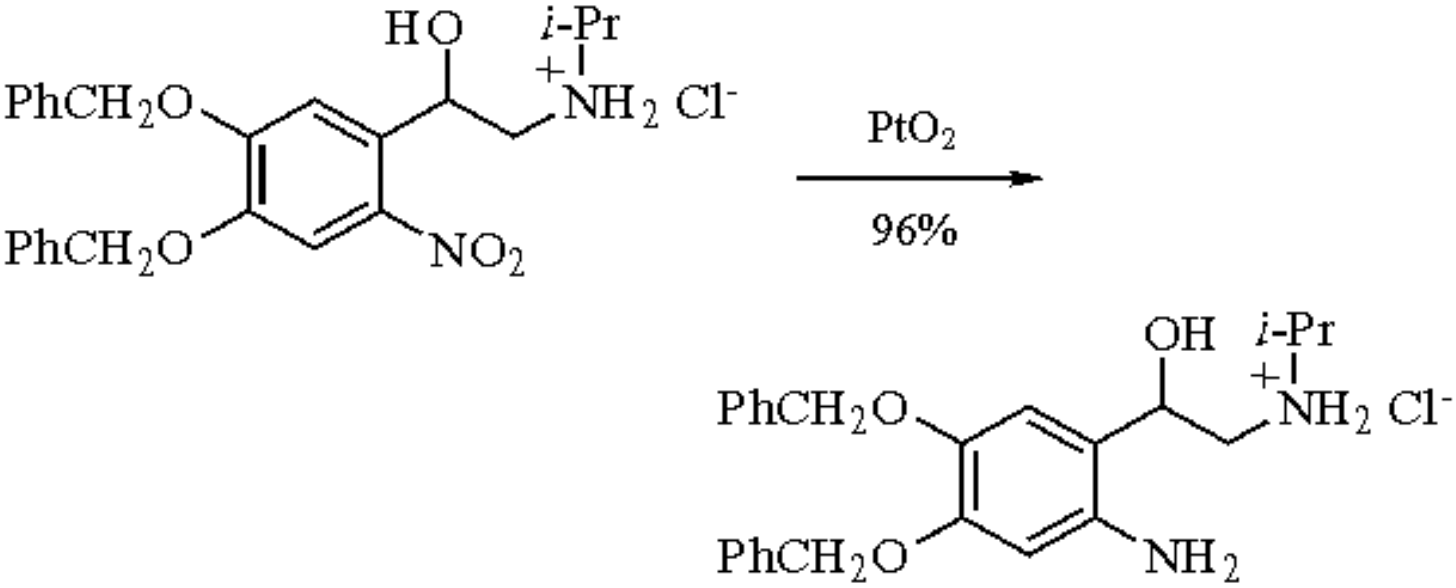

(5)

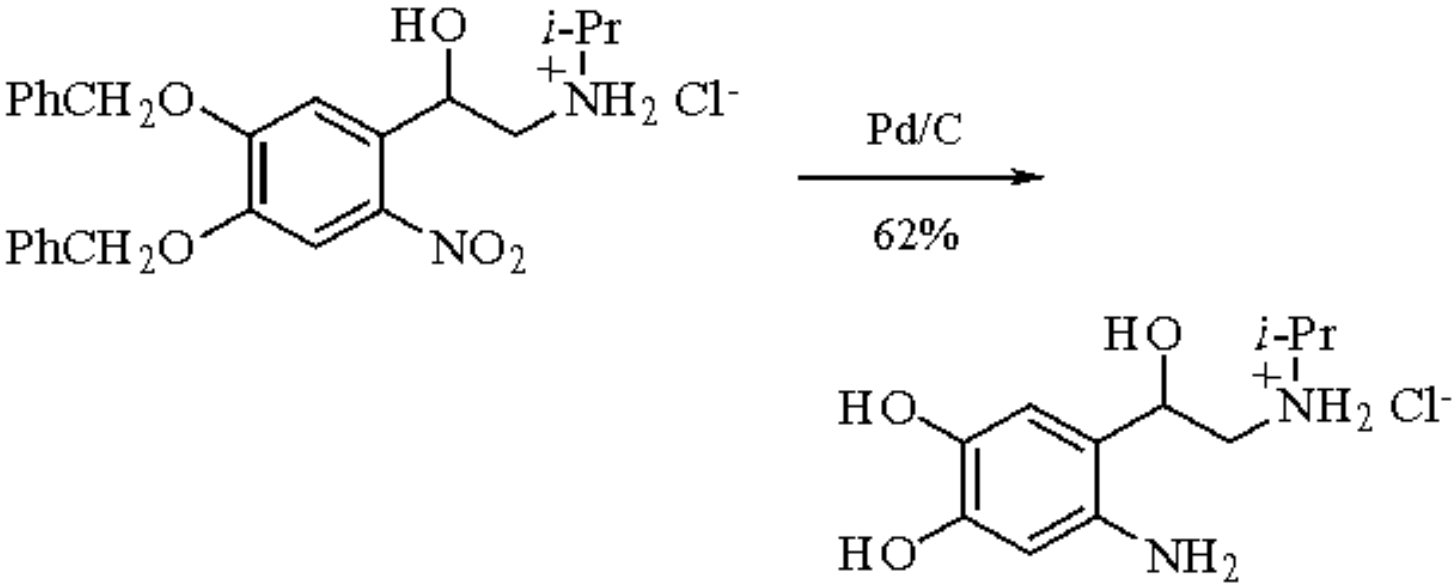

(6)

Hydrogenation of nitrobenzene in the presence of ***Hydrogen Fluoride*** gave *p*-fluoroaniline.[10] Hydrogenation of oximes is best carried out in acidic media to minimize secondary amine formation.[11] A quantitative yield of the amine was obtained when 3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carbaldoxime was reduced in alcoholic ***Hydrogen Chloride*** with this catalyst.[12] Amines can also be generated easily from azides,[13] imines,[14] and nitriles.[15] Similar to oximes, hydrogenation of nitriles should be conducted in acidic solvents to minimize di- or trialkylamine formation.

Hydrogenation of ketones in the presence of this catalyst can be carried out in acidic, neutral, or basic media. In general, with cyclic ketones axial alcohols predominate in acidic media while equatorial alcohols are favored in neutral or basic media. Thus the stereochemical outcome of ketone reduction may be controlled by varying the pH of the solvent.[16] In strong acids the reduction of dialkyl ketones in the presence of alcoholic solvents at rt with PtO_2 leads to the formation of ethers instead of alcohols.[17] It was suggested that acetals and enol ethers are generated under the reaction conditions before hydrogenation or hydrogenolysis. Although PtO_2 is often used to minimize hydrogenolysis of functional groups such as alcohols and halides, the hydrogenolysis of ketones under acidic conditions can give methylenic products (eq 7).[18]

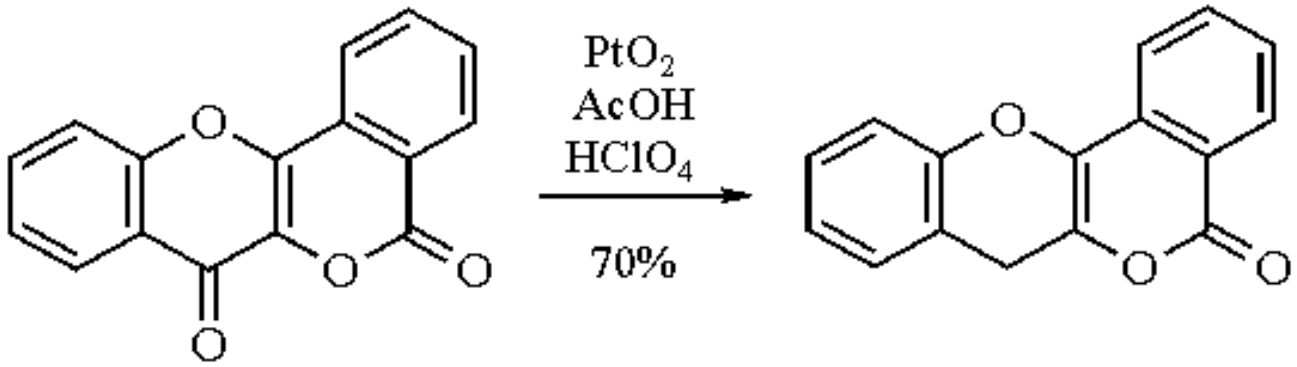

(7)

By converting enolizable ketones to the enol triflates, neutral conditions can be used to effect the overall hydrogenolysis of ketones (eq 8).[19]

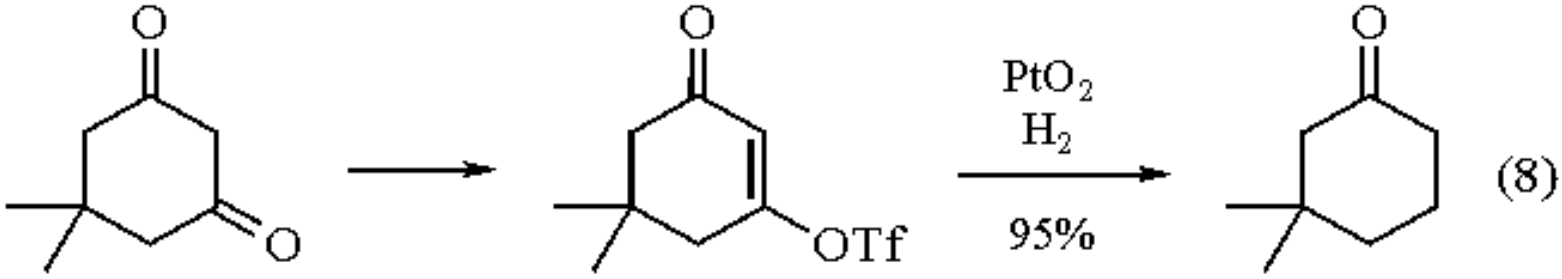

Certain α-diketones can be selectively hydrogenolyzed to monoketones by conversion to cyclic unsaturated oxyphosphoranes followed by treatment with hydrogen in the presence of the catalyst (eq 9).[20] The benzylic position, which is the more reactive site, was hydrogenolyzed selectively. Amide carbonyls are very difficult to reduce in general, but reduction has been observed in special cases (eq 10).[21] In one report, an anhydride was reduced to an ether at 5000 psi H_2 in HF.[22]

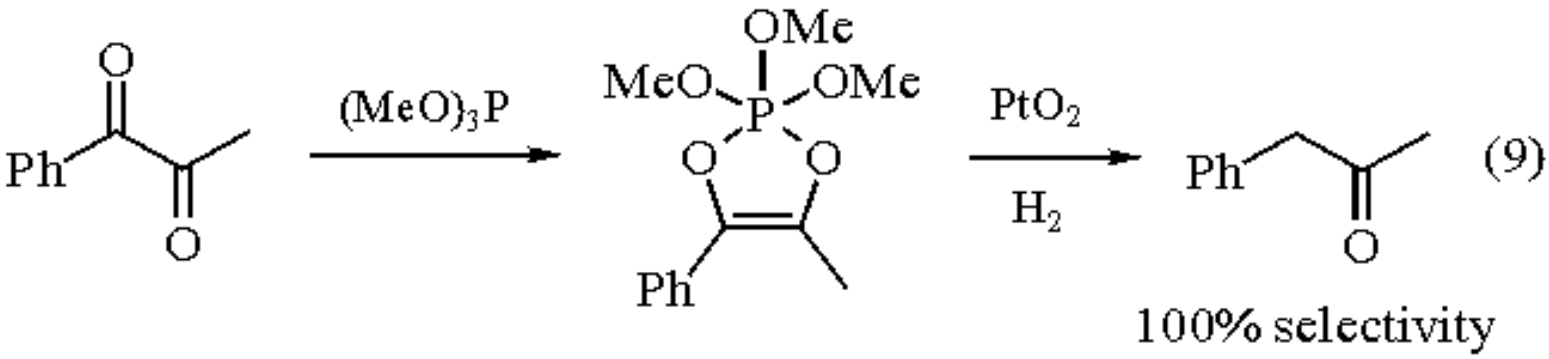

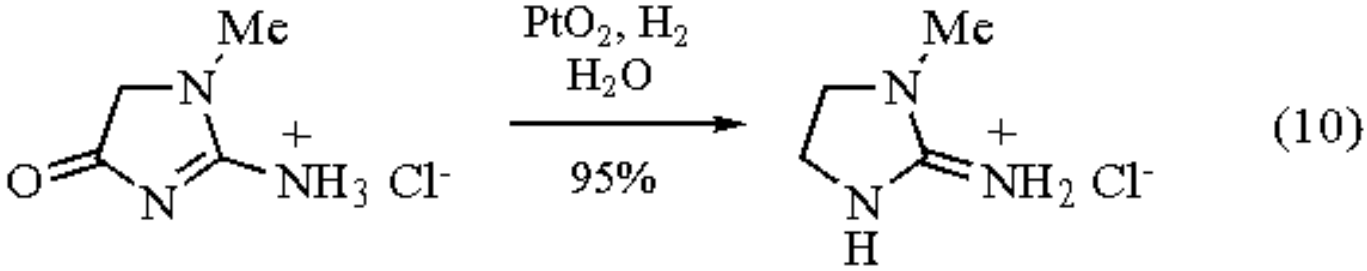

Benzyl groups attached to a heteroatom, such as oxygen and nitrogen, are removed using Pd catalysts, but the removal of phenyl groups of diphenyl phosphonates with these catalysts is ineffective. These phenyl groups can be hydrogenolyzed using PtO_2, but high catalyst loading is necessary.[23] *p,p´*-Dinitrobenzhydryl has been used for the protection of alcohols. This protecting group can be selectively removed in the presence of other hydrogenolyzable protecting groups, such as benzyl and trityl, by the use of platinum oxide followed by mild acid hydrolysis (eq 11).[24]

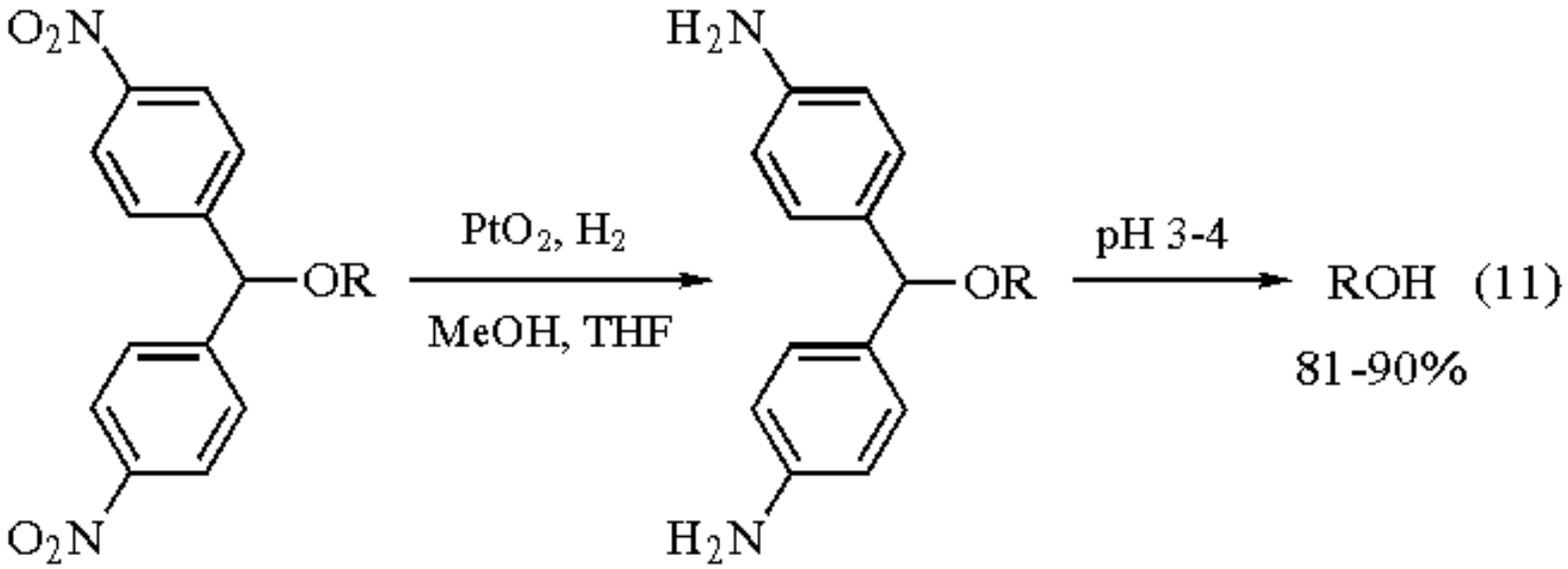

Hydrogenolysis of the N-N bond of hydrazines,[25] the N-O bond of nitrones,[26] and the C-C bond in cyclopropanes[27] are readily accomplished using this catalyst.

Aromatic ring reduction can be carried out with PtO_2 in acidic solvents such as acetic acid and alcoholic or aqueous HCl.[28] Complete ring reduction without the concomitant hydrogenolysis of benzylic alcohols has been accomplished.[29] Reduction of phenols provides cyclohexanols[30] and pyridines are reduced to piperidines.[31] ***Imidazole*** is difficult to reduce, but this has been accomplished in the presence of ***Acetic Anhydride*** to give the diamide.[32] Oxazoles are cleaved to amides (eq 12),[33] and isoxazoles give enamino ketones (eq 13).[34]

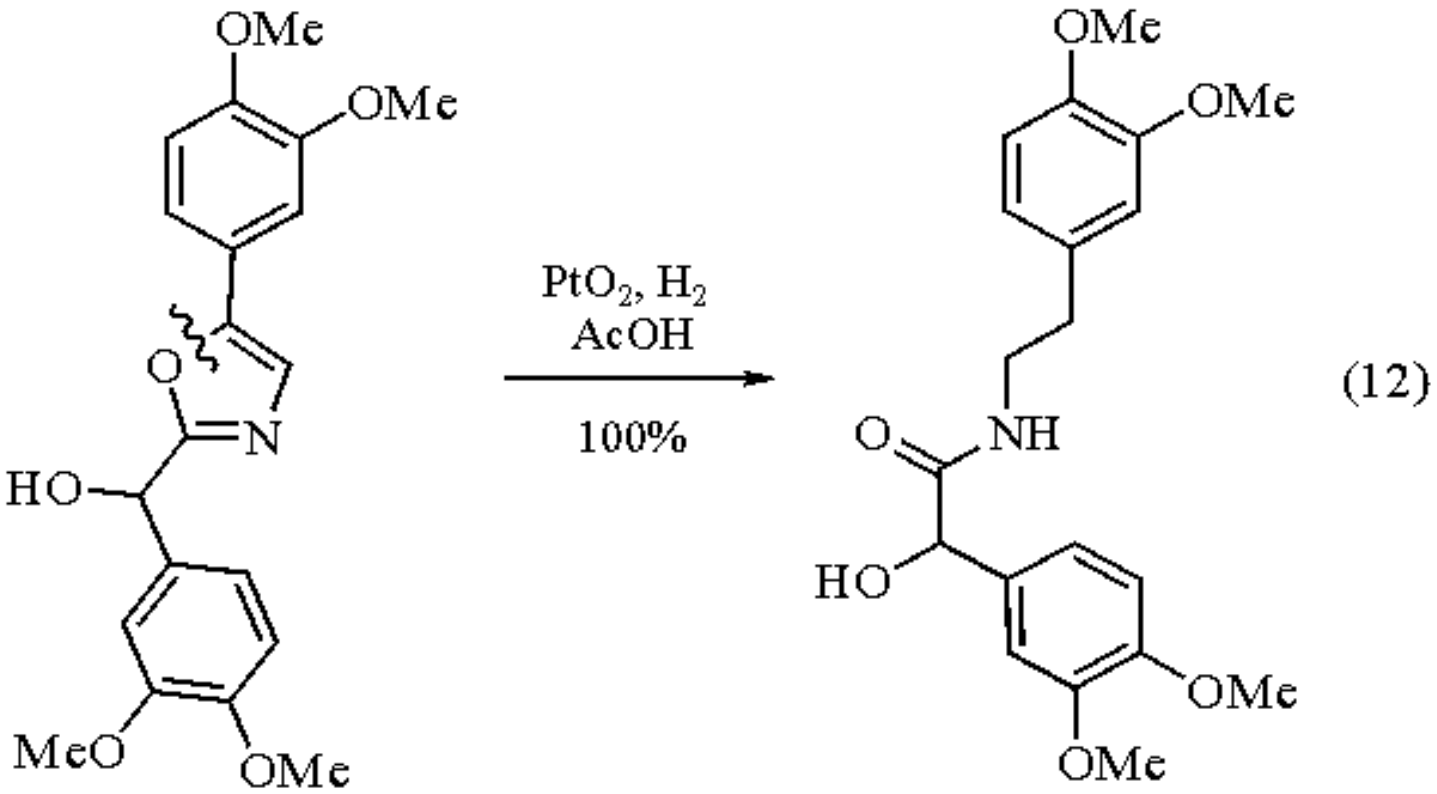

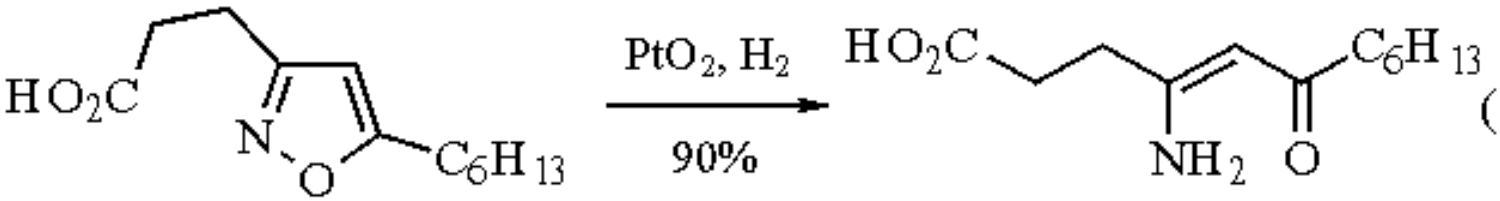

(13)

Dehydrogenation.

PtO_2 has also been used as a dehydrogenation catalyst. An example to obtain a pyridazine from a 1,4-diketone and hydrazine is shown below (eq 14).[35]

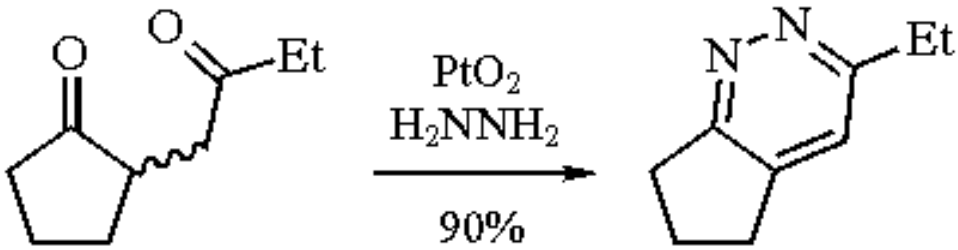

(14)

Oxidation.

The Pt black generated from prereduction of PtO_2 with hydrogen, also catalyzes the oxidation of alcohols to carbonyl compounds with oxygen. Primary alcohols are preferentially oxidized to carboxylic acids in the presence of secondary alcohols. Amides, sulfonamides, and azides are stable under the oxidizing reaction conditions.[36] Benzyldimethylamine can be oxidized to *N*-benzyl-*N*-methylformamide in 85% yield using benzene as the solvent.[37] When water was used as the solvent, *N*-demethylation was observed instead.[38]

Pt black was also used in the electrolytic *N*-ethylation of benzylamine in ethanol to give *N*-ethylbenzylamine in 96% yield. The Pt black anode first oxidized the ethanol to acetaldehyde which in turn formed a Schiff base with the amine. H_2 was generated at the Pt coil cathode and was picked up by the suspended Pt black for the hydrogenation of the imine.[39]

Irradiation of primary amines in the presence of a mixture of Pt black and TiO_2 gave low yields of secondary amines (8-67%). For example, diethylamine was formed in 33% yield from ethylamine and 1,4-diaminobutane gave pyrrole in 67% yield.[40]

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Anthony O. King & Ichiro Shinkai

Platinum (Sulfided) on Carbon

Pt(S)/C

[7440-06-4] · Pt · Platinum (Sulfided) on Carbon · (MW 195.08)

(catalyst for the hydrogenation of nitro compounds;[1-4] hydrogenolysis of disulfides;[5] reductive alkylation of amines with ketones[5])

Solubility: insol all organic solvents.

Form Supplied in: typically 5 wt % of Pt on black powder or granules poisoned with S; in dry or 50 wt % water wet form; commercially available.

Analysis of Reagent Purity: atomic absorption.

Handling, Storage, and Precautions: can be stored safely in a closed container under air but away from solvents and potential poisons such as sulfur- and phosphorus-containing compounds; pyrophoric in the presence of solvents; general precautions for handling hydrogenation catalysts should be followed; the catalyst must be suspended in the organic solvent under an atmosphere of N_2; during filtration the filter cake must not be allowed to go dry; if a filter aid is necessary, cellulose-based materials should be used if catalyst recovery is desired. Use in a fume hood.

Hydrogenations.

Sulfided platinum on carbon is a deactivated catalyst which gives useful selectivity in hydrogenation of polyfunctionalized compounds. Because of the deactivation, hydrogenation reaction conditions needed with this catalyst can be quite vigorous sometimes. Even so, many functional groups, including aromatic rings, ketones, aryl halides, sulfides, nitriles, amides, and esters, are stable under these conditions.

The reduction of halogenated nitrobenzenes to amines was effected without dehalogenation. Both chlorine (eq 1)[1] and bromine (eq 2)[2] survived the reduction conditions.

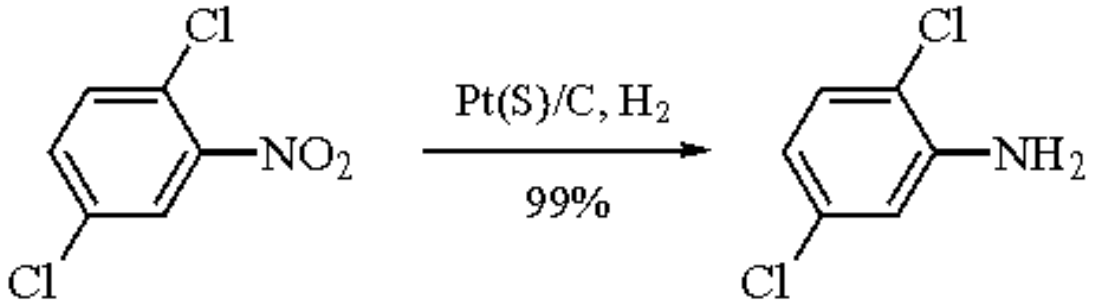

(1)

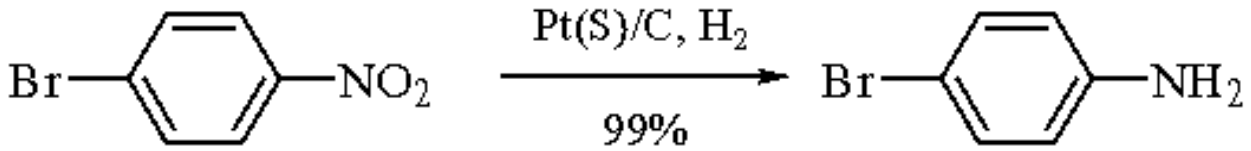

(2)

Appropriately substituted nitro compounds may lead to cyclized products after amine formation (eq 3).[3]

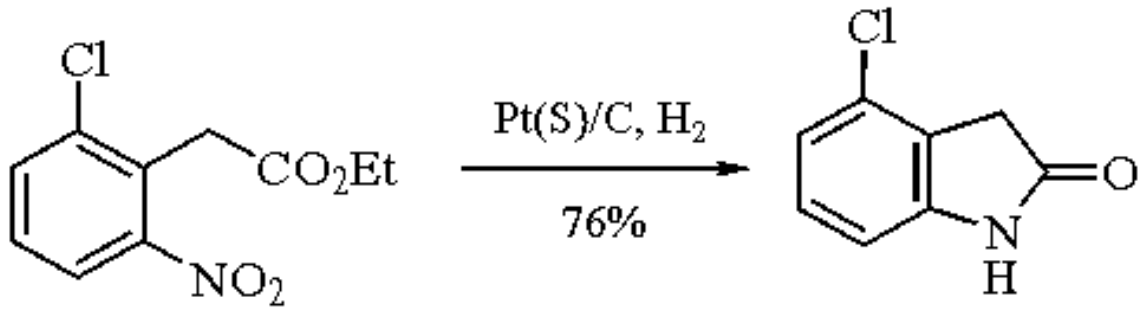

(3)

The catalyst is also insensitive to poisons. Even in the presence of a sulfide, a nitro group was reduced readily to the amine (eq 4). The benzhydryl (diphenylmethyl) protecting group was stable to the reaction conditions and was not hydrogenolyzed.[4] The diamine was reacted directly with alloxan monohydrate to give 10-[2-(diphenylmethylthio)ethyl]isoalloxazine in 51% yield.

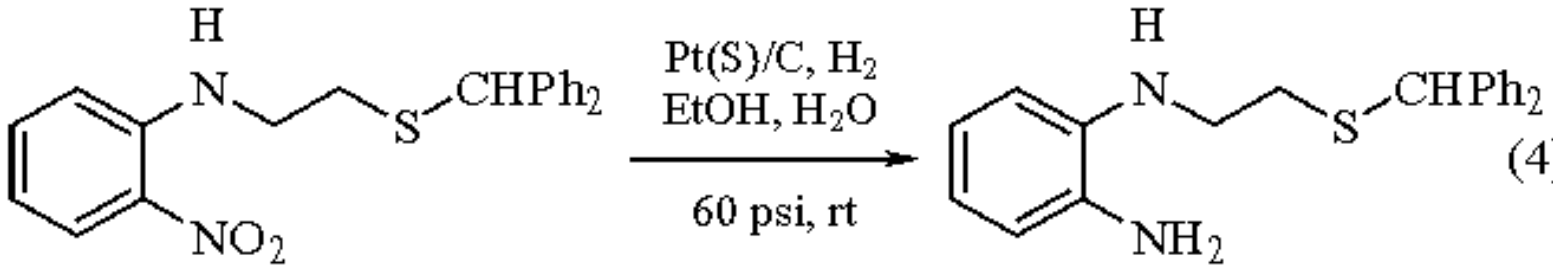

(4)

Aryl disulfides are hydrogenolyzed to thiophenols and no further reduction to the hydrocarbons and hydrogen sulfide was observed.[2]

The low reactivity of this catalyst towards ketone hydrogenation and hydrogenolysis allows the reductive alkylation of amines or amine precursors and ketones in excellent yields with no competitive reduction of the ketone to an alcohol.[5] The absence of ketone reduction is further illustrated in eq 5. When compared with ***Palladium on Carbon*** and ***Platinum on Carbon*** catalysts, which gave the nitro alcohol and the amino alcohol, respectively, Pt(S)/C is by far the most selective catalyst.

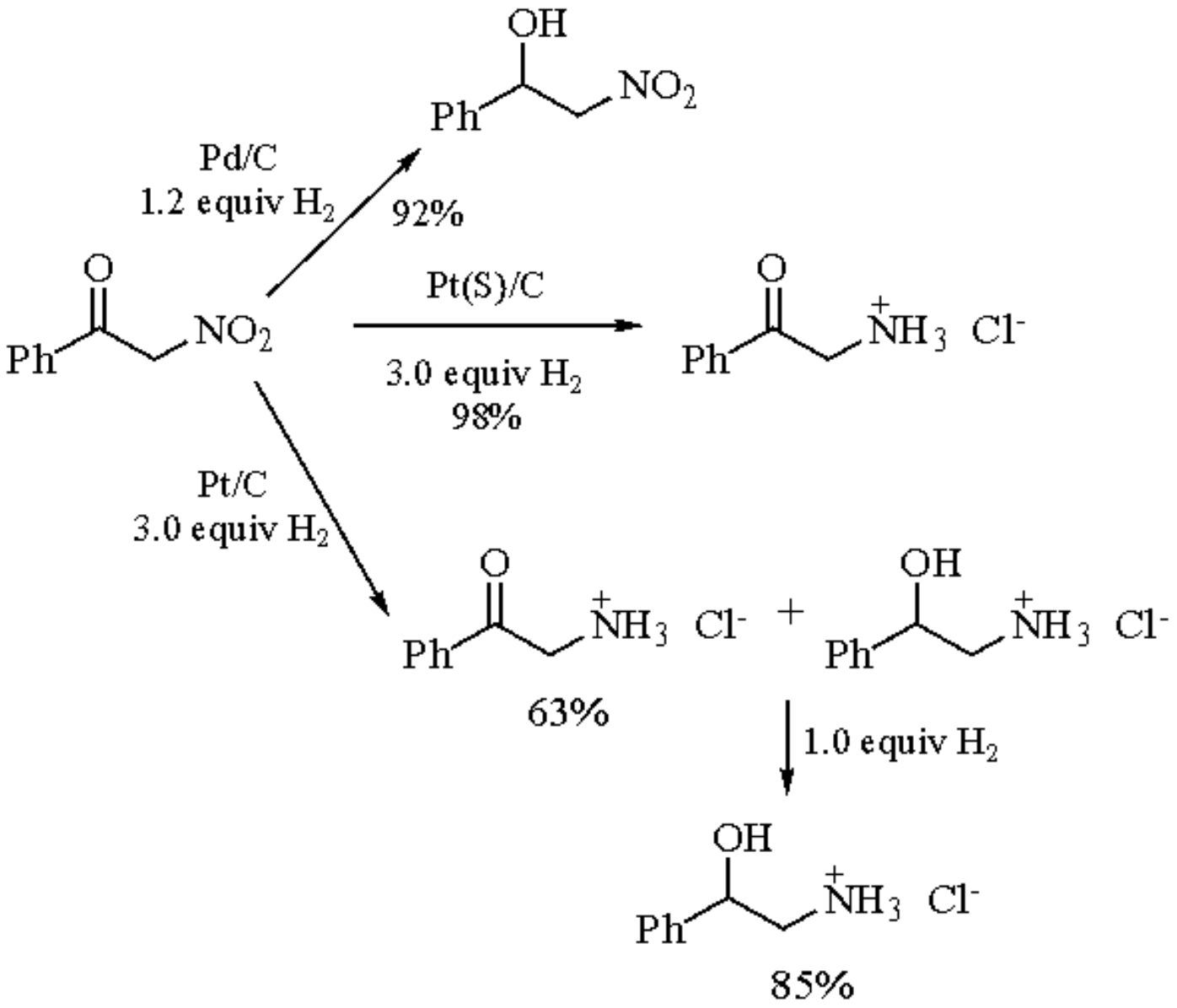

(5)

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Polyhexamethylenecarbodiimide[1]

$$-[(CH_2)_6N{=}C{=}N]_n-$$

[31667-72-8] · $(C_7H_{12}N_2)_n$ · Polyhexamethylenecarbodiimide · (MW)*n*(124.21)

(insoluble carbodiimide condensation reagent)

Solubility: insol CH_2Cl_2.

Preparative Method: by catalytic decarboxylation of 1,6-diisocyanatohexane, followed by several purification steps.[1]

Peptide Bond Formation.[1]

In what may be termed a reverse Merrifield approach, an *N*-protected amino acid is reacted with a sizable molar excess of the polymeric carbodiimide, suspended in CH_2Cl_2, and an equimolar amount of a *C*-protected amino acid (side chain reactive groups of the amino acid derivatives also appropriately protected). After removal of the catalyst by filtration, and washing with aqueous acid and base, evaporation of solvent leaves the substantially pure coupled material in good yields (82-93%).

The coupling and workup procedures are similar to those used in the classical ***1,3-Dicyclohexylcarbodiimide*** coupling. Both this and the water-soluble carbodiimide ***1-Ethyl-3-(3´-dimethylaminopropyl)carbodiimide Hydrochloride***, which requires no filtration step, are commercially available, and perform these same reactions with equal facility. They are, moreover, required in only stoichiometric proportions, and are accordingly very widely used, in distinct contrast to this polymeric reagent.

Other insoluble polymeric carbodiimides[2] have also been reported. Another,[3] which is soluble in typical reaction solvents (CH_2Cl_2, DMF, DMSO), but subsequently precipitated by addition of ether, is also known. None of these appear to have found any great popularity either.

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Peter Ham

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Polyphosphate Ester

[-] · $C_8H_{20}O_{12}P_4$ · Polyphosphate Ester · (MW 432.14)

(dehydrating agent; used in the Bischler-Napieralski reaction;[1] Friedel-Crafts acylation;[2] conversion of carboxylic acids to esters,[3] thiol esters,[4] amides,[5,6] and nitriles;[6,7] Beckmann rearrangement;[7] and heterocycle preparation; an alternative to PPA in dehydration reactions)

Alternate Name: PPE.

Physical Data: d 1.463 g cm^{-3}; *n* 1.440.[8]

Solubility: sol $CHCl_3$; reacts vigorously with H_2O.

Form Supplied in: not commercially available. May be prepared as described below. It is a colorless to yellowish substance which forms a stiff gel below 0 °C.

Analysis of Reagent Purity: PPE (3% solution in $CHCl_3$) shows a characteristic band in its IR spectrum at 1330 cm^{-1}. This band disappears and a new, broad band appears at 1200-1260 cm^{-1} when PPE is treated with a trace amount of H_2O.[5] ^1H and ^{31}P NMR techniques may be employed to determine composition of the mixture and structural features of each component.[9] Elemental analysis is not reliable.[9]

Preparative Methods: was originally prepared by Langheld,[12] and has been referred to as Langheld esters.[9,10] The preparation reported by Cava et al.[13] is a compilation of three previous procedures.[8,14,15] ***Phosphorus(V) Oxide*** (150 g) is added to a solution of anhydrous ether (300 mL) and alcohol-free ***Chloroform*** (150 mL). The reaction mixture is refluxed under dry nitrogen for 4 d and the resulting clear solution decanted from a small amount of residue. The solution is concentrated to a colorless syrup in a rotary evaporator; residual traces of solvent are removed by heating the syrup for 36 h at 40 °C in vacuo.[13] More harsh conditions result in unusable material.[11] While this preparation is sufficient for most synthetic applications, Van Wazer et al. reported that PPE prepared from triethyl orthophosphate and phosphorus pentoxide was superior for biochemical studies.[9]

Handling, Storage, and Precautions: Usually prepared fresh, but may be stored for at least 1 month.[4] PPE is unstable above 110-120 °C. A gradual decomposition occurs which becomes vigorous with evolution of gas at 150-160 °C.[11] Direct contact with PPE should be avoided. Use in a fume hood.

Reagent Description.

PPE is another of the phosphate-based reagents that are related to ***Polyphosphoric Acid*** (PPA) (see also

Phosphorus(V) Oxide-Methanesulfonic Acid). It differs from PPA in that it is aprotic and soluble in organic media. It is often compared to the related polyphosphoric acid trimethylsilyl ester (PPSE). In general, the advantages of PPE include its solubility in organic solvents, the mild conditions under which it is used, and its relatively nonhazardous, nonnoxious nature. A disadvantage is its time-consuming preparation.[16] The reagent is composed of a mixture of polymeric phosphoric acid esters.[8-10] Variations in the reactants and the reaction conditions may result in differences in the reagent's composition.[5,9,10] It is presumed to activate carboxylic acids through formation of mixed anhydrides.[17]

Bischler-Napieralski Reaction.[1,18]

One of the most cited uses of PPE is as a reagent in the Bischler-Napieralski reaction (eq 1).[18a] The utility of PPE compares favorably to other reagents, such as ***Phosphorus Oxychloride***, ***Phosphorus(V) Oxide***, and PPA.[18a,b,h,i]

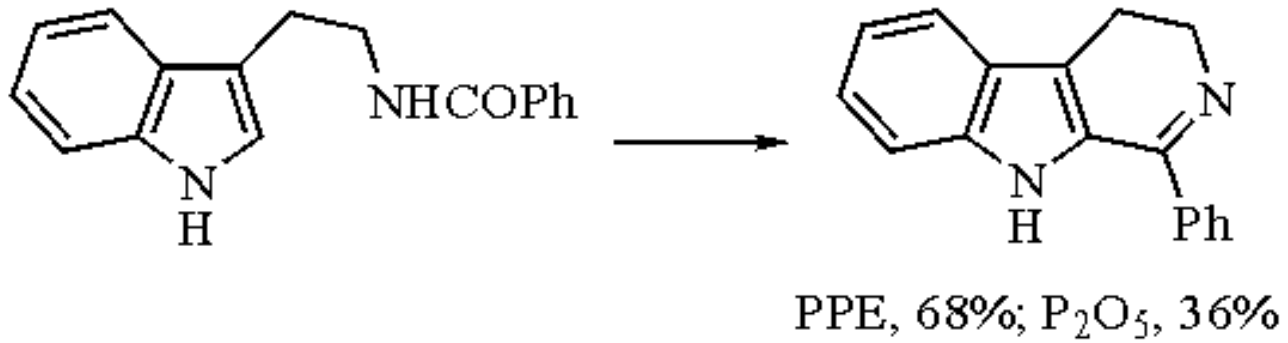

(1)

Friedel-Crafts Acylation.[2,19]

Intramolecular Friedel-Crafts acylations have been carried out by treatment of aromatic acids with PPE (eq 2).[19a] Depending on the substrate, PPE may be as effective[20] or more effective[21] than other reagents.

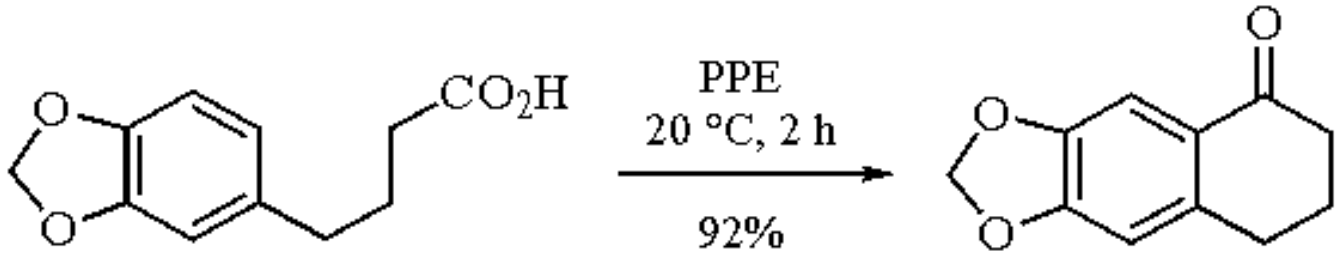

(2)

Carboxylic Acid Derivatives.

Esters,[3] lactones,[22] thiol esters,[4] thiolactones,[23] amides,[5] and acylureas[24] have all been prepared from a PPE-mediated reaction of a carboxylic acid and the appropriate coupling partner. There are many excellent methods for effecting the above transformations;[25] PPE is distinguished from these mainly by its low cost. Eq 3 describes the synthesis of phenyl esters,[3a] which were shown to be stable in PPE. This is in contrast to PPA, which can effect the Fries rearrangement of phenyl esters.[3a] Aryl and alkyl thiols have been condensed with alkyl, alkenyl, and aryl carboxylic acids,[4] and malonic acid.[26] Hindered thiol esters can be prepared by this method (eq 4).[4] Sensitive

substrates such as penicillin G could be reacted at low temperature with the addition of pyridine.[4]

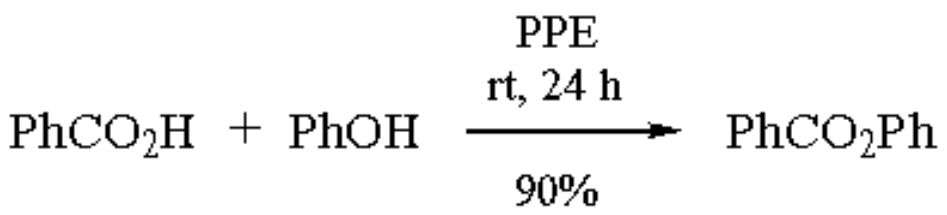

(3)

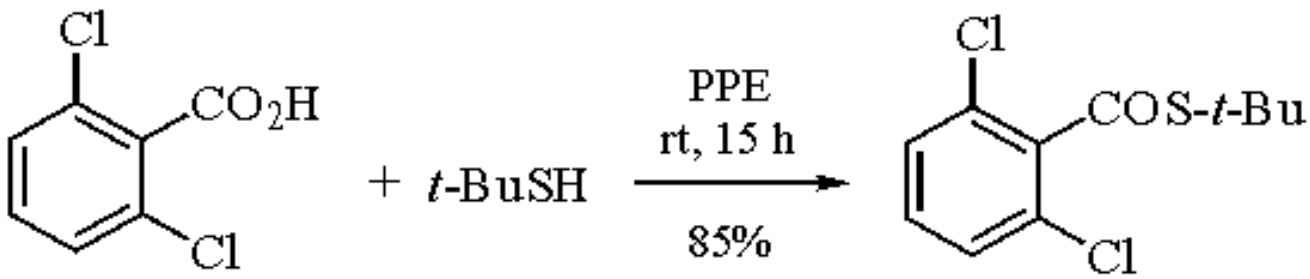

(4)

Conversion of Carboxylic Acids and Amides to Nitriles.

PPE has been used to dehydrate amides to nitriles.[27] More recently, a one-pot conversion of carboxylic acids to nitriles has been reported.[6] Treatment of an acid with PPE under an atmosphere of ammonia results in the formation of an intermediate amide, which upon further treatment with PPE undergoes dehydration to provide the nitrile (eq 5).[6] The amide may be obtained upon quenching the reaction after the initial condensation. Advantages of this method include use of a nonnoxious reagent, and reaction conditions that are relatively mild.[5,6,16] In an example of this reaction in a more complex substrate, this methodology has been applied to a synthesis of the canthine alkaloid skeleton.[28]

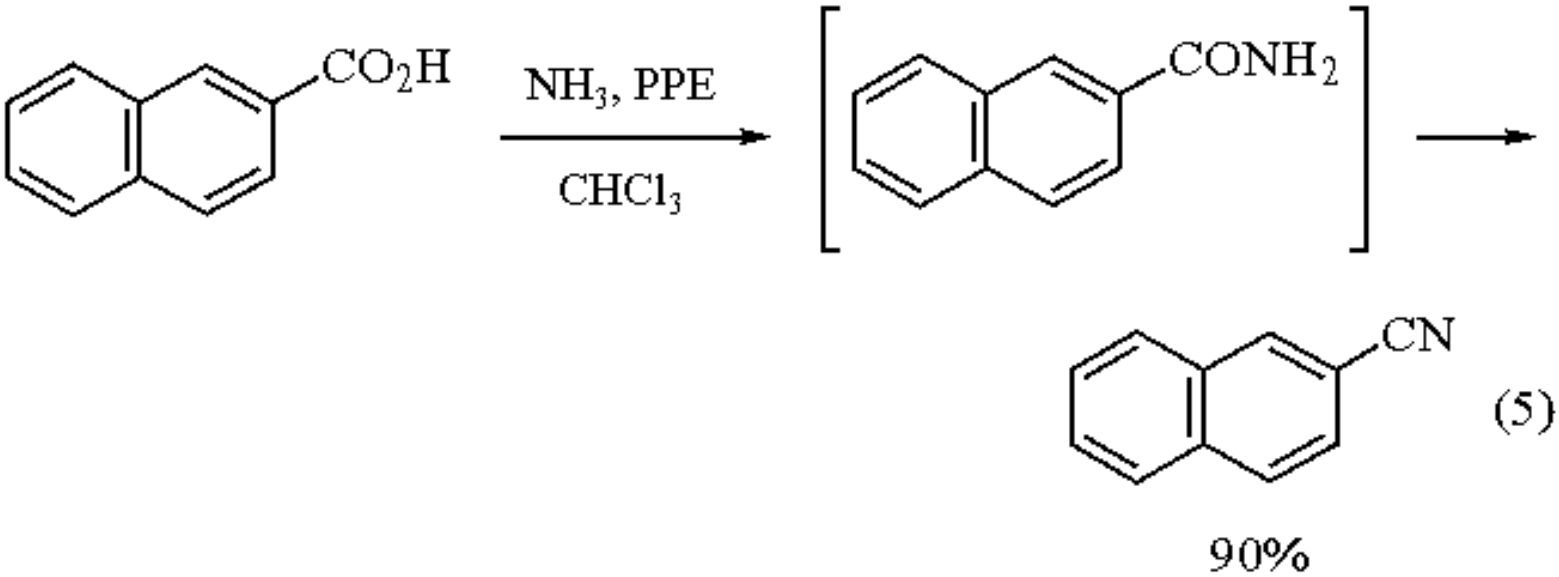

(5)

Beckmann Rearrangement.

Upon treatment with PPA, ketoximes have undergone the Beckmann rearrangement (eq 6).[7] Under more forcing

conditions, ketoximes provide amidines (eq 6). Submission of the oxime of benzaldehyde to similar conditions failed to produce benzamide; the only product obtained was benzonitrile. Treatment of benzamide under the same conditions did not lead to the nitrile. This suggests that dehydration of the aldoxime did not proceed through the intermediacy of the amide.[7] PPE was found to be equivalent to PPSE in terms of yields obtained in the Beckmann rearrangement of oximes.[29]

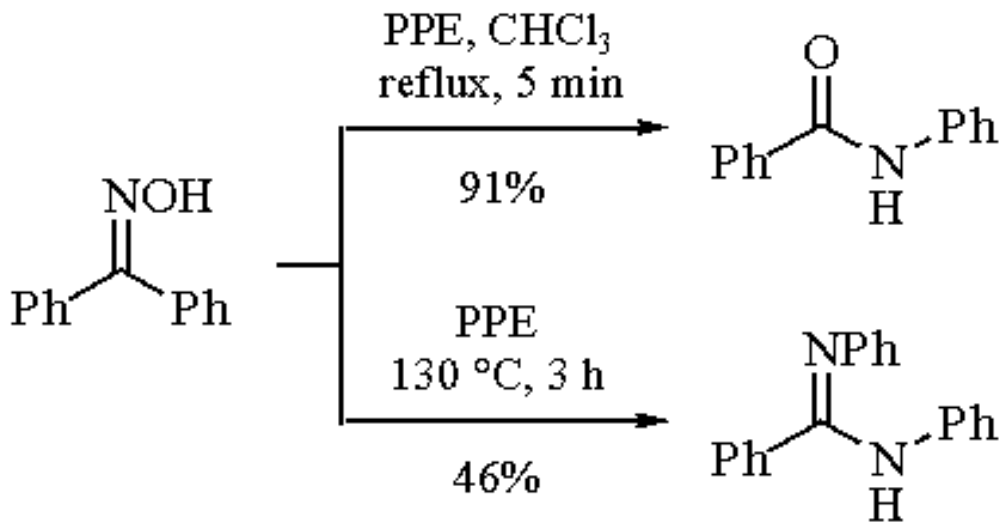

(6)

Fischer Indole Synthesis.

PPE has been utilized in the Fischer indole synthesis. Yields obtained ranged from 21 to 86% (eq 7).[30] A side product was the C-3 alkylated indole (see the section on ethylation).[30]

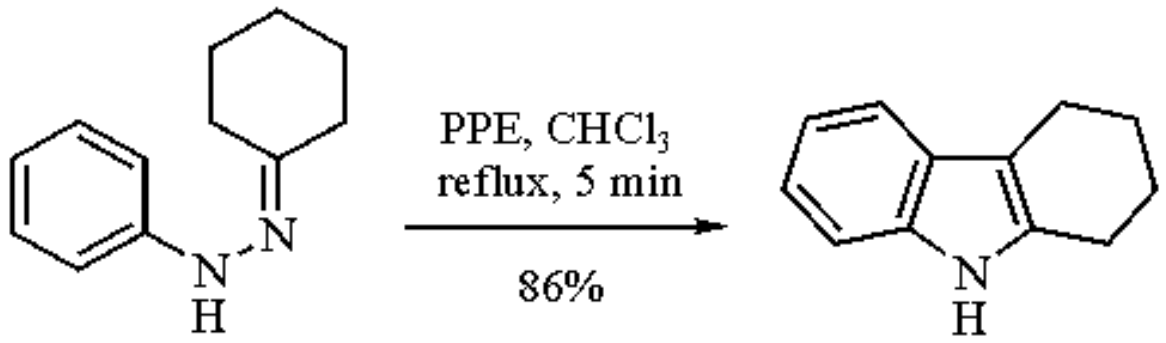

(7)

Heterocycle Preparation.

Various heterocycles have been produced through PPE-mediated cyclization reactions. Benzimidazoles (eq 8),[14] benzoxazoles,[31] and benzothiazoles[31] have been prepared through condensation of an *ortho*-substituted aniline and an acid (eq 8).[14]

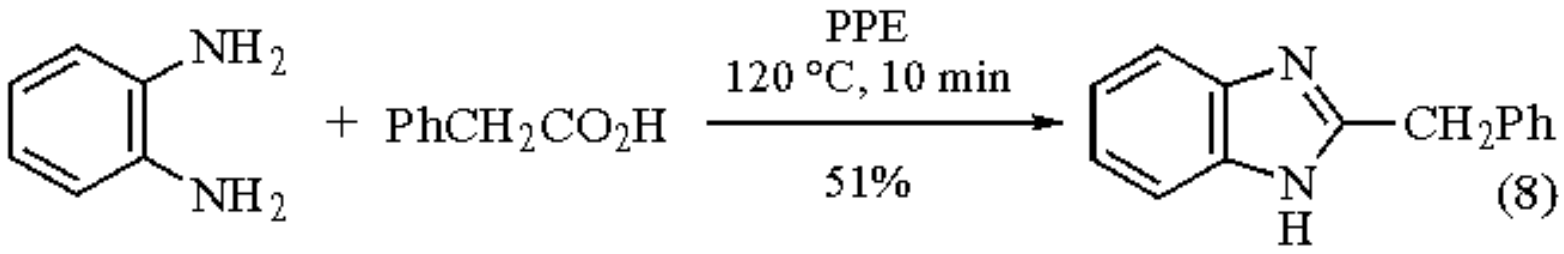

In related work, it was reported that PPE was utilized in the synthesis of benzothiazoles.[32] However, in the preparation of benzimidazoles, 6 N HCl was reported to be the preferred reagent; in the preparation of benzoxazoles, PPA was a better reagent.[32a] Other heterocycles prepared using PPE as a reagent include pyrrolo[2,3-*b*]pyridines,[33] pyrrolo[3,4-*b*]pyridines,[34] pyrrolo[3,2-*b*]pyridines,[35] benzimidazo[1,2-*c*]indazolo[2,3-*a*]quinazolines,[36] 1,3-diazepines,[37] 1,3-diazocines,[37] 1,4-dihydro-4-oxoquinolines,[38] and 1,3-thiazin-4-ones.[39]

Miscellaneous Transformations.

5,6-Dihydro-2(1*H*)-pyridinones have been prepared stereoselectively by condensing 3-alkenamides with aryl aldehydes (eq 9).[40] PPA is also effective in this reaction; however, the yields are lower.

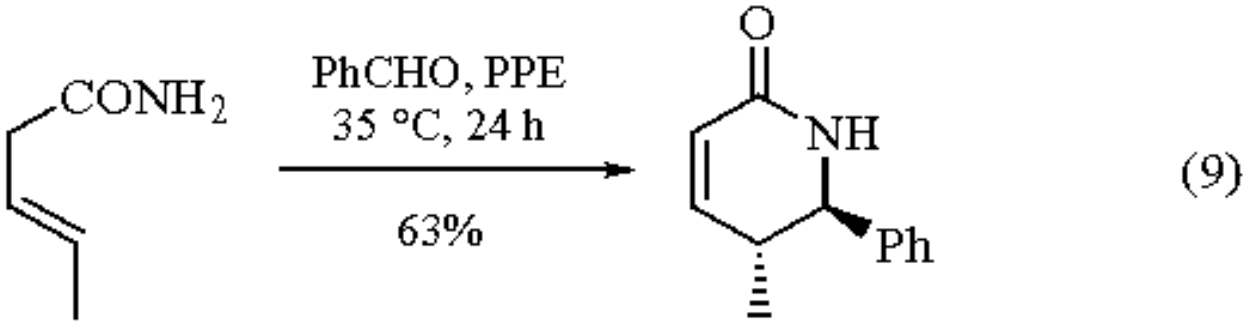

A one-carbon homologation of benzyl alcohols to amides or esters is shown in eq 10. Alkyl (and aryl) alcohols and secondary amines react with a cobalt intermediate to provide products with yields ranging from 20-82%.[41]

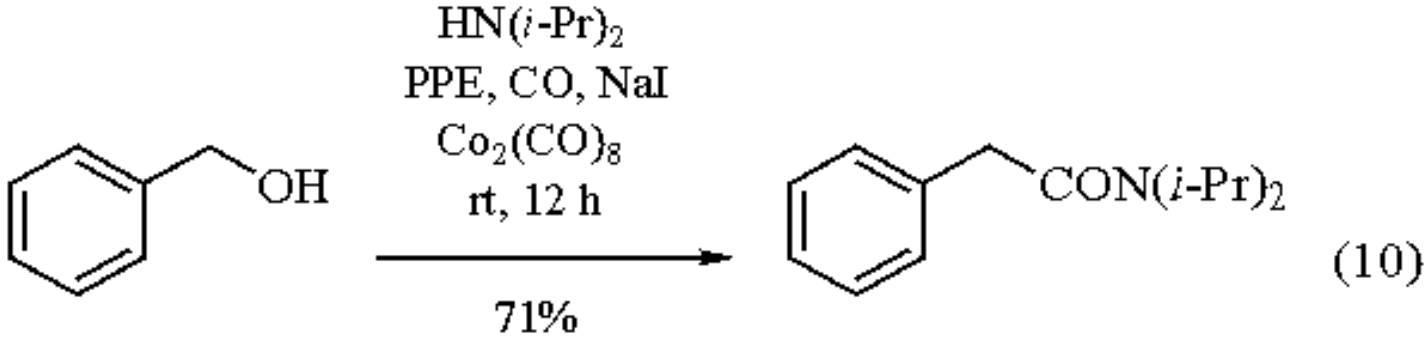

Ethylation.

During a Fischer indole synthesis, PPE was observed to alkylate indoles.[30] Further studies revealed that at 160 °C the ethyl indolenine was obtained in moderate yield. The diethyl and *N*-ethyl compounds were obtained in minor amounts

(eq 11).[11]

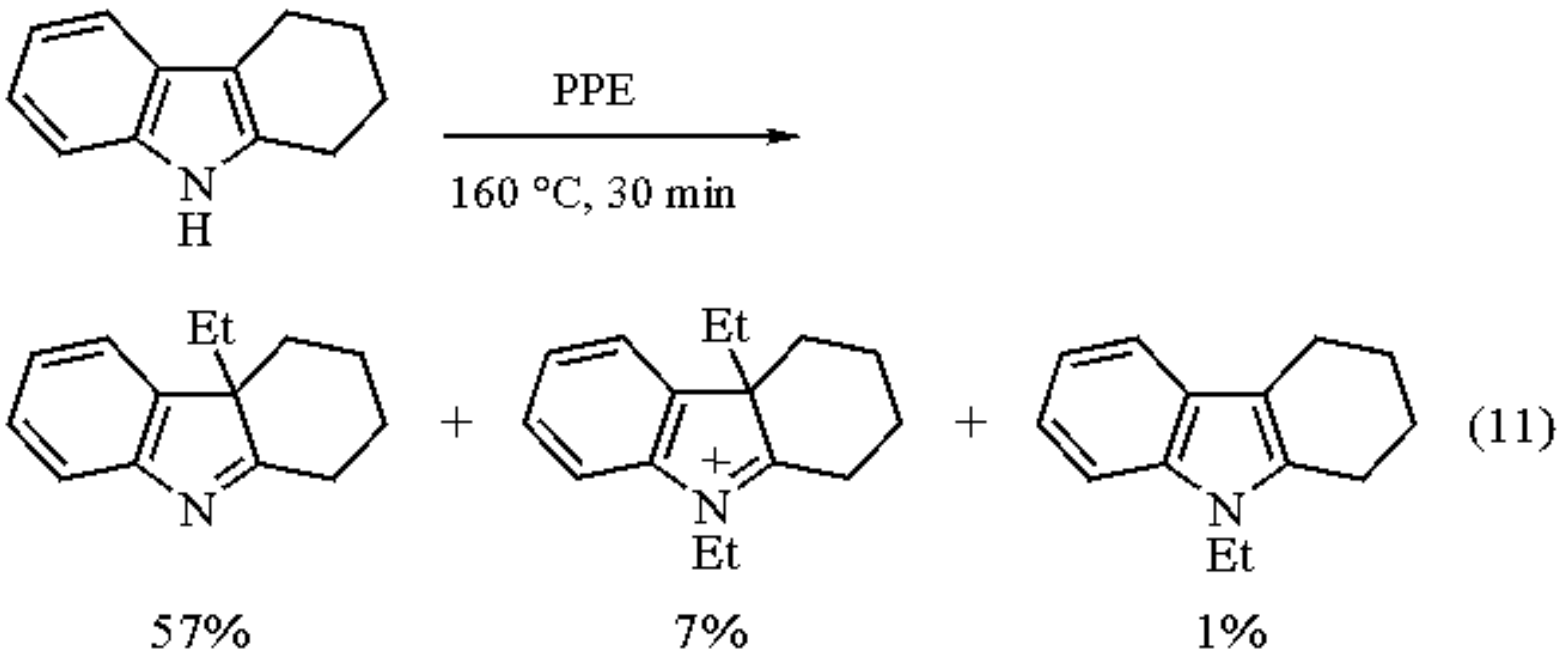

N-Alkylation of various amines has been reported. A tautomeric imidazole was alkylated in 74% yield (eq 12).[42] Yields for other methylation (polyphosphate methyl ester) or ethylation (polyphosphate ethyl ester) reactions varied from 44-74%.[42]

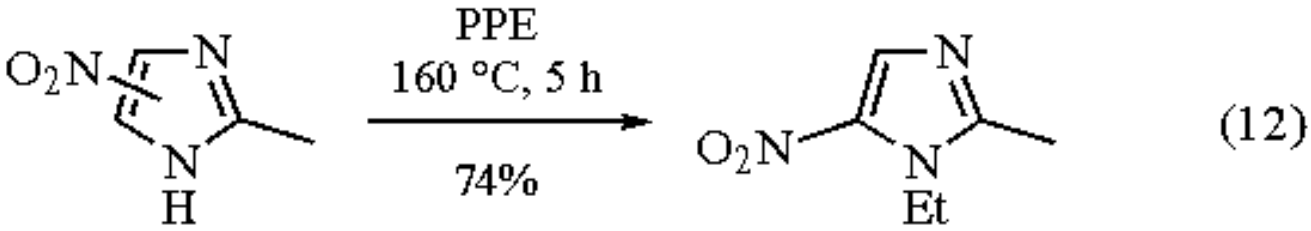

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Lisa A. Dixon

Polyphosphoric Acid[1]

[8017-16-1]

(moderately strong mineral acid with powerful dehydrating properties; used for intramolecular and intermolecular acylations, heterocyclic synthesis, and acid-catalyzed rearrangements)

Alternate Name: PPA.

Physical Data: hygroscopic, highly viscous, clear, colorless, or light amber; specific gravity 2.060 at 83% phosphorus pentoxide content.

Solubility: dissolution in any protic solvent will result in solvolysis of the reagent; dissolution in polar aprotic solvents could result in dehydration or destruction of the solvent; polyphosphoric acid is neither soluble in nor reacts with nonpolar organics such as toluene or hexane.

Form Supplied in: inexpensive and commercially available from most major suppliers.

Preparative Methods: by mixing *x* mL of ***Phosphoric Acid*** (85%, *d* 1.7 g mL^{-1}) with 2.2 *x* g of ***Phosphorus(V) Oxide*** (P_2O_5) followed by heating to 200 °C for 30 min.

Handling, Storage, and Precautions: normally used as the solvent so that a 10-50 fold excess is routinely employed. Due to high viscosity, PPA is difficult to pour and stir at rt, but is much easier to work with at temperatures above 60 °C. Addition of cosolvents, such as xylene, has facilitated the difficult workup usually associated with PPA.[2] Eaton's reagent (see ***Phosphorus(V) Oxide-Methanesulfonic Acid***) has been found to perform similar chemistry at lower temperatures without the viscosity problems. When diluting PPA or working up a reaction, ice is normally used to moderate the exothermic reaction that occurs with water. PPA has the ability to burn mucous membranes immediately and unprotected skin with time. Other than the corrosive nature of this reagent it has low inherent toxicity. Use in a fume hood.

Description.

Polyphosphoric acid is a mixture of orthophosphoric acid and linear phosphoric acids. In order to simplify discussion of this reagent, the complex mixture is described empirically as a wt % of P_2O_5 in water. The distribution of phosphoric acids that are found in PPA is dependent upon the wt % of P_2O_5. Commercially available PPA contains 82-85% P_2O_5, with 83% P_2O_5 considered to be the standard. At this concentration there is no free water and the distribution of phosphoric acids is approximately 6% orthophosphoric acid, 19% pyrophosphoric acid, and 11% triphosphoric acid, while the remaining material is linear phosphoric acids up to a chain length of approximately 14 phosphoric acid units.[3] Only at wt % of P_2O_5 over 84% do appreciable high weight polymeric species occur.

Neutralization of the most acidic protons in PPA is accomplished at pH 3.8-4.2 and corresponds to one strongly acidic proton for each phosphorus atom.

The powerful dehydrating properties of PPA, low nucleophilicity of the phosphoric acid media, and moderate acidity explain why this reagent is so widely used. Unlike ***Sulfuric Acid***, PPA has a low propensity to cause oxidation of the substrate and is also able to dissolve organic compounds. PPA has demonstrated rates of dehydration equal to that of 100% sulfuric acid even though it is a much weaker acid.

Cyclization of Acids, Esters, Ketones, Aldehydes, Acetals, Alcohols, and Alkenes onto Aromatic Rings.

Polyphosphoric acid is the reagent of choice to cyclize aromatic carboxylic acids to indanones (eq 1),[4] tetralones (eq 2),[5] and benzosuberones (eq 3).[6] Anomalous results for the cyclization of 3-(2-methoxyphenyl)propionic acid led researchers to discover a method for synthesis of metacyclophanes (eq 4).[7] Another interesting reaction that demonstrates the utility of PPA in forming cyclic aromatic ketones is the double cyclization of biscarboxylic acids (eq 5).[8] Carboxylic esters often demonstrate the ability to be cyclized as readily as the acids (eq 6).[9]

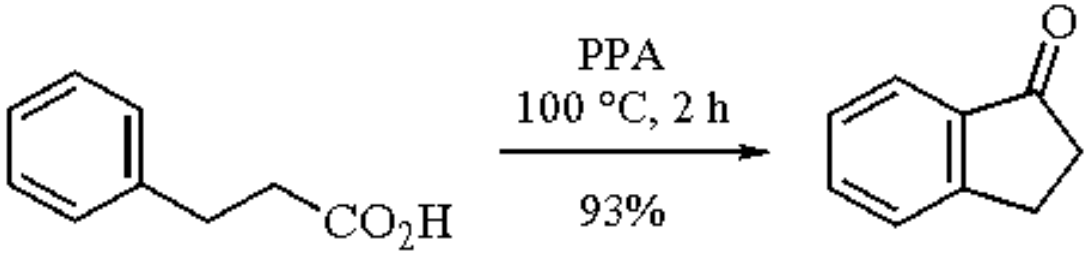

(1)

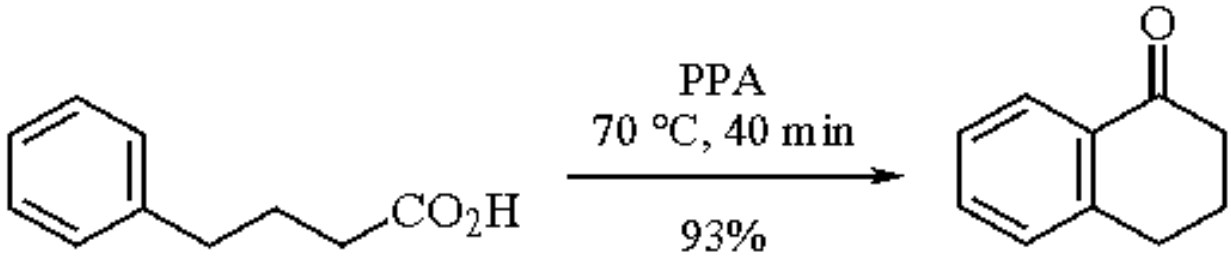

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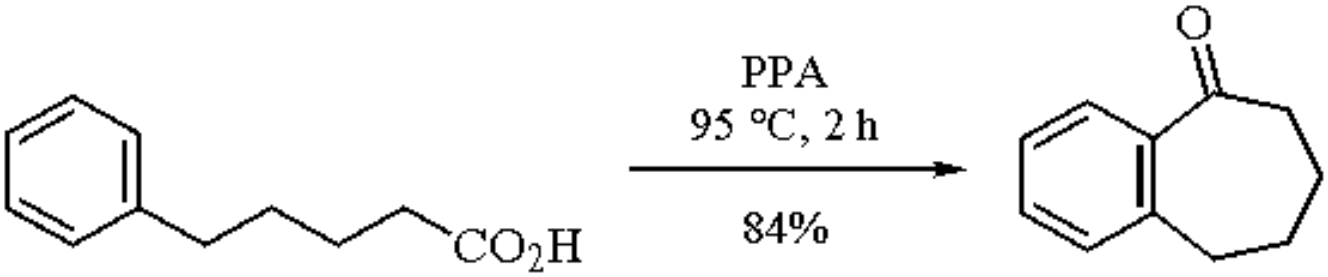

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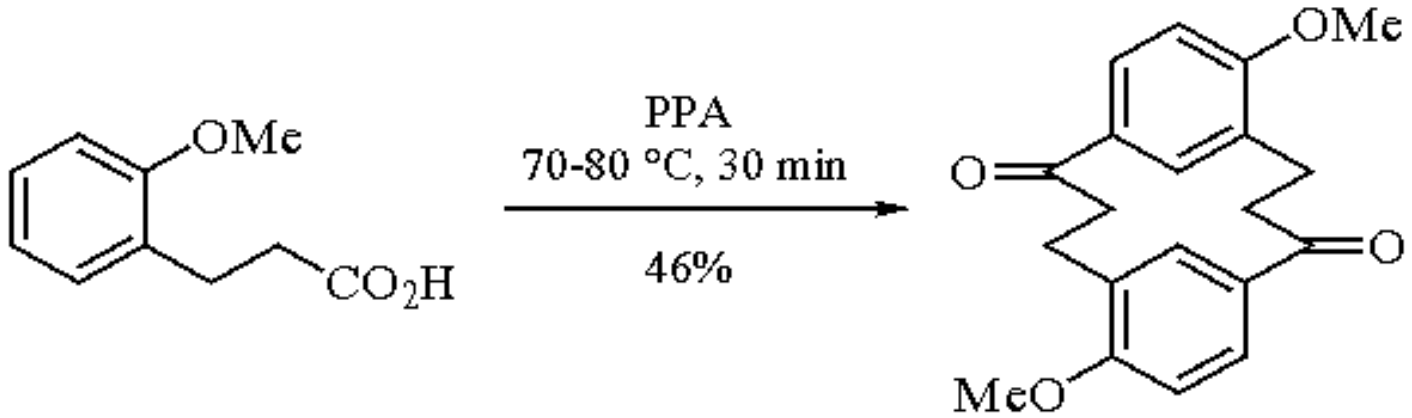

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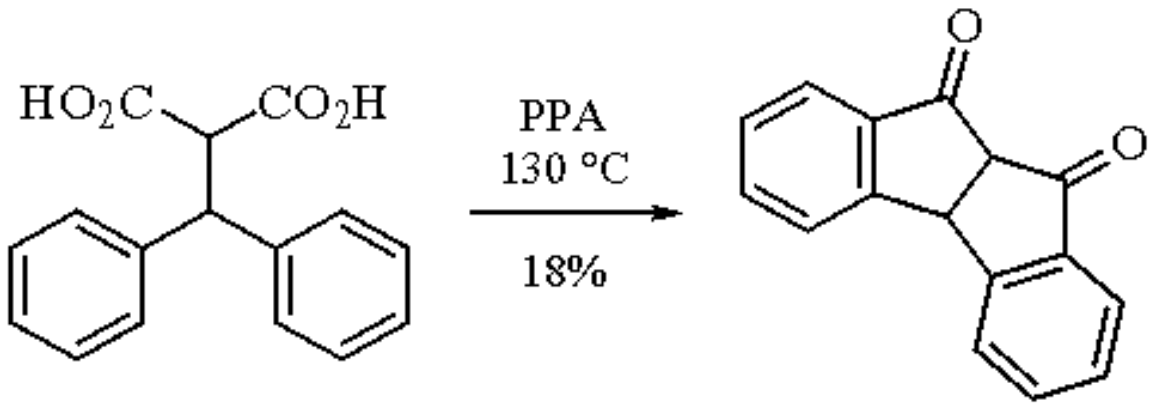

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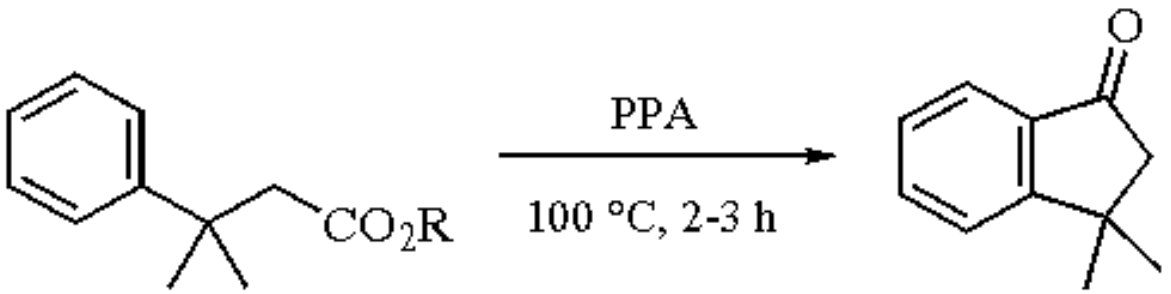

(6)

R = H, 74%
R = Et, 72%

Methoxy or alkyl substitution of the aromatic ring has also been found to allow shorter reaction times and lower reaction temperatures.[10] Cyclization of ketones (eq 7),[11] aldehydes (eq 8),[12] and acetals (eq 9)[13] occurs with dehydration to give cyclic alkenes. Tertiary or benzylic alcohols are usually the only alcohols which give straightforward cyclization products (eq 10).[14] Secondary and primary alcohols usually rearrange (Wagner-Meerwein rearrangements) before cyclization can occur. Just as in alcohols, alkenes are also prone to rearrangement unless the carbonium ion formed upon protonation is tertiary or benzylic. Low to moderate yields have been reported for cyclization of alkenes onto aromatic rings (eq 11).[15]

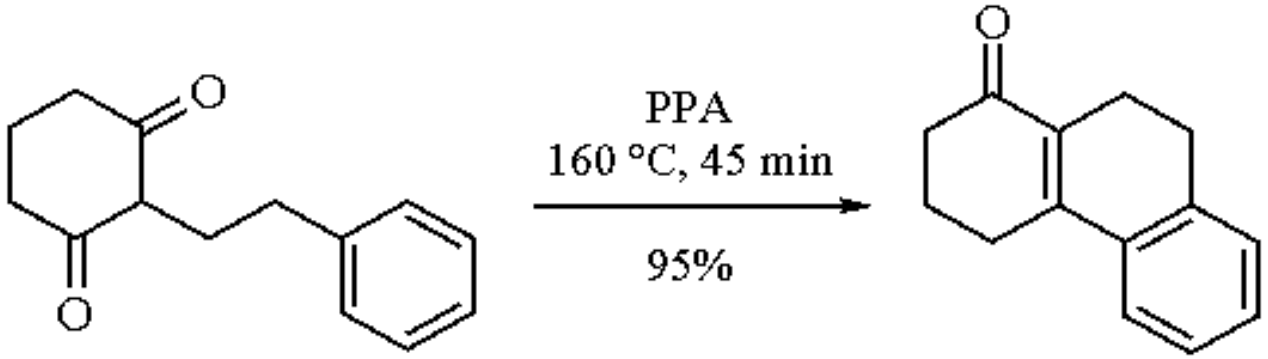
O
O
PPA
160 °C, 45 min
95%
O

(7)

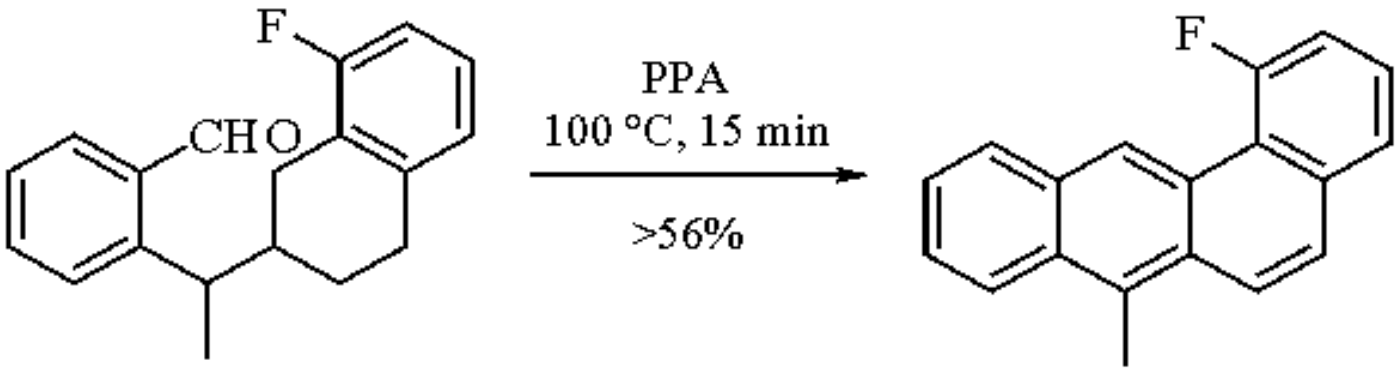
F
CH O
PPA
100 °C, 15 min
>56%
F

(8)

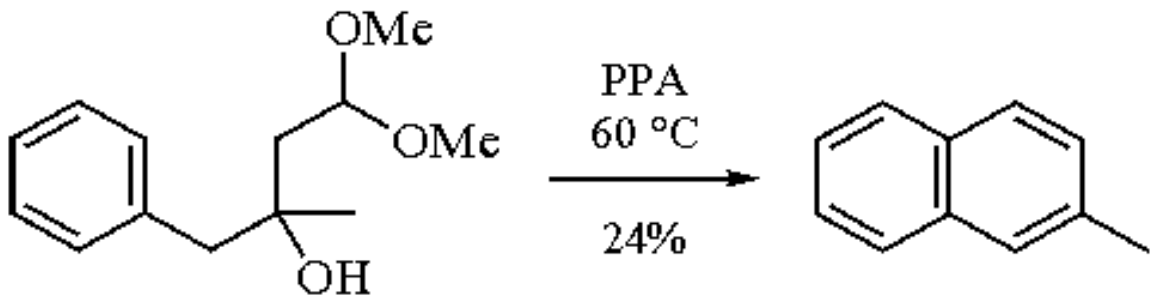
OMe
OMe
OH
PPA
60 °C
24%

(9)

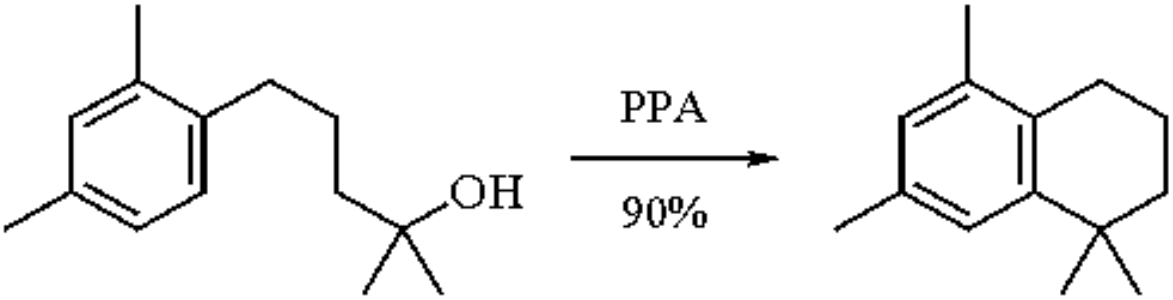
OH
PPA
90%

(10)

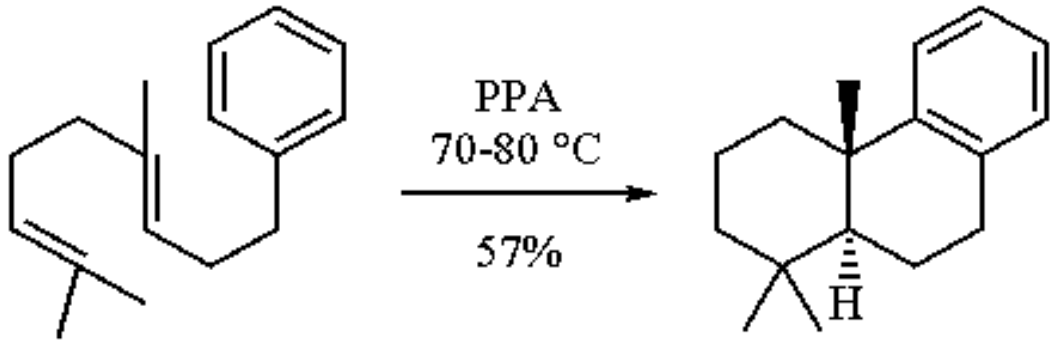

(11)

Cyclization onto Nonaromatic Moieties.

Cyclopentenones have been synthesized from carboxylic acids in good yield (eqs 12-14).[16] Compared with other protic acids, PPA has demonstrated the ability to favor carbon-carbon bond formation over lactone formation.[17]

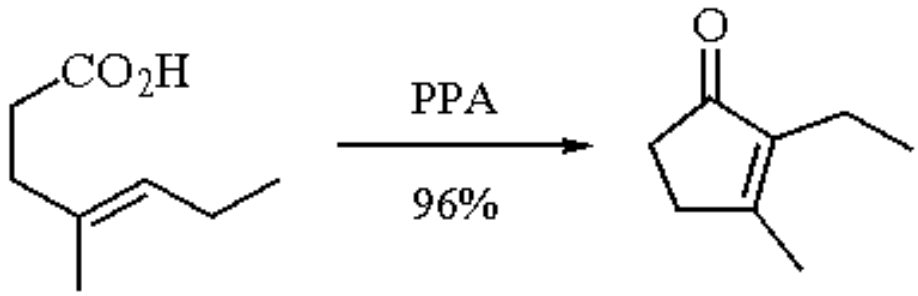

(12)

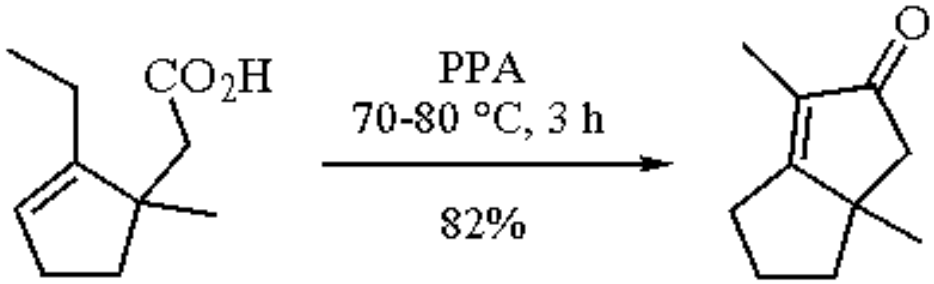

(13)

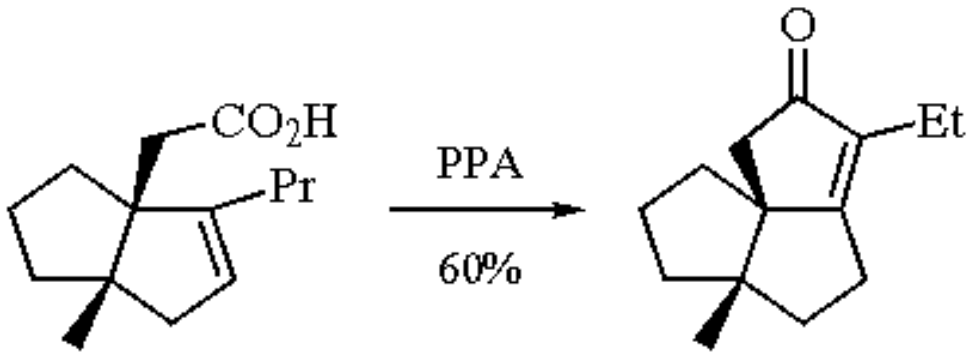

(14)

Synthesis of cyclohexenones from alkenyl acids has been demonstrated (eq 15);[18] however, formation of methylcyclopentenones and lactones may occur when possible (eq 16).[19]

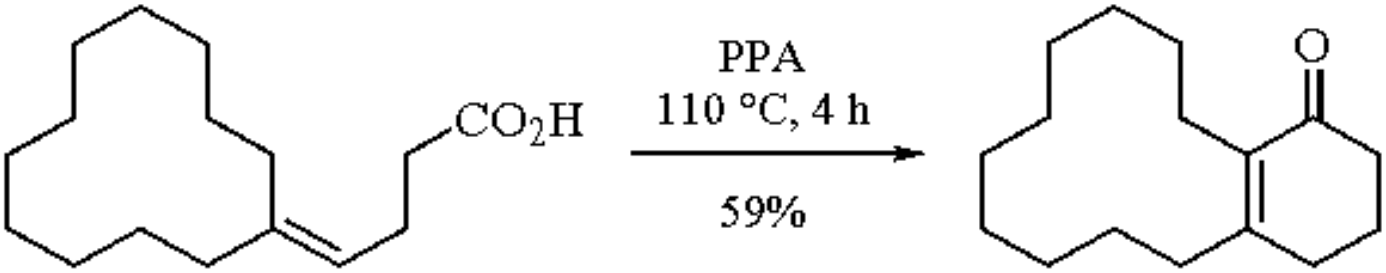

(15)

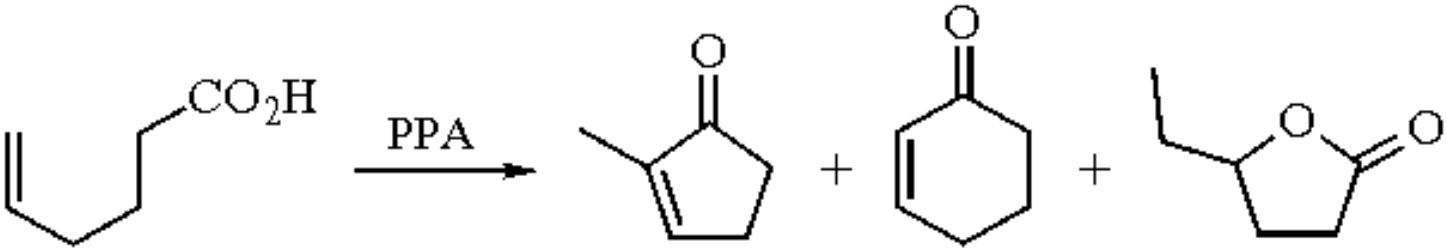

(16)

90 °C	2%	5%	47%
120 °C	22%	13%	34%
140 °C	29%	3%	3%

Cyclization Reactions which Form Heterocycles.

Use of PPA as an acid catalyst to form heterocyclic compounds has been exhaustively reviewed in the literature.[1] The ability of PPA to be used in place of more acidic or more nucleophilic reagents has led to applications in a variety of heterocyclic systems.

Nitrogen Heterocycles.

Although ***Zinc Chloride*** is normally used as catalyst, indoles substituted in the 2-position can be obtained from hydrazones by ring closure with PPA (Fisher indole synthesis) (eq 17).[20]

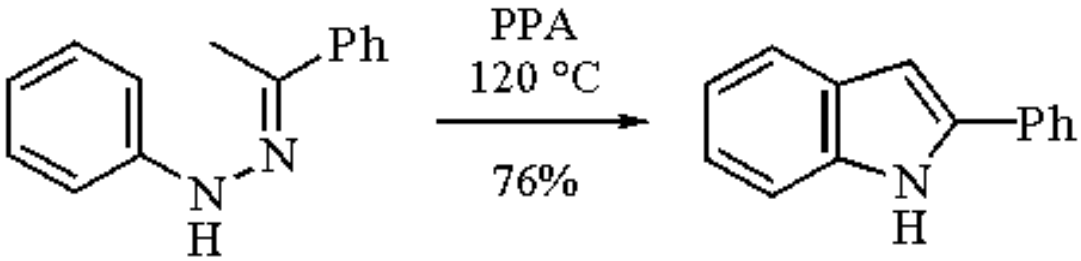

(17)

Use of PPA in the Bischler-Napieralski reaction has shown superior results to other reagents for construction of the isoquinoline ring system.[21] For example, dihydroisoquinolines are obtained from phenethylformamides in yields superior to phosphorus pentoxide (eq 18).[22] In the first report which popularized the use of PPA in organic synthesis, treatment of *N*-acetyl-β-phenethylamine with PPA gave the 1-methyl-3,4-dihydroisoquinoline in 23% yield (eq 19).[23] Synthesis of isoquinolines using a PPA-catalyzed Pomeranz-Fritsch reaction has been reported (eq 20),[24] but the low yields and poor reproducibility of this reaction have been overcome by the use of ***Hydrogen Chloride***/dioxane to

cyclize the *N*-tosyl derivative.[25]

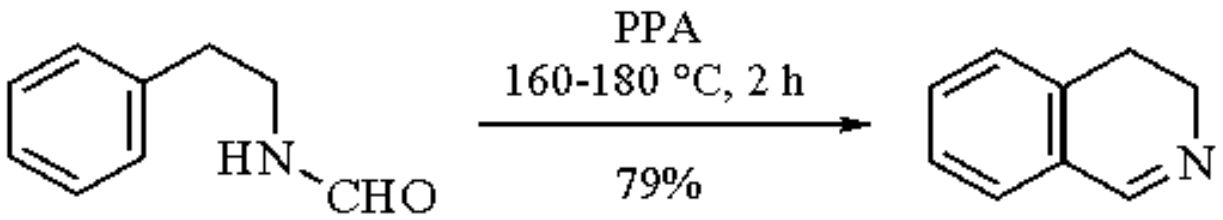

(18)

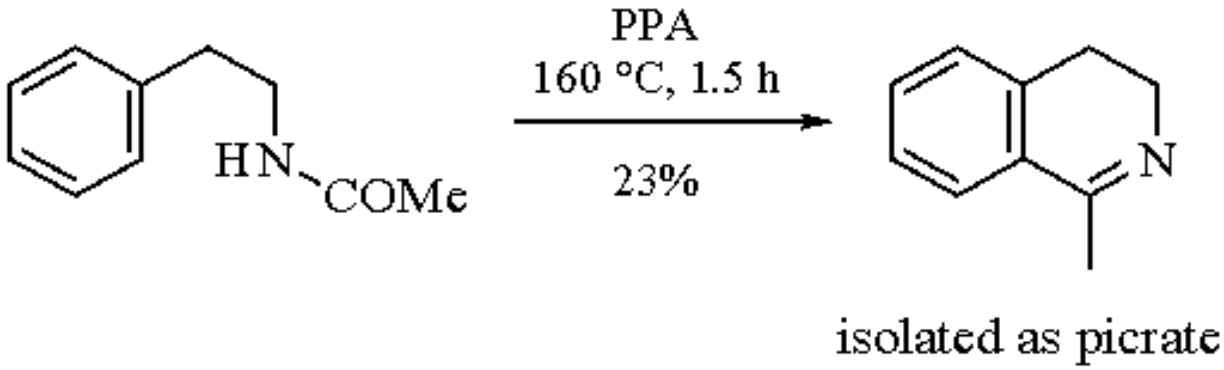

(19)

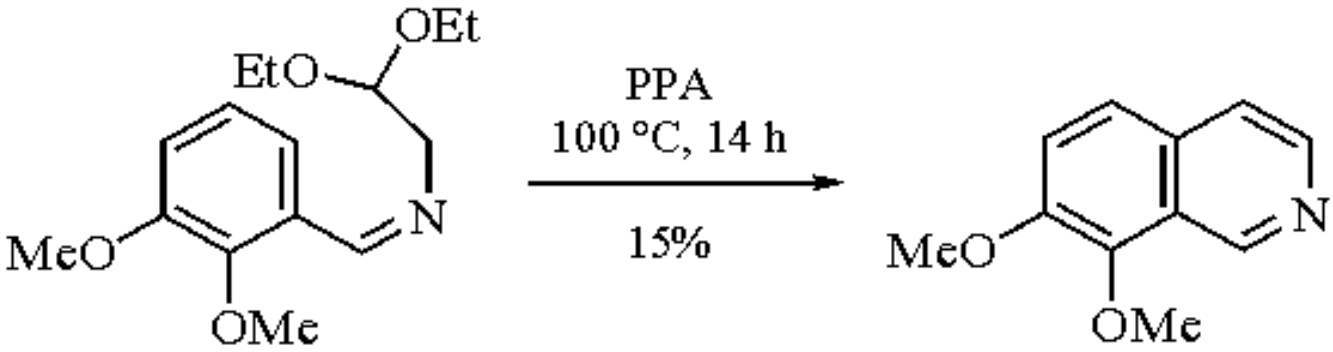

(20)

The quinoline carbon framework can be assembled by ring closure of an aromatic acid to give a keto quinoline (eq 21).[26] Using PPA as catalyst, phenylquinolinones can be prepared from 3-aryl-3-hydroxypropionanilides (eq 22),[27] or from amido ketones (eq 23).[28]

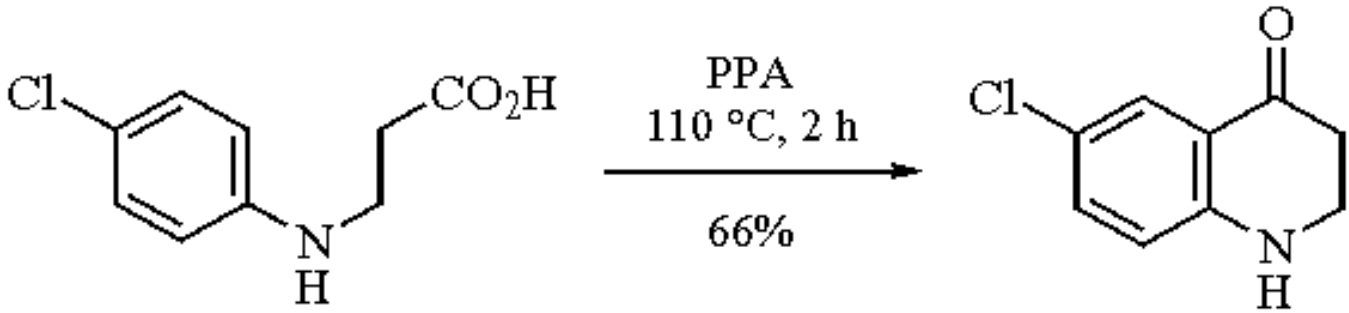

(21)

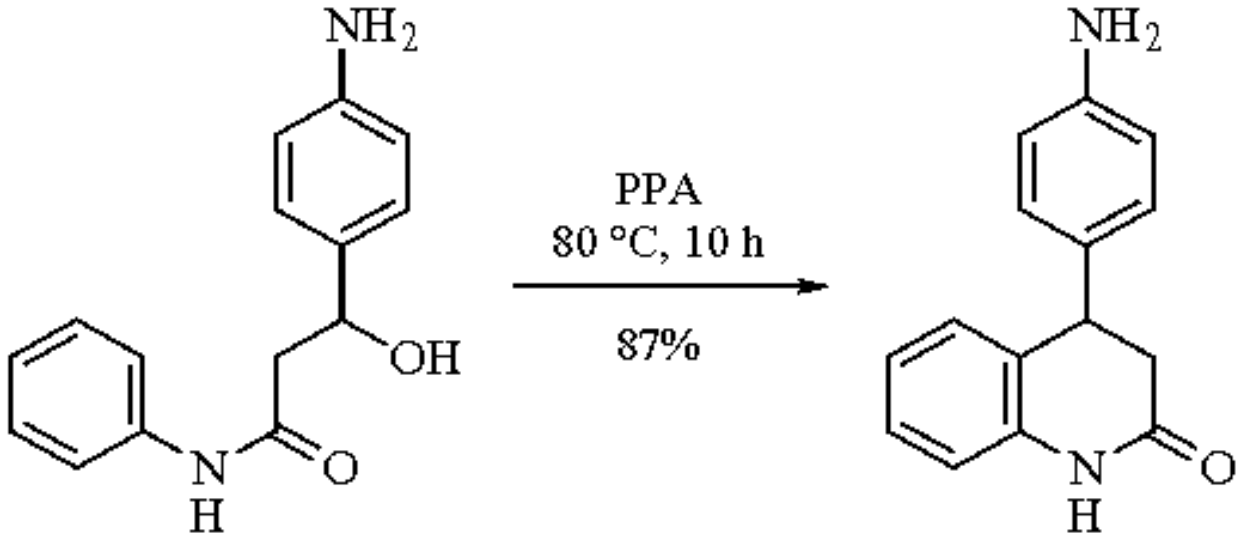

(22)

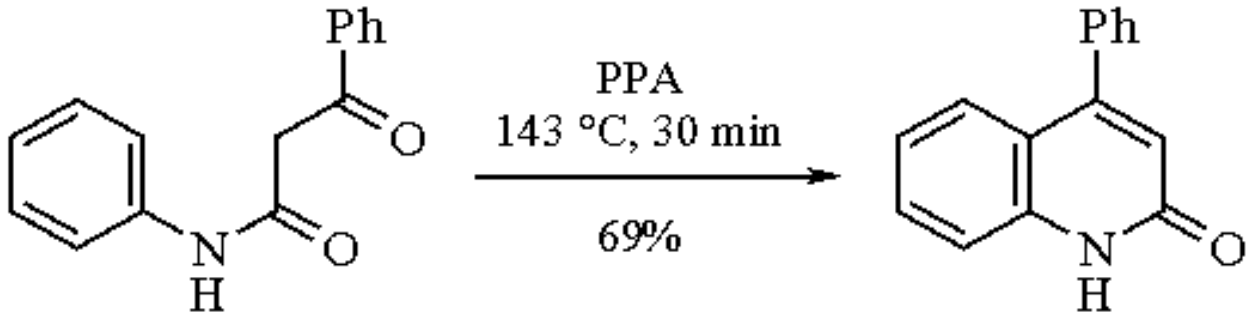

(23)

When attempting to effect a Beckmann rearrangement it was found that the oxime of a hexahydrobenzindolizine did not give the expected amide but instead dehydrated. This was followed by ring opening then ring closure to give a dihydrobenzonaphthyridinone (eq 24). When the hexahydrobenzindolizine itself was treated with PPA the compound simply dehydrated without rearrangement to give the dihydrobenzindolizone (eq 25). Sulfuric acid completely failed to effect this dehydration and Eaton's reagent was reported to give lower yields of product.[29]

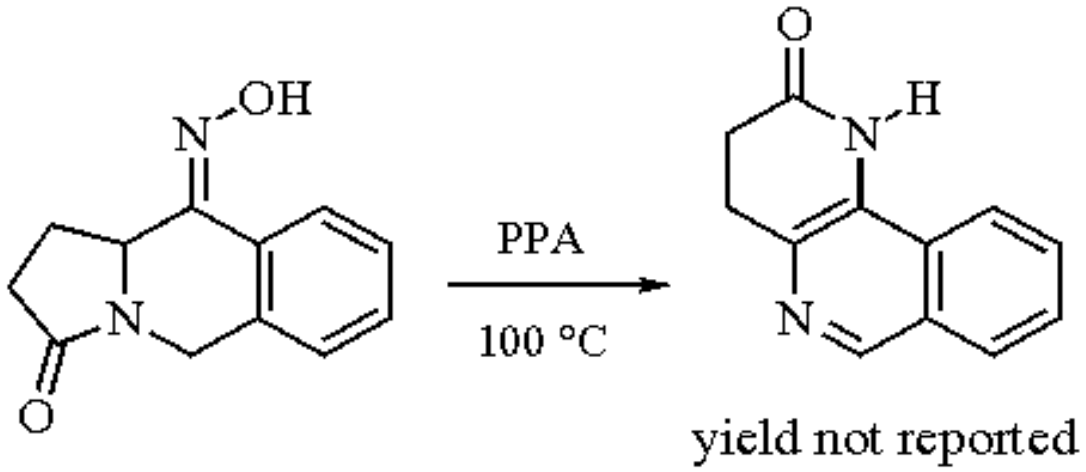

(24)

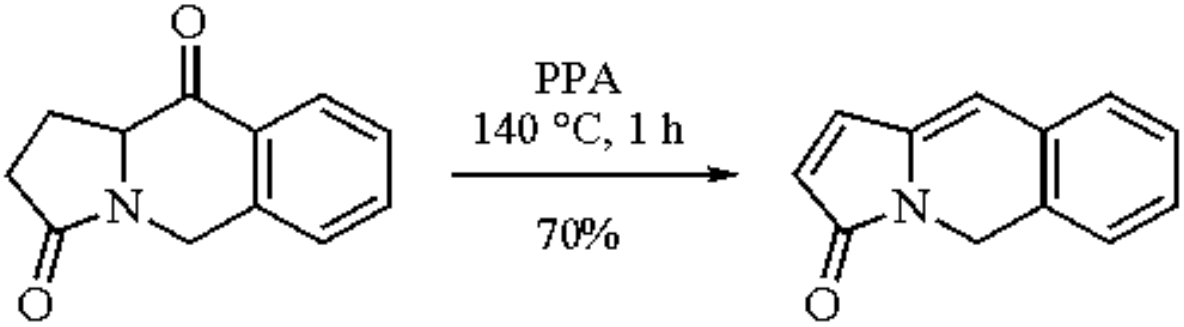

(25)

Alkyl- or chloro-substituted isatins were obtained more conveniently with PPA than with sulfuric acid (eq 26).[30] Synthesis of the bacterial coenzyme methoxatin was facilitated by use of PPA to synthesize the pivotal isatin intermediate (eq 27).[31]

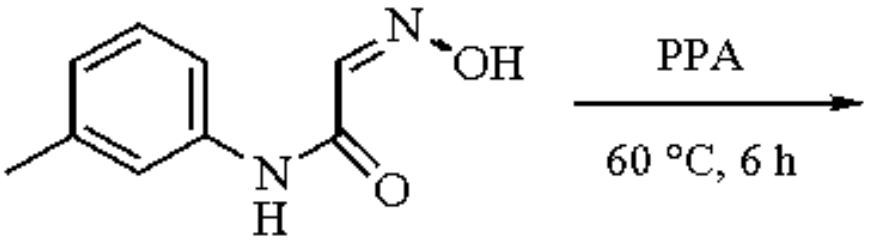

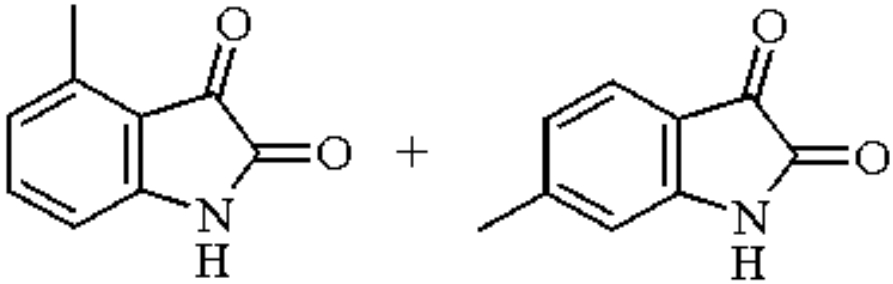

26% 43%

(26)

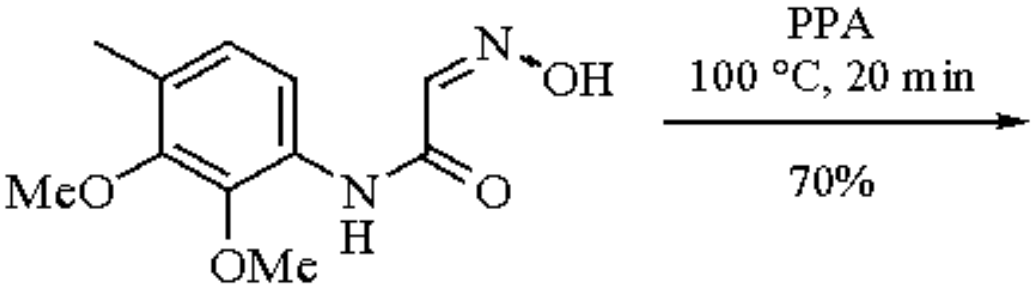

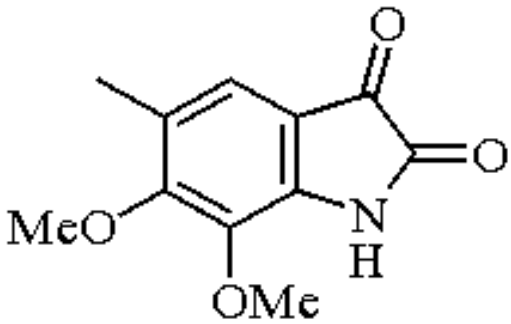

(27)

Complex lactams were stereoselectively assembled in a beautifully simple reaction between 3-alkenamides and benzaldehyde (eq 28).[32] Oxazolinones can be made utilizing the Erlenmeyer azlactone synthesis. Use of PPA cleanly affords the (*E*) isomer whereas other methods provide only the (*Z*) isomers or mixtures of (*E*) and (*Z*) isomers (eq 29).[33] Other nitrogen-containing heterocyclic systems which can be obtained using PPA include benzimidazoles (eq 30)[34] and triazoles (eq 31).[35]

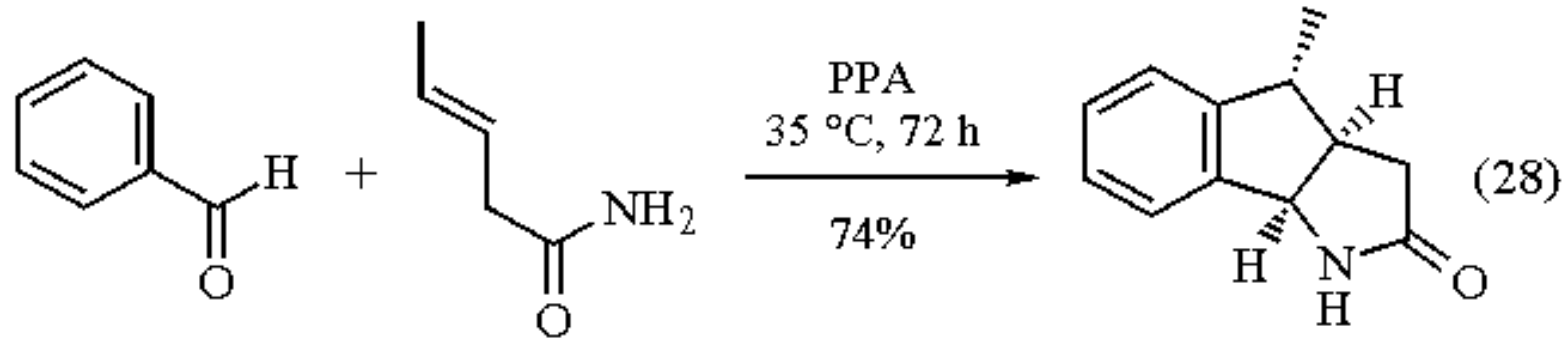

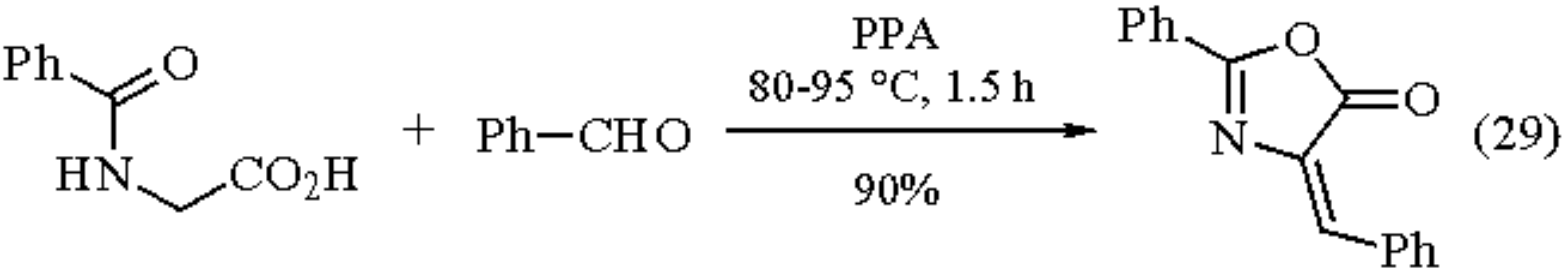

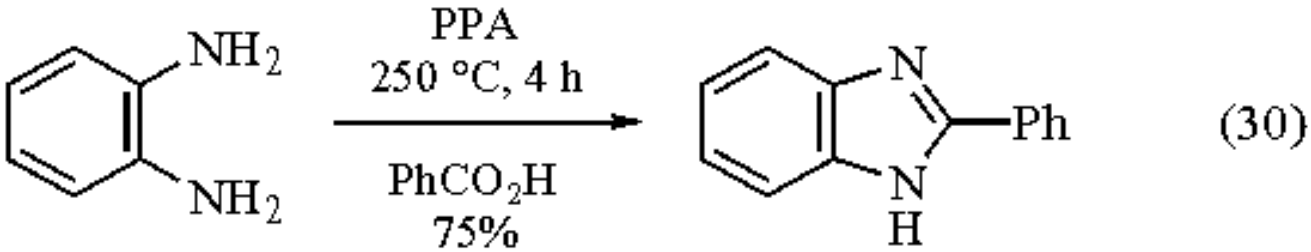

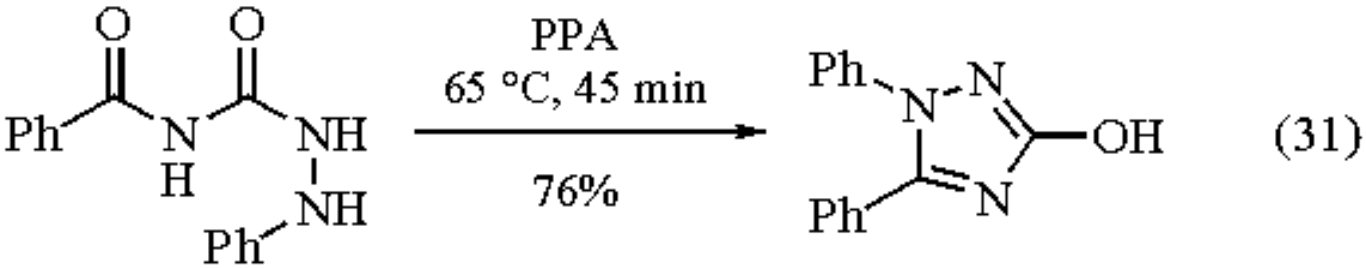

Oxygen and Sulfur Heterocycles.

Diphenylfurans are formed in higher yields with PPA than with sulfuric acid, ***Acetic Anhydride***, or phosphorus pentoxide as the dehydrating/cyclization agent (eq 32).[36] Similar to cyclization of aromatic acids to form aromatic cyclic ketones, the replacement of the benzylic methylene group with an oxygen affords chromanones in good yield (eq 33).[37] The structurally related flavones can be prepared by an intramolecular 1,4-addition catalyzed by PPA (eq

34).[38] Seven-membered rings which contain oxygen, such as benzoxepinones, can be made in good yield from 4-phenoxybutyric acids (eq 35).[39] Benzofurans are formed in good yield by cyclization of α-phenoxy ketones (eq 36).[40] Thienopyrroles are obtained by ring closure of a pyrrolecarboxylic acid (eq 37).[41]

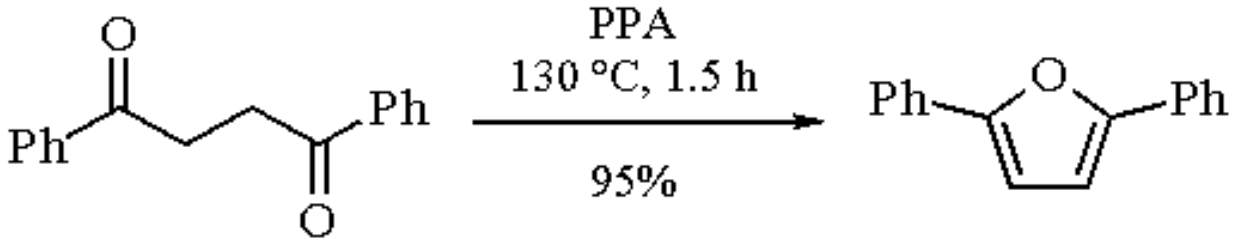

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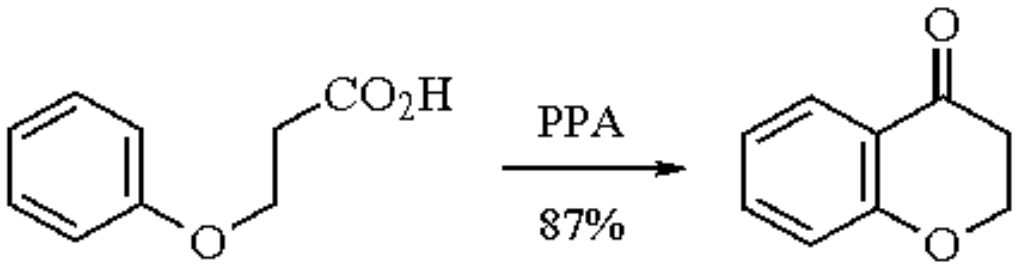

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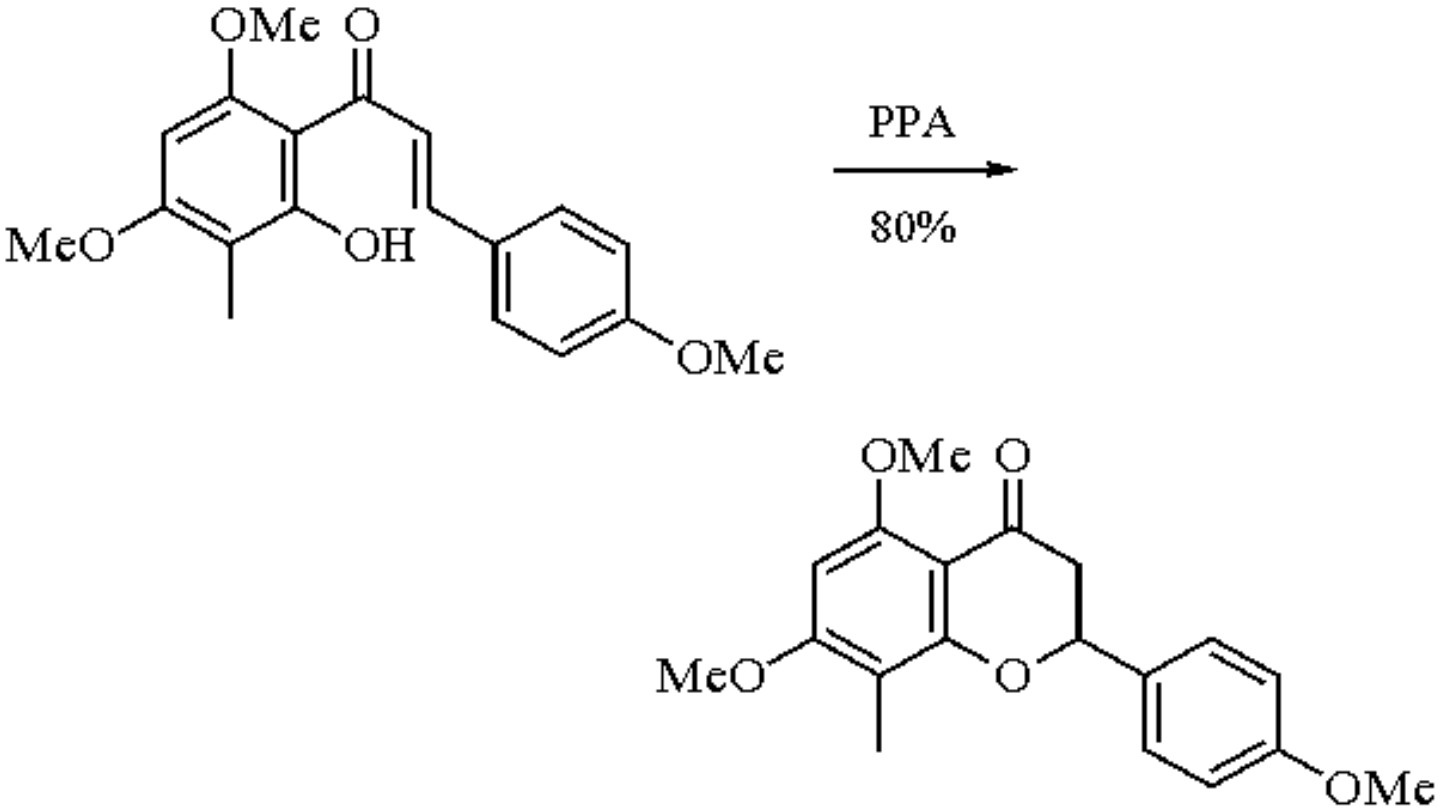

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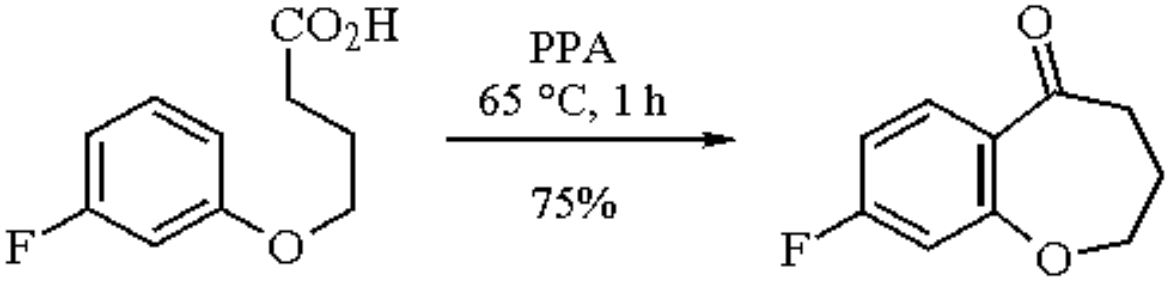

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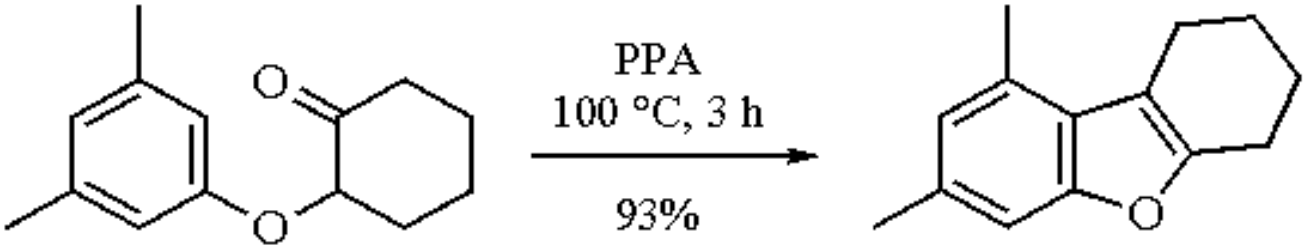

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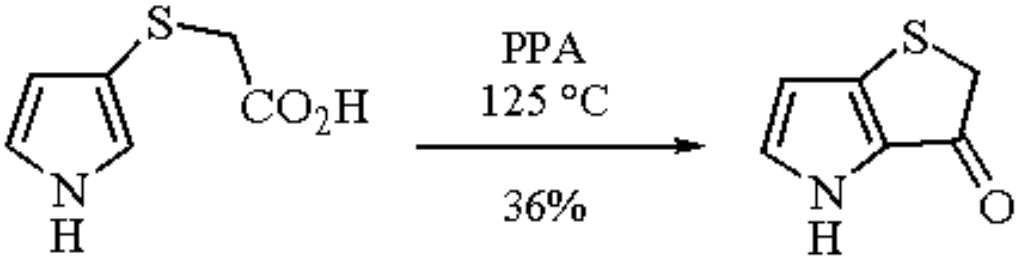

(37)

Rearrangements and Isomerizations.

The same characteristics which facilitate cyclizations, such as media with low nucleophilicity, good solvation power, relatively mild acidity, and low oxidation potential, are also conducive to clean, high-yielding acid-catalyzed rearrangements. PPA has been considered to be an effective reagent to carry out conversion of oximes into amides (Beckmann rearrangement) (eq 38).[42] Rearrangement of a decalin oxime could be carried out with ***p-Toluenesulfonyl Chloride*/*Pyridine*** to maintain the original *cis*-decalin stereochemistry or PPA could be used to allow formation of the *trans*-decalin system through an alternative mechanism (eq 39).[43]

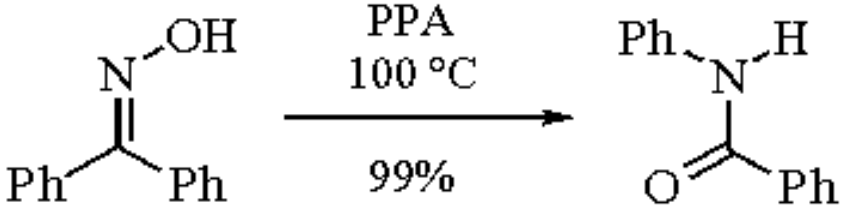

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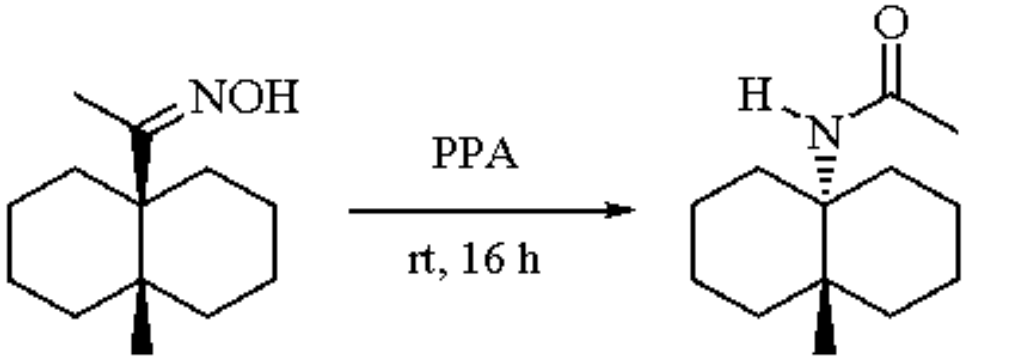

(39)

yield not specified

Treatment of aromatic carboxylic acids with ***Nitromethane*** and PPA (Lossen rearrangement) gives high yields of anilines (eq 40).[44] Although PPA can be used to catalyze the reaction of ***Hydrazoic Acid*** with carboxylic acids, ketones, and aldehydes (Schmidt rearrangement), sulfuric acid is usually the reagent of choice. One example of PPA being equivalent to sulfuric acid in the Schmidt rearrangement is when it is applied to acetophenone (eq 41).[45]

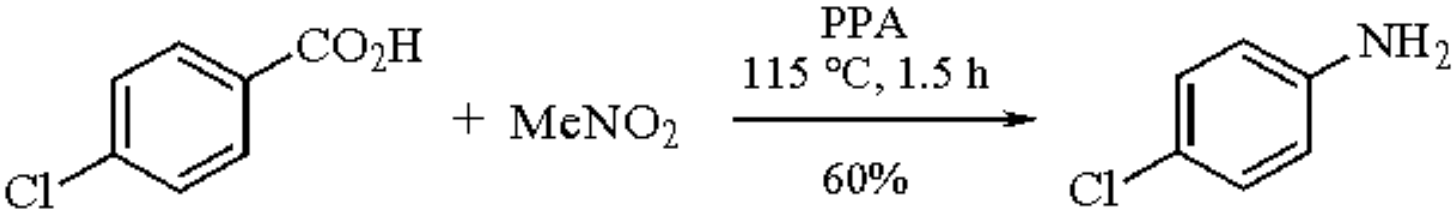

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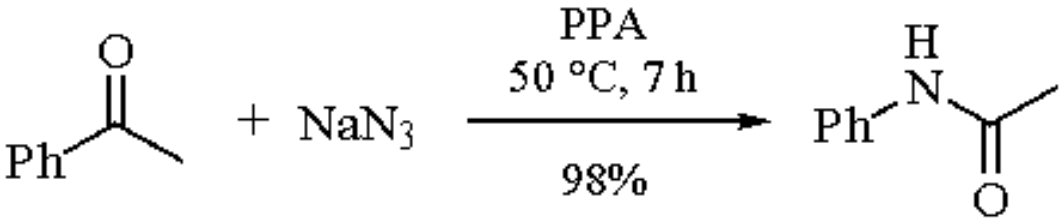

(41)

Wagner-Meerwein rearrangements and, more generally, carbonium ion-mediated carbon skeleton rearrangements can be effected with PPA. Lewis acids are generally preferred due to the ease of use and workup. An example of a high yield PPA induced Wagner-Meerwein rearrangement is formation of the phenanthrene skeleton from substituted fluorenes (eq 42).[46] Ring contraction was found to occur when a thiochromene was treated with PPA (eq 43).[47]

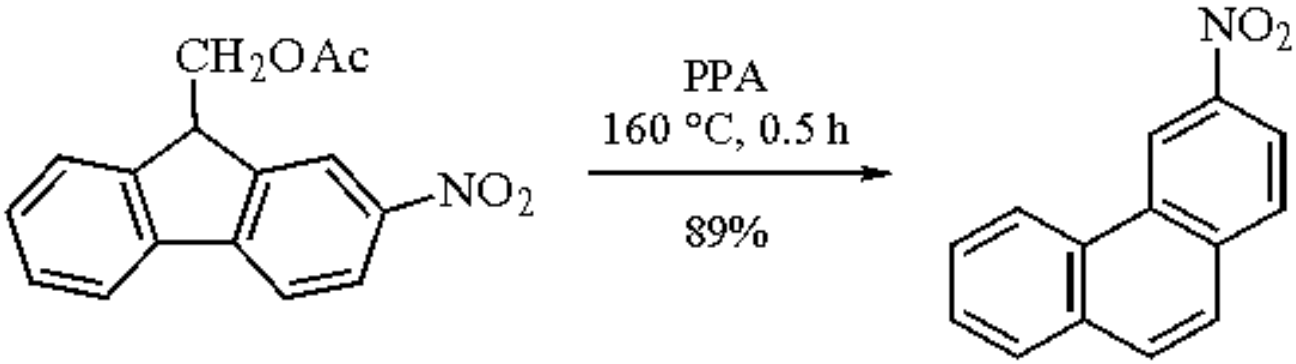

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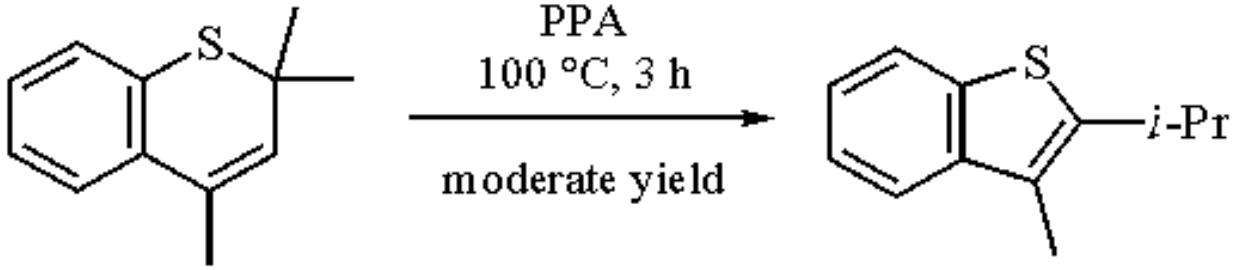

(43)

Acid-catalyzed isomerizations which can be affected with PPA include conversion of *trans*-cinnamic acid to *cis*-cinnamic acid (eq 44), *trans,trans*-diene conversion to *trans,cis*-dienes (eq 45),[48] and azlactone isomerizations (eq 46).[33]

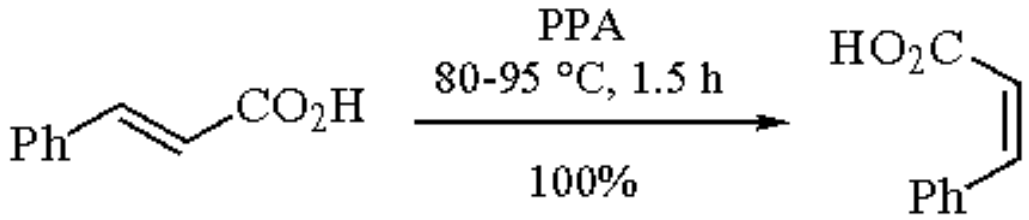

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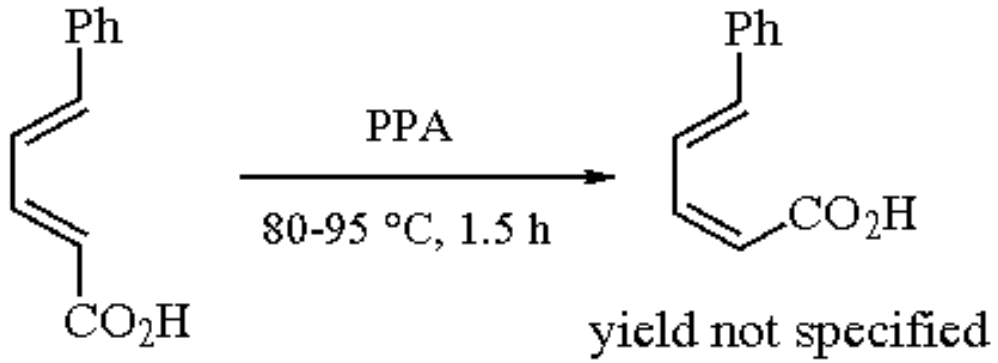

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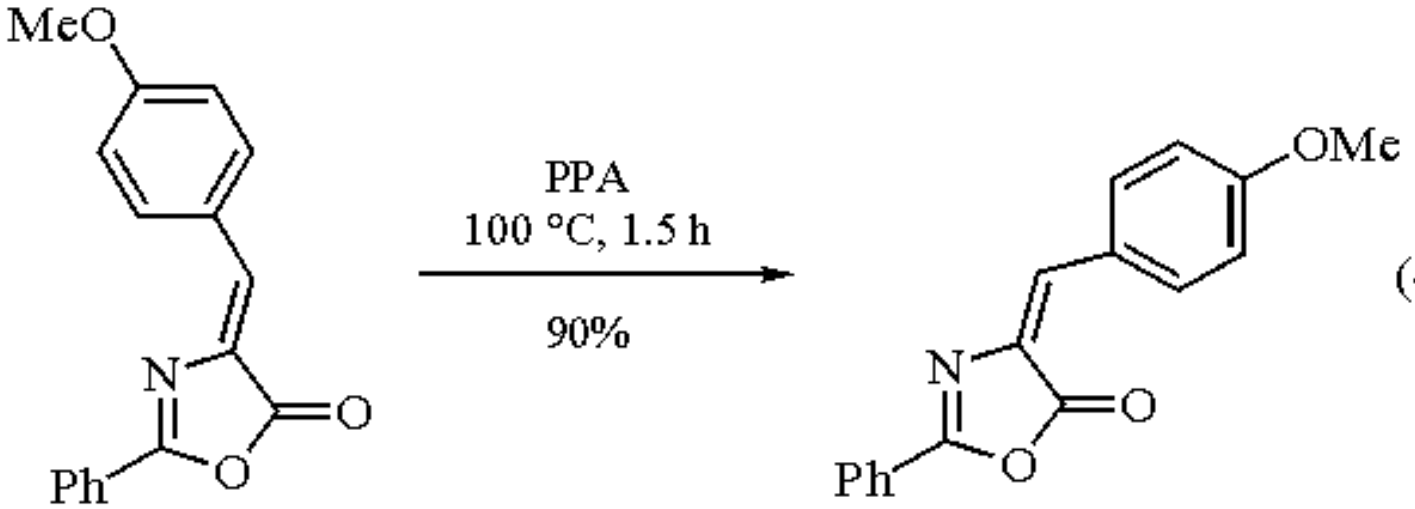

(46)

Intermolecular Reactions.

PPA is generally used as an intramolecular catalyst but has demonstrated limited utility for intermolecular alkylations.

Due to the elevated temperatures necessary to achieve catalysis (and reduce PPA viscosity), most reactions give mixtures of products favoring multiple substitution. Consequently, most Friedel-Crafts alkylations are carried out with ***Aluminum Chloride*** or another Lewis acid which can be more readily controlled. In the case of activated aromatics, such as phenol, alkylation can proceed under moderate conditions (eq 47).[49]

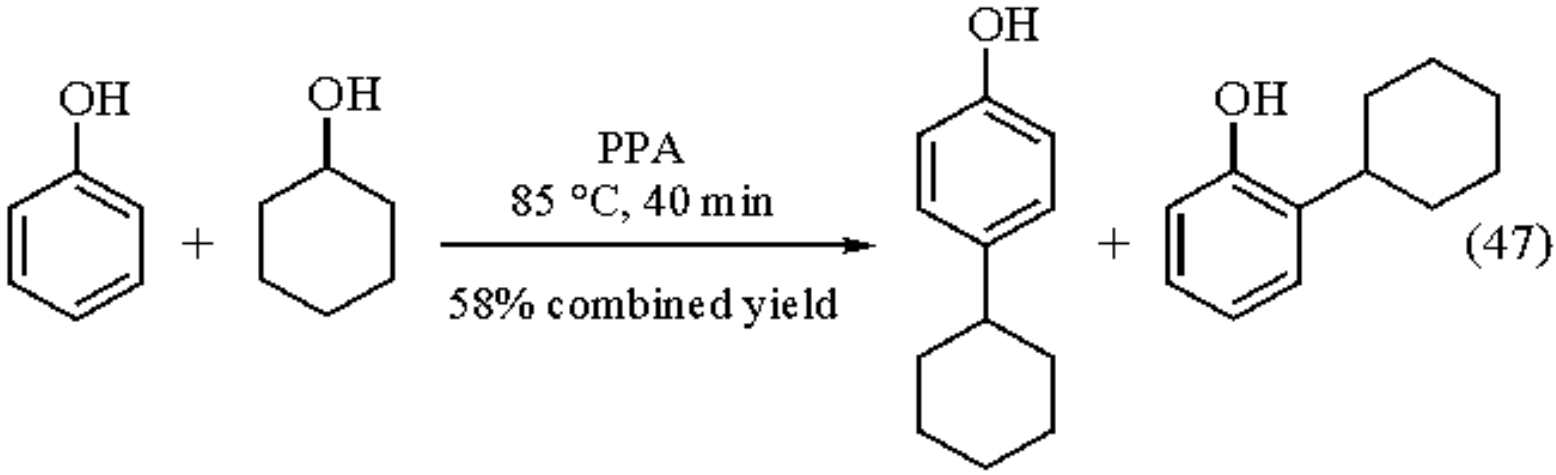

Acylations with PPA are much more prevalent. In the seven years between the first popularized use of PPA in 1950[23] and the Popp and McEwen review,[1b] over 200 intermolecular acylations were reported. One of the first acylations was the reaction between cyclohexene and ***Acetic Acid*** (eq 48).[50] Acylation of activated aromatics proceeds in high yield (eq 49).[51] Acylation of phenols is problematic due to competing ester formation (eq 50).[52]

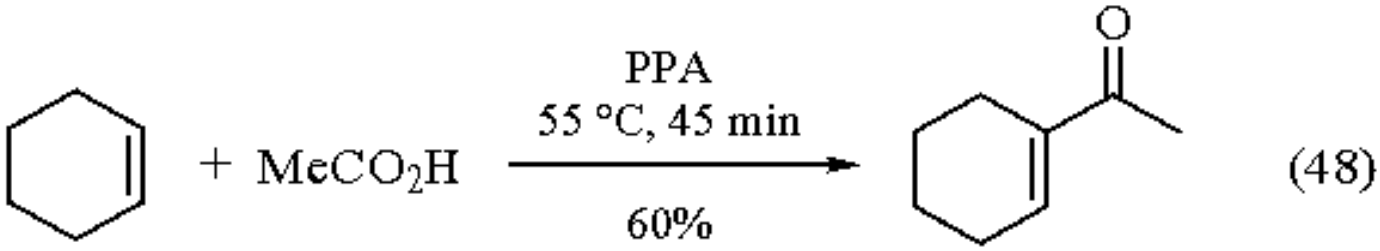

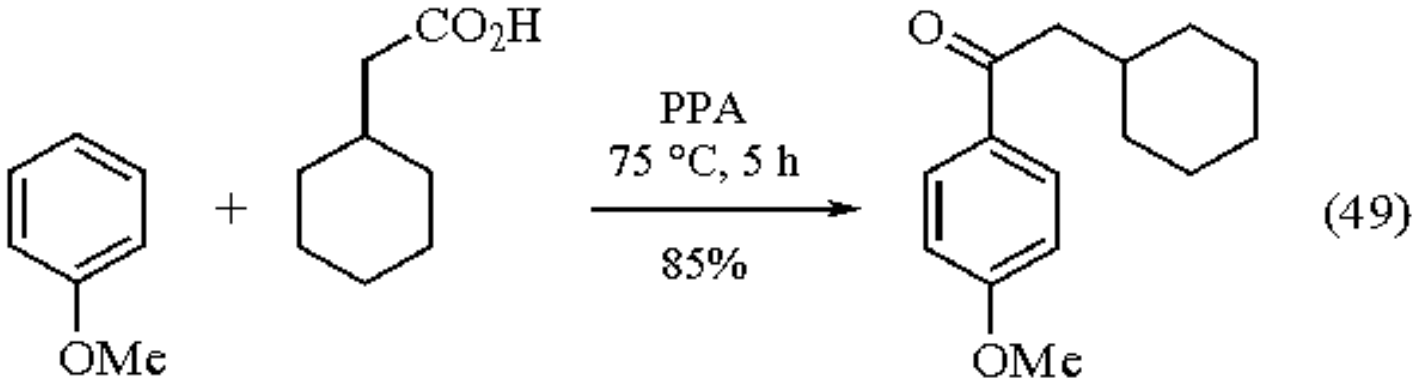

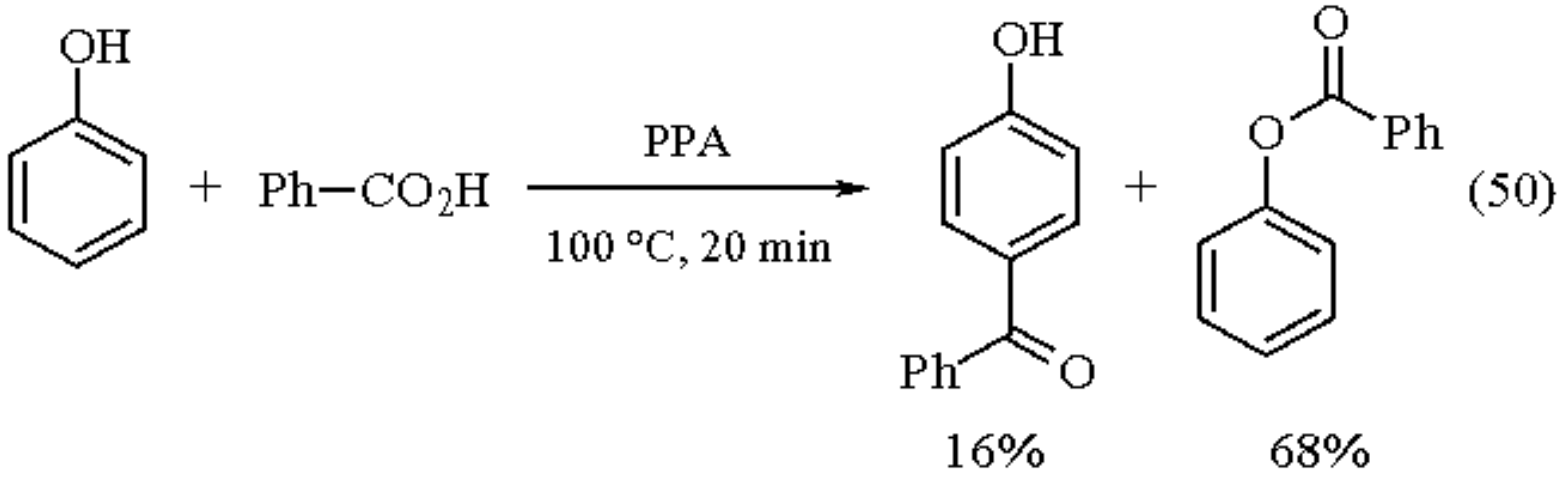

Miscellaneous Uses of Polyphosphoric Acid.

Nitrile hydrolysis to amides is commonly carried out using PPA. At 100-110 °C, nitriles are routinely converted to amides (eq 51).[53]

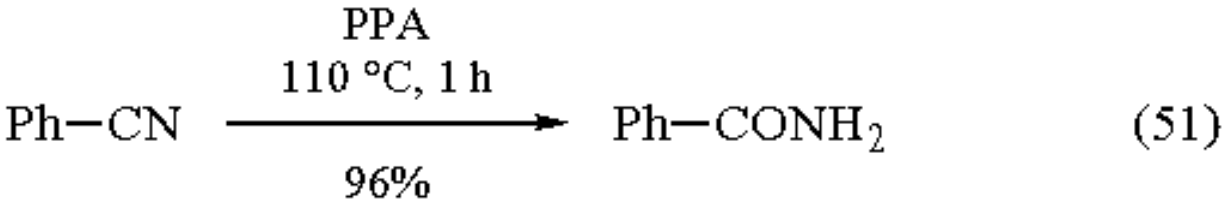

When the temperature is raised to 200 °C, decyanation of aromatic nitriles often results.[54] Reagents with unique abilities have been developed by mixing PPA with other agents. The reduced acidity of PPA compared to other mineral acids proved beneficial when a PPA/***Ethanethiol*** mixture was used to open one epoxide selectively in a bis-epoxy steroid (eq 52).[55] PPA/$POCl_3$ affords a medium which is used to convert tertiary alcohols into chlorides (eq 53).[56]

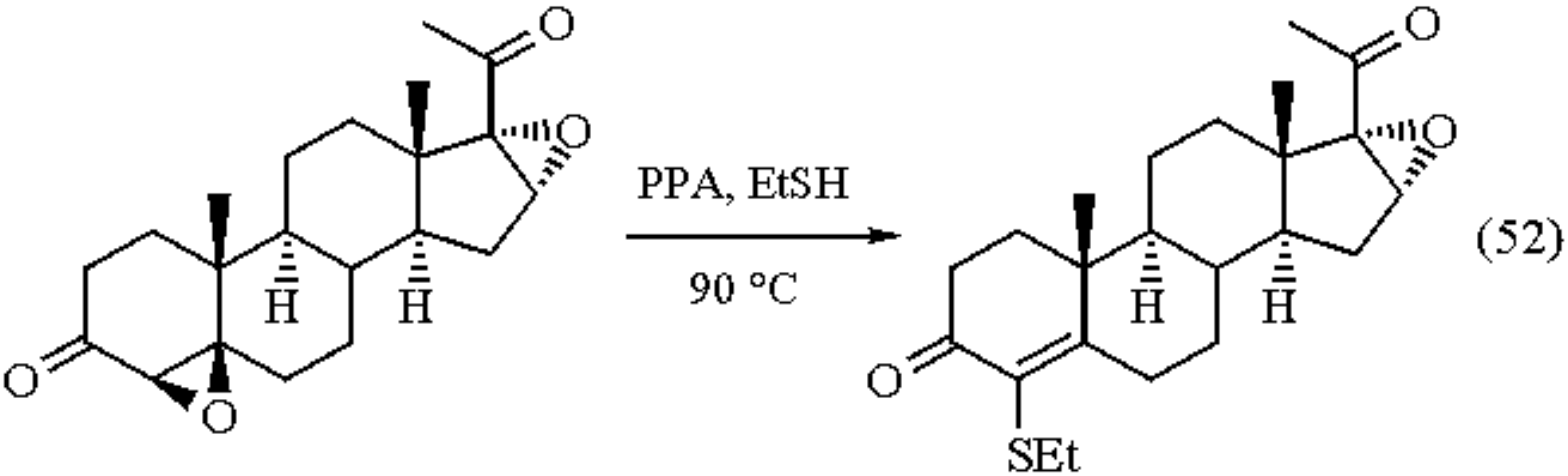

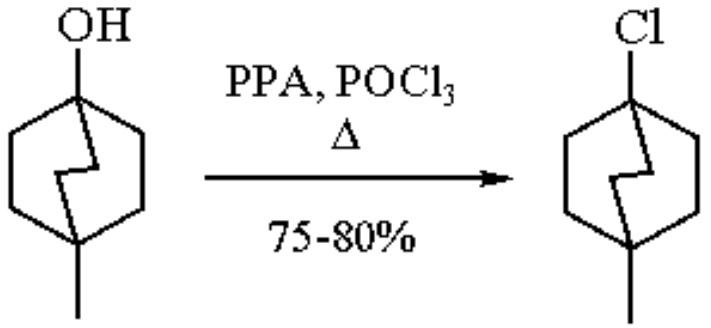

(53)

In an attempt to generate HCl in situ during cyclization of a tetraamine, a PPA/NaCl mixture was superior to PPA alone (eq 54).[57] PPA/***Acetic Acid*** was used to synthesize nonenolizable β-diketones (eq 55).[58] Although Wagner-Meerwein rearrangements predominate when primary carbonium ions are formed with PPA, a mixture of PPA/***Potassium Iodide*** allowed conversion of a primary methyl ether to a primary alkyl iodide in high yield (eq 56).[59] It has been reported that nitrations carried out using PPA/***Nitric Acid*** are less hazardous than Ac_2O/HNO_3 mixtures (eq 57).[60]

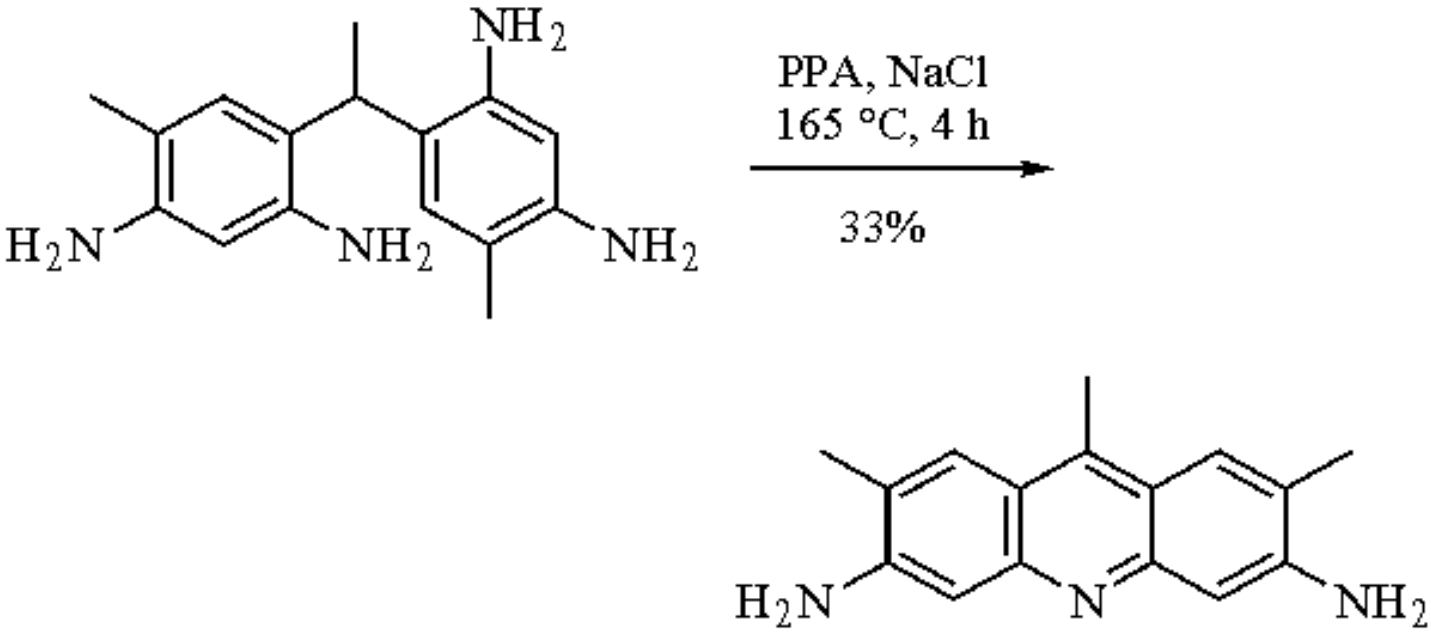

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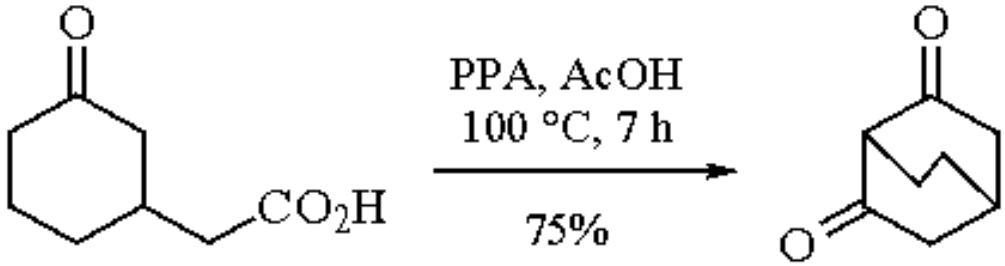

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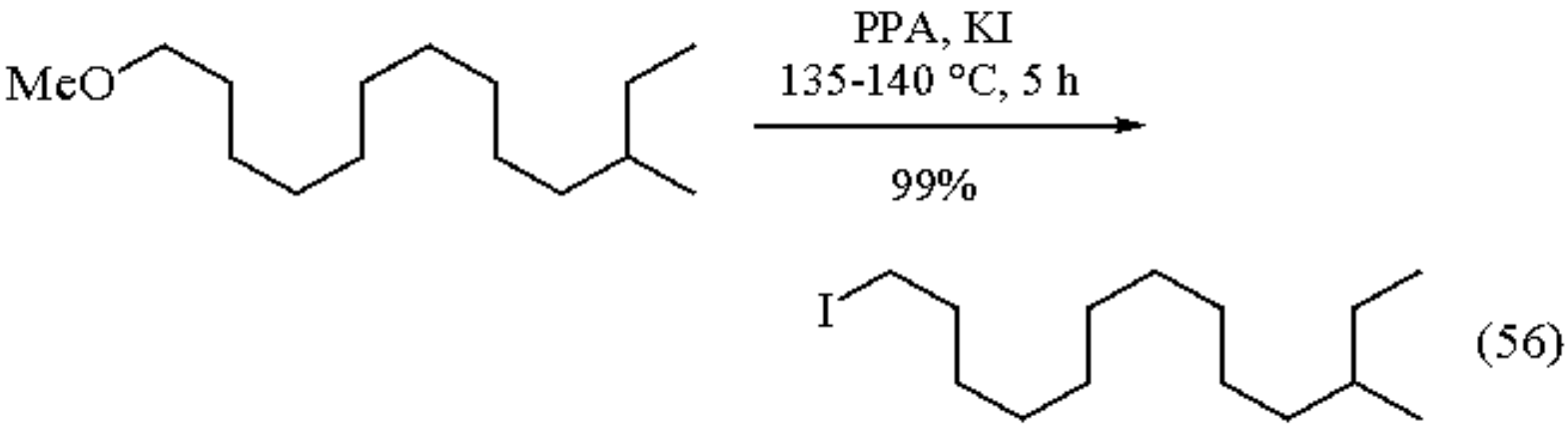

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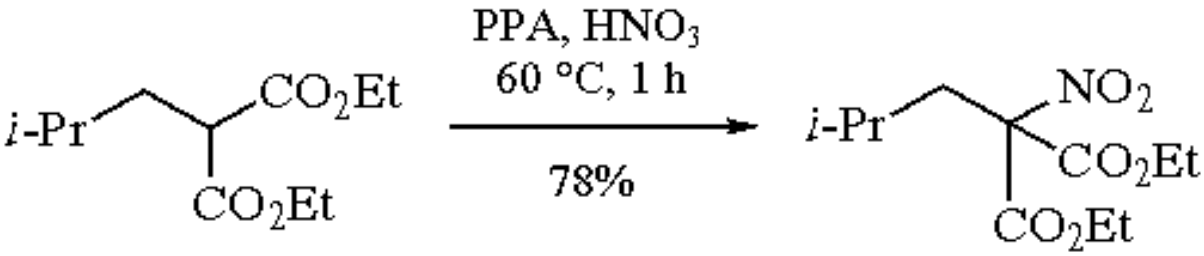

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John H. Dodd

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Poly(4-vinylpyridine)[1]

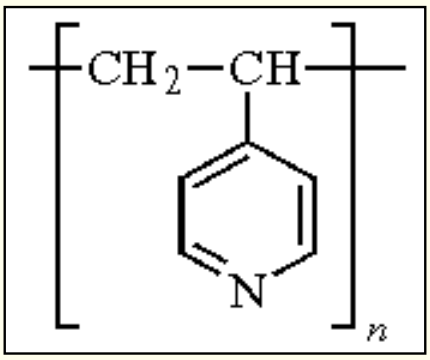

[9017-40-7] · $(C_7H_7N)_n$ · Poly(4-vinylpyridine) · (MW)*n*(105.15) (.HCl)

[29323-87-3] · $(C_7H_8ClN)_n$ · Poly(4-vinylpyridine hydrochloride) · (MW)*n*(141.60)

(pyridine functional group in easily regeneratable solid form;[1] acid scavenger;[2] basic catalyst for Knoevenagel reactions;[2] acid salts are mild acid catalysts[3])

Alternate Names: P(4-VP); Reillex™.

Physical Data: Reillex 402: *d* 0.45 g cm^{-3}. Reillex 425: *d* 0.29 g cm^{-3}.

Solubility: insol all solvents; polymer swells when added to aqueous and nonaqueous solvents.

Form Supplied in: Reillex 402: 60 mesh, off-white granular powder. Reillex 425: 18-50 mesh, off-white beads. *Drying:* water may be removed from the polymer with toluene or other solvents that form water azeotropes.

Analysis of Reagent Purity: aqueous titration with acid; Reillex 402 has 8.8 mequiv/g H^+ capacity and Reillex 425 has 5.5 mequiv/g H^+ capacity.

Handling, Storage, and Precautions: extremely stable polymer best stored in tightly closed containers; after use the free base form of the polymer can be regenerated for further use by treatment with aqueous NaOH.

Acid Scavenger and Basic Catalyst.

Poly(4-vinylpyridine) is a polymeric reagent that replaces liquid ***Pyridine*** as acid acceptor in aqueous and nonaqueous media for reactions that produce acids as a byproduct.[2] ***Hydrogen Chloride*** generated during esterification using acyl

halides (eq 1),[4] from silylation of a primary alcohol with diphenyl-*t*-butylchlorosilane (DPBSiCl) (eq 2),[5] and mixed acid anhydride preparation from acyl halides and acids were trapped on the polymer (eq 3).[6] Since the polymer is a solid, filtering it from the reaction mixture simplifies workup. After recovery, the polymer can be regenerated and used in further reactions.

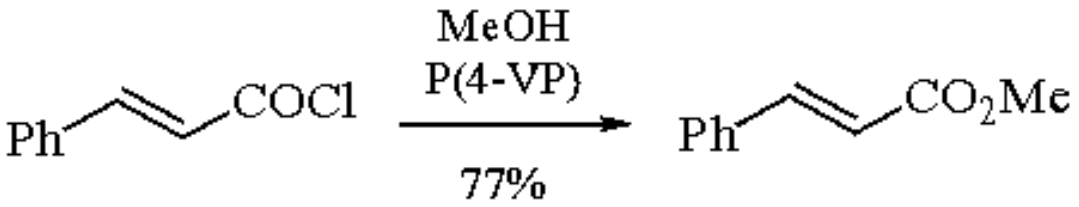

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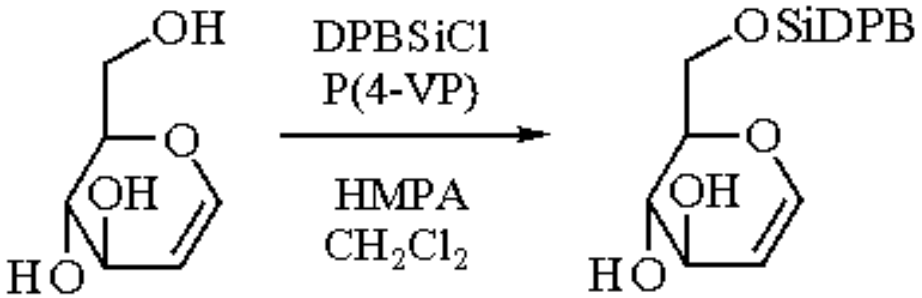

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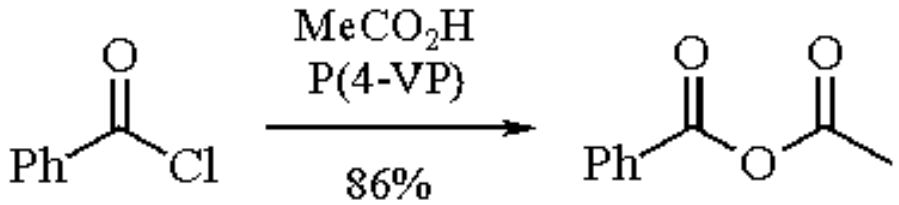

(3)

In a recent method for the synthesis of azulenes, P(4-VP) was uniquely effective as an ***Tetrafluoroboric Acid*** scavenger that does not react with the tropylium tetrafluoroborate reagent or the carbocationic intermediates involved in the [3 + 2] annulation (eq 4).[7] In the absence of this scavenger, protodesilylation of the allenylsilane starting material is observed.

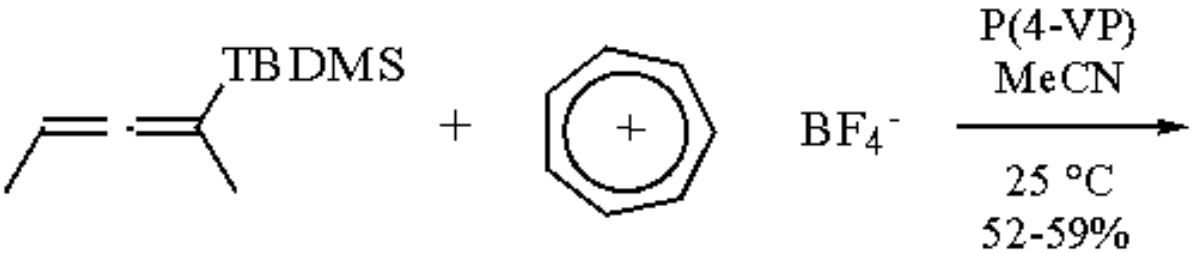

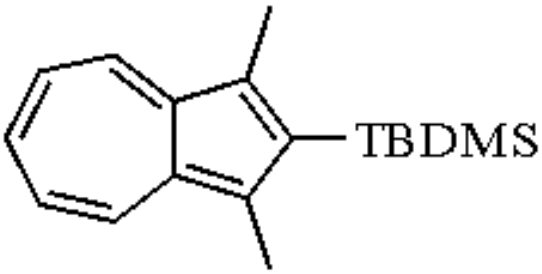

(4)

In the synthesis of hydroxylamines, the polymer has also been used to trap benzoic acid in the oxidation of secondary amines with ***Dibenzoyl Peroxide*** (eq 5).[8]

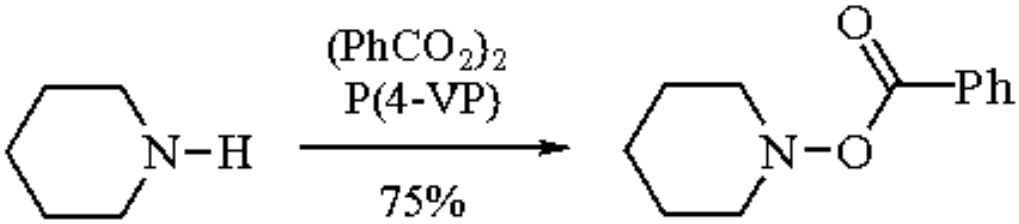

(5)

Poly(4-vinylpyridine) also functions as a basic catalyst in Knoevenagel reactions (eq 6).[2]

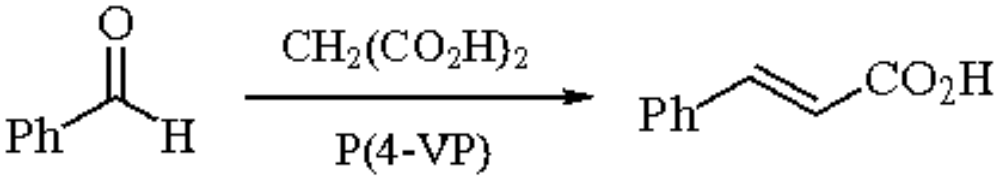

(6)

Mild Acid Catalyst.

The hydrochloride salt of poly(4-vinylpyridine) is a polymeric reagent that acts as a mild acid catalyst in the preparation of acetals and carboxylic acid esters (eq 7)[3] and in the preparation of tetrahydropyranyl derivatives of alcohols and phenols (eq 8).[9]

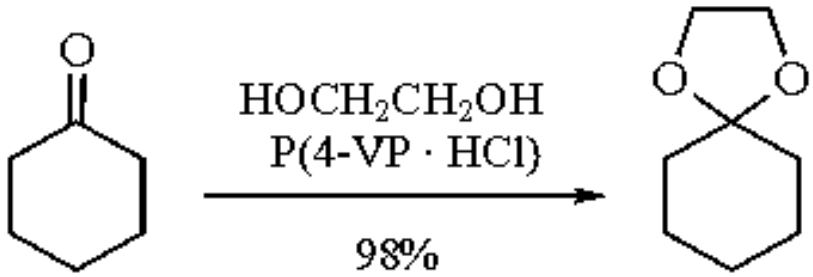

(7)

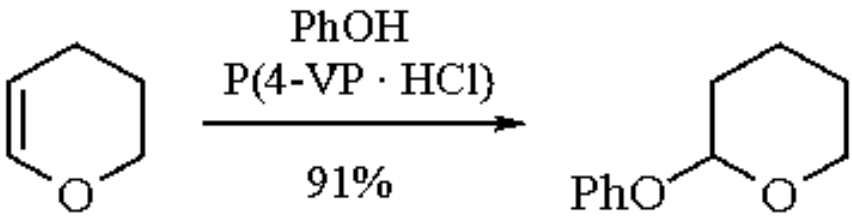

(8)

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1. (a) Goe, G. L.; Marston, C. R.; Scriven, E. F. V.; Sowers, E. E. In *Catalysis of Organic Reactions*; Blackburn, D. W., Ed.; Dekker: New York, 1990; pp 275-286. (b) Fréchet, J. M. J.; de Meftahi, M. V. *Br. Polym. J.* **1984**, *16*, 193.
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9. Johnston, R. D.; Marston, C. R.; Krieger, P. E.; Goe, G. L. *S* **1988**, 393.

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Poly(4-vinylpyridinium bromide perbromide)[1]

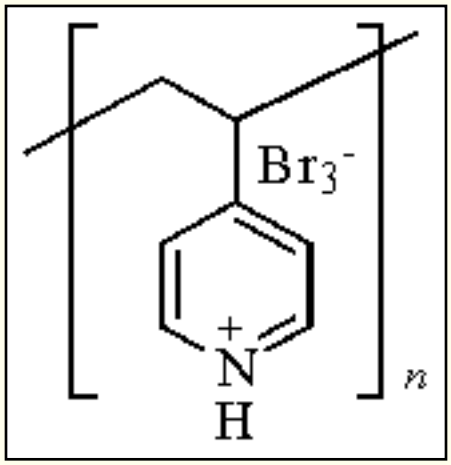

[91650-35-0] · $(C_7H_8Br_3N)_n$ · Poly(4-vinylpyridinium bromide perbromide) · (MW)*n*(345.86)

(polymeric reagent used in the bromination of alkenes and ketones[2])

Alternate Name: P(4-VPBPB).

Solubility: insol all solvents; polymer swells when added to aqueous and nonaqueous solvents.

Form Supplied in: orange solid granules with ~4 mequiv Br_3^-/g resin.

Handling, Storage, and Precautions: store in a tightly closed container in a cool dry place; handle in a fume hood.

Bromination of Alkenes and Ketones.

Poly(4-vinylpyridinium bromide perbromide) can replace free ***Bromine*** in bromination of alkenes (eq 1) and ketones (eq 2).[2] This reagent is stable in storage and is safer to use than liquid bromine. Product isolation is simplified since the polymer can be removed from the reaction mixture by filtration. After

use, the reagent may be regenerated by addition of bromine or it can be converted to ***Poly(4-vinylpyridine)*** by treatment with aqueous ***Sodium Hydroxide***.[2] A variation of this reagent is the poly(4-vinylpyridine bromine complex) which brominates alkenes and alkynes[3] and effects side chain allylic bromination of alkyl-substituted aromatic molecules.[4]

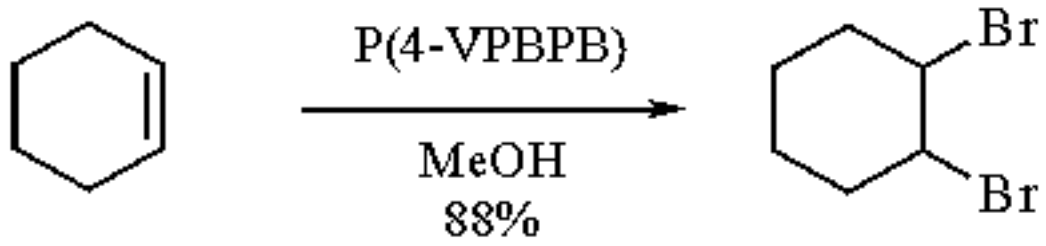

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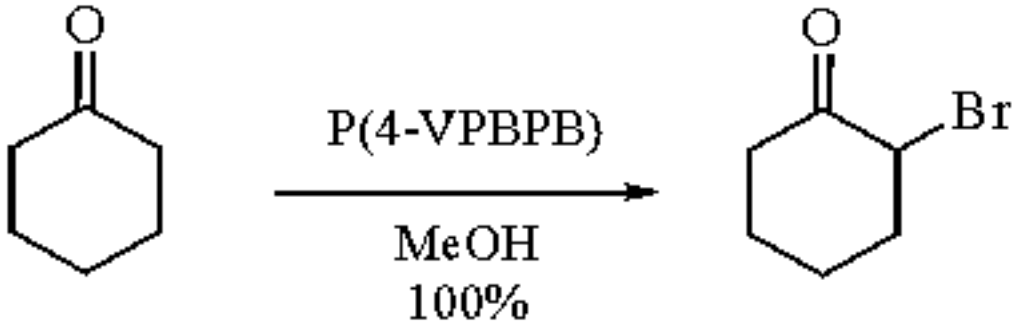

(2)

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1. (a) Goe, G. L.; Marston, C. R.; Scriven, E. F. V.; Sowers, E. E. In *Catalysis of Organic Reactions*; Blackburn, D. W., Ed.; Dekker: New York, 1990; pp 275-286. (b) Fréchet, J. M. J.; de Meftahi, M. V. *Br. Polym. J.* **1984**, *16*, 193.
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Poly(4-vinylpyridinium dichromate)[1]

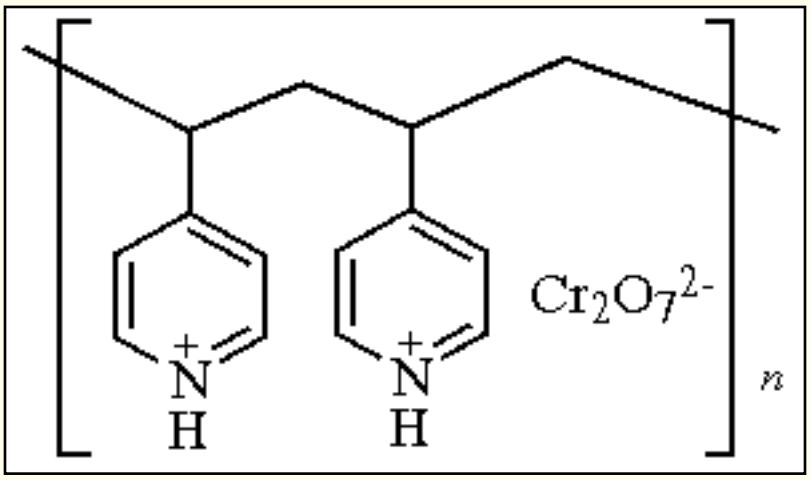

[82246-45-5] · $(C_{14}H_{16}Cr_2N_2O_7)_n$ · Poly(4-vinylpyridinium dichromate) · (MW)*n*(428.32)

(polymeric oxidizing agent used to convert alcohols to aldehydes and ketones[2])

Alternate Name: P(4-VPDC).

Physical Data: mp >300 °C.

Solubility: insol all solvents; polymer swells when added to aqueous and nonaqueous solvents.

Form Supplied in: brown powder.

Handling, Storage, and Precautions: store in a tightly closed container in a cool dry place.

Oxidation of Alcohols to Aldehydes and Ketones.

Poly(4-vinylpyridinium dichromate) is a solid polymeric reagent that readily oxidizes primary and secondary alcohols to aldehydes and ketones (eq 1).[2,3] The reagent works best when it is soaked in water, filtered, and used in a nonpolar solvent such as cyclohexane. All chromium ions in oxidized or reduced form are retained on the polymer. Product isolation is simplified since the polymer is removed from the reaction mixture by filtration. This reagent may be regenerated.[2,3] A variation of this polymeric reagent

is a silver dichromate-poly(4-vinylpyridine) complex that rapidly converts alcohols to the corresponding aldehyde or ketone.[4]

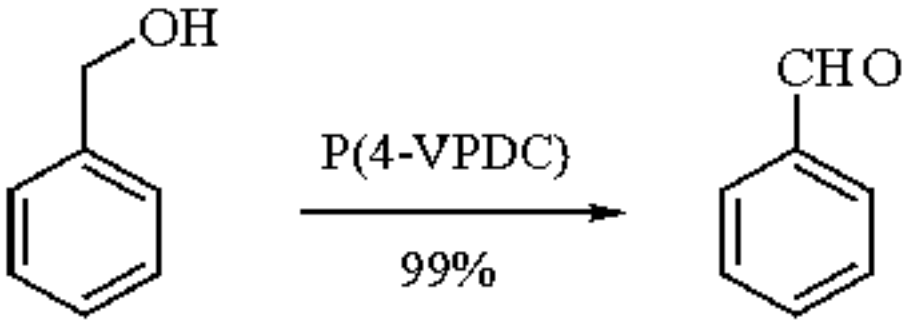

(1)

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1. (a) Goe, G. L.; Marston, C. R.; Scriven, E. F. V.; Sowers, E. E. In *Catalysis of Organic Reactions*; Blackburn, D. W., Ed.; Dekker: New York, 1990; pp 275-286. (b) Fréchet, J. M. J.; de Meftahi, M. V. *Br. Polym. J.* **1984**, *16*, 193.
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Potassium

[7440-09-7] · K · Potassium · (MW 39.10)

(reducing agent for aromatic rings,[1] carbonyl compounds,[2] and various functional groups,[3] including alcohols[4] in the presence of crown ethers; reagent for the preparation of Rieke's metals;[5] reacts with proton donors;[6] promotes $S_{RN}1$ arylation reactions;[7] modified reactivity occurs with deposition on alumina,[8] insertion in graphite,[9] or dispersion by ultrasound[10])

Physical Data: mp 64 °C; bp 760 °C; *d* 0.86 g cm^{-3}; soft silvery (fresh cut) metal.

Solubility: sol liquid ammonia, 1,2-ethylenediamine, aniline; slightly sol ethers.

Form Supplied in: widely available as ingots, sticks, under mineral oil, or in ampules; common impurities are other alkali metals, aluminum, calcium, boron, silicon.

Handling, Storage, and Precautions: reacts violently with water, oxygen, halogens. In air, potassium forms the yellow peroxide KO_2, which is dangerous in contact with organic compounds. Reacts with many solvents; inert in saturated and some aromatic hydrocarbons. For safe handling, see Fieser and Fieser.[6] Potassium fires should be treated with inert powders or sand.

Reduction of Aromatic Compounds.

[1] Birch- and Benkeser-type reductions of aromatic rings are achieved by potassium dissolved in liquid ***Ammonia*** or amines. However, potassium is used less often than ***Lithium*** or ***Sodium***. The reducing ability of potassium is illustrated by the total reduction of the B-ring of equilenin to estrone, which cannot be achieved with sodium (eq 1).[11]

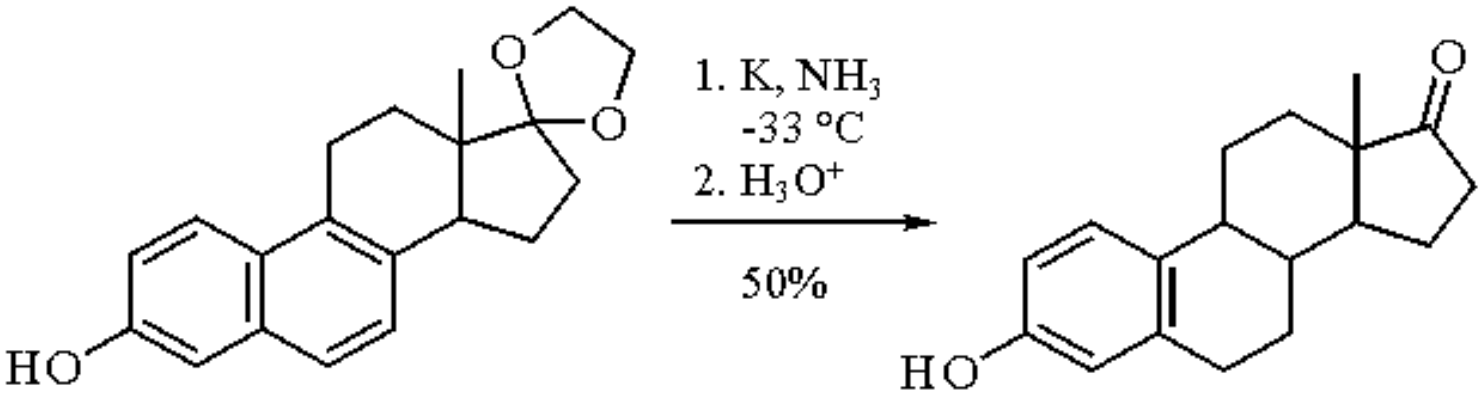

(1)

Proton donors are frequently used in potassium reductions. The accepted mechanism consists of a sequence of single-electron transfer (SET), a protonation, and a second SET. The anion thus formed can be trapped by an electrophile to give the reduction-alkylation product (eq 2).[12]

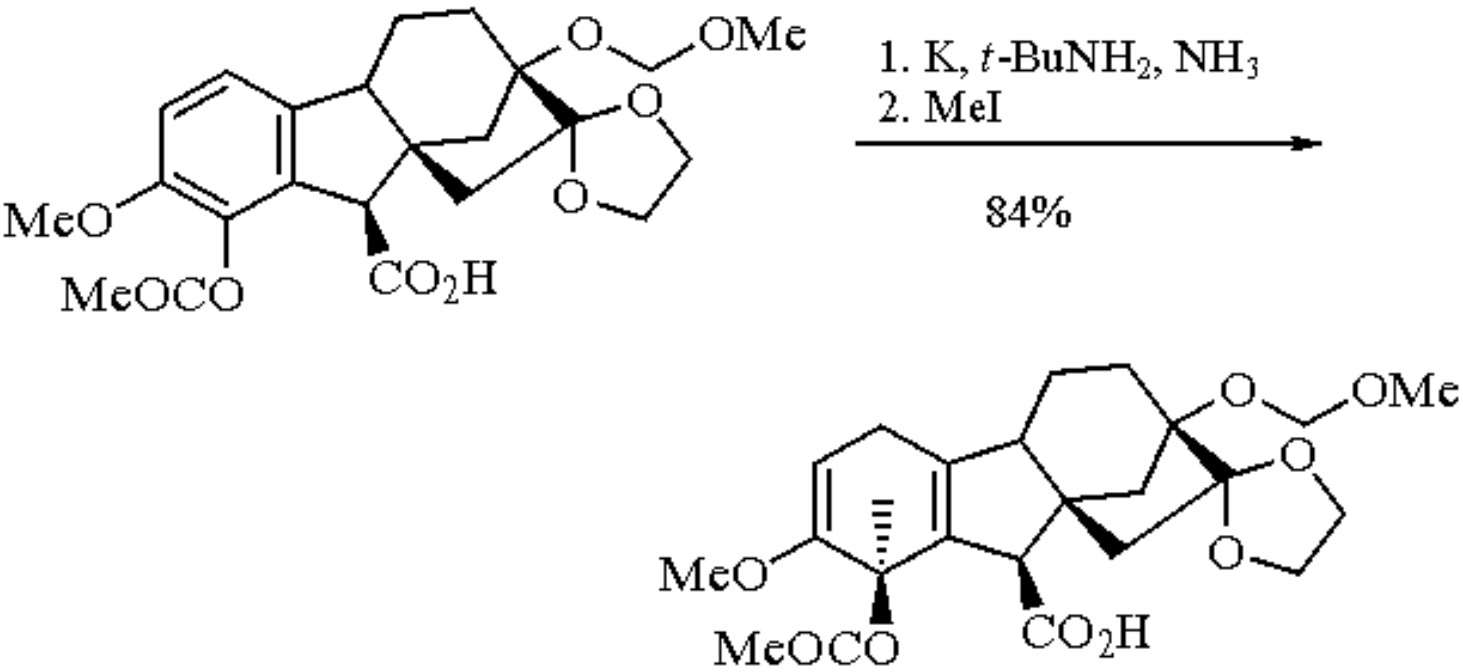

(2)

Reduction of Saturated and Unsaturated Carbonyl Groups.

Alkali metal reduction of ketones to alcohols in the presence or absence of proton donors has been studied in detail.[2] The use of potassium decreases the amount of pinacol coupling products,[13] and increases the reaction rate and yields of desired product.[14] The stereoselectivity, which depends on the structure of the intermediate ketyl radical anion, is frequently lower with K in comparison to lighter alkali metals. Recently, reductions with K have been conducted in THF under sonication with stereoselectivity similar to that of the usual method (eq 3).[15]

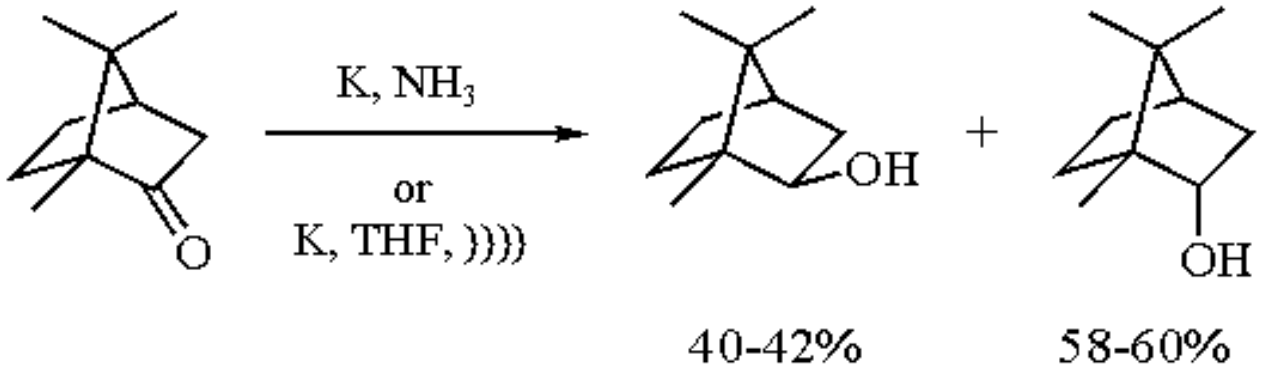

(3)

When an unsaturated functional group is closely positioned with respect to the carbonyl group, the ketyl radical anion adds to the multiple bond producing products of reductive cyclization (eq 4).[16]

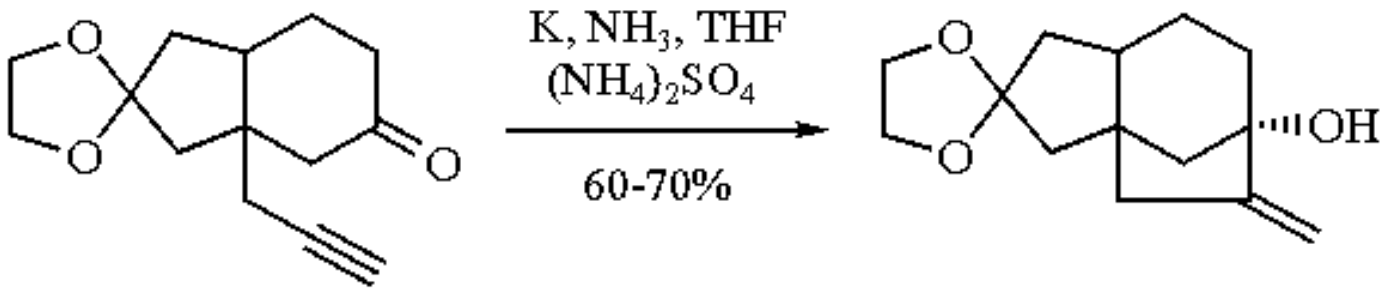

(4)

In the case of α,β-unsaturated carbonyl groups,[2a,17] the radical anion is readily transformed to the dianion, especially with K. When protonation occurs, an enolate results which can be trapped with an electrophile, giving rise to alkylation on the α-carbon. The stereoselectivity at the β-position does not seem to be strongly dependent on the nature of the metal, although exceptions are known (eq 5).[18]

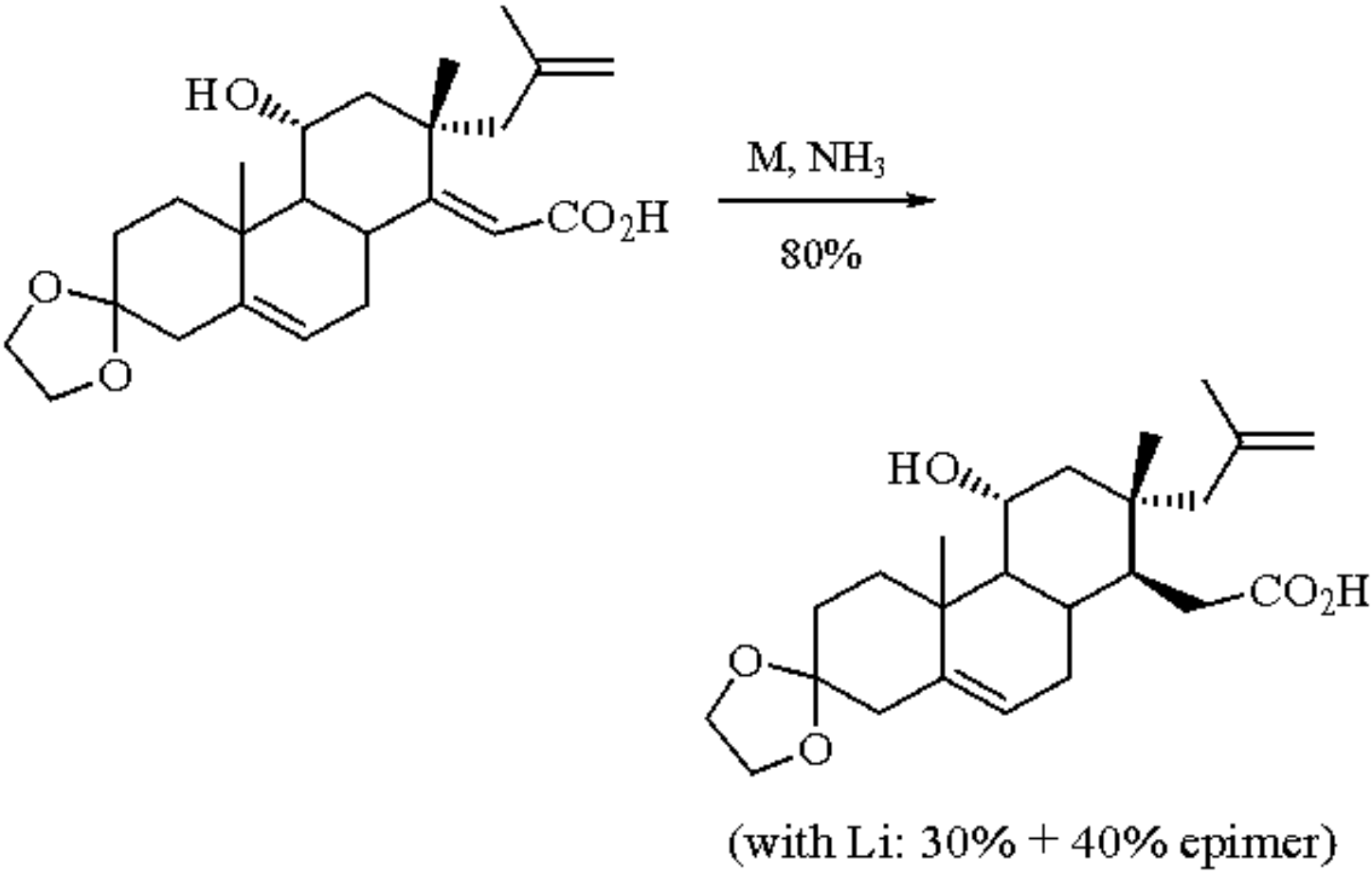

(5)

In the absence of a proton source, the dianion can be alkylated on the β-carbon. The increased yields obtained in some cases with potassium result from the higher reactivity of the potassium dianion, as compared with reactions with lithium or sodium (eq 6).[17,19]

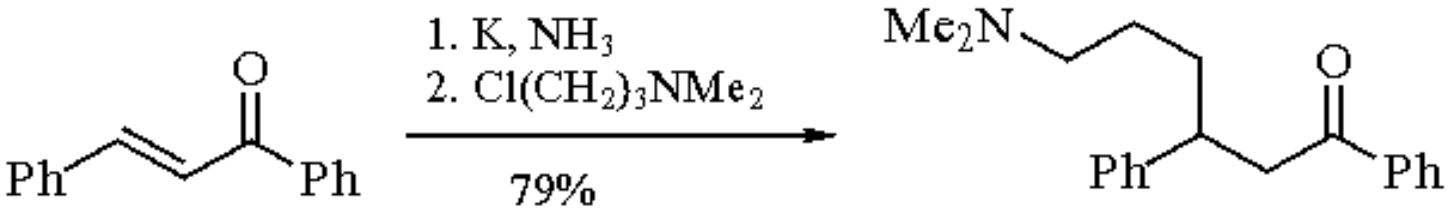

(6)

Reduction of Functional Groups.

Various functional groups are reduced by potassium in liquid ammonia (eqs 7-9).[3,20,21] In many cases the reaction is accomplished in the presence of crown ethers, which generate K^+K^- ion pairs.

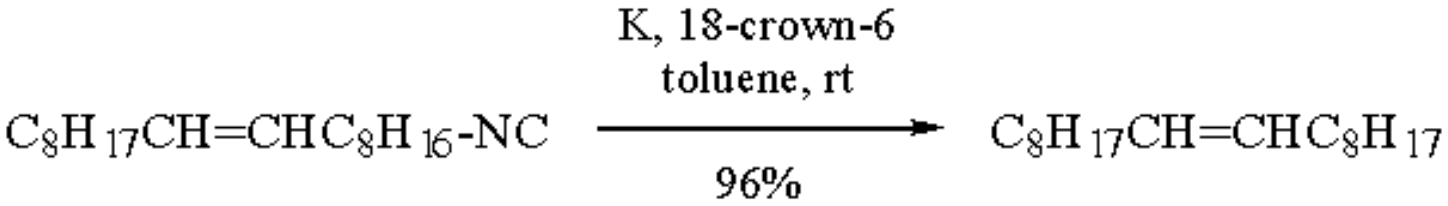

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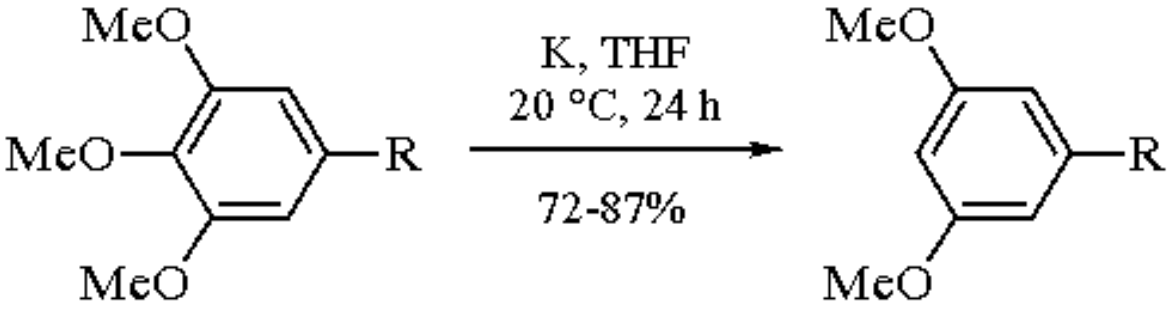

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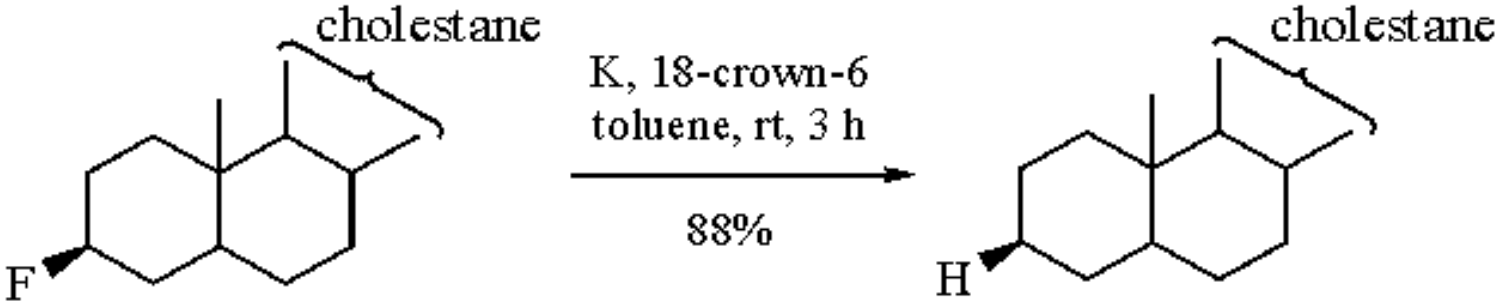

(9)

Alcohol deoxygenation occurs[4] via carboxylic, thiocarbamic (eq 10),[22] and phosphoric esters (eq 11).[23] Free benzylic alcohols can be reduced with potassium in the presence of 4,4´-di-*t*-butylbiphenyl in THF under sonication.[24]

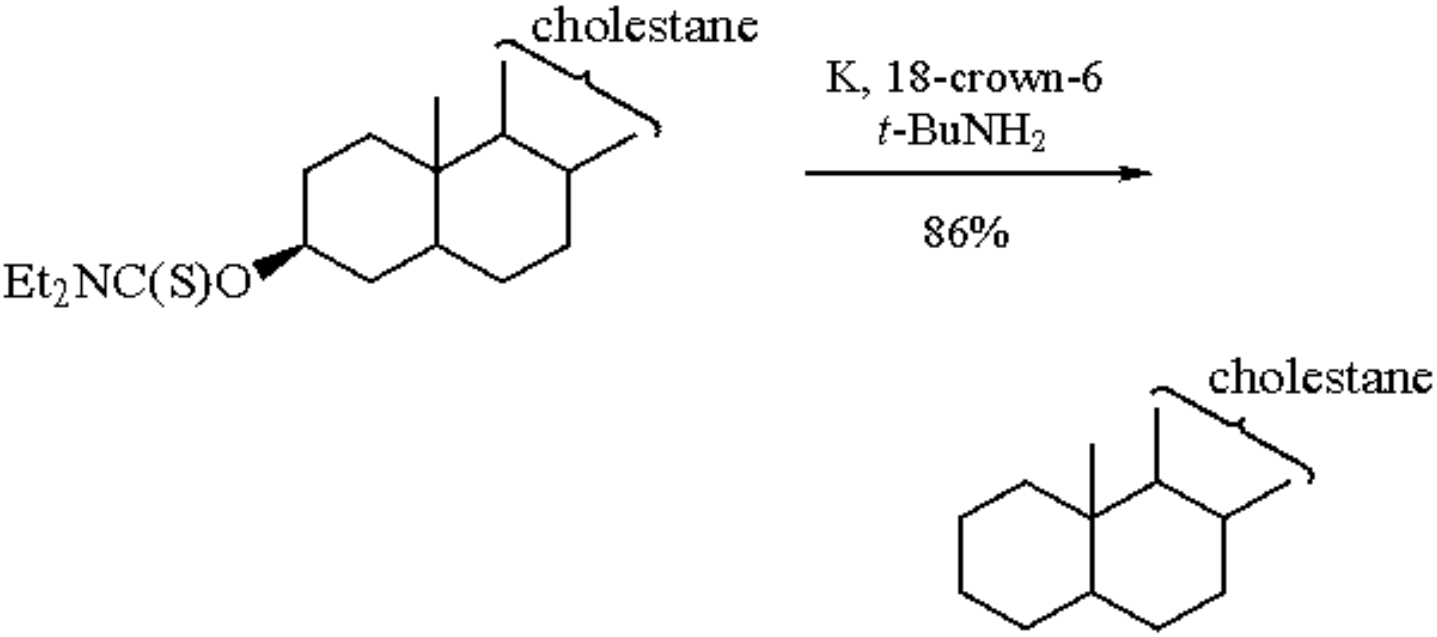

(10)

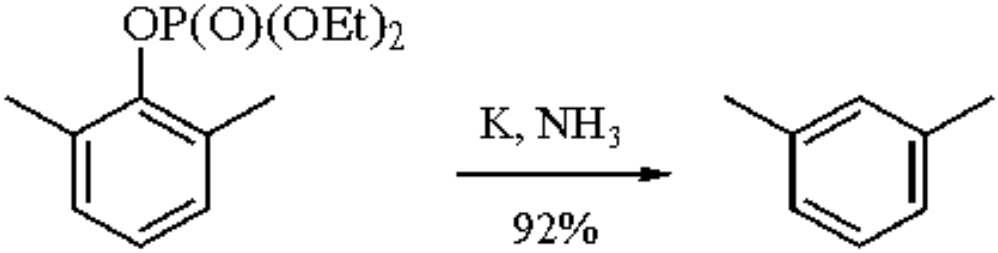

(11)

Reduction of Metal Salts (Rieke's Metals).

Potassium reduces metal salts to finely dispersed metals in refluxing THF or DME (eq 12). Activated metal slurries can be prepared, which exhibit a high reactivity with organic compounds.[5] The method was improved by replacing potassium with lithium in the presence of an electron transport agent.[25]

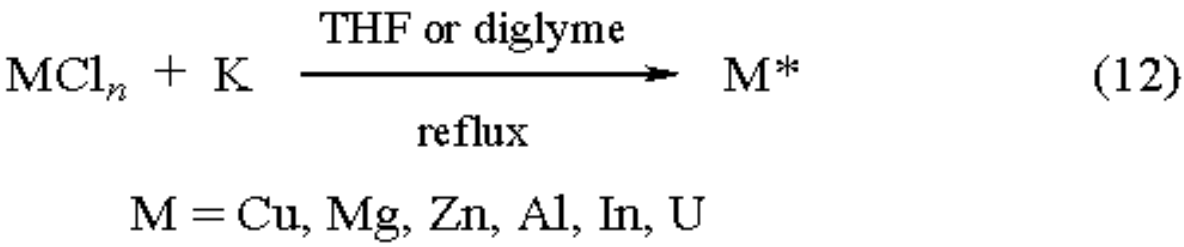

Reaction with Proton Donors.

Potassium reacts with acidic hydrogen compounds such as alcohols. This reaction is used to prepare the useful potassium alkoxides (e.g. ***Potassium t-Butoxide***).[6] Some potassium amides, such as 3-aminopropanamide, are readily prepared in quantities up to 25 mmol from the metal and 1,3-propanediamine in the presence of a trace of iron(III) nitrate under sonication (eq 13).[26]

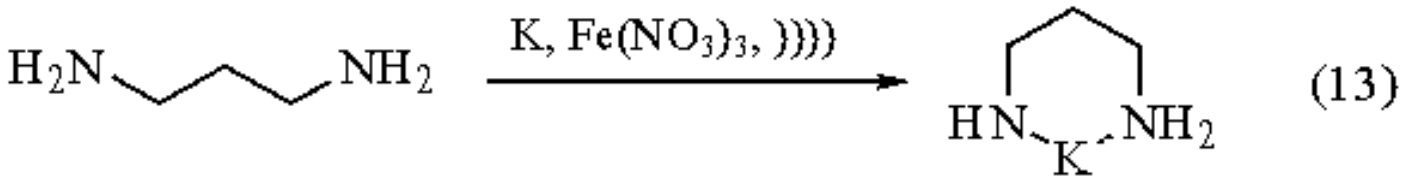

Alkylation and $S_{RN}1$ Reactions.

Deprotonation-alkylation of γ-lactones has been reported. In the case of acylation, it occurs only on the carbon atom (eq 14).[27]

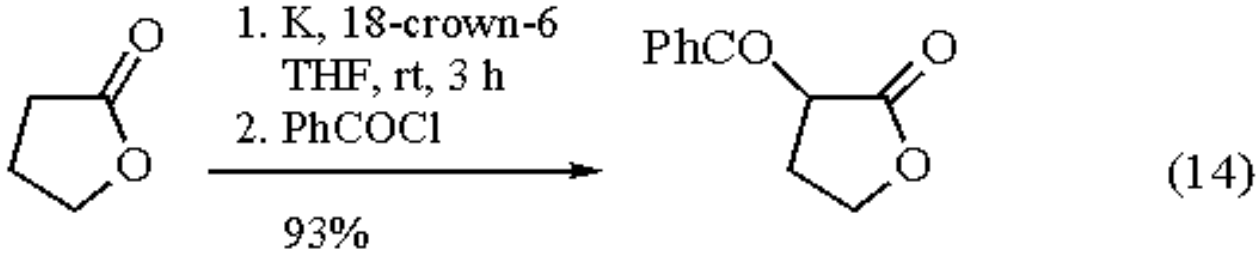

Substitution of aromatic halides, phosphate esters, trialkylammonium groups, and sulfides by an anionic nucleophile occurs with complete regioselectivity in the presence of potassium in liquid ammonia or DMSO (eq 15).[7] These reactions are now more generally effected with a potassium alkoxide under photochemical activation.[28]

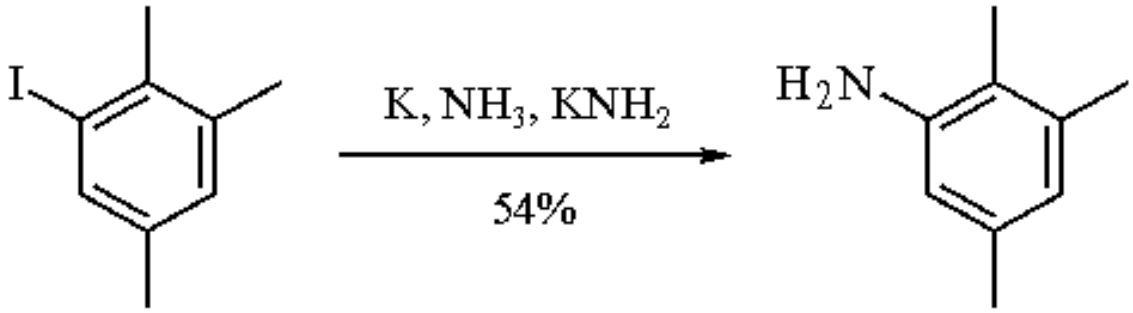

(15)

Supported Potassium on Alumina (K/Al_2O_3) or Graphite (C_8K).

Potassium on Alumina is prepared by melting the metal in the presence of Al_2O_3. ***Potassium-Graphite*** is obtained by vaporizing the metal on graphite. Both reagents are sensitive to oxygen and moisture. Various reductive processes take place with alkenes, nitriles, or halides (eqs 16 and 17).[8,29]

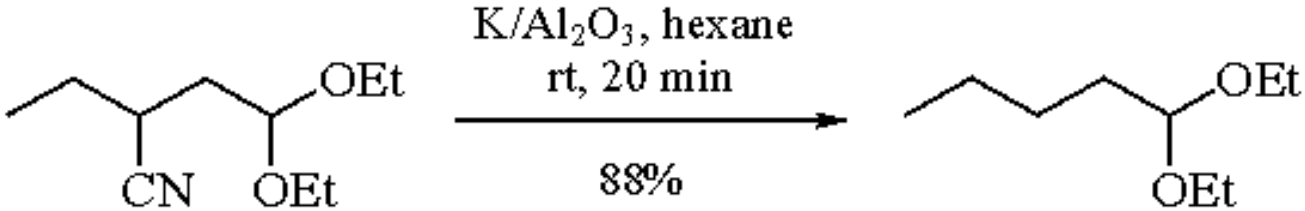

(16)

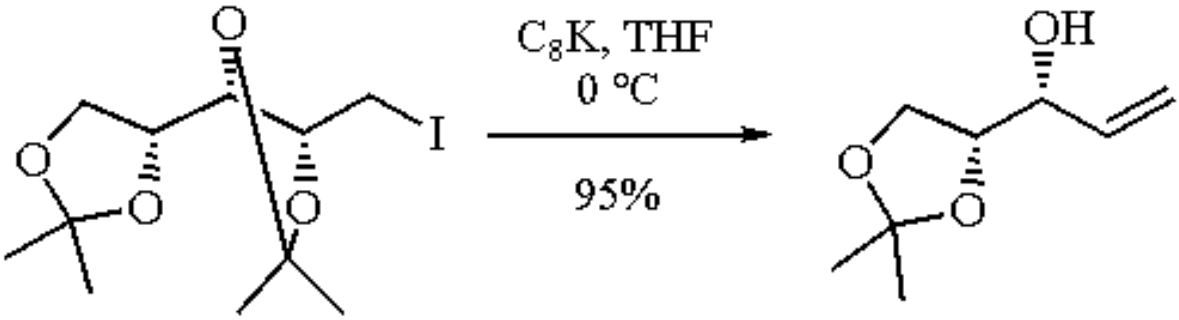

(17)

Ultrasonically Dispersed Potassium (UDP).

Sonication of potassium metal in aromatic solvents (toluene, xylene) produces a silvery blue suspension. The reaction of this reagent with water is much milder than that of potassium metal. This suspension can behave as a base or as a single-electron transfer agent. The Dieckman cyclization of diethyl adipate (eq 18)[10] and the dimerization of succinates (eq 19)[30] occur readily at rt in excellent yield.

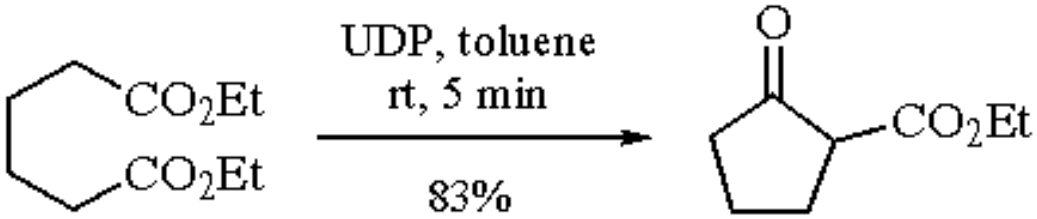

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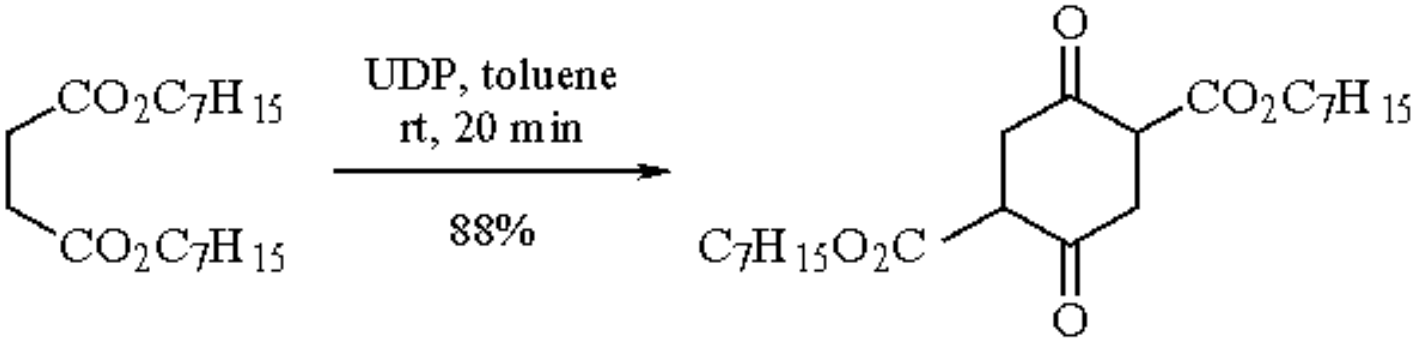

(19)

The carbon-sulfur bond in sulfolene is cleaved to a radical anion, which can be alkylated to provide open chain sulfones. The inconvenience of long irradiation times was solved by running the reaction in the presence of proton sources, water, or phenol (eq 20).[31]

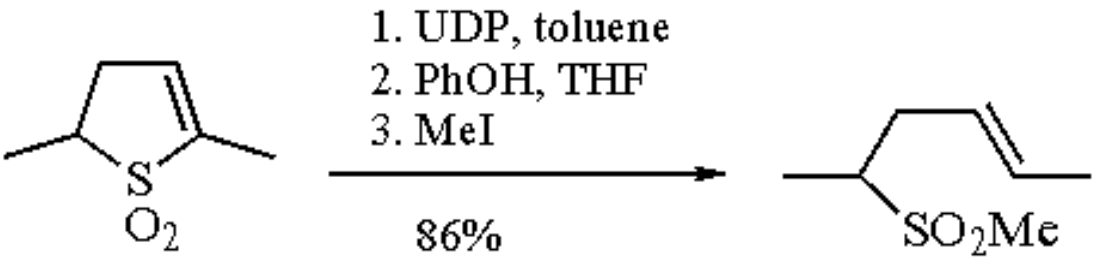

(20)

Related Reagents.

Sodium-Potassium Alloy; ***Titanium(III) Chloride-Potassium***.

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Potassium on Alumina

K/Al_2O_3

[7440-09-7] · K · Potassium on Alumina · (MW 39.10)

(catalyst for hydrogenations,[1,7] double bond isomerizations,[1-4] dehydrations, and skeletal rearrangements;[2-4] metalating agent;[5] effects reductive decyanation[6])

Physical Data: blue powder if the metal content is in the range of 2-15%; at higher loading the reagent has a gray to black appearance. The X-ray spectrum of a 14% K on Al_2O_3 reagent shows no observable reflections due to potassium.[6] A metal content in the range of 2-15% usually leads to the highest catalytic activity.[1]

Preparative Method: by adding potassium to thoroughly dried basic or neutral alumina under argon with vigorous stirring at temperatures >100 °C until a homogeneous appearance is reached.

Handling, Storage, and Precautions: nonpyrophoric solid which can be stored under argon for extended periods of time; must be handled under inert atmosphere; catalytic activity may decrease if impure or moist solvents are used; can be safely destroyed by slowly adding isopropanol to a suspension of the reagent in hexane with good stirring.

Catalytic Activity.

K/Al_2O_3 is the most efficient among the series of alkali metals finely dispersed on alumina, although ***Sodium-Alumina*** (sometimes termed high surface sodium) essentially effects the same types of transformations. In a model system, the following order of activity for the different alkali metals supported on alumina has been established: K &egt; Rb >> Cs &AApprox; Na.[1a]

K/Al_2O_3 readily effects both configurational as well as positional alkene isomerizations with the following three trends being observed. Firstly, alkene groups are usually shifted (with few exceptions) towards higher degrees of substitution (eq 1).[2] Secondly, an alkene of accentuated conformational preference will accumulate; this is evidenced, for example, by the formation of the thermodynamically more stable (*Z*,*Z*)-cyclodeca-1,6-diene from (*E*,*Z*)-cyclodeca-1,5-diene (eq 2),[1] as well as by the preponderance of (-)-aristolene in the equilibrium mixture obtained upon treatment of (+)-calaren with K/Al_2O_3 (eq 3).[2] Thirdly, the double bonds in 1,*n*-(cyclo)alkadienes are shifted towards conjugation independent of their initial position in the starting material (eqs 4 and 5).[1,2] Similarly, 1,2,4-trivinylcyclohexane quantitatively affords 1,2,4-triethylbenzene in a highly exothermic process.[3] Although the mechanism responsible for such positional changes is not yet elucidated, allyl anion intermediates are likely.[1] This

picture is supported by the observation that successive treatment of γ-***Alumina*** with ***Sodium Hydroxide*** and Na leads to a solid superbase (pK_b &egt; 37), which effects the same types of alkene isomerizations via allyl anion species.[8]

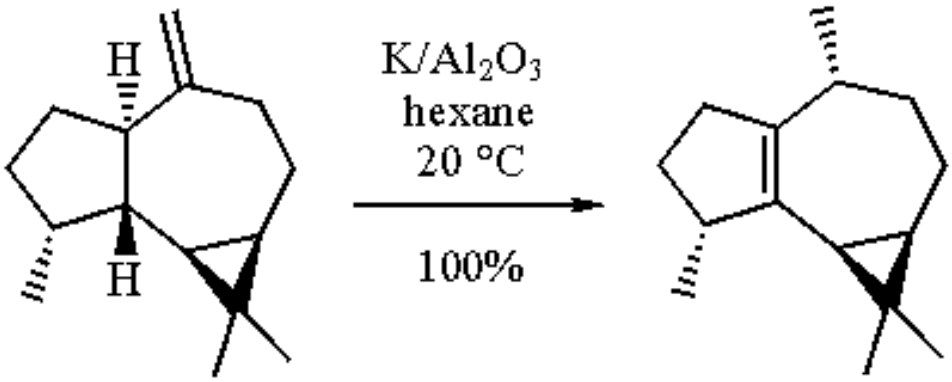

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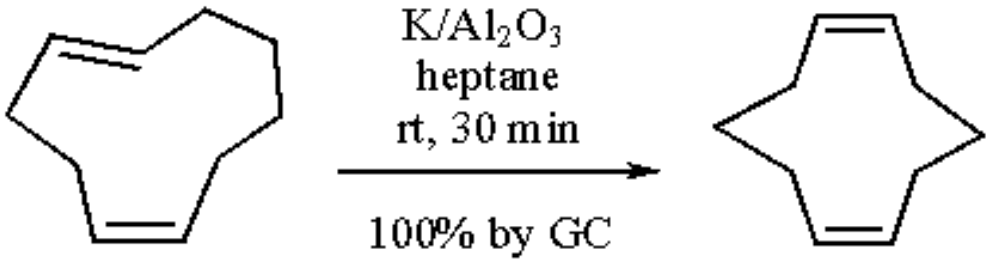

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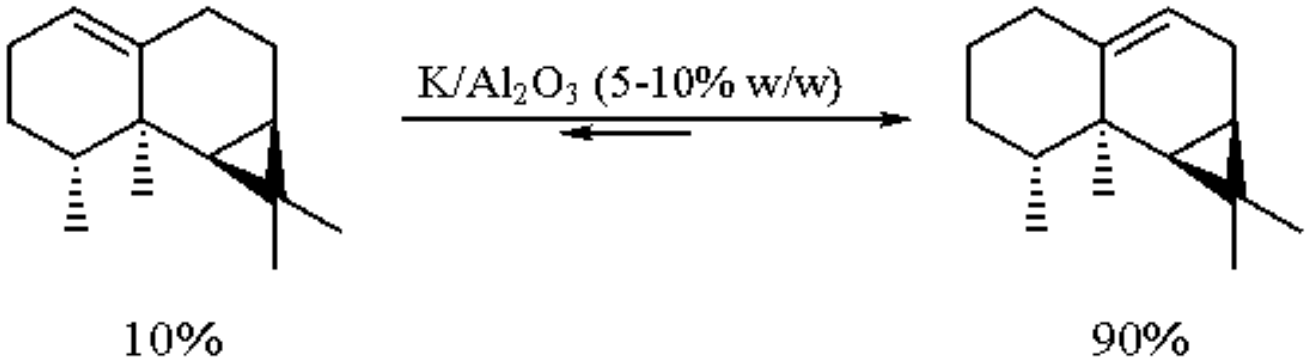

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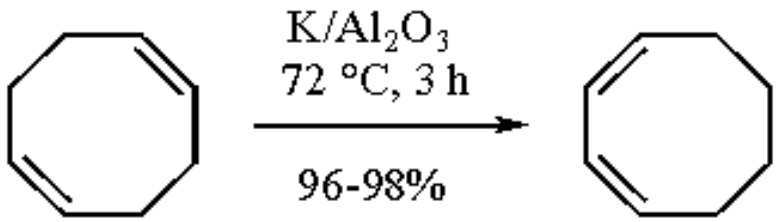

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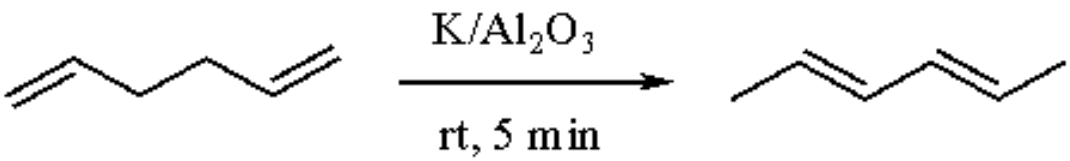

(5)

Macrocyclic 1,3-cycloalkadienes produced by isomerization of 1,*n*-cycloalkadienes are slowly reduced to cycloalkenes even in the absence of external hydrogen.[1] Residual water or -OH groups on the alumina in combination

with the adsorbed potassium may serve as the hydrogen source in this process. Under a hydrogen atmosphere (1 atm), however, this selective hydrogenation of conjugated dienes by M/Al_2O_3 (M = Na, K) is considerably accelerated, with no overreduction to the respective cycloalkane being observed.[1]

K/Al_2O_3 exhibits a distinct propensity to catalyze transannular reactions of unsaturated macrocyclic systems as well as skeletal rearrangements leading to ring contraction, as shown with (+)-longifolene as substrate.[2]

Catalytic Cascades.

Six-membered rings bearing two alkene and/or cyclopropyl groups in the vicinity are smoothly aromatized when exposed to M/Al_2O_3 (M = Na, K) as catalyst by a sequence of double-bond isomerizations followed by dehydrogenation (eq 6).[2,3]

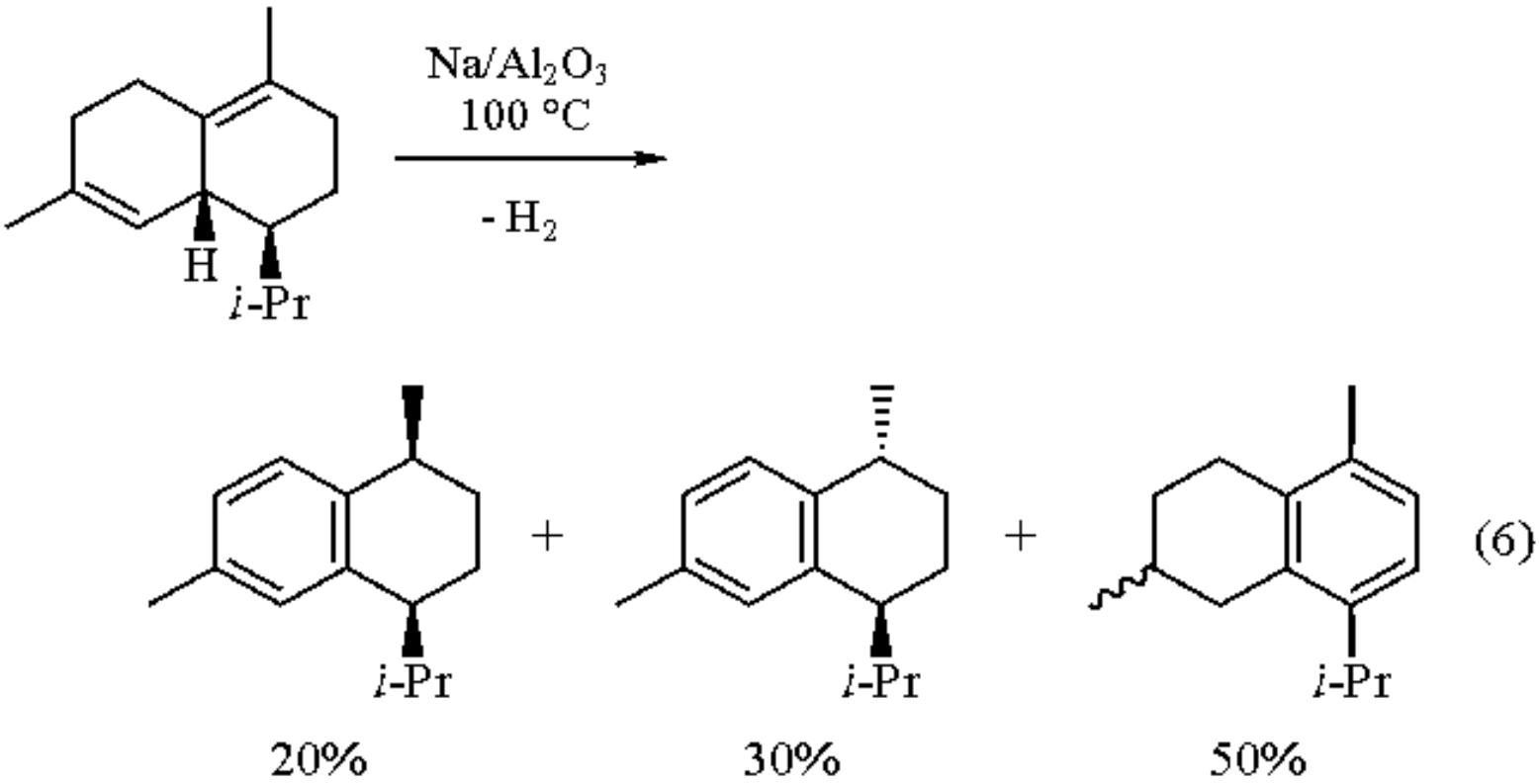

In a one-pot procedure (*Z*,*E*,*E*)-cyclododeca-1,5,9-triene as substrate runs through a cascade of catalytic processes induced by Na/Al_2O_3. This sequence comprises a transannular reaction, double bond isomerizations, and selective hydrogenation of the conjugated diene produced in the presence of hydrogen. Final ozonolysis of the crude reaction mixture afforded cyclododeca-1,7-dione in good yield (eq 7).[4]

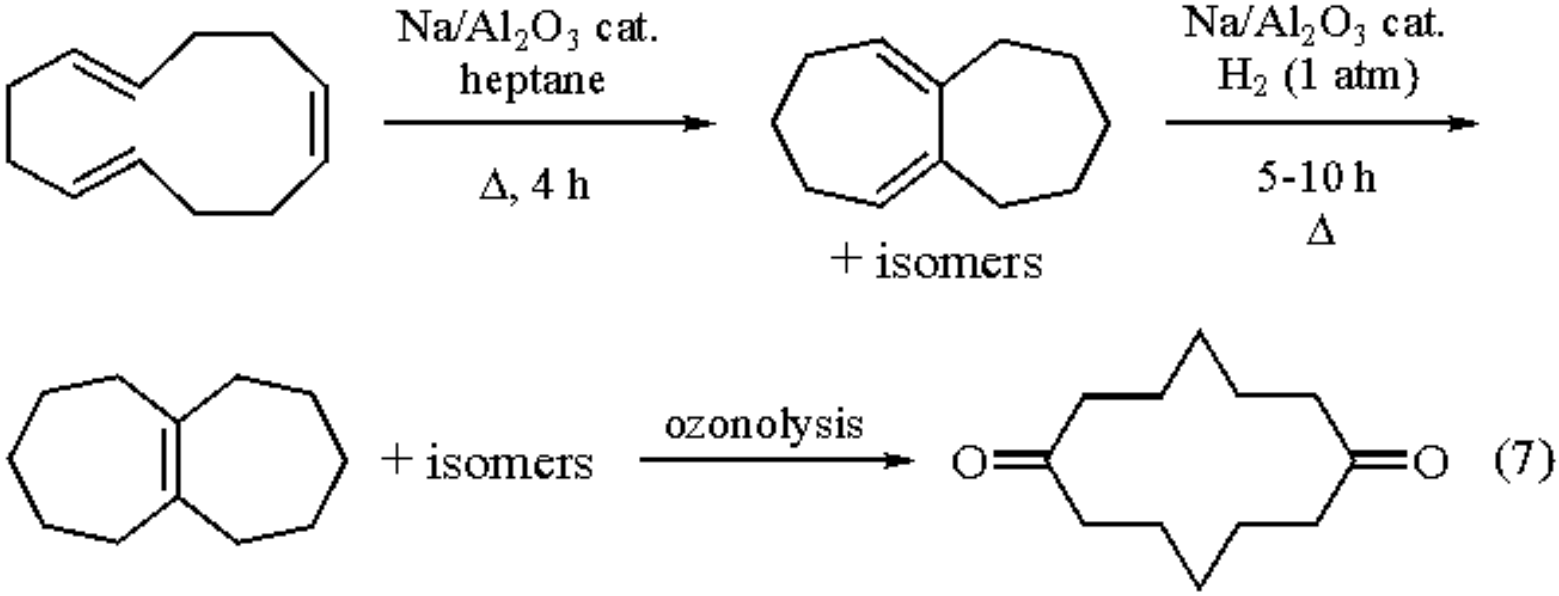

Organometallic Synthesis.

K/Al_2O_3 has been used as base to metalate ketones, ethyl phenylacetate, alkyl nitriles, aldehyde-*N*,*N*-dimethylhydrazones, or *N*-cyclohexylketimines.[5] However, an excess of the reagent was necessary and the yields reported for alkylation of the intermediate potassium carbanions were moderate. In the case of alkyl nitriles as starting materials, the choice of solvent turned out to be decisive for the reaction path: while deprotonation of these substrates predominates in THF, they are readily decyanated when treated with K/Al_2O_3 in hexane as the reaction medium.[6] Residual -OH groups on the alumina may be the proton sources in this reductive C-C bond cleavage. While the reaction leaves acetal groups and disubstituted alkene moieties in the substrates unaffected (eq 8), terminal double bonds are rearranged to internal ones during the decyanation process (eq 9).[6] Recently, Na/Al_2O_3 has been used as reducing agent for ketones, esters, and oximes.[9] It also serves as a catalyst for the Tischenko coupling of benzaldehyde to benzyl benzoate,[10] and may be employed for preparing activated zinc and titanium samples.[11]

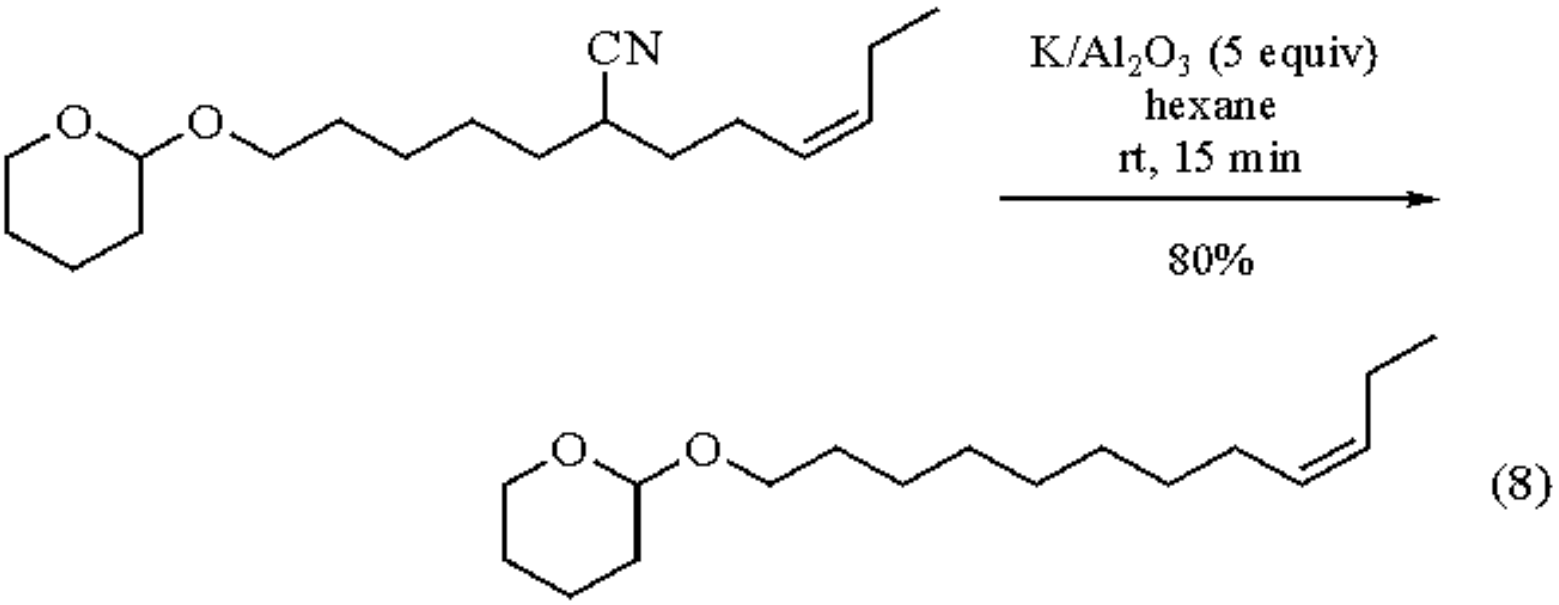

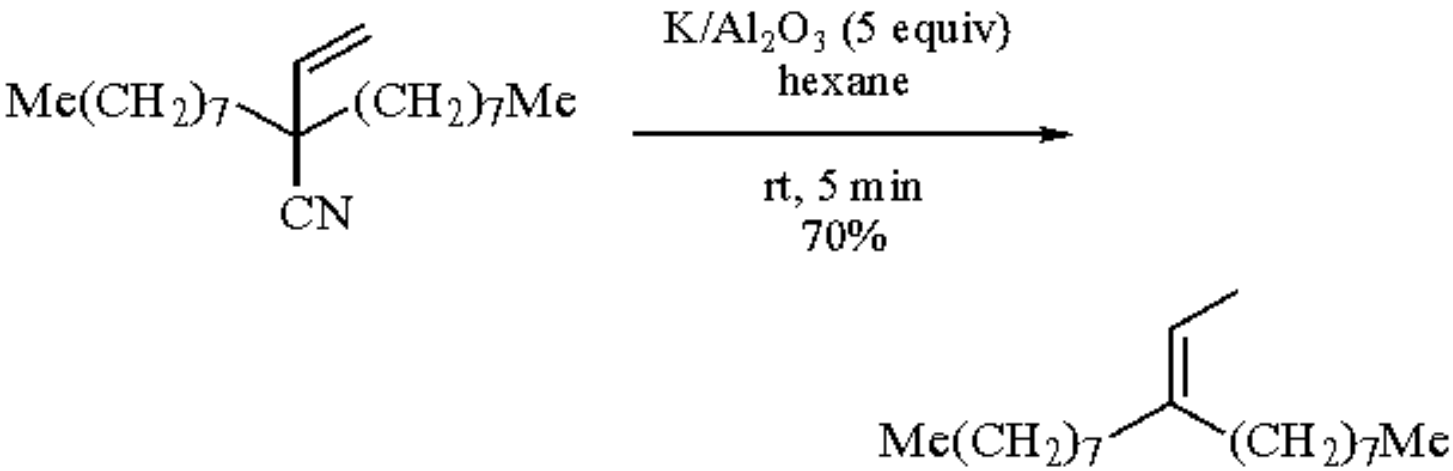

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Potassium Amide

KNH_2

[17242-52-3] · H_2KN · Potassium Amide · (MW 55.13)

(strong base and nucleophile; used for the generation and trapping of arynes; has been used extensively to study the reactivity of heterocyclic systems)

Solubility: 1.7 M in liquid ammonia;[1] 1.3×10^{-4} M in THF.[2]

Preparative Methods: a solution of potassium amide in liquid ammonia is prepared by adding pieces of ***Potassium*** to liquid ***Ammonia*** in an ordinary three-necked flask equipped with a mechanical stirrer.[3] A piece of potassium is added to liquid ammonia and after the appearance of a blue color, a few crystals of iron(III) nitrate hydrate are added as catalyst. The remaining pieces of potassium are added at a rate which maintains active hydrogen evolution. Discharge of the deep blue color indicates complete conversion to potassium amide. External cooling is not required since the evaporation of ammonia will provide ample cooling.[4] If the reaction must be maintained at -78 °C then a dry ice-acetone condenser is necessary, otherwise an air condenser is sufficient. The resulting opaque mixture contains potassium amide which is mostly in solution. A more elaborate two-flask assembly for the generation and transfer of a potassium amide solution has also been described.[5]

Handling, Storage, and Precautions: potassium amide is flammable and ignites on contact with moisture. Excess material is destroyed by careful treatment with ethanol or isopropanol. In the preparation of potassium amide the following precautions should be noted. Potassium is a silvery gray metal but it can form an explosive peroxide coating. If it acquires an orange or red color or an appreciable oxide coating it should be considered extremely hazardous. Extreme caution should be exercised in any attempt to isolate potassium amide as it is suspected to be shock sensitive following partial oxidation. An explosion has been reported during the isolation of dry potassium amide.[6] Reactions should be performed in a fume hood to prevent exposure to ammonia. Hydrogen is evolved during the generation of potassium amide. No ignition source should be present.

Introduction.

Potassium amide is both a strong base and a strong nucleophile and thus it has been used most effectively in reactions which exploit both of these properties, such as the generation and trapping of arynes, the amination of aromatic systems, and the rearrangement of various heterocyclic systems. Examples of these types of transformations are described below. The reagent has also been used simply as a strong base to induce deprotonation or elimination reactions, provided there are no competing nucleophilic reaction pathways available. This is currently a less important

feature of the reagent given the ready availability of strong, nonnucleophilic bases, but a few examples are described at the end of this section.

Aryne Formation.

Potassium amide in liquid ammonia has been used extensively in the generation and trapping of benzynes via dehydrohalogenation of phenyl halides.[7] One of the definitive experiments providing evidence for the existence of benzyne involved the treatment of [1-^{14}C]chlorobenzene with potassium amide in liquid ammonia to provide equal amounts of [1-^{14}C]aniline and [2-^{14}C]aniline (eq 1).[8] The potassium amide-ammonia system has since been used for the preparation of various substituted anilines.[9]

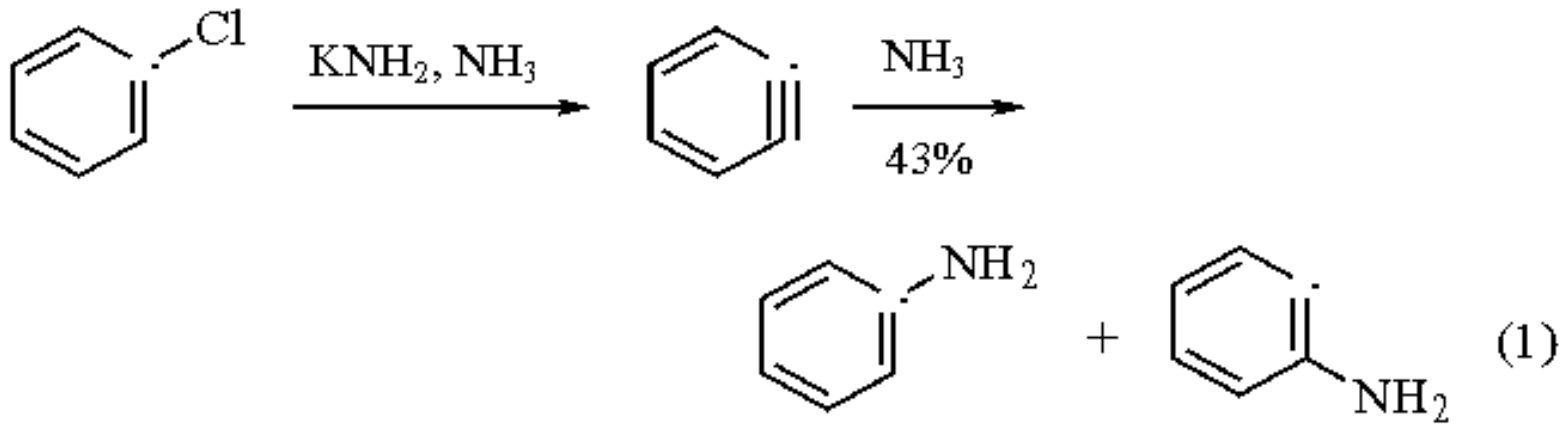

Potassium amide has also been utilized extensively for the generation and trapping of various six-membered hetarynes including those generated from halogenated pyridines, diazines, isoquinolines, naphthyridines, and certain multicyclic systems.[10] Of the various hetarynes, the evidence supporting the existence of 3,4-pyridyne is recognized as the most convincing. Treatment of either 3- or 4-chloropyridine with potassium amide in liquid ammonia provides a constant ratio of the isomeric amine products (eq 2).[11]

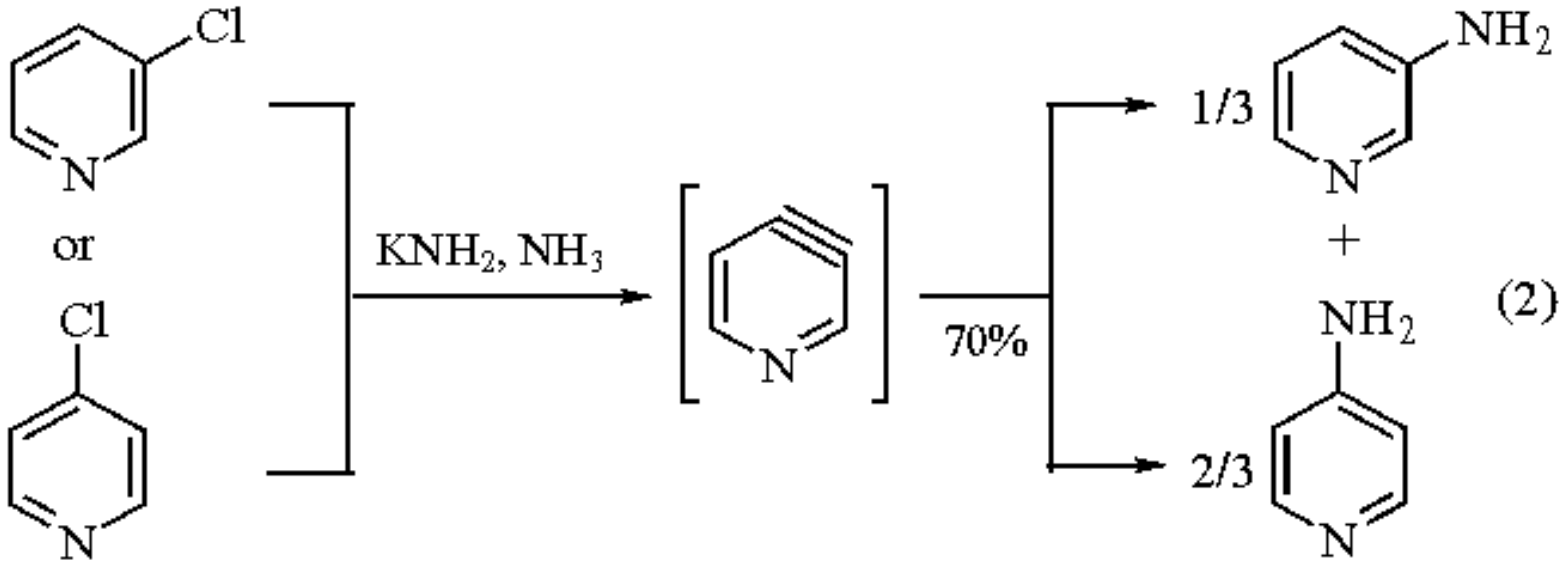

Although mixtures of amines are usually formed in potassium amide-induced aryne formations, in some cases selectivity for one isomer can be achieved. For example, it was found that treatment of a tricyclic

bromobenzo[*f*]quinoline with potassium amide in liquid ammonia provided only one product via its postulated hetaryne intermediate (eq 3).[12] Steric interference by the angular ring is presumed to block formation of the other isomer.

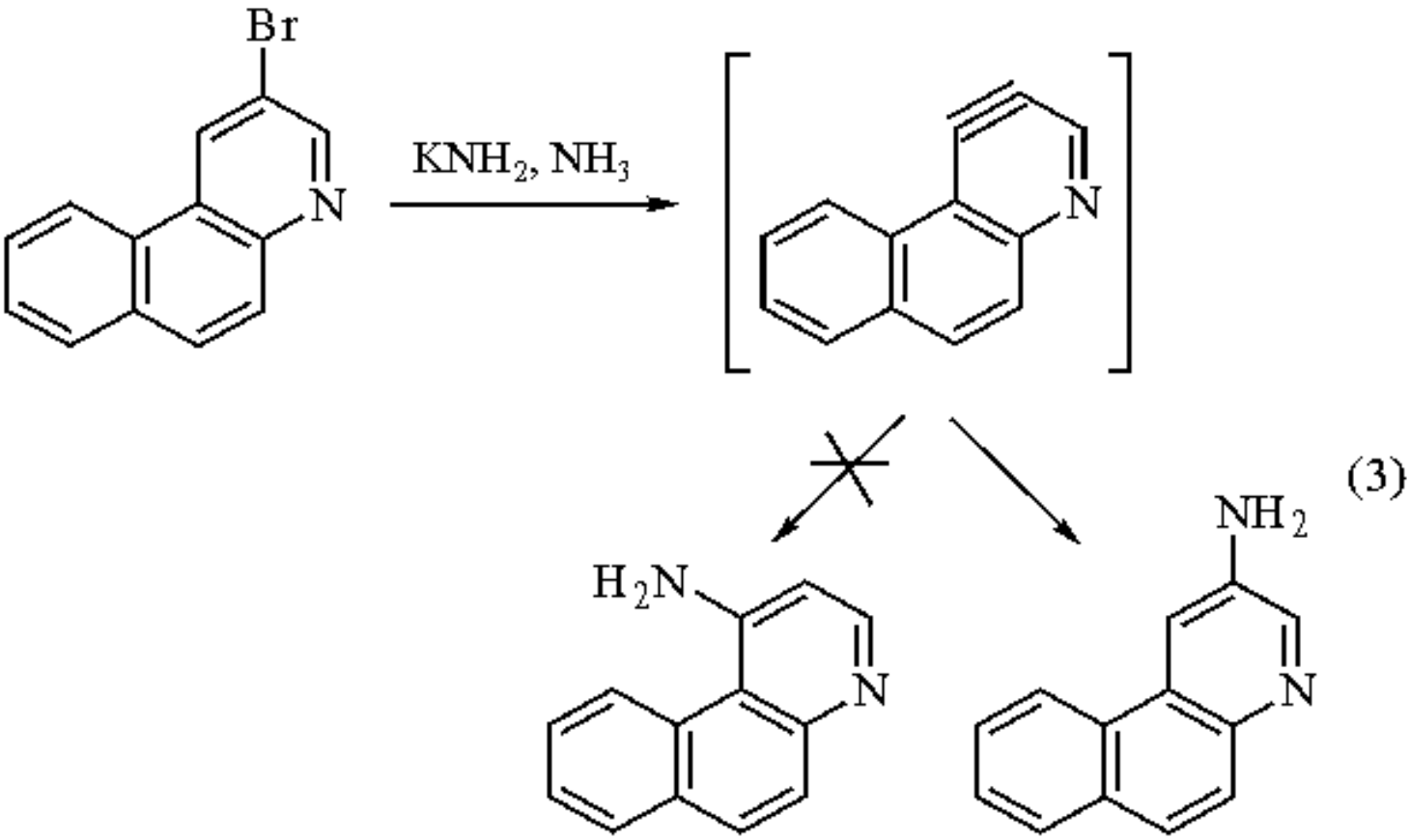

(3)

Even in the presence of potassium amide, an intramolecular nucleophile can often compete effectively with amide ion to trap an aryne intermediate, resulting in ring closure. For example, 2-phenylbenzothiazole has been prepared in 90% yield utilizing this strategy (eq 4).[13] Intramolecular cyclization onto potassium amide-generated benzyne derivatives has been achieved with carbon, nitrogen, oxygen, and sulfur nucleophiles.[14] The strategy has also been successfully used with certain hetarynes, particularly 5-substituted 3,4-pyridynes (eq 5).[15] In some cases, however, when potassium amide is used as the aryne-generating base, competitive amination can occur to a significant extent (eq 6).

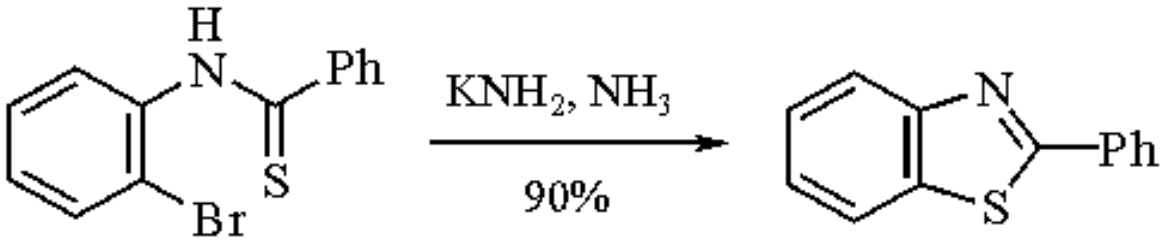

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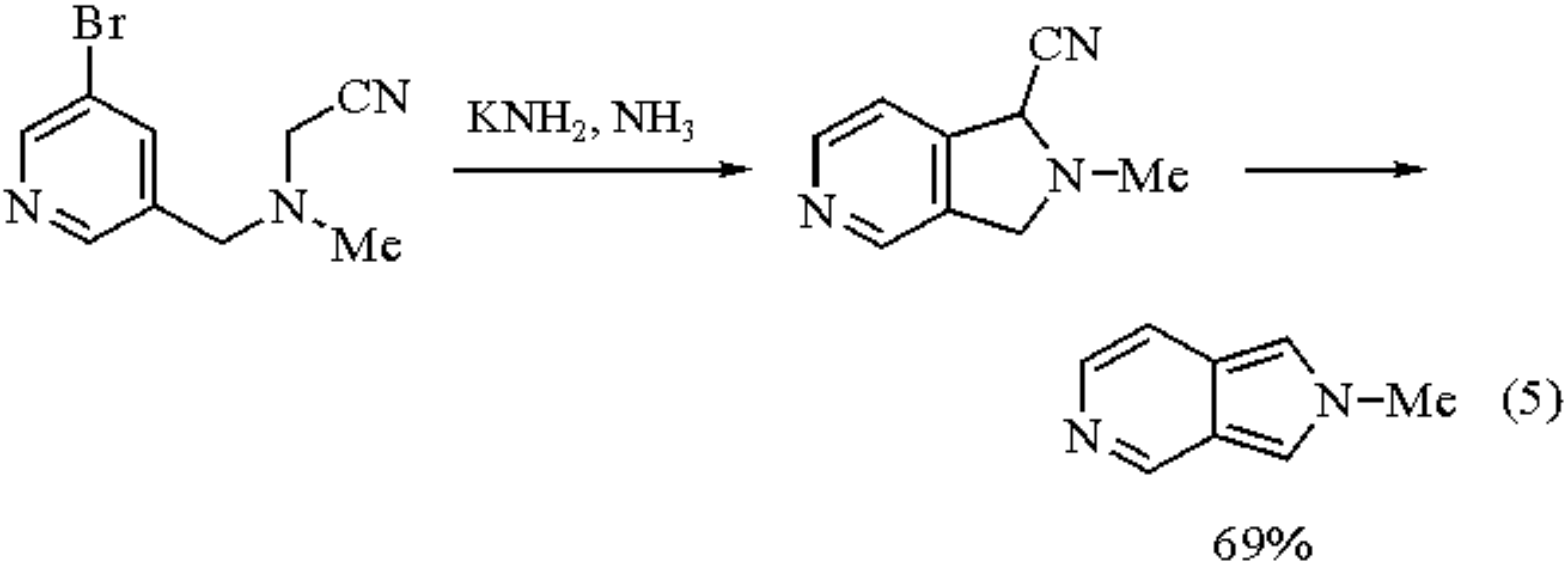

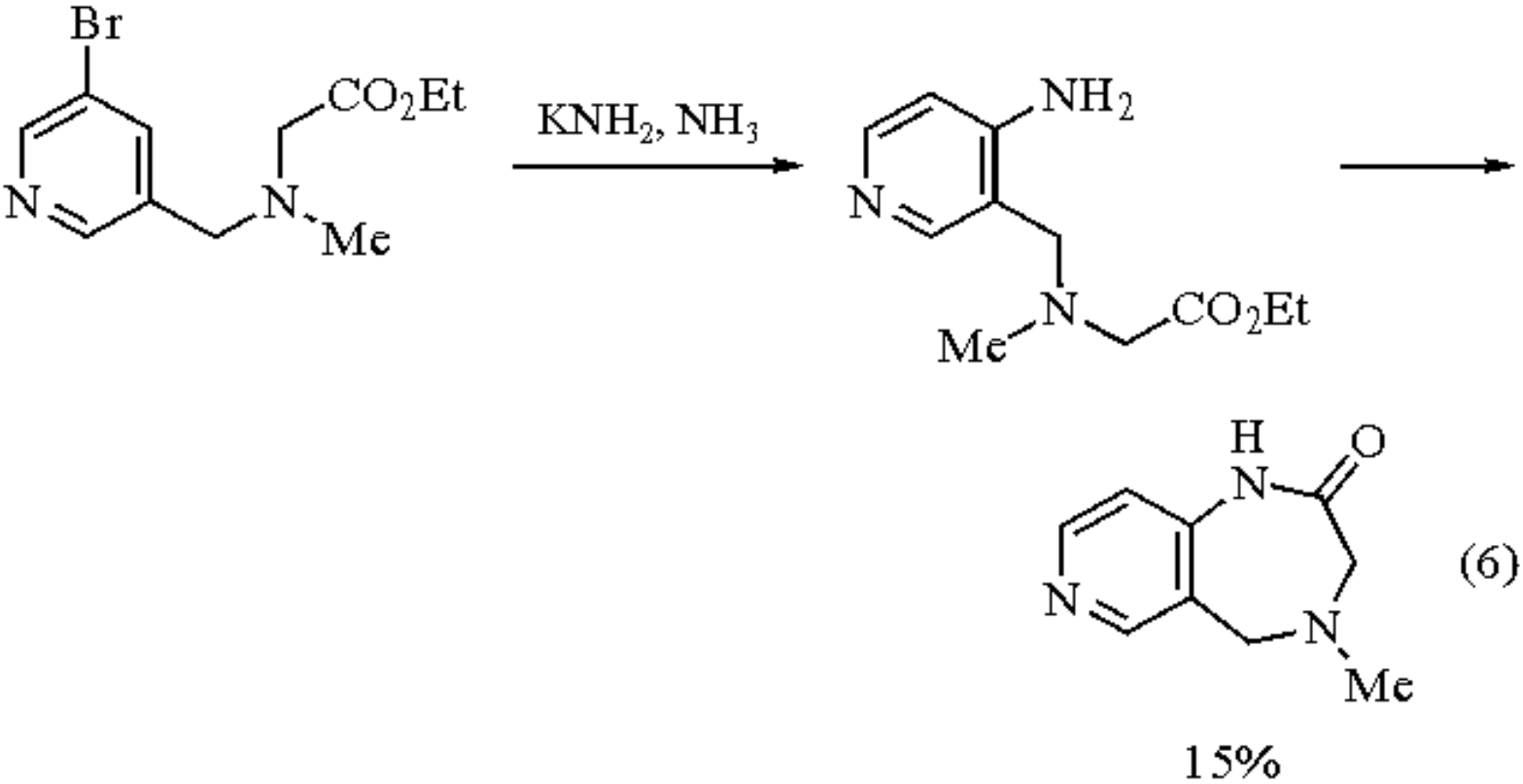

Potassium amide-generated arynes can also be trapped intramolecularly by a sufficiently nucleophilic phenyl ring. For example, appendage of a negatively charged atom to an aromatic ring can confer sufficient nucleophilicity to the *ortho* and *para* positions for this type of reaction.[16] An example of this strategy is shown in the synthesis of phenanthridines from haloanils (eq 7).[17] In this case, potassium amide is used not only to generate the requisite benzyne but also to activate the system to ring closure via addition of amide ion to the azomethine linkage. For the reaction to succeed, the nucleophilic addition of the amide ion must be very fast relative to the formation of the benzyne. This phenanthridine synthesis tolerates a variety of substituents in the aniline ring, with the exception of hydroxy and nitro groups which are thought to slow the amide addition to the azomethine group significantly.[18]

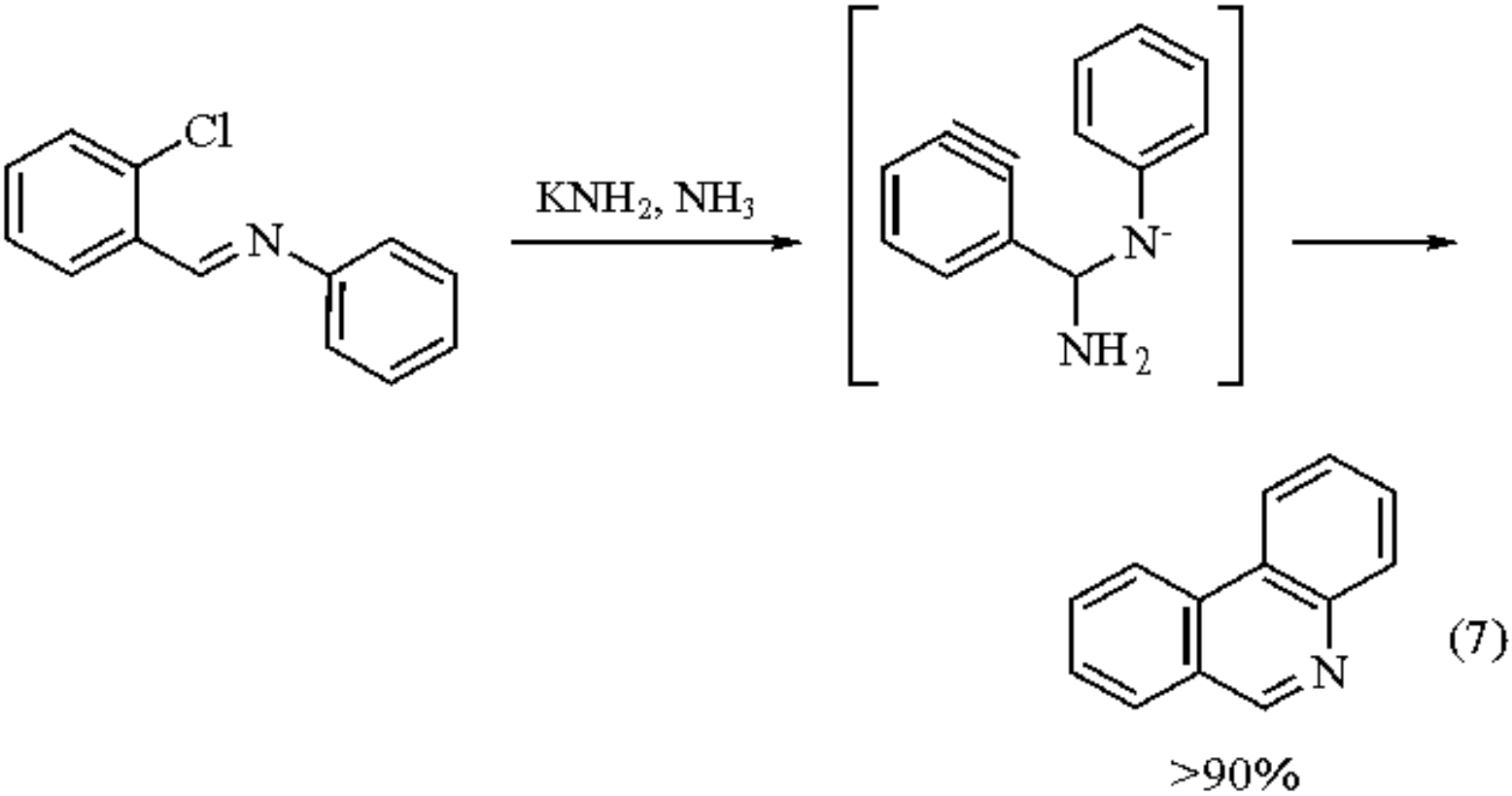

Rearrangement of Heterocyclic Systems.

The generation of pyridyne utilizing potassium amide prompted the investigation of the reaction of potassium amide with other heterocyclic azine systems in a search for other hetarynes. However, the halogenated precursors to hetarynes are often more reactive toward nonaryne reactions and in some cases alternative mechanisms for amination are involved. Although it was initially believed that 4-bromo-6-phenylpyrimidine reacted with potassium amide via a 6-substituted 4,5-didehydro intermediate, extensive examinations of the reaction of potassium amide with halopyrimidines led to the elucidation of another mechanism for nucleophilic substitution which proceeds through a ring opened intermediate (eq 8).[19] This mechanism is referred to as S_N(ANRORC) for addition of the nucleophile, ring opening, and ring closure. The evidence accumulated to support its existence has been reviewed.[20] In particular, labeling studies have been used to demonstrate that the amide anion nitrogen becomes incorporated into the ring system (eq 9). This mechanism has been shown to be operative (to a greater or lesser extent) in the reaction of potassium amide with a variety of halogen-substituted heterocyclic systems in addition to pyrimidines, including quinazolines, triazines, and purines. A review of the extensive literature in the area, categorized by ring type, is available.[21]

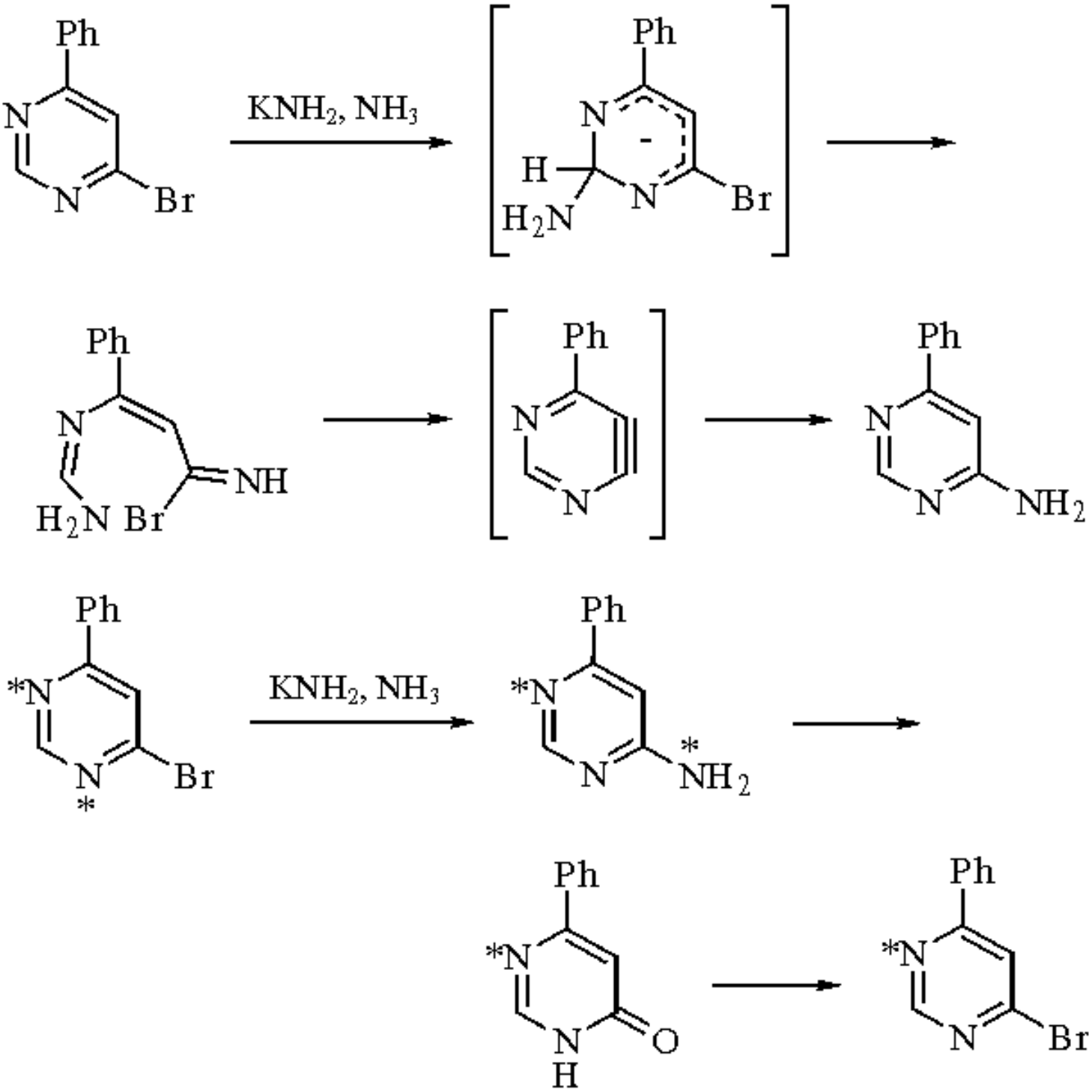

Under the conditions of potassium amide in liquid ammonia, many other examples of skeletal rearrangements of heterocyclic systems are known.[22] For example, ring contractions have been documented, such as that of 2-chloropyrazine to 2-cyanoimidazole (eq 10).[23] In this system, as in many cases, multiple rearrangement pathways lead to multiple products. The details of these potassium amide-induced heterocyclic ring transformation studies are available in a monograph.[22a]

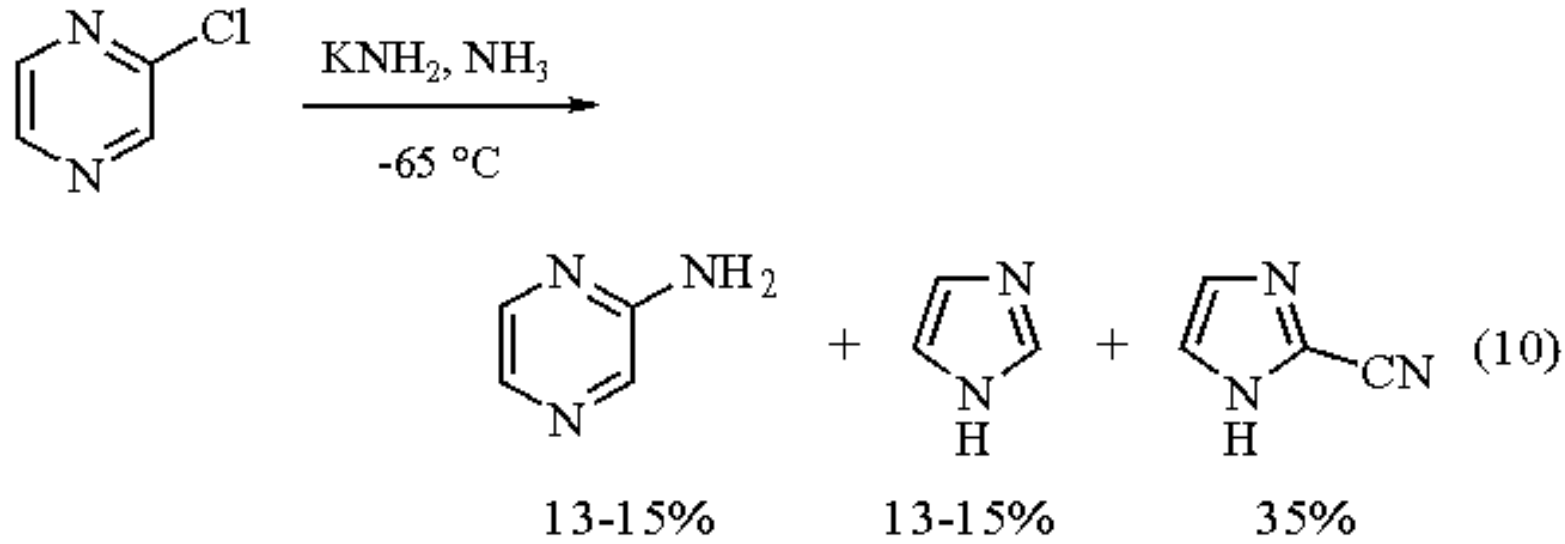

A particularly useful transformation is the rearrangement of 2-substituted 4-halopyrimidines into *s*-triazines via a ring-opened intermediate (eq 11).[24] This reaction allows for the preparation of unsymmetrically substituted *s*-triazines which are difficult to obtain by other methods. Competing formation of the 4-aminopyrimidine is minimized by utilizing the chloro derivatives (X = Cl).

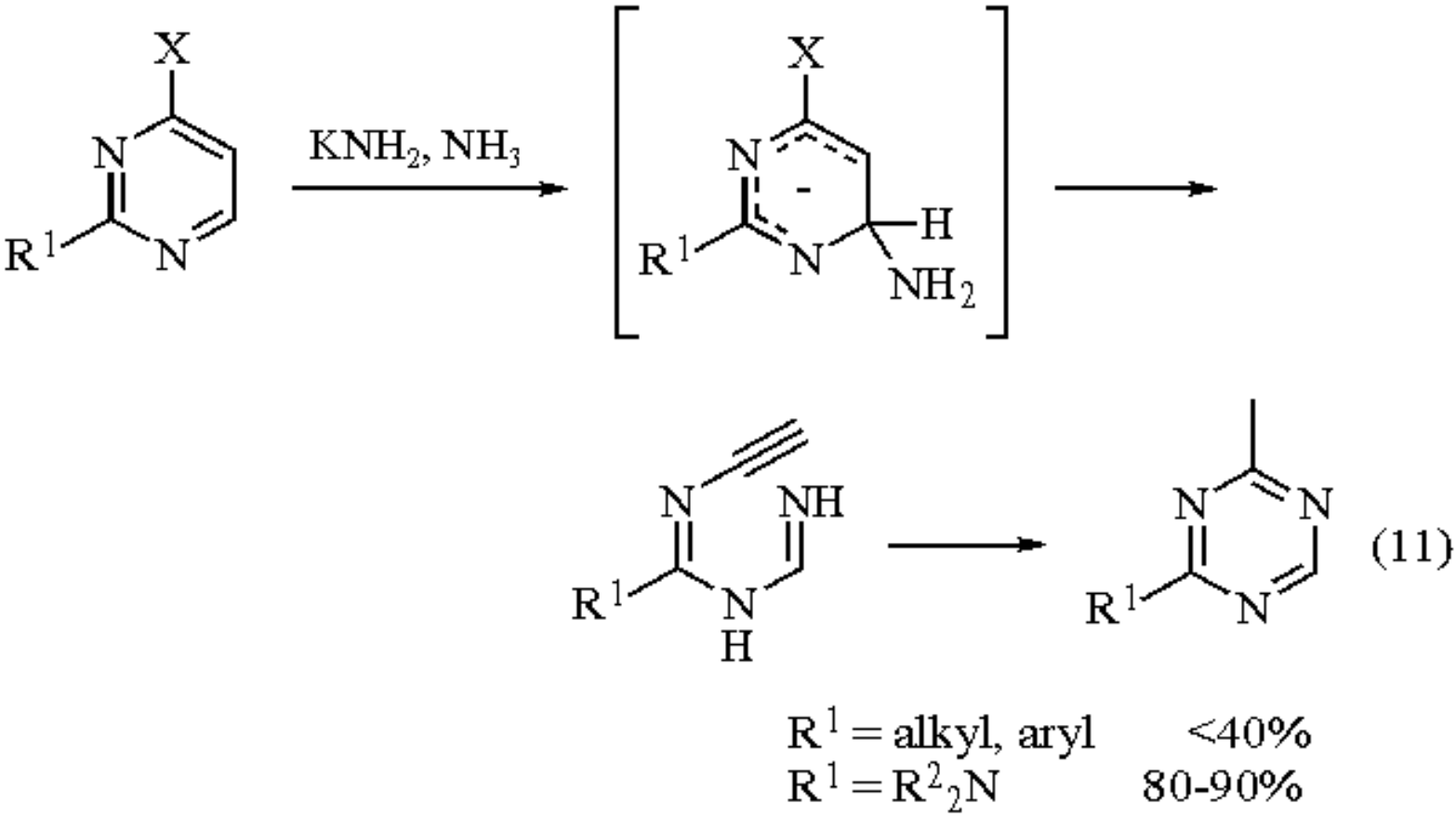

Direct Amination of Aromatic Rings.

Potassium amide can be used to induce a direct nucleophilic substitution of amide anion for hydrogen in certain azines.[25] Potassium amide in liquid ammonia adds readily to pyrazine, pyrimidine, and pyridazine to give anionic σ-

adducts which can be oxidized by ***Potassium Permanganate*** to give the corresponding aminoaza heterocycle in good yield (eq 12).[26] More highly electron deficient systems, like pteridines and nitroaza aromatics, are able to add ammonia itself to give neutral σ-adducts which are also oxidized by $KMnO_4$ to heteroarylamines.[27] This modified Chichibabin reaction has been reviewed elsewhere.[28]

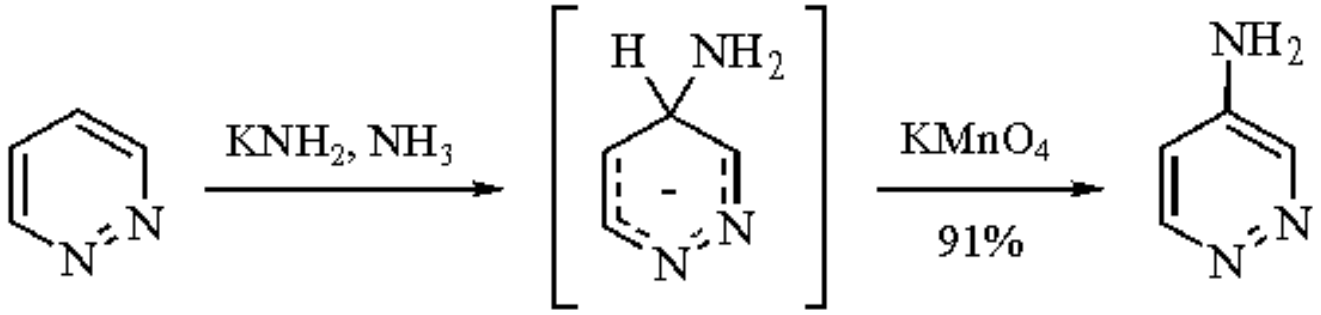

(12)

Potassium amide can also displace a suitably situated halide on a heteroaromatic ring to provide the aromatic amine, but this reaction is often accompanied by other products from competing rearrangement pathways (eq 10). Simple phenols can be converted to the corresponding aniline in a two-step process involving treatment of the aryl diethyl phosphate ester with potassium amide and potassium metal in liquid ammonia (eq 13).[29]

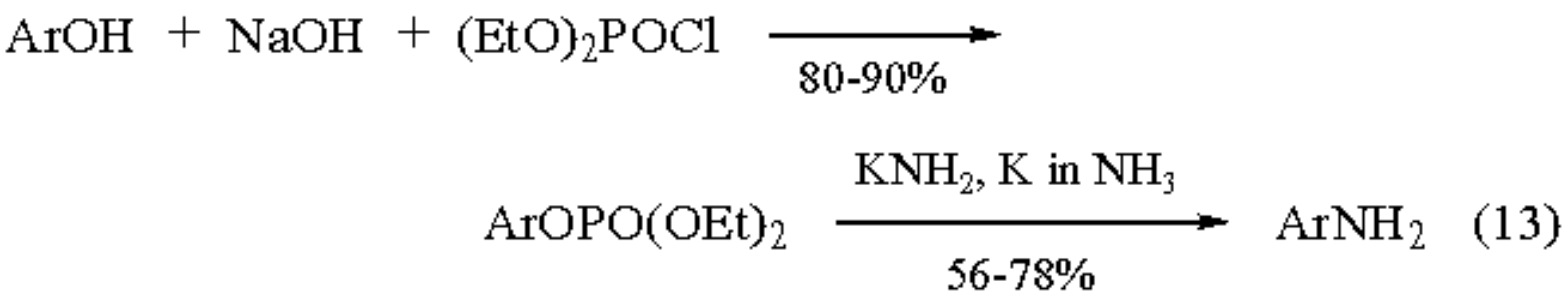

(13)

Anion Generation.

Potassium amide is a strong base which can be used in simple deprotonation reactions for the generation of various anions. In enolate chemistry, potassium amide in liquid ammonia has been used to generate the dianions of β-diketones and β-ketoaldehydes.[30] These species can then be regioselectively alkylated at the γ-position. In unsymmetrical β-diketones the second deprotonation occurs at the less substituted γ-position (eq 14). The scope of this reaction, including a tabular survey of known examples, has been carefully reviewed.[30] Potassium amide in liquid ammonia has also been used for the preparation of 1,3-dinitro-2-keto derivatives from the reaction of cycloalkanones with alkyl nitrates.[31]

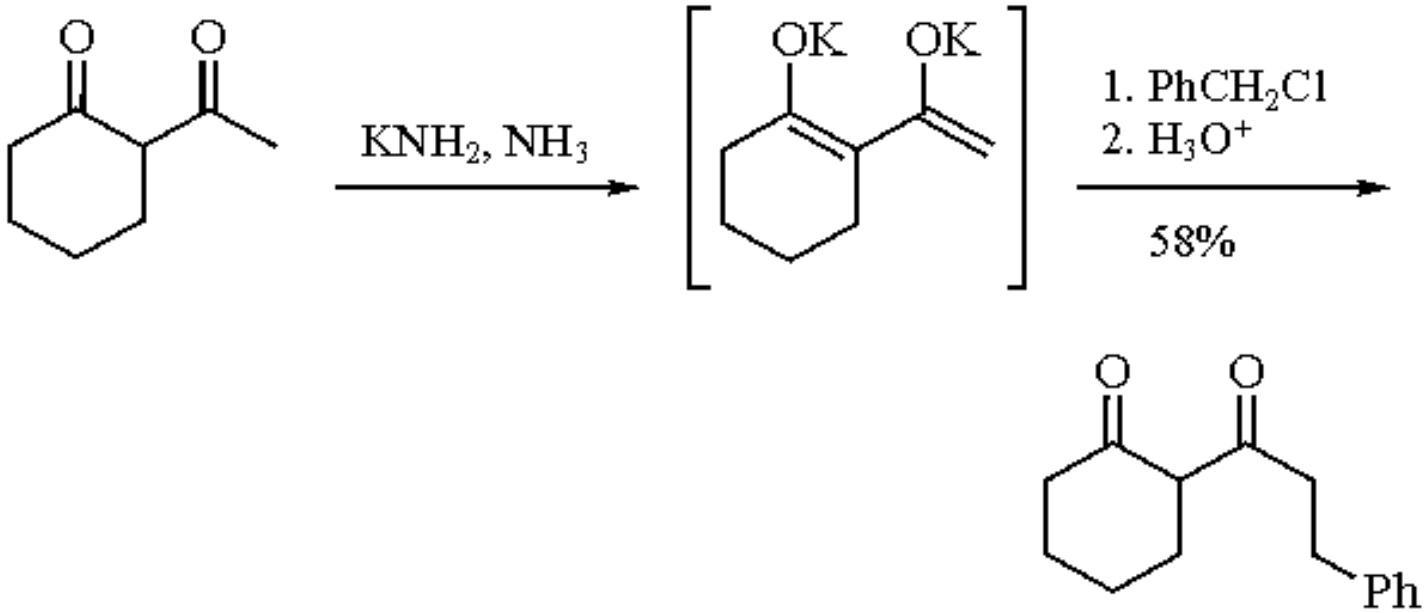

(14)

Deprotonation of benzyl ethers by potassium amide in liquid ammonia has been used to effect the Wittig rearrangement.[32] In a preparation of phenanthrene, use of potassium amide accomplished the rearrangement to the carbinol in 90% yield after 1 h, whereas ***Phenyllithium*** required 1 week (eq 15).[33]

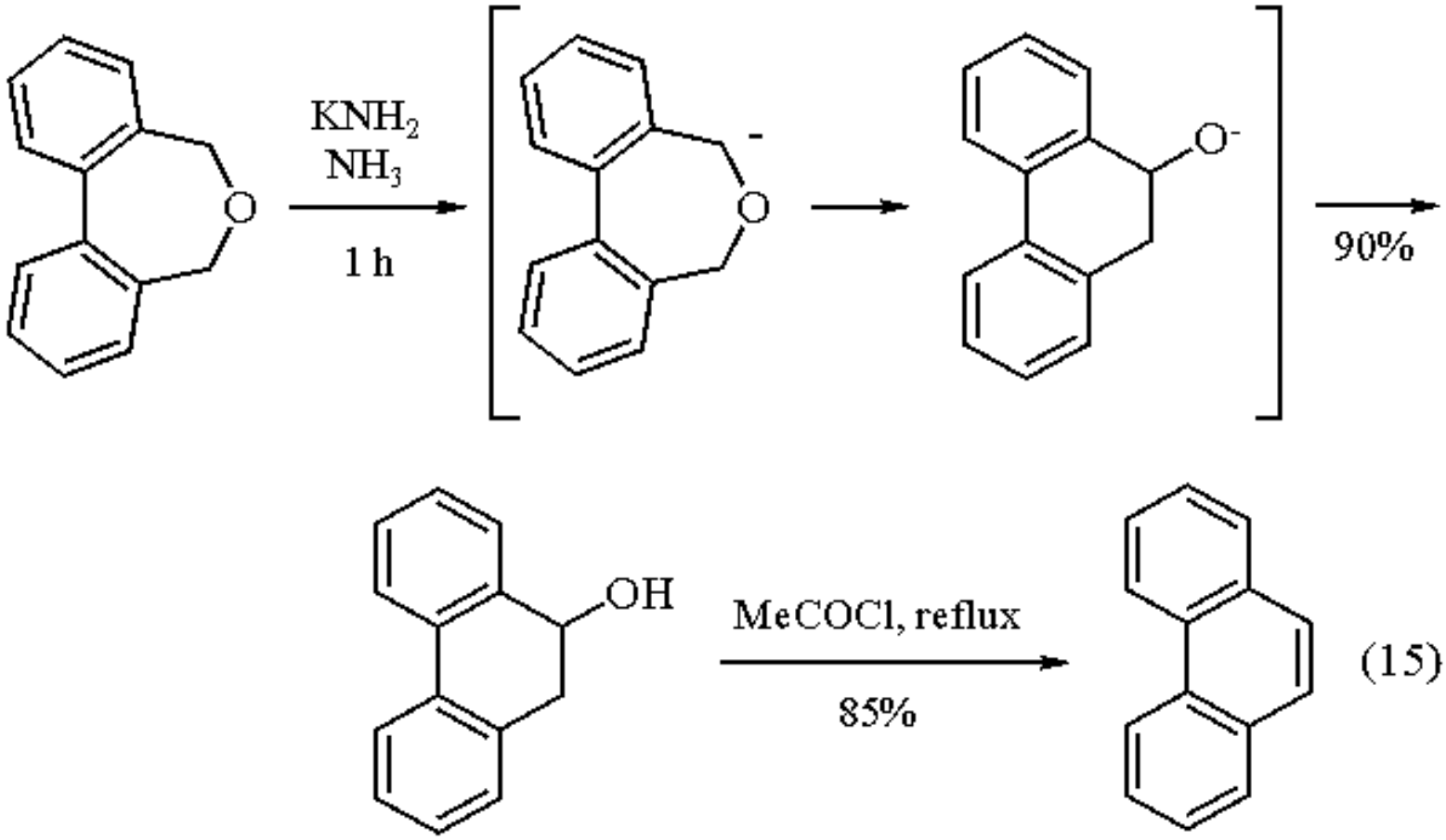

(15)

Examples of large-scale preparations utilizing potassium amide in liquid ammonia for the benzylic deprotonation of lutidine and diphenylacetonitrile have been published.[3,34] Allylic deprotonation of 2-chloromethyl-1-butene with potassium amide in THF at 65 °C has been used in an effective preparation of vinylcyclopropane (eq 16).[35]

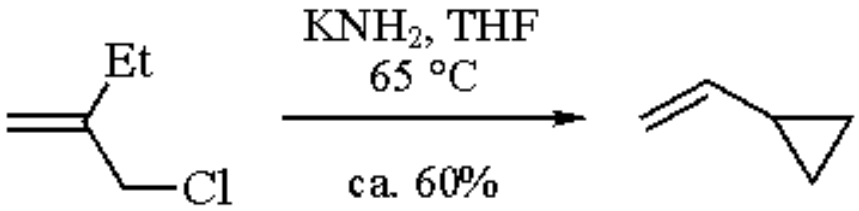

(16)

Elimination Reactions.

Potassium amide in liquid ammonia can be used as a base to induce elimination reactions.[36] For example, this reagent has been used in a preparation of dimethoxycyclopropene via an intramolecular alkylation followed by elimination (eq 17).[37] Potassium amide-induced elimination followed by an additional deprotonation has also been used to generate 8,8-dimethylcyclooctatrienyl anion (eq 18).[38]

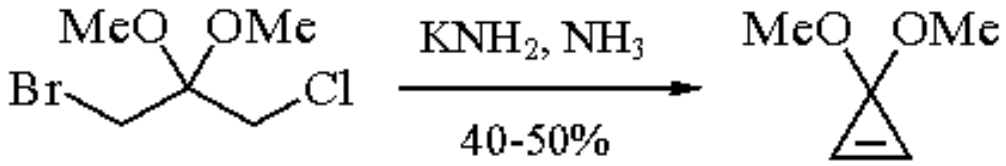

(17)

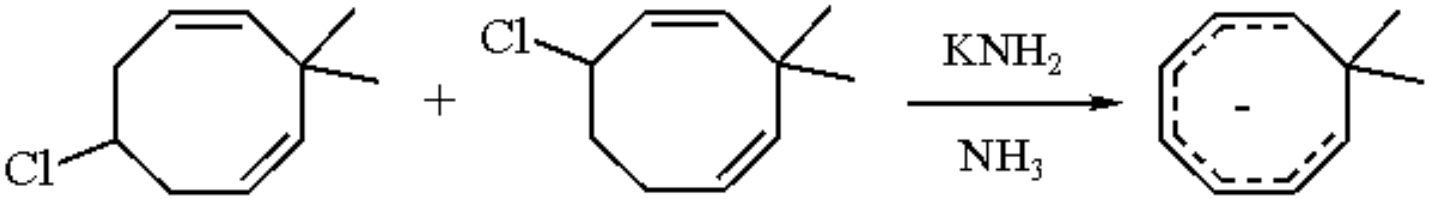

(18)

Related Reagents.

Lithium Amide; ***Lithium Diisopropylamide***; ***Potassium 3-Aminopropylamide***; ***Potassium Hexamethyldisilazide***; ***Potassium Diisopropylamide***; ***Sodium Amide***.

---

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Potassium 3-Aminopropylamide

$KNH(CH_2)_3NH_2$

[56038-00-7] · $C_3H_9KN_2$ · Potassium 3-Aminopropylamide · (MW 112.24)

(strong base[1] used primarily for the isomerization of internal alkynes to terminal alkynes;[2] can also be used to isomerize alkenes;[3] also used to promote intramolecular transamidation reactions[4])

Alternate Name: KAPA.

Solubility: highly sol (&egt;1.5 M) in excess 1,3-diaminopropane

Preparative Methods: usually prepared as a solution in excess, dry 1,3-diaminopropane.[5] The most common preparation involves the direct, quantitative reaction of ***Potassium Hydride*** with excess amine at 20-25 °C.[6] Alternative preparations have been developed to avoid the handling and purification of KH. The reagent has been prepared by the reaction of ***Potassium Amide*** and 1,3-diaminopropane followed by evaporation of excess ***Ammonia*** in vacuo.[7] The reagent has also been prepared by heating ***Potassium*** and 1,3-diaminopropane under sonication.[8] A trace of iron(III) nitrate increases the rate of reagent formation, although it is not essential. Addition of ***Potassium t-Butoxide*** to lithium 3-aminopropylamide (from ***Lithium*** and 1,3-diaminopropane) probably generates KAPA in situ via cation exchange.[9]

Handling, Storage, and Precautions: moisture sensitive. A solution of KAPA in 1,3-diaminopropane appears stable for at least 8 h at rt and possibly even for 2-3 days.[2,10] Use in a fume hood.

Isomerization of Alkynes.

Potassium 3-aminopropylamide is best known for its use in the acetylene zipper reaction.[2] This reagent induces a rapid migration of triple bonds from the interior of a carbon chain to the terminus. Previously reported isomerizations of alkynes required very strong bases (e.g. ***Sodium***, ***Sodium Amide***) and elevated temperatures to effect a one-position isomerization of a 2-alkyne to a 1-alkyne. Migrations over more than one position were reported to be generally unsatisfactory or very slow. By contrast, KAPA produces rapid, multiposition alkyne migrations to provide the terminal alkyne within seconds at 0 °C (eq 1). Although internal alkynes are favored thermodynamically, this isomerization is driven forward by the formation (possibly aided by precipitation) of the stable metal acetylide. Quenching of the acetylide with water provides the terminal alkyne in excellent yield. In nonlinear systems, migration is blocked by branching in the chain.

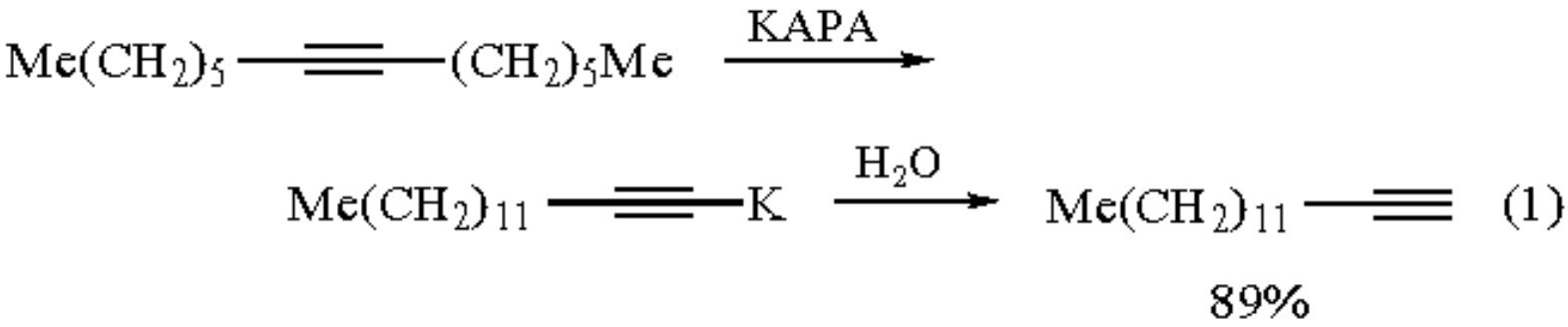

The reaction has also been studied in functionalized systems. In alkynic alcohols, KAPA-induced migration of the triple bond proceeds to the chain terminus which is remote from the OH function (eq 2).[11] It is believed that the anionic intermediate in the migration of the triple bond is inhibited from migrating toward the similarly charged alkoxide.[11a] If the hydroxy group is attached to a chiral carbon, this phenomenon protects the configuration of that carbon during the migration process. Isomerization of chiral propargylic alcohols proceeds to give the terminal alkynic alcohols with no significant loss of enantiomeric purity (eq 3).[12]

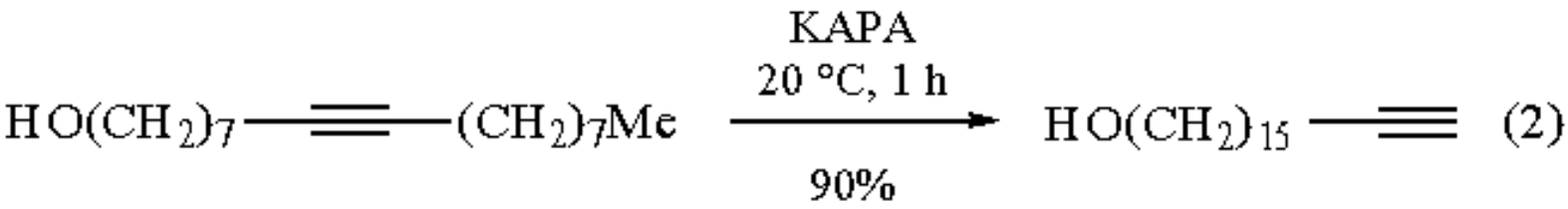

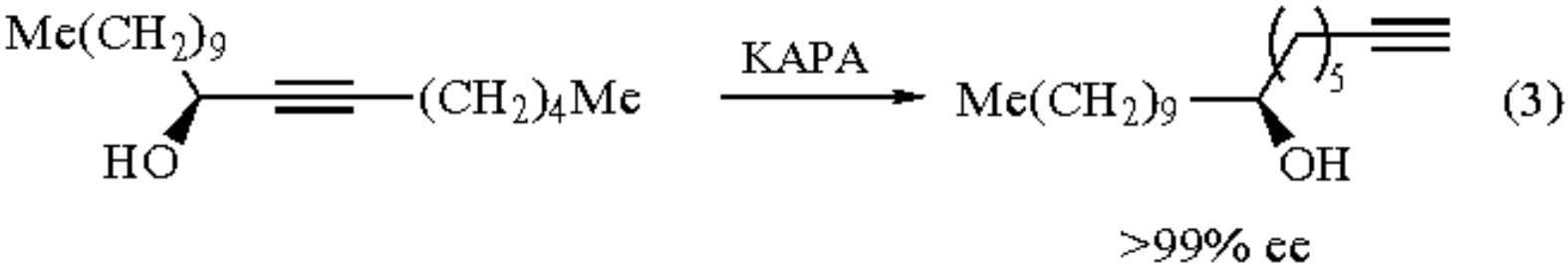

Successful isomerizations have also been carried out with o-alkynylorganoboranes and propynyl ethers.[13] Isomerizations of alkynic carboxylic acids generally lead to a mixture of products and poor yields of the terminal alkyne.[14] However, if the carboxylic acid group is separated from the alkyne by an intervening carbinol, the carboxylate can be carried through the migration reaction without difficulty.[15]

KAPA can also be used for the in situ generation of an internal alkyne which then rapidly isomerizes to the terminal position. Allenes, vinyl sulfides, and cyclic ethers have been used as alkyne equivalents to provide terminal alkynes (eq 4).[16]

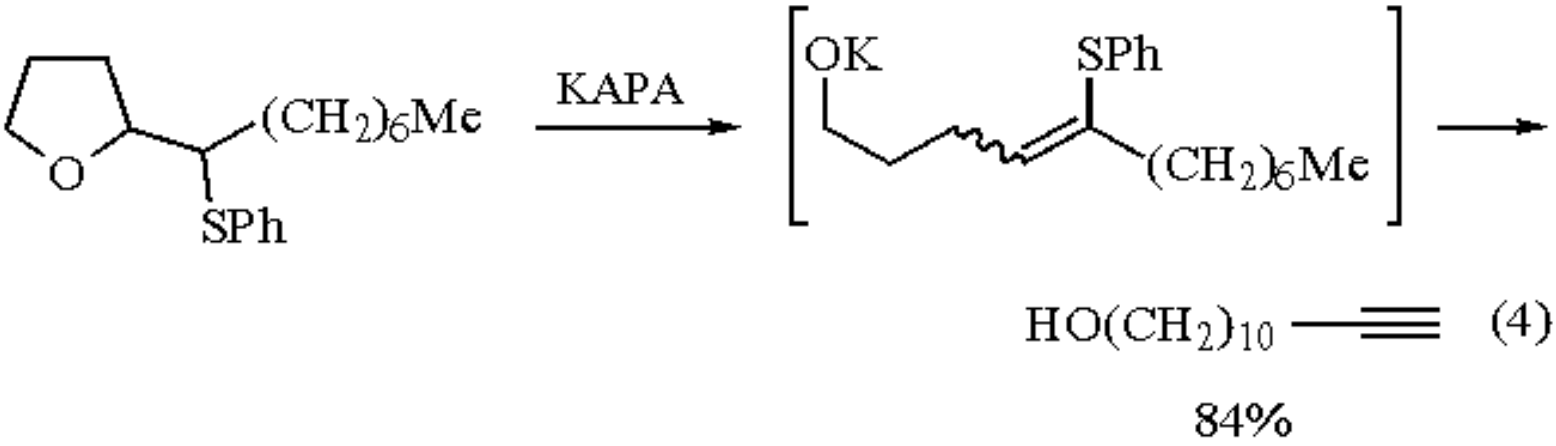

Isomerization of Exocyclic Alkenes.

Trace quantities of KAPA can be used in a two-phase reaction to effect the rapid, low-temperature isomerization of neat, exocyclic alkenes on a large scale.[3] In particular, KAPA has been used for the isomerization of (-)-β-pinene to the less accessible (-)-α-pinene in high yield and without racemization (eq 5).[17]

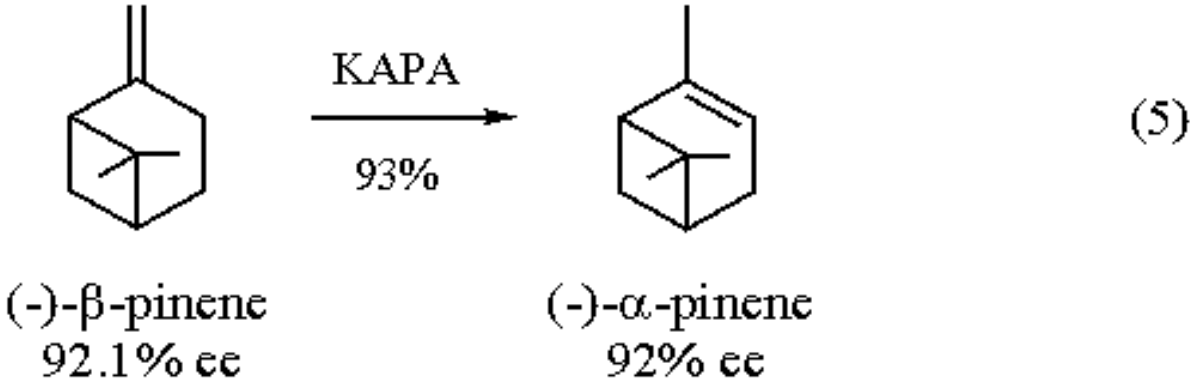

Intramolecular Transamidation Reactions.

KAPA is recommended for use in the zip reaction for the ring enlargement of aminolactams (eq 6).[4,18] It is believed that the reaction is driven in part by formation of the resonance-stabilized amide anion.

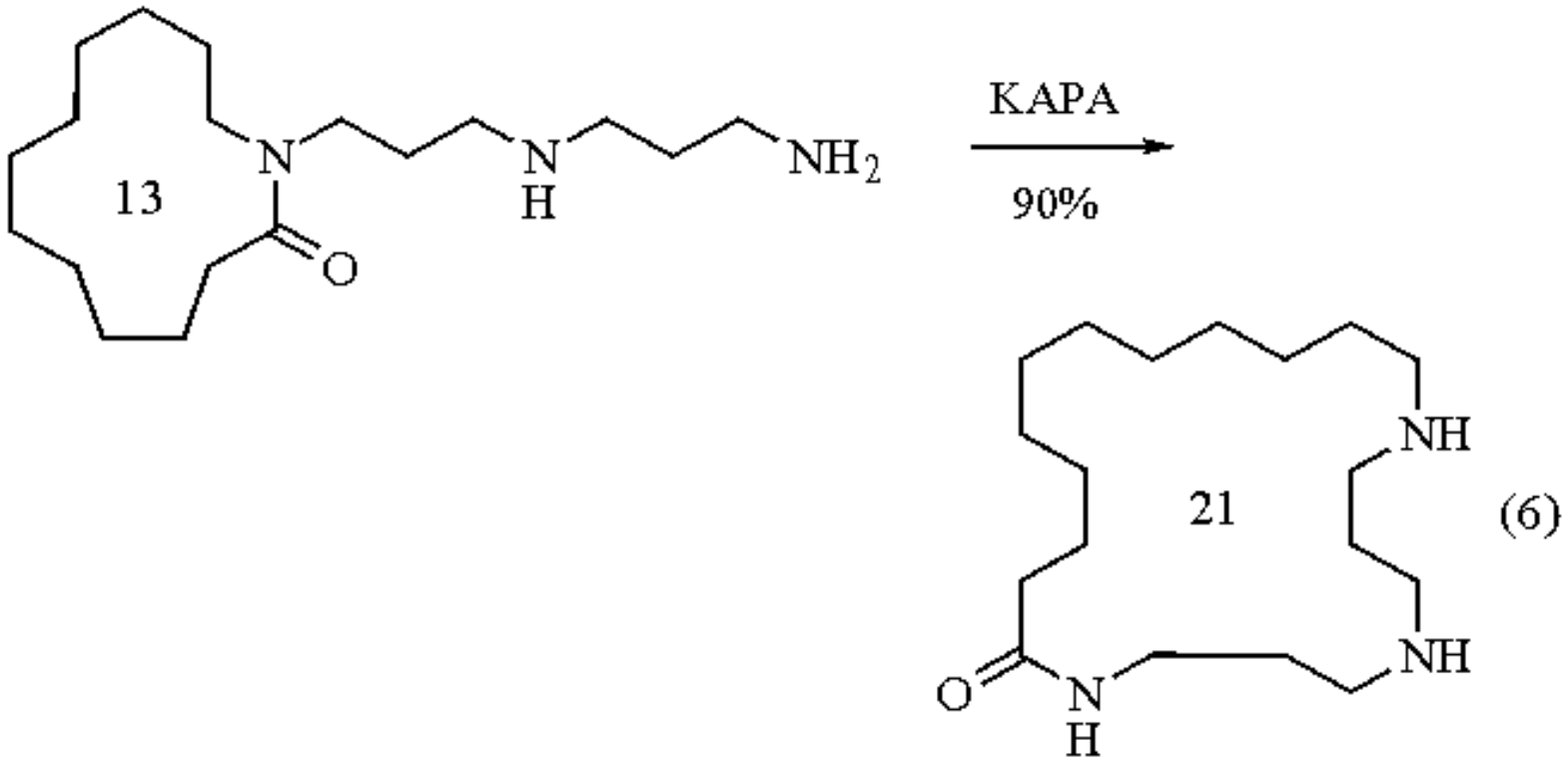

Related Reagents.

Lithium Amide; ***Lithium Diisopropylamide***; ***Potassium Hexamethyldisilazide***; ***Potassium Diisopropylamide***.

---

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Potassium Azodicarboxylate

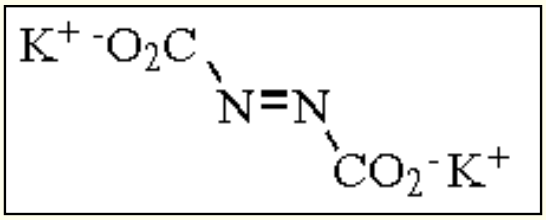

[4910-62-7] · $C_2K_2N_2O_4$ · Potassium Azodicarboxylate · (MW 194.24)

(used for the generation of diimide[1])

Alternate Name: azodicarboxylic acid, potassium salt.

Physical Data: crystalline yellow solid; properties do not appear to be recorded.

Solubility: insol aprotic organic solvents; partially sol protic organic and aqueous organic solvents.

Form Supplied in: not currently commercially available.

Preparative Method: by the reaction of potassium hydroxide with $H_2NCON{=}NCONH_2$[2] (which is commercially available).

Handling, Storage, and Precautions: there has been one report that potassium azodicarboxylate exploded violently when left exposed to bright sunlight for about 30 min;[3] there have been other reports of suspected nonviolent decomposition of the compound on storage;[4] it is advisable to dry the compound in vacuo and not store in a sealed container. Extreme care must be exercised in the preparation, isolation, storage, and use of potassium azodicarboxylate.

The treatment of potassium azodicarboxylate with a carboxylic acid in protic or aprotic organic solvents results in the ultimate formation of ***Diimide***, which is a very useful reagent for the mild, noncatalytic reduction of C-C π-systems. Potassium azodicarboxylate is prepared by the reaction of ***Potassium Hydroxide*** with azodicarboxamide (eq 1).[2]

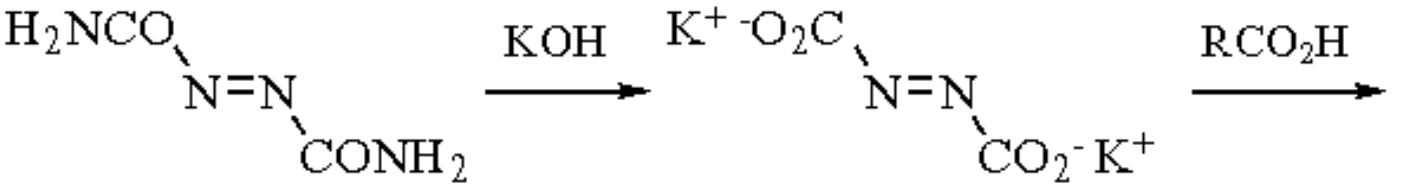

HN=NH (1)

The use of potassium azodicarboxylate as a source of diimide is particularly useful for the generation of deuterium- and tritium-labeled diimide in aprotic organic solvents for the position-, facial- and stereoselective reduction of C-C π-systems, as illustrated in eq 2.[5] In these reduction reactions the substrate and an excess of the potassium azodicarboxylate are placed in an appropriate solvent and a slight excess of the carboxylic acid is slowly added to the mixture. The yields of product are generally very high.

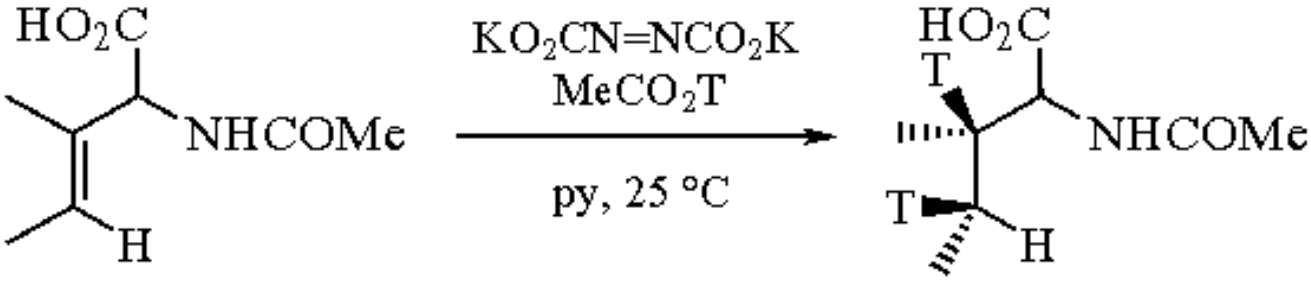

(2)

This procedure is also very useful for the *syn* reduction of alkynyl halides, as illustrated in eq 3.[6]

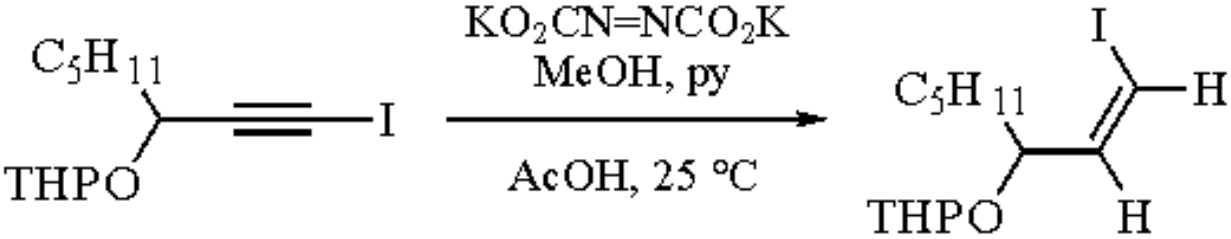

(3)

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Daniel J. Pasto

Potassium Bromate

$KBrO_3$

[7758-01-2] · $BrKO_3$ · Potassium Bromate · (MW 167.00)

(convenient source of molecular bromine;[1a] used for bromination of deactivated aromatics;[2] used in chemical oscillating reactions[3])

Physical Data: mp ~350 °C, dec ~370 °C with evolution of oxygen; *d* 3.27 g cm^{-3}.

Solubility: sol 12.5 parts water, 2 parts boiling water; almost insol alcohol.

Form Supplied in: white crystals or granules; widely available. *Drying:* for analytical work dry at 100-110 °C for 1 h.

Handling, Storage, and Precautions: potassium bromate is a strong oxidizing agent (standard potential 1.44 V). Toxicity is low. Keep from contact with mineral acids and organic compounds during storage. Potassium bromate is an analytical standard for iodometry. Standard solutions are stable indefinitely.

Generation of Bromine and Bromination Reactions.

Potassium bromate and ***Sodium Bromate*** react with bromide ion in dilute acid solution[1] to produce bromine according to eq 1.

$$BrO_3^- + 5\,Br^- + 6\,H^+ \longrightarrow 3\,Br_2 + 3\,H_2O \qquad (1)$$

As such, it is a convenient reagent for the bromination of alkenes, phenols, salicylic acid, aniline, and other activated compounds.[4] Synthetically useful brominations of methyl ketones,[5,6] 3-substituted cyclohexenones,[7] thiophene (in a two-phase system),[8] organoboranes (to produce an α-bromoorganoborane which rearranges to the alcohol),[9] cyclopentamethylenediphenylstannane (to form cyclopentamethylenedibromostannane),[10] and sulfonylhydrazides (to form sulfonyl bromides)[11] have been reported.

Bromination of Deactivated Aromatics.

Potassium bromate in the absence of added bromide is an effective brominating agent. An early report[12] that

potassium bromate in ***Sulfuric Acid***, in the absence of added bromide, brominated benzene went unnoticed for over 100 years. An efficient procedure for the bromination of deactivated aromatic compounds has appeared.[2] For example, nitrobenzene[2] has been brominated in 88% yield in this fashion (eq 2). The reaction is dependent on the concentration of the sulfuric acid. This method is arguably superior to other methods for nitrobenzene bromination.[13] (Warning! potassium bromate decomposes rapidly in 70% sulfuric acid solution with the evolution of heat.[2])

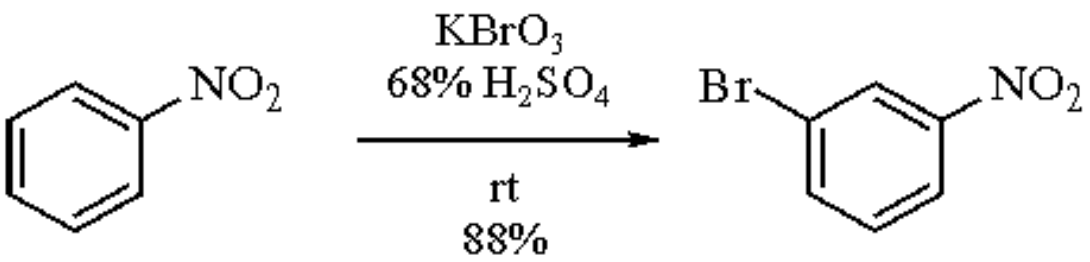

(2)

Other deactivated aromatics that can be brominated by this method include benzoic acid,[2,14] halobenzoic acids,[15] phthalic acid,[2] hydroxybenzoic acid,[16] halobenzenes,[15,17] benzonitrile,[16] benzanilide,[16] cinnamic and hydrocinnamic acids,[16] phenylacetic acid,[16] benzophenone,[16] acetophenone,[2] and 2,5-dimethyl-1,3,4-oxadiazoles.[18] In the case of acetophenone, the bromination occured at the aromatic ring and not on the methyl group,[19] which is the normal position for attack using molecular bromine (eq 3).

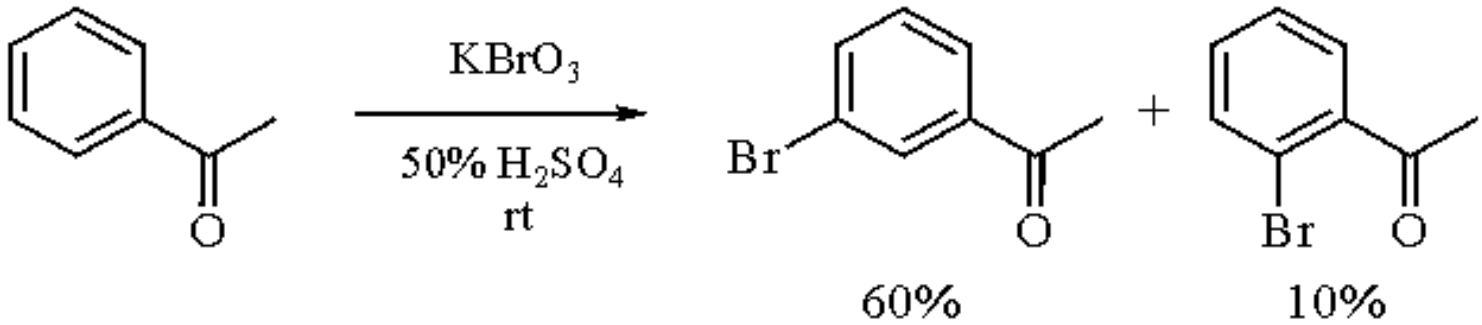

(3)

One report in which sodium bromate is used in combination with ***Bromotrimethylsilane*** for the bromination of aromatic rings has appeared.[20] While activated rings such as anisole and phenol react satisfactorily, deactivated rings do not. Toluene gave the benzyl bromide product instead of the ring brominated product.[20]

Chemical Oscillators.

Chemical oscillating reactions such as the Belousov-Zhabotinski reaction[3] and a clock reaction[21] have been reported using potassium bromate/sodium bromate. Chemical oscillations such as these are driven by a combination of bromination and oxidation reactions. A generalized mechanism for bromate-driven oscillators controlled by bromide has appeared.[22] This is still an active area for investigation.[23]

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Potassium *t*-Butoxide

***t*-BuOK**

[865-47-4] · C_4H_9KO · Potassium *t*-Butoxide · (MW 112.23)

(strong alkoxide base capable of deprotonating many carbon and other Brφnsted acids; relatively poor nucleophile[1])

Physical Data: mp 256-258 °C (dec).

Solubility: sol/100g solvent at 25-26 °C: hexane 0.27 g, toluene 2.27 g, ether 4.34 g, *t*-BuOH 17.80 g, THF 25.00 g.

Form Supplied in: white, hygroscopic powder; widely available commercially; also available as a 1.0 M solution in THF.

Preparative Methods: sublimation (220 °C/1 mmHg; 180 °C/0.05 mmHg) of the commercial material prior to use is recommended. For critical experiments, the reagent should be freshly prepared prior to use. Solutions of the reagent in *t*-BuOH may be prepared by reaction of the anhydrous alcohol with ***Potassium*** under nitrogen,[2] or the solvent may be removed (finally at 150 °C/0.1-1.0 mmHg for 2 h) and solutions prepared using other solvents.[3]

Handling, Storage, and Precautions: do not breathe dust; avoid contact with eyes, skin, and clothing. Reacts with water, oxygen, and carbon dioxide, and may ignite on exposure to air at elevated temperatures. Handle in an inert atmosphere box or bag and conduct reactions under an inert atmosphere in a fume hood. Store in small lots in sealed containers under nitrogen.

Introduction.

Potassium *t*-butoxide is intermediate in power among the bases which are commonly employed in modern organic synthesis. It is a stronger base than the alkali metal hydroxides and primary and secondary alkali metal alkoxides,[1] but it is a weaker base than the alkali metal amides and their alkyl derivatives, e.g. the versatile strong base ***Lithium Diisopropylamide***.[4] The continued popularity of *t*-BuOK results from its commercial availability and the fact that its base strength is highly dependent on the choice of reaction solvent. It is strongly basic in DMSO, where it exists primarily as ligand-separated ion pairs and dissociated ions, but its strength is significantly decreased in solvents such as benzene, THF, and DME, where its state of aggregation is largely tetrameric. DMSO is able to enhance the basicity of the *t*-butoxide anion by selectively complexing with the potassium cation. Other additives, such as the dipolar

aprotic solvent ***Hexamethylphosphoric Triamide*** (HMPA) and ***18-Crown-6***, have a similar effect. This section will provide cursory coverage of the reactions of *t*-BuOK in *t*-BuOH and in relatively nonpolar aprotic solvents. The unique features of ***Potassium t-Butoxide-Dimethyl Sulfoxide***, ***Potassium t-Butoxide-Hexamethylphosphoric Triamide***, and ***Potassium t-Butoxide-18-Crown-6***, as well as those of the ***Potassium t-Butoxide-t-Butyl Alcohol Complex*** (1:1), are described elsewhere in this encyclopedia.

Alkylations.

Many bases which are weaker than *t*-BuOK are capable of essentially quantitative conversion of active methylene compounds into the corresponding enolates or other anions.[5] However, the alkylation of diethyl malonate with a bicyclic secondary tosylate (eq 1)[6] and the alkylation of ethyl *n*-butylacetoacetate with *n*-BuI (eq 2)[7] provide examples of cases where the use of *t*-BuOK in *t*-BuOH is very effective. In the latter reaction, cleavage of the product via a retro-Claisen reaction is minimized with the sterically hindered base and yields obtained are higher than when ***Sodium Ethoxide*** or EtOK in EtOH, ***Sodium*** in dioxane or toluene, or ***Sodium Hydride*** in toluene are used for the enolate formation.

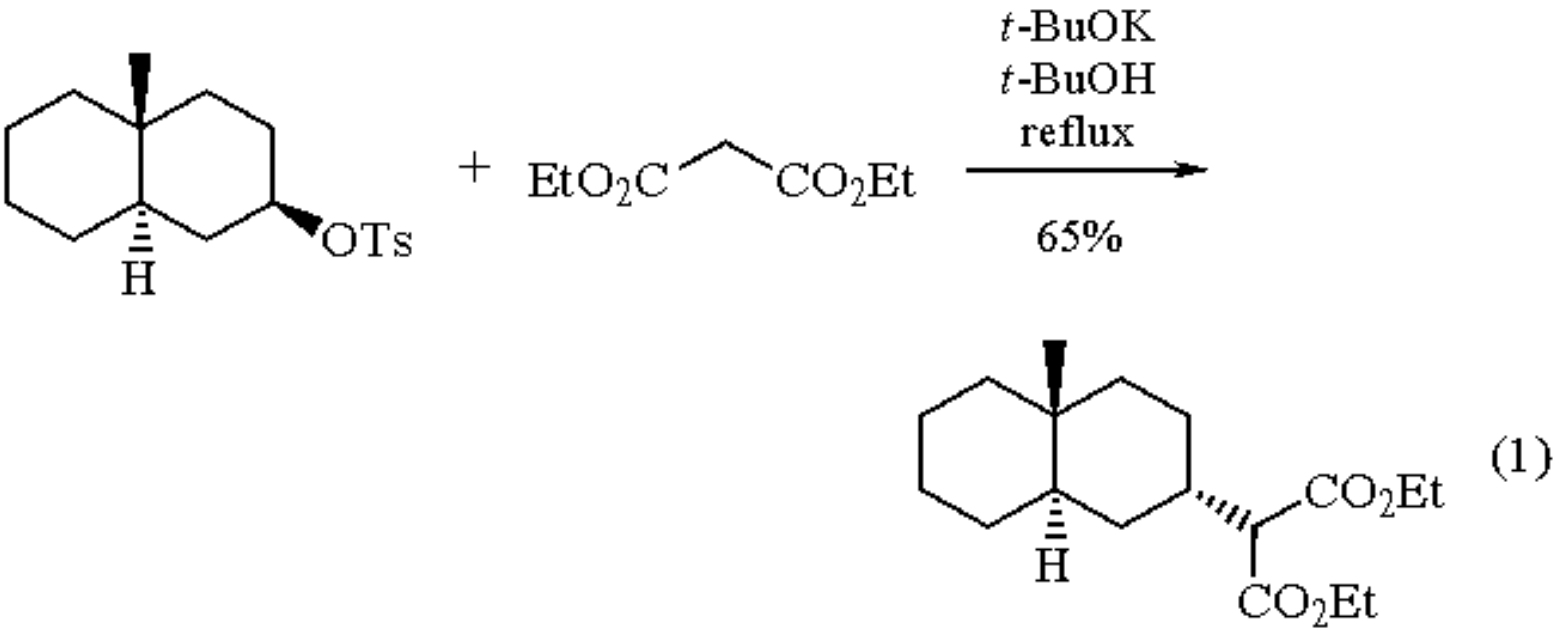

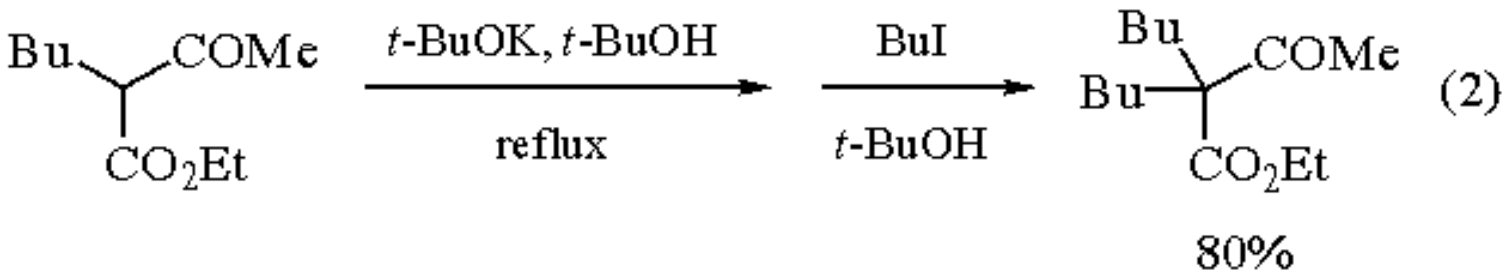

Potassium *t*-butoxide in *t*-BuOH or ethereal solvents is not capable of effecting quantitative formation of enolates of unactivated saturated ketones;[8] also, because potassium enolates are subject to rapid proton transfer reactions, their intermolecular alkylations are complicated by equilibration of structurally isomeric enolates, polyalkylation, and aldol condensation reactions.[9] Thus reactions of preformed lithium enolates (generated by deprotonation of ketones with LDA or by indirect procedures) with alkylating agents provide the method of choice for regioselective alkylation of

unsymmetrical ketones.[9,10] However, as illustrated in eqs 3 and 4,[11,12] ketones capable of forming only a single enolate, such as symmetrical cyclic ketones and those containing α-methylene blocking groups, are readily alkylated via *t*-BuOK-promoted reactions. Also, *t*-BuOK in *t*-BuOH or benzene frequently has been employed for the alkylation of α,α-disubstituted aldehydes.[9]

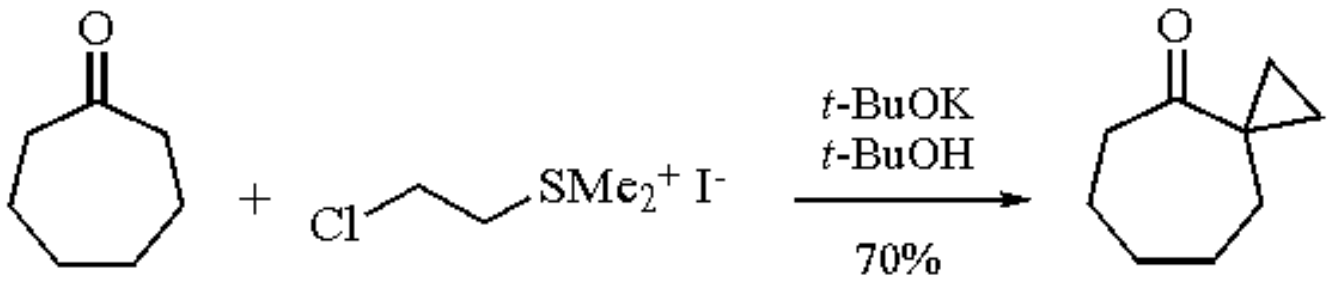

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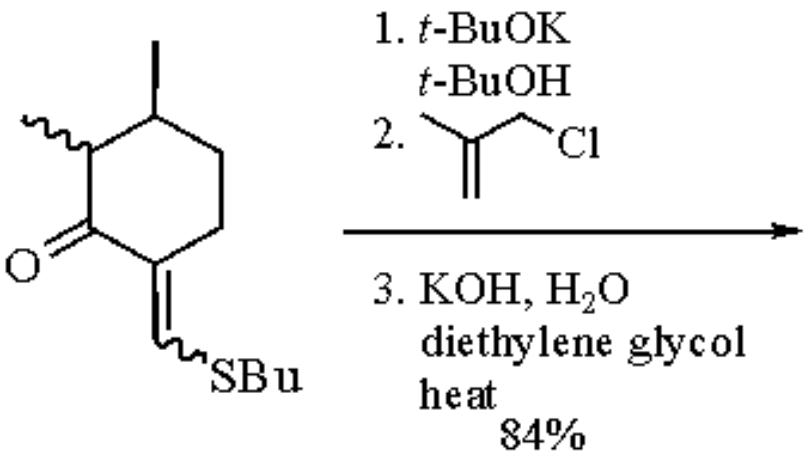

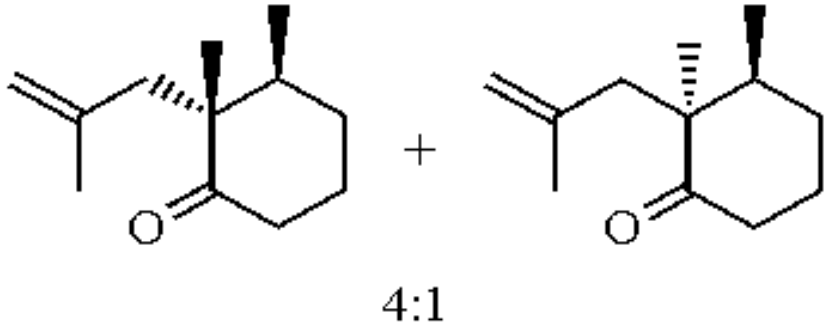

(4)

As illustrated in eq 5, α,β-unsaturated ketones undergo α,α-dialkylation when treated with excess *t*-BuOK/*t*-BuOH and an alkylating agent.[13] The α,α-dimethylated β,γ-unsaturated ketone is formed by conversion of the initially produced α-methylated β,γ-unsaturated ketone to its dienolate, which undergoes a second methylation faster than the β,γ-double bond is isomerized to the α,β-position.[14]

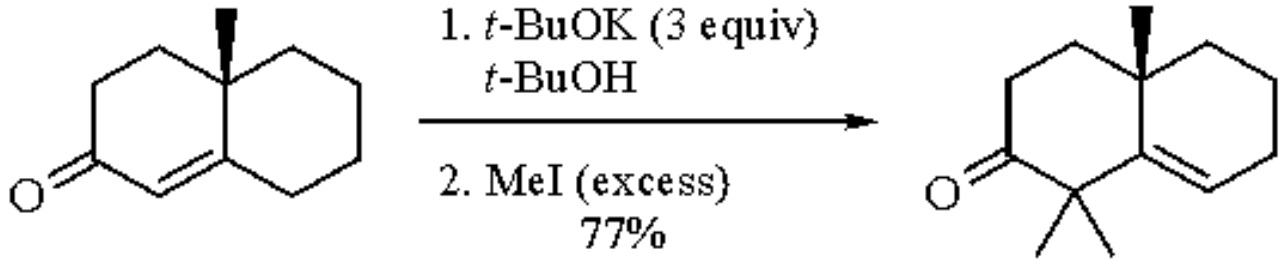

(5)

In contrast to intermolecular processes, intramolecular alkylations are frequently performed with *t*-BuOK in various solvents.[19] In eqs 6 and 7 are shown examples of *endo*- and *exo*-cycloalkylations of cyclic saturated ketones which lead to new five-membered rings.[15,16]

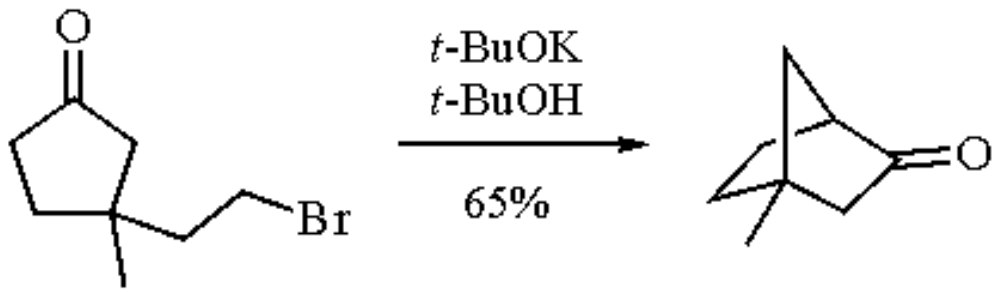

(6)

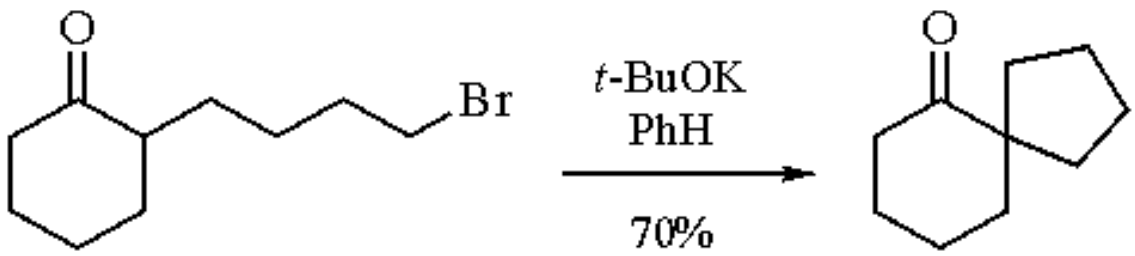

(7)

An interesting example of how a change in the base can influence the course of a cycloalkylation reaction is shown in eq 8.[17] Since the reaction with *t*-BuOK involves equilibrating conditions, *exo*-cycloalkylation occurs via the more-substituted enolate, which is more thermodynamically stable. On the other hand, when LDA is used as the base, *endo*-cycloalkylation occurs via the kinetically formed terminal enolate.

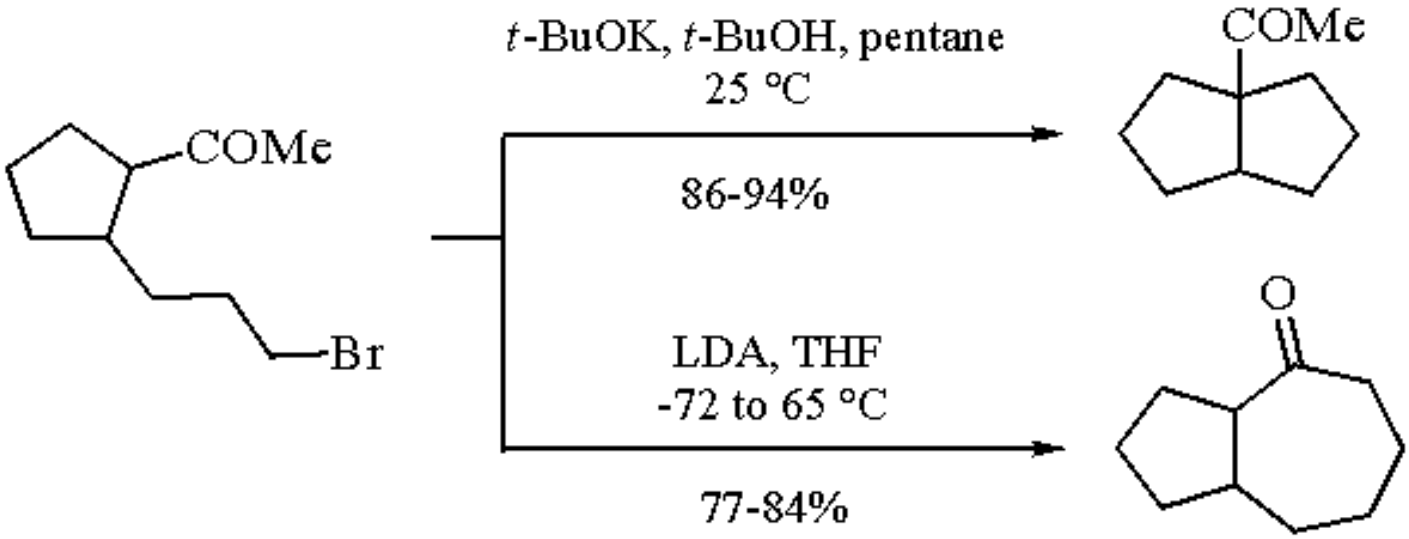

(8)

Intramolecular alkylations of α,β-unsaturated ketones may occur at the α-, α´-, or γ-positions depending upon the nature of the base, the leaving group, and other structural features. A recent example involving α-cycloalkylation using *t*-BuOK is shown in eq 9.[18]

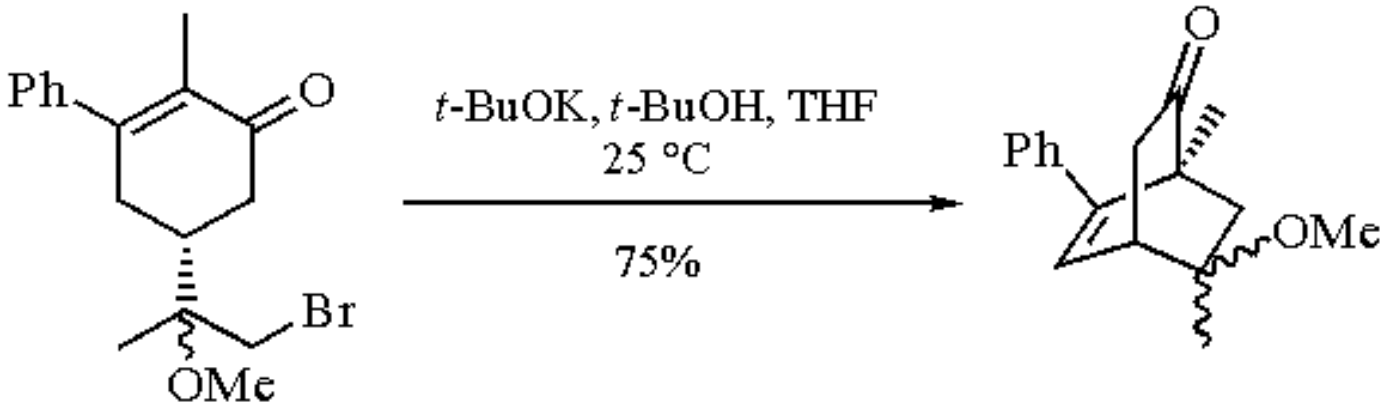

(9)

The reaction of α-halo esters, ketones, nitriles, and related compounds with appropriate organoboranes in the presence of *t*-BuOK can lead to replacement of the halogen with an alkyl or an aryl group.[19] An example of this reaction using an α-bromo ester is shown in eq 10.[20] THF is a more effective solvent than *t*-BuOH for alkylations of α-bromo ketones using this methodology.[21] Potassium 2,6-di-*t*-butylphenoxide, a mild, sterically hindered base, is much more effective than *t*-BuOK for the alkylation of highly reactive α-halo ketones, e.g. bromoacetone, and α-halo nitriles.[22]

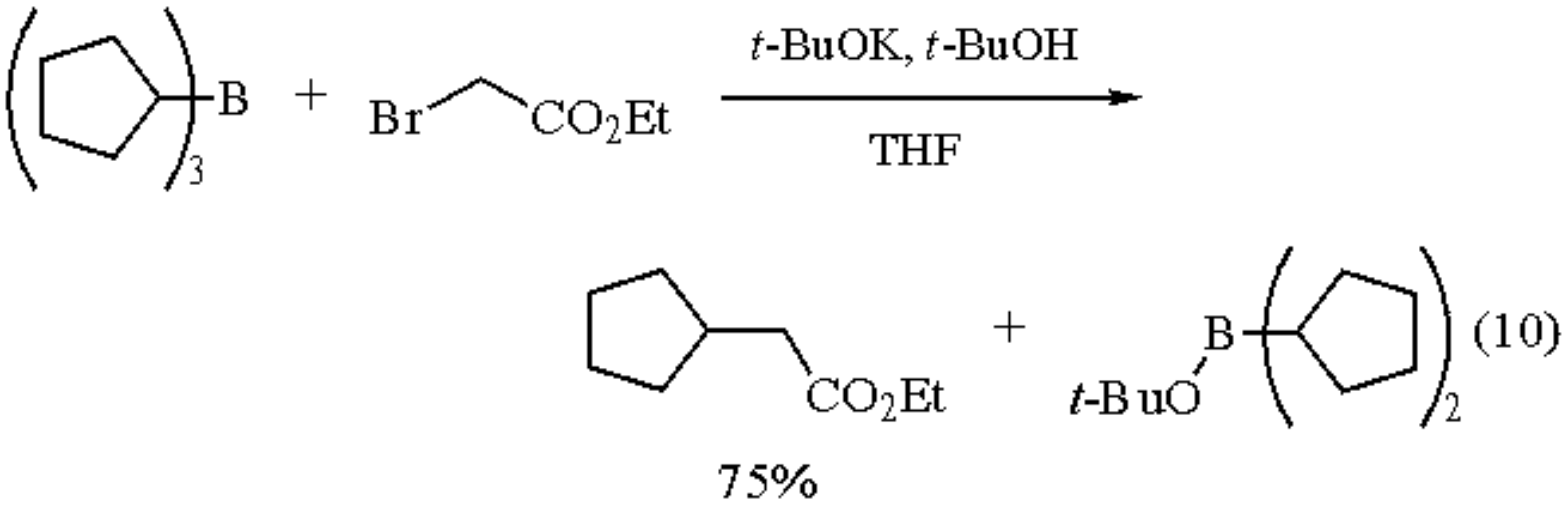

(10)

Condensation Reactions.

Traditionally, intermolecular aldol condensation reactions have been performed under equilibrating conditions using weaker bases than *t*-BuOK in protic solvents.[23] Since the mid-1970s, new methodology has focused on directed aldol condensations which involve the use of preformed ***Lithium*** and Group 2 enolates,[24] Group 13 enolates,[25] and transition metal enolates.[26] Although examples of the use of *t*-BuOK in intramolecular aldol condensations are limited, complex diketones (eq 11)[27] and keto aldehydes (eq 12)[28] have been cyclized with this base.

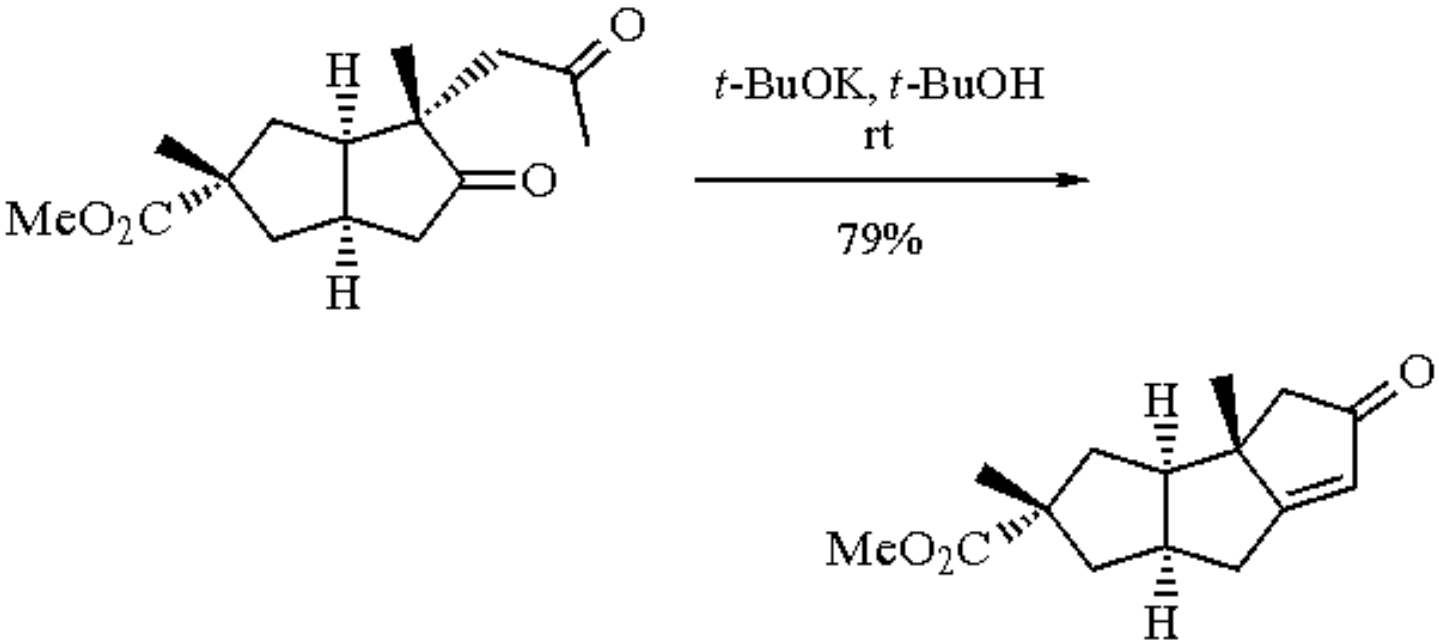

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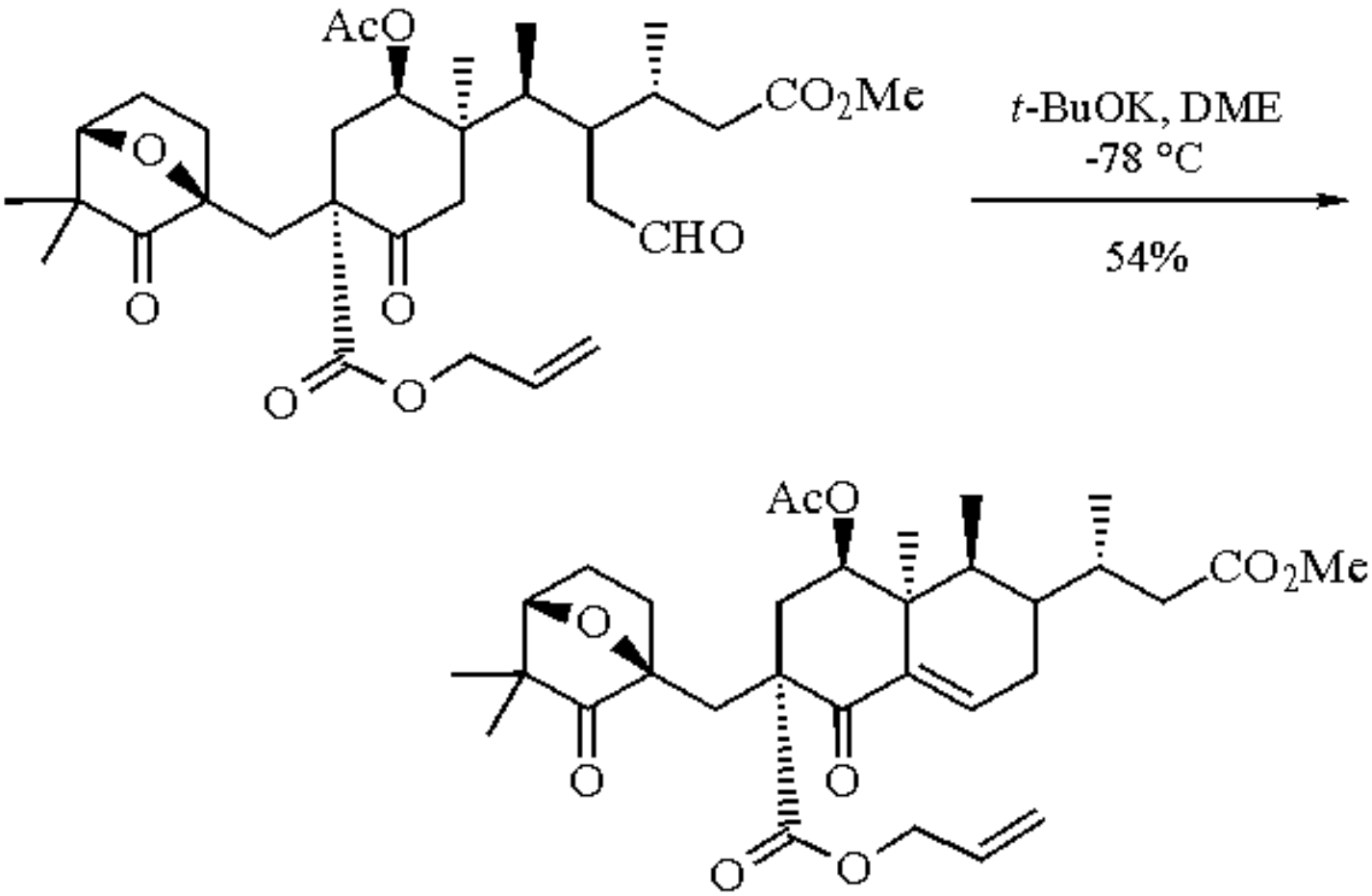

(12)

t-BuOK is the most commonly used base for the Darzens condensation of an α-halo ester with a ketone or an aromatic aldehyde to yield an α,β-epoxy or glycidic ester.[29] In the example shown in eq 13,[30] the aldol step is reversible and the epoxide ring closure step is rate limiting. This leads to the product with the ester group and the bulky β-substituent *trans*. However, in other systems the opposite stereochemical result often occurs because the aldol condensation step is rate limiting. In addition to esters, a wide variety of α-halo compounds that contain electron-

withdrawing groups may participate in these types of reaction.[29c]

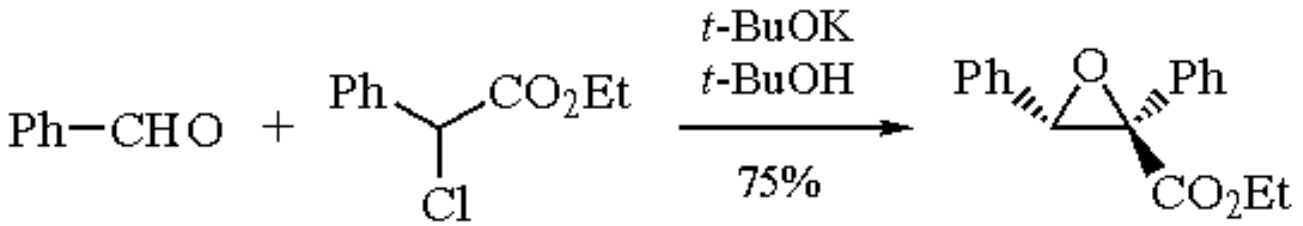

(13)

The Dieckmann cyclization of diesters and related reactions has found an enormous amount of use in the synthesis of five-, six-, seven-, and even larger-membered rings.[31] In unsymmetrical systems, steric effects and the stability of the product enolates determine the regiochemistry of the reaction. As shown in eqs 14 and 15,[32,33] *t*-BuOK is an effective base for these reactions when used in *t*-BuOH or other solvents such as benzene. In the former example, 40% of unchanged starting material is recovered when MeONa/PhH is used to effect the cyclization.

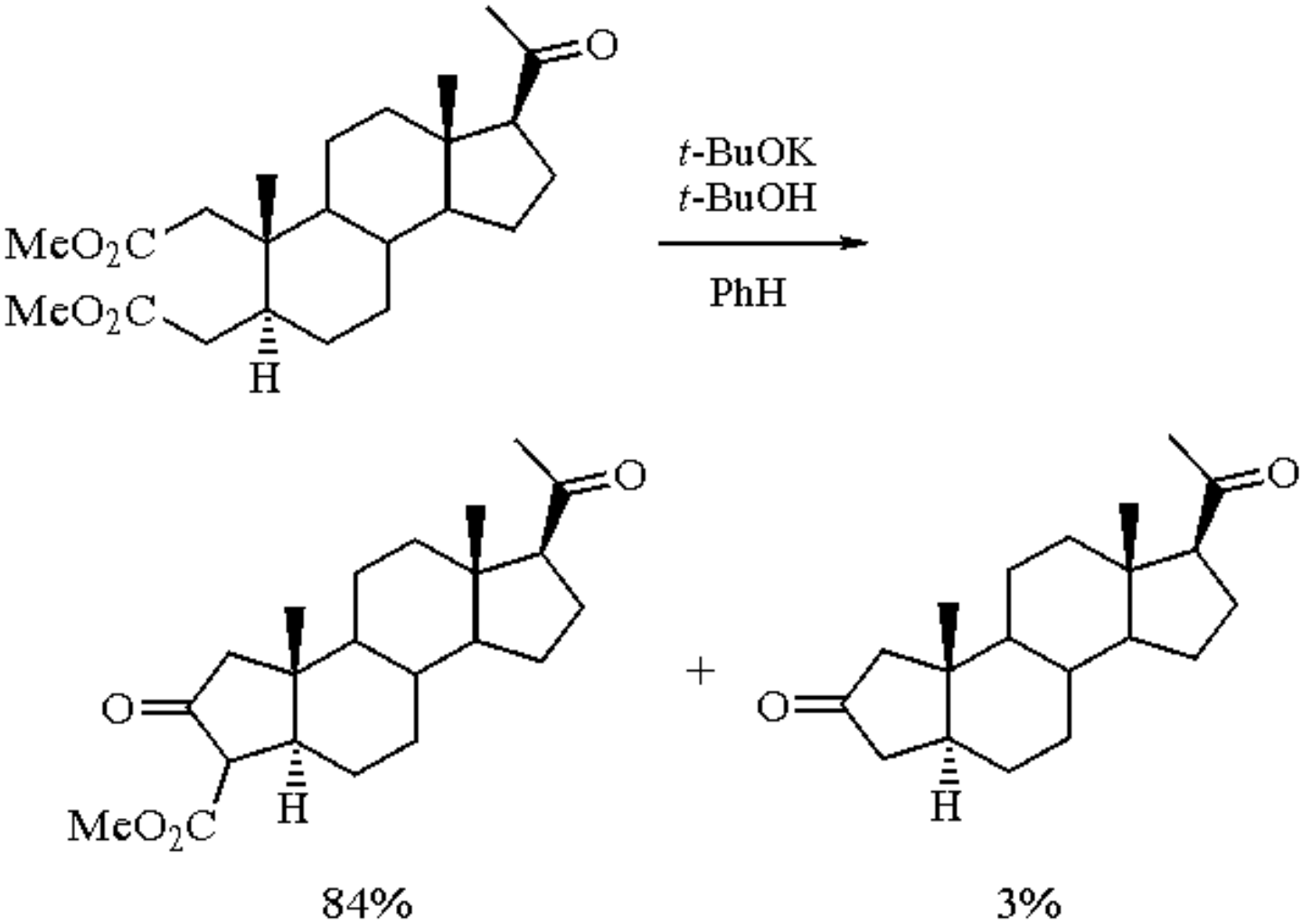

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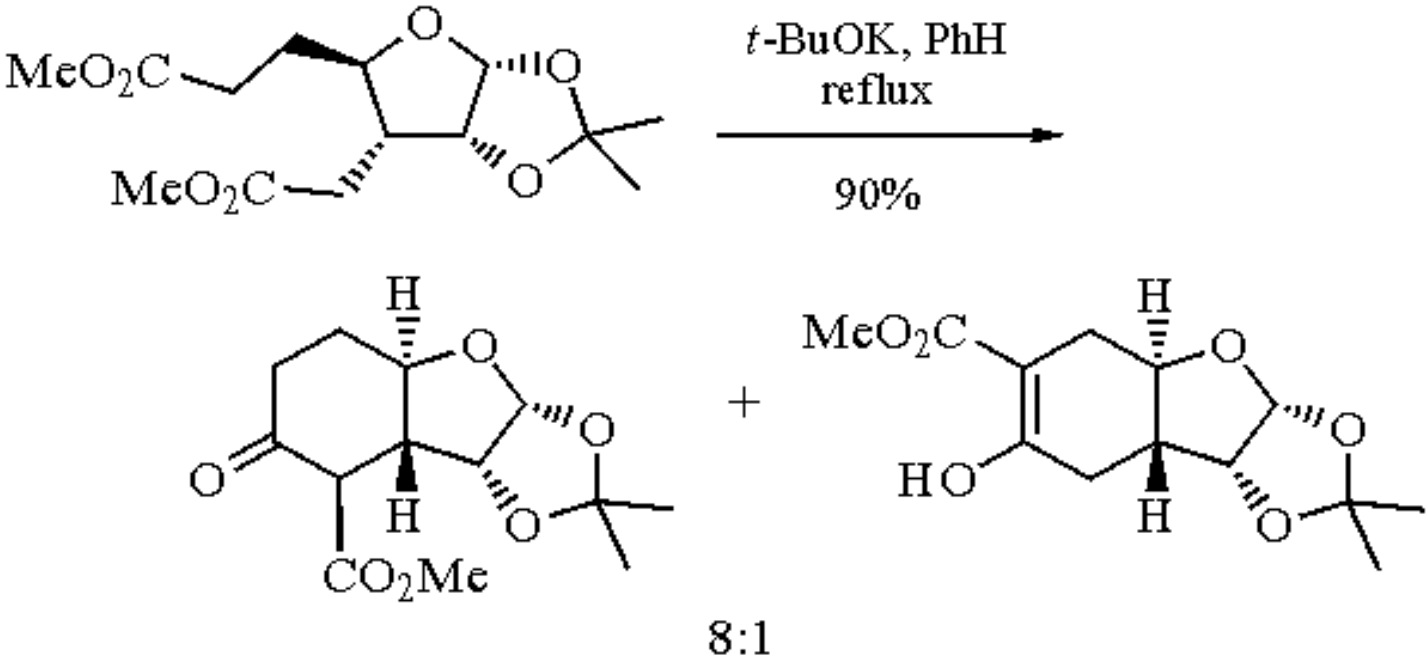

(15)

The nature of the base can profoundly influence the regiochemistry of the reaction. *t*-BuOK favors kinetic control in the reaction shown in eq 16 and the product derived from cyclization of the enolate having a β-amino group is obtained. However, when EtONa/EtOH is employed, the more stable β-keto ester enolate resulting from thermodynamic control is obtained.[34] In addition to diesters, dinitriles, ε-keto esters, ε-cyano esters, ε-sulfinyl esters, and ε-phosphonium esters may participate in these reactions.[31]

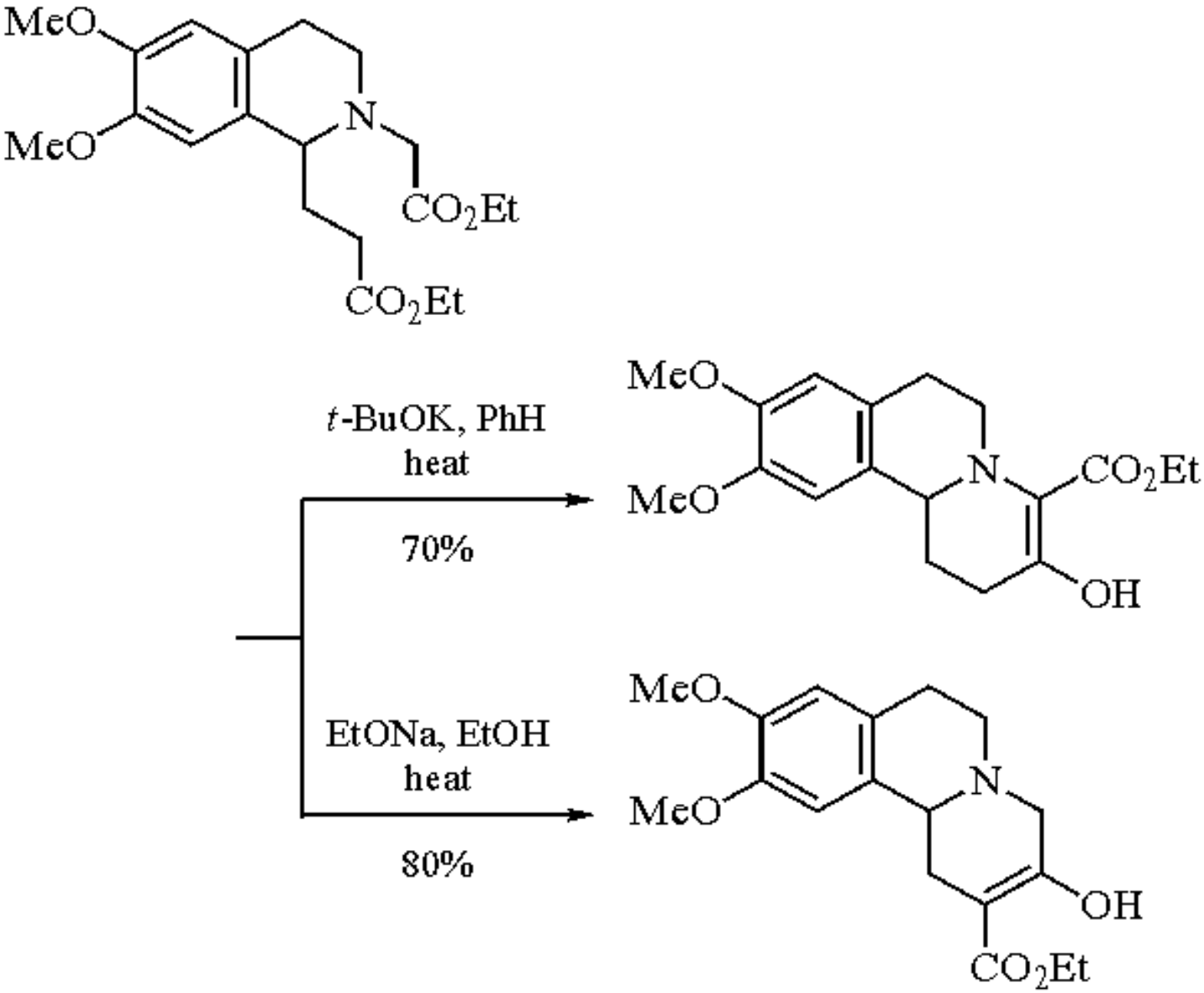

(16)

t-BuOK is a better base than EtONa for the Stobbe condensation (eq 17) because yields are higher, reaction times are shorter, and frequent side reactions of ketone or aldehyde reduction are avoided.[35]

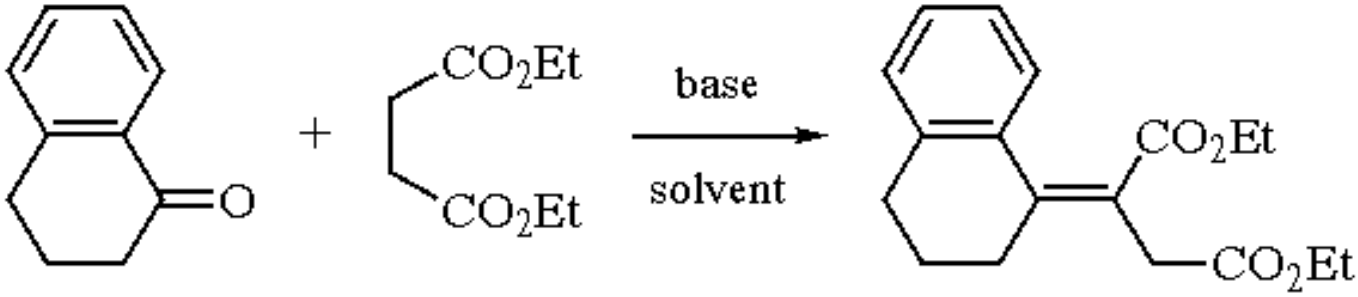

Base, solvent	Yield (%)
EtONa (2 equiv), EtOH, reflux, 6 h	79
t-BuOK (1.1 equiv), *t*-BuOH, reflux, 40 min	89-94

Although the use of *t*-BuOK for the generation of unstabilized ylides from phosphonium salts has been rare, it is the base of choice for the generation of ***Methylenetriphenylphosphorane*** for the Wittig reaction of hindered ketones (eq 18).[36] No 1,1-di-*t*-butylethylene is obtained from di-*t*-butyl ketone when NaH/DMSO is used to generate the ylide.[37]

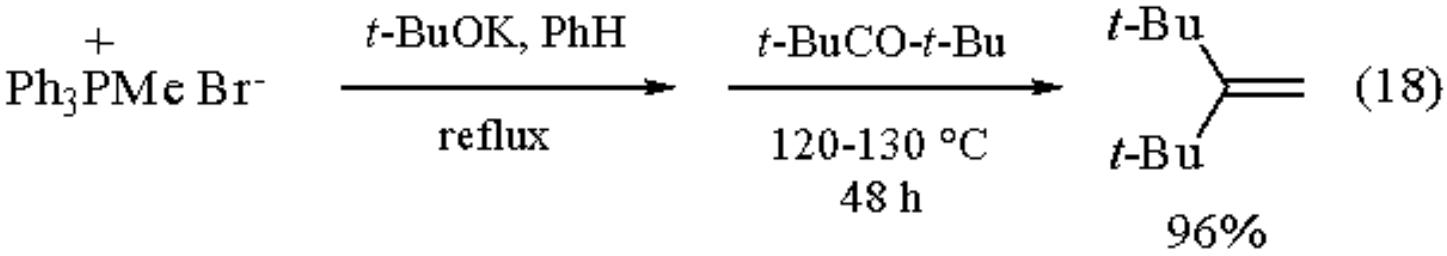

Elimination Reactions.

t-BuOK is a widely used base for both α- and β-elimination reactions. It is the most effective base in the conventional alkoxide-haloform reaction for the generation of dihalocarbenes.[38] This procedure still finds general use (eq 19),[39] but since it requires anhydrous conditions, it has been replaced to a degree by use of phase-transfer catalysts.[40] Vinylidene carbenes have also been produced from the reaction of α-halo allenes with *t*-BuOK.[41]

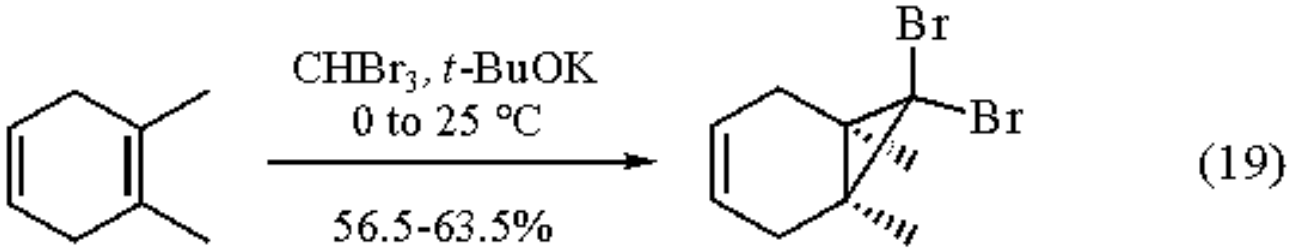

Substrates containing a host of leaving groups, such as alkyl chlorides (eqs 20 and 21),[42,43] bromides (eqs 22-24),[44-46] tosylates, mesylates (eq 25),[47] and even sulfenates and sulfinates (eq 26),[48] undergo β-eliminations with *t*-BuOK in the solid phase or in *t*-BuOH or various nonpolar solvents.

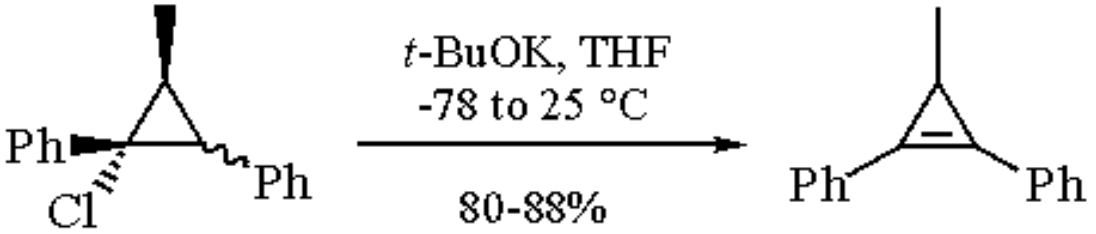

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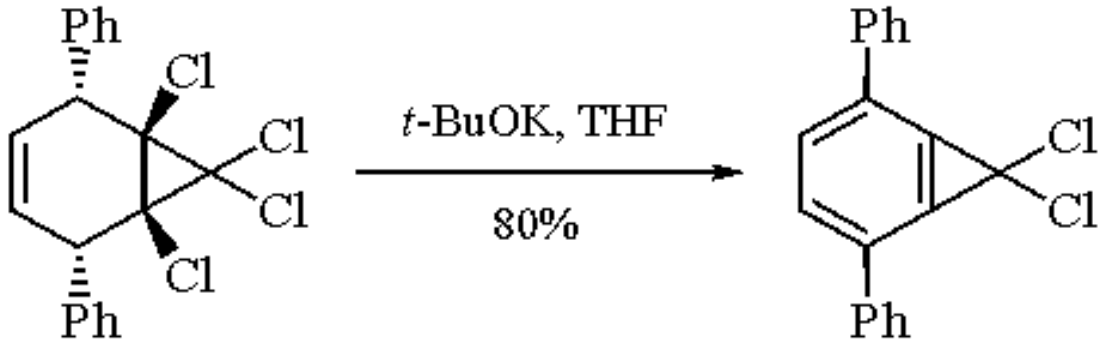

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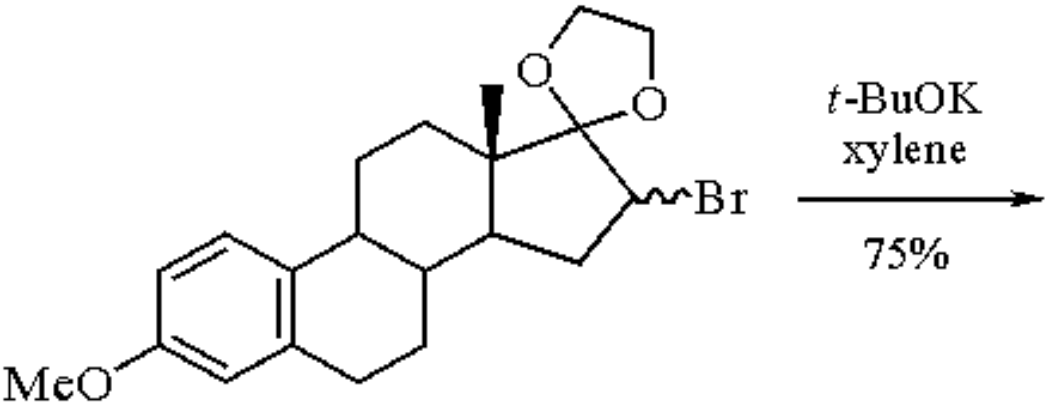

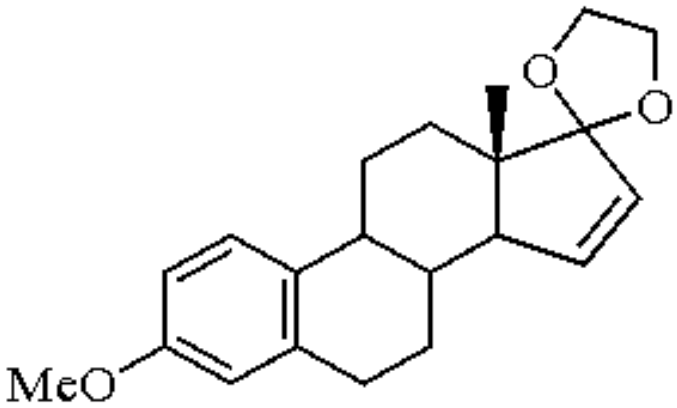

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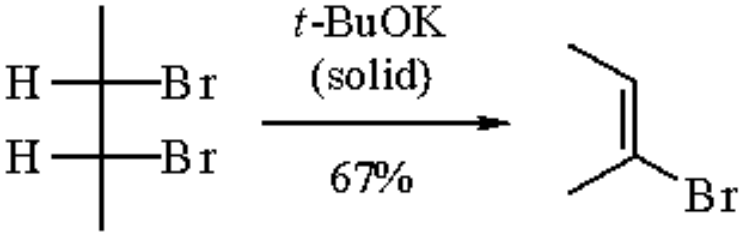

(23)

anti-elimination

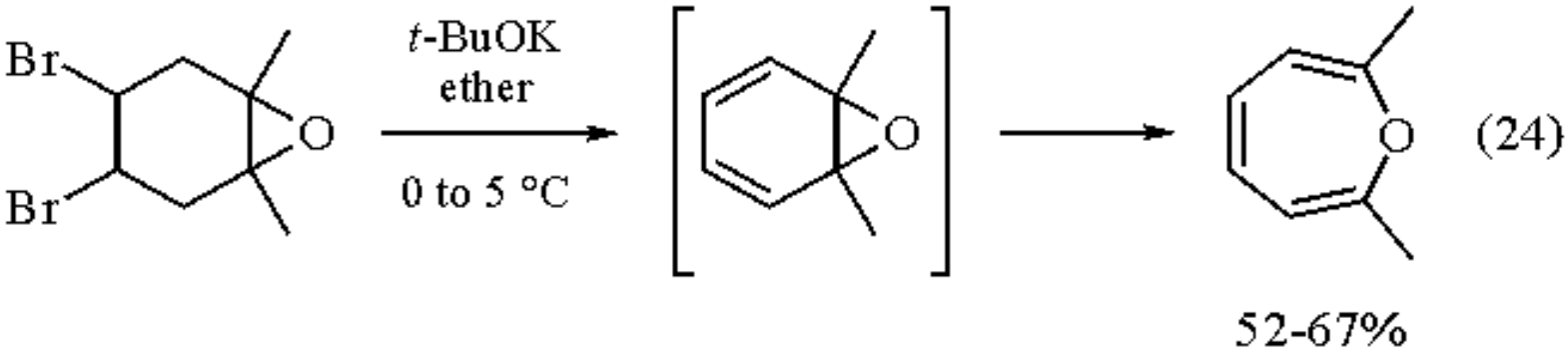

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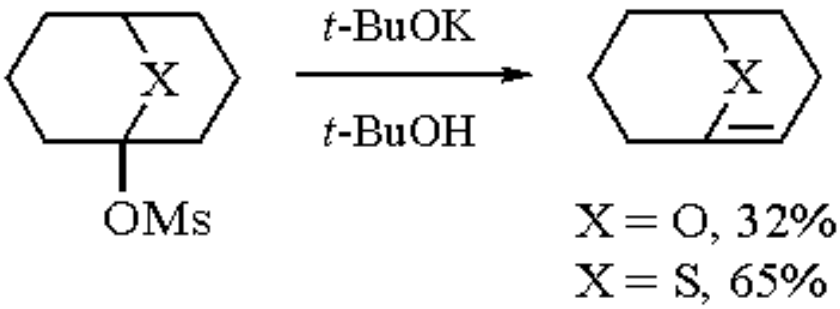

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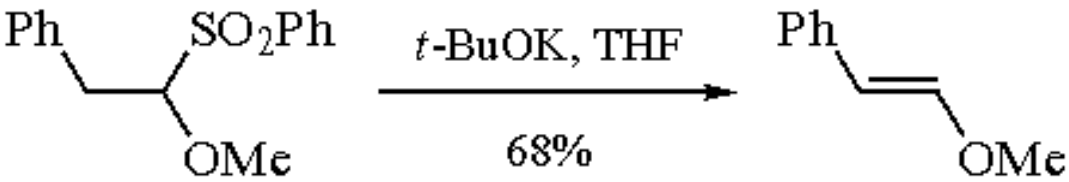

(26)

The regiochemical and stereochemical results of β-eliminations of 2-substituted acyclic alkanes with *t*-BuOK in various solvents have been extensively investigated.[49] Space does not permit the details of these investigations to be presented, but a few brief generalizations may be noted. (1) *t*-BuOK normally gives more of the terminal alkene than primary alkoxide bases but less than extremely bulky bases such as potassium tricyclohexylmethoxide. (2) A greater proportion of the terminal alkene is produced in solvents such as *t*-BuOH, where the base is highly aggregated, than in DMSO where it is substantially monomeric and partially dissociated. (3) The lower the state of aggregation of the base, the higher the *trans*:*cis* ratio of the disubstituted 2-alkene. (4) As base aggregation increases, the *syn*:*anti* elimination ratio increases. As far as the *trans*:*cis* ratio is concerned, cyclic halides give the opposite results from open-chain systems, i.e. this ratio is higher when base aggregation is greater (eq 27).[50]

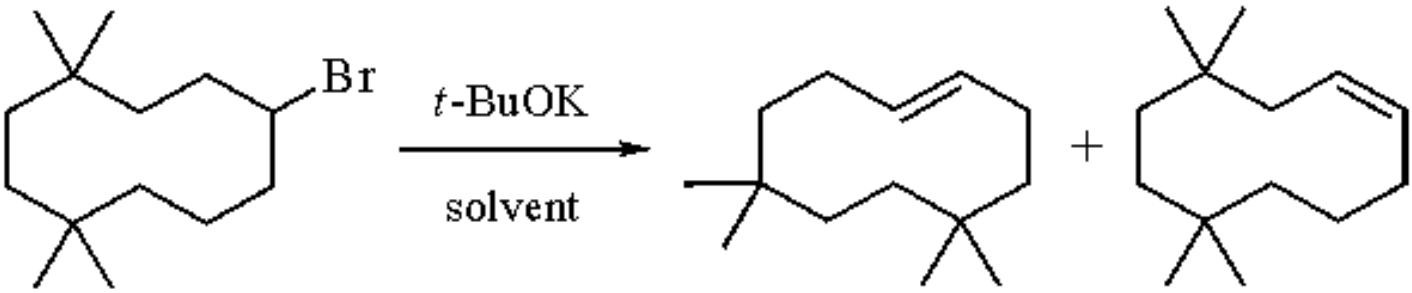

(27)

Solvent	*trans* (%)	*cis* (%)
PhH	83	1.5
PhH, dicyclo-hexyl-18-crown-6	9	76
DMF	7	72

Fragmentation Reactions.

Because it is a relatively strong base and a relatively weak nucleophile, *t*-BuOK has been the most popular base for effecting Grob-type fragmentations of cyclic 1,3-diol derivatives.[51] In *t*-BuOH or nonpolar solvents, sufficiently high concentrations of alkoxide ions of 1,3-diol derivatives are produced for fragmentations to proceed smoothly if relatively good leaving groups are present (eq 28).[52] When relatively poor leaving groups, e.g. sulfinates, are involved, it is necessary to increase the strength of *t*-BuOK by the addition of a dipolar aprotic solvent (eq 29).[53] Other base-solvent combinations which may offer advantages over *t*-BuOK/*t*-BuOH for certain fragmentation substrates include NaH/THF, $DMSO^-$ Na^+/DMSO, and LAH/ether.[51]

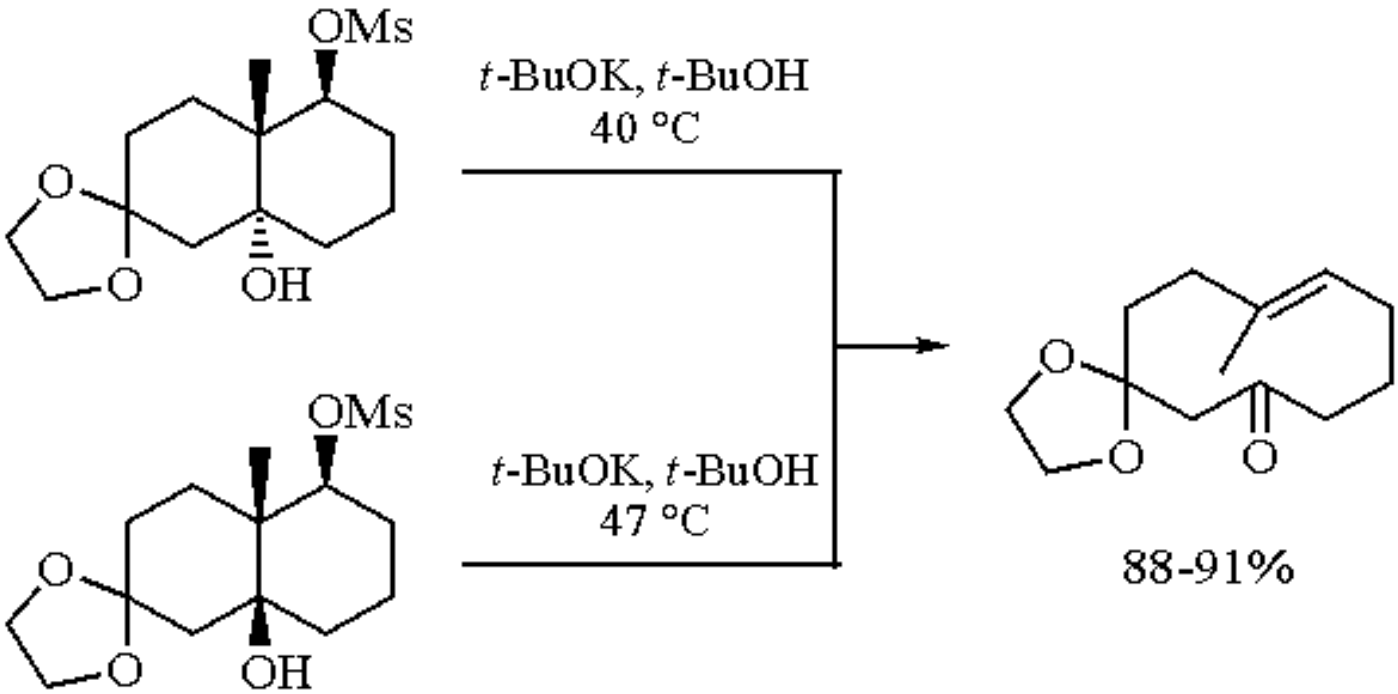

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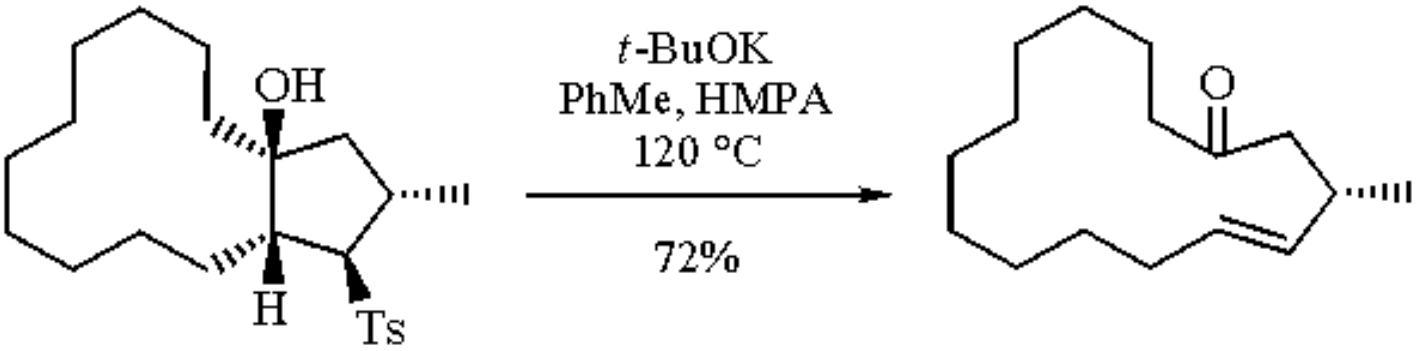

(29)

Isomerizations of Unsaturated Compounds.

t-BuOK is an effective base for bringing about migrations of double bonds in alkenes and alkynes via carbanion intermediates,[1] but since the base promotes these reactions most effectively in DMSO, they will be described in more detail under ***Potassium t-Butoxide-Dimethyl Sulfoxide***. Important examples of enone deconjugations with *t*-BuOK/*t*-BuOH which proceed via di- and trienolate intermediates are shown in eqs 30 and 31.[54,55] Potassium *t*-pentoxide is effective in promoting the latter reaction, but various lithium amide bases are not, apparently because they deprotonate the enone at the α´-position regioselectively. The isomerization of α,β-unsaturated imines to alkenyl imines (eq 32) is an important step in an alternative method for reduction-alkylation of α,β-unsaturated ketones.[56]

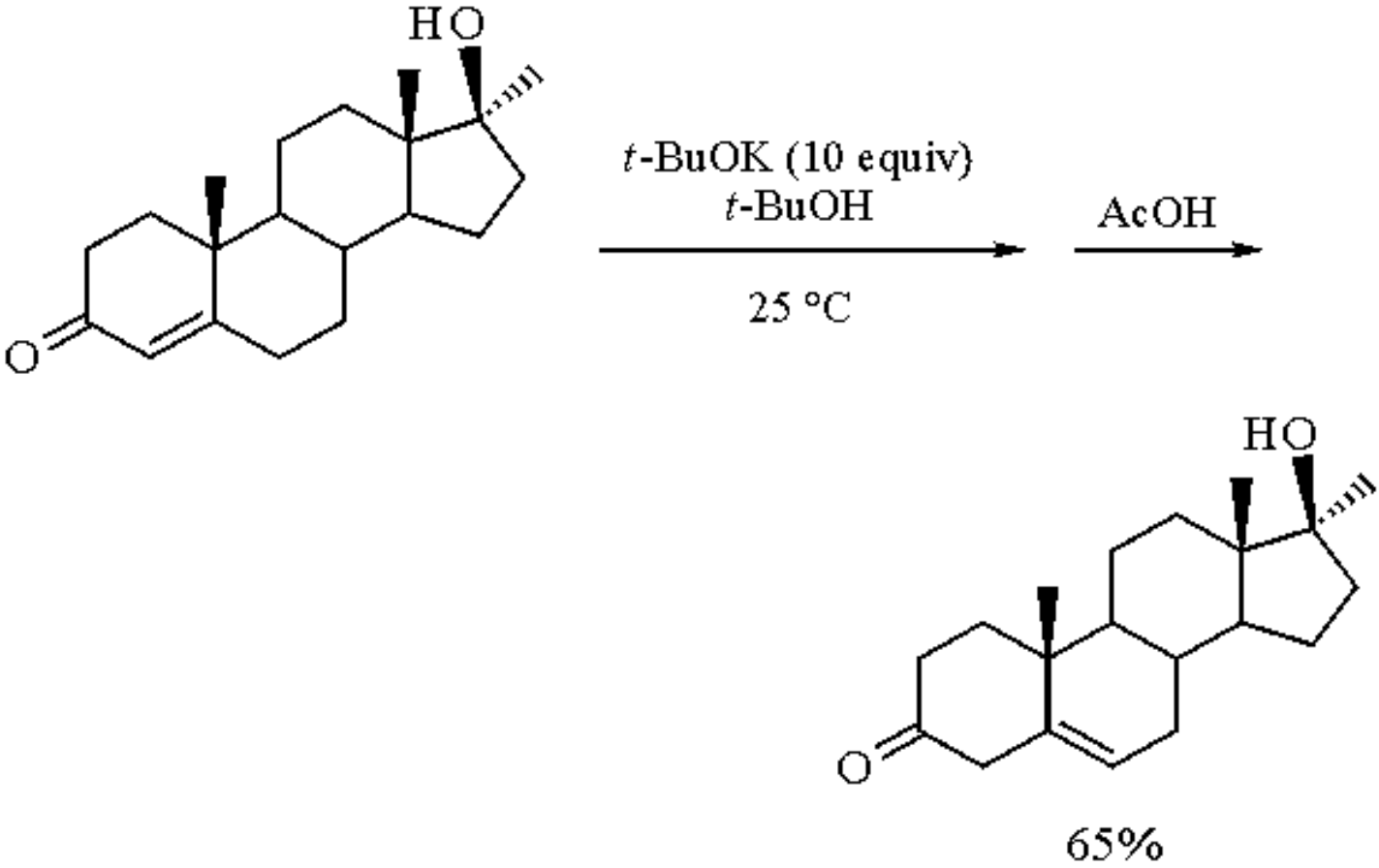

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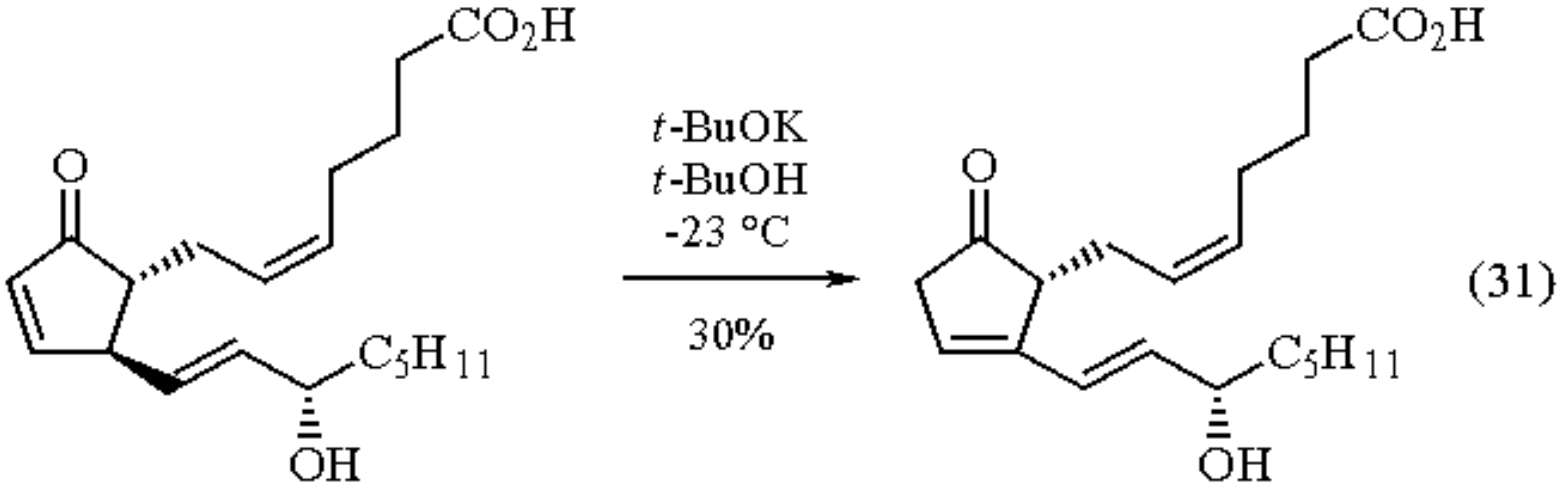

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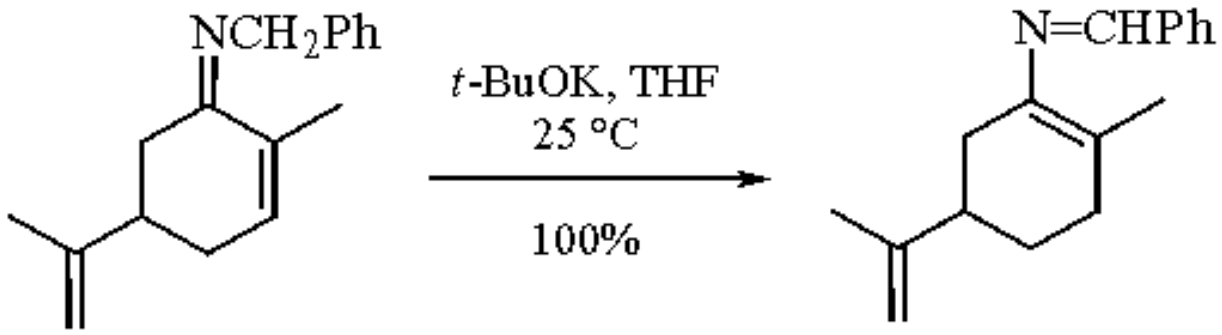

(32)

Ketone Cleavage Reactions.

t-BuOK in ether containing water is the medium of choice for the cleavage of nonenolizable ketones such as nortricyclanone (eq 33).[57] Optically active tertiary α-phenyl phenyl ketones are cleaved in fair yields with high retention of configuration with the base in *t*-BuOH or PhH (eq 34).[58] *t*-BuOK is more effective than *t*-BuONa or ***Lithium t-Butoxide*** in these reactions.

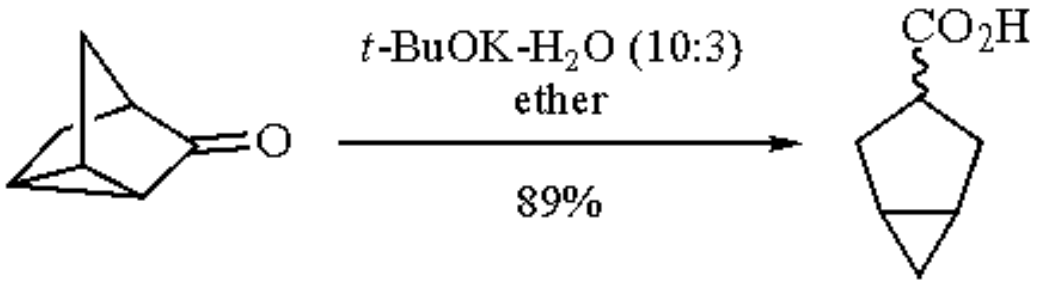

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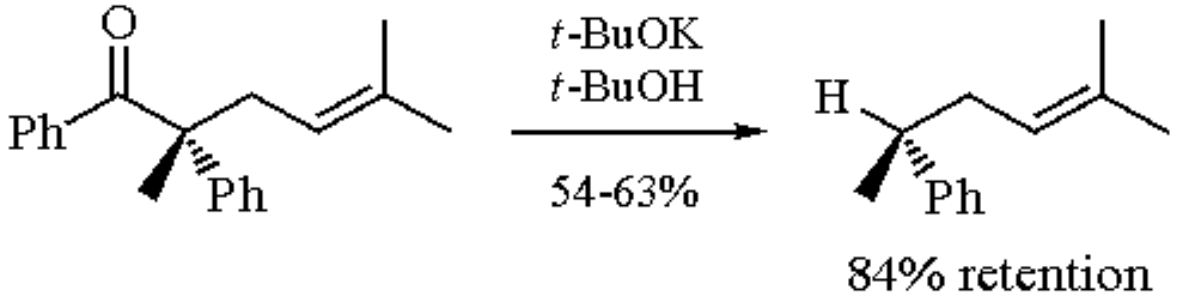

(34)

Michael Additions.

t-BuOK is one of an arsenal of bases that can be used in Michael addition reactions.[59] A catalyst prepared by impregnation of xonotlite with the base promotes the Michael addition of the β-diketone dimedone to 2 mol of MVK (eq 35).[60] Unsymmetrical ketones like 2-methylcyclohexanone yield Michael adducts primarily at the more substituted α-carbon atom (eq 36).[8a] Active methylene compounds undergo double Michael additions to enynes in the presence of *t*-BuOK (eq 37).[61] This type of reaction has been used in the total synthesis of griseofulvin. A tricyclo[5.3.1.0^{1,5}]undecanedione, a precursor of (±)-cedrene, is available by a highly regioselective intramolecular Michael addition using *t*-BuOK (eq 38).[62]

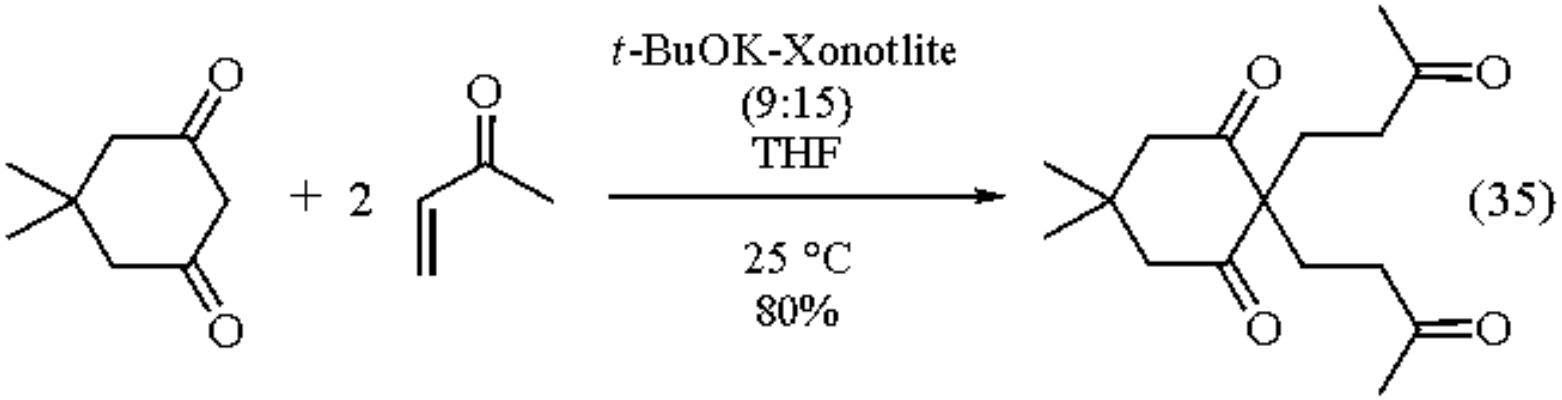

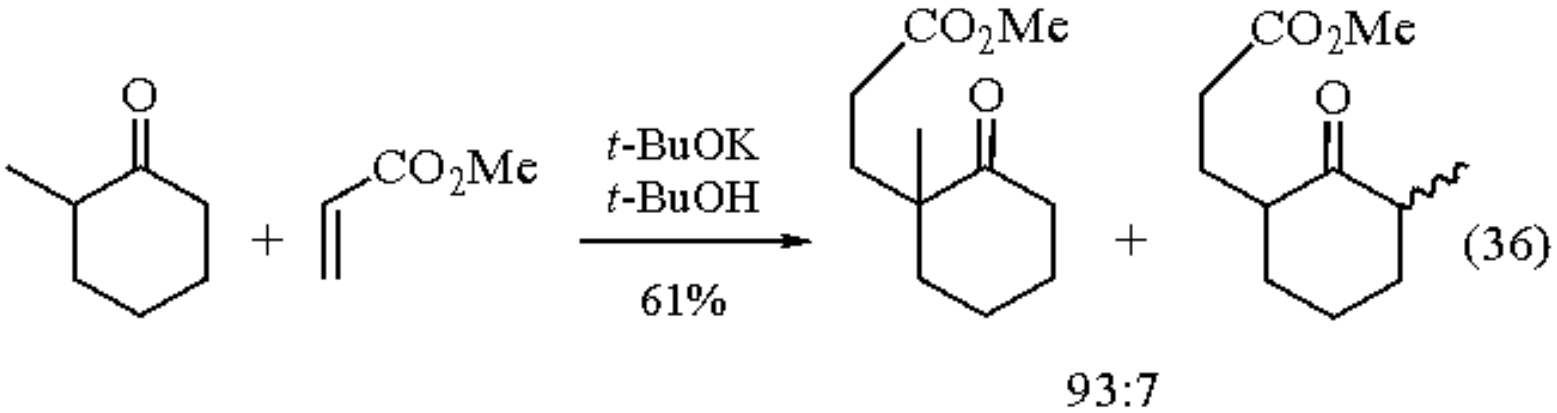

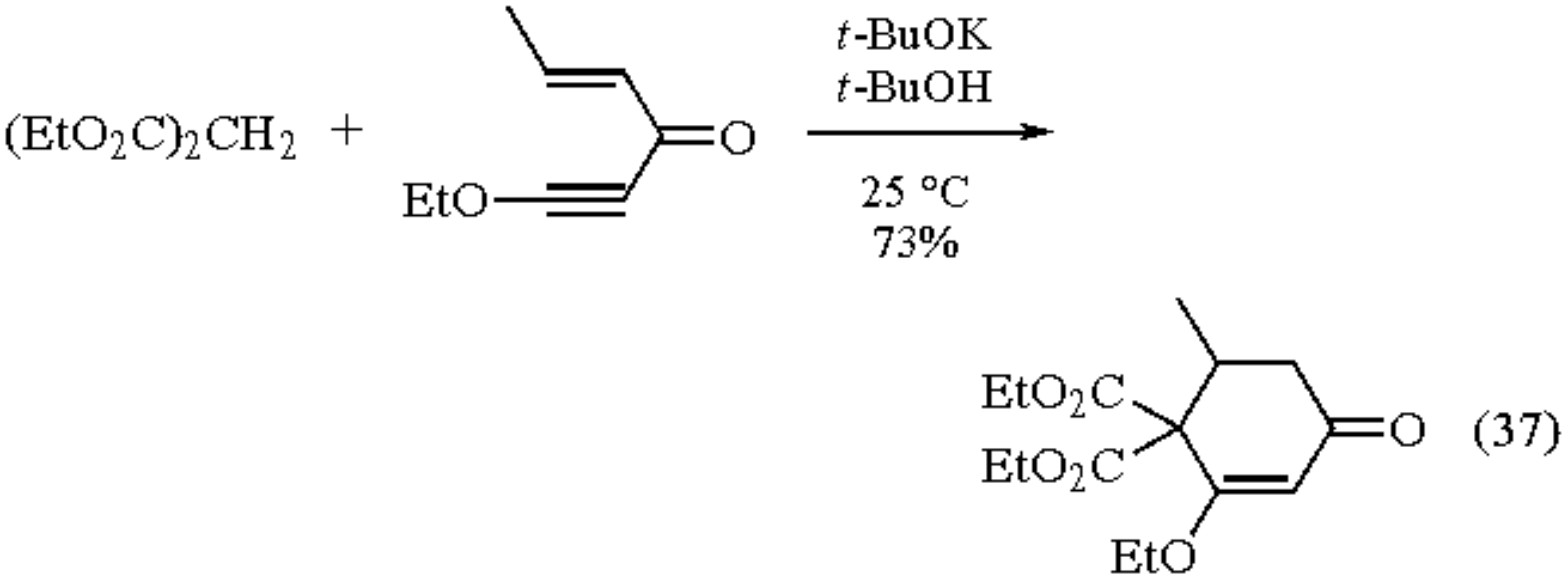

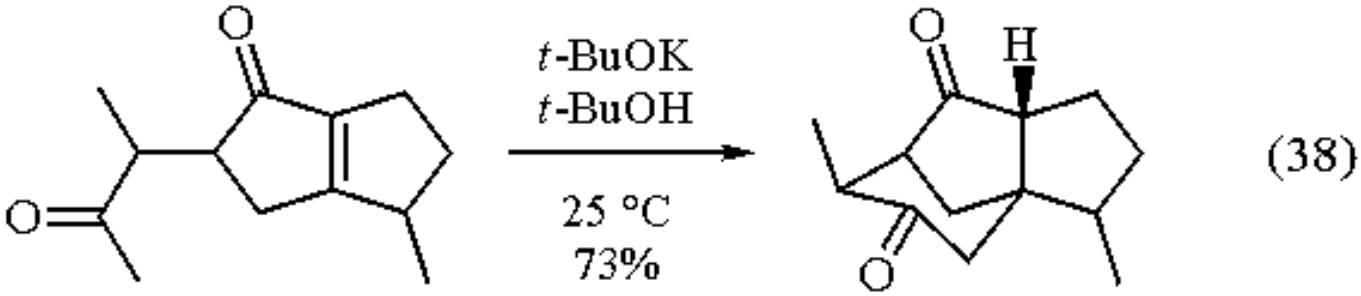

Oxidation Reactions.

The use of *t*-BuOK to convert organic substrates to carbanionic species which react with molecular oxygen via a radical process has been reviewed.[1] Ketones and esters are the most common substrates for these reactions. Oxidations of unsymmetrical ketones occur via the more thermodynamically stable potassium enolates; tetrasubstituted enolates yield stable hydroperoxides, while hydroperoxides derived from trisubstituted enolates are further oxidized to α-diketones or their enol forms.[9a]

Rearrangement Reactions.

Benzil is converted into the ester of benzylic acid in high yield upon treatment with *t*-BuOK in *t*-BuOH/PhH (eq 39).[63] Lower yields are obtained if the individual solvents alone are used or if the base is replaced by MeONa or EtONa.

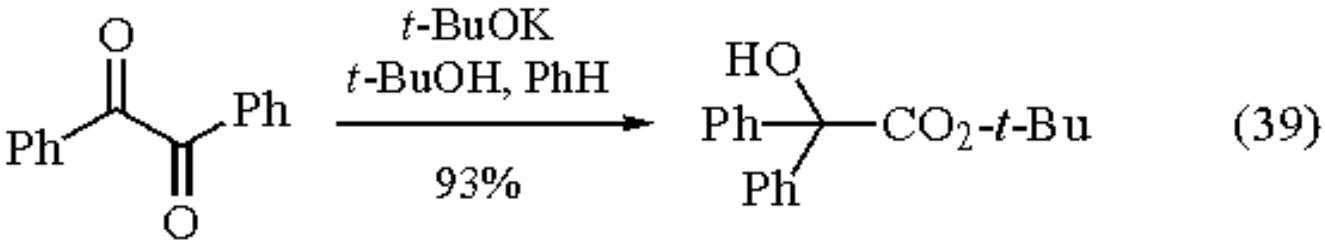

Monotosylates of *cis*-1,2-diols, such as that derived from α-pinene, undergo pinacol-type rearrangements upon treatment with *t*-BuOK (eq 40).[64] The *trans* isomer is converted to the epoxide under the same conditions (eq 41).[64] 4-Benzoyloxycyclohexanone undergoes a mechanistically interesting rearrangement to benzoylcyclopropanepropionic acid when treated with *t*-BuOK/*t*-BuOH (eq 42).[65]

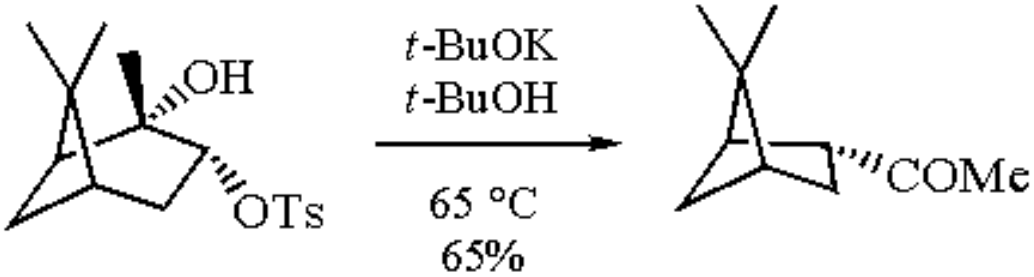

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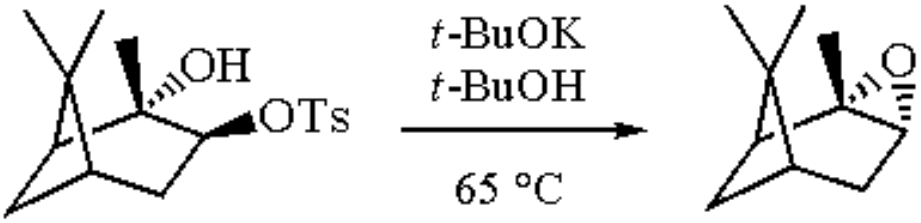

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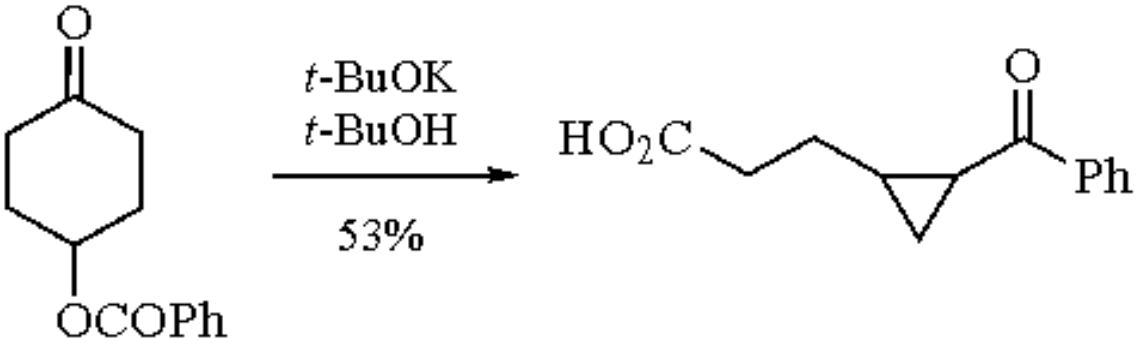

(42)

The Ramberg-Bäcklund rearrangement of α-halo sulfones is frequently carried out with *t*-BuOK.[66] This reaction provides a useful route to deuterium-labeled alkenes (eq 43).[67] *t*-BuOK is presumably the active base in a modification which involves the direct conversion of a sulfone into an alkene with KOH and a mixture of *t*-BuOH/CCl_4.[68] The base converts the sulfone to the α-sulfonyl carbanion, which undergoes chlorination with CCl_4 by a single-electron transfer process. Proton abstraction from the α´-position of the α-chloro ketone by the base yields a thiirane 1,1-dioxide which loses SO_2 to yield the alkene. *t*-BuOK is frequently used directly in this modified procedure (eq 44).[69] Cyclic enediynes are available from the corresponding α-chloro sulfones using *t*-BuOK to effect the Ramberg-Bäcklund rearrangement.[70]

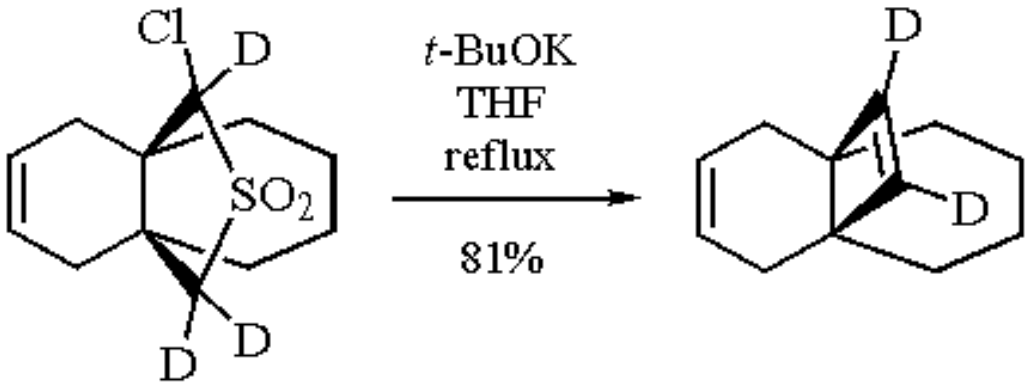

(43)

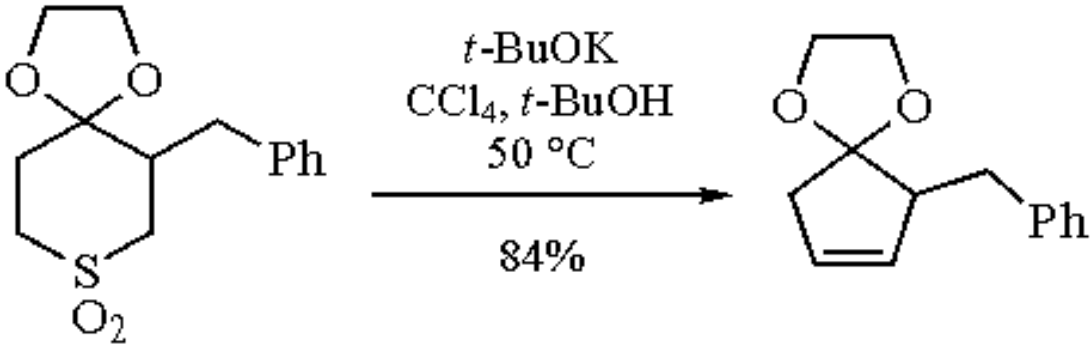

(44)

Bromomethylenecyclobutanes undergo ring enlargement reactions to 1-bromocyclopentenes when heated in the presence of solid *t*-BuOK (eq 45).[71]

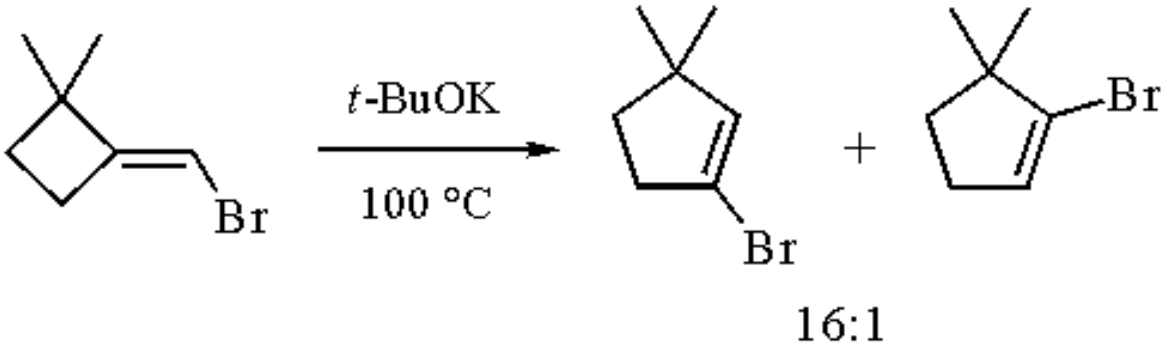

(45)

Reduction Reactions.

A modification of the Wolff-Kishner reduction, which is particularly useful for the reduction of α,β-unsaturated ketones, involves the reaction of carbonyl hydrazones and semicarbazones with *t*-BuOK in PhMe at reflux.[72] The reduction of (±)-3-oxo-α-cadinol to (±)-α-cadinol and its isomer (eq 46) provides an example of this method.[73]

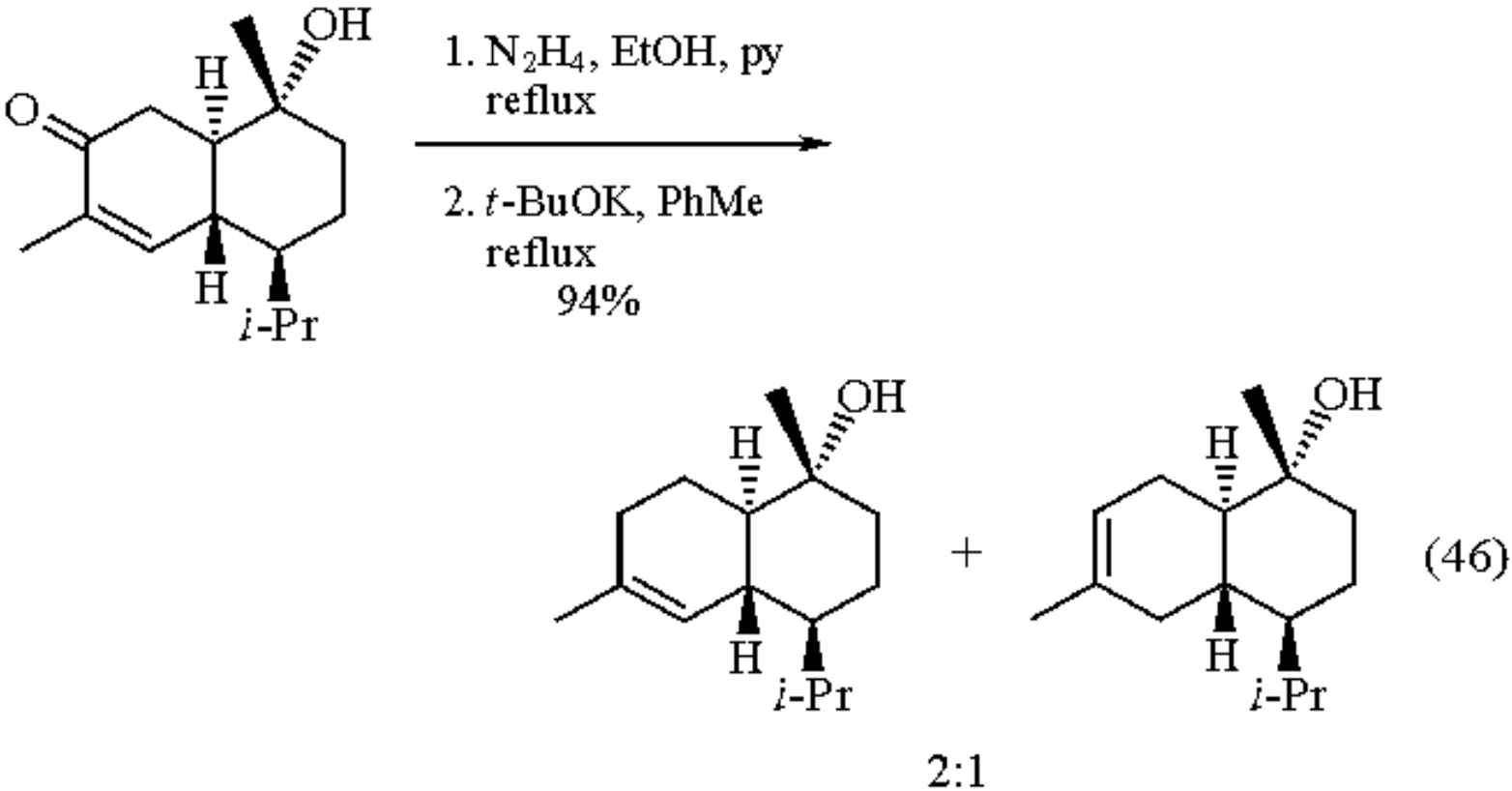

Related Reagents.

n-Butyllithium-Potassium t-Butoxide; ***Potassium Amide***; ***Potassium Hexamethyldisilazide***; ***Potassium t-Butoxide-Benzophenone***; ***Potassium t-Butoxide-t-Butyl Alcohol Complex***; ***n-Butyllithium-Potassium t-Butoxide***; ***Potassium t-Butoxide-18-Crown-6***; ***Potassium t-Butoxide-Dimethyl Sulfoxide***; ***Potassium t-Butoxide-Hexamethylphosphoric Triamide***; ***Potassium Diisopropylamide***; ***Potassium t-Heptoxide***; ***Potassium Hydroxide***; ***Potassium 2-Methyl-2-butoxide***.

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Potassium *t*-Butoxide-Benzophenone

***t*-BuOK-Ph_2CO**

(*t*-BuOK)

[865-47-4] · C_4H_9KO · Potassium *t*-Butoxide-Benzophenone · (MW 112.23) (Ph_2CO)

[119-61-9] · $C_{13}H_{10}O$ · Potassium *t*-Butoxide-Benzophenone · (MW 182.23)

(Oppenauer-type oxidations of amino alcohols[1])

Physical Data: Ph_2CO: mp 49-51 °C; bp 158 °C/10 mmHg. For *t*-BuOK, see ***Potassium t-Butoxide***.

Solubility: Ph_2CO: nonpolar organic solvents; insol H_2O.

Form Supplied in: Ph_2CO: white crystalline solid; widely available commercially.

Preparative Methods: in situ, usually in a ca. 1:3 molar ratio of the base to the ketone.

Purification: commercially available benzophenone is normally of sufficient purity to be used directly; if further purification is needed, it should be recrystallized from a nonpolar solvent such as cyclohexane and sublimed.[2]

Handling, Storage, and Precautions: Ph_2CO: irritant; avoid contact with the eyes, skin, and clothing; use in a fume hood.

Oppenauer-Woodward Oxidation.

The Oppenauer oxidation of alcohols is usually carried out with ***Aluminum Isopropoxide*** and a ketone.[3] However, since the aluminum alkoxide complexes with amino groups, this procedure is not useful for oxidizing amino alcohols to amino aldehydes or ketones. This difficulty has been overcome by the use of a procedure often called the Oppenauer-Woodward oxidation, which employs *t*-BuOK as the base to generate the alkoxide anion of the alcohol and Ph_2CO as the hydride acceptor.[1] The hydroxy groups of alkaloids are oxidized by the reagent; for example, quinine is oxidized to quininone (eq 1)[1a] and various morphine derivatives are oxidized to the corresponding ketones in good to excellent yields.[1b,c]

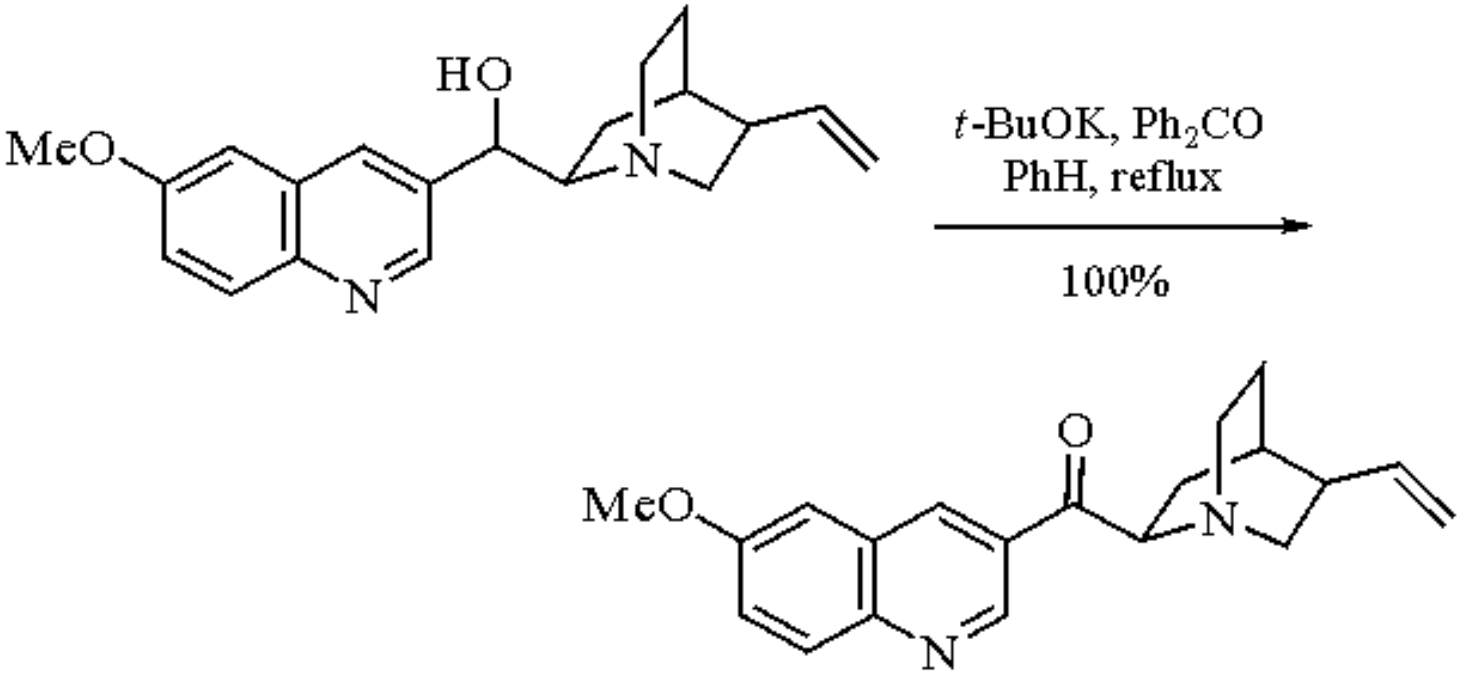

(1)

Oppenauer-Woodward oxidations are normally conducted in refluxing benzene. If the more reactive hydride acceptor fluorenone is substituted for Ph_2CO, oxidations can be accomplished at rt,[4] although extended reaction times may be required.[4b] The oxidation of a 4-hydroxypiperidine derivative to the corresponding 4-ketopiperidine, as shown in eq 2, provides an example of this modification.[4c] *t*-BuOK/fluorenone is also useful for the oxidation of nonnitrogenous alcohols.[4a,5] For example, the less-hindered hydroxy group of a proanthocyanidine derivative is preferentially oxidized by the reagent (eq 3).[5]

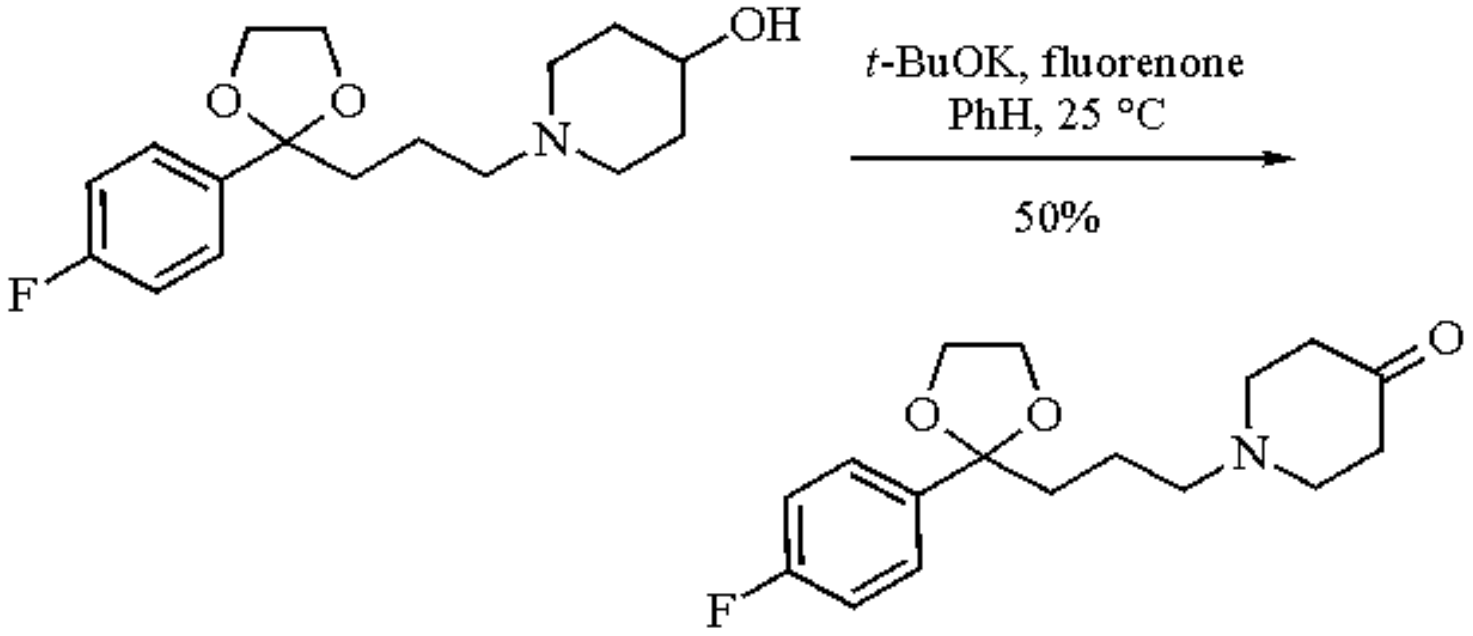

(2)

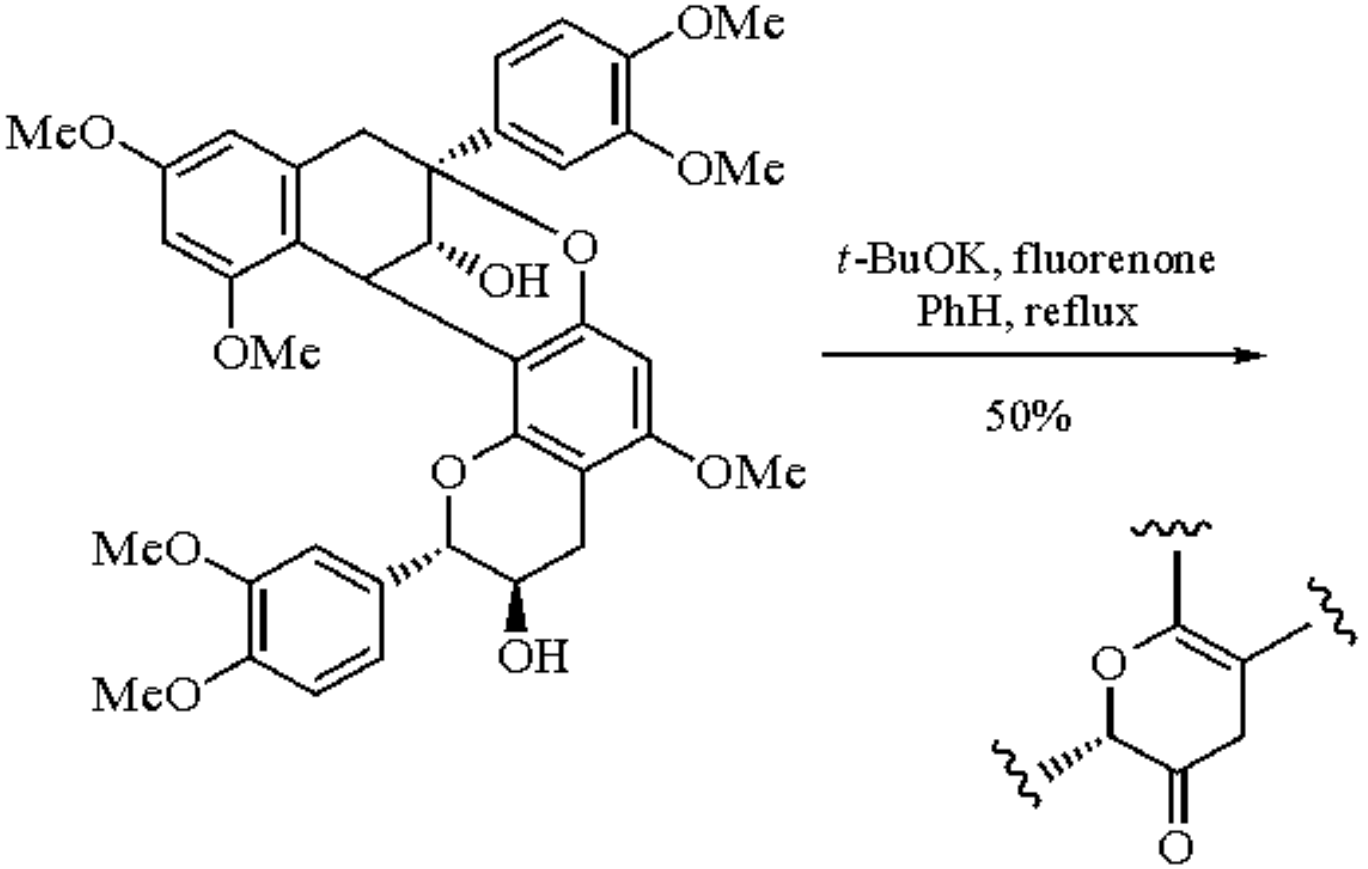

(3)

The allylic anion produced upon reaction of the $Cr(CO)_3$ complex of *p*-allylanisole with *t*-BuOK in THF undergoes addition followed by in situ oxidation when treated with excess PhCHO (eq 4).[6] Benzaldehyde and other aldehydes have been used as hydride acceptors in a modification of the Oppenauer oxidation which utilizes magnesium alkoxides as hydride donors.[7]

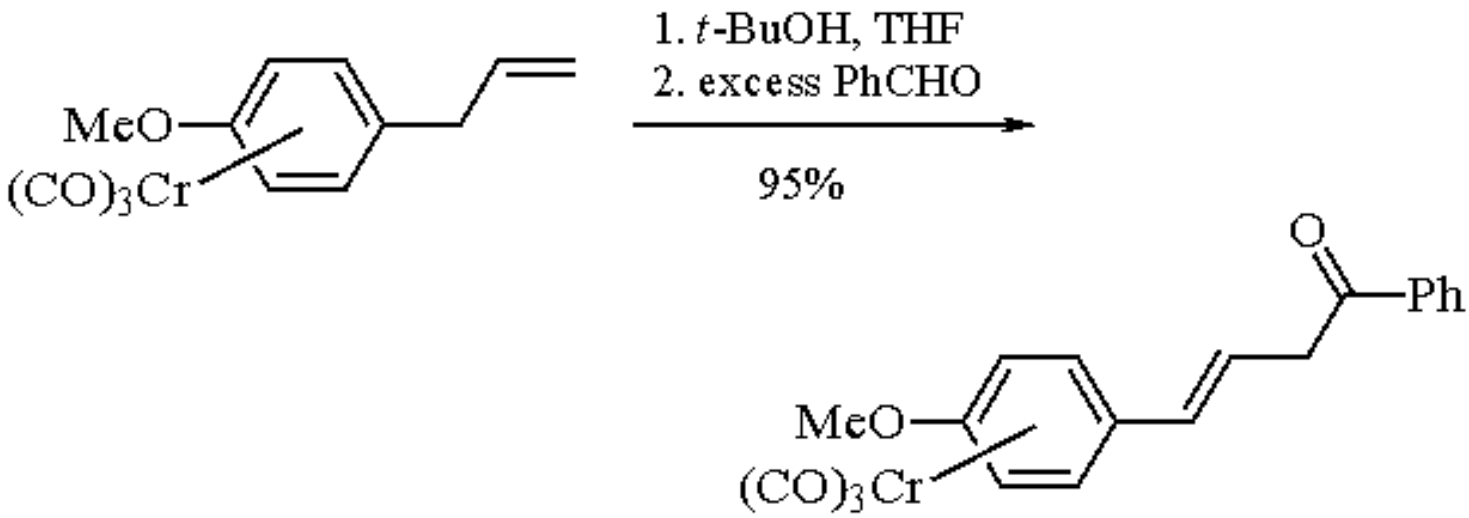

(4)

Tandem Oppenauer-Woodward oxidations-aldol condensations can be performed with appropriate substrates. Eqs 5 and 6 provide examples of the use of these reactions in connection with the total synthesis of lycopodine[8] and elaeocarpine[9] alkaloids, respectively.

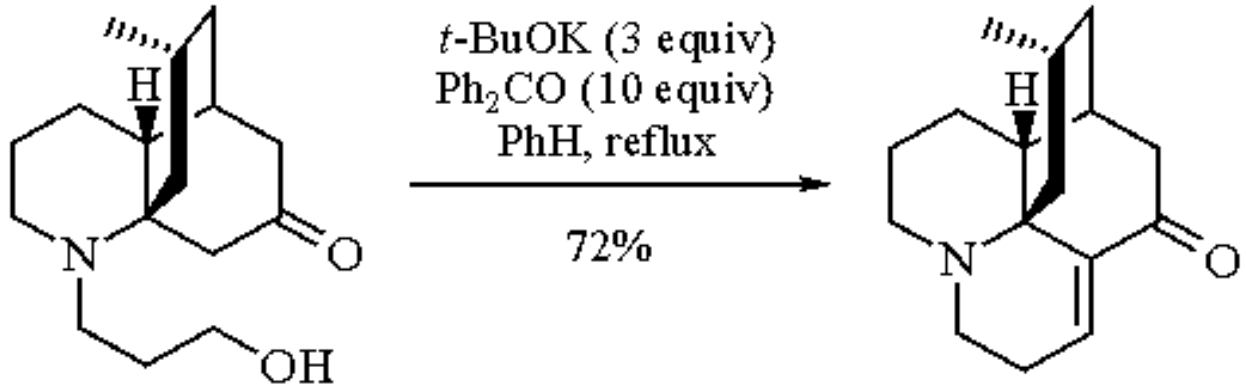

(5)

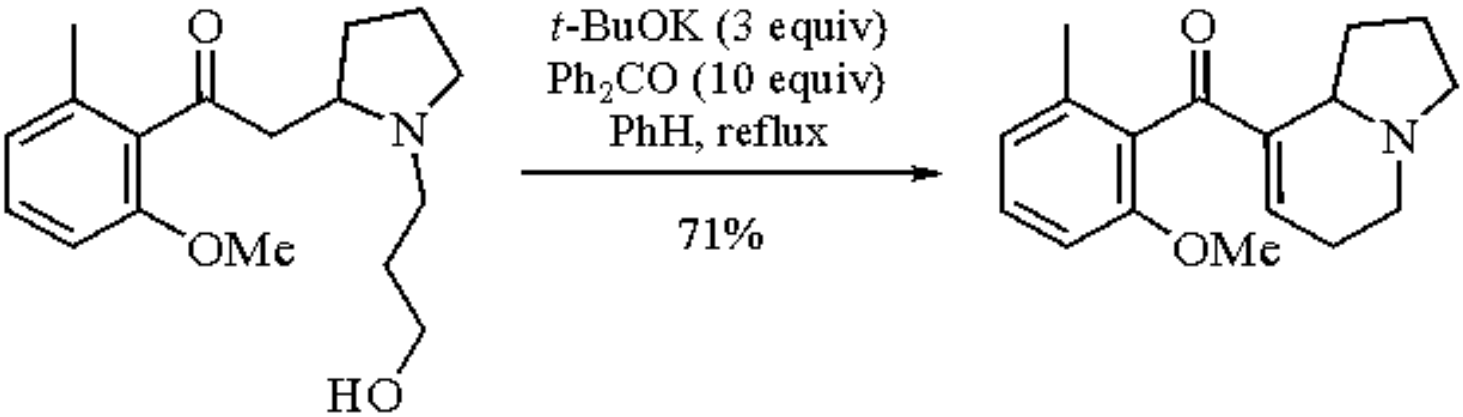

(6)

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Potassium *t*-Butoxide-*t*-Butyl Alcohol Complex

***t*-BuOK/*t*-BuOH**

[135329-82-7] · $C_8H_{19}KO_2$ · Potassium *t*-Butoxide-*t*-Butyl Alcohol Complex · (MW 186.37)

(see ***Potassium t-Butoxide***)

Physical Data: white, hygroscopic powder.

Preparative Methods: by removal of the solvent from a solution of *t*-BuOK in *t*-BuOH at 50 °C/1 mmHg.[1]

Wittig Reactions.

When ***Methylenetriphenylphosphorane*** is prepared by treating the corresponding phosphonium salt with an organolithium compound in an aprotic solvent, the betaine-lithium ion pairs produced upon reaction with aldehydes and ketones undergo decomposition to alkenes extremely slowly.[2] The addition of at least 1.1 equiv of the *t*-BuOK/*t*-BuOH complex markedly accelerates the betaine decomposition rate and improves the yields of the products. The solvent-free base is less effective than the complex in these reactions.[2] The role of the additive is probably to exchange the lithium cation for the potassium cation, which allows more of the free betaine to be present in equilibrium with the ion pair.[2] The *t*-BuOH proton donor may play an important role as well. Wittig reactions involving methylenetriphenylphosphorane can be run more efficiently by treating the phosphonium salt directly with *t*-BuOK in *t*-BuOH or aprotic solvents, e.g. ether, prior to addition of the carbonyl component.[3] The proton donor solvent is particularly effective.

Alkene Isomerization Reactions.

Dialkyl 2-propynylamines are efficiently isomerized into the corresponding dialkylamino allenes using the *t*-BuOK/*t*-BuOH complex in HMPA (eq 1).[4] The use of *t*-BuOK/DMSO as the base-solvent combination leads to the formation of substantially more of the isomeric 1-dialkylamino alkyne. Nitrogen-substituted allenes are also available from the corresponding 2-propynes by reaction with *t*-BuOK in THF followed by addition of an equivalent amount of *t*-BuOH.[5]

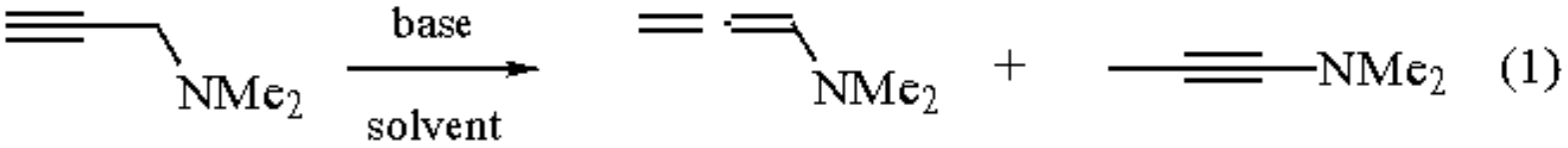

t-BuOK/*t*-BuOH, HMPA, >85%	96:4
t-BuOK, DMSO	80:20

Intramolecular Acyl Transfer Reactions.

The *t*-BuOK/*t*-BuOH complex is a useful base for the intramolecular transfer of aliphatic acyl groups in the Baker-Venkataraman reaction for the synthesis of β-diketones (eq 2).[6] Variable yields of the β-diketone are obtained when 5-(allyloxy)-2-hydroxyacetophenone is converted to its dianion with ***Lithium Diisopropylamide*** (2 equiv) at 0 °C or -78 °C and reacted with crotonoyl chloride.[6] The X-ray crystal structure of the *t*-BuOK/*t*-BuOH complex has recently been determined.[7]

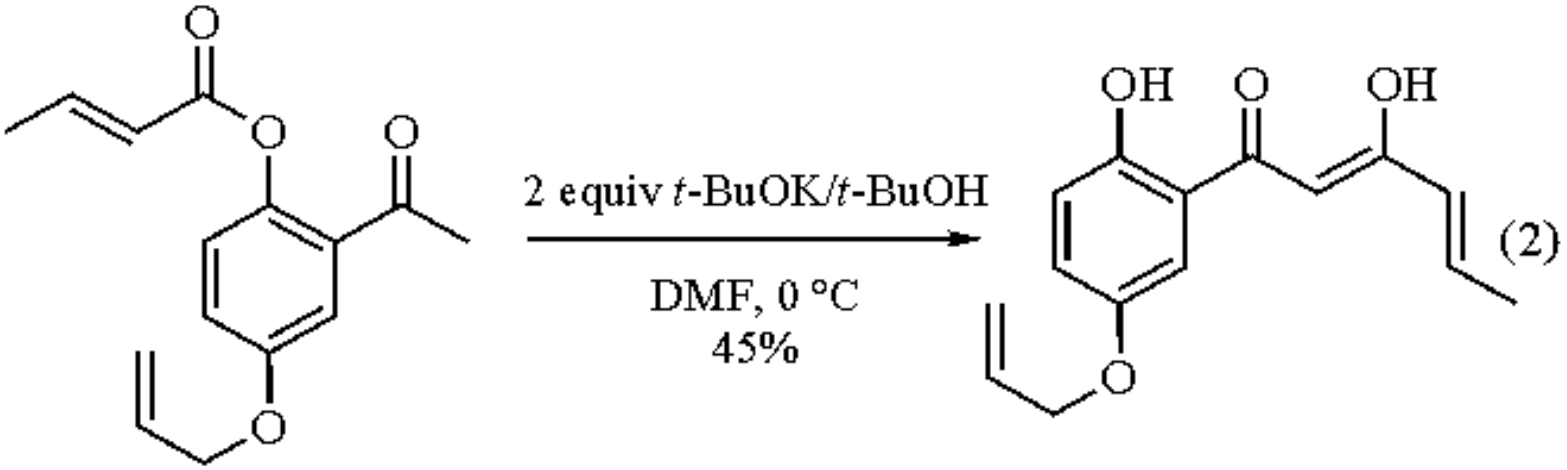

Related Reagents.

Potassium t-Butoxide; ***Potassium Methoxide-Dicyclohexano-18-crown-6***.

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Potassium *t*-Butoxide-18-Crown-6

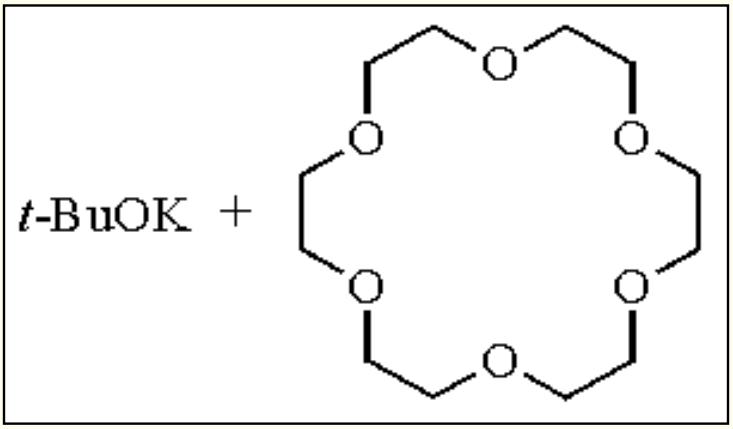

(*t*-BuOK)

[865-47-4] · C_4H_9KO · Potassium *t*-Butoxide-18-Crown-6 · (MW 112.23) (18-crown-6)

[17455-13-9] · $C_{12}H_{24}O_6$ · Potassium *t*-Butoxide-18-Crown-6 · (MW 264.36)

(basic and especially nucleophilic crown ether complex of *t*-BuOK)

Preparative Method: prepared in situ by mixing the base and the crown ether in an appropriate solvent.

Handling, Storage, and Precautions: see ***18-Crown-6*** and ***Potassium t-Butoxide***.

General Discussion.

The ability of 18-crown-6 to complex potassium cations is well known.[1] When the crown ether is added to solutions of *t*-BuOK in nonpolar, aprotic solvents, where it exists primarily in the form of aggregated ion pairs,[2] the equilibrium is shifted in the direction of ligand-separated ion pairs and dissociated *t*-butoxide anions.[3] Thus in the presence of the crown ether, the basicity and especially the nucleophilicity of the *t*-butoxide anion are enhanced. Dipolar aprotic solvents such as DMSO, which strongly solvate potassium cations, also produce relatively high concentrations of *t*-butoxide anions.[2] However, in such media these anions exhibit high basicity vis-à-vis nucleophilicity because solvent-assisted deprotonation reactions are favorable.[4] 18-Crown-6 is an expensive reagent, but it is useful in catalytic as well as stoichiometric amounts to activate *t*-BuOK. As already noted, the combination of this additive and a nonpolar solvent provides a relatively favorable medium for the *t*-butoxide ion to behave as a nucleophile.[2] If an increase in the basicity of *t*-BuOK is all that is required, there still may be an advantage in using 18-crown-6 instead of DMSO, the most popular activator of the base (see ***Potassium t-Butoxide-Dimethyl Sulfoxide***), for certain substrates. The recovery of relatively water-soluble reaction products from DMSO solutions is

difficult, while the crown ether can usually be removed easily with silica gel. Also, DMSO solutions contain significant concentrations of $DMSO^{-}K^{+}$ which may cause unwanted side reactions.[2]

18-Crown-6 catalyzes the conversion of phosphonium salts to unstabilized phosphoranes with potassium *t*-butoxide in nonpolar solvents.[5] The nature of the solvent has a remarkable effect on the stereochemistry of the subsequent Wittig reactions with aldehydes. The use of THF favors the production of *cis*-alkenes, while CH_2Cl_2 favors the formation of *trans*-isomers. When stabilized ylides are employed, *trans*-alkenes are favored in both solvents. Methylenations of 2-(dimethylaminomethyl)cycloalkanones occur in high yield using this procedure (eq 1).[5c]

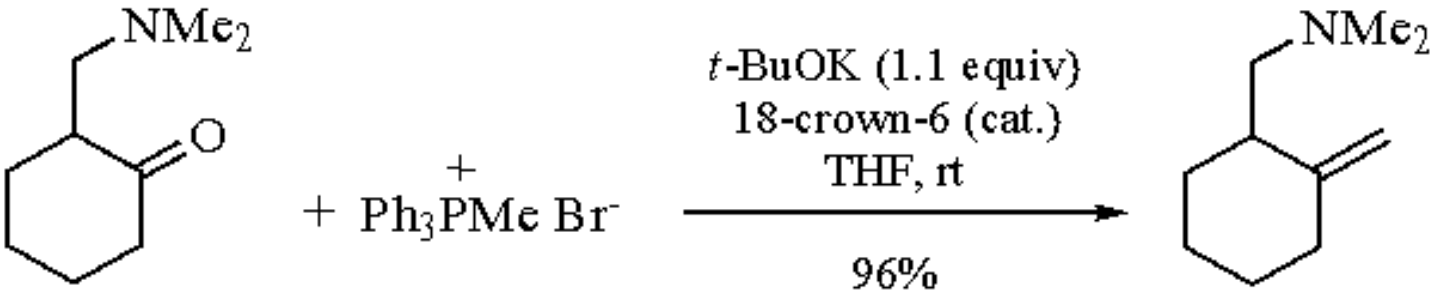

(1)

Dihalotoluenes yield free halophenyl carbenes when treated with *t*-BuOK in benzene in the presence of 18-crown-6, but halophenyl carbenoids are produced in the absence of the crown ether.[6] Primary and other alkyl halides are readily converted into alkenes with *t*-BuOK in petroleum ether solvents with a catalytic amount of 18-crown-6.[7] This procedure is particularly useful for primary halides (eq 2), which yield alkyl *t*-butyl ethers under the usual conditions.[7] Alkynes are produced in excellent yields from 1,1- and 1,2-dihalides (eq 3) under similar conditions.[8]

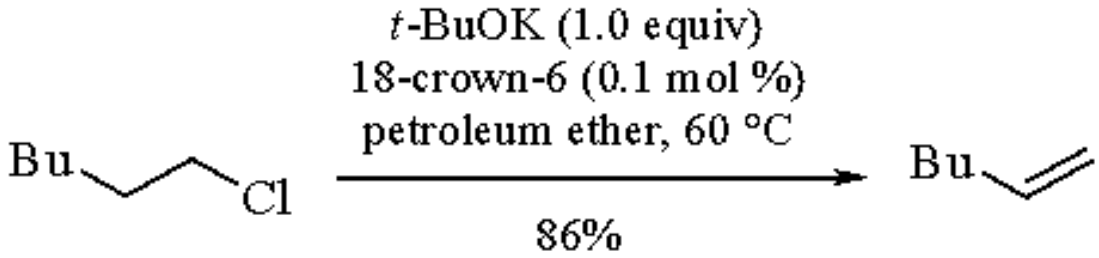

(2)

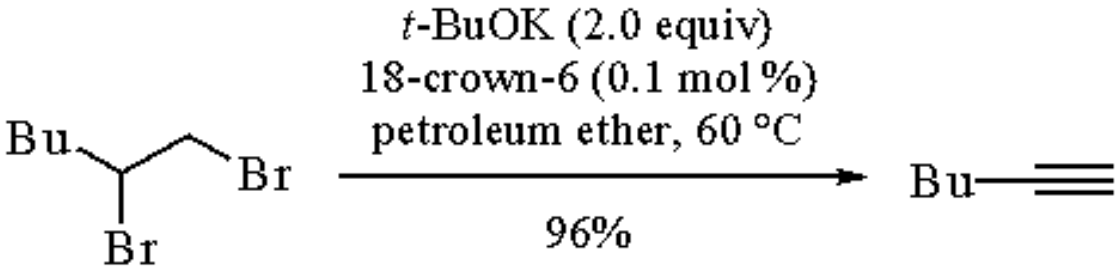

(3)

Benzyl *t*-butyl ether is obtained in good yield upon treatment of ***Benzyl Chloride*** with *t*-BuOK in the presence of 5-10 mol % 18-crown-6 (eq 4).[3] The enhanced nucleophilicity of the *t*-butoxide ion in the presence of 18-crown-6 is evident, because in its absence the reaction is extremely slow. If *t*-BuOK is used in dipolar aprotic solvents (e.g. DMSO), stilbene, which is derived from initial deprotonation of benzyl chloride, is the major reaction product.

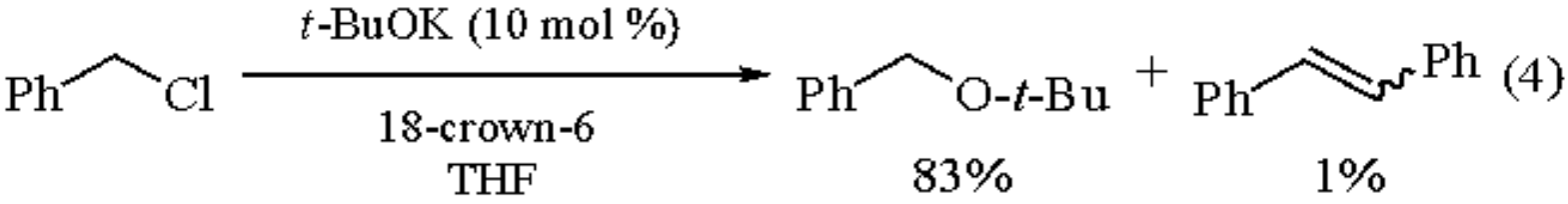

18-Crown-6 improves yields in the *t*-BuOK-catalyzed oxidations of nitriles to carboxylic acids with loss of the cyano group (eq 5).[9] *N*-Alkylations of aromatic nitrogen heterocycles are accomplished in high yields using crown ether-activated *t*-BuOK in ether or benzene (eq 6).[10]

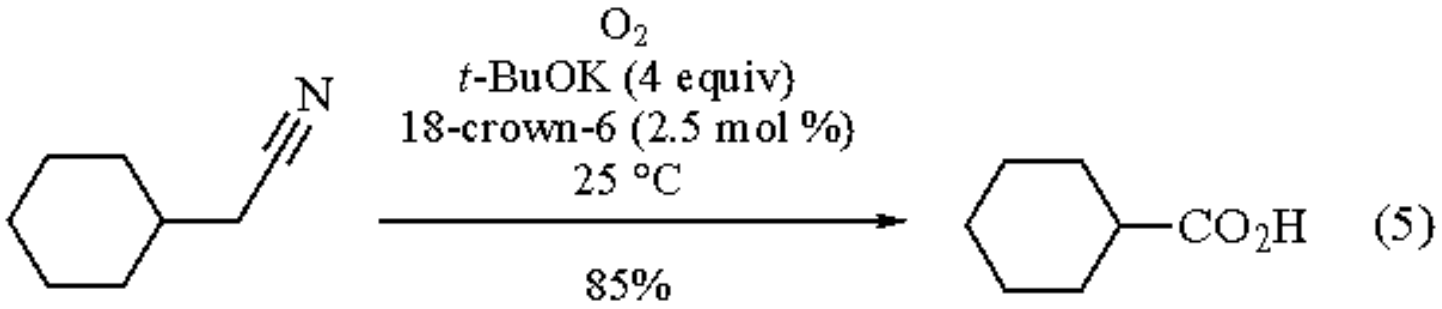

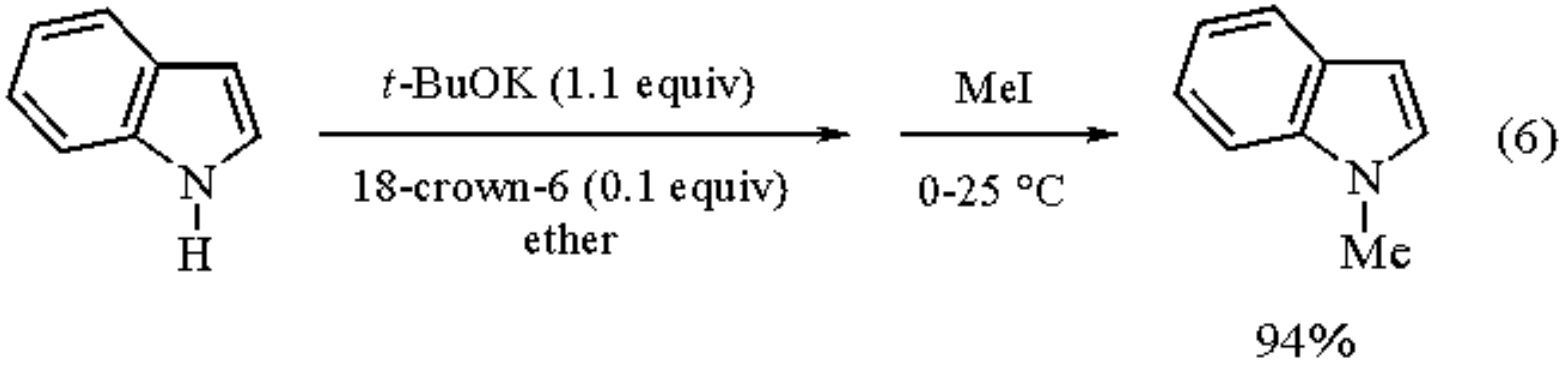

Alkynyloxiranes undergo isomerization to furan derivatives when treated with *t*-BuOK in the presence of 18-crown-6 (eq 7).[11] *t*-BuOK complexes of C_2-symmetric chiral derivatives of 18-crown-6 are efficient catalysts for the asymmetric Michael addition of phenylacetic acid esters to ***Methyl Acrylate***.[12]

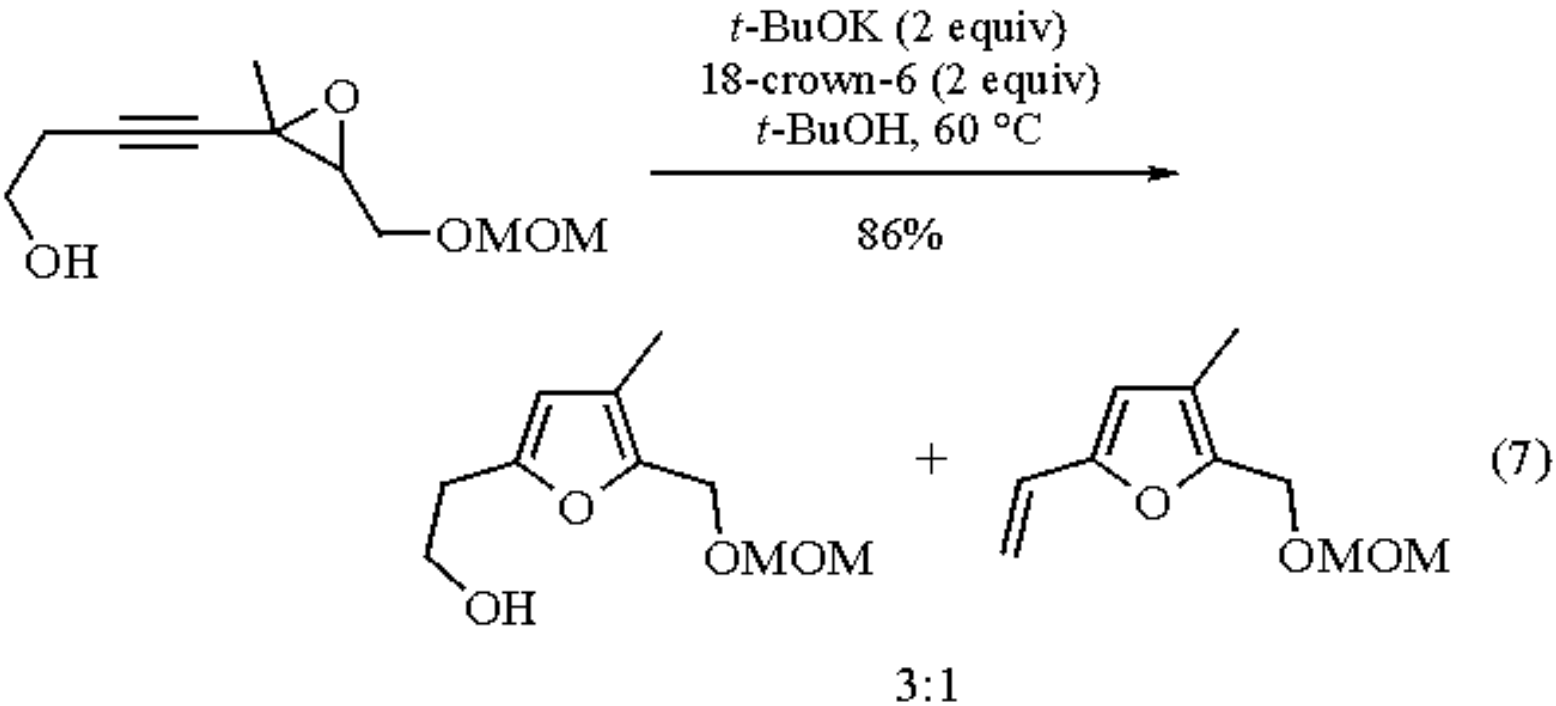

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Potassium *t*-Butoxide-Dimethyl Sulfoxide[1]

***t*-BuOK/Me_2SO**

(*t*-BuOK)

[865-47-4] · C_4H_9KO · Potassium *t*-Butoxide-Dimethyl Sulfoxide · (MW 112.23) (DMSO)

[67-68-5] · C_2H_6OS · Potassium *t*-Butoxide-Dimethyl Sulfoxide · (MW 78.15)

(highly basic reagent; useful for β-elimination and alkene isomerization reactions[1])

Preparative Methods: prepared in situ from anhydrous *t*-BuOK and anhydrous DMSO.[2a] Anhydrous DMSO is prepared by distillation from ***Calcium Hydride*** or ***Sodium Hydride*** under reduced pressure at 60 °C.

Handling, Storage, and Precautions: see ***Potassium t-Butoxide*** and ***Dimethyl Sulfoxide***. Store over 4 Å molecular sieves.[2b] Use in a fume hood.

Introduction.

Solutions of *t*-BuOK in DMSO are highly basic because the solvent strongly complexes with potassium cations, producing activated ligand-separated and dissociated *t*-butoxide anions in a medium of high dielectric constant.[1,2a,3] This base/solvent system is capable of deprotonating weakly acidic carbon and other acids.[2a,3] It is widely used to effect β-elimination reactions and isomerizations of unsaturated systems.[1,2a,3] $DMSO^-K^+$ is present in low concentrations in *t*-BuOK/DMSO solutions.[4]

β-Elimination Reactions.

A change in solvent from *t*-BuOH to DMSO affects the regiochemistry and stereochemistry of β-eliminations of alkyl halides with *t*-BuOK. For example, for 2-iodobutane both the 2-butene:1-butene and the *trans*:*cis*-2-butene ratios are increased (eq 1).[6] This is because the base is much more hindered in *t*-BuOH, where it is highly aggregated, than in DMSO, where the equilibrium is shifted toward less bulky free *t*-butoxide anions.[1,5,6] Chlorocyclodecane is dehydrochlorinated to *cis*-cyclodecene in good yield with *t*-BuOK/DMSO.[7a] Interestingly, if the elimination is effected with lithium dicyclohexylamide in Et_2O-hexane, the *trans*-isomer is produced. It was suggested that the dissociated *t*-butoxide anion should favor *anti* elimination, while the associated amide base should favor *syn* elimination.[1] However, it was later shown that isomerization of the thermodynamically less stable *trans*-isomer to the more stable *cis*-isomer accounts for the formation of the latter with *t*-BuOK/DMSO.[7b] For hindered acyclic substrates the reagent favors the usual *anti*-coplanar β-elimination mechanism, whereas *syn* elimination is the major pathway

when solutions of the base in THF or *t*-BuOH are employed (eq 2).[3] Presumably, the aggregated ion pairs of the base in the latter solvents assist in the removal of the leaving group and the β-proton in a *syn* alignment.[5,8] *Anti* elimination also results when ***18-Crown-6*** is added to THF solutions of *t*-BuOK because dissociated *t*-butoxide anions are produced. The strained alkene 3,3-dimethylcyclopropene is obtained in good yield from 1-halo-2,2-dimethylcyclopropanes with the reagent;[9] the presence of *t*-BuOH reduces the yield considerably.

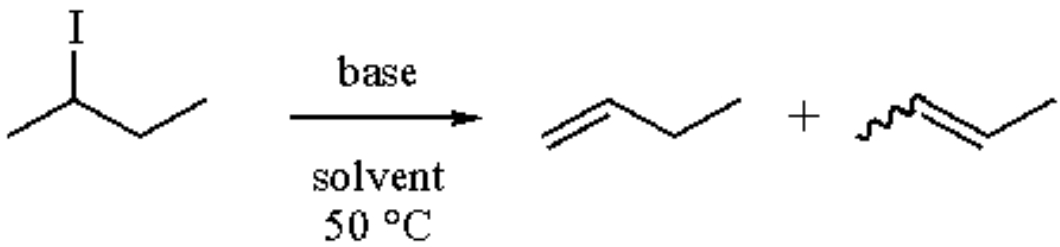

(1)

Base/solvent			*trans*/*cis* 2-butene ratio
t-BuOK/DMSO	~21%	~79%	2.99
t-BuOK/*t*-BuOH	34%	66%	2.17

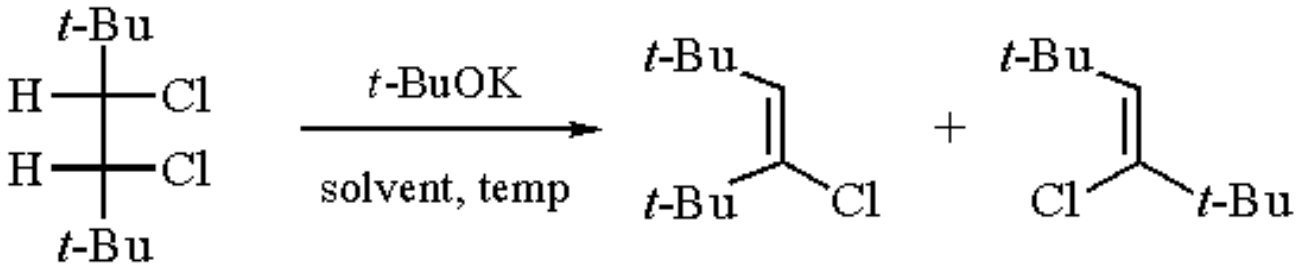

(2)

Solvent/temp		
DMSO, 20 °C	93	7
THF, 60 °C	8	92
THF + 18-crown-6, 60 °C	87	13

β-Phenylthio chlorides, tosylates, and mesylates undergo β-elimination to vinyl sulfides in high yield upon treatment with *t*-BuOK/DMSO (eq 3).[10] This type of reaction is an important step in a synthetically useful 1,2-carbonyl transposition sequence.[10]

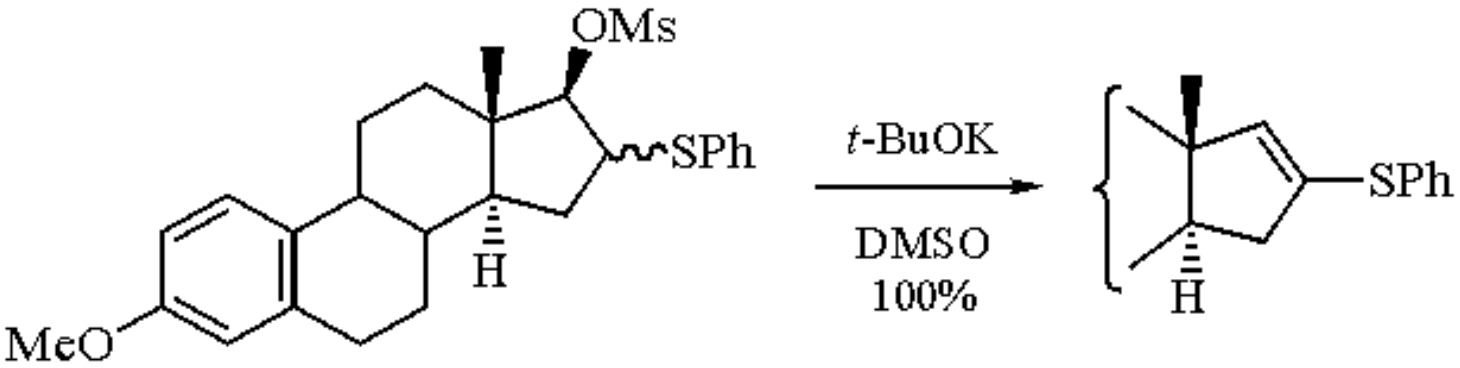

(3)

Primary tosylates are more prone than bromides to form *t*-butyl ethers by S_N2 displacement by the *t*-butoxide anion in DMSO.[11] Sulfonate esters of flexible cyclic and secondary acyclic alcohols give predominately alkenes in the presence of *t*-BuOK/DMSO.[12] With sulfonate esters of 3-hydroxy steroids, there is competition between β-elimination and attack of the *t*-butoxide ion on sulfur to form alcohols;[13] mesylates are more prone to this reaction than tosylates. Sulfonate esters of 3α-acetoxy-12α-hydroxycholanate undergo mainly β-elimination with *t*-BuOK/DMSO (eq 4).[14] In this case, substitution of various other aprotic solvents for DMSO and $DMSO^-Na^+$ for *t*-BuOK was not as effective. Treatment of both the mesylate and the tosylate of cholesterol with *t*-BuOK/DMSO gives the conjugated diene, 3,5-cholestadiene, in high yield.[15]

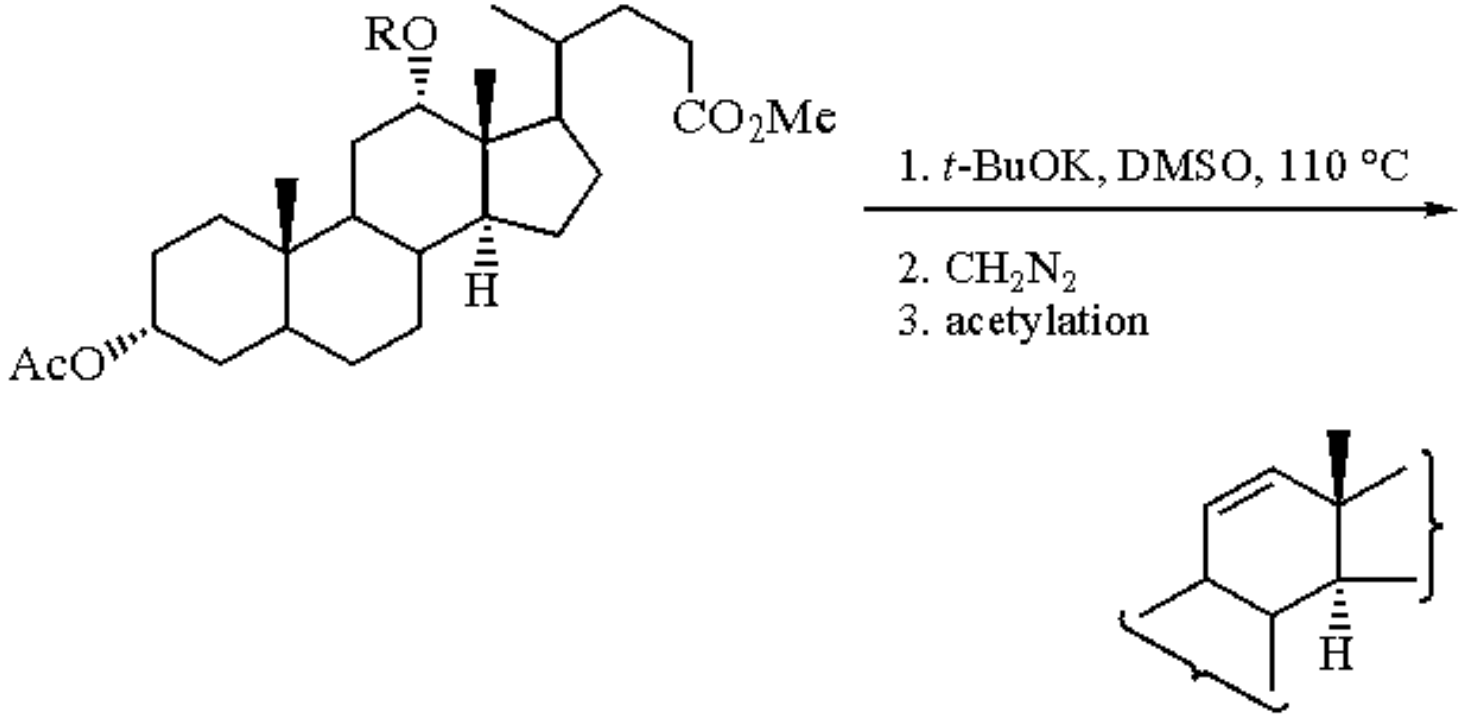

(4)

R = Ts, ~74%; Ms, ~55%

1,2-Dibromo-[16a] and 2,2-dichloro-3,3-dimethylbutane derivatives[16b] undergo double dehydrohalogenation with *t*-BuOK/DMSO to yield *t*-butylacetylene (eq 5). The reagent converts eight- and nine-membered ring 2-bromo-3-methoxy *trans*-cycloalkenes into the corresponding methoxy cycloalkynes via *anti* elimination in reasonably good yields (eq 6).[17] 1-Chloro-4-methylcyclohexene is converted largely into the corresponding 1-*t*-butyl ether derivative in the presence of the base (eq 7).[18] An allene, 5-methyl-1,2-cyclohexadiene, is probably an intermediate in the reaction.

The related allene derived from 1-bromocyclohexene has been trapped with 1,3-diphenylbenzo[*c*]furan under similar conditions.[19] *t*-BuOK/DMSO reacts with bromobenzene to give *t*-butyl phenyl ether in low yield, presumably via the intermediacy of benzyne.[20]

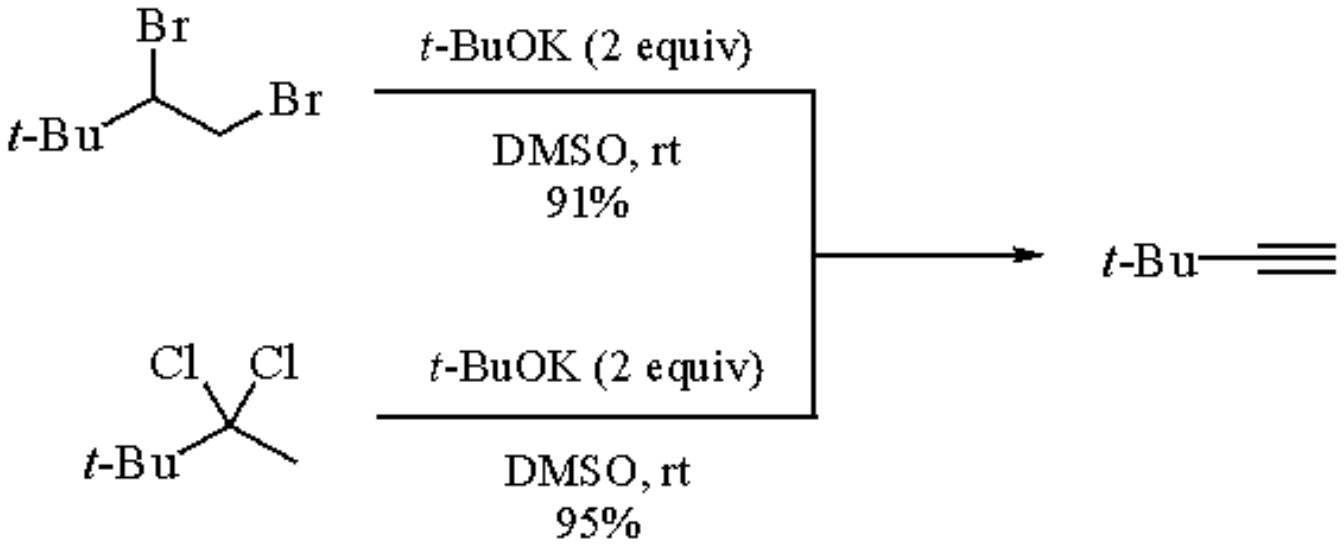

(5)

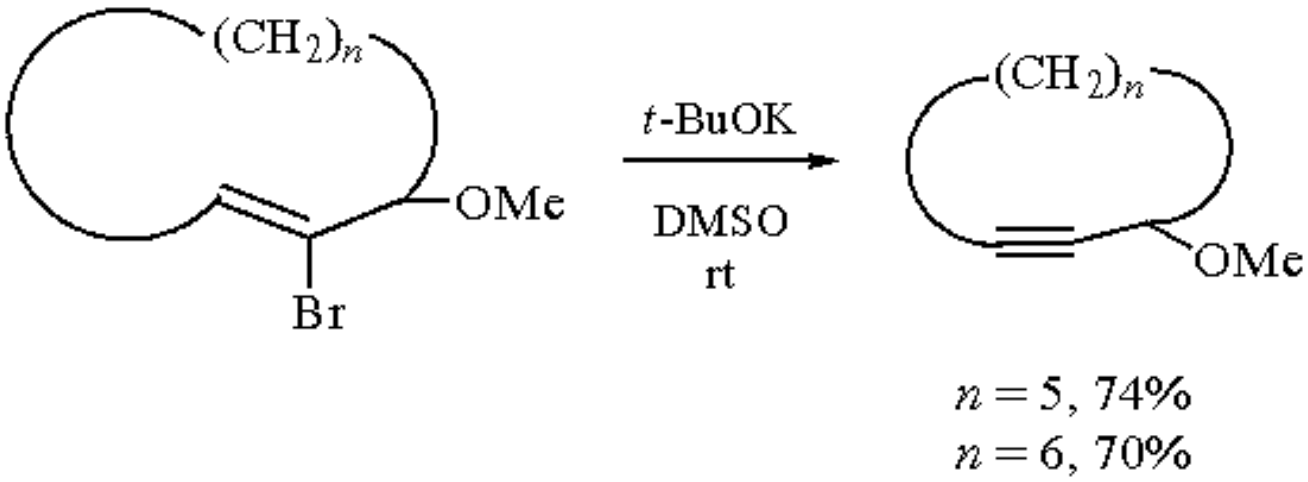

(6)

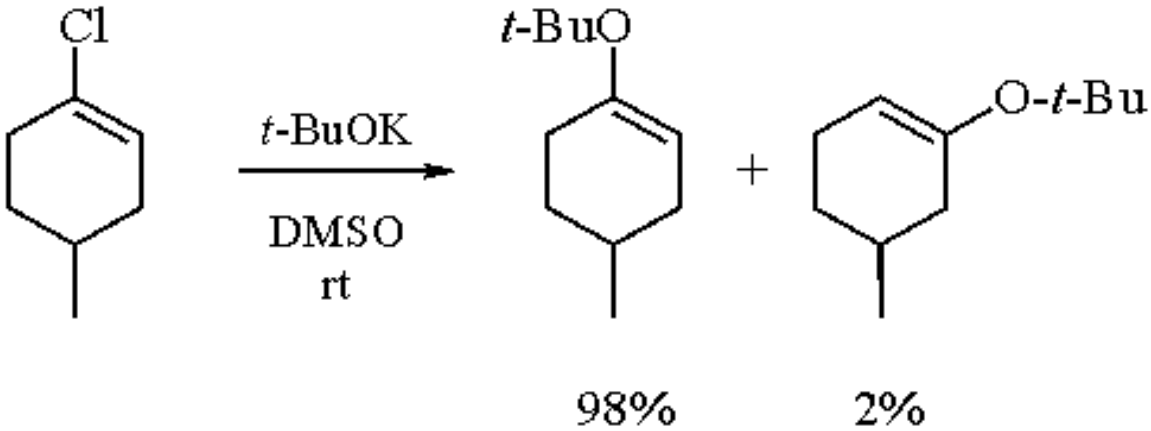

(7)

β-Elimination with Double Bond Isomerization.

t-BuOK in DMSO is sufficiently basic to isomerize less thermodynamically stable multiple bond systems to more

stable isomeric compounds (see below). Therefore, it is not surprising that β-eliminations with this reagent are frequently accompanied by isomerizations of initially formed products. *gem*-Dihalocyclopropane derivatives are particularly prone to these reactions (eqs 8 and 9);[21] such reactions may also occur with *t*-BuOK in other solvents.[21c] Certain *gem*-dichlorocyclopropanes yield enynes by processes involving cleavage of the three-membered ring upon reaction with *t*-BuOK/DMSO.[21d,e] The base converts 7,7-dichlorobicyclo[4.1.0]heptane to a complex mixture of products containing mainly ethylbenzene.[22] The extra carbon atom apparently comes from the solvent, DMSO. An example of an isomerization of an initially formed diene to a more stable isomer is found in the reaction of the tosylate of the terpene alcohol nopol with excess *t*-BuOK/DMSO (eq 10).[23]

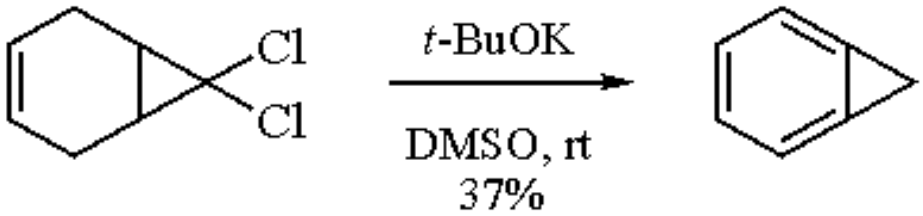

(8)

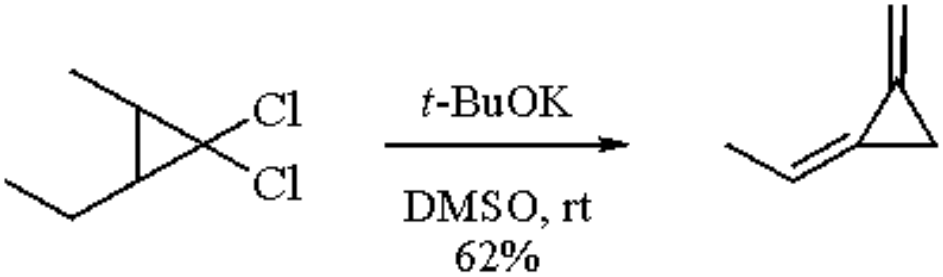

(9)

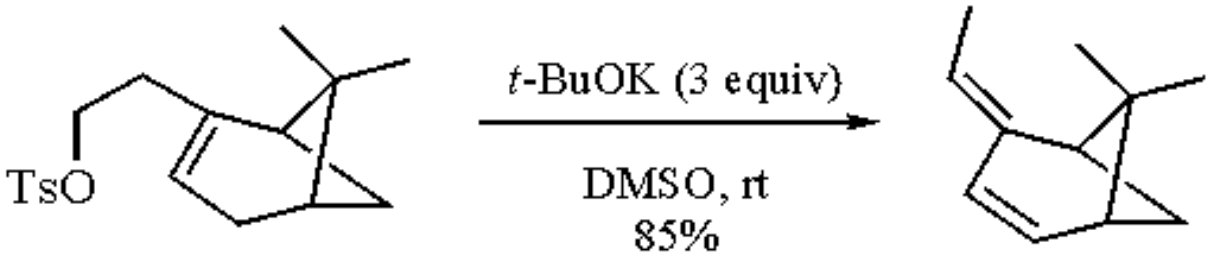

(10)

Isomerizations of Unsaturated Systems.

t-BuOK/DMSO is a sufficiently powerful base to produce carbanions in a low equilibrium concentration by the deprotonation of sp^3-hybridized carbon atoms adjacent to multiple C-C bonds.[1] Thus the base can effect isomerizations of less thermodynamically stable unsaturated systems to more stable isomers. The rearrangement of terminal alkenes into internal isomers,[2a,3] alkylcyclopropenes into alkylidenecyclopropanes (eq 11),[24] and a variety of allylic compounds into the corresponding vinylic compounds are representative examples of these reactions. It is interesting that this base converts allyl ethers to *cis*-enol ethers stereospecifically and in high yields (eq 12).[25]

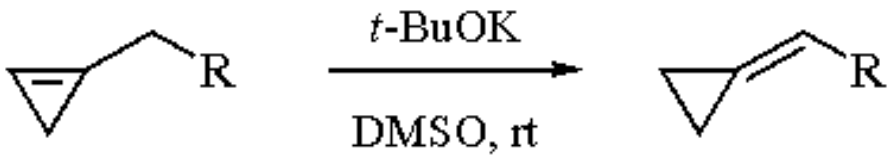

(11)

R = H, 100%
R = Me, 85%

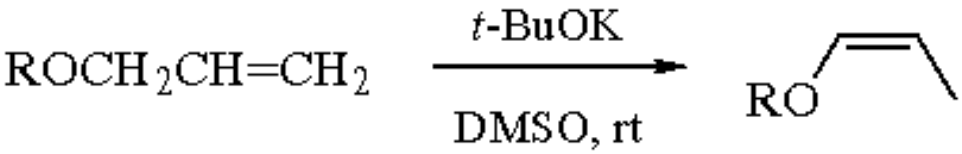

(12)

R = Ph, 99%
R = , 85-90%

The base converts steroidal 1,4-dien-3-ones into 1,3,5-trienolates which yield 1,5-dien-3-ones upon addition of water (eq 13).[26] This reaction does not occur with *t*-BuOK/*t*-BuOH. The *t*-BuOK/DMSO reagent isomerizes cyclic 1,4- (eq 14)[27] and 1,5-dienes (eq 15)[28] into the corresponding conjugated dienes.

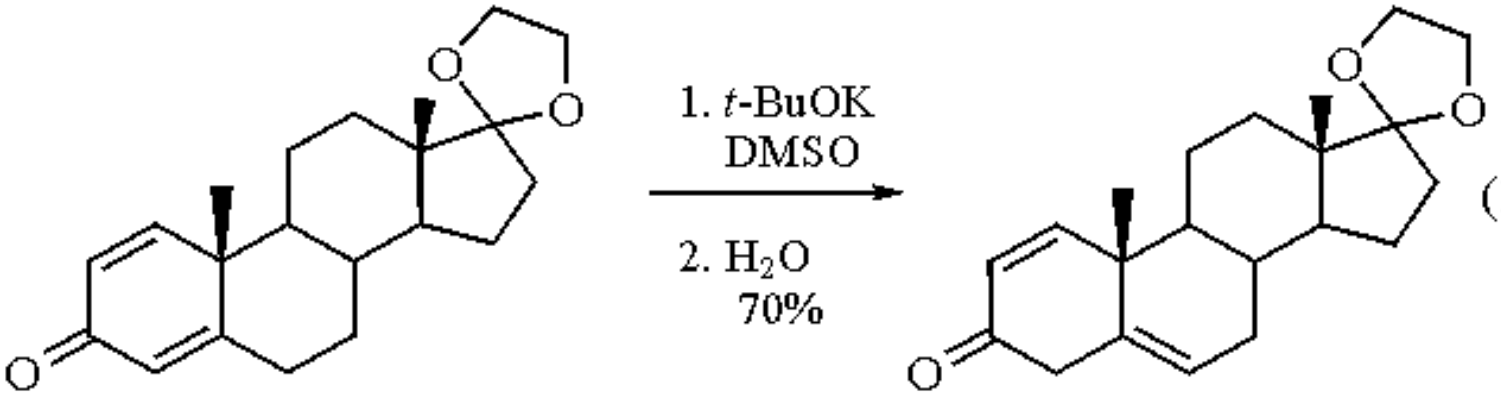

(13)

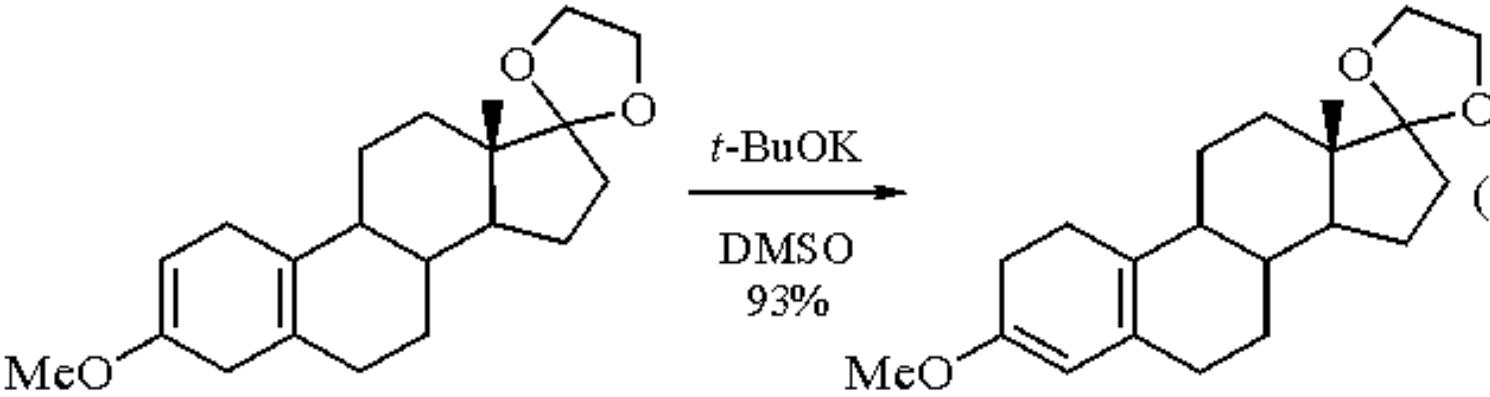

(14)

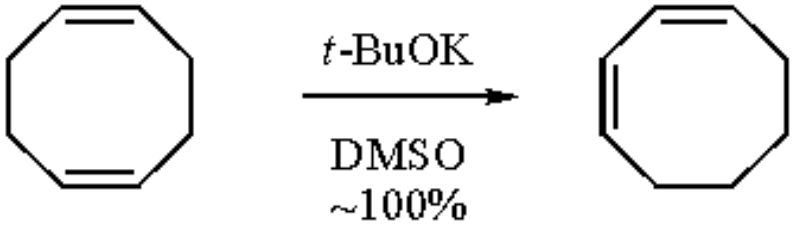

(15)

Acyclic enynes and cumulenes are converted into conjugated trienes with a catalytic amount of *t*-BuOK in DMSO.[29] The conversion of a cyclic allene into a cyclic alkyne (eq 16) occurs with this base, while ***Potassium t-Butoxide-t-Butyl Alcohol Complex*** and other bases are ineffective.[30]

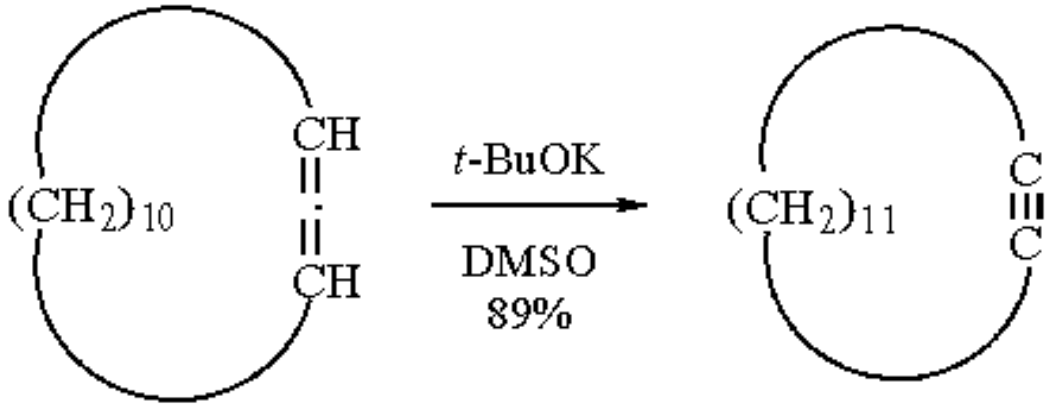

(16)

Other Reactions.

In the reaction shown in eq 17, *t*-BuOK/DMSO effects the conversion of a γ-bromophosphonium salt into a cyclopropylidenephosphorane which reacts with cyclopropanecarbaldehyde to form cyclopropylmethylenecyclopropane.[31] This product is converted into dicyclopropylidenemethane in two steps.

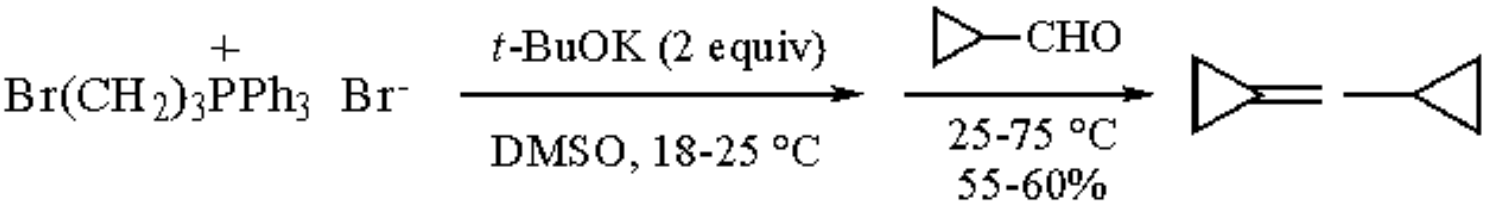

(17)

Oxiranes are obtained by treating β-hydroxy alkylselenonium or β-hydroxy alkylsulfonium salts with *t*-BuOK/DMSO.[32] Although the stereochemistry of the reactant is uncertain, only the *cis*-oxirane is obtained in the reaction shown in eq 18.[32b] An interesting example of oxirane formation involving a fragmentation of a β,δ´-dihalo ether is shown in eq 19.[33]

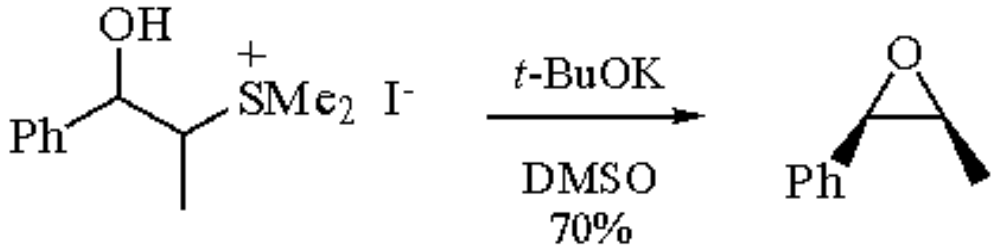

(18)

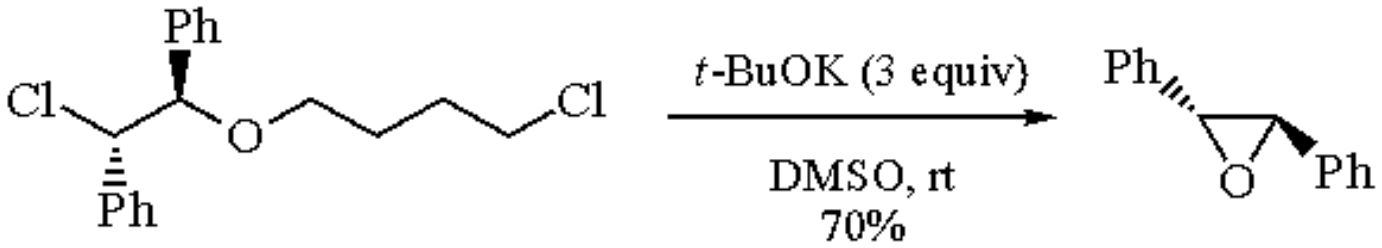

(19)

Upon reaction with *t*-BuOK/DMSO, medium-ring β-keto esters containing 4-oxopentyl side chains undergo three-carbon ring expansion reactions via an aldol-retroaldol process (eq 20).[34] Similar reactions of related cyclic ketones containing electron-withdrawing α-substituents occur in *t*-BuOK/THF.[35]

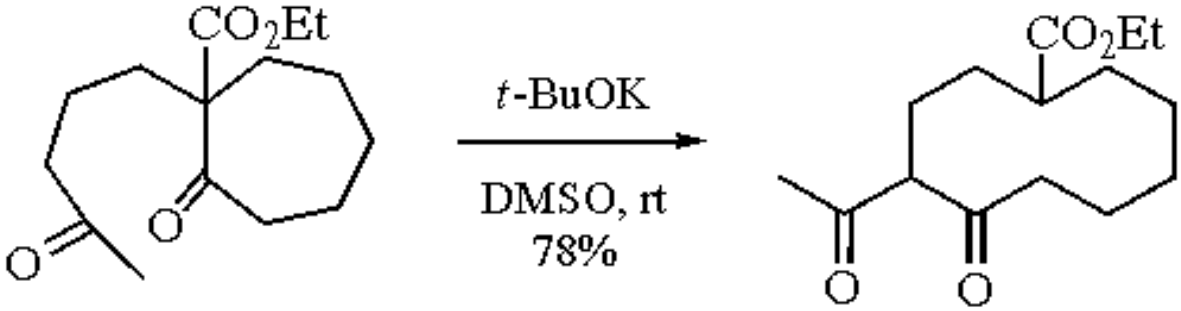

(20)

An interesting modification of the Wolff-Kishner reduction involves the slow addition of a preformed hydrazone to *t*-BuOK/DMSO at rt.[36] However, other modifications of this reduction reaction are more widely used in organic synthesis.[37] *t*-BuOK/DMSO effects O-alkyl cleavage of sterically hindered methyl esters in high yields (eq 21).[38]

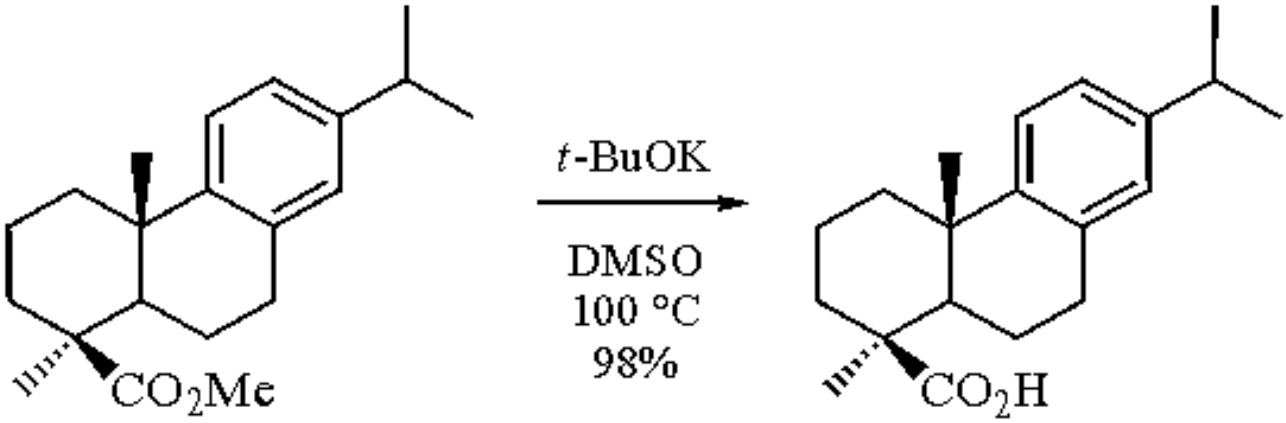

(21)

Protiodesilylations of α- (eq 22) and certain β-hydroxysilanes with *t*-BuOK in wet DMSO occur with retention of configuration.[39] Similar conditions allow protiodesilylations of cyclic saturated (eq 23)[40] and unsaturated siloxanes.[41]

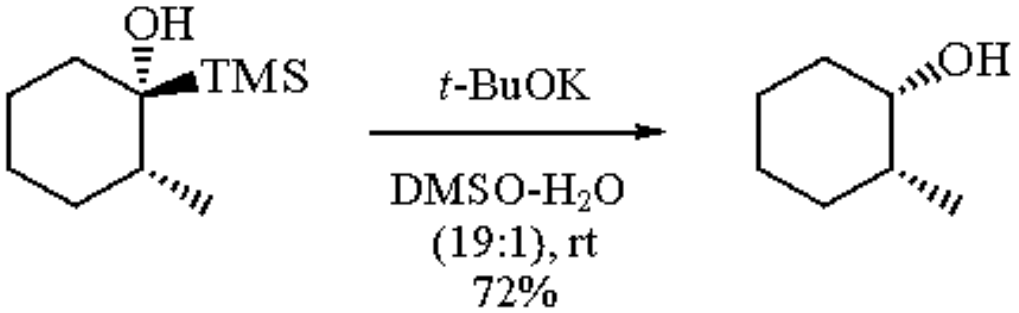

(22)

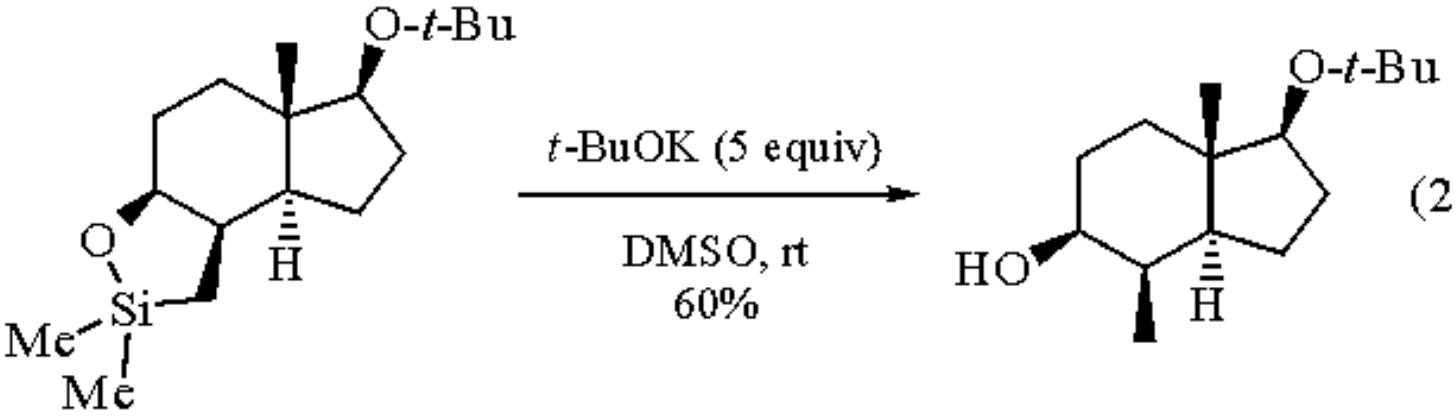

(23)

Related Reagents.

Potassium t-Butoxide; ***Potassium Methoxide-Dimethyl Sulfoxide***.

---

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Potassium *t*-Butoxide-Hexamethylphosphoric Triamide

t-BuOK/$(Me_2N)_3PO$

(*t*-BuOK)

[865-47-4] · C_4H_9KO · Potassium *t*-Butoxide-Hexamethylphosphoric Triamide · (MW 112.23) (HMPA)

[680-31-9] · $C_6H_{18}N_3OP$ · Potassium *t*-Butoxide-Hexamethylphosphoric Triamide · (MW 179.24)

(useful base for deprotonating weakly acidic substrates[2])

Preparative Method: prepared in situ from anhydrous *t*-BuOK and anhydrous HMPA. Anhydrous HMPA is obtained by distillation from ***Sodium*** metal or ***Calcium Hydride*** under reduced pressure at 60 °C.[1]

Handling, Storage, and Precautions: see ***Potassium t-Butoxide*** and ***Hexamethylphosphoric Triamide***. HMPA is a cancer-suspect agent which should be handled with extreme care; do not breathe the vapor and avoid contact of the solid or liquid with eyes, skin, or clothing. Store over 4 Å molecular sieves. Use in a fume hood.

Introduction.

HMPA is capable of strongly solvating potassium cations and producing solutions of *t*-BuOK which contain substantial amounts of highly basic ligand-separated ion pairs and dissociated *t*-butoxide anions.[2] Deprotonation reactions are favored by the highly polar medium. Unlike ***Dimethyl Sulfoxide***, HMPA is not deprotonated by the *t*-butoxide anion.

Michael Addition-Intramolecular Alkylation Reactions.

t-BuOK is an effective additive for accelerating the rates of cycloalkylation of lithium enolates produced in the Michael addition of lithium enolates of esters to ε-iodo-α,β-unsaturated esters.[3] Three-, five-, six-, and seven-membered ring carbocyclic diesters are available by these reactions. When a six-membered ring is produced in the cycloalkylation reaction (eq 1), the stereochemistry of the cyclic diester products is strongly dependent upon the nature of the solvent. If THF alone is employed, the *syn*-diester is the major product, but if a 4:1 mixture of THF-HMPA is used, the *anti*-diester is highly favored.[3] The observation of such a high degree of stereochemical control in the production of extracyclic stereocenters is remarkable.

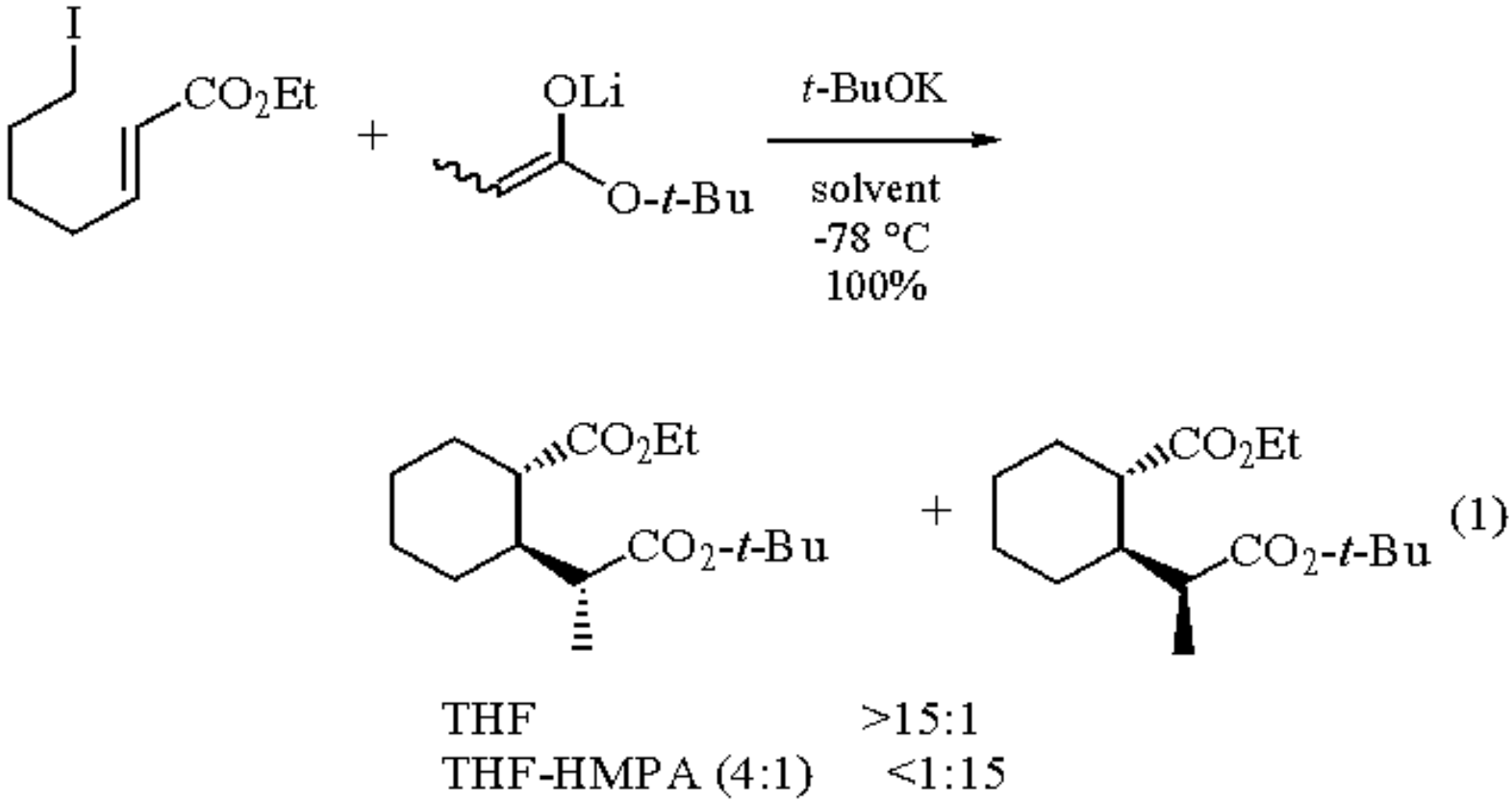

Autooxidation Reactions.

HMPA is more effective than sulfolane, ***Dimethyl Sulfone***, or DMSO as an activator for *t*-BuOK in the base-promoted autooxidation of alkylbenzene derivatives to aromatic acids.[4] The medium is also useful for the autooxidation of acetophenone to benzoic acid,[5] and for oxidation of a variety of other benzene derivatives.[6]

Other Reactions.

The expansion of the 12-membered ring of the epoxy sulfone shown in eq 2 to a 15-membered ring enone occurs in a reasonable yield with *t*-BuOK in *t*-BuOH-HMPA.[7] This reaction involves formation of an α-sulfonyl carbanion, intramolecular nucleophilic opening of the epoxide ring by this species, and Grob fragmentation of the γ-sulfonyl alkoxide intermediate. *t*-BuOK/HMPA efficiently isomerizes 2-alkynyl dialkylamines to dialkylamino allenes and 2-alkynyl ethers to allenic ethers.[8] A catalytic amount of *t*-BuOK in HMPA has been used to generate 1,1-difluoroallyl anions from difluoroallyl(dimethylphenyl)silanes by attack of the *t*-butoxide anion on silicon.[9] These anions undergo addition to carbonyl compounds (eq 3).[9]

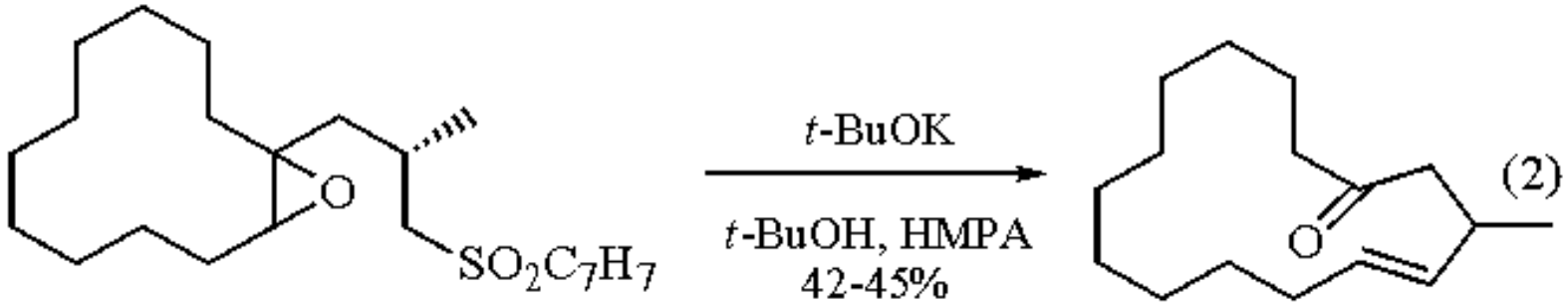

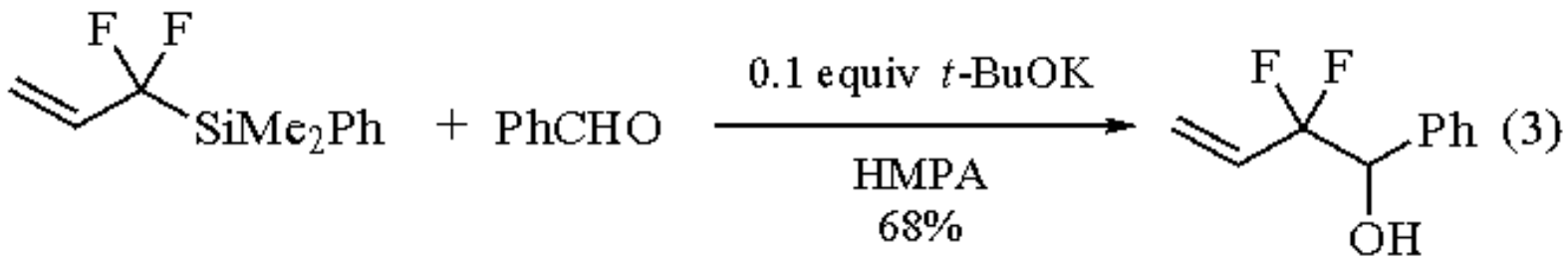

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Potassium Carbonate[1]

K_2CO_3

[584-08-7] · CK_2O_3 · Potassium Carbonate · (MW 138.21)

(inorganic base used in the alkylation of phenols[2] and 1,3-dicarbonyl compounds;[7] generation of sulfur[12] and phosphorus ylides;[13] also used to dry organic solvents[16])

Physical Data: mp 891 °C; *d* 2.43 g cm^{-3}; hygroscopic until 16.4% water is absorbed; pH of saturated aqueous solution is 11.6.

Solubility: 1.12 g mL^{-1} in water at 20 °C; practically insol alcohol.

Form Supplied in: white solid; widely available. Use in form supplied for best results.

Purification: crystallize from water 70 °C; dry over H_2SO_4.

Handling, Storage, and Precautions: keep in a tightly sealed container; avoid inhalation.

Alkylation of Phenols.

The mildly basic nature of this reagent makes it ideal for the selective deprotonation of organic acids. This property makes K_2CO_3 a useful reagent for the alkylation of phenols. The procedure[2] for phenol alkylation involves dissolving the phenol and alkylating agent in acetone with excess K_2CO_3 added as an insoluble component (eq 1). The reaction is run at reflux. Workup consists of removal of solvent and addition of water. The product is isolated by either extraction or filtration. Popular alternative solvents are DMF[3] and MeCN.[4] If the aqueous solution needs to be neutralized, it is convenient to remove excess K_2CO_3 via filtration before solvent removal and subsequent water addition.

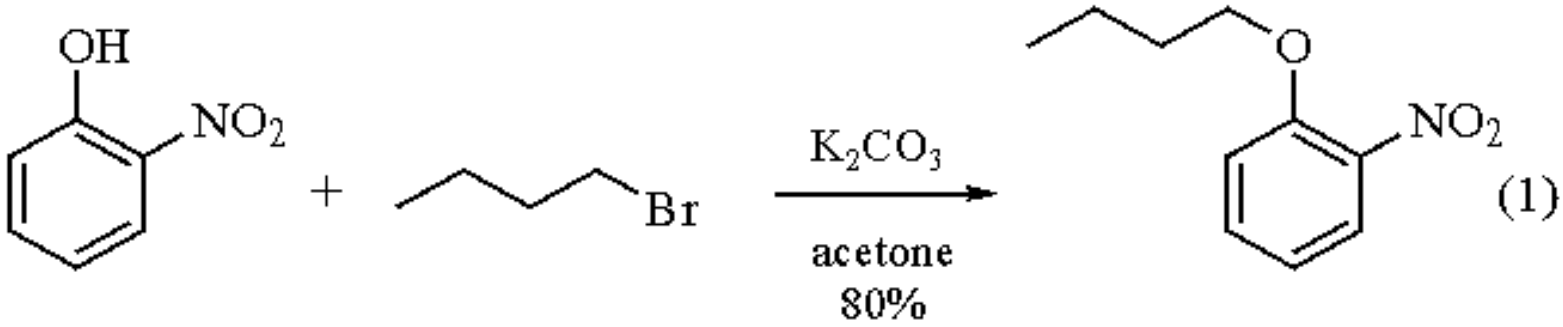

Sulfides can also be alkylated using K_2CO_3 in DMF, as demonstrated in the shell closure reaction used to capture guests within linked anisyl moieties.[5]

Hydrolysis Reactions.

Ester hydrolysis using K_2CO_3 in MeOH was found to give clean conversion to the allylic alcohol (eq 2).[6]

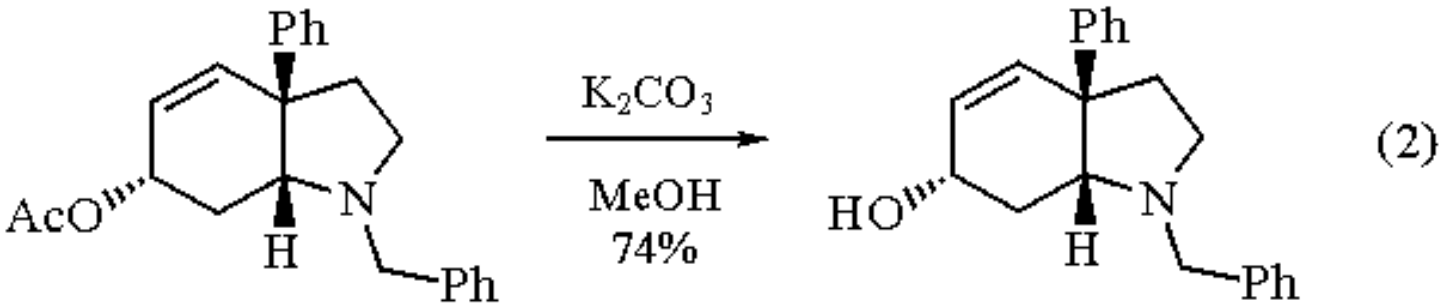

When amides that contain α,β-amino alcohols undergo diazotization followed by treatment with aqueous K_2CO_3,[7] they are cleanly converted to the epoxide (eq 3), while the β-amino ester gives the corresponding alcohol (eq 4).

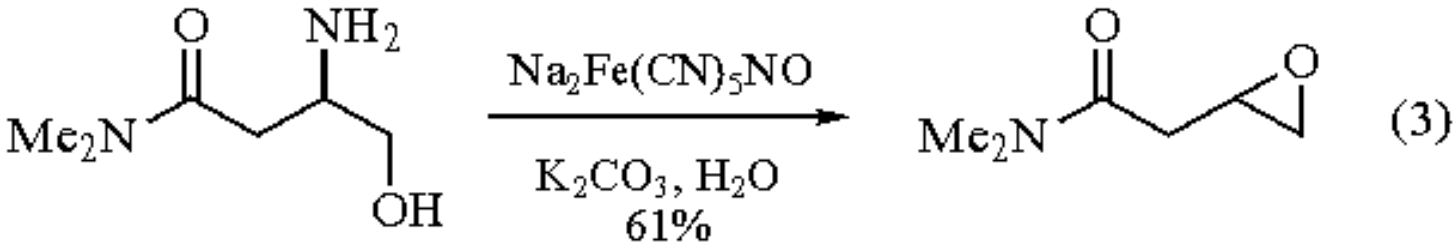

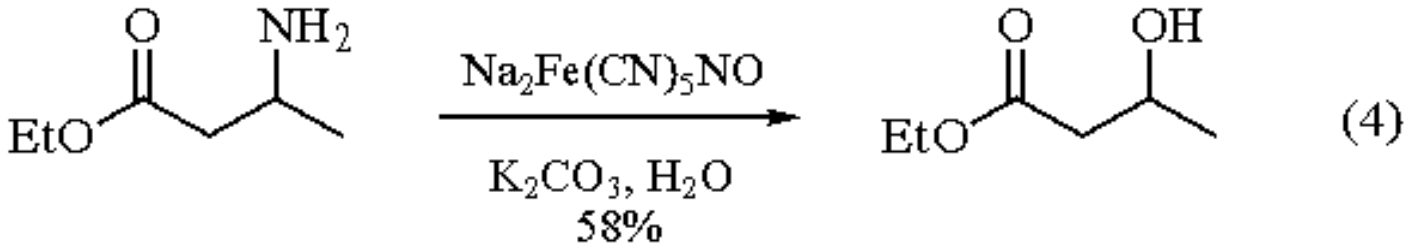

Reactions of 1,3-Dicarbonyl Compounds.

The enolate of β-keto esters can be alkylated in a procedure developed by Claisen[8] that is analogous to the alkylation of phenols. The β-keto ester and alkylating agent are combined with K_2CO_3 in acetone and the reaction heated to reflux. The reaction is useful for the *C*-alkylation of substrates. In the case of ethyl 2-oxocyclopentanecarboxylate[9] the reaction gave good yields and high selectivity for *C*-alkylation with unobstructed alkylating agents (eq 5).

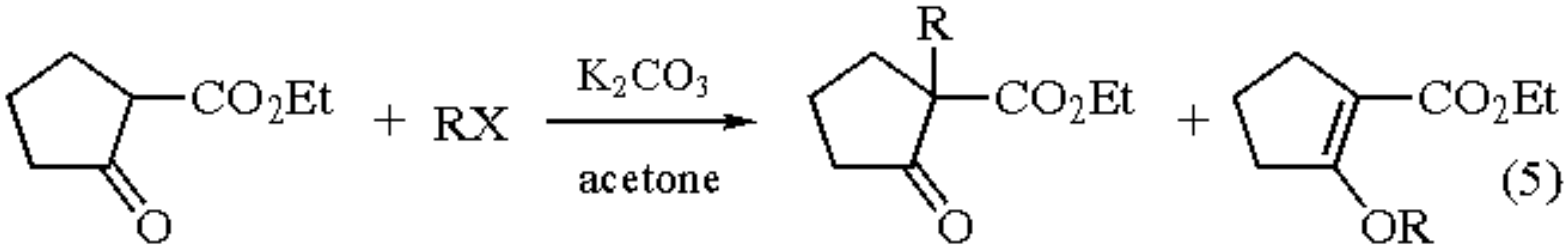

RX	*C*-alkylation (%)	*O*-alkylation (%)
MeI	100	<1
$(MeO)_2SO_2$	100	<1
$H_2C{=}CHCH_2Br$	91	<1
$BrCH_2CO_2Et$	92	<1
i-PrI	78	18
$PhCH_2OCH_2Cl$	49	21

The reagent also shows good selectivity in the monoalkylation of β-dicarbonyl compounds. The reaction of 2-chloro-2-methylproponal with malonic esters in THF or ether gives good yield of the monoalkylated malonic ester (eq 6).[10]

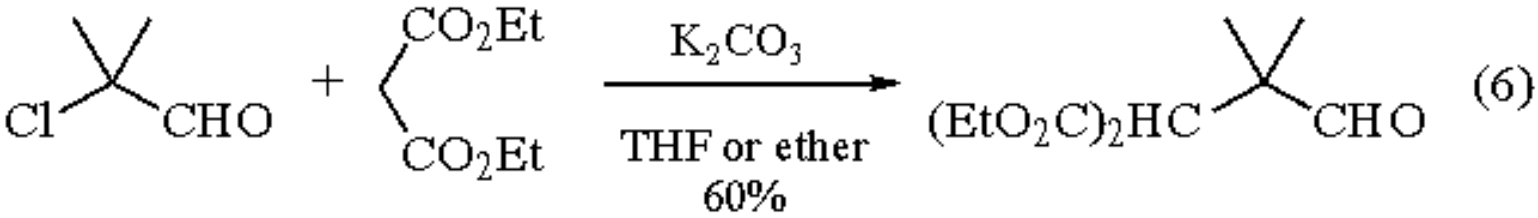

Aldehydes can be reacted with 1,3-dicarbonyl compounds in THF to give α,β-unsaturated carbonyl compounds with good (*Z*/*E*) selectivity (eq 7).[11]

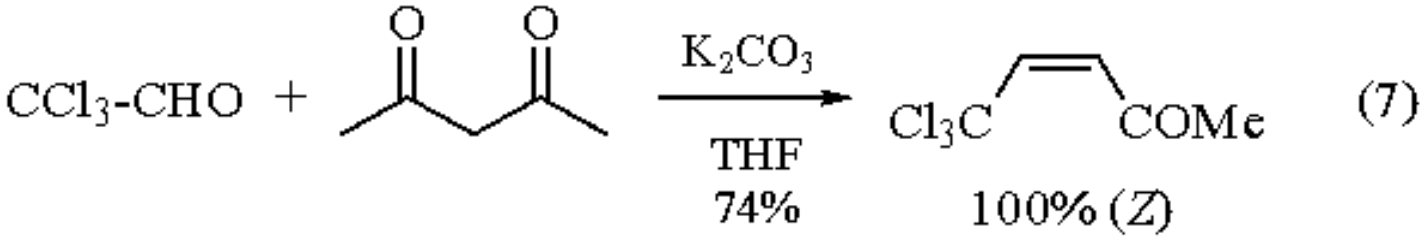

The reagent is also useful for the generation of intramolecular Michael addition products with excellent stereoselectivity (eq 8).[12]

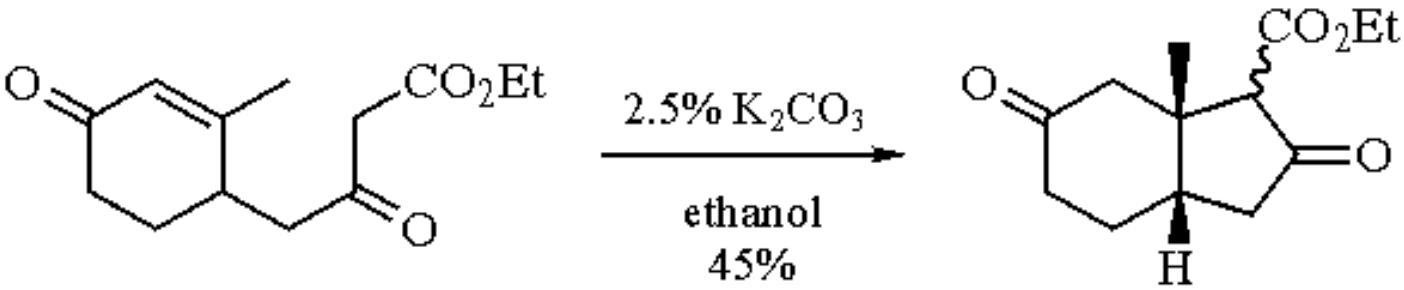

(8)

Generation of Phosphorus Ylides.

Wittig reactions can be done either under heterogeneous (water-1,4-dioxane) conditions[13] or more conveniently using 18-crown-6 as a phase-transfer catalyst (see ***Potassium Carbonate-18-Crown-6***).[14] The phase-transfer conditions give alkenes in good yields with a preference for the (*E*)-isomer (eq 9). The procedure involves the combination of alkylphosphonium salt, K_2CO_3, aldehyde, and ***18-Crown-6*** in either CH_2Cl_2 or THF. The solvent is removed, product extracted with petroleum ether, and filtered through silica gel.

$$R^1CHO + Ph_3\overset{+}{P}CH_2R^2\ X^- \xrightarrow[CH_2Cl_2 \text{ or THF}]{K_2CO_3,\ 18\text{-crown-}6} R^1CH{=}CHR^2 \quad (9)$$

R^1	R^2	(*E*) %
Ph	Ph	70
Ph	Me	78
Et	Ph	75

Generation of Sulfur Ylides.

β-Ketosulfonium salts react with K_2CO_3 to generate the corresponding ylide. α-Methylthio ketones are reacted with allylic halides to afford sulfonium salts that are reacted with aqueous K_2CO_3 to generate a sulfur ylide[15] that can undergo [2,3]-sigmatropic rearrangement (eq 10).

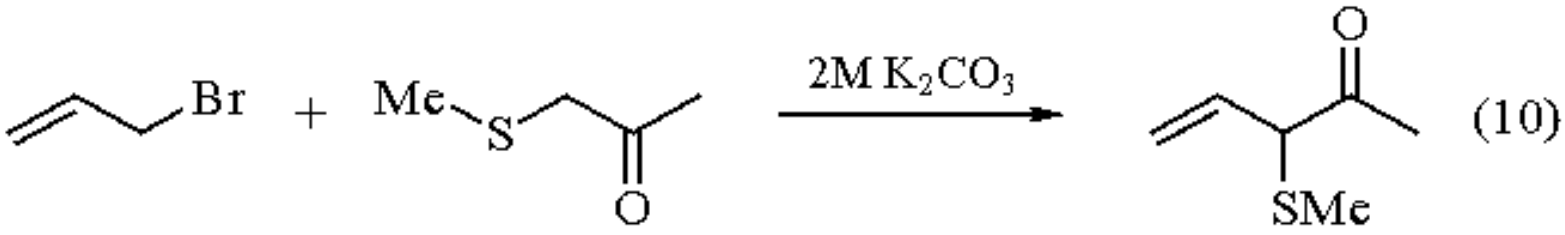

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Potassium Carbonate-18-Crown-6

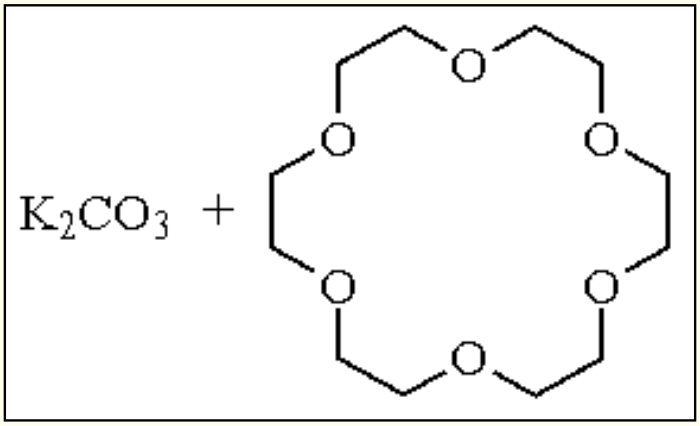

(K_2CO_3)

[584-08-7] · CK_2O_3 · Potassium Carbonate-18-Crown-6 · (MW 138.21) (18-crown-6)

[17455-13-9] · $C_{12}H_{24}O_6$ · Potassium Carbonate-18-Crown-6 · (MW 264.36)

(basic reagent combination that operates efficiently under catalytic two-phase conditions, yet is sufficiently gentle not to hydrolyze or otherwise destroy sensitive products;[1,2] capable of promoting *trans*-alkene formation during Wittig condensations;[3] heightens selectivity and reactivity of carbanions in nonpolar solvents[4])

Physical Data: prepared in situ.

Solubility: while 18-crown-6 is soluble in aprotic solvents, potassium carbonate exhibits very limited solubility. As a consequence, it is believed that proton abstraction occurs on the surface of the solid carbonate.[1] For this reason, it is particularly important to recognize that K_2CO_3 is a finely powdered material that exhibits no tendency to aggregate and form lumps.

Handling, Storage, and Precautions: this reagent combination eliminates the need to prepare anhydrous solvents and is convenient because the prior preparation of carbanions is unnecessary. Furthermore, hazardous and expensive ingredients are not involved.

Efficiency as a Base.

Phase-transfer catalysis of reactions by aqueous hydroxide in an inert organic medium is often disadvantaged by competing saponification if the starting materials are prone to hydrolysis. To regain efficiency, it is advantageous to turn instead to a liquid-solid two-phase system constituted of ***Potassium Carbonate*** and an aprotic solvent, such as

CH_2Cl_2 or benzene, to which ***18-Crown-6*** is added to facilitate transport of the conjugate base into the organic phase. Under these conditions, ***Diethyl Malonate*** readily undergoes highly selective monoalkylation (eq 1).[1] Other notably sensitive esters respond well to this rather mild base (eqs 2 and 3),[1] despite the fact that somewhat higher temperatures are sometimes required.

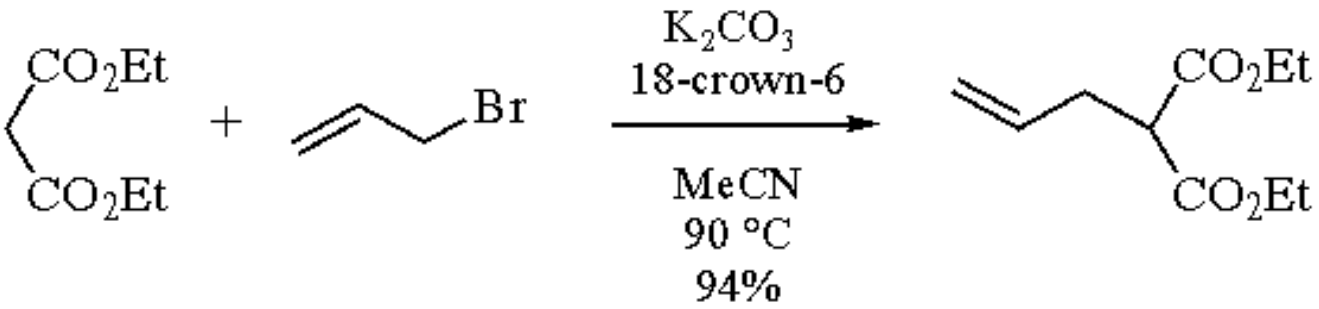

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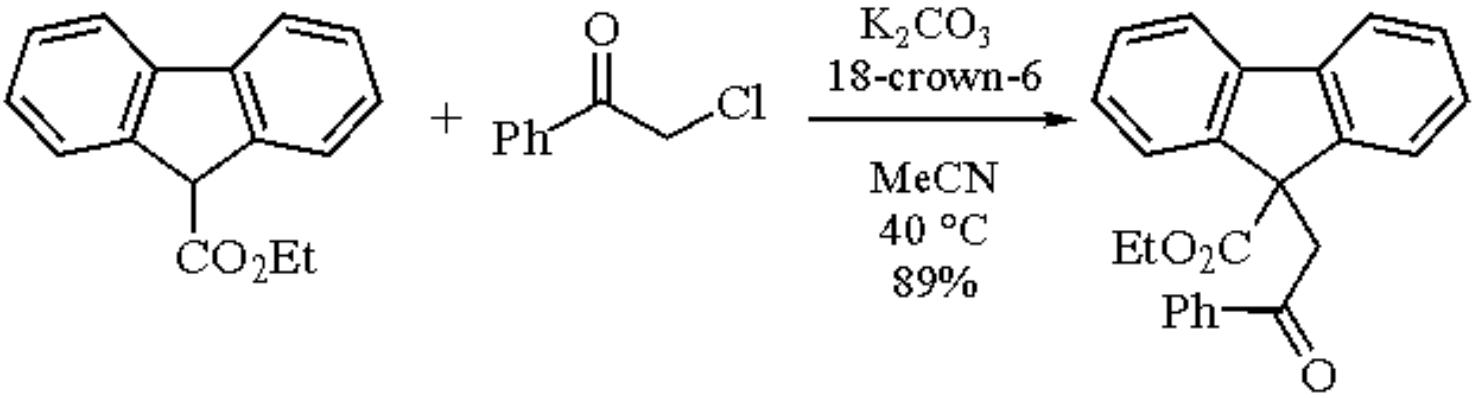

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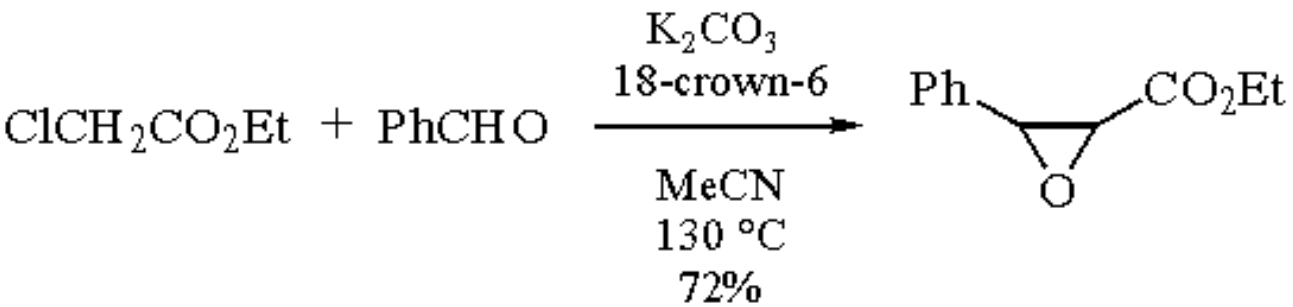

(3)

In addition to the Darzens reaction, it is also possible to prepare dibromocarbene, ethers by the Williamson synthesis, phosphonates by Michaelis-Becker alkylation, and alkenes by the Wittig reaction. In this last process, the conditions are sufficiently mild that solvent effects can be utilized to control product stereochemistry.[3] When nonstabilized ylides are involved, the use of THF leads predominantly to the *cis*-alkenic isomer in a manner akin to salt-free conditions (eq 4). In CH_2Cl_2 solution the product distribution is reversed. If the ylide is stabilized, either solvent leads to the *trans*-alkene.

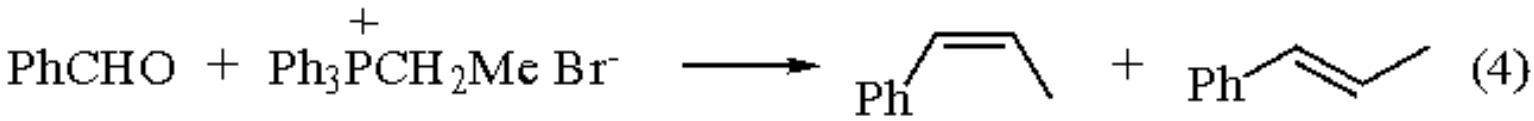

K_2CO_3, 18-crown-6, THF, Δ, 96%	85:15
K_2CO_3, 18-crown-6, CH_2Cl_2, Δ, 93%	22:78

Dendritic polymers having an average molecular weight in excess of 100 000 have been produced by initiating polycondensation with the title reagent system.[5]

Methylation and Silylation Reactions.

Neat dimethyl carbonate can supplant ***Dimethyl Sulfate*** as methylating agent when reaction is promoted by potassium carbonate and 18-crown-6 (eq 5).[6] The same catalyst system appears ideally suited to the methylation of carboxylic acids and phenols with methyl trichloroacetate (eqs 6 and 7).[7,8] Since the byproducts are $CHCl_3$ and CO_2, product isolation is conveniently realized. Primary and allylic trichloroacetates can be substituted with equal success. An added major advantage of this technology is its lack of dependence on stoichiometric base.

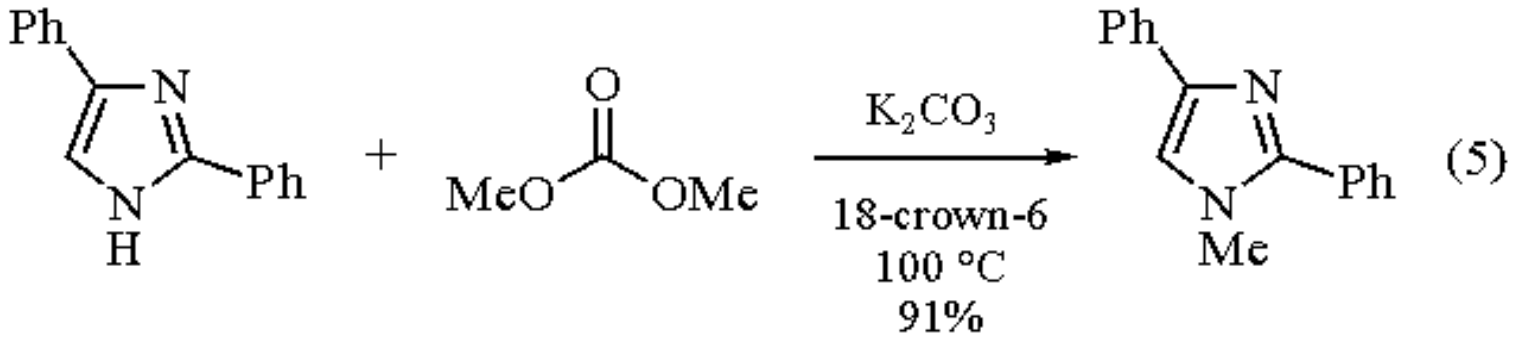

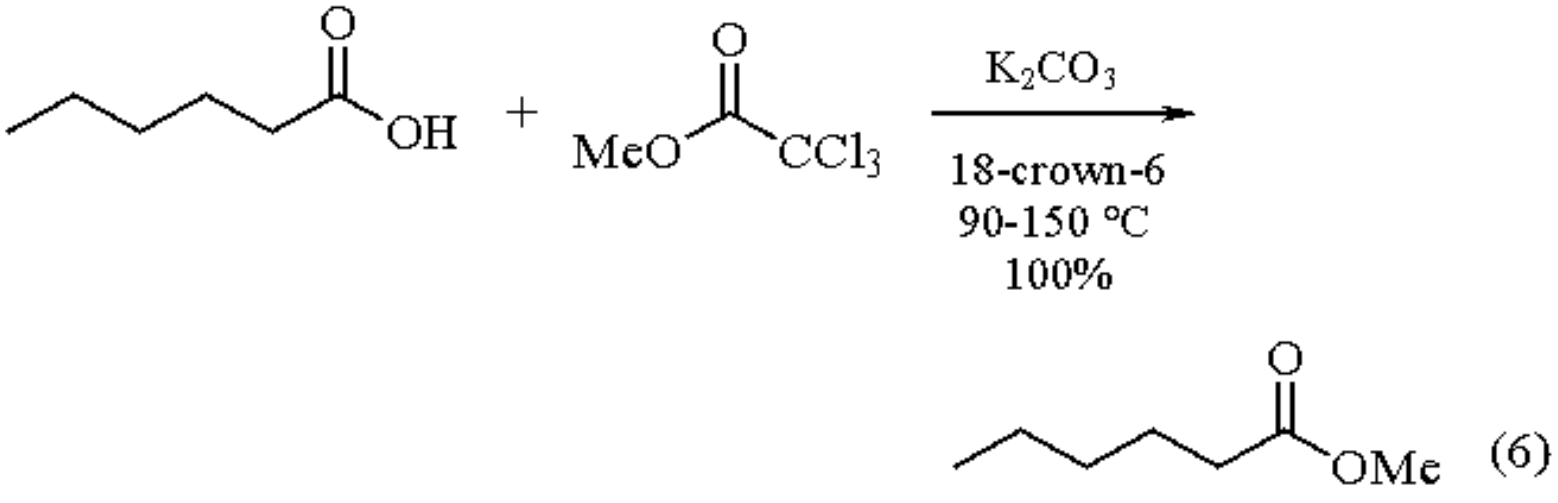

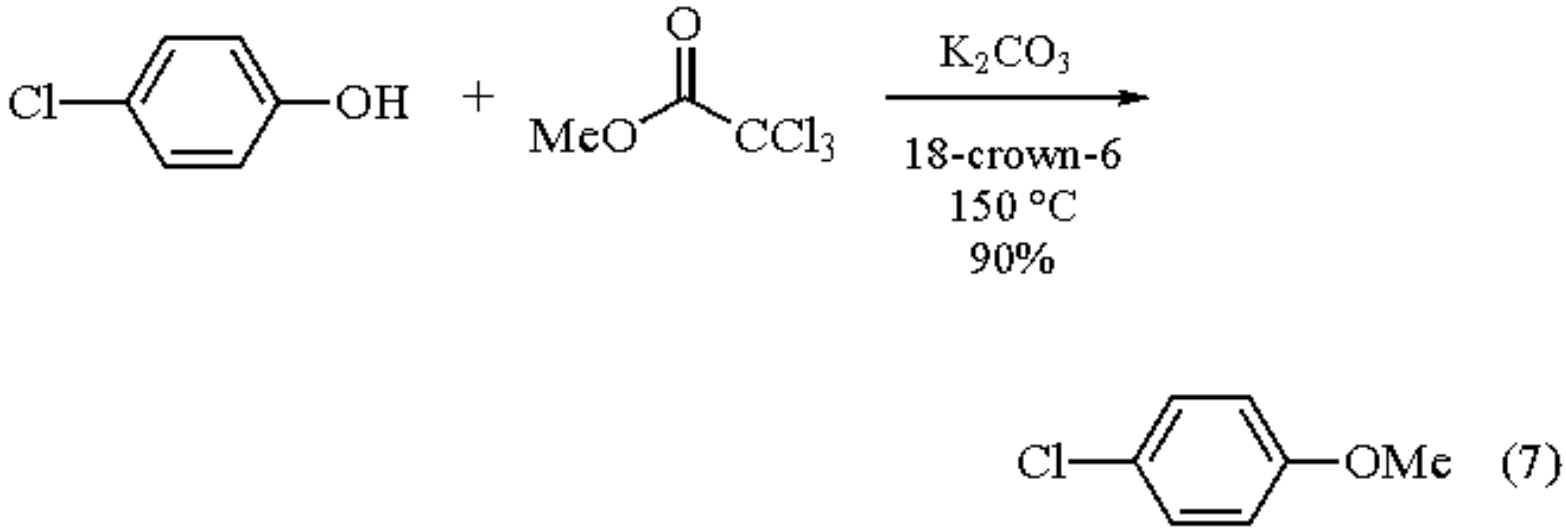

The companion reagent trimethylsilyl trichloroacetate has been developed into a convenient tool for the salt-free silylation of compounds carrying an acidic hydrogen (carboxylic acids, phenols, amides, thiols, terminal alkynes, etc). As before, a catalytic amount of potassium carbonate/18-crown-6 gives rise to CO_2 and $CHCl_3$ in addition to product (eq 8).[9] When aldehydes or ketones are involved, trimethylsilyl trichloromethyl carbinols are formed efficiently (eq 9).

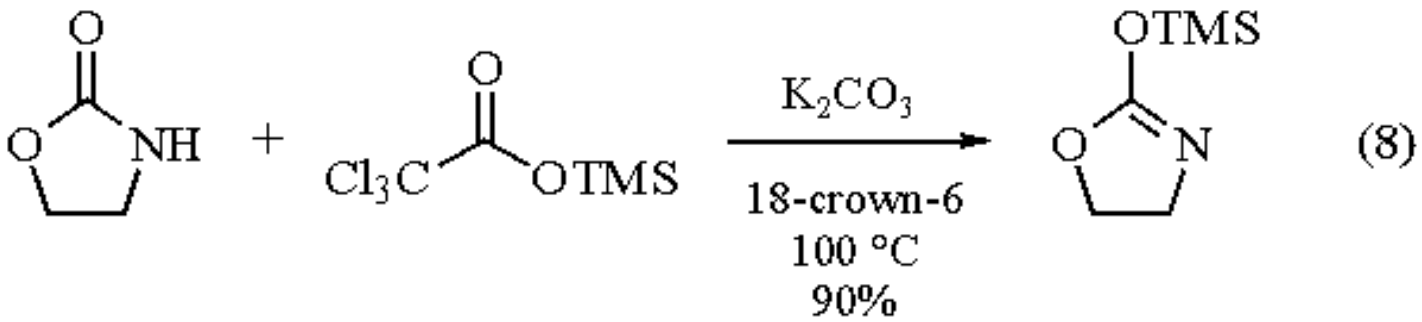

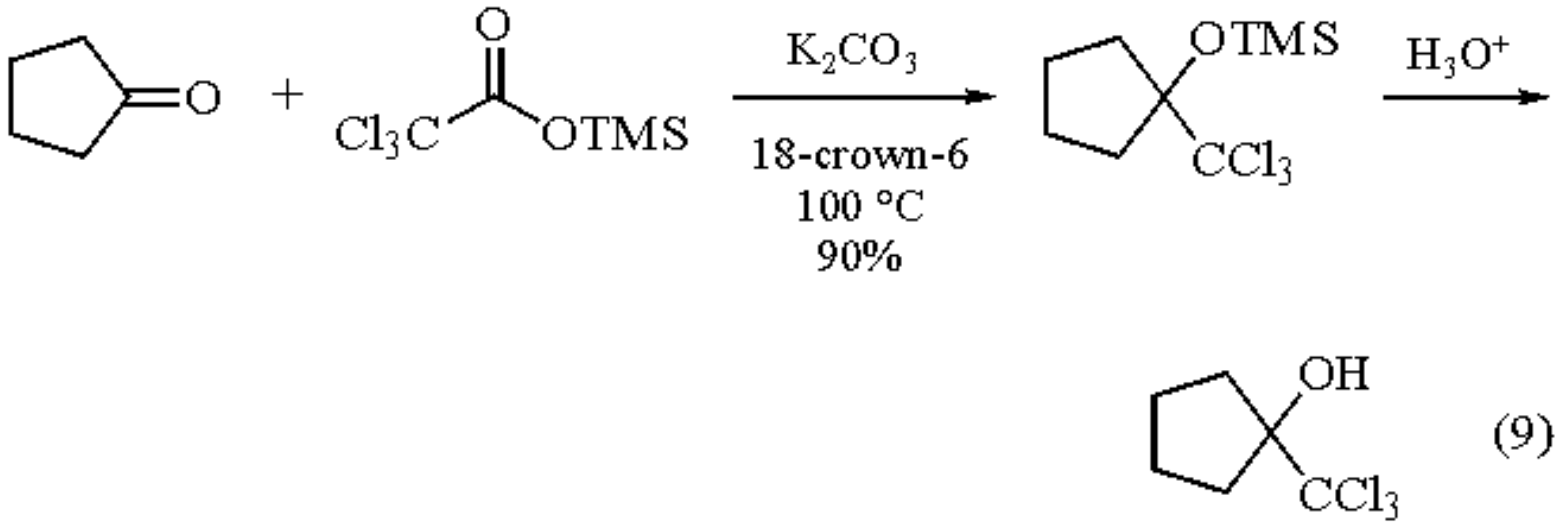

Intramolecular Wadsworth-Emmons Cyclizations.

Attempts to prepare bicyclo[3.3.0]oct-1-en-3-one and derivatives thereof by intramolecular cyclization have been

fraught with complications because of the sensitivity of both the starting material and product to basic conditions. This problem has been resolved by making recourse to potassium carbonate and 18-crown-6 in benzene or toluene at 60 °C (eq 10).[2] The gentle nature of this reagent has proven highly serviceable in a number of related ring closures (eqs 11 and 12),[10,11] including macrocyclizations (eq 13).[12]

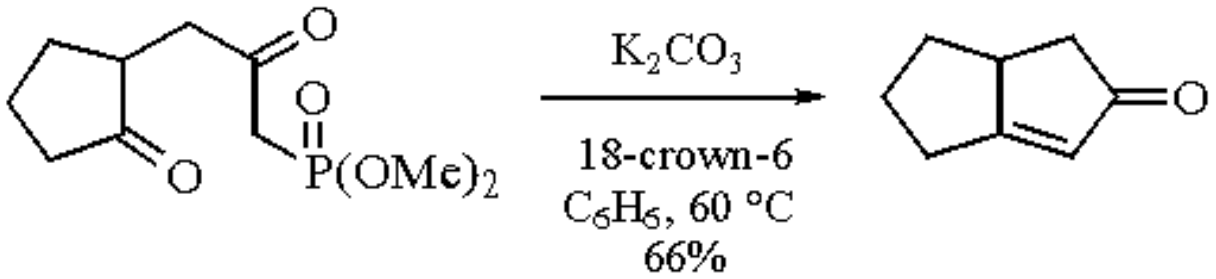

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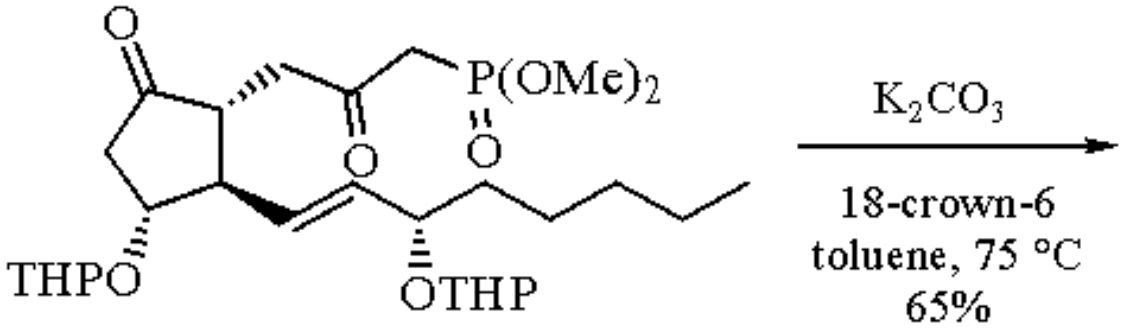

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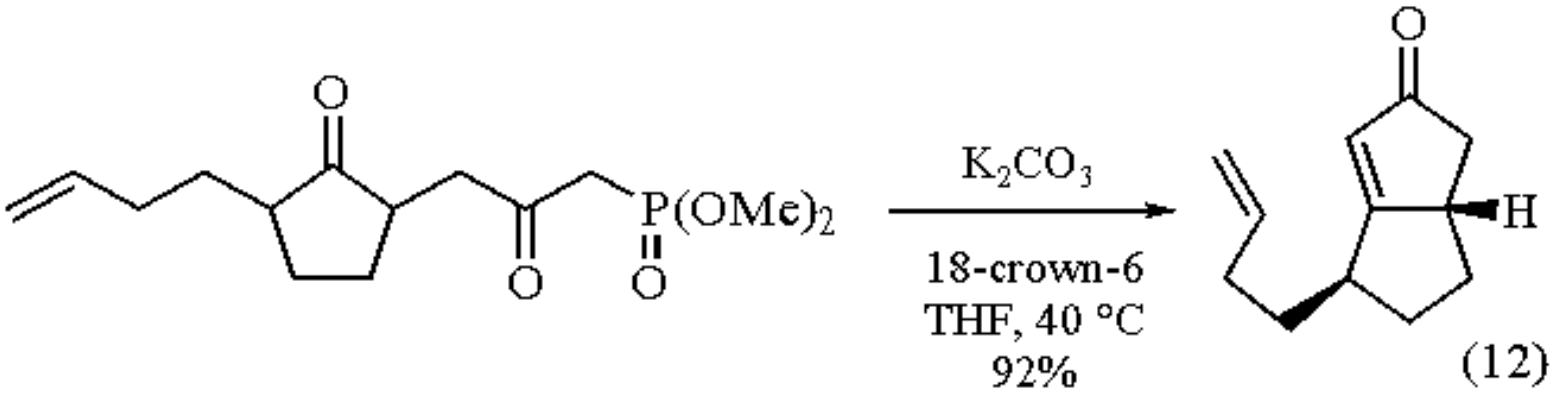

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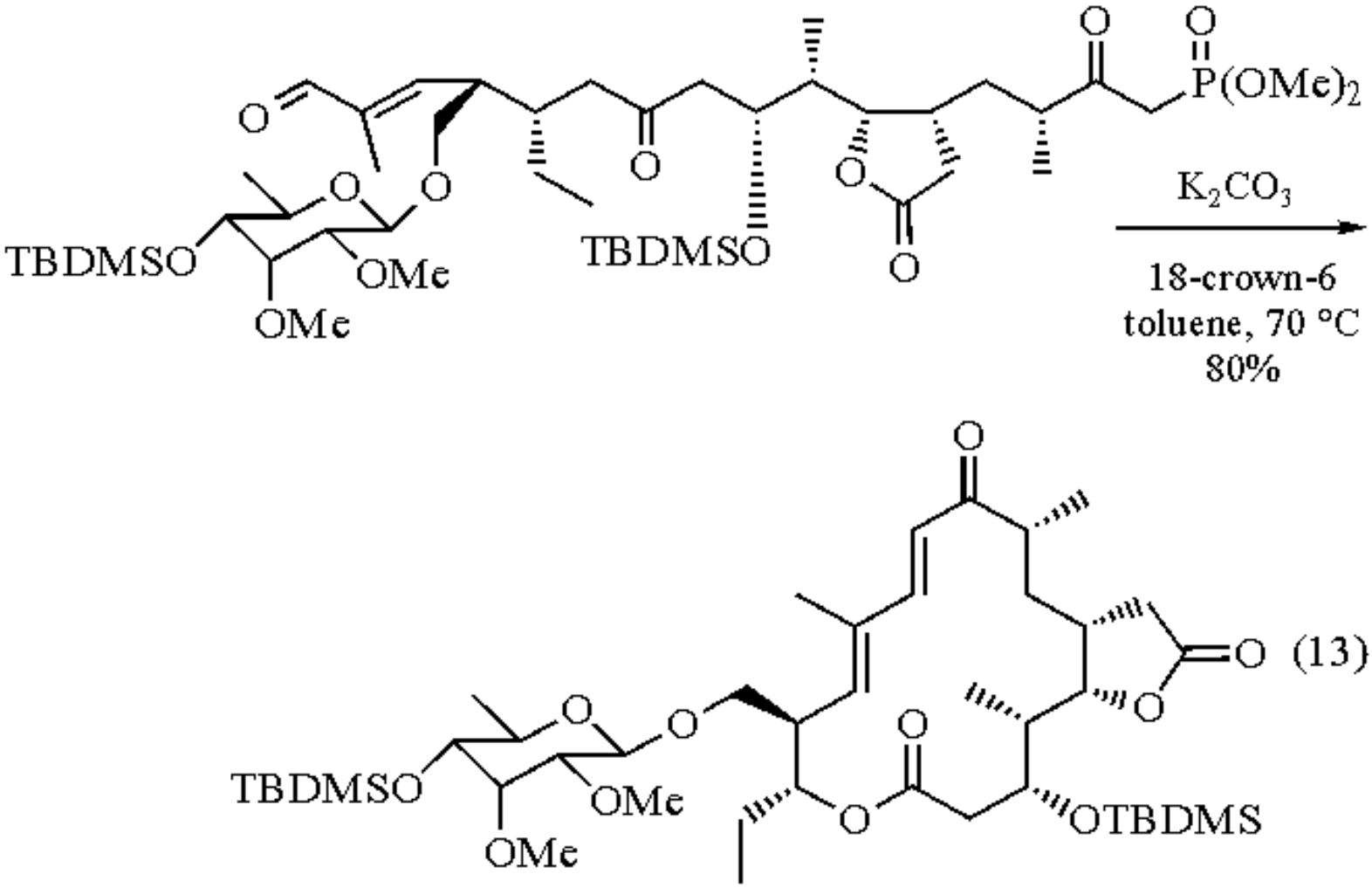

(13)

Formation of Carbonate Esters.

Historically, it has not been practical to prepare organic carbonates from inorganic carbonate. However, the advent of solid-liquid phase techniques has opened the door to striking developments in this area. A catalyst other than potassium carbonate is necessary for acceleration and the realization of high-yield conversions. Suitable candidates are ***Tri-n-butylchlorostannane***,[13] hexabutyldistannoxane,[13] hexabutyldistannathiane (eq 14),[13] potassium hydrogen carbonate,[14] and quaternary ammonium salts.[15] Polycarbonates have similarly been produced from α,α´-dibromo-*p*-xylene.[13]

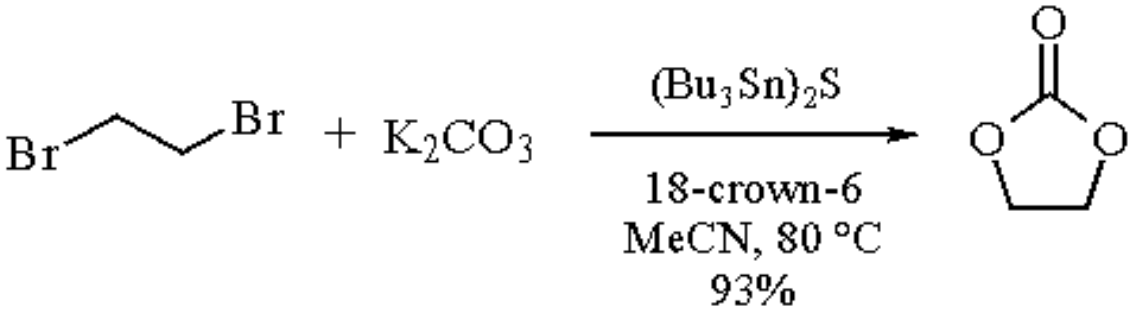

(14)

Cyclic carbonates are likewise readily available via the reaction of oxiranes with ***Carbon Dioxide*** under phase-transfer catalysis of potassium carbonate/18-crown-6 (eq 15).[16] Homopolymerization is not a serious complication as long as

the crown ether is present.

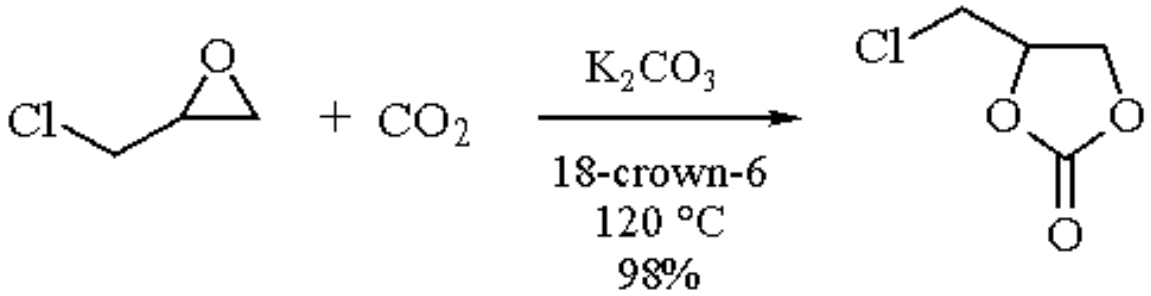

(15)

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Potassium Chromate

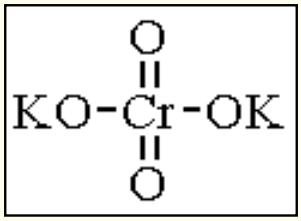

[7789-00-6] · CrK_2O_4 · Potassium Chromate · (MW 194.20)

(reagent for converting primary allylic and benzylic halides to aldehydes)

Physical Data: mp 968.3 °C; *d* 2.732 g cm^{-3}.

Solubility: H_2O (62.9 g/100 mL at 20 °C).

Form Supplied in: yellow crystals.

Preparative Methods: the reagent is prepared in ***Hexamethylphosphoric Triamide*** (HMPA) in the presence of ***Dibenzo-18-crown-6*** or ***Dicyclohexano-18-crown-6***.[1]

Handling, Storage, and Precautions: potassium chromate is a highly toxic cancer suspect agent. All chromium(VI) reagents must be handled with care. The mutagenicity of Cr^{VI} compounds is well documented.[2] HMPA is also a highly toxic cancer suspect agent. This reagent should be handled in a fume hood.

Oxidation of Primary Allylic and Benzylic Halides to Aldehydes.

Potassium chromate in HMPA in the presence of dibenzo-18-crown-6 or dicyclohexano-18-crown-6 at 100 °C converts primary allylic (eq 1) and benzylic (eq 2) halides to aldehydes.[1] The yields are lower with alkyl halides. The yields of all primary halides are improved by use of polymer-supported chromic acid in benzene[3] or ***Bis(tetrabutylammonium) Dichromate*** in $CHCl_3$.[4]

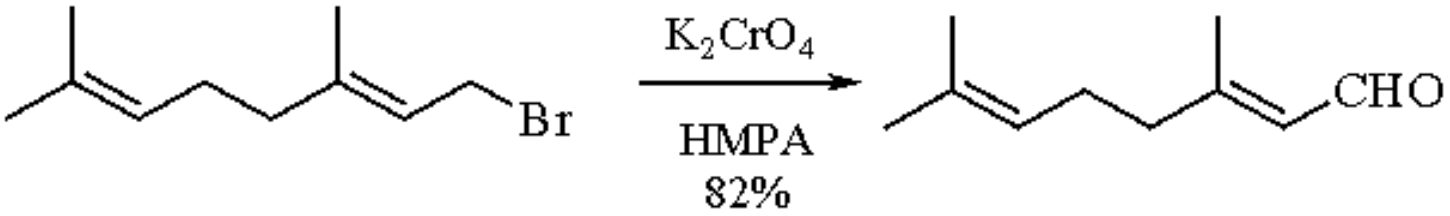

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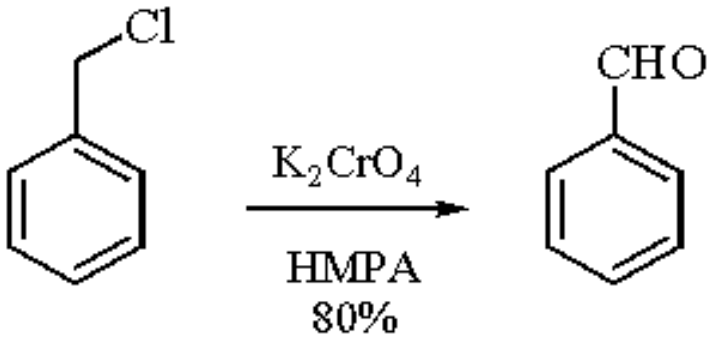

(2)

Other Applications.

Primary and secondary alcohols are oxidized to aldehydes and ketones, respectively, by potassium chromate and sulfuric acid in a two-phase system (water-$CHCl_3$) in the presence of tetrabutylammonium hydrogen sulfate catalyst.[5] Allylic alcohols and acid-sensitive alcohols are oxidized to carbonyl compounds in good yields.

Related Reagents.

In addition to polymer supported ***Chromic Acid*** in benzene[3,6] and ***Bis(tetrabutylammonium) Dichromate*** in $CHCl_3$,[4] other reagents oxidizing halides to carbonyl compounds include ***Chromium(VI) Oxide*** in aqueous acetic acid, which oxidizes α-chlorohydrindene to α-hydrindanone,[7] and chromic acid in aqueous acetone in the presence of silver chromate, which oxidizes a steroidal vicinal dibromide to an α-bromo ketone in the synthesis of corticoids.[8] In aqueous systems it is possible that the halide is hydrolyzed to an alcohol which is oxidized to the carbonyl compound.

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Potassium Cyanide[1]

KCN

[151-50-8] · CKN · Potassium Cyanide · (MW 65.12)

(reagent for the synthesis of nitriles,[2] cyanohydrins,[3] and α-amino nitriles;[4] catalyst for benzoin condensation[5] and transesterification[6])

Physical Data: mp 634 °C; *d* 1.520 g cm^{-3}.

Solubility: sol 2 parts cold water, 1 part boiling water, 2 parts glycerol, 100 parts ethanol, 25 parts methanol. The aq soln is strongly alkaline (pH = 11.0) and rapidly dec.

Form Supplied in: white granular powder or fused pieces; widely available.

Purification: see Perrin[7] for purification and recrystallization procedures.

Handling, Storage, and Precautions: highly toxic; may be fatal if inhaled, swallowed, or absorbed through the skin. Exposure may cause nausea, dizziness, headache, lung irritation, and cyanosis (toxicity data: orl-hmn LDLo 2857 μg kg^{-1}, orl-rat LD_{50} 5 mg kg^{-1}). Air and moisture sensitive; keep in a tightly closed container and store in dry area. Use only in a chemical fume hood. Do not breath the dust or allow it to get in eyes, on skin, or on clothing. In case of fire, water spray must be used with caution since direct contact of KCN with water or steam will cause decomposition, liberating highly toxic HCN gas as well as generating a highly hazardous solution of dissolved cyanide which must be kept out of sewers and watercourses. KCN also forms explosive mixtures, sometimes spontaneously, with chlorates, nitrates, and nitrogen trichloride plus ammonia. Incompatible with acids, strong oxidizing agents, alkaloids, chloral hydrate, iodine, and metallic salts. Thermal decomposition produces toxic fumes of hydrogen cyanide, carbon monoxide, carbon dioxide, and nitrogen oxides.

Nitrile Synthesis.

The transformation of alcohols to nitriles is an important method for the elongation of carbon chains or the synthesis of useful intermediates in organic synthesis.[8] The usual procedure involves activation of alcohols by conversion into halides or sulfonates, followed by displacement with a cyano group. Among the methods for direct one-pot conversion of alcohols to nitriles,[9,10] the most general and convenient is treatment with KCN in the presence of ***Tri-n-butylphosphine***, CCl_4, and ***18-Crown-6*** (eq 1).[10] Displacement of primary, benzylic, or allylic halides with KCN produces nitriles in very good yields; the same reaction proceeds in moderate yield with secondary halides,[8,11] while

it fails completely for tertiary halides, giving elimination under these conditions. The use of KCN in MeCN containing 18-crown-6 produces cyanide anions (naked anions)[12] which are strong nucleophiles and displace halides smoothly and quantitatively (eq 2).[13] Mesylates are converted into nitriles in about 70% yield by reaction with KCN in H_2O/C_6H_6 at 5-6 h reflux with phase-transfer catalysis.[14] 2,3´-*O*-Isopropylidene-5´-*O*-tosylates of nucleosides react with KCN only when the reagent has been complexed with 18-crown-6 (eq 3),[15] while reaction of substituted benzylamines with cyanide ions furnish the corresponding benzonitriles.[16] Ketones are converted into nitriles by way of tosylhydrazones[17a,b] or methoxycarbonyl hydrazones.[17c] Thus the tosylhydrazone derivative of a ketone upon treatment with KCN in MeOH/AcOH is converted into a cyano hydrazide, which is heated at 180 °C for 2 h to give the nitrile (eq 4).[18] Hydrocyanation of conjugated double[19] or isolated double[20] and triple[21] bonds proceed smoothly with KCN. Similarly, KCN in combination with NH_4Cl results in 1,4-addition of HCN to cholestanone derivatives, affording the 5α- and 5β-cyano ketones in 1:1 ratio.[22] The use of organoaluminum cyanides increases the selectivity of the reaction.[19]

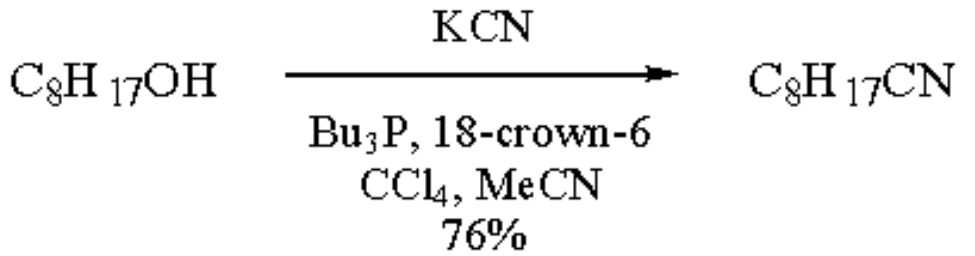

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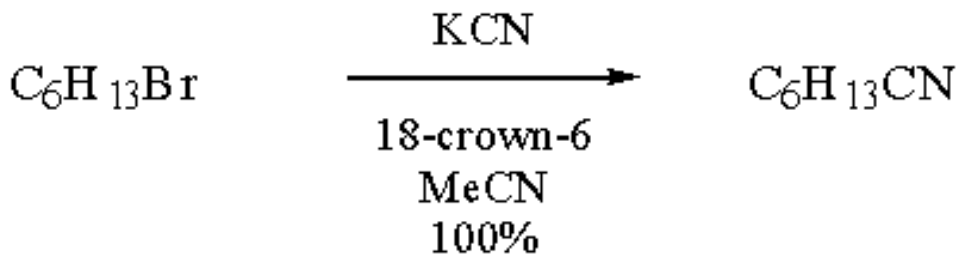

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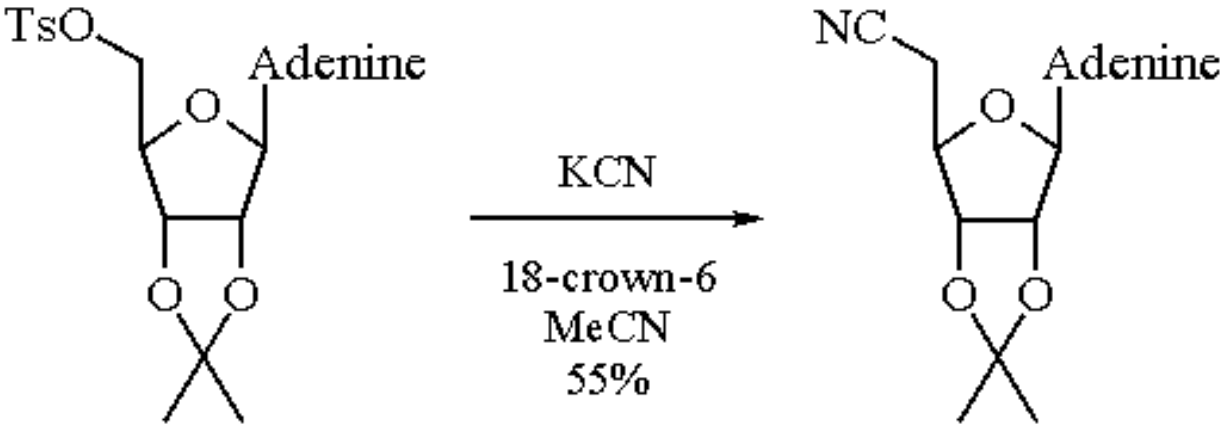

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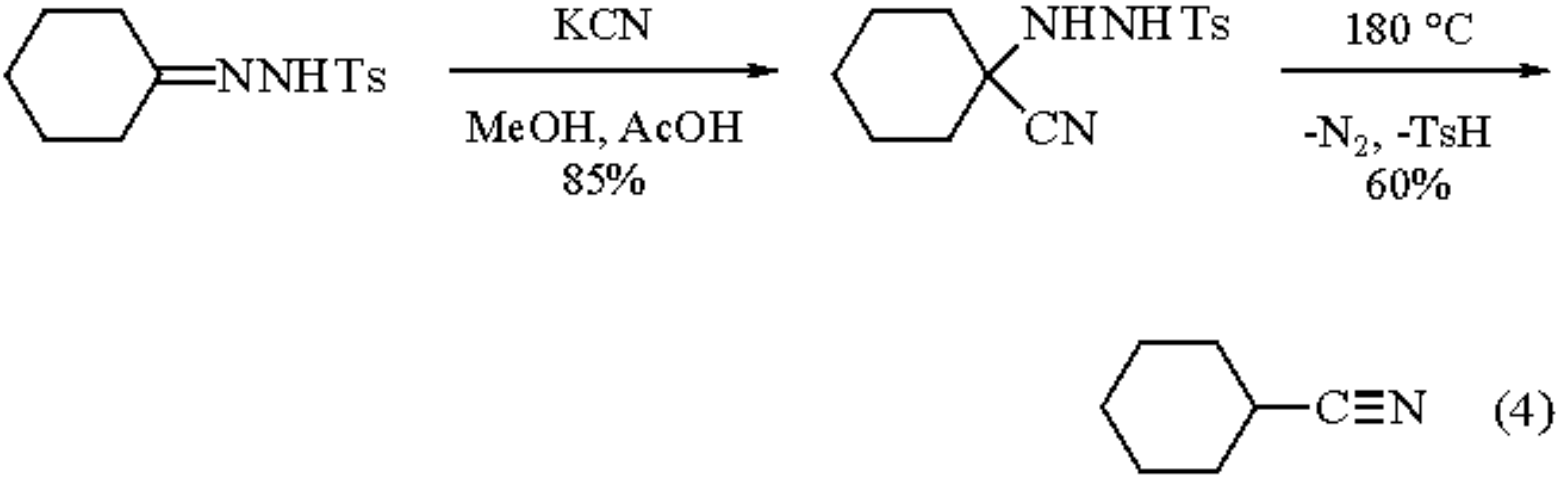

(4)

Vinyl bromides are converted into α,β-unsaturated nitriles by reaction with KCN in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** and 18-crown-6. The reaction is highly stereospecific and proceeds in almost quantitative yield (eq 5).[23] Vinyl sulfones on exposure to KCN and ***Dicyclohexano-18-crown-6*** in refluxing *t*-butyl alcohol are smoothly converted to α,β-unsaturated nitriles, providing a particularly useful route for the construction of trisubstituted alkenes.[24]

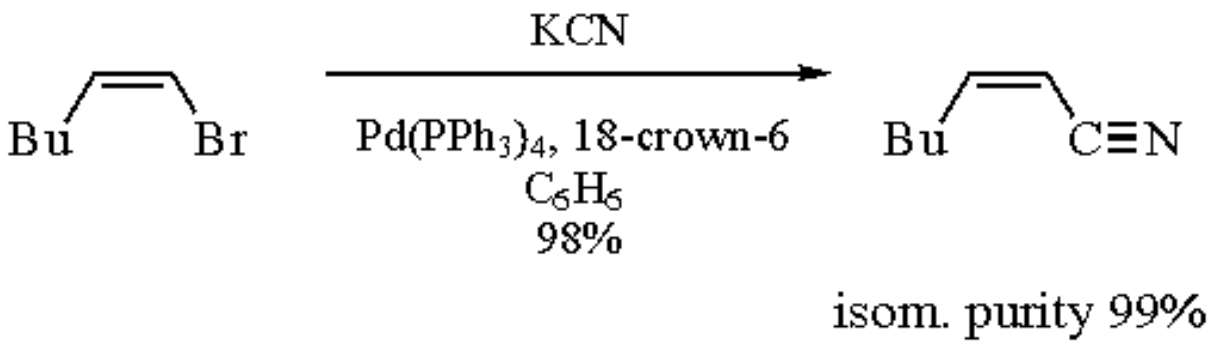

(5)

Treatment of benzaldoximes with KCN in the presence of a phase-transfer catalyst (18-crown-6 or quaternary ammonium salt) produces a 3:1 mixture of a benzonitrile and benzamide (eq 6),[25] thus providing a general, one-pot conversion of aromatic aldehydes to aryl nitriles. Photochemically induced cyanation of arenes[26] furnishes only moderate to low yields of aryl nitriles, but the use of KCN in conjunction with 18-crown-6 (naked cyanide ion) doubles the yield.[27] Photolysis of arylthallium ditrifluoroacetates in the presence of excess KCN proceeds via in situ formation of the complex ions $[ArTl(CN)_3]^-K^+$ and produces aryl nitriles in good yields.[28] Cyanation of aromatic heterocycles by means of KCN and ***Benzyltriethylammonium Chloride*** followed by reaction with an acyl chloride furnishes the corresponding Reissert products (eq 7)[29] in better yields than the conventional conditions.[30]

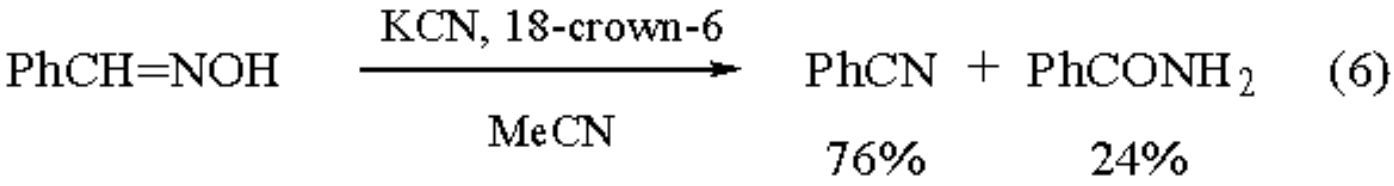

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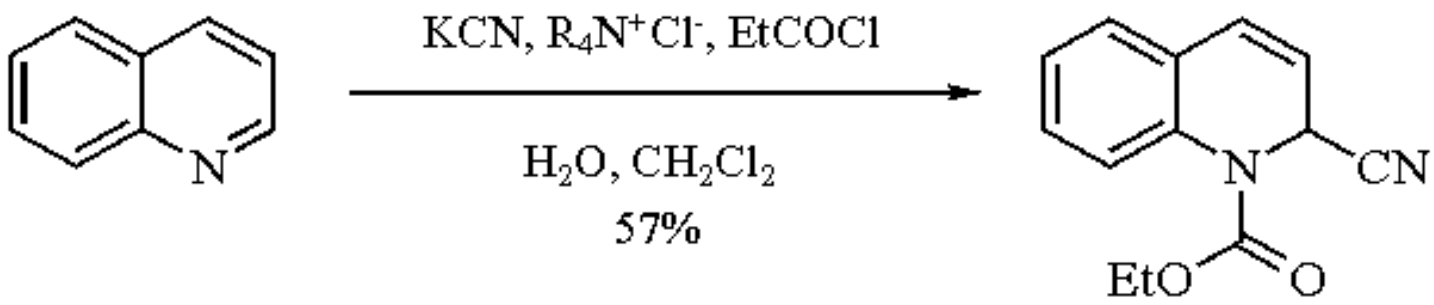

(7)

The classical method for the synthesis of acyl cyanides is the reaction of an acyl halide with heavy metal cyanides at high temperatures.[31] Recent modifications using aryl iodide[32] or a phase-transfer catalyst[33] have led to some improvements. On the contrary, aroyl cyanides are prepared by reaction of aroyl chlorides with KCN in MeCN. The presence of trace amounts of water markedly accelerates the rate and improves the yield (eq 8).[34] However, the use of too much water lowers the yield of the product due to hydrolysis and dimer formation.[34] Aromatic or heteroaromatic acyl cyanides may be prepared at lower reaction temperatures by ultrasonic treatment of the heterogeneous mixture of an aroyl chloride and KCN in MeCN (eq 9).[35] Several phenylacetonitriles are obtained in good yield by reaction of the appropriate benzyl halide with the cyanide form of an anion exchange resin.[36] The direct conversion of aromatic iodides into aroyl nitriles in good yields is accomplished by their carbonylation catalyzed with ***Iodo(phenyl)bis(triphenylphosphine)palladium(II)***[37] and in situ reaction with KCN (eq 10).[38] Cyanoformates are obtained from the corresponding chloroformates by reaction with KCN in the presence of 18-crown-6 as catalyst (eq 11).[39]

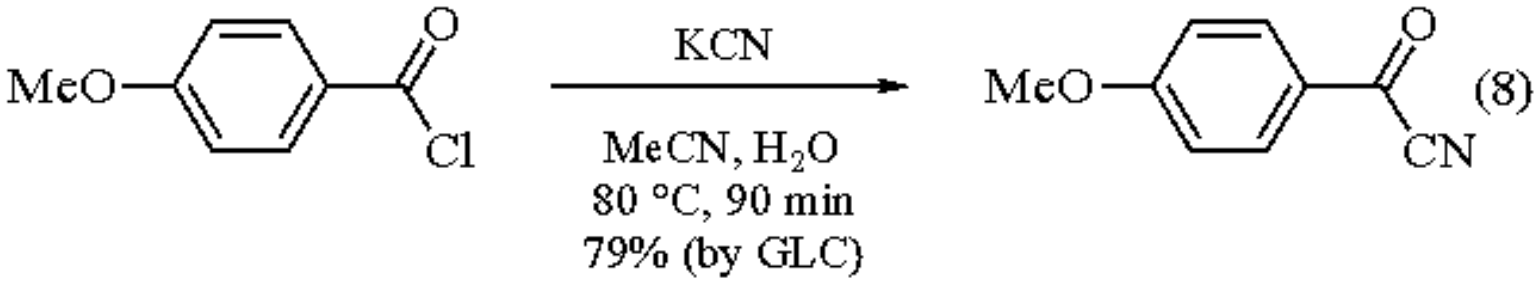

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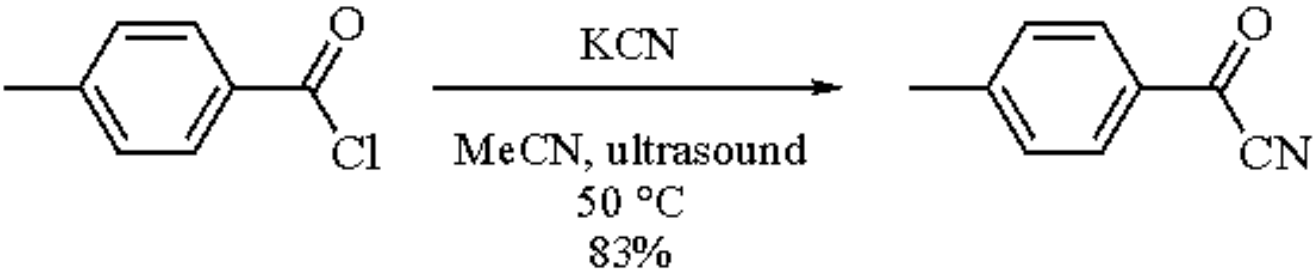

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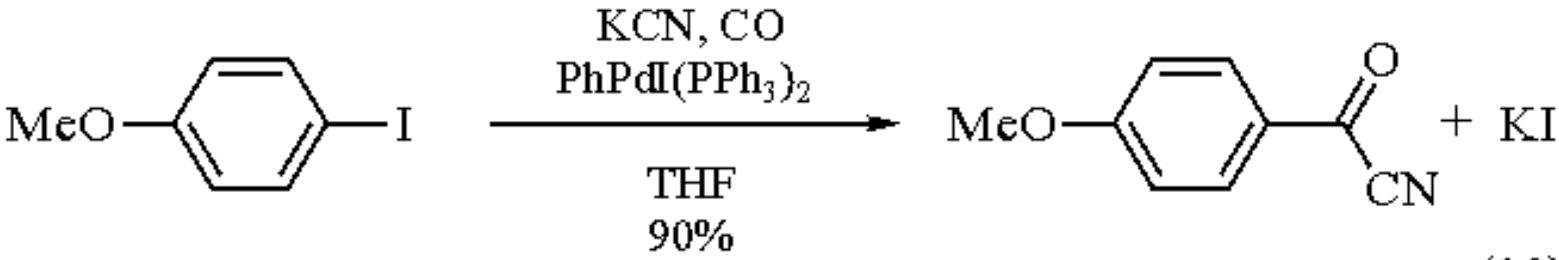

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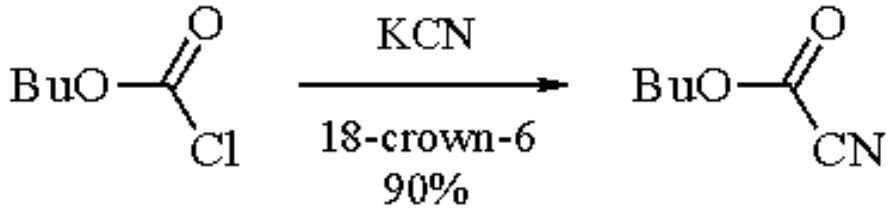

(11)

α-Cyanoenamines are obtained either by conversion of amides to α-chloroenamines and subsequent treatment with KCN in MeCN (eq 12),[40] or starting with aldehydes and proceeding via α-chloroaldimines and reaction with KCN in MeOH (eq 13).[41] These compounds are recognized as reactive intermediates since they can easily be converted to the corresponding α-diketones or dihydropyrazine derivatives.[40]

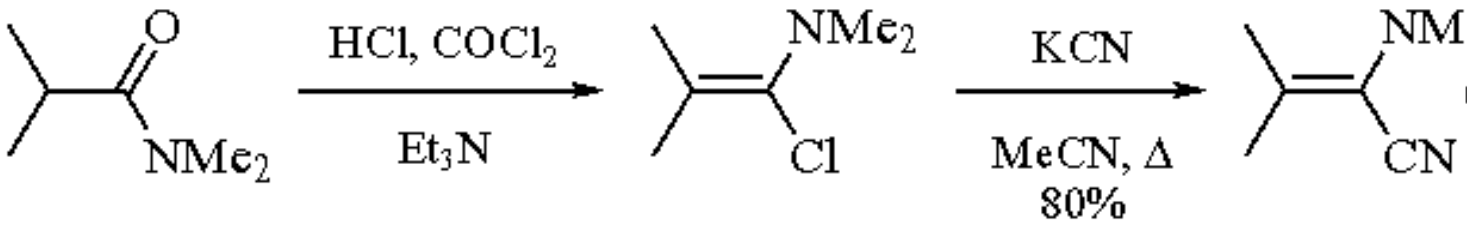

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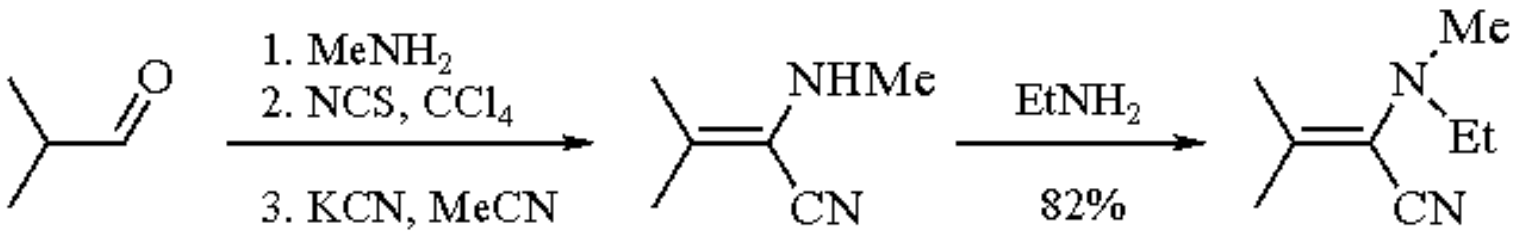

(13)

Cyanotributylstannane, which is an efficient cyanation agent for acyl chlorides, is obtained in very good yield by treatment of ***Tri-n-butylchlorostannane*** with KCN in MeCN (eq 14).[42] Similarly, ***Cyanotrimethylsilane*** is prepared by treatment of ***Chlorotrimethylsilane*** with H_2SO_4 and KCN (eq 15).[43]

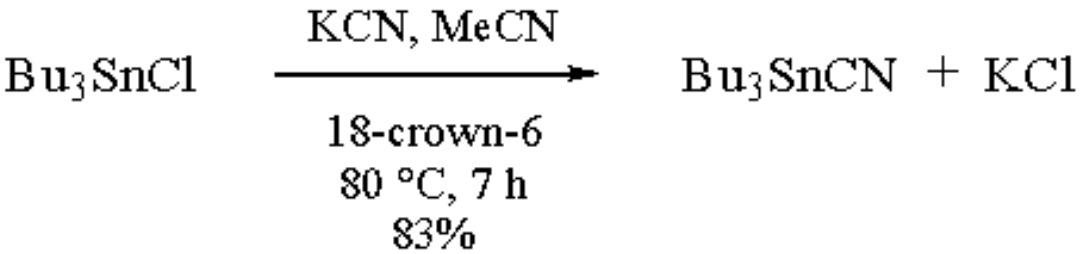

(14)

$$2\ TMSCl + H_2SO_4 \xrightarrow[-2HCl]{} [TMSO]_2SO_2 \xrightarrow[-K_2SO_4,\ 65\text{-}83\%]{2\ KCN} 2\ TMSCN \quad (15)$$

Cyanohydrin Synthesis.

Cyanohydrins are versatile starting materials for the synthesis of several classes of compounds.[44] They are prepared by treatment of aldehydes or ketones with KCN and AcOH in various organic solvents.[45] This is an equilibrium reaction which proceeds smoothly except with sterically hindered ketones or aromatic aldehydes, in which case the benzoin condensation competes. Cyanohydrin synthesis was first applied to carbohydrates by Kiliani[46] in 1885 as the key step of a route (modified later by Fischer[47]) which allows the construction of two epimeric aldoses having one carbon atom more than the parent aldose. More recent studies have confirmed that the ratio of epimers (eq 16) is pH dependent.[48] Thus reaction of D-arabinose with KCN at acidic pH furnishes D-glucononitrile as the predominant epimer, while under alkaline conditions D-mannonitrile is the predominant epimer. Similarly treatment of formaldehyde with KCN gave glyconitrile (eq 17).[49] Cyanohydrin synthesis is important in the construction of steroid sidechains.[50] Thus 17-keto steroids are transformed to corticoids via their 17β-cyanohydrins (eq 18).[51] Treatment of β-hydroxy ketones with KCN/TMSCN in the presence of ***Zinc Iodide*** produces *syn*-β-hydroxy cyanohydrins in high distereomeric excess (eq 19).[52]

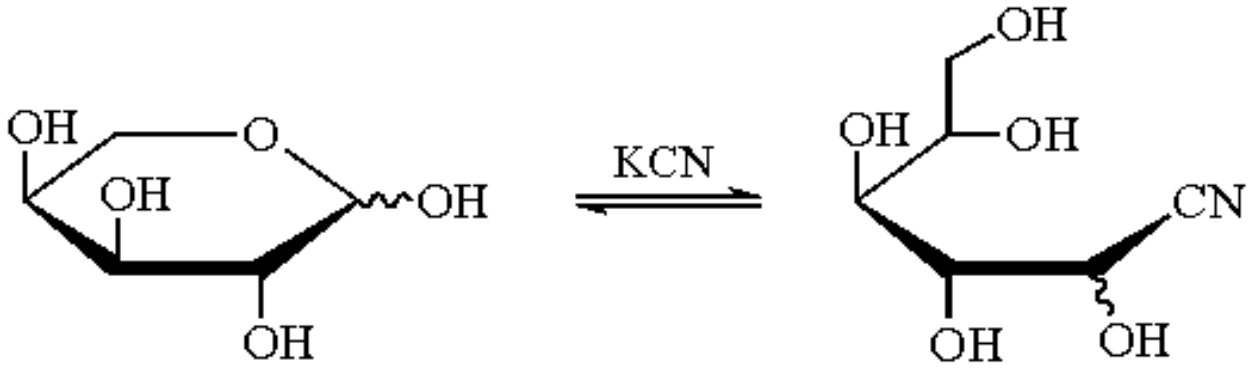

(16)

$$CH_2O + KCN + H_2O \xrightarrow[80\%]{} HOCH_2CN + KOH \quad (17)$$

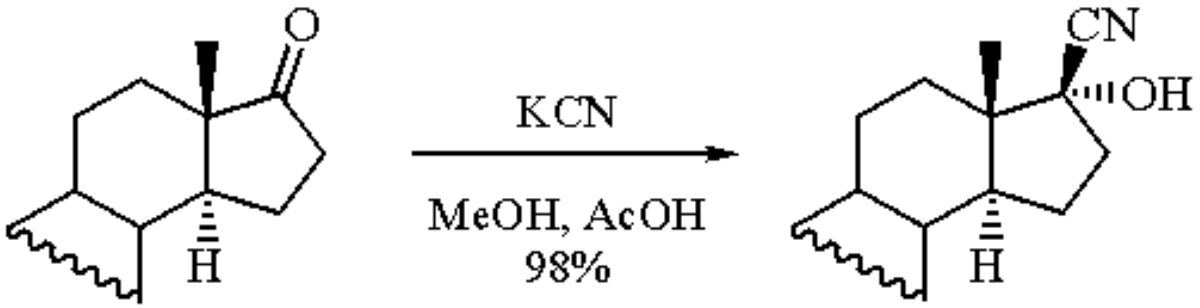

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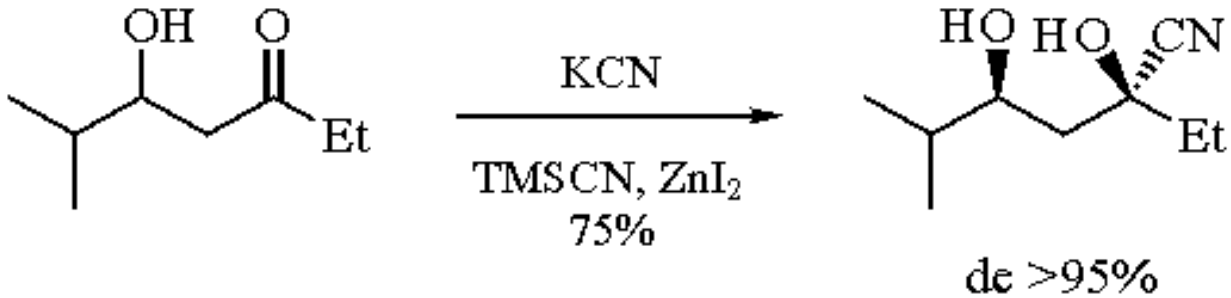

(19)

Optically active cyanohydrins are obtained using KCN and enzymatic catalysis.[53] Thus treatment of benzaldehyde with oxynitrilase (extracts of ground defatted almonds) in 1N KCN/AcOH buffer (pH 5.4) furnishes exclusively (*R*)-(+)-α-hydroxyphenylacetonitrile (eq 20).[54] The other enantiomer is obtained by kinetic resolution of racemic cyanohydrins either by using a lipoprotein lipase from *Pseudomonas* species[55] or by incubation with *Pichia miso* (IAM 4682), which hydrolyzes selectively the acetate of the (*R*)-enantiomer, leaving the (*S*)-enantiomer intact.[56] Silylated cyanohydrins are obtained in high yields by a one-pot reaction using KCN in combination with TMSCl (eq 21).[57,58] The presence of ZnI_2 enhances the rate of cyanosilylation, while the presence of 18-crown-6 has very little effect on the yield or the rate.[57]

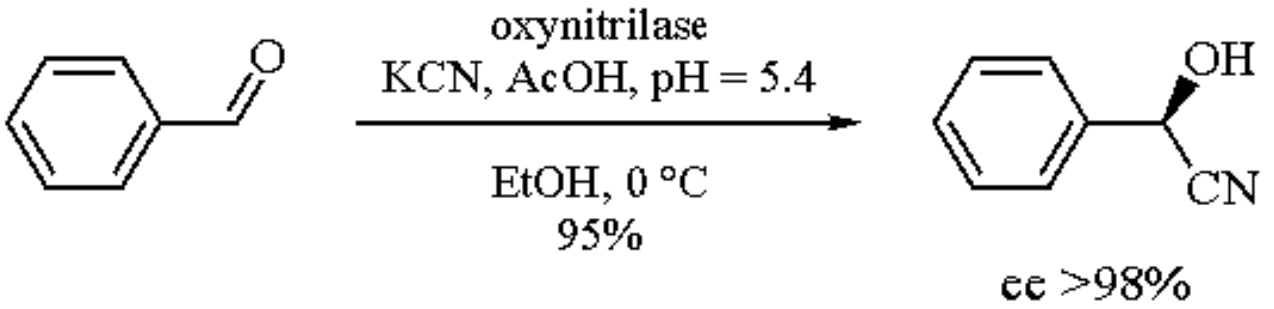

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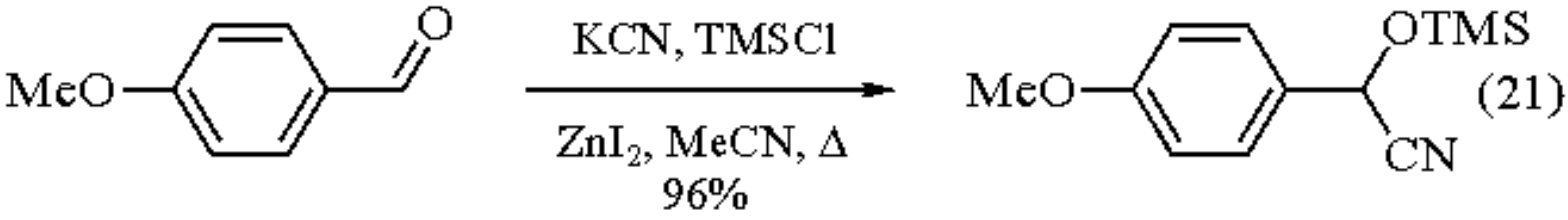

(21)

α-Amino Nitriles.

The preparation of α-amino nitriles is the key reaction of the Strecker synthesis,[59] which is considered to be the most

convenient experimental protocol for the preparation of α-amino acids[4] and 1,2-diamines[60] on the preparative scale. The classical procedure in which an aldehyde or ketone is treated with KCN, NH_4Cl,[59] is sensitive to the nature of the ketone substitution, involves lengthy reaction times and tedious work-up procedures, and leads to considerable amounts of cyanohydrin byproduct.[61] Modifications using Al_2O_3 and ultrasound in MeCN have improved the yield slightly.[62] On the contrary, stepwise synthesis either by displacement of the hydroxy group of α-amino alcohols with cyanide[63] using KCN, AcOH, or via cyanohydrins[64] by treatment with ammonia or NaN_3 have greatly improved the yields. Recently, however, two simple one-pot procedures have been reported. These produce α-amino nitriles efficiently, in almost quantitative yields, by treatment of carbonyl compounds with KCN and either alkyl- or benzylamines in an aqueous solution of $NaHSO_3$ (eq 22)[65] or benzylamine in methanolic AcOH (eq 23).[66] It is noteworthy that the α-amino nitrile synthesis (Strecker method) with substituted cyclic ketones furnishes preferentially α-amino acids of one geometrical isomer (eq 24),[67] while the opposite isomer is obtained via the spirohydantoin synthesis (Bucherer method) (eq 25).[67] Optically active α-amino nitriles are obtained when a chiral auxiliary is used. Thus reaction of *R*-(-)-2-phenylglycinol with isobutylaldehyde furnishes the two diastereomers in an 84:16 ratio (eq 26).[68]

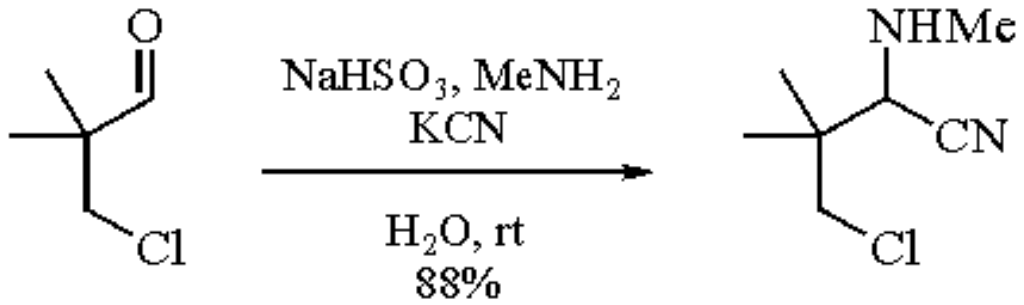

(22)

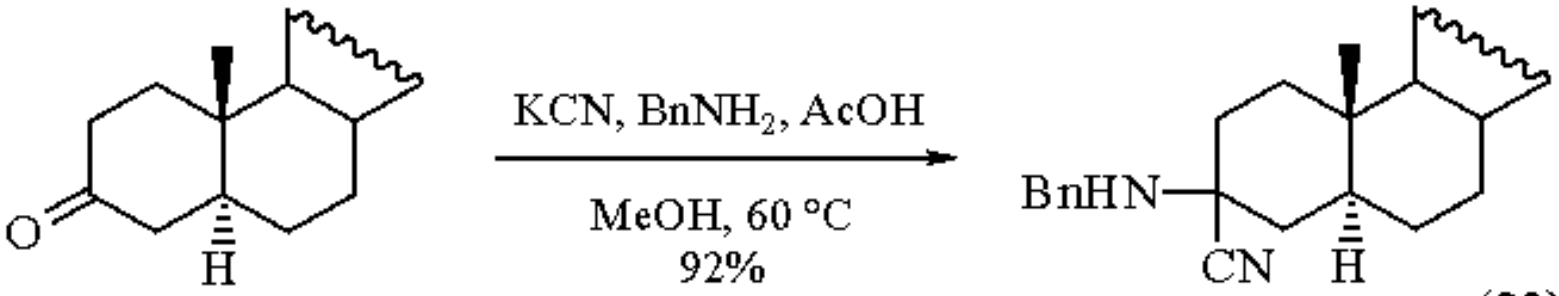

(23)

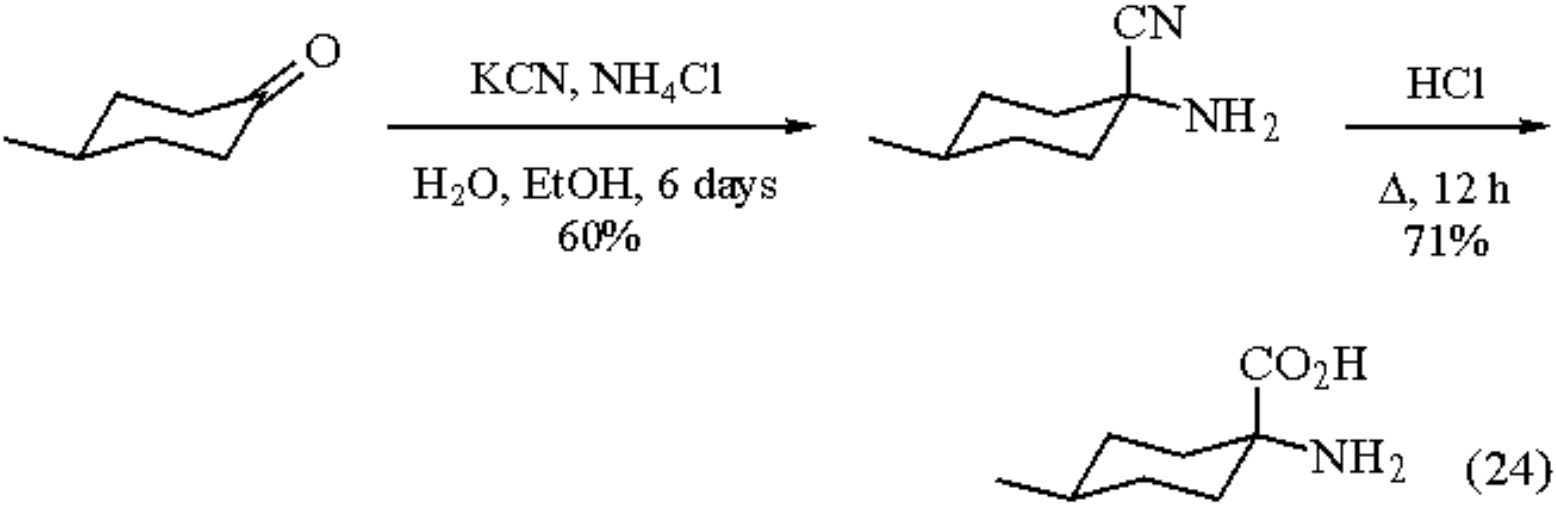
O
KCN, NH4Cl
H2O, EtOH, 6 days
60%
CN
NH2
HCl
Δ, 12 h
71%
CO2H
NH2

(24)

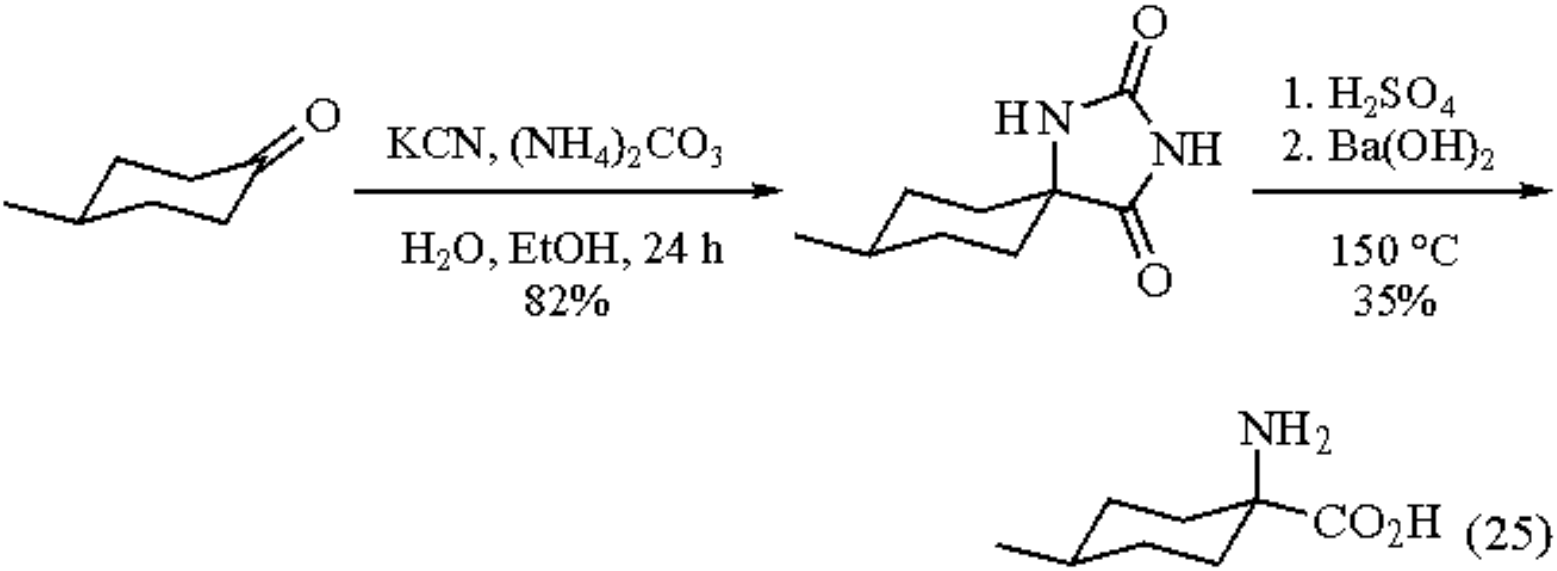
O
KCN, (NH4)2CO3
H2O, EtOH, 24 h
82%
O
HN
NH
O
1. H2SO4
2. Ba(OH)2
150 °C
35%
NH2
CO2H

(25)

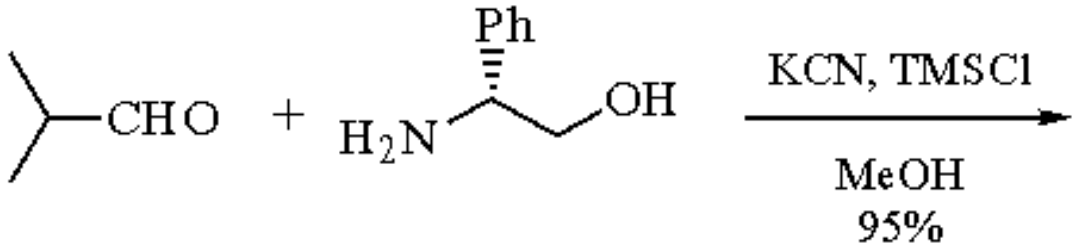
CHO
+
Ph
H2N
OH
KCN, TMSCl
MeOH
95%

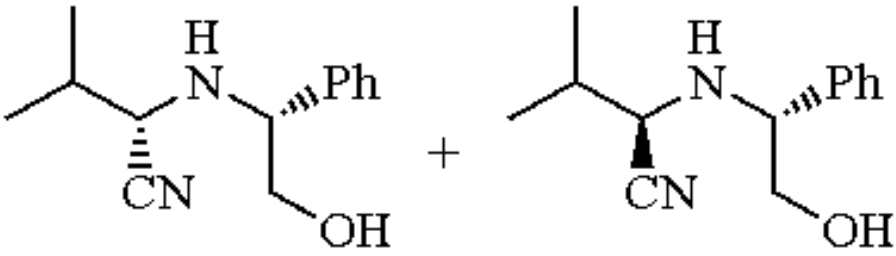
H
N
Ph
CN
OH
+
H
N
Ph
CN
OH

(26)

84:16

Benzoin Condensation.

Aromatic[69] or heteroaromatic aldehydes[70] are condensed in a KCN-catalyzed process to form benzoins (α-hydroxy ketones) (eq 27). The reaction mechanism involves the formation of a cyano-stabilized carbanion,[71] facilitated by the use of an aprotic solvent. KCN is a highly specific catalyst, since it performs three functions:[72] (i) acts as a nucleophile, (ii) permits loss of the aldehyde proton with its electron-withdrawing ability, and (iii) at the end, acts as a leaving group. The benzoin-type reaction has been extended to include a catalyzed addition of aldehydes to α,β-unsaturated nitriles.[73] Thus 4-keto nitriles are obtained by addition of aromatic aldehydes to α,β-unsaturated nitriles under KCN catalysis (eq 28). Similarly, benzoin-type condensation of tetraphthalaldehyde bisbisulfite with benzaldehyde under KCN catalysis furnishes the bisbenzoin product (eq 29).[74]

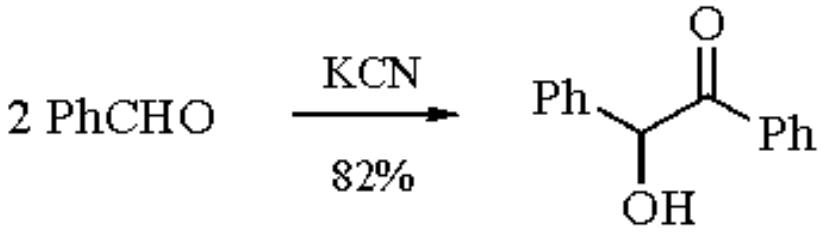

(27)

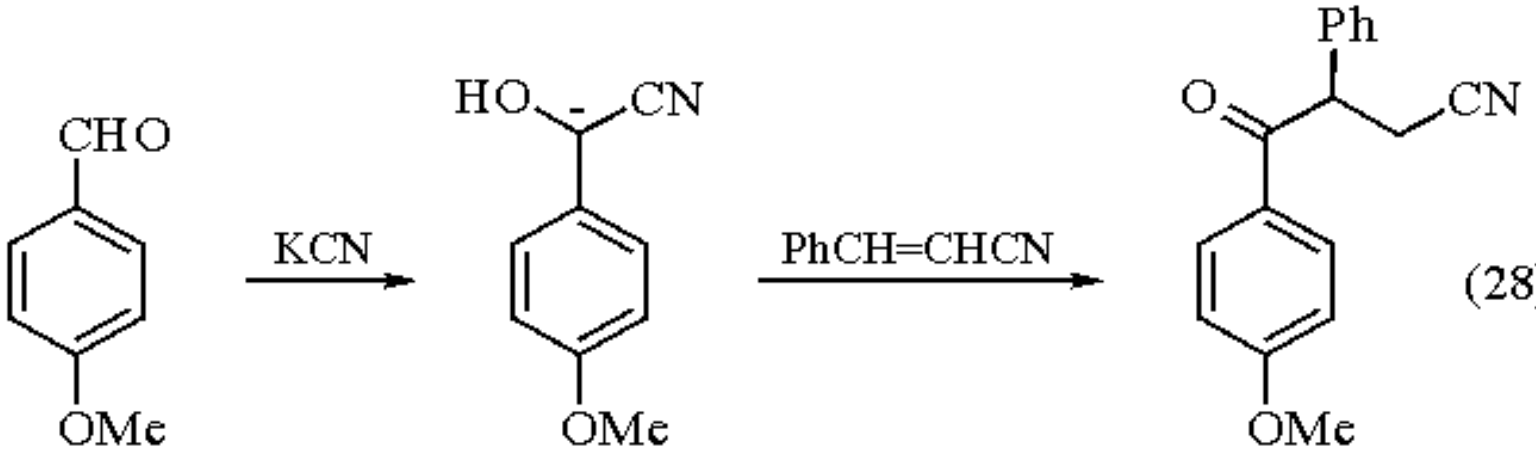

(28)

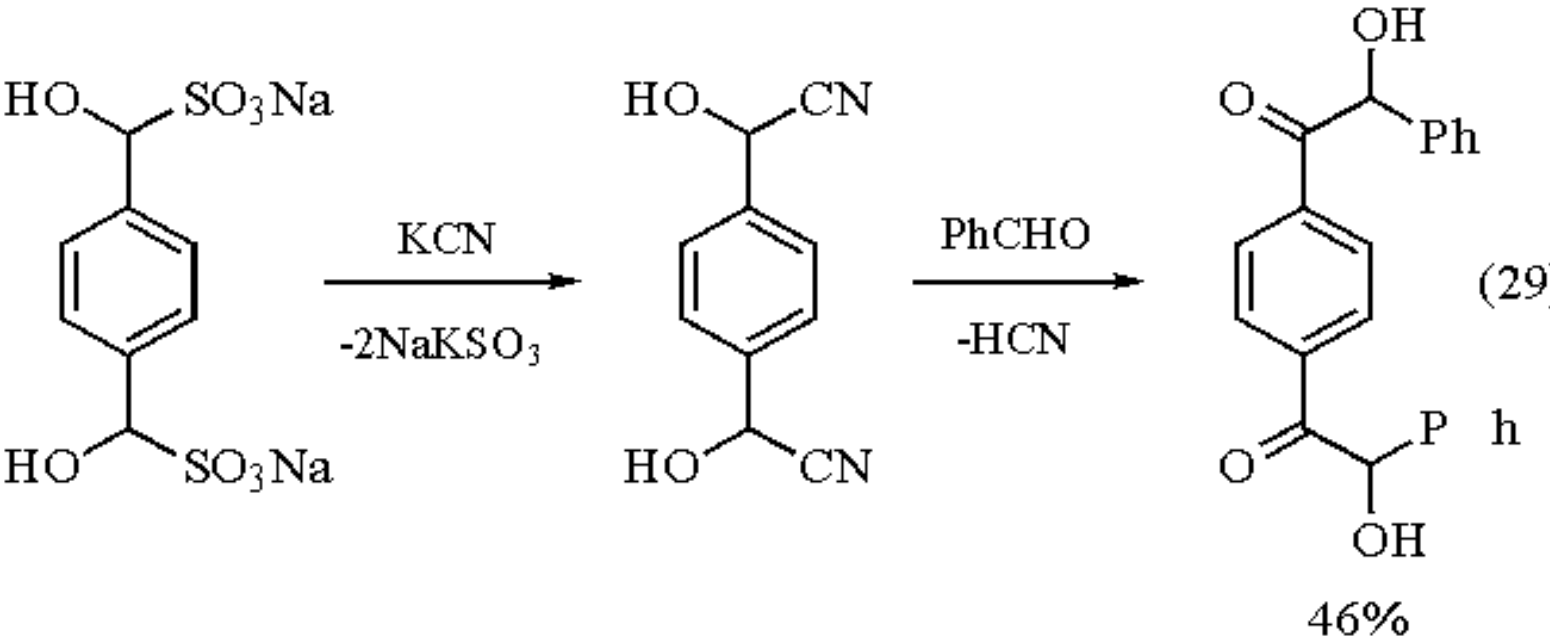

(29)

Transesterification.

KCN is a mild and effective catalyst for the transesterification of α,β-unsaturated esters without isomerization of the conjugated double bond. Thus methyl *trans,trans*-farnesoate is readily converted into the ethyl ester with very slight *cis*/*trans* isomerization (eq 30).[75] Similarly, KCN in combination with 18-crown-6 is an effective catalyst for cyanoesterification.[76] On the other hand, treatment of δ-lactones with methanol in the presence of KCN results in lactone ring opening and methyl ester formation (eq 31).[77]

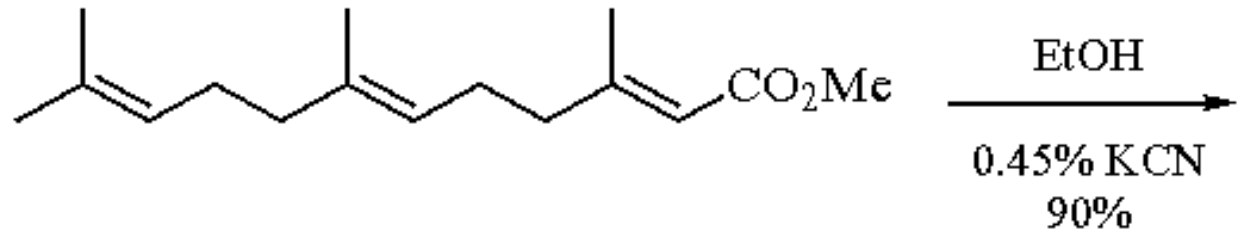

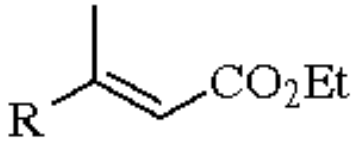

(30)

2-trans:*2-cis* = 94:3

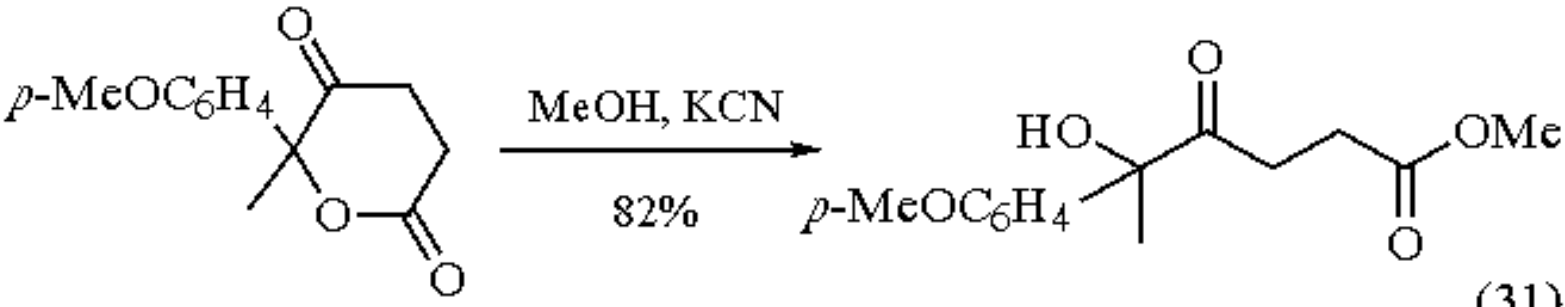

(31)

Ring Formation and Ring Opening.

Reaction of α-chloro ketimines with KCN in MeOH results in nucleophilic addition and subsequent intramolecular nucleophilic substitution, yielding the corresponding α-cyano aziridines (eq 32).[78] Treatment of 2-bromodeoxybenzoin with KCN in the presence of solid adsorbent (silica gel or alumina) gives stereoselectively *cis*-2,3-diphenyl-2-cyanooxirane in good yield (eq 33).[79] Cold aqueous ethanolic KCN converts *N*-methyl-*C*-phenyl nitrone into 1-methyl-4,5-diphenylimidazole via the intermediate cyanoimine (eq 34).[80] *N*-Allyl-*N*-3-butenyl-*N*-Cbz-amine on treatment with thexylborane, followed by cyanidation, affords an azacyclone, which can be transformed into δ-coniceine by catalytic reduction (eq 35).[81] On the other hand, alkaline solutions of KCN in the presence of ***Tetra-n-butylammonium Bromide*** open 1,2-epoxides, yielding β-hydroxy nitriles (eq 36).[82] Similarly activated cyclopropane rings are cleaved by reaction with KCN.[83]

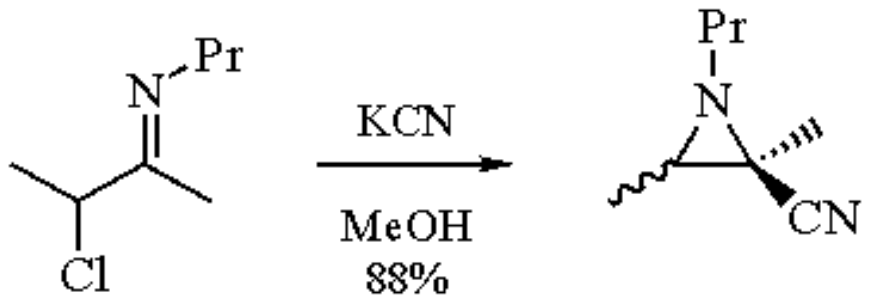

(32)

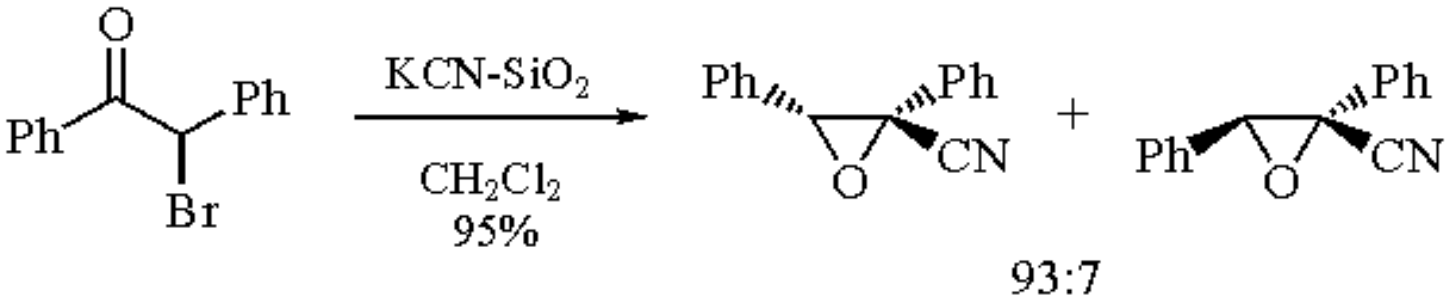

(33)

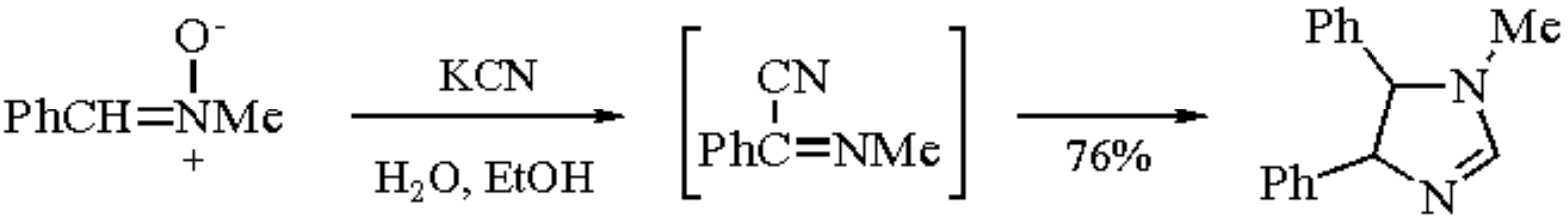

(34)

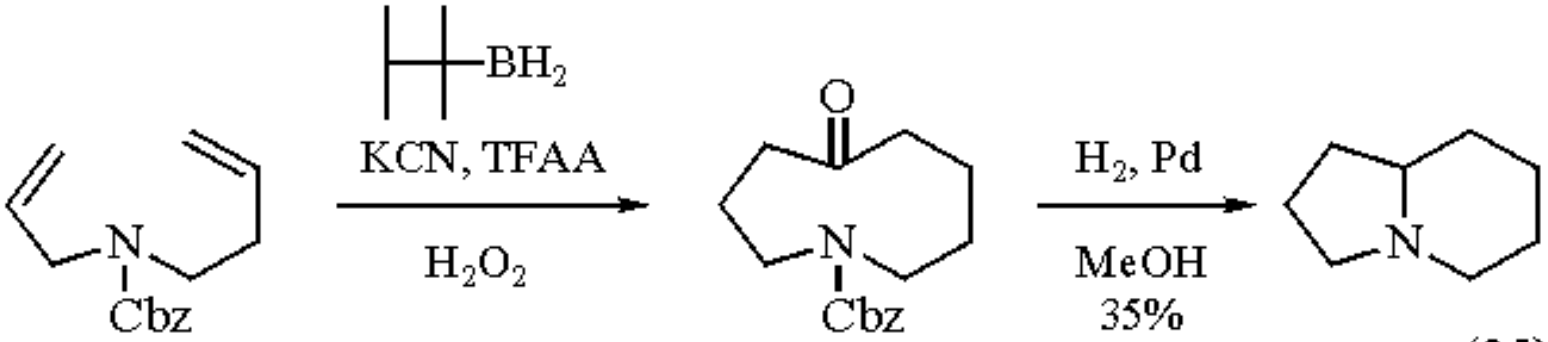

(35)

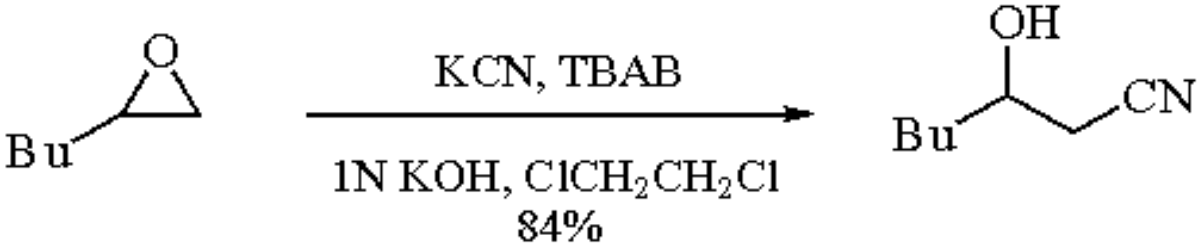

(36)

Aromatization.

KCN in DMF is an effective reagent for the conversion of 2,4-cyclohexadien-1-ols to benzene derivatives.[84] The same conditions were applied for the aromatization of 2,4-cyclohexadiene-6-imine derivatives (eq 37).[85]

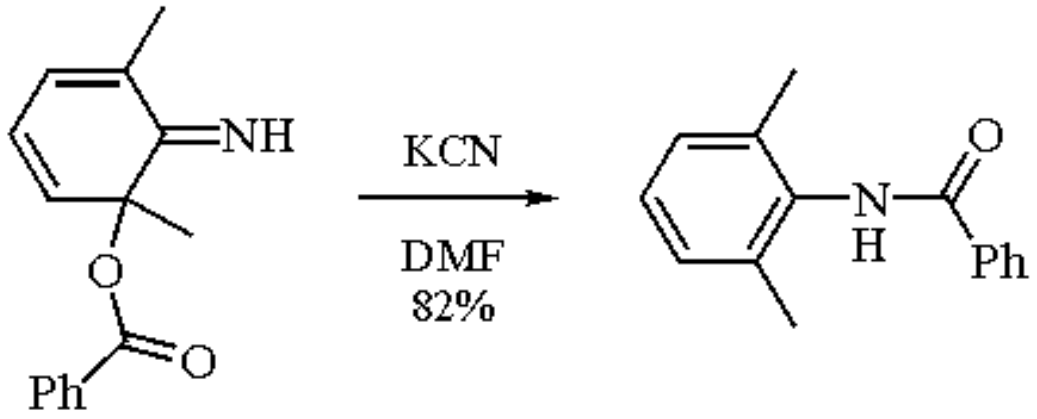

(37)

Reduction.

0.1 N aqueous KCN solutions of aromatic nitro compounds upon UV irradiation undergo deoxygenation to the corresponding nitroso compounds (eq 38).[86]

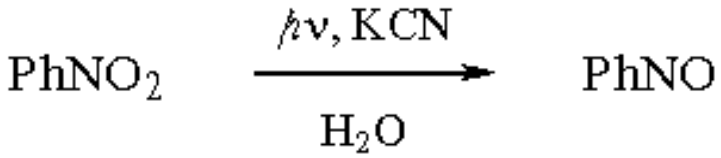

(38)

Related Reagents.

Acetone Cyanohydrin; ***Acetyl Cyanide***; ***t-Butyldimethylsilyl Cyanide***; ***Cyanotributylstannane***; ***Cyanotrimethylsilane***; ***Diethylaluminum Cyanide***; ***Hydrogen Cyanide***; ***Tetraethylammonium Cyanide***; ***Zinc Cyanide***.

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Potassium Decacarbonylhydridochromate

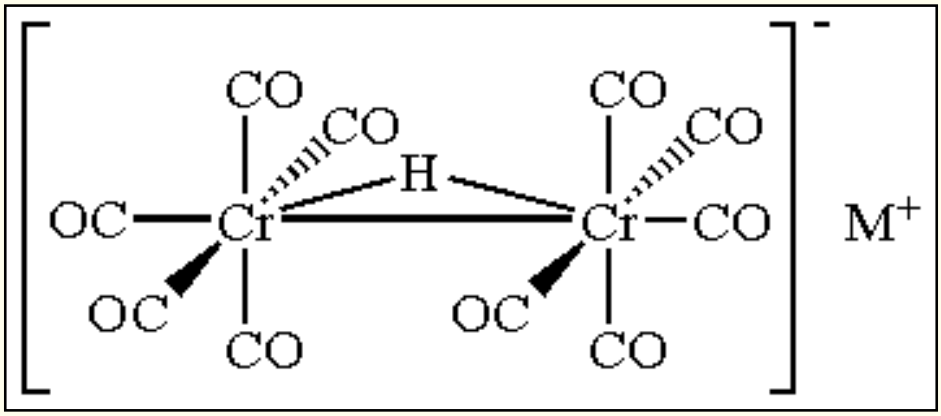

(M = K)

[61453-56-3] · $C_{10}HCr_2KO_{10}$ · Potassium Decacarbonylhydridochromate · (MW 424.21)
(M = Na)

[12082-96-1] · $C_{10}HCr_2NaO_{10}$ · Sodium Decacarbonylhydridochromate · (MW 408.10)

(selectively hydrogenates α,β-unsaturated carbonyl compounds[1])

Physical Data: red crystals.

Solubility: sol THF.

Form Supplied in: not commercially available.

Preparative Methods: prepared by treating ***Hexacarbonylchromium*** with ***Potassium-Graphite*** or ***Sodium Amalgam***.[1]

Purification: used in situ following the above preparation.

Handling, Storage, and Precautions: air and moisture sensitive.

Hydrogenation of α,β-Unsaturated Carbonyl Compounds.

Hydrogenation of α,β-unsaturated carbonyl compounds is readily effected by treatment with either potassium or sodium decarbonylhydridochromate. Unsaturated ketones, aldehydes, esters, and nitriles are all reduced by this reagent, with no problems arising from reduction of the carbonyl or nitrile functionalities. The reagent is totally specific for reduction of the α,β-unsaturated site. Neither isolated double bonds, nor the γ,δ-unsaturated site in α,β,γ,δ-unsaturated carbonyl compounds are reduced by these reagents. Although these reagents exhibit excellent selectivity, the procedures are operationally more difficult than other reducing agents (eq 1).[2]

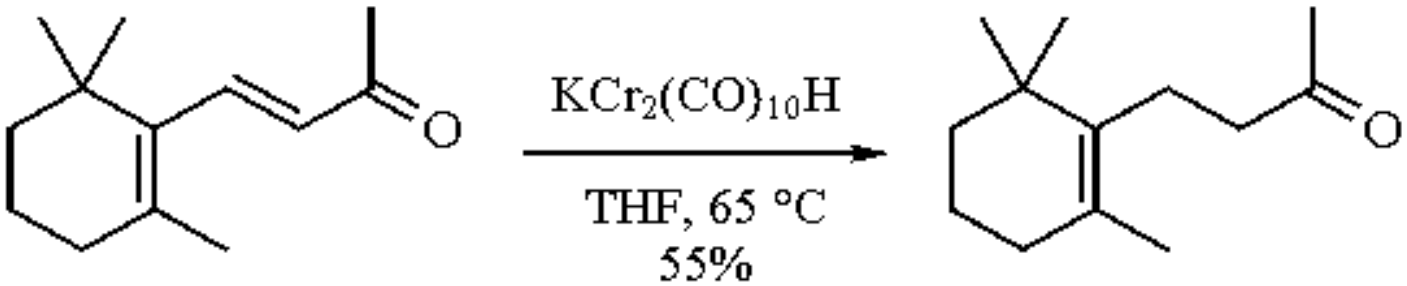

(1)

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Potassium Dichromate

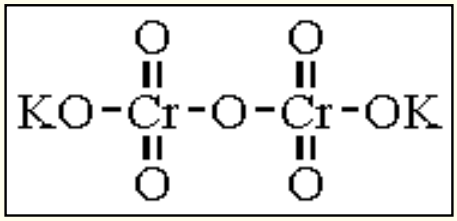

[7778-50-9] · $Cr_2K_2O_7$ · Potassium Dichromate · (MW 294.20)

(reagent for converting alcohols to aldehydes, carboxylic acids, and ketones)

Physical Data: mp 398 °C; *d* 2.676 g cm^{-3}.

Solubility: H_2O (4.9 g/100 mL at 0 °C), DMSO, polyethylene glycol (PEG).

Form Supplied in: red crystals.

Handling, Storage, and Precautions: highly toxic cancer suspect agent. All chromium(VI) reagents must be handled with care. The mutagenicity of Cr^{VI} compounds is well documented.[1] This reagent should be handled in a fume hood.

Oxidation of Alcohols to Carbonyl Compounds.

Primary alcohols in CH_2Cl_2 are oxidized to aldehydes and secondary alcohols are oxidized to ketones in high yields by potassium dichromate in 9 M sulfuric acid in the presence of tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst. The reaction is complete in a few seconds at rt, the yields are lower with water-soluble alcohols, and double bonds may be cleaved.[2] Adogen 464, a mixture of methyltrialkylammonium chlorides, facilitates the solubilization of potassium dichromate in several apolar organic solvents including benzene, CH_2Cl_2, $CHCl_3$, and CCl_4.[3] The solution in benzene is a mild oxiding agent which converts alcohols to carbonyl compounds with some selectivity.

Allylic and benzylic alcohols are oxidized to carbonyl compounds (70-80%) by potassium dichromate in either ***Dimethyl Sulfoxide*** (DMSO) or polyethylene glycol (PEG).[4] Oxidations with potassium dichromate in PEG are comparable to those in crown ethers or ***Hexamethylphosphoric Triamide***.[5] A novel one-pot procedure for the selective oxidation of 5-substituted 2-hydroxy-3-hydroxymethylbenzaldehydes (**1**), via the *N,N´*-ethylene bis(5-substituted 3-hydroxymethylsalicylaldimino)copper complexes (**2**), to 5-substituted 2-hydroxy-1,3-benzenedicarbaldehydes (**3**) by potassium dichromate in DMSO at 100 °C is shown in eq 1.[6] The complexes (**2**), which were prepared (90-95%) from (**1**), ***1,2-Diaminoethane***, and ***Copper(II) Acetate***, are oxidized by ***Potassium***

Permanganate in aqueous ***Pyridine*** to 5-substituted 3-formyl-2-hydroxybenzoic acids (25-40%).[6]

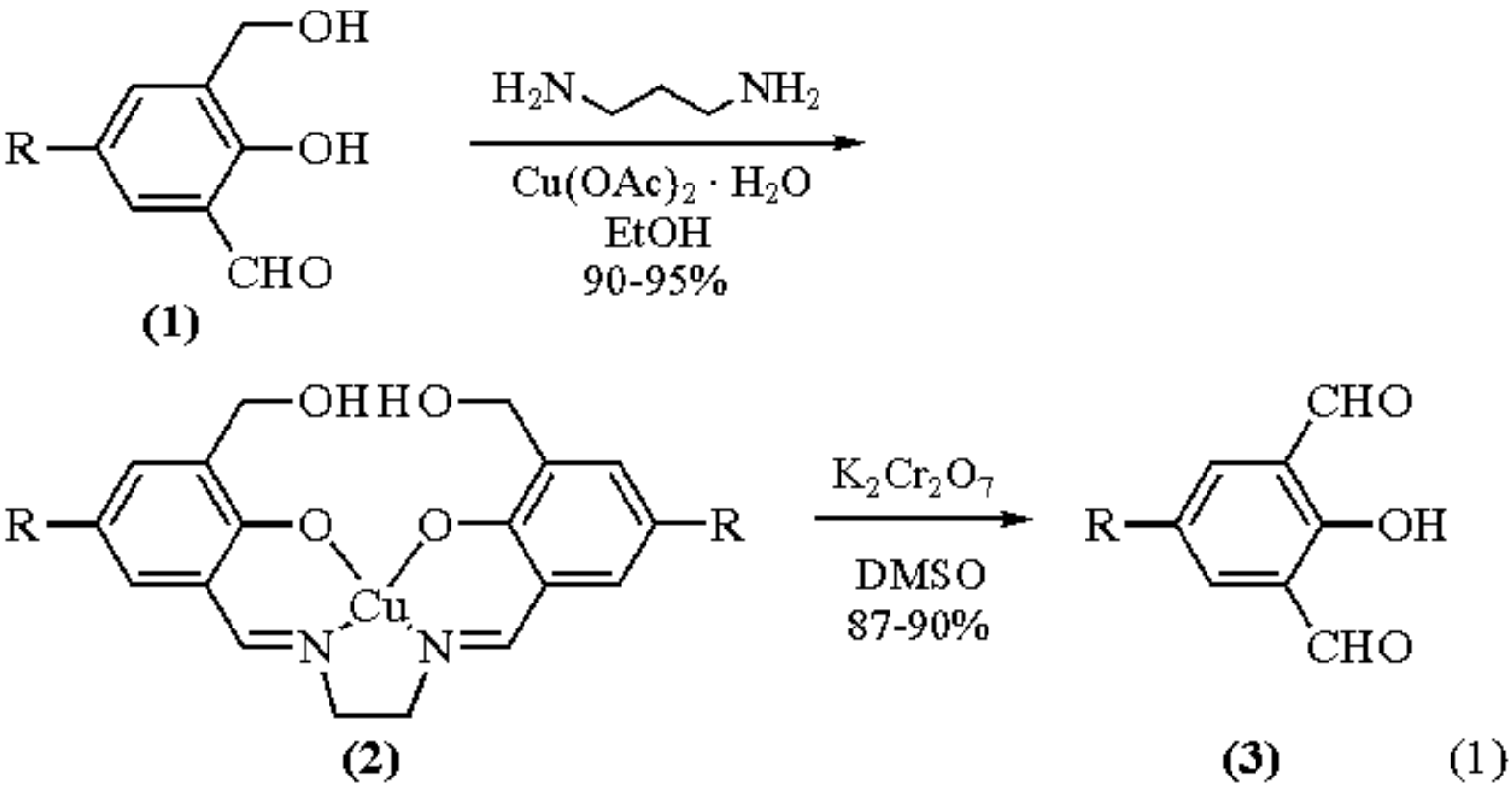

Oxidation of Cyclobutanols and Cyclobutanones to γ-Butyrolactones.

Cyclobutanols and cyclobutanones are oxidized by potassium dichromate in aqueous sulfuric acid to γ-butyrolactones.[7] Cyclobutanones tetrasubstituted at C-2, C-3, or at C-2, C-4 are oxidized to γ-butyrolactones in good yields (eqs 2 and 3).[8] The oxidation is not applicable to larger cyclic ketones.

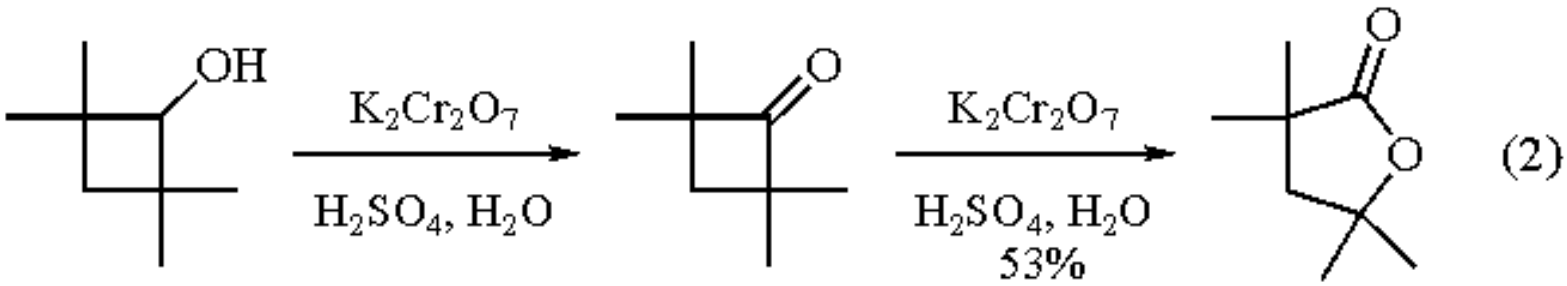

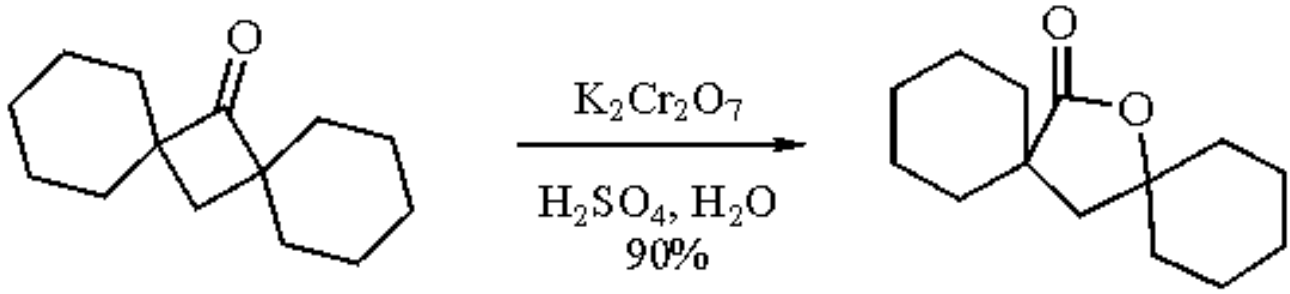

(3)

Oxidation of α-Nitro Alcohols to α-Nitro Ketones.

α-Nitro alcohols are oxidized to α-nitro ketones by potassium dichromate under phase-transfer conditions (CH_2Cl_2, tetrabutylammonium sulfate, 30% sulfuric acid).[9] Reaction of an aldehyde and a nitroalkane on alumina followed by in situ oxidation allows for a one-pot synthesis (eq 4).

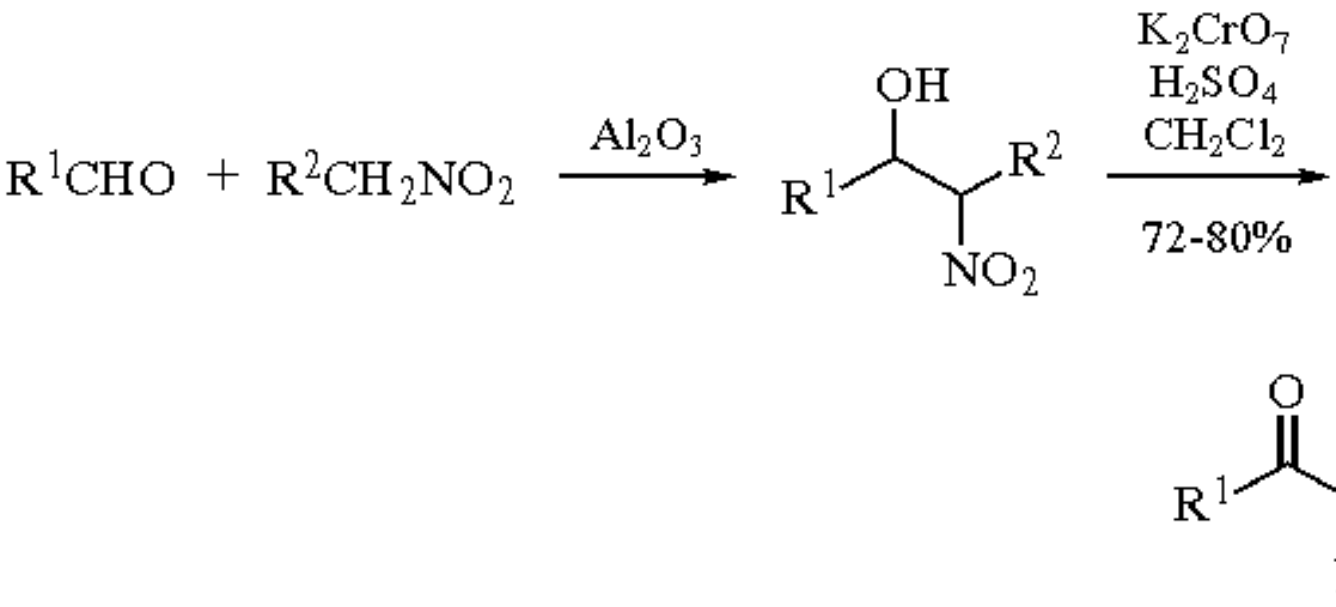

(4)

Oxidation of Primary Alcohols to Acids.

Adding primary alcohols to an excess of potassium dichromate in sulfuric acid affords the corresponding carboxylic acids in good to excellent yields.[10,11]

Other Applications.

Potassium dichromate in benzene in the presence of Adogen 464[3] oxidizes *o*-allylphenols to 3-chromenes (eq 5).[12] *o*-Quinone methides are postulated intermediates. Although *o*-quinones are generally prepared from the corresponding catechol, potassium dichromate in sulfuric acid oxidizes 2-amino-4,5-dimethylphenol to 4,5-dimethyl-*o*-quinone (45%).[13] 4-Aminonaphthol is oxidized to 1,4-naphthoquinone (78-81%) by potassium dichromate in sulfuric acid.[14] Furfural is oxidized to furoic acid (75%) by potassium dichromate in aqueous sulfuric acid.[15] Potassium dichromate in aqueous acetic acid oxidizes *N*,*N*-bis-4-nitrobenzylhydroxylamine to the 4-nitrophenyl nitrone of 4-

nitrobenzaldehyde (98%).[16] Aqueous potassium dichromate selectively oxidizes 2-methylnaphthalene to 2-naphthoic acid without ring degradation or formation of a considerable amount of 2-methylnaphthoquinone.[17,18]

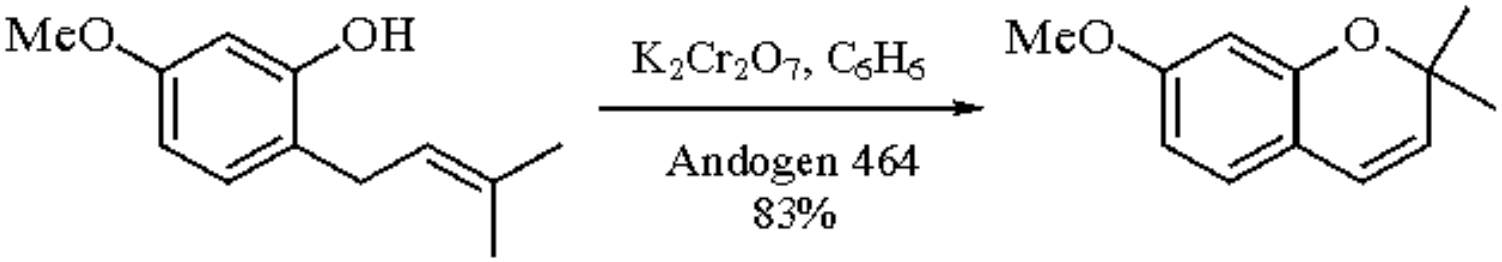

(5)

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Potassium Diisopropylamide

KN(*i*-Pr)$_2$

[67459-71-6] · $C_6H_{14}KN$ · Potassium Diisopropylamide · (MW 139.31)

(non-nucleophilic strong base)

Alternate Name: KDA.

Solubility: sol THF; insol benzene.

Analysis of Reagent Purity: amide bases can be titrated utilizing 1,6-dihydro-6-butyl-2,2´-bipyridine.[1] This indicator is able to determine the concentration of amide base solutions even in the presence of alkoxide.

Preparative Methods: KDA is prepared in situ immediately prior to use. In the original paper, the reagent was prepared either by the addition of diisopropylamine to a mixture of *n*-butylpotassium-lithium *t*-butoxide in hexane at 0 °C, or by the addition of ***n-Butyllithium*** to a solution of ***Potassium t-Butoxide*** and ***Diisopropylamine*** in THF at -78 °C.[2] It is also common to treat a solution of ***Lithium Diisopropylamide*** with potassium *t*-butoxide.[3] This reagent has been referred to in the literature as KDA, KDA-lithium *t*-butoxide, and LIDAKOR (lithium diorganylamide potassium alcoholate), but an examination of the experimental procedures indicates that all of the authors are, for practical purposes, referring to the same reagent. The exchange of lithium for potassium between organolithium compounds and potassium alkoxides is well established and has been reviewed.[4]

Handling, Storage, and Precautions: moisture sensitive. Use in a fume hood.

Deprotonation Reactions.

KDA is used to effect deprotonations when a strong, non-nucleophilic base is required. It is considerably more reactive than its lithium counterpart and thus it is often used in situations where ***Lithium Diisopropylamide*** (LDA) has been tried and shown to be ineffective. Even in cases where LDA is effective for deprotonation, KDA can be used advantageously to promote anion generation more rapidly and at lower temperatures and to provide a more reactive derivative. KDA is also used when the potassium counterion is important for the outcome of a reaction. For example, it is well recognized that, in contrast to lithium enolates, when potassium enolates are employed, enolate equilibration is normally faster than alkylation, resulting in predominant alkylation of the thermodynamically more stable enolate.[5] The examples outlined below have been selected to illustrate these types of situations in which the unique properties of KDA are exploited.

KDA is used periodically for the generation of enolates. In a recent example, an oxindole system was successfully alkylated with an aziridine via the dianion formed by treatment with 2 equiv of KDA in THF at -78 °C (eq 1).[6] KDA can also be used to generate the dianions of carboxylic acids which then add predominantly 1,2 to α,β-unsaturated carbonyl compounds.[7] The counterion in this reaction has a pronounced effect on the ratio of 1,2- to 1,4-addition. The heightened reactivity of KDA has proved useful when enolate stability is a concern. In one example it was determined that the enolate of a particular pyrrolidinone was unstable above -70 °C, but the compound was successfully deprotonated at -90 °C within 20 min using KDA.[8] KDA has also been used when greater reactivity is required in the generated enolate. Potassium enolates have been shown to undergo a conjugate addition to a vinyl sulfone in cases where the lithium enolate was completely unreactive.[9]

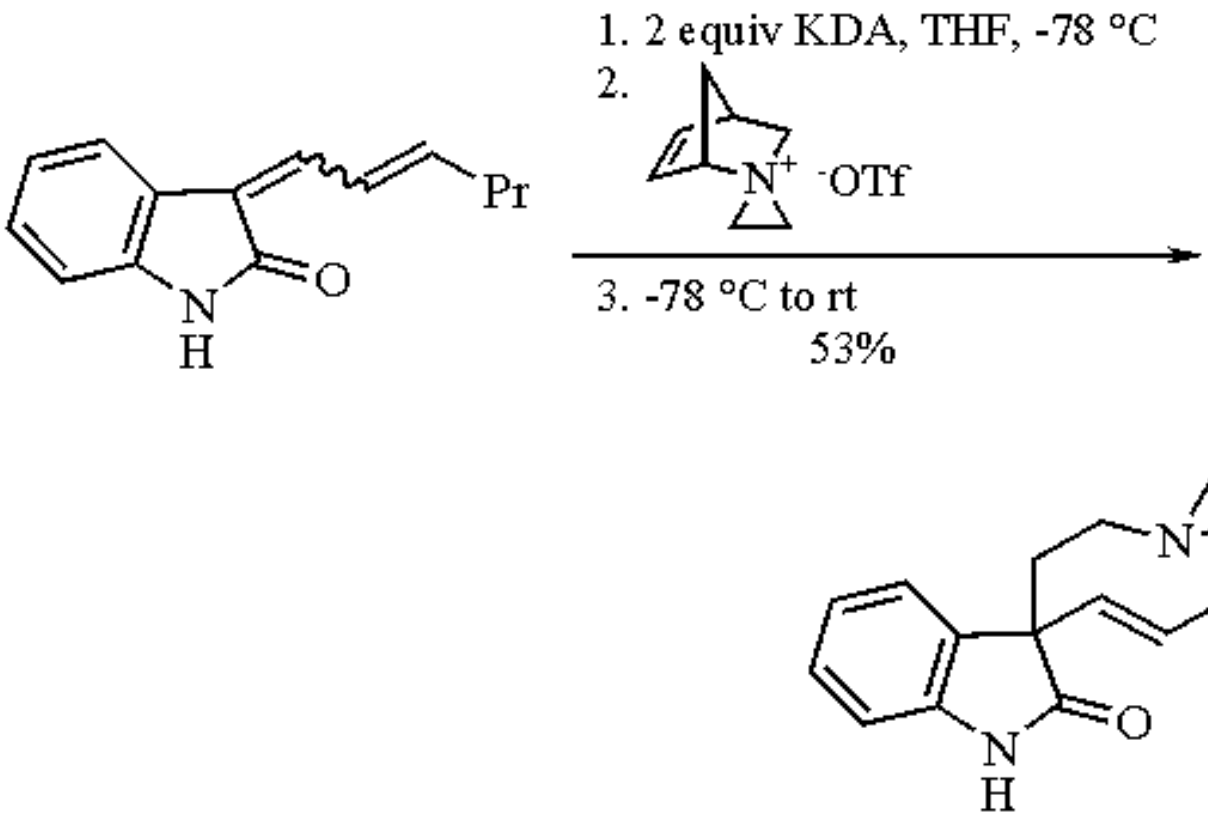

(1)

In one of the first reports of this reagent, it was shown that KDA can be used for the metalation of nitrosamines (eq 2).[10] The reaction takes place more rapidly than with LDA and gives a more reactive intermediate toward alkylation. KDA is also preferred over LDA for the generation of alkyl phosphonate anions prior to mono- or difluorination using *N*-fluorobenzenesulfonimide.[11] In the deprotonation of alkoxyalkyl phenyl sulfones (acyl anion equivalents), KDA must be used if the anion is to be added to a ketone rather than simply alkylated.[12]

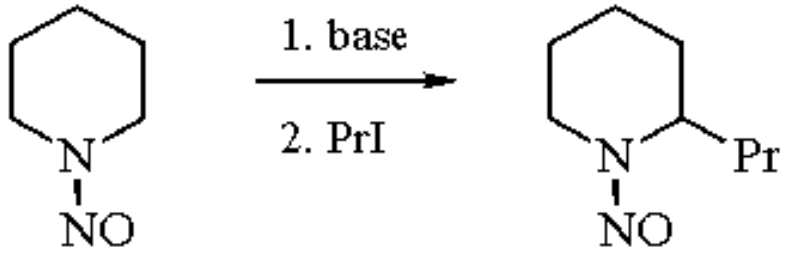

(2)

Base	Time (min)	Yield
LDA	210	37%
KDA	30	41%
LDA, HMPA	90	49%
KDA, HMPA	30	60%

KDA has been used for the deprotonation of dimethylhydrazones and oxime ethers.[13] In most cases, deprotonation is complete in THF at -78 °C within 15 min. By contrast, the conditions for successful deprotonations using *n*-butyllithium or LDA are substrate dependent, requiring more time for optimization on a case by case basis. The anion of acetone dimethylhydrazone, generated by treatment with KDA, has been added to a vinyl sulfone and the resulting α-sulfonyl anion further alkylated (eq 3).[14]

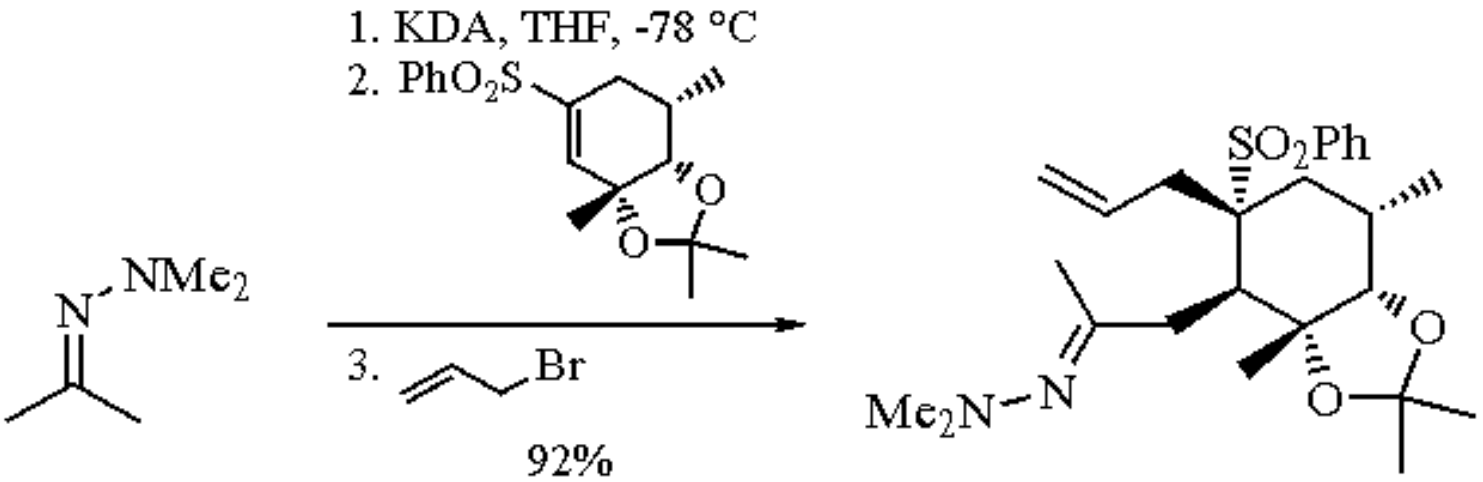

(3)

KDA appears to be the base of choice for the generation of selenium-stabilized carbanions. It has been used to effect the deprotonation of 1-(phenylseleno)alkenes and bis(phenylseleno)acetals to give carbanions which react rapidly with a variety of electrophiles (eq 4).[15] Carbonyl compounds which contain an α-hydrogen undergo carbonyl addition rather than enolate formation. By comparison, LDA does not deprotonate these systems at an appreciable rate. In the case of α-aryl bis(phenylseleno)-acetals, the use of LDA results in the recovery of a significant amount of starting material while the use of KDA produces only the desired product (eq 4).[16] KDA will also successfully deprotonate simple benzyl selenides and 1,1,1-tris(trifluoromethylseleno)methane.[16,17] However, when dibenzyl diselenide is treated with KDA, cleavage of the Se-Se bond is the predominant reaction in a rare example of KDA acting as a nucleophile.[18]

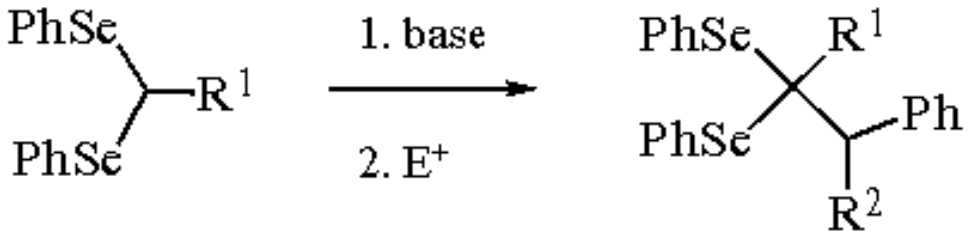

(4)

R^1	Base	E	R^2	Yield
Me	LDA	$PhCH_2Br$	H	0%
Me	KDA	$PhCH_2Br$	H	88%
Ph	LDA	PhCHO	OH	26%
Ph	KDA	PhCHO	OH	79%

KDA has been used for the deprotonation of phenylthiotributylstannyltrimethylsilylmethane (eq 5).[19] The potassium anion is formed in 15 min and readily alkylated, whereas the analogous lithium anion is formed in only 80% after 1 h and requires a complexing agent like TMEDA to achieve good yields of alkylated product. Transmetalation of the tributylstannyl group with *n*-butyllithium followed by alkylation provides α-silyl sulfides which can be subsequently converted to ketones. If, instead of an alkyl halide, the potassium anion is reacted with a nonenolizable carbonyl compound, a vinylstannane is obtained via a Peterson reaction (eq 5).[20] No control over alkene geometry was observed in this case. However, cation dependent geometric control has been shown to occur in the Peterson reaction between bistrimethylsilyl acetate enolates and aldehydes (eq 6).[21] Employing the potassium enolate generated with KDA gives significant selectivity for the (*E*)-isomer, suggesting that elimination occurs largely from a nonchelated intermediate.

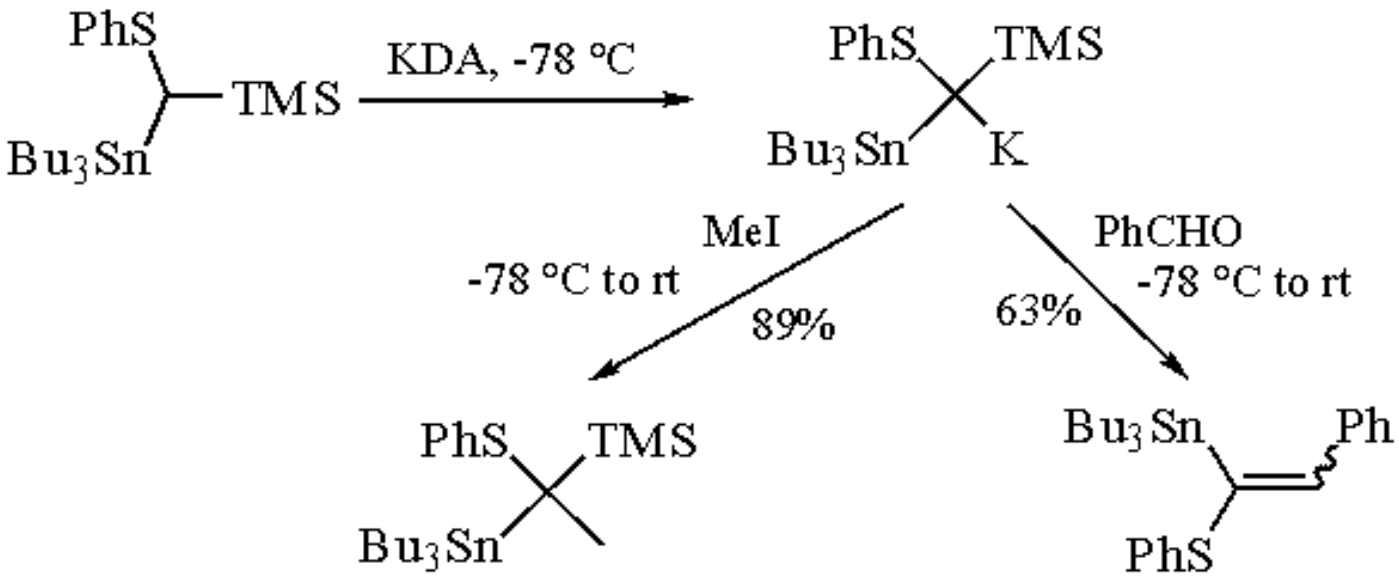

(5)

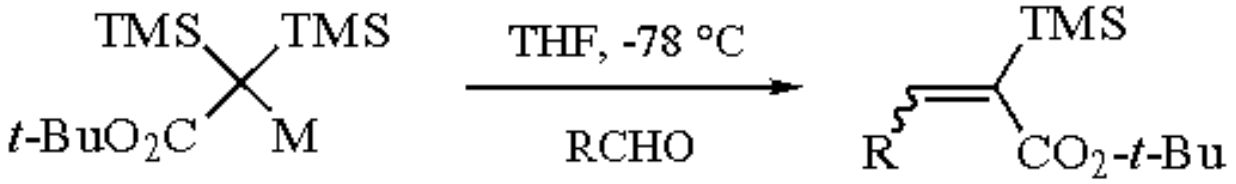

(6)

M	R	(*E*):(*Z*)
K	*i*-Pr	>100:1
Li	*i*-Pr	6.5:1
K	Ph	17:1
Li	Ph	9.4:1

KDA has been used for the metalation of imidazoles in cases where *n*-butyllithium and LDA were ineffective.[22] In a synthesis of a dinucleating hexaimidazole ligand, both rings of a bis-imidazole system were metalated and derivatized using KDA.[23]

The high reactivity and kinetic basicity of KDA allow it to deprotonate even simple aromatic methyl groups. For this reason, toluene is not recommended as a solvent for KDA reactions. The deprotonation of dimethylnaphthalene, dimethylanthracene, and dimethyltriptycene systems have been studied using KDA.[24] KDA has also been used for the direct metalation of isoprene.[25]

Elimination Reactions.

KDA has been used for the generation of dienols from homoallylic cyclic ethers (eq 7).[26] KDA promotes the ring-opening elimination without reacting with the resulting diene. By contrast, the use of LDA decreases yields dramatically. In this system, KDA is generated from LDA in the presence of a catalytic amount (10 mol %) of potassium *t*-butoxide. Presumably the product potassium alkoxide that is formed reacts with remaining LDA to generate a constant, low level of KDA which helps to minimize undesirable side reactions.

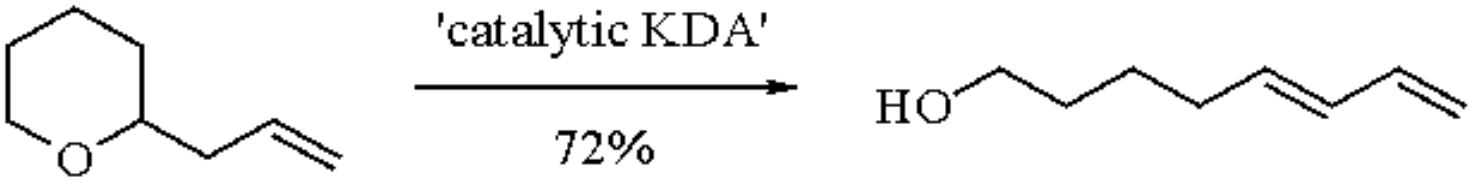

(7)

KDA has also been used to promote the smooth ring opening of epoxides to generate allylic alcohols in good yields.[27] It is felt that the combination of lithium and potassium bases used in the generation of KDA both play important roles in facilitating this reaction: the electrophilic lithium may help to open the epoxide while the heavier alkali metal potassium confers maximum basicity to its anion to facilitate deprotonation. Where possible, *trans*-alkenols are the preferred or exclusive product, probably arising via a *syn*-periplanar elimination route.

KDA has been cited in an improved procedure for the Wharton transposition.[28] This multistep 1,3-transposition of oxygen proceeds through a base-induced rearrangement of an α,β-epoxyhydrazone. For stable epoxyhydrazones, yields are improved considerably by the use of KDA or potassium *t*-butoxide (eq 8).

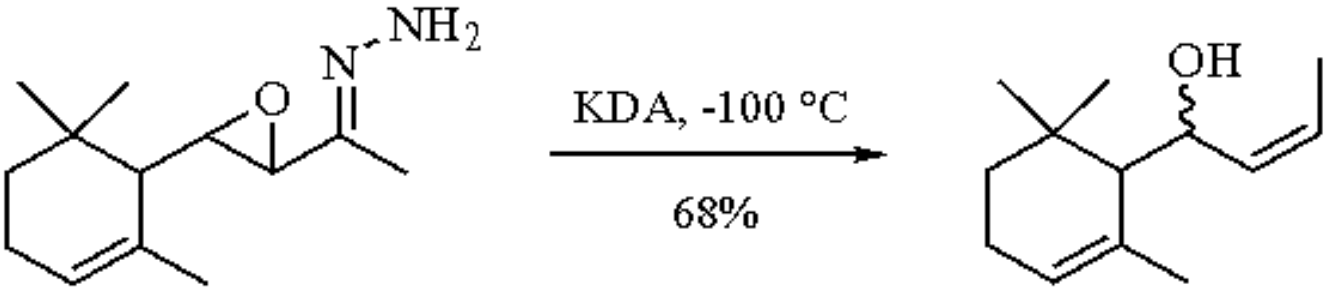

(8)

Related Reagents.

Lithium Diisopropylamide; ***Potassium 3-Aminopropylamide***.

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Potassium Ferrate

K_2FeO_4

[13718-66-6] · FeK_2O_4 · Potassium Ferrate · (MW 198.05)

(selective oxidant for alcohols and amines[1])

Solubility: sol water; insol typical organic solvents.

Form Supplied in: violet solid; typical impurities present include potassium chloride and iron(III) oxide.

Analysis of Reagent Purity: analysis of K_2FeO_4 by chromite ion has been reported.[2] The ferrate concentration may be determined by measurement of the absorption band at 510 nm.[3]

Preparative Methods: NaOCl (20 g) is added to a solution of NaOH (30 g in 75 mL H_2O) while keeping the solution temperature under 20 °C. Solid NaOH (70 g) is added with stirring, while maintaining the solution temperature at 25-30 °C, the solution cooled to 20 °C and filtered. $Fe(NO_3)_3.9H_2O$ (25 g) is added slowly, and the solution saturated with NaOH while being kept at 30 °C. After filtration, the filtrate of sodium ferrate is placed in a 20 °C bath and treated with saturated aqueous KOH (100 mL), stirred for 5 min, and filtered. The precipitate is washed several times with 10 mL portions of 3 M KOH into 50 mL of chilled saturated KOH solution, and a further 50 mL of chilled saturated KOH solution added to the washings. After stirring for 5 min, the solution is filtered, and the precipitate washed with benzene (10 mL) and several times with ethanol (20 mL). The precipitate is stirred with ethanol (1 L) for 20 min and the ethanol removed by filtration; this process is repeated three times. The precipitate is finally washed with Et_2O under a drying tube, and drying continued in a vacuum desiccator.[4]

Handling, Storage, and Precautions: dry K_2FeO_4 is stable and should be stored in a desiccator. K_2FeO_4 is very unstable in acidic solutions, but decomposes only slowly in basic solutions.

Oxidations.

Potassium ferrate has been reported to be a mild reagent for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively (eq 1).[1,5,6] In addition, primary and secondary amines are also oxidized to aldehydes and ketones (eq 2). Allylic and benzylic alcohols react much more readily than saturated ones, and

primary alcohols react more readily than secondary ones. Reactions are normally carried out in basic aqueous (or water/*t*-butanol) solution. Yields are normally high with allylic and benzylic alcohols and amines, but much more variable for saturated alcohols. Several functional groups are stable to this reagent, including carbon-carbon double bonds, nitro groups, tertiary alcohols and amines, aldehydes, and ketones. Sulfur compounds (sulfides, sulfoxides) do not tolerate this reagent.

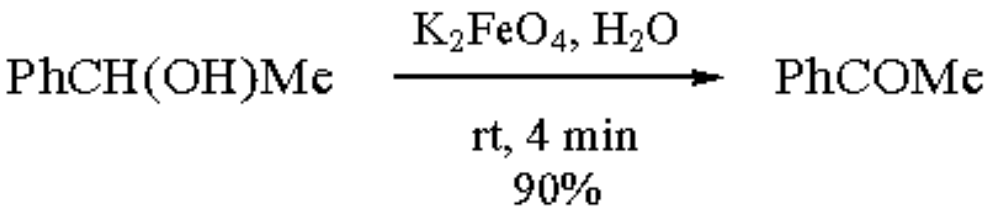

(1)

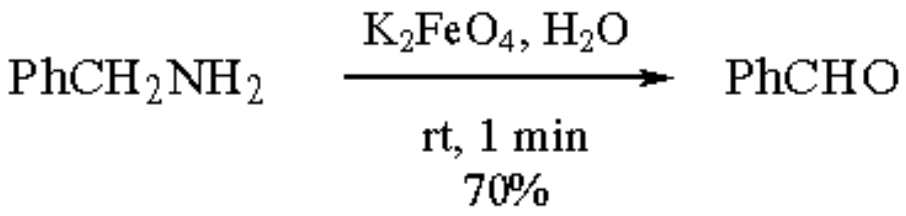

(2)

A modification employing a two-phase system (benzene/10% aqueous NaOH) and ***Benzyltriethylammonium Chloride*** as a phase-transfer catalyst has been reported to be highly successful for allylic and benzylic substrates (eq 3).[7] A second modification using a mixture of K_2FeO_4 (8 mmol), aluminum oxide (0.8 g), and $CuSO_4.5H_2O$ (0.8 g) for 2 mmol of substrate affords a simple workup and highly selective oxidations (eq 4).[6]

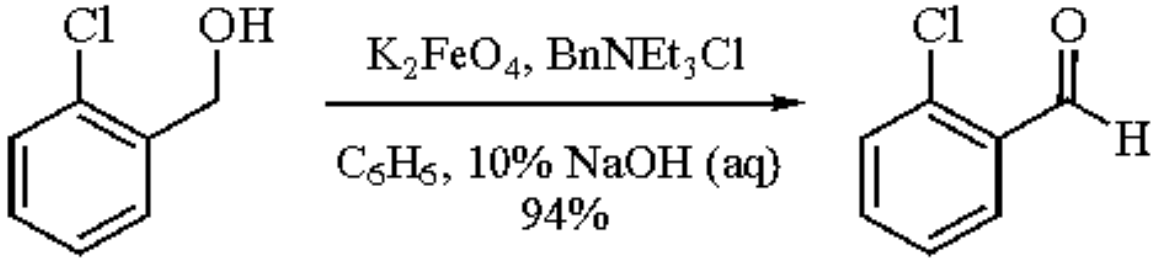

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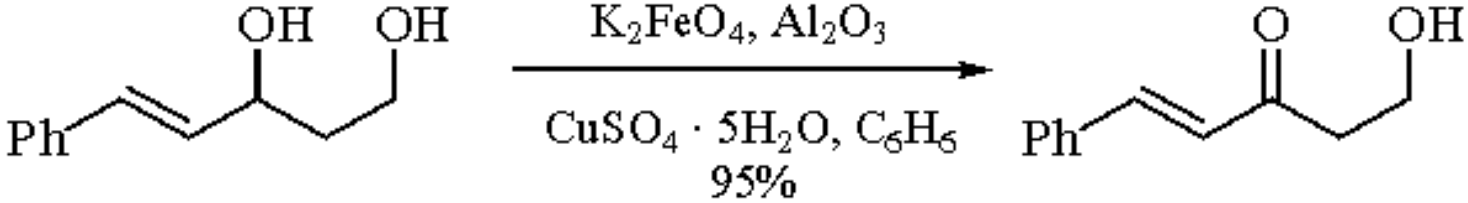

(4)

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Potassium Ferricyanide[1]

$K_3Fe(CN)_6$

[13746-66-2] · $C_6FeK_3N_6$ · Potassium Ferricyanide · (MW 329.27)

(mild oxidizing agent for functional groups;[1] capable of oxidative coupling of phenols;[2] can function as reoxidant in osmium-catalyzed asymmetric dihydroxylation of alkenes[3])

Alternate Name: potassium hexacyanoferrate(III).

Physical Data: d 1.890 g cm^{-3}.

Solubility: sol 33 g/100 ml in cold water, 77.5 g/100 ml in hot water; insol alcohol.

Form Supplied in: orange crystalline solid; widely available.

Handling, Storage, and Precautions: stable in air; light sensitive. Aqueous solutions decompose slowly on standing. Contact with strong acid liberates highly toxic gas. Avoid contact with skin and eyes. Avoid breathing dust. Use in a fume hood.

Functional Group Oxidations.

$K_3Fe(CN)_6$, a one-electron oxidant, is often used in an alkaline solution with an organic solvent. Since it is soluble in the aqueous phase but insoluble in most organic solvents, the reaction can be easily worked up by simple aqueous extraction. $K_3Fe(CN)_6$ has been reported to oxidize quaternary ammonium salts to pyridones,[4] acyloins to diketones,[5] and 3,4-disubstituted 4-halo-2-pyrazolin-5-ones to disubstituted alkynes (eq 1).[6] Demethylation has been reported for certain tertiary amines,[7] while diacids have been shown to undergo decarboxylation.[8]

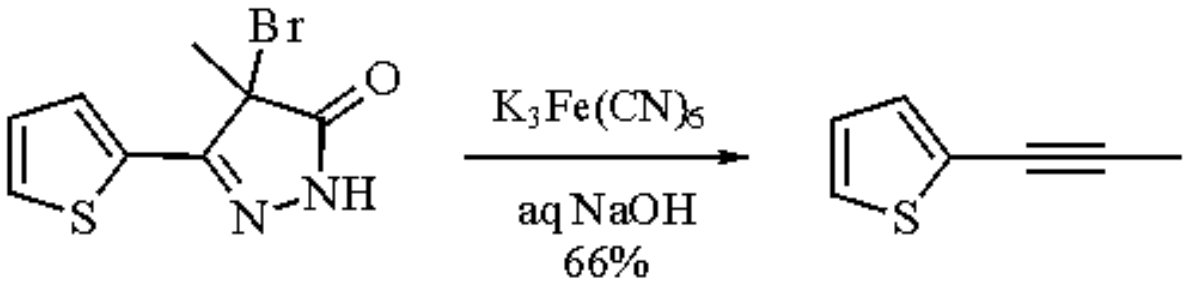

(1)

Oxidative Coupling of Phenols.

One of the most important uses of $K_3Fe(CN)_6$ is the oxidation of phenols. Stable aroxyl radicals can be prepared by reacting 2,4,6-trisubstituted phenols with alkaline $K_3Fe(CN)_6$ (eq 2).[9] With appropriate substituents, the dimer product from intermolecular oxidative coupling can be obtained in good yield (eqs 3 and 4).[10,11]

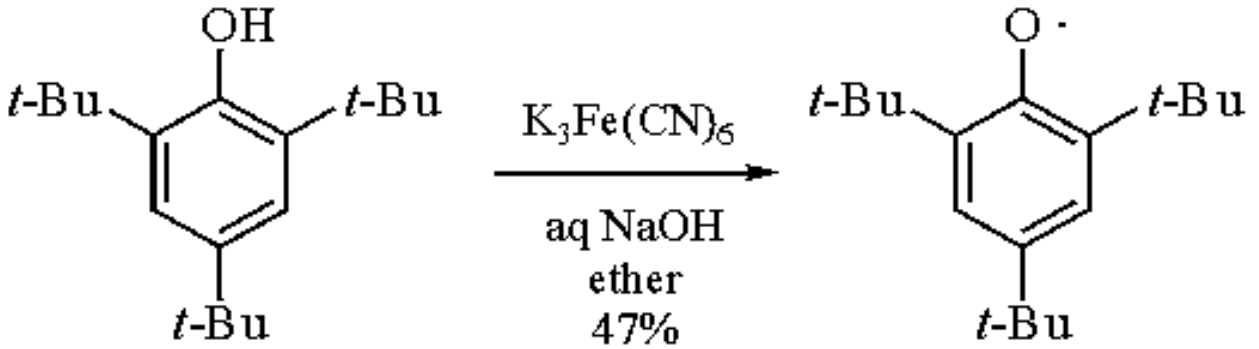

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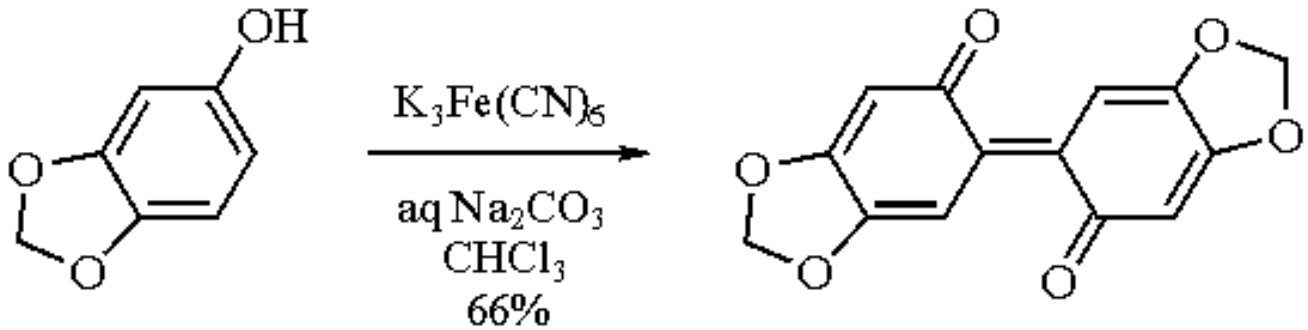

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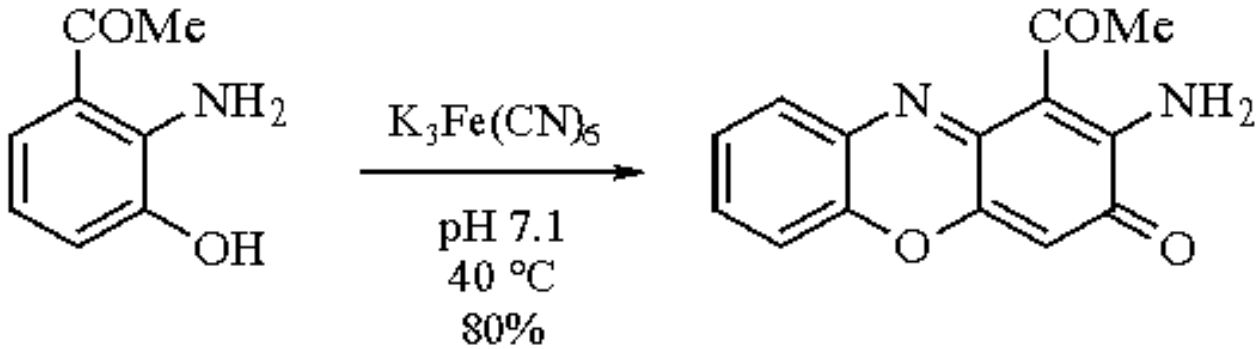

(4)

A stereospecific and stereoselective oxidative coupling of a chiral tetrahydronaphthol using $K_3Fe(CN)_6$ has also been demonstrated (eq 5).[12]

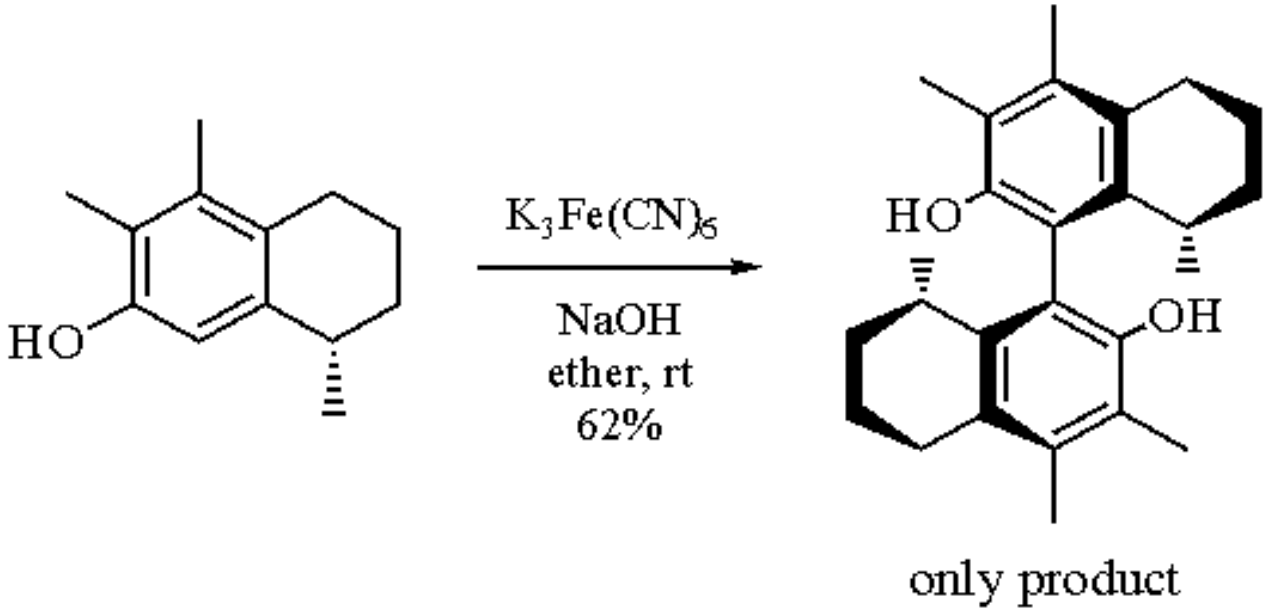

(5)

$K_3Fe(CN)_6$ has been used extensively for intramolecular oxidative coupling of phenolic substrates,[2] often with remarkably high yields (eqs 6 and 7).[13,14]

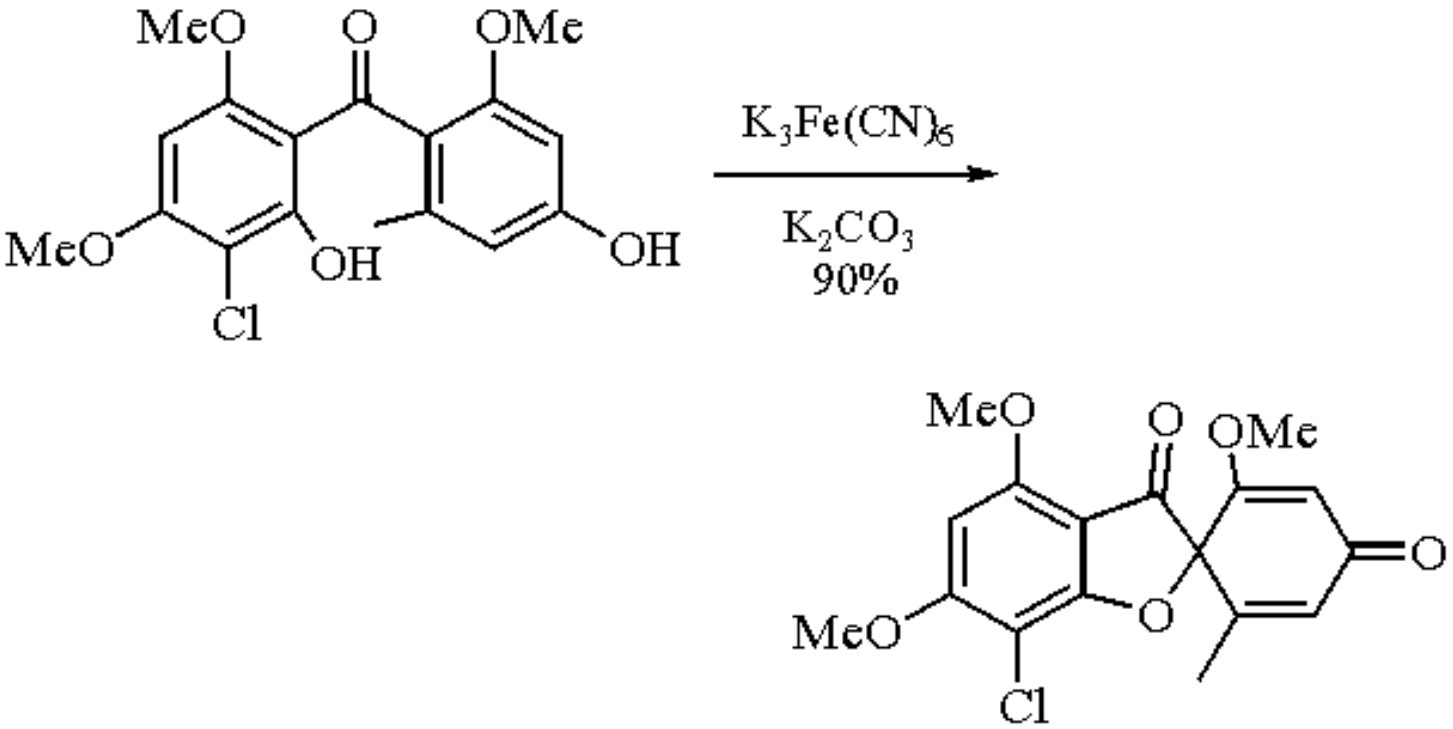

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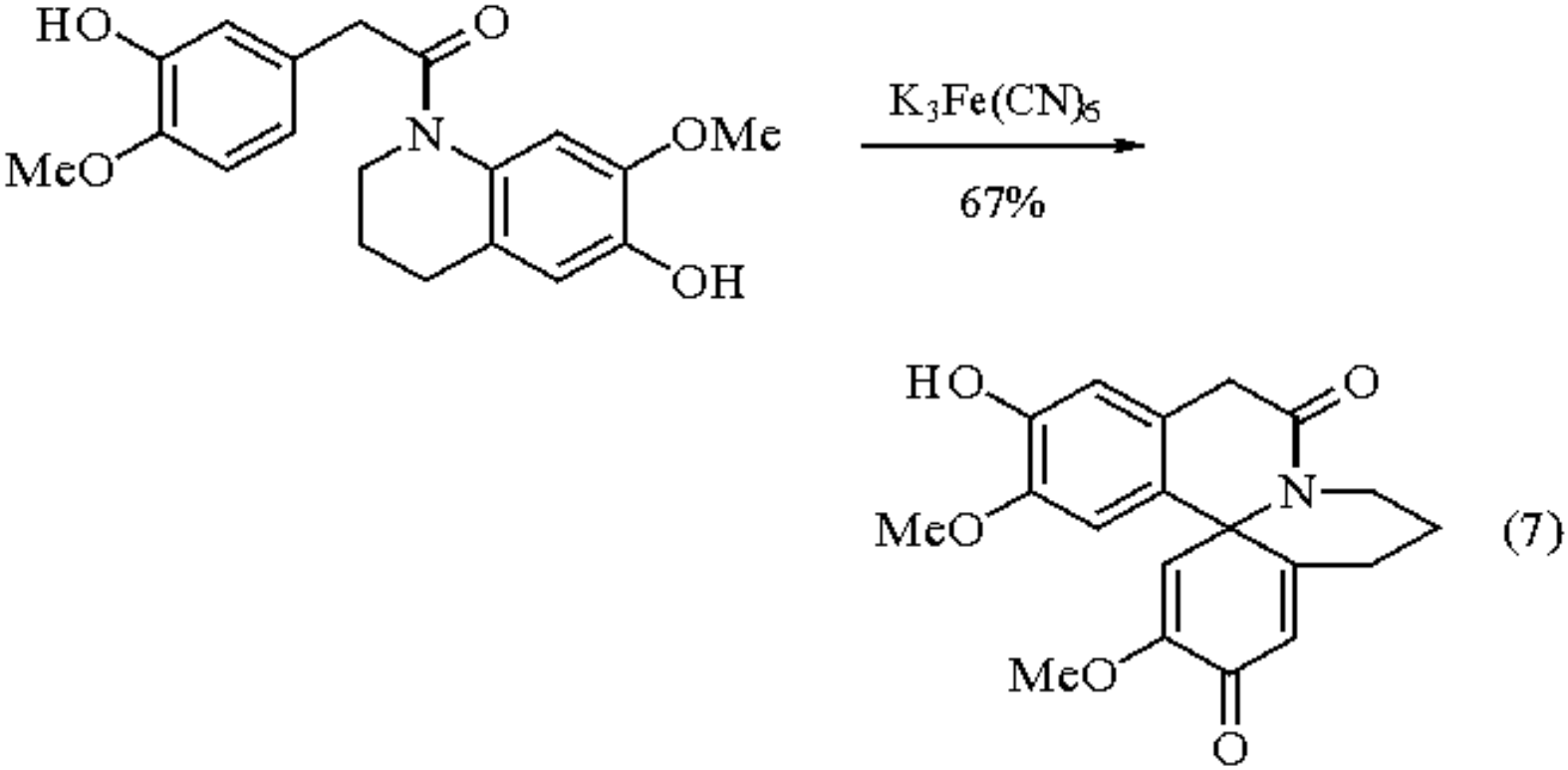

Other oxidants that have been commonly used for oxidative phenolic coupling are ***Iron(III) Chloride***, ***Iron(III) Chloride-Silica Gel***, ***Manganese Dioxide***, ***Lead(IV) Oxide***, ***Mercury(II) Oxide***, ***Silver(II) Oxide***, ***Phenyliodine(III) Bis(trifluoroacetate)***, ***Thallium(III) Trifluoroacetate***, ruthenium trifluoroacetate, ***Vanadyl Trichloride***, and ***Vanadyl Trifluoride***.[2] For the oxidation of a phenolic β-diketone, $K_3Fe(CN)_6$ gives the coupling product in very good yield (eq 8),[15] while several other oxidants (e.g. $FeCl_3$, VOF_3, $VOCl_3$, ***Copper(II) Chloride***) were unsuccessful. However, $VOCl_3$ has been shown to be superior to $K_3Fe(CN)_6$ in the oxidation of a diphenolic substrate (eq 9).[16]

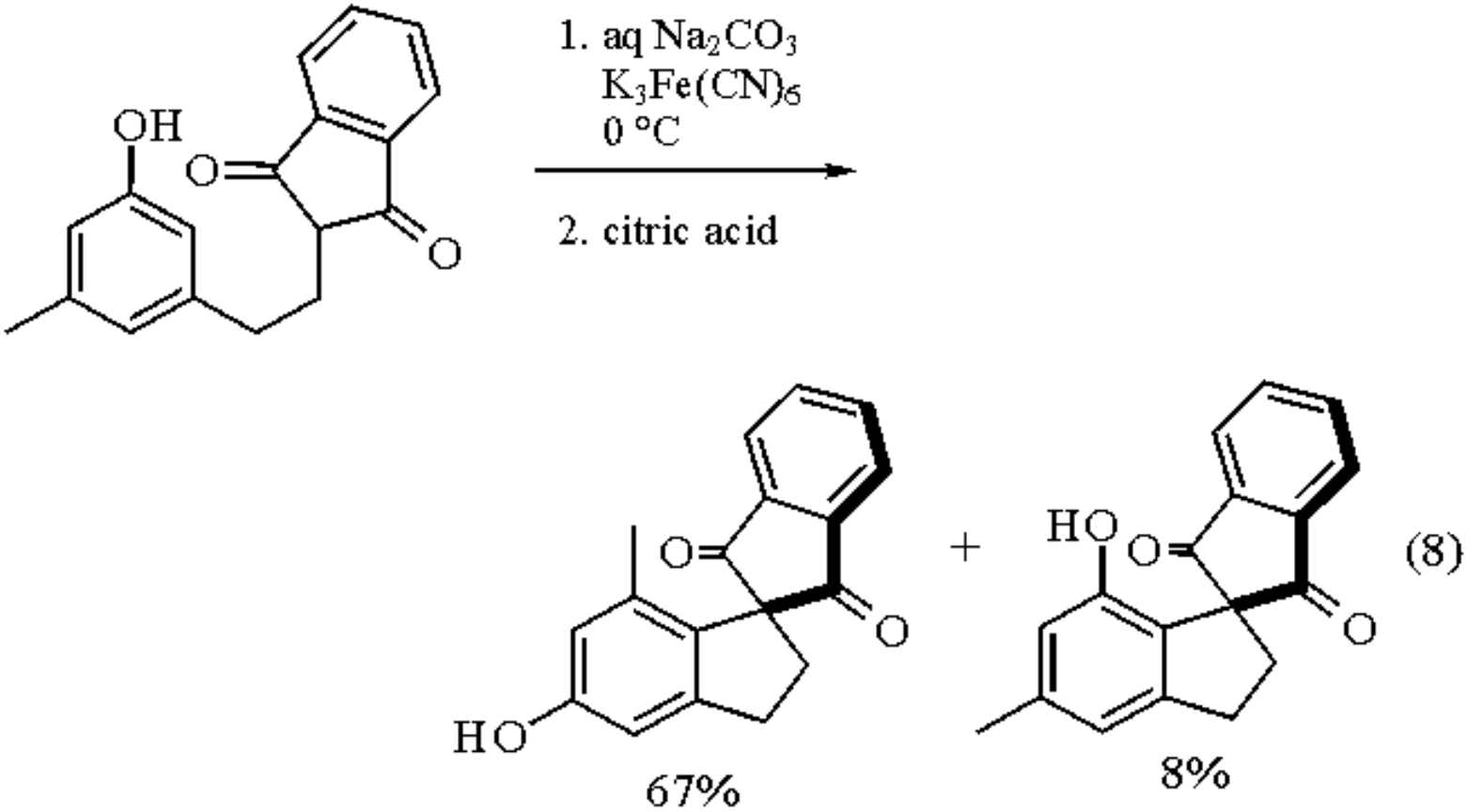

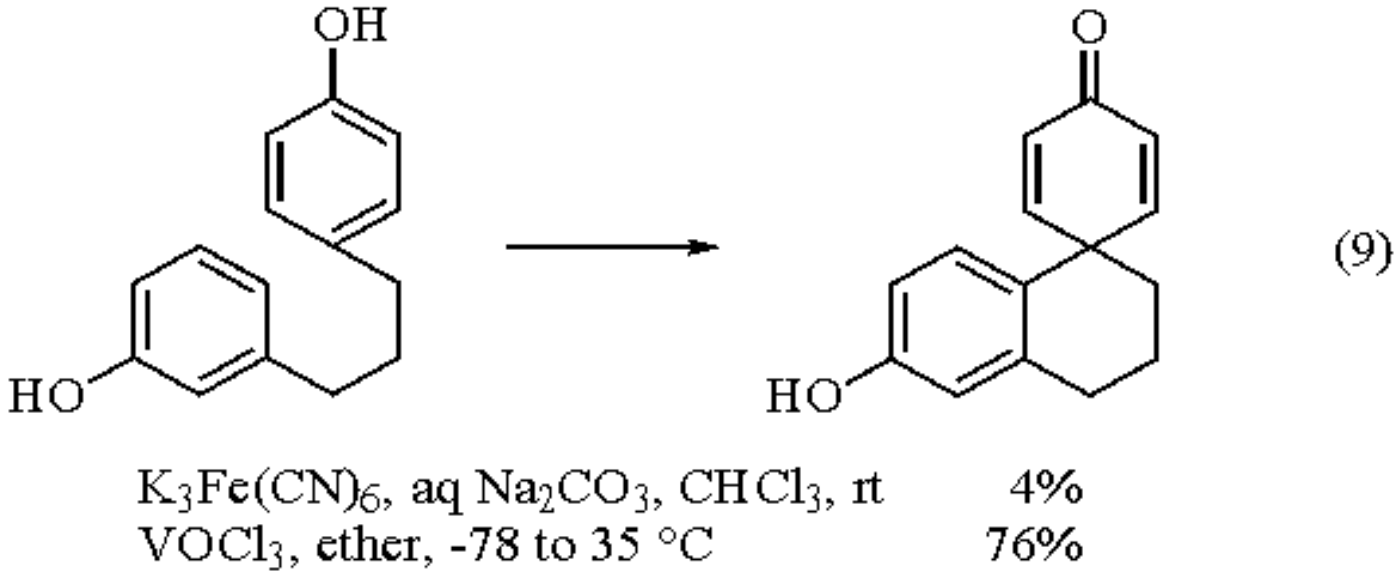

$K_3Fe(CN)_6$ has also been used in the synthesis of hydroxyindoles by the oxidation of suitably substituted hydroquinones.[17]

As Reoxidant in Osmium-Catalyzed Dihydroxylation.

Another very important use of alkaline potassium ferricyanide is as a stoichiometric reoxidant in the osmium-catalyzed dihydroxylation of alkenes to give diols (eq 10).[18] Sodium sulfite is usually added to the reaction mixture to quench the excess ferricyanide before work-up.

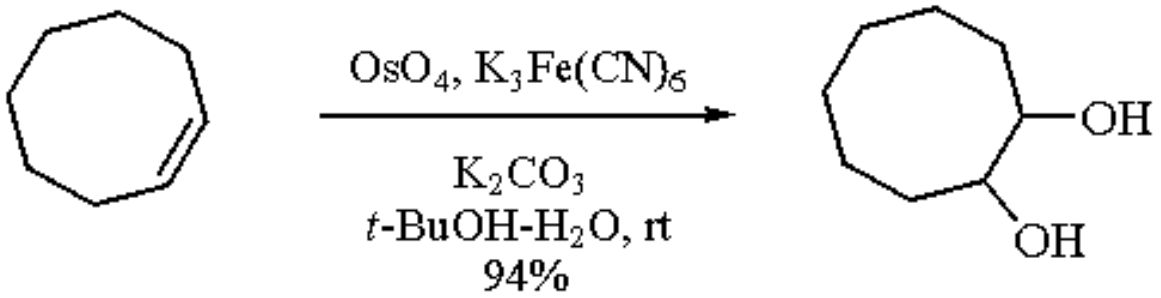

(10)

Other co-oxidants, such as sodium or potassium chlorate,[19] ***Hydrogen Peroxide*** in *t*-butyl alcohol,[20] ***t-Butyl Hydroperoxide*** under alkaline conditions,[21] and amine *N*-oxides,[22] have also been used for this purpose. Although catalytic *cis*-dihydroxylation using perchlorates or hydrogen peroxide usually gives good yield of diol, over-oxidation is difficult to avoid. Both $K_3Fe(CN)_6$ and ***N-Methylmorpholine N-Oxide*** (NMO) have proven to be very mild and effective co-oxidants. However, $K_3Fe(CN)_6$ has been shown to be the most efficient oxidant in the osmium-catalyzed asymmetric dihydroxylation of prochiral alkenes with derivatives of dihydroquinidine (DHQD) and dihydroquinine (DHQ) as chiral ligands to give chiral diols. The use of this oxidant precludes the second cycle which gives very low enantioselectivity and leads to enantioselectivities not obtainable with the use of other oxidants (eqs 11 and 12).[23]

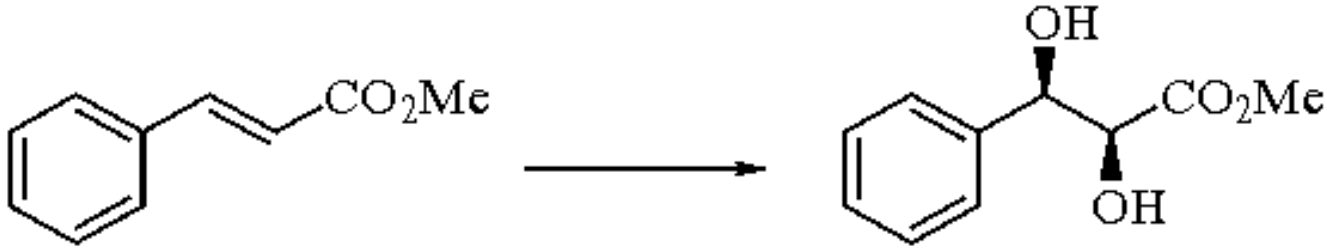

(11)

cat OsO_4, cat DHQD-*p*-chlorobenzoate
$K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH-H_2O, rt — 95% ee

cat OsO_4, cat DHQD-*p*-chlorobenzoate
NMO, acetone, water, 0 °C — 60% ee

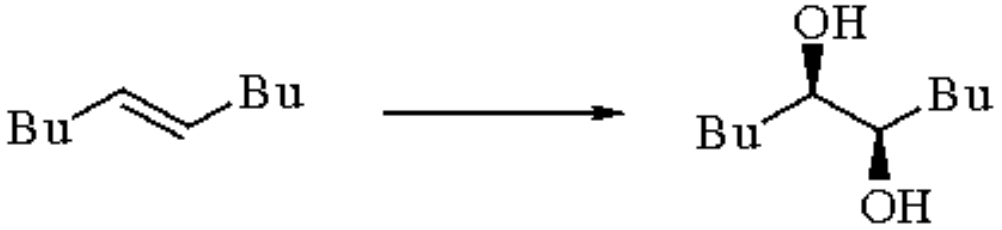

(12)

cat OsO_4, cat DHQD-*p*-chlorobenzoate
$K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH-H_2O, rt — 74% ee

cat OsO_4, cat DHQD-*p*-chlorobenzoate
NMO, acetone, water, 0 °C — 20% ee

Related Reagents.

Osmium Tetroxide; ***Osmium Tetroxide-Potassium Ferricyanide***.

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Potassium Fluoride[1]

KF

[7789-23-3] · FK · Potassium Fluoride · (MW 58.10)

(fluorinating reagent;[1] desilylating reagent;[11] base[29])

Physical Data: mp 846 °C; bp 1505 °C; *d* 2.48 g cm^{-3}; vapor pressure 1 mmHg at 885 °C.

Solubility: sol water, HF, NH_3; slightly sol alcohol; insol most organic solvents.

Form Supplied in: white to colorless crystals and powder.

Handling, Storage, and Precautions: anhydrous KF should be handled and used under dry N_2 for best results. KF reacts with acid to form the toxic gas hydrogen fluoride.

Fluorination Reagent.

Potassium fluoride is widely used as a fluorinating reagent to prepare various organic fluorides. Aromatic[1] or vinyl fluorides[2] activated by electron-withdrawing groups are readily prepared from an exchange reaction of KF with aromatic or vinyl chlorides in polar aprotic solvents such as DMF, DMSO, or tetramethylene sulfone. In the presence of Ph_4PBr[3] or phthaloyl difluoride,[4] the fluoride ion replaces not only chlorine but also the nitro group in activated nitrobenzenes in DMSO. Reaction of polychlorobenzenes with KF gives mono-, di-, and trifluorobenzenes, depending on the reaction conditions.[1f,5] Perfluorobenzene and perfluoropyridine have been available from chlorine-fluorine exchange reactions.[6] The best results are obtained from heating a mixture of perchloroaromatic substrates and KF in the absence of solvent at an elevated temperature. Displacement of halide by fluoride ion also occurs with alkyl halides,[7] particularly in the presence of CaF_2,[8] but it becomes more difficult with polychloroalkanes.

The chlorine-fluorine exchange reaction has been applied to prepare acyl or sulfonyl fluorides.[9] Aryl acyl fluorides, alkyl acyl fluorides and sulfonyl fluorides are readily obtained from the reaction of acyl or sulfonyl chlorides with KF in the presence of CaF_2 in MeCN at rt, although the reaction is slow with KF alone.[8] Perfluorinated analogs are more active and the exchange reaction with KF is completed within a few hours in MeCN at rt.[10]

Desilylating Reagent.

Due to formation of a strong silicon-fluorine bond, KF readily reacts with trialkylsilyl ethers[11] or acyl,[12] alkyl,[13] vinyl,[14] and alkynyl[15] silanes to remove the trialkylsilyl group. In the presence of a leaving group in the β-position, the silanes undergo smooth β-elimination reactions with KF in DMSO. Alkenes are obtained from saturated silanes (eq 1),[16] and alkynes[17] and allenes (eq 2)[18] are produced from vinyl silanes. Silylvinyl triflates are decomposed with KF and a crown ether at -20 °C to give vinylidene carbenes in essentially quantitative yield and which can be trapped by alkenes to give cyclopropanes (eq 3).[19]

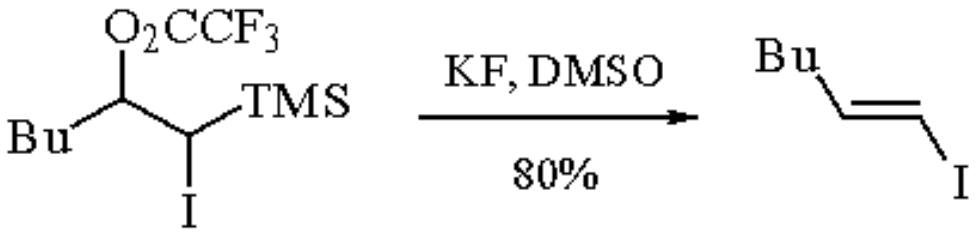

(1)

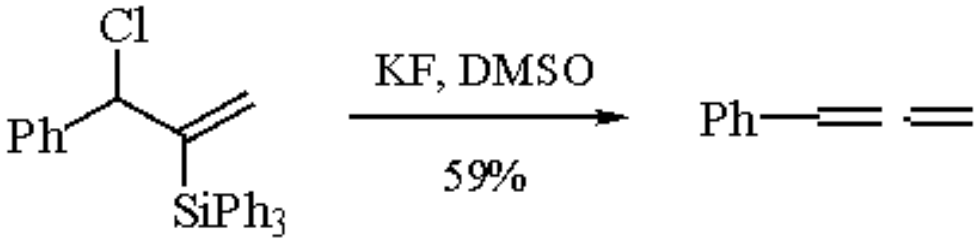

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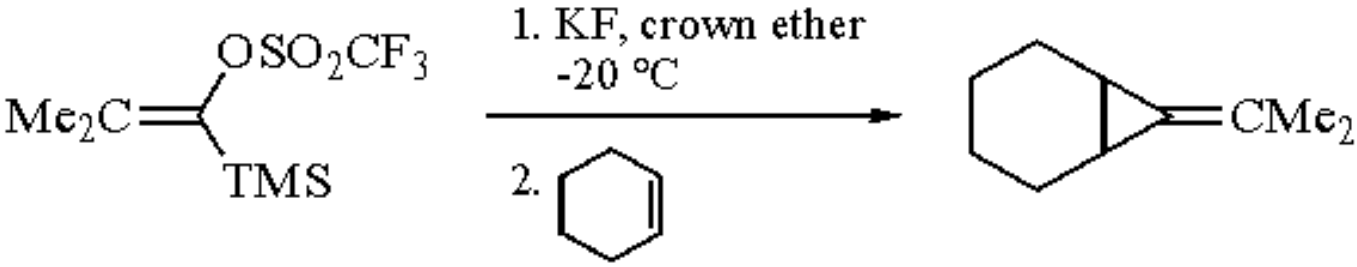

(3)

Vinyl trialkylsilyl ethers liberate ketones or aldehydes with KF and a proton source.[20] In the presence of a carbonyl group, aldol condensation occurs to give β-hydroxy ketones (eq 4).[21] The intramolecular aldol reaction also goes smoothly to produce a cyclic product (eq 5).[22]

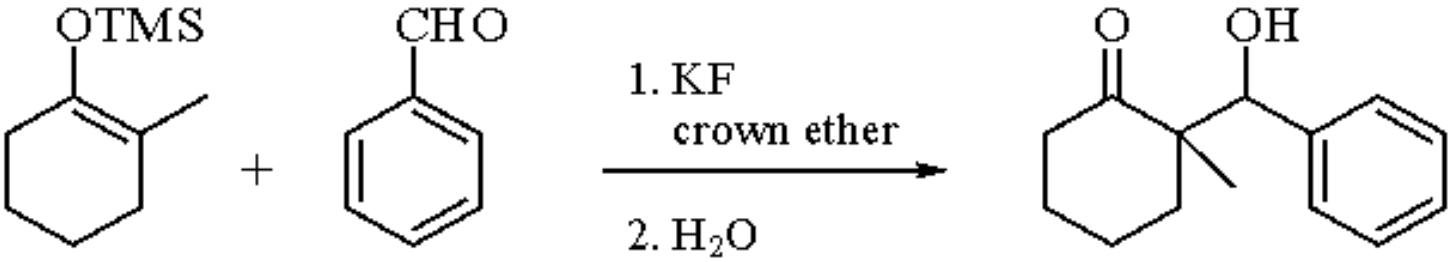

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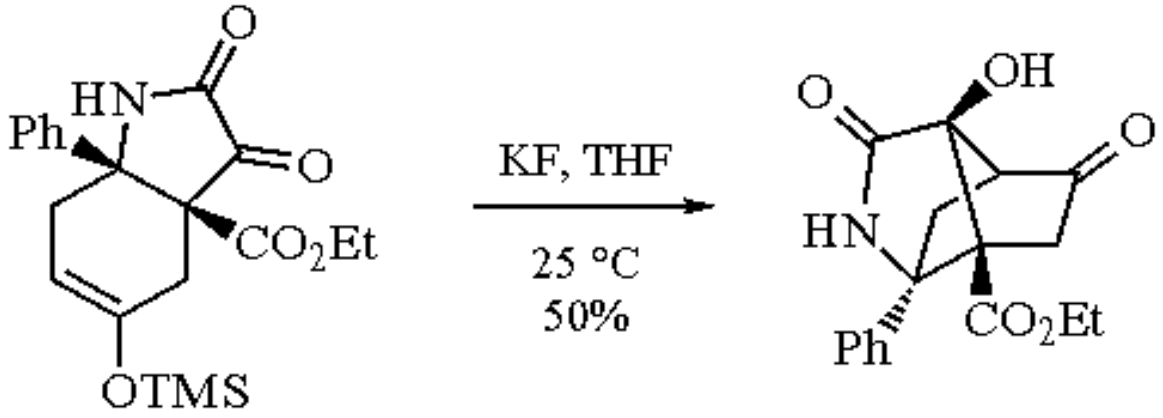

(5)

In the presence of KF, perfluoroalkyl-[23] or perfluorophenyltrimethylsilanes[24] react with aldehydes, ketones, and acyl fluorides to give fluoro alcohols (eq 6). Sulfones were obtained in good yields when sulfonyl fluorides were used as substrates. These reactions usually proceed in aprotic solvents, such as MeCN and PhCN, at or near rt.

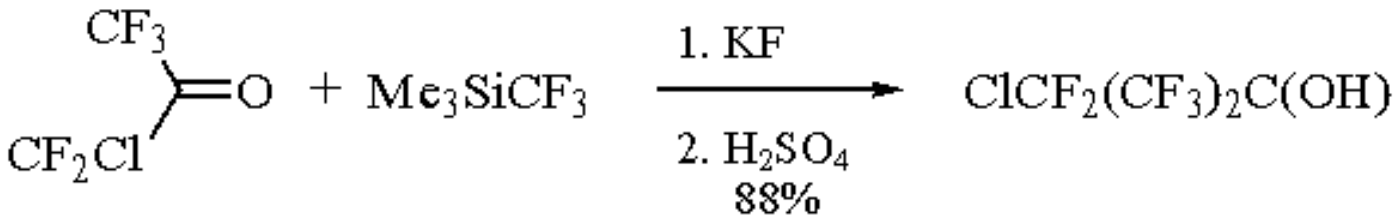

(6)

Certain carbon-silicon bonds can be oxidized with 30% ***Hydrogen Peroxide*** and KF to give the corresponding alcohols in good yields.[25] This method is applicable to one-pot synthesis of anti-Markovnikov alcohols from terminal alkenes by hydrosilylation and oxidation (eq 7).[26] The oxidizing ability of 90% H_2O_2 is only slightly greater than that of 30% H_2O_2; 70% ***t-Butyl Hydroperoxide*** is less active. Although ***m-Chloroperbenzoic Acid*** also works well, 30% H_2O_2 is more economical and the reaction is cleaner. The stereochemistry of the reaction center is retained under these conditions (eq 8).[27] Various chiral diols are available by asymmetric catalytic intramolecular hydrosilylation of internally substituted alkenes using Rh complexes as catalysts, followed by oxidation with H_2O_2 and KF (eq 9).[28] Vinylsilanes are also oxidized with H_2O_2 and KF to give ketones.[26]

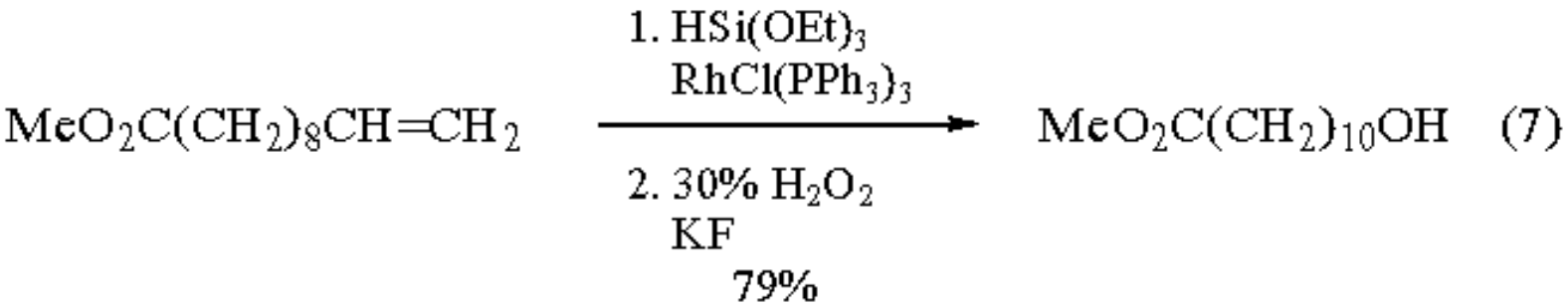

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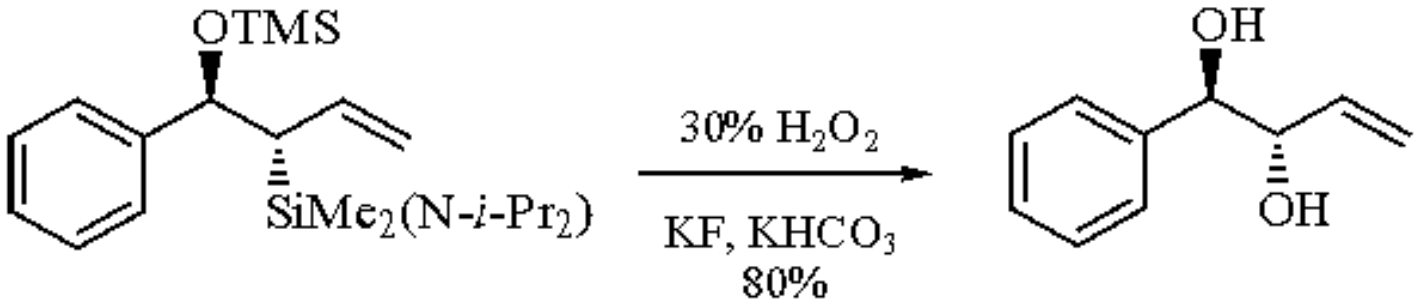

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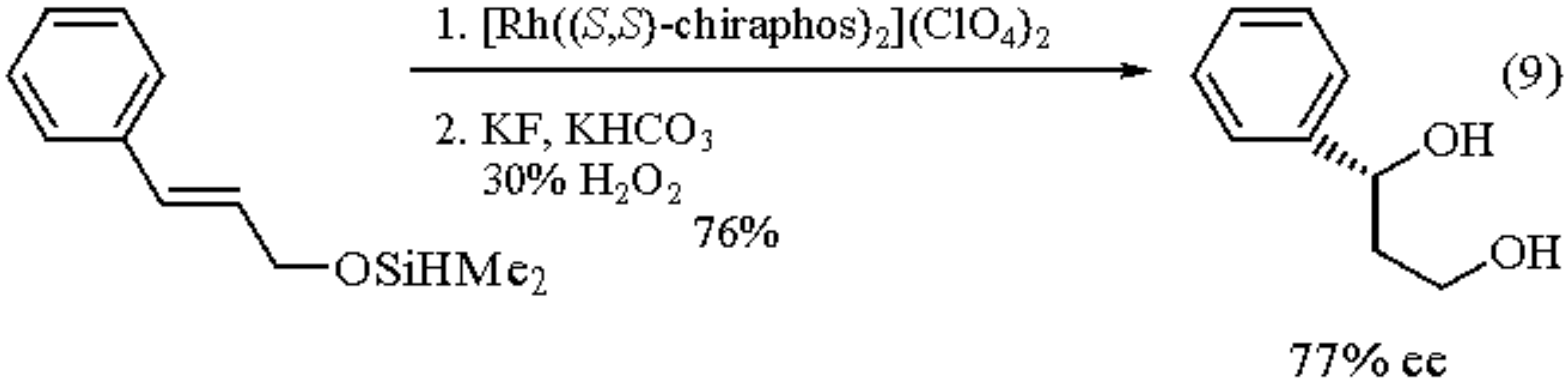

(9)

KF promotes carbonylative coupling reactions of organofluorosilanes with aryl iodides in the presence of a palladium catalyst (eq 10).[52]

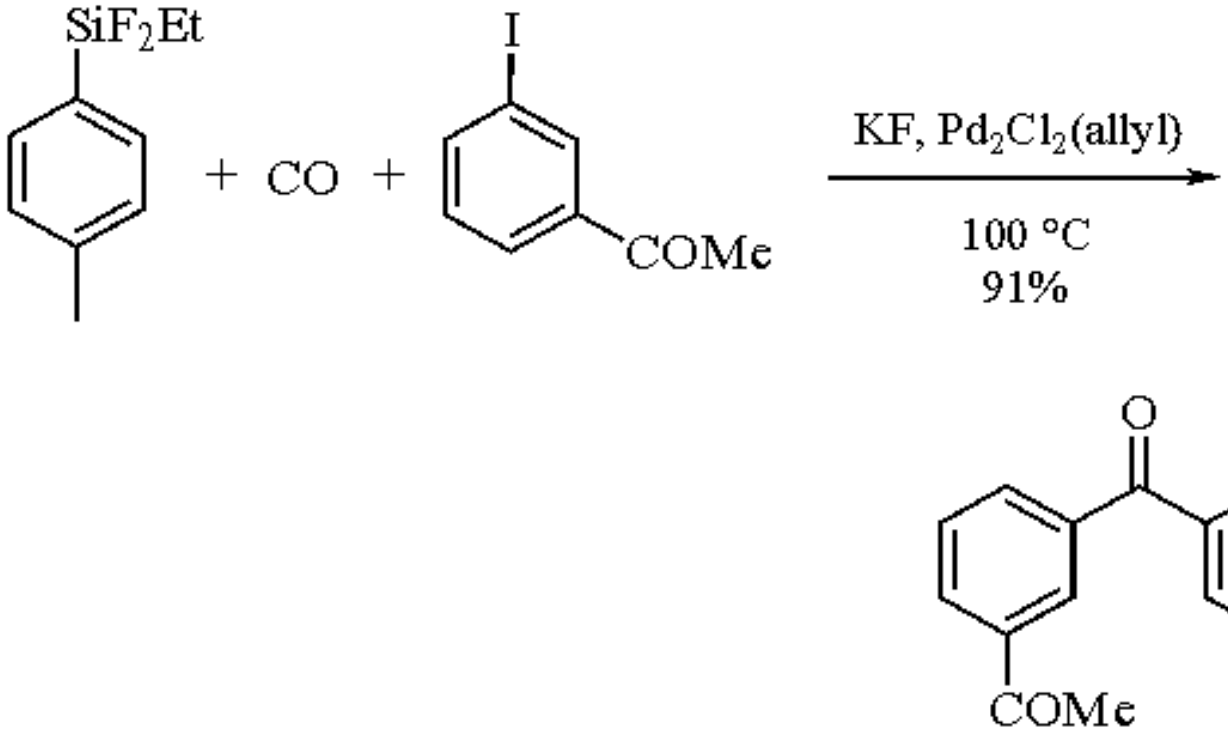

(10)

Use as a Base.[29]

KF in DMSO is a good dehydrohalogenation reagent for vinyl and alkyl halides to form alkynes,[30] allenes,[30] alkenes,[31] and dienes.[32] The presence of crown ethers facilitates the elimination reaction, particularly when MeCN is

used as a solvent.[30]

Alkylation of alcohols,[33] phenols,[34] thiols,[35] and amines[36] with alkyl halides is promoted by KF. This method has been applied to synthesis of crown ethers.[37] Heterocycles are also readily alkylated with allyl halides (eq 11).[38] Arylation of phenols with activated aryl fluorides has been accomplished by using KF as a catalyst.[39]

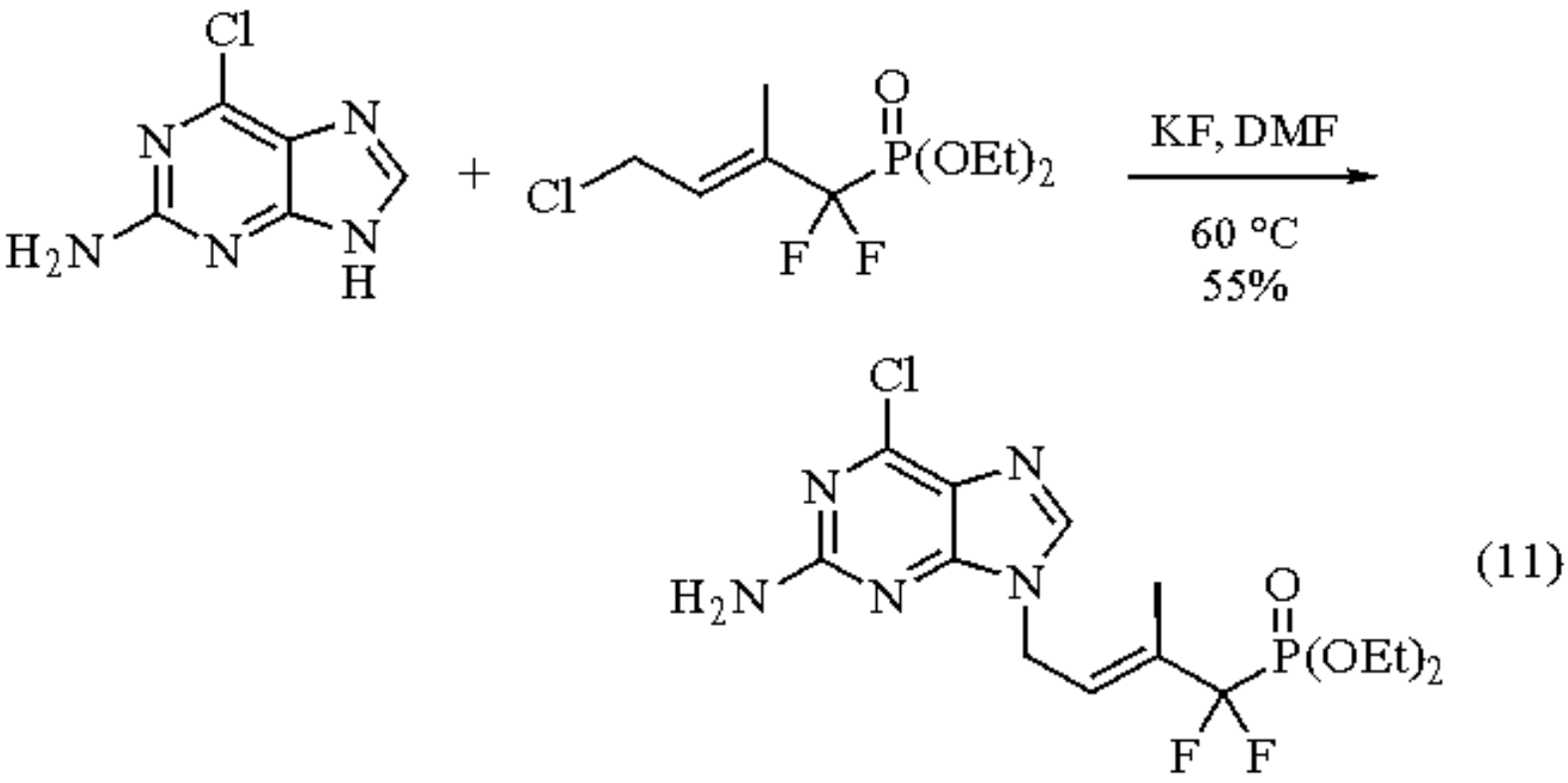

The conversion of carboxylic acids and alkyl halides to esters (eq 12) has proven especially useful since employment of KF gives high yields of products.[39] This reaction may be conducted by using the reactant acid as the bulk solvent; DMF can be used as a solvent when starting acids are solids.[40] The alkyl iodides are the most reactive substrates.[35]

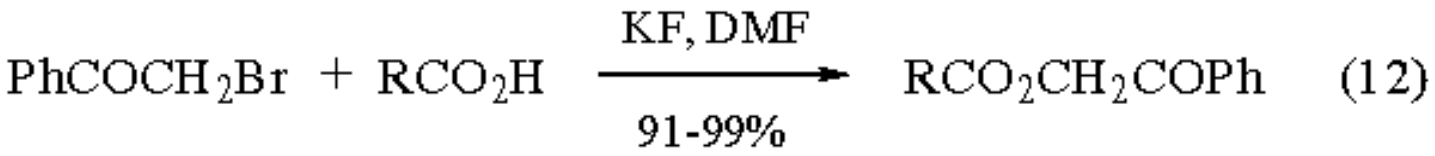

KF is widely used as a catalyst in Michael additions and aldol and Knoevenagel condensations. The use of KF has several advantages: a strong base is not required; catalytic amounts of KF are sufficient; separation of the catalyst is easy; yields are high with high selectivity; and the reactions are often successful when other strong bases are ineffective. Nitro compounds,[41] nitriles,[42] esters,[43] 1,3-diketones,[44] and heterocycles such as imidazoles (eq 13)[45] are usually used as Michael addition donors, and α,β-unsaturated aliphatic ketones, esters, nitro compounds, and nitriles are employed as the acceptors. Protic solvents such as ethanol are the most common, presumably due to the good solubility of KF in these solvents.[46] MeCN and benzene are also employed, but the presence of a crown ether such as ***18-Crown-6*** is necessary for this reaction.[47]

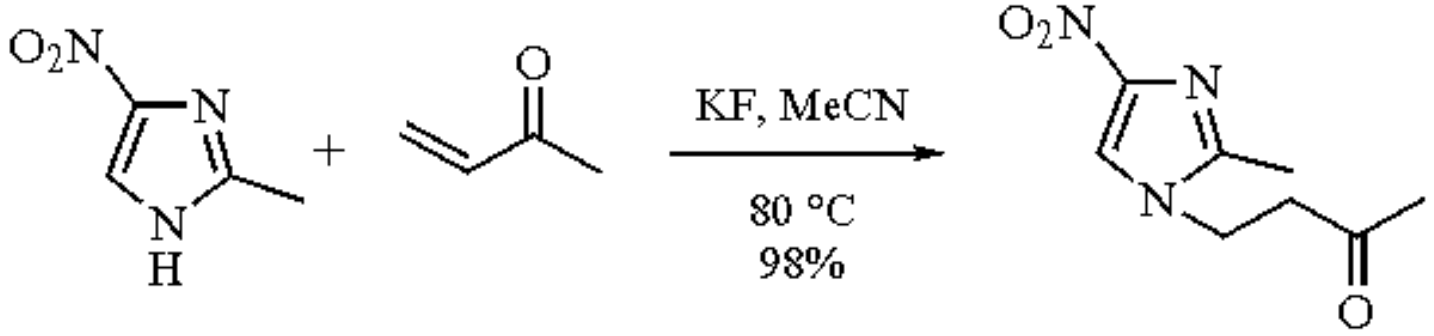

(13)

Various nitro alcohols are obtained by aldol condensation of nitroalkanes with aldehydes.[48] At elevated temperatures, the Knoevenagel reaction occurs to give unsaturated products (eq 14).[49] The cyclization of 1,4-diketones to cyclopentenones is also achieved with KF and a crown ether in refluxing xylene (eq 15).[50] Aromatic compounds are, however, usually obtained upon treatment of 1,3-diketones with KF in DMF (eq 16).[51] Reaction of 1,2-diketones with KF/DMF gives 1,4-benzoquinone derivatives (eq 17).[51]

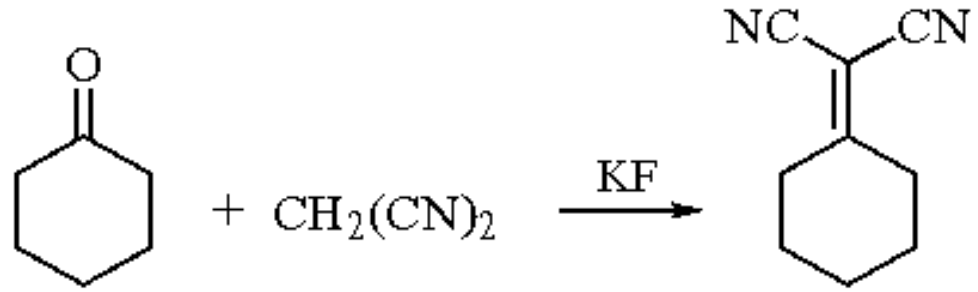

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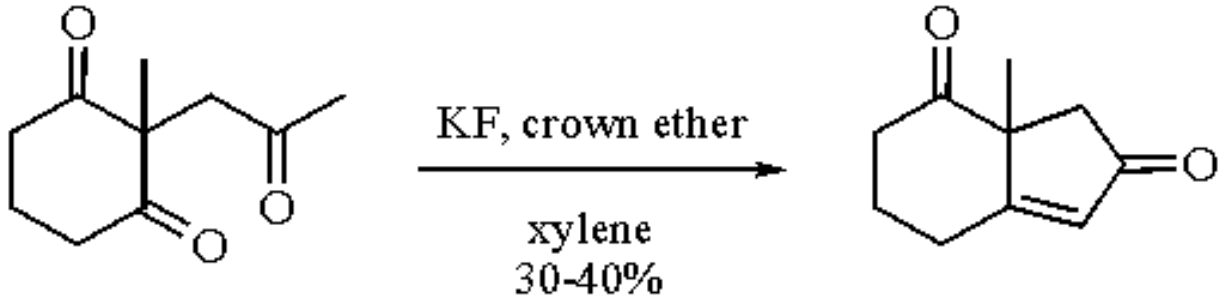

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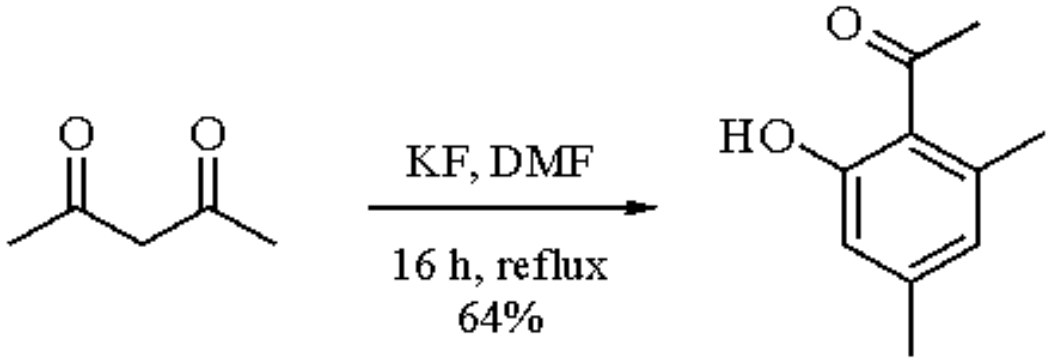

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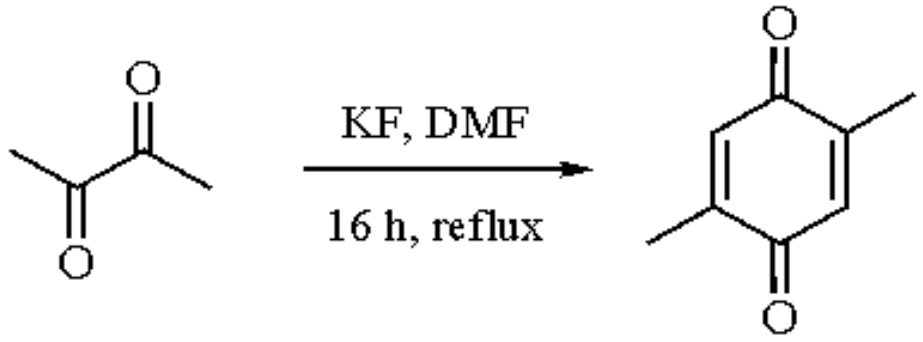

(17)

Related Reagents.

Lithium Fluoride; ***Potassium Fluoride-Alumina***; ***Potassium Fluoride-Celite***.

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DuPont Merck, Wilmington, DE, USA

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Potassium Fluoride-Alumina[1]

KF/Al_2O_3

(KF)

[7789-23-3] · FK · Potassium Fluoride-Alumina · (MW 58.10) (Al_2O_3)

[1344-28-1] · Al_2O_3 · Potassium Fluoride-Alumina · (MW 101.96)

(demethylation and desilylation of phenol ethers;[1,2] a solid base catalyst for elimination,[3] addition,[17] and condensation reactions[3])

Form Supplied in: white powder.

Preparative Method: to a stirred solution of ***Potassium Fluoride*** (20 g) in water (150 mL) is added neutral ***Alumina*** (60-80 mesh, 30 g) in water (150 mL); after 30 min the water is then evaporated in a rotary evaporator at ~60 °C. When most of the water has been removed, the remaining mixture is heated to 140-150 °C and maintained at that temperature under vacuum (5 mmHg) for 6 h to give 50 g of KF-alumina reagent.

Handling, Storage, and Precautions: anhydrous KF-alumina is usually handled and used in dry N_2 for best results, but in some cases a trace amount of water facilitates reactions. KF reacts with acid to form the toxic gas hydrogen fluoride. Use in a fume hood.

Deprotecting Reagent.

KF-alumina is an effective reagent for demethylation of methyl phenyl ethers. Heating various methyl phenyl ethers with KF-alumina at 210-215 °C gives phenols. Ethyl phenyl ethers, alkyl methyl ethers, and methylamines do not react with KF-alumina (eq 1).[1] It is also used to remove *t*-butyldimethylsilyl groups from aryl ethers at rt, whereas benzyl *t*-butyldimethyl ethers and 2-(trimethylsilyl)ethoxymethyl ethers of phenols are stable to the reagent (eq 2).[2]

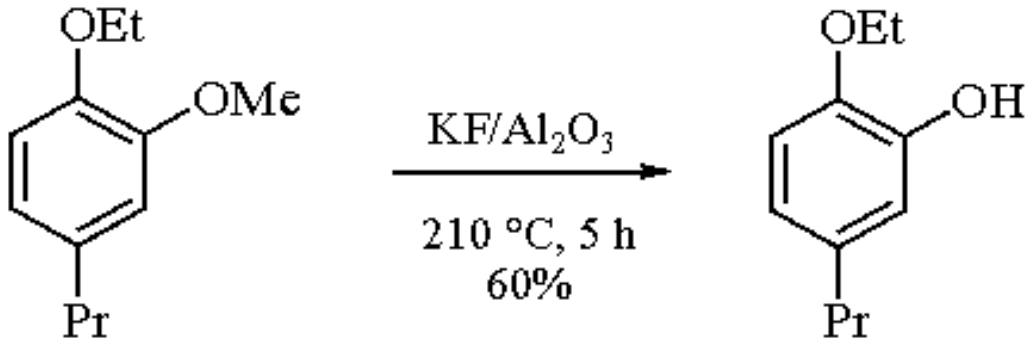

(1)

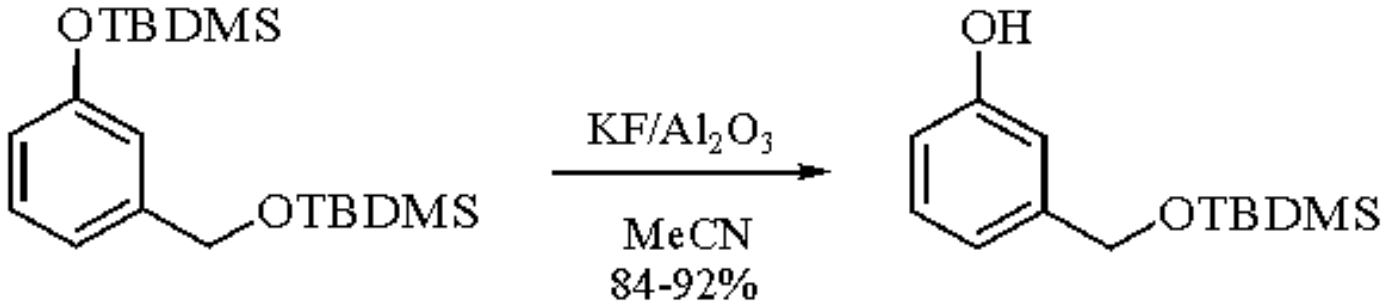

(2)

Use as a Base.

KF-alumina reagent is a stronger base than KF alone, and it is used as a solid base for eliminations,[3] alkylations, additions, isomerizations,[4,5] and condensations.[3] These reactions can be carried out without any solvent, but addition of a trace amount of water facilitates some reactions, such as Wittig and Wittig-Horner reactions.[6]

Phenethyl bromides react with KF-alumina to give the corresponding alkenes in good yield. Vinyl bromides or dibromides afford alkynes. However, when simple alkyl halides are used as substrates, hydrolysis becomes the main reaction and alcohols are obtained along with the desired alkenes.[3]

KF-alumina promotes alkylations of amides, lactams, and N-heterocycles in MeCN or DME at rt.[7] The alkylations occur exclusively at nitrogen atoms. In addition to simple acyclic amides, cyclic amides of various ring sizes are readily alkylated in excellent yields (eq 3). Methylation of uracil and xanthine derivatives is very effective (eq 4).[7] Arylation of phenols, thiophenols, and anilines with fluorobenzonitriles is also achieved by using KF-alumina as a catalyst.[8]

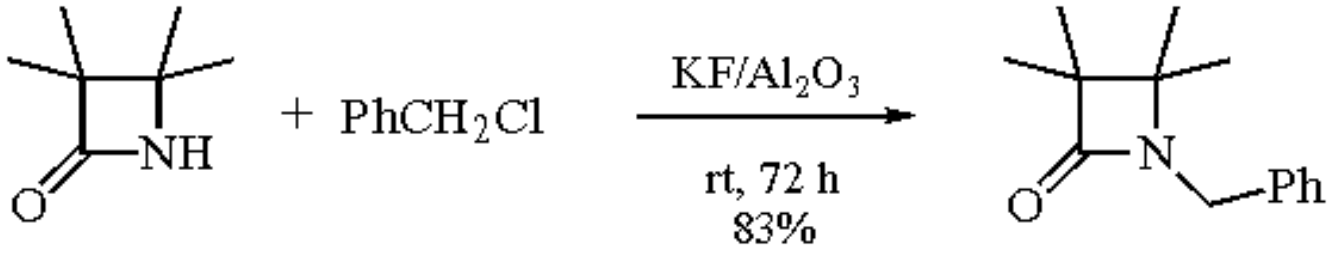

(3)

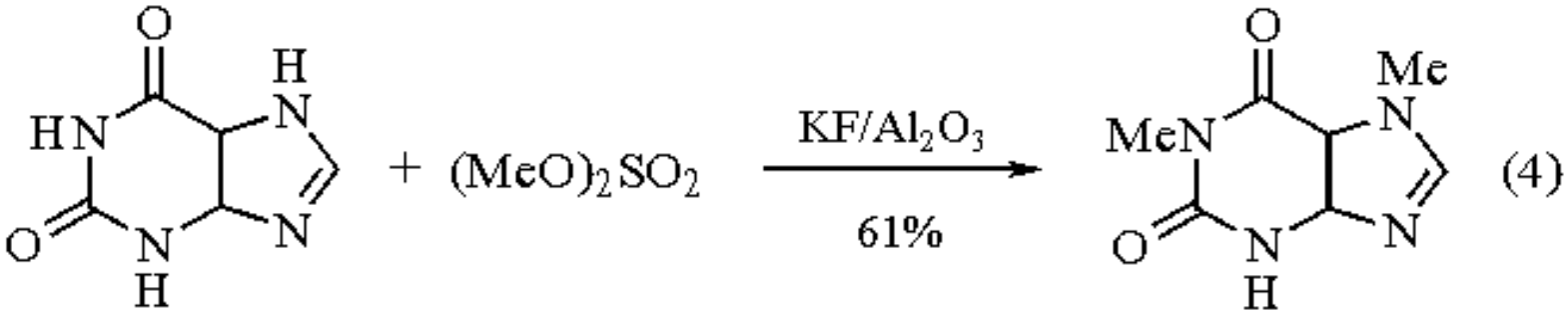

1-Hydroxyalkane phosphonic esters are readily available from KF on alumina catalyzed addition of dialkyl phosphites to aldehydes or activated ketones.[9] By using KF-γ-alumina, the addition proceeds smoothly with nonactivated ketones such as dialkyl, diaryl, and aryl alkyl ketones at rt (eq 5).[10] Reactions of nitroalkanes with aldehydes also occur to give 2-nitroalkanols.[11] The reaction times are shorter than with alumina alone so that aromatic nitroalcohols are readily obtained without dehydration to nitroalkenes.

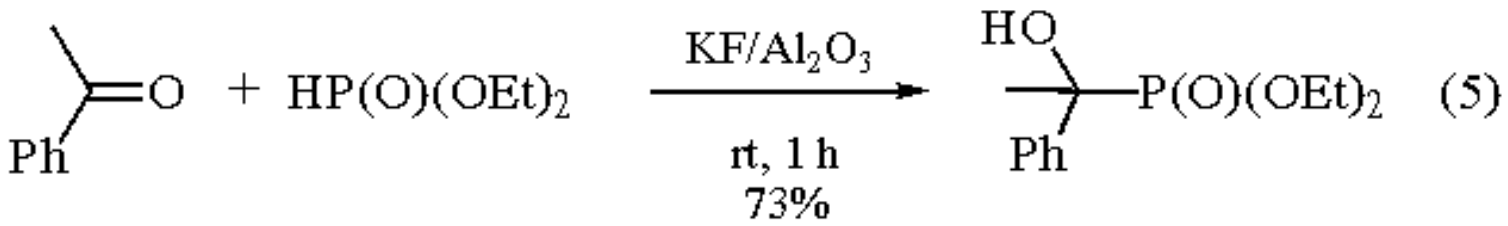

Michael addition proceeds readily at rt or below in the presence of catalytic amounts of KF-alumina.[3,12] Aprotic solvents, such as THF and MeCN, are mostly used, in contrast to employment of KF alone as a catalyst in protic solvents.[13] Secondary nitroalkanes readily add to α,β-unsaturated esters with KF on neutral alumina while primary nitroalkanes give byproducts resulting from multiple Michael additions.[14] When basic alumina is used as the support, the side reaction can be avoided and the reaction proceeds well with α,β-unsaturated ketones and acrylate esters.[14] With α,β-unsaturated α-cyano esters and α,β-unsaturated α-cyano nitriles, cyclopropane derivatives are formed (eq 6).[15] On the other hand, reactions of secondary nitroalkanes with α,β-unsaturated keto esters and sulfones give dihydrofurans instead of cyclopropanes (eq 7).[16] When primary nitroalkanes are used as Michael addition donors, the major products are furans along with dihydrofurans as byproducts (eq 8).[16] The isoxazoline *N*-oxides are available from nitroalkenes (eq 9).[16]

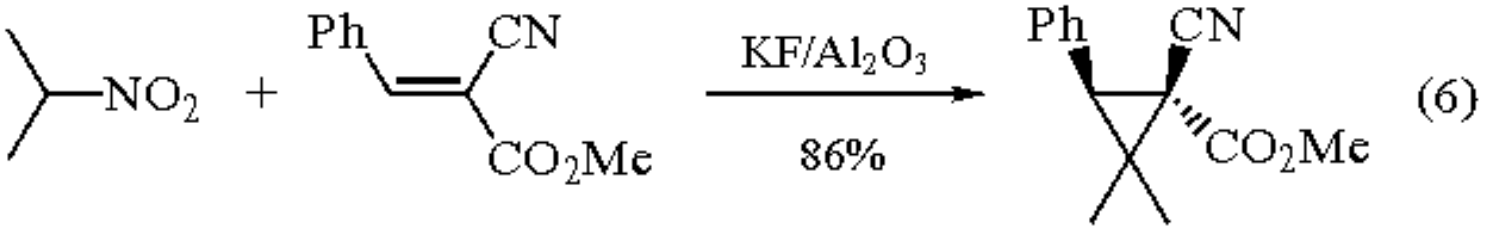

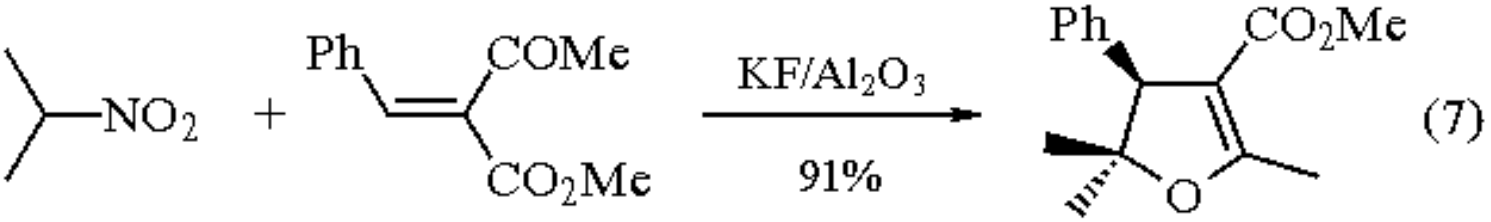

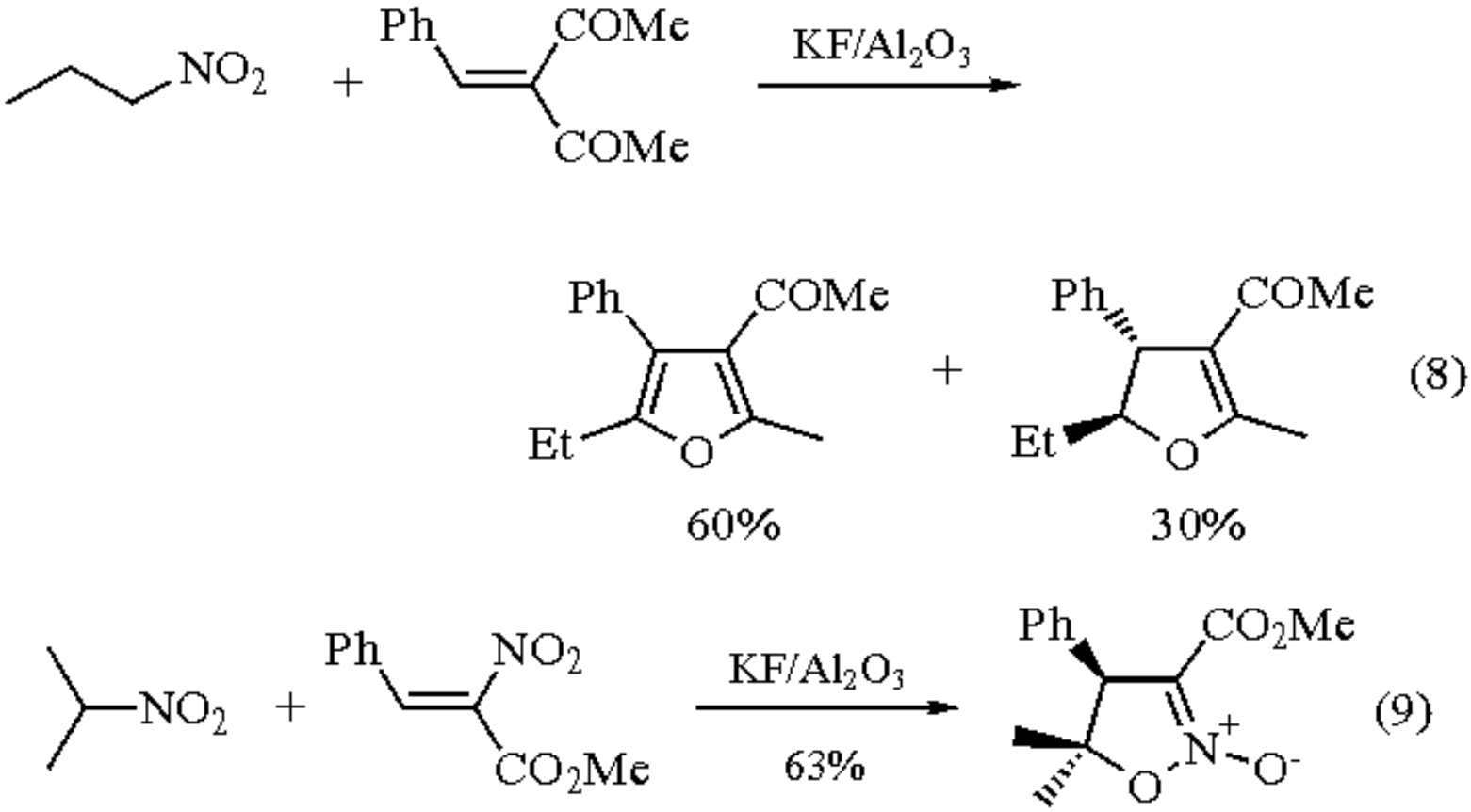

KF-alumina is an efficient base for condensation of active methylene groups with carbonyl compounds. Reaction of various sulfones[17] and phosphonates[6] containing active methylene groups with aldehydes in the absence of solvent under microwave irradiation gave α,β-unsaturated sulfones and phosphonates, respectively (eqs 10 and 11). However, condensation of malononitrile and acetone gives a 2-azabicyclo[2.2.2]octane derivative in 92% yield; presumably the initial product is isopropylidenemalononitrile, which undergoes KF-alumina-catalyzed Michael addition and cyclization reactions to give the final cyclic product (eq 12).[18] Even less acidic methylene compounds condense with aldehydes to afford alkenes (eq 13).[19] Under similar conditions, trimethylsulfonium iodide[6] or arsonium salts[20] react with aldehydes to give epoxides (eq 14).

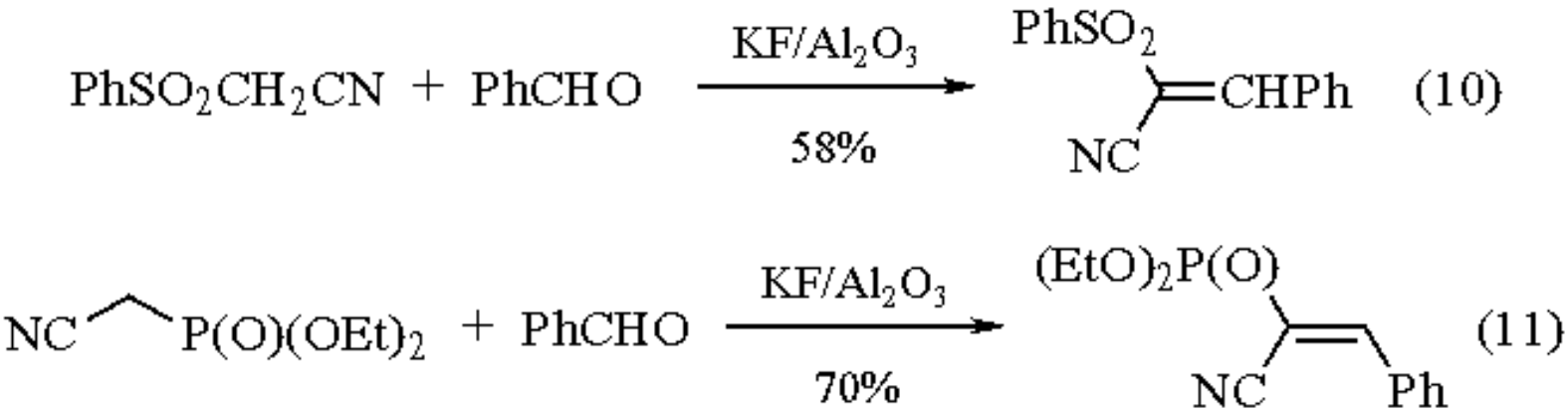

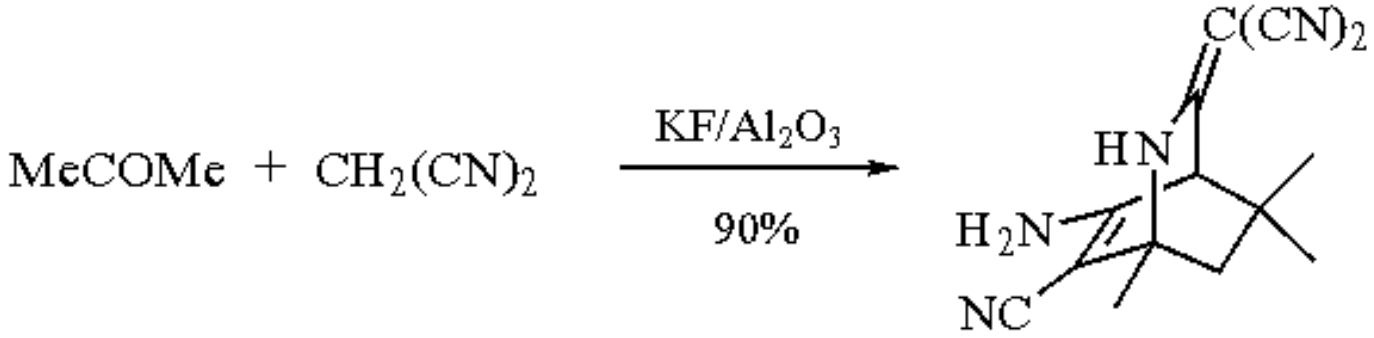

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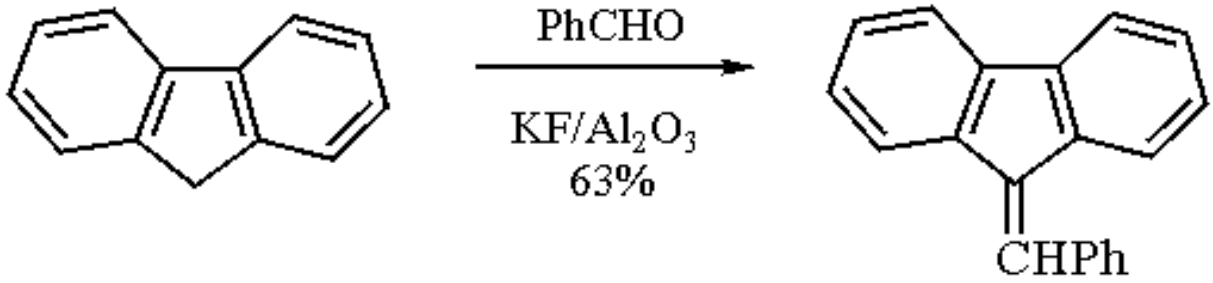

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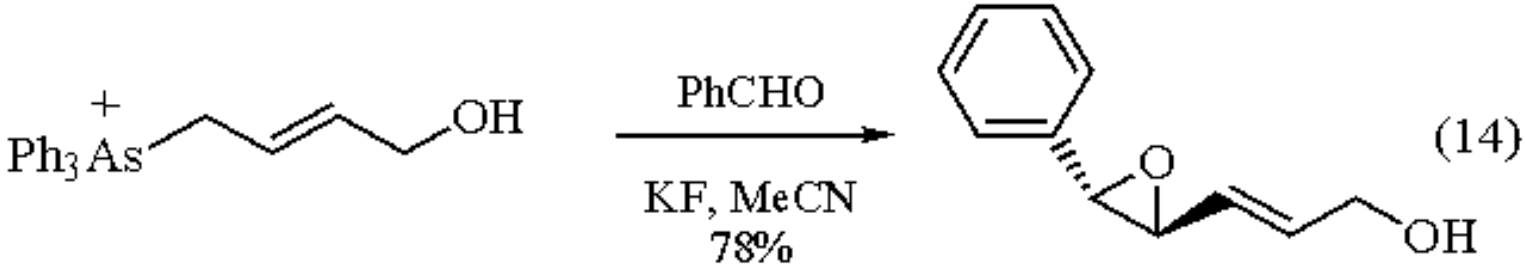

(14)

α-Diazo ketones and esters can be prepared by KF-alumina-catalyzed diazo transfer reactions of tosyl azide with the ketones or esters (eq 15).[21]

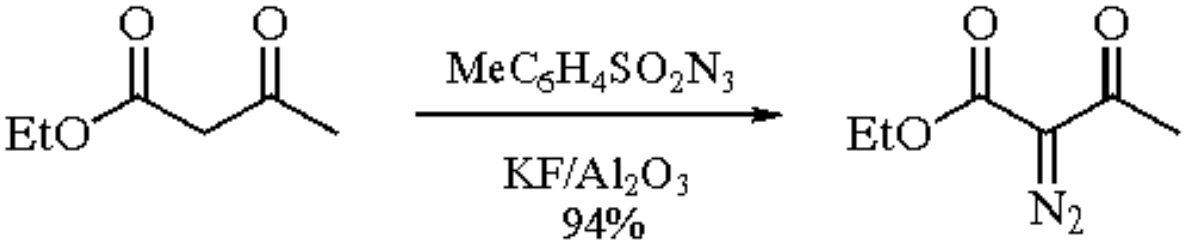

(15)

Condensations of active methylene compounds with carbon disulfide lead to ketene thioacetals under KF-alumina catalysis. Various α-keto, α-cyano, and α-carboxyl ketene thioacetals,[22] as well as α-phosphonic ketene dithioacetals (eq 16),[23] are available from the reaction of active methylene compounds with ***Carbon Disulfide***, followed by methylation with ***Iodomethane***. The dithioacetals are also directly obtained by reaction of the methylene compounds with 2 equiv of *S*-methyl methanesulfonothioate under microwave irradiation.[24] α-Alkynic alcohols react with carbon disulfide to give 4-alkylidene-2-thione-1,3-oxathiolanes without solvent at rt (eq 17).[25] The presence of solvent in the previous reaction causes side reactions.[25] Aldehydes can be directly converted into the corresponding nitriles by treatment with carbon disulfide, KF-alumina, hydroxylamine, and HCl in one pot (eq 18).[26] KF-alumina also promotes hydrolysis of nitriles into amides in refluxing butanol.[27]

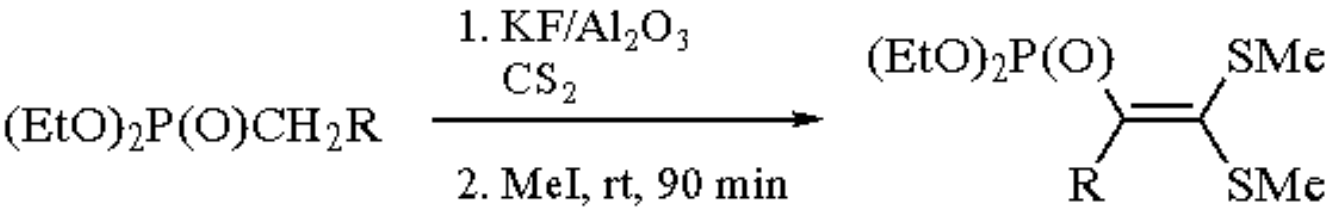

(16)

R = $(EtO)_2P(O)$ 95%
R = CO_2Et 85%

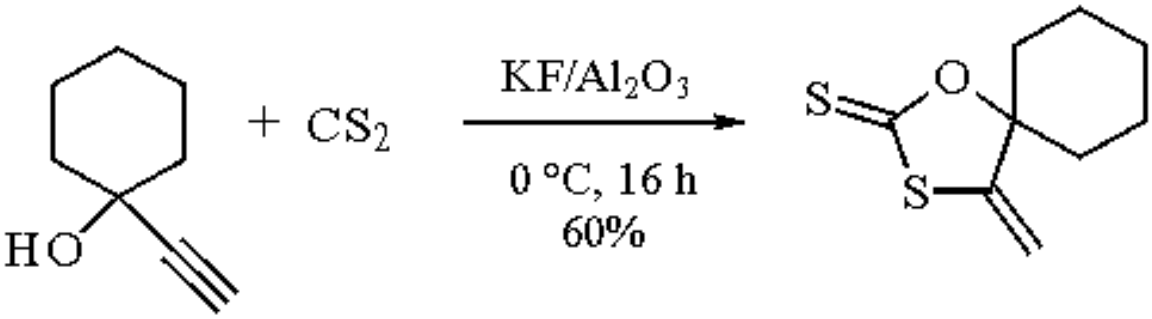

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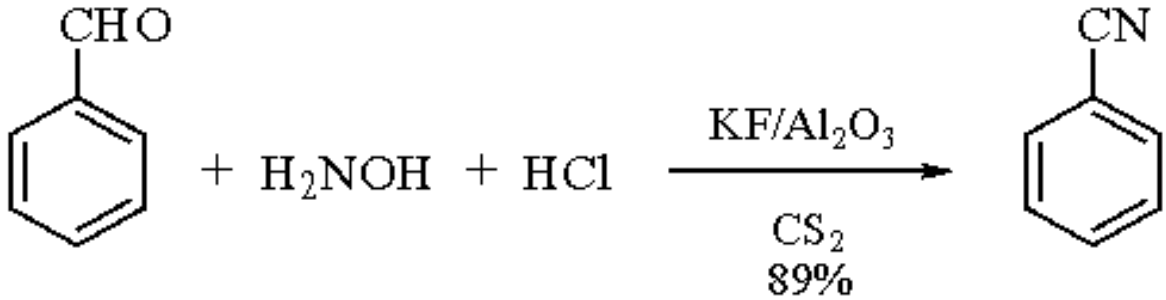

(18)

Related Reagents.

Lithium Fluoride; ***Potassium Fluoride***; ***Potassium Fluoride-Celite***.

---

1. (a) Clark, J. H. *CRV* **1980**, *80*, 429. (b) Radhakrishna, A. S.; Prasad Rao, K. R. K.; Suri, S. K.; Sivaprakash, K.; Singh, B. B. *SC* **1991**, *21*, 379.
2. Schmittling, E. A.; Sawyer, J. S. *TL* **1991**, *32*, 7207.
3. Yamawaki, J.; Kawate, T.; Ando, T.; Hanafusa, T. *BCJ* **1983**, *56*, 1885.
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5. Bhujanga Rao, A. K. S.; Gundu Rao, C.; Singh, B. B. *SC* **1991**, *21*, 443.
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8. Schmittling, E. A.; Sawyer, J. S. *JOC* **1993**, *58*, 3229.
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10. Texier-Boullet, F.; Lequitte, M. *TL* **1986**, *27*, 3515.
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19. Villemin, D.; Ricard, M. *TL* **1984**, *25*, 1059.
20. Wang, W. B.; Shi, L. L.; Li, Z. Q.; Huang, Y. Z. *TL* **1991**, *32*, 3999.
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Potassium Fluoride-Celite[1]

KF/Celite

(KF)

[7789-23-3] · FK · Potassium Fluoride-Celite · (MW 58.10) (Celite)

[61790-53-2]

(mild heterogeneous basic catalyst for alkylation[1] and Michael addition[5])

Form Supplied in: white solid.

Preparative Method: ***Celite*** 545 (20.0 g) is mixed with ***Potassium Fluoride*** (20.0 g) in water (500 mL), and the water removed at 50-60 °C in a rotary evaporator. The solid obtained is then shaken in MeCN (100 mL), filtered, washed with two portions (50 mL) of MeCN and dried in a desiccator at rt.

General Discussion.

The main use of KF/Celite is as a catalyst for alkylation with alkyl halides. The alkylation proceeds smoothly with aniline, amines, and thiophenol in MeCN between rt and 70 °C, dependent on reactivity of the alkyl halides.[1] Workup can be carried out under nonaqueous conditions: addition of ether, filtration, washing with ether, evaporation of the solvents, and distillation or recrystallization.[1] Alkylation of 1,3-diketones gives monoalkylated products.[1] 1,3-Indanedione gives rise to dialkylated 1,3-indanedione exclusively, even if less than 2 equiv of alkylating reagent are used (eq 1).[2]

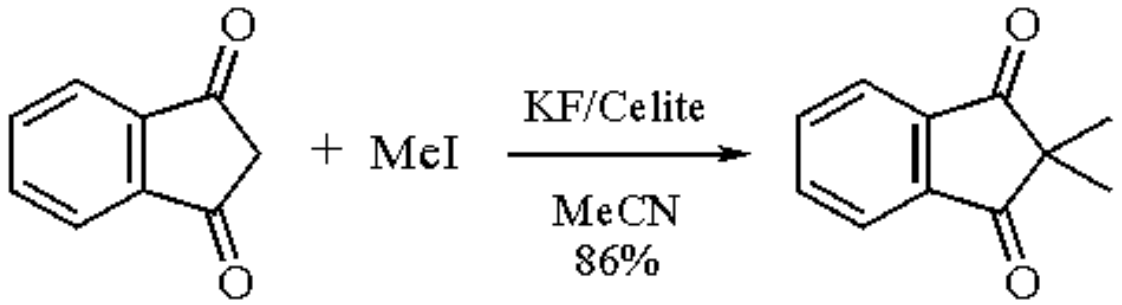

(1)

A nucleophilic aromatic substitution on activated nitro- or chlorobenzenes is effected by KF/Celite. Reaction of various 1,3-diketones with cyclopentadienyliron-complexed nitro- or chlorobenzenes gives the corresponding 1,3-diketone substituted products without deacetylated byproducts (eq 2).[3] In contrast, deacetylated byproducts are often observed using alternative methods unless precautions are taken during workup.[4]

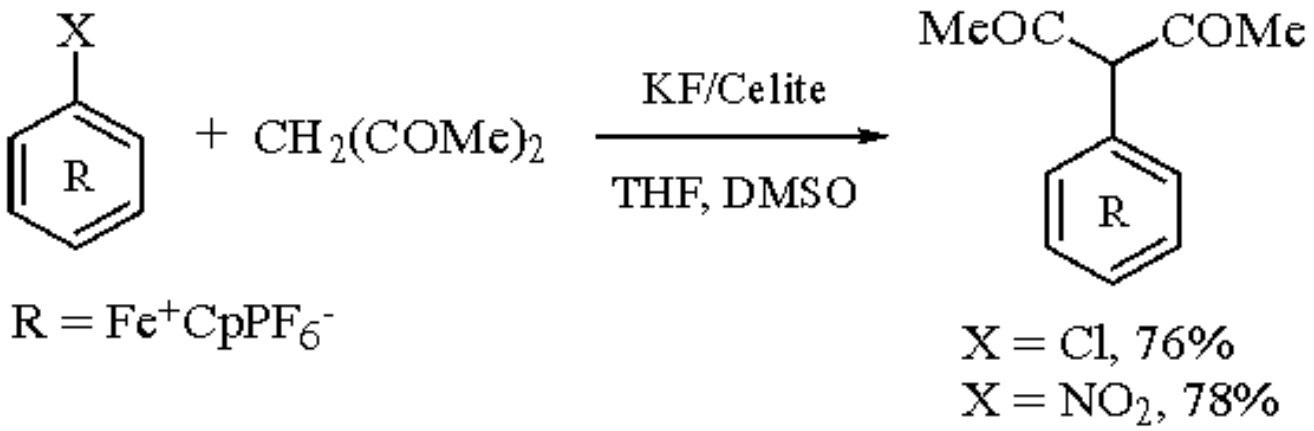

(2)

KF/Celite-catalyzed intramolecular Michael addition provides a new approach to flavanones. One example is the synthesis of bavachinin by intramolecular addition of a phenol group to an α,β-unsaturated ketone in methanol (eq 3).[5] Use of free KF, KF/alumina, and ***Tetra-n-butylammonium Fluoride*** in this reaction is less successful.[5]

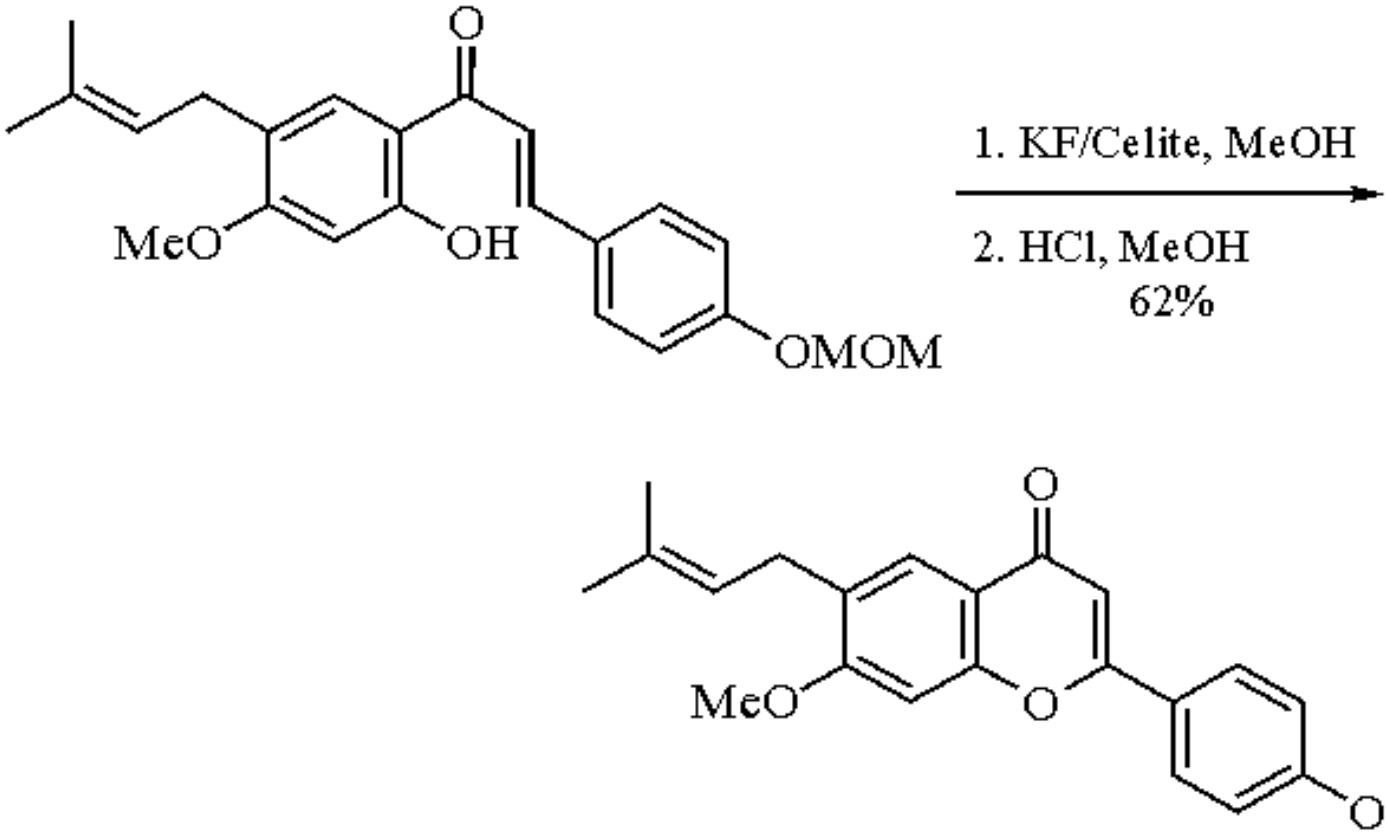

(3)

Related Reagents.

Lithium Fluoride; ***Potassium Fluoride***; ***Potassium Fluoride-Alumina***.

---

1. Ando, T.; Yamawaki, J. *CL* **1979**, 45.
2. Bloch, R.; Orvane, P. *SC* **1981**, *11*, 913.

3. Sutherland, R. G.; Abd-El-Aziz, A. S.; Piorko, A.; Lee, C. C. *SC* **1987**, *17*, 393.
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5. Harwood, L. M.; Loftus, G. C.; Oxford, A.; Thomson, C. *SC* **1990**, *20*, 649.

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Potassium-Graphite Laminate

[12081-88-8] · C_8K · Potassium-Graphite · (MW 135.18)

(powerful reducing agent for many functional groups;[1] metalating agent;[1] Lewis base;[1] hydrogenation catalyst;[1,2] catalyst for double bond isomerization and for anionic polymerization;[2] tool for preparing activated metals[1])

Physical Data: paramagnetic bronze-colored powder; *d* ~0.73 g cm^{-3}; interlayer distance 5.34 Å; all carbon layers are separated by one layer of potassium; space group D^6_2 *C*222.

Solubility: may be suspended in hydrocarbon and ethereal solvents; reacts violently with water, alcohols, and ammonia; THF, DME, 1,4-dioxane, and many arenes (e.g. benzene, toluene, pyridine, furan) are able to penetrate into the interlayer space, causing considerable swelling.

Preparative Methods: by stirring potassium and graphite powder at &egt;150 °C under argon without any solvent for 5-10 min. Natural as well as synthetic graphite are suited for its preparation.

Handling, Storage, and Precautions: pyrophoric and must be handled under argon in thoroughly dried solvents. Small quantities should be weighed in a glove box; it can be stored under argon without any significant loss in activity for extended periods of time.

Introduction.

Potassium-graphite laminate may be regarded as a polymeric array of naphthalenide anions and effects almost any reaction that the latter would promote. A major advantage in using C_8K as a substitute for ***Lithium Naphthalenide***, for example, lies in its increased reactivity and the easy work-up, consisting of filtration of the graphite only instead of the sometimes tedious removal of naphthalene.[1] Moreover, C_8K-promoted reactions can be readily monitored by the characteristic color change from bronze of the reagent to black of the graphite host.[1]

Functional Group Reductions.

Alkyl chlorides and aryl halides are generally reduced to the corresponding hydrocarbons, whereas alkyl iodides afford Wurtz-type coupled products. Alkyl bromides show a reactivity pattern between alkyl chlorides and alkyl iodides. Single-electron transfer is an important pathway in these reductions, since characteristic radical

rearrangements are observed with hex-5-enyl halides as mechanistic probes (eq 1).[3] *vic*-Dihalides form alkenes in high yield (eq 2).[3,4] C_8K leads to reductive cleavage of the C-O bond of aryl ethers, whereas in sulfonate esters the S-O rather than the C-O bond is broken selectively, with formation of the parent alcohols (eq 3).[3] Aryl ether and C-Cl cleavage can be done simultaneously, thus allowing the ready destruction of toxic polyhalodibenzodioxines or -dibenzofurans at rt.[5] Vinyl sulfones and allyl sulfones afford the corresponding alkenes (the latter after initial isomerization of their double bond) (eq 4).[6] The (*E*):(*Z*) ratio in these desulfuration reactions is low, with the (*E*)-isomer being slightly favored.

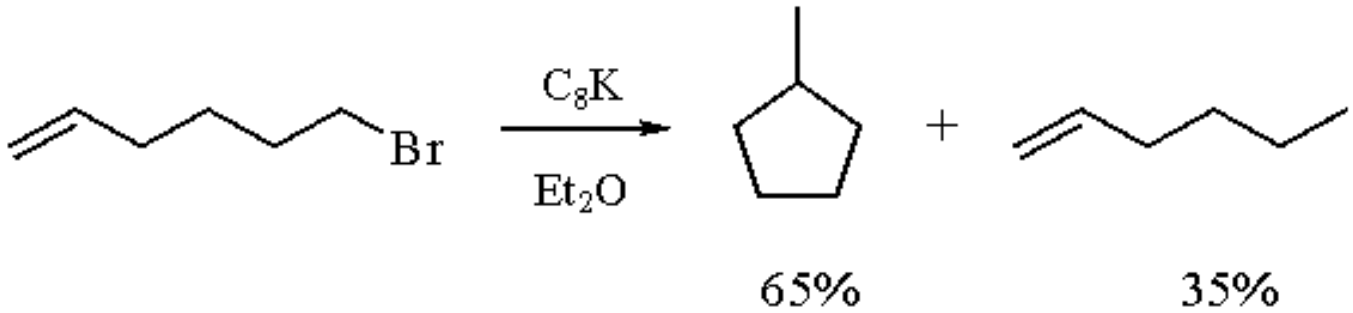

(1)

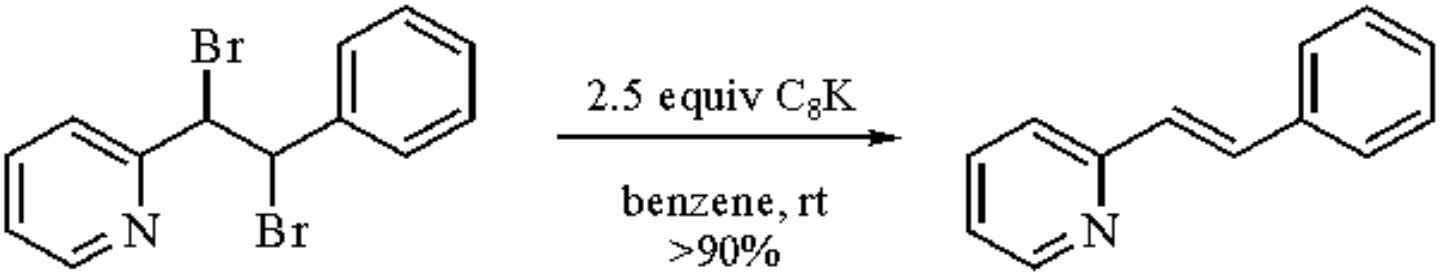

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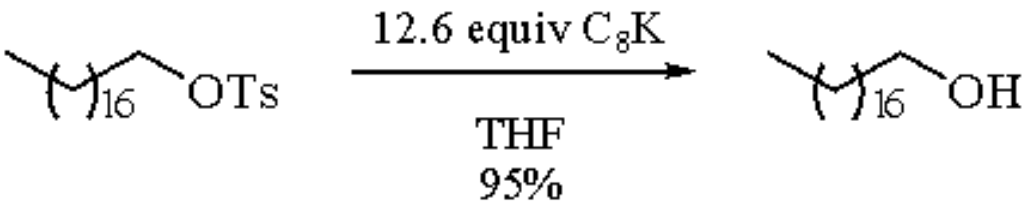

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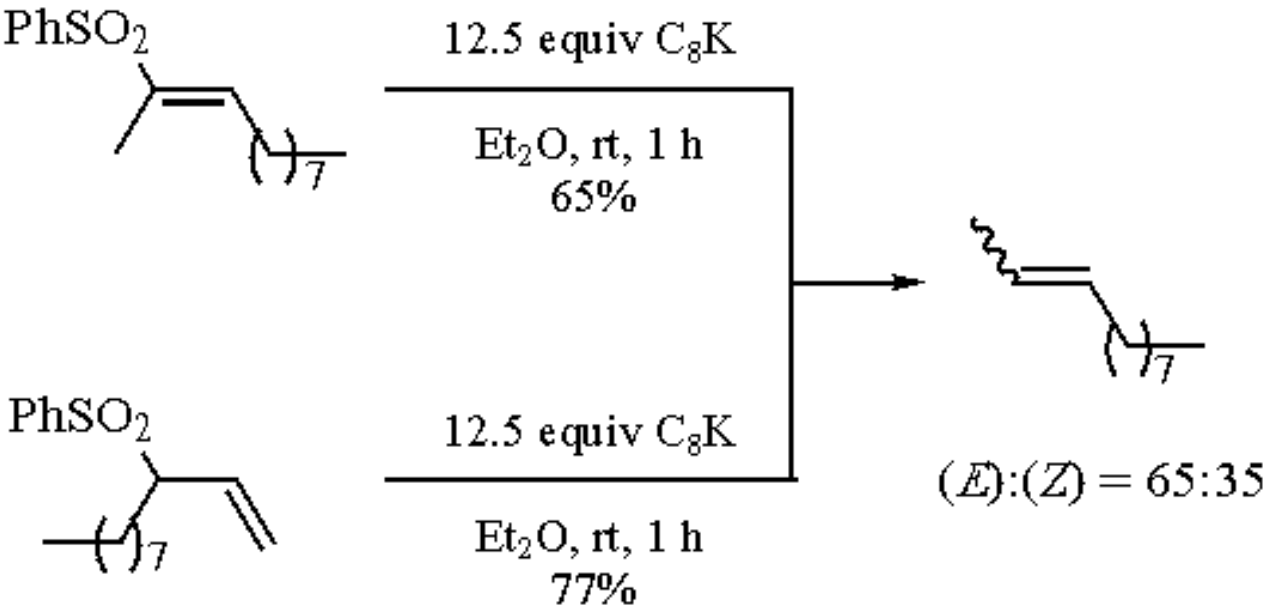

(4)

With ***Hexamethyldisilazane*** as cosolvent, C_8K in THF selectively reduces the double bond of enones at rt without affecting nonconjugated alkenes (eq 5).[7] α,β-Unsaturated acids are similarly reduced at 55 °C, while enoates give dimerization products. Imines afford amines in high yields with this reagent (eq 6),[7] whereas ketones may afford mixtures of alcohols and pinacols.[8] A large excess of the reagent is required to effect Birch-type reductions of arenes, as exemplified by a series of substituted naphthalene derivatives.[9] On treatment with C_8K in THF, benzil undergoes a unique coupling of the phenyl rings with formation of 9,10-phenanthrenequinone (eq 7).[10] This arene coupling can be extended to 2,3-diphenylquinoxaline and related heterocycles, which afford dibenzo[*a*,*c*]phenazine derivatives.[11]

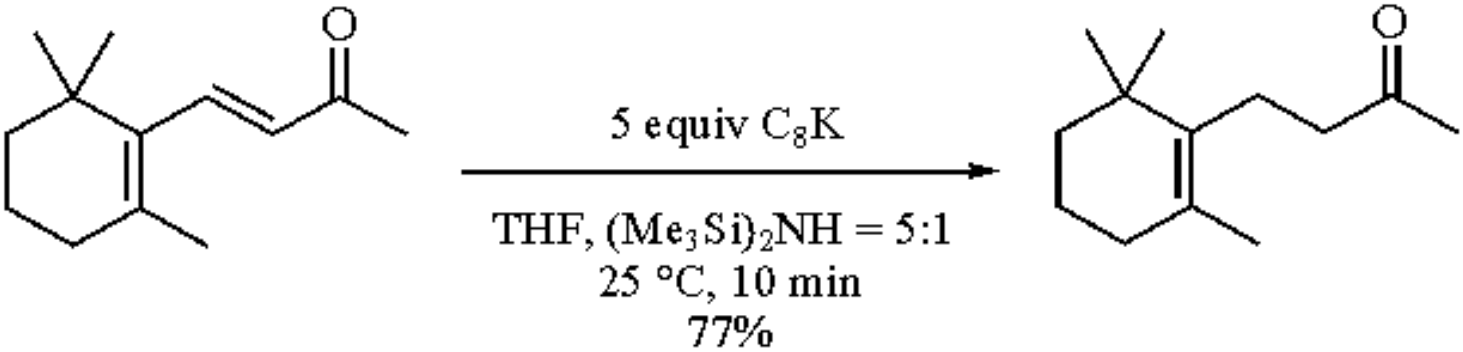

(5)

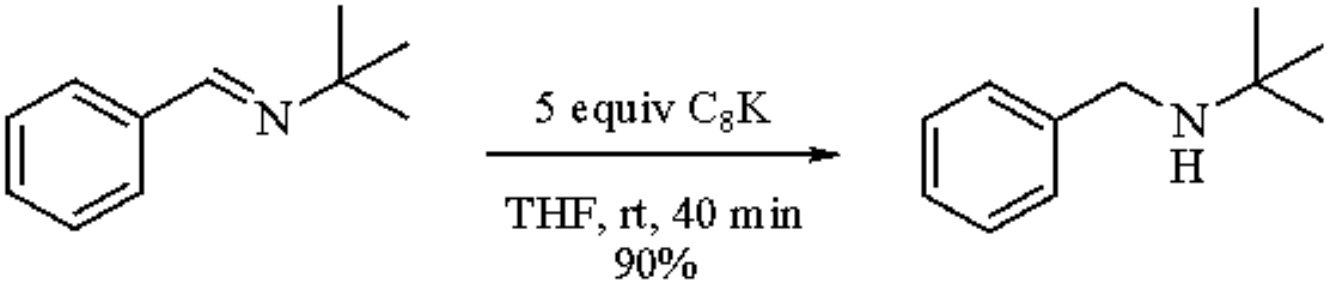

(6)

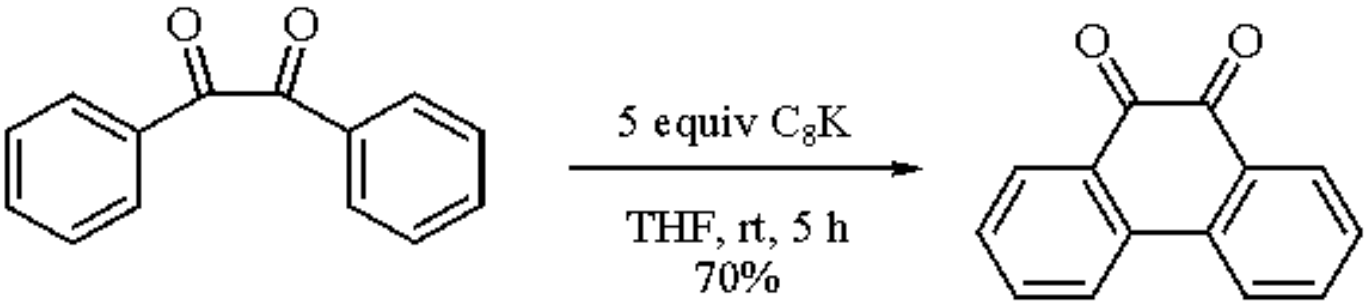

(7)

Although C_8K was considered for a long time to be of limited value in organic synthesis due to its high reactivity,[3] it turned out to be the reagent of choice for the synthesis of furanoid glycals in terms of yield, reaction rate, and flexibility. The intermediate potassium alcoholates, formed upon treatment of 2,3-*O*-alkylidene glycosyl halides with C_8K in THF at low temperature, can be protected in situ with a wide variety of electrophiles (eq 8).[12] Aryl thioglycosides can also be reduced to the corresponding glycals by means of C_8K.[12b] Comparable reaction sequences consisting of C_8K-induced fragmentations followed by trapping of the intermediate alcoholates have also been carried out successfully with a series of carbohydrate-derived primary halides (eq 9).[13]

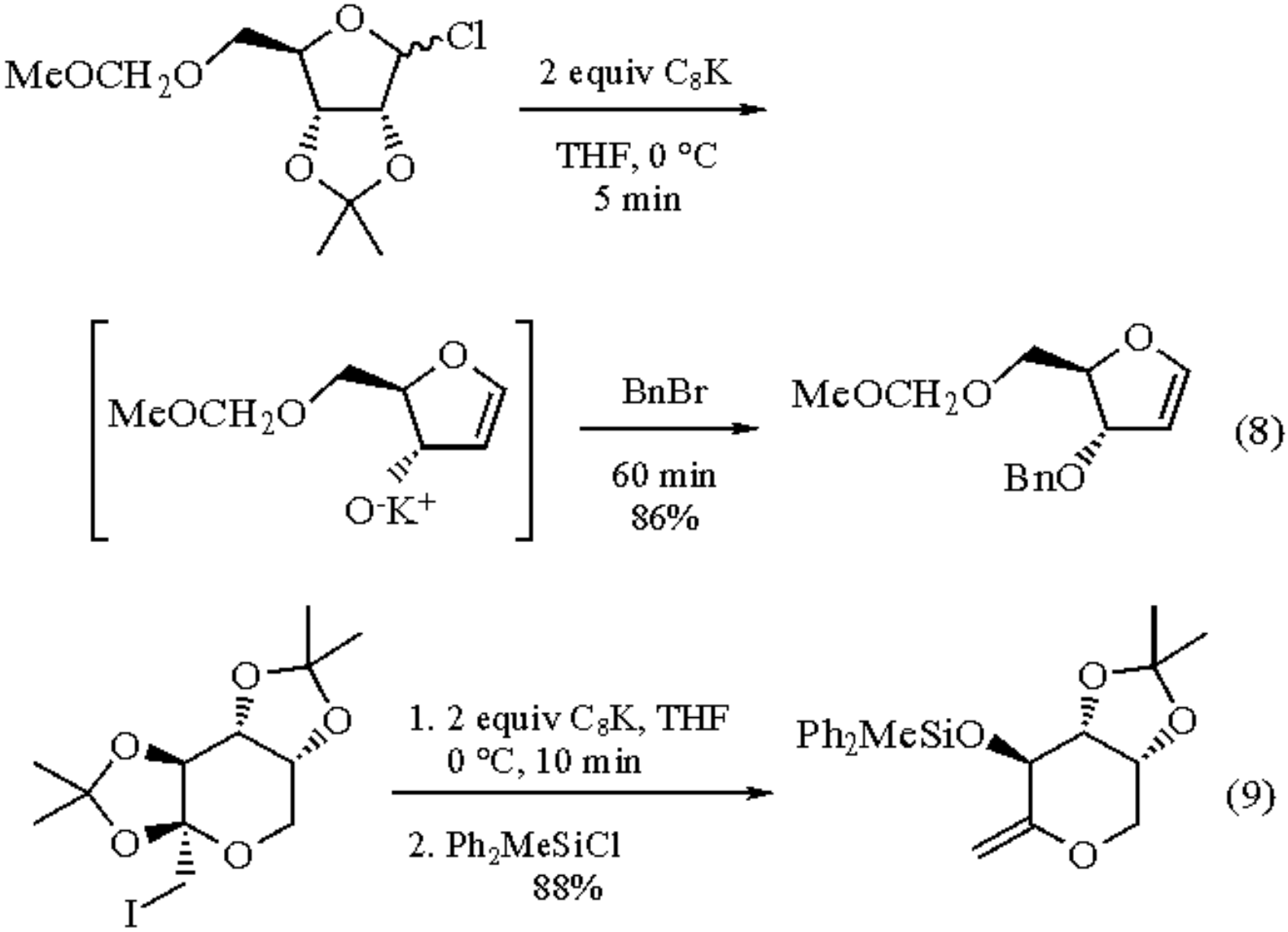

Chlorosilanes are rapidly converted by C_8K to disilanes in high to quantitative yields in THF at ambient temperature.[14] Phenyl-substituted disilanes may be further reduced to the corresponding silyl potassium reagents, which can be transmetalated with various transition metal halides (***Copper(I) Iodide***, ***Copper(I) Cyanide***, MnI_2, VCl_3) to highly selective nucleophilic silylating agents. They react cleanly with enoates, enones, and acid chlorides, the last affording acyl silanes in a one-pot procedure (eq 10).[14a]

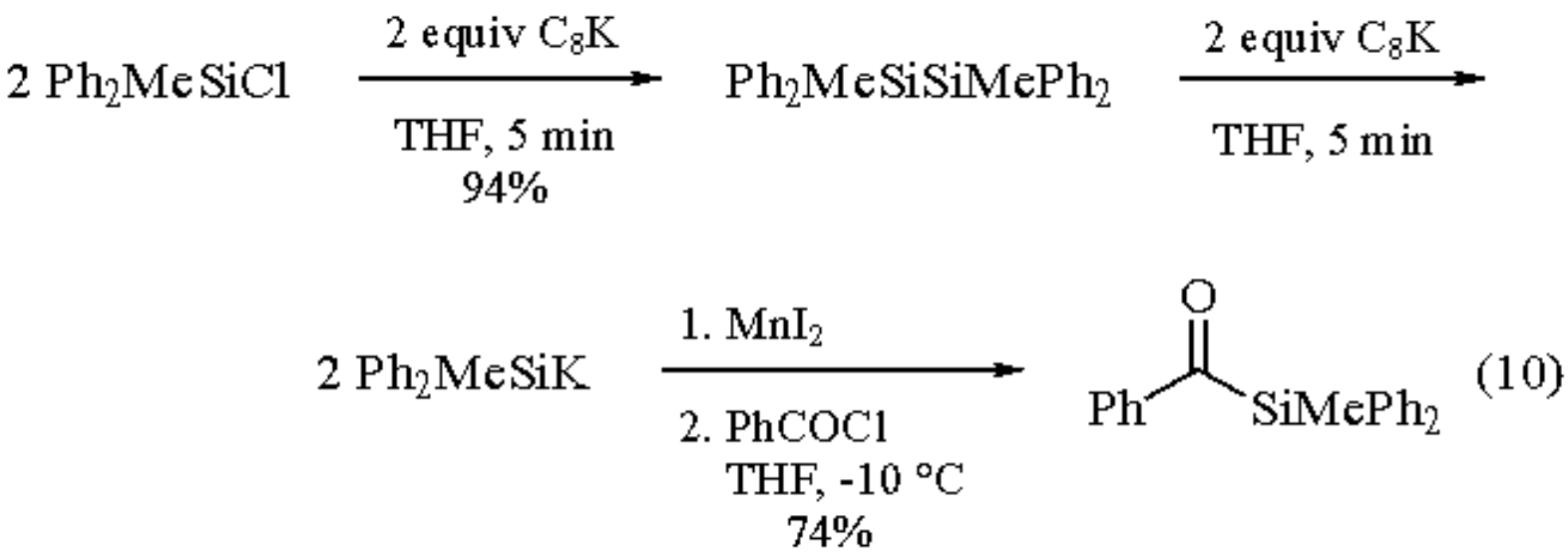

C_8K as Polymeric Lewis Base.

The reactivity of C_8K towards Brønsted acids is substrate size dependent.[3] C_8K has been used to achieve selective monoalkylation of alkyl nitriles and phenylacetic acid esters (substrate:C_8K:alkyl halide = 1:2:2) at -60 °C in 40-70% yield, with only small amounts of dialkylated products (0-7%) interfering.[15] Imines and dihydro-1,3-oxazine derivatives can likewise be deprotonated by this reagent at rt, followed by exclusive *C*-alkylation of the azaallyl anion (eq 11).[16] Some examples of selective dehydrohalogenations in the carbohydrate series due to the basisity of C_8K have also been reported (eq 12).[17]

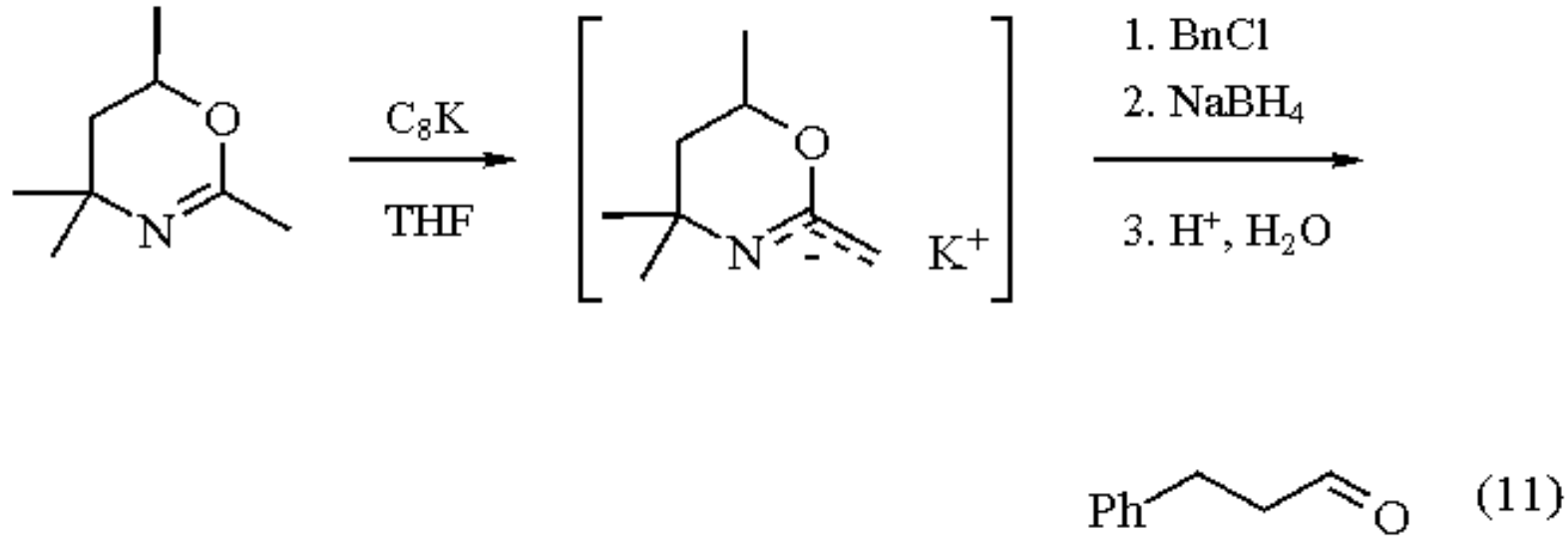

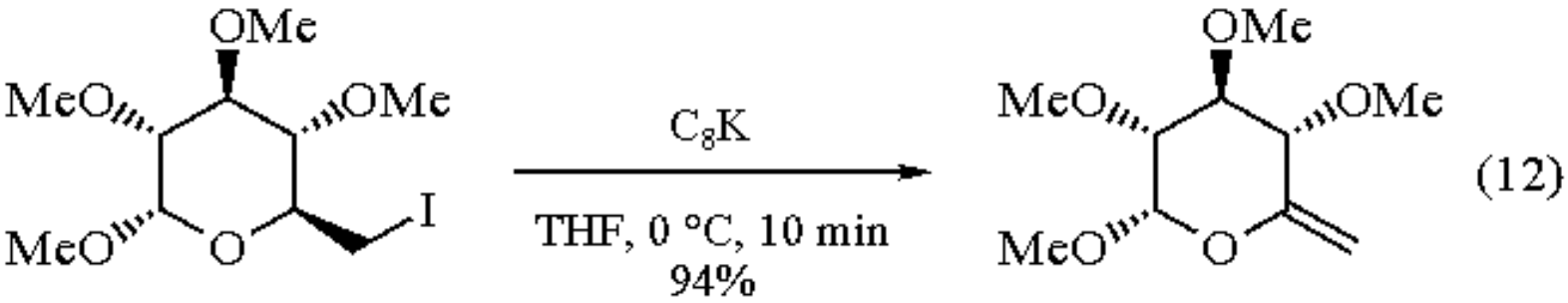

Organometallic Chemistry.

C_8K is an effective reducing agent for transition metal compounds.[1] Particularly relevant to organic synthesis is the ready reduction of ***Hexacarbonylchromium*** to $K_2Cr(CO)_5$, which forms chromium carbenes upon reaction with amides or esters in presence of ***Chlorotrimethylsilane*** (eq 13). This procedure allows an improved entry into the rich chemistry of chromium carbenes, with a comparative study clearly pointing out the superiority of C_8K as reducing agent over naphthalenide anions.[18] Moreover, C_8K is the only reagent that cleanly reduces $[CpNi_2(CO)]_2$ to the highly nucleophilic nickelate $[Cp(CO)Ni]^- K^+$, which affords allylnickel complexes on reaction with ***Allyl Bromide***.[19]

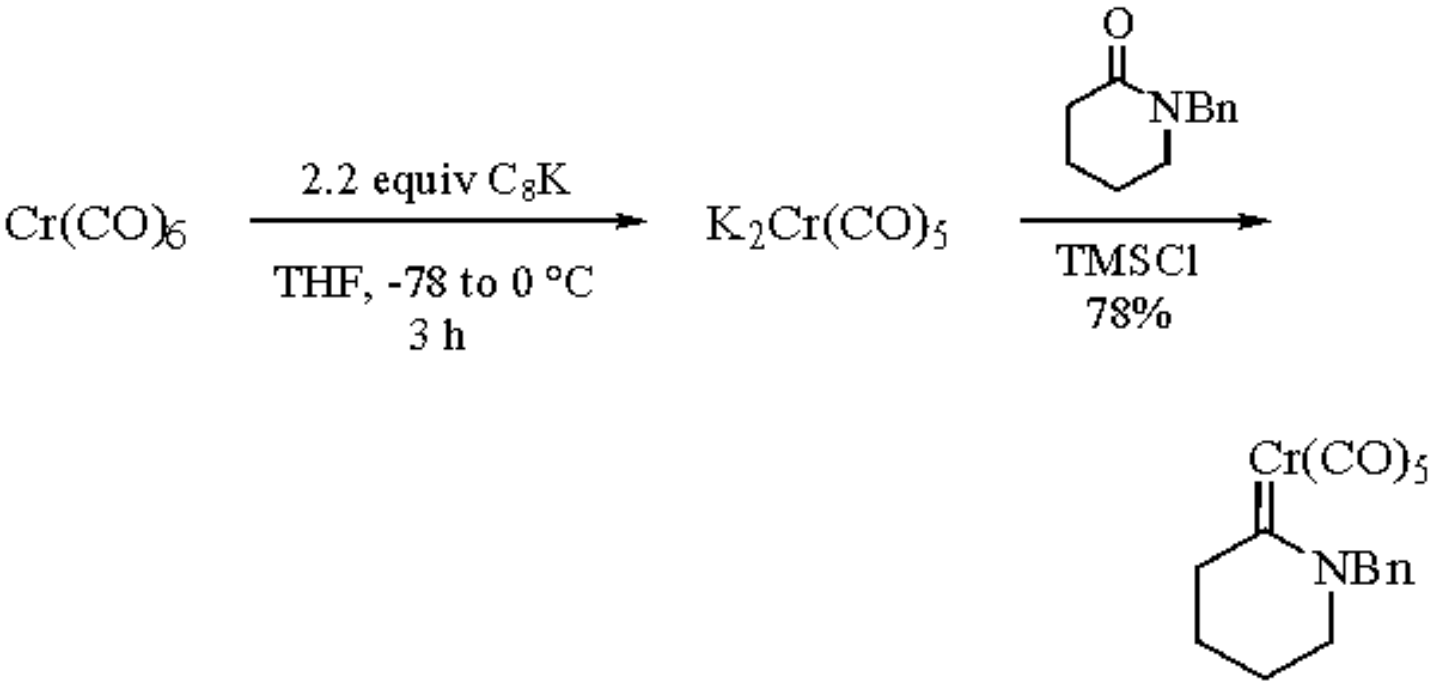

(13)

Metal-Graphite Reagents.[1]

C_8K may be used to reduce metal salts in ethereal solvents to metal-graphite reagents (eq 14). Due to the even distribution and small size (usually in the range of 2-10 nm in diameter) of the metal particles adsorped on the surface of the graphite support, these reagents exhibit very high and sometimes unprecedented degrees of reactivity and are easily removed by simple filtration after use.[1] Almost any metal may be activated by this technique.

$$MX_n + n\,C_8K \longrightarrow M^* \text{ on graphite} + n\,KX \qquad (14)$$

$$MX_n = ZnCl_2\ (AgOAc),\ TiCl_3,\ TiCl_4,\ SnCl_2,\ PdCl_2,\ PtCl_2,\ NiBr_2,\ MgCl_2,\ FeCl_3$$

Zinc-Graphite doped with 10 mol % ***Silver*** exhibits an exceptionally high reactivity and wide scope. This reagent promotes Reformatsky reactions at temperatures well below 0 °C with different kinds of halo esters, including the

rather unreactive chloroalkanoates (see also ***Ethyl Bromozincacetate***).[20] Tandem reactions comprising a Reformatsky step followed by glycidate formation or a Peterson elimination, respectively, have been carried out.[21] Zn/Ag-graphite transforms glycosyl halides to the corresponding glycals under aprotic conditions, independent of the ring size and the protecting groups employed (eq 15).[22] Deoxyhalosugar derivatives are reductively ring opened by Zn/Ag-graphite with formation of enantiomerically pure enal building blocks of wide applicability to natural product synthesis (eq 16).[13,17,23] It is the only reagent that affords such fragmentations under essentially neutral conditions in anhydrous ethereal solvents, exhibits excellent tolerance towards a wide range of functional groups in the substrates, and is therefore well suited for selective transformations of polysubstituted molecules.[24] This was shown in a total synthesis of 9-dihydro-FK-506 (eq 17).[25] Zn/Ag-graphite is also suitable for metalating functionalized aryl halides at rt.[31]

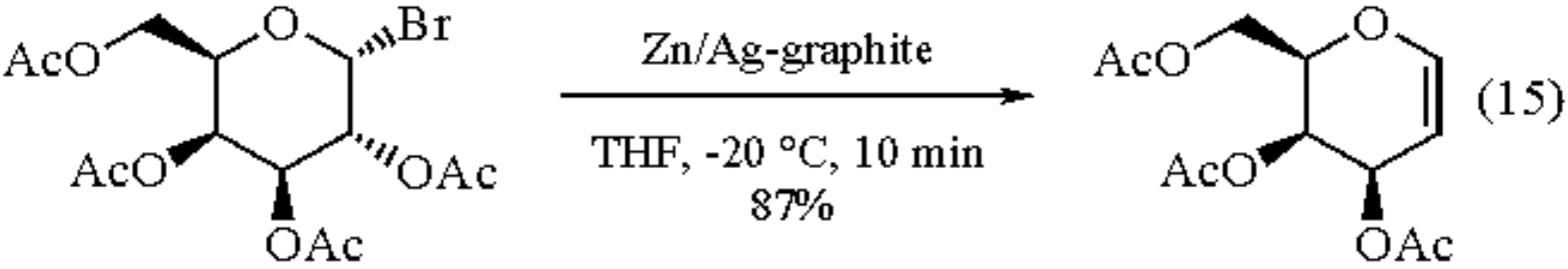

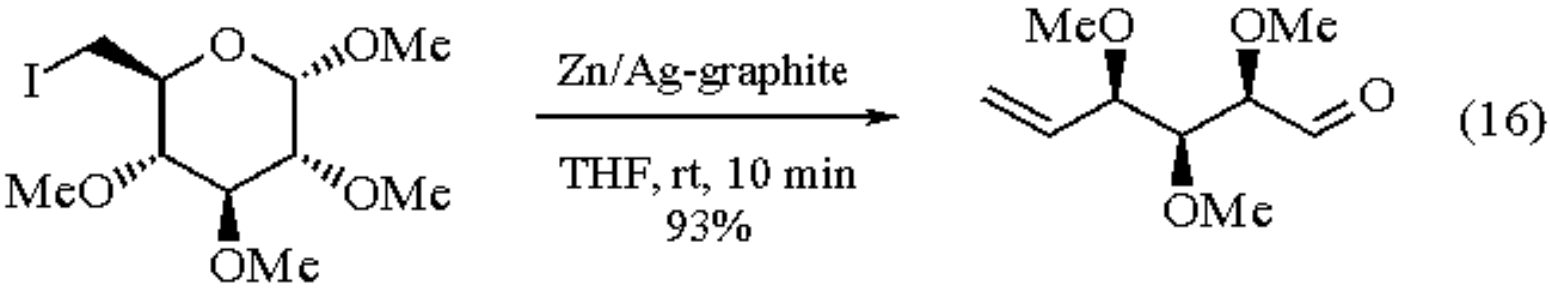

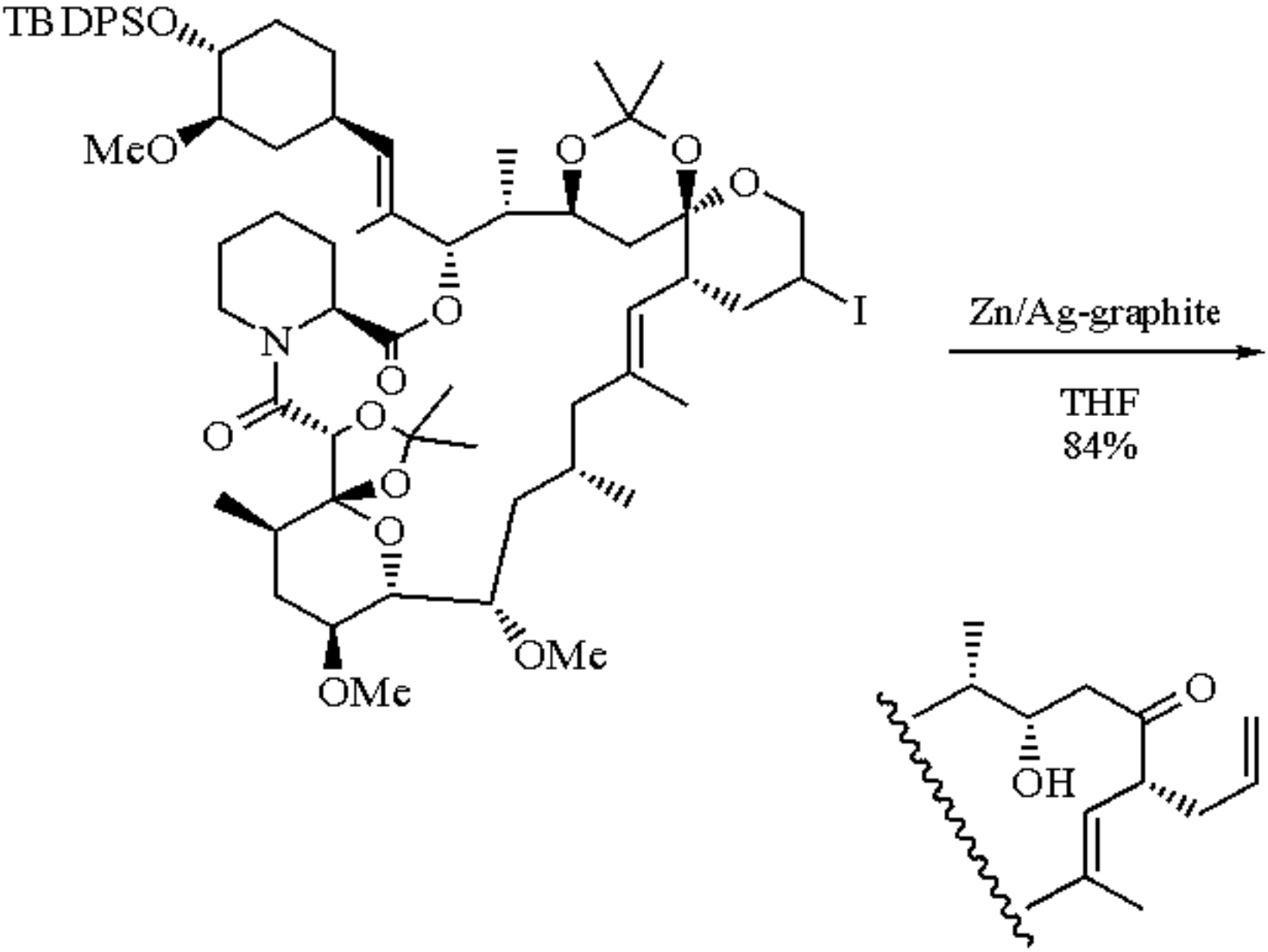

(17)

Titanium on graphite deserves special emphasis as one of the most efficient reagents for all kinds of carbonyl coupling reactions. It promotes both inter- as well as intramolecular McMurry reactions of (di)ketones and (di)aldehydes (eq 18),[26-28] cyclizes oxo esters to cyclanones,[26] and was successfully applied to polyoxygenated substrates in cases when other titanium reagents failed to effect any conversion (eq 19).[28] Recently, it was used to cyclize acyloxycarbonyl and acylamidocarbonyl compounds to furans, benzo[*b*]furans, and indoles (eq 20), respectively.[29] This new entry to aromatic heterocycles by reductive C-C bond formation of easily accessible precursors is compatible with a variety of other reducible sites in the substrates.[29]

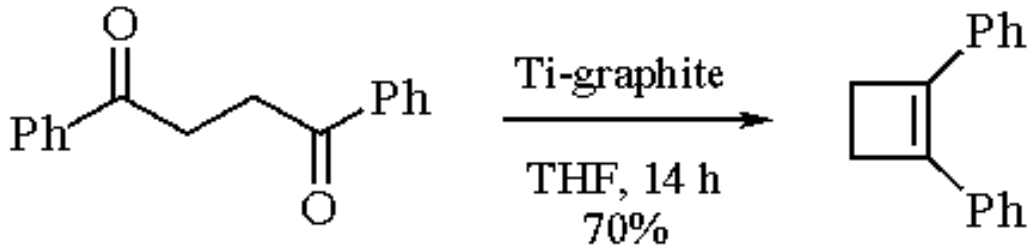

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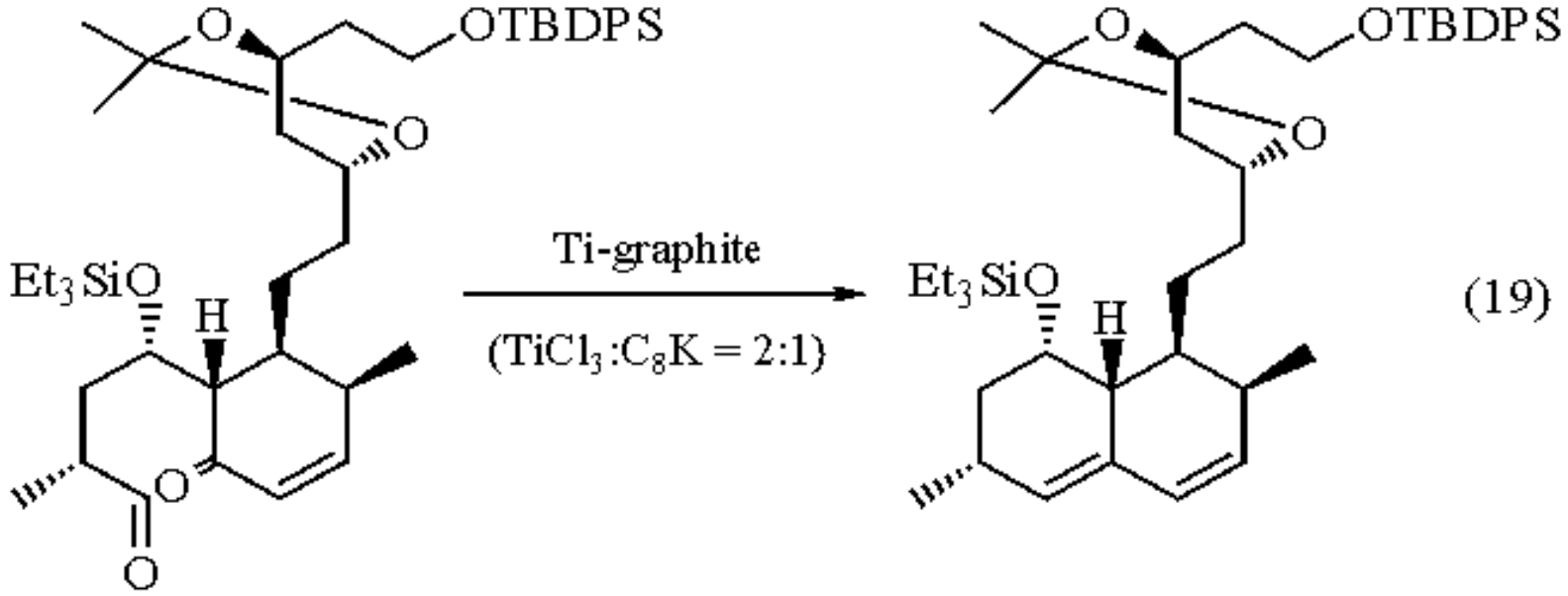

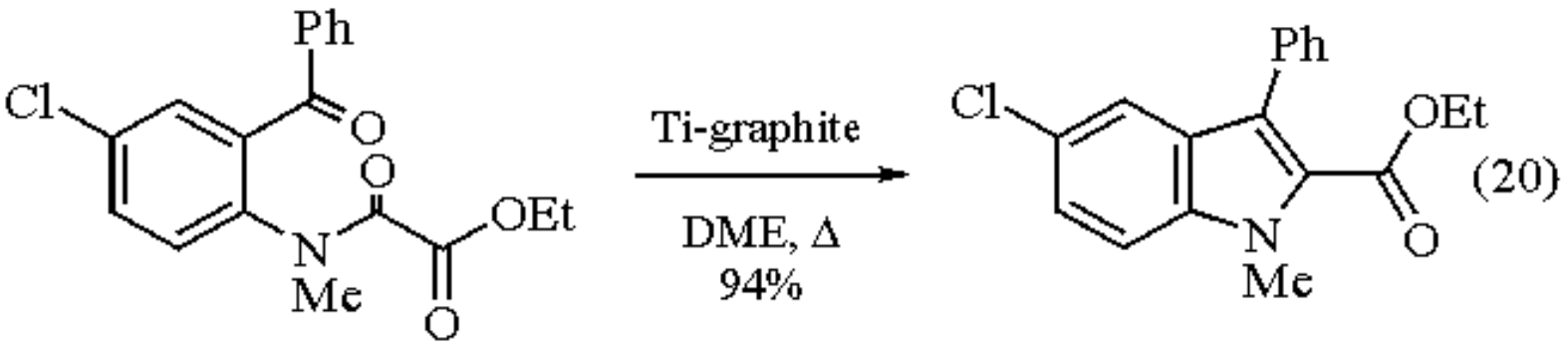

The performance of magnesium-graphite in reductive carbonyl coupling processes compares favorably to all other kinds of pinacol-forming agents described so far (eq 21).[26b] Metal-graphite combinations of platinum, palladium, and nickel have been used as highly efficient and selective catalysts for hydrogenation reactions as well as for catalytic C-C bond formations.[30] Preparative advantages have also been drawn from the use of other graphite reagents in organic and organometallic synthesis.[1,27a]

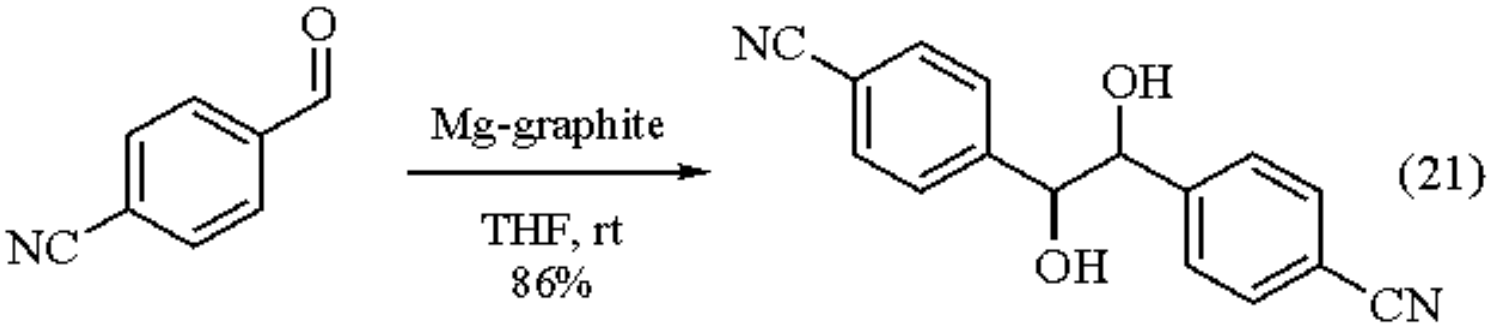

Related Reagents.

Nickel-Graphite; ***Palladium-Graphite***; ***Platinum on Carbon***; ***Zinc-Graphite***.

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Potassium *t*-Heptoxide

Et_3COK

[20484-37-1] · $C_7H_{15}KO$ · Potassium *t*-Heptoxide · (MW 154.32)

(strong, sterically hindered alkoxide base; particularly capable of effecting Hofmann elimination of alkyl halides[1])

Alternate Name: potassium triethylmethoxide.

Solubility: sol THF, DME, aromatic hydrocarbons.

Preparative Methods: 3.0 M solution of the red reagent in Et_3COH is prepared by reacting potassium metal with an excess of the anhydrous alcohol at 140 °C for 2.5 h.[1] Solutions of the base of approximately 2.0 M concentration in xylene or undecane are obtained by heating potassium metal with 1.2 equiv of the alcohol at 160 °C for 6.0 h.[1] The reaction of the anhydrous alcohol with a slight excess of oil-free ***Potassium Hydride*** in THF or other solvents produces the reagent in 3-15 min.[2] After the excess insoluble KH settles, the solution of the base is removed via a cannula or a syringe.

Handling, Storage, and Precautions: Et_3COK solutions should be handled with the same precautions that are employed for ***Potassium t-Butoxide*** solutions, i.e. avoid contact with the eyes, skin, and clothing. Conduct reactions under a dry nitrogen or argon atmosphere. For critical experiments, it is recommended that the reagent be freshly prepared. Use in a fume hood.

Formation of Potassium Enolates.

The basicity of tertiary potassium alkoxide bases increases as the bulk of the alkyl substituents increases. Therefore Et_3COK is a stronger base than *t*-BuOK or ***Potassium 2-Methyl-2-butoxide***.[3] For example, the value of the equilibrium constant for the reaction of pinacolone with Et_3COK in THF to form its potassium enolate and the alcohol is 57 (eq 1), while it is only 6.7 and 10.0 for *t*-BuOK and $EtCMe_2OK$, respectively.[3]

(1)

β-Elimination Reactions.

Et_3COK is a poor nucleophile, and its steric bulk and high basicity make it an excellent reagent for effecting Hofmann-type eliminations of alkyl halides.[1] As indicated in eq 2, the reaction of 2-bromo-2-methylbutane with Et_3COK gives a higher 1-alkene/2-alkene ratio than when either *t*-BuOK or $EtCMe_2OK$ are employed under the same conditions.[1a] Also, other tertiary halides such as 1-chloro-1-methylcyclohexane (eq 3), the hydrochloride of α-cedrene, and 2-chloro-2,3-dimethylbutane give the less-substituted alkenes in good yields when treated with an excess of the base in xylene solution at 60 °C.[1b] Because the three fluorine atoms enhance the acidity of the protons at C-3, dehydrohalogenation of 2-chloro-4,4,4-trifluoro-2-methylbutane with Et_3COK in Et_3COH at 40 °C gives largely 4,4,4-trifluoro-2-methyl-2-butene.[4] However, the corresponding 1-butene derivative is obtained if a highly hindered pyridine derivative or a metal oxide is employed as the base.[4] The reaction of 2-bromobutane with Et_3COK/Et_3COH also gives a higher 1-butene/2-butene ratio than does *t*-BuOK/*t*-BuOH (eq 4).[5]

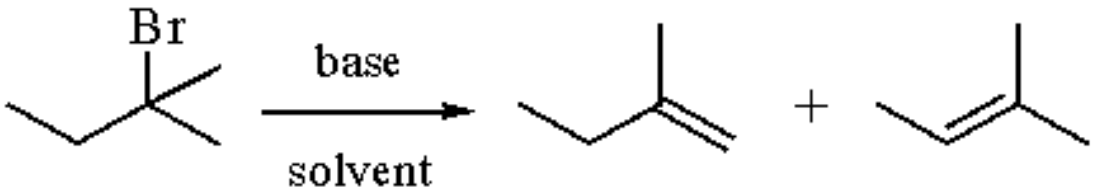

(2)

Base/solvent		
Et_3COK/Et_3COH	89%	11%
t-BuOK/*t*-BuOH	73%	27%
$EtCMe_2OK/EtCMe_2OH$	78%	22%

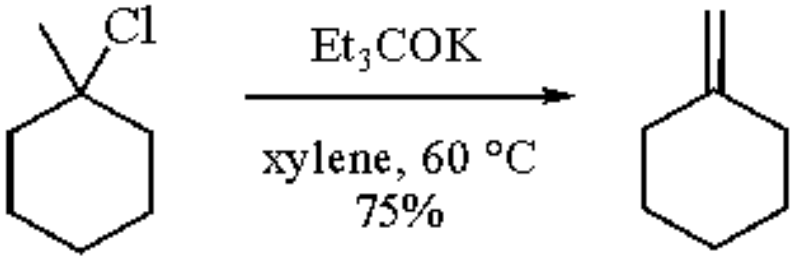

(3)

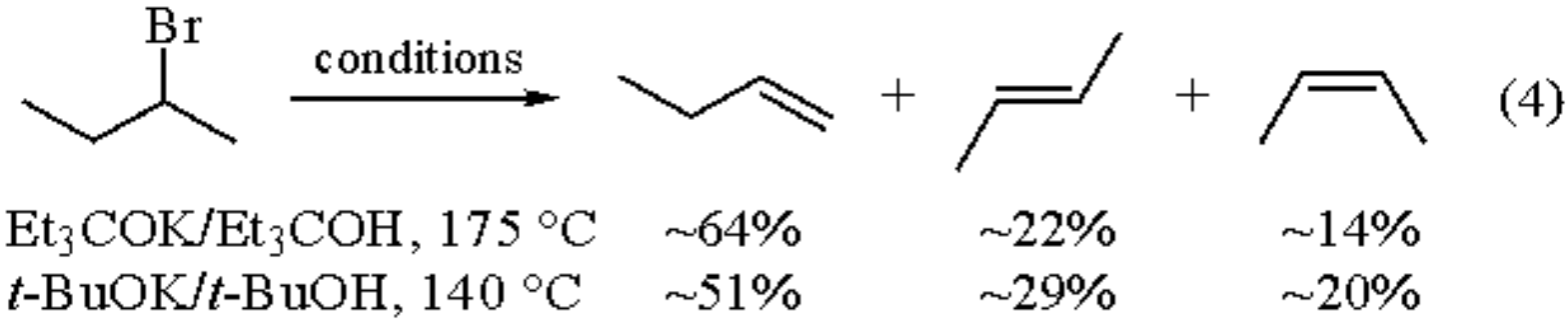

Ramberg-Bäcklund Rearrangement.

Et_3COK in DME/HMPA at 70 °C is effective for promoting the Ramberg-Bäcklund reaction of the complex α-chloro sulfone shown in eq 5.[6] The use of less-hindered bases causes dechlorination of the reactant or partial decomposition of the product. This reaction is a key step in the recent total synthesis of the natural product (+)-eremantholide.[6]

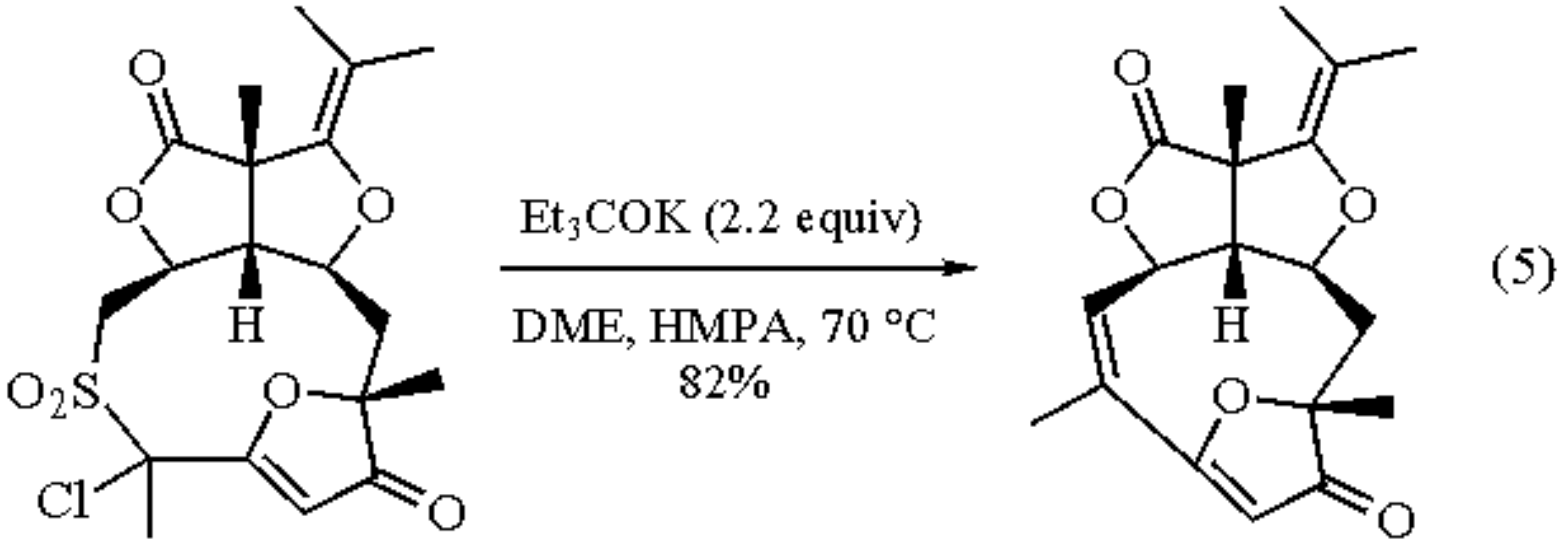

Metalation Reactions.

Mixtures of alkyllithium reagents and potassium tertiary alkoxides are powerful metallating agents for weakly acidic compounds.[7] Because of higher solubilities of Et_3COK and $EtCMe_2OK$ in hydrocarbons, mixtures of these bases and ***n-Butyllithium*** are more effective than *n*-BuLi/*t*-BuOK in promoting dimetalation of benzene.[8]

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Potassium Hexachloroosmate(IV)-Zinc

K_2OsCl_6-Zn

(K_2OsCl_6)

[16871-60-6] · Cl_6K_2Os · Potassium Hexachloroosmate(IV)-Zinc · (MW 481.10) (Zn)

[7440-66-6] · Zn · Potassium Hexachloroosmate(IV)-Zinc · (MW 65.39)

(catalyst for the cycloadditive dimerization of α,β-unsaturated ketones[1])

Physical Data: K_2OsCl_6: mp dec.

Solubility: K_2OsCl_6: sol EtOH, MeOH.

Form Supplied in: K_2OsCl_6: hydrated crystals. Zn: powder. Both are commercially available.

Purification: K_2OsCl_6: recrystallized from hot dilute aqueous HCl. Zn: stirred with 2% aqueous HCl (3 L kg^{-1} Zn dust) for 1 min, filtered, washed with 2% HCl (3 L), three times with distilled water (1 L each), twice with 95% ethanol (1 L each), and once with diethyl ether (2 L), and then dried under vacuum. The reagents, along with the substrate, are mixed prior to reflux.

Handling, Storage, and Precautions: zinc dust is flammable.

Dimerization-Cyclopentannulation of Enones.

Treatment of α,β-unsaturated ketones with potassium hexachloroosmate(IV) and ***Zinc*** leads to the reductive dimerization-cyclization product, the cyclopentanol derivative, in nearly quantitative yield (eq 1).[1] This unique transformation has unfortunately only been examined for two substrates, dibenzylideneacetone and 1,3-diphenyl-2-propenone.

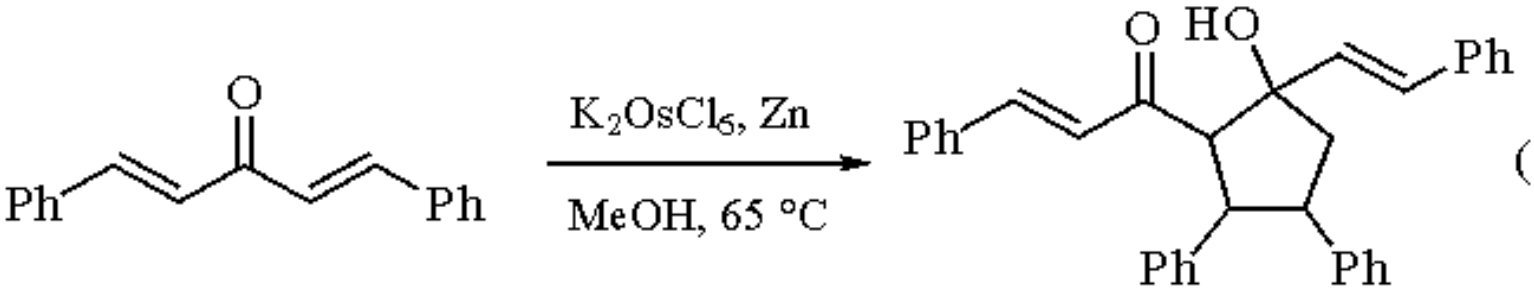

(1)

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Potassium Hexachlorotungstate(IV)

K_2WCl_6

[16923-43-6] · Cl_6K_2W · Potassium Hexachlorotungstate(IV) · (MW 474.75)

(reduces 1,2-diols to alkenes[1])

Physical Data: red crystals.

Solubility: sol liquid ammonia.

Form Supplied in: not commercially available.

Preparative Method: prepared by heating a mixture of ***Tungsten(VI) Chloride*** and ***Potassium Iodide*** at 130 °C in the absence of air.[2]

Purification: the compound from the above procedure is used without further purification.

Handling, Storage, and Precautions: air and moisture sensitive.

Conversion of 1,2-Diols to Alkenes.

Treatment of potassium hexachlorotungstate(IV) with the dialkoxides derived from deprotonation of 1,2-diols leads to alkenes.[1] The procedure represents a one-pot method to effect this transformation; sequential treatment of 1,2-diols with ***n-Butyllithium***, followed by potassium hexachlorotungstate(IV), leads to the desired alkene in high yield. The reaction is fastest for tetrasubstituted diols and slows with decreasing substitution (eq 1). Predominant but not exclusive retention of stereochemistry is observed in the reaction, due to partial isomerization of the dialkoxides under the conditions of the reaction; the isomerization is thought to proceed via a reversible pinacol coupling. The advantages of this method are that it is a one-pot procedure, and that it is efficient for hindered substrates.[3]

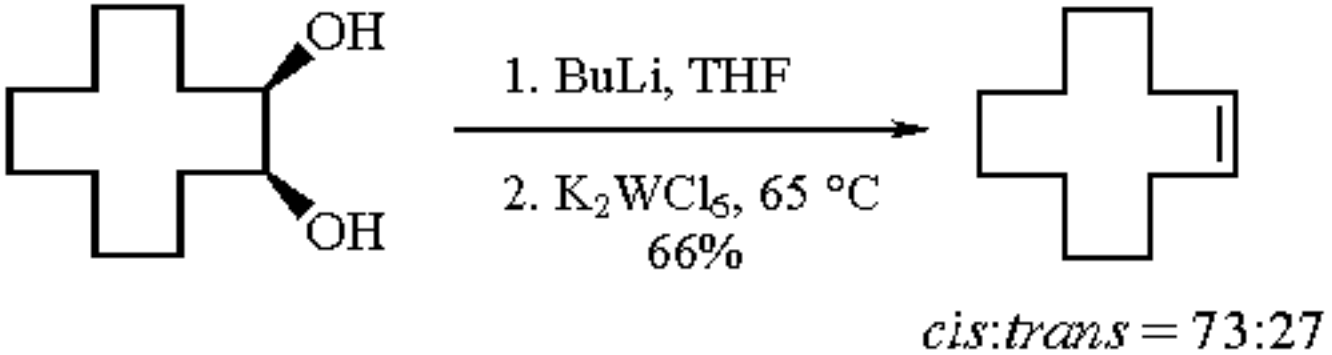

(1)

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Potassium Hexacyanodinickelate

$K_4Ni_2(CN)_6$

[52186-89-7] · $C_6K_4N_6Ni_2$ · Potassium Hexacyanodinickelate · (MW 429.90)

(hydrocyanation-reduction of alkynes;[2] dimerization of benzylic, allylic, and vinylic halides;[3] carbonylation of halides to afford ketones and esters;[3] conversion of vinylic halides to nitriles[3])

Physical Data: diamagnetic red solid.

Solubility: sol water; insol ethanol, liquid ammonia.

Form Supplied in: deep red solid.

Preparative Method: prepared from the reduction of potassium tetracyanonickelate with ***Potassium*** in ammonia. The product precipitates from solution as a deep red solid.[1]

Handling, Storage, and Precautions: blood red aqueous solutions of the reagent are decolorized by oxygen. The reagent must be handled under an inert atmosphere.

Preparation of Nitriles.

The title reagent has been little used in organic synthesis, but several reports indicated that it has some potential. For example, potassium hexacyanodinickelate reacts with alkynes in the presence of ***Sodium Borohydride*** to afford nitriles (eq 1).[2] Conversion of cinnamyl bromide to the corresponding nitrile can be accomplished in aqueous acetone at rt in 83% yield.[3]

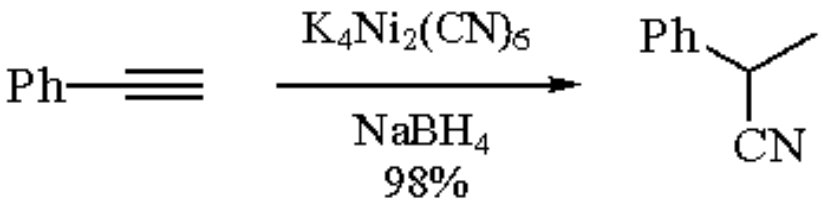

(1)

Halide Coupling.

Treatment of benzylic halides with potassium hexacyanodinickelate in water affords bibenzyls in good yields (eq 2).[4]

The coupling of α-bromo ketones to 1,4-dicarbonyl compounds has also been reported although the yields are modest.[3] When the reactions are performed in the presence of ***Carbon Monoxide***, ketones are obtained (eq 2).[3] Similar reactions have been reported with vinylic and allylic halides with varying results.[3]

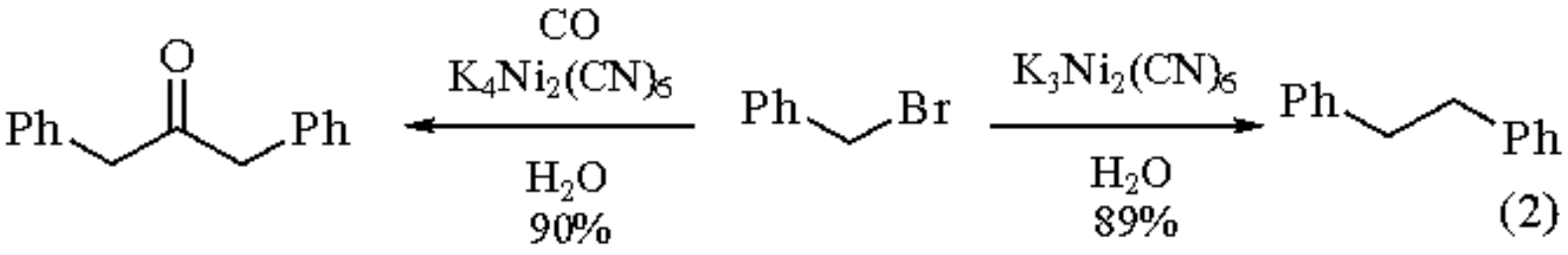

(2)

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Potassium Hexafluorophosphate

KPF_6

[17084-13-8] · F_6KP · Potassium Hexafluorophosphate · (MW 184.07)

(production of diaryliodonium and alkylaryliodonium hexafluorophosphates and triarylsulfonium hexafluorophosphates used as photoinitiators for cationic polymerization; used for the preparation of organic hexafluorophosphates; used to produce catalysts for peptide coupling reactions)

Physical Data: mp 575 °C; *d* 2.55 g cm^{-3}.

Solubility: sol water (9.3 g/100 ml at 25 °C and 20.6 at 50 °C), sol diglyme (40 g/100 ml at 25 °C).

Form Supplied in: white powder; commercially available.

Analysis of Reagent Purity: volumetric method for determination of total fluoride;[1,2] ion selective electrode for determination of soluble fluoride (KF) impurity;[3] gravimetric method of analysis for determination of PF_6 by using tetraphenylarsonium chloride.[4]

Handling, Storage, and Precautions: stable at ambient temperature. This material can be stored in polyethylene, Teflon® or metal containers. The OSHA permissible exposure limit[5] and American Conference of Governmental Industrial Hygienists (ACGIH) established Threshold Limit Value[6] (TLV) as a time-weighted average for fluorides is 2.5 mg (as fluoride) per cubic meter of air.

Diaryliodonium Hexafluorophosphates.

Diaryliodonium hexafluorophosphates are prepared by the metathesis reaction of diaryliodonium bisulfates and potassium hexafluorophosphate. There are many methods reported in the literature for the synthesis of diaryliodonium bisulfates.[7-10] Aromatic substrates bearing electron-withdrawing groups such as NO_2, halogens, CO_2H, or $MeSO_2$ are best coupled by the method used by Masson and co-workers[7] employing iodyl sulfate to produce symmetrical diaryliodonium bisulfate (eq 1).

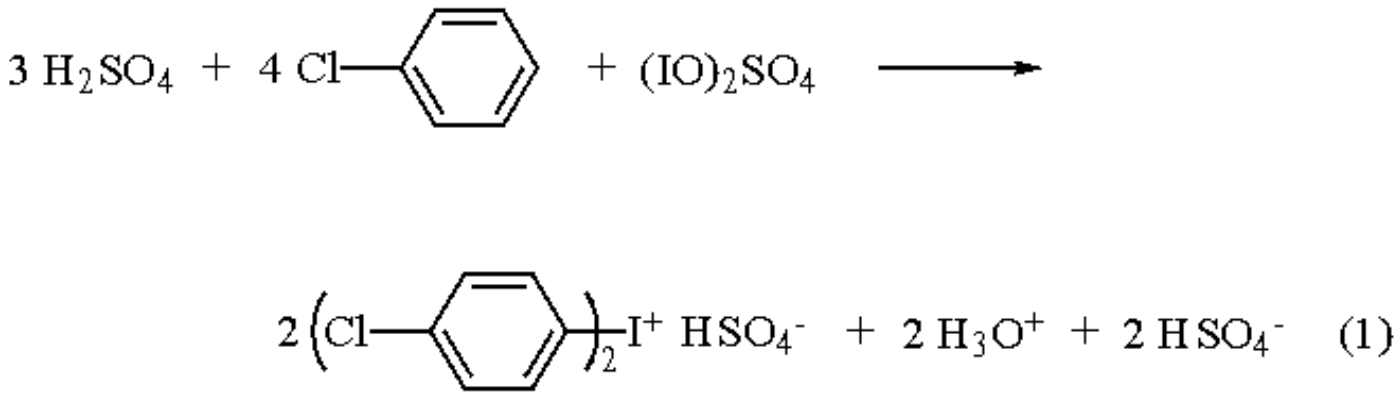

Diaryliodonium bisulfates having electron-donating groups on the aromatic ring are readily prepared by the direct coupling of their aromatic precursor compounds using an alkali iodate in a mixture of acetic acid, acetic anhydride, and sulfuric acid (eq 2).[8,9]

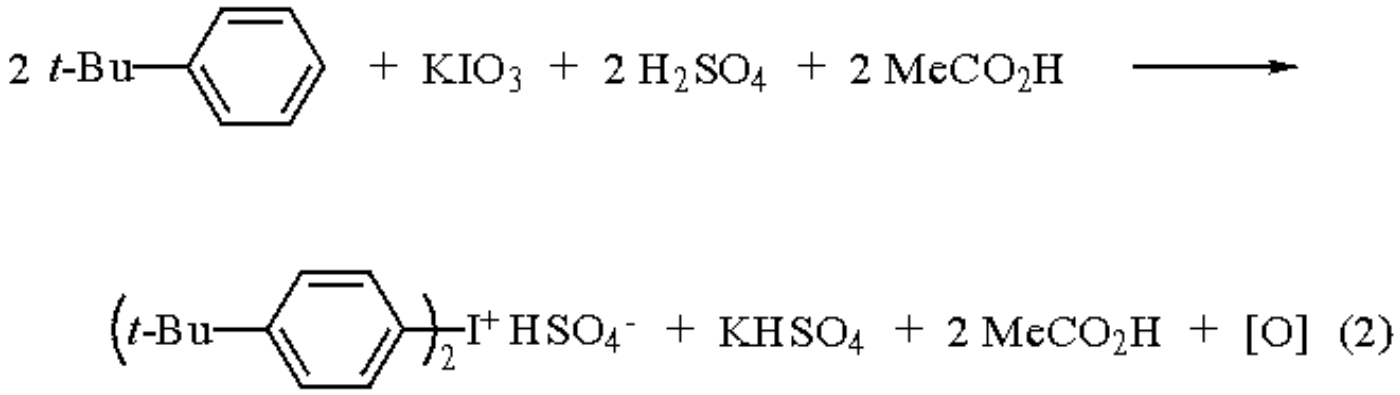

Unsymmetrical iodonium bisulfates can be prepared by the direct coupling of an aromatic compound with an iodoso compound in the presence of a strong protonic acid (eq 3).[10]

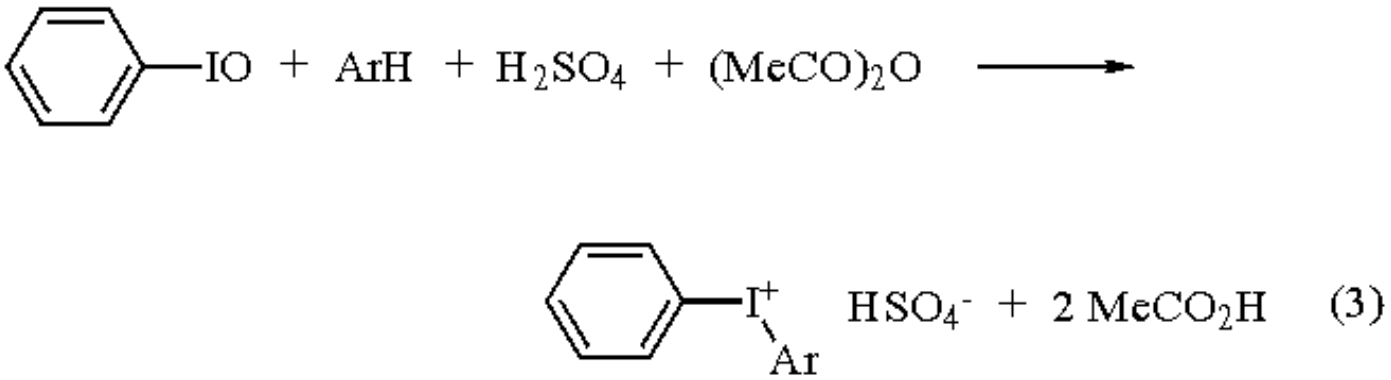

Diaryliodonium hexafluorophosphates are efficient photoinitiators for the cationic polymerization of a variety of monomers (eqs 4-6). The 4,4´-dimethyldiphenyliodonium hexafluorophosphate, bis(4-*t*-butylphenyliodonium) hexafluorophosphate, and diphenyliodonium hexafluorophosphate can be prepared by using Crivello and Lam's method.[11-13]

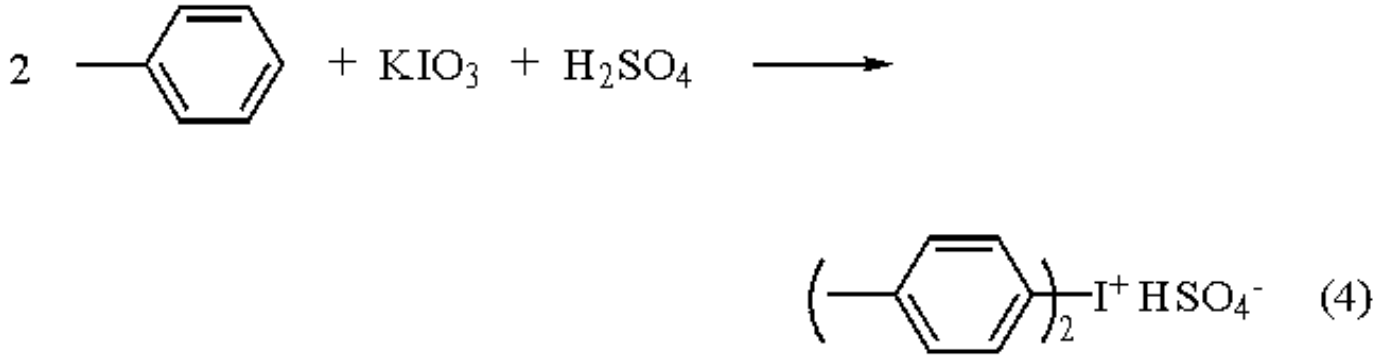

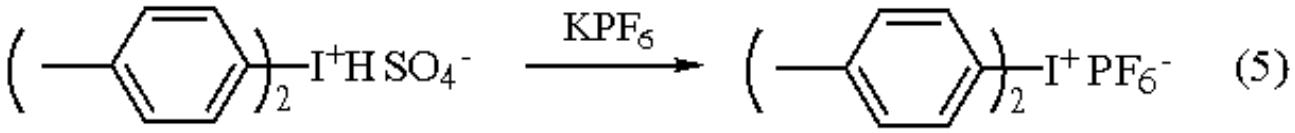

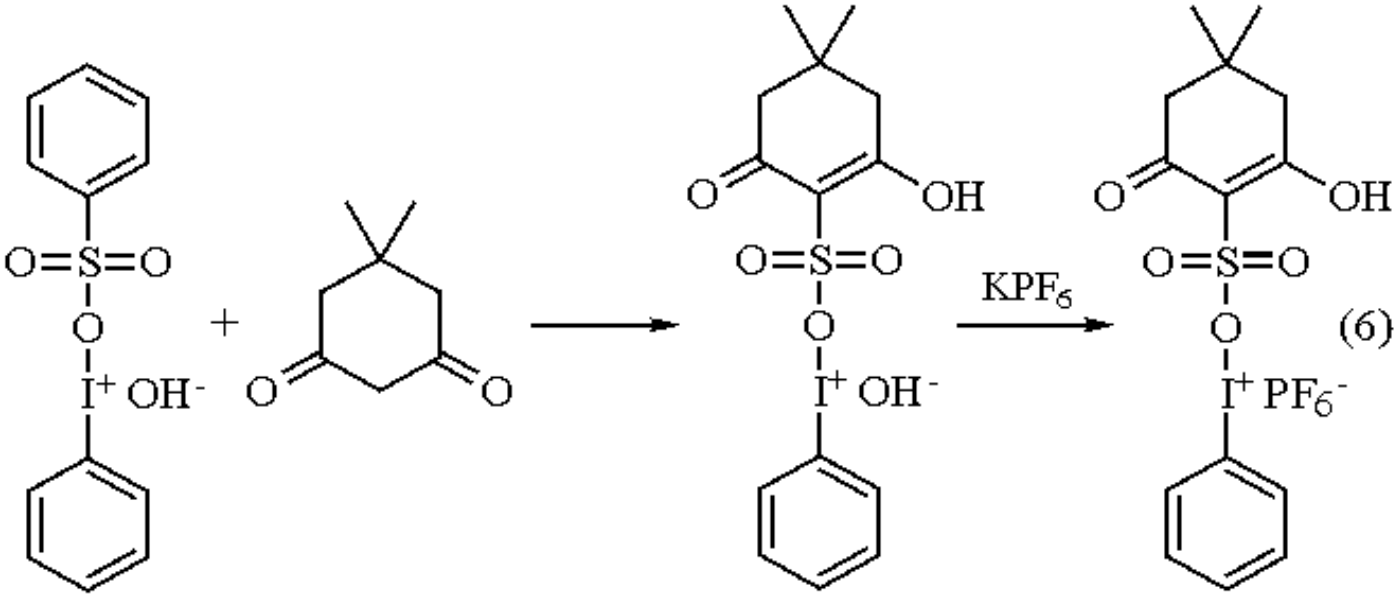

(6)

Diphenyliodium hexafluorophosphate is used in copper(I or II) catalyzed polymerization (eq 7).[14]

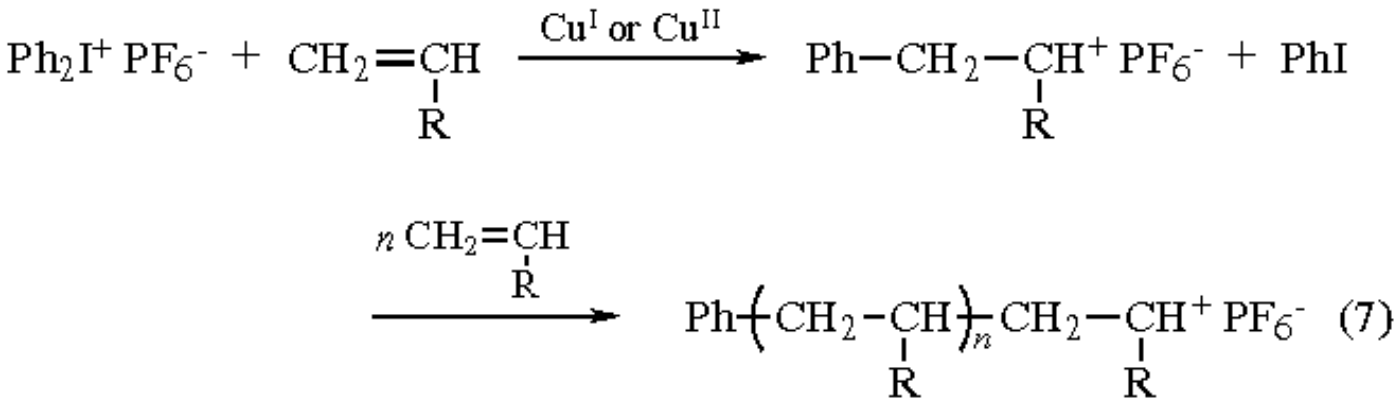

(7)

Diaryliodium hexafluorophosphates are used to prepare trialkylsulfonium hexafluorophosphate (eqs 8 and 9).[15,16]

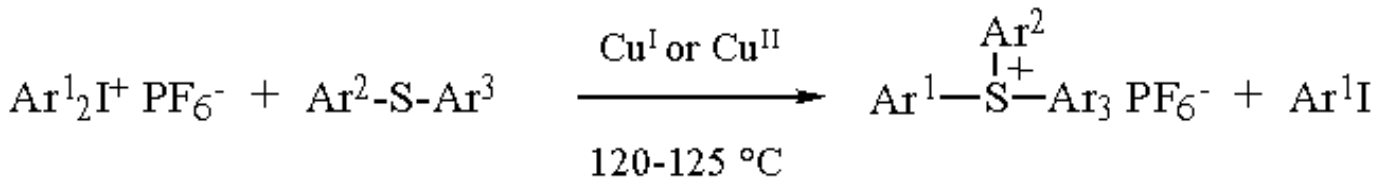

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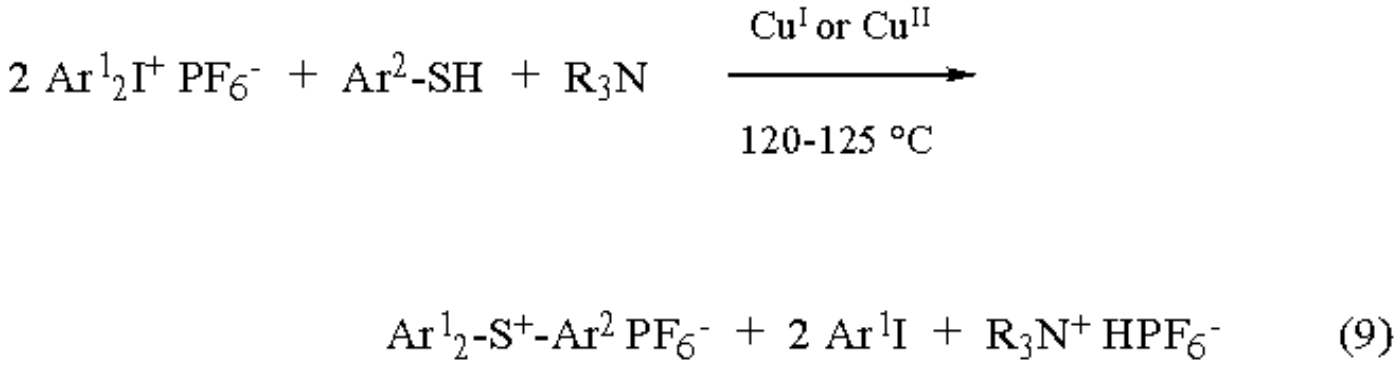

(9)

Diaryliodium hexafluorophosphates are also used in polymerization, where ring opening of the monomer takes place (eq 10).[17]

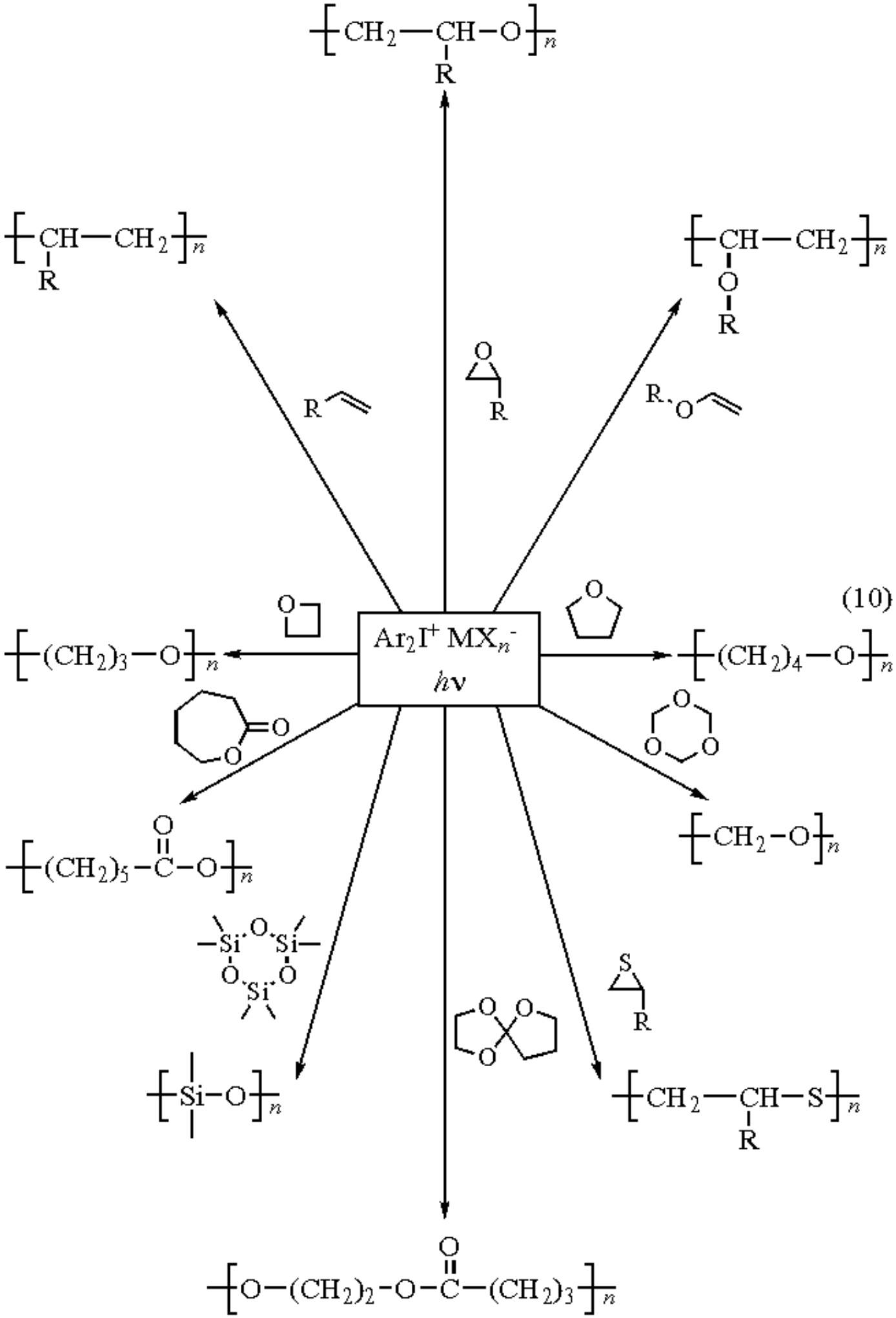
Ar2I+ MXn-
hν
(10)

Triarylsulfonium Hexafluorophosphates.

To a solution of 21.5 g (0.05 mol) of tris(3,5-dimethyl-4-hydroxyphenyl)sulfonium chloride in hot ethanol was added 9.2 g (0.05 mol) of potassium hexafluorophosphate. About 100 mL of water was added and crystallization of the sulfonium hexafluorophosphate took place. The salt was filtered, washed thoroughly with water, then with ether, and dried (eqs 11 and 12).

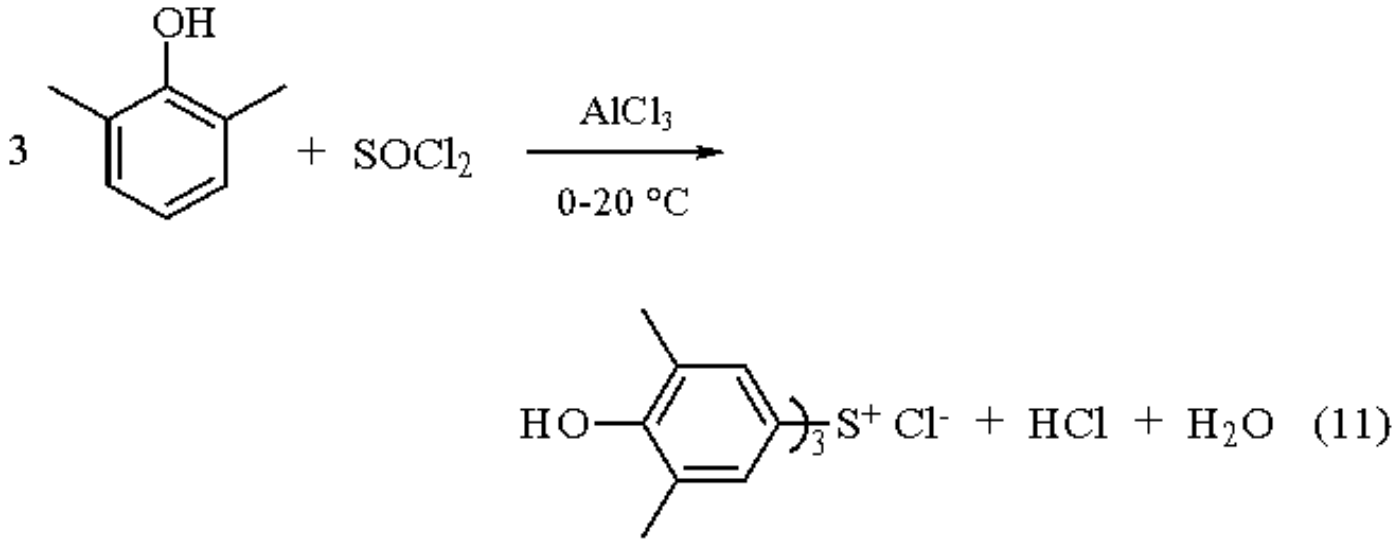

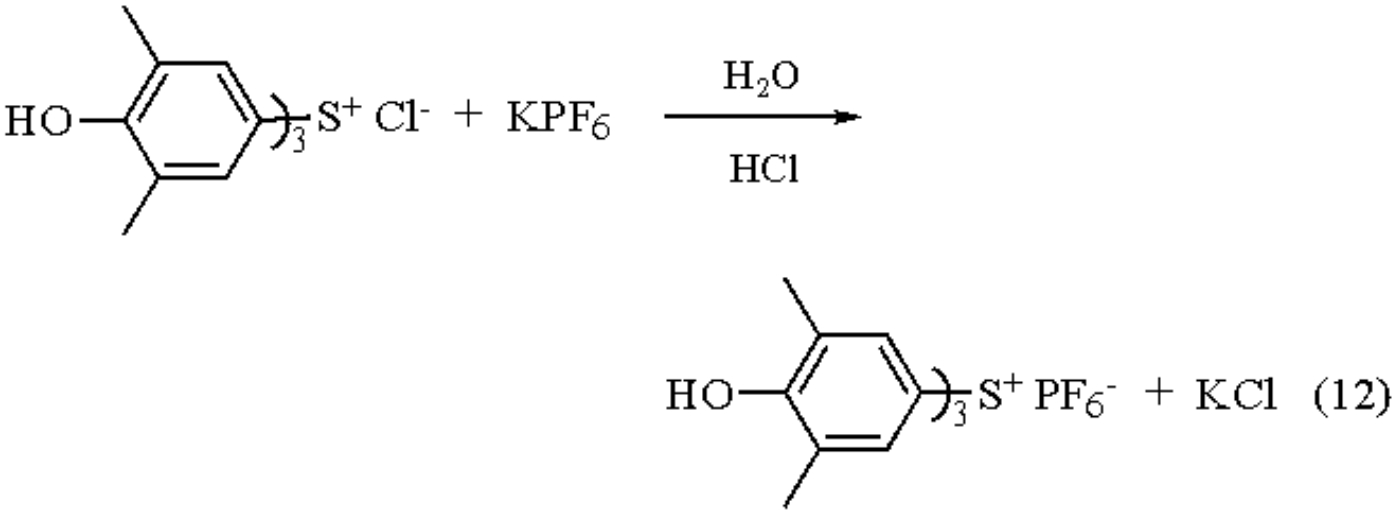

Triarylsulfonium hexafluorophosphates are used in photoinitiated cationic polymerization (eqs 13-15).[18]

Photolysis

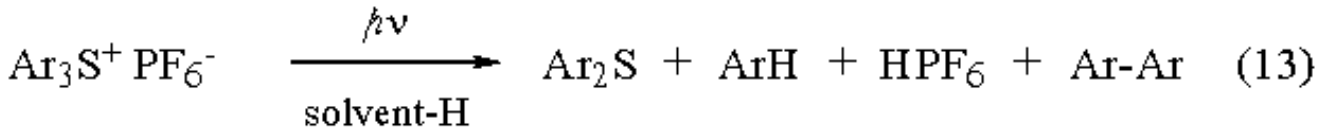

Initiation

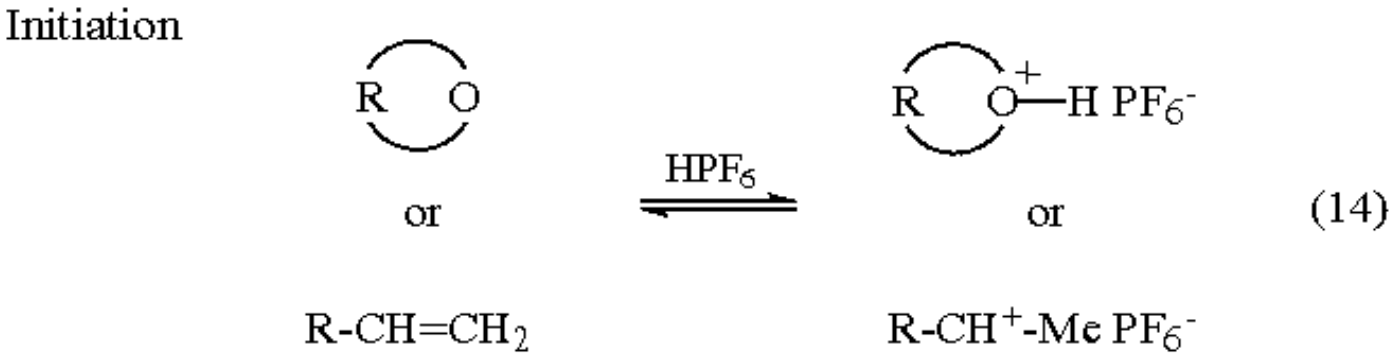

(14)

Propagation

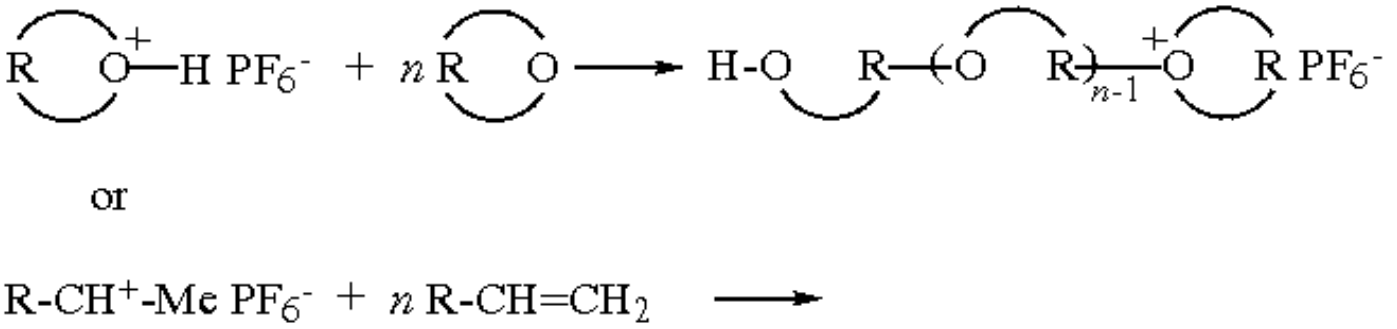

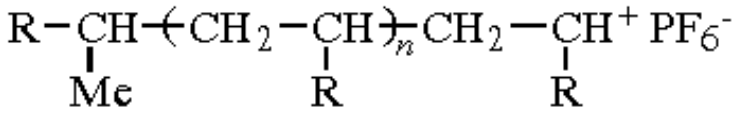

(15)

Peptide Coupling Reaction.

Potassium hexafluorophosphate is used to produce azidotris(dialkylamino)phosphonium salts as reagents for peptide coupling (eqs 16 and 17).[19]

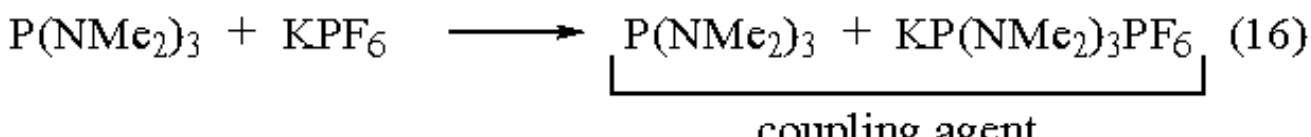

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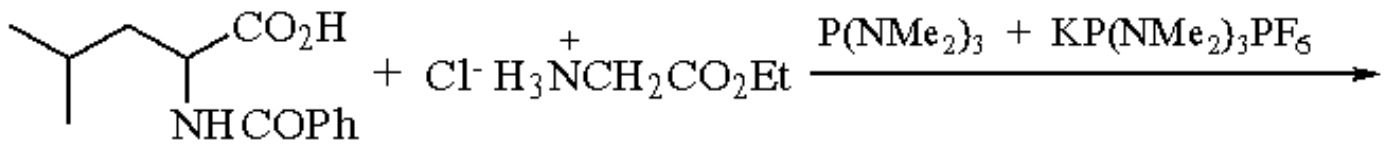

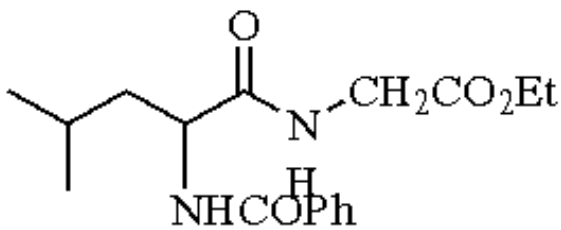

(17)

[Bz-Leu-Gly-OEt]

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Tariq Mahmood

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Potassium Hexamethyldisilazide

$KN(SiMe_3)_2$

[40949-94-8] · $C_6H_{18}KNSi_2$ · Potassium Hexamethyldisilazide · (MW 199.53)

(sterically hindered base)

Alternate Names: KHMDS; potassium bis(trimethylsilyl)amide.

Solubility: sol THF, ether, benzene, toluene.[1]

Form Supplied in: commercially available as moisture-sensitive, tan powder, 95% pure, and 0.5 M solution in toluene.

Analysis of Reagent Purity: solid state structures of $[KN(SiMe_3)_2]_2$[3] and $[KN(SiMe_3)_2.2\ toluene]_2$[4] have been determined by X-ray diffraction; solutions may be titrated using fluorene,[2] 2,2´-bipyridine,[5] and 4-phenylbenzylidene benzylamine[6] as indicators.

Preparative Methods: prepared and isolated by the procedure of Wannagat and Niederpruem.[1] A more convenient in situ generation from ***Potassium Hydride*** and ***Hexamethyldisilane*** is described by Brown.[2]

Handling, Storage, and Precautions: the dry solid and solutions are inflammable and must be stored in the absence of moisture. These should be handled and stored under a nitrogen atmosphere. Use in a fume hood.

Use as a Sterically Hindered Base for Enolate Generation.

Potassium bis(trimethysilyl)amide, $KN(TMS)_2$, has been shown to be a good base for the formation of kinetic enolates from carbonyl groups bearing α-hydrogens.[7] For example, treatment of 2-methylcyclohexanone with $KN(TMS)_2$ at low temperature followed by trapping with ***Triethylborane*** and ***Iodomethane*** gave good selectivity for 2,6-dimethylcyclohexanone (eq 1). In comparison, the use of ***Potassium Hydride*** for this transformation gave good selectivity for 2,2-dimethylcyclohexanone, which is the product derived from the thermodynamic enolate (eq 2).[8]

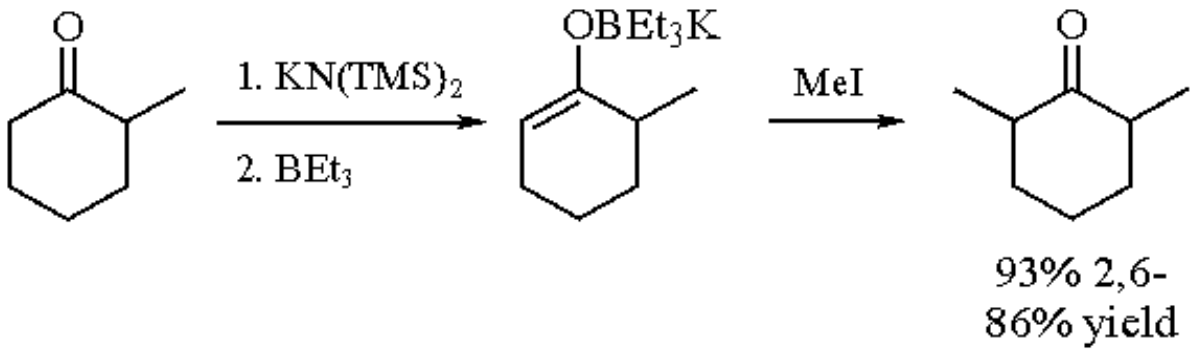

(1)

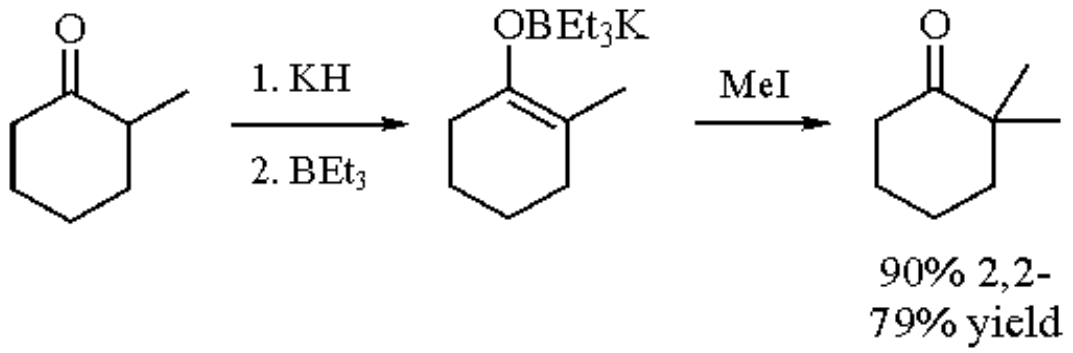

(2)

This reagent has been shown to be a good base for the generation of highly reactive potassium enolates;[9] for example, treatment of various ketones and esters bearing α-hydrogens with $KN(TMS)_2$ followed by 2 equiv of N-F-saccharinsultam allowed isolation of the difluorinated product (eq 3).

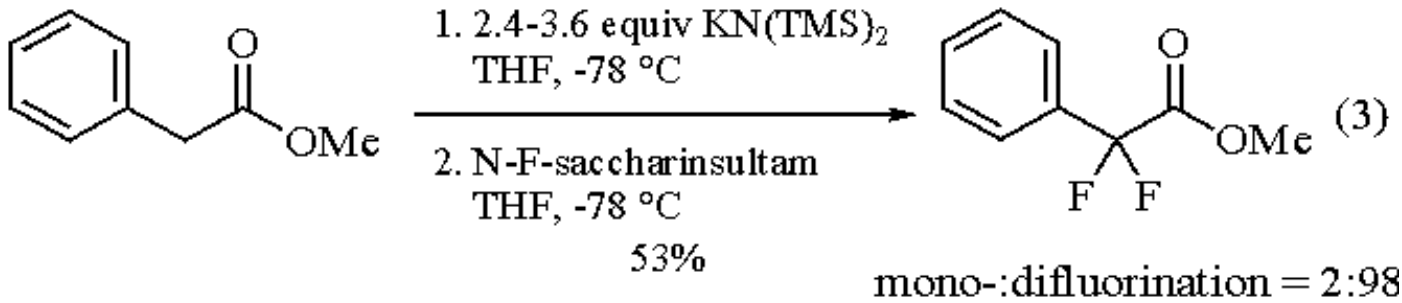

(3)

In a study on the electrophilic azide transfer to chiral enolates, Evans[10] found that the use of potassium bis(trimethylsilyl)amide was crucial for this process. The $KN(TMS)_2$ played a dual role in the reaction; as a base, it was used for the stereoselective generation of the (*Z*)-enolate (**1**). Reaction of this enolate with trisyl azide gave an intermediate triazene species (**2**) (eq 4). The potassium counterion from the $KN(TMS)_2$ used for enolate formation was important for the decomposition of the triazene to the desired azide. Use of other hindered bases such as ***Lithium Hexamethyldisilazide*** allowed preparation of the intermediate triazene; however, the lithium ion did not catalyze the decomposition of the triazene to the azide.[10a] This methodology has been utilized in the synthesis of cyclic tripeptides.[10b]

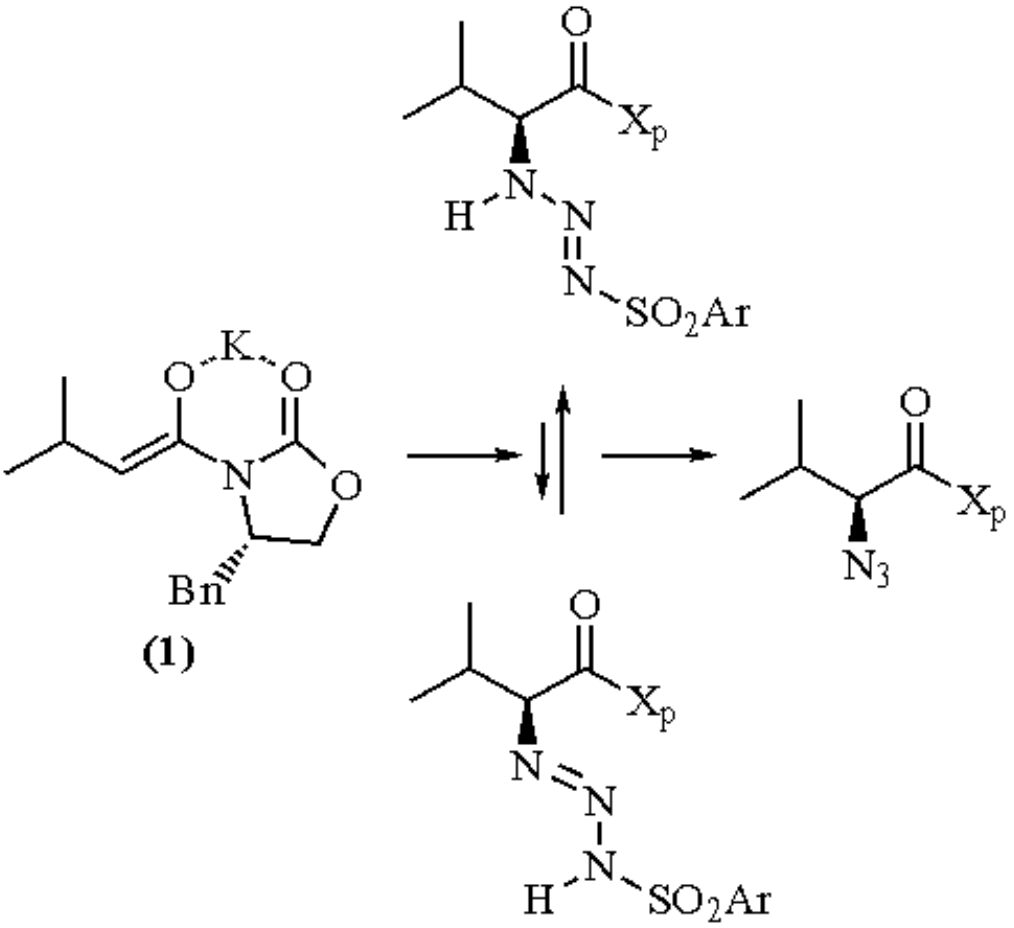

(4)

(2)

Treatment of carbonyl species bearing acidic α-hydrogens with potassium bis(trimethylsilyl)amide has also been shown to generate anions which, due to the larger, less coordinating potassium cation, allow the negative charge to be stabilized by other features in the molecule rather than as the potassium enolate. Treatment of 9-acetyl-*cis,cis,cis,cis*-cyclonona-1,3,5,7-tetraene with this reagent gave an anionic species which was characterized by spectroscopic methods to be more like the [9]annulene anion than the nonafulvene enolate. In this case the negative charge is more fully stabilized by delocalization into the ring to form the aromatic species rather than as the potassium enolate. Use of the bis(trimethylsilyl)amide bearing the more strongly coordinating lithium cation led to an intermediate which appeared to be lithium nonafulvene enolate. Addition of ***Chlorotrimethylsilane*** to each of these intermediates gave the same nonafulvenesilyl enol ether (eq 5).[11]

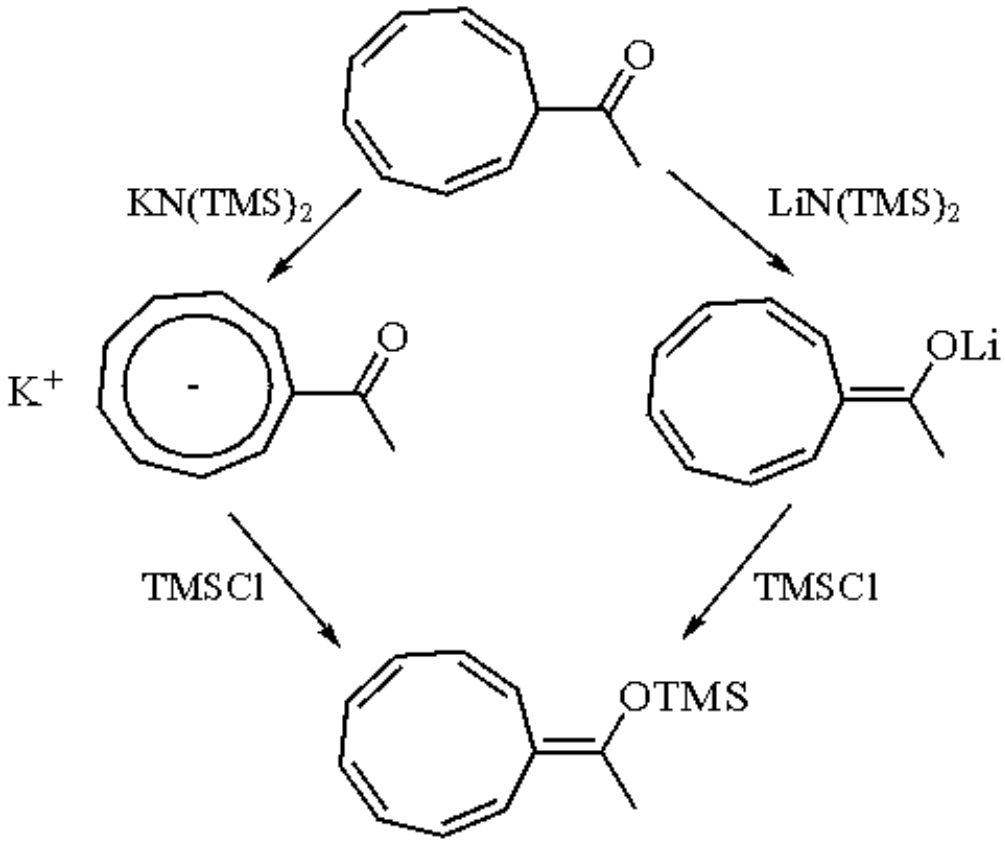

(5)

Selective Formation of Linear Conjugated Dienolates.

Potassium bis(trimethylsilyl)amide has been shown to be an efficient base for the selective generation of linear-conjugated dienolates from α,β-unsaturated ketones.[12] As shown in eqs 6 and 7, treatment of both cyclic and acyclic α,β-unsaturated enones with $KN(TMS)_2$ in a solvent mixture of DMF/THF (2:1) followed by quenching with ***Methyl Chloroformate*** gave excellent selectivities for the products derived from the linear dienolate anion. In comparison, the use of lithium bases for this reaction gave products derived from the cross-conjugated dienolate anions. This methodology, however, did not work for 1-cyclohexenyl methyl ketone, in which case the product from the cross-conjugated dienolate anion was isolated exclusively (eq 8).

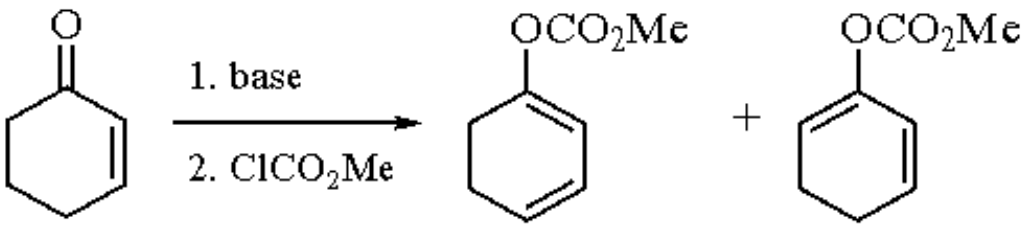

(6)

Base	Linear	Cross	Yield (%)
$KN(TMS)_2$	>99	-	34
$LiN(TMS)_2$	75	25	68
LDA	-	99	44

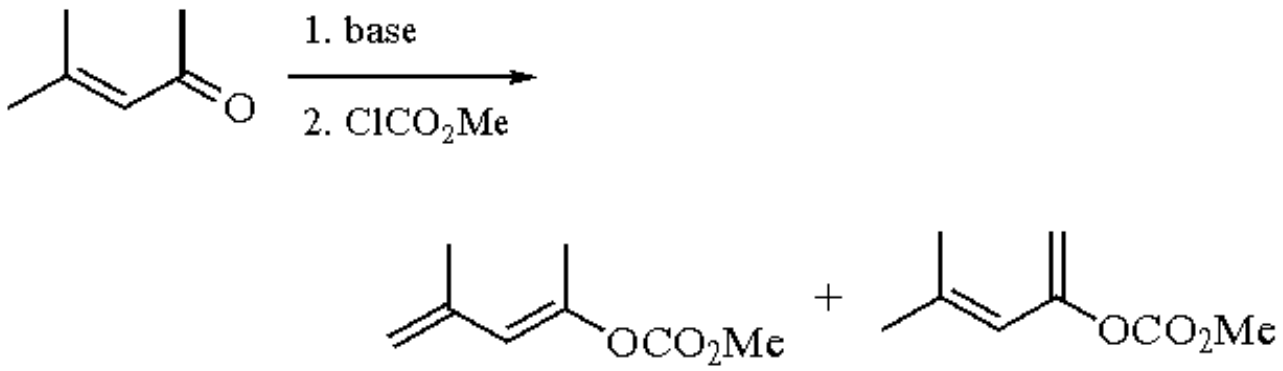

(7)

Base	Linear	Cross	Yield (%)
$KN(TMS)_2$	99	-	34
LDA	16	84	50

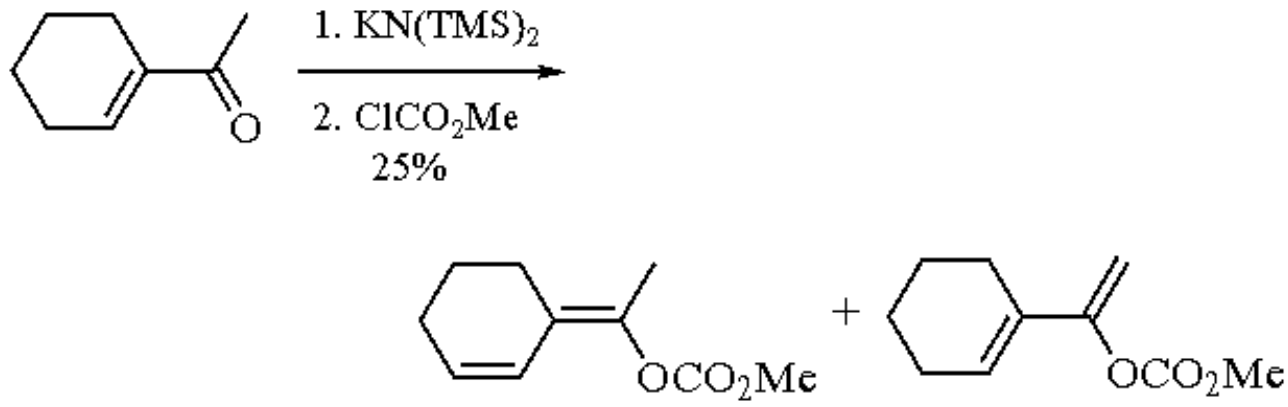

(8)

not detected >99

Stereoselective Generation of Alkyl (*Z*)-3-Alkenoates.

Deconjugative isomerization of 2-alkenoates to 3-alkenoates occurs via γ-deprotonation of the α,β-unsaturated ester to form an intermediate dienolate anion. In most cases, the α-carbon is more reactive to protonation[13] and allows for the isolation of the 3-alkenoate. If the C-4 position bears a methyl group, this transformation is usually stereospecific, leading to the (*Z*)-3-alkenoate; however, when groups larger than a methyl occupy the C-4 position, the reaction becomes increasingly stereorandom.[13d] Potassium bis(trimethylsilyl)amide, however, was shown to be a good base for the stereoselective isomerization of 2,4-dimethyl-3-pentyl (*E*)-2-dodecenoate, which bears a long C-4 substituent, to the corresponding (*Z*)-3-dodecenoate (eq 9).[14a]

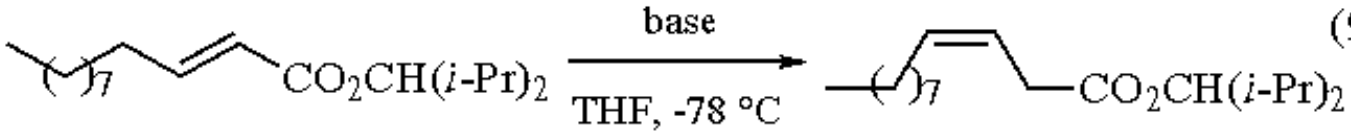

(9)

Base	(*Z*):(*E*)	Yield (%)
LDA/HMPA	84:16	85
$KN(TMS)_2$	97:3	64

This reagent has been used to stereoselectively prepare (*Z*)-3-alkenoate moieties for use in the syntheses of insect pheromones.[14]

Generation of α-Keto Acid Equivalents (Dianions of Glycolic Acid Thioacetals).

Potassium bis(trimethylsilyl)amide was found to be the optimal reagent for the generation of the dianion of glycolic acid thioacetals. This reagent may be used to effect a nucleophilic α-keto acid homologation. Treatment of the starting bis(ethylthio)acetic acid with $KN(TMS)_2$ proceeded to give the corresponding soluble dianionic species. This underwent alkylation with a variety of halides and tosylates (eq 10) and subsequent hydrolysis allowed isolation of the desired α-keto acids.[15]

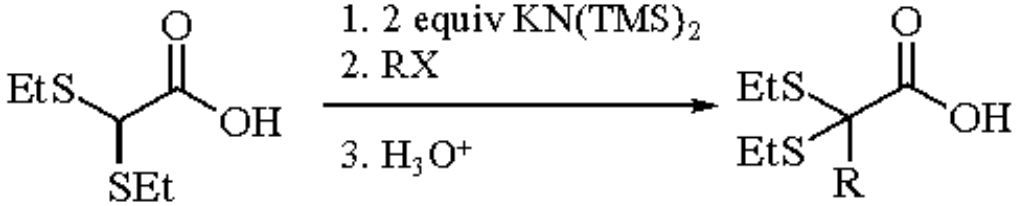

(10)

RX	Yield (%)
MeI	100
EtOTs	100
i-PrOTs	72
CyOTs	64
$PhCH_2Cl$	100

The dianion was also shown to undergo ring-opening reactions with epoxides and aziridines (eq 11).

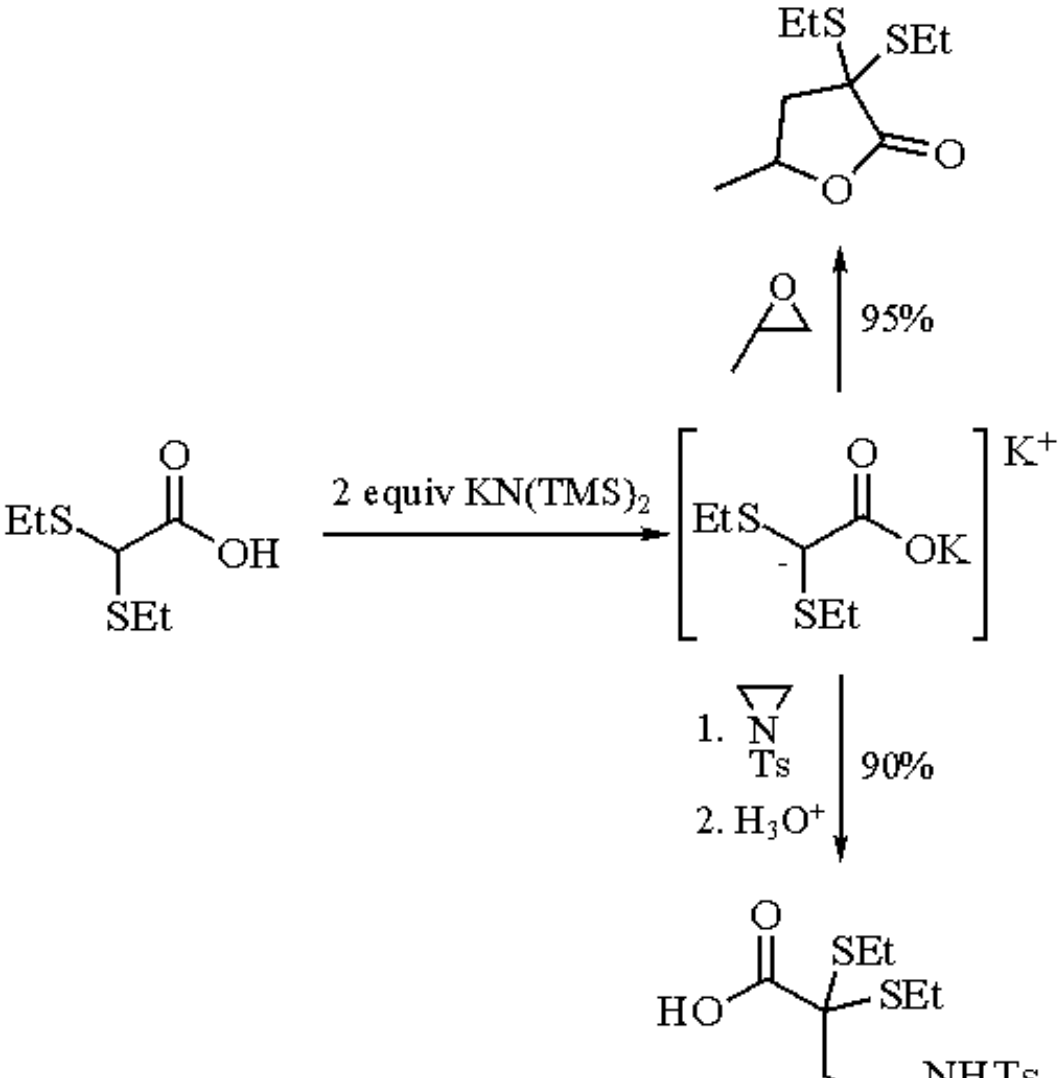

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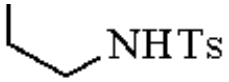

Generation of Ylides and Phosphonate Anions.

Ylides.

In the Wittig reaction, lithium salt-free conditions have been shown to improve (*Z*/*E*) ratios of the alkenes which are prepared;[16] ***Sodium Hexamethyldisilazide*** has been shown to be a good base for generating these conditions. In a Wittig-based synthesis of (*Z*)-trisubstituted allylic alcohols, potassium bis(trimethylsilyl)amide was shown to be the reagent of choice for preparing the starting ylides.[17] These were allowed to react with protected α-hydroxy ketones and depending upon the substitution pattern of the ylide and/or the ketone, stereoselectivities ranging from good to excellent were achieved (eqs 12-14).

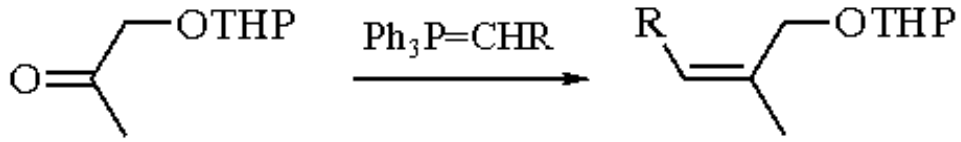

(12)

R	(*Z*):(*E*)	Yield (%)
n-Pr	60:1	87
i-Pr	6:1	45

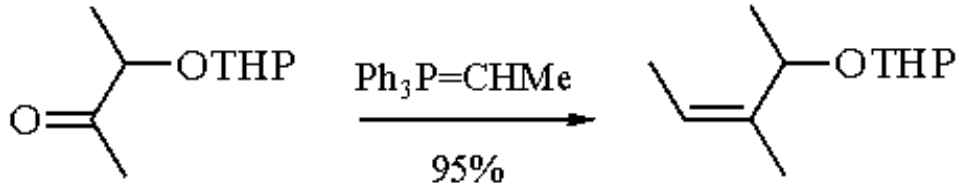

(13)

(*Z*):(*E*) = 200:1

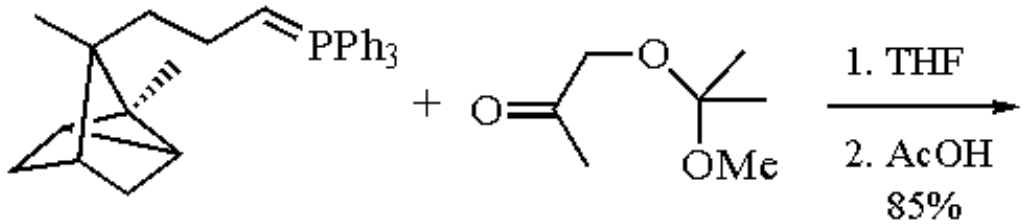

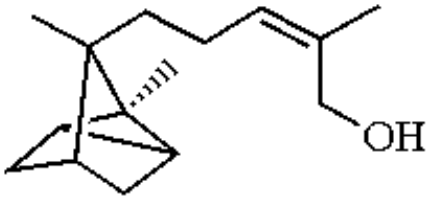

(14)

>99% stereoisomeric purity

Phosphonates.

In a Horner-Emmons-based synthesis of di- and trisubstituted (*Z*)-α,β-unsaturated esters, the strongly dissociated base system of potassium bis(trimethylsilyl)amide/***18-Crown-6*** was used to prepare the desired phosphonate anions. This base system, coupled with highly electrophilic bis(trifluoroethyl)phosphono esters, gave phosphonate anions which, when allowed to react with aldehydes, gave excellent selectivity for the (*Z*)-α,β-unsaturated esters (eq 15).[18]

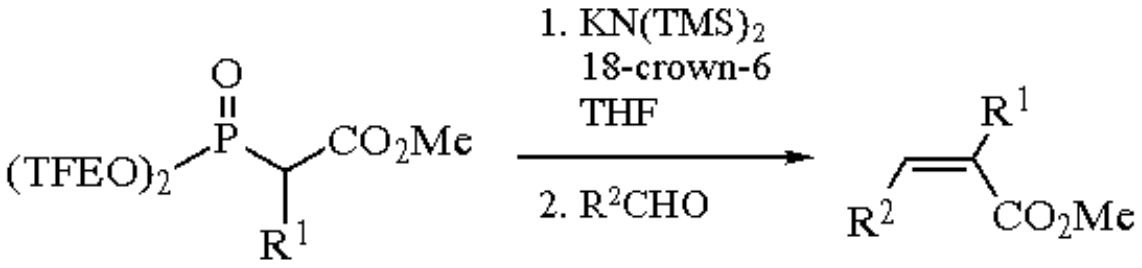

(15)

R^2CHO	R^1	*(Z)*:*(E)*	Yield (%)
$Me(CH_2)_6CHO$	H	12:1	90
$Me(CH_2)_6CHO$	Me	46:1	88
$Me(CH_2)_2CH{=}CHCHO$	H	>50:1	87
$Me(CH_2)_2CH{=}CHCHO$	Me	>50:1	79
CyCHO	H	4:1	71
CyCHO	Me	>50:1	80
PhCHO	H	>50:1	95
PhCHO	Me	30:1	95

Intramolecular Cyclizations.

Haloacetal Cyclizations.

Intramolecular closure of a carbanion onto an α-haloacetal has been shown to be a valuable method for the formation of carbocycles.[19a] Potassium bis(trimethylsilyl)amide was found to be the most useful base for the formation of the necessary carbanions. This methodology may be used for the formation of single carbocycles (eq 16), for annulation onto existing ring systems (eq 17), and for the formation of multiple ring systems in a single step (eq 18). In the case of annulations forming decalin or hydrindan systems, this ring closure proceeded to give largely the *cis*-fused bicycles (eq 17). For the reaction shown in eq 18, in which two rings are being formed, the stereochemistry of the ring closure was found to be dependent upon the counter ion of the bis(trimethylsilyl)amide; use of the potassium base allowed isolation of the *cis*-decalin system as the major product (95%), whereas use of lithium bis(trimethylsilyl)amide led to the isolation of the *trans*-decalin (95%).[19]

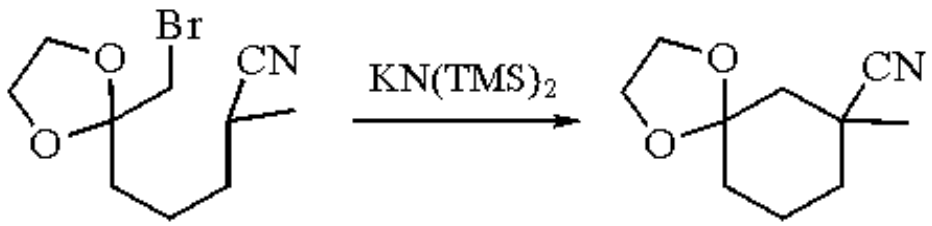

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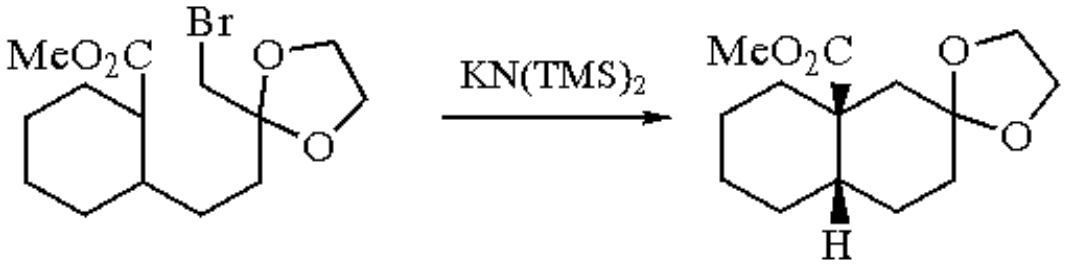

(17)

95% *cis* + 5% *trans* (18)

Intramolecular Lactonization.

In a general method for the formation of 14- and 16-membered lactones via intramolecular alkylation,[20] potassium bis(trimethylsilyl) amide was shown to be a useful base for this transformation (eq 19).

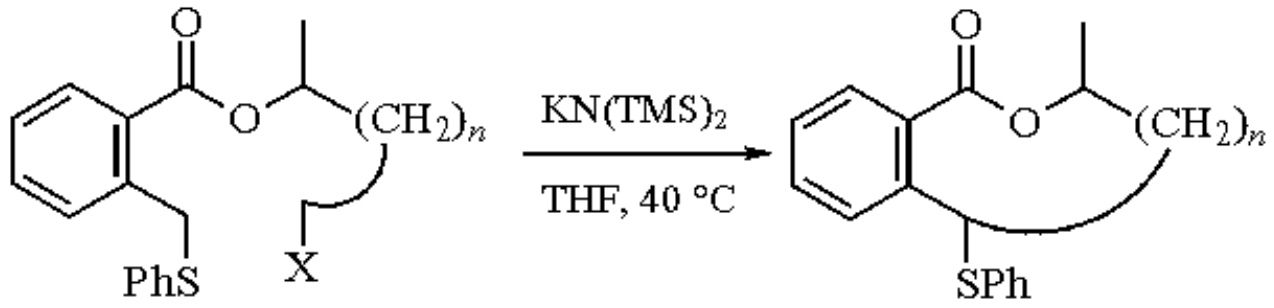

$n = 5$, 0%; 7, 75%; 8, 71% (19)

Intramolecular Rearrangement.

Potassium bis(trimethylsilyl)amide was shown to be a good base for the generation of a diallylic anion which underwent a biogenetically inspired intramolecular cyclization, forming (±)-dicytopterene B (eq 20).[21]

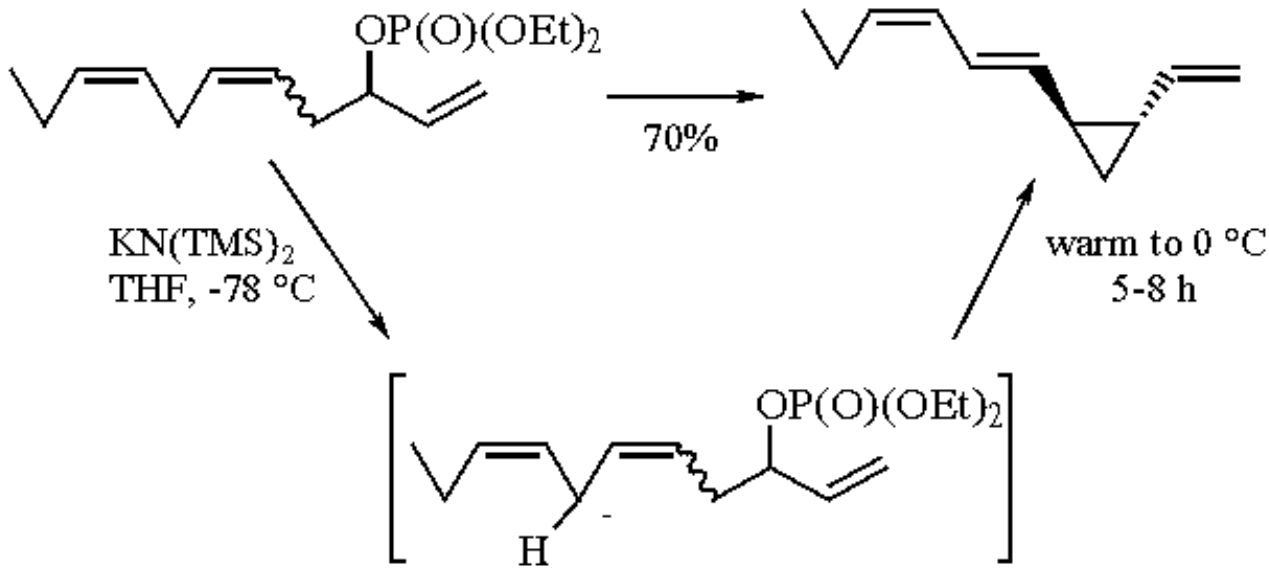

(20)

Synthesis of Vinyl Fluorides.

Addition of potassium bis(trimethylsilyl)amide to β-fluoro-β-silyl alcohols was shown to selectively effect a Peterson-type alkenation reaction to form vinyl fluorides (eq 21).[22] Treatment of a primary β-fluoro-β-silyl alcohol with $KN(TMS)_2$ led cleanly to the terminal alkene. Use of a *syn*-substituted secondary alcohol led to the stereoselective formation of the (*Z*)-substituted alkene (eq 22); reaction of the *anti*-isomer, however, demonstrated no (*Z*:*E*) selectivity.

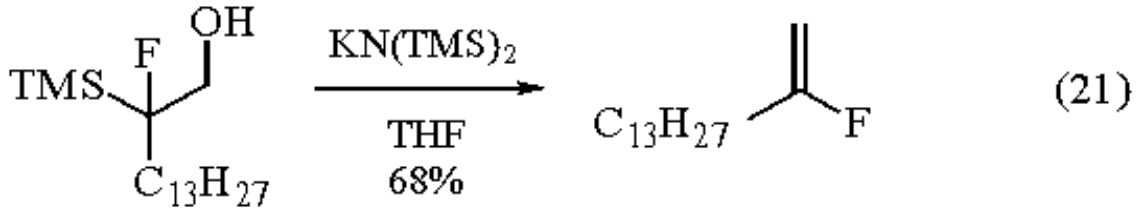

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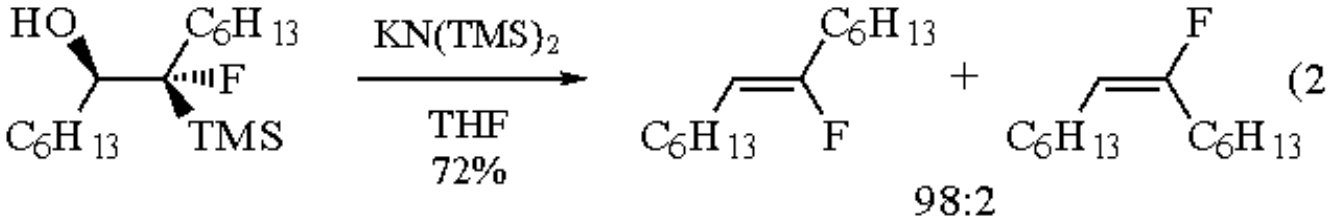

(22)

Oxyanionic Cope Rearrangement.

Potassium bis(trimethylsilyl)amide/18-crown-6 was shown to be a convenient alternative to potassium hydride for the generation of anions for oxyanionic Cope rearrangements (eq 23).[23]

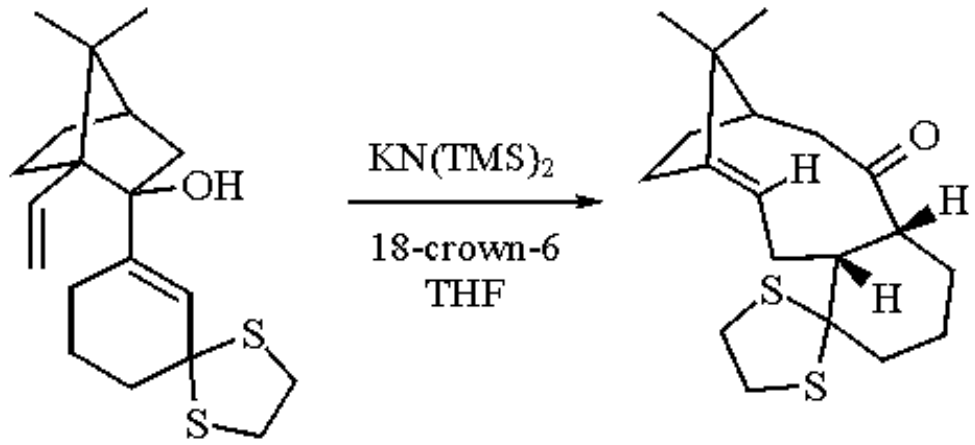

(23)

Stereoselective Synthesis of Functionalized Cyclopentenes.

Potassium bis(trimethylsilyl)amide was shown to be an effective base for the base-induced ring contraction of thiocarbonyl Diels-Alder adducts (eq 24).[24] ***Lithium Diisopropylamide*** has also been shown to be equally effective for this transformation.

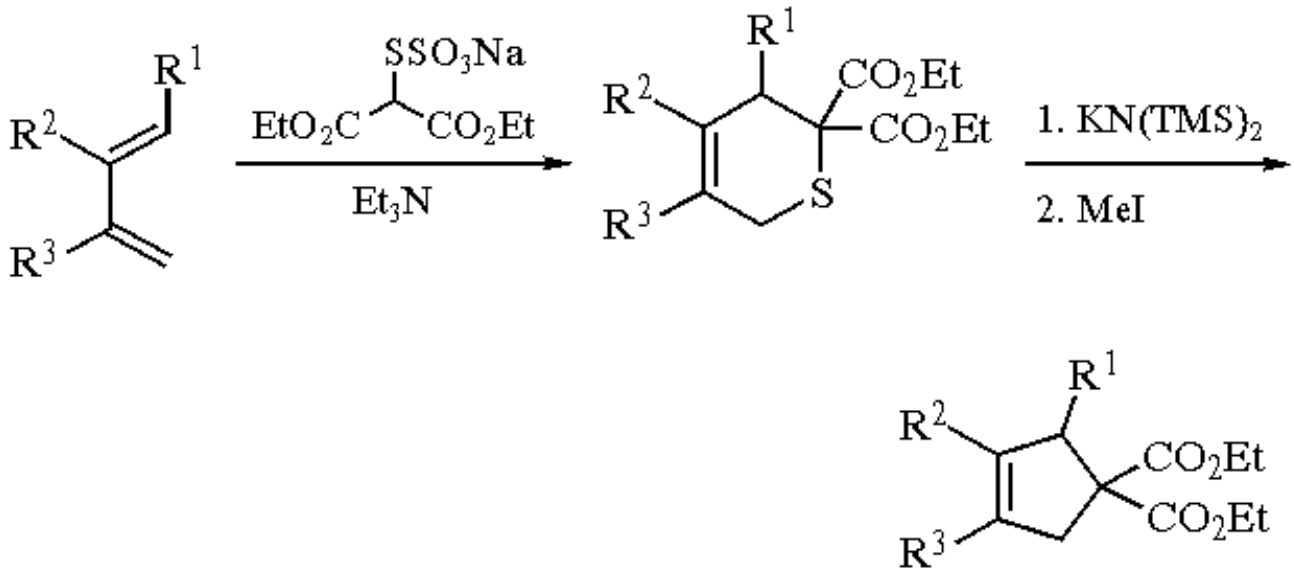

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Potassium Hydride[1]

KH

[7693-26-7] · HK · Potassium Hydride · (MW 40.11)

(base and hydride donor to Lewis acids such as boranes and borates; used for deprotonation, cyclization-condensation, elimination, rearrangement reactions, and as a reducing agent).

Physical Data: solid; dec on heating; *d* 1.47 g cm^{-3}; n_D 1.453.

Solubility: dec in cold and hot water; insol CS_2, ether, benzene.

Form Supplied in: as a dispersion in mineral oil, 20-35% by weight. A standardization procedure has been published.[1]

Purification: commercial KH dispersion is made by reduction of metallic potassium,[2] and so KH is often contaminated with traces of potassium or potassium superoxide. These can be removed by pretreatment with iodine to produce a reagent with superior consistency in several reactions that are sensitive to such impurities.[3]

Handling, Storage, and Precautions: dispersion is a liquid, and tends to settle upon standing. Prolonged storage produces a compacted solid that must be broken up to achieve a homogeneous dispersion. Brown suggests[1] using a long-handled screwdriver to break up the compacted material and leaving a Teflon-covered stir bar in the container to aid dispersion. Clamping the sealed polyethylene bottle containing the dispersion to a Parr shaker for 15 min also works well.

The mineral oil may be removed by adding pentane to small quantities of the dispersion, stirring the slurry, then allowing the hydride to settle. The pentane/mineral oil supernatant may be pipetted off, but care should be exercised to quench carefully any hydride present in the supernatant with a small amount of methanol or ethanol before disposal. Two or three such rinses are sufficient to remove all traces of mineral oil.

Irritant. Great care must be taken in handling, and all operations involving the manipulation of the dry solid material should be conducted under an inert atmosphere in a fume hood.

Introduction.

The following is divided into two major classes of reactions: KH as a base, and KH as a reducing agent. The acid-base reactions are further divided into the type of acid (OH, NH, CH, or Sn/GeH). Secondary effects, such as rate acceleration in oxy-Cope reactions, are listed under the appropriate acid-base reaction.

The reactions of saline hydrides occur at the crystal surface. The crystal lattice energies decrease from LiH to CsH; KH appears to have the optimum lattice energy and hydride radius for surface reactions. It is thus usually superior to LiH or NaH in the reactions discussed below.

Acid-Base Reactions.

Oxygen Acids.

Potassium hydride reacts rapidly and quantitatively with acids such as carboxylic acids, phenols, and alcohols.[1] Of particular note is its ability to rapidly deprotonate tertiary alcohols and hindered phenols, instances where ***Sodium Hydride*** or elemental ***Potassium*** react sluggishly or not at all. For example, triethylcarbinol and 2,6-di-*t*-butylphenol are quantitatively deprotonated in less than 5 min by KH in either ether or diglyme at 20 °C (eqs 1 and 2). For triethylcarbinol, NaH is ineffective, and K is sluggish in comparison.[4]

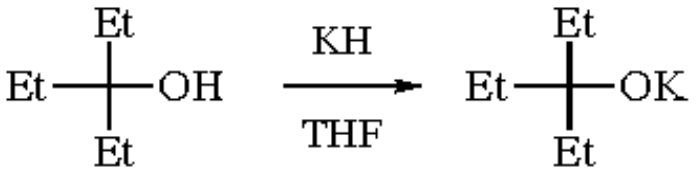

(1)

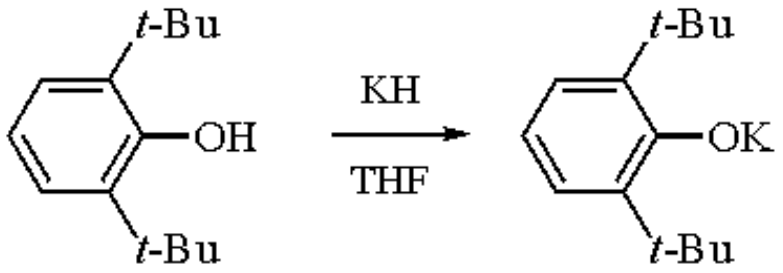

(2)

An interesting conformational effect is seen when *p-t*-butylcalix[4]arene is tetraethylated. When KH is used as the base, the partial cone conformation predominates, whereas with NaH, the cone is produced exclusively (eq 3).[5]

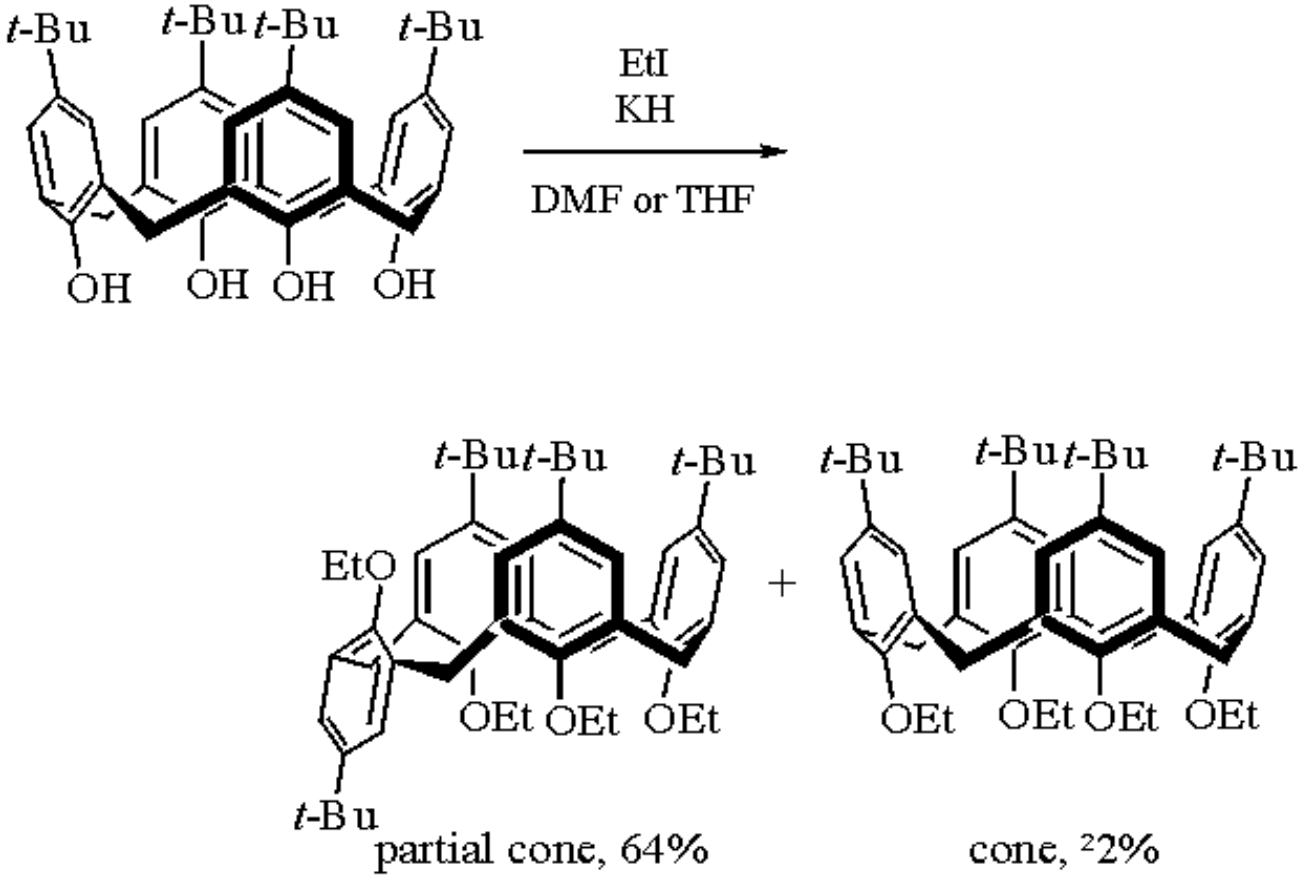

(3)

An unusual cyclization of hydroxyallenes to dihydrofurans is mediated by KH (eq 4).[6] The reaction only proceeds when the K is complexed to ***18-Crown-6***, or when the base is ***Potassium t-Butoxide*** in refluxing *t*-butanol. Interestingly, no products of [1,3]- or [3,3]-rearrangement were detected.

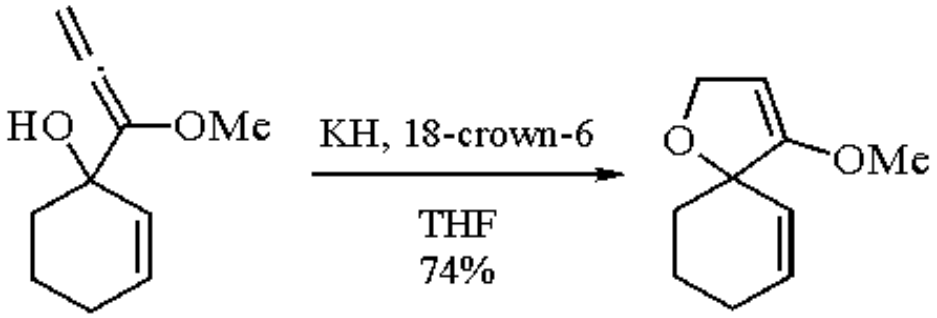

(4)

Cyclization of a KH-generated alkoxide is a method for the 100% stereoselective formation of spiroacetals by an intramolecular 1,4-addition to sulfoxides (eqs 5 and 6).[7] Lower selectivity resulted when either NaH or ***n-Butyllithium*** was used in the first step.

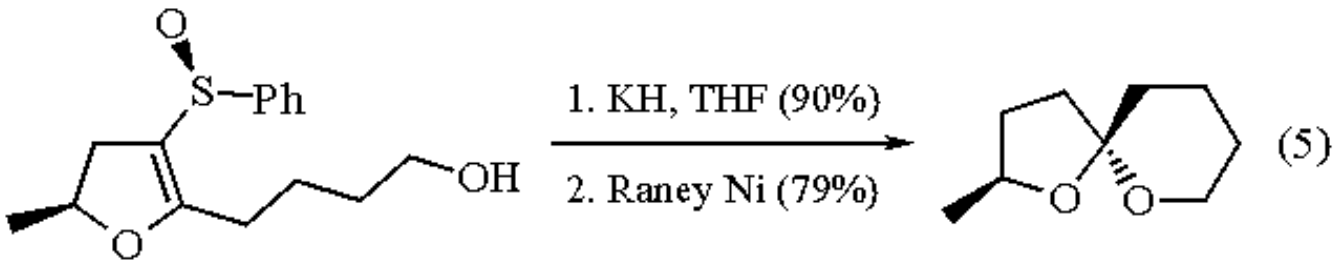

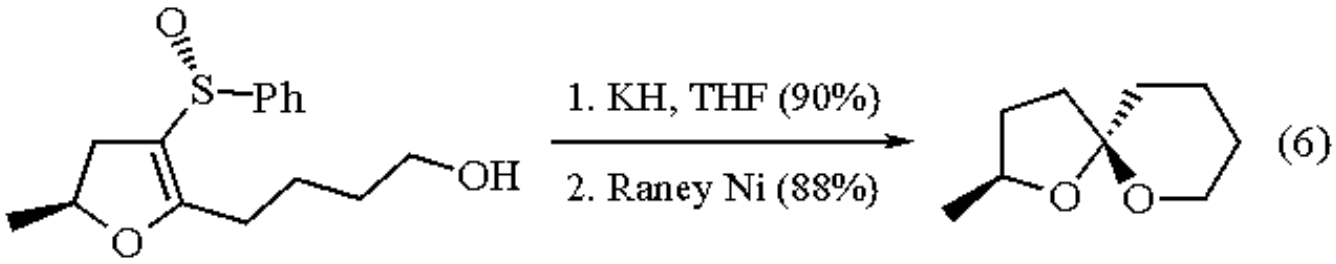

The elimination of trimethylsilanol from β-hydroxysilanes is a highly selective *syn* elimination when mediated by KH (eq 7).[8] In contrast, acid-catalyzed elimination is *anti* selective. The KH reaction is complete in 1 h at rt, whereas NaH requires 20 h in HMPA and results in a lower yield of product.

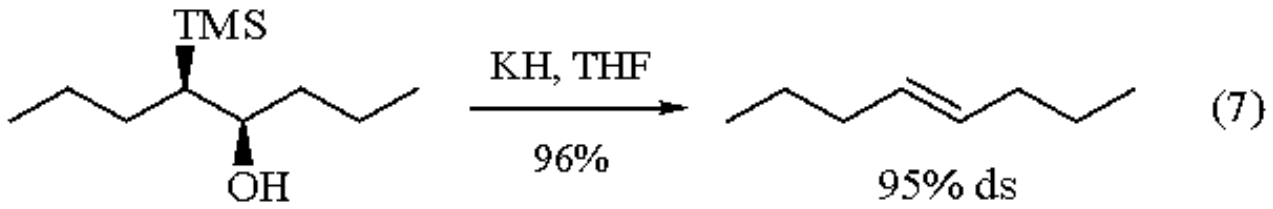

The *syn* elimination (eq 7) can be coupled with an intramolecular epoxide ring-opening to effect a stereoselective synthesis of α-alkylidenetetrahydrofurans (eq 8).[9]

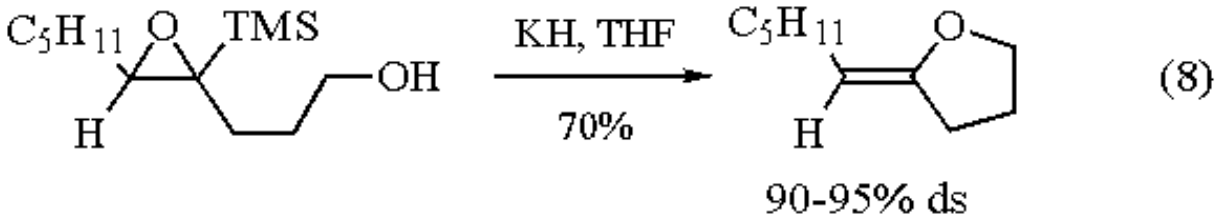

Rate enhancements on the order of 10^{10} to 10^{17} are observed for a [3,3]-sigmatropic rearrangement (oxy-Cope) of an *endo*-vinylbicyclo[2.2.2]octene alkoxide (generated with KH in the presence of HMPA or crown ether) vs. the alcohol (eq 9).[10] Certain substrates for this reaction are quite sensitive to impurities in the KH, but pretreatment with ***Iodine*** eliminates the problem.[3]

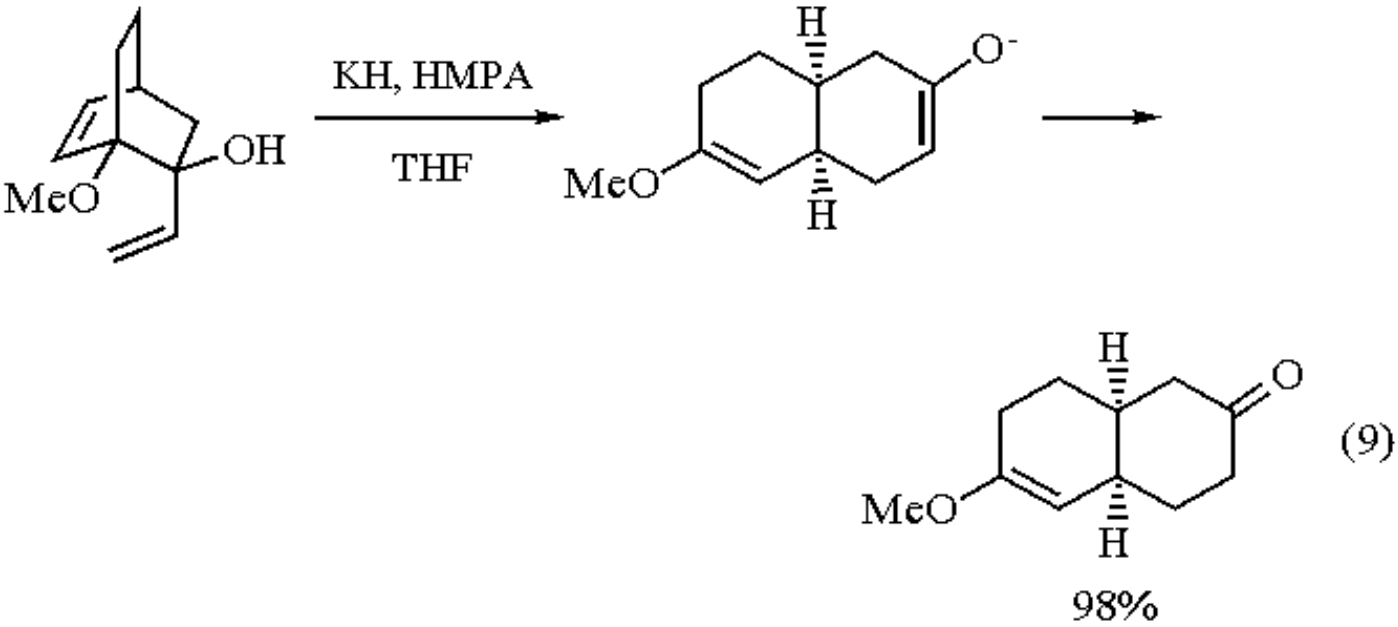

Rate accelerations of &egt;10^6 by alkoxides have been observed for a [4 + 2] cycloreversion (Alder-Rickert reaction).[11] Eq 10 illustrates an example; replacement of the methyls with either BOM or acetonide protecting groups is also possible.[12]

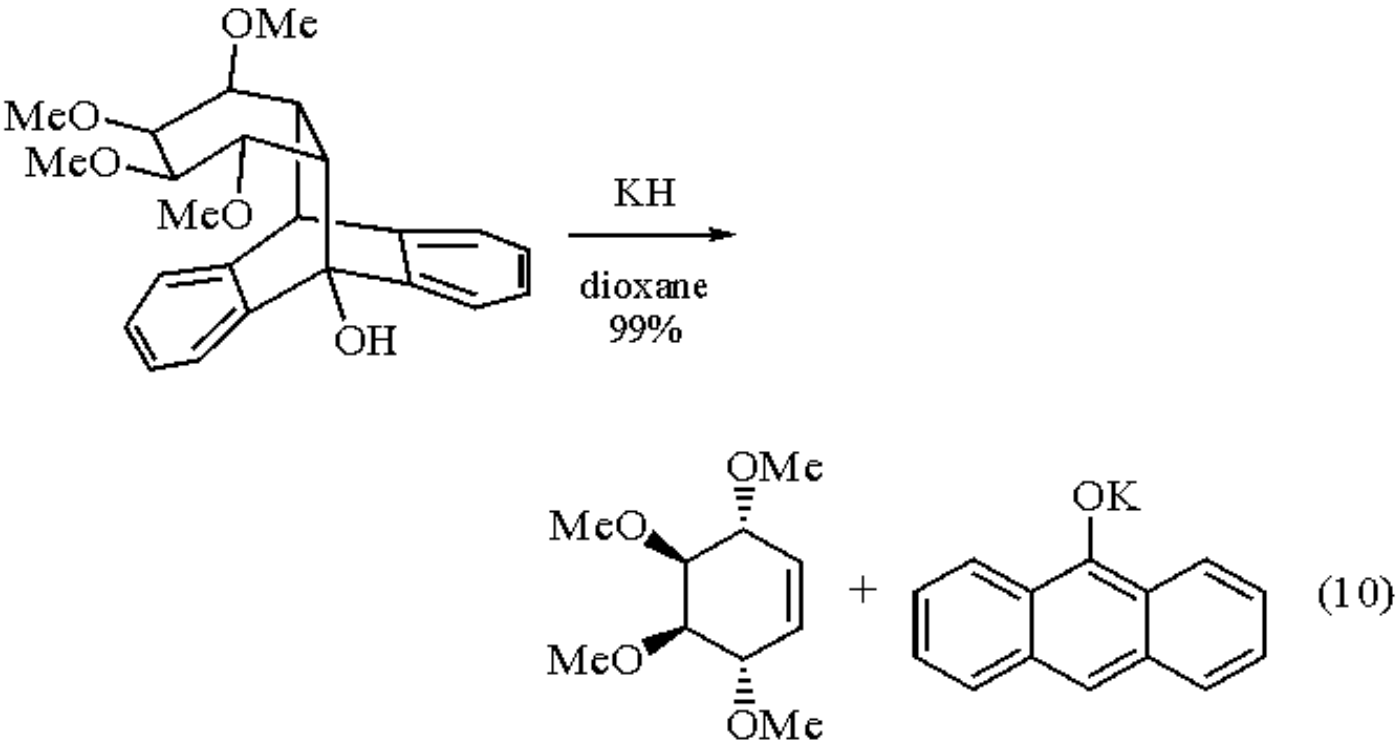

Nitrogen Acids.

Amines such as ***Diisopropylamine*** are not deprotonated by KH, although ***1,2-Diaminoethane***, diisobutylamine, and ***Pyrrolidine*** may be kaliated in excess amine solvent.[4a] *N*-Isopropylaniline and ***Hexamethyldisilazane*** are kaliated effectively and quantitatively in THF (eqs 11 and 12).[1,4b]

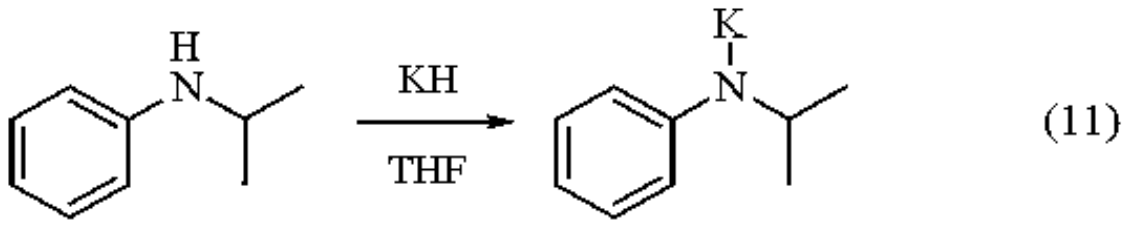

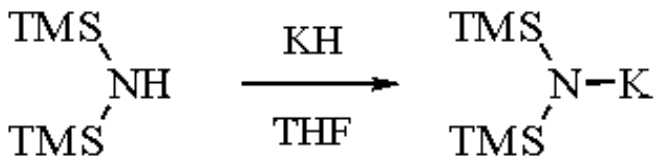

(12)

Deprotonation of indoles is also effective, and has been used to protect the N-H bond prior to a lithium-halogen exchange.[13] Subsequent reaction with an electrophile occurs selectively at the lithiated position (eq 13).

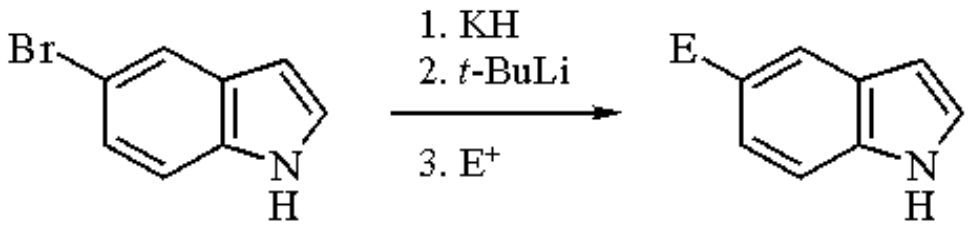

(13)

E = CHO, MeCO, $CONH_2$, TMS, $SnMe_3$

Carbon Acids.

Dimethyl Sulfoxide is deprotonated in <=10 min with KH in THF at rt (eq 14).[1] Under similar conditions, NaH is essentially unreactive. Cyclopentadiene (eq 15) and fluorene are deprotonated quantitatively as well.[1]

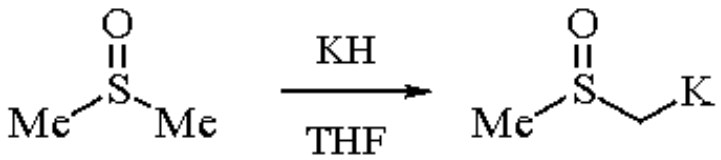

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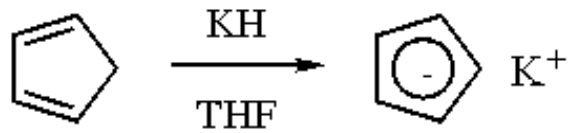

(15)

Triphenylmethane is not deprotonated directly by KH, unless a catalytic amount of DMSO[1] (via in situ formation of dimsylpotassium, which in turn deprotonates triphenylmethane) or a crown ether is present (eq 16).[14]

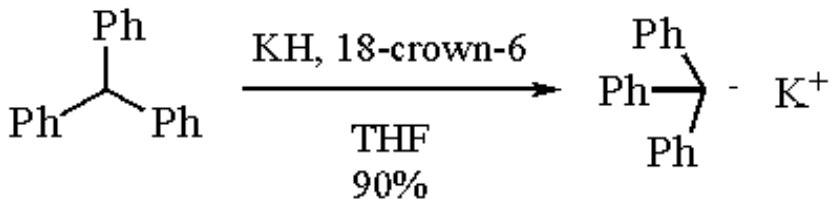

(16)

Potassium hydride deprotonates ketones such as acetone, cyclohexanone, and isobutyrophenone with little or no self-condensation or reduction.[1] For unsymmetrical ketones such as 2-methylcyclohexanone, a mixture of regioisomers is produced. *O*-Acylation[15] and silylation[16] are thus facilitated. Permethylation of cyclopentanone can be achieved by addition of the ketone to a THF suspension of KH, followed by ***Iodomethane*** (eq 17).[17]

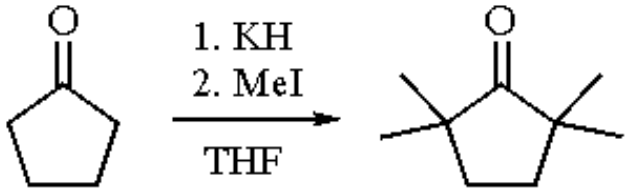

(17)

Monoalkylation can be achieved by treating the potassium enolate with ***Triethylborane*** prior to alkylation (eq 18).[18]

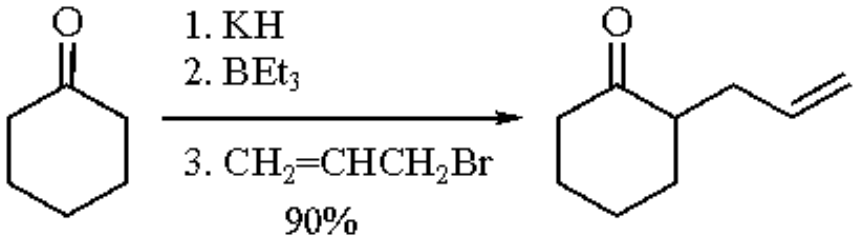

(18)

α,β-Unsaturated ketones give γ-alkylation, although polymerization can be a problem.[1] The enamines of β-diketones, however, can be alkylated in good yield (eq 19).[19] KH also mediates the Claisen condensation of esters (eq 20).[20]

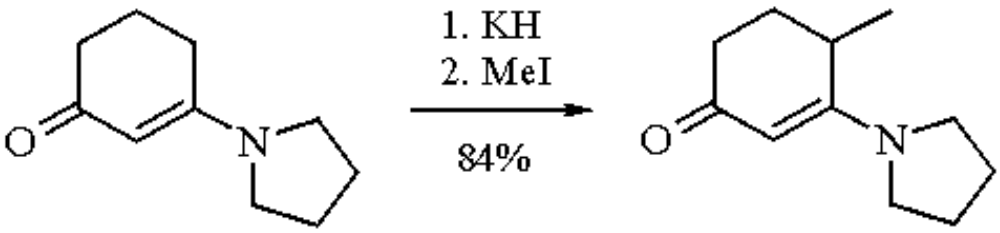

(19)

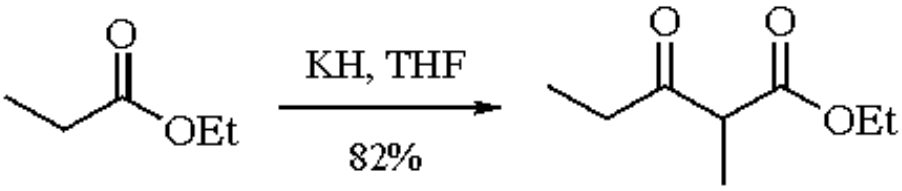

(20)

Potassium hydride facilitated a tandem intramolecular Michael reaction-Claisen condensation in the synthesis of aklavinones.[21] In the absence of any additive, the unnatural *C*-10 isomer was the only product observed in the NMR, but in the presence of 2.2.2-cryptand, the desired isomer was produced in 53% isolated yield (eq 21).

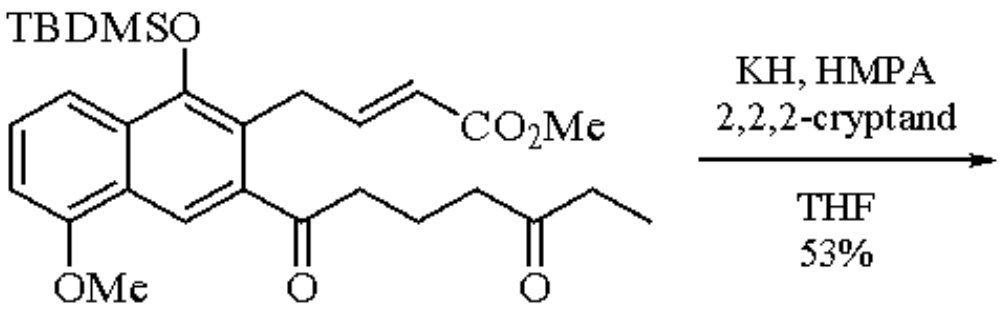

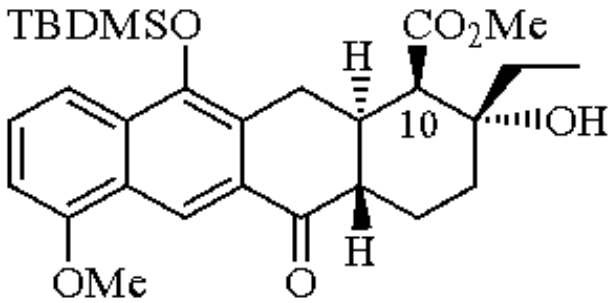

(21)

Ester enolate formation has been used to eliminate an acylamino group in a synthesis of condensed heterocycles, such as the indanone shown in eq 22.[22] The azabicycloheptene starting material is available by a Diels-Alder reaction, and the *N*-acyl group is removed in situ.

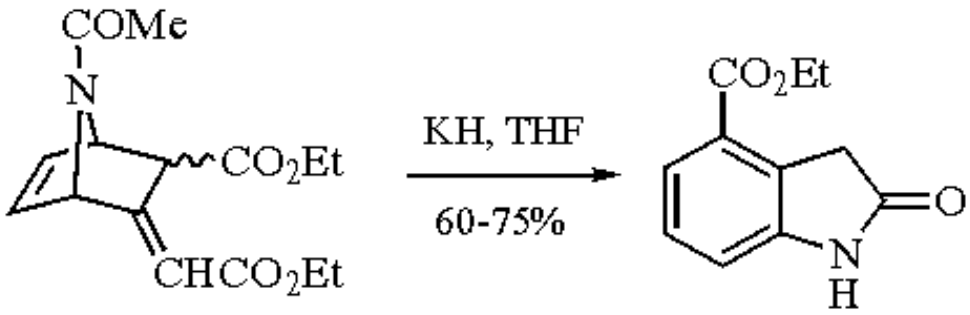

(22)

Silicon, Tin, and Germanium Acids.

Trimethylsilane, tributylstannane, and tributylgermane are efficiently metalated by KH (eq 23).[23] These reactions are sensitive to impurities in the KH,[24] but pretreatment of the KH with iodine alleviates the difficulties.[3]

$$R_3XH \xrightarrow[60\text{-}80\%]{KH,\ THF} R_3X^-\ K^+ \qquad (23)$$

X = Si, Sn, Ge
R = Me, Bu, Ph

Reductions.

Potassium salts of selenanes,[25] silanes, and stannanes are also produced by reduction of Se-Se, Si-Si, and Sn-Sn bonds by KH (eq 24).[23]

$$R_nXXR_n \xrightarrow{KH,\ THF} R_nX^-\ K^+ \qquad (24)$$

X = Se ($n = 1$), Si, Sn ($n = 3$)
R = Me, Ph

Potassium hydride reduces hindered boranes and borates to trialkyl (or trialkoxy) borohydrides.[1,26] For example, tri-*s*-butylborane is reduced in 93% yield (eq 25).

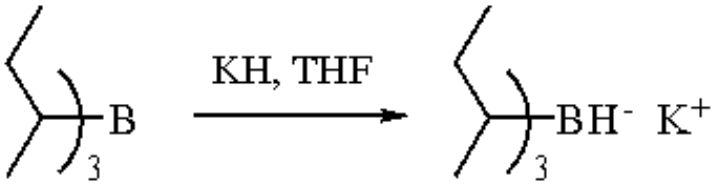

(25)

Reduction of butylpotassium with hydrogen produces a superactive form of KH that reduces ketones and alkyl halides in high yields (eq 26).[27] This active hydride also deprotonates aldehydes and ketones at low temperature, but reduction is often a side reaction.

$$C_9H_{19}CH_2Br \xrightarrow[95\%]{KH^*,\ THF} C_9H_{19}Me \qquad (26)$$

Related Reagents.

Calcium Hydride; ***Potassium Hydride-s-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine***; ***Potassium Hydride-Hexamethylphosphoric Triamide***; ***Sodium Hydride***.

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Potassium Hydride-*s*-Butyllithium-*N,N,N´,N´*-Tetramethylethylenediamine

KH-*s*-BuLi-$Me_2NCH_2CH_2NMe_2$

(KH)

[7693-26-7] · HK · Potassium Hydride-*s*-Butyllithium-*N,N,N´,N´*-Tetramethylethylenediamine · (MW 40.11) (*s*-BuLi)

[598-30-1] · C_4H_9Li · Potassium Hydride-*s*-Butyllithium-*N,N,N´,N´*-Tetramethylethylenediamine · (MW 64.07) (TMEDA)

[110-18-9] · $C_6H_{16}N_2$ · Potassium Hydride-*s*-Butyllithium-*N,N,N´,N´*-Tetramethylethylenediamine · (MW 116.24)

(α,β-dideprotonation of γ,δ-unsaturated ketones[1,2] and their analogs,[1,3,4] producing dianions, d^5-synthons,[5] which react with electrophiles exclusively at the δ-position[2,3])

Physical Data: see entries for ***Potassium Hydride***, ***s-Butyllithium***, and ***N,N,N´,N´-Tetramethylethylenediamine***.

α,β-Dideprotonation of Unsaturated Ketones.

This combination of reagents is used to dideprotonate γ,δ-enones in two steps. The relatively acidic α-proton is abstracted with 1 equiv of KH in THF (eq 1) and the less acidic β-proton is removed with 1 equiv of *s*-BuLi and 1 equiv of TMEDA (eq 2).[1,3] These last two reagents are simply added to the solution of the enolate. The resulting dianions, (**1**) (eq 3) and (**2**) (eq 4), react with suitable electrophiles exclusively at the δ-position[2,3] and are thus d^5-synthons.[5]

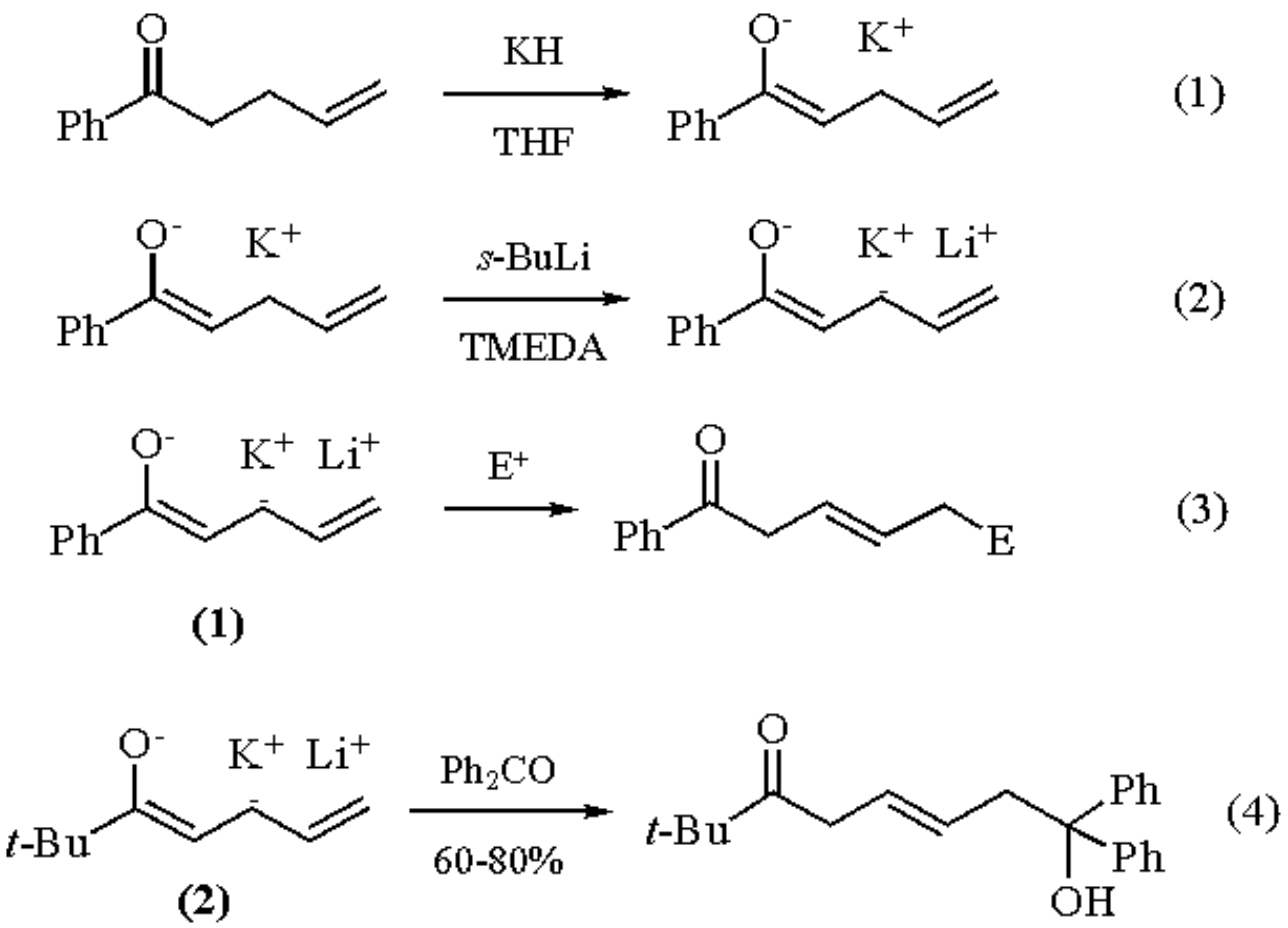

Analogous α,β-dideprotonation of γ,δ;ε,ζ-dienones yields dianions which also react with electrophiles exclusively at the terminal position. Higher yields are generally obtained when the nucleophile lacks any readily enolizable α´-protons.[1] Aldehydes, ketones (eq 4), and alkyl halides (eq 5) are all suitable electrophiles.[1,2]

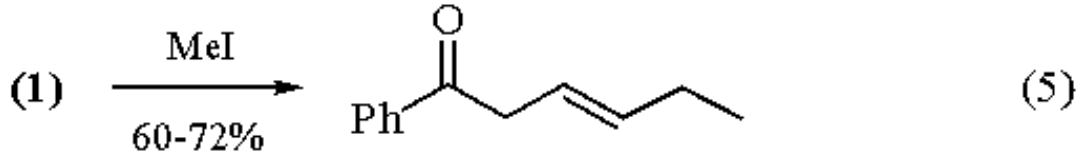

Acylation of dianions (**1**) and (**2**) does not give good yields.[1] Isolated double bonds in the electrophile (eq 6) are usually not affected, and conjugated double bonds (eq 7) give Michael adducts.[1]

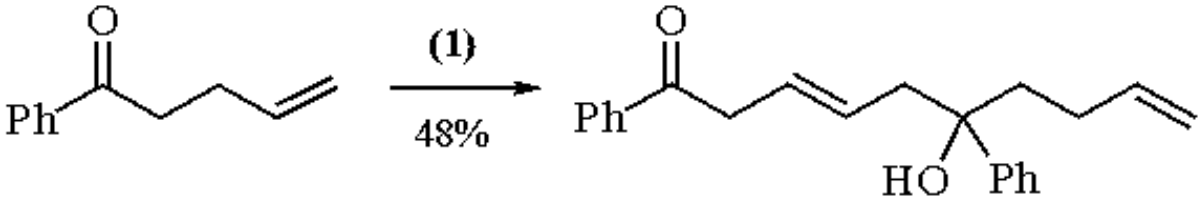

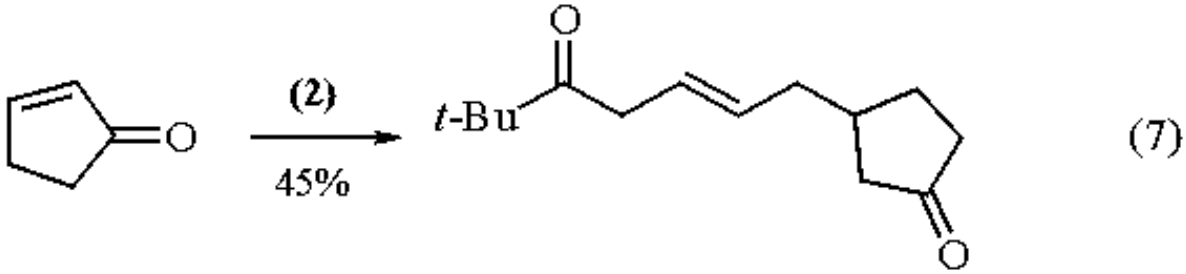

Alkylations and carbonyl condensations using dianions (**1**) and (**2**) are not very diastereoselective.[1] Excellent stereoselectivity can, however, be obtained with the use of epoxides as the electrophiles (eq 8).[1]

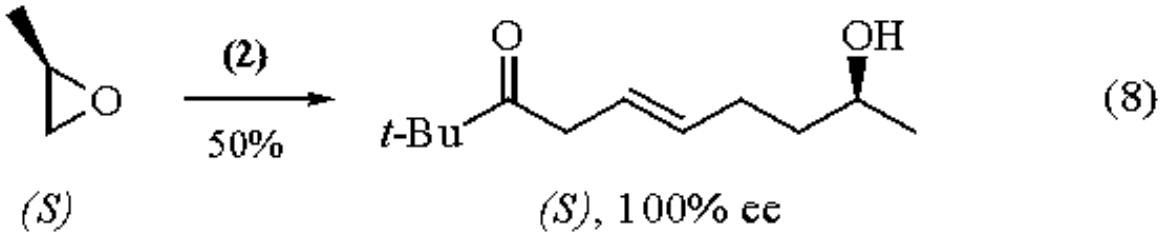

Enols such as the products of eq 4 and eq 8 cyclize, when treated with ***Sodium Methoxide*** in methanol, into THF (eq 9) and THP (eq 10) derivatives, respectively.[1,2]

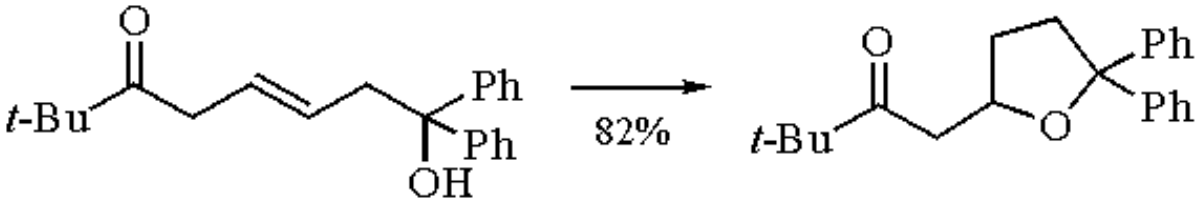

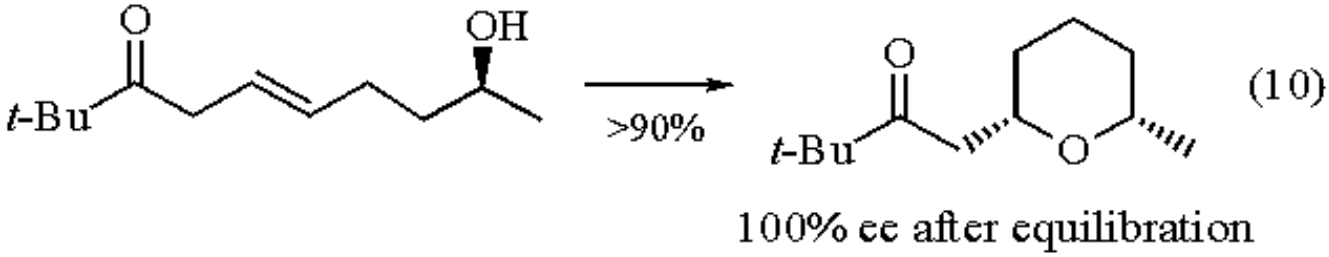

α,β-Dideprotonation of Ketone Analogs.

While carboxylic acids, esters, and amides do not undergo this reaction,[3] other ketone analogs do.[1,3,4] α´-Hydroxy ketones work well (eq 11),[1] but the trianion, instead of the dianion, derivative must first be made. This is accomplished by using an extra equivalent of KH in the first step. The resulting ketones are very useful products, since they may be reacted with glycol cleaving agents to yield carboxylic acids which are then amenable to many useful transformations.[1]

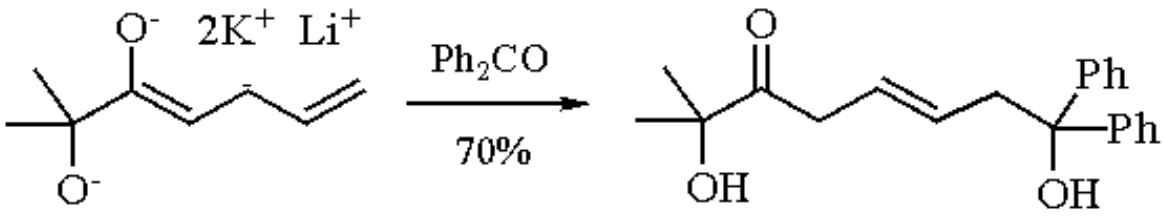

(11)

Dideprotonation of dithioesters yields dianions of type (**3**) that react with electrophiles in the same fashion (eq 12).[1,4] Alternatively, the adduct (**4**) can be quenched with methyl iodide to give ketene thioacetals (eq 13).[1,4]

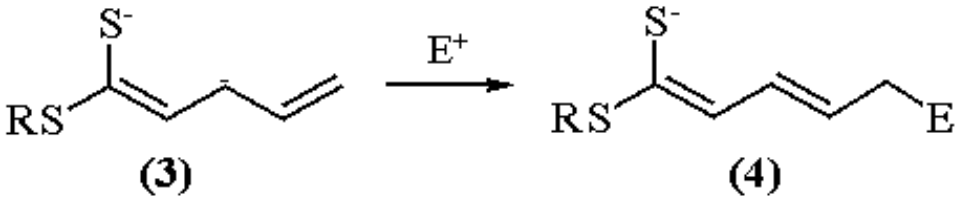

(3) (4)

(12)

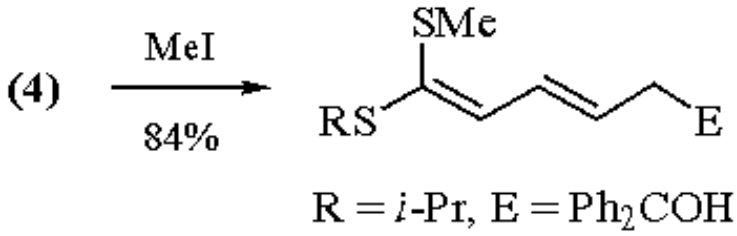

(13)

These ketene thioacetals can be deprotonated using excess ***Lithium Diisopropylamide*** and protonated with acid or alkylated with an alkyl halide at the acetal carbon to give products of type (**5**) which can then be hydrolyzed to the ketone (eq 14).[1]

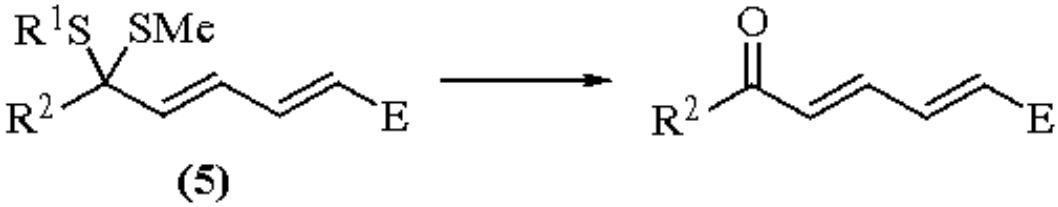

(5)

(14)

Most of the reaction products illustrated here can undergo further functional group transformations, furnishing a variety of useful synthetic intermediates.[1] There are a variety of other d^5-synthons[5] reported in the literature, some similar to those presented here. They range from Wittig reagents derived from carboxylic acid salts[6] or protected ketones,[7] to nitro compounds,[8] alkynes,[9] Grignard reagents,[10] thio-Claisen substrates,[11] and others.[12] A similar combination of reagents has also been used to dideprotonate β-carboline formamidine to produce a dianion that alkylates at C-1 (eq 15).[13]

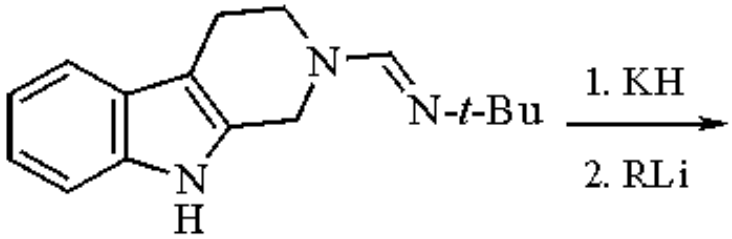

R = Me, Bu or *t*-Bu

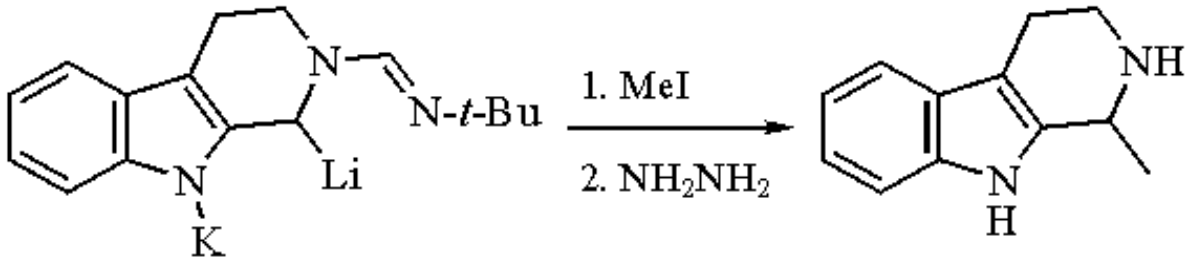

(15)

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Potassium Hydride-Hexamethylphosphoric Triamide[1]

$KH/(Me_2N)_3PO$

(KH)

[7693-26-7] · HK · Potassium Hydride-Hexamethylphosphoric Triamide · (MW 40.11) (HMPA)

[680-31-9] · $C_6H_{18}N_3OP$ · Potassium Hydride-Hexamethylphosphoric Triamide · (MW 179.24)

(strong base used for the deprotonation of alcohols, ketones, and silanes; HMPA appears to facilitate subsequent transformations such as fragmentations and sigmatropic rearrangements)

Physical Data: see entries for ***Potassium Hydride*** and ***Hexamethylphosphoric Triamide***.

Oxygen Acids.

Potassium hydride is superior to both ***Sodium Hydride*** and lithium hydride in the deprotonation of a number of weak acids (see ***Potassium Hydride***). In the presence of HMPA, alkoxides of several allylic alcohols may be induced to fragment to allyl anions and ketones. Subsequent deprotonation of the ketone by the allylpotassium liberates propene, and workup affords a mixture of unsaturated ketones (eqs 1 and 2).[2]

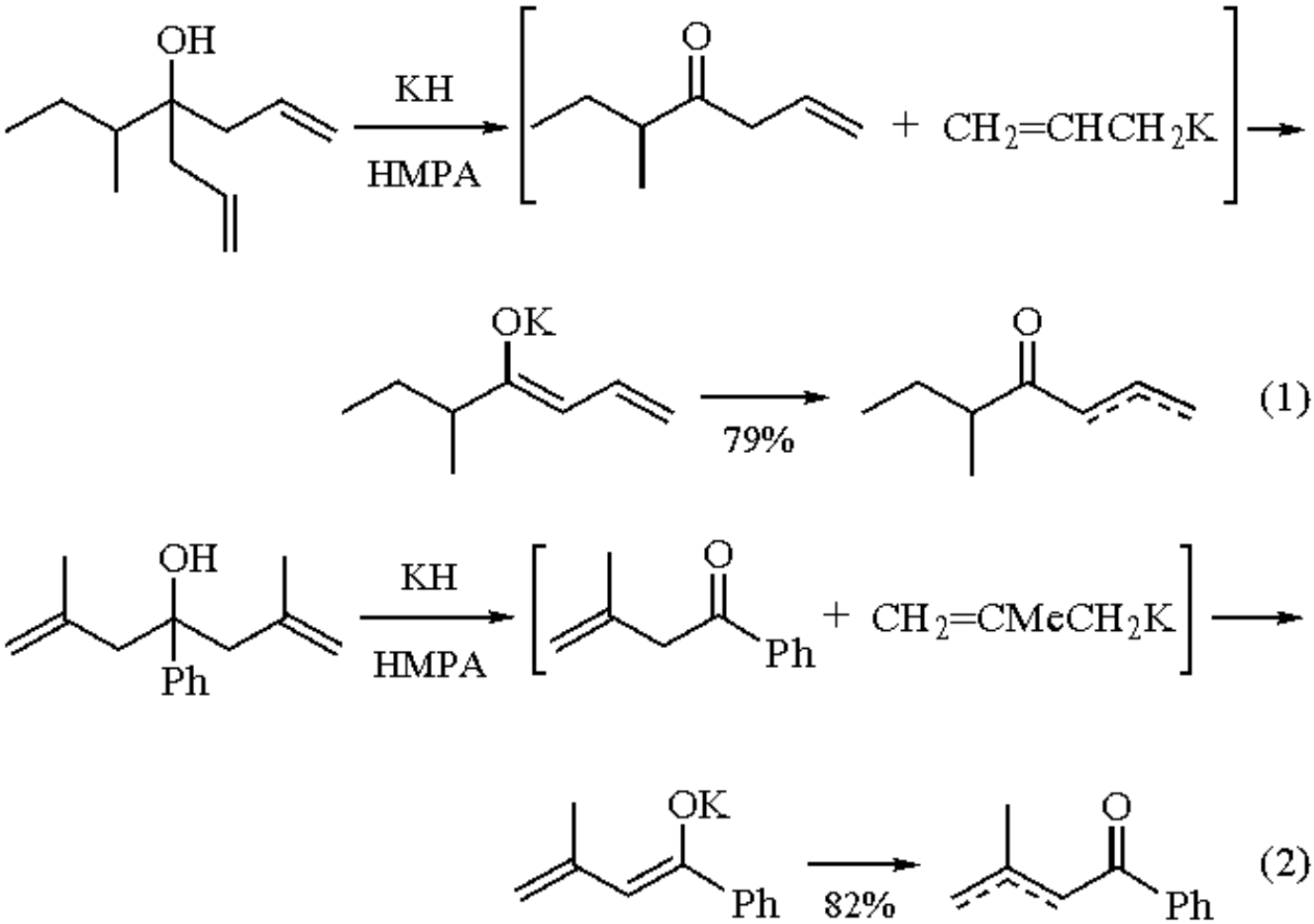

In the total synthesis of the antibiotic ionomycin, Evans used the asymmetric alkylation of a prolinol amide (eq 3). Deprotonation of the

hydroxy group with KH, then deprotonation of the amide with ***Lithium Diisopropylamide***, produced the dianion. Addition of HMPA and a primary alkyl iodide afforded the alkylation product in good yield and excellent stereoselectivity.[3] Note that there are relatively few methods for the highly selective alkylation of enolates, since most enolates tend to be unreactive toward unactivated (nonallylic) alkyl halides at the low temperatures required for high selectivity.

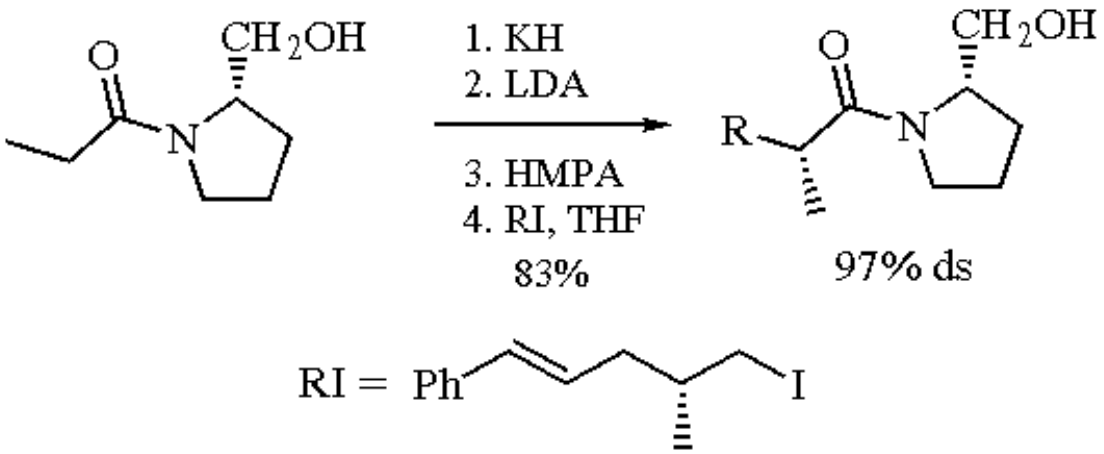

(3)

When α-hydroxysilanes are treated with KH in HMPA, the alkoxide undergoes a stereospecific Brook rearrangement[4] producing a silyl ether which, upon hydrolysis, affords the desilylated alcohol. This rearrangement has been observed for aryl-, alkyl-, and vinyl-substituted α-hydroxysilanes (eq 4).[5]

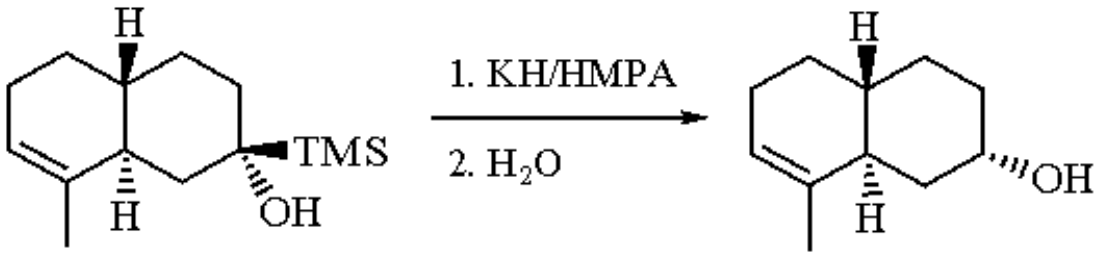

(4)

Potassium salts of 1-vinylcyclobutanols rearrange readily to form cyclohexanones when a sulfur substituent is present at the 2-position. This reaction proceeds by a fragmentation/Michael addition mechanism (eqs 5 and 6) and provides a synthetically useful route to cyclohexanones functionalized with a 4-phenylthio group.[6]

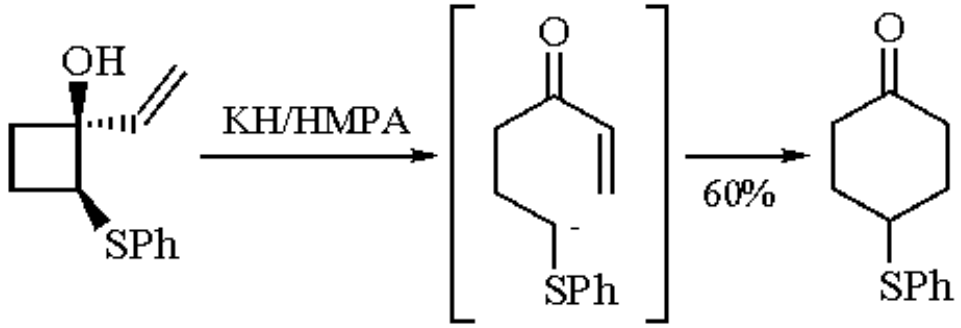

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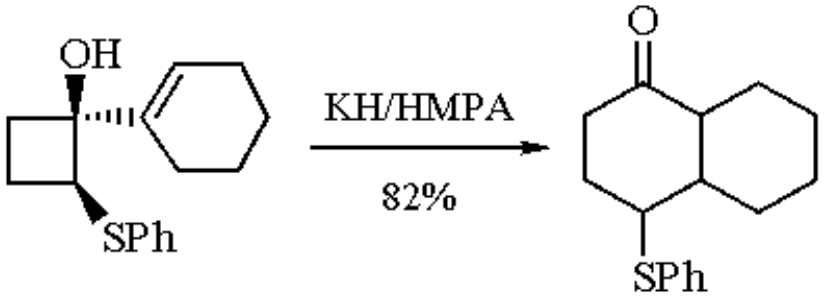

(6)

The KH/HMPA combination reagent also accelerates [1,3]- and [3,3]-sigmatropic rearrangements. For medium-sized ring 1-vinyl alcohols, [1,3]-sigmatropic shifts predominate at rt under the influence of KH and HMPA (eq 7).[7] In contrast, thermal rearrangements of the corresponding trimethylsilyl ethers require temperatures of approximately 300 °C.

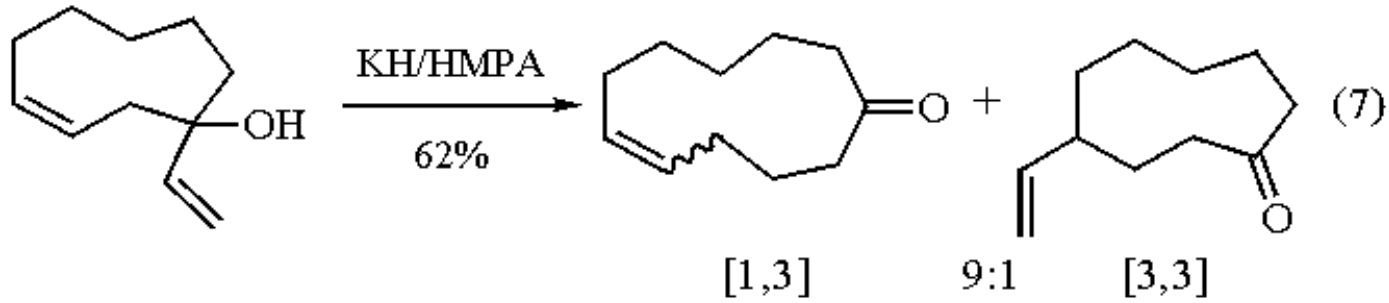

Evans found rate enhancements on the order of 10^{10} to 10^{17} for a [3,3]-sigmatropic rearrangement of an *endo*-vinyl-bicyclo[2.2.2]octene alkoxide (in the presence of HMPA or crown ether) vs. the alcohol (eq 8).[8]

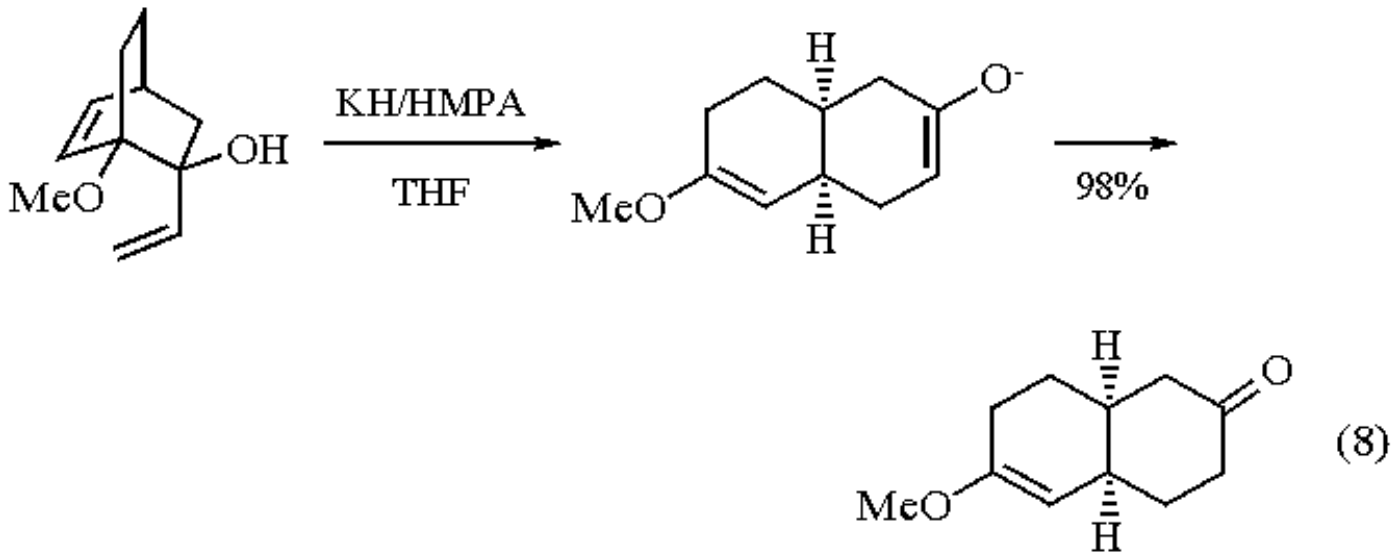

Carbon Acids.

Potassium hydride may be used for the deprotonation of ketones, as illustrated by eq 9. In this example, attempts to alkylate the lithium enolate were unsuccessful.[9]

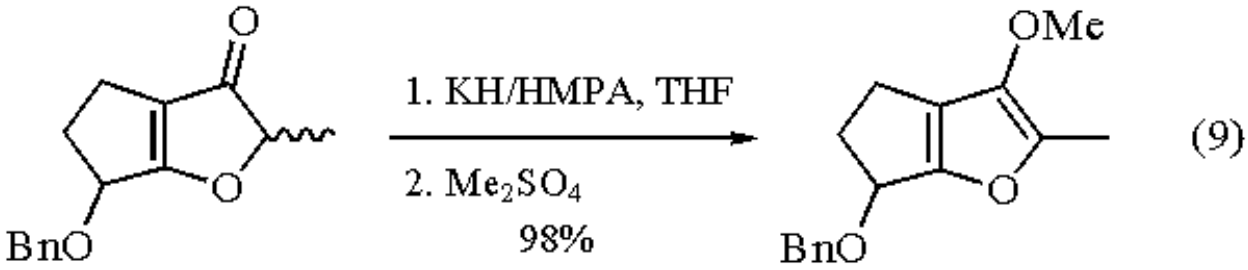

Deprotonation and alkylation of β-keto esters using KH/HMPA constitutes a key step in a cyclopentenone annulation strategy (eq 10).[10] In the absence of HMPA, the yield of this one-pot annulation drops to 27%.

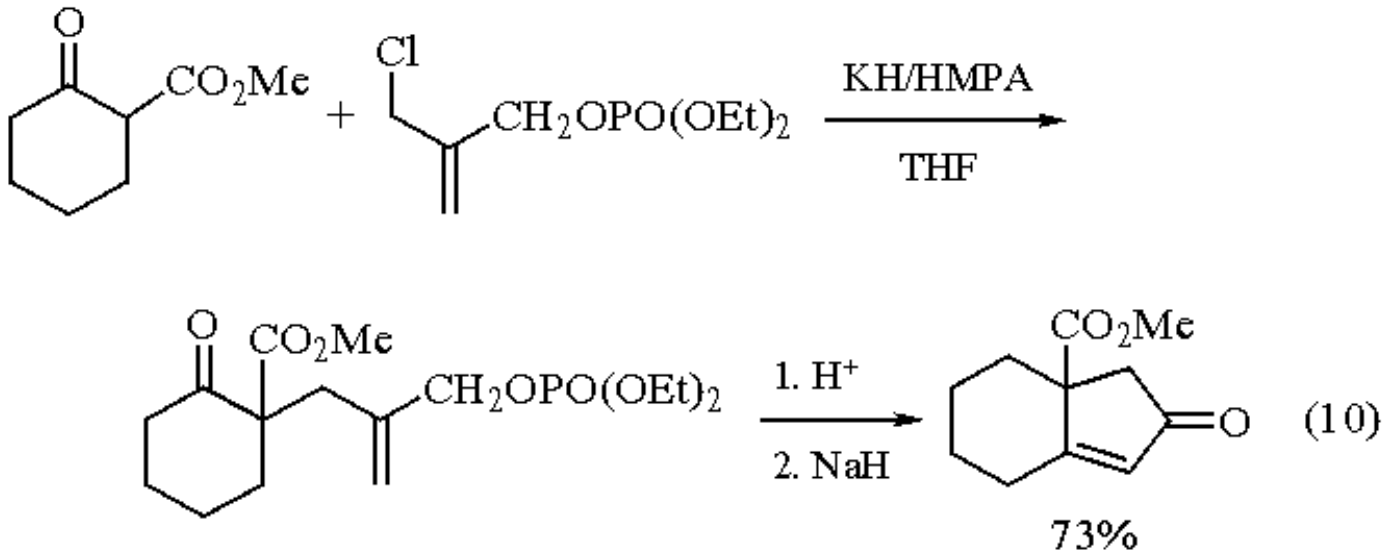

In an enantiodivergent synthesis of (+)- and (-)-nonactic acid, Bartlett employed a deprotonation and intramolecular *O*-alkylation of a carbonate to obtain a tetrahydrofuran in 90% yield (eq 11).[11] It was noted that this intramolecular reaction was surprisingly facile due to the stereoelectronic effect of the *syn-syn* geometry of the carbonate. A diastereomeric furan was obtained by acid-catalyzed cyclization of the corresponding diol.

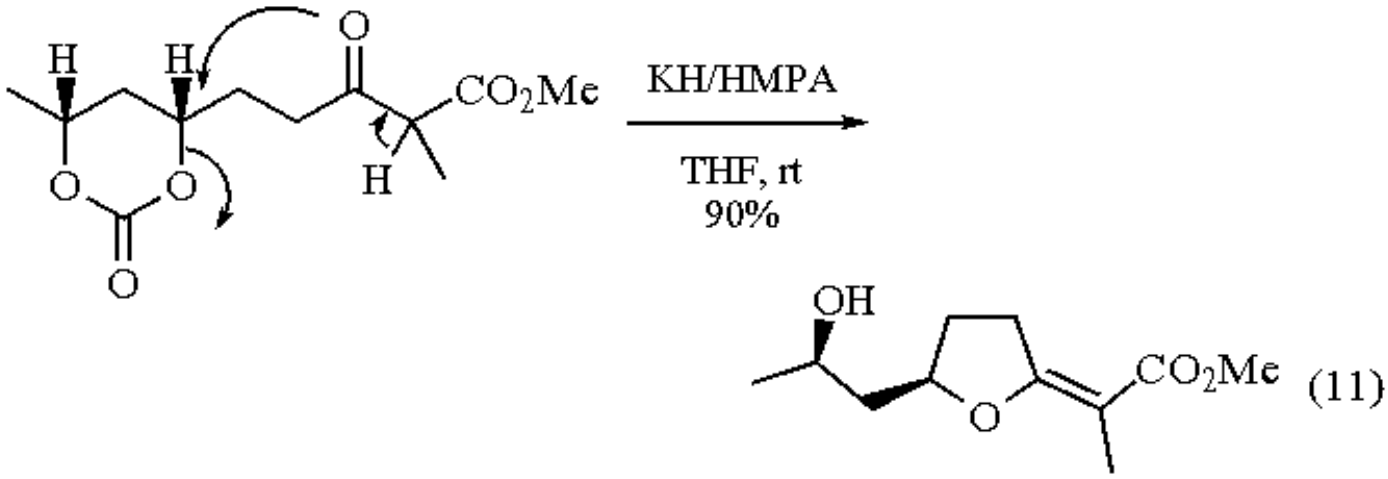

Deprotonation of a ketone with KH/HMPA may also be used in an enolate acylation process (eq 12).[12]

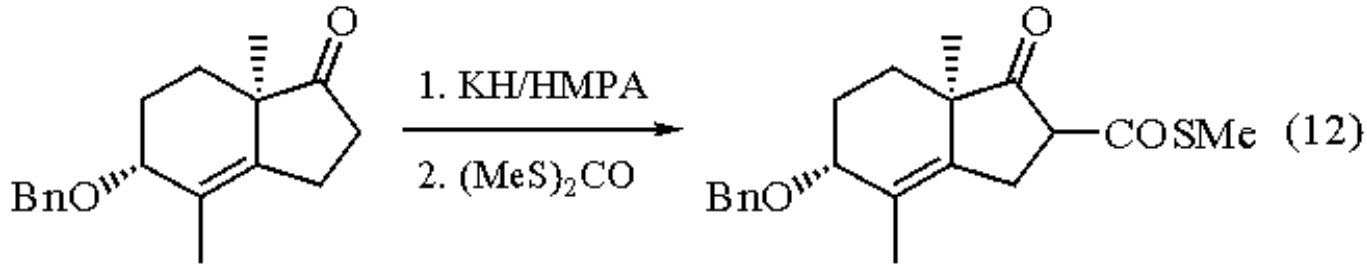

Rate accelerations of Claisen rearrangements were observed when aryl sulfones were deprotonated with KH/HMPA (eq 13);[13] thus significant improvements in yield (from 40 to 78%) resulted. Note that the regiochemistry of the rearrangement is thermodynamically controlled, as the more stable anion is formed even though rearrangement takes place at the more hindered site.

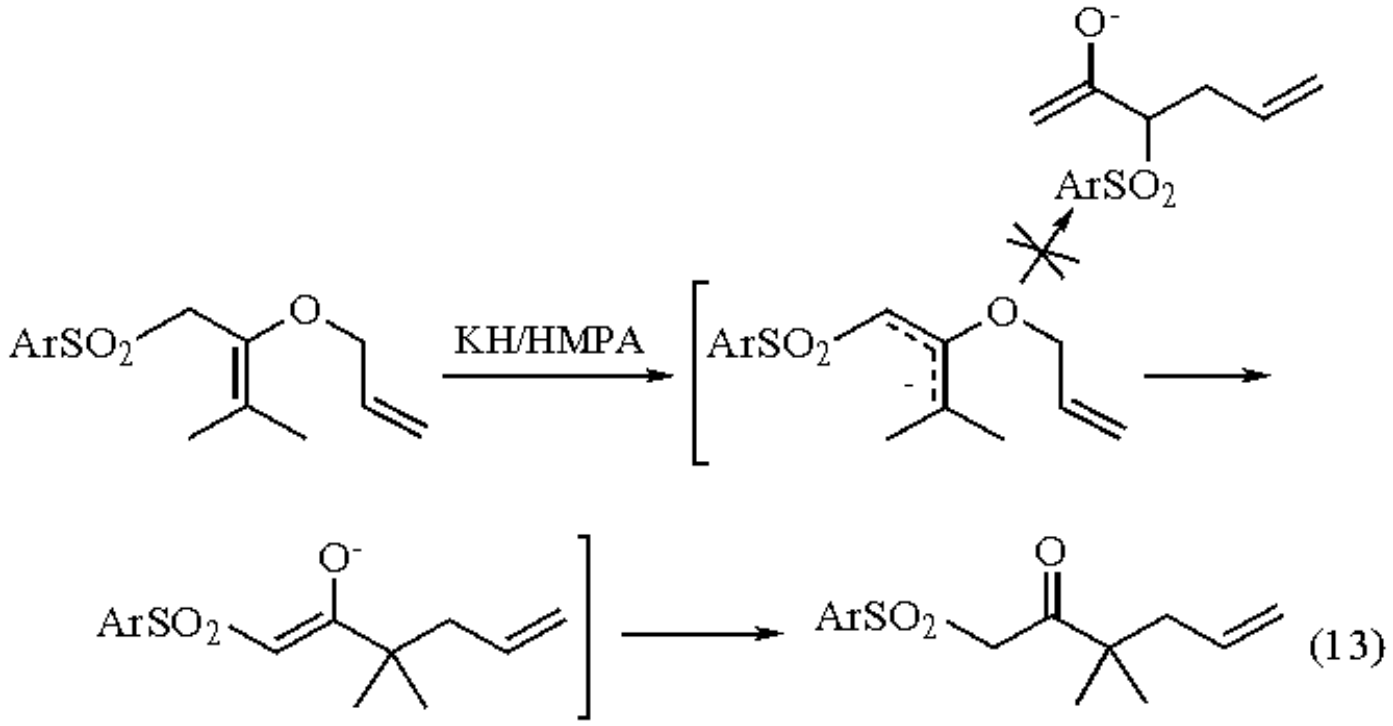

Silicon Acids.

Finally, when triphenylsilane is treated with KH in 1:1 HMPA/DME, triphenylsilylpotassium is produced in high yield (eq 14).[14]

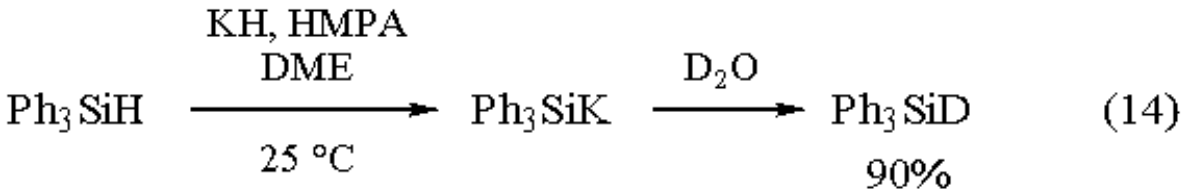

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Potassium Hydrogen Sulfate

$KHSO_4$

[7646-93-7] · HKO_4S · Potassium Hydrogen Sulfate · (MW 136.18)

(used in the preparation of acetals;[1] dehydrating agent[2])

Alternate Name: potassium bisulfate.

Physical Data: mp 214 °C; *d* 2.322 g cm^{-3}.

Solubility: sol water, isopropyl alcohol, acetone.

Form Supplied in: white powder or granules; fused solid.

Purification: crystallized from ethanol.

Handling, Storage, and Precautions: store in a cool dry place; hygroscopic, corrosive; wash thoroughly after repeated handling; causes burns.

Acetalization Reagent.

Isobutyraldehyde is efficiently protected as its acetal with 2-ethylhexanol in the presence of $KHSO_4$ in 93% yield (eq 1).[1] $KHSO_4$ is comparable as a catalyst to benzenesulfonic acid in yield and crude product purity and gives a better colored product as compared to the same reaction catalyzed by ***Sulfuric Acid*** (see also ***p-Toluenesulfonic Acid***).

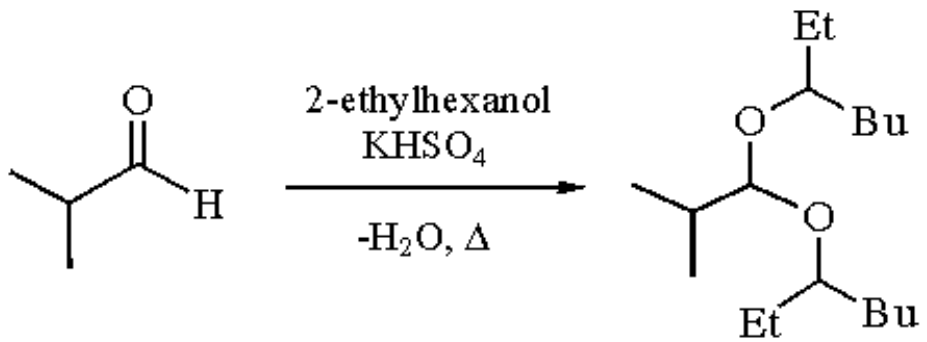

(1)

Dehydrating Agent.

Dienones can be generated using $KHSO_4$ under acidic conditions. For example, a steroidal tosylate was refluxed for 45 min with $KHSO_4$ in acetic acid to produce the dienone as the major product (eq 2).[3] A carotenoid aldehyde has been prepared by dehydrating a monoprotected triol with $KHSO_4$ at 150 °C (eq 3).[4] The unsaturated aldehyde was produced in quantitative yield.

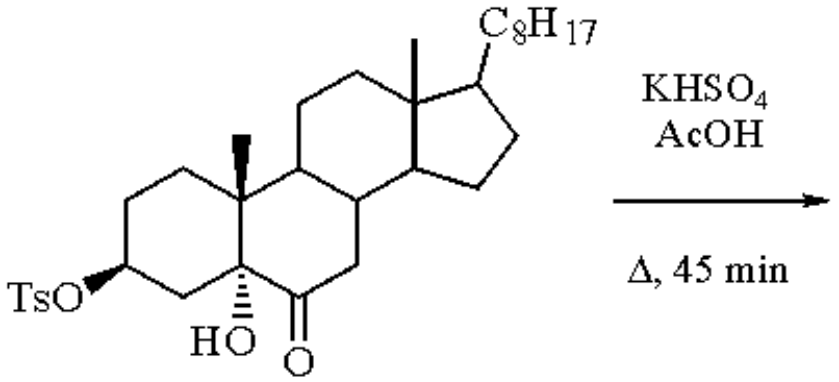

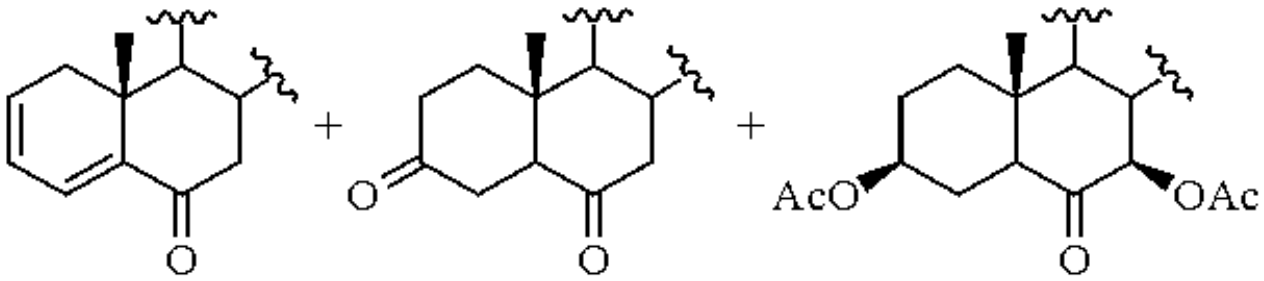

(2)

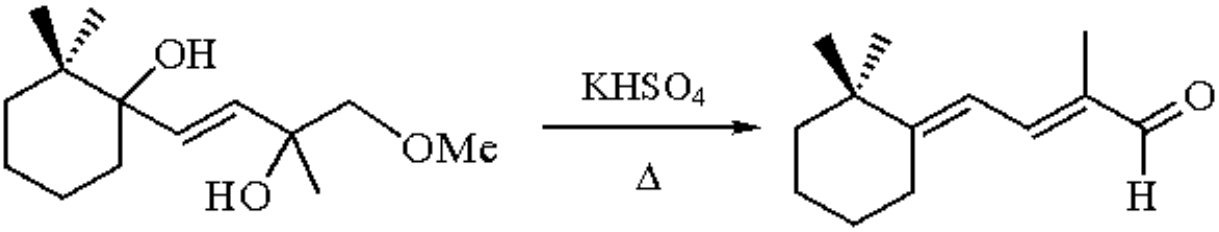

(3)

Treating aryl alcohols with fused $KHSO_4$ affords the corresponding alkene. For example, *m*-chlorophenylmethylcarbinol, $KHSO_4$, and a catalytic amount of *p*-*t*-butylcatechol under partial vacuum for 6 h gave *m*-chlorostyrene in 80-83% yield (eq 4).[2] Aryl alcohols are also dehydrated when treated with $KHSO_4$ in the presence of ***Copper*** powder. For example, treatment of 1-(2-fluorenyl)ethanol with a mixture of $KHSO_4$/Cu followed by sublimation at 180-200 °C for 30 min afforded the corresponding terminal aryl alkene in 31% yield and a coupled product in 17% yield.[5] $KHSO_4$ has also been used to prepare butadienes. Dehydration of 4-phenylbut-3-en-2-ol with $KHSO_4$ gave *trans*-1-phenylbuta-1,3-diene (see also ***Alumina***).[6]

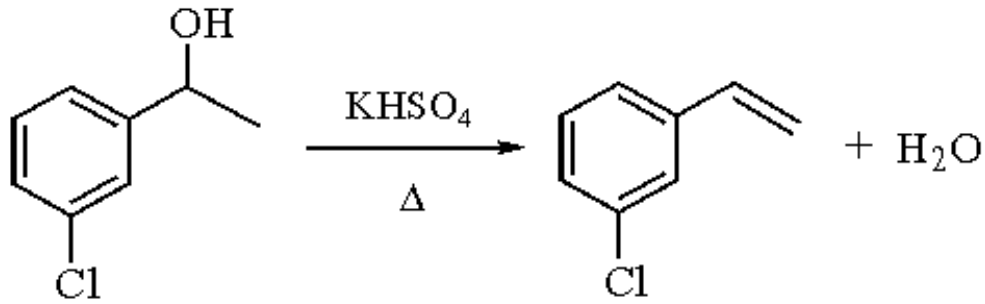

(4)

Pyruvic acid has been prepared by dehydrating tartaric acid with $KHSO_4$ at 210-220 °C (eq 5).[7] Key intermediates in the synthesis of branched long chain fatty acids involve the use of $KHSO_4$. For example, treatment of the diol produced from the reaction of methyl *n*-pentyl ketone with the Grignard complex of but-4-yn-1-ol with $KHSO_4$ followed by catalytic hydrogenation and oxidation afforded 4-methylnonane-1-carboxylic acid (eq 6).[8]

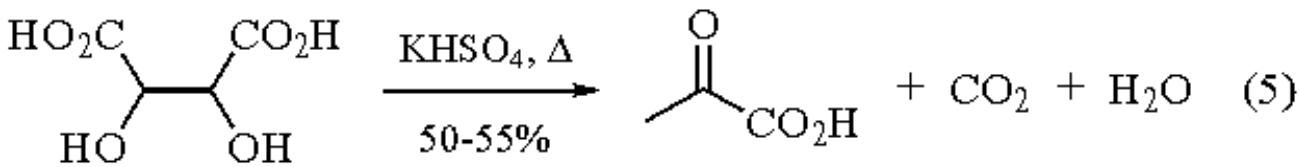

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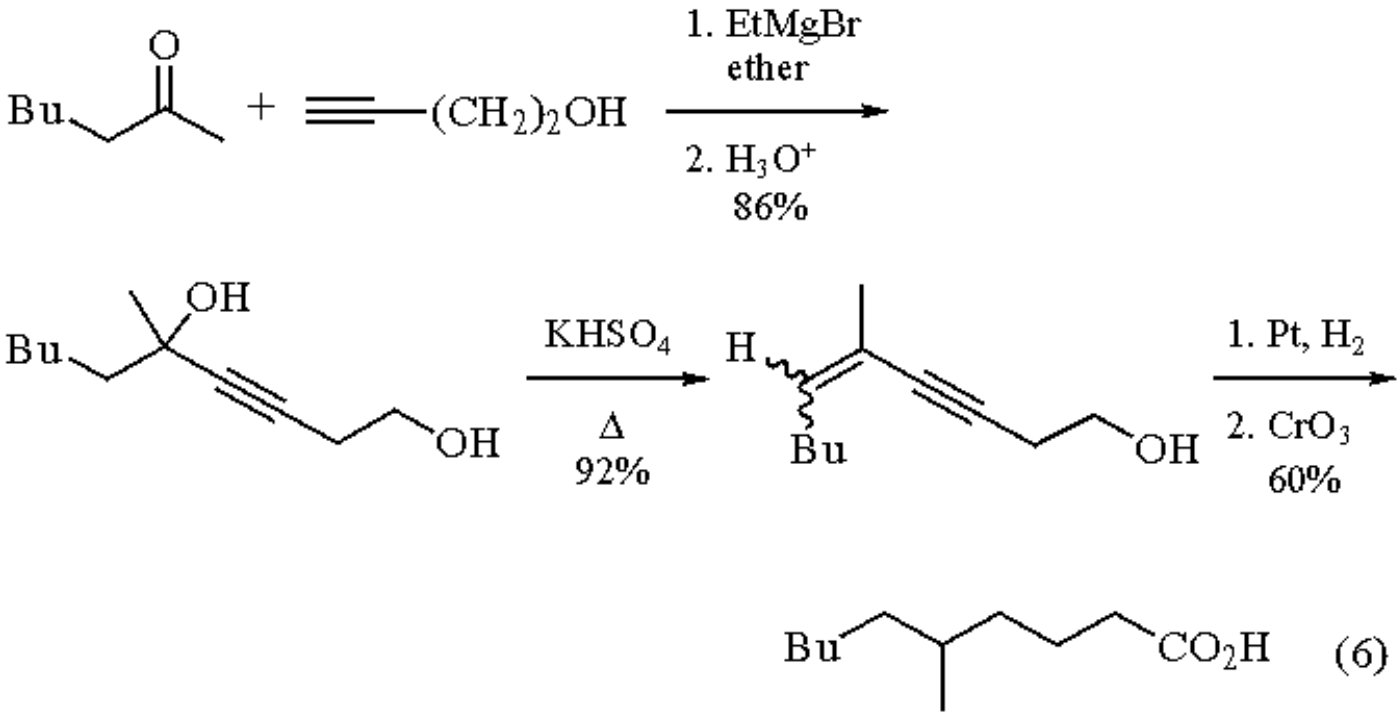

(6)

Dehydrative coupling using $KHSO_4$ has been used in the synthesis of vitamin K_1. Thus treatment of 2-methyl-1,4-naphthohydroquinone-1-acetate and phytol with $KHSO_4$ in dioxane for 90 min at 76 °C gave the corresponding allene (eq 7).[9] Hydrolysis of this product gave vitamin K_1 in 50% overall yield.

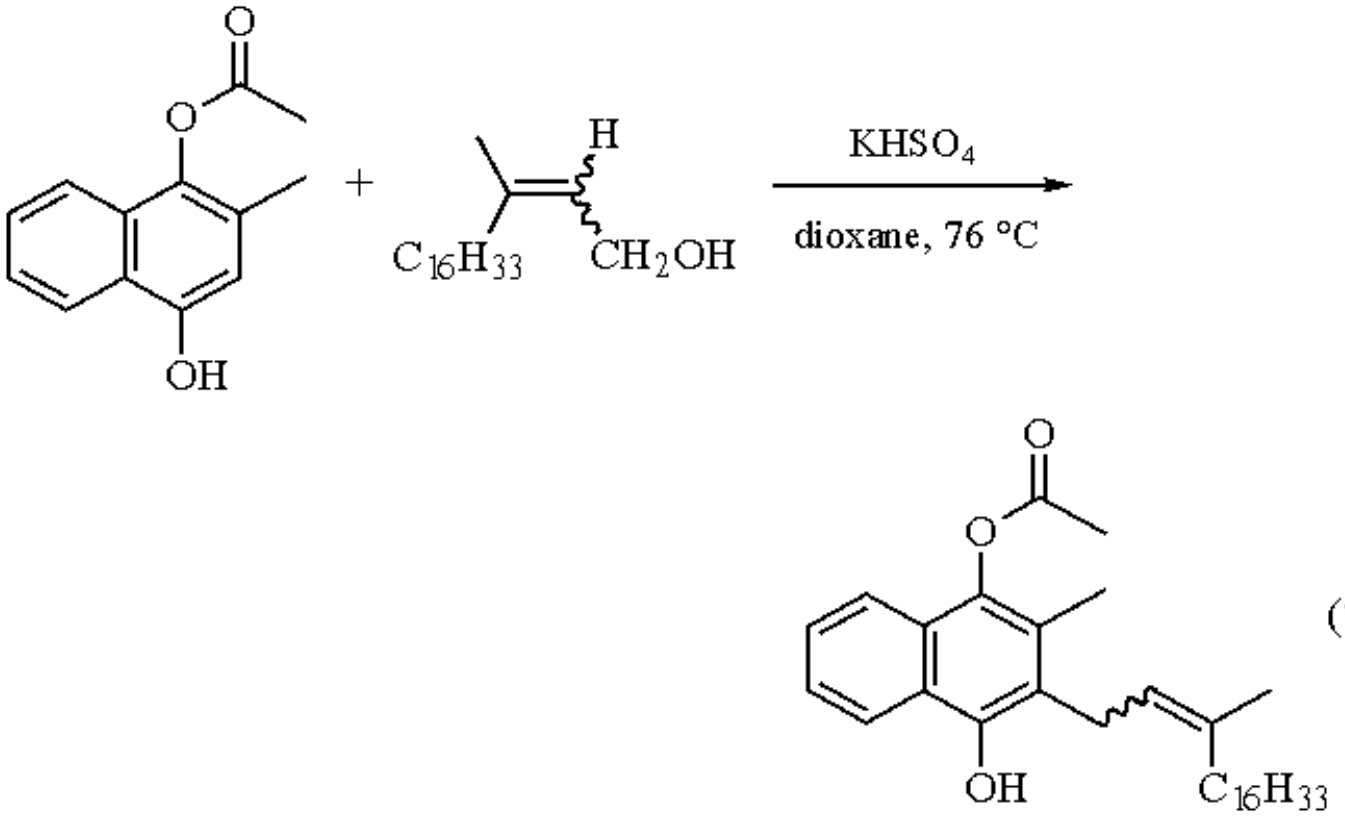

(7)

$KHSO_4$ can be used to generate ethers. For example, naphthalan has been prepared in 81% yield by heating fused $KHSO_4$ and 1,8-naphthalyl alcohol for 10 min at 120 °C (eq 8).[10] Highly selective monoetherification of symmetrical diols has been accomplished by using $KHSO_4$ supported on silica gel. Treating 1,4-butanediol and dihydropyran with a catalytic amount of $KHSO_4$-SiO_2 in hexane afforded, after 50 min, 91% yield of monoether and 6% diether.[11] This catalyst system also efficiently dehydrates alcohols.[12]

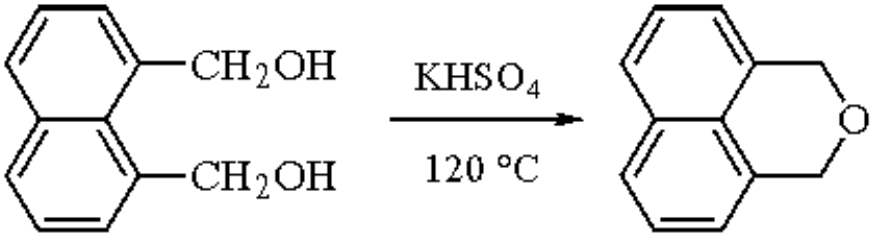

(8)

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Potassium Hydrogen Sulfide

KSH

[1310-61-8] · HKS · Potassium Hydrogen Sulfide · (MW 72.18)

(a nucleophile and reducing agent similar to NaSH; useful in the synthesis of thiols,[1] thioethers,[2] and thiocarbonyl compounds[3])

Physical Data: mp 455 °C; *d* 1.68-1.70 g cm^{-3}.

Solubility: very sol H_2O; sol EtOH.

Form Supplied in: commercially available as a crystalline solid; colorless when pure. May be contaminated with $K_2S_2O_3$ and K_2CO_3.

Preparative Methods: saturation of ethanolic KOH by H_2S.[4]

Handling, Storage, and Precautions: extremely hygroscopic. Darkens on heating to yellow, then deep red at mp. Aqueous solutions evolve H_2S on heating (KSH + H_2O &ibond; KOH + H_2S), and decompose in air to polysulfides and H_2S. Oxygen also yields $K_2S_2O_3$ and traces of K_2SO_3. Carbon dioxide yields H_2S and K_2CO_3. For other precautions and toxicity see ***Sodium Hydrogen Sulfide***.

Thiols.[1]

Yields from organic halides may be less satisfactory than with NaSH because of formation of greater amounts of thioether with KSH.[5] The amount of thiol may be increased at the expense of the thioether by addition of ***Hydrogen Sulfide*** or ***Sulfuric Acid***. Phase transfer catalysis is useful (eq 1).[6]

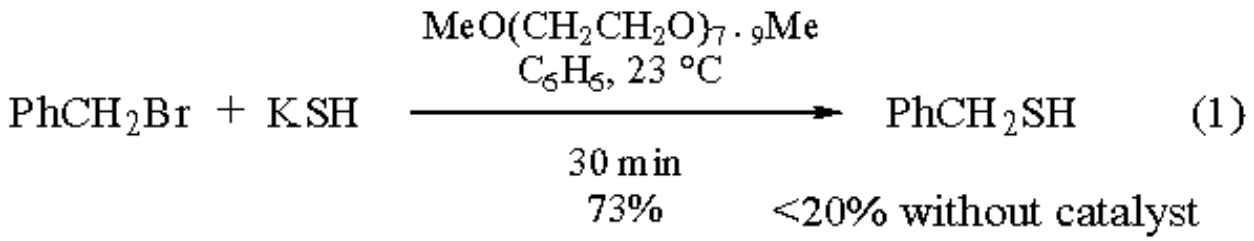

Thiocarboxylic Acids.[7]

Thiobenzoic acid (PhCOSH) is obtained in 61-76% yield by addition of ***Benzoyl Chloride*** to ethanolic KSH;[4b] it is an intermediate in the preparation of benzoyl disulfide.[4c] Anhydrides (eq 2)[8] and esters also are suitable.

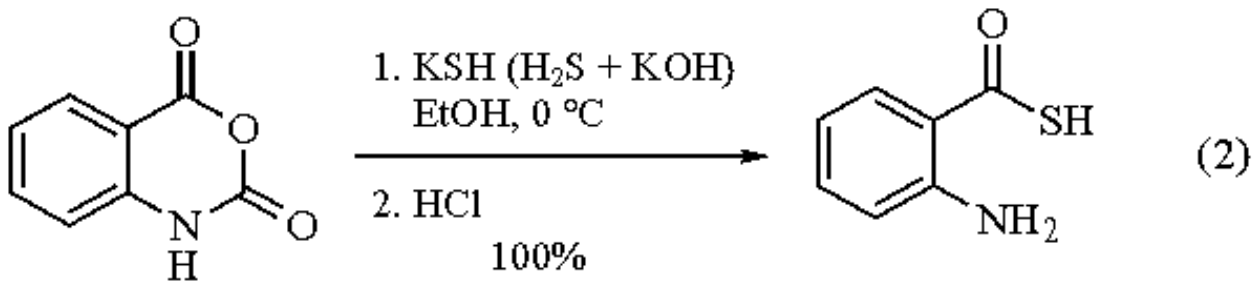

Thioethers (Sulfides).[2]

As noted above, thioether formation from organic halides occurs to a greater extent with KSH than with NaSH. Modest yields (15-50%) of sulfides are obtained, along with polymers, by Michael addition of KSH to α,β-unsaturated ketones or sulfones generated in situ from ketone or sulfone and formaldehyde (eq 3).[9]

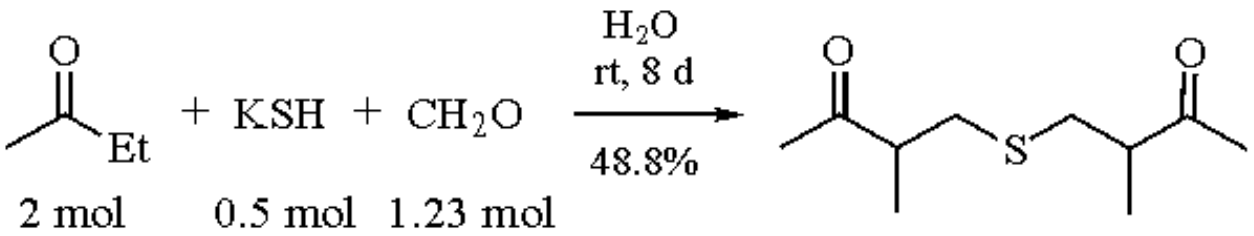

(3)

Thiocarbonyl Compounds.[3]

In general, KSH and NaSH are interchangeable with respect to their use in the generation of the thiocarbonyl functional group. The thiolysis of benzotrichloride yields the potassium salt of dithiobenzoic acid, an intermediate in the preparation of thiobenzoylthioglycolic acid, a useful thiobenzoylating agent (eq 4).[4a] Other trichlorides behave similarly.

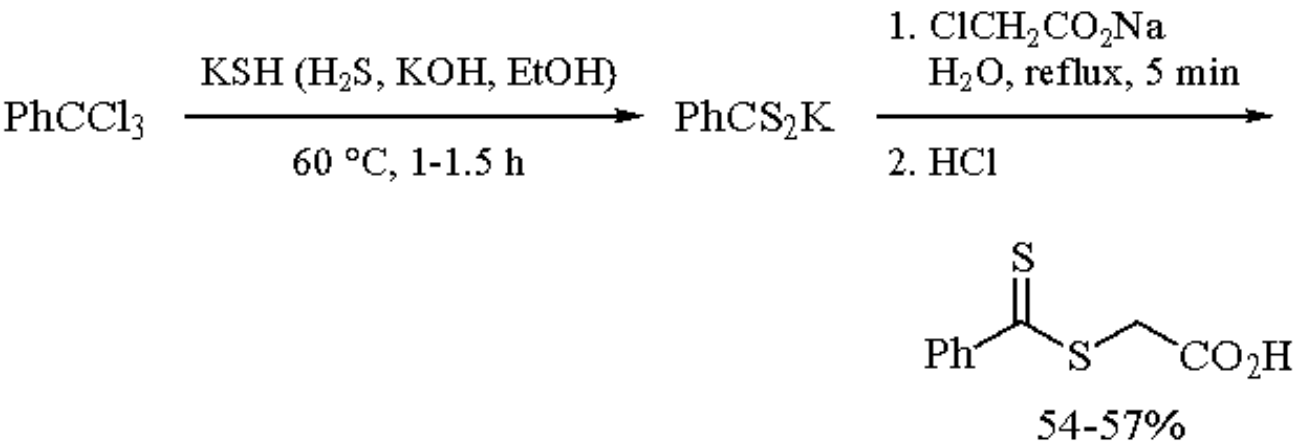

(4)

Miscellaneous.

Treatment of 2-alkoxy-2-oxo-1,3,2-dioxaphospholanes with KSH gives a phosphodiester with a β-mercaptoethyl group that functions as a protective group easily removed by treatment with base (eq 5).[10] The *S*-substituted derivatives are more useful as protective groups since they are stable to bases as well as acids.

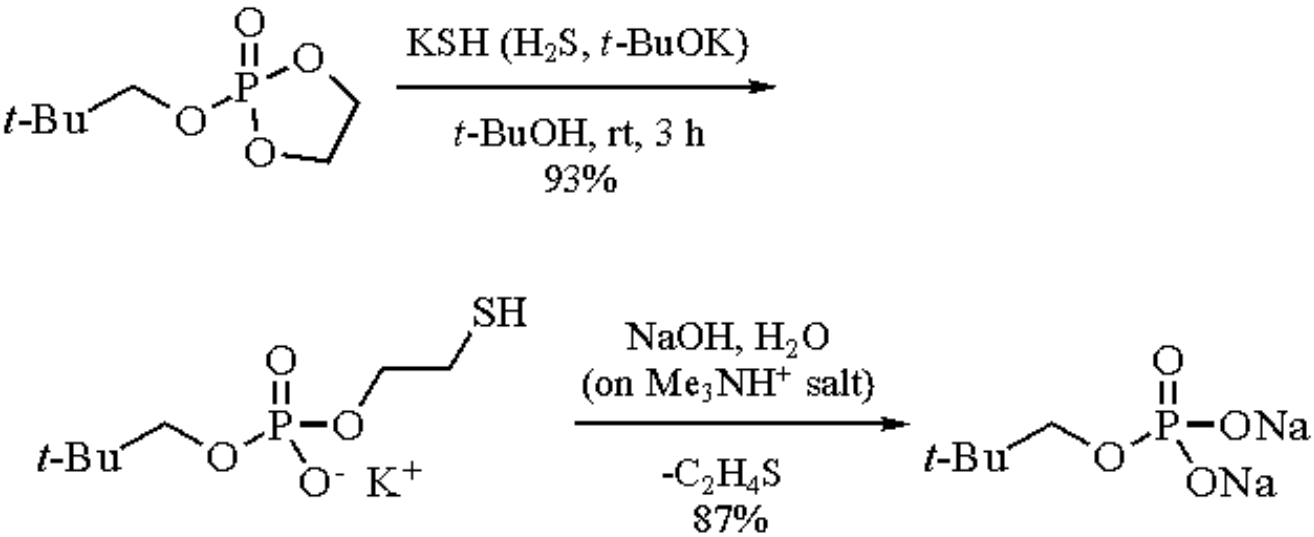

(5)

Related Reagents.

Bis(trimethylsilyl) Sulfide; ***Hydrogen Sulfide***; ***Sodium Hydrogen Sulfide***; ***Sodium Sulfide***.

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Potassium Hydroxide

KOH

[1310-58-3] · HKO · Potassium Hydroxide · (MW 56.11)

(very strong alkali; reacts readily with acids; used in nucleophilic substitution reactions, addition reactions, and basic hydrolysis reactions; occasionally employed as a catalyst for aldol-type reactions; ethanolic solution (alcoholic KOH) is traditionally used in dehydrohalogenation of halides)

Physical Data: mp 361 °C; *d* 2.044 g cm^{-3}.

Solubility: sol 0.9 part water, 0.6 part boiling water, or 3 parts ethanol; its dissolution in water is exothermic.

Form Supplied in: white lumps, rods, or pellets; commercially available pellets contain 85-88% KOH and 10-15% water.

Handling, Storage, and Precautions: toxic (oral-rat: LD_{50}: 365 mg kg^{-1}). Corrosive. Harmful if swallowed, inhaled, or absorbed through skin. Material is extremely destructive to tissue of the mucous membranes and upper respiratory tract. Inhalation may be fatal. Do not breathe dust. Avoid contact with eyes, skin, and clothing. Store in a cool dry place. Extremely hygroscopic. Wash thoroughly after handling.[1]

Incompatible with acids, acid chlorides, acid anhydrides, and aluminum metal. Absorbs moisture and CO_2 from air.

Elimination Reactions.

Alcoholic KOH is the most frequently used base for dehydrohalogenation of alkyl halides in the synthesis of alkenes.[2] Some representative examples showing the use of KOH in elimination reactions are listed here.

Preparation of Diphenylacetylene.

Diphenylacetylene was prepared via the dehydrohalogenation of stilbene dibromide. The dibromide was heated at reflux temperature with KOH in absolute ethanol for 24 h. After workup and recrystallization, a 66-69% yield of pure diphenylacetylene was obtained (eq 1).[3]

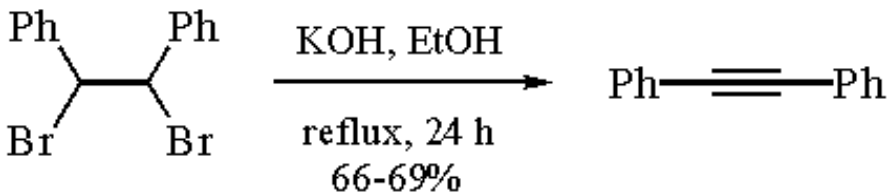

(1)

An alternative procedure for the synthesis of diphenylacetylene used the quaternary enammonium salt of deoxybenzoin via a Hofmann elimination reaction. Thus treatment of the methylated pyrrolidine enamine of deoxybenzoin (**1**) with 40% aq KOH at reflux afforded an 86% yield of diphenylacetylene (eq 2). The reaction was not as successful with other enamines.[4]

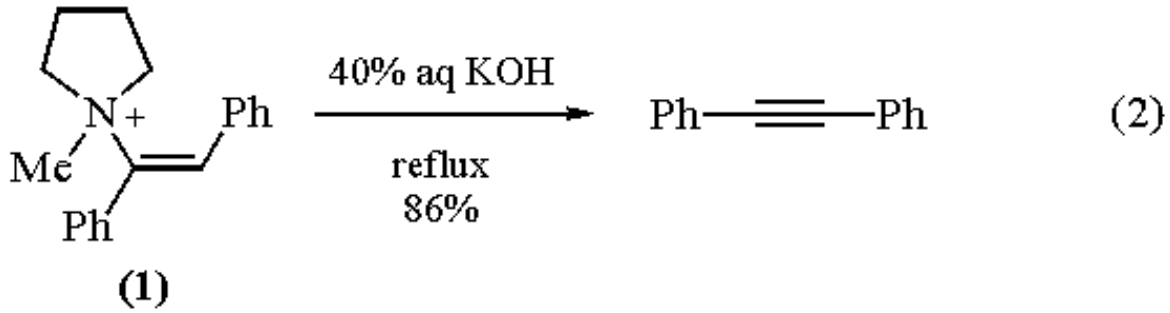

Preparation of Muconic Acid.

Muconic acid (1,3-butadiene-1,4-dicarboxylic acid) (**3**) was prepared by dehydrohalogenation and hydrolysis of diethyl α,δ-dibromoadipate (**2**) upon heating with KOH in MeOH at reflux (eq 3). The acid was obtained in 37-43% yield.[5]

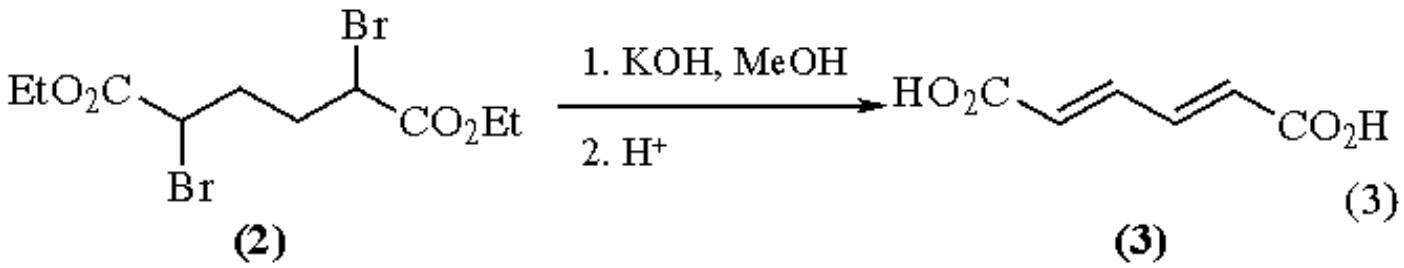

Synthesis of Coumarilic Acid.

2-Benzofurancarboxylic acid (coumarilic acid) (**5**) was prepared from coumarin dibromide (**4**) by the action of alcoholic KOH (eq 4). The product was isolated, after acidification, in 82-88% yield.[6]

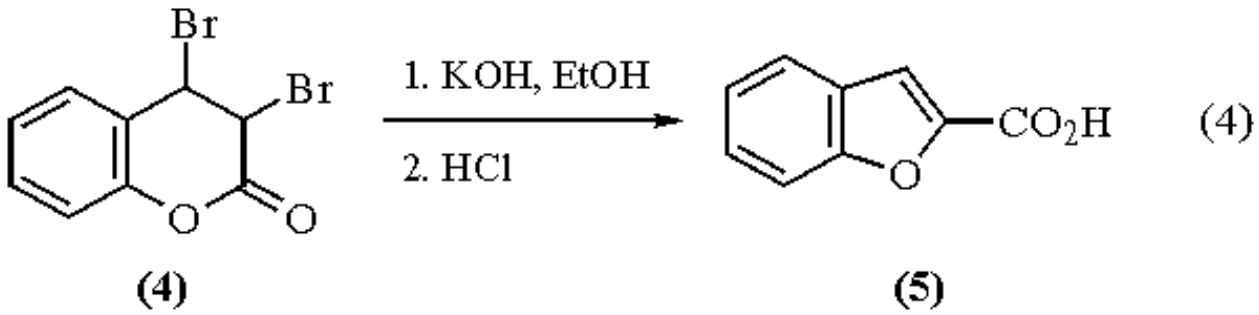

Hydrolysis of Hindered Esters.

A solid-liquid phase-transfer catalysis system without organic solvents was developed for the hydrolysis of hindered esters such as mesitoic esters. The system consists of powdered KOH and 2% Aliquat 336 (methyltrioctylammonium chloride). The best results were obtained with 5 mol equiv of powdered KOH + 2% Aliquat 336 at 85 °C for 5 h (eq 5).[7]

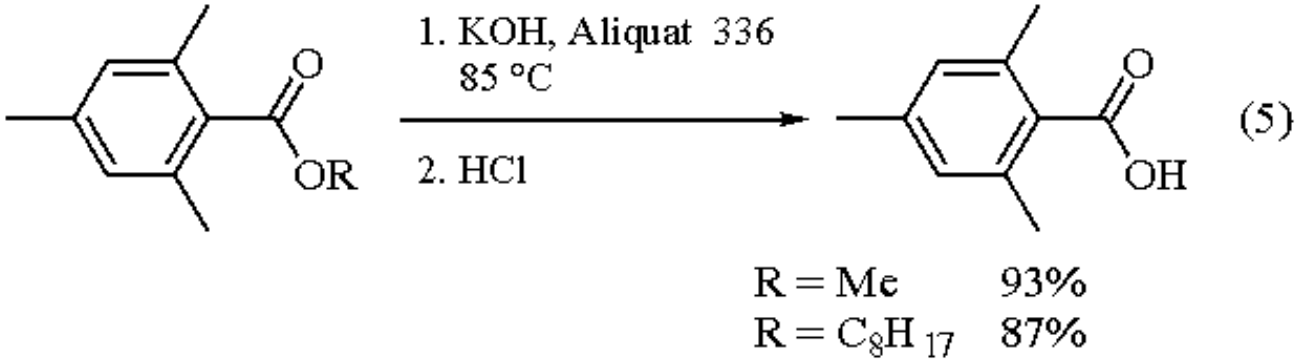

Hydrolysis of Nitriles to Amides.

Several nitriles were chemoselectively hydrolyzed to the corresponding amides when heated at reflux in *t*-butyl alcohol containing powdered solid KOH. Thus benzonitrile was converted to benzamide in 94% yield when refluxed in *t*-BuOH containing powdered KOH for 20 min (eq 6). The amides were not further hydrolyzed to the carboxylic acids under these conditions; this was explained by the formation of an insoluble K salt which thus precluded further nucleophilic attack. The use of MeOH as a solvent resulted in a lower yield and more hydrolysis to the carboxylic acid.[8]

$$\mathrm{PhCN} \xrightarrow[\text{reflux, 20 min, 94\%}]{\text{solid KOH, } t\text{-BuOH}} \mathrm{PhCONH_2} \qquad (6)$$

Formation of Hydroxamic Acids from Ethyl Benzoate.

Potassium benzohydroxamate was prepared in 60% yield by treatment of ethyl benzoate with hydroxylamine in the presence of KOH in MeOH. The K salt was converted to benzohydroxamic acid with dil AcOH (eq 7).[9]

$$\mathrm{PhCO_2Et} + \mathrm{H_2NOH} \xrightarrow[\text{2. AcOH, 60\%}]{\text{1. KOH, MeOH}} \mathrm{PhCONHOH} \qquad (7)$$

Reduction of Aromatic Aldehydes via Crossed Cannizzaro Reaction.

Certain benzyl alcohols were prepared from the corresponding aromatic aldehydes via the crossed Cannizzaro reaction with formaldehyde and KOH in 80-90% yield.[10] Thus the reaction of *p*-tolualdehyde with formalin and KOH in methanol at 60-70 °C gave about 80% yield of *p*-methylbenzyl alcohol (eq 8).[11]

$$p\text{-}\mathrm{MeC_6H_4CHO} \xrightarrow[\text{MeOH, 60-70 °C}]{\text{HCHO, KOH}} p\text{-}\mathrm{MeC_6H_4CH_2OH} + \mathrm{HCO_2K} \qquad (8)$$

Intramolecular Aldol Reactions.

Treatment of several substituted 5-keto-2-hexenals (**6**) with KOH (2-3 equiv) in anhyd MeOH at rt for 2-3 h resulted in intramolecular aldol condensation reactions which led to the formation of the substituted phenols (**7**) in 74-100% yields (eq 9). Other catalysts including pyrrolidinium acetate, pyridinium tosylate, and $BF_3.Et_2O$ were ineffective.[12]

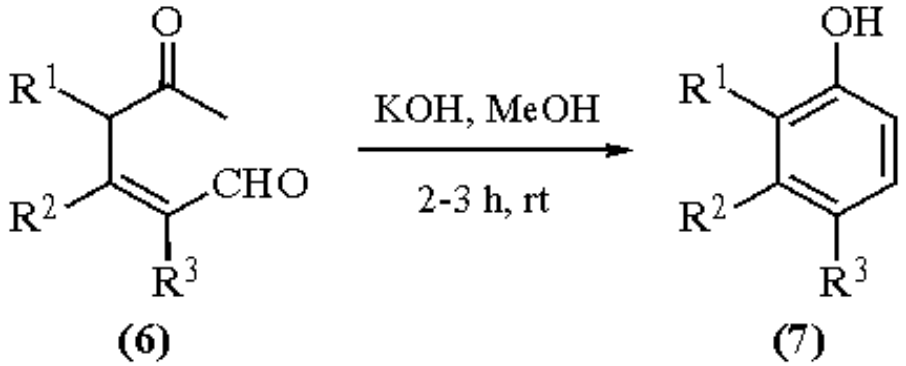

(9)

R^1	$R^2 + R^3$	Yield
H	$-CH_2CH_2CH(t\text{-Bu})CH_2-$	92%
Me	$-CH_2CH_2CH(t\text{-Bu})CH_2-$	96%
Me	$-CH_2CH_2CH_2-$	80%
Me	$-CH_2CH_2CH_2CH_2CH_2-$	74%

Hydroxydeamination of Primary Amines.

Treatment of 1-substituted 1-tosylhydrazines (**8**) with KOH in refluxing ethanol in the presence of atmospheric oxygen afforded the corresponding alcohols (**9**) in high yields (eq 10). The reaction is believed to proceed via the hydroperoxide (**10**), since it was the major isolated product at rt. When the hydroperoxide was subjected to the typical reaction conditions, the corresponding alcohol (**9**) was obtained in excellent yield, with ethanol presumably acting as the reductant. The procedure provides a convenient route for replacement of the nitrogen of a primary amine by a hydroxy group. The sequence includes the conversion of the primary amine into the corresponding *p*-toluenesulfonamide followed by *N*-amination using ***Chloramine*** or ***O-(Mesitylsulfonyl)hydroxylamine*** to form the tosylhydrazine.[13]

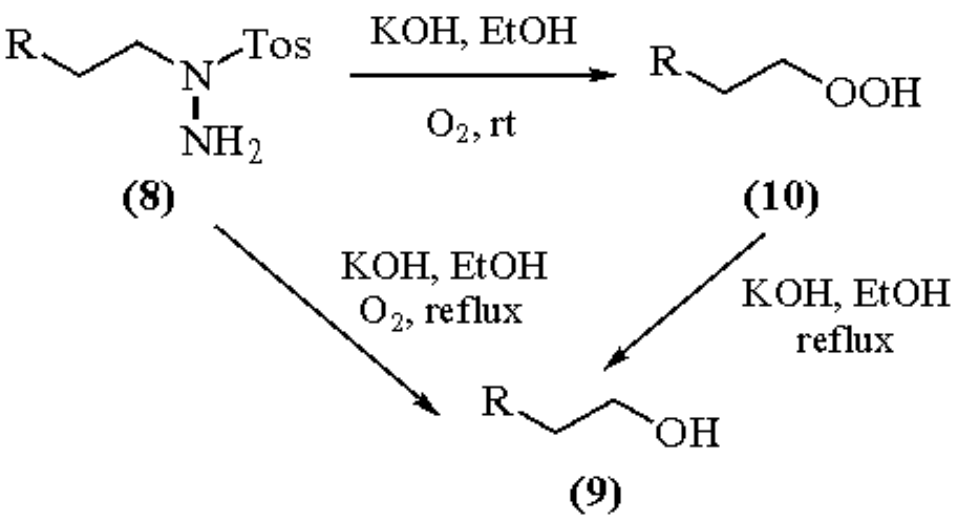

(10)

yields from tosylhydrazine:	$R = p\text{-}MeOC_6H_4$	98%
	$R = p\text{-}ClC_6H_4$	95%
	$R = C_{14}H_{29}$	91%

Reactions with Alkyl Halides.

The alkali hydroxides including KOH are very effective in nucleophilic substitution reactions of alkyl halides. Aq KOH is traditionally used to convert alkyl halides to alcohols.[14] Occasionally, it is used to convert *gem*-dihalides to ketones and trihalomethyl compounds to carboxylic acids.[15]

Reactions with Trichloromethyl Derivatives.

Treatment of a trichloromethyl derivative with KOH usually gives the corresponding carboxylic acid, e.g. 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethane (**11**) was converted to bis(*p*-chlorophenyl)acetic acid (**12**) in 69-73% yield when reacted with KOH in aq diethylene glycol at 134-137 °C (eq 11).[15]

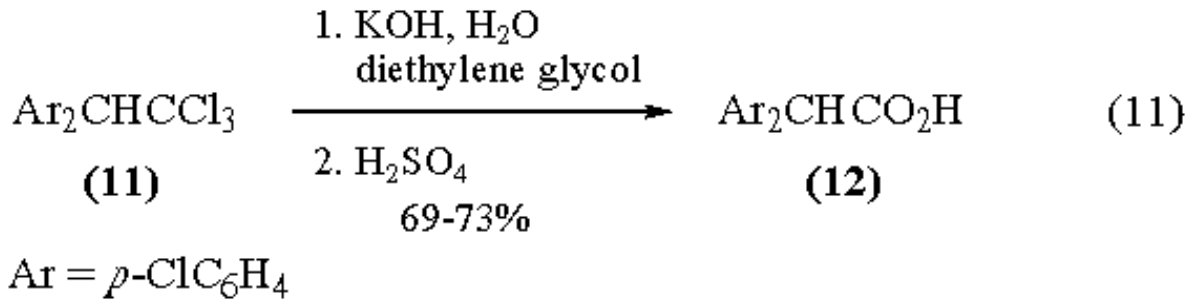

Substituted 1,1,1-trichloromethyl-2-ols [(trichloromethyl)carbinols] react with methanolic KOH to form substituted α-methoxyacetic acids (**15b**) in excellent yields if the substituent group is aryl, alkyl or dialkyl, or vinyl. The reaction fails with ethynylcarbinols. The reaction works equally well if methanol is replaced by ethanol or other alcohols. In a proposed mechanism, the (trichloromethyl)carbinol (**13**) is converted in situ to the dichloro epoxide (**14**). The epoxide is opened by methanol to give (**15a**) which is converted to the acid (**15b**) under the reaction conditions and workup (eq 12).[16]

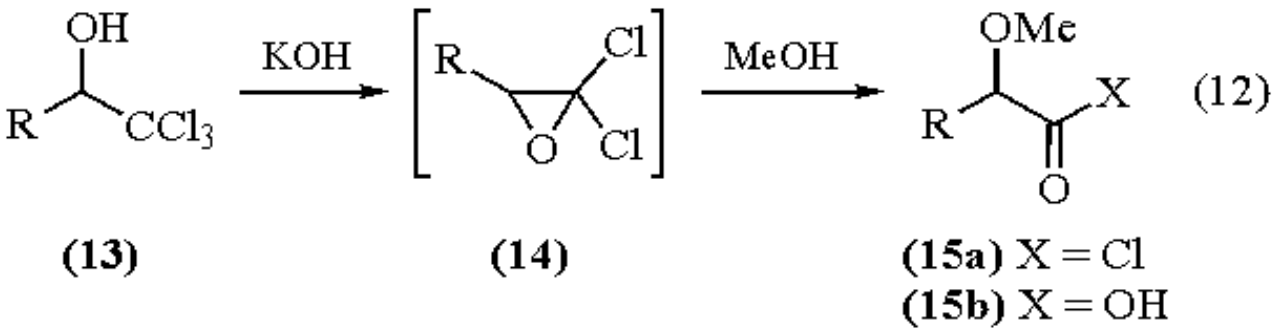

Preparation of (Trichloromethyl)carbinols.

Several (trichloromethyl)carbinols were synthesized in very good yields from aldehydes or ketones upon treatment with $CHCl_3$ in DMF in the presence of methanolic KOH (eq 13). The MeOH/DMF mixture provided a homogeneous reaction that permitted facile product formation at low temperature and was superior to using either solvent alone.[17]

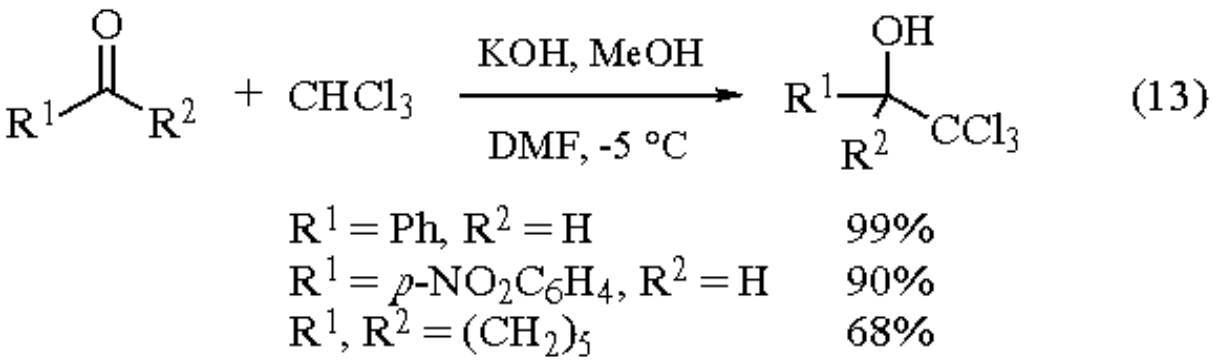

Oxidation of Aromatic Compounds.

2,3-Dimethyltetrahydroanthraquinone (**16**) was dehydrogenated to 2,3-dimethylanthraquinone (**17**) upon treatment with ethanolic KOH and air for 24 h (eq 14). The product was isolated in 94-96%.[18]

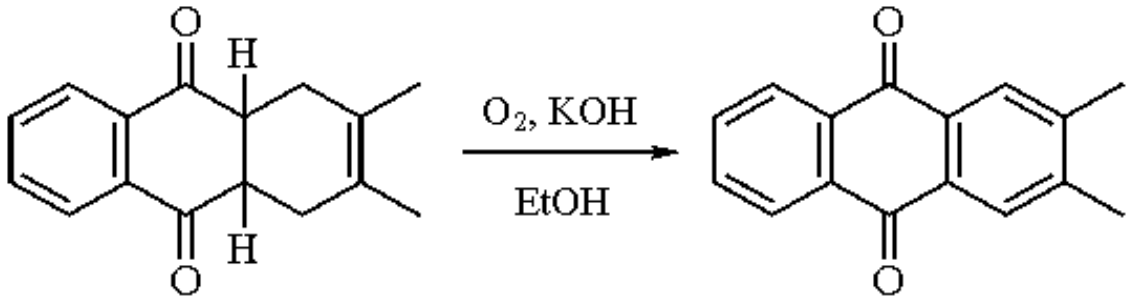

(14)

(16) **(17)**

Benzylation of Aromatic Primary Amines.

Heating a mixture of a primary aromatic amine and benzyl alcohol in the presence of KOH at a temperature between 250-280 °C (eq 15) gave the corresponding *N*-benzyl aromatic amine in high yield.[19] For example, heating a mixture of 2-aminopyridine (1 equiv) and benzyl alcohol (1.4 equiv) to 250 °C in the presence of a catalytic amount of KOH (0.14 equiv) afforded 2-(benzylamino)pyridine in 98-99% yield.[20]

$$ArNH_2 + PhCH_2OH \xrightarrow[250\text{-}280\ ^\circ C]{KOH} ArNHCH_2Ph \qquad (15)$$

Ar = 2-pyridyl, 98-99%

Reductive Benzylation of Aromatic Nitro Compounds.

Treatment of various aromatic nitro compounds with excess benzylamine and KOH at 225-260 °C, while removing the water generated, resulted in the formation of *N*-benzyl aromatic amines in low yields (11-51%). Under these conditions the nitro compound was first reduced to the aniline, which was benzylated according to the previous reference (eq 16).[21]

$$ArNO_2 \xrightarrow[KOH]{PhCH_2OH} [ArNH_2] \xrightarrow[KOH]{PhCH_2OH} ArNHCH_2Ph \qquad (16)$$

Conversion of Lactones into Benzyloxy Carboxylic Acids.

Treatment of lactones with benzyl chlorides and powdered KOH in dry toluene at reflux temperature resulted in their conversion to the corresponding benzyloxy carboxylic acids.[22] The reaction was used to prepare γ-, δ-, and ε-benzyloxy or *p*-methoxybenzyloxy carboxylic acids from the appropriate lactones (eq 17).[23]

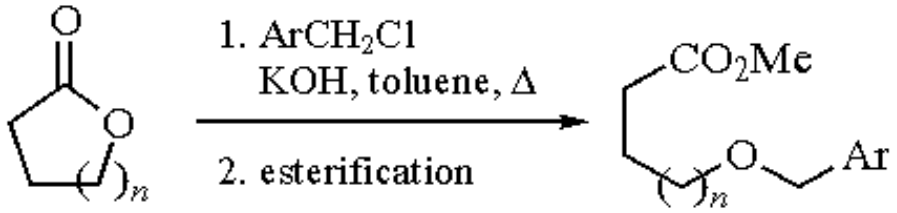

(17)

$n = 1$, 2, or 3 Ar = Ph, p-$MeOC_6H_4$

Rearrangement.

The substituted 4-hydroxycyclohexanone (**18**) rearranged partially to the isomeric compound (**19**) when heated with KOH in 35:1 *t*-BuOH-H_2O at reflux (eq 18). The reaction was reversible and the ratio of (**18**):(**19**) at equilibrium was 65:35. The rearrangement was explained by

a base-induced transannular 1,4-hydride shift.[24]

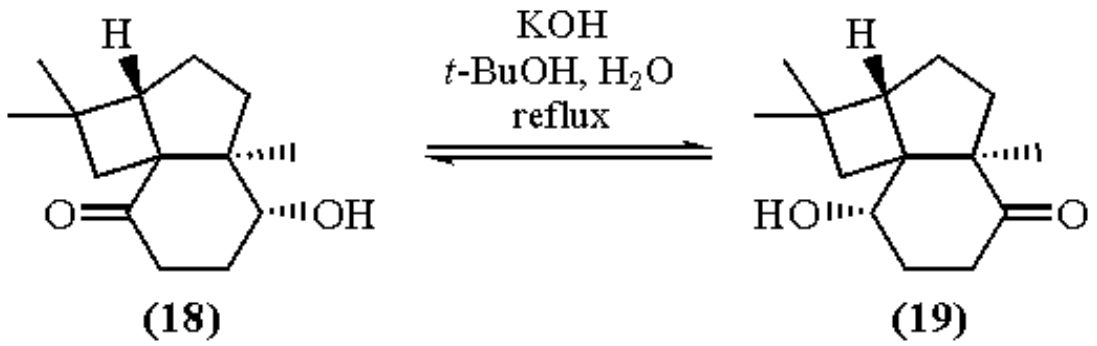

(18)

Epimerization of *meso*-Hydrobenzoins.

(±)-Hydrobenzoin (**21**) was obtained in 64% yield by heating either *erythro*- or *threo*-3-phenylglyceric acid (**20a**) with KOH to 160 °C under reduced pressure. Under these conditions the (±)-diastereomer of hydrobenzoin is the thermodynamically more stable isomer. Thus applying the reaction to *meso*-hydrobenzoin (**20b**) gave the pure (±)-isomer in 90% yield in a few minutes (eq 19). Lower conversion (70%) was obtained with ***Potassium*** metal in refluxing toluene, and an attempt to use NaOH was unsuccessful. The KOH epimerization was applied successfully to certain other substituted *meso*- and *erythro*-hydrobenzoins.[25]

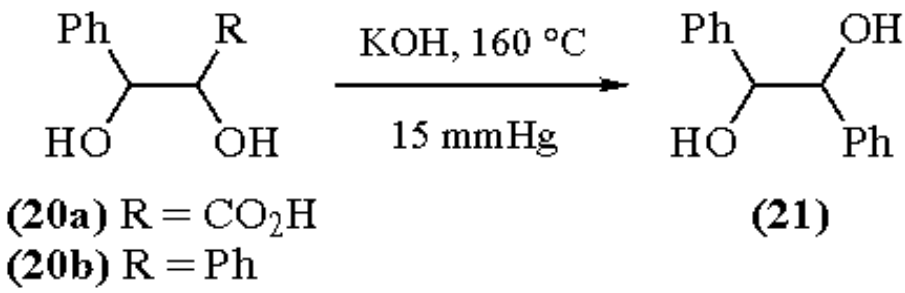

(19)

Huang-Minlon Modification of the Wolff-Kishner Reduction.

The use of KOH was introduced as a substitute for metallic ***Sodium*** or ***Sodium Methoxide*** in Wolff-Kishner reductions of ketones. This modification allowed the use of ***Hydrazine*** hydrate and made the procedure simpler and economical.[26]

Removal of 2-Hydroxypropyl Group in *p*-Ethynylbenzoic Acid Synthesis.

Potassium *p*-ethynylbenzoate (**23**) was obtained from 4-[4-(methoxycarbonyl)phenyl]-2-methyl-3-butyn-2-ol (**22**) in 98.5% yield and 99% purity upon heating at reflux in BuOH and 4 equiv of KOH (or NaOH) for 10 min (eq 20). The salt was precipitated from solution as it was formed.[27]

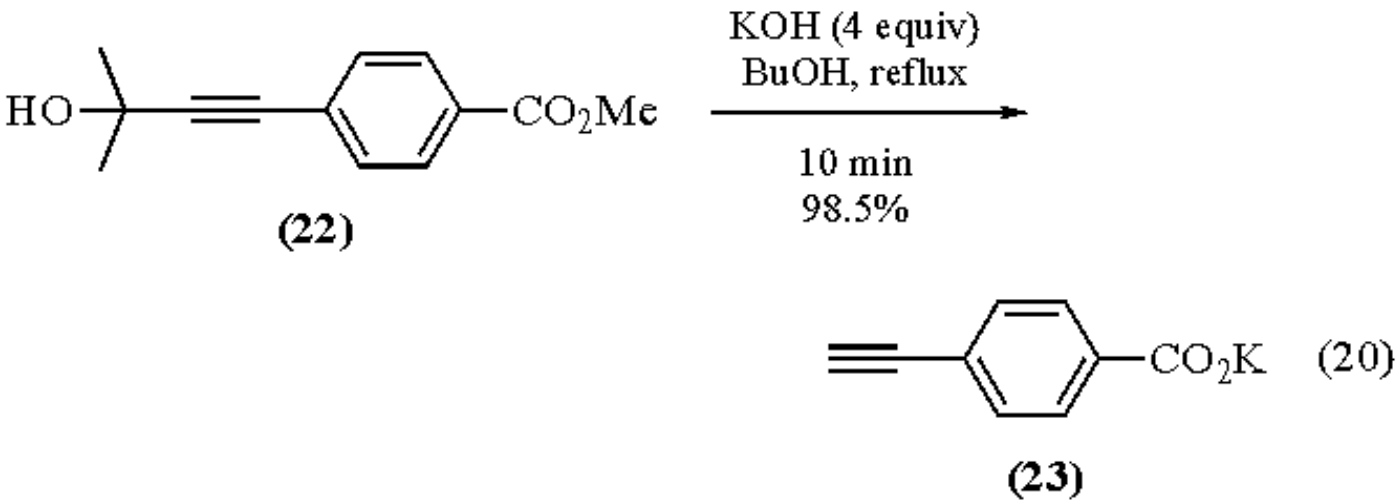

(20)

Related Reagents.

Potassium Hydroxide-Alumina; ***Potassium Hydroxide-Carbon Tetrachloride***; ***Potassium Hydroxide-18-Crown-6***; ***Potassium Hydroxide-Dimethyl Sulfoxide***; ***Potassium Hydroxide-Hexamethylphosphoric Triamide***.

---

1. For complete safety data on KOH, see: *The Sigma-Aldrich Library of Chemical Safety Data*; Lenga, R. E., Ed.; Sigma-Aldrich: Milwaukee, WI, 1985; p 1535C.
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7. Loupy, A.; Pedoussaut, M.; Sansoulet, J. *JOC* **1986**, *51*, 740.
8. Hall, J. H.; Gisler, M. *JOC* **1976**, *41*, 3769.
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Potassium Hydroxide-Alumina

KOH/Al_2O_3

(KOH)

[1310-58-3] · HKO · Potassium Hydroxide-Alumina · (MW 56.11) (Al_2O_3)

[1344-28-1] · Al_2O_3 · Potassium Hydroxide-Alumina · (MW 101.96)

(hydrolysis of esters; alkylation of alcohols, amides, and phenylacetonitrile)

Physical Data: see entries for ***Potassium Hydroxide*** and ***Alumina***.

Preparative Methods: mixing neutral alumina and a KOH solution produces a nearly homogeneous adsorbate (reagent **1**), referred to as basic alumina.[1] Another form of basic alumina (reagent **2**) is prepared by mixing dried neutral alumina (100 °C for 24 h) with solid KOH.[2]

Hydrolysis of Esters.

Cholestan-3β-yl 3,5-dinitrobenzoate and other steroidal and triterpenoid 3,5-dinitrobenzoate esters were readily hydrolyzed by adsorbing a benzene solution of the ester on a column of reagent (**1**) and eluting it with a 3:1 benzene-ether mixture to give the alcohol in good yield (eq 1).[3]

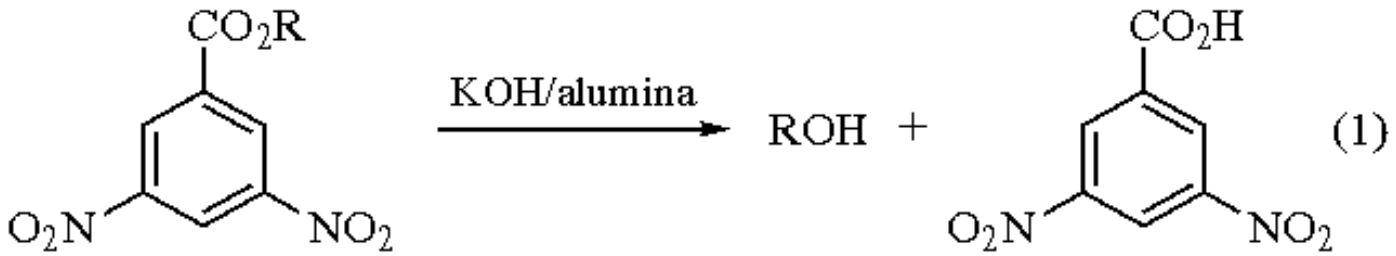

Reagent (**1**) gave slower reaction rates with less reactive esters[3] and better results were obtained from reagent (**2**). Stirring a solution of *n*-decyl benzoate in ether with reagent (**2**) at rt for 48 h gave *n*-decyl alcohol and benzoic acid in 91% and 89% isolated yields, respectively (eq 2).[2] Other esters were hydrolyzed in isolated yields between 80-100% for either the alcohol or acid product. Control experiments showed that a dried KOH/alumina reagent at 110 °C gave no reaction and a small amount of water was required for the hydrolytic activity.[2]

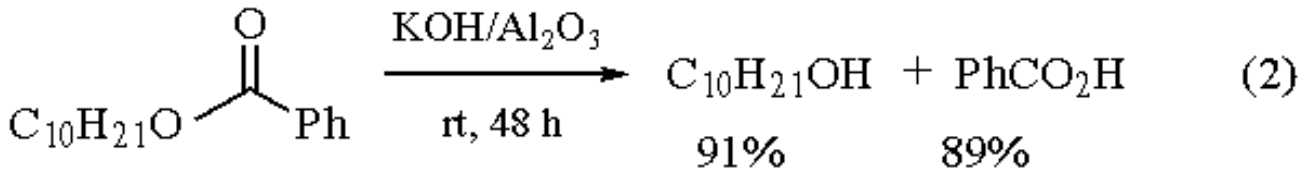

Various reactions of basic alumina (reagent **1**) with several classes of organic compounds were reported in an early short review.[4] Some of these reactions are presented in eqs 3-5. Treatment of allyl bromide or propargyl bromide with basic alumina in ether for 4 days gave diallyl ether and dipropargyl ether, respectively, in low yields (eq 3).[4]

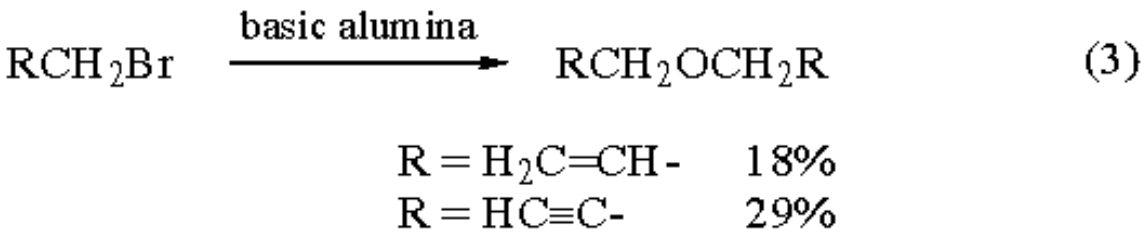

Either 1-chloro- or 1-bromocyclohexanone was converted to 2-hydroxycyclohexanone in 64% yield after a few minutes upon treatment with basic alumina.[4] The product dimerized slowly upon standing at rt (eq 4).

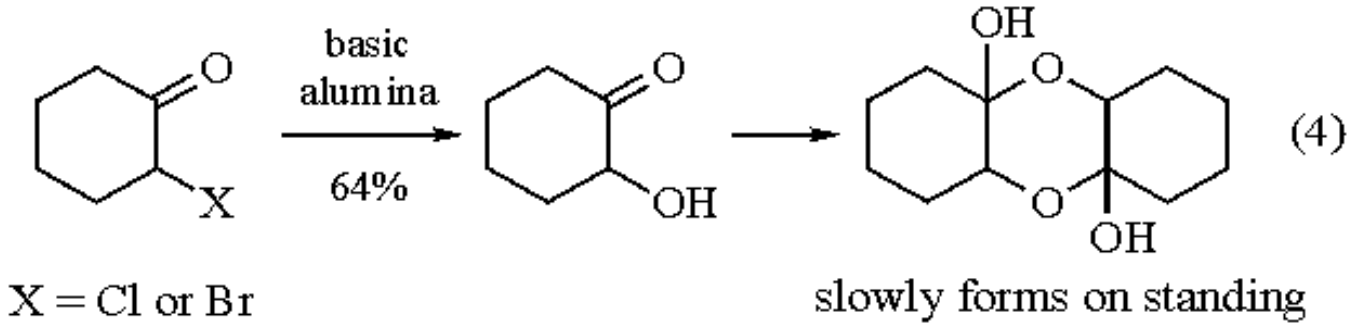

Preparation of β-ethoxycinnamaldehyde by the hydrolysis of the corresponding dimethyliminium perchlorate salt was achieved with basic alumina in nearly quantitative yield (eq 5).[4]

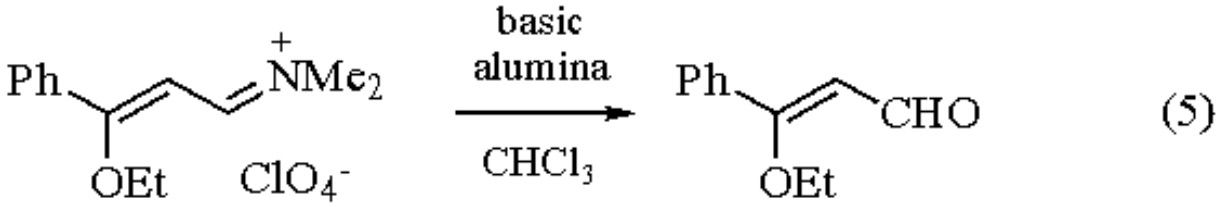

Selective α-Monoalkylation of Phenylacetonitrile.

Alumina impregnated with KOH acted as an efficient base for the selective α-monoalkylation of phenylacetonitrile with alkyl halides in benzene (eq 6). It was suggested that the reaction occurs predominantly in the pores of the KOH/Al_2O_3 solid base. The high selectivity towards monoalkylation in nonpolar solvents was explained by the tight adsorption of the anion of the initial monoalkyl product onto the wall of the pore, thus rendering it strongly sterically hindered for a second alkylation.[5]

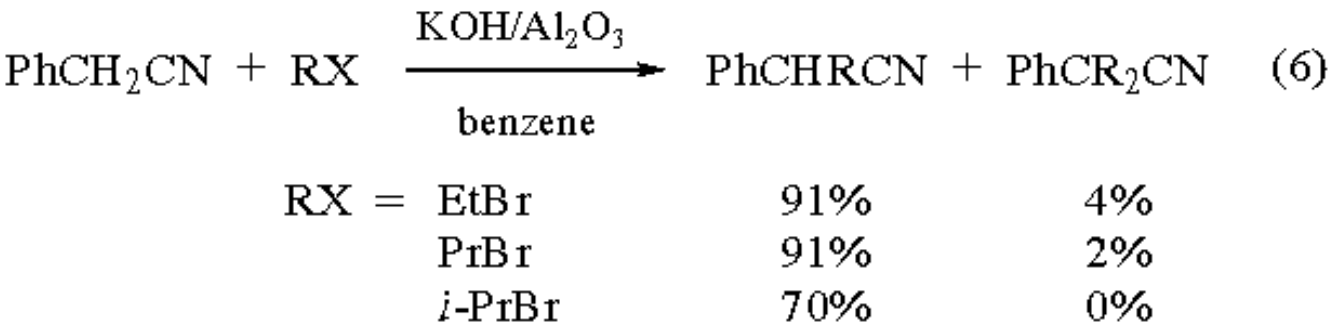

Selective *N*-Monoalkylation of Amides with Alkyl Halides.

Selective *N*-monoalkylation of amides was carried out successfully using KOH-alumina (eq 7). The best solvent for this reaction was dioxane which gave consistently the highest mono:dialkyl ratio. Unlike the previous reaction, the use of a mixture of powdered KOH and alumina was superior to the use of the KOH-impregnated alumina in both yield and selectivity. Also, alkyl bromides were better than the iodides. Reported yields ranged from 56% to 80% with selectivity towards *N*-monoalkylation ranging between 82-99%.[6]

$$R^1CONH_2 + R^2X \xrightarrow[\text{dioxane}]{KOH/Al_2O_3} R^1CONHR^2 \qquad (7)$$

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Potassium Hydroxide-Carbon Tetrachloride

KOH-CCl_4

(KOH)

[1310-58-3] · HKO · Potassium Hydroxide-Carbon Tetrachloride · (MW 56.11) (CCl_4)

[56-23-5] · CCl_4 · Potassium Hydroxide-Carbon Tetrachloride · (MW 153.81)

(ketones, alcohols, and sulfones react with CCl_4/KOH, usually in *t*-BuOH, to give a variety of products[1])

Physical Data: see entry for ***Potassium Hydroxide***.

Reactions with Ketones.

Reactions of ketones with CCl_4-KOH in *t*-BuOH generally fall into four categories.[1,2]

- 1)Ketones with α- and α´-hydrogens were transformed into carboxylic acids, resulting from Favorskii rearrangement of an intermediate α-chloro ketone (eq 1).[1,2]

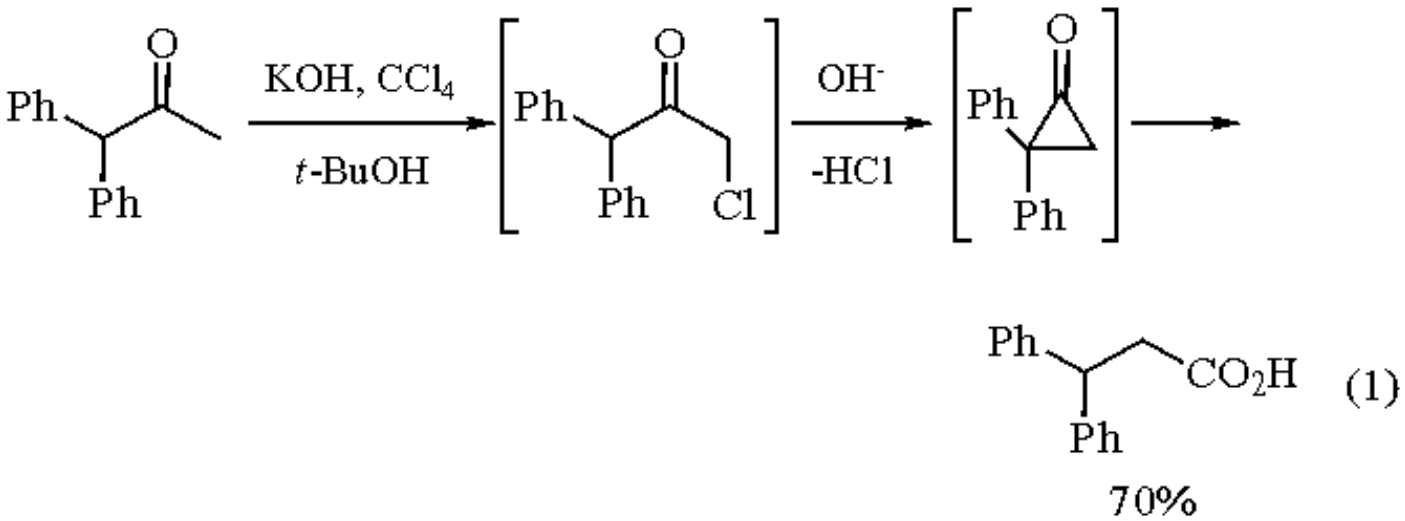

- 2)Hindered ketones with α- but no α´-hydrogens were α-chlorinated but do not undergo any further reaction, e.g. the reaction with ketone (**1**) to give the α-chloro ketone (**2**) (eq 2).[2]

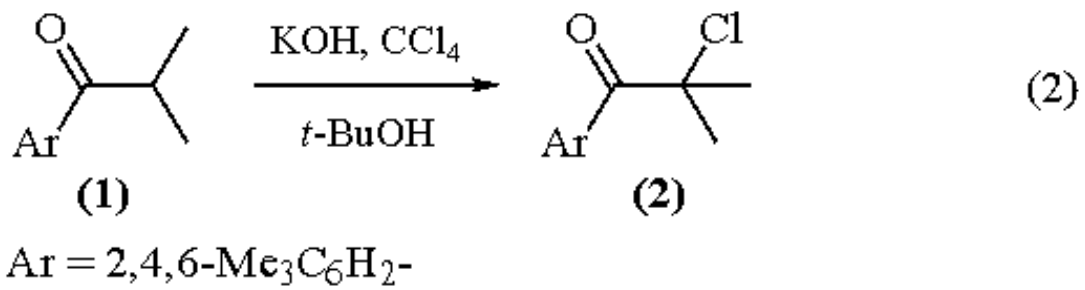

- 3)Some ketones with α- but no α´-hydrogens were α-chlorinated and then converted to the α-hydroxy derivative (eq 3).[2]

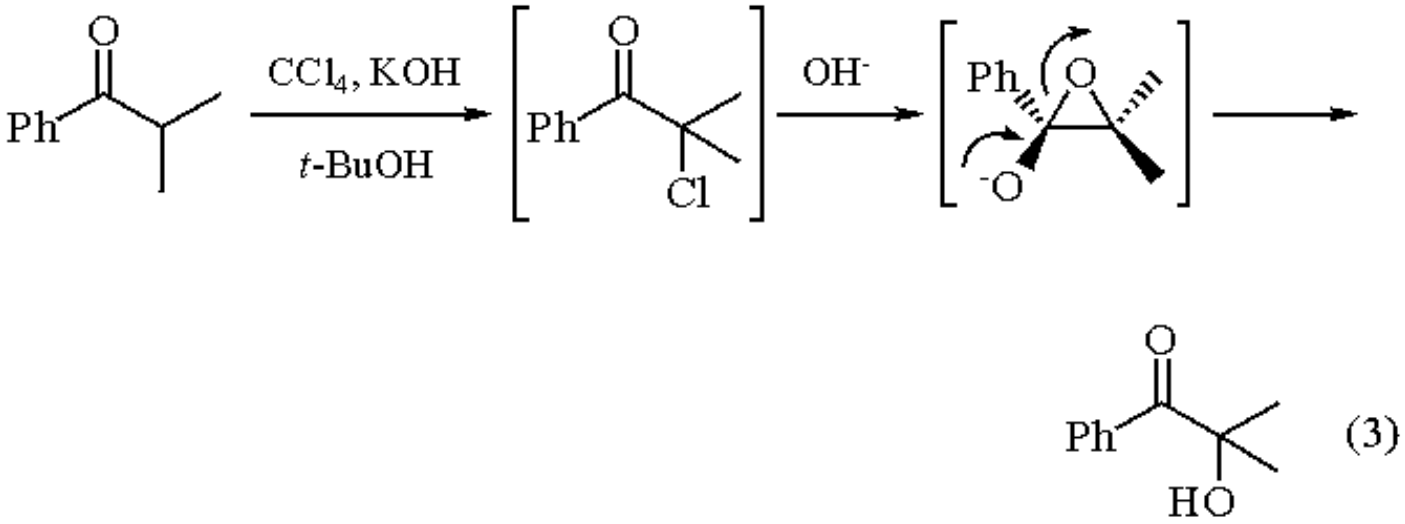

- 4)Some ketones with α- but no α´-hydrogens were α-chlorinated and subsequently cleaved into carboxylic acids,[1,2] e.g. pinacolone gave ***Pivalic Acid*** in 80% yield (eq 4).

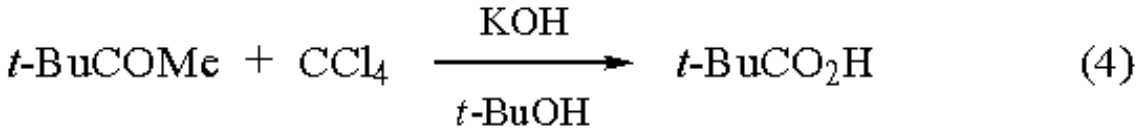

Another example was the reaction with estrone and estrone 3-methyl ether (**3a,b**) which gave the α,α-dichloro derivatives (**4**) that were rapidly cleaved to the 16,16-dichlorodoisynolic acids (**5**) (eq 5).[2]

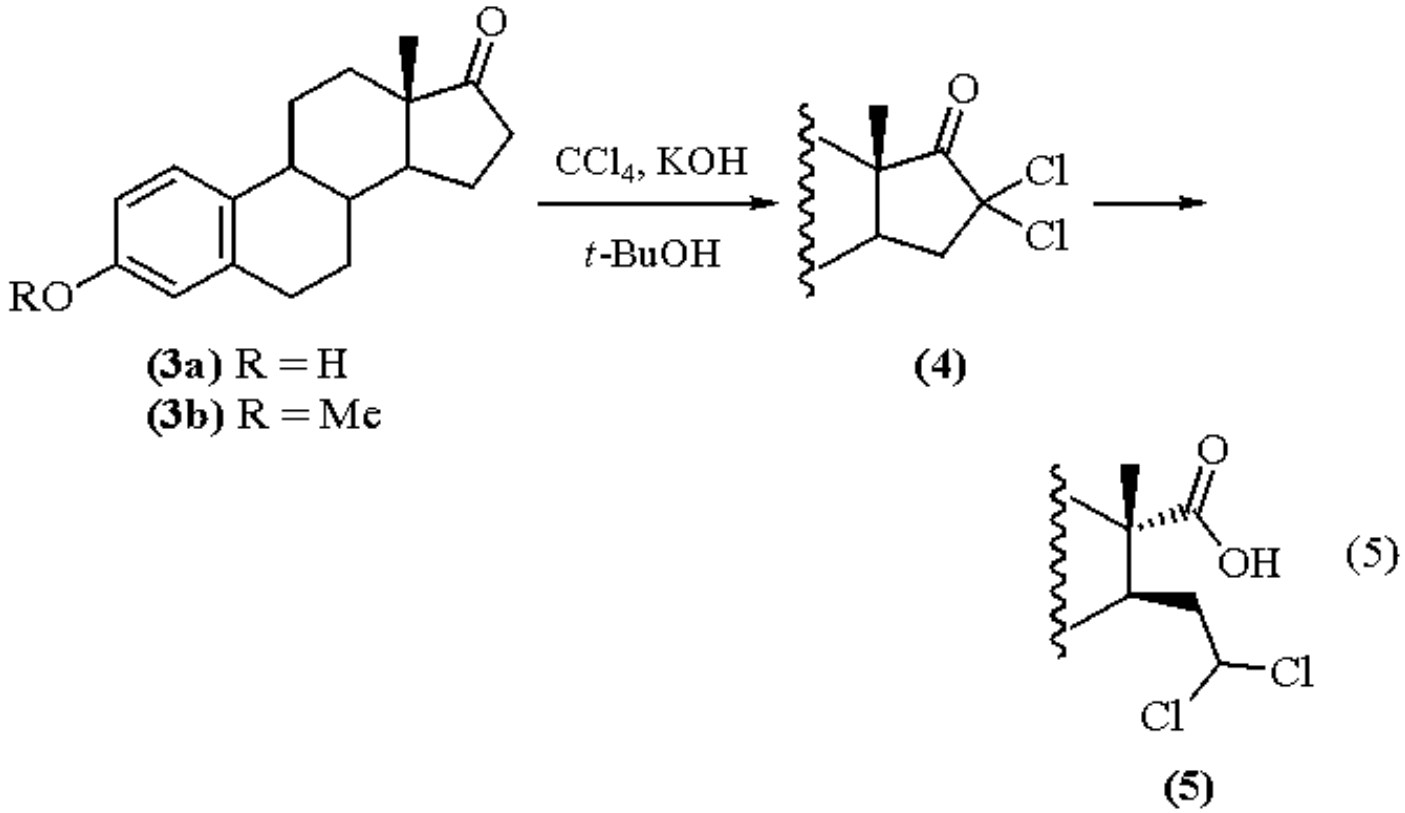

Reactions with Alcohols.

Primary and secondary alcohols were oxidized to aldehydes and ketones respectively upon reaction with CCl_4-KOH in *t*-BuOH. Both initial products further react to form other products. Stable aldehydes (e.g. pivalaldehyde) and stable ketones (e.g. benzophenone) could be isolated. Tertiary alcohols were unreactive.[1]

Reactions with Sulfones.

Based on their structure and the outcome of the reaction, sulfone reactions can be classified into three categories.[1]

- 1)Aryl alkyl sulfones were mono-, di-, and trichlorinated (eq 6). Intermediate trichloromethyl sulfones may be cleaved to aryl sulfonic acids under the reaction conditions (eq 7).[1]

$$PhSO_2CH_2Ph \xrightarrow[100\%]{KOH,\ CCl_4} PhSO_2CCl_2Ph \qquad (6)$$

$$ArSO_2Me \xrightarrow[CCl_4]{KOH} ArSO_2CH_2Cl \rightleftharpoons ArSO_2CCl_3 \longrightarrow ArSO_3H \qquad (7)$$

- 2)Dibenzyl sulfones were converted to stilbenes. This was explained by the initial formation of α-chloro sulfones, then a 1,3-elimination of HCl, followed by extrusion of SO_2 to form the alkene; a sequence known as the Ramberg-Bäcklund reaction (eq 8).[1]

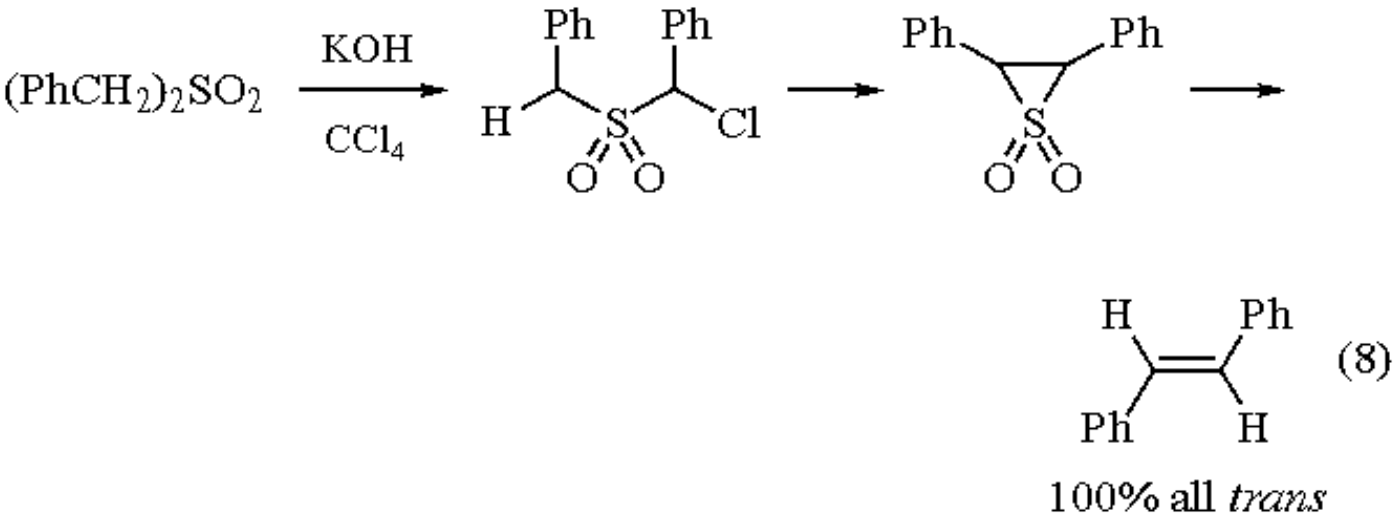

Treatment of the cyclic sulfone (**6**) with KOH-CCl_4 and *t*-BuOH at 50 °C overnight resulted in a similar Ramberg-Bäcklund reaction to give a mixture of the hydroindenones (**7**) and (**8**) (eq 9).[3]

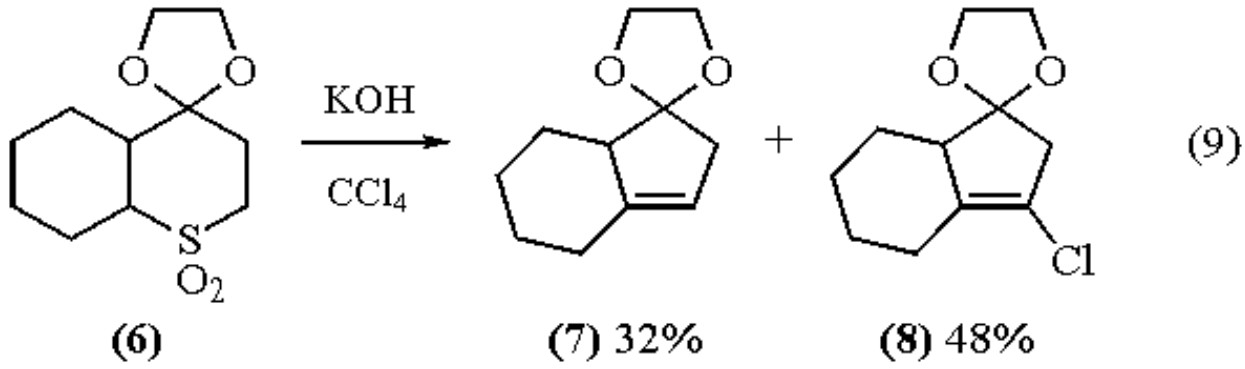

The conjugated triene (**10**) was similarly obtained from the diallyl sulfone (**9**) by KOH-CCl_4 at rt (eq 10).[4]

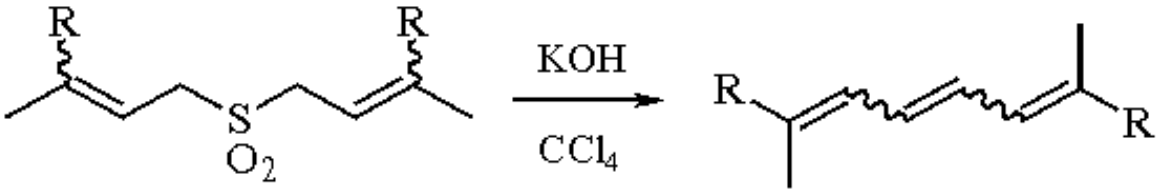

(10)

(9) **(10)**

Di-primary alkyl sulfones (**11**) gave, unexpectedly, the *cis*-dialkylethylenesulfonic acid K salts (**12**) (eq 11). Symmetrical sulfones gave single isomeric *cis* products while unsymmetrical sulfones gave two isomeric *cis* products.[5,6]

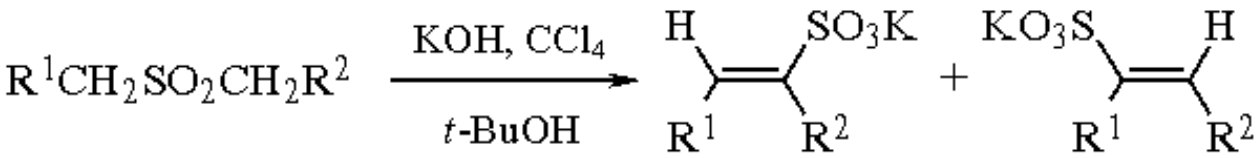

(11)

(11) **(12a)** **(12b)**

- 3)Di-*s*-alkyl sulfones were converted into alkenes and alkene-dichlorocarbene adducts (1,1-dichlorocyclopropanes).[1]

Dichlorocyclopropanation of Alkenes.

The generation of dichlorocarbene in the reaction of KOH-CCl_4 with sulfones in *t*-BuOH was used as a tool for dichlorocyclopropanation of alkenes in yields ranging from 45-93%, e.g. the reaction of 1,1-diphenylethylene with KOH, CCl_4, *t*-BuOH, and Me_2SO_2 to give 1,1-dichloro-2,2-diphenylcyclopropane in 93% yield (eq 12).[7]

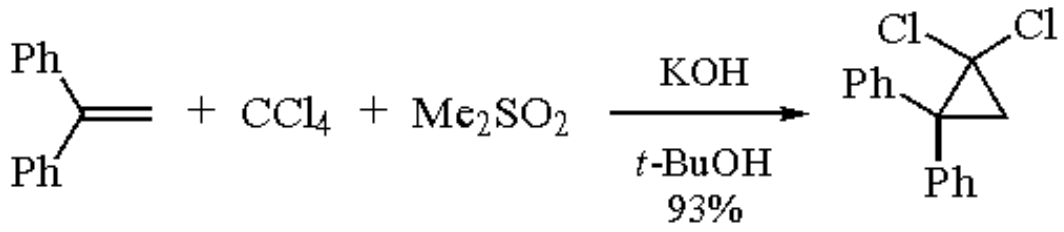

(12)

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Potassium Hydroxide-18-Crown-6

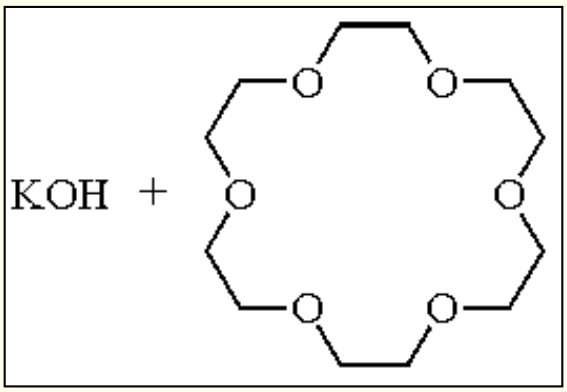

(KOH)

[1310-58-3] · HKO · Potassium Hydroxide-18-Crown-6 · (MW 56.11) (18-crown-6)

[17455-13-9] · $C_{12}H_{24}O_6$ · Potassium Hydroxide-18-Crown-6 · (MW 264.36) (dicyclohexano-18-crown-6)

[16069-36-6] · $C_{20}H_{36}O_6$ · Potassium Hydroxide-Dicyclohexano-18-crown-6 · (MW 372.56) (dibenzo-18-crown-6)

[14187-32-7] · $C_{20}H_{24}O_6$ · Potassium Hydroxide-Dibenzo-18-crown-6 · (MW 360.44)

(ester hydrolysis; nucleophilic substitutions; ketone alkylation)

Physical Data: see entries for ***Potassium Hydroxide***, ***18-Crown-6***, ***Dicyclohexano-18-crown-6***, and ***Dibenzo-18-crown-6***.

Hydrolysis of Sterically Hindered Esters.

Methyl and *t*-butyl esters of mesitoic acid were saponified by the KOH complex of dicyclohexano-18-crown-6 in aromatic hydrocarbons such as toluene at reflux temperature (104-111 °C) for 5 h to give mesitoic acid in high yields (eq 1).[1]

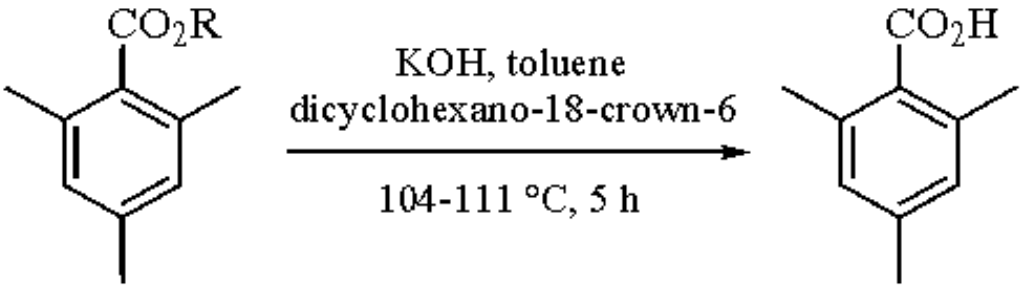

(1)

R = Me, 93%; *t*-Bu, 94%

Aromatic Nucleophilic Substitutions.

The KOH/dicyclohexano-18-crown-6 complex in toluene was prepared by solvent exchange from MeOH.[1] It contained 11% hydroxide ion and 89% methoxide ion.[2] Reaction of *o*-dichlorobenzene with this complex at 90 °C for 1 h gave *o*-chloroanisole in 40-50% yield. No phenol or other products from hydroxide ion were obtained. *m*-Chloroanisole was obtained from *m*-dichlorobenzene in a low yield.[2]

2-Alkoxy-3-cyanopyridines were prepared by the nucleophilic displacement of 2-chloro-3-cyanopyridine with alcohols in toluene and KOH/18-crown-6. Primary alcohols reacted within 3 h at 25 °C and gave the 2-alkoxy-3-cyanopyridines in about 85% yields (eq 2).

Secondary alcohols reacted slower and gave lower yields, while *t*-BuOH did not react. The less reactive 2-chloropyridine required heating.[3] Similar results were obtained from ***Sodium Hydroxide***-Aliquat 336 in toluene (see ***Methyltrioctylammonium Chloride***).

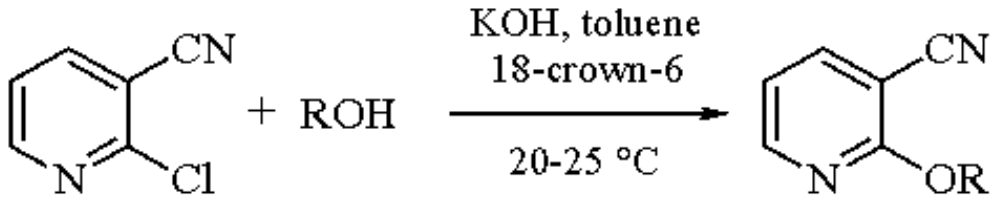

(2)

R	time	yield (%)
Bn	3 h	85
C_8H_{17}	3 h	85
i-Pr	18 h	67

Removal of Benzylidene Blocking Groups.

Benzylidene groups blocking the α-methylene positions of several ketones were removed under relatively mild conditions when treated with 4-aminobutyric acid and KOH in DMSO or HMPA in the presence of dibenzo-18-crown-6 as a catalyst. The reaction temperature varied from 85 to 115 °C and the isolated yields were 41-56%. The yields were lower in the absence of the amine and the reaction was slower in the absence of the crown ether. The retroaldol cleavage of the intermediate β-hydroxy ketone is facilitated by the imine formation (eq 3).[4]

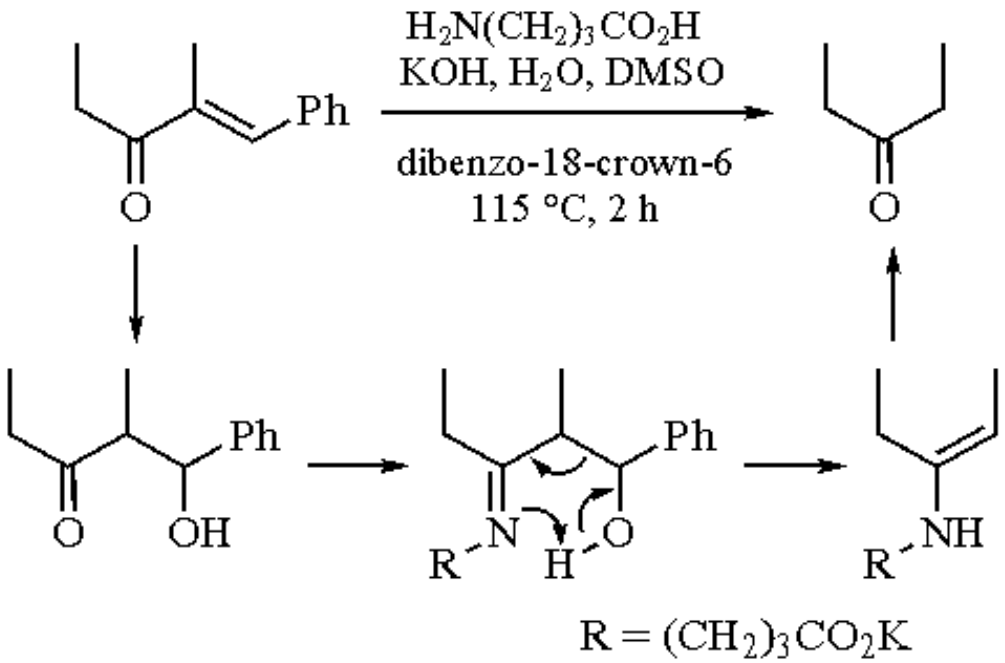

(3)

Alkylation of Arylalkynes.

Terminal arylalkynes were alkylated efficiently with alkyl iodides in benzene at 80 °C in the presence of powdered KOH and a catalytic amount of 18-crown-6 (eq 4).[5]

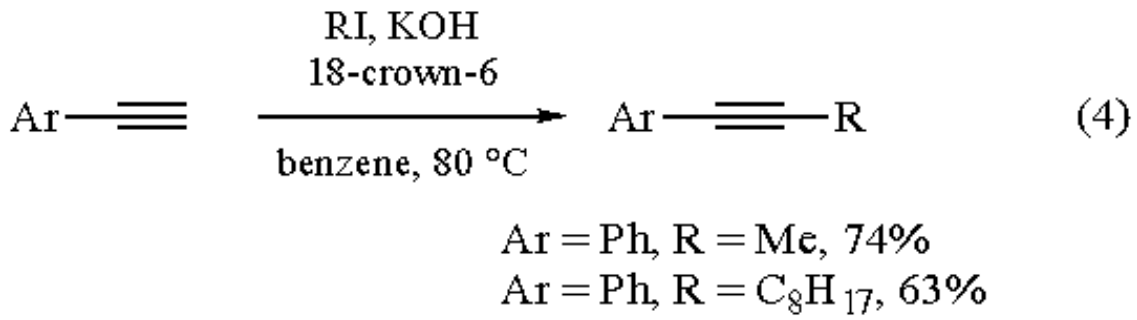

Permethylation of Ketones.

Several ketones were completely methylated at their α-position(s) when treated with ***Iodomethane***, powdered KOH, and a catalytic amount of 18-crown-6 in toluene at 70 °C,[6] e.g. 2,2,6,6-tetramethylcyclohexanone was prepared from cyclohexanone and pivalophenone from acetophenone (eq 5) in 93% and 89%, respectively, via this procedure.

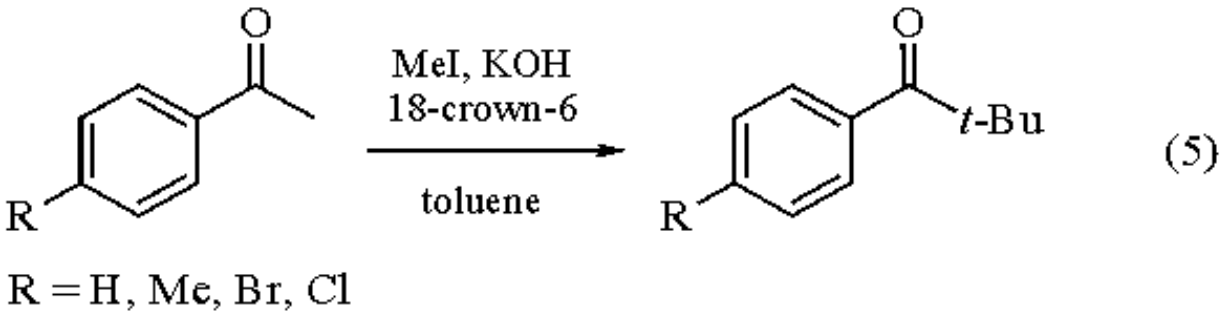

Reduction of Aromatic Nitro Compounds.

Aromatic amines were prepared by reduction of the corresponding nitroarenes with ***Dodecacarbonyltriiron*** in benzene and the catalytic effect of KOH/18-crown-6 at rt under N_2 in 60-84% yield. Twice the amount of $Fe_3(CO)_{12}$ at reflux temperature was needed in the absence of the KOH/18-crown-6 system.[7]

Decarboxylation of Activated Esters.

Malonic esters, β-keto esters, and α-cyano esters were decarboxylated via a one-pot procedure upon treatment with KOH and equimolar amounts of 18-crown-6 in benzene-ethanol or dioxane-ethanol (eq 6).[8]

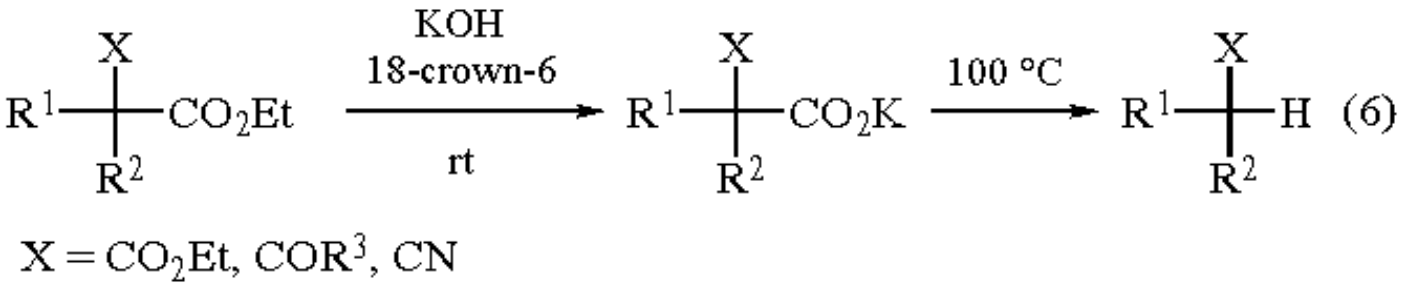

Synthesis of α,β-Unsaturated Nitriles.

MeCN was condensed smoothly with a variety of aldehydes and ketones when treated with KOH in the presence or absence of 18-crown-6 to give α,β-unsaturated nitriles in isolated yields ranging from 50 to 86% (eq 7).[9]

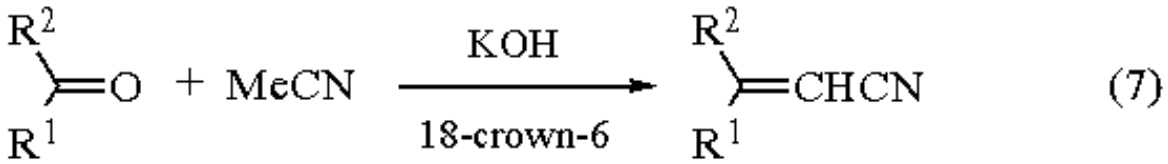

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Potassium Hydroxide-Dimethyl Sulfoxide

KOH-Me_2SO

(KOH)

[1310-58-3] · HKO · Potassium Hydroxide-Dimethyl Sulfoxide · (MW 56.11) (DMSO)

[67-68-5] · C_2H_6OS · Potassium Hydroxide-Dimethyl Sulfoxide · (MW 78.15)

(very strong base; low nucleophilicity due to low solubility which allows only surface reactivity[2])

Physical Data: see entries for ***Potassium Hydroxide*** and ***Dimethyl Sulfoxide***; KOH/DMSO has pK_a of 27 or higher.[1]

Alkylation of Amides, Phenols, Alcohols, and Acids.

A variety of carboxamides were alkylated with primary alkyl halides using KOH in DMSO to give the *N*-alkyl amides (eq 1) in 54-90% yield. Most reactions were carried out at rt, but in some cases heating to 90 °C was required.[3] Similar conditions were applied to alcohols, phenols, and acids to form ethers and esters.[4] The procedure applies to MeI and all primary halides. Secondary alkyl halides show evidence of competitive dehydrohalogenation, while tertiary halides do not give any alkylation products. The procedure was applied to the *N*- and *O*-permethylation of peptides.[4] It was also applied to the methylation of hydroxypyridines in 39-78% yield.[5] In all the above cases, the substrate and alkyl halide were added to powdered KOH in DMSO and stirred at rt. It was unnecessary to use especially dry DMSO or to protect the reaction mixture from atmospheric moisture.

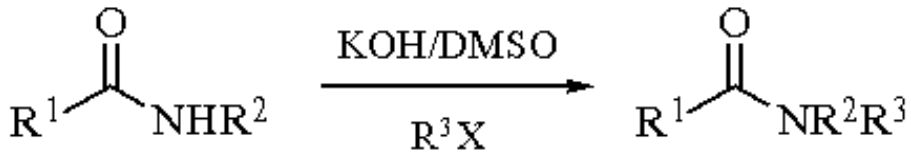

(1)

N-Alkylation of Indoles and Pyrroles.

N-Alkyl indoles and pyrroles were prepared in high yields (85-95%) by reaction of indoles and pyrroles with primary alkyl halides in DMSO and powdered KOH at rt (eq 2). The yields were lower with secondary halides (60% for *N*-isopropylindole), while tertiary halides gave no alkylation products.[6]

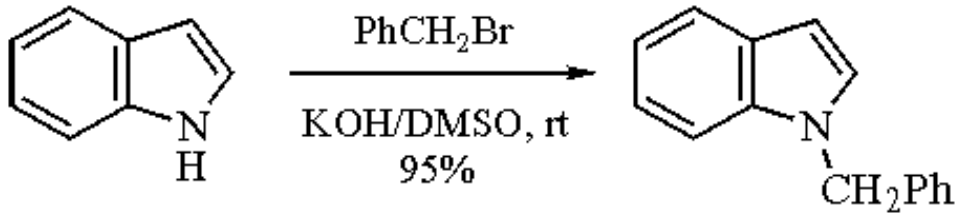

(2)

Alkylation of Ketones.

Ketones can be permethylated with ***Iodomethane*** in DMSO containing solid KOH. Cyclobutanone, cyclopentanone, and indanone gave the corresponding tetramethyl ketones in 49, 90, and 75% yields, respectively. All reagents can be used without drying and KOH can be used as pellets or as a powder.[2]

Synthesis of *O*-Arylhydroxylamines.

Reaction of tricarbonylchromium complexes of aryl halides (**1**) with *N*-*t*-butoxycarbonylhydroxylamine (**2**) in DMSO and powdered KOH under N_2 at rt resulted in the nucleophilic substitution of the Cl to give the corresponding tricarbonyl[(*t*-butoxycarbonylaminoxy)arene]chromium complexes (**3**) (eq 3). Consecutive I_2 treatment and acid hydrolysis gave the *O*-arylhydroxylamines in high overall yields.[7]

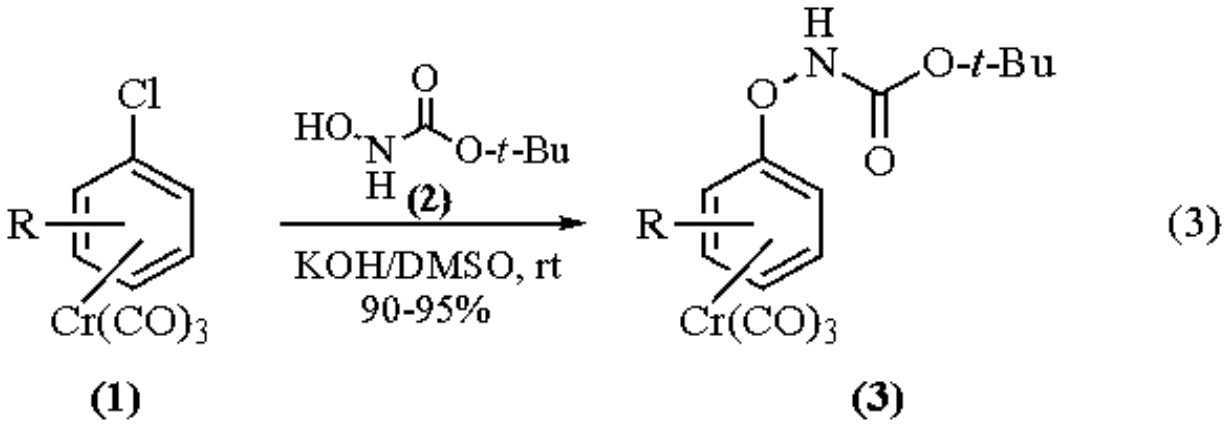

Hydroxylation of Ketones.

Treatment of the ketone (**4**) with KOH in warm DMSO in the presence of O_2 followed by the in situ reduction of the intermediate hydroperoxide with dithionite gave (**5**) as a 1:1 mixture of diastereomers (eq 4).[8]

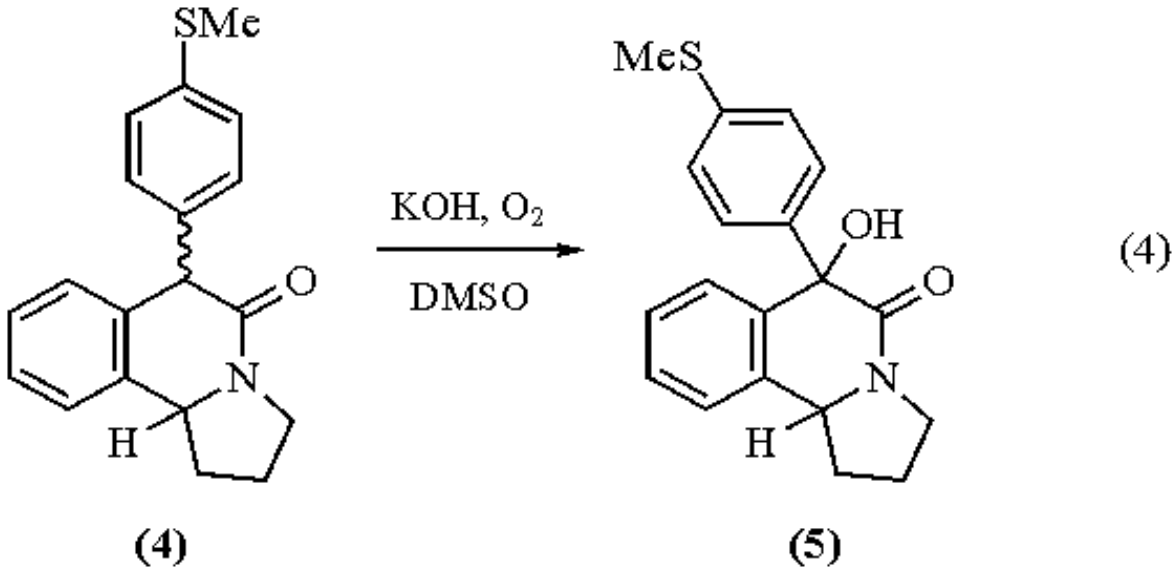

Synthesis of (*E*)-β-(Benzyloxy)styrenes from Benzyl Alcohols.

(*E*)-β-(Benzyloxy)styrenes (**7**) were obtained from the reaction of benzyl alcohols (**6**) with KOH/DMSO (eq 5) in 56-92% yields. This result was explained by an initial oxidation to the benzaldehyde followed by a condensation with DMSO anion to form intermediate (**8**). Subsequent addition of benzyloxide anion to (**8**) and elimination of $MeSO^-$ gives the product (**7**). The incorporation of the DMSO carbon was confirmed by ^2H and ^{13}C labelling. The methyl styryl sulfoxide intermediate (**8**) was independently synthesized and converted into (**7**) under identical reaction conditions.[9]

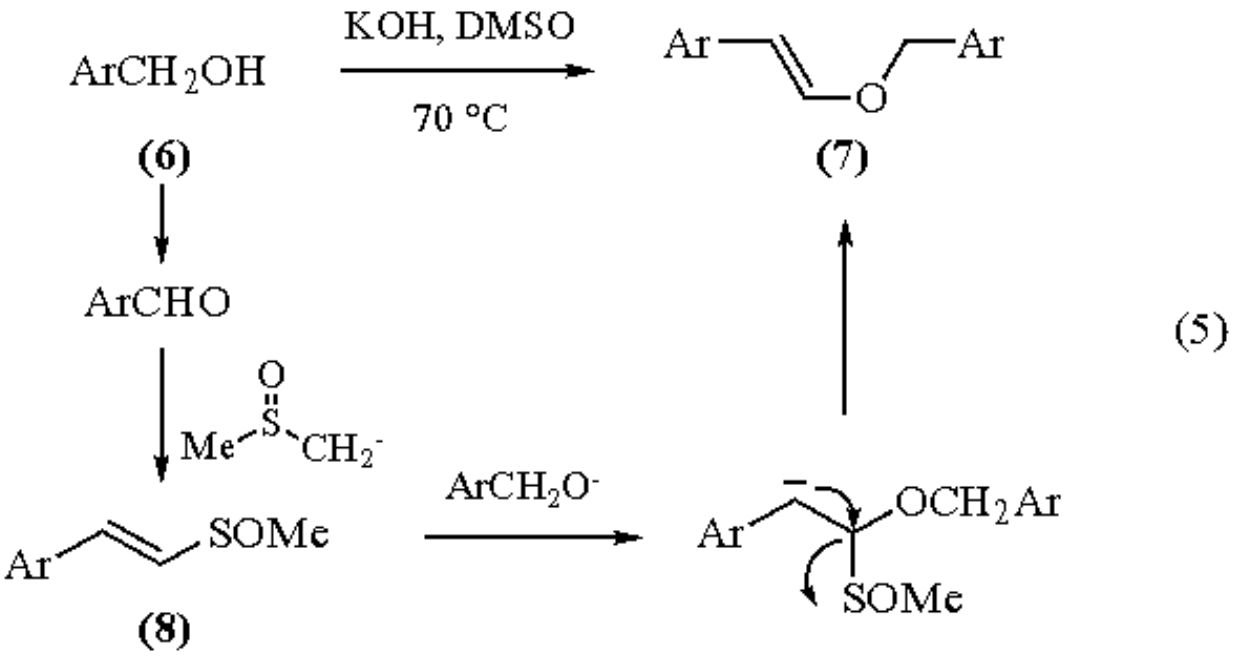

(5)

Preparation of *N*-Vinylpyrroles.

The reaction of ketoximes having at least one α-CH_2 group with acetylene in DMSO/KOH at 80-120 °C under atmospheric pressure gave *N*-vinylpyrroles in average yields of 70-80% via an intermediate pyrrole (eq 6). The conditions are also suitable for *N*-vinylation of pyrroles and other NH heterocycles in good yields.[1b]

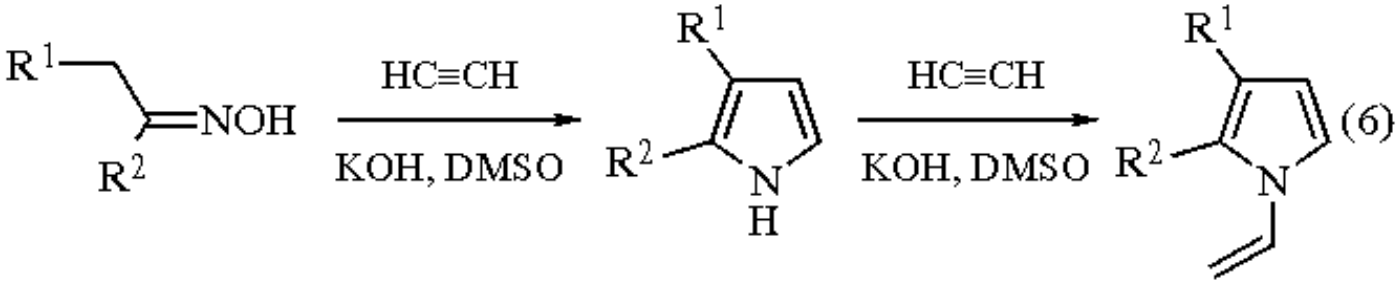

(6)

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Potassium Hydroxide-Hexamethylphosphoric Triamide

$KOH\text{-}(Me_2N)_3PO$

(KOH)

[1310-58-3] · HKO · Potassium Hydroxide-Hexamethylphosphoric Triamide · (MW 56.11) (HMPA)

[680-31-9] · $C_6H_{18}N_3OP$ · Potassium Hydroxide-Hexamethylphosphoric Triamide · (MW 179.24)

(strongly basic; esterification of hindered acids; additions to alkynes; ketone oxidations)

Physical Data: see entries for ***Potassium Hydroxide*** and ***Hexamethylphosphoric Triamide***.

Esterification of Hindered Carboxylic Acids.

Esters of hindered carboxylic acids, such as dialkyl and trialkyl acetic acids and mesitoic acid, were synthesized in high yields using alkyl halides, HMPA and EtOH as cosolvents, and KOH at 50 °C (eq 1). Esterifications were very rapid, near quantitative, and allowed the preparation of methyl and other alkyl esters.

$$RCO_2H + R'X \xrightarrow[\text{EtOH, 50 °C}]{\text{KOH/HMPA}} RCO_2R' \qquad (1)$$

Under these conditions, some dialkyl acetic acids were esterified to the methyl esters in 5 min with 98% conversion. The trialkyl acetic acid 2-methyl-2-propylpentanoic acid (**1a**) was quantitatively converted to the methyl ester (**1b**) in 30 min. Interestingly, the rate of reaction for the branched acid (**1a**) was about 5 times that of its straight chain analog, nonanoic acid. Mesitoic acid (**2a**) was esterified with ***Iodomethane*** in 20 min to give the methyl ester (**2b**) in 96% yield and with 2-iodooctane to give the 2-octyl ester (**2c**) in 80% yield in 2 h. The reaction was slower in the absence of HMPA as a cosolvent and gave significantly lower conversions.[1]

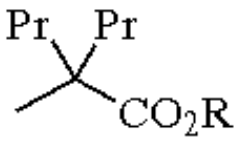

(1a) R = H
(1b) R = Me

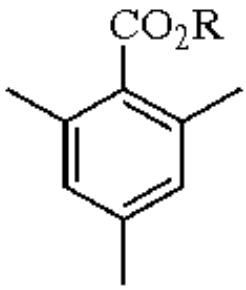

(2a) R = H
(2b) R = Me
(2c) R = 2-octyl

Additions to Acetylene.

Addition of H_2S to acetylene in the superbasic medium of KOH/HMPA gave ethanethiol as the only product. Under these conditions, the initial addition product, the vinylthiol anion, was reduced to give the product (eq 2).[2] The reaction in DMSO gave, among other products, divinyl sulfide.[2]

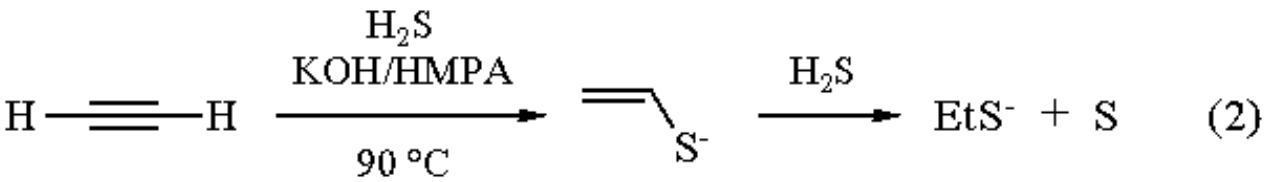

The reaction of elemental tellurium with acetylene in HMPA and KOH gave divinyl telluride in >50% yield (eq 3).[2]

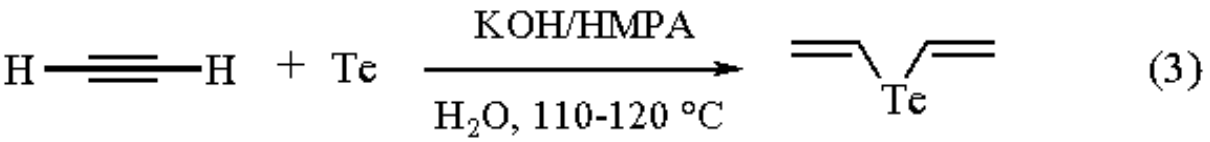

Preparation of Divinyloxypropenes.

Divinyloxypropenes (**3**) and (**4**) were obtained from the reaction of glycerol with acetylene in HMPA in the presence of KOH under a pressure of 10 atm at 150-160 °C for 2 h (eq 4). The product mixture (~25% overall yield) contained *cis*- and *trans*-1,2-divinyloxypropenes (**3**) (11%) and 2,3-divinyloxypropene (**4**) (1%) in addition to 2-methyl-4-vinyloxymethyl-1,3-dioxolane (**5**) (~7%) and 2-vinyloxy-1,3-butadiene (**6**) (~5%).[3] In the absence of HMPA the major reaction product was the 1,3-dioxolane (**5**) (33-66%), depending on the reaction conditions.[4]

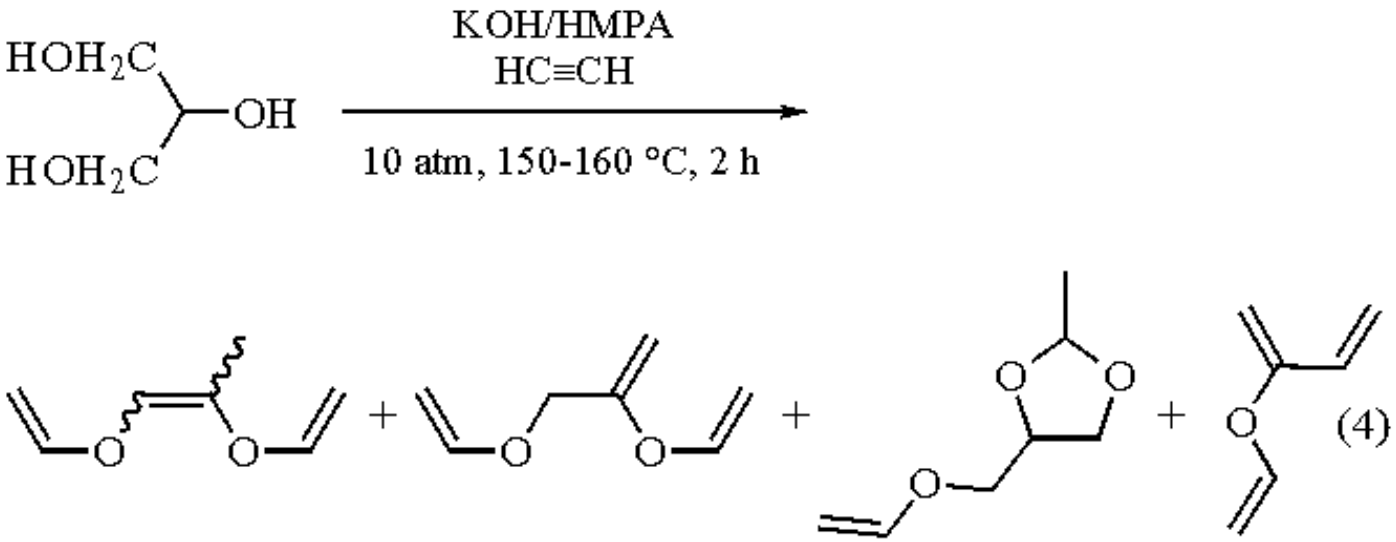

(3) **(4)** **(5)** **(6)**

Oxidation of Ketones.

Oxidations of acetophenone to benzoic acid (eq 5) and cyclic ketones to dicarboxylic acids (eq 6) were carried out with O_2 in the presence of KOH (or NaOH) in HMPA. The use of HMPA was superior to hydroxylic solvents, water, DMF, or DMSO. Either KOH or NaOH was an equally effective base catalyst, but LiOH was extremely poor. In the oxidation of acetophenone, addition of water slowed down the rate of oxidation but minimized the side reactions arising from the ketone enolate, thus increasing the selectivity to acidic products. Yields were moderate to excellent.[5]

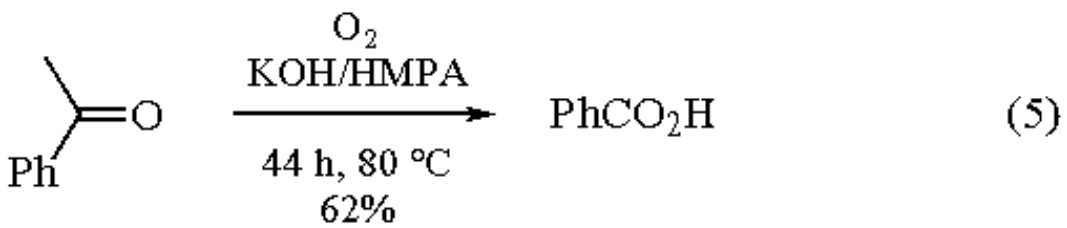

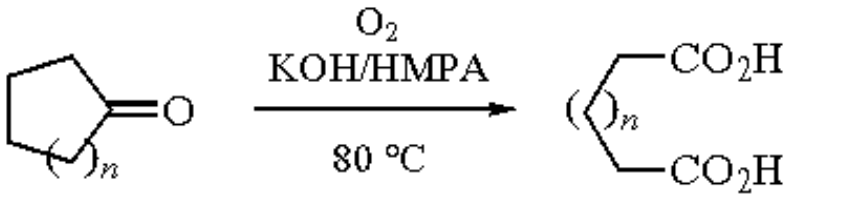

(6)

$n = 1$, 24 h, 76%
$n = 2$, 68 h, 82%

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Potassium Iodide[1]

KI

[7681-11-0] · IK · Potassium Iodide · (MW 166.00)

(source of iodide ion for nucleophilic displacement reactions;[4-9] cleaves some ethers in the presence of acid;[10-12] acts as a mediator in electrochemical oxidations of aldehydes;[13] reacts with sulfonyl chlorides to give symmetrical thiosulfonic *S*-esters;[14] with oxidizing agents, iodinates aromatic compounds;[15] iodinates organothallium compounds[16])

Physical Data: mp 681 °C; bp 1330 °C; *d* 3.130 g cm^{-3}.

Solubility: very sol cold H_2O (127.5 g/100 mL, 6 °C), hot H_2O (208.0 g/100 mL, 100 °C); sol alcohol (1.88 g/100 mL, 25 °C), acetone (1.31 g/100 mL, 25 °C); slightly sol ether, ammonia.[2]

Form Supplied in: white solid (crystalline, granular, or powder); widely available. *Drying:* can be dried under vacuum over P_2O_5 at 70-100 °C.[3]

Handling, Storage, and Precautions: slightly deliquescent in moist air, and upon long exposure to air will turn yellow due to liberation of iodine; storage in a dry or inert atmosphere recommended.

Introduction.

KI is used primarily as a source of iodide in organic synthesis. KI can often be used interchangeably with NaI (see ***Sodium Iodide*** and ***Tetra-n-butylammonium Iodide***).

Displacement Reactions.

KI will react with alkyl halides to give alkyl iodides. Alkyl iodides have been prepared from alkyl chlorides and bromides using KI supported on alumina.[4] The product iodide may be isolated or may react with a second nucleophile (e.g. ***Dimethyl Sulfoxide***).[5] KI/***Phosphoric Acid*** has been used to convert 1,6-hexanediol to 1,6-diiodohexane[6] and cyclohexene to cyclohexyl iodide.[7] KI reacts with aryl diazonium compounds to give aryl iodides.[8] This reaction has been shown to involve radicals, and proceeds faster and in higher yield in the absence of oxygen.[9]

Ether Cleavage Reactions.

KI in acetic acid or formic acid has been used to cleave aryl methyl ethers in high yield (yields were somewhat higher with KI than with NaI).[10] KI/H_3PO_4 has been used to convert THF to 1,4-diiodobutane.[11] KI/***Boron Trifluoride Etherate*** cleaves methyl, allyl, and benzyl ethers and opens cyclic alkyl ethers (including THF and epoxides) to give iodo alcohols.[12] Aryl methyl ethers are cleaved slowly by this reagent, allowing for some selectivity.

Electrochemical Oxidations.

KI has been used as a catalytic mediator in the electrochemical oxidation of aldehydes to esters[13] and nitriles.[13c] (NaI and Et_4NI may be used in place of KI in these electrochemical oxidations.)

Preparation of Symmetrical Thiosulfonic *S*-Esters.

KI reacts with sulfonyl chlorides (RSO_2Cl) to give thiosulfonic *S*-esters (RSO_2SR).[14]

Iodination of Aromatic Hydrocarbons.

$KI/O_2/NO^+BF_4^-$ in TFA/CH_2Cl_2 or TFA iodinates aromatic hydrocarbons; however, the reaction fails with electron-deficient aromatics.[15] (NaI, *n*-Bu_4NI, and ***Iodine*** may be substituted for KI.) KI reacts with arylthallium bis(trifluoroacetate) compounds to give aryl iodides (and thallium triiodide) (eq 1).[16] Vinyl iodides have been prepared similarly from vinylthallium bis(trifluoroacetates).[16f]

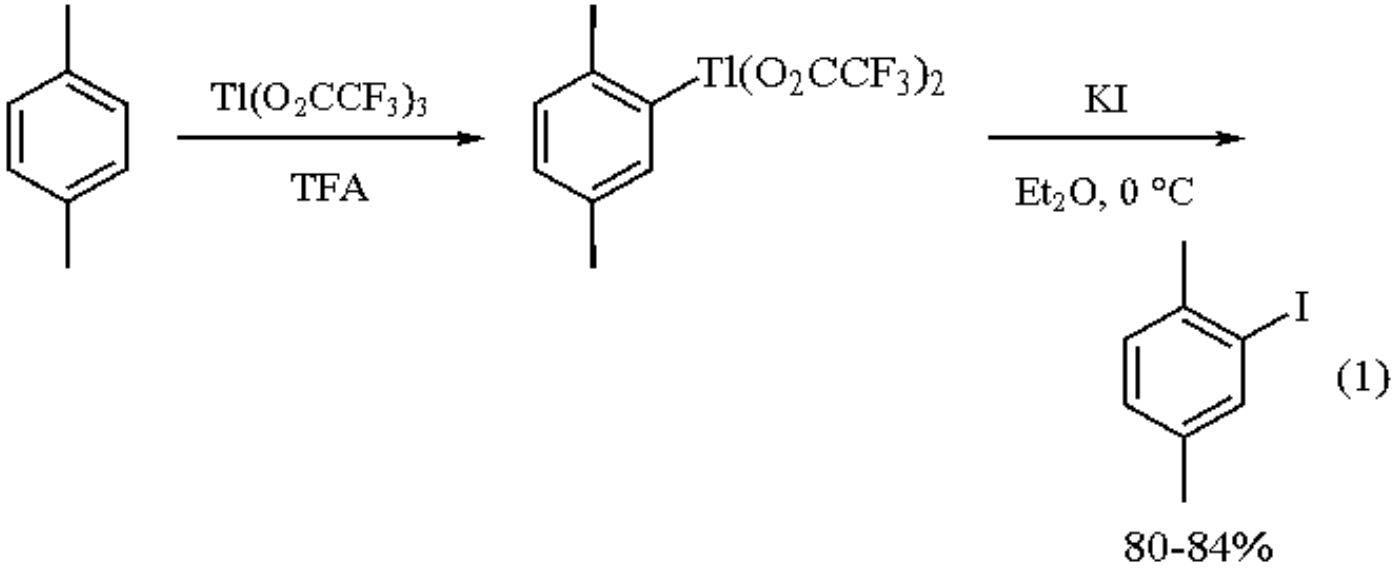

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Potassium Iodide-Zinc/Copper Couple

KI-Zn/Cu

(KI)

[7681-11-0] · IK · Potassium Iodide-Zinc/Copper Couple · (MW 166.00) (Zn/Cu)

[53801-63-1]

(agent for elimination of vicinal oxygen functionality[1])

Physical Data: see entries for ***Potassium Iodide*** and ***Zinc/Copper Couple***.

Vicinal Oxygen Elimination.[1]

Vicinal sulfonyloxy groups are eliminated by this reagent (eq 1). Although the reported yield from (**1**) is low, this procedure represented an improvement in both yield and reproducibility over previous methodology (zinc dust-sodium iodide).[2] With different *O*-protection, however, the fairly vigorous conditions caused loss of the 4-benzoyl group of (**2**) (eq 2), although it is still noteworthy that, in both cases, epimerization was not observed. The reaction is reported[1] to be slightly slower if ***Sodium Iodide*** is used in place of the potassium salt, although such a modification has been reported elsewhere[3] as quite adequate to eliminate the diol monosulfonate (**3**) (eq 3).

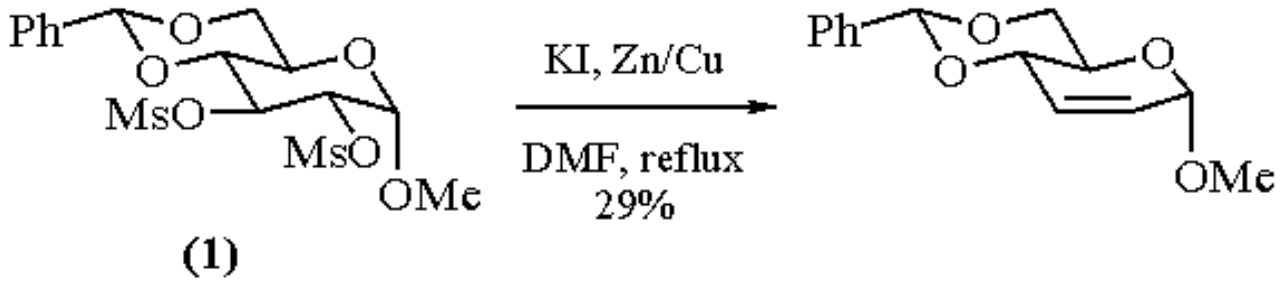

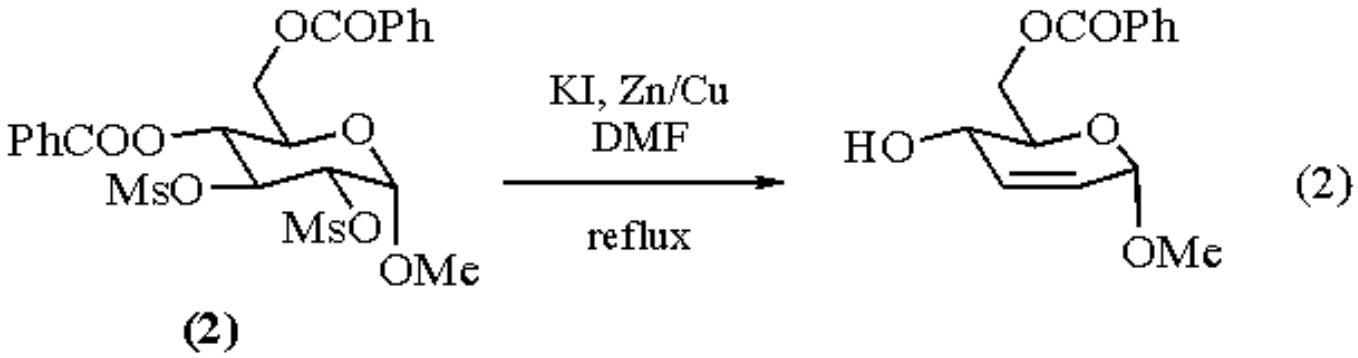

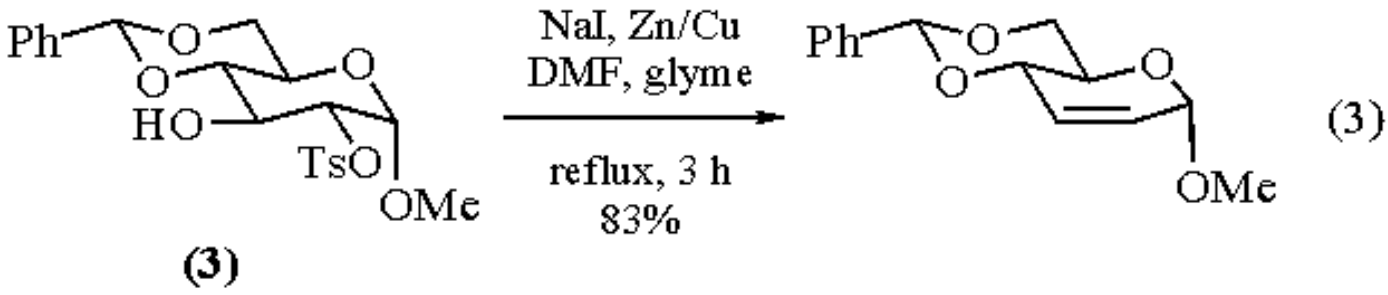

This reductive elimination of vicinal disulfonates has also been reported with NaI alone[4] in ketonic solvent, and with ***Sodium Anthracenide***[5] (for mesylates but not tosylates). With the exception, perhaps, of the latter, all of these comparable methods seem to be sufficiently mild to work effectively in the area of stereochemically sensitive molecules, the carbohydrates.

Related Reagents.

Sodium Iodide; ***Sodium Iodide-Copper***; ***Zinc***; ***Zinc-Acetic Acid***; ***Zinc Iodide***.

---

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Potassium Methoxide-Dicyclohexano-18-crown-6

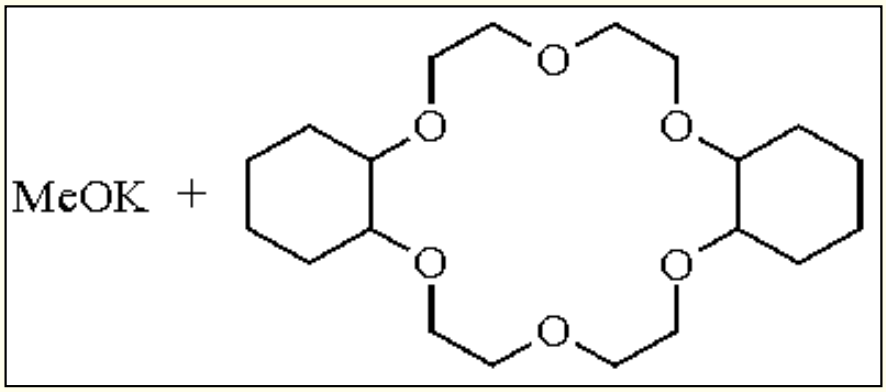

[52374-55-7] · $C_{21}H_{39}KO_7$ · Potassium Methoxide-Dicyclohexano-18-crown-6 · (MW 442.70)

(complex provides a strongly basic and nucleophilic methoxide ion[2])

Physical Data: reagent is prepared in situ.

Form Supplied in: MeOK is commercially available as a white powder in 95% purity; a mixture of the *syn-cis* and *anti-cis* crown ethers is commercially available.[1]

Preparative Methods: a toluene solution referred to as containing ***Potassium Hydroxide*** and ***Dicyclohexano-18-crown-6*** is obtained by mixing the crown ether and 85% KOH in MeOH, adding toluene, removing the MeOH at 100 °C under vacuum, and filtering the mixture.[3] However, the solubility of the KOH-crown ether complex is apparently much less than the MeOK complex.[2] Thus the toluene solution contains ca. 89% of the methoxide ion and only 11% of the hydroxide ion.[2] The direct preparation of the hydroxide complex was unsuccessful.[4]

Experimentally, complexes are most often generated in situ by adding 1.0 equiv or more of the crown ether to a solution of the base in MeOH or another solvent.

Handling, Storage, and Precautions: do not breathe dust from the base or vapor from the crown ether; avoid contact of both substances and the complex with the eyes, skin, or clothing. Handle reagents and conduct reactions under an inert nitrogen or argon atmosphere.[1] Use in a fume hood.

Nucleophilic Substitution Reactions.

The ability of dicyclohexano-18-crown-6 to dissociate MeOK by complexation with the potassium cation clearly manifests itself in various nucleophilic aromatic substitution reactions. The complex prepared by the solvent exchange reaction described above reacts with *o*-dichlorobenzene at 90 °C over 16 h to give *o*-chloroanisole in 40-50% yield (eq 1).[2] *m*-Dichlorobenzene is converted into *m*-chloroanisole under the same conditions, but the yield is much lower. Isomeric products which may arise from a benzyne intermediate are not produced in either case. Thus the nucleophilic aromatic substitution must proceed by an addition-elimination mechanism.[2]

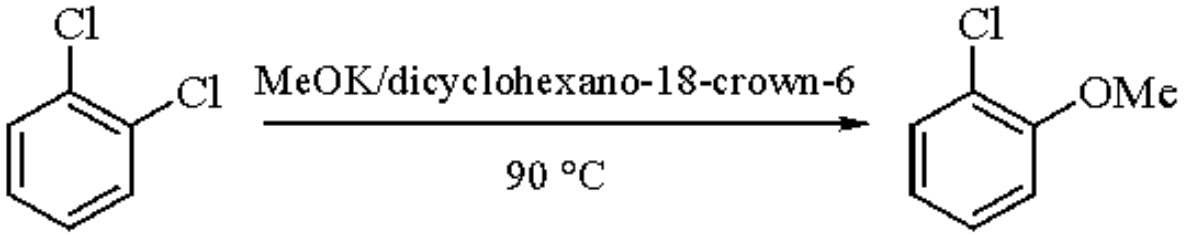

(1)

The rates of nucleophilic aromatic substitution of *o*- and *p*-fluoronitrobenzene by MeOK/MeOH are approximately the same; also, the addition of dicyclohexano-18-crown-6 has a negligible effect on the *ortho*:*para* rate ratio.[5] On the other hand, if ***Potassium t-Butoxide-t-Butyl Alcohol Complex*** is employed for the reaction, the *ortho*:*para* reactivity ratio is 3.6×10^2. The higher reactivity of the *ortho* isomer in the solvent of lower polarity, i.e. *t*-BuOH, is attributable to bridging between the oxygen atoms of the nitro group and the potassium cation. When 1.0 equiv of dicyclohexano-18-crown-6 is added to the *t*-BuOK/*t*-BuOH, the *ortho*:*para* reactivity ratio approaches unity because the potassium ion is strongly complexed to the crown ether and is unable to assist in the substitution reaction of the *o*-fluoronitrobenzene.[5]

When 1.0 equiv of dicyclohexano-18-crown-6 is added to a solution of MeOK in 99% PhH-MeOH, there is a 300-fold increase in the rate of nucleophilic aromatic substitution of 1-chloro-2,4-dinitrobenzene.[6] However, in MeOH containing less than 50% by weight of benzene, the addition of the crown ether has a negligible effect on the rate.[4] Because of the relatively high polarity of MeOH, the reactivity of the methoxide ion is not influenced significantly by the presence of the crown ether.

Dehydrohalogenation Reactions.

In the dehydrohalogenation of 2-bromobutane, the use of MeOK in MeOH, or other primary alkoxides in the corresponding alcohols, greatly favors Saytzeff elimination and gives a relatively large *trans*:*cis*-2-butene ratio, i.e. 3.34:1 (eq 2).[7] However, with tertiary alkoxides, e.g. *t*-BuOK, in the corresponding alcohols Hofmann elimination becomes much more important and the *trans*:*cis*-2-butene ratio approaches unity.[7] This trend is explained by the postulate that in the solvent of lower polarity, the elimination is promoted by the associated metal alkoxide. As expected, the addition of 1.0 equiv of dicyclohexano-18-crown-6 to the MeOK/MeOH has little effect on the 1-butene:2-butene ratio or the *trans*:*cis*-2-butene ratio.[7] However, when the crown ether is added to the *t*-BuOK/*t*-BuOH, the 1-butene:2-butene ratio decreases and the *trans*:*cis*-2-butene ratio increases.

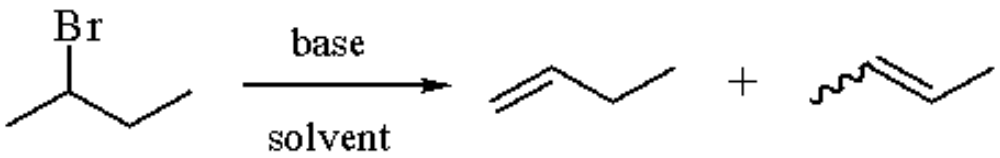

(2)

			trans:*cis*-2-butene
MeOK/MeOH	15.4%	84.6%	3.34:1
MeOK/dicyclohexano-18-crown-6/MeOH	16.3%	83.7%	3.43:1
t-BuOK/*t*-BuOH	41.6%	58.4%	1.78:1
t-BuOK/dicyclohexano-18-crown-6	31.2%	68.8%	3.20:1

Experiments in which metal alkoxides are used to effect β-elimination of methoxide ion from 1-methoxy-2-deuterioacenaphthenes show that an ElcB mechanism is involved (eq 3).[8] The more associated bases, e.g. *t*-BuOLi/*t*-BuOH, strongly favor exchange and elimination of the hydrogen *syn* to the methoxy group. This is attributable to strong coordination between the metal cation of the ion pair and the ether oxygen of the substrate. With a relatively dissociated base such as MeOK/MeOH, the *syn* and *anti* protons undergo exchange at comparable rates and *anti* elimination of the methoxide ion is slightly favored over *syn* elimination. The addition of dicyclohexano-18-crown-6 does not alter the stereochemistry of the exchange with MeOK. The use of *t*-BuOK/*t*-BuOH favors *syn* elimination and exchange somewhat, but in the presence of 1.0 equiv of the crown ether *anti* exchange and elimination

are both favored.[8] Apparently, when the potassium cation is no longer able to complex with the oxygen of the substrate, the *t*-butoxide ion abstracts the *anti* proton preferentially for steric reasons.

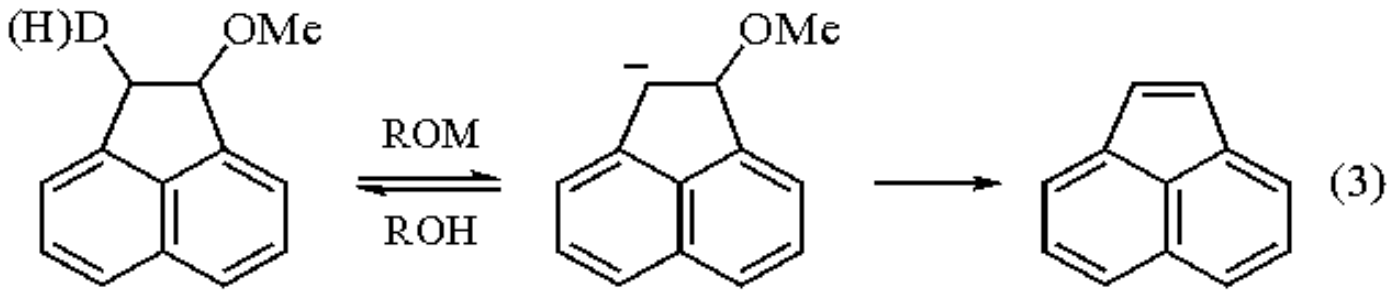

Other Reactions.

MeOK/dicyclohexano-18-crown-6 has been used rather infrequently for transformations other than nucleophilic aromatic substitutions and β-eliminations. However, it is a useful base for the deprotonation of a ketone in the formation of the TMS enol ether of acetophenone using ethyl trimethylsilylacetate (eq 4).[9]

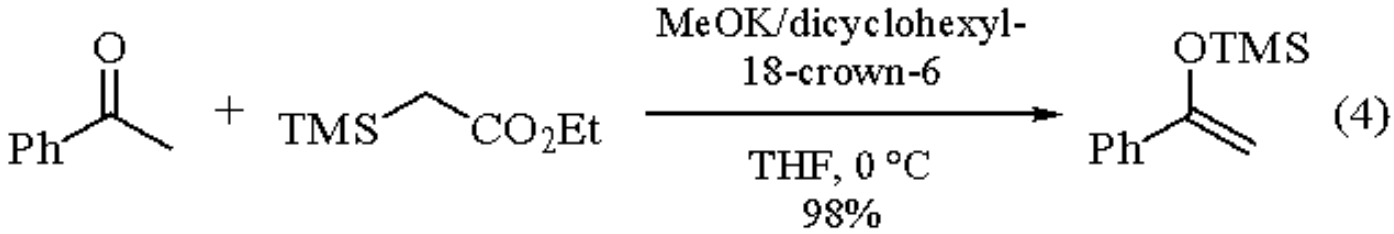

Related Reagents.

Potassium t-Butoxide; ***Potassium t-Butoxide-Benzophenone***; ***Potassium t-Butoxide-t-Butyl Alcohol Complex***; ***Potassium t-Butoxide-18-Crown-6***; ***Potassium t-Butoxide-Dimethyl Sulfoxide***; ***Potassium t-Butoxide-Hexamethylphosphoric Triamide***; ***Potassium Hydroxide-18-Crown-6***; ***Potassium Methoxide-Dimethyl Sulfoxide***; ***Sodium Methoxide***.

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Potassium Methoxide-Dimethyl Sulfoxide

MeOK/Me_2SO

(MeOK)

[865-33-8] · CH_3KO · Potassium Methoxide-Dimethyl Sulfoxide · (MW 70.14) (DMSO)

[67-68-5] · C_2H_6OS · Potassium Methoxide-Dimethyl Sulfoxide · (MW 78.15)

(highly basic reagent; used occasionally for deprotonation of weakly acidic carbon acids, β-elimination, and alkene isomerization reactions[2])

Physical Data: prepared in situ.

Form Supplied in: MeOK: commercially available in 95% purity; white powder. DMSO: commercially available (see ***Dimethyl Sulfoxide***).

Preparative Methods: prepared from anhydrous MeOK and anhydrous DMSO,[2b] in much the same manner as ***Potassium t-Butoxide-Dimethyl Sulfoxide***.[5]

Handling, Storage, and Precautions: MeOK: solid is flammable, corrosive, and hygroscopic.[1] Use the same precautions as for *t*-BuOK/DMSO. Use in a fume hood.

Deprotonation Reactions.

MeOK in DMSO solution forms a highly basic and nucleophilic medium, since the dipolar aprotic solvent strongly coordinates with potassium cations producing activated, solvent-separated, and dissociated methoxide anions in a medium of high dielectric constant.[2] Rate constants of base-catalyzed racemization and hydrogen isotope exchange reactions, as well as dehydrohalogenation and alkene isomerization reactions, indicate that MeOK/DMSO is a less basic medium than *t*-BuOK/DMSO. Apparently, the *t*-butoxide anion is not solvated as well as the methoxide ion in DMSO.[2b] In this dipolar, aprotic solvent it might have been expected that the order of basicity of the anions would be the same as in the gas phase, i.e. MeO^- > *t*-BuO^-.[3] Solutions of *t*-BuOK in DMSO are known to contain dimsyl anions;[4] this may have an influence on the basicity of the medium.[2b]

The rate of the MeOK-catalyzed racemization of (+)-2-methyl-3-phenylpropionitrile increases by 10^9 when the solvent is changed from MeOH to DMSO.[5] In MeOH the methoxide ion has relatively lower activity because it is strongly hydrogen bonded by the solvent molecules. MeOK catalyzes the hydrogen-tritium exchange reaction between tritiated toluene and DMSO, but the reaction rate is ca. 250 times faster when *t*-BuOK is employed as the base.[2b]

Substitution and Elimination Reactions.

Upon treatment with alkoxide bases in 83.7 mol % DMSO/alcohol mixtures, 1-bromodecane gives mixtures of alkyl decyl ethers via substitution (S_N2) reactions and 1-decene via an elimination (E2) reaction (eq 1).[6] The E2/S_N2 ratio is 0.14 for MeOK, but it is ca. 1.8 for *t*-BuOK; thus under these conditions the methoxide ion is a much better nucleophile than the *t*-butoxide ion. The addition of ***18-Crown-6*** to the above solution has very little effect on the overall reaction rate or the E2/S_N2 ratio when MeOK is employed as the base. The same is true for KOH and EtOK. However, in the presence of the crown ether the reaction is ca. 3.6 times faster, and the E2/S_N2 ratio increases slightly when *t*-BuOK is used as the base. From linear extrapolation of the Brønsted relation (ln *k* vs. H_-), it has been suggested that at very high values of the acidity function (H_-), where the anions would be largely desolvated, the order of basicity of alkoxide ions should be MeO^- > EtO^- > *t*-BuO^-, i.e. the same as in the gas phase.[6]

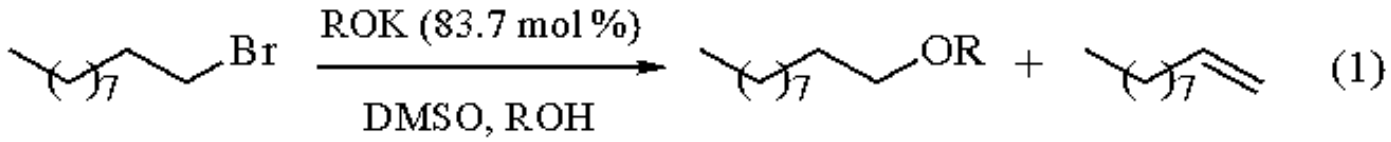

R = Me	88%	12%
R = *t*-Bu	35.6%	64.4%

Alkene Isomerization Reactions.

Both MeOK and *t*-BuOK effect the isomerization of 1-butene to *cis*-2-butene primarily in DMSO (eq 2).[7,2b] However, the rates are markedly dependent upon the anion; the reaction is ca. 125 times faster with *t*-BuOK than with MeOK. The stereoselectivity of the reaction is presumably controlled by the fact that the *cis*-allylic anion produced upon deprotonation of the alkene is more thermodynamically stable than its *trans* isomer.[7]

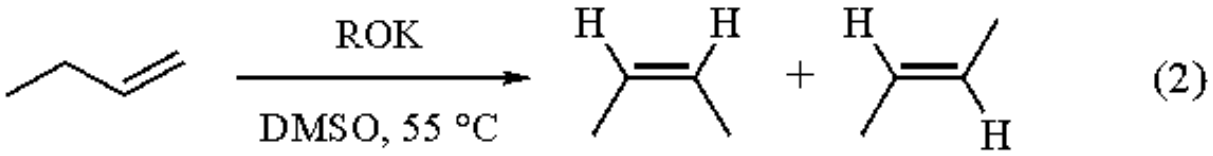

R = Me	14:1
R = *t*-Bu	13:1

Related Reagents.

Potassium t-Butoxide-Dimethyl Sulfoxide; ***Potassium Methoxide-Dicyclohexano-18-crown-6***; ***Sodium Ethoxide***; ***Sodium Methoxide***.

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1. *The Sigma-Aldrich Library of Chemical Safety Data*, 2nd ed.; Lenga, R. E., Ed.; Sigma-Aldrich: Milwaukee, 1988; Vol. 2, p 2906.
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Potassium 2-Methyl-2-butoxide

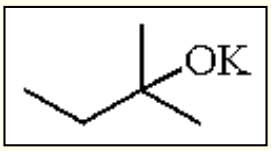

[41233-93-6] · $C_5H_{11}KO$ · Potassium 2-Methyl-2-butoxide · (MW 126.26)

(strong, sterically hindered alkoxide base)

Alternate Name: potassium *t*-pentoxide.

Form Supplied in: 1.5-2.0 M solution in benzene.

Solubility: sol THF, DME, aromatic hydrocarbons.

Preparative Methods: amber-colored 0.15-0.20 M $EtCMe_2OH$ solutions of the reagent are prepared in situ by refluxing oxide-free potassium metal in the anhydrous alcohol for 3-4 h.[1] Solutions of the base which are 1.0-2.0 M in THF, benzene, or toluene are prepared by treating oil-free ***Potassium Hydride*** with an equivalent amount of anhydrous *t*-pentyl alcohol in the anhydrous solvent under an inert atmosphere.[2]

Handling, Storage, and Precautions: solutions should be handled with the same precautions that are used for solutions of *t*-BuOK (see ***Potassium t-Butoxide***). Avoid contact with the eyes, skin, and clothing. Conduct all reactions under a dry nitrogen or argon atmosphere. In the absence of air and moisture, solutions of the base in benzene or toluene may be stored in a refrigerator for up to 1 year without significant deterioration.[2b] However, for critical experiments it is recommended that the reagent be freshly prepared. Use in a fume hood.

Enolate Formation and Alkylation.

The basicity of tertiary potassium alkoxides increases as the bulk of the alkyl substituents increases.[2a] For example, the equilibrium constant for the conversion of pinacolone into its enolate anion by $EtCMe_2OK$ in THF (eq 1) is 10, while it is 6.7 for the less bulky base *t*-BuOK, and 57 and 710, respectively, for the more bulky bases Et_3COK and Cy_3COK.[2a] Increased steric hindrance, which interferes with aggregation and solvation of the ion pair, presumably accounts for this.

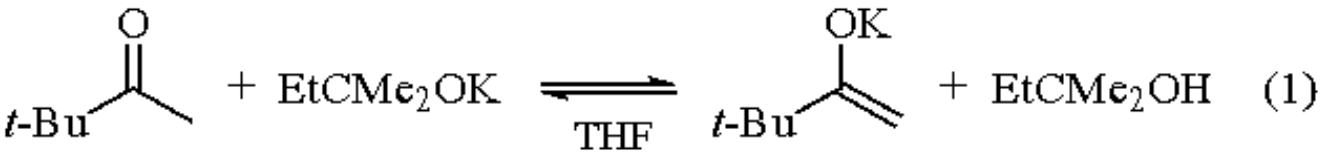

Although potassium alkoxides can produce potassium enolates of most ketones in high concentrations, alkylation of these species is frequently a problem because of their tendency to undergo rapid proton transfer reactions which lead to polyalkylation, aldol condensation, and equilibration of structural isomers in unsymmetrical systems.[3] However, monoalkylation products are obtained in satisfactory yields even with cyclopentanone, which is highly prone to side reactions, using $EtCMe_2OK$ in DME as the base and a large excess of a reactive alkylating agent such as ***Iodomethane*** or ***Benzyl Bromide*** with a very short reaction time (eq 2).[4] The α-alkylation of α,β-unsaturated ketones such as 1-carvone is also accomplished in good yield using this base/solvent system and a reactive alkylating agent (eq 3).[4] The weakly acidic enone 1,10-dimethyl-$\Delta^{1,9}$-2-octalone is converted into its linearly conjugated dienolate with $EtCMe_2OK$ in benzene. This species can be α-methylated with MeI in 93% yield;[5] the yield is only 24% if *t*-BuOK is employed as the base.[6]

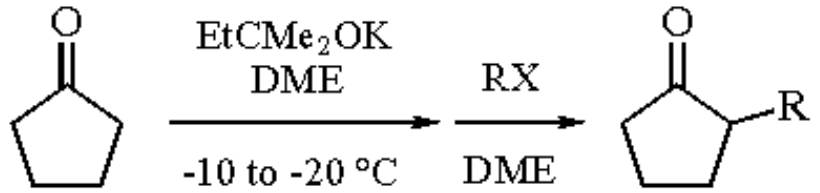

(2)

RX = MeI, 75%; BnBr, 77%

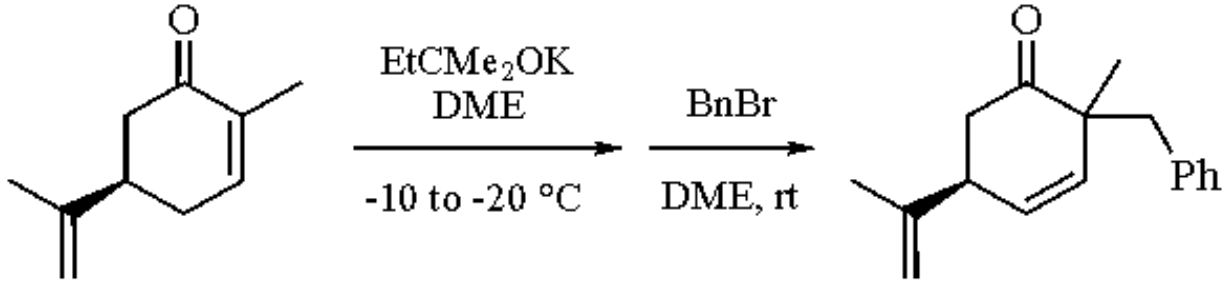

(3)

80%

Wittig Reactions.

Potassium alkoxides are frequently used as bases in Wittig reactions because the potassium cation does not strongly associate with the oxyanion of the betaine intermediate, and thus decomposition of this species to the alkene is relatively rapid.[7] The Wittig alkenation of sterically hindered 20-keto steroids such as pregnenolone with various triphenylalkylphosphoranes occurs in good yields using $EtCMe_2OK$ in benzene as the base/solvent system (eq 4).[2b] (*E*)-20(22)-Dehydro steroid derivatives are the exclusive products. These products are isolated in poor yields when $EtCMe_2ONa$ in benzene is used to generate the phosphorane from the phosphonium salt.[8]

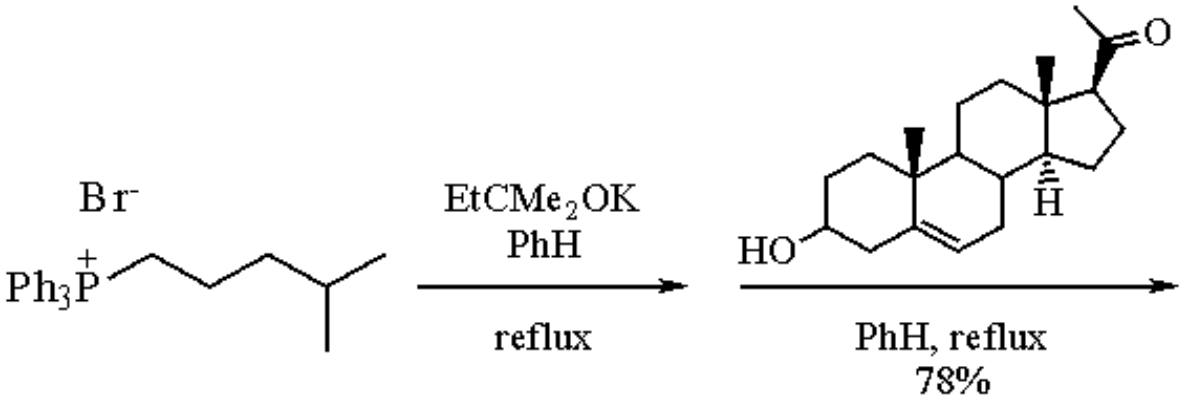

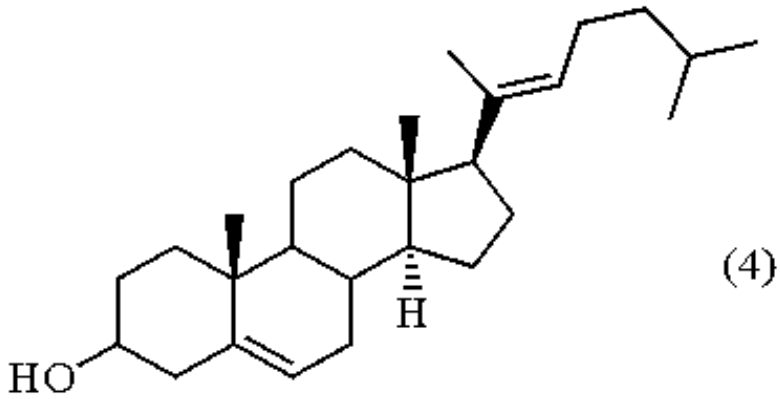

(4)

Dehydrohalogenation Reactions.

As illustrated for the dehydrobromination of 2-bromo-2-methylbutane in eq (5), an increase in the steric hindrance of the potassium alkoxide base increases the 1-alkene/2-alkene ratio of the β-elimination products.[9] $EtCMe_2OK$ gives a 1-alkene/2-alkene ratio which is

intermediate between that of the less bulky *t*-BuOK and the more bulky Et_3COK.[9]

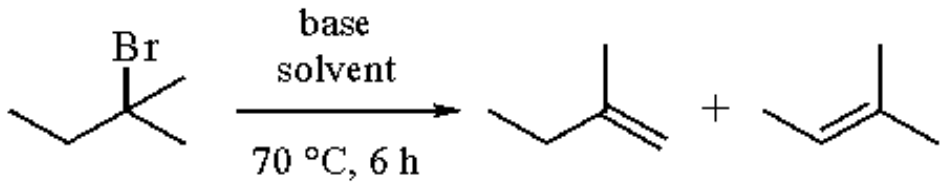

(5)

base		
t-BuOK, *t*-BuOH	73%	27%
$EtCMe_2OK$, $EtCMe_2OH$	78%	22%
Et_3COK, Et_3COH	89%	11%

Lethargic Reactions.

Highly hindered acetophenone derivatives are converted to their oximes by treatment with ***Hydroxylamine*** hydrochloride in the presence of 2.0 equiv of $EtCMe_2OK$ in $EtCMe_2OH$ at rt for 1 month or longer (eq 6).[1b] Efforts to force the reaction by using higher temperatures result in lower yields. The $NHOH^-$ anion is presumed to be the reactive species.[1b]

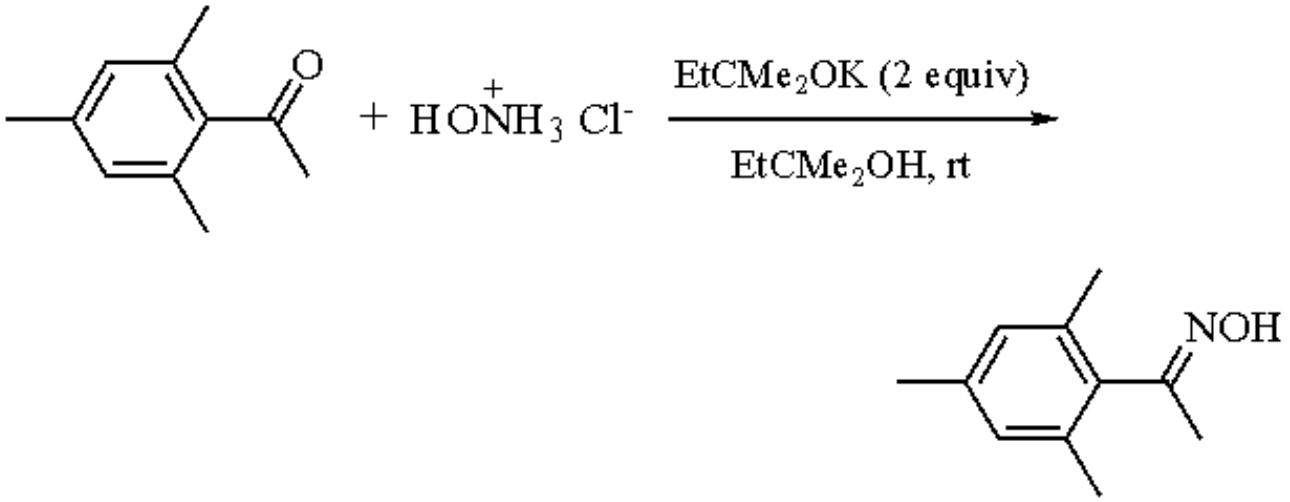

(6)

Rearrangement Reactions.

The reagent is used to extrude selenium from Se-acylmethyl selenocarboxylates to produce β-diketones (eq 7),[10] and for rearranging nitronates into hydroxamates (eq 8).[11]

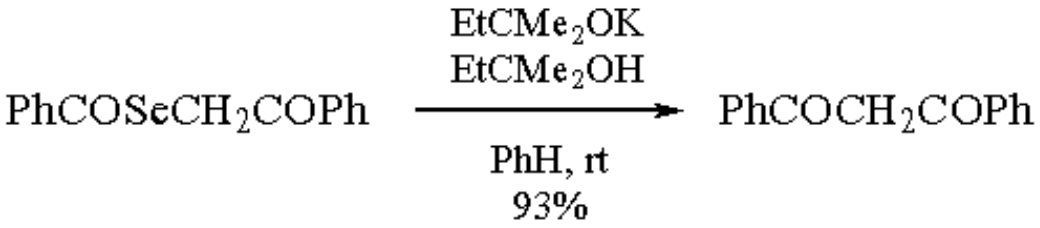

(7)

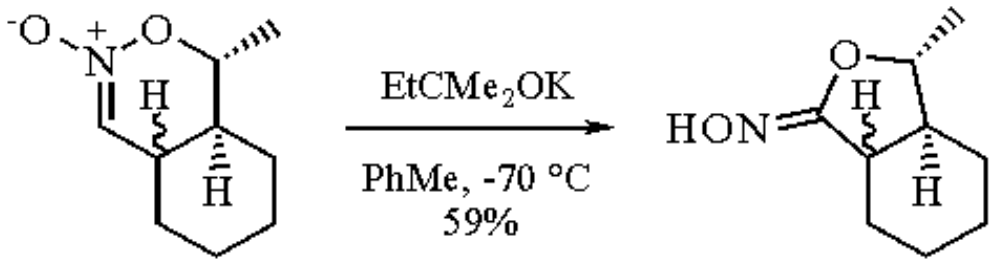

(8)

Metalation Reactions.

Mixtures of alkyllithium reagents and tertiary potassium alkoxides are powerful metalating agents for weakly acidic compounds.[12] For example, phenylpotassium is produced from the combination of ***n-Butyllithium*** and $EtCMe_2OK$ in benzene.[13]

Related Reagents.

Potassium t-Butoxide; ***Potassium t-Heptoxide***.

---

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2. (a) Brown, C. A. *CC* **1974**, 680. (b) Schow, S. R.; McMorris, T. C. *JOC* **1979**, *44*, 3760.
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Potassium Methylsulfinylmethylide[1]

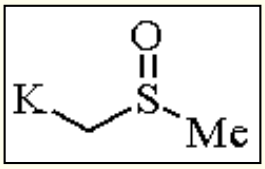

[15590-26-8] · C_2H_5KOS · Potassium Methylsulfinylmethylide · (MW 116.24)

(a strong base and nucleophile, very useful for the introduction of the methylsulfinylmethyl group[1])

Alternate Name: potassium dimsylate; dimsylpotassium; KDMSO.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: titration with formanilide or 2,6-di-*t*-butylphenol using triphenylmethane as indicator.[2,3]

Preparative Methods: prepared by the reaction of ***Potassium Amide*** or ***Potassium Hydride*** with ***Dimethyl Sulfoxide*** (DMSO).[3,4] Equilibrium quantities of KDMSO may be prepared using ***Potassium t-Butoxide*** in DMSO.[5]

Handling, Storage, and Precautions: best prepared as needed although synthesis and storage procedures similar to those used in some preparations of ***Sodium Methylsulfinylmethylide*** (NaDMSO) would probably result in long shelf life.[6] Hydrogen gas may be emitted during the preparation of this reagent and due caution should be exercised in its preparation, particularly on a large scale. Problems encountered in the preparation of NaDMSO may be relevant to KDMSO.[7]

Introduction.

The conjugate base of dimethyl sulfoxide (pK_a = 35) represents a powerful base and nucleophile. It is expected that much of the chemistry of KDMSO will be the same as that of related metal salts and this is indeed the case (see ***Lithium Methylsulfinylmethylide*** and ***Sodium Methylsulfinylmethylide***).

It should be noted that the generation of KDMSO with *t*-BuOK in DMSO results in the formation of only equilibrium amounts of carbanion. While this is sufficient to make products derived from KDMSO attack preponderant in many instances (e.g. nucleophilic addition), when this combination is used for its basic properties it is likely that the active agent is *t*-BuOK and not KDMSO.[8]

Potassium Methylsulfinylmethylide as Base.

Alkene Isomerization.

KDMSO has been used to conjugate dienes in natural oils such as linseed oils.[9] KDMSO works much better than NaDMSO in facilitating this reaction. This isomerization procedure has also been used with synthetic compounds (eq 1).[10]

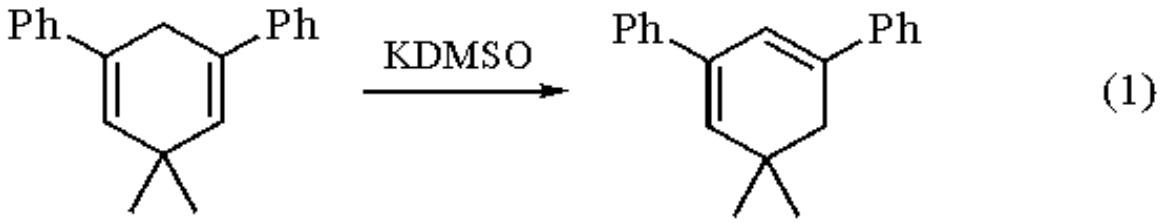

In work involving the nature of stabilizing effects in dianions it has been demonstrated that in the presence of excess KDMSO, 2-(diphenylmethyl)-1,1,3,3-tetraphenylpropene can be deprotonated to a dianion which is y-aromatic (eq 2).[11]

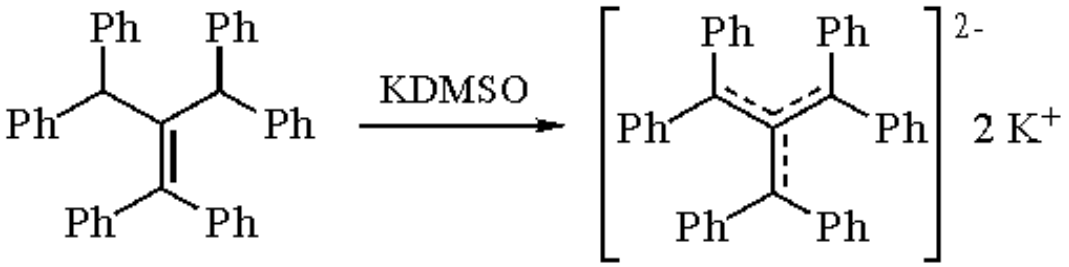

(2)

Elimination Reactions.

Elimination reactions allegedly using KDMSO probably involve *t*-BuOK when the latter is used to generate KDMSO in DMSO.[8] Such eliminations are not covered here. There are bona fide examples of eliminations using KDMSO produced stoichiometrically.

For example, as part of a total synthesis of elfamycin, treatment of bis-epoxide (**1**) gave the tetrahydrofuran (**2**) in a tandem elimination-ring closure sequence (eq 3).[12]

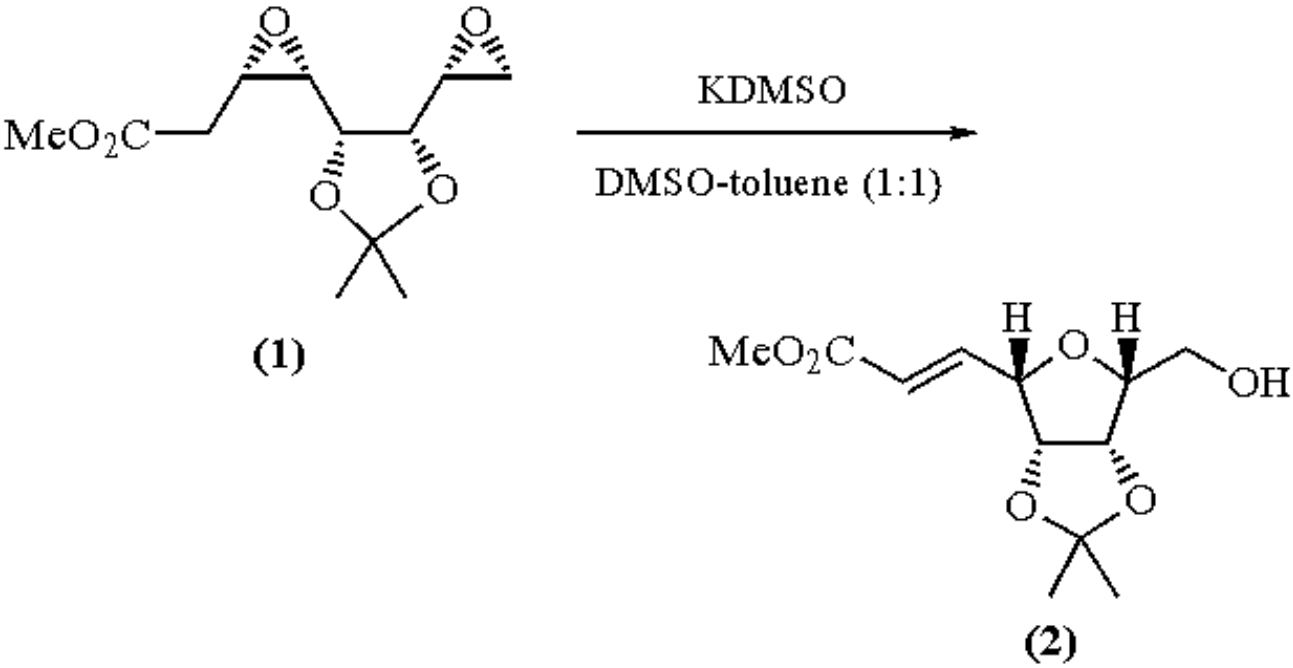

(3)

A new, general synthesis of *ortho*-alkenyl anilines is based on an elimination reaction of benzothiazines to give sulfinanilides in high yield (eq 4).[13] The latter are easily hydrolyzed to free anilines.

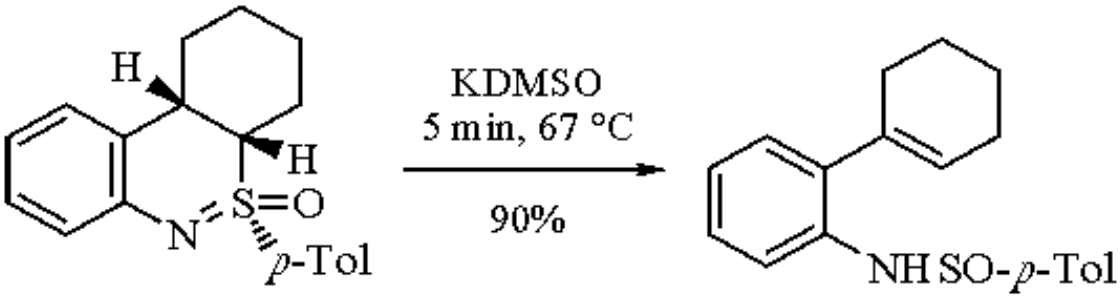

(4)

Ether Synthesis.

The exhaustive *O*-alkylation of oligo- and polysaccharides (Hokomori reaction) greatly facilitates the handling and analysis of such compounds. The use of KDMSO as a base in this application of the Williamson ether synthesis and its superiority over NaDMSO have been documented.[14]

Potassium Methylsulfinylmethylide as Nucleophile.

Reactions with Esters.

The reaction of dimsyl anions with esters leads generally to β-keto sulfoxides. KDMSO generated from *t*-BuOK in DMSO has been used for this purpose (eq 5).[15] The importance of this reaction lies in the synthetic utility of β-keto sulfoxides.[16] For example, they are readily and regioselectively alkylated and desulfurized to give ketones (eq 6) and, inter alia, can be converted to α-keto aldehydes (eq 7).[15]

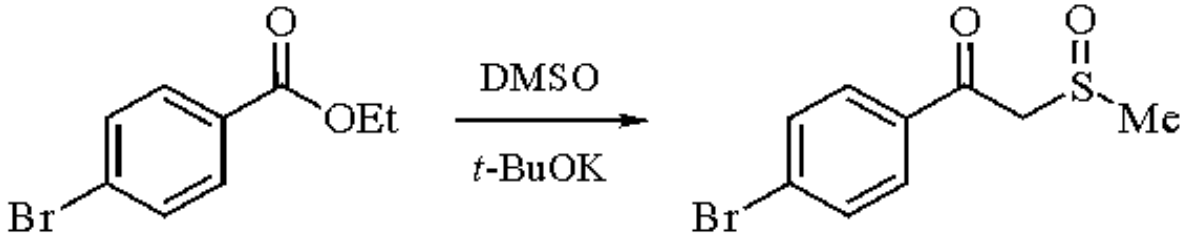

(5)

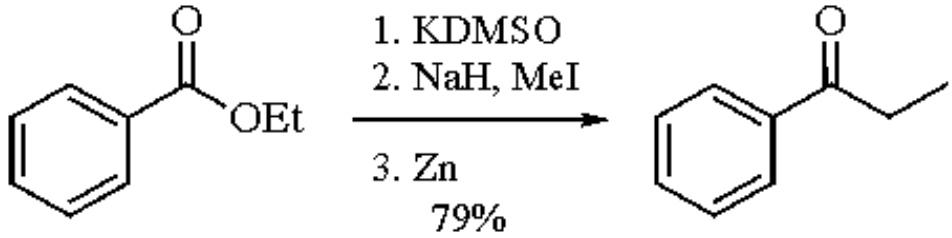

(6)

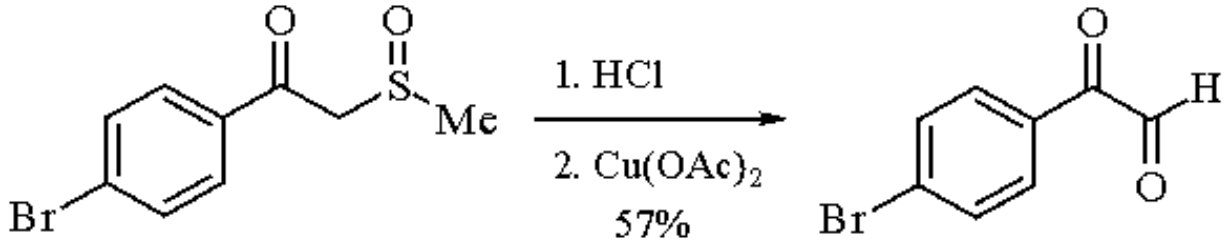

(7)

Reactions with Aldehydes and Ketones.

KDMSO derived from *t*-BuOK in DMSO reacts with aromatic aldehydes to give the expected products.[5] Interestingly, at higher temperatures and in the presence of diphenylmethane, a series of transformations takes place which result in the formation of an alkene containing no sulfur, but including a molecule of diphenylmethane (eq 8).[17]

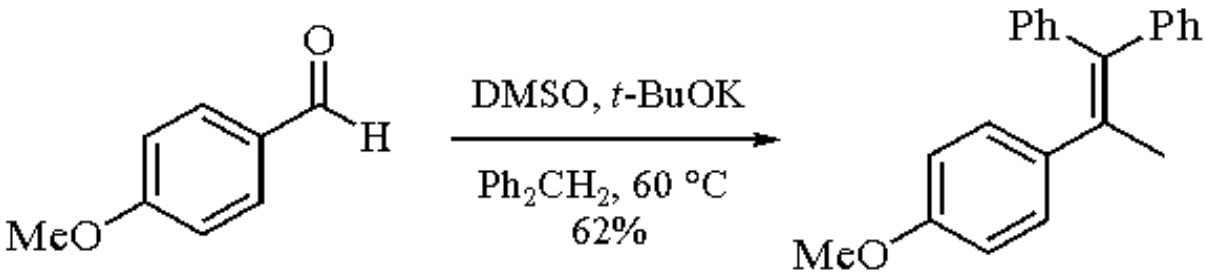

(8)

Even more interesting is the report of diene diol formation from an epoxy ketone (eq 9).[18] A related reaction may be taking place in the conversion of cyclohexanone to 2-methylenecyclohexanol (eq 10).[19]

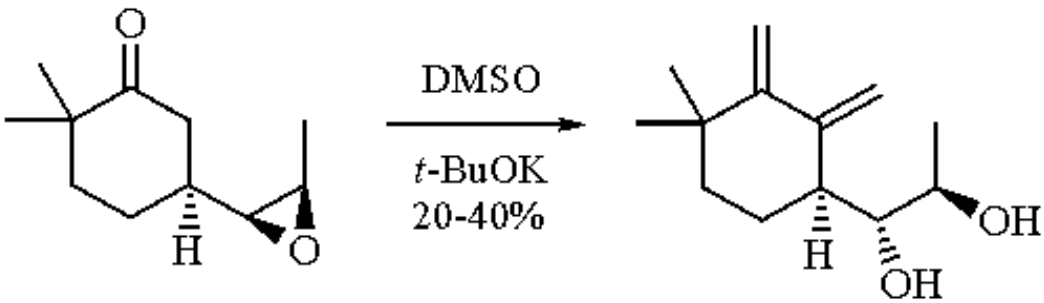

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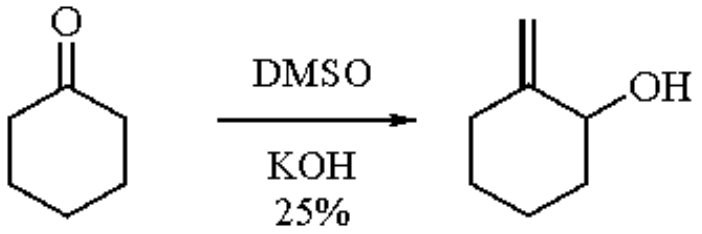

(10)

Reactions with Alkenes.

Dimsyl anions do undergo additions to Michael acceptors, even those which are not very activated. Two examples using KDMSO are illustrative of the diverse types of alkenes which can be expected to be subject to nucleophilic attack using KDMSO (eqs 11 and 12).[10,20] Cyclopropane formation, though potentially useful, is probably better accomplished using sulfur ylides or related compounds.

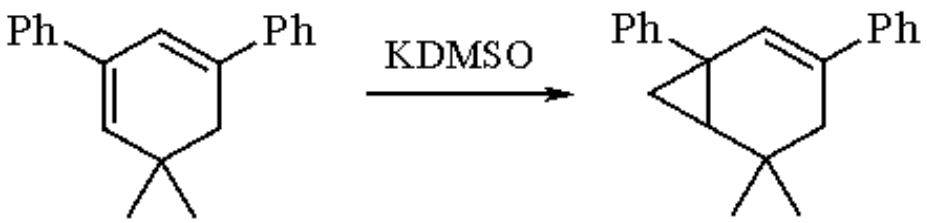

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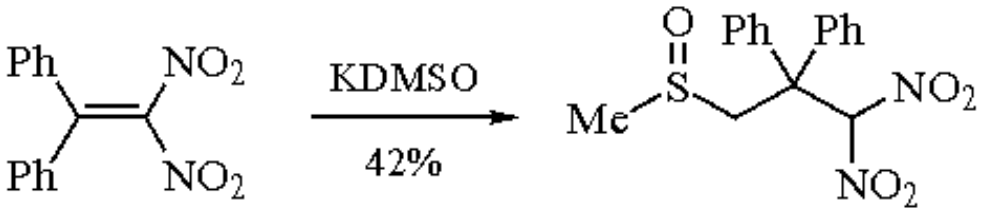

(12)

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Potassium Naphthalenide

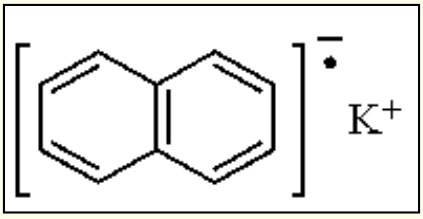

[4216-48-2] · $C_{10}H_8K$ · Potassium Naphthalenide · (MW 167.28)

(functions as a base in the α-alkylation of γ- and δ-lactones;[1] deprotonates β-lactones to provide α,β-unsaturated carboxylic acids and esters;[1] reductively cleaves *O,S*-acetals[2] and alkyl halides[3,4])

Solubility: sol THF, DME.

Analysis of Reagent Purity: ^{39}K NMR (0.2 M THF, 20 °C) 20 ppm.

Preparative Methods: a 1.0 M solution of the reagent is prepared by adding ***Potassium*** metal (1.0 equiv) to a solution of naphthalene (1.0 equiv) in THF (or DME) under an argon atmosphere. The mixture is stirred until all of the potassium metal has dissolved (ca. 2 h). The resulting solution exhibits the characteristic dark green color of the radical anion.[5] Potassium is an extremely flammable solid and should always be handled with care under an argon atmosphere.

Handling, Storage, and Precautions: both air and moisture sensitive. Stock solutions of the reagent are flammable and should be handled under an inert atmosphere.

Use as a Base.

Potassium naphthalenide acts as an efficient base in the α-alkylation of γ- and δ-lactones (eqs 1 and 2).[1] Lactone enolates prepared from alternate bases (e.g. ***Sodium Methoxide***, ***Lithium Diisopropylamide***) undergo competitive self-condensation and dialkylation reactions.[6]

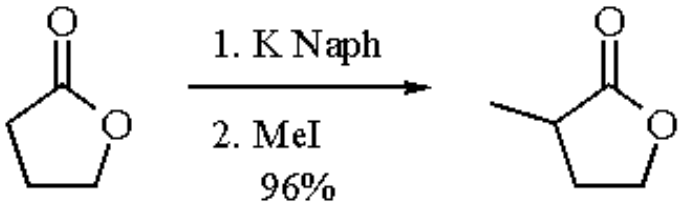

(1)

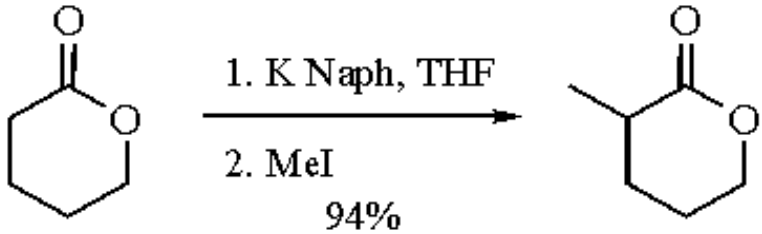

(2)

β-Lactones fragment to α,β-unsaturated carboxylate anions when reacted with potassium naphthalenide/***18-Crown-6***. α,β-Unsaturated carboxylic acids or esters are readily prepared by subsequent protonation or alkylation of the carboxylate anions (eq 3). Products of (*E*)-alkene configuration are formed exclusively.

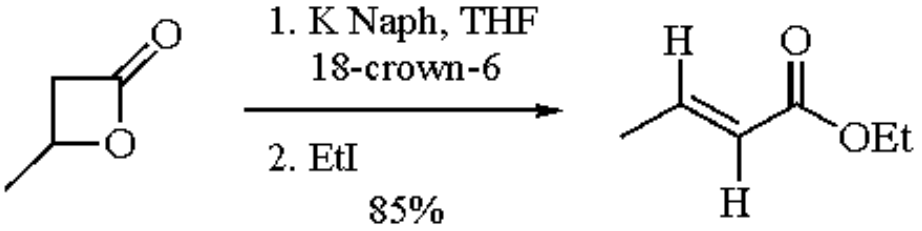

(3)

Use as a Reducing Agent.

α-Alkoxy potassium compounds are generated by the reductive cleavage of *O*,*S*-acetals with potassium naphthalenide. The *O*,*S*-acetals derived from allylic alcohols undergo reduction followed by [2,3]-Wittig rearrangement.[2] Homoallylic alcohols of preferential (*Z*)-alkene configuration are prepared in this manner (eq 4). K-, Li-, Cs-, and Rb-naphthalenides are equally effective at initiating the [2,3]-Wittig rearrangement. Reduced yields occur with ***Sodium Naphthalenide***.

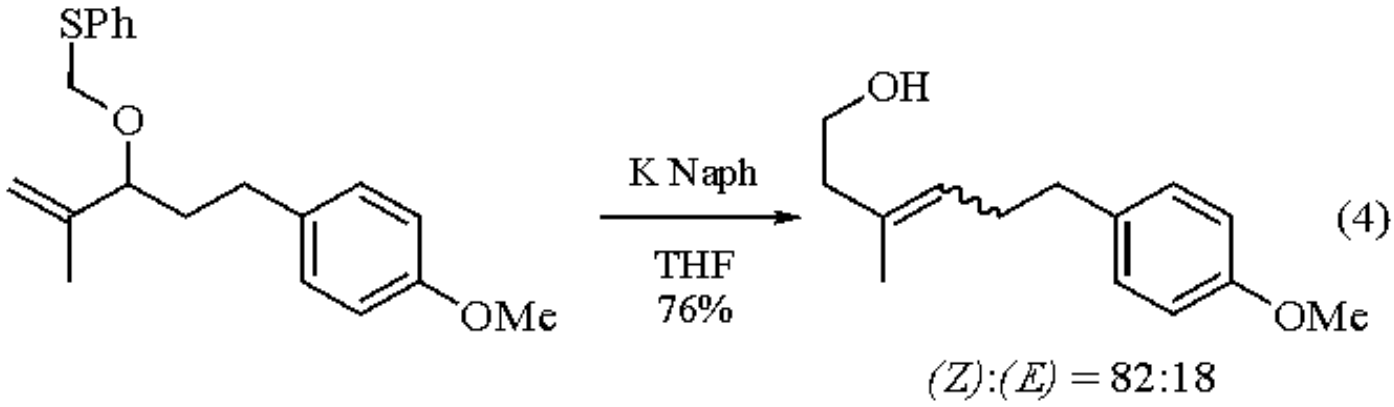

(4)

Cyclopropyl halides react with potassium naphthalenide to form dehalogenated products (eq 5).[3] The *gem*-dihalocyclopropane in eq 6 undergoes skeletal rearrangement with potassium naphthalenide, while the parent hydrocarbon is formed upon treatment with ***Sodium-Ammonia***.[4]

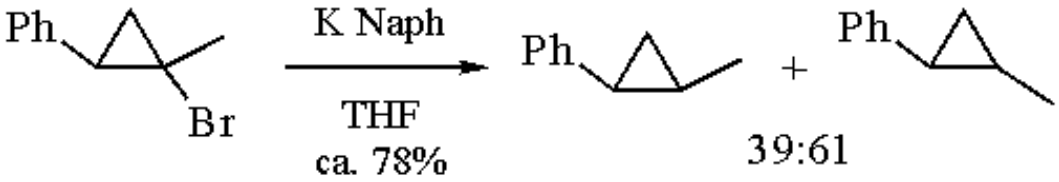

(5)

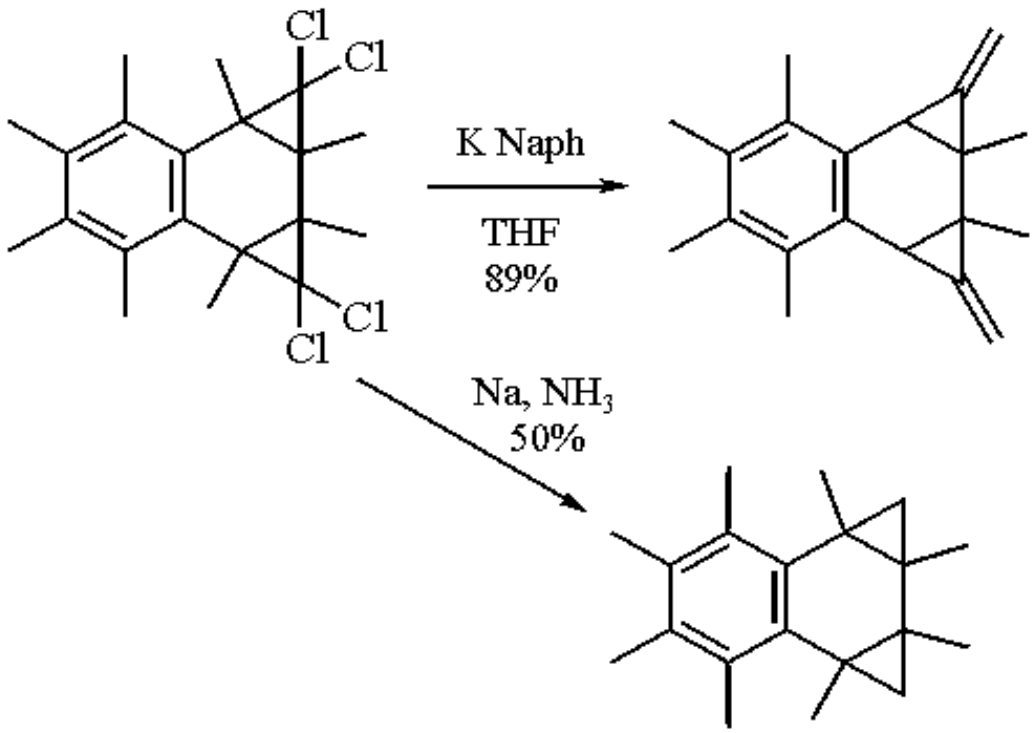

(6)

Related Reagents.

Copper(I) Iodide-Potassium Naphthalenide.

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Potassium *o*-Nitrobenzeneperoxysulfonate

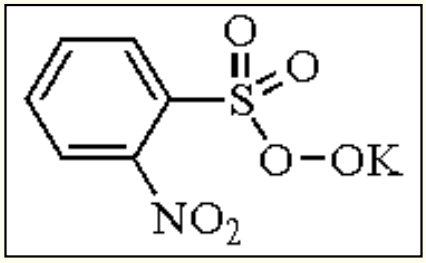

[-] · $C_6H_4KNO_6S$ · Potassium *o*-Nitrobenzeneperoxysulfonate · (MW 257.28)

(epoxidizes alkenes[1] and arenes;[2] oxidizes aryl methylenes,[3] thiocarbonyl compounds,[4] and sulfoxides[5])

Solubility: sol MeCN, DMF.

Form Supplied in: not commercially available.

Preparative Methods: reactive intermediate (**1**) is generated in situ according to eq 1. Many experiments suggest that the reactive intermediate formed by mixing (**3**) and (**4**) is a radical;[6] however, the existence of the anion (**2**) cannot be ruled out.

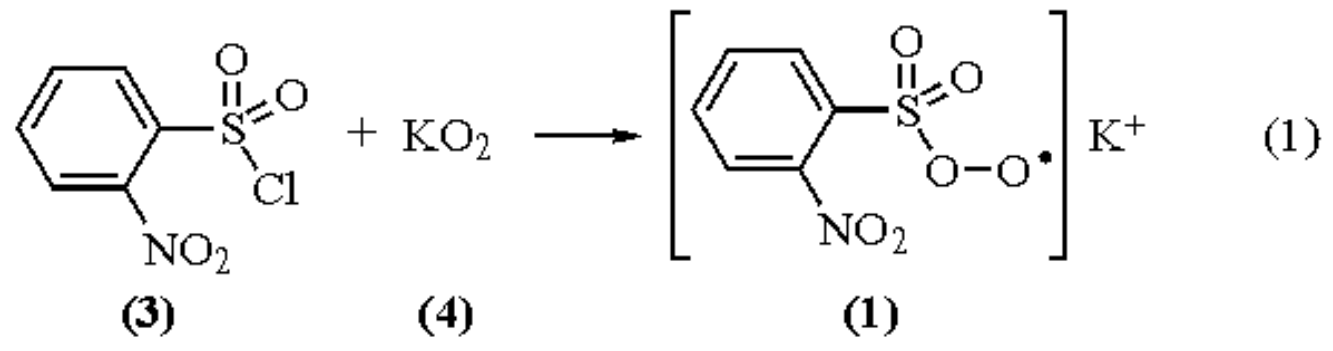

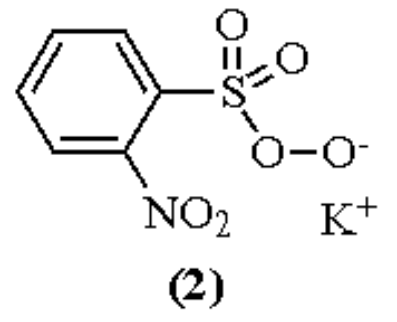

Handling, Storage, and Precautions: intermediate (**1**) cannot be stored, but is generated and reacted in situ. Reactions are carried out under dry argon atmosphere.

Epoxidation of Alkenes.

Alkenes are epoxidized under mild conditions in high yields by the peroxy intermediate (**1**); for example, see the preparation of epoxide (**6**) from (-)-carvone (**5**) (eq 2).

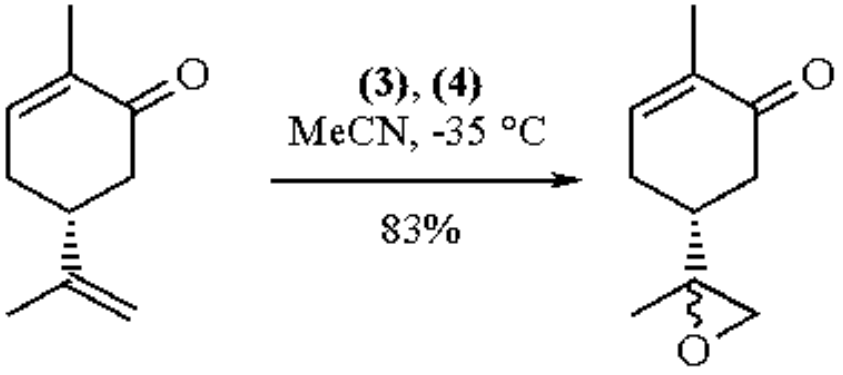

(2)

(5) (6)

A solution of sulfonyl chloride (**3**) (0.22 g, 1.0 mmol) and (-)-carvone (**5**) (0.09 g, 0.6 mmol; MeCN, 2.0 mL) is added to a heterogeneous solution of KO_2 (0.222 g; 3.0 mmol, MeCN, 1.0 mL) at -35 °C under dry argon atmosphere. After stirring at -35 °C for 4 h, the reaction mixture is concentrated and then extracted with $CHCl_3$. The residue obtained after removal of solvent is purified by preparative TLC to furnish (**6**) in 83% yield.[1]

Epoxidation of *cis*-stilbene (**7**) by reaction with the intermediate (**1**) furnishes a 70:30 mixture of oxides (**8**) and (**9**); this reaction suggests that the reactive intermediate is a radical.[2]

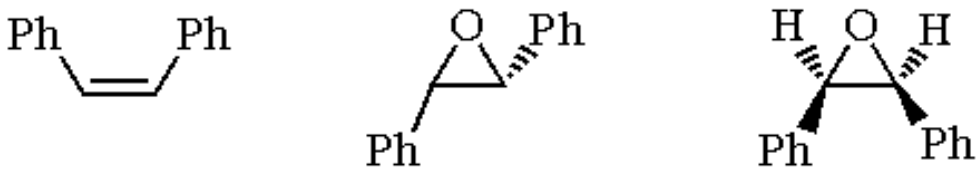

(7) (8) (9)

Metal peroxides have low solubility in organic solvents and are usually used in the presence of crown ethers. KO_2 is soluble enough in aprotic solvents such as MeCN and DMF; hence there is no need to use crown ether for preparing the intermediate according to eq 1.[2]

Epoxidation of Arenes.

Certain arenes (acenaphthylene, phenanthrene, and pyrene) are readily oxidized to the corresponding arene oxides by the peroxy intermediate (**1**) generated from sulfonyl chloride (**3**) in polar aprotic solvents such as MeCN and DMF. Superoxide (**4**) is a strong base and reactions with (**1**) take place under mild and basic conditions. Acenaphthylene oxide (**10**) is unstable under acidic conditions but is more stable under basic conditions. Oxide (**10**) was obtained in 95% yield.[2]

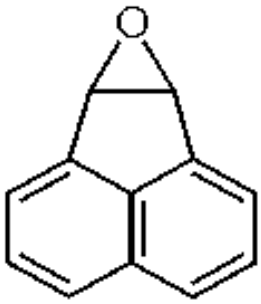

(10)

Oxidation of Benzylic Methylene Compounds.

The peroxy intermediate (**1**) generated from sulfonyl chloride (**3**) oxidized compounds containing benzylic methylene groups to

ketones under mild conditions (-35 °C) (eq 3).[3]

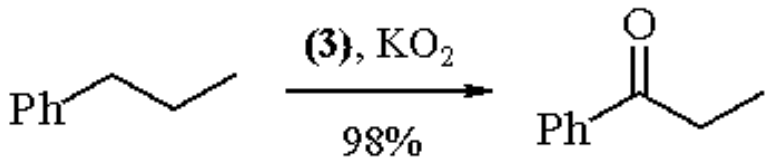

(3)

Oxidative Desulfurization of Thiocarbonyl Compounds.

Thiocarbonyl compounds such as substituted thioureas, thioamides, and thiocarbamates undergo oxidative desulfurization in high yields when reacted with the peroxy intermediate (**1**) under mild conditions (eq 4).[4]

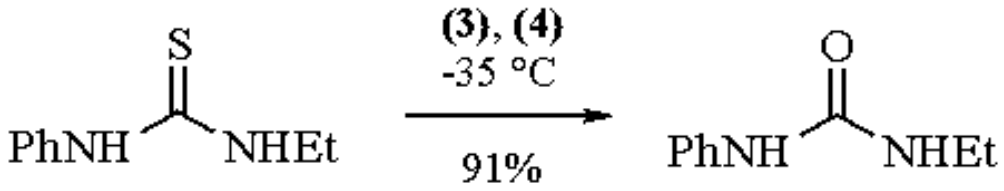

(4)

Oxidation of Sulfoxides.

Dialkyl, alkyl aryl, and diaryl sulfoxides are readily oxidized to sulfones in excellent yields under mild conditions (-30 °C) in MeCN by the peroxy intermediate (**1**). Oxidation of the unsaturated sulfoxide (**11**) was chemoselective; it furnished the sulfone (**12**) in 70% yield when reacted with (**1**) for 5 h. The double bond was not epoxidized.[5] Similar chemoselective epoxidation has been carried out with only one other reagent (potassium hydrogen persulfate).[7]

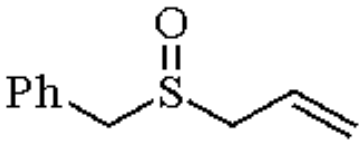

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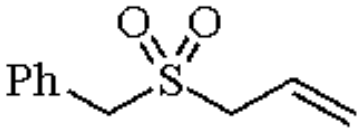

(12)

The peroxy intermediate (**1**) is an excellent reagent for the synthesis of acid-sensitive benzylic epoxides from alkenes, the oxidation of benzylic CH_2 to C=O, and the chemoselective oxidation of alkene sulfoxides to alkene sulfones. It is noteworthy that the reactions are carried out under mild conditions (-35 °C).

---

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Potassium Nitrosodisulfonate[1]

$(KSO_3)_2NO$

[14293-70-0] · $K_2NO_7S_2$ · Potassium Nitrosodisulfonate · (MW 268.35)

(oxidizing reagent for synthesis of quinones from phenols,[2] naphthols,[9] and anilines;[18] oxidant for conversion of benzylic alcohols to aldehydes or ketones[30] and amino acids to α-keto acids;[31] preparation of heterocyclic quinones;[20-22] oxidative aromatization[29])

Alternate Name: Fremy's salt.

Solubility: sol H_2O.

Form Supplied in: orange powder; widely available.

Preparative Methods: see Zimmer et al.[1]

Handling, Storage, and Precautions: in solid form, this reagent is rather unstable. It sometimes undergoes spontaneous decomposition which occasionally results in a violent explosion attributed to impurities such as chloride ion, manganese dioxide, or nitrite ion. Stored in a desiccator over calcium oxide in the presence of ammonium carbonate to provide an ammoniacal atmosphere, it is stable for several months.

Phenol Oxidations.

This reagent oxidizes phenols to the corresponding 1,2- or 1,4-quinones under mild conditions and usually in good yield. The substituents on the aromatic ring control the ratio of *ortho*- and *para*-quinones.[2] *para*-Unsubstituted phenols bearing a variety of substituents in the *ortho* and *meta* positions (e.g. alkyl,[3,4] alkyloxy and/or bromine,[5] crown ether substituents,[6] and *p*-hydroxybenzylamines and primary *p*-hydroxybenzamides[7]) are generally converted to 1,4-quinones. Phenols with easy-to-displace *para* substituents, such as CH_2OH, Br, Cl, CO_2H, $CONH_2$, and CH(OH)CN, undergo oxidation to form 1,4-quinones. 1,2-Quinones are formed if the *para* substituents are alkoxy, alkyl, or aryl.[8] See also ***Lead(IV) Oxide*** and ***Salcomine***.

Naphthol Oxidations.

α-Naphthols can be oxidized to 1,2- or 1,4-naphthoquinones by Fremy's salt.[9] Again, the nature of the *para* substituent is critical. 1,4-Naphthoquinones predominate if the *para* position is unsubstituted.[10] 1,2-Naphthoquinones are formed if an alkyl or aryl group occupies the *para* position,[9] if there is a hydroxy group in the 2-position,[9] or if the *para* position is hindered.[11] Approximately equal amounts of 1,2- and 1,4-naphthoquinones are obtained if a hydroxy group occupies the 5-position.[9] It has been reported that 1,4-naphthoquinones are produced from oxidation of 2- or 9-SMe substituted phenols.[12] β-Naphthols are generally oxidized to 1,2-naphthoquinones (eq 1).[13]

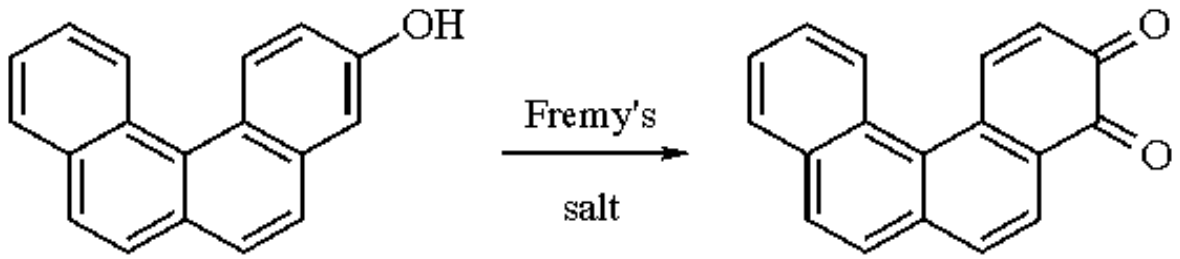

(1)

The methyl ether of a β-naphthol has been reported to afford a 1,2-quinone (eq 2).[14]

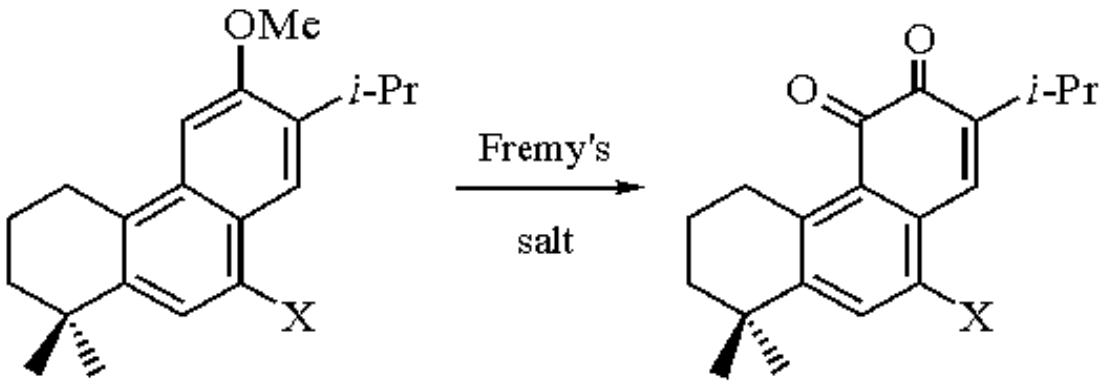

(2)

X = F, Cl, Br

Aniline Oxidations.

1,4-Quinones are formed by the reaction of 2,6-disubstituted and 2,3,6-trisubstituted anilines and Fremy's salt.[15] Other *ortho* or *meta* methoxy-substituted aromatic amines were converted to the corresponding 1,4-quinones[16] and 1,2-quinones.[17] In one case the oxidation intermediate, a quinone imine which subsequently undergoes hydrolysis to the quinone, has been isolated (eq 3).[18]

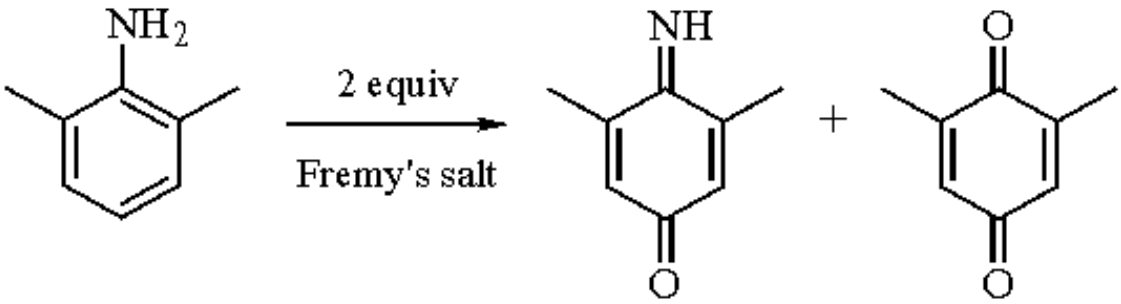

(3)

Hypoxanthine analogs were formed by Fremy's salt oxidation (eq 4).[19]

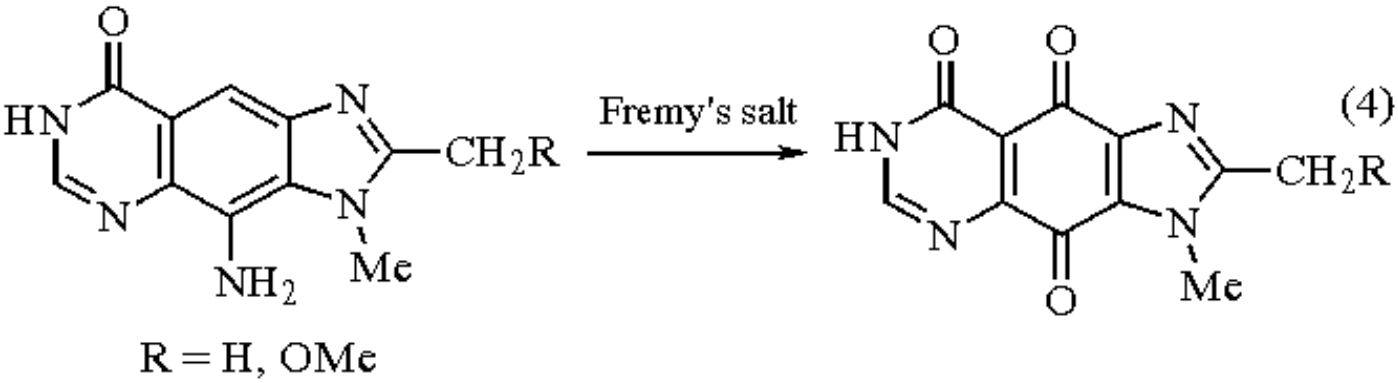

(4)

R = H, OMe

Oxidations to Quinoline Quinones.

Quinolinols are converted to quinoline quinones (eq 5).[20]

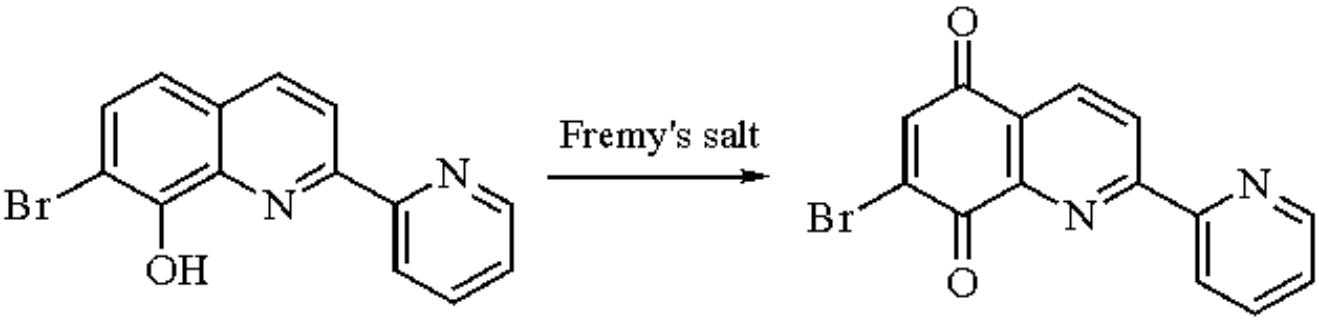

(5)

In an approach to streptonigrin, Fremy's salt was utilized to oxidize a methoxy aniline by a phase-transfer procedure (eq 6).[21]

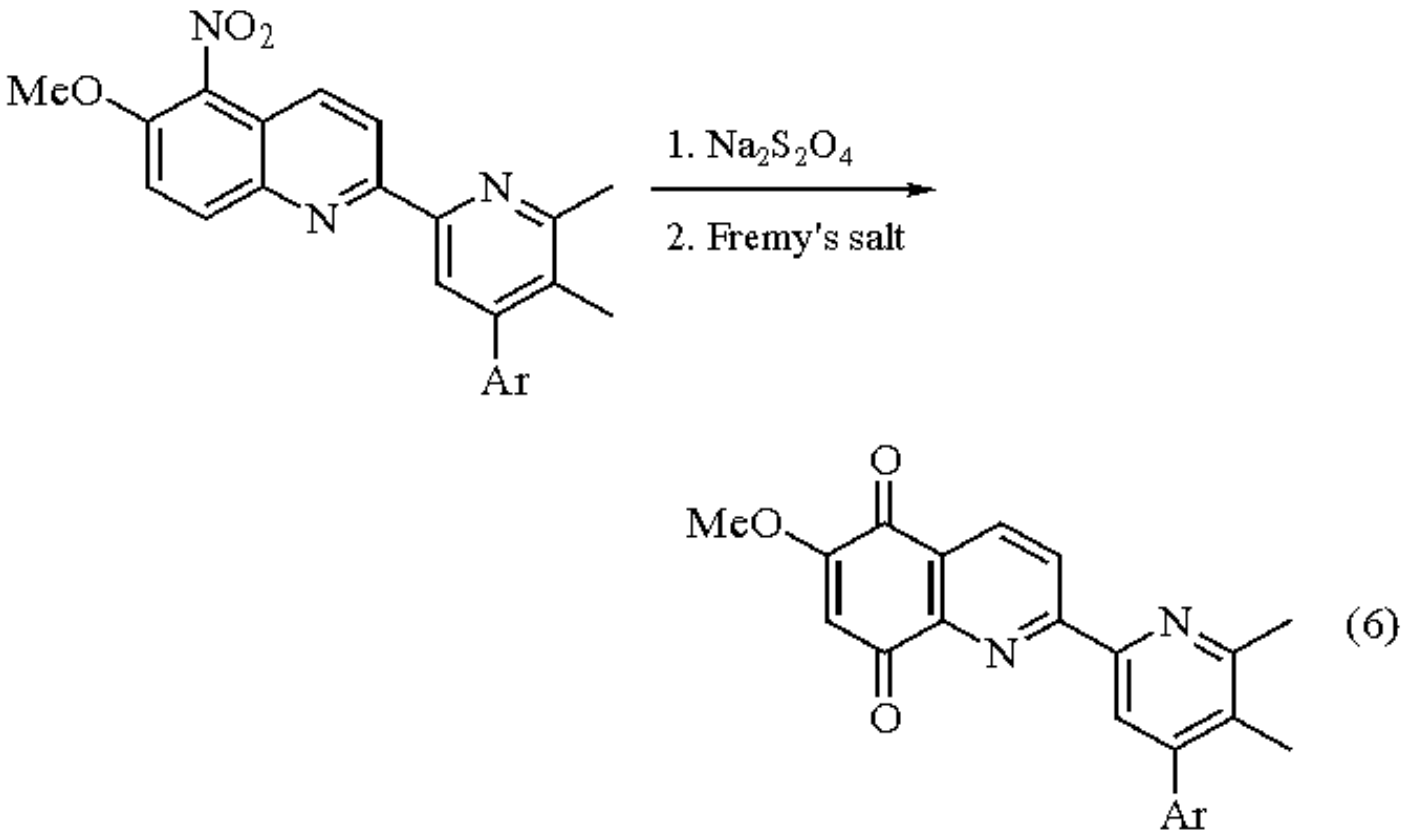

Oxidations to Indole Derivatives.

The derivatives of *ortho*-hydroxy phenethylamine were converted into indoles (eq 7).[22] Presumably the primary oxidation product is protected from secondary oxidation by protonation at lower pH. Likewise, in solution at different pH, 2-methylindole dimerizes to different products (eq 8).[23]

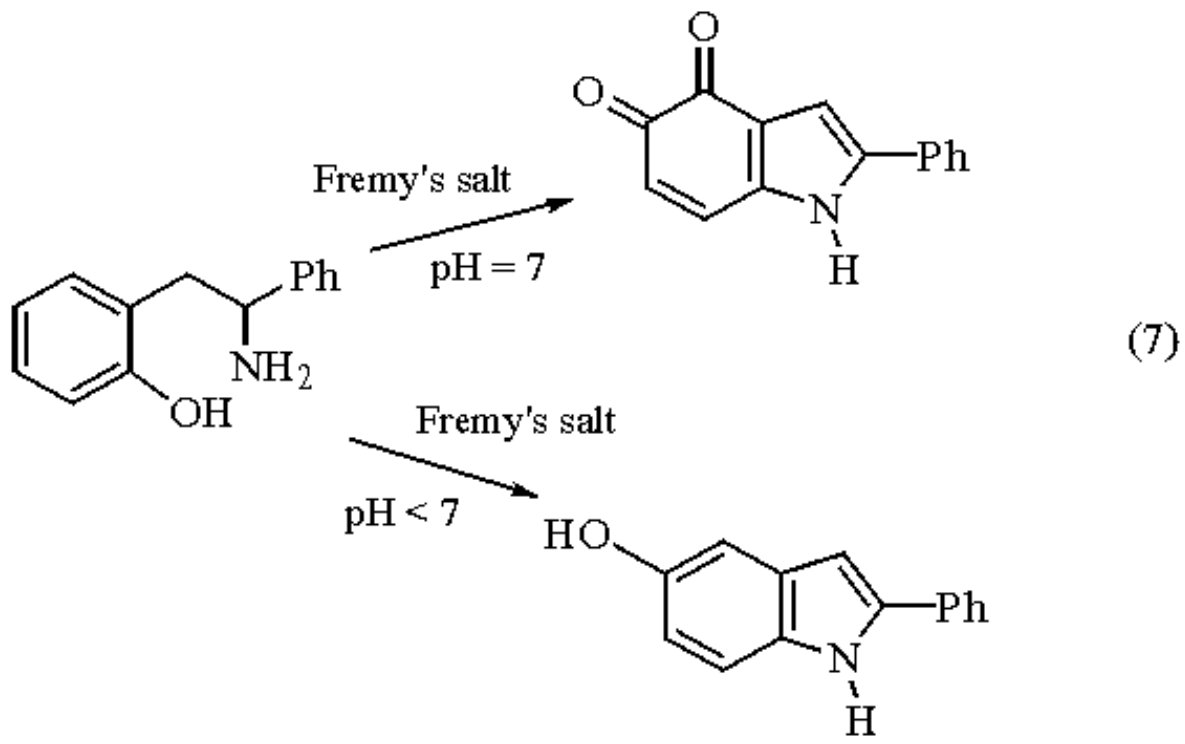

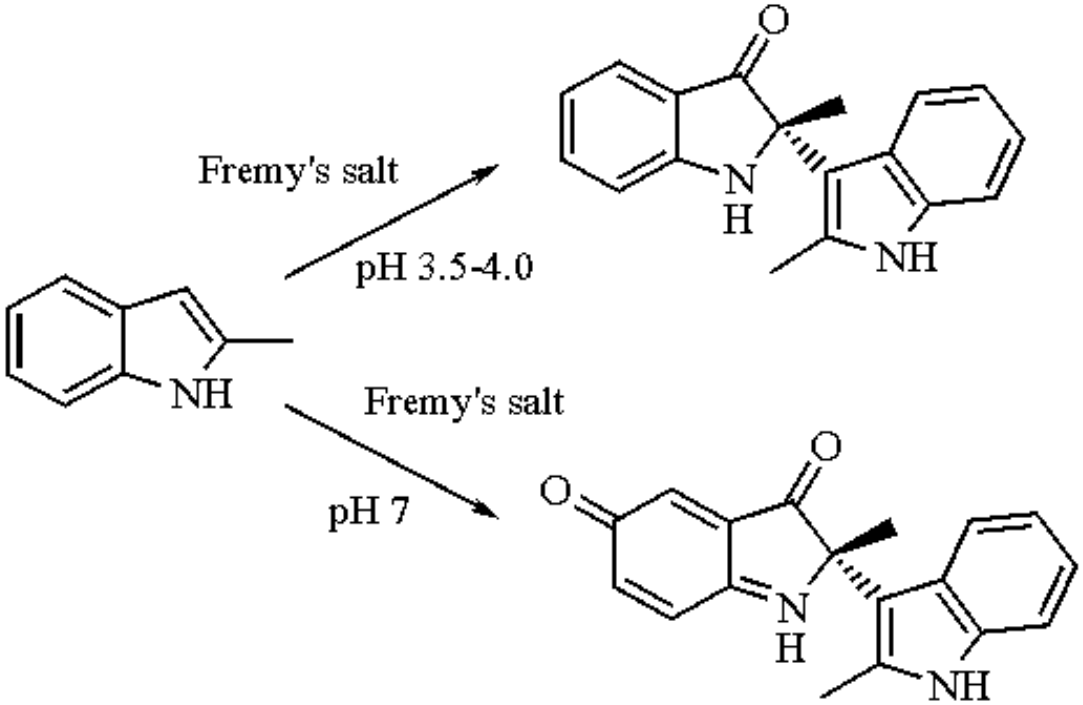

(8)

The derivatives of *ortho*-aminophenethylamine were converted to indoline 1,4-quinone imides (eq 9).[24] No oxidation at the 3-position or 4-position was observed if the α-position was occupied by two alkyl groups.

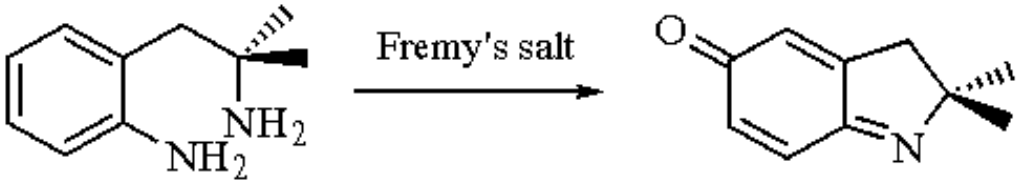

(9)

A novel route to heterocyclic quinones, based on Fremy's salt promoted oxidation, has been developed recently (eq 10).[25]

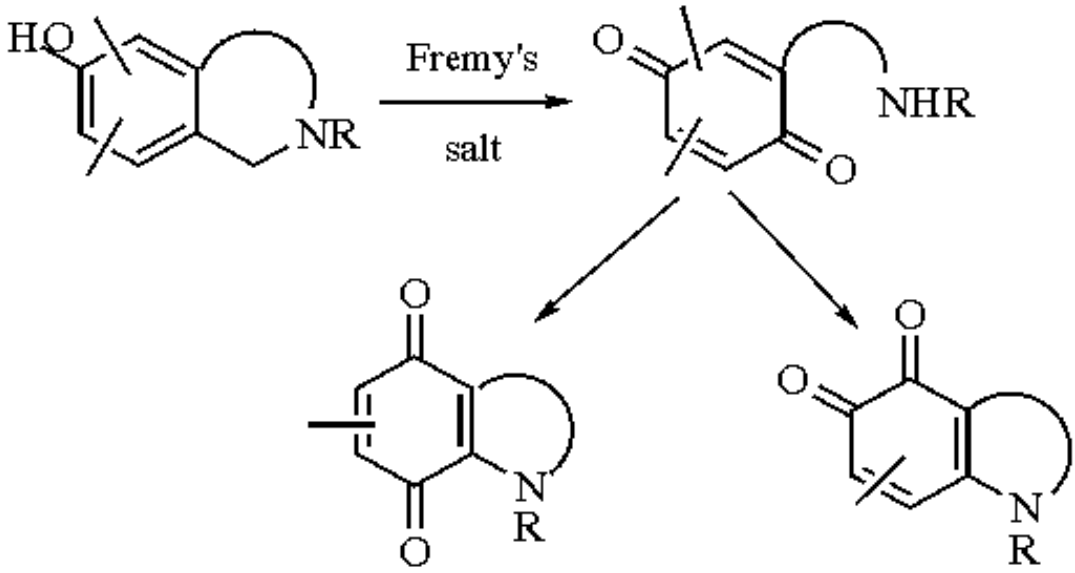

(10)

With this methodology, isoquinoline derivatives were converted with ring contraction to the 1,2-quinone indoles in a buffered (pH 6.1) two-phase (CH_2Cl_2-H_2O) system (eq 11).

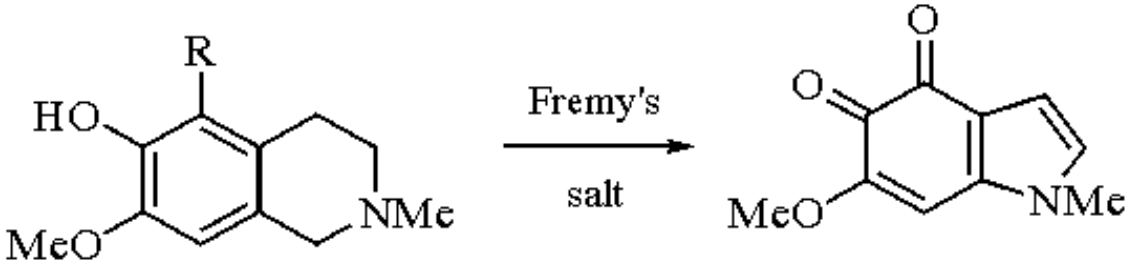

(11)

R = H or OMe

5-Hydroxybenzofuran is oxidized to the 4,5-*ortho*-quinone.[26] Bisquinones[27] and other heterocyclic quinones[28] were prepared by Fremy's salt oxidation.

Tetrahydroisoquinoline Oxidation.

Papaveraldine could be produced by Fremy's salt oxidation over 7 days in 30% yield (eq 12). The corresponding *N*-alkyl tetrahydroisoquinolines give cleavage products (eq 13).[29]

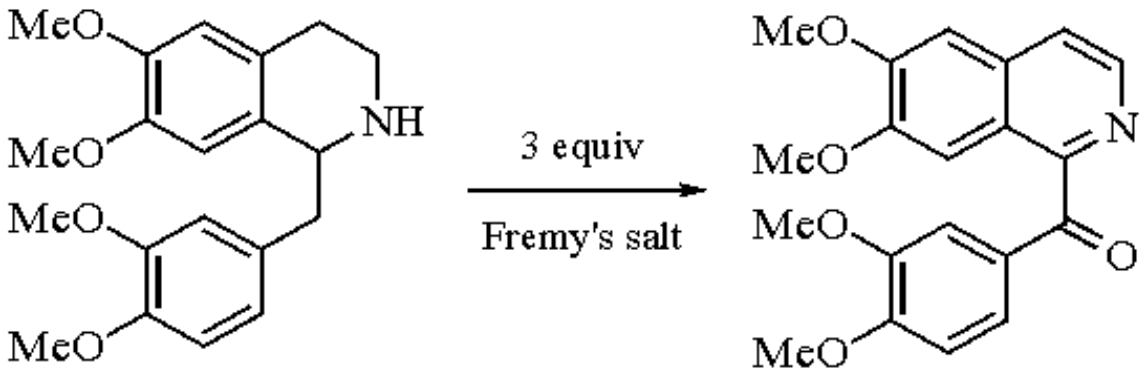

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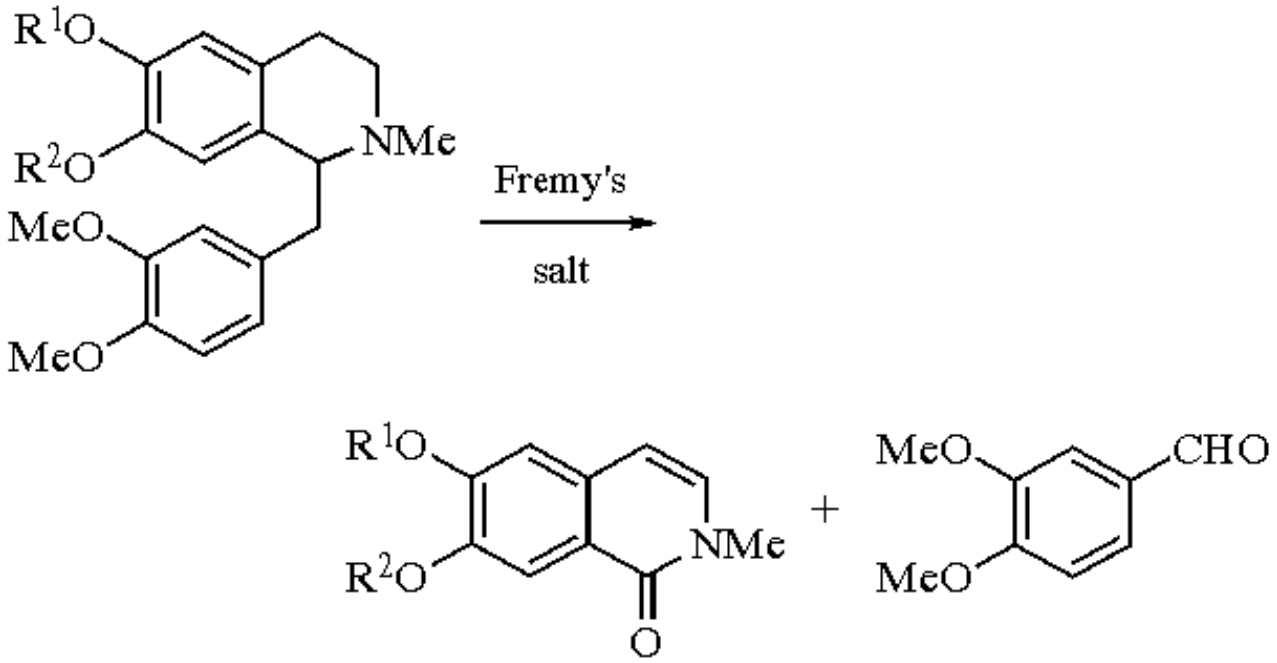

(13)

(a) $R^1 = R^2 = Me$; (b) $R^1 + R^2 = CH_2$

Other Reactions.

Benzylic alcohols could be selectively oxidized to aldehydes or ketones in the presence of allylic alcohols and saturated alcohols by Fremy's salt in a phase-transfer system.[30]

Some α-amino and α-hydroxy acids were oxidized to the corresponding α-keto acids (dehydrogenation) and/or to the acids or amides (with decarboxylation) (eq 14).[31]

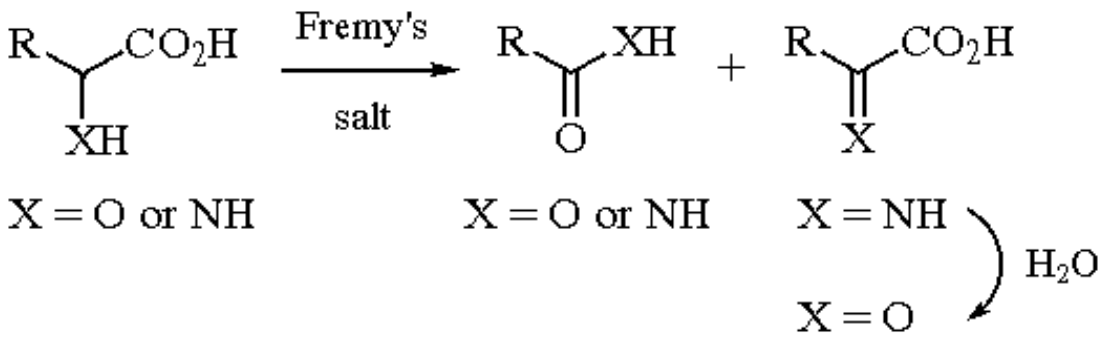

(14)

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Potassium Permanganate[1-4]

$KMnO_4$

[7722-64-7] · $KMnO_4$ · Potassium Permanganate · (MW 158.04)

(oxidant; conversion of arenes into carboxylic acids,[10,11] α-ketones,[12-15] or α-alcohols;[14] degradation of aromatic rings;[3] preparation of diols,[17,18] ketols,[5,19,20,22] and α-diketones[22-24] from nonterminal alkenes; preparation of carboxylic acids,[27] aldehydes[26] and 1,2-diols[28] from terminal alkenes; oxidation of alkynes to α-diones;[29,30] oxidation of enones to 1,4-diones;[31] conversion of 1,5-dienes into substituted tetrahydrofurans[32,33] or lactones;[34] conversion of primary and secondary alcohols into carboxylic acids[1,2,37] and ketones,[1-4,9,35] respectively; oxidation of allylic alcohols to α,β-unsaturated ketones[35] and other unsaturated alcohols and α,o-diols to lactones;[36,37] oxidation of aliphatic thiols to disulfides and aromatic thiols to sulfonic acids;[4] oxidation of sulfides and sulfoxides to sulfones,[4,38-40] sulfinic acids to sulfonic acids,[43] sulfites to sulfates,[44] and thiones to ketones;[45] preparation of tertiary nitroalkanes from the corresponding amines;[47] oxidation of tertiary amines to amides or lactams;[48-50] allylic oxidations when used in conjunction with *t*-butyl hydroperoxide;[51] preparation of iodoaromatic compounds when used with I_2 and sulfuric acid;[52] oxidation of nucleic acids to the corresponding diols and ketols;[53] oxidation of guaiol and related compounds to rearranged ketols;[54] oxidation of poly(vinyl alcohol) to poly(vinyl ketone);[56] oxidation of nitroalkanes to aldehydes or ketones; oxidation of imines to nitrones)

Alternate Name: potassium manganate(VII).

Physical Data: d 2.70 g cm^{-3}; decomposition 237 °C.

Solubility: water (at 20 °C) 63.8 g L^{-1}; sol acetone, methanol.

Form Supplied in: purple solid; commercially available.

Handling, Storage, and Precautions: stable at or below rt. Because it is a strong oxidant it should be stored in glass, steel, or polyethylene vessels. Sulfuric acid should never be added to permanganate or vice versa. Permanganate acid, an explosive compound, is formed under highly acidic conditions.

Introduction.

Permanganate is an inexpensive oxidant that has been widely used in organic syntheses. Its most common salt, $KMnO_4$, is soluble in water and as a consequence oxidations have traditionally been carried out in aqueous solutions or in mixtures of water and miscible organic solvents such as acetone, acetic acid, acetonitrile, benzonitrile, tributyl phosphate, or pyridine. The discovery that $KMnO_4$ can, with the aid of phase-transfer agents, be readily dissolved in nonpolar solvents such as CH_2Cl_2, and the recent observation that is adsorption onto a solid support produces an effective heterogeneous oxidant, has further expanded its usefulness.

The general features of the reactions of permanganate dissolved in aqueous solutions, or in organic solvents with the aid of a phase-transfer agent, and as a heterogeneous oxidant will be briefly described, followed by specific examples.

Aqueous Permanganate Oxidations.

Potassium permanganate is a general, but relatively nonselective, oxidant when used in aqueous solutions. When an organic compound contains only one site at which oxidation can readily occur, this reagent is a highly efficient and effective oxidant. For example, oleic acid is converted into dihydroxystearic acid in quantitative yield when oxidized in a dilute aqueous solution of $KMnO_4$ at 0-10 °C.[5]

If the aqueous solution is made acidic by addition of mineral acid, the rate of reaction increases, most probably because of formation of permanganic acid[1] which is known to be a very strong oxidant.[6] The rate of the reaction is also accelerated by addition of sodium or potassium hydroxide. It has been proposed that this acceleration may be due to ionization of the organic reductant; for example, conversion of an alcohol into an alkoxide ion.[1] However, similar observations for the oxidation of compounds such as sulfides, which lack acidic hydrogens, suggests that other factors may be involved.[7]

Under acidic conditions, permanganate is reduced to soluble manganese(II) or -(III) salts, thus allowing for a relatively easy workup. However, under basic conditions the reduction product is a gelatinous solid, consisting primarily of manganese dioxide, that is difficult to separate from the product. As a consequence, for laboratory scale preparations the reaction product is not isolated until after the MnO_2 has been reduced by addition of HCl and sodium bisulfite. For large scale (industrial) processes, MnO_2 is removed either by filtration or by centrifugation.

Phase-Transfer Assisted Permanganate Oxidations.[2]

$KMnO_4$ may be dissolved in nonpolar solvents such as benzene or CH_2Cl_2 by complexing the potassium ion with a crown ether or by replacing it with a quaternary ammonium or phosphonium ion. Although most reactions observed are similar to those found in aqueous solutions, the ability to dissolve permanganate in nonpolar solvents has greatly increased the range of compounds that can be oxidized.

The first example of a phase-transfer assisted permanganate oxidation involved the complexing of the potassium ion by a crown ether in benzene;[8] however, it was later found that the use of quaternary ammonium or phosphonium salts was less expensive and just as efficient.[2]

Phase transfer into a nonpolar solvent can occur either from an aqueous solution or from solid $KMnO_4$. Evaluation of various phase-transfer agents for these purposes has indicated that benzyltributylammonium chloride is highly efficient for transfer from aqueous solutions while alkyltriphenylphosphonium halides, tetrabutylammonium halides, and benzyltriethylammonium halides are all effective for the transfer from solid $KMnO_4$.[2] Adogen 464, an inexpensive quaternary ammonium chloride commercially available, is usually satisfactory for both purposes.

Quaternary ammonium and phosphonium permanganates can also be used as stoichiometric oxidants. For descriptions of their properties, refer to the separate articles on ***Methyltriphenylphosphonium Permanganate*** and ***Benzyltriethylammonium Permanganate***.

Heterogeneous Permanganate Oxidations.

The use of permanganate, activated by adsorption on a solid support, as a heterogenous oxidant has further increased the scope of these reactions. CH_2Cl_2 or 1,2-dichloroethane (if a high reflux temperature is required) are the preferred solvents and ***Alumina***, silica, or hydrated ***Copper(II) Sulfate*** are the most commonly used solid supports. The selectivity of the oxidant is dramatically altered by use of a solid support. For example, although carbon-carbon double bonds are very easily cleaved in homogeneous permanganate solutions, secondary allylic alcohols can be cleanly oxidized to the corresponding α,β-unsaturated ketones without disruption of the double bond under heterogeneous conditions.[9]

In addition to increased selectivity, the use of permanganate under heterogeneous conditions allows for easy product isolation. It is necessary only to remove spent oxidant by filtration followed by flash evaporation or distillation of the solvent. Products isolated in this way are often sufficiently pure to permit direct use in subsequent synthetic procedures.

Benzylic Oxidations.

Permanganate oxidizes side chains of aromatic compounds at the benzylic position.[3] In aqueous solution, carboxylic acids are usually obtained (eqs 1 and 2).[10,11]

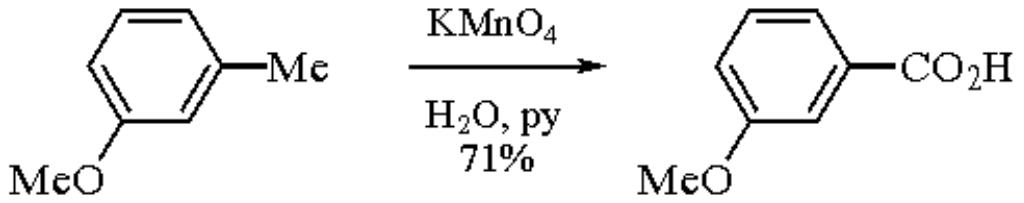

(1)

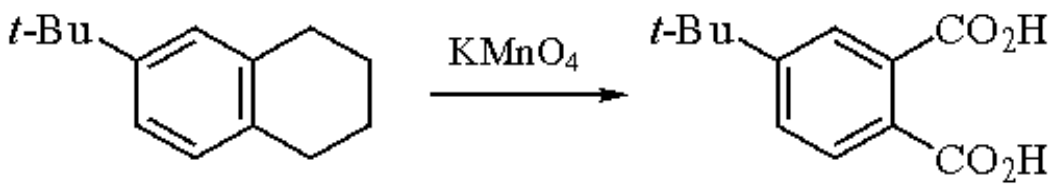

(2)

The oxidation of alkylbenzenes proceeds through the corresponding α-ketones, which can occasionally be isolated (eqs 3 and 4).[12,13]

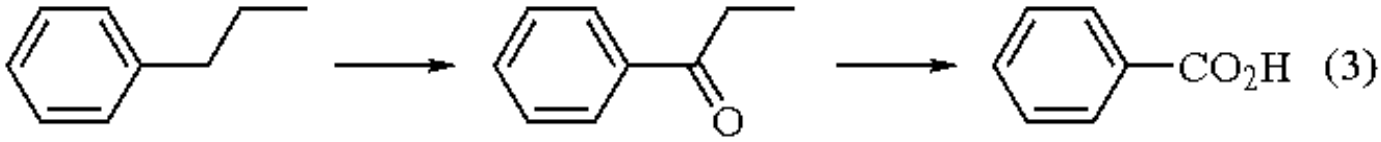

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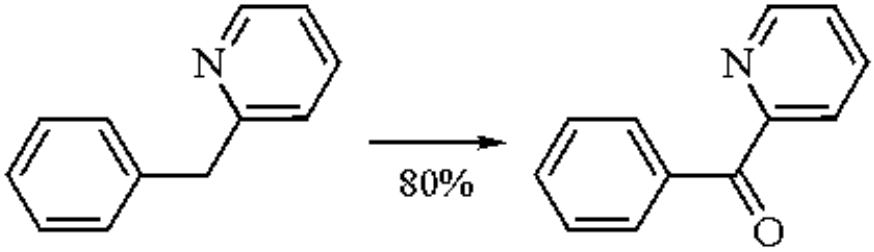

(4)

Under heterogeneous conditions where alumina (acid, Brockman, activity 1)[14] or copper sulfate pentahydrate[15] is used as the solid support, α-ketones and alcohols are obtained with little or no carbon-carbon cleavage (eqs 5-8).

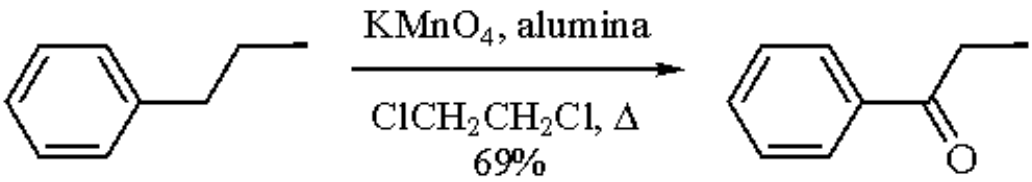

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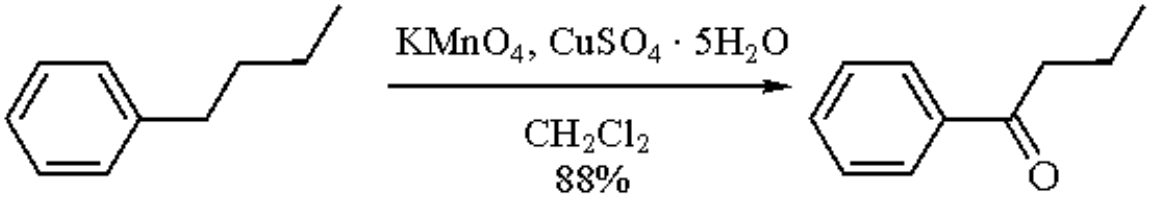

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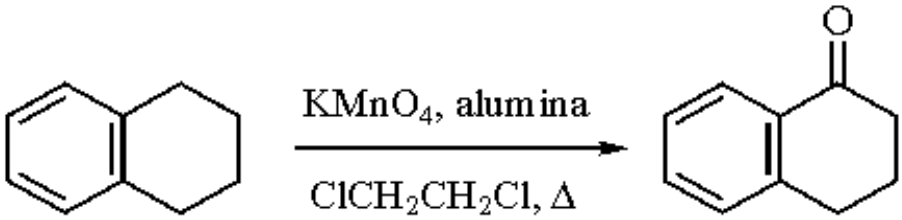

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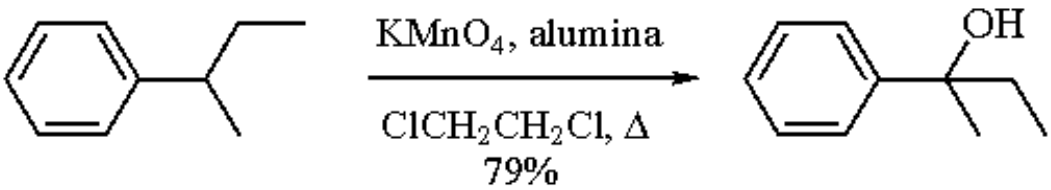

(8)

Oxidation of Aromatic Rings.

Permanganate will oxidatively degrade aromatic rings under both acidic and basic conditions.[3] The effect of acid and base on the reaction has been demonstrated by the oxidation of 2-phenylpyridine; under basic conditions the product is benzoic acid (presumably because the oxidant attacks the site of greatest electron density) (eq 9), while under acidic conditions (where the nitrogen would be protonated) the product is picolinic acid (eq 10).[3]

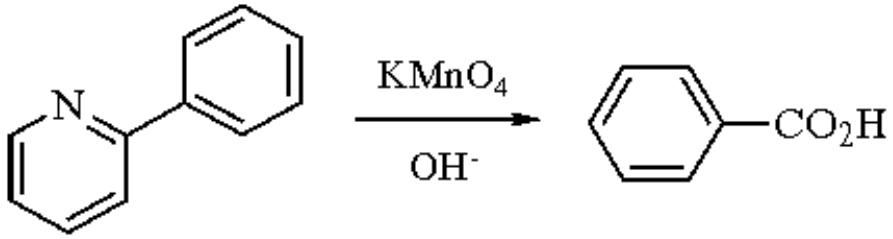

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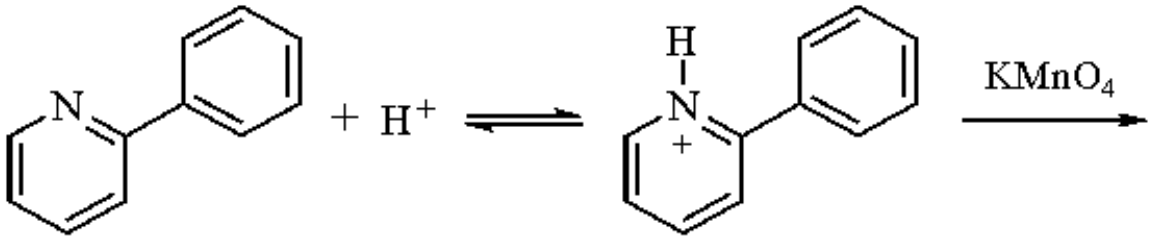

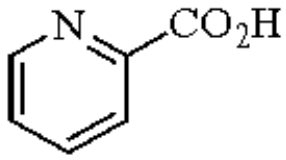

(10)

Polycyclic aromatic compounds are also oxidatively degraded to a single-ring polycarboxylic acid (eq 11).[16]

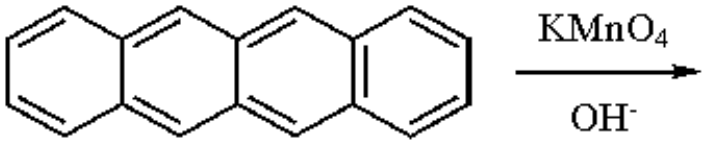

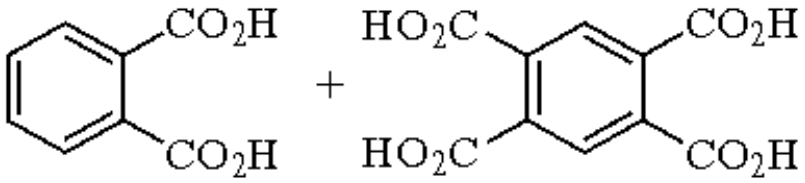

(11)

Oxidation of Nonterminal Alkenes.

Nonterminal alkenes can be converted into 1,2-diols, ketols, or diketones by choice of appropriate conditions. The reaction, which proceeds by *syn* addition of permanganate to the double bond as indicated, gives the corresponding *cis*-diol under aqueous alkaline conditions (eq 12).[17]

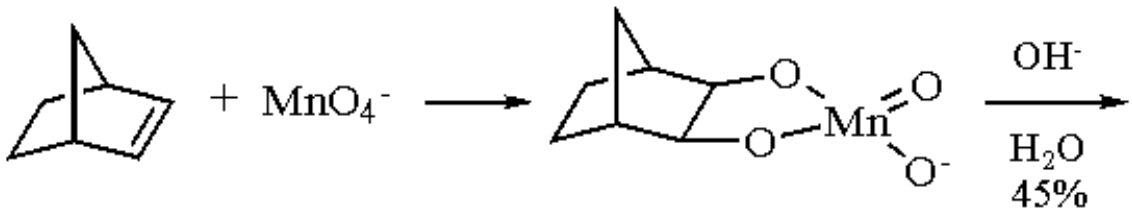

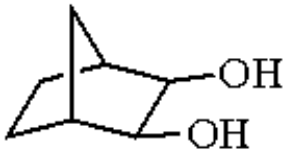

(12)

Syn addition can also be achieved in nonaqueous solvents with the aid of a phase-transfer agent (PTA). Subsequent treatment with aqueous base gives 1,2-diols in good yields[2] (eq 13).[18] Equally good results were reported when the reaction was carried out in aqueous *t*-butyl alcohol.[18]

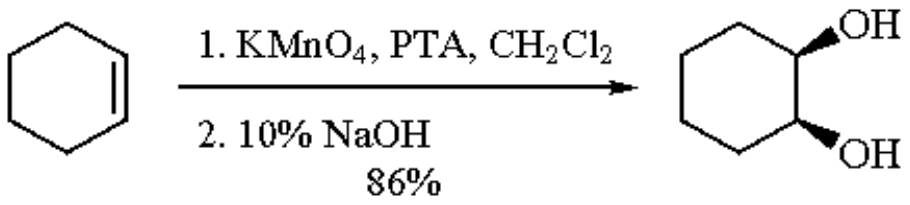

(13)

Under neutral conditions the product obtained from the oxidation of alkenes is the corresponding ketol.[5] Good yields are obtained when aqueous acetone containing a small amount of acetic acid (2-5%) is used as the solvent. The function of acetic acid is to neutralize hydroxide ions produced during the reduction of permanganate. The oxidations of 5-decene and methyl 2-methylcrotonate provide typical examples (eqs 14 and 15).[19,20]

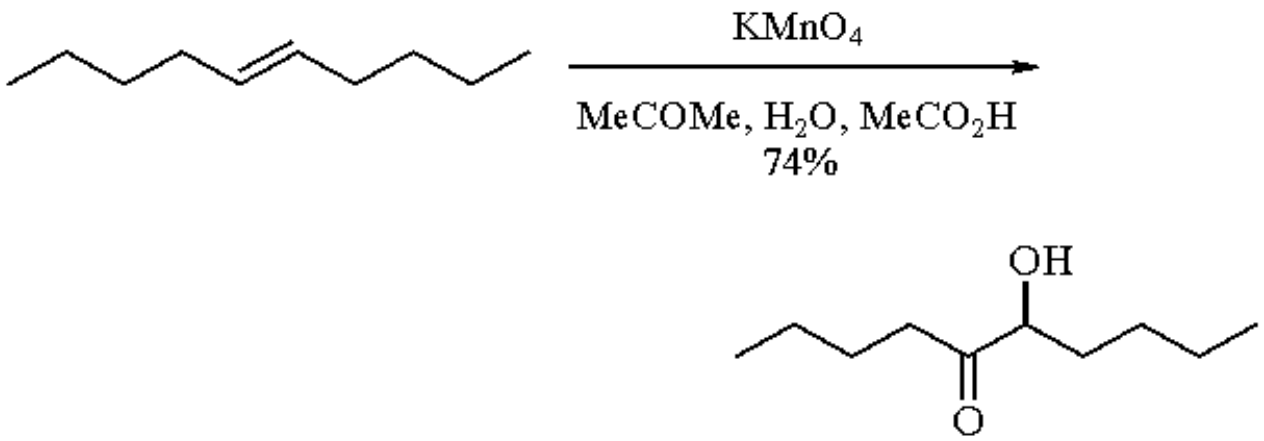

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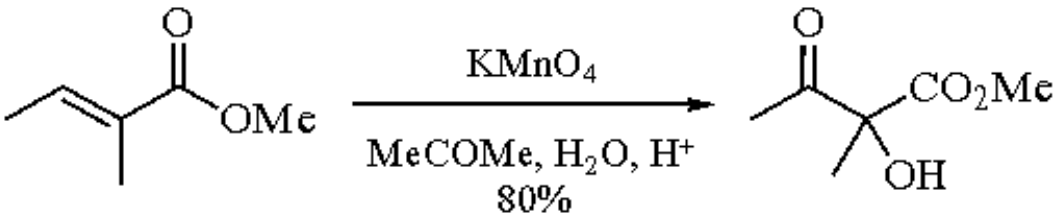

(15)

Heterogeneous oxidations of alkenes with a small amount of *t*-butyl alcohol and water present to provide an omega phase[21] results in the formation of α-ketols in modest to good yields (eqs 16 and 17).[22]

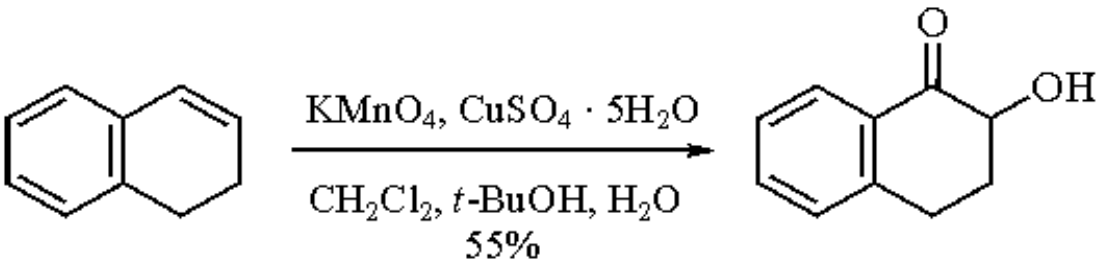

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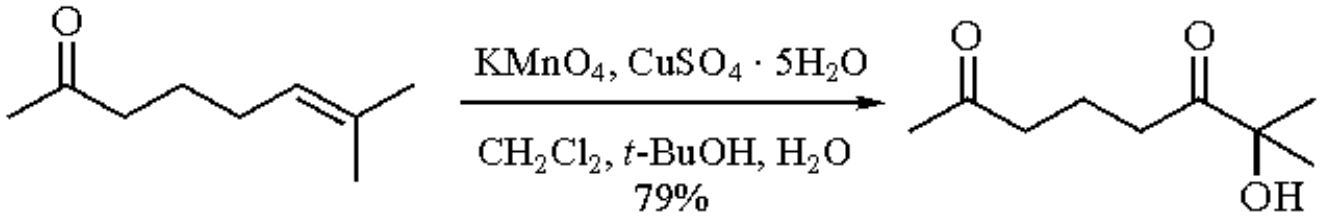

(17)

Under anhydrous conditions, 1,2-diones are formed in good yields when alkenes are oxidized by permanganate. Appropriate conditions can

be achieved by using acetic anhydride solutions (eq 18)[23] or by dissolving permanganate in CH_2Cl_2 with the aid of a phase-transfer agent (eq 19).[24]

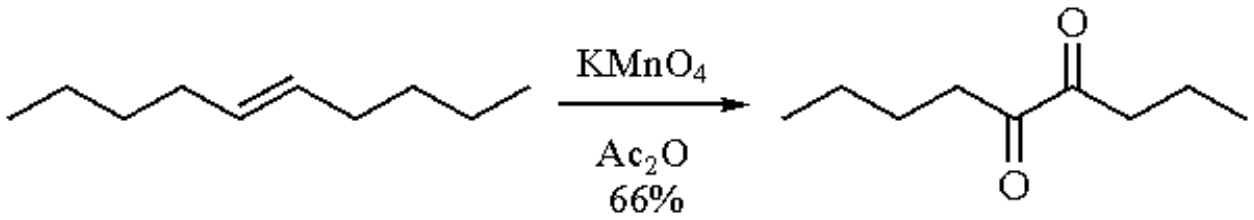

(18)

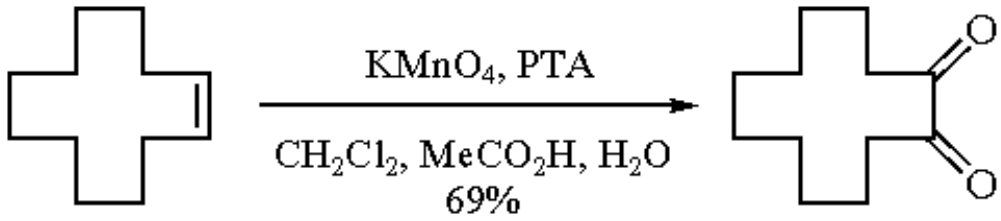

(19)

Similar yields are obtained under heterogeneous conditions, where workup procedures are much easier.[22]

The carbon-carbon double bonds of alkenes can also be oxidatively cleaved to give carboxylic acids in good yield by use of the Lemieux-von Rudloff reagent (aqueous potassium periodate containing catalytic amounts of permanganate).[3,25] Under heterogeneous conditions, either aldehydes or carboxylic acids are obtained, depending on the conditions used (eqs 20 and 21).[26]

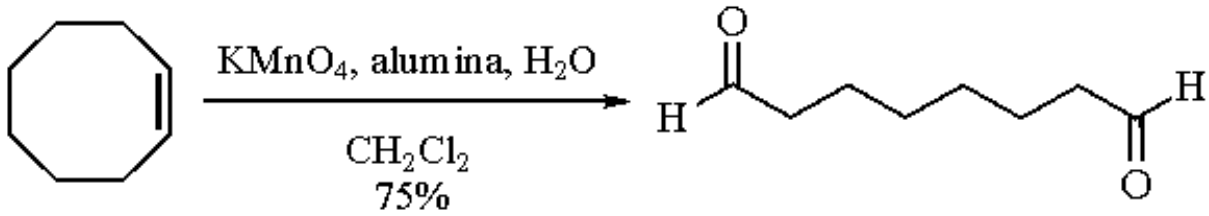

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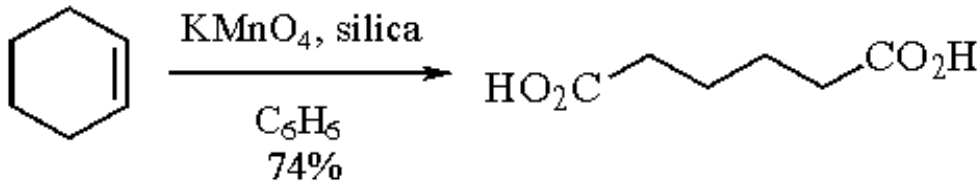

(21)

Oxidation of Terminal Alkenes.

Although oxidation of terminal alkenes by permanganate usually results in cleavage of the carbon-carbon double bond to give either a carboxylic acid[27] or an aldehyde,[26] 1,2-diols can be obtained through use of a phase-transfer assisted reaction (eqs 22-24).[2,28]

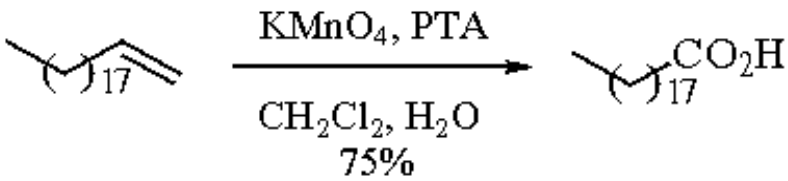

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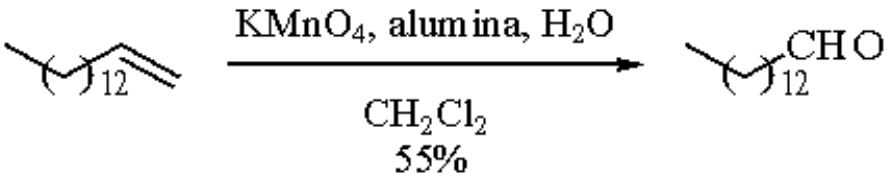

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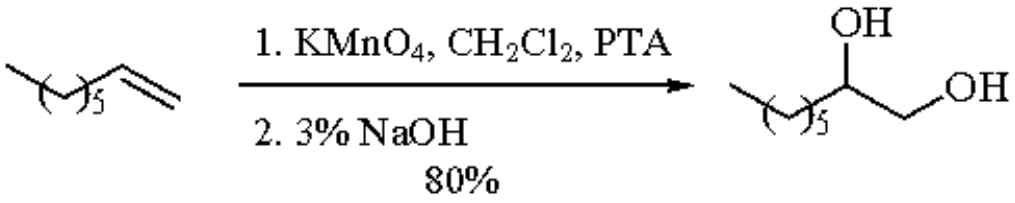

(24)

Oxidation of Alkynes.

Oxidation of nonterminal alkynes results in the formation of α-diones. Good yields are obtained when aqueous acetone containing $NaHCO_3$ and $MgSO_4$,[29] or CH_2Cl_2 containing about 5% acetic acid,[30] is used as the solvent (eqs 25-27). A phase-transfer agent to assist in dissolving $KMnO_4$ must be used when CH_2Cl_2 is the solvent. Terminal alkynes are oxidatively cleaved, yielding carboxylic acids containing one carbon less than the parent alkyne.

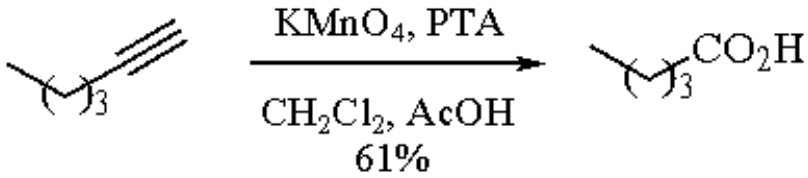

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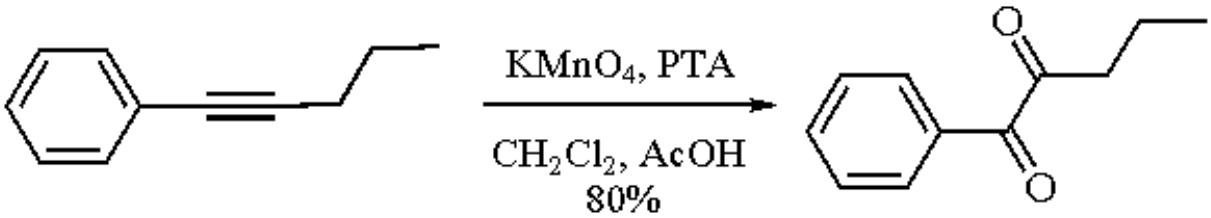

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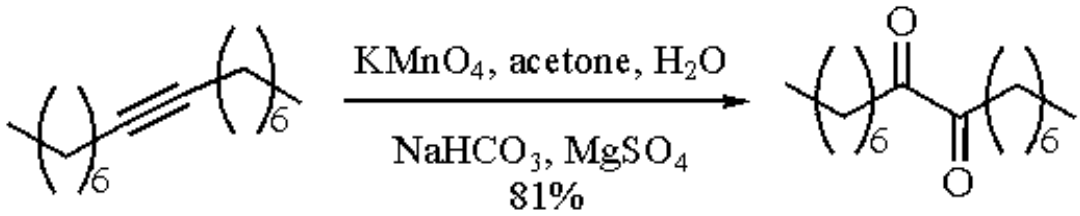

(27)

Oxidation of Enones to 1,4-Diones.

Enones react with nitroalkanes (Michael addition) to form γ-nitro ketones that can be oxidized in good yield to 1,4-diones under heterogeneous conditions (eq 28).[31]

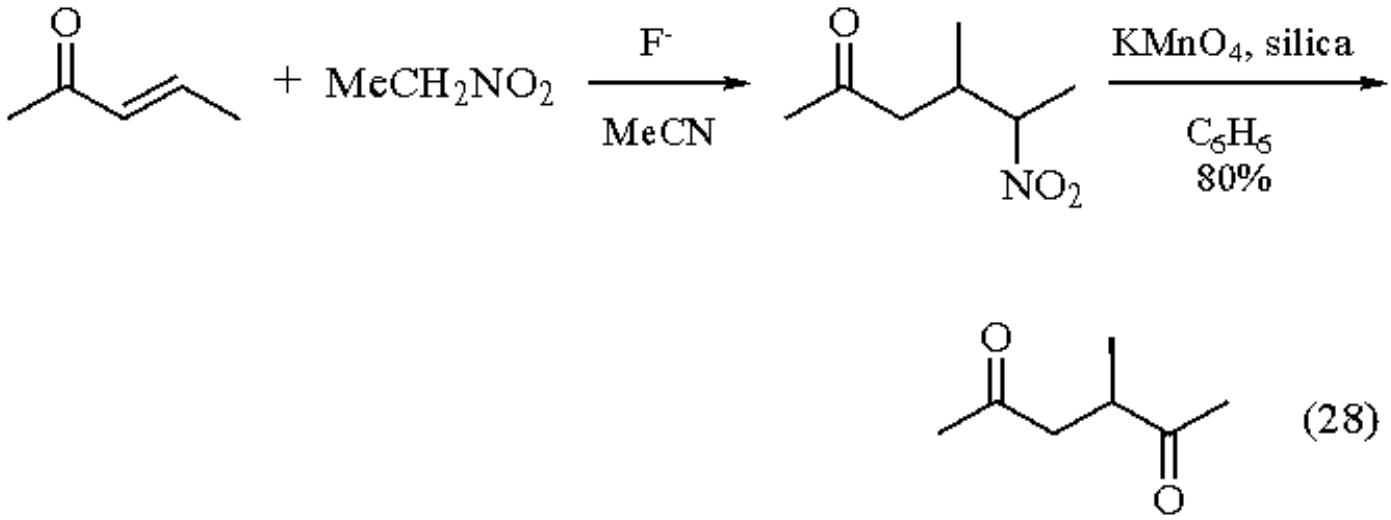

(28)

Oxidation of 1,5-Dienes.

The oxidation of 1,5-dienes results in the formation of 2,5-bis(hydroxymethyl)tetrahydrofurans with the indicated stereochemistry (eq 29).[32] When R^6 in (eq 29) is chiral, a nonracemic product is obtained.[33] Use of heterogeneous conditions results in the formation of lactones (eq 30).[34]

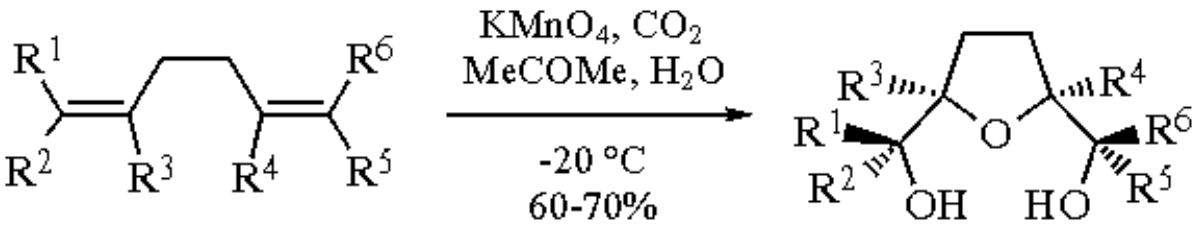

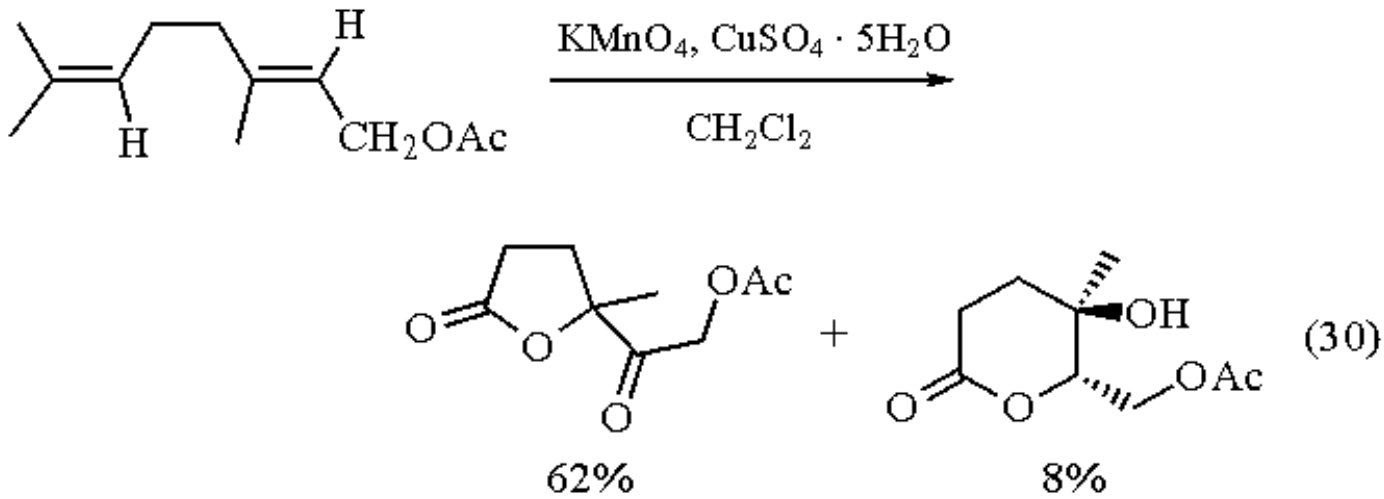

Oxidation of Alcohols and Diols.

Primary and secondary alcohols are converted to carboxylic acids and ketones, respectively, when oxidized by aqueous permanganate under either acidic or basic conditions (eq 31).[1] Similar results are obtained with phase-transfer assisted oxidations in organic solvents such as CH_2Cl_2 (eq 32).[2]

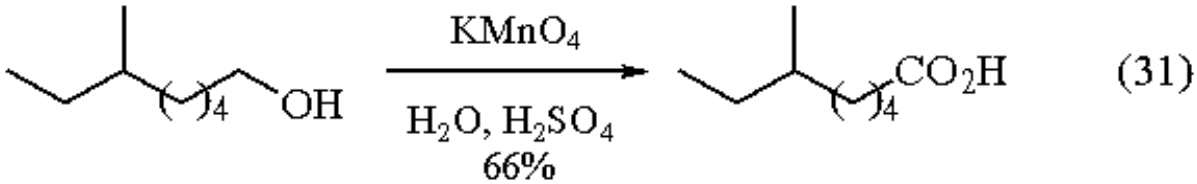

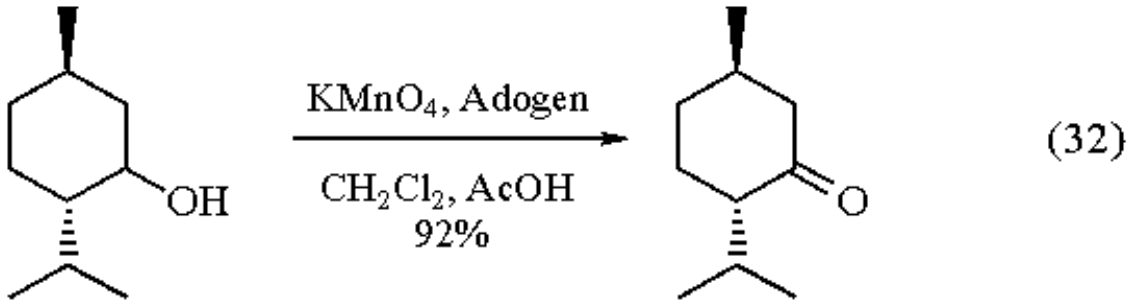

Heterogeneous oxidations are very effective with secondary alcohols (eq 33)[35] and provide the added advantage that allylic secondary alcohols can be converted to the corresponding α,β-unsaturated ketones without disruption of the double bond (eq 34).[9] Unsaturated secondary alcohols in which the double bond is not adjacent to the carbon bearing the hydroxy group are resistant to oxidation (eq 35) unless an omega phase[21] is created by adding a small amount of water (50 µL per g $KMnO_4$). The products are lactones under these conditions (eq 36).[36]

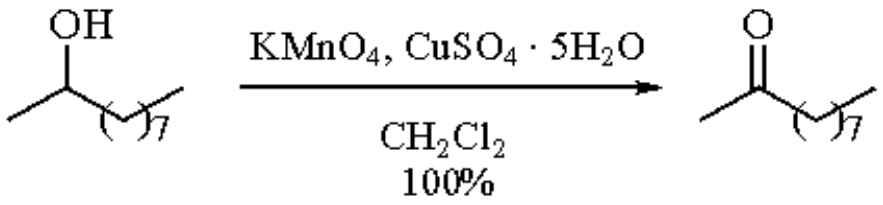

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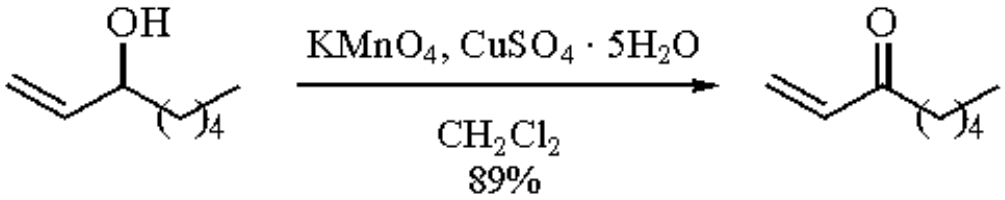

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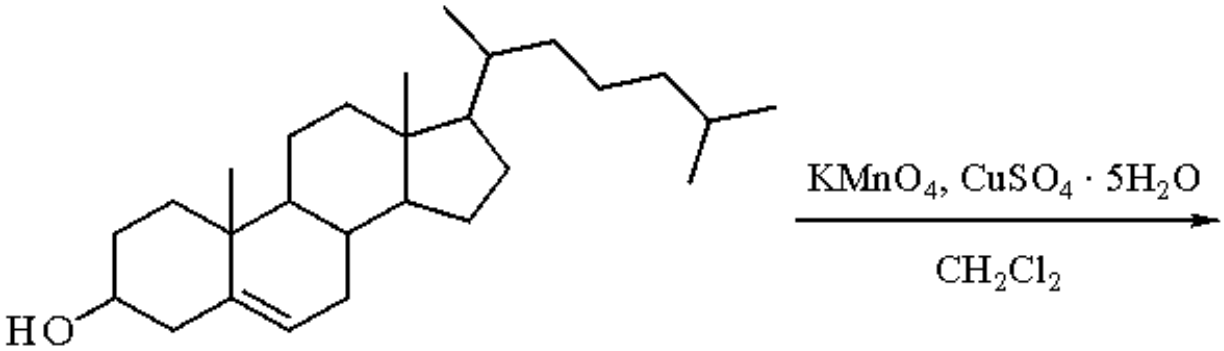

no product (35)

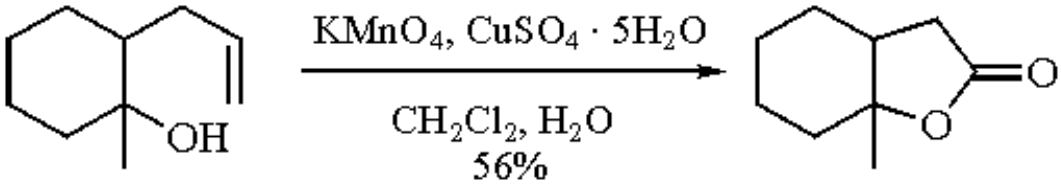

(36)

Good yields of carboxylic acids are obtained from primary alcohols under heterogeneous conditions ($KMnO_4/CuSO_4.5H_2O$) only when a base such as KOH or $Cu(OH)_2.CuCO_3$ is intermixed with the solid support.[37] Under these conditions the reagent has also been reported to be selective for primary alcohols.[37]

The oxidation of α,o-diols under heterogenous conditions results in the formation of lactones. A good example is found in the preparation of 3-hydroxy-*p*-menthan-10-oic acid lactone (eq 37).[37]

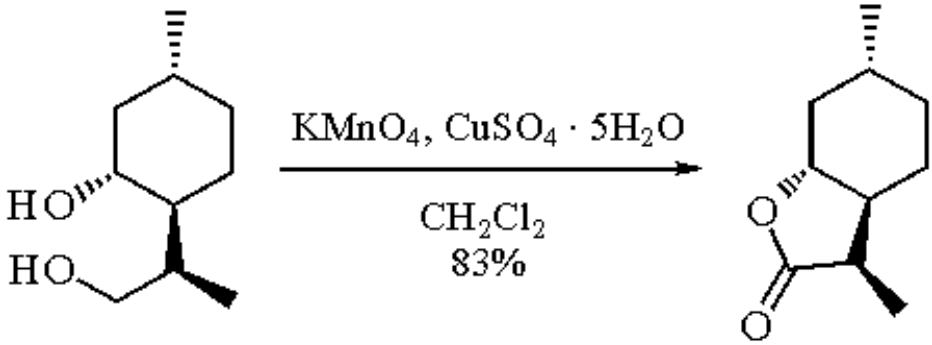

(37)

Oxidation of Organic Sulfur Compounds.

Aromatic thiols are oxidized by permanganate to the corresponding sulfonic acids while aliphatic thiols usually give disulfides, which are resistant to further oxidation.[4] Sulfides and sulfoxides are easily oxidized in CH_2Cl_2 to the corresponding sulfones under both homogeneous[38,39] and heterogeneous conditions (eqs 38-42).[40]

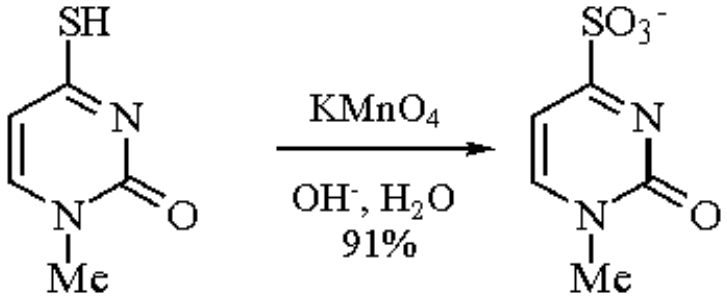

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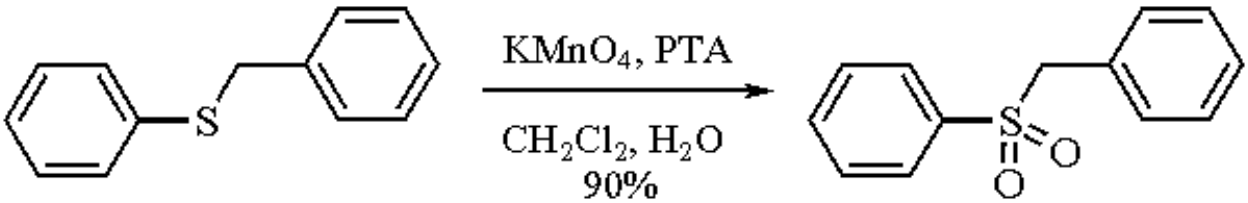

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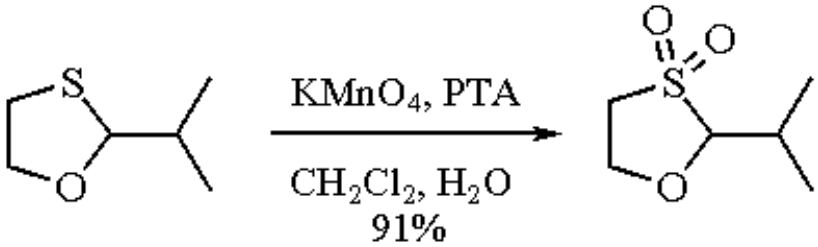

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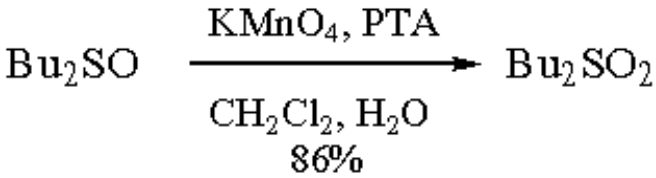

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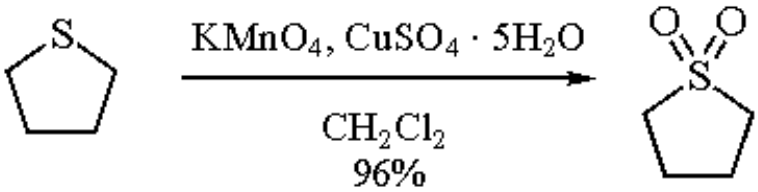

(42)

Permanganate oxidizes sulfoxides more readily than sulfides, as indicated by the products obtained from the oxidation of compounds containing both sulfide and sulfoxide functional groups (eqs 43 and 44).[41,42]

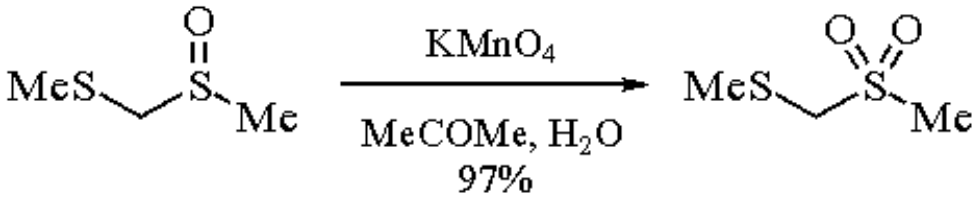

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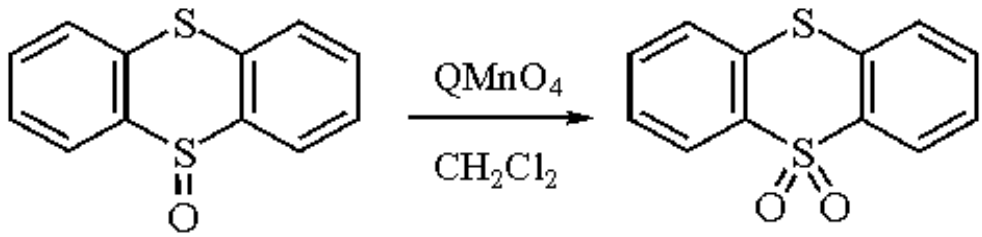

(44)

Q = benzyltriethylammonium ion

The greater ease of oxidation of sulfoxides is also responsible for the observation that *gem*-disulfides are oxidized to monosulfones.[42] Monosulfoxides, although not isolated, are likely to be intermediates in these reactions (eq 45).

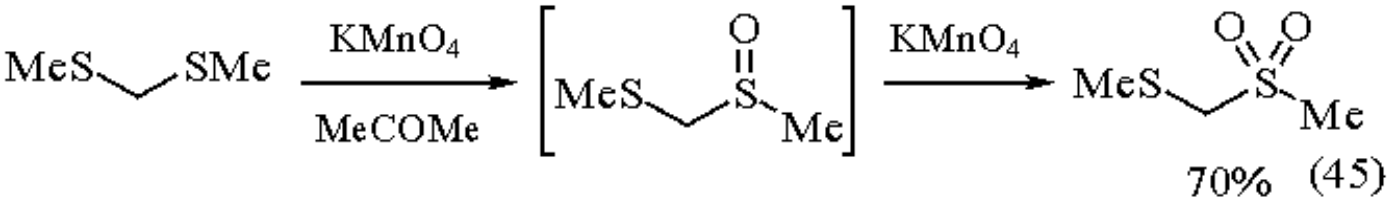

(45)

Oxidation of sulfinic acids results in the formation of sulfonic acids,[43] while sulfites give sulfates (eqs 46 and 47).[44]

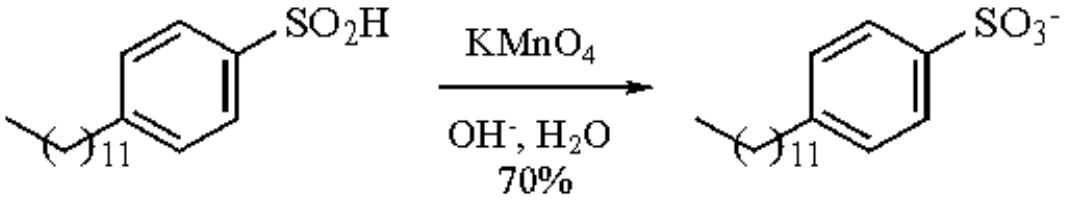

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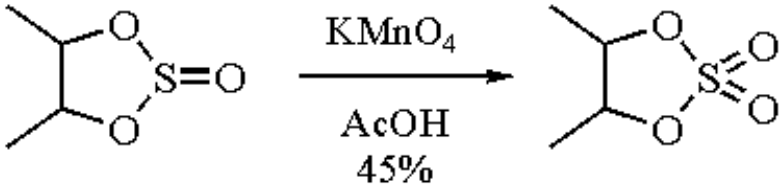

(47)

Cyclic thiones are readily oxidized to the corresponding ketones by permanganate (eq 48).[45]

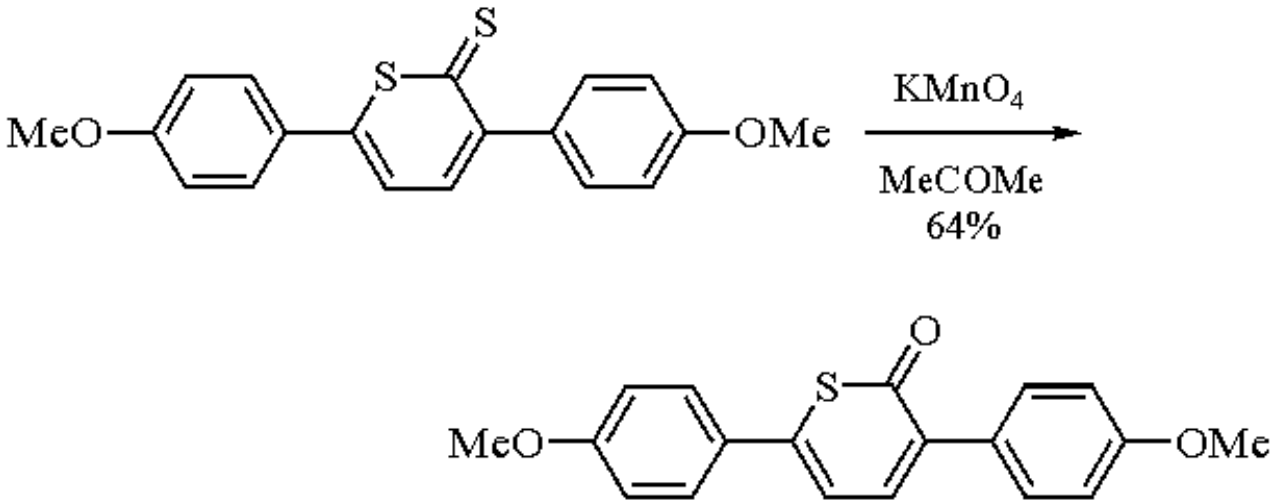

(48)

Oxidation of Amines.

The synthetic usefulness of permanganate as an oxidant for aliphatic amines is decreased by the fact that a complex mixture of products is often obtained.[4,46] Good yields of tertiary nitroalkanes can, however, be obtained from the oxidation of the corresponding amines (eq 49).[47]

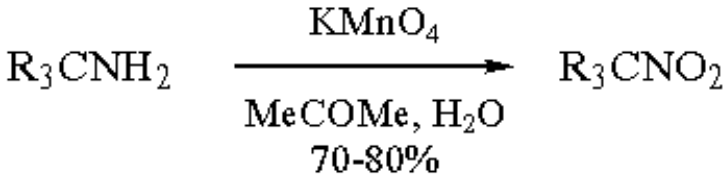

(49)

Primary and secondary amines react with permanganate in buffered, aqueous *t*-butyl alcohol to give aldehydes and ketones (eq 50).[46]

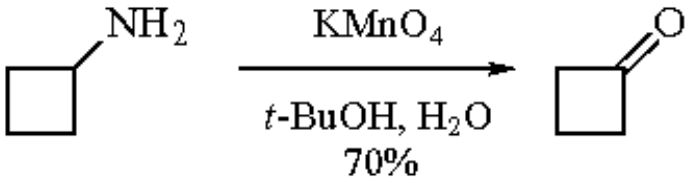

(50)

Amides (or lactams, if the amine is cyclic) are obtained from the oxidation of tertiary amines (eqs 51 and 52).[48-50]

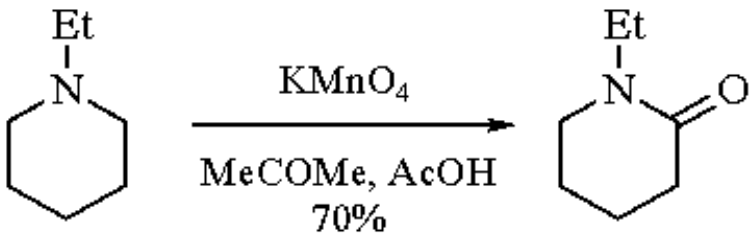

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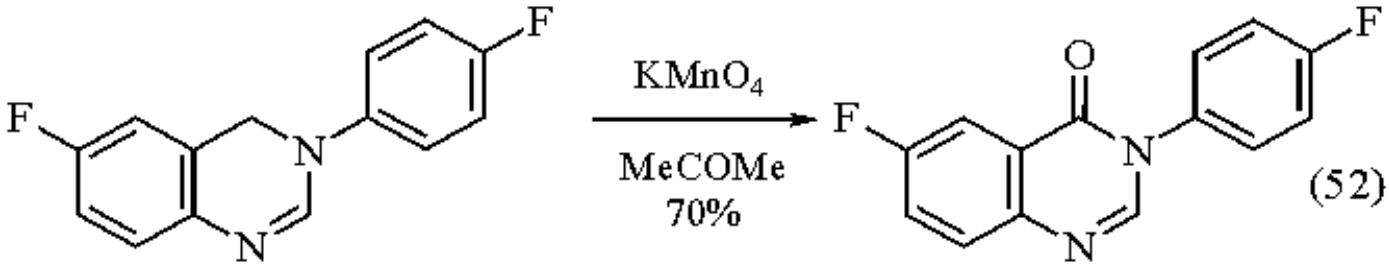

(52)

Miscellaneous Oxidations.

Use of permanganate in conjunction with ***t-Butyl Hydroperoxide*** results in allylic oxidation (eq 53).[51]

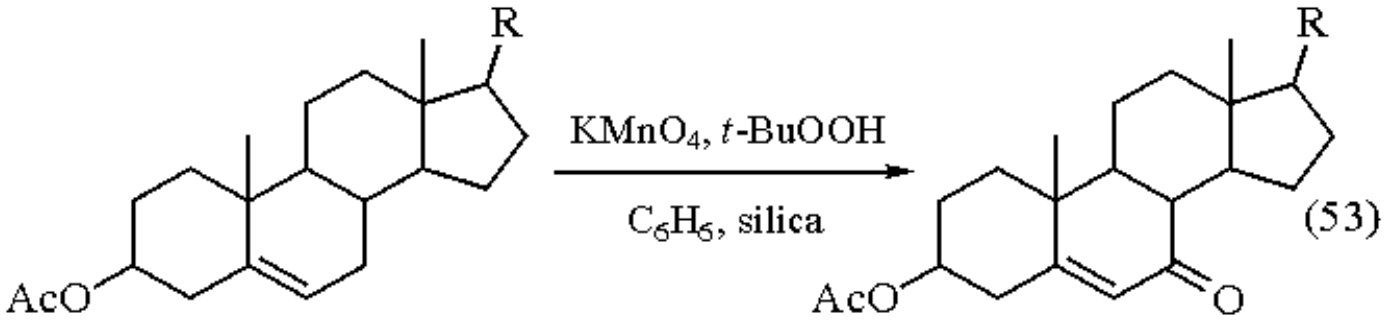

(53)

Aromatic compounds are oxidized to aryl iodides when treated with permanganate, ***Iodine***, and ***Sulfuric Acid*** (eq 54).[52]

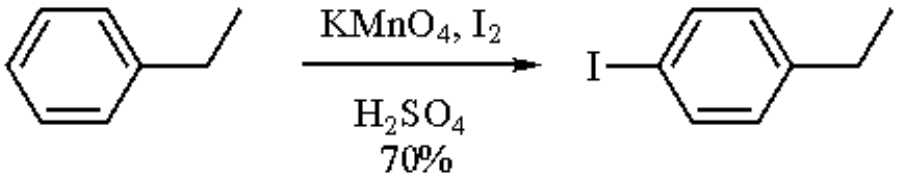

(54)

Chemical modification of nucleic acids by treatment with permanganate results in oxidation of the Δ^5 double bond to give either diols or ketols (eq 55).[53]

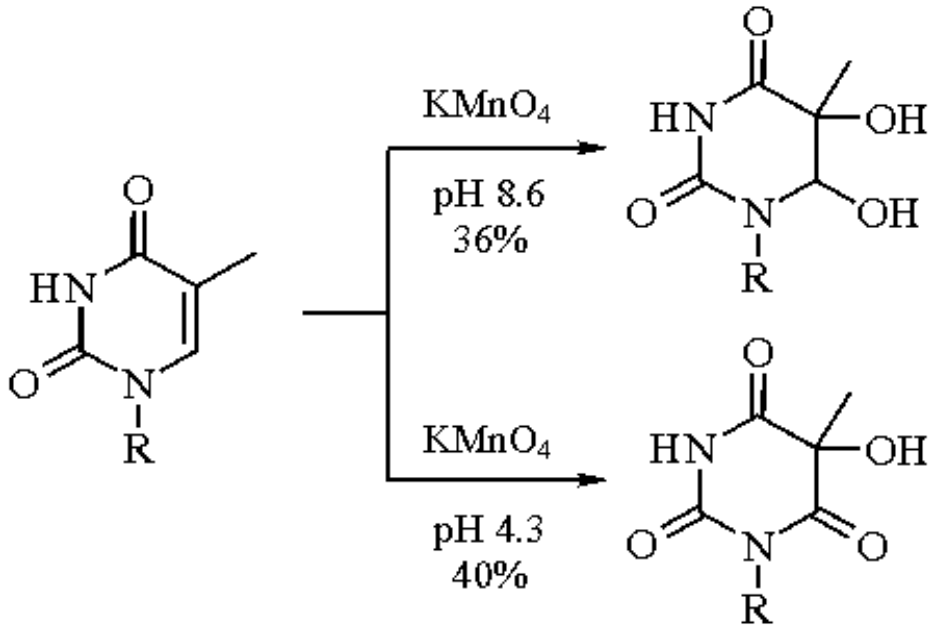

(55)

Guaiol and related compounds can be oxidized to rearranged ketols using aqueous glyme as the solvent (eq 56).[54]

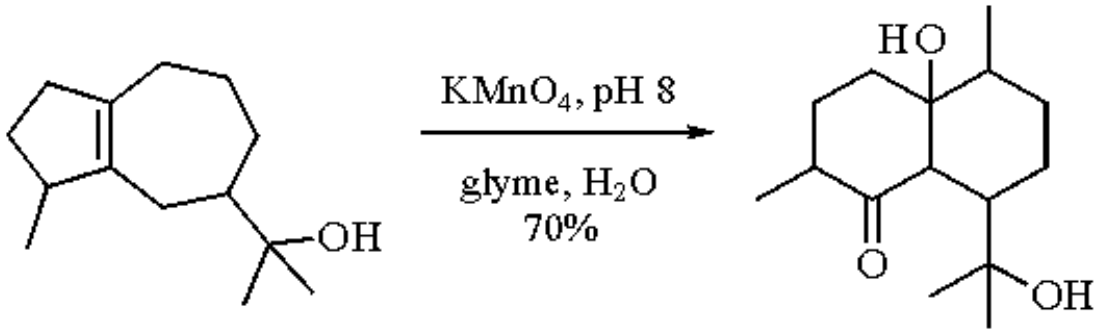

(56)

cis-2,5-Dihydro-2,5-dimethoxyfuran is oxidized to the corresponding α-diol in preference to the *trans* compound (eqs 57 and 58).[55]

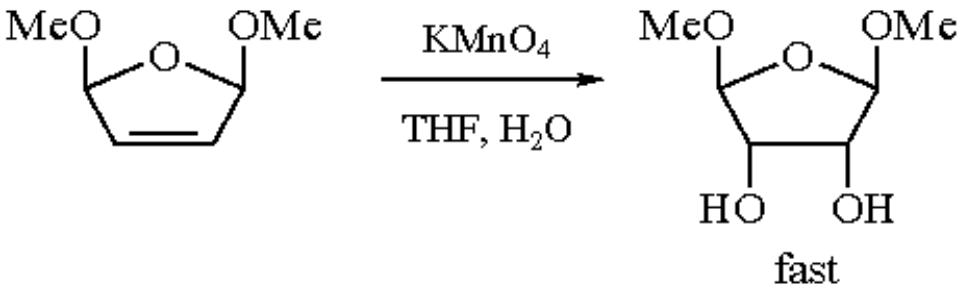

(57)

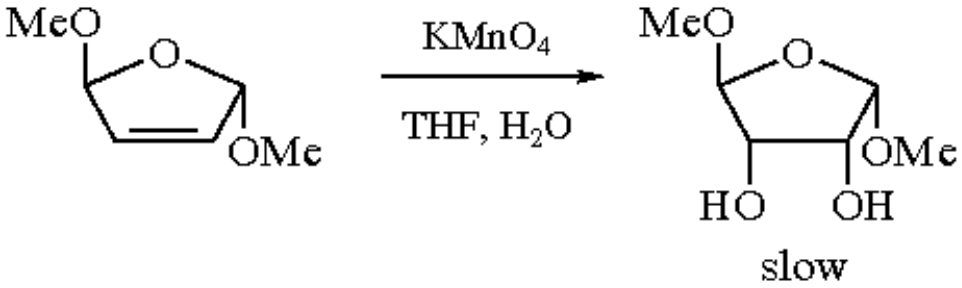

(58)

Oxidation of poly(vinyl alcohol) by permanganate results in the formation of poly(vinyl ketone) (eq 59).[56]

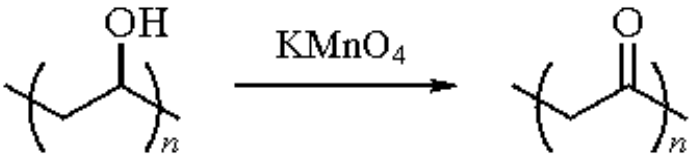

(59)

Treatment of Δ^5-unsaturated steroids with $KMnO_4/CuSO_4.5H_2O$ in CH_2Cl_2 containing catalytic amounts of *t*-butyl alcohol and water results in formation of the corresponding 5β,6β-epoxide (eq 60).[22,57]

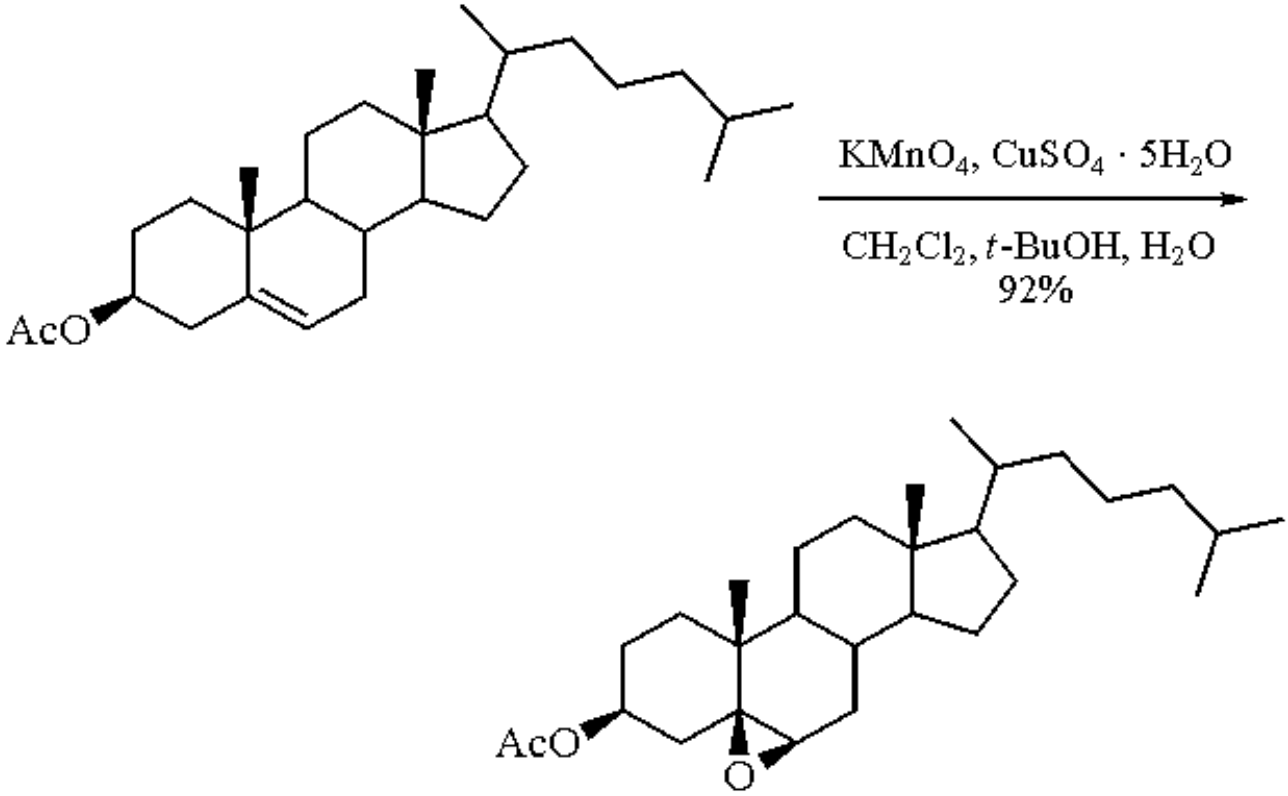

(60)

The oxidation of Δ^7-cholesterol acetate by $KMnO_4$ under neutral or slightly basic conditions results in formation of all-*cis*-epoxydiol (eq 61).[58]

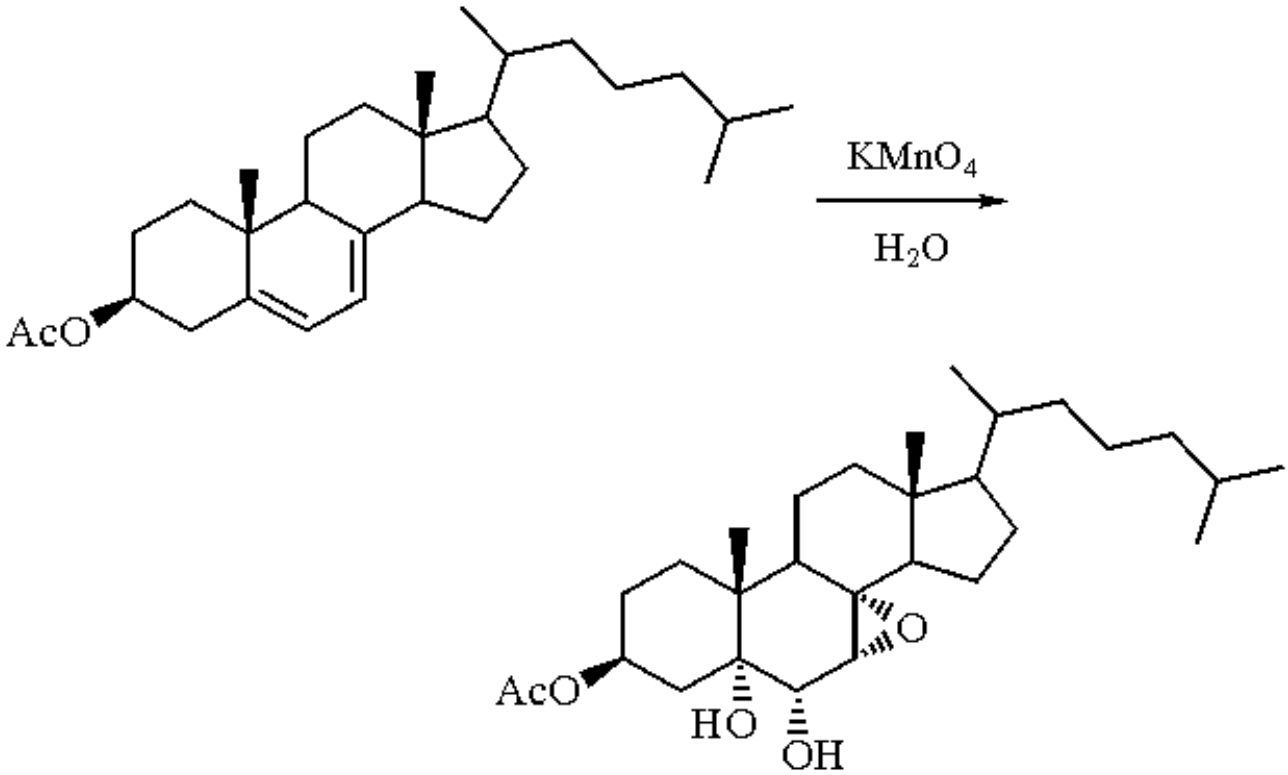

(61)

Aliphatic nitro compounds are converted into the corresponding oxo compounds on treatment with basic permanganate.[59,60] Because these reactions are carried out under basic conditions, it is likely that anions are intermediates, as suggested in eqs 62-64.

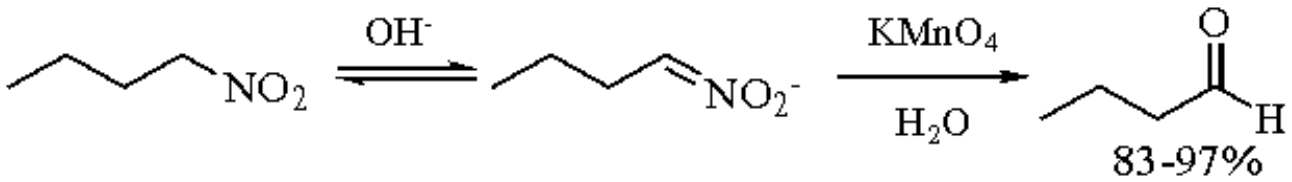

(62)

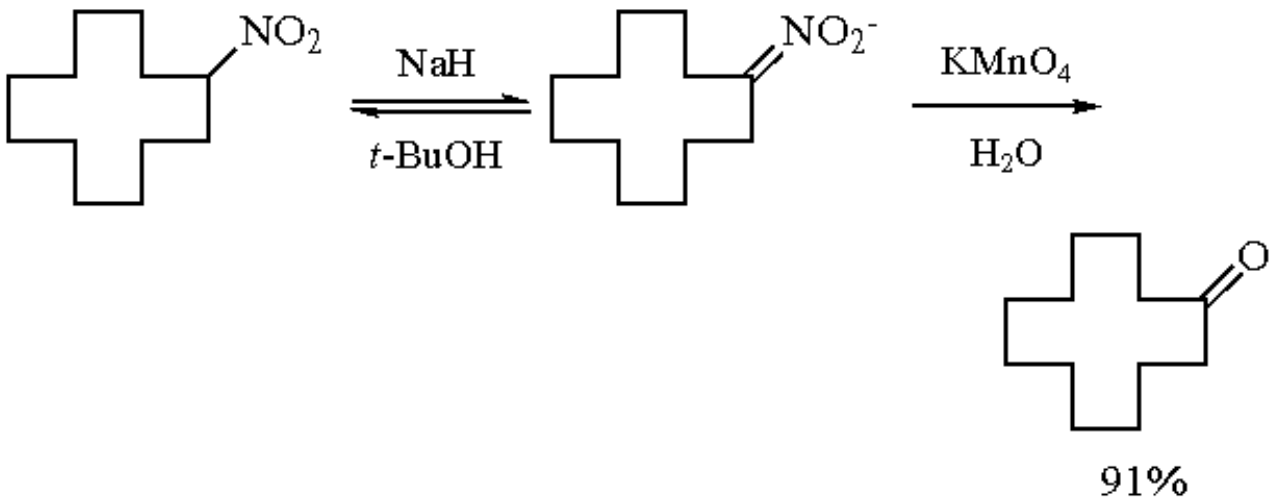

(63)

(64)

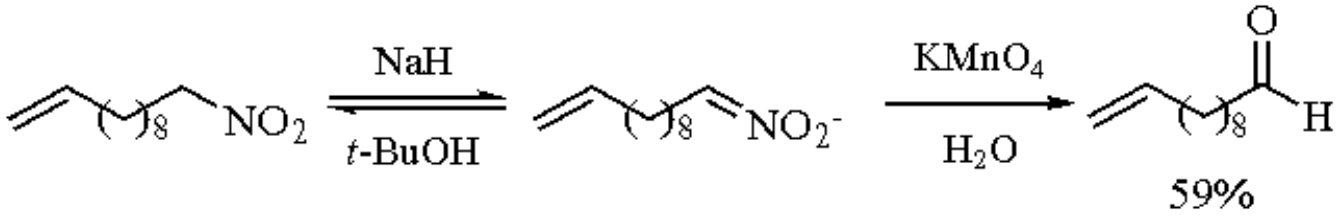

Nitrones can be obtained from the oxidation of imines by $KMnO_4$ in a two-phase CH_2Cl_2/H_2O solution containing a phase-transfer agent (PTA) such as tetrabutylammonium chloride (eq 65).[61]

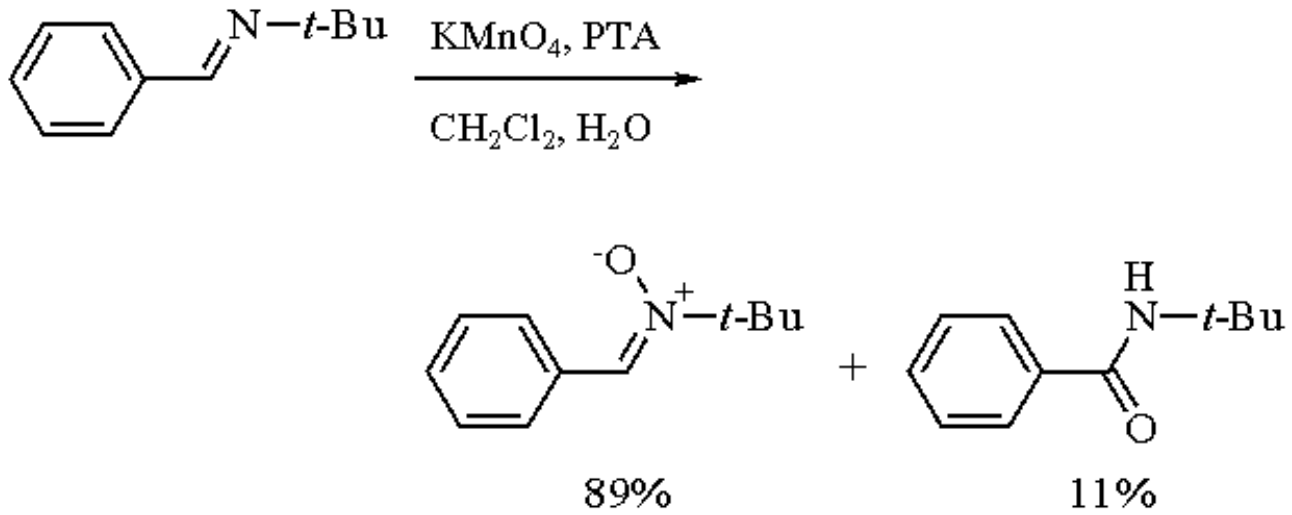

(65)

Related Reagents.

Potassium Permanganate-Copper(II) Sulfate; ***Sodium Periodate-Potassium Permanganate***.

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Potassium Permanganate-Copper(II) Sulfate

$KMnO_4$-$CuSO_4.5H_2O$

($KMnO_4$)

[7722-64-7] · $KMnO_4$ · Potassium Permanganate-Copper(II) Sulfate · (MW 158.04) ($CuSO_4.5H_2O$)

[7758-99-8] · CuO_4S · Potassium Permanganate-Copper(II) Sulfate · (MW 249.72)

(oxidant; capable of converting saturated primary alcohols into carboxylic acids,[1] saturated secondary alcohols into ketones,[2] α,β-unsaturated alcohols into α,β-unsaturated ketones,[3] dialkyl and diaryl sulfides into sulfones,[4] diphenyl selenide into diphenyl selenone,[4] α,o-diols into lactones,[1] alkenes into diketones and α-hydroxy ketones,[5] o-hydroxy alkenes into o-lactones,[6] 1,5-dienes into 5-substituted butanolides,[7] and Δ^5-unsaturated steroids into the corresponding 5β,6β-epoxy steroids)

Physical Data: mixture of high melting solids; see entries for ***Potassium Permanganate*** and ***Copper(II) Sulfate***.

Solubility: sol cold H_2O; insol CH_2Cl_2.

Form Supplied in: $KMnO_4$: purple solid. $CuSO_4.5H_2O$: blue solid.

Handling, Storage, and Precautions: oxidant; store in glass containers at rt.

Introduction.

The use of $KMnO_4$ adsorbed on a solid support as a heterogeneous oxidant in nonaqueous solvents such as CH_2Cl_2 has two very practical advantages. First, in common with most heterogeneous reactions, the product can be isolated simply by filtering to remove the spent oxidant, followed by flash evaporation of the solvent. Second, adsorption of potassium permanganate onto a solid support remarkably improves its selectivity. Various supports have been used (e.g. molecular sieves,[9] ***Alumina***,[10,11] and silica[10,12,13]) with ***Copper(II) Sulfate*** being the most convenient and versatile.

The water of hydration is important; without it very little or no product is obtained.[2] While the role of water in controlling the nature of the products is empirically well documented, a theoretical understanding of its function has been the subject of only preliminary discussions.[11,14]

Oxidation of Secondary Alcohols to Ketones.

When potassium permanganate (3 g) and copper(II) sulfate pentahydrate (2 g) are ground together, a reagent capable of oxidizing both saturated and α,β-unsaturated secondary alcohols into the corresponding ketones is produced. When the alcohols (3 mmol) dissolved in 20 mL of CH_2Cl_2 are added and the heterogeneous mixture refluxed for several hours, ketones are formed in excellent yields;[3] however, primary alcohols, alkenes, and alcohols unsaturated at a more remote position are not oxidized unless water or a base are added.

Oxidation of Sulfides and Selenides.

Under similar conditions, sulfides and selenides are converted to sulfones and selenones.[4]

Oxidation of Primary Alcohols and α,o-Diols.

If a base ($Cu(OH)_2.CuCO_3$ or KOH) is added, primary alcohols are oxidized to the corresponding carboxylic acids in yields of 80-96% and in a competition experiment it was found that primary alcohols are oxidized in preference to secondary alcohols.[1] Under similar

conditions, α,o-diols are converted to lactones in good yields (eq 1).

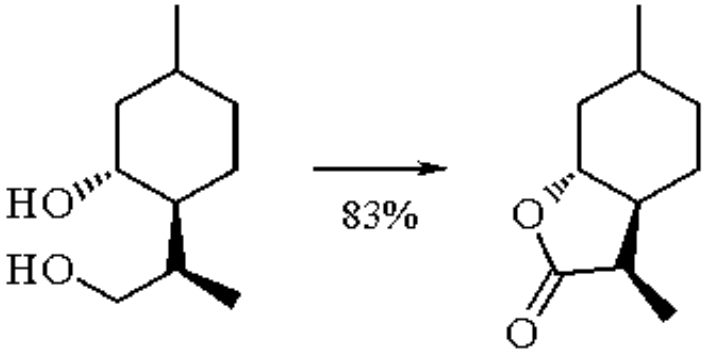

(1)

Oxidation of Alkenes.

The presence of a small additional amount of moisture along with some *t*-butyl alcohol introduces a modification to the reactivity of the reagent by formation of an omega phase[15] surrounding the solid support. Under such conditions alkenes are oxidized to α-diketones and/or α-hydroxy ketones. For example, when 200 µL of water was added to a finely ground mixture of potassium permanganate (4.0 g) and copper(II) sulfate pentahydrate (2.0 g) followed by cyclooctene (4 mmol) in CH_2Cl_2 (15 mL) and *t*-butyl alcohol (1.0 mL), α-hydroxycyclooctanone was obtained in 50% yield after refluxing for 30 min. Under similar conditions, but with the addition of $Cu(OAc)_2.H_2O$ (1.0 g), 1,2-cyclooctadione was obtained in 48% yield (eq 2).

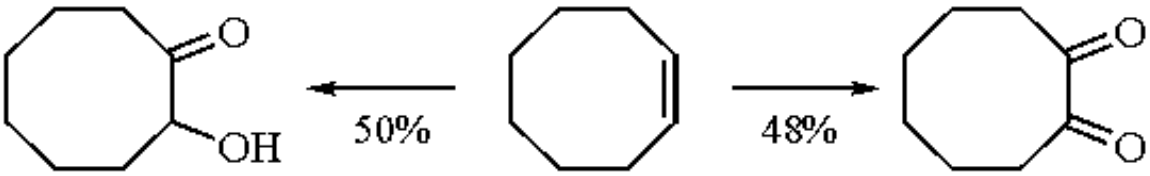

(2)

With some alkenes, epoxides are obtained instead of ketones. For example, Δ^5-unsaturated steroids are readily converted into the corresponding 5β,6β-epoxides in 90-95% yield (eq 3).[5,8]

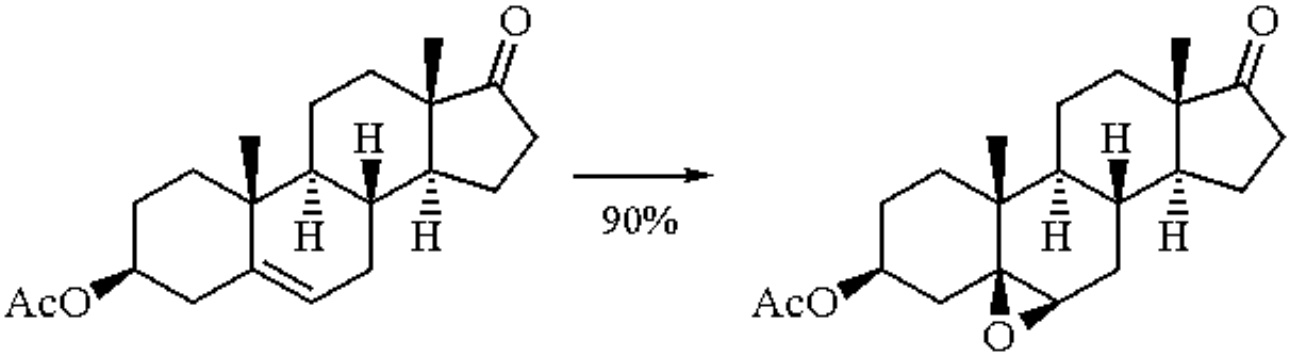

(3)

Oxidation of o-Hydroxy Alkenes and 1,5-Dienes.

When the omega phase is produced by adding 400 µL of water to powdered $KMnO_4$ (8 g) and $CuSO_4.5H_2O$ (4 g), o-hydroxy alkenes are oxidized with the loss of one or more carbons (eq 4).[6]

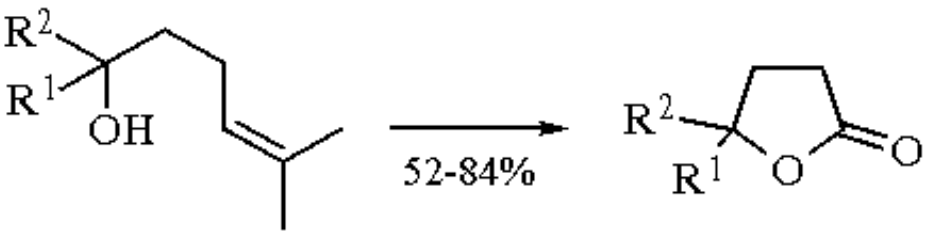

(4)

Under similar conditions, 1,5-dienes are converted to 5-substituted butanolides,[7] as opposed to 2,5-bis(hydroxymethyl)tetrahydrofurans

which are formed in the corresponding aqueous reactions (eq 5).[16]

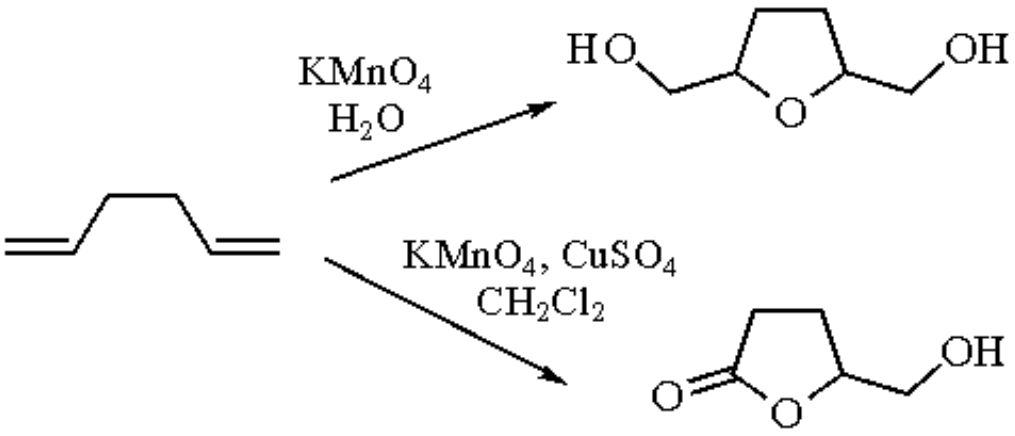

(5)

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Potassium Monoperoxysulfate

$2KHSO_5.KHSO_4.K_2SO_4$

[37222-66-5] · $H_3K_5O_{18}S_4$ · Potassium Monoperoxysulfate · (MW 614.81)

(oxidizing agent for a number of functional groups, including alkenes,[16] arenes,[17] amines,[26] imines,[30] sulfides;[37] used for the preparation of dioxiranes[5])

Alternate Names: potassium caroate, potassium hydrogen persulfate, Oxone®.

Physical Data: mp dec; *d* 1.12-1.20 g cm^{-3}.

Solubility: sol water (25.6 g 100 g, 20 °C), aqueous methanol, ethanol, acetic acid; insol common organic solvents.

Form Supplied in: white, granular, free flowing solid. Available as Oxone® and as Curox® and Caroat®.

Analysis of Reagent Purity: iodometric titration, as described in the Du Pont data sheet for Oxone®.

Handling, Storage, and Precautions: the Oxone triple salt $2KHSO_5.KHSO_4.K_2SO_4$ is a relatively stable, water-soluble form of potassium monopersulfate that is convenient to handle and store. Oxone has a low order of toxicity, but is irritating to the eyes, skin, nose, and throat. It should be used with adequate ventilation and exposure to its dust should be minimized. Traces of heavy metal salts catalyze the decomposition of Oxone. For additional handling instructions, see the Du Pont data sheet.

Oxidation Methodology.

Oxone ($2KHSO_5.KHSO_4.K_2SO_4$) is a convenient, stable source of potassium monopersulfate (caroate), which serves as a stoichiometric oxidizing agent under a variety of conditions. Thus aqueous solutions of Oxone can be used to perform oxidations in homogeneous solution and in biphasic systems using an immiscible cosolvent and a phase-transfer catalyst. Recently, solid-liquid processes using supported Oxone reagents have been developed. Other oxidation methods involve the generation and reaction of a secondary reagent under the reaction conditions, as with the widely employed aqueous Oxone-ketone procedures, which undoubtedly involve dioxirane intermediates.[1-4] In other instances, oxaziridine derivatives and metal oxo complexes appear to be the functional oxidants formed in situ from Oxone. Synthetically useful examples of these oxidations are grouped below according to the functional groups being oxidized.

Ketones and Other Oxygen Functions.

Various ketones can be converted to the corresponding dioxiranes by treatment with buffered aqueous solutions of Oxone (eq 1). Of particular interest are dimethyldioxirane[5] ($R^1 = R^2 = Me$) and methyl(trifluoromethyl)dioxirane[6] ($R^1 = Me$, $R^2 = CF_3$) derived from acetone and 1,1,1-trifluoro-2-propanone, respectively. The discovery of a method for the isolation of dilute solutions of these volatile dioxiranes in the parent ketone by codistillation from the reaction mixture has opened an exciting new area of oxidation chemistry (see ***Dimethyldioxirane*** and ***Methyl(trifluoromethyl)dioxirane***). Solutions of dioxiranes derived from higher molecular weight ketones have also been prepared.[5,7]

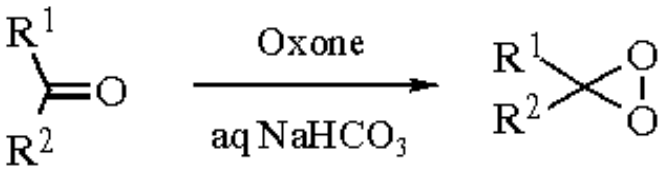

(1)

Interestingly, the reaction of a solid slurry of Oxone and wet ***Alumina*** with solutions of cyclic ketones in CH_2Cl_2 provokes Baeyer-Villiger oxidation to give the corresponding lactones (eq 2).[8] The same wet alumina-Oxone reagent can be used to oxidize secondary alcohols to ketones (eq 3).[9] Aldehydes are oxidized to acids by aqueous Oxone.[5,10]

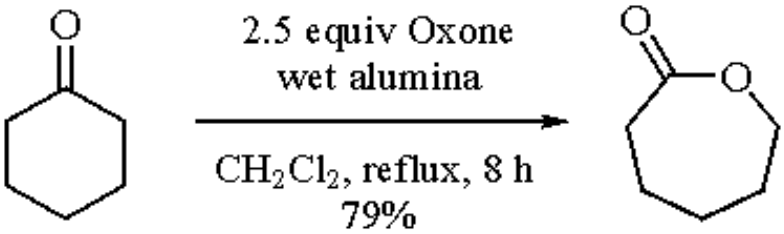

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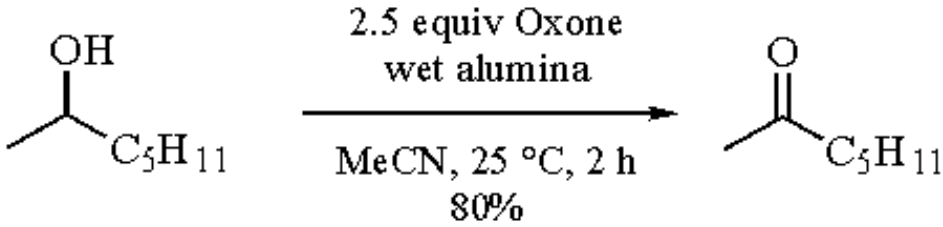

(3)

Alkenes, Arenes, and Alkanes.

Aqueous solutions of Oxone can epoxidize alkenes which are soluble under the reaction conditions; for example, sorbic acid (eq 4)[11] (the high selectivity for epoxidation of the 4,5-double bond here is noteworthy). Alternatively, the use of a cosolvent to provide homogeneous solutions promotes epoxidation (eq 5).[11] Control of the pH to near neutrality is usually necessary to prevent hydrolysis of the epoxide. Rapidly stirred heterogeneous mixtures of liquid alkenes and aqueous Oxone solutions buffered with $NaHCO_3$ also produce epoxides, as shown in eq 6.[12]

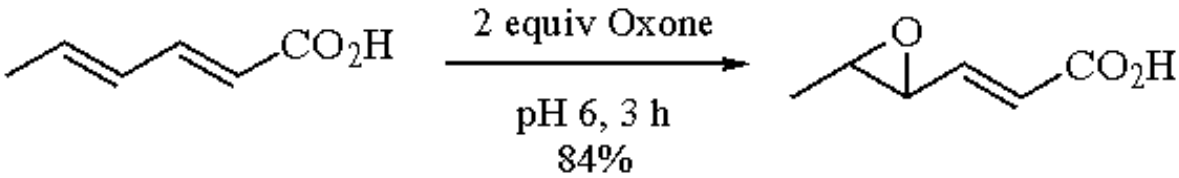

(4)

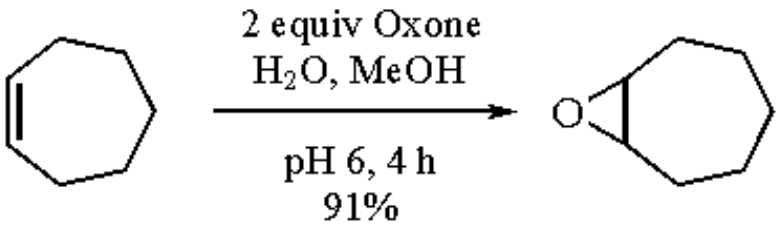

(5)

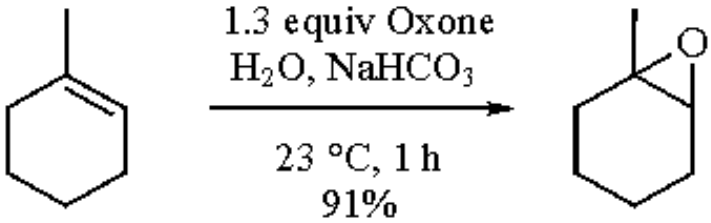

(6)

An in situ method for epoxidations with dimethyldioxirane using buffered aqueous acetone solutions of Oxone has been widely applied.[1-4] The epoxidation of 1-dodecene is particularly impressive in view of the difficulty generally encountered in the epoxidation of relatively unreactive terminal alkenes (eq 7).[13] A biphasic procedure using benzene as a cosolvent and a phase-transfer agent was utilized in this case. Equally remarkable is the epoxidation of the methylenecyclopropane derivatives indicated in eq 8, given the propensity of the products to rearrange to the isomeric cyclobutanones.[14]

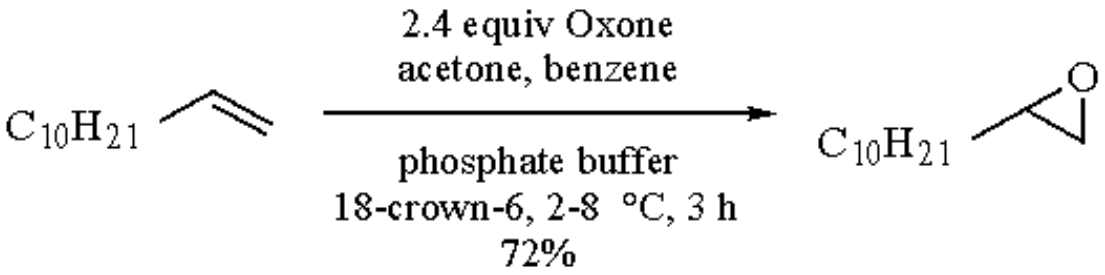

(7)

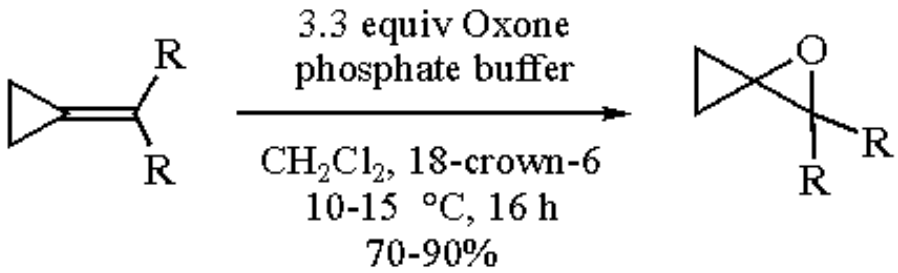

(8)

The epoxidation of conjugated double bonds also proceeds smoothly with the Oxone-acetone system, as illustrated by eq 9.[15] The conversion of water-insoluble enones can be accomplished with this method using CH_2Cl_2 as a cosolvent and a quaternary ammonium salt as a phase-transfer catalyst. However, a more convenient procedure utilizes 2-butanone both as a dioxirane precursor and as an immiscible cosolvent (eq 10).[16] No phase-transfer agent is required in this case.

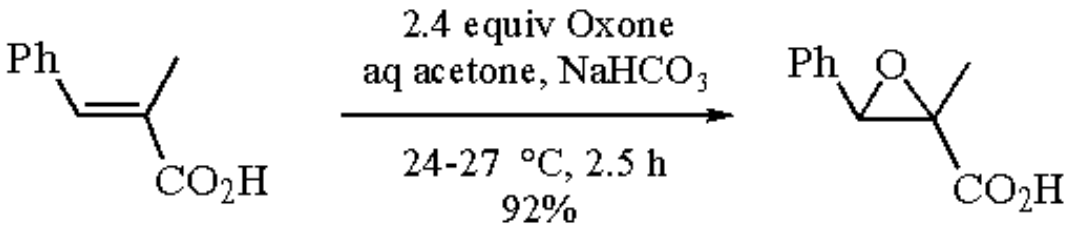

(9)

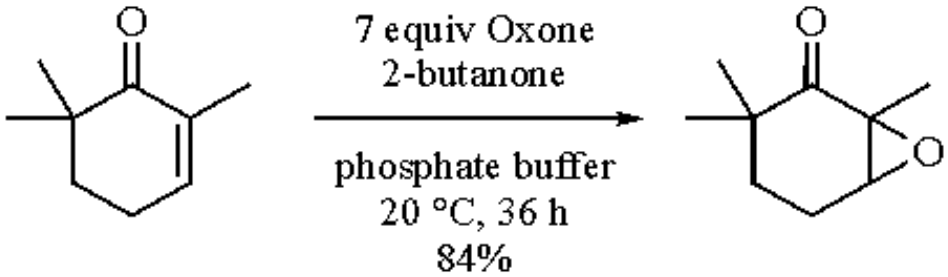

(10)

The epoxides of several polycyclic aromatic hydrocarbons have been prepared by the use of a large excess of oxidant in a biphasic Oxone-ketone system under neutral conditions, as shown for the oxidation of phenanthrene (eq 11).[17] However, the use of isolated dioxirane solutions is more efficient for the synthesis of reactive epoxides, since hydrolysis of the product is avoided.[5,18] A number of unstable epoxides of various types have been produced in a similar manner, as discussed for ***Dimethyldioxirane*** and ***Methyl(trifluoromethyl)dioxirane***.

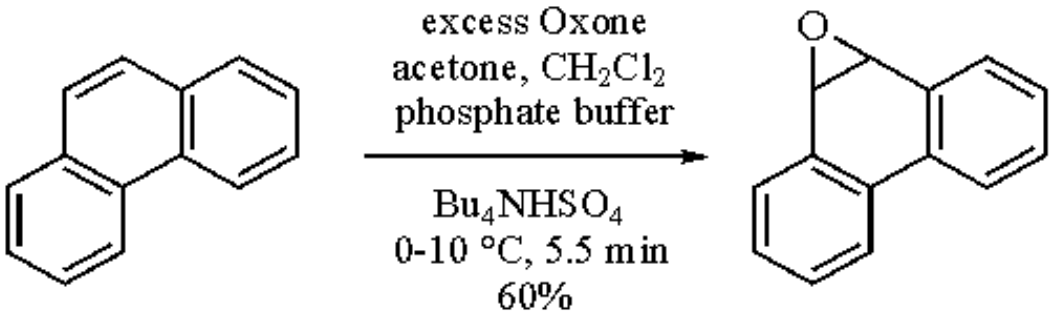

(11)

Epoxidations have also been performed with other oxidizing agents generated in situ from Oxone. An intriguing method uses a catalytic amount of an immonium salt to facilitate alkene epoxidation in a process which apparently involves an intermediate oxaziridium species as the active oxidant.[19] This procedure is carried out by adding solid Oxone and $NaHCO_3$ to a solution of the alkene and catalyst in MeCN containing a very limited quantity of water (eq 12). Finally, Oxone is the stoichiometric oxidant in interesting modifications of the widely

studied metal porphyrin oxidations, where it has obvious advantages over some of the other oxidants commonly used.[20] The potential of this method is illustrated by the epoxidation reaction in eq 13.[21] In this conversion, only 1.4 mol % of the robust catalyst tetrakis(pentafluorophenyl)porphyrinatomanganese chloride (TFPPMnCl) is required. The catalytic hydroxylation of unactivated hydrocarbons is also possible (eq 14).[22] Other metal complexes promote similar oxidations.[23-25]

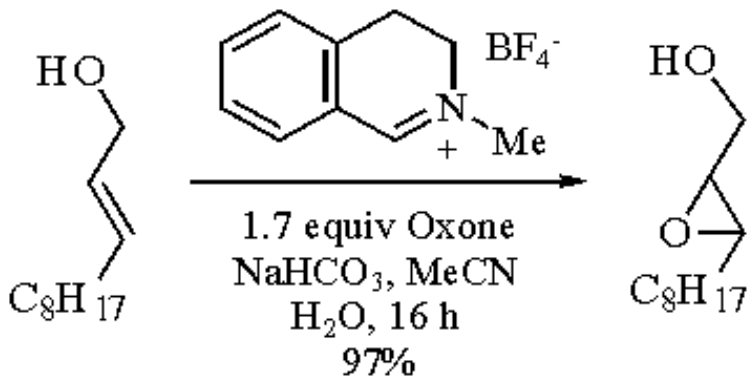

(12)

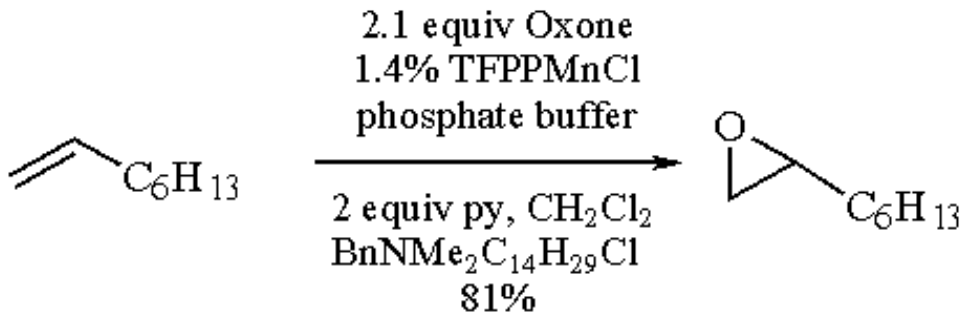

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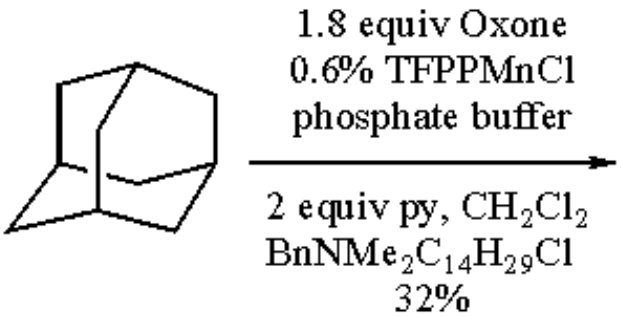

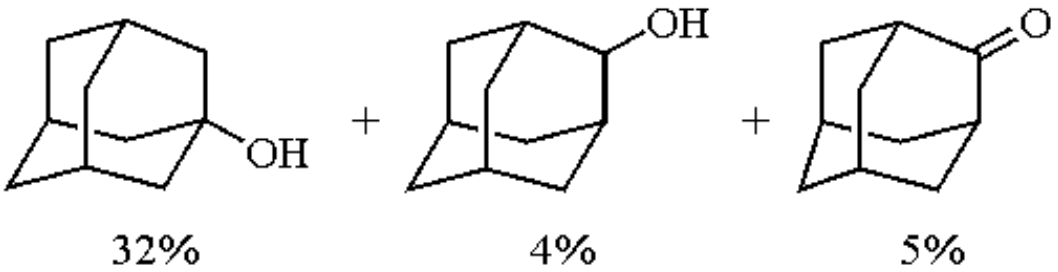

(14)

Nitrogen Compounds.

The aqueous Oxone-acetone combination has been developed for the transformation of certain anilines to the corresponding nitrobenzene derivatives, as exemplified in eq 15.[26] This process involves sequential oxidation steps proceeding by way of an intermediate nitroso compound. In the case of primary aliphatic amines, other reactions of the nitrosoalkane species compete with the second oxidation step (for example, dimerization and tautomerization to the isomeric oxime), thereby limiting the synthetic generality of these oxidations.[27] An overwhelming excess of aqueous Oxone has been used to convert cyclohexylamine to nitrocyclohexane (eq 16).[27]

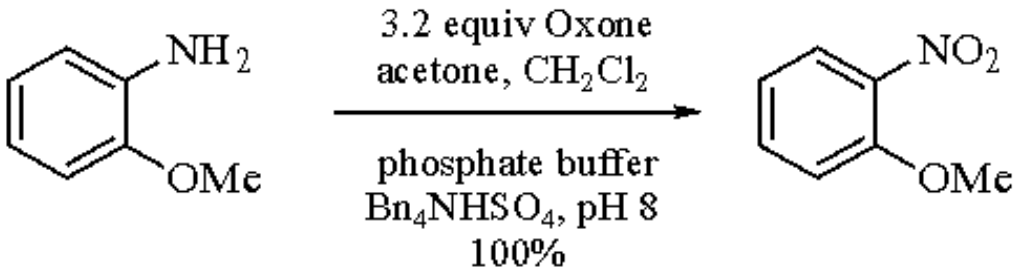

(15)

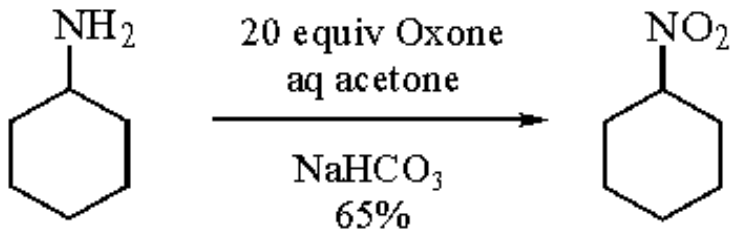

(16)

Pyridine is efficiently converted to its *N*-oxide by the Oxone-acetone oxidant.[5] Cytosine and several of its derivatives give the N^3-oxides selectively upon reaction with buffered Oxone (eq 17).[28] A similar transformation of adenosine 5´-monophosphate yields the N^1-oxide.[29]

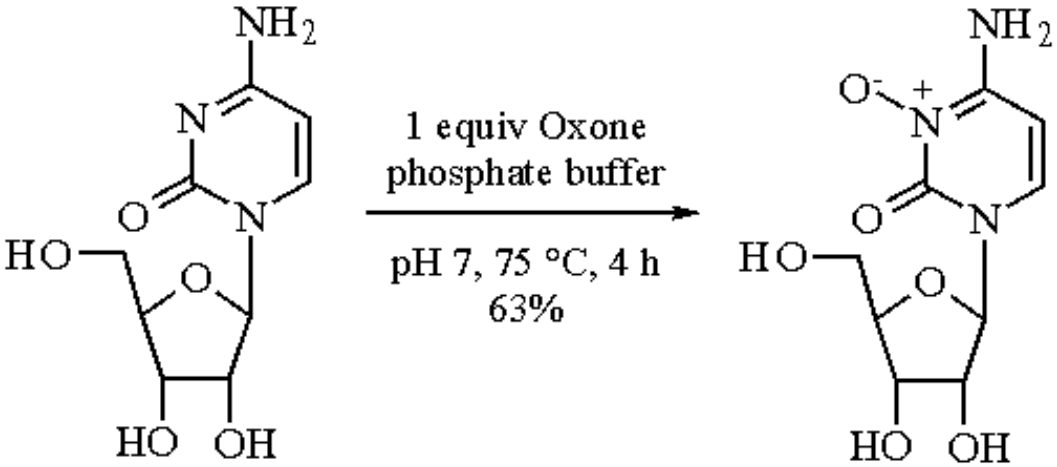

(17)

The very useful *N*-sulfonyloxaziridines are conveniently prepared by treating *N*-sulfonylimines with Oxone in a biphasic solvent system (eq 18).[30,31] Either bicarbonate or carbonate can be used to buffer this reaction, but reaction is much faster with carbonate, suggesting that the monopersulfate dianion is the oxidizing species (for illustrations of the remarkable chemistry of these oxaziridines, see ***N-(Phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine***).

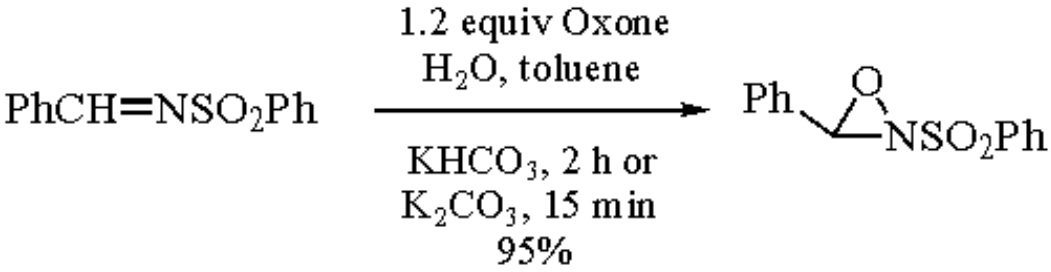

(18)

The Oxone-acetone system has also been employed for the synthesis of simple oxaziridines from *N*-alkylaldimines (eq 19).[32] Interestingly, the *N*-phenyl analogs produce the isomeric nitrones rather than the oxaziridines (eq 20). It is noteworthy that MeCN can replace acetone as the solvent in this procedure.

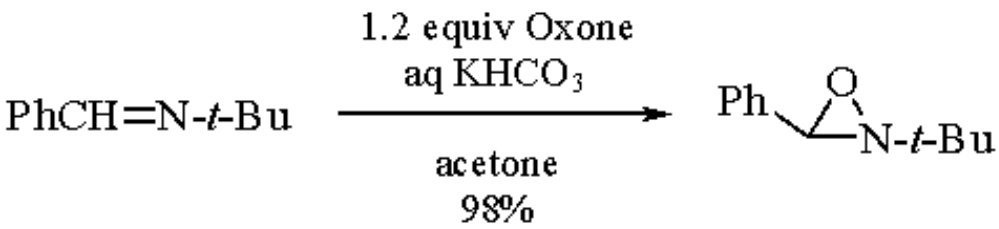

(19)

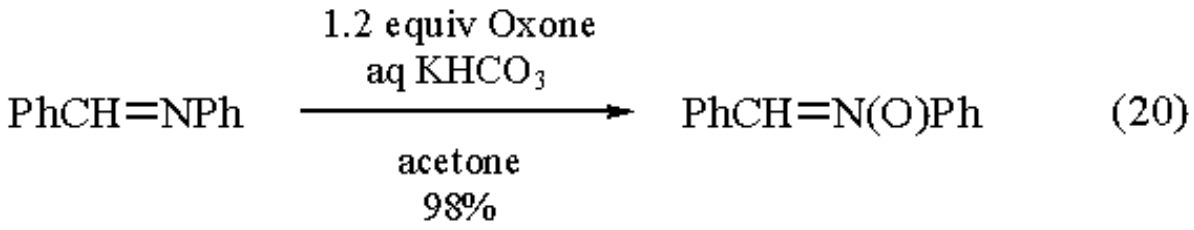

(20)

Finally, the chlorination of aldoximines gives the corresponding hydroximoyl chlorides, as shown in eq 21.[33] The combination of Oxone and anhydrous HCl in DMF serves as a convenient source of hypochlorous acid, the active halogenating agent.

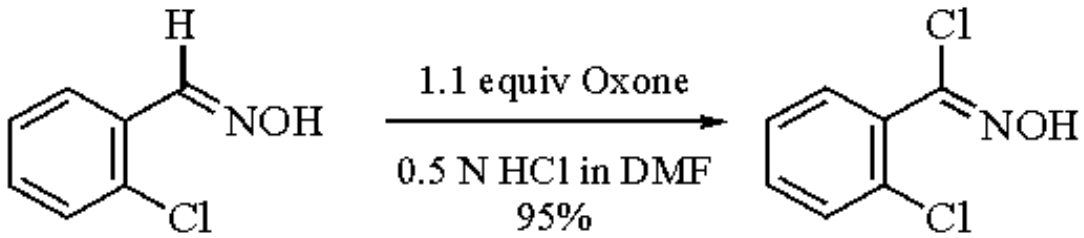

(21)

Sulfur Compounds.

Some of the earliest applications of Oxone in organic synthesis involved the facile oxidation of sulfur functions. For example, aqueous Oxone selectively oxidizes sulfides to sulfones even in highly functionalized molecules, as illustrated in eq 22.[34] Sulfones can also be prepared by a convenient two-phase system consisting of a mixture of solid Oxone, wet ***Montmorillonite K10*** clay, and a solution of the sulfide in an inert solvent.[35]

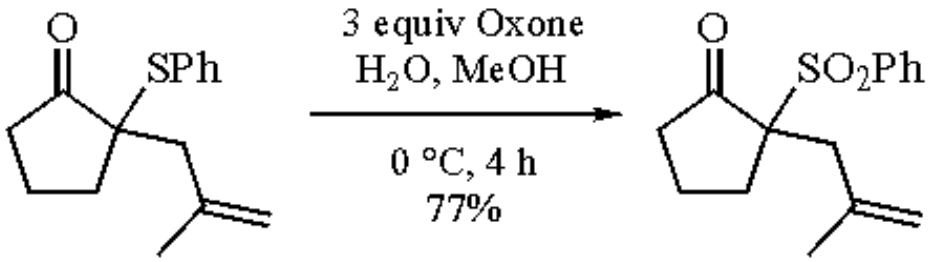

(22)

The partial oxidation of sulfides to sulfoxides has been accomplished in a few cases by careful control of the reaction stoichiometry and conditions.[34] A biphasic procedure for sulfoxide formation from diaryl sulfides is shown in eq 23.[36] However, a more attractive and versatile procedure uses a solid Oxone-wet alumina reagent with a solution of the sulfide.[37] This method permits control of the reaction to form either the sulfoxide or the sulfone simply by adjusting the amount of oxidant and the reaction temperature, as illustrated in eq 24. These oxidations are compatible with other functionality.

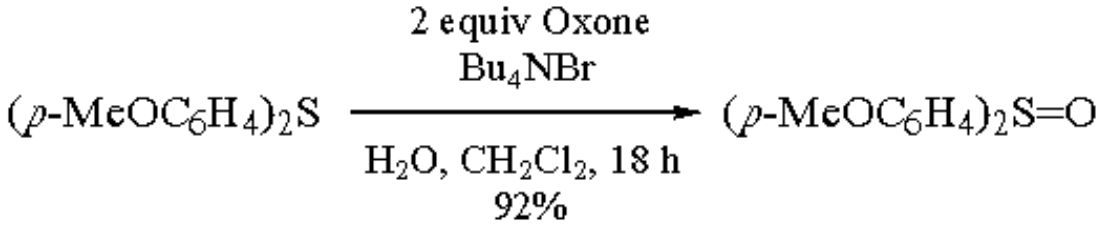

(23)

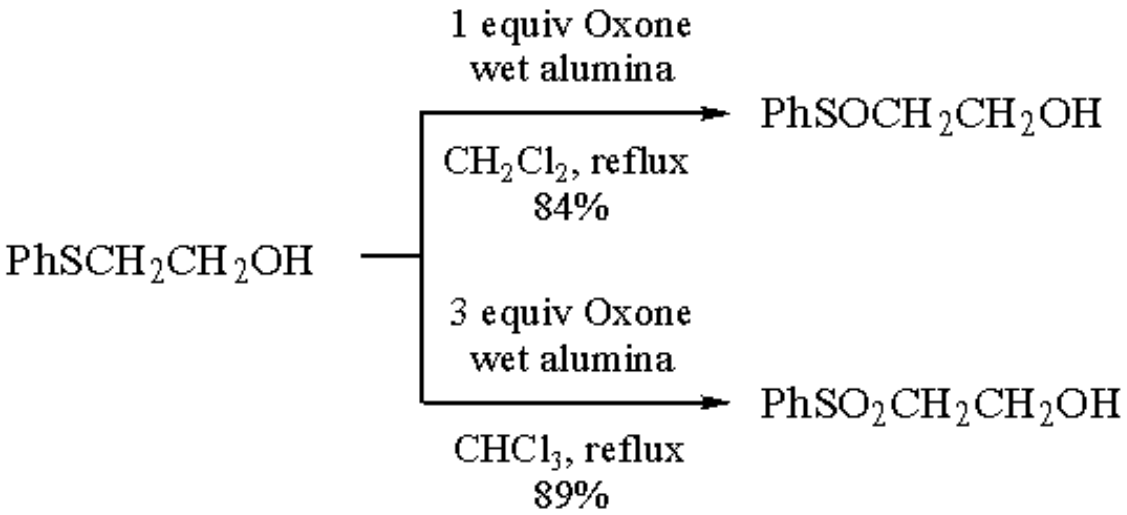

(24)

Another intriguing method for the selective oxidation of sulfides to sulfoxides (eq 25) uses buffered Oxone in a biphasic solvent mixture containing a catalytic amount of an *N*-phenylsulfonylimine as the precursor of the actual oxidizing agent, the corresponding *N*-sulfonyloxaziridine.[38] The oxaziridine is smoothly and rapidly formed by reaction of the imine with buffered Oxone and regenerates the imine upon oxygen transfer to the sulfide. The greater reactivity of the sulfide relative to the sulfoxide accounts for the preference for monooxidation in this procedure. The biphasic nature of this reaction prevents direct oxidation by Oxone, which would be less selective.

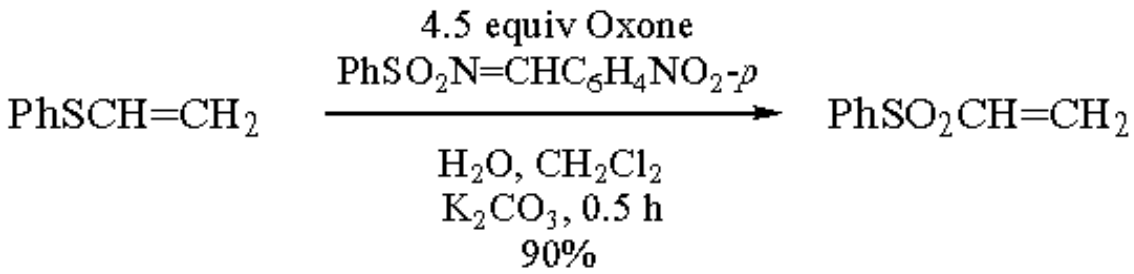

(25)

Oxone sulfoxidations can show appreciable diastereoselectivity in appropriate cases, as demonstrated in eq 26.[39] Enantioselective oxidations of sulfides to sulfoxides have been achieved by buffered aqueous Oxone solutions containing bovine serum albumin (BSA) as a chiral mediator (eq 27).[40] As little as 0.05 equiv of BSA is required and its presence discourages further oxidation of the sulfoxide to the sulfone. Oxone can be the active oxidant or reaction can be performed in the presence of acetone, trifluoroacetone, or other ketones, in which case an intermediate dioxirane is probably the actual oxidizing agent. The level of optical induction depends on structure of the sulfide and that of any added ketone. Sulfoxide products show ee values ranging from 1% to 89%, but in most examples the ee is greater than 50%.

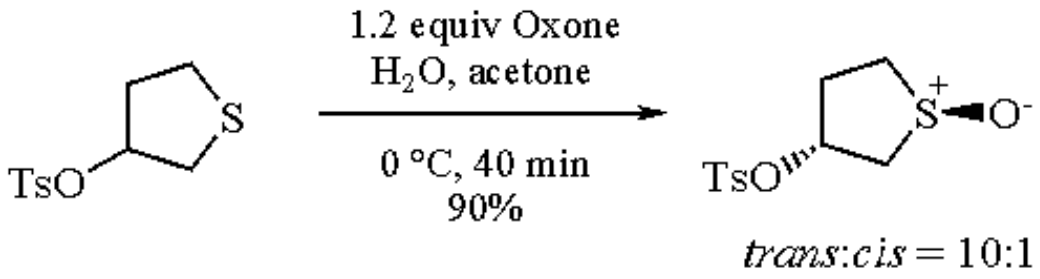

(26)

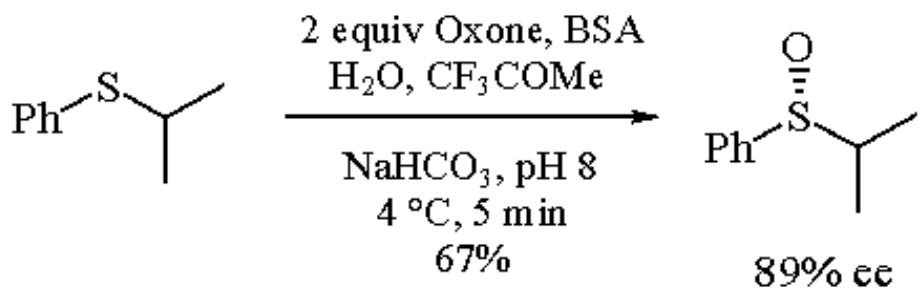

(27)

1-Decanethiol is efficiently oxidized to decanesulfonic acid (97% yield) by aqueous Oxone.[10] In a similar manner an acylthio function was converted into the potassium sulfonate salt, as shown in eq 28.[41]

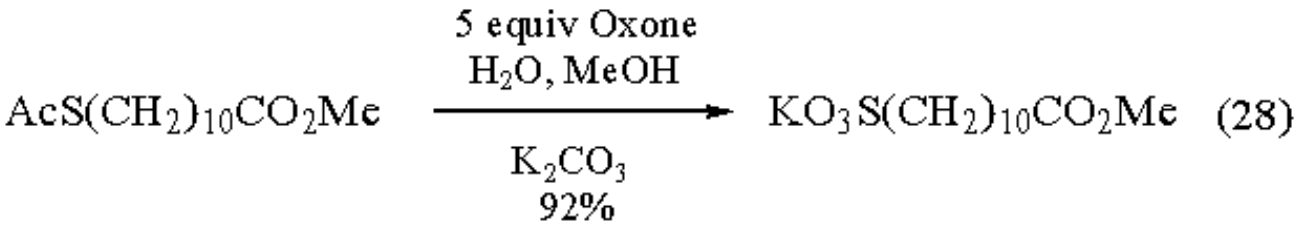

(28)

Finally, certain relatively stable thioketones can be transformed into the corresponding thione *S*-oxides by the aqueous Oxone-acetone reagent (eq 29).[42]

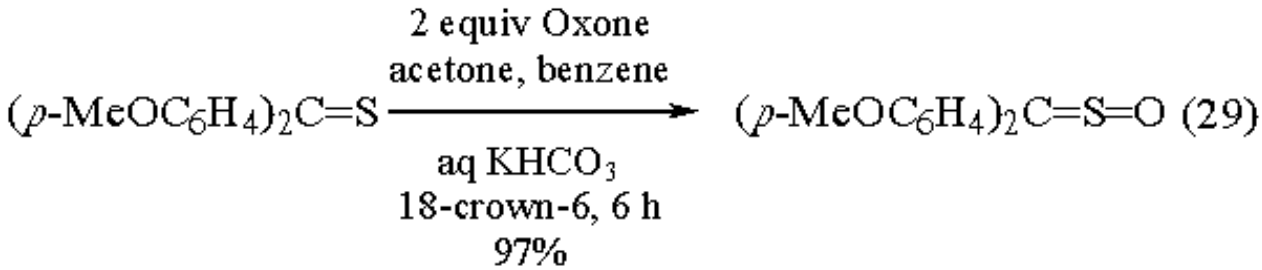

(29)

Related Reagents.

Dimethyldioxirane; ***Methyl(trifluoromethyl)dioxirane***.

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Potassium Ruthenate

K_2RuO_4

[14931-42-1] · K_2O_4Ru · Potassium Ruthenate · (MW 243.27)

(powerful oxidant capable of oxidizing primary alcohols to carboxylic acids and secondary alcohols to ketones;[1] in combination with persulfate can oxidize nitro compounds[2] and activated halides[3] and will selectively oxidize allylic alcohols under phase-transfer conditions[4])

Alternate Name: potassium tetraoxoruthenate(VI).

Physical Data: d 3.07 g cm^{-3}.

Solubility: sol H_2O; insol organic solvents.

Form Supplied in: green-black crystals (anhyd), deep red crystals (hyd); not commercially available.

Preparative Method: K_2RuO_4 has been prepared according to the method of Krauss.[5] To molten KOH in a nickel crucible is added equimolar amounts of Ru and KNO_3. The mixture is cooled, dissolved in H_2O, and K_2RuO_4 crystallized by slow evaporation over P_2O_5.

Handling, Storage, and Precautions: unstable in all but basic media and should be prepared and used as such. The toxicological properties of Ru have not been thoroughly investigated.

Functional Group Oxidations.

K_2RuO_4 functions as a two-electron oxidant in the oxidation of aliphatic alcohols, allylic alcohols, diols, aldehydes, halides, and nitro compounds. The reactions are generally performed in aqueous base using catalytic $[RuO_4]^{2-}$ with persulfate ($S_2O_8^{2-}$) as the secondary oxidant. A typical workup procedure involves either extraction of the solution with ether if the product is a ketone, or acidification of the solution to pH 2 with H_2SO_4, followed by ether extraction if carboxylic acids are produced. The organic extracts are combined and concentrated before passage through a Celite pad to remove any residual Ru. The solvent is then removed under reduced pressure to give the pure ketone or carboxylic acid. Alternatively, phase-transfer conditions[1,4] may be used to effect the oxidation of alkyl halides and alcohols.

Oxidation of Primary Alcohols.

Primary alcohols are oxidized to carboxylic acids by the $[RuO_4]^{2-}/S_2O_8^{2-}$ system (eq 1).[1,3] Under phase-transfer conditions[3] this reagent gives aldehydes in good yields (eq 2).

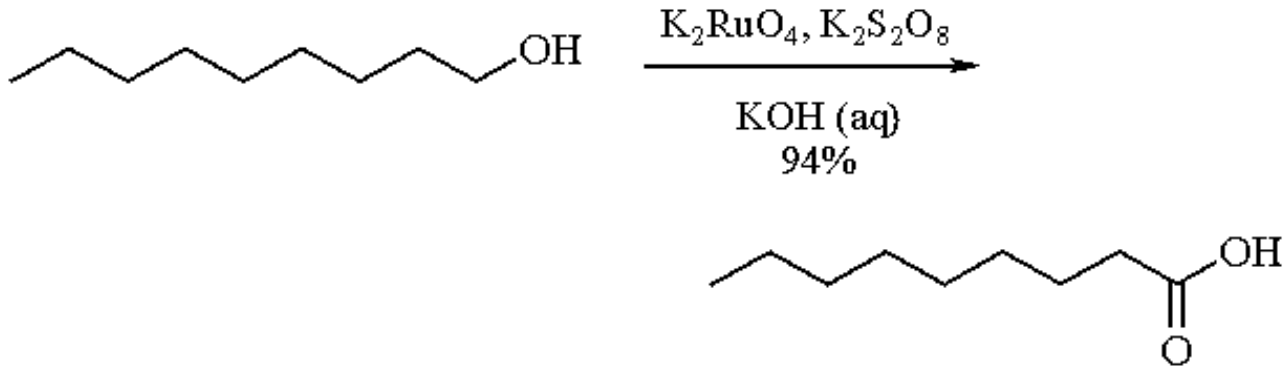

(1)

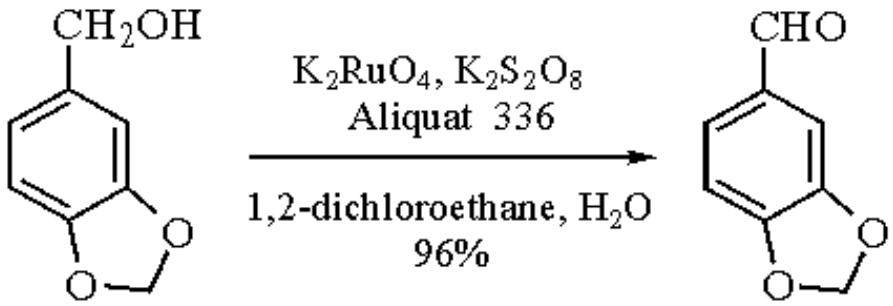

(2)

The rate of oxidation of a series of substituted benzyl alcohols varies according to the electron-withdrawing or -donating capacity of the substituent; the oxidation rate decreases in the order 4-NO_2 > 4-H > 4-OMe.[1] Similar rate effects have been noted for oxidations with CrO_3[6] and $[FeO_4]^{2-}$.[7]

Oxidation of Secondary Alcohols.

Secondary alcohols are oxidized to ketones by catalytic ruthenate in a similar manner (eq 3).[1,3] However, oxidation of secondary alcohols under phase-transfer conditions results in poor yields of the desired ketone.[3]

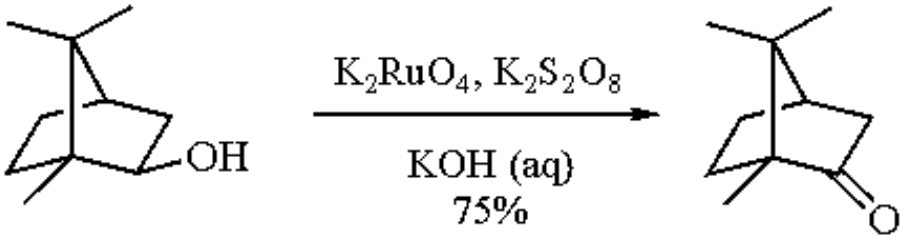

(3)

Oxidation of mandelic acid and hydrobenzoin gives benzoic acid arising from additional carbon-carbon bond cleavage.[1] However, this only occurs with oxidatively sensitive substrates, as oxidation of methyl mandelate proceeds to give the corresponding glyoxylate with no such cleavage.[1]

Allylic Alcohols.

Unlike other two-electron oxidants such as ***Chromium(VI) Oxide***, ***Ruthenium(VIII) Oxide*** and ***Osmium Tetroxide***,[8] catalytic ruthenate exhibits low reactivity towards double bonds and as such is particularly useful for the oxidation of allylic and homoallylic alcohols.[1,9] Thus allyl alcohol[1] and *trans*-cinnamyl alcohol (eq 4)[1,9] are cleanly oxidized to the corresponding unsaturated acids.

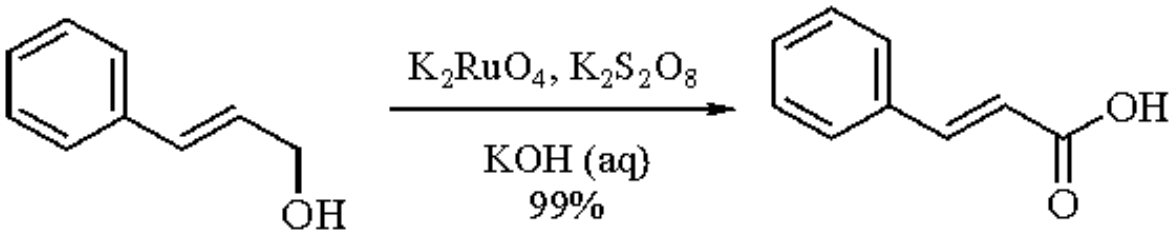

(4)

Diols.

These are oxidized to their corresponding dicarboxylic acids under similar conditions (eq 5).[1,10]

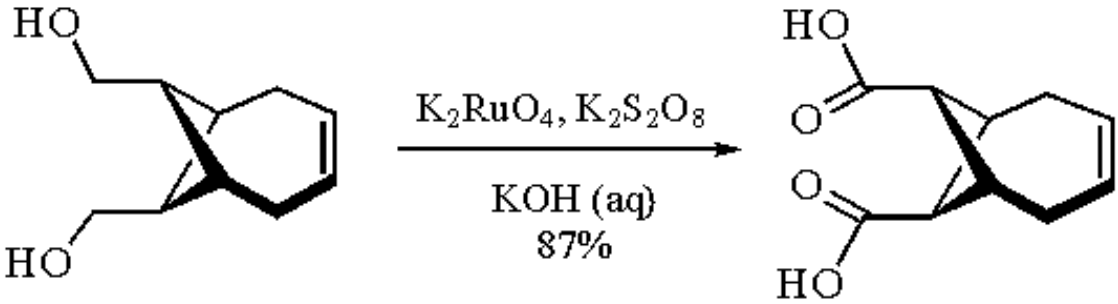

(5)

Aldehydes.

As expected, aldehydes are oxidized to carboxylic acids under both aqueous[1,3,9] and phase-transfer[3] conditions.

Activated Halides.

The best known methods for the oxidation of alkyl halides are the noncatalytic Sommelet or Kornblum reactions.[11] Ruthenate may be used catalytically to effect the (large scale) oxidation of allylic and benzylic primary alkyl halides to acids and secondary halides to ketones.[3]

Nitro Compounds.

Catalytic ruthenate oxidizes primary nitroalkanes to carboxylic acids[3] and on one occasion has been used for the production of a ketone from a secondary nitro compound (eq 6).[2]

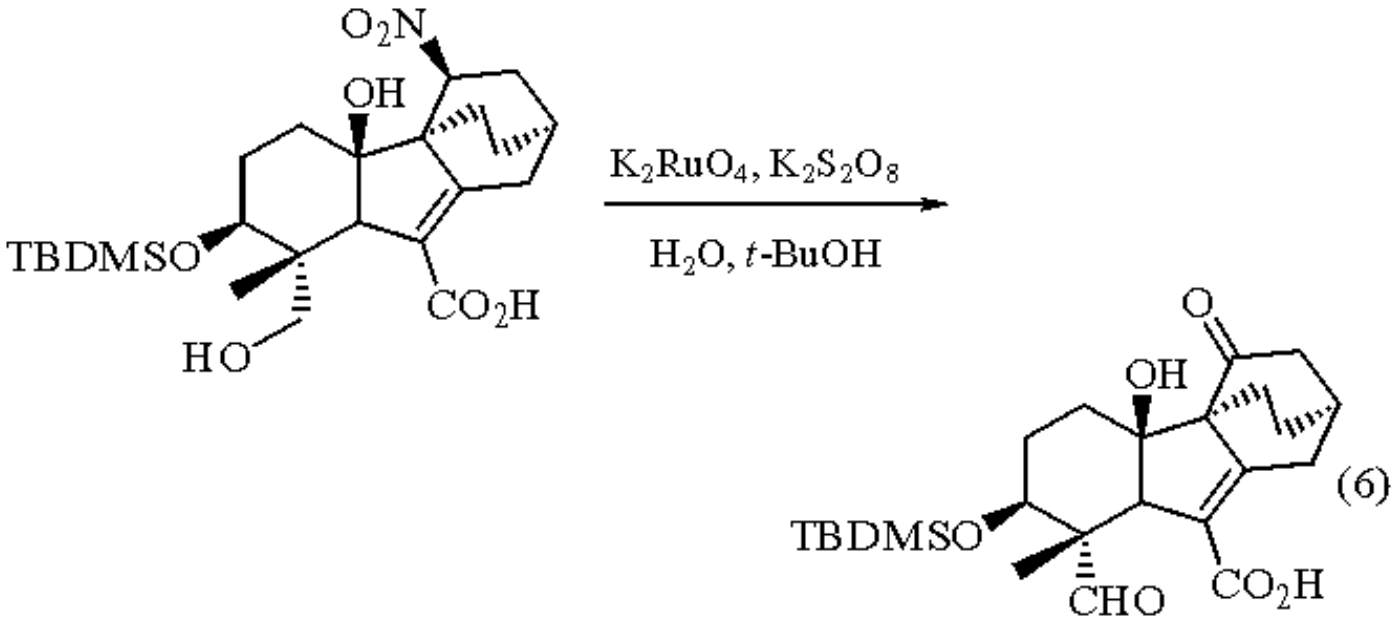

(6)

Selective Oxidations.

Although several reagents for the selective oxidation of allylic and benzylic alcohols have been reported,[12] these oxidants suffer from variable selectivity and lack of general applicability. For example, the widely used reagent ***Manganese Dioxide*** oxidizes aliphatic alcohols in certain cases[13] and even Cr^{VI} reagents such as ***Bis(tetrabutylammonium) Dichromate*** and ***4-(Dimethylamino)pyridinium Chlorochromate*** oxidize primary and secondary alcohols to a significant extent.[12b,c] However, catalytic ruthenate under phase-transfer conditions is a selective oxidant for allylic and benzylic alcohols in the presence of aliphatic alcohols (eq 7).[4]

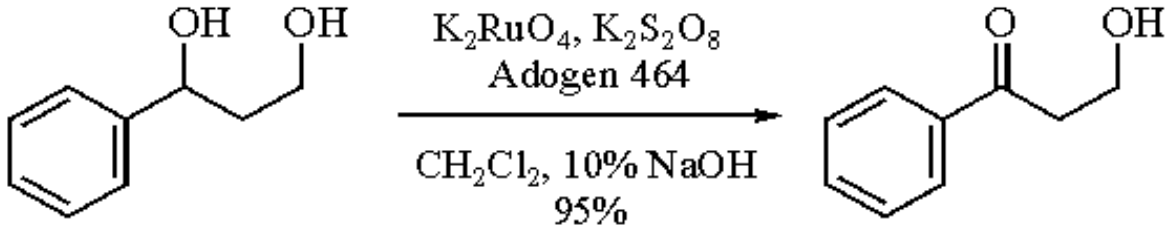

(7)

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Potassium Selenocyanate[1]

KSeCN

[3425-46-5] · CKNSe · Potassium Selenocyanate · (MW 144.08)

(synthesis of organoselenocyanates;[1] deoxygenation of epoxides;[2,3] isomerization of disubstituted alkenes;[4] synthesis of selenoaldehydes and selenoketones;[5,6] in combination with Me_3SiCl, selective cyanosilylation of aldehydes[7])

Physical Data: mp 100 °C; *d* 2.347 g cm^{-3}.

Solubility: sol H_2O, DMF, DME, HMPA, MeCN, MeOH; slightly sol THF.

Form Supplied in: colorless crystalline solid; widely available.

Handling, Storage, and Precautions: crystalline KSeCN is hygroscopic and decomposes with elimination of selenium upon prolonged exposure to air. It should be stored in sealed containers. KSeCN is highly toxic and foul smelling. Use in a fume hood.

Organic Selenocyanates.

Organoselenocyanates are useful synthetic intermediates that participate in a variety of reactions.[1] KSeCN is a versatile reagent for the preparation of organoselenocyanates. Nucleophilic displacement of halides and tosylates with KSeCN is the most convenient route to aliphatic selenocyanates, whereas nucleophilic displacement of diazo group is preferred in aromatic compounds.[1] Owing to the high nucleophilicity of selenium,[8] the selenocyanate ion reacts predominantly at selenium in reactions at electrophilic carbon centers. This reactivity contrasts that of their sulfur analog, the thiocyanate ion, which reacts at both sulfur and nitrogen.[9] Electrophilic substitution reactions involving dicyanodiselenide, $(SeCN)_2$, obtained by oxidation of KSeCN, also have been used for the preparation of organoselenocyanates.[1,10,11] Other known selenocyanate salts include AgSeCN, CsSeCN, $(Me_4N)SeCN$, and $LiSeCN.Et_2O$.[12,13] The latter offers greater solubility compared to KSeCN and could represent a useful alternative source of selenocyanate ion in less polar solvents.[12] Synthetic organic application of KSeCN originate mainly from the synthesis and reactivity of organoselenocyanates. Some potentially promising synthetic organic transformations based on the chemistry of organoselenocyanates derived from KSeCN are summarized below.

Deoxygenation of Epoxides.

Epoxides can be deoxygenated upon treatment with KSeCN in polar protic solvents at 23-65 °C to afford alkenes with retention of configuration (eq 1).[2,3] The reaction depends on the solvent; best results are obtained in polar protic solvents such as H_2O/MeOH, while the reaction fails in aprotic solvents such as DMF and DMSO.[3] The reaction proceeds in high yields for straight chain terminal epoxides, but for cyclic epoxides the reactivity is varied.[3] For instance, reaction of cyclohexene oxide affords cyclohexene in a quantitative yield at 23 °C; however, epoxides of cyclopentene and cyclooctene remain unreacted even after prologed heating at 65 °C.[3] KSeCN-mediated deoxygenation of epoxides has been utilized in the synthesis of (+)-aucantene and other selectively functionalized cyclohexenes.[14]

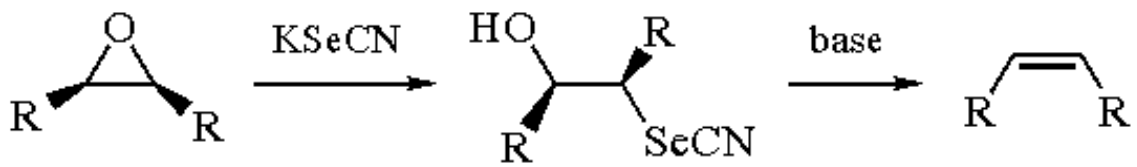

(1)

Isomerization of Disubstituted Alkenes.

Conversion of disubstituted alkenes to bromohydrins followed by sequential treatment with KSeCN in DMF and a base results in overall isomerization of the starting alkenes (eq 2).[4] The reaction of bromohydrin with KSeCN results in nucleophilic displacement of bromide with inversion of configuration to stereospecifically afford the α-hydroxy selenocyanate intermediate, treatment of which with a base

affords the isomerized alkenes.

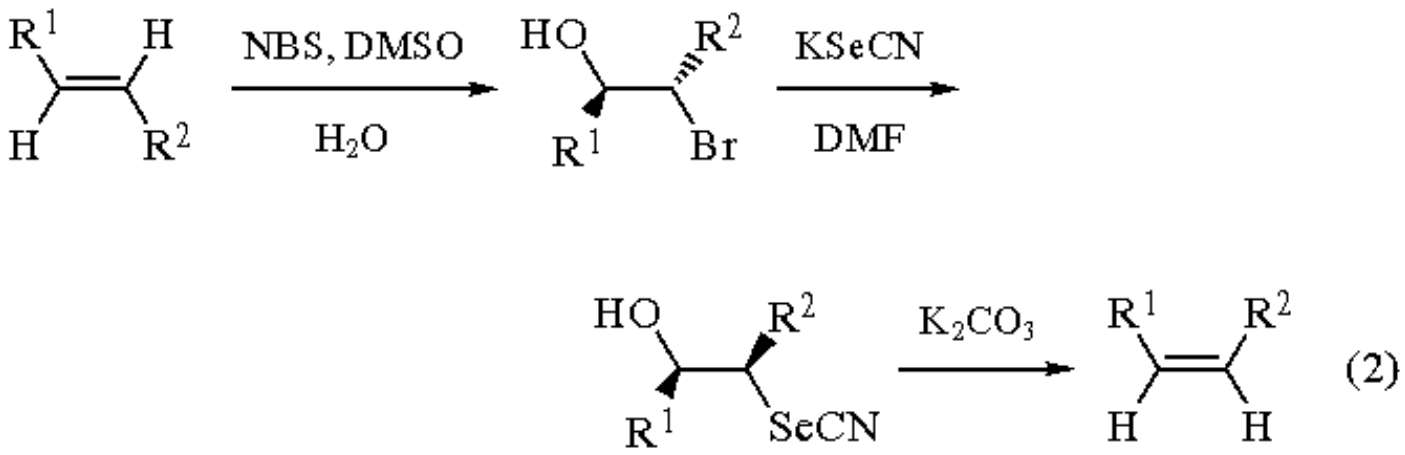

Synthesis of Selenoaldehydes and Selenoketones.

Certain organoselenocyanates derived from KSeCN undergo fluoride-[5] and base-induced[5,6] elimination of cyanide to afford highly reactive selenocarbonyl intermediates (eqs 3 and 4). These selenocarbonyl intermediates exhibit rich cycloaddition chemistry (Diels-Alder and 1,3-cycloadditions) to afford selenium-containing heterocycles.[5,6]

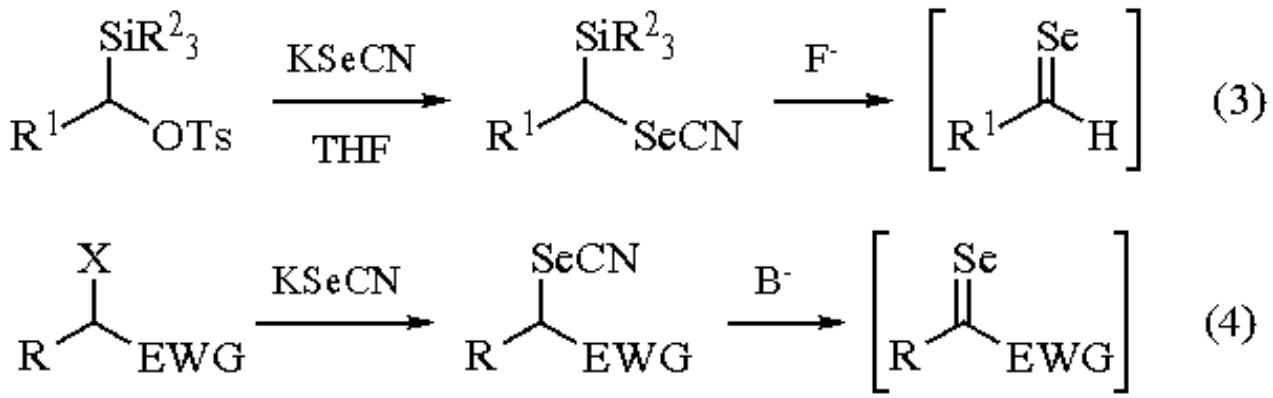

Selective Cyanosilylation of Aldehydes.

Trimethylsilylisoselenocyanate ($Me_3SiNCSe$), generated in situ from the reaction of KSeCN with ***Chlorotrimethylsilane***, can be used for the chemoselective cyanosilylation of aldehydes in presence of a catalyst (eq 5).[7] Higher reactivity and yields are obtained in hexane with ***Zinc Chloride*** catalysis. Ketones do not undergo this reaction.

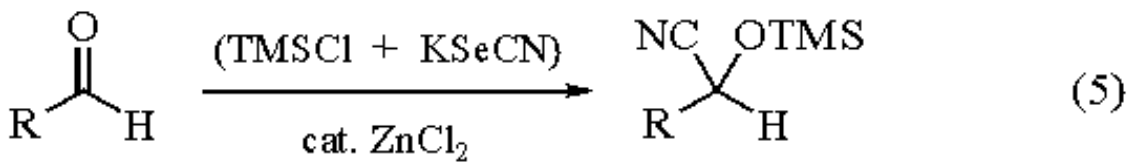

Related Reagents.

Potassium Thiocyanate; ***Sodium Thiocyanate***; ***Isoselenocyanatotrimethylsilane***.

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Potassium 9-Siamyl-9-boratabicyclo[3.3.1]nonane[1]

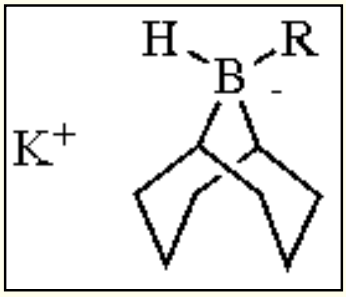

(R = siamyl, 3-methyl-2-butyl)

[125392-39-4] · $C_{13}H_{26}BK$ · Potassium 9-Siamyl-9-boratabicyclo[3.3.1]nonane · (MW 232.30) (R = *n*-Bu)

[119875-90-0] · $C_{12}H_{24}BK$ · Potassium 9-Butyl-9-boratabicyclo[3.3.1]nonane · (MW 218.27) (R = *t*-Bu)

[119875-89-7] · $C_{12}H_{24}BK$ · Potassium 9-*t*-Butyl-9-boratabicyclo[3.3.1]nonane · (MW 218.27)

(selective reducing agent for ketones[2] and aromatic nitriles to aldehydes[3])

Physical Data: colorless in THF solution.

Solubility: sol THF; evolves hydrogen in protic solvents.[1]

Analysis of Reagent Purity: the reagents exhibit typical upfield ^{11}B NMR resonances in THF (e.g. KHR-9-BBN: R = *n*-Hx, δ -13.2 (d, J_{B-H} = 70 Hz); R = Ipc, -6.1 (d, J_{B-H} = 73 Hz); R = *t*-Bu, -10.4 (t, J_{B-H} = 75 Hz) ppm).[2,4]

Preparative Methods: prepared as stable THF solutions from the reaction of a purified suspension of ***Potassium Hydride*** in THF with the appropriate *B*-alkyl-9-BBN.[4] KH is purified by removal of the mineral oil by successive pentane washing and decantation of the supernatant under an inert atmosphere, treatment with a solution of ***Lithium Aluminum Hydride*** in THF followed by additional washings with fresh dry THF. This provides KH which reacts with *B*-alkyl-9-BBN in THF to form the borohydrides in <30 min at 25 °C. It is recommended that the initial addition be carried out at 0 °C to prevent an exothermic reaction with unhindered derivatives. Stable solutions of $KHB(O\text{-}i\text{-}Pr)_3$ can be used stoichiometrically to prepare KHR-9-BBN from *B*-R-9-BBN or, alternatively, as a catalyst for the KH method.[5]

Handling, Storage, and Precautions: THF solutions of the reagent are indefinitely stable at 25 °C when stored under a nitrogen atmosphere. Exposure to atmospheric oxygen, moisture, or protic solvents results in its potentially dangerous rapid oxidation and/or the exothermic generation of hydrogen gas. The generation and use of KHR-9-BBN involves the handling of dangerously pyrophoric or flammable reagents (i.e. KH, $LiAlH_4$, or *B*-R-9-BBN). Individuals should thoroughly familiarize themselves with the special handling techniques required for such reagents prior to their

use.[1] The reagent should be used in a well ventilated hood.

Selective Reduction of Ketones.

Cyclic and bicyclic ketones are quantitatively reduced to the corresponding alcohols with KHR-9-BBN reagents, the diastereofacial selectivities being determined both by steric and conformational effects in the substrate and the steric bulk of the *B*-R substituent in the reagent (eq 1).[2] Thus KH(*t*-Bu)-9-BBN exhibits selectivities which are comparable to the high selectivity ***Lithium Trisiamylborohydride*** reagent, exceeding those of less hindered borohydrides such as ***Lithium Tri-s-butylborohydride*** or KH(OR)-9-BBN.

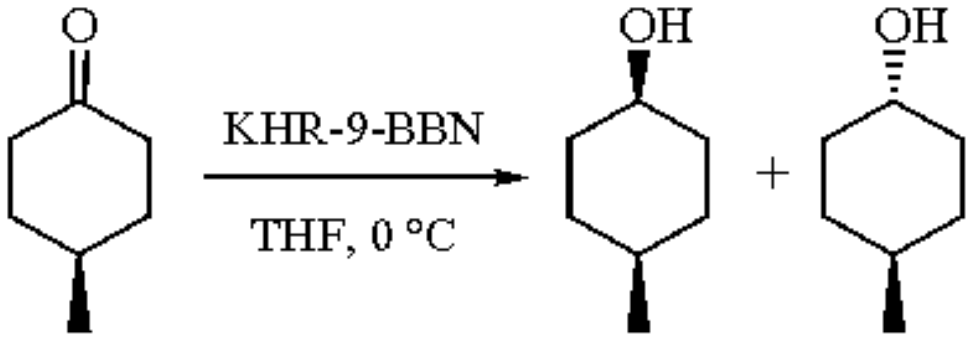

(1)

R		
Bu	61	39
Sia	90	10
t-Bu	94	6

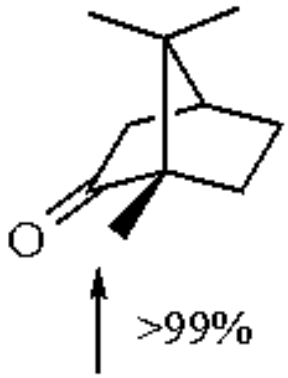

Aldehydes from Nitriles.

Aromatic nitriles are efficiently reduced to aldehydes (60-98%) with 1 equiv of KH(Sia)-9-BBN (24 h, 25 °C; eq 2).[3] In competitive experiments, the selective reduction of aromatic nitriles can be accomplished in the presence of their aliphatic counterparts which are recovered intact. The reagent also readily reduces acid chlorides, esters, lactones, aldehydes, ketones, and epoxides to the corresponding alcohols. Amines, carboxylic acids, oximes, and aliphatic nitro compounds are not reduced.[2b]

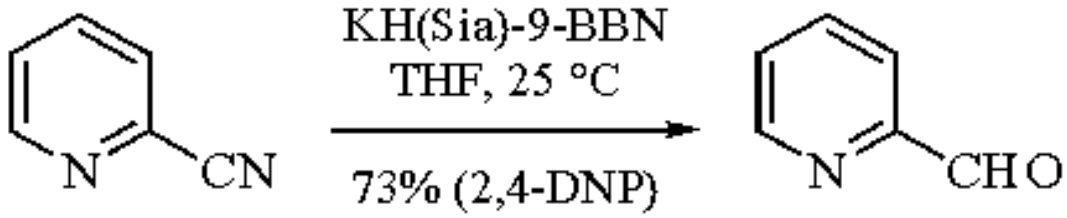

(2)

Related Reagents.

Lithium 9-boratabicyclo[3.3.1]nonane; ***Lithium Tri-s-butylborohydride***; ***Lithium Trisiamylborohydride***.

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Potassium Sodium Tartrate[1]

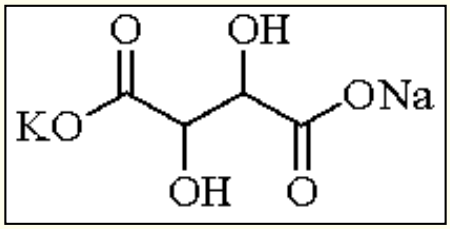

[304-59-6] · $C_4H_4KNaO_6$ · Potassium Sodium Tartrate · (MW 210.17) (.4H_2O)

[6381-59-5] · $C_4H_{12}KNaO_{10}$ · Potassium Sodium Tartrate · (MW 282.25)

(chelating agent for metal ions)

Alternate Names: Rochelle salt; Seignette salt.

Physical Data: tetrahydrate:[1c] mp 70-80 °C; loses 3H_2O at 100 °C; becomes anhydrous at 130-140 °C; dec 220 °C; *d* 1.79 g cm^{-3}. The physicochemical properties of this tartrate salt are well documented.[1b]

Solubility: (g 100 mL^{-1} H_2O) 42 at 0 °C, 82 at 16 °C, 140 at 29 °C, 225 at 40 °C;[11] insol alcohol.

Form Supplied in: the tetrahydrate is widely available as translucent crystals or as a white crystalline solid.

Analysis of Reagent Purity: by nonaqueous titration.[2]

Purification: can be recrystallized from a chilled solution of distilled H_2O.[3]

Handling, Storage, and Precautions: purgative; reactions should be performed in a well-ventilated fume hood.

Introduction.

Tartrate esters and metal salts of tartaric acid have found increasing synthetic use as metal chelating agents. Although Rochelle salt has been extensively studied with regard to its electrical, magnetic, and optical properties, and has found industrial utility, e.g. in photography, ceramics, electrodeposition, and analytical spectrophotometry, its use in organic synthesis has been limited. It is perhaps best known as a constituent of Fehling's solution (alkaline copper(II) tartrate), the classic reagent for the characterization of aldehydes.[1a,4]

Chelating Agent.

The complexing ability of the tartrate ion has been utilized in the workup of reactions involving metal alkoxides. For example, in the Oppenauer oxidation of cholesterol,[5] a saturated aqueous solution of Rochelle salt was used to keep the resulting aluminum byproduct in the aqueous layer during the workup (eq 1). The Δ^4-cholesten-3-one was thus readily isolated by extraction and subsequent crystallization in ca. 80% yield.

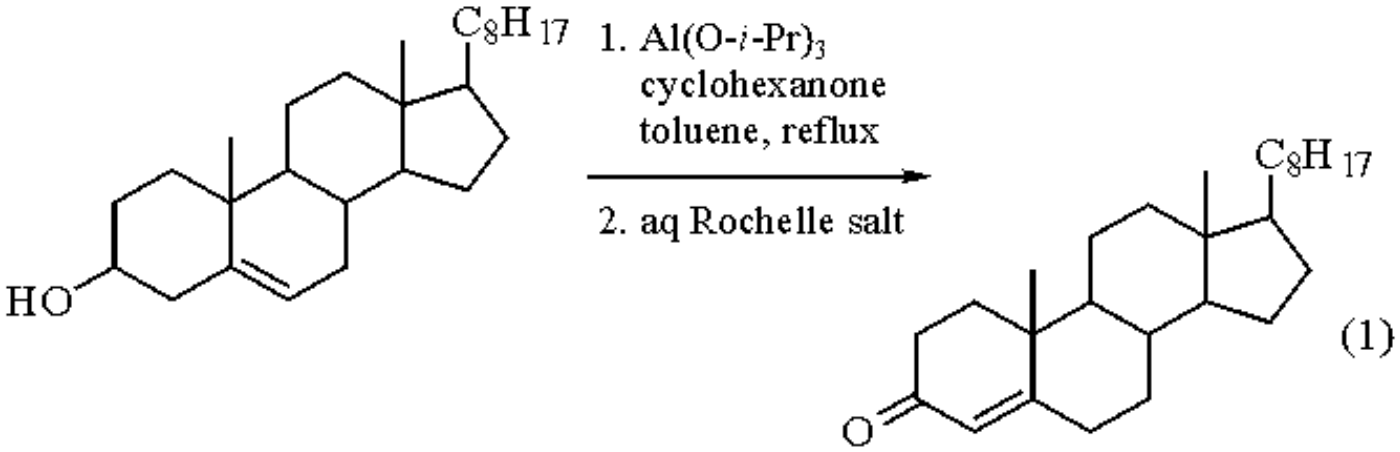

In a later study,[6] after reduction of the cholesten-3-one was accomplished with ***Lithium Tri-t-butoxyaluminum Hydride***, the resulting mixture was hydrolyzed with ice-cold alkaline Rochelle salt (eq 2). The resulting Δ^4-cholesten-3β-ol was easily extracted with ether in 87% yield.

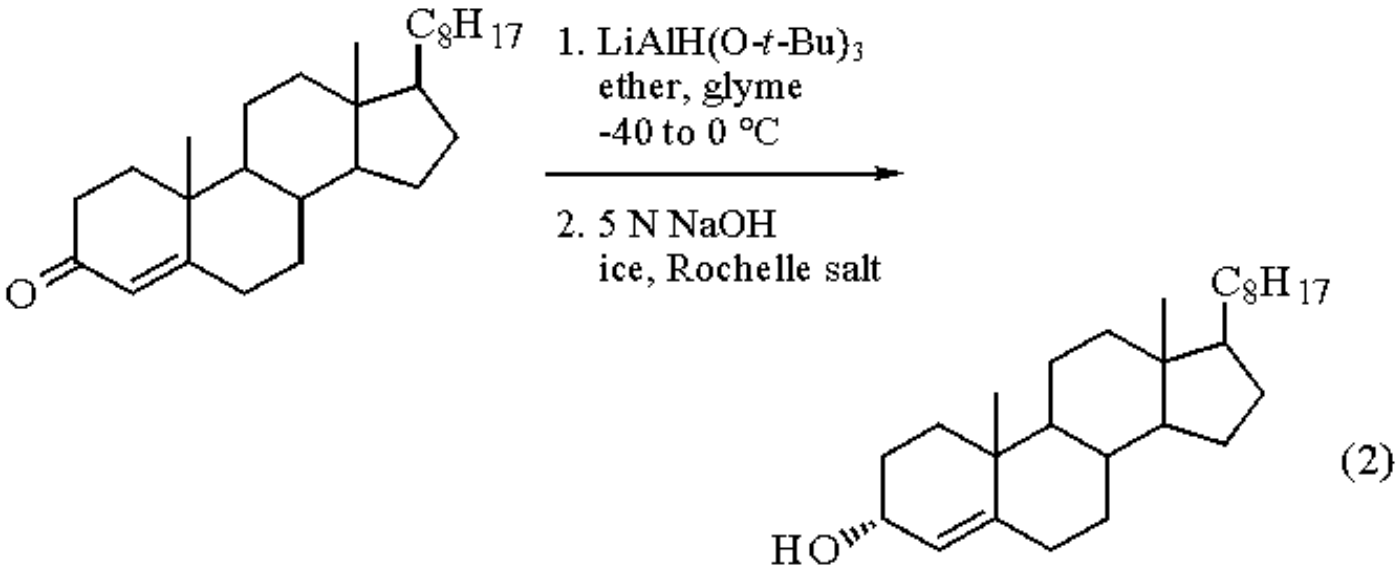

With Rochelle salt workup, 6α-methylandrost-4-ene-3,17-dione has been prepared from the corresponding 5α-hydroxy-6β-methylandrostane derivative in the presence of ***Aluminum t-Butoxide*** (eq 3).[7] Isolation of the ***Lithium Aluminum Hydride*** reduction products of α-silyl esters (eq 4) is also facilitated by ice-cold aqueous Rochelle salt.[8]

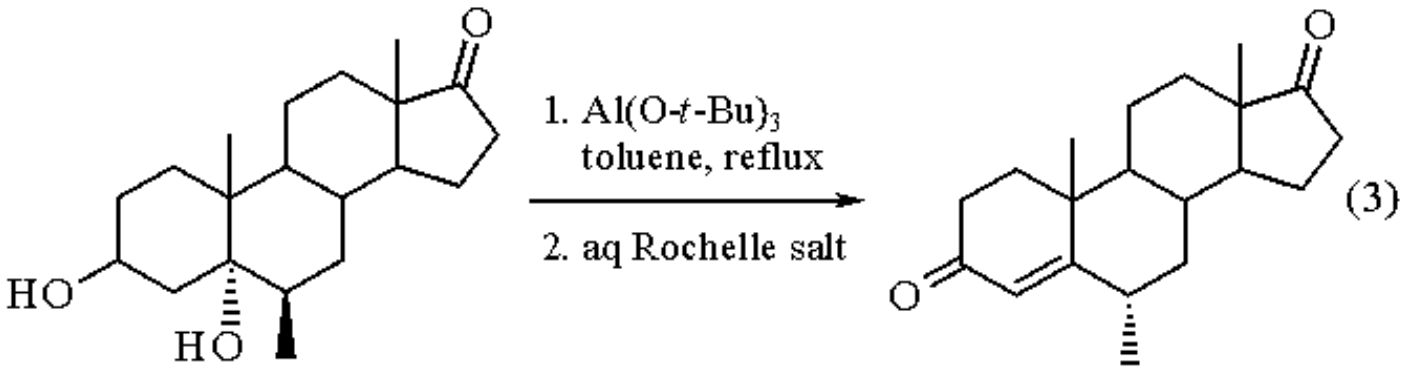

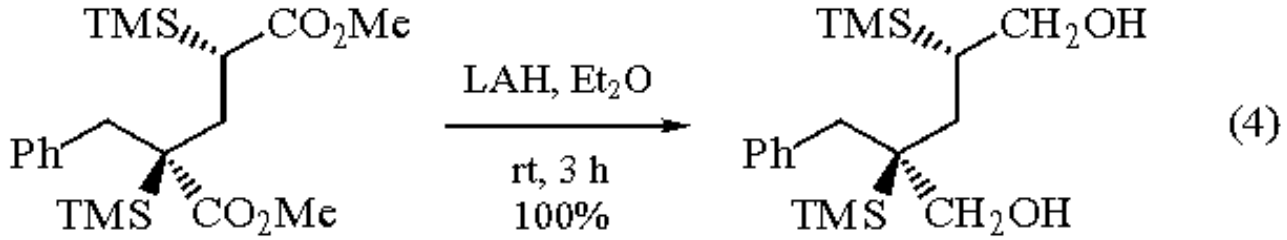

In a synthesis of a leukotriene antagonist, introduction of the required asymmetric center was achieved by chiral reduction of the ketone precursor with (-)-*B*-chlorodiisopinocampheylborane eq 5).[9] Acetone quenching and addition of 20% aqueous Rochelle salt solution allowed isolation of the product alcohol in 87% yield.

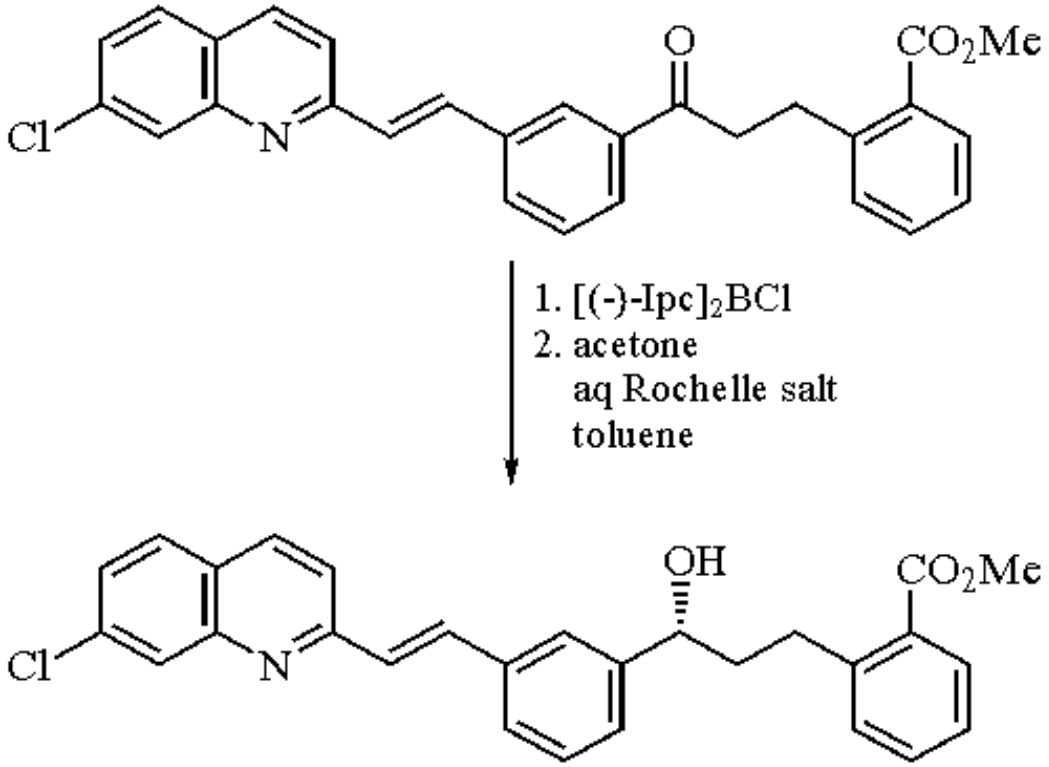

(5)

Chiral Metal(II) (+)-Tartrate Lewis Acids.

A number of metal(II) tartrates synthesized from Rochelle salt have found recent use as heterogeneous chiral Lewis acid catalysts in the asymmetric ring-opening reactions of *meso*-epoxides (eqs 6 and 7).[10] Thiols, aniline, and trialkylsilyl azides give the corresponding adducts in varying chemical yields and enantiomeric excess using 10 mol % concentrations of metal (+)-tartrate catalyst.

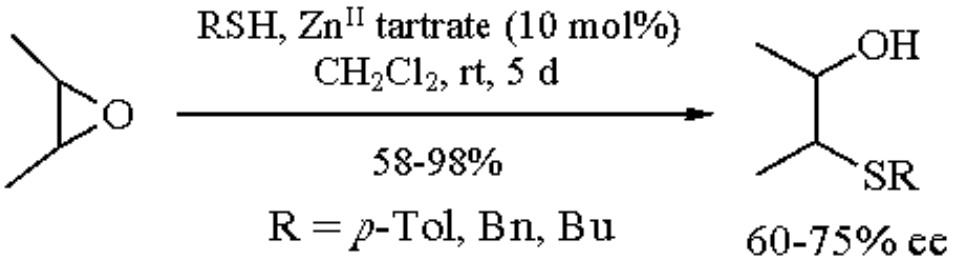

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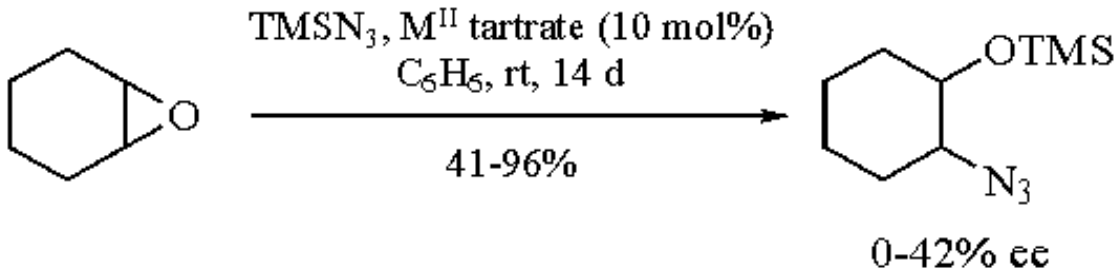

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Potassium Superoxide[1]

KO_2

[12030-88-5] · KO_2 · Potassium Superoxide · (MW 71.10)

(reactive species is the superoxide anion, O_2^-; solubility of KO_2 in aprotic organic solvents is facilitated by crown ethers[2,3] or other phase-transfer catalysts;[4] O_2^- reacts with most organic substrates either as an anion or as an electron-transfer (reducing) agent; reacts as a nucleophilic anion toward alkyl halides, sulfonates, and carbonyl groups; other net displacement reactions such as with halocarbons may be initiated by electron transfer; reacts as a basic anion toward substrates bearing acidic protons; used in situ with a variety of activated halogens to form peroxy anions useful for further oxygen transfer, e.g. epoxidations[1])

Physical Data: mp 500 °C.[5]

Solubility: slightly sol DMSO; crown ethers are useful for bringing KO_2 into organic solvents such as DMSO,[2] DMF, MeCN, THF, benzene;[3] reacts rapidly with H_2O and protic solvents.

Form Supplied in: small chunks of light yellow powdery solid.

Handling, Storage, and Precautions: chunks of solid may be handled briefly in the atmosphere; prolonged exposure to the atmosphere results in reaction with H_2O; storage should be under dry conditions such as a desiccator; reaction with H_2O produces O_2, H_2O_2, and OH^-.

Dialkyl Peroxide Synthesis.

Primary and secondary alkyl bromides[9] and alkyl sulfonates react with KO_2 in aprotic organic solvents (except DMSO, see below), giving acyclic (eq 1)[3,10] and cyclic (eq 2)[11] dialkyl peroxides. The reactions are greatly facilitated by the addition of crown ethers or other phase-transfer catalysts to the reaction medium. The reaction at secondary carbon atoms proceeds with >95% inversion of configuration[3,12] and is accompanied by formation of significant amounts of alkene due to elimination reactions. Because of the mechanism by which the dialkyl peroxides are generated, this method is best suited for synthesis of symmetrical dialkyl peroxides.

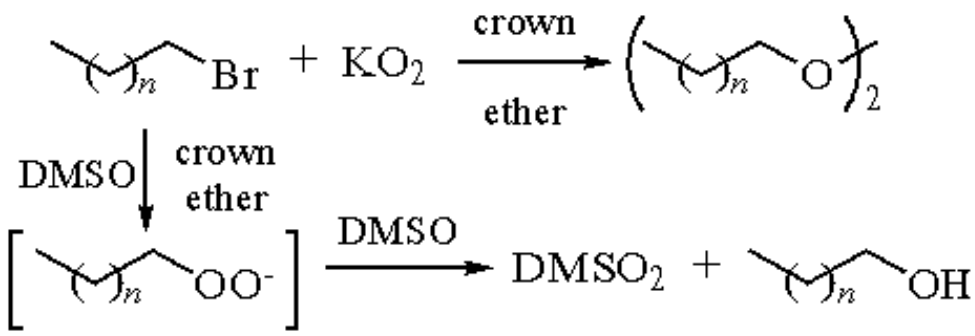

(1)

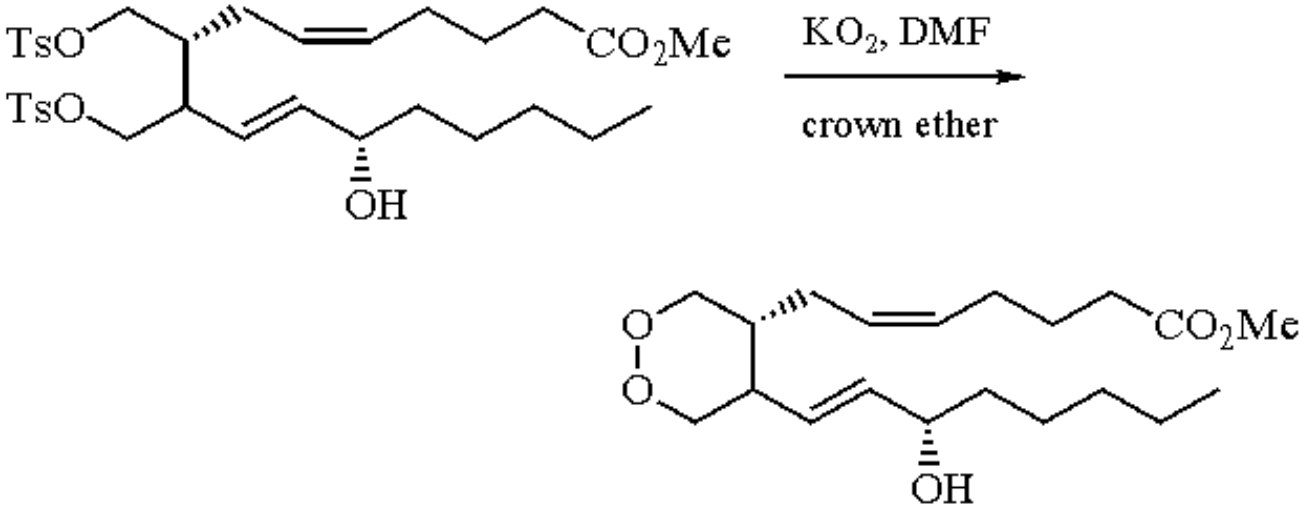

(2)

Alcohol Inversion.

When the reaction between alkyl bromides or alkyl sulfonates and KO_2 is performed in DMSO, the major product is an alcohol[12] as a consequence of oxygen transfer from the intermediate peroxy anion to the DMSO (eq 1).[13] Such displacements of tosylate (eq 3)[14] or mesylate (eqs 4 and 5)[15,16] by KO_2 in DMSO have been used for inversion of the configuration of secondary alcohols and this method is of comparable efficiency to the modified[18] Mitsunobu sequence[17] used for the same purpose.

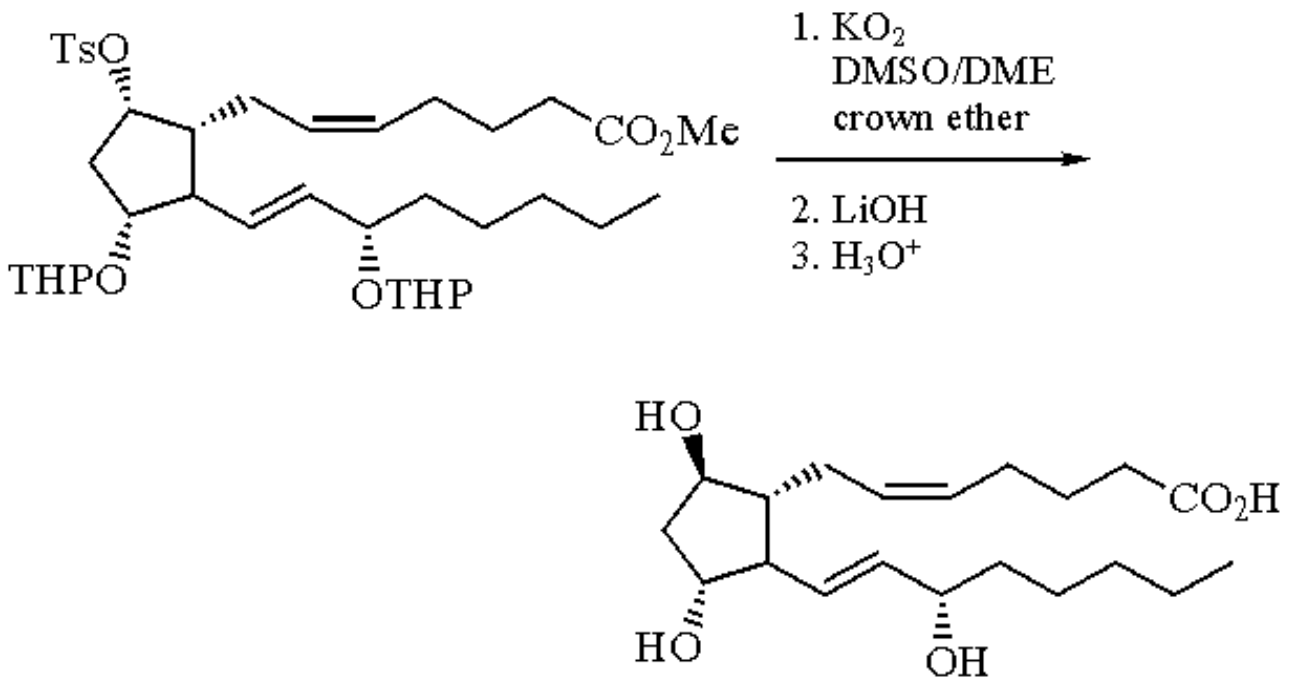

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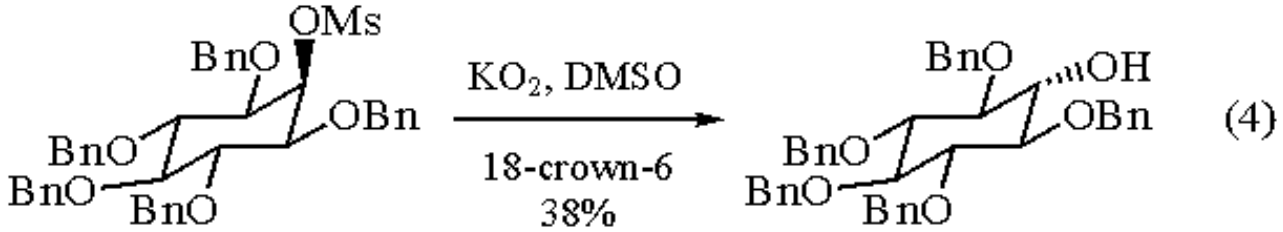

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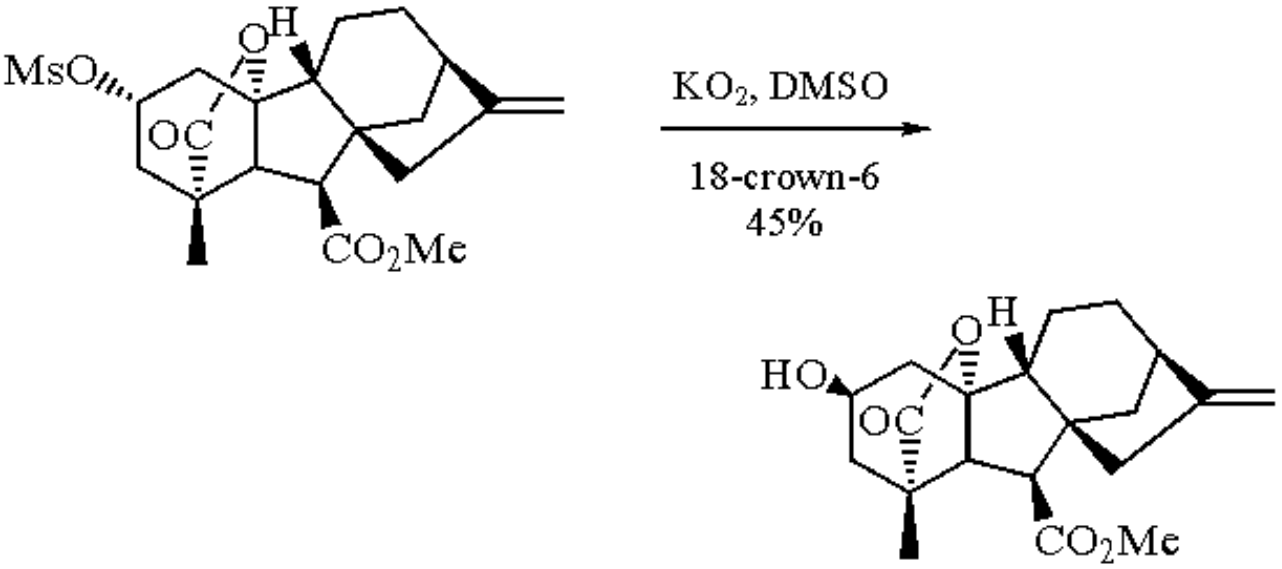

(5)

Ester Cleavage.

Carboxylic acid esters are cleaved by O_2^-, giving the corresponding carboxylic acid and alcohol.[19] Several studies of the mechanism of this process have been reported.[20] Qualitatively, displacement of halide or sulfonate ester occurs in preference to ester hydrolysis (see eq 2). The use of KO_2 for ester cleavage generally offers no advantage over conventional ester saponification methods.

Diacyl Peroxide Synthesis.

Acid chlorides react with O_2^- to give diacyl peroxides,[21] which in turn are susceptible to further reaction with O_2^-.[22] Acyl peroxy anions are formed as intermediates in the reactions with acid chlorides and diacyl peroxides as well as in the reaction of O_2^- with anhydrides as detected by epoxidation of alkenes.[22] Applications of this approach to oxygen-transfer chemistry is discussed further below. Eq 6 summarizes the primary events but is an incomplete account of all the reactions occurring between O_2^- and these substrates. Amides, aldehydes, and nitriles are unreactive with KO_2 under most conditions.

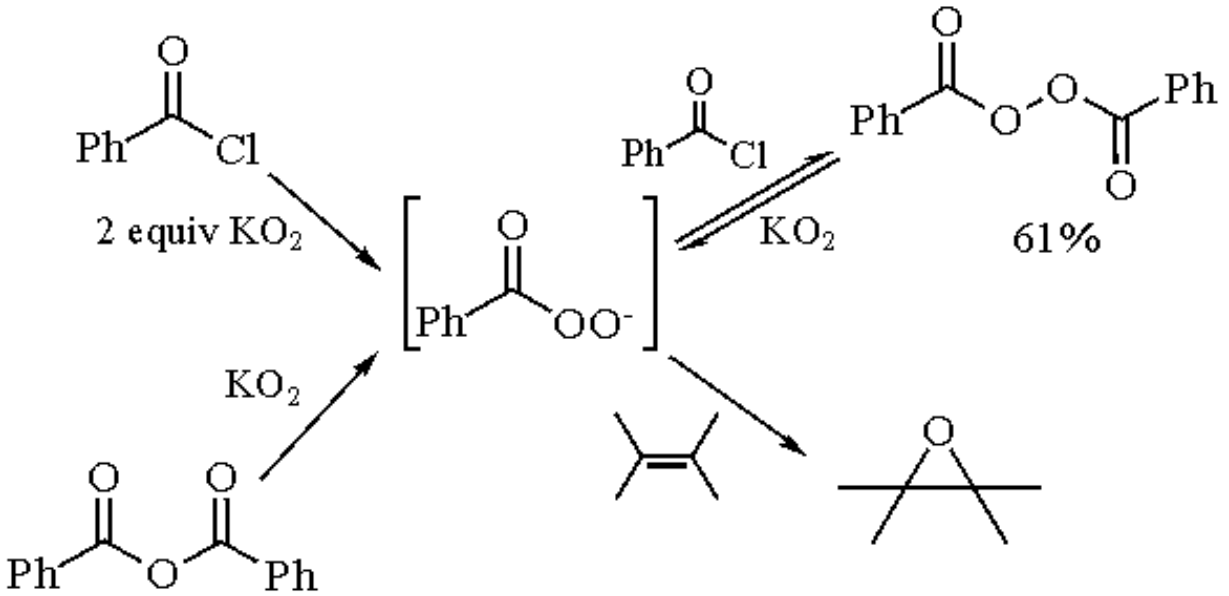

(6)

Oxygen Transfer via Peroxy Anions.

A number of reagents react with superoxide to form transient peroxy anions which oxidize electrophilic functional groups such as alkenes, sulfides, sulfoxides, etc. Among the reagents forming peroxy anions useful in such oxidations are aryl sulfonyl halides[23] (especially 2-nitrobenzenesulfonyl chloride[24]), acid chlorides,[22,25] halocarbons such as carbon tetrachloride,[26] dialkyl chlorophosphates[27] and alkyl dichlorophosphates,[28] carbon dioxide,[29] *N*-(-)-menthoxycarbonyl-4-tolylsulfonimidoyl chloride,[30] and phosgene.[31] Representative examples of oxidations by these systems include the epoxidation of limonene (eq 7),[24] the oxidation of sulfides to sulfoxides (eq 8),[32] selective oxidation of sulfoxides to sulfones in the presence of alkenes (eq 9),[33] oxidation of benzylic methylenes to ketones (eq 10),[34] and

cleavage of tosylhydrazones to ketones or aldehydes (eq 11).[35]

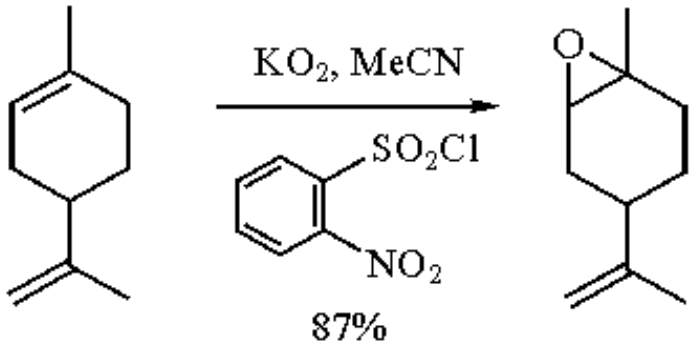

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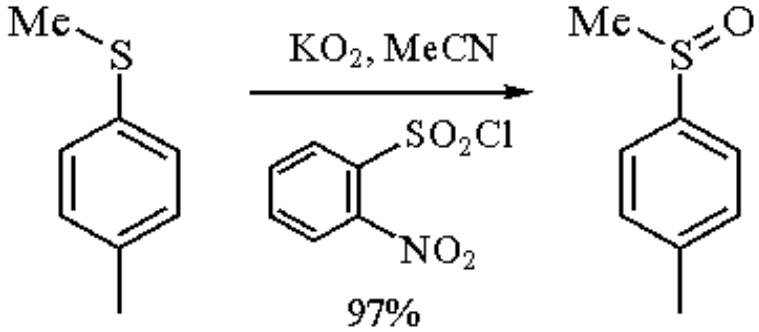

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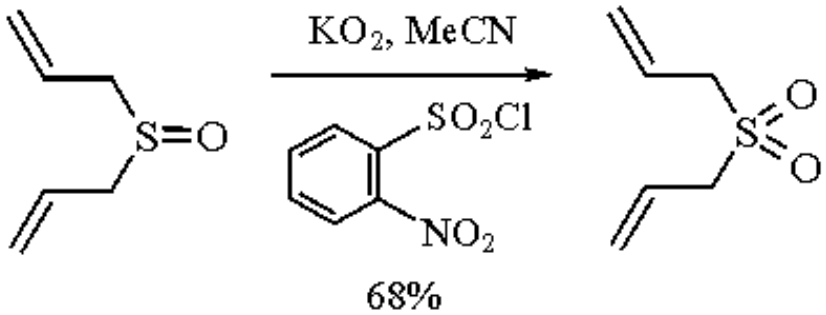

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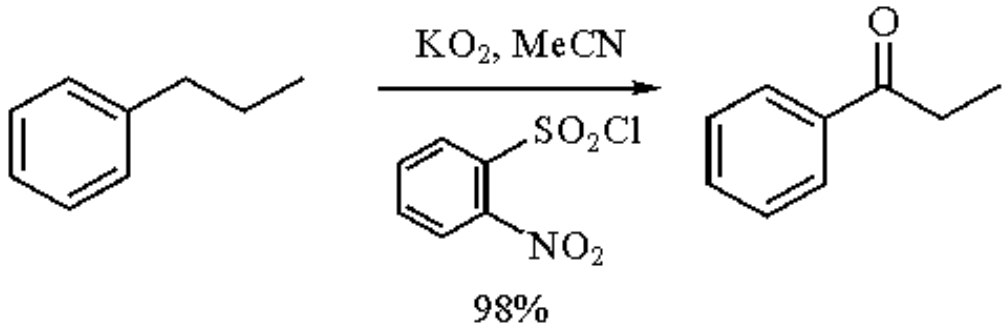

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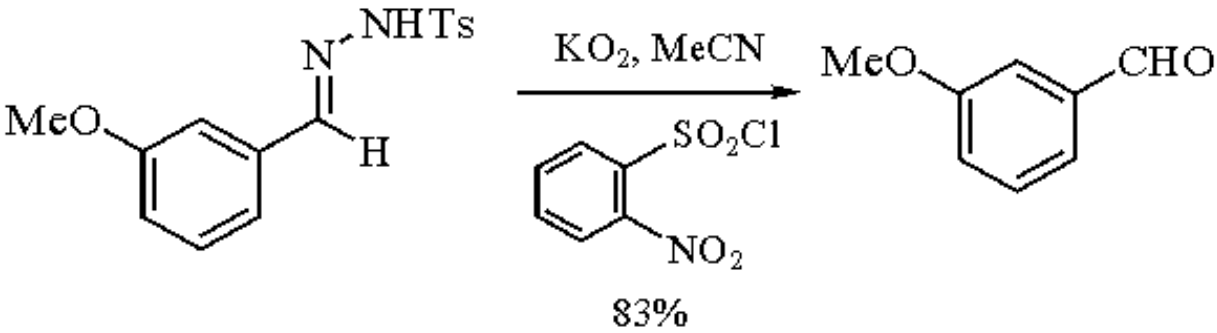

(11)

These approaches to oxygen transfer have not been tested beyond the original reports. Comparisons with other established oxygen-transfer reagents such as the peracids (e.g. ***m-Chloroperbenzoic Acid***) and the dioxiranes (e.g. ***Dimethyldioxirane***) still must be explored.

Electron-Transfer Chemistry.

Certain reactions of O_2^- whose net result appears to be that of either a nucleophilic addition or displacement reaction, instead may be the result of an electron transfer followed by capture of oxygen, giving the peroxy radical. Oxygen labeling experiments are necessary to distinguish between the two mechanisms.

Nucleophilic Displacement of Aromatic Halides.

Aromatic halides substituted with electron-withdrawing groups undergo nucleophilic displacement by KO_2[36] (eq 12)[37] as well as by electrochemically generated O_2^-.[38] Yields of phenols are generally good to excellent in these reactions.

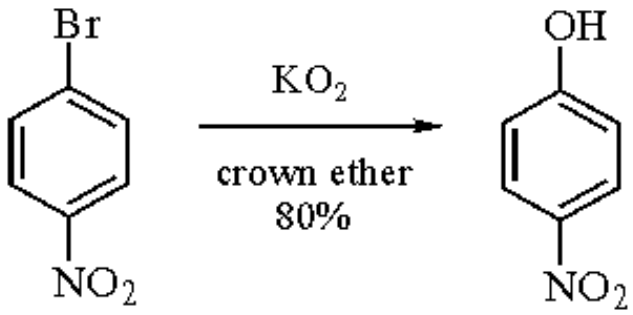

(12)

Reactions with Electron-Deficient Alkenes.

cis-2,2,6,6-Tetramethylhept-4-en-3-one, a molecule designed as a probe for electron transfer, is isomerized to the *trans*-enone by KO_2, consistent with electron transfer from reagent to the enone.[39] Cyclohexenone is epoxidized (30% yield) by electrochemically generated superoxide anion,[10] but is converted to a trimeric ketone structure with KO_2.[40] Other cyclohexenones react with KO_2 only when acidic protons are present in the molecule, and then are transformed into mixtures of oxidized products.[40] The cyclohexenone system of cholest-4-en-3-one reacts with KO_2 to give a mixture of at least five oxidation products.[41] Chalcones react with KO_2 in a series of steps initiated by electron transfer to yield aryl carboxylic acids (52-72%) (eq 13).[42] A series of alkenes highly substituted with electron-withdrawing groups (e.g. 1,2-diphenyl-1-nitroethylene) react with KO_2 yielding products of oxidation, e.g. benzoic acid (85%) (eq 14).[43] The conversions by KO_2 of tetraarylcyclopentadienones to 2-hydroxy-2,4,5-triarylfuran-3-ones[44] or to furan-3-ones, 3,4,5,6-triarylpyran-2-ones, and carboxylic acids[45] are initiated by electron transfer.

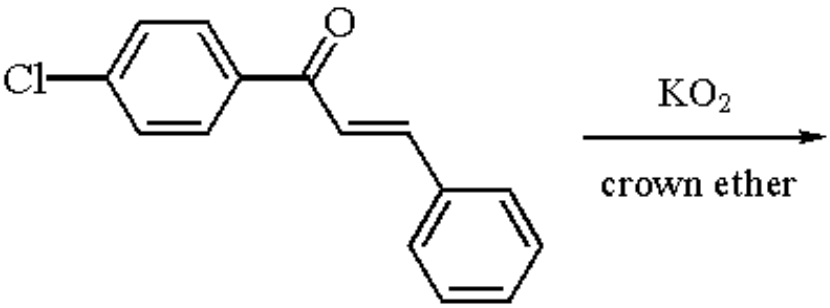

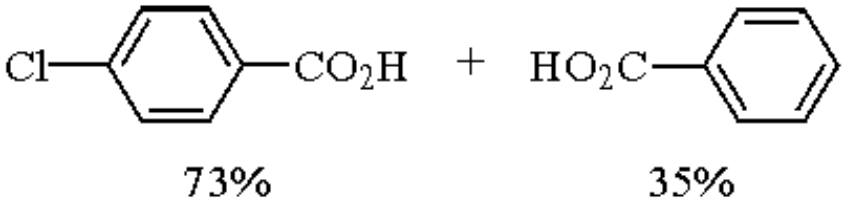

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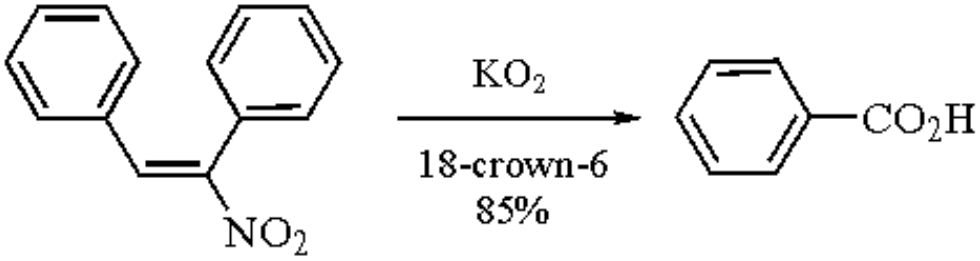

(14)

Reactions with Anilines.

Aniline, various substituted anilines, and α-naphthylamine do not react with KO_2 suspended in THF at 80 °C,[46] but several anilines are converted into azobenzenes by KO_2 in benzene containing a crown ether[47,48] or in DMSO.[49] Both *o*- and *p*- but not *m*-phenylenediamines are converted into azobenzenes by KO_2 suspended in THF or pyridine as shown in eq 15. Both *o*- and *p*-aminophenol likewise are transformed into azobenzenes[46] (**Caution**: two laboratories have reported violent explosions of mixtures containing *o*-aminophenol and KO_2 in either THF or toluene[50]). 2-Mercaptoaniline with KO_2 gives 2,2´-dithiobisaniline in 85% yield,[46] the result of coupling of the thiol rather than of the amine substituent.

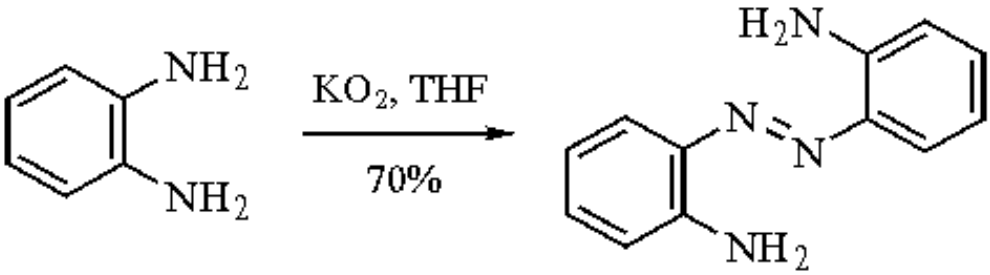

(15)

Reaction with Thiols.

Under mild conditions (suspension of KO_2 in toluene), thiophenols and aliphatic thiols are converted into disulfides by KO_2 (eq 16).[51] Under more vigorous reaction conditions (elevated temperature[51] or KO_2/crown ether in pyridine[52]) these thiols are converted into sulfonic acids. Certain thiols (e.g. 2-mercaptophenol) are transformed into sulfonic acids even under the mild reaction conditions. Ethane-1,2-dithiol and propane-1,3-dithiol are converted under mild conditions into the cyclic disulfides 1,2,5,6-tetrathiocan and 1,2,6,7-tetrathiothiecan (eq 17), respectively, while butane-1,4-dithiol forms 1,2-dithian by reaction with KO_2.[51]

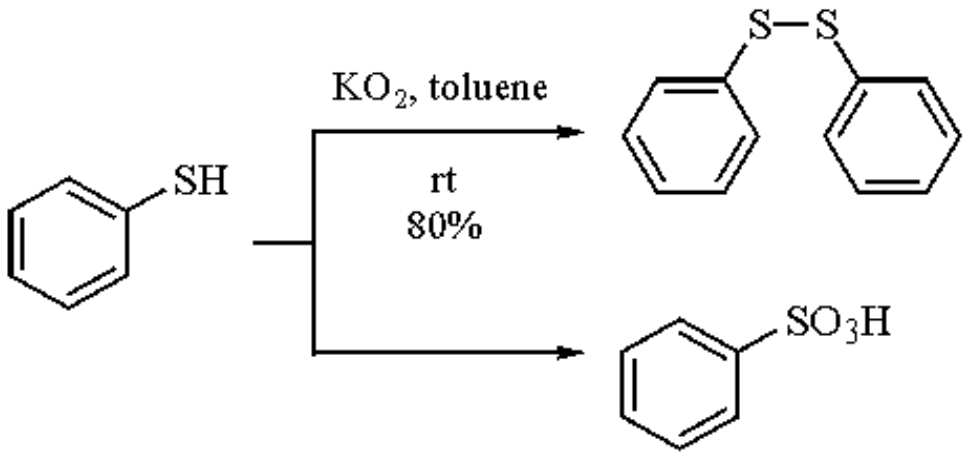

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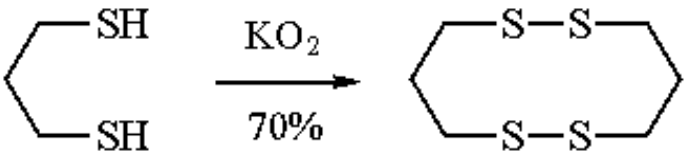

(17)

Reactions with Phenols, including Catechols and Tocopherols.

Monophenolic compounds do not generally undergo any net change with KO_2. Naphthalene diols react with KO_2 suspended in a toluene-pyridine mixture under an inert atmosphere to form mono- or dihydroxynaphthoquinones in good yields (eq 18).[53]

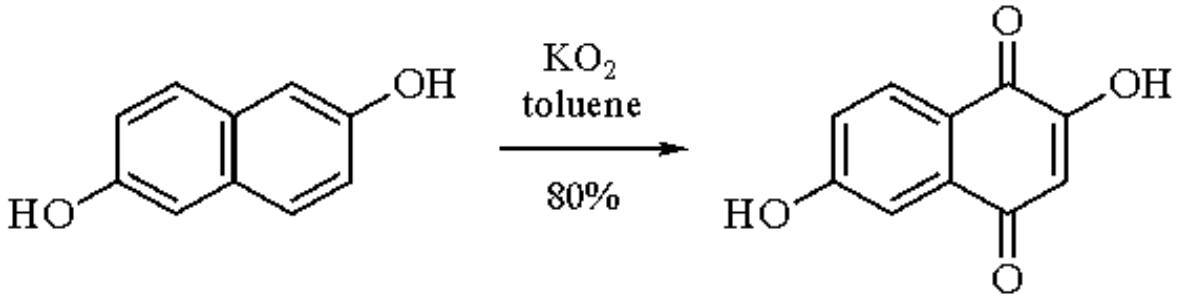

(18)

Catechols are first oxidized to *o*-quinones upon treatment with KO_2 followed by further oxidation to a variety of products.[54,55] Catechol itself is converted to *cis,cis*-muconic acid in very low yields accompanied by much polymeric byproduct. 9,10-Dihydroxyphenanthrene is converted to diphenic acid in good yield (90%). 3,5-Di-*t*-butylcatechol is converted to a mixture of oxidized products. The tocopherol model compound 2,2,5,7,8-pentamethylchroman-6-ol is converted by KO_2 suspended in THF into 6-hydroxy-2,2,6,7,8-pentamethylchroman-5(6*H*)-one (20%)[56] but, with a solution of KO_2 in AcCN, a low yield (12%) of a diepoxide together with as many as six other compounds are isolated.[57] The analogous diepoxide together with a complex mixture was isolated from the reaction of tocopherol with KO_2.[57]

Miscellaneous Transformations.

Practical syntheses of ethyl glyoxylate (72%) and diethyl oxomalonate (83%, via diethyl cyanomalonate) from ethyl cyanoacetate with electrochemically generated superoxide have been reported, as shown in eq 19.[58]

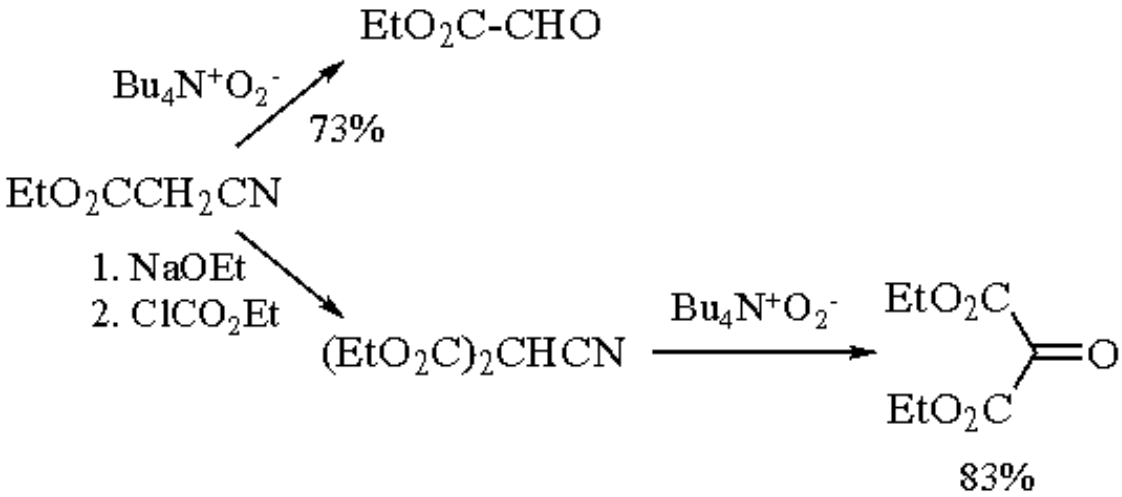

(19)

Aromatic nuclei to which quinones, cyclic alcohols, or cyclic ketones are fused are converted (52-88%) into the aromatic dicarboxylic acids upon reaction with a large excess of KO_2/crown ether in DMF (eq 20).[59]

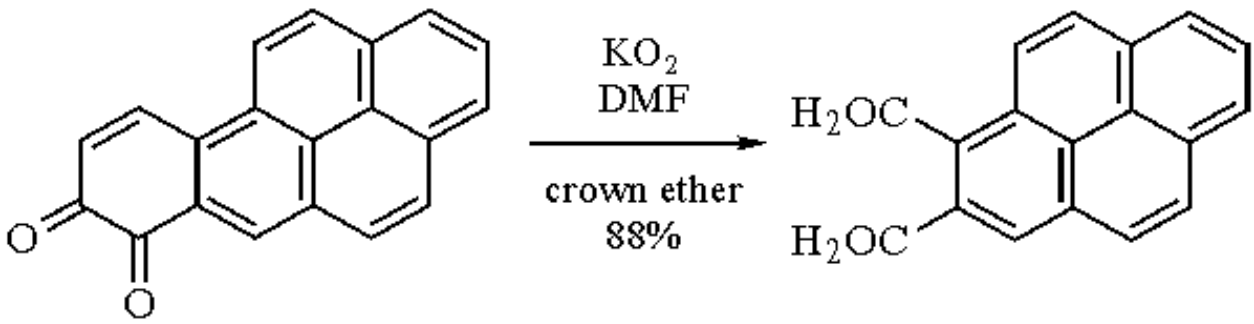

(20)

Tetramethyl- and tetraethylammonium ozonide, whose uses as reagents in organic chemistry are unexplored, have been prepared from the reaction of tetraalkylammonium superoxide and an alkali metal ozonide in liquid ammonia.[60] The question of whether the oxygen released following transfer of an electron from superoxide to a substrate is singlet oxygen is discussed in Frimer's excellent review.[1a] Potassium superoxide was considered to have the molecular formula K_2O_4 until quantum mechanics predicted the structure of O_2^- and experimental

confirmation of the radical anion nature of the molecule was performed.[61]

Related Reagents.

Electrochemically generated O_2^- (for which a tetraalkylammonium cation usually serves as the counter ion);[6] tetramethylammonium superoxide (Me_4NO_2);[7] NaO_2; radiolysis of O_2 in water is used to generate transient O_2^- in aqueous media.[8]

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Potassium Tetrachloropalladate(II)

K_2PdCl_4

[10025-98-6] · Cl_4K_2Pd · Potassium Tetrachloropalladate(II) · (MW 326.42)

(used as a soluble form of $PdCl_2$)

Physical Data: mp 534 °C (dec).

Solubility: sol water, MeOH, EtOH.

Form Supplied in: brown powder; commercially available.

Preparative Method: easily prepared by the reaction of $PdCl_2$ with 2 equiv of KCl in methanol and used without isolation.

Handling, Storage, and Precautions: air stable; not hygroscopic.

General Considerations.

The title reagent is most often used as a soluble source of palladium chloride (see ***Palladium(II) Chloride***). For a related reagent see ***Disodium Tetrachloropalladate(II)***.

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Potassium Tetrafluorocobaltate(III)[1]

$KCoF_4$

[22391-97-5] · CoF_4K · Potassium Tetrafluorocobaltate(III) · (MW 174.03)

(moderately strong reagent used for the fluorination of a wide range of organic substrates in the solid/vapor phase)

Physical Data: mp unknown; *d* ca 3.9 g cm^{-3}.

Solubility: reacts violently with water and hydroxylic solvents. Will fluorinate most organic compounds at relatively low temperatures.

Form Supplied in: pink-purple solid when pure, darkens on exposure to moisture; not commercially available.

Preparative Methods: usually prepared by the reaction of potassium cobaltate(II) with elemental fluorine at temperatures in the range 250-350 °C, usually in a stirred bed or static bed reactor preferably constructed of nickel or less satisfactorily of copper. The reagent is reacted with organic substrates in the same reactor in the manner described for reactions of ***Cobalt(III) Fluoride***.[2] Its crystal structure has been reported by Hoppe.[3]

Handling, Storage, and Precautions: normally prepared and used in situ. Can be stored under dry conditions under nitrogen for a considerable period. Releases HF on contact with moist air and must be handled with suitable protection. This reagent should be handled in a fume hood.

General Considerations.

Until recently, the whole of the published work on the reactions of this reagent have been by the Birmingham group over the period 1962-1993.

Whereas cobalt(III) fluoride is a very indiscriminate fluorinating agent which generally produces saturated fluorocarbons and fluorohydrocarbons with the loss of functional groups, $KCoF_4$ is a much milder reagent and affords more lightly fluorinated materials, often without affecting functionality and unsaturation present in the substrate. This makes it especially useful for the fluorination of heterocyclic materials.

Fluorination of Alkanes.

The fluorination of hydrocarbons to give perfluorocarbons by CoF_3 has been described,[2] but there is relatively little known concerning the preparation of the potentially useful fluorohydrocarbons (HFCs) with this reagent. With its milder reactivity, probably due to its lower oxidation potential relative to CoF_3,[4] $KCoF_4$ was an obvious reagent to use for this kind of fluorination. The fluorination of ethane (the only full study so far reported[5]) was shown to yield a mixture of fluorinated ethanes (eq 1). It is notable that even at 420 °C there is still only a low degree of fluorination; for comparison, CoF_3 at 165 °C affords almost exclusively penta- and hexafluoroethane in equal proportions. This work has recently been repeated with essentially the same results in a Japanese patent.[6]

$$C_2H_6 \xrightarrow{420\ ^\circ C} \underset{25.4\%}{CH_2FCH_2F} + \underset{10.9\%}{MeCHF_2} + \underset{29.1\%}{CH_2FCHF_2} + \underset{3.3\%}{MeCF_3} + \underset{9.8\%}{CHF_2CHF_2} + \underset{6.2\%}{CH_2FCF_3} + \underset{1.6\%}{C_2F_5H} + \underset{2.1\%}{C_2F_6} + \underset{2.1\%}{CF_4} \quad (1)$$

Fluorination of Alkenes.

The fluorination of alkenes with $KCoF_4$ has again only been sparsely studied. The original work (reported only in the patent literature) describes the fluorination of vinyl halides (eqs 2-4). These fluorinations provide a very simple one-step route to a number of halofluorocarbons which are quite difficult to prepare by conventional fluorine technology. The fluorination of ethylene has been described and yields essentially the same products as found for the fluorination of ethane.[5,6]

$$C_2H_4 \xrightarrow{300\ ^\circ C} \underset{45.7\%}{CH_2FCH_2F} + \underset{5.1\%}{MeCHF_2} + \underset{37.2\%}{CH_2FCHF_2} + \underset{5.8\%}{CHF_2CHF_2} \qquad (2)$$

$$CHBr{=}CBr_2 \longrightarrow \underset{25\%}{CHF_2CBr_2F} + \underset{75\%}{CHBrFCBr_2F} \qquad (3)$$

$$CCl_2{=}CCl_2 \longrightarrow \underset{88\%}{CCl_2FCCl_2F} + \underset{12\%}{CClF_2CCl_2F} \qquad (4)$$

Fluorination of Arenes.

The fluorination of arenes by $KCoF_4$ might be expected, if the proposed mechanism for high valency metal fluoride fluorinations is tenable, to be significantly different from that of CoF_3.[7] This proved to be so, as shown for the case of benzene (eq 5). Fluorobenzene and *p*-difluorobenzene gave essentially the same products in the same proportions, suggesting that they are intermediates in the fluorination. The fluorination of polycyclic arenes has been investigated for naphthalene (eq 6)[8] and tetralin,[9] anthracene (eq 7), phenanthrene (eq 8), and pyrene (eq 9).[10] The compounds from these reactions have been used as sources of the corresponding perfluoroarenes.[10,11]

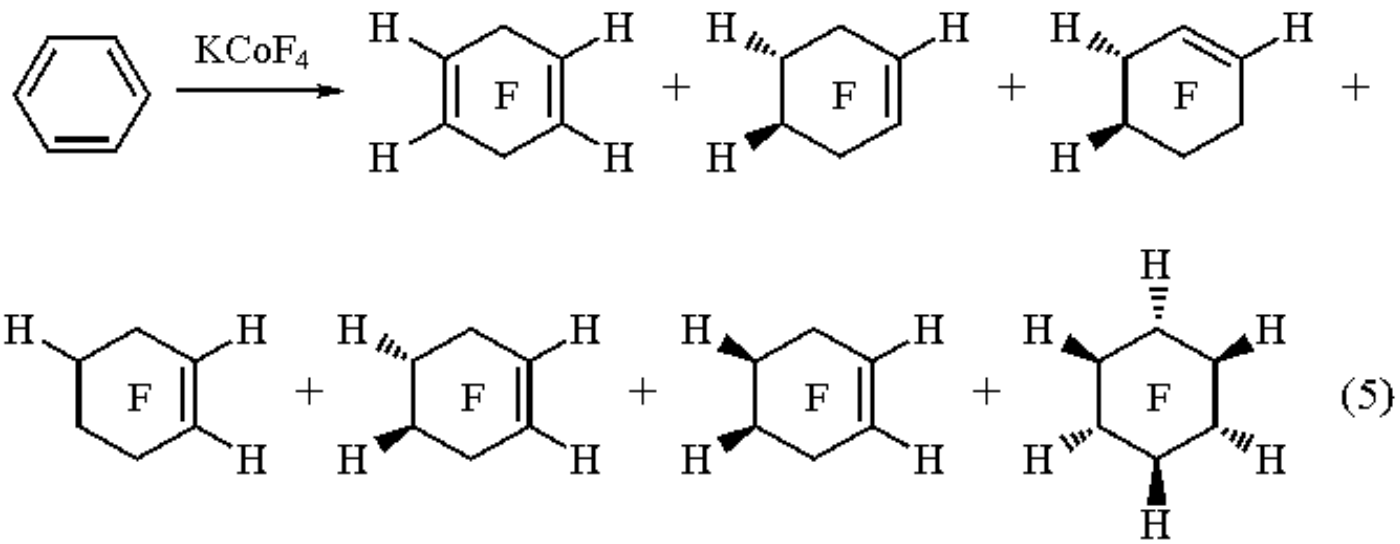

all unmarked bonds are joined to fluorine

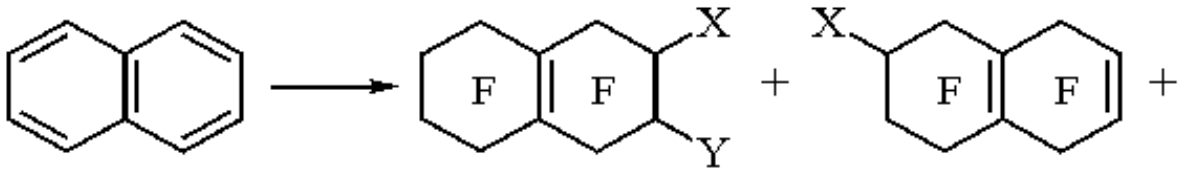

X = Y = F
X = H, Y = F
X = Y = H

X = F, H

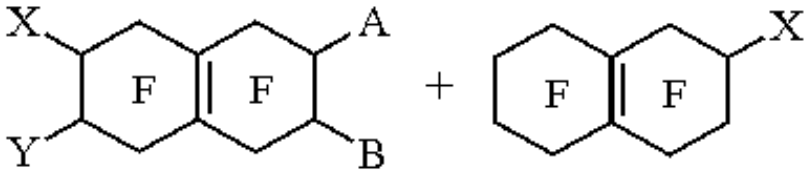

(6)

X = Y = H
A = B = H
or
X = B = H
Y = A = F

X = F, H

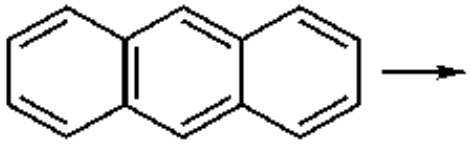

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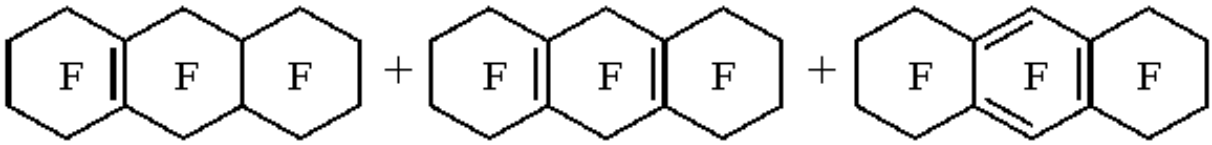

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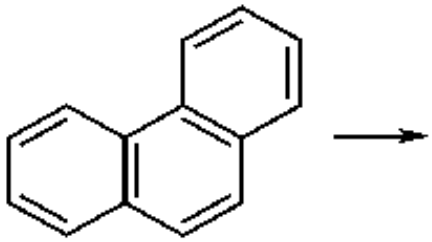

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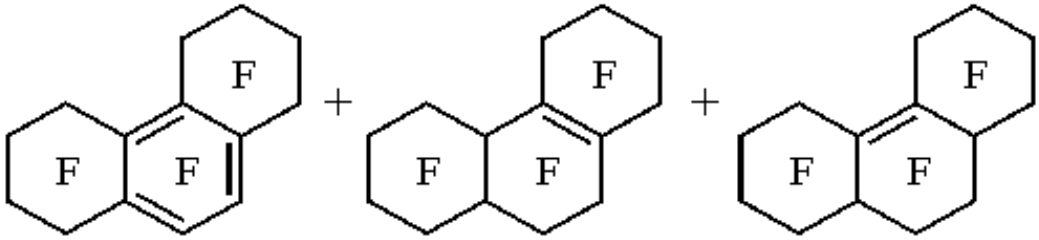

(8)

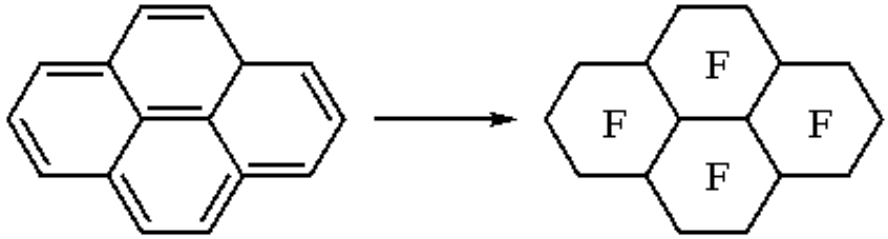

(9)

(3)

Fluorination of Heterocycles.

A wide range of heterocycles have been fluorinated, ranging from THF to 4-methylpyridine and some polyfluoropyridines. At temperatures between 200 and 400 °C, fluorination of THF yields a mixture of six products (eq 10). In this reaction there are two major products, again illustrating the relative mildness of the reagent.[12] This is further illustrated by the fluorination of 2-methyltetrahydrofuran,[13] where essentially only one product is isolated (eq 11).

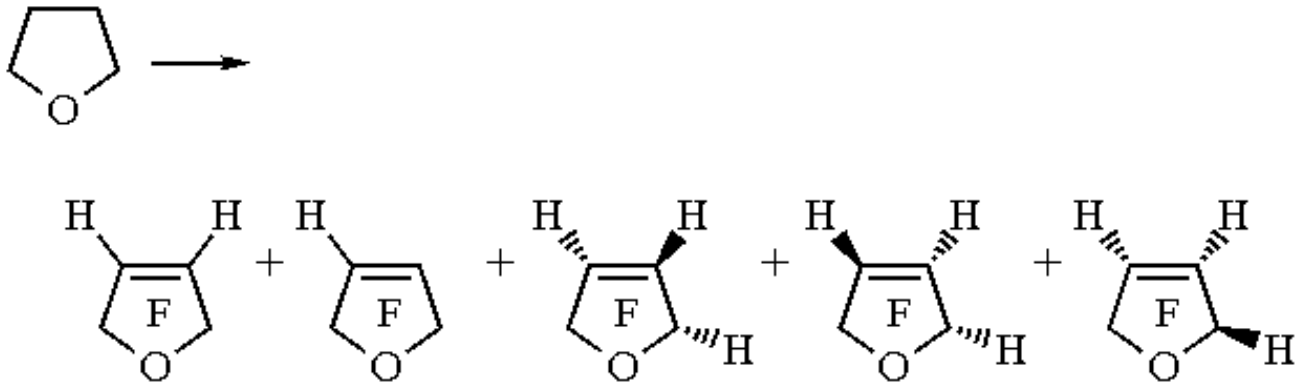

(10)

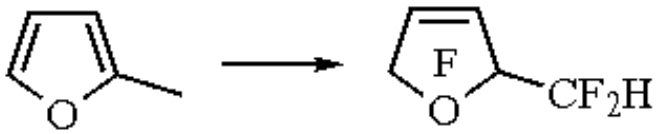

(11)

The fluorination of thiophene (eq 12), tetrachlorothiophene (eq 13),[14] and 2-methylthiophene (eq 14)[15] have also been carried out, with results essentially similar to those obtained for THF.

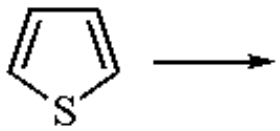

(4)

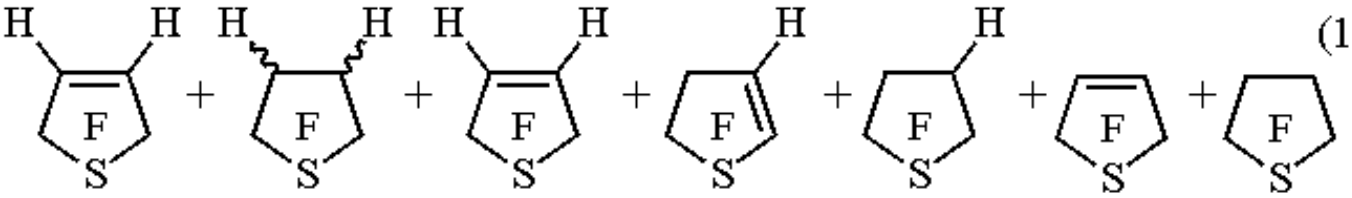

(12)

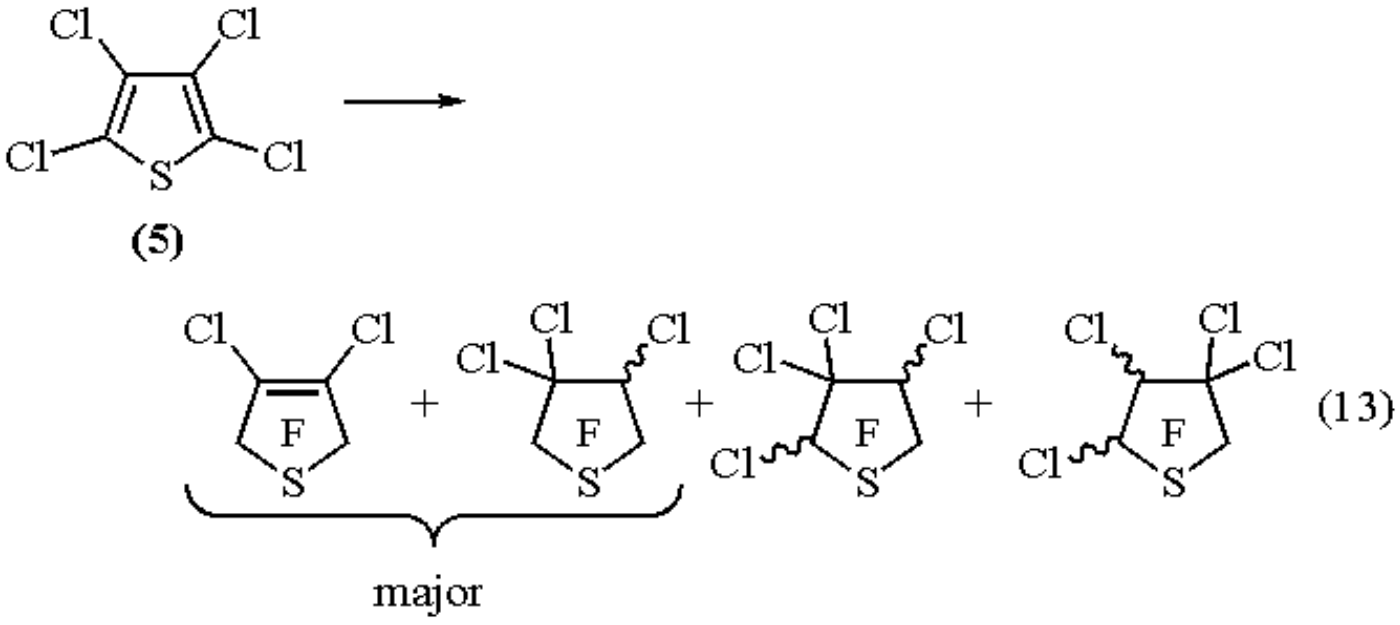

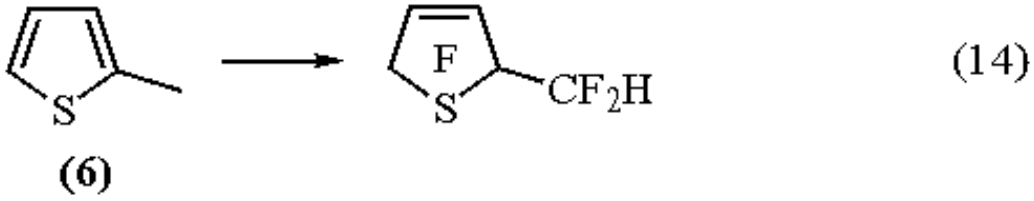

Fluorination of 1-methylpyrrole at 200-240 °C gave a mixture of products slightly different from the pattern of the other heterocycles in that they are all saturated (eq 15).[16]

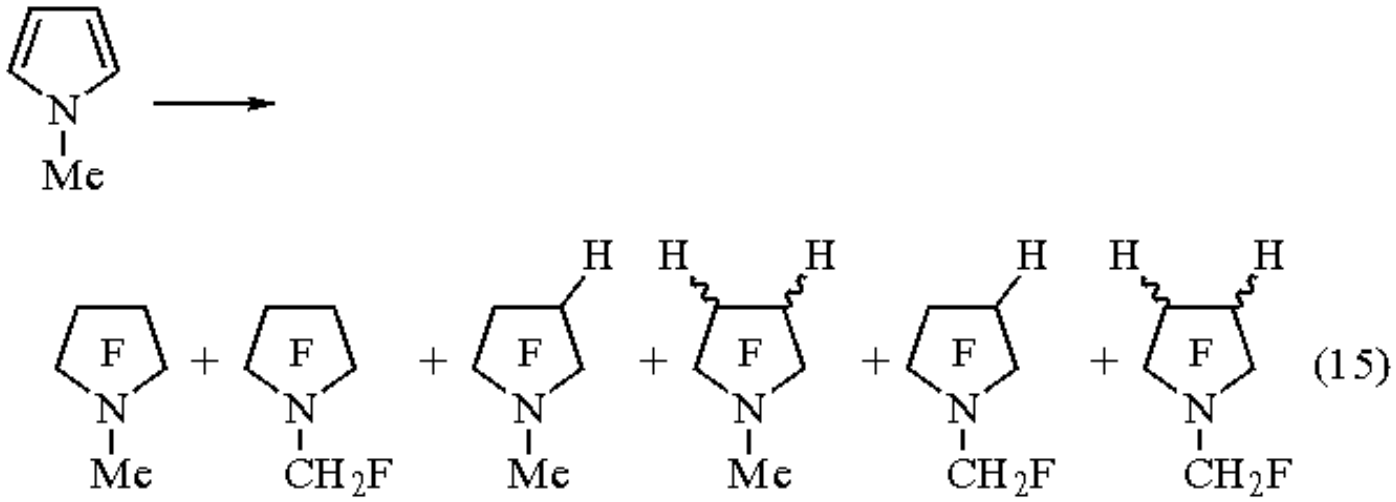

Fluorination of pyridine (eq 16) is a notable exception in the fluorination of heterocycles in that the major products are all ring-opened, although small amounts of fluoropyridines are detected.[17] Fluorination of polyfluoropyridines (eqs 17 and 18), however, lead to ring-retained compounds.[18]

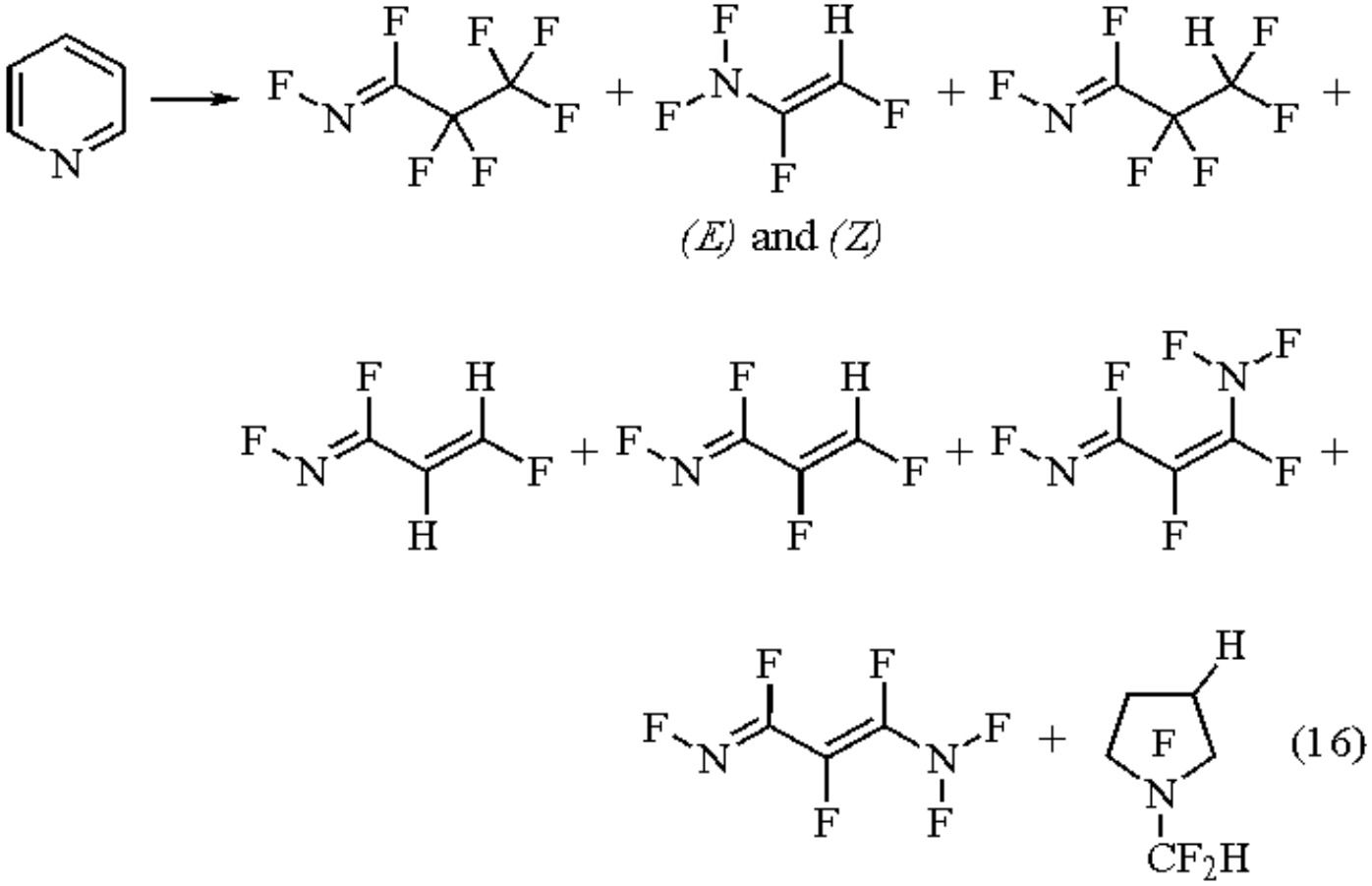

(16)

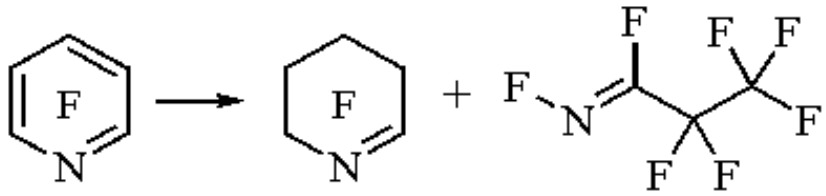

(17)

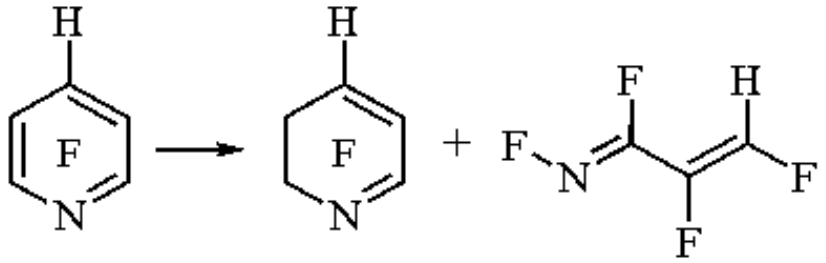

(18)

Miscellaneous Fluorinations.

Limited studies of the fluorination of functional group-containing compounds have been made. In strong contrast to CoF_3 fluorinations, the functional group is largely retained. Thus, fluorination of diethyl ketone (eq 19) yields a mixture of fluorinated ethanes and a nonvolatile fraction of acyl fluorides which was isolated by reaction withe ethanol to give a mixture of the ethyl esters of 2-fluoro- and 2,2-difluoropropionic acids.[19] This clearly comes from some kind of Lewis acid-induced cleavage of the ketone followed by fluorination, since at low temperatures the unfluorinated acyl fluoride is the sole product. The fluorination of halo ketones leads mostly to cleavage products (e.g. fluorotrichloromethane from hexachloroacetone) but some fluorodichloro esters (ca. 25%) are isolated. The fluorination of esters (eqs 20 and 21) and acyl halides yields mixtures of fluorinated esters.[20]

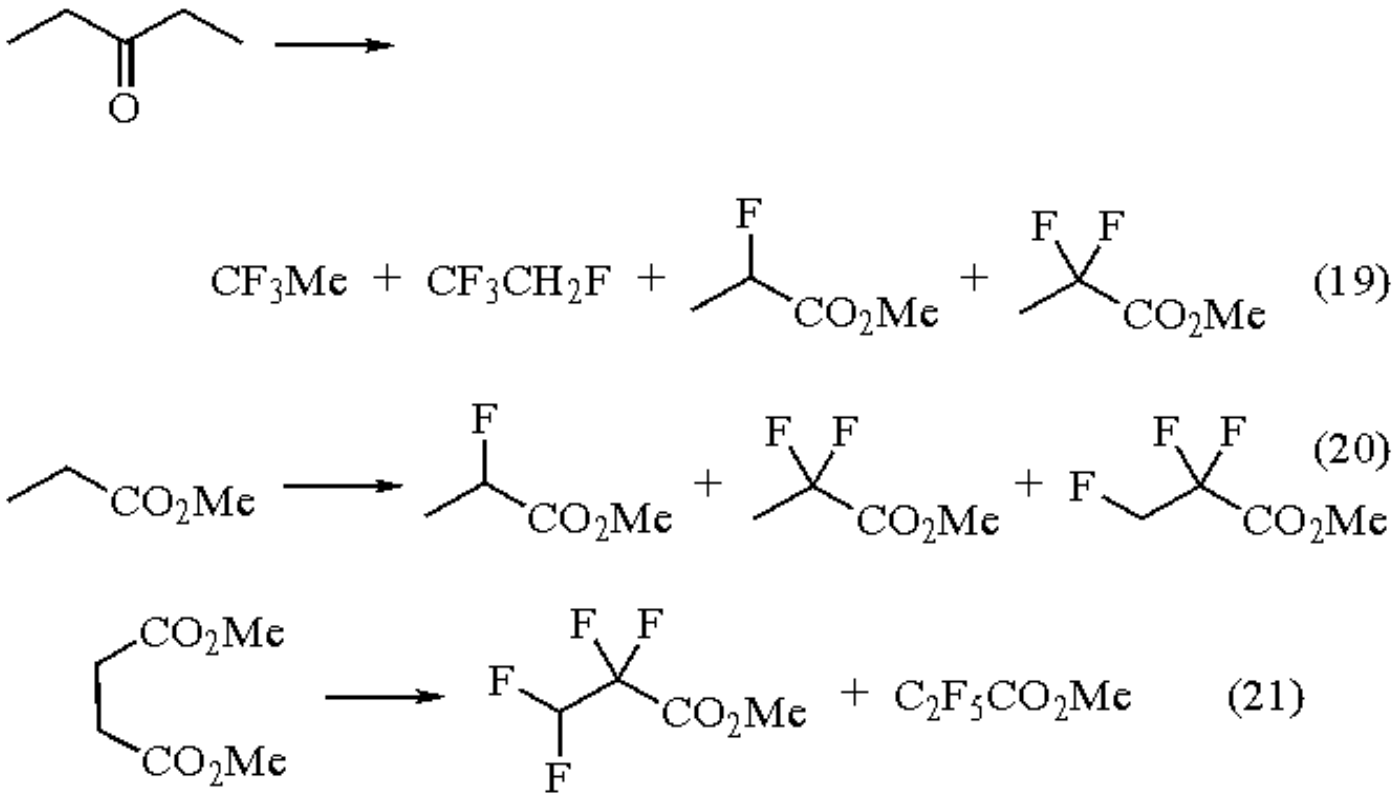

Clearly there is scope for optimization of these fluorinations since the compounds formed are extremely difficult to prepare by other routes; even though the yields here are relatively modest, they nonetheless do yield working quantities of the desired products in a simple single-step reaction. There is but one example of the fluorination of nitriles and the main result of value which comes from the work is that MeCN is a good solvent for fluorinations at or below its boiling point.[21] The fluorination of ethers has also been reported without significant differences from the results obtained from cobalt trifluoride fluorination.[22]

It is clear that potassium tetrafluorocobaltate is a useful fluorinating agent but has the constraints of needing special apparatus and a good reliable source of elemental fluorine.

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Potassium Thiocyanate[1]

KSCN

[333-20-0] · CKNS · Potassium Thiocyanate · (MW 97.19)

(reagent for the thiocyanation and isothiocyanation of many compounds;[1] converts oxiranes to thiiranes stereospecifically[11])

Physical Data: mp 173 °C; *d* 1.886 g cm^{-3}.

Solubility: very sol H_2O (217 g/100 mL at 20 °C); sol acetone (21 g/100 mL at 22 °C); sol EtOH.

Form Supplied in: colorless or white crystals; also available as volumetric standard in water (0.1 N). *Drying:* by heating to 165 °C under vacuum.

Purification: recrystallized from water or alcohol.

Handling, Storage, and Precautions: should be stored in a dark bottle.

Substitution Reactions.

Many early substitution reactions of metal thiocyanate salts were plagued by the ambident character of thiocyanate. Substitution via S affords a thiocyanate while attack via N yields an isothiocyanate. Often both products were formed and the efficiency of a synthesis of one product was measured by the rate ratio for the formation of both possible products, k_S/k_N. Reactions of KSCN with primary and secondary halides and sulfonates usually afforded products with a high k_S/k_N ratio, while the reaction of tertiary halides gave a ratio close to 1.[2] The use of other metal thiocyanates (Ba or $Ca(SCN)_2$) on an inorganic solid support provides a method for switching the S or N nucleophilicity for reactions with tertiary bromides (eq 1).[3] Solid-supported KSCN gives exclusive S attack of primary and simple benzylic halides but the k_S/k_N ratio remains moderate for tertiary systems.[4] Phase transfer catalysts enhance the smooth transformation of halides to thiocyanates with KSCN.[1,5] Alkyl isothiocyanates can be prepared in good yield by preparing the analogous thiocyanate and heating, preferably in the presence of metal salts, acids, or excess thiocyanate.[6] The isothiocyanate is usually the thermodynamically preferred product.[1] Various metal thiocyanates have been used to prepare acyl, phosphoryl, and sulfonyl isothiocyanates, probably by S attack of thiocyanate on a reactive acid derivative and then isomerization.[1]

$$t\text{-BuBr} \xrightarrow[\text{cyclohexane}]{\text{MSCN}} t\text{-BuSCN} + t\text{-BuNCS} \qquad (1)$$

KSCN on Al_2O_3	72%	8%
$Ba(SCN)_2$ on $CaCO_3$	54%	3%
$Ba(SCN)_2$ on CaF_2	0.8%	78%

Potassium thiocyanate is an effective reagent for the substitution on unsaturated systems to form thiocyanates. Nitrogen of diazonium salts is replaced by thiocyanate, but use of a cocatalyst is recommended to improve the yield and the k_S/k_N ratio. Thiocyanates have also been formed from the substitution reaction of KSCN with imidoyl chlorides,[1] allenyl chlorides,[7] some

chloroalkenes,[1] and nitrophenyl halides.[1] Thiocyanate supplants the halide of some phenyl iodides and bromides when these are treated with charcoal-supported CuSCN, a reagent which was prepared with the aid of KSCN (eq 2).[8] KSCN performs a selective alkyne substitution on alkynyl(*p*-phenylene)bisiodonium ditriflates (eq 3).[9] KSCN is the preferred reagent for the thiocyanation of saccharides.[10]

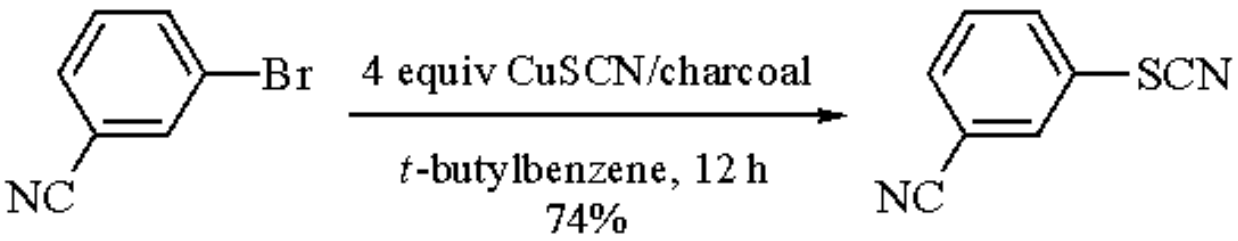

(2)

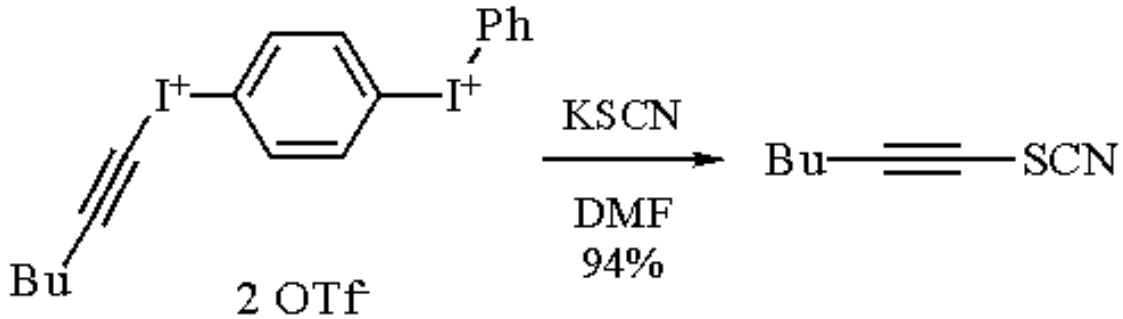

(3)

Sulfur Heterocycles.

Potassium thiocyanate is one of several reagents that converts oxiranes to thiiranes. KSCN seems to be the reagent of choice for a broad range of substituted oxiranes,[11] but reagents such as ***Thiourea***,[11] ***N,N-Dimethylthioformamide***,[12] or 3-methylbenzothiazole-2-thione[13] may have advantages in specific cases. With KSCN, various ring fused thiiranes can be formed (eq 4). In its reaction with substituted oxiranes, KSCN reacts by a stereospecific mechanism in that the substituent geometry of the oxirane is preserved in the thiirane. However, the reaction of KSCN with bromohydrins derived from *trans*-alkenes affords *cis*-thiiranes.[14] Hence, starting with a single 1,2-disubstituted alkene, a thiirane of either substituent geometry can be obtained. KSCN supported on silica is also effective for thiirane synthesis (eq 4).[15]

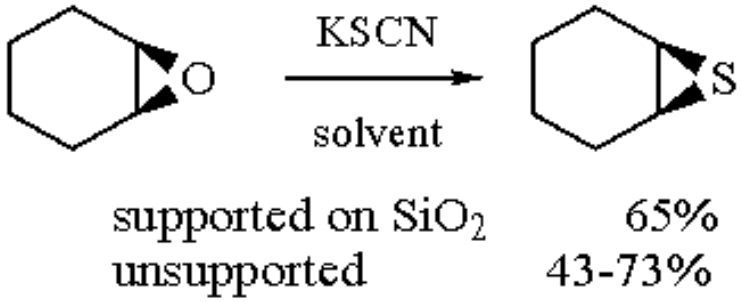

(4)

The reaction of cyclic carbonates with KSCN has been shown to be a method for the synthesis of some thiiranes[16] and thietanes,[17] depending on the number of carbons and nature of substituents in the starting material (eq 5).[7]

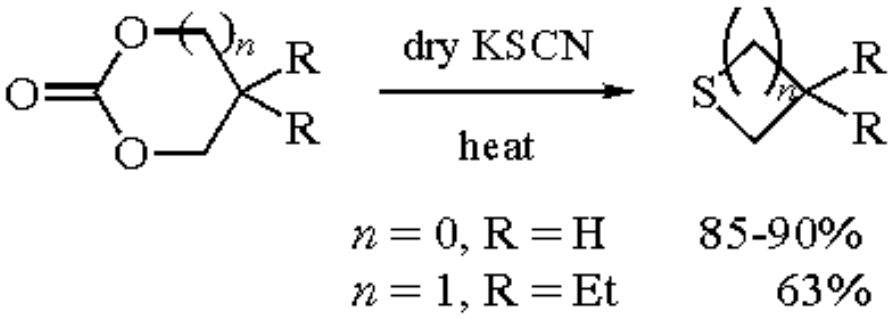

(5)

Related Reagents.

Sodium Thiocyanate.

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Potassium Tri-*s*-butylborohydride[1]

K(*s*-Bu)$_3$BH

[54575-49-4] · $C_{12}H_{28}BK$ · Potassium Tri-*s*-butylborohydride · (MW 222.31)

(reducing agent for various functional groups;[2] selective reducing agent;[3-7] stereoselective reducing agent for ketones;[8-10] used for reduction of conjugated enones;[11] regioselective reducing agent for cyclic anhydrides;[12] reacts with carbon monoxide in the presence of free trialkylborane;[13] used for stereoselective synthesis of *cis*-alkenylboranes[14])

Alternate Names: K-Selectride®; potassium hydrotris(1-methylpropyl)borate.

Physical Data: not isolated; prepared and used in solution.

Solubility: solubility limits have not been established. The reagent is normally used as a 1.0 M solution in THF or Et_2O, but use of toluene as solvent is also reported.

Form Supplied in: 1.0 M solutions in THF or Et_2O.

Analysis of Reagent Purity: solutions of pure reagent exhibit doublets (J = 68-71 Hz) centered in the range δ -7.1 to δ -7.5 in the ^{11}B NMR spectrum.[15,16a,17] Concentration of hydride is determined by hydrolysis of aliquots and measurement of the hydrogen evolved or by quenching aliquots in excess 1-iodooctane and analysis of the octane formed by GLC.[18] Concentration of boron is verified by oxidizing aliquots using alkaline hydrogen peroxide and analyzing the 2-butanol formed by GLC.[19]

Preparative Methods: direct reaction of tris(1-methylpropyl)borane with ***Potassium Hydride*** is satisfactory,[15] especially with activated KH.[16] The reagent is also formed by reaction of the trialkylborane with ***Potassium Triisopropoxyborohydride***.[17]

Handling, Storage, and Precautions: solutions are air- and water-sensitive and should be handled in a well ventilated hood under an inert atmosphere using appropriate techniques.[20] Potentially pyrophoric tris(1-methylpropyl)borane is a byproduct of reductions; thus standard organoborane oxidation[19] is recommended as part of the workup.

Functional Group Reductions.

The reducing characteristics of the reagent have been studied systematically.[2a] At 0 °C it liberates H_2 quantitatively with various active hydrogen compounds, including primary alcohols, phenols, thiols, carboxylic acids, primary amides, aliphatic nitro compounds, and oximes. Secondary and tertiary alcohols and primary amines are inert. Carboxylic acids, amides, nitro compounds, and oximes are not reduced further. Aldehydes, ketones, and acyl chlorides are reduced rapidly to the alcohol stage. Acyclic esters are reduced more slowly, but lactones are rapidly reduced to diols. Cyclic anhydrides are reduced to lactones if steps are taken to avoid further reduction of the latter. Terminal epoxides are reduced rapidly and cleanly to the Markovnikov alcohols. Internal epoxides are reduced slowly. Nitriles are reduced sluggishly. Pyridine and quinoline consume hydride, but the products have not been characterized. Disulfides are reduced to thiols. Primary iodides and bromides are reduced rapidly, chlorides more slowly. Cyclohexyl bromide and tosylate react sluggishly.

A reagent derived by adding 2 equiv of K-Selectride to 1 equiv of CuI effectively displaces halide from various aryl halides, and in one example an internal alkyne, dec-5-yne, is converted predominantly to the (*Z*)-alkene (*Z*:*E* = 88:12).[2b]

Selective Reductions.

Ketones are reduced selectively in the presence of other functional groups: esters,[3] including methyl esters[3a,d] and γ-lactones;[3b] a cyclic carbamate;[4] amides[5] including 2-acetyl β-lactams[5a-c] and benzenesulfonamides;[5f] azides;[6] and internal epoxides.[3d] Steroid 3,17- or 3,20-dione systems undergo selective reduction at the 3-position,[7] as does a 5-ene-3,17-dione system.[11c] Conjugated enones are reduced selectively in the presence of esters.[11e-g]

Stereoselective Reductions.

Like L-Selectride (***Lithium Tri-s-butylborohydride***), K-Selectride is useful for diastereoselective reduction of alkyl-substituted cyclic ketones to alcohols.[15a] Other applications to various types of cyclic ketones have been reported.[3d,4,7,8] Diastereoselective reduction is also observed for acyclic ketones,[9] including keto esters,[3a-c] keto amides,[5] and a keto azide.[6] A chiral dione is diastereoselectively reduced to a diol.[10]

Various theoretical models are used to rationalize observed diastereoselectivity.[21] In simple cases, the bulk of the reagent appears to dictate that hydride approach from the less sterically hindered face of the carbonyl.[15a] However, complexation effects of heteroatoms,[8a] crown ethers,[3c,9i] and cryptands[9i] may reverse the direction of approach. Also, the coordinating ability of the solvent influences the ratio of diastereomers.[3b]

Reduction of Conjugated Enones.

A reasonably systematic study of conjugated enone reductions has been conducted.[11a] Acyclic enones undergo 1,2-addition with stereoselective formation of allylic alcohols upon protonation. Cyclohexenones with no β-substitution yield saturated ketones as a consequence of 1,4-addition with 1 equiv of hydride, while a β-methyl results in exclusive 1,2-addition; 3 equiv of hydride results in stereoselective formation of saturated alcohols. Both cyclopentenones and cycloheptenones give mixtures of products. The enolate resulting from 1,4-addition may be alkylated instead of protonated, but this α-alkylation appears to work better with L-Selectride. Attempted reduction of α,β-unsaturated esters leads to Claisen condensation products.

Further examples of 1,2-addition to cyclohexenones involve the 5-en-3-one function of steroids[11b,c] or analogous systems.[11b] This is reduced selectively in 2α-fluoro-4-androstene-3,17-dione.[11c] Stereoselectivity in reduction of testosterone, which yields predominantly the 3β,17β-diol (3β:3α = 88:12), is reversed for 2α-fluorotestosterone, which yields exclusively the 3α,17β-diol.[11c]

A conjugated cyclohexadienone undergoes 1,4-addition so that only the α,β-double bond is reduced.[11d] Stereoselectivity results on 1,4-addition to (*S*)-(+)-carvone (eq 1).[11e]

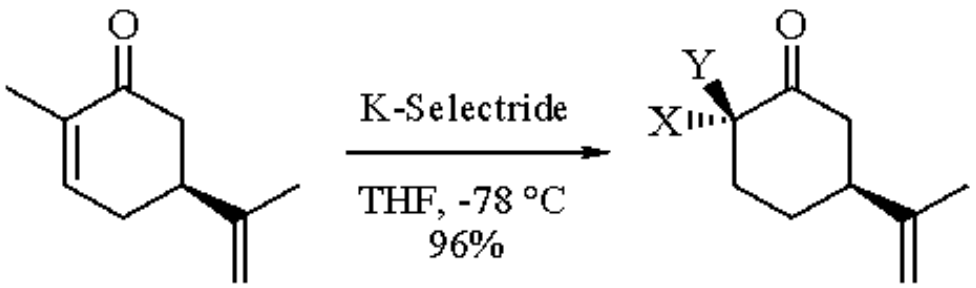

(1)

X = Me; Y = H (79%)
X = H; Y = Me (17%)

An enone incorporated into a 14-membered macrolide undergoes stereoselective 1,2-addition while the lactone is not affected.[11f] With 3 equiv of K-Selectride, the cyclopentenone in the prostanoid 15(*S*)-PGA_2 is reduced stereoselectively to the corresponding cyclopentanol while a methyl ester remains untouched.[11g] A procedure utilizing 2 equiv of K-Selectride in the presence of 2 equiv of ethanol reduces a cyclohexenone stereoselectively to the cyclohexanol in the presence of methyl ester, acetate, and γ-lactone functions (eq 2).[11h] An α,β-alkynic ketone undergoes exclusive 1,2-addition with stereoselective formation of the propargylic alcohol.[9b]

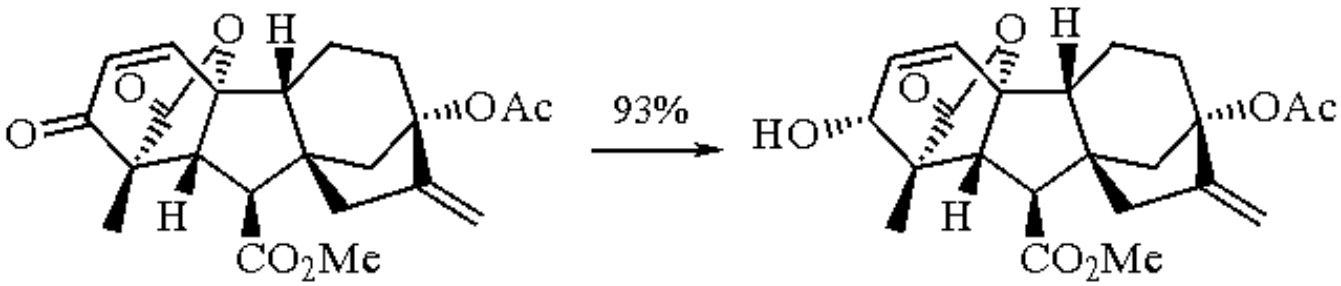

(2)

Regioselective Reduction of Cyclic Anhydrides.

Various succinic and phthalic anhydrides are reduced by the reagent to lactones.[12] With certain exceptions (eq 3),[12b] reduction occurs preferentially at the less hindered carbonyl function. A mechanistic interpretation of the results has been proposed.[12b,e]

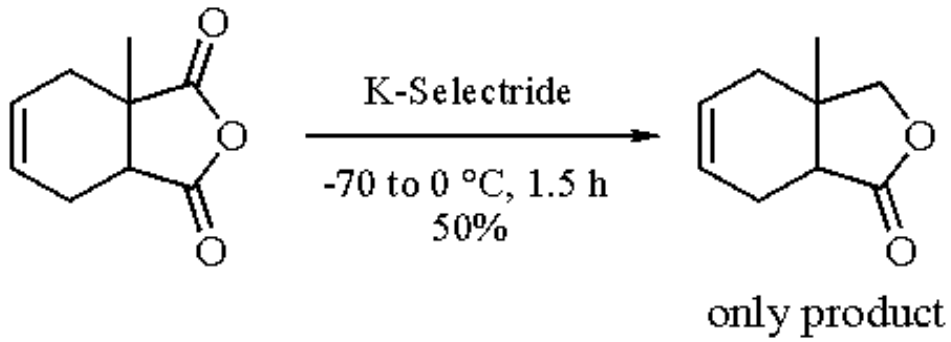

(3)

Reaction with Carbon Monoxide.

Carbonylation of KBH-(*s*-Bu)$_3$ followed by treatment with refluxing aqueous ***Sodium Hydroxide*** yields 2-methyl-1-butanol.[13a] It is now evident that KBH(*s*-Bu)$_3$ is an intermediate in the hydride-induced carbonylation of *s*-Bu$_3$B using ***Potassium Triisopropoxyborohydride***,[13b,17] so that different workup procedures may produce 2-methylbutanal[13c] or 3,5-dimethyl-4-heptanol.[13d]

Stereoselective Synthesis of *cis*-Alkenylboranes.

Reaction of 1-halo-1-alkenylboranes with KBH(*s*-Bu)$_3$ produces *cis*-alkenylboranes, but the ease of removing triethylborane makes ***Lithium Triethylborohydride*** the reagent of choice.[14]

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Potassium Triethylborohydride

$KBEt_3H$

[22560-21-0] · $C_6H_{16}BK$ · Potassium Triethylborohydride · (MW 138.13)

(reducing agent in organic and organometallic synthesis)

Physical Data: mp 95 °C,[1] *d*204 0.902 g cm^{-3} for 1 M solution in THF.

Solubility: sol THF, diethyl ether, benzene, toluene.

Form Supplied in: 1 M solution in THF.

Analysis of Reagent Purity: ^{11}B NMR (THF, standard $BF_3.Et_2O$), δ -12.83 ppm (d, J_{B-H} 70 Hz).[2] Active hydride is determined by hydrolysis and measuring the hydrogen evolved according to the standard procedure;[4] potassium, by hydrolysis and titration against standard acid;[2] boron, by oxidation and GC analysis of alcohol produced after oxidation.[2]

Preparative Methods: by the reaction of ***Potassium Hydride*** with ***Triethylborane*** in THF,[2] or benzene.[1] From ***Potassium Triisopropoxyborohydride*** and triethylborane in THF[3] and from sodium triethylborohydride and potassium amalgam in benzene.[1]

Handling, Storage, and Precautions: the solution in THF is moisture- and air-sensitive, corrosive, and flammable. Reacts violently with water. Handle and store under nitrogen or argon in a cool place. Stable over prolonged periods of time. Use in a fume hood. Avoid contact with eyes, skin, and clothing.

Selective Reductions.

Potassium triethylborohydride belongs to the family of trialkylborohydrides. It is a powerful reducing agent, reacting with many functional groups. Lower *O*-chelating ability of potassium as compared to lithium and sodium cations, bulkiness, and stability to disproportionation of the anion are its features. The reducing characteristics of potassium triethylborohydride are shown in Table 1.[5]

Table 1 Reactivity of Various Functional Groups Toward Potassium Triethylborohydride in THF at 0 °C

Functionality or compound	Reactivity[a]	Products (remarks)
Aldehydes, ketones	f	Alcohol
Carboxylic acids		(Hydrogen evolution, no further reaction)
Esters	f	Alcohol
Acid chlorides	f	Alcohol
Acid anhydrides	f	Alcohol and acid
Lactones	f	Alcohol
Epoxides	m	Alcohol (Markovnikov opening)
Amides, primary	s or nr	(Benzamide not reduced, capramide slow rate)
Amides, tertiary	s	
Nitriles	s or nr	Amine (benzonitrile 2 hydrides used, capronitrile 1 hydride used)
Nitro compounds	f	(2 Hydrides used)
Azo, azoxy compounds	s	
Oximes		(Hydrogen evolution, no further reaction)
Phenyl isocyanate	f	Formanilide (1 hydride used)
Pyridine	f	(2 Hydrides used)
Sulfoxides, sulfonic acids	nr	
Disulfides	f	Thiol
Sulfones, cyclohexyl tosylate	s	(Diphenyl sulfone reduced to eth ylbenzene at reflux)
n-Octyl bromide	f	Octane
n-Octyl chloride	m	Octane
Cyclohexyl bromide	s	Cyclohexane

[a] f, fast; m, moderate; s, slow; nr, no reaction.

2-Methylcyclohexanone is reduced to 2-methylcyclohexanol (*cis*:*trans* = 79:21), 4-*t*-butylcyclohexanone to 4-*t*-butylcyclohexanol (*cis*:*trans* = 20:80), norcamphor to norborneol (*endo*:*exo* = 97:3), and anthraquinone to 9,10-dihydro-9,10-dihydroxyanthracene.[5] Ethyl caproate, ethyl cyclohexylcarboxylate, and ethyl and isopropyl benzoate are reduced in the presence of cyclohexanone oxime, *N*,*N*-dimethylcaproamide, and capronitrile. Ethyl esters are reduced preferentially to *t*-butyl esters.[6]

2´-Alkyl-3´-oxo amides are reduced to the corresponding 3-hydroxy amides with high *anti* diastereoselectivity (20:1 to 80:1). Optically active 2´-alkyl-3´-oxo amides give even higher stereoselectivity (>99:1). The reaction provides an alternative to asymmetric aldol condensation (eq 1).[7] ***Zinc Borohydride***, having a cation of higher chelating ability than potassium, reacts with *syn* diastereoselectivity, presumably via an intermediate six-membered chelate. 2-Aryl-2-methyl-1-indanones are stereoselectively reduced to 2-aryl-2-methyl-1-indanols.[8]

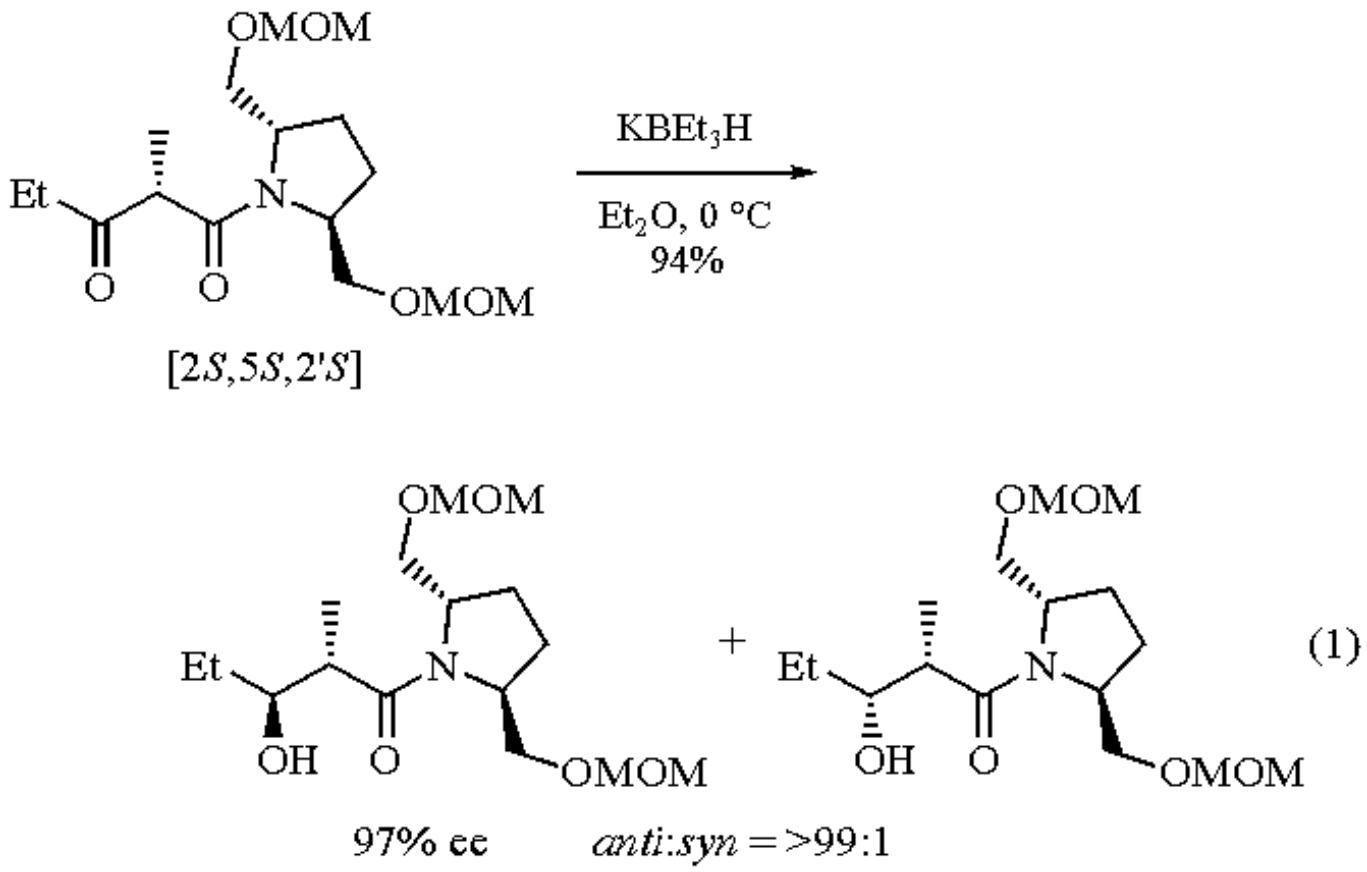

Carbonylation of Organoboranes.

In the presence of triethylborane, potassium triethylborohydride reacts with carbon monoxide. The organoborane intermediate produced yields 1-propanol upon oxidation (eq 2).[9] The reaction is an example of a hydride-induced carbonylation of organoboranes leading to alcohols and aldehydes.[10] Lithium trimethoxyaluminum hydride (LTMA)[11] and ***Potassium Triisopropoxyborohydride*** (KIPBH)[12] are the hydrides most often used in these reactions.

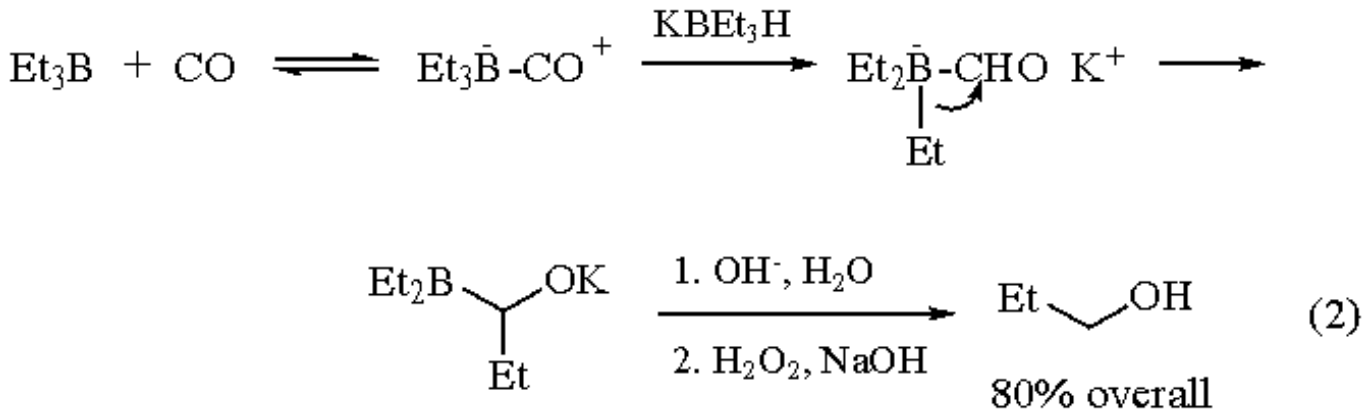

Organometallic Synthesis.

Potassium triethylborohydride finds application in the reduction of metal-metal bonds in transition metal dinuclear carbonyl complexes, e.g. Bi-Mo,[13] and Fe-Fe.[14,15] Metal carbonyl monoanions and dianions are generated and can be used for further transformations (eq 3).

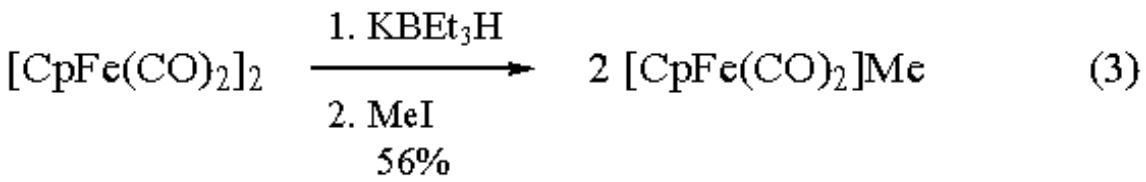

Mononuclear anionic transition metal formyl complexes are prepared by the reduction of neutral carbonyl complexes with potassium triethylborohydride and other dialkylborohydrides (eq 4).[16] The method is of considerable generality. Formyl-transition metal complexes appear to be the intermediates in the Fischer-Tropsch industrial process. The reagent is also used in other organometallic syntheses.[17]

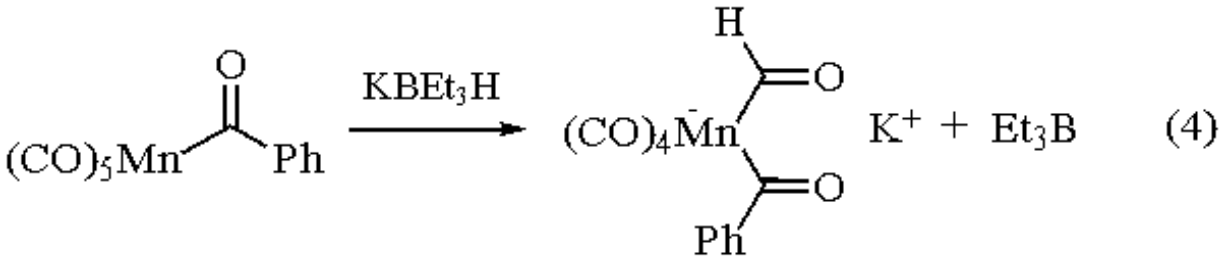

Related Reagents.

Diisobutylaluminum Hydride; ***Lithium Aluminum Hydride***; ***Lithium Tri-s-butylborohydride***; ***Lithium Trisiamylborohydride***; ***Potassium Tri-s-butylborohydride***; ***Sodium Borohydride***.

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Potassium Triisopropoxyborohydride[1]

$KBH(O\text{-}i\text{-}Pr)_3$

[42278-67-1] · $C_9H_{22}BKO_3$ · Potassium Triisopropoxyborohydride · (MW 228.22)

(mild reducing agent for carbonyl compounds,[1] disulfides,[2c,3] and haloboranes[2a-c])

Alternate Name: KIPBH.

Physical Data: d (1.0 M THF solution) 0.912 g cm^{-3}.

Solubility: sol THF, Et_2O, monoglyme.[2]

Form Supplied in: no longer commercially available (formerly available as 1.0 M THF soln).

Analysis of Reagent Purity: IR (THF): 2210 cm^{-1} ($\nu_{B\text{-}H}$), 1375 cm^{-1} ($\nu_{B\text{-}O}$). ^{11}B NMR (THF; $BF_3.Et_2O$ as ref, with δ downfield from $BF_3.Et_2O$ assigned as positive): 6.1 δ (d, $J_{B\text{-}H}$ 118 Hz).[2] Samples can be hydrolyzed with H_2O and K and B contents measured as KOH and H_3BO_3, while hydride concentration can be estimated by measuring the H_2 evolved from acidic hydrolysis,[2] and isopropoxide can be evaluated by GLC analysis as *i*-PrOH.[2a]

Preparative Methods: THF solutions can be obtained by adding 1.0 mol of freshly distilled ***Triisopropyl Borate*** to 1.5 mol of ***Potassium Hydride*** suspended in 400 ml of solvent.[2c] Solutions in Et_2O or monoglyme were prepared in a similar way.[2a]

Purification: if THF solutions are contaminated by $K(i\text{-}PrO)_4B$, they can be purified by gentle reflux over an excess of KH for about 24 h.[2]

Handling, Storage, and Precautions: the solution must be stored under N_2 in the absence of moisture, but it is quite stable to disproportionation (over 6 months, when stored in the presence of a slight excess of KH at ambient temperature[2a]). It is incompatible with strong oxidizing agents, water, and acids (H_2 is evolved).

General Considerations.

Potassium triisopropoxyborohydride, in contrast to the less hindered trialkoxyborohydrides, is stable in THF solution toward disproportionation. It is a mild reducing agent, similar to ***Sodium Borohydride*** in that it reduces only aldehydes and ketones while almost all other functional groups are unaffected. KIPBH offers some advantages over simple borohydrides: it is soluble in nonhydroxylic solvents, it is more chemo- and stereoselective, and its kinetics are easier to study since it carries only 1 equiv of hydride per molecule.[1,2b]

Active hydrogen compounds (alcohols, phenols, thiols, amines, carboxylic acids) evolved H_2 sluggishly when treated with KIPBH in THF at 0 °C.[2c] Anhydrides, acyl chlorides, esters, lactones, epoxides, amides, nitriles, nitro compounds, oximes, isocyanates, quinones are not cleanly reduced by KIPBH. With few exceptions, most of these functional groups are completely unaffected by KIPBH.[2c]

Reduction of Carbonyl Compounds.

Both aldehydes and ketones are rapidly reduced to the corresponding alcohols by KIPBH, even at temperatures below 0 °C.[2b-c,4] Unsaturated carbonyl compounds are usually reduced to allylic alcohols (1,2-attack).[2c] KIPBH is particularly efficient for the diastereoselective reduction of cyclic ketones. The less stable *cis* epimer (from axial attack) is usually obtained in high diastereomeric excess (up to 96% de),[2c,4] but even better results can be obtained using other complex boro- or aluminium hydrides.[2b,d,4,5]

Chiral 2-oxo esters (from (-)-8-phenylmenthol[6a] or (-)-menthol[6b,c]) have been reduced to the corresponding 2-hydroxy esters (up to 90% de) by using KIPBH in THF. The new chiral center has the (*R*) configuration (eq 1). It is worth noting that, by using the same chiral auxiliary, addition of the Grignard reagent to the aldehyde or reduction of the ketone affords products with opposite configuration.[6a] In

some examples, better diastereoselectivity can be obtained using other complex boro- or aluminum hydrides.[6b,c] Similarly, the *anti* diastereoselective reduction of chiral 2-alkyl-3-oxoamides[6d] (from *trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine) can be performed in high de by using KIPBH, but ***Potassium Triethylborohydride*** gives the best results.

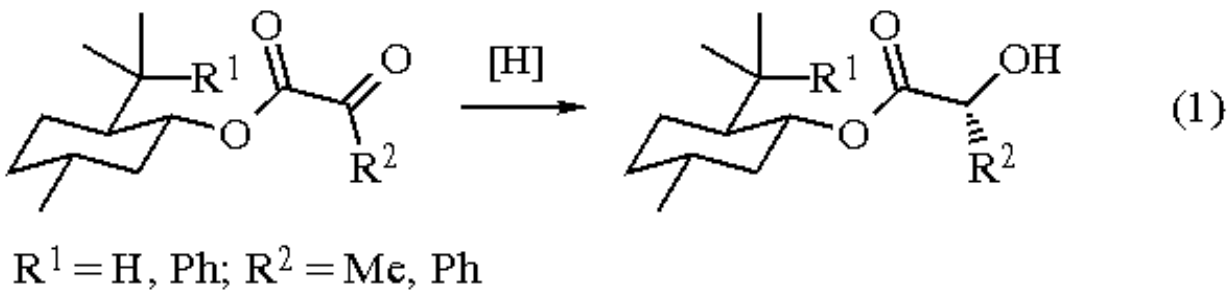

Reduction of Disulfides.

Both aryl and alkyl disulfides are reduced to the corresponding thiols by KIPBH in THF at 0 °C.[2c,3] Aromatic disulfides can be selectively reduced in the presence of aliphatic ones.[3] Other reducing reagents ($LiAlH_4$, $NaBH_4/AlCl_3$, $NaBH_4$, Zn/AcOH) suffer serious disadvantages, since they are either less chemoselective or give rise to heterogeneous systems.

Reduction of Heterocycles.

KIPBH has been tested (along with other boro- and aluminum hydrides) in the Fowler synthesis of dihydropyridines (eq 2), i.e. the reduction of the *N*-alkoxycarbonylpyridinium ions (**1**) formed in situ from a pyridine and a chloroformate ester.[7] The regiochemistry of the reduction depends mainly on the ring substituents. Sterically undemanding donor substituents favor reduction at C-2, despite the bulkiness of the reductant. However, branched substituents are more sensitive to steric factors in the hydride and acceptor substituents are poorly regiodirective.

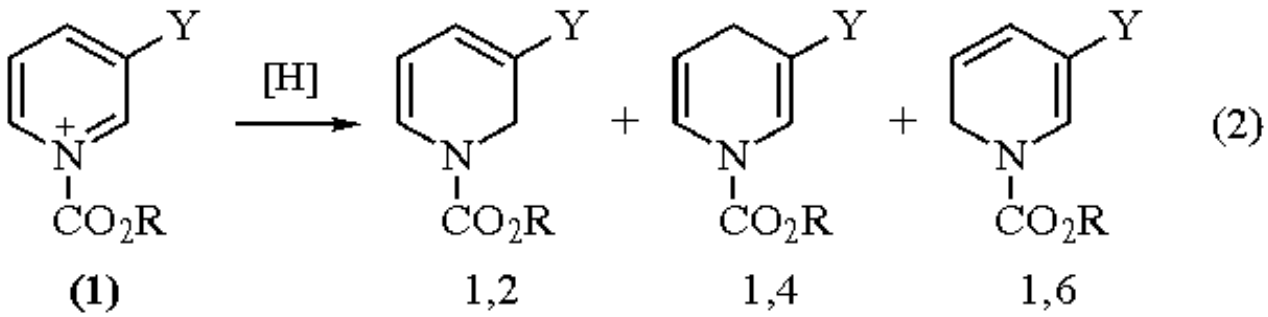

Applications to Boron Chemistry.

Although KIPBH is a very mild reducing agent, it is very effective in reducing haloboranes. This reaction has been used to synthesize unsymmetrically substituted trialkylboranes, from which unsymmetrical ketones can be obtained via carbonylation or cyanidation (eq 3).[2c,8] In contrast to the method using ***Thexylborane***, terminal alkenes can be employed in the reaction with thexylchloroborane and many different functional groups may be present in the alkenes introduced in the third step. The overall process is best carried out if the reduction of the thexylalkylborane (**2**) is performed in the presence of the second alkene. Use of a diene allows the synthesis of cyclic ketones.[8]

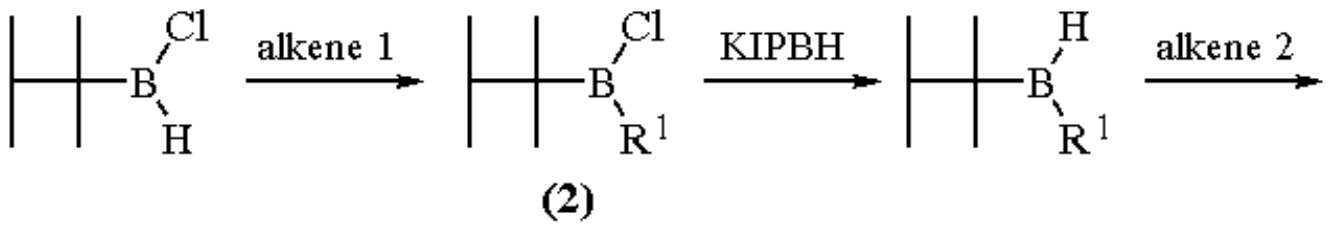

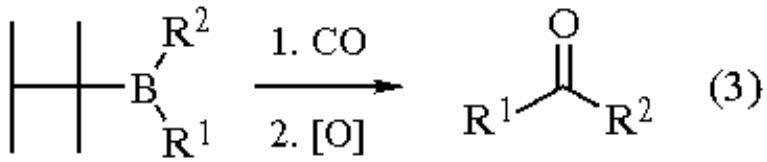

Reaction of KIPBH with (*Z*)-(1-bromo-1-alkenyl)boronic esters (obtained from reaction of 1-bromoalkynes with dibromoborane, followed by treatment of the resulting alkenyldibromoboranes with an alcohol) in Et_2O at ambient temperature provides a rapid access to stereochemically pure (*Z*)-1-alkenylboronic esters (**3**) (eq 4).[2b-c,9] These intermediates have found broad application in the stereoselective synthesis of arylated alkenes, conjugated alkadienes,[9b] conjugated dienones,[9c] and conjugated alkanedienoates[9d] via palladium-catalyzed cross-coupling reactions with aryl iodides, 1-bromoalkenes, 3-halo-2-alken-1-ones, and 3-bromo-2-alkenoates, respectively. Moreover, (*Z*)-1-alkenylboronic esters (**3**) can be employed in the synthesis of stereochemically defined (*E*)-1-bromo-1-alkenes (via reaction with Br_2, followed by treatment with MeONa) and (*Z*)-1-iodo-1-alkenes (via reaction with $NaOH/I_2$).[9e]

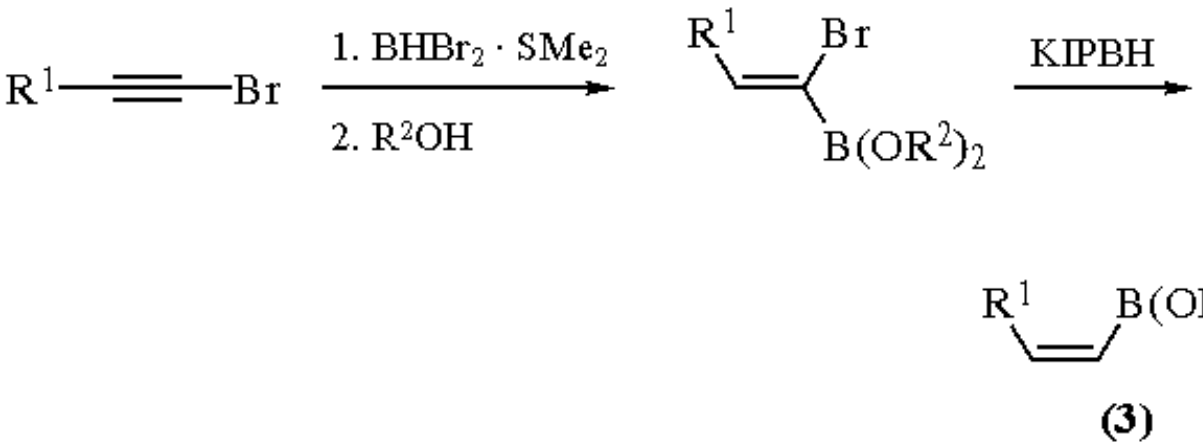

(4)

One-carbon homologation of boronic esters can be realized through reaction with ***Dichloromethyllithium***, followed by in situ reduction with KIPBH.[10] This procedure is of value in permitting the synthesis of boron derivatives not directly available through hydroboration and can be applied also to α-chiral boronic esters in order to obtain β-chiral boronic esters in an enantiospecific manner.[10b,c] The KIPBH reduction of α-chloro boronic esters is thought to proceed through the intermediate formation of the corresponding borohydride.[10b]

KIPBH is also effective in the carbonylation of organoboranes at 0 °C to obtain aldehydes or primary alcohols.[11] This reagent is superior to complex aluminum hydrides (lithium trimethoxyaluminum hydride and ***Lithium Tri-t-butoxyaluminum Hydride***, for example) because of its greater stability, chemoselectivity, and its simpler workup (no gelatinous precipitates). $LiBH_4$ undergoes the same reaction at ambient temperature.

KIPBH rapidly transfers hydride even to severely hindered trialkylboranes, which fail to react with KH, providing a convenient route to highly hindered potassium trialkylborohydrides.[2c,12]

Miscellaneous.

Transition metal formyl complexes can be prepared by reaction of transition metal carbonyl compounds with KIPBH.[12,13a-c]

Other uses of KIPBH in organometallic chemistry have been reported.[13d,e]

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(*S*)-Proline[1]

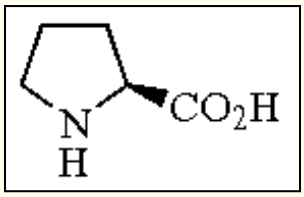

[147-85-3] · $C_5H_9NO_2$ · (*S*)-Proline · (MW 115.15)

(chiral auxiliary[1] in asymmetric synthesis)

Physical Data: mp 228-233 °C (dec.); [α]20D = -84° (*c* = 4, H_2O); ninhydrin yellow in color.

Solubility: sol H_2O, alcohol; insol ether.

Form Supplied in: white solid; widely available; inexpensive.

Analysis of Reagent Purity: measurement of optical rotation; mp.

Handling, Storage, and Precautions: cold and dry storage.

General Considerations.

In addition to its use in peptide chemistry, (*S*)-proline is often applied as a chiral precursor in the total syntheses of natural products, e.g. odorin,[2] pumiliotoxin,[3] petasinecine,[4] or threonine.[5] Some highly effective pharmaceuticals, such as optically pure ACE inhibitors, are prepared from L-proline.[6] In the last two decades, (*S*)-proline has attracted much attention as an optically active auxiliary in asymmetric synthesis.

Asymmetric Aldolization.

Proline mediates the asymmetric aldol cyclization of the prochiral triketone (**1a**) to the optically active bicyclic enedione (*S*)-(**3a**) (eq 1).[7,8] Optical yields up to 94% are realized, depending on the solvent used. The enedione (**3**) is prepared directly in the presence of an acid such as $HClO_4$. In the absence of acid, the aldol (**2**) is frequently isolated. Among the amino acids tested, (*S*)-proline gives the best results in almost every case. With (*S*)-proline the (*S*) configured products (**3**) are usually obtained. Enediones such as (**3**) are important building blocks for the synthesis of steroids or alkaloids[9] because natural steroids have the same configuration at C-13. Analogously, the Wieland-Miescher ketone (*S*)-(**3e**) is prepared with 70% ee from the cyclic prochiral triketone (**1e**) in the presence of (*S*)-proline.[10] Optically pure enedione (*S*)-(**3e**) is obtained by a single crystallization of the product mixture having an enantiomeric excess over 50%.

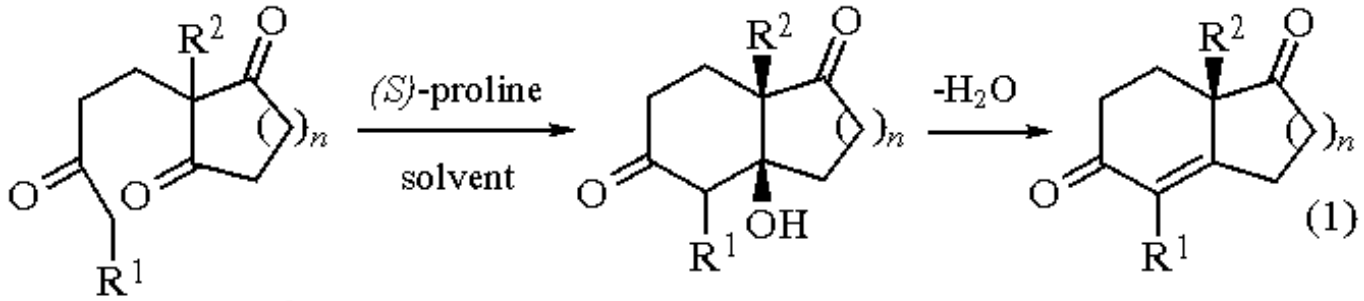

(1a) R = H, R^2 = Me, $n = 1$ **(2)** **(3)**
(1b) R = H, R^2 = Et, $n = 1$
(1c) R = $(CH_2)_2CH{=}CH_2$, R^2 = Me, $n = 1$
(1d) R = $(CH_2)_2$-2-(6-Me-pyridyl), R^2 = Me, $n = 1$
(1e) R = H, R^2 = Me, $n = 2$
(1f) R = Me, R^2 = Me, $n = 2$

An asymmetric aldolization was successfully applied to the preparation of gibbane.[11] The total synthesis of the macrolide antibiotic erythromycin was developed involving an asymmetric aldolization step catalyzed by proline.[12] Since the mid-1970s, a flood of papers has appeared dealing with the asymmetric aldolization of various triketones. Some results are listed for comparison in Table 1.

Table 1 Asymmetric Aldolization of Prochiral Triketones (**1**)

Educt	(*S*)-Proline (mol %)	Solvent	Product	Chemical yield (%)	Optical yield (%)
(1a)	4	DMF	**(2a)**[13]	97	94
(1a)	47/$HClO_4$	MeCN	**(3a)**[13]	90	82
(1a)	100	MeCN	**(2a)**[8]	97	97
(1a)	50/$HClO_4$	MeCN	**(3a)**[7]	87	84
(1a)	3	DMF	**(2a)**[8]	100	93
(1b)	30	DMF	**(2b)**[8]	71	100
(1b)	50/HCl	DMF	**(3b)**[7]	76	80
(1c)	100/$HClO_4$	MeCN	**(3c)**[14]	22	20
(1d)	120/$HClO_4$	MeCN	**(3d)**[15]	67	26
(1e)	5	DMSO	**(3e)**[10]	71	70
(1e)	50/$HClO_4$	MeCN	**(3e)**[7]	83	71
(1f)	13.7	DMSO	**(3f)**[16]	43	38
(1f)	50/$HClO_4$	MeCN	**(3f)**[17]	74	15

The intramolecular asymmetric cyclization of open chain symmetrical triketone (**4**) leading to (*R*)-(**5**) proceeds with 16% ee (eq 2).[18]

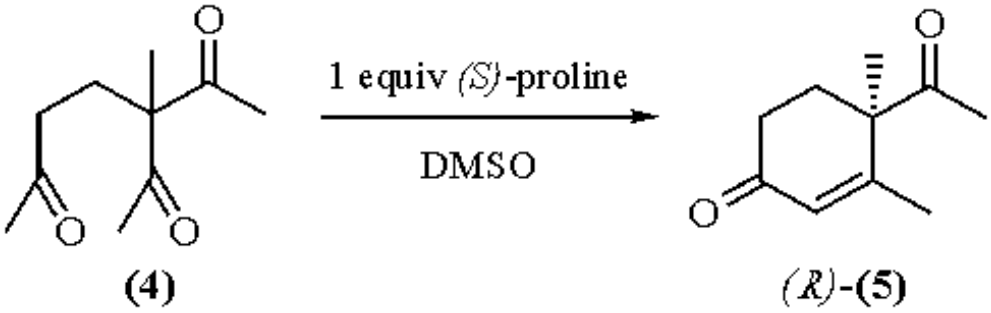

(2)

Even acyclic 1,5-diketones (**6**) are cyclized enantioselectivitely in the presence of (*S*)-proline.[19] Depending on the structure of the cyclic α,β-unsaturated ketone, (R)-(**7**) is obtained in up to 43% (R = Me) optical yield (eq 3).

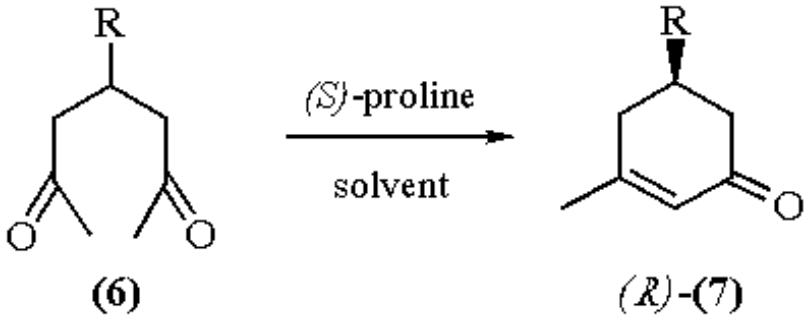

(3)

The mechanism of the proline-catalyzed enantioselective aldol reaction has been studied.[20] An extension of the asymmetric aldolization deals with the cyclization of diketones.[21] Also investigated was the dehydration of racemic β-ketols in the presence of (*S*)-proline and a kinetic resolution was observed.[22]

Asymmetric Michael Addition.

An intramolecular Michael reaction catalyzed by (*S*)-proline leads to the chiral thiadecalin (**9**) and thiahydrindan (**11**) and (**12**).[23] Enone (**8**) undergoes cyclization in the presence of (*S*)-proline to give exclusively the *trans* isomer (**9**) (eq 4). The thiahydrindandions (**11**) and (**12**) are obtained from (**10**) as a 1:1 mixture of the *cis* and *trans* isomers (eq 5).

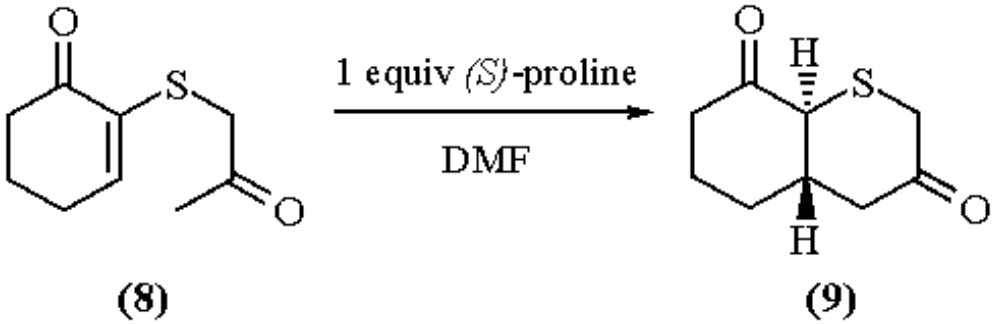

(4)

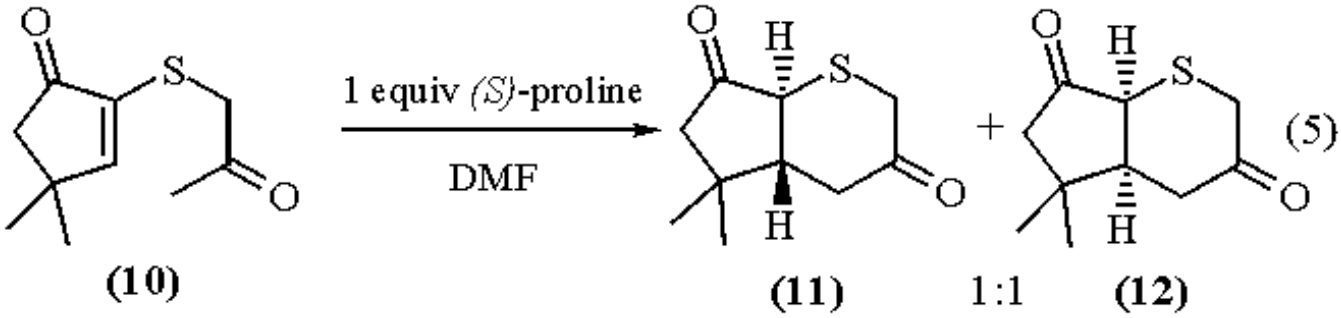

(5)

The intramolecular asymmetric Michael reaction of acyclic compounds obtained from chiral alkaloid building blocks using amines and (*S*)-proline has been investigated.[24] The Michael addition of dimethyl malonate to α,β-unsaturated aldehydes proceeds smoothly with a catalytic amount of (*S*)-proline lithium salt.[25] However, no asymmetric induction was observed.

Asymmetric Halolactonization.

An asymmetric halolactonization reaction using proline as a chiral auxiliary has been reported.[26] Optically active α-hydroxy acids (**16**) are prepared from α,β-unsaturated acids via the corresponding (*S*)-proline amide (**13**) involving an asymmetric bromolactonization step (eq 6).[26a]

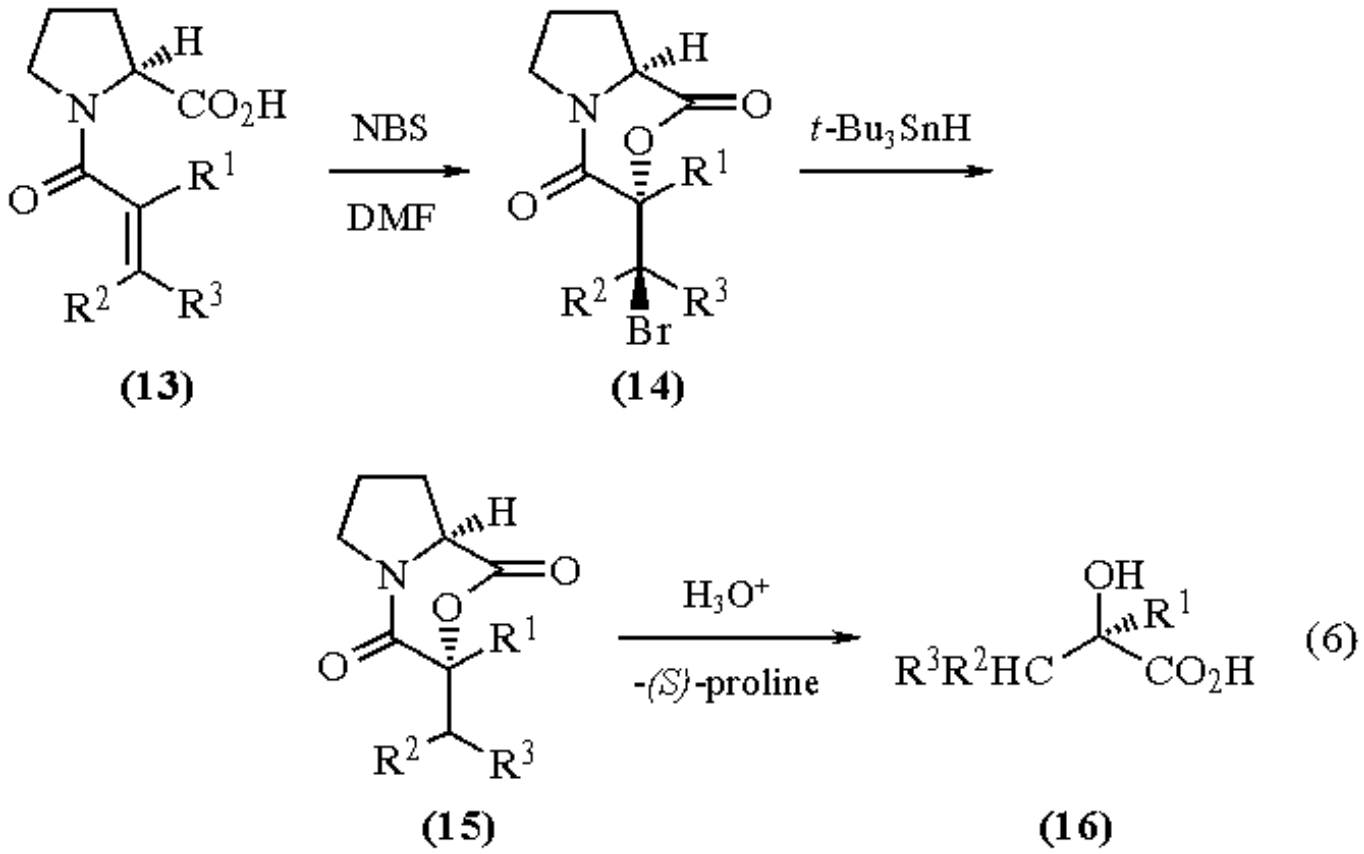

The unsaturated carboxylic acid (**13**) undergoes an asymmetric bromolactonization when treated with ***N-Bromosuccinimide*** in DMF. The bromolactone (**14**) and its diastereomer are obtained in a 94.5:5.5 ratio. Reduction and hydrolysis yields the α-hydroxy acid (**16**) in an overall optical yield of 90%. The same procedure gives chiral α-hydroxy ketones.[26c]

A modification of the asymmetric bromolactonization leads to optically active α,β-epoxy aldehydes (**18**).[26d,e] Treatment of the bromolactone (**14**) with ***Sodium Methoxide*** results in the formation of the epimeric epoxy ester (**17**) in a ratio of 2:1 (eq 7).

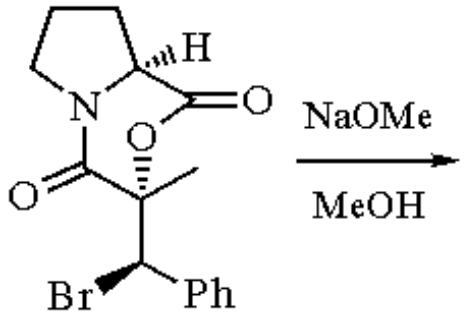

(14)

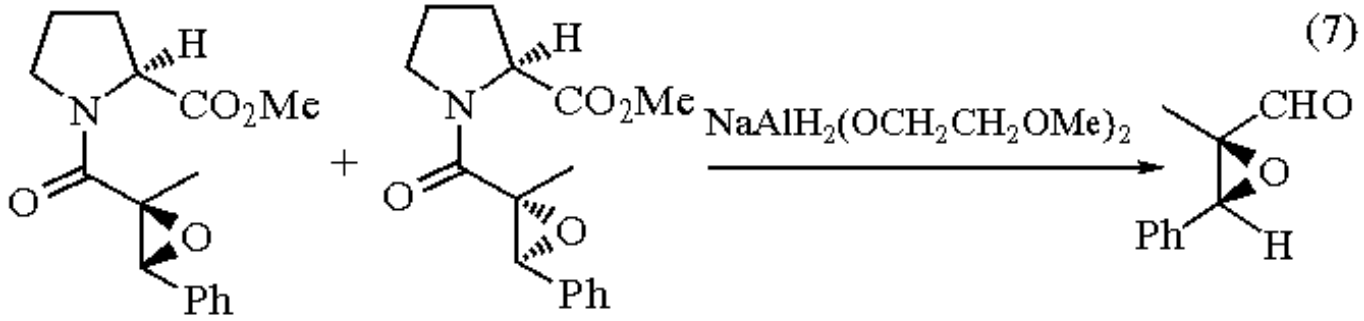

(7)

(17a) 2:1 (17b) (2*R*,3*S*)-(**18**)

The reductive cleavage of the proline derivative yields the chiral α,β-epoxy aldehyde (2*R*,3*S*)-(**18**) in 98% ee. Even natural product syntheses can be realized utilizing the bromolactonization procedure.[26h,i]

Reduction of C=O and C=N Bonds.

Asymmetric reductions of prochiral ketones (**19**) to the corresponding chiral alcohols (**20**) using (*S*)-proline-modified borohydride reagents as the reductant have been published. The borane reductions of ketones (**19**) employing (*S*)-proline as chiral mediator proceeds with enantiomeric excesses up to >95%. It is proposed that the in situ produced (*S*)-prolinol reacts with borane to form the oxazaborolidine (*S*)-(**21**) as the reducing catalyst (eq 8).[27]

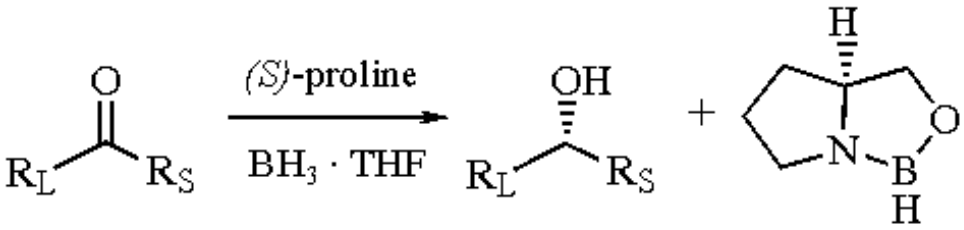

(8)

(**19**) (*R*)-(**20**) (*S*)-(**21**)

The (*S*)-prolinate-borane complex (*S*)-(**22**) reduces ketones to the corresponding alcohols with optical yields up to 50%.[28] The asymmetric reduction of cyclic imines (**24**) with chiral sodium triacyloxyborohydride (*S*)-(**23**) was utilized to prepare optically active alkaloids (**25**) with optical yields up to 86% (eq 9).[29]

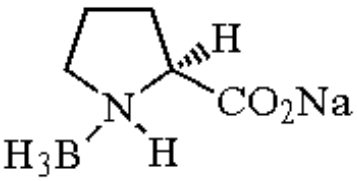

(*S*)-(**22**)

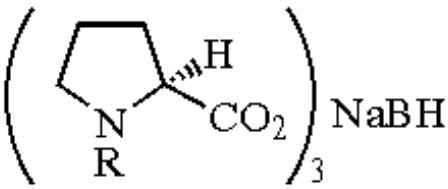

(*S*)-(**23**)

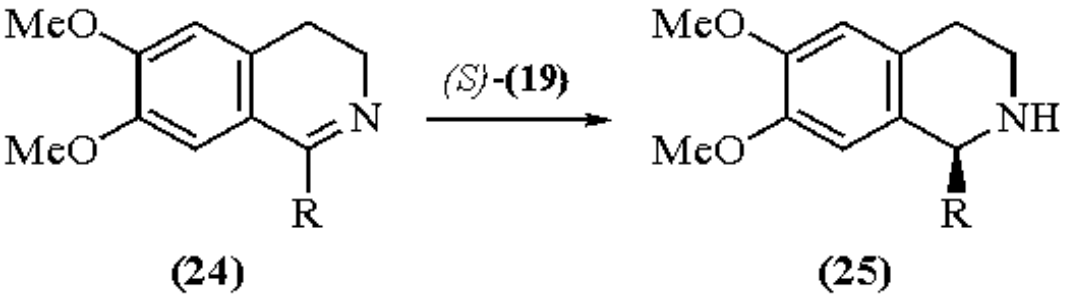

(9)

The hydrogenation of various ketones with heterogeneous ***Palladium on Carbon*** or ***Raney Nickel*** catalysts in the presence of (*S*)-proline proceeds to produce the corresponding optically active alcohols with low optical yields (up to 23%).[30]

Reduction of C=C Bonds.

The reduction of the C=C double bond of isophorone (**26**) with Pd/C in the presence of (*S*)-proline yields the saturated ketone (**27**) with 60% optical purity (eq 10).[30a,31] With (*S*)-proline ester/Pd (or Pt) systems the hydrogenation of ethyl pyruvate, an α-keto ester, was investigated, but only insignificant enantioselectivities were reached.[32]

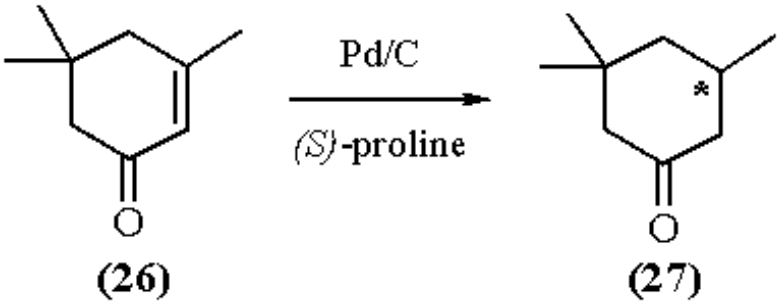

(10)

An efficient synthesis of (*S*)-amino acids from α-keto acids via a diastereoselective hydrogenation step with (*S*)-proline as the chiral inducer was reported (eq 11).[33] Optical yields up to 90% were reached.

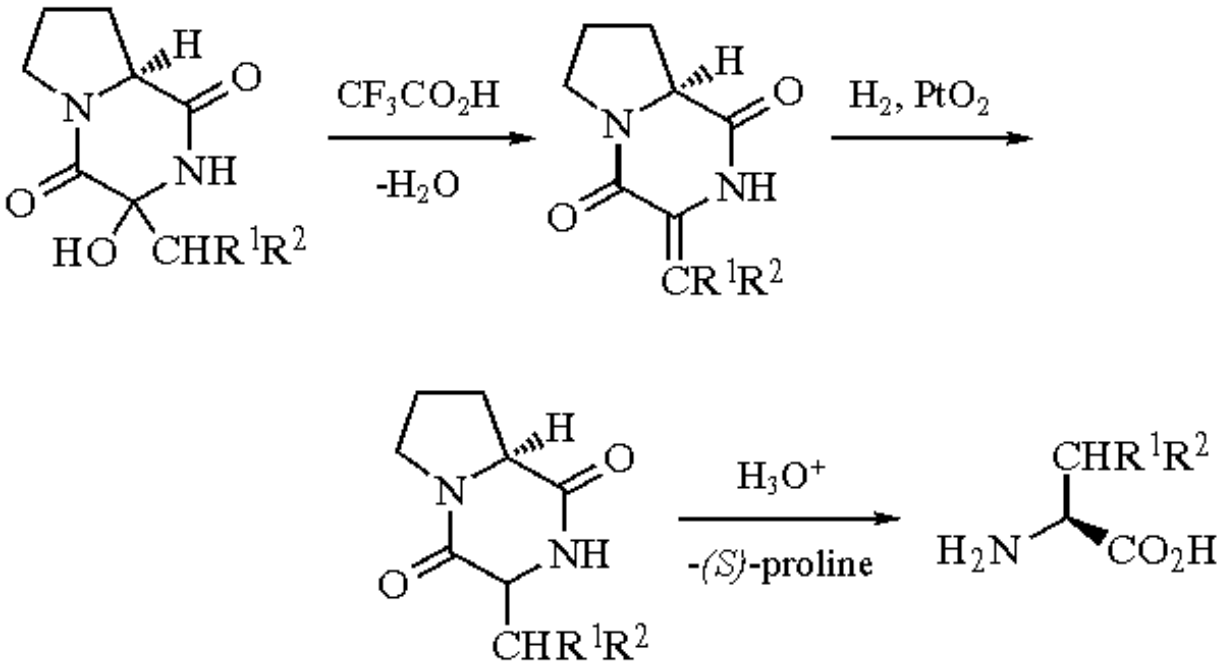

(11)

Racemization of Amino Acids.

The synthesis of (*R*)-alanine was achieved starting from (*S*)-alanine via formation of the imidazoline with (*S*)-proline.[34] This result can be explained in terms of epimerization and stereoselective protonation with asymmetric induction by the chiral center originating from (*S*)-proline.

Resolution of Amino Acids.

For the optical resolution of racemic threonine via replacing resolution, (*S*)-proline was utilized as an optically active cosolute although the structure of the imino acid is different from that of threonine.[35] The same procedure was applied less sucessfully to the resolution of (*R*,*S*)-thiazolidine carboxylic acid.[36]

Synthesis of Unnatural (*S*)-Proline Derivatives.

The condensation of pivaladehyde with (*S*)-proline yields stereoselectively, after lithiation and reaction with an electrophile, the bicyclic compound (**28**), which is a versatile educt for the synthesis of many α-substituted proline analogs (**29**) (eq 12).[37] The reactions proceed via the formation of a chiral lithium enolate without the use of a chiral auxiliary (self-reproduction of chirality). The reaction with a variety of electrophiles *cis* to the *t*-Bu group yields a plethora of α-substituted (*S*)-proline derivatives (**29**). A limitation of this strategy is the acetal cleavage of some substituted products (**28**).[38]

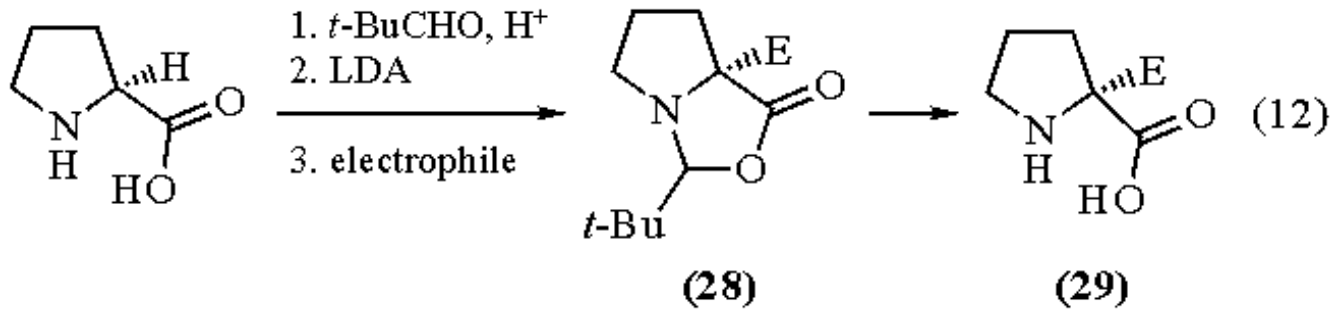

The β-amino acid homoproline can be synthesized via an Arndt-Eistert reaction from (*S*)-proline.[39]

Synthesis of Optically Active Phophorus Compounds.

A series of chiral organophosphorus compounds (**33**) have been prepared in which the phophorus atom is the stereogenic center (eq 13).[40] The best stereoselectivity is reached with (*S*)-proline esters (**30**) as the chiral auxiliary. The reaction of phosphonic acid chloride (**31**) with (*S*)-proline ethyl ester affords a mixture of diastereomeric amides (**32**) in high stereoselectivity. The diastereomers can easily be purified by chromatography. The chiral organophosphorus compounds (**33**) are obtained from hydrolysis of (**32**).

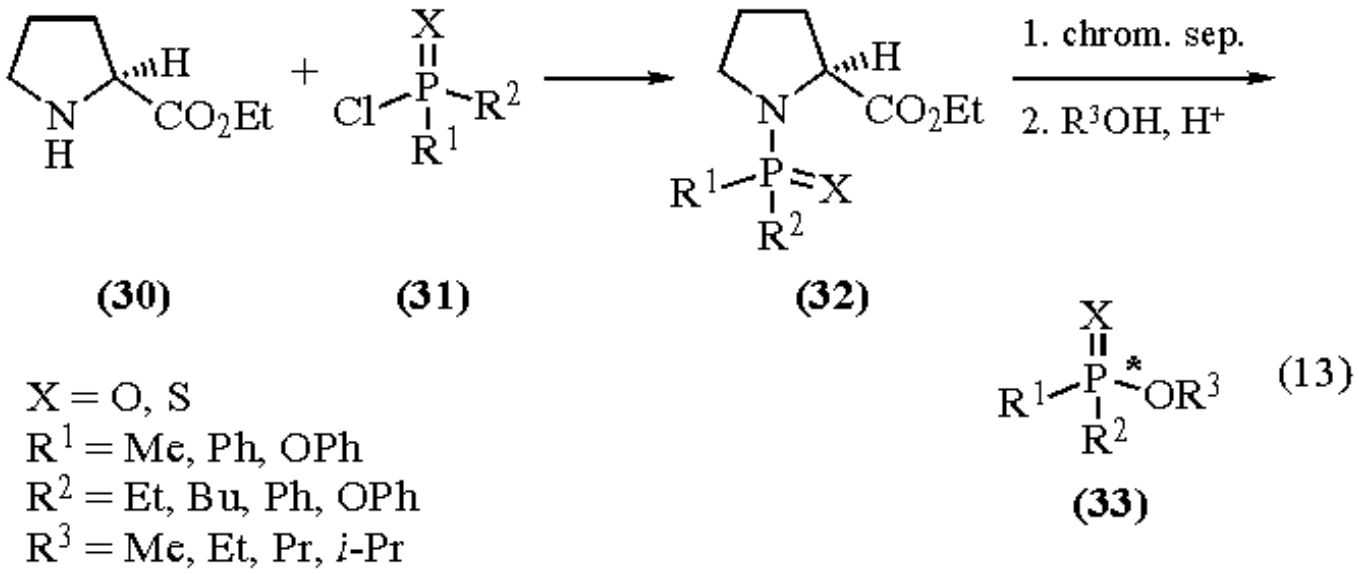

Alkylations and Allylations.

The asymmetric alkylation of chiral enamines derived from (*S*)-proline esters has been disclosed.[41] The α-alkylation of cyclohexanone proceeds with an optical purity of 59%. (*S*)-Proline catalyzes the alkylation of xanthopurpurin (**34**) by 2-hydroxytetrahydropyran[42] yielding (**35**), which was later used in the synthesis of the racemate of the pigment averufanin (eq 14).[43] With phenylacetaldehyde, two molecules react to build up an anomeric mixture of lactols with a new pyran ring.[44] In each case, no enantioselectivity is detected.

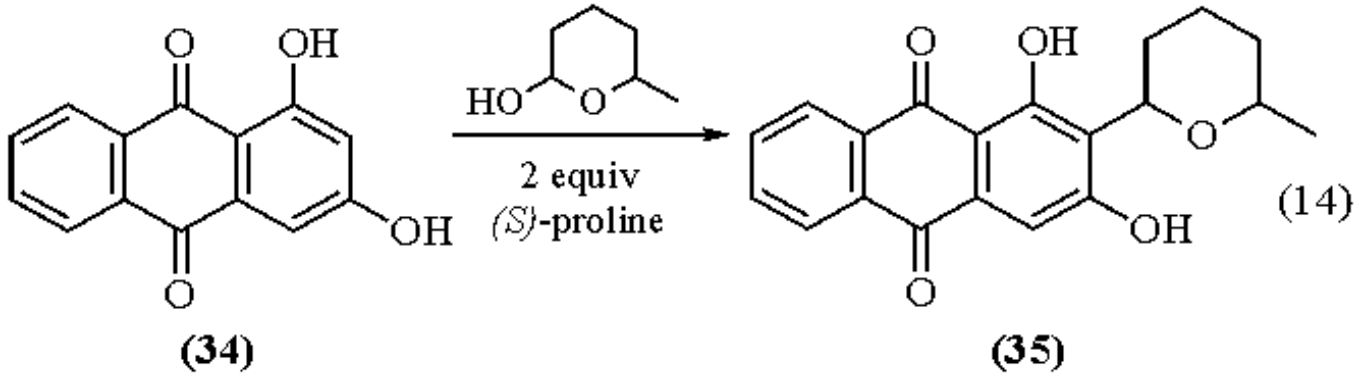

The stereoselective allylation of aldehydes was reported to proceed with allyltrifluorosilanes in the presence of (*S*)-proline.[45] The reaction involves pentacoordinate silicate intermediates. Optical yields up to 30% are achieved in the copper-catalyzed allylic acetoxylation of cyclohexene with (*S*)-proline as a chiral ligand.[46]

The intramolecular asymmetric palladium-catalyzed allylation of aldehydes, including allylating functionality in the molecules, via chiral enamines prepared from (*S*)-proline esters has been reported (eq 15).[47] The most promising result was reached with the (*S*)-proline allyl ester derivative (**36**). Upon treatment with ***Tetrakis(triphenylphosphine)palladium(0)*** and PPh_3 in THF, the chiral enamine (**36**) undergoes an intramolecular allylation to afford an α-allyl hemiacetal (**37**). After an oxidation step the optically active lactones (**38**) with up to 84% ee were isolated in high chemical yields. The same authors have also reported sucessful palladium-catalyzed asymmetric allylations of chiral allylic (*S*)-proline ester enamines[48] and amides[49] with enantiomeric excesses up to 100%.

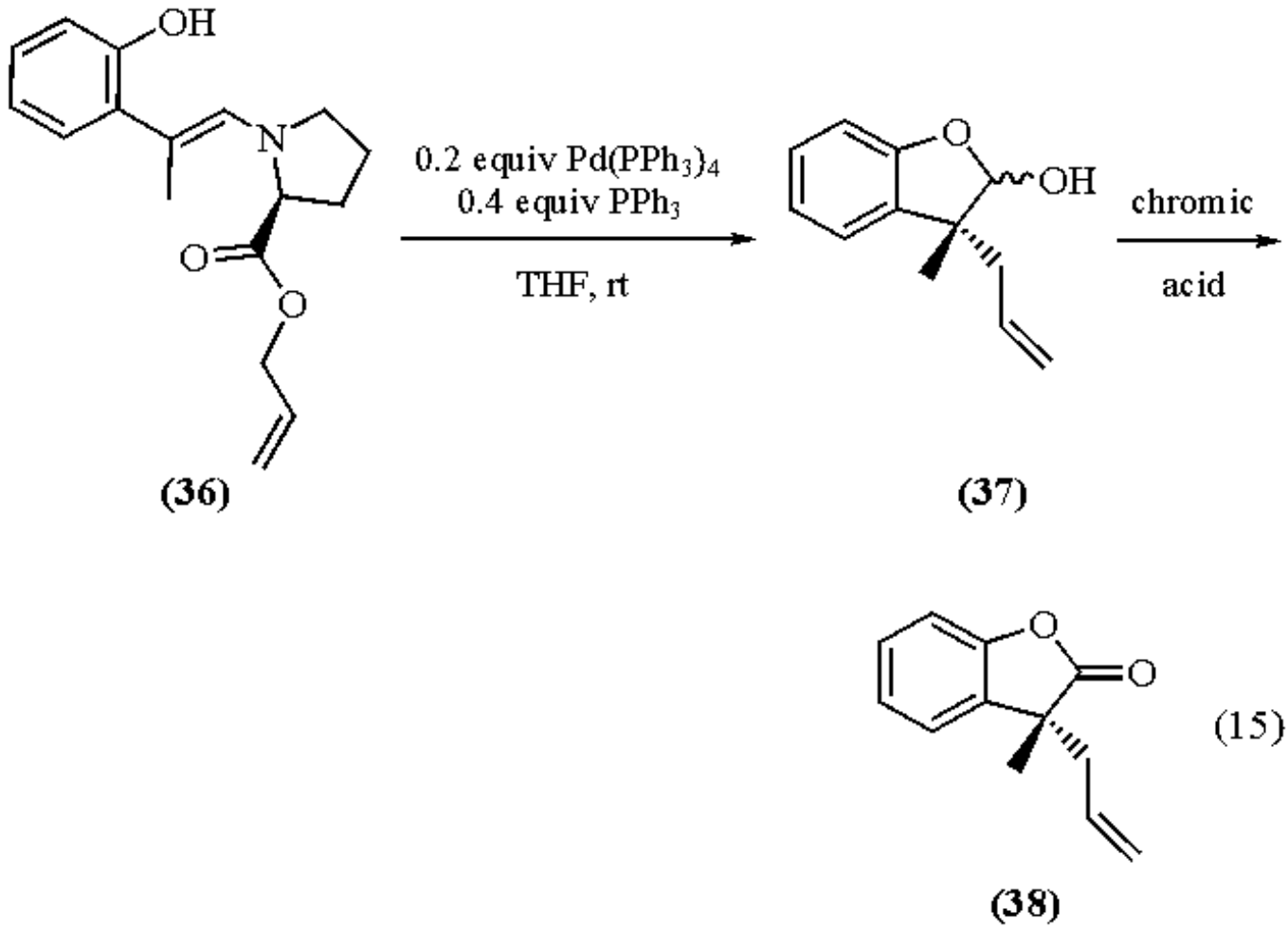

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1,3-Propanediol[1]

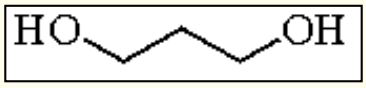

[504-63-2] · $C_3H_8O_2$ · 1,3-Propanediol · (MW 76.10)

(preparation of acetals,[2,3] quinolines,[4] indoles,[5] boron esters;[6] traps Wacker aldehyde intermediates;[7] reaction solvent for Wolff-Kishner reduction[8])

Alternate Name: trimethylene glycol.

Physical Data: liquid, bp 214 °C; mp -27 °C; *d* 1.053 g cm^{-3}.

Solubility: sol H_2O, alcohol; ν sol ether; sol (hot) benzene.

Form Supplied in: >97% purity, depending on supplier.

Purification: dried with K_2CO_3 and distilled under reduced pressure.

Reactions with Carbonyls.

The chemistry of 1,3-propanediol (**1**) is dominated by acetal[2,3,9,10] formation.[11] Its ketone acetals show differential hydrolytic stability: cyclopentanone acetals hydrolyze faster than cyclohexanone acetals, and both hydrolyze faster than ethylene glycol-derived acetals (Table 1).[3a] The ketone-acetal equilibrium lies far to the left.[3] Its aldehyde acetals, however, show the opposite behavior and are hydrolytically more stable than ethylene glycol acetals.[3b,12] Polyketones[3] and 1,4-diones[13] may be selectively protected by judicious choice of substituted 1,3-propanediols. For protection of steroidal ketones, (**1**) is preferred over ethylene glycol, which is susceptible to attack by alkyllithium reagents.[10]

Table 1 Relative Hydrolysis Rates of 5α-Androstane Acetals

Glycol	3-Acetal	17-Acetal
Ethylene glycol	1.0	1.64
1,3-Propanediol	14.5	40.5

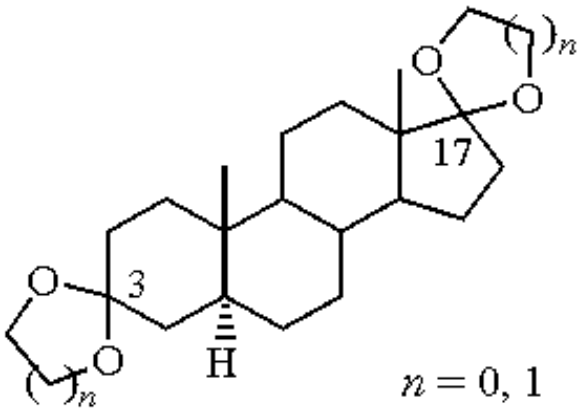

Conversion to Reactive Intermediates.

Acrolein condenses with (**1**) to give 2-(2-bromoethyl)-1,3-dioxane,[2] which finds use as a three-carbon homologating agent (eq 1)[14] and in the preparation of γ-keto aldehydes.[15] Use of (**1**) is essential as the corresponding ethylene glycol dioxolane is thermally unstable[2] and gives Grignard reagents that tend to autodestruct.[15,16] Hydrolysis of the product acetals requires special conditions.[14,15]

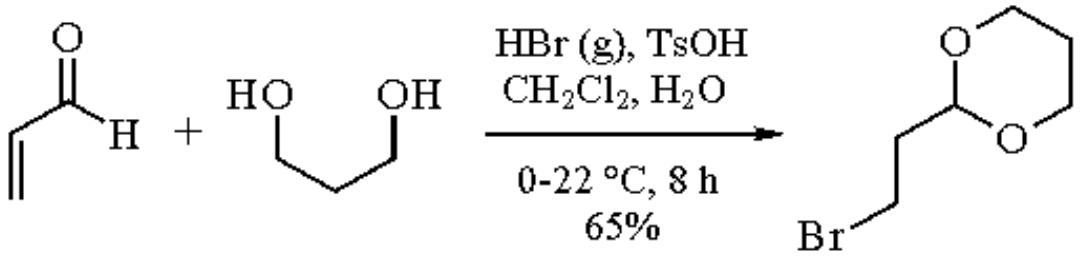

(1)

Diol (**1**) is used to prepare cyclopropenone acetal (**2**).[17,18] Its highly nucleophilic double bond forms addition products with alcohols and amines[17] and cycloaddition products with dienes to give norcarenes,[17] ketones to give furanones and oxetanes,[17] aldehydes to give butenolide, furan, and γ-keto ester derivatives (eq 2),[18] electrophilic alkenes to give cyclopropanes[19] and functionalized cyclopentenones,[20] and an α-pyrone to give a cycloheptatrienone.[21]

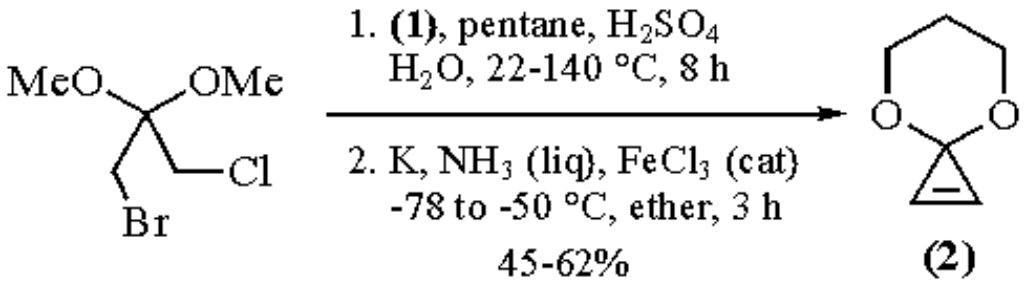

(2)

Formation of Boron Esters.

Esterification of boronic acid derivatives occurs readily with (**1**), and has been used in many hydroboration reaction sequences.[6,22] The six-membered ring boronates are more stable than the corresponding five-membered ring or acyclic products made from 1,2-diols or alcohols. The title reagent has been used to regenerate carbohydrates from boronate derivatives.[23]

Heterocycle Synthesis.

Alkyl (**3**)[24] and alkoxy (**4**)[25] 1,3,2-dioxophosphorinane 2-oxides are prepared in good yields by base-catalyzed condensation of (**1**) with the appropriate phosphonous dichloride. Iminosulfinyl dichlorides react similarly.[26] With DCC, (**1**) gives 2-imino-1,3-oxazine (**5**) (CuCl, 95%) which is converted into urea derivatives in high yields.[27]

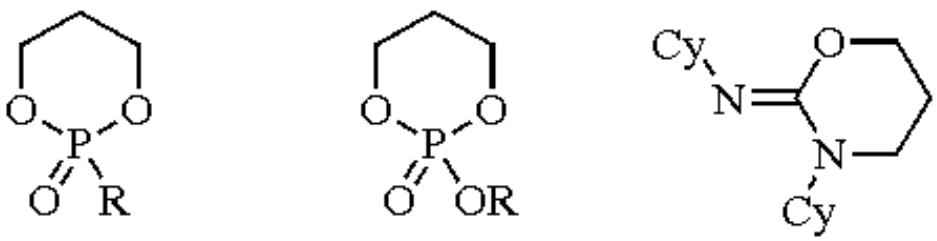

(3) (4) (5)

In an alternative route to the Skraup synthesis, quinolines are prepared from (**1**) and primary anilines (eq 3). Choice of stoichiometry, solvent, and ligand greatly affect yield.[4]

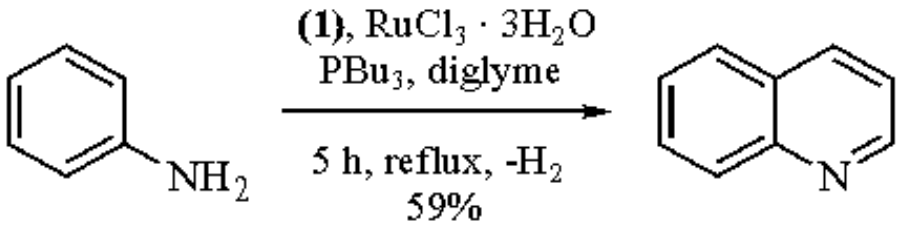

(3)

Regioselective synthesis of indoles is accomplished by in situ trapping of Wacker aldehydes with (**1**) (eq 4). *o*-Vinylacetanilides give indoles directly under similar reaction conditions.[5] Isocoumarins and 1-isoquinolinones are also prepared by this chemistry.[28] Electron-deficient alkenes give acetals with (**1**) under Wacker conditions (see ***Palladium(II) Chloride-Copper(I) Chloride***).[7]

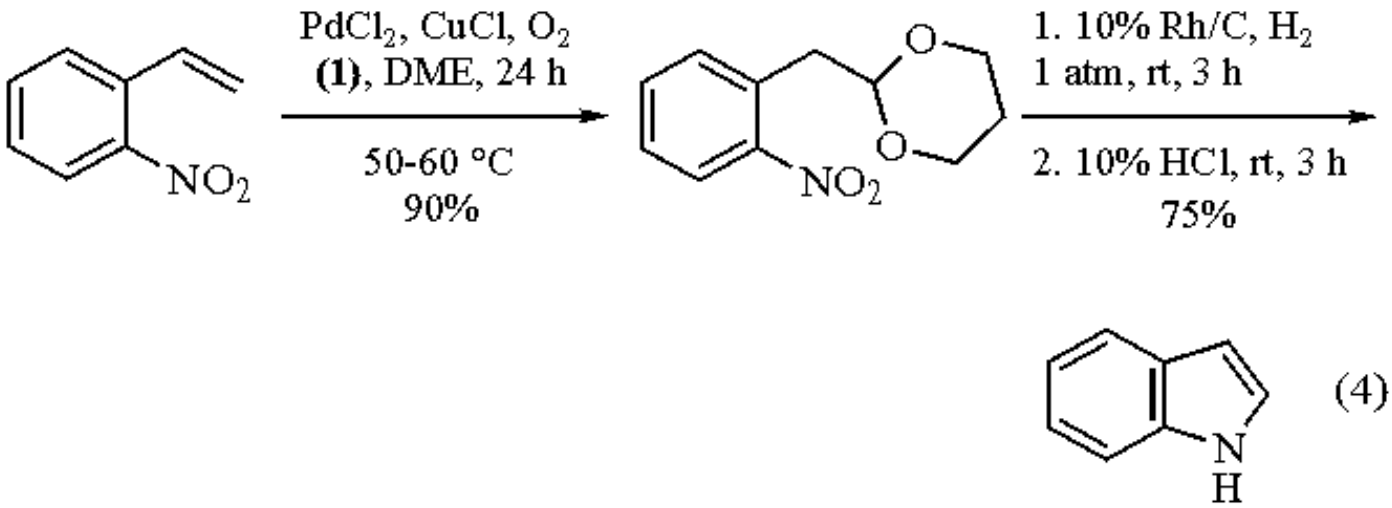

(4)

Miscellaneous Transformations.

1,3-Propanediol can be converted to 3-chloro-1- (60%),[29] 3-iodo-1- (68%),[30] and 3-bromo-1-propanol (90%)[31] or to 1,3-dibromopropane (85-95%).[32] With imidoyl chlorides, 3-chloropropyl benzoates are produced.[33] The title reagent has good solvent properties and finds use in the Wolff-Kishner reduction.[8] Cyclohexenones and (**1**) give hydroxypropyl phenols under oxidative conditions (eq 5).[34]

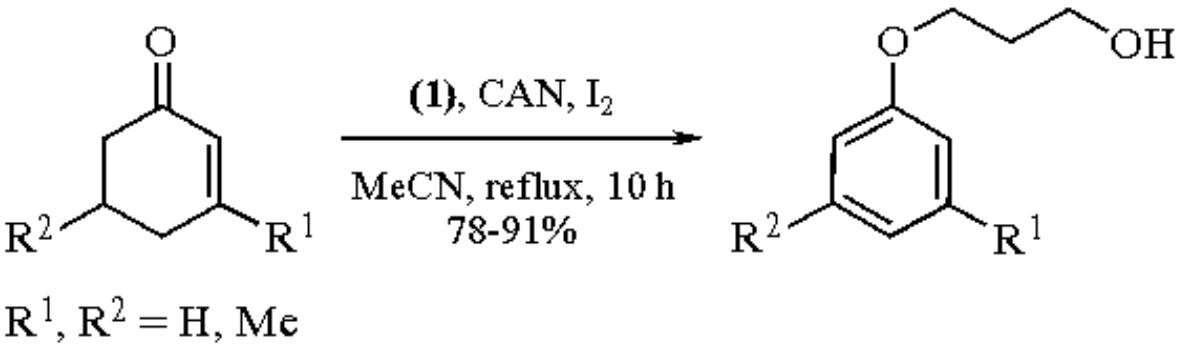

(5)

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1,3-Propanedithiol[1]

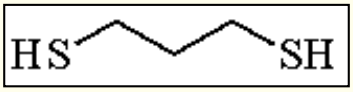

[109-80-8] · $C_3H_8S_2$ · 1,3-Propanedithiol · (MW 108.25)

(1,3-dithiane formation; reduction (carbonyl to methylene, azide to primary amine, peptidic disulfide to dithiol, demercuration); ketene dithioacetal formation)

Physical Data: d^{20} 1.077 g cm^{-3}; bp 170 °C/760 mmHg, 92-98 °C/56 mmHg.

Solubility: slightly sol water; miscible with many organic solvents.

Form Supplied in: liquid; widely available.

Handling, Storage, and Precautions: stench! Use in a fume hood. Can undergo air oxidation to form disulfides. The cyclic disulfide forms a polymeric precipitate in methanol.[17a] Extraction into aqueous NaOH serves to separate thiols from nonacidic impurities.[1f] For toxicity data, see ***1,2-Ethanedithiol***.

1,3-Dithiane Formation.

1,3-Propanedithiol (**1**) condenses under protic or Lewis acid catalysis with aldehydes and ketones to afford 1,3-dithianes (eqs 1-4).[2-5] Useful for carbonyl protection, the 1,3-dithianyl group is compatible with aqueous acid, strong bases, anionic (eq 3)[4] and Pd-catalyzed (eq 5)[6a] C-C bond-forming reactions, catalytic hydrogenation in the presence of the Crabtree catalyst,[6b] and many other synthetic processes.[7] Often, (**1**) shows useful selectivity in reactions with dicarbonyl compounds (eq 3; structures **2-5**).[4,8] In contrast to acetalization with diols,[9a] (**1**) reacts selectively with α,β-alkenyl ketones in the presence of moderately hindered saturated ketones;[1c] double bond migration is not observed;[1a] conjugate addition can compete if sterically favored.[9b] In α,β-alkynyl ketones (not aldehydes),[10a] conjugate addition prevails (eq 6).[10b]

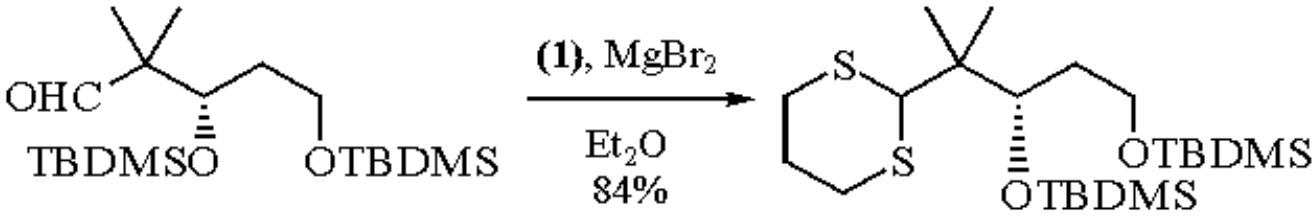

(1)

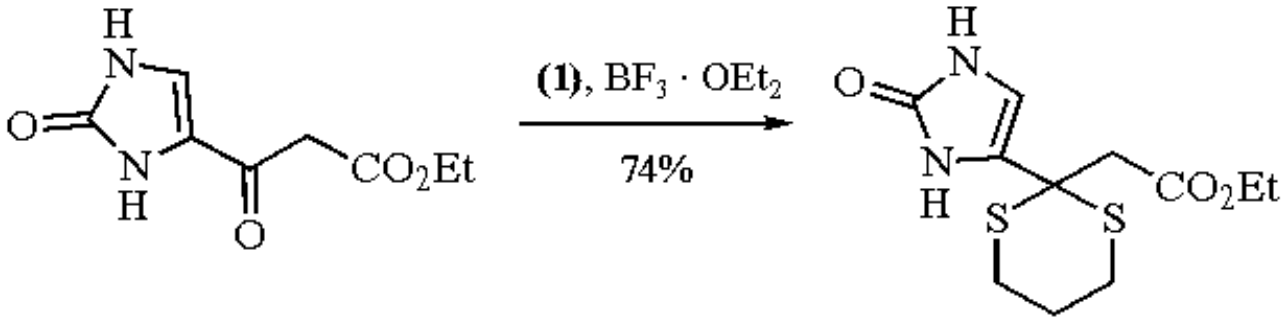

(2)

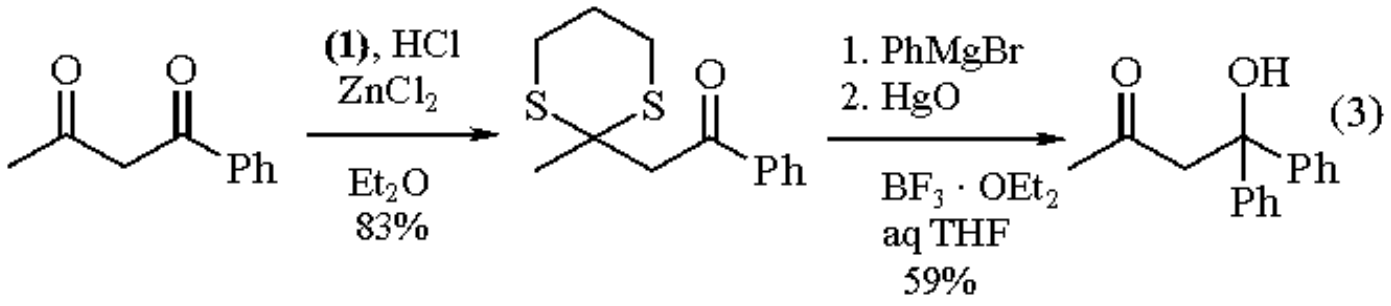

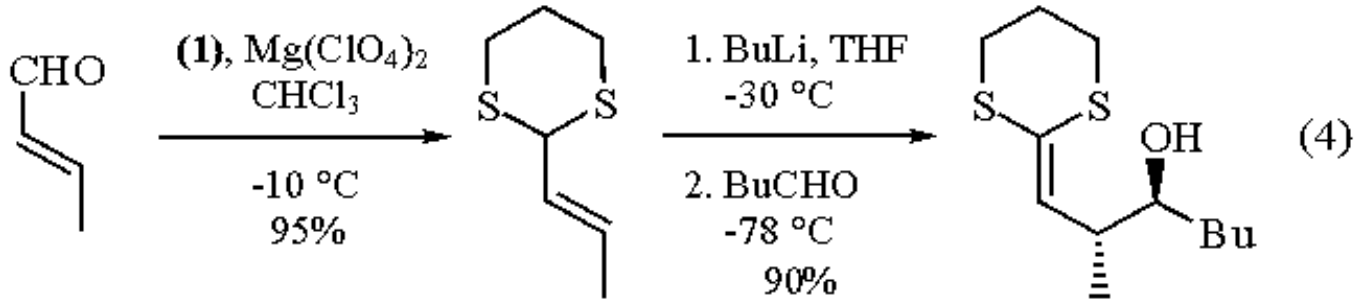

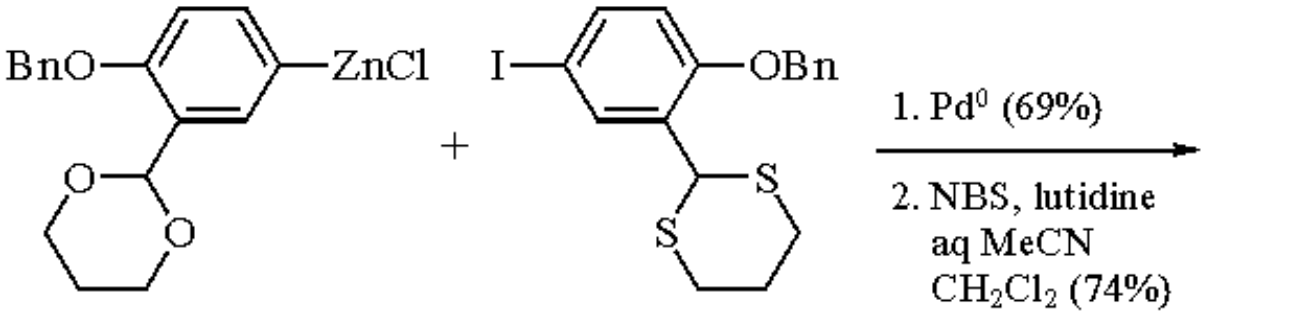

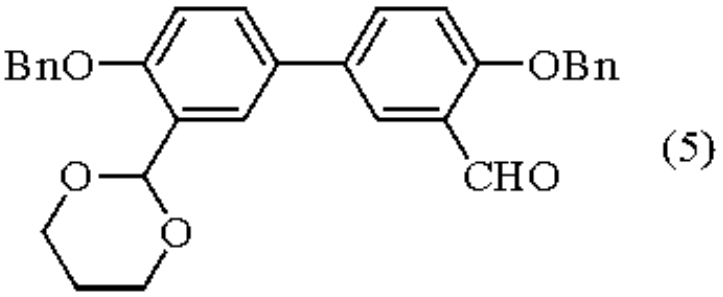

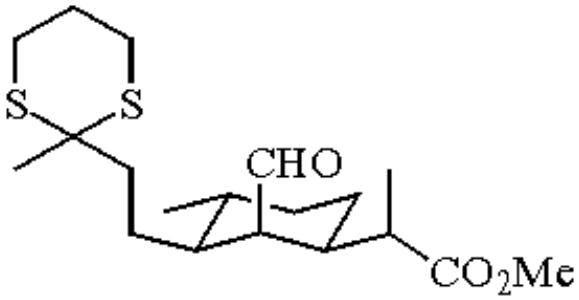

(2) [**(1)**, $BF_3 \cdot OEt_2$, 55-65%]

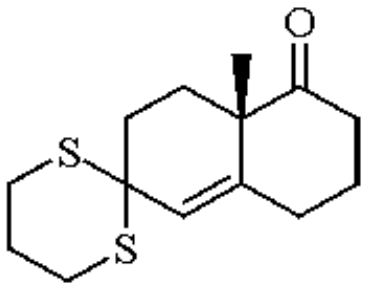

(3) [**(1)**, $TeCl_4$, 68%]

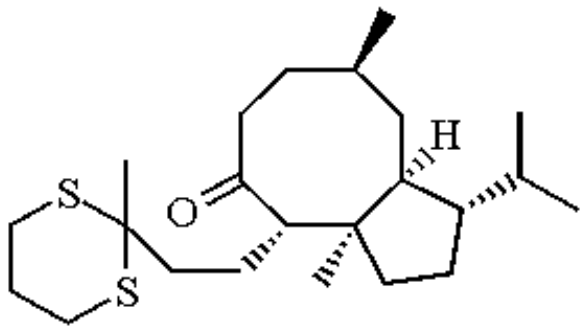

(4) [(**1**), $BF_3 \cdot OEt_2$, >98%]

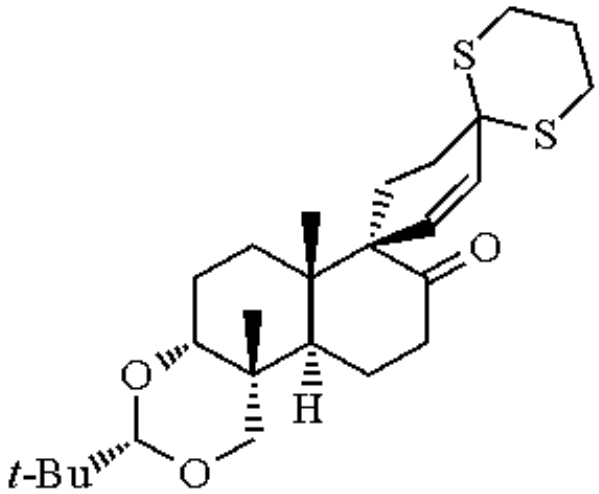

(5) [bis-TMS-(**1**), ZnI_2, 88%]

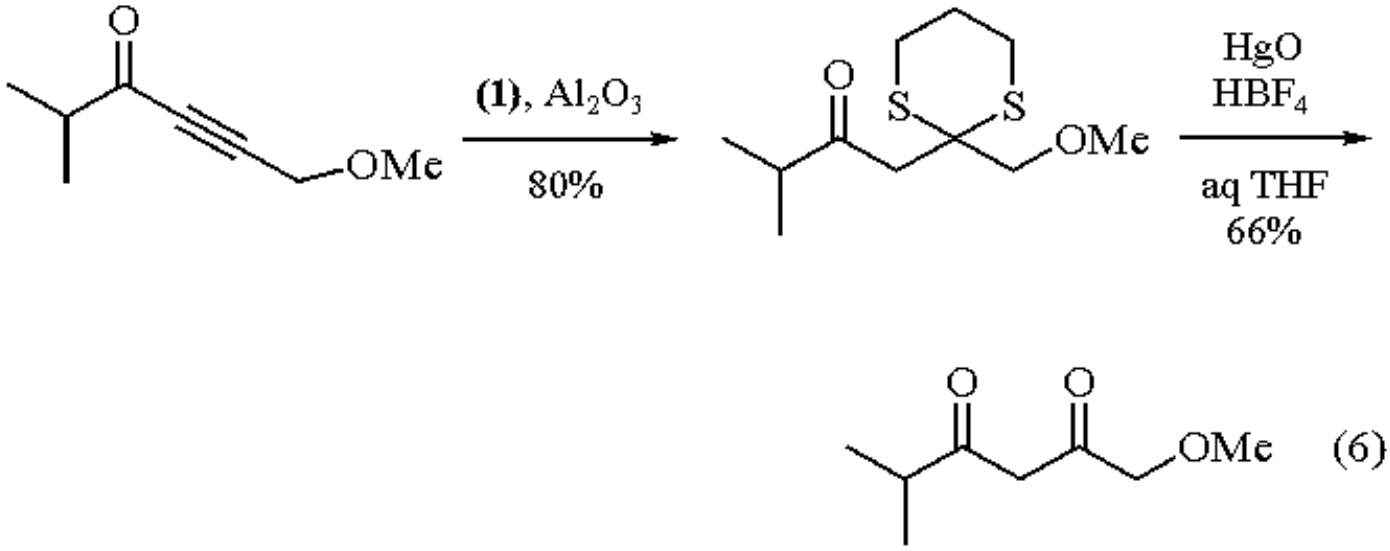

(6)

Acetals, enol ethers, and oxazolidines also give dithianes with (**1**) (eqs 7-12).[11a-f,12] This reaction can be useful for opening resistant cyclic structures;[13a,c] ***Titanium(IV) Chloride*** is an especially effective catalyst in such cases.[13b] Reaction of (**1**) with dihalomethanes,[14a,b] or with carboxylic acids in the presence of ***Tin(II) Chloride***,[14c] also yields 1,3-dithianes.

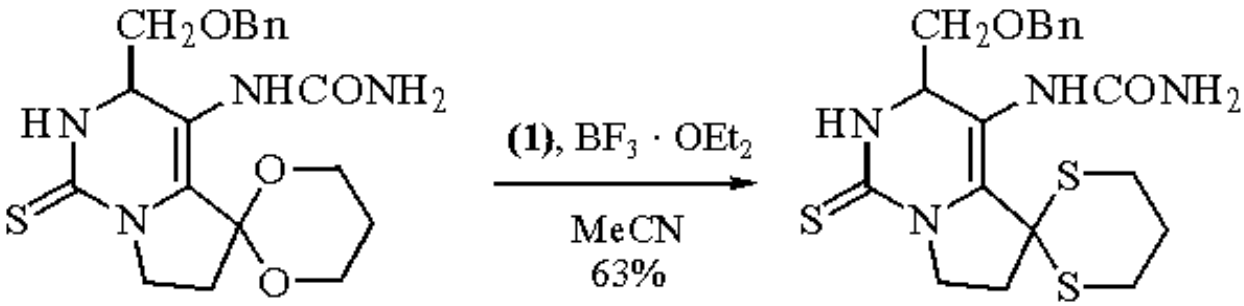

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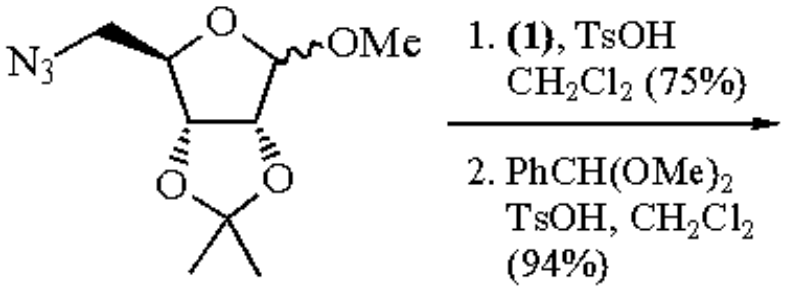

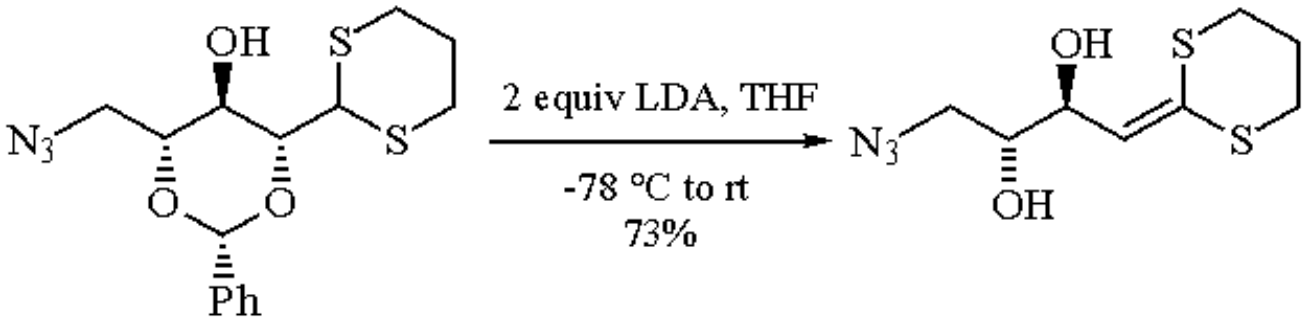

(8)

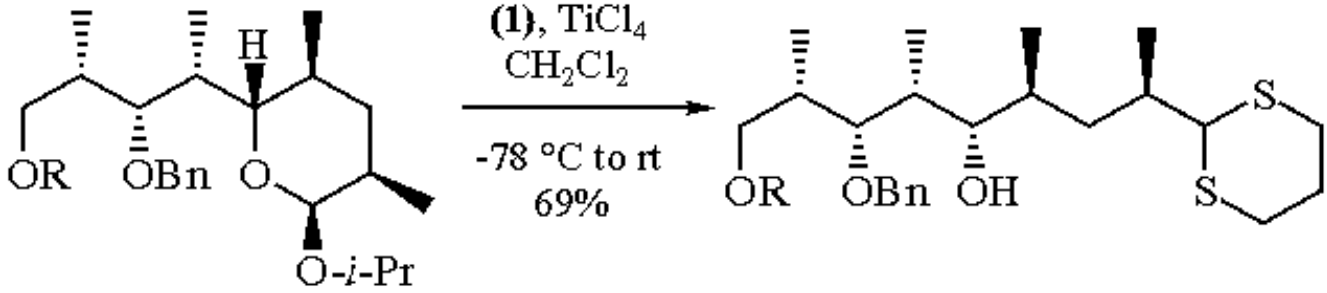

(9)

R = $SiPh_2$-*t*-Bu

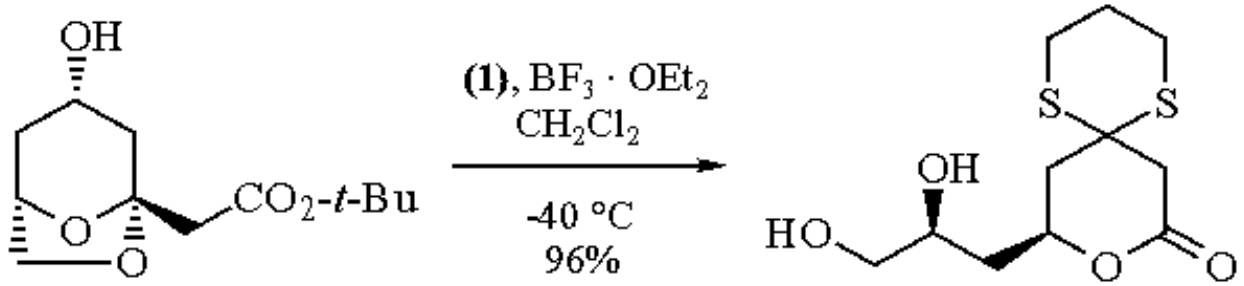

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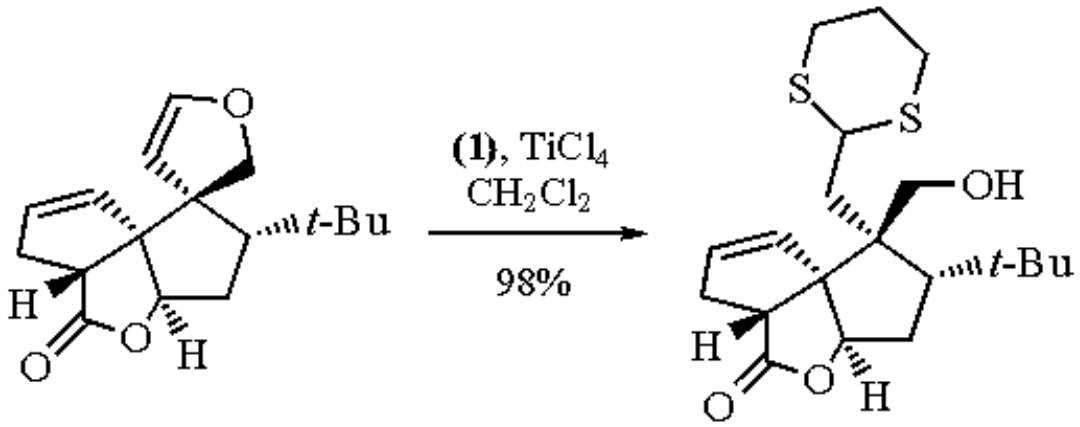

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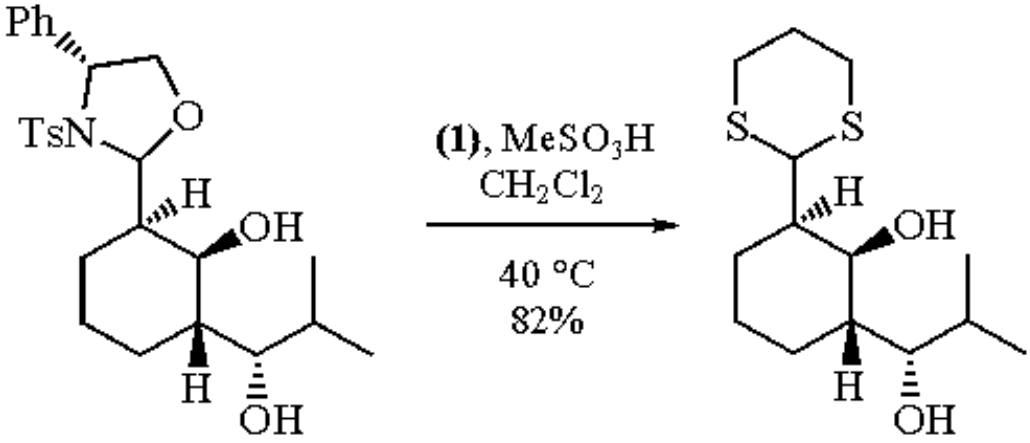

(12)

1,3-Dithianes derived from aldehydes are important synthetic intermediates because they undergo deprotonation to 2-lithio-1,3-dithianes which function as carbonyl anion equivalents (umpolung reagents).[1b-e] The vinylogous process (eq 4)[5] is a subject of current study.[15]

Regeneration of the carbonyl group can entail a trial-and-error process with the many procedures available.[1a-e] Hg^{II} salts and *N*-halo amides remain the most frequently employed reagents. Aqueous ***Iodomethane*** is a mild alternative.[8c] Epimerization at an α stereocenter does not normally attend the formation or removal of the dithianyl group (eqs 8, 9, 12, 13).

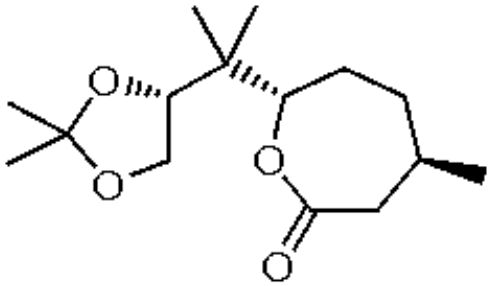

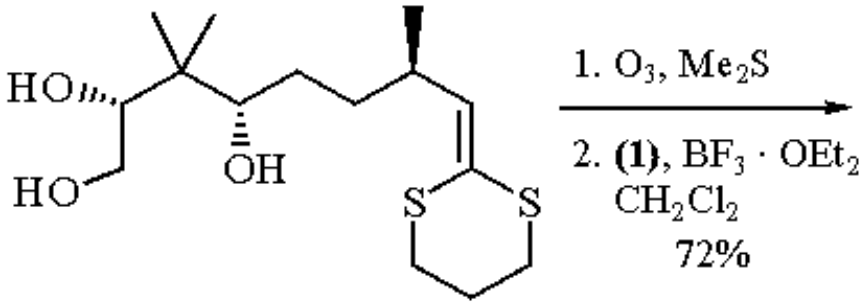

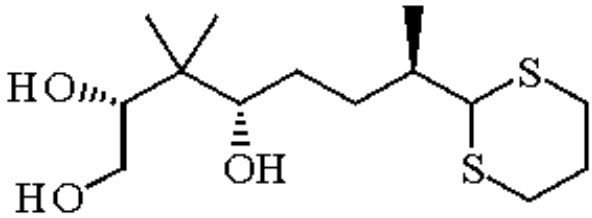

(13)

Reduction.

Raney Nickel treatment of thioacetals is a standard method for carbonyl-to-methylene reduction.[1b] In the presence of ***Triethylamine***, (**1**) reduces azides to primary amines (eq 14).[16a,b] Under the acidic conditions employed for thioacetal formation, this reduction does not occur (eq 8).[11b,16c] Reduction of peptidic disulfides to dithiols can be conveniently accomplished with (**1**).[17] Treatment with (**1**) effected demercuration α to an ester diastereoselectively (eq 15).[18]

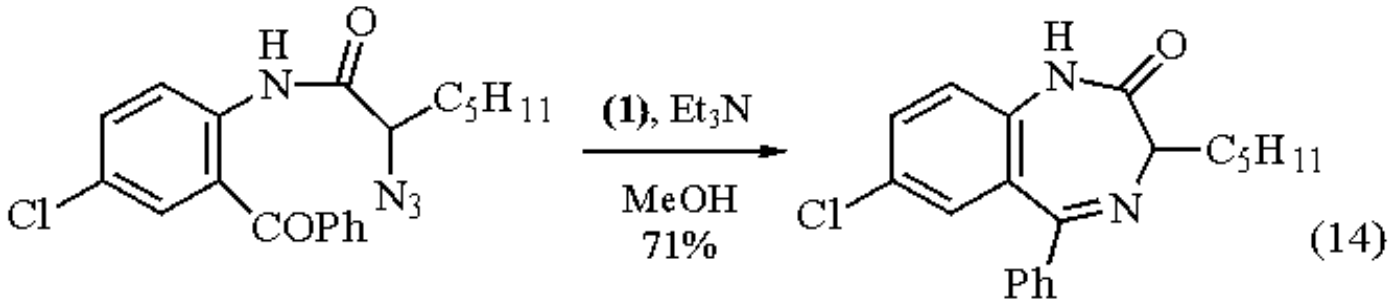

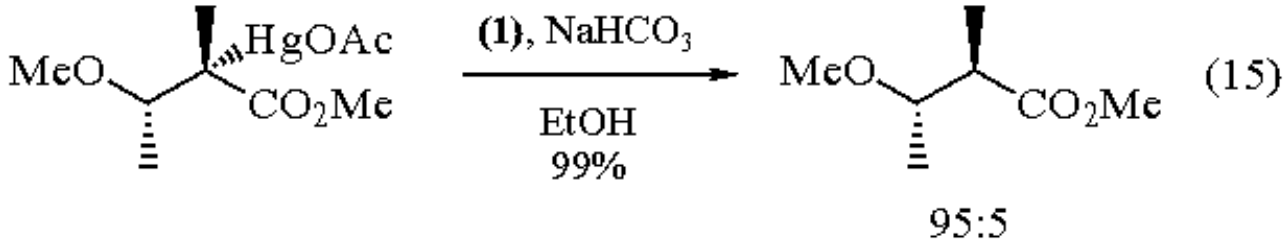

Ketene Dithioacetal Formation.

These versatile intermediates[1c] arise from 1,3-dithiane anions by elimination (eq 8)[11b,19] or vinylogous alkylation (eq 4),[5] and by condensation of carboxylic acid derivatives with (**1**) (eq 13).[20a] Ketene dithioacetals derived from lactones can cyclize to give dithio orthoesters, which can be selectively deprotected (eq 16).[20b]

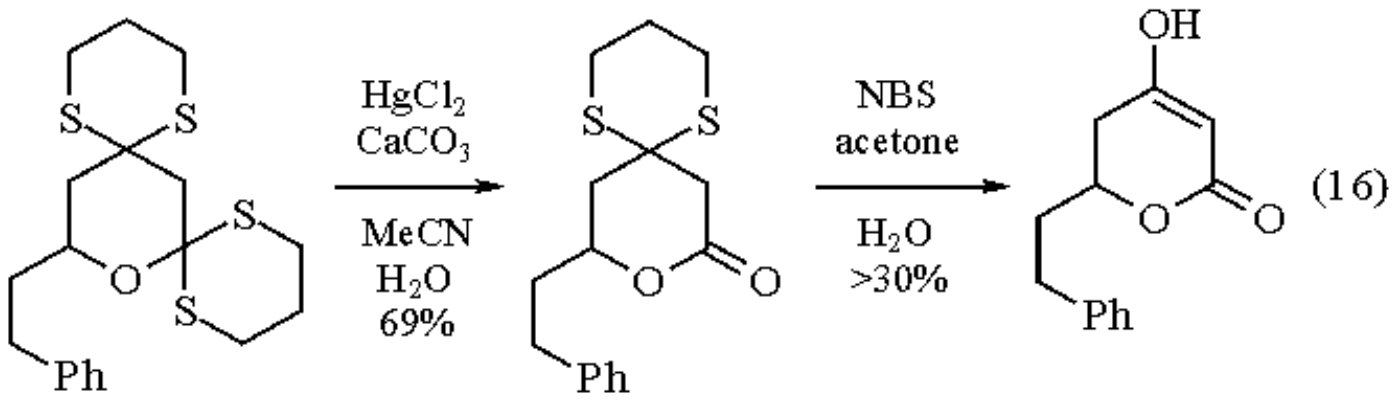

Related Reagents.

1,2-Ethanedithiol.

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1,3-Propanedithiol Bis(*p*-toluenesulfonate)[1]

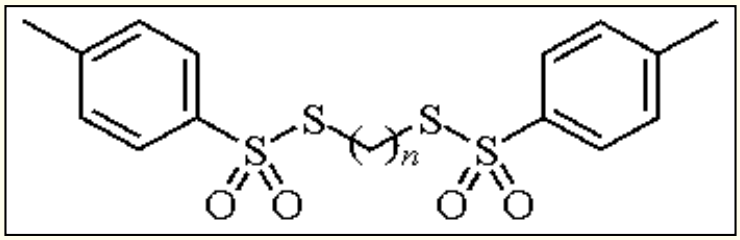

(*n* = 3)

[3866-79-3] · $C_{17}H_{20}O_4S_4$ · 1,3-Propanedithiol Bis(*p*-toluenesulfonate) · (MW 416.65) (*n* = 2)

[2225-23-2] · $C_{16}H_{18}O_4S_4$ · 1,2-Ethanedithiol Bis(*p*-toluenesulfonate) · (MW 402.62)

(dithianylation and dithiolanylation of methylene groups adjacent to carbonyl;[2] α,α-dithianyl cycloalkanones undergo oxidative ring scission;[3] oxidation of ketones to 1,2-diketones can be achieved by α,α-dithianylation or dithiolanation of ketones followed by hydrolysis[4])

Physical Data: 1,3-propanedithiol bis(*p*-toluenesulfonate): mp 67 °C; 1,2-ethanedithiol bis(*p*-toluenesulfonate): mp 76 °C.

Preparative Methods: treatment of potassium thiotosylate, itself made by the reaction of ***p-Toluenesulfonyl Chloride*** with ***Potassium Hydrogen Sulfide***, with 1,3-dibromopropane or 1,2-dibromoethane in the presence of ***Potassium Iodide*** affords 1,3-propanedithiol bis(*p*-toluenesulfonate) and 1,2-ethanedithiol bis(*p*-toluenesulfonate), respectively.[5]

Oxidative Ring Cleavage of Cycloalkanones.

Ketones can be α,α-dithianylated or α,α-dithiolanylated by treatment of their enamines or α-formyl derivatives with 1,3-propanedithiol or 1,2-ethanedithiol bis(*p*-toluenesulfonate), respectively.[1,2] Subjection of α,α-dithianyl ketones to ***Potassium Hydroxide*** in *t*-BuOH results in carbonyl carbon-dithiane carbon bond cleavage, affording o-dithianyl acids (eq 1).[3] Presumably, a mechanism similar to the benzilic acid rearrangement is operative. Consistent with this assumption is the observation that easily enolizable and sterically hindered dithianyl ketones are inert to these conditions. The lack of examples of similar cleavage of α,α-dithiolanyl ketones may be related to the inability of dithiolanes to support anion formation.[6] Alternative methods for effecting this type of cleavage, such as ozonolysis of an enol derivative, frequently are poorly reproducible.

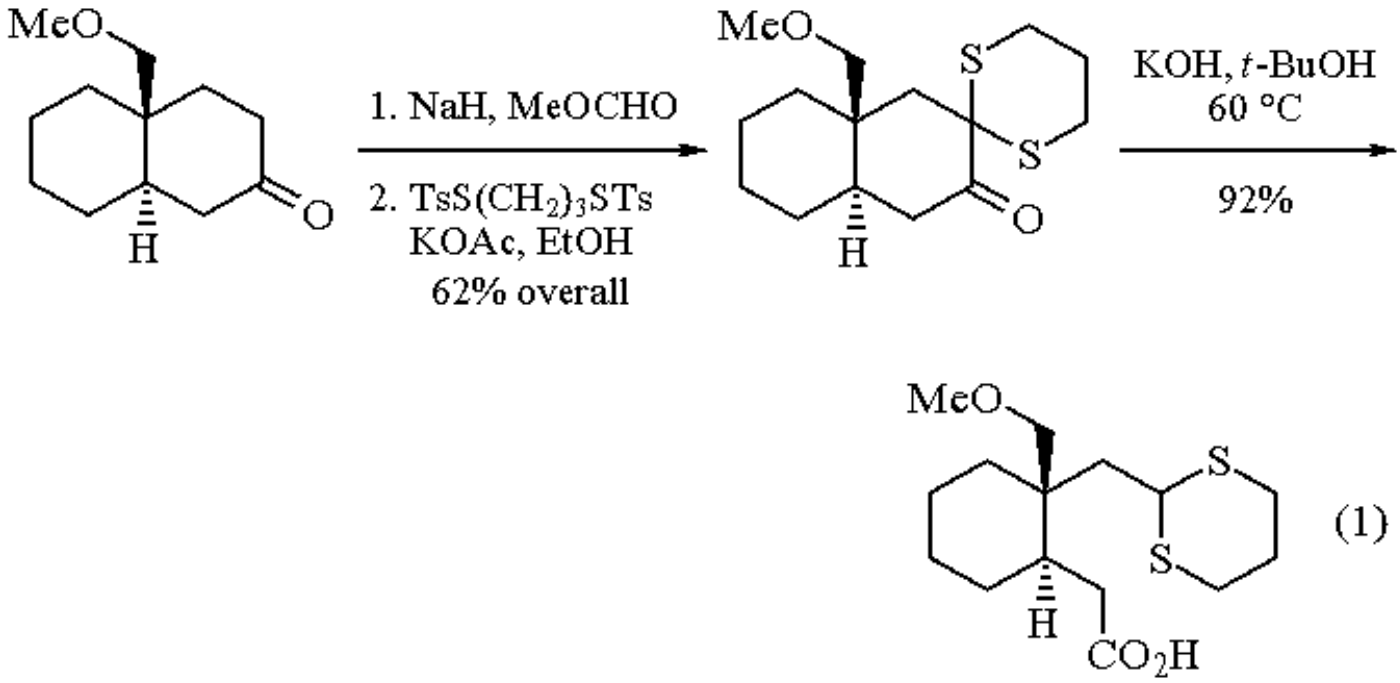

(1)

The exquisite regioselectivity possible in enamine formation or α-formylation of cycloalkanones, followed by α,α-dithianation and ring cleavage, has been exploited in several natural product syntheses (eqs 2-4).[7-10]

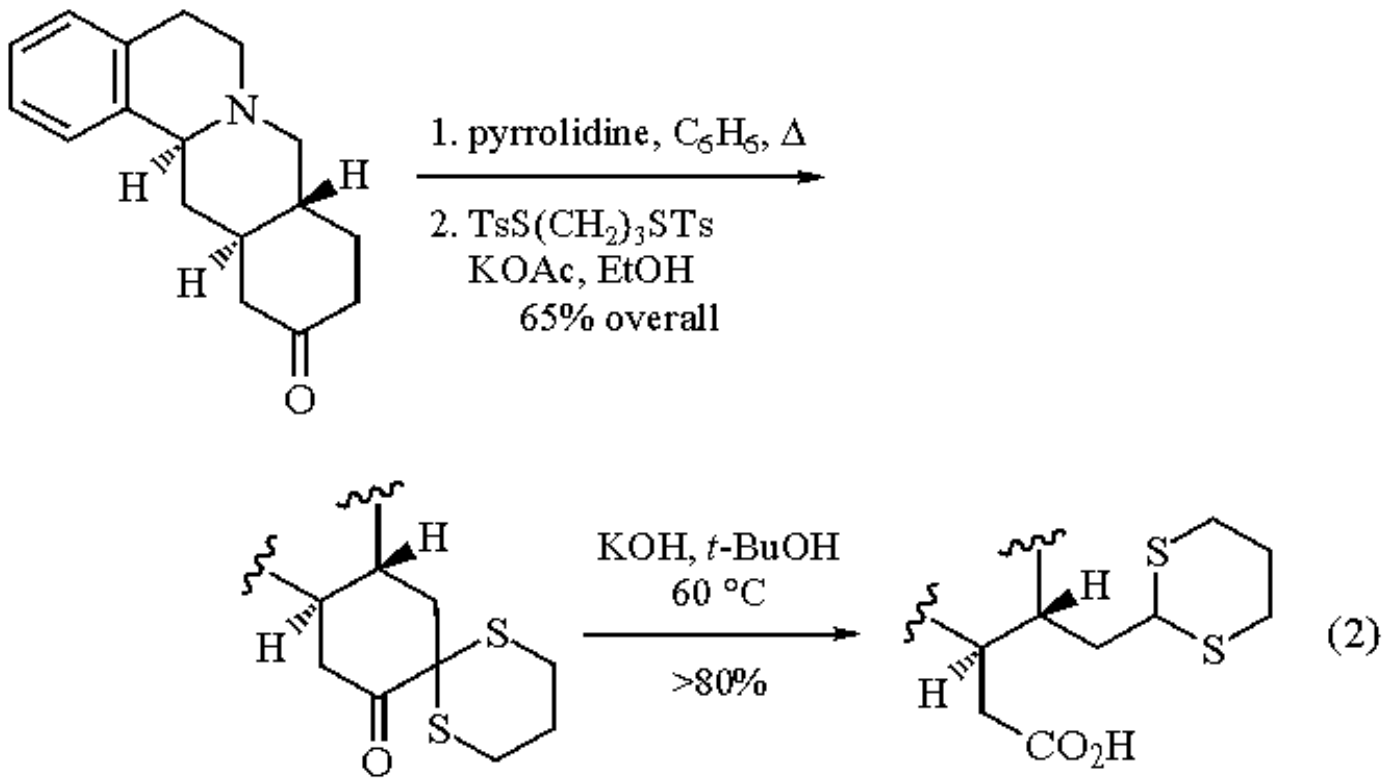

(2)

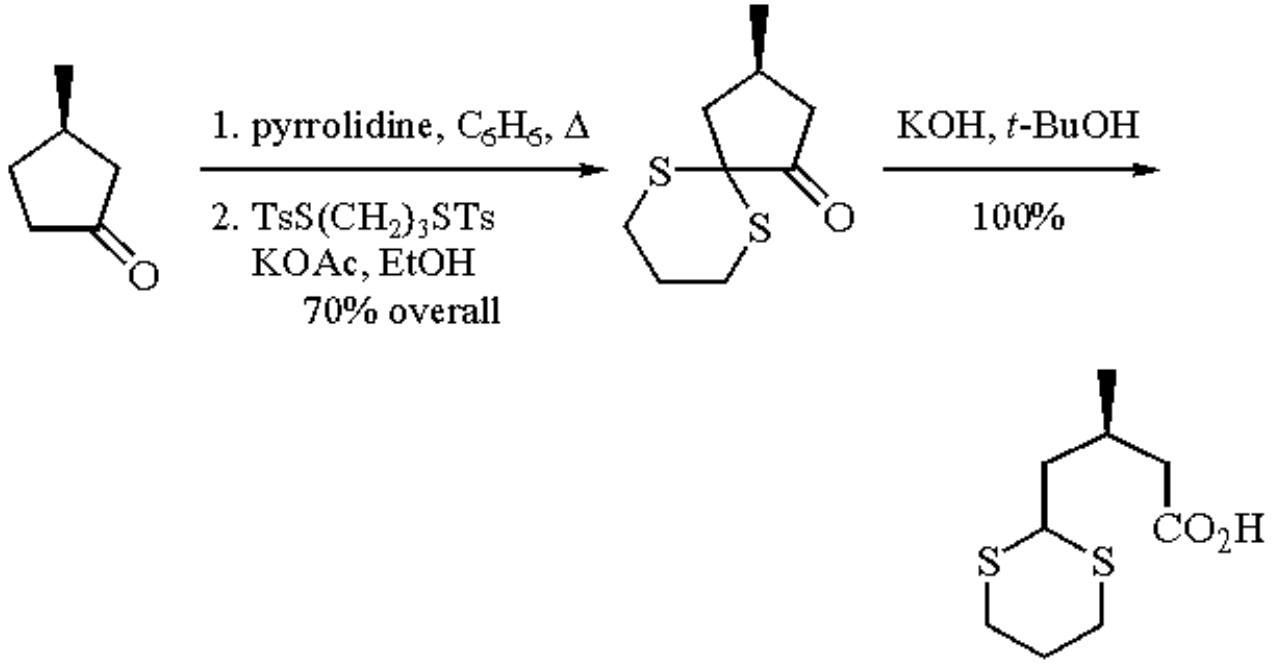

(3)

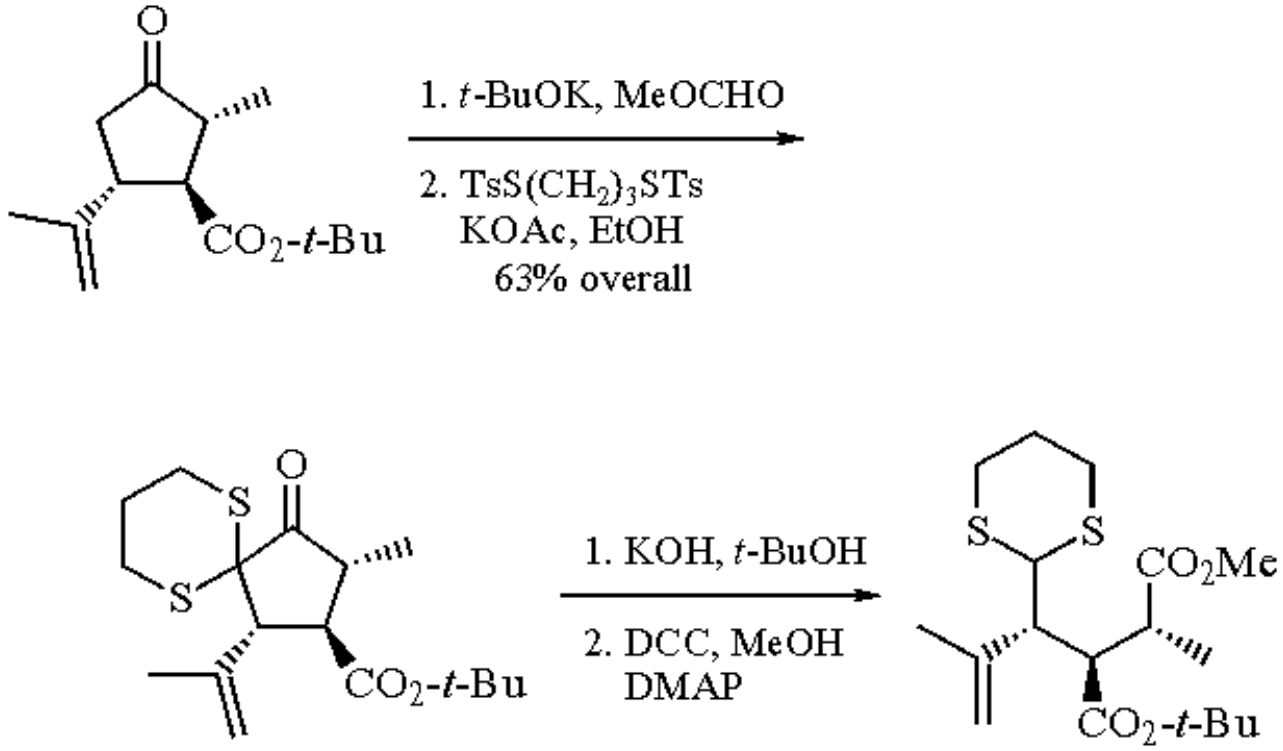

(4)

Addition of organometallics to the carbonyl carbon, followed by base cleavage of the resulting α,α-dithianyl carbinols, generates o-dithianyl ketones (eq 5).[11]

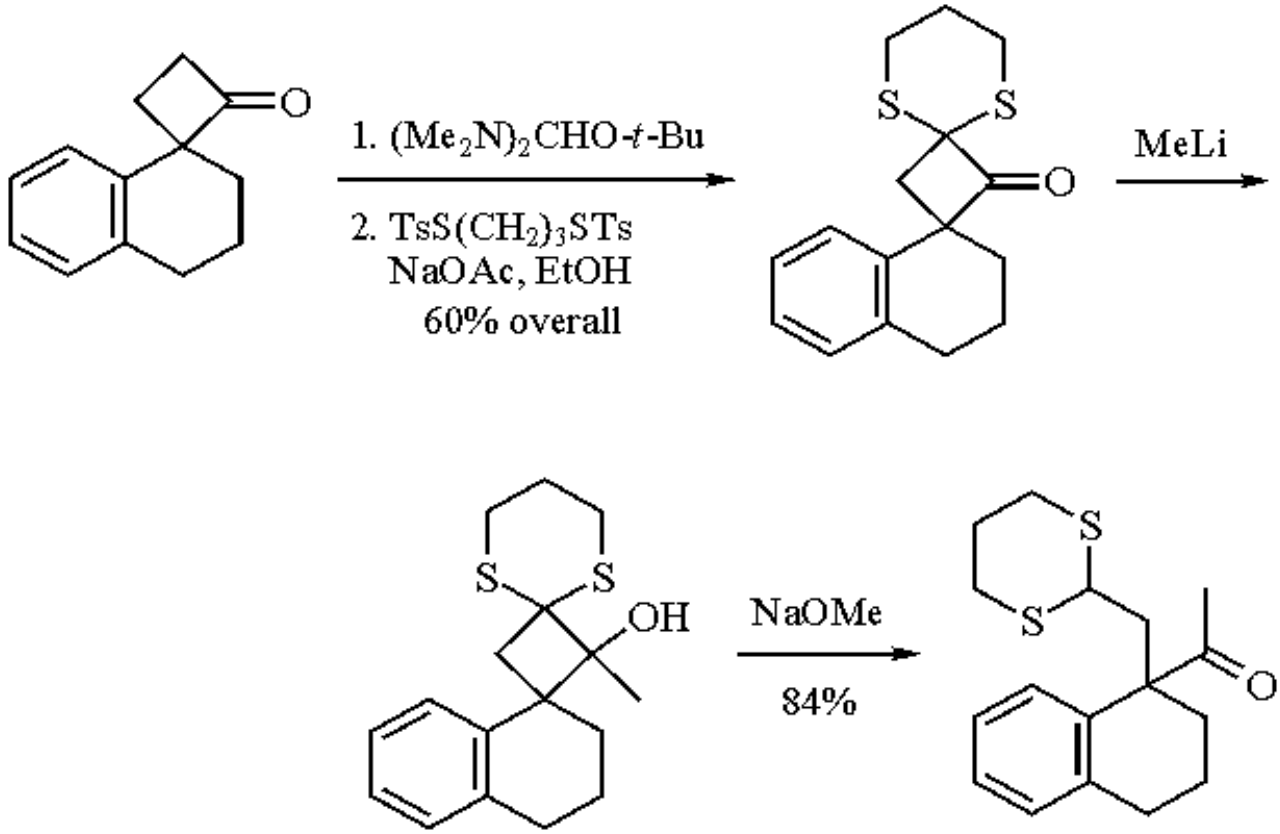

(5)

1,2-Carbonyl Transposition and Methylene Protection.

Dithianes and dithiolanes can be removed under hydrolytic or reductive conditions (see ***1,3-Propanedithiol*** and ***1,2-Ethanedithiol***). As α,α-dithianyl- and dithiolanylation of ketones effects oxidation of the α-carbon, hydrolytic removal of the protecting group affords 1,2-diketones (eq 6).[4,12] Chemical modification of the carbonyl carbon before hydrolytic removal of the dithiane or dithiolane effects 1,2-carbonyl transposition (eq 7).[13]

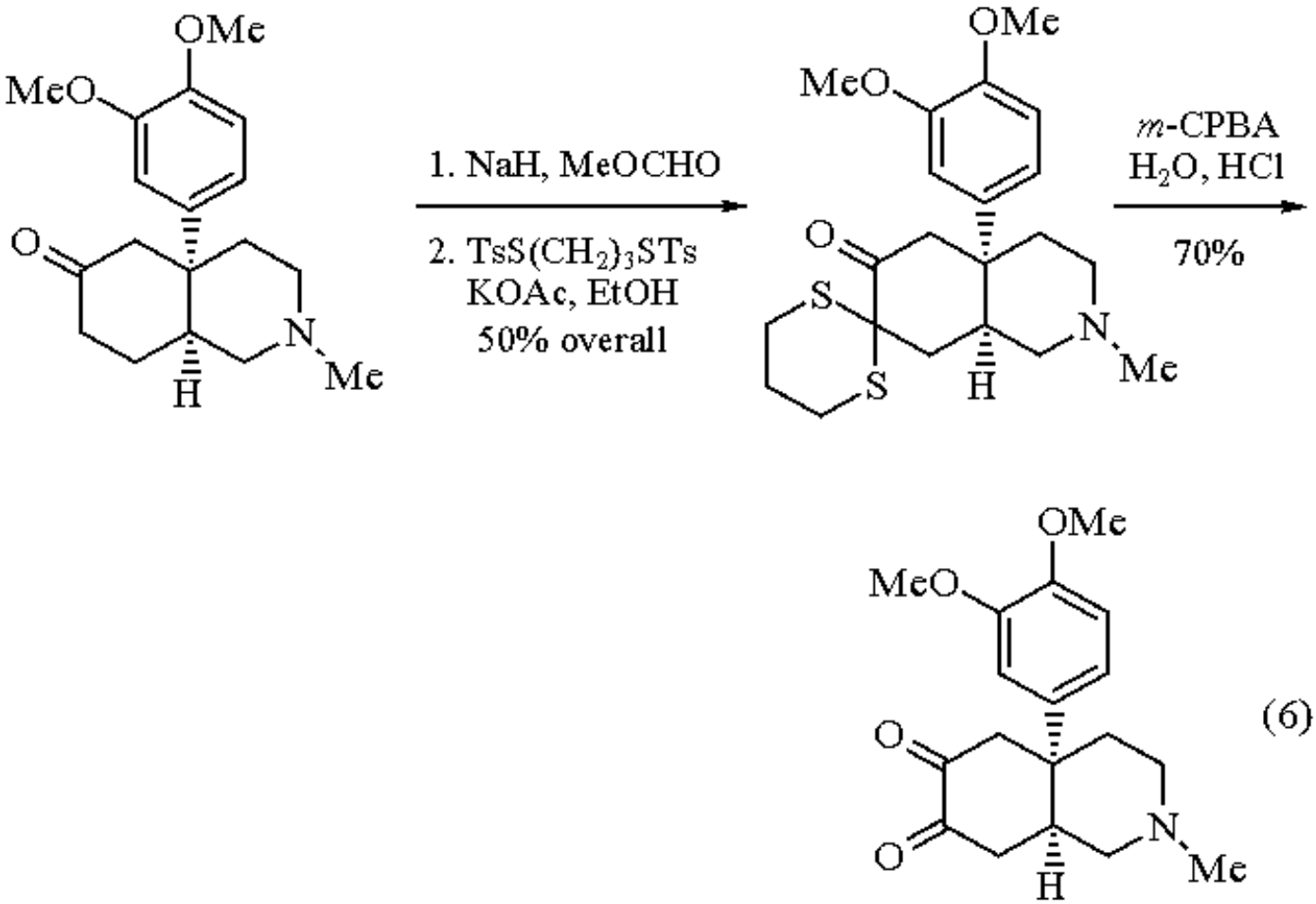

(6)

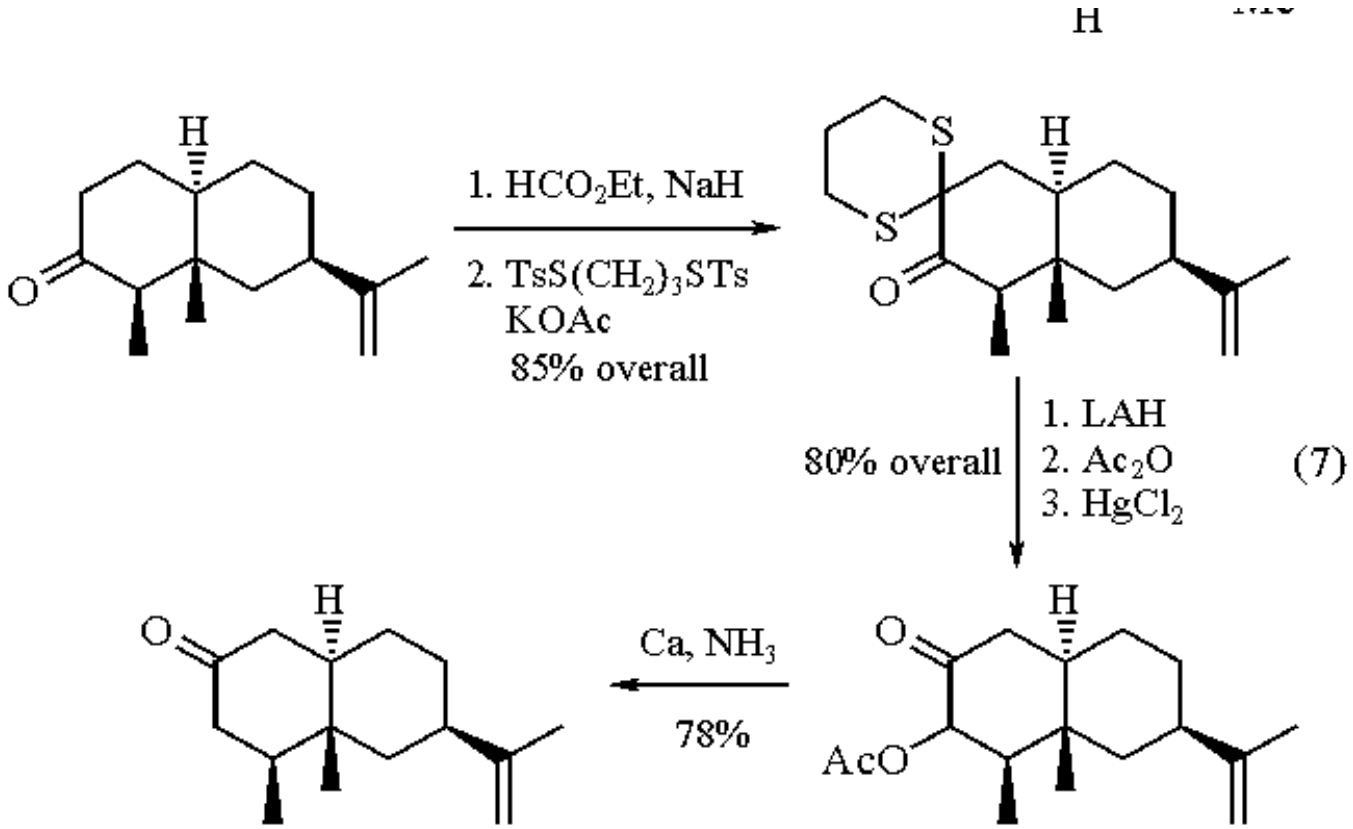

The ability to convert a dithianyl or dithiolanyl carbon to methylene by treatment with ***Raney Nickel*** enables methylene protection α to a carbonyl. For example, the less enolizable α-methylene of a cycloalkanone can be alkylated by the sequence: (a) dithiolanylation of the more enolizable methylene; (b) enolization and alkylation at the remaining methylene; (c) reductive removal of the dithiolane group (eq 8).[14]

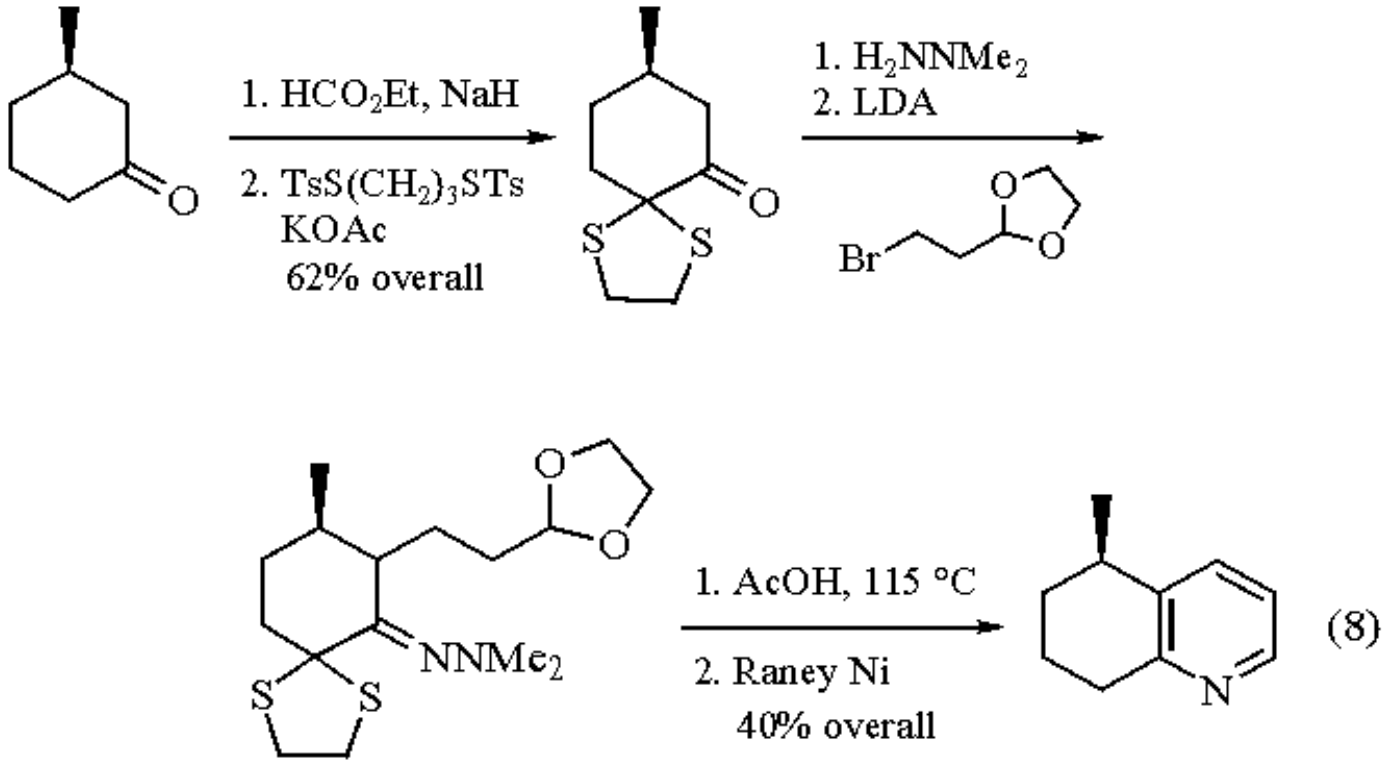

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Propargyl Alcohol

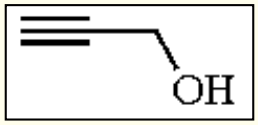

[107-19-7] · C_3H_4O · Propargyl Alcohol · (MW 56.07)

(cyclopentenone annulation;[1] three-carbon building block for organic synthesis[2,3])

Alternate Name: 2-propyn-1-ol.

Physical Data: mp -53 °C; bp 114-115 °C; *d* 0.963 g cm^{-3}. Monohydrate: fp -20 to -60 °C; *d* 0.968 g cm^{-3}.

Solubility: insol aliphatic hydrocarbons; sol H_2O, benzene, chloroform, 1,2-dichloroethane, ethanol, ether, acetone, dioxane, tetrahydrofuran, pyridine; mod sol carbon tetrachloride.

Form Supplied in: colorless liquid; commercially available.

Purification: commercial material contains a stabilizer. An aq solution of propargyl alcohol can be concentrated by azeotropic distillation with butanol or butyl acetate. Dry over K_2CO_3 and distil under reduced pressure in the presence of about 1% succinic acid through a column packed with glass helices.

Handling, Storage, and Precautions: this highly toxic reagent causes severe irritation and is readily absorbed through the skin. Flammable liquid. Forms explosive mixtures in air. Use only in a chemical fume hood. Polymerized by heat or base. Distillation just prior to use is recommended.

Preparation of the Dilithium Derivative.

A hexane solution of ***n-Butyllithium*** (2 equiv) is added to a THF solution of propargyl alcohol.[4] When 1 equiv of *n*-BuLi is added, the viscosity of the reaction mixture increases. Therefore, more than 3 mL of THF per 1 mmol of propargyl alcohol should be used.

Cyclopentenone Annulation.

The adducts of propargyl alcohol and ketones have been employed as divinyl ketone equivalents for the Nazarov cyclization.[1] The particular significance of this reaction is the regio- and stereochemical outcome in cyclopentenone annulation.[4] The more substituted α-carbon of 2-methylcyclohexanone is selectively incorporated into a five-membered ring (eq 1). This transformation exhibits stereoselectivity as summarized in eq 2 when applied to alkyl-substituted derivatives of the adduct. These results are explained in terms of the conrotatory ring closure of the thermodynamically most favorable pentadienyl cation intermediates. Analogous reactions have been applied to the total synthesis of (±)-nootkatone (eq 3)[5] and (±)-muscopyridine (eq 4).[6]

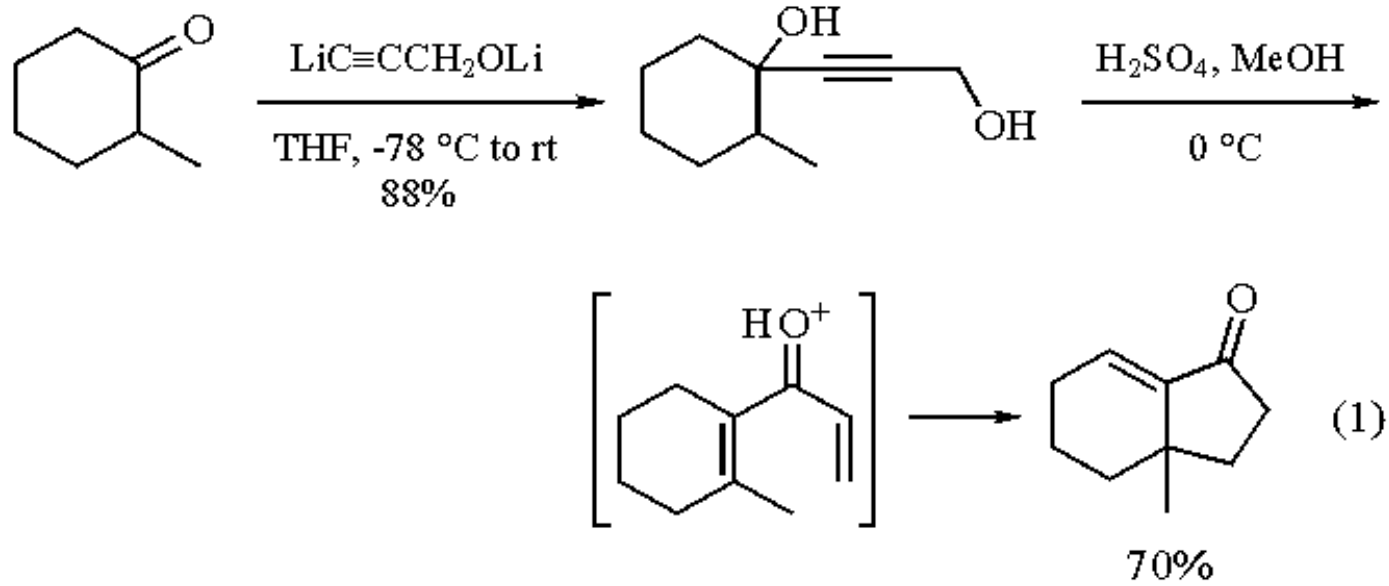

(1)

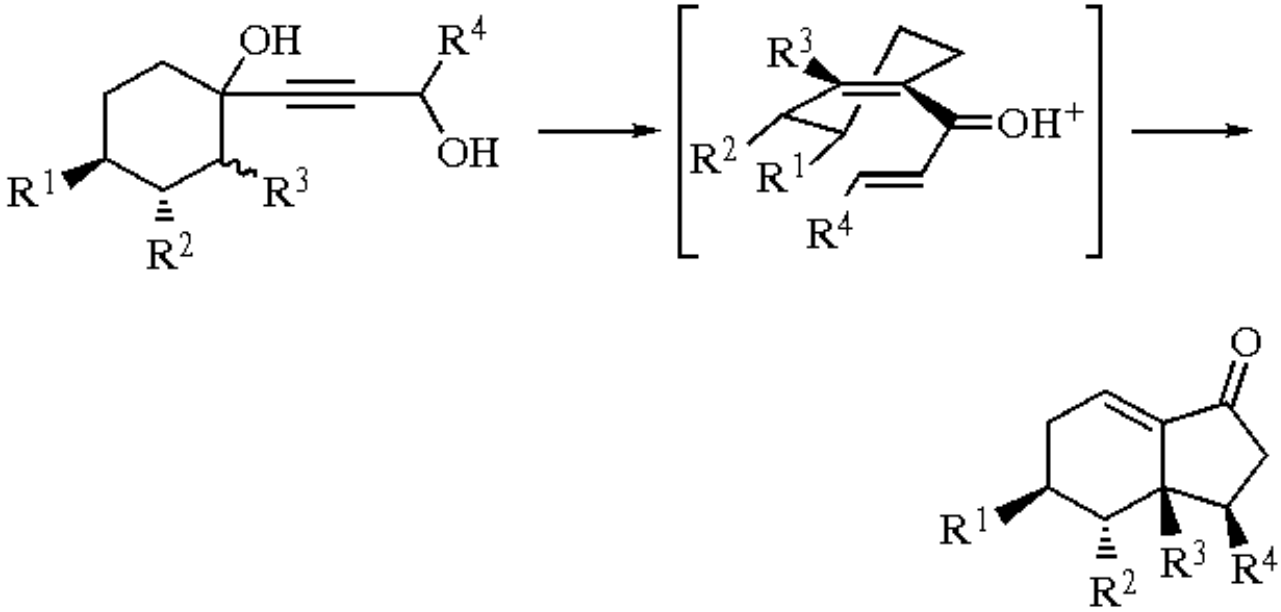

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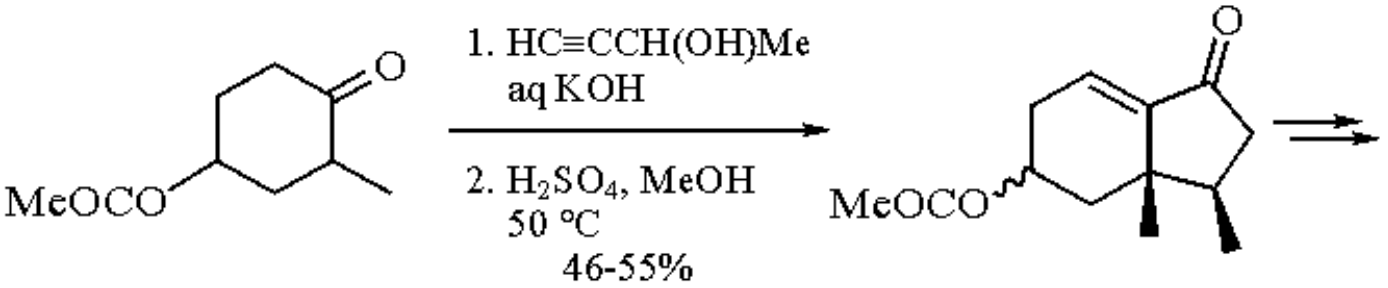

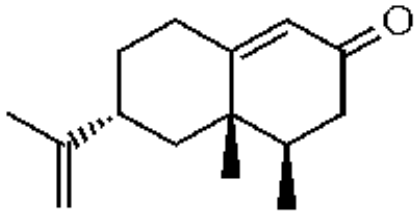

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Nootkatone

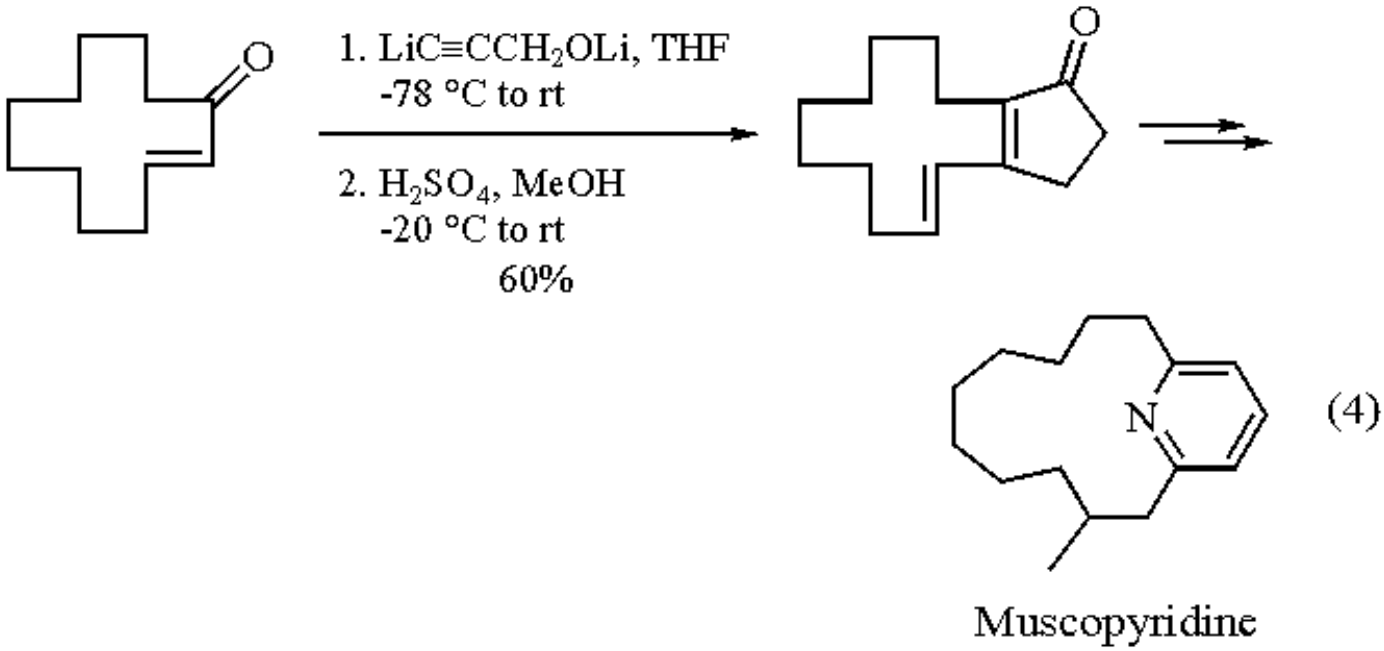

(4)

Three-Carbon Building Block for Organic Synthesis.

Propargyl alcohol has been widely employed as a C_3 building block for homologation (eqs 5-7).[7-9] Dihydrofurans are obtained from the adducts of propargyl alcohol and ketones or aldehydes (eq 8).[10] Propargyl alcohol has been used for alkylation under acidic conditions (eq 9).[11]

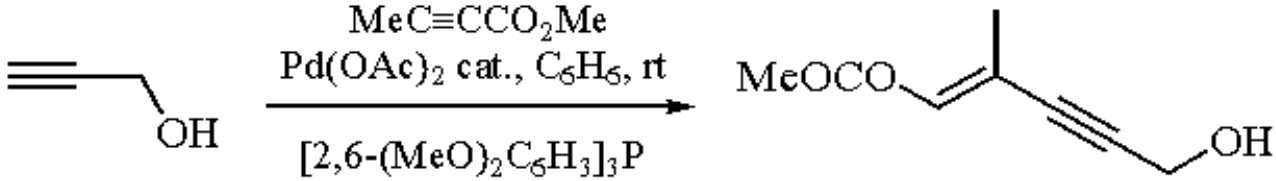

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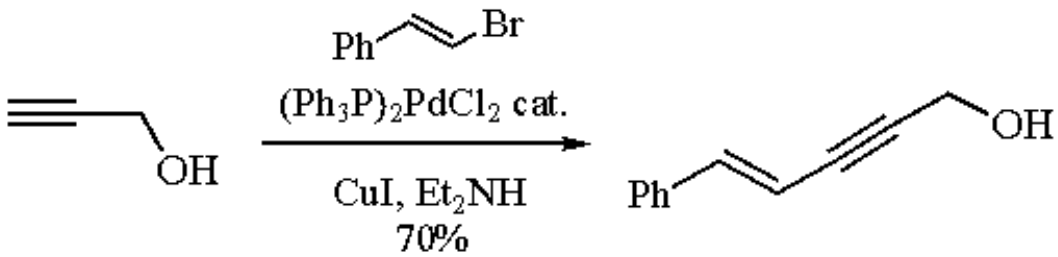

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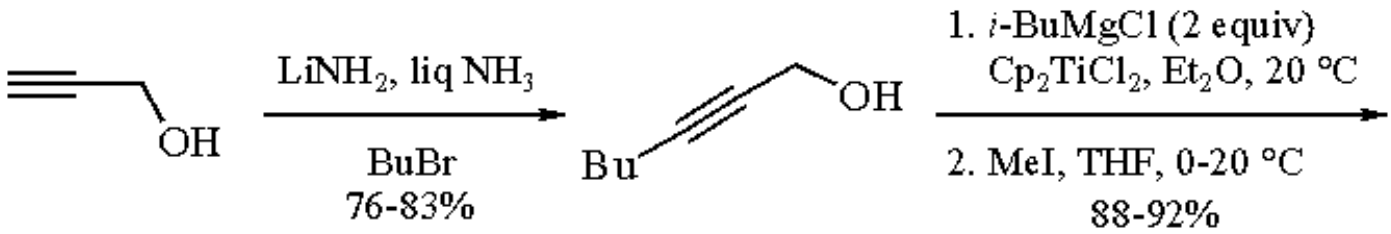

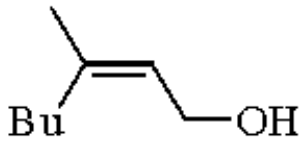

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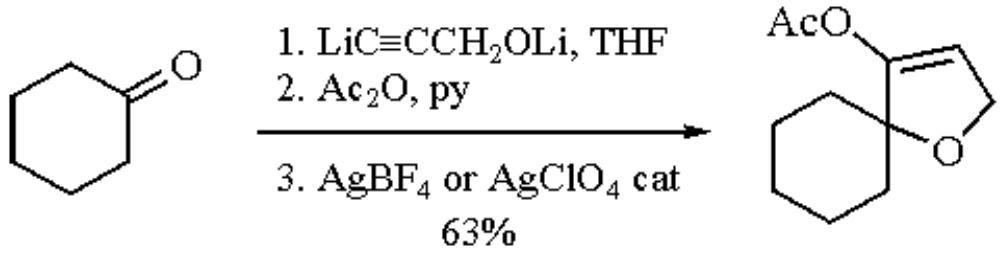

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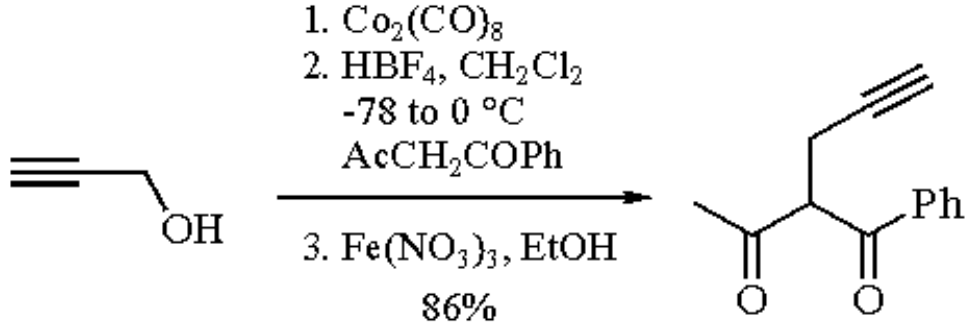

(9)

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Propargyl Aldehyde

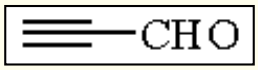

[624-67-9] · C_3H_2O · Propargyl Aldehyde · (MW 54.05)

(conjugate acceptor; dienophile)

Alternate Names: 2-propynal; propiolaldehyde.

Physical Data: bp 59-61 °C.

Solubility: sol H_2O, alcohol, ether, benzene, toluene, acetone.

Form Supplied in: not commercially available.

Preparative Method: most simply prepared by oxidation of ***Propargyl Alcohol***.[1,2]

Handling, Storage, and Precautions: great care should be taken in handling the neat liquid as an explosion has been reported.[3] The explosion was attributed to rapid polymerization, probably catalyzed by base or a radical initiator. It is recommended that handling of 2-propynal should include the use of a nonglass container and dilution with a sufficient volume of an inert solvent to absorb the heat of polymerization without boiling, e.g. <=10% in toluene. Use in a fume hood.

Addition to the Carbonyl Group.

Grignard reagents add well to 2-propynal, as in the preparation of 1-hexyn-5-en-3-ol (eq 1).[4] Aryl Grignard reagents also add successfully.[5] Although most heteronucleophiles add in a conjugate fashion (see next section), aniline has been reported to form the corresponding imine.[6] A pyrrole synthesis has been developed which relies on an aldol reaction of 2-propynal with a 3-silyl-2-azetidinone (eq 2).[7]

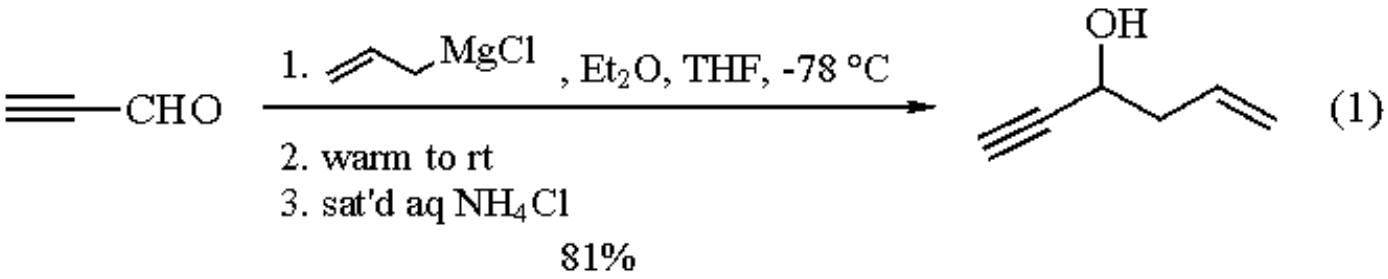

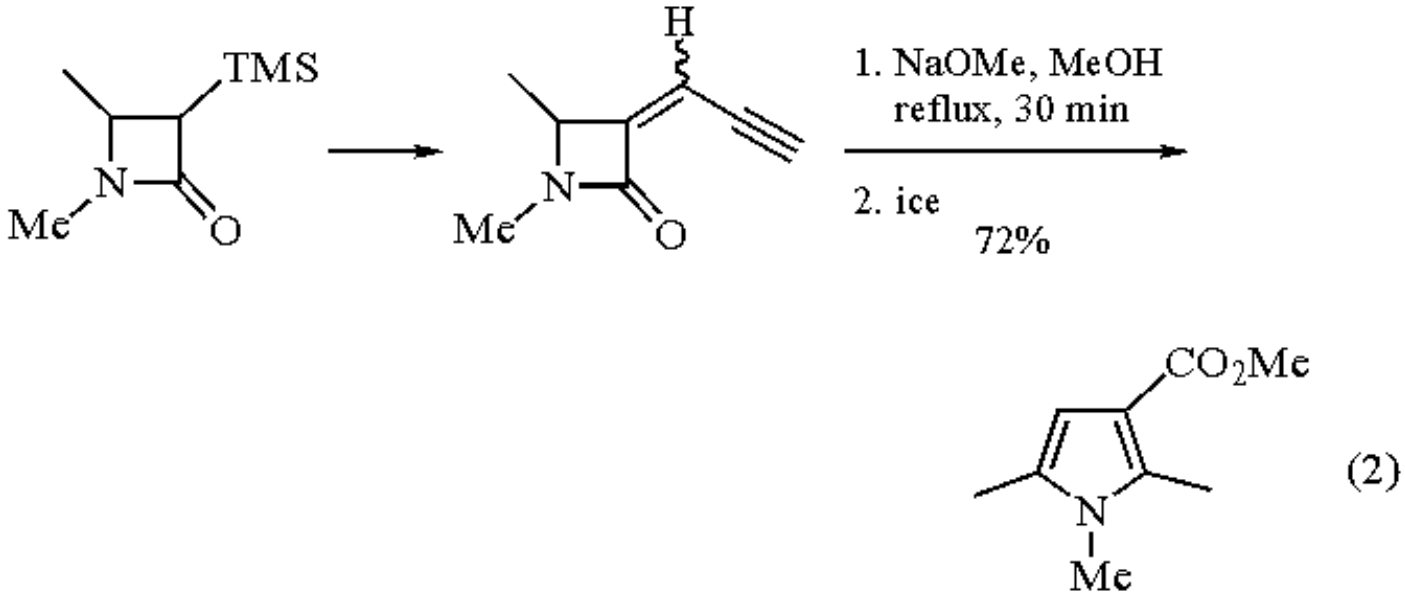

Addition to the Triple Bond.

Conjugate additions of nucleophiles based on oxygen (eq 3),[8,9] nitrogen (eq 4),[10] and sulfur (eq 5)[11] leading to 3-substituted acroleins have been reported.

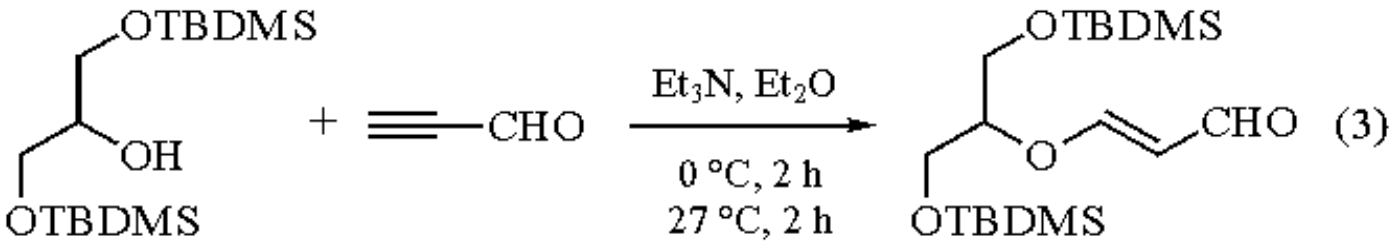

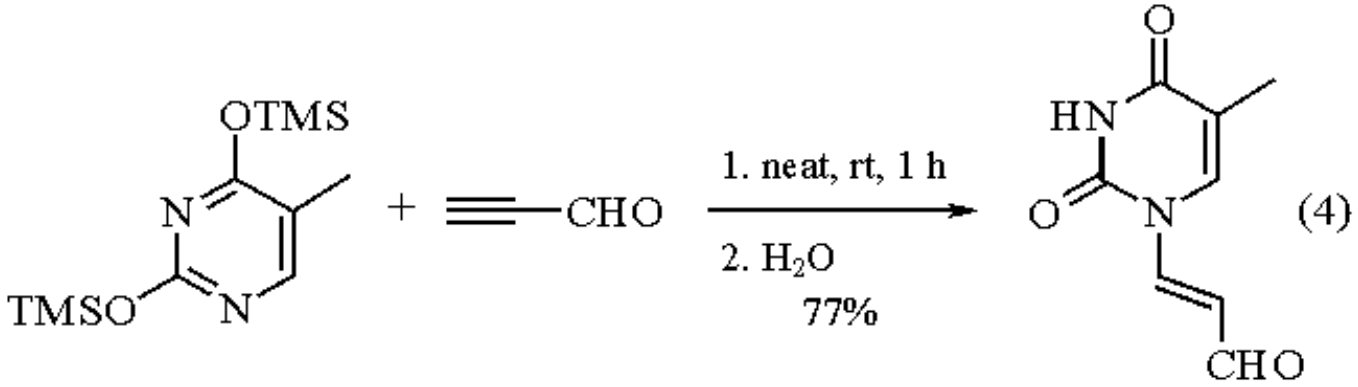

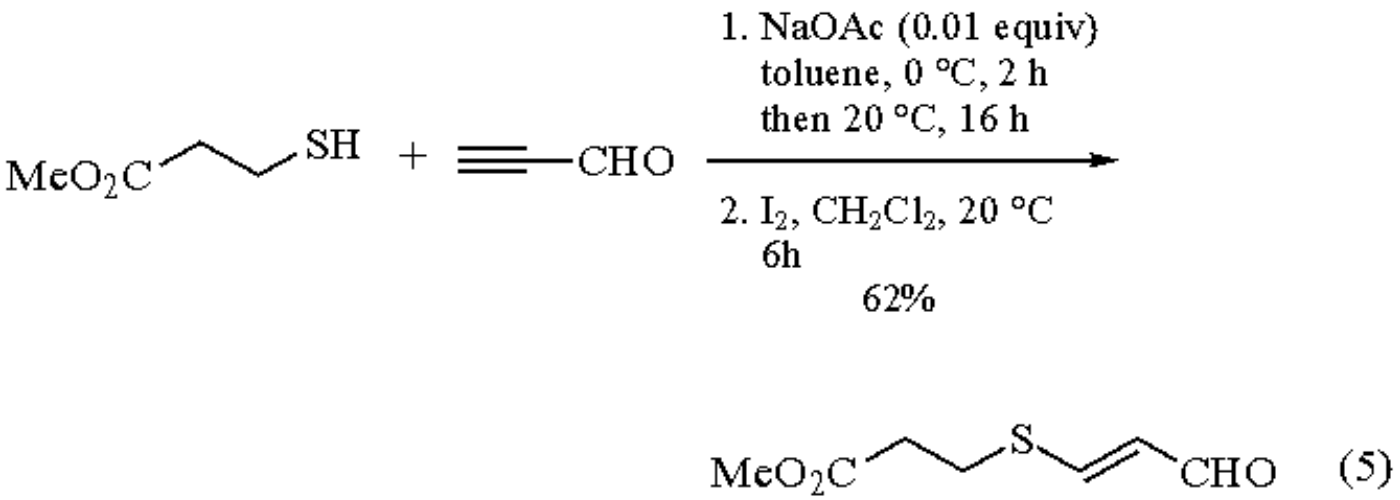

Cycloadditions.

2-Propynal reacts as a typical dienophile in Diels-Alder reactions with a variety of dienes. Nucleophilic dienes add without catalysis (eqs 6 and 7).[12,13] Some dienes require Lewis-acid catalysis to react, as in the preparation of *ansa*-secosteroids (eq 8).[14]

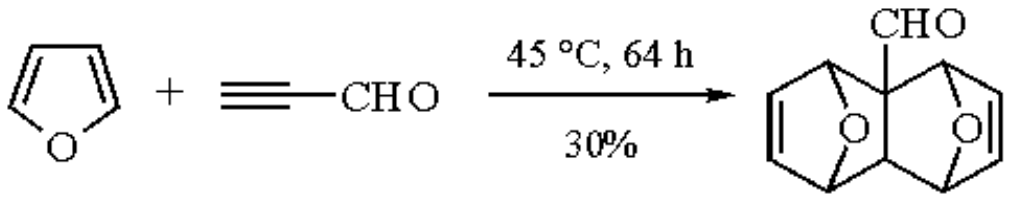

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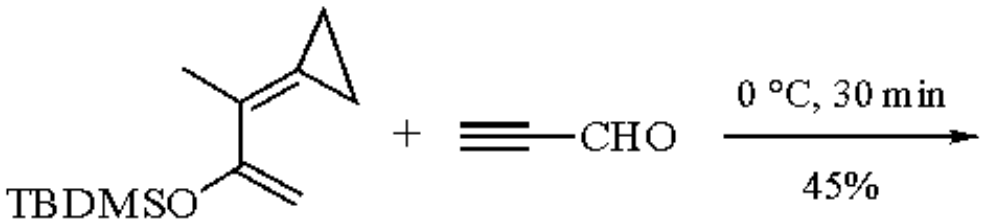

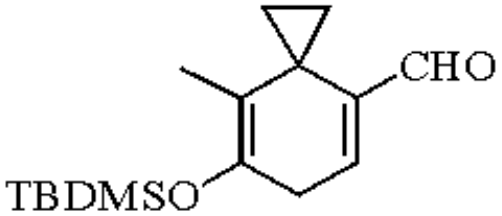

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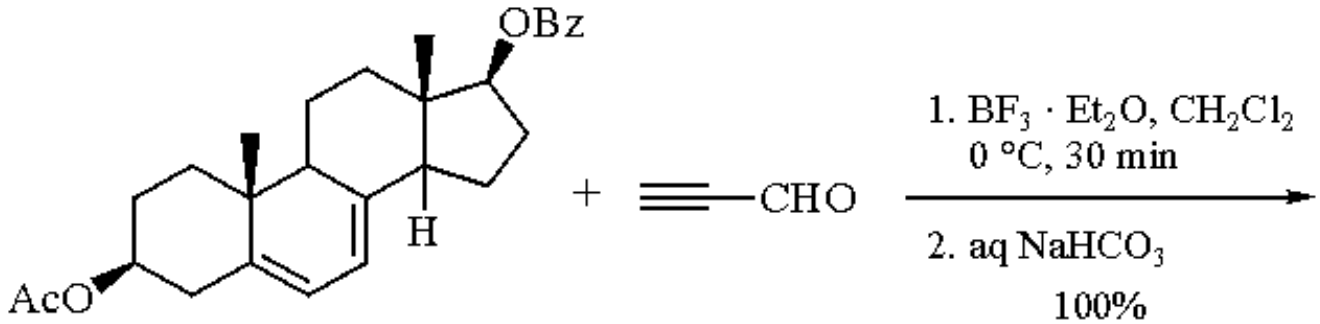

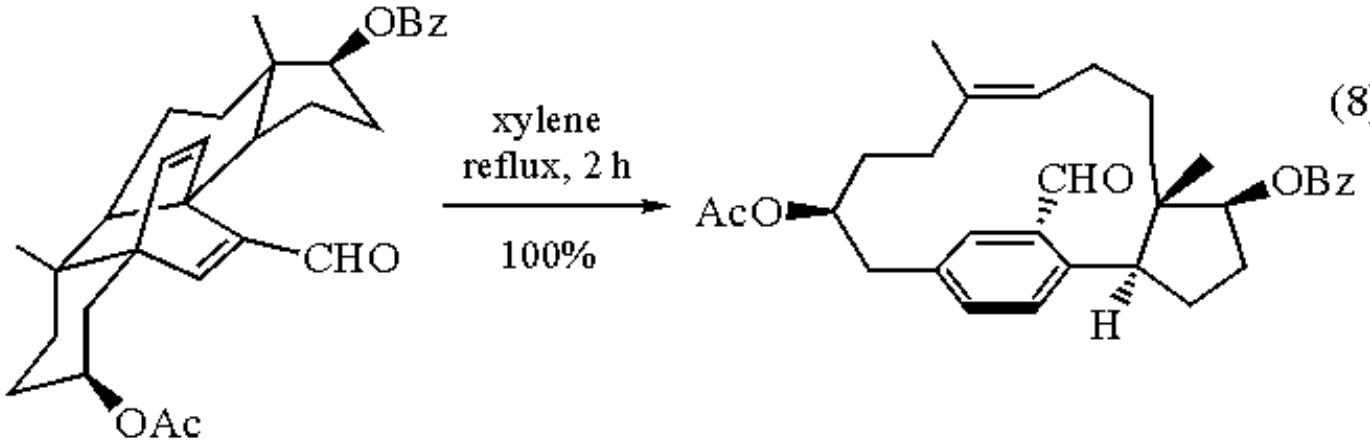

(8)

Lanthanide salts catalyze the 1,2-cycloaddition of 2-propynal to ketene imines (eq 9).[15] ***Sodium Azide*** cycloadds to 2-propynal across the triple bond, yielding a 1,2,3-triazole.[16]

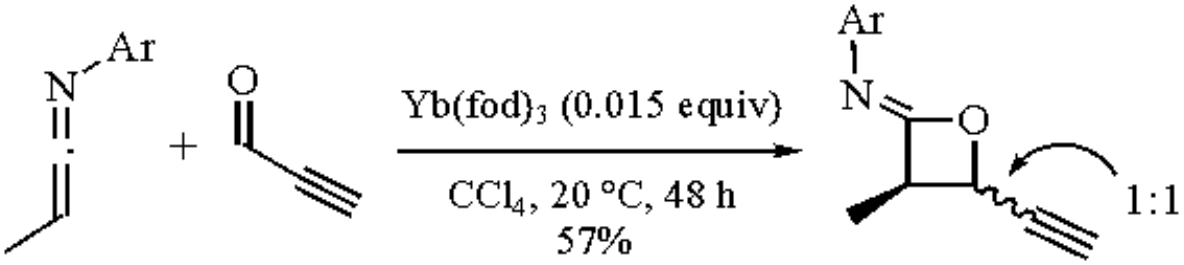

(9)

Cyclocondensations.

Heating 2-propynal with 3-amino-2-cyclohexenones provides a simple route to tetrahydroquinoline derivatives as in eq 10.[17,18] Tetraazaannulenes may be prepared simply by heating *o*-phenylenediamines with 2-propynal (eq 11).[19]

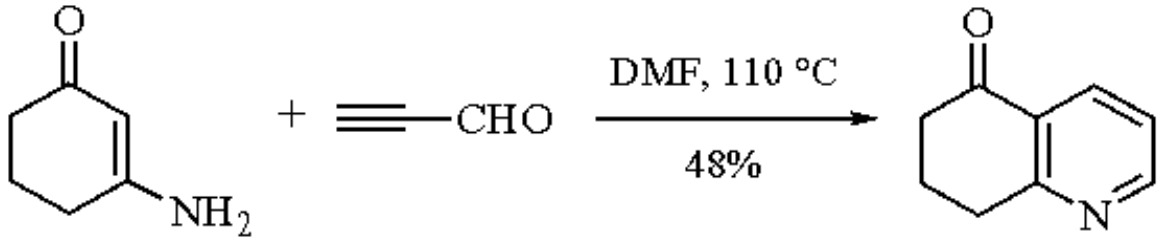

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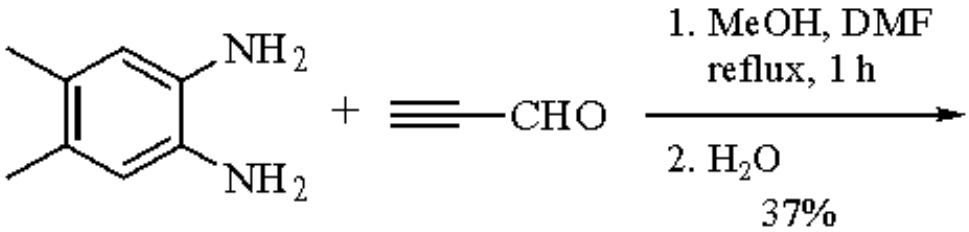

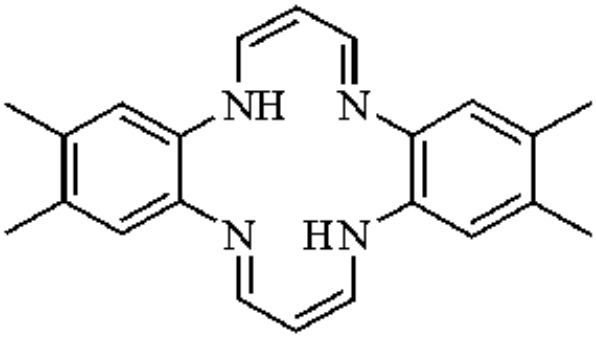

(11)

Related Reagents.

3-Butyn-2-one; ***3,3-Diethoxy-1-propyne***; ***Ethyl Lithiopropiolate***; ***Methyl Propiolate***; ***Propargyl Alcohol***.

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Propargyl Chloride

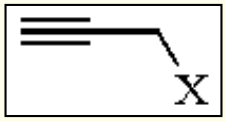

(X = Cl)

[624-65-7] · C_3H_3Cl · Propargyl Chloride · (MW 74.51) (X = Br)

[106-96-7] · C_3H_3Br · Propargyl Bromide · (MW 118.96) (X = OTf)

[41029-46-3] · $C_4H_3F_3O_3S$ · Propargyl Triflate · (MW 188.14)

(three-carbon alkylating agent;[1] acetone carbenium ion equivalent and annulating agent;[2] propargylic or allenic nucleophile after conversion to an organometallic[3])

Alternate Name: 3-chloro-1-propyne.

Physical Data: X = Cl: bp 58 °C; *d* 1.030 g cm^{-3}. X = Br: bp 88-90 °C; *d* 1.579 g cm^{-3}; *d* (80% toluene solution) 1.335 g cm^{-3}.

Form Supplied in: propargyl chloride is supplied as a liquid in 98% purity. Because of a reported shock-sensitivity of the neat material, propargyl bromide is supplied as an 80% (by weight) solution in toluene.

Preparative Method: propargyl triflate is not commercially available but is prepared by treating ***Propargyl Alcohol*** with ***Pyridine/Trifluoromethanesulfonic Anhydride***.[4]

Handling, Storage, and Precautions: in the presence of copper(I) halides, propargyl halides can isomerize to a mixture of the parent compound and a halopropadiene.[5] Because of an instability at ambient temperature, the triflate is typically prepared in solution and used directly. Purification of the triflate by distillation is possible, albeit in low yield.[6]

Electrophilic Alkylation.

As an electrophile, propargyl chloride has been employed in the propynylation of a variety of substrates, including Grignard reagents,[1,7] carbanions,[8] enolates,[9] carbonyl compounds,[10] alcohols,[4,11] phenols,[12] carboxylates,[13] amines,[14] amides,[15] sulfonamides,[16] sulfones,[17] thiols,[18] thioamides,[19] and alkyl phosphonates.[20] An unusual *N*-alkylation of a phenothiazine has been reported whereby the 1-propynyl derivative is isolated.[21] Because of the basic nature of the above alkylation reactions, isomerization to the allene can take place.[22] The extent to which isomerization occurs is dependent upon the reaction time, temperature, and the specific base employed.[15a,23] Trialkyl borates[24] and alkylaluminum species,[25] in the presence of a copper(I) halide, couple with propargyl bromide (preferred over the chloride) to give exclusively the terminal allene. By contrast, the reaction of bromopropadiene (derived from propargyl bromide) with an alkylaluminum affords solely the terminal alkyne.[26] Alkylation of a trithiocarbonate, followed by intramolecular cyclization, leads to the formation of a thione.[27] In a similar manner, thioamides can be alkylated and further elaborated to thiazoles[28] or thiophenes.[29]

Annulation Reactions.

When the alkylation with propargyl bromide is followed by hydration with ***Mercury(II) Oxide*** the net result is equivalent to an alkylation with ***Acetone***. More often, when alkylation occurs α to a carbonyl, the product is further treated with base to give a fused cyclopentenone (eq 1) (see also ***Isopropenyl Acetate***, ***Methallyl Chloride***, ***2-Methoxyallyl Bromide***).[2,30] A radical-based annulation is also possible. By generating a radical center δ to the triple bond, cyclization to a five-membered ring system with an exocyclic methylene occurs.[16,31]

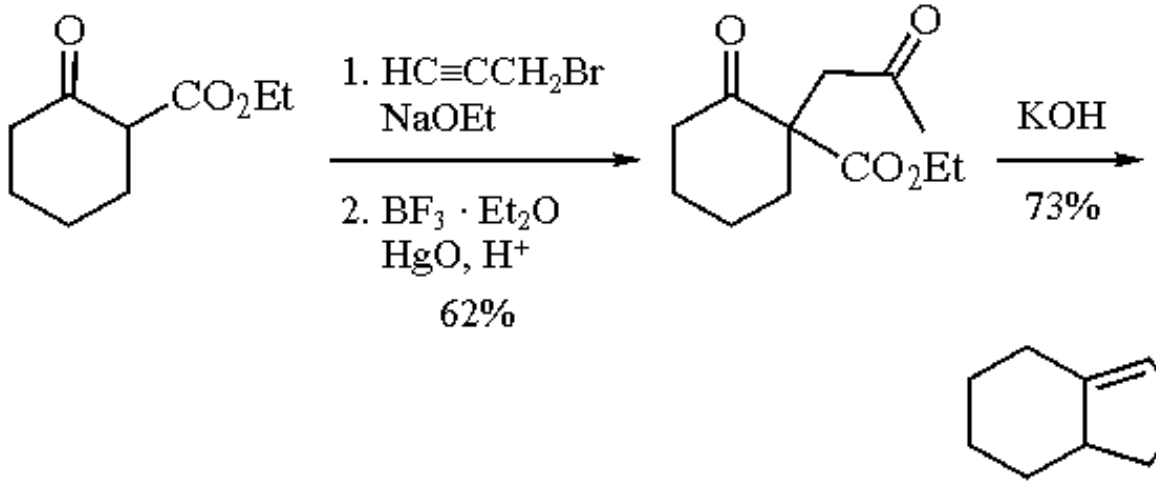

(1)

Sigmatropic Rearrangements.

Because of the triple bond, alkylation with propargyl chloride can provide intermediates further capable of intramolecular rearrangement. Crotyl propargyl ethers undergo [2,3]-Wittig rearrangement with high *erythro* or *threo* selectivity, dependent upon the starting alkene geometry.[32] The corresponding chiral analog allows for an asymmetric [2,3]-Wittig rearrangement with a high degree of enantioselectivity.[33] Under thermal conditions, propargylated phenols undergo a [3,3]-sigmatropic rearrangement to give an allenyl enol. A [1,5]-hydrogen shift, followed by electrocyclic ring closure results in the formation of a benzopyran (eq 2).[34,35]

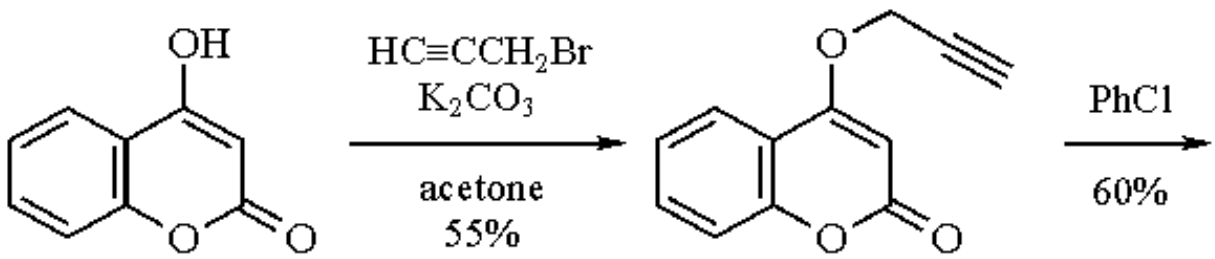

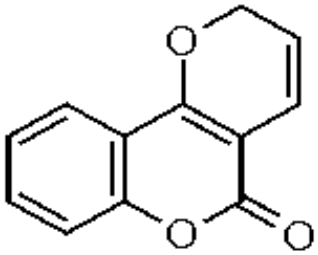

(2)

Cycloadditions.

When appropriately appended, the propargyl group can serve as a dienophile for the intramolecular Diels-Alder reaction with ***Furan***,[36] styrene,[37] and triazine[38] derivatives. Under the typically basic reaction conditions, cycloaddition is believed to proceed via the allenyl ether intermediates. Propargyl bromide can also function as a 1,3-dipolarophile in the [3 + 2] cycloaddition reaction with nitrile oxides to form isoxazoles.[39]

Nucleophilic Additions.

As a halide, propargyl bromide can be converted to a variety of organometallic species, which then add to aldehydes and ketones. The Grignard reagent[40] is proposed to exist in the allenic form,[41] and reacts to form predominantly homopropargylic alcohols. Whereas the organozinc reagent reacts to give both α-allenic and β-alkynic alcohols,[42] the organoaluminum reagent can be used to generate products which are free of allenic isomers.[43] The reaction between carbonyl compounds and the tin reagent favors α-allenic alcohol formation.[44] However, the mixed metal system of tin and aluminum allows for selective formation of the homopropargylic alcohol.[45] A chiral tin complex can be formed with propargyl bromide and (+)-diethyl tartrate and made to react with aldehydes to give enantiomerically enriched α-allenic alcohols.[46] Other organometallic species prepared from propargyl halides include those of chromium,[3] lead,[47] and mercury.[48]

The Grignard reagent reacts with ***Trimethyl Borate*** to give, after hydrolysis, allenylboronic acid (eq 3). Further reaction with diethyl tartrate (DET) generates a chiral allenylboronic ester which enantioselectively adds to aldehydes to give chiral homopropargylic alcohols.[49]

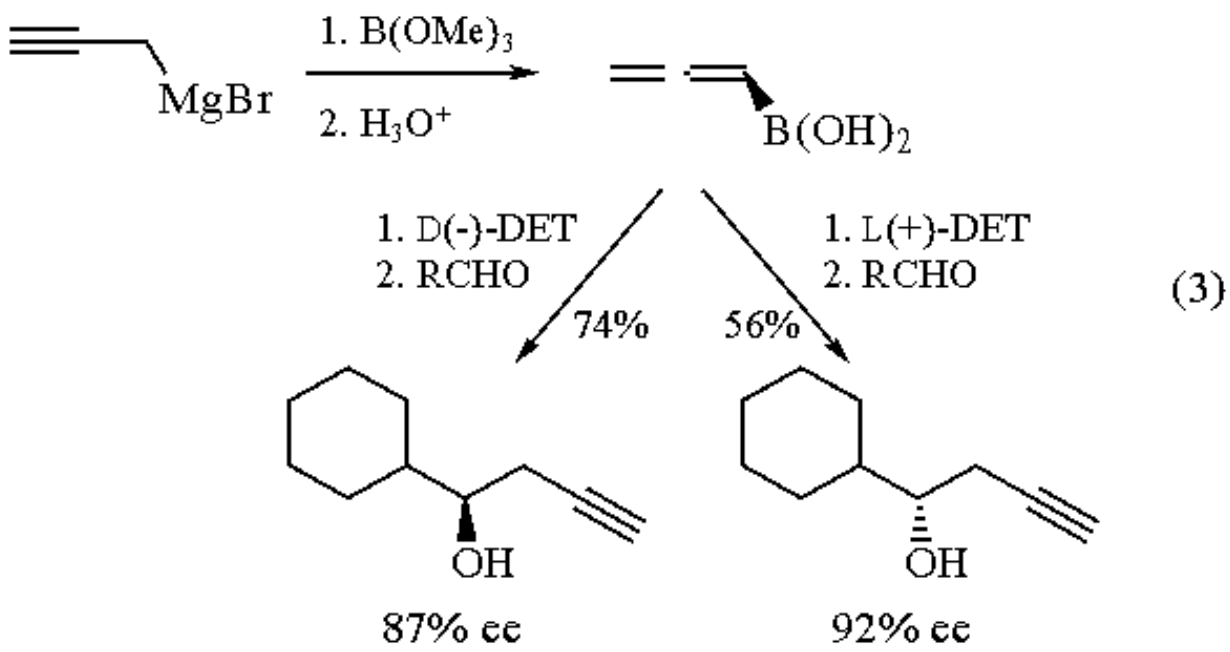

Because of the acidic C-H bond, deprotonation generates the propargylic anion which may also serve as a nucleophile. In addition to simple acylation,[50] lithium chloropropargylide adds to trialkylboranes to give a lithium trialkylalkynylborate. Dependent upon the subsequent reaction conditions, substituted allenes,[51] alkynes,[52] or homopropargylic and α-allenic alcohols[53] may be formed.

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Propargylmagnesium Bromide

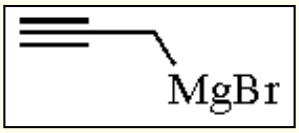

[13254-27-8] · C_3H_3BrMg · Propargylmagnesium Bromide · (MW 143.27)

(propargylation and propadienylation of electrophilic centers)

Physical Data: prepared and used in situ.

Solubility: sol ether, THF.

Preparative Methods: prepared from propargyl bromide (see ***Propargyl Chloride***) and amalgamated magnesium, generated in situ from ***Magnesium*** and ***Mercury(II) Chloride***. Without $HgCl_2$, only a mixture of acetylenic and allenic hydrocarbons is obtained. Reaction at reflux temperature in ether using a recycling reactor[1] results in a greater than 90% yield of Grignard reagent consisting of a 4:1 ratio of allenic and acetylenic forms.[2] Low temperature and slow addition of a dilute solution of a mixture of propargylic bromide and substrate to a reacting mixture, initiated with a small amount of the bromide, is a technique that reduces equilibration of the Grignard reagent before its reaction with the substrate.[3,4] The same slow addition of a dilute ether solution of propargyl bromide to an initiated reaction is said to lead to the pure allenic Grignard reagent.[5] The Grignard reagent prepared from propargyl bromide has been converted into a solid powder by complexation with tris(3,6-dioxaheptyl)amine.[6]

Handling, Storage, and Precautions: the reagent should be prepared and used when needed. Solutions undergo disproportionation to propyne, allene, the acetylenic Grignard reagent, and di-Grignard reagent over days. The reagent is easily hydrolyzed to gaseous hydrocarbons and must be handled and used in a dry and inert atmosphere. Pure propargyl bromide, the compound required for preparing the Grignard reagent, is shock sensitive.[7] Propargyl bromide is also supplied as an 80% by wt solution in toluene, which does not show this hazardous property.[8]

Propargylation by Addition to Carbonyl Compounds.

Propargylmagnesium bromide adds to ketones,[9] aldehydes,[10] esters,[11] and ***Carbon Dioxide***[12] to give a mixture of propargylic and allenic adducts. Additions to ketones and aldehydes (which can be present in the reaction mixture as the Grignard reagent is produced)[3,4] lead to mixtures of homopropargylic and allenic alcohols. Low reaction temperatures, ranging from 25 to -100 °C have been employed to favor formation of the acetylenic alcohol. Addition of propargylmagnesium bromide to benzaldehyde at 0 °C is highly regioselective for the acetylenic isomer (eq 1).[10c] The selectivity of this reaction is better than the 93:7 obtained by the addition of propargylzinc bromide to phenacyltrimethylsilane. The propargylzinc halide/acyltrimethylsilane route gives consistently higher selectivity for the acetylenic alcohol than the aldehyde/Grignard route with higher propargyl homologs (eq 2).[10c]

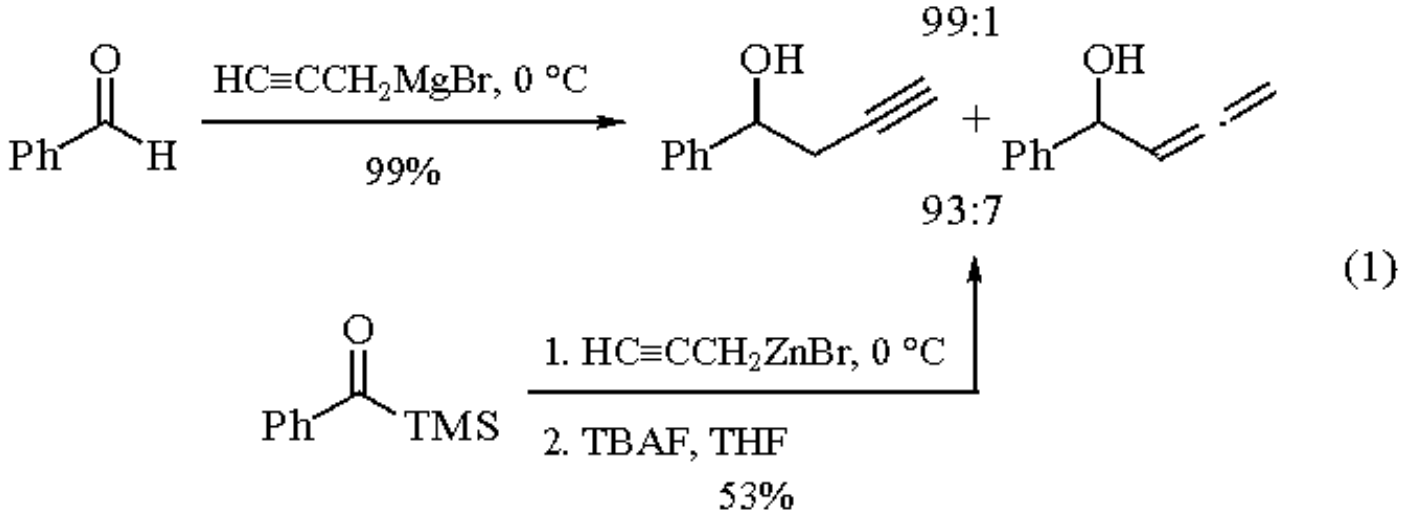

(1)

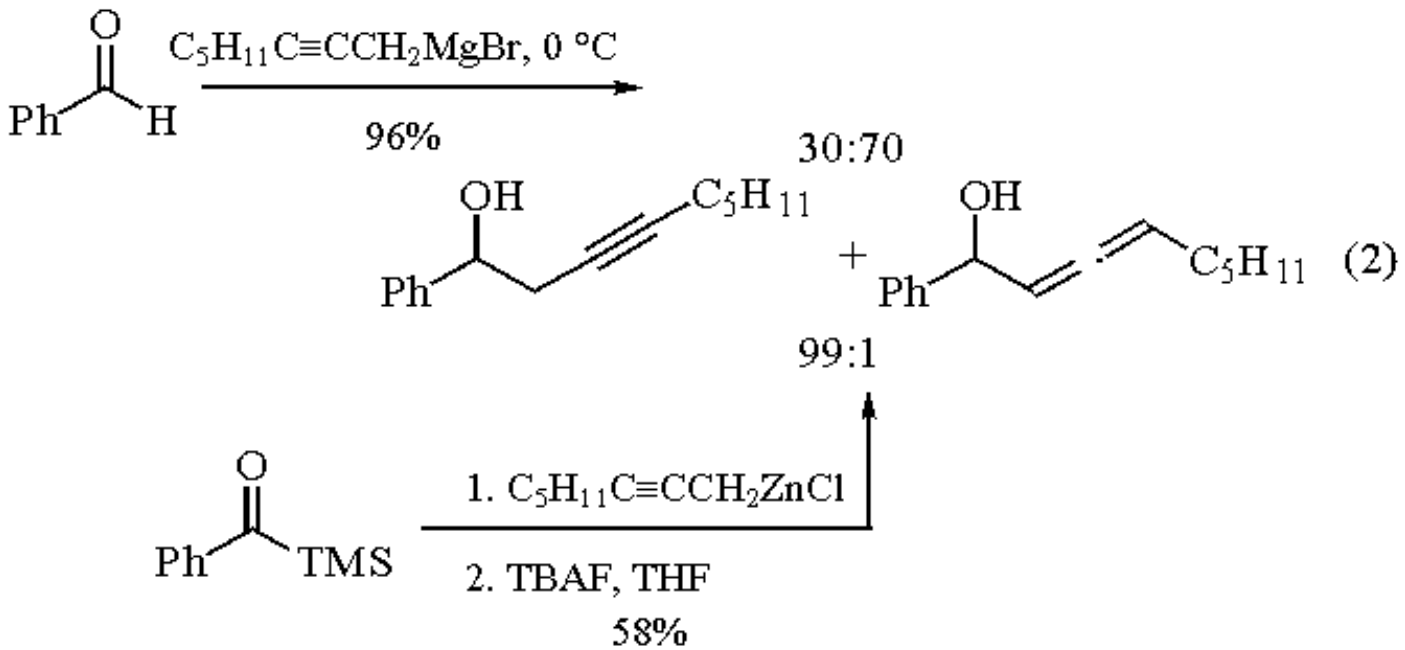

(2)

The 1,2-addition to α,β-unsaturated ketones gives consistently high yields and is a highly regioselective process that does not show competition from conjugate additions (eq 3).[9] A protocol is available, however, for conjugate propargylation of α,β-unsaturated ketones using stannylallenes generated from propargylmagnesium bromide.[13] The addition of propargyl Grignard reagents to esters is usually a low yield reaction.[11] Low temperature and reverse addition techniques ensure that the reaction gives the ketone as the product. Predominance of the acetylenic or allenic ketone depends on the ester. For example, ethyl acetate is converted in 18% yield to a mixture of ketones consisting of 70% of 1,2-pentadien-4-one and 30% of 1-pentyn-4-one. Ethyl propionate gives a 30% yield of a 63:37 mixture of 1-hexyn-4-one and 1,2-hexadien-4-one, respectively.[11b,c] Carboxylation of propargylmagnesium bromide with CO_2 is also a low yield reaction that gives a mixture of acetylenic and allenic carboxylic acids.[12] The yield of carboxylic acids is better with the higher homologs of the propargyl Grignard reagent.

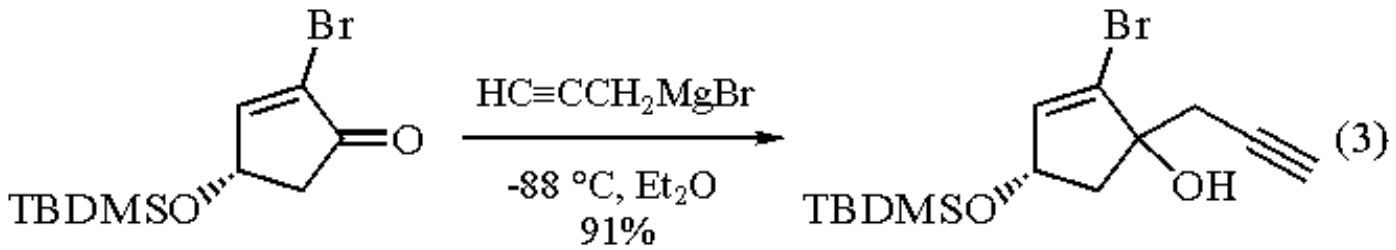

(3)

Propargylation by Addition to C=N Bonds.

A Grignard reagent prepared from propargyl bromide, described as allenylmagnesium bromide, adds efficiently to the C=N bonds of benzoxazoles, benzothiazoles,[14] quinoxalines,[15] and pyrimidines.[16] Benzoxazoles and unsubstituted benzothiazole add two propargyl groups at the 2-position to give ring-opened compounds (eqs 4 and 5). 2-Substituted benzothiazoles, on the other hand, add only one propargyl group, no matter how much Grignard reagent is present (eq 6). Quinoxaline adds a propargyl group to each of the C=N bonds (eq

7), whereas 2,3-dimethylquinoxaline affords a monoadduct regardless of how much excess Grignard reagent is present. 2-Chloro-3-methylquinoxaline gives 2-propargyl-3-methylquinoxaline, the product of nucleophilic aromatic substitution, when treated with a 50% excess of allenylmagnesium bromide (eq 8). Chloropyrimidines, however, only undergo addition to the C=N bond with allenylmagnesium bromide, uncomplicated by nucleophilic aromatic substitution (eq 9).

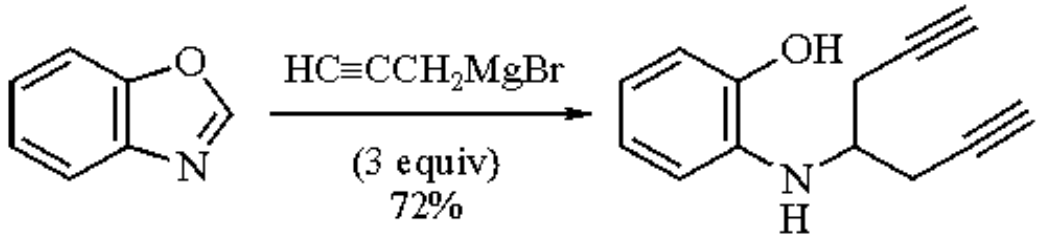

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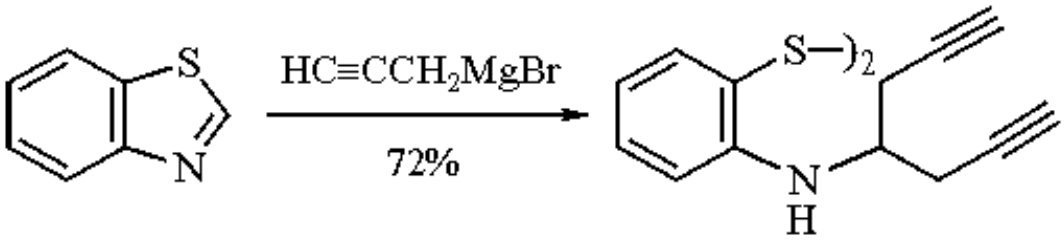

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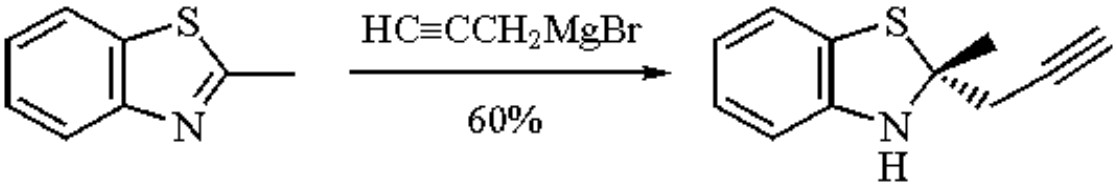

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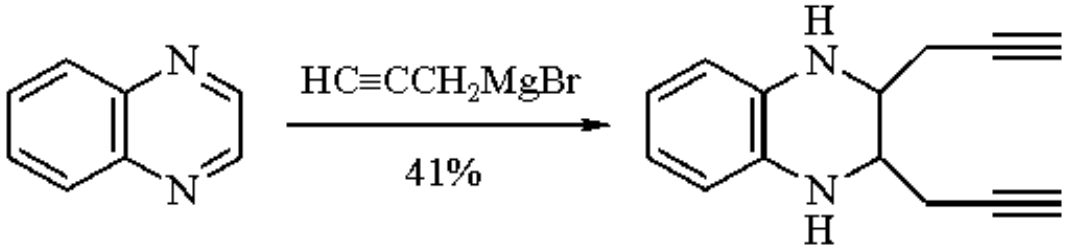

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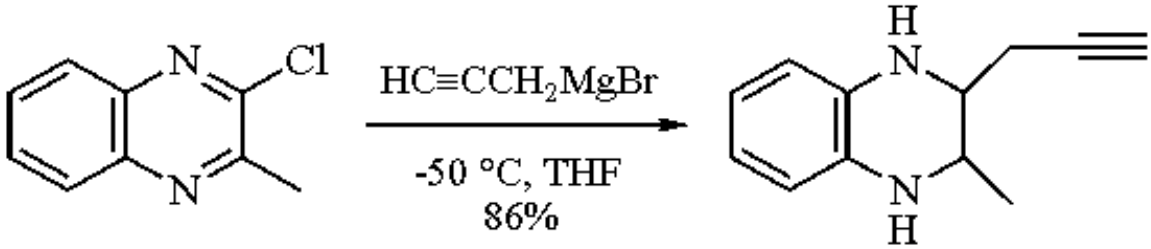

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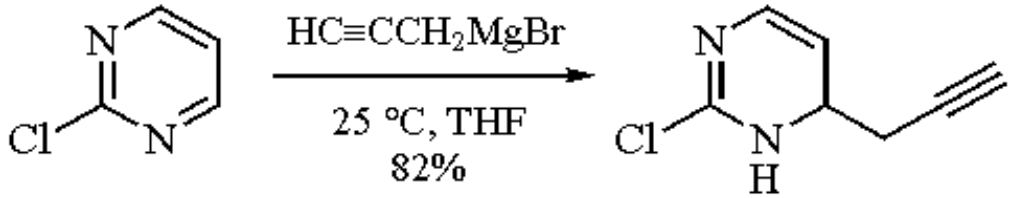

(9)

Propargylation by Substitution.

The Grignard reagent from propargyl bromide reacts poorly with saturated alkyl halides, but very well with allylic,[17] benzylic,[17] and some propargylic[18] halides. For example, *trans*-1,4-dibromo-2,3-dimethyl-2-butene is converted to an enediyne in 51% yield using allenylmagnesium bromide (eq 10), whereas use of 3-lithio-1-trimethylsilylpropyne gives less than a 5% yield. ***Allyl Bromide***, however, gives a mixture in which the allenic product predominates (eq 11).[19] With benzylic halides, bromides react better than chlorides. The palladium(0)-catalyzed cross coupling with benzyl halides is more efficient (eq 12).[20] The reaction of propargylmagnesium bromide with

trimethylsilylpropargyl bromide is reported to be a high yield route to the 1,5-diyne (eq 13).[18] Propargylmagnesium bromide can open epoxides with regioselectivity that depends on the steric effect of substituents on the epoxide (eq 14).[21] Alkoxymethyldialkylamines are converted in high yields to β-acetylenic tertiary amines.[22] Regioselectivity is usually high and is also affected by steric factors at the carbon bearing the alkoxy leaving group (eq 15). β-Acetylenic amines are accessible from the addition of propargylmagnesium bromide to *N*-trimethylsilyl imines followed by hydrolysis.[23] Propargyl Grignard reagents also displace the acetoxy group from dialkoxymethyl acetates to give homopropargylic acetals.[24]

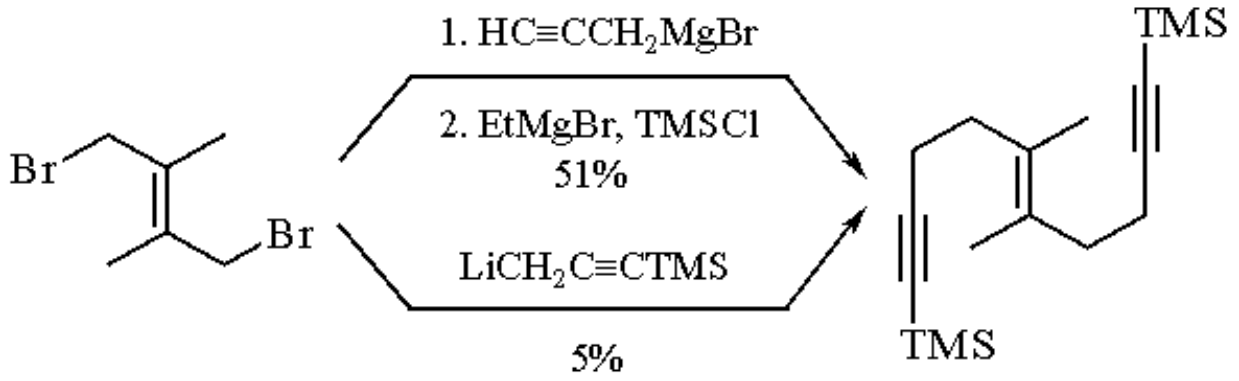

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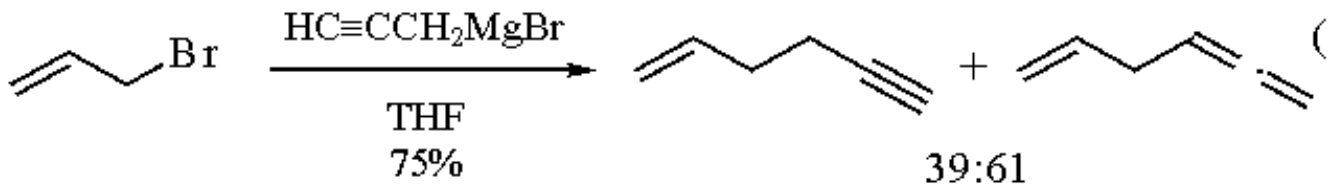

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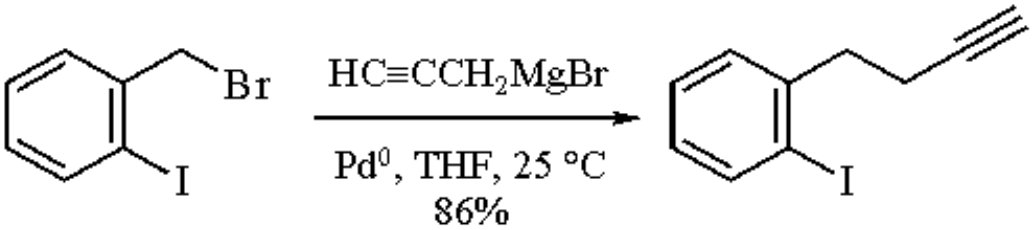

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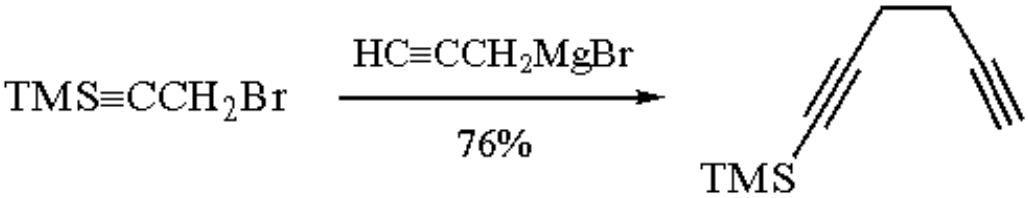

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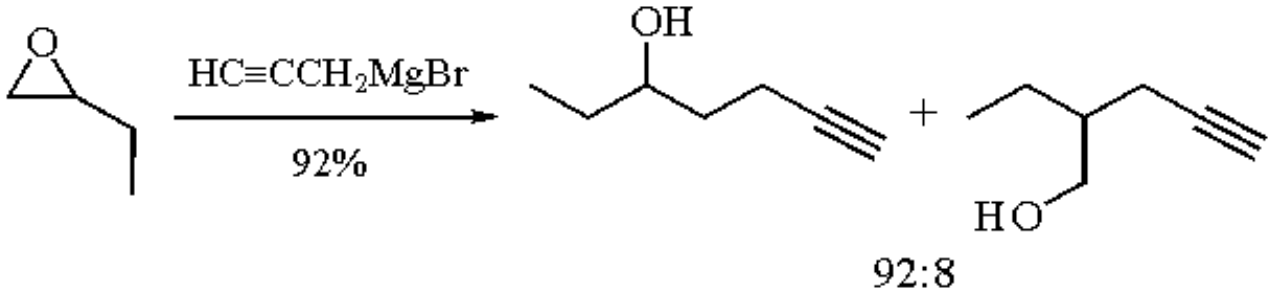

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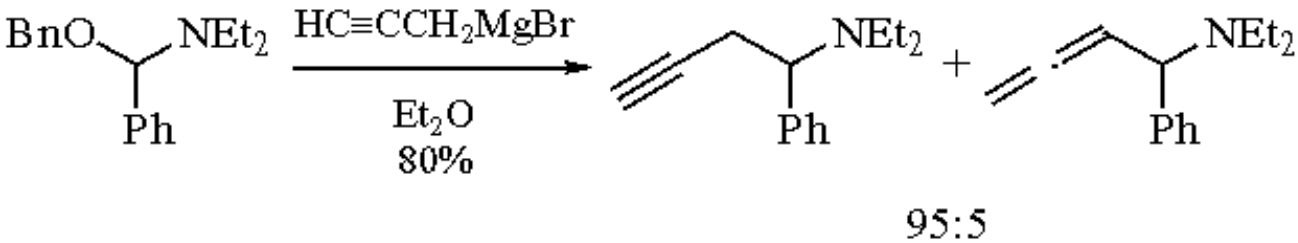

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Propargyltriphenylphosphonium Bromide

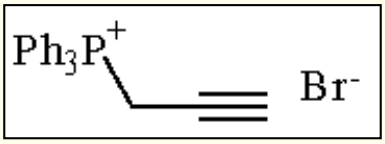

[2091-46-5] · $C_{21}H_{18}BrP$ · Propargyltriphenylphosphonium Bromide · (MW 381.26)

(Wittig reagent; synthon for β-amino- and β-iminopropenyltriphenylphosphonium bromides, precursors of heterocyclic systems)

Physical Data: mp 156-158 °C,[1] 179 °C;[2] IR;[3] ^{1}H NMR;[2] ^{13}C NMR;[4] pK_a.[5]

Preparative Method: readily available from ***Triphenylphosphine*** and propargyl bromide (see ***Propargyl Chloride***) (eq 1).[1,2] The presence of hydrogen bromide is absolutely necessary, otherwise the base Ph_3P causes the formation of tarry products.[1]

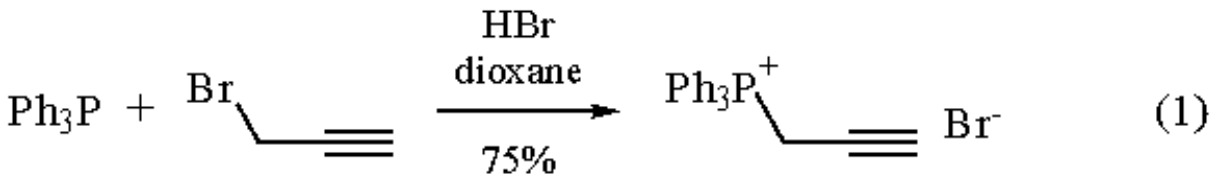

Wittig Reactions.

Deprotonation of propargyltriphenylphosphonium bromide with liquid ***Ammonia*** affords the corresponding phosphonium ylide which, in the presence of aldehydes, undergoes Wittig reaction to give enynes (eq 2).[1] Other bases which are usually used for the generation of phosphonium ylides from their salts give rise to the formation of dark, resinous products. Furthermore, only conjugated aldehydes are suitable substrates for the Wittig reactions under these conditions, leading to stereoisomeric mixtures.[1,6] Formation of an isomeric cumulene instead of the expected enyne, presumably as a consequence of an isomerization of the propargylidenephosphorane to the corresponding allylidene species, has been observed when ***n-Butyllithium*** is used as base.[7]

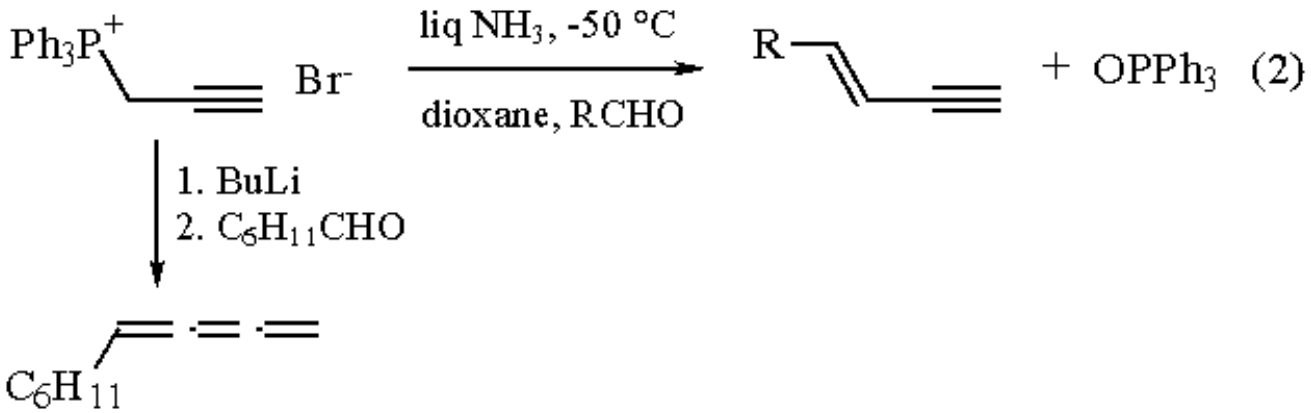

Isomerization.

Isomerization of propargyltriphenylphosphonium bromide to give the corresponding propadienyl and prop-1-ynyl salts can be accomplished by treatment with a catalytic amount of ***Potassium t-Butoxide*** or by heating with phenol, respectively (eq 3).[2]

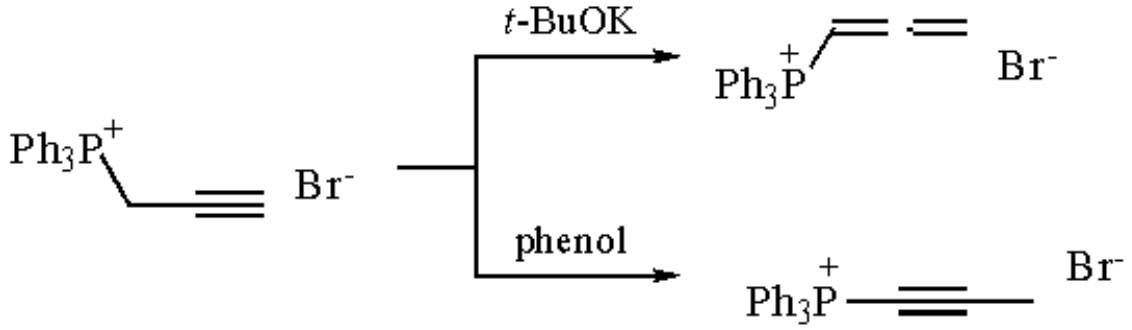

(3)

Addition of Nucleophiles.

Propargyltriphenylphosphonium bromide adds oxygen, sulfur, and nitrogen nucleophiles, yielding β-substituted propenyltriphenylphosphonium bromides (eq 4),[2,8-18] obviously via intermediate formation of propadienyltriphenylphosphonium bromide.[2]

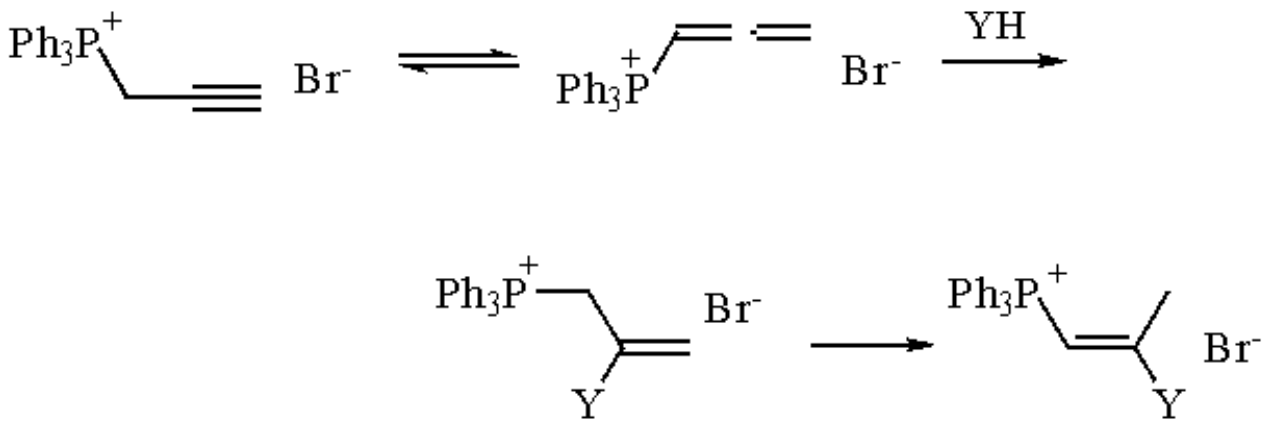

(4)

Y = OR, SR, NR^1R^2

The addition of various amino compounds has been investigated in most detail (eq 5).[2,8-15,18]

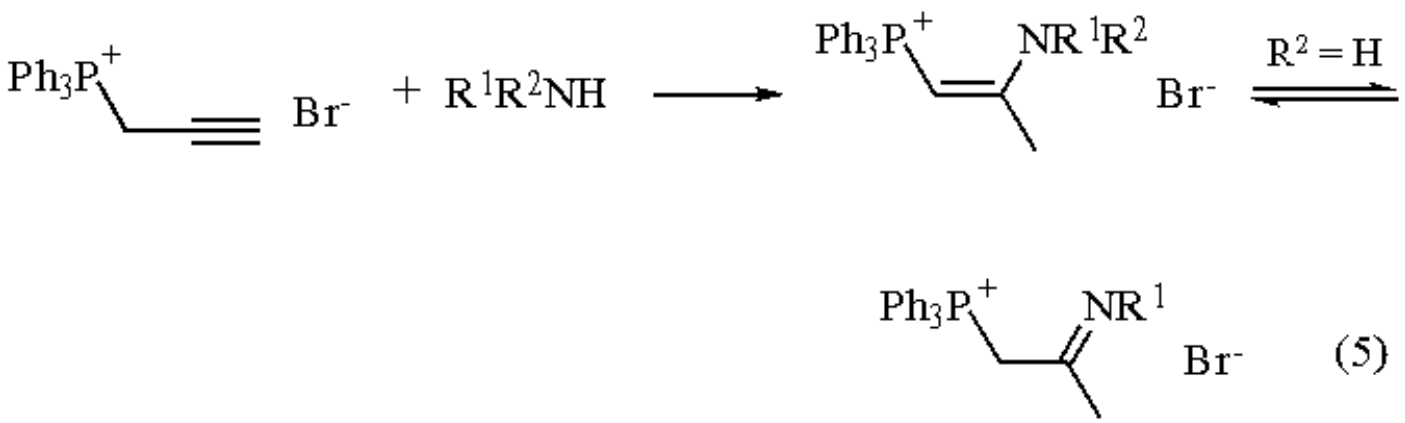

(5)

The resulting β-aminovinylphosphonium salts, which can be in equilibrium with the isomeric β-iminopropyl compounds,[2] are very useful reagents for Wittig reactions. Deprotonation affords the corresponding phosphoranes, which can be used in typical ylide reactions. Ylide generation followed by a Wittig reaction represents an efficient synthesis of 2-amino-1,3-butadienes (eq 6).[18]

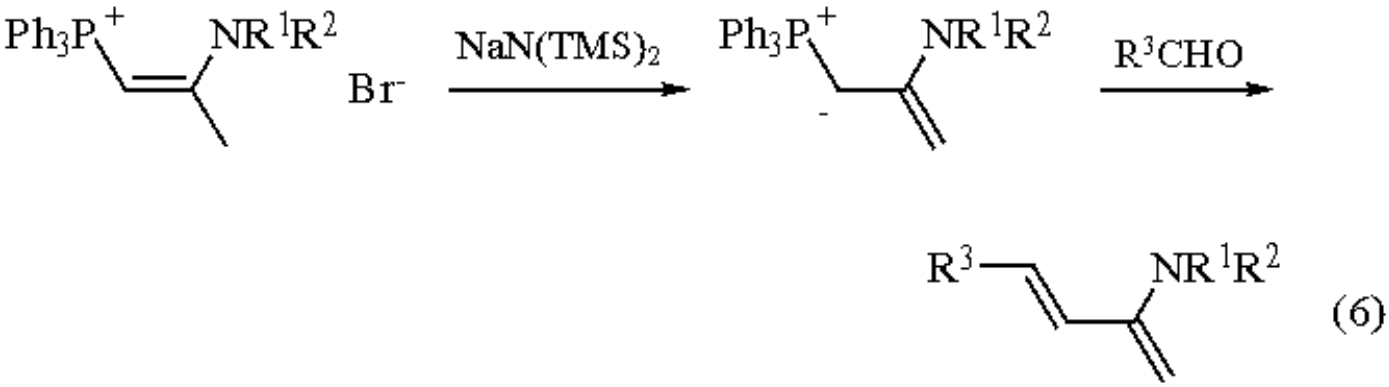

A variety of heterocycles has been synthesized starting from propargyltriphenylphosphonium bromide and amino compounds (eq 7). This can be realized if the intermediate phosphonium salt is substituted in such a manner to allow intramolecular Wittig reaction[2,8] or intramolecular attack at the β-C-atom of the vinyl group followed by extrusion of methylenetriphenylphosphorane.[2,9,12]

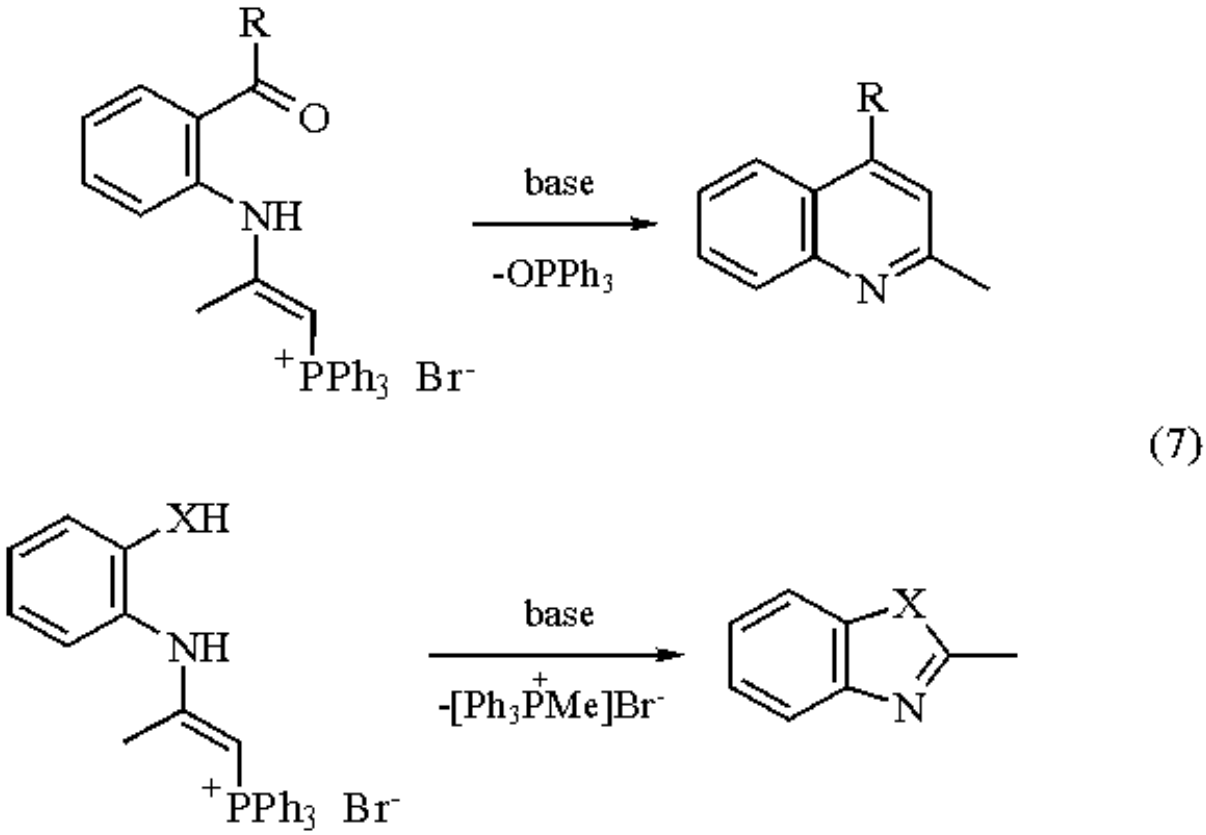

Heterocycles may also result from thermal rearrangement of primarily formed open-chain Wittig products which are available from β-hydrazonopropylphosphonium bromides.[11,14,15] The phosphonium salts resulting from azirines and propargyltriphenylphosphonium bromide also undergo rearrangements affording phosphorus-substituted heterocycles.[13]

Reaction with Iminophosphoranes.

Reactions of propargyltriphenylphosphonium bromide with iminophosphoranes or phosphazines give 2-imino-3-phosphoranylidene phosphonium salts (eq 8), which can formally be rationalized as the result of a [2 + 2] cycloaddition followed by an electrocyclic ring opening.[8,11,19,20]

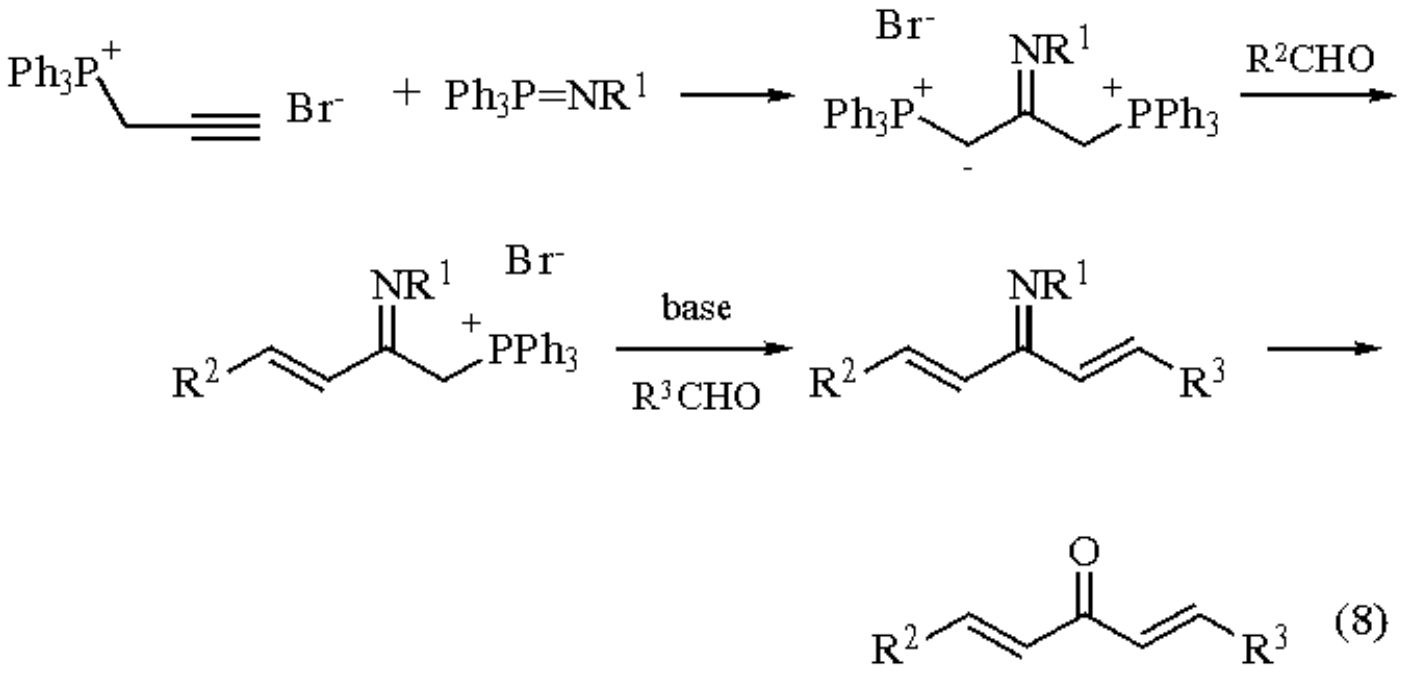

The resulting ylide salts are versatile precursors for the synthesis of β-enamino phosphonium salts, divinylic ketimines, and the corresponding ketones.[19,20] In some cases the resulting Wittig products undergo cyclization, affording heterocyclic compounds.[11]

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1-Propenyl Bromide[1]

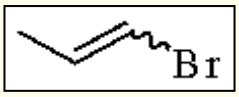

(*Z*)

[590-13-6] · C_3H_5Br · 1-Propenyl Bromide · (MW 120.98) (*E*)

[590-15-8]

(precursor for (*E*)- or (*Z*)-1-propenyllithium and 1-propenylmagnesium bromide; reagent for electrophilic propenylation)

Alternate Name: 1-bromo-1-propene.

Physical Data: bp 58.5 °C (*Z*), 64.5 °C (*E*); *d* 1.420 g cm^{-3} (*Z*), 1.428 g cm^{-3} (*E*); *n*25D 1.4508 (*Z*), 1.4534 (*E*).

Solubility: insol water; sol alcohol, ether, most other organic solvents.

Form Supplied in: colorless liquid; commercially available (*Z*-isomer of 97% purity or a 70:30 *Z*/*E* mixture).

Preparative Methods: (*Z*)- and (*E*)-1-propenyl bromides can be obtained through spinning band distillation of the commercially available mixture of isomers (*Z*/*E* = 70/30). However, the (*E*)-isomer can only be obtained with difficulty due to thermal isomerization to the (Z)-isomer. Pure (*Z*)-1-propenyl bromide can be prepared by bromination of (*E*)-crotonic acid followed by bromodecarboxylation of the resulting *erythro*-2,3-dibromobutanoic acid in the presence of ***Triethylamine*** or ***Diisopropylethylamine*** at 40 °C (eq 1).[2] (*E*)-1-Propenyl bromide can be obtained[3] in 98% purity by treatment of the commercially available mixture of isomers (*Z*/*E* = 70/30) with ***Sodium Hydroxide*** in *n*-BuOH at reflux until no (*Z*)-1-propenyl bromide is detected by GLC.

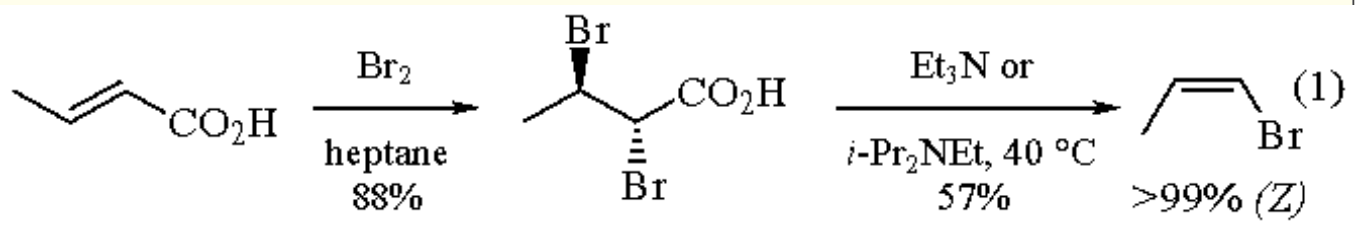

Handling, Storage, and Precautions: stored in a refrigerator to inhibit thermal and acid-catalyzed isomerization. Avoid breathing vapor and contact with skin and eyes. Use in a fume hood.

General Discussion.

Both (*E*)- and (*Z*)-1-propenylmagnesium bromides are prepared in THF[4] from the corresponding bromides with 80% and 90% retention of the configuration,[5] respectively. They react with various electrophiles[1,6] (eqs 2 and 3)[7] (see also ***Isopropenylmagnesium Bromide*** and ***Vinylmagnesium Bromide***). Pure (*E*)-1-propenylmagnesium bromide can also be prepared from ***1-Propenyllithium*** and anhydrous ***Magnesium Bromide*** in diethyl ether.[8]

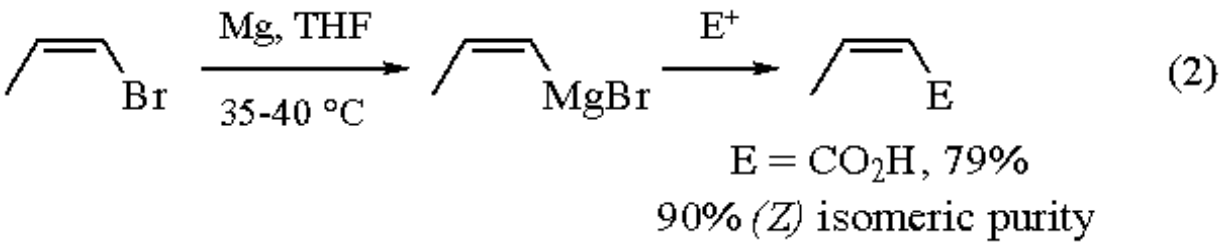

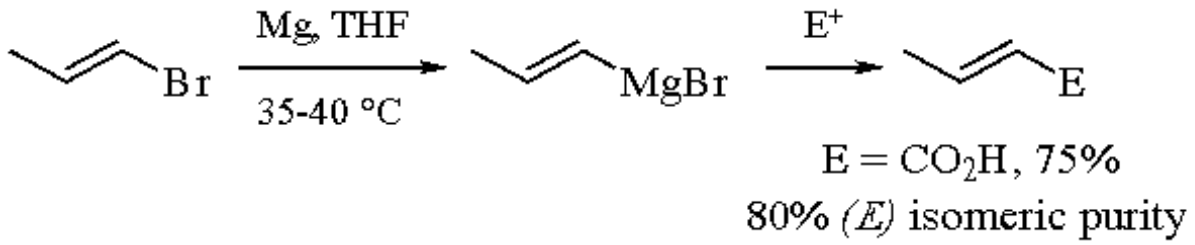

(*Z*)- or (*E*)-1-propenyl bromide gives (*Z*)- or (*E*)-***1-Propenyllithium*** by reaction with ***Lithium*** powder (eq 4)[9] or by metal-halogen exchange reaction with ***t-Butyllithium*** (eq 5).[10]

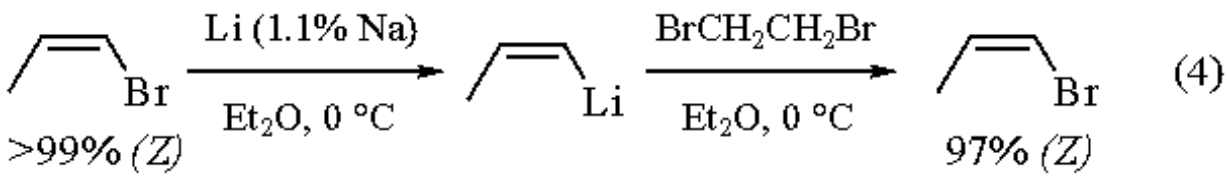

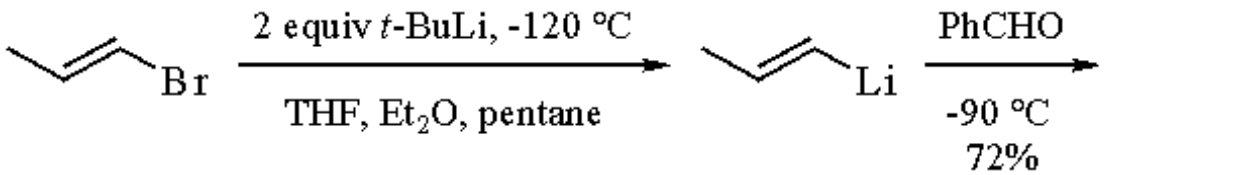

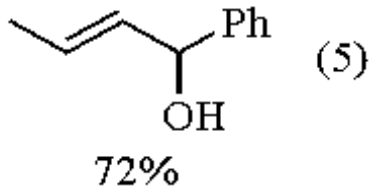

Vinylation of Grignard reagents can be achieved easily with (*Z*)- or (*E*)-propenyl bromide in the presence of an iron or palladium complex catalyst[11] (eqs 6 and 7).[3,11a]

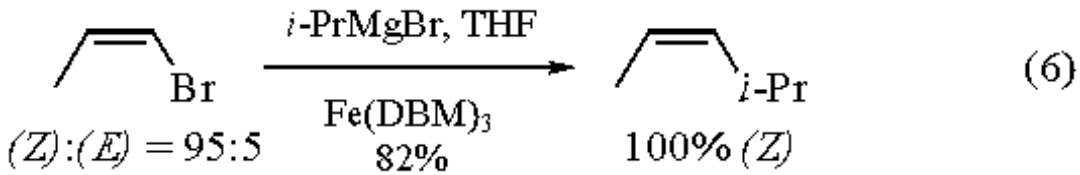

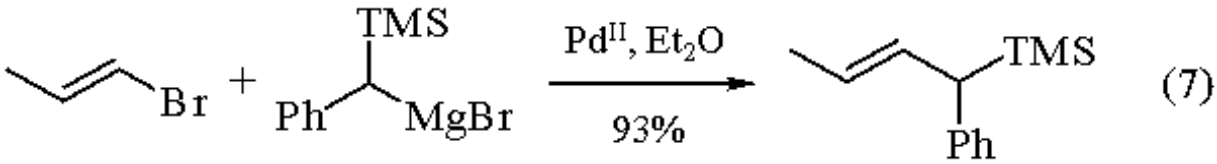

Under the influence of ***Nickel(II) Chloride*** hydrate, in the presence of ***Zinc*** and ***Pyridine***, (*Z*)-1-propenyl bromide reacts with ***Ethyl Acrylate***, ***Acrylonitrile***, and ***Methyl Vinyl Ketone*** (eq 8).[12]

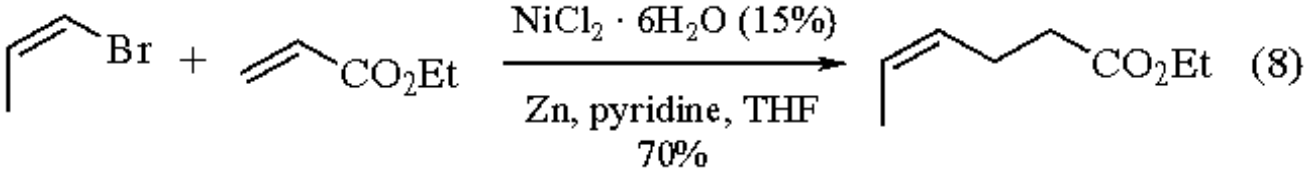

In the presence of a palladium(0) complex and ***Copper(I) Iodide***, (*Z*)-1-propenyl bromide reacts stereospecifically with terminal alkynes to give (*Z*)-enynes (eq 9).[13]

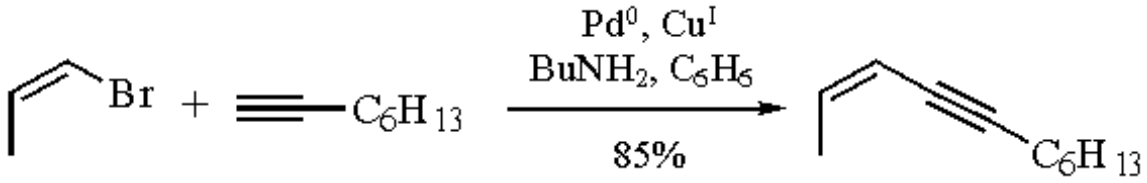

(9)

Under palladium catalysis, reaction of (*E*)-1-propenyl bromide with an allene hydrocarbon generates a transient π-allyl palladium complex which is trapped by sodium ***Diethyl Malonate*** to give a conjugated diene in high yield (eq 10).[14]

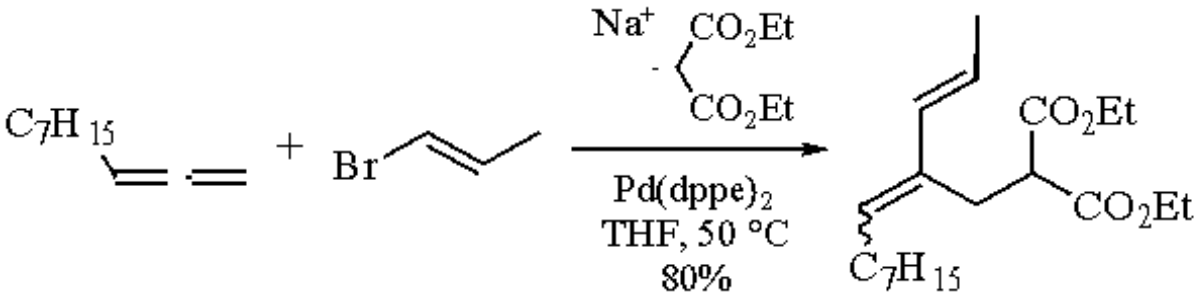

(10)

Magnesio Derivatives.

In the presence of ***Silver(I) Nitrate*** and palladium or nickel complexes, (*Z*)- or (*E*)-1-propenyl magnesium bromide couples with alkyl (eq 11),[15] vinyl (eq 12),[16,17] and aryl halides (eq 13).[17]

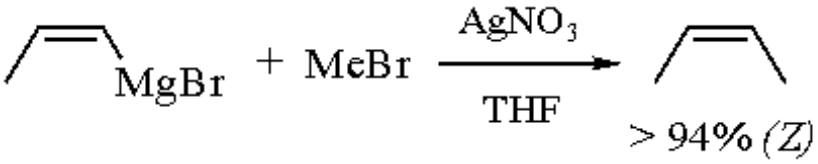

(11)

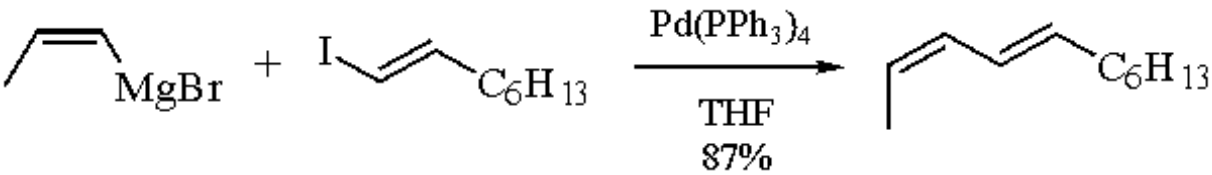

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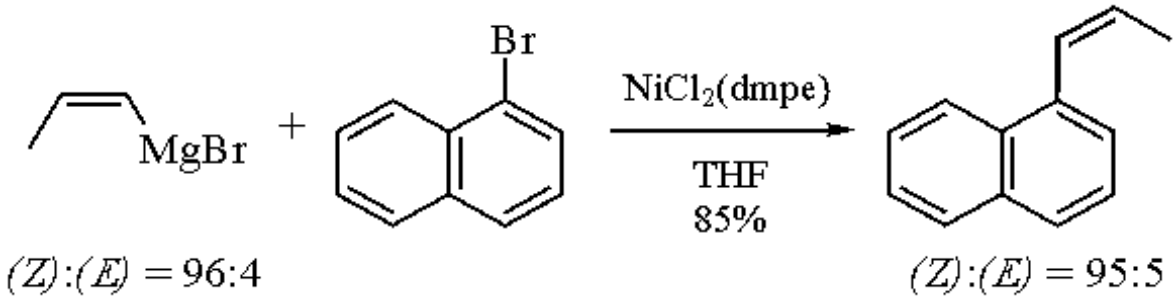

(13)

(*E*)-1-Propenylmagnesium bromide stereospecifically dimerizes on treatment with ***Copper(I) Chloride***.[18] However, the propenyl unit can be transferred by standard cuprate reactions[19] (eq 14)[20] (see also ***2-Propenylmagnesium Bromide-Copper(I) Iodide***).

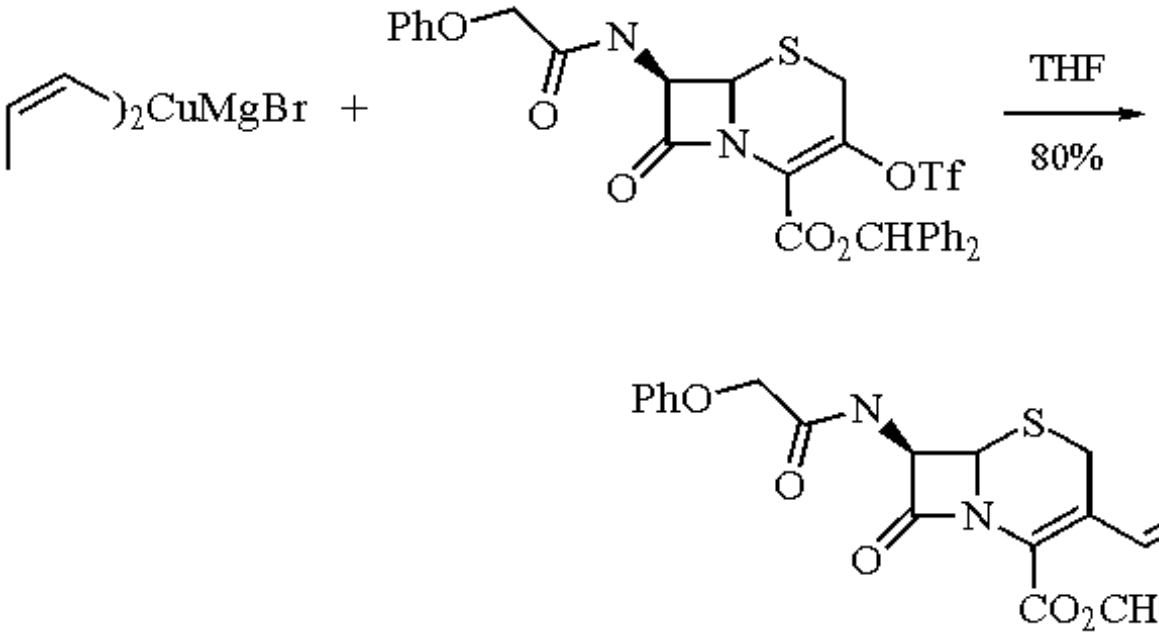

(14)

The transmetalation of 1-propenylmagnesium bromide with ***Tri-n-butylchlorostannane***[6e,21] or ***Manganese(II) Chloride***[22] forms 1-propenyl tin and manganese compounds. The latter react with α,β-unsaturated aldehydes in 1,4-fashion (eq 15).[23]

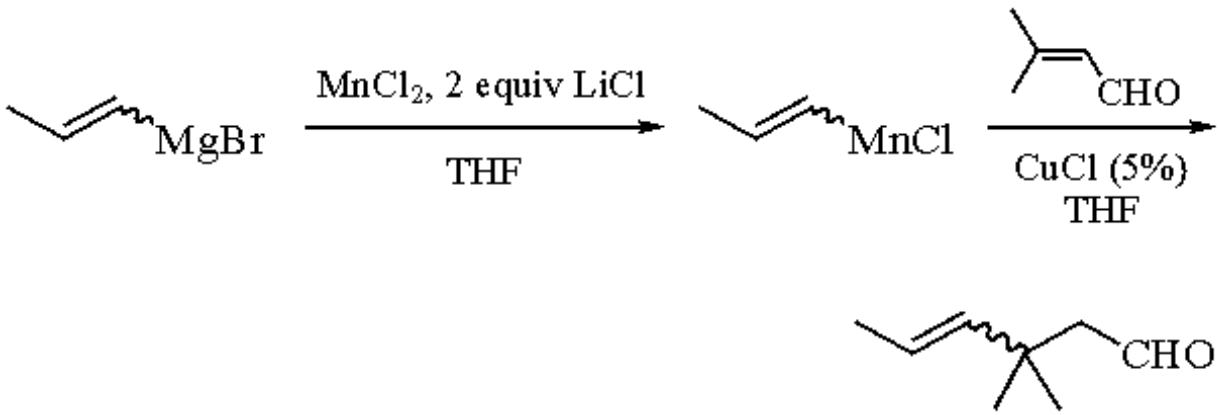

(15)

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1-Propenyllithium[1]

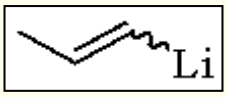

(*E*)

[6386-72-7] · C_3H_5Li · 1-Propenyllithium · (MW 48.02) (*Z*)

[6524-17-0]

(precursor of propenyl metals[2])

Physical Data: ^1H and ^{13}C NMR spectra have been reported.[2g]

Preparative Methods: prepared by reaction of 1-chloro- or 1-bromopropene with ***Lithium*** powder (containing 2% of sodium in the case of the chloride) in diethyl ether (eqs 1 and 2).[4] This reaction occurs with a slight loss of stereochemistry.[4d] The reagent can also be prepared by metal-halogen exchange reaction between 1-bromopropene and ***t-Butyllithium*** (eq 3),[5] and by transmetalation of tin derivatives by an organolithium compound (eq 4).[2g,6] In the two latter cases, the reactions are stereospecific.

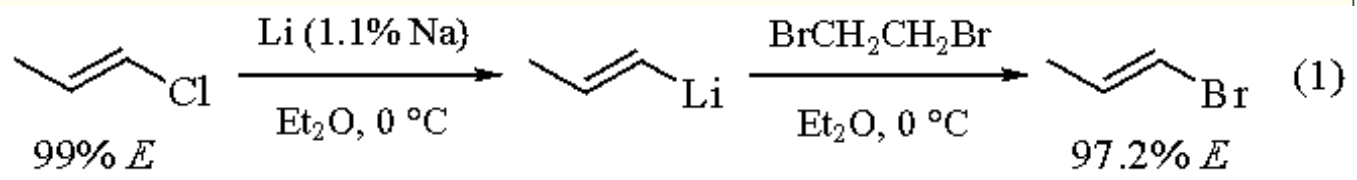

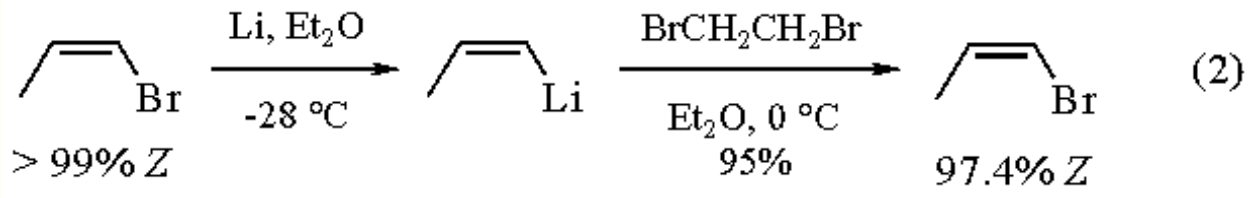

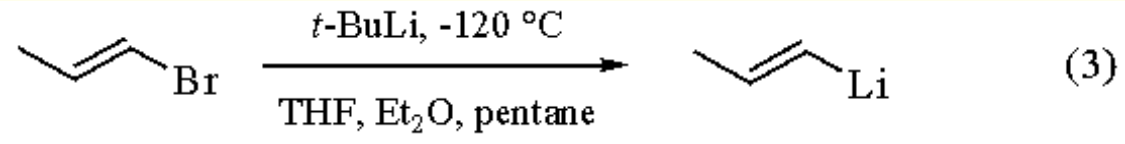

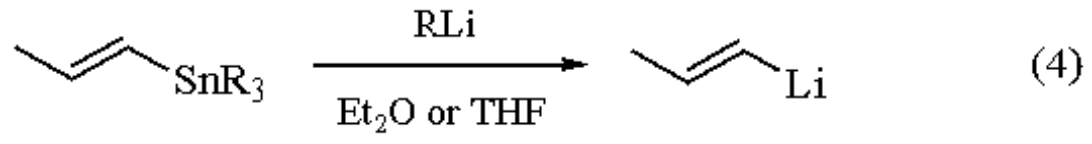

Handling, Storage, and Precautions: the solution of propenyllithium in diethyl ether must be handled with care since it is flammable and may ignite on contact with moisture and air. It should be stored and handled in an inert atmosphere (argon) and measured or transferred by means of a hypodermic syringe or cannula. The solution may deteriorate with time and the concentration of the reagent should be titrated before use.[3]

General Discussion.

Both (*Z*)- and (*E*)-1-propenyllithium reagents react with various electrophiles[2g,4-6] with retention of configuration (eqs 5 and 6).[7,8]

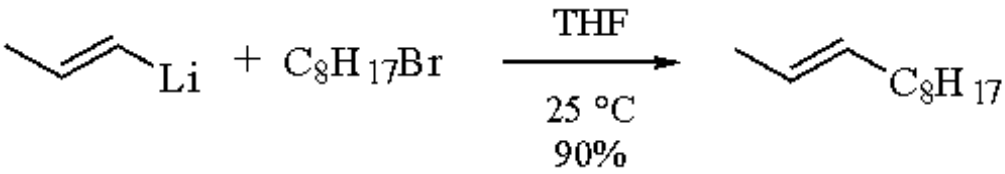

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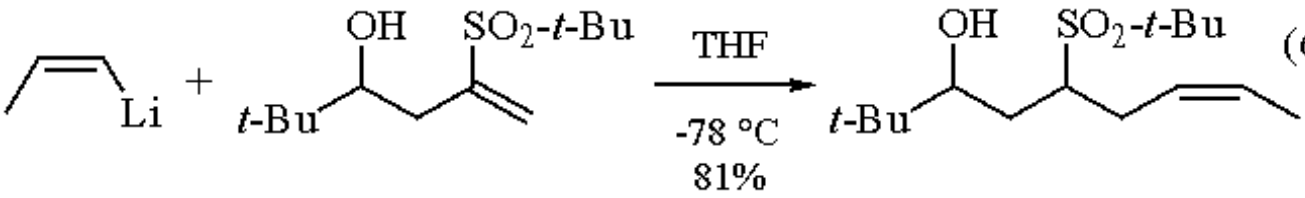

(6)

When treated with 2-halogenoalkyl boronates in diethyl ether, (*Z*)- or (*E*)-1-propenyllithium leads to allyl boronates (eqs 7 and 8).[9]

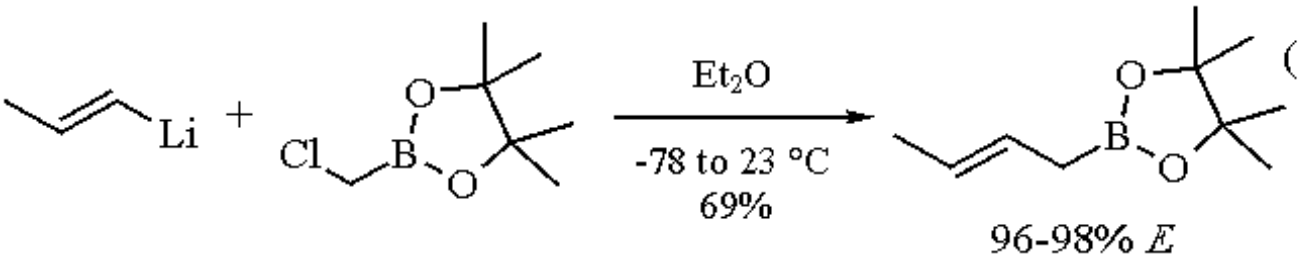

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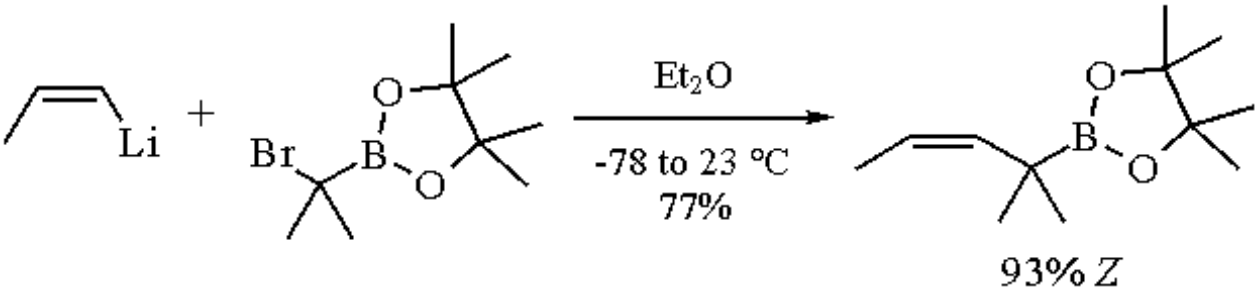

(8)

The reaction of (*Z*)- or (*E*)-1-propenyllithium with ***Copper(I) Iodide*** or silver iodide leads to the corresponding organometallic compound which undergoes thermal decomposition to give 2,4-hexadiene with retention of configuration at the double bonds (eq 9).[4d,f]

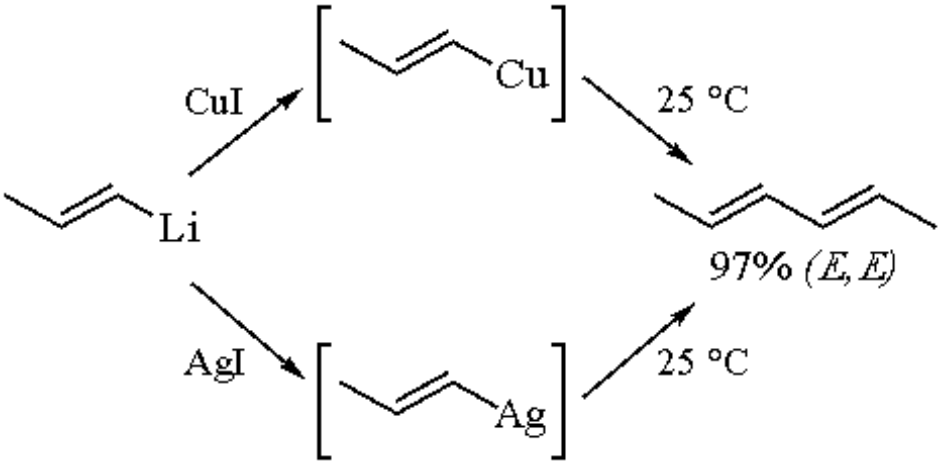

(9)

Pure (*Z*)- and (*E*)-1-propenylcuprates, prepared according to standard cuprate procedures,[2] undergo conjugate addition to α,β-unsaturated carbonyl compounds[10] (eqs 10 and 11)[10a] and react readily with alkyl halides (eq 12)[11] and epoxides (eq 13).[12]

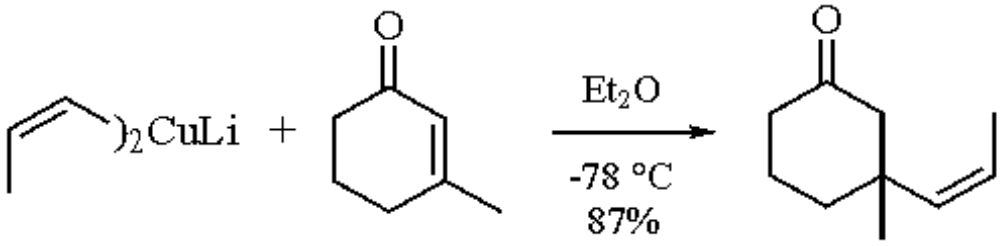

(10)

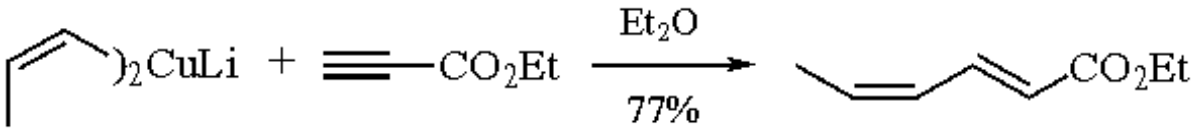

(11)

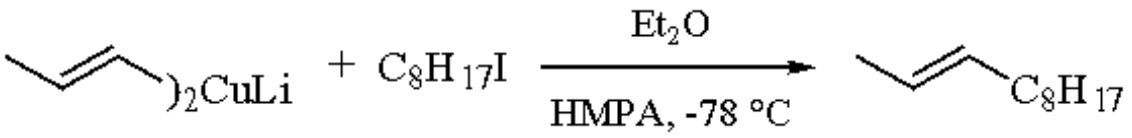

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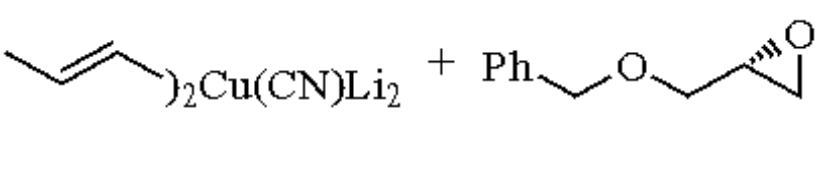

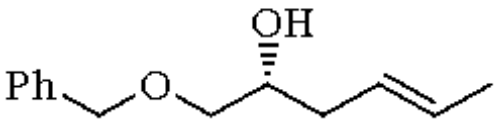

(13)

When treated with allylic chlorides (e.g. (*E*)-1-chloro-2-octene), they lead to skipped dienes without isomerization or rearrangement (eq 14).[13]

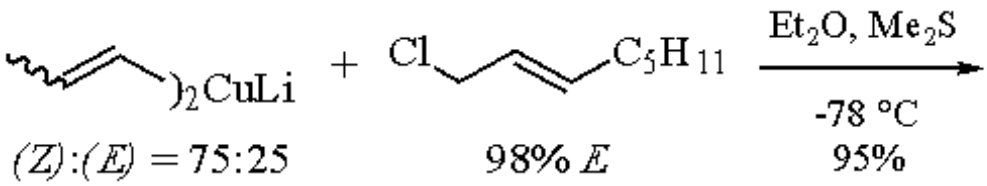

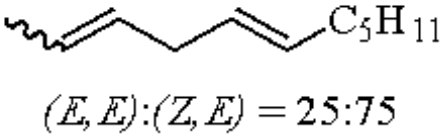

(14)

Addition of (*E*)-1-propenylcuprate to α-hydroxy aldehydes in the presence of ***Magnesium Bromide*** etherate proceeds stereoselectively to give allylic alcohols (eq 15).[14]

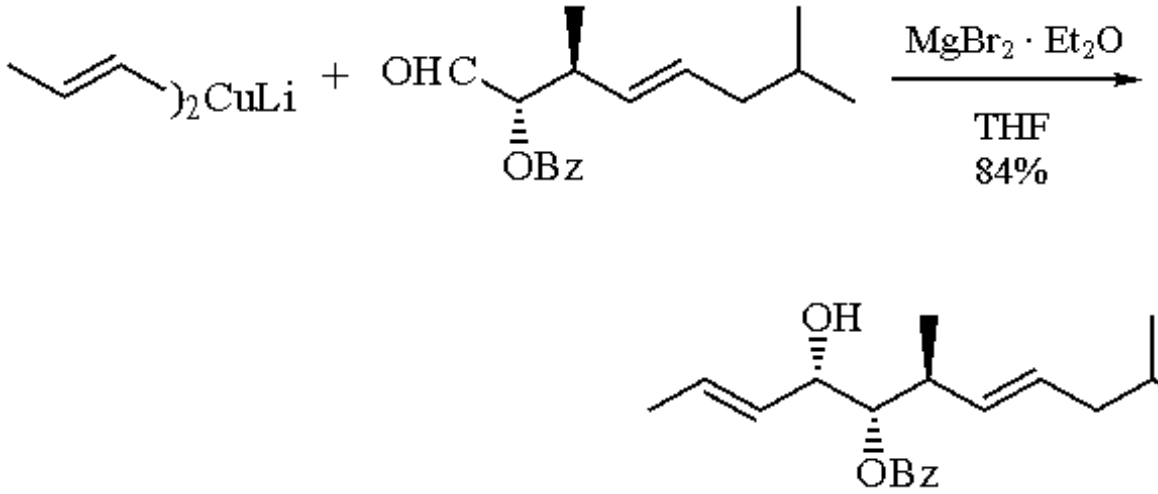

(15)

The transmetalation of 1-propenyllithium with tributyltin bromide allows the preparation of 1-propenyltributyltin with retention of configuration (eq 16).[15]

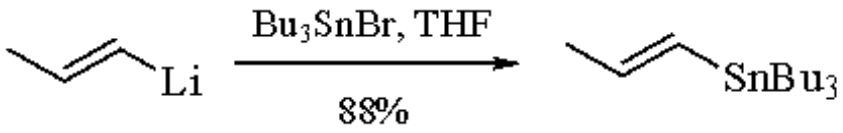

(16)

In the presence of lithiated (+)-*N*-methylephedrine or (+)-2-(dimethylamino)-1,2-diphenylethanol, (*Z*)-1-propenylzinc bromide (prepared by transmetalation of (*Z*)-1-propenyllithium) adds enantioselectively to a variety of aldehydes (eq 17).[16]

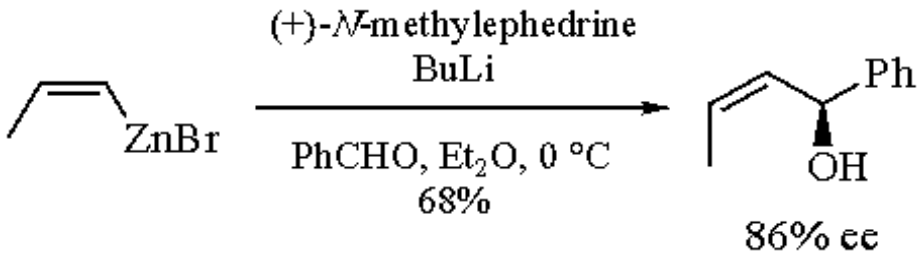

(17)

Related Reagents.

(*E*)- and (*Z*)-alkenyllithium derivatives, prepared in the same way as (*E*)- and (*Z*)-propenyllithium reagents, are useful precursors of alkenyl organometallic compounds, particularly alkenyl cuprates.

Alkenylmanganese compounds, obtained by transmetalation of organolithium derivatives with manganese halides, are chemoselective reagents and react with acid chlorides to give α,β-unsaturated ketones (eq 18).[17] Under copper catalysis, they add to α,β-unsaturated ketones in 1,4-fashion (eq 19).[18]

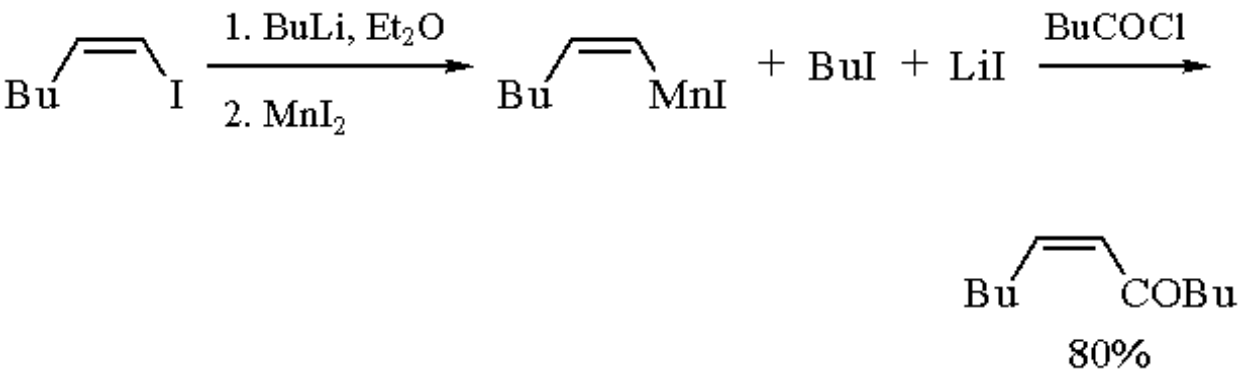

(18)

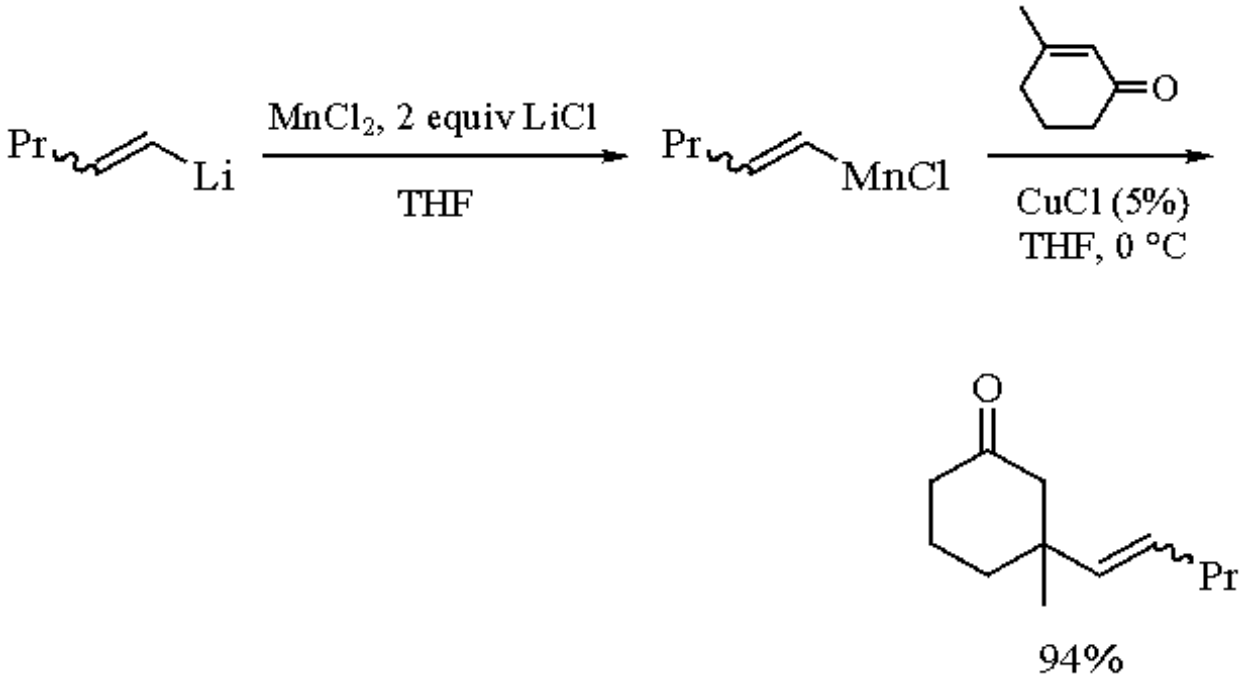

(19)

Alkenyllithium reagents bearing an alcohol function in the allylic position[6a] are useful intermediates in synthesis[2f] (eq 20).[19] The corresponding cuprates react regioselectively with epoxides (eq 21).[20]

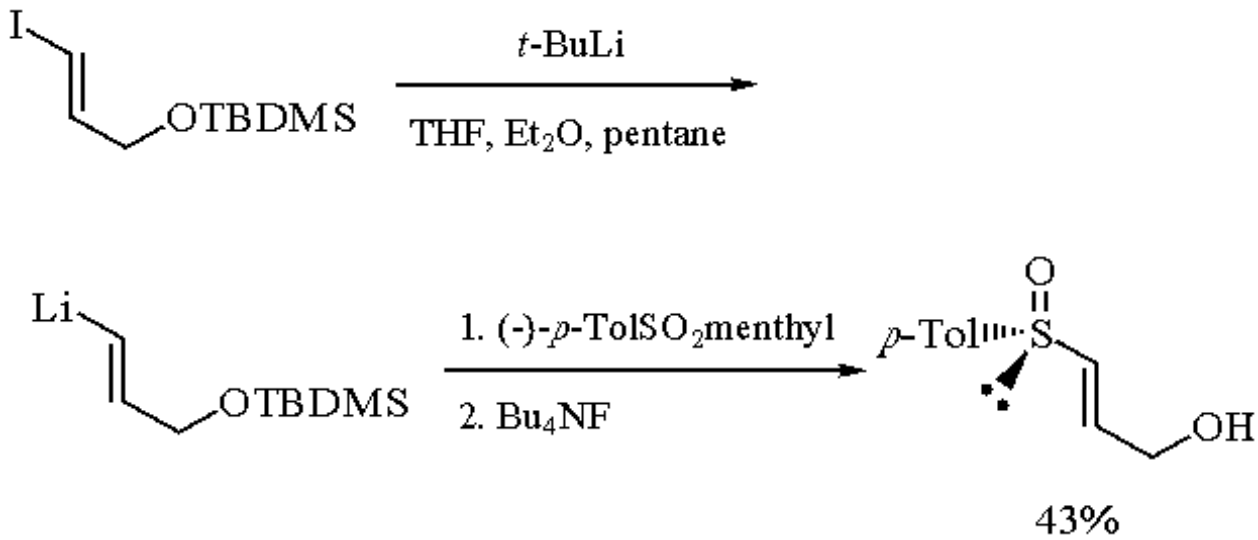

(20)

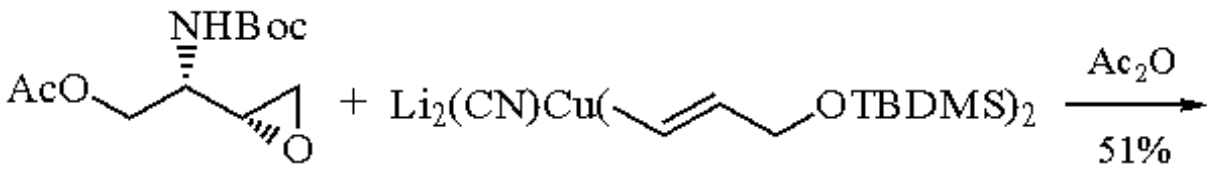

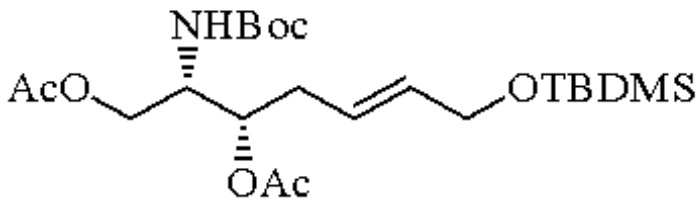

(21)

(*E*)-3-Hydroxy-1-octenyllithium is a key intermediate in prostaglandin synthesis.[21] Several convenient approaches to prostaglandins commence with a preformed cyclopentane nucleus bearing suitable functionality for elaboration of at least one of the side chains. The second chain may be attached by a variety of methods. However, by far the most successful approach involves the conjugate addition of a vinyl copper to a cyclopentenone precursor (eq 22).[22]

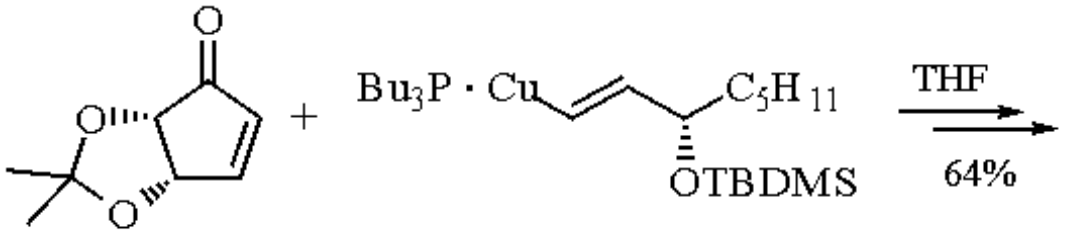

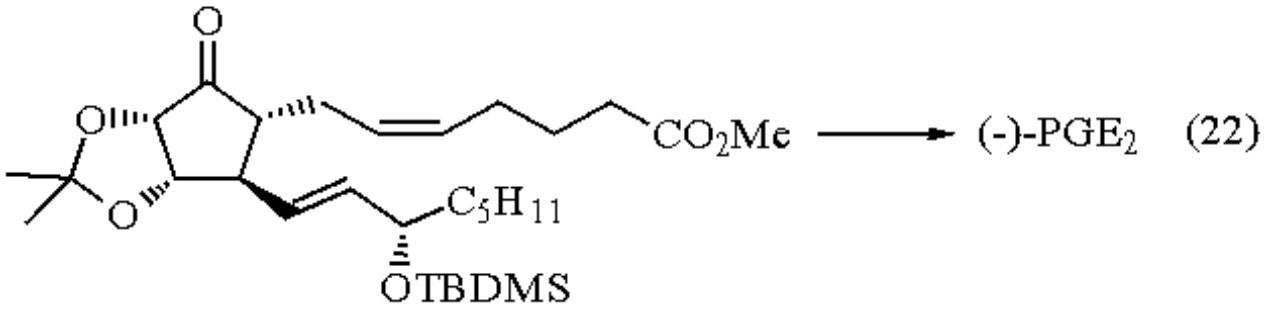

Related Reagents.

Isopropenyllithium; ***Vinyllithium***.

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2-Propenylmagnesium Bromide-Copper(I) Iodide[1]

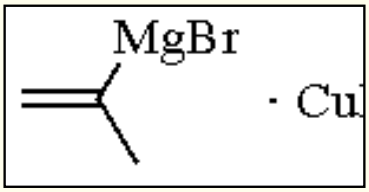

(2-propenylmagnesium bromide)

[13291-18-4] · C_3H_5BrMg · 2-Propenylmagnesium Bromide-Copper(I) Iodide · (MW 145.29) (CuI)

[7681-65-4] · CuI · 2-Propenylmagnesium Bromide-Copper(I) Iodide · (MW 190.45)

(undergoes conjugate addition to cyclohexenone;[2] adds regioselectively to β,γ-epoxides[3])

Preparative Method: prepared in situ under anhydrous conditions by reacting 2-propenylmagnesium bromide (**1**) with ***Copper(I) Iodide*** (**2**) in varying molar ratios.

Handling, Storage, and Precautions: use in a fume hood.

Conjugate Addition.

Cyclohexenone reacts with (**1**) in the presence of catalytic (**2**) to give 3-isopropenylcyclohexanone (**3**) (eq 1).[2] Attempts to access (**3**) via dehydration of (**4**) result in mixtures of (**3**) and the cyclohexenone (**5**) (eq 2).

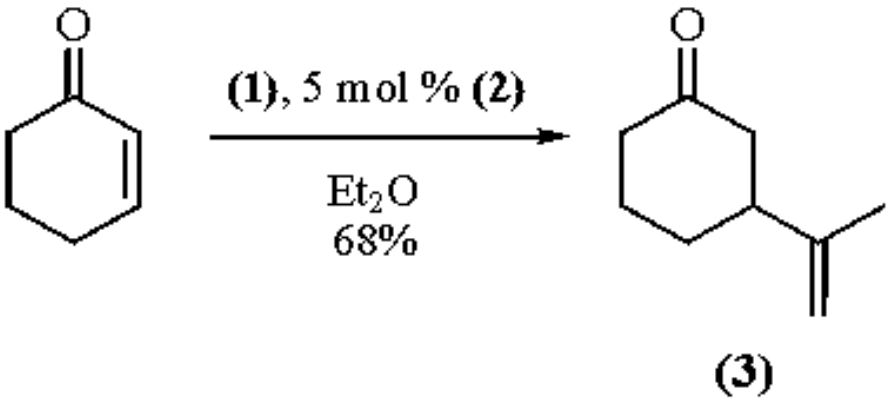

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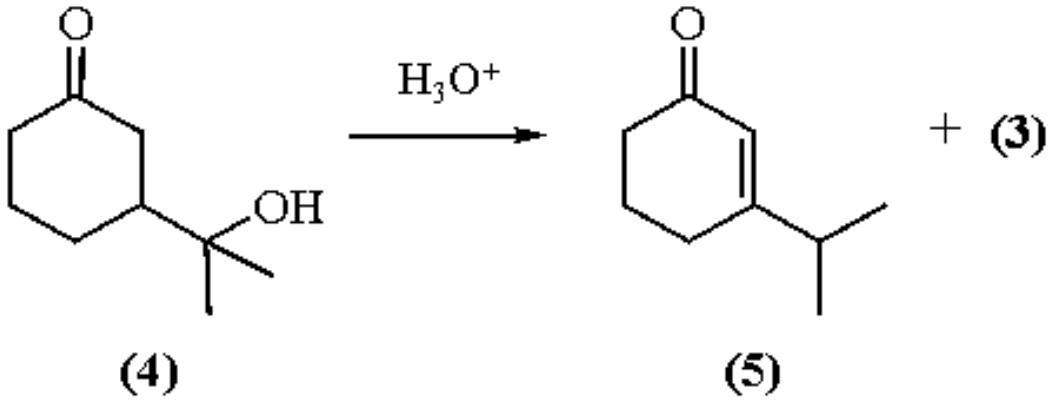

Regioselective Opening of β,γ-Epoxy Alcohols.

Epoxy alcohol (**6**) reacts with (**1**) and catalytic (**2**) to give 1,3 diol (**7**) with high regioselectivity for addition at C-2; none of the 1,2-diol resulting from addition to C-3 is observed (eq 3).[3] The reaction is dependent upon temperature and solvent. Reactions involving vinylic Grignard reagents give best results when carried out at -20 to -25 °C; THF is an essential cosolvent. Regioselectivity in related epoxy alcohols ranges from 4:1 to 7:1.

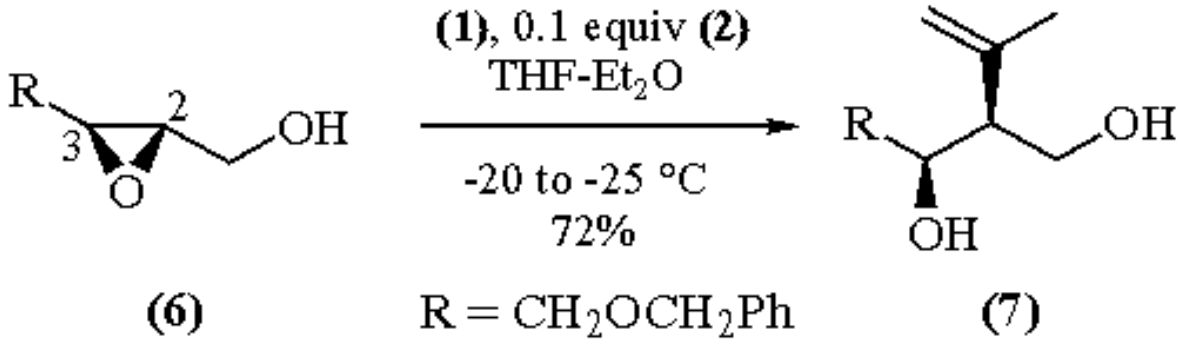

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1. For a recent review of organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135.
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β-Propiolactone[1]

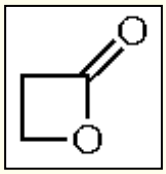

[57-57-8] · $C_3H_4O_2$ · β-Propiolactone · (MW 72.07)

(three-carbon homologating electrophile for synthesis of carboxylic acids and β-hetero propionates; β-hydroxypropionylating reagent)

Physical Data: mp -33.4 °C; bp 162 °C; *d* 1.146 g cm^{-3}.

Solubility: miscible with alcohol, acetone, ether, chloroform.

Form Supplied in: colorless oil: widely available.

Preparative Methods: prepared by reaction of ***Ketene*** and ***Formaldehyde*** under the influence of a Friedel-Crafts catalyst,[1,3] by ring-closure of β-halo propionic acids with base,[4] or by dehydration of 3-hydroxypropionic acid with various condensation reagents.[5]

Handling, Storage, and Precautions: can be stored in the refrigerator for several months without noticeable changes; reacts with bacteriophage DNA causing inactivation, repair, and recombination.[2] Owing to its carcinogenic property, β-propiolactone should be handled with due care.

General Discussion.

Although β-propiolactone (**1**) is prone to polymerization,[6] it also readily undergoes ring opening with a variety of nucleophiles to give selectively alkylated products, in which two reaction pathways are involved (eq 1).[1a]

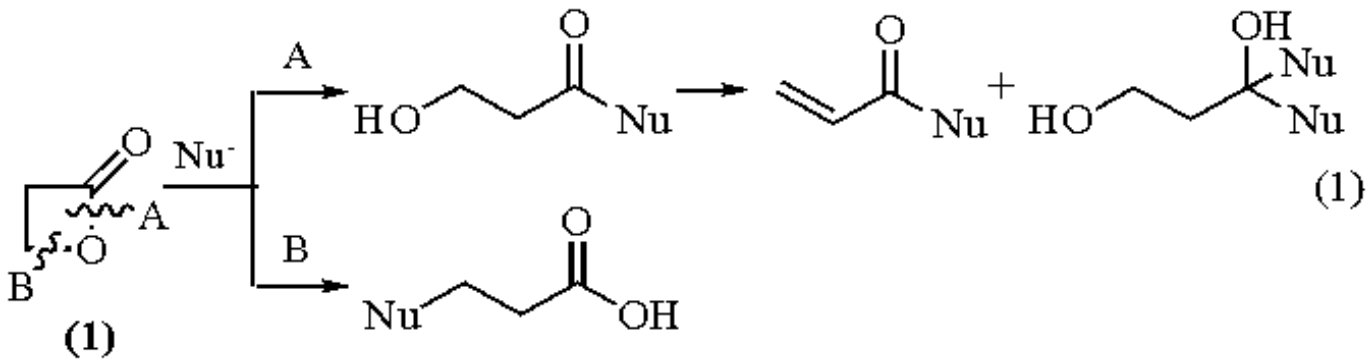

The addition to carbonyl carbon predominates to give α,β-unsaturated ketones or 1,4-diols (path A), when organolithium reagents,[7] Grignard reagents,[8] and (trifluoromethyl)trimethylsilane-fluoride anion[9] are used as nucleophiles, while organocadmium reagents,[7] enamines,[10] thiols,[11] and aminosilanes[12] effect C-O bond fission to give propionic acid derivatives (path B). Studies using Group 14 organometallics such as Me_3MNEt_2 (M = Sn, Ge, Si) indicate that the regiochemistry of the ring opening is also dependent on the metal used.[13] For example, the acyl-oxygen bond is cleaved by the tin reagent (path A), whereas the alkyl-oxygen bond is cleaved by the silicon and germanium reagents.

Organocopper reagents exhibit interesting regiochemistry in the ring opening of β-propiolactone. Selective β-attack is accomplished by the use of organocopper reagents.[14] As shown in eq 2 and Table 1, organocuprate prepared from 2 equiv of Grignard reagent and 1 equiv of ***Copper(I) Iodide*** gives β-alkylated propionic acids in better yields than those prepared from the corresponding organolithium reagents. In the presence of a catalytic amount of a copper(I) salt, Grignard reagents open up the lactone ring at the β-carbon to the carbonyl in good yields.[15] However, organolithium reagents, in the presence of catalytic amounts of copper(I) salts effect ring opening at the carbonyl carbon to give acylated products.[7] The organocopper-phosphine complexes,[16] prepared from organolithium reagents with ***Tri-n-butylphosphine*** and copper(I) iodide, attack selectively at the β-carbon.

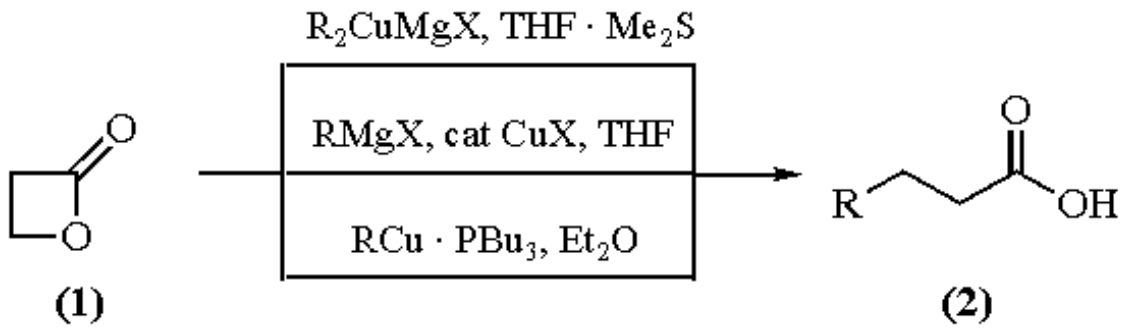

Table 1 Ring Opening of b-Propiolactone with Organocopper Reagents (eq 2)

R	Yield of (2) (%)		
	R_2CuMgX	$RCu{\cdot}PBu_3$	RMgX + cat CuCl
Me	86	80	87
Bu	92	92	90
t-Bu	88	76	85
Ph	80	69	77
Vinyl	87	37	59
Allyl	65	8	trace

The application of this three-carbon elongation reaction to the construction of naturally occurring products has been demonstrated in several examples. Dialkylcopper reagents prepared from Grignard reagents and copper(I) iodide react with acetylene to give the corresponding di-(*Z*)-1-alkenylcuprates (**3**), which in turn react with β-propiolactone to afford (*Z*)-4-alkenoic acids (**4**), in good yields with excellent (*Z*) selectivity (eq 3).[17] (*Z*)-4-Heptenoic acid (**4**) (R = Et) serves as a useful starting material for syntheses of perfume and flavor components such as *cis*-jasmone (**5**), methyl jasmonate (**6**), and jasmolone (**7**) (eqs 4-6).[18]

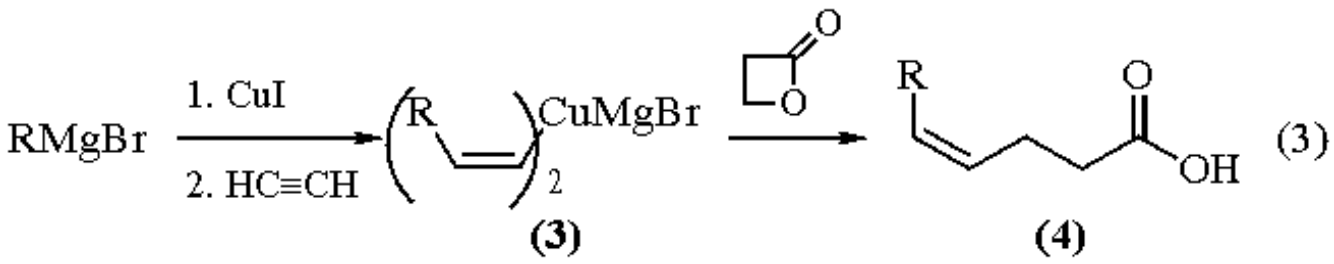

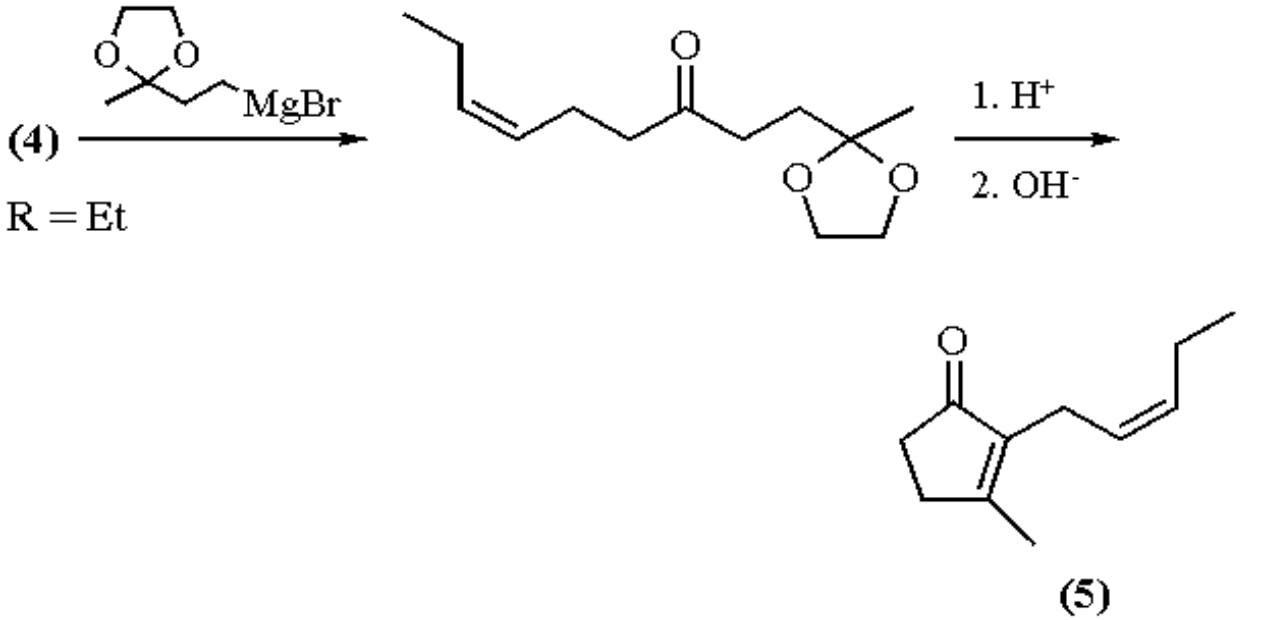

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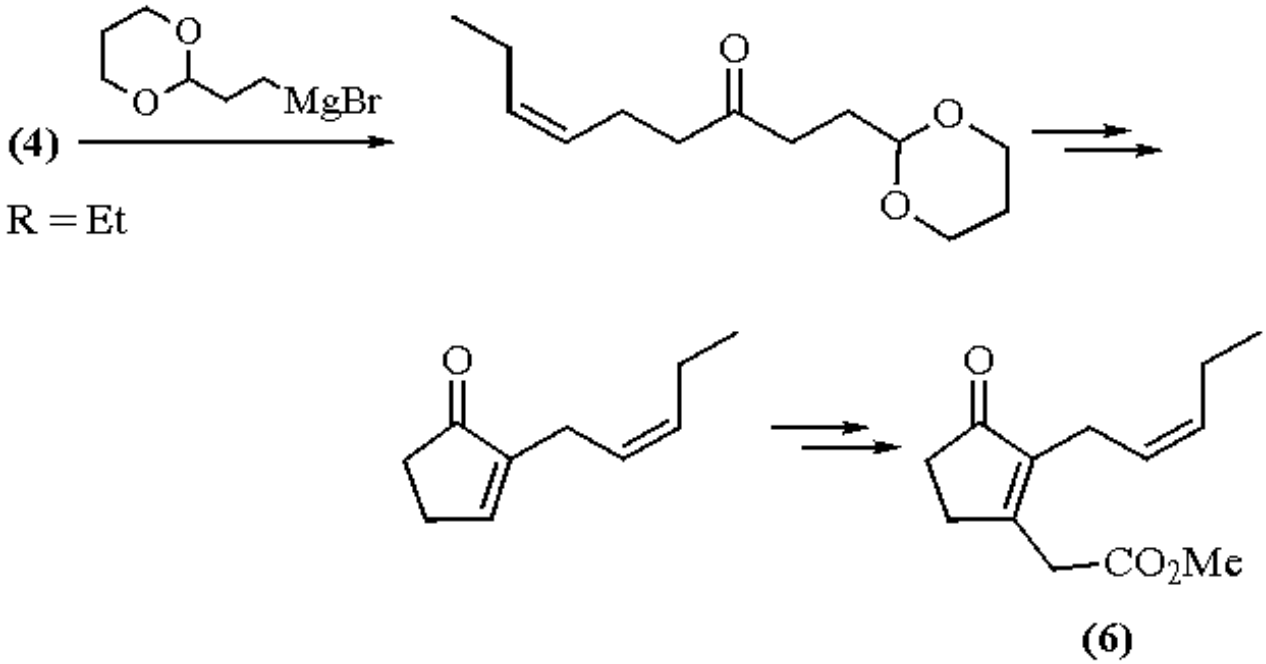

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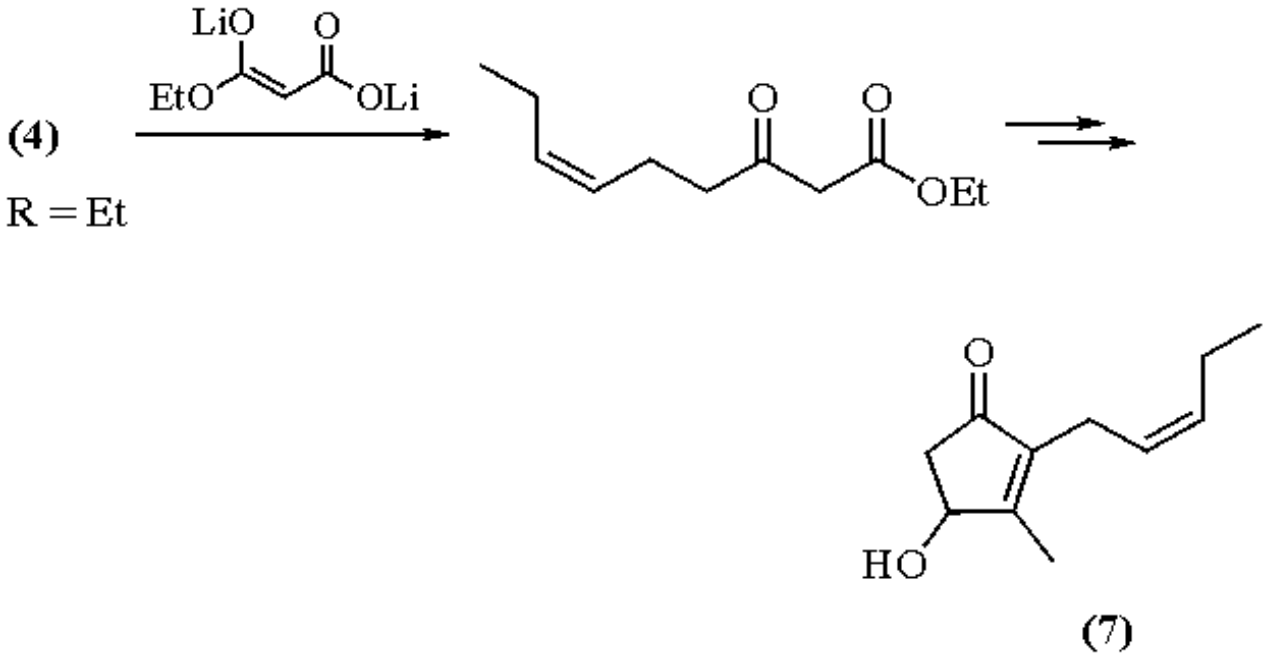

(6)

Lactones possessing large-membered rings are prepared by ring opening of β-propiolactone. In the presence of a catalytic amount of a copper salt, o-alkoxy or metalloxy Grignard reagents react with β-propiolactone to give the corresponding homologated carboxylic acids, which can cyclize to form macrocyclic lactones (**8**) (eq 7)[19] α,o-Di-Grignard reagents also serve as good chain elongation reagents for the synthesis of macrolides (**9**) (eq 8).[20] β-Propiolactone is converted into the β-lactam (**10**) (eq 9) by ring opening with a nitrogen nucleophile and the products are used for the synthesis of β-lactam antibiotics.[21]

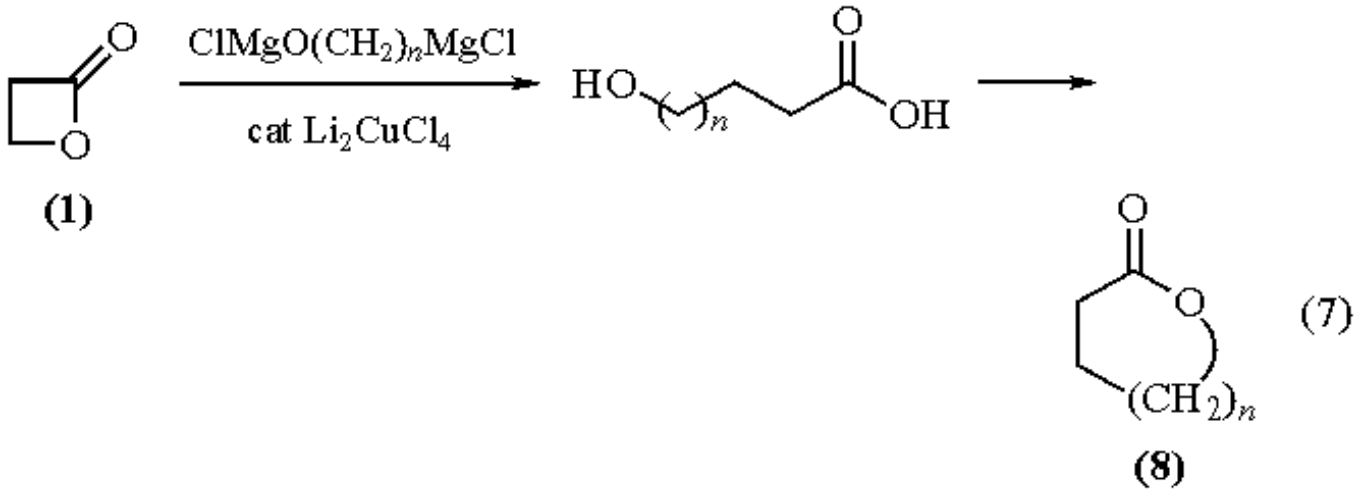

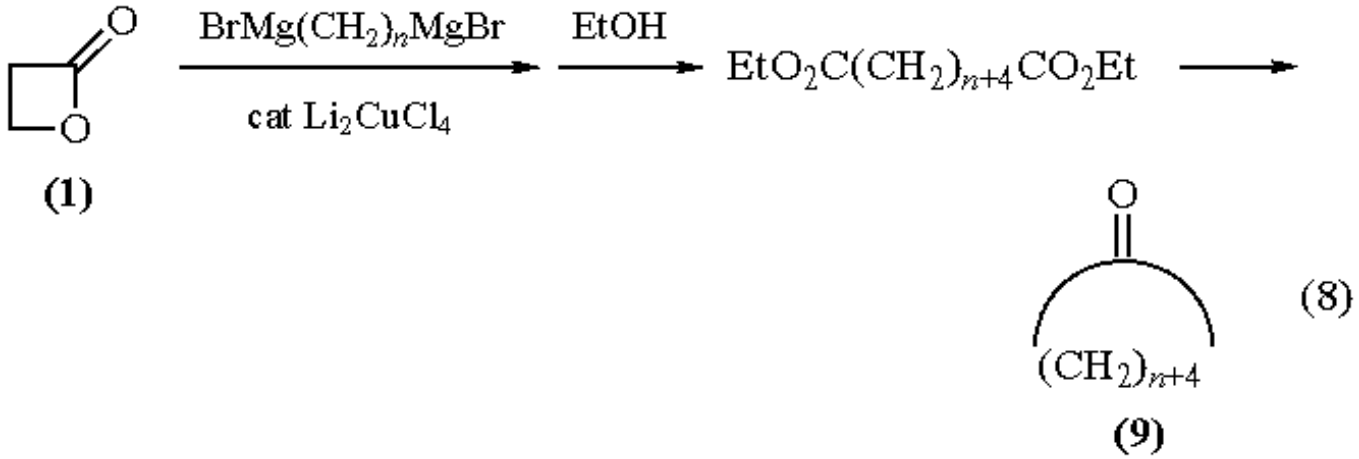

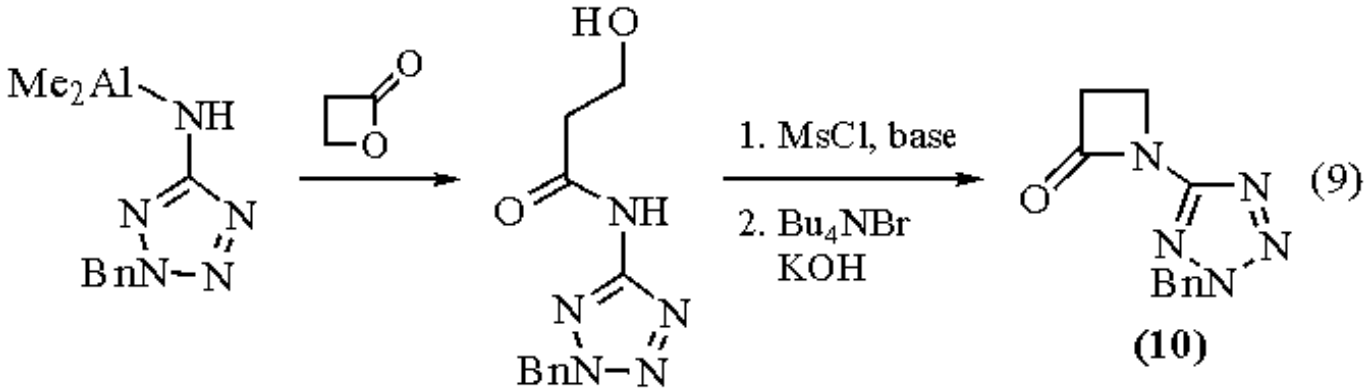

The ring opening of β-lactams with nitrogen nucleophiles is used for the synthesis of macrocyclic polyamine derivatives (**11**) (eq 10).[22] The regiochemistry of the ring opening is dependent on the solvent; acetonitrile is the solvent of choice for *N*-alkylation.

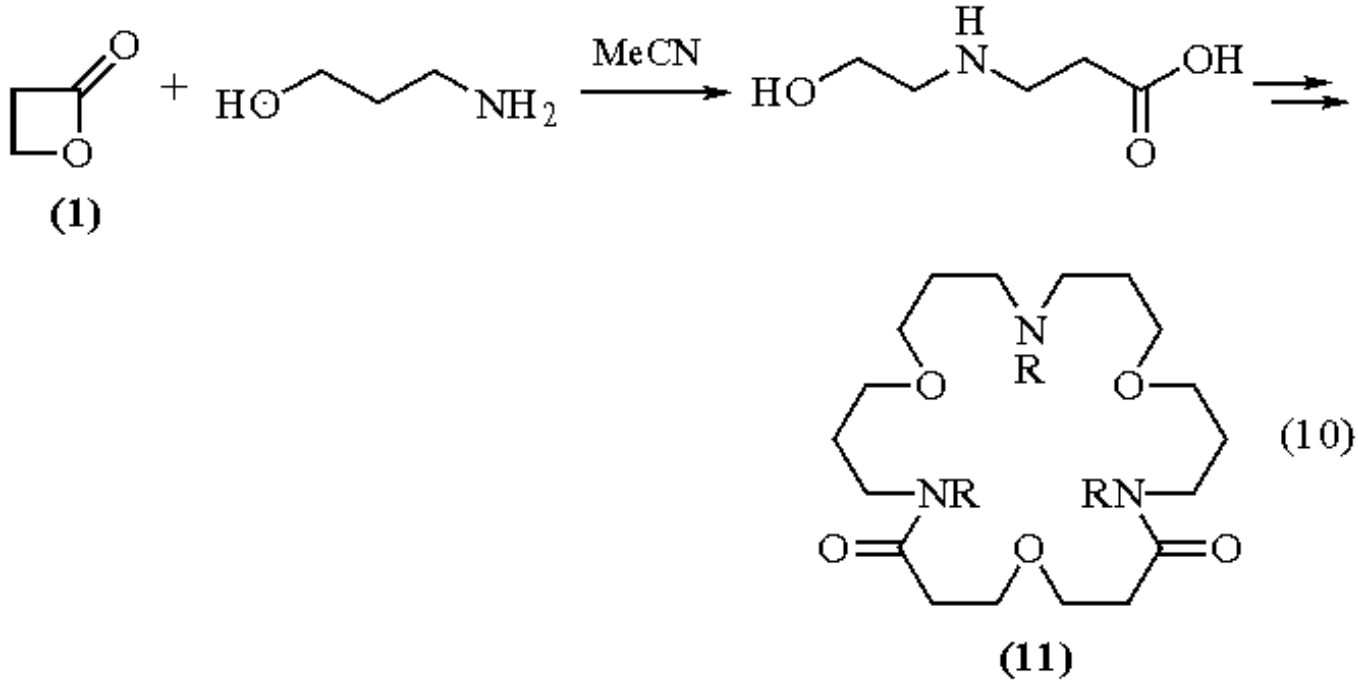

An intriguing C-C bond fission occurs upon reaction of β-propiolactone with ***Potassium-18-Crown-6*** or ***Potassium Naphthalenide*** to give acetates or their alkylated derivatives in good yield (eq 11). The potassium solution generated by contact of a potassium mirror with a solution of 18-crown-6 in THF at -20 °C effects the formation of enolate anion (**12**) derived from C-C bond cleavage. Upon treatment with ***Hydrochloric Acid*** or alkyl halides, the acetate (**13**) or its alkylated derivatives (**14**) are obtained, respectively.[23] On the other hand, acrylic acid (**15**) is formed by the action of the potassium naphthalenide-18-crown-6 complex.[24] Subsequent alkylation with alkyl halides gives the α,β-unsaturated esters (**16**).

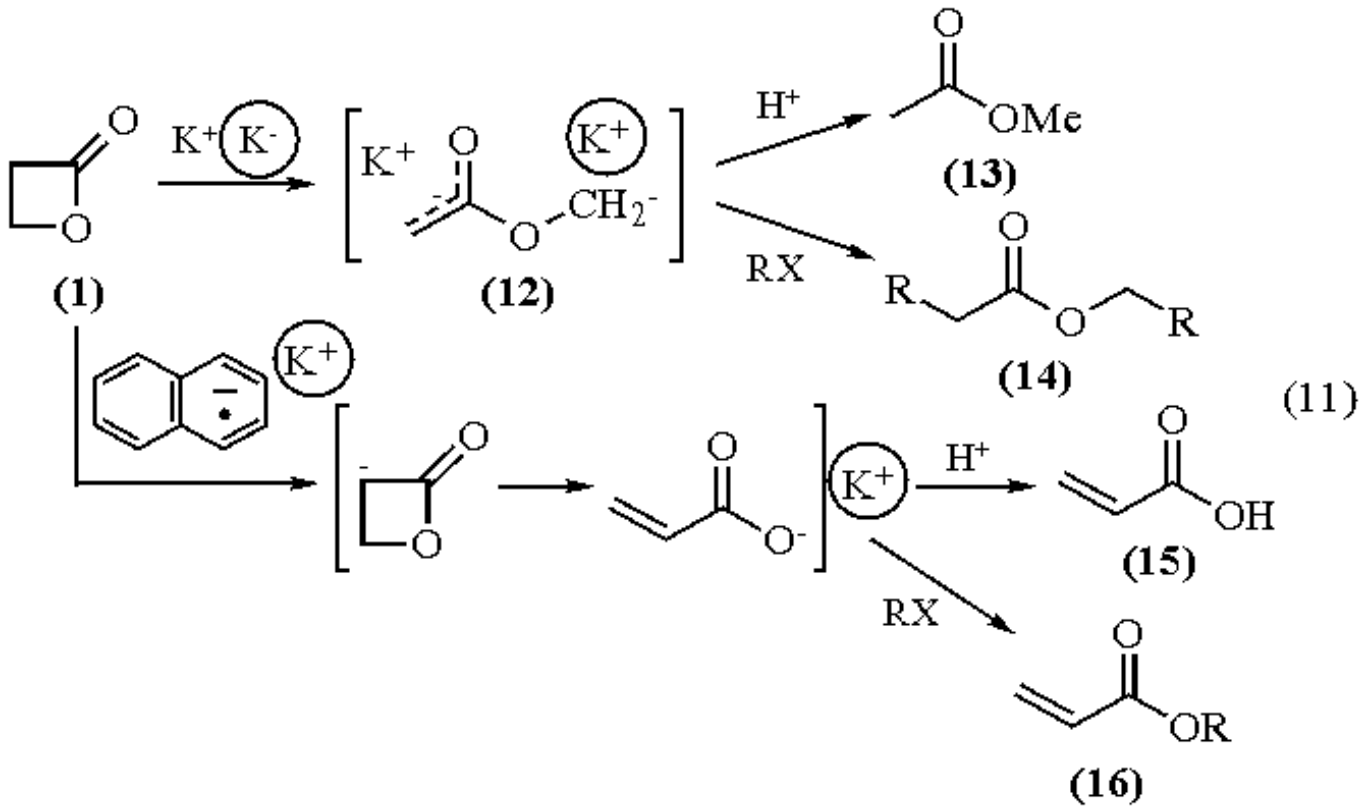

β-Propiolactone readily interacts with transition metals such as platinum,[25] cobalt, and rhodium to give ring-opened products, (eq 12) and, under an atmosphere of carbon monoxide, γ-butyrolactone (**17**) is formed (eq 13).[26]

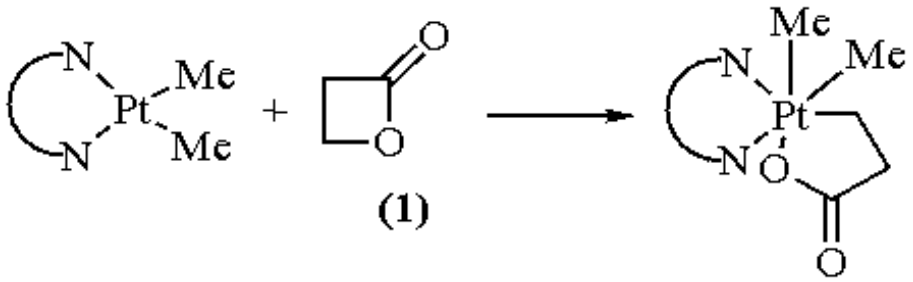

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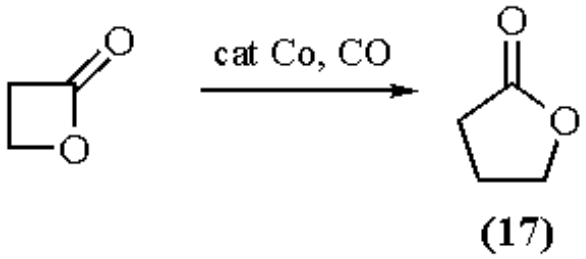

(13)

Related Reagents.

N-Benzyloxycarbonyl-L-serine β-***Lactone***; α,β-***Butenolide***; γ-***Butyrolactone***; ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***; β-***Ethynyl***-β-***propiolactone***; β-***Methyl***-β-***propiolactone***.

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Propionaldehyde *t*-Butylimine[1]

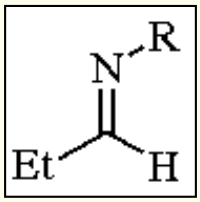

(R = *t*-Bu)

[7020-81-7] · $C_7H_{15}N$ · Propionaldehyde *t*-Butylimine · (MW 113.23) (R = *t*-Bu, Li salt)

[75261-61-9] · $C_7H_{14}LiN$ · 2-Lithiopropionaldehyde *t*-Butylimine · (MW 119.16) (R = Cy)

[6898-80-2] · $C_9H_{17}N$ · Propionaldehyde Cyclohexylimine · (MW 139.27)

(two-carbon nucleophile in enolate alkylations, conjugate addition reactions, and directed aldol condensations; especially useful for α-monoalkylations and three-carbon homologations[1])

Physical Data: R = *t*-Bu: bp 103 °C,[2] 48-50 °C/115 mmHg,[3] 47-49 °C/95 mmHg.[4] R = Cy: bp 63-64 °C/15 mmHg,[4] 62-63 °C/12 mmHg;[5] *n*16D 1.4450.

Solubility: sol THF, ether, CCl_4, pentane, benzene, toluene.

Form Supplied in: colorless liquid when freshly distilled; darkens on prolonged standing

Analysis of Reagent Purity: NMR or IR.

Preparative Methods: the general method adapted by Stork and Dowd from the procedure developed earlier by Tiollais is said to be highly efficient for the synthesis of aldimines from low-boiling aldehydes.[2] Quantitative yields have also been reported when propanal is added to a preformed amine-***Titanium(IV) Chloride*** complex.[6] Lithiopropionaldehyde *t*-butylimine is usually prepared by reaction with a slight excess of a hindered nonnucleophilic base like ***Lithium Diethylamide*** in THF or ether at -78 °C under N_2 or argon.[7,8] A variation of this method calls for addition of ***Hexamethylphosphoric Triamide*** to the reaction mixture.[8b]

Handling, Storage, and Precautions: best used when freshly prepared. Imines can be distilled, but they tend to polymerize upon long standing. Stored samples are distilled over KOH to remove high-boiling condensation products prior to use. Storage as neat liquids is not recommended for long periods, but solutions in dry THF (0.4 M) can be stored at -20 to -30 °C with minimal deterioration.[9] In acidic solutions, the imine reverts to propanal and the amine. The lithiated imine is generally prepared in situ under N_2 or argon. Use in a fume hood.

Condensation Reactions.

The synthetic value of these reagents lies in their facile conversion to imine anions and their low propensity for self-aldol condensation. These characteristics favor their use over propionaldehyde in directed crossed-aldol condensation reactions. (*E*)-α,β-Unsaturated aldehydes are stereoselectively formed upon hydrolysis and dehydration of the α-methyl-β-hydroxy aldehyde adducts. This strategy is illustrated in the synthesis of nuciferal (eq 1) and sinensal,[7] and in a variety of intermediates for the synthesis of natural products,[1,10]

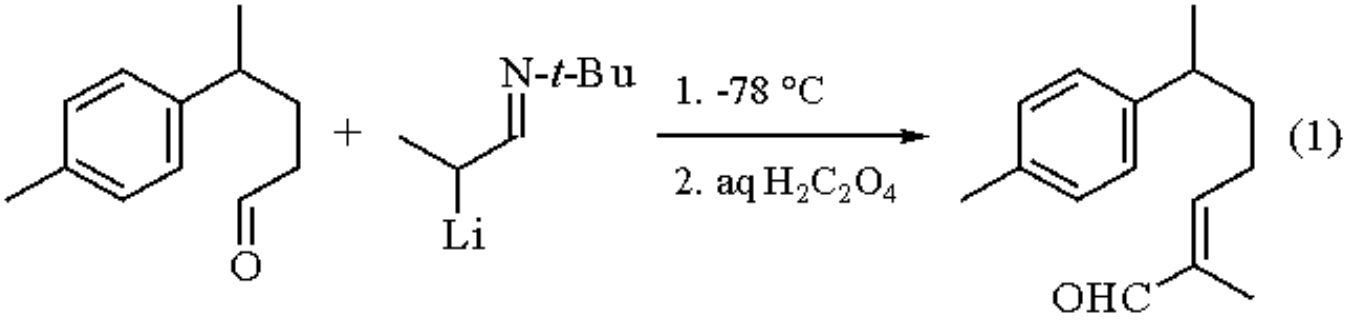

These reagents can tolerate the presence of other functional groups in the electrophile (eq 2).[10] Phosphonates[11] and trialkylsilyl groups[3,8,12] have been used to stabilize the lithio imine anions in these reactions.

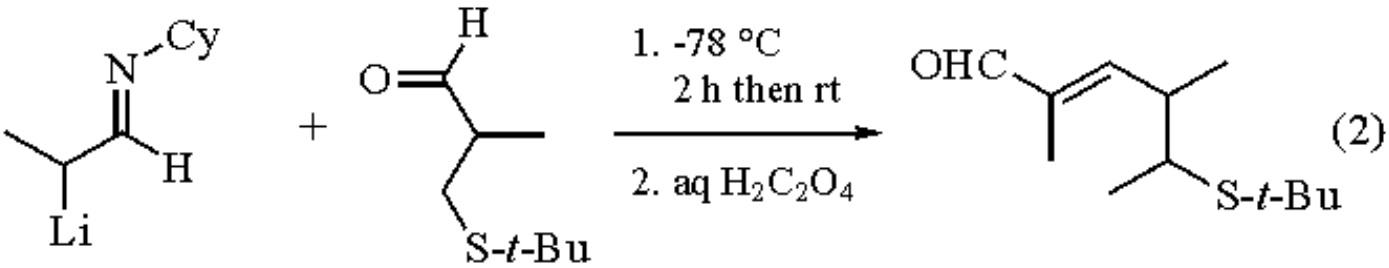

γ-Diketones have been prepared by Michael-type additions of the *t*-Bu imine anion and by alkylation with allylic halides followed by ozonolysis.[13]

Heterocycles.

The ease with which metalloenamines undergo α-monoalkylation in the presence of alkyl halides extends the usefulness of these reagents. Yields are usually high and no rearrangement is observed even with allyl halides. In contrast, propionaldehyde tends to undergo self-aldol condensation in the presence of base and is not alkylated by primary and secondary alkyl halides. Enamines, on the other hand, tend to undergo *N*-alkylation.[14] With dihalides as alkylating agents, subsequent intramolecular reactions can be utilized to effect ring closure. Nitrogen heterocycles like tetrahydropyridines (eq 3)[15] and substituted azetidines (eq 4)[16] have been synthesized in this manner. Other ring closure reactions using these imines have afforded 2-amino-5-cyanopyrroles,[17] azaphosphorines,[18] azaphospholenes,[18] substituted 4-methylpyrrolidines,[19] and substituted 3-pyridinecarboxylic acids and their derivatives.[20]

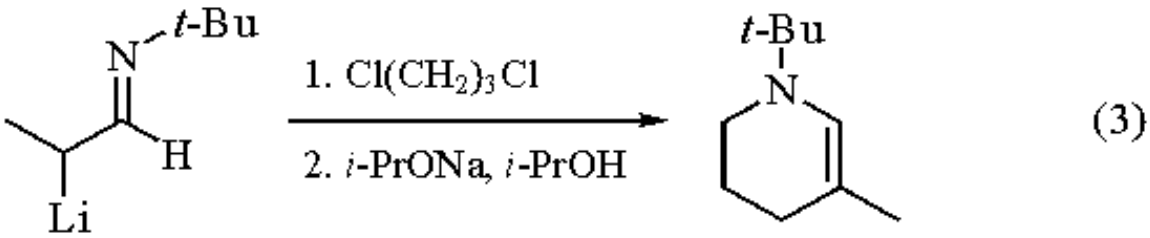

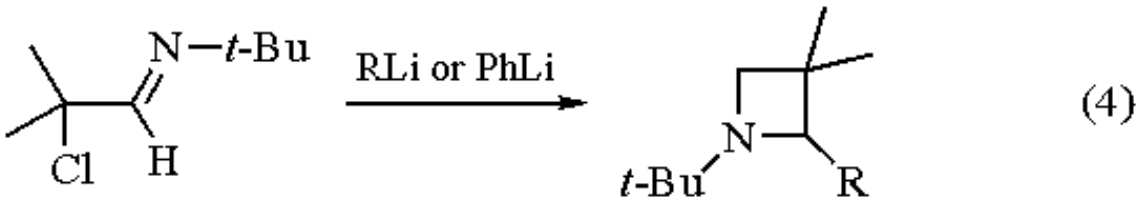

Other Reactions.

Functionalization at the α-position can be achieved using a variety of reagents. ***N-Chlorosuccinimide*** can be used for α-chlorination. A stereoselective reaction with a chiral sulfinate ester affords (*Z*)-β-enamino sulfoxides,[4] while nitration with an alkyl nitrate yields 1-alkylamino-2-nitro-1-alkenes (eq 5).[21] The (*Z*) stereochemistry is preferred due to stabilization by intramolecular H-bonding. These reagents also provide a useful route for the synthesis of vinyl isocyanates by reaction with ***Phosgene***[22] and secondary propanamines by chemical reduction using ***Sodium Cyanoborohydride***[23] or catalytic hydrogenation with ***Raney Nickel***.[24] Hydrolysis of the elaborated imines is often a final step in a reaction sequence involving these reagents. Such hydrolyses are facile and are often carried out using cold,

aqueous acid, e.g. NaOAc-HOAc-H_2O (1:2:2),[25] ***Oxalic Acid***,[7] NH_4Cl,[16] and ***Zinc Chloride***.[3] Cold 10% oxalic acid is most commonly used.

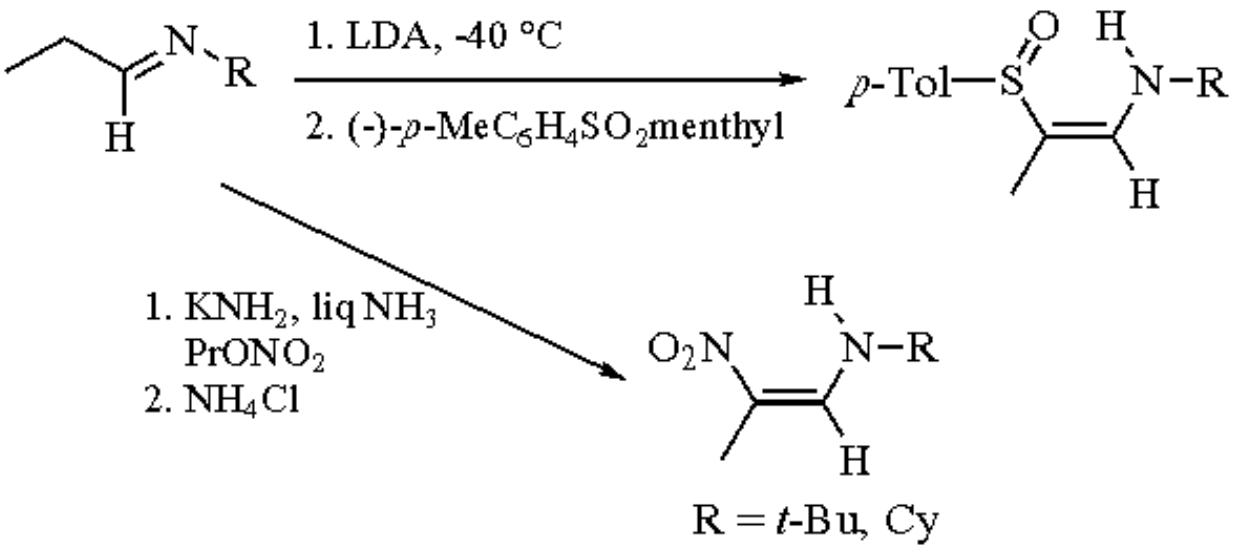

(5)

Related Reagents.

Acetaldehyde N-t-Butylimine; ***Acetone Cyclohexylimine***; ***Acetone Hydrazone***; ***t-Butylamine***; ***2-Chloro-2-methylpropanal N-Isopropylimine***; ***1-(N,N-Dimethylamino)-2-methyl-1-propene***.

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Propionic Acid

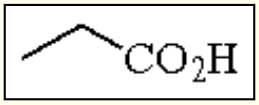

[79-09-4] · $C_3H_6O_2$ · Propionic Acid · (MW 74.09)

(catalyst for orthoester Claisen rearrangement;[1] solvent for malonate diester decarboxylation[13] and porphyrin synthesis[14])

Alternate Name: propanoic acid.

Physical Data: clear liquid, bp 141 °C, 40 °C/10 mmHg; mp -23 °C; *d* 0.993 g cm^{-3}.[1]

Solubility: miscible with water, ethanol, ether, chloroform.

Form Supplied in: neat liquid; commercially available.

Analysis of Reagent Purity: by titrimetric assay; carbonyl compound impurity tests are known.[15]

Purification: usually by repeated fractional distillation.[16]

Handling, Storage, and Precautions: corrosive organic acid with an acrid odor. It is especially destructive to tissue of mucous membranes and upper respiratory tract, eyes, and skin. Inhalation is a major hazard and may be fatal. Use of a NIOSH/MSHA approved respirator is recommended. Use gloves, eye protection, and protective clothing to avoid contact. The acid should never be mixed with basic solvents, oxidizers, and reducing agents. Use in a fume hood.

Orthoester Claisen Rearrangement.

Propionic acid is the classic acid catalyst for the Johnson orthoester Claisen rearrangement of an allylic alcohol and trialkyl orthoester (see ***Triethyl Orthoacetate***). Examples have been reported for all allylic bond substitutions, including 1,1-disubstituted (eq 1),[2] (*E*),[3] (*Z*),[4] trisubstituted,[5] and tetrasubstituted.[6]

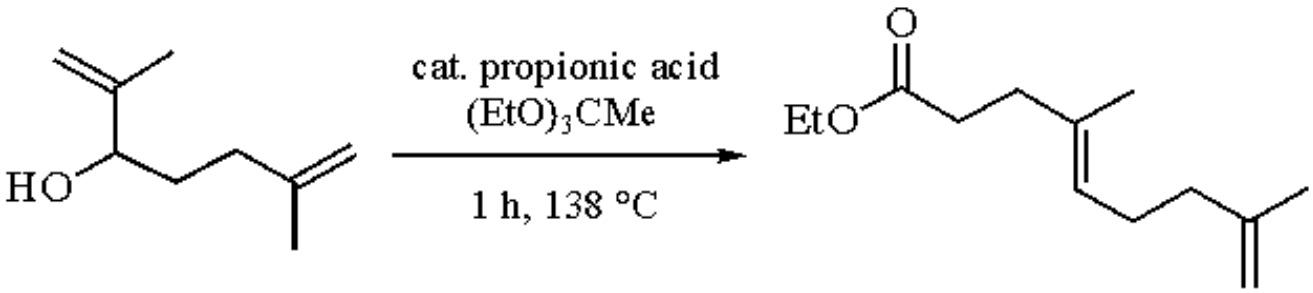

(1)

The reaction of a propargyl alcohol and triethyl orthoacetate produces an allene ester (eq 2).[7] Allenic alcohols react in a similar manner to give diene esters in moderate yield (eq 3).[8]

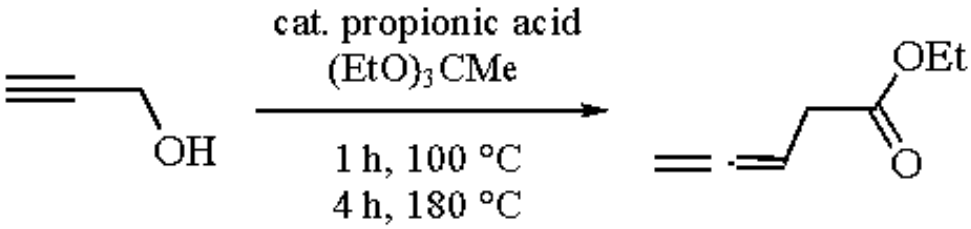

(2)

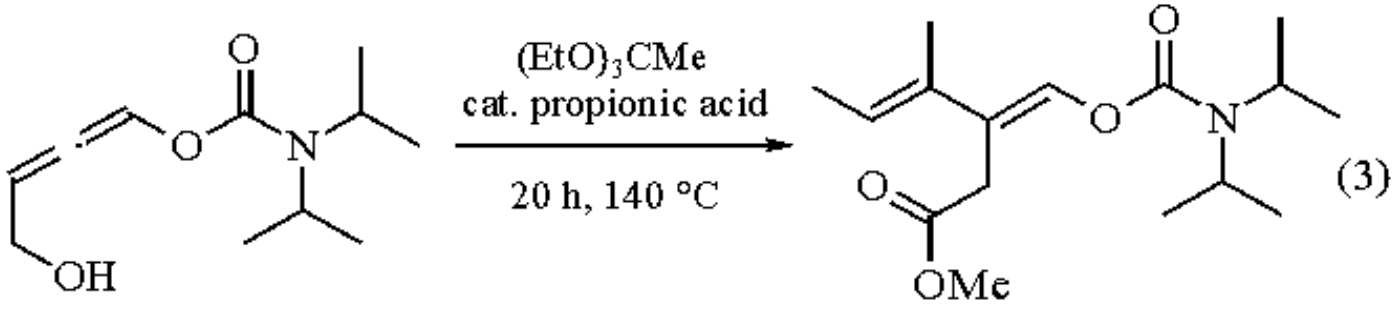

The reaction of 2-butynediol with excess trimethyl orthopropionate and catalytic propionic acid yields a symmetrical diene diester through the novel double Claisen orthoester rearrangement (eq 4).[9]

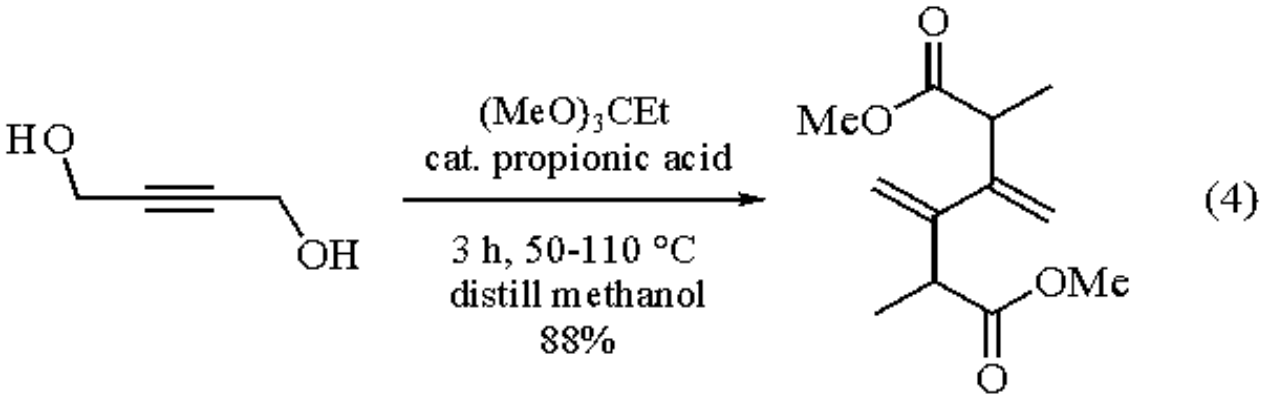

Other Variations on the Orthoester Claisen Rearrangement.

The condensation of a dialkyl acetal and a primary allylic alcohol to form an unsaturated ketone has been catalyzed with propionic acid (eq 5).[10] The condensation of an allylic alcohol with ***Triethyl Methanetricarboxylate*** yields, after decarboxylation, an unsaturated ester (eq 6).[11]

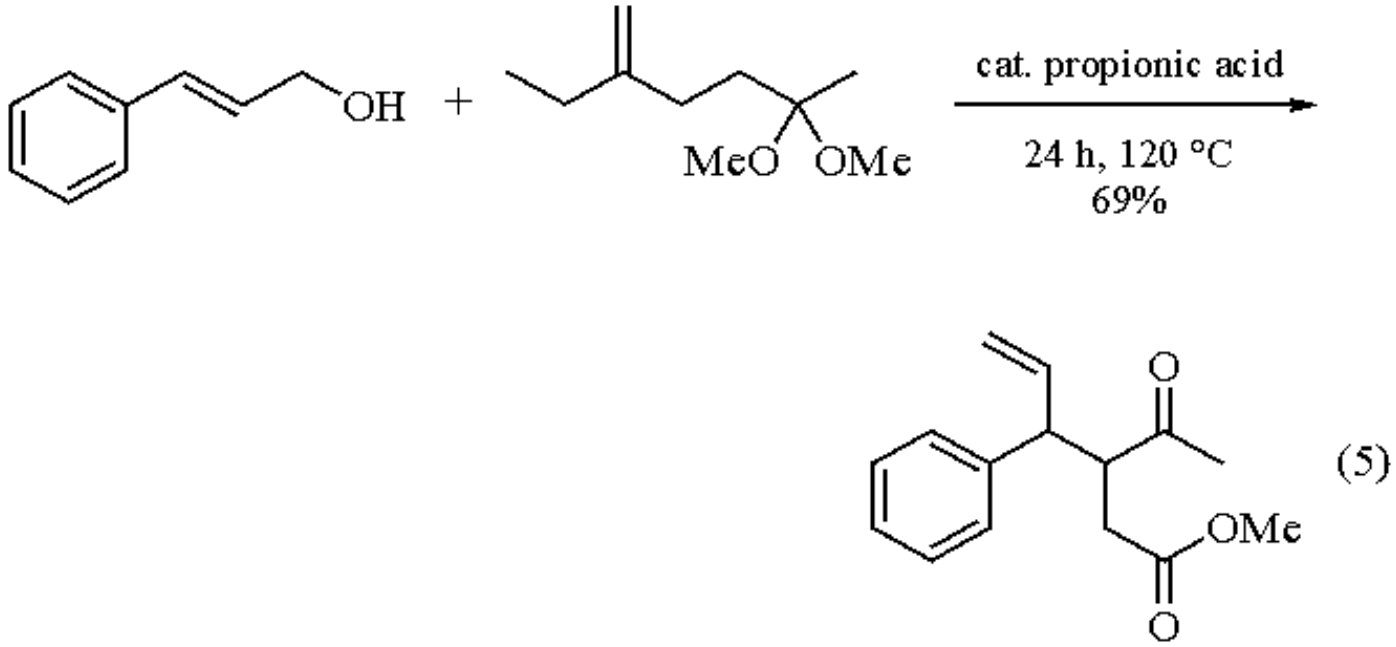

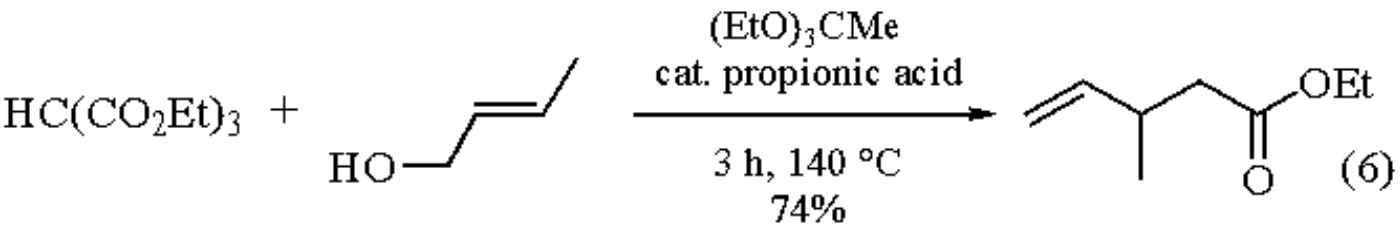

Decarboxylation of Malonic Esters.

The decarboxylation of malonic ester derivatives to esters is general in propionic acid (eq 7).[12] This reaction is complementary to the basic hydrolysis of malonate esters to carboxylic acids.

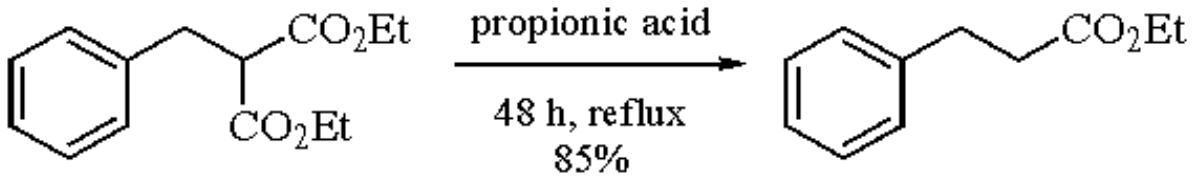

(7)

Synthesis of Porphyrins.

The condensation of an aldehyde and pyrrole in propionic acid leads to the formation of a tetrasubstituted porphyrin.[13] In an improved porphyrin synthesis, 2-acylpyrroles are reduced to the corresponding alcohols and converted to porphyrins by condensation and oxidation in refluxing propionic acid (eq 8).[14]

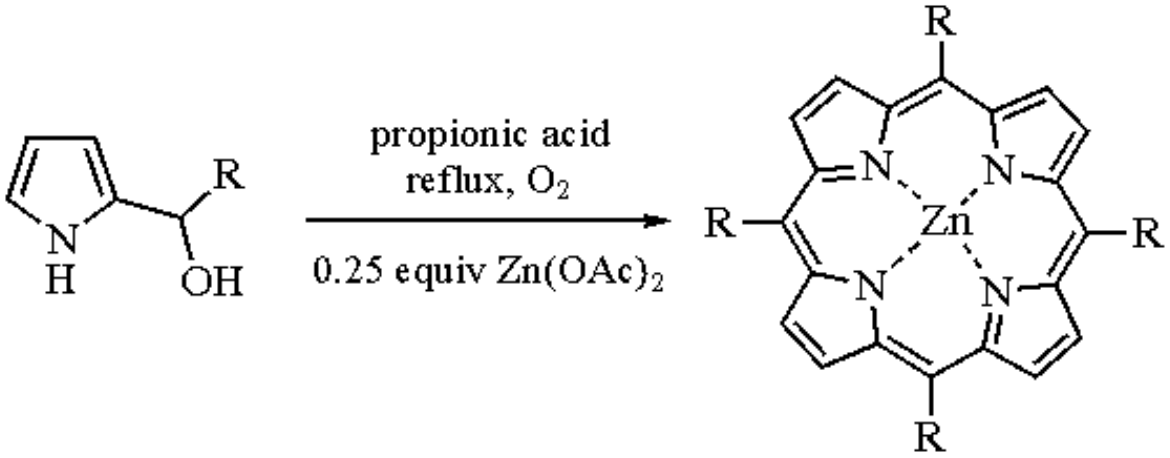

(8)

Related Reagents.

Acetic Acid; ***Pivalic Acid***; ***p-Toluenesulfonic Acid***; ***Trifluoroacetic Acid***; ***2,4,6-Trimethylbenzoic Acid***.

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Kirk F. Eidman

3-Propionylthiazolidine-2-thione[1]

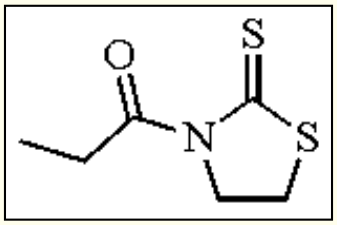

[85260-51-1] · $C_6H_9NOS_2$ · 3-Propionylthiazolidine-2-thione · (MW 175.30)

(synthesis of β-hydroxy-α-methyl carboxylic esters, amides, and aldehydes,[2] propionate equivalent for the diastereo- and enantioselective aldol reactions[2,3])

Physical Data: bp 151 °C/4 mmHg.

Form Supplied in: sticky, slightly yellow oil.

Preparative Methods: from propionyl chloride and ***1,3-Thiazolidine-2-thione*** in the presence of ***Triethylamine***, or from ***Propionic Acid*** and thiazolidine-2-thione in the presence of triethylamine and ***2-Chloro-1-methylpyridinium Iodide***.[4]

Handling, Storage, and Precautions: use in a fume hood.

Diastereoselective Aldol Reactions.

The tin(II) enolate generated from 3-propionylthiazolidine-2-thione (**1**), ***Tin(II) Trifluoromethanesulfonate***, and ***1-Ethylpiperidine*** reacts with aldehydes at -78 °C to afford the aldol adducts in high yields with high *syn* selectivities (eq 1).[2,3] 3-Acetylthiazolidine-2-thione (**2**) (bp 125-128 °C/2 mmHg)[2,3,5,8] and 3-(3-phenylpropanoyl)thiazolidine-2-thione (**3**) (mp 66.0-67.5 °C)[2-4] also work well under the same reaction conditions.[2,3]

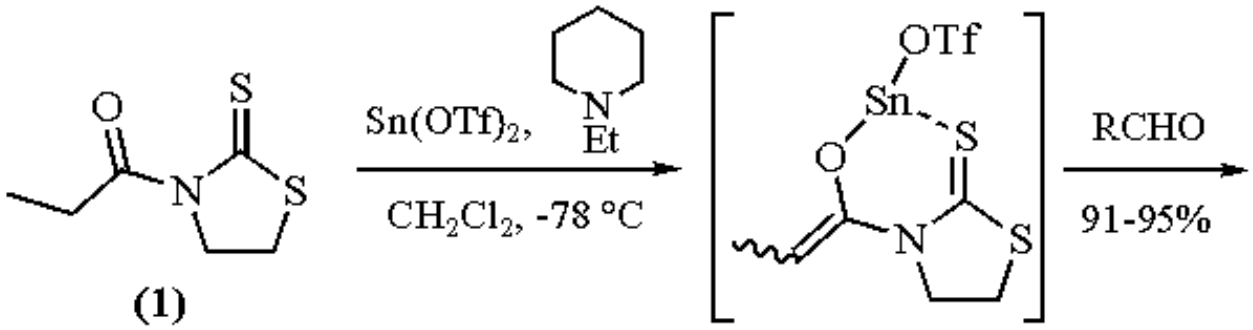

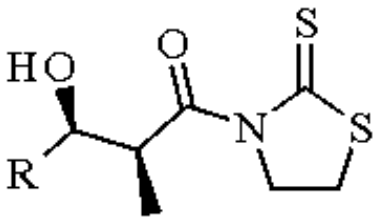

(1)

(4) *syn*:*anti* = >97:3

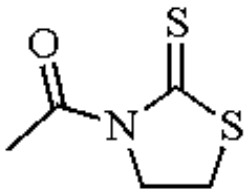

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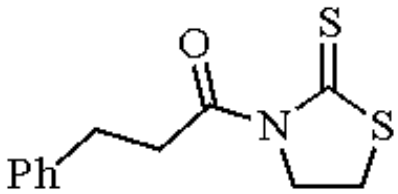

(3)

The aldol adducts (**4**) are easily converted to the corresponding β-hydroxy-α-methyl esters, amides, and aldehydes. Treatment of (**4**) (R = Ph) with methanol or ethanol in the presence of ***Potassium Carbonate*** at room temperature gives the methyl or ethyl ester in high yield (eq 2).[2] Similarly, the amide is spontaneously formed by mixing (**4**) with the amine in dichloromethane (eq 3).[2] The preparation of the aldehyde is carried out by using ***Diisobutylaluminum Hydride*** as a reductant after protection of the hydroxy function of (**4**) with the dimethylisopropylsilyl group (eq 4).[2,4] No isomerization occurs during these conversions.

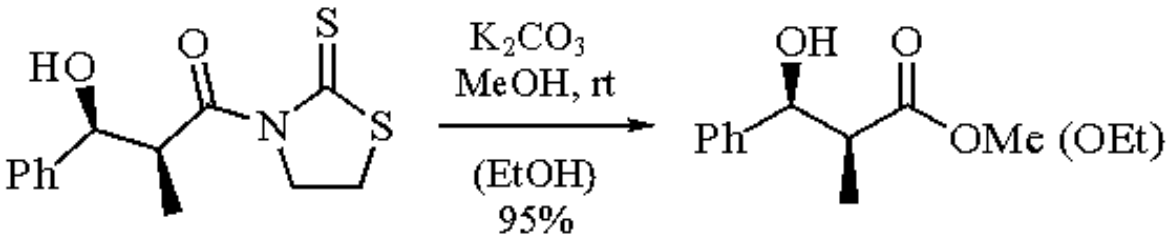

(4a) (4; R = Ph) (2)

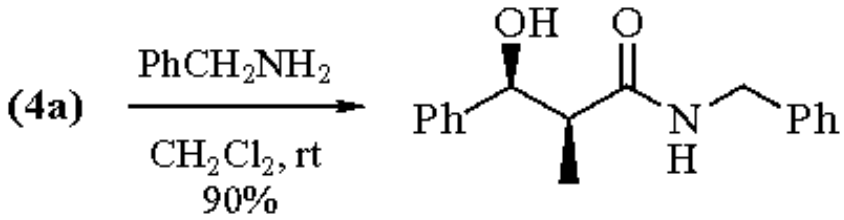

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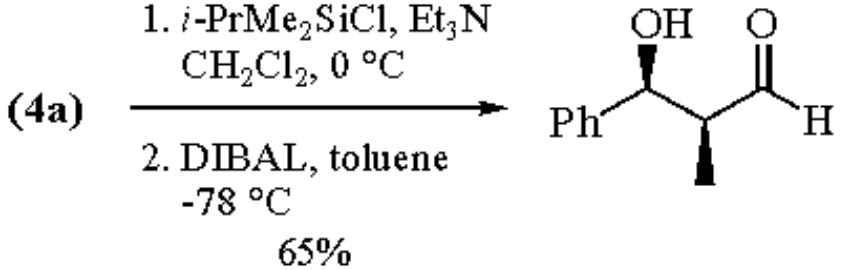

(4)

Enantioselective Aldol Reactions.

A highly enantioselective aldol reaction of the tin(II) enolate derived from (**2**) with aldehydes is carried out in the presence of the chiral diamine (**5**) as a ligand (eq 5).[3,5,6] Aromatic and aliphatic ketones instead of (**2**) are good substrates in the present asymmetric aldol reaction,[3,7] and enantioselectivities are influenced strongly by the structure of the chiral diamines.

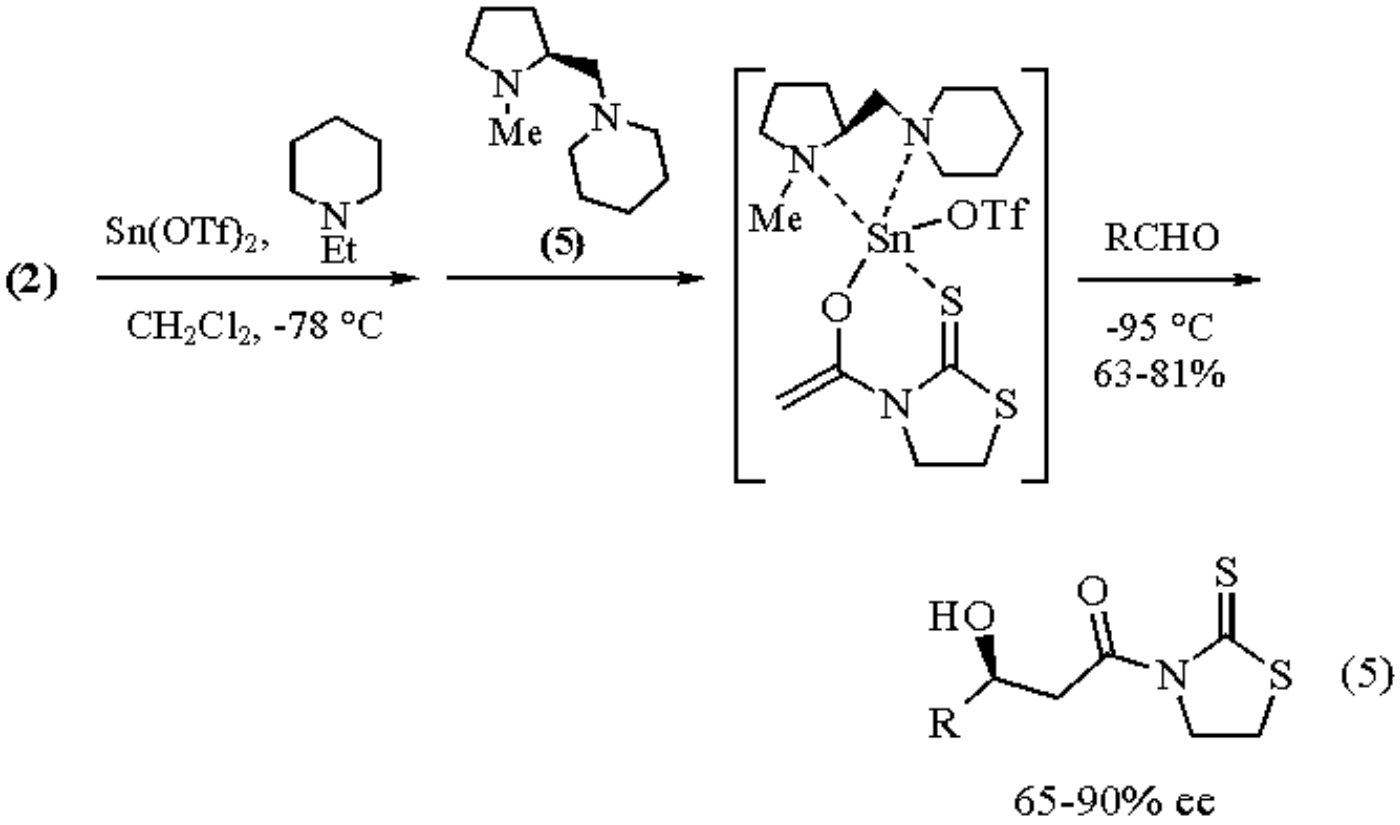

The tin(II) enolate of (**2**) reacts with α-keto esters in the presence of the chiral diamine (**6**) to give optically active 2-substituted malic acid ester derivatives in high yields with high ee (eq 6).[8]

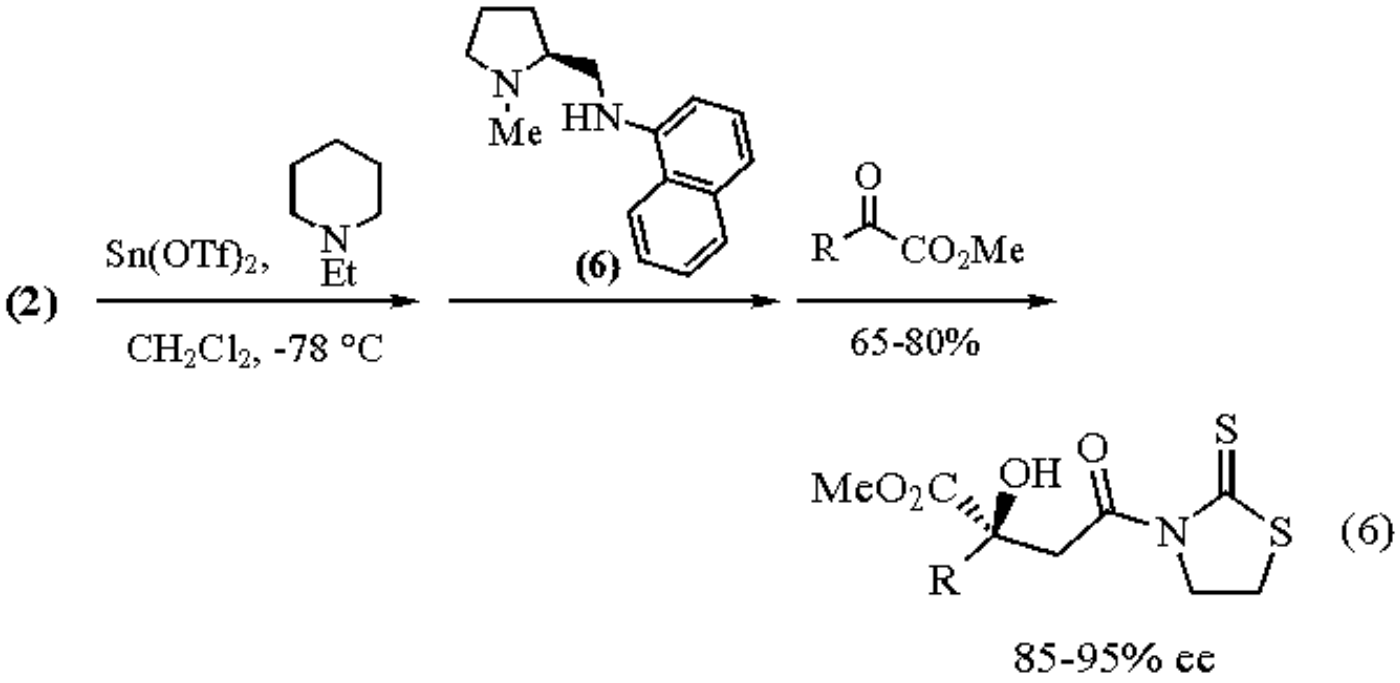

The tin(II) enolate of (**2**) also reacts with chiral aldehydes in the presence of (**5**). Diastereoselectivities can be controlled by the absolute configuration of the chiral diamines (eqs 7 and 8).[1f]

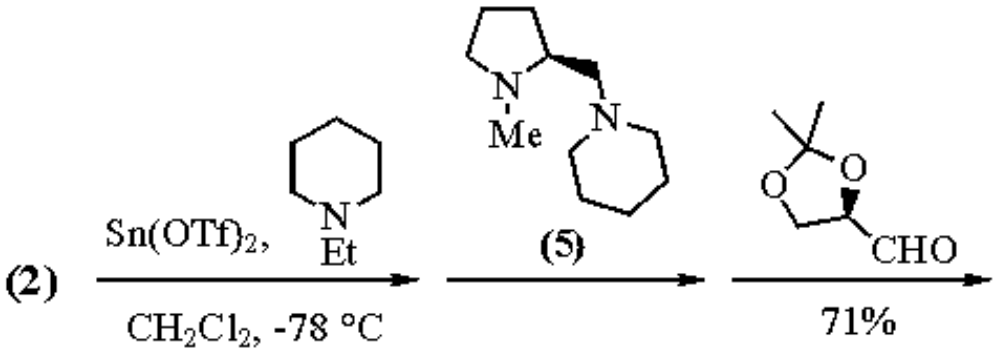

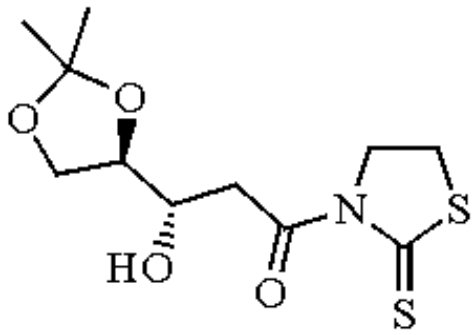

(7)

syn:*anti* = 7:93

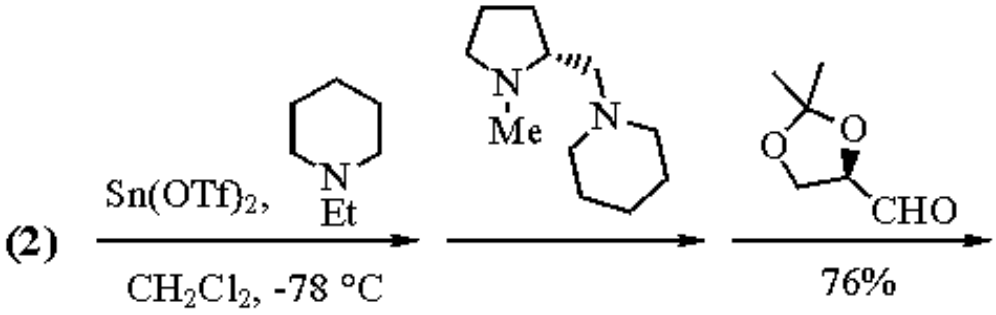

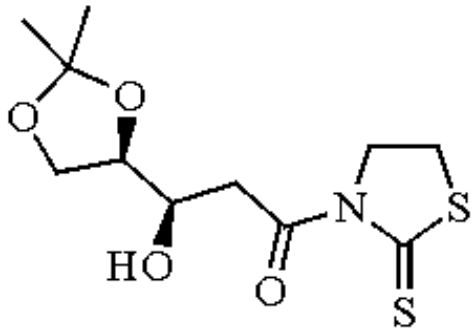

(8)

syn:*anti* = 83:17

In the reaction of the tin(II) enolate derived from (**1**) with aldehydes, enantioselectivities are disappointingly low, while good diastereoselectivities are observed. Highly diastereo- and enantioselective aldol reactions of propionate derivatives with aldehydes have been achieved by using the ketene silyl thioacetal (**7**) instead of the tin(II) enolate. The complex (**8**) produced by mixing tin(II) triflate and the chiral diamine (**6**) works as an efficient chiral Lewis acid. The reaction of (**7**) with various aldehydes proceeds smoothly in the presence of (**8**) and dibutyltin diacetate in dichloromethane to afford the *syn* aldol adducts in high yields with almost perfect stereochemical control (eq 9).[9]

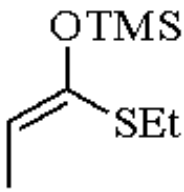

(7)

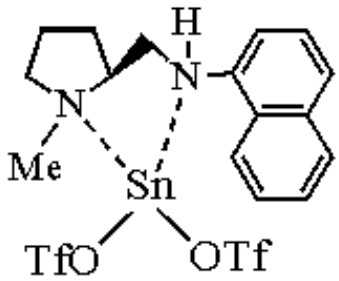

(8)

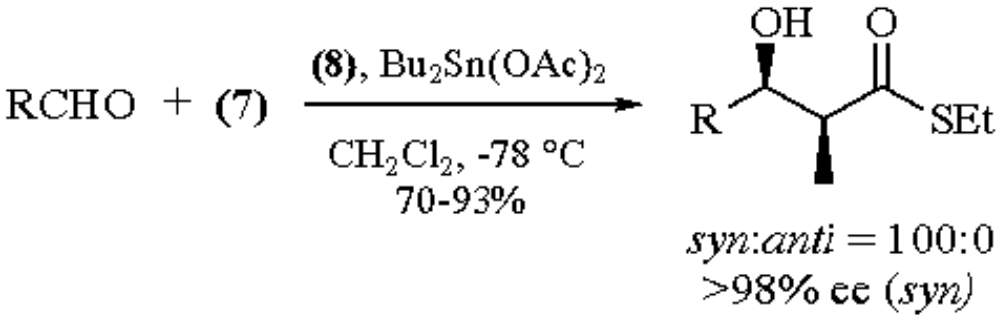

(9)

While stoichiometric amounts of tin(II) triflate, (**6**), and the tin(IV) compound are necessary in the reaction shown in eq 9, the truly catalytic asymmetric aldol reaction of (**7**) with aldehydes is realized by using (**8**) as a Lewis acid catalyst (eq 10).[10] The reaction is carried out in propionitrile by slow addition of the substrates to the catalyst.

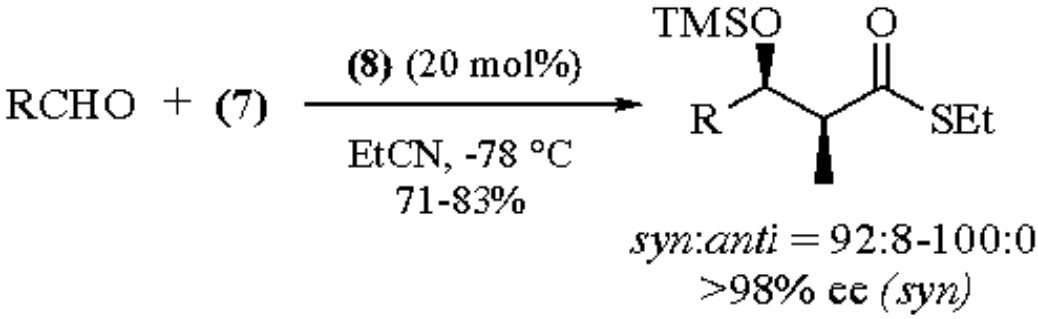

(10)

Related Reagents.

3-(2-Benzyloxyacetyl)thiazolidine-2-thione; ***2,6-Dimethylphenyl Propionate***; ***2-Methyl-2-(trimethylsilyloxy)-3-pentanone***; ***1,3-Thiazolidine-2-thione***; ***Tin(II) Trifluoromethanesulfonate***.

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Propylene Oxide[1]

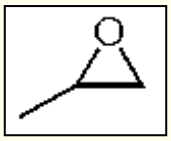

[75-56-9] · C_3H_6O · Propylene Oxide · (MW 58.09)

(monomer for polymerization; electrophile; chiral building block)

Alternate Names: 1,2-epoxypropane; methyloxirane.

Physical Data: mp -112 °C; bp 34 °C; *d* 0.859 g cm^{-3}; [α]20D +14.6° for the (*R*)-enantiomer, corrected to 100% ee.

Solubility: sol H_2O (405 g L^{-1}); miscible with organic solvents.

Form Supplied in: colorless liquid; commercially available as a racemic mixture and as the enantiomers. *Drying:* distillation from calcium hydride or calcium. Upon cooling, a hydrate $C_3H_6O.(H_2O)_{16}$ of mp -3 °C is precipitated from the moist oxirane as white crystals.[2]

Analysis of Reagent Purity: ^{13}C NMR ($CDCl_3$): δ 47.1, 46.8 (C-1, C-2), 17.2 (C-3) ppm; determination of ee by complexation gas chromatography on nickel(II) bis[3-heptafluorobutanoyl-(1*R*)-camphorate] in squalane, separation factor α 1.24 at 50 °C;[3] other suitable chiral stationary phases are nickel(II) bis[2-heptafluorobutanoyl-(*S*)-4-methylthujan-3-onate] and manganese(II) bis[3-heptafluorobutanoyl-(1*R*)-camphorate].[4]

Preparative Methods: (*R*)-propylene oxide is prepared (eq 1) in three steps: diazotization of (*S*)-alanine with ***Sodium Nitrite*** in hydrochloric acid; to give (*S*)-2-chloropropanoic acid; reduction to 2-chloropropan-1-ol with ***Lithium Aluminum Hydride***; and cyclization by distillation from ***Potassium Hydroxide*** pellets.[4,5]

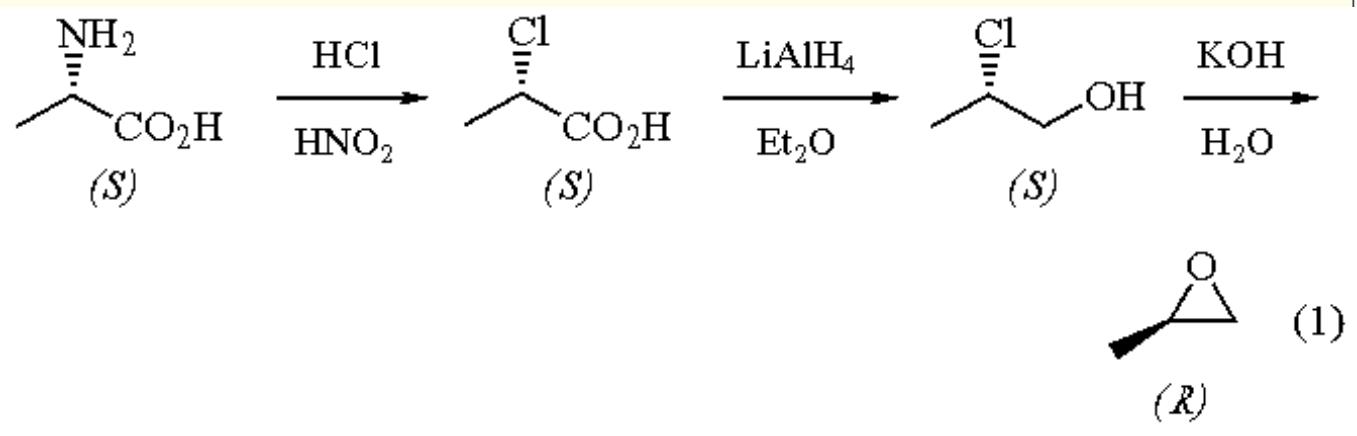

The (*S*)-enantiomer is prepared from ***(S)-Ethyl Lactate*** via (*S*)-propane-1,2-diol, and cyclization of a mixture of (*S*)-2-acetoxy-1-bromopropane and (*R*)-2-bromo-1-acetoxypropane (eq 2).[6,7]

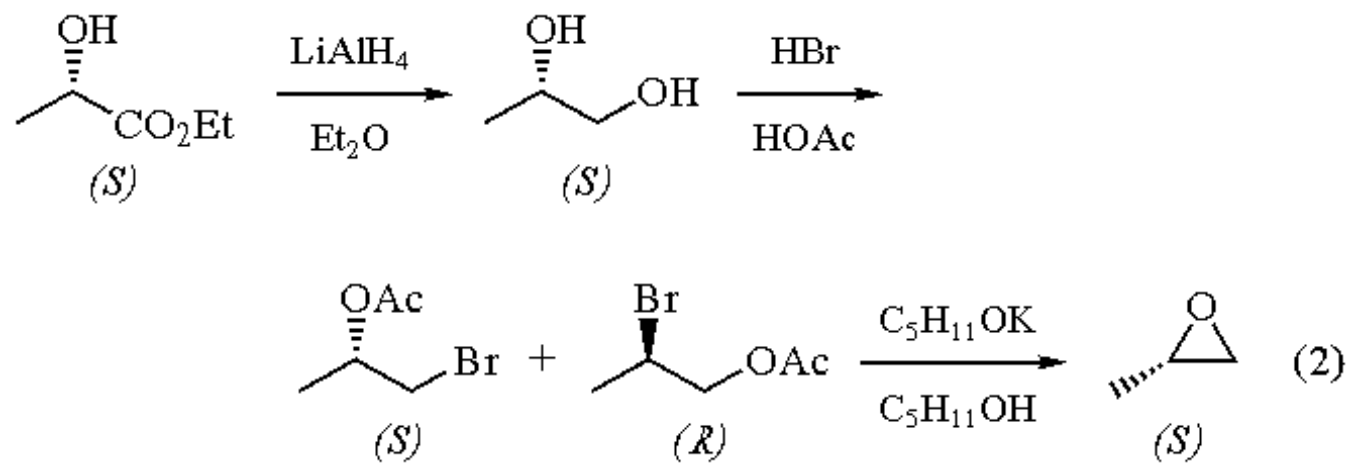

Alternatively, conversion of (*S*)-ethyl lactate into the mesylate is followed by reduction of the ester group with ***Aluminum Hydride***/THF and ring closure with aqueous KOH.[8] Another route to (*S*)-propylene oxide involves protection of the (secondary) hydroxyl group of (*S*)-ethyl lactate with ***Ethyl Vinyl Ether***, followed by reduction of the ester group with $LiAlH_4$, conversion of the primary hydroxyl group into the tosylate, acidic deprotection of the secondary hydroxyl group, and cyclization with aqueous KOH.[9] By means of a combined microbial/chemical synthesis, (*R*)-propylene oxide is obtained from glucose with ee >99%.[10] Metal-mediated access to both enantiomers is provided by either chromatographic or kinetic resolution of racemic propylene oxide, and also by asymmetric epoxidation of propylene.[11]

Handling, Storage, and Precautions: a suspected carcinogen for humans; it is inflammable and explosive; because of its high volatility, cooling to 0 °C before use is recommended. Use in a fume hood.

Polymerization of Propylene Oxide.

Monoalkyl-substituted oxiranes are polymerized by a great variety of initiators (cationic, anionic, or ionic-coordinated). Cationic initiators tend to give irregular enchainments, as ring opening occurs in both the α- and β-positions. With anionic initiators, such as ***Potassium t-Butoxide*** and KOH, the stereoselective formation of head-to-tail polymers is straightforward; in the case of propylene oxide, the chain ends are left unsaturated, giving rise to secondary reactions.[12] Enantioselective polymerization of racemic propylene oxide is mediated by initiators formed from ***Diethylzinc*** and various chiral auxiliaries;[13] the reaction proceeds with complete inversion at the stereogenic center and, with achiral initiators, an equimolar mixture of homochiral polymers (*R*)-(*R*)-(*R*)... and (*S*)-(*S*)-(*S*)... is formed.[14] Oligoethers are formed with tetraphenylporphinatoaluminium chloride as initiator species (eq 3); ring opening in the β-position is followed by insertion of the monomer unit into the Al-Cl bond. In subsequent steps, the monomer is inserted into the Al-O bond, leading to a polymer that bears a secondary hydroxyl group at one chain end and a chloromethyl group at the other.[15]

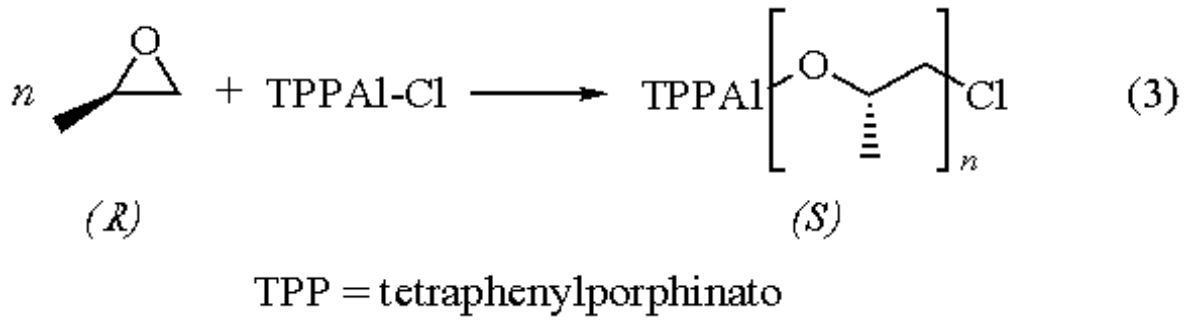

Reaction with Carbon Dioxide.

The stereoselective reaction of propylene oxide with ***Carbon Dioxide*** to give 4-methyl-1,3-dioxolan-2-one (eq 4) is catalyzed by metal salts and also by transition metal complexes; high pressures and high temperatures are necessary.[16]

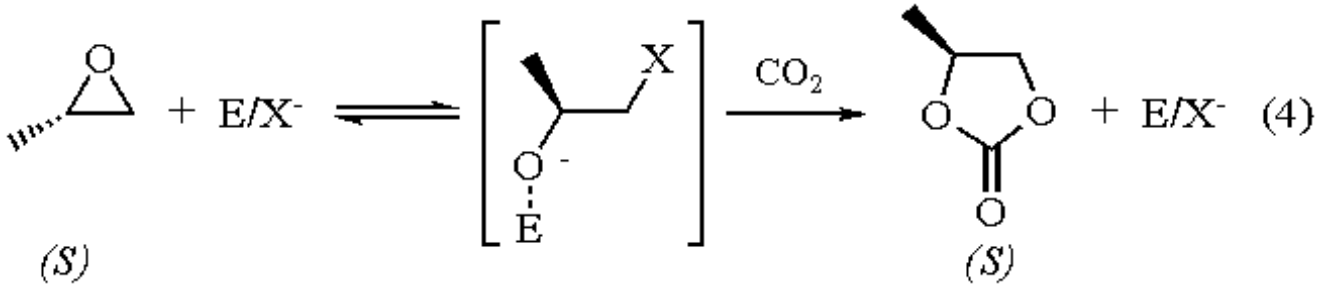

Reaction with Heteronucleophiles.

Nucleophiles preferentially attack the unsubstituted carbon atom; since secondary amines are more basic than primary amines, the reaction of (*S*)-propylene oxide with the latter leads to polyfunctional amino diols (eq 5).[17]

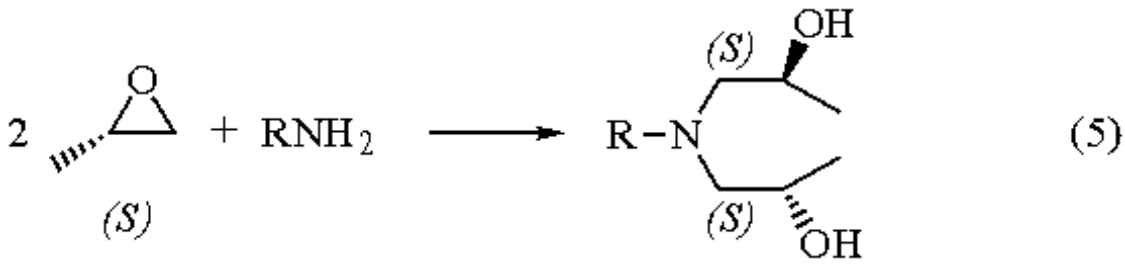

As shown in eq 6, a primary amino group is introduced into an alkyloxirane by ring opening with lithium dibenzylamide, followed by hydrogenolytic deprotection of the amine.[18]

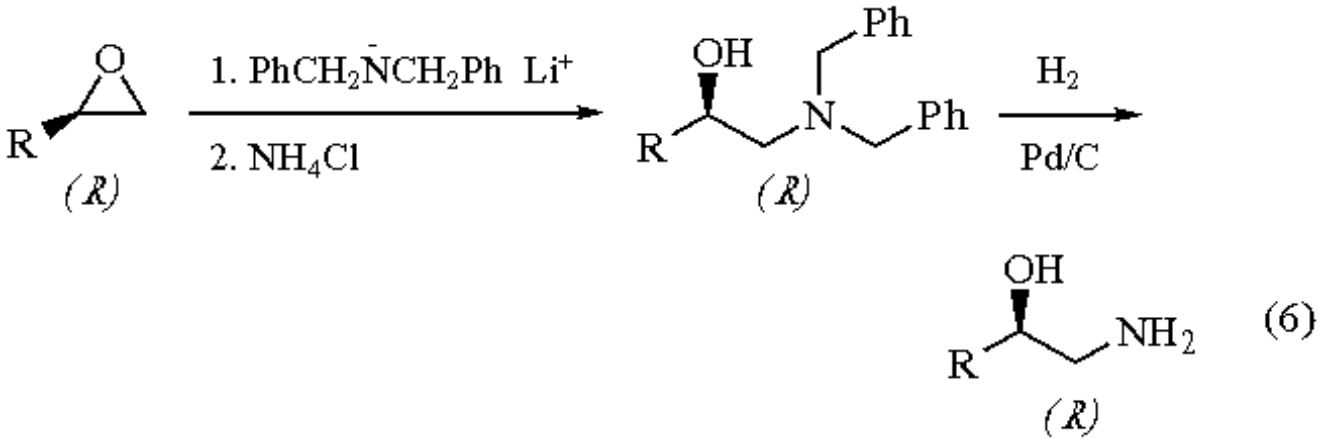

(*S*)-Propylene oxide reacts with ***Hydrogen Chloride/Lithium Chloride*** to give (*S*)-1-chloro-2-propanol (eq 7). This can be converted to 1-benzylthio-2-propanol by lithiation with ***n-Butyllithium*** followed by reaction with ***Lithium Naphthalenide*** to give highly reactive C-metalated alkoxides.[19]

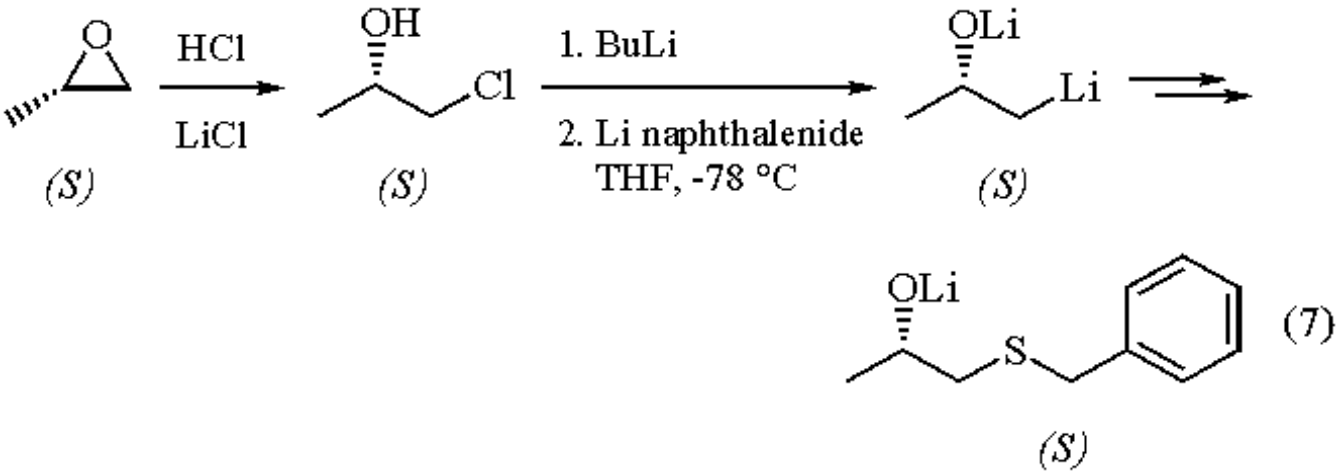

Reaction with Grignard Reagents.

The C-C-coupling reaction between oxiranes and Grignard reagents is catalyzed by copper(I) compounds. As depicted in eq 8, (*R*)- and (*S*)-sulcatol are prepared in a straightforward manner from (*R*)- and (*S*)-propylene oxide, respectively, and an allylic Grignard reagent, using ***Copper(I) Iodide*** as catalyst.[20]

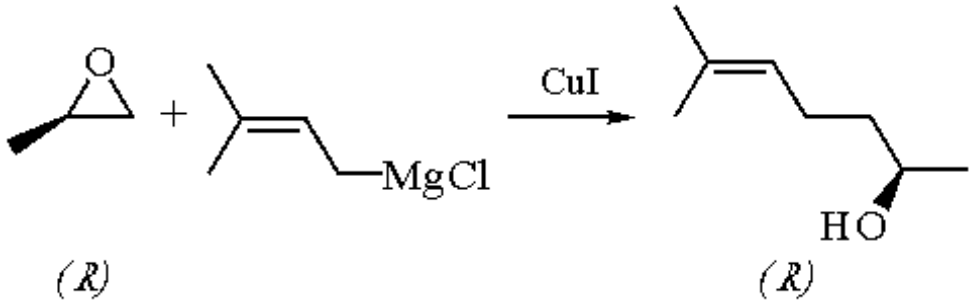

(8)

A convenient route to (*R*)-α-methylene-γ-lactones (eq 9) comprises reaction of a vinylic Grignard reagent with propylene oxide, electrophilic replacement of the trimethylsilyl group, and ring closure with ***Tetrakis(triphenylphosphine)palladium(0)*** and ***Carbon Monoxide*** in acetonitrile.[21]

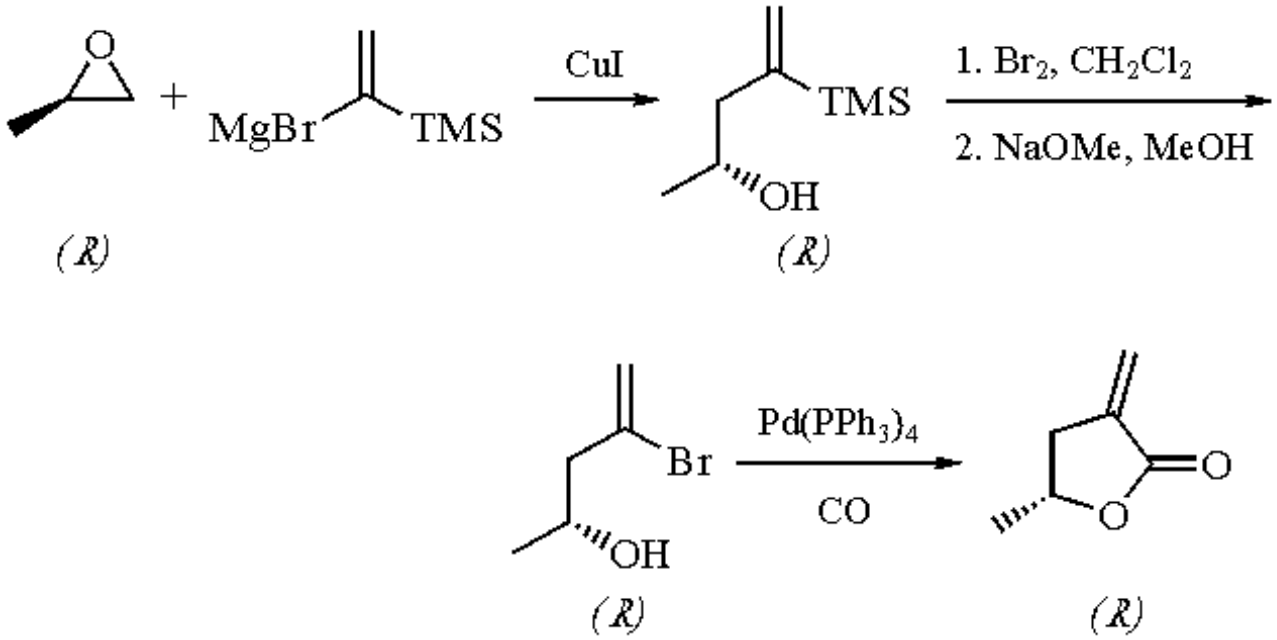

(9)

In eq 10, the total synthesis of (*R*)-mellein is depicted via the *O*-methoxymethylene-protected aryl Grignard compound derived from 3-bromophenol, which is added to (*R*)-propylene oxide using $CuBr.SMe_2$ (see ***Copper(I) Bromide***) as the catalyst. After ring lithiation with ***n-Butyllithium*** and carboxylation with ***Carbon Dioxide***, treatment with methanolic hydrochloric acid leads to the final product.[22]

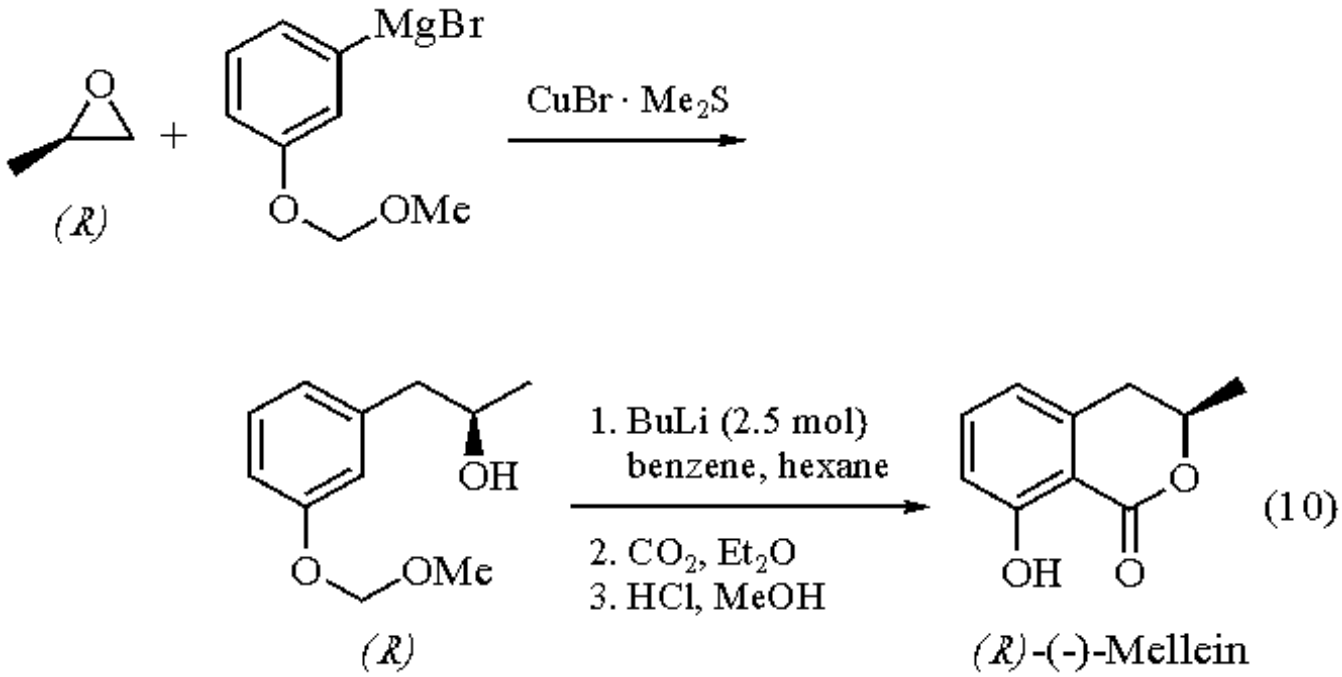

An illustration of protection and deprotection of two hydroxy groups is displayed in eq 11. Reaction of an aliphatic bromomagnesium compound with propylene oxide in the presence of 1,4-cyclooctadiene-***Copper(I) Chloride***, followed by protection with ***3,4-Dihydro-2H-pyran***, hydrogenolytic debenzylation of the primary hydroxy group, and oxidation with ***Pyridinium Chlorochromate*** yields an aldehyde that is transformed into melochinine by a multistep procedure.[23]

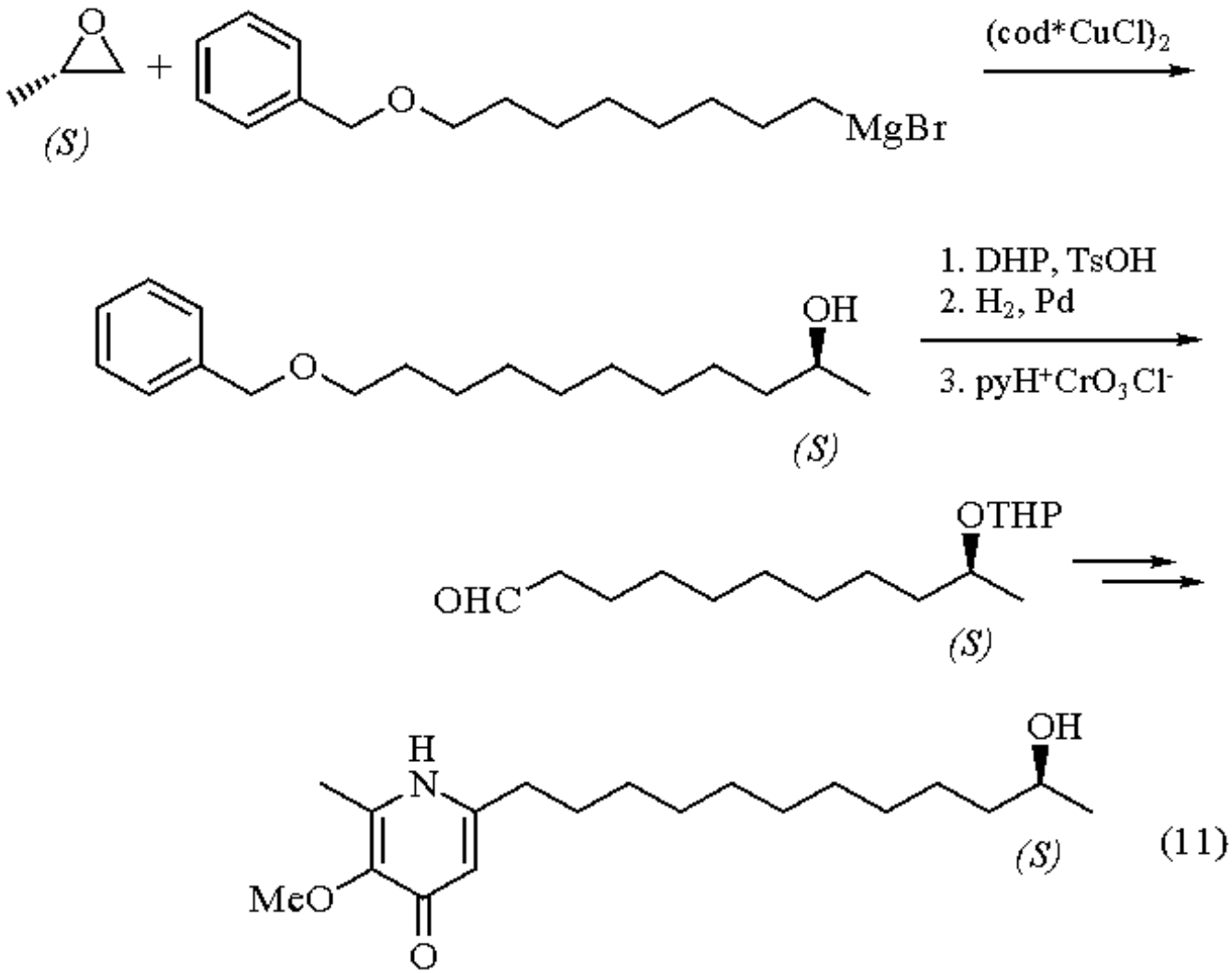

This scheme is paralleled by eq 12, where an aliphatic chloromagnesium compound reacts with propylene oxide. In a multistep procedure, the secondary hydroxy group is protected, and the primary hydroxy group is deprotected and eventually oxidized to a carboxylic function. The final product, (*S*)-13-methyl-(*Z*)-5-tridecenolide, is a macrolide aggregation pheromone of the flat grain beetle.[24]

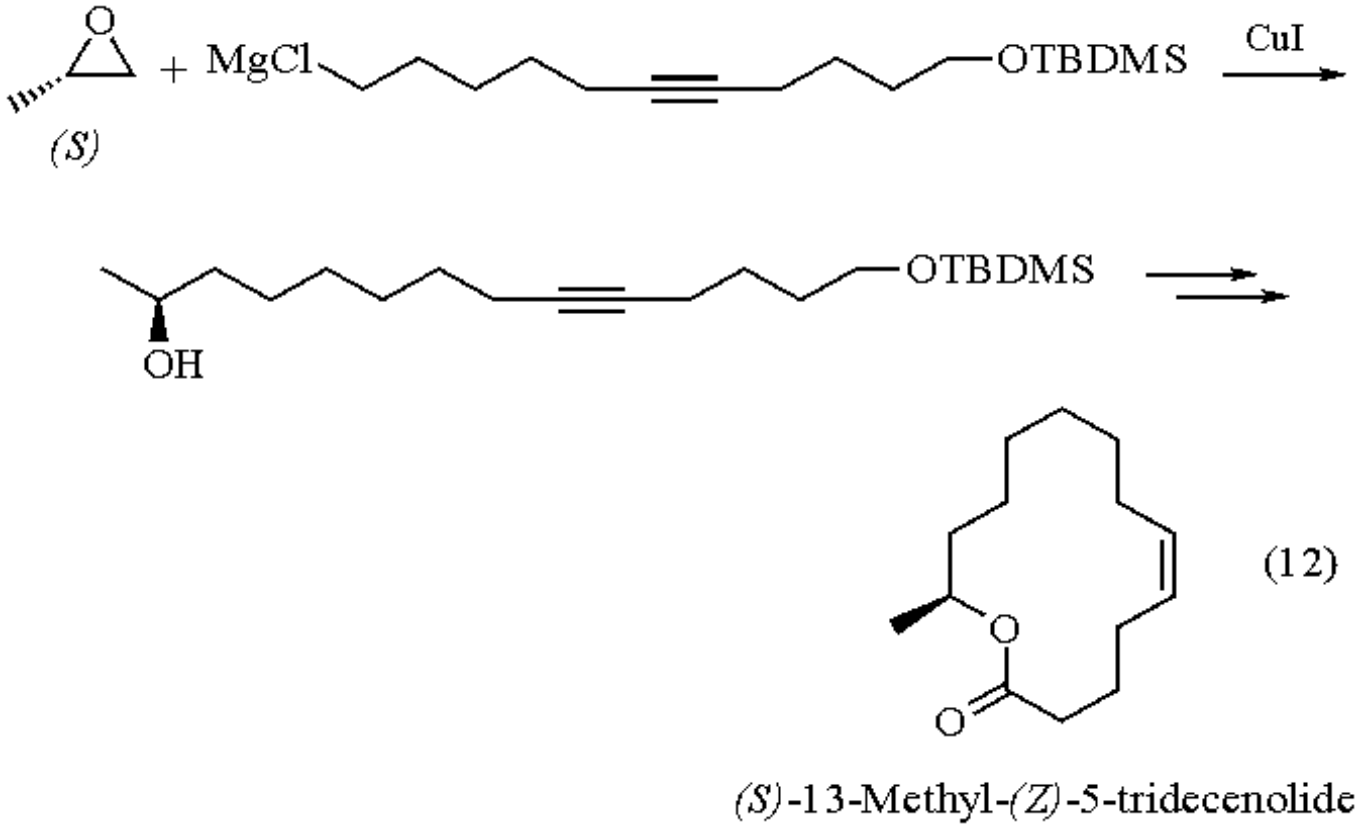

Reaction with Organoaluminum Compounds.

The macrocyclic lactone (*R*)-recifeiolide is prepared via ring opening of (*R*)-propylene oxide with a lithium vinylaluminate, and conversion of another vinyl group into a carboxymethylene function via the sequence shown in eq 13.[25]

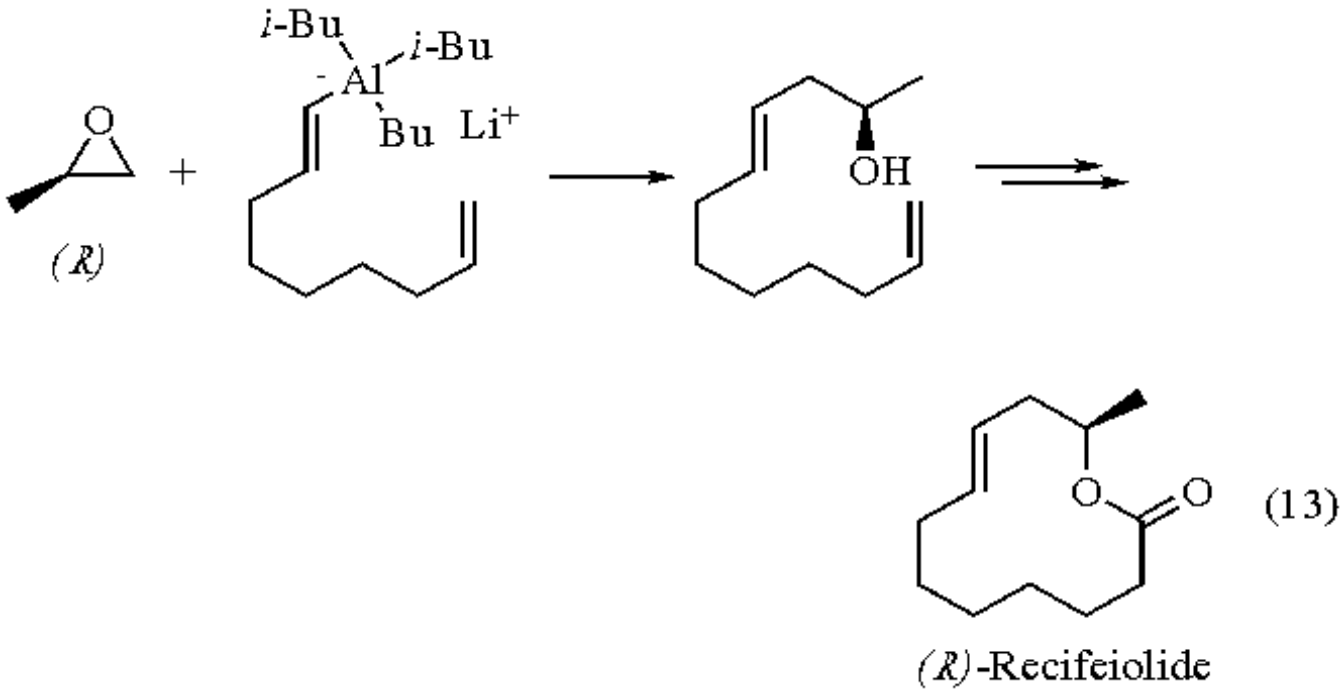

Reaction with Organolithium Compounds.

(*R*)-2-Hydroxypropylfuran is available by lithiation of furan with *n*-BuLi and alkylation with (*R*)-propylene oxide (eq 14).[26]

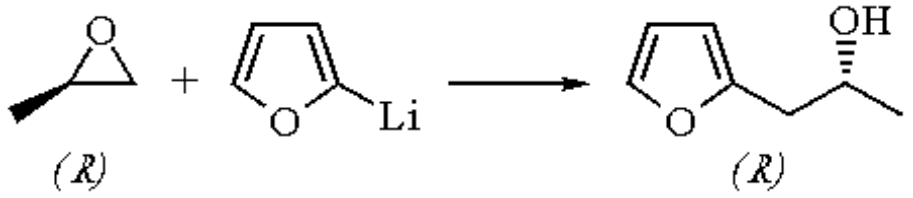

(14)

The total synthesis of grahamimycin A_1, a macrolide antibiotic, starts with ring opening of propylene oxide by means of a lithium acetylide (eq 15). Initially, (*S*)-propylene oxide was used to prepare the unnatural (*S*,*S*)-(+)-enantiomer;[27] the use of the (*R*)-enantiomer to produce the natural (*R*,*R*)-(-)-grahamimycin has also been described.[28]

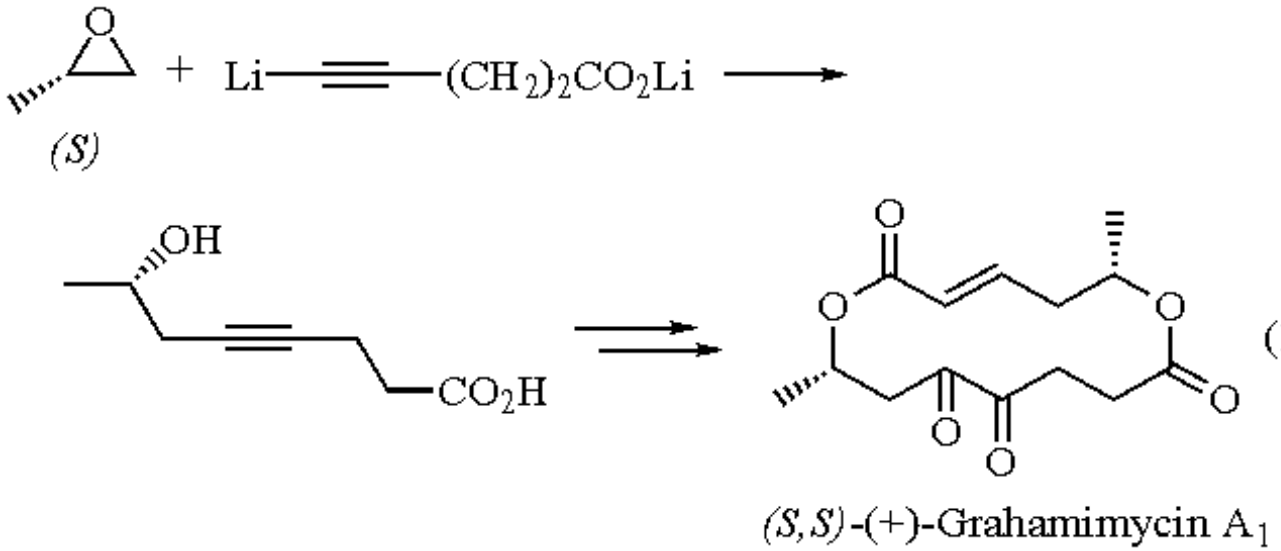

(15)

As outlined in eq 16, ring opening of (*S*)-propylene oxide with a lithiated sulfone serves as a key step in the synthesis of (2*R*,5*S*)-*cis*-2-methyl-5-hexanolide, a sex pheromone of the carpenter bee. In the same way, the (*R*)-enantiomer is used to prepare (2*S*,5*R*)-*cis*-2-methyl-5-hexanolide in high enantiomeric purity.[29]

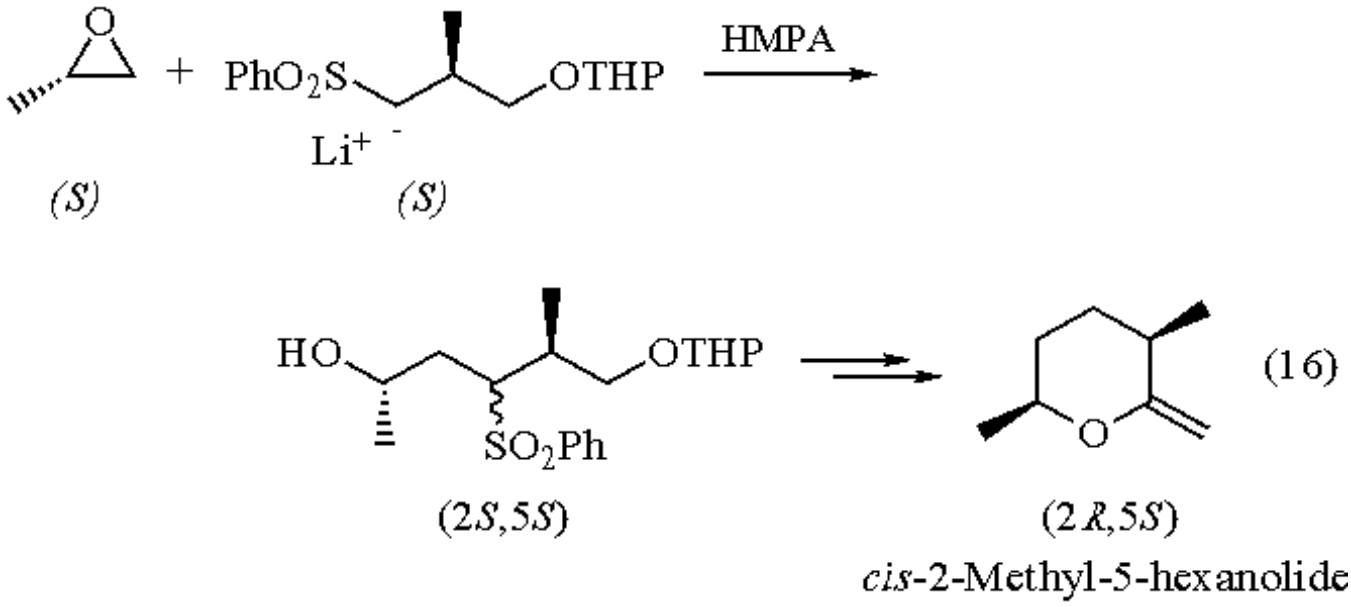

(16)

Reaction with Enolates.

The pheromone components of *Paravespula vulgaris*, the (*E*)- and (*Z*)-isomers of 2-methyl-1,6-dioxaspiro[4.5]decane with the (*S*)-configuration at C-2, are obtained by alkylation of the α-acetyl-δ-valerolactone dianion with (*S*)-propylene oxide (eq 17).[30]

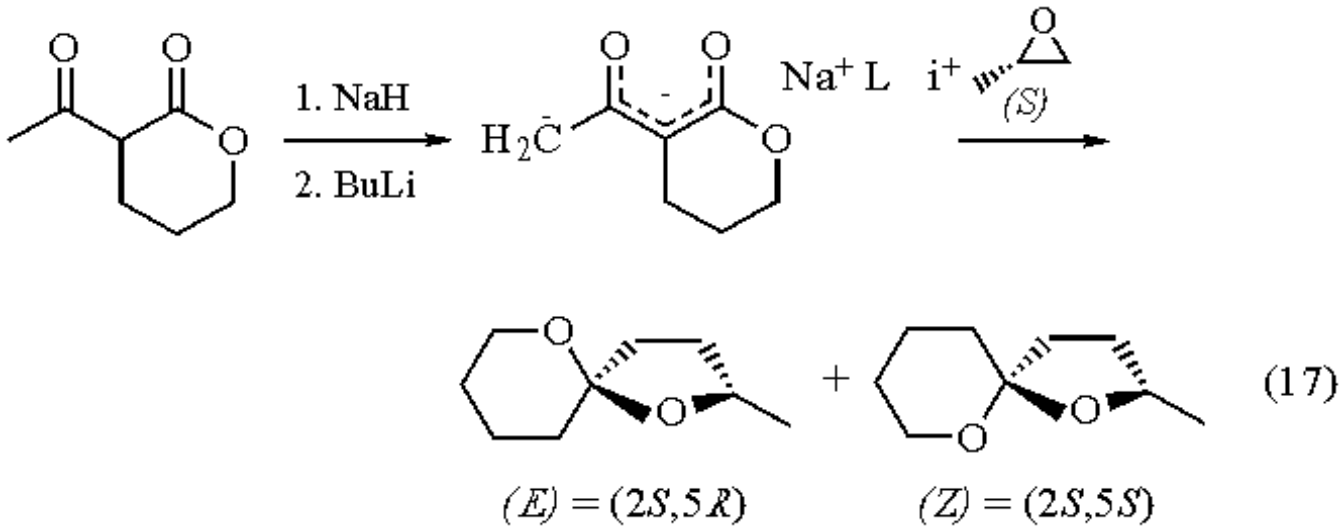

Alkylation of methyl acetoacetate with (*R*)-propylene oxide yields (*R*)-2-acetyl-4-pentanolide. This is converted into a mixture of (*E*,*E*)- and (*Z*,*E*)-exogonic acid (eq 18).[31]

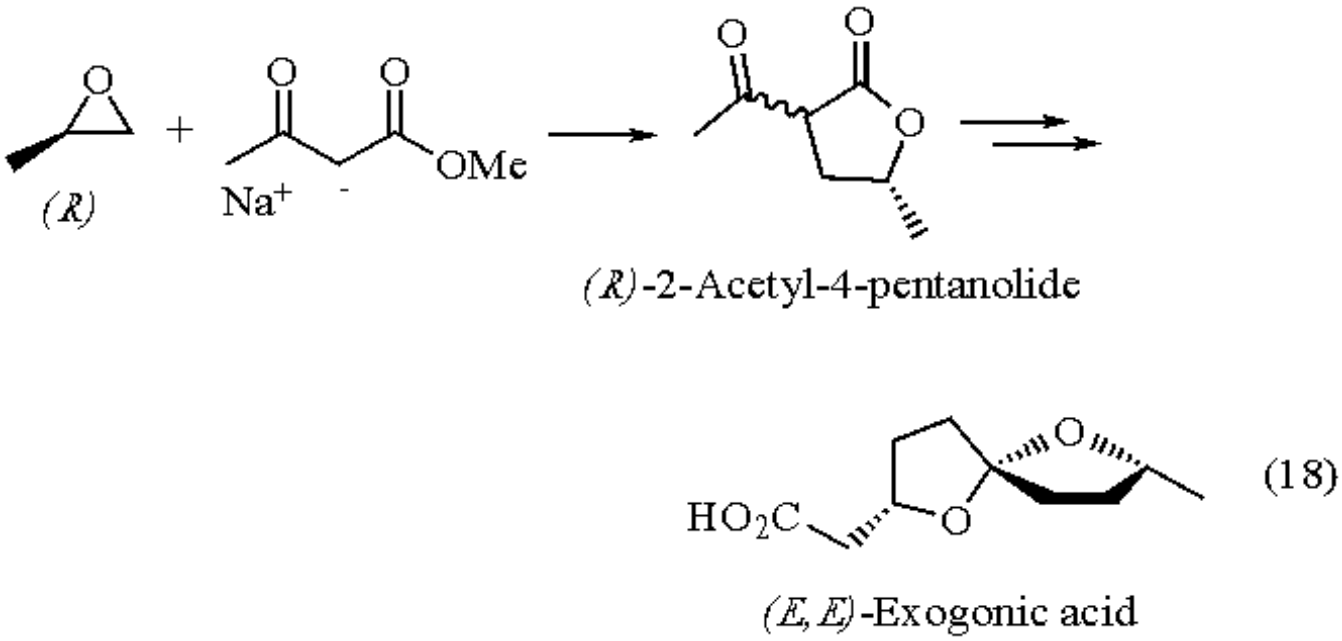

Related Reagents.

Ethylene Oxide; ***Glycidol***; ***Isoprene Epoxide***.

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University of Tübingen, Germany

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n-Propylphosphonic Anhydride

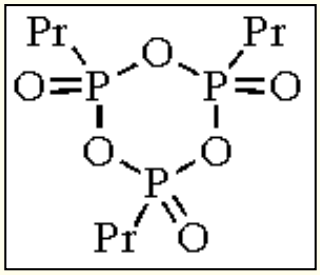

[68957-94-8] · $C_9H_{21}O_6P_3$ · *n*-Propylphosphonic Anhydride · (MW 318.21)

(peptide coupling reagent[1])

Alternate Name: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trioxide.

Physical Data: colorless, water-clear syrup, bp 200 °C/0.3 mmHg. The structure is considered to be a trimer.

Solubility: sol dichloromethane, dioxane, THF, DMF, *N*-methyl-2-pyrrolidinone.

Form Supplied in: not commercially available.

Preparative Method: prepared in high yield by hydrolysis of propylphosphonic dichloride to propylphosphonic acid, followed by heating and distillation under reduced pressure (eq 1).[2]

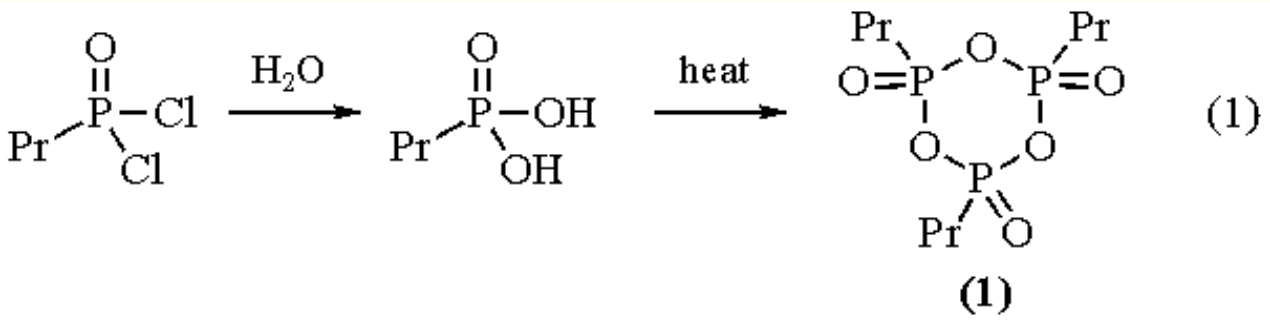

Purification: can be purified by vacuum distillation.

Handling, Storage, and Precautions: as a 50% w/v solution in dichloromethane, the anhydride can be stored in a brown bottle for several months.[1] It is reported to be relatively nontoxic.[1]

Peptide Synthesis.

Alkylphosphonic anhydrides have been explored as condensing agents for the synthesis of peptides and this reagent (**1**) was identified as the most useful of this class.[1,2] It shows good shelf stability and good solubility and leads to little racemization of the protected amino acid substrates. In addition, unlike reagents such as the carbodiimides, the byproduct formed from the condensing agent (an alkylphosphonic acid derivative) is soluble in water and easily removed from the peptide product by extraction with aqueous alkaline buffers (eq 2).

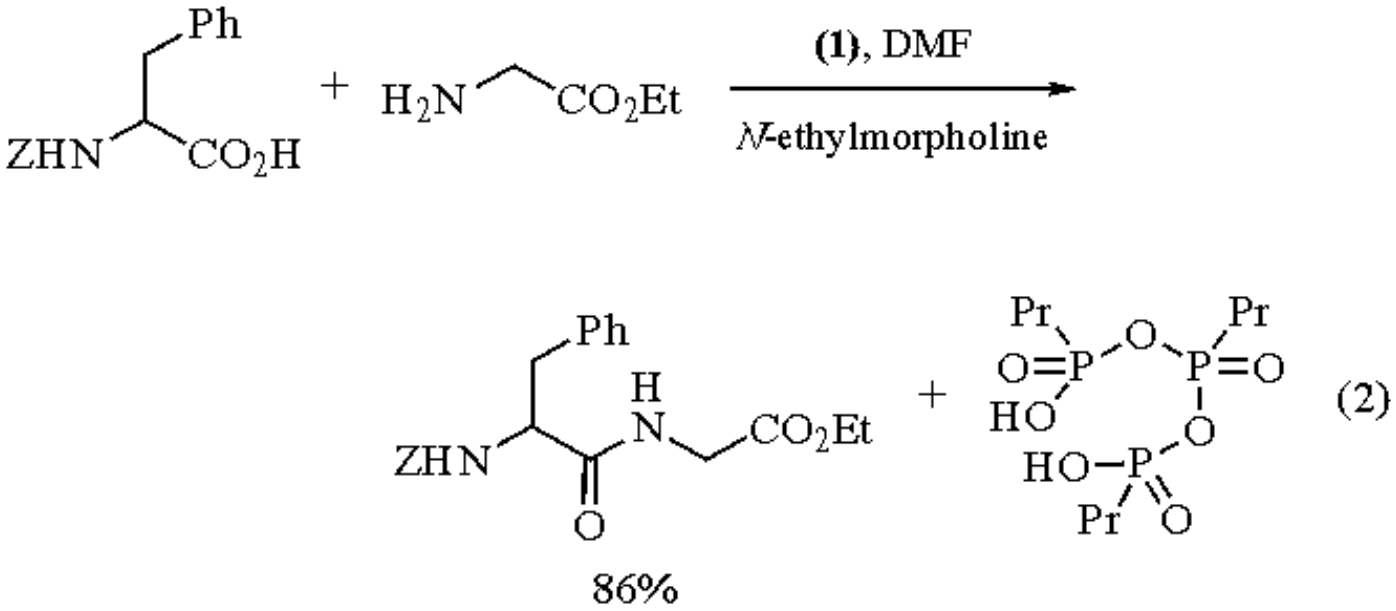

The use of (**1**) on a technical scale has been explored and its toxicity has been investigated.[1] It appears to be relatively nontoxic (no intoxication at 2000 mg kg^{-1} in mice, orally administered). In addition to the synthesis of dipeptides, (**1**) has been used for the synthesis of larger peptides such as a dodecapeptide from the *C*-terminal region of adenovirus 82 K-protein, a dodecapeptide related to ACTH, and other ACTH and LHRH derivatives.[1,3,4] The level of racemization observed using (**1**) has been shown to be as low as with the best other peptide condensing agents and it has been shown to couple sterically hindered peptides with little problem.[1,3] A recent patent has appeared covering the use of (**1**) in a quick and technically simple synthesis of tripeptides.[5] A brief reference has been made to the use of (**1**) in the esterification of *N*-protected amino acids with alcohols.[3]

Cyclic Peptides.

(**1**) has also been used in the synthesis of the linear undecapeptide precursor of the cyclic undecapeptide cyclosporin.[6] In addition, the use of (**1**) in excess along with ***4-Dimethylaminopyridine*** at 10^{-3} M leads to cyclization of the unprotected linear undecapeptide to give cyclosporin in 65% yield (eq 3).[6]

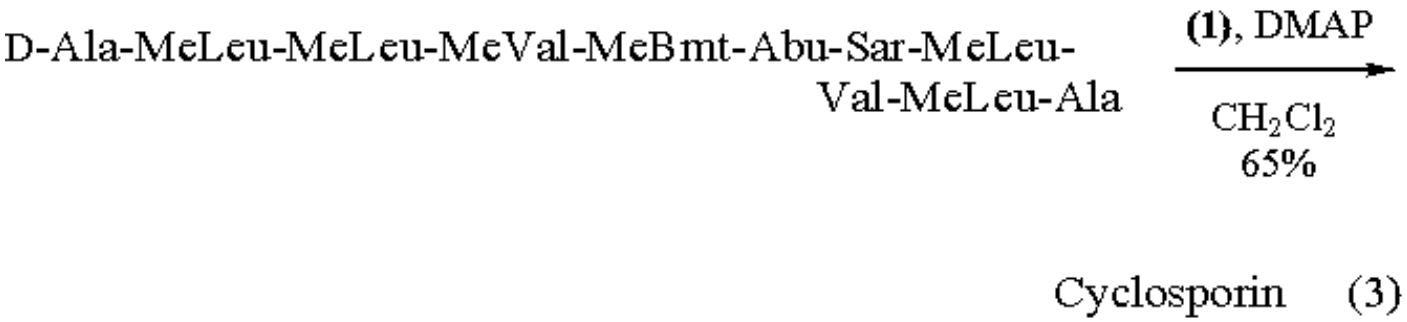

Polyamides.

Propylphosphonic anhydride (**1**) in ***1-Methyl-2-pyrrolidinone*** (NMP) has been used for the direct synthesis of polyamides from dicarboxylic acids and diamines.[7] Thus reaction of isophthalic acid and 4,4´-oxydianiline with an excess of (**1**) in NMP at 100 °C for 2 h gives a virtually quantitative yield of the polyamide (eq 4).[7] The same authors also describe the use of (**1**) in the synthesis of a number of simple amides from carboxylic acids and amines.[7]

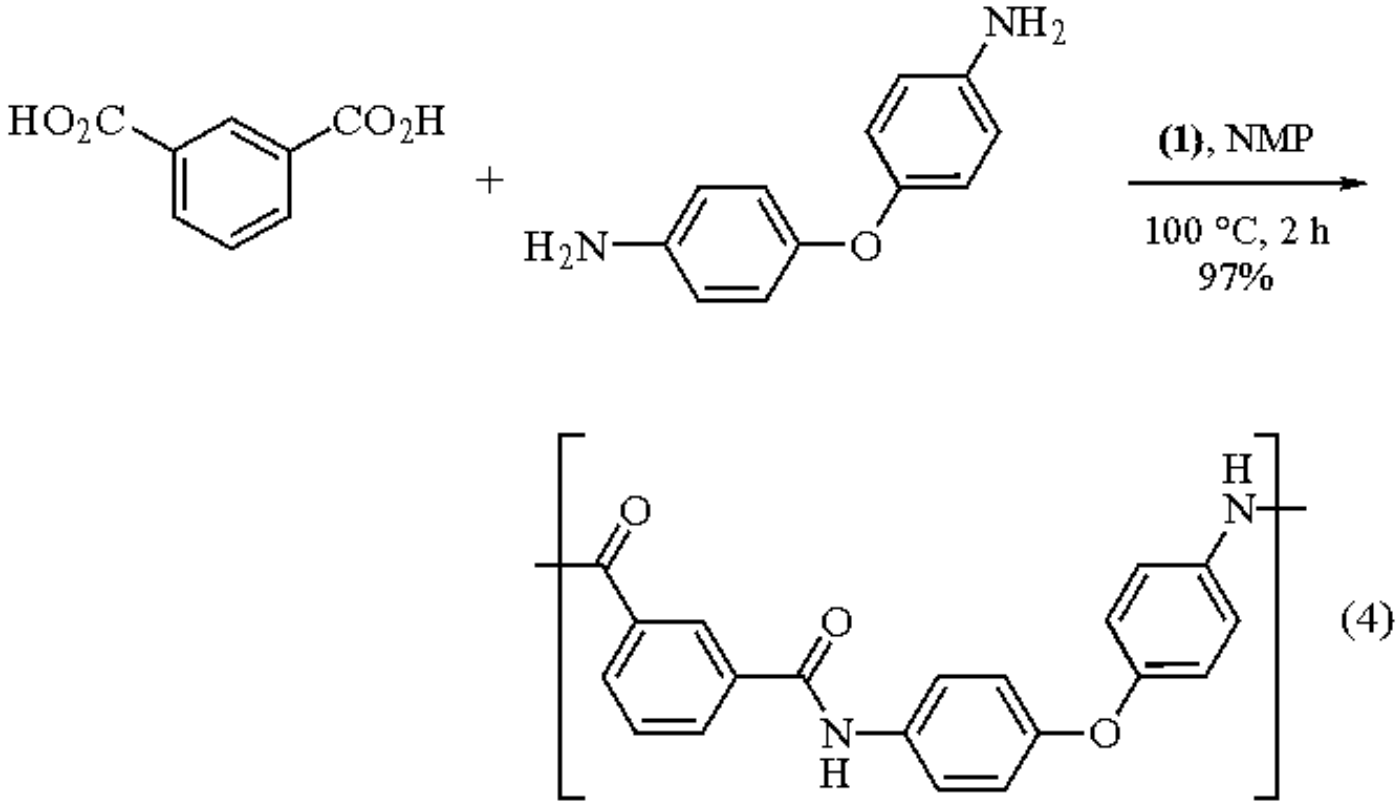

1. Wissmann, H. *PS* **1987**, *30*, 645.
2. Wissmann, H.; Kleiner, H-J. *AG(E)* **1980**, *19*, 133.
3. Wissmann, H.; Koenig, W.; Teetz, V.; Geiger, R. *Pept., Proc. Eur. Pept. Symp.* **1980**, *16th*, 174 (*CA* **1983**, *98*, 54439s).
4. Wissmann, H.; Koenig, W.; Geiger, R. in *Pept.: Struct. Funct., Proc. 8th Am. Pept. Symp.*; Hruby, V. J.; Rich, D. H., Eds.; 1983; p 111 (*CA* **1984**, *101*, 55 513d).
5. Flemming, H. W.; Rukwied, M.; Schmidt, M. *Ger. Offen.* 3 839 379, 1990 (*CA* **1990**, *113*, 212 687f).
6. Wenger, R. M. *HCA* **1984**, *67*, 502.
7. Ueda, M.; Honma, T. *Polym. J. (Tokyo)* **1988**, *20*, 477 (*CA* **1988**, *109*, 110 976z).

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Propynenitrile

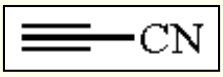

[1070-71-9] · C_3HN · Propynenitrile · (MW 51.05)

(nucleophilic conjugate addition to give (*Z*)-alkenes;[1,2] Diels-Alder reactions,[3] dipolar cycloadditions with nitrones[4] and diazo compounds[5])

Alternate Names: cyanoacetylene; propiolonitrile.

Physical Data: mp 5 °C; bp 41 °C.

Solubility: sol benzene, EtOH, acetonitrile, cyclohexane, toluene, ether.

Analysis of Reagent Purity: IR (gas) 863, 2077, 2272, 3327 cm^{-1}.

Preparative Method: not commercially available, but can be prepared[6,7] on a several gram scale by the dehydration of propynamide (propiolamide) with ***Phosphorus(V) Oxide*** (eq 1). The reactants are well ground together under nitrogen, and upon subjection of the resulting solid mixture to high temperature treatment, propynenitrile is collected as a distillate in a receiver held at 5 °C.

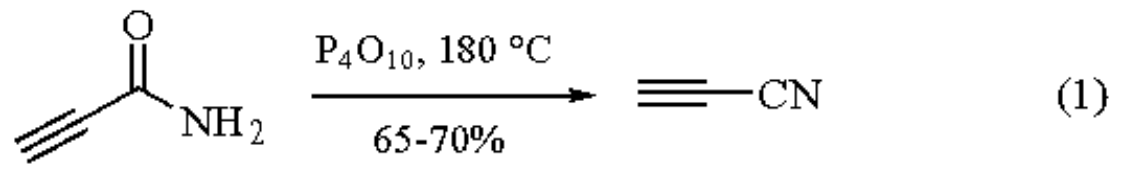

Purification: distillation.

Handling, Storage, and Precautions: decomposes in solution; sensitive to air and light.

Procedures Involving Nucleophilic Conjugate Addition.

Propynenitrile is an excellent conjugate addition electrophile. Simple transformations of this sort are given in eqs 2 and 3,[1,7] which show the (*Z*) stereoselectivity that is expected.

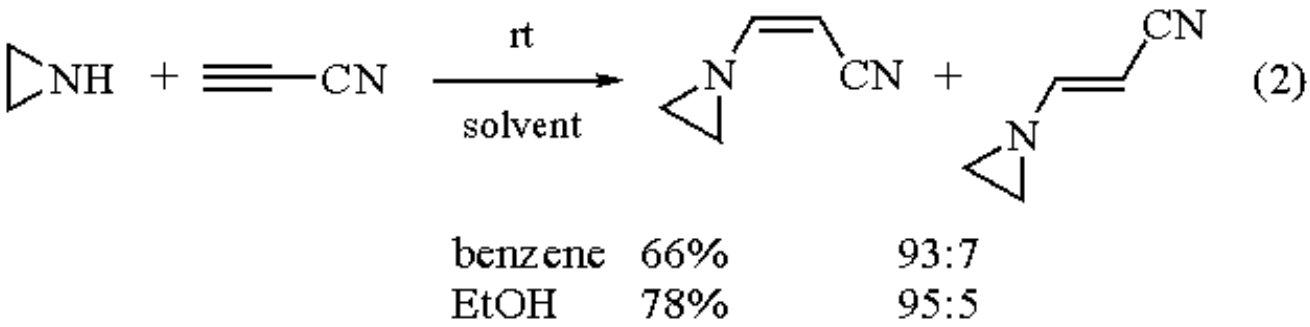

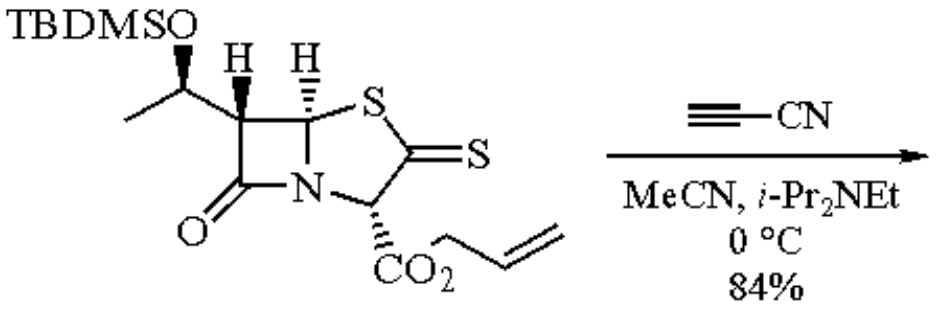

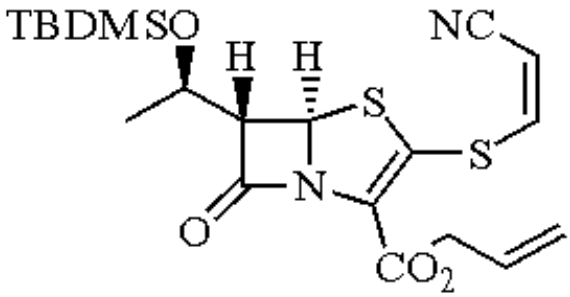

(3)

An interesting heterocycle-forming process that depends on nucleophilic conjugate addition to propynenitrile as well as to the reagent's nitrile group is illustrated in eq 4.[8] This transformation evidently proceeds through the indicated tricyclic intermediate, which is further transformed hydrolytically in situ.

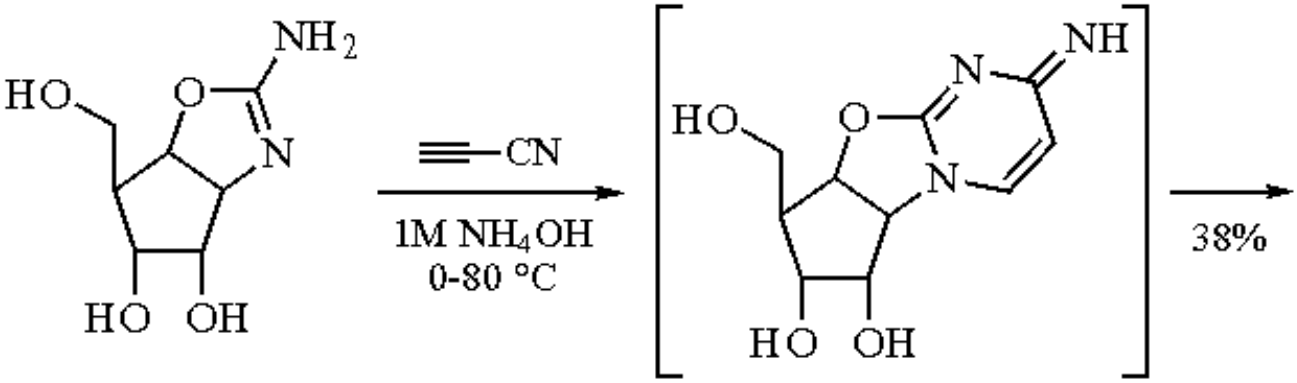

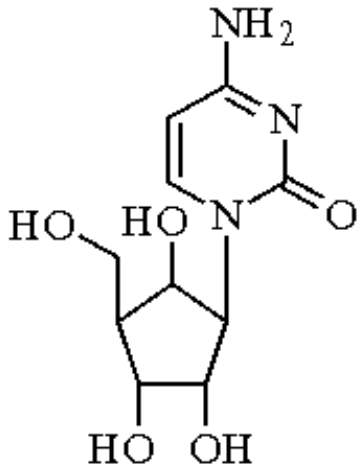

(4)

Propynenitrile affords (*Z*)-enynes that arise formally from the conjugate addition of an acetylide nucleophile. This clever transformation is brought about by the in situ conjugate addition of bromide to give (*Z*)-3-bromopropenenitrile and its subsequent palladium-induced coupling with an alkyne (eq 5).[2]

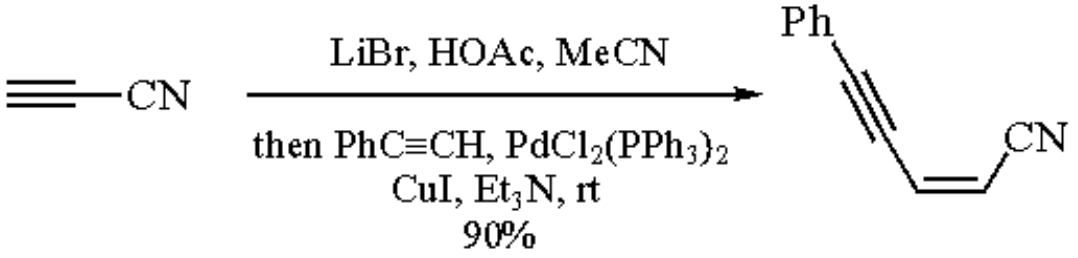

(5)

Ritter Reactions.

This reagent can be involved in the Ritter reaction, but with only modest success (eq 6); other examples proceed even less efficiently.[9] A more successful transformation that operates on the nitrile group is shown in eq 7.[9]

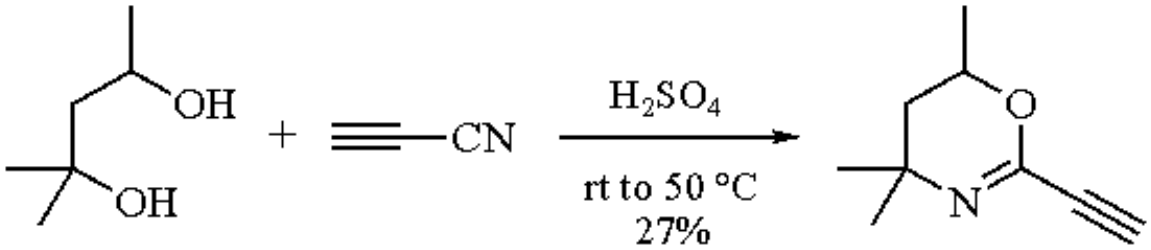

(6)

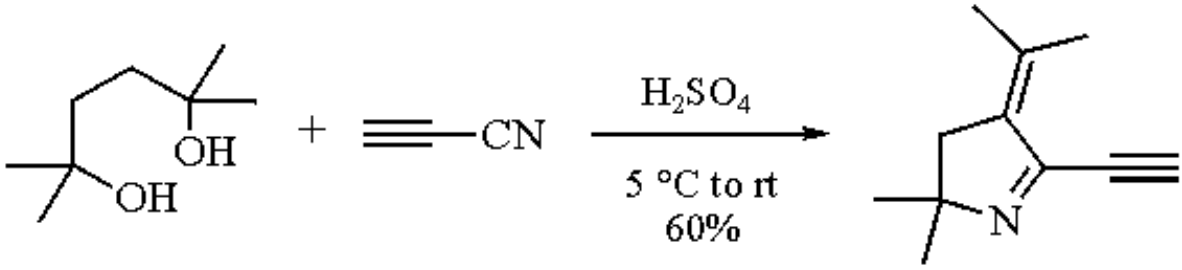

(7)

Diels-Alder Cycloadditions.

Propynenitrile engages suitable dienes in Diels-Alder cycloadditions. For example, a neat mixture of propynenitrile and ***Cyclopentadiene*** held at rt affords the expected bicyclo[2.2.1]heptadiene product in good yield (eq 8).[10] A more elaborate example is shown in eq 9,[3] in which the regiochemical directive effects of the substituents converge to give the cyclohexadiene product shown.

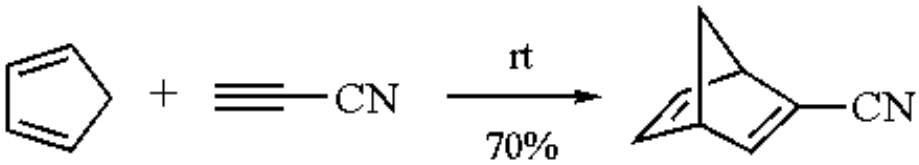

(8)

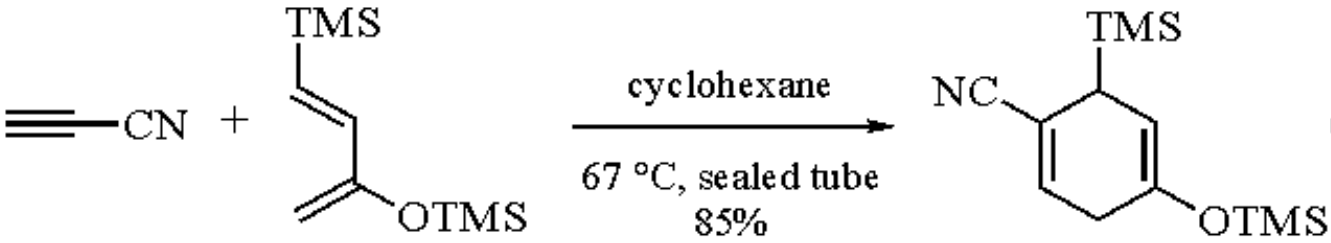

(9)

Dipolar Cycloadditions.

Reactions of this type include examples involving nitrones (eq 10)[4] and diazo compounds (eq 11).[5]

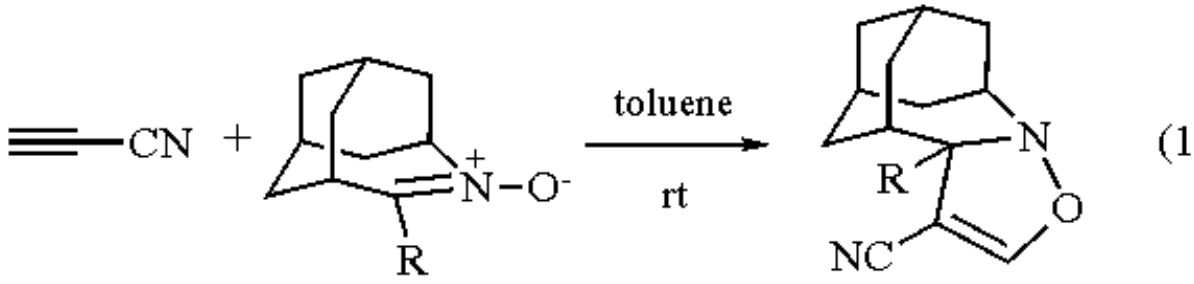

(10)

R = H, 79%; Me, 93%

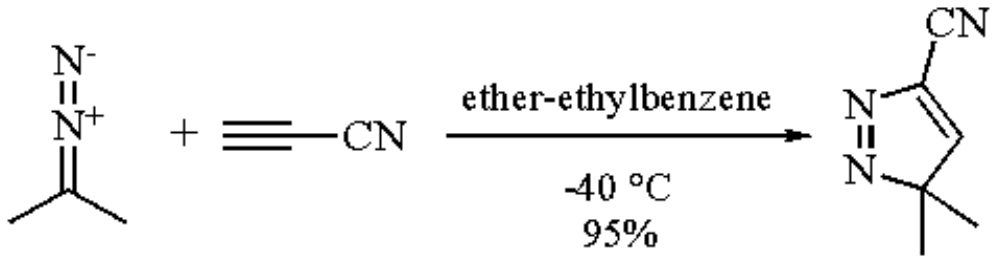

(11)

Miscellaneous Ring-Forming Processes.

Two ring-forming transformations brought about with this reagent that are not mechanistically straightforward are illustrated in eqs 12 and 13. In eq 12, two molecules of propynenitrile are incorporated in the product, whose structure was determined by X-ray crystallography.[6] Eq 13 depicts an unusual cyclooctatetraene synthesis.[11]

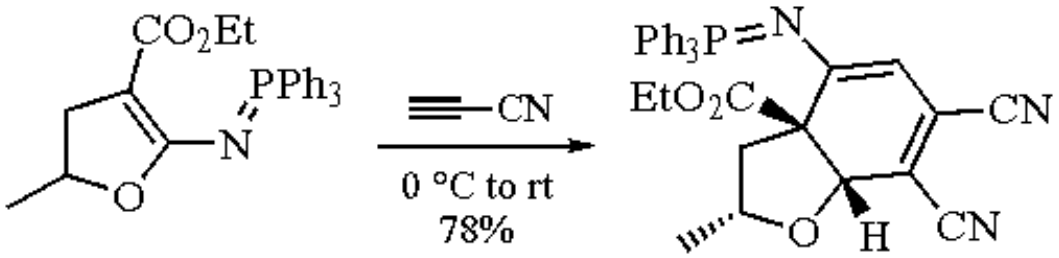

(12)

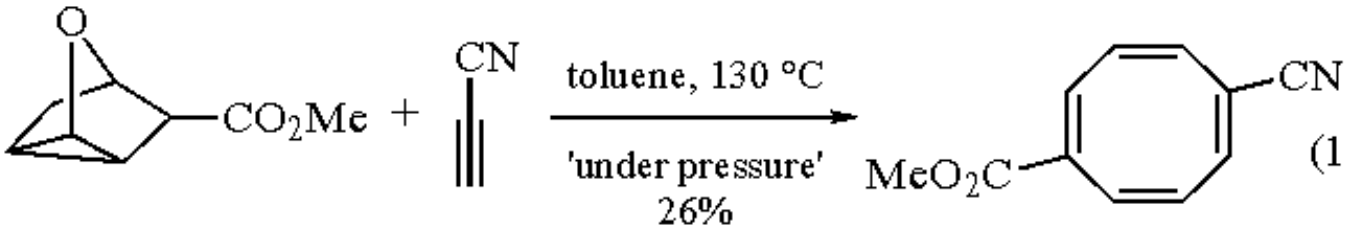

(13)

Related Reagents.

Dimethyl Acetylenedicarboxylate; ***Methyl Propiolate***.

---

1. Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildonger, K. J.; Ratcliffe, R. W.; Christensen, B. G. *T* **1983**, *39*, 2505.
2. Lu, X.; Huang, X.; Ma, S. *TL* **1992**, *33*, 2535.
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11. Figeys, H. P.; Van Lommen, G.; Belladone, M.; Destrebecq, M. *TL* **1980**, *21*, 2365.

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Propynyllithium[1]

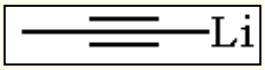

[4529-04-8] · C_3H_3Li · Propynyllithium · (MW 46.00)

(powerful nucleophilic source of the propynyl unit for many electrophiles)

Solubility: sol liquid ammonia; partially sol THF, ether.

Form Supplied in: white suspension in THF; prepared in situ and used directly.

Preparative Methods: prepared in situ under nitrogen by reaction of propyne (condensed into cold THF) with ***n-Butyllithium*** in THF at -78 °C[2] or ***Lithium Amide*** in ether/liquid ammonia below -50 °C,[3] or by reaction of 1,2-dibromopropane with 3 equiv of ***Lithium Diisopropylamide*** (double elimination of hydrogen bromide and deprotonation) at -60 °C to 0 °C in THF.[4]

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture.

Additions to Carbonyl Compounds.

Propynyllithium adds readily to aldehydes and ketones to give the corresponding secondary and tertiary alcohols. The reaction with isobutyraldehyde at -78 °C gives a precursor to the (+)-Prelog-Djerassi lactone after oxidation and enantioselective ketone reduction (eq 1).[2] Additions proceed under nonchelation-controlled conditions and are less stereoselective than the corresponding additions of ***Propynylmagnesium Bromide***.[5] The linear nature of the reagent allows addition to hindered ketones to give the propargylic alcohols which can be transformed into allenyl sulfoxides with ***Benzenesulfenyl Chloride*** (eq 2).[6] Propynyllithium prepared from 1,2-dibromopropane also reacts smoothly with aldehydes and ketones in high yield (eq 3).[4]

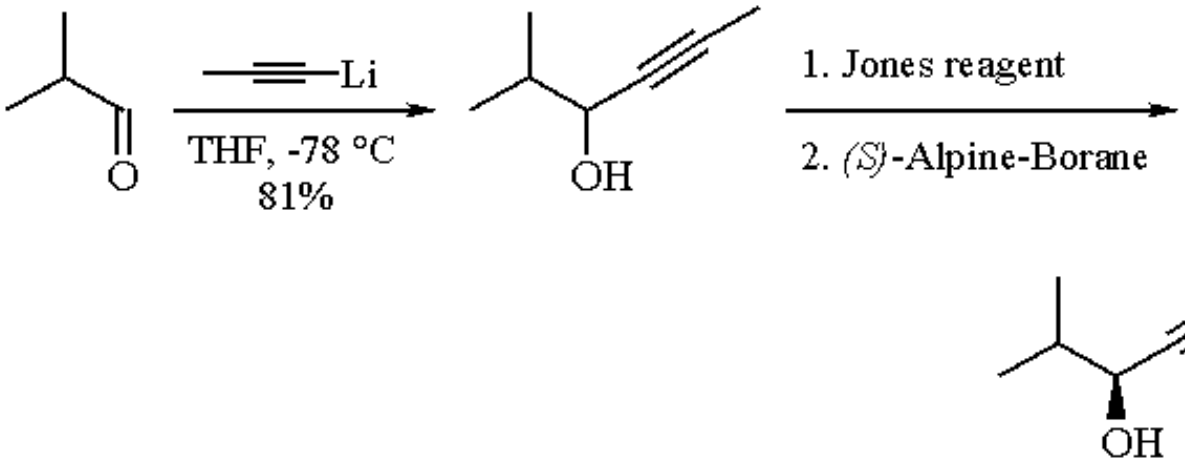

(1)

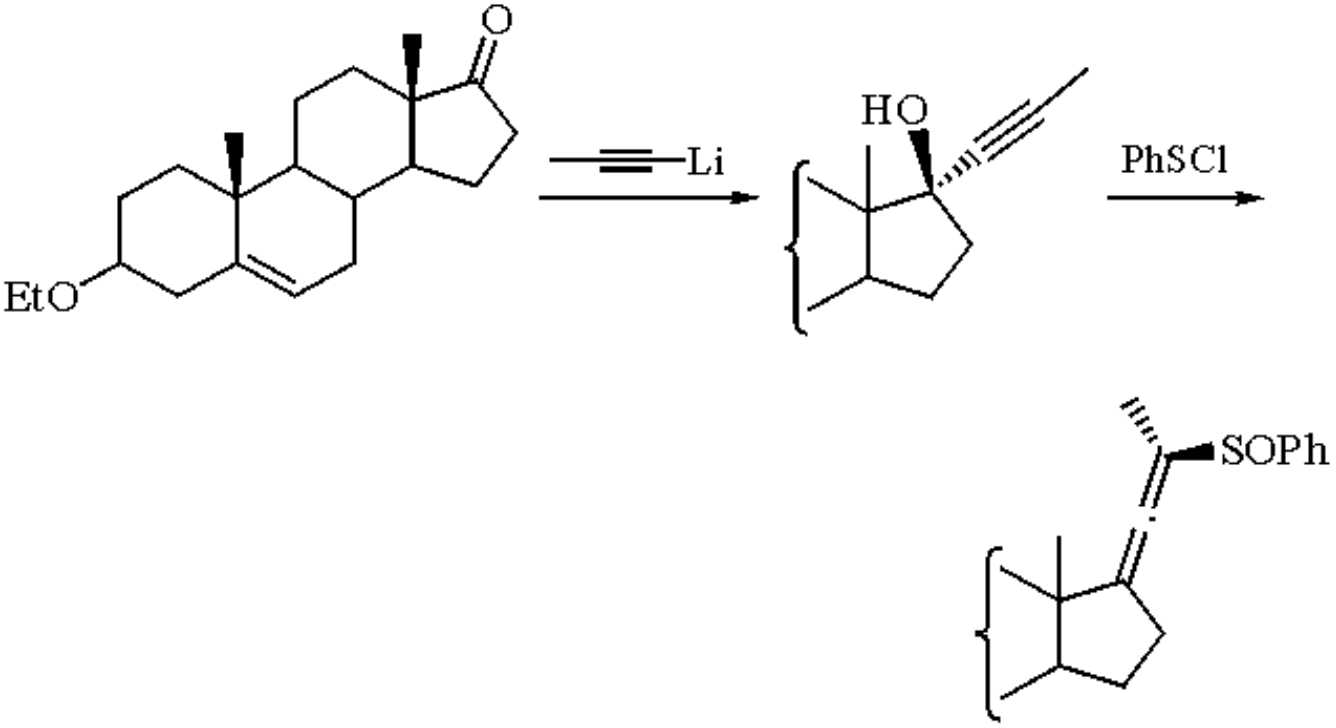

(2)

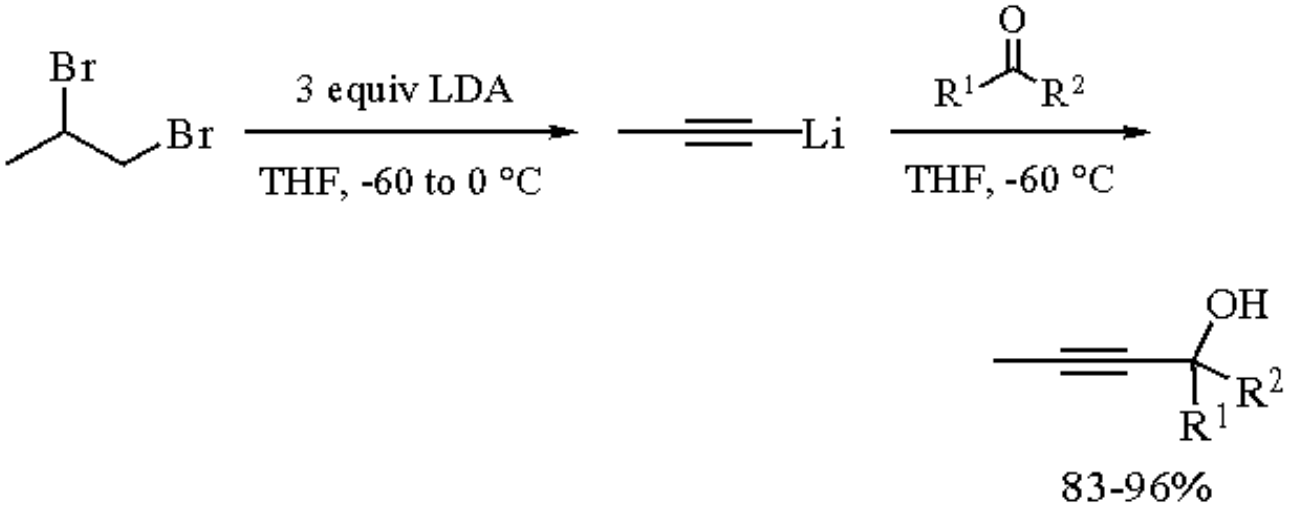

(3)

Direct methylation of the lithium alkoxide, formed from addition of propynyllithium to easily enolizable ketones such as cyclopentanone and cyclohexanone, with ***Iodomethane*** is achieved by addition of a polar cosolvent such as ***Dimethyl Sulfoxide*** (eq 4).[7] Optimum results are observed with 50 mol % of anhydrous ***Lithium Bromide*** as an additive and a ratio of hexane/THF/DMSO of 2:2:3. Alkylation of the adduct formed from propynyllithium and dimethyl squarate with a propargyl iodide gives the cyclobutenone (**1**), which undergoes thermolysis in refluxing xylene to give the methylenebenzofuran (**2**) (eq 5).[8]

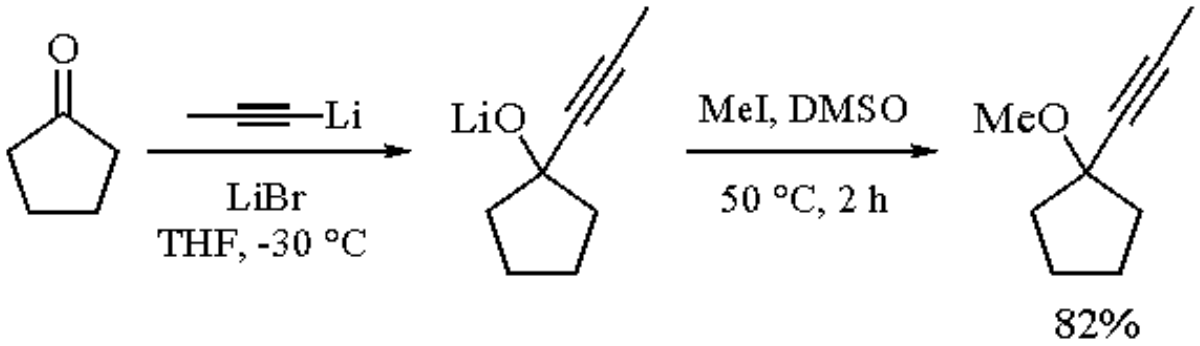

(4)

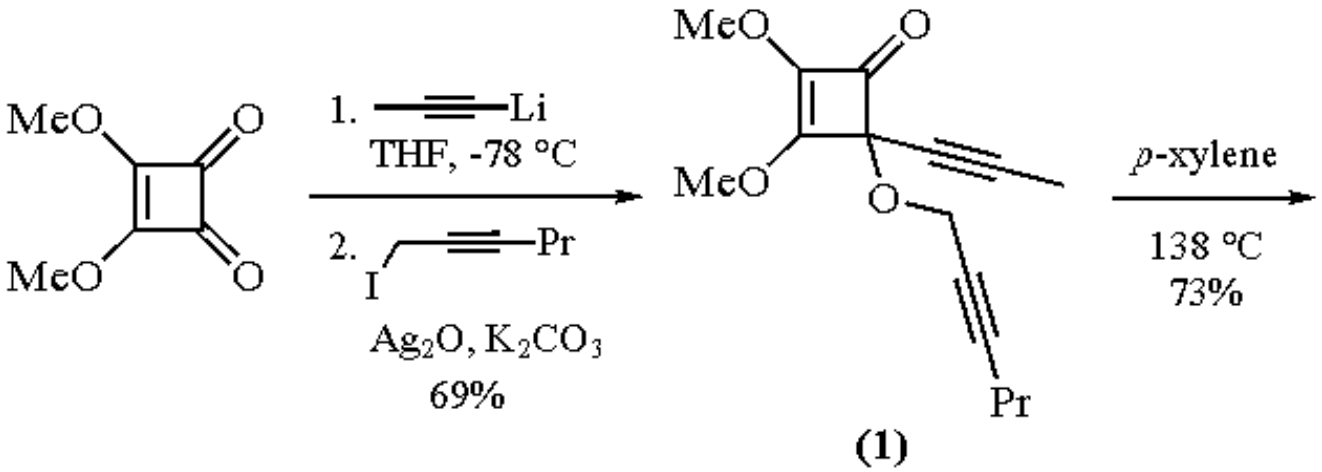

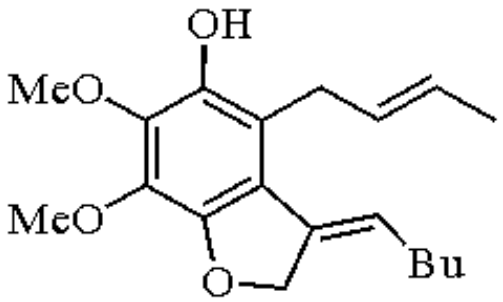

(2) (5)

Additions to Carboxylic Acid Derivatives.

Propynyllithium adds to valerolactone[9] at low temperature and to *N*,*N*-dialkyl carboxamides[10] to give the corresponding acetylenic ketones after acidic workup. ***Boron Trifluoride Etherate*** has been used to promote the coupling to elaborate the side chain of pseudomonic acid C (eq 6).[11] Alternatively, reaction with anhydrous ***Zinc Chloride*** in THF produces propynylzinc chloride, which couples smoothly with acid chlorides.[10]

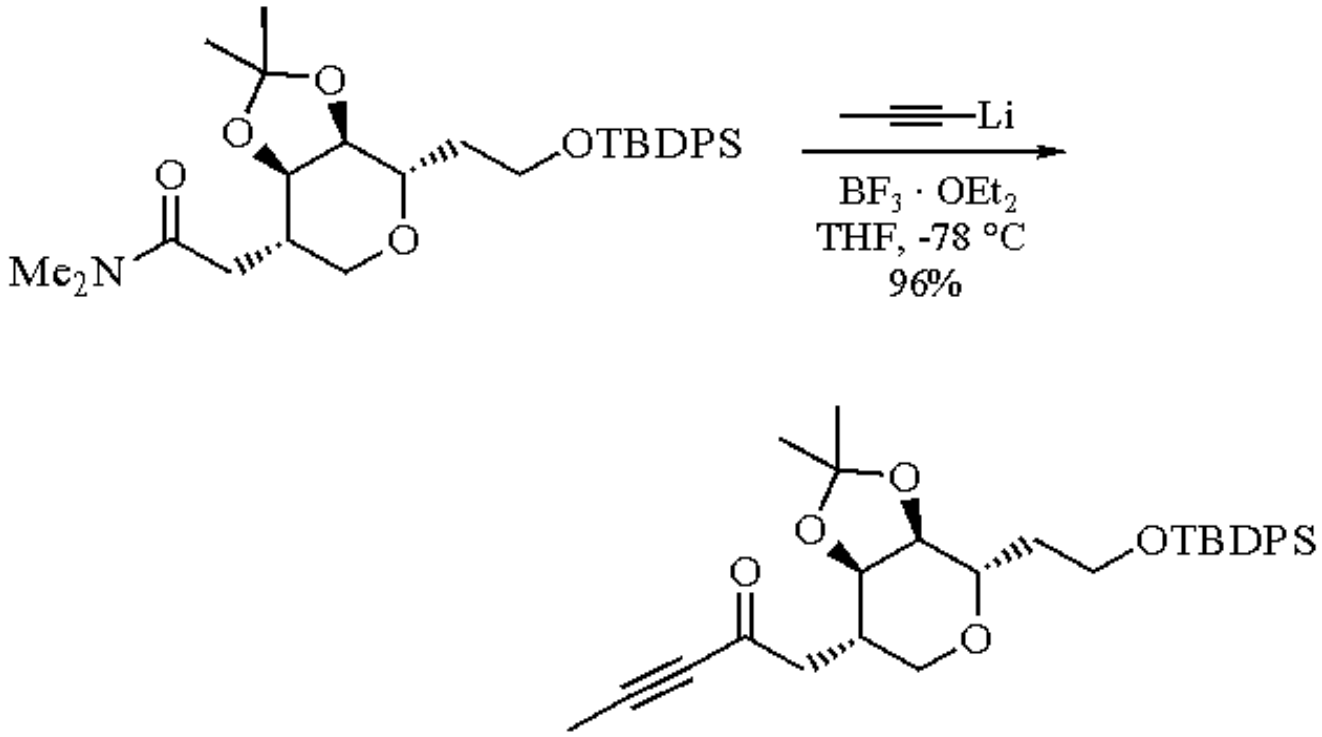

(6)

Additions to Epoxides.

Propynyllithium, generated in ether/liquid ammonia by the addition of propyne and ether to a suspension of lithium amide at -50 °C, reacts with ***Ethylene Oxide*** to give the β-hydroxyalkylated product (eq 7). The reaction is sluggish in THF or ether and fails with the sodio derivative.[3] Boron trifluoride has been used to promote epoxide opening in an approach to rifamycin (eq 8).[12]

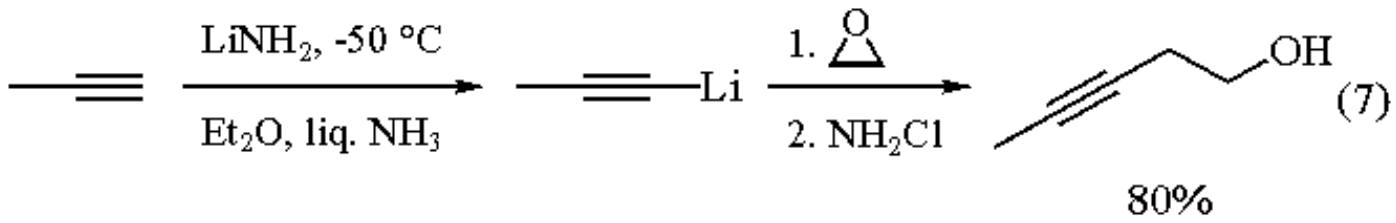

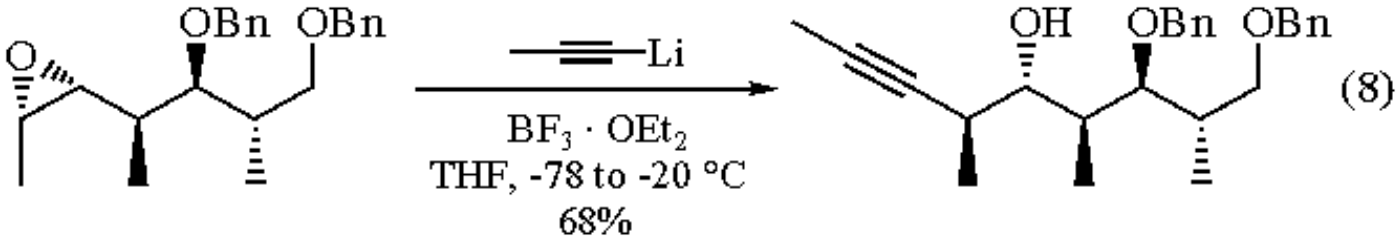

Reactions with Other Electrophiles.

Lithium 1-propynyltrialkylborates, formed by addition of propynyllithium to trialkylboranes, react with ***Trimethylsilylmethyl Trifluoromethanesulfonate*** followed by protonolysis to give allylsilanes (eq 9).[13] Propynyllithium displaces the nitro group of 3-nitro-4,5-dihydroisoxazole to give a precursor for deoxy-3-aminohexoses,[14] and reacts with the hindered aromatic chlorophosphine to give the 3*H*-phosphaallene after rearrangement (eq 10), while the less basic propynylmagnesium bromide gives the tautomeric alkynyl-1*H*-phosphine.[15] *N*,*N*-Bis(trimethylsilyl) ynamines, synthetic equivalents for primary ynamines, have been prepared by addition of propynyllithium to the crystalline hindered hydroxylamine mesitylenesulfonate (eq 11).[16]

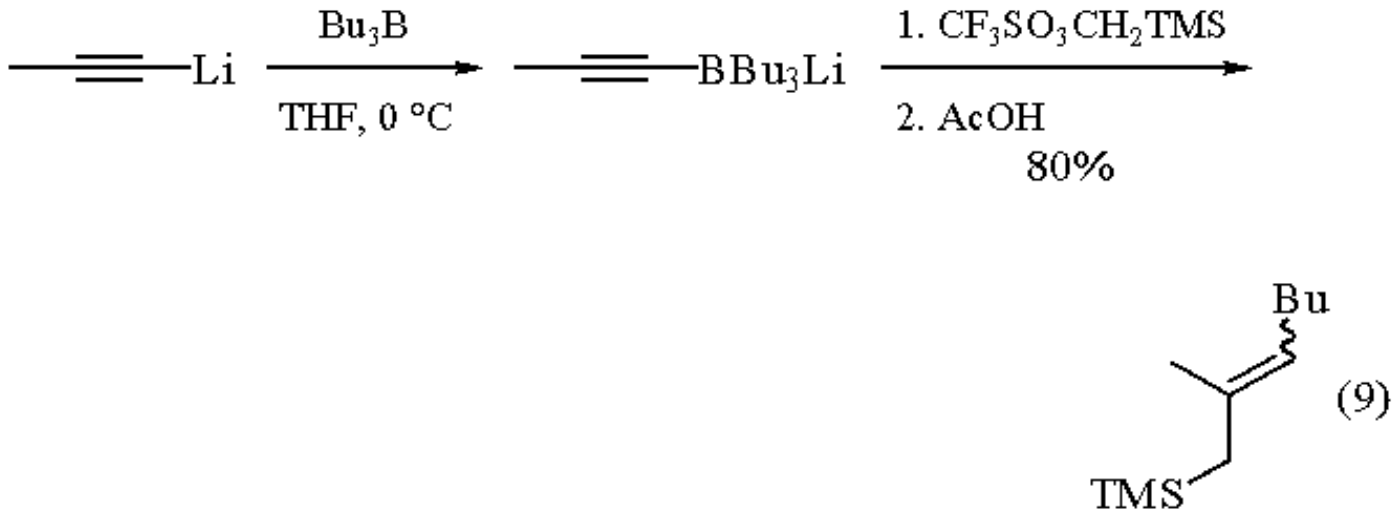

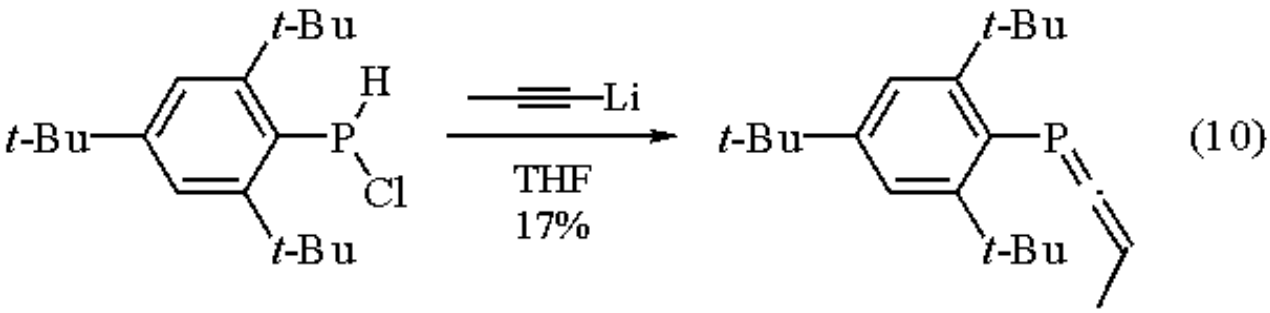

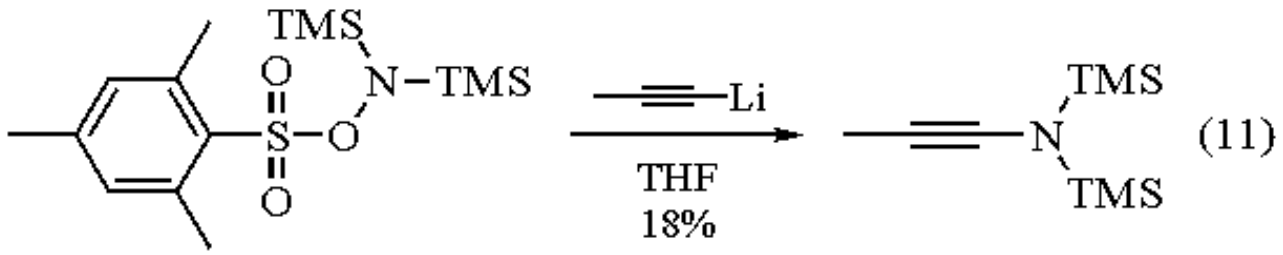

Related Reagents.

The lithium derivatives of various protected forms of propargyl alcohol display very similar reactivity. ***3-Tetrahydropyranyloxy-1-propyne***, after lithiation in THF with *n*-BuLi, selectively displaces the bromide of 1-chloro-3-bromopropane after 20 h at 70 °C[17] or couples with one end of 1,3-dibromopropane in the presence of ***Hexamethylphosphoric Triamide***.[18] The sluggishness of these alkylations has been overcome by the use of triflate as the leaving group and a mixed solvent system of THF-***N,N´-Dimethylpropyleneurea*** (6:1). Under these conditions, the TBS ether of propargyl alcohol, after lithiation, displaces the primary triflate, which is a particularly difficult substrate due to the β-oxygen functionality, in 10 min at -20 °C (eq 12).[19] The α-ethoxyethyl ether of propargyl alcohol, after lithiation in THF with *n*-BuLi, has been used in a double addition to a dione in an approach to [5]peristylane (eq 13).[20]

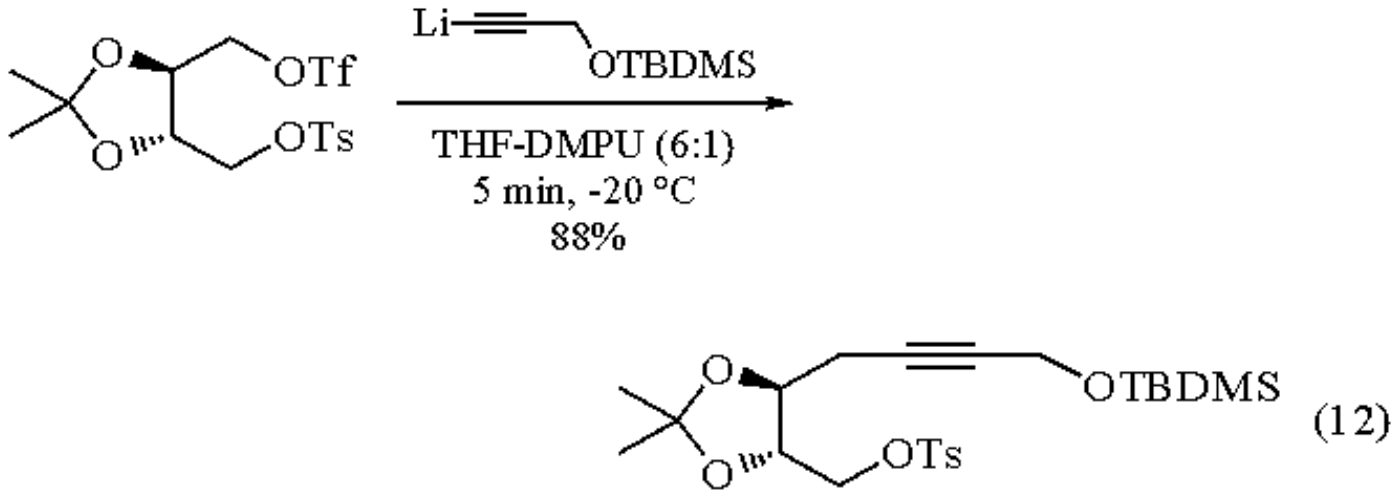

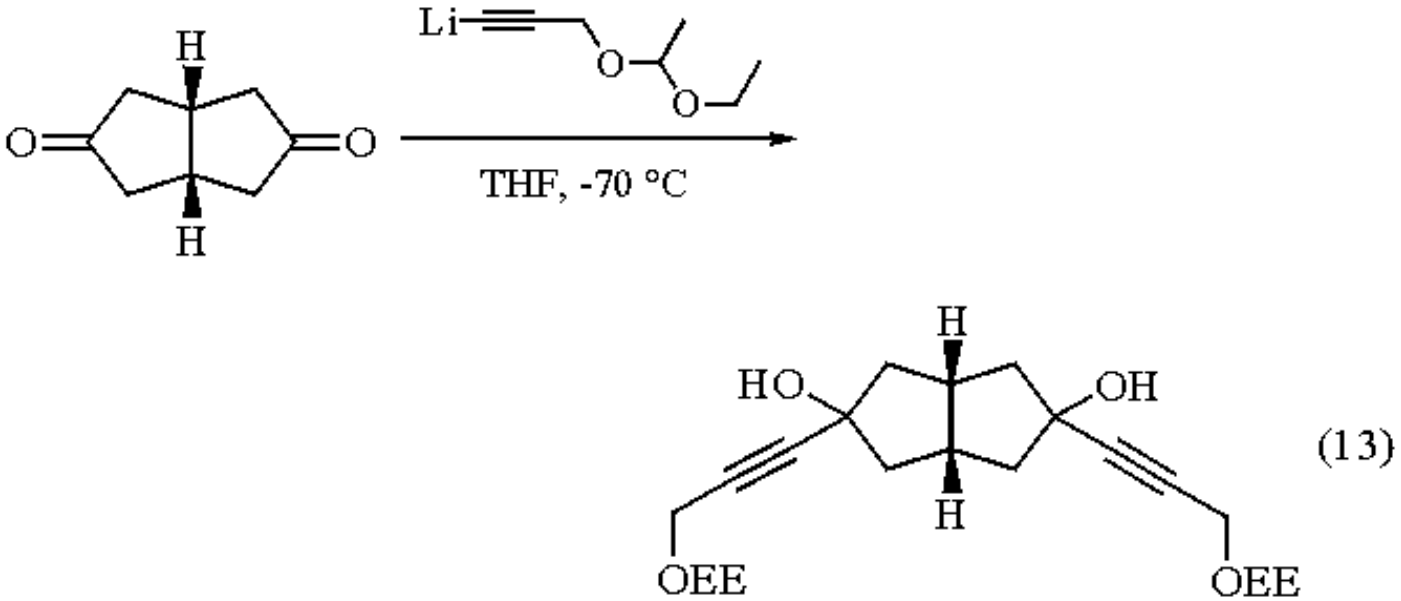

Related Reagents.

3-Chloro-1-propynyllithium; ***1-Lithio-3-trimethylsilyl-1-propyne***; ***Lithium Acetylide***; ***Lithium (Trimethylsilyl)acetylide***; ***Propynylmagnesium Bromide***.

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Propynylmagnesium Bromide[1]

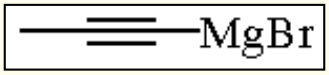

[32423-84-0] · C_3H_3BrMg · Propynylmagnesium Bromide · (MW 143.27)

(powerful nucleophilic source of the propynyl unit for many electrophiles)

Solubility: sol THF, ether.

Form Supplied in: green viscous oil in ethereal solution; prepared in situ and used directly.

Preparative Method: prepared in situ by bubbling dried propyne through a solution of ***Ethylmagnesium Bromide*** in refluxing ether[2] or THF[3] at room temperature.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture.

Additions to Carbonyl Compounds.

Propynylmagnesium bromide adds readily to aldehydes[2] and ketones to give the corresponding secondary and tertiary alcohols. Addition of the optically active 2-chromanylacetaldehyde to propynylmagnesium bromide in ether gives a 2:1 mixture of the corresponding alcohols (eq 1).[4] Intramolecular Diels-Alder/retro-Diels-Alder reactions of alkynones, prepared by propynylmagnesium bromide addition to aldehydes and Swern oxidation (see ***Dimethyl Sulfoxide-Oxalyl Chloride***) of the resulting alcohols, give ring-fused thiophene derivatives (eq 2).[5] Stereoselective addition to the *exo* face of a norbornenone is observed with only 4% of the minor isomer being formed (eq 3).[6] Chelation-controlled addition to the β-alkoxy enone gives the (*R*) enantiomers of both geometric isomers with only traces of the diastereoisomers (eq 4), whereas addition of ***Propynyllithium*** to the corresponding aldehyde is less selective.[3] ***Lithium Aluminum Hydride*** reduction of the propargylic alcohol, generated by addition of propynylmagnesium bromide to α-chlorocyclohexanone, is accompanied by migration to give the homoallylic alcohol (eq 5).[7]

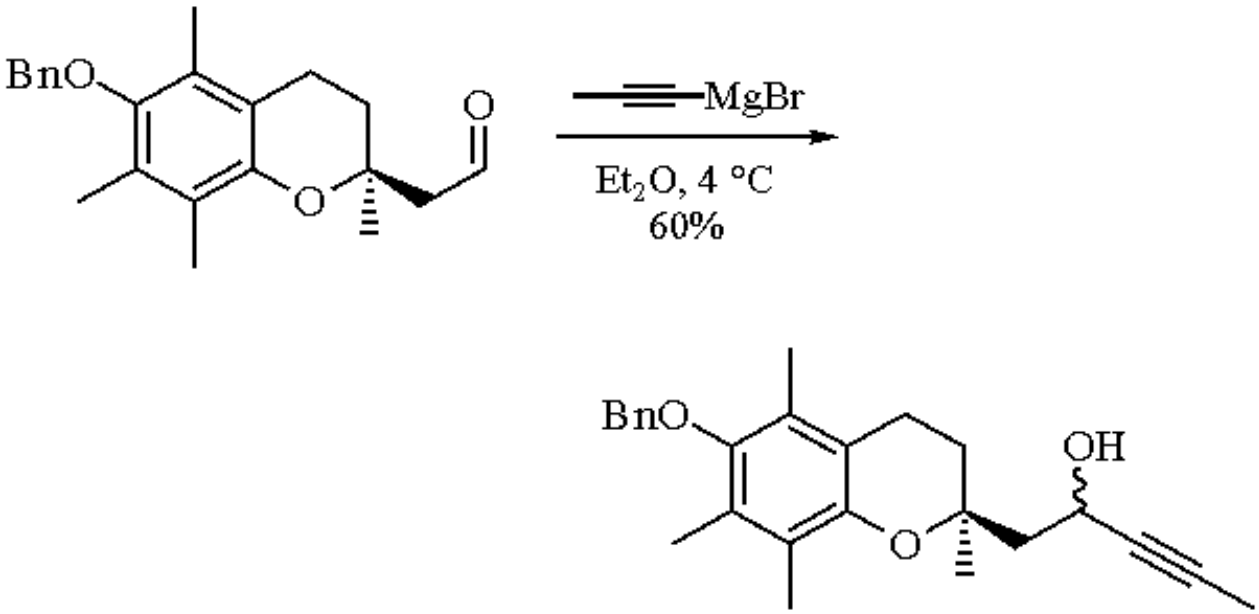

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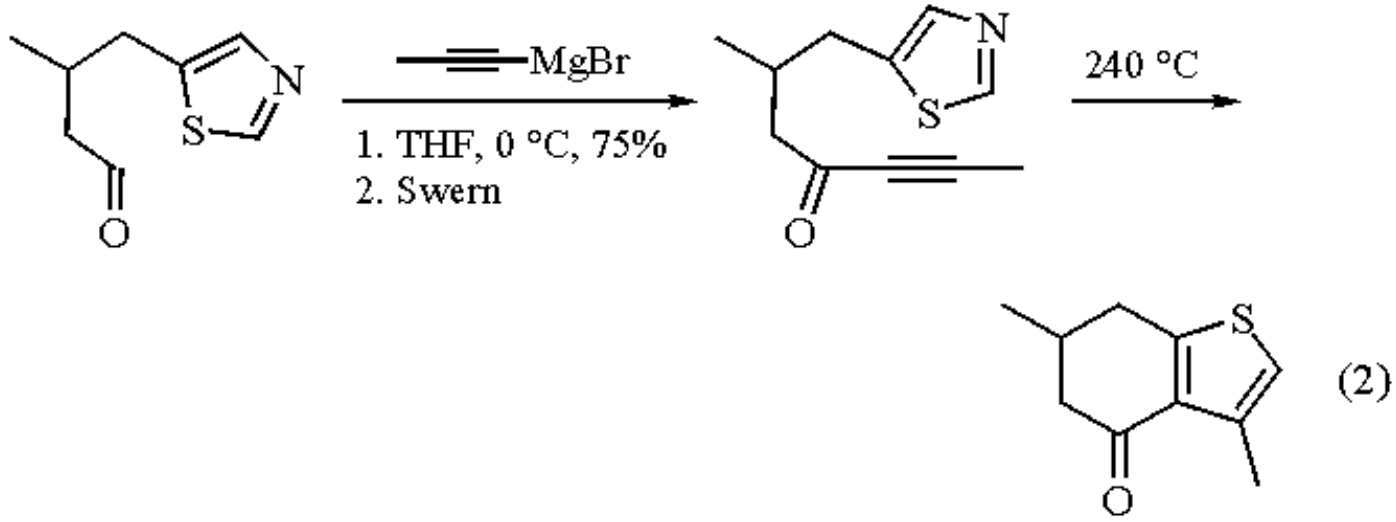

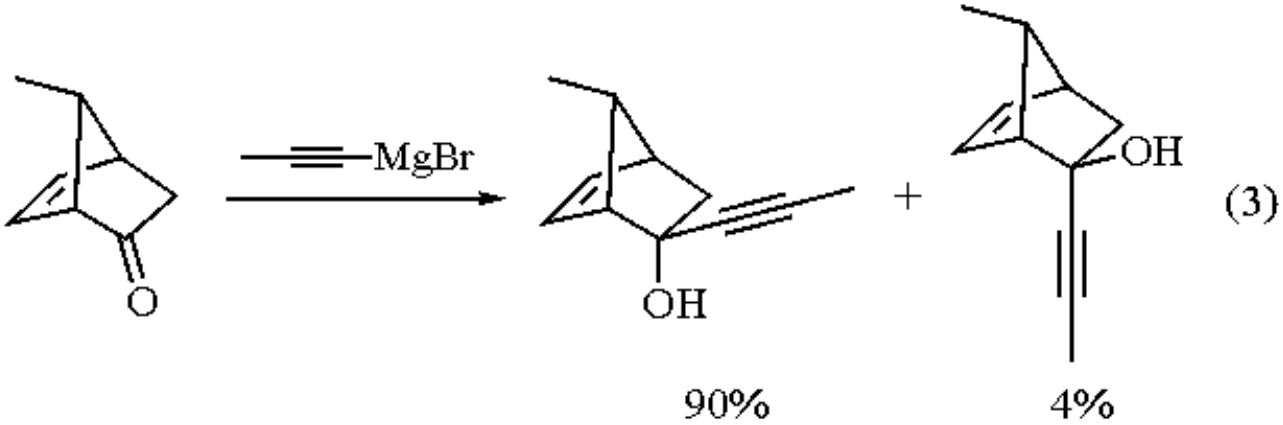

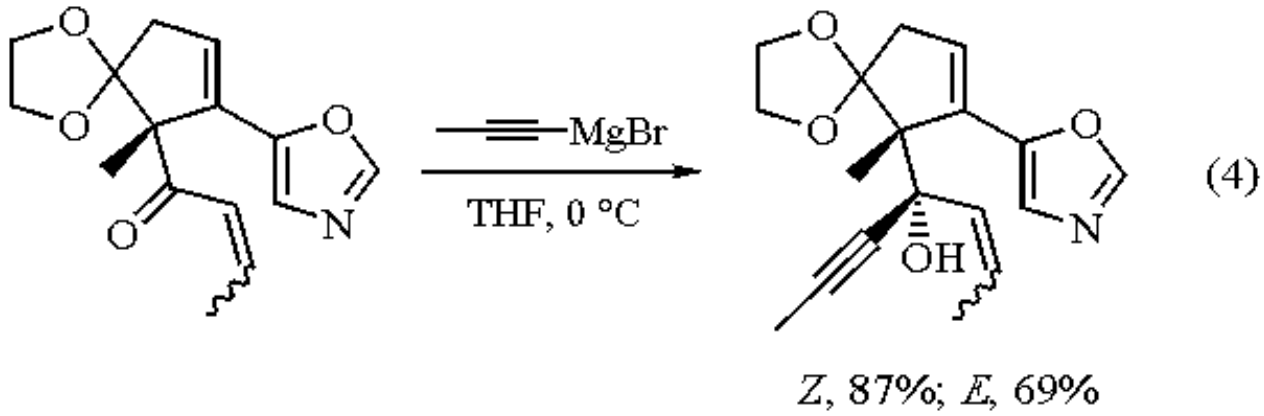

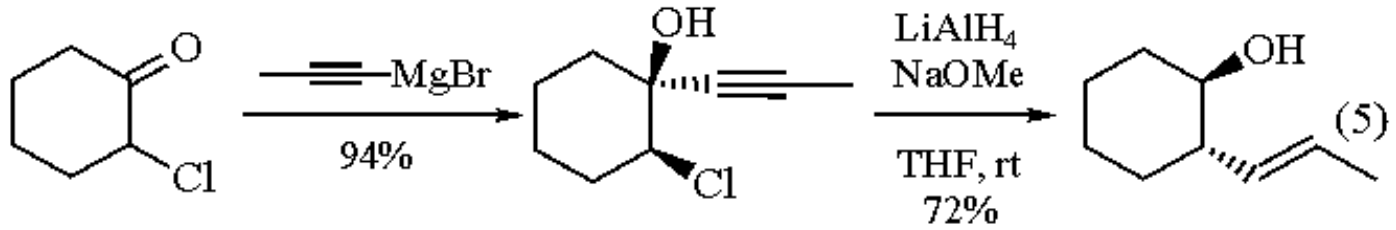

Alkylations of Alkyl Halides.

α-Chlorination of cyclic sulfides with ***N-Chlorosuccinimide*** gives the corresponding chlorides, which react with propynylmagnesium bromide to give the propargylic sulfides. Sulfonium salt formation followed by treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) causes a ring expansion via [2,3]-sigmatropic rearrangement to the diene (eq 6).[8] In a related transformation, propynylmagnesium bromide couples with a cationic glycine equivalent to give the α-alkynic amido ester free from allenic products (eq 7).[9]

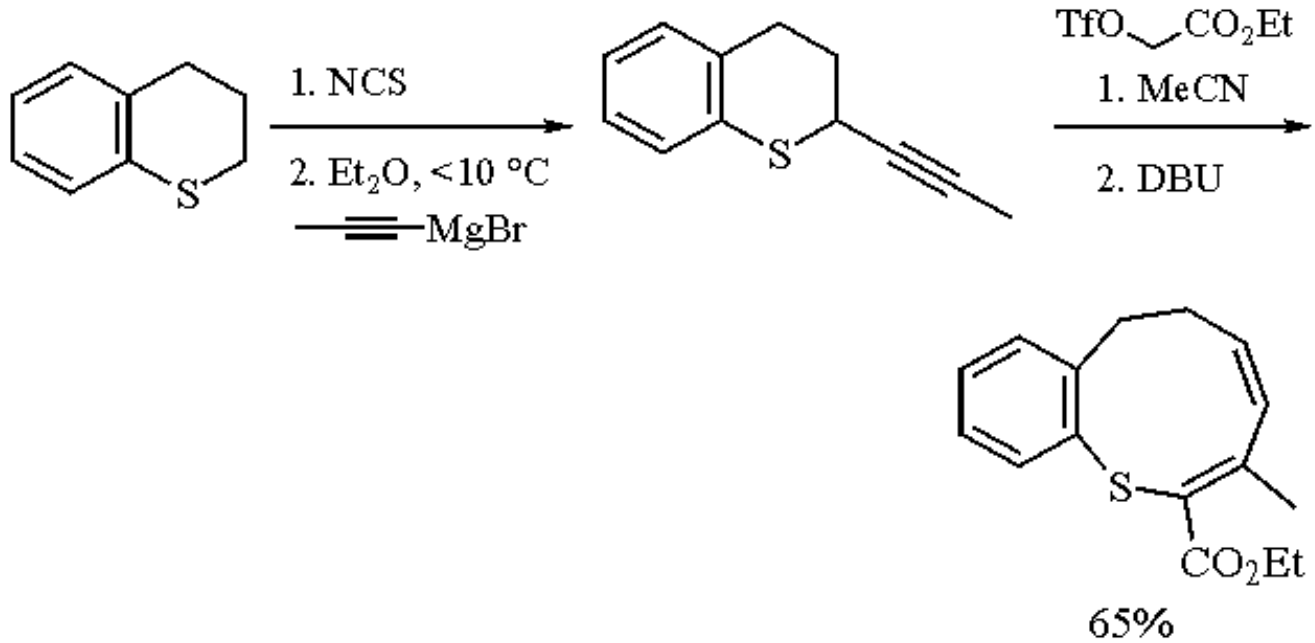

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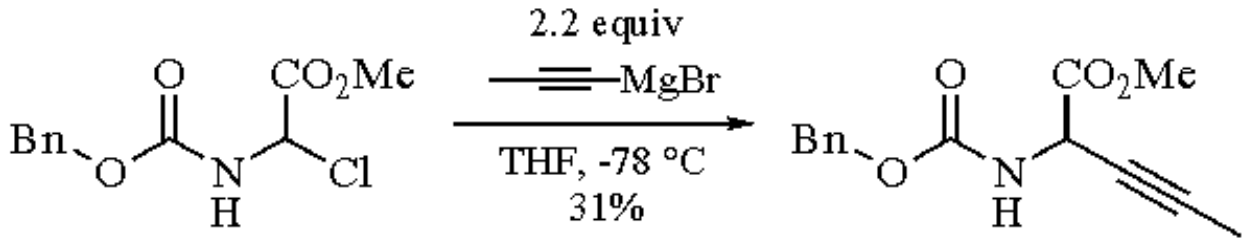

(7)

Reactions with Other Electrophiles.

Enynes can be prepared by a double ring contraction sequence which involves reaction of propynylmagnesium bromide with cyclooctatetraene oxide to give the cycloheptatrienyl alcohol and subsequent dehydration with ***Thionyl Chloride*** (eq 8).[10] Activation of ***Pyridine*** by reaction with ***Methyl Chloroformate*** facilitates addition of propynylmagnesium bromide to the resulting iminium salt (eq 9).[11] Propynylmagnesium bromide reacts with the hindered aromatic chlorophosphine to give the alkynyl-1*H*-phosphine by direct substitution (eq 10), while the more basic propynyllithium gives the tautomeric 3*H*-phosphaallene.[12]

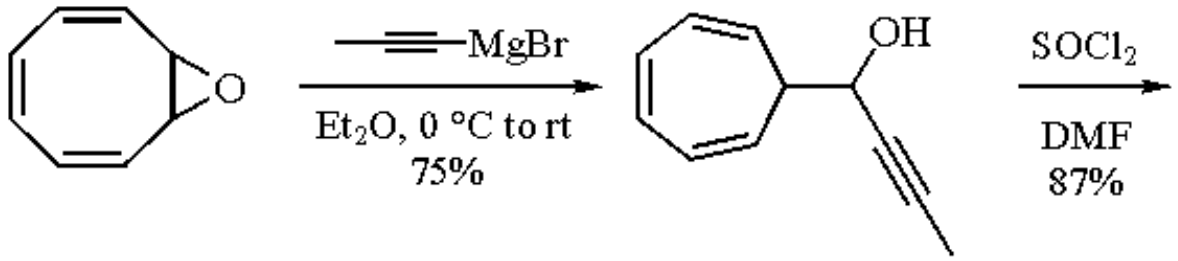

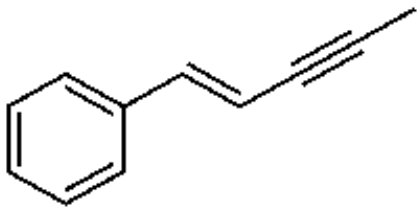

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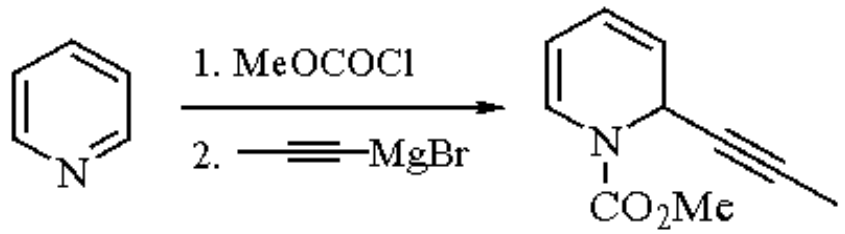

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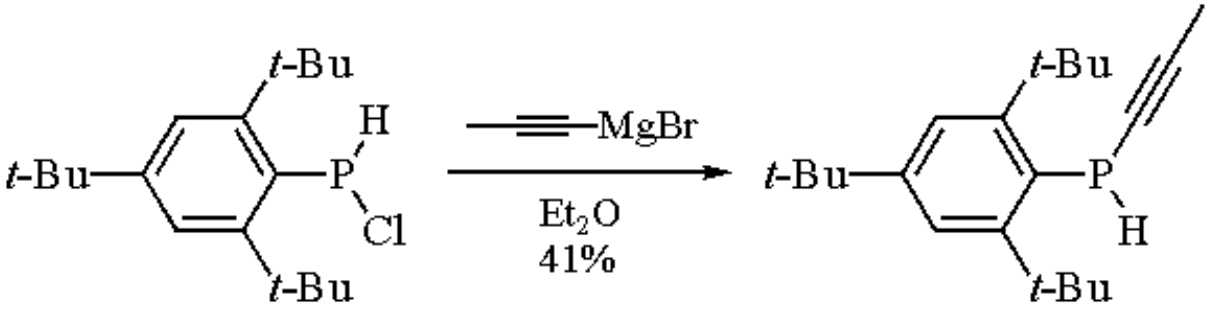

(10)

Related Reagents.

Ethynylmagnesium Bromide; ***Propynyllithium***.

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1*H*-Pyrazole-1-carboxamidine Hydrochloride

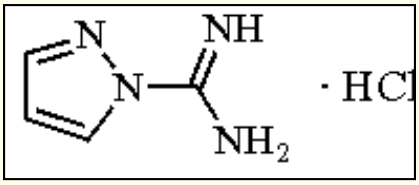

[4023-02-3] · $C_4H_7ClN_4$ · 1*H*-Pyrazole-1-carboxamidine Hydrochloride · (MW 146.60)

(electrophilic agent capable of specific reaction with nitrogen nucleophiles such as amines and hydrazines, yielding substituted guanidines and aminoguanidines by displacement of pyrazole;[1,2] synthesis of substituted *s*-triazines[1,3])

Alternate Name: 1-guanylpyrazole hydrochloride.

Physical Data: mp 167-168 °C.

Solubility: insol ether, hexane; very sol H_2O, DMF, alcohol; in the presence of 1 equiv ***Diisopropylethylamine*** (free base), very sol (>1.5 M) DMF, H_2O, and alcohol, and sol CH_2Cl_2, $CHCl_3$, THF, acetone, and acetonitrile; the free base is slightly sol EtOAc, ether.

Form Supplied in: nonhygroscopic, white crystalline solid.

Preparative Method: to a mixture of pyrazole (0.36 mol) ***Cyanamide*** (0.36 mol), and 320 mL of *p*-dioxane is added 95 mL of 4 N HCl in *p*-dioxane. The mixture is gradually warmed to 55-60 °C with mechanical stirring under N_2. After about 1 h the product crystallizes and the mixture is cooled to rt. Ether (100 mL) is added with stirring and the product is collected by filtration, washed with ether, and dried in vacuo, yielding 51.2 g (97%).

Handling, Storage, and Precautions: indefinitely stable (at least two years) at rt in a tightly sealed bottle. Cool, dry, and dark conditions are recommended for long term storage. The toxicological properties are not known, but pyrazole is considered a possible teratogen. Use in a fume hood.

Synthesis of Substituted Guanidines.

1*H*-Pyrazole-1-carboxamidine (**1**) reacts with many amines and hydrazines at room temperature under a variety of conditions to give substituted guanidines in good yields (eq 1).[1,2] In this context, the carboxamidine (**1**) is significantly more reactive than 3,5-dimethylpyrazole-1-carboxamidine nitrate[4] and other commercially available guanylating agents (see also ***Cyanamide***, ***O-Methylisourea***, and ***S-Methylisothiourea***).[2] Because of its superior reactivity, good solubility properties, stability, and ease of preparation, the carboxamidine (**1**) is the guanylating agent of choice for many applications, including solid-phase peptide synthesis of arginine-containing peptides by quantitative guanylation of the δ-amino group(s) of ornithine-containing precursor sequences.[2] The general use of the guanylating agent (**1**) for the preparation of various arginine peptides by such a strategy (eq 2) in this author's laboratory has not yet necessitated the evaluation of commercially unavailable ***Aminoiminomethanesulfonic Acid***,[5,6] with questionable stability[7] and solubility properties, as an alternative guanylating agent for this purpose.

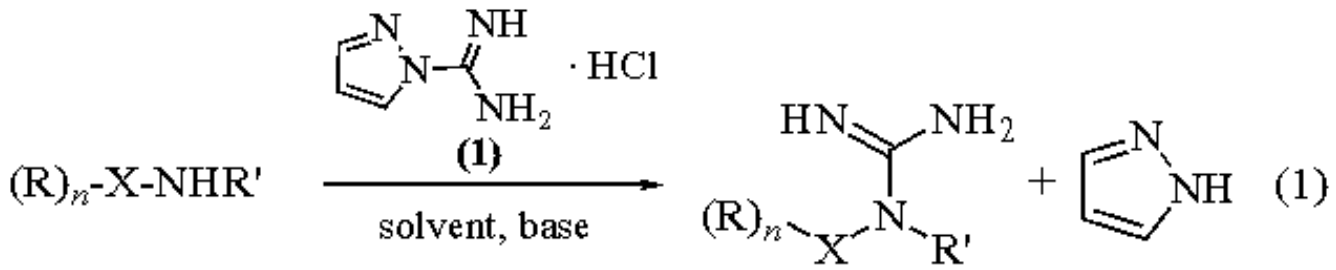

X = CH_2, CH, C, NH
R = aryl, alkyl, H
R' = aryl, alkyl, H

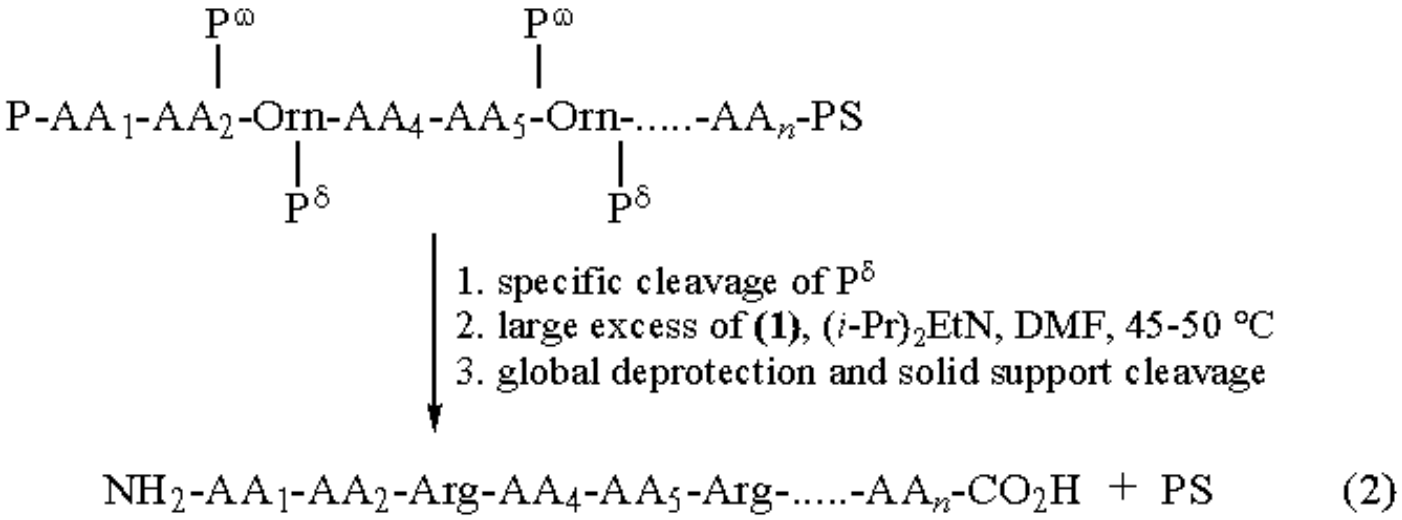

$AA_1....AA_n$ = arbitrary amino acids
P = α-amino protecting group
P^{ω} = ω-side chain protecting group
P^{δ} = δ-amino protecting group
PS = polystyrene solid support

For amine guanylation, the reactivity of the carboxamidine (**1**) appears to be limited to primary, secondary, and aryl amines that are not deactivated by steric, electronic, or resonance effects. For example, guanidine products cannot be obtained from diisopropylamine, dicyclohexylamine, 2,2,2-trifluoroethylamine, *p*-nitroaniline, and α- or β-naphthylamine. In these cases only the diguanidine (**2**), formed by slow self condensation of (**1**), can be isolated (eq 3).[2] The diguanidine (**2**) also slowly forms at room temperature in the presence of tertiary amines and is unreactive with cyclohexylamine at room temperature.[2]

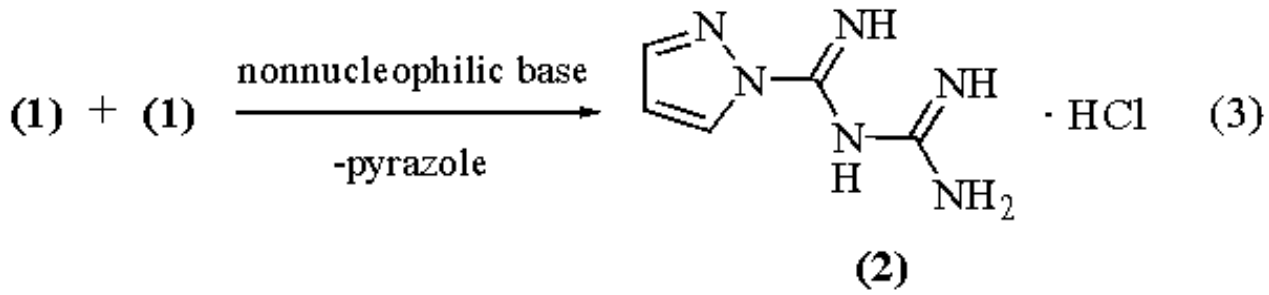

Modification of Proteins.

Like 3,5-dimethylpyrazole-1-carboxamidine nitrate, the carboxamidine (**1**) in aqueous buffer can guanylate the ε-amino groups of lysine residues (and to a lesser extent the *N*-terminal α-amino group) in proteins to produce homoarginine residues.[8] The extent of guanylation by these reagents depends on molar ratio, concentrations, pH, temperature, and time.[8] These reagents are particularly suitable

when extensively modified proteins are desired. For more specific, less extensive lysine modification, the use of other less reactive, water soluble reagents may be advantageous.

Synthesis of *N,N´*-Disubstituted and Diprotected Guanidines.

The *N*-allyl derivative (**3**) of the reagent (**1**) has been prepared (eq 4)[9] and, although less reactive, has been found to react slowly, specifically and essentially completely at room temperature with the δ-amino group of L-ornithine (eq 5) to allow facile isolation of N^G-allyl-L-arginine (**4**) in 70% yield.[9] This result suggests that other *N,N´*-dialkylguanidines may be obtainable via the appropriate *N*-alkyl derivatives of the reagent (**1**).

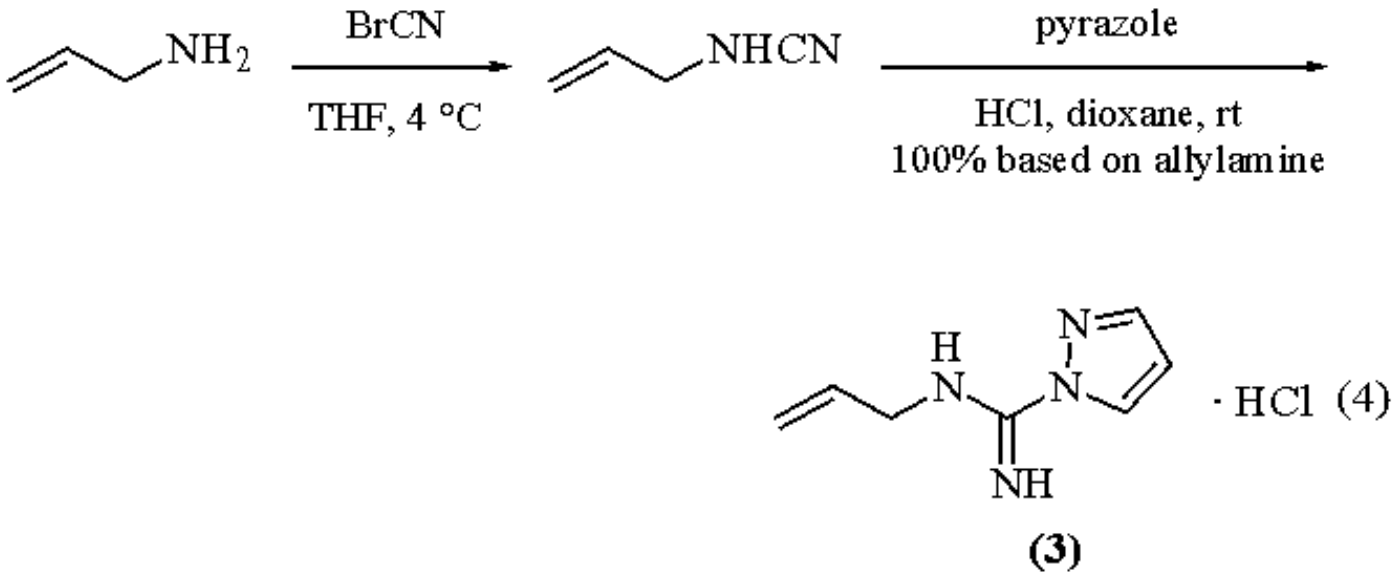

The *N,N´*-bis-Cbz and bis-Boc derivatives (**5a,b**) of the carboxamidine (**1**) have been recently prepared in good yields by two sequential acylations (eq 6).[10,11] These derivatives are substantially more reactive than the parent carboxamidine (**1**) and react readily with aniline and 2,2,2-trifluoroethylamine at room temperature to give *N,N´*-bis-protected guanidines that can be smoothly deprotected under typical conditions to provide otherwise inaccessible monosubstituted guanidines in good yields (eq 7).[10] Although the *N,N´*-bis-urethane-protected carboxamidines (**5a,b**) fail to guanylate diisopropylamine and dicyclohexylamine,[10] they nonetheless represent a valuable and complementary alternative to the use of the reagent (**1**) when the guanylation of relatively nonnucleophilic amines under mild conditions is required, they also provide more flexibility in the formulation of synthesis schemes targeting complex guanidine-containing molecules. Alternative reagents reported for the preparation of *N,N´*-bis-Boc-guanidines from amines are *N,N´*-bis-Boc-thiourea[12] and *N,N´*-bis-Boc-*S*-methylisothiourea.[13]

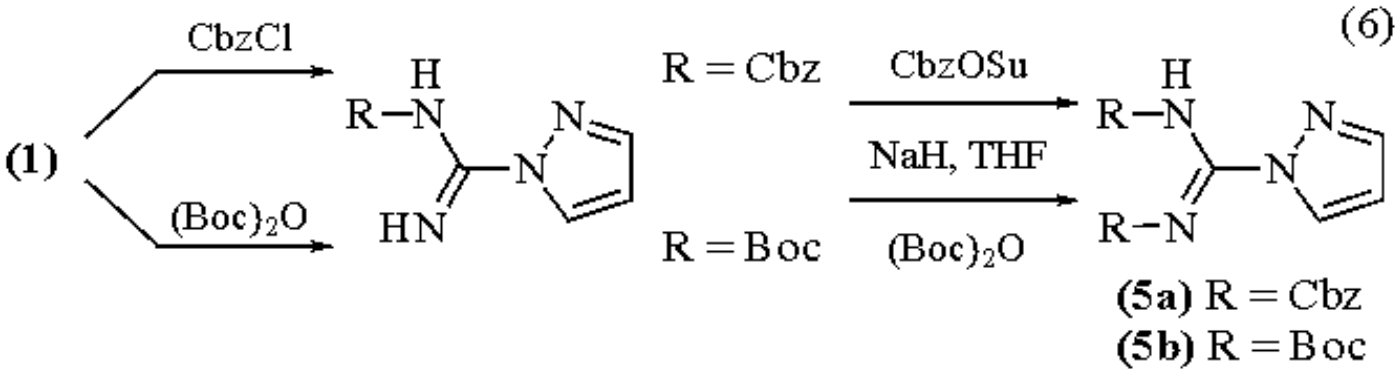

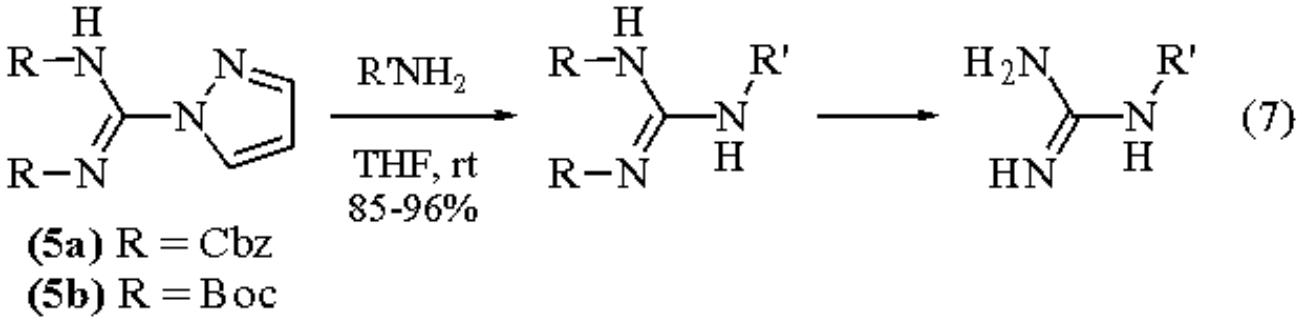

Synthesis of 2-Amino-Substituted *s*-Triazines.

The carboxamidine (**1**) reacts readily with ***1,3,5-Triazine*** yielding 2-(pyrazol-1-yl)-*s*-triazine (**6**) which reacts with ***Ammonia***, many amines, and ***Hydrazine*** to produce 2-monosubstituted *s*-triazines (**7**) in good yields (eq 8).[1,3]

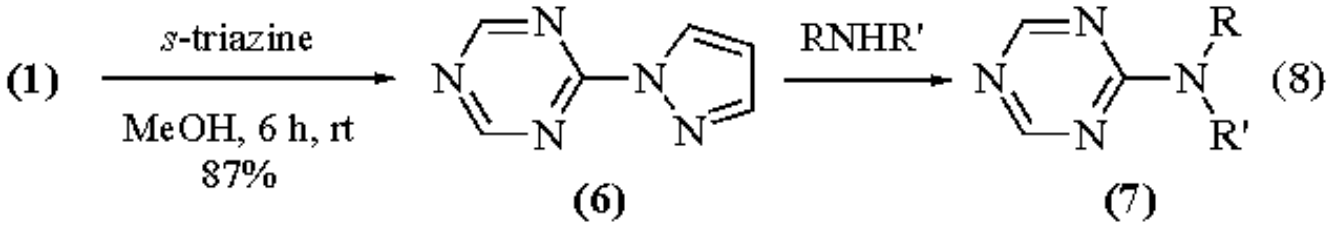

Related Reagents.

Aminoiminomethanesulfonic Acid; ***Diphenyl Cyanocarbonimidate***; ***S-Methylisothiourea***; ***O-Methylisourea***.

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Pyridine

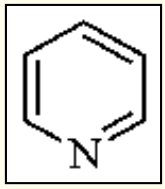

[110-86-1] · C_5H_5N · Pyridine · (MW 79.11)

(weak base useful as acid scavenging solvent or catalyst, especially for condensation,[1] dehalogenation,[2] halogenation,[3] and acylation[4] reactions)

Physical Data: [5] bp 115.3 °C; mp -41.6 °C; forms azeotropic mixture with water, bp 93.6 °C (41.3 wt % H_2O); steam volatile; *d* 0.9830 g cm^{-3} at 20 °C; pK_a 5.22 (in H_2O at 20 °C).

Solubility: miscible water, alcohol, ether, petroleum ether, and numerous other organic solvents.

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: titration, GLC.

Purification: distillation.

Handling, Storage, and Precautions: flammable solvent with flash point 20 °C; hygroscopic; LD_{50} rat (oral) 891 mg kg^{-1};[5] minimum detectable odor 0.012 ppm;[5] incompatible with acids, acid chlorides, oxidizing agents, and chloroformates.[6]

Use as a Base in Condensation Reactions.

Pyridine can be used as a base in cyclocondensation reactions. When the reaction of 2-acylphenoxyacetic acids in acetic anhydride is carried out in the presence of pyridine, formation of benzofuran-2-carboxylic acids is preferred. When weaker bases such as sodium acetate or sodium formate are used for the reaction, mixtures of benzofurans and benzofuran-2-carboxylic acids are produced, with the benzofuran derivatives as the major products.[7] For example, 2-acetyl-4-nitrophenoxyacetic acid (**1**) gives 65% 3-methyl-5-nitrobenzofuran-2-carboxylic acid (**2**) and 25% 3-methyl-5-nitrobenzofuran (**3**) when treated with ***Acetic Anhydride*** in pyridine. The same reaction in the presence of sodium acetate instead of pyridine gives a reversal of products with (**2**) as the minor product (33%) and (**3**) as the major product (60%) (eq 1).

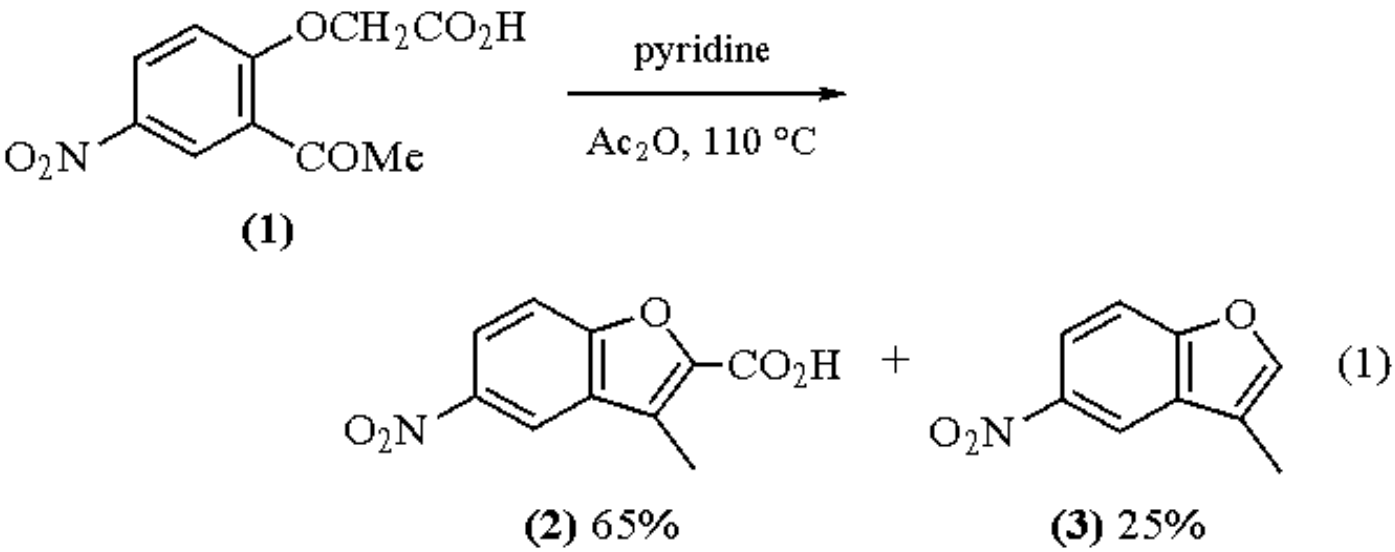

Pyridine has been used effectively as a catalyst in the Knoevenagel condensation reaction.[8] Depending upon the nature of the base employed, the product selectivity can be altered. Different stereochemistry has been observed for aromatic heterocyclic bases such as pyridine and aliphatic tertiary amines such as ***Triethylamine***. Reaction of hexanal (**4**) with ***Malonic Acid*** (**5**) in the presence of pyridine as the base gives the α,β-unsaturated acid (**6**) as the major product (91:9 α,β:β,γ). When bases such as triethylamine are used in the reaction, a higher overall yield is obtained (76%); however, the corresponding β,γ-unsaturated acid (**7**) is the predominant product[1] (2:98 α,β:β,γ) (eq 2). One factor that appears important in determining the product ratio is the steric hindrance of the base. Pyridine, without the steric hindrance, shows a definite preference for the α,β-unsaturated carboxylic acid.

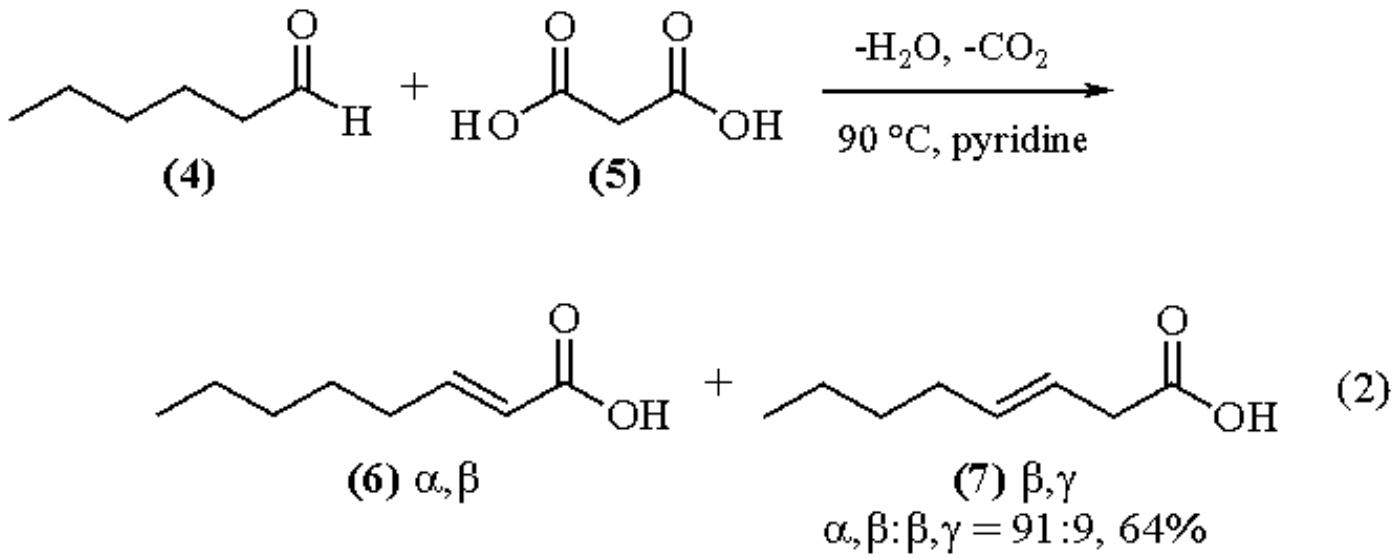

Condensation of furfural (**8**) with malonic acid (**5**) in the presence of pyridine affords an excellent yield of furylacrylic acid (**9**) (eq 3).[9] Similarly, condensation of *m*-nitrobenzaldehyde with malonic acid proceeds in the presence of pyridine as catalyst.[10]

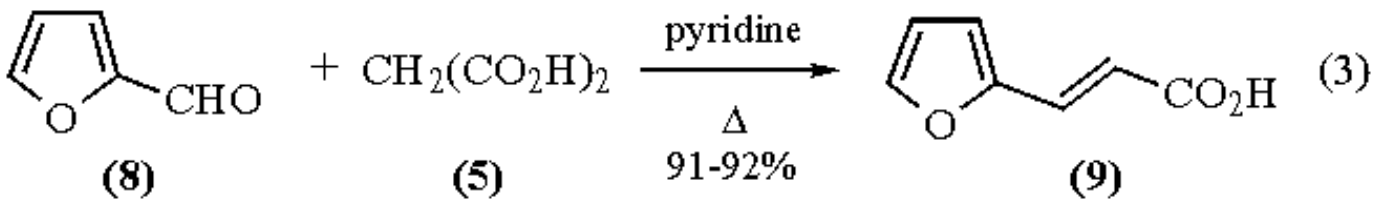

Yield improvements in the Knoevenagel condensation reaction have been obtained when the reaction is carried out in the presence of ***Titanium(IV) Chloride*** and pyridine in either tetrahydrofuran or dioxane solvent.[11] For example, the condensation of ***Acetaldehyde*** (**10**) with ***Diethyl Malonate***, (**11**) affords an 86% yield of product (**12**), as compared to a 25% yield without the promoter (eq 4).[8,12]

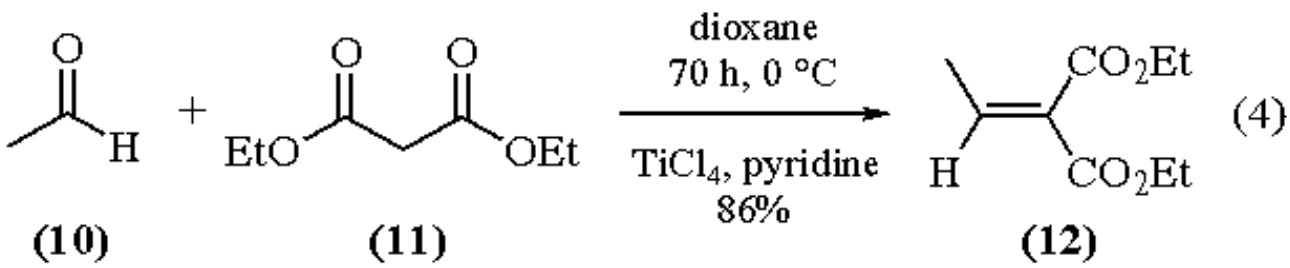

Condensation of carboxylic acids with amines in pyridine in the presence of a phosphorous(III) acid/iodine complex is an effective method for the synthesis of amides (eq 5).[13] Pyridine acts as a base and a solvent in this reaction.

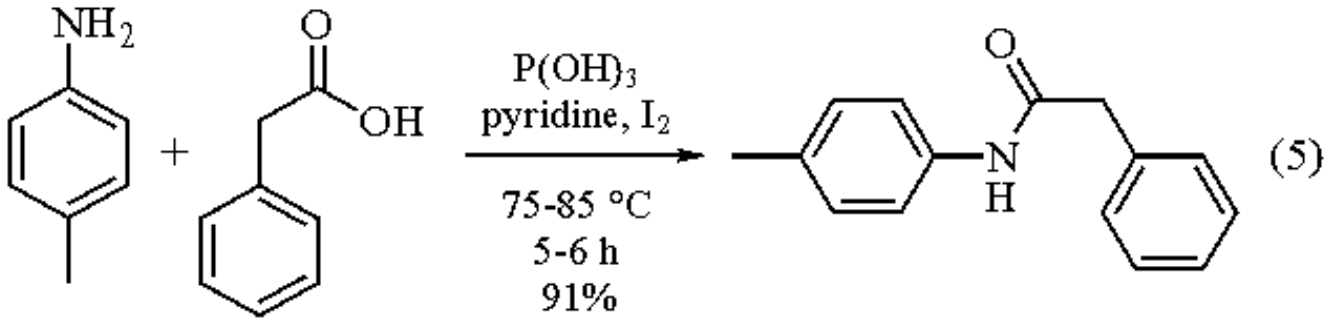

Organoaluminum compounds such as ***Diisobutylaluminum Phenoxide*** with pyridine are good reagents for the regioselective aldol condensation of methyl ketones.[14] This system works effectively with pyridine acting as a base to inhibit undesirable proton transfer reactions (eq 6). Commonly used methods such as formation of the silyl enolate are not practicable here since they do not undergo regioselective attack on the methyl side of the ketone. Cross-aldol condensation reactions can also be carried out regiospecifically in the presence of a tertiary amine such as pyridine or ***2,6-Lutidine***.[15]

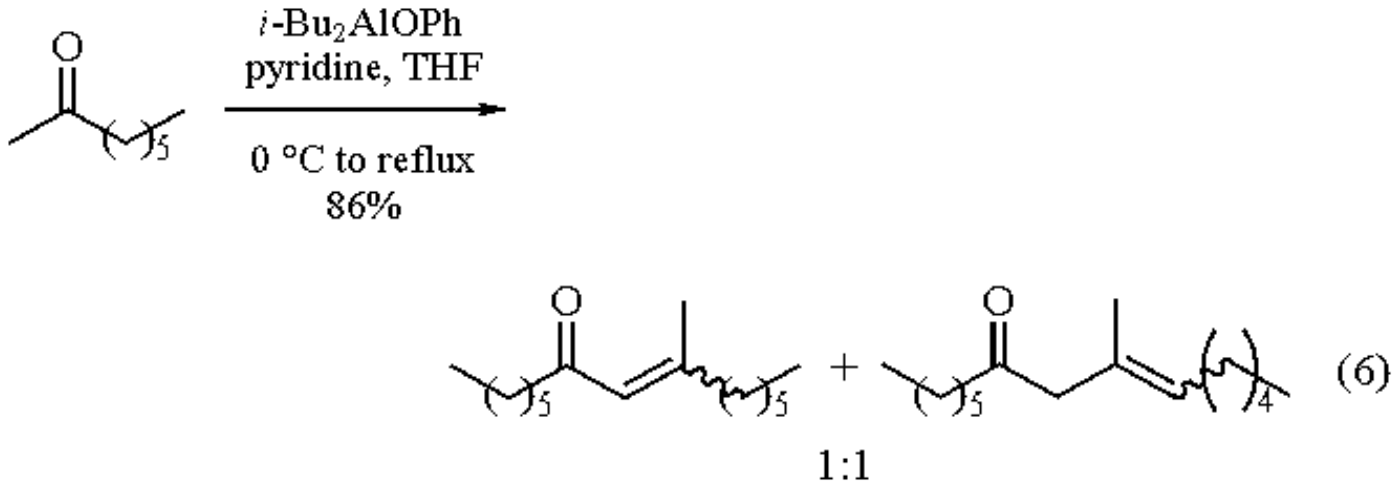

Oxidation Reactions.

An extensive amount of research has been carried out on the Gif system, and related systems, for the selective oxidation of saturated hydrocarbons. Pyridine is commonly used as a solvent in these reactions which involve a metal-catalyzed oxidation using ***Hydrogen Peroxide*** in a pyridine-acetic acid solvent system (eq 7). Copper, zinc, and iron are commonly used in the reactions.[16-19] Conversions are typically in the range of 10-25%; however, the selectivities are nearly quantitative.

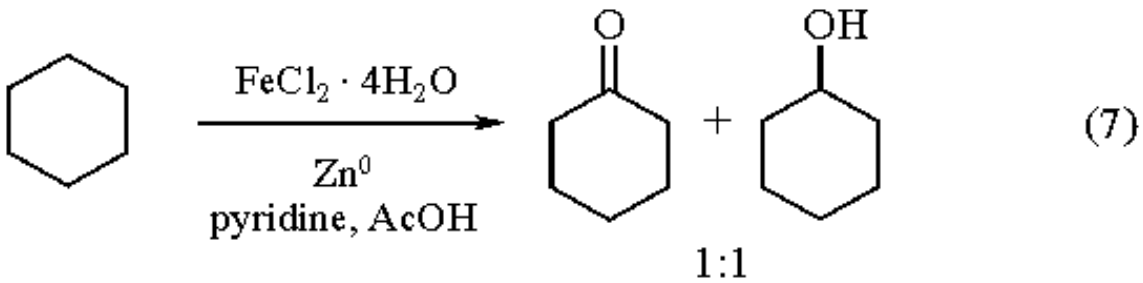

Oxidation reactions of alcohols by ***Lead(IV) Acetate*** can be accelerated in the presence of pyridine. A kinetic study of this reaction has been carried out by Banerji using benzyl alcohol (**13**) as substrate (eq 8).[20]

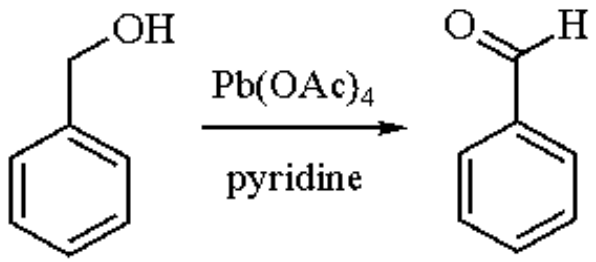

(8)

(13)

Oxidation of alcohols can also be effectively carried out using ***Chlorine*** in pyridine to give aldehydes and ketones. Secondary alcohols can be selectively oxidized in the presence of primary alcohols.[21] For example, treatment of 5β-cholestane-3β,19-diol (**14**) with chlorine and pyridine affords selective oxidation to 19-hydroxy-: 5β-cholestan-3-one (**15**) in almost quantitative yield (eq 9).

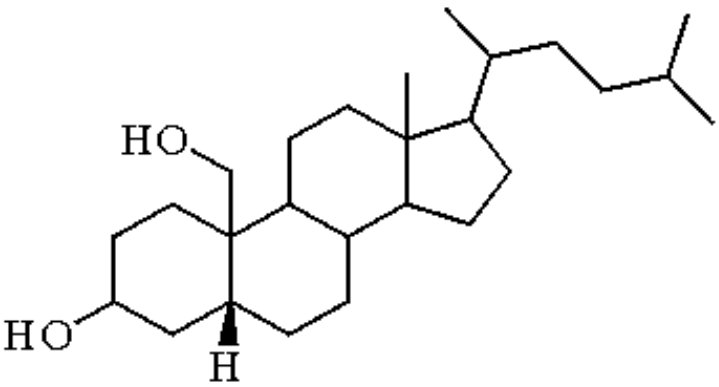

(14)

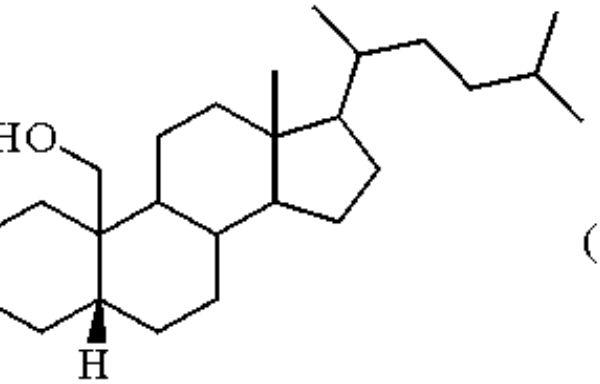

(9)

(15)

Aqueous pyridine is a very effective solvent for the oxidation of sulfides to sulfoxides with ***Phenyliodine(III) Dichloride***. High yields of the sulfoxides are typically obtained without contamination by sulfones (eq 10).[22]

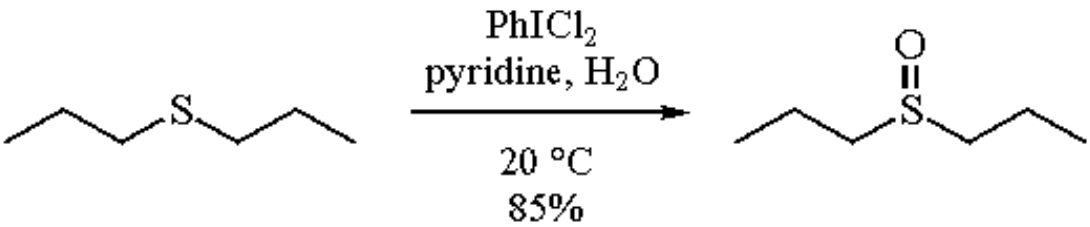

(10)

Halogenation Reactions.

Treatment of enones with ***Iodine*** and pyridine in carbon tetrachloride results in direct iodination. Good yields of 2-iodo enones are obtained when a solution of iodine (1.2-1.4 equiv) dissolved in a 1:1 (v/v) mixture of pyridine/carbon tetrachloride is added to cycloalkenones (eq 11).[23]

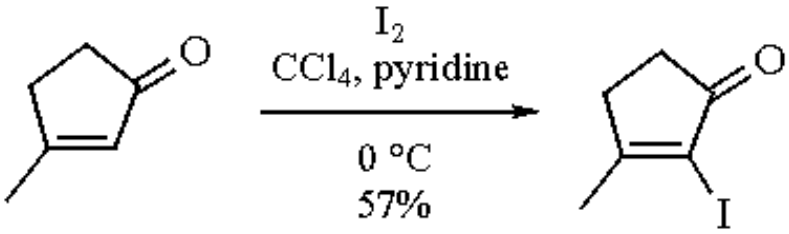

(11)

Pyridine is employed as a base in the conversion of tetrahydrofurfuryl alcohol (**16**) to the corresponding bromide (**17**). A fair yield of the bromide is obtained (eq 12).[24] Addition of pyridine greatly increases the yield of product.[3]

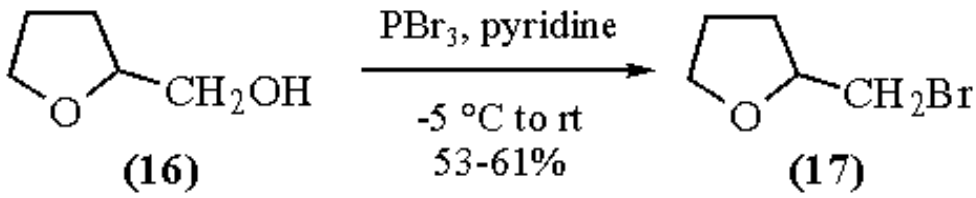

(12)

In the bromination of 1-methylaminoanthraquinone (**18**), a good yield of 1-methylamino-4-bromoanthraquinone (**19**) is obtained using pyridine as acid scavenger and solvent (eq 13).[25]

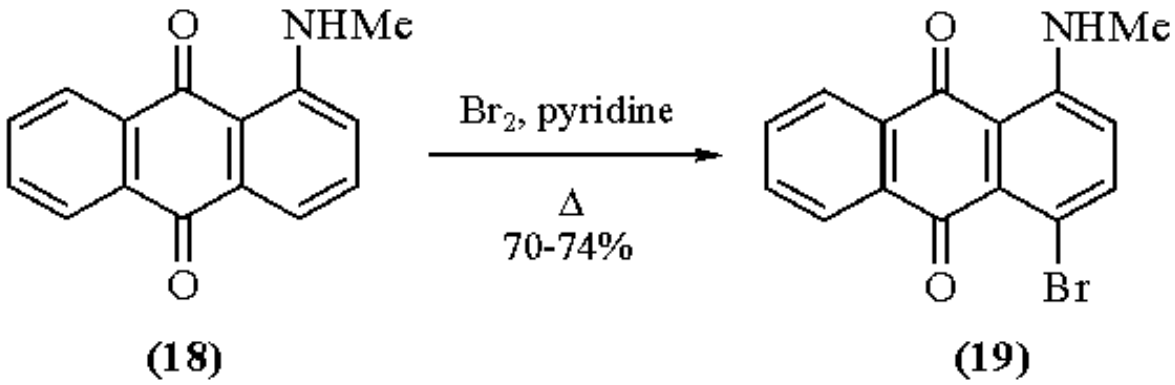

(13)

Pyridine and 2,6-lutidine are useful as acid scavengers in the chlorination of α,β-unsaturated ketones and esters. For the ketones, the pyridine bases typically favor the Markovnikov isomer; however, for esters, pyridine shows little effect on the Markovnikov (alkoxy adjacent to carbonyl)/anti-Markovnikov isomer ratios (eq 14).[26]

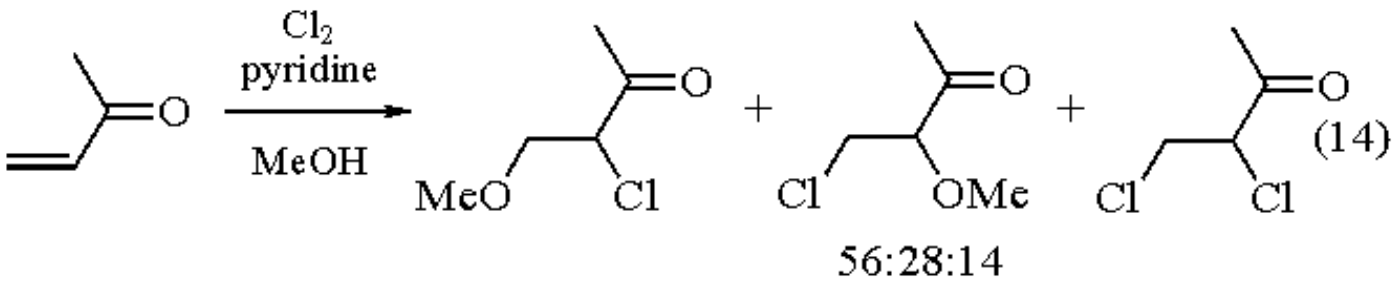

(14)

Dehalogenation Reactions.

Dehalogenation of α-halo ketones can be effected by a number of reagents including pyridine and ***Tin(II) Chloride*** (eqs 15 and 16).[2] In the absence of the pyridine, the yield of acetophenone (**20**) drops to 75% and the yield of cyclohexanone (**21**) to 10%. Sulfur compounds such as sodium sulfite and ***Sodium Sulfide***, as well as benzene and aniline, are capable of dehalogenation in the presence of a promoter such as tin(II) chloride. An advantage of this reaction is that both aliphatic and aromatic α-halo ketones can be dehalogenated in good to excellent yields.

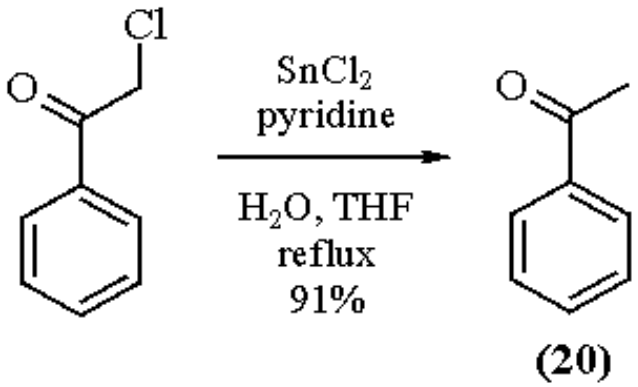

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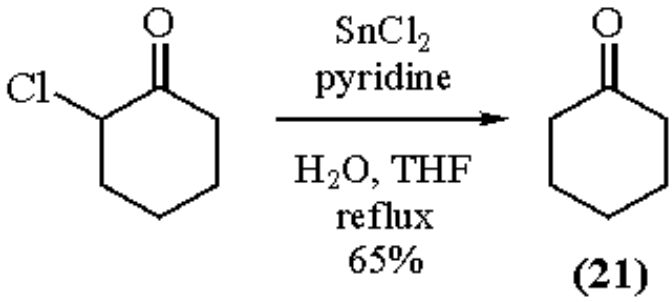

(16)

Dehydrochlorination of 2-(1-chloroethyl)thiophene (**22**) in the presence of pyridine gives 2-vinylthiophene (**23**) in 50-55% overall yield starting from thiophene (eq 17).[27] Didehydrochlorination of 2,2-dichloro-4-alkylbutanolides affords 4-alkylidene-2-butenolides upon reflux in pyridine (eq 18).[28]

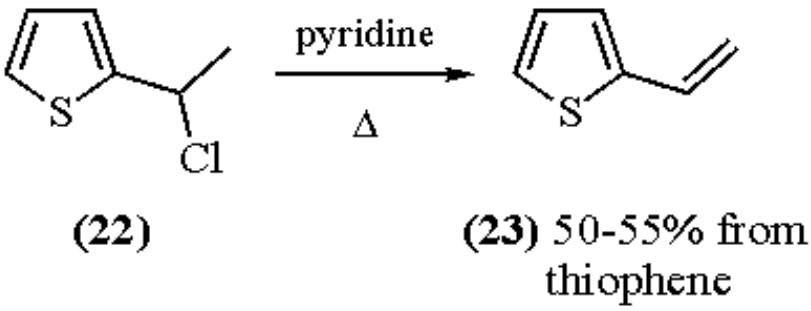

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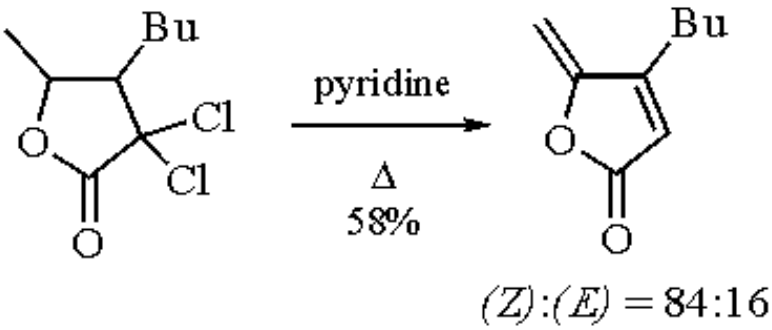

(18)

Epoxidations.

Taking advantage of its utility as a base, pyridine has been used for epoxidations in anhydrous organic systems with α-azo hydroperoxides as the epoxidizing reagents (eq 19).[29] ***Sodium Hydroxide*** works equally well or better with some of the epoxidizing agents; however, with the hydroperoxide (**24**), sodium hydroxide is a poor catalyst. Sodium hydroxide-catalyzed dehydration of the azo hydroperoxide, which affords *N*-(4-bromophenyl)-*N*´-benzyldiazene, is a competing side reaction.[30]

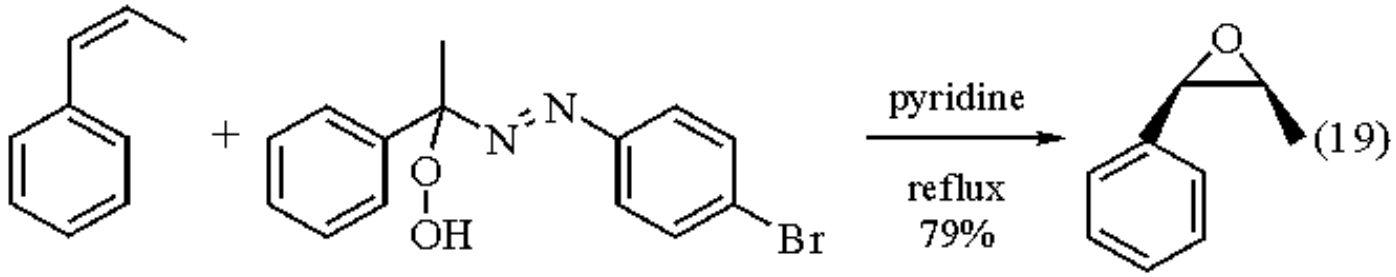

(24)

Coupling Reactions.

Dimerization of aromatic nitrile oxides can be catalyzed by pyridine, affording 3,6-diaryl-1,4,2,5-dioxadiazines in good yields (eq 20).[31] Other nucleophiles such as 4-phenylpyridine, 4-methylpyridine, ***4-Dimethylaminopyridine***, and ***N-Methylimidazole*** are also suitable catalysts for the reaction.

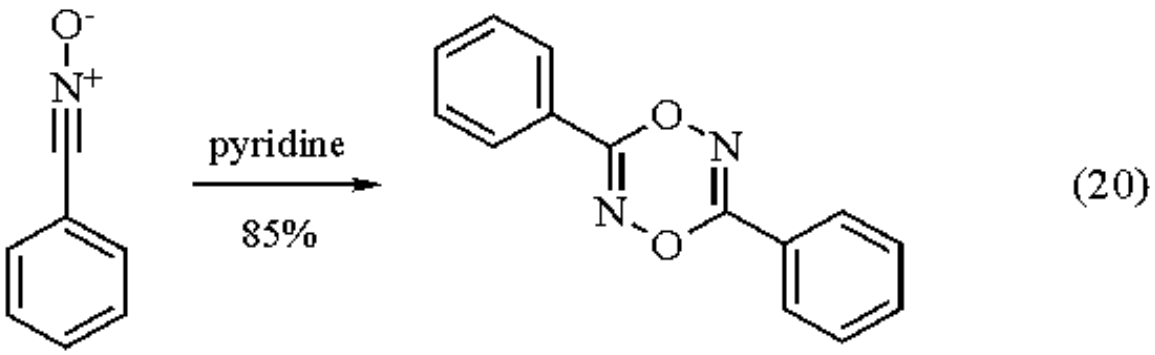

Esterifications.

Pyridine is a widely used catalyst for acylation reactions. Acetylation reactions are effectively carried out in the presence of hexachlorocyclophosphazatriene and pyridine.[32] Acetylation of phenols by ***Acetic Anhydride*** in carbon tetrachloride is also catalyzed by pyridine. In the absence of the pyridine catalyst, at 0 °C and 25 °C, no acylation of the phenols is observed (eq 21).[4]

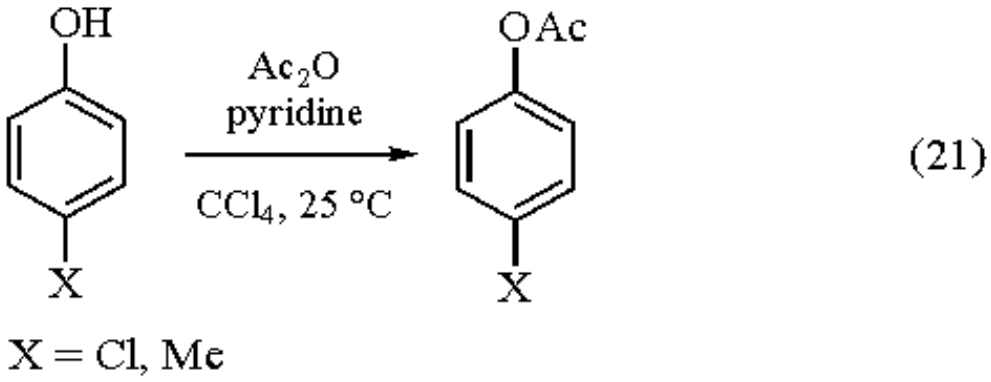

Acylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**25**) with acetic anhydride in pyridine affords 2-acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (**26**) in 72-77% yield (eq 22).[33]

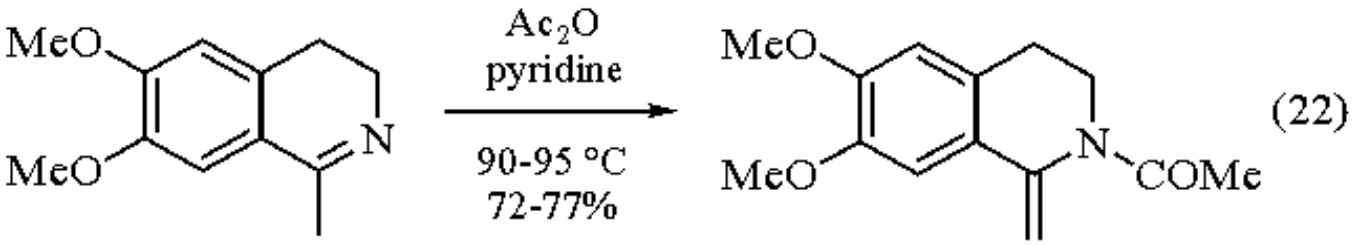

(25) (26)

Treatment of *o*-hydroxyacetophenone (**27**) with ***Benzoyl Chloride*** in pyridine affords *o*-benzoyloxyacetophenone (**28**) in excellent yield (eq 23).[34]

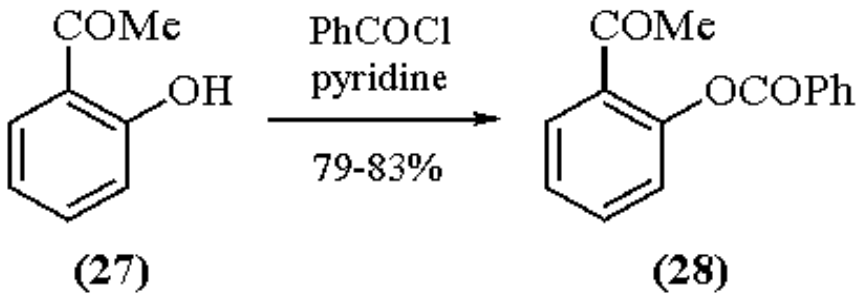

(23)

Synthesis of Benzonitriles.

Arylthallium(III) salts with ***Copper(I) Cyanide*** or copper(II) cyanide afford fair to excellent yields of benzonitriles when heated at reflux in pyridine solvent (eq 24).[35] The use of acetonitrile as solvent gives lower product yields.

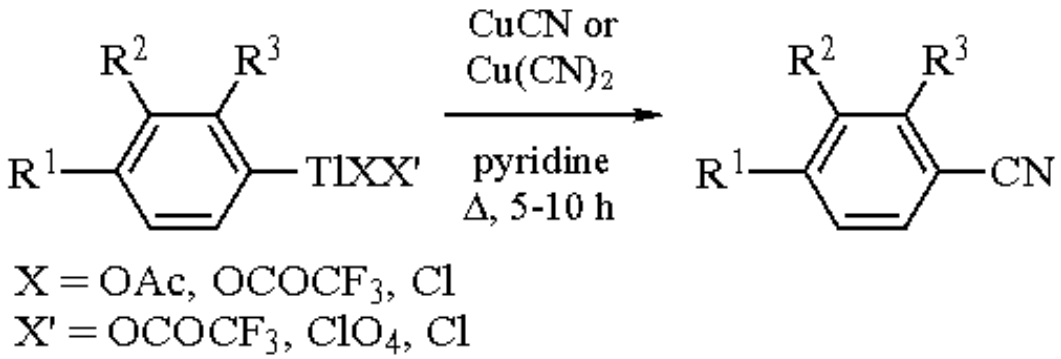

(24)

Catalyst Poison.

Pyridine and ***Quinoline*** have been used in conjunction with ***Palladium on Barium Sulfate*** as a catalyst system for the reduction of alkynes to *cis*-alkenes.[36]

Related Reagents.

Borane-Pyridine; ***Chlorine-Pyridine***; ***Copper(II) Sulfate-Pyridine***; ***Di-t-butyl Chromate-Pyridine***; ***Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine***; ***Sulfur Trioxide-Pyridine***.

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Pyridine *N*-Oxide

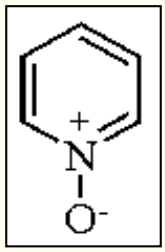

[694-59-7] · C_5H_5NO · Pyridine *N*-Oxide · (MW 95.11)

(oxidation of alkyl halides to aldehydes; oxidative decarboxylation of certain carboxylic acids, anhydrides, and α-halo acids; dehydrogenation of carboxamides)

Physical Data: mp 66 °C; bp 270 °C.

Solubility: sol water, most polar solvents.

Form Supplied in: deliquescent colorless solid.

Analysis of Reagent Purity: ^{1}H NMR δ 7.35 (3H, m), 8.35 (3H, m).

Purification: distillation at aspirator pressure.

Handling, Storage, and Precautions: very hygroscopic; irritant; use in a fume hood.

Oxidative Decarboxylation.

Certain substituted acetic acids and their anhydrides undergo oxidative decarboxylation to aldehydes and ketones on treatment with pyridine *N*-oxide in toluene or xylene at reflux (eqs 1-3). Acids require an equivalent of ***Acetic Anhydride*** to dehydrate them to the anhydride.[1,2]

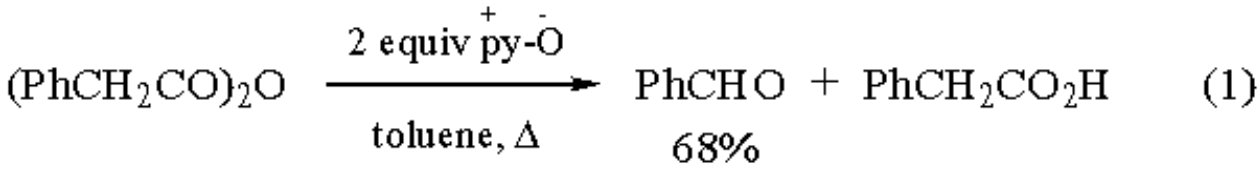

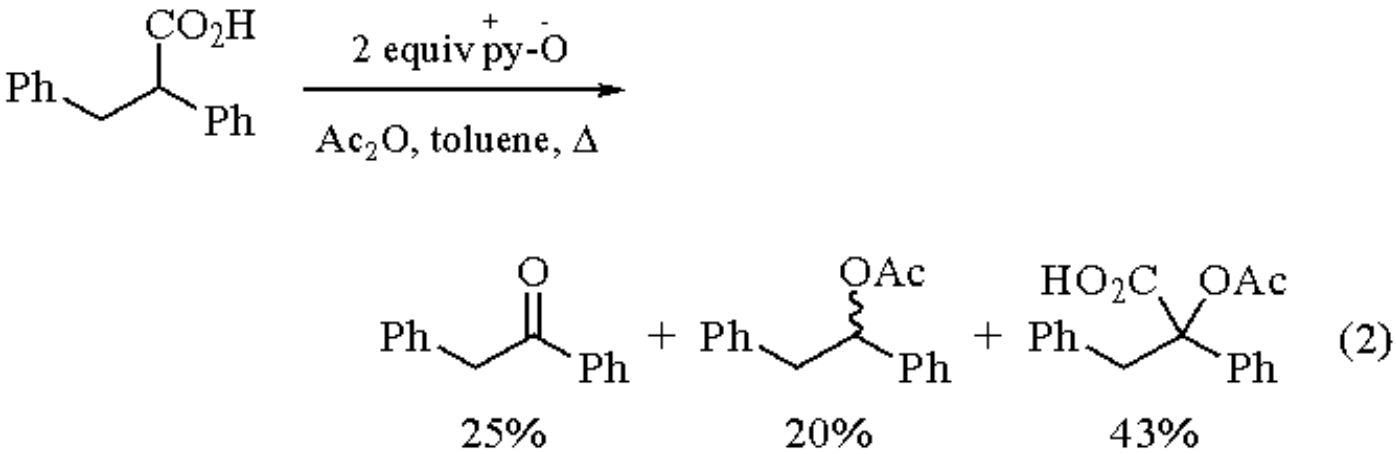

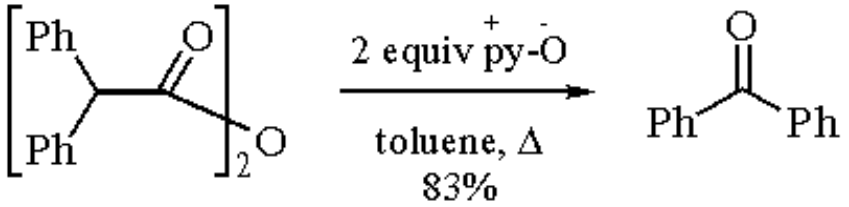

(3)

In a reaction of perhaps greater synthetic interest, α-halo acids are converted with 4 equiv of pyridine *N*-oxide to aldehydes and ketones, losing a carbon atom in the process (eqs 4-6).[3,4]

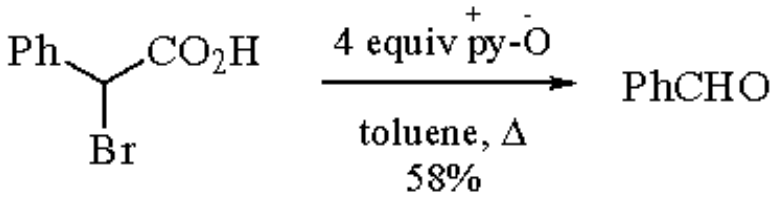

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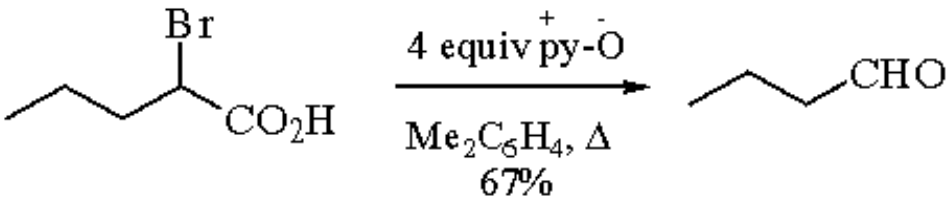

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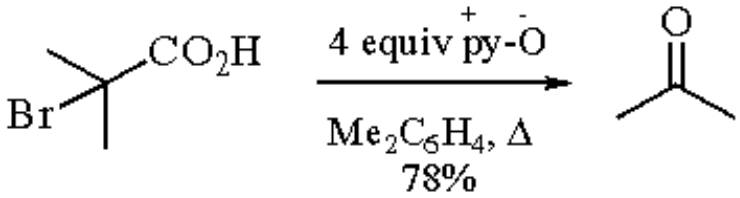

(6)

Oxidation of Alkyl Halides.

Pyridine *N*-oxide oxidizes even unactivated alkyl halides to carbonyl compounds (eqs 7-9). This is of some importance as most related methods[9] (e.g. Kröhnke and Kornblum oxidations) are limited to activated halides. The reaction can be performed in two ways. In the first, the halide is treated with the *N*-oxide in the presence of a base such as $NaHCO_3$. In the second, the intermediate *N*-alkoxypyridinium salt is isolated before base treatment.[5-7] 2-Picoline *N*-oxide may be used in a similar oxidation reaction.[8]

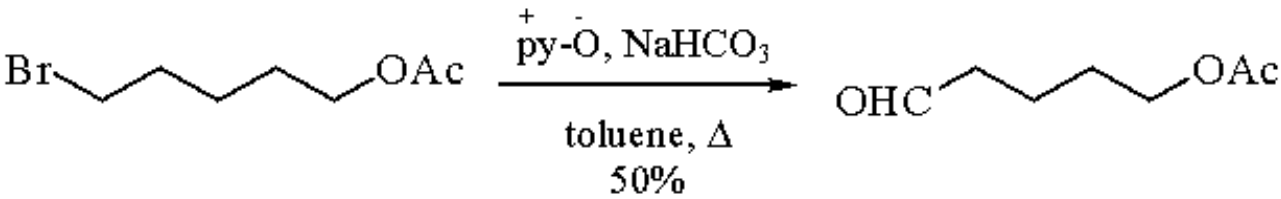

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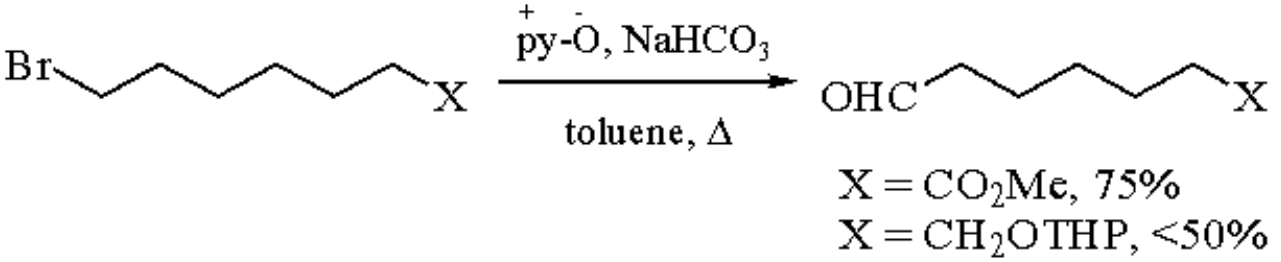

(8)

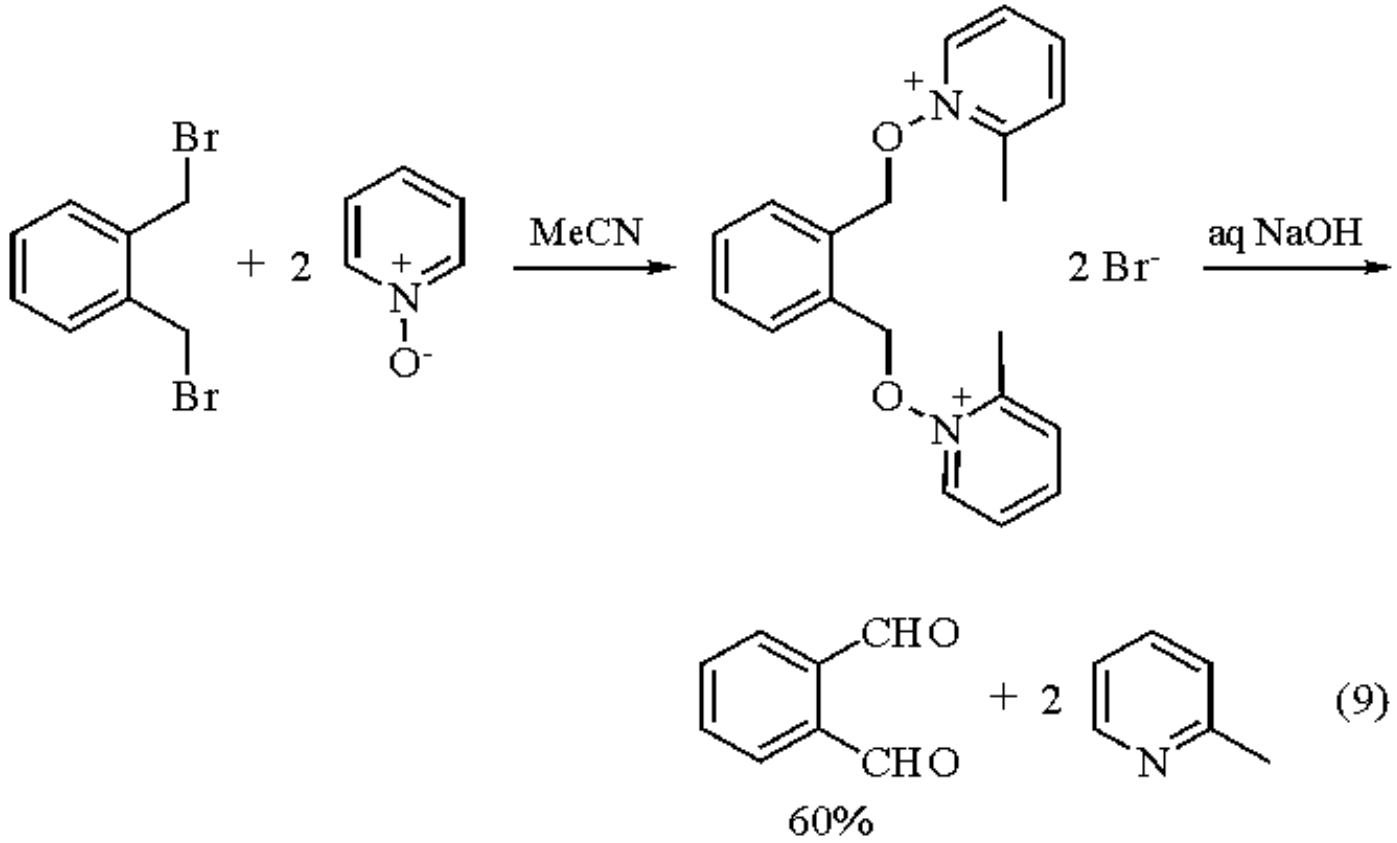

(9)

The method is excellent for the synthesis of α-keto esters.[9] In the examples in eqs 10 and 11, the α-bromo ester or acid is treated with pyridine *N*-oxide and ***Silver(I) Nitrate*** at 0 °C. Decomposition of the isolated salt with mild base gives the dicarbonyl compound in high yield.

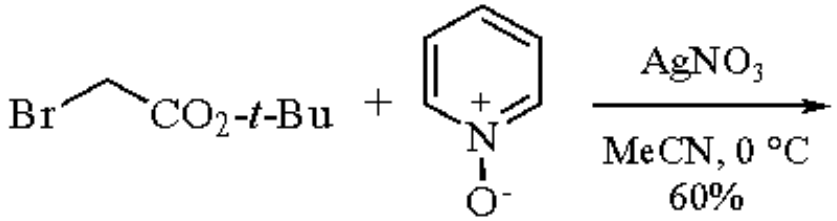

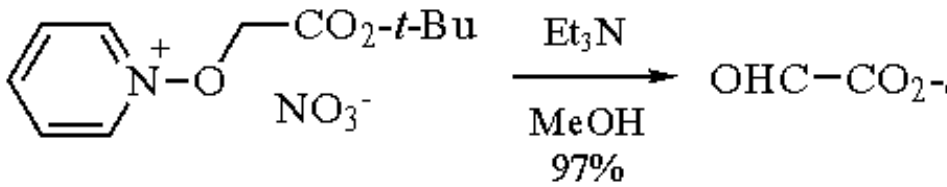

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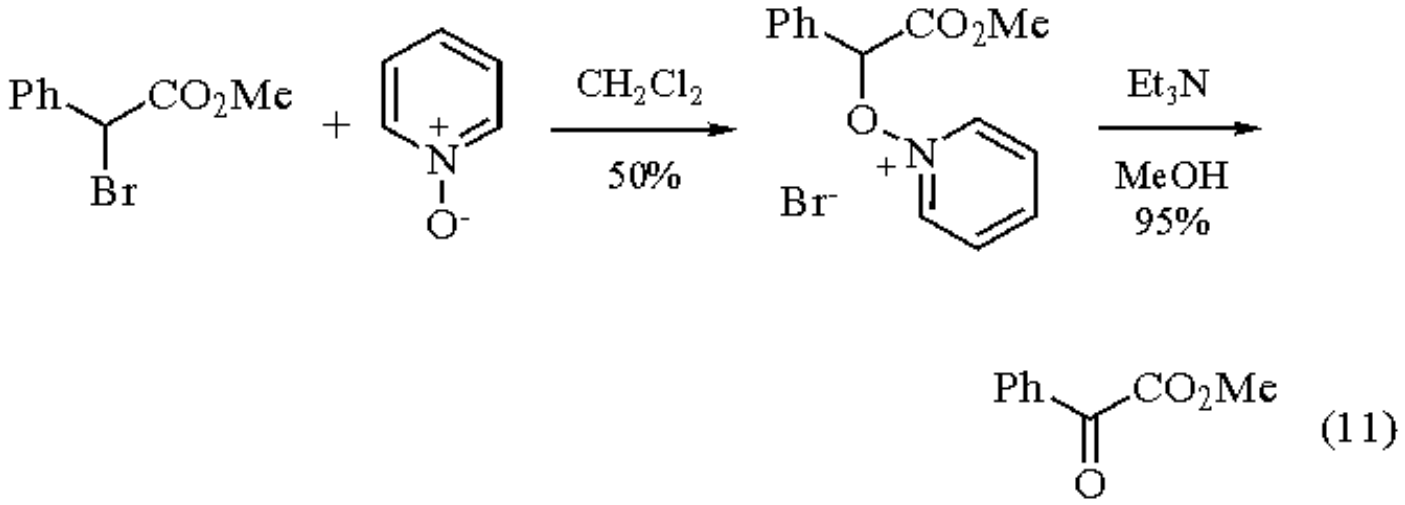

In some cases (e.g. eq 11), it is unnecessary to add silver nitrate, and the bromide salt may be used. For some substrates (e.g. secondary halides), the more powerful nucleophile DMAP 1-oxide may offer some advantages (eq 12).[10] However, oxidation of cyclohexyl bromide still fails, due to elimination.

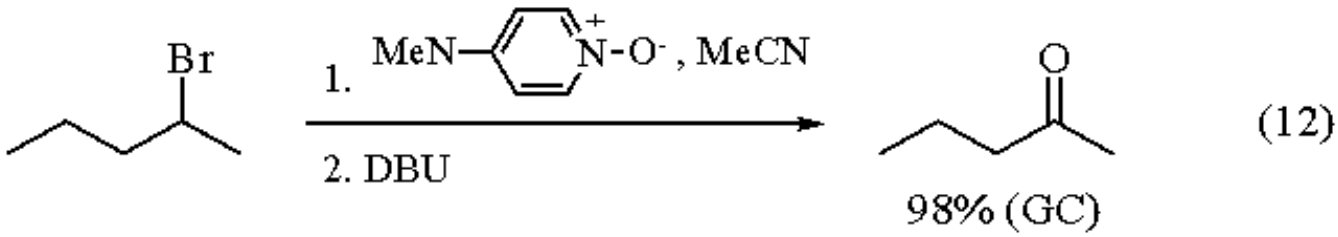

Dehydrogenation of Carboxamides.

Treatment of the imidoyl chlorides of tertiary amides with pyridine *N*-oxide and ***Triethylamine*** in $CHCl_3$ results in dehydrogenation, giving the α,β-unsaturated amides (eqs 13-15).[11]

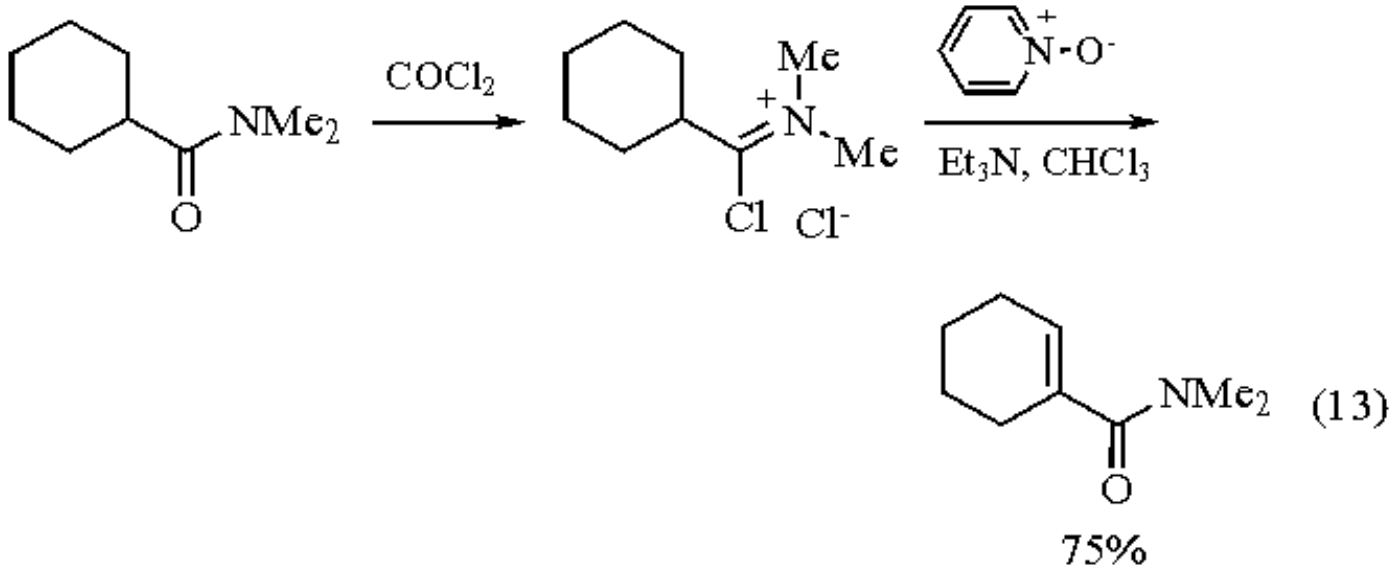

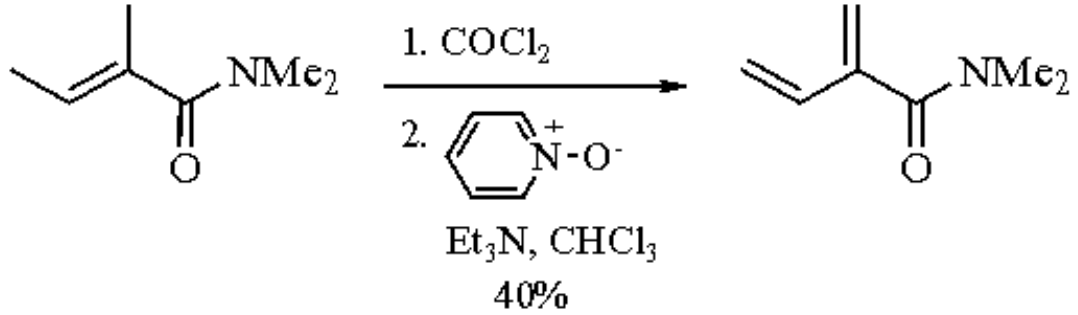

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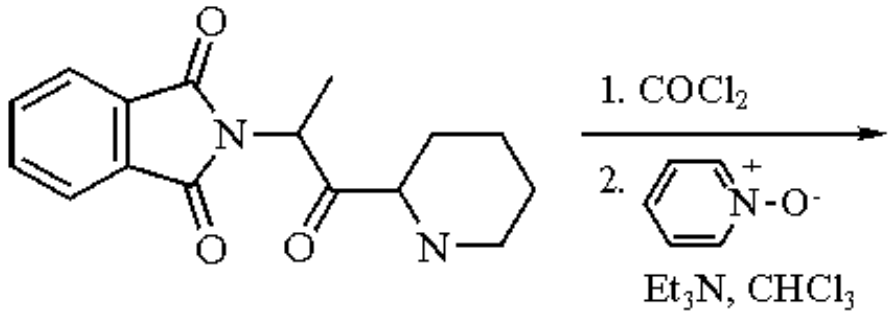

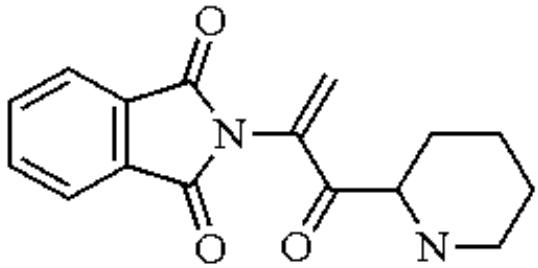

(15)

Diphenyl sulfoxide may be used as the oxidant, but purification is more difficult. The synthesis of dehydroamino acids derivatives by this reaction is noteworthy (e.g. eq 15).[12] The amide must be branched in the α-position, otherwise the sole product formed is the α-chloro amide (eq 16).

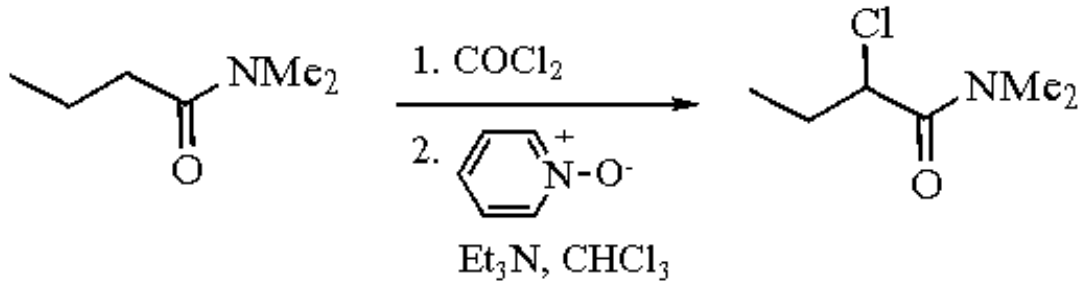

(16)

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2. Rüchardt, C.; Eichler, S.; Krätz, O. *TL* **1965**, 233.
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S. Nicholas Kilényi

2-Pyridineselenenyl Bromide

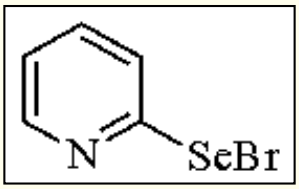

[91491-61-1] · C_5H_4BrNSe · 2-Pyridineselenenyl Bromide · (MW 236.96)

(selenoxide elimination to afford alkenes;[1-4] episelenonium ions[3,4])

Physical Data: mp 115-116 °C (dec).

Solubility: sparingly sol THF, dichloromethane, methanol.

Preparative Method: by reaction of ***2,2´-Dipyridyl Diselenide*** with ***Bromine*** in an appropriate solvent. An analytically pure sample is obtained by the filtration of the precipitate thus formed and washing. This preparation should not be carried out in ***Acetonitrile*** since 2-pyridineselenenyl bromide adds to acetonitrile.

Handling, Storage, and Precautions: use in a fume hood.

Selenoxide Elimination.[1-4]

For the dehydrogenation of ketones to enones, the introduction of a 2-pyridineselenenyl group on the α-carbon of the ketone and subsequent oxidation of the selenide to induce the selenoxide elimination is one of the most convenient procedures.[1,2] 2-Pyridineselenenyl bromide (or chloride) is a useful reagent for this sequence and three kinds of reaction have been reported for the introduction of a 2-pyridineselenenyl group onto the α-carbon of the ketones. They are: (1) the reaction of ketones with 2-pyridineselenenyl bromide (PySeBr) in the presence of ***Hydrochloric Acid*** (eq 1); (2) the reaction of the lithium enolate of the ketones with PySeBr (eq 2); and (3) the reaction of the enol silyl ether of the ketones (or aldehydes) with PySeBr (eq 3). The 2-pyridineselenenyl group has been reported to be a better leaving group than the benzeneselenenyl group. The 2-pyridineselenenyl group has also been used in selenoxide eliminations to afford vinylic amides[4] and vinylic ethers.[3]

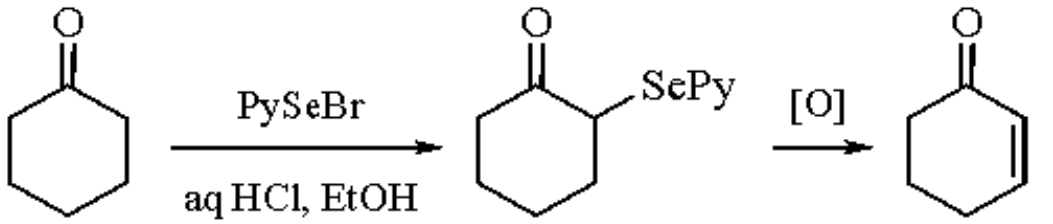

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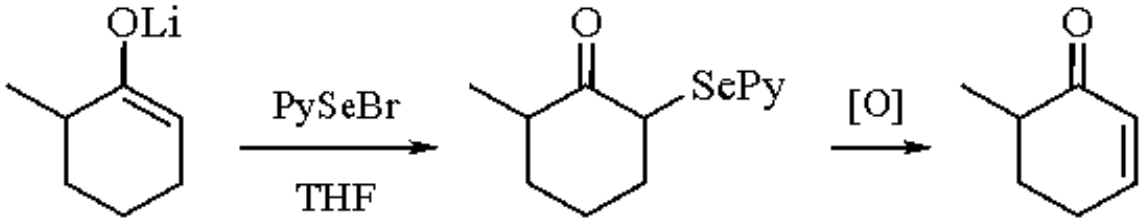

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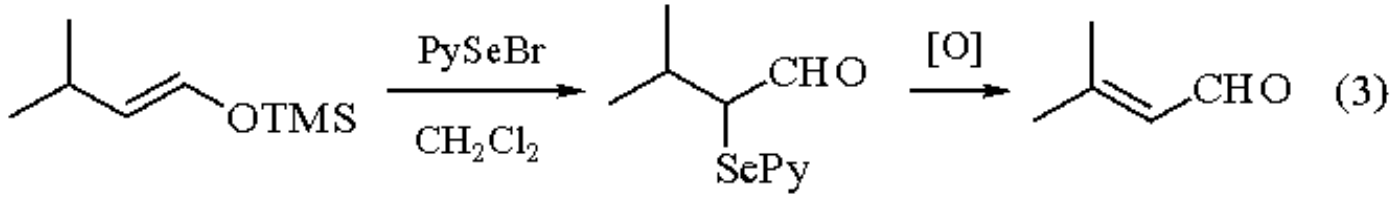

Vinylic Selenides.

2-Pyridineselenenyl bromide is an important starting material for the preparation of 2-pyridyl vinylic selenides from alkenes via β-methoxyalkyl 2-pyridyl selenides (eq 4).[3] Deprotonation and subsequent alkylation of 2-pyridyl vinylic selenides proceed with retention of the stereochemistry, which has not yet been realized by the use of other vinylic selenides.[3] It should also be noted that the reaction conditions for the deprotonation of 2-pyridyl vinylic selenides are much milder than those required for the corresponding phenyl vinylic selenides. This may be due to the chelation of the nitrogen atom of the pyridine with a lithium atom, as depicted in eq 5.

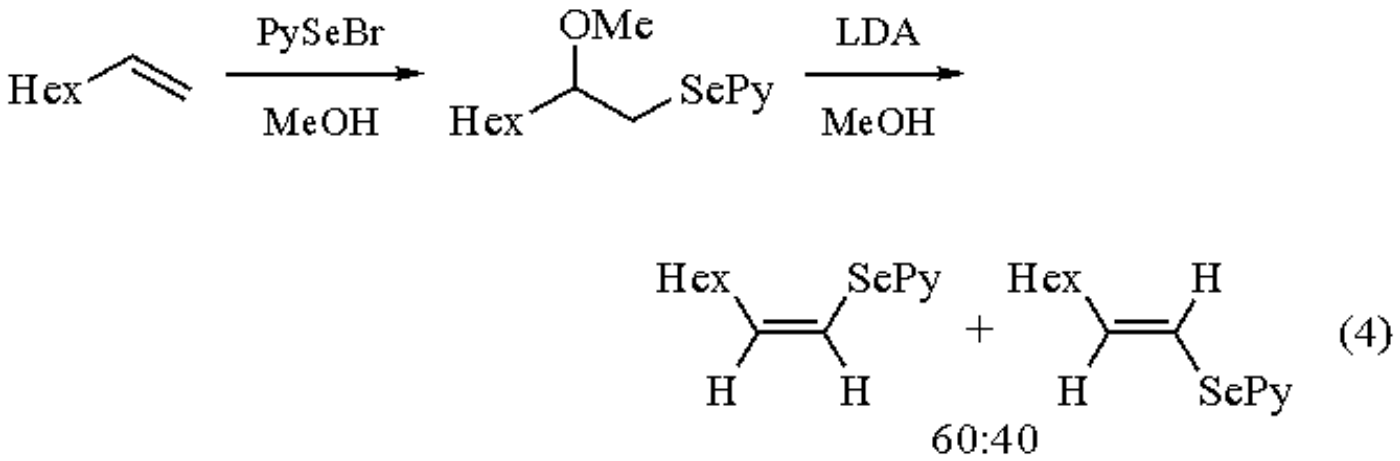

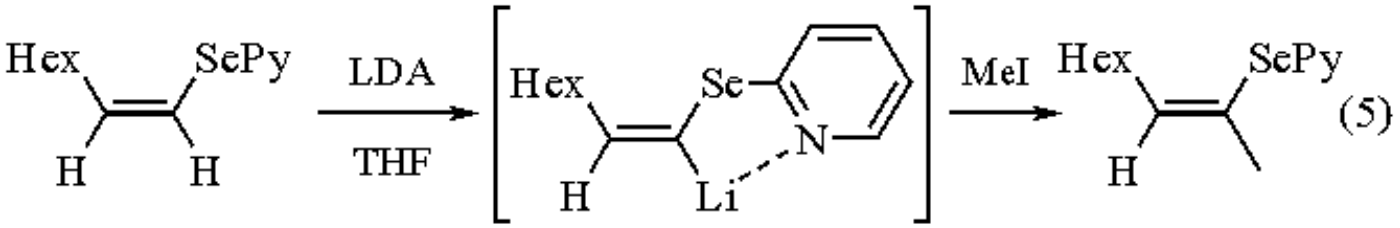

Episelenonium Ions.

β-Methoxyalkyl 2-pyridyl selenides have also been used as intermediates for the introduction of 2-pyridineselenenyl and acylamino groups into trisubstituted alkenes (eq 6).[4] This reaction represents the preparation of tertiary amine derivatives. The use of the 2-pyridineselenenyl group is essential as phenyseleno-substituted tertiary carbocations are too stable and do not react with nitriles.

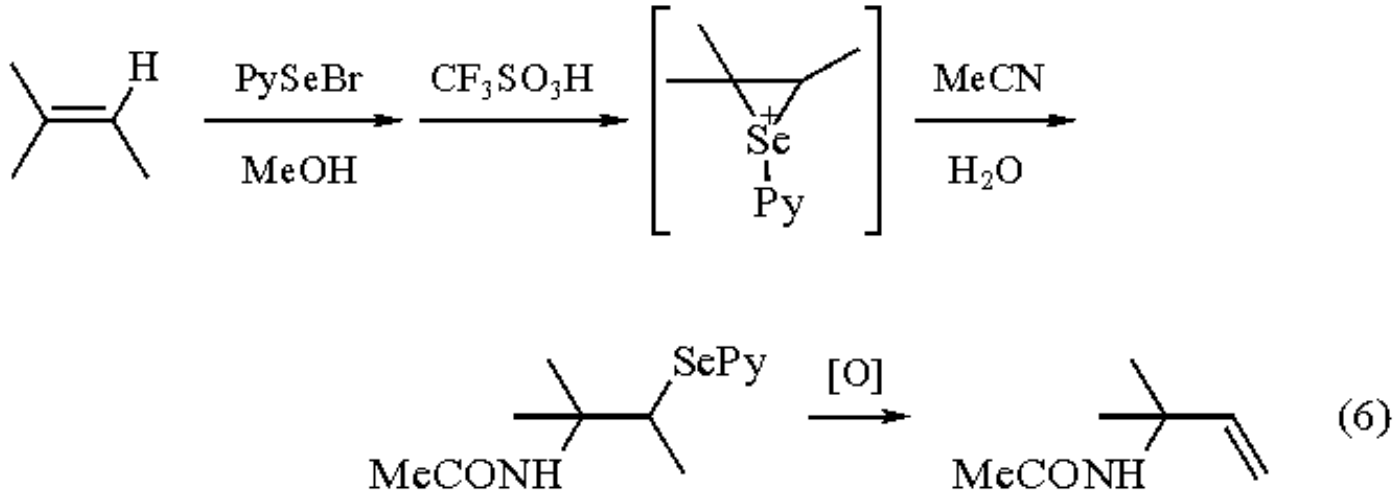

Related Reagents.

Benzeneselenenyl Bromide; ***Benzeneselenenyl Chloride***; ***2,2´-Dipyridyl Diselenide***; ***2,2´-Dipyridyl Disulfide***.

---

1. Toshimitsu, A.; Owada, H.; Terao, K.; Uemura, S.; Okano, M. *JOC* **1984**, *49*, 3796.
2. Takagaki, H.; Abe, M.; Watanabe, M.; Takeuchi, K.; Nakanishi, S.; Aihara, H.; Yamazaki, K. Jpn. Patent 63 277 694 (*CA* **1988**, *111*, 23 792j).
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4. Toshimitsu, A.; Hayashi, G.; Terao, K.; Uemura, S. *JCS(P1)* **1988**, 2113.

Akio Toshimitsu

Kyoto University, Japan

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2-Pyridinesulfenyl Bromide

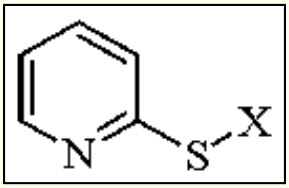

(X = Br)

[66715-65-9] · C_5H_4BrNS · 2-Pyridinesulfenyl Bromide · (MW 190.07) (X = Cl)

[59089-57-5] · C_5H_4ClNS · 2-Pyridinesulfenyl Chloride · (MW 145.62)

(electrophilic sulfenylation agents used for unsymmetrical disulfide synthesis,[1] deprotection of specific thiol protecting groups,[2] enolate sulfenylation,[3] and *N*-sulfenylation of amides[4])

Physical Data: yellow powder.

Solubility: normally used in anhydrous HOAc; may also be used in dry DMF; rapidly decomposes in the presence of moisture.

Preparative Method: the 2-pyridinesulfenyl halides are generated as needed from ***2,2´-Dipyridyl Disulfide***. Treatment of 2,2´-dipyridyl disulfide in petroleum ether or dichloromethane with either ***Chlorine*** or ***Bromine*** at 20 °C results in 2-pyridinesulfenyl halide generation after 1-2 h. Isolation through evaporation of solvent provides a yellow powder with a pungent odor.[1,2,5]

Handling, Storage, and Precautions: the 2-pyridinesulfenyl halides demonstrate instability, especially in the presence of moisture. Although the isolated powder may tolerate short-term storage in a well sealed vial or ampule, most work involving these reagents has utilized freshly prepared material. Solutions in anhydrous HOAc are reported to be stable for several hours.[2] The reagent is corrosive and must be handled accordingly. The reaction with moisture generates HCl and 2-pyridylsulfenic acid (stench, toxic). Handling of these reagents should be confined to a fume hood.

Deprotection of the Thiol Group.

The initial application of 2-pyridinesulfenyl chloride as a deprotection reagent focused on a synthesis program based on cysteine.[2] Specifically, cysteine residues protected as the trityl, diphenylmethyl, or acetamidomethyl derivatives, or as the *t*-butyl sulfide or the *t*-butyl disulfide, react with 2-pyridinesulfenyl chloride to generate a mixed disulfide (eq 1).

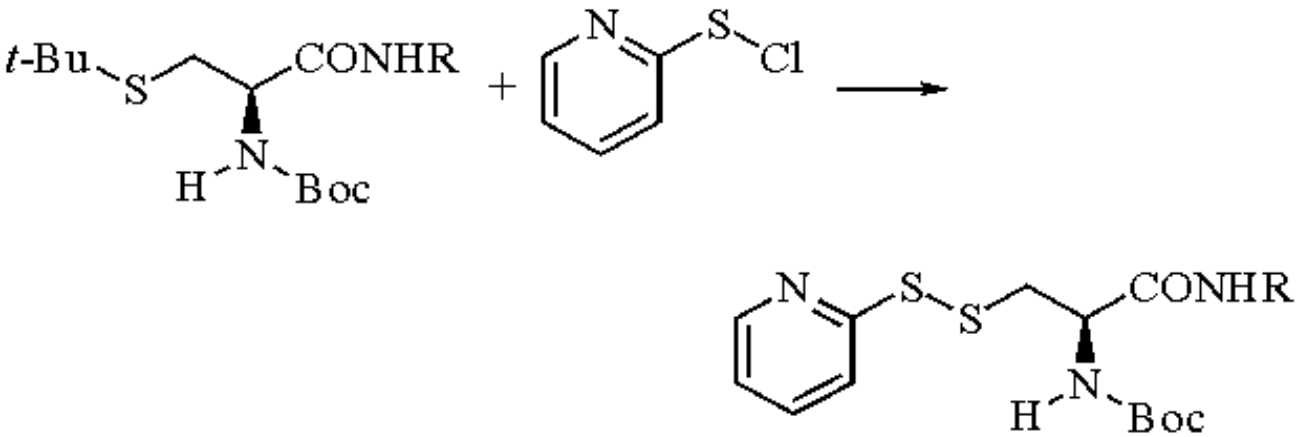

(1)

This reaction occurs rapidly at room temperature and can be conducted to utilize the endpoint provided by the bright yellow 2-pyridinesulfenyl chloride solution. Deprotection under these conditions tolerates 10-20 mol % of ***Triethylamine*** for the protection of the Boc group from any HCl generated from residual moisture. 2-Pyridinesulfenyl chloride avoids the use of strong acid (TFA, HBr)

conditions that are associated with the removal of the listed protecting groups. The resulting mixed disulfide is stable to acids, but is unstable to alkali. Several equivalents of ***2-Mercaptoethanol*** generates a cysteine thiol group from the mixed disulfide.

Unsymmetrical Disulfides.

The mixed disulfide indicated in eq 1 provides a route to other mixed disulfides through the reaction of a thiol with the intermediate disulfide in HOAc. Unsymmetrical 2-pyridyl disulfides result from the reaction of 2-pyridinesulfenyl chloride and a thiol (eq 2).[1,5]

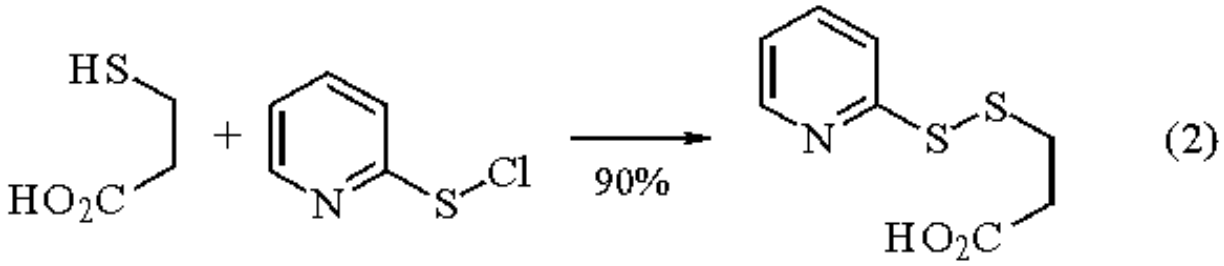

Enolate Sulfenylation.

2-Pyridinesulfenyl bromide provides an opportunity for regiocontrol in the synthesis of methyl dehydrojasmonate.[3] A 2,3-disubstituted cyclopentenone is regiochemically activated through formylation, resulting in a β-diketo enolate. 2-Pyridinesulfenyl bromide reacts with the enolate and promotes a deformylation (eq 3). 2,2´-Dipyridyl disulfide also provides the desired product, but in a lower yield. Attempts to trap the enolate with dimethyl disulfide or diphenyl disulfide are not successful. Subsequent oxidation and sulfoxide thermolysis provides the desired cyclopentenone product.

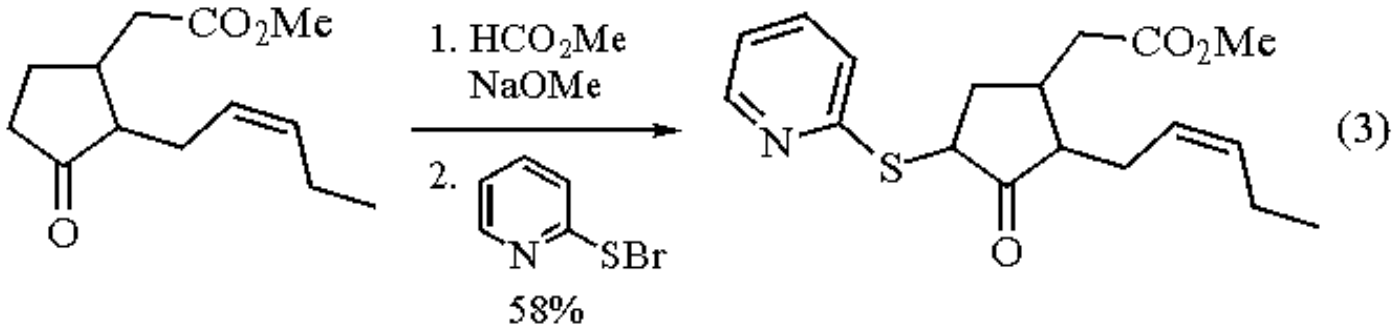

N-Sulfenylation of Amides.

A solution of 2-pyridinesulfenyl bromide in DMF has been used to sulfenylate a deprotonated amide (eq 4).[4]

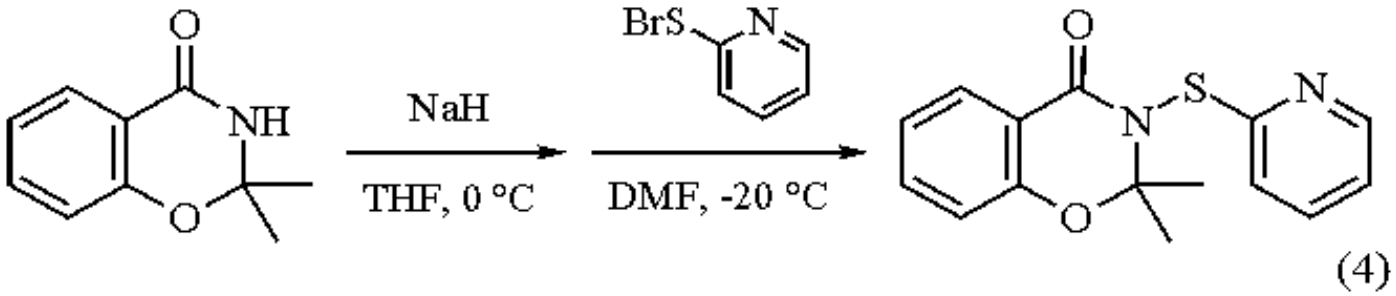

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1. (a) Senter, P. D.; Pearce, W. E.; Greenfield, R. S. *JOC* **1990**, *55*, 2975. (b) Another reagent used as an electrophilic sulfenylation agent is *N*-(2-pyridinesulfenyl)morpholine: Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M. *JOC* **1991**, *56*, 6697, 6702.
2. Castell, J. V.; Tun-Kyi, A. *HCA* **1979**, *62*, 2507.
3. Dubs, P.; Stüssi, R. *HCA* **1978**, *61*, 998.
4. Tachikawa, R.; Wachi, K.; Sato, S.; Terada, A. *CPB* **1981**, *29*, 3529.
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2-Pyridinesulfonyl Chloride

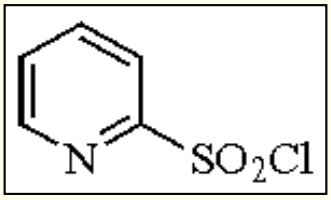

[66715-65-9] · $C_5H_4ClNO_2S$ · 2-Pyridinesulfonyl Chloride · (MW 177.62)

(heteroarylsulfonyl chloride for the formation of 2-pyridinesulfonate esters which are excellent metal-assisted leaving groups in S_N2 displacement reactions with magnesium halides,[2] as well as in elimination reactions;[2] alkyl 2-pyridinesulfonate esters are transformed into 2-alkylpyridines upon treatment with organometallic reagents[3])

Physical Data: colorless crystalline solid.

Solubility: sol chlorinated hydrocarbons and in dipolar aprotic solvents; insol cold water (gradual hydrolysis).

Preparative Method: prepared essentially according to the published procedure.[1] ***Chlorine*** gas is bubbled into a solution of ***2-Pyridinethiol*** (4 g, 36 mmol) in concd. ***Hydrochloric Acid*** (32 mL) at 0 °C for 90 min. The solution is poured into ice-water (100 mL), and the precipitate is rapidly filtered and washed with ice-cold water (50 mL). The colorless crystalline product is dried at 0 °C (pump), then stored at 0 °C for use; yield 3.6 g (55%).

Handling, Storage, and Precautions: the crystalline reagent is stable when stored at 0 °C under argon for several months. Use in a fume hood.

Preparation of 2-Pyridinesulfonates.[2]

The reagent (3.0 g, 3.5 mmol) is added in portions to a solution of the alcohol (3.00 mmol) in dry pyridine (5 mL) at 0 °C. After stirring for a few hours (cholestanol, 3 h; *t*-butylmethyl alcohol, 18 h), the solution is poured into ice-water and the 2-pyridinesulfonate is isolated by filtration in some cases. Otherwise, the aqueous solution is extracted with dichloromethane, which is then washed with dil. HCl and water and processed in the usual way. The 2-pyridinesulfonate is isolated by crystallization or by flash chromatography. For example, 2-pyridinesulfonates are prepared from cholestanol (quant.), mp 127-128 °C; 1,2:3,4-di-*O*-isopropylidene-D-galactose (97%), mp 89-90 °C; L-borneol (93%), mp 99-100 °C; *t*-butylmethanol (90%), mp 47 °C; 1-octanol (94%), 2-octanol (85%), and ethyl lactate (93%), isolated as oils.

Preparation of Alkyl Halides from 2-Pyridinesulfonates.

The conceptual basis in designing novel nucleofugal esters such as 2-pyridinesulfonates was predicated upon the anticipation of an accelerated, metal-assisted S_N2 displacement reaction especially with divalent ions. Indeed, upon treatment of primary and secondary 2-pyridinesulfonates with ***Magnesium Bromide*** etherate (1.3 equiv) in dichloromethane at 0 °C, the corresponding bromides are obtained within seconds or minutes (eq 1).[2] With carbohydrate derivatives, the displacements are slower (several hours) presumably because of the presence of ether-type oxygen atoms which can also coordinate with the reagent. Comparisons of the reaction of various norbornyl sulfonates demonstrates the extremely efficient transformations using 2-pyridinesulfonates (1.3 equiv $MgBr_2.Et_2O$, 5 mL CH_2Cl_2): 8-quinolinesulfonate (120 min); tosylate (70 min); *p*-nitrobenzenesulfonate (40 min); 2-pyridinesulfonate (30 s, 70% of isolated bromide). Replacement of $MgBr_2.Et_2O$ with other sources of bromide ion (***Lithium Bromide***, ***Tetra-n-butylammonium Bromide*** in DMF or CH_2Cl_2), requires heating and longer reaction times, while the addition of an external source of bromide does not accelerate the reaction.

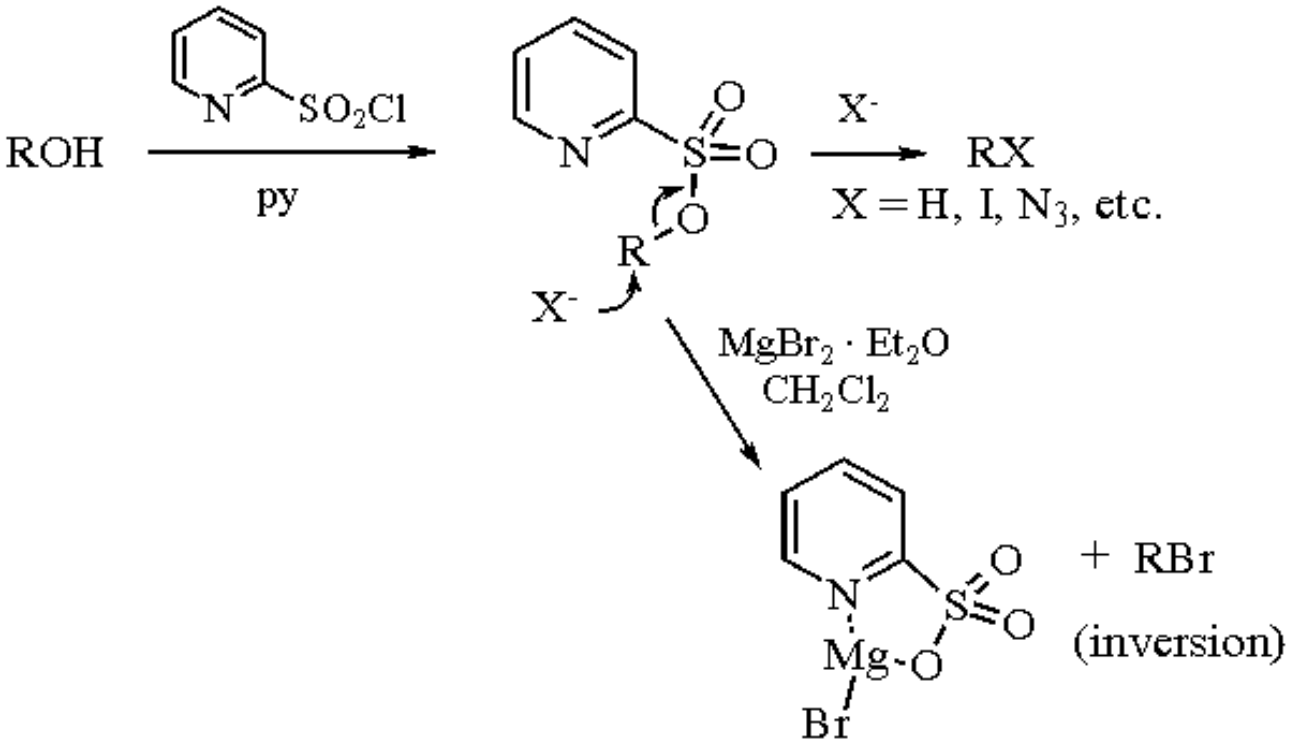

(1)

Typical products are 1-octyl bromide (0 °C, 5 min; 88%); 2-octyl bromide, $[\alpha]_D^{25}$ +33.4° (*c*, 4.23), (0 °C, 30 s, 74%); 2-benzyloxy-1-bromoethane (0 °C, 30 min, 94%); (*R*)-ethyl 2-bromopropionate, $[\alpha]_D^{25}$ +32.4° (*c*, 3.93), (0 °C, 10 min, 81%); *exo*-2-bromobicyclo[2,2,1] heptane, (0 °C, 30 s, 70%); and 3α-cholestanyl bromide, mp 102 °C, $[\alpha]_D^{25}$ +30° (*c*, 1.0), (0 °C, 5 min, 82%). Nucleophilic displacement reactions based on the remote activation of the nucleofugal component have also been demonstrated with alkyl imidazolylsulfonates,[4] and in the synthesis of *O*-, *C*-, and related glycosides.[5,6] Related heteroatom and metal-assisted S_N2 displacement reactions of tosylates have been recently reported.[7]

Miscellaneous Reactions of 2-Pyridinesulfonates.

Other reactions well known for arenesulfonates are also possible with 2-pyridinesulfonates. For example, treatment of 3β-cholestanyl 2-pyridinesulfonate with ***Sodium Borohydride*** (DMF, 80 °C), ***Lithium Iodide*** (1,2-dichloroethane, 25 °C, 3 h), and LiN_3 (DMF, 80 °C, 4 h), gives cholestane (78%), 3α-iodocholestane (76%), and 3α-azidocholestane (63%), respectively.[8] Treatment of 3β-cholestanyl 2-pyridinesulfonate with ***Palladium(II) Chloride*** (2 equiv) in DMF (80 °C, 30 min), gives 2-cholestene (80%).[9]

2-Substituted Pyridines.

Although there are examples of the synthesis of 2-alkylpyridines[10] by direct and indirect methods, the yields in some cases are low and the conditions harsh. Treatment of alkyl 2-pyridinesulfonates (methyl, propyl, *t*-butylmethyl) with ***n-Butyllithium***, *n*-butylmagnesium bromide, ***Allylmagnesium Bromide***, and ***Phenyllithium*** at -78 °C (lithium reagents) or at 0 °C (Grignard reagents), gives the corresponding 2-substituted pyridines in 68-80% yields (eq 2). In principle, any alkyl 2-pyridinesulfonate can be used. However, for convenience of handling, the crystalline *t*-butylmethyl 2-pyridinesulfonate can be used.

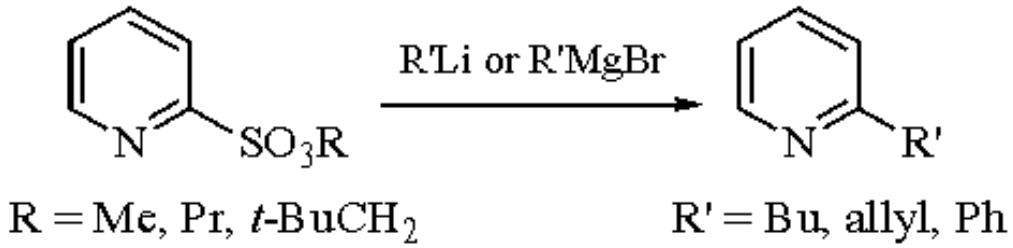

(2)

Related Reagents.

Benzenesulfonyl Chloride; ***4-Bromobenzenesulfonyl Chloride***; ***Mesitylenesulfonyl Chloride***; ***p-Toluenesulfonyl Chloride***.

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2-Pyridinethiol

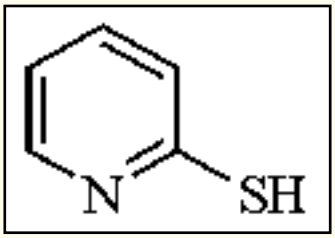

[2637-34-5] · C_5H_5NS · 2-Pyridinethiol · (MW 111.18)

(reagent for the synthesis of thiolesters which acylate nucleophiles[1] or yield ketones with organometallic reagents;[2] utilized in protection and deprotection chemistry;[3,4] glycoside coupling agent;[5,6] component of a selective reducing agent;[7] precursor of electrophilic sulfur reagents;[8,9] applied to dienophile synthesis[10])

Physical Data: mp 128-130 °C.

Solubility: sol most organic solvents; sol aqueous base.

Form Supplied in: crystalline solid, available from various suppliers.

Analysis of Reagent Purity: mp measurement is indicative of purity; values below 120 °C suggest an impure sample.

Purification: recrystallization from benzene.

Handling, Storage, and Precautions: demonstrates good stability if stored in a well sealed vial under an inert atmosphere at room temperature. On continued exposure to air the reagent becomes contaminated with moisture and disulfide. 2-Pyridinethiol is irritating to eyes and skin and imparts a stench.

Thiolester Synthesis and Utility.

Thiolesters represent a class of acylating agents.

Synthesis.

Pyridine-based thiolester generation utilizes carboxylic acids and 2-pyridinethiol under ***1,3-Dicyclohexylcarbodiimide*** coupling conditions (EtOAc, 0 °C).[11] Quantitative conversions of the carboxylic acid to the 2-pyridyl thiolester involve premixing 2-pyridinethiol and ***Phosgene*** before introduction of the acid.[12] A mixed anhydride method (***Trichloroacetyl Chloride***, ***Triethylamine***) of acid

activation successfully generates the thiolester[13] as does use of an acyl chloride.[14] Other methods of acid activation provide routes to the 2-pyridyl thiolesters.[15] Alternate methods are available from ***2,2´-Dipyridyl Disulfide***.[16] 2-Pyridyl thiolesters may also be generated from ketenes[17] using the tin(II) sulfides obtained from 2-pyridinethiol.[18] This technique provides a tin(II) enolate which reacts with aldehydes with *syn* selectivity and provides a 3-hydroxy thiolester.

Acylation of Nucleophiles.

2-Pyridyl thiolesters and 2-pyridyl esters provide a coupling technique in peptide synthesis.[11a] Macrolactonization with a thiolester has been demonstrated.[16] Alkylation of the 2-pyridylthiolester with nonthiophilic agents such as ***Triethyloxonium Tetrafluoroborate*** provides successful acylation of phenols, amines, and carboxylic acids.[1] Using 2 equiv of ***Methylenetriphenylphosphorane***, 2-pyridyl thiolesters provide a route to stabilized ylides.[11d]

Ketone Generation from a Carboxylic Acid Derivative.

An historical quest for organic chemists has been the generation of ketones from carboxylic acid derivatives. Carbon nucleophiles select the intermediate ketone in preference to the acid derivative, resulting in alcohol products. The stabilized intermediate provided by Grignard addition to a 2-pyridyl thiolester provides isolation of ketones from a carboxylic acid derivative.[2] Successful application of this technique to complex molecules requires a tolerance for other functional groups. Ketone formation has been accomplished in the presence of imide,[19] *t*-butoxycarbonyl, and ester[11b,13] moieties. A comparison of acid activation agents used for ketone formation from Grignard reagents examined 2-pyridyl thiolesters.[20] Investigations of ketone formation using alkynylmetals suggest that *N*-alkoxyamides may be better substrates for these organometallic reagents[21] (see ***N,O-Dimethylhydroxylamine***).

Protecting Group Chemistry.

2-Pyridinethiol provides reagents for facile protection of amines as the benzyloxycarbonyl or *t*-butoxycarbonyl protected species.[3,22] 2-Pyridinethiol protects the imide function of uridine and guanosine units in nucleotide synthesis and is displaced by nucleophiles such as amines.[23] Deprotection of thiols[24] and the azetidinone nitrogen[4] is accomplished with 2-pyridinethiol as the reagent of choice.

Glycoside Synthesis.

Thioglycosides generated from 2-pyridinethiol provide important synthetic intermediates in glycoside chemistry. The synthesis of the thioglycosides utilizes an acid[5,6,25] or Lewis acid catalyst.[26] Silyl enol ethers react with the 2-pyridylthioglycosides generating *C*-glycosides. Using ***Silver(I) Trifluoromethanesulfonate*** (silver triflate) activation, the electrophilic glycoside center accomplishes electrophilic aromatic substitution of electron-rich aromatic rings.[5] *N*-Alkylation of the 2-pyridyl thioglycoside provides the activation for facile glycosidic linkage formation.[6]

Selective Reducing Agent.

2-Pyridinethiol, ***Tin(II) Chloride***, and Et_3N produce a complex that provides selective reduction of azides to primary amines, primary and secondary nitro alkanes to oximes, and tertiary nitro alkanes and nitro aromatics to hydroxylamines.[7] This complex tolerates ketone, sulfoxide, sulfone, nitrile, and ester functional groups. Applications to macrolactamization have been demonstrated.[27]

Synthesis of Electrophilic Agents.

The chloramine generated from ***Morpholine*** reacts with 2-pyridinethiol to generate an electrophilic sulfenylation agent.[8] This reagent provides a mixed disulfide containing a 2-pyridyl unit (see also ***2-Pyridinesulfonyl Chloride*** and ***2-Pyridinesulfenyl Bromide***) which is *N*-alkylated by nonthiophilic agents such as ***Triethyloxonium Tetrafluoroborate***. The resulting salt is readily displaced to generate mixed disulfides (from thiols, thioamides, dithiocarbamates, thiocyanate), sulfenamides (from amines), or sulfides (from β-dicarbonyl nucleophiles).

2-Pyridinethiol is transformed into methyl 2-pyridinesulfinate using MeOH and ***N-Bromosuccinimide***. Enolate sulfinylation with this reagent, followed by thermal elimination, provides a formal dehydrogenation to an enone with (*E*) selectivity. Generating this reagent from 2-pyridinethiol provides an internal buffering during the elimination step.[9]

Application to Diels-Alder Chemistry.

Conjugate addition of 2-pyridinethiol to menthol propiolate results in a *cis*-alkene which undergoes a diastereoselective oxidation of sulfur using ***m-Chloroperbenzoic Acid*** to yield a highly reactive dienophile. Subsequent application to cycloaddition chemistry has been demonstrated.[10,28]

Other Applications.

2-Pyridinethiol photochemically adds to alkenes to yield a bis(2-pyridylethyl) disulfide.[29] 2-Pyridinesulfenylation of 2,5-piperazinediones provides an opportunity for carbon-carbon bond formation using silver triflate activation in the presence of a silyl enol ether.[30] Under nickel catalysis, 2-pyridinethiol provided a 2-pyridyl unit in an aryl-aryl coupling with subsequent loss of sulfur.[31]

---

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Pyridinium Chloride

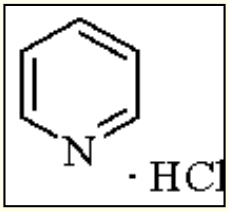

[628-13-7] · C_5H_6ClN · Pyridinium Chloride · (MW 115.57)

(cleavage of oxiranes to chlorohydrins;[3] cleavage of phenol methyl ethers;[1,5] removal of *N*-trityl protecting groups;[6] catalyst for Fischer indole synthesis[7])

Alternate Name: pyridine hydrochloride.

Physical Data: mp 144 °C (dec).

Solubility: sol water, chloroform, ethanol; insol ethyl ether.

Form Supplied in: white hygroscopic crystalline solid.

Preparative Method: precipitates as a 98% yield of 99.8% pure white crystals when ***Hydrogen Chloride*** gas is passed through a solution of ***Pyridine*** in ether.[1,2]

Purification: recrystallize from chloroform/ethyl acetate and wash with ethyl ether. Can be dried by refluxing in benzene with azeotropic removal of water.

Handling, Storage, and Precautions: stable solid, with no apparent decomposition after several years of storage at room temperature. The salt is very hygroscopic and must be protected from moist air.

Cleavage of Oxiranes.

The title reagent (**1**) reacts with a variety of cyclic and acyclic oxiranes to give chlorohydrins. Typically, a 2:1 ratio of (**1**) to oxirane is employed and the reactions are carried out at ambient temperature in chloroform or pyridine (eqs 1 and 2).[3]

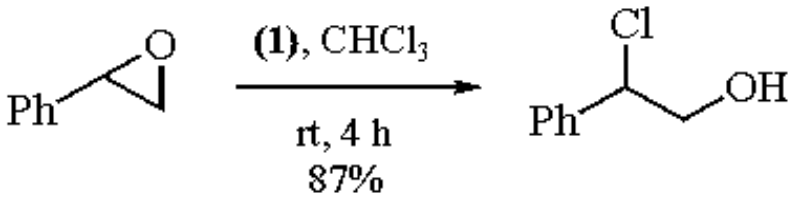

(1)

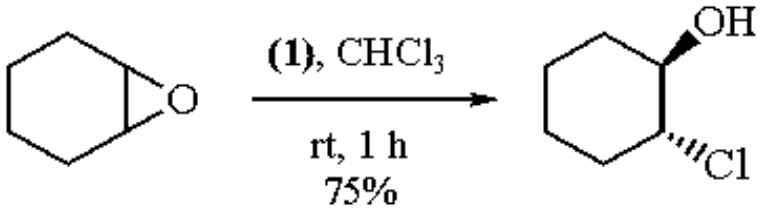

(2)

Cleavage of Phenol Methyl Ethers.

Treatment of anisole with 3 equiv of (**1**) at 200-220 °C provides phenol (eq 3).[4] A modification of the procedure is reported which allows

for a more convenient in situ preparation of (**1**).[5] The use of the title reagent to cleave phenol methyl ethers avoids the strong acidic or basic conditions of alternative methods. This has found utility in the cleavage of substrates with acid- or base-sensitive moieties (eq 4).[5]

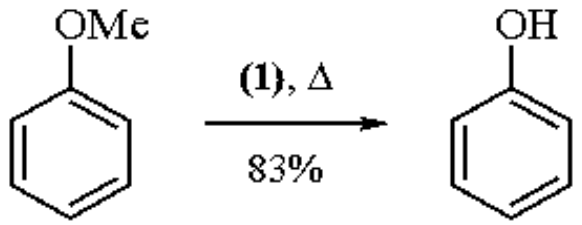

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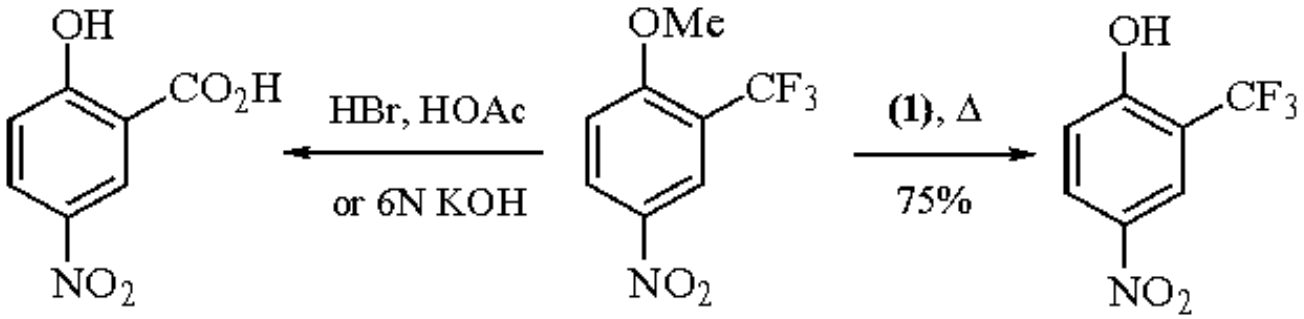

(4)

Cleavage of *N*-α- and *N*-τ-Trityl Groups from Histidine.

The title reagent (**1**) catalyzes cleavage of trityl protecting groups from the *N*-α position of histidine, as well as the *N*-τ position on the imidazole moiety of histidine.[6] In a typical reaction, the trityl group is cleaved with 5% of (**1**) in MeOH at 60 °C. It appears to have application in orthogonal peptide protection schemes. Boc and Fmoc protecting groups are unaffected under these conditions (eq 5).

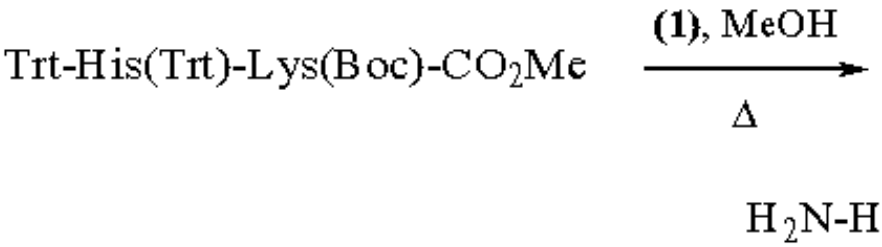

(5)

Catalysis of the Fischer Indole Synthesis.

Reagent (**1**) displays utility as a mild catalyst for the Fischer indole synthesis of substrates with strong acid sensitivity (eq 6).[7]

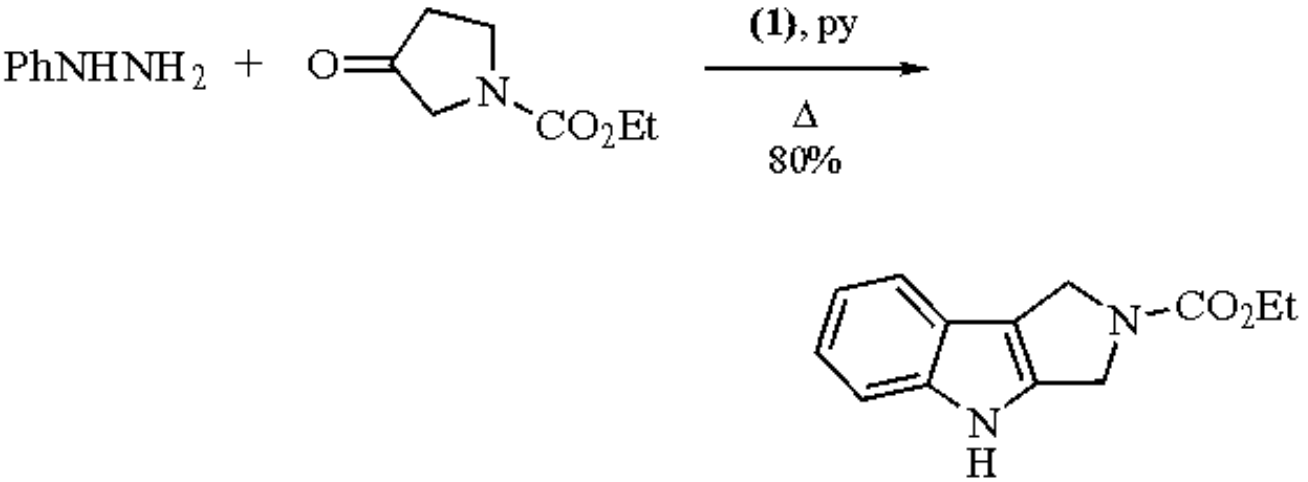

(6)

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Pyridinium Chlorochromate[1]

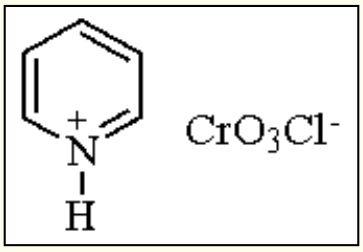

[26299-14-9] · $C_5H_6ClCrNO_3$ · Pyridinium Chlorochromate · (MW 215.57)

(stable versatile oxidizing agent for many functional groups;[1a] can oxidize activated C-H bonds,[2b] C-C bonds,[2b] and C-B bonds;[2b] can halogenate enol silyl ethers[2b])

Alternate Name: PCC.

Physical Data: mp 205 °C (dec).

Solubility: insol dichloromethane, benzene, diethyl ether; sol acetone, acetonitrile, THF.

Form Supplied in: yellow-orange solid; widely available.

Handling, Storage, and Precautions: the dry solid may be stored in contact with air, but in the absence of moisture. Reaction solvents should generally be purified and anhydrous. Reported to be a cancer suspect agent. Should be used in a fume hood.

Oxidation of Primary and Secondary Alcohols.

PCC has the capability to convert primary and secondary alcohols to aldehydes and ketones with great efficiency. The yields are typically equal to or greater than those obtained by the Collins method (see ***Dipyridine Chromium(VI) Oxide***), which customarily requires a fivefold excess of reagent. PCC oxidations are normally carried out in dichloromethane with 1.5 equiv of reagent suspended in the organic solvent at room temperature and are usually complete within 1-2 h (eqs 1-4).[2a]

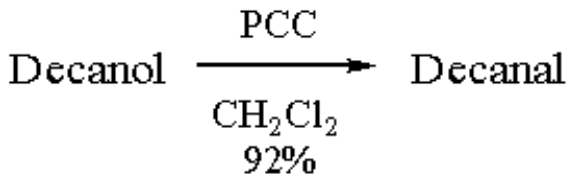

(1)

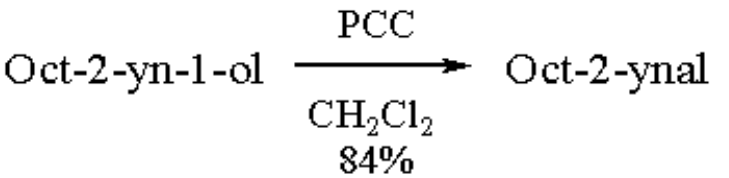

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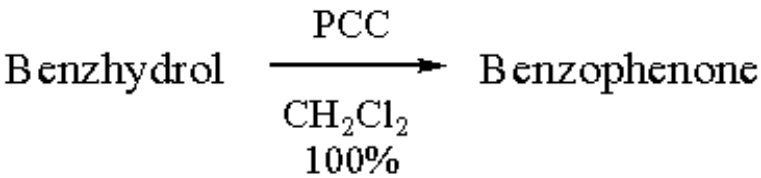

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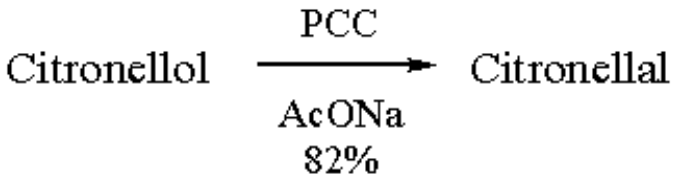

(4)

More polar solvents, such as acetonitrile or acetone, in which PCC has higher solubility, lead to longer reaction times. Overoxidations are rare, but acids can be directly prepared from aldehydes with stoichiometric ***Sodium Cyanide*** and PCC in THF.[3] The reagent shows a slightly acidic character. With compounds bearing acid-sensitive groups, the reaction can be buffered with powdered sodium acetate. However, *cis-trans* isomerization of some allylic alcohols can occur under these conditions (eq 5).[2a]

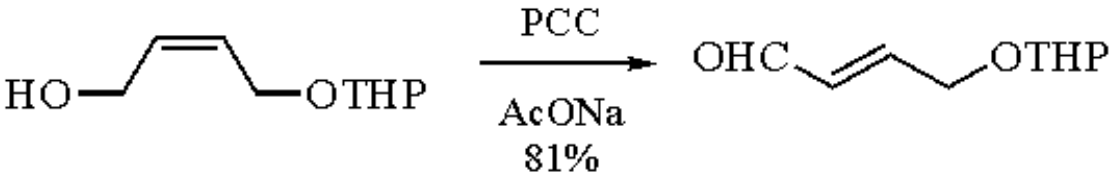

(5)

PCC appears to be particularly suitable for moderate to large scale preparations, and it has proven to be the reagent of choice for the oxidation of primary alcohols to aldehydes and of secondary alcohols to ketones.[2a,b] Good yields of ketones and aldehydes are regularly obtained.[2a,b] Advantages of PCC include the fact that it does not possess the hygroscopic nature of the chromium trioxide-pyridine complex, and it is prepared via a much less hazardous procedure. However, workup and removal of chromium-containing byproducts is often tedious and difficult with the oxidant.[2a] Several modifications of PCC have been developed to increase both the efficiency and the selectivity of the reagent, and to reduce side reactions.[4] The chlorochromate anion has been supported on a polymeric matrix. Poly(vinylpyridinium chlorochromate), easily prepared, is a recyclable and useful reagent in the oxidation of alcohols to carbonyl compounds in 60-100% yield. This reagent has advantages with regard to product isolation, although its use is limited by the scale of the reaction that can be performed conveniently.[5] Furthermore, the reactivity of PCC in the oxidation of alcohols can be increased by adding anhydrous ***Acetic Acid*** as catalyst to the reaction mixture[6] or by using sonochemical conditions.[7] The addition of ***Molecular Sieves*** in the oxidation of various alcohols results in a dramatic rate enhancement.[8a] Comparative studies indicate that 3 Å sieves give the best results (3 Å > 4 Å > 10 Å > 5 Å).[8b] PCC can perform oxidations of slow-reacting alcohols, such as the secondary hydroxyl groups in carbohydrates and nucleosides. These reactions proceed readily in refluxing benzene, but they are very slow in dichloromethane.[9] The oxidations are conveniently carried out by adding 3 Å molecular sieves to a suspension of PCC in dichloromethane, providing an efficient synthesis of keto sugars and keto nucleosides (eq 6).[8a]

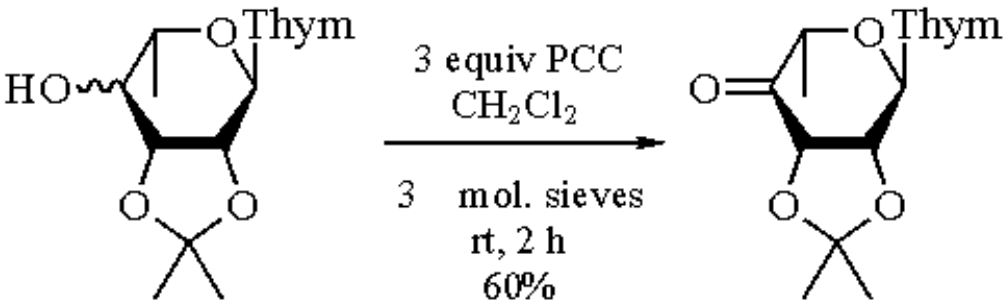

(6)

The use of molecular sieves in many types of oxidations is now commonplace. 2-Nitro alkanols, available by a nitro-aldol reaction, can be oxidized by PCC and molecular sieves to α-nitro ketones in 60-85% yield. Usually the starting compounds undergo a retro-aldol reaction under acidic conditions (eq 7).[8c] On the other hand, (*Z*)-2-butene-1,4-diols are converted by reaction with PCC and molecular sieves into substituted furans in 35-90% yields (eq 8).[10]

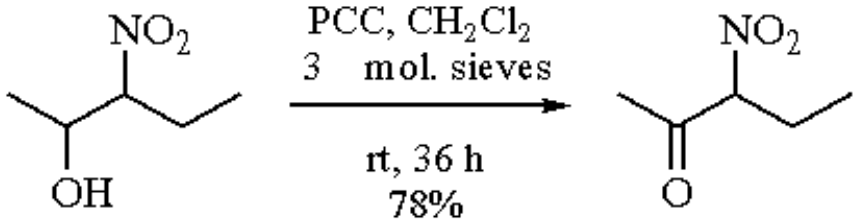

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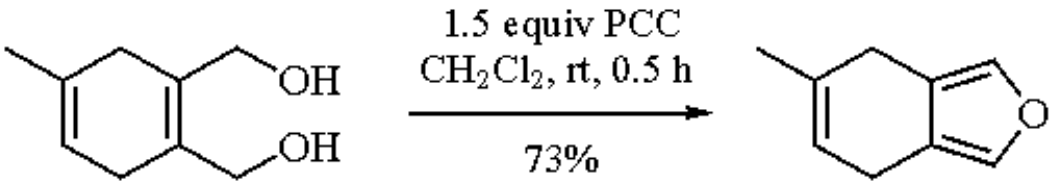

(8)

Synthetically useful changes in the properties of pyridinium chlorochromate have been introduced in the oxidation of hydroxy steroids. PCC, in refluxing benzene, is a convenient reagent for the oxidation and concomitant isomerization of steroidal Δ^5-3β-alcohols to the corresponding Δ^4-3-ketones in high yield.[11] However, in the presence of anhydrous calcium carbonate, PCC can effect the high yield, selective oxidation of steroidal homoallylic alcohols to the corresponding β,δ-unsaturated ketones.[12] Remarkable selectivity is obtained in the oxidation of steroid allylic alcohols by adding 2% of ***Pyridine*** to the reagent in dichloromethane at 2-3 °C. Quasiequatorial allylic alcohols are oxidized faster than nonallylic axial ones (eq 9).[13] Similar properties are found for the combination of PCC and pyrazole (2%),[14] PCC and 2,3-dimethylpyrazole (2%),[15] and PCC and benzotriazole (2%).[16]

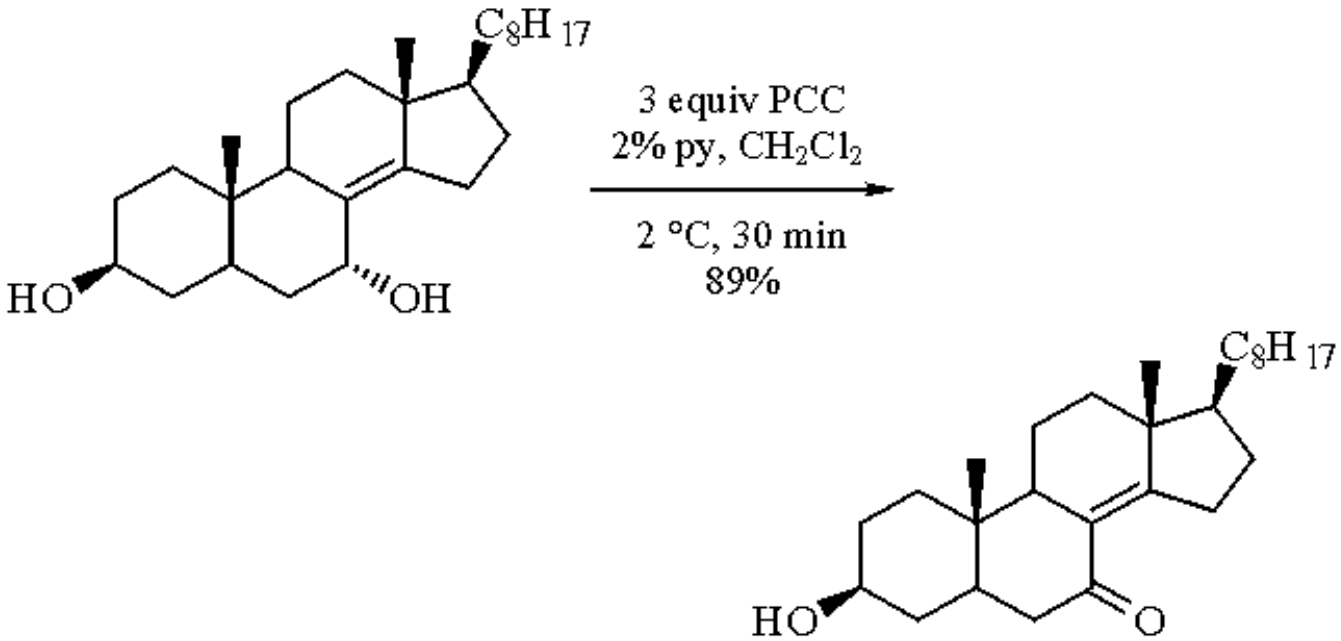

(9)

Oxidation of Unsaturated and Cyclopropyl Tertiary Alcohols.

Tertiary allylic alcohols, obtained by the addition of ***Vinyllithium*** or vinylmagnesium chloride to a ketone, undergo oxidative rearrangements to α,β-unsaturated aldehydes in good yields in the presence of PCC. The absence of diene products is remarkable in view of the sensitivity of the starting compounds towards dehydration. The process involves a two-carbon chain-lengthening of the starting ketones, and is synthetically equivalent to a direct crossed-aldol condensation between a ketone and acetaldehyde (eq 10).[17]

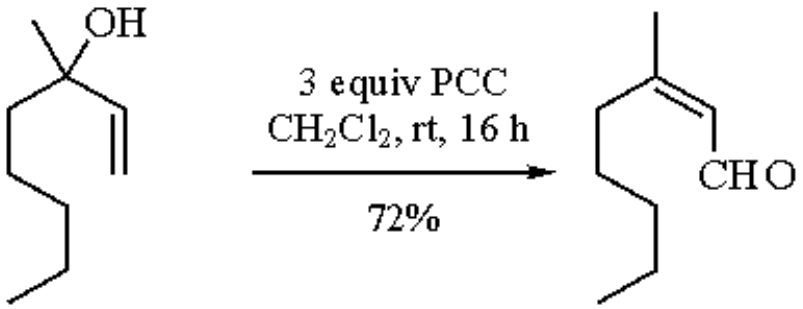

(10)

The oxidation of tertiary cyclopropyl alcohols leads to the formation of the corresponding β,γ-unsaturated ketones (eq 11). The reaction represents an excellent method for converting ketones to chain-extended β,γ-enones, since the starting compounds can be prepared by addition of cyclopropyl organometallic reagents to ketones.[18]

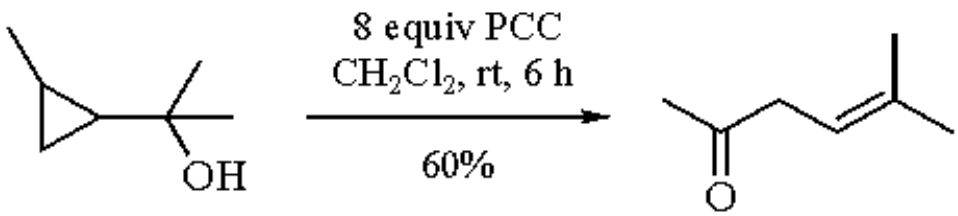

(11)

Cyclic tertiary allylic alcohols, prepared by 1,2-addition of alkyllithium reagents to α,β-enones, are oxidized by PCC to transposed γ-alkyl-α,β-unsaturated ketones. Yields are excellent in the case of cyclic alcohols, but only moderate with acyclic alcohols. The overall result of this reaction sequence is an efficient method for alkylative 1,3-carbonyl transposition (eq 12).[19a-d]

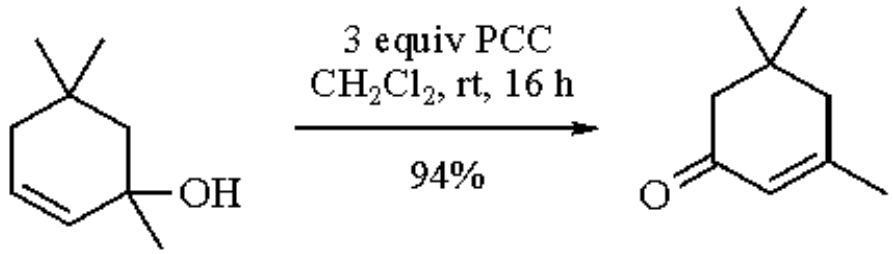

(12)

When the tertiary allylic alcohol is suitably disposed near an alkene double bond, PCC is able to perform synthetically useful substituent-directed oxidations, the result of which depends on the relative position of the two groups. Cyclic tertiary γ-hydroxy alkenes can undergo a regio- and stereoselective cyclization, giving a single β-hydroxy cyclic ether through an intramolecular C=C oxidation initiated by PCC (eq 13),[20a] while linear γ,δ-dihydroxy alkenes are cyclized to *cis*-2,5-disubstituted tetrahydrofurans (eq 14).[20b]

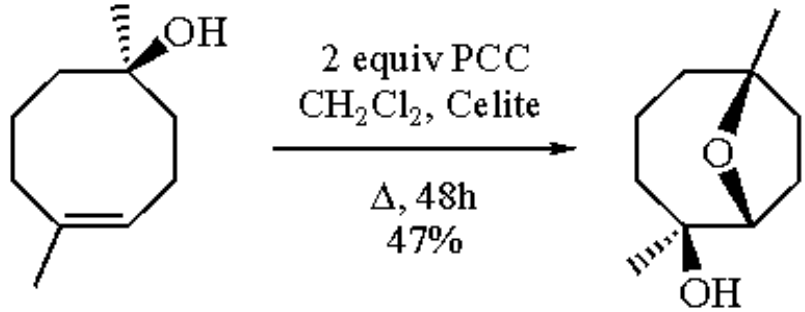

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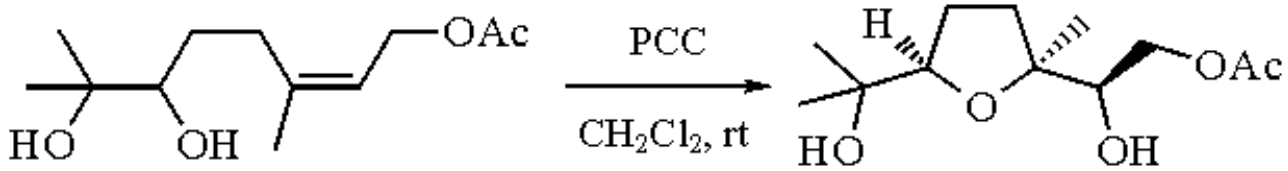

(14)

On the other hand, the oxidation of tertiary γ-hydroxy terminal alkenes brings about both oxidative cyclization and fragmentation of the double bond with loss of one carbon atom, and thus provides an efficient route to γ-lactones (eq 15).[21]

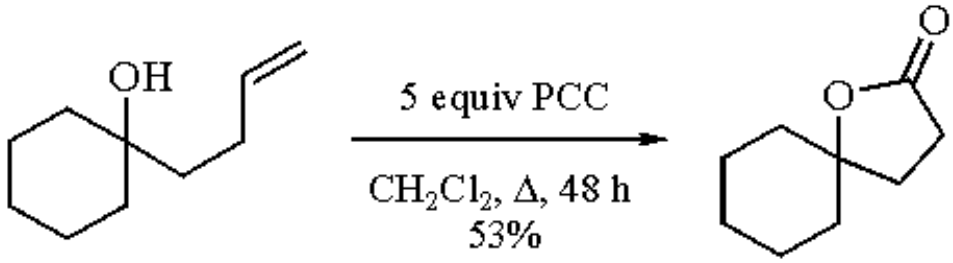

(15)

When a tertiary alcohol is homoallylic, reaction with PCC can yield a ketone resulting from oxidative fragmentation. The cyclic tertiary homoallylic alcohol shown in eq 16 furnishes a mixture of two isomeric cyclopentenones in a 1:1.7 ratio in 62% yield.[22] Another interesting example of PCC reactivity is the conversion of the acyclic tertiary homoallylic alcohol in eq 17 to a keto lactone, albeit in moderate yield. A large excess of oxidant is necessary.[21d]

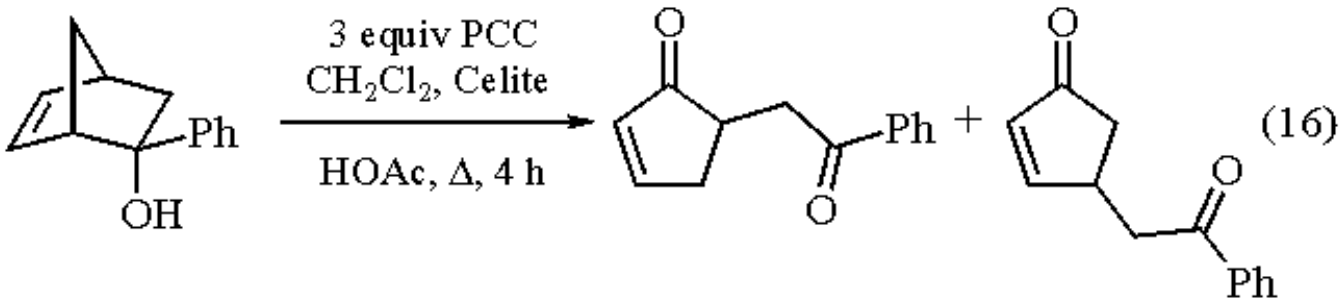

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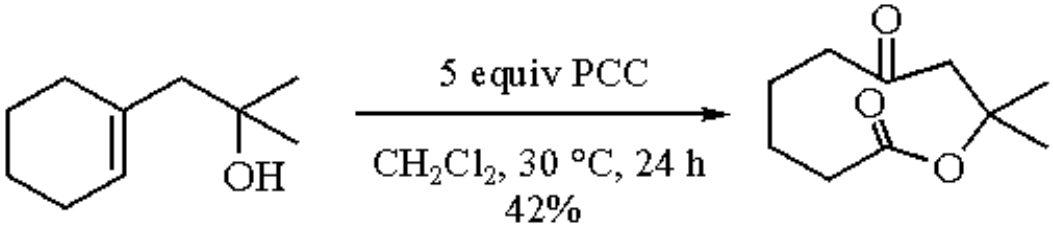

(17)

If a homoallylic alcohol is secondary, reaction with PCC leads to the formation of a mixture of γ-hydroxy-α,β-unsaturated enones, through a γ-oxy functionalization (eq 18).[23]

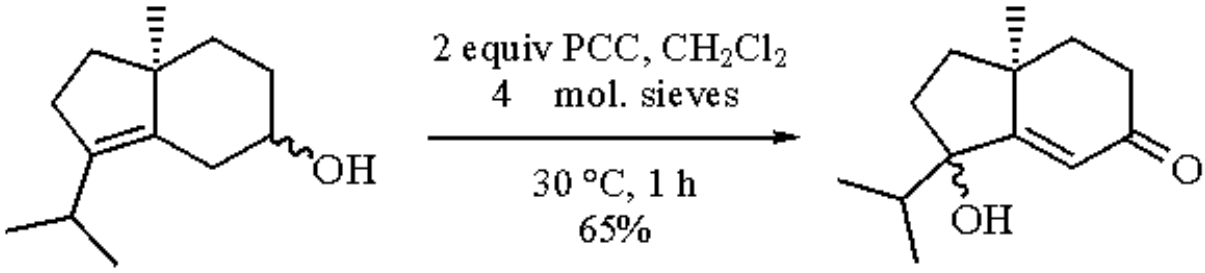

(18)

Oxidative Cationic Cyclization.

The mild acidic character of PCC has been used to advantage in an essential one step conversion of (-)-citronellol to (-)-pulegone (eq 19).[24]

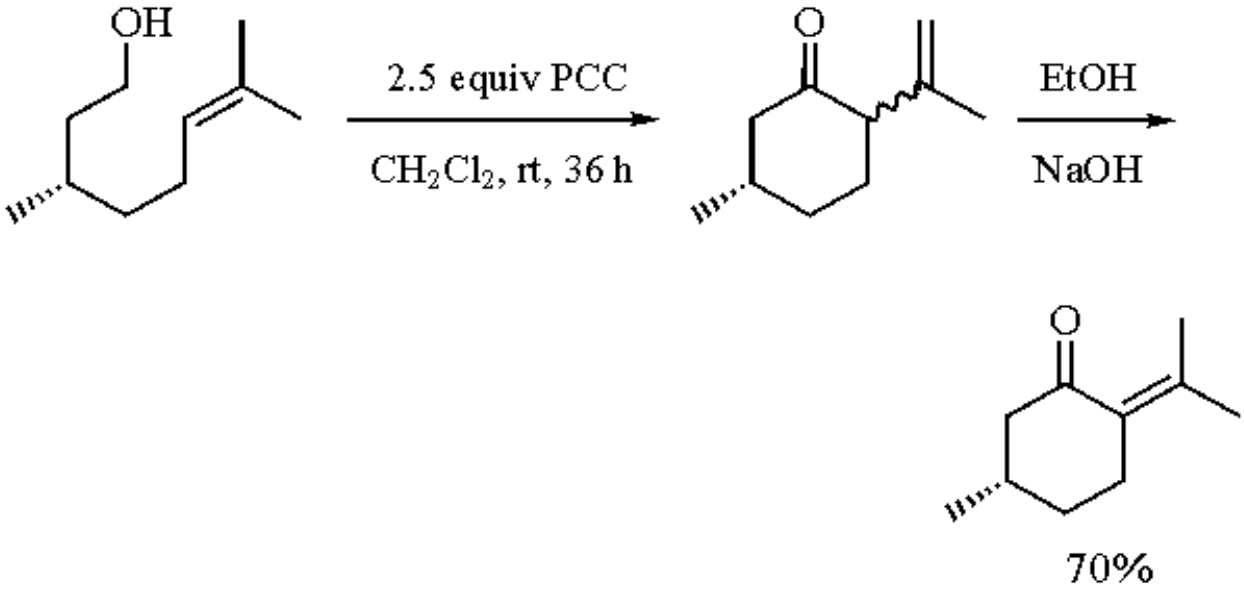

(19)

The oxidative cationic cyclization is useful for the annulation of linear and cyclic unsaturated alcohols or aldehydes to form cyclohexenones (eqs 20 and 21).[25]

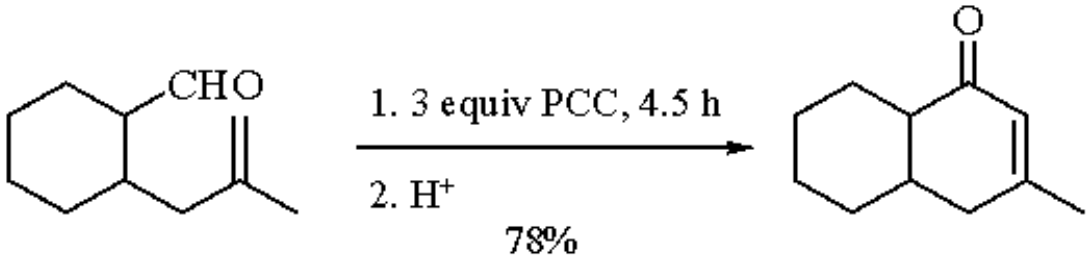

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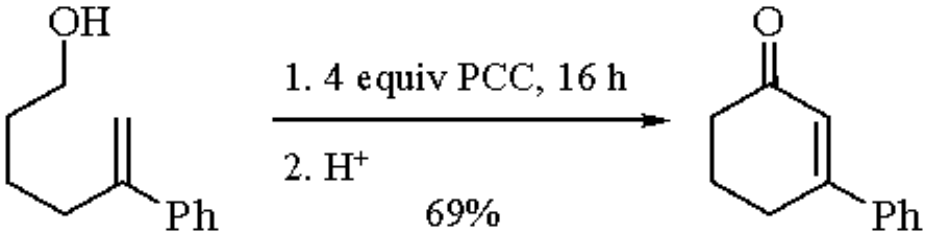

(21)

A limitation is that this reaction cannot be used for formation of cyclopentenones. The reaction is also limited to preparation of β,β-disubstituted α,β-unsaturated cyclohexenones: in fact, cyclization is only observed with substrates capable of affording a tertiary cation as the initial cyclic intermediate. Other substrates (e.g. **1**) do not undergo cyclization, even under more forcing conditions. However, the process represents a milder and more efficient alternative to the two-step cationic cyclization for preparing α,β-unsaturated enones.[26]

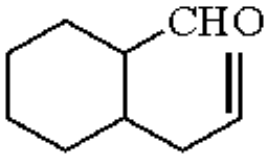

(1)

Oxidation of Activated C-H Bonds.

PCC is of value in the allylic oxidation of compounds containing activated methylenes. 5,6-Dihydropyrans (eq 22)[27] and 2,5-dihydrofurans (eqs 23 and 24) are oxidized to the corresponding lactones.[28] The reaction is limited to cyclic benzylic and allylic ethers.

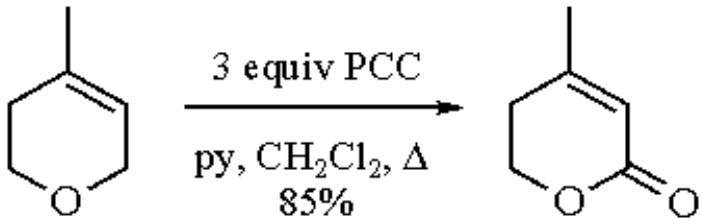

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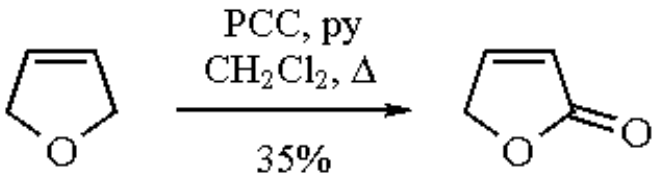

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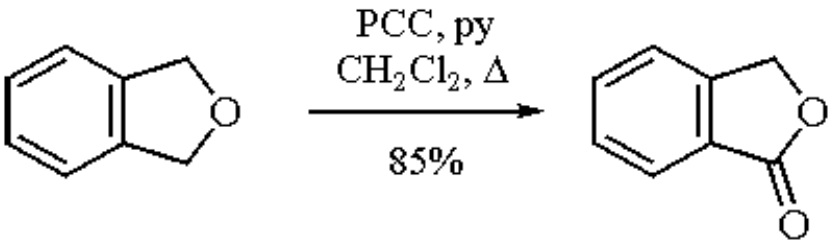

(24)

PCC is the reagent of choice in the allylic oxidation of Δ^5-steroids to 7-keto derivatives. The reaction can be carried out using PCC in refluxing benzene or PCC in DMSO solution at 100 °C (eq 25).[29] These solvents are claimed to be superior to dichloromethane, which must be used in large excess in this reaction.[30]

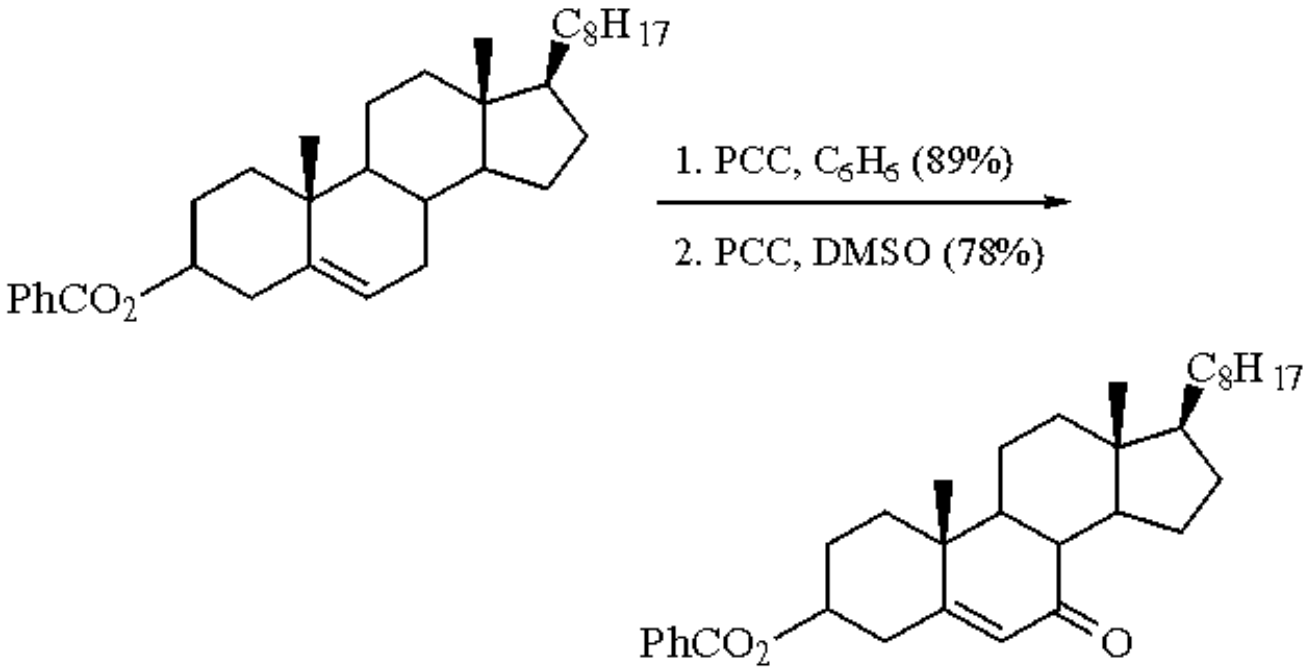

(25)

The capability of PCC to selectively perform allylic oxidation of methylene groups has frequently been utilized,[31] as in the synthesis of a key intermediate related to the taxol ring A (eq 26).[31b]

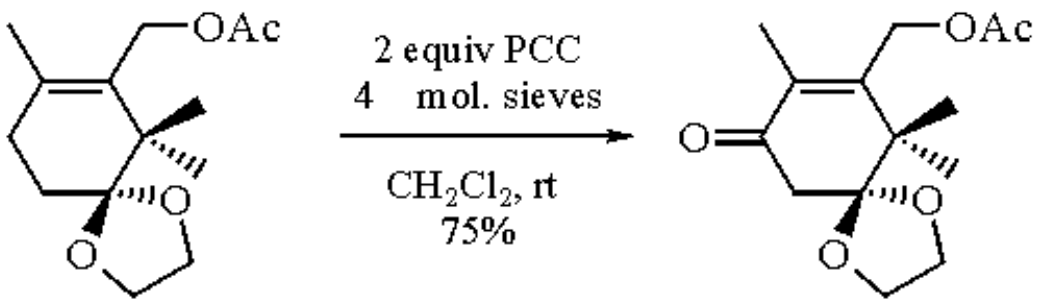

(26)

In a similar fashion, the smooth oxidation of benzylic hydrocarbons to aryl ketones can be achieved by adding a powdered and homogenized mixture of PCC and ***Celite*** to a benzene solution of the substrates (eqs 27 and 28).[32] The reaction has been successfully applied to a variety of compounds, such as 1,2,3,4-tetrahydrophenanthrene,[33] 12-methoxypodocarpa-8,11,13-triene,[34] and biscyclophanes.[35]

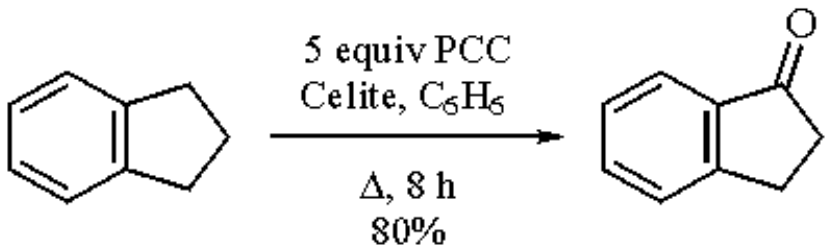

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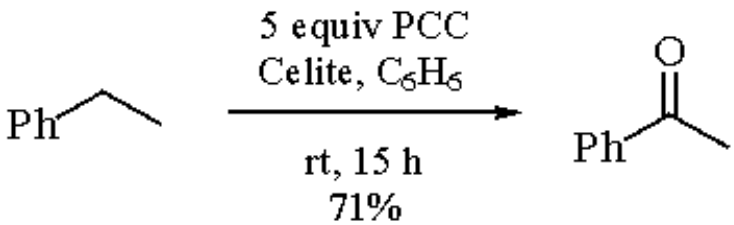

(28)

The transformation of activated methylene groups to ketones shows particular applicability to the conversion of benzyl alkyl ketones to the corresponding 1,2-diketones in high yields (eq 29).[28] Since the starting materials appear to be sensitive to the acidic PCC, anhydrous pyridine must be added to the reaction. This oxidation fails with dialkyl ketones.[28]

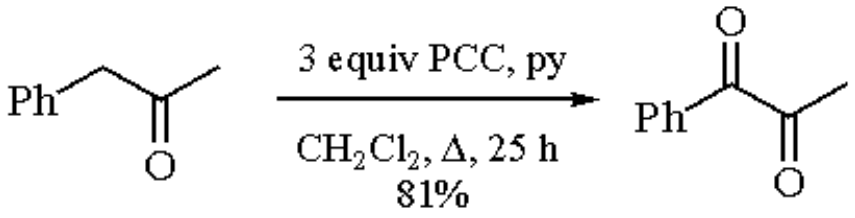

(29)

PCC is able to oxidize cyclic 1,4-dienes to dienones (eq 30).[36] PCC does not effect oxidation of isolated double bonds, or of more reactive systems such as diphenylmethane or allylbenzene. Complementary selectivity (1:3) is achieved with the Collins reagent.

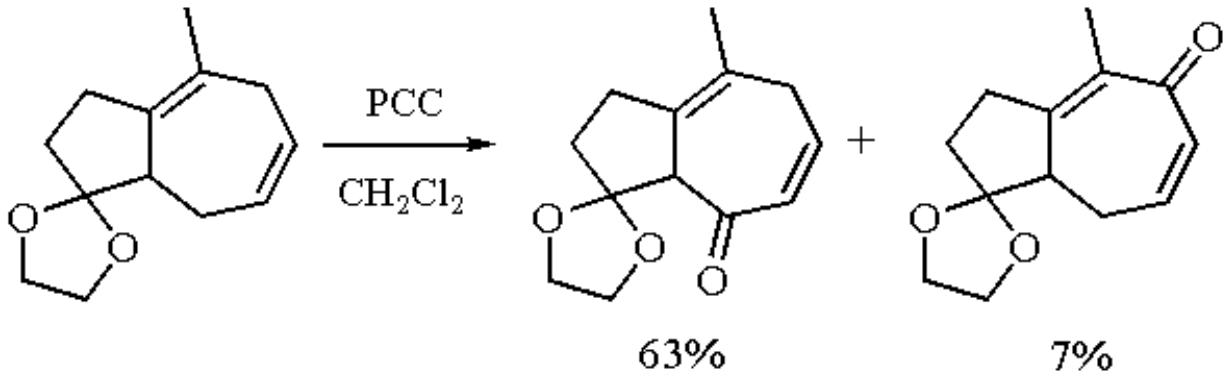

(30)

Phenyloxiranes can undergo a one step C-C bond cleavage to carbonyl compounds by reaction with PCC and molecular sieves (52-75%) (eq 31).[37] The presence of a phenyl group seems to be essential for efficient C-C cleavage. Under similar conditions, alkyl-substituted oxiranes are prevalently converted into α-hydroxy ketones (eq 32).

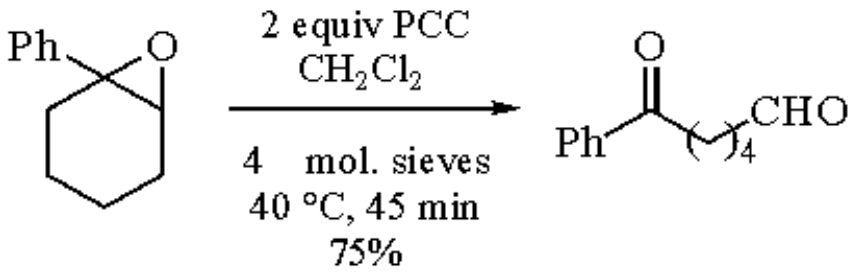

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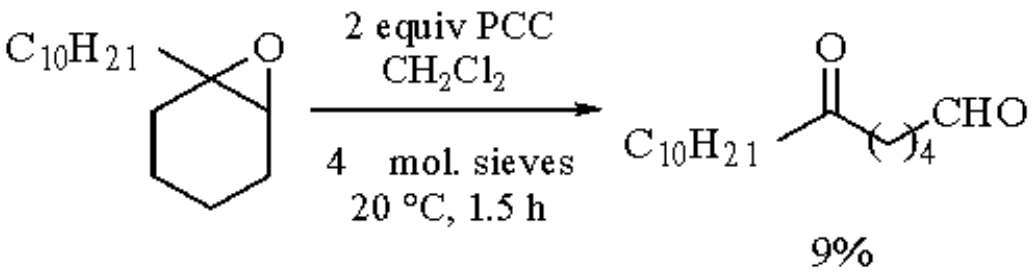

(32)

PCC is reported to perform oxidative fragmentation of carbon-carbon bonds of 1,2-diols to give carbonyl compounds in excellent yields (eq 33).[38] Hydroxymethyl cyclic ethers also undergo fragmentation; tetrahydrofuranmethanol derivatives lead to γ-lactones in 52-95% yield (eqs 34 and 35),[39] while 5-hydroxymethyl groups of 1-methoxy-2,3-*O*-isopropylidene-D-ribose are cleaved to γ-lactone derivatives in 50-60% yield (eq 36).[40] These transformations usually require more vigorous conditions than those needed for alcohol oxidation.

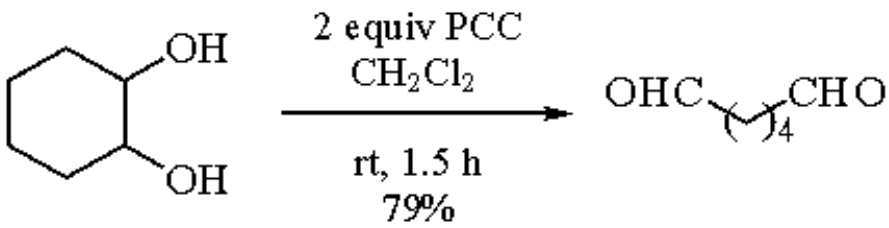

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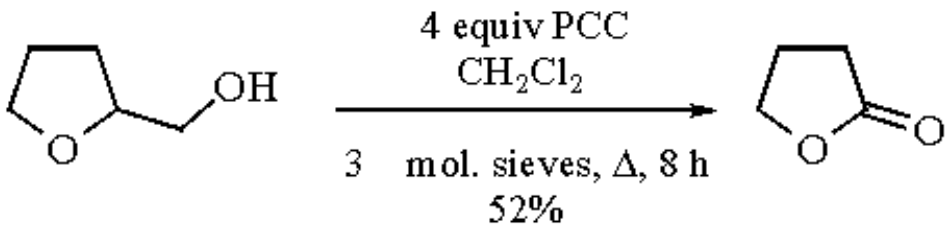

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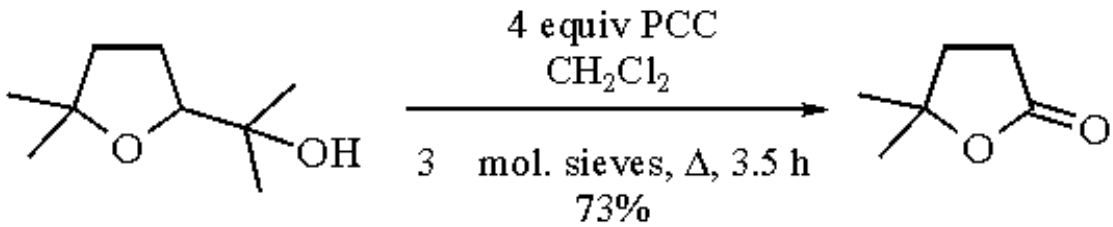

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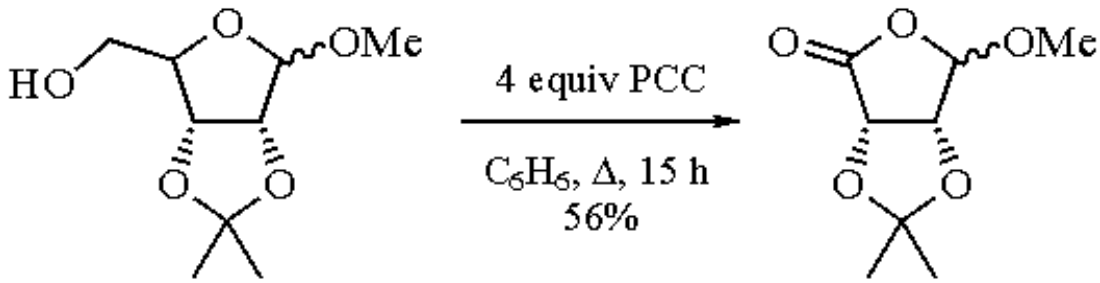

(36)

Oxidation of C=C Activated Double Bonds.

PCC can behave as an oxidizing, weakly electrophilic species, capable of attacking particularly nucleophilic alkenes and of bringing about interesting reactions. PCC oxidizes linear and cyclic enol ethers to esters and lactones in 75-95% yield (eqs 37 and 38).[41]

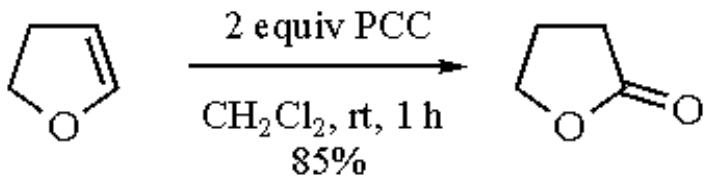

(37)

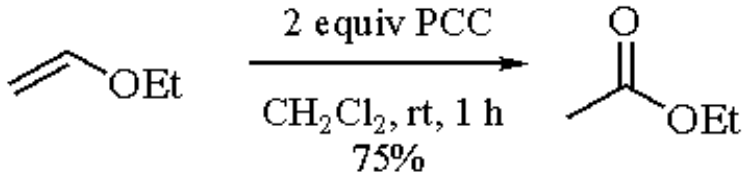

(38)

According to the reported mechanism, the key step involves a 1,2-hydride shift from the α- to the β-carbon of the ether. When the enol ethers are α,α´-disubstituted, there is no possibility for such a hydride shift; reaction with PCC then yields a smooth oxidative cleavage of the nucleophilic alkene to esters or keto lactones in 45-90% yield (eqs 39 and 40).[42]

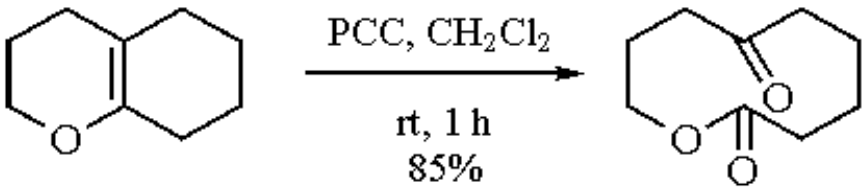

(39)

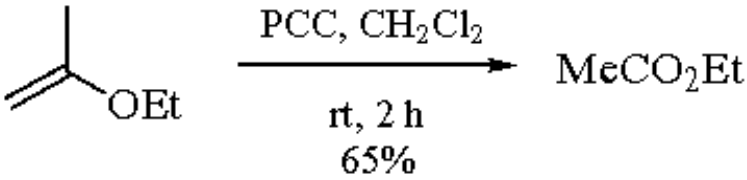

(40)

The reaction can be applied only to cyclic enol ethers. However, the simplicity of the procedure and the high yields obtained make the methodology synthetically useful for preparative purposes. In fact, the reaction has been extensively applied as a general approach to γ-lactones from the corresponding α-alkylidene five-membered enol ethers using as conditions treatment with 4 equiv of PCC and celite at room temperature in dichloromethane (eqs 41 and 42).[43] An important feature of this procedure is that, under the reaction conditions, other isolated carbon-carbon double bonds and benzylic groups present in the molecule are not affected.

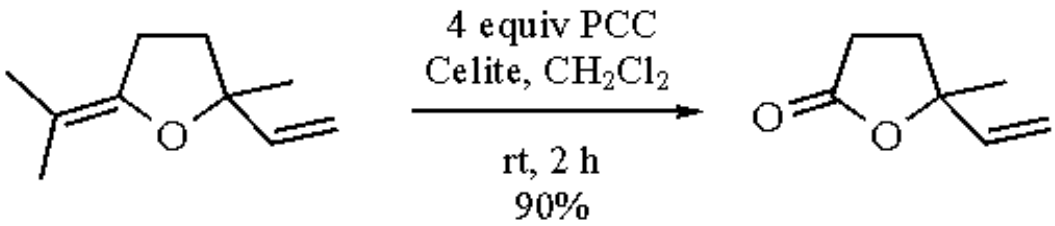

(41)

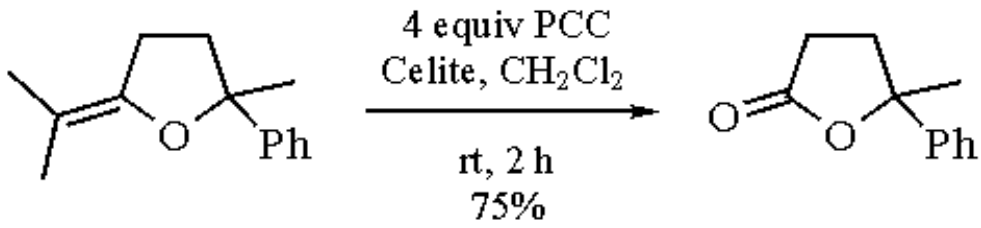

(42)

PCC has proven to be the reagent of choice for the selective oxidation of a specific class of cyclic enol ethers: 1,4-dioxenyl alcohols. The allylic alcohols can be easily obtained by addition of 2-lithio-5,6-dihydro-1,4-dioxin to ketones and aldehydes. Reaction with PCC thus provides a method for one-carbon homologation of ketones and aldehydes to α-hydroxy acids (39-61%) (eq 43) and α-keto acids (54%) (eq 44), respectively.[44] The oxidation occurs regiospecifically at the dioxene site. While the oxidation of the allylic alcohols occurs in a few minutes, the α,β-unsaturated ketones require a longer reaction time, owing to the deactivation of the carbon-carbon double bond.

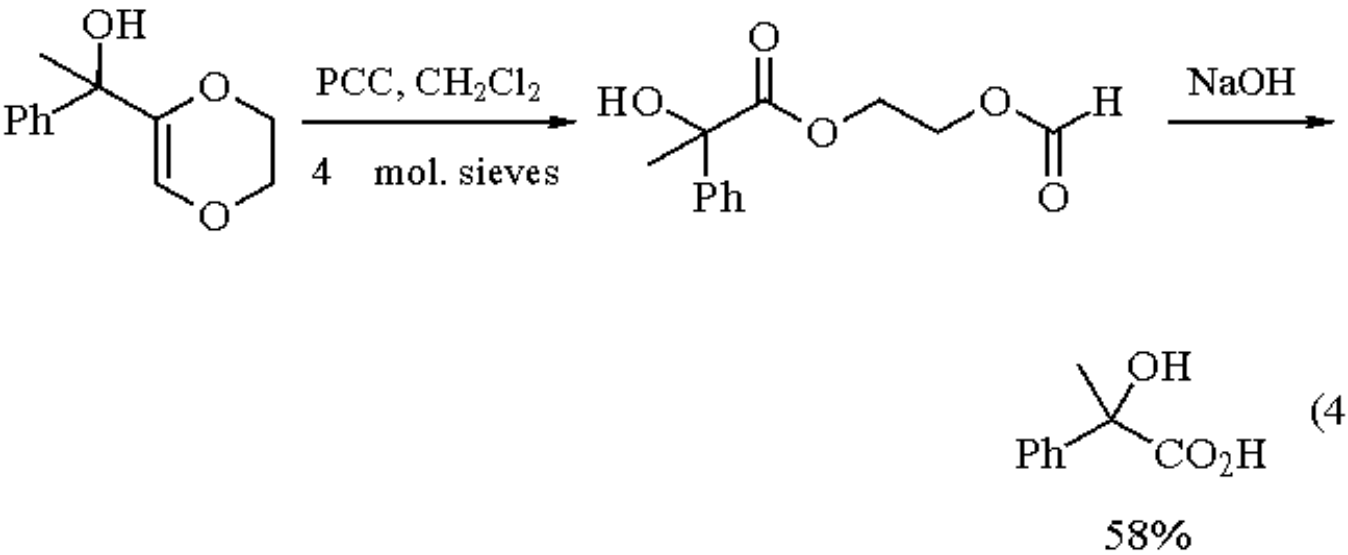

(43)

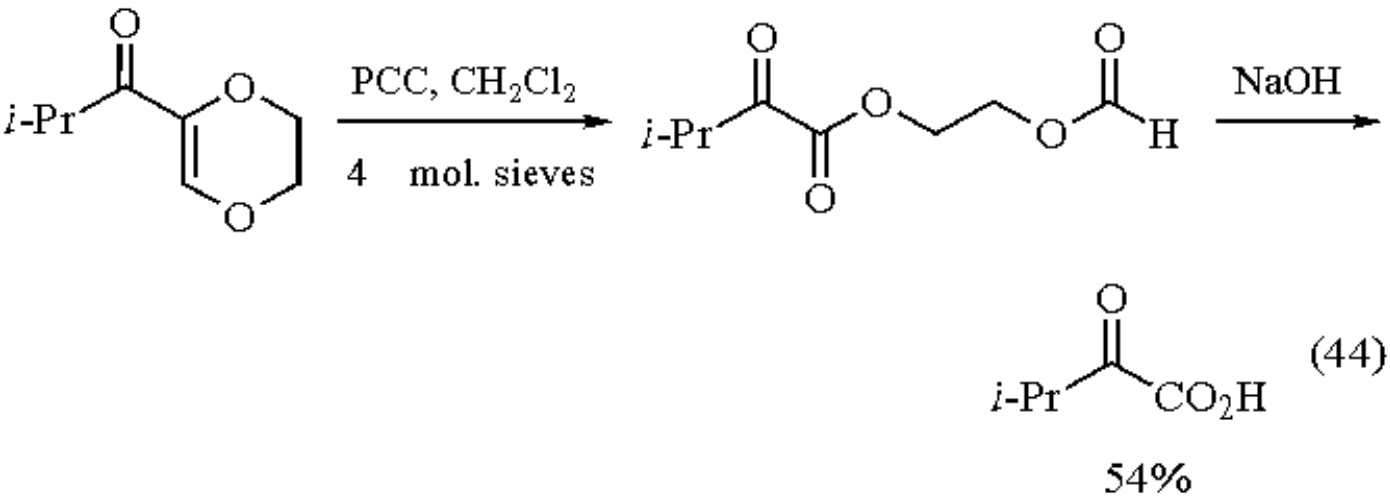

(44)

Aryl-substituted alkenes can be selectively cleaved in the presence of alkyl-substituted alkenes. Treatment of acyclic aryl alkenes with PCC and celite in dichloromethane under reflux results in oxidative opening of the carbon-carbon double bond to the corresponding carbonyl compounds in 72-90% yield (eq 45).[45] Alkyl-substituted acyclic alkenes are in general unreactive towards PCC, while cyclic alkenes undergo allylic oxidation, albeit in low yield (eq 46).[45]

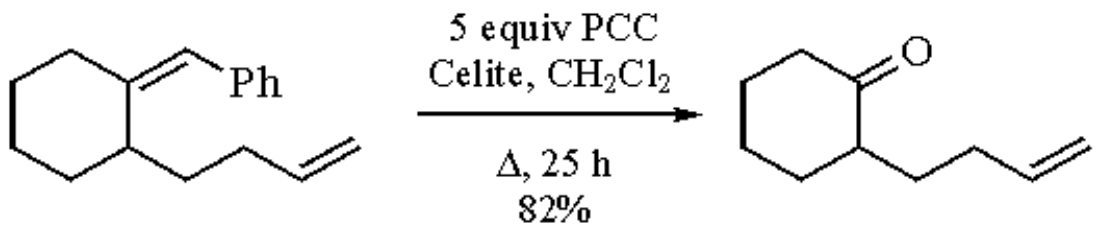

(45)

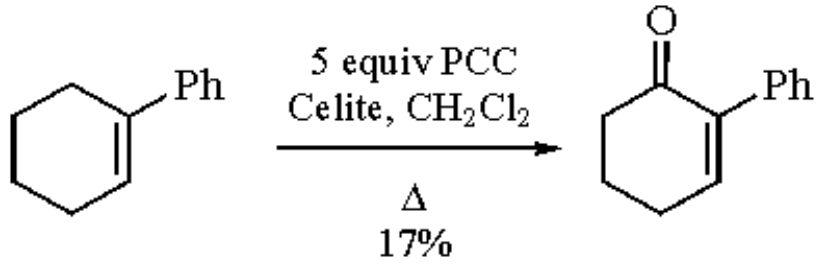

(46)

PCC has demonstrated its particular reactivity towards furan derivatives, which are well known for their sensitivity to oxidizing and electrophilic reagents.[46] Thus 5-methyl-2-furylcarbinols undergo oxidative ring enlargement to hexenuloses in very high yields (90-94%) (eq 47).[47]

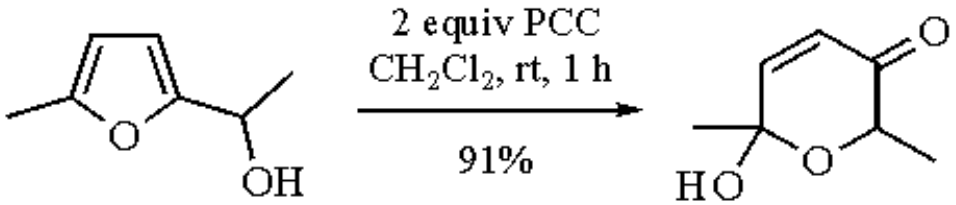

(47)

Another application involves 5-bromo-2-furylcarbinols, which are converted by PCC into γ-hydroxybutenolides in 60-75% yield (eq 48).[48] Both conversions point out an unusual regiospecific reactivity of pyridinium chlorochromate, since only the oxidation of the furan ring occurs, in spite of the presence of a secondary alcoholic function, which remains untouched. Different behavior is observed when the heteroaromatic nucleus is deactivated by the presence of a nitro group; in this case, PCC oxidizes the alcohol function, leading to alkyl 5-nitro-2-furyl ketones (eq 49).[49]

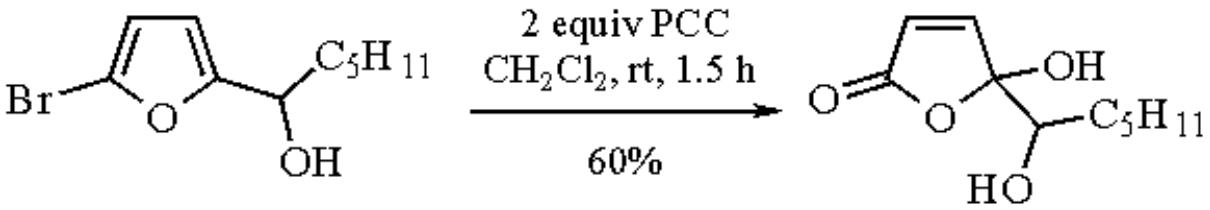

(48)

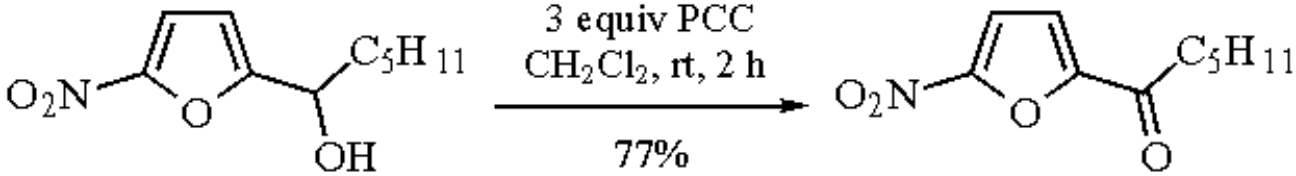

(49)

A further and important application of PCC involves the conversion of 2,5-dialkylfurans, via oxidative ring fission, to *trans*-α,β-unsaturated 1,4-dicarbonyl compounds in a very simple manner. The reagent must be utilized in a large excess in dichloromethane at reflux for 24 h. Invariably, the products are obtained with *trans* configuration. The *cis*-isomers are formed first and are then isomerized by the acidic reagent (eq 50).[50] Lower yields of enedicarbonyl compounds are obtained from 2-alkylfurans (eq 51).[50]

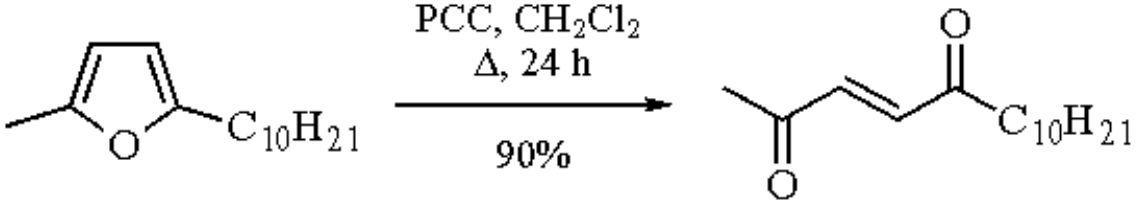

(50)

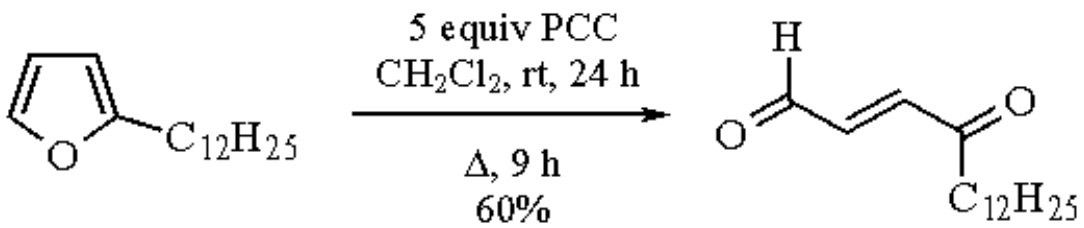

(51)

PCC shows a remarkable reactivity towards more nucleophilic furans, such as 2-alkylthiofurans, which are rapidly converted by action of the reagent in dichloromethane at room temperature for 2 h into *S*-alkyl 4-oxo-2-alkenethioates in high yields (eq 52).[51] (*Z*)-(*E*) Isomerization can be observed with longer reaction times, due to the acidic character of PCC. 2-Methoxy-5-methylfuran, which requires only 10 min of reaction, affords methyl (*Z*)-4-oxo-2-pentenoate, without the (*E*)-isomer being detectable (eq 53).[51]

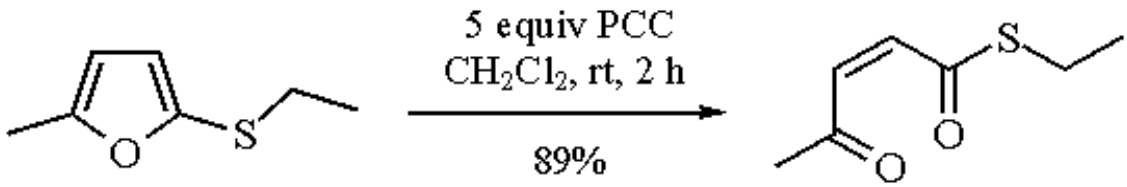

(52)

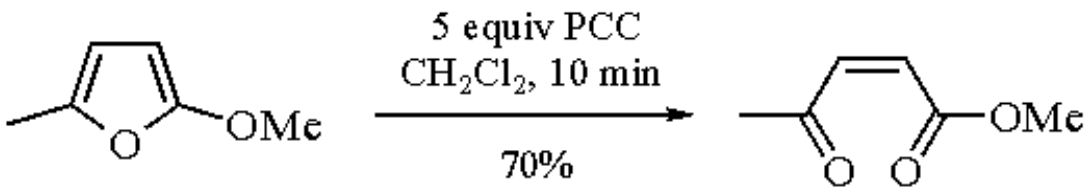

(53)

Oxidation of Carbon-Boron Bonds.

PCC is a superior reagent for the oxidation of organoboranes to carbonyl derivatives by a convenient and mild procedure. Trialkylboranes, obtained by treatment of linear and cyclic di- and trisubstituted alkenes with ***Boron Trifluoride-Lithium Borohydride*** or ***Borane-Tetrahydrofuran***, afford the corresponding ketones by reaction with PCC in high yields (eqs 54 and 55).[52,53] Similar oxidation of dialkylchloroboranes, derived from cyclic alkenes by reaction with ***Monochloroborane-Dimethyl Sulfide***, gives ketones in 70-85% yield (eq 56).[54]

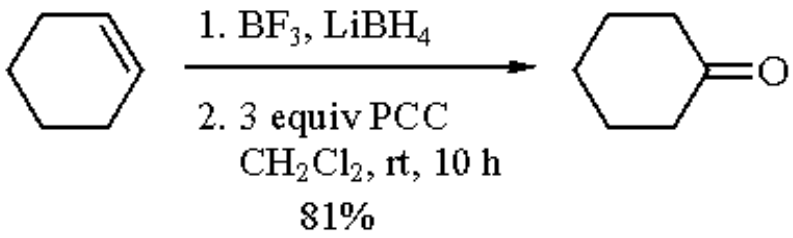

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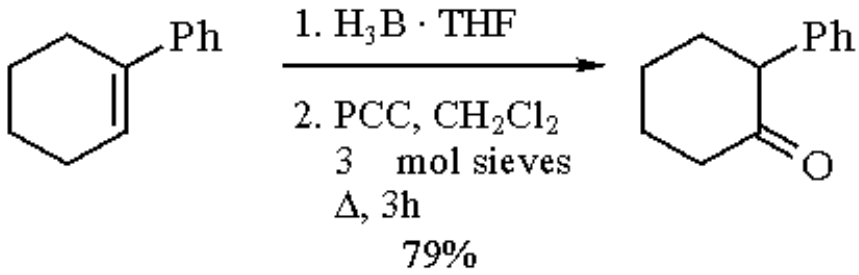

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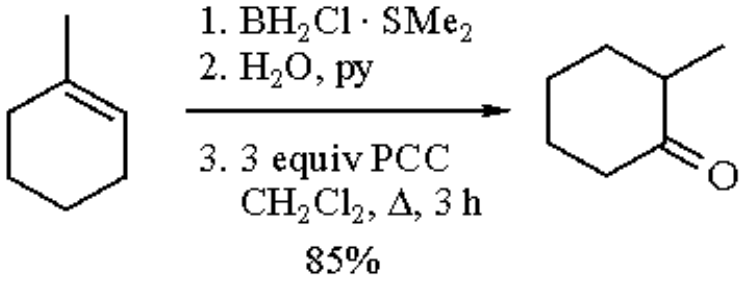

(56)

The success of this method for the conversion of terminal alkenes into aldehydes often depends on the nature of the hydroborating agent. In view of the poor regioselectivity (only 94% primary alkyl groups) and functional group tolerance of borane-THF and borane-dimethyl sulfide,[54] ***Disiamylborane*** is frequently utilized as a more selective hydroborating agent. Alkyldisiamylboranes are oxidized by PCC to aldehydes in 55-72% yield. The ester groups are compatible with the reaction (eq 57).[54,55b] The need for a large excess of PCC (6 equiv) for the oxidation of alkyldisiamylboranes can be avoided by using dialkylhaloboranes, which can be prepared with excellent regioselectivity (>99% primary alkyl groups) by hydroboration of terminal alkenes with monochloroborane-dimethyl sulfide complex. Dialkylchloroboranes are hydrolized in the presence of pyridine, and the resulting boronic anhydride is oxidized with PCC (3 equiv) to aldehydes in satisfactory yields (eq 58).[54]

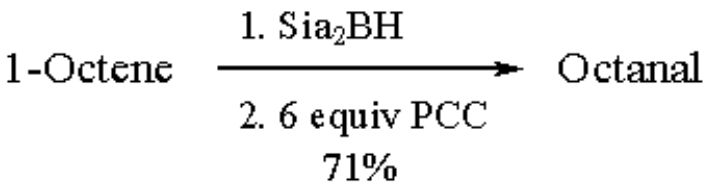

(57)

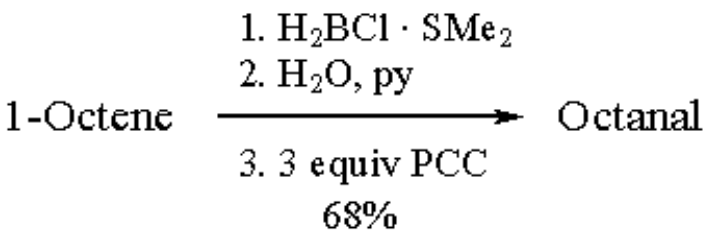

(58)

The selective formation of aldehydes from various types of double bonds in dienes can be conveniently carried out via PCC oxidation of the resulting organoboranes, prepared by utilizing either disiamylborane (eq 59) or ***Chloro(thexyl)borane*** (eq 60) for the regioselective monohydroboration of the diene.[54]

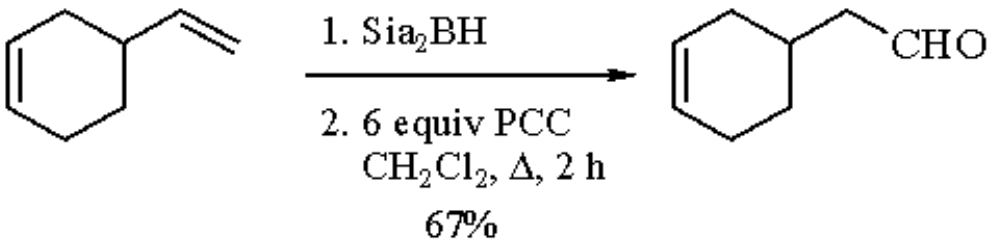

(59)

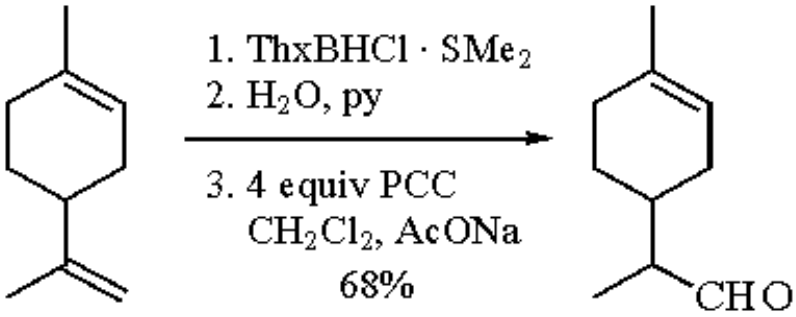

(60)

Other organoboranes, such as trialkyl borates and trialkyl boroxins, can also be oxidized with PCC. Trialkyl borates are rapidly prepared either by esterification of boric acids or by reaction of alcohols with ***Borane-Dimethyl Sulfide***. These intermediates, on reaction with PCC in boiling dichloromethane, are oxidized to give good yields of aldehydes and ketones (eq 61).[56] The method does not seem to have significant advantages over the direct oxidation of the alcohols, but it may prove useful for the one-pot conversion of carboxylic acids into the corresponding aldehydes. Both aliphatic and aromatic carboxylic acids are easily reduced by borane-dimethyl sulfide to trialkoxyboroxins, which are smoothly oxidized to aldehydes with PCC (eq 62).[57]

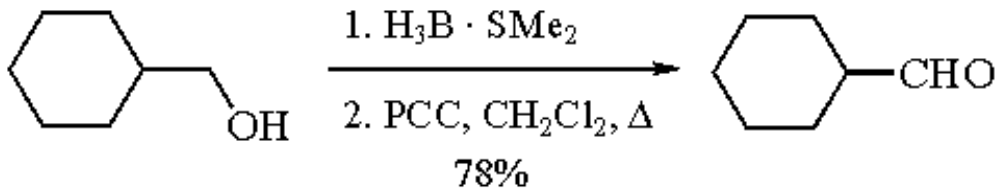

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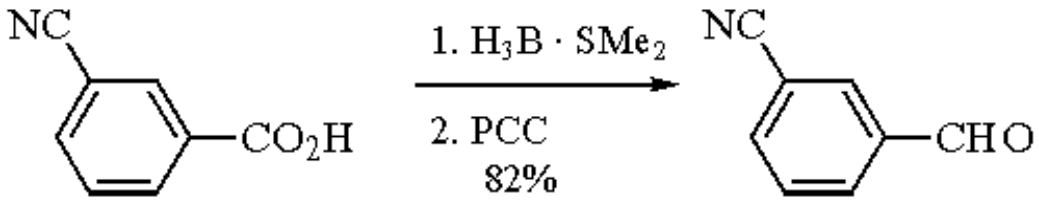

(62)

Oxidation of Silicon-Containing Molecules.

PCC is able to effect the deprotection-oxidation of *p*-hydroquinone silyl ethers to *p*-quinones, except where there are electron-withdrawing substituents on the aromatic ring. The reaction proceeds both with bis(trimethylsilyl) and bis(*t*-butyldimethylsilyl) ethers of *p*-hydroquinones in 60-99% yield. The bis(trimethylsilyl) ethers are slightly more reactive than the bis(*t*-butyldimethylsilyl) ethers (eq 63).[58]

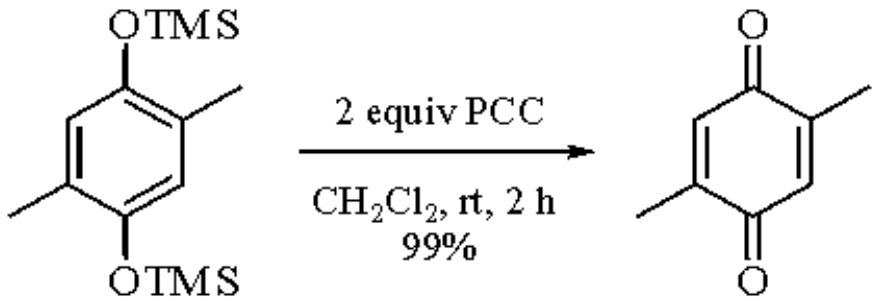

(63)

The deprotection-oxidation method can be applied to the preparation of ketones from trimethylsilyl-protected secondary alcohols.[59] However, the ***Pyridinium Dichromate-Chlorotrimethylsilane*** combination seems to be more efficient for the transformation. A related application of PCC involves its capability to selectively convert 1-trialkylsilyl-1,2-diols into aldehydes, presumably by electrofugal loss of the silicon moiety (eq 64).[60]

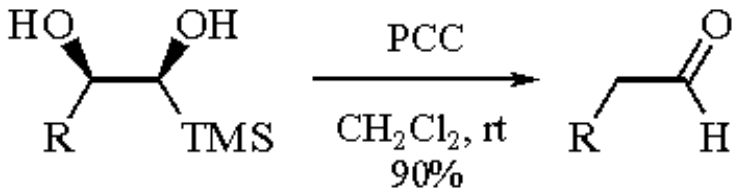

(64)

Both cyclic and linear enol silyl ethers can be converted to α-iodocarbonyl compounds by treatment with the pyridinium chlorochromate-***Iodine*** system in dichloromethane in 76-100% yield (eq 65). The yields of α-iodocarbonyl compounds from enol methyl ethers and dihydropyran are lower (19-53%) (eq 66). The method fails with enamines.[61]

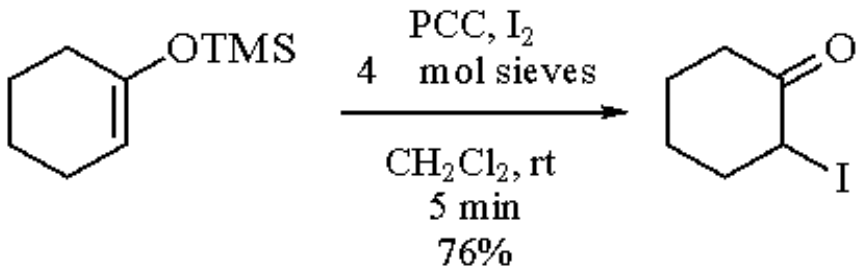

(65)

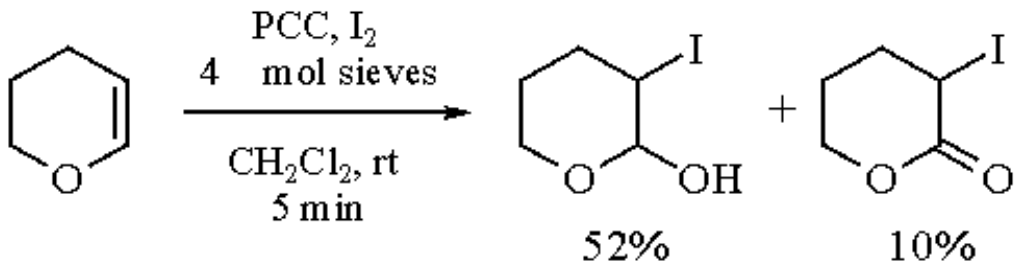

(66)

Oxidation of Oximes.

PCC can be conveniently employed for oxidative cleavage of oximes to carbonyl compounds. Aldehydes and ketones can be recovered from the oxime derivatives by treatment with PCC in dichloromethane at room temperature for 12-24 h in 30-85% yield.[62] PCC-***Hydrogen Peroxide*** is more effective as a deblocking agent: cleavage of oximes occurs within 10 min at 0-10 °C when 30% hydrogen peroxide is added to an acetone solution of PCC. Ketoximes are converted to ketones in 55-88% yield. For aldoximes, over-oxidation to acids has been observed.[63] On the other hand, aryl hydroxylamines can be oxidized to aryl *C*-nitroso compounds by treatment with PCC in tetrahydrofuran in 50-90% yield.[64]

Oxidation of Sulfur-Containing Molecules.

PCC dimerizes aromatic, but not aliphatic, thiols to their corresponding disulfides in good yields.[65] Sulfides may undergo oxidation to give sulfones.[4]

Changes in the properties and reactivity of pyridinium chlorochromate have been brought about by altering the amine ligand associated with the chlorochromate anion. It has been found that heterocyclic chlorochromates show a trend where their strength as oxidant is inversely proportional to the donor strength of the heterocyclic ligand. Several aromatic amines have been examined, which give rise to the related chlorochromate-derived reagents. Enhanced reactivity is found for complexes containing a bidentate ligand.[4]

Related Reagents.

Pyridinium Chlorochromate-Alumina.

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Pyridinium Chlorochromate-Alumina[1]

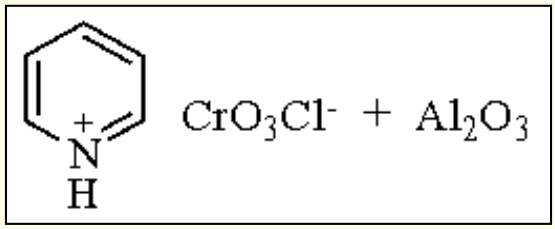

(PCC)

[26299-14-9] · $C_5H_6ClCrNO_3$ · Pyridinium Chlorochromate-Alumina · (MW 215.57) (Al_2O_3)

[1344-28-1] · Al_2O_3 · Pyridinium Chlorochromate-Alumina · (MW 101.96) (SiO_2)

[7631-86-9] · O_2Si · Pyridinium Chlorochromate-Silica Gel · (MW 60.09)

(mild and selective oxidizing agent for primary and secondary alcohols;[2] can aromatize 1,4-dihydropyridines[5])

Solubility: insol *n*-hexane, benzene, dichloromethane.

Form Supplied in: PCC-alumina: yellow orange solid; not commercially available. PCC-silica: light orange solid; not commercially available.

Preparative Methods: PCC-alumina:[2a] ***Pyridine*** (60 mmol) is added to a solution of ***Chromium(VI) Oxide*** (60 mmol) in 11 mL of 6 N ***Hydrochloric Acid*** over 10 min at 40 °C. The mixture is then kept at 10 °C until a yellow-orange solid forms. Reheating to 40 °C gives a solution. Neutral ***Alumina*** (50 g) is then added to the solution with stirring at 40 °C. After concentration (rotary evaporator), the resulting orange solid is dried in vacuum for 2 h at rt. Care must be taken not to evaporate pyridine during this process; some workers recommend that additional pyridine should be added to ensure that the reagent is not acidic. The average capacity of the dried reagent is 1 mmol g^{-1} of alumina. PCC-silica:[2c] commercial grade PCC (12 mmol) is ground with 70-240 mesh silica gel (1 wt equiv) in a mortar; the resultant free-flowing light orange solid is ready for use in oxidations.

Handling, Storage, and Precautions: PCC-alumina: the reagent can be stored for several weeks under vacuum in the absence of light without losing its activity. PCC-silica: no data are available. Pyridinium chlorochromate is reputed to be a cancer suspect agent. The reagent should be used in a fume hood.

Oxidation of Primary and Secondary Alcohols.

Pyridinium Chlorochromate oxidizes a wide variety of alcohols to carbonyl compounds with high efficiency. However, workup and removal of the chromium-containing byproducts are often tedious and difficult. In addition, PCC shows acidic character which can give rise to complications and side reactions. PCC adsorbed on alumina has been demonstrated to be a mild and selective reagent for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones (eqs 1 and 2).[2]

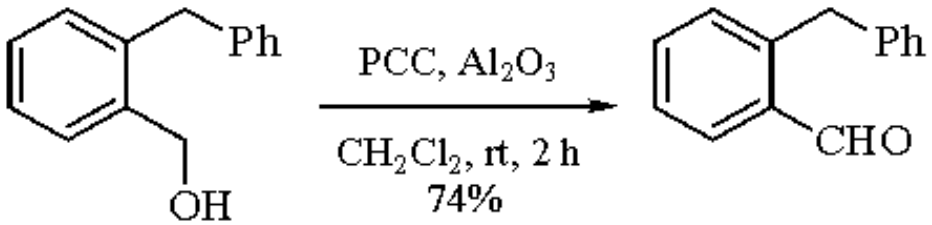

(1)

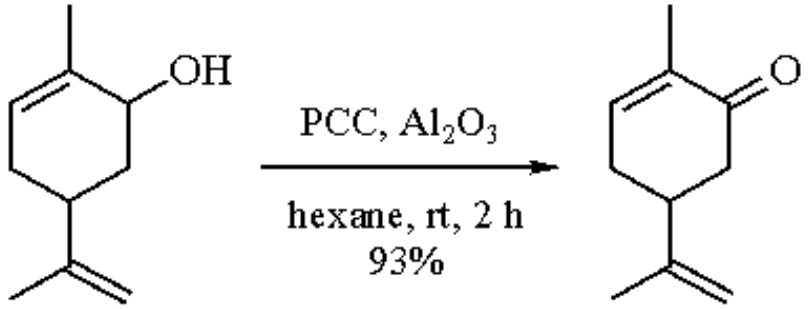

(2)

The acidic nature of PCC is diminished by alumina, which presumably acts as a buffer and enhances the reactivity of PCC as well, often resulting in cleaner oxidations. These reactions are performed by stirring excess oxidant with alcohols in solvents such as *n*-hexane, benzene, and dichloromethane at rt for 2-3 h. An additional advantage of using a solid support is that it acts as an in situ adsorbent of the reduced byproduct chromium tars,[2] and workup then requires only filtration and then concentration. The oxidation seems compatible with many acid-sensitive groups (eq 3).[3]

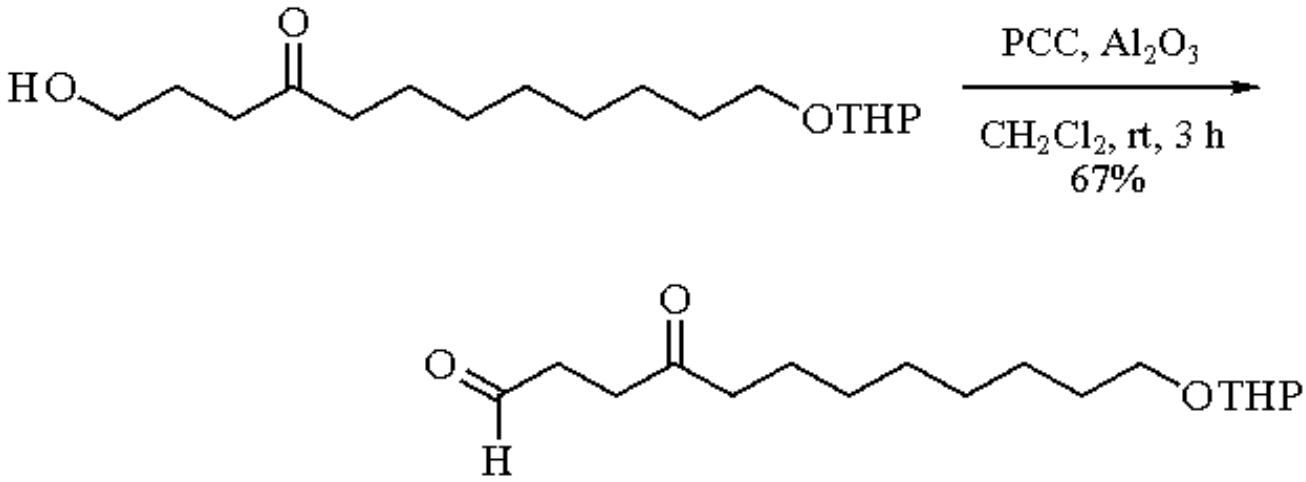

(3)

Citronellol is directly oxidized to citronellal in 82% yield without any cationic cyclization.[2] The oxidation of cholesterol to 5-cholesten-3-one is performed in 80% yield.[2] No formation of 4-cholesten-3-one is observed. γ,δ-Unsaturated alcohols can be smoothly oxidized in good yield to the corresponding γ,δ-unsaturated aldehydes by using PCC in the presence of alumina (eq 4).[4]

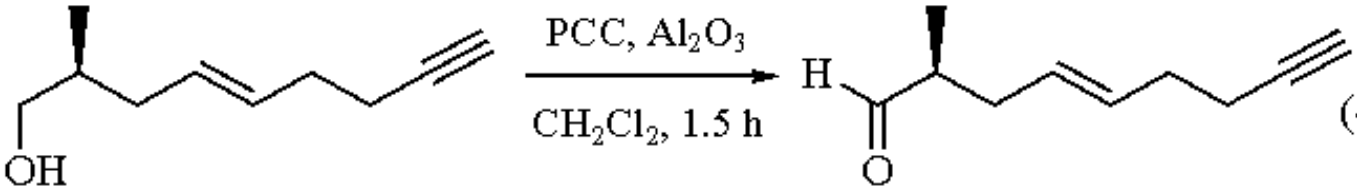

(4)

Oxidative Aromatization.

Interestingly, PCC-alumina is efficient for the oxidative aromatization of 1,4-dihydropyridines into pyridines in yields exceeding 90% (eq 5).[5] It is noteworthy that dealkylation (in addition to aromatization) occurs when the starting dihydropyridines bear a secondary alkyl group or a benzyl group at the 4-position.

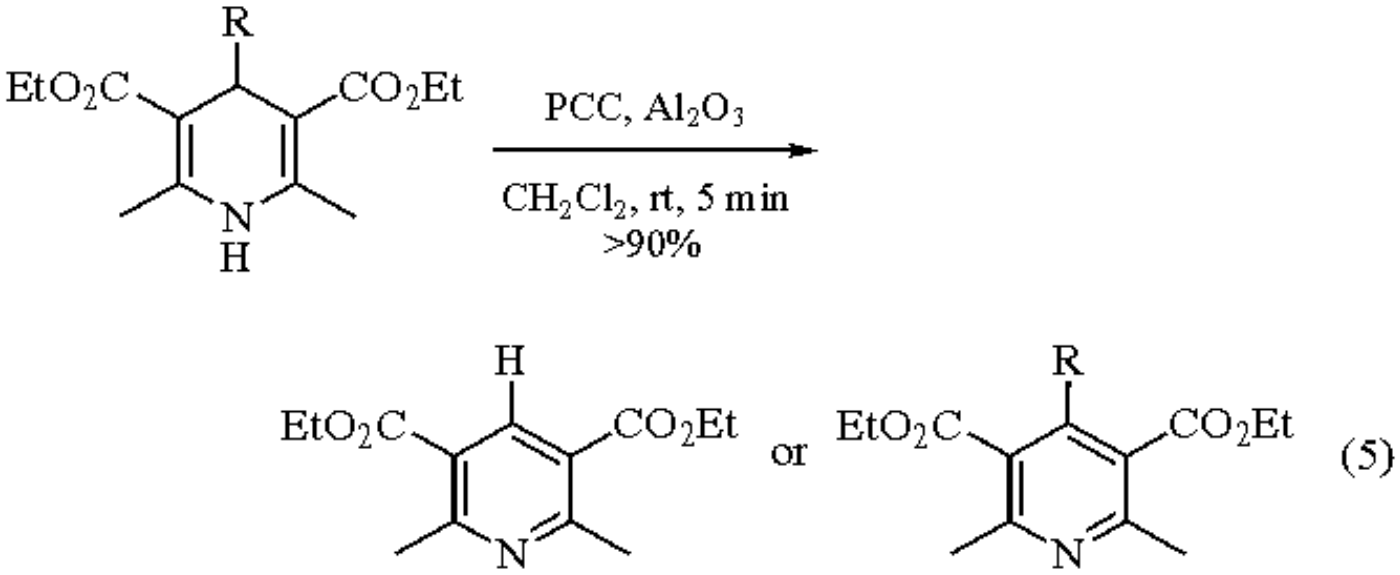

Oxidations using PCC-Silica.

The oxidation of primary and secondary alcohols with PCC-silica employs dichloromethane as solvent and requires no added buffers, even for compounds bearing acid-sensitive groups. As with PCC-alumina, this reagent offers superior results in terms of simplicity of workup, since silica gel absorbs the byproduct chromium tars and is easily filterable. However, oxidations with this reagent require longer reaction times than the usual PCC procedure. The use of ultrasound in PCC-silica oxidations of alcohols gives rise to a great reaction rate enhancement, reducing the oxidation times generally from hours to minutes and improving the yields of the corresponding carbonyl compounds (60-94%). Acid-labile groups resist the experimental conditions. Neither (*E*)-(*Z*) isomerization nor overoxidation are observed (eq 6).[6]

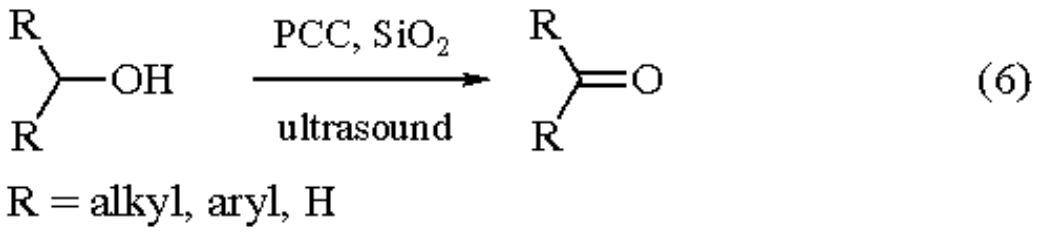

PCC-silica was found to be the most efficient reagent system for the 1,3-oxidative rearrangement of an unsaturated secondary alcohol to the corresponding α,β-unsaturated aldehyde (eq 7).[7]

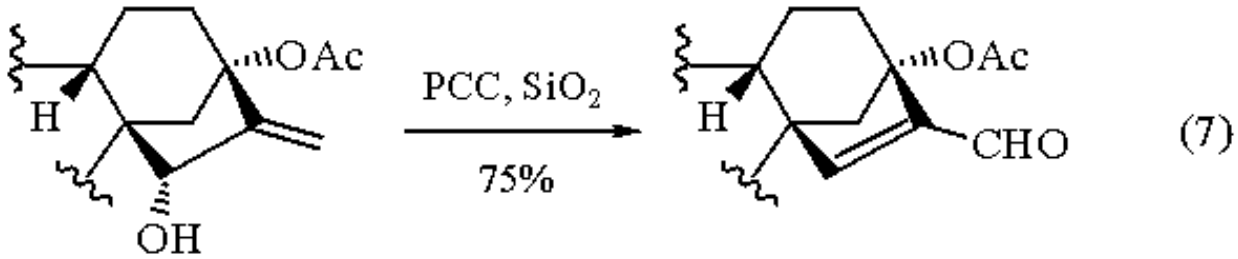

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Pyridinium Dichromate[1]

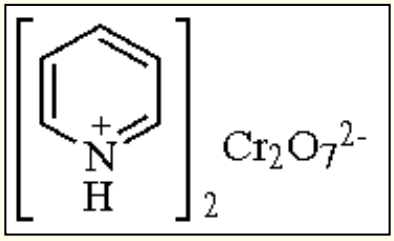

[20039-37-6] · $C_{10}H_{12}Cr_2N_2O_7$ · Pyridinium Dichromate · (MW 376.24)

(mild and selective oxidizing agent for primary and secondary alcohols;[2a] can oxidize unsaturated tertiary alcohols,[2b] silyl ethers,[11] the carbon-boron bond,[20] and oximes[23])

Alternate Name: PDC.

Physical Data: mp 152-153 °C

Solubility: sol DMF, DMSO, acetonitrile; sparingly sol dichloromethane, chloroform, acetone; insol hexane, ether, ethyl acetate.

Form Supplied in: bright orange solid; widely available.

Handling, Storage, and Precautions: the dry solid can be stored in contact with air. Reaction solvents must be anhydrous and free of reducing impurities. Pyridinium dichromate is reported to be a cancer suspect agent. The reagent should be used in a fume hood.

Oxidation of Primary and Secondary Alcohols.

PDC is an oxidizing agent complementary to ***Pyridinium Chlorochromate*** (PCC) for alcohols containing acid-sensitive groups. PDC is less acidic than pyridinium chlorochromate, and has more neutral character than the Collins reagent (***Dipyridine Chromium(VI) Oxide***). PDC is reported to exhibit greater oxidation efficiency than the Collins reagent, especially for large scale preparations. Initially, PDC was used either as a solution in DMF or as a suspension in dichloromethane. In solution in DMF, PDC oxidizes primary and secondary allylic alcohols to the corresponding α,β-unsaturated carbonyl compounds (eqs 1 and 2). Overoxidation of primary allylic alcohols is not observed, and (*E*)-(*Z*) isomerization does not take place.[2a]

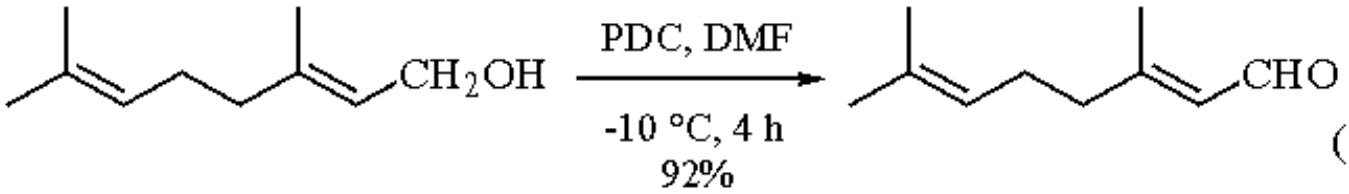

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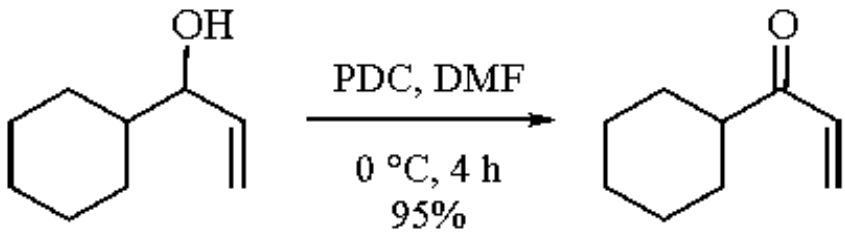

(2)

Under similar conditions, saturated primary alcohols and aldehydes yield carboxylic acids. The preparation of carboxylic acids from primary alcohols (via the aldehyde intermediate) is usually achieved using 3.5 equiv of PDC at rt for 7-9 h (eqs 3 and 4).[2a]

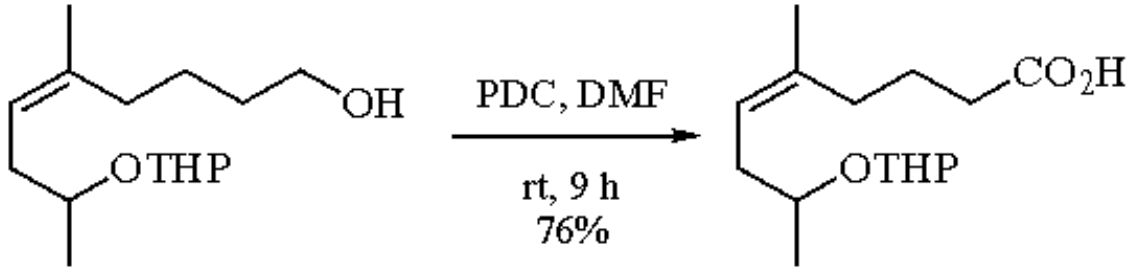

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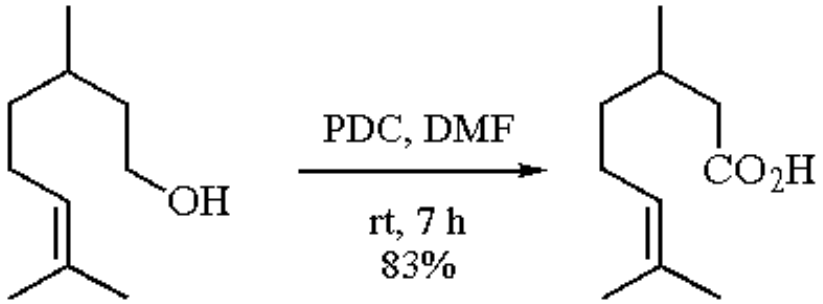

(4)

An interesting example of the mildness of PDC is the oxidation of citronellol to the corresponding acid in 83% yield. The same oxidation with acidic PCC is complicated by cationic cyclization of the aldehyde intermediate. Aliphatic methyl esters can be directly prepared from aldehydes by oxidation with PDC (6 equiv) in the presence of methanol in yields of 60-80%. This method is not useful for aromatic aldehydes or higher esters.[3] Saturated secondary alcohols are rapidly and conveniently converted into ketones, even in the presence of very sensitive groups, such as a thioacetals.

In suspension in dichloromethane, PDC shows considerably different behavior, becoming a milder and selective reagent for the preparation of both saturated and unsaturated aldehydes and ketones (eqs 5-7). Allylic alcohols are oxidized faster than saturated ones, but some (*E*)-(*Z*) isomerization is observed.[2a]

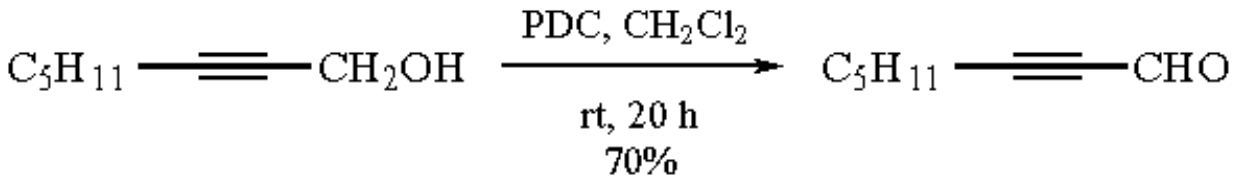

(5)

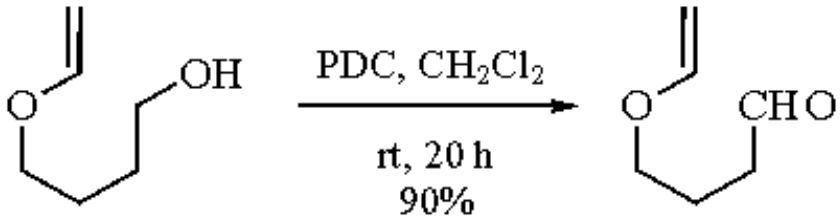

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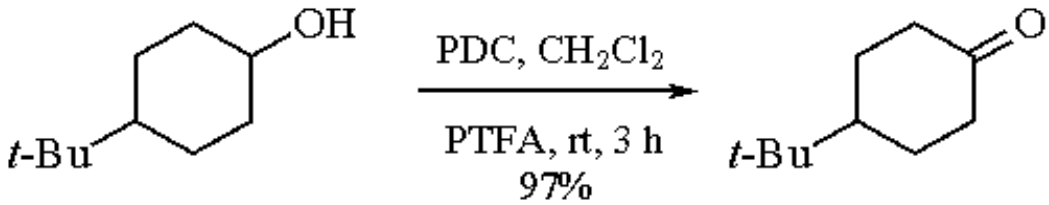

(7)

PDC does not attack isolated alkenic and alkynic bonds; in fact, o-alkynyl alcohols are oxidized by PDC in dichloromethane to the corresponding o-alkynyl carbonyl compounds in good yield (eq 8).[4]

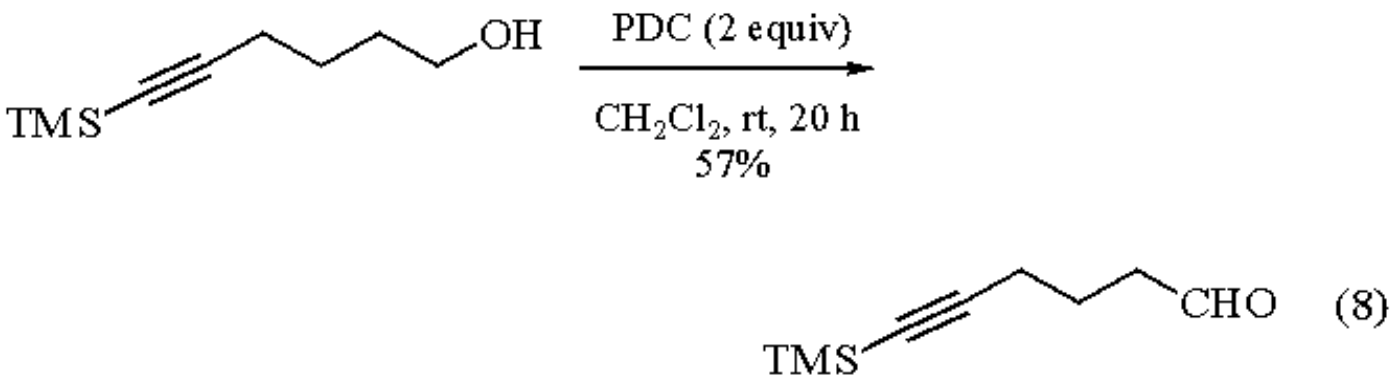

PDC and PCC may show a different chemoselectivity. Thus PDC oxidizes the secondary hydroxyl groups of 5-bromo-2-furylcarbinols to the corresponding ketones in 80% yield, while PCC attacks the furan ring giving γ-hydroxy Δ^2-butenolides (eq 9).[5]

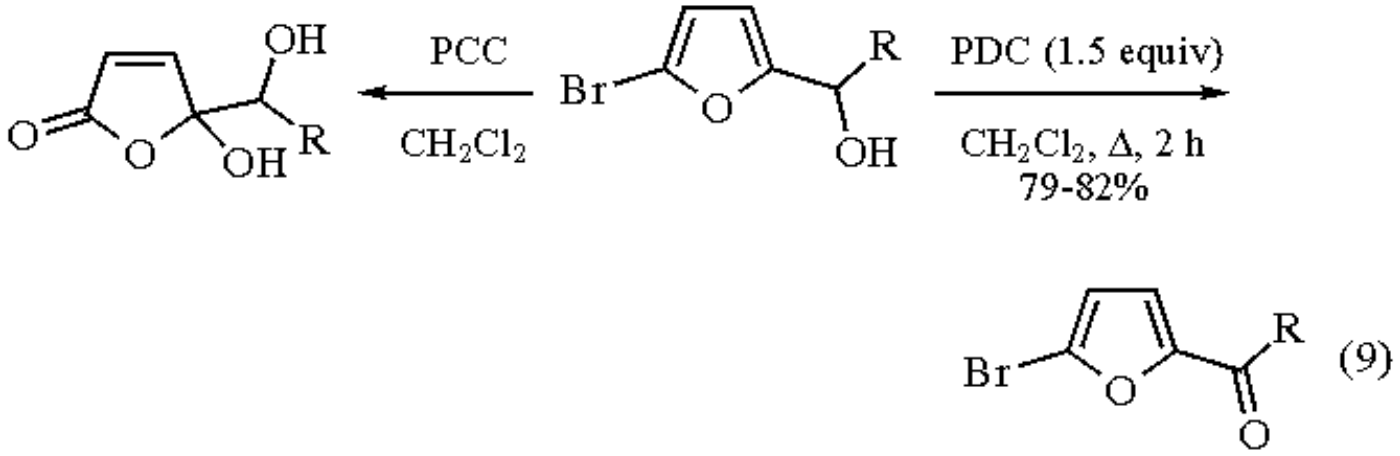

Several modified procedures have been employed to enhance the rate and the efficacy of PDC. Addition of pyridinium trifluoroacetate (0.4 equiv) causes an increase in the reaction rate, and less oxidant is necessary for oxidation (eq 7). ***Molecular Sieves*** enhance the oxidation rate with a wide variety of substrates.[6] A combination of PDC, molecular sieves, and ***Acetic Acid*** has a dramatic effect on the oxidation of carbohydrate alcohols, reducing oxidation time from days to minutes (eq 10).[7] Furthermore, the addition of acetic acid has been utilized for the selective oxidation of secondary allylic alcohols in carbohydrates (eq 11).[8]

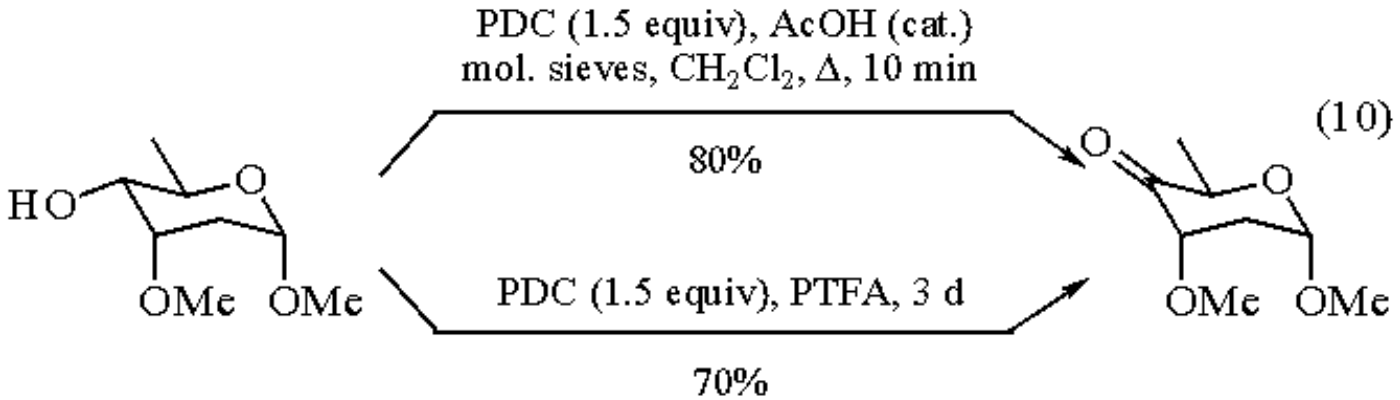

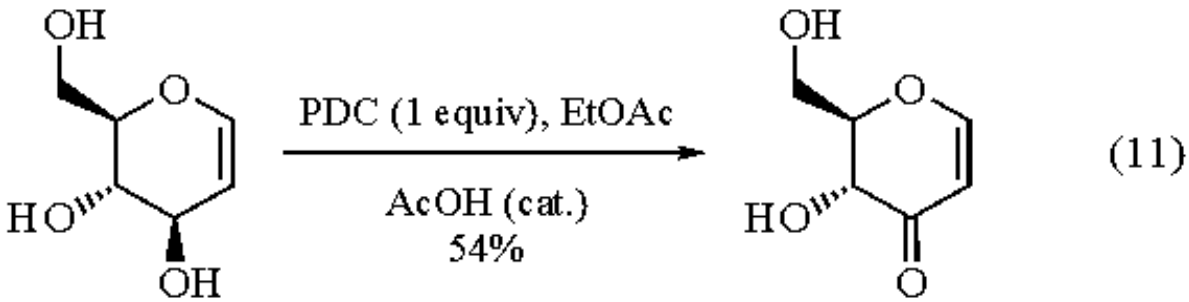

The PDC-***Acetic Anhydride*** combination gives rise to a strong and neutral oxidant. This system (0.6-0.7 equiv of PDC and 3 equiv of Ac_2O) can be used for the selective oxidation of primary and secondary alcohols of carbohydrates to the corresponding carbonyl

compounds in high yields. The addition of DMF as cosolvent to the reaction mixture prevents overoxidation (eq 12).[9] Interestingly, the PDC-Ac_2O combination is able to perform an oxidative fragmentation of 5´-hydroxymethyl groups in 2´,3´-*O*-isopropylidene nucleosides to form the corresponding γ-lactone nucleosides, albeit in moderate yield (eq 13).[10]

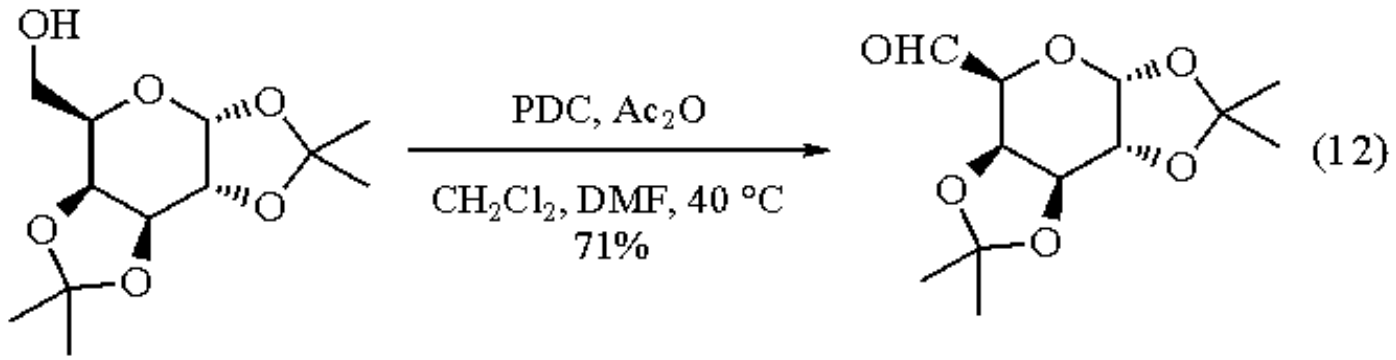

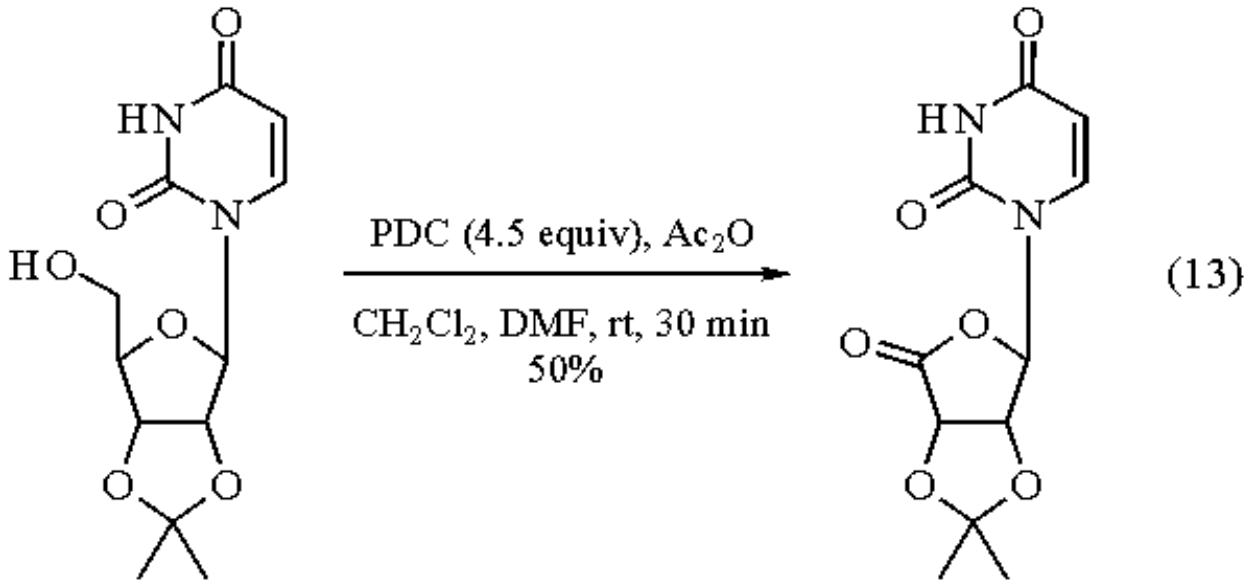

Oxidation of primary and secondary alcohols to carbonyl compounds can be carried out with PDC-***Chlorotrimethylsilane***, which is a rapid and selective oxidant.[11] This combined reagent system can effect the deprotection-oxidation of silyl ethers and enol silyl ethers. Primary and secondary trimethylsilyl and *t*-butyldimethylsilyl ethers, usually stable to PDC, may be converted by the above combination directly into the corresponding carbonyl groups in high yields (eq 14). The method can be applied to the preparation of quinones from hydroquinone silyl ethers (eq 15) with higher efficiency than that using PCC and this reagent is applicable to substrates both with electron-donating and electron-withdrawing groups.[11]

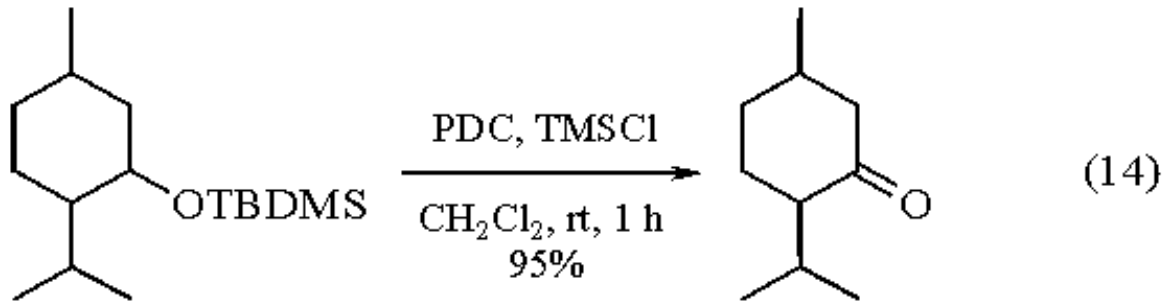

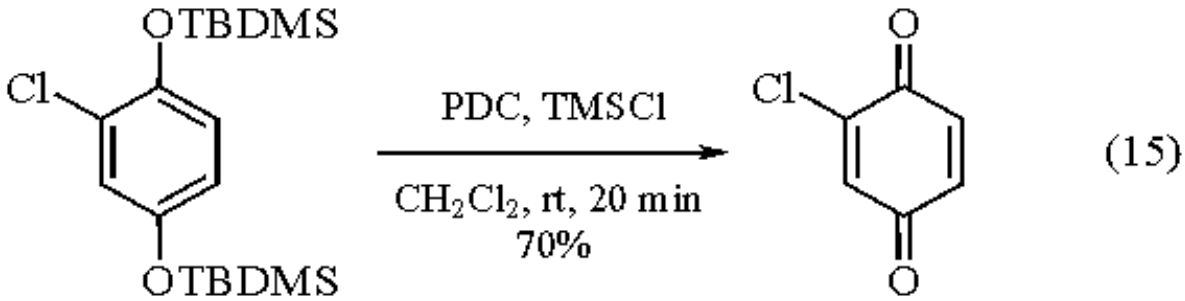

Catalytic PDC Oxidation of Alcohols.

PDC can be utilized as a catalytic oxidant when coupled with ***Bis(trimethylsilyl) Peroxide*** as cooxidant. The method has proven to be mild and useful not only for the oxidation of a wide range of primary and secondary alcohols, saturated and unsaturated, but also for the conversion of homoallylic alcohols to the corresponding β,γ-enones (eq 16).[12]

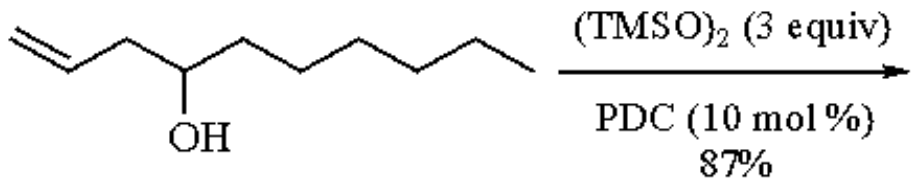

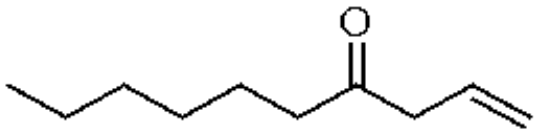

(16)

Oxidation of Cyanohydrins.

Cyanohydrins of nonconjugated aldehydes are oxidized to carboxylic acids by PDC-***N,N-Dimethylformamide*** in excellent yields. Cyanohydrins from α,β-enals (as the *O*-trimethylsilyl derivatives) behave differently, being converted by PDC-DMF into α,β-unsaturated γ-lactones (Δ^2-butenolides), in cases in which the β-carbon is disubstituted and the γ-carbon possesses at least one hydrogen. This reaction is performed with PDC (3 equiv) in DMF at rt for 12 h, and provides a mixture of two isomeric Δ^2-butenolides, whose ratio (4:1) indicates that oxidative attack at the γ-methyl is favored over the γ-methylene (eq 17).[13]

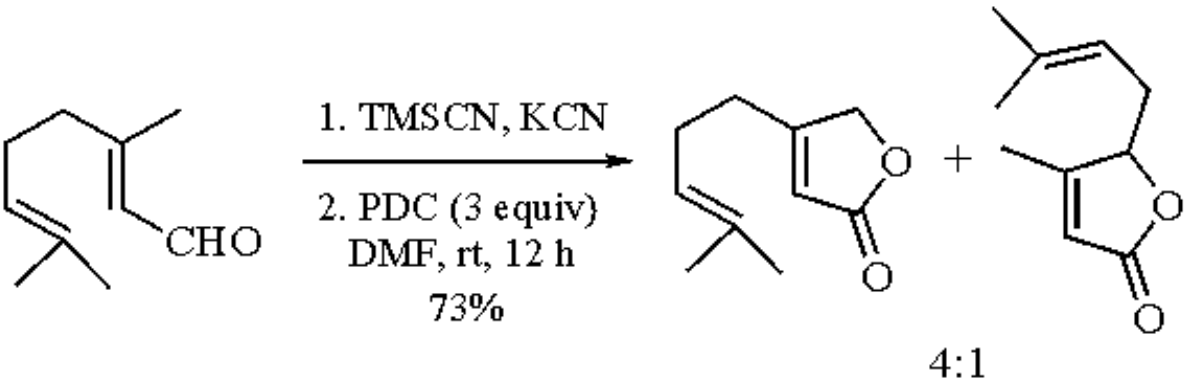

(17)

Oxidation of Activated Methylene Groups.

PDC can perform allylic oxidation of methylene groups, but a large excess of oxidant is required. Δ^5-Steroids are selectively transformed into Δ^5-7-keto steroids by treatment with PDC (25 equiv) and molecular sieves in pyridine at 100 °C for 24 h; yields range from 63-86% (eq 18).[14]

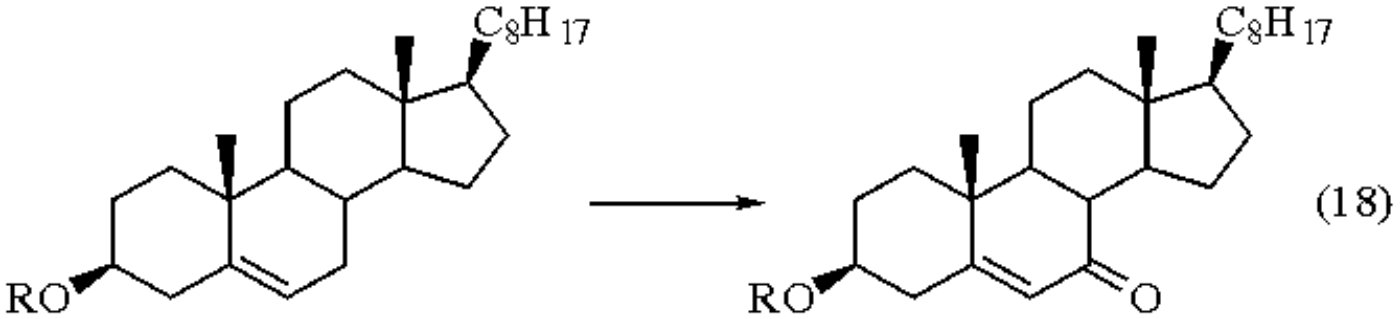

(18)

R = Bz	PDC, py, 100 °C, MS	64%
R = Ac	PDC, *t*-BuOOH, Celite, rt	81%

A PDC-***t-Butyl Hydroperoxide*** mixture (1:1) has proven to be useful for the mild oxidation of cyclic 1,4-dienes to the corresponding cyclic 2,5-dienones (eq 19).[15] The use of the combination of PDC, *t*-butyl hydroperoxide, and ***Celite*** is particularly suitable for the oxidation of benzylic methylenes into aryl ketones (eq 20)[16] and for the highly regioselective conversion of Δ^5-steroids into the corresponding Δ^5-7-keto steroids (eq 18).[16] The method is rather poor for allylic oxidation of linear and cyclic alkenes, furnishing α,β-enones in 23-44% yield (eq 21).[16]

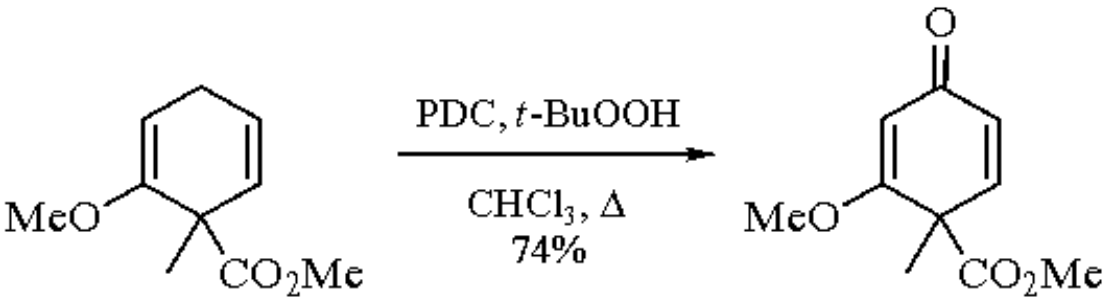

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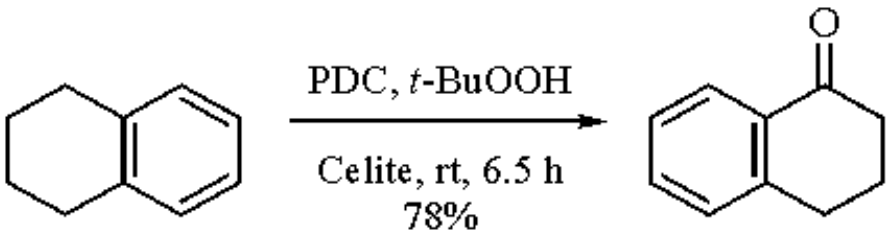

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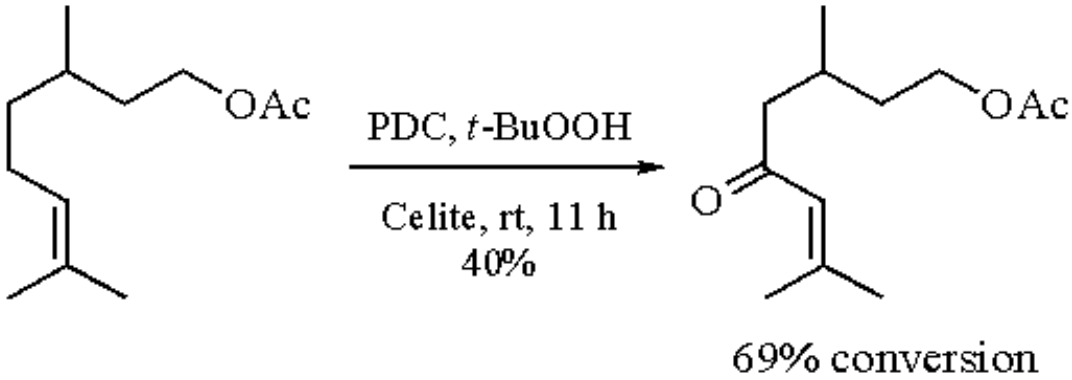

(21)

Oxidative Rearrangement of Unsaturated Alcohols.

Linear and cyclic secondary homoallylic alcohols are oxidized by PDC-DMF to *trans*-enediones in 53-75% yield. The one-pot procedure seems to be particularly convenient for the oxidation of steroidal substrates, which contain a rigid and sterically congested structure. Thus 3β-hydroxy Δ^5-steroids afford the corresponding 3,6-diketo-Δ^4-steroids (eq 22).[17] The method is rather unsatisfactory for linear homoallylic alcohols and fails with alcohols possessing a terminal allylic group.

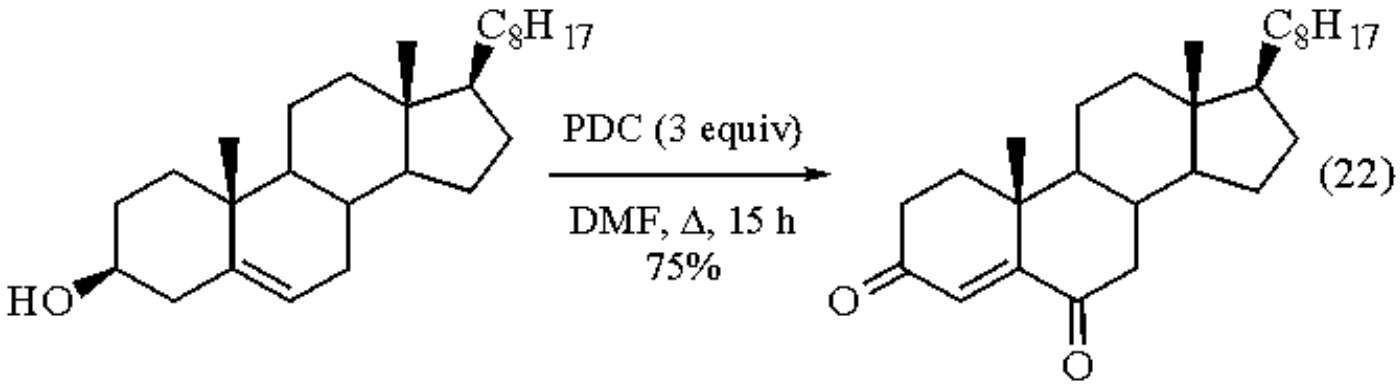

(22)

PDC is the oxidant of choice for the oxidation of tertiary allylic dienols. These alcohols, easily prepared by addition of ***Vinyllithium*** to conjugated cyclohexenones or cyclopentenones, undergo a 1,3-oxidative rearrangement to afford the corresponding conjugated dienones in moderate to good yield (eq 23). The rearrangement is completely regiospecific, leading to the formation of the more stable isomers. The reaction does not suffer from the presence of withdrawing substituents on the alkene system, but linear α-dienols give lower yields of rearranged isomeric products (eq 24).[18]

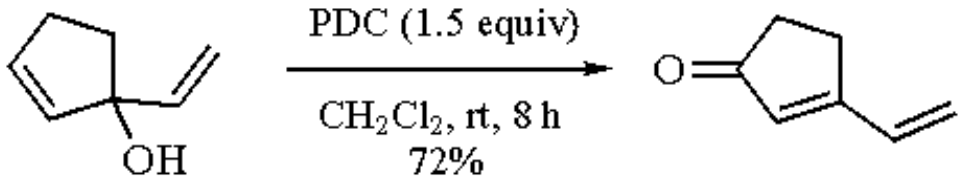

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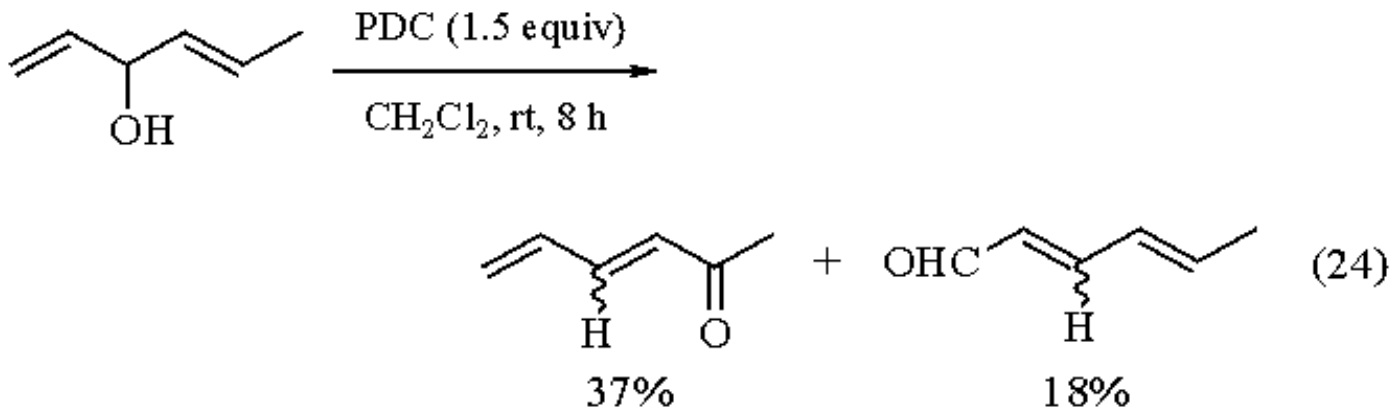

(24)

In a similar fashion, tertiary α-enynols are converted by reaction with PDC in dichloromethane to the corresponding conjugated enynones; yields are good to excellent. These rearrangements are completely regioselective, involving only the alkene. The procedure is limited to cyclic allylic alcohols and shows wide applicability only with enynols containing (*Z*) double bonds (eq 25).[19]

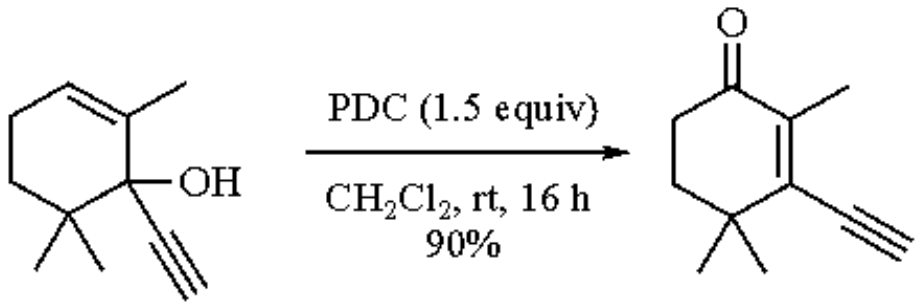

(25)

Oxidation of Carbon-Boron Bonds.

A synthetically useful procedure has been developed for the conversion of terminal alkenes into carboxylic acids via oxidation of organoboranes obtained by hydroboration of terminal alkenes. The oxidation works well with organoboranes derived from ***Dibromoborane-Dimethyl Sulfide***, but other reagents may be utilized such as monobromoborane-dimethyl sulfide, ***Monochloroborane-Dimethyl Sulfide***, ***Thexylborane***, and ***Dicyclohexylborane***. Alkyldibromoboranes are hydrolyzed to alkylboronic acids, which undergo a facile oxidation with PDC-DMF (5 equiv) at rt for 24 h to provide carboxylic acids in 62-78% yield (eq 26).[20] In some cases PCC may effect the same reaction in higher yields; however, carboxylic acids are often best obtained with ***Chromium(VI) Oxide*** as oxidant in 90% aqueous acetic acid.[20]

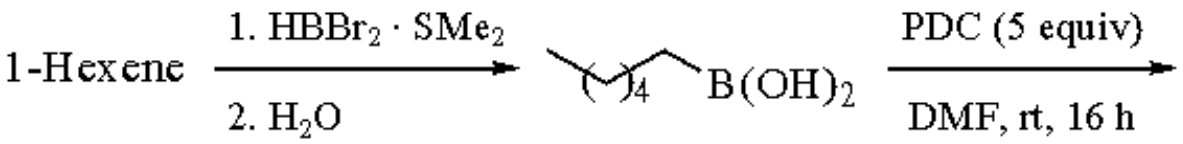

Hexanoic acid (26)
75%

Oxidation of Enol Ethers.

PCC is a selective reagent for the oxidative cleavage of enol ethers and PDC shows a similar but modest reactivity. PDC can effect oxidative double bond fragmentation of cyclic enol ethers to esters and keto lactones (eq 27).[21]

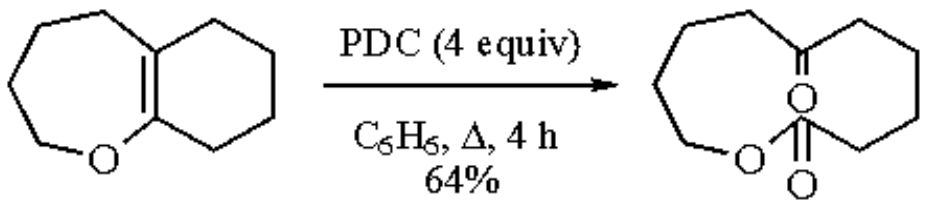

(27)

Interestingly, the PDC-*t*-BuOOH combination can achieve the one-step conversion of 3,4-dihydro-2*H*-pyrans into 5,6-dihydro-2*H*-pyran-2-ones under very mild conditions; yields are moderate. The reaction is performed at 0 °C in dichloromethane with PDC-*t*-BuOOH for 2-4 h. *t*-Butylperoxy derivatives are obtained as byproducts (eq 28).[22] This reagent system can chemoselectively oxidize 3,4-dihydro-2*H*-pyrans to the corresponding α,β-unsaturated lactones without affecting pendant hydroxyl groups (eq 29).

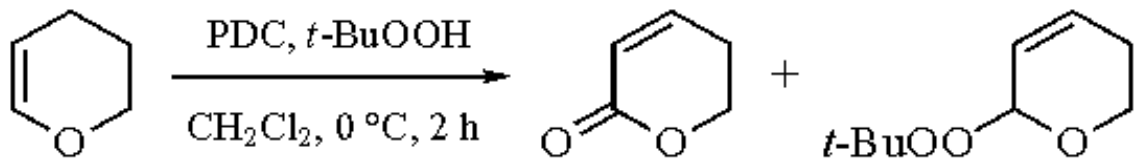

50% 6% (28)

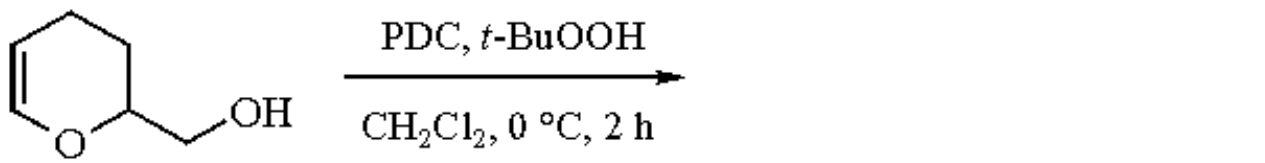

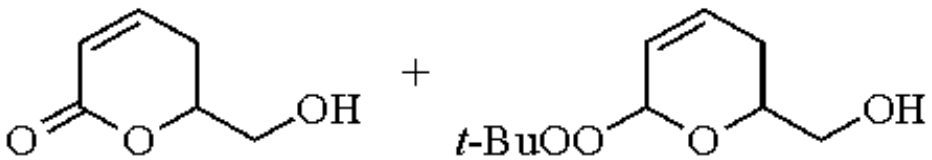

30% 14% (29)

Oxidative Cleavage of Oximes.

PDC can perform oxidative cleavage of oximes to ketones and aldehydes in excellent yield (eq 30). The reagent seems to be superior to PCC for this transformation. The rate of deoximation is increased by adding 3 Å molecular sieves, but the yields of carbonyl compounds are lowered.[23]

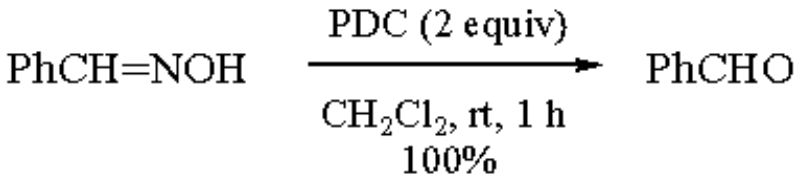

(30)

Oxidation with Iodine and PDC.

PDC has been utilized for oxidation of cyclic alkene-iodine complexes to α-iodo ketones (eq 31). The yields range from 50 to 70%.[24] The reaction shows a wide applicability; Δ^2-cholestene is selectively converted, by the same procedure, into 3α-iodocholestan-2-one in 70% yield (eq 32). The reaction fails with linear alkenes; however, it seems to be characteristic of PDC. In contrast, PCC converts the cyclohexene-iodine complex into *trans*-1-chloro-2-iodocyclohexane (66%), while the α-iodo ketone is a byproduct (8%).[24]

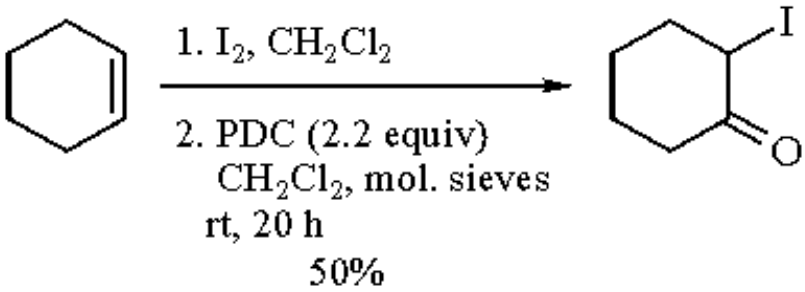

(31)

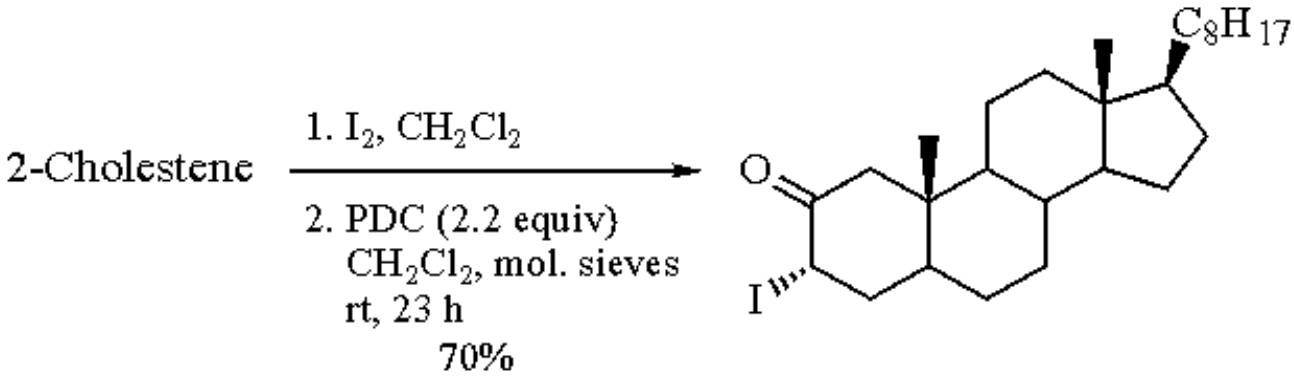

(32)

Cyclic trisubstituted alkenes, activated with ***Iodine***, are easily converted into iodohydrins and epoxides by PDC, which acts as nucleophilic and iodide removing agent. Iodohydrins can be isolated in 48-65% yield when the starting alkenes have a mobile conformation. The reaction is performed in dichloromethane with PDC (2.5 equiv) and 4 Å molecular sieves at rt for 3 h. More prolonged reaction times (16 h) lead to epoxides in 50% yield (eq 33).[25] Conformationally rigid alkenes are directly converted into epoxides in 51-86% yield, since the iodohydrin intermediates undergo a fast elimination of iodide by the oxidant (eq 34).

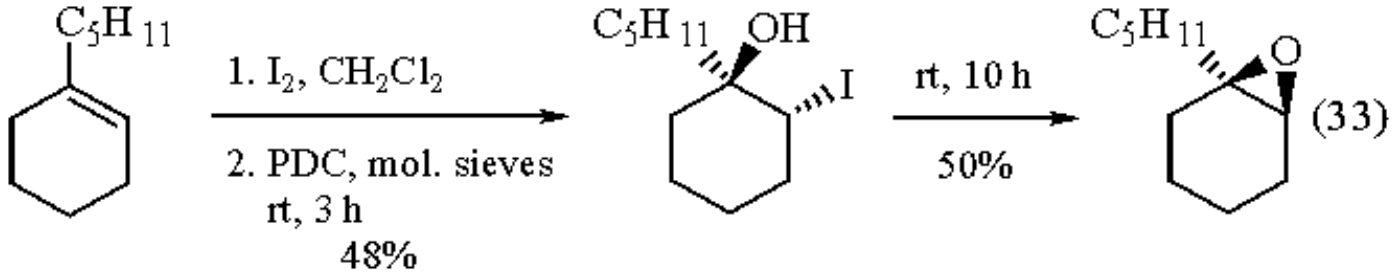

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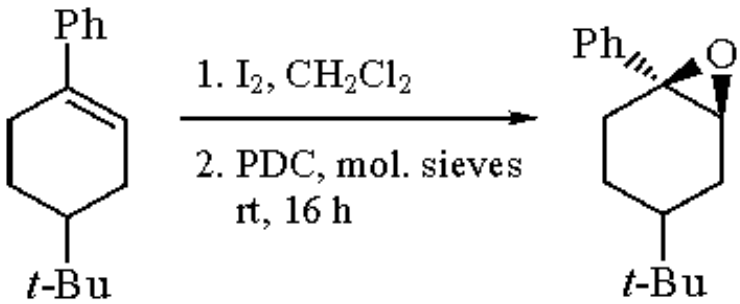

(34)

Some naturally-occurring polyenes such as (*E*,*Z*)-geranyl acetate undergo a regioselective conversion to terminal epoxides by a two-step sequence, which includes the formation of the corresponding terminal iodohydrins by reaction with PDC-iodine and subsequent conversion to the epoxides by adsorption on neutral alumina (30-65% yield) (eq 35).[25]

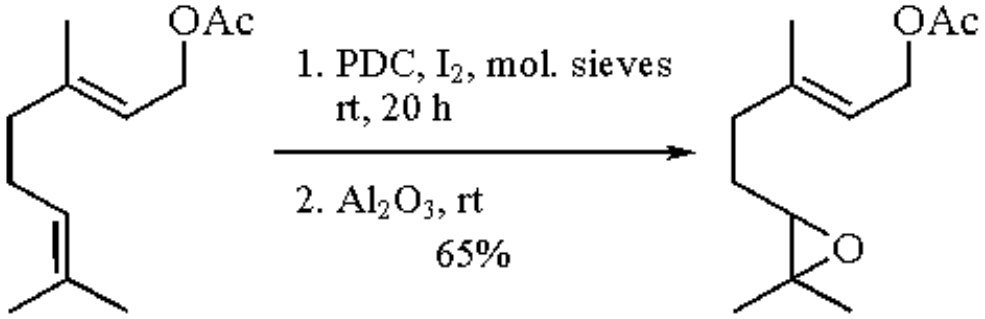

(35)

The nucleophilic and oxidizing properties of PDC can be utilized for a one-pot conversion of α-ynol-iodine complexes to α,β-unsaturated α-iodo aldehydes in 30-66% yield. This reaction is performed by adding PDC (2.2 equiv) to a solution of α-ynol and iodine (1:1), in the presence of 4 Å molecular sieves at rt for 24 h (eq 36). The conversion is regio- and stereospecific, yielding only one of two possible geometrical isomers and shows wide applicability.[26]

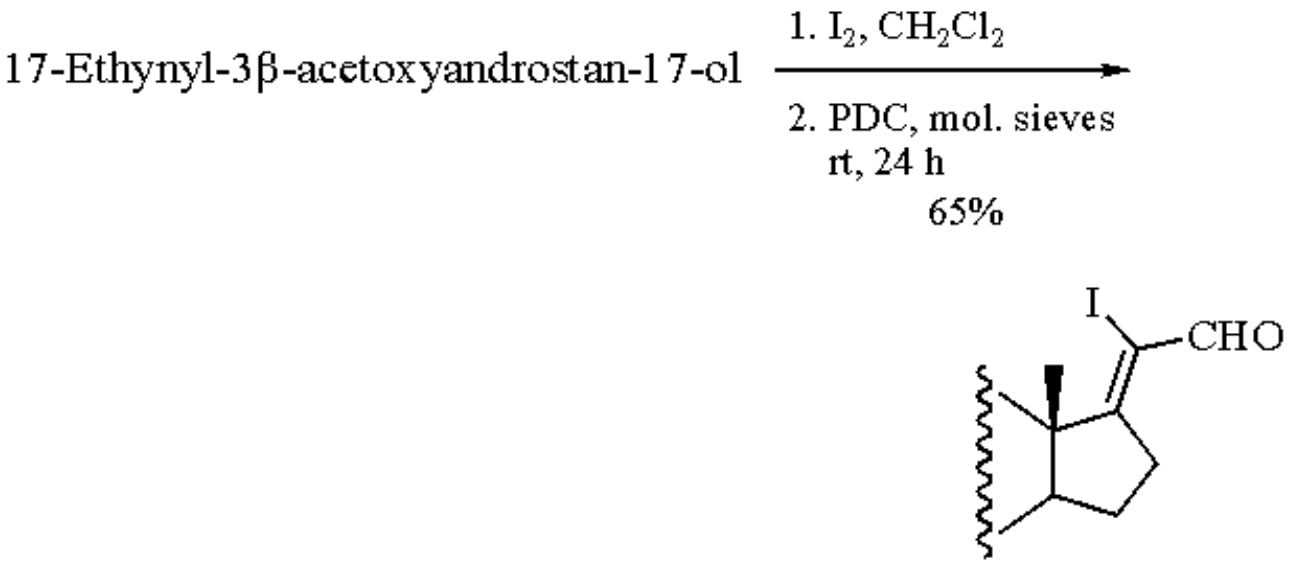

(36)

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Pyridinium Fluorochromate[1]

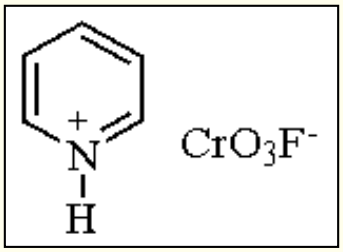

[83042-08-4] · $C_5H_6CrFNO_3$ · Pyridinium Fluorochromate · (MW 199.12)

(mild oxidizing agent for primary and secondary alcohols;[2] can oxidize activated C-H bonds[2b])

Alternate Name: PFC.

Physical Data: mp 106-108 °C.

Solubility: sol DMF, acetonitrile, acetone; less sol dichloromethane; sparingly sol benzene, carbon tetrachloride, chloroform, hexane.

Form Supplied in: not commercially available.

Preparative Method: prepared from ***Pyridine***, aqueous 40% ***Hydrofluoric Acid***, and ***Chromium(VI) Oxide*** in a molar ratio 1:1.5:1. The bright orange, crystalline reagent is isolated by filtration and dried in vacuo; yield 93-94%. The procedure can be performed on a 200 g scale.[2]

Handling, Storage, and Precautions: the dry orange crystalline reagent can be stored in sealed polythene bags for long periods without decomposition. Reaction solvents must be anhydrous and free of reducing impurities. Chromium(VI) derivatives are reputed to be toxic agents. The reagent should be used in a fume hood.

Oxidation of Primary and Secondary Alcohols.

PFC is an effective reagent for the oxidation of a wide range of alcohols. With 1.5 equiv of reagent in dichloromethane at rt for 1-3 h, primary and secondary alcohols are converted to aldehydes and ketones in yields ranging from 77 to 98% (eqs 1-3).[2,3] (*E*)-(*Z*) isomerization has been observed during the oxidation of some allylic alcohols.[3]

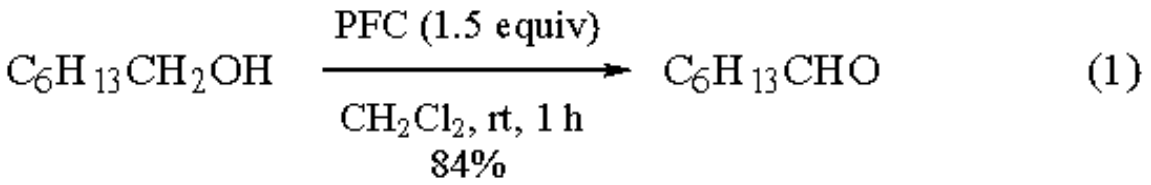

(1)

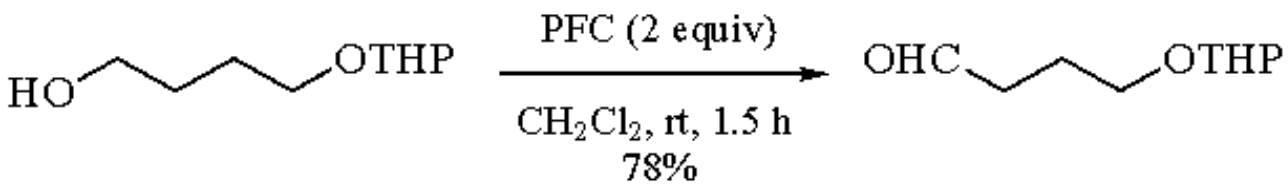

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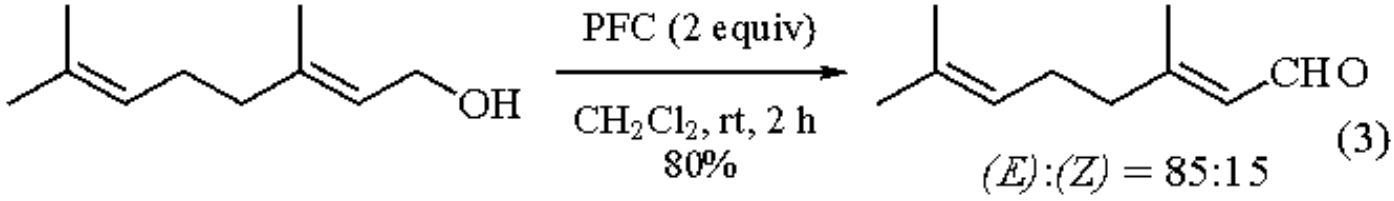

PFC seems to have certain advantages over similar oxidizing agents in terms of the amount of oxidant and solvent required, shorter reaction times, and improved yields of products. Since its acidity is less pronounced than that of ***Pyridinium Chlorochromate***, compounds with acid-sensitive groups can be oxidized without buffering the reaction mixture. PFC can be used in the oxidation of a secondary alcohol in the presence of a primary alcohol protected as a silyl ether (eq 4).[3] The more acidic PCC does attack silyl ether groups.

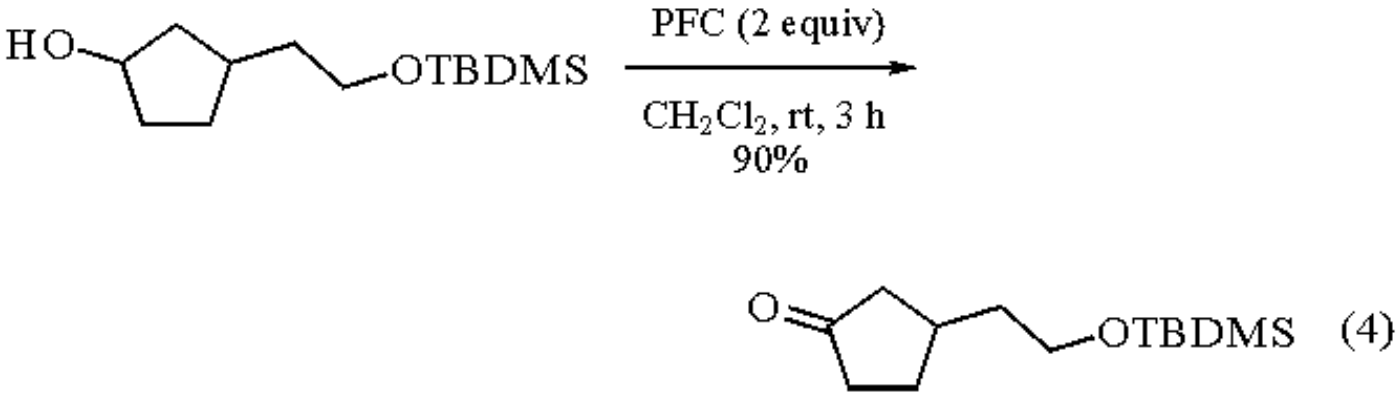

The fluorochromate anion has been supported on a polymeric matrix, the cross-linked ***Poly(4-vinylpyridine)***. Poly(4-vinylpyridinium fluorochromate) oxidizes primary and secondary alcohols to aldehydes and ketones in very good yield in both hexane or benzene. It is essential that the reagent be wet; use of dry reagent does not afford the desired product.[4] No products of overoxidation are found in the reaction mixture. In addition, the wet supported oxidant can be employed as an efficient reagent for the cleavage of aldoximes and ketoximes to the corresponding parent carbonyl compounds in excellent yield.[4]

Oxidation of Activated C-H Bonds.

PFC can be utilized for selective oxidation of certain aromatic hydrocarbons. Anthracene and phenanthrene are converted by the oxidant (2.5 equiv) at rt into the corresponding anthraquinone (eq 5) and phenanthrene-9, 10-quinone in 68% and 52% yield. The yields may be raised to 98% and 72% by using ***Acetic Acid*** as the reaction medium.[2]

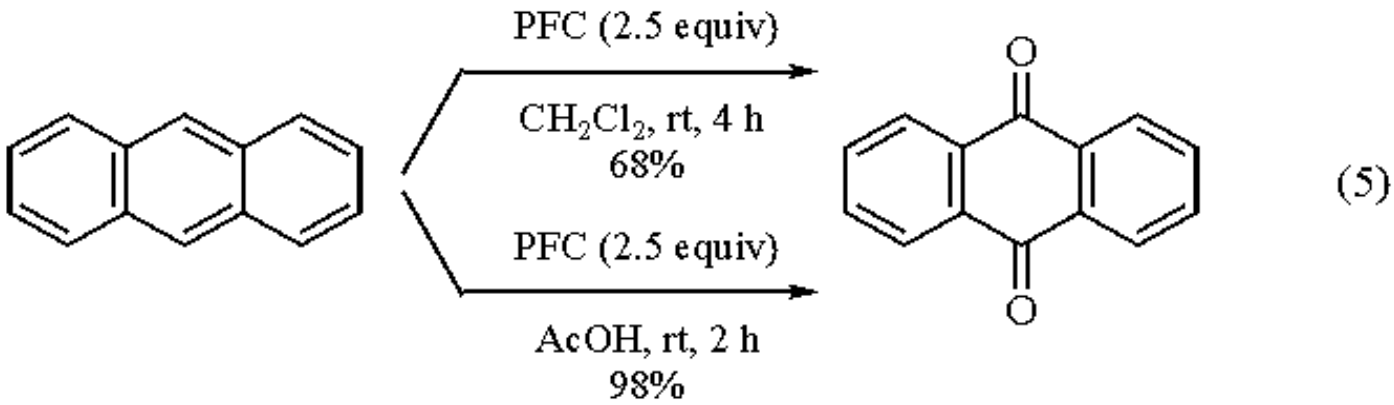

Several reports have suggested that PFC is a suitable oxidant for both allylic[5] and benzylic C-H bonds,[6] although no yields have been reported. Oxidation of Δ^3-carene in aqueous acetic acid containing perchloric acid gives rise to a variety of ketonic products.[5] By the same procedure, oxidation of substituted toluenes afford the corresponding aldehydes as the main products.[6c] Diphenylmethane and fluorene are converted mainly into benzophenone and fluorenone.[6b] PFC can oxidize a tertiary benzylic C-H bond: triphenylmethanol is obtained in 90% yield from triphenylmethane by reaction with the oxidant in acetic acid containing perchloric acid (eq 6).[7]

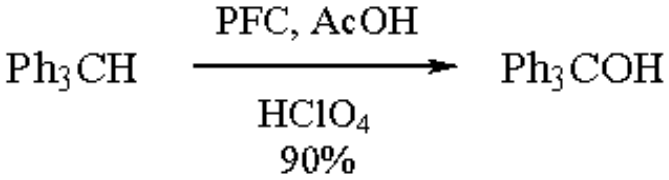

(6)

PFC in DMF has the capability to oxidize selectively organic sulfides into sulfoxides. No yields are reported.[8]

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Pyridinium Hydrobromide Perbromide[1]

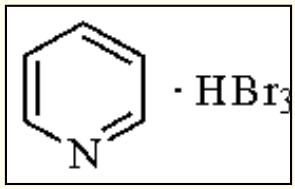

[39416-48-3] · $C_5H_6Br_3N$ · Pyridinium Hydrobromide Perbromide · (MW 319.86)

(selective brominating reagent for ketones,[2] acetals,[3] alkenes,[4] activated phenols,[5] anilines,[6] and nitrogen heterocycles;[7] mild oxidation/dehydrogenation reagent[8])

Alternate Names: PHBP; pyridinium bromide perbromide; pyridinium perbromide; pyridinium tribromide.

Physical Data: mp 101-103 °C (39.7% Br), mp 132-134 °C (47% Br),[7] 135 °C (50% Br).[9]

Solubility: sol acetic acid, methanol, ethanol, *n*-butanol, THF, ether (wet); insol water, carbon tetrachloride, ethyl bromide, ether (anhydrous), benzene, toluene, ligroin, petroleum ether.[9]

Form Supplied in: red-orange solid, generally 90-97% pure; commercially available.

Analysis of Reagent Purity: iodometric titration.[10]

Preparative Method: from pyridine, 48% hydrobromic acid, and bromine.[1,7] The bromine content varies depending on the method of preparation.[7,11]

Purification: recrystallization from ethanol.[12] Recrystallization from acetic acid reduces the bromine content. Pure material can be obtained by adding bromine to impure material until a paste is produced. Excess bromine is allowed to evaporate, giving pure material, mp 135 °C (50% Br).[9]

Handling, Storage, and Precautions: protect from moisture, strong acids, and bases. This toxic reagent must be used in a fume hood.

Introduction.

Pyridinium hydrobromide perbromide is a solid complex of ***Pyridine*** with bromine that is used as a source of ***Bromine***. It is more convenient to measure small amounts of active bromine with this stable reagent than with bromine itself. Its mild reactivity makes it ideal for selective brominations and dehydrogenations of sensitive molecules.[1]

α-Bromination of Ketones.

PHBP has been used to α-brominate steroid keto groups in good yields with high stereoselectivity.[2,13] Flavinones react with PHBP giving α-brominated products.[14] Tetrahydroindoles also react with PHBP (eq 1); however, better yields were obtained for this transformation with ***Copper(II) Bromide***.[15] PHBP reacts with cyclohexanones in ***Acetic Acid*** to give equatorially substituted α-bromocyclohexanones. In contrast, bromine in carbon tetrachloride gives mostly axial products.[16] The cyclopentenone shown in eq 2 was successfully brominated with PHBP when an equivalent of pyridine was present.[17] ***Phenyltrimethylammonium Perbromide*** is reported to give better yields of monobrominated ketones.[18]

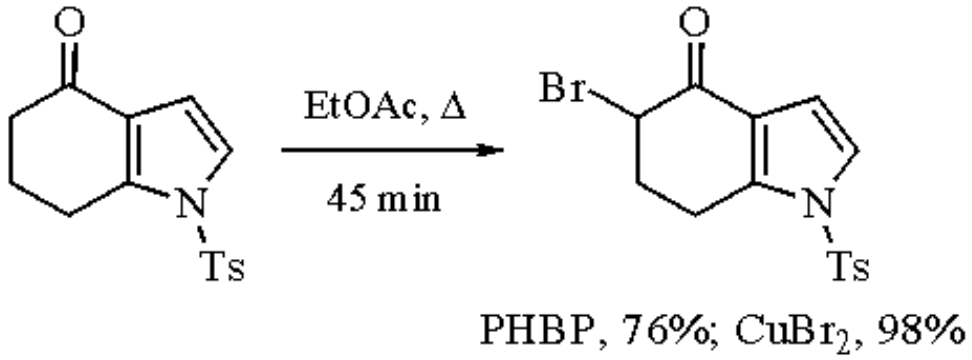

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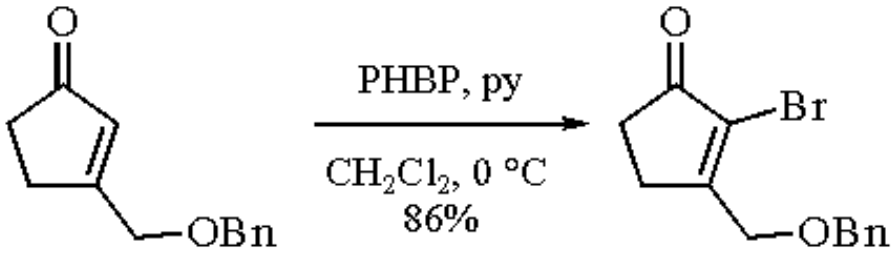

(2)

α-Bromination of Acetals.

PHBP reacts with acetals to give good yields of their α-brominated derivatives.[3] With chiral acetals, different ratios of stereoisomers can result when the solvent or the brominating agent are changed (eq 3).[19]

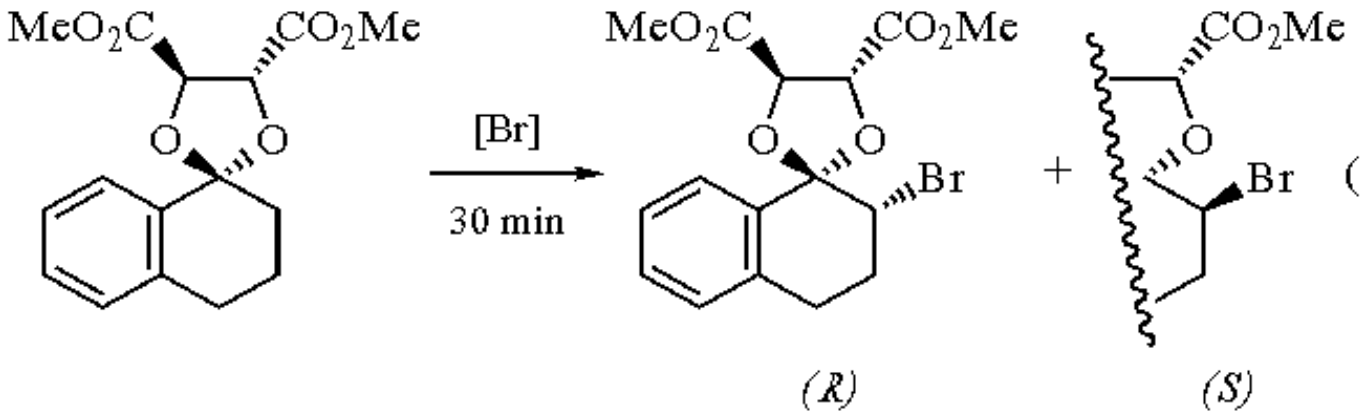

(3)

PHBP:	THF	(R):(S) = 95:5
	CH_2Cl_2	(R):(S) = 58:42
Br_2:	THF	(R):(S) = 1:99
	CH_2Cl_2	(R):(S) = 25:75

Phenyltrimethylammonium perbromide is a comparable acetal bromination reagent which has better solubility in THF at low temperatures.[20] Acetals of benzophenone derivatives are more effectively brominated with ***Bromine-1,4-Dioxane*** rather than PHBP.[21]

Bromination of Alkenes.

PHBP readily adds in an *anti* fashion to carbon-carbon double bonds to give predominantly one stereoisomer.[4] Studies of PHBP addition to cyclohexenes show that diaxial products are favored over diequatorial ones.[22] There is a preference for 1,2- rather than 1,4-addition with conjugated dienes.[23] Enones react with PHBP in methanol to give anti-Markovnikov addition products.[24] Unlike bromine, this reagent adds to the double bond of unsaturated alcohols without brominating the alcohol.[25] Alkenes can be protected by generating their dibromides with PHBP. Deprotection using controlled-potential electrolysis or cathodic debromination regenerates the alkenes.[26]

Bromination of Aromatic Compounds.

The reduced reactivity of PHBP is ideal for monobrominating activated aromatic ethers and phenols such as pyrogallol.[5,27] A kinetic study of the reaction of phenols with PHBP has been reported.[28] Anilines are selectively monobrominated with mostly *para* substitution in 75-95% yield.[6] PHBP has been used for the analytical detection of phenols[30] and anilines.[31] Bromine-dioxane is a comparable reagent for brominating phenols. [18]Annulene has been monobrominated with PHBP in 44% yield.[29]

Heating PHBP to 230 °C affords 3-bromopyridine (37%) and 3,5-dibromopyridine (33%).[7] In contrast, indoles,[32] imidazoles,[33] phenothiazines,[34] and azathiabenzenes[35] are readily monobrominated with PHBP at rt or at lower temperatures.

Dehydrogenations/Oxidations.

PHBP is a convenient reagent for conversion of cyclohexenones to phenols in steroids,[8] tricyclic diterpenoids (eq 4),[36] and other polycyclic compounds.[37]

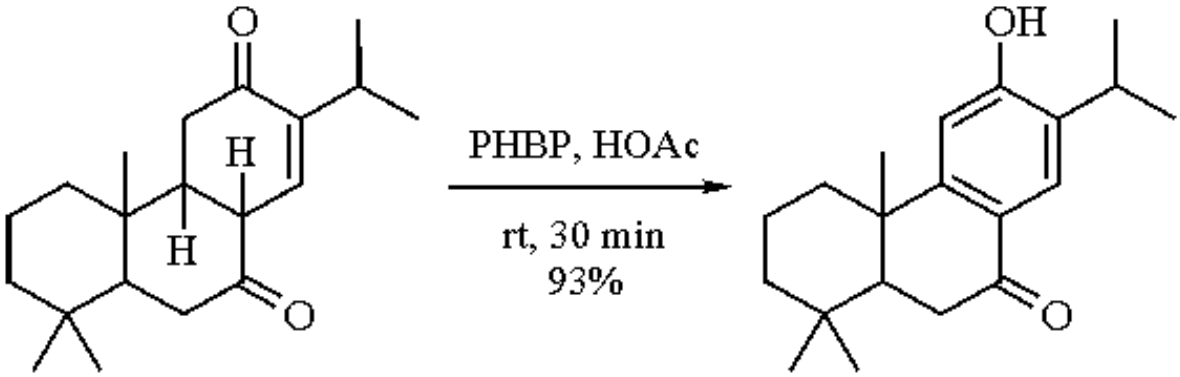

(4)

Combination oxidation-brominations have been reported to occur using PHBP in conjunction with *t*-butyl alcohol (eq 5).[38] Enediol silyl ethers are converted to 1,2-diones with PHBP (eq 6).[39] Oxidations of phosphinic and phosphonic acids are reported to be first order in both the oxyacid and PHBP.[40] Phosphites are oxidized to phosphates in the presence of alcohols and PHBP.[41]

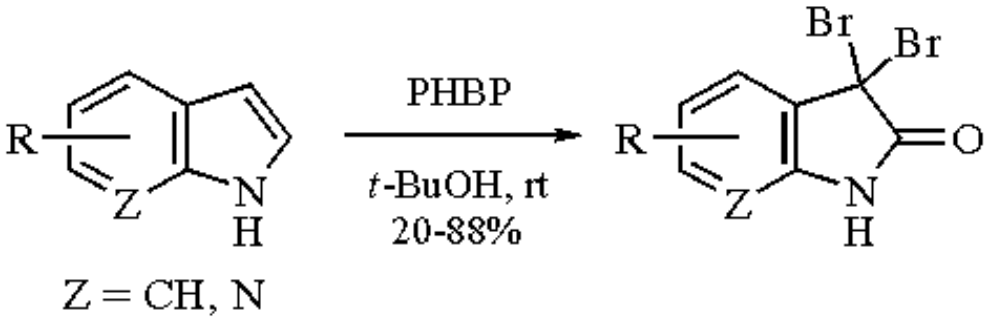

(5)

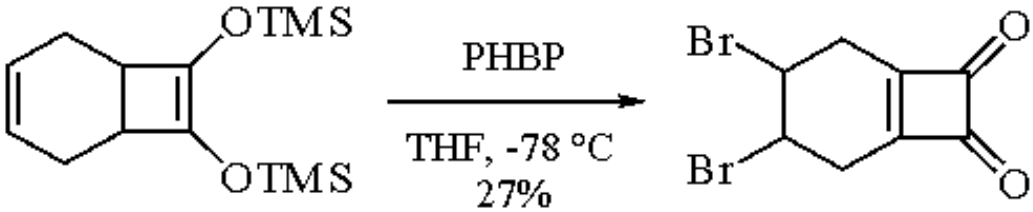

(6)

Kinetic and mechanistic studies on the oxidation of primary alcohols by PHBP have been reported;[10] however, many other more selective reagents are commonly used to oxidize alcohols (e.g. see Jones reagent (see ***Chromic Acid***), ***Manganese Dioxide***, ***Pyridinium Dichromate***, etc.).

Bromination of Organometallic Compounds.

PHBP is an effective bromination reagent for compounds that are highly sensitive or prone to decomposition. If bromine is substituted for PHBP in eq 7, the nickel-cyclobutadiene complex decomposes.[42] Good yields are obtained when bromine from PHBP displaces an aryl group from the bismuth compound of eq 8.[43] Studies of brominations of metal chelates of β-diketones and β-keto esters have been described.[44]

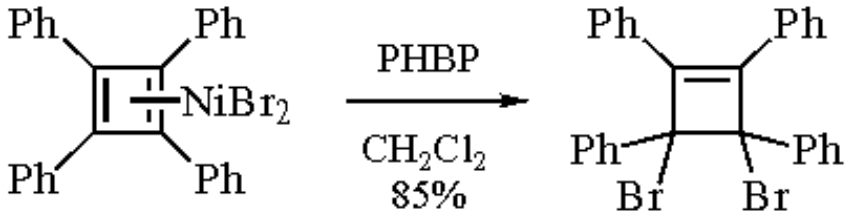

(7)

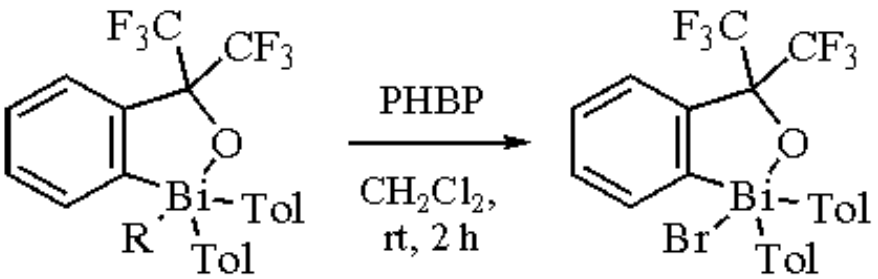

(8)

R = $C_6H_4CF_3$, 88%; C_6H_4Me, 82%; Me, 70%

Other Applications.

PHBP has been used to prepare alkyl bromides from alcohols.[45] It is also effective in phase transfer nitrosation of amines.[46] Thioacetals are oxidized in 78-91% yield to ketones and aldehydes with PHBP under phase transfer conditions.[47] Dihydropyridines have been heated with PHBP to afford lactones via the postulated bromomethyl intermediate shown in eq 9.[48] This intermediate is stable at low temperatures and can be reacted with nucleophiles to give varying yields of substituted dihydropyridines.[49] PHBP has also been used to monobrominate active methylene groups.[50]

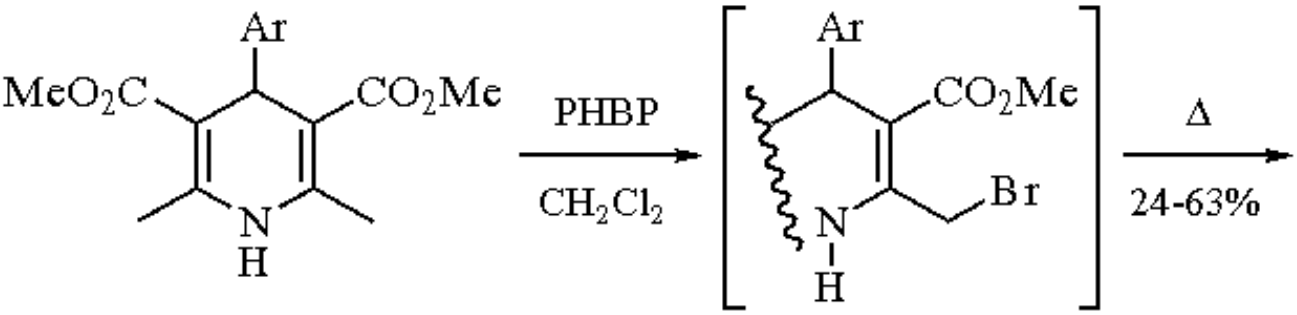

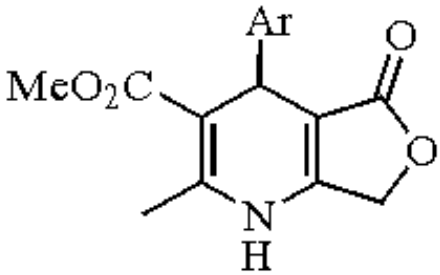

(9)

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Pyridinium Poly(hydrogen fluoride)[1]

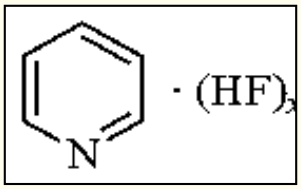

($C_5H_5N.9HF$; 30% pyridine, 70% HF by wt)

[32001-55-1] · $C_5H_{14}F_9N$ · Pyridinium Poly(hydrogen fluoride) · (MW 259.20)

(convenient, less volatile form of anhydrous HF with enhanced nucleophilicity; substitutes F for secondary or tertiary hydroxy groups,[2] other halides,[3] or primary amine[4] groups; adds HF to alkenes and alkynes;[1d] with halonium ion sources, halofluorinates alkenes and alkynes;[1a,5] opens and adds HF to oxiranes (epoxides), aziridines, azirines, and cyclopropanes;[1] oxidatively fluorinates when combined with electrolytic processes or Pb^{IV} compounds[1c,e])

Alternate Names: Olah's reagent; hydrogen fluoride-pyridine

Physical Data: dissoc 55 °C; at 80-110 °C, liq phase is primarily py.5HF; at reflux (160-170 °C) the stoichiometry is py.3HF; low-temperature phase behavior and X-ray crystal structures for some phases are known.[6]

Solubility: sol CH_2Cl_2, MeCN, Et_2O, THF, toluene, sulfolane.

Form Supplied in: light brown liquid in plastic bottles; H_2O most likely impurity (from HF used); commercially available.

Preparative Method: condensation of anhydrous ***Hydrogen Fluoride*** into ***Pyridine*** at -78 °C, followed by gradual warming to rt; *caution*: highly exothermic.[1d,e]

Purification: best approach is to purify components (pyridine, HF) before mixing.[7] HF can also be dried using ***Antimony(V) Fluoride***,[8] BiF_5,[8,9] high-pressure ***Fluorine***,[10] or electrolysis.

Handling, Storage, and Precautions: toxic, hygroscopic, corrosive. Moisture drastically inhibits fluorination activity. Compatible materials: polyethylene, fluoro polymers (FEP, PFA, PTFE). Hydrogen pressure may accumulate in metal HF storage containers. Avoid contact with glass. ***Sodium Fluoride***, aq base, and $CaCl_2$ are useful for neutralization and workup. Reagent contains a small equilibrium concentration of HF. Although the reduced HF vapor pressure in py.$(HF)_x$ reduces the potential for exposure, extreme care should be used in handling this material; handle only in a fume hood, wear safety goggles or a face shield, and wear appropriate impermeable clothing. Effects of exposure to HF are often delayed for several hours, but the burns are extremely painful and can be slow to heal. Exposure to py.$(HF)_x$ should be treated in the same way as for HF. Thus users and coworkers should be familiar with and be prepared to administer the proper first aid treatment.[11]

Substitution Reactions.

Fluorodehydroxylation.

Secondary and tertiary alcohols react with py.$(HF)_x$ to give alkyl fluorides. The tertiary compounds react quickly at temperatures as low as -70 °C, while rt is usually sufficient for secondary alcohols. This can provide significant regioselectivity as shown for reactions at the competitive sites in a steroid (eq 1).[12] Primary alcohols require the addition of NaF for the substitution to occur. The probable S_N2 mechanism of the reaction is illustrated by the lack of rearrangement upon fluorination of neopentyl alcohol (eq 2)[2] (for alternative reagents, see fluoroalkylamine reagents (FAR), ***N,N-Diethylaminosulfur Trifluoride*** (DAST)).

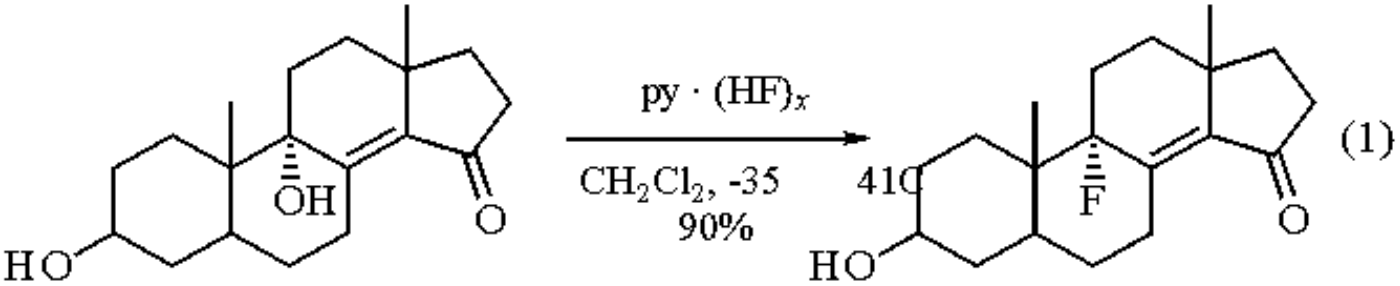

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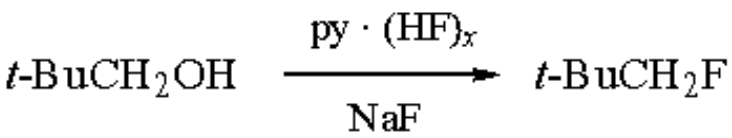

(2)

Halogen Exchange.

No fluorination of tertiary alkyl halides occurs unless the halide is abstracted by an agent such as a nitronium salt (eq 3).[3] Related $R_3N.3HF$ complexes are more effective for nucleophilic halide replacement.[1c]

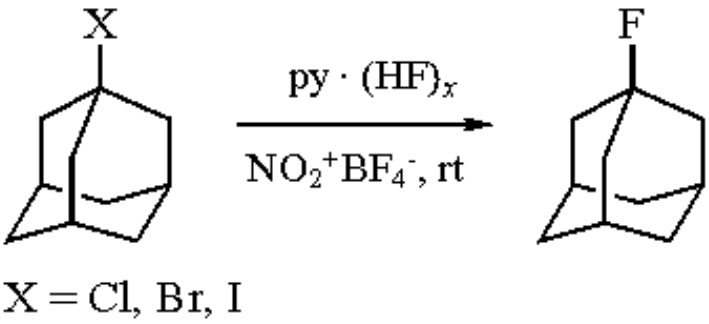

(3)

Fluorodeamination.

Substitution of F for NH_2 is achieved by an in situ diazotization-fluorinative dediazotization sequence. For example, α-fluorocarboxylic acids are obtained from α-amino acids, as shown for 2-aminobutanoic acid (eq 4).[4] Retention of configuration is usually observed.

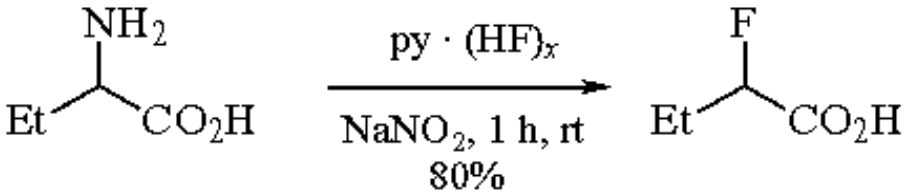

(4)

Addition Reactions.

Hydrofluorination of Alkenes and Alkynes.

Addition of HF takes place in Markovnikov fashion. Among alkenes, branched derivatives and cycloalkenes give higher yields (eq 5).[1d,e] As expected, *gem*-difluoro derivatives are obtained from alkynes (eq 6).[1d] THF is often used as a cosolvent since the starting materials are generally insoluble in py.$(HF)_x$. The related melamine.$(HF)_x$ reagent is especially effective for hydrofluorination of unsaturated substrates and can be used repeatedly in pentane or CCl_4 two-phase systems.[1c]

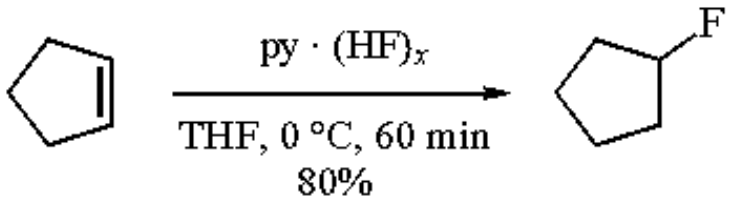

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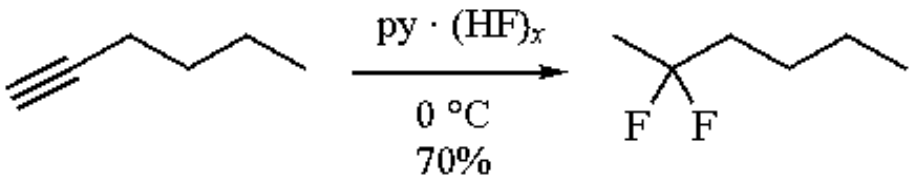

(6)

Halofluorination of Alkenes and Alkynes.

When these unsaturated compounds are combined with py.$(HF)_x$ and a source of halonium ion (e.g. *N*-halosuccinimides, *N*-haloacetamides, or ***1,3-Dibromo-5,5-dimethylhydantoin*** (DBH)), addition of XF (X = Cl, Br, I) to the multiple bond is the result. Alkenes provide several potentially useful extensions from the initial 1,2-halofluoroalkane products.[1a] For example, addition of ***Silver(I) Fluoride*** to the initial product results in halogen exchange yielding vicinal difluorides without isolation of the intermediates. Similarly, reduction of the intermediates with a tin hydride reagent gives products corresponding to Markovnikov addition of HF to the starting alkene. Elimination reactions of the intermediates with base lead to vinyl fluorides. Alkene halofluorination was found to exhibit Markovnikov and anti-Markovnikov orientation in the case of 1-phenyl-4-*t*-butylcyclohexene.[13]

Bromofluorination of phenylacetylene using py.$(HF)_x$ and DBH in sulfolane (eq 7)[5] gave a mixture of (*Z*) and (*E*) isomers but with good regio- and stereoselectivity.

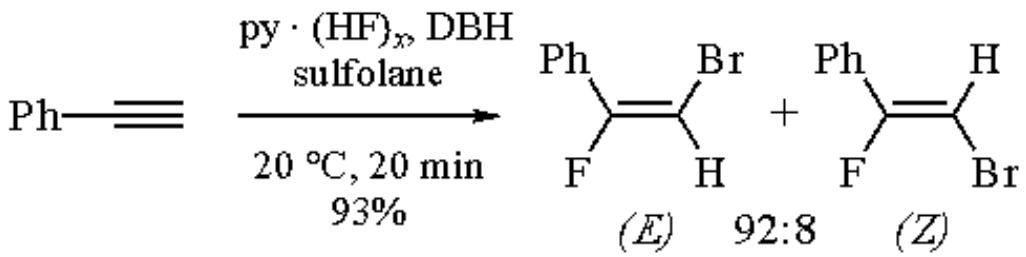

(7)

Ring-Opening Fluorination.

The fluoride ion donor ability of py.$(HF)_x$ is shown by the cleavage of cyclopropane (eq 8),[14] in which fluoride traps the primary cation before it can rearrange. Regioselective conversion of oxiranes to fluorohydrins has become an important process in the steroid field (eq 9).[15] An iterative cyclization/ring opening approach has served in the conversion of a tetrachlorocyclohexanol to its tetrafluoro analog with complete regio- and stereoselectivity.[16] In the case of aziridines the ring opening is regioselective in that fluoride becomes bound to the carbon best able to stabilize a positive charge, but the stereochemistry depends strongly on the starting material and the fluorinating agent.[1c,e] Substituted 1-azirines give difluorinated amines or α-fluoro ketones, depending on the substituents.[1c,e]

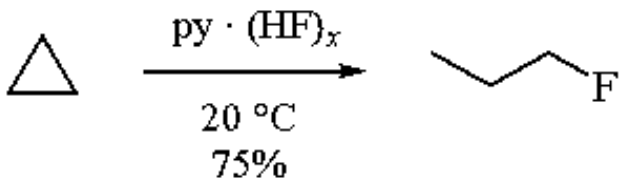

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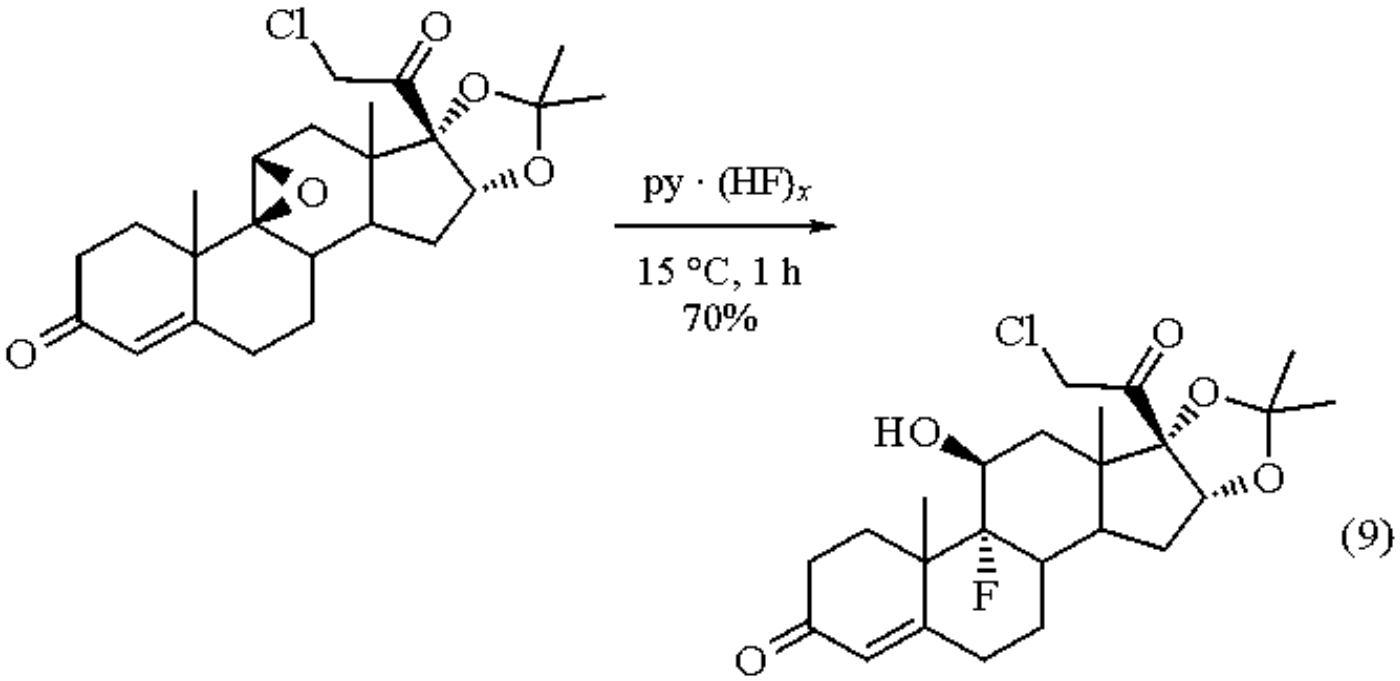

Oxidative Fluorination.

With py.$(HF)_x$ and stoichiometric amounts of Pb^{IV}, phenols are converted to difluorodienones (eq 10). Benzene reacts very slowly to give the same product.[1b,c] Similar reactions can be conducted using anodic oxidation in place of the lead compounds. In both situations, cations or radical cations are proposed as the initially generated species, which then react with fluoride. For these reactions, ***Triethylamine***.3HF is used most often.

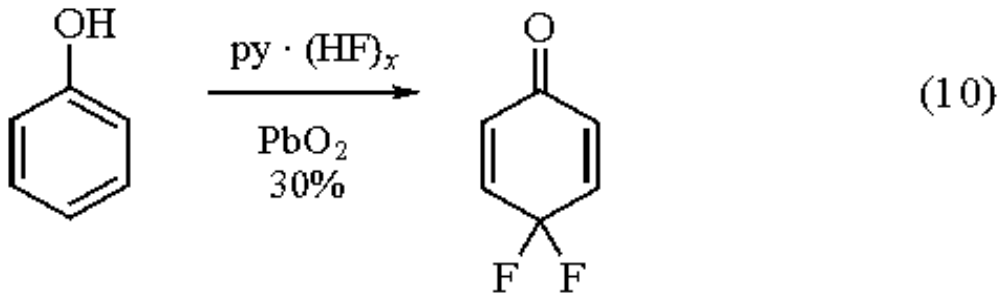

Related Reagents.

Several applications of Et_3N.3HF and melamine.$(HF)_x$ have been mentioned above. In addition, 2,4,6-trimethylpyridine.$(HF)_x$ [*45725-47-1*] is useful since it is a commercially available solid melting at 90 °C. A polymer-supported agent containing about 35-40% HF, poly[4-vinylpyridinium poly(hydrogen fluoride)], is also available.[17]

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Pyridinium *p*-Toluenesulfonate

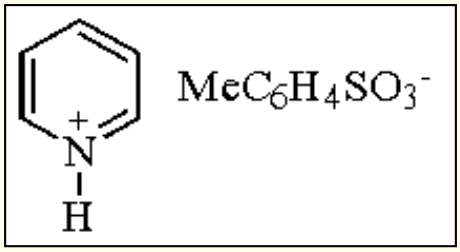

[24057-28-1] · $C_{12}H_{13}NO_3S$ · Pyridinium *p*-Toluenesulfonate · (MW 251.33)

(used as an acid catalyst for the protection and deprotection of alcohols and acetals)

Alternate Name: PPTS.

Physical Data: mp 120-121 °C.[1,2]

Solubility: sol benzene, toluene, dichloromethane, chloroform, ethanol, and acetone.

Form Supplied in: white, moisture-sensitive crystalline solid.

Preparative Method: prepared in a 95% yield by the addition of ***p-Toluenesulfonic Acid*** to ***Pyridine*** at 22-24 °C.[1,2]

Purification: recrystallized from acetone.[1,2]

Handling, Storage, and Precautions: the title reagent is moisture sensitive, requiring storage under nitrogen in a desiccator over a suitable drying agent. Stored in this manner, the reagent has an excellent shelf life. Irritant; handle with gloves.

Properties and General Considerations.

PPTS (**1**) is a weakly acidic salt frequently used in catalytic quantity for the protection of alcohols as tetrahydropyranyl (eq 1)[1] and trimethylsilyl ethers (eq 2).[3]

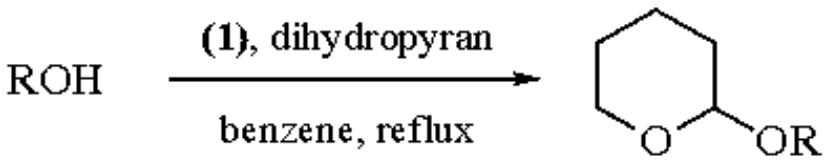

(1)

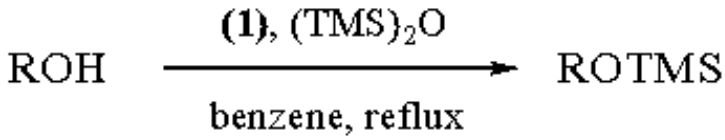

(2)

PPTS is particularly favored for use with acid-sensitive functionalities such as allylic alcohols, epoxides, and acetals. *N*-Tosyl-L-norephedrine has been converted to its oxazolidine using a catalytic amount of (**1**) (25 mol%) and ***Triethyl Orthoformate*** (eq 3).[3]

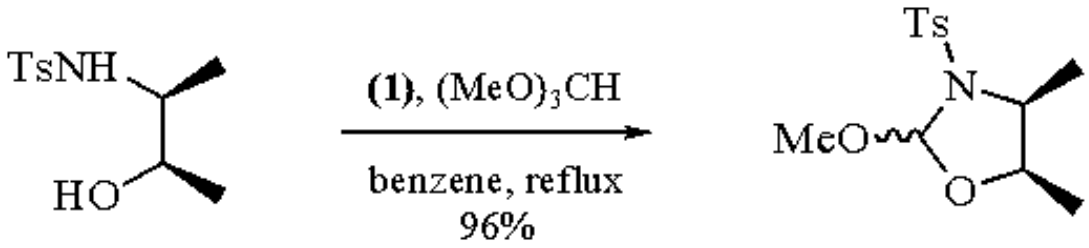

(3)

p-Methoxyphenol has been protected as its THP ether (80% yield) using 4 equiv of (**1**).[4] All these reactions are run in dry aprotic solvent (benzene, toluene, or dichloromethane) and water formed during the course of the reaction is removed by azeotropic distillation or by 4 Å molecular sieves. Yields are good to excellent.

Cleavage of *t*-Butyldimethylsilyl Ethers.

A catalytic quantity of (**1**) (30 mol %) in ethanol selectively cleaves *t*-butyldimethylsilyl ethers in the presence of *t*-butyldiphenylsilyl ethers (eq 4).[5]

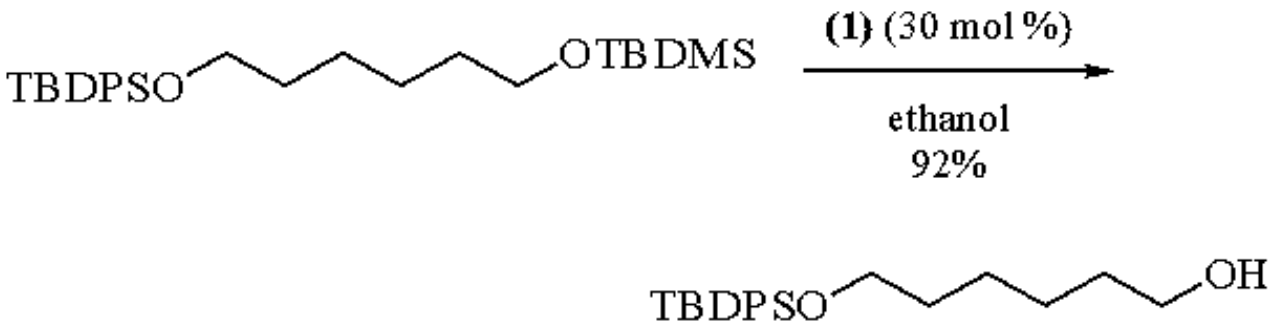

(4)

Acetalization.

PPTS is an excellent catalyst for the preparation of 1,3-dioxolane acetals from ketones and ethanediol (90-95% yield).[6] The weak acidic nature of (**1**) makes it ideal for acid-sensitive compounds.

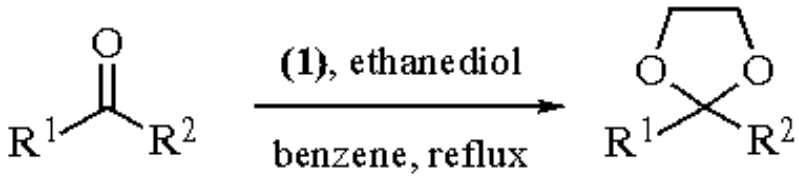

(5)

The reaction is carried out using 10-30 mol % of (**1**) in refluxing benzene, accompanied by the azeotropic removal of water (Dean-Stark apparatus). Similar conditions have been used for the preparation of acetals using (*R*,*R*)-hydrobenzoin and a tricyclic benzaldehyde derivative.[7]

Deprotection of Acid-Sensitive Protecting Groups via Transacetalization.

PPTS is a versatile catalyst for the deprotection of acid-sensitive acetal protecting groups. For example, 10-30 mol % of (**1**) efficiently cleaves tetrahydropyran ethers (THP) (eq 6),[1] 1,3-dioxolanes (eq 7),[6] methoxymethyl ethers (MOM), and methoxyethoxymethyl ethers (MEM) (eq 8).[8]

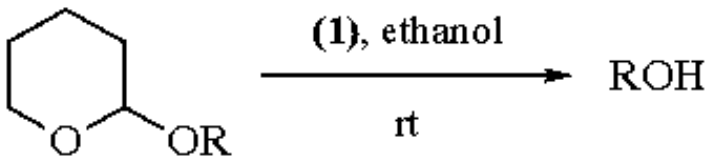

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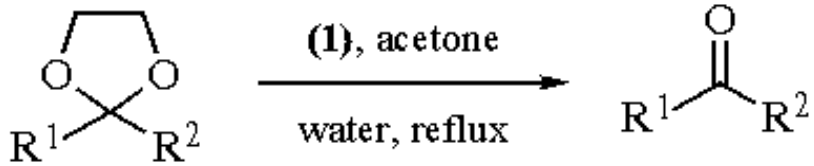

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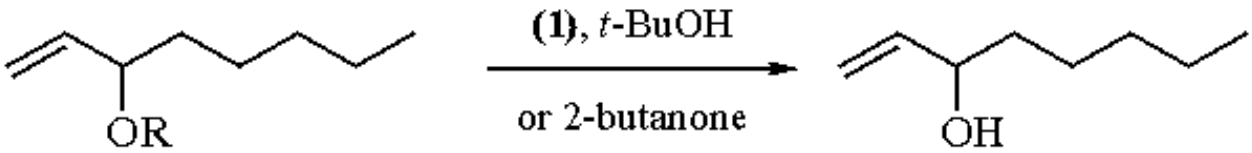

(8)

R = CH_2OMe (MOM), 94%
R = $CH_2OCH_2CH_2OMe$ (MEM), 93%

2-Methoxybutadienes.

PPTS catalyzes the isomerization of allenyl ethers to 1-alkyl-2-methoxybutadienes. Freshly prepared crude allenyl ethers are treated with (**1**) (1 mol %) in dichloromethane at room temperature (eq 9).[9]

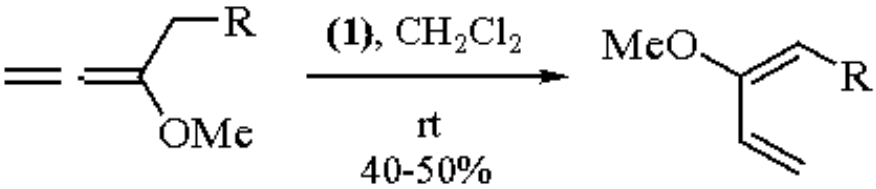

(9)

2-Alkyl-3-acylfurans.

PPTS converts 5-acetoxy-4,5-dihydrofurans to the corresponding furans (eq 10).[10] The reaction is carried out in refluxing toluene for 3-6 h. Yields are poor to modest.

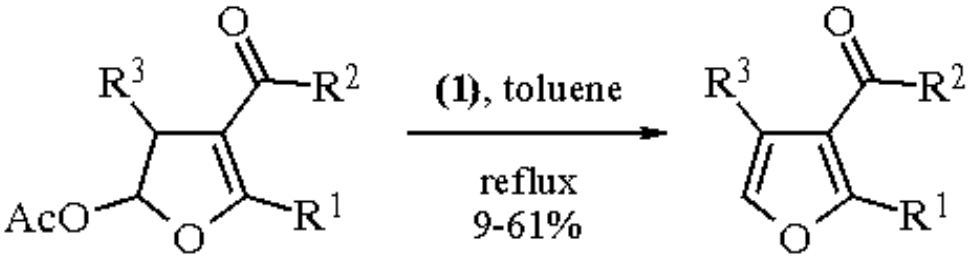

(10)

α-Alkoxyhydrazines.

Reaction of α-sulfinylhydrazones with alcohols in the presence of (**1**) (10-30 mol %) results in α-oxy substituted hydrazines (eq 11).[11]

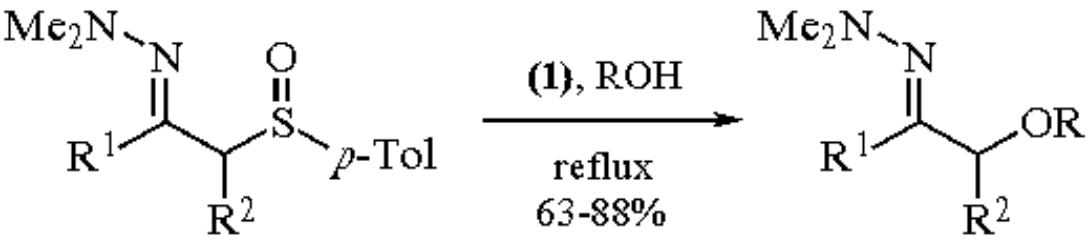

(11)

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2-Pyridone[1]

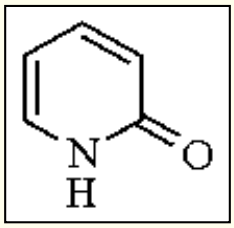

[142-08-5] · C_5H_5NO · 2-Pyridone · (MW 95.11) (iminol tautomer)

[72762-00-6]

(ambident nucleophile,[2] diene for [4 + 2] cycloaddition;[3] used to form active esters in peptide synthesis[4])

Alternate Name: α-pyridone.

Physical Data: mp 105-107 °C; bp 280-218 °C; λ_{max} 293 nm (ε 5900, H_2O).

Solubility: sol H_2O, EtOH, $CHCl_3$; moderately sol Et_2O, C_6H_6; sparingly sol ligroin, hexane.

Form Supplied in: crystalline; widely available.

Purification: commercial material is distilled under vacuum (181-185 °C/24 mmHg) to remove colored impurities. The distillate is recrystallized from EtOH, $CHCl_3$/ether, C_6H_6, C_6H_6/hexane, or CCl_4.[5] Alternatively, high purity material can be prepared by sequential recrystallization,[2] sublimation,[6] or a combination of both techniques.[7]

Handling, Storage, and Precautions: store refrigerated, preferably under an inert atmosphere. Uses of the iminol tautomer of this reagent as a coupling agent are considered under ***2-Hydroxypyridine***.

General Considerations.

2-Pyridone (**1**) is a classical substrate for the study of iminol-amide tautomerism (eq 1). In polar media the pyridone form is favored;[6] the tautomeric equilibrium shifts to the hydroxypyridine form as solvent polarity decreases. In the vapor phase the hydroxypyridine form predominates.[8] Consequently, nucleophilic substitution reactions using various electrophilic reagents can and sometimes do provide mixtures of isomeric products. In the case of simple alkylation, *N*-alkylation is most commonly observed when the conjugate base of (**1**) is used as nucleophile,[2,9,10] as illustrated by the conjugate addition-elimination product (**2**) (eq 2) formed by addition of (**1**) to 3-chloro-5,5-dimethyl-2-cyclohexenone in the presence of ***Potassium Carbonate***.[11]

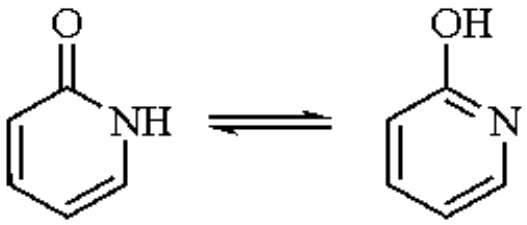

(1)

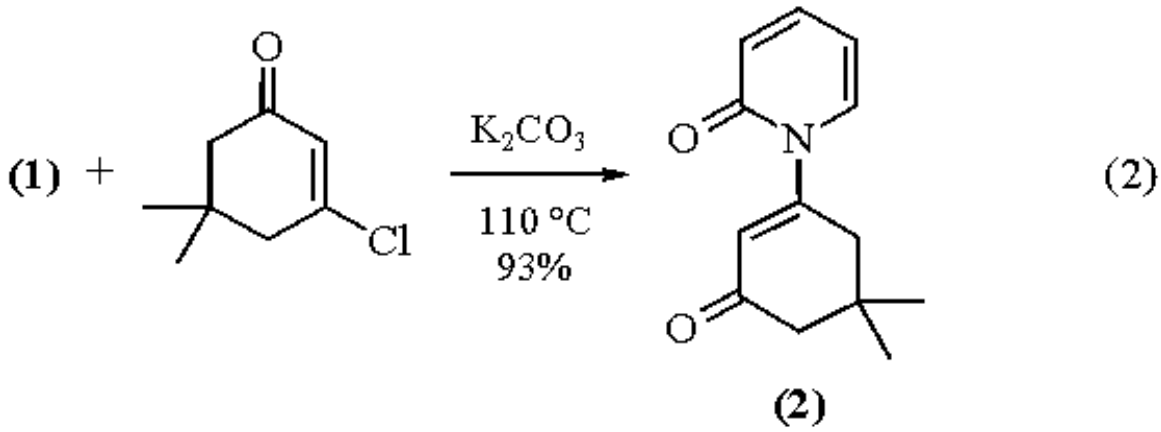

Regiospecific *N*-alkylation also is observed with Pt- and Pd-catalyzed allylations[12] and with sulfenium ions generated from a Pummerer reaction of tetramethylene sulfoxide.[13] Solvent and counterion effects are substantial: polar solvents favor *N*-alkylation, while the Ag salt of (**1**) is highly biased towards *O*-alkylation.[2] Silyl ethers form when ***Trimethylsilyl Trifluoromethanesulfonate*** is used as electrophile with ***Triethylamine*** present;[13] similarly, the dimethylphosphinite is the sole product when (**1**) is reacted with chlorodimethylphosphine.[7a] Kinetically controlled methylation of (**1**) with ***Diazomethane*** provides ~60:40 ratio of *N*-methyl and *O*-methyl products,[7b] while hard electrophiles such as 2-methoxybiphenyl-2´-yldiazonium fluoroborate provide exclusive *O*-methylation.[14] Other things being equal, substrate identity can influence the regiospecificity of alkylation (eq 3).[15]

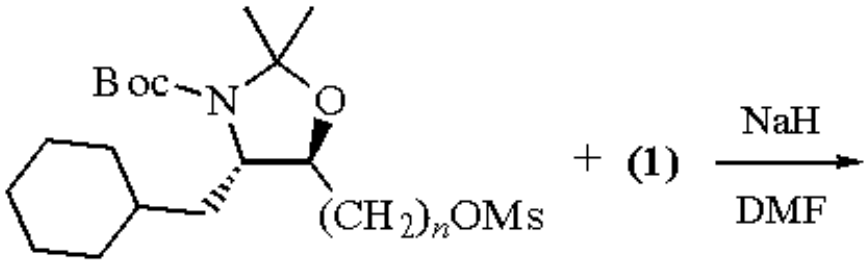

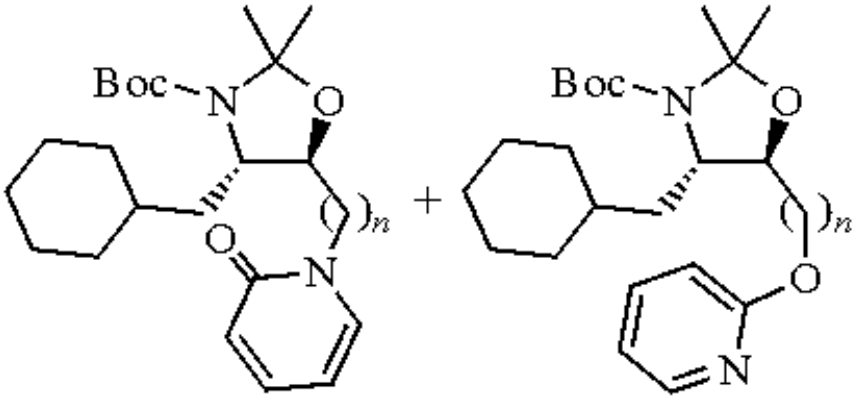

(3)

n		
1	19%	38%
2	-	76%

Acylations of (**1**) are less well known: acetylation at cold temperatures results in a mixture of products; the *N*-acetyl derivative rearranges to the thermodynamically preferred *O*-acetyl isomer upon warming to room temperature (eq 4).[16] Benzoylation[17] and triflation[18] provide only ester products from attack at the oxygen of (**1**).

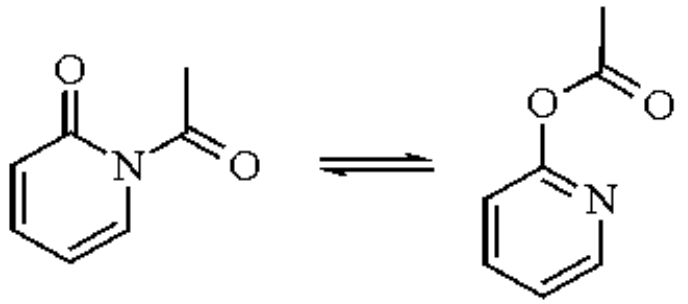

(4)

[4 + 2] Cycloaddition reactions of (**1**) usually are difficult to achieve.[3] 2-Pyridone itself is prone to undergo conjugate addition reactions with dienophiles,[19] but *N*-alkyl derivatives, especially *N*-methyl and *N*-alkenyl derivatives, are found to form *N*-alkylated isoquinuclidine adducts with highly reactive dienophiles such as ***Dimethyl Acetylenedicarboxylate*** (eq 5),[19,20] ***Maleic Anhydride***, and benzyne[21] under thermal or high pressure conditions. When heated, the adducts can aromatize via alkyl isocyanate extrusion. Related *N*-arylsulfonyl-3-(*p*-toluenesulfonyl)-2-pyridones are relatively good dienes in inverse electron demand Diels-Alder reactions with vinyl ether dienophiles;[3] these cycloadditions are facilitated by high pressure.

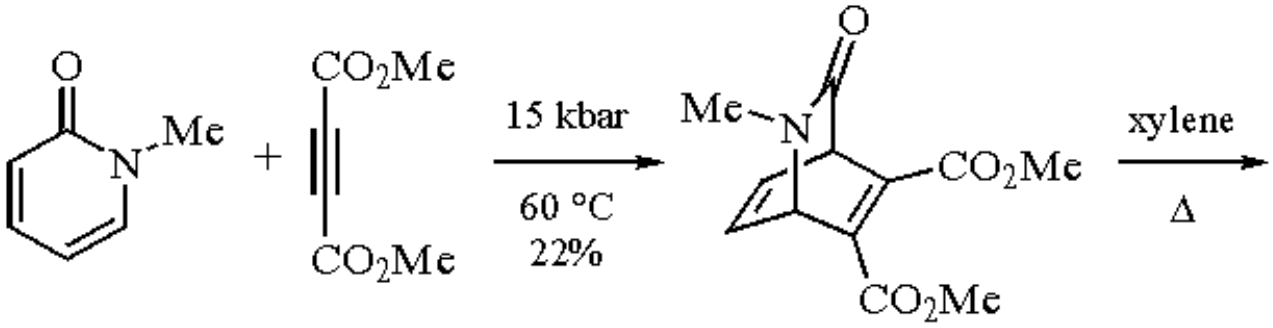

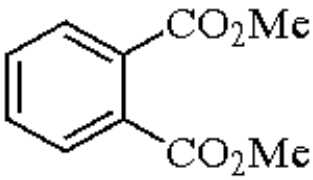

+ MeNCO (5)

Although intramolecular [4 + 2] cycloadditions of *N*-(o-alkenyl)-2-pyridones have been unsuccessful,[21a] photosensitized intramolecular [2 + 2] cycloadditions of these substrates provide a simple route to stereochemically defined tricyclic lactams.[10] A unique intramolecular 1,3-dipolar cycloaddition between DMAD and an azomethine ylide generated from *N*-(3´-diazoacetonyl)-2-pyridone provides indolizinone products.[9]

2-Pyridone is useful in the preparation of active esters for solid-phase peptide synthesis;[4] these esters are considerably more reactive than the corresponding *p*-nitrophenyl esters when peptide coupling is performed in CH_2Cl_2. In one application to peptide synthesis, 2-pyridyl esters serve as intermediates in the preparation of 2,2,2-trichloroethyl esters of amino acids (eq 6).[22]

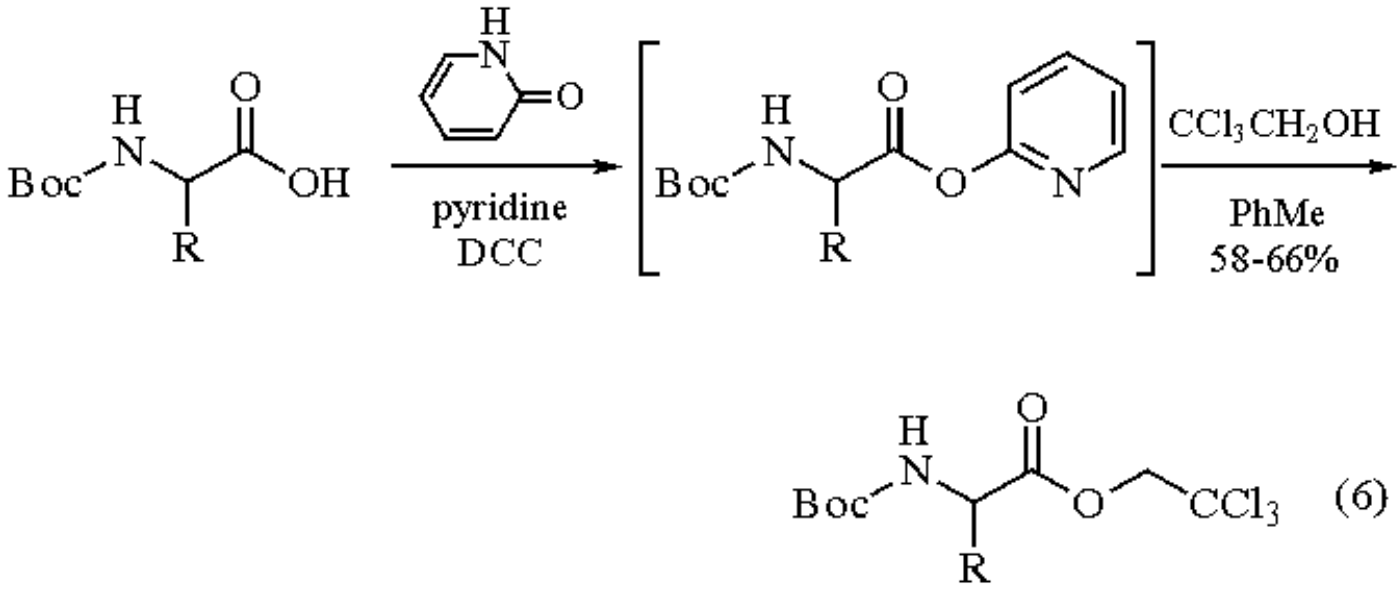

Other uses of 2-pyridone include that as a ligand in transition metal complexes, such as the preparation of complexes derived from chloro-bridged Ru^{IV} bis(allyl) dimers[23] and triruthenium carbonyl complexes from $Ru_3(CO)_{12}$.[24] *N*-Hydroxy-2-pyridone can be used to effect radical decarboxylation: *N*-dihydrocinnamyloxy-2-pyridone is reduced by ***Tri-n-butylstannane*** with ***Azobisisobutyronitrile*** initiation to provide ethylbenzene in 73% yield.[25] Finally, 2-hydroxypyridinium tosylate acts as an acid catalyst in the dimerization of α-aminoacrylonitrile.[26]

Related Reagents.

Methanesulfonic Anhydride.

---

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2-Pyrone[1]

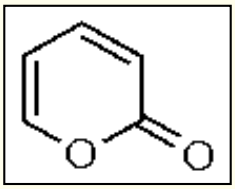

[504-31-4] · $C_4H_4O_2$ · 2-Pyrone · (MW 96.08)

(diene for cycloadditions[2] and inverse electron demand cycloadditions;[3] used in the synthesis of cyclobutadiene[4])

Physical Data: mp 8-9 °C; bp 206-209 °C (slight dec), 102-103 °C/20 mmHg; *d*204 1.200 g cm^{-3}; *n*20D 1.530.

Solubility: miscible with H_2O.

Form Supplied in: liquid; available in 95-98% purity commercially.

Preparative Methods: can be prepared in 66-70% chemical yield by pyrolytic decarboxylation of coumalic acid on copper turnings at 650 °C.[5] Alternatively, the dihydro analog, 5,6-dihydro-2*H*-pyran-2-one, can be prepared by acid-catalyzed condensation of vinylacetic acid and ***Formaldehyde***.[6] Allylic bromination followed by dehydrobromination provides 2-pyrone in overall chemical yields of ca. 18%.

Handling, Storage, and Precautions: decomposes upon heating.

General Considerations.

2-Pyrone and its analogs (see ***3-Hydroxy-2-pyrone***, ***2-Pyridone***) find use in cycloaddition reactions, providing bicyclolactone adducts which can be elucidated into a variety of highly functionalized cyclohexadienes and benzenes. This pyranone reacts with a wide variety of standard dienophiles, including ***Maleic Anhydride***,[7] ***Dimethyl Acetylenedicarboxylate***,[8] fumarates,[9] ***Methyl Vinyl Ketone***,[10] and acrylates.[9,10] Under typical thermal conditions the bicyclolactone intermediate is not isolated; in situ decarboxylation leads to cyclohexadiene or benzene products. In the former case, a second equivalent of dienophile may undergo cycloaddition with the initial product, leading to 2:1 adducts from tandem cycloaddition.[11] High pressure cycloaddition conditions may alter this outcome (eq 1).[7,9]

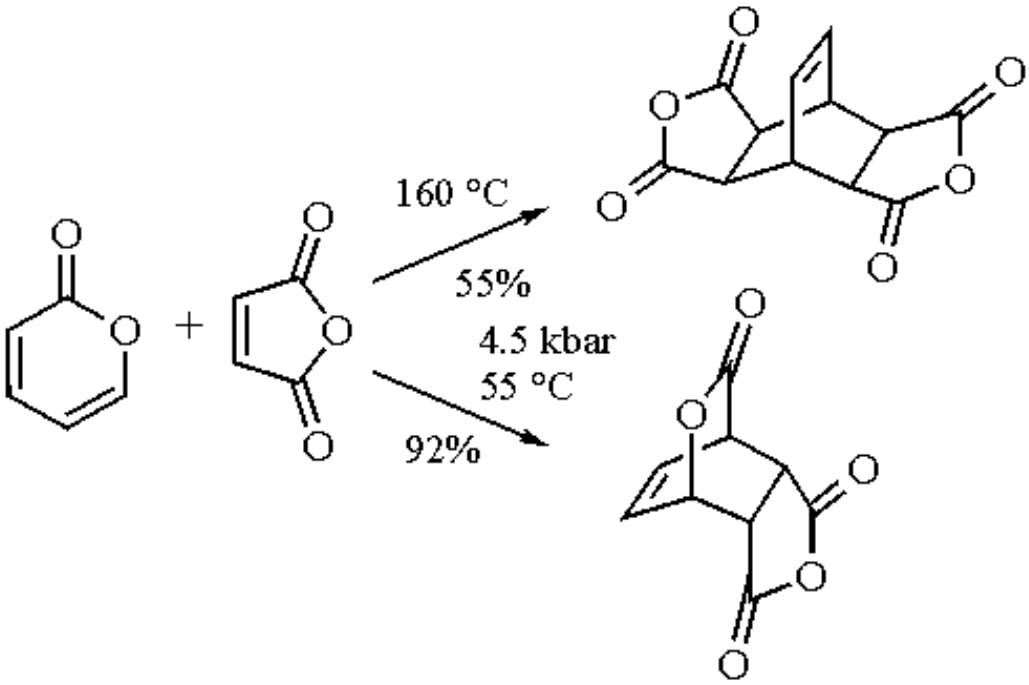

(1)

This approach has been used to prepare barrelene[10] and other molecules of interesting topologies.[12] A two-step, intramolecular version of this tandem cycloaddition using an unactivated double dienophile (eq 2)[13a] represents a convergent approach to polycyclic compounds of interest in natural products synthesis.[13,14]

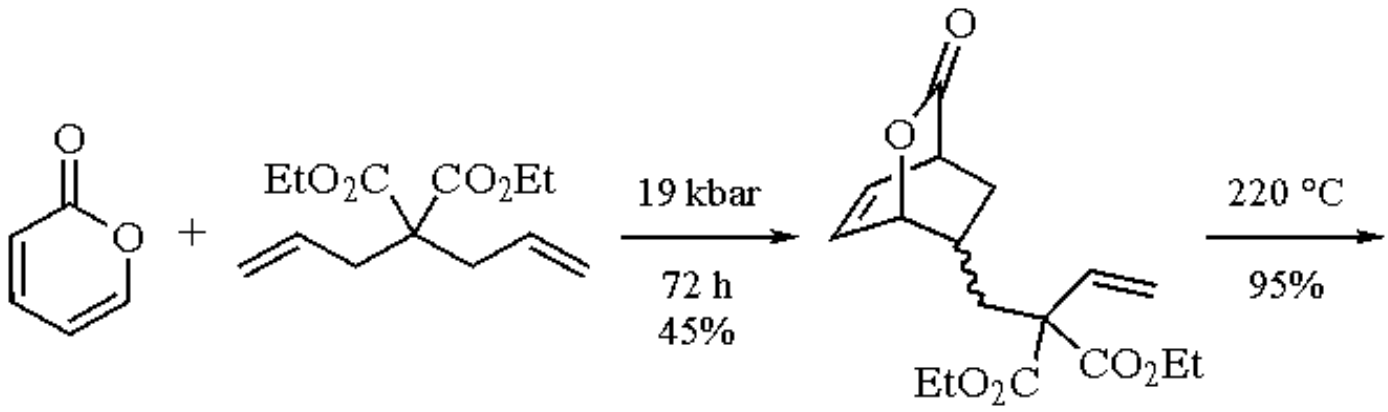

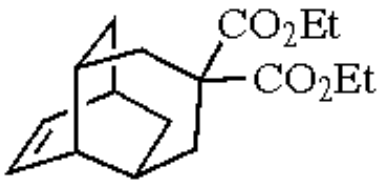

(2)

When itaconic anhydride is used as dienophile and the resultant adduct decarboxylated, the interesting toluene tautomer 5-methylene-1,3-cyclohexadiene is produced;[15] similarly, use of benzocyclobutene as the dienophile, followed by in situ decarboxylation, provides a route to chemically and theoretically interesting benzocyclooctatriene.[16] With benzoquinones as dienophiles, substituted 2-pyrones provide strategic diene subunit synthons in anthraquinone synthesis.[17] Alkyne dienophiles always result in *o*-disubstituted benzene products,[8,18] with rare exception.[19] [4 + 2] Cycloaddition reactions using cyclopropanes[20] and nitrosobenzene[21] have been reported, as have [4 + 2], [3 + 4], and [3 + 2] cycloadditions using a 1,1-/1,3-dipole cyclopropenone acetal.[22]

Thermal or high pressure dimerizations for the most part lead to polymerization.[23] At very high (625 °C) temperatures, rearrangement by reversible electrocyclic ring opening to provide intermediate ketene aldehydes can be observed.[24] On the other hand, photosensitized dimerization of 2-pyrone yields a mixture of the expected *exo* dimers (**1**) and (**2**).[25] Direct irradiation of 2-pyrone in ether leads to bicyclo[2.2.0]pyran-2-one (**3**),[26] the direct precursor to cyclobutadiene via photodecarboxylation (eq 3).[27]

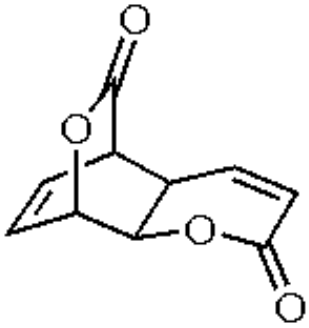

(1)

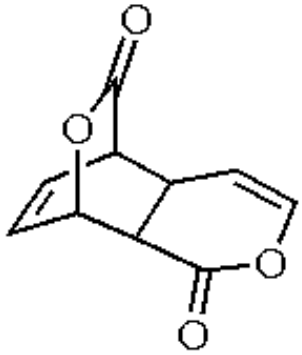

(2)

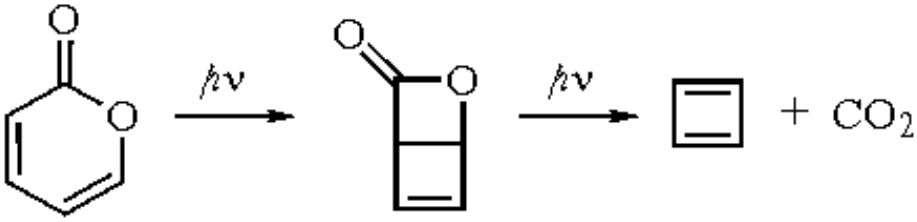

(3)

(3)

Nucleophilic addition reactions of 2-pyrone can be complex; benzylthiolate, cysteine, cysteine methyl ester, and *N*-acetylcysteine all give complex mixtures of products when reacted with 2-pyrone.[28] Grignard reagents undergo 1,2-additions to the carbonyl moiety,[29] as do alkoxides.[30] Metal hydrides can provide either 1,2-addition or 1,6-addition.[31] Reaction with ammonia affords 2-pyridone; ***Diazomethane***[32] and cyanide attack at C-6 (eq 4).[33]

(4)

Electrophilic substitutions of 2-pyrones are possible.[1] In the case of bromination or chlorination, 3-halo-2-pyrones form by means of sequential halogenation-dehydrohalogenation, rather than by direct electrophilic substitution.[34] 3-Bromo-2-pyrone itself undergoes metal-halogen exchange with ***Lithium Dimethylcuprate***, resulting in 3-cuprio-2-pyrone.[35] This organocopper reagent, which is the least nucleophilic of those reported in the literature, has properties reminiscent of organocopper reagents derived from α-bromoacrolein and α-bromoacrylates (see ***Lithium (3,3-Diethoxy-1-propen-2-yl)(phenylthio)cuprate***).

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Pyrophosphoryl Chloride

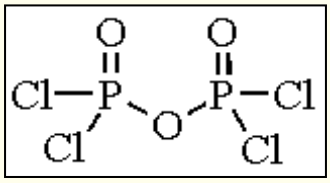

[13498-14-1] · $Cl_4O_3P_2$ · Pyrophosphoryl Chloride · (MW 251.74)

(phosphorylating agent used in nucleoside synthesis;[5,7] used in Vilsmeier formylation and glyoxylation reactions[4,8])

Alternate Names: diphosphoryl chloride; pyrophosphoryl tetrachloride.

Physical Data: bp 60-65 °C/0.1 mmHg, 90 °C/12 mmHg.

Solubility: sol most organic solvents but reacts with alcohols.

Form Supplied in: liquid; available commercially.

Purification: redistil under reduced pressure.

Preparative Methods: prepared in 30% yield by heating ***Phosphorus(V) Oxide*** and ***Phosphorus Oxychloride*** in a sealed tube and separating the resulting mixture by fractional distillation.[1] Alternatively, can be prepared by reaction of phosphoryl chloride with a controlled amount of water.[2] Until recently, the most convenient method involved the reaction of phosphoric anhydride with ***Phosphorus(III) Chloride*** and ***Chlorine***.[3] A recent procedure involves the reaction at reflux of phosphoryl chloride with 0.2 equiv of methanol for 21 days followed by removal of the excess phosphoryl chloride and distillation of the residue to give the reagent (**1**) in 49% yield (eq 1).[4]

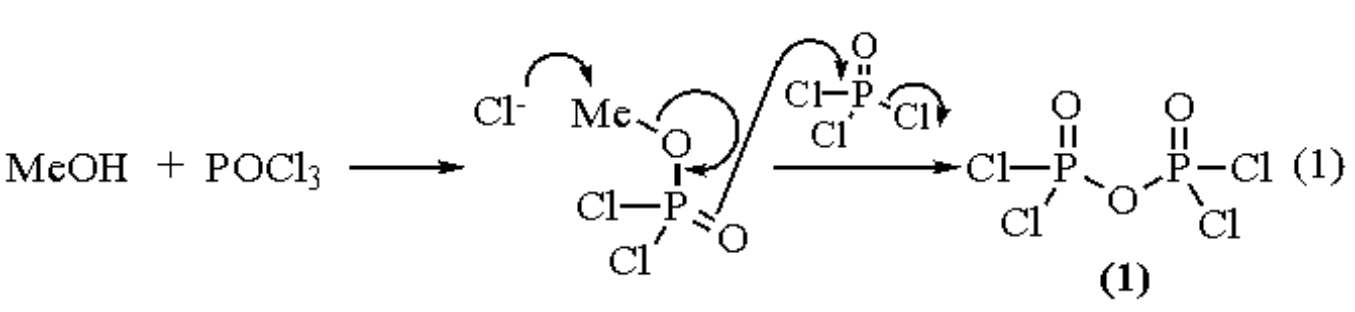

Handling, Storage, and Precautions: corrosive; reacts violently with water; irritating to eyes, respiratory system, and skin. Use in a fume hood.

Phosphorylation.

Pyrophosphoryl chloride (**1**) has been used in the phosphorylation of a variety of primary alcohols. It reacts with primary alcohols according to the scheme in eq 2. Thus reaction at low temperature between (**1**) and a primary alcohol in the absence of solvent gives a dichlorophosphoric acid derivative (**2**), which on treatment with water gives a monophosphate (**3**).

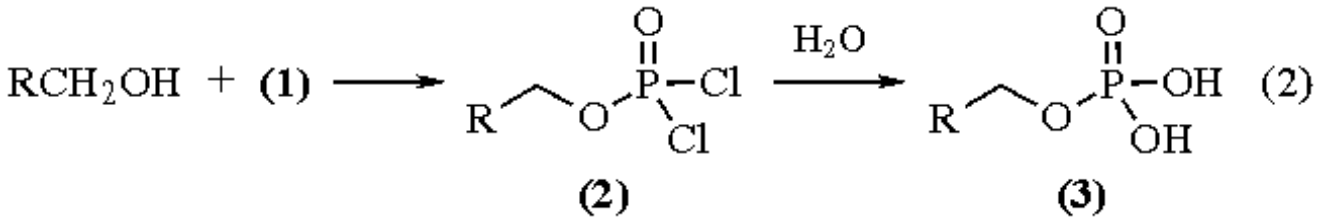

This is a particularly effective sequence for the synthesis of nucleoside monophosphates. For example, treatment of 2´,3´-isopropylideneadenosine (**4**) with (**1**) below rt followed by treatment with water and subsequent removal of the isopropylidene group gave adenosine 5´-phosphate in 65-85% yield (eq 3).[5] 2´,3´-Isopropylideneguanosine reacted similarly. This method avoids the need for base catalysis and removal of organic residues.

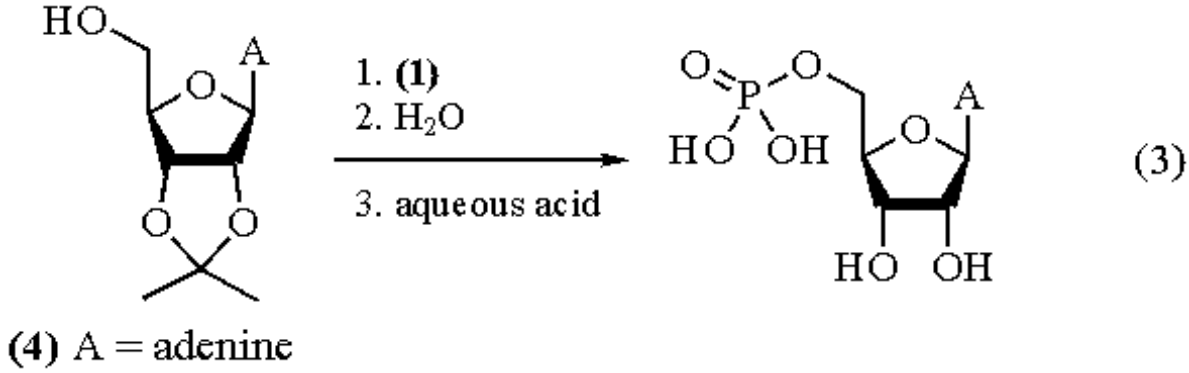

This has been applied to systems other than nucleotides. For example, a range of C-21-hydroxylated steroids have been phosphorylated in high yield by reaction with (**1**) at 0 °C followed by quenching in ice water.[6] The reaction fails with cortisone and produces considerable quantities of dehydration product with C-11-hydroxy steroids. These authors also report that little or no phosphorylation was observed when (**1**) was used in organic solvents.

Pyrophosphate Esters.

In addition to the synthesis of monophosphates, pyrophosphoryl chloride has also been used to prepare pyrophosphate esters. Reaction of (**1**) with 2´,3´-isopropylideneadenosine (**4**) in the presence of ***Triethylamine*** gave the pyrophosphate ester (**5**), which on hydrolysis with aqueous ***Formic Acid*** gave a 22% yield of adenosine diphosphate (ADP) (**6**) (eq 4).[7]

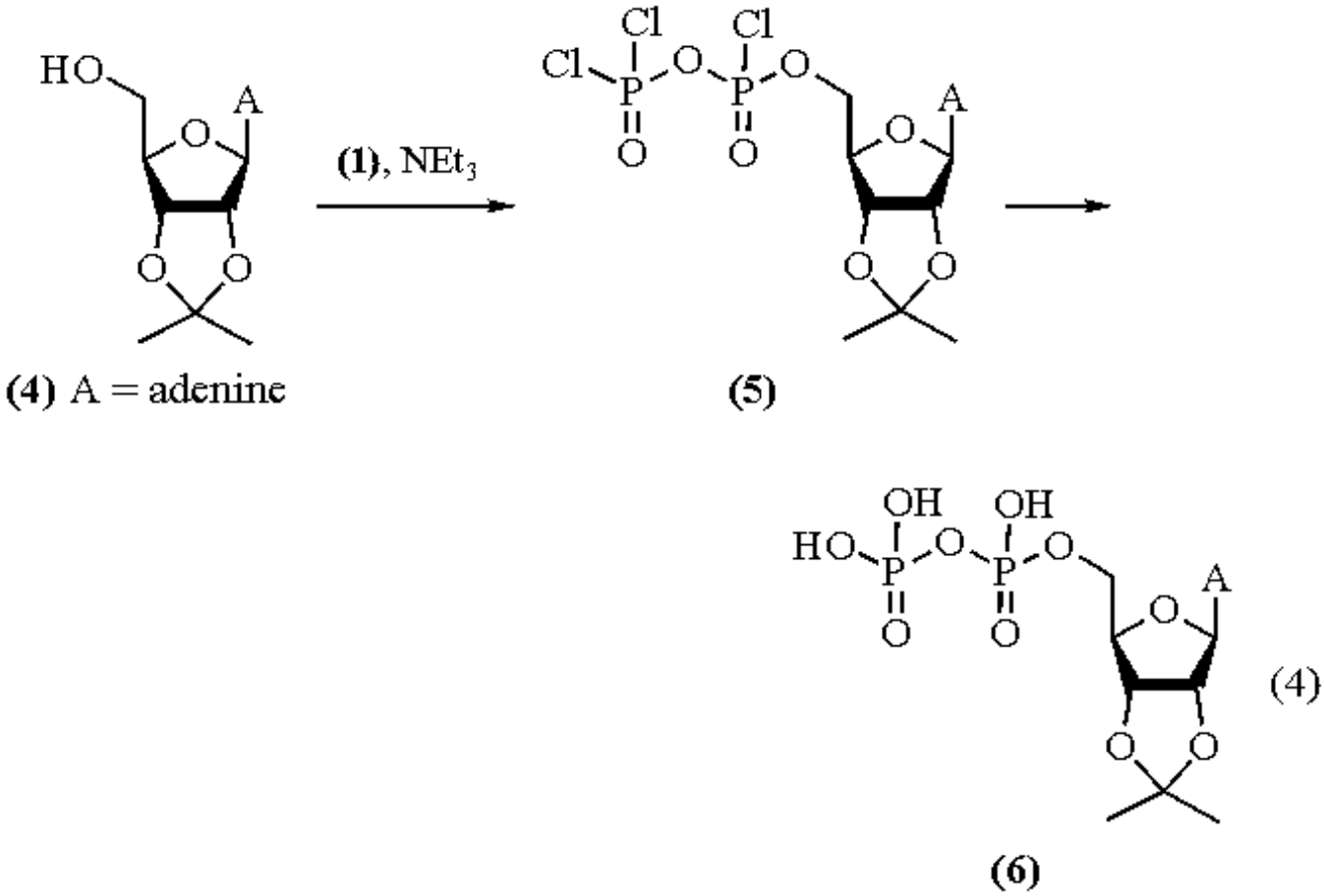

This approach to pyrophosphate esters has been extended to mixed esters such as coenzyme A, although the yield was very low (<1%).[7]

Formylation.

In the classical Vilsmeier reaction, ***N,N-Dimethylformamide*** and phosphoryl chloride are used and the reaction is usually assumed to involve the

N,*N*-dimethylchloromethyleneiminium ion as the electrophile (see also ***Dimethylchloromethyleneammonium Chloride***). Recently, pyrophosphoryl chloride (**1**) has been investigated as the activating agent.[4] Reaction of (**1**) with an excess of DMF or *N*-methylformanilide at 0 °C in the presence of an electron-rich aromatic compound followed by heating (for unreactive aromatics) or simply standing (for reactive substrates) followed by treatment with ***Sodium Hydroxide*** gave aromatic aldehydes in good yields (eq 5). The reaction gave 4-methoxybenzaldehyde from the usually unreactive anisole in 72% yield.

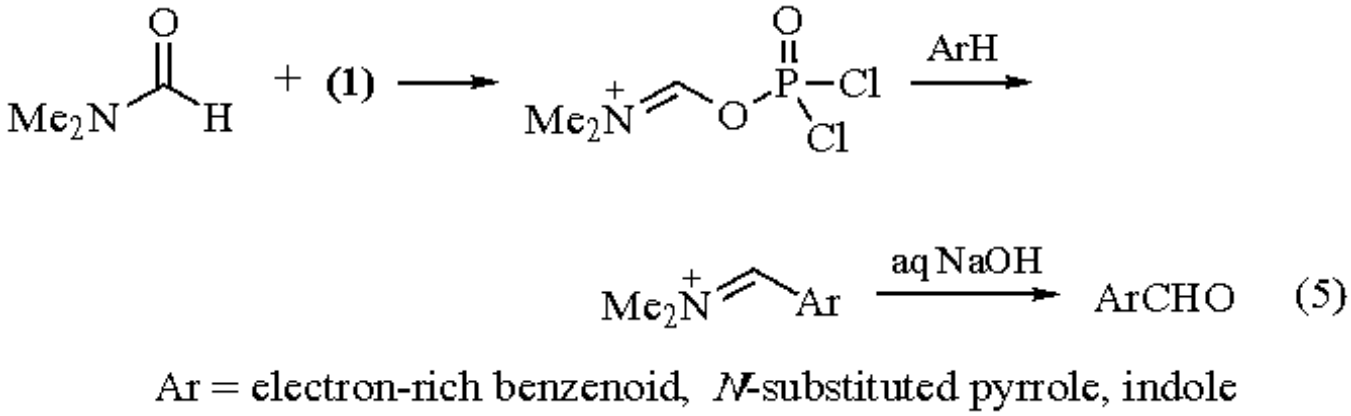

This reaction has been extended to a greater range of heterocycles, including furan and thiophene derivatives, and it has been shown that the bulky nature of the electrophilic species biases the reaction to give attack at the least hindered position.[8] In addition, glyoxylation of dioxygenated benzenes, *N*-alkylpyrroles, and *N*-alkylindoles has been achieved in good yield using (**1**) and methyl oxamates derived from methyl oxalyl chloride and either pyrrolidine or morpholine (eq 6).[8]

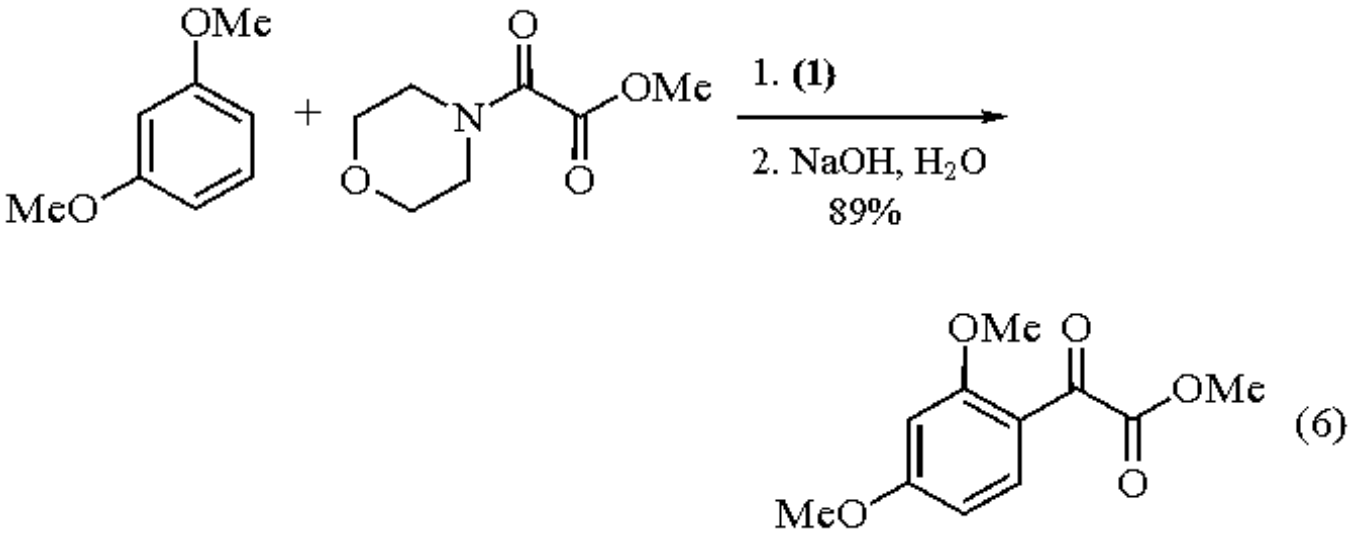

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King's College London, UK

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Pyrrolidine

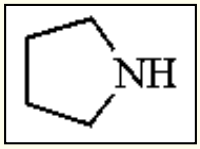

[123-75-1] · C_4H_9N · Pyrrolidine · (MW 71.14)

(secondary amine used for the formation and utilization of enamines;[2] catalyst for aldol cyclization[17] and Mannich condensation;[23] formation of secondary amides[28])

Physical Data: bp 88.5-89 °C; *d* 0.8618 g cm^{-3}; pK_a 11.1.

Solubility: miscible with water; sol alcohol, chloroform, and ether.

Form Supplied in: liquid, 99%; widely available.

Purification: distilled under nitrogen after drying with sodium or BaO.[1]

Handling, Storage, and Precautions: flammable; fumes in air; strong base; irritant. Use in a fume hood.

Enamine Preparation and Utilization.[2]

The principal use of pyrrolidine in synthesis is in the formation and utilization of ketone and aldehyde enamines. For preparation of the enamine a benzene or toluene solution of the carbonyl compound and pyrrolidine is heated at reflux with azeotropic removal of water. Acid catalysts or molecular sieves as water trapping agents are frequently employed. Cyclopentanone[3-5] and cyclohexanone,[3-6] for example, react in benzene to form enamines without added acid catalyst (eqs 1 and 2), as does β-tetralone (eq 3).[7]

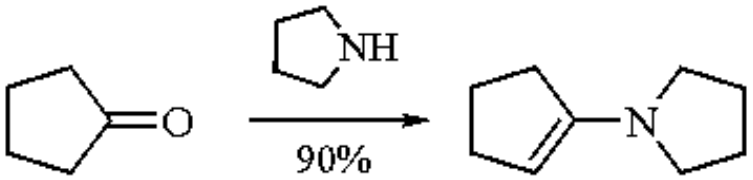

(1)

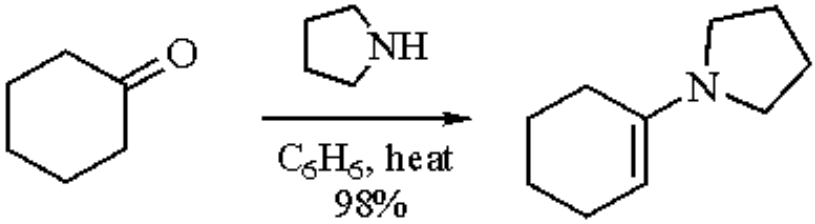

(2)

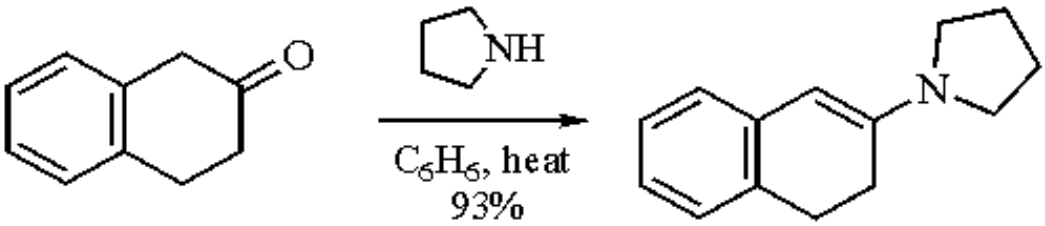

(3)

In toluene solution, cyclododecanone is converted to the pyrrolidine enamine in the presence of ***Boron Trifluoride Etherate*** (eq 4).[8]

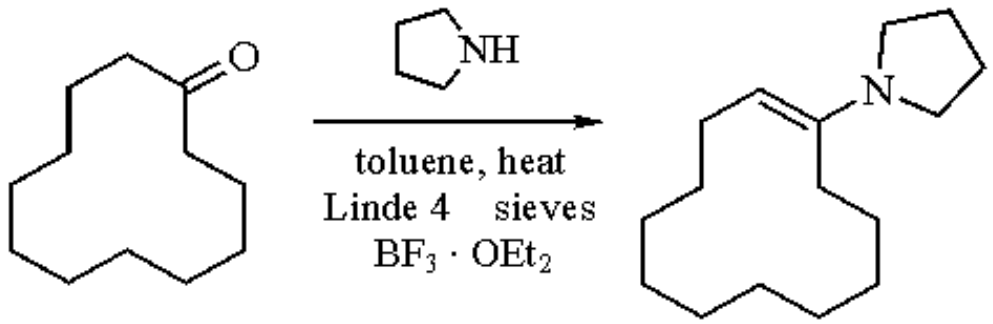

(4)

Acyclic ketones form pyrrolidine enamines sluggishly or with significant self-condensation. The enamine of diethyl ketone may be prepared in modest yield in the presence of 4 Å molecular sieves (eq 5).[5]

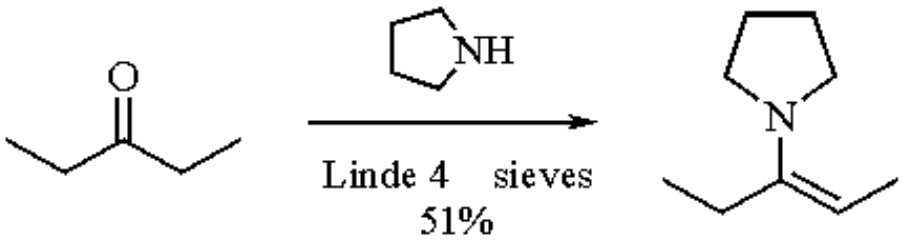

(5)

The pyrrolidine enamine of a relatively low-boiling aldehyde, isobutyraldehyde,[9] may be prepared by heating the base and the carbonyl component without additional solvent (eq 6).

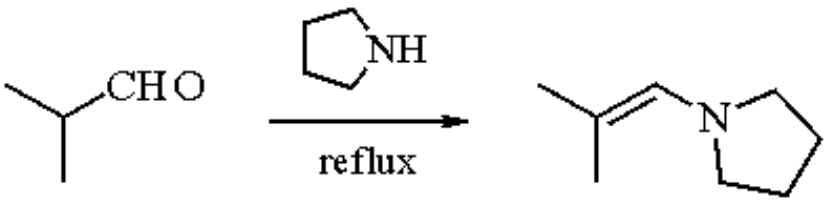

(6)

The reaction of ketones with pyrrolidine, ***Dimethyl Diazomethylphosphonate***, and base yields the pyrrolidine enamine of the homologous aldehyde (eq 7).[10]

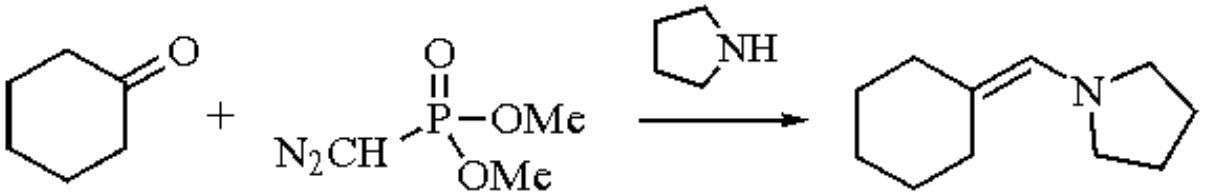

(7)

Enamino ketones have been prepared from β-chlorovinyl ketones (eq 8)[11] or directly from the corresponding β-dicarbonyl compound (eq 9).[12]

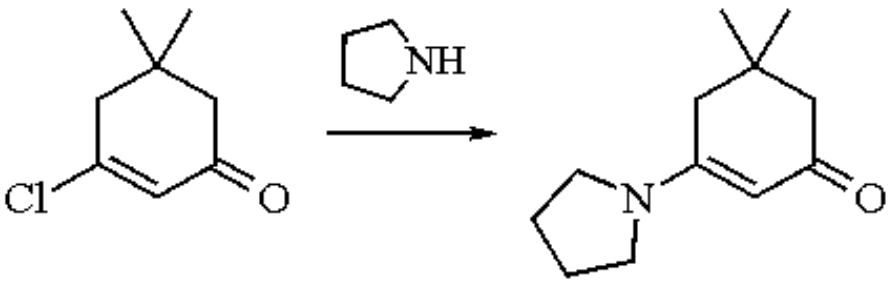

(8)

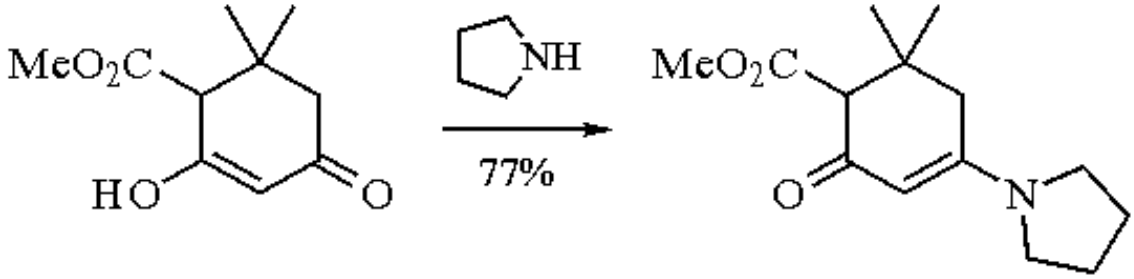

(9)

The reaction of pyrrolidine with monoalkylated cyclohexanones results in the formation of the less substituted enamine as the major product (eq 10).[5]

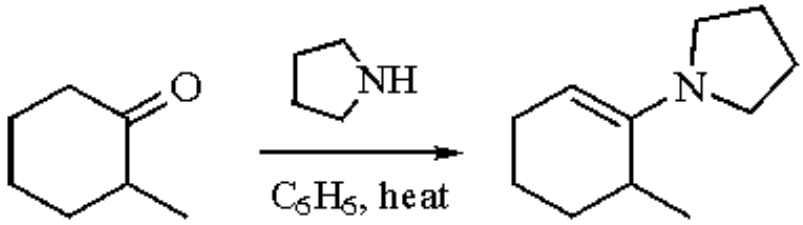

(10)

Regioselectivity is also observed in the formation of an enamine from 3-tri-*n*-butylstannylcyclohexanone and pyrrolidine (eq 11).[13]

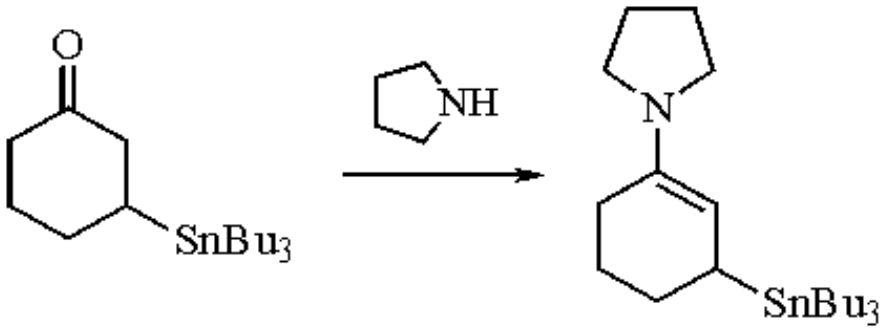

(11)

Pyrrolidine enamines react with both alkyl halides and electrophilic alkenes[2-5,7,14] to provide α-alkylated ketones and aldehydes (eqs 12 and 13). The great advantage of enamines over simple enolates in these reactions is that they do not overalkylate. Monosubstitution products are generally obtained. Acylation at carbon to afford β-dicarbonyl compounds occurs upon exposure of pyrrolidine enamines to acyl halides, but less effectively than with the corresponding morpholine enamine.[5]

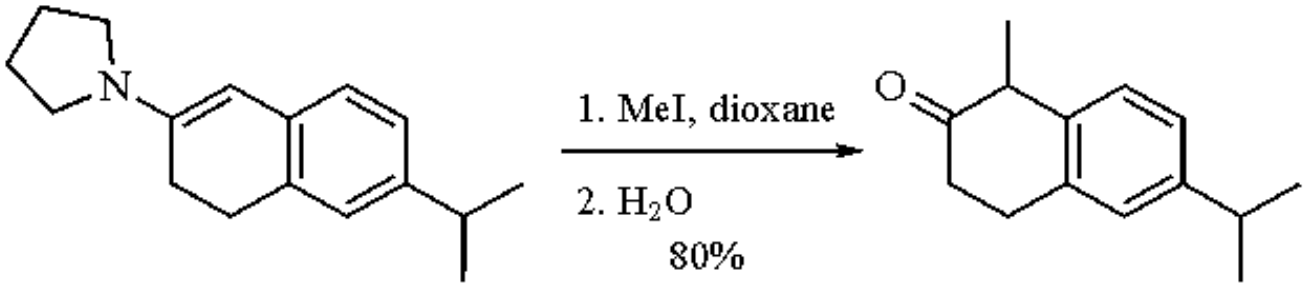

(12)

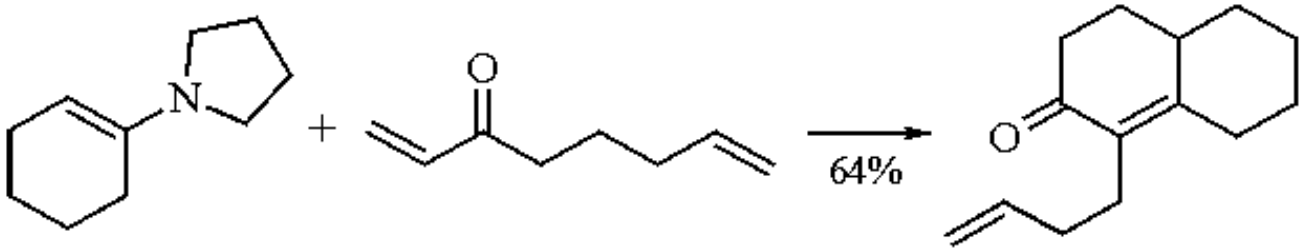

(13)

Pyrrolidine enamines also undergo [2 + 4] cycloaddition reactions with ***1,2,4-Triazine*** to provide, following loss of dinitrogen and aromatization, substituted pyridines (eq 14) and isoquinolines.[15,16]

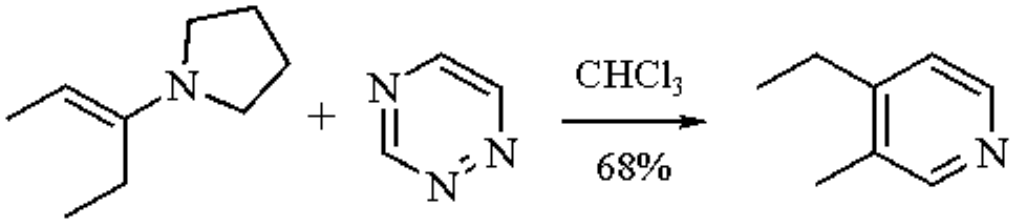

(14)

Condensation Reactions.

Pyrrolidine is a common catalyst for the aldol cyclization phase of the Robinson annulation process for both diketones[14,17-20] and keto aldehydes (eqs 15 and 16).[21]

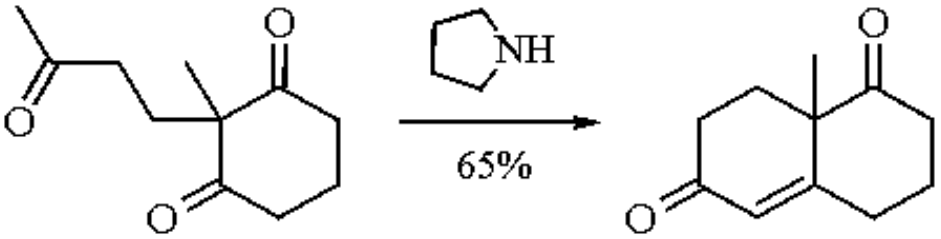

(15)

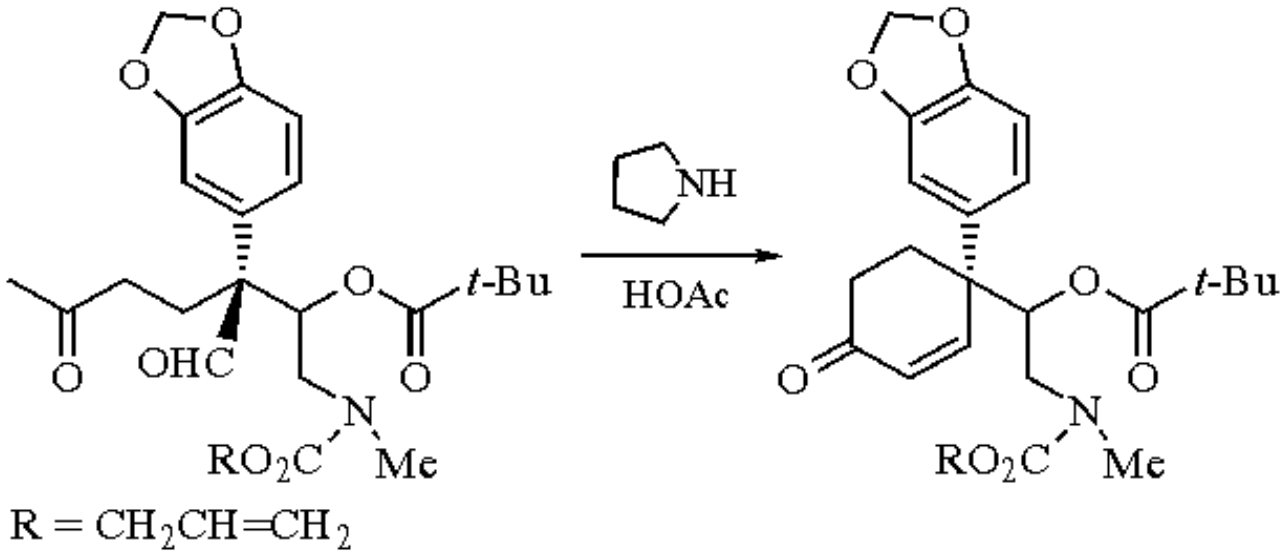

(16)

Spirocyclization has been shown to be favored over hydronaphthalenone closure in the reactions of substituted formylcyclohexanedione ethers (eq 17).[22]

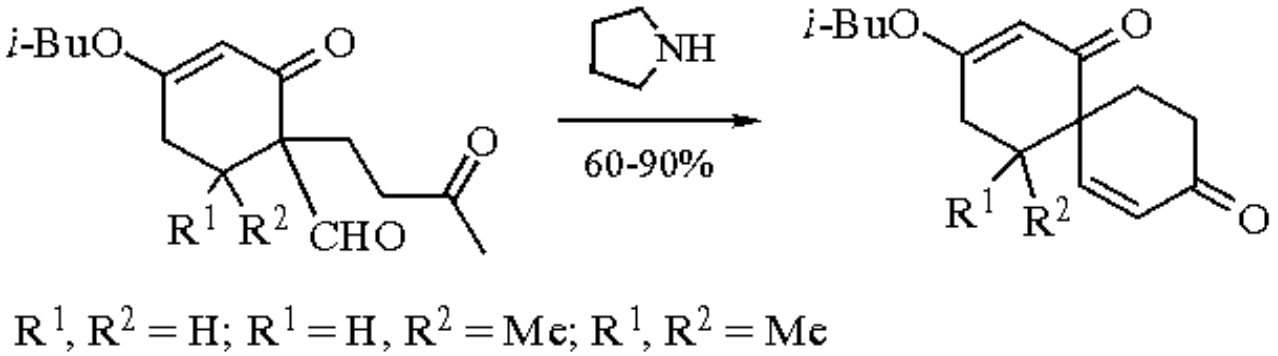

(17)

In similar fashion to aldol cyclizations, Mannich-type condensations are frequently carried out with pyrrolidine as the secondary amine component. The enamine of cyclohexanone reacts with an *o*-hydroxyacetophenone to afford a spirochromanone product (eq 18).[23]

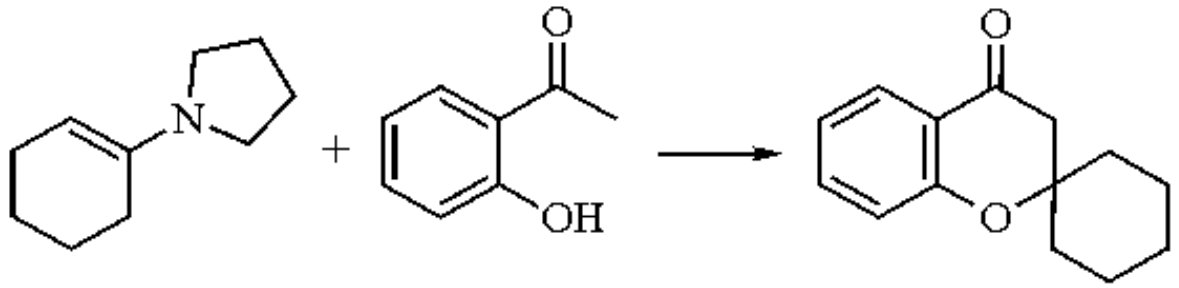

(18)

Phenols acting as the enol component of the Mannich process react with aldehydes in the presence of pyrrolidine (eq 19).[24]

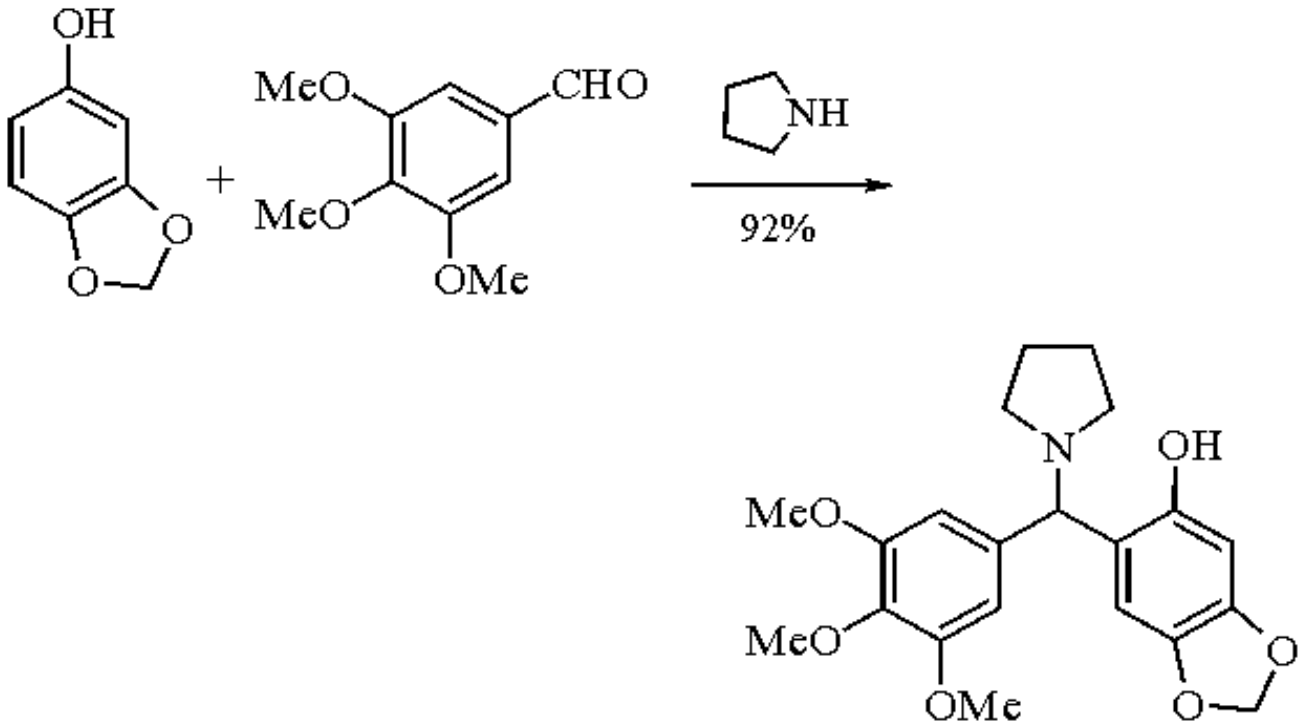

(19)

Pyrrolidine is also the most effective catalyst for the condensation of both aldehydes and ketones with cyclopentadiene to provide fulvenes (eqs 20 and 21).[25-27] In these cases the pyrrolidine has been shown to play the roles of both base catalyst and enamine-forming amine. The rates of such condensations are greater with pyrrolidine than with other secondary amine catalysts, a result attributable to the minimum steric hindrance exhibited by the cyclic amine.

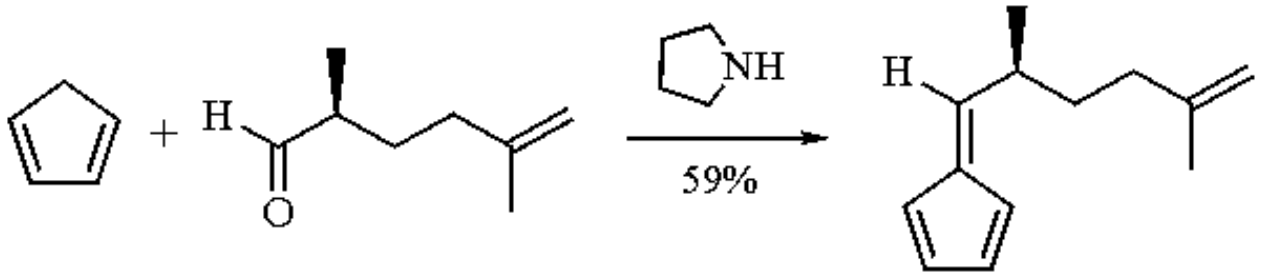

(20)

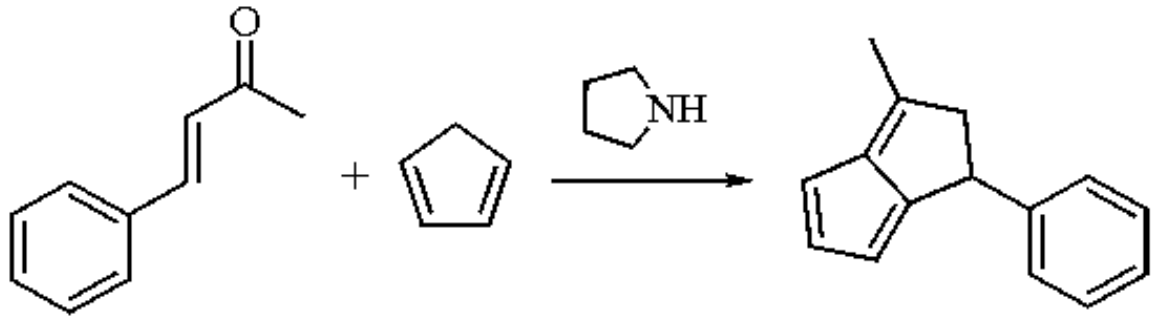

(21)

Amide Formation.

Pyrrolidine is an effective reagent for the formation of secondary amides from esters (eq 22) and urethanes from thiocarbonates (eq 23).[28,29]

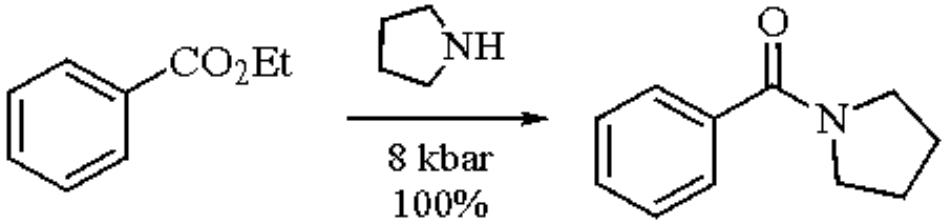

(22)

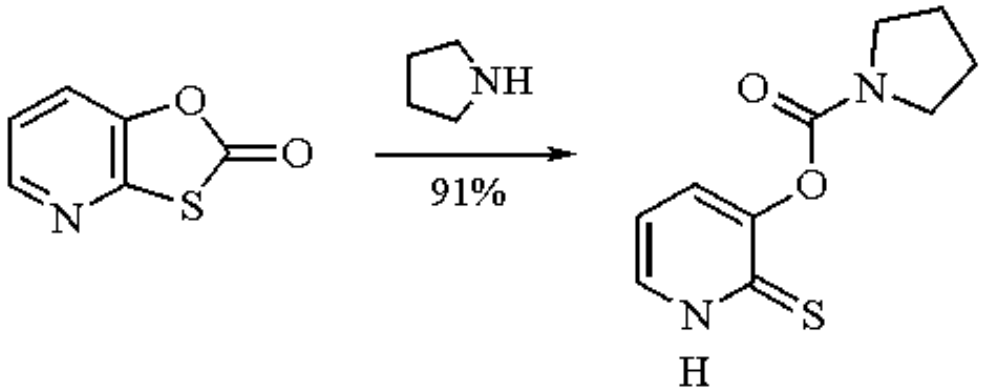

(23)

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1-Pyrrolidino-1-cyclohexene

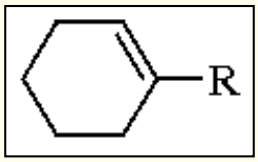

(**1**; R = 1-pyrrolidino)

[1125-99-1] · $C_{10}H_{17}N$ · 1-Pyrrolidino-1-cyclohexene · (MW 151.28) (**2**; R = 4-morpholino)

[670-80-4] · $C_{10}H_{17}NO$ · 4-Morpholino-1-cyclohexene · (MW 167.28) (**3**; R = 1-piperidino)

[2981-10-4] · $C_{11}H_{19}N$ · 1-Piperidino-1-cyclohexene · (MW 165.31) (**4**; R = 1-perhydroazepino)

[23430-63-9] · $C_{12}H_{21}N$ · 1-Perhydroazepino-1-cyclohexene · (MW 179.34) (**5**; R = Me_2N)

[13815-46-8] · $C_8H_{15}N$ · Dimethylamino-1-cyclohexene · (MW 125.24)

(both the enamine nitrogen and its β-carbon atom are nucleophilic, undergoing substitution or conjugate addition;[1] can take part in 1,2- or 1,4-cycloadditions;[1] iminium salts act as electrophiles[1,2])

Physical Data: (**1**) bp 114-115 °C/15 mmHg; *n*20D 1.5217; IR (C=C) 1638 cm^{-1}. (**2**) bp 118-120 °C/10 mmHg; *n*20D 1.5146; IR (C=C) 1641 cm^{-1}. (**3**) bp 108-109 °C/12 mmHg; *n*20D 1.5144; IR (C=C) 1637 cm^{-1}. (**4**) bp 122-126 °C/8 mmHg; *n*20D 1.5251; IR (C=C) 1632 cm^{-1}. (**5**) bp 171-172 °C; *n*20D 1.4747.

Preparative Methods: the most commonly used method of preparation for these enamines is the acid-catalyzed condensation of a secondary amine with cyclohexanone.[3] An example is the reaction of ***Pyrrolidine*** with cyclohexanone (eq 1).[3a] The use of a preformed ***Titanium(IV) Chloride***-amine complex with cyclohexanone greatly decreases the reaction time while maintaining high yields.[4]

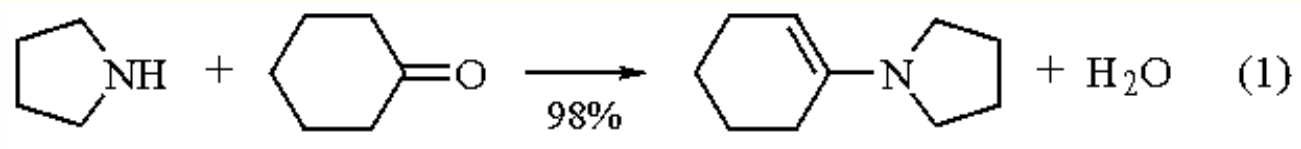

This technique is also is effective with functionalized cyclohexanones.[5] When unsymmetrical tin(II) amides are allowed to react with cyclohexanone, good yields of enamines result.[6,7]

Handling, Storage, and Precautions: readily reacts with water or atmospheric oxygen; should be stored under dry nitrogen.

Alkylation.

Alkylation at the carbon α to a carbonyl group can be accomplished by use of metal alkoxides to form an enolate anion. However, this may lead to poor results with ketones because of rapid proton exchange and incomplete conversion to the enolate. Although the introduction of lithium dialkylamide bases has solved this long-standing problem, enamine alkylation has certain other advantages. These advantages are the following: (1) strongly basic (or acidic) conditions are not required; (2) the major product is the monoalkylated derivative; (3) when dialkylation is observed (using excess of alkyl halide), it occurs at the least substituted carbon, in contrast to alkylation with base, where the α-disubstituted product is formed; hence 1-pyrrolidino-1-cyclohexene on treatment with 2 equiv of ***Allyl Bromide*** followed by hydrolysis gives 2,6-diallylcyclohexanone (eq 2);[8] (4) the byproduct formed by alkylation at nitrogen is easily removed from the desired *C*-alkylation product.

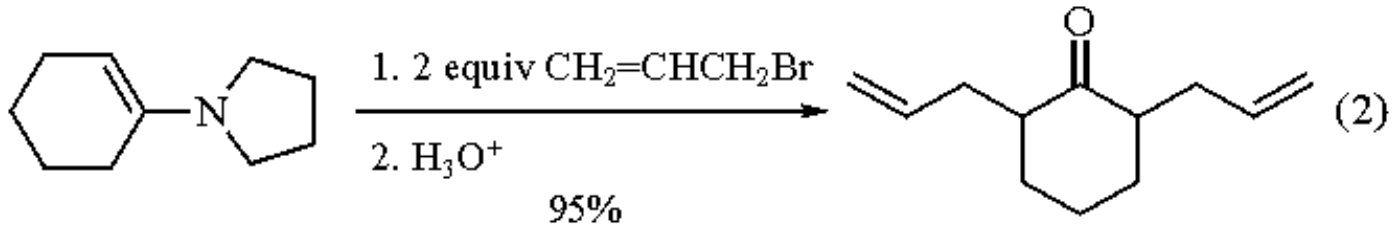

The size of the heterocyclic amine rings is an important factor in determining the ratios of *C*-alkylation to *N*-alkylation. The pyrrolidine enamine gives some of the best yields whereas morpholine enamines give poorer yields. Since enamines are generally weaker nucleophiles than enolate anions, the list of generally useful alkylation agents is restricted to methyl-, allyl-, or benzyl-type halides (eq 3).[9]

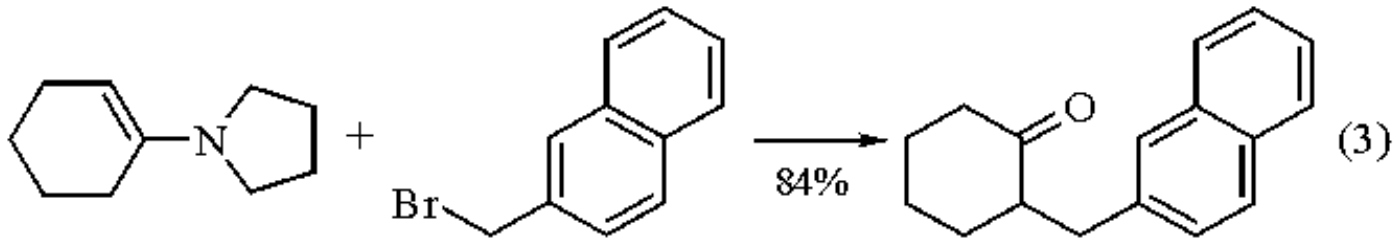

Electrophilic radicals have been used to alkylate cyclic enamines (eq 4),[10] and reductive alkylation of enamines via a radical pathway has been shown to be stereoselective (eq 5).[11,12]

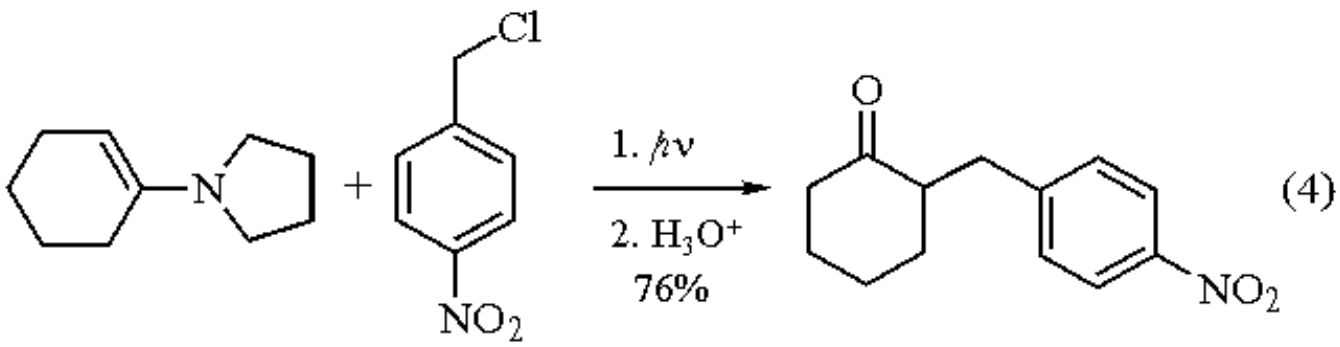

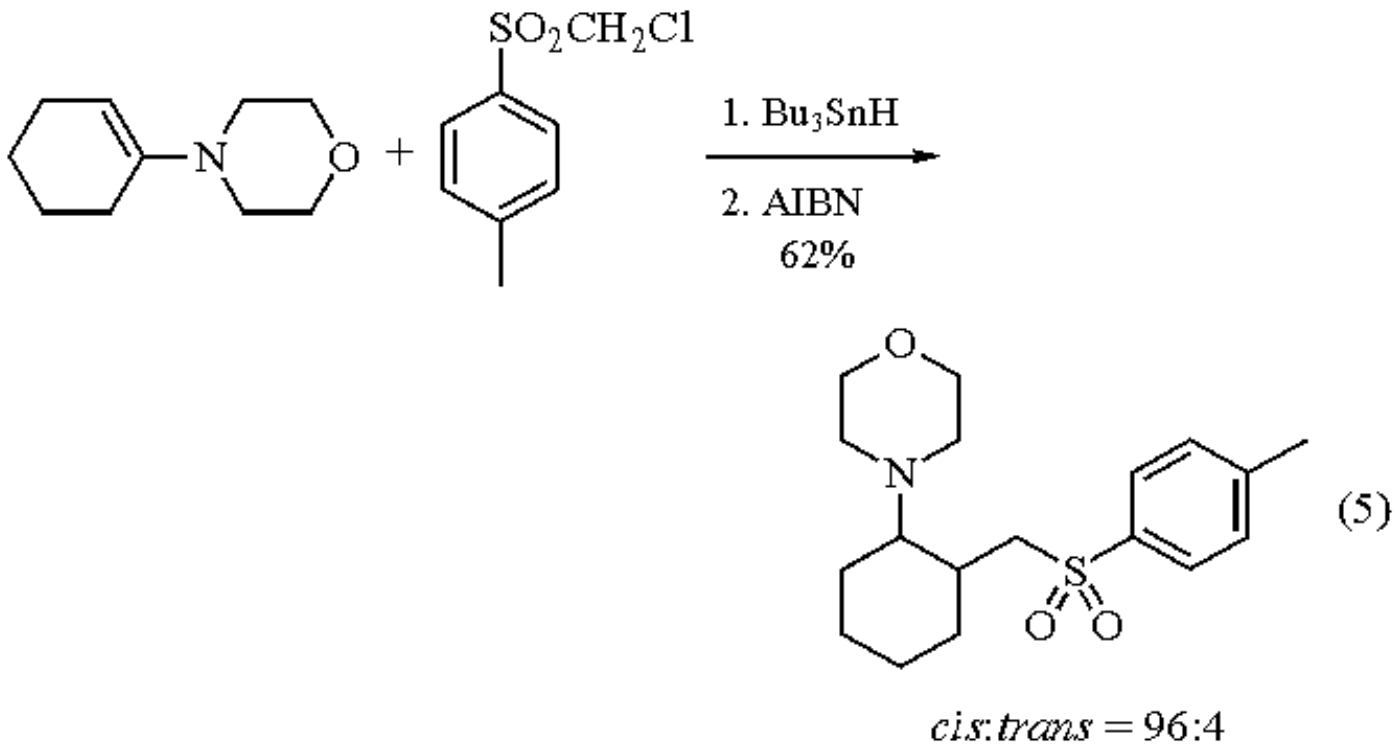

A photoinduced electron transfer reaction with difluorodiiodomethane gives 2-(trifluoromethyl)cyclohexanone (eq 6).[13] This reaction apparently involves elimination of iodide and addition of fluoride, either before or after the α-alkylation reaction.

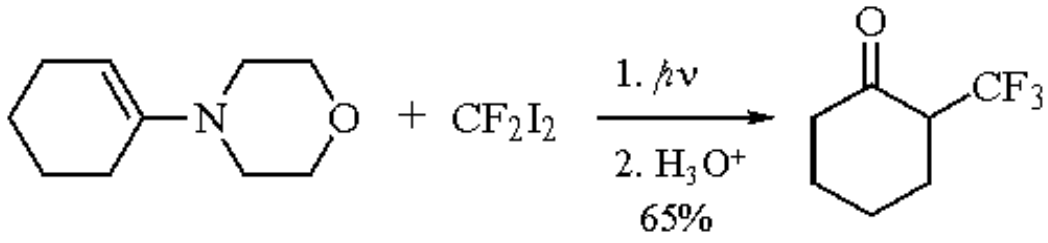

(6)

The series of electrophilic alkenes that typically undergo Michael addition to cyclic enamines are α,β-unsaturated ketones (eq 7),[14] α,β-unsaturated nitriles (eq 8),[1a] α,β-unsaturated esters,[1a] α,β-unsaturated sulfones,[15] and nitroalkenes (eq 9).[16] Electrophilic alkenes generally attack enamines of cycloalkanones in a stereospecific antiparallel manner.[1,17,18]

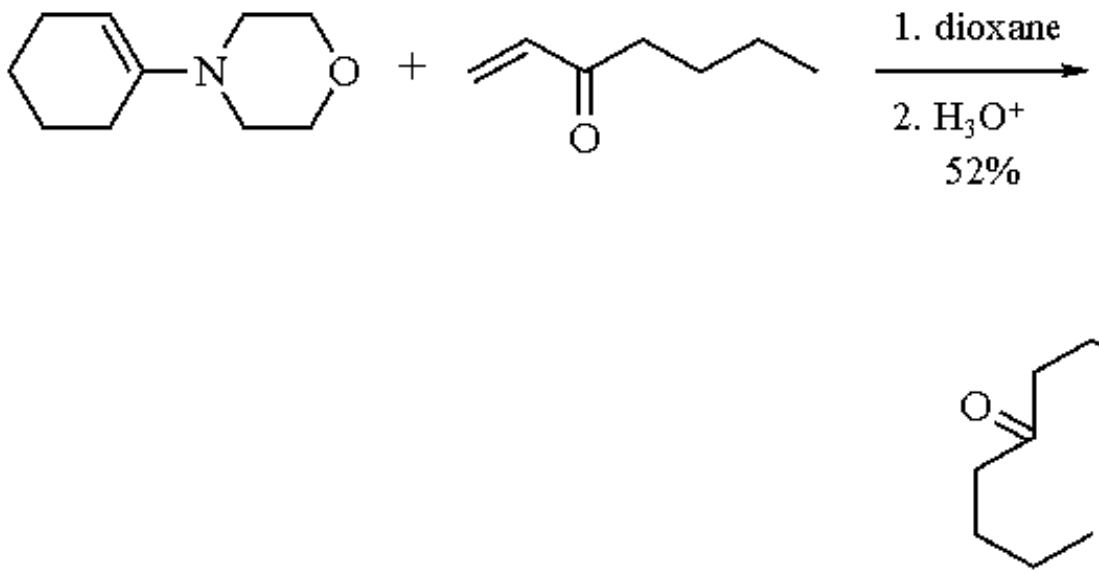

(7)

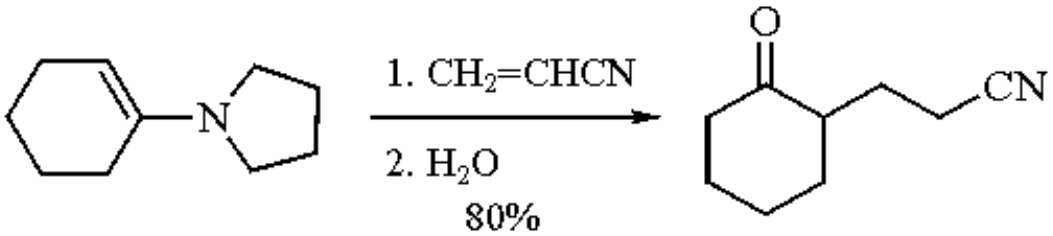

(8)

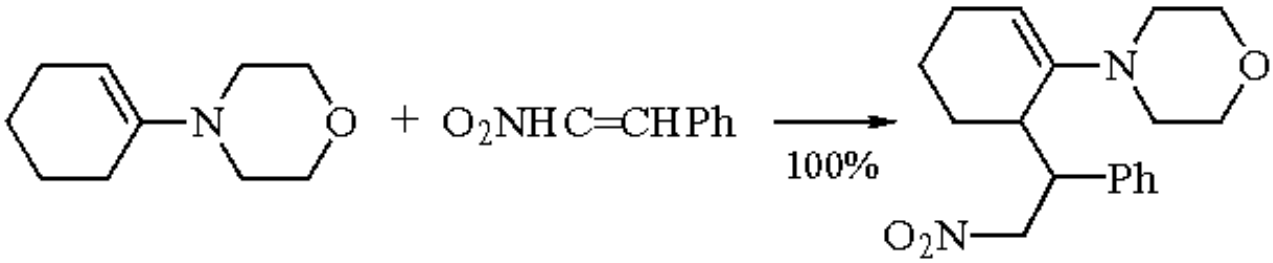

(9)

Acylation.

Acylation of cyclohexanone enamines using acyl halides takes place readily.[19] The morpholine enamine gives the best yields (eq 10).[1a] An extra mole of enamine must be present to remove the liberated HCl. Alternatively, an organic base such as ***Triethylamine*** can be used for this purpose. Acylation using acid chlorides having a β-hydrogen in the presence of triethylamine usually proceeds via the ketene and subsequent cycloaddition. The intermediate cyclobutanone is then opened to give the enamino ketone, which is hydrolyzed to the 2-acylcyclohexanone.[20]

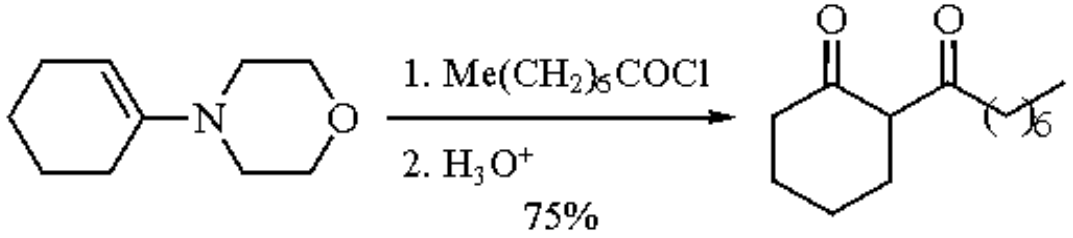

(10)

Arylation.

Aryl halides with a halogen activated by electron-withdrawing groups react with enamines (eq 11).[21]

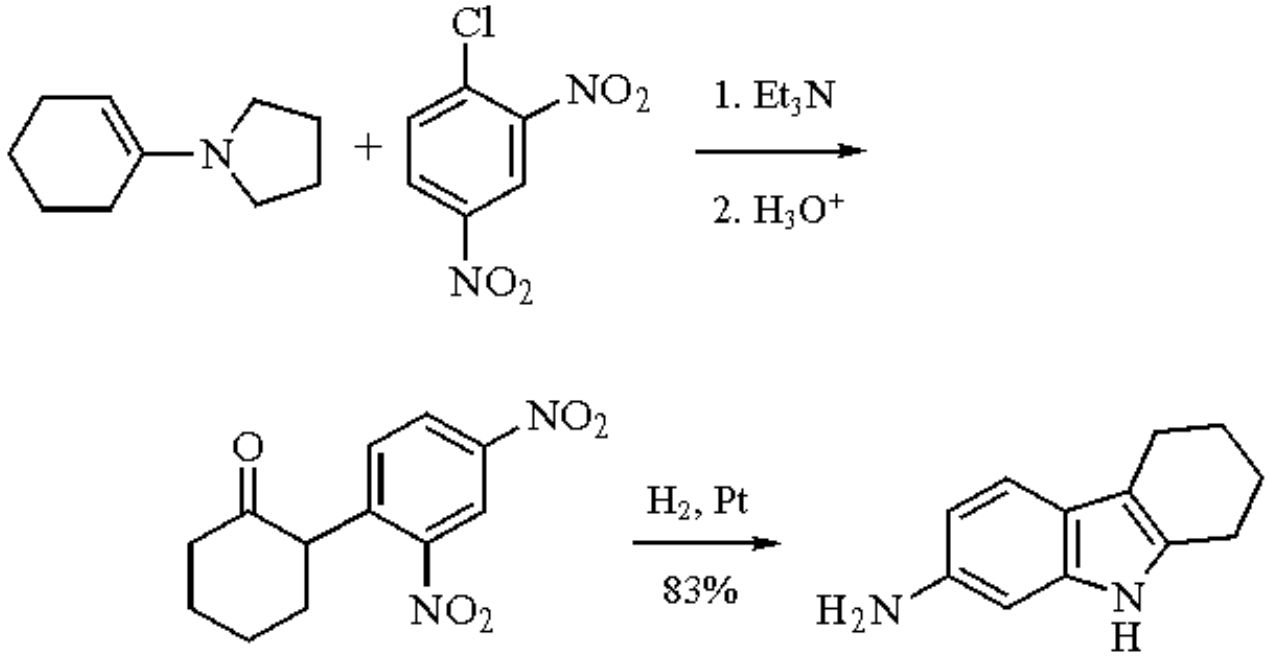

(11)

Cycloaddition.

Cycloadditions and annulation reactions take place when cyclohexanone enamines are allowed to react with 1-buten-3-one,[1a] 1,3-butadienephosphonate,[22] acrolein,[23-25] 1,4-diacetoxy-2-butene with ***Palladium(II) Acetate***,[26] or 5-nitropyrimidine (Scheme 1).[27]

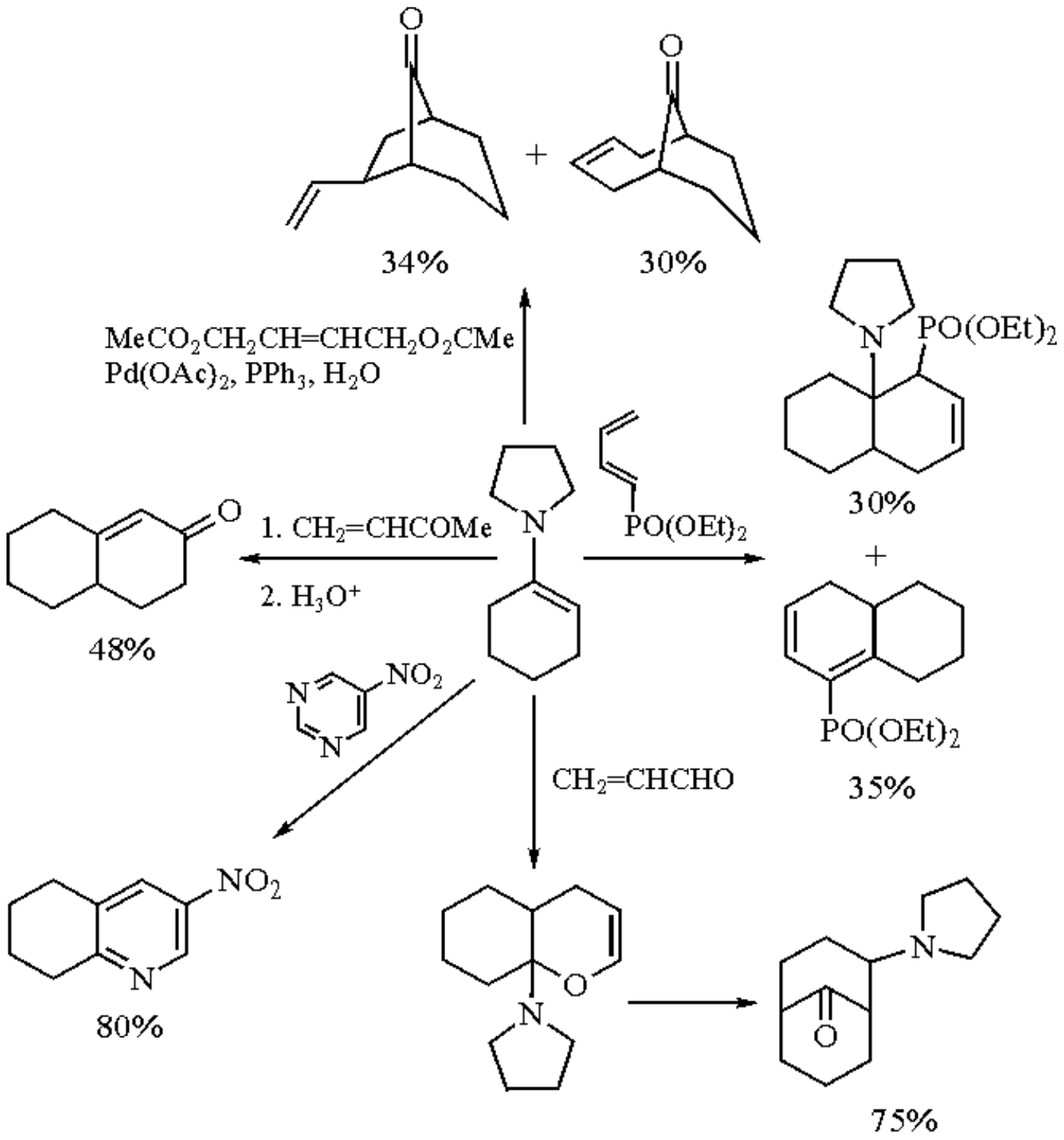

Scheme 1

Further 2,3-(ethylenedisulfonyl)-1,3-butadiene acts as a diene in Diels-Alder reactions with enamines (eq 12).[28]

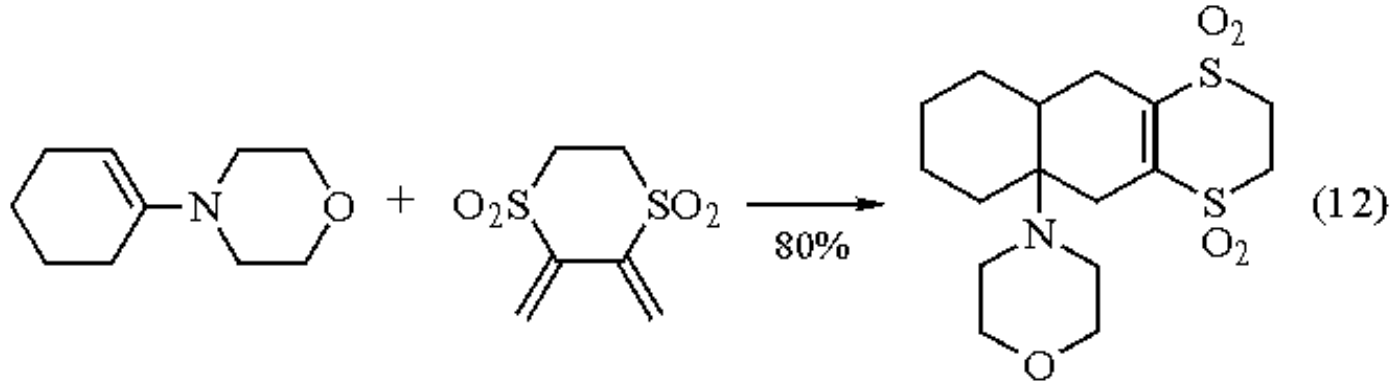

(12)

[2 + 2] Cycloaddition takes place with benzyne[21] and ***Dimethyl Acetylenedicarboxylate*** (Scheme 2).[29]

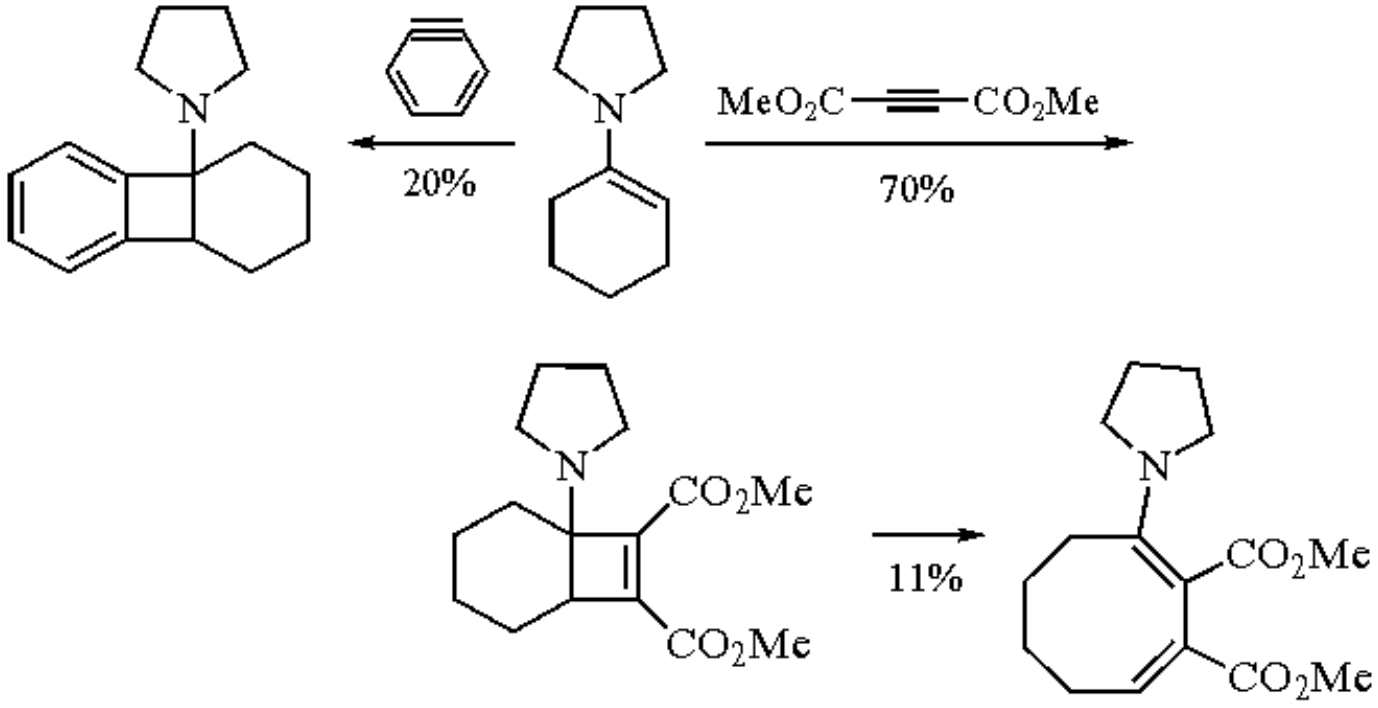

Scheme 2

Oxidation and Reduction.

Photooxygenation using singlet oxygen leads to α-diketones.[30] Use of *N*-sulfonyloxaziridines gives α-amino ketones (Scheme 3).[31]

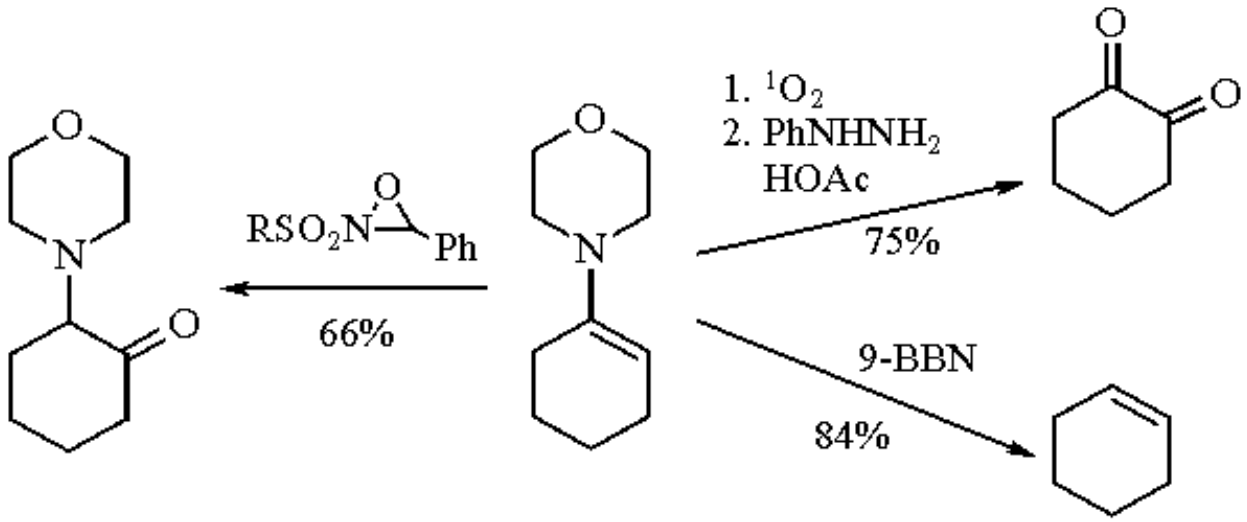

Scheme 3

Use of trimethylene dithiotosylate produces the dithiane of cyclohexanone (eq 13).[3a]

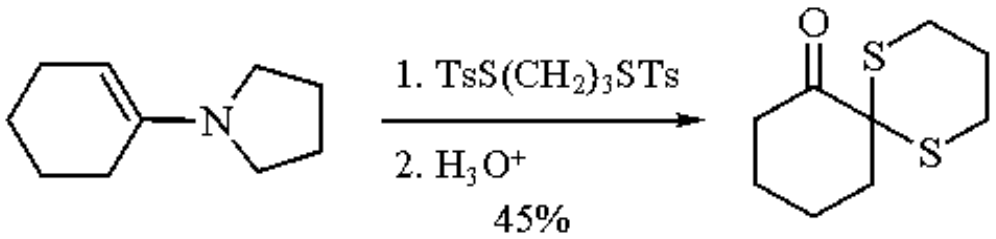

(13)

The enamine is readily converted to cyclohexene via hydroboration (Scheme 3).[32]

Related Reagents.

Acrolein; ***Dimethyl Acetylenedicarboxylate***; ***1-(N,N-Dimethylamino)-2-methyl-1-propene***; ***Morpholine***; ***Pivalaldehyde***; ***Pyrrolidine***; ***1-Pyrrolidino-1-cyclopentene***; ***Bis[N,N-bis(trimethylsilyl)amino]tin(II)***.

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1-Pyrrolidino-1-cyclopentene

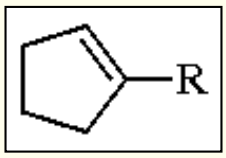

(**1**; R = 1-pyrrolidino)

[7148-07-4] · $C_9H_{15}N$ · 1-Pyrrolidino-1-cyclopentene · (MW 137.25) (**2**; R = 4-morpholino)

[936-52-7] · $C_9H_{15}NO$ · 4-Morpholino-1-cyclopentene · (MW 153.25) (**3**; R = 1-piperidino)

[1614-92-2] · $C_{10}H_{17}N$ · 1-Piperidino-1-cyclopentene · (MW 151.28) (**4**; R = 1-perhydroazepino)

[7374-91-6] · $C_{11}H_{19}N$ · 1-Perhydroazepino-1-cyclopentene · (MW 165.31) (**5**; R = Me_2N)

[4840-12-4] · $C_7H_{13}N$ · Dimethylamino-1-cyclopentene · (MW 111.21)

(either the enamine nitrogen or its β-carbon atom is nucleophilic, undergoing substitution or conjugate addition;[1] can take part in 1,2- or 1,4-cycloadditions[1])

Physical Data: (**1**) bp 88-92 °C/15 mmHg; *n*20D 1.5155; IR (C=C) 1630 cm^{-1}. (**2**) bp 105-106 °C/12 mmHg; *n*20D 1.5118; IR (C=C) 1630 cm^{-1}. (**3**) bp 90-91 °C/12 mmHg; *n*20D 1.5042; IR (C=C) 1634 cm^{-1}. (**4**) bp 83-85 °C/1 mmHg; *n*20D 1.517; IR (C=C) 1630 cm^{-1}. (**5**) bp 68 °C/45 mmHg; IR (C=C) 1648 cm^{-1}.

Preparative Methods: the most commonly used method of preparation for these enamines is the acid-catalyzed condensation of a secondary amine with cyclopentanone (eq 1).[1a]

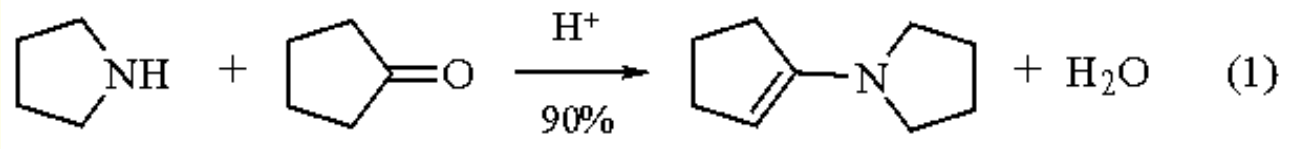

The use of a stoichiometric amount of ***Titanium(IV) Chloride*** makes it possible to produce highly hindered as well as ordinary enamines.[2,3] More highly hindered ketones react more rapidly with dimethylamine than with heterocyclic secondary amines such as ***Pyrrolidine*** (eq 2).[2]

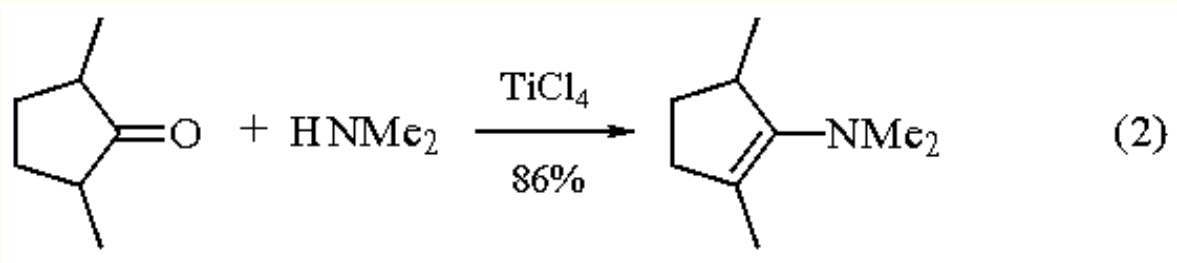

Handling, Storage, and Precautions: readily reacts with water or atmospheric oxygen; should be stored under dry nitrogen.

Alkylation.[4]

Alkylation of these enamines can take place with activated alkyl halides or electrophilic alkenes. A biphilic combination of these two alkylating agents has been used in an annulation sequence (eq 3).[5]

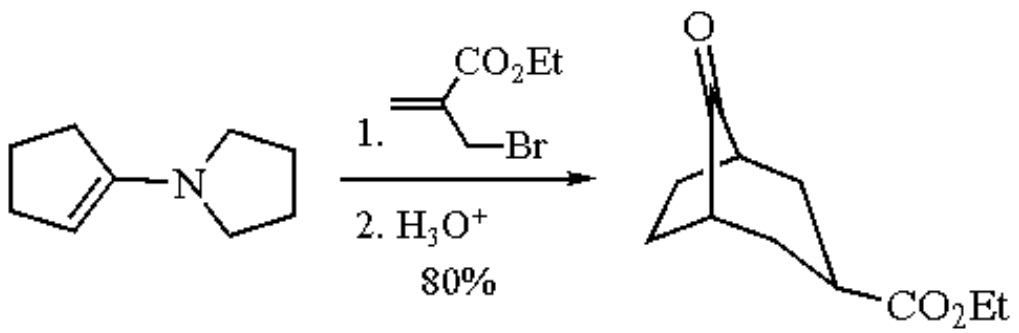

(3)

Acylation.[6]

Acylation of morpholine enamines with acyl halides can take place in a normal manner (eq 4).[7]

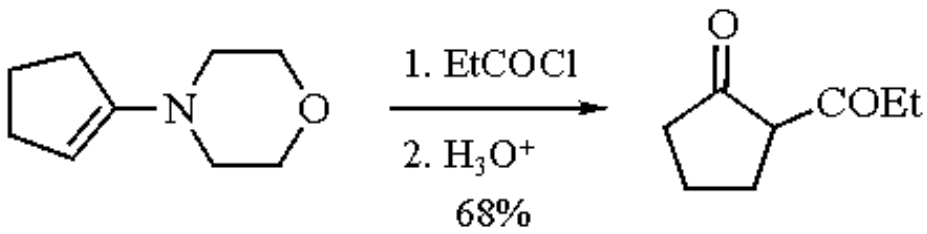

(4)

Cycloadditions.

Diethyl maleate and ***Methyl Propiolate*** rapidly add to the enamines to form [2 + 2] adducts.[8,9] The propiolate adduct upon heating rearranges to a cycloheptadiene derivative (Scheme 1).[9]

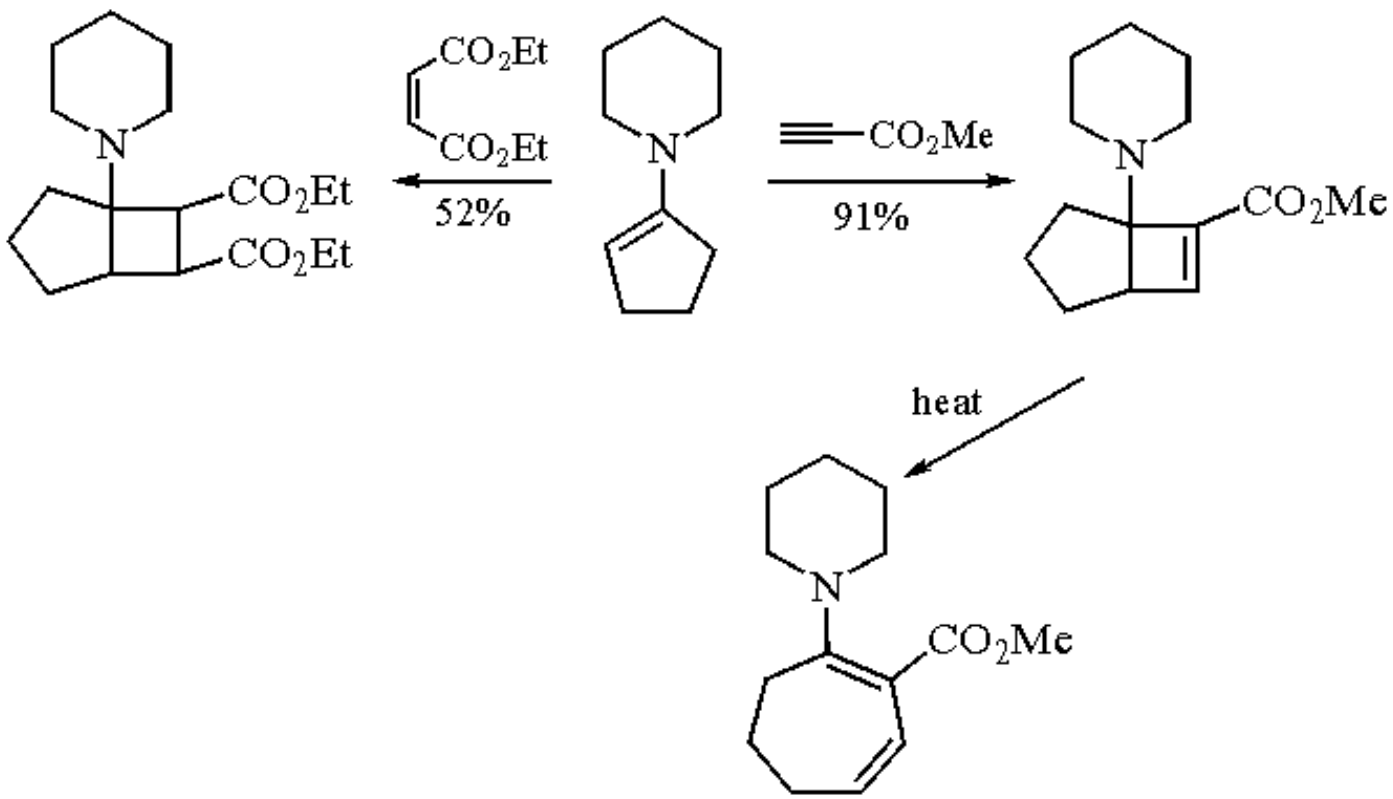

Scheme 1

A similar cycloaddition takes place with ***Dimethyl Acetylenedicarboxylate*** in nonpolar solvents, but a pyrrolizine is formed in the polar solvent methanol.[10]

Reduction.

Hydroboration of 1-morpholino-1-cyclopentene with ***9-Borabicyclo[3.3.1]nonane*** followed by mild heating in methanol produces cyclopentene (eq 5).[11]

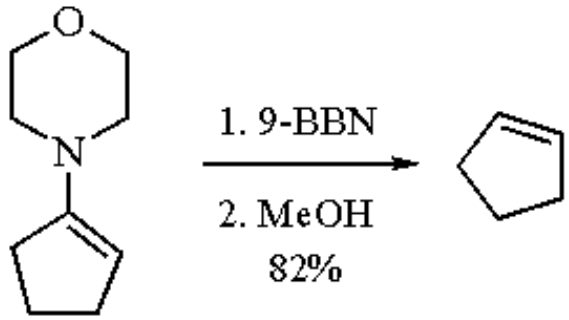

(5)

Related Reagents.

Dimethyl Acetylenedicarboxylate; ***(Dimethylamino)methyl Methyl Ether***; ***Methyl Propiolate***; ***Morpholine***; ***Pivalaldehyde***; ***Pyrrolidine***; ***1-Pyrrolidino-1-cyclohexene***.

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2-Pyrrolidone Hydrotribromide

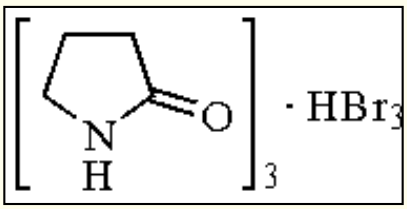

[52215-12-0] · $C_{12}H_{22}Br_3N_3O_3$ · 2-Pyrrolidone Hydrotribromide · (MW 496.07)

(selective brominating reagent for ketones;[1] used in bromination/dehydrobromination and bromination/oxidation sequences when high selectivity is required)

Alternate Name: PHT.

Physical Data: mp 88-90 °C.

Solubility: sol THF, dioxane, DMSO.

Form Supplied in: commercially available as red crystalline solid.

Analysis of Reagent Purity: active bromine content by $KI/Na_2S_2O_3$ titration.

Handling, Storage, and Precautions: irritant, hygroscopic solid; complex is stable.

Selective Brominations.

The reaction of molecular ***Bromine*** with 2-pyrrolidone in $CHCl_3$ yields the crystalline 2-pyrrolidone hydrotribromide. PHT contains 31.6% available bromine and has been found to be a remarkably selective brominating agent.[2] The relative reactivities towards bromination are: ketones >> alkenes >> enol acetates.[1] Reactions are generally run in THF. As the reaction proceeds, the solution loses the red color of the PHT and $(pyrrolidone)_2.HBr$ is precipitated from solution as colorless needles. This not only facilitates the recovery of the pyrrolidone, but offers a convenient method of monitoring the reaction.

Acid sensitive molecules can be protected by adding excess pyrrolidone to the reaction to trap liberated HBr. The mild conditions have allowed many functional groups to survive. These include enones (eq 1),[1] nitroxyl radicals (eq 2),[3] ergot alkaloids (eq 3),[4] benzothiophenes,[5] and numerous polyfunctional intermediates in natural products synthesis (eqs 4 and 5).[6,7]

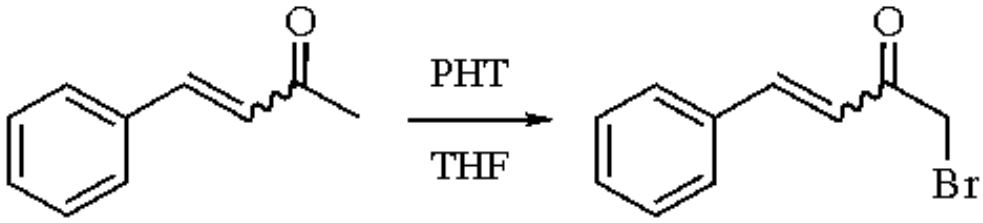

(1)

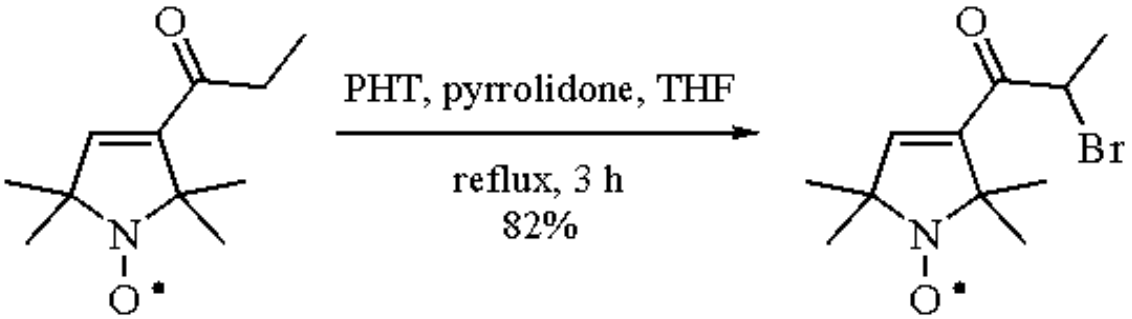

(2)

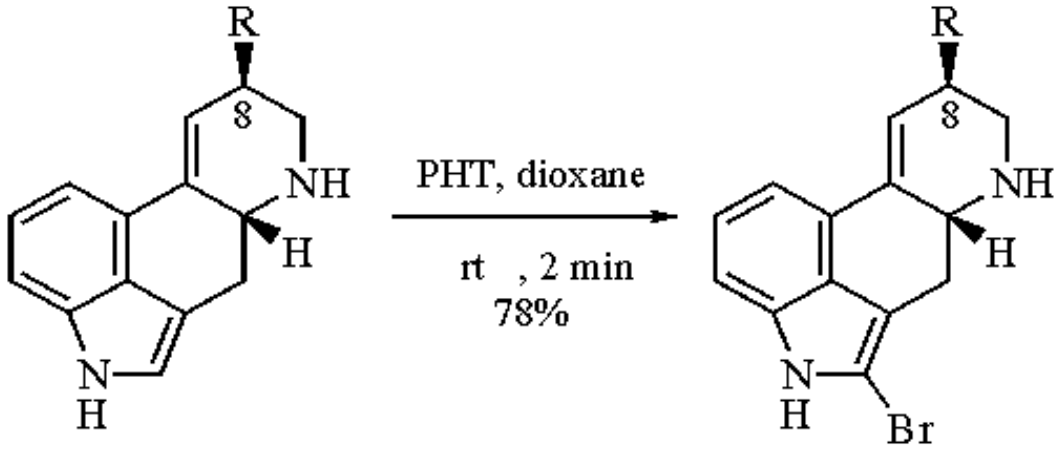

(3)

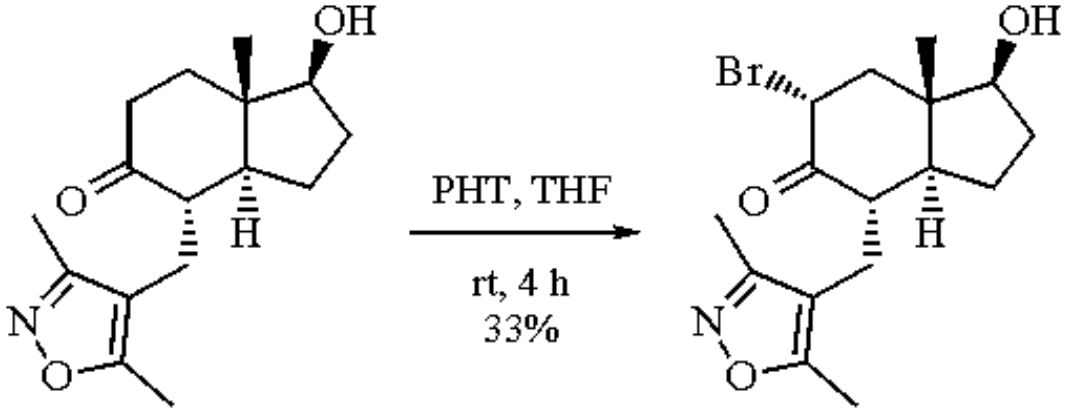

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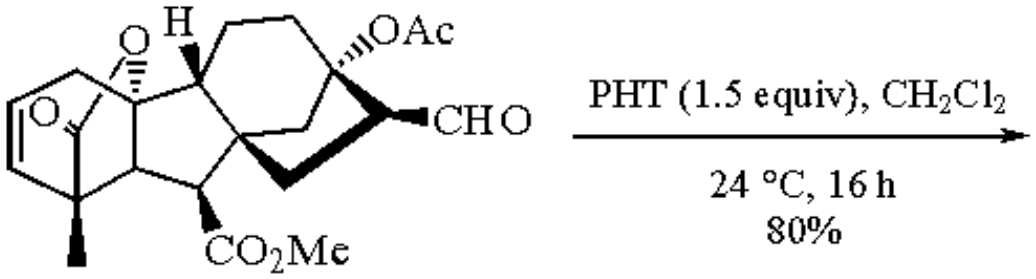

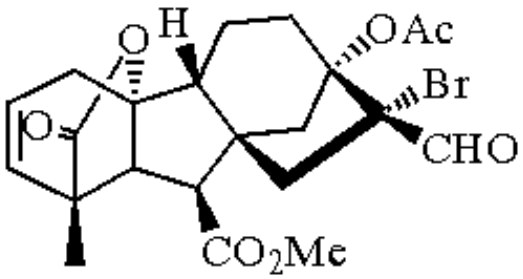

(5)

The solvent used can also play an important role in PHT brominations. Since the bromination is a radical reaction, trace hydroperoxides present in solvents such as THF and dioxane facilitate the bromination. If hydroperoxide-poor solvents are used, radical initiators may be used.[4] When DMSO is used, either dehydrobromination[8] or oxidation[9] can occur, depending on the molecule (eqs 6 and 7).

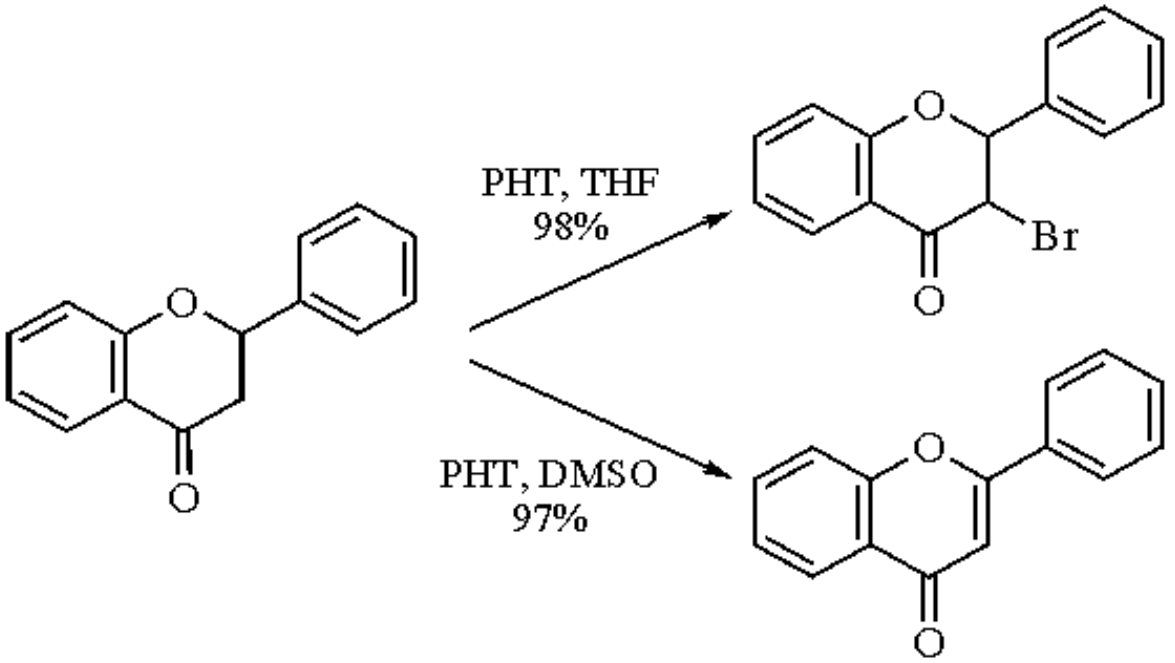

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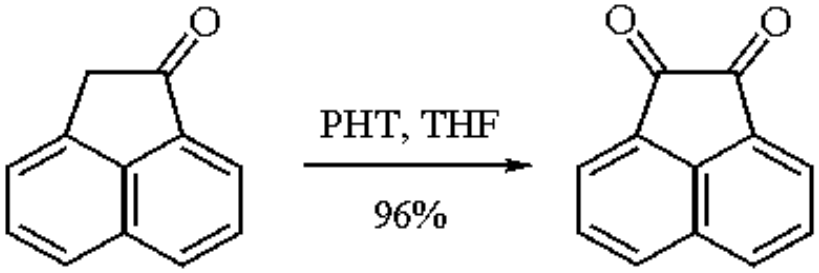

(7)

The use of PHT selectivity followed by subsequent dehydrobromination[10-12] or oxidation[13] has contributed to the value of this reagent. The selectivity of PHT is considered superior to that of ***Phenyltrimethylammonium Perbromide*** (PHAT).[1]

---

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1-Pyrroline 1-Oxide[1]

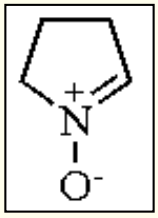

[24423-88-9] · C_4H_7NO · 1-Pyrroline 1-Oxide · (MW 85.12)

(prototypical cyclic nitrone for intermolecular 1,3-dipolar cycloadditions[1,2])

Physical Data: bp 74-76 °C/0.1 mmHg.

Solubility: sol dichloromethane, chloroform, ether, aromatic hydrocarbons, water.

Form Supplied in: not commercially available.

Preparative Methods: usually prepared by oxidation of 1-hydroxypyrrolidine with two equivalents of yellow ***Mercury(II) Oxide*** (HgO) in dichloromethane or chloroform at 0-10 °C.[3] After 4 h, the mixture is filtered to remove mercury salts and the nitrone is most often used without further purification, with or without solvent exchange. An alternative procedure is the direct oxidation of pyrrolidine with 30% aqueous ***Hydrogen Peroxide*** catalyzed by $Na_2WO_4.H_2O$ in water, followed by extraction with dichloromethane and chromatographic purification.[4] Although the yield is lower, this method has the advantages of pyrrolidine as the starting material and of avoiding the use and disposal of large quantities of mercury(II) salts.

A regiospecific oxidative decarboxylation of *N*-alkyl-α-amino acids under phase transfer conditions using H_2O_2 and Na_2WO_4 catalyst has been used successfully with proline to afford 1-pyrroline 1-oxide in 55% yield.[10] The method appears to be efficient and convenient for other cyclic as well as acyclic nitrones.

1,3-Dipolar Cycloadditions.

One of the more recent reviews cites 20 examples of cycloaddition between 1-pyrroline 1-oxide and acyclic and cyclic alkenes to give bicyclic (or tricyclic) isoxazolidines.[1a] These reactions are carried out in toluene at reflux or neat at 100 °C; however, α,β-unsaturated esters often react smoothly at room temperature. Numerous substituted 1-pyrroline 1-oxides have been studied, and intramolecular examples are known. The six-membered ring analog, 2,3,4,5-tetrahydropyridine 1-oxide, is also useful.[1a,4] The cycloadditions are both stereoselective and regioselective. Terminal alkenes give exclusively 5-substituted isoxazolidines with the substituent *cis* to the hydrogen at the ring fusion (*exo* transition state) (eq 1).[5] This is the expected regiochemistry for a nitrone LU-controlled process. When methyl crotonate was the educt alkene, the methoxycarbonyl group showed a preference for an *endo* transition state, as well as being positioned at C-4 in the isoxazolidine under conditions of kinetic control (eq 2).[6]

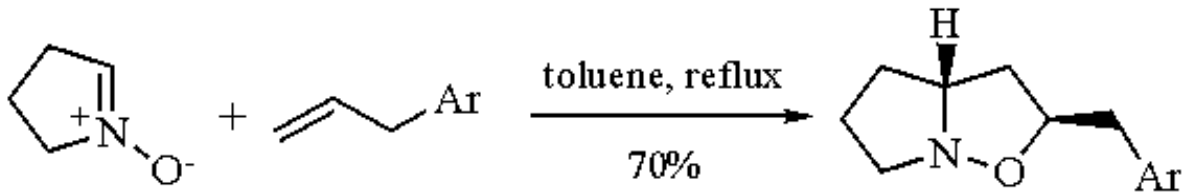

(1)

Ar = *p*-$MeOC_6H_4$

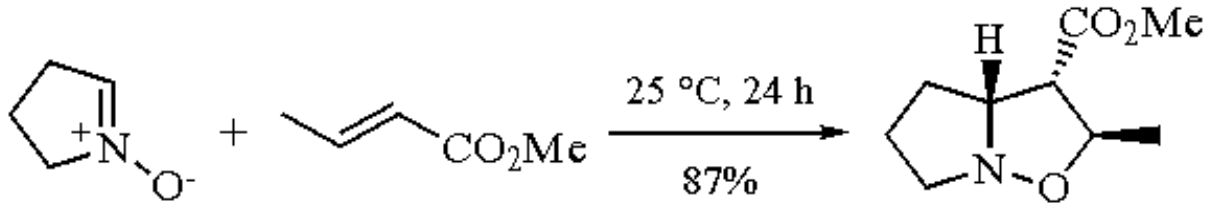

(2)

Electron-rich alkenes, i.e. vinyl ethers and enamines, undergo cycloaddition at slow rates and often give poor yields because of decomposition of the nitrone. High pressure conditions can obviate the problem (eq 3).[7]

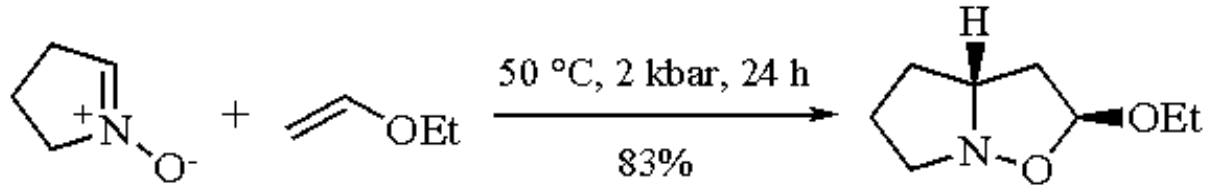

(3)

One of the two syntheses of (±)-cocaine by Tufariello and co-workers[3] involved both an intermolecular and an intramolecular cycloaddition, and it utilized some of the numerous further transformations of the isoxazolidine ring that enhance the versatility of 1,3-dipolar cycloadditions of nitrones in synthesis (eq 4). A similar approach was taken to synthesize anatoxin-a.[8] The oxidative ring opening with ***m-Chloroperbenzoic Acid*** to generate an intermediate nitrone, the key to the success of this strategy, has recently been carried out on other polycyclic isoxazolidines with magnesium monoperoxyphthalate hexahydrate (MMPP).[9]

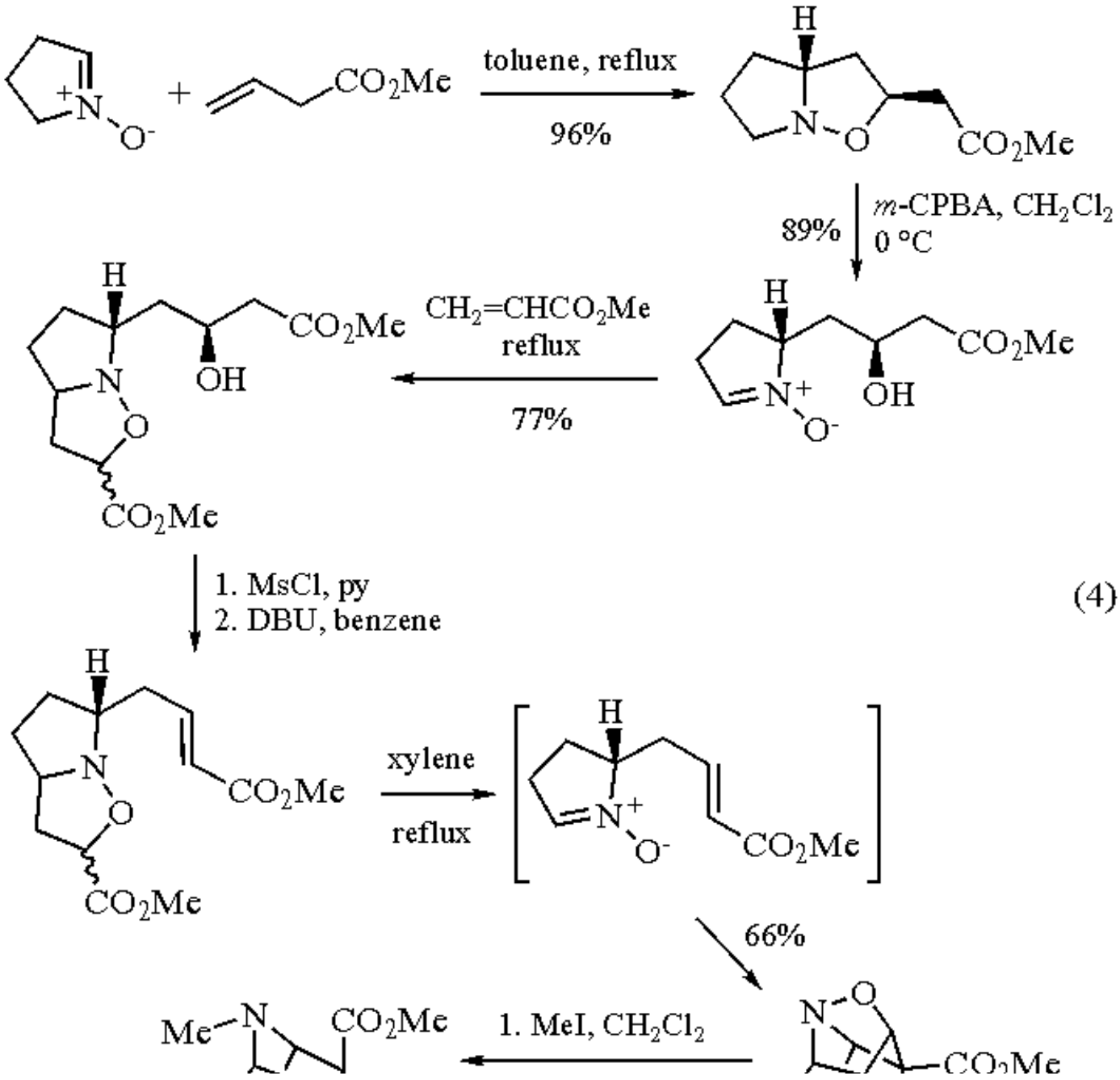

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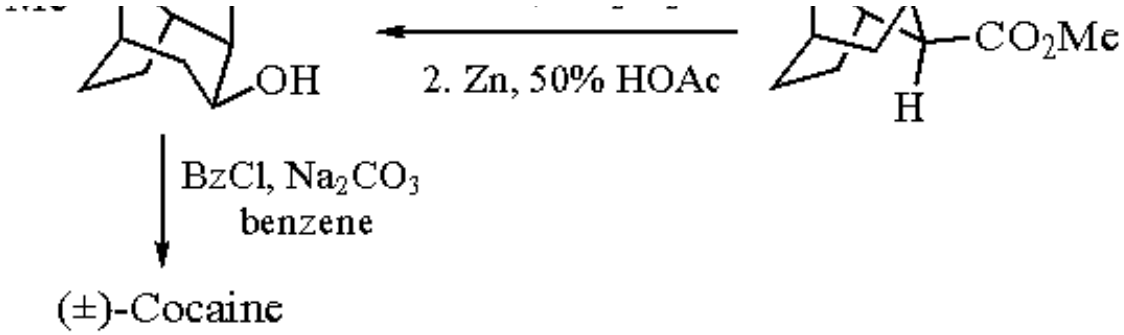

Other Reactions.

Like other nitrones, 1-pyrroline 1-oxide undergoes reactions with nucleophiles, electrophiles, and radicals, addition of organometallic reagents,[4] reduction, oxidation, etc.[2a] However, these reactions have their greatest utility with substituted analogs such as 5,5-dimethyl-1-pyrroline 1-oxide (DMPO), a useful spin trapping reagent for biologically generated radicals.

---

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Pyruvaldehyde Diethyl Acetal

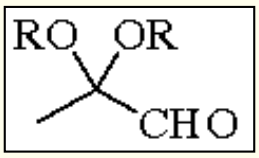

(R = Et)

[16330-13-5] · $C_7H_{14}O_3$ · Pyruvaldehyde Diethyl Acetal · (MW 146.21) (R = Me)

[18218-94-5] · $C_5H_{10}O_3$ · Pyruvaldehyde Dimethyl Acetal · (MW 118.15) (R,R = $-CH_2CH_2-$)

[39050-39-0] · $C_5H_8O_3$ · Pyruvaldehyde Ethylene Acetal · (MW 116.12)

(reagents for preparation of α-ethylenic[1] and α-allenic[2] carbonyl compounds)

Alternate Names: 2,2-diethoxypropanal; methylglyoxal diethyl acetal.

Physical Data: R = Et: bp 27-29 °C/3 mmHg. R = Me: bp 27.5-28 °C/6 mmHg. R,R = $-CH_2CH_2-$: bp 32-35 °C/5 mmHg.

Preparative Methods: preparations involve either reductive ozonolysis of methyl vinyl ketone dioxolane[3] or reduction of ***Ethyl Pyruvate Diethyl Acetal*** followed by oxidation of the resulting alcohol.[2,4] 2,2-Dialkoxypropionaldehydes can also be obtained by alcohol addition to α-alkoxyacroleins.[5]

Handling, Storage, and Precautions: these liquid compounds should be stored under inert gas and at low temperature.

Wittig Reactions.

Reaction with ***Cyclopropylidenetriphenylphosphorane*** gives the expected α,β-ethylenic acetal, which leads to the corresponding α,β-ethylenic carbonyl compound by deacetalization with moist silica gel (eq 1).[1]

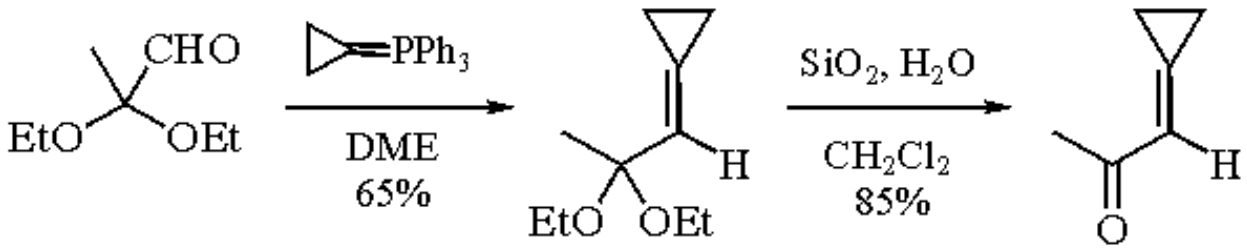

(1)

Reactions with Organometallic Compounds.

Reaction between methylglyoxal ethylene acetal and ***Ethynylmagnesium Bromide*** followed by oxidation of the intermediate alcohol leads to 1-pentyne-3,4-dione 4-ethylene acetal (eq 2).[3] Other propargylic alcohols can also be prepared by reaction with organomagnesium compounds. Their corresponding mesylates react with organocopper species prepared from a Grignard reagent and ***Copper(I) Bromide*** to give α,β-allenic acetals. These acetals are hydrolyzed to α,β-allenic ketones by column chromatography on silica gel. Overall yields are fair to moderate (eq 3).[2] The same reactions may be carried out with phenylglyoxal diethyl acetal.[2]

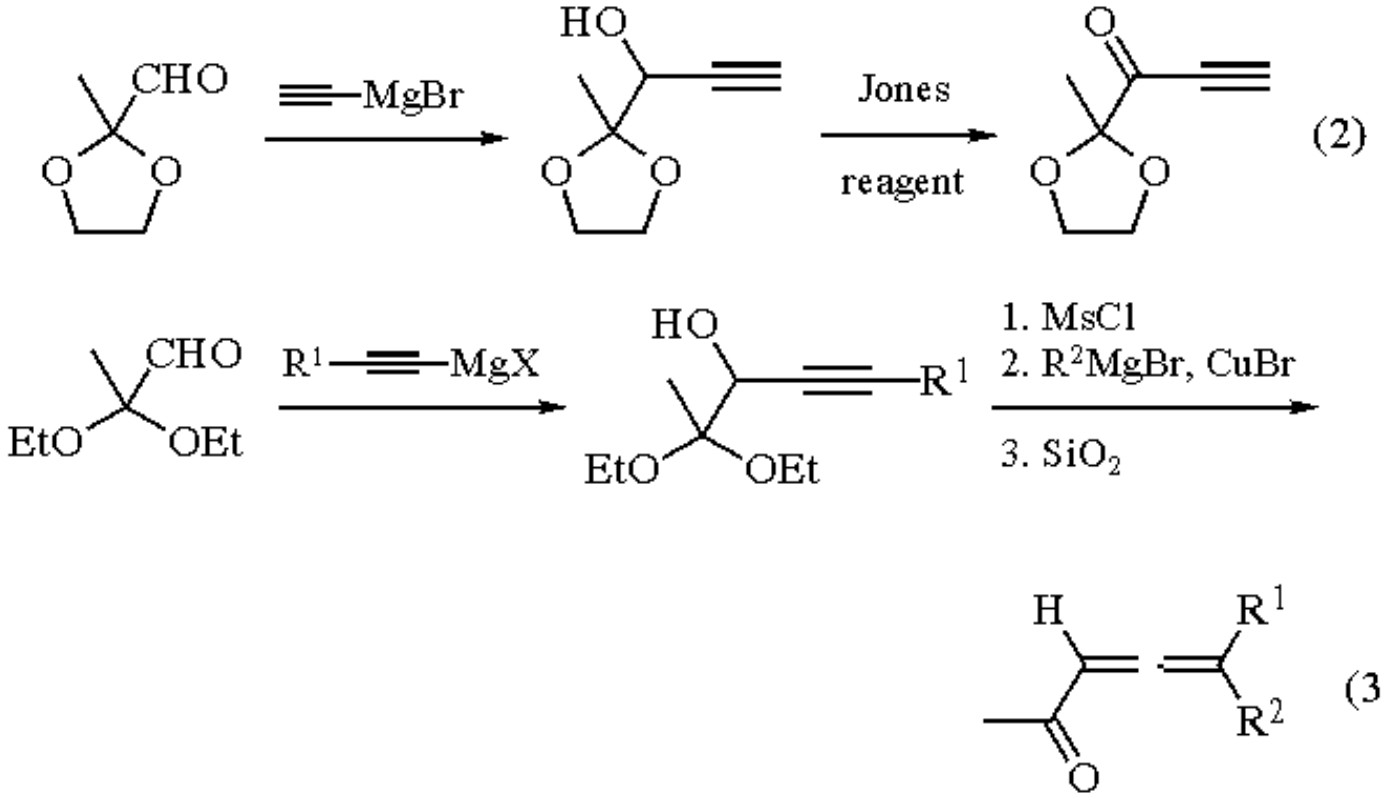

Related Reagents.

(2-Dimethylaminoethyl)triphenylphosphonium Bromide; ***Ethyl 3,3-Diethoxypropanoate***; ***Pyruvaldehyde 2-Phenylhydrazone***.

---

1. Lechevallier, A.; Huet, F.; Conia, J. M. *T* **1983**, *39*, 3307 (*CA* **1984**, *100*, 120 544k).
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5. (a) Shostakovskii, M. F.; Keiko, N. A.; Filippova, A. Kh. *IZV* **1967**, 392 (*CA* **1967**, *67*, 21 241c). (b) Shostakovskii, M. F.; Keiko, N. A.; Chichkarev, A. P.; Filippova, A. Kh. *IZV* **1967**, 2351 (*CA* **1968**, *68*, 39 005j).

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Pyruvaldehyde 2-Phenylhydrazone

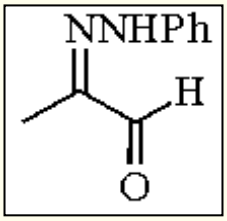

[7013-79-8] · $C_9H_{10}N_2O$ · Pyruvaldehyde 2-Phenylhydrazone · (MW 162.21)

(synthesis of α,β-unsaturated γ-diketones,[1] γ-halo-α,β-unsaturated esters,[4] pyrroles,[1] 1,4-diones,[1] pyridazin-3-ones;[5] aldol-type condensation with a pyruvaldehyde unit[1])

Alternate Name: 2-(phenylhydrazono)propanal.

Physical Data: mp 125 °C,[1] 125.5-126 °C.[2]

Solubility: weakly sol benzene, ethanol, dioxane; can be used in suspension.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: condensation of 1,1-dimethoxy-2-propanone with ***Phenylhydrazine*** in aqueous medium, followed by acidic hydrolysis (eq 1).[1]

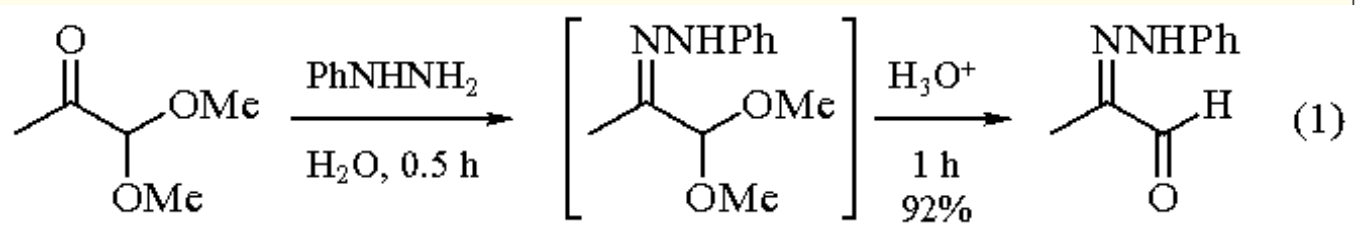

Alternative methods, giving lower yields, involve condensation of 1-(*N*-piperidino)-1-propene with phenyldiazonium salts (eq 2),[2,3] or oxidation of acetone phenylhydrazone with ***Selenium(IV) Oxide*** (eq 3).[4]

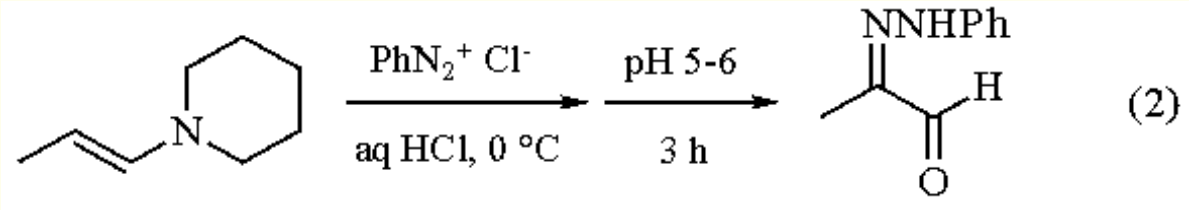

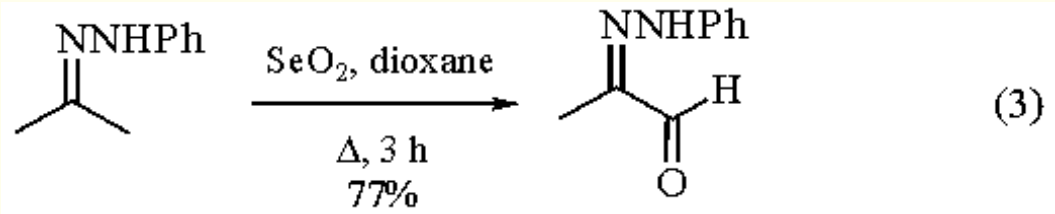

Handling, Storage, and Precautions: fairly stable pyruvaldehyde derivative; store in the refrigerator, well-protected from moisture; in acidic medium, isomerization takes place to the more stable 1-phenylhydrazone. Use in a fume hood.

Synthesis of Enediones.[1]

Condensation of equimolar amounts of pyruvaldehyde 2-phenylhydrazone with acetophenones, 2-acetylfuran, or 2-acetylpyridine, in the presence of potassium ethoxide in ethanol at rt gives aldol-type condensation products, i.e. γ-(phenylhydrazono)-α,β-unsaturated ketones, which are converted into α,β-unsaturated γ-diketones upon treatment with aqueous ***Hydrogen Chloride*** in the presence of ***Formaldehyde*** (eq 4).[1] This aldol-type reaction with acetone gives various side products.[1] However, the use of pyruvaldehyde 2-(4-nitrophenyl)hydrazone in condensations with aliphatic methyl ketones, e.g. ***Acetone*** and 3-methyl-2-butanone, does not show this disadvantage.[1] The aldol reaction is not limited to methyl ketones as the title reagent condensed smoothly with indanone to afford the corresponding enedione monohydrazone and 1,4-dione (eq 5).[1]

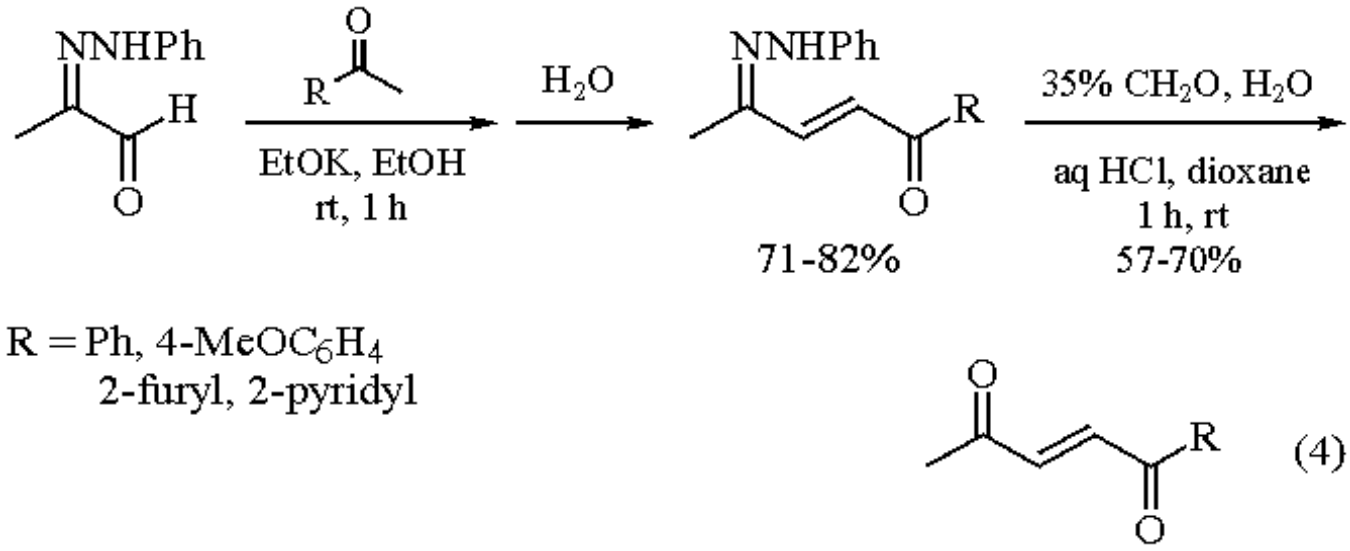

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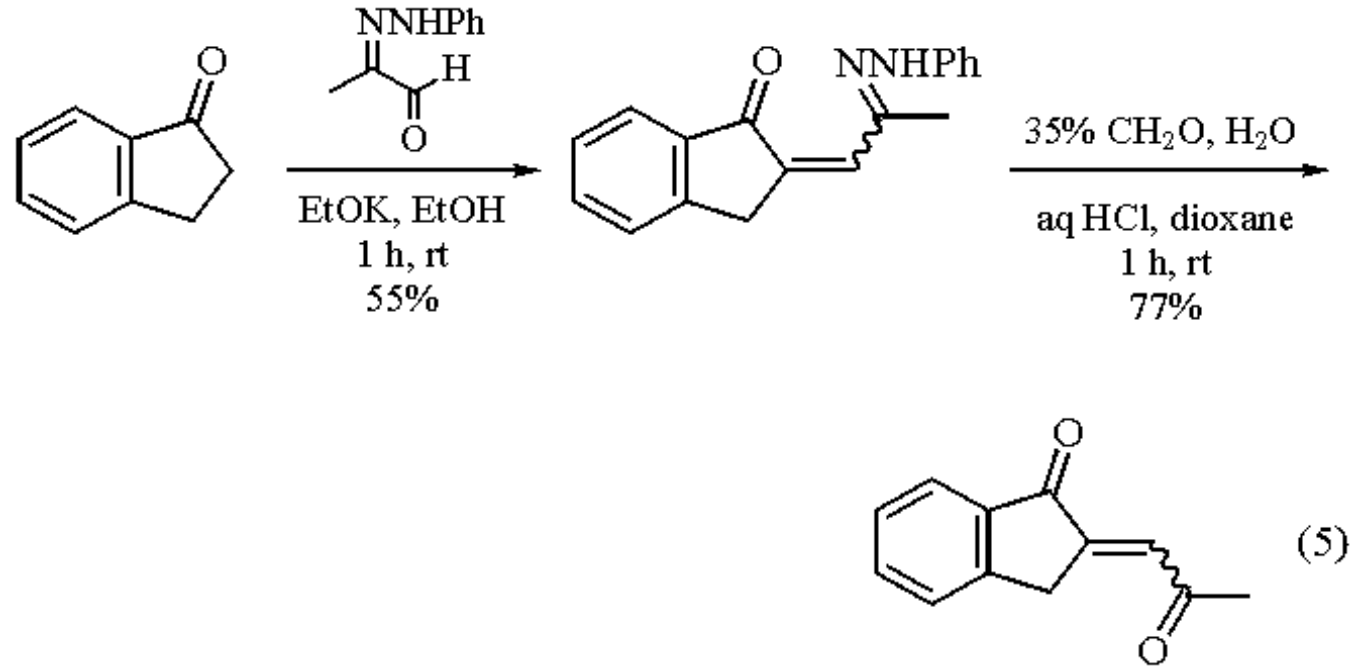

(5)

As shown by the condensation reactions above, pyruvaldehyde 2-phenylhydrazone is a suitable building block in aldol-type reactions. This behavior contrasts with the reactivity of pyruvaldehyde, which is known to undergo predominantly self condensation under aldol-type reaction conditions.

Synthesis of γ-Keto-α,β-unsaturated Esters.[4]

Pyruvaldehyde 2-phenylhydrazone condensed with ***(Ethoxycarbonylmethylene)triphenylphosphorane*** to yield the corresponding γ-hydrazono-α,β-unsaturated ester, which is hydrolyzed to ethyl 4-oxo-2-pentenoate (eq 6).[4]

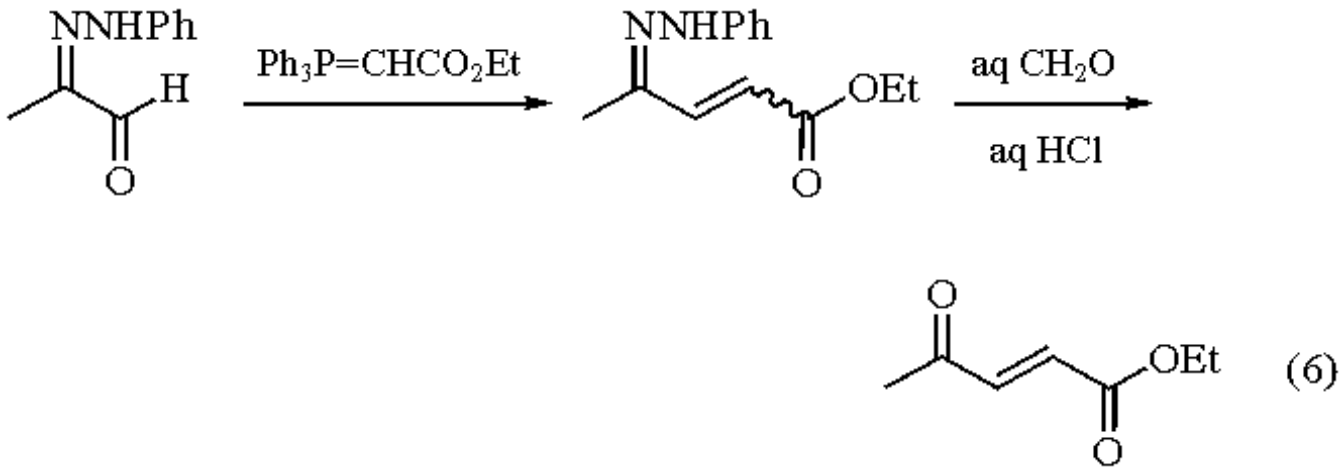

Synthesis of Pyridazin-3-ones.[5]

Active methylene compounds such as ***2,2-Dimethyl-1,3-dioxane-4,6-dione*** (Meldrum's acid) condensed with pyruvaldehyde 2-phenylhydrazone under the catalytic influence of piperidine acetate at room temperature to afford the expected Knoevenagel condensation product (eq 7).[5] However, if the reaction is performed at reflux, cyclization to 2,3-dihydro-6-methyl-2-phenyl-3-oxopyridazine-4-carboxylic acid takes place (eq 8).[5]

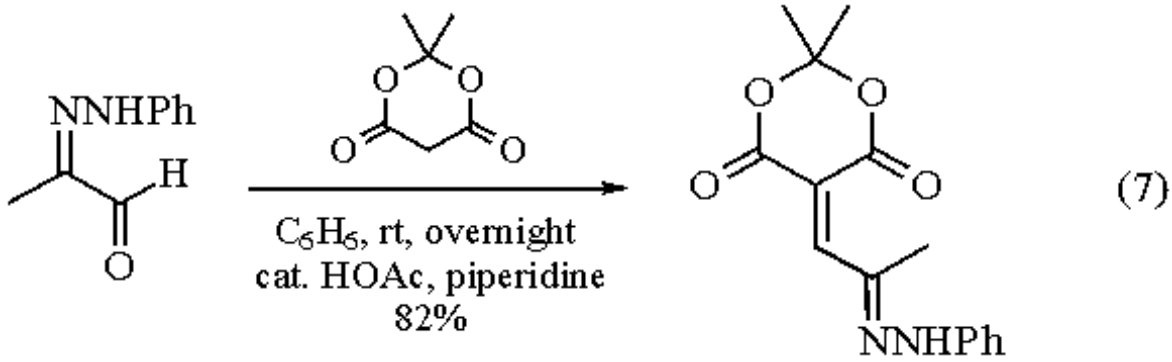

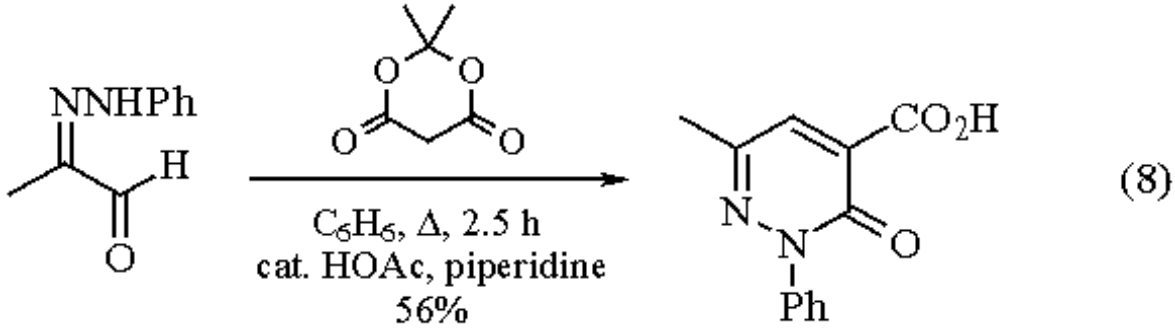

At 0 °C or below, pyruvaldehyde combines with phenylhydrazine to give the 2-phenylhydrazone in a kinetically controlled reaction.[6] In acidic solution, isomerization to the more stable 1-phenylhydrazone occurs at room temperature, the latter compounds being suitable building blocks for the synthesis of 4-hydroxypyrazoles (eq 9).[5]

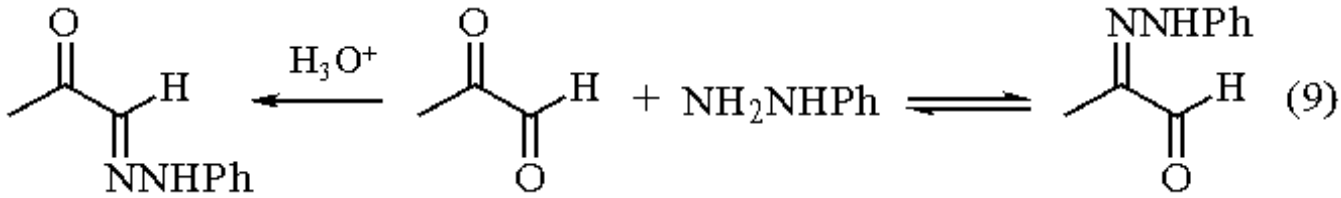

Synthesis of 1,4-Diones and Pyrroles.

Reduction of γ-(phenylhydrazono)-α,β-unsaturated ketones with ***Tin(II) Chloride*** and concentrated aqueous hydrogen chloride in dioxane provides good yields of 1,4-diones (eq 10),[1] while direct access to pyrroles is obtained via reaction of the same starting materials with ***Sodium***

Dithionite (eq 11).[1]

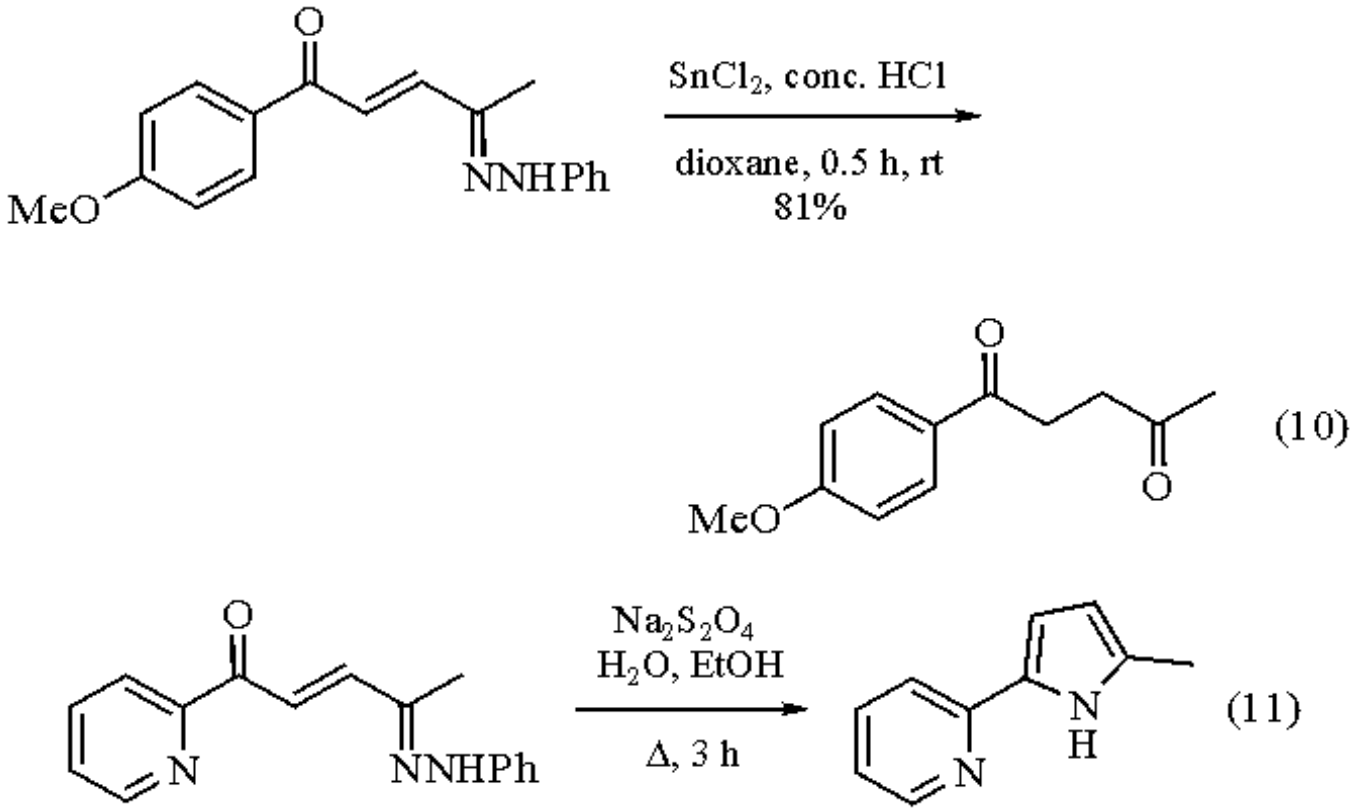

Related Reagents.

Acetone Cyclohexylimine; ***Acetone Hydrazone***; ***1-(N,N-Dimethylamino)-2-methyl-1-propene***; ***Ethyl Pyruvate Diethyl Acetal***; ***Propionaldehyde t-Butylimine***; ***Pyruvaldehyde Diethyl Acetal***.

---

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Pyruvoyl Chloride[1]

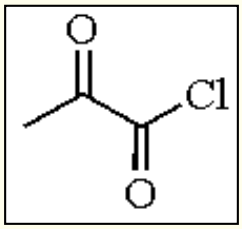

[5704-66-5] · $C_3H_3ClO_2$ · Pyruvoyl Chloride · (MW 106.51)

(α-ketoacylating agent; selective oxidation of alcohols)

Physical Data: light yellow liquid; bp 53 °C/126 mmHg.

Solubility: sol CCl_4, Et_2O, THF, etc.

Preparative Methods: most of the conventional reagents for the synthesis of acid chlorides from carboxylic acids are unsatisfactory for the preparation of pyruvoyl chloride. For example, treatment of pyruvic acid with ***Phosgene*** or ***Oxalyl Chloride***[11] affords the acid chloride in low yield. The method of choice for the preparation of the title compound[1] is the reaction of pyruvic acid with ***Dichloromethyl Methyl Ether***[12,13] to yield chloromethoxymethyl pyruvate, which readily decomposes into pyruvoyl chloride and methyl formate at 50 °C (eq 1).[13] This simple and economical procedure has also been used for the preparation of other α-keto acid chlorides.[1]

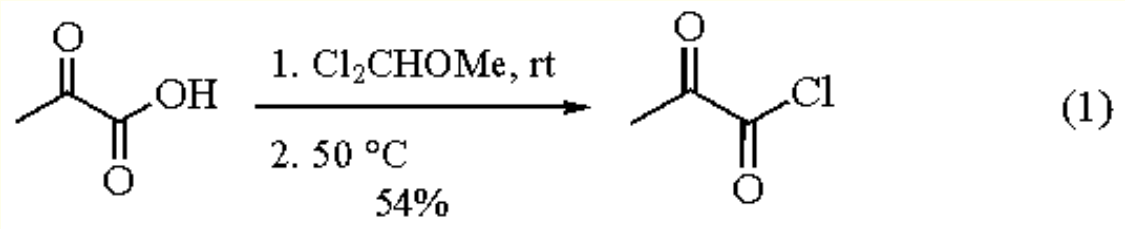

Another facile, but less often used, method for the preparation of pyruvoyl chloride involves the treatment of trimethylsilyl pyruvate, derived from pyruvic acid and ***Chlorotrimethylsilane***, with oxalyl chloride in DMF solution (eq 2).[2]

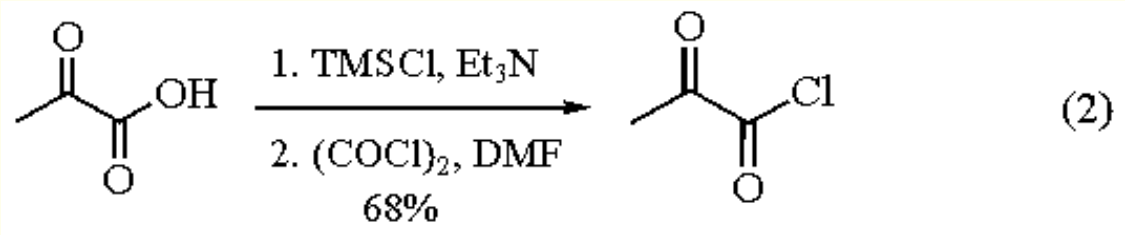

Handling, Storage, and Precautions: pyruvoyl chloride reacts vigorously with moisture, giving off fumes of HCl. It should be stored at -20 °C as the pure liquid in a sealed tube or in CCl_4 solution. The compound may be characterized as the *p*-nitroanilide derivative.[1a] Use in a fume hood.

Reaction of the Acyl Chloride Function.

Of the two functional groups present in pyruvoyl chloride, the acyl chloride function is more reactive than the keto group. The title compound seems to be the reagent of choice for the formation of esters of pyruvic acid.[3,4] This method offers the advantage of mild reaction conditions and broad applicability compared to the older procedure starting from pyruvic acid.[14] Irradiation of the resulting pyruvate esters furnishes aldehydes, ketones, lactones, enones,[3,4] etc., depending on the starting materials employed. Primary alcohols are oxidized to aldehydes without further reaction (eq 3). This procedure is more versatile than ***Dipyridine Chromium(VI) Oxide*** or

Ruthenium(VIII) Oxide oxidation and it seems to be more consistent than the DMSO-based reactions.

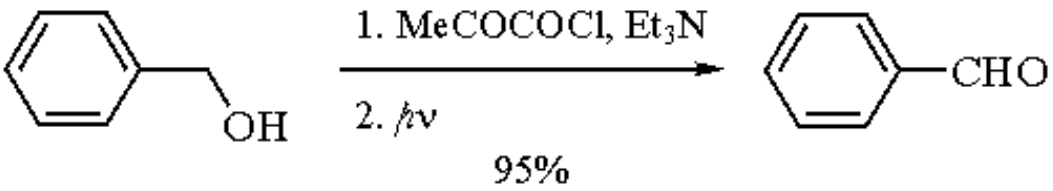

(3)

In the presence of the proper base, pyruvoyl chloride reacts with amines,[5] phenol,[6] and anilines[7-9] to furnish the corresponding α-keto-amides, phenyl α-keto acetates, and α-keto anilides. Other nucleophiles employed are hydroxylamine, oxime amine, and amides.[10,15] In general, amines are more reactive than alcohols or amides, and anilines react faster than phenols.

Palladium and platinum complexes of pyruvoyl chloride have been prepared by the oxidative addition of the acid chloride to both $Pt(PPh_3)_4$ and ***Tetrakis(triphenylphosphine)palladium(0)*** in benzene.[16] Both classes of compounds are stable as solids and in benzene solution at 25 °C, but slowly decompose to acyl complexes when heated at 65 °C. They can serve as synthetic equivalents of the acetyl moiety, e.g. reaction with Et_2NH affords Et_2NAc as the major product.[16]

At rt, pyruvoyl chloride adds to C=N double bonds[10] to form chloroacetoamides (Leuch's reaction).[17] In an analogous manner, condensation of the acyl chloride with nitriles gives the chloroformamidines.[18] Pyruvoyl chloride also adds to C=C double bonds,[19] provided an electron-withdrawing group is attached to the alkene.

Reaction of the Keto Function.

Once the acyl chloride function of the title compound has reacted with nucleophiles the α-keto function can manifest its reactivity. With phosphorus ylides it undergoes a Wittig reaction to form the corresponding alkenes.[19,20] Asymmetric reduction with ***B-3-Pinanyl-9-borabicyclo[3.3.1]nonane***[21] or catalytic hydrogenation[22] using chiral rhodium(I) complexes and subsequent hydrolysis furnishes optically active α-hydroxypropanoic acid. Diastereoselective reduction of the keto group in a chiral ester[23] or amide[24] has also been reported.

The dual reactivity of pyruvoyl chloride has been used to construct both five-membered[7] and six-membered[8,10,15,25] rings. An example of the latter synthesis is given in eq 4.[15b]

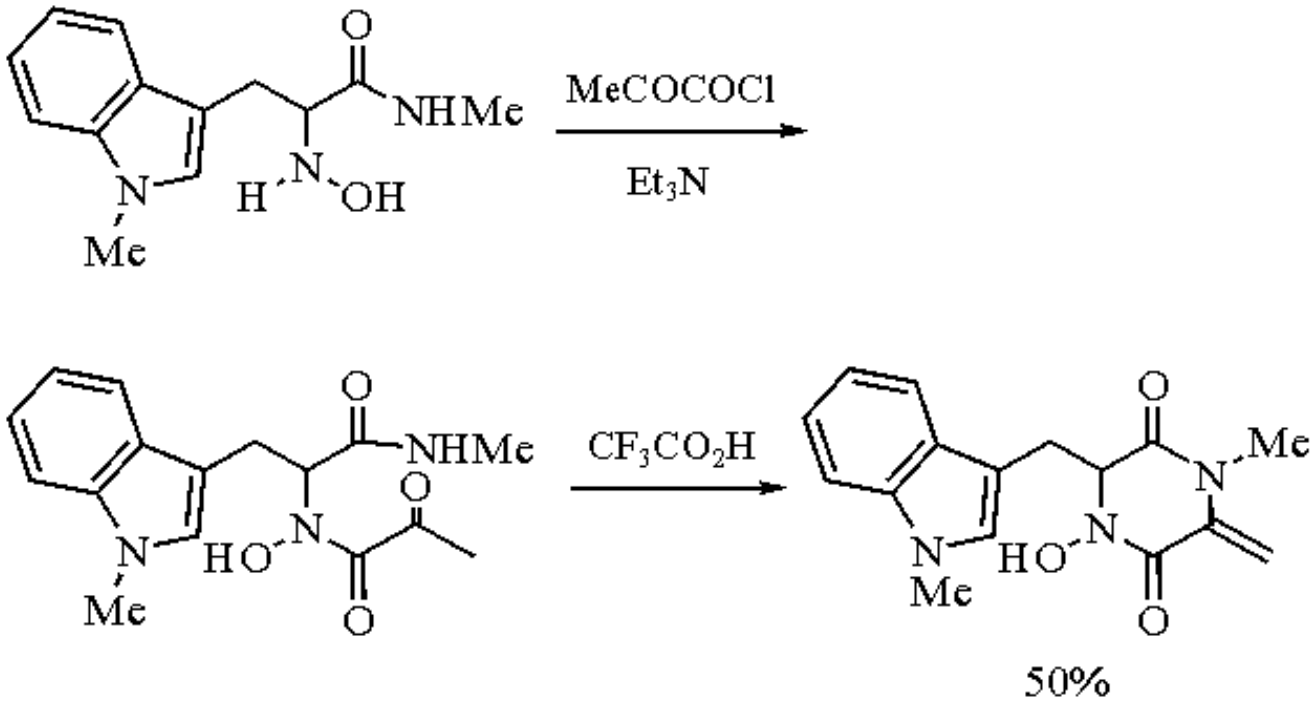

(4)

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Quinine

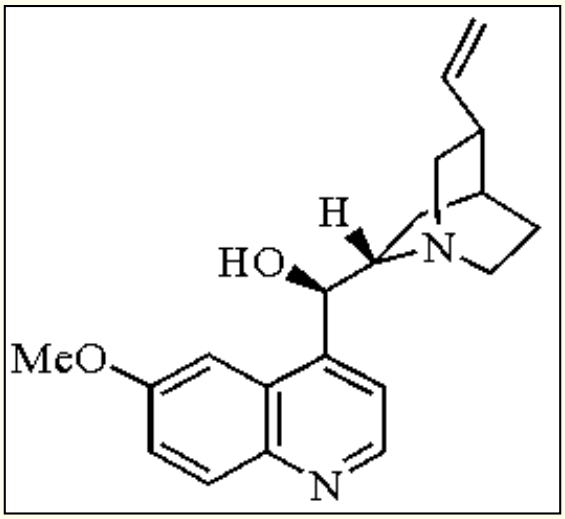

[130-95-0] · $C_{20}H_{23}N_2O_2$ · Quinine · (MW 324.45)

(chiral catalyst[1-14])

Physical Data: mp 173-175 °C.

Solubility: sol hot water, methanol, benzene, chloroform, ether, glycerol; insol pet ether.

Form Supplied in: crystalline solid; 90% purity.

Analysis of Reagent Purity: NMR, mp.

Preparative Methods: commercially available from several sources.

Purification: recrystallize from absolute ethanol.

Handling, Storage, and Precautions: toxic; irritant.

Asymmetric Diels-Alder Reactions.

Chiral bases, including quinine, have been used as catalysts in Diels-Alder reactions (eq 1).[1] The reactions take place at room temperature or below and require 1-10% equiv of the alkaloid. The asymmetric induction that is observed can be attributed to complex formation between the achiral dienolate and the chiral amine.[1]

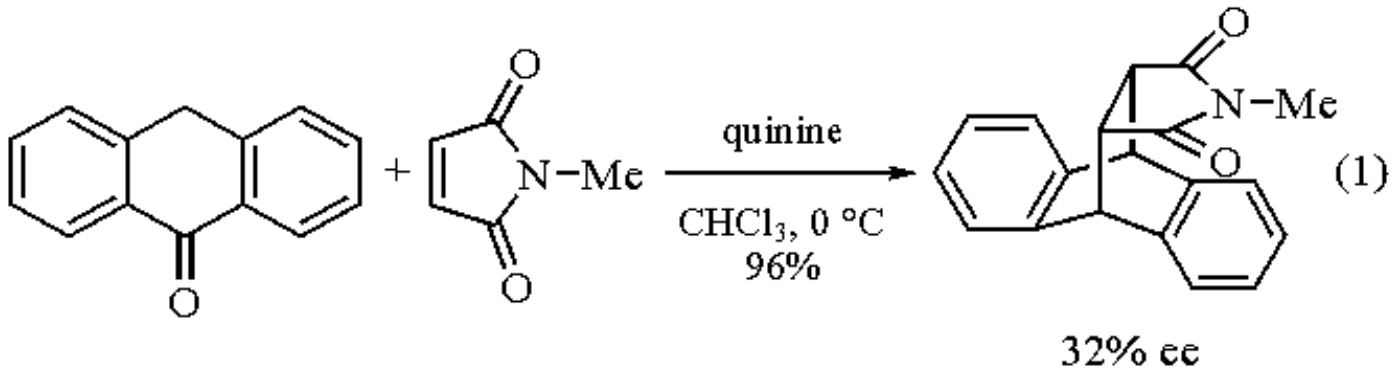

(1)

Preparation of Chiral Sulfinates.

Optically active sulfinates can be prepared by reaction of a symmetrical sulfite with ***t-Butylmagnesium Chloride*** in the presence of an optically active amino alcohol. The best enantioselectivity has been observed using quinine as the optically active amine (eq 2).[2] An alternative approach to this new enantioselective asymmetric synthesis of alkyl *t*-butylsulfinates would be reaction of a racemic sulfinate with *t*-butylmagnesium chloride complexed by optically active alkaloids (eq 3).[2] In this case, kinetic resolution of the racemic sulfinate leads to an optically active sulfinate and an optically active sulfoxide.

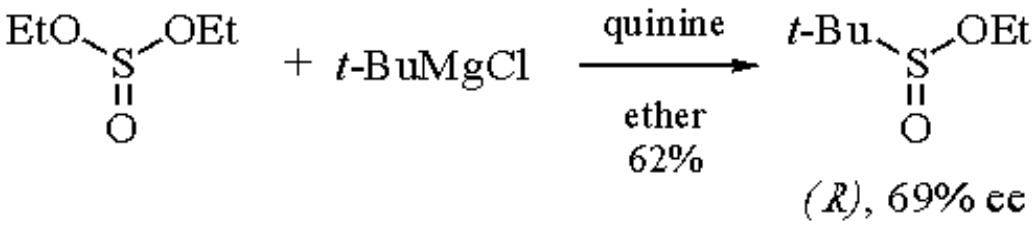

(2)

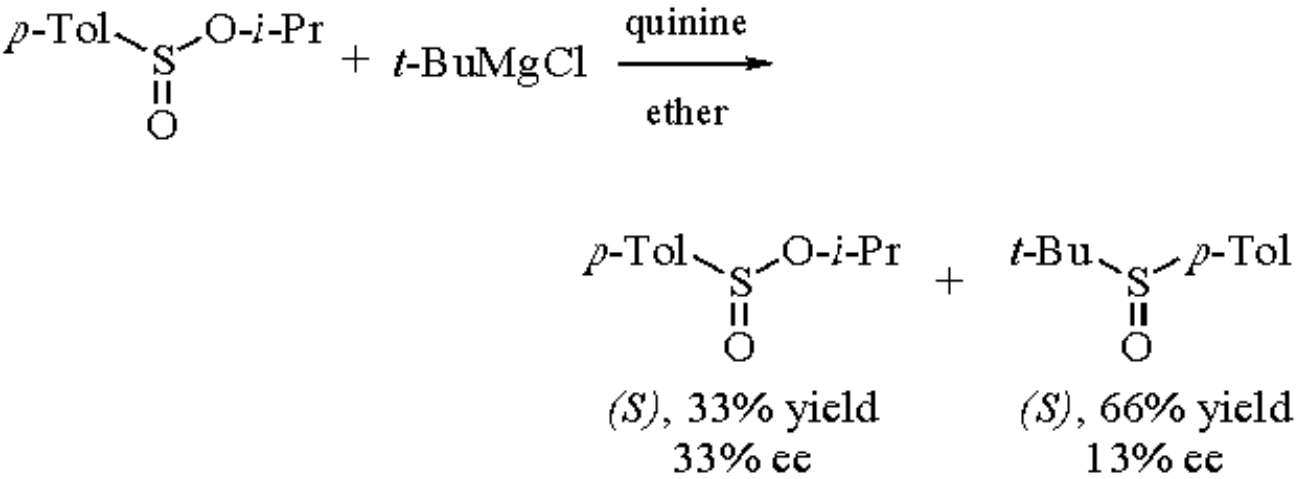

(3)

Stereoselective Addition of Diethylzinc to Aldehydes.

Wynberg has found that the cinchona alkaloids catalyze the reaction of ***Diethylzinc*** and aldehydes to form optically active alcohols (eq 4).[3] The highest enantiomeric excess obtained was from reactions which used quinine as the catalyst. Results show that the hydroxyl group of the catalyst hydrogen bonds with the aldehyde and that the diethylzinc interacts with the vinyl group of the catalyst as well, but it has not been determined if one or two catalyst molecules are involved in the transition state. Similar results have been obtained using a furan aldehyde.[4]

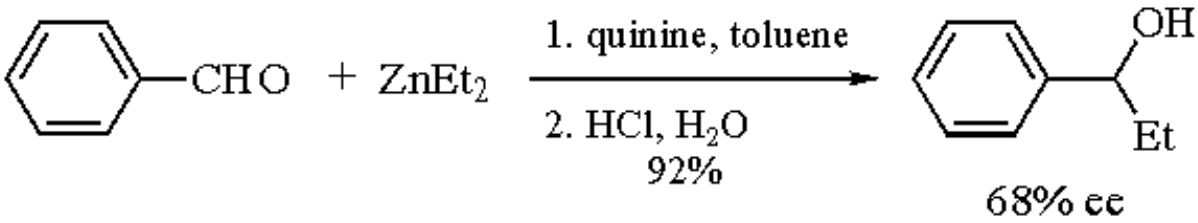

(4)

Synthesis of Optically Active Epoxides.

Alkaloids and alkaloid salts have been successfully used as catalysts for the asymmetric synthesis of epoxides. The use of chiral catalysts such as quinine or quinium benzylchloride (QUIBEC) have allowed access to optically active epoxides through a variety of reaction conditions, including oxidation using ***Hydrogen Peroxide*** (eq 5),[5] Darzens condensations (eq 6),[6] epoxidation of ketones by ***Sodium Hypochlorite*** (eq 7),[6] halohydrin ring closure (eq 8),[6] and cyanide addition to α-halo ketones (eq 9).[6] Although the relative stereochemistry of most of the products has not been determined, enantiomerically enriched materials have been isolated. A more recent example has been published in which optically active 2,3-epoxycyclohexanone has been synthesized by oxidation with ***t-Butyl Hydroperoxide*** in the presence of QUIBEC and the absolute stereochemistry of the product established (eq 10).[7]

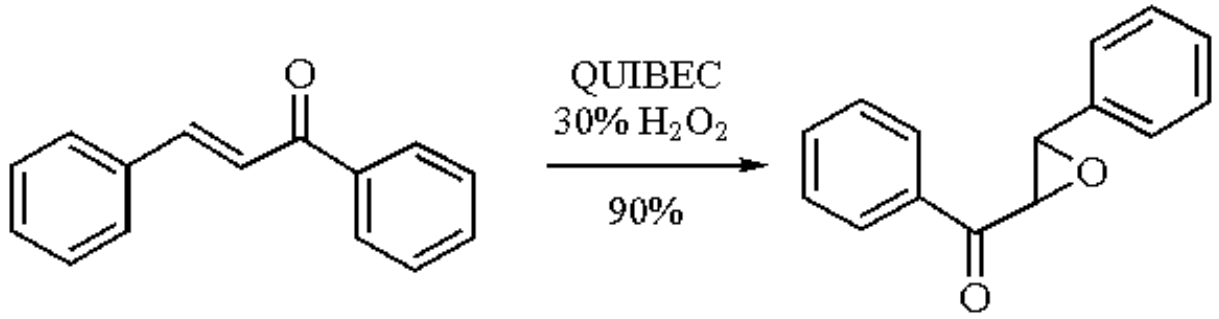

(5)

(optical purity not determined)

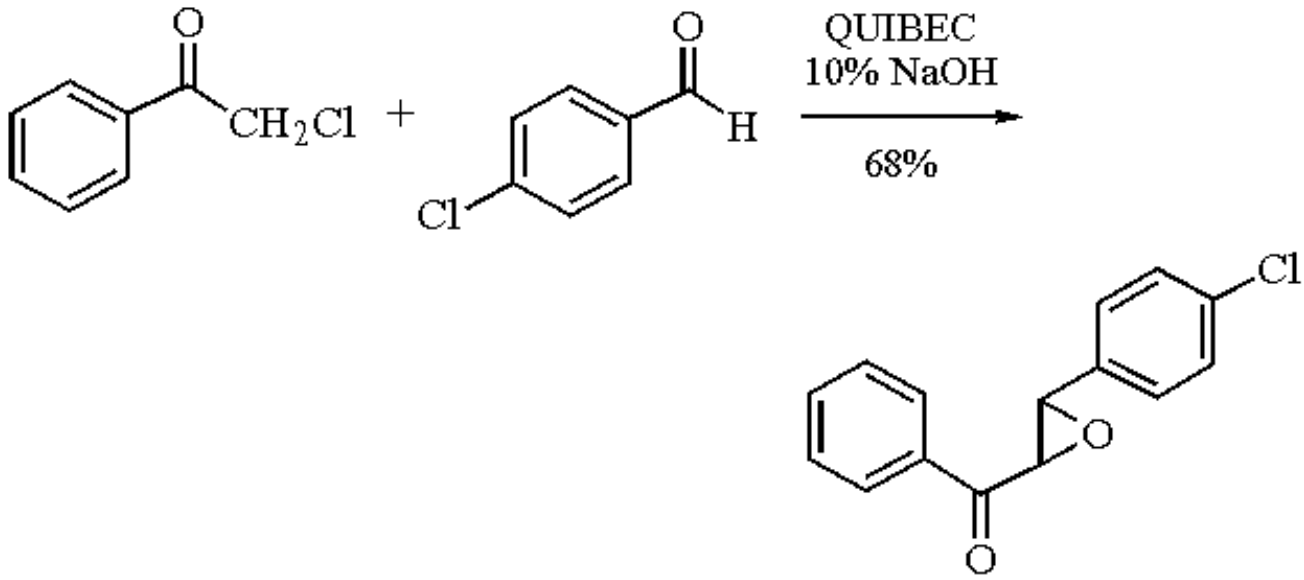

(6)

8% ee

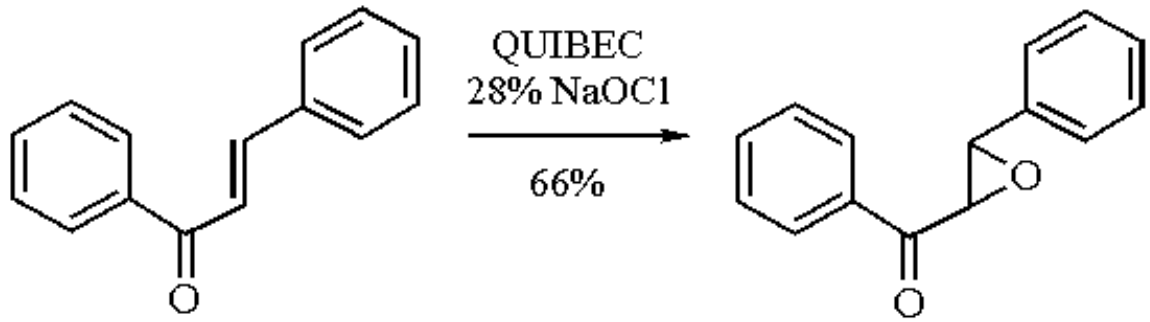

(7)

25-30% ee

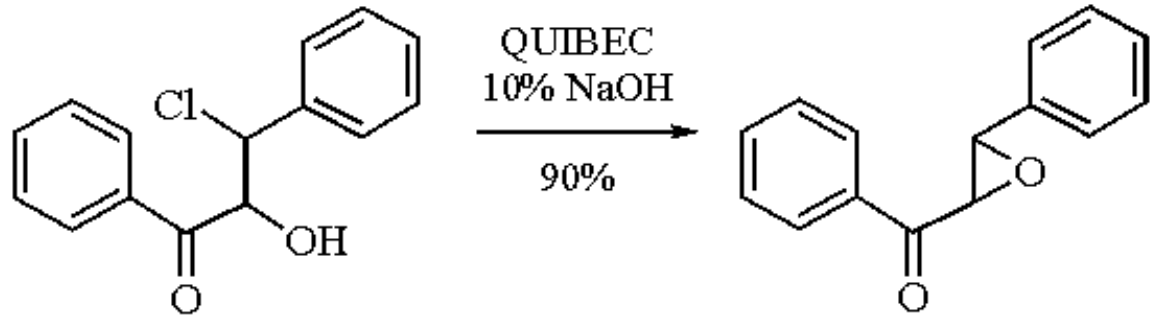

(8)

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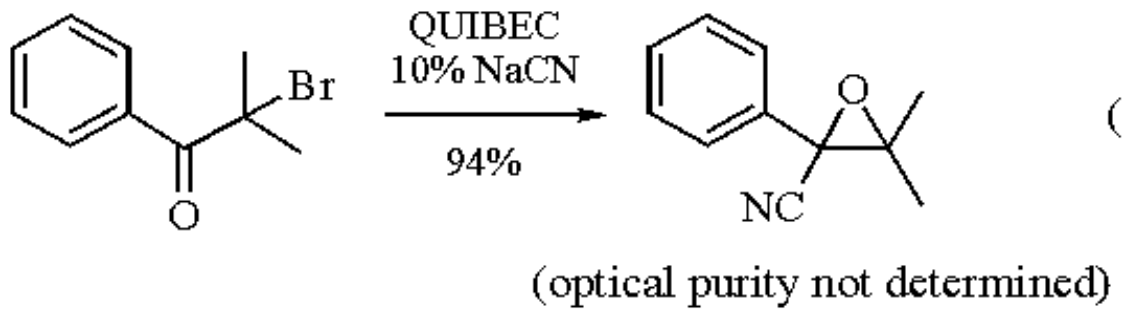

(9)

(optical purity not determined)

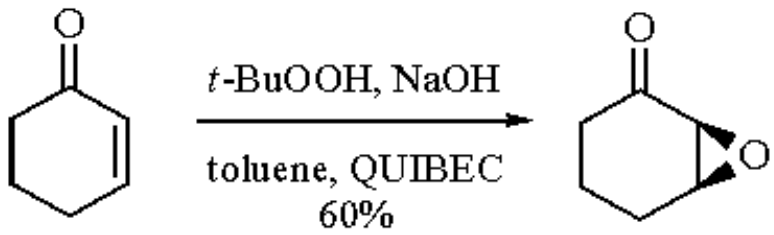

(10)

20-23% ee

Asymmetric Michael Reactions.

Asymmetric induction has been observed in Michael-type addition reactions that are catalyzed by chiral amines.[8] The *N*-benzyl fluoride salt of quinine has been particularly successful since the fluoride ion serves as a base and the aminium ion as a source of chirality.[9] Drastic improvements in optical purity (1-23%) have resulted by changing from quinine to the *N*-benzyl fluoride salt (eq 11).[9]

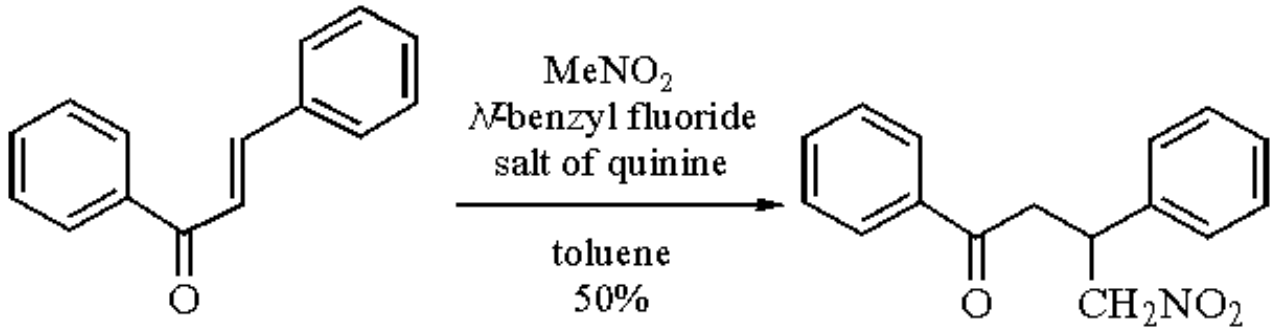

(11)

23% ee

Asymmetric Synthesis of β-Keto Sulfides.

Quinine can be used to catalyze asymmetrically the addition of thiols to cyclohexenone, thus forming β-keto sulfides (eq 12).[10] The absolute stereochemistry of the products has not been determined.

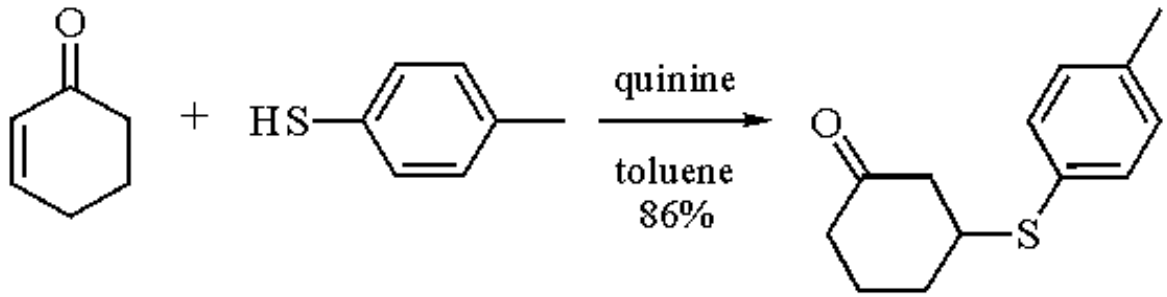

(12)

46% ee

Asymmetric Reduction of Ketones.

Alkyl phenyl ketones can be asymmetrically reduced to the corresponding alcohol using ***Sodium Borohydride*** under phase-transfer conditions in the presence of a catalytic amount of QUIBEC (eq 13).[11] The results indicate that the asymmetric reduction is due to the rigidity of the catalyst as well as the β-position of the hydroxyl group on the quinine molecule. The asymmetric induction is much lower with a γ-hydroxyl group.[11]

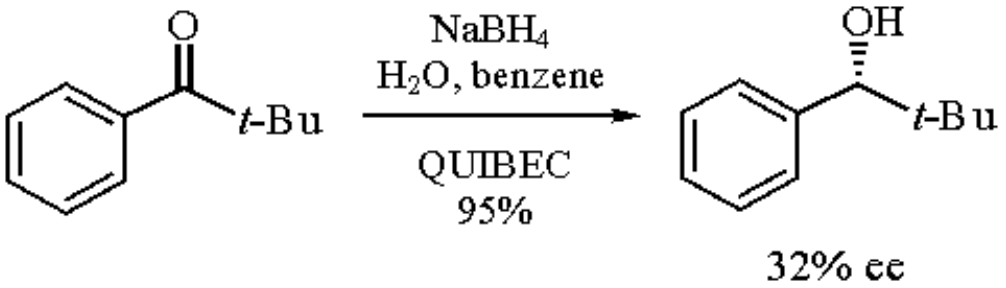

(13)

Synthesis of Optically Active β-Hydroxy Esters.

Chiral amino alcohols such as quinine have been used in the enantioselective synthesis of β-hydroxy esters via an indium-induced Reformatsky reaction (eq 14).[12] Although the enantioselectivities are not particularly high, aromatic aldehydes have produced the best results to date. The absolute stereochemistry of the products has not yet been assigned.

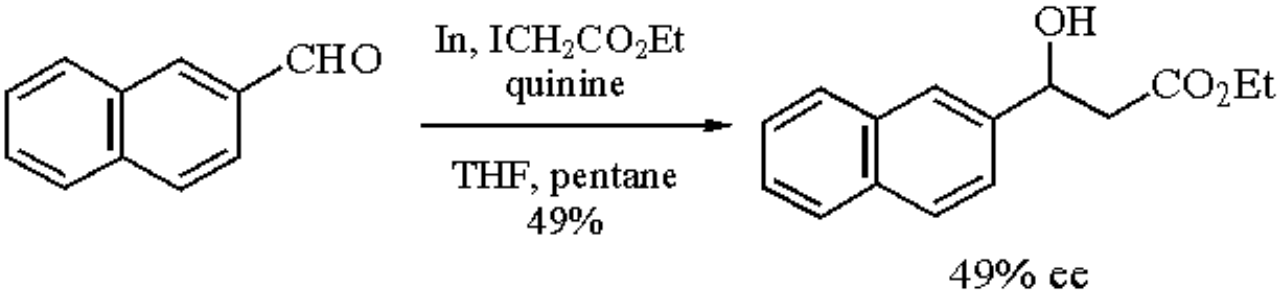

(14)

Preparation of Polymeric Catalyst.

A quinine/***Acrylonitrile*** copolymer has been successfully synthesized via radical polymerization using ***Azobisisobutyronitrile*** (AIBN) as initiator (eq 15).[13] The polymer can be prepared such that the vinyl group is the connecting site and the amino alcohol portion can either be free or protected. These copolymers are thermally stable and are soluble in polar aprotic solvents such as DMF and DMSO, but insoluble in common organic solvents. Preliminary experiments have shown that these copolymers can be used as asymmetric catalysts.[13]

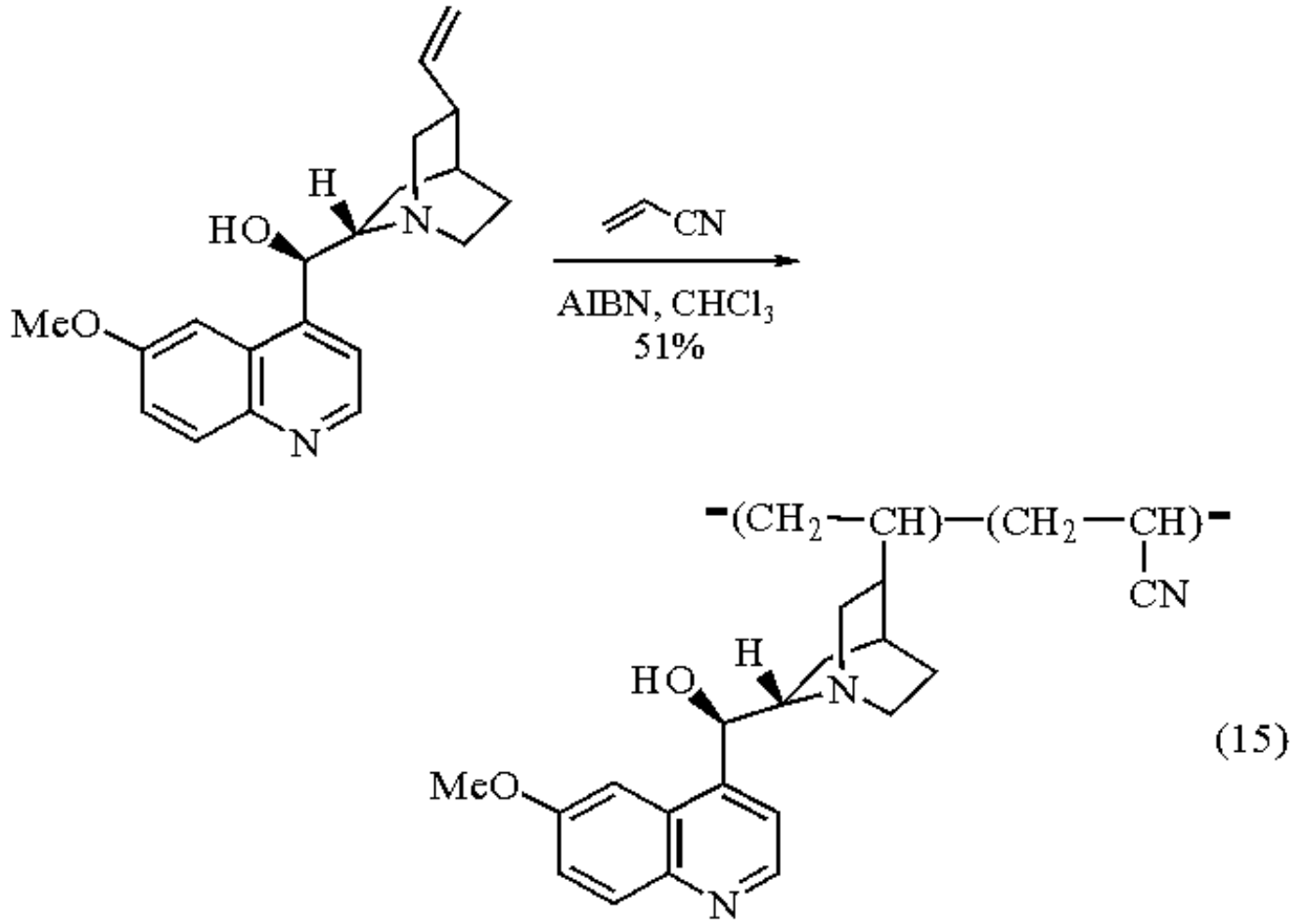

Asymmetric Addition of Thioglycolic Acid to Nitro Alkenes.

Quinine has been used to catalyze the addition of thioglycolic acid to nitro alkenes (eq 16).[14] Enantiomerically enriched materials have been isolated, although the absolute stereochemistry of the products has not been assigned. The direction and extent of asymmetric induction seems to be dependent on the catalyst/acid ratio, thereby pointing to interaction between the carbonyl of the acid and the alkaloid nitrogen as being responsible for the asymmetric induction.[14]

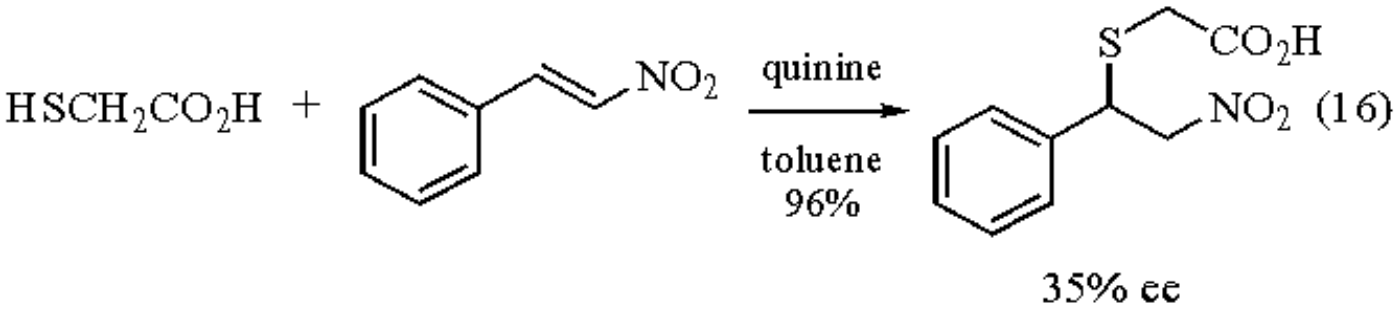

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1. Riant, O.; Kagan, H. B. *TL* **1989**, *30*, 7403.
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Quinoline

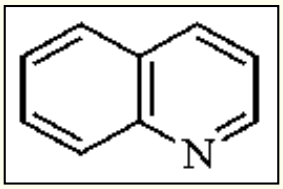

[91-22-5] · C_8H_7N · Quinoline · (MW 129.16)

(useful as a base, solvent and/or catalyst, especially for decarboxylation reactions[1] and the Rosenmund reaction[2,3])

Physical Data: mp -15 °C; bp 237.6 °C;[4] steam volatile; *d* 1.0858 g cm^{-3} at 30 °C; pK_a 9.5.[5]

Solubility: sol ethanol, ethyl ether, acetone, carbon disulfide; more readily sol hot water than cold water; quinoline dissolves sulfur, phosphorus, and arsenic trioxide.

Form Supplied in: colorless liquid.

Analysis of Reagent Purity: GLC.

Purification: distillation.

Handling, Storage, and Precautions: very hygroscopic; darkens on storage in light; package with protection from light and moisture; LD_{50} rat (oral) 460 mg kg^{-1}; incompatible with strong oxidizing agents and strong acids.[5,6]

Dehydrohalogenation Reactions.

Quinoline is sometimes used as a base or solvent for dehydrohalogenation reactions because of its basic properties. A wide variety of substrates, ranging from very simple to quite complex compounds, have been effectively dehydrohalogenated with quinoline. For example, 3-bromo-3-methyl-2-butanone (**1**) underwent reaction with quinoline to give a mixture of products, 3-methyl-2-butanone (**2**) and 2-methyl-1-buten-3-one (**3**) (eq 1).[7]

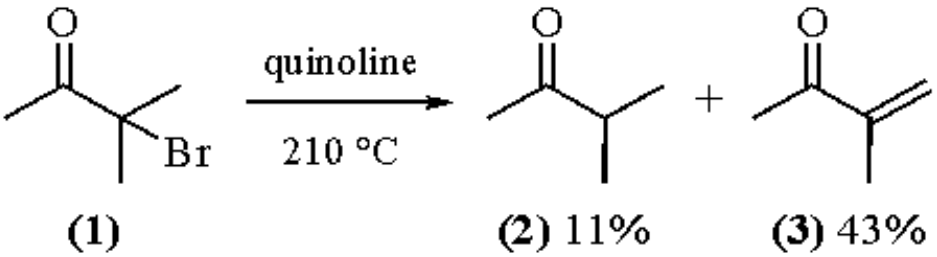

(1)

Trans-3-penten-2-one (**5**) has been prepared from 4-chloropentan-2-one (**4**) using quinoline as the acid scavenger (eq 2).[8]

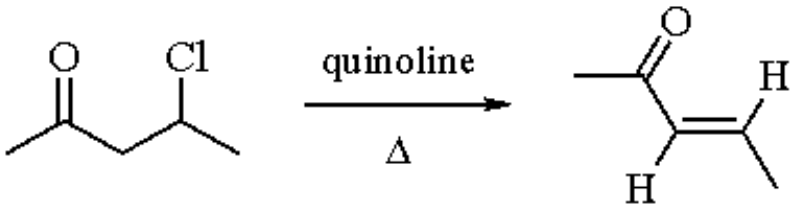

(2)

(4)

(5) 25-37% overall from propylene and acetyl chloride

Dehydrochlorination of 2-oxa-7,7-dichloronorcarane (**6**) in quinoline gives an 83% yield of 2,3-dihydro-6-chlorooxepine (**7**) (eq 3).[9]

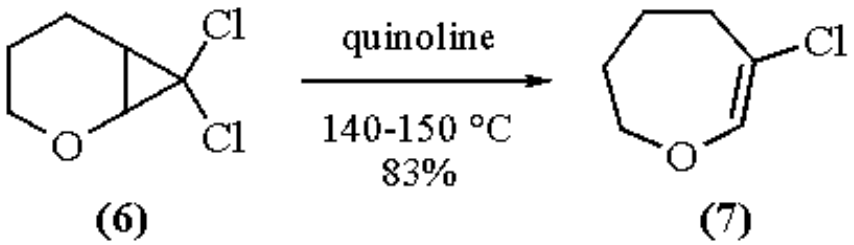

(3)

Similarly, when 7,7-dibromonorcarane (**8**) is treated with quinoline, by manipulation of reaction conditions the bromocyclohepta-1,3-diene derivatives can be isolated or total dehydrobromination to ***1,3,5-Cycloheptatriene*** (**9**) can be effected (eq 4).[10]

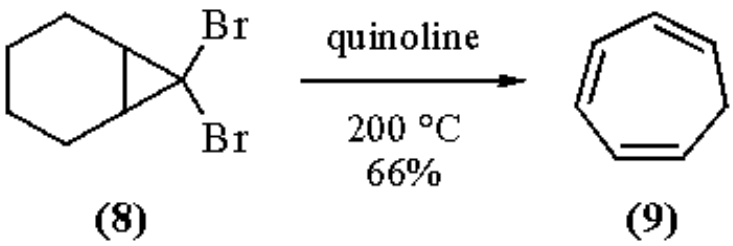

(4)

Selective dehydrobromination of (α-bromovinyl)chlorosilanes can be carried out in quinoline, affording fair to good yields of the corresponding ethynylchlorosilanes (eq 5).[11]

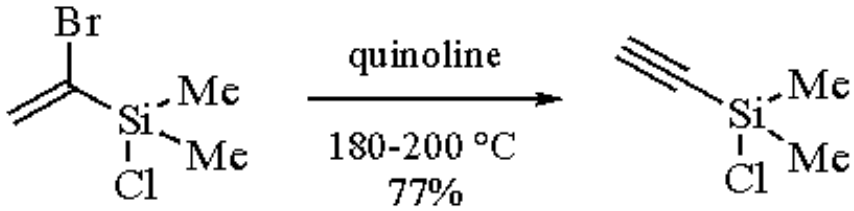

(5)

Decarboxylation Reactions.

Taking advantage of its basic properties, quinoline is generally useful as a solvent for decarboxylation reactions. It is especially suitable because its relatively high boiling point facilitates the decarboxylation. Examples include the decarboxylation of 3-methyl-2-furoic acid (**10**) to 3-methylfuran (**11**) (eq 6),[12] *m*-nitrocinnamic acid (**12**) to *m*-nitrostyrene (**13**) (eq 7),[1] and α-phenylcinnamic acid (**14**) to *cis*-stilbene (**15**) (eq 8).[13] Copper catalysts such as ***Copper*** or ***Copper Chromite*** are used to effect the decarboxylations.

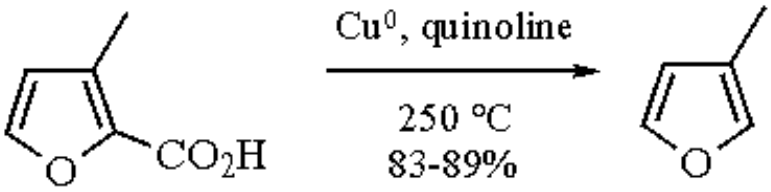

(6)

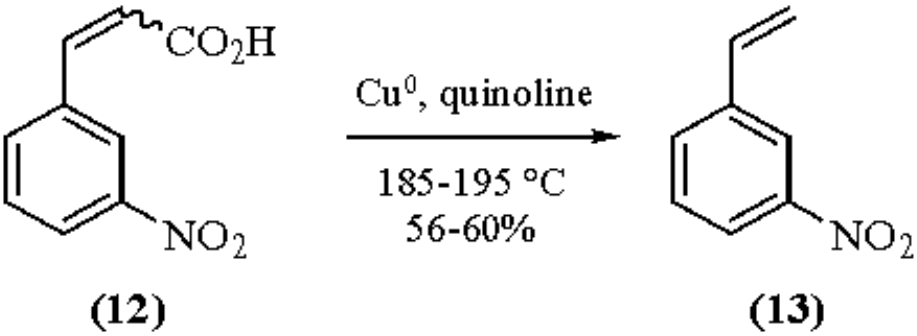

(7)

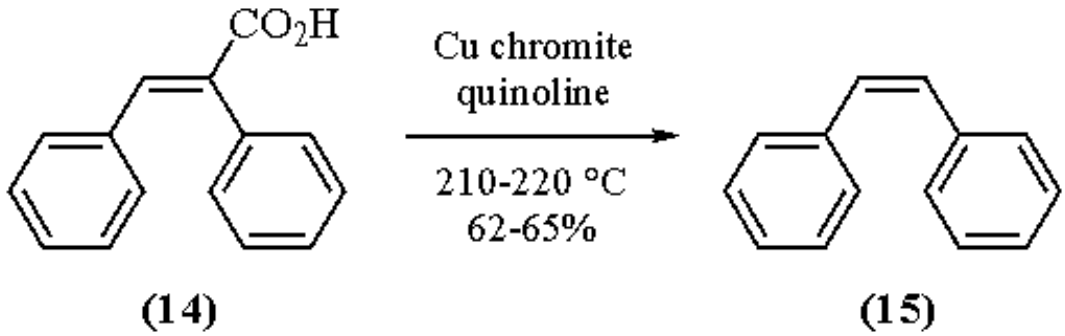

(8)

Preparation of Isothiocyanates.

Ethoxycarbonyl Isothiocyanate (**18**), useful as a synthetic reagent for heterocyclic syntheses,[14] can be prepared in excellent yield from the reaction of ***Ethyl Chloroformate*** (**16**) with ***Sodium Thiocyanate*** (**17**) using quinoline as a base catalyst (eq 9).[15] Only trace amounts of the isomeric thiocyanates are formed in the reaction. In the absence of the base catalyst, only a moderate (65%) yield of the desired product is obtained, along with significant (10%) contamination by the isomeric ethoxycarbonyl thiocyanate. ***Pyridine*** can also be used as the catalyst here; however, it reacts faster, which sometimes leads to undesired byproduct formation.

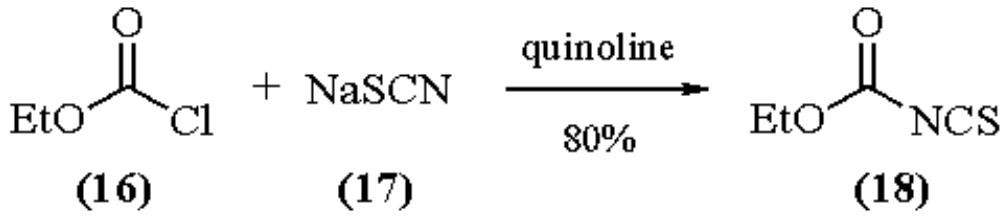

(9)

Quinoline as a Solvent.

When quinoline is used as a solvent for the reaction of ***Phenylcopper*** with iodoarenes, metal-halogen exchange and unsymmetrical coupling reactions occur as shown in eq 10.[16] The products suggest that basic solvents such as quinoline solvate the phenylcopper, leading to a complex mixture of products. Similar activity is observed in pyridine solvent.

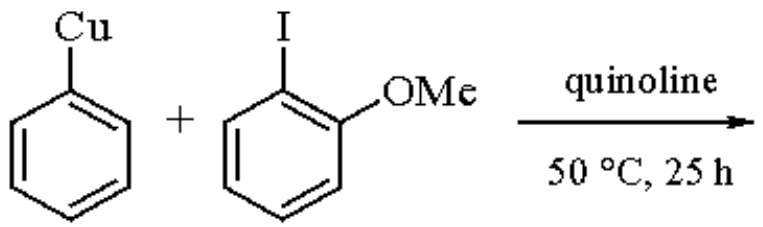

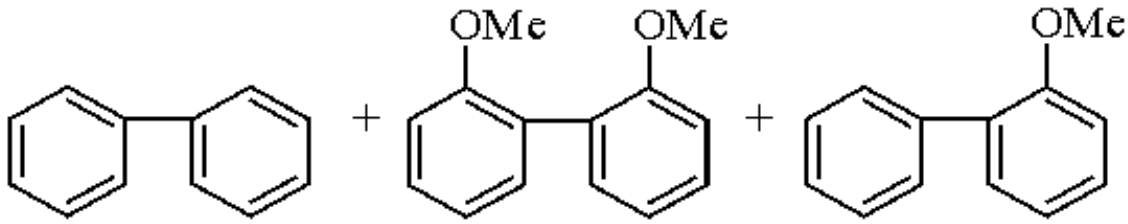

(10)

4:3:1

Acylation Reactions.

Many basic catalysts have been used to carry out acylation reactions. The stereoselectivity of the reaction of diacetoxy or dibenzoyloxysuccinic anhydrides with racemic alcohols is affected by the choice of base catalyst. Quinoline is one of the most effective base catalysts for enhancing the stereoselectivity of the reaction of (2*R*,3*R*)-2,3-diacetoxysuccinic anhydride with 1-phenylethanol in comparison with catalysts such as pyridine, 3- and 4-methylpyridines, and isoquinoline. Other effective basic catalysts are pyridine derivatives substituted in the 2-position of the ring such as 2-methylpyridine and 2,6-dimethylpyridine.[17]

Formation of Allenes.

Quinoline can be used as an acid scrubber in the preparation of allenes via vinyl triflate intermediates. The elimination of ***Trifluoromethanesulfonic Acid*** in quinoline proceeds in good yield (eqs 11 and 12).[18]

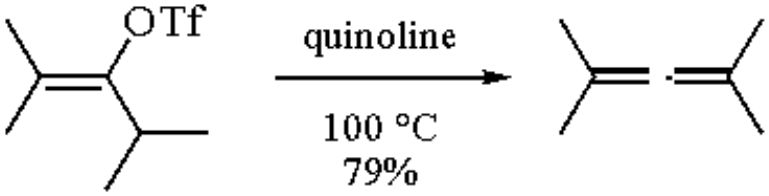

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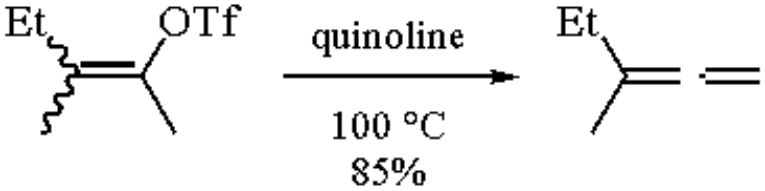

(12)

Rosenmund Reaction.

A catalyst poison prepared from quinoline and ***Sulfur*** is useful for controlling the reaction of β-naphthoyl chloride (**19**) with hydrogen gas and ***Palladium on Barium Sulfate*** catalyst.[2] If control of the reaction is not maintained by catalyst poisoning to reduce activity, further reduction beyond the desired β-naphthaldehyde product (**20**) is often observed (eq 13).[3]

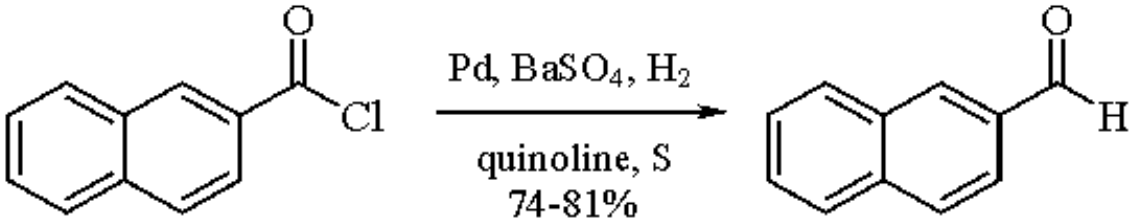

(13)

(19) **(20)**

Elimination Reactions.

Quinoline in DMSO facilitates the elimination of dimethyl sulfide from sulfonium salt (**21**), affording the very reactive cyclobutenone derivative (**22**) (eq 14).[19]

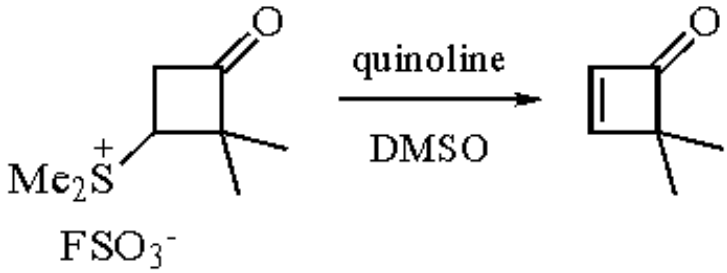

(14)

(21) **(22)**

Related Reagents.

Chromium(VI) Oxide-Quinoline; ***Copper Chromite-Quinoline***.

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3-Quinuclidinol

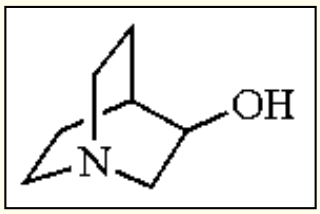

[1619-34-7] · $C_7H_{13}NO$ · 3-Quinuclidinol · (MW 127.21)

(cleavage of β-keto esters;[1] catalyst for Baylis-Hillman reaction;[2-6] synthesis of monoesters;[7] oxygenation of branched aldehydes[8])

Physical Data: mp 223-224 °C.

Solubility: sol water, ethanol, methanol.

Form Supplied in: crystalline solid; >98% purity.

Analysis of Reagent Purity: NMR, mp.

Preparative Methods: commercially available from several sources.

Purification: recrystallize from benzene or acetone.

Handling, Storage, and Precautions: corrosive.

Cleavage of β-Keto Esters.

3-Quinuclidinol selectively cleaves β-keto esters to ketones (eq 1).[1] Typical reaction conditions involve heating the ester with a fivefold excess of quinuclidinol in *o*-xylene. The reaction is also successful for cleavage of vinylogous β-keto esters (eq 2).[1]

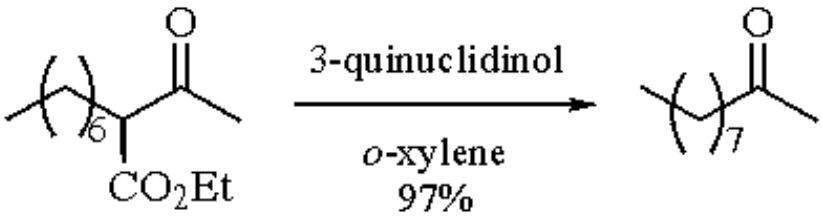

(1)

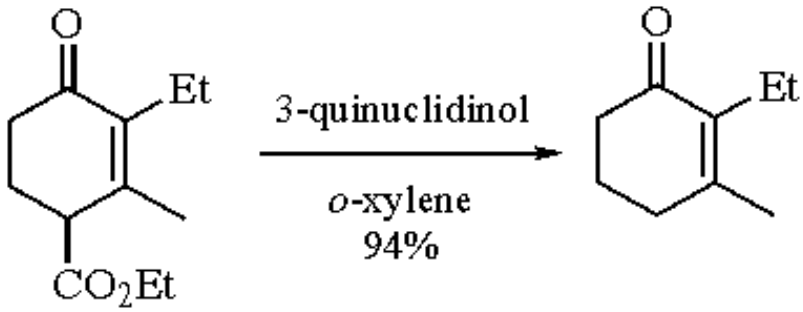

(2)

Baylis-Hillman Reaction.

3-Quinuclidinol is a much more efficient catalyst than ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO) for the Baylis-Hillman reaction, yielding 2-hydroxyalkenoate esters (eqs 3 and 4).[2] Reaction times are much shorter, typically less than 24 h as compared to 4-7 days.[3] The same results have been observed for the synthesis of hydroxy enones (eq 5).[4] It has been speculated that the rate enhancement can be due to hydrogen-bonding stabilization of the catalyst-acrylate adduct[5] by the hydroxyl group of quinuclidinol, which does not occur with DABCO. This methodology has also been extended to include the use of aromatic aldehydes (eq 6).[6]

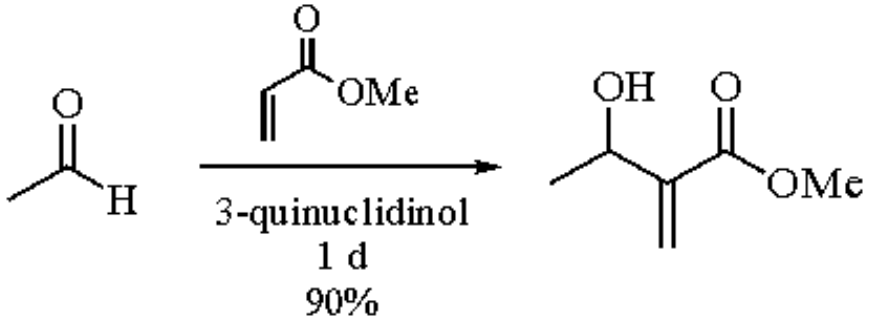

(3)

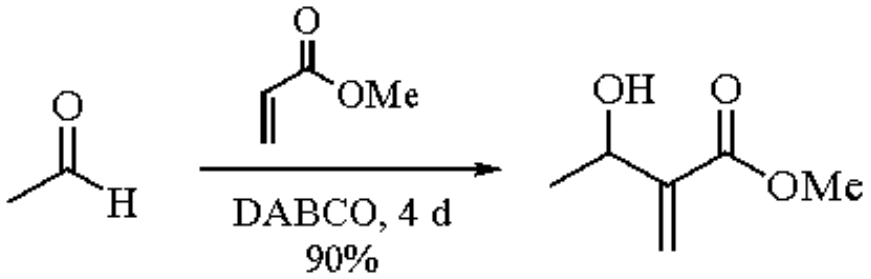

(4)

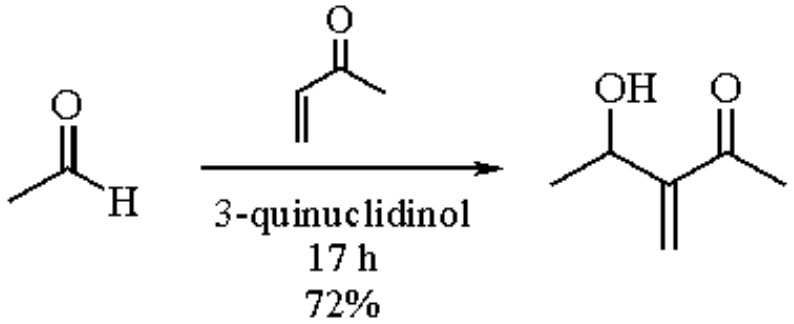

(5)

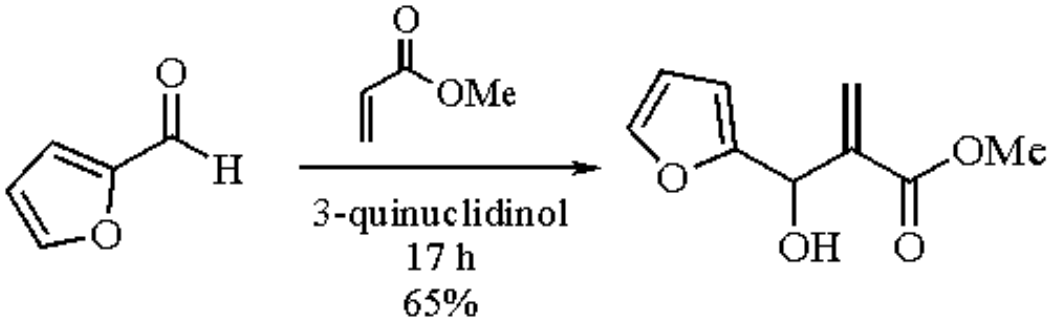

(6)

Synthesis of Monoesters.

Geminal diesters are converted to the corresponding monoester with quinuclidinol (eq 7).[7] Other bicyclic amines such as DABCO and ***1,5-Diazabicyclo[4.3.0]non-5-ene*** (DBN) can also be used.[7] These cleavage conditions are advantageous in that they involve a one-step process compared with two steps involving formation of the monoacid followed by esterification. More importantly, these reaction conditions are perfectly suited to cases where acid or base labile groups are present or where the compounds are not soluble in aqueous solutions.

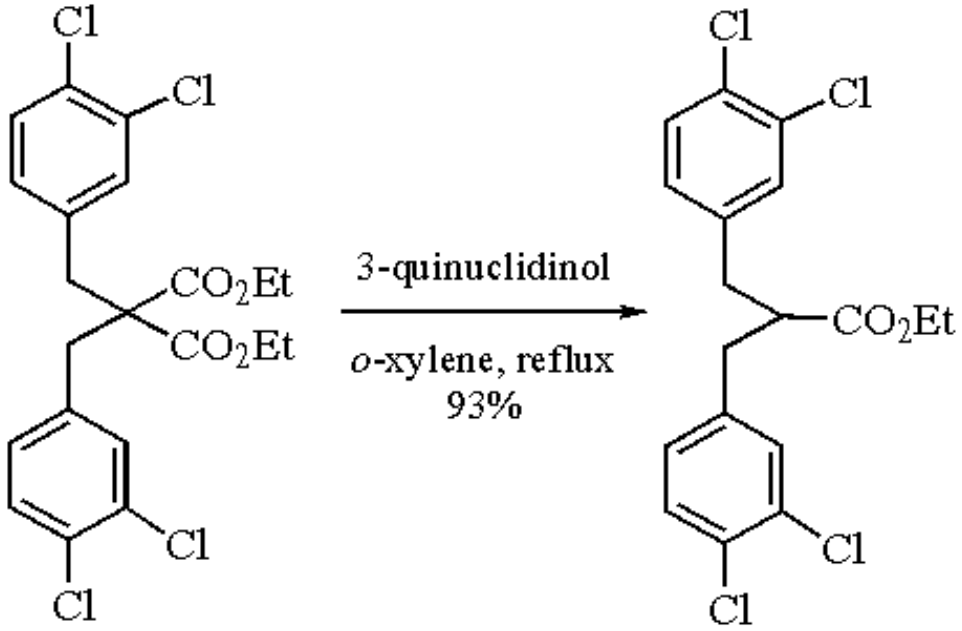

(7)

Oxygenation of Branched Aldehydes to Ketones.

Copper-catalyzed oxygenation of α-branched aldehydes in weakly basic media yields ketones having one less carbon (eq 8).[8] Van Rheenen found that the optimum reaction conditions use ***Copper(II) Acetate*** complexed with 2,2´-bipyridyl or 1,10-phenanthroline as catalyst and bicyclic amines such as DABCO or 3-quinuclidinol in polar aprotic solvents rather than in alcohols.[8]

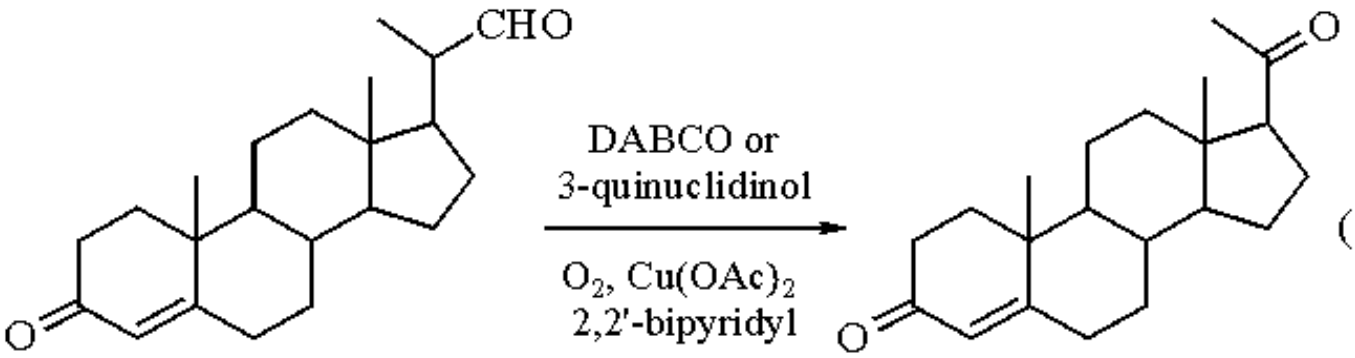

(8)

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Raney Nickel[1]

Ni

[106-51-4] · Ni · Raney Nickel · (MW 58.69)

(useful as a reducing agent for hydrogenation of organic compounds[1])

Solubility: insol all organic solvents and water.

Form Supplied in: black solid.

Preparative Methods: there are many types of Raney nickel; they differ based on their methods of preparation. These methods essentially determine the hydrogen content as well as the reactivities of various types of Raney nickel. The most popular W-type Raney nickels can be prepared as the seven different types listed in Table 1.

Table 1 Types of Raney Nickel

Type	NaOH/Al (molar)	NaOH soln. conc. (wt%)	Temp. (°C) (time, h)	Water wash method
W-1	1.35	17	115 120 (4)	Decant to neutral
W-2	1.71	20	75 80 (8 12)	Decant to neutral
W-3	1.73	20	50 (0.83)	Continuous to neutral
W-4	1.73	20	50 (0.83)	Continuous to neutral
W-5	1.80	21	50 (0.83)	Continuous to neutral
W-6	1.80	21	50 (0.83)	Cont. to neut. under H_2
W-7	1.80	21	50 (0.83)	Directly washed with EtOH[1c]

Handling, Storage, and Precautions: Raney nickel is generally stored in an alcoholic solvent, or occasionally in water, ether, methylcyclohexane, or dioxane. The activity of Raney nickel decreases due to loss of hydrogen over a period of about 6 months. Raney nickel ignites on contact with air and should never be allowed to dry.

Desulfurization.

The most widespread application of Raney nickel is the desulfurization of a wide range of compounds including thioacetals, thiols, sulfides, disulfides, sulfoxides, sulfones, thiones, thiol esters, and sulfur-containing heterocycles.

The well-known desulfurization of dithianes remains one of the most efficient methods for reductive deoxygenation of ketones. Recently, Rubiralta demonstrated an example in his synthesis of the aspidosperma alkaloid framework. Dithiane (**1**) was reduced to indole derivative (**2**) in 85% yield without reduction of the alkene (eq 1).[2]

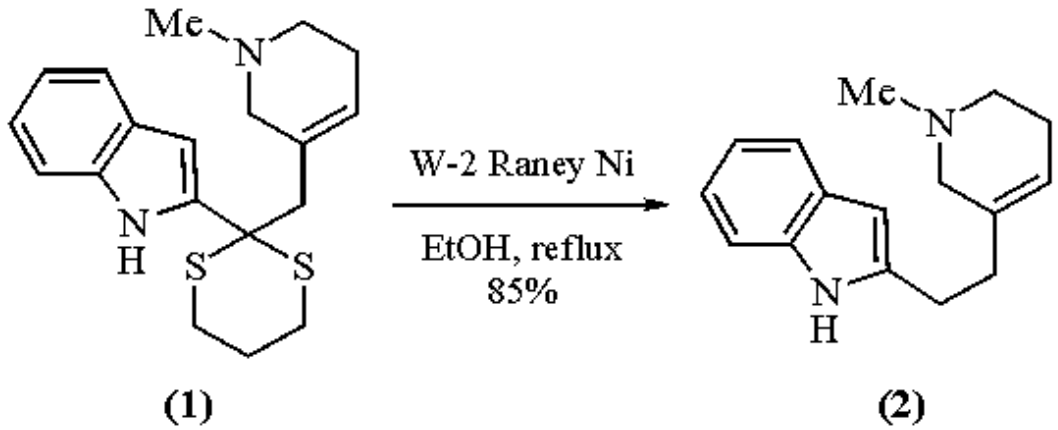

(1)

Raney nickel is frequently used to remove the sulfur atom of thiols,[3] sulfides, and disulfides from a carbon skeleton, regardless of whether the sulfur is attached to an alkyl carbon,[4] an aryl carbon,[5] or a carbon atom in a heterocycle.[6] Several examples are shown in eqs 2-5. A solvent effect was observed in the Raney nickel reduction of vinyl sulfide (**11**), which gave glycoside (**12**) in methanol, whereas the double bond remained intact to produce alkene (**13**) in THF (eq 6).[7]

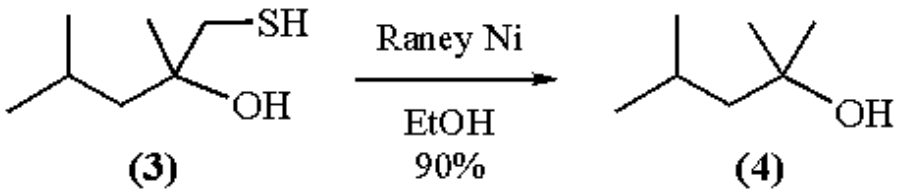

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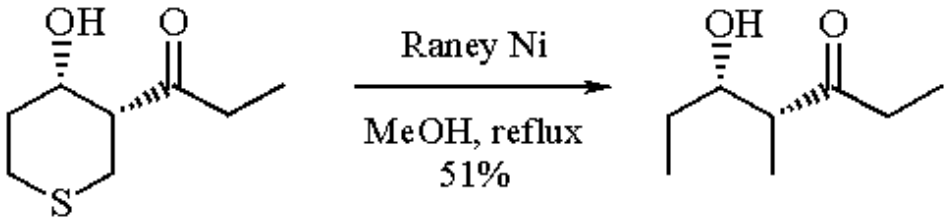

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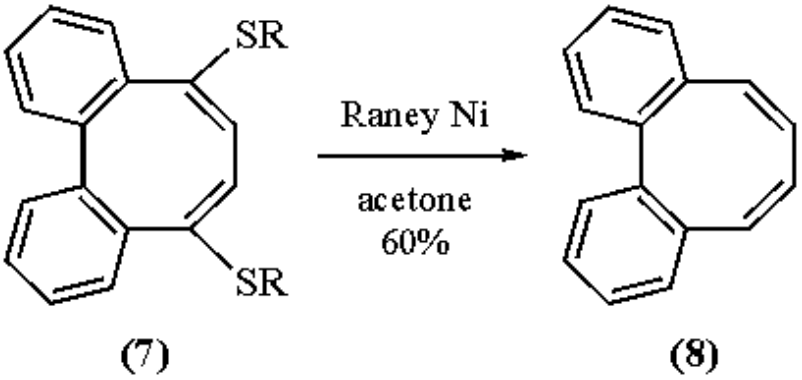

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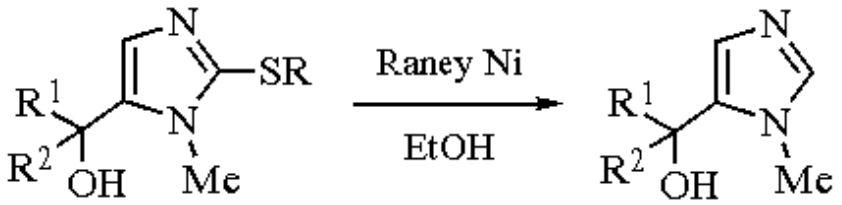

(9) (10) (5)

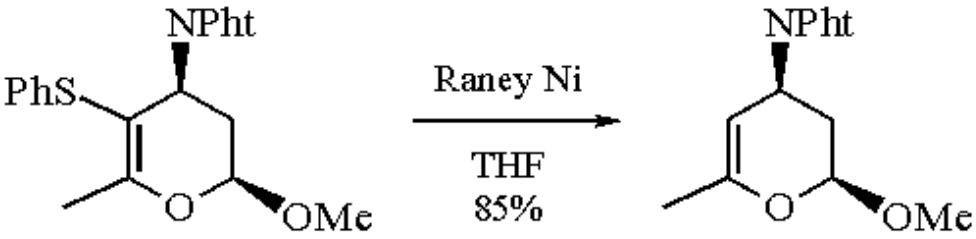

(11) Pht = phthaloyl (13)

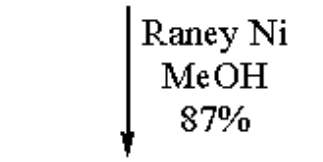

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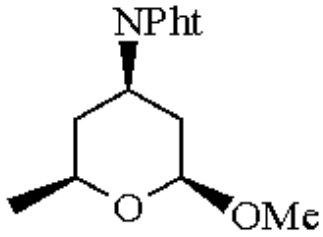

(12)

The sulfur atom can be part of a heterocycle. Högberg[8] and Tashiro[9] used Raney nickel to remove sulfur from thiophene derivatives (**14**) and (**16**) to give compounds (**15**) and (**17**), respectively (eqs 7 and 8).

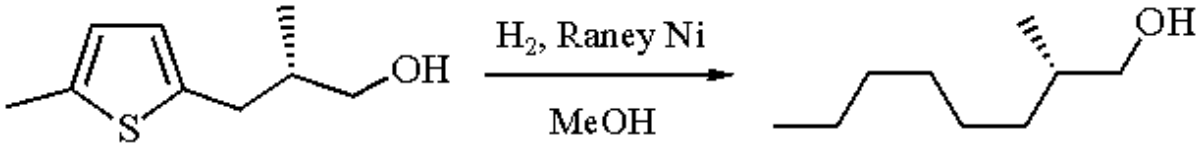

(14) (15) (7)

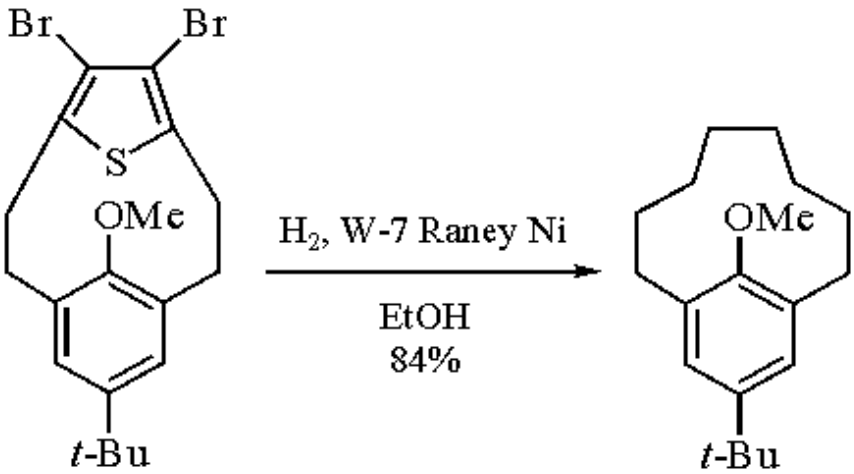

(16) (17) (8)

Raney nickel can remove the sulfinyl and sulfonyl groups from sulfoxides and sulfones under neutral conditions (eqs 9 and 10).[10,11] Cox demonstrated the cleavage of both sulfur-carbon bonds in sulfoxide (**22**) and noted that the stereogenic center remained untouched (eq 11).[12]

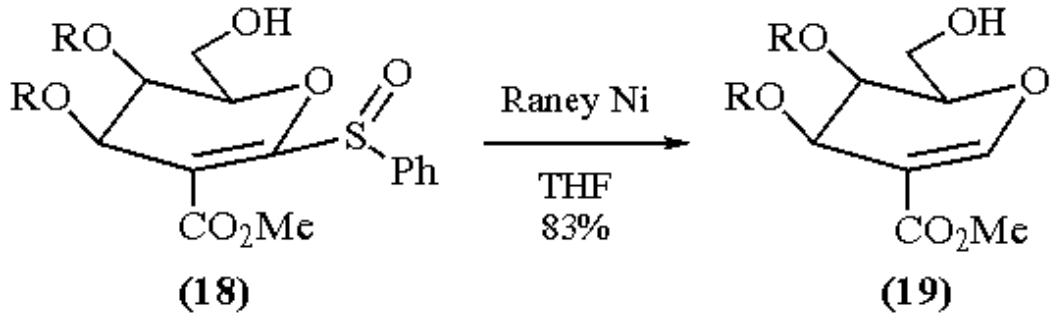

(9)

(18) **(19)**

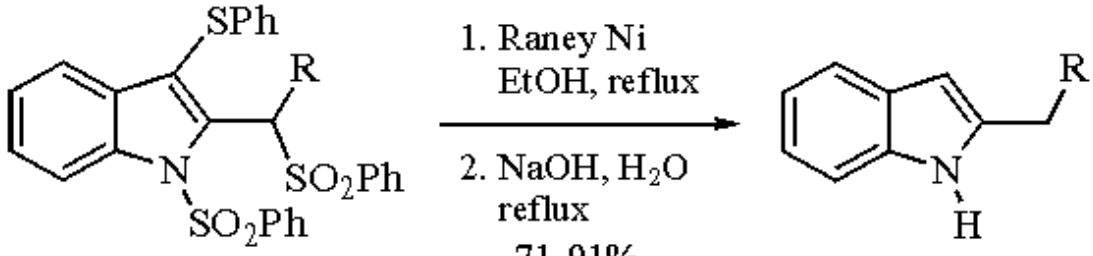

(10)

(20) R = alkyl, aryl **(21)** 3 examples

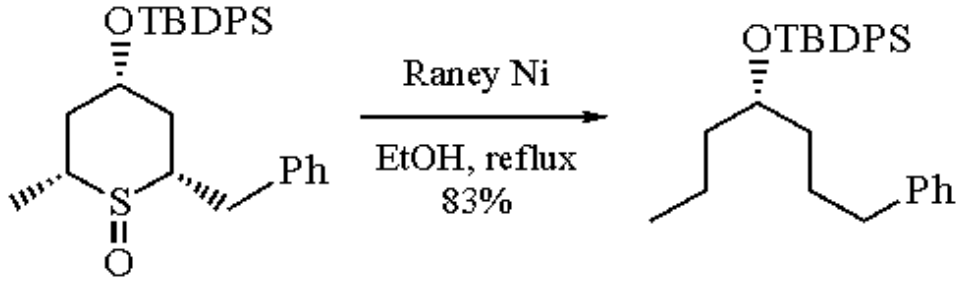

(11)

(22) **(23)**

Some thioamides are reduced by Raney nickel to the corresponding imines. Two typical examples are shown in eqs 12 and 13.[13,14] Thiones have been reported to give alkanes, but only low or unstated yields are reported (eqs 14 and 15).[15,16]

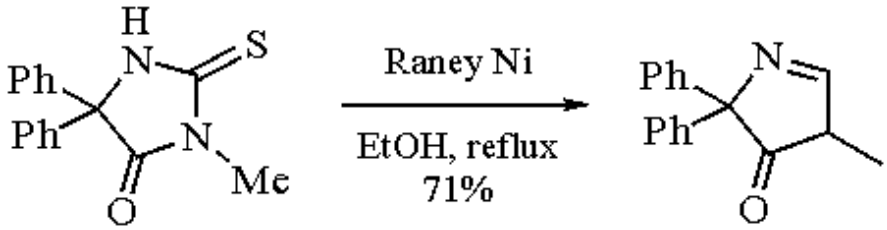

(12)

(24) **(25)**

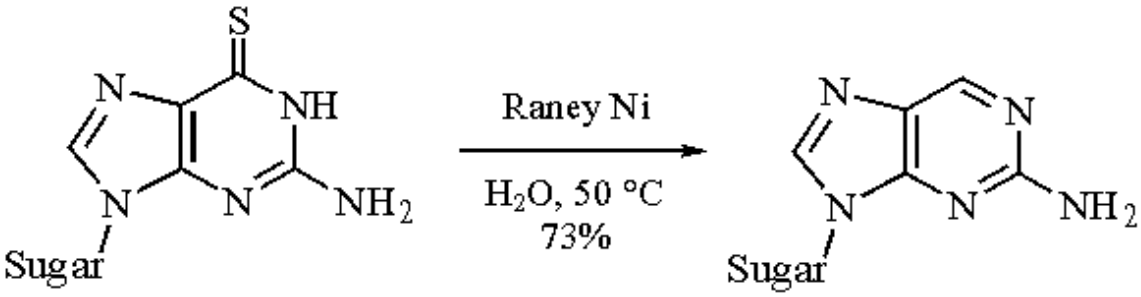

(13)

(26) **(27)**

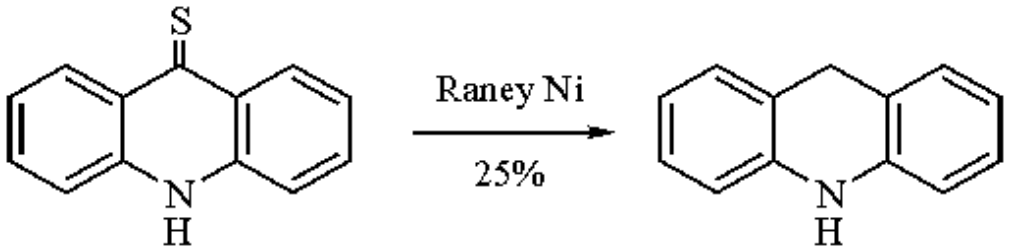

(28) (29) (14)

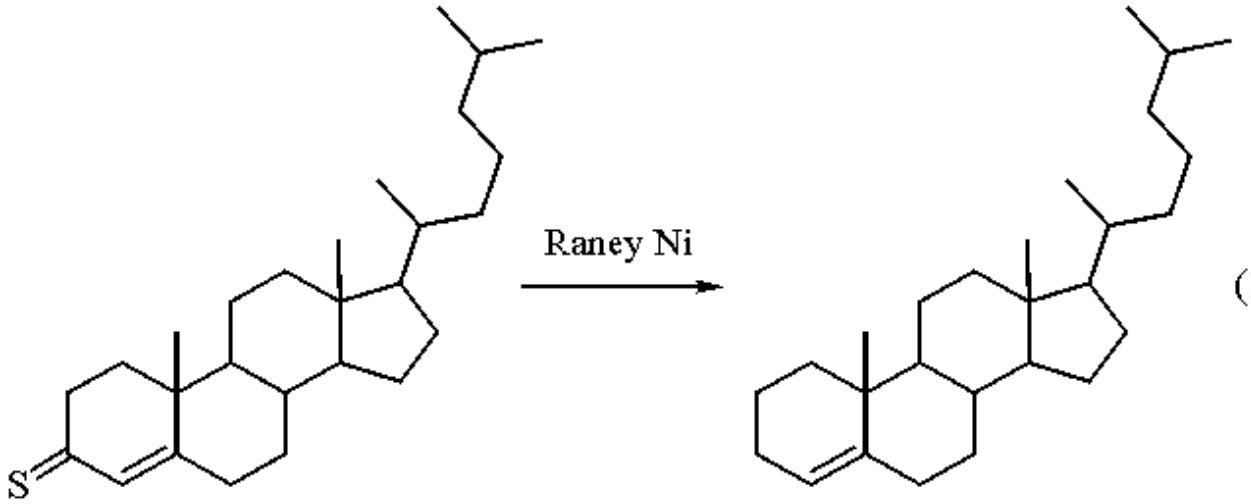

(30) (31) (15)

Liu and Luo[17] used Raney nickel to reduce glycidic thioester (**32**) to the corresponding 1,3-diol (**33**) in good yield (eq 16). With ***Sodium Borohydride*** at ambient temperature or ***Lithium Aluminum Hydride*** at -78 °C, glycidic thioester (**32**) was reduced chemoselectively to furnish 2,3-epoxy alcohol (**34**) in 82% yield (eq 16).[17]

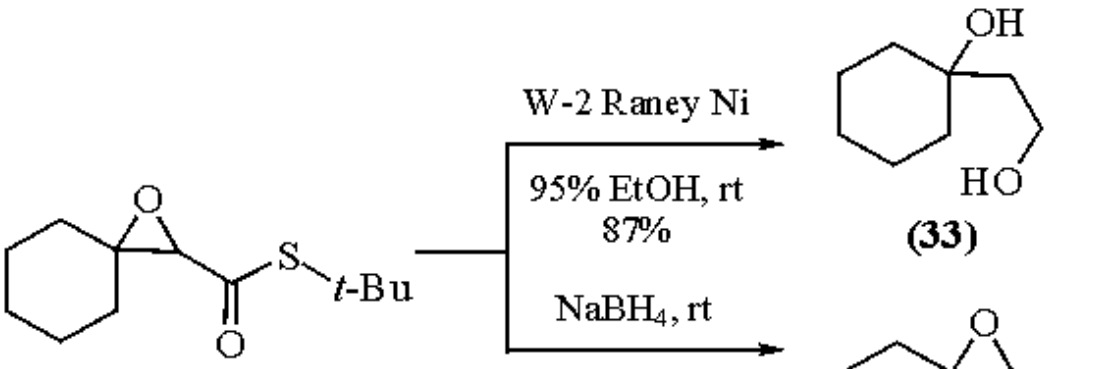

(32) (33) (34) (16)

Deoxygenation and Deamination.

Besides the widely used desulfurization process, Raney nickel can be used to reduce benzylic nitrogen and oxygen atoms. Behren's report shows the partial deoxygenation of diol (**35**) to mono alcohol (**36**) in 75-96% yields (eq 17).[18] Ikeda used W-2 Raney nickel to remove the benzyl protecting group from compound (**37**). However, partial epimerization occurred in this reaction to produce a 3.7:1 mixture of the 6α- and 6β-alcohols (**38**) (eq 18).[19] Azetidine (**39**) was opened by Raney nickel in refluxing ethanol, to give acyclic amine (**40**) in 88% yield (eq 19).[20]

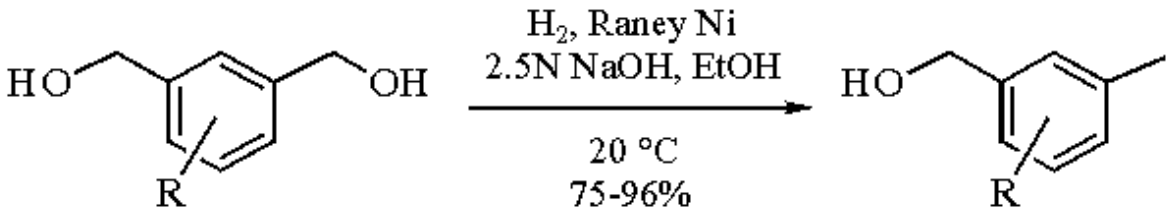

(17)

(35) **(36)**

R = H, CN, NH_2, CH_2NH_2

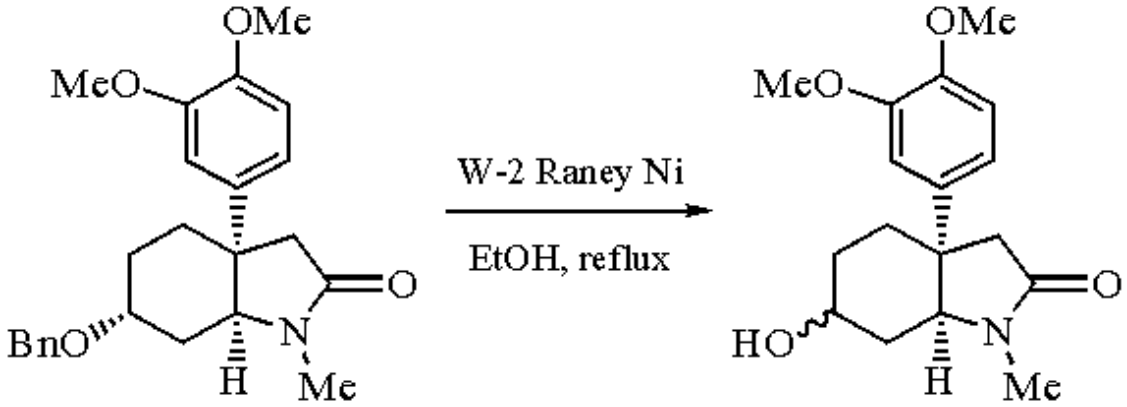

(18)

(37) **(38)**

α:β = 3.7:1

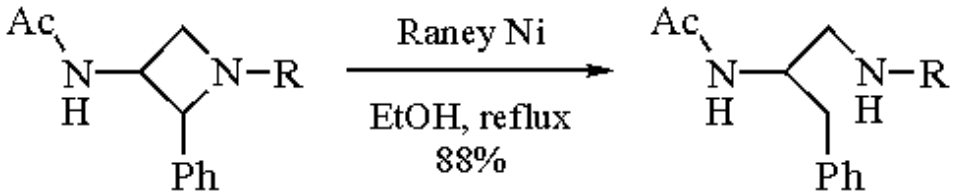

(19)

(39) **(40)**

Krafft reported that tertiary alcohols were also deoxygenated to alkanes by Raney nickel (eq 20). On the other hand, primary alcohols were oxidized to aldehydes and then subsequently decarbonylated (eq 21), and secondary alcohols were oxidized to the corresponding ketones (eq 22).[21]

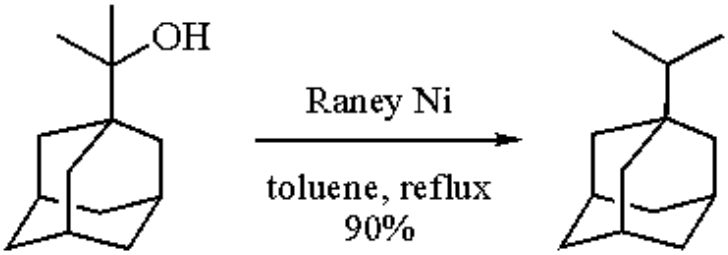

(20)

(41) **(42)**

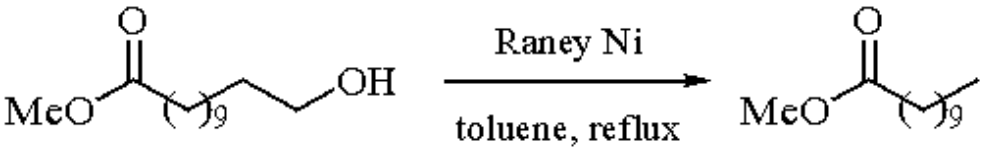

(21)

(43) **(44)**

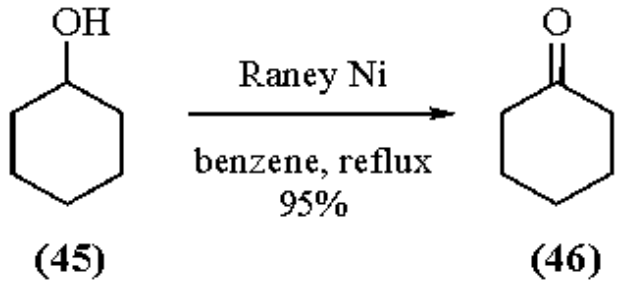

(22)

Recently, Ohta reported Raney nickel would deoxygenate *N*-oxide (**47**) to pyrazine (**48**), while ***Phosphorus(III) Bromide*** gave many side products (eq 23).[22]

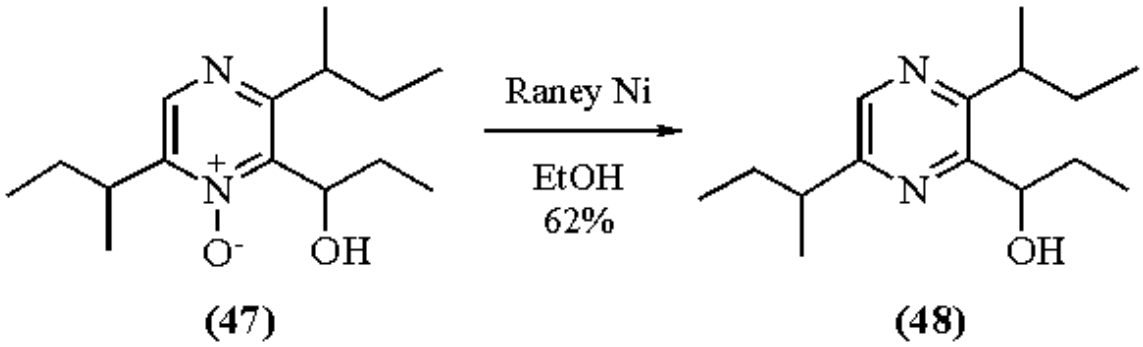

(23)

Cleavage of Heteroatom-Heteroatom Bonds.

Both N-N and N-O bonds can be cleaved by Raney nickel in the presence of hydrogen. Alexakis reported that hydrazine (**49**) was easily cleaved to the free amine by Raney nickel under hydrogen atmosphere, then protected to give carbamate (**52**) (eq 24).[23] In addition, he found even hindered hydrazines (**50**) and (**51**) were successfully deaminated to free amines (**56**) and (**57**), respectively, without racemization if the reactions were assisted by ultrasound.[24]

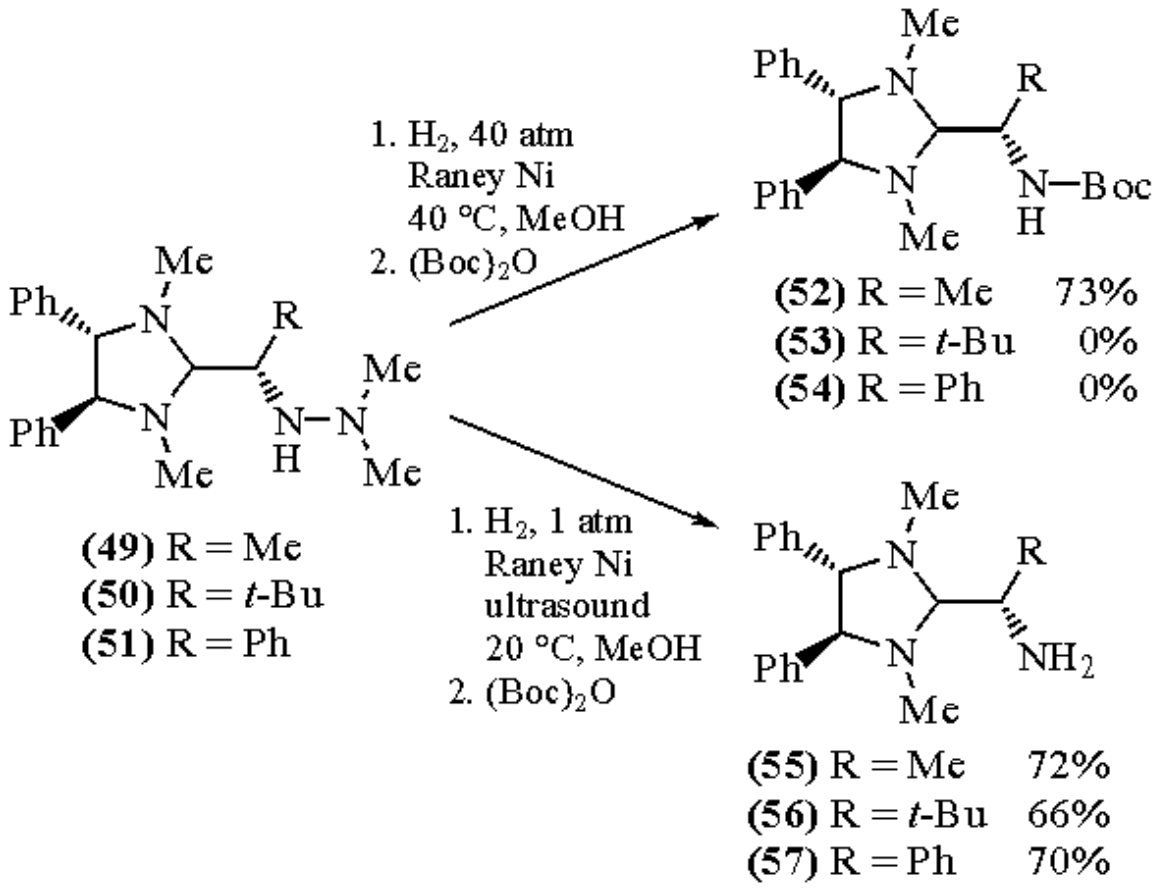

(24)

The N-O bonds in 1,2-oxazine (**58**) and isooxazolidine (**60**) were cleaved by Raney nickel via a radical mechanism to produce 1,4-diketone (**59**) and β-lactam (**61**), respectively (eqs 25 and 26).[25,26]

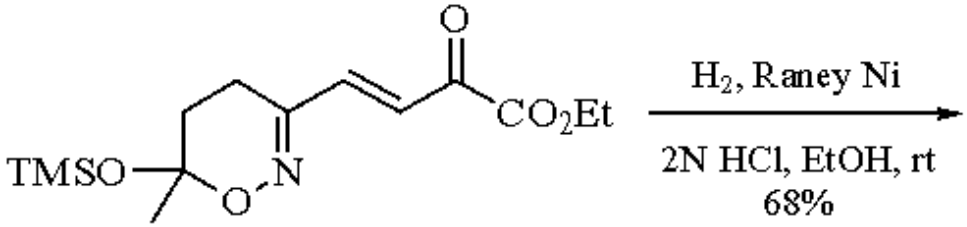

(58)

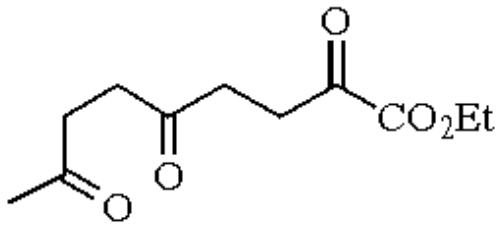

(59) (25)

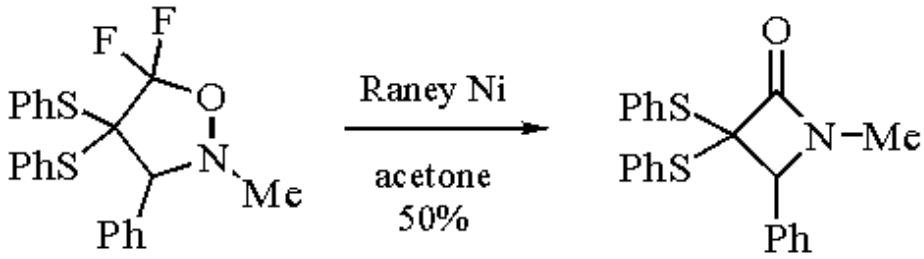

(60) (61) (26)

Hydrogenation of Multiple Bonds.

Applications in this area are not very popular for Raney nickel. Raney nickel in dilute base is, however, an effective reagent for reduction of pyridines to the corresponding piperidines. The reaction is accelerated by substituents in the 2-position and by electron-withdrawing groups in the 3- and 4-positions, while electron-donating groups in the 3- and 4-positions retard the reaction (eq 27).[27] Occasionally, Raney nickel is used to reduce acyclic multiple bonds. An example for selective reduction of triple bonds to *cis* double bonds is shown in eq 28.[28]

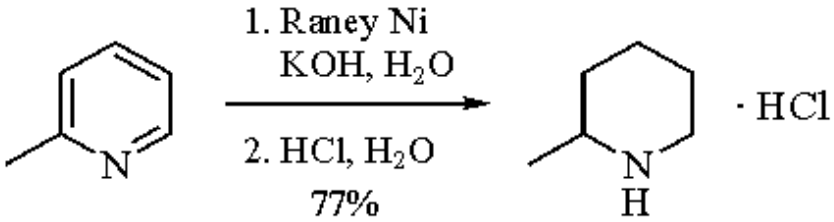

(62) (63) (27)

18 other examples

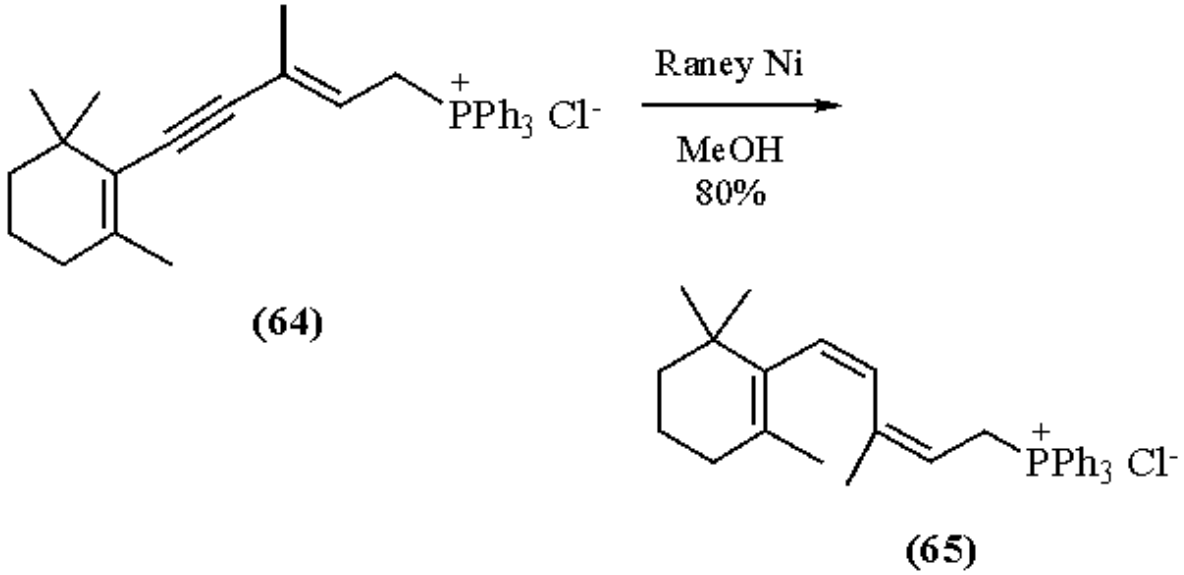

(28)

Deselenation.

Similar to the desulfurization process, Raney nickel can be used to remove selenium from selenoketones, diselenides, selenides, and selenooxides. Typical examples are shown in eqs 29-33.[29-31] Moreover, Raney nickel has been used for a hydrodetelluration of chiral compound (**76**) without any racemization (eq 34).[32]

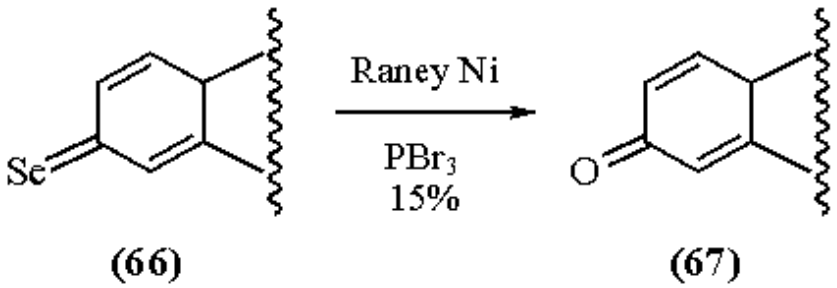

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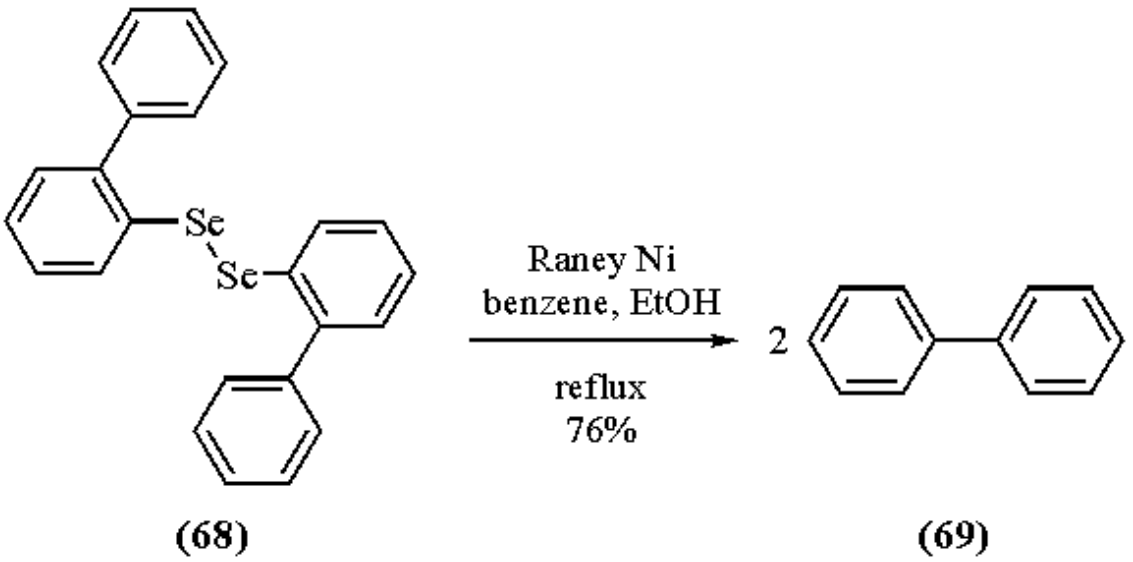

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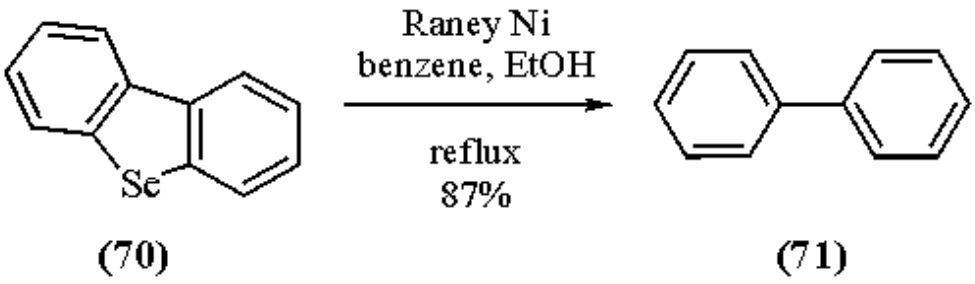

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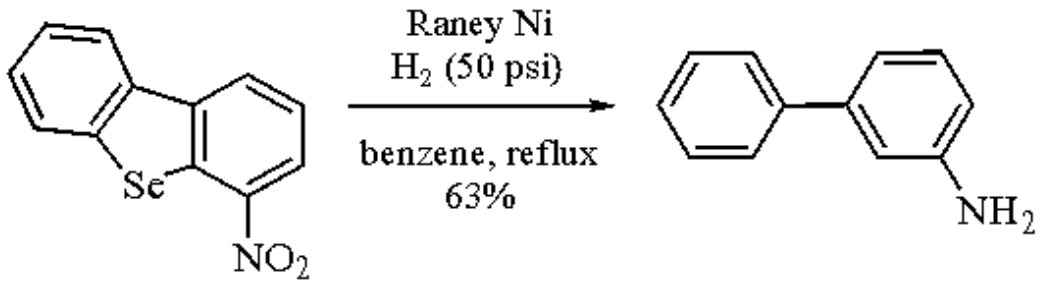

(72) (73) (32)

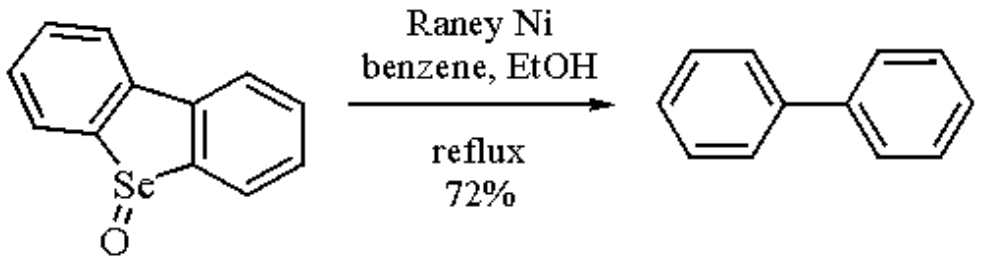

(74) (75) (33)

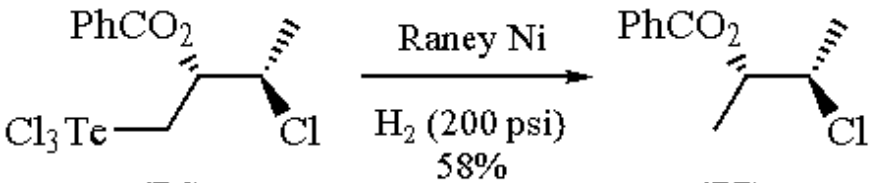

(76) (77) (34)

Reductive Amination of Carbonyl Groups.

Reactions of this type can be accomplished by reduction of intermediate imines or oximes.[33-35] Recently, Chan and co-workers found that Raney nickel can be an efficient catalyst in the preparation of phenylalanine. Treatment of sodium phenylpyruvate with either ***Ammonia*** gas or aqueous ammonia solution in the presence of Raney nickel under 200 psi pressure gave >98% of phenylalanine (eq 36). Other α-keto esters such as 4-hydroxyphenylpyruvic acid, pyruvic acid, and benzoyl acid also gave the corresponding amino acids in excellent yield.[36]

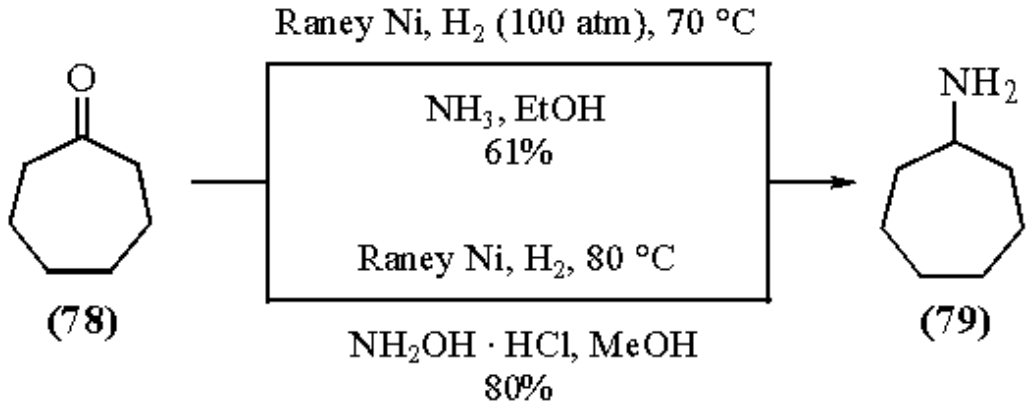

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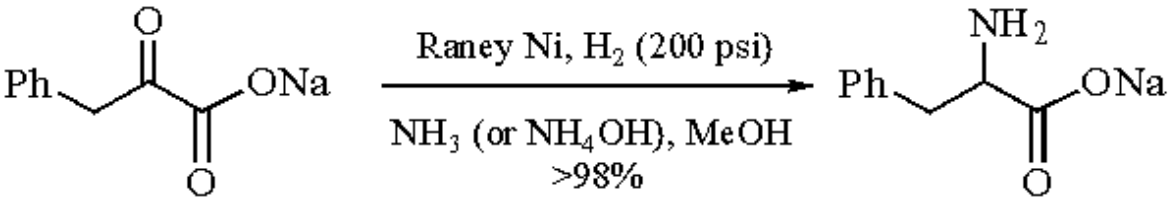

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Asymmetric Reduction.

Recently, asymmetric synthesis has become a center of attention for synthetic chemists. The use of Raney nickel and tartaric acid was recently reported by Bartok. Reduction of ketone (**82**) gave alcohols (**83**) and (**84**) as a 92:8 mixture in 70% chemical yield.[37] Takeshita et al.[9] also reported an asymmetric reduction of β-keto ester (**85**) to give the corresponding β-hydroxy ester (**86**) in 80% ee (eq 38). In addition, it was found that enantioselectivities were improved by treatment of the Raney nickel with ultrasound prior to use.[38] Blacklock et al. reported an asymmetric reductive amination of α-keto ester (**88**) in which they used the chiral amine (**87**) instead of a chiral catalyst. The result, shown in eq 39, indicates that the amino ester (**89**) was produced in 80% yield with 74% de.[39]

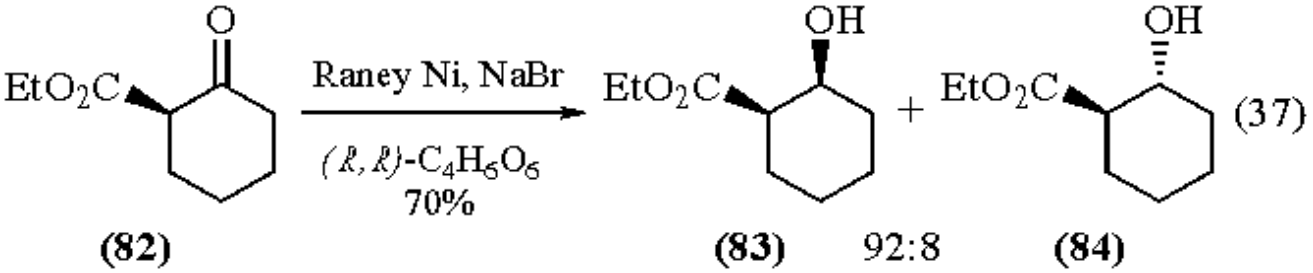

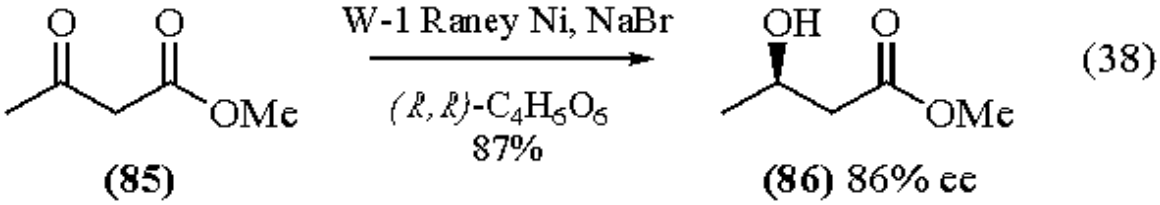

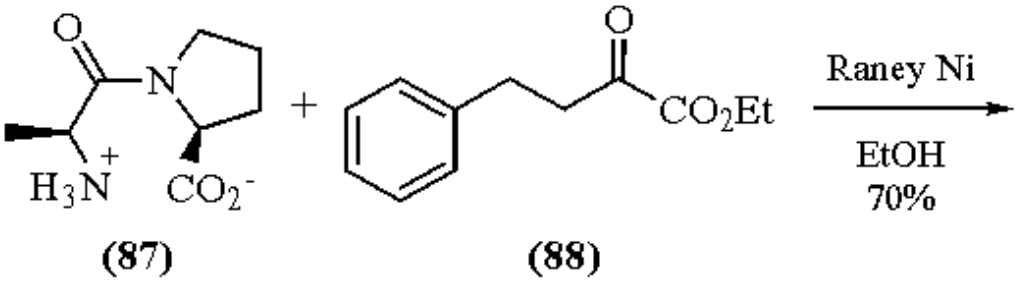

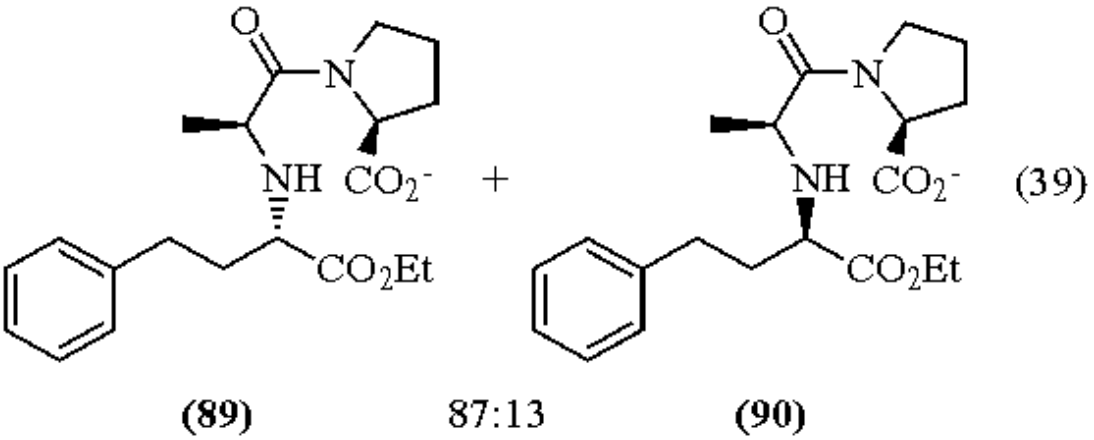

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Rhodium on Alumina[1]

Rh/Al_2O_3

[7440-16-6] · Rh · Rhodium on Alumina · (MW 102.91)

(active catalyst under mild conditions for hydrogenation of unsaturated compounds including aldehydes, ketones,[1h,7] and aromatic carbocyclic[1] and heterocyclic structures;[1a,g,k] high stereospecificity and low hydrogenolytic activity)

Form Supplied in: rhodium supported on alumina, carbon, or silica containing 0.5-5.0% of the metal are available commercially.

Handling, Storage, and Precautions: the unused supported catalysts are not pyrophoric but rhodium supported on a finely divided carbon, like carbon itself, can undergo a dust explosion. After use, the catalysts are likely to contain adsorbed hydrogen which may ignite when the catalyst dries.[1f,h] Use in a fume hood.

Introduction.

The catalytic properties of rhodium, like the other platinum metals, depend secondarily on the support. ***Alumina*** is commonly used but other supports may furnish advantages in particular circumstances. Rhodium black avoids possible influences of the support.[2] The high activity of rhodium often permits its use at room temperature and atmospheric pressure but higher temperatures and pressures may be used to advantage.

Alkenes and Alkynes.

Although rhodium catalyzes the hydrogenation of alkenes, dienes, and alkynes under mild conditions, it is not the most selective platinum catalyst if double bond migration or isomerization can adversely affect the desired stereochemistry or if a selective hydrogenation of a diene or alkyne is sought.[1h] The tendency of rhodium for alkene isomerization relative to hydrogenation is only a little greater than that of ruthenium (see ***Ruthenium Catalysts***), which results in the formation of a greater fraction of *cis*-1,2-dimethylcyclohexane using Ru (93.5%) than using Rh (87.6%) in hydrogenating 1,2-dimethylcyclohexene at 25 °C/1 atm H_2.[3]

The hydrogenation of the double bond in vinyl or allylic compounds is achieved with some success with Rh but generally Pd or Ru is more effective, particularly with vinyl ethers.[1h] However, the high activity of Rh allows the reaction to be conducted at lower temperatures than with other metals. For example, the asperuloside tetraacetate, which contains both a vinyl and an allyl ether structural unit, was hydrogenated over Rh/C starting at -30 °C and raising the temperature slowly during 3 h to 0 °C to give a virtually quantitative yield of the tetrahydro product (eq 1).[4]

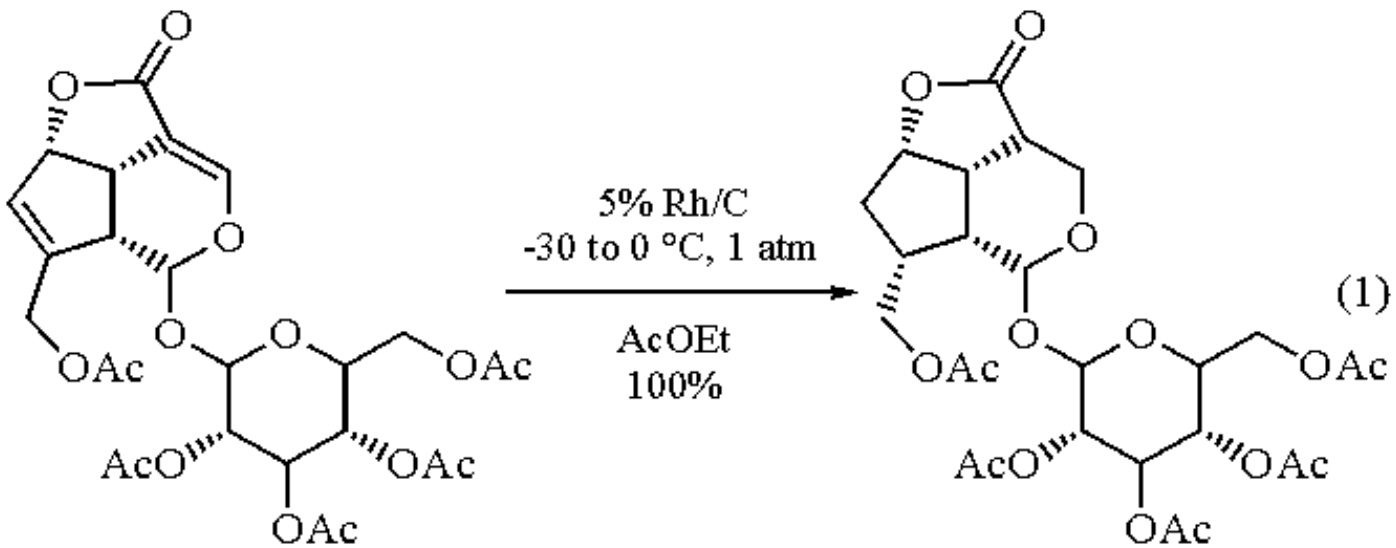

The activity of Rh/C also is shown by the hydrogenation of the double bond in the β-acyloxy-α,β-unsaturated esters and ketones without causing hydrogenolysis as given by ***Platinum(IV) Oxide*** (eq 2).[5]

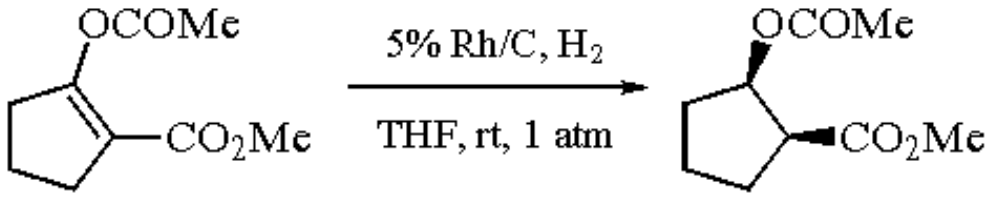

(2)

Rh/Al_2O_3 in combination with ***Palladium on Carbon*** effected the saturation of an isomer of dodecamethyl[6]radialene (**1**) to all-*trans*-hexaisopropylcyclohexane (**2**) when separately the same catalysts failed (eq 3).[6] Apparently the reduction required high reactivity for both hydrogenation (Rh) and alkene isomerization (Pd).

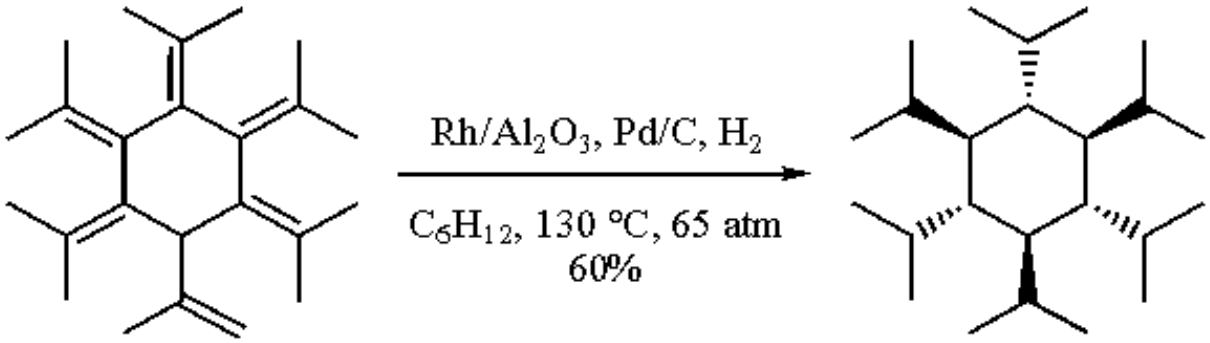

(3)

(1) (2)

Aldehydes and Ketones.

Rhodium is an excellent catalyst for the hydrogenation of aldehydes and ketones under mild conditions.[1a,e,h,7] The reduction of aliphatic carbonyl compounds can be accomplished without the hydrogenolysis of susceptible groups attached elsewhere in the molecule.

In the hydrogenation of cyclohexanones, rhodium excels in the formation of the axial hydroxyl group from monosubstituted compounds; the effect is especially notable for alkyl substituents.[1d,8] With methoxy groups in place of alkyl groups at the 2- and 4-positions the fraction of axial isomer increases markedly for Pd, Ir (see ***Iridium***), and Pt but not Rh.[9a] Hydrogenation of unhindered cyclohexanones in isopropyl alcohol or THF in the presence of small amounts of ***Hydrogen Chloride*** gives excellent yields of axial alcohols (eq 4).[9b] Steroidal 3,17- and 3,20-diones are selectively hydrogenated at C-3 to yield the corresponding 3-axial-hydroxy ketones.

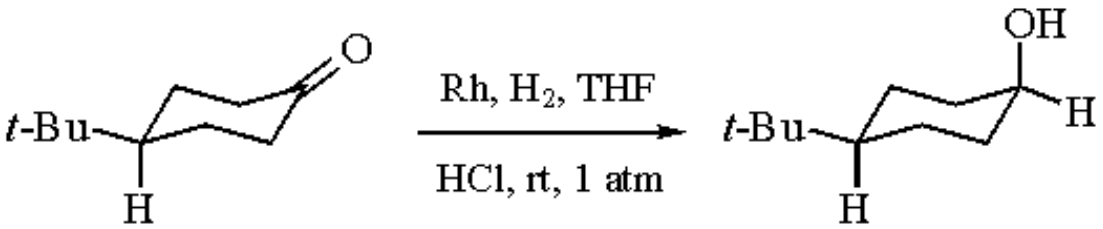

(4)

Imines.

Imines are thought to be important intermediates in the hydrogenation of nitriles, anilines, and oximes.[1] ***Ammonia*** and primary amines condense with aldehydes to give imines which may be hydrogenated. Freifelder describes the conversion of 3,4-dimethoxybenzaldehyde to the benzylamine over Rh/C in 95% ethanol containing ammonia (aq) and NH_4OAc, (rt, 3 atm, 64% yield).[1k]

Nitriles.

The products of hydrogenating a nitrile depend on the catalyst and whether the nitrile is aliphatic or aromatic.[1a,h] The reaction conditions including the solvent, the temperature, and the H_2 pressure, are important variables. Rhodium catalysts are most useful in the preparation of either primary or secondary amines.

The hydrogenation of an aliphatic nitrile leads to the formation of an imine which in turn may be hydrogenated to a primary amine.[1a,g,h] However, secondary amines are often the principal product, which apparently follows the condensation of the imine and the primary amine.[1g] Whether the condensations occur in the homogeneous medium, as first proposed by von Braun et al.,[10] or on the surface of the catalyst, is unsettled.[11] Recently, the analysis of a kinetic study of the hydrogenation of propionitrile on Rh/C and Rh/Al_2O_3, to form propylamine and dipropylamine, led to the claim that the results do not support the proposal that the condensations occur in the liquid phase.[11] A mechanism involving only surface reactions is proposed to explain the authors' results as well as the literature record.

The catalyst's support influences the effect of increasing pressure on the distribution of the products of hydrogenating pentanenitrile in methanol at rt.[12] At 4 atm, Rh/C, Rh/Al_2O_3, and Rh_2O_3 mainly yield dipentylamine (93%, 87%, and 77% respectively). Raising the pressure increases the yield of the primary amine. At 90 atm it is the sole product from unsupported Rh (Rh_2O_3), 54% yield is obtained from Rh/Al_2O_3, and 29% yield from Rh/C, the remainder being the secondary amine. At an intermediate pressure (50 atm), Rh/C yields only the secondary amine.[1g] Using Rh/C in the presence of a large excess of butylamine (mole ratio 1.7-6.6) the yield of butylpentylamine is 95-100%.[1g]

Aromatic nitriles are hydrogenated over Rh/C under mild conditions to dibenzylamines in excellent yields (25 °C, 4 atm).[1g]

Most recently, acetic acid was shown to be an excellent solvent for the Rh/Al_2O_3 or Rh/C catalyzed hydrogenation of aliphatic, aromatic carbocyclic, and aromatic heterocyclic nitriles to secondary amines (eq 5).[13] 3-Hydroxypropanenitrile formed a tertiary amine as a single isomer (eq 6) and the reduction of the tosylate of β-cyanoalanine formed a lactam (eq 7).

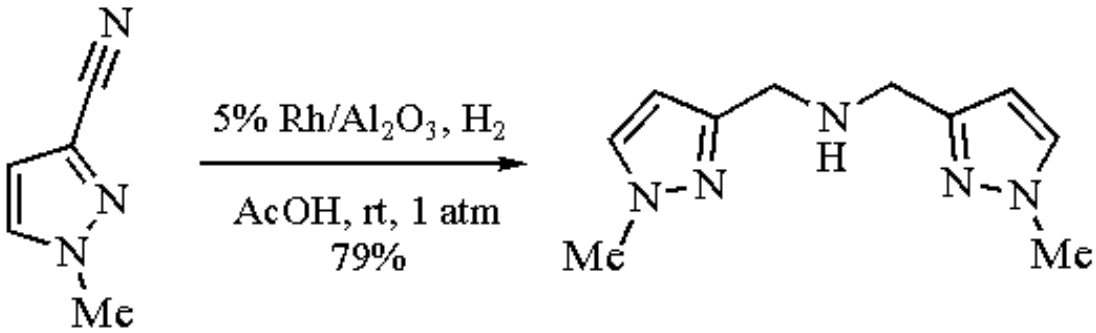

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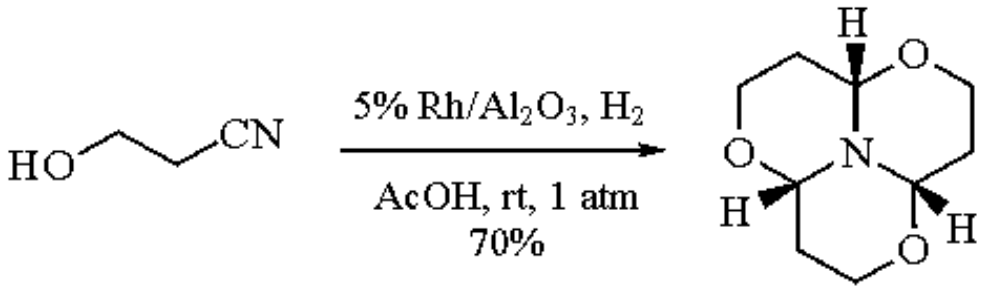

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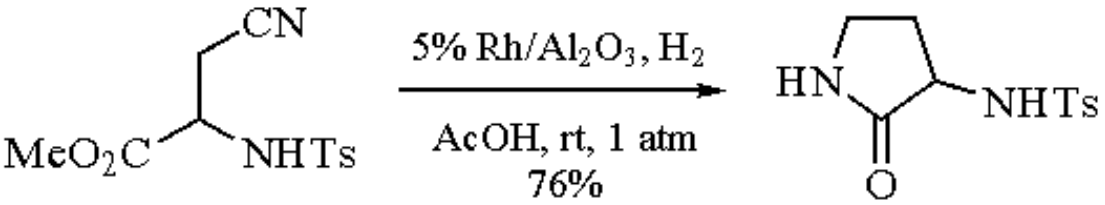

(7)

Oximes.

Although few examples of its use for the reduction of oximes have been recorded, rhodium has given excellent results, being especially useful in place of catalysts which yield excessive amounts of secondary amines.[1h] Freifelder et al. found the 5% Rh/Al_2O_3-catalyzed hydrogenation of cycloheptanone oxime in methanol (60 °C, 0.75-1.0 atm) gave an 80% yield of cycloheptylamine.[1a,14] 3-Amino-2-methyl-2-butanone and 1-(1-aminoethyl)cyclohexanol were prepared by the 5% Rh/Al_2O_3-catalyzed hydrogenation of the oximes of 3-hydroxy-3-methyl-2-butanone and 1-acetylcyclohexanol (eq 8) in 90-92% yields.[15]

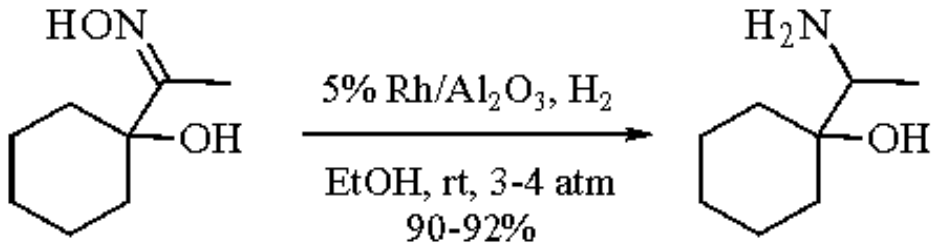

(8)

Carbocyclic Aromatic Compounds.

Rhodium provides highly active catalysts for the hydrogenation of the aromatic carbocycle under mild conditions (25-80 °C and 1-3 atm).[1] It is particularly useful when hydrogenolysis of attached hydroxy or alkoxy groups or benzylic alcohols or ethers is to be avoided.[16] The selectivity of rhodium under mild conditions is shown by the Rh/Al_2O_3-catalyzed hydrogenation in acetic acid at room temperature of (2-methoxyphenyl)propan-2-one to *cis*-1-(2-methoxycyclohexyl)propan-2-one (eq 9).[17]

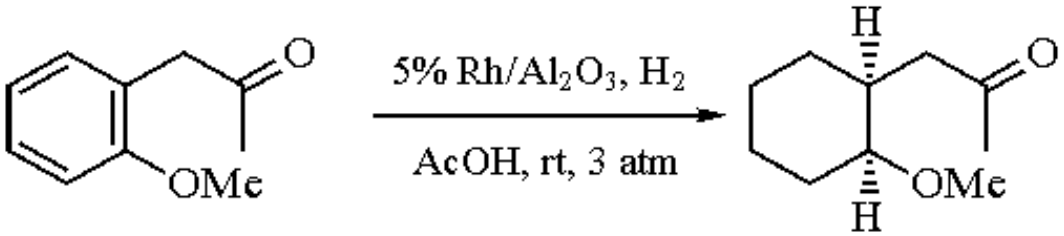

(9)

The consecutive addition of hydrogen atoms to the adsorbed cycle presumably proceeds through adsorbed cyclohexadienes and cyclohexenes, but only the desorption of the latter has been observed.[18] Of the platinum metals, ruthenium yields the largest amount of cyclohexenic intermediates when hydrogenated in the presence of water, which is also an unusual promoter of ruthenium's catalytic activity (see ***Ruthenium Catalysts***). In nonaqueous media, Rh yields the largest concentrations of cyclohexenic intermediates, as in the hydrogenation of *t*-butylbenzenes and *t*-butylbenzoic acids or esters in EtOH, HOAc, or saturated hydrocarbon solvents.[1f,19]

The Rh/C-catalyzed hydrogenation of 2-*t*-butylbenzoic acid initially yields *cis*-2-*t*-butylcyclohexanecarboxylic acid (75%), 6-*t*-butyl-1-cyclohexenecarboxylic acid (22%), and 2-*t*-butyl-1-cyclohexenecarboxylic acid (2%); *trans*-2-*t*-butylcyclohexanecarboxylic acid is formed only after the unsaturated intermediates begin to be reduced, which occurs when about 80% of the benzoic acid has been converted.[19] The result supports the earlier proposal that the formation of *trans* isomers in the hydrogenation of the xylenes arises from the saturation of desorbed cyclohexenes, even though the latter are undetected.[18]

The rate of the rhodium-catalyzed hydrogenation of the aromatic ring diminishes with alkyl substitution but with multiple substituents the arrangement of the groups affect the reactivity. The selective hydrogenation of the unsubstituted ring in *o*-anisylmethylphenylphosphine oxide illustrates that alkoxy groups also lower the reactivity of the benzene ring (eq 10).[20]

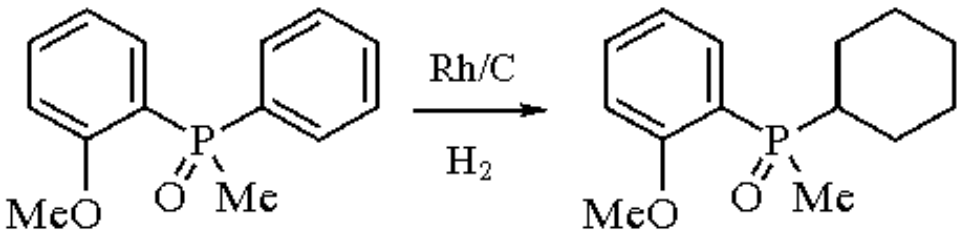

(10)

Although rhodium is generally effective in saturating polycarbocyclic aromatic compounds, it is not useful if the selective reduction of a particular cycle is sought.[1g-i]

Phenols and Phenyl Ethers.

A useful application of rhodium catalysts is the hydrogenation of phenols and phenyl ethers which are sensitive to hydrogenolysis, a particular problem in hydrogenating di- and polyhydroxybenzenes.[1a-c,21] Smith and Stump furnish an informative study, both kinetic and preparative, of the hydrogenation of hydroxybenzenes catalyzed by Pt and Rh/Al_2O_3.[22] The kinetic evidence indicates that the mechanism of formation of the cyclohexanols from the phenols does not require ketone intermediates, although some are formed. The authors propose that cyclohexenols are intermediates which may be reduced to cyclohexanols, hydrogenolyzed to cyclohexanes, or isomerized to cyclohexanones. The conversion of resorcinol to dihydroresorcinol (1,3-cyclohexandione) in high yield is described (eq 11).

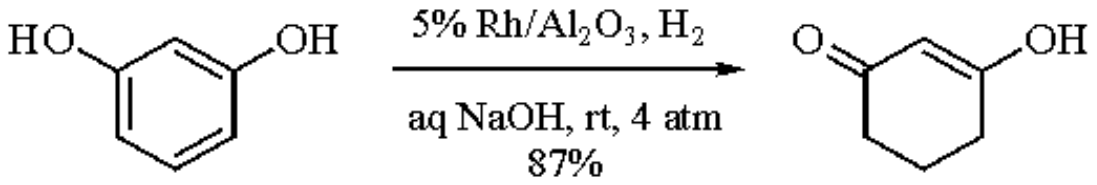

(11)

The hydrogenation of the cresols at 80 °C and 80-100 atm forms intermediate ketones in amounts which permit a quantitative analysis of the kinetics of the process to give a good estimate of the fraction of the cresol which is converted via the ketone to the cyclohexanol.[23] The stereochemistry of the final product is determined by the fraction formed via the cyclohexanone (knowing the fraction of *cis* and *trans* isomers it forms upon reduction), with the remainder of the product alcohol being the *cis* isomer. In principle, if cyclohexenol intermediates desorb from the catalyst, readsorption followed by the suprafacial addition of hydrogen could yield some *trans* isomers.[18]

The hydrogenation of 1-naphthol over Rh/Al_2O_3 in ethanol or methanol (25 °C, 4 atm) gave good yields of the isomeric decalols in the ratio of 13.3:3.2:1, the largest component being the *cis,cis* isomer; the configurations of the others were not specified; hydrogenolysis to decalin was low (3%).[24] Of the unsupported platinum metals used to catalyze the hydrogenation of 2-naphthol and the intermediate tetrahydro-2-naphthol (*t*-BuOH, 80 °C, 50 atm), Rh and Ru are highly stereospecific in forming the *cis,cis*-2-decalols and afford only small amounts of hydrogenolysis products.[25]

Anilines.

Ruthenium is generally the preferred catalyst for the hydrogenation of anilines to cyclohexyl amines (see ***Ruthenium Catalysts***), but rhodium catalysts have been used successfully.[1g,h] To diminish the formation of dicyclohexylamine, the best solvents were found to be *t*-butyl or isopropyl alcohol; the addition of a small amount of a strong base, preferably ***Lithium Hydroxide***, to Rh hydroxide furnished a catalyst that almost eliminated the diamine's formation.[26] Rhodium oxide prepared by $LiNO_3$ fusion with ***Rhodium(III) Chloride***, and used in isopropyl or *t*-butyl alcohol, leads to excellent yields of the isomeric methoxy- or ethoxycyclohexylamines from the corresponding anilines (eq 12).[27] Aniline has been converted to cyclohexylamine (96%, dicyclohexylamine 4%) catalyzed by Rh/Al_2O_3 in *i*-PrOH (23-26 °C, 55-70 atm).[28]

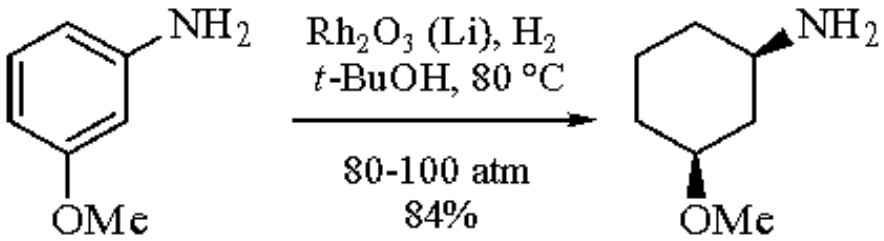

(12)

Heterocyclic Aromatic Compounds.

Rhodium has been used effectively to catalyze the hydrogenation of furans, pyrroles, pyridines, and other structures containing aromatic heterocycles.[1a,h]

Furans.

Furans are saturated under mild conditions with Rh/C. 2,5-Diferrocenylfuran is hydrogenated quantitatively to *cis*-2,5-diferrocenyltetrahydrofuran (5% Rh/C, rt, 1 atm, 2 h) (eq 13); after a time (6 h) at higher pressures (60 atm) the ether linkages are hydrogenolized to form 1,4-diferrocenylbutane.[29]

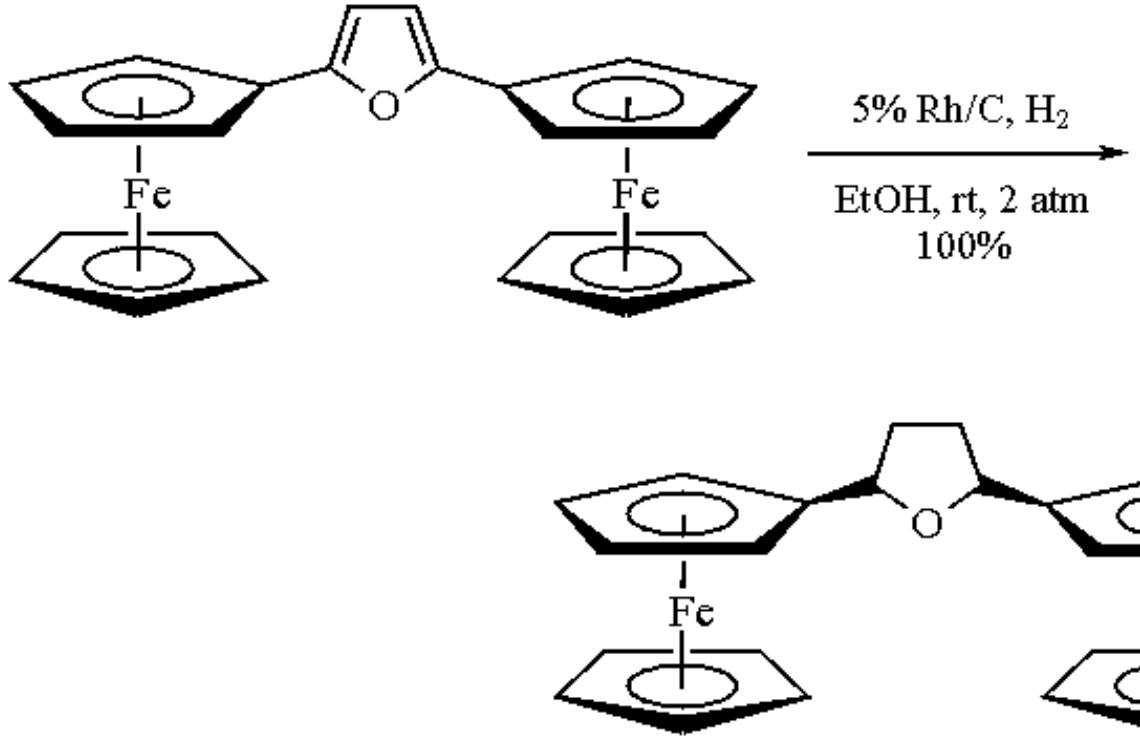

(13)

Pyrrole.

Rhodium is the preferred catalyst for the hydrogenation of pyrroles.[30] Pyrrole and 1-methylpyrrole, without solvent, are reduced to the pyrrolidines in high yield over Rh/Al_2O_3 (rt, 2-3 atm).[1g] In compounds containing an aromatic carbocycle which is not fused to the pyrrole, the carbocycle tends to be reduced preferentially,[1g] but the reverse selectivity has also been observed (eq 14)[31] and attributed to the trisubstitution in the carbocyclic ring.[1g]

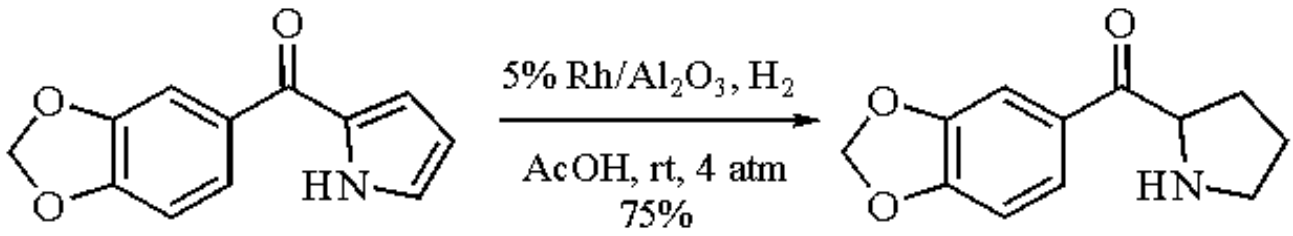

(14)

The high *cis* selectivity in the Rh/Al_2O_3-catalyzed hydrogenation of a 2,5-disubstituted pyrrole is illustrated in (eq 15).[32]

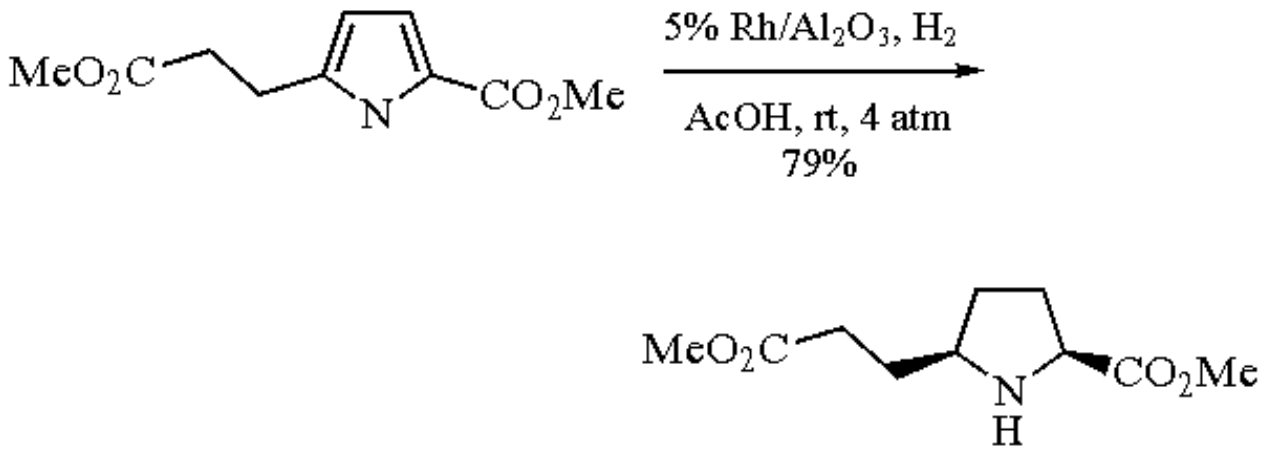

(15)

Pyridine.

For the hydrogenation of pyridines, rhodium is the most effective catalyst under mild conditions and maintains its advantage at higher pressures.[1h] 2,6-Dimethylpyridine in glacial AcOH is hydrogenated to *cis*-2,6-dimethylpiperidine over 5% Rh/Al_2O_3 (eq 16).[33]

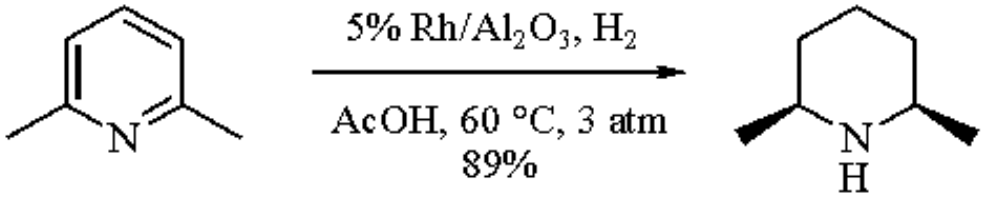

(16)

Although a variety of catalysts can affect satisfactorily the reduction of the 2- and 4-pyridinecarboxylic acids, the decarboxylation observed with the other catalysts in the hydrogenation of nicotinic acid (pyridine-3-carboxylic acid) is avoided by 5% Rh/Al_2O_3 in aqueous ammonia (eq 17).[34]

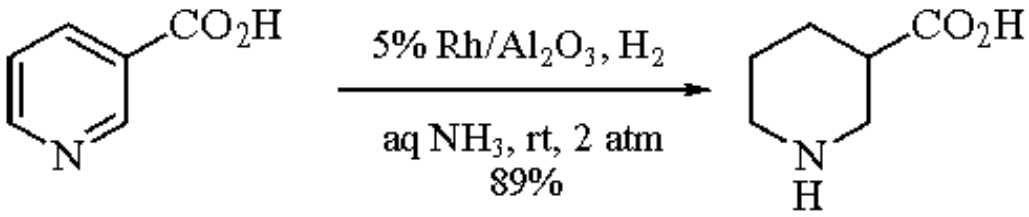

(17)

Generally, catalytic hydrogenation of pyridines with attached or fused aromatic carbocycles occurs preferentially in the pyridyl ring.[1h] 4-Benzylpyridine is converted quantitatively to 4-benzylpiperidine (5% Rh/C, EtOH, 60 °C, 4 atm).[35] The pyridine ring in (3-methoxy-2-pyridyl)-2-propanone is reduced selectively with Rh/Al_2O_3 in water containing one equiv of ***Hydrogen Bromide***, the selectivity is achieved only when the pyridylpropanone has been carefully purified by distillation (eq 18).[36]

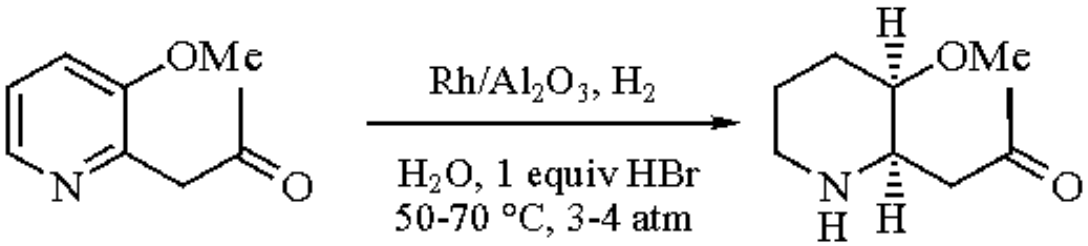

(18)

A variety of other nitrogen heterocycles have been hydrogenated successfully over rhodium catalysts.[1g,1k]

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Rhodium(III) Chloride

$RhCl_3$

[10049-07-7] · Cl_3Rh · Rhodium(III) Chloride · (MW 209.26) (hydrate)

[20765-98-4]

(isomerizes alkenes and strained carbocycles;[1] reduction precatalyst;[5] oxidation catalyst[7])

Physical Data: mp 450 °C.

Solubility: insol water; sol aq sodium hydroxide, aq potassium cyanide.

Form Supplied in: available as anhydrous solid and hydrated solid.

Analysis of Reagent Purity: elemental analysis.

Isomerizations.

Rhodium trichloride catalyzes the isomerization of alkenes, typically generating the thermodynamically more stable isomer. The exposure of an arylmethylenechroman-4-one to this reagent results in the efficient migration of the exocyclic alkene (eq 1).[1a] This example nicely illustrates the mild nature of the isomerization method as basic media induce degradation of the chroman-4-one, acidic media do not produce a reaction, and ***Raney Nickel*** affords a mixture of the desired alkene isomer and a reduced compound. Enones to which alkenes are attached are transformed into phenols upon reaction with rhodium trichloride (eq 2).[2] Unsaturated imines are converted to anilines via an analogous process (eq 3).[2] This reagent also allows the removal of an allyl protecting group from a wide variety of heteroatoms through an isomerization-hydrolysis pathway (eq 4).[3]

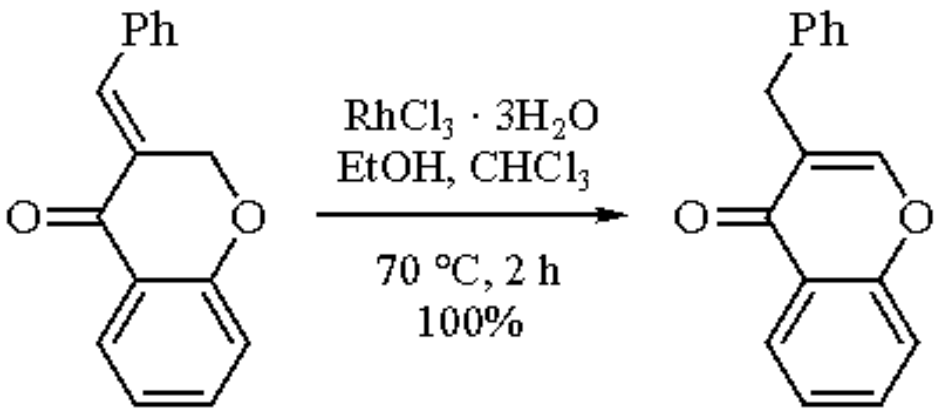

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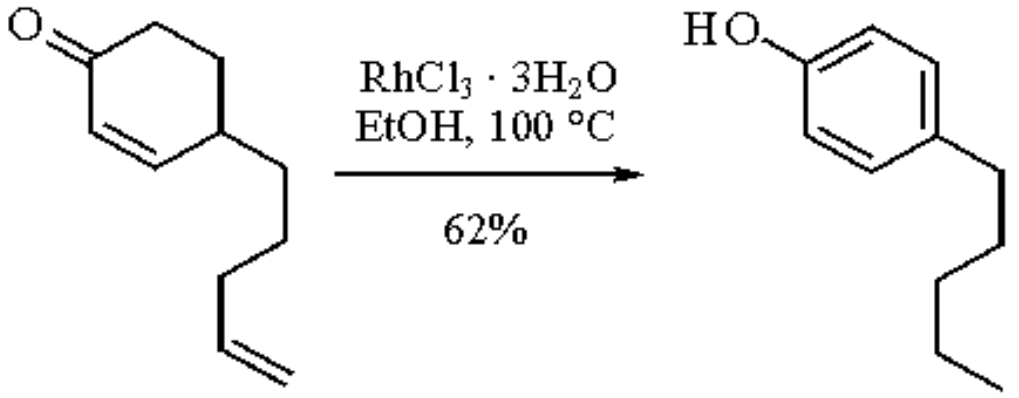

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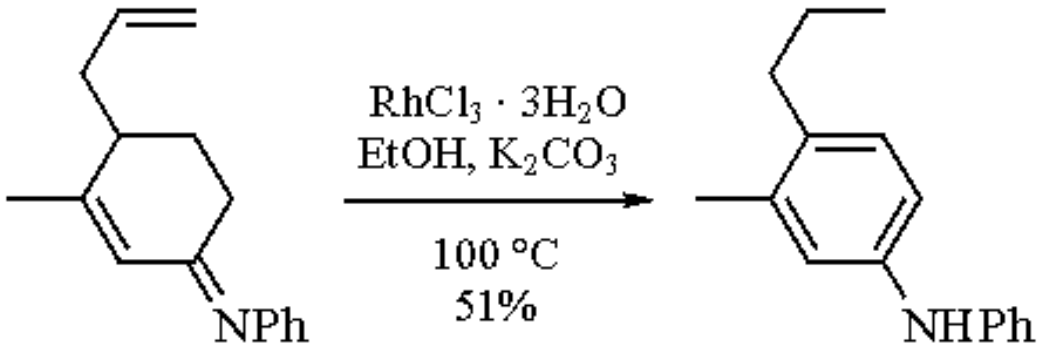

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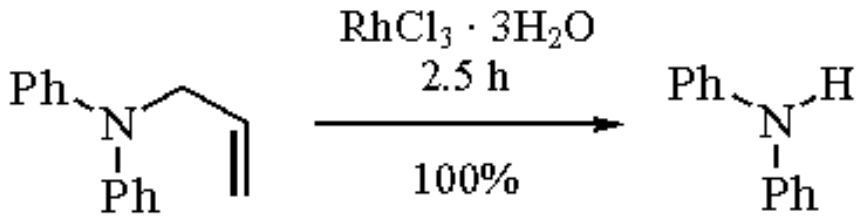

(4)

Furthermore, rhodium trichloride can isomerize strained carbocycles (eq 5).[4] In comparison, Ir^{III}, Ru^{III}, and Pt^{IV} are effective in bringing about similar rearrangements; Fe^{III}, Ni^{II}, and Hg^{II} are not active in the same fashion. Deuterium exchange studies indicate that this process most likely involves a metal hydride.

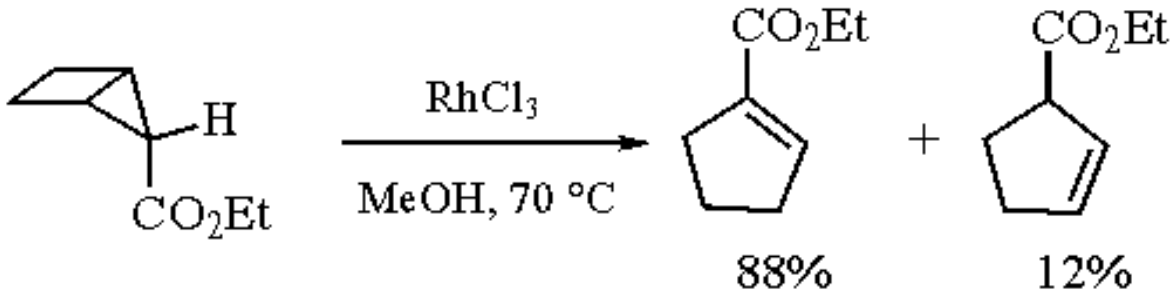

(5)

Reductions.

A mixture of ***Sodium Borohydride*** and rhodium trichloride forms a selective reagent for the reduction of aromatic systems (eq 6).[5] This method does not affect carboxylic acids, esters, or amides; ketones are partially reduced; alkenes are competitively reduced. The fact that aromatic nuclei typically require severe conditions for reduction underscores the usefulness of this mild process.

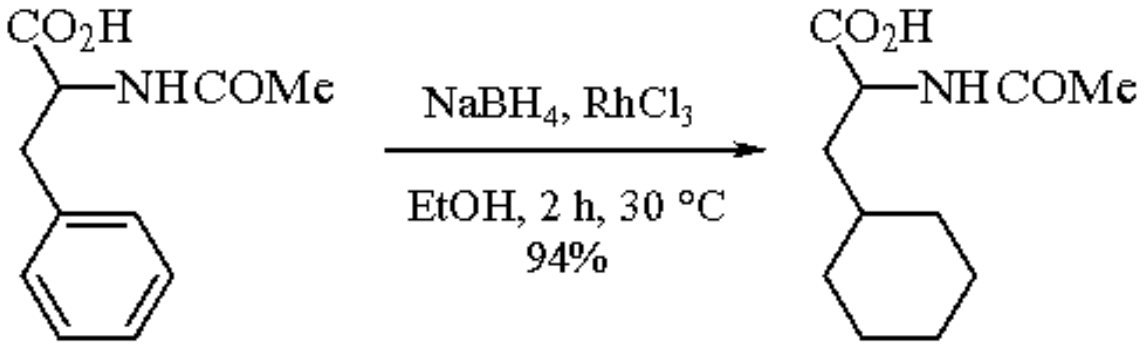

(6)

Rhodium trichloride, in the presence of the phase transfer catalyst Aliquat 336, serves as a hydrogenation catalyst that preferentially reduces alkenes in the presence of aromatic nitro groups (eq 7).[6] In general, the reduction of the nitro functionality is the most facile hydrogenation process.

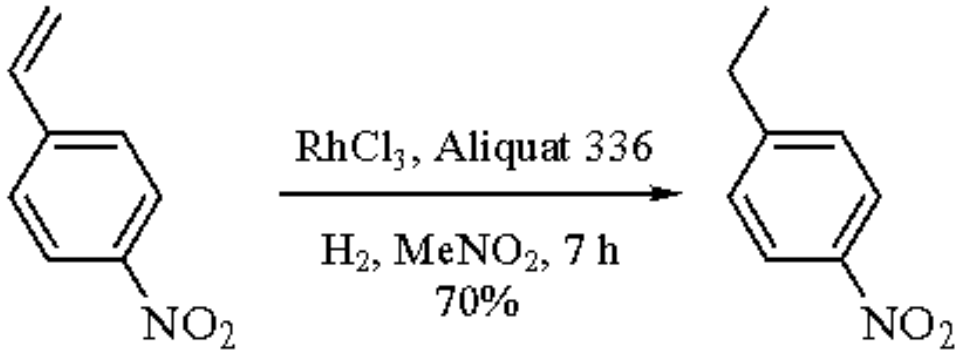

(7)

Oxidation.

Phase transfer catalysis allows the oxidation of alkenes to proceed in the presence of rhodium trichloride (eq 8).[7] Tetrabutylammonium hydrogen sulfate (THS) is of general use as a catalyst. Other quaternary ammonium salts will also serve this role. Mechanistically, it is thought that this reaction is analogous to the Wacker oxidation. This is in contrast to another report describing the use of rhodium trichloride as a homogeneous oxidation catalyst.[8]

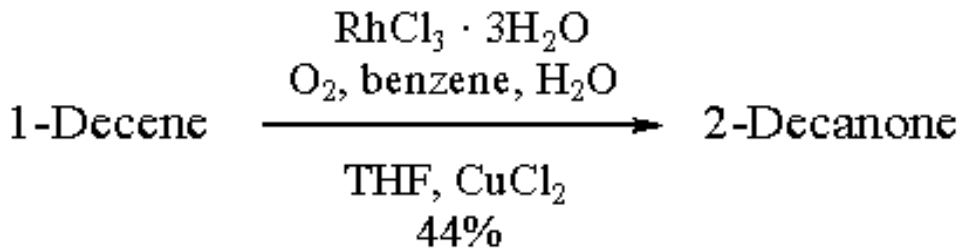

(8)

Acetylene Hydration.

Rhodium trichloride in acidic media catalyzes the hydration of ***Acetylene*** (eq 9).[9] The rate of this reaction is accelerated by the introduction of ligating additives such as ***Lithium Chloride***. In comparison, ***Ruthenium(III) Chloride*** also catalyzes alkyne hydration but at one-third the rate of rhodium trichloride.

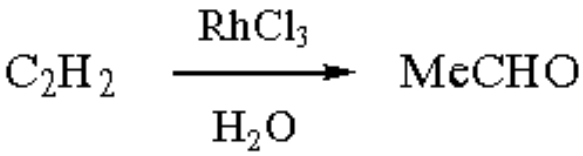

(9)

Hydrosilylation Catalyst.

The hydrosilylation of α,β-unsaturated esters to form dimethylketene trimethylsilyl acetals is catalyzed by rhodium trichloride (eq 10).[10] The use of rhodium trichloride rather than ***Chlorotris(triphenylphosphine)rhodium(I)***, the typical rhodium catalyst employed, results in a faster reaction with improved yields and product purities.

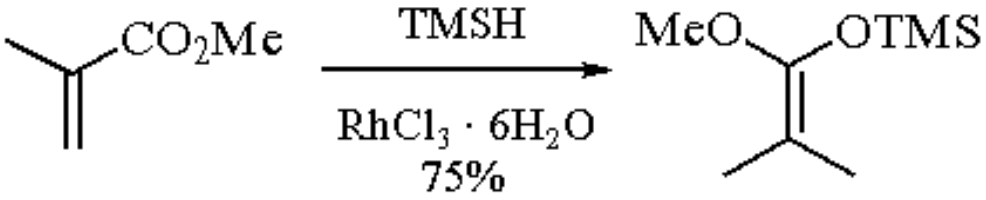

(10)

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Ruthenium Catalysts[1]

Ru

[7440-18-8] · Ru · Ruthenium Catalysts · (MW 101.07)

(selective hydrogenation catalysts,[1] high regio- and stereoselective addition to alkenes,[2] low activity for alkene isomerization,[3] actively hydrogenates carbonyls,[4] low hydrogenolytic activity,[5] high stereoselective perhydrogenation of aromatic carbocyclic and many aromatic heterocyclic compounds[6,7])

Form Supplied in: ruthenium supported on alumina or carbon and RuO_2 are available commercially.

Preparative Methods: ***Ruthenium(III) Chloride*** is converted by aq. ***Sodium Hydroxide*** or ***Lithium Hydroxide*** to $Ru(OH)_3$, which may be dried in a vacuum at room temperature for later use.[6] Ruthenium black can be prepared by the reduction of $RuCl_3.3H_2O$ with ***Formaldehyde***, washed repeatedly with distilled water, and stored in ethanol.[8]

Handling, Storage, and Precautions: the unused supported catalysts are not pyrophoric but ruthenium on finely divided carbon, like carbon itself, can undergo a dust explosion.[1d] After use, the catalysts are likely to contain adsorbed hydrogen which may ignite when dried.[1c,1d] Use in a fume hood.

Introduction.

The catalytic characteristics of ruthenium, like other platinum metals, depend secondarily on the support.[1c,d] The discovery of RuO_2 as a selective hydrogenation catalyst encouraged its use.[5,7,9] Later the supported catalysts Ru/C and Ru/Al_2O_3 became readily available. Supported catalysts are the more efficient users of the metal but may not furnish the maximum yield of a desired product if, for example, intraparticle mass transport affects the product distribution.[1d]

Ruthenium-catalyzed hydrogenations often show a variable and sometimes lengthy induction period which can be avoided by agitating the catalyst and solvent mixture in hydrogen (1 atm) for 1-2 h before introducing the substrate.[2,10] The common solvents are water, water-acetic acid, alcohols, and dioxane. Water is a powerful promoter of the activity of ruthenium hydrogenation catalysts.[1d,2,6]

Alkenes and Alkynes.

Ruthenium exhibits a lower tendency than rhodium (see ***Rhodium on Alumina***) to isomerize alkenes (relative to hydrogenation), particularly at high pressures which are often used with ruthenium catalysts.[1c,1d] Under mild conditions, a monoalkyl substituted ethylene is hydrogenated selectively in the presence of di- and trisubstituted ethylenes; hydrogenation of alkynes gives the corresponding alkane.[2] Ruthenium catalysts add hydrogen suprafacially (*cis*) to a carbon-carbon double bond, as in the hydrogenation of alkyl substituted cyclohexenes (eq 1),[3,11] bicyclo[2.2.0]hexenes or bicyclo[2.2.0]hexadienes (eq 2),[12] and bicyclo[4.4.0]decene.[13]

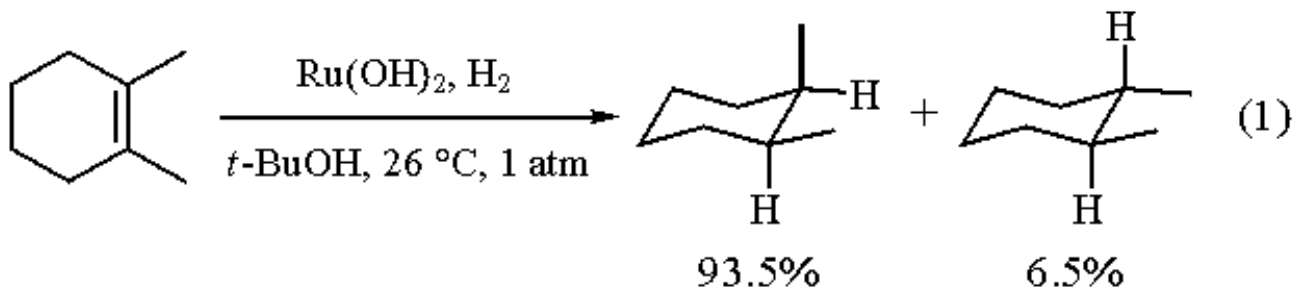

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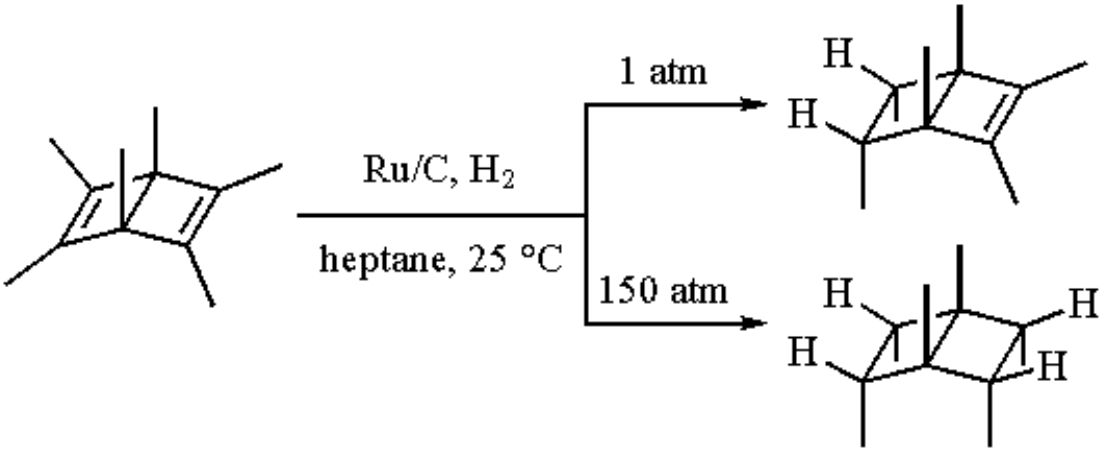

(2)

Carbonyl Compounds.

Ruthenium is an excellent catalyst for the hydrogenation under mild conditions of aliphatic carbonyl compounds and aldehydes such as furfural (eq 3).[4] Industrially, it is used for the conversion of glucose to sorbitol.[1d]

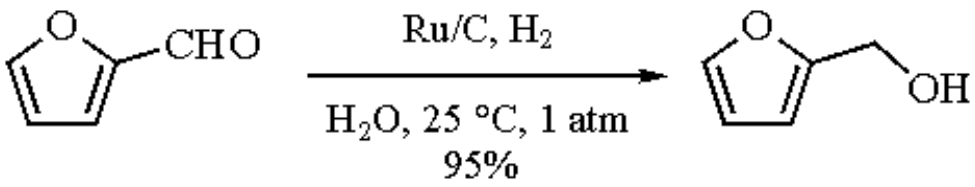

(3)

Elevated temperatures and pressures have been used successfully, as in the 5% Ru/C catalyzed hydrogenation of tetramethyl-1,3-cyclobutanedione which gave a mixture of stereoisomers (98%), a far better result than that given by Pd, Pt, or Rh (eq 4).[14]

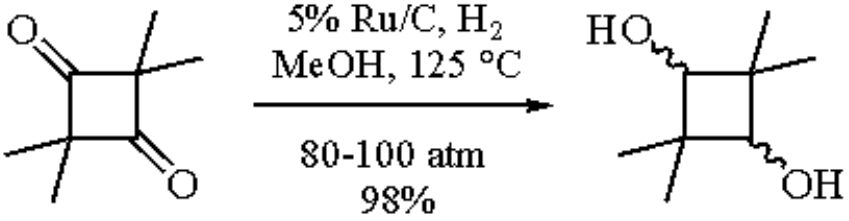

(4)

Felföldi has given a broad review of the stereochemistry of the hydrogenation of substituted cyclic ketones which includes comparisons of ruthenium with other metals as catalysts.[15]

Carboxylic Acids to Alcohols.

Either RuO_2 or Ru/C catalyzes the hydrogenation of carboxylic acids, both mono- and dicarboxylic, in water to the corresponding alcohols at around 150 °C and 500-700 atm (eq 5).[16] Rhenium oxides, particularly ReO, effect this reduction under less vigorous conditions.[17]

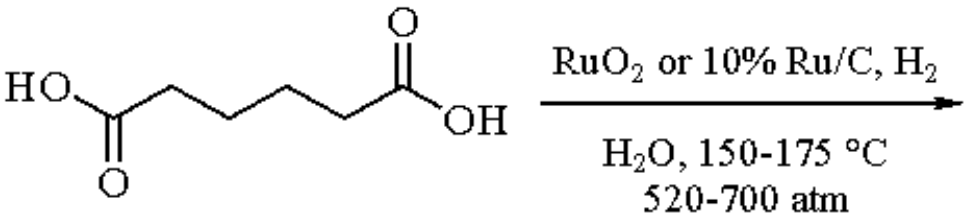

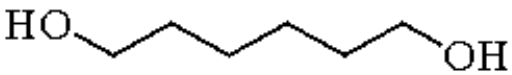

(5)

Hydrogenation of Nitro Alkynes.

Ru/C or Ru/Al_2O_3 favor the reduction of the aromatic nitro group in (3-nitrophenyl)acetylene.[18] To avoid the observed deactivation of the catalyst, the alkyne was converted to the acetone adduct, 2-methyl-4-(3-nitrophenyl)-3-butyn-2-ol, which was hydrogenated to 2-methyl-4-(3-aminophenyl)-3-butyn-2-ol (eq 6). The base-catalyzed removal of acetone released the amino alkyne quantitatively.

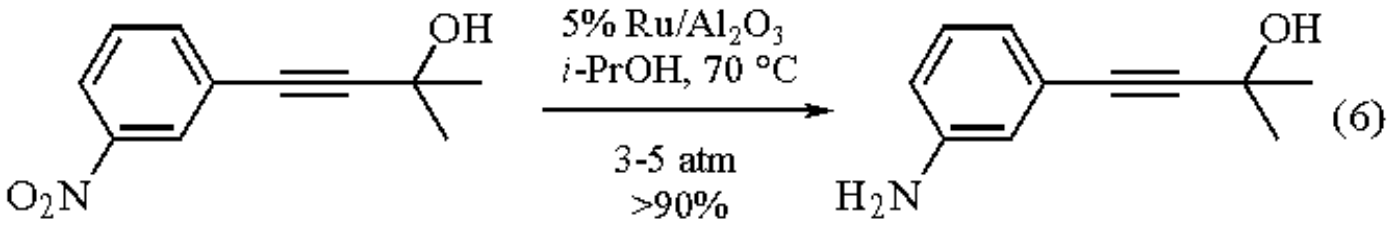

Carbocyclic Aromatic Compounds.

Ruthenium, as well as rhodium, is noted for its effective catalysis of the hydrogenation of aromatic carbocycles.[1e,6] Other reducible functional groups usually remain intact. With more than one substituent attached, the configuration of the saturated product corresponds mainly to addition of hydrogen to one face of the aromatic cycle. As with other platinum metals, the selectivity is affected by the extent to which unsaturated intermediates desorb from the catalytic sites and whether the intermediates are readsorbed and reduced with selectivities differing from that of their precursor, or transformed to products other than those of simple hydrogen addition.

Aromatic Hydrocarbons.

Of all the platinum metals studied, ruthenium forms the largest amount of an observable cyclohexene in the hydrogenation of benzene or the xylenes at near atmospheric pressures.[19] Don and Scholten showed the importance of water in maximizing the yield of cyclohexene when ruthenium is the catalyst.[20] The formation of *trans* saturated isomers from substituted benzenes has been attributed to the hydrogenation of the desorbed intermediates.[21]

The $Ru(OH)_3$-catalyzed hydrogenation of *o*-xylene at 85 °C and 80-100 atm yields a *cis*/*trans* ratio of 1,2-dimethylcyclohexanes of 12.3 compared to 9.5 for Rh (eq 7).[6] Only Os and Ir (see ***Iridium***) yield larger fractions of the *cis* isomer.

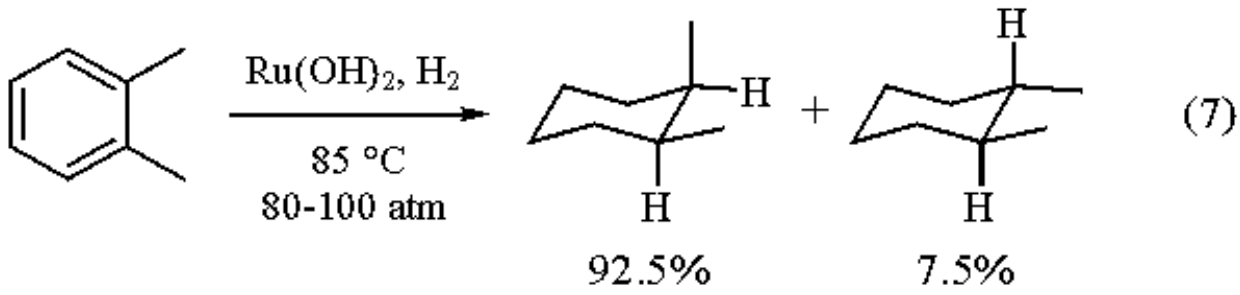

Ruthenium is the most stereoselective catalyst for the perhydrogenation of naphthalene or methylnaphthalenes (95% *cis*).[13] High stereoselectivity is shown in the hydrogenation of triptycene to the *cis*-*anti*-perhydrotriptycene (eq 8).[22]

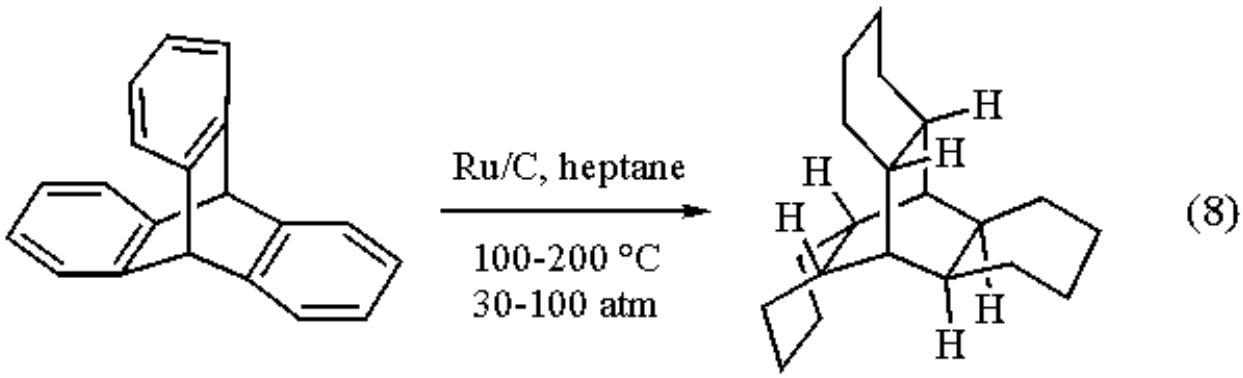

Fullerenes C_{60} and C_{70} in a ca. 85:15 ratio, dissolved in toluene and with an equal volume of water added, were hydrogenated over 5% Ru/C to yield a mixture of hydrogenated fullerenes from $C_{60}H_2$ to $C_{60}H_{40}$.[23] The hydrides retain the fullerene carbon skeleton.

Phenols and Phenyl Ethers.

Among the first reported uses of Ru was the hydrogenation of a phenolic ring contained in a polycyclic compound.[9] The reductions were performed with RuO_2 at 50 °C and 100 atm H_2, which avoided hydrogenolysis of the hydroxyl group and was stereoselective.

The hydrogenation of phenols produces cyclohexanone intermediates which probably arise from the isomerization of a cyclohexenic intermediate, a vinyl alcohol. Palladium gives the highest yields of cyclohexanone, approaching 100%; ruthenium yields are smaller but more than is obtained with other platinum metals.[24] The maximum diminishes with an increase of pressure while the fraction of the *cis* saturated product increases. This result indicates that the hydrogenation of the ketone is not as *cis* stereoselective as is the direct hydrogenation of the phenol.

That enols are among the initial desorbed intermediates in the hydrogenation of phenols is supported by the study of the hydrogenation of ethyl *p*-tolyl ether in ethanol over unsupported platinum metals (25 °C, 1 atm).[25] Ruthenium affords the simplest result in that the enol ether is the principal intermediate; ethyl 4-methyl-3-cyclohexenyl ether is formed in smaller amounts (eq 9). With platinum metals other than Ru, the hydrogenation is accompanied by the formation of 4-methyl-1,1-diethoxycyclohexane and loss of the ethoxy group, leading to 4-methylcyclohexanone and 4-methylcyclohexanol. For Ru, the *cis*/*trans* ratio diminishes with conversion as the fraction of the saturated ether formed via the direct path diminishes.

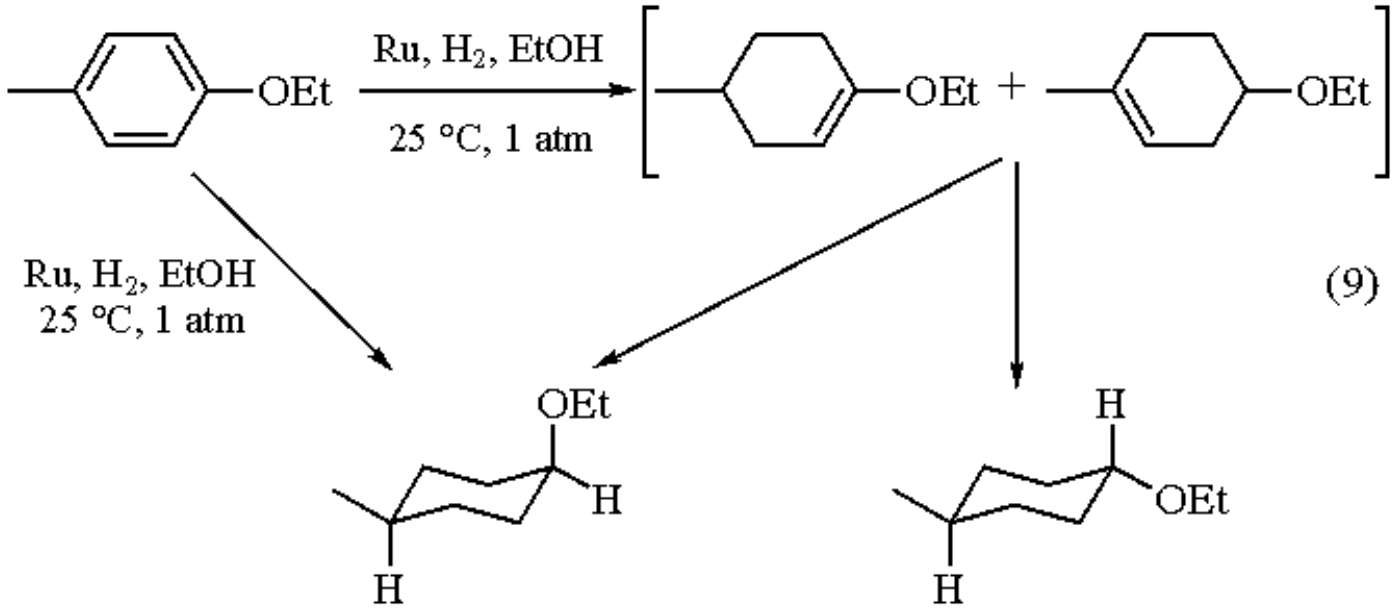

(9)

To avoid the hydrogenolysis of the ether linkages, 5% Ru/Al_2O_3 was used to hydrogenate ***Dibenzo-18-crown-6*** in 1-butanol to ***Dicyclohexano-18-crown-6*** (eq 10).[26] Other crown ethers were treated similarly using RuO_2 or the supported catalyst and the conversions were thought to be nearly quantitative.

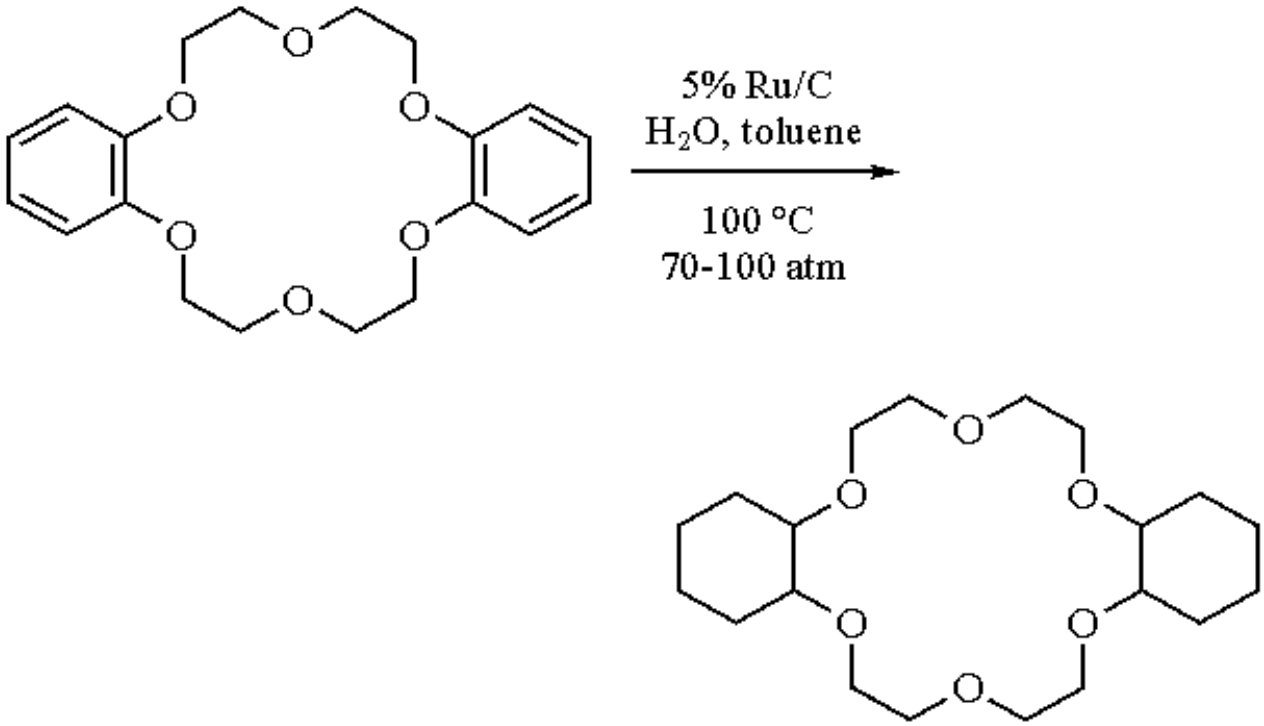

(10)

Using Ru/Al_2O_3 (110-126 °C, 70 atm) the cresols are converted to the methylcyclohexanols with high selectivities (94-98%) but with moderate *cis* stereoselectivities, which are larger in ethanol than in water.[27]

The selectivities of the platinum metals in the hydrogenation of 2-naphthol are comparable in the formation of the two tetrahydro derivatives, 1,2,3,4- and 5,6,7,8-tetrahydronaphthols, for their tendency towards hydrogenolysis, and for their stereochemistry in the formation of the saturated products (eq 11).[28]

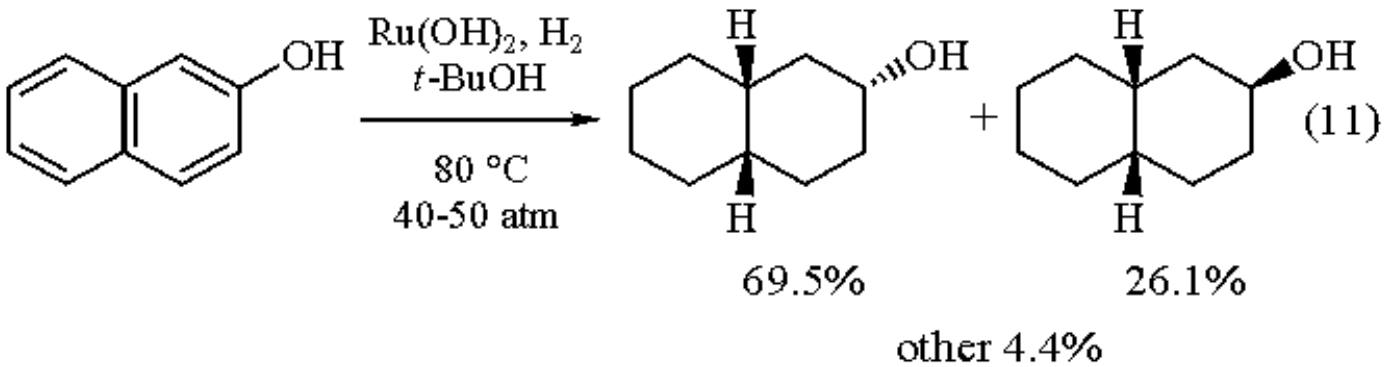

Anilines.

A large number of substituted anilines have been hydrogenated successfully to the cyclohexyl amines over ruthenium catalysts.[1c-f] Normally, varying amounts of dicyclohexylamines are formed which arise from the reaction of the unsaturated intermediates. At elevated pressures, ruthenium catalysts usually give the least amount of such coupled products.[29]

The formation of the dicyclohexylamine from aniline as a function of the alcohol used as solvent decreases in the order methyl > ethyl >> isopropyl &AApprox; *t*-butyl; the addition of a small amount of either NaOH or LiOH further inhibits the formation of the dialkylamine.[30]

Ru/Al_2O_3 catalyzes the hydrogenation of alkyl-substituted anilines with high chemoselectivities to the substituted cyclohexylamine (>90% except for *o*- and *m*-*t*-butylaniline) and stereoselectivities, mainly *cis*, in ethanol on Ru/Al_2O_3 (110 °C, 70 atm).[1e,27] On the same catalyst the hydrogenation of the isomeric toluidines, aminophenols, and alkoxyanilines gives similar results. Although the rate of hydrogenation diminishes by substituting acetyl or alkyl for H in the amino group, the yields and stereoselectivities remain equally good (eq 12).

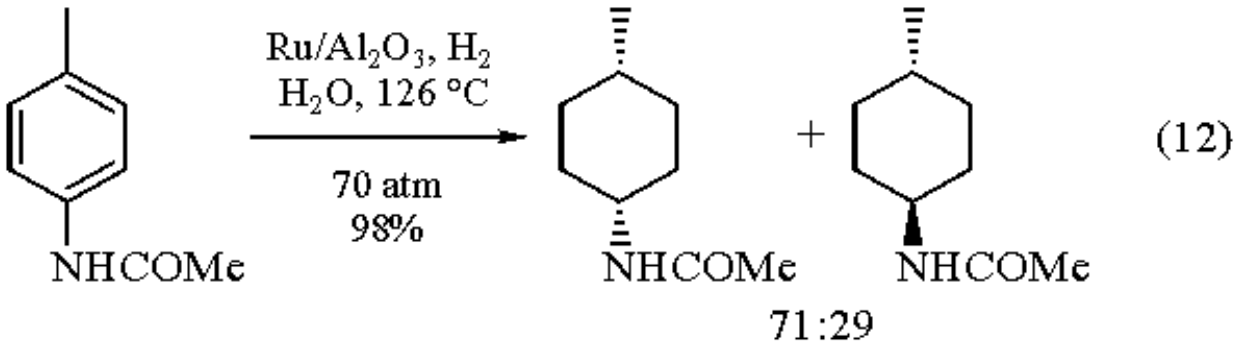

Substituted Benzoic Acids.

Ruthenium has been used to hydrogenate benzoic acids, or their esters, which are substituted with alkyl, hydroxyl, amino, or additional carboxyl groups.[1e,31] Generally, the stereoselectivities are greater than those observed with other metals except possibly Rh, which may be used at lower temperatures.

Ru/C is included amongst the catalysts used in the study of the hydrogenation of *o*-, *m*-, and *p*-*t*-butylbenzoic acids (20 °C, 1 atm).[32] Rh/C gave the largest amount of the unsaturated intermediate while Ru/C resulted in the higher stereoselectivity (*cis*). The Ru/C-catalyzed hydrogenation of terephthalic acid qualifies as a preparative procedure for *cis*-cyclohexene-3,6-dicarboxylic acid (70%) (eq 13).[33]

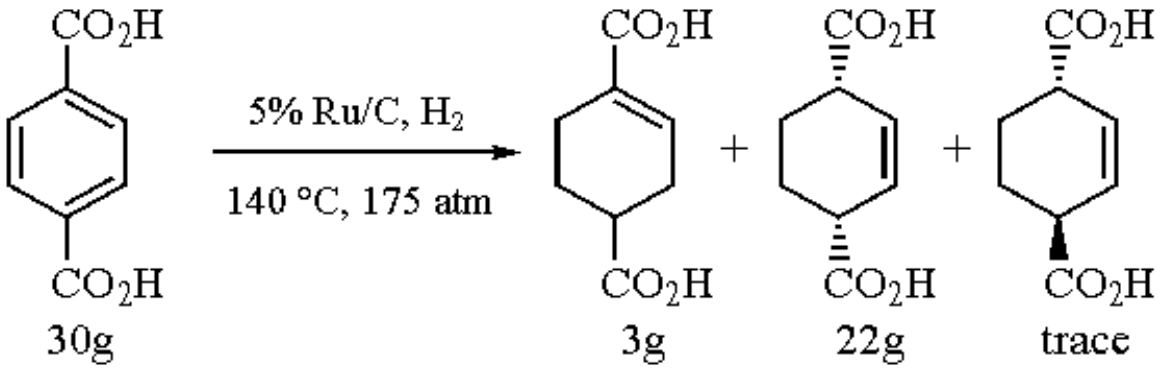

(13)

Heterocyclic Compounds.

Ruthenium is most effective for the perhydrogenation of aromatic heterocycles such as pyrroles, pyridines, and furans. Hydrogenolysis of the cycle or that of attached negative groups is generally small.[1d] ***Pyridine*** is converted quantitatively to ***Piperidine*** using RuO_2 at 95 °C and 70-100 atm of H_2, in less than 0.5 h.[7] A large variety of substituted pyridines also were hydrogenated in water, methanol, or ethanol under comparable conditions, with 80-94% yields.

Reaction conditions can affect the chemoselectivity. The RuO_2-catalyzed hydrogenation of 3-cyanopyridine to 3-aminomethylpyridine was done in a mixed solvent, methanol and ***Ammonia***, at 95 °C and 120 atm H_2 (68%); 3-aminomethylpiperidine was obtained in comparable yield from the cyanopyridine in ammonia at 100-125 °C and 150 atm (eq 14).

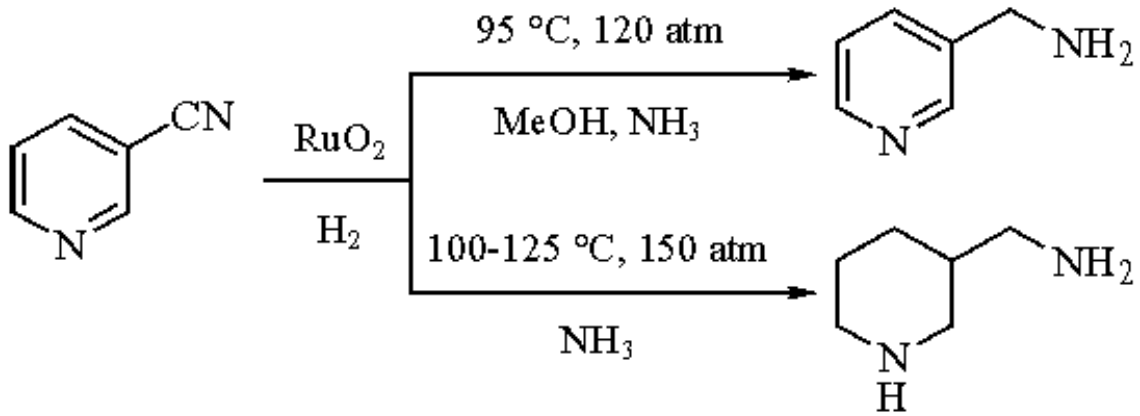

(14)

A kinetic study of the Ru/C-catalyzed hydrogenation of ***Quinoline***, 2- and 8-methylquinoline, and isoquinoline shows the high selectivity towards 1,2,3,4-tetrahydroquinolines.[34] The latter as well as the 5,6,7,8-tetrahydro derivatives are converted more slowly to the decahydroquinolines (eq 15).

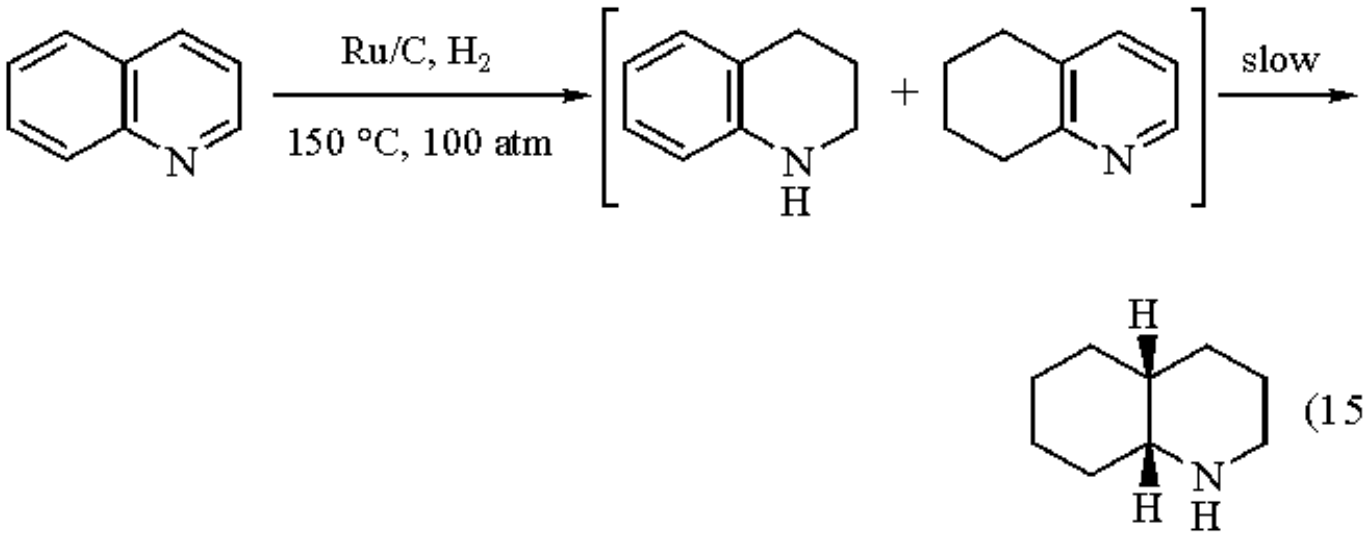

(15)

Five-membered heterocyclic aromatic compounds which contain nitrogen or oxygen also have been hydrogenated over ruthenium catalysts. 2,5-Bis-(3-oxobutyl)furan in dioxane is converted to 2,5-bis(3-hydroxybutyl)tetrahydrofuran over Ru/C (eq 16).[35] RuO_2 or Ru/C (70-100 °C, 100 atm) catalyze the perhydrogenation of pyrrole, 2-methylpyrrole, and carbazole.[1b]

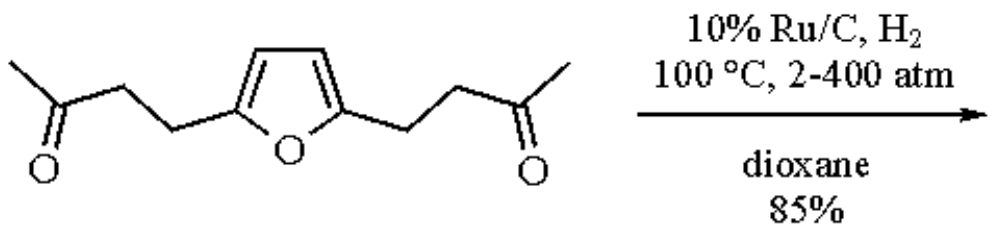

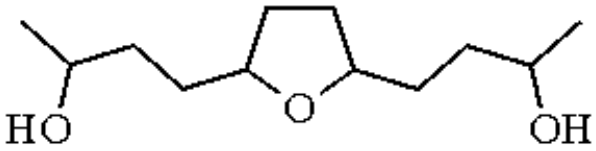

(16)

Aromatic heterocyclic diazines such as 2-methylpyrazine and cinnoline (5,6-benzopyridazine) also are hydrogenated on RuO_2 or Ru/C.[1b]

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Ruthenium(III) Chloride

$RuCl_3$

[10049-08-8] · Cl_3Ru · Ruthenium(III) Chloride · (MW 207.42) (hydrate)

[14898-67-0]

(Lewis acid;[1] catalyst for alkyne functionalization[4] and oxidation[6a])

Physical Data: mp >500 °C for anhydrous material.

Solubility: α-$RuCl_3$ (black lustrous crystals) insol alcohol, water; β-$RuCl_3$ (dark-brown, fluffy crystals) sol alcohol.

Form Supplied in: available as anhydrous solid and hydrated solid.

Analysis of Reagent Purity: elemental analysis.

Lewis Acid.

Ruthenium trichloride can serve as a mild Lewis acid. Treatment of norbornene oxide with this reagent results in a hydrocarbon skeletal rearrangement (eq 1).[1] Other ruthenium reagents such as ***Ruthenium(VIII) Oxide*** are ineffective at bringing about the desired transformation. Ruthenium trichloride, in the presence of alcohols, also catalyzes the formation of allylic ethers from allylic alcohols (eq 2).[2] It is likely that this process occurs via an allylic carbonium ion since racemization ensues when enantiomerically pure allylic alcohols are employed. The Prins reaction is catalyzed by ruthenium trichloride (eq 3).[3] While it is possible that this reaction is proceeding in a fashion analogous to the Wacker oxidation, simple Lewis acid activity can explain the observed products.

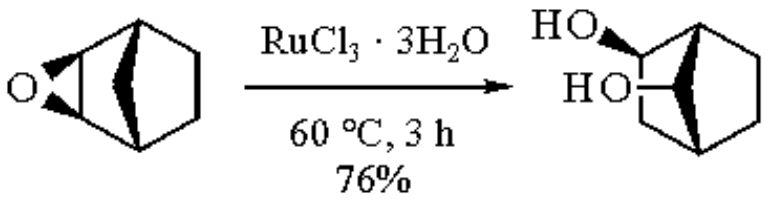

(1)

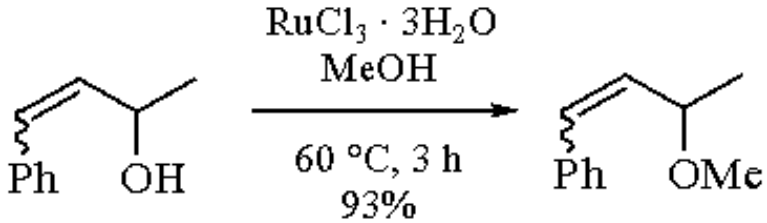

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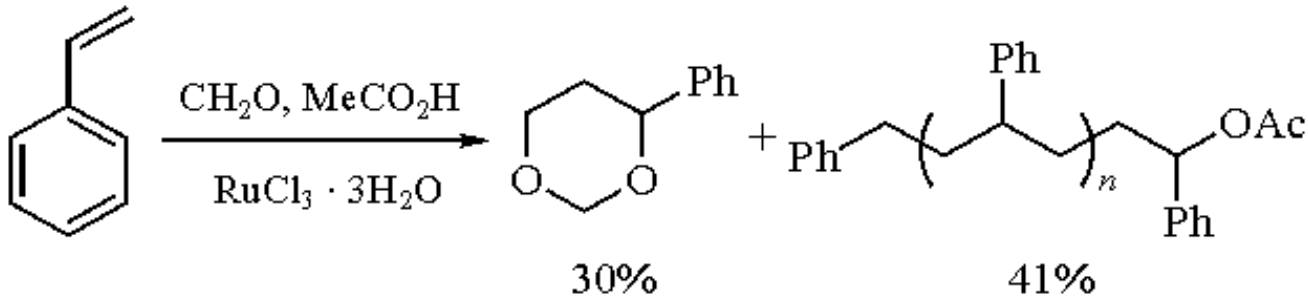

(3)

Alkyne Functionalization.

Ruthenium trichloride catalyzes the reaction of ***Acetylene*** with ***Carbon Dioxide*** and secondary amines, providing vinyl carbamates in low to moderate yields (eq 4).[4] Primary amines do not participate in this reaction and ruthenium dodecacarbonyl fails to catalyze this process. In an analogous transformation, ruthenium trichloride catalyzes the addition of carboxylic acids to terminal alkynes (eq 5).[5] Higher selectivities and increased yields are obtained when ***Tri-n-butylphosphine*** is added to the reaction mixture.

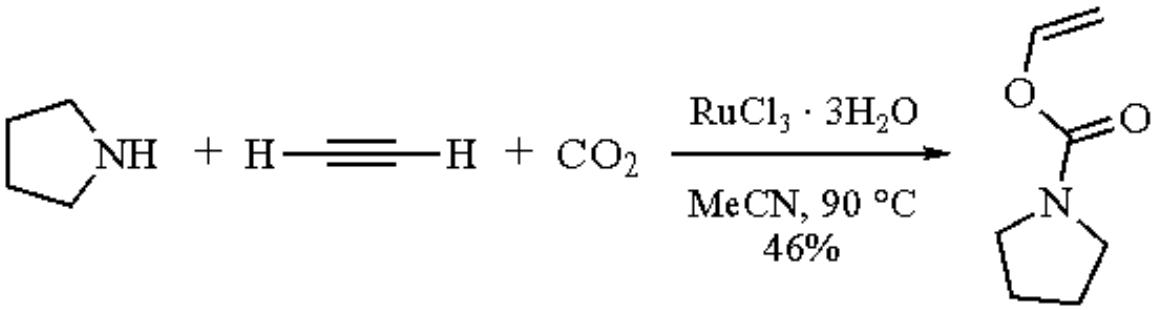

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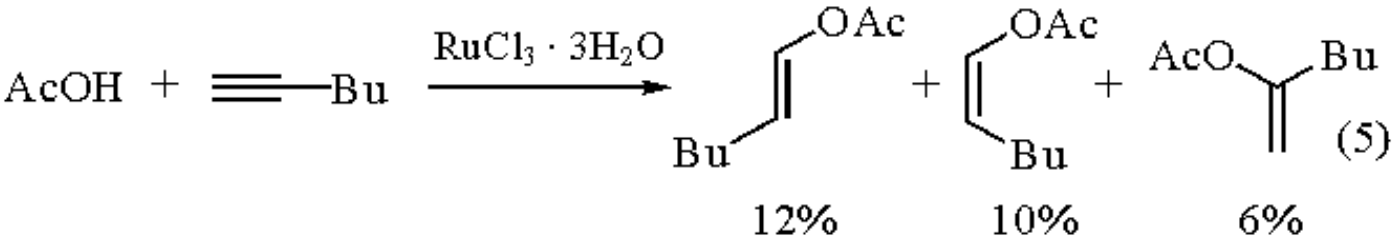

(5)

Oxidations.

Ruthenium trichloride catalyzes the oxidation of alcohols in the presence of stoichiometric ***N-Methylmorpholine N-Oxide*** (eq 6).[6a] A slight preference is noted for primary over secondary alcohols. Also, tertiary amines are oxidized to amine oxides in the presence of ruthenium trichloride and molecular ***Oxygen***.[7a]

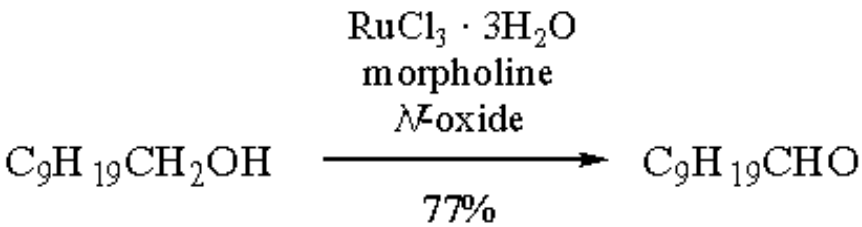

(6)

C-H Activation.

Furan and thiophene undergo an alkylation-coupling process when exposed to ruthenium trichloride, an alcoholic solvent, and elevated temperatures (eq 7).[8]

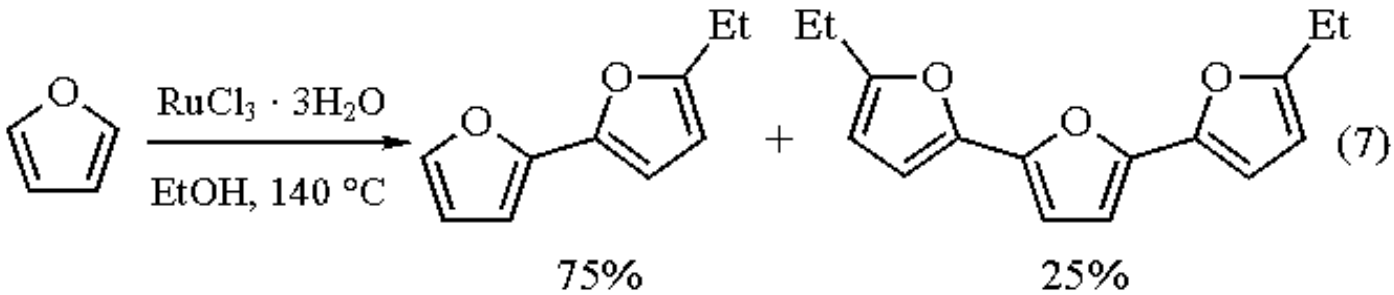

(7)

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Ruthenium(VIII) Oxide[1]

RuO_4

[20427-56-9] · O_4Ru · Ruthenium(VIII) Oxide · (MW 165.07)

(strong oxidant for many functional groups; can cleave double bonds, aromatic rings, and diols[1])

Alternate Name: ruthenium tetroxide.

Physical Data: yellow form: mp 25.5 °C; bp 40 °C; *d* 3.29 g cm^{-3}. Brownish orange form: mp 27 °C; bp 108 °C (dec).

Solubility: slightly sol water; highly sol $CHCl_3$, CCl_4.

Form Supplied in: although the reagent is commercially available either in solid form or stabilized aqueous solution, it is usually prepared in situ from black solid RuO_2 (mw 133.07) *[120236-10-1;.x*H_2O*, 32740-79-7]* or dark brown (or black) $RuCl_3$ (mw 207.42) *[10049-08-8;.x*H_2O*, 14898-67-0]*, in stoichiometric or catalytic amounts, and an oxidation agent; both of the above Ru salts are widely available.

Handling, Storage, and Precautions: handle in a fume hood only. Inhalation should be avoided; vapors irritating to eyes and respiratory tracts, since it readily oxidizes tissue, leaving a deposit of ruthenium dioxide.[2] It attacks rubber and reacts explosively with paper filter and alcohol, and violently with ether, benzene, and pyridine.[3] However, *the use of the catalytic system greatly minimizes the risk in its manipulation*, and its usage is strongly recommended.

Introduction.

When RuO_4 was introduced into organic synthesis it was generally used in stoichiometric amounts, usually prepared by oxidation of ***Ruthenium(III) Chloride*** or RuO_2 with aqueous periodate or hypochlorite and then extracted into carbon tetrachloride. This yellow solution could be roughly analyzed by treating an aliquot with ethanol to reduce the tetroxide to the black dioxide, which was collected and weighed.[4]

However, since ruthenium compounds are expensive and occasionally it is difficult to separate the products from precipitated ruthenium dioxide, it is more convenient to use a system formed by a catalytic amount of the ruthenium compound (RuO_2 or $RuCl_3$) along with an appropriate co-oxidant, usually in a biphasic solvent system. These reagents actually act as catalysts, because they are reoxidized after the reaction with organic compounds by one of the oxidants previously mentioned. Ruthenium tetroxide is usually prepared in situ from ruthenium dioxide or ruthenium trichloride by oxidation with ***Sodium Hypochlorite***,[5] ***Sodium Bromate***,[6] ***Peracetic Acid***,[6] periodic acid,[7] ***Sodium Periodate***,[8] ***Oxygen***,[9] cerium sulfate,[10] ***Potassium Permanganate***,[10] electrochemically generated ***Chlorine***,[11] or ***Potassium Monoperoxysulfate*** (Oxone®).[12]

It appears that contact between RuO_4 and the material to be oxidized takes place in the organic phase, where they are both most soluble. The ruthenium dioxide produced when oxidation occurs is insoluble in all solvents and migrates to the interface where it contacts the co-oxidant (in the aqueous layer) and is reoxidized. Thus best results are obtained when the mixture is shaken or stirred vigorously throughout the course of the reaction to achieve good contact between all components.

It has been pointed out that $RuCl_3.H_2O$ is not a good Ru source under acidic conditions (pH < 5), because it initially gives an orange Ru^{IV} chloro aquo complex, which is slowly oxidized to RuO_4. In such cases, RuO_2 is the alternative recommended.[10] In the reactions carried out at pH > 9, any RuO_4 produced in the aqueous phase is unstable, being reduced to green perruthenate (RuO_4^-), and subsequently to orange ruthenate (RuO_4^{2-}). Both species are insoluble in CCl_4. Although in most of the cited mixtures RuO_4 is considered the oxidant, it cannot be ruled out that the real oxidant is another lower valent ruthenium species. The only way to ensure that RuO_4 is really the oxidizing agent is if it is isolated after its preparation, as cited in the early literature.[2,4] UV analysis of the RuO_4 solutions can provide some information about this, because RuO_4 gives absorption bands at λ_{max} 310 nm (strong) and 380 nm. These bands are replaced by others at λ_{max} 310 nm (strong), 385 nm (strong), and 460 nm when base is added to the solution, corresponding to the formation of the perruthenate ion (RuO_4^-) and subsequently to absorption bands at λ_{max} 385 nm and 460 nm (strong), produced by RuO_4^{2-}.[1,13]

RuO_4 is a strong oxidant. However, conditions for ruthenium-catalyzed reactions are very mild; usually a few hours (or less) at room temperature (or below) is sufficient. A thorough study of oxidations with RuO_4 generated in situ from $RuO_2.xH_2O$ and $RuCl_3.xH_2O$ shows the importance of the presence of water in the reaction.[10,14] Thus many ruthenium-catalyzed reactions have been performed in the CCl_4-H_2O solvent system. The addition of ***Acetonitrile*** to the system greatly improves yields and reaction times,[8] especially when carboxylic groups are present or generated in the reaction. MeCN probably disrupts the insoluble carboxylate complexes and returns the ruthenium to the catalytic cycle, acting as a good ligand for the lower valent (III/II) ruthenium present.[15]

An important feature of RuO_4-catalyzed oxidations is that the stereochemistry of the stereocenters close to the reaction site (eqs 1 and 2)[16,17] remains unaffected.

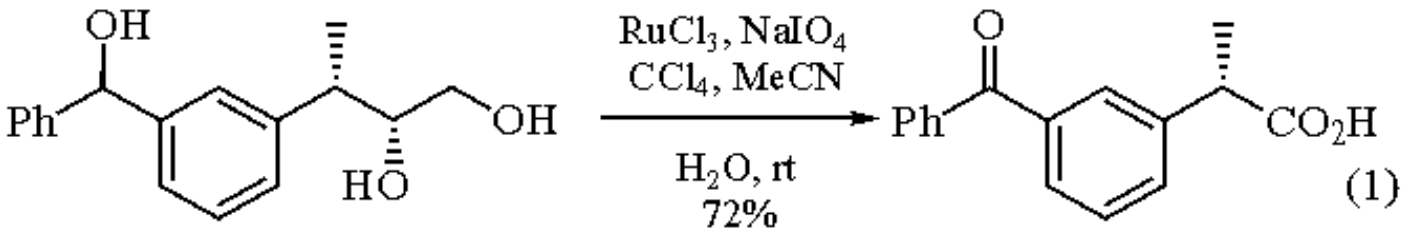

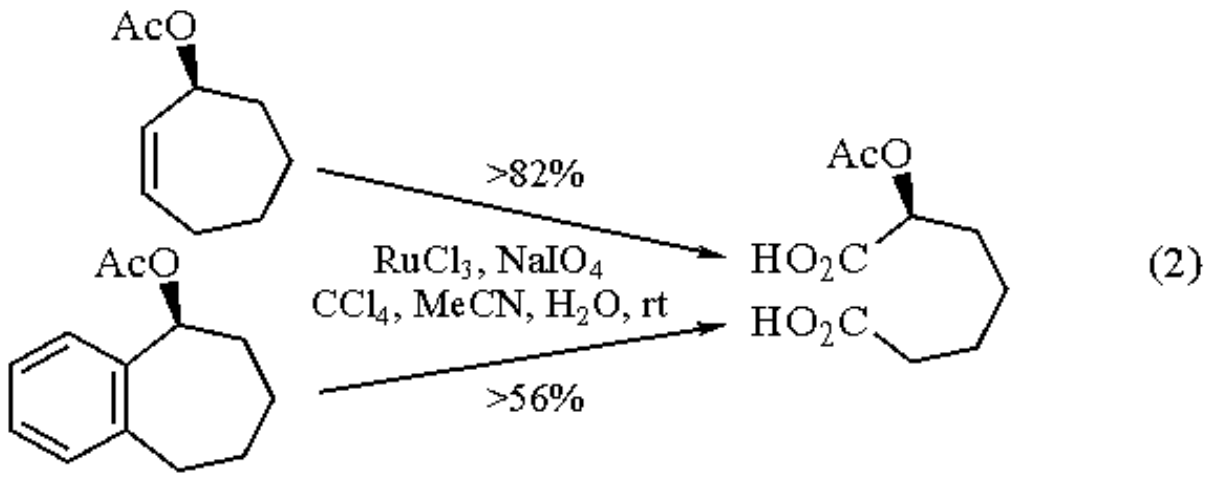

In a typical procedure,[8] to a stirred mixture of 2 mL of CCl_4-2 mL of MeCN-3 mL of H_2O/mmol of organic compound are added 4.1 mmol of ***Sodium Periodate***/mmol of organic compound and 2.2 mmol% of $RuCl_3.xH_2O$ ($RuO_2.xH_2O$ is equally effective) sequentially. The mixture is stirred vigorously at 0-25 °C until the end of the reaction (TLC or GC monitoring). Then 20 mL of diethyl ether are added and the vigorous stirring is continued for 10 min to precipitate black RuO_2. The reaction mixture is then dried ($MgSO_4$) and filtered through qualitative Whatman filter paper 2. The solid residue is then washed with diethyl ether (3 × 5 mL). The combined organic phases are concentrated to yield the crude oxidation product.

Functional Group Oxidations without Bond Cleavage.

One of the most common synthetic uses of ruthenium-catalyzed oxidations is the reaction with alcohols. A mixture of RuO_2 or $RuCl_3$ with strong co-oxidants converts primary alcohols to carboxylic acids[18] (eq 3),[19] including epoxy alcohols (eq 4),[8] but under milder (***Iodosylbenzene***,[20] molecular oxygen,[21] ***Calcium Hypochlorite*** (eq 5),[22] or amine *N*-oxides[23]) or controlled conditions,[19] aldehydes are obtained (eq 6).[24]

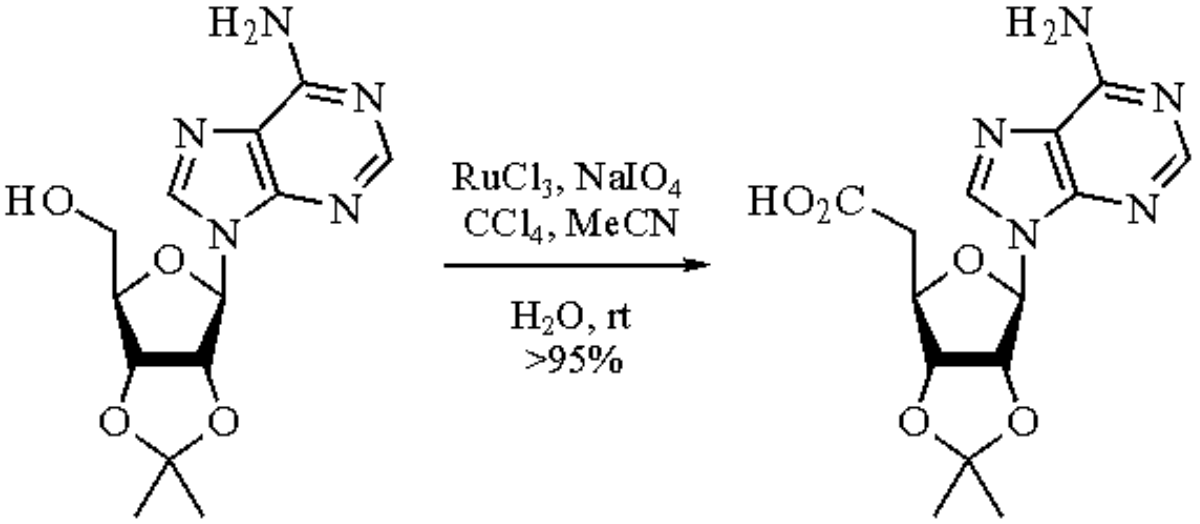

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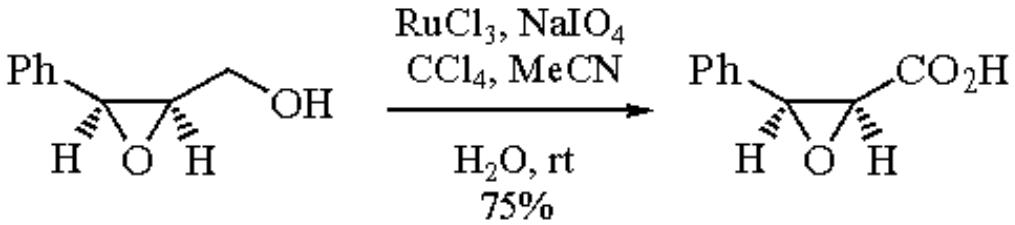

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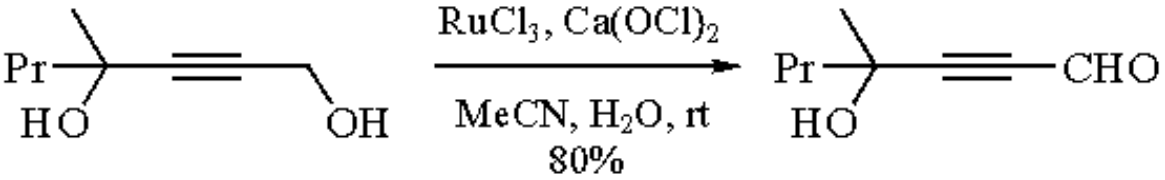

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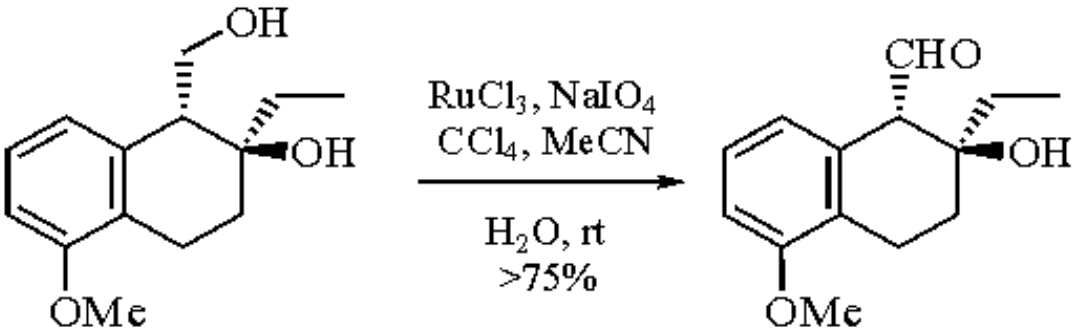

(6)

Secondary alcohols are transformed into ketones.[1,3,25] The yields obtained from the oxidation of secondary alcohols are usually excellent. Since the reactions are carried out under very mild conditions, there is little danger of the product undergoing secondary reactions. Ketones can also be prepared using a great variety of other oxidants[26] (see, for example ***Chromium(VI) Oxide*** and ***Dimethyl Sulfoxide*** based oxidant reagents), which in some cases are more readily available and less expensive. However, RuO_4 is recommended for reactions which require a vigorous oxidant under mild conditions. Thus it can be used to oxidize alcohols which are resistant to other oxidants: (**1**) is successfully oxidized with RuO_4, while attempts made with 15 other standard oxidizing procedures failed (eq 7);[27] oxidation of (**2**) is successful in good yield using RuO_4 (eq 8), being fruitless with CrO_3 in either ***Pyridine***, ***Acetone***, ***Acetic Acid***, or Al(O-*i*-Pr)$_3$, $KMnO_4$, ***Lead(IV) Acetate*** in acetone, with CrO_3 in *i*-BuOH giving the ketone in very low yield.[28] Numerous examples of the advantages of RuO_4 over ***Dipyridine Chromium(VI) Oxide*** for the oxidation of carbohydrates have been cited.[29]

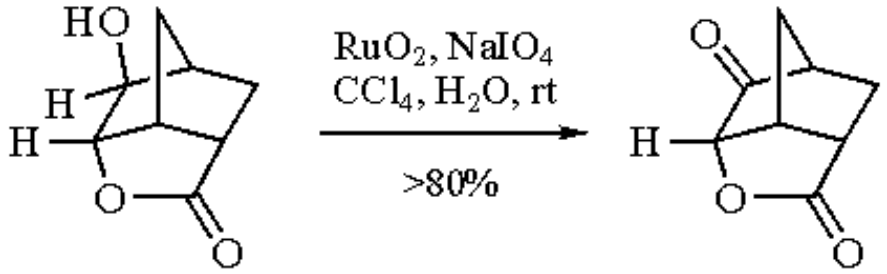

(1) (7)

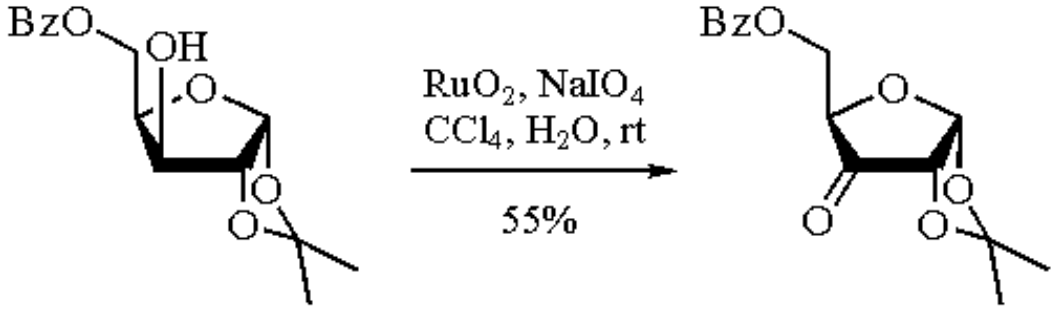

(2) (8)

RuO_4 is also reported to provide higher yields when other oxidizing procedures give poor yields. As examples can be cited the conversions of cyclobutanols to cyclobutanones (eq 9)[30] and the transformation of lactones into the corresponding ketocarboxylates under basic conditions (60-97%) (eq 10). Significantly higher yields are obtained compared with $KMnO_4$ under alkaline conditions.[31]

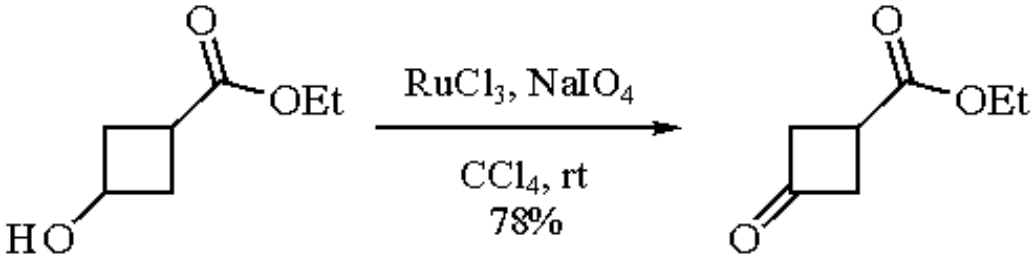

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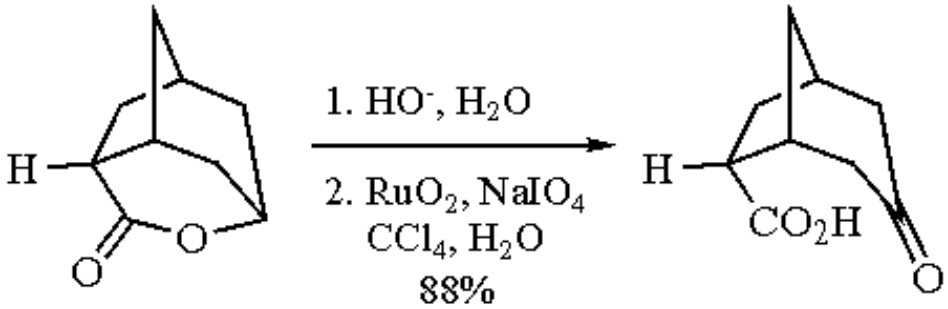

(10)

Vicinal diols can be oxidized to diketones but only in low yields, the principal reaction being the oxidative cleavage of the C-C bond.[1] If the hydroxyl groups are not adjacent, then diketones can be prepared (eq 11).[32]

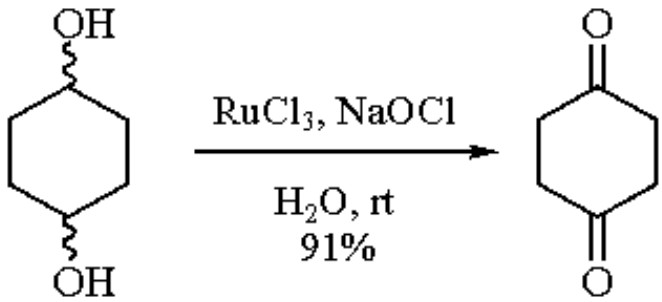

(11)

The catalytic procedure is also applicable to the oxidation of aldehydes to carboxylic acids,[1,2,23,33] primary alkyl iodides to carboxylic acids (eq 12),[34] aromatic hydrocarbons to quinones,[25] and sulfides to sulfones,[25] including an improved and simple method to obtain water-soluble sulfones using periodic acid as the co-oxidant in high concentration conditions (eq 13).[35]

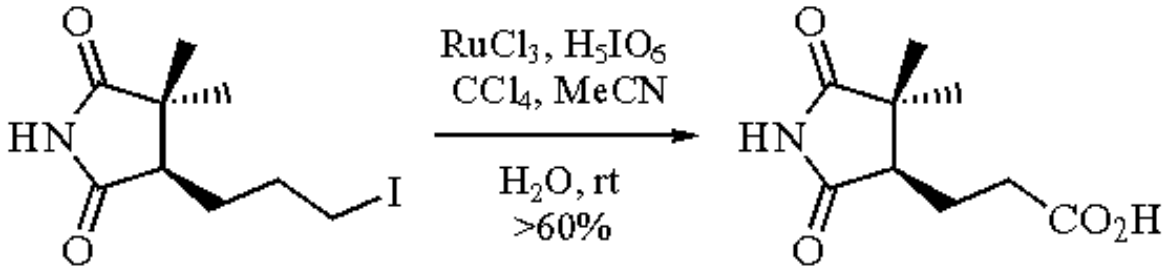

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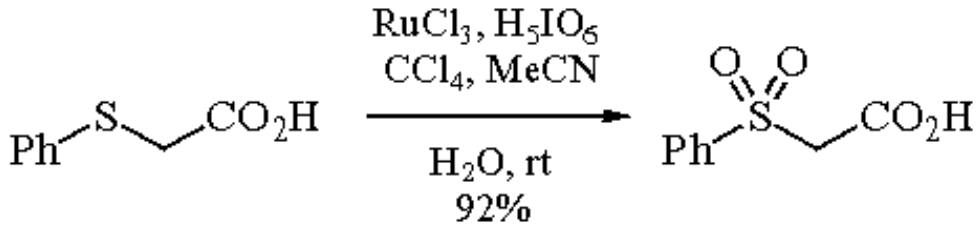

(13)

Oxidation of 1,2-cyclic sulfites to 1,2-cyclic sulfates with RuO_4 has been reported as a part of a method to activate diols for further nucleophilic attack (eq 14).[36]

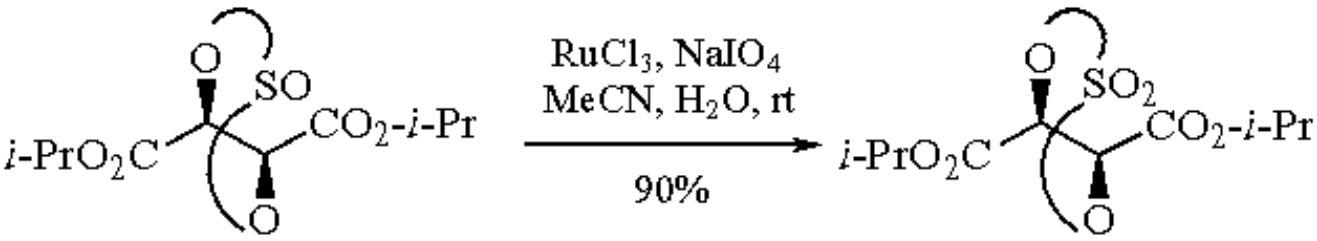

(14)

Along with these types of oxidations, RuO_4 is used to carry out transformations that involve oxidation of methylene groups α to heteroatoms such as oxygen and nitrogen. Thus it is possible to convert acyclic ethers into esters, such as methyl ethers into methyl esters (eq 15),[8] ethyl ethers into acetates,[37] and benzyl ethers into benzoates (eq 16).[38] It is possible to avoid the benzyl-benzoyl group transformation by carrying out the reaction at 0 °C and/or in the presence of base (eq 17).[39]

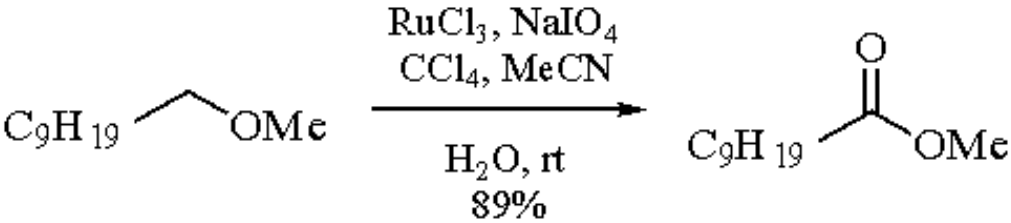

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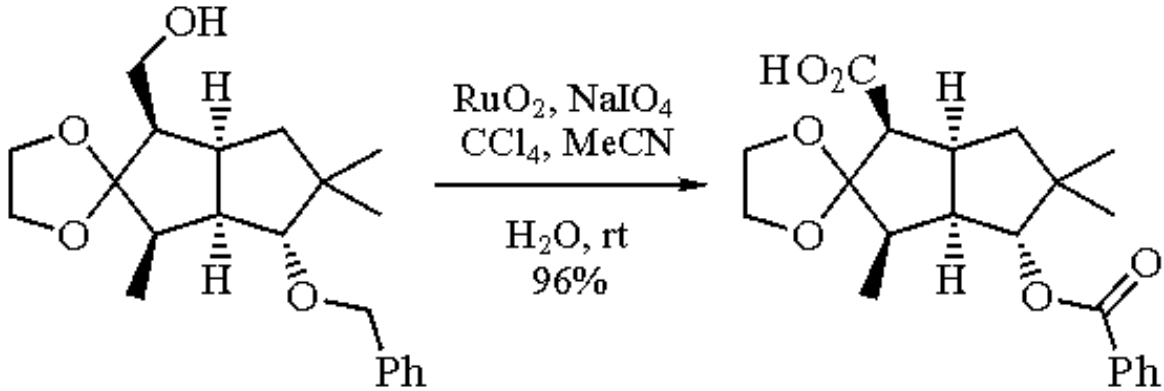

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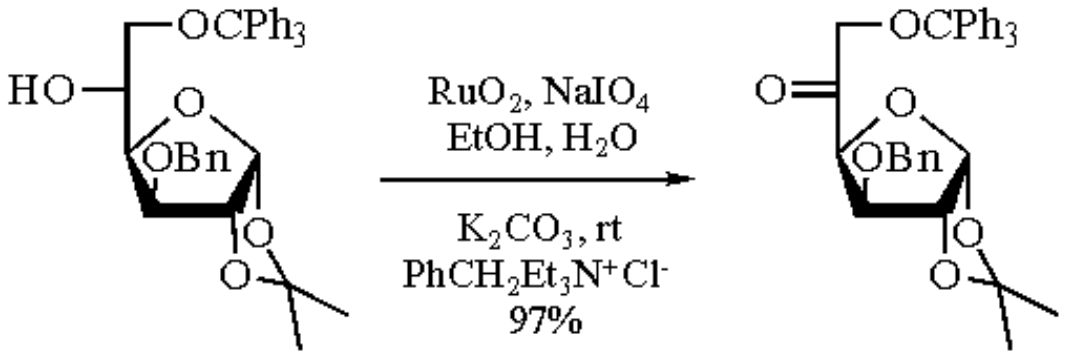

(17)

Cyclic ethers are also oxidized, yielding lactones (eq 18).[40] Although secondary positions are usually more reactive towards oxidation than tertiary positions, the regioselectivity of RuO_4 can be strongly dependent on steric factors (eq 19).[41] In those cases in which lactones are unstable under aqueous conditions (notably δ- and ε-lactones), the corresponding diacids are the final products, presumably via the intermediacy of lactols (eq 20).[42]

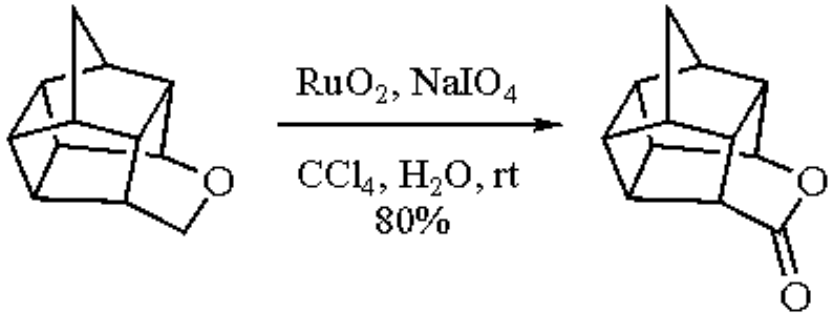

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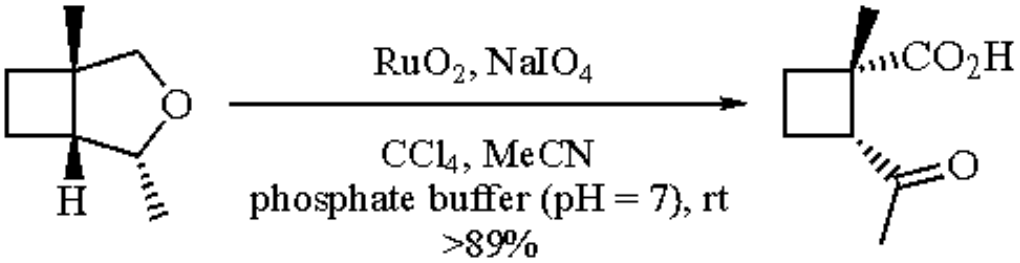

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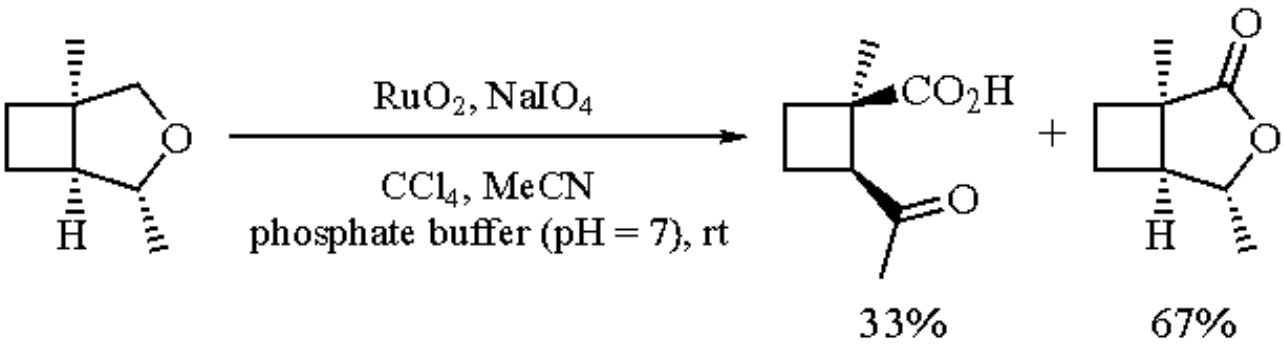

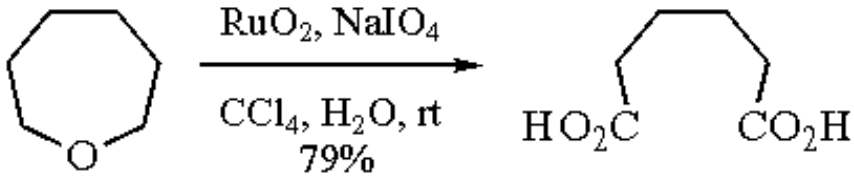

(20)

RuO_4 also oxidizes alkyl amines to mixtures of nitriles and amides,[43] cyclic amines to lactams,[44] and amides (cyclic or acyclic) to imides (eq 21),[45] including an improved procedure that uses ethyl acetate as the organic solvent in the biphasic solvent system, enhancing both the solubility of the substrates and the rate of reaction.[46]

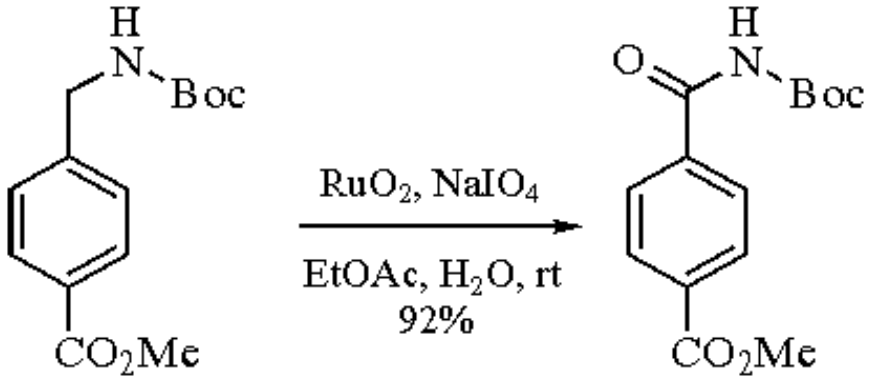

(21)

RuO_4 usually reacts with unsaturated systems, giving cleavage of the C-C bonds. Although epoxide formation has been detected in small amounts (ca. 1%),[47] it can be the principal reaction when the double bond is located in a very hindered position (eq 22).[48] With 1,5-dienes, unexpected oxidation results are obtained. Thus oxidation of geranyl acetate leads to a tetrahydrofuran mixture, instead of the cleavage products (eq 23).[8] Nonterminal alkynes are also oxidized without cleavage, yielding vicinal diketones (eq 24).[49]

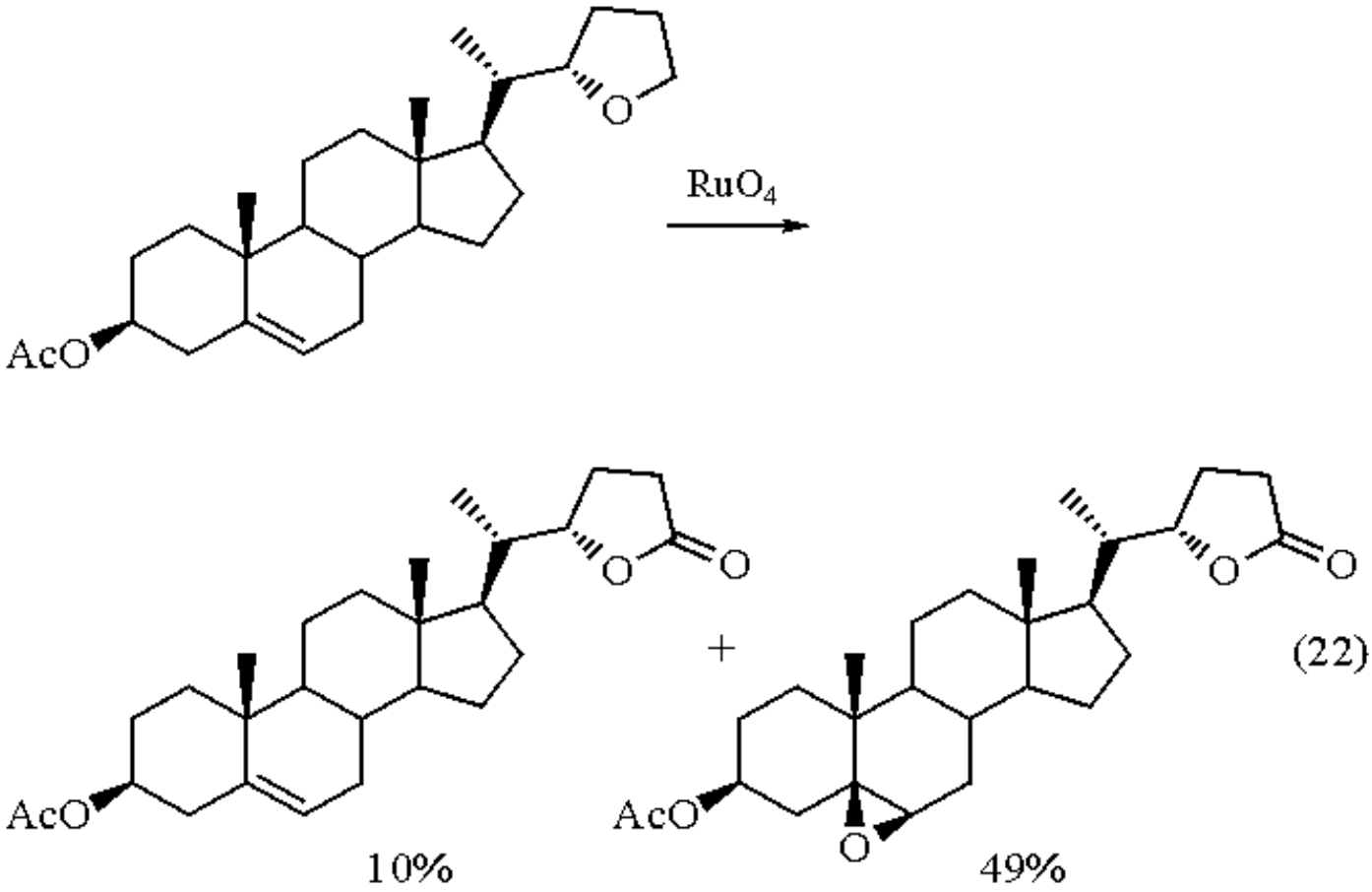

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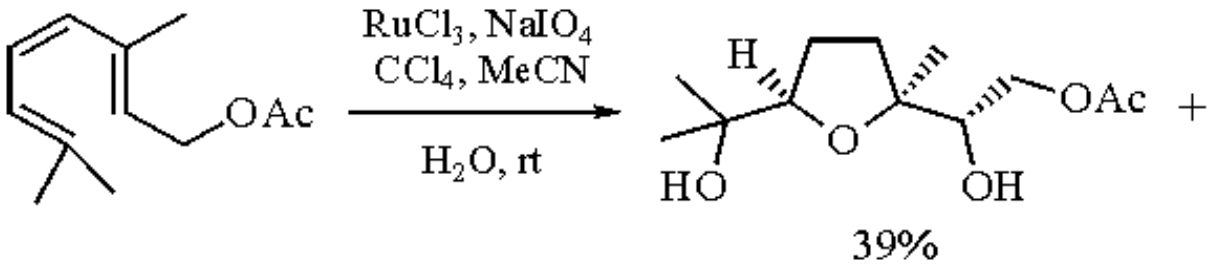

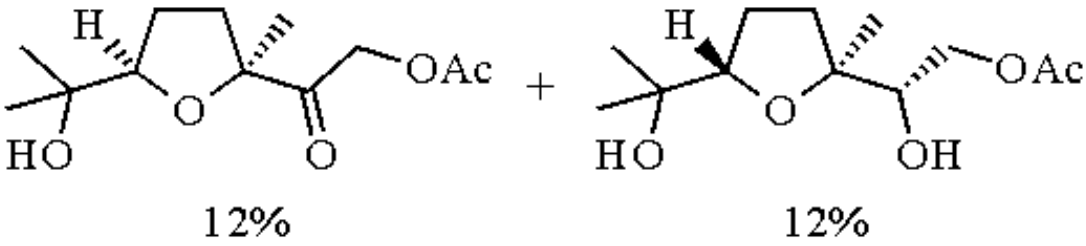

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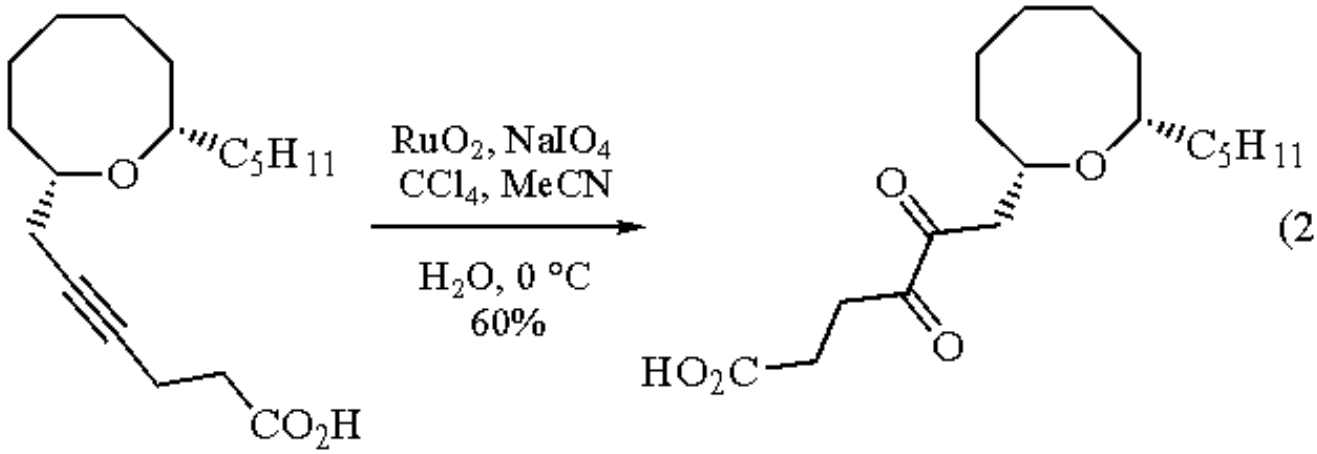

(24)

RuO_4 is also capable of oxidizing C-H bonds in bridged bicyclic and tricyclic alkanes to alcohols by insertion of oxygen (eq 25).[50] Although epoxides survive RuO_4 oxidations, when such functionality is located in this kind of bridged system a tandem ruthenium-catalyzed rearrangement/oxidation occurs (eq 26).[51]

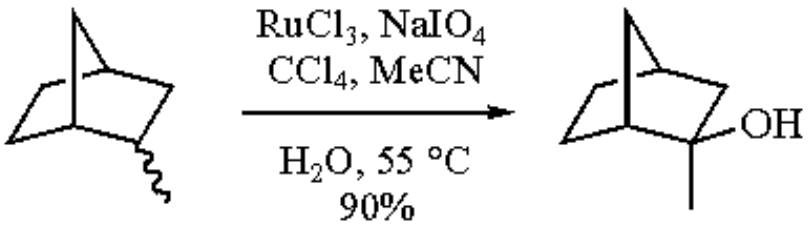

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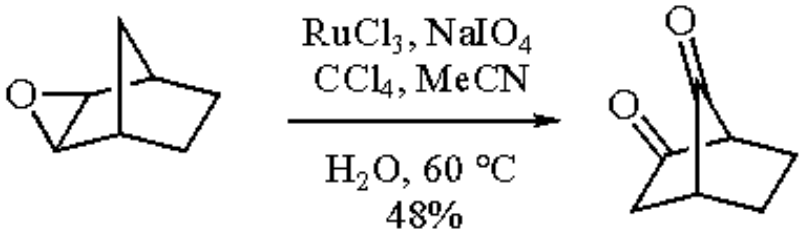

(26)

Most of the common protecting groups used in organic synthesis are stable under RuO_4 oxidation conditions (eq 27).[52] Generally it is only necessary to carry out the reaction at 0 °C or perform it under buffered conditions when acid-sensitive groups are present, such as tetrahydropyranyl (eq 28)[33] or silyl ethers (eq 29).[53]

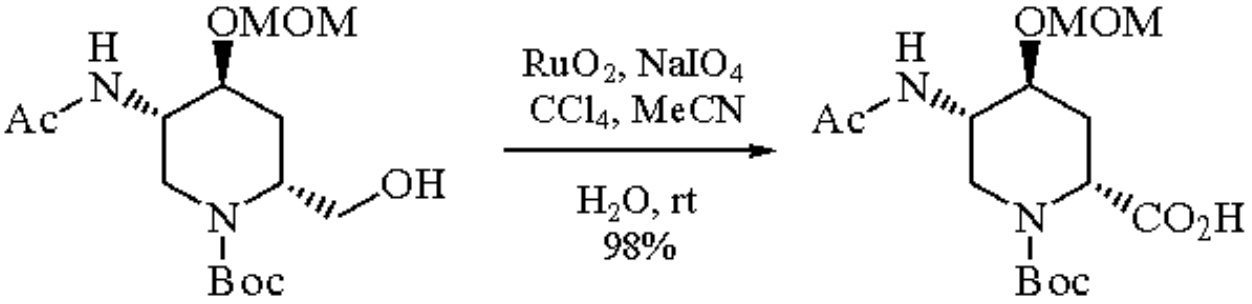

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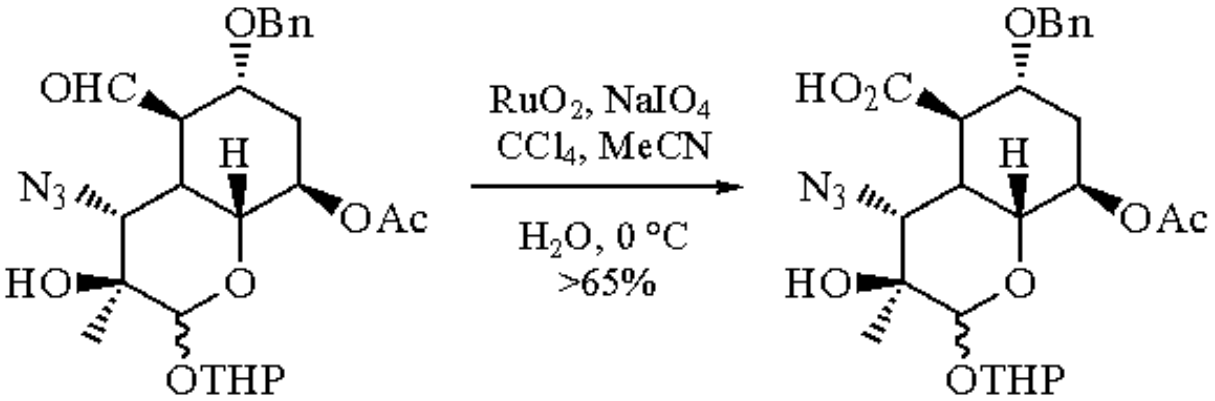

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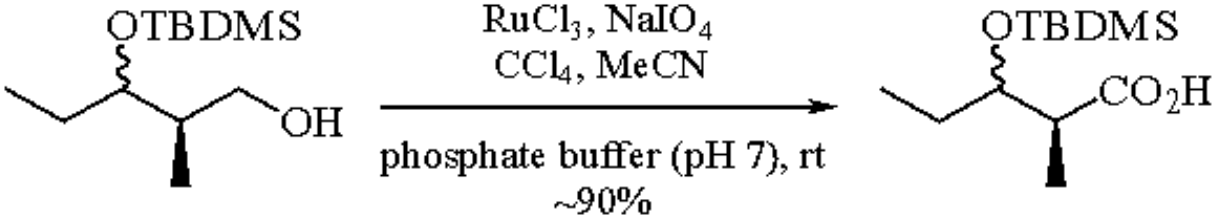

(29)

Functional Group Oxidations with Bond Cleavage.

Carbon-carbon double bonds are readily cleaved by RuO_4 to give ketones and aldehydes or carboxylic acids. In this respect the greater vigor of RuO_4 as an oxidant stands in marked contrast to that of ***Osmium Tetroxide*** (eq 30),[54] which also reacts with C-C double bonds but does not cleave them. While carboxylic acids are usually the final products, sometimes under neutral conditions aldehydes can be obtained from double bonds that are not fully substituted.[55] The cleavage of such double bonds proceeds by the route: alkene -> dialdehyde -> diacid.[5a] RuO_4 is also indicated to carry out oxidations of substrates with double bonds resistant to other oxidizing agents, such as OsO_4, ***Potassium Permanganate***, and ***Ozone*** (eq 31).[56] Degradative oxidations of unsaturated C-C bonds with loss of carbon atoms occur with terminal alkynes (eq 32),[5b] cyclic allylic alcohols (eq 33),[57] and α,β-unsaturated ketones.[57]

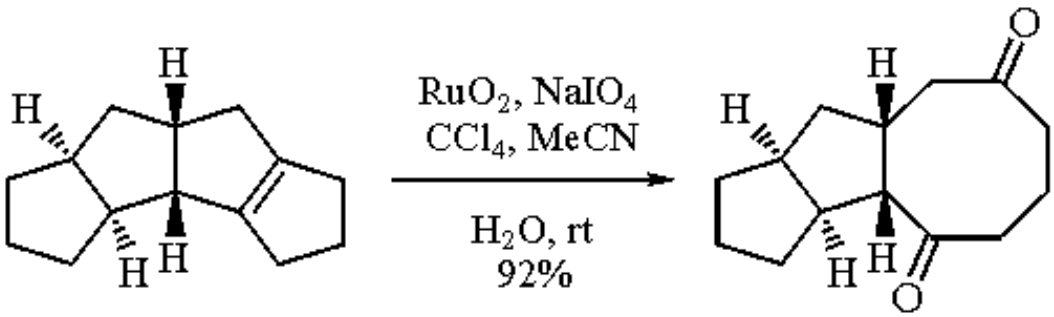

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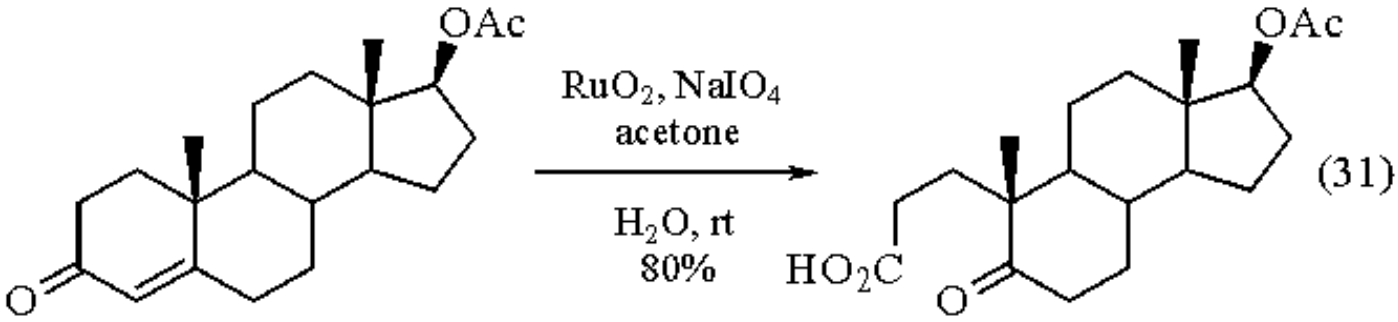

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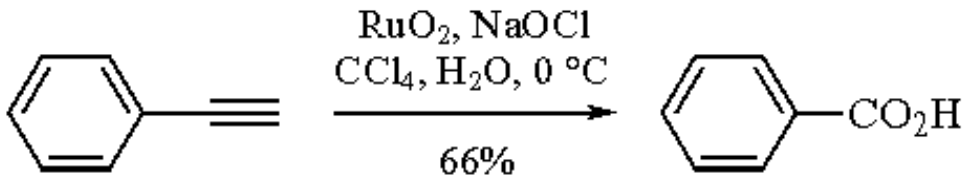

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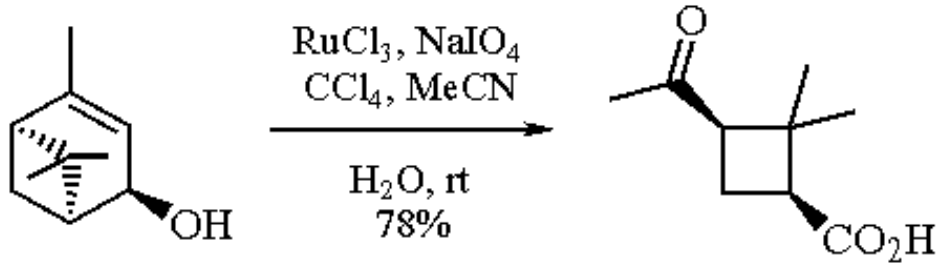

(33)

RuO_4 also cleaves α-chloroenol derivatives obtained from α,α´-dichlorocyclobutanones to give dicarboxylic acids through successive treatment with ***n-Butyllithium***, ***Acetic Anhydride***, and ***Sodium Periodate***-RuO_2 (eq 34).[58,59]

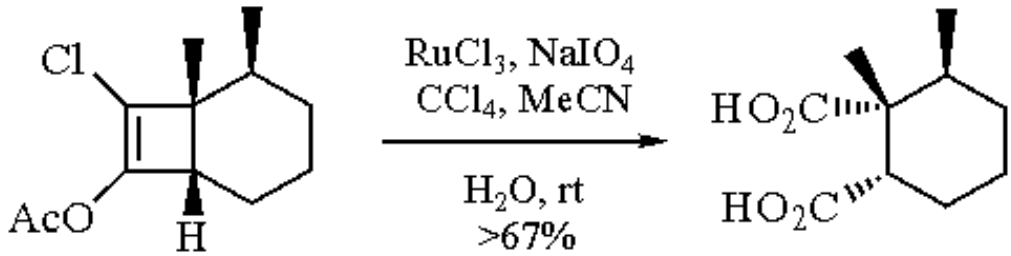

(34)

RuO_4-catalyzed oxidation of arenes can proceed in two ways: (a) the phenyl ring can be cleaved from R-Ph to R-CO_2H (eq 35);[8] (b) the phenyl ring can be degraded to form a dicarboxylic acid in polycyclic aromatic hydrocarbons (eq 36).[60] An electron-donating substituent favors cleavage of the substituted ring, while an electron-withdrawing substituent favors cleavage of the unsubstituted ring. Thus selective oxidation of the more activated ring can be performed with high selectivity. When acid-sensitive groups are not present, an improved procedure that utilizes periodic acid instead of sodium periodate can be used, preventing the problems associated with the precipitated sodium iodate, allowing the reaction to go to completion, and permitting oxidation reactions to be run on larger scales (eq 37).[61]

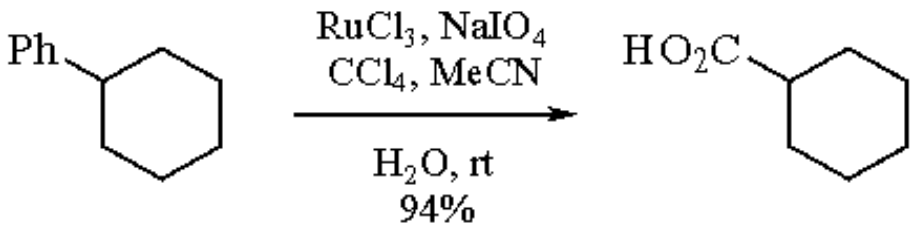

(35)

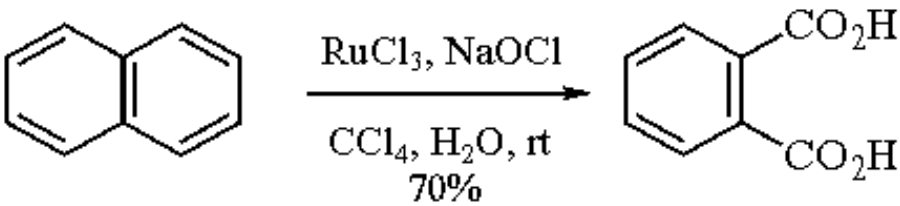

(36)

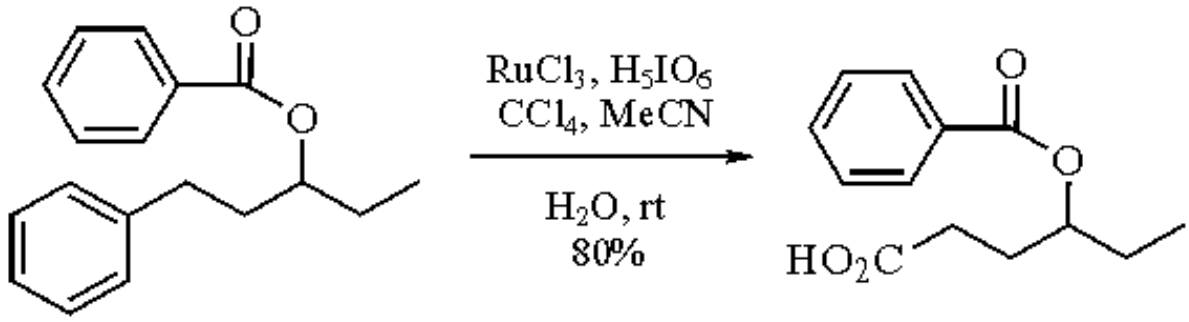

Furan[62] (eq 38),[63] thiophene (eq 39),[64] and benzopyridine rings (eq 40)[65] are also cleaved by catalytic RuO_4 to carboxylic acids. When pyridine derivatives are not oxidized, they can be transformed into their *N*-oxides prior to the oxidation to decrease the ability of the nitrogen to complex with ruthenium, albeit with low yields (eq 41).[64]

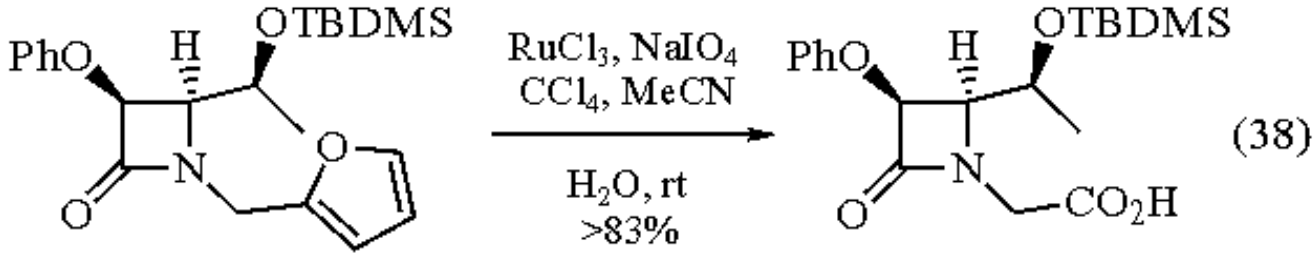

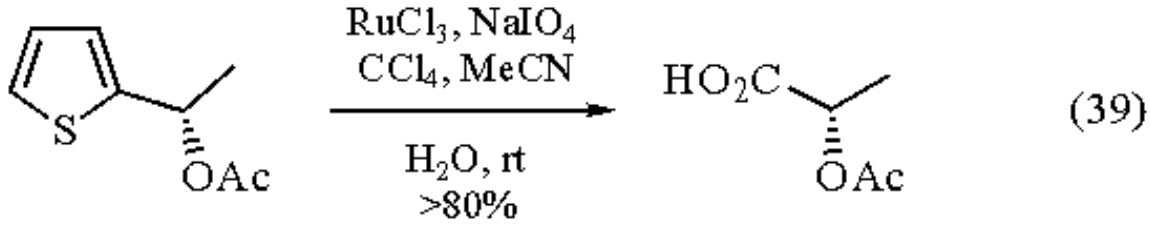

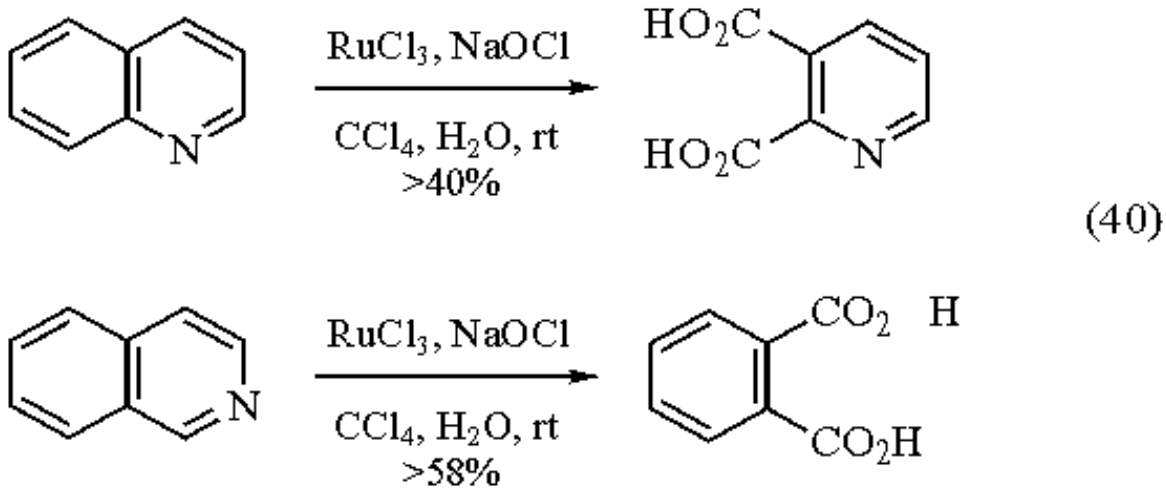

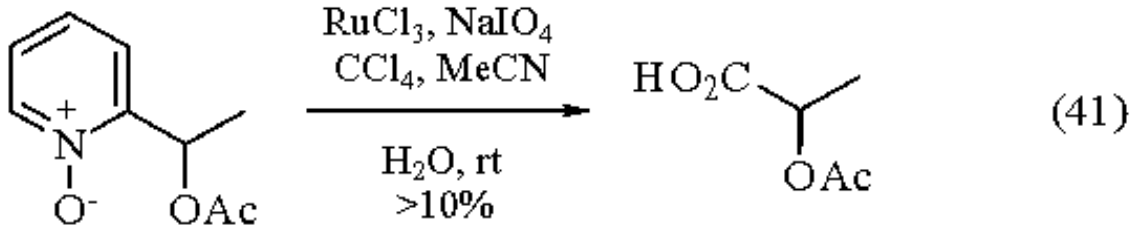

Vicinal diols are cleaved to give carboxylic acids (eq 42) following the route: glycol -> α-ketol -> diacid. A diketone is apparently not an intermediate in this oxidation.[5a] The mildness of the reaction conditions is underscored by the lack of epimerization shown in eq 43.[8] This feature has been proved to be general when RuO_2-$NaIO_4$ is used to oxidize chiral diol benzoates, this being a useful method to synthesize chiral α-benzoylcarboxylic acids (eq 44).[66]

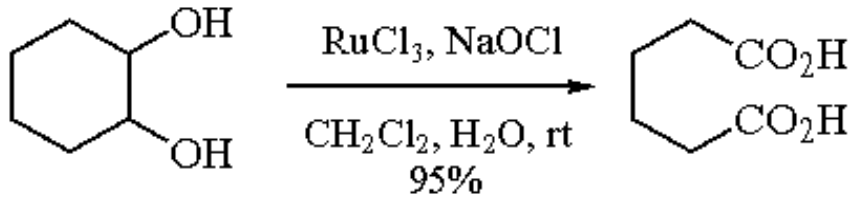

(42)

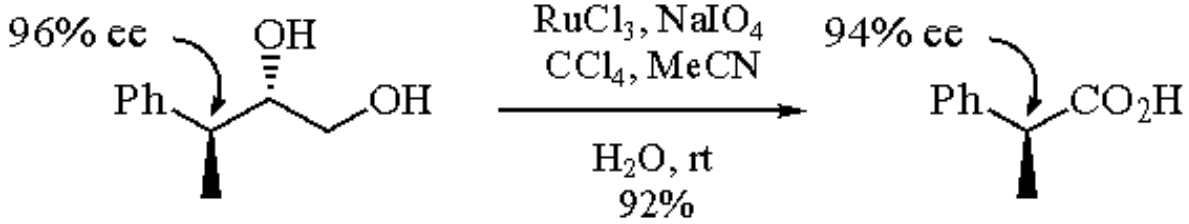

(43)

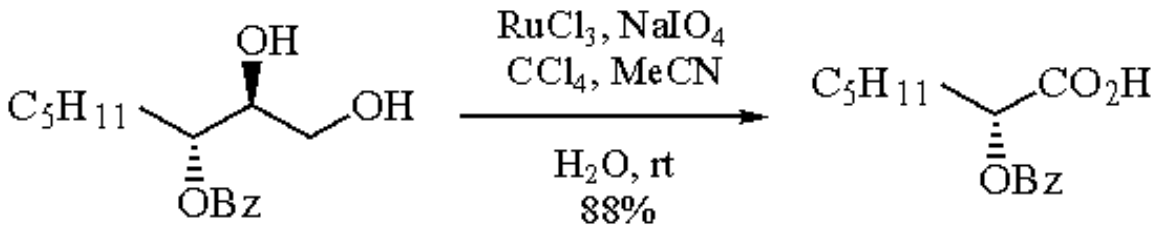

(44)

Other vicinal dioxygenated functionalities present (eq 45)[5a] or generated in situ undergo oxidation with C-C bond cleavage by RuO_4 to give carboxylic acids, with (eq 46)[67] or without (eq 47)[68] loss of carbon atoms.

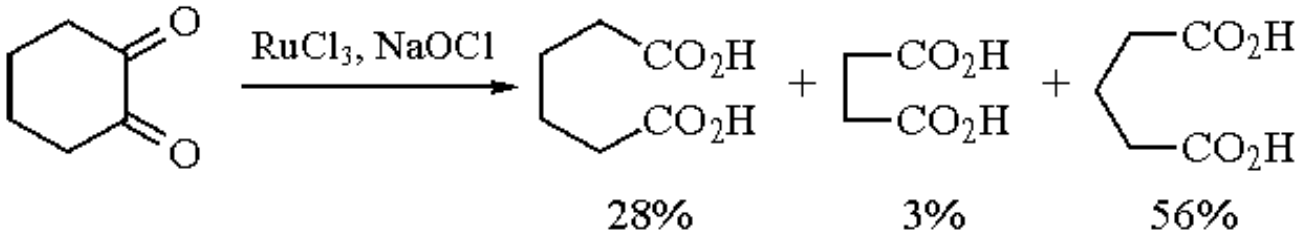

(45)

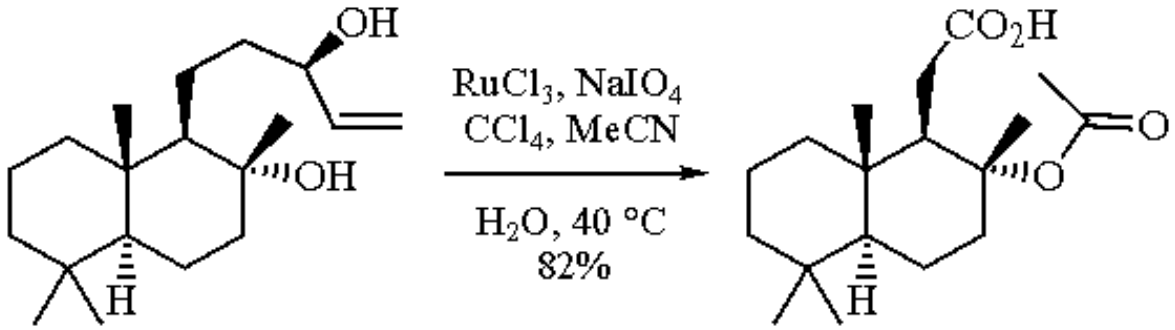

(46)

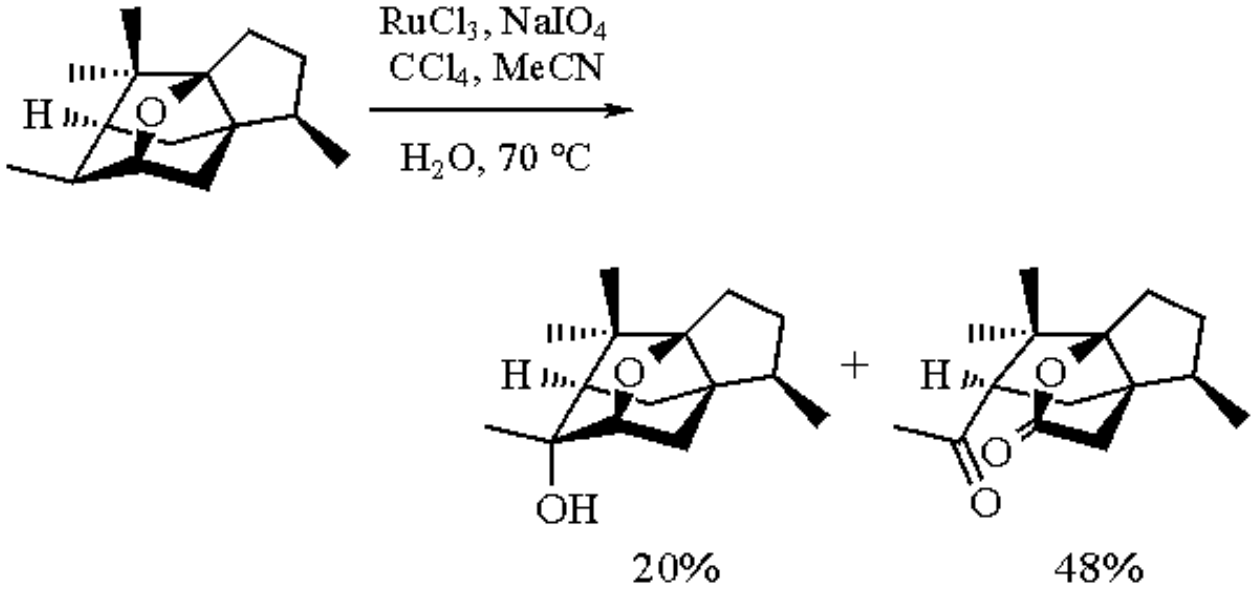

(47)

RuO_4 is also used to cleave oxidatively carbon-boron bonds in cyclic alkylboranes, presenting advantages over the usage of Cr^{VI} for the same purpose or even the oxidation of the corresponding alcohols (eq 48).[69]

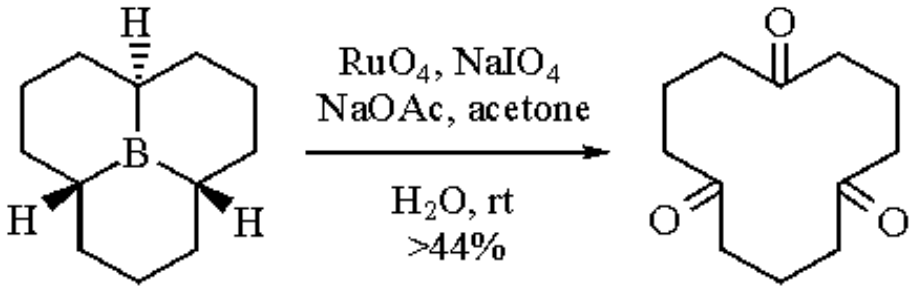

(48)

Another formal carbon-heteroatom bond cleavage occurs in the oxidation of cyclic ethers that give cyclic products unstable to the oxidation conditions (eq 49).[42]

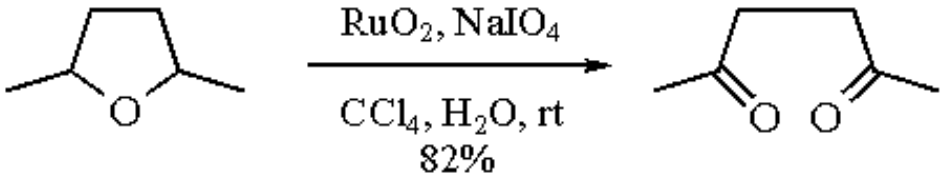

(49)

As pointed out, ketones are stable under RuO_4 oxidation conditions, although cyclic ketones can undergo Baeyer-Villiger reaction when ***Sodium Hypochlorite*** is used as co-oxidant (eq 50).[70]

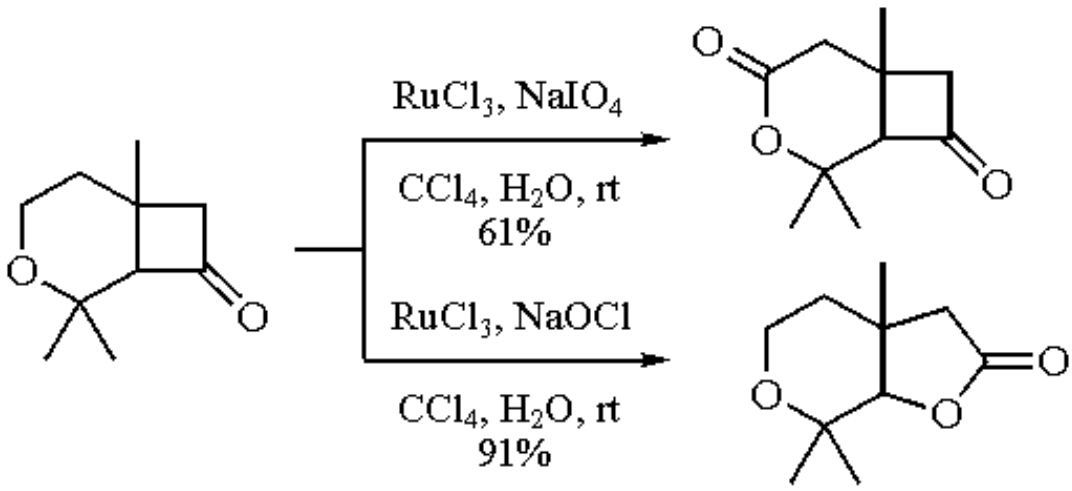

(50)

Other Ruthenium-Based Oxidation Reagents.

Less reactive oxidants are obtained by lowering the oxidation state of ruthenium. One example is the ruthenate ion (RuO_4^{2-}) which, as mentioned above, is formed when RuO_4 is treated with alkaline solutions. The most important synthetic applications of such ions is in the oxidation of alcohols in basic media to give carboxylic acids or ketones.[71] In general, RuO_4^{2-} does not appear to oxidize isolated C-C double bonds at room temperature (eq 51).[72]

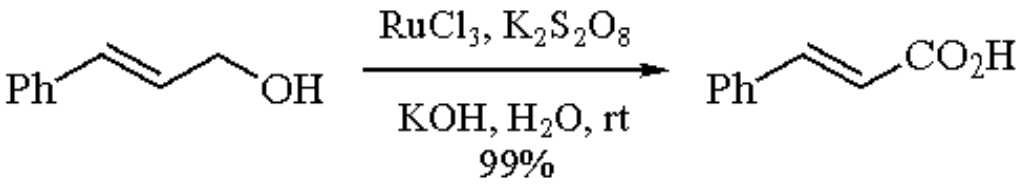

(51)

When there is no reductive pathway for the elimination of ruthenate esters, RuO_4^{2-} has been used as an alternative to RuO_4 (eq 52).[40]

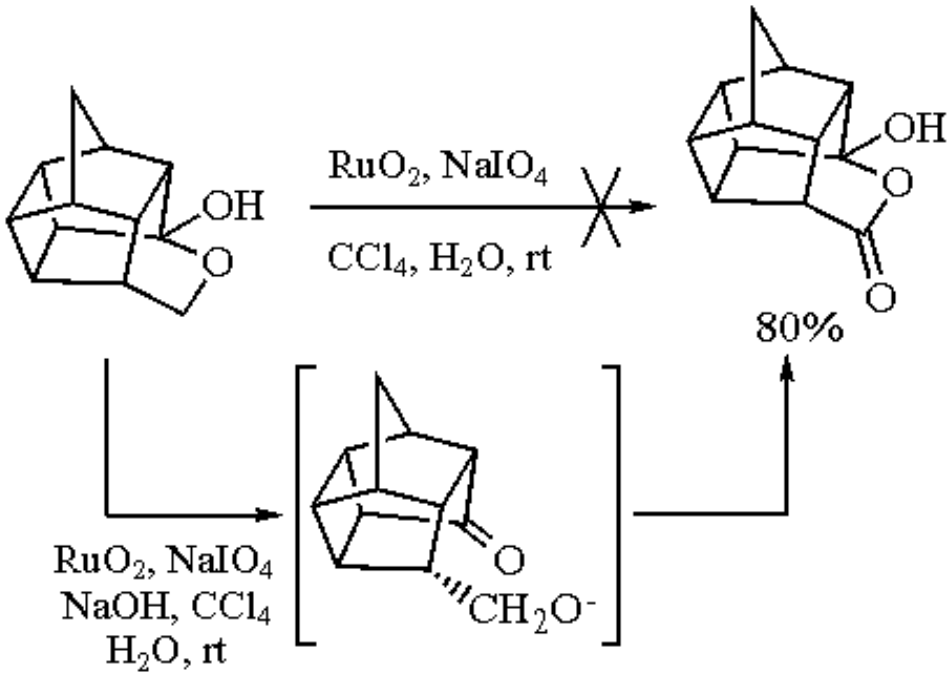

(52)

The perruthenate ion RuO_4^- is also useful for the oxidation of primary alcohols, nitroalkanes, primary halides, and aldehydes to acids.[73] When tetraalkylammonium salts are added to the RuO_4^- solutions, stable tetraalkylammonium perruthenates are obtained. Tetra-*n*-butylammonium perruthenate (TBAP) and tetra-*n*-propylammonium perruthenate (TPAP) are used to oxidize successfully alcohols to carbonyl compounds (eq 53),[23] and sulfides to sulfones[74] under very mild conditions, employing as co-oxidant ***N-Methylmorpholine N-Oxide*** (NMO) (see ***Tetra-n-propylammonium Perruthenate***).

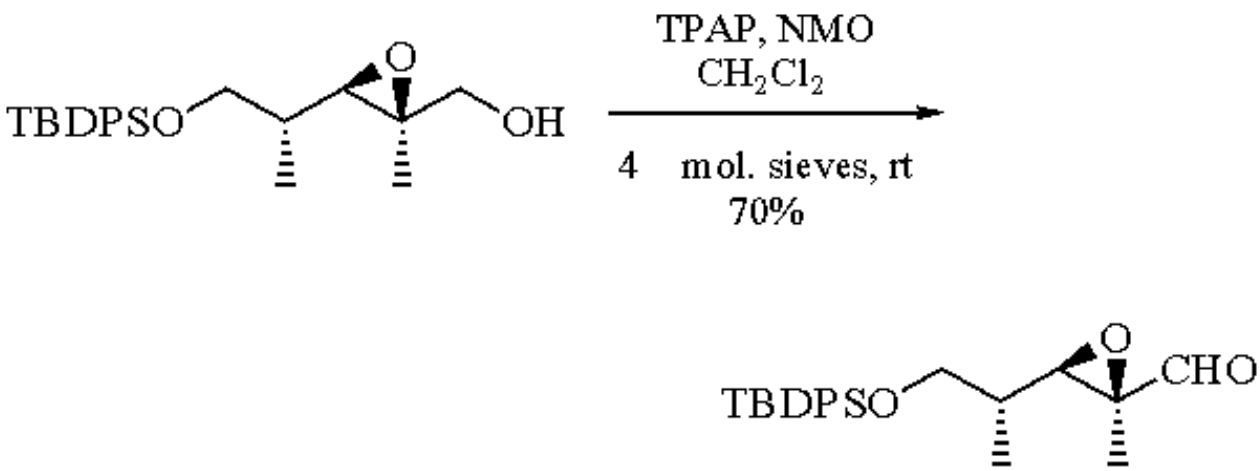

(53)

The behavior of inorganic transition metal oxidizing agents can be modified by the introduction of ligands. Electron-rich ligands, which increase the basicity of the metal and moderate its oxidizing power, have been used to improve the selectivity of these oxidation reactions.

Thus porphyryl-[75] and bipyridyl-Ru complexes epoxidize alkenes, instead of cleaving the double bond (eq 54).[47]

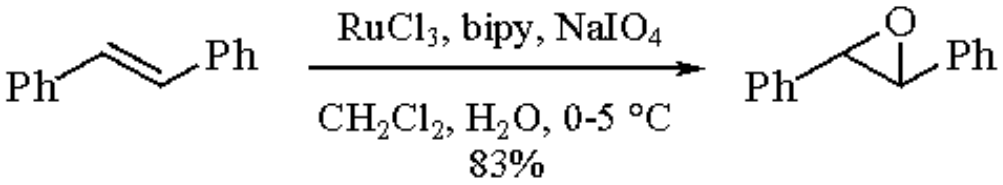

(54)

Several other Ru complexes, along with co-oxidants or hydrogen acceptors, are used as catalysts in oxidation reactions, $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ being the most commonly utilized. The conversion of alkanes and alcohols to aldehydes or ketones is achieved with $RuCl_2(PPh_3)_3$[76] and molecular oxygen,[77] ***Bis(trimethylsilyl) Peroxide***,[78] ***Iodosylbenzene***,[20] ***N-Methylmorpholine N-Oxide*** (eq 55),[79] ***t-Butyl Hydroperoxide***,[80] and hydrogen acceptors.[81] Selective oxidations of primary vs. secondary alcohols are possible (eq 56),[78] and it is also possible to stop the oxidation of primary alcohols at the aldehyde stage by simply controlling the co-oxidant equivalents and reaction times.[20] α-Diketones can be obtained from vicinal diols (eq 57)[82] and nonterminal alkynes (eq 58).[83]

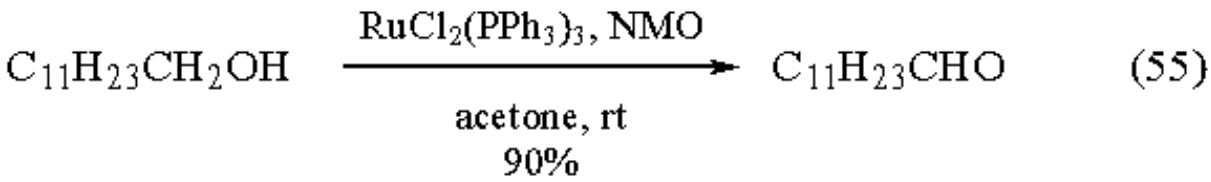

(55)

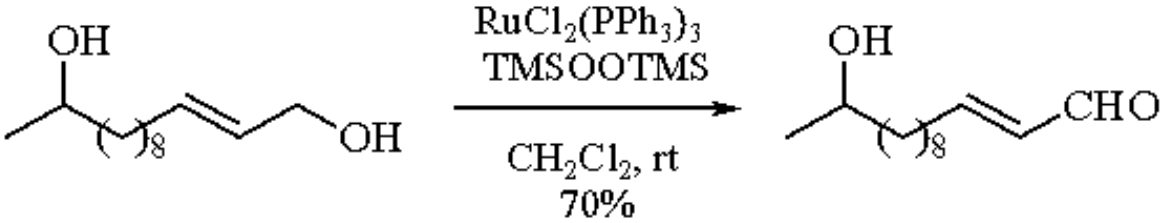

(56)

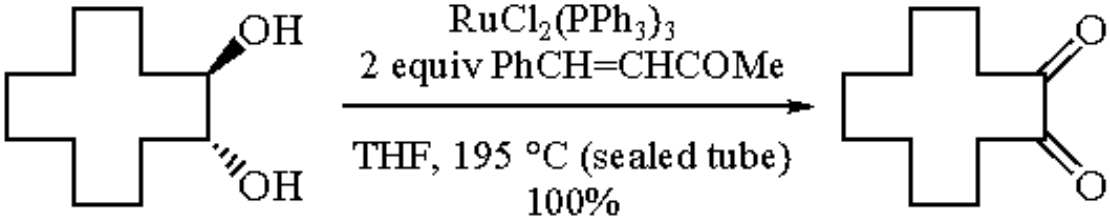

(57)

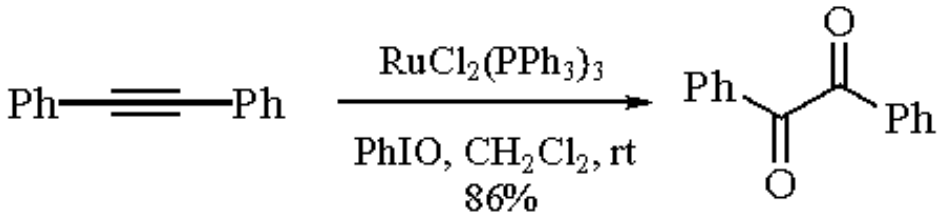

(58)

The combination of $RuH_2(PPh_3)_4$ plus a hydrogen acceptor, like benzalacetone or ***Acetone***, converts unsymmetrically substituted 1,4- and 1,5-diols into β-substituted γ-lactones and γ-substituted δ-lactones, respectively (eqs 59 and 60),[84] also allowing the oxidative condensation of alcohols, or aldehydes and alcohols, to give esters (eq 61).[85]

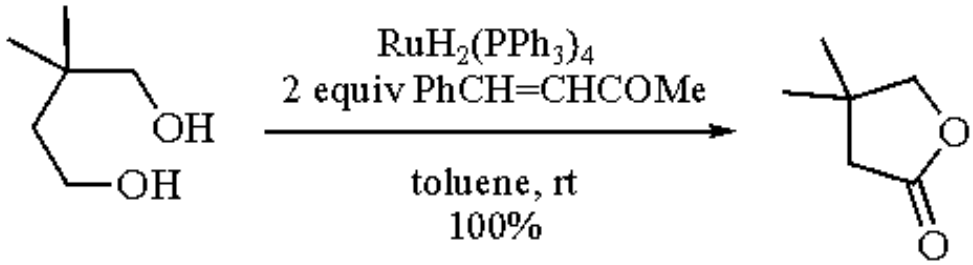

(59)

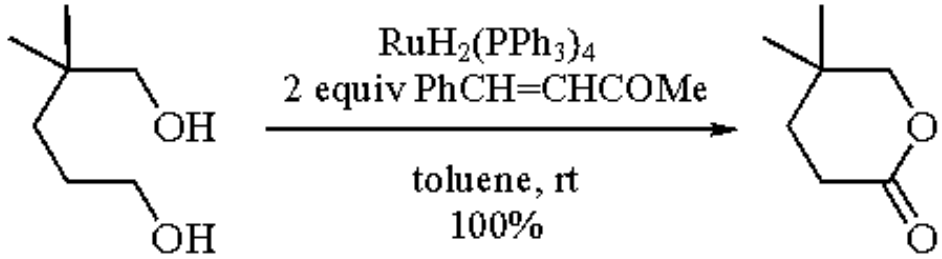

(60)

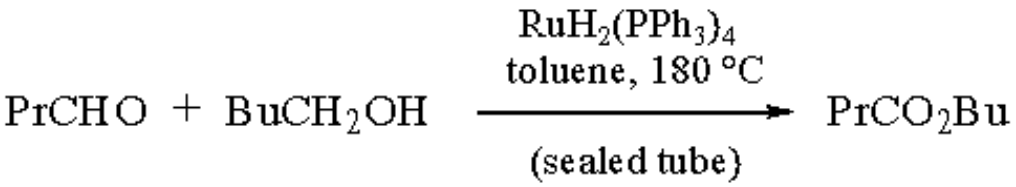

(61)

Oxoruthenium species are also useful in organic oxidations. Thus oxoruthenium(V) complexes obtained from lower valent ruthenium species effect α-oxygenation of tertiary amines[86] and β-lactams (eq 62).[87] $[PPh_4][RuO_2(OAc)Cl_2].2AcOH$ generated from RuO_4 is used to oxidize alcohols and benzyl halides to carbonyl compounds.[88]

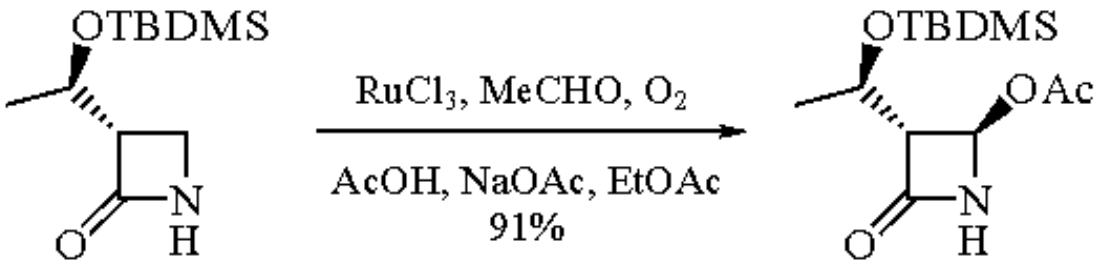

(62)

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Salcomine[1]

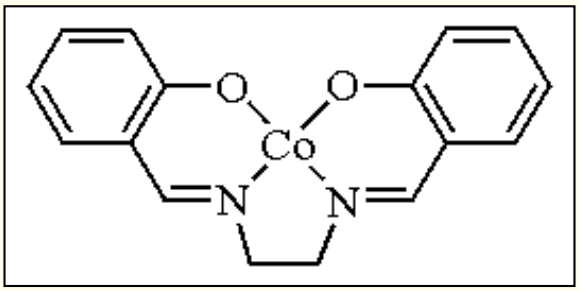

[14167-18-1] · $C_{16}H_{14}CoN_2O_2$ · Salcomine · (MW 325.25)

(oxidizing agent for conversion of phenols to quinones;[3-8] *N*-dealkylation of anilines;[10] 1,4-acetoxylation of dienes;[14] nonoxidative hydration of alkenes and alkynes;[16-18] oxidative carbonylation of amines;[19,20] oxidative cleavage of fused heterocycles;[21,22] oxidation of hydrazones to diazo compounds;[23] catalyst for rearrangements[25,26])

Alternate Names: bis(salicylidene)ethylenediiminocobalt(II); Co^{II}(salen); Co(salen).

Solubility: sol nonpolar solvents including DMF, methanol, chloroform.

Form Supplied in: brown or black-grey powder.

Preparative Method: see Diehl and Hack.[1]

Handling, Storage, and Precautions: may be stored at room temperature in air for long periods of time.

Phenol and Aniline Oxidations.

Salcomine is usually the reagent of choice for the oxidation of *para*-unsubstituted phenols to 1,4-quinones. It serves as a catalyst in this transformation in which molecular ***Oxygen*** is the stoichiometric oxidant. Salcomine compares favorably in ease of preparation, handling, and convenience of workup with the well-known Fremy's salt, previously the standard reagent for this conversion. Reactions take place at room temperature and are generally conducted in DMF.

Originally studied as a synthetic oxygen carrier,[2] salcomine attracted attention in the 1980s when its catalysis of the phenol-to-quinone oxidation[3] was discovered and exploited by synthetic chemists.[4] Its use appears to be restricted to the oxidation of phenols which do not bear electron-withdrawing groups. For example, Parker and Petraitis were unable to oxidize 2-hydroxy-3-methoxypropiophenone to the corresponding *p*-quinone,[5] but found that the acetalized substrate gave a good yield of the acetal quinone (eq 1).[6]

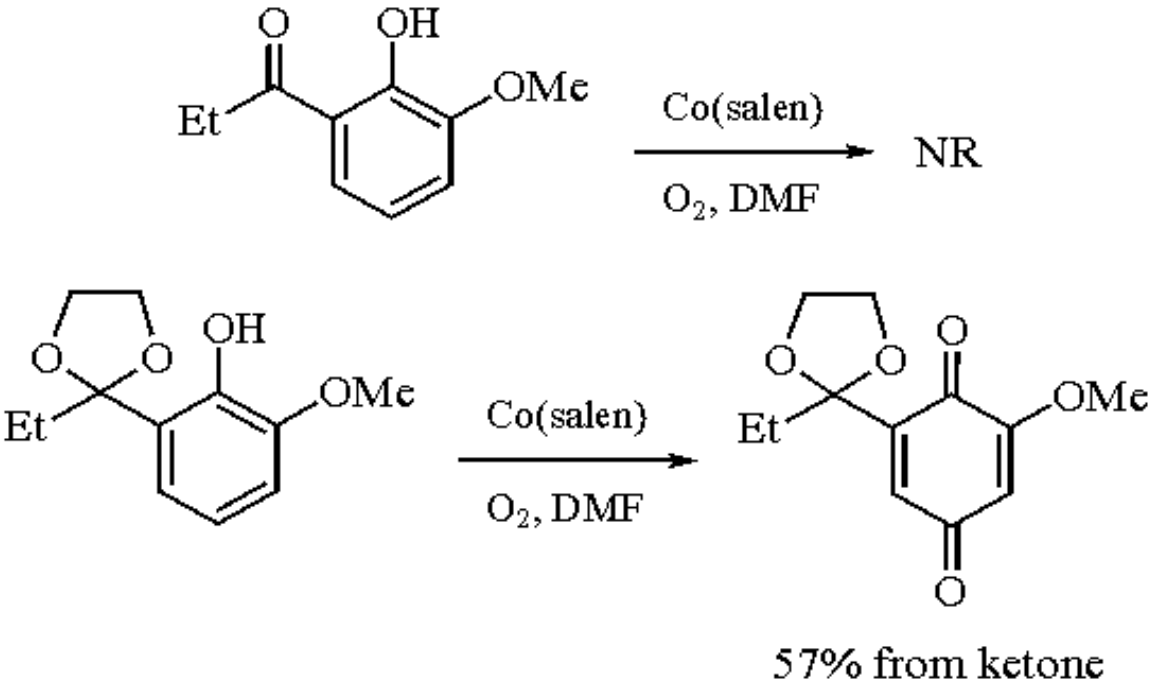

A particularly useful example of the phenol-to-quinone conversion is the oxidation of inexpensive 1,5-naphthalenediol to a 5:1 mixture of juglone and its *o*-quinone regioisomer (eq 2). The salcomine oxidation of 5-methoxy-1-naphthol produces juglone methyl ether and its regioisomer as a 4:1 mixture.[7]

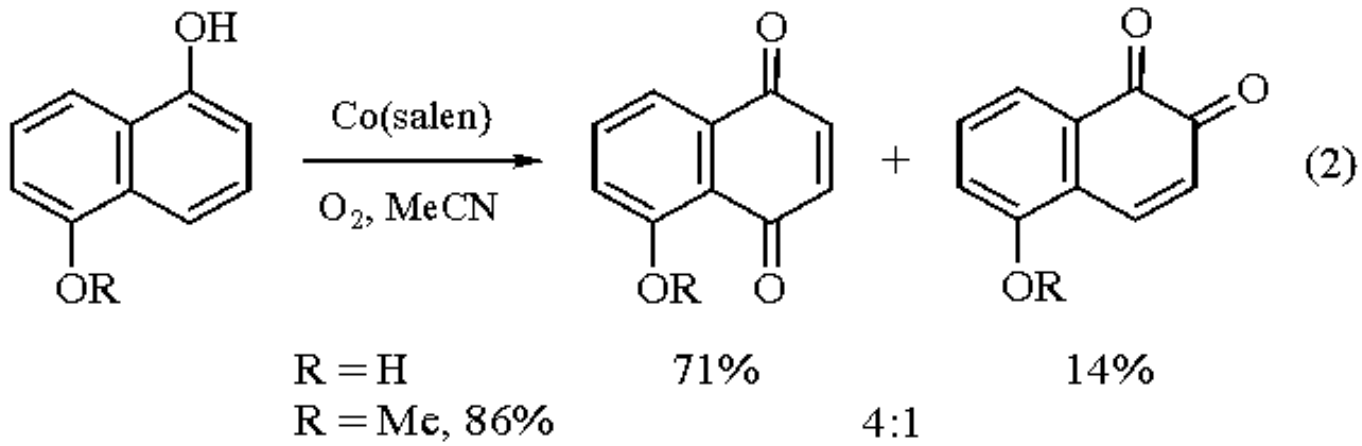

Thymoquinone, viewed as a convenient starting material for the synthesis of sesquiterpenes, was conveniently obtained from thymol in 71-84% yield and from carvacrol in 79-93% yield (eq 3).[8]

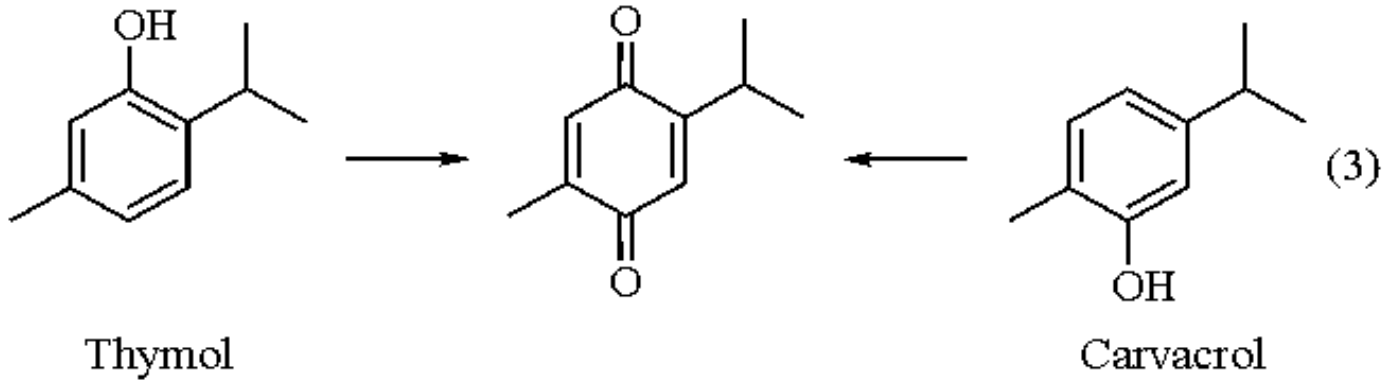

The oxidation of estrone to the corresponding quinol and an interesting, highly oxygenated steroid was effected by salcomine catalysis (eq 4).[9]

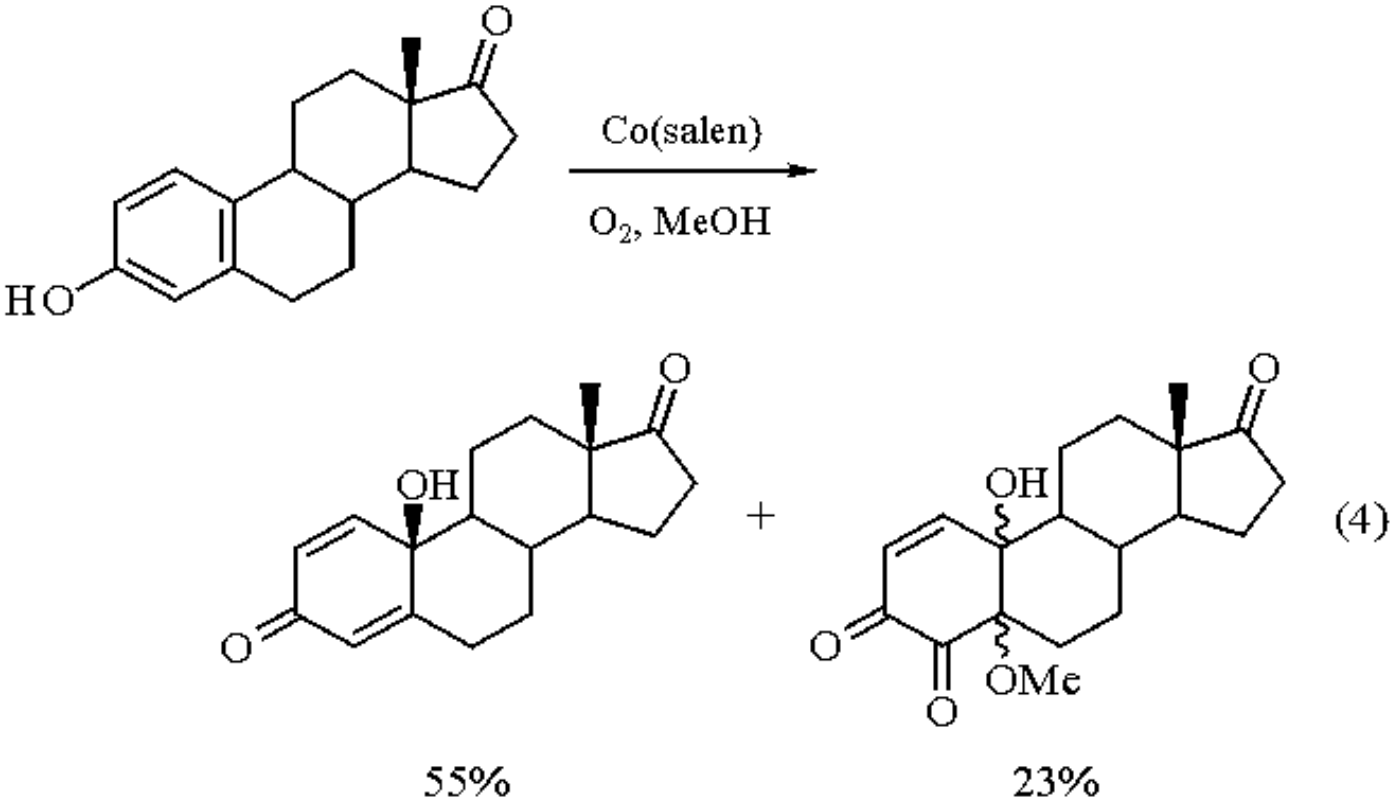

Salcomine-catalyzed O_2 oxidation of *N*-alkyl aromatic amines (substituted at the *meta* or *para* position) has been examined. Optimized conditions convert *N*-*n*-butyl-4-phenylaniline to 4-phenylaniline in 69% yield.[10] For some examples the imine intermediate has been isolated.[11,12] A 4-methoxy-2,6-disubstituted aniline was converted to the corresponding quinone imine. However, 2,4,6-trisubstituted anilines (where the substituents are *t*-butyl and aryl) are converted to 4-peroxy-2,5-cyclohexadien-1-imines and nitrobenzenes.[13]

Other Oxidations.

A triple catalytic system involving Pd^{II}, ***1,4-Benzoquinone***, salcomine, and air was used to effect the 1,4-acetoxylation of conjugated dienes (eq 5).[14] Co(salophen) (**1**) and Co(TPP) (TPP = tetraphenylporphyrin) were more efficient reagents for this transformation, however. Co(salophen) and Co(TPP) also served to reoxidize hydroquinone to quinone in an allylic oxidation system (eq 6). ***Iron(II) Phthalocyanine*** (Fe(Pc)) was more effective in this system and Co(salen) was not active.

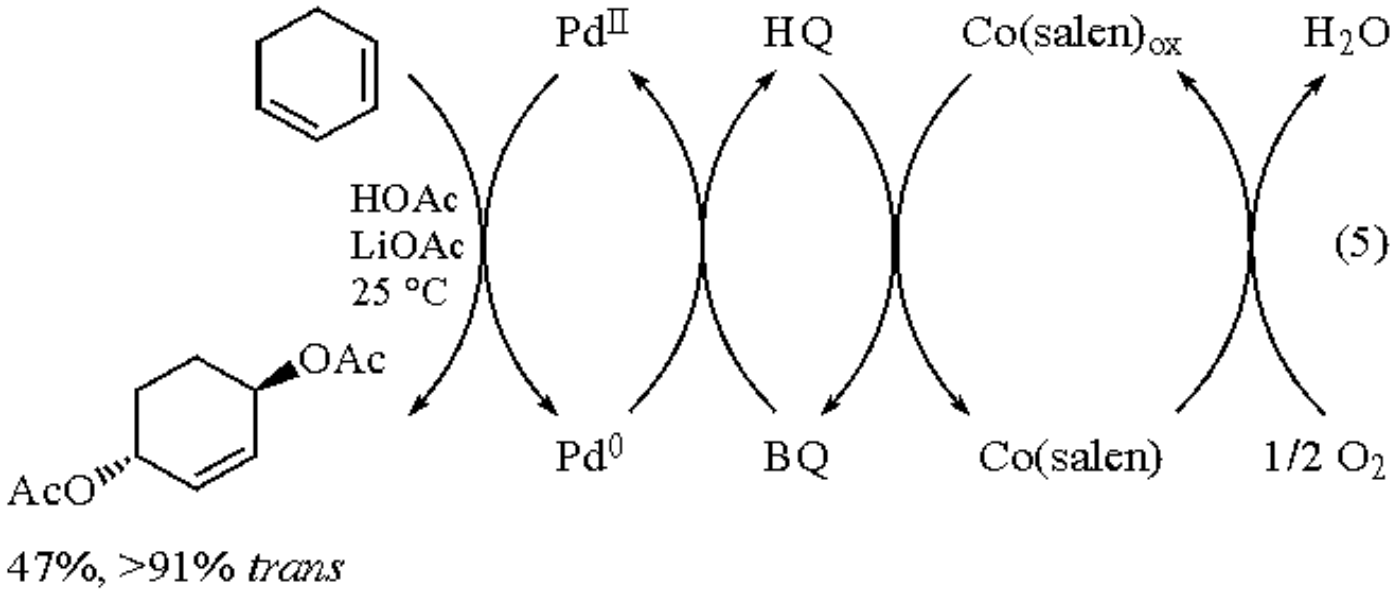

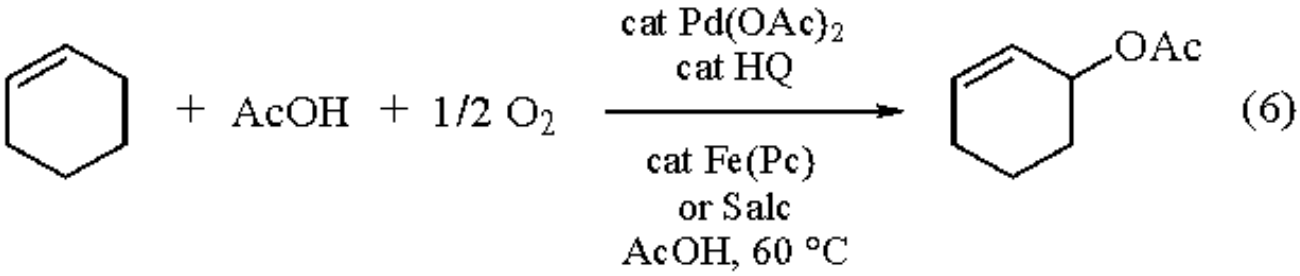

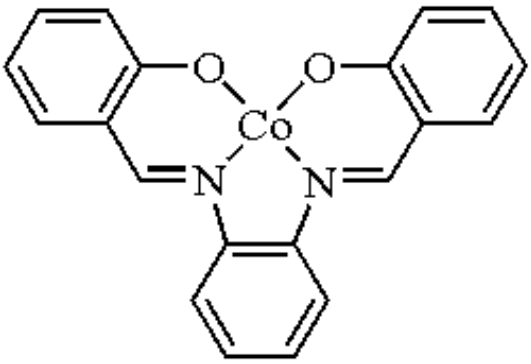

(1)

An oxidation-reduction mechanism is postulated for the salcomine-catalyzed hydration of styrenes. Further oxidation of the product affords aryl ketones.[15] The Co(TPP) oxidation can be carried out in the presence of borohydride, and under these conditions only the benzylic alcohol product is obtained.[16] When chiral Co(salen) derivatives were used in the styrene hydration, modest yields (18-31%) of 1-phenylethanol with modest enantiomeric excesses (0-38%) were reported.[17]

The analogous hydration of terminal alkynes is also proposed to proceed through an oxidation-reduction mechanism.[18] Mandelic and glyoxylic ester byproducts are also produced.

Salcomine catalyzes the oxidative carbonylation of primary aromatic amines in methanol. The primary products in most cases are the symmetrical urea and the methyl carbamate. Under optimized conditions, *o*-aminobenzamide affords the quinazolinedione in 64% yield (eq 7).[19] Iodide was found to promote the oxidative carbonylation in some systems.[20]

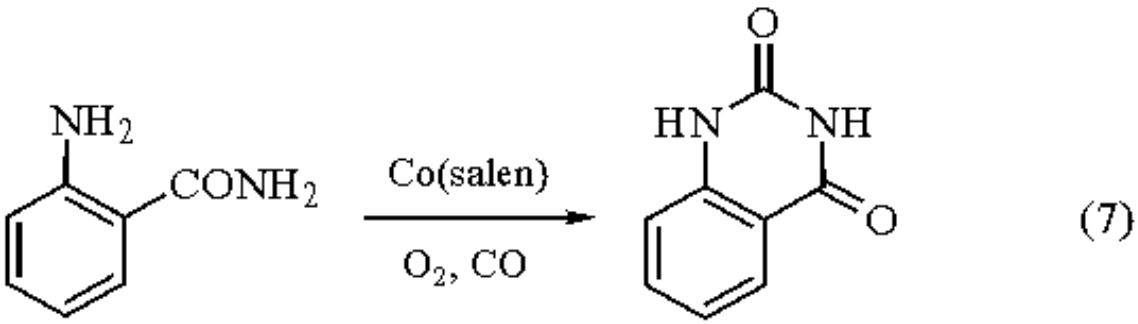

Several other oxidations have been the subject of limited studies. Salcomine and its derivatives catalyze the oxidative cleavage of fused heterocycles, including the conversion of 3-hydroxyflavones to *o*-aryloxybenzoates[21] and 3-substituted indoles to *o*-formylaminoacetophenone derivatives.[22] Hydrazones are oxidized to diazo compounds.[23] The reduction of NO to N_2 is effected by ***Sodium Borohydride*** in the presence of Co^{II}(salen).[24]

Nonoxidative Conversions.

Co(TPP) and Co^{II}(salen) catalyze the rearrangement of monocyclic endoperoxides to furans.[25] Salcomine and several analogs are reported to catalyze the cycloreversion of TMDC-Q to TMDC-NBD (eq 8). Carboxy-*N*,*N*-disalicylidenephenylenediiminatocobalt was immobilized on alumina to afford a packing material for a fixed bed reactor which was effective in catalyzing this reaction.[26]

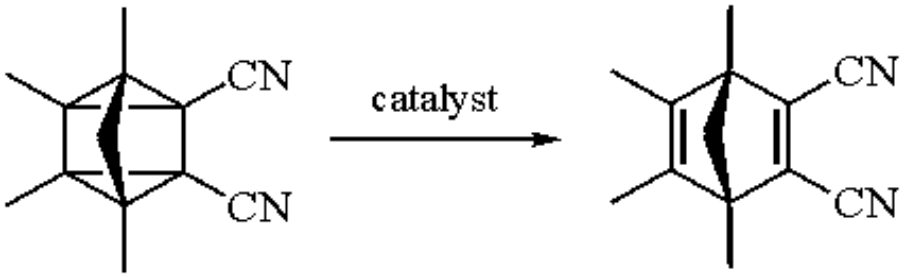

(8)

TMDC-Q TMDC-NBD

Related Reagents.

Cobalt Salen Complexes; ***Cobalt Salophen Complexes***.

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Samarium(0)[1]

Sm

[7440-19-9] · Sm · Samarium(0) · (MW 150.36)

(used with diiodomethane to iodomethylate ketone and aldehyde substrates;[2] cyclopropanates esters and α-halo ketones in the presence of diiodomethane to generate the one-carbon homologated product;[2a,b,3] promotes the selective and directed cyclopropanation of allylic alcohols[4-6])

Physical Data: mp 1072 °C; bp 1900 °C; *d* 7.470 g cm^{-3}.

Form Supplied in: silvery metal; tarnishes on exposure to air; 40 mesh solid, ingot, chip, and foil (all commercially available).

Handling, Storage, and Precautions: moderately air- and moisture-sensitive. Should be handled accordingly under an inert atmosphere.

Iodomethylation of Ketones and Aldehydes.

Samarium metal may be utilized in conjunction with ***Diiodomethane*** to accomplish iodomethylation reactions.[2] A wide variety of ketone and aldehyde substrates may be converted to the corresponding iodohydrins in good to high yields, providing an efficient means for one-carbon homologation (eq 1).

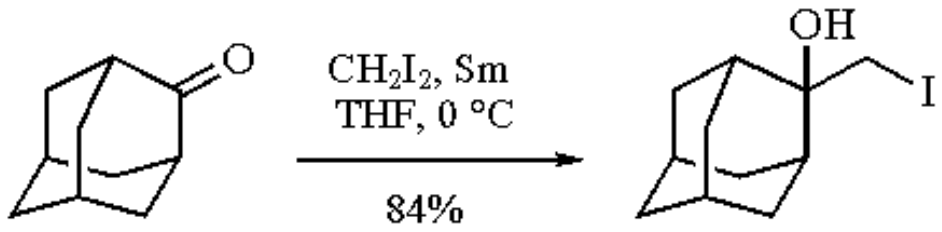

(1)

Even readily enolizable substrates such as cyclopentanone are converted to the corresponding iodohydrin in high yield upon treatment with samarium and diiodomethane (eq 2). Highly hindered ketones do not undergo iodomethylation; α,β-unsaturated carbonyl compounds subjected to these reaction conditions provide only moderate yields of the desired products.

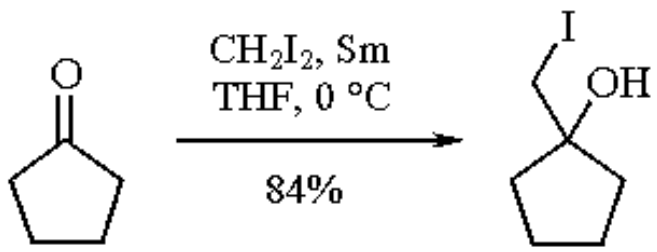

(2)

Cyclopropanation of Esters and α-Halo Ketones.

Esters react with diiodomethane in the presence of samarium to afford the 1-substituted cyclopropanols, thereby providing a one-carbon homologation route to these molecules (eq 3).[3] Likewise, α-halo substituted ketones react in a similar manner to provide cyclopropanols (eqs 4 and 5) via a Simmons-Smith-type cyclopropanation of the samarium enolate.[2a,b]

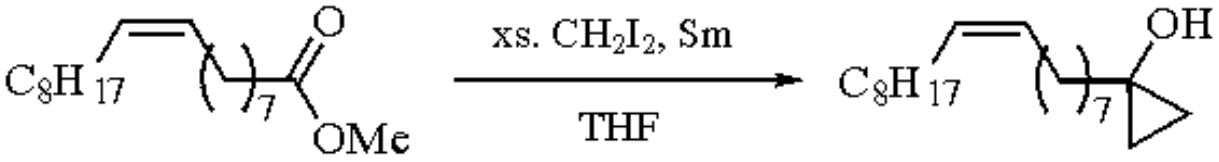

(3)

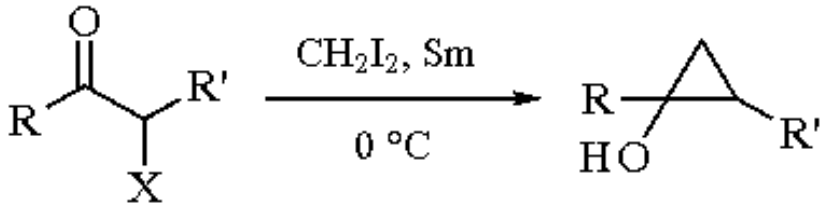

(4)

R, R', X=Ph, H, Br	81%
Ph, H, I	88%
$-(CH_2-)_4$, Br	81%

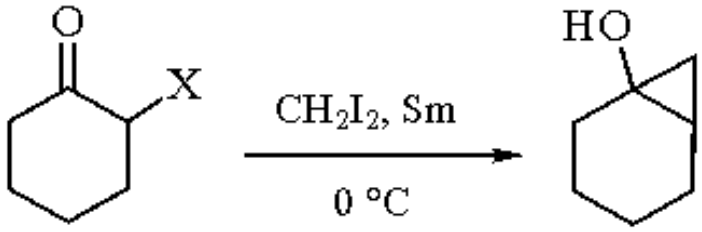

(5)

Directed Cyclopropanation of Allylic Alcohols.

A more efficient method of achieving cyclopropanation involves the use of Sm(Hg) in the presence of ***Chloroiodomethane*** (eq 6).[4] The resulting samarium carbenoid generated under these reaction conditions reacts exclusively with allylic alcohols. Many other functionalities such as isolated alkenes, homoallylic alcohols, and other functionalized alkene substrates are inert under these reaction conditions.

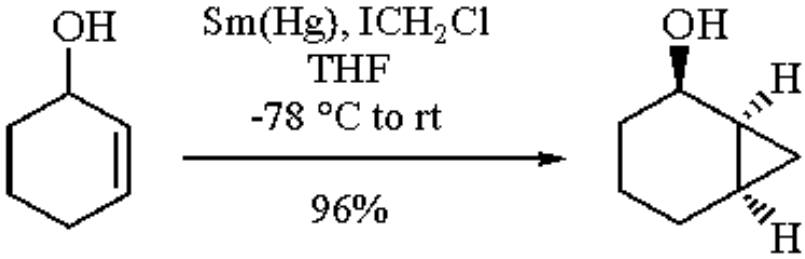

(6)

Thus geraniol and nerol, when subjected to these reaction conditions, undergo cyclopropanation at only the allylic alkene, each producing a single diastereomeric product in excellent yield (eqs 7 and 8).[4a,b] Consequently, the Sm(Hg) protocol is preferential to the Simmons-Smith and related reagents which typically provide approximately 5% of byproducts resulting from cyclopropanation at the isolated alkene in geraniol. In addition to the exceptional chemoselectivity that this reagent possesses, the Sm(Hg) reagent displays excellent stereospecificity with respect to alkene geometry. Cyclopropanation of geraniol and nerol demonstrates that complete stereospecificity is obtained when subjected to the Sm(Hg) reagent.

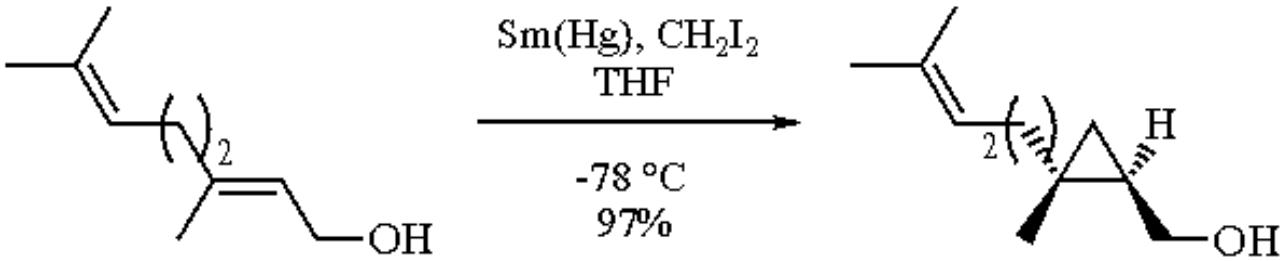

(7)

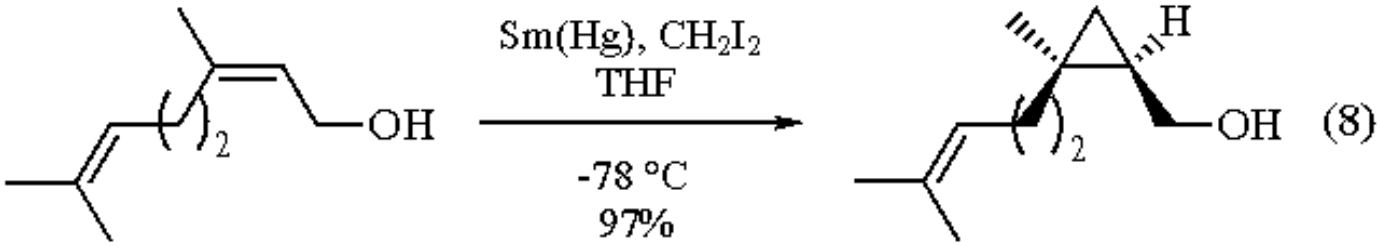

Use of metalated alkenes containing tin or silicon substituents also react with excellent diastereoselectivity under similar reaction conditions, providing highly functionalized cyclopropanes (eq 9).[4d] The stannylated product may be transmetalated and the resulting lithium anion may be reacted with various electrophiles, thereby providing a route to diastereomers inaccessible by direct cyclopropanation (eq 10).

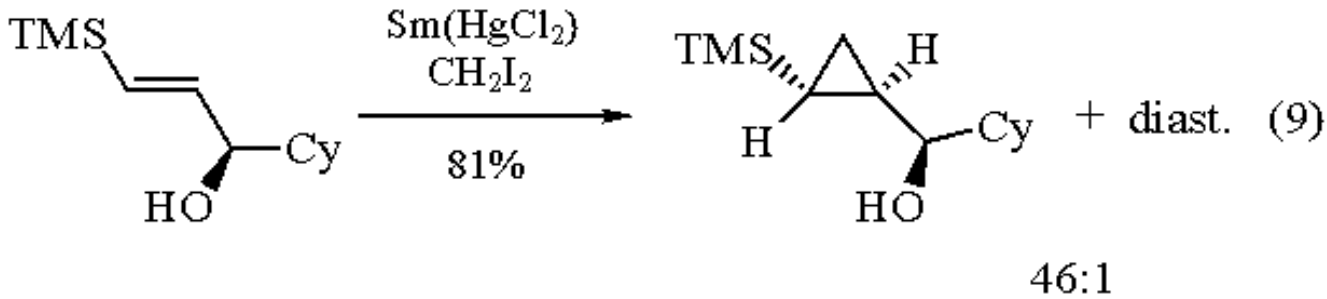

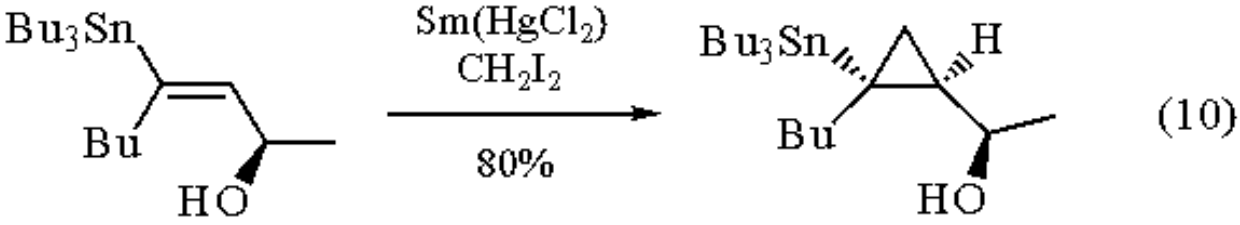

The samarium amalgam-mediated cyclopropanation has been used in the synthesis of 1,25-dihydroxycholecalciferol to generate the cyclopropyl alcohol stereospecifically and in high yield (eq 11).[5] Likewise, the desired stereochemistry was generated under the influence of the two stereogenic centers on the (*R*,*R*)-2,3-butanediol acetal (eq 12).[5]

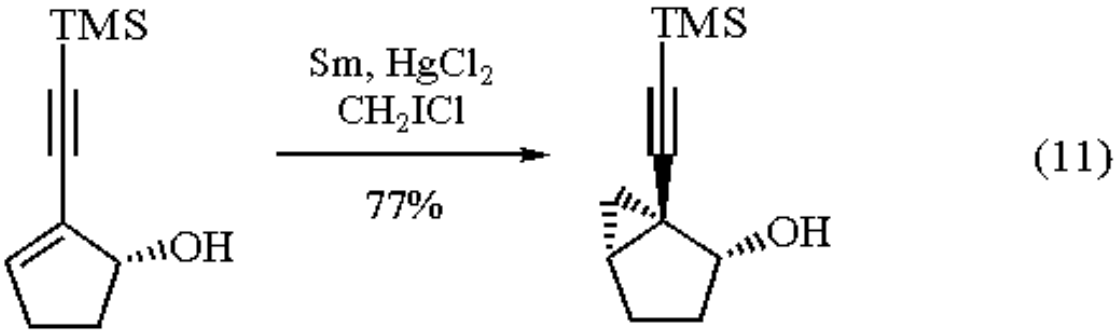

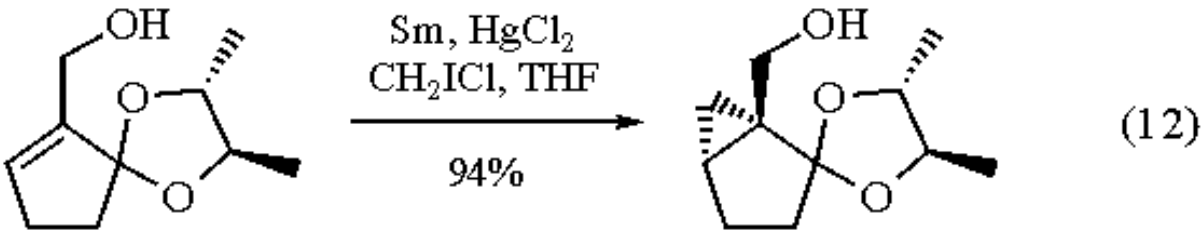

The Sm(Hg) method may also be utilized to perform ethylidenation reactions (eq 13).[4a,b,6] This protocol is preferential since use of pyrophoric ***Diethylzinc*** may be avoided; additionally, the samarium-promoted reaction permits higher diastereoselectivities to be realized in this transformation.

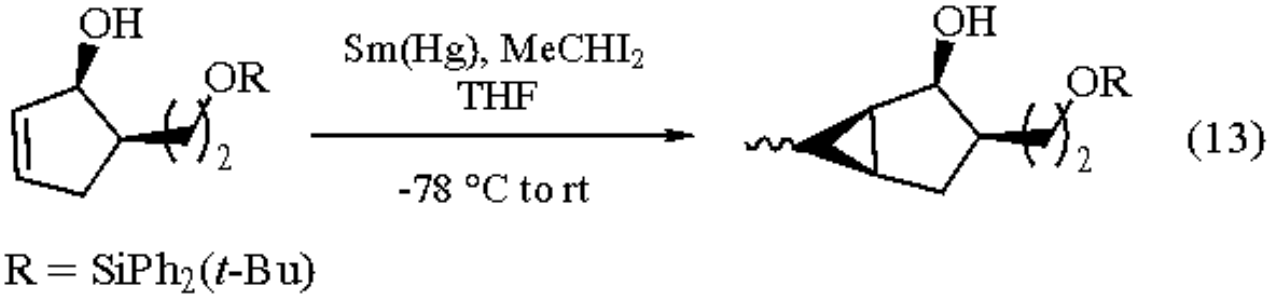

R = $SiPh_2(t\text{-}Bu)$

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1. (a) Molander, G. A. *CRV* **1992**, *92*, 29. (b) Molander, G. A. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Ed.; Wiley: Chichester, 1989; Vol. 5, Chapter 8.
2. (a) Imamoto, T.; Takeyama, T.; Koto, H. *TL* **1986**, *27*, 3243. (b) Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y.; Yoshizawa, T. *JCS(P1)* **1991**, 3127. (c) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *TL* **1986**, *27*, 3891. (d) Imamoto, T.; Takiyama, N. *TL* **1987**, *28*, 1307.
3. Imamoto, T.; Kamiya, Y; Hatajima, T.; Takahashi, H. *TL* **1989**, *30*, 5149.
4. (a) Molander, G. A.; Etter, J. B. *JOC* **1987**, *52*, 3942. (b) Molander, G. A.; Harring, L. S. *JOC* **1989**, *54*, 3525. (c) Yamazaki, T.; Lin, J. T.; Takeda, M.; Kitazume, T. *TA* **1990**, *1*, 351. (d) Lautens, M.; Delanghe, P. H. M. *JOC* **1992**, *57*, 798.
5. Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskoković, M. R. *TL* **1991**, *32*, 2343.
6. (a) Clive, D. L. J.; Daigneault, S. *CC* **1989**, 332. (b) Clive, D. L. J.; Daigneault, S. *JOC* **1991**, *56*, 3801.

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Samarium(III) Chloride

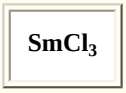

[10361-82-7] · Cl_3Sm · Samarium(III) Chloride · (MW 256.71)

(promotes electrochemical coupling reactions of aromatic diketones and aromatic esters to yield the 1,2-diol or 1,2-diketone, respectively;[1,2] catalyzes aldol condensations and facilitates cyanohydrin formation;[3] forms an organosamarium species with stannanes that adds 1,2 to conjugated ketones;[5] catalyzes the ring opening of epoxides and chemoselective removal of acetal protecting groups;[6,7] promotes acetylation of aldehydes[8])

Physical Data: mp 678 °C; *d* 4.46 g cm^{-3}.

Solubility: sol 6.4 g/100mL pyridine; 99.9 g/100 mL hot water; 92.4 g/100 mL cold water.

Form Supplied in: white-yellowish powder, ampouled under argon.

Handling, Storage, and Precautions: somewhat air and water sensitive. Reactions are typically performed under an inert atmosphere of argon or nitrogen.

Formation of Cyclopropane Diols and 1,2-Diketones.

Samarium(III) chloride can be utilized in the formation of cyclopropane diols via the coupling of carbonyl compounds (eq 1). In this process an active Sm^{II} species is generated by the electrochemical reduction of a catalytic amount of Sm^{III}.[1] The use of this method, however, is restricted to carbonyls containing aromatic functionality.

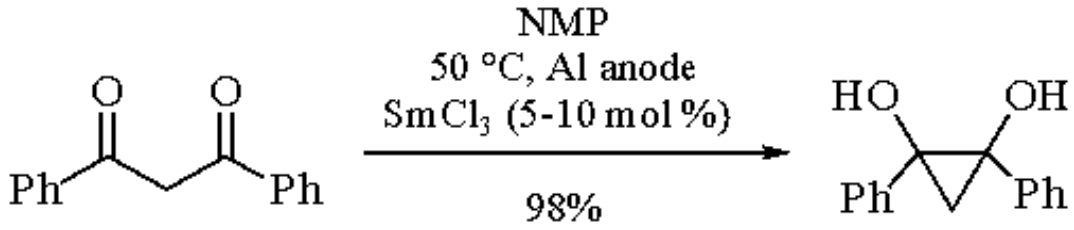

(1)

Diaryl 1,2-diketones are obtained in moderate to good yields in a similar method by electrochemical coupling of aromatic esters (eq 2).[2] This transformation utilizes the in situ preparation and regeneration of the Sm^{II} species but is limited to substrates with aromatic functionality on the ester. Halides on the aromatic moiety undergo reduction under these conditions.

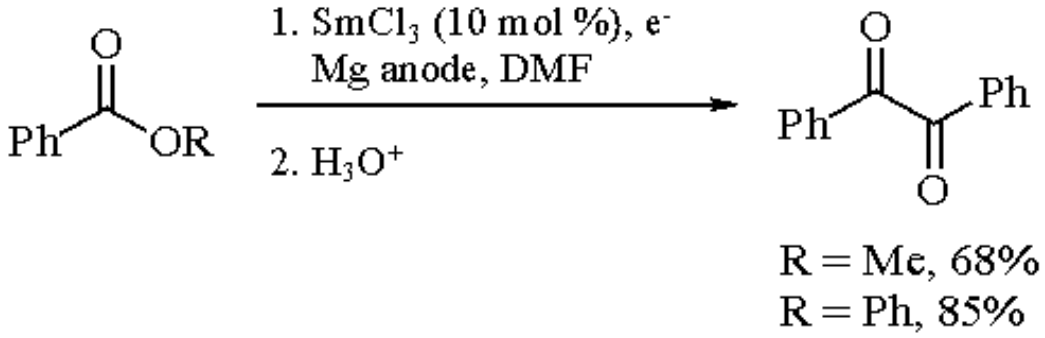

(2)

Aldol Reactions and Cyanohydrin Formation.

$SmCl_3$ catalyzes the aldol addition of silyl enol ethers to aldehydes wherein the product is isolated as a mixture of the alcohol and TMS

ether (eq 3).[3]

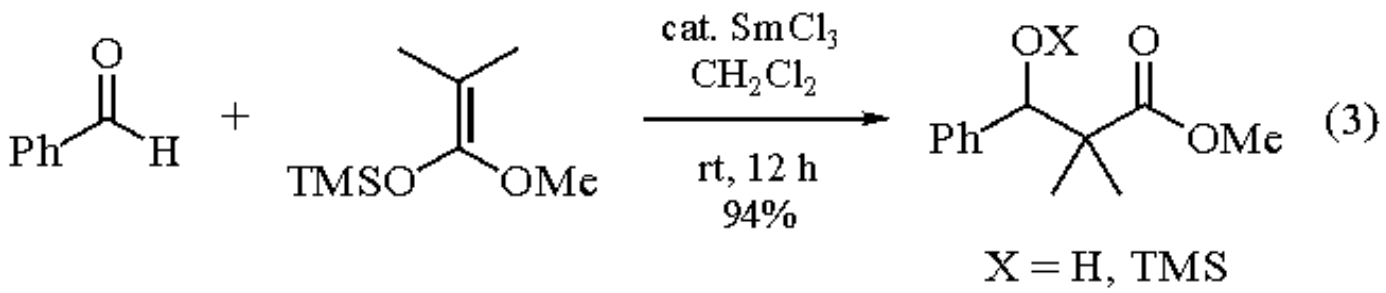

(3)

Additionally, samarium(III) chloride facilitates the formation of cyanohydrins from aryl or alkyl aldehydes and ***Cyanotrimethylsilane*** (eq 4).[3] Epoxides undergo regioselective ring opening when treated with $SmCl_3$ and Me_3SiCN to afford the corresponding cyanohydrin (eq 5).[3]

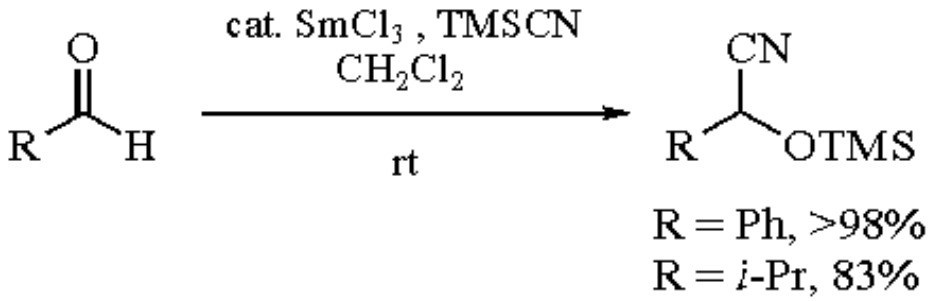

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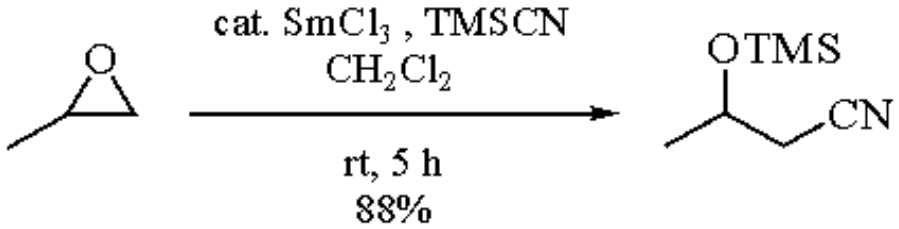

(5)

Ether Formation.

Ethers and thioethers are formed in good yield upon treatment of allylic alcohols with catalytic $SmCl_3$ (eqs 6 and 7).[4]

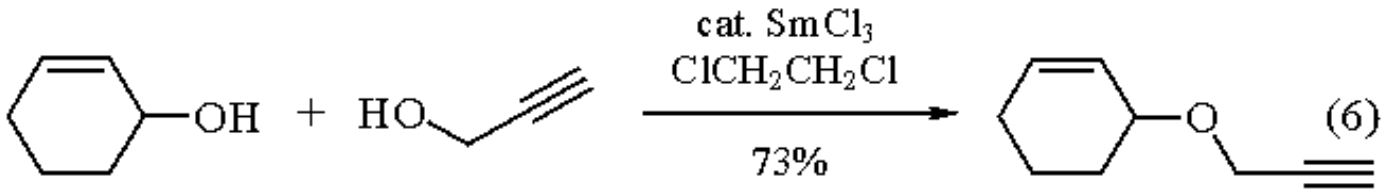

(6)

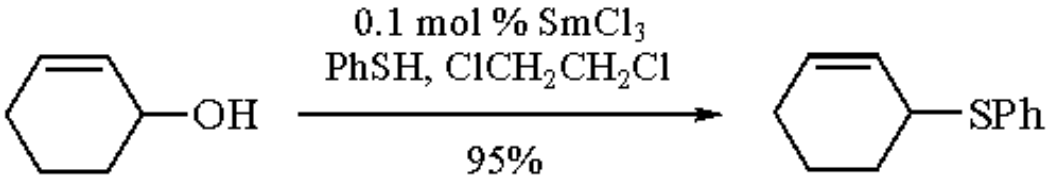

(7)

1,2-Addition to Conjugated Ketones.

Treatment of α,β-unsaturated ketones with samarium(III) chloride, ***n-Butyllithium***, and ***Tetraallylstannane*** results in excellent yields of product resulting from 1,2-addition of the organosamarium reagent generated under the reaction conditions (eq 8).[5]

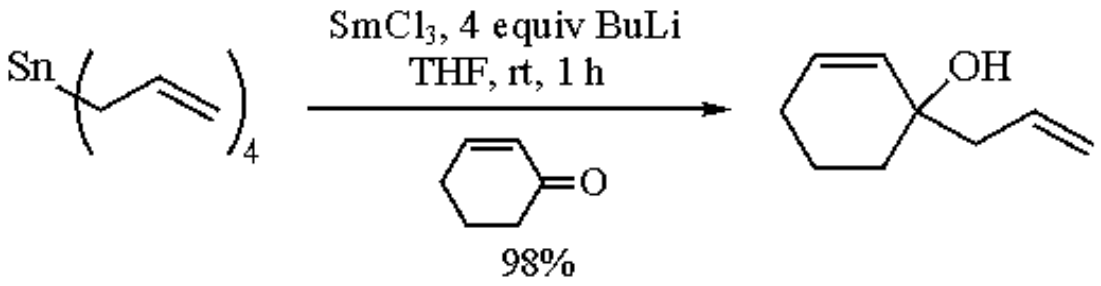

(8)

Epoxide Ring Opening and Protecting Group Removal.

$SmCl_3$ catalyzes the stereoselective and regioselective ring opening of epoxides (eqs 9 and 10) by thiol nucleophiles to generate the resulting thioalcohol in high yield.[6] The samarium(III) chloride protocol has advantages over other Lewis acid catalysts in that shorter reaction times are required.

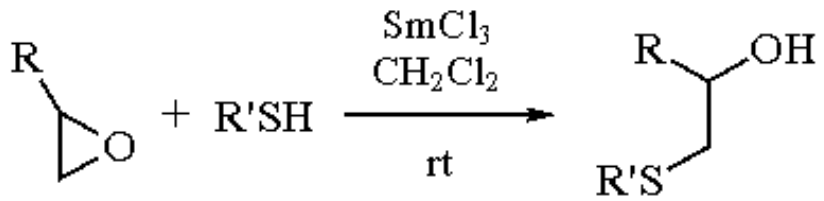

(9)

R	R'	% Yield
Me	*p*-anisyl	84
Et	CH_2Ph	77

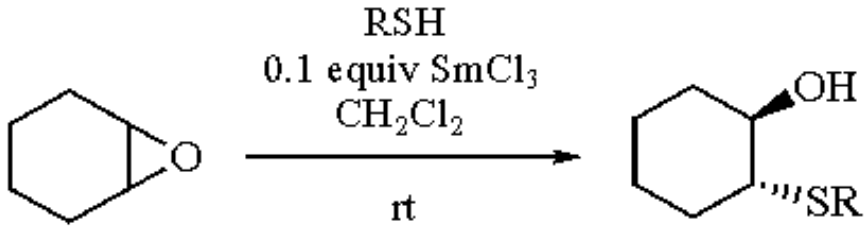

(10)

R = Ph, 48 h, 84%
R = Bn, 120 h, 78%

Samarium(III) chloride is also effective in the removal of protecting groups. Cyclic acetals undergo cleavage faster than acyclic acetals, providing an efficient means for selective removal of protecting group functionality (eqs 11 and 12).[7] Additionally, transformation of acetals to aldehydes is slower than that to ketones, providing excellent chemoselectivity in protecting group removal. Acid-sensitive functionalities such as *t*-butyldimethylsilyl ethers and methoxymethyl ethers are inert to these reaction conditions, as are methyl and benzyl ethers.

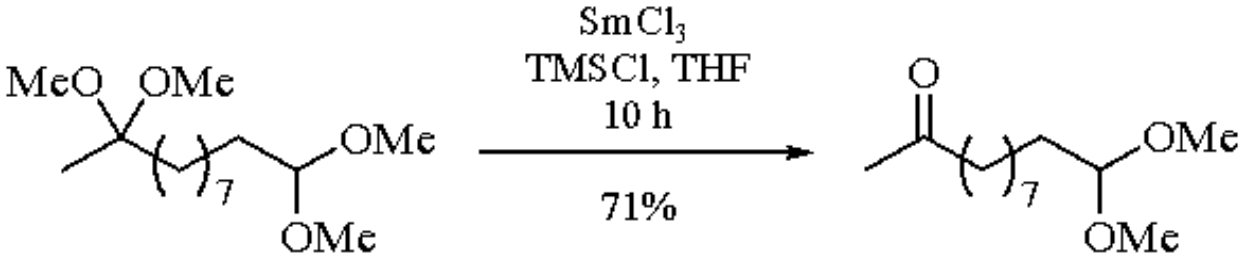

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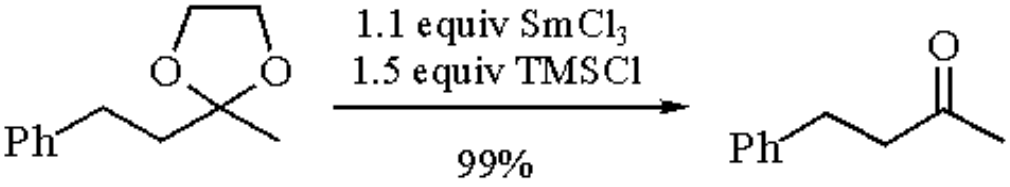

(12)

Chemoselective Acetalization of Aldehydes.

Samarium(III) chloride possesses the ability to chemoselectively acetalize aldehydes in the presence of the carboxylic acid functionality, i.e. no esterification occurs under these reaction conditions (eq 13).[8]

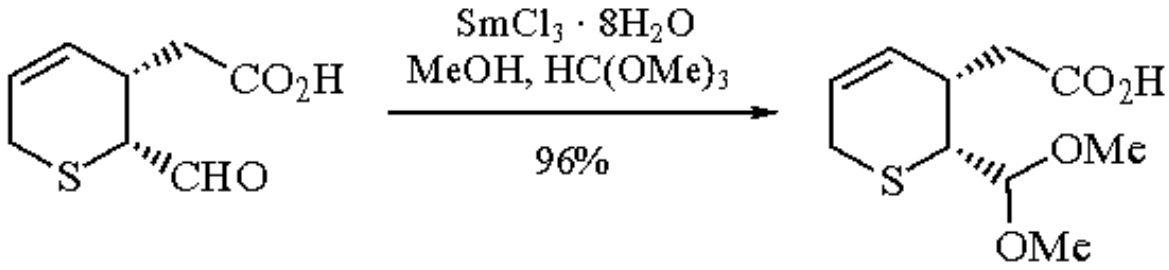

(13)

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2. Hébri, H.; Duñach, E.; Heintz, M.; Troupel, M.; Périchon, J. *SL* **1991**, 901.
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6. Vougioukas, A. E.; Kagan, H. B. *TL* **1987**, *28*, 6065.
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8. Lawson, K. R.; McDonald, B. P.; Mills, O. S.; Steele, R. W.; Sutherland, J. K.; Wear, T. J.; Brewster, A.; Marsham, P. R. *JCS(P1)* **1988**, 663.

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Samarium(II) Iodide[1]

SmI_2

[32248-43-4] · I_2Sm · Samarium(II) Iodide · (MW 404.16)

(one-electron reducing agent possessing excellent chemoselectivity in reduction of carbonyl, alkyl halide, and α-heterosubstituted carbonyl substrates;[1] promotes Barbier-type coupling reactions, ketyl-alkene coupling reactions, and radical cyclizations[1])

Physical Data: mp 527 °C; bp 1580 °C; *d* 0.922 g cm^{-3}.

Solubility: soluble 0.1M in THF.

Form Supplied in: commercially available as a 0.10 M solution in THF.

Preparative Methods: typically prepared in situ for synthetic purposes. SmI_2 is conveniently prepared by oxidation of ***Samarium(0)*** metal with organic dihalides.[2]

Handling, Storage, and Precautions: is air sensitive and should be handled under an inert atmosphere. SmI_2 may be stored over THF for long periods when it is kept over a small amount of samarium metal.

Reduction of Organic Halides and Related Substrates.

Alkyl halides are readily reduced to the corresponding hydrocarbon by SmI_2 in the presence of a proton source. The ease with which halides are reduced by SmI_2 follows the order I > Br > Cl. The reduction is highly solvent dependent. In THF solvent, only primary alkyl iodides and bromides are effectively reduced;[2] however, addition of HMPA effects the reduction of aryl, alkenyl, primary, secondary, and tertiary halides (eq 1).[3,4] Tosylates are also reduced to hydrocarbons by SmI_2. Presumably, under these reaction conditions the tosylate is converted to the corresponding iodide which is subsequently reduced.[4,5]

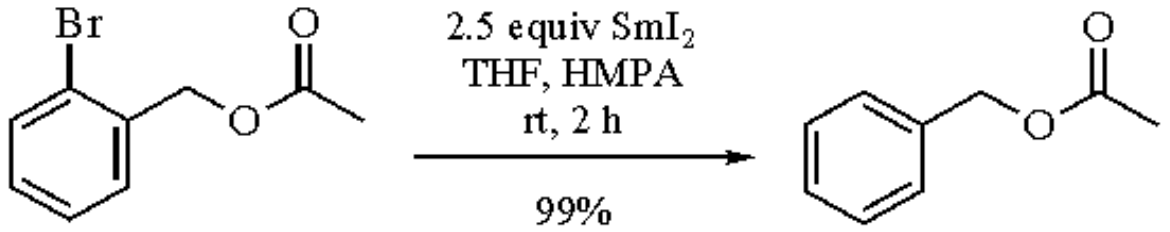

(1)

Samarium(II) iodide provides a means to reduce substrates in which the halide is resistant to reduction by hydride reducing agents (eq 2).

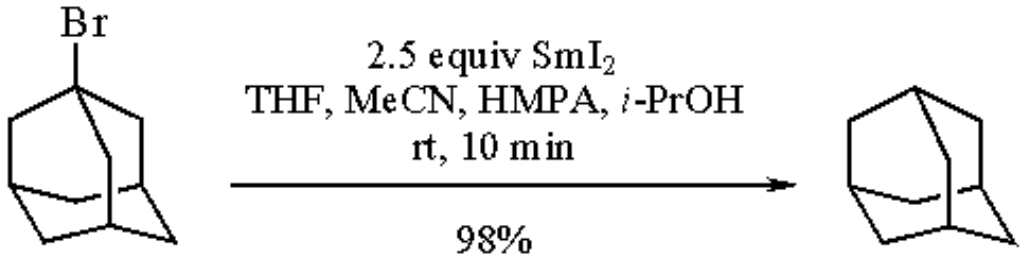

(2)

Samarium(II) iodide has been utilized as the reductant in the Boord alkene-type synthesis involving ring scission of 3-halotetrahydrofurans (eq 3).[6] SmI_2 provides an alternative to the sodium-induced reduction which typically affords mixtures of

stereoisomeric alkenes and overreduction in these transformations. When SmI_2 is employed as the reductant, isomeric purities are generally >97% and overreduction products comprise <3% of the reaction mixture.

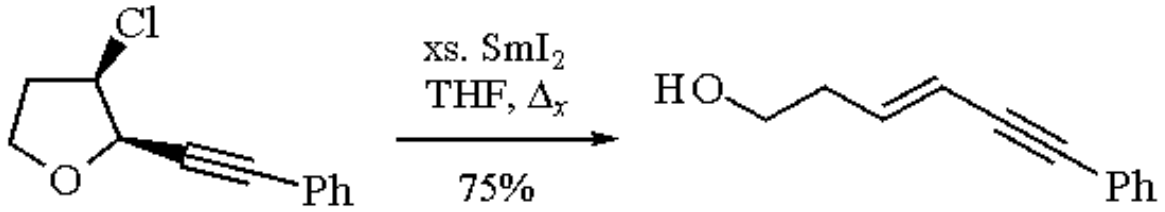

(3)

Reduction of α-Heterosubstituted Carbonyl Compounds.

Samarium(II) iodide provides a route for the reduction of α-heterosubstituted carbonyl substrates. A wide range of α-heterosubstituted ketones is rapidly reduced to the corresponding unsubstituted ketone under mild conditions (eq 4).[7] The reaction is highly selective and may be performed in the presence of isolated iodides as well as isolated ketones.[7]

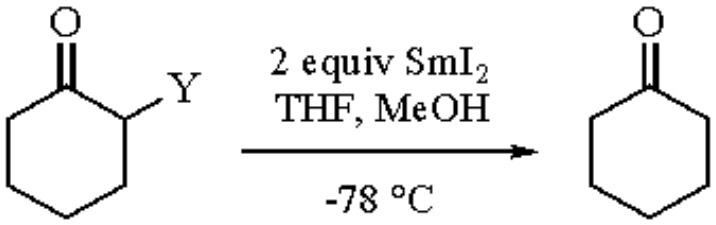

(4)

Y	Isolated yield (%)
Cl	100
SPh	76
S(O)Ph	64
SO_2Ph	88

Samarium(II) iodide-induced reductive cleavage of α-hydroxy ketones provides a useful entry to unsubstituted ketones (eq 5).[8]

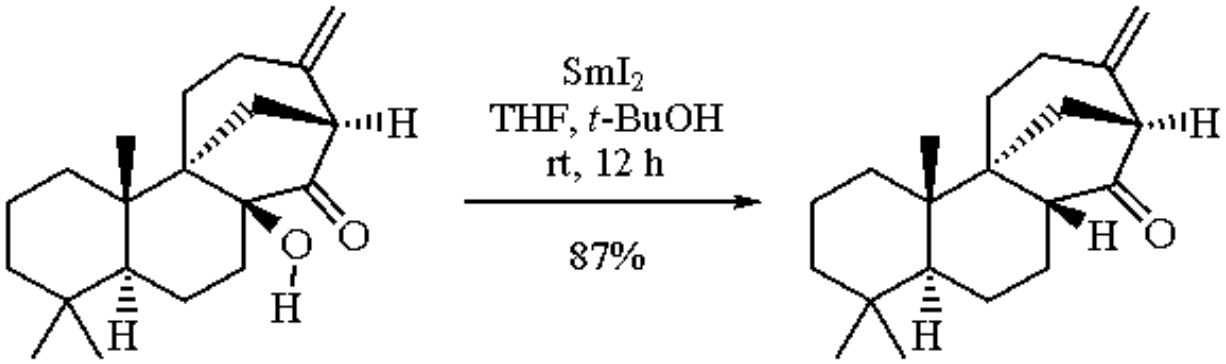

(5)

Samarium(II) iodide promotes the reductive cleavage of α-alkoxy ketones. Pratt and Hopkins have utilized this protocol in synthetic studies en route to betaenone B (eq 6).[9]

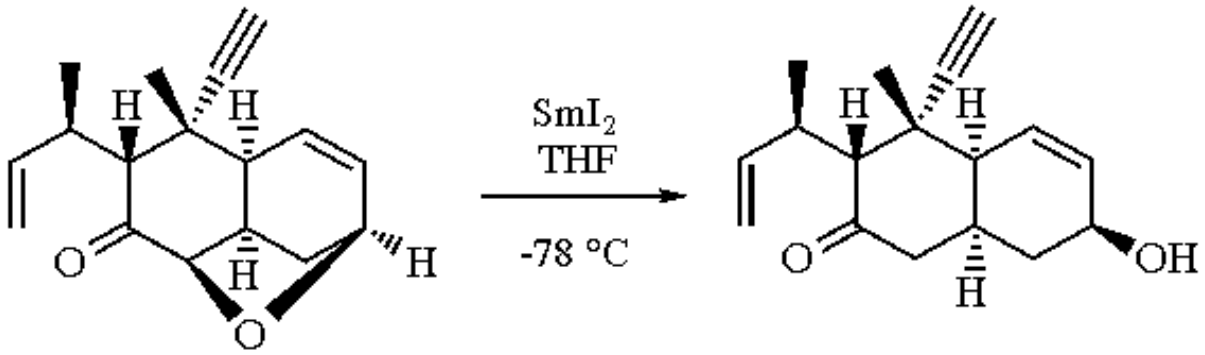

(6)

Likewise, this procedure provides a route for the reduction of α,β-epoxy ketones and α,β-epoxy esters to generate the corresponding β-hydroxy carbonyl compounds (eqs 7 and 8).[3,10] The epoxy ketone substrates may be derived from Sharpless asymmetric epoxidation. Consequently, this procedure provides a means to prepare a variety of chiral, nonracemic β-hydroxy carbonyl compounds that are difficult to acquire by more traditional procedures.

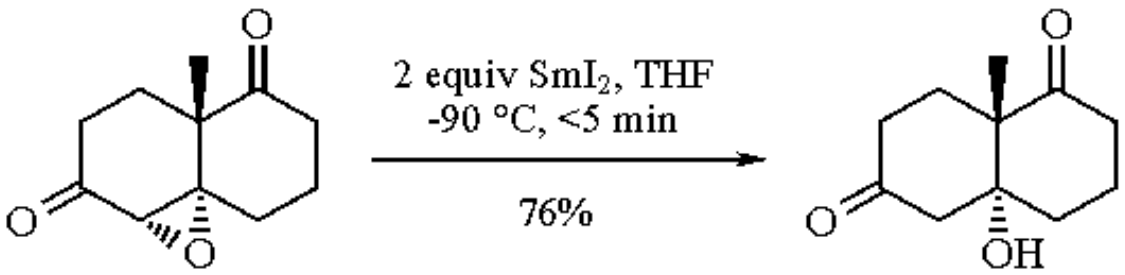

(7)

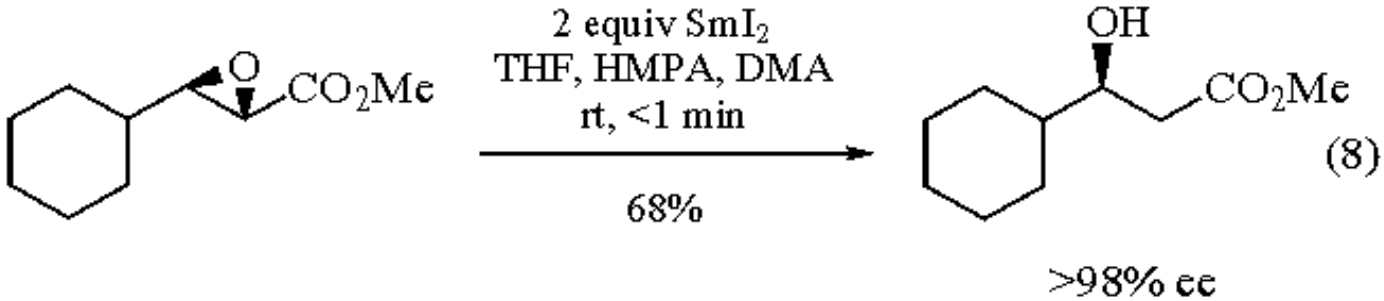

(8)

Vinyloxiranes undergo reductive epoxide ring opening with samarium(II) iodide to provide (*E*)-allylic alcohols (eq 9).[3,10b,11] These reaction conditions are tolerant of ketone, ester, and nitrile functional groups. Again, Sharpless asymmetric epoxidation chemistry may be utilized to gain entry to the desired nonracemic substrates, thereby providing a useful entry to highly functionalized, enantiomerically enriched allylic alcohols.

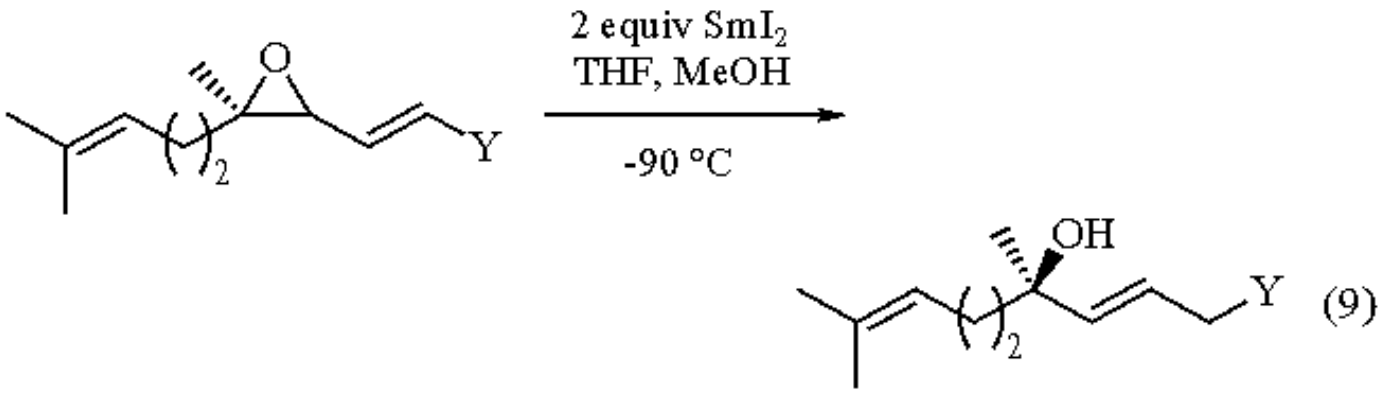

Y	Isolated yield (%)
COSEt	80
SO_2Ph	82
$P(O)(OEt)_2$	84
H	69
Me	42
SPh	54

A useful method for preparation of β-hydroxy esters is accomplished by SmI_2-promoted deoxygenation of an α-hydroxy ester followed by condensation with a ketone (eq 10).[12] In some instances, excellent diastereoselectivities are achieved, although this appears to be somewhat substrate dependent.

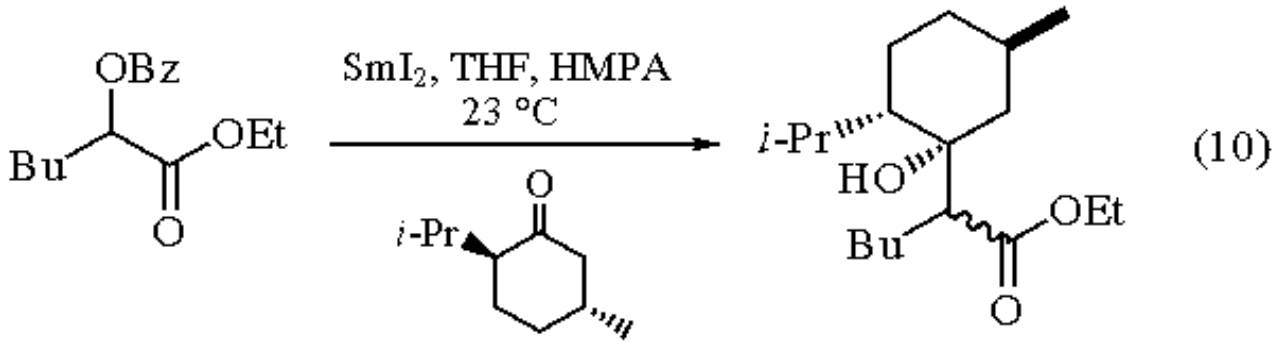

A useful reaction sequence for transforming carbonyl compounds to one-carbon homologated nitriles has evolved from the ability of SmI_2 to deoxygenate cyanohydrin *O,O′*-diethyl phosphates (eq 11).[13] The procedure is tolerant of a number of functional groups including alcohols, esters, amides, sulfonamides, acetals, alkenes, alkynes, and amines. Furthermore, it provides a distinct advantage over other previously developed procedures for similar one-carbon homologations.

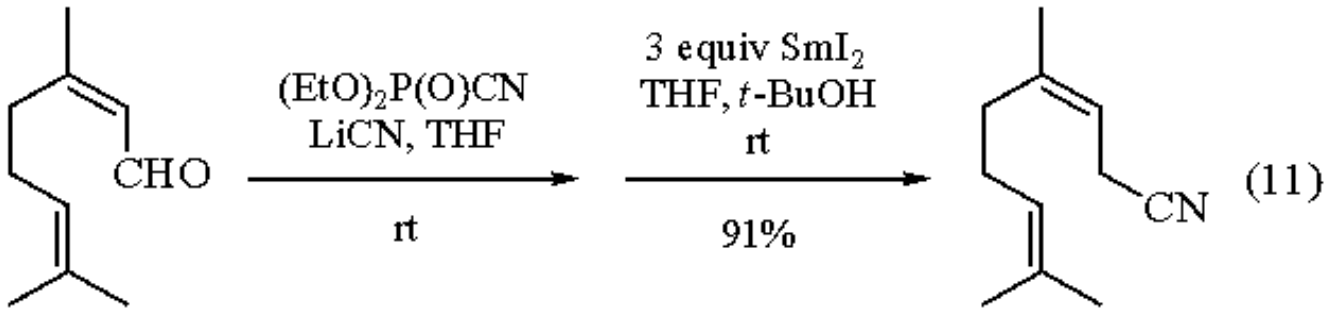

Deoxygenation Reactions.

Sulfoxides are reduced to sulfides by SmI_2 (eq 12).[2,3,14] This process is rapid enough that reduction of isolated ketones is not a competitive process. Likewise, aryl sulfones are reduced to the corresponding sulfides by SmI_2 (eq 13).[3,12]

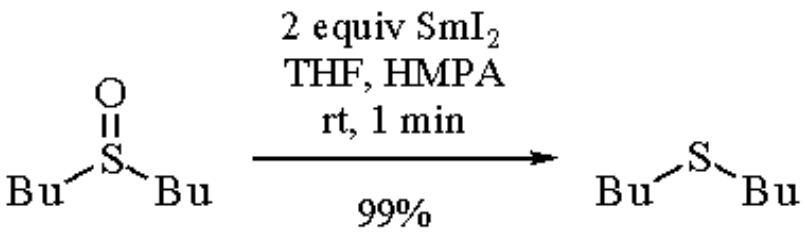

(12)

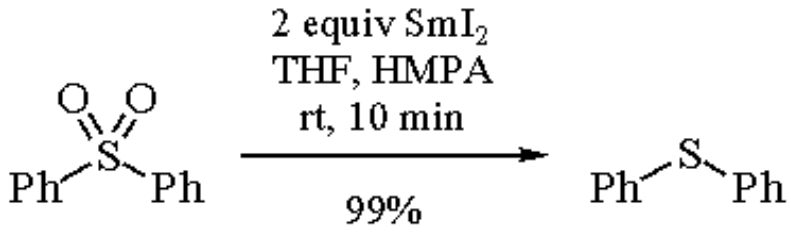

(13)

Barbier-Type Reactions.

Samarium(II) iodide is quite useful in promoting Barbier-type reactions between aldehydes or ketones and a variety of organic halides. The efficiency of SmI_2 promoted Barbier-type coupling processes is governed by the substrate under consideration in addition to the reaction conditions employed. In general, alkyl iodides are most reactive while alkyl chlorides are virtually inert. Typically, catalytic ***Iron(III) Chloride*** or ***Hexamethylphosphoric Triamide*** can be added to SmI_2 to reduce reaction times or temperatures and enhance yields. Kagan and co-workers have recently applied an intermolecular SmI_2-promoted Barbier reaction towards the synthesis of hindered steroidal alcohols. An intermolecular Barbier-type reaction between the hindered ketone and ***Iodomethane*** produced a 97:3 mixture of diastereomers in excellent yield (eq 14).[15]

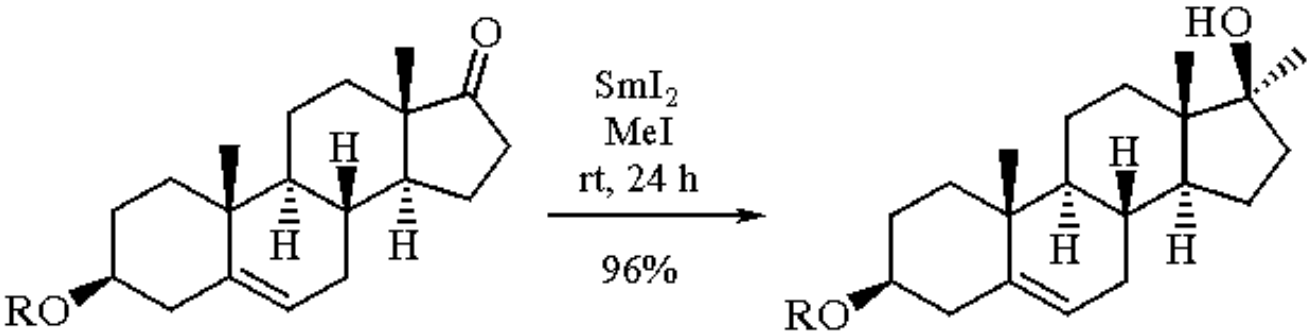

(14)

R = TBDMS

97:3

Samarium(II) iodide-promoted intramolecular Barbier-type reactions have also been employed to produce a multitude of cyclic and bicyclic systems.[1] Molander and McKie have employed an intramolecular Barbier-type reductive coupling reaction to promote the formation of bicyclo[*m.n.*1]alkan-1-ols from the corresponding iodo ketone substrates in good yield (eq 15).[16]

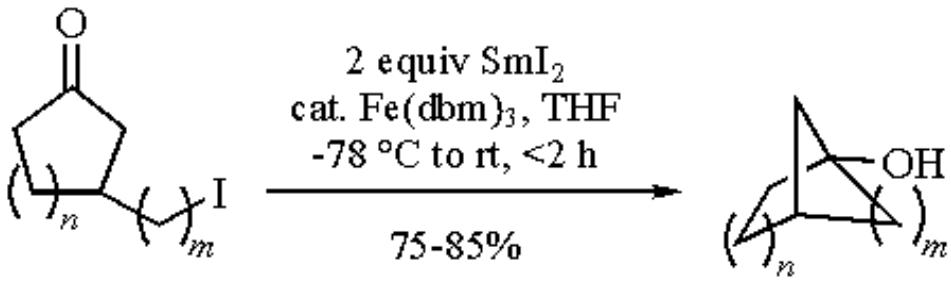

(15)

Annulation of five- and six-membered rings proceeds with excellent diastereoselectivity via an intramolecular Barbier-type process (eq 16).[17] The Barbier-type coupling scheme provides a reliable and convenient alternative to other such methods for preparing fused bicyclic systems.

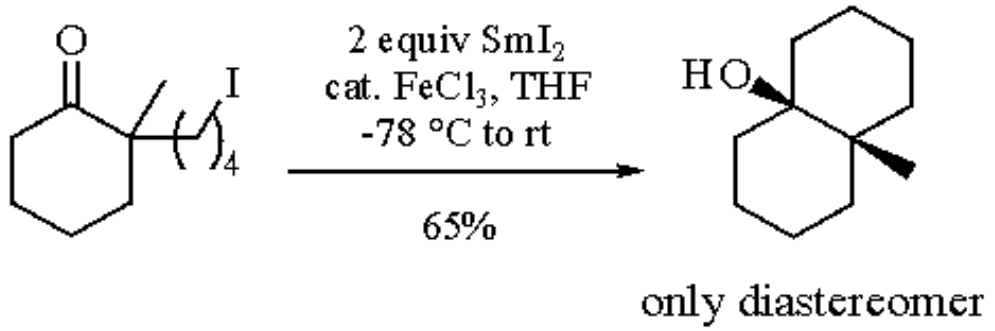

(16)

The SmI_2-promoted Barbier-type reaction has also been utilized in the synthesis of polyquinanes. Cook and Lannoye have employed this method to effect a bis-annulation of an appropriately substituted diketone (eq 17).[18]

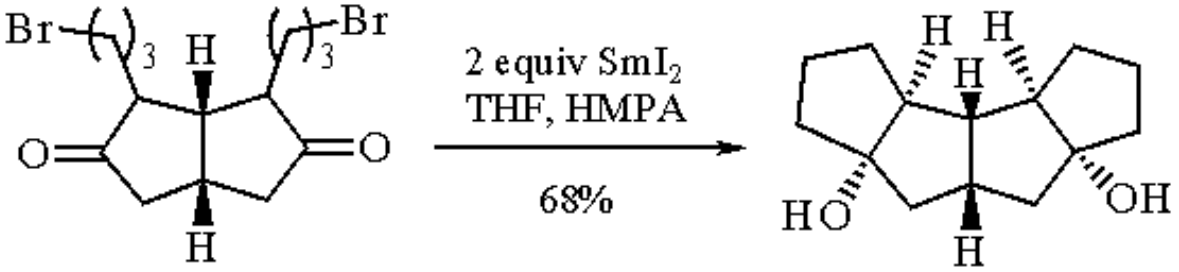

(17)

Substituted β-keto esters also provide excellent substrates for the intramolecular Barbier cyclization (eq 18).[19] Diastereoselectivities are typically quite good but are highly dependent on substituent and solvent effects.

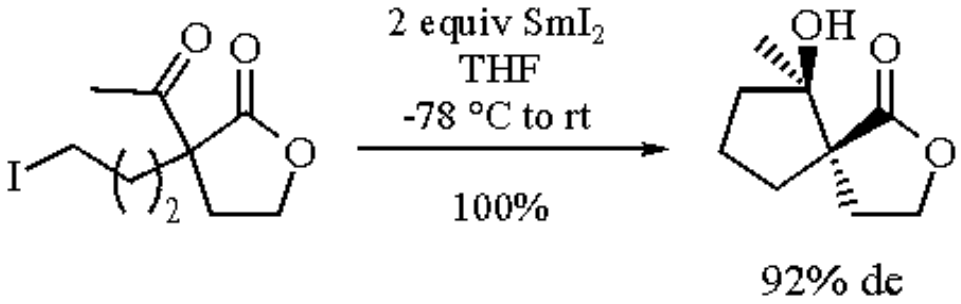

(18)

Nucleophilic Acyl Substitutions.

Samarium(II) iodide facilitates the highly selective intramolecular nucleophilic acyl substitution of halo esters (eqs 19 and 20).[20]

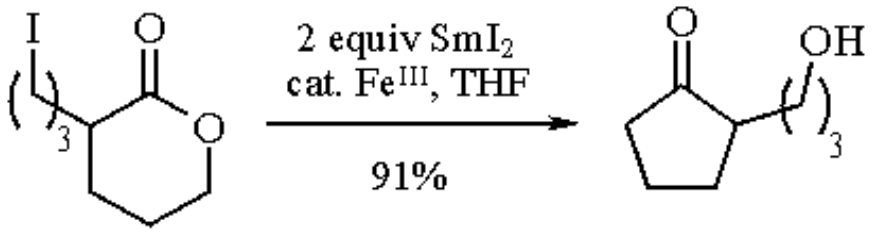

(19)

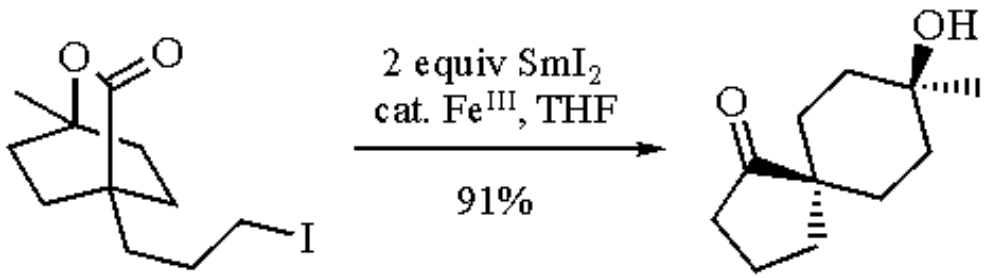

(20)

Unlike organolithium or organomagnesium reagents, SmI_2-promoted nucleophilic substitution does not proceed with double addition to

the carbonyl, nor are any products resulting from reduction of the final product observed. With suitably functionalized substrates, this procedure provides a strategy for the formation of eight-membered rings (eq 21).

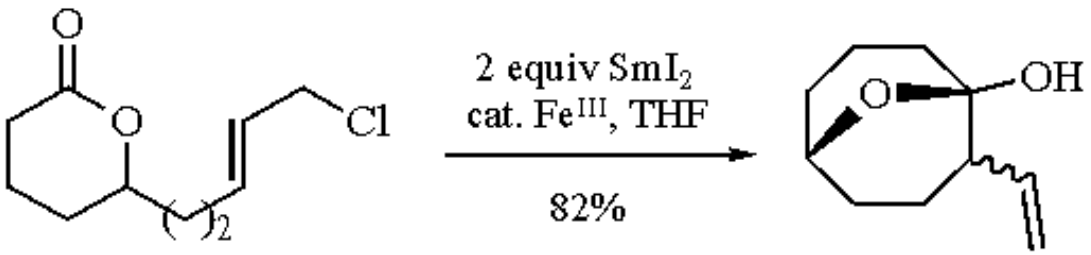

Ketone-Alkene Coupling Reactions.

Ketyl radicals derived from reduction of ketones or aldehydes with SmI_2 may be coupled both inter- and intramolecularly to a variety of alkenic species. Excellent diastereoselectivities are achieved with intramolecular coupling of the ketyl radical with α,β-unsaturated esters.[21] In the following example, ketone-alkene cyclization took place in a stereocontrolled manner established by chelation of the resulting Sm(III) species with the hydroxyl group incorporated in the substrate (eq 22).[21b]

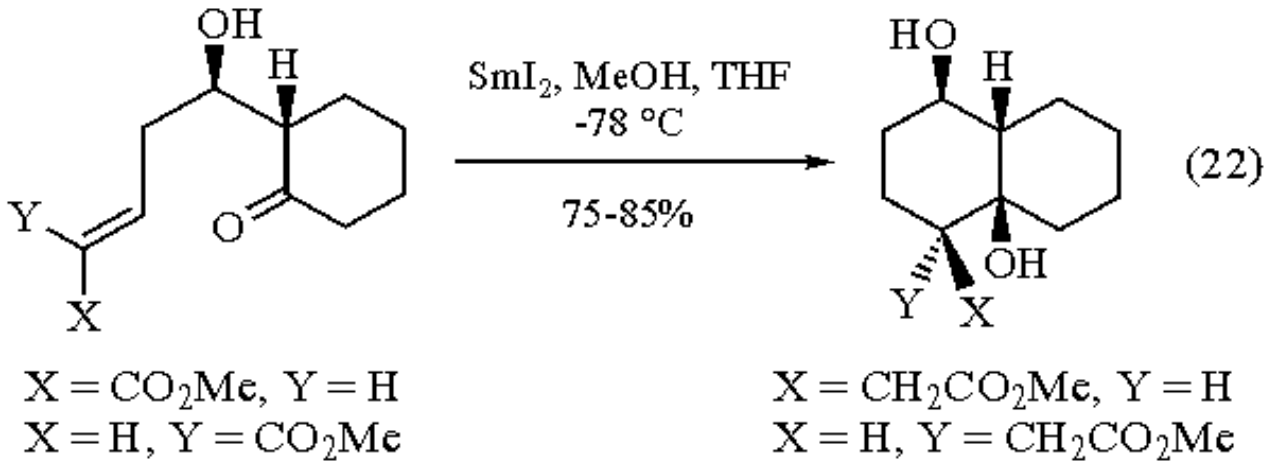

A similar strategy utilizing β-keto esters provided very high diastereoselectivities in the ketyl-alkene coupling process. In these examples, chelation control about the developing hydroxyl and carboxylate stereocenters was the source of the high diastereoselectivity achieved (eq 23).[22]

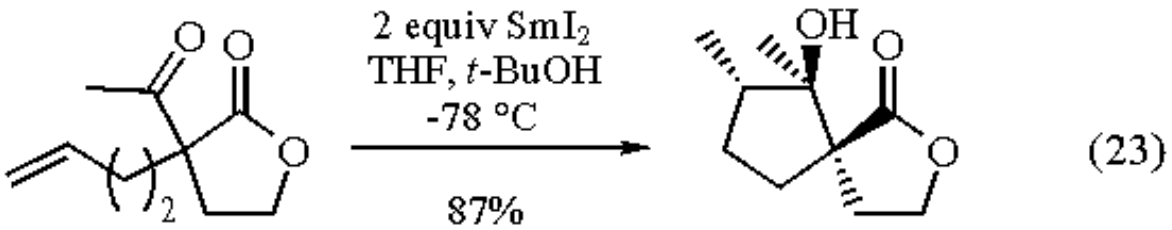

Alkynic aldehydes likewise undergo intramolecular coupling to generate five- and six-membered ring carbocycles. This protocol has been utilized as a key step in the synthesis of isocarbacyclin (eq 24).[23] SmI_2 was found to be superior to several other reagents in this conversion.

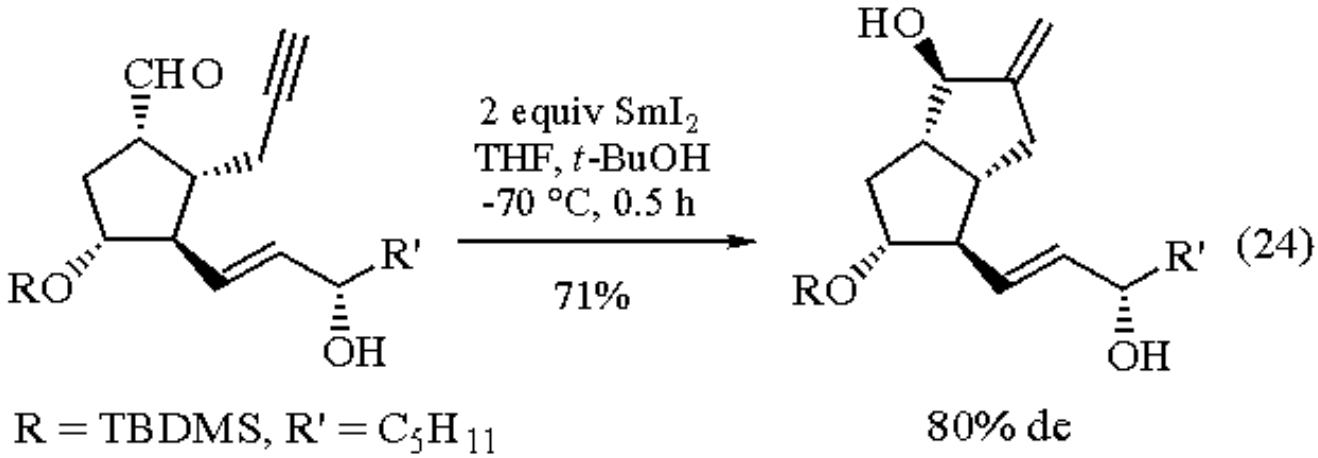

Samarium(II) iodide in the presence of HMPA effectively promotes the intramolecular coupling of unactivated alkenic ketones by a reductive ketyl-alkene radical cyclization process (eq 25). This protocol provides a means to generate rather elaborate carbocycles through a sequencing process in which the resulting organosamarium species is trapped with various electrophiles to afford the cyclized product in high yield.[24]

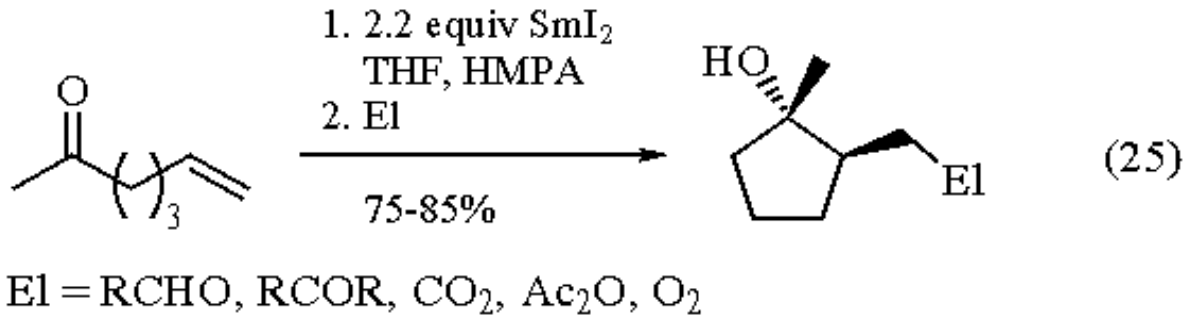

Pinacolic Coupling Reactions.

In the absence of a proton source, both aldehydes and ketones are cleanly coupled in the presence of SmI_2 to the corresponding pinacol.[25] Considerable diastereoselectivity has been achieved in the coupling of aliphatic 1,5- and 1,6-dialdehydes, providing near exclusive formation of the *cis*-diols (eq 26).[26]

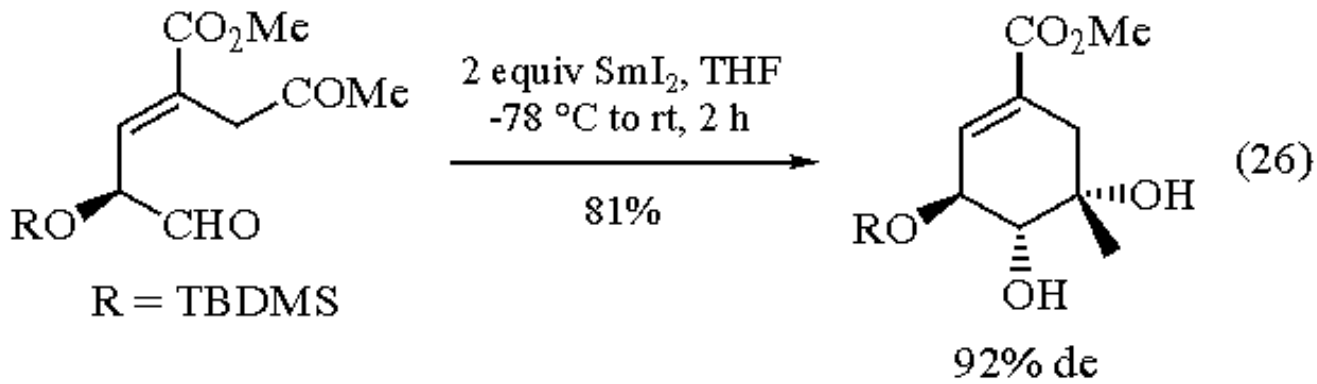

Intramolecular cross coupling of aldehydes and ketones proceeds with excellent diastereoselectivity and high yield in suitably functionalized systems wherein chelation control by the resulting Sm^{III} species directs formation of the newly formed stereocenters (eq 27).[22a,27] A similar strategy has been utilized with a β-keto amide substrate to provide a chiral, nonracemic oxazolidinone species. This strategy permits entry to highly functionalized, enantiomerically pure dihydroxycyclopentanecarboxylate derivatives (eq 28).

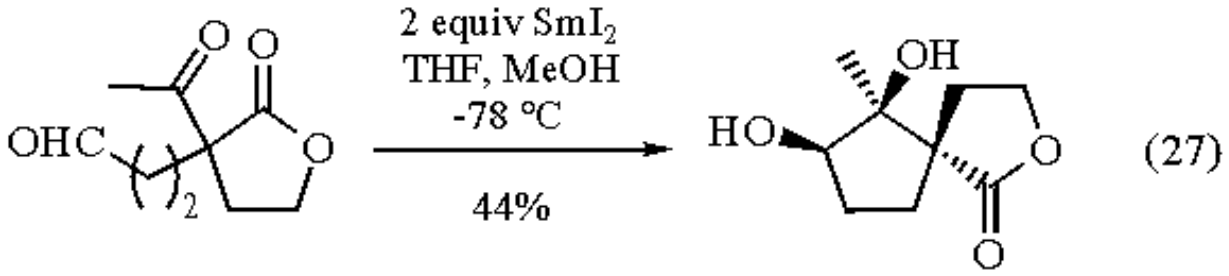

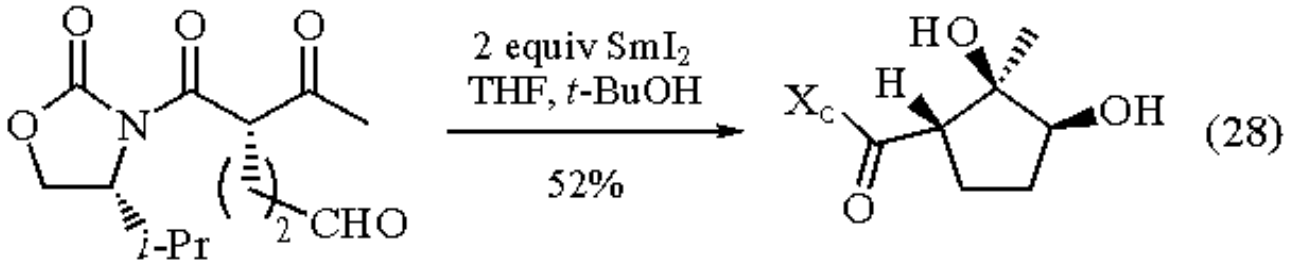

Radical Addition to Alkenes and Alkynes.

Samarium(II) iodide has proven effective for initiation of various radical addition reactions to alkenes and alkynes. Typically, tin reagents are used in the initiation of these radical cyclization reactions; however, the SmI_2 protocol often provides significant advantages over these more traditional routes.

Samarium(II) iodide-mediated cyclization of aryl radicals onto alkene and alkyne acceptors provides an excellent route to nitrogen- and oxygen-based heterocycles (eq 29).[28]

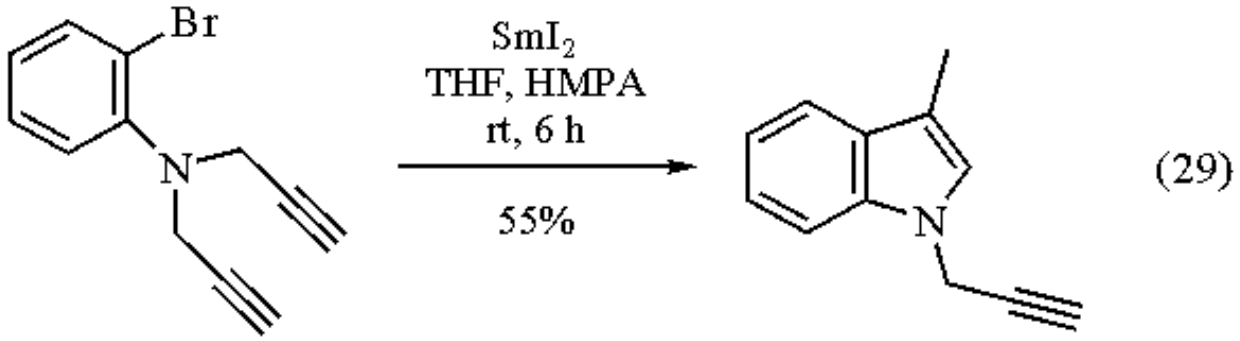

The SmI_2 reagent is unique in that it provides the ability to construct more highly functionalized frameworks through a sequential radical cyclization/intermolecular carbonyl addition reaction.[29] Thus the intermediate radical formed after initial cyclization may be further reduced by SmI_2, forming an organosamarium intermediate which may be trapped by various electrophiles, affording highly functionalized products (eq 30).

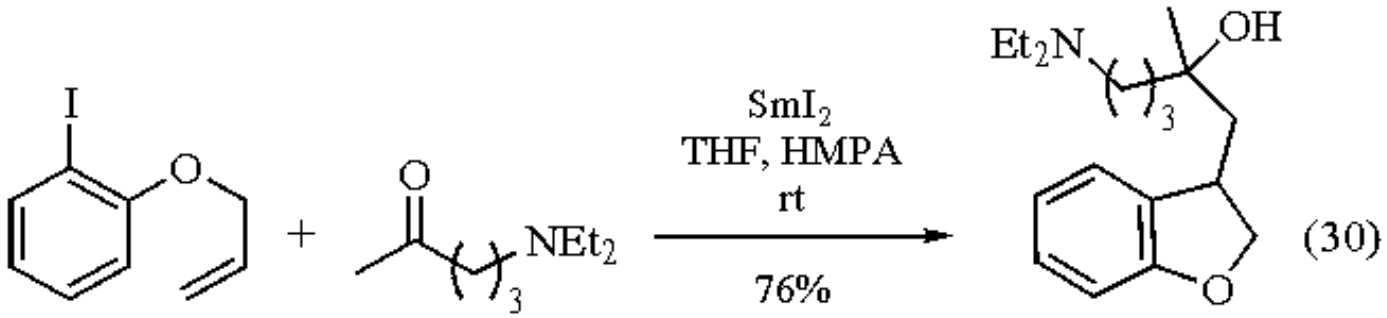

Samarium(II) iodide further mediates the cyclization reactions of alkynyl halides (eq 31).[30] When treated with SmI_2, the alkynyl halides are converted to the cyclized product in good yield. Addition of DMPU as cosolvent provides slightly higher yields in some instances.

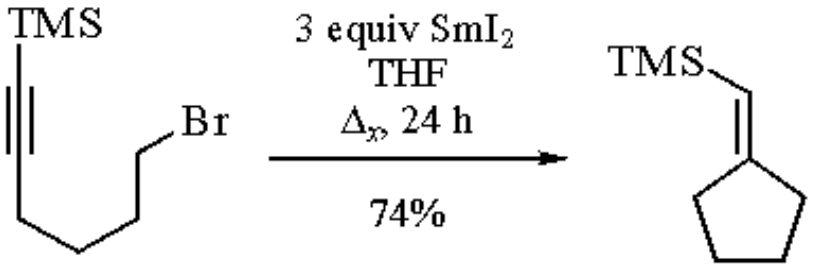

(31)

Highly functionalized bicyclic and spirocyclic products are obtained in good yield and high diastereoselectivity by a tandem reductive cleavage-cyclization strategy (eq 32).[31] Radical ring opening of cyclopropyl ketones mediated by samarium(II) iodide-induced electron transfer permits the elaboration of a tandem ring opening-cyclization strategy wherein the resultant samarium enolate may be trapped by either oxygen or carbon electrophiles.

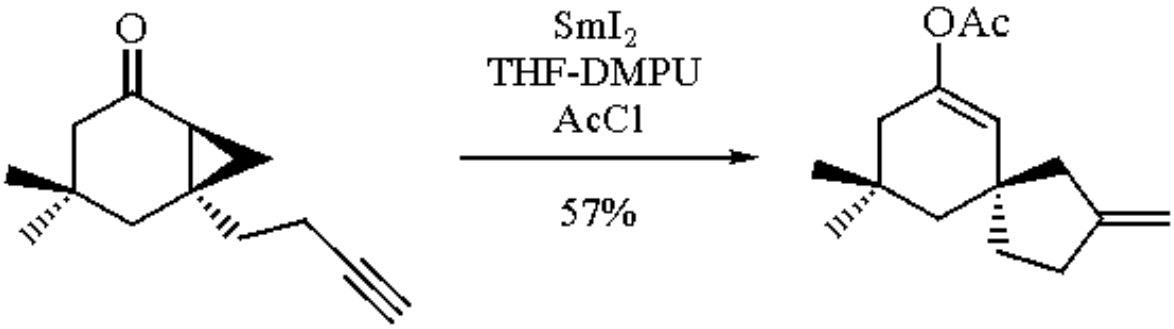

(32)

Related Reagents.

Samarium(II) Iodide-1,3-Dioxolane.

---

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Sugiura, S.; Manabe, K.; Tomimori, K.; Kato, Y.; Kurozumi, S.; Noyori, R. *T* **1990**, *46*, 6689.
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Samarium(II) Iodide-1,3-Dioxolane

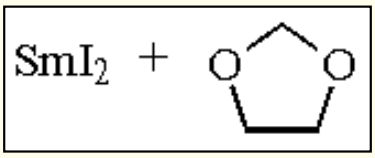

(SmI_2)

[32248-43-4] · I_2Sm · Samarium(II) Iodide-1,3-Dioxolane · (MW 404.16) (1,3-dioxolane)

[646-06-0] · $C_3H_6O_2$ · Samarium(II) Iodide-1,3-Dioxolane · (MW 74.09)

(used as a formyl anion equivalent in carbonyl addition reactions of aldehyde and ketone substrates)

Solubility: sol 0.1 M in dioxolane.

Preparative Methods: SmI_2 prepared in dioxolane with addition of ***Acetonitrile*** to aid in dissolving SmI_2.

Handling, Storage, and Precautions: SmI_2 is air sensitive and should be handled accordingly.

General Discussion.

Samarium(II) Iodide in conjunction with 1,3-dioxolane and an aryl halide has been utilized in the masked formylation of aldehydes and ketones (eqs 1 and 2).[1] Aryl halides do not undergo Barbier-type coupling reactions with ketones in the presence of samarium diiodide; instead, the generated aryl radical abstracts a hydrogen atom from 1,3-dioxolane, which is used as the solvent in these types of reactions. The resulting dioxolanyl radical may then couple with the aldehyde or ketone substrate, yielding the carbonyl addition product.

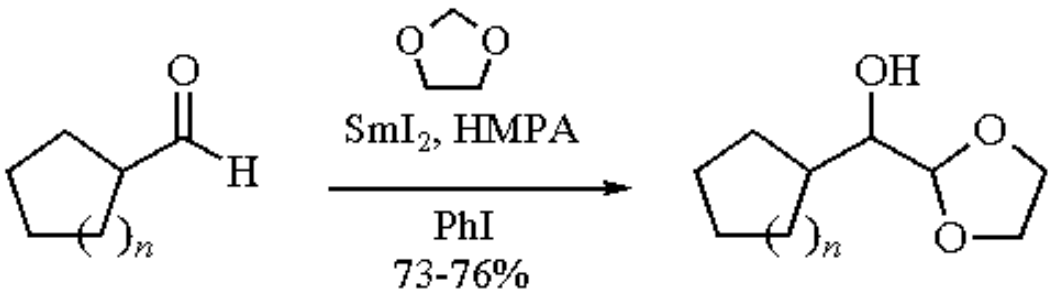

(1)

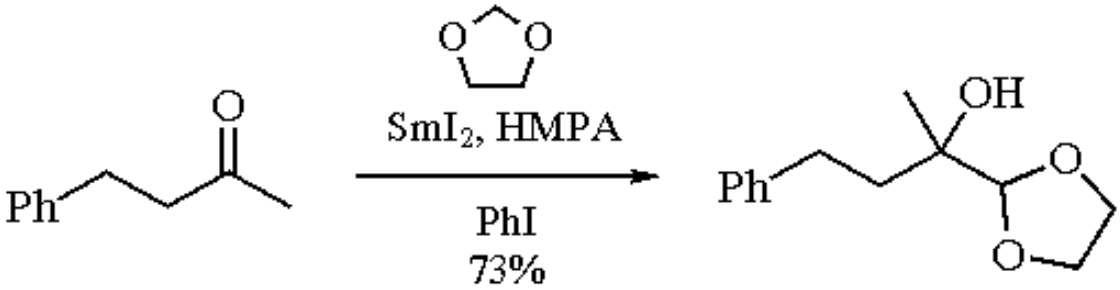

(2)

Little selectivity is achieved with chiral substrates as the reaction of 4-*t*-butylcyclohexanone yielded a 1:1 mixture of diastereomers (eq 3).

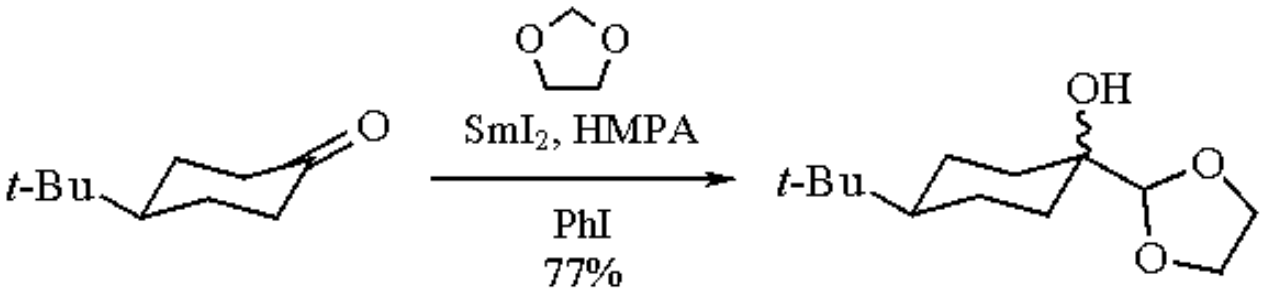

(3)

Typical yields for the reaction are in the range of 73-77%. This reagent provides a useful method for introduction of a one-carbon unit in the aldehyde oxidation state and is in general quite mild. The reaction is limited, however, in that 1,3-dioxolane must be utilized as solvent. Consequently, more highly functionalized dioxolane substrates which are less readily available may not be suitable partners in similar reactions.

---

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Selenium[1-4]

Se

[7782-49-2] · Se · Selenium · (MW 78.96)

(source of selenium compounds,[5,6] catalyst of alkene isomerization,[43-46] dehydrogenation reagent of cyclic hydrocarbons,[48-54] carbonylation catalyst of amines, alcohols, thiols, and related compounds with carbon monoxide[60])

Physical Data: mp 220.5 °C; bp 685 °C; *d* 4.82 g cm^{-3}.

Solubility: insol H_2O and organic solvents.

Form Supplied in: powder, pieces, or ingot.

Preparative Methods: red amorphous selenium is prepared by reduction of selenious acid in cold water with reducing reagents such as sulfur dioxide and hydrazine or by oxidation of its reduced form (hydrogen selenide or its salts) with air.

Handling, Storage, and Precautions: storage under inert atmosphere is recommended since it is oxidized gradually in air at room temperature. Elemental selenium is harmless upon ingestion. Use in a fume hood.

Formation of Organoselenium Compounds.[5-42]

Selenium reacts with organolithium, -sodium, and -magnesium compounds at room temperature or below to form metal selenolates (RSeM, M = Li,[7-10] Na,[11] MgX[12,13]) which afford selenides by the reaction with electrophiles (eqs 1 and 2),[7-11] diselenides by oxidation,[12] and selenols by acidification.[13]

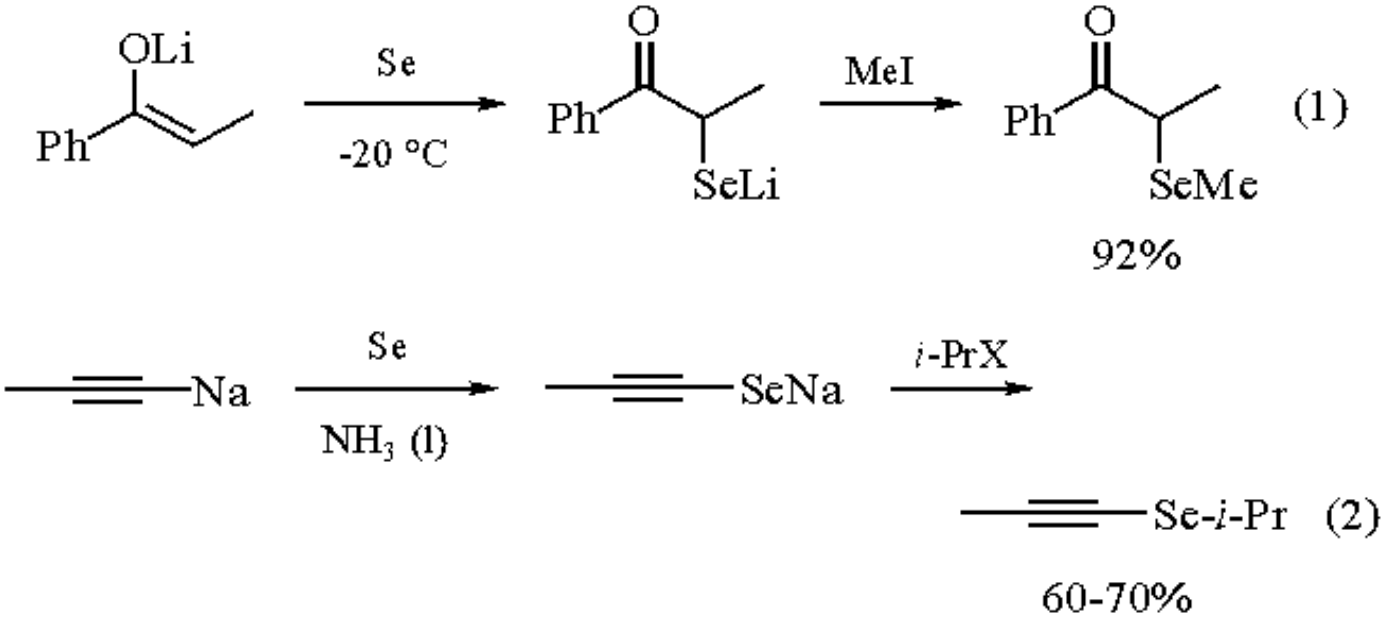

Selenium is reduced in several ways[14-31] to ammonium or metal salts of hydrogen selenide or diselenide (H_2Se, H_2Se_2) which are also useful precursors of selenides and diselenides, respectively, as well as selenoamides.[28,29] Commonly used reducing reagents are rongalite (***Sodium Hydroxymethanesulfinate***, $NaSO_2CH_2OH$) in aq NaOH,[14] ***Hydrazine***,[15,16] Li or Na in liq. NH_3[17-20] or THF (eq 3),[21] Mg in MeOH,[22] ***Samarium(II) Iodide*** in THF,[23] ***Sodium Borohydride*** in EtOH or H_2O (eq 4),[24] ***Lithium Triethylborohydride*** in THF,[25] and ***Carbon Monoxide*** in H_2O.[26-30] Reduction with tetraalkylammonium borohydride in toluene directly affords dialkyl selenides.[31]

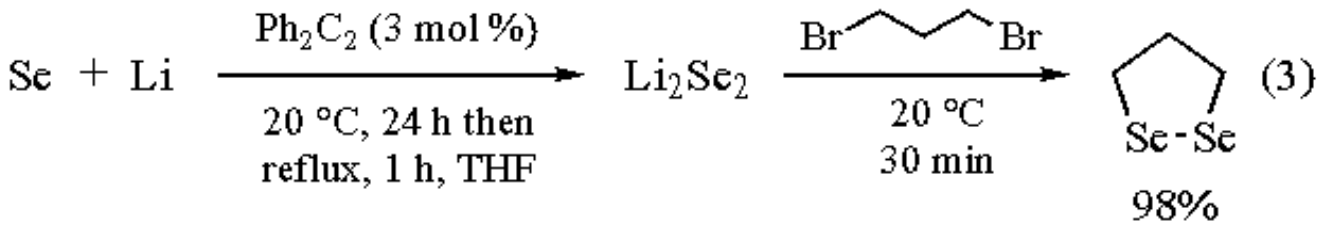

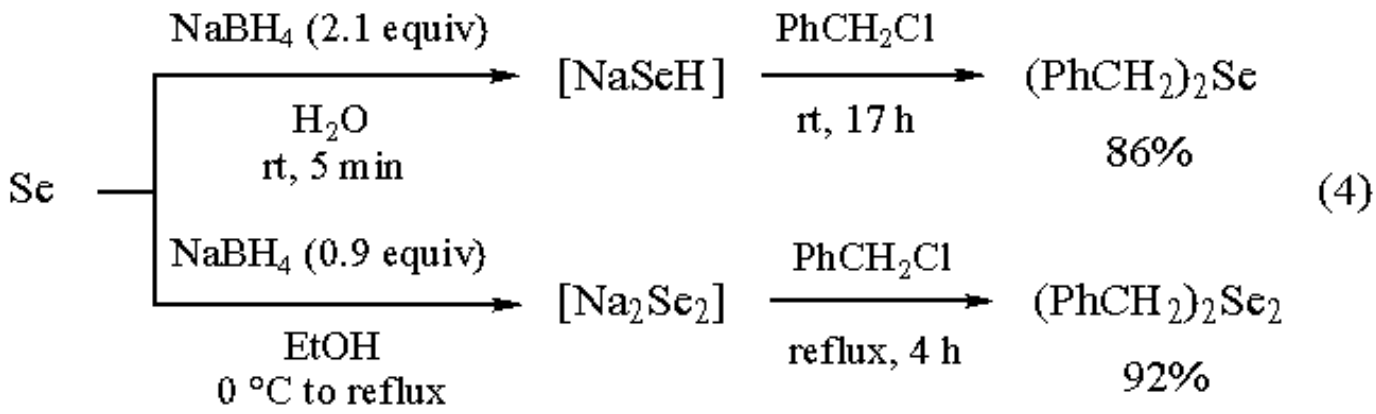

Elemental selenium reacts with hydrazones,[32-34] sulfonium[35] or phosphonium[36,37] ylides, and α-halo carbanions[38] to give selones. Sterically hindered selones can be isolated (eq 5).[32-34] Less hindered selones generated in situ readily react with ylides or dienes to afford alkenes (see below) or selenium-containing heterocycles (eqs 6 and 7).[35-38]

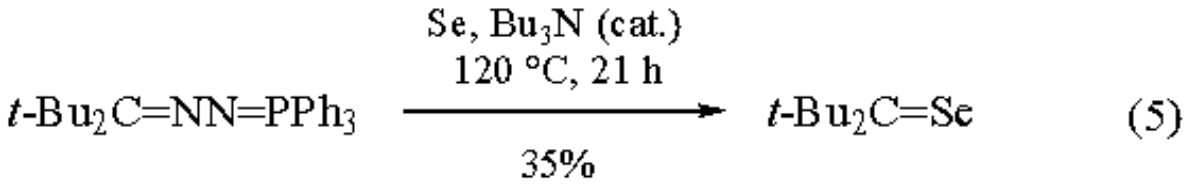

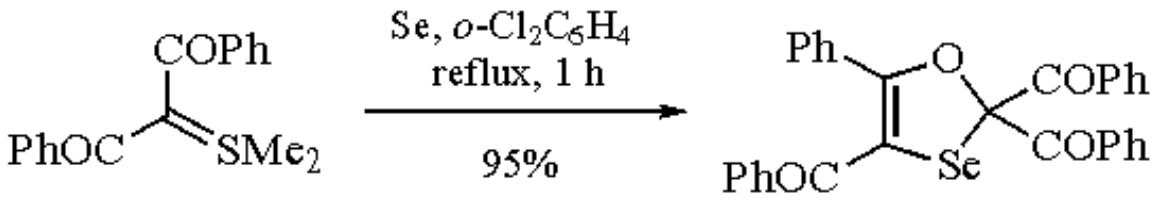

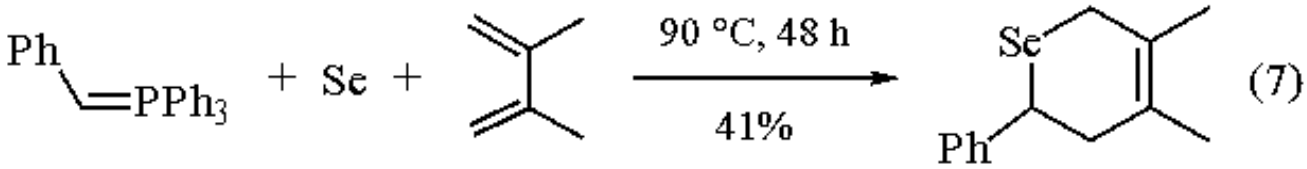

Selenium adds to a diaminoalkyne[39] and isocyanides[40-42] to yield a diselenoamide and isoselenocyanates, respectively (eqs 8 and 9). Selenium catalyzes the formation of isothiocyanates from isocyanides and ***Sulfur*** less efficiently than ***Tellurium***.[40] Reactions of selenium with ***Potassium Cyanide***, phosphines, or dichloromethane afford KSeCN, $R_3P{=}Se$, or CSe_2, respectively.[5,6]

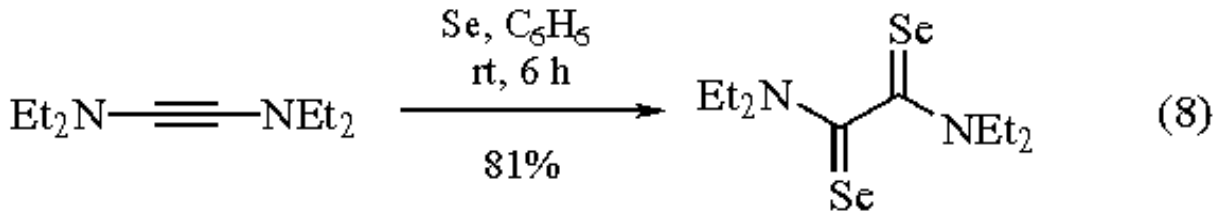

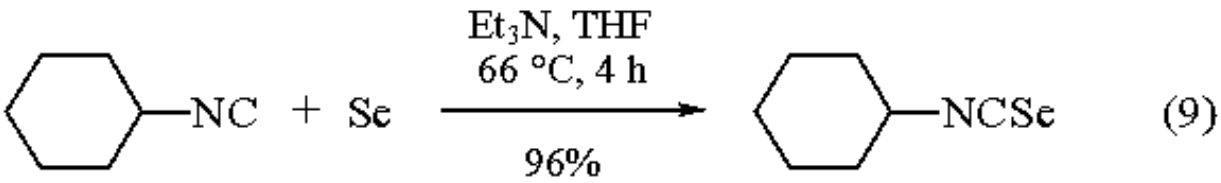

Synthesis and Isomerization of Alkenes.

Selones prepared from selenium and hydrazones are useful precursors of hindered alkenes (eq 10).[32-34] Wittig reagents afford alkenes with the aid of selenium (eq 11).[36,37]

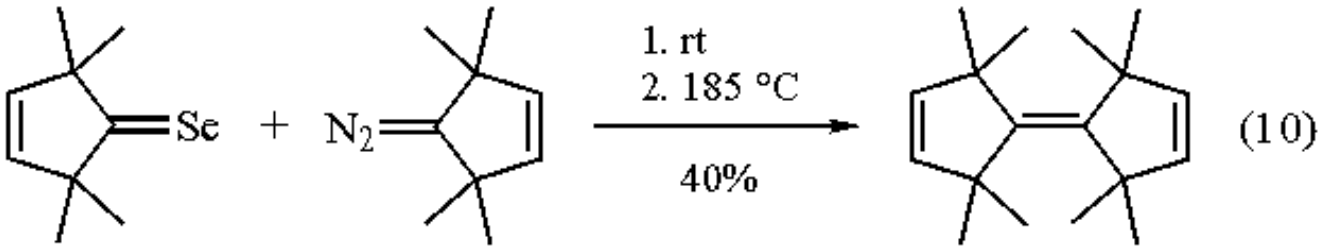

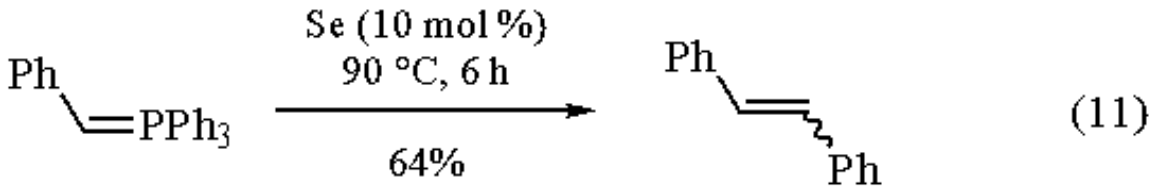

(*E*):(*Z*) = 84:16

Selenium catalyzes isomerization of alkenes at high temperatures (ca. 200 °C) to give an equilibrium mixture of *cis* and *trans* isomers when complete (eq 12).[43-46] Kinetic studies suggest the intermediacy of π-complexes of alkenes with selenium. For the isomerization of *cis*-stilbene, the activation energy of the selenium-catalyzed reaction is about 63 kJ mol^{-1} (15 kcal mol^{-1}) lower than that of thermal isomerization[44] and the relative rates using selenium, ***Methanesulfonic Acid***, and ***Potassium t-Butoxide*** are 734:20.6:1, respectively, at 190 °C.[43] In the isomerization of alkenes having an allylic hydrogen, some regioisomers are formed concomitantly, especially at high temperatures, and selenium gradually loses its catalytic activity by the formation of selenium-containing byproducts.[45]

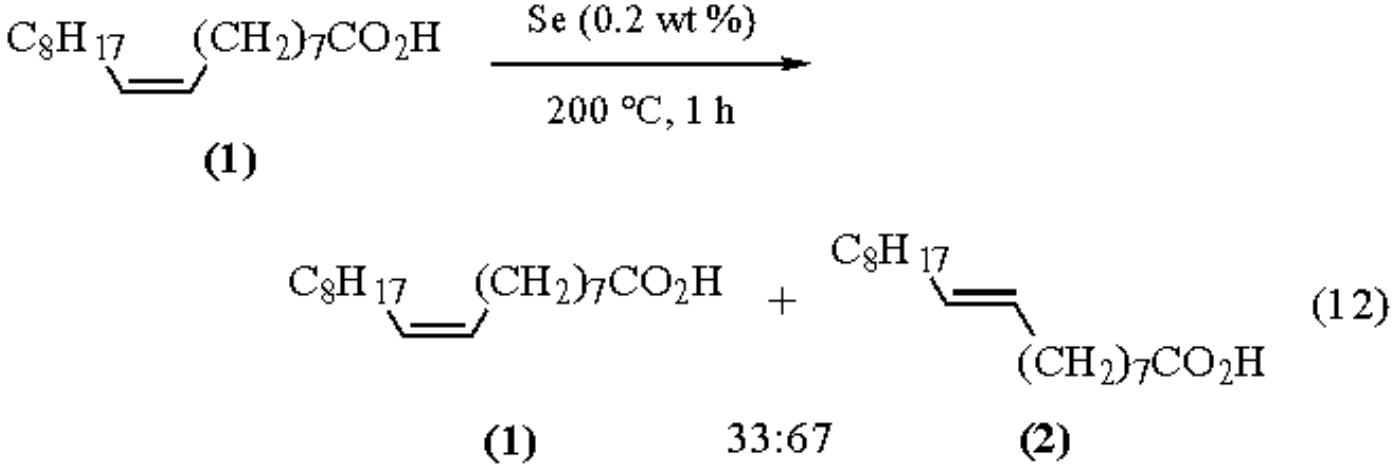

Reduction by the Use of Se.

Selenols, hydrogen selenide, and their salts are very useful reagents not only for introduction of selenium moieties into organic molecules but also for reduction of a variety of functional groups (for details, see ***Benzeneselenol***, ***Methaneselenol***, ***Diphenyl Diselenide***, ***Hydrogen Selenide***, ***Sodium Hydrogen Selenide***, ***Lithium Selenide*** or ***Sodium Selenide***, etc). What should be emphasized here is that reduction can be performed by the use of a catalytic amount of selenium or diselenides in the presence of an appropriate reducing reagent, as shown generally by eq 13.[5,47]

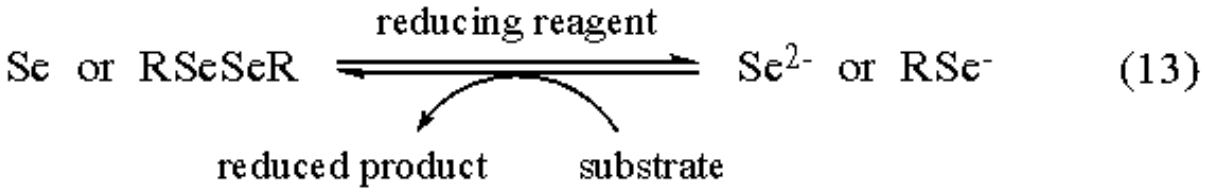

Oxidation with Selenium.

Six-membered cyclic and polycyclic hydrocarbons undergo dehydrogenation at ca. 300 °C to give aromatic compounds in moderate yields by reaction with an excess amount of metallic or amorphous selenium, where selenium is reduced to hydrogen selenide (eq 14).[48,49] The selenium-promoted aromatization may be accompanied by elimination of alkyl or heteroatom groups. Ethyl groups are cleaved in preference to hydrogen with the formation of ethaneselenol (eq 15).[49] Hydroxyl groups are also prone to removal (eq 16).[50] Methyl groups can be lost when attached to a quaternary carbon.[51] At higher temperatures, hydrogenation of double bonds, rearrangement of carbon skeletons, and cyclization of side chains may take place during aromatization (eq 17).[52] This reaction is applicable to dehydrogenation of heterocyclic compounds (eq 18).[53] Similar dehydrogenation with sulfur is known, but the reaction hardly proceeds with tellurium.[54]

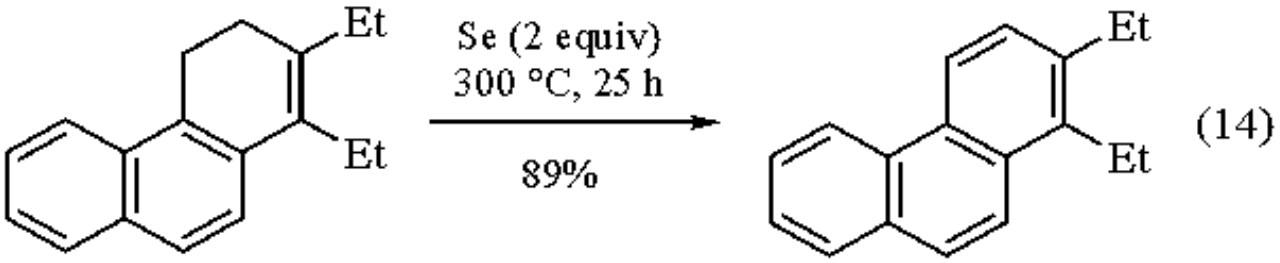

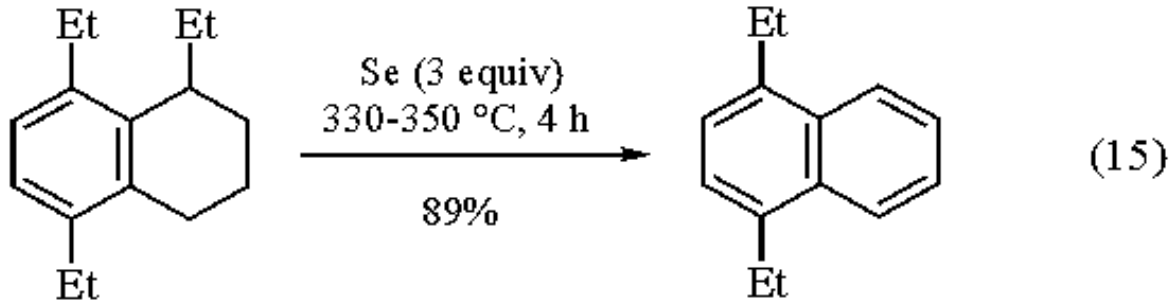

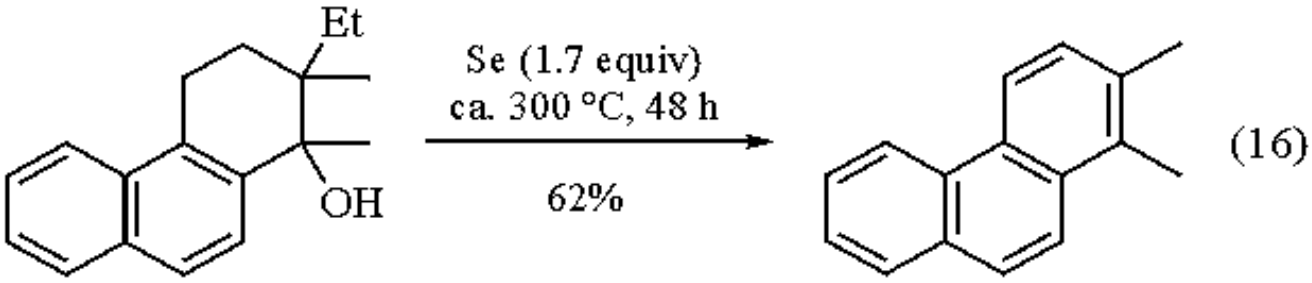

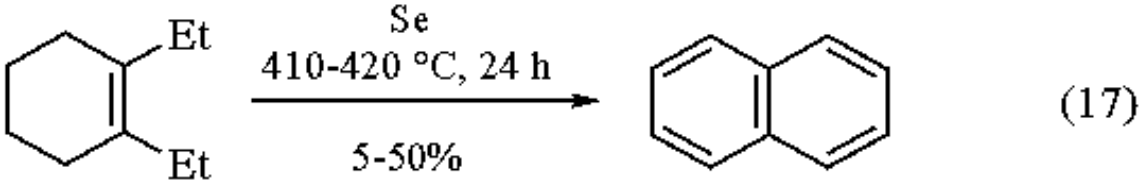

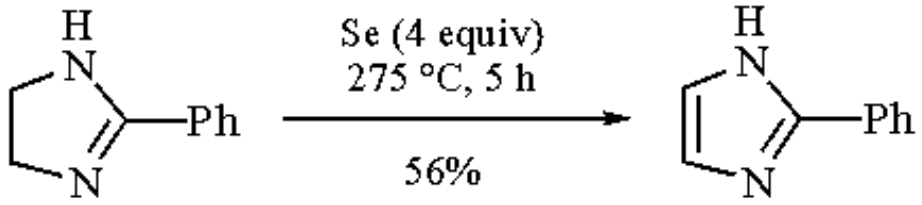

(18)

Formates are oxidized to carbonates with selenium in the presence of a sodium alkoxide (eq 19). Since NaSeH formed in this process regenerates selenium upon oxidation, the reaction can be carried out by the use of a catalytic amount of selenium in the presence of oxygen.[55] Formamides can be oxidized to carbamates similarly, but less efficiently.[56]

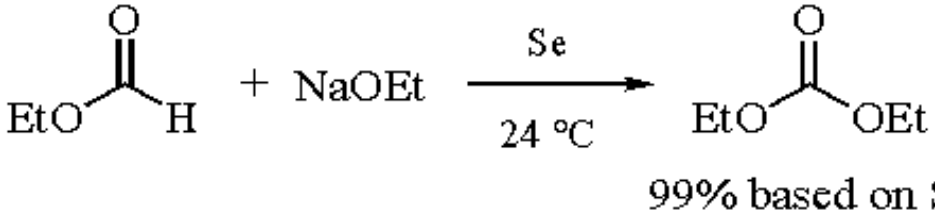

(19)

Selenium-Catalyzed Carbonylation and Related Reactions.

A variety of primary amines are carbonylated with carbon monoxide to give urea derivatives by the use of a catalytic amount of selenium under mild conditions in the presence of oxygen (eq 20).[57-59] The turnover number of selenium reaches up to 10^4 at 120 °C under 30 atm of carbon monoxide.[60]

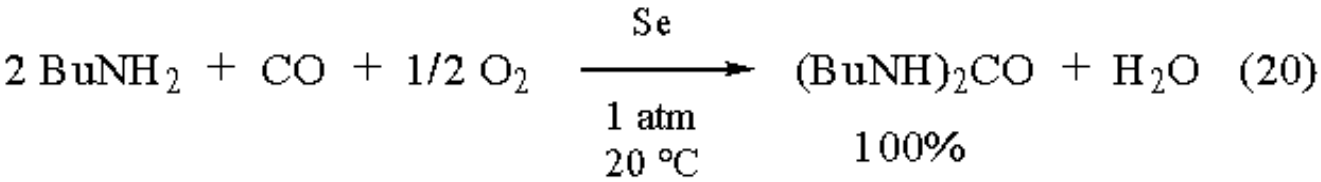

(20)

In these reactions, ureas are probably formed by the aminolysis of isocyanates generated by the elimination of hydrogen selenide from ammonium carbamoselenoates (**3**), which are formed in situ by the reaction of selenium, an amine, and carbon monoxide. Oxidation of the hydrogen selenide formed with air regenerates selenium. Some secondary amines such as ***Pyrrolidine***, ***Piperidine***, and dimethylamine afford corresponding ureas in excellent yields under similar conditions.[60] Several control experiments suggest that carbonylation of secondary amines proceeds via aminolysis of biscarbamoyl diselenides formed by the oxidation of ammonium carbamoselenoate intermediates (**3**) (eq 21).[61]

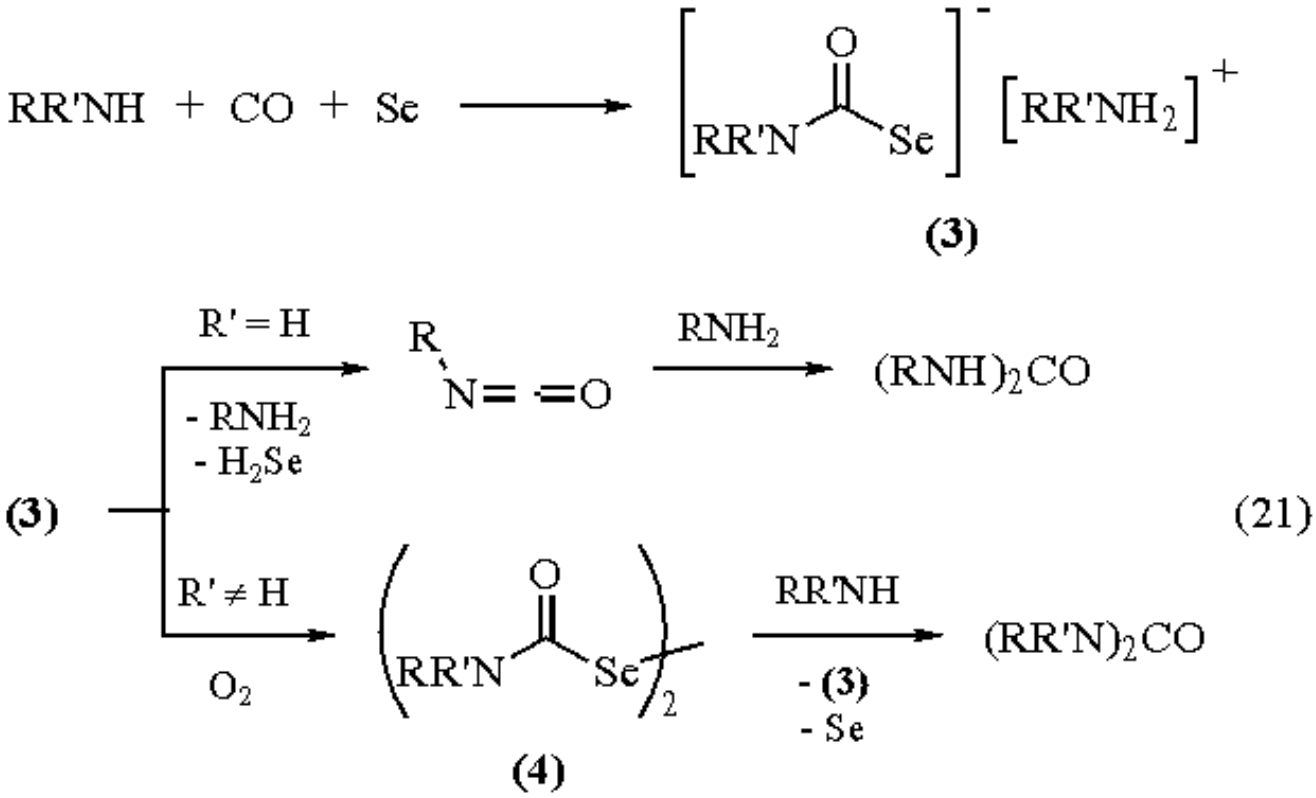

Unsymmetrical ureas can be obtained by the addition of a different amine to the ammonium salts (eqs 22 and 23).[57,62] Under mild conditions, acyclic dialkylamines other than dimethylamine do not afford corresponding ureas due to the steric hindrance. In this case, biscarbamoyl diselenides (**4**) are formed, which eliminate selenium to yield ureas upon pyrolysis via biscarbamoyl selenide (**5**) (eq 24).[63] Biscarbamoyl diselenides are good carbamoylation reagents of arenes[64] and cyclic ethers[65] (eqs 25 and 26). Carbamoselenoates (**3**) quantitatively afford carbonyl selenide by acidification[66] and *Se*-alkyl carbamoselenoates by trapping with alkyl halides (eq 24).[67]

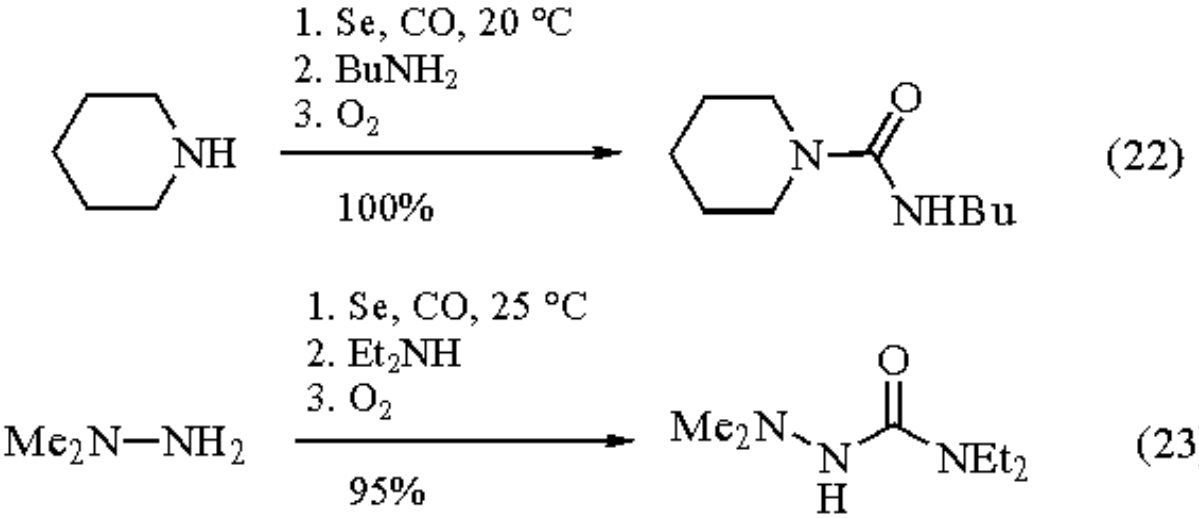

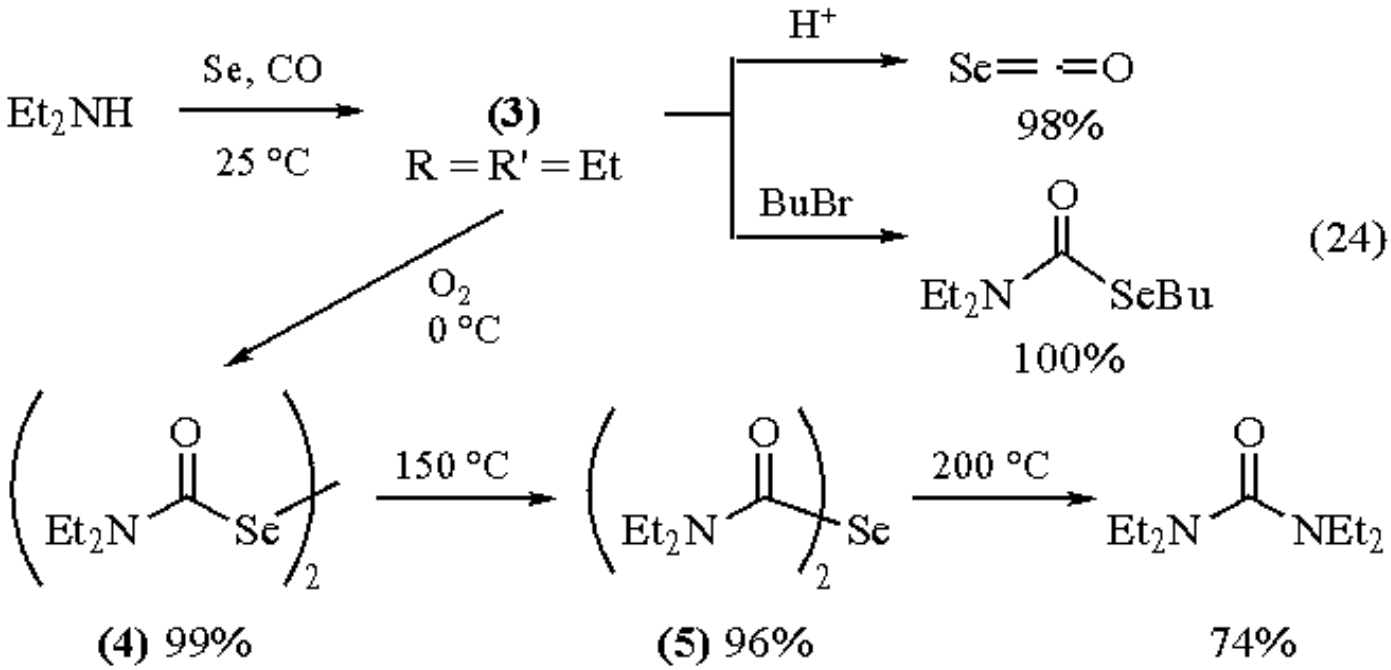

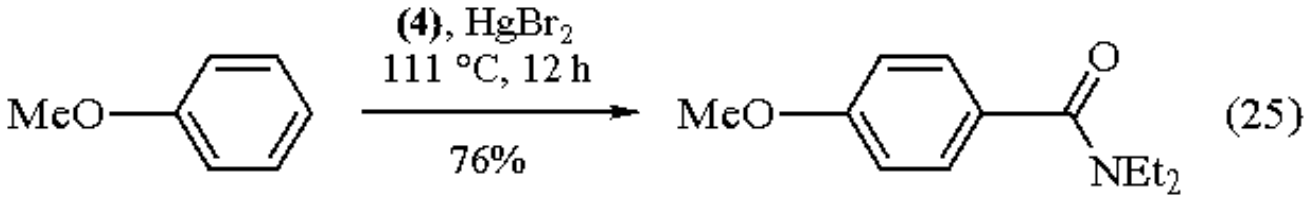

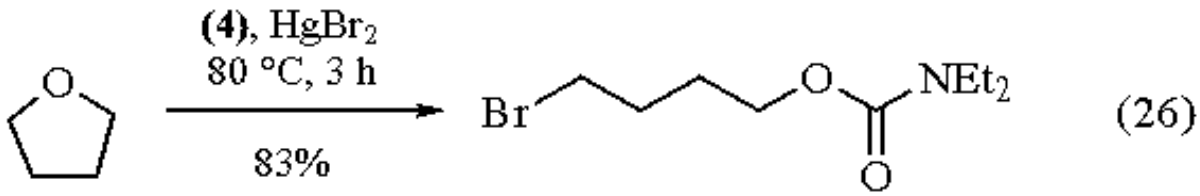

This selenium-mediated carbonylation with CO was discovered and expanded by Sonoda to include synthesis of a variety of cyclic and acyclic ureas (eq 27),[68-70] carbamates (eqs 28 and 29),[69-73] thiocarbamates (eqs 30 and 31),[70,72-75] carbonates (eq 32),[76,77] thiocarbonates (eq 33),[78] and heterocyclic compounds (eqs 34-37).[69,70,79-81]

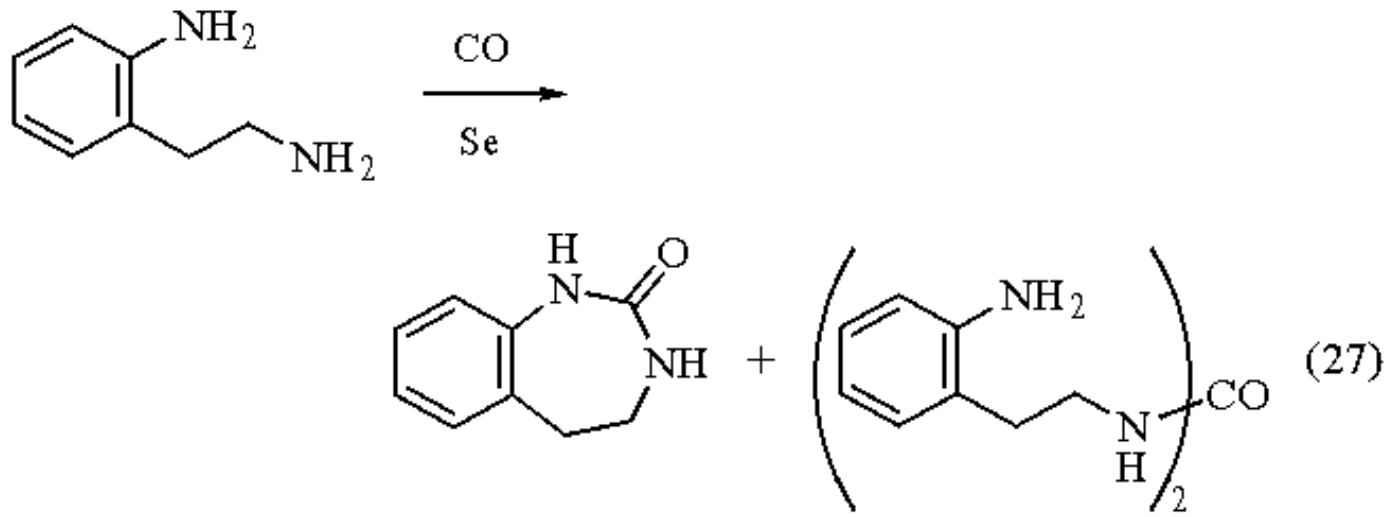

stoichiometric conditions	85%	< 1%
catalytic conditions	< 1%	95%

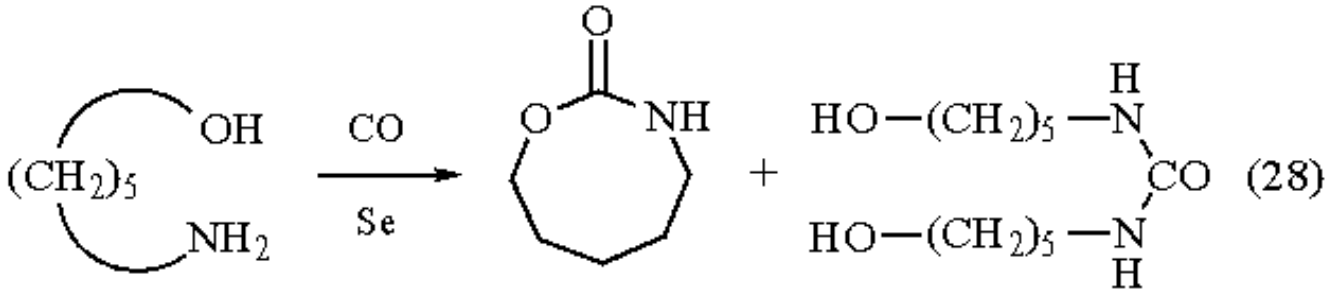

stoichiometric conditions	87%	-
catalytic conditions	2%	93%

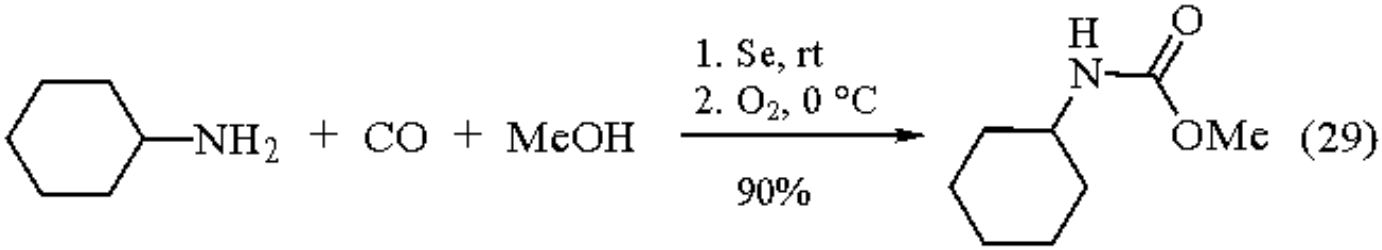

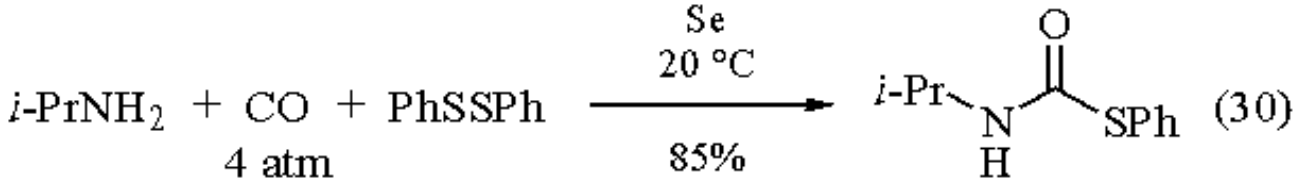

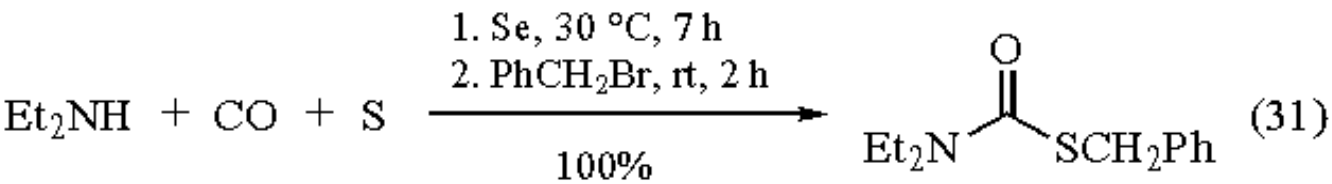

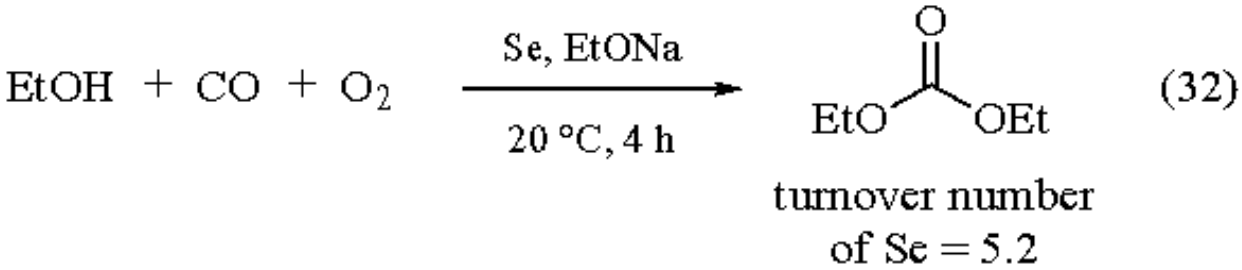

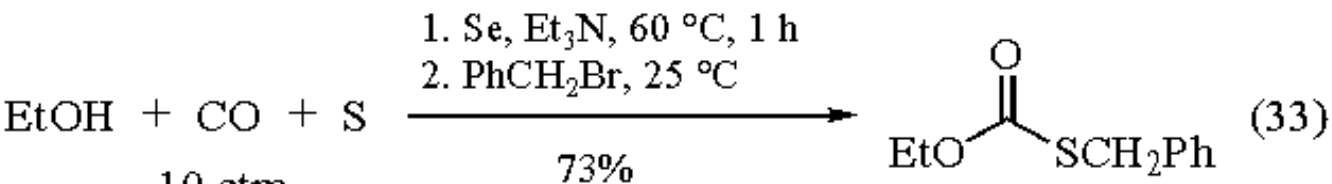

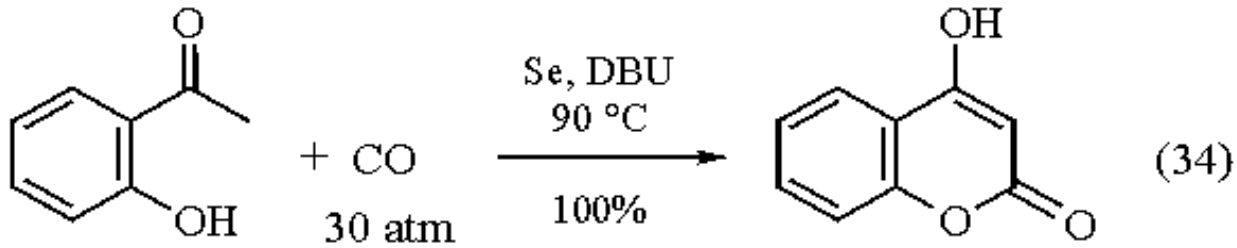

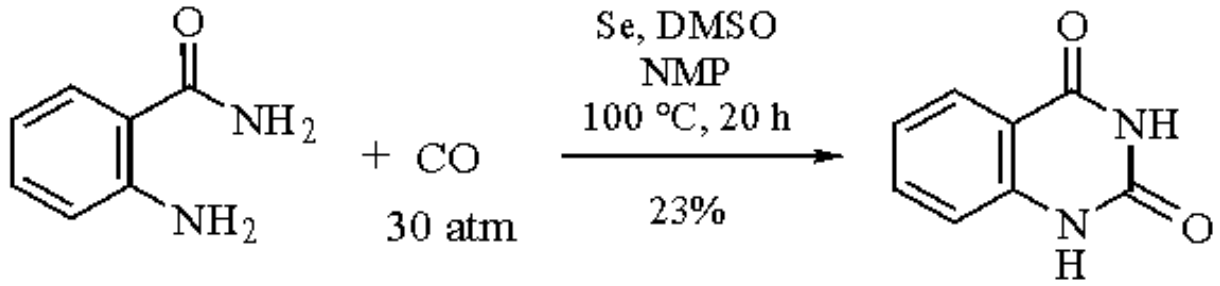

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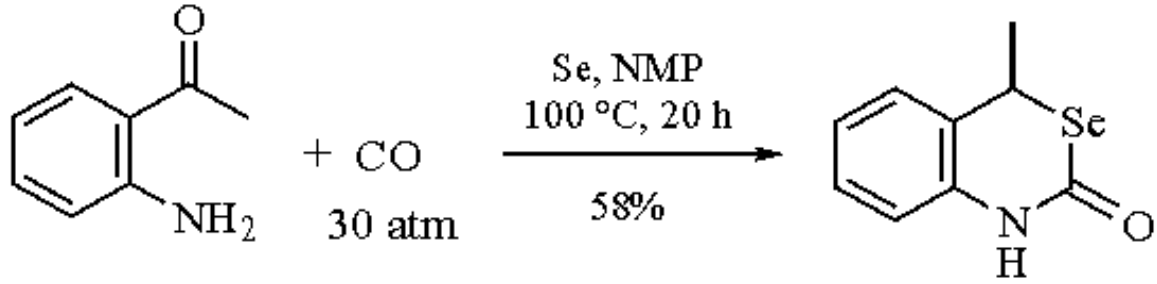

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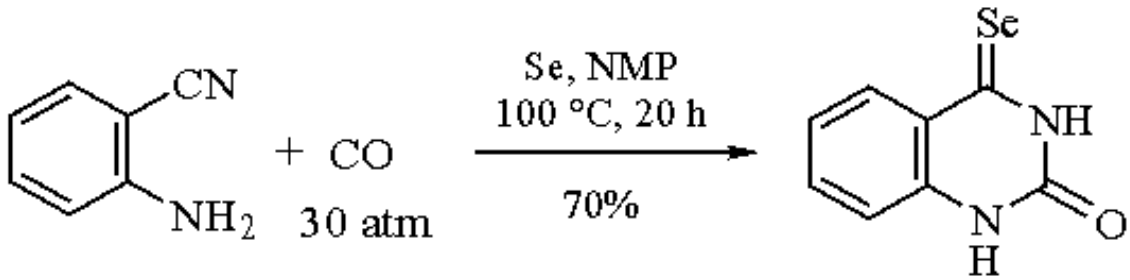

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Selenium(IV) Oxide

SeO_2

[7446-08-4] · O_2Se · Selenium(IV) Oxide · (MW 110.96)

(oxidant of activated, saturated positions)

Alternate Name: selenium dioxide.

Physical Data: mp 315 °C (subl); *d* 3.95 g cm^{-3}.

Solubility: sol water, methanol, ethanol, acetone, acetic acid.

Form Supplied in: off-white powder;[1] widely available.

Purification: by sublimation, or by treatment with HNO_3.[28]

Handling, Storage, and Precautions: toxic; corrosive; causes intense local irritation of skin and eyes; use in a fume hood.

Allylic Hydroxylation.

Selenium(IV) oxide is known primarily for hydroxylation of activated carbon-bearing positions, particularly at allylic (or propargylic) sites. Studies by Guillemonat and others have led to the following hydroxylation selectivity rules:[2,3]

- 1)Hydroxylation occurs α to the more substituted end of the double bond.
- 2)The order of facility of oxidation is $CH_2 > CH_3 > CH$.
- 3)When the double bond is in a ring, oxidation occurs within the ring when possible, and α to the more substituted end of the double bond.
- 4)Oxidation of a terminal double bond affords a primary alcohol with allylic migration of the double bond.

An example of rules (1) and (2) is shown in the oxidation of 3-methyl-3-butene, where the allylic methylene position is oxidized in preference to the methyl or methine positions (eq 1).[2] Alkene-selective oxidation of 5,6-dihydroergosterol in ethanol, an example of rule (3), occurs at C-14 and is followed by allylic rearrangement to give a 7α-ethoxy product (eq 2).[4] The mechanism of the allylic oxidation reaction is proposed to be initiated by ene addition, followed by dehydration and [2,3]-sigmatropic rearrangement of the resultant allylseleninic acid.[5,6] In a key step of the synthesis of α-onocerin, α-oxidation in acetic acid leads to an unsaturated γ-lactone product in good yield (eq 3).[7] The milbemycins have been hydroxylated in the 13β-position by selenium dioxide.[8] Because selenium dioxide forms selenious acid (H_2SeO_3) in the presence of water, hydroxylations of alkenes containing acid-labile groups (e.g. acetals) have been run in pyridine.[9]

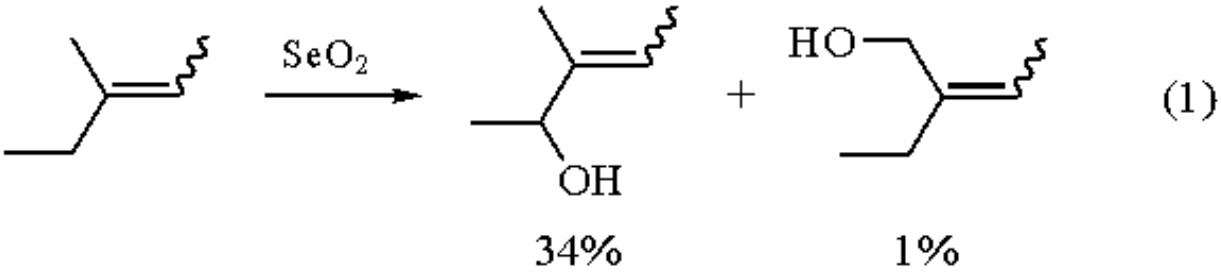

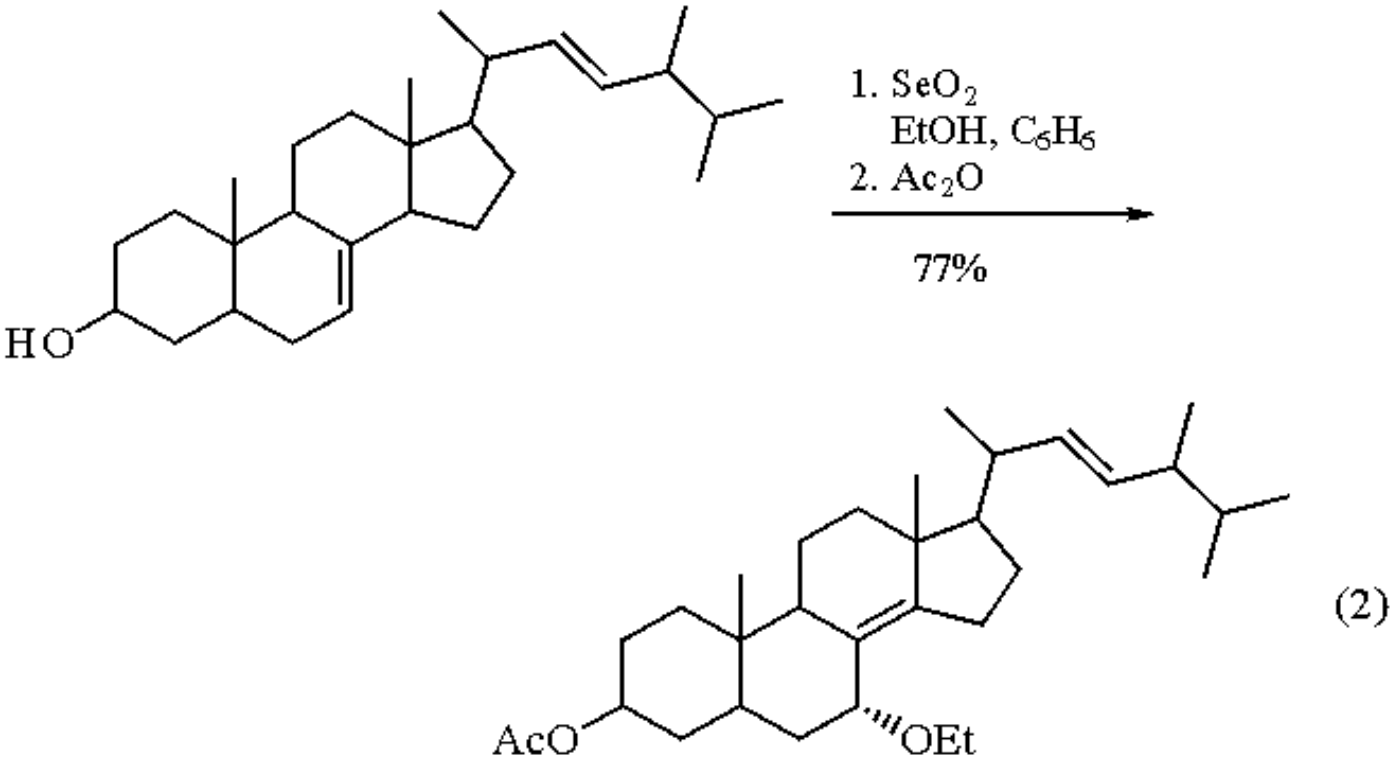

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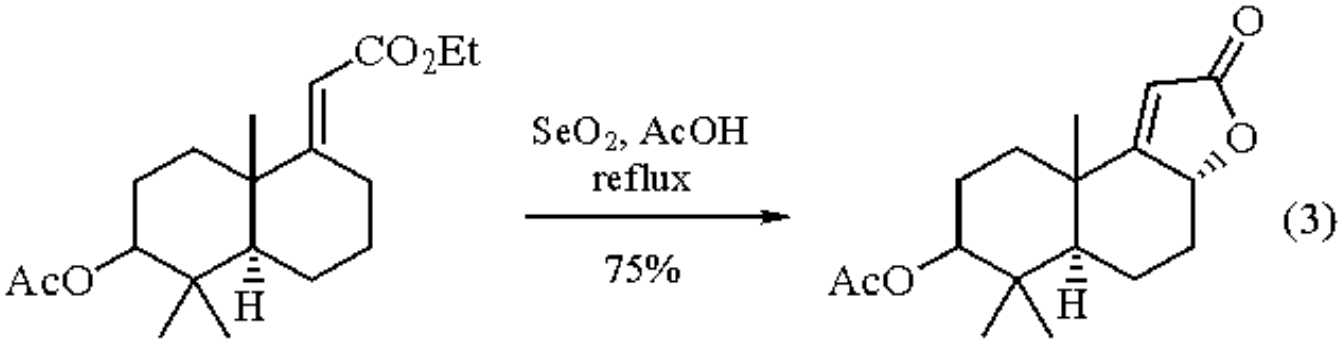

(3)

Higher-Order Oxidations.

Selenium dioxide can introduce carbonyl functionality at activated positions, and can also effect dehydrogenation[10-13] at highly activated saturated sites. For instance, phenylglyoxal is isolated in high yield from α-oxidation of acetophenone (eq 4).[14] On a large scale, dissolution of the selenium dioxide in aqueous dioxane at 55 °C is required prior to acetophenone addition. Similarly, 6-methyluracil is readily converted to orotaldehyde in acetic acid (eq 5).[15] Oxidation of aryl-substituted succinic acids to maleic anhydride analogs occurs readily in acetic anhydride (eq 6).[16] This is a preferred method, since oxidations of this type with ***N-Bromosuccinimide*** give bromoarene byproducts. Additionally, selenium dioxide in the presence of ***Trimethylsilyl Polyphosphate*** has been used to aromatize cyclohexenes and cyclohexadienes.[17] Using only a slight excess (1.2 molar equiv) of selenium dioxide in pyridine, methyl 2-methyl-4-pyrimidinecarboxylate has been prepared regioselectively from 2,4-dimethylpyrimidine after methanolysis of the carboxylic acid product (eq 7).[18] Interestingly, ***Sulfuric Acid***-catalyzed oxidation of 1-octene in acetic acid affords a 1,2-diacetate product (eq 8).[19] Only a trace amount of 1-acetoxy-3-octene is observed.

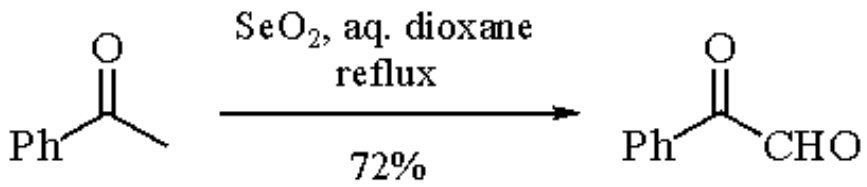

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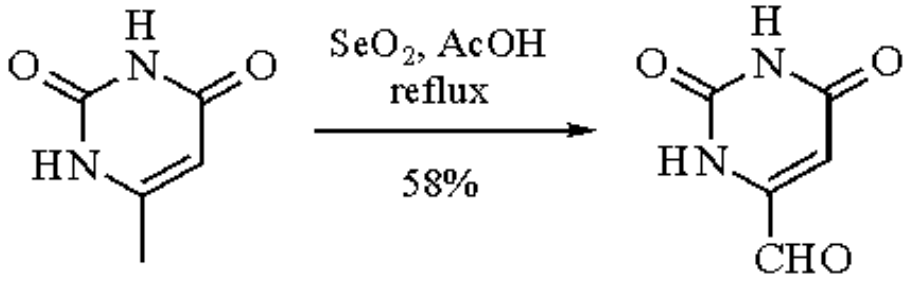

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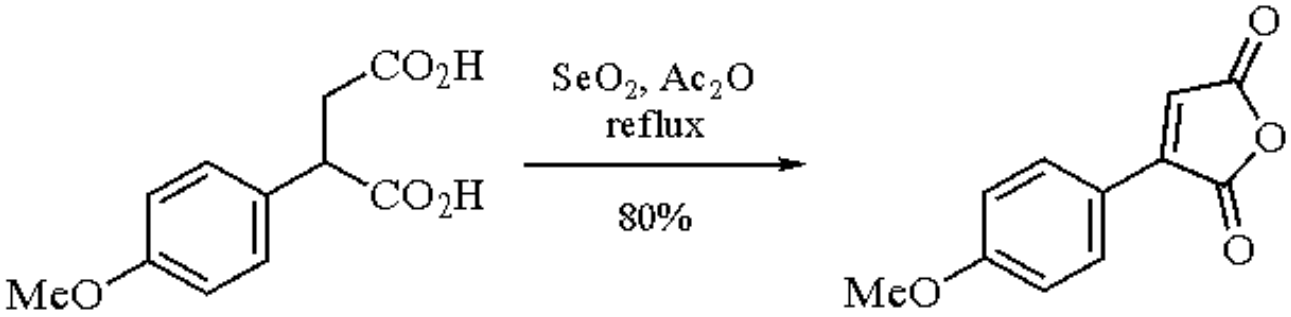

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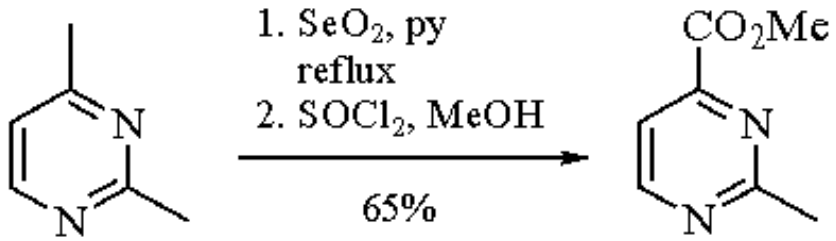

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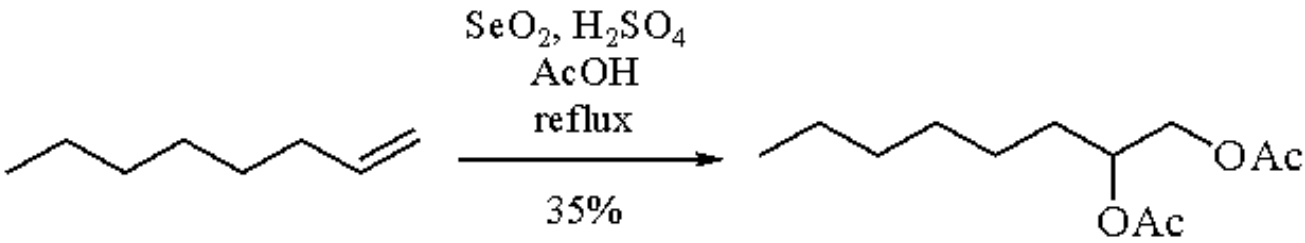

(8)

Oxidative Cleavage.

Attack of selenium dioxide at activated positions can lead to oxidative bond cleavage when appropriate leaving groups are present. Aryl propargyl ethers undergo oxidation at the α-alkynyl position to afford a phenolic species and propargyl aldehyde (eq 9).[20] The analogous aryl allyl ether fragmentations occur in somewhat lower yields. (Hydroxyaryl)pyrazolines have been oxidized, with nitrogen extrusion, to afford 2´-hydroxychalcone products (eq 10).[21] Oxidations of pyrazolines with ***Bromine***, ***Potassium Permanganate***, ***Chromium(VI) Oxide***, and other reagents result in pyrazole formation.

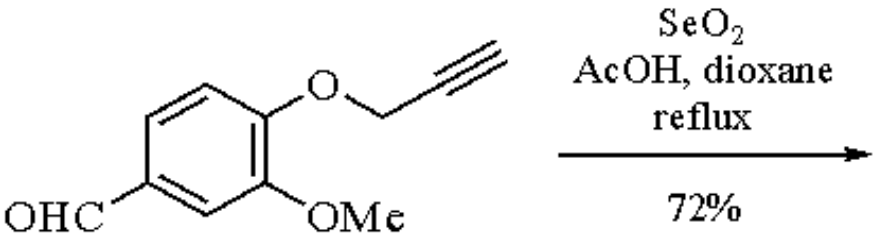

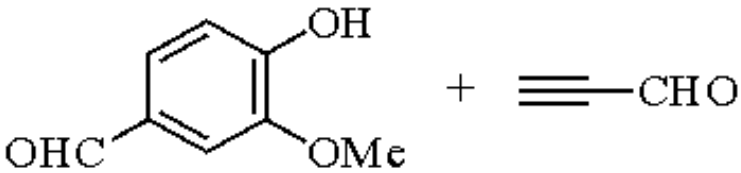

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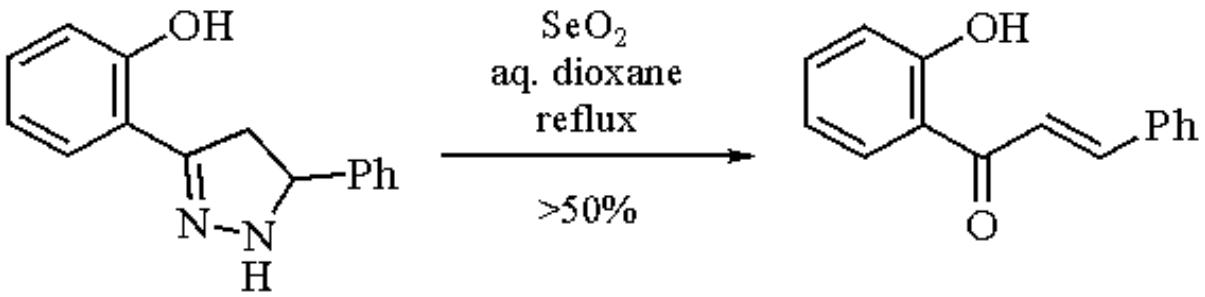

(10)

Miscellaneous Transformations.

Alkyl and aryl nitriles can be prepared from the corresponding aldehydes via conversion to the aldoxime, followed by catalytic selenium dioxide-mediated elimination (eq 11).[22,23] Aliphatic nitriles are formed at rt, while aryl nitrile formation requires heating. 1,2,3-Selenadiazoles have been synthesized by treatment of an *N*-benzylazepine 4-semicarbazone with selenium dioxide (or selenoyl dichloride) (eq 12).[24,25] The *N*-benzyl proximal product is formed with high regioselectivity vis-à-vis the distal product in polar solvents. Nonpolar solvents give ca. 3:1 mixtures (proximal/distal). The oxygen-catalyzed reaction of trialkylboranes with 1 equiv of selenium dioxide affords a dialkyl selenide as the major product.[26] Similarly, dialkyl selenides have been prepared by reaction of alkyllithiums or Grignard reagents with selenium dioxide.[27]

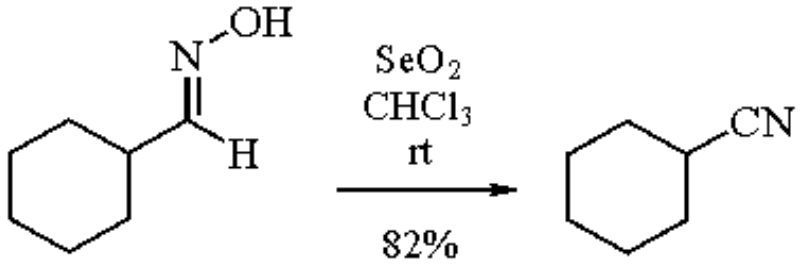

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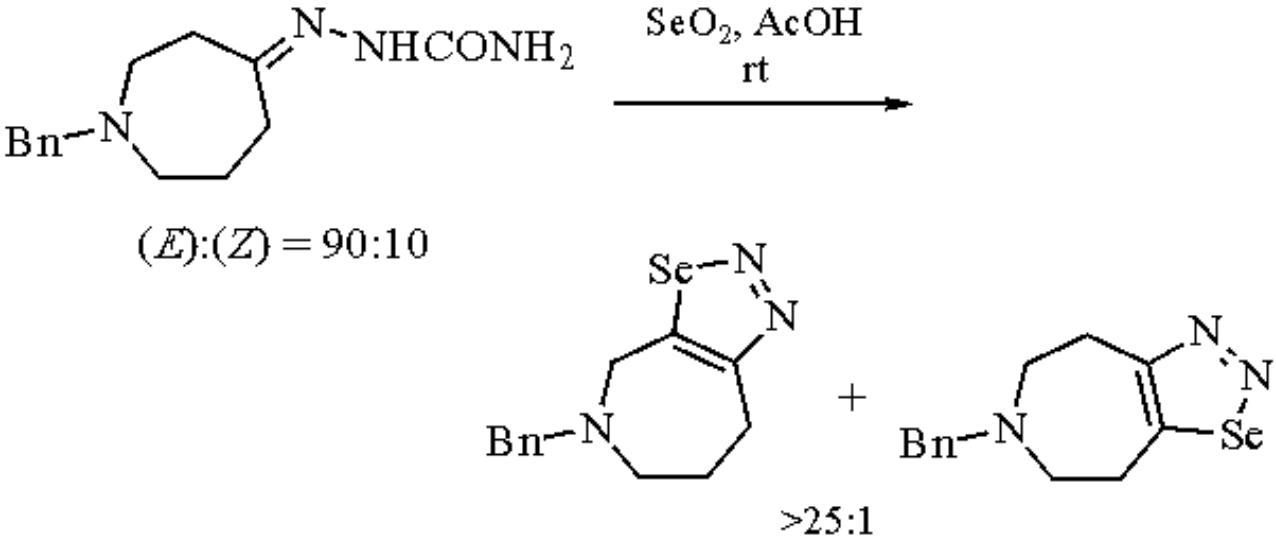

(12)

Related Reagents.

Selenium(IV) Oxide-t-Butyl Hydroperoxide.

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Selenium(IV) Oxide-*t*-Butyl Hydroperoxide[1]

SeO_2-*t*-BuOOH

(SeO_2)

[7446-08-4] · O_2Se · Selenium(IV) Oxide-*t*-Butyl Hydroperoxide · (MW 110.96) (*t*-BuOOH)

[75-91-2] · $C_4H_{10}O_2$ · Selenium(IV) Oxide-*t*-Butyl Hydroperoxide · (MW 90.14)

(oxidizes alkenes to allylic alcohols or to α,β-unsaturated aldehydes or ketones)

Physical Data: SeO_2:[2] mp 340 °C. 90% *t*-BuOOH:[3] fp 35 °C; *d* 0.901 g cm^{-3}. See ***Selenium(IV) Oxide*** and ***t-Butyl Hydroperoxide***.

Form Supplied in: SeO_2: solid. *t*-BuOOH: liquid. Commercially available.

Handling, Storage, and Precautions: SeO_2[2] is irritating to the eyes and skin and is highly toxic and corrosive. *t*-BuOOH[1,3] is a flammable liquid and, as with all peroxides, should be handled with care. Use in a fume hood.

Allylic Oxidations.

Selenium(IV) oxide in combination with *t*-butyl hydroperoxide (TBHP) is an effective system for insertion of oxygen into an allylic carbon-hydrogen bond (eq 1).[4] Reaction conditions (CH_2Cl_2, 0 °C) are much milder than those required for oxidation with selenium(IV) oxide alone and, as a result, yields are higher with fewer oxidation, dehydration, and rearrangement byproducts. Furthermore, the problem of the removal of colloidal selenium is circumvented, and in many cases only catalytic amounts of selenium(IV) oxide are required to effect oxidations in high yields. Over-oxidations to the corresponding aldehyde or ketone products are observed. The rules regarding allylic oxidations by selenium(IV) oxide, proposed by Guillemonat[5] and Rapoport,[6] apply to these reaction conditions: (1) oxidation occurs at the more highly substituted end of the alkene; (2) the order of reactivity of C-H bonds is $CH_2 > CH_3 > CH$ (rule 1 takes precedence over rule 2); (3) when the double bond is within a ring, oxidation occurs within the ring; (4) *gem*-dimethyl trisubstituted alkenes oxidize stereospecifically to give (*E*)-α-hydroxy alkenes.

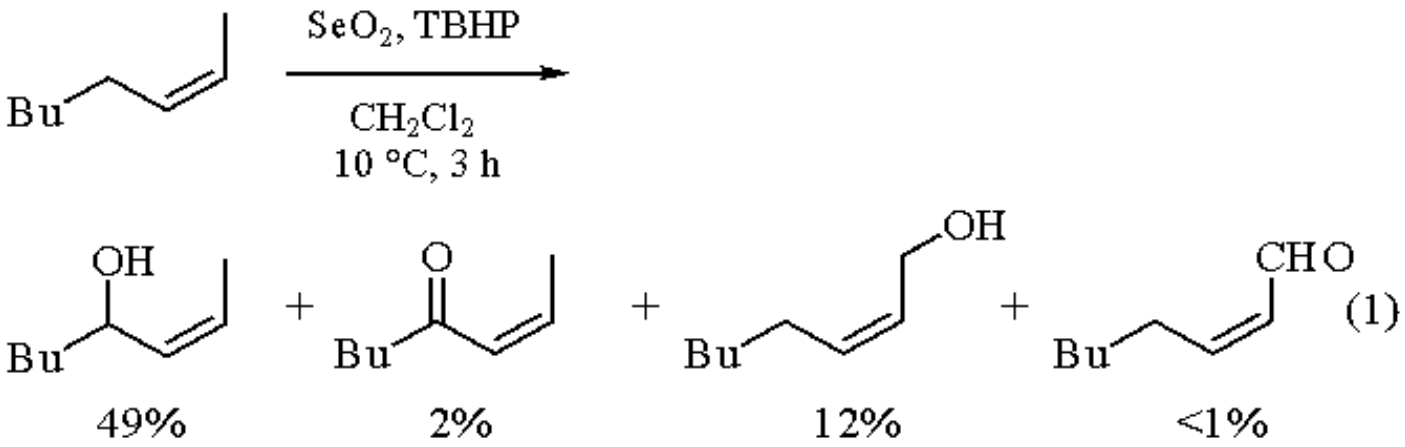

Studies of the reaction intermediates suggest that the reaction proceeds via a combination-dissociation-recombination pathway,[7] which may explain the double bond migration seen in some selenium(IV) oxide oxidations (eq 2).[8]

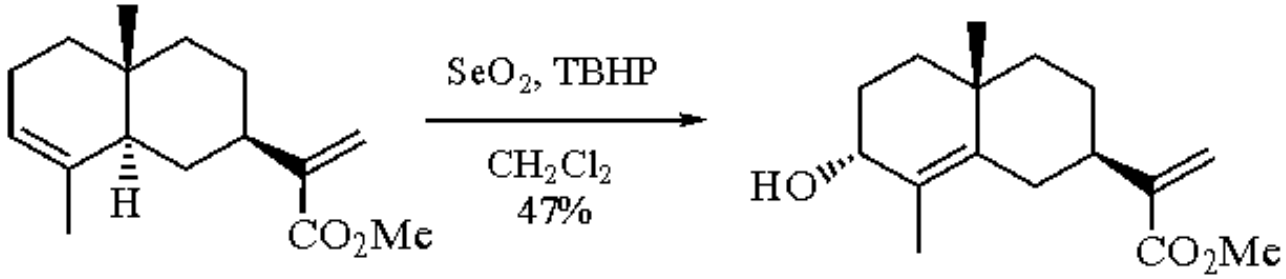

(2)

Selenium(IV) oxide supported on silica gel in the presence of TBHP oxidizes methyl allylic sites with no evidence of competing oxidation at methylene allylic positions (eq 3).[9]

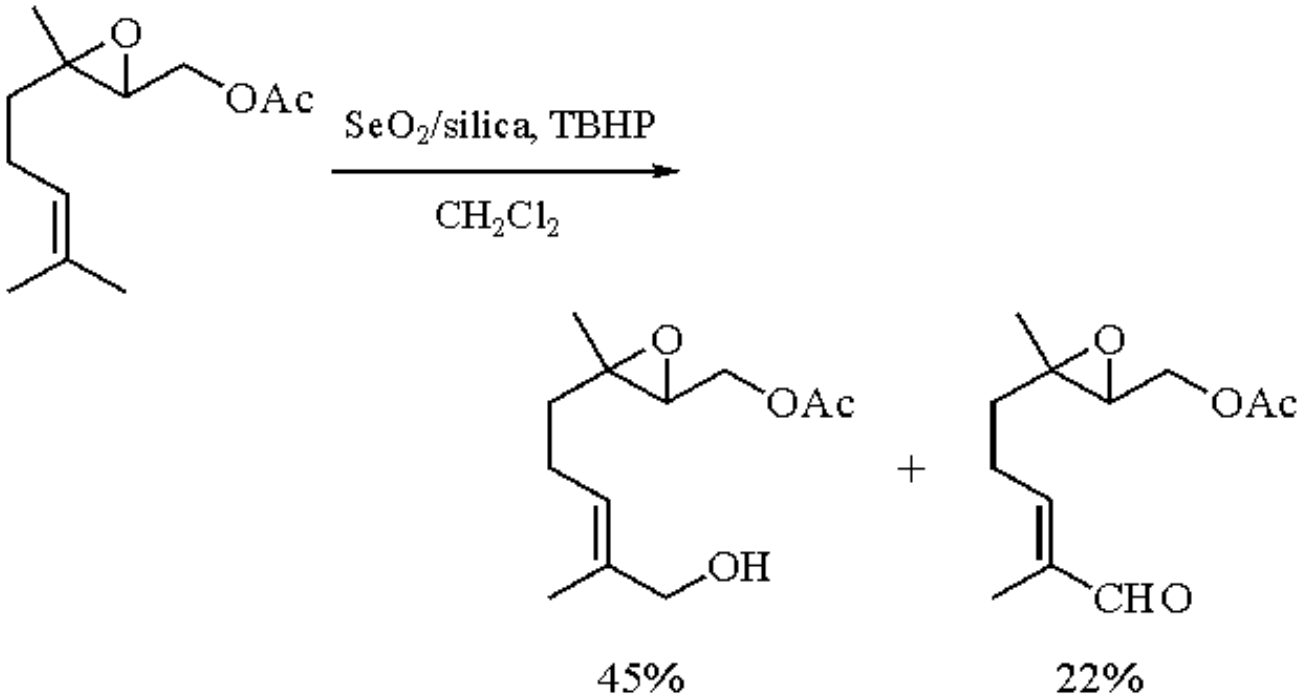

(3)

The selenium(IV) oxide-TBHP combination has also been used to oxidize alkenes to their corresponding α,β-unsaturated ketones (eq 4)[10] or aldehydes[11] using either the standard conditions over extended reaction periods or silica gel-supported selenium(IV) oxide.[11a]

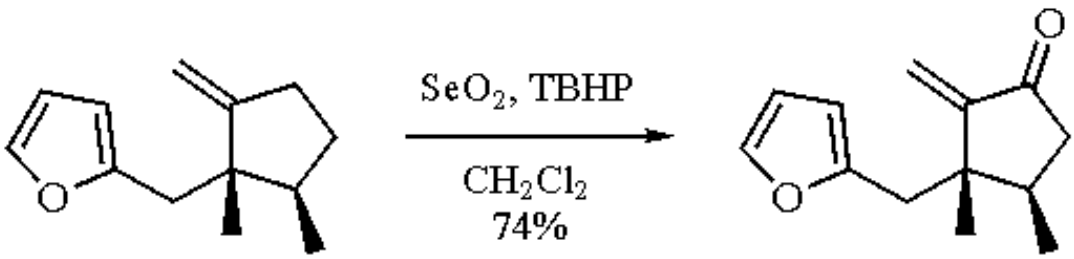

(4)

Oxidation of Alkynes.

Alkynes are similarly oxidized to give α-hydroxy alkynes in good to moderate yields.[1] Methine and methylene C-H bonds are more reactive than methyl C-H bonds. Internal alkynes can be oxidized to give alkynediols in good yields with little or no oxidation of the alcohols to ketone products (eq 5).[12]

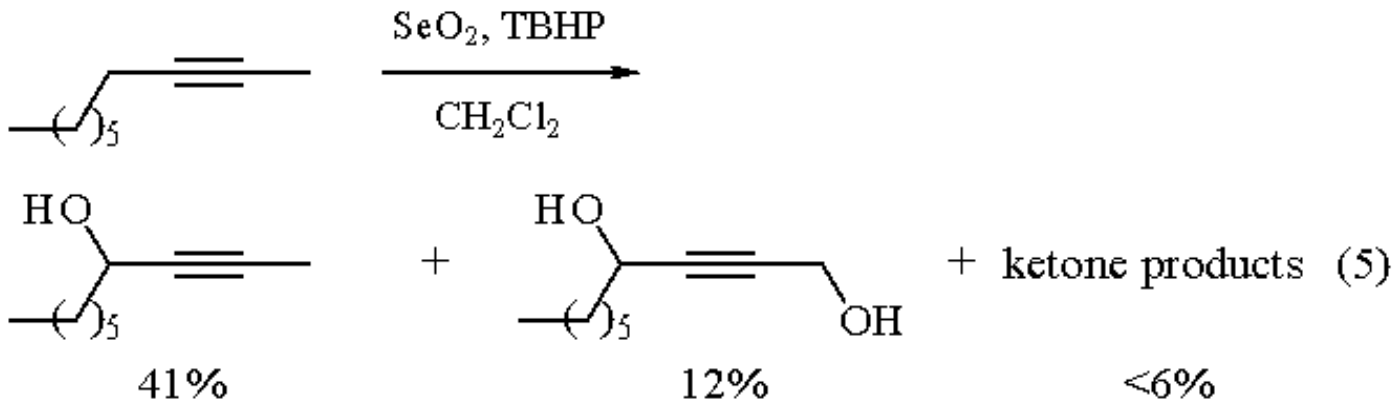

Oxidation of Allylic Alcohols.

Selenium(IV) oxide supported on silica gel with TBHP has been used to selectively oxidize primary allylic alcohols to α,β-unsaturated aldehydes in high yields.[13] Secondary allylic, benzylic, and saturated alcohols are unaffected by these reaction conditions.

Related Reagents.

t-Butyl Hydroperoxide; ***Selenium(IV) Oxide***.

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Semicarbazide[1]

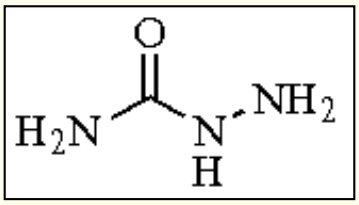

[57-56-7] · CH_5N_3O · Semicarbazide · (MW 75.09) (HCl salt)

[563-41-7] · CH_6ClN_3O · Semicarbazide Hydrochloride · (MW 111.55)

(potent nucleophile; forms many crystalline carbonyl derivatives[1])

Physical Data: HCl salt: mp 175-177 °C (dec).

Solubility: HCl salt: relatively sol water.

Form Supplied in: the HCl salt is widely available from commercial suppliers as a crystalline material; it can be further purified by recrystallization from 75% aq. ethanol and dried under vacuum over calcium sulfate.[2]

Handling, Storage, and Precautions: reactive nucleophile with significant ability to bind to various enzymes; exercise reasonable caution.

Derivatization.

The most straightforward use of semicarbazide is in its reaction with the carbonyl group of aldehydes and ketones (eq 1) to afford derivatives known as semicarbazones.[3] These semicarbazones are commonly crystalline with characteristic melting points. An excellent procedure for isolation of aldehydes and/or ketones from other functionalized materials in a mixture is to heat that mixture with semicarbazide on a silica gel support, filter off the solid, and regenerate the carbonyl compound by heating the support with oxalic acid in a two-phase aqueous/organic system.[4]

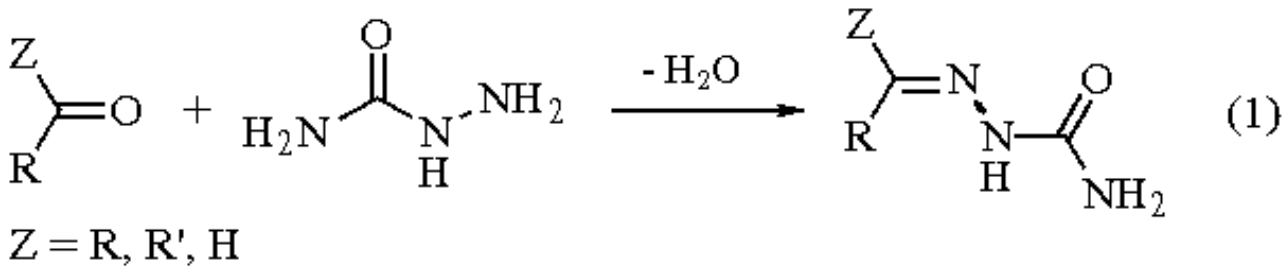

Role as a Nucleophile.

Semicarbazide often serves as a typical nucleophilic reagent in studies involving carbonyl chemistry. The mechanism of semicarbazone formation has been repeatedly studied.[5] Many fundamental physical organic studies have been published on the interconversion of a trigonal carbonyl carbon into a tetrahedral carbon intermediate. Investigations focusing on generation of these tetrahedral intermediates, especially the formation of carbinolamines via addition of nitrogen-containing nucleophiles (eq 2), have often employed semicarbazide as a reactant.[6] These include specialized experimental studies such as examination of secondary isotope effects[7] and proton NMR.[8] Because of the presence of the two adjacent nitrogen atoms in semicarbazide, this molecule has figured prominently in several studies of the so-called α effect.[9] Semicarbazide has often been employed in comparisons of relative nucleophilicity.[10] Especially significant are the many investigations of aminolysis.[11] Application of this research to enzymes has been extensive, as is illustrated by work on arylamine *N*-acetyltransferase,[12] monoamine oxidase,[13] urease,[14] chymotrypsin,[15] *N*-methylglutamate synthetase,[16] and pyruvamide-dependent histidine decarboxylase.[17] A comparison of semicarbazide with other nucleophiles in nucleophilic aromatic substitution (eq 3) has been

published.[18] Diaryl and heteroaryl disulfides are cleaved to the corresponding thiols by semicarbazide.[19]

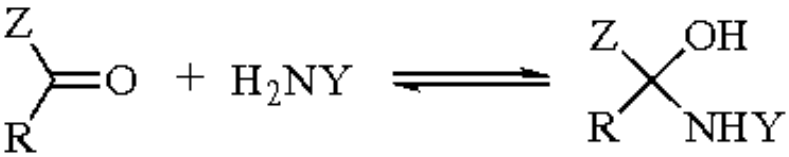

(2)

Z = R, R', H, OR", etc.

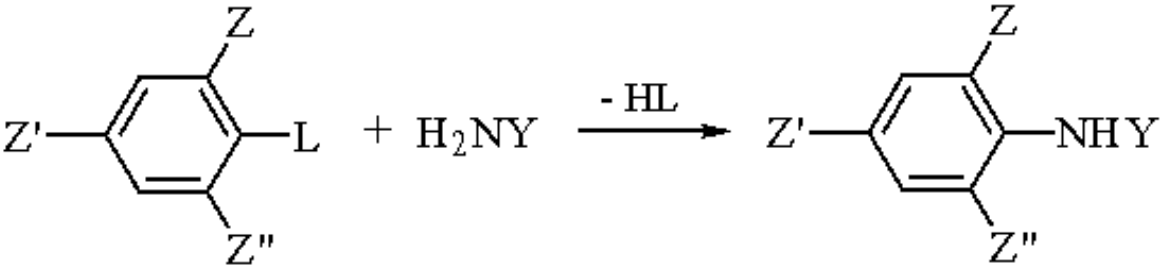

(3)

Generation of Heterocycles.

Conversion of cyclic ketones to semicarbazones followed by ***Selenium(IV) Oxide*** oxidation produces 1,2,3-selenadiazoles. Pyrolysis of the selenadiazole affords the corresponding cycloalkyne (eq 4).[20] Conversion of a pyranulose glycoside to the semicarbazone, reaction with HCl/dioxane, and heating in acetic acid leads to the novel triazine (**1**) (eq 5).[21] The antimicrobial activity of the nitrofurans has inspired a tremendous effort directed at the preparation of analogs. Many of these have involved elaboration of various appended side chains by reaction of the carbonyl functionality with semicarbazide.[22] Reaction of semicarbazide with enones[23] (eq 6) and ynones[24] with subsequent dehydration provides an efficient route to pyrazole derivatives. Certain pyrimidines can be made to undergo ring-contraction to pyrazoles by heating with semicarbazide in an acidic medium (eq 7).[25] Reaction of α-hydroxymethylene ketones with semicarbazide has been shown[26] to generate pyrazoline derivatives (eq 8). α-Diketones afford *as*-triazines upon reaction with semicarbazide followed by dehydration and hydrogenolysis (eq 9).[27] Heating of an acylanthranilic acid in the presence of semicarbazide provides the corresponding 2,3-disubstituted 4-oxo-3,4-dihydroquinazoline.[28] Reaction of dithioesters with semicarbazide with subsequent dehydration and aromatization has been employed for the preparation of thiadiazoles.[29] In an investigation of heterocyclic quinones, combination of semicarbazide with 6-chloroquinoline-5,8-dione hydrochloride provided a reasonable yield of oxadiazino[6,5-*g*]quinoline-5,10-dione (eq 10).[30]

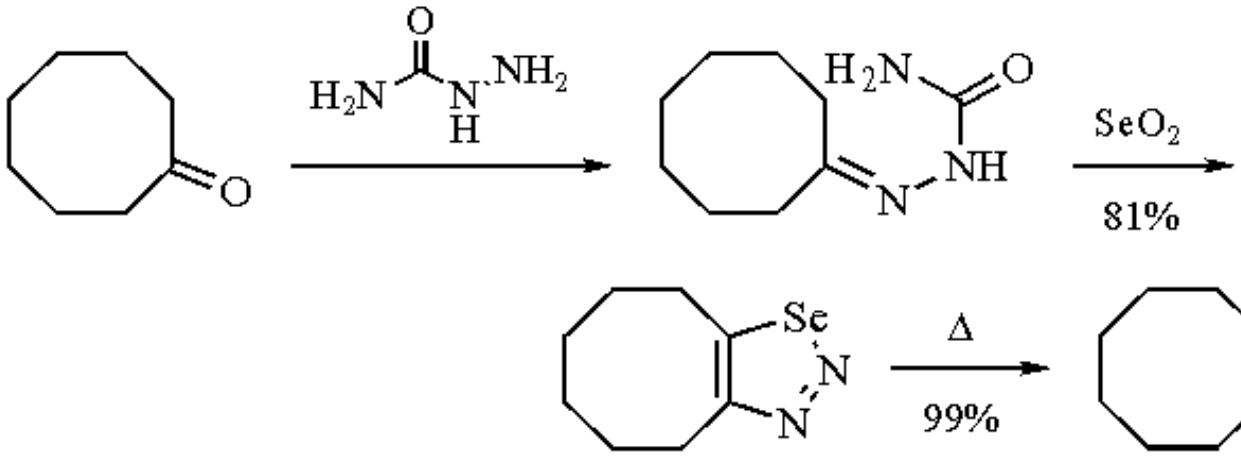

(4)

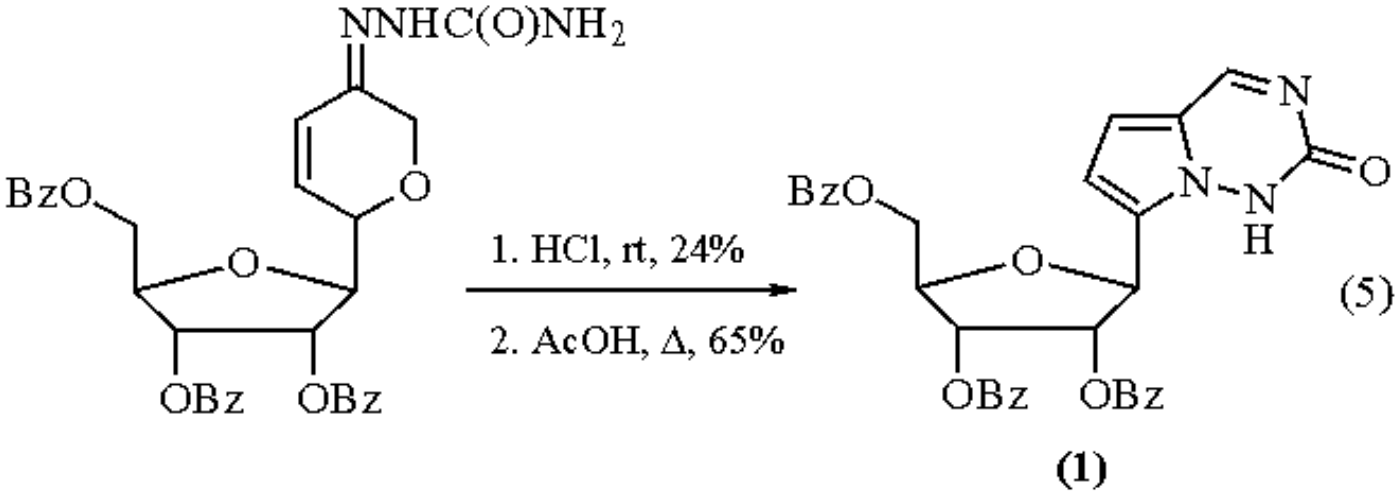
NNHC(O)NH2
BzO
O
OBz
OBz
1. HCl, rt, 24%
2. AcOH, Δ, 65%
N
O
N
N
H
(5)
(1)

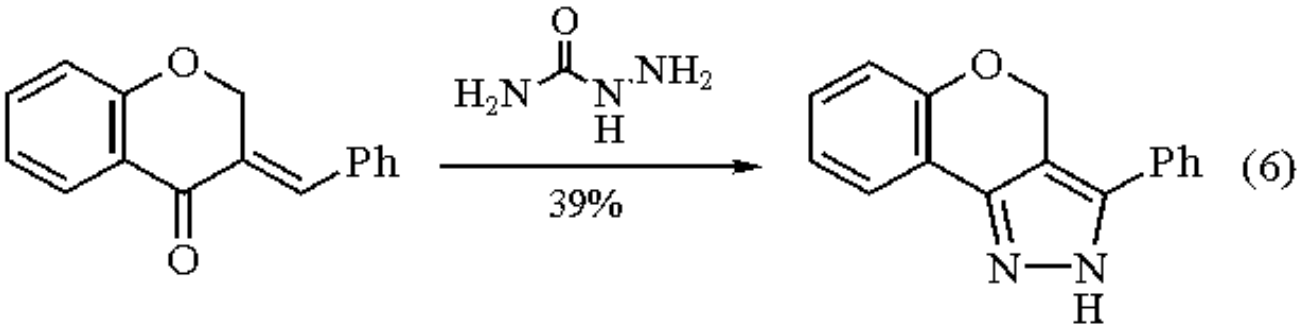
O
Ph
H2N
NH2
N
H
39%
(6)

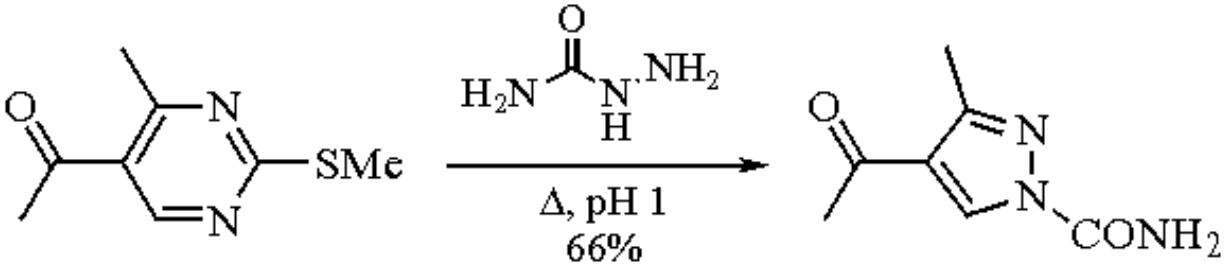
O
N
SMe
H2N
NH2
N
H
Δ, pH 1
66%
CONH2
(7)

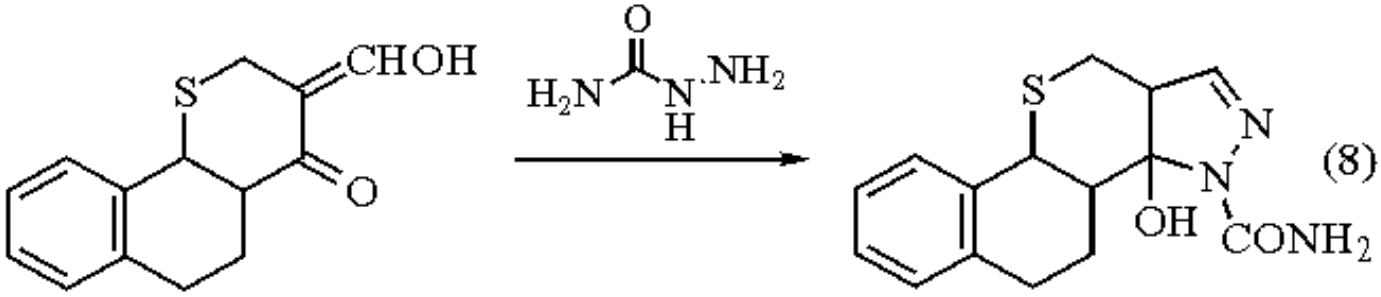
S
CHOH
O
H2N
NH2
N
H
OH
CONH2
(8)

2.47 g 1.8 g

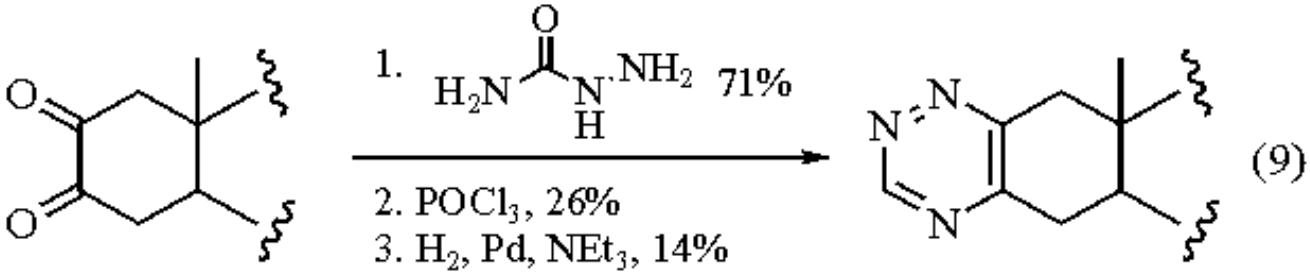
O
1.
H2N
NH2
N
H
71%
2. POCl3, 26%
3. H2, Pd, NEt3, 14%
N
(9)

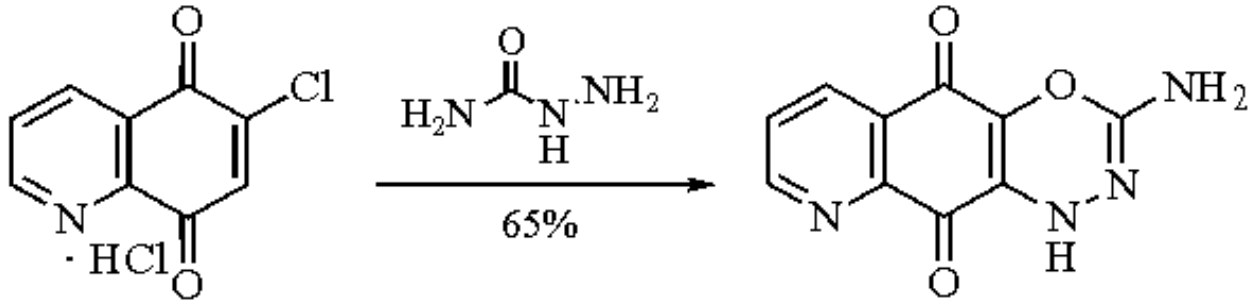

(10)

Applications to Biological Chemistry.

In studies concerned with the effects of atmospheric pollutants on erythrocyte membranes, semicarbazide has been utilized as an ozone scavenger.[31] The effect of semicarbazide on the course of various photochemical processes that occur in chloroplasts has been investigated.[32] In reconstitution experiments, semicarbazide has a significant effect on collagen fiber formation and properties.[33]

Related Reagents.

N,N-Dimethylhydrazine; ***Hydrazine***; ***Hydroxylamine***; ***Phenylhydrazine***.

---

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Silicon(IV) Fluoride[1]

[7783-61-1] · F_4Si · Silicon(IV) Fluoride · (MW 104.08)

(efficient Lewis acid and fluorination reagent)

Physical Data: mp -90.2 °C; bp -86.0 °C; *d* (-95 °C) 1.66 g cm^{-3}.

Solubility: sol ether, chloroform, dichloromethane, acetonitrile.

Form Supplied in: colorless gas, commercially supplied in cylinders.

Handling, Storage, and Precautions: very pungent odor similar to that of hydrogen chloride; highly irritating; corrosive to skins and eyes. See also ***Hydrogen Fluoride***.

General Discussion.

Silicon tetrafluoride is an abundant byproduct of fertilizer manufacture. Several attempts have been made to use SiF_4 as a fluorinating agent.[2] However, tedious experimental procedures and the low nucleophilicity of the fluorine attached to silicon have restricted application of SiF_4 as a fluorinating agent. In the presence of ***Aluminum Chloride***, ethyl orthoformate is fluorinated with silicon tetrafluoride (eq 1). Besides ethyl fluoride, the reaction products are ethyl formate and ether.[3]

$$HC(OEt)_3 + SiF_4 \xrightarrow[88\%]{AlCl_3} EtF + HCO_2Et + EtOEt \qquad (1)$$

The reactions of silicon tetrafluoride with carbon tetrachloride (eq 2) and ***Phosgene*** (eq 3) in the vapor phase at elevated temperature give chlorofluorocarbons and carbonyl fluorochloride, respectively.[4] The reactions are carried out by passing a mixture of the substrate and silicon tetrafluoride through an electrically heated quartz tube, which is filled with Henger quartz granules.

$$CCl_4 + SiF_4 \longrightarrow CF_3Cl + CF_2Cl_2 + CFCl_3 \qquad (2)$$

	conv.			
600 °C	57.8%	0%	18.9%	81.1%
800 °C	77.1%	17.2%	51.3%	31.5%

$$ClCOCl + SiF_4 \xrightarrow[42\%]{420\ °C} ClCOF \qquad (3)$$

The ability of silicon tetrafluoride to function as a mild fluorination reagent is demonstrated in the ring-opening fluorination of epoxides (**1**) and (**3**) (eqs 4 and 5).[5] Aromatic epoxides undergo ring-opening fluorination with silicon tetrafluoride in the presence of ***Diisopropylethylamine***, whereas aliphatic epoxides give fluorohydrins with silicon tetrafluoride only in the presence of ***Tetra-n-butylammonium Fluoride*** or water; the involvement of hypervalent fluorosilanes (SiF_5^- or SiF_6^{2-}) is postulated.[6] Application of this methodology to epoxysilanes affords, after Peterson-type alkenation, fluoroalkenes (**5**).[7] Desilylation of the initially formed fluorohydrin (**4**) is effected by a catalytic use of ***Sodium Hydride*** in the presence of ***18-Crown-6***, giving the desilylated compound (**6**) with retention of

the configuration at the carbon bearing fluorine.

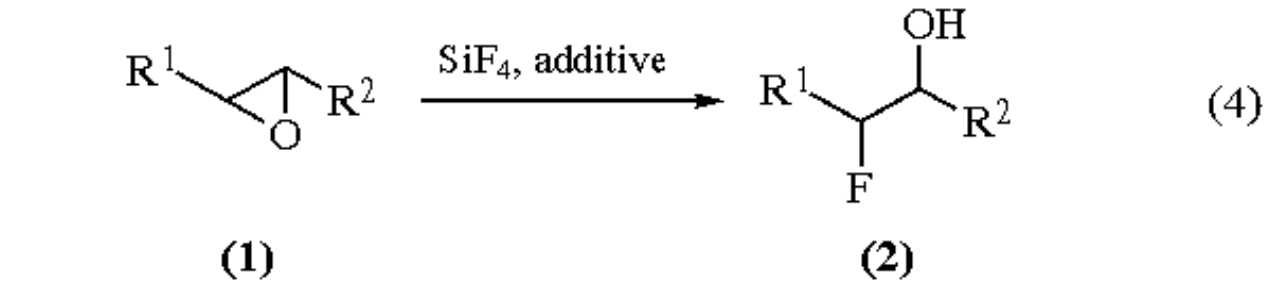

(4)

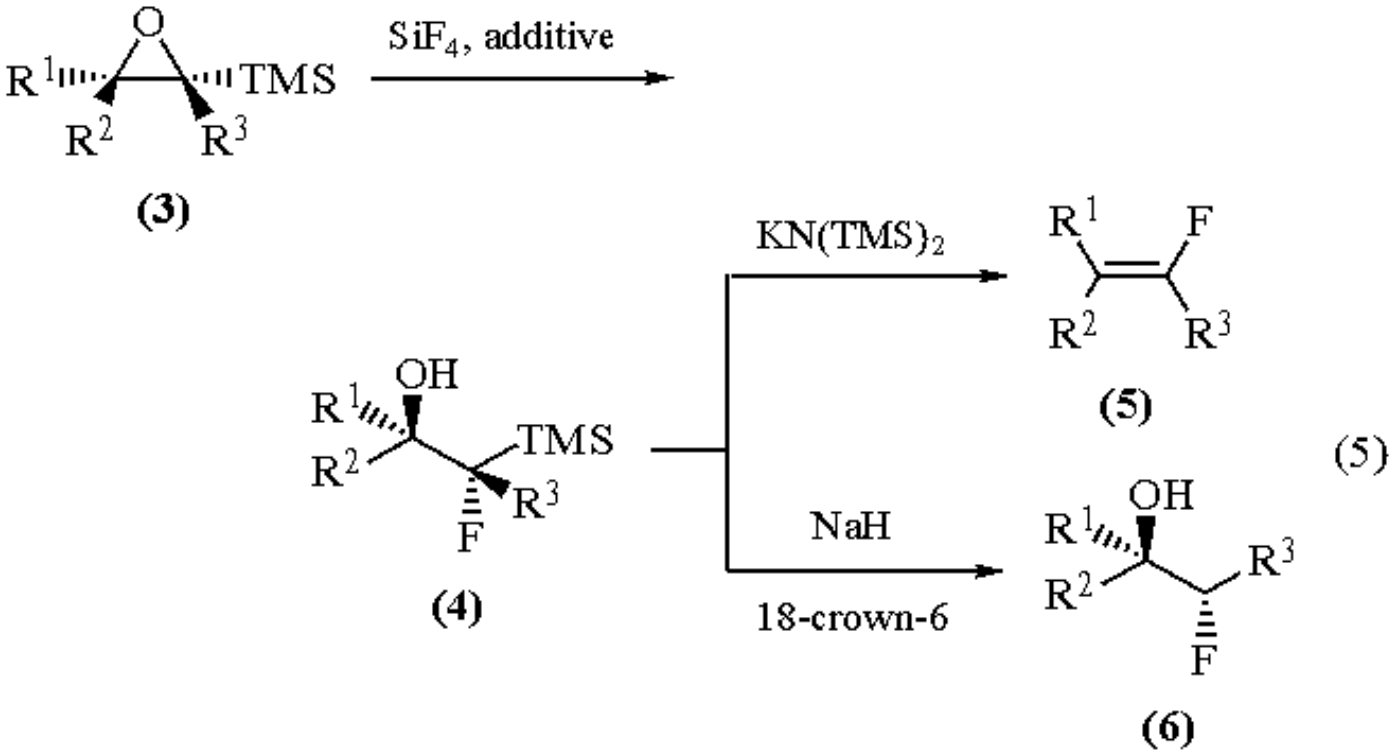

(5)

Alkenes are converted into the corresponding bromofluorides with silicon tetrafluoride-***1,3-Dibromo-5,5-dimethylhydantoin*** (DBH) and water in 1,4-dioxane.[8] Stereoselectivity in the bromofluorination of (*E*)- and (*Z*)-1-phenylpropenes (**7**) is noteworthy (eq 6). Both give the *anti*-bromofluoride (**8**) selectively, making a contrast to the reagents previously reported for the halofluorination of alkenes.

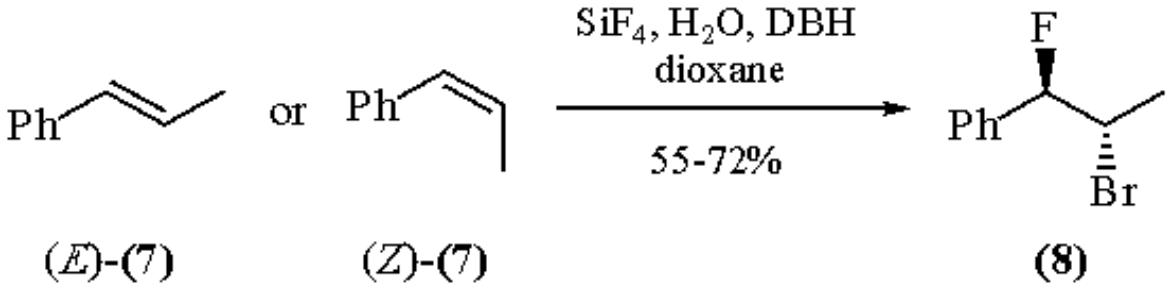

(6)

Silicon tetrafluoride is a useful catalyst for glycosylation.[9] The condensation of appropriately protected glycopyranosyl fluorides (**9**) and trimethylsilyl ethers is conducted under the action of silicon tetrafluoride (eq 7). The pronounced solvent effect is noteworthy: the glycosylation in acetonitrile gives the β-glycosides (**11**) with moderate to high selectivity, whereas the reaction in ether affords the α-anomers (**10**) predominantly.

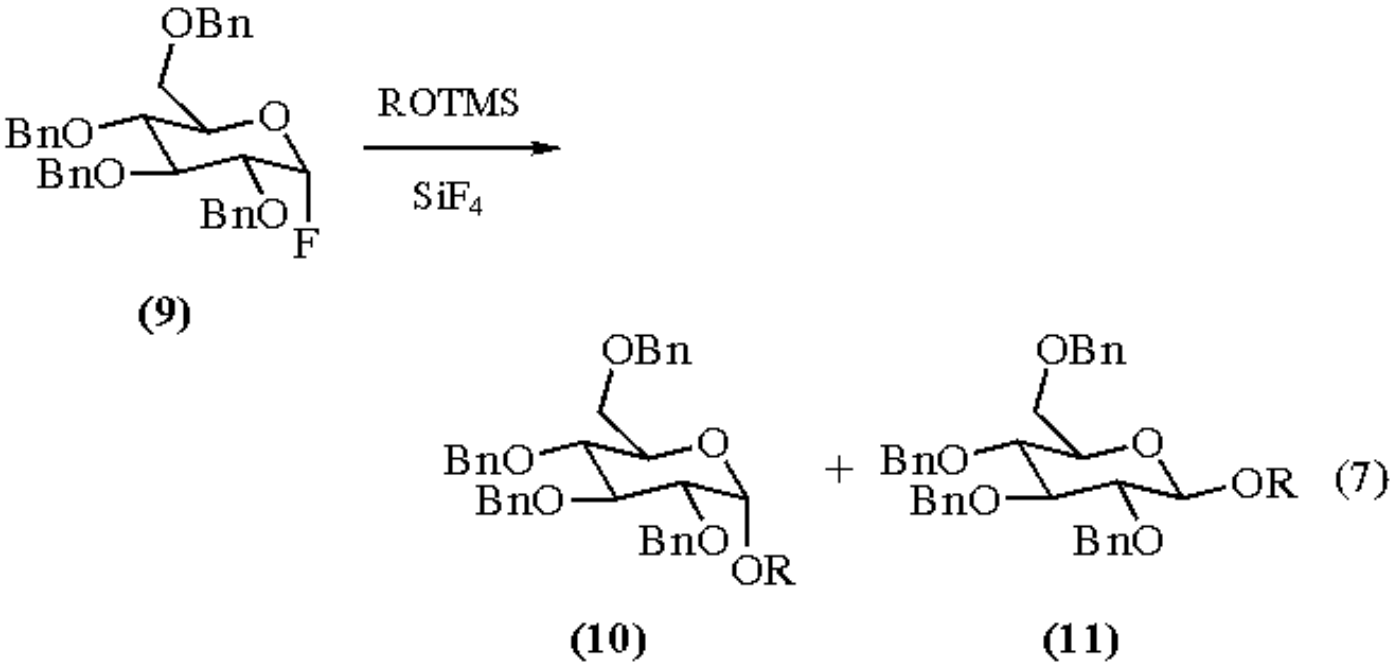

2-Oxazolines (**13**) are formed from the reaction of epoxides (**12**) with nitriles promoted by silicon tetrafluoride (eq 8).[10] Control experiments show that the ability of silicon tetrafluoride to promote this type of reaction is similar to that of aluminum chloride.

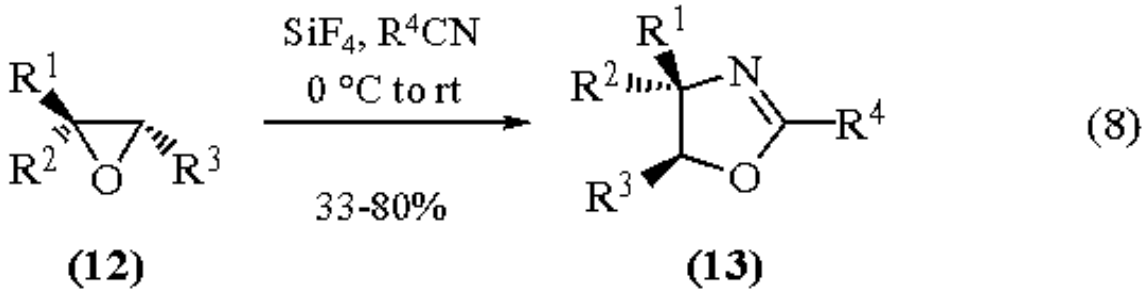

Silicon tetrafluoride is a mild and selective reagent for the cleavage of silyl-protected alcohols.[11] The cleavage of various *t*-butyldimethylsilyl groups by silicon tetrafluoride takes place at ambient temperature in methylene chloride or acetonitrile (eq 9).

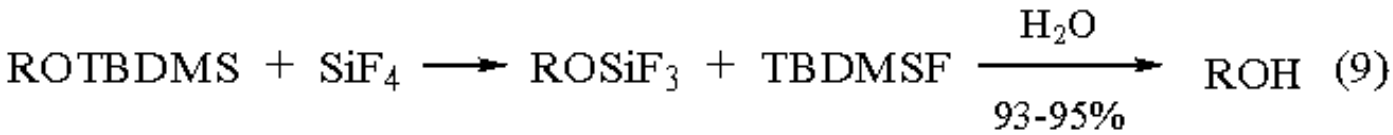

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Makoto Shimizu

Mie University, Japan

Silicon(IV) Methoxide[1]

$Si(OMe)_4$

[681-84-5] · $C_4H_{12}O_4Si$ · Silicon(IV) Methoxide · (MW 152.25)

(methanol synthon in aprotic media[2])

Alternate Names: tetramethyl orthosilicate; tetramethoxysilane.

Physical Data: bp 121-122 °C; mp 4-5 °C; *d* 1.032 g cm^{-3}; *n*20D 1.3688.

Solubility: sol common organic solvents.

Form Supplied in: commercially available as a colorless liquid.

Analysis of Reagent Purity: ^1H NMR.

Purification: by distillation.

Handling, Storage, and Precautions: can be stored in a glass bottle but must be protected from moisture. Can cause blindness; special eye protection is required.

Acetal Synthesis.[2]

Acetalization of carbonyl compounds can be achieved by using an alkoxysilane and a catalytic amount (10 mol %) of ***Iodotrimethylsilane*** (eqs 1 and 2). Silicon(IV) methoxide is convenient for use in these reactions because silicon(IV) can be readily removed from the reaction mixture as a siloxane polymer after hydrolysis.

$$PhCHO + (MeO)_4Si \xrightarrow[87\%]{\text{TMSI, -78 °C to rt}} PhCH(OMe)_2 \qquad (1)$$

$$Me(CH_2)_2CHO + (MeO)_4Si \xrightarrow[91\%]{\text{TMSI, -40 to 0 °C}} Me(CH_2)_2CH(OMe)_2 \qquad (2)$$

In a related reaction, 1,2-bis(trimethylsiloxy)ethane can be used for the formation of cyclic acetals (eq 3). Ketones react with alkyl silyl ethers in the presence of a catalytic amount of ***Trimethylsilyl Trifluoromethanesulfonate*** to give the corresponding acetals; cyclohex-2-enone forms the acetal without double bond migration.[3]

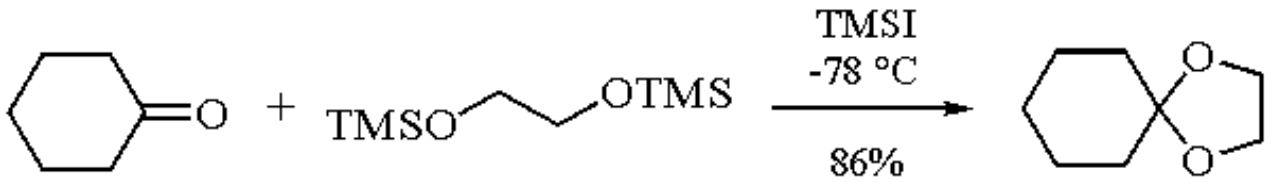

(3)

Synthesis of Homoallyl Ethers.

Treatment of a mixture of an aldehyde, silicon(IV) methoxide, and ***Allyltrimethylsilane*** gives homoallyl ethers exclusively (eqs 4 and 5).[4]

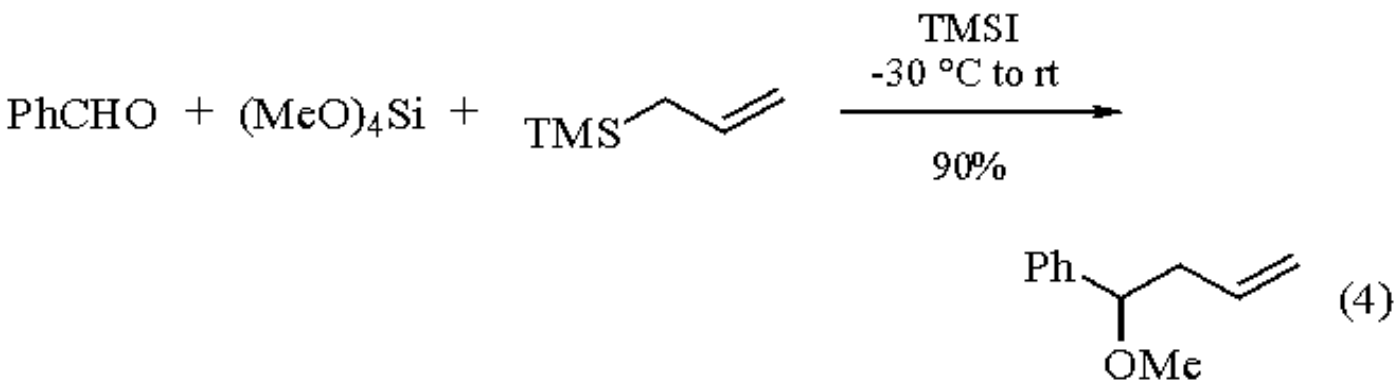

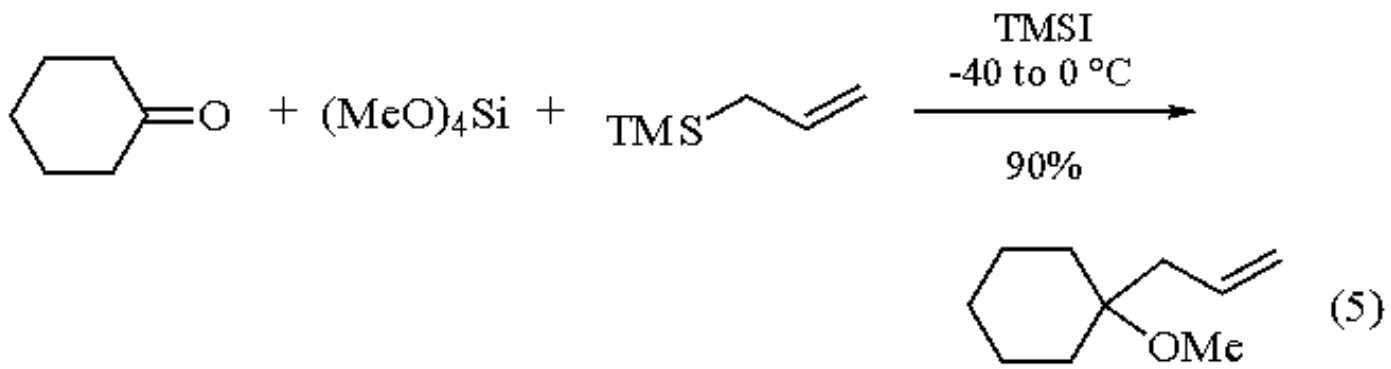

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Silver

Ag

[7440-22-4] · Ag · Silver · (MW 107.87)

(catalyst for valence isomerizations[1] and for coupling reactions involving Grignard reagents,[2] alkenes,[3] and carbenoid species[4])

Physical Data: white, lustrous, malleable metal; mp 960.5 °C.

Solubility: insol most solvents, but see preparation of soluble silver below.

Form Supplied in: widely available as rods, wire, foil, powder, etc.

Preparative Method: soluble silver is prepared as follows: ***Silver(I) Nitrate*** (5 mmol) is treated in ether with a 1.0 M solution of ***Ethylmagnesium Bromide*** (30 mL) at 0 °C for 3 h; the supernatant is 7.5 M in soluble silver and stable at refrigerator temperatures.[2]

Handling, Storage, and Precautions: the powder is flammable, and may cause skin and/or eye irritation.

Although the predominant use of silver as a catalyst is in industrial oxidation processes,[5] it has found use in laboratory applications, as in the valence isomerization of benzvalene to benzene (eq 1).[1] It also enables the smooth coupling of Grignard reagents with bromides, although both alkyl groups must be the same to ensure acceptable yields (eq 2).[2]

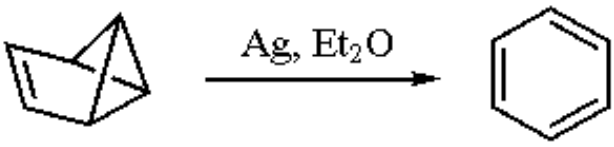

(1)

$$BuBr + BuMgBr \xrightarrow[\text{25 °C, 5 h; 79\%}]{\text{Ag, THF}} C_8H_{18} \qquad (2)$$

When supported on ***Alumina*** silver effects the coupling of perfluoroalkyl iodides with alkenes at high temperatures (eq 3),[3] and, in combination with ***Zinc***, it enables the preparation of highly strained alkenes from halogen-bearing precursors (eq 4).[4]

$$C_8H_{17}I + H_2C{=}CH_2 \xrightarrow[\text{125 °C, 11 h; 94.5\%}]{\text{Ag/Al}_2\text{O}_3} C_8H_{17}CH_2CH_2I \qquad (3)$$

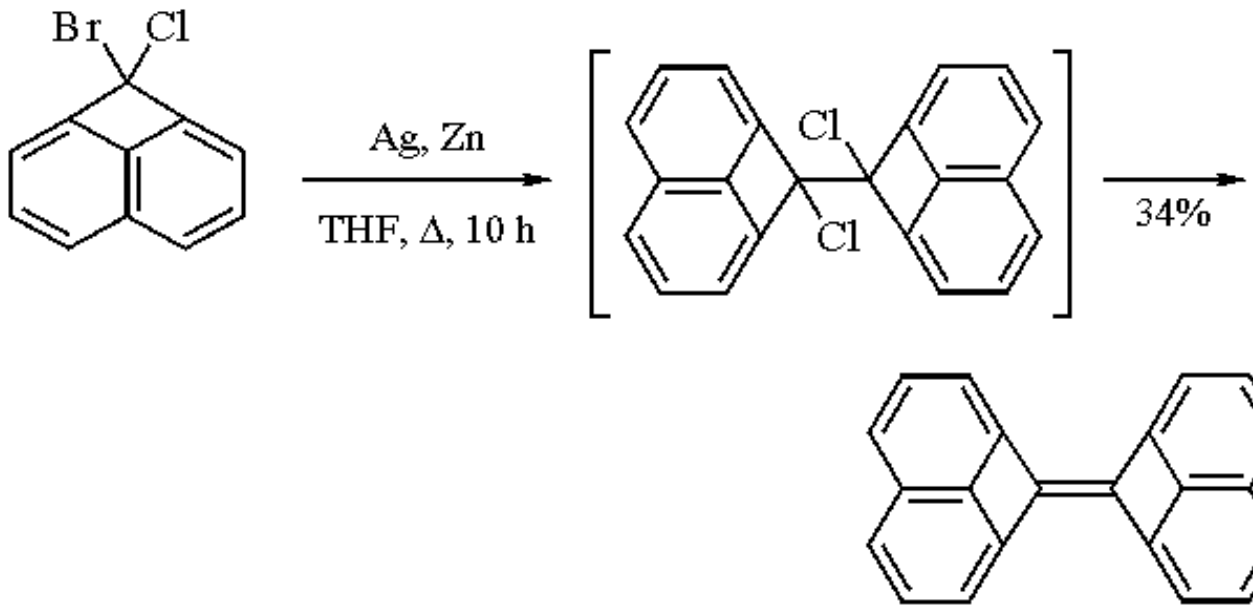

(4)

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Silver(I) Acetate

$MeCO_2Ag$

[563-63-3] · $C_2H_3AgO_2$ · Silver(I) Acetate · (MW 166.92)

(nucleophilic substitutions;[5] cyclizations;[1] couplings;[14] disulfide cleavage[13])

Alternate Names: silver acetate; silver monoacetate.

Physical Data: d 3.26 g cm^{-3}.

Solubility: sol in 100 parts of cold water, 35 parts of boiling water; freely sol dil nitric acid.

Form Supplied in: white to slightly grayish lustrous needles or crystal powder.

Handling, Storage, and Precautions: causes irritation to skin, eyes, mucous membranes, and upper respiratory tract. May cause discoloration of skin and deep tissues. In case of contact with skin or eyes, immediately rinse with copious amounts of water. Light sensitive. Store in cool dry place. Incompatible with strong oxidizing agents and strong acids. May discolor on exposure to light.

Formation of Cyclic Ethers.

Alcohols that have a hydrogen in the δ-position can be cyclized with silver acetate and ***Bromine*** (eq 1). The ring closure occurs via an intermediate hypobromite. The reaction can be run under a variety of conditions (presence/absence of light, acidity, solvent, temperature). Because of this variety and the products formed, there has been some disagreement about the role silver plays in the hypobromite decomposition.[1]

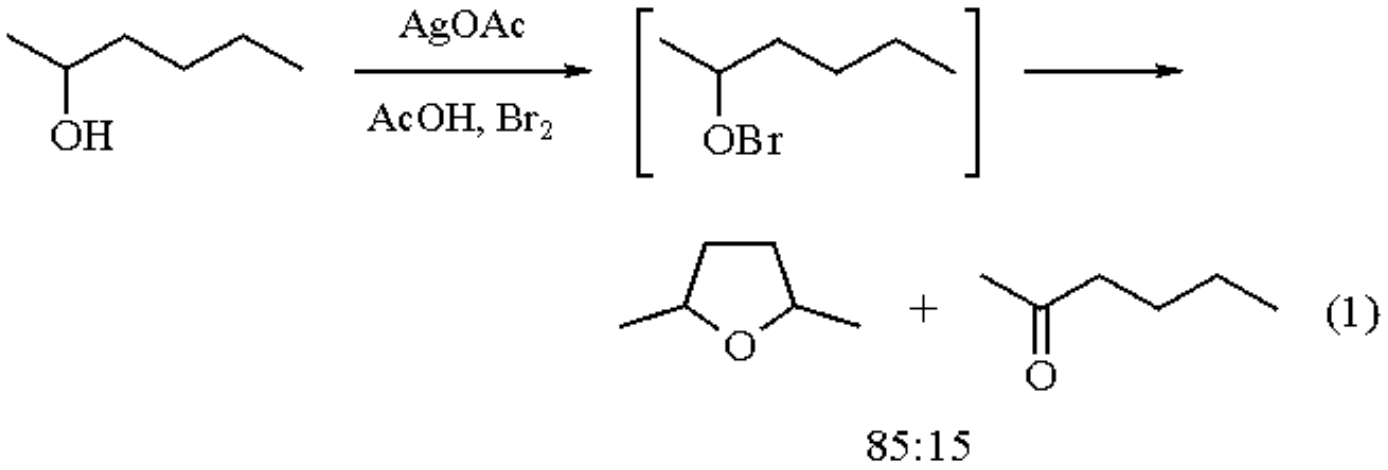

Rearrangements.

Regioselective ring contractions are possible via bromination of cyclobutyl ketones. The intermediate bromo ketone, when treated with silver acetate in acetic acid (120 °C, 6 h), affords a mixture of the cyclopropyl ketone and the acetoxy ketone (57% and 28% isolated yield, respectively, eq 2).[2]

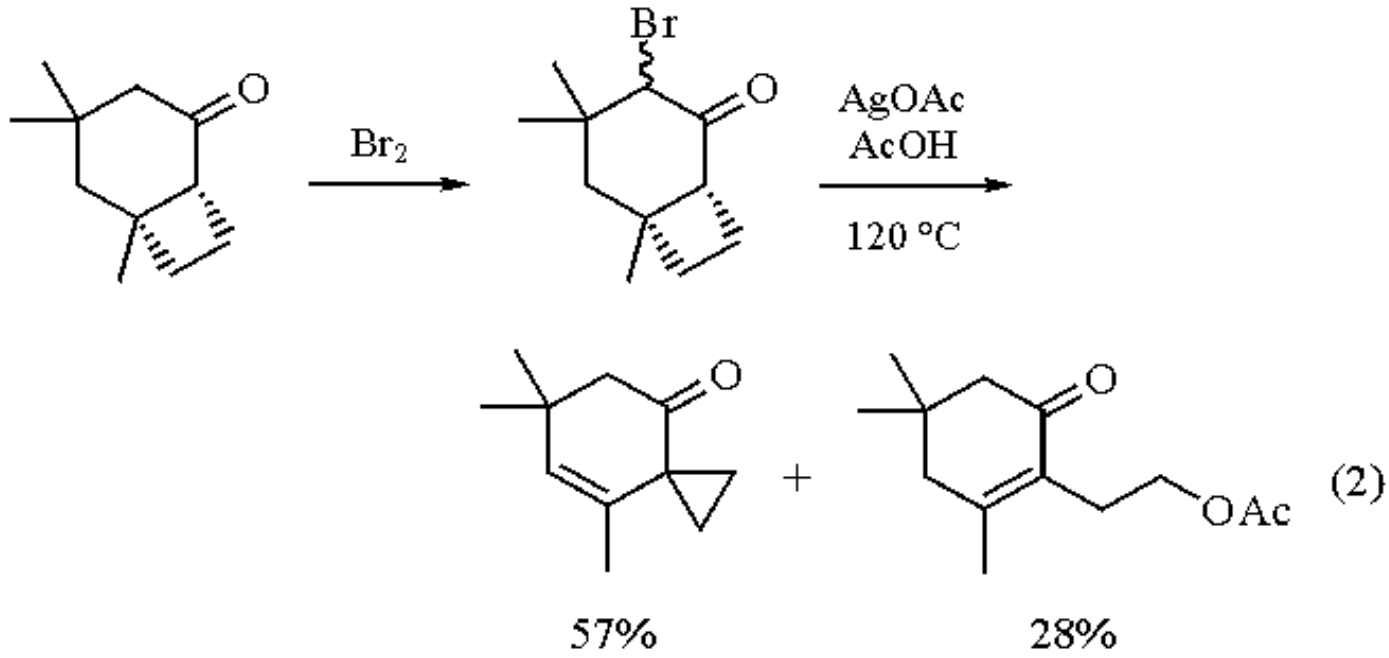

Ring expansions and chain extensions are observed when *gem*-dihalocyclopropanes, derived from alkenes, are treated with silver acetate and acetic acid (eqs 3 and 4).[3]

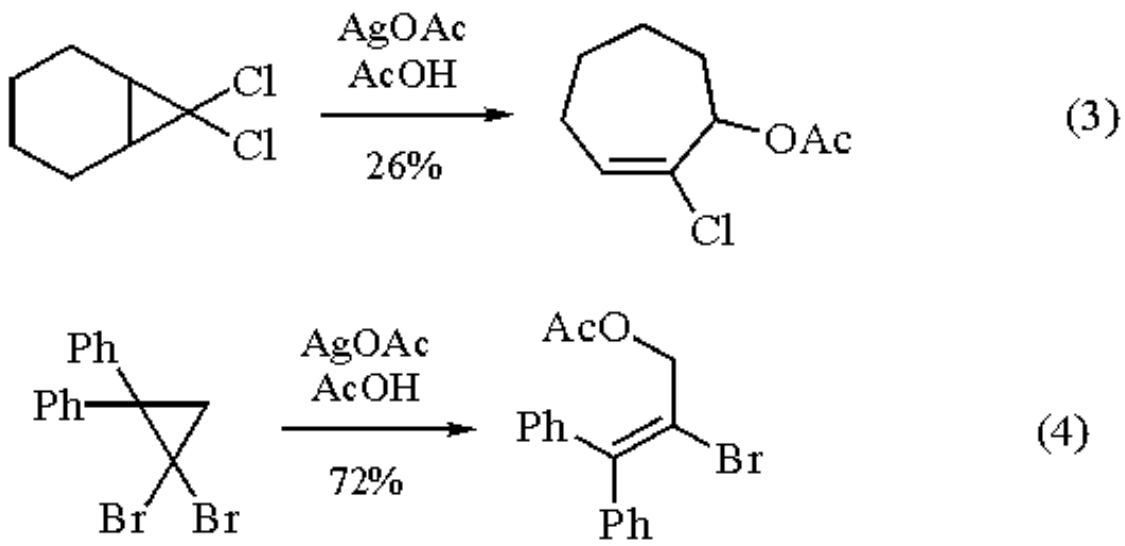

Displacement.

When *meso*-stilbene dibromide is heated with silver acetate under anhydrous conditions, the product is the *meso*-diol diacetate (eq 5). However, when the starting material is heated for 10 min on a steam bath with silver acetate, acetic acid, and water, a significant amount of (±)-diol monoacetate is formed.[4]

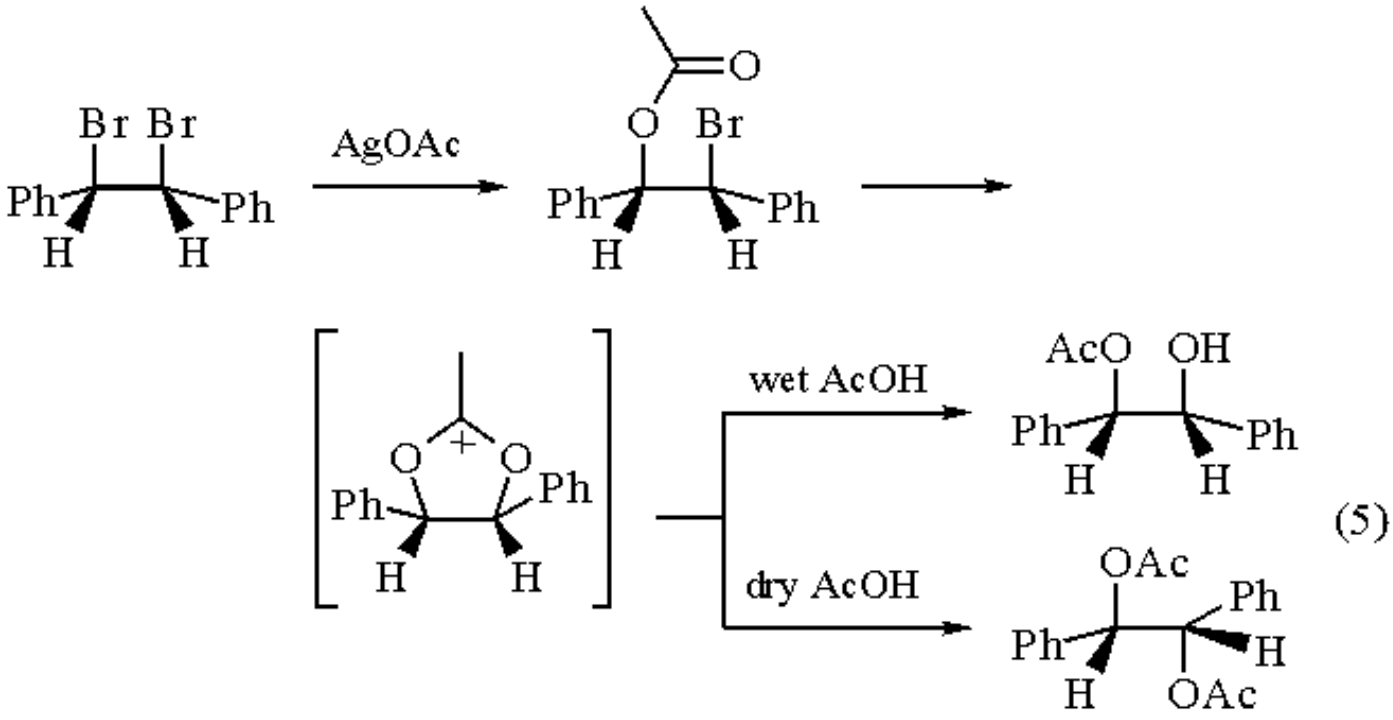

(5)

There has been extensive reporting of the use of silver acetate for direct nucleophilic substitution.[5] 3-Chloroindolenines react with silver acetate to give the product of direct displacement (eq 6). This is in contrast to reactions with softer nucleophiles (I^-, PhS^-, PO_3) which give the parent indole.[6]

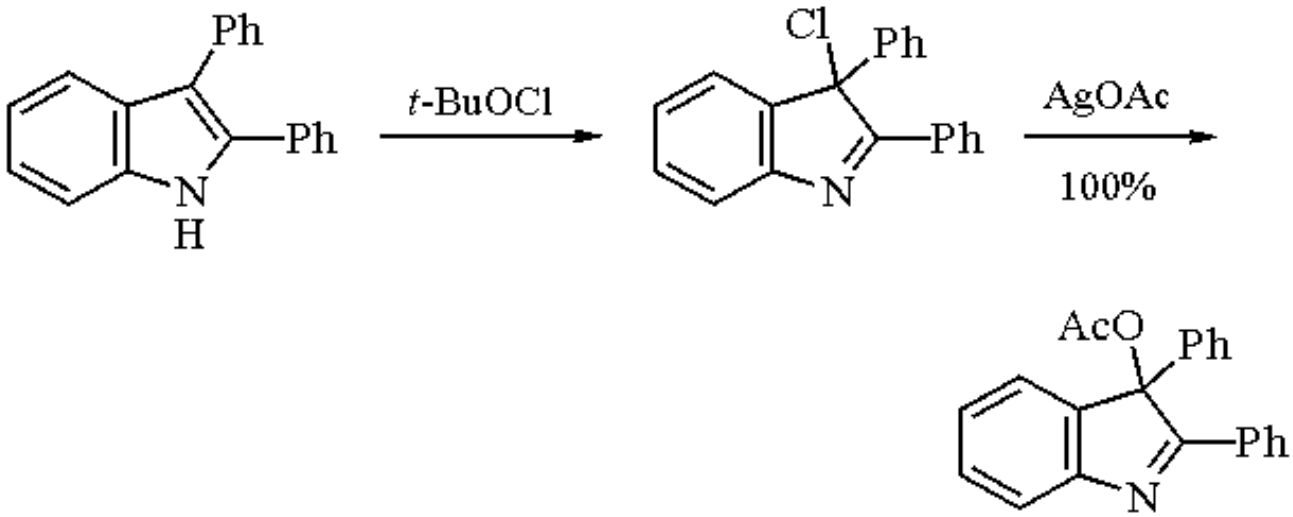

(6)

Reacting π-cyclohexenylpalladium complexes with stoichiometric amounts of silver acetate, and then with carbon monoxide and benzene, produces the diastereoisomerically pure (>95%) allylic acetate (yield 70%) (eq 7).[7]

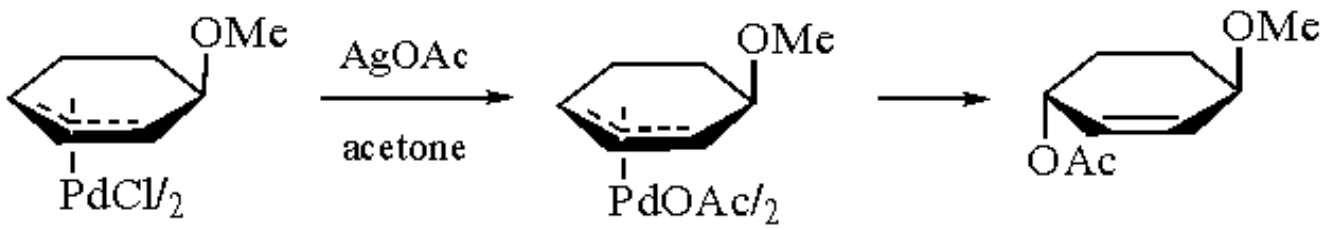

(7)

Other Reactions.

Halofluorocyclopropanes are opened with silver acetate in acetic acid (eq 8).[8] Arenes can be oxidized with silver acetate in the presence of 2,2´-bipyridine and potassium peroxydisulfate in high yields (eq 9).[9]

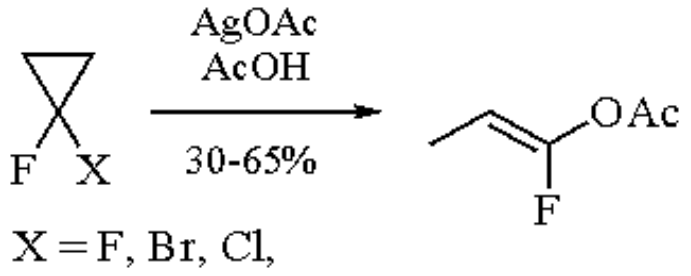

(8)

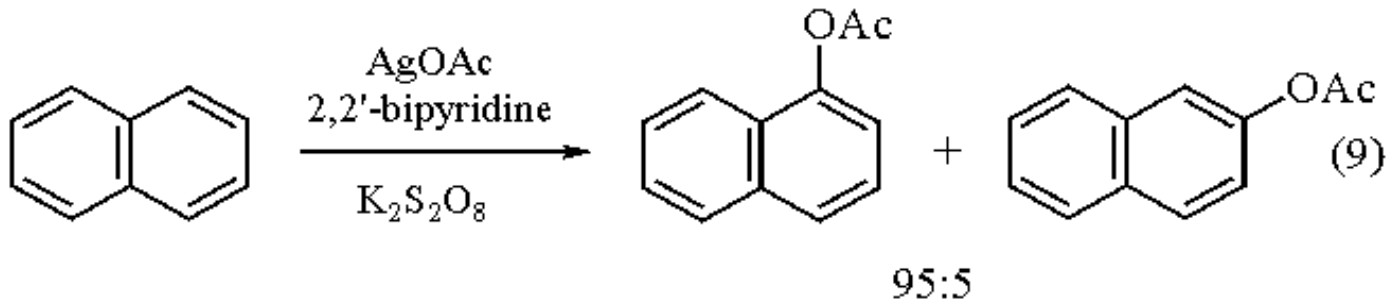

(9)

Acetyl hypobromite is generated when a bromine/carbon tetrachloride solution is added to a stirred suspension of silver acetate in carbon tetrachloride. This solution can then be used in the conversion of alkenes to bromohydrin acetates (eq 10).[10]

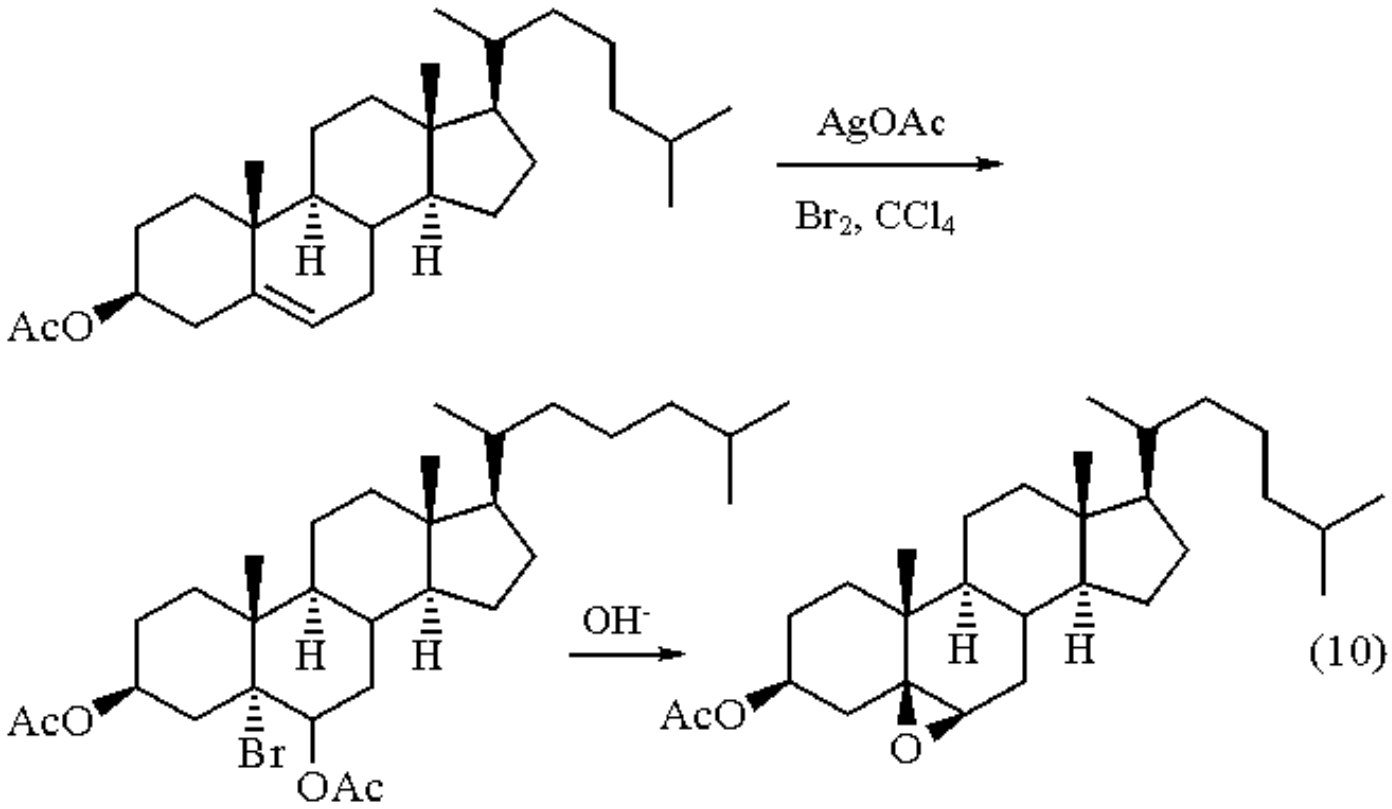

(10)

The Simmons-Smith reagent is generated by adding granular ***Zinc*** to a hot solution of silver acetate in acetic acid (eq 11). The ***Zinc/Silver Couple*** is decanted and washed with acetic acid and ether. The addition of a small amount of silver wool assures stabilization. Silyl enol ethers can be cyclopropanated using this reagent in good to moderate yields (ca. 75%). Acid hydrolysis can be avoided by the addition of an amine to the mixture.[11] An example of the use of this reagent is in the conversion of 2,3-bis(trimethylsiloxy)-1,3-butadiene to the bicyclopropyl derivative (eq 12).[12]

$$AgOAc + AcOH + Zn^0 \longrightarrow Zn(Ag) \qquad (11)$$

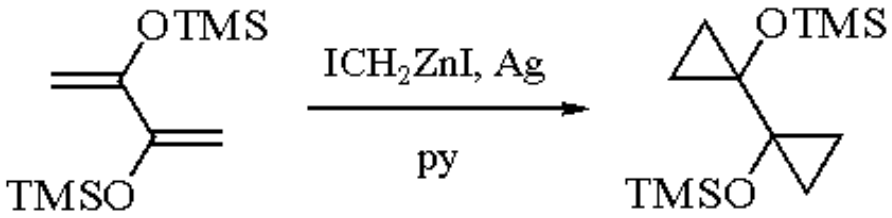

(12)

Sulfenamides can be synthesized by a metal-assisted reaction with disulfides and amines (eq 13).[13] Conjugated dienols can be synthesized in a highly chemo-, regio-, and stereoselective manner from vinylic halides and allylic alcohols (eq 14). Silver acetate (or silver carbonate) and a catalytic amount of ***Palladium(II) Acetate*** in DMF are the preferred conditions. The reaction is very attractive because it requires only one functionalized alkene reactant and the addition of the vinylic group only occurs at the terminal carbon of the allylic alcohol.[14]

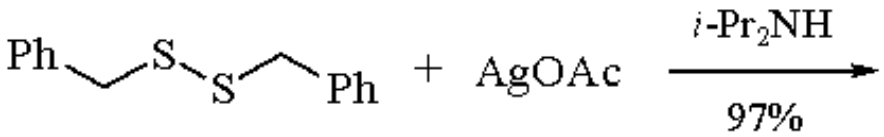

$Ag(SCH_2Ph) + PhCH_2SN(i\text{-}Pr)_2$ (13)

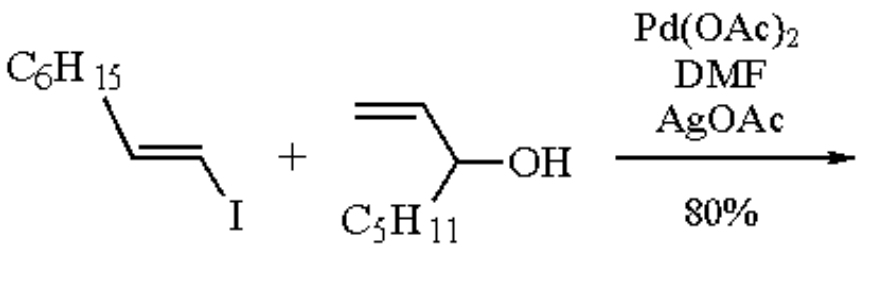

(14)

Related Reagents.

N-Bromoacetamide-Silver Acetate-Acetic Acid; ***Iodine-Silver Acetate***; ***Palladium(II) Chloride-Silver(I) Acetate***.

---

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14. Jeffery, T. *CC* **1991**, *5*, 324.

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Silver(I) Benzoate

$PhCO_2Ag$

[532-31-0] · $C_7H_5AgO_2$ · Silver(I) Benzoate · (MW 228.99)

(nucleophile;[2-4] Wolff rearrangement promoter[1])

Solubility: sol water (0.262 g/100 mL); alkali (0.017 g/100 mL).

Form Supplied in: white powder and chunks.

Preparative Methods: prepared by equimolar reaction of solutions of ***Silver(I) Nitrate*** and sodium benzoate. The solid is collected and dried in vacuo.[1]

Handling, Storage, and Precautions: may be harmful by inhalation, ingestion, or skin absorption and may cause argyria. Store in a tightly closed container away from light in a cool, dry place. Incompatible with strong oxidizing agents. May discolor on exposure to light. Hazardous products from decomposition are carbon monoxide and carbon dioxide.

Introduction.

For additional information on silver benzoate and its reaction with iodine, see ***Iodine-Silver Benzoate***.

Silver Benzoate as a Nucleophile.

The first use of silver benzoate was reported by Larock in which *n*-butyl iodide was reacted with silver benzoate in the presence of $B(O_2CPh)_3$ to give *n*-butyl benzoate in low yield (20%) (eq 1).[2]

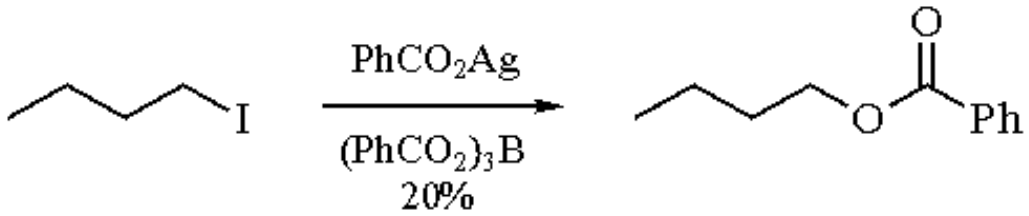

(1)

It has been used in a reaction with 4,7-dichloro-3,8-diphenyl-1,2-diazocine to prepare 4-benzoyloxy-7-chloro-3,8-diphenyl- and 4,7-bis(benzoyloxy)-3,8-diphenyl-1,2-diazocine (eq 2).[3]

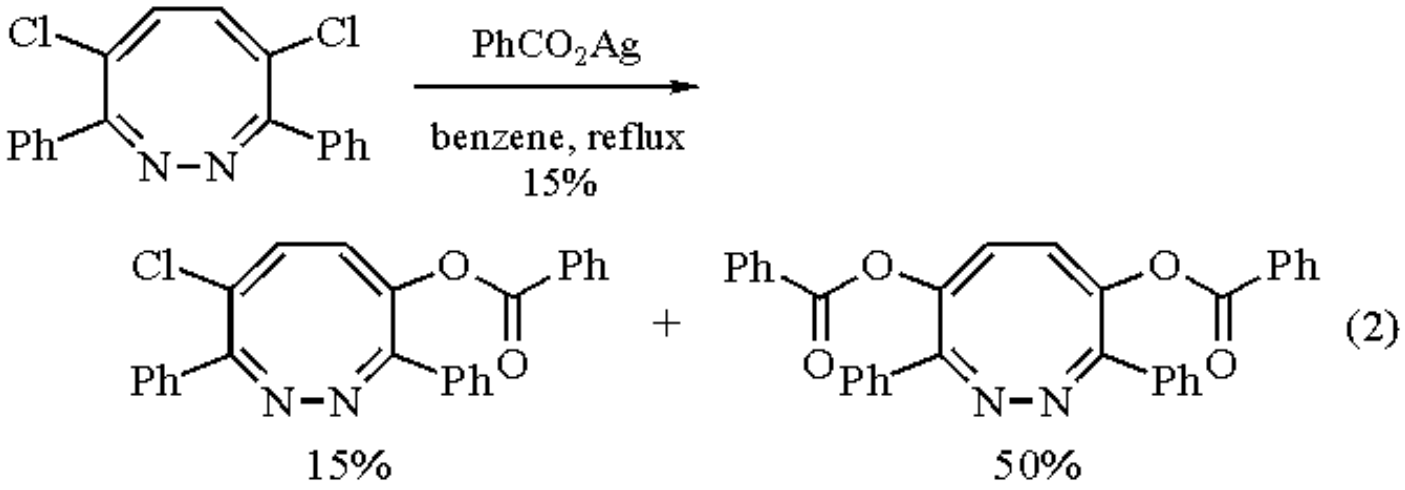

Isomides (Ar^1 = *p*-$MeOC_6H_4$, Ph, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$; Ar^2 = 2,4-$(NO_2)_2C_6H_3$) have been prepared by the reaction of the appropriately substituted silver benzoate with *N*-(2,4-dinitrophenyl)benzimidoyl chloride (eq 3).[4]

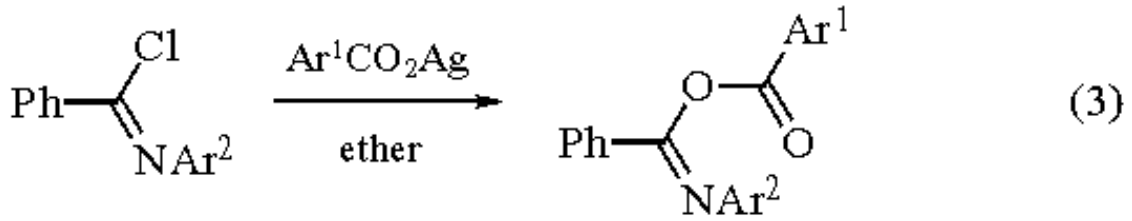

Wolff Rearrangement.

Newman and Bead developed a procedure for a Wolff rearrangement under mild, homogeneous reaction conditions. In an example of this protocol, diazoacetophenone is treated with a few drops of filtered silver benzoate in triethylamine (eq 4). Nitrogen evolution commences immediately. Silver benzoate is added in portions until gas evolution ceases. The product is obtained in 92% yield.[1]

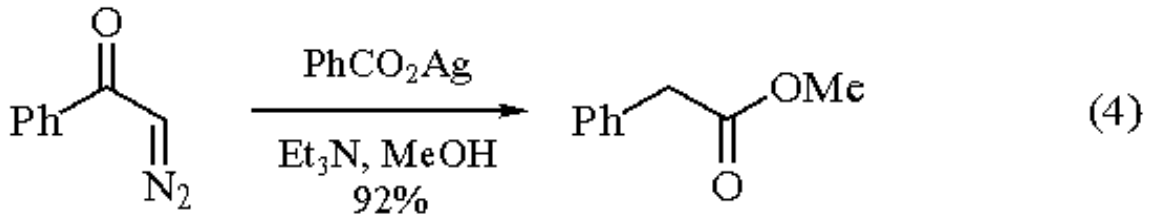

Related Reagents.

Iodine-Silver Benzoate.

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2. Larock, R. C. *JOC* **1974**, *39*, 3721.
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Silver(I) Carbonate on Celite

Ag_2CO_3/Celite

(Ag_2CO_3)

[534-16-7] · CAg_2O_3 · Silver(I) Carbonate · (MW 275.75)

(mild oxidizing agent, which operates under neutral and heterogeneous conditions[1-3])

Physical Data: Ag_2CO_3: mp 210 °C (dec); *d* 6.077 g cm^{-3}.

Solubility: insol water, organic solvents; destroyed by acids.

Form Supplied in: green-yellow powder. Commercially available reagent contains ca. 50 wt% Ag_2CO_3.

Preparative Method: ***Silver(I) Nitrate*** (30 g) is dissolved in 200 mL of distilled water, and ***Celite*** (30 g) is added. To the stirred mixture, a solution of ***Sodium Carbonate*** ($Na_2CO_3.10H_2O$) (30 g) in distilled water (300 mL) is slowly added. The yellow-green precipitate is filtered and washed to neutrality with distilled water. It is then dried (4 h) by rotatory evaporation on a steam bath, preferably in the dark. The reagent can be stored in the dark at room temperature for several years without significant loss of activity. When prepared according to this procedure, 0.6 g of this reagent contains approximately 1 mmol of Ag_2CO_3. Since an excess of silver carbonate on Celite is necessary for the reaction to proceed at a reasonable rate, recovery of silver is often required. This can be easily achieved by dissolving the used reagent in nitric acid. The filtered solution after concentration gives back silver nitrate (poorly soluble in nitric acid).

Handling, Storage, and Precautions: can be safely handled in the dry state. Moisture or exposure to light are not critical; can be stored for years in the dark. Silver salts are toxic.

Introduction.

Silver carbonate on Celite oxidizes primary alcohols to aldehydes, and secondary alcohols to ketones. 1,2-Diols are either cleaved or oxidized to α-hydroxy ketones or sometimes to α-diketones; 1,4-, 1,5-, and 1,6-diols with one primary hydroxyl group may give lactones. Lactols are converted to lactones. Hydroquinones and catechols afford quinones. Steric factors play an important role in determining the outcome of these reactions, including the generally high regioselectivity in polyol oxidations.

Oxidation, rearrangement, or glycosylation with the help of silver carbonate on Celite are usually carried out in aromatic solvents, sometimes in chloroform or methylene chloride, and, in the case of carbohydrates, in methanol. Reactions are easily monitored by TLC. As soon as the reaction is over, the solid is filtered off, and the solution evaporated. The price of the reagent makes it difficult to use on a large scale, unless the recovery of silver is contemplated. The mildness and the simplicity of the workup may, in some cases, overcome this drawback. Many protective groups (acetals, formate, acetate, tetrahydropyranyl, silyl derivatives), as well as sensitive functionality such as furan, indole, and *N*-substituted pyrrole ring systems, are not affected by the reagent. A critical evaluation of several solid supported reagents has been published.[52]

Oxidation of primary alcohols.

Primary alcohols (saturated, allylic, polyunsaturated, benzylic) are normally converted into aldehydes in good to excellent yield. A few examples out of many reported are listed in Table 1.[4-6]

Table 1 Oxidation of Primary Alcohols to Aldehydes

Alcohol	Solvent	Yield (%)
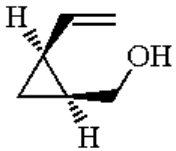	Benzene	80
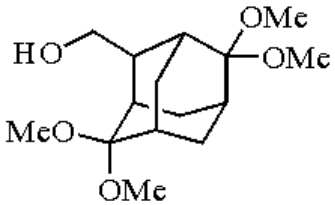	Benzene	100
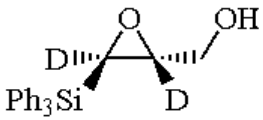	Benzene	~30

In contrast to the oxidation of other primary alcohols, α-hydroxymethyl cyclic ethers give lactones instead of the expected aldehydes (Table 2).[7,8]

Table 2 Oxidation of α-Hydroxymethyl Cyclic Ethers

Alcohol	Product	Solvent	Yield (%)
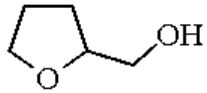	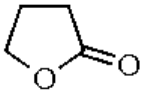	Benzene	70
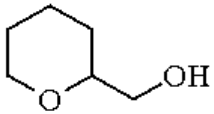	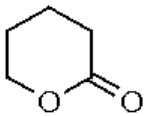	Benzene	80
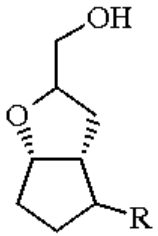	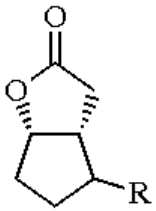	Benzene Toluene	31 37

Due to a strong isotope effect, tritiated primary alcohols are oxidized to aldehydes, with virtually no loss of tritium (eq 1).[9]

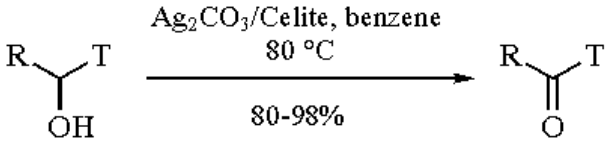

(1)

Ketones from Secondary Alcohols.

A large number of secondary alcohols, usually bearing other functional groups sensitive to acids and oxidizing agents, has been transformed into ketones.[3] A few typical examples are recorded in Table 3.[10-13]

Table 3 Oxidation of Secondary Alcohols to Ketones

Alcohol	Solvent	Yield (%)
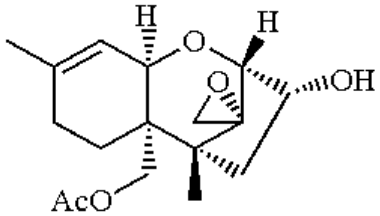	Toluene	70
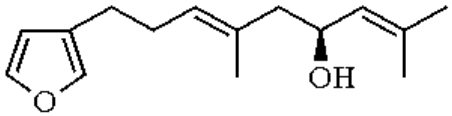	Benzene	86
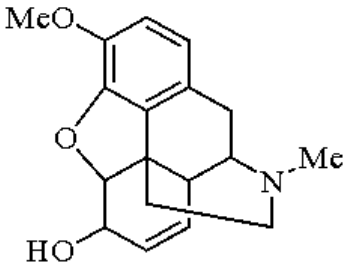	Benzene	84
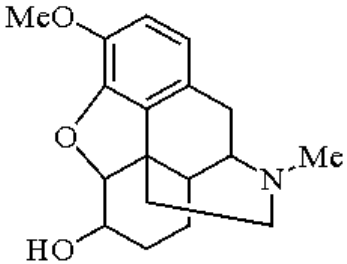	Benzene	75

Allylic alcohols are rapidly oxidized. In sharp contrast, oxidation of a homoallylic alcohol such as cholesterol (in carefully deoxygenated benzene, under argon) leads to an intractable mixture of unidentified products. Celite (the best inert support tested so far) is essential. Thus codeine has been oxidized either by standard silver carbonate, or by silver carbonate on Celite, but only the latter reagent could oxidize dihydrocodeine. Some strained cyclobutanols afford γ-lactones in addition to the expected ketone (eq 2).[14] A case of molecular rearrangement has been mentioned (eq 3).[15]

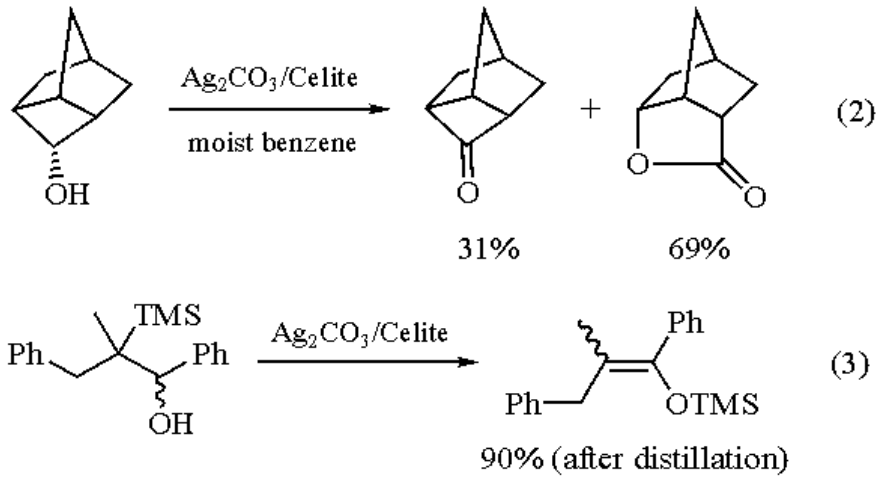

Oxidation of Tertiary Alcohols.

Tertiary alcohols are generally quite stable towards the reagent, with the exception of ethynyl carbinols which are cleaved in quantitative yield (Table 4)[16] at a rate comparable to that of allylic alcohol oxidation. Cyanohydrins behave similarly. The use of the ethynyl group as a ketone protective group has been suggested.

Table 4 Oxidation of Tertiary Alcohols

Alcohol	Product	Yield (%)
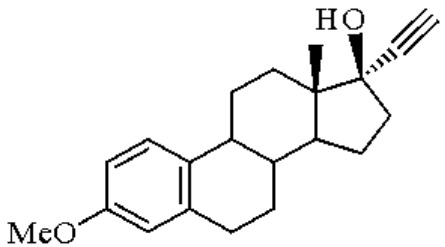	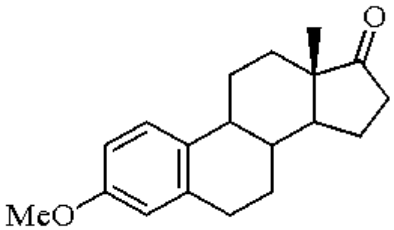	100
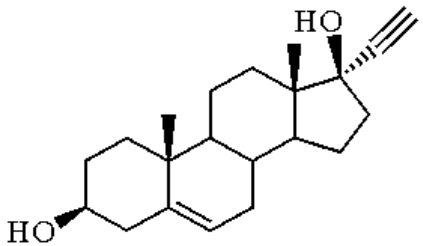	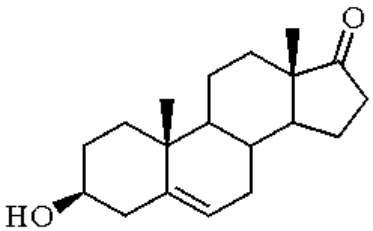	100

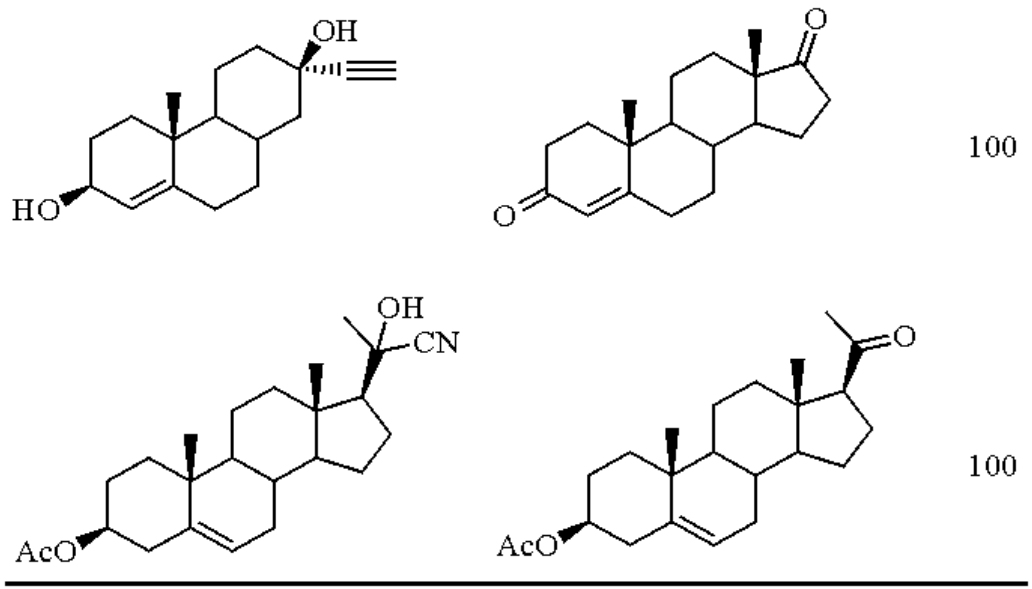

Oxidation of Diols.

Depending upon their structure and stereochemistry, and the experimental conditions (reaction time) chosen, 1,2-diols are either cleaved (to dialdehydes or keto aldehydes) or oxidized to α-hydroxy ketones. In some cases, α-diketones have been obtained in reasonable yield (Table 5).[17-23]

Table 5 Oxidation of 1,2-Diols

Diol	Product	Solvent	Yield (%)
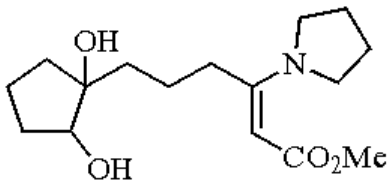	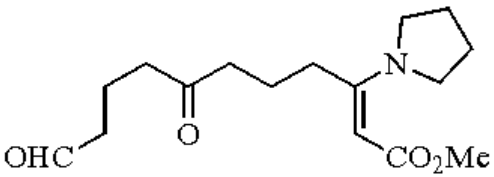	Benzene	65-75
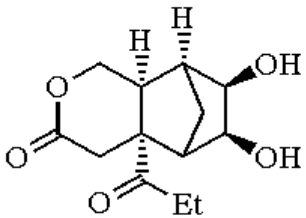	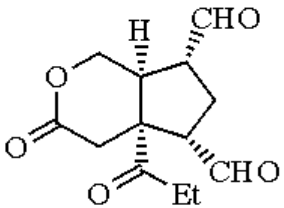	Benzene	major

Silver(I) Carbonate on Celite

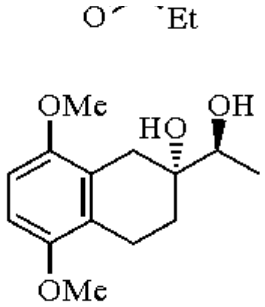	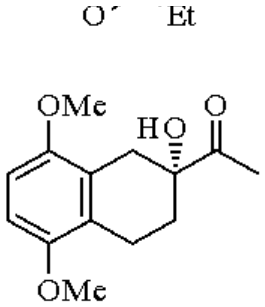	Benzene		90
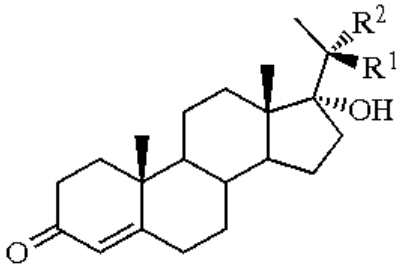	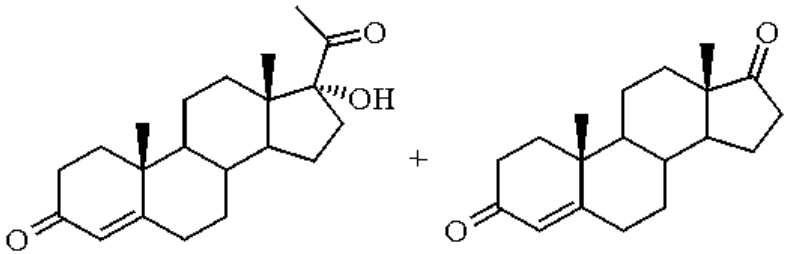	Benzene	$R^1 = H, R^2 = OH$ $R^1 = OH, R^2 = H$ $R^1 = H, R^2 = OH$ $R^1 = OH, R^2 = H$	54 27 11 63
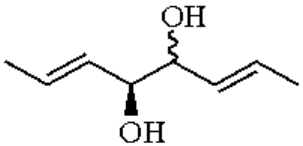	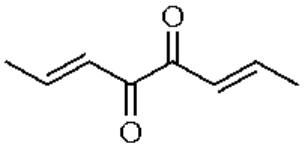	Benzene		
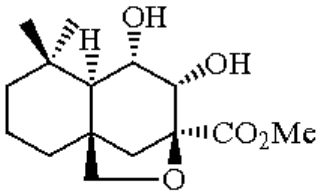	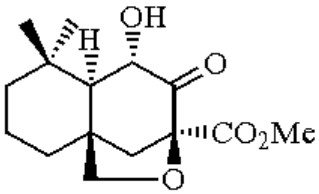	Benzene Toluene		<33 major
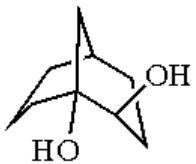	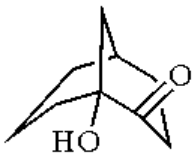	Acetone		53

Oxidation of 1,3-diols with silver carbonate on Celite leads to β-hydroxy ketones. Retroaldolization has occasionally been observed.[29] In benzene as solvent, a secondary hydroxyl group seems to be oxidized somewhat faster than a primary one. Aliphatic 1,4-, 1,5-, and 1,6-diols behave in the same manner, unless one of the hydroxyl groups is primary. Many diols of this type, in which one of the functions is primary, have been oxidized to lactones, generally in good yield (Table 6).[24-28]

Table 6 Oxidation of Nonvicinal Diols[a]

Diol	Product	Yield (%)
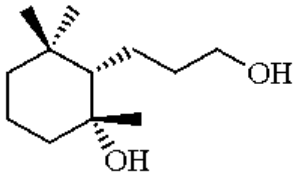	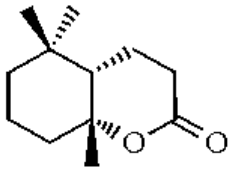	86
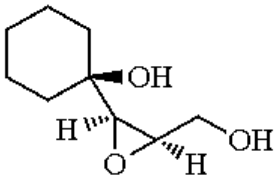	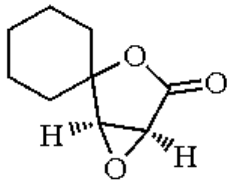	70
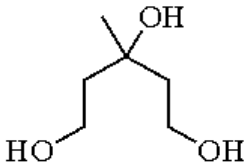	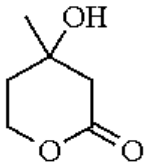	74
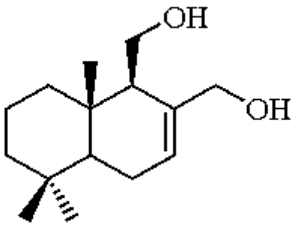	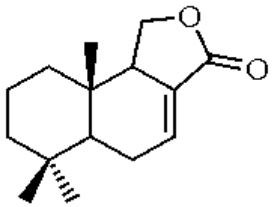	100
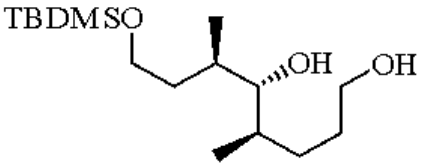	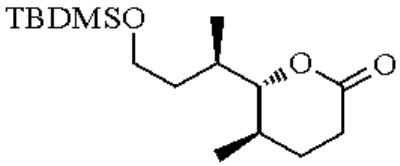	86

[a] In benzene.

Quite often, oxidations of polycyclic polyols with silver carbonate on Celite are highly regioselective. A tentative mechanism has been proposed which explains most of the results obtained so far[3,30] and has therefore reasonable predictive power for the synthetic organic chemist. A few examples are listed in Table 7.[1,31-34]

Table 7 Selective Oxidation of Polyhydroxy Compounds

Starting material	Product	Solvent	Yield (%)
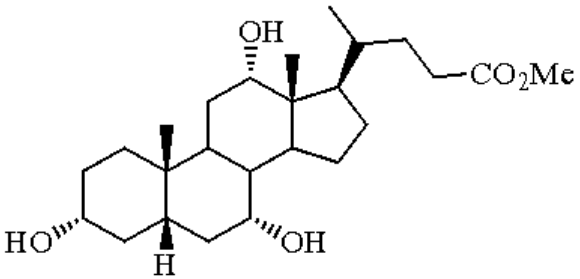	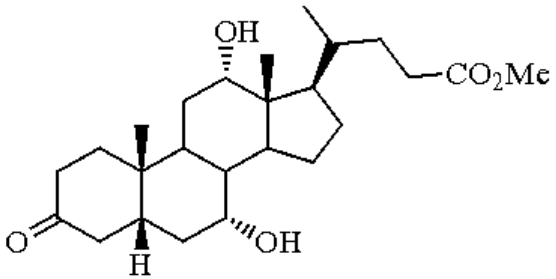	Benzene	90
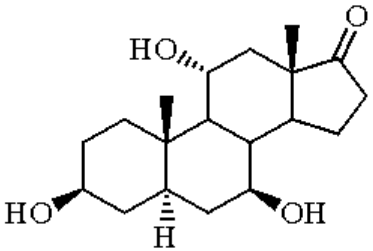	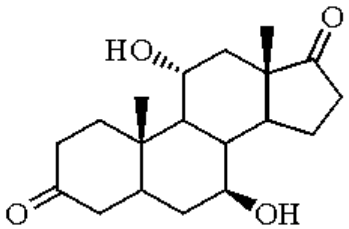	Toluene	72
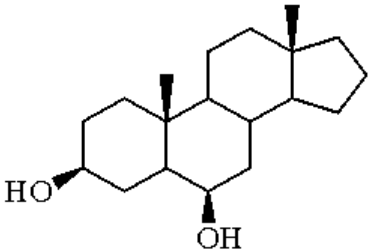	3-one, 6-β-OH 3-β-OH, 6-one 3,6-dione	Benzene	29 43 15
	3-one, 6-β-OH 3-β-OH, 6-one	Benzene, chloroform	68 31
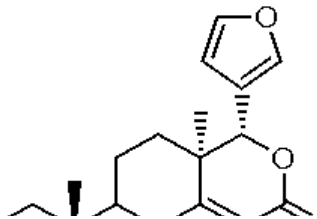			

Silver(I) Carbonate on Celite			
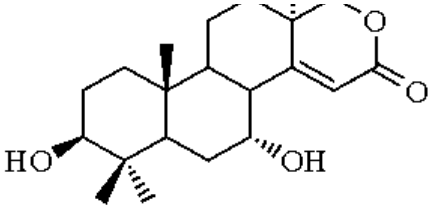	3-one	Benzene	57
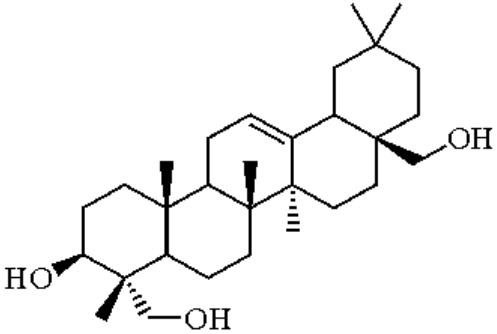 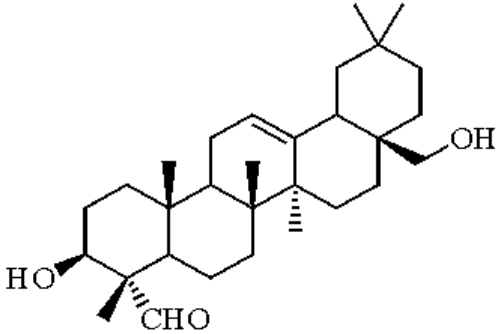		Benzene	90

Oxidation of Lactols to Lactones.

Silver carbonate oxidation of lactols is faster than the oxidation of any other type of hydroxyl derivative, and can therefore be achieved without protection of alcohols in the same molecule. Some representative examples are shown in Table 8.[35-37]

Table 8 Selective Oxidation of Lactols[a]

Starting material	Product	Yield (%)
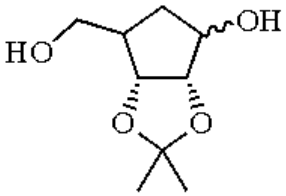	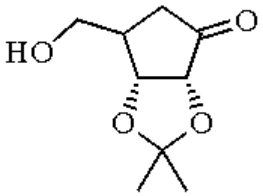	92
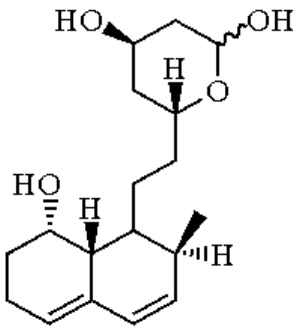	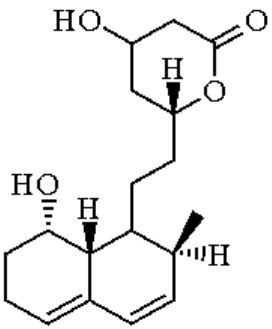	-
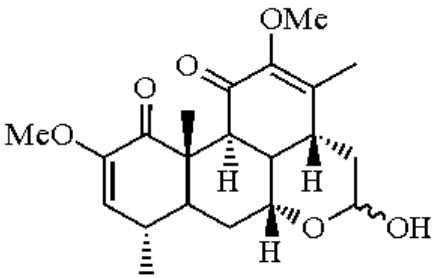	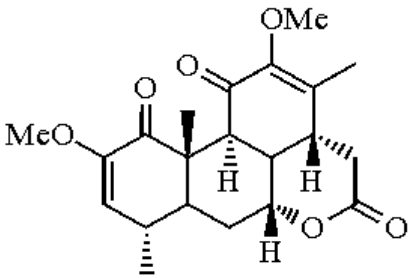	77

[a] In benzene.

Oxidation and Degradation of Carbohydrates.

A considerable amount of work has been devoted to the oxidation and degradation of carbohydrates using silver carbonate on Celite. If the hydroxyl at C-1 is free, and the reaction is carried out in benzene, toluene, or a mixture of benzene and DMF, then the corresponding lactone is obtained. However, if there is an unprotected OH group at C-2, and especially in methanol, a cleavage between C-1 and C-2 takes place as illustrated in eq 4.[38] Hydrolysis of the intermediate formate leads to D-threose.

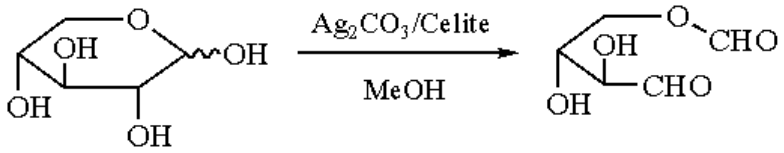

(4)

Methyl Esters from Aldehydes.

With the exception of α-substituted aldehydes of the type reported in Table 2, the oxidation of aldehydes in benzene does not lead to carboxylic acid derivatives. Those which can spontaneously give hemiacetals with another hydroxyl group of the molecule are not an exception, since lactols are very rapidly oxidized to lactones. It is therefore noteworthy that, in methanol, some aldehydes can be converted to methyl esters in modest yield (Table 9).[39,40]

Table 9 Oxidation of Aldehydes to Esters

Starting material	Product	Solvent	Yield (%)
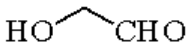	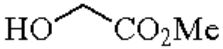	MeOH	55
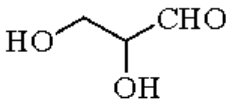	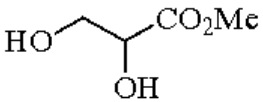	MeOH	56
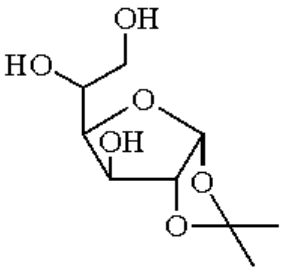	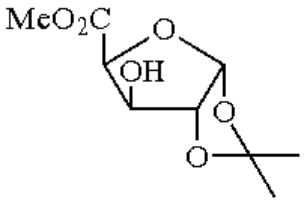	MeOH	68

Oxidation of Phenols.

Hydroquinones and catechols are oxidized to *p*-quinones and *o*-quinones, respectively, with this reagent.[41,42] 4,4´-Dihydroxybiphenyls and 4,4´-dihydroxystilbenes lead to diphenoquinones and stilbenequinones. Hindered phenols (e.g. 2,6-dimethylphenol, 2,4,6-trimethylphenol) are dimerized, and give diphenoquinones or stilbenequinones in high yield, as illustrated in eq 5. Unhindered phenols give complex mixtures. For instance, *p*-cresol affords a 65% yield of Pummerer's ketone (eq 6).[43] A systematic survey of silver carbonate on Celite oxidation of phenols has been published.[44]

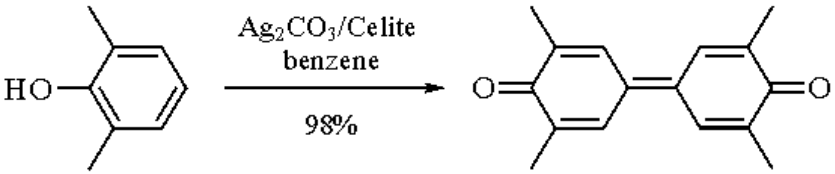

(5)

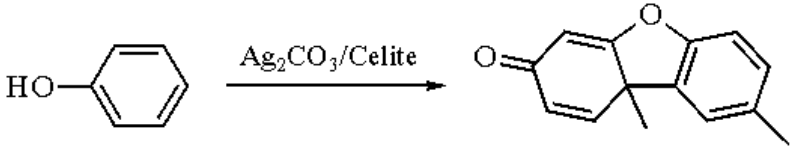

(6)

benzene, 0%
acetonitrile, 65%

Oxidation of Amines.

Very little is known so far on the oxidation of aliphatic amines. Anilines give azobenzenes in modest yield (Table 10).[3,45]

Oxidation of Hydrazines and Hydrazones.

Symmetrically disubstituted hydrazines and hydrazides are rapidly oxidized to the corresponding azo compounds (Table 10). Hydrazones are converted in a few minutes into diazoalkanes, generally in high yield (Table 10).[45,46]

Table 10 Oxidation of Amino Compounds[a]

Starting material	Product	Yield (%)
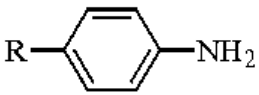	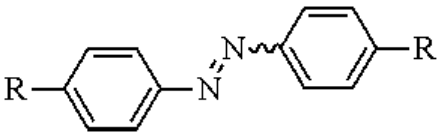	R = H 38 R = Cl 35 R = NO_2 5
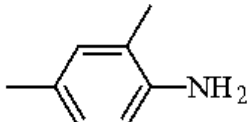	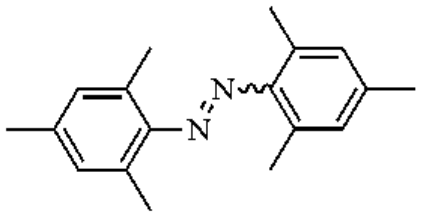	75
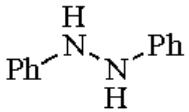	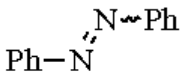	100
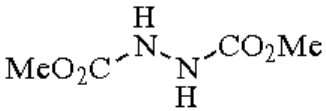	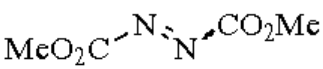	80

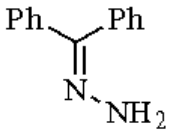	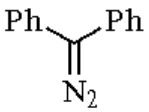	88

[a] In benzene.

Nitroso Compounds from Hydroxylamines.

N-Monosubstituted hydroxylamines lead to nitroso compounds, or their dimers, in good yield upon treatment with silver carbonate on Celite.[47] If a double bond is suitably placed, a cyclization of the nitroso intermediate gives a nitroxide free radical (Table 11).[48]

Nitrile Oxides from Oximes.

Benzaldoximes react with silver carbonate on Celite to give nitrile oxides, which undergo 1,3-dipolar cycloaddition with the original oxime. The nitrile oxides can also be trapped by other dipolarophiles such as nitriles and ethylenic compounds (Table 11).[46-48]

Table 11 Oxidation of Hydroxylamines and Oximes

Starting material	Product	Solvent	Yield (%)
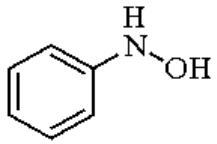	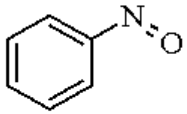	CH_2Cl_2	85
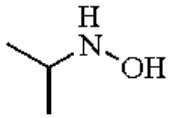	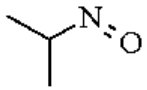	CH_2Cl_2	90
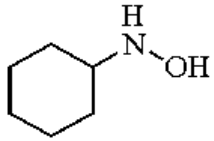	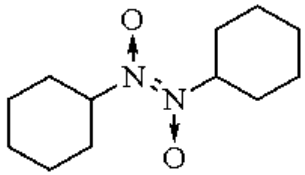	CH_2Cl_2	95
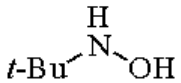	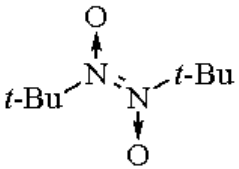	$CFCl_3$	57

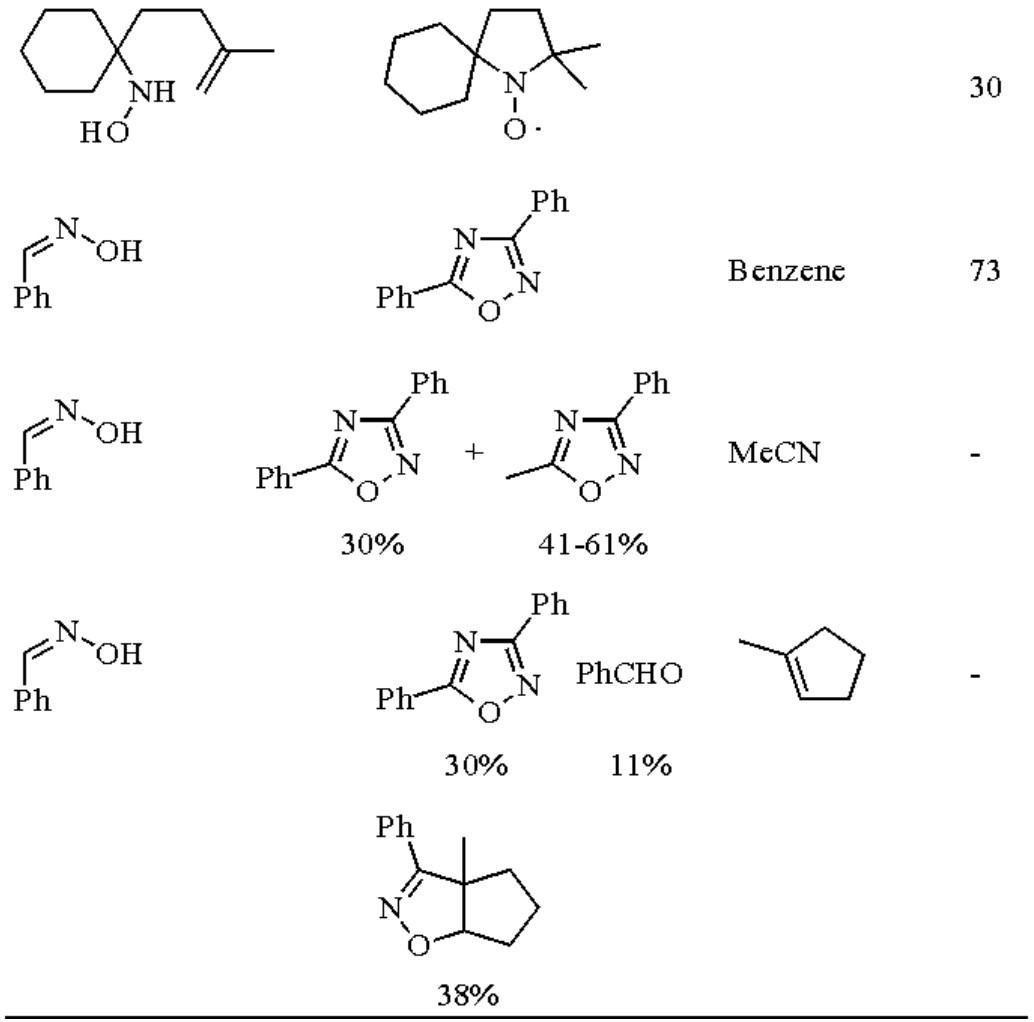

Miscellaneous Reactions.

Halohydrins are smoothly converted by this reagent into epoxides or rearranged into aldehydes or ketones.[49,50] Silver carbonate on Celite has also been proposed to improve *O*-glycosylation[51] (Koenigs-Knorr reaction).

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20. Bastard, J.; Fétizon, M.; Gramain, J. C. *T* **1973**, *29*, 2867.
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Silver(I) Cyanide

AgCN

[506-64-9] · CAgN · Silver(I) Cyanide · (MW 133.89)

(preparation of isocyanides,[1] preparation of hindered esters[5])

Physical Data: mp >300 °C; dec 320 °C; *d* 3.95 g cm^{-3}.

Solubility: sol nitric acid, ammonium hydroxide; slightly sol cold water; sparingly sol methylene chloride.

Form Supplied in: white to off-white powder.

Handling, Storage, and Precautions: may be fatal if inhaled, swallowed, or absorbed through the skin. It causes eye and skin irritation and may cause argyria (blackening of the skin). It is highly toxic and light sensitive; contact with acids should be avoided (releases HCN gas). The solid should be stored in a cool dry place under an inert atmosphere. Use in a fume hood.

Preparation of Isocyanides.

Silver cyanide can be used to prepare a number of isocyanides. Ethyl isocyanide,[1] for example, can be prepared by heating ***Ethyl Iodide*** with silver cyanide (eq 1). This reaction should be carried out in a well ventilated area because of its vile odor. Ethyl isocyanide has also been known to explode, so all heated operations should be done behind a safety shield. *N*-Acyl isocyanides[2] are highly unstable compounds which can be readily prepared by the reaction of acyl iodides with AgCN (eq 2). These compounds are capable of reacting as electrophilic carbenes, unlike alkyl and aryl isocyanides, which makes them attractive for cycloadditions (eq 3).[2] Silver cyanide also reacts with 4-ethoxybromobutane to give the corresponding isocyanide.[3]

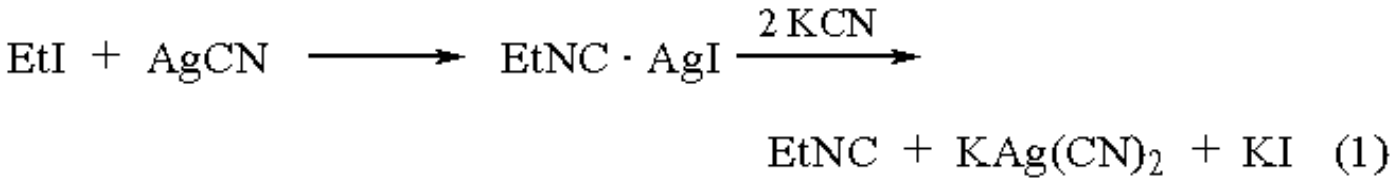

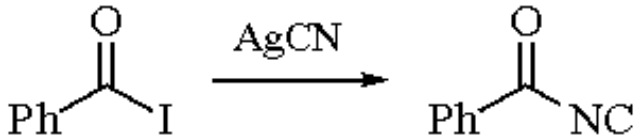

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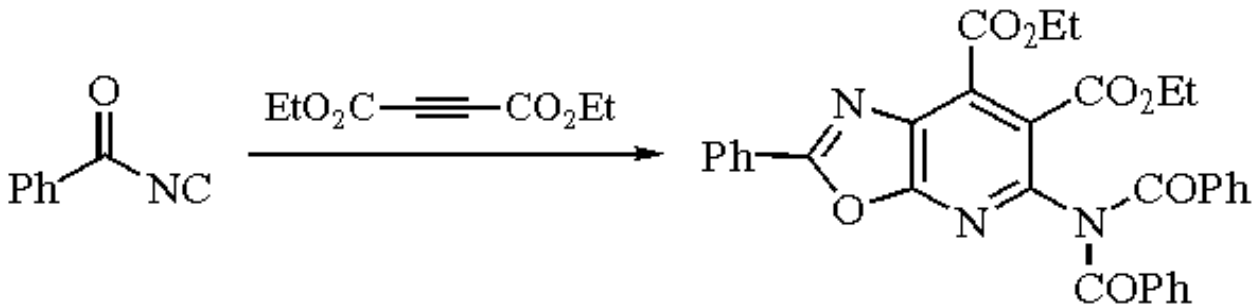

(3)

1-Isocyano sugars can be prepared in good yields by the reaction of AgCN with benzyl-protected halogenated glycosides at room temperature (eq 4).[4]

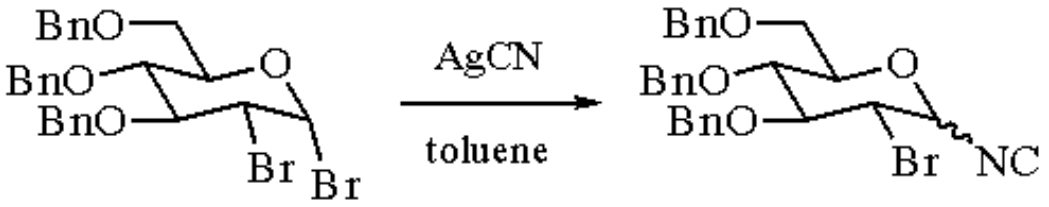

(4)

Preparation of Highly Hindered Esters.

The conventional method for preparing esters by the reaction of an acyl chloride with an alcohol in the presence of pyridine is not useful in certain hindered ester cases, where this method is too slow and incomplete. Hindered esters can generally be synthesized rapidly and in higher yields by reacting an acyl chloride with an alcohol in the presence of AgCN.[5] Highly hindered steroidal esters,[6] for example, have been prepared from the appropriate steroidal alcohol and a hindered acid chloride, such as pivaloyl chloride, using AgCN (eq 5).

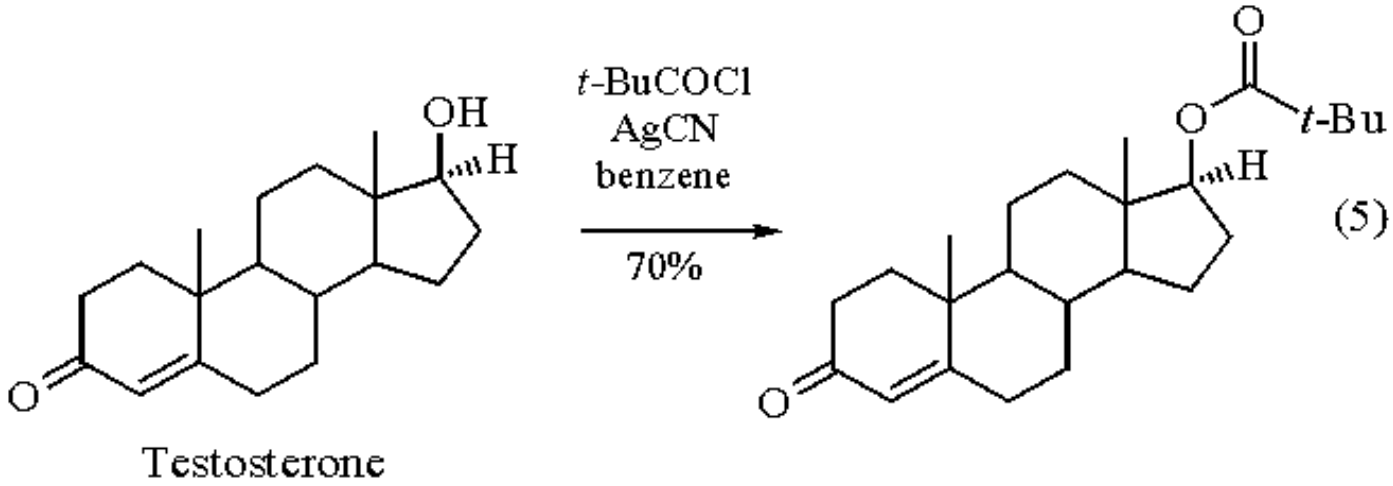

(5)

Treatment of o-hydroxyamines with ***t-Butyl Isocyanide*** in the presence of AgCN yields cyclized products in high yields. By varying the structure of the starting material, a wide variety of heterocycles are available including 2-oxazolines, 2-imidazolines, tetrahydro-2-pyrimidines, thiazolines, and dihydro-1,3-oxazines (eq 6).[7]

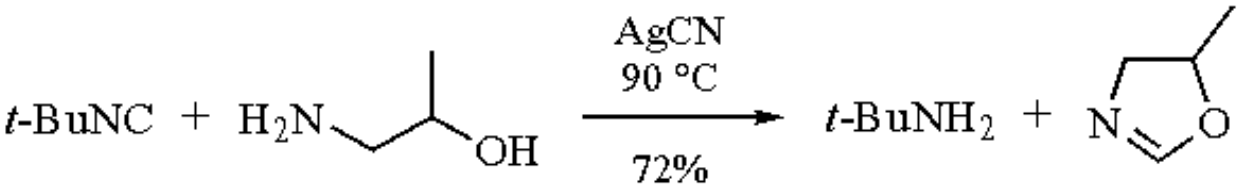

(6)

Silver cyanide can also be used as a catalyst in the reactions of organomagnesium reagents with chlorosilanes, which afford tetraorganosilanes[8] in higher yields than in the uncatalyzed reactions. When dioctylmagnesium reacts with ***Methyltrichlorosilane*** in the presence of AgCN (eq 7) an 80% yield is achieved while in the uncatalyzed reaction the product yield is only 16%.

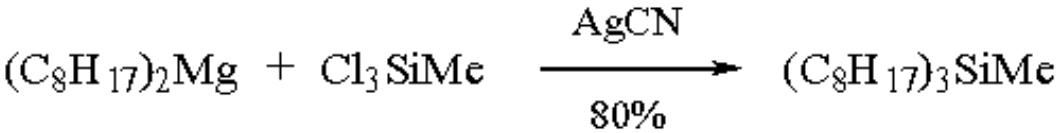

(7)

Other Applications.

Although phosphoroisothiocyanatidates (**1**) are readily accessible compounds, an isomer[9] (eq 8) was first prepared in 1972 by the reaction of AgCN and bis(neopentyloxy)phosphorosulfenyl chloride which yielded dineopentyl phosphorothiocyanatidate.

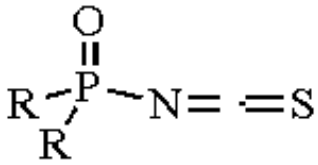

(1)

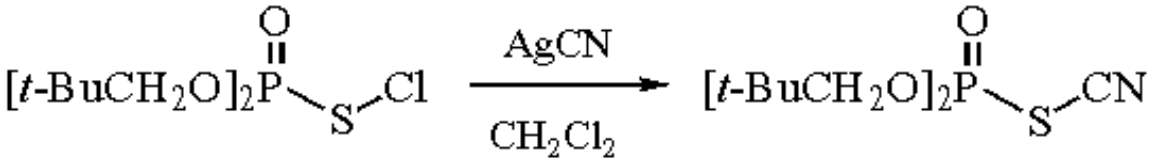

The first trifluoromethyl-iodine compound with more than one iodine-carbon bond was obtained by the reaction of AgCN with trifluoromethyliodine dichloride in methylene chloride (eq 9).[10] Silver cyanide reacts with difluoroaminocarbonyl chloride (eq 10) to give *N*,*N*-difluoroaminocarbonyl cyanide.[11]

$$CF_3ICl_2 + 2\ AgCN \longrightarrow CF_3I(CN)_2 + 2\ AgCl \qquad (9)$$

$$NF_2C(O)Cl + AgCN \longrightarrow NF_2COCN + AgCl \qquad (10)$$

---

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Silver(I) Fluoride

AgF

[7775-41-9] · AgF · Silver(I) Fluoride · (MW 126.87)

(fluorinating agent[1])

Physical Data: mp 435 °C; bp 1150 °C; *d* 5.852 g cm^{-3}.

Solubility: highly sol water (182 g/100 g H_2O), anhydrous hydrogen fluoride (83.2 g/100 g at 11.9 °C); slightly sol methanol (1.5 g/100 mL).

Form Supplied in: golden-yellow powder; commercially available, but very expensive.

Preparative Methods: by the reaction of Ag_2CO_3 or ***Silver(I) Oxide*** in anhydrous ***Hydrogen Fluoride*** or aqueous ***Hydrofluoric Acid***

Handling, Storage, and Precautions: a light sensitive, hygroscopic solid. It should be stored in a dark container under an inert atmosphere. It is extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin. It emits toxic fumes under fire conditions. It also forms explosive adducts with ammonia; reactions involving liquid or gaseous ammonia should be carried out with extreme caution. Use in a fume hood.

Fluorinations with Silver Fluoride.

Reaction of AgF with alkyl and aryl halides often results in the formation of the corresponding fluorides usually under mild conditions. With geminal dihalides, this conversion has been shown to involve a carbonium ion intermediate (eq 1).[2] Chloro quinones react with AgF under high pressure and temperature conditions to give partial conversion to the fluoro quinone (eq 2).[3] *Cis*- and *trans*-2,3-difluoro-2,3-dihydrobenzofuran can be similarly obtained by the reaction of AgF with *trans*-2,3-dibromo-2,3-dihydrobenzofuran (eq 3).[4] Bromoadamantanes[5] and 1-bromobicyclo[3.3.1]nonan-3-one[6] undergo fluorination with AgF to yield bridgehead fluorine derivatives (eq 4).

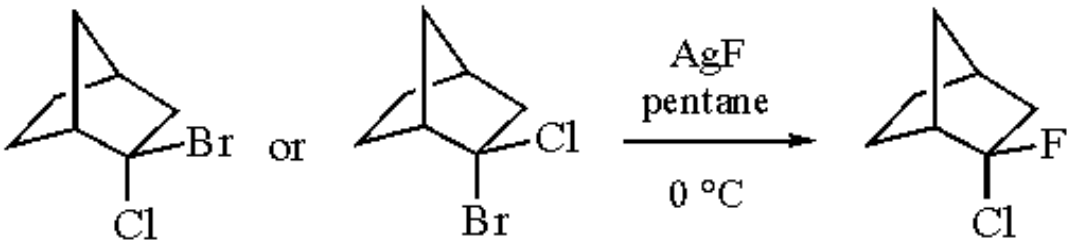

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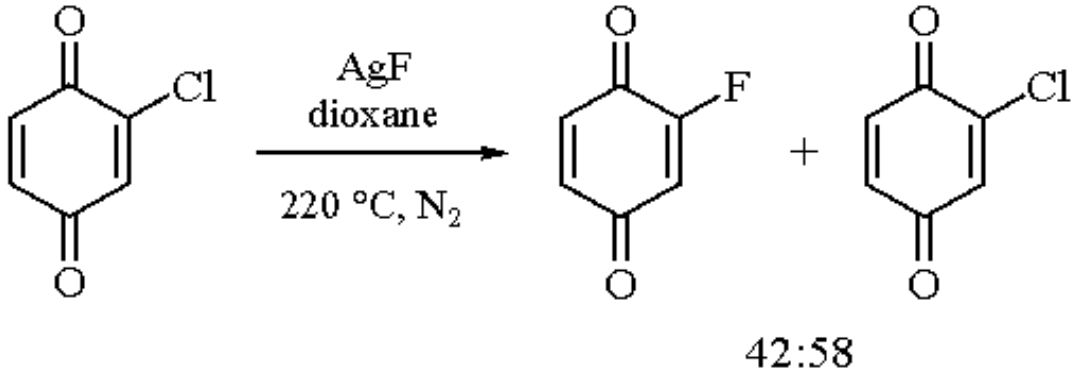

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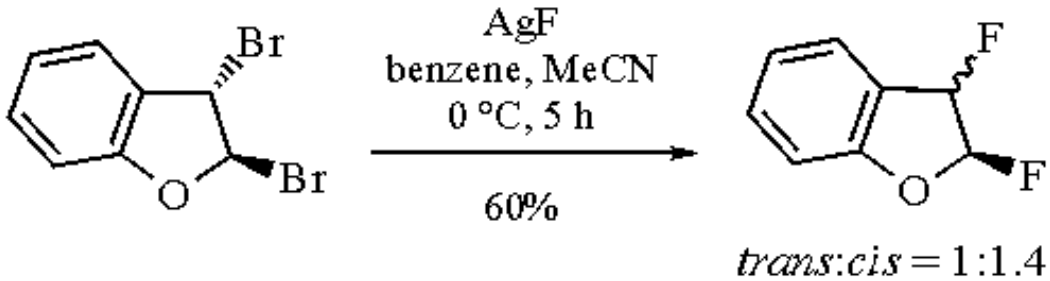

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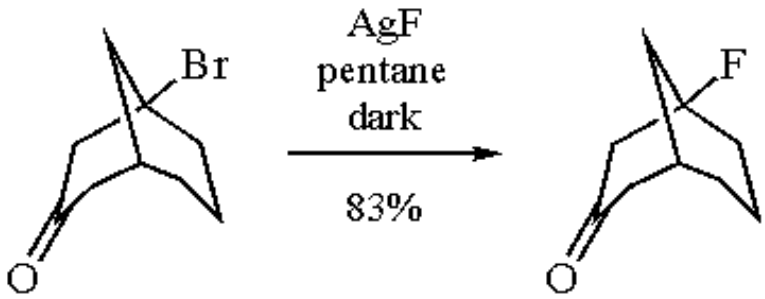

(4)

Fluorination of Alkenes by Addition Reactions.

β-Fluoro thioethers can be prepared by the addition of sulfenyl chlorides to alkenes in the presence of AgF. The addition to alkyl-substituted terminal alkenes usually produces anti-Markovnikov adducts with a primary fluorine. Unlike the corresponding chlorides, these materials do not undergo rearrangement to the thermodynamically more stable Markovnikov products (eq 5).[7]

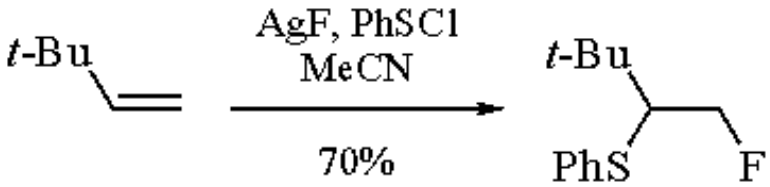

(5)

Silver fluoride adds to electron deficient alkenes. The reaction of 1,1-dichloro-2,2-dicyanoethylene with AgF, for example, does not produce the expected 1,1-difluoro derivative. Instead, this reaction yields the silver salt of trifluoromethylmalononitrile, presumably through the 1,1-difluoro derivative by subsequent addition of AgF to the strongly electrophilic double bond.[8] Perfluoroalkylsilver compounds can be prepared by the addition of AgF to perfluoroalkenes.[9] The fluorination of tetrabromo-2,3-diaza-1,3-butadiene affords the tetrafluoro derivative.[10]

Other Fluorinations using AgF.

α-Fluoro-α,β-unsaturated ketones and esters can be formed by the reaction of α-diazo esters with benzeneselenenyl fluoride (prepared by the reaction of ***Benzeneselenenyl Bromide*** with AgF).[11] ***Trifluoromethylthiocopper(I)*** can be readily prepared by the reaction of AgF, carbon disulfide, and copper(I) bromide in acetonitrile. This reagent reacts with iodoaromatics to yield the corresponding trifluoromethylthio derivatives.[12] Certain geminal dibromocyclopropanes undergo solvolysis with subsequent fluorination and ring expansion by treatment with AgF in acetonitrile (eq 6).[13] Silver fluoride mediates the opening of perfluoro sultones which, in the presence of an appropriate trapping agent, lead to the formation of fluoroalkoxysulfinyl fluorides (eq 7).[14]

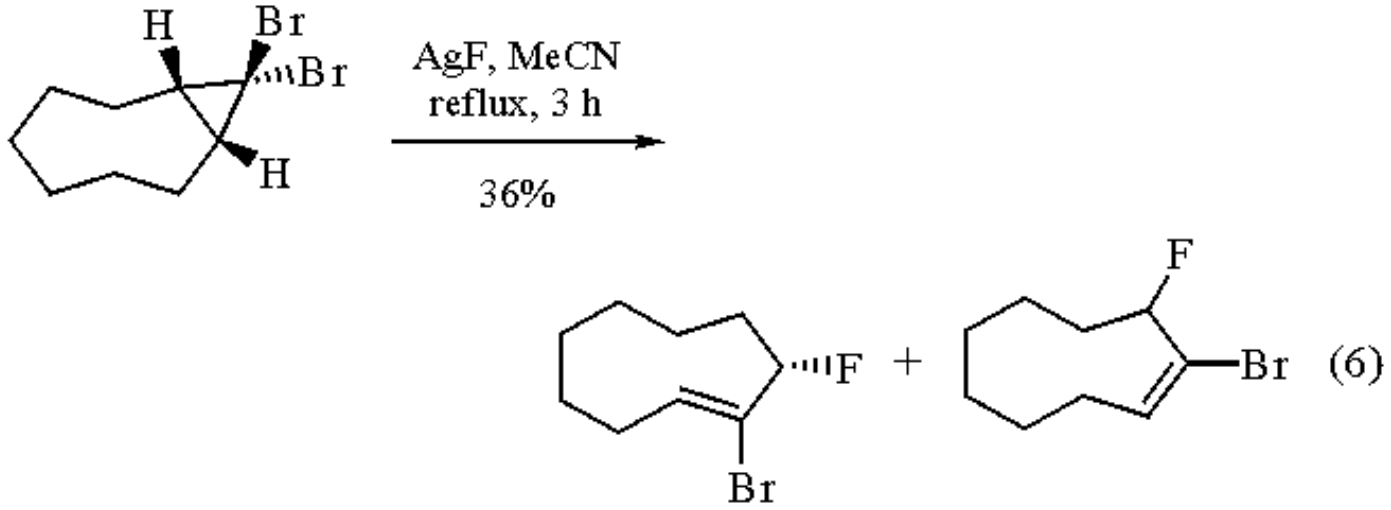

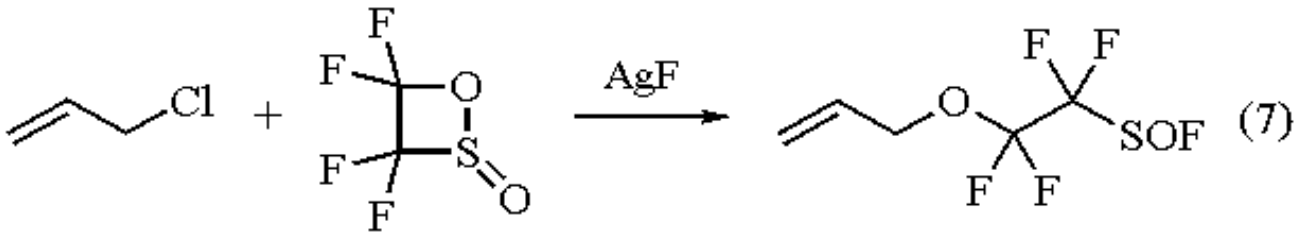

Silver Fluoride as a Desilylating Agent.

A number of unrelated synthetic methods take advantage of AgF as a strong fluoride source. In these methods, fluoride unmasks a reactive intermediate by desilylation, allowing for the desired reaction, in most examples a cyclization or cycloaddition, to take place. For example, *t*-butyldimethylsilyl carbamates can be treated with AgF, resulting in formation of cyclic carbamates by an intramolecular reaction (eq 8). Only (*E*)-allyl chlorides provide the cyclic carbamate, since the proposed cyclic transition state is not possible with the corresponding (*Z*)-allyl chlorides.[15] *Threo* selectivities for the cyclization are poor (3-5:1), but can be dramatically improved by using catalytic allylpalladium(II) chloride. In the absence of a suitable intramolecular trap, decarboxylation takes place. The reaction of AgF with a silyloxycyclopropane, followed by treatment with an allylic chloride, results in the formation of an δ,ε-unsaturated ketone (eq 9).[16]

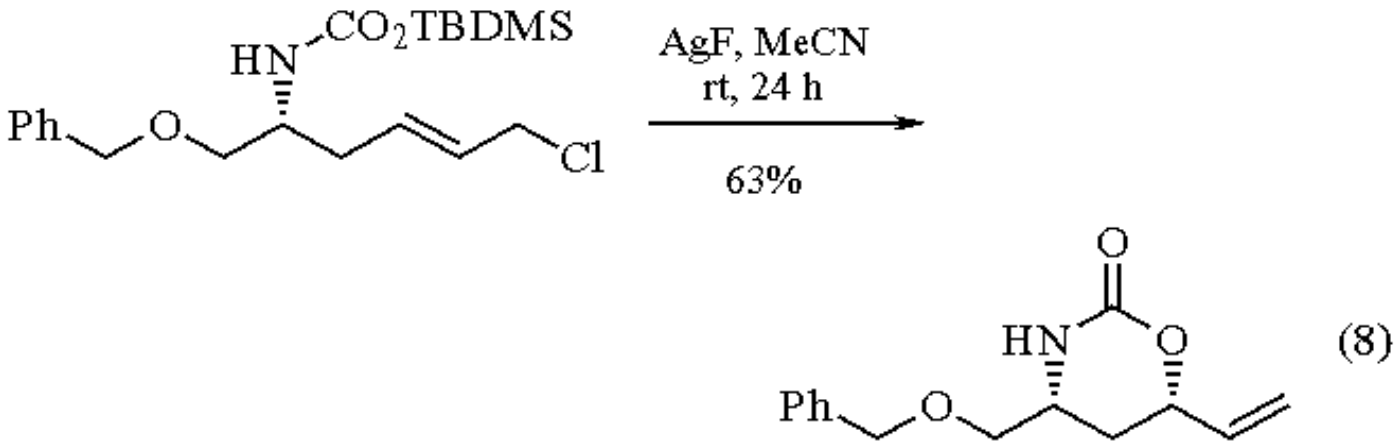

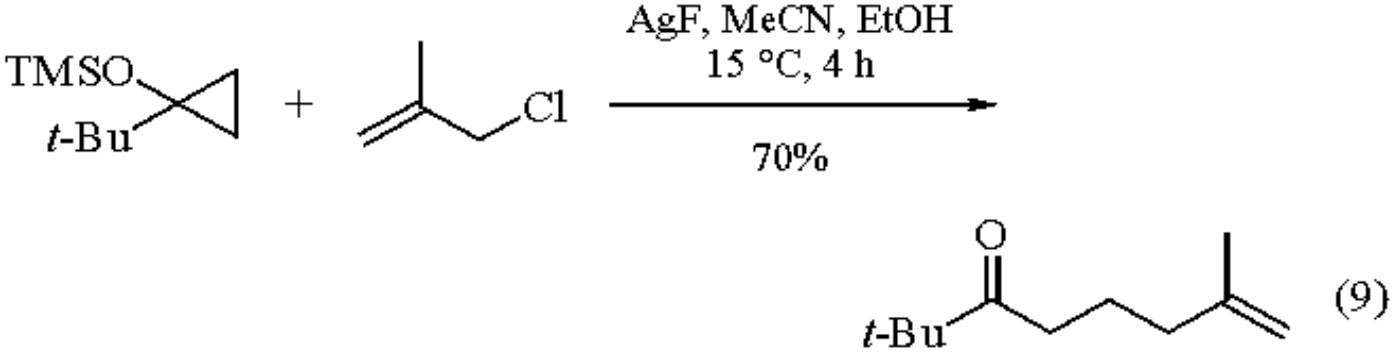

Treatment of a silylmethylindole with AgF, followed by exposure to an appropriate dipolarophile, results in the formation of a 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (eq 10). This cycloaddition works well with a number of related *N*-[(trimethylsilyl)methyl]-substituted indoles, providing cycloadducts with yields in the range 53-83%. The formation of the azomethine ylide assumes that silver is acting as a very specific Lewis acid, attacking the indole ring to give a silver-bonded carbonium ion.[17] α-Cyanoaminosilanes have also been used to generate azomethine ylides for the preparation of pyrrolidines in high yields.[18] Reaction of these azomethine ylides with ethyl propiolate yields the fully aromatized pyrroles (eq 11).[19]

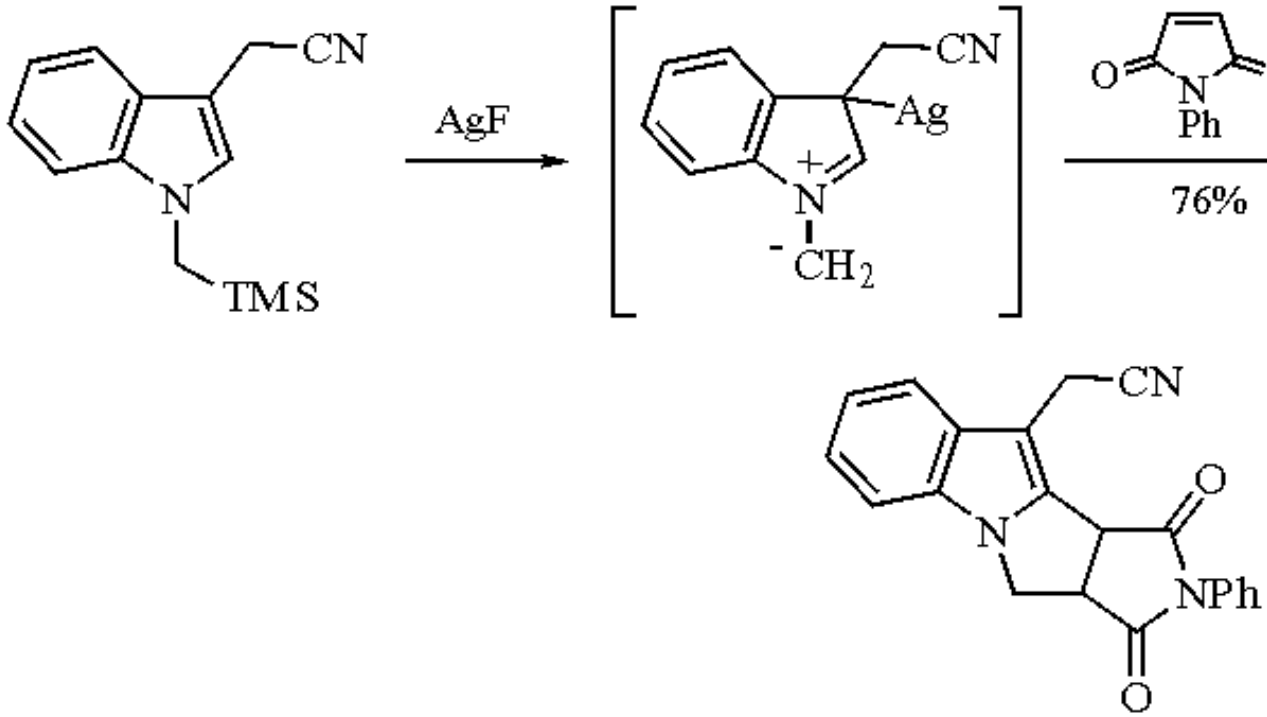

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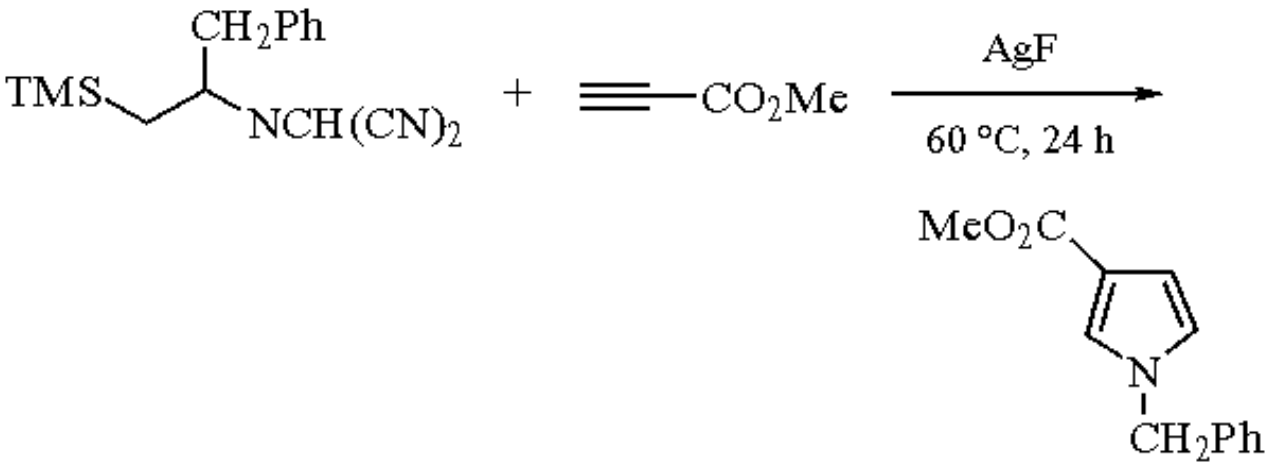

(11)

In work by Evans and co-workers, deprotection of a silyl ether with AgF leads to the formation of an intermediate positioned to undergo a rapid Cope rearrangement. Subsequent loss of methanol results in the formation of the deoxylapachol product in 95% yield (eq 12).[20] Additionally, certain nitrosoalkenes, which can be active dienes in [4 + 2] cycloadditions, can be prepared from α-chlorosilyloximes by 1,4-elimination in the presence of an appropriate fluoride source, such as AgF.[21] Successful cycloadditions are also observed with ***Cesium Fluoride*** and ***Potassium Fluoride*** (eq 13).

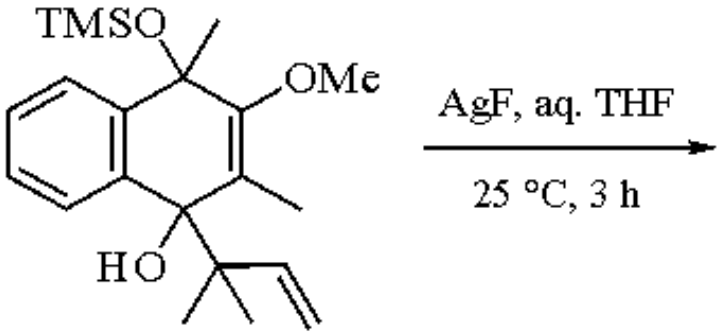

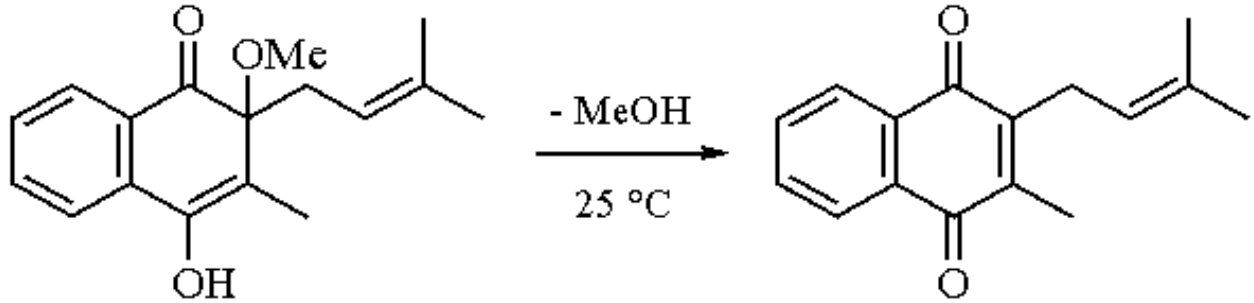

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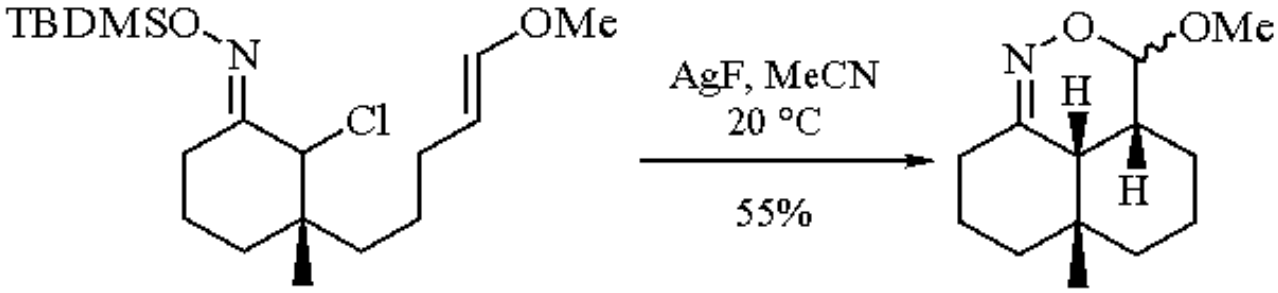

(13)

Other Reactions with AgF.

Treatment of vicinal dibromo steroids with aqueous AgF results in the formation of epoxides.[22,23] The AgF-initiated methanolysis of 2,2-dibromo-1,3-dimethylcyclopropanecarboxylic acid has also been studied in detail.[24] Thiophilic heavy metal salts such as AgF have been used for ring opening of penicillin derivatives (eq 14),[25] although other catalysts such as ***Silver(I) Oxide*** are better. Treatment of (*E*)-aryl- and -alkenylpentafluorosilicates with silver fluoride affords symmetrical (*E*,*E*)-1,3-dienes in high yields (eq 15).[26]

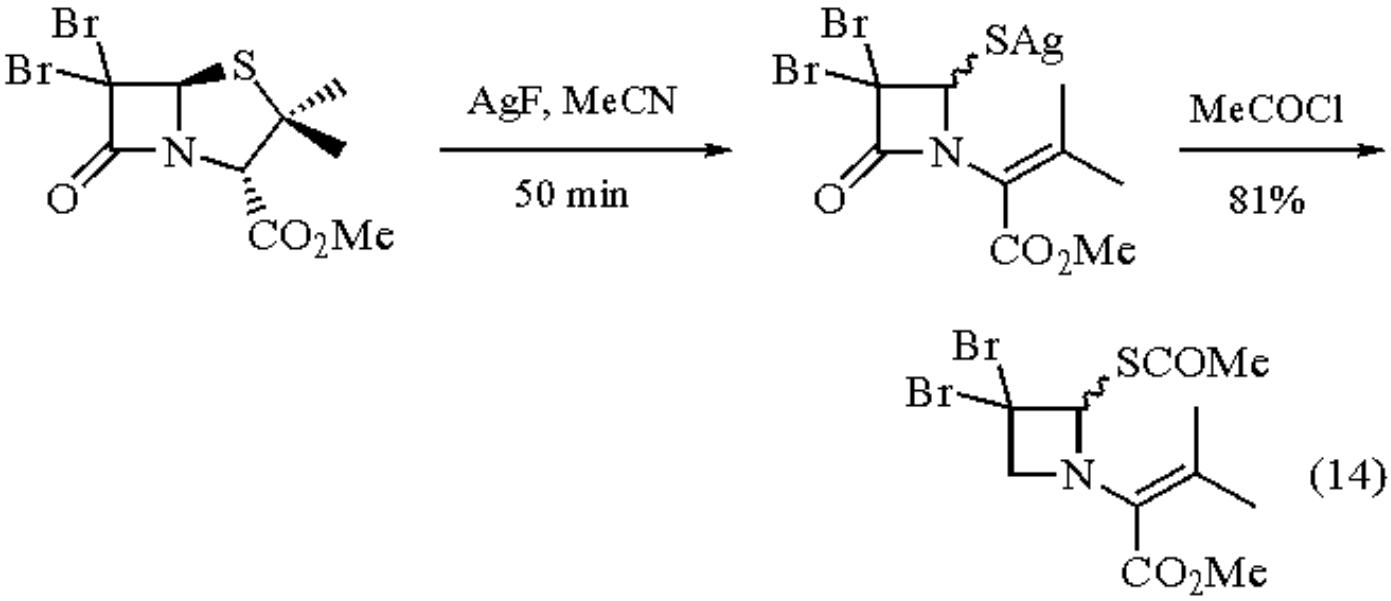

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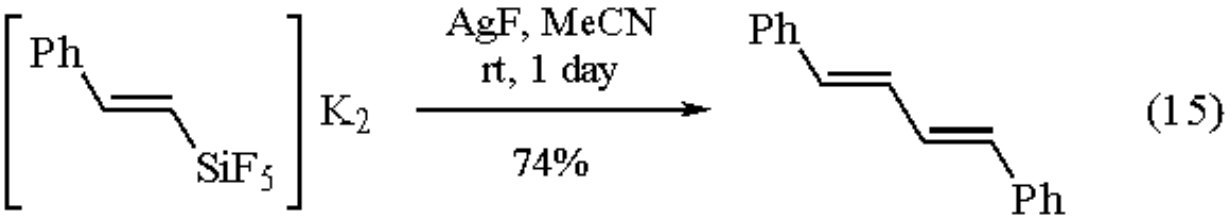

(15)

Related Reagents.

Iodine-Silver(I) Fluoride; ***Silver(I) Fluoride-Calcium Fluoride***.

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Silver(I) Fluoride-Calcium Fluoride[1]

AgF/CaF_2

(AgF)

[7775-41-9] · AgF · Silver(I) Fluoride-Calcium Fluoride · (MW 126.87) (CaF_2)

[7789-75-5] · CaF_2 · Silver(I) Fluoride-Calcium Fluoride · (MW 78.08)

(fluorination reagent,[2] useful for conversion of alkyl halides to alkyl fluorides and for halofluorination of alkenes)

Form Supplied in: white free-flowing granular powder.

Preparative Method: ***Silver(I) Fluoride*** is supported on calcium fluoride by slowly evaporating a mixture of silver carbonate, 50% aqueous ***Hydrofluoric Acid***, and CaF_2 in water to a dry granular powder.[2]

Handling, Storage, and Precautions: highly hydroscopic and light sensitive.

Halogen Exchange.

Silver fluoride dispersed on the surface of calcium fluoride shows improved fluoride nucleophilicity for halogen exchange with alkyl and benzyl halides. Thus treatment of 1-bromooctane with AgF/CaF_2 in acetonitrile for 30 min at 75 °C affords 1-fluorooctane in 41% yield (eq 1).

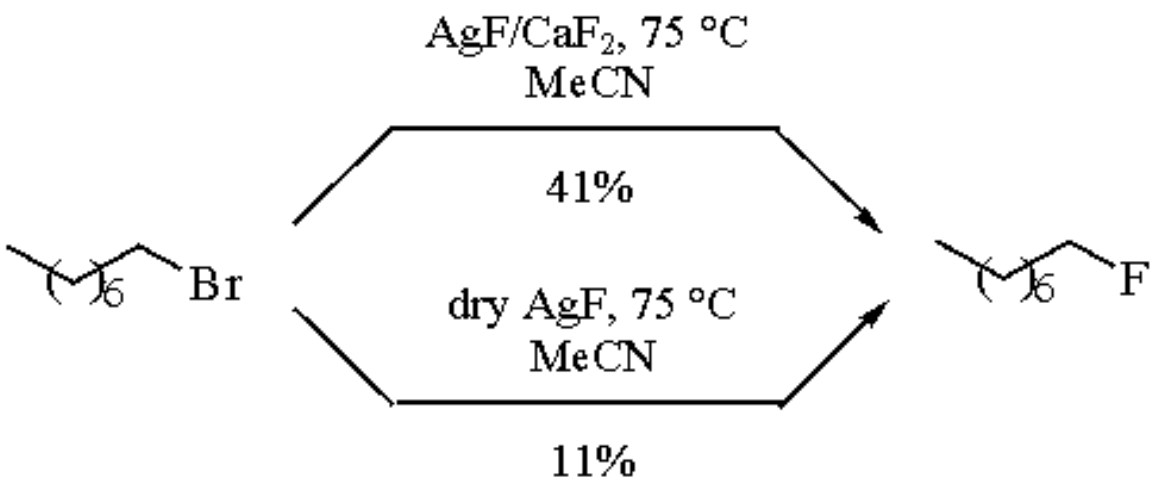

(1)

This reagent also proves superior to KF/CaF_2 and CsF/CaF_2, although the presumably high cost of the reagent could outweigh the increase in yield when used on a large scale. A comparative example is shown in eq 2. In general, alkyl iodides give better yields than bromides, which in turn give better yields than chlorides.

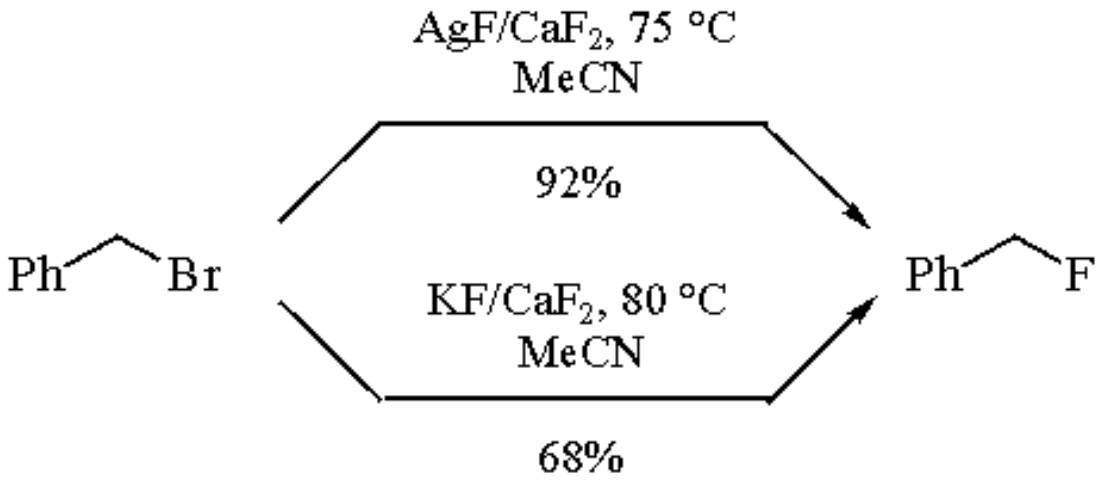

(2)

Alkene Additions.

Silver fluoride has been used in the presence of a halogen or a suitable *N*-haloamide for the in situ generation of halogen fluorides XF (X = I, Br, Cl) which add to alkenes.[3] Halofluorination of alkenes using the AgF/CaF_2 reagent has also been reported.[2] Bromofluorination is most effective with ***1,3-Dibromo-5,5-dimethylhydantoin*** (DBH) (eq 3). ***N-Bromosuccinimide*** gives poor results, as dibromide byproducts are formed. Iodofluorination is equally effective using either ***Iodine*** or ***N-Iodosuccinimide*** with AgF/CaF_2; the yield of ca. 50% is similar to the literature values (eq 4).[3]

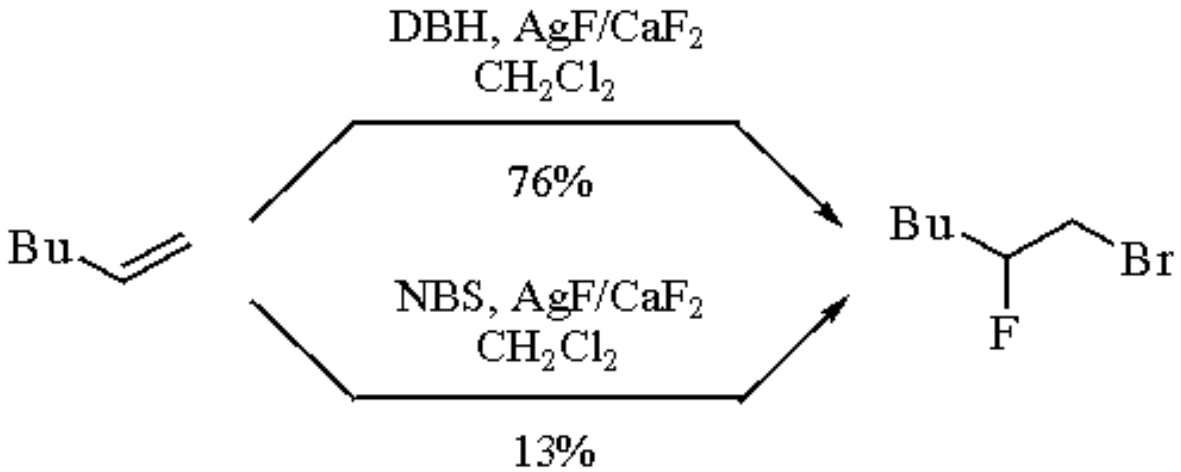

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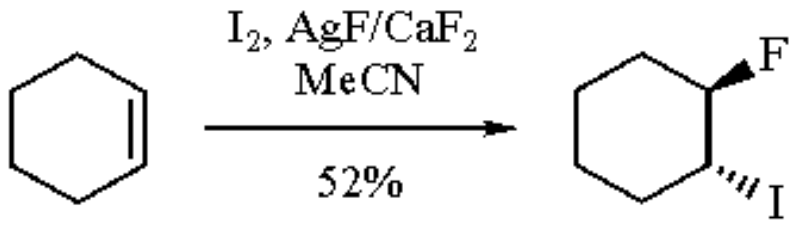

(4)

Related Reagents.

Bromine Monofluoride; ***Cesium Fluoride***; ***Iodine Monofluoride***; ***Potassium Fluoride***.

---

1. Wilkinson, J. A. *CRV* **1992**, 505.
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3. Hall, L. D.; Jones, D. L. *CJC* **1973**, *51*, 2902.

Silver(I) Heptafluorobutanoate

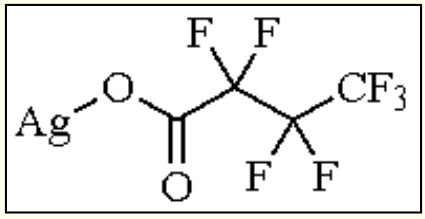

[3794-64-7] · $C_4AgF_7O_2$ · Silver(I) Heptafluorobutanoate · (MW 320.91)

(decomposition of 3-diazocamphor;[2] NMR shift reagent)

Physical Data: mp 292-294 °C.

Solubility: no readily available data, but probably soluble in a range of solvents, e.g. $CHCl_3$, CH_2Cl_2, MeCN, alcohol, THF.

Form Supplied in: white powder; widely available.

Handling, Storage, and Precautions: handle in a fume hood with rubber gloves and safety glasses; avoid skin contact and inhalation. Store in a tight container in a cool place. Light sensitive. Severe eye irritant with an obnoxious smell. The toxicology of this compound has not been fully evaluated.

Little published work has appeared describing the use of this compound as a reagent since the work reviewed in Fieser and Fieser[1] on the $AgOCOC_3F_7$-assisted decomposition of 3-diazocamphor and its 4-methyl analog, via a carbene intermediate, to the corresponding tricyclanone (eq 1).[2] The reaction also occurs with ***Silver(I) Tetrafluoroborate*** at 0 °C but no other silver salts have been evaluated.

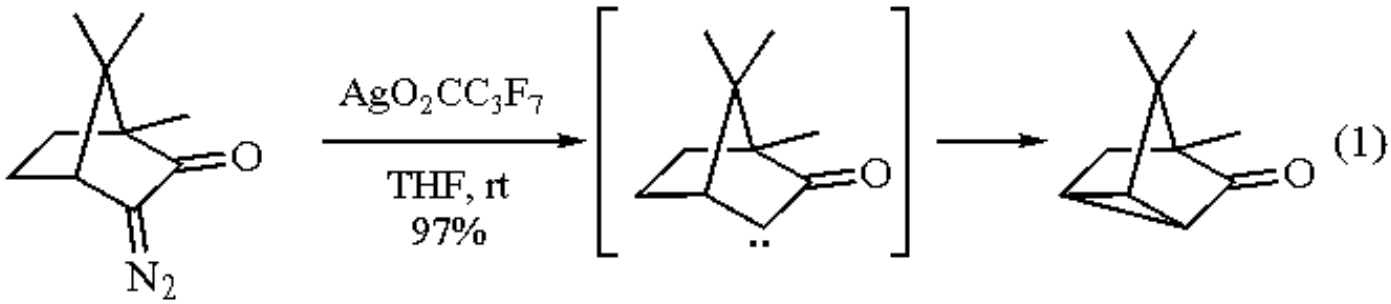

Shift Reagent.

The reagent has also been used in combination with the lanthanide agent $Ln([^2H_9]fod)_3$ as an NMR shift reagent for alkenes.[3]

---

1. *FF* **1977**, *6*, 515.
2. Brown, C. F.; Morris, D. G.; Murray, A. M. *SC* **1975**, *5*, 477.
3. Evans, D. F.; Tucker, J. N.; de Vellardi, G. C. *CC* **1975**, 205.

Duncan R. Rae

Organon Laboratories, Motherwell, UK

Silver(I) Hexafluoroantimonate

$AgSbF_6$

[26042-64-8] · AgF_6Sb · Silver(I) Hexafluoroantimonate · (MW 343.62)

(metathetical reagent with organic[1] and organometallic halides; mild Lewis acid catalyst for rearrangement of α-halo ketones,[3] pinacols,[4] epoxides,[5] and propargyl esters[6])

Physical Data: white crystalline powder; *d* 4.75 g cm^{-3}.[23]

Solubility: sol (and forms 1:2 complexes with) benzene, toluene, xylene;[24] sol nitromethane, liq SO_2;[7] insol HF, petroleum ether.[7,25]

Form Supplied in: anhydrous white powder; commercially available.

Analysis of Reagent Purity: the SbF_6^- ion can be determined as the nitron salt.[26]

Preparative Methods: has been made from SbF_3 (or Sb_2O_3), AgCl, and ***Bromine Trifluoride***,[27] but is more readily prepared by reacting ***Antimony(V) Fluoride*** and ***Silver(I) Fluoride*** in anhydrous HF at -78 to 0 °C, washing with pet ether, and drying in vacuo.[7]

Handling, Storage, and Precautions: this heavy metal salt is hygroscopic, light sensitive, and very corrosive. Storage in tightly sealed, opaque bottles in a moisture-free atmosphere is recommended. Incompatible with strong oxidizing agents; decomposition products include HF.[28] Reactions should be performed in a well-ventilated fume hood.

Metathesis.

Silver hexafluoroantimonate provides a useful alternative, as a metathetical reagent, to ***Silver(I) Perchlorate*** and ***Silver(I) Tetrafluoroborate***.[2] Thus in a similar fashion to the $AgBF_4$ reagent, silver hexafluoroantimonate has been utilized in the generation of stable carbocation salts for solution NMR or crystal structure analysis. Examples include the 4-chloro-1,2,3,4-tetramethylcyclobutenium cation,[1] the parent benzenonium cation,[8] and the red crystalline salt derived from phenyl(2-chlorophenyl)dichloromethane (eq 1).[9] Acylium salts, $RCO^+SbF_6^-$, are available from treatment of acid halides with $AgSbF_6$ in liq SO_2.[7] Stable thiobenzoyl hexafluoroantimonate salts are generated in a like manner.[10] Application of this silver-assisted ionization method to chloroformates provides an interesting route to highly reactive carbocation species (eq 2).[11]

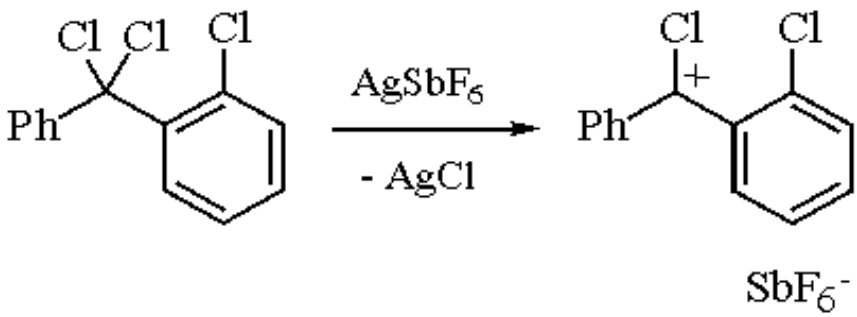

(1)

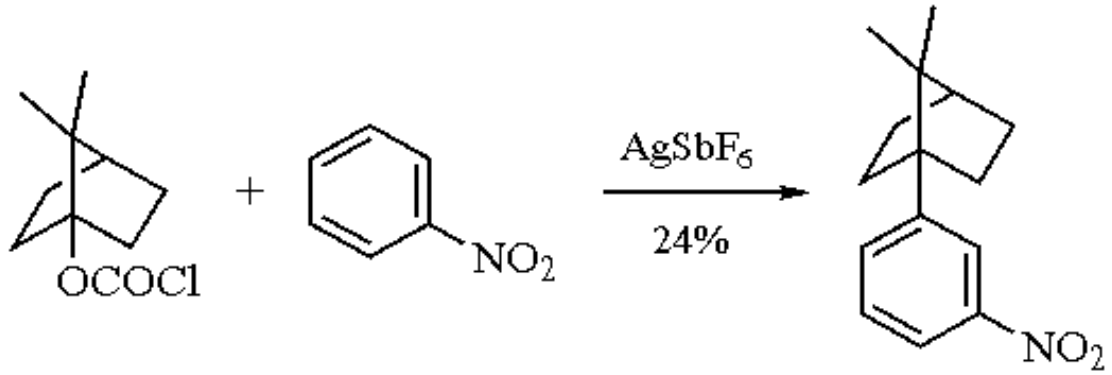

(2)

Rearrangements.

Silver(I) salts are noted for dehalogenative rearrangements of a variety of halide substrates, and $AgSbF_6$ is no exception. Dehalogenative rearrangement of α-bromo ketones appears to be a particularly effective niche for this salt of a super acid. Select examples include cases of multiple hydride shifts to functionalize remote carbons (eq 3)[3] and 1,2-aryl (and vinyl) shifts (eq 4).[12] A recent X-ray study of stable crystalline complexes of α-bromo ketones with $AgSbF_6$ and $SbCl_5$ has established an interesting difference in the coordination of the soft Lewis acid (Ag^+) with that of $SbCl_5$ which accounts for the preferential activation of the C-Br bond by silver(I).[13]

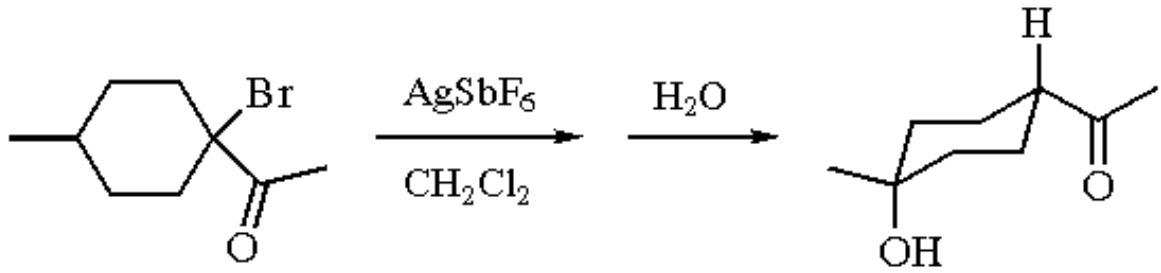

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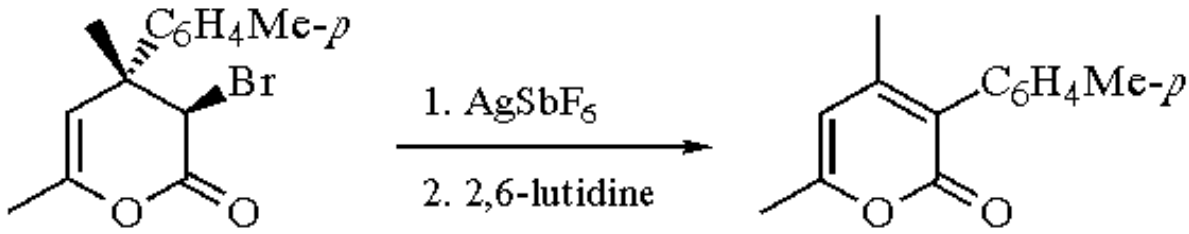

(4)

In a 1:1 combination, ***Antimony(V) Chloride*** and $AgSbF_6$ form a potent Lewis acid catalyst which is superior to either reagent alone in Friedel-Crafts acylations,[14] in Beckmann[14] and pinacol[4] rearrangements, and in the formation of ethers directly from epoxides via a tandem rearrangement-reductive condensation process (eq 5).[5] Trityl hexafluoroantimonate is an effective and superior catalyst in the latter case. Thiophenylation of aromatics is also promoted by the mixed catalyst system (eq 6).[15]

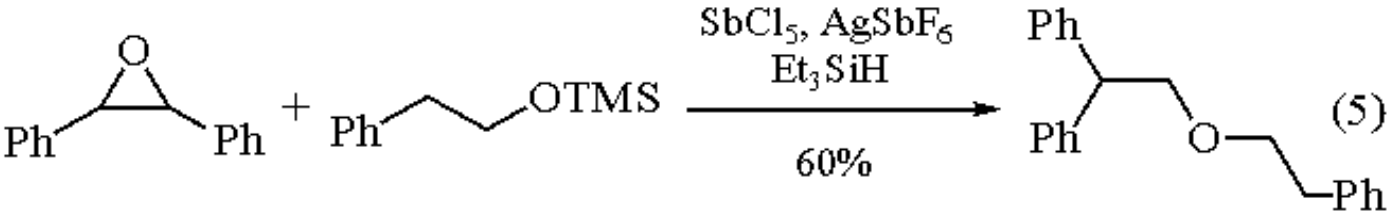

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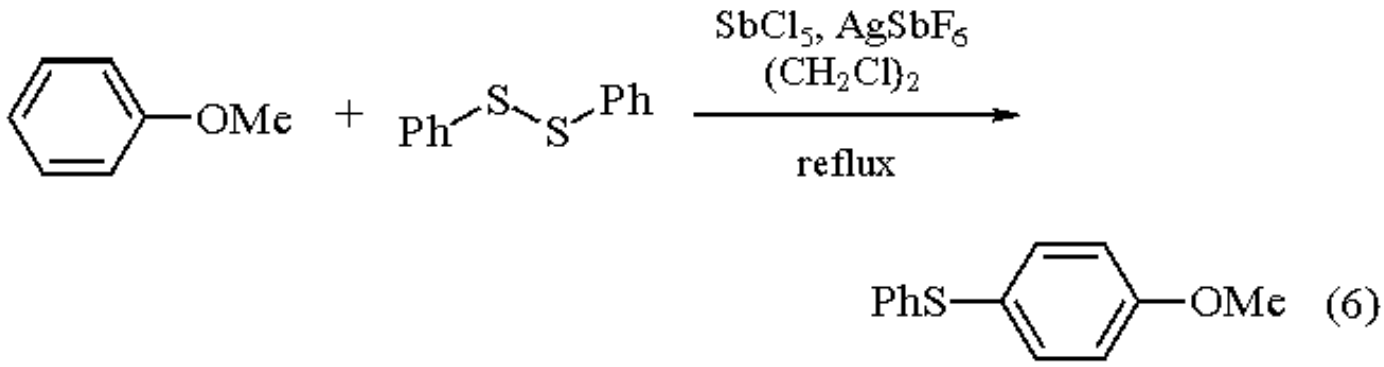

The silver(I) salt-catalyzed allylic rearrangement of propargyl esters to their allenyl counterparts[16] has found increasing synthetic development with the discovery[17] that extended exposure to Ag^+, with heating, promotes further isomerization to the 1,3-dienylic esters. ***Silver(I) Trifluoroacetate***[17] and ***Silver(I) Acetate***[18] have been employed in this respect, but the hexafluoroantimonate salt appears to be equally effective (eq 7).[6] Silver perchlorate is also reported to effect the similar isomerization and subsequent cyclization of butyne-1,4-diol monoacetates (eq 8).[19]

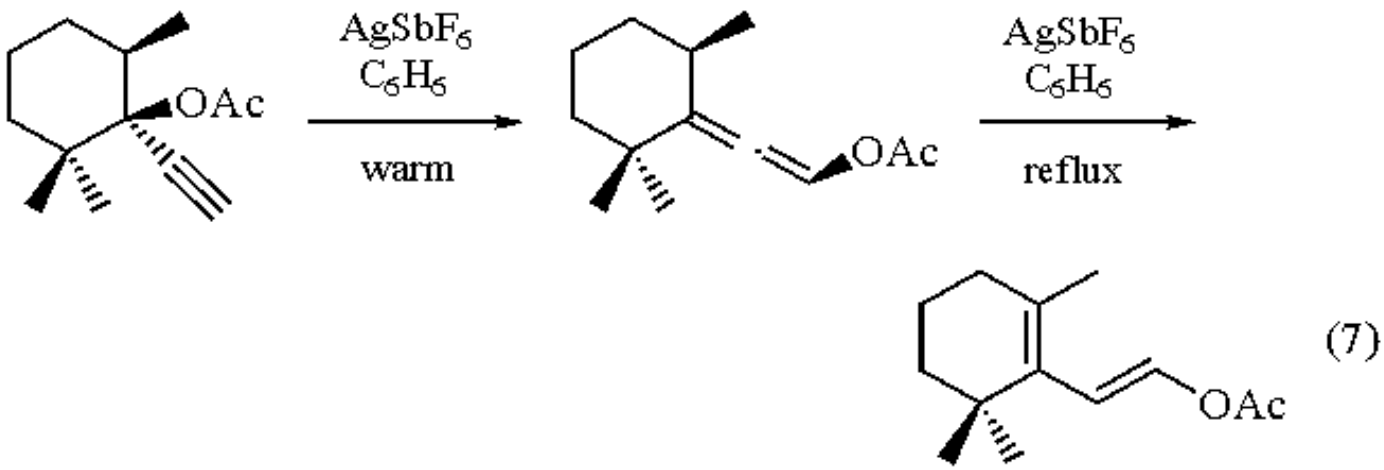

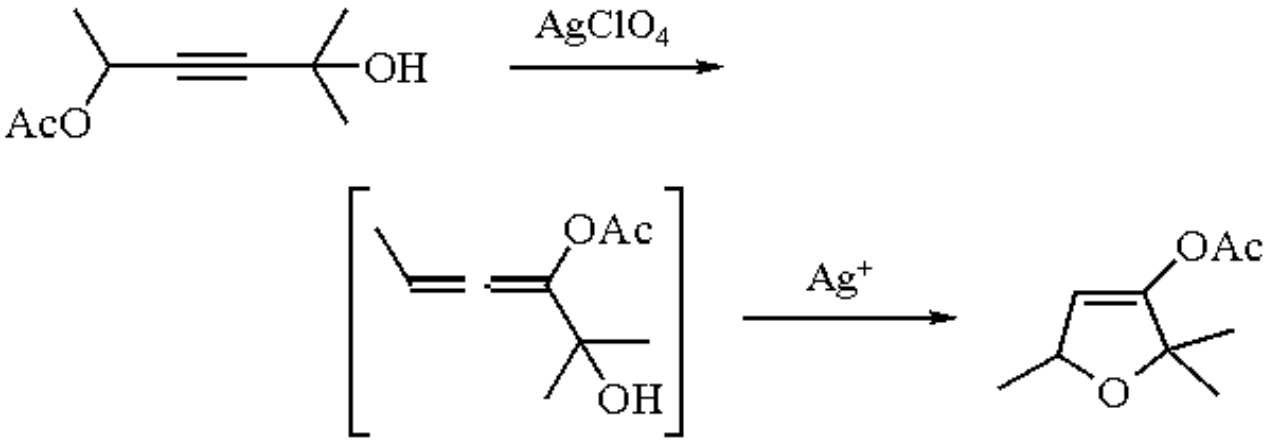

Although the use of $AgClO_4$ as a weak Lewis acid catalyst is frequently cited, as in the facile rearrangement of substituted cyclopropenes (eq 9),[20] it is not to be recommended, especially in stoichiometric quantities (e.g. eq 10)[21] in view of the well-known explosive hazard of perchlorate salts in organic solvents. Occasionally, however, there are reports of this salt being the reagent of choice, an example being the macrolactonization of o-hydroxy thiol esters of 2-amino-4-mercapto-6-methylpyrimidine (eq 11).[22] Otherwise, the hexafluoroantimonate or tetrafluoroborate salts of silver(I) should constitute acceptable substitutes.

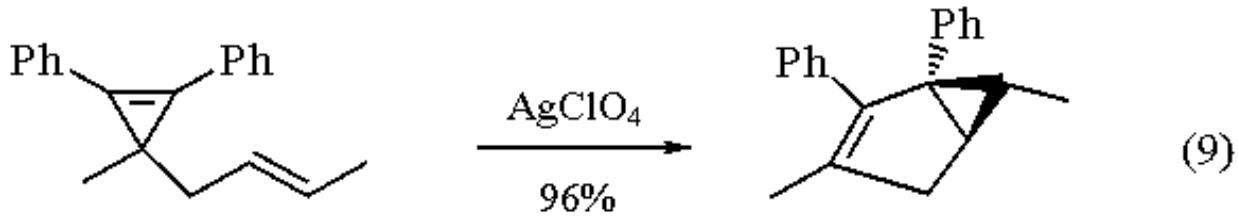

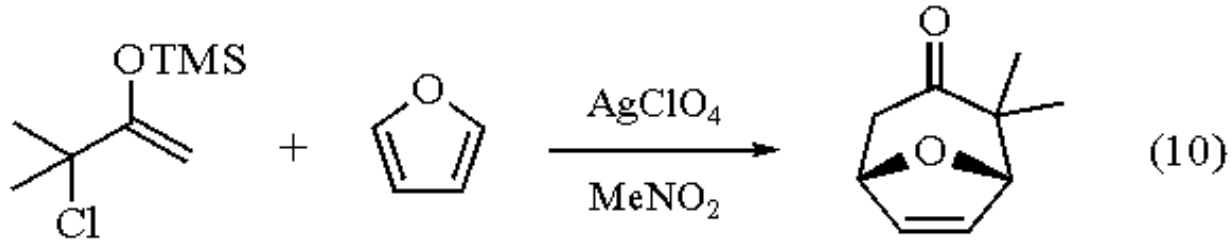

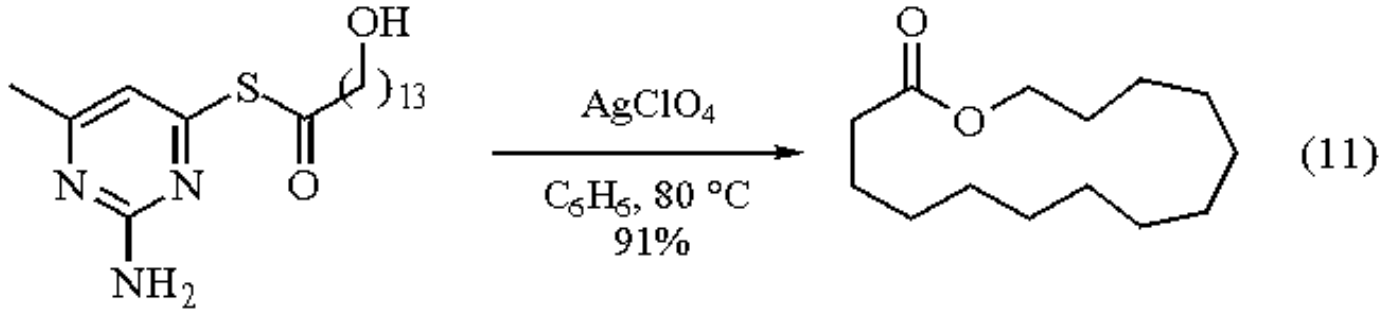

Related Reagents.

Antimony(V) Chloride; ***Antimony(V) Fluoride***; ***Hydrogen Fluoride-Antimony(V) Fluoride***; ***Silver(I) Acetate***; ***Silver(I) Tetrafluoroborate***; ***Silver(I) Trifluoroacetate***.

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8. Olah, G. A. *JACS* **1965**, *87*, 1103.
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28. *The Sigma-Aldrich Library of Chemical Safety Data*, 2nd ed.; Lenga, R. E., Ed.; Sigma-Aldrich: Milwaukee, 1988; Vol. 2, p 3095.

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Silver(I) Imidazolate

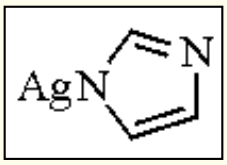

[42879-93-6] · $C_3H_3AgN_2$ · Silver(I) Imidazolate · (MW 174.95)

(preparation of glycosides)

Preparative Method: prepared by precipitation from an alkaline solution of ***Silver(I) Nitrate*** and ***Imidazole***.[1,2]

Glycosidation.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl chloride reacts with aglycones such as 1,2:3,4-di-*O*-isopropylidene-D-α-galactopyranose, in the presence of silver imidazolate and ***Mercury(II) Chloride***, to give predominantly the 1,2-*cis*-glycoside with lesser amounts of the 1,2-*trans*-glycoside (eq 1).[2] Without either reagent, only degradation of the starting materials occurs. With the more hindered glycone 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, only the 1,2-*cis*-glycoside is formed (eq 2).

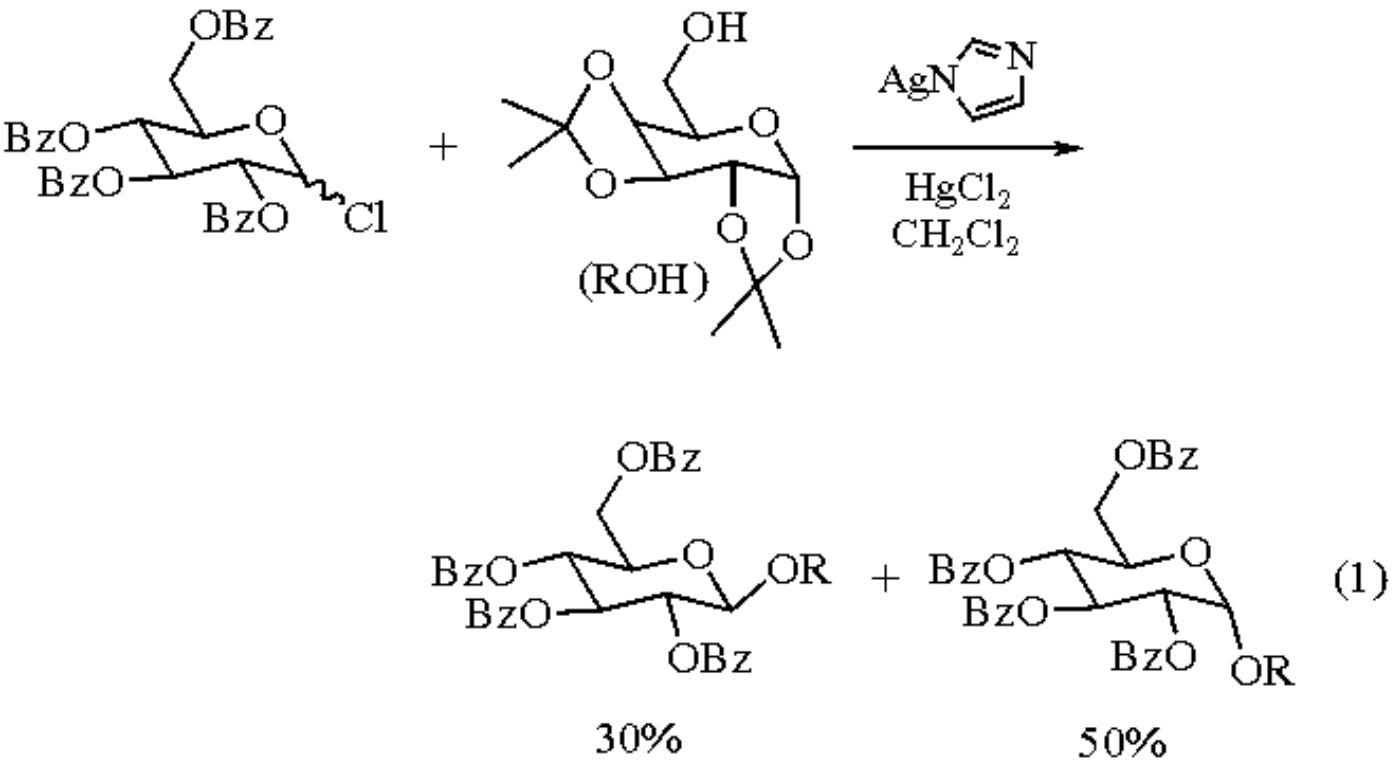

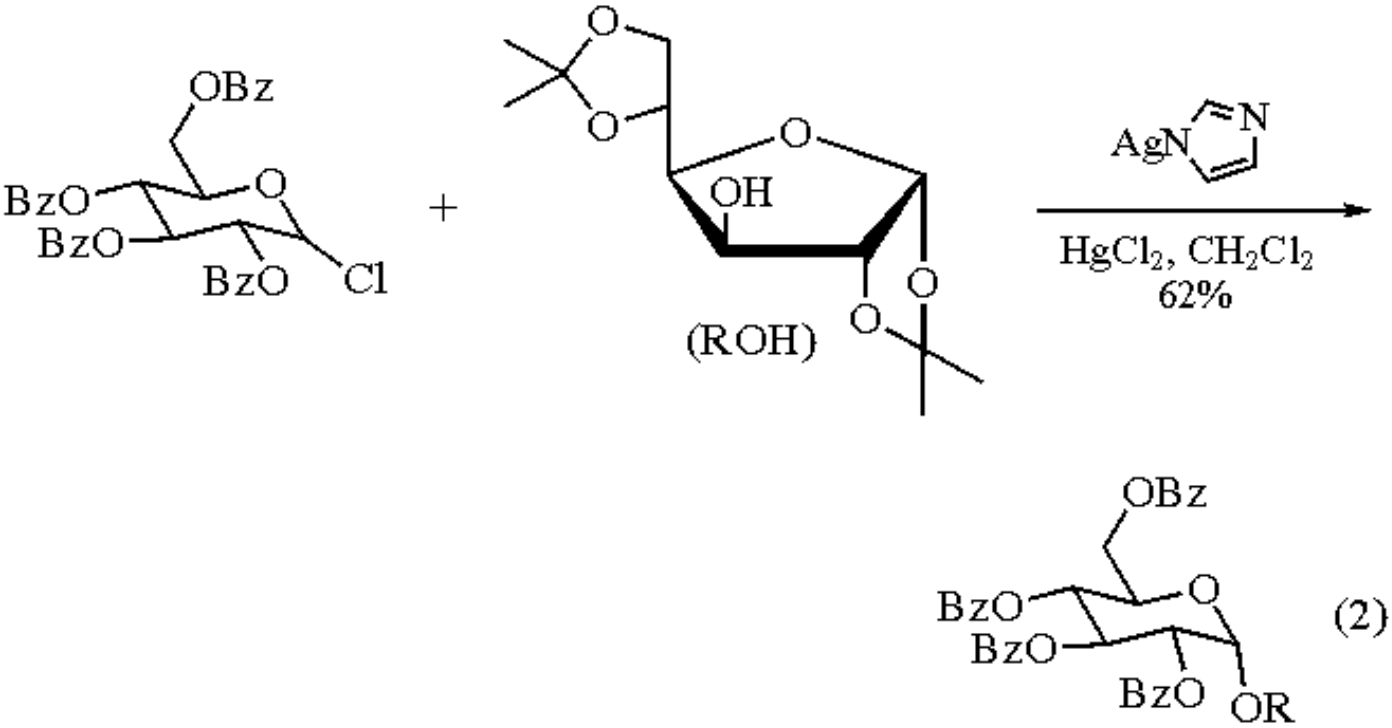

(2)

Tetrabutylammonium chloride greatly enhances glucosidation rates without affecting product ratios. Better yields of the 1,2-*trans*-glycosides are obtained when the pyranosyl bromide, glycone, silver imidazolate, and ***Zinc Chloride*** are reacted in a ratio of 1.5:1:0.75:~6, respectively.[3] In this way the unhindered alcohol 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose gives the 1,2-*trans*-glycoside in 90% yield (eq 3), and the hindered alcohol 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose gives the corresponding 1,2-*trans*-glycoside in 30% yield (eq 4).

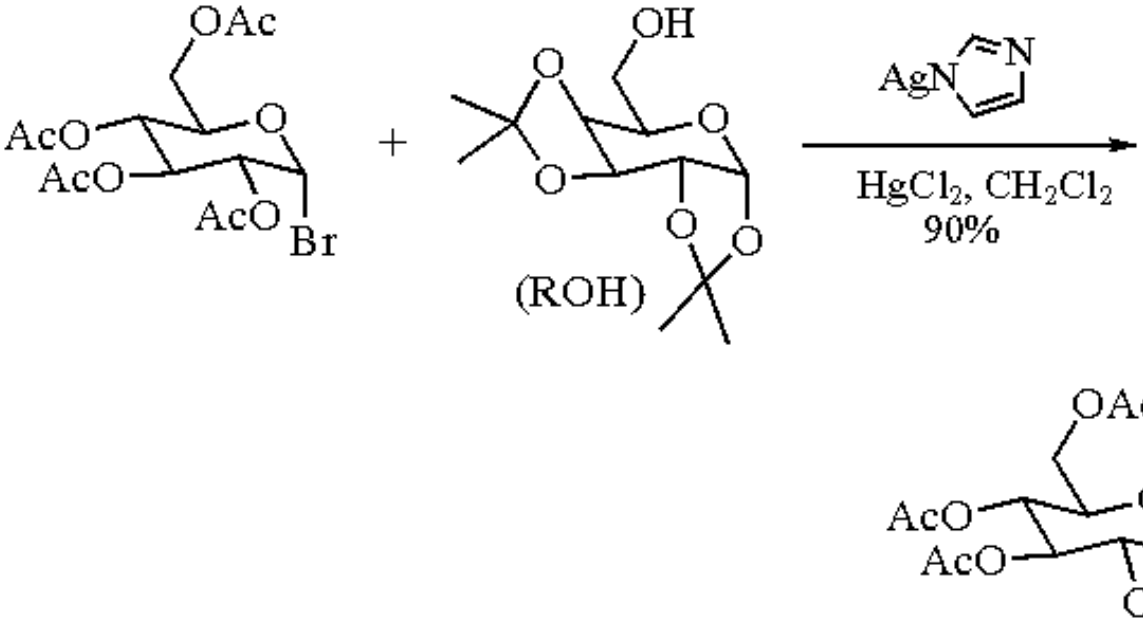

(3)

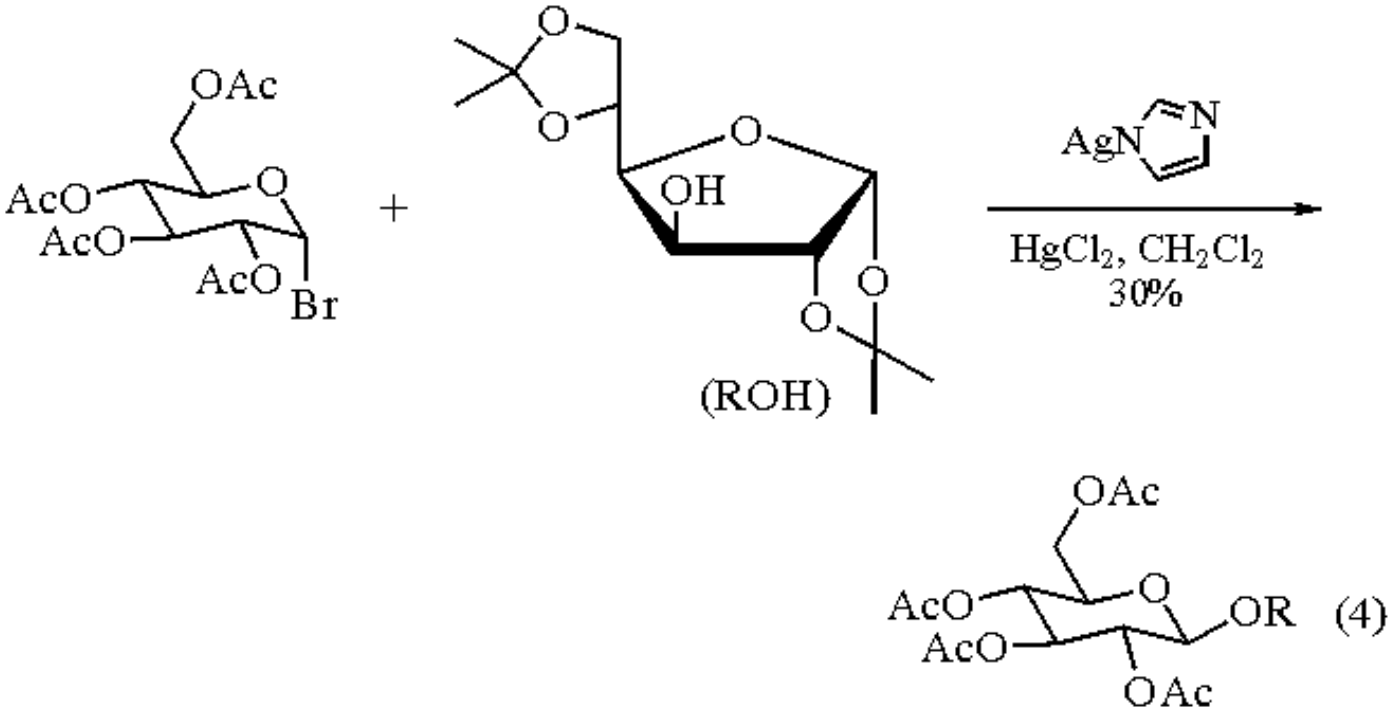

2-Iodo-α-pyranosyl Chlorides.

Treatment of 3,4,6-tri-*O*-acetyl-D-glucal with silver imidazolate and ***Iodine*** in the presence of $HgCl_2$ gives an almost quantitative yield of a mixture of 2-iodo-α-D-glucopyranosyl chloride and 2-iodo-β-D-mannopyranosyl chloride in a ratio of 5:1 (eq 5), which is an improvement over the existing method using ***Iodine Monochloride***.[4]

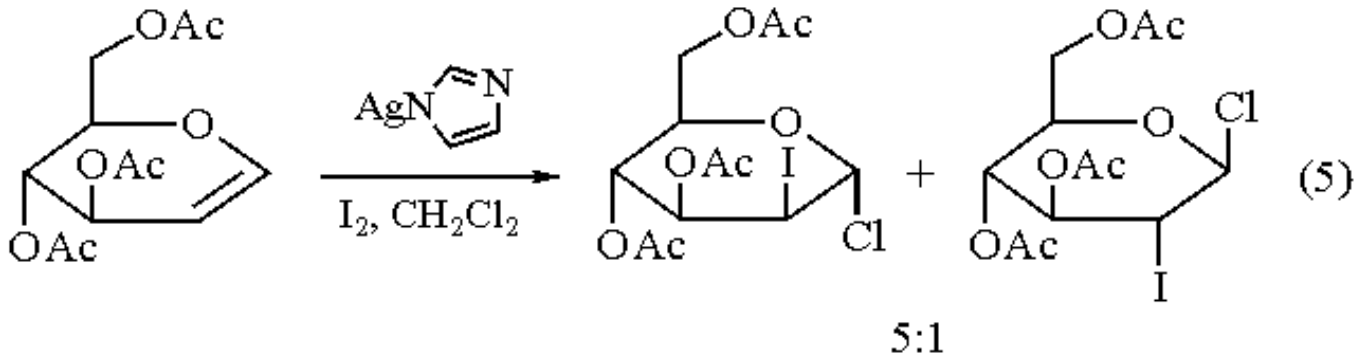

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Silver(I) Nitrate

$AgNO_3$

[7761-88-8] · $AgNO_3$ · Silver(I) Nitrate · (MW 169.88)

(mild oxidizing agent and Lewis acid used in a wide variety of chemical reactions)

Physical Data: mp 212 °C; *d* 4.352 g cm^{-3}.

Solubility: sol H_2O, MeCN, alcohol, acetonitrile, DMF.

Form Supplied in: white crystalline solid; widely available.

Handling, Storage, and Precautions: mild oxidizing agent; may be fatal if inhaled or swallowed.

Deprotection.

Silver nitrate is used as a deprotecting agent for a number of functional groups. Thus *S*-trityl ethers are readily cleaved ($AgNO_3$/***Pyridine***, 5 min, rt)[1a] to the thiol silver salts which are converted to the thiols on treatment with ***Hydrogen Sulfide***. The method has been applied to *S*-trityl ethers in nucleoside,[1a] peptide,[1b] and β-lactam[1c] chemistry, although it is not always successful.[2] Selective cleavage of an *S*,*S*-diaryl phosphorodithioate in the presence of an *O*-dimethoxytrityl group occurs using a large excess of $AgNO_3$ (eq 1).[3] Other deprotecting agents such as $NaIO_4$, H_2O_2, and NCS are unsuccessful in this process.[3]

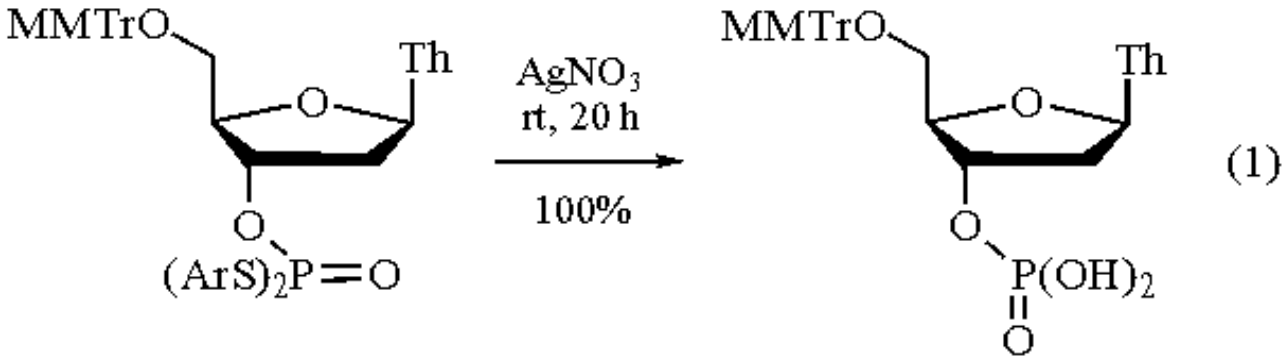

Thioacetals,[4] 1,3-dithianes,[5] and 1,3-oxathianes[6] are converted, on treatment with $AgNO_3$/***N-Chlorosuccinimide*** (or ***N-Bromosuccinimide***), to the corresponding ketones. The method is specially useful when sensitive 1,4-unsaturated diones are being liberated.[5b] Cyanuric acid can be used in place of NCS for the particularly difficult task of converting a diphenyl thioacetal to its ketone derivative.[7] Benzothiazoles are readily converted, via their 2-lithio derivatives, to a variety of intermediates.[8] Treatment of these derivatized benzothiazoles with ***Iodomethane*** followed by ***Sodium Borohydride*** gives the corresponding *N*-methylbenzothiazolines, which are readily cleaved with $AgNO_3$ in methanol to the corresponding aldehydes in high yields. This is a useful high yielding procedure for the preparation of α,β-unsaturated aldehydes.[8] Cleavage of *O*-methylethoxymethoxy ethers (OMEM ethers) in the presence of a dithiane is accomplished by converting the OMEM ether to the *O*-isopropylthiomethyl ether, which is then cleaved to the desired alcohol with $AgNO_3$ in the presence of ***2,6-Lutidine***.[9] $AgNO_3$ has also been used for the hydrolysis of enol thioethers,[10] tetrahydropyranylthio ethers,[11] *S*-*t*-butyl esters,[12] and thiobenzoates,[12] to the respective alcohols, for the conversion of dithiobenzoates to *S*-benzoates,[13] thioamides to amides,[14] thioureas to ureas,[15] and for the conversion of orthothioesters to orthoesters.[16]

Protection.

Reaction rates for the conversion of the primary OH groups of nucleosides to the protected *O*-trityl ethers with 4,4´,4´´-tris(4,5-dichlorophthalimido)trityl bromide are considerably enhanced by the addition of $AgNO_3$.[17] $AgNO_3$ is also used for the selective

preparation of primary *t*-butyldimethylsilyl ethers by the reaction of nucleosides with ***t-Butyldimethylchlorosilane*** in MeCN.[18] Yields in both reactions are high. $AgNO_3$ is an effective agent for the conversion of several glucopyranoses to their 1,2-orthoacetates[19] and as an agent for the formation of glycosides[20] (see also ***Silver(I) Nitrite***).

Ring Expansions, Contractions, and Rearrangements.

$AgNO_3$-promoted rearrangements occur in numerous instances; a few examples are given. Thus the 4-cyano-4,5-dihydroazepine in eq 2 gives the furo[2,3-*b*]pyridine on heating with an aqueous solution of $AgNO_3$.[21] Treatment of the *N*-chloroenolamine in eq 3 with a threefold excess of $AgNO_3$ gives the β-lactam; yields are about 50%, depending on the substituent used.[22] The 1,1´-bishomocubane in eq 4, on treatment with $AgNO_3$ in aqueous methanol, rearranges to the pentacycle in quantitative yield.[23]

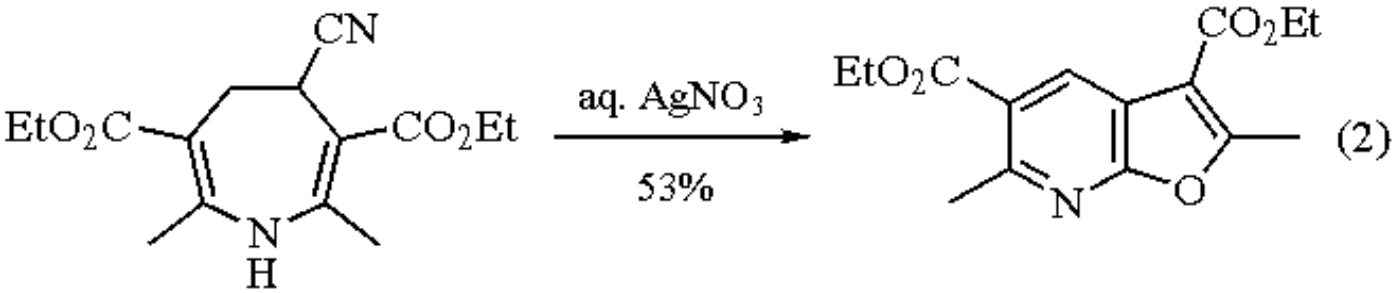

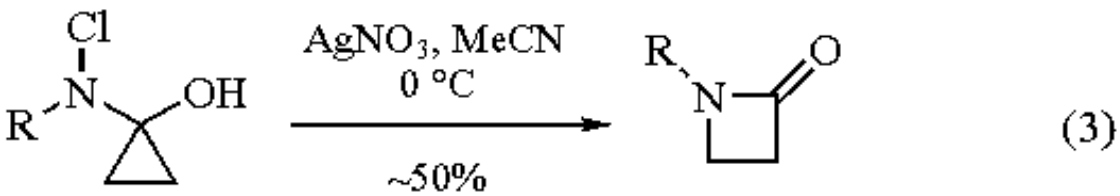

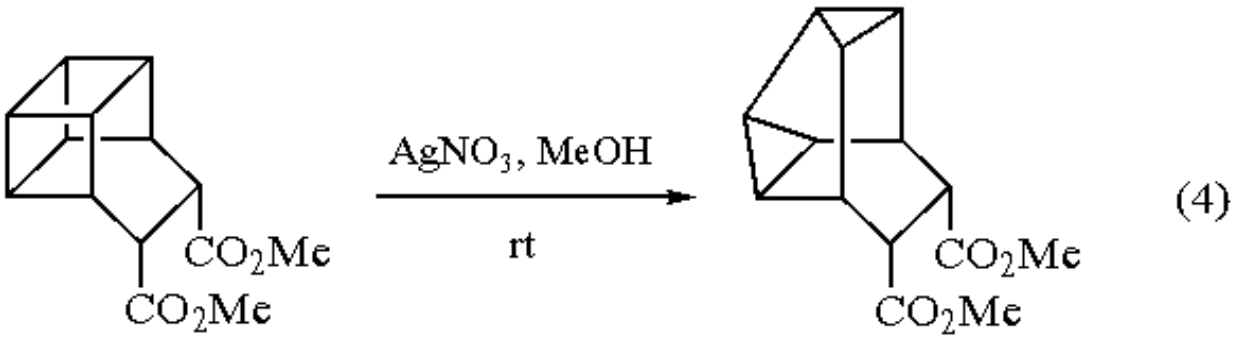

Dehalogenations.

$AgNO_3$ has been widely used for solvolysis with concomitant rearrangement of dihalocyclopropanes. Thus the trichlorocyclopropa[*c*]chromene in eq 5 gives the (dichloromethylene)chroman-4-one in 93% yield.[24] Many other examples are known. Dehydrobromination of the bromotetralone in eq 6 with $AgNO_3$ gives exclusively the endocyclic unsaturated ketone in 90% yield; other reagents for this reaction give mixtures of the exo- and endocyclic alkenes.[25]

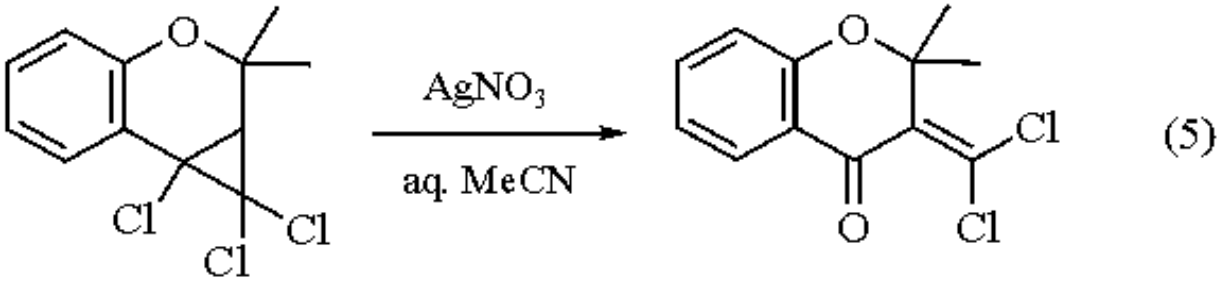

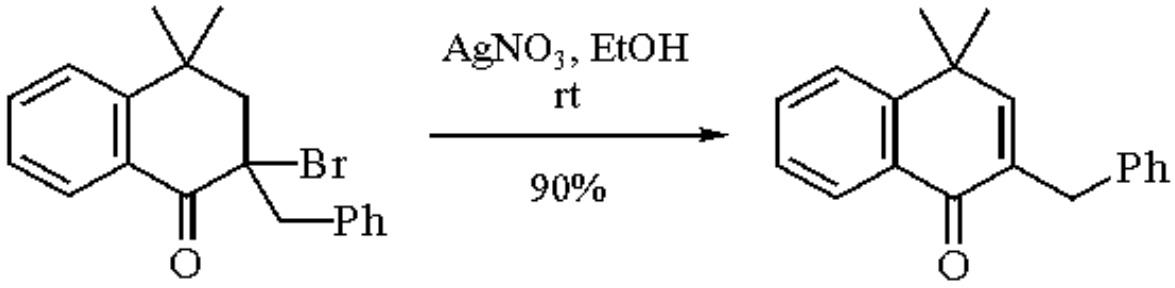

(6)

Solvolysis of arylmethyl halides with $AgNO_3$ in hot aqueous ethanol gives the corresponding alcohols,[26] whereas a similar reaction on alkyl bromides in MeCN is reported to be an excellent procedure for the preparation of pure nitrate esters.[27] Benzyl dibromides are converted to the corresponding aldehydes in high yields,[28] and α-bromo ketones give high yields (>80%) of the corresponding α-diketones on treatment with $AgNO_3$ in MeCN.[29]

Cycloadditions.

The electrophilic nature of $AgNO_3$ enables it to complex with alkynes and allenes, thus enabling intramolecular cycloadditions to proceed. For example, treatment of a series of phenolic keto-ynes (eq 7) with a catalytic amount of $AgNO_3$ in methanol promotes cycloaddition to the triple bond in high yield.[30] Similarly, α-hydroxyallenes are rapidly converted to 2,5-dihydropyrans on treatment with $AgNO_3/CaCO_3$ in aq acetone (eq 8).[31]

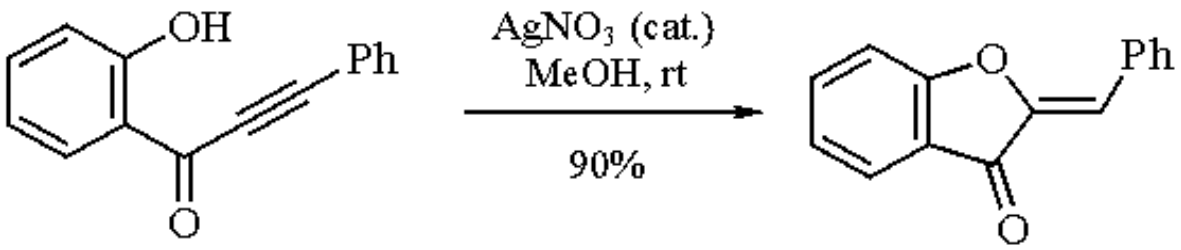

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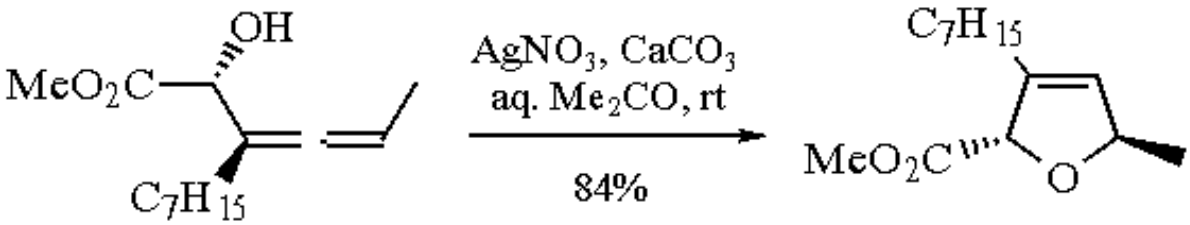

(8)

On extending the hydroxy alkyl chain from the allenic group by two or three carbon atoms, cyclization results in the formation of the corresponding α-vinyltetrahydrofuran[32] or α-vinyltetrahydropyran,[33] respectively, both in high yields. In a similar manner, treatment of α-, γ- and δ-aminoallenes with $AgNO_3$ in aqueous acetone gives the corresponding 2,3-dihydropyrroles,[34] α-vinylpyrrolidines,[35] and α-vinylpiperidines,[35] respectively, in good yields.

Oxidative Couplings.

Alkylboranes, formed on reaction of terminal alkenes with diborane, dimerize on treatment with an aqueous solution of $AgNO_3$/NaOH. Thus hexene gives a 66% yield of dodecane,[36] and the dienes 1,5-hexadiene and geranyl acetate are converted to cyclohexane (66%) and *trans-p*-menthane (85%).[37] Although the use of $AgNO_3$/NaOH for these coupling reactions is, to all accounts, equivalent to the use of ***Silver(I) Oxide***, oxidative cyclization is reported to be less successful when this latter reagent is used. Oxidative dimerization of the dianions of α,β-unsaturated carboxylic acids with $AgNO_3$/THF gives moderate yields of the dienedioic acids, but the use of ***Iodine*** for this coupling gives higher yields (40-80%).[38]

Coverage of the use of $AgNO_3$/NaOH for oxidation of alcohols, aldehydes, etc., has not been included in this section as this ostensively amounts to the use of ***Silver(I) Oxide***.

Related Reagents.

Zinc-Copper(II) Acetate-Silver Nitrate.

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Silver(I) Nitrite

$AgNO_2$

[7783-99-5] · $AgNO_2$ · Silver(I) Nitrite · (MW 153.88)

(preparation of aliphatic nitro compounds[2] and *N*-nitroso compounds;[8,9] aromatic nitration;[6,7] preparation of other reagents such as nitryl iodide,[10] phenylselenium nitrite,[14,15] thionyl chloride nitrite,[16] and palladium complexes[17,18])

Physical Data: mp 140 °C (dec); *d* 4.453 g cm^{-3}.

Solubility: sol water, acetonitrile, acetic acid, NH_4OH; insol alcohol.

Form Supplied in: pale yellow solid; widely available.

Introduction.

The main use of $AgNO_2$, particularly in the older literature, is in the Victor Meyer[1] reaction for the preparation of primary nitroalkanes from the corresponding primary bromo- or iodoalkanes (eq 1). Good conditions for this reaction have been established[2] and, provided the reaction temperatures are kept low, the amount of the nitrite ester can be kept to a minimum. Higher temperatures[3] shorten the reaction time, but lower yields are obtained. The reaction is best suited for alkyl halides with >3 carbon atoms, although, exceptionally, in a series of o-ethoxyalkyl bromides, the reaction was successful only for a four-carbon chain.[4] Branching on the bromoalkyl halide at the γ-carbon does not seriously affect the yield of nitro product, but branching on the β-carbon atom lowers the yield considerably.[2a] The reaction is generally unsuccessful for secondary and tertiary halides although, in an analogous reaction,[5] adamantyl hexafluoroantimonate gives 1-nitroadamantane (eq 2) on treatment with $AgNO_2$ using ***Arsenic(III) Fluoride*** as a suitable (sic) solvent. The corresponding reactions with trityl and *t*-butyl hexafluoroantimonates are unsuccessful.

$$RCH_2X \xrightarrow[\text{0-25 °C, 48 h}]{AgNO_2\text{, ether}} \underset{80\%}{RCH_2NO_2} + \underset{11\text{-}13\%}{RCH_2ONO} \qquad (1)$$

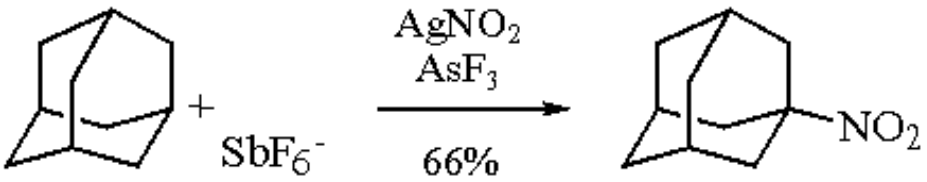

(2)

Aromatic Nitration.

Nitration of azupyrene with $AgNO_2$ gives 4-nitroazupyrene (eq 3).[6] In a similar reaction, azulene is converted to 1-nitroazulene (77%).[6] Direct substitution of 1,3-dibromoazulene results in the displacement of only one bromine atom to give 1-nitro-3-bromoazulene (eq 4).[7]

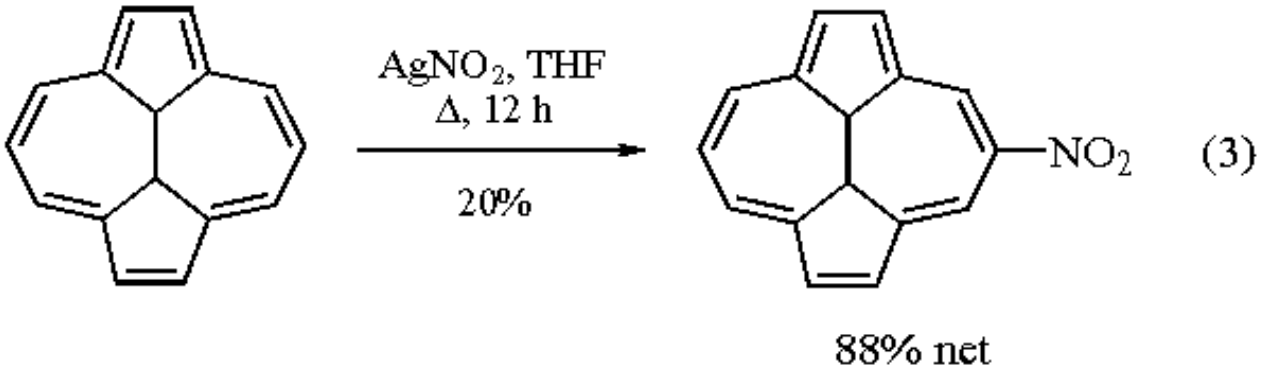

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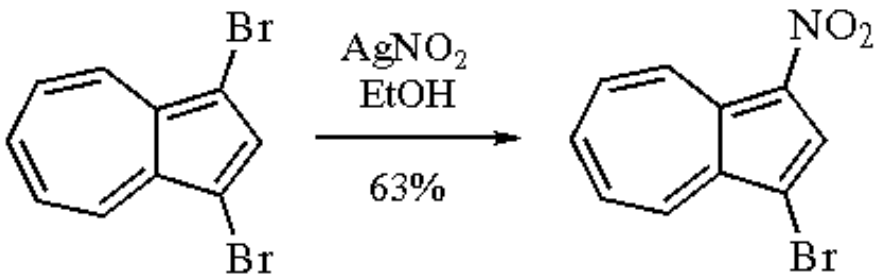

(4)

N-Nitrosation.

$AgNO_2$ is a mild reagent for *N*-demethylation of *N*,*N*-dimethyl amines, resulting in *N*-nitroso-*N*-methyl amines in moderate yields.[8] The reagent is also used for the conversion of imidoyl or sulfonimidoyl chlorides to *N*-nitroso amides (eq 5).[9]

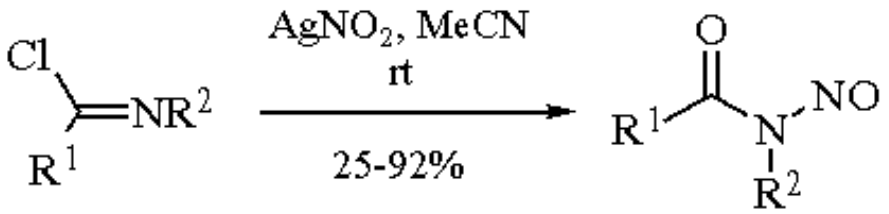

(5)

$AgNO_2$ as an Adjunct for the Preparation of Other Reagents.

Nitryl Iodide.

This pseudohalogen, prepared by the reaction of $AgNO_2$ with ***Iodine***, adds stereo- and regiospecifically to alkenes to give 1-nitro-2-iodo compounds which, on loss of HI, afford nitroalkenes (eq 6).[10]

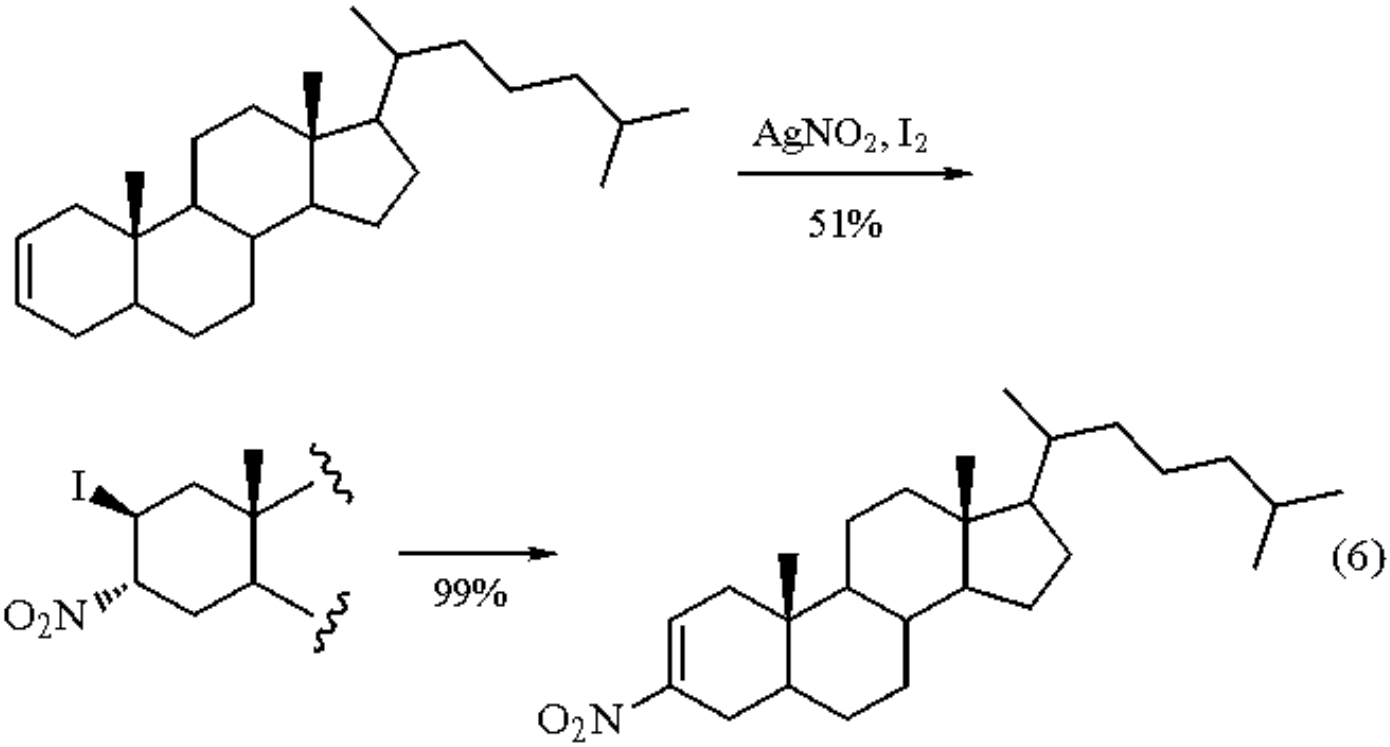

In a similar manner, β-substituted styrenes give *trans*-β-nitrostyrenes (eq 7).[11] Since ring nitration does not occur with this reagent, it offers an advantage over the use of ***Mercury(II) Chloride***/***Sodium Nitrite***. A reverse addition to alkenes has also been reported.[12]

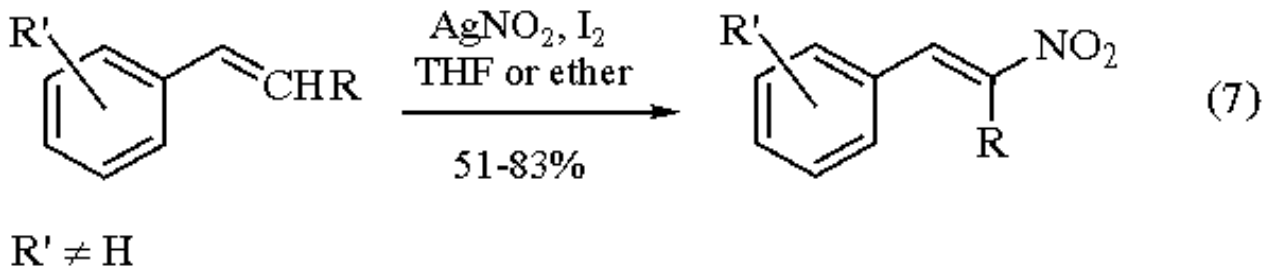

The ambident nature of nitryl iodide is also demonstrated in its use as a mild agent for the iodination of alkylbenzenes (eq 8).[13]

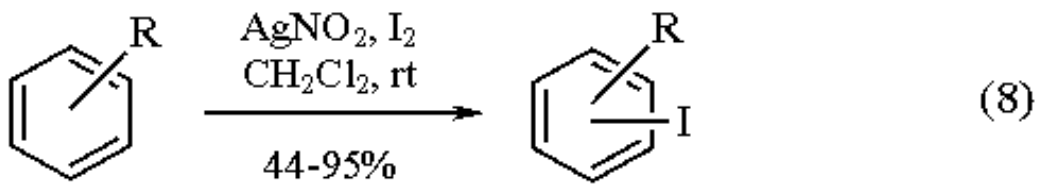

Phenylselenium Nitrite.

This reagent, prepared by the reaction of ***Benzeneselenenyl Chloride*** and $AgNO_2$, is useful for the nitroselenation of alkenes[14] (eq 9) or conjugated dienes (eq 10).[15] Both reactions are catalyzed by $HgCl_2$ which also inhibits nitrite formation. Oxidative deselenation with ***Hydrogen Peroxide*** gives nitroalkenes in high yields.

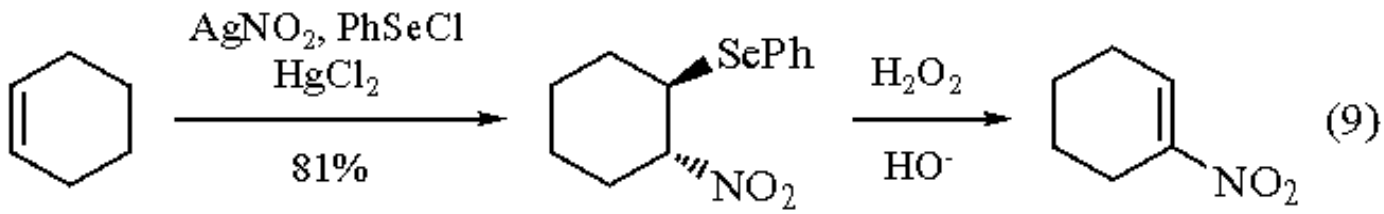

This process has the advantage over nitromercuration in that reactions can be carried out in nonaqueous solvents, thus opening up the procedure to a wider range of alkenes. The reaction with dienes is particularly useful since the reactive 2-nitro-1,3-dienes, formed by

oxidative deselenation or by treatment of the nitro selenide with ***4-Dimethylaminopyridine***,[15b] can be trapped as the epoxides or reacted in situ with, for example, ***Ethyl Vinyl Ether*** to give, after acidification of the intermediate nitronate, unsaturated 1,4-diketones (eq 10).

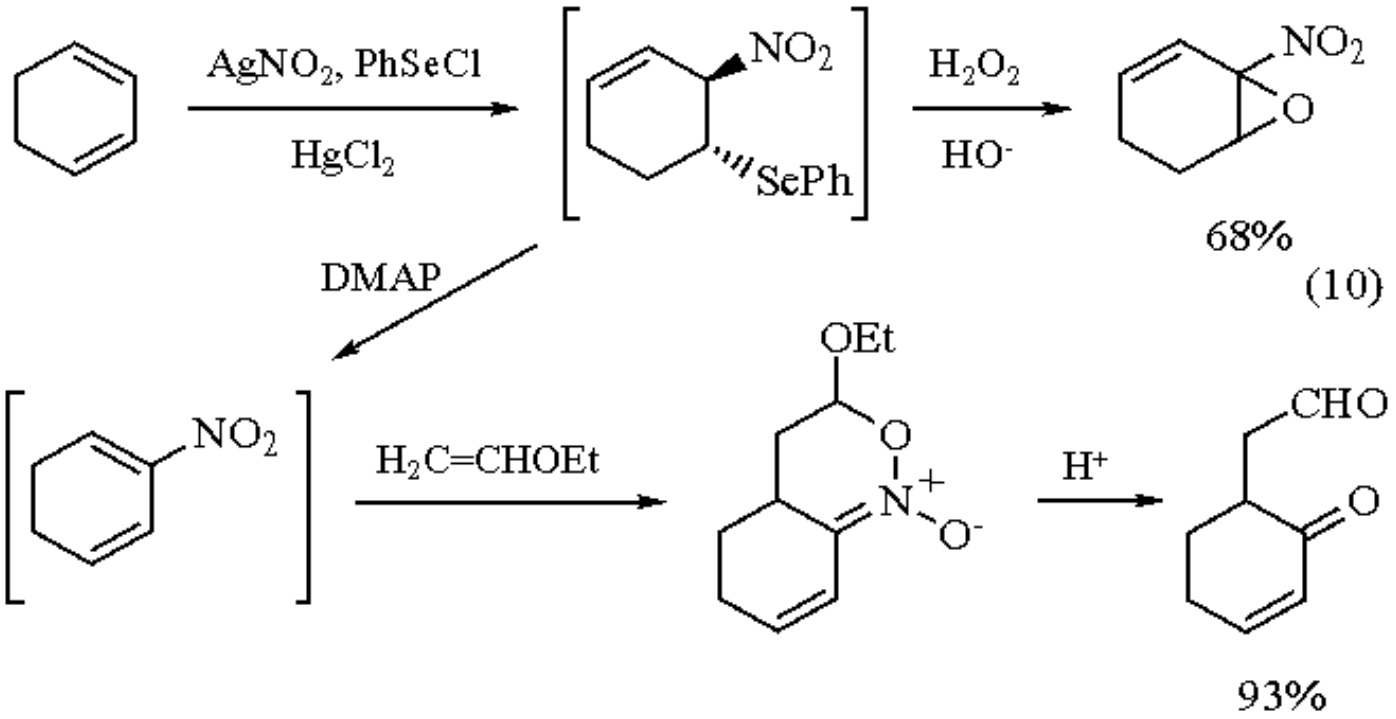

Thionyl Chloride Nitrite.

This compound, prepared by the reaction of $AgNO_2$ with ***Thionyl Chloride*** (1:1), is a mild and selective agent for the preparation of nitrite esters (eq 11).[16]

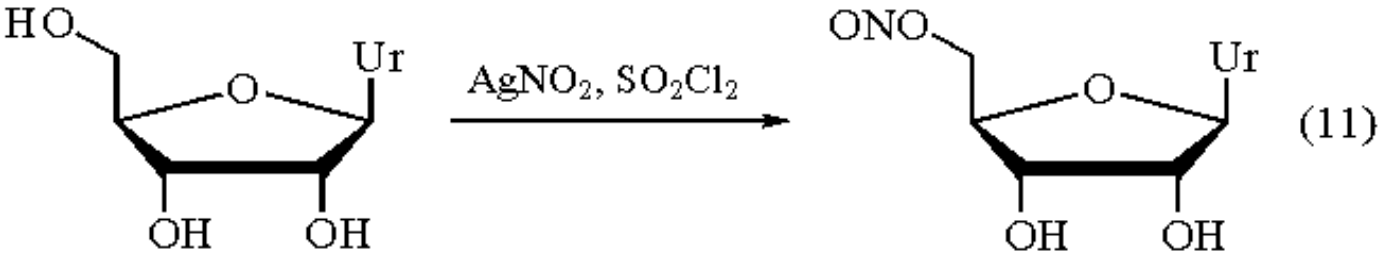

Palladium complexes.

$AgNO_2$ has been used in the preparation of Pd complexes for the conversion of terminal alkenes to nitroalkenes[17] or as a catalyst[18] for the oxidation of terminal alkenes to methyl ketones.

Related Reagents.

Mercury(II) Chloride-Silver(I) Nitrite.

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Duncan R. Rae

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Silver(I) Oxide

Ag_2O

[20667-12-3] · Ag_2O · Silver(I) Oxide · (MW 231.74)

(oxidizing reagent for conversion of hydroquinones to quinones,[1] alkylphenols to quinone methides,[5] and aldehydes to acids;[7] oxidative coupling reactions;[12,13] a Lewis acid with halides[18,20] and thioethers;[24] Wolff rearrangement[26])

Physical Data: dec at about 200 °C; *d* 7.22 g cm^{-3}.

Solubility: practically insol alcohol; sol in 40 000 parts H_2O; sol dilute nitric acid, ammonia; moderately sol NaOH.

Form Supplied in: brownish-black, heavy, odorless powder; widely available.

Handling, Storage, and Precautions: protect from light. Reduced by hydrogen, carbon monoxide, and most metals. Skin contact with this toxic reagent should be carefully avoided.

Hydroquinone Oxidation.

This reagent is a powerful oxidizing reagent for the conversion of hydroquinones to the corresponding quinones. 1,4-Hydroquinones are generally converted to quinones by treatment with Ag_2O (eq 1).[1] Other reagents (e.g. ***Cerium(IV) Ammonium Nitrate***) are less expensive and easier to handle. However, Ag_2O in nonhydroxylic solvents can be used to produce electron-deficient quinones which are unstable to nucleophiles. For example, Ag_2O oxidation of nitro hydroquinones affords nitro quinones (eq 2).[2]

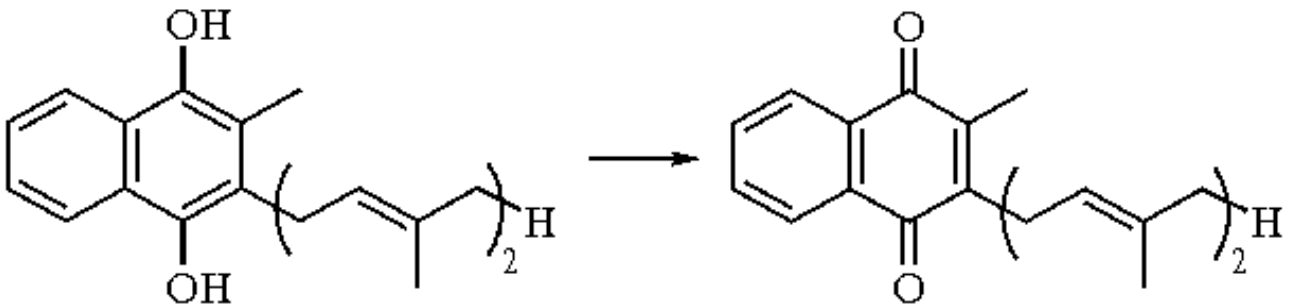

(1)

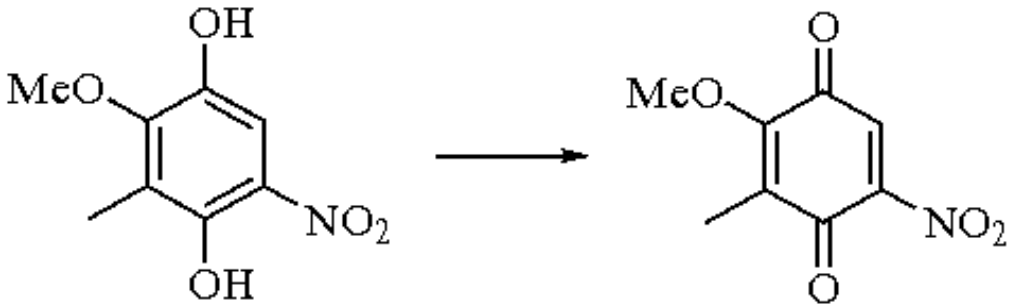

(2)

A one-pot technique has been developed to oxidize 1,4-hydroquinones and utilize the quinone products as dienophiles in Diels-Alder reactions (eq 3).[3] Tetrahydrophenanthrene-9,10-quinones have also been prepared by a one-pot double Diels-Alder reaction (eq 4).[4]

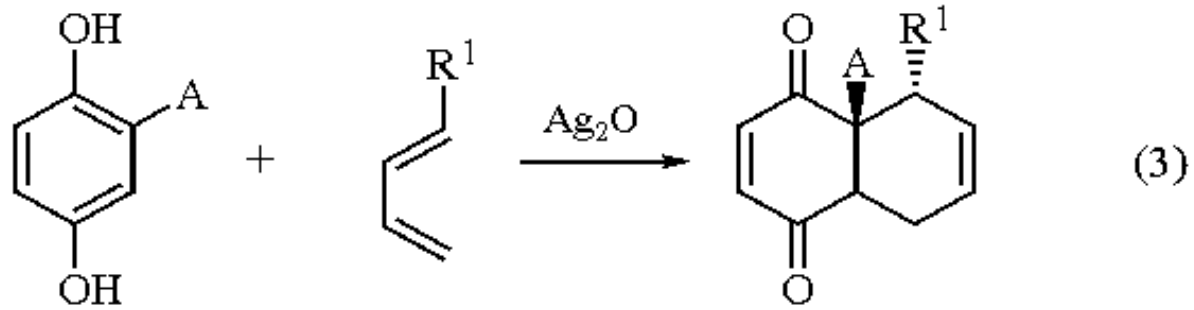

A = CO_2Me or CHO
R^1 = OTMS, CH_2CO_2Et

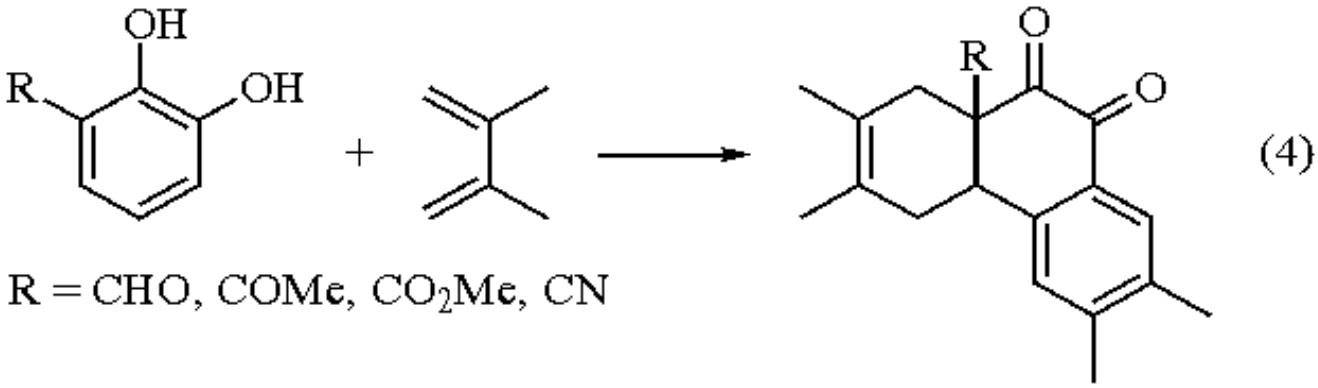

R = CHO, COMe, CO_2Me, CN

Alkylphenol Oxidation.

1,4-Quinone methides can be obtained by the reaction of *p*-alkylphenols with Ag_2O. These reactive compounds may undergo subsequent transformations, for example, a Lewis acid promoted cyclization (eq 5).[5] 1,2-Quinone methides can also be formed by Ag_2O oxidation of appropriately substituted phenols (eqs 6 and 7).[6]

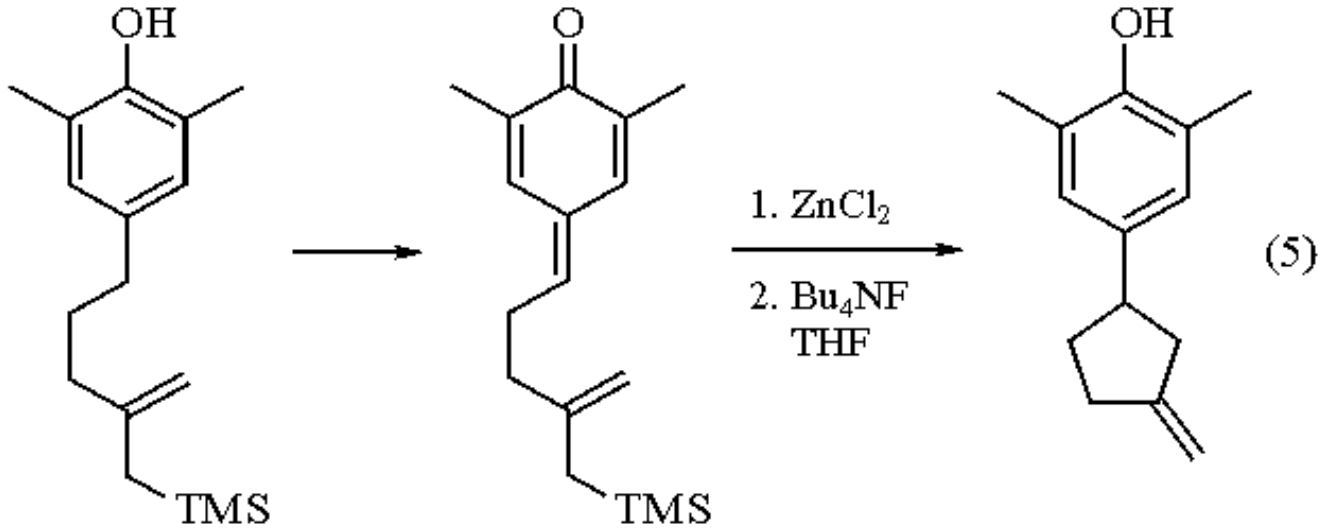

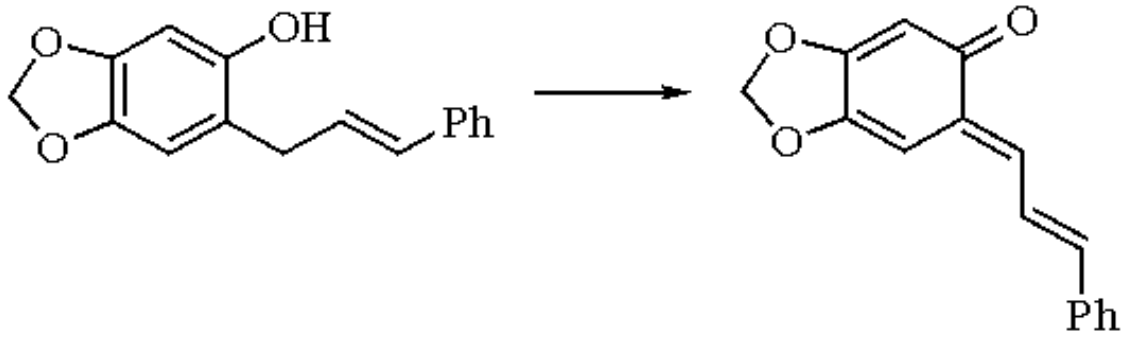

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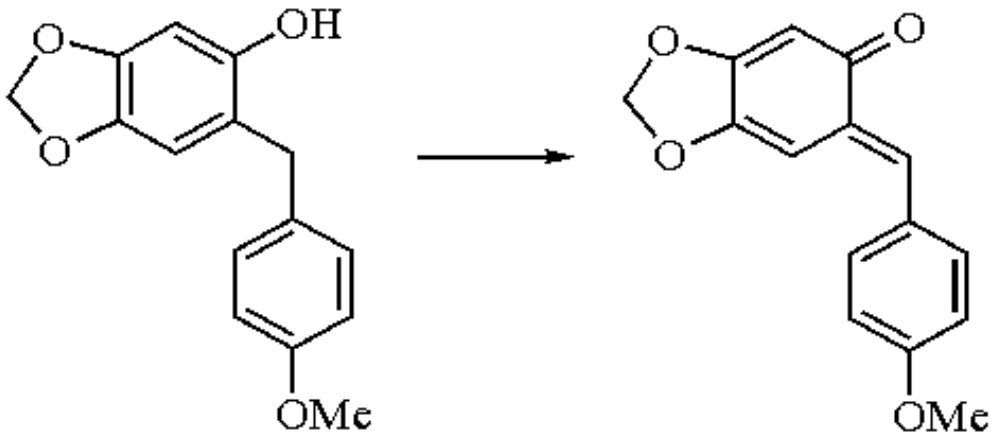

(7)

Other Oxidation Reactions.

Ag_2O oxidizes aldehydes to acids,[7] and conjugated keto aldehydes to conjugated keto acids.[8] For example, Ag_2O was used to selectively oxidize one of two formyl substituents of an intermediate in the total synthesis of inhibitor K-76 (eq 8).[9] The unreactive formyl substituent is conjugated with the hydroxyl and alkoxy substituents.

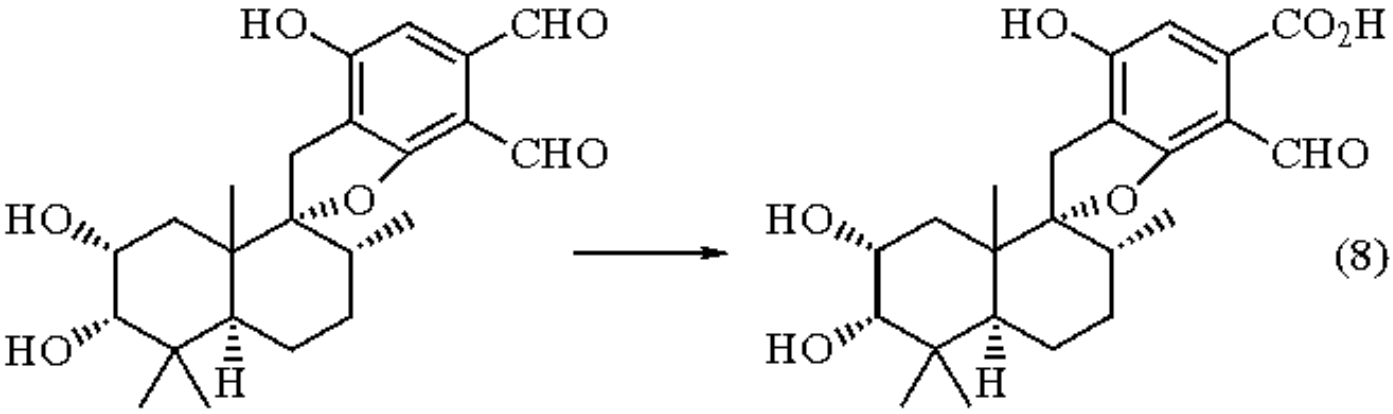

(8)

Oxidative Coupling Reactions.

Radicals produced by Ag_2O oxidation can undergo coupling reactions. For example, 2-(vinyloxy)phenols undergo Ag_2O oxidation-induced coupling.[10] Acylacetates and monosubstituted malonates are oxidatively dimerized in the presence of Ag_2O and DMSO (eq 9).[11]

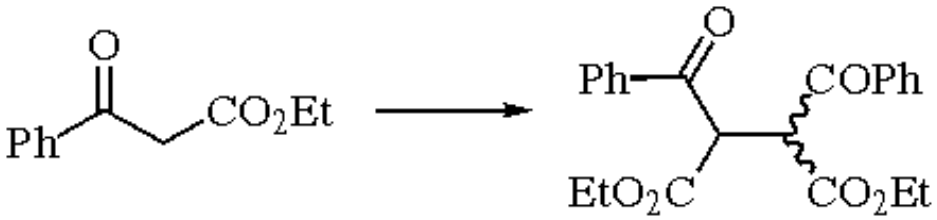

(9)

Radical coupling followed by nucleophilic attack of hydroxyl on a quinone methide intermediate is postulated as the mechanism of the

key step in the syntheses of silybin and eusiderin (eq 10).[12] 1,4-Diketones are produced in the reaction of silyl enol ethers with Ag_2O in DMSO (eq 11).[13]

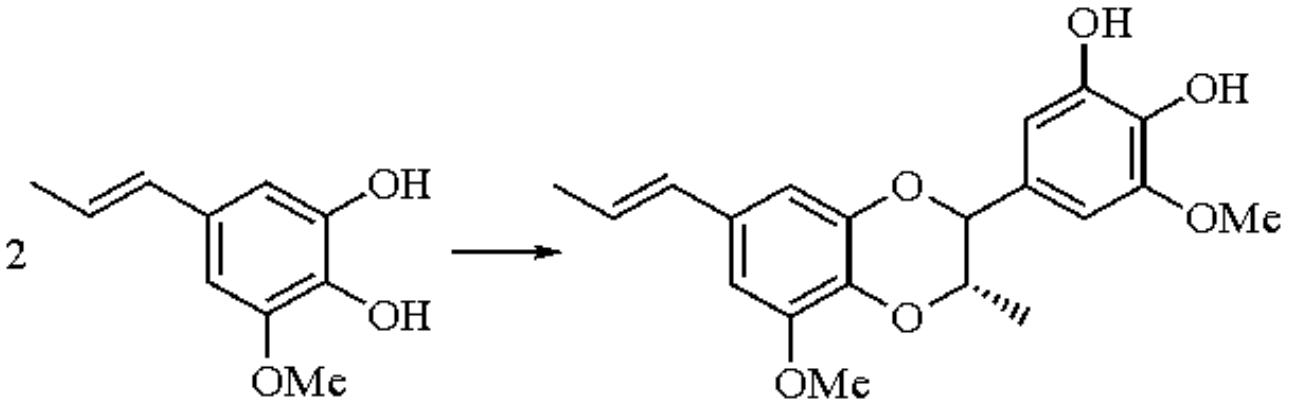

(10)

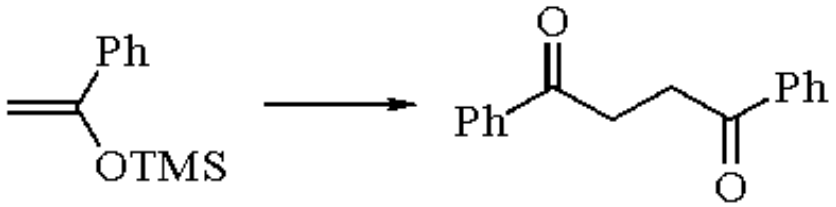

(11)

Lewis acid with Halides.

Ag_2O can activate halide as a leaving group by coordination. Methylation of carbohydrates[14] and 5-benzylidenebarbituric acid[15] have been carried out with Ag_2O and ***Iodomethane*** in DMF. Triphenyltin trifluoroacetate was obtained from the reaction of triphenyltin iodide and trifluoroacetic acid in the presence of silver oxide.[16] Ag_2O converts *trans*-halohydrins to epoxides (eq 12)[17] or rearranged products (eq 13)[18]. It is reported that the reaction is nonstereoselective, and that *trans*-epoxides are the major products when *cis*-alkenes are the reactants.[19]

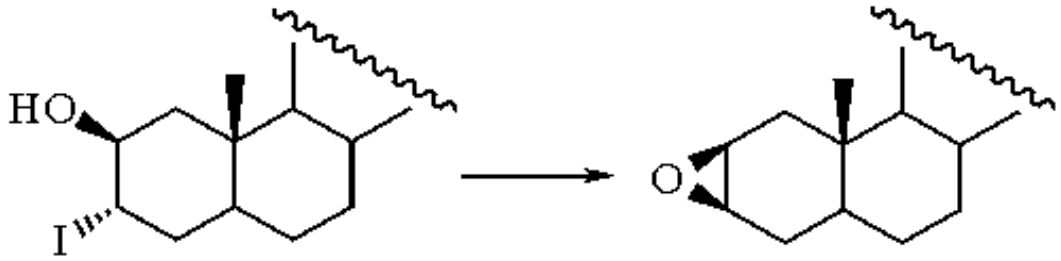

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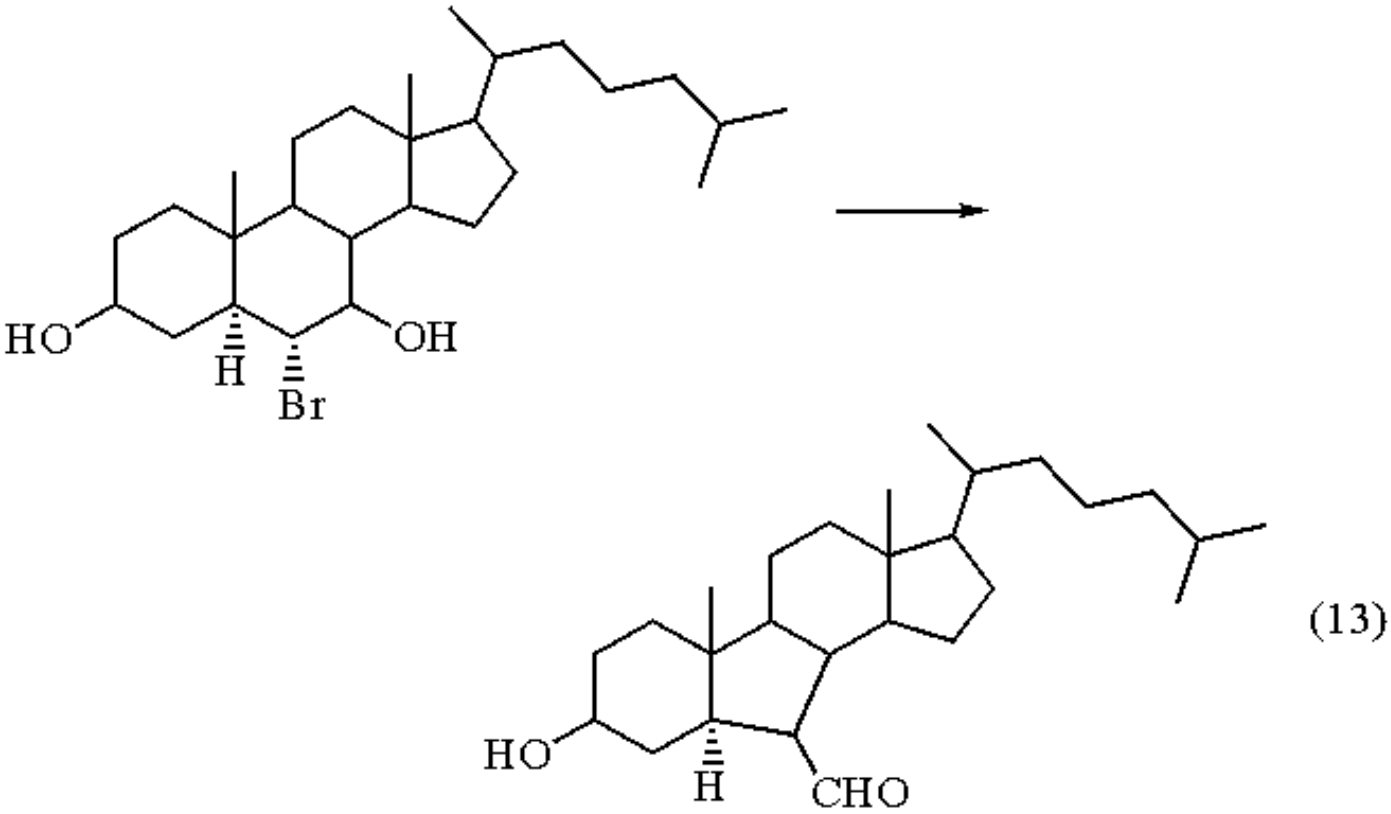

(13)

2-Arylpropionaldehydes are produced from 1-aryl-1-propene by oxidative rearrangement with ***Iodine*** and Ag_2O in dioxane-H_2O (eq 14).[20] The mechanism may involve the 1,2-shift of the aryl group through a bridged phenonium ion in the iodohydrin intermediate.

(14)

In the total synthesis of mycophenolic acid, electrophilic substitution was promoted by Ag_2O (eq 15).[21] α,β-Unsaturated nitriles are formed from the corresponding γ-bromo-β-oxo nitriles with Ag_2O (eq 16).[22] Arylsulfenylation and arylselenenylation at the 5-position of uracils are promoted by Ag_2O (eq 17).[23]

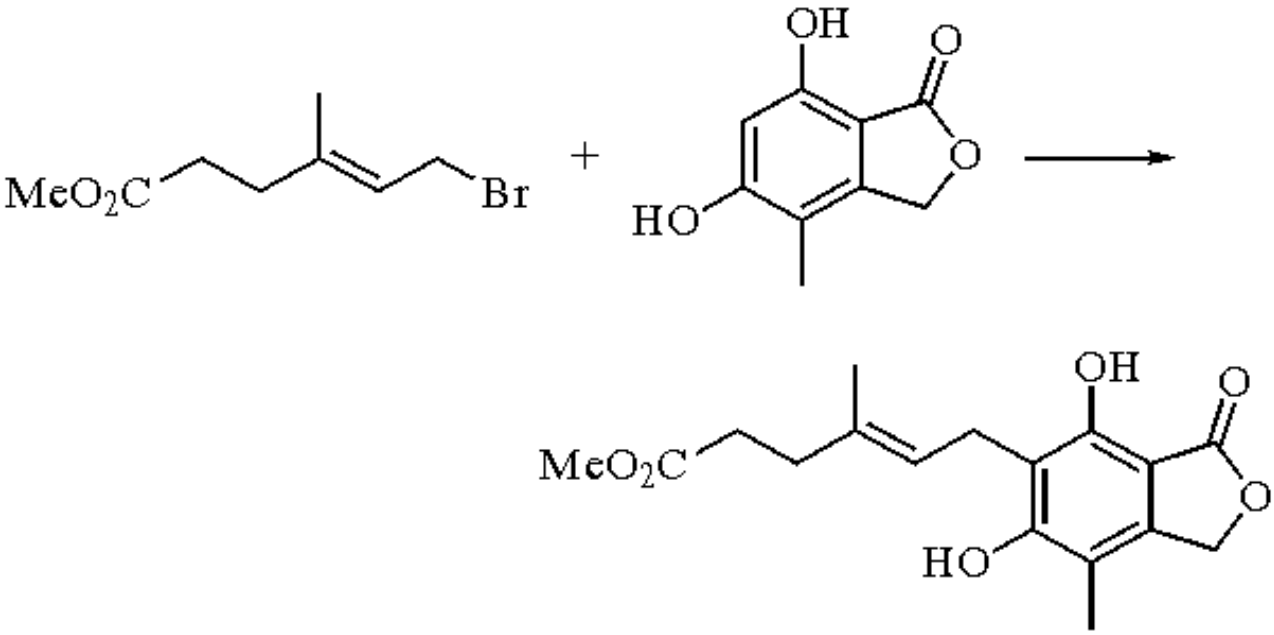

(15)

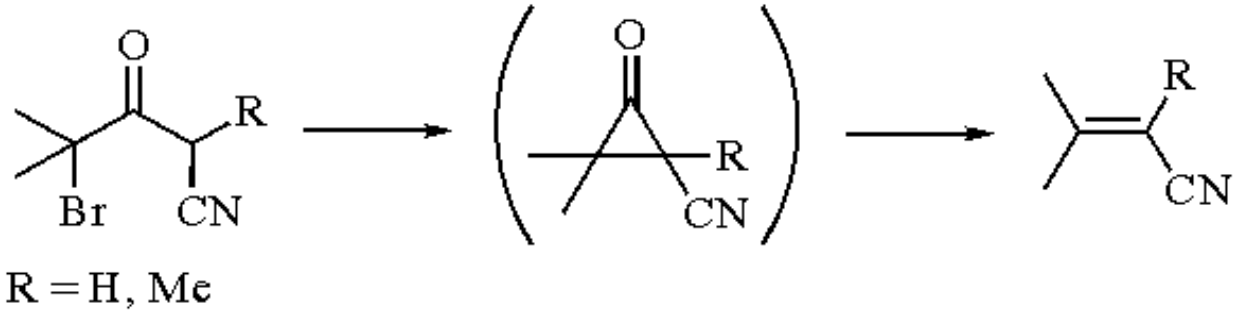

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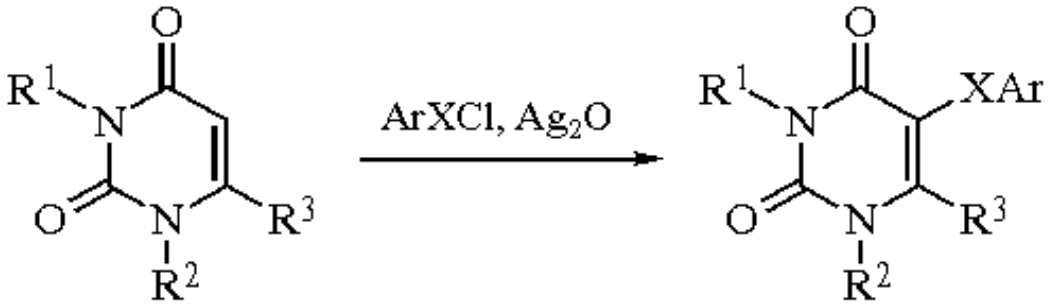

(17)

$R^1 = H, Me; R^2 = Me$, acyclic chain, ribose; $R^3 = H, Me, N{=}PPh_3$
$X = S, Se$

Lewis Acid with Thioethers.

Ag_2O has been applied to the 1,2-cleavage of penicillins in a strong nonnucleophilic base, such as ***1,5-Diazabicyclo[4.3.0]non-5-ene***,[24] and to the hydrolysis of thioacetals.[25]

Wolff Rearrangement.

The Wolff rearrangement of diazo ketones is promoted by Ag_2O (eq 18).[26]

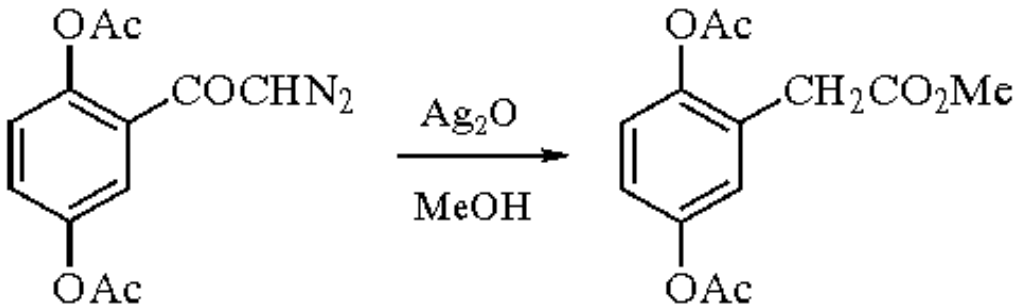

(18)

Related Reagents.

Bromine-Silver(I) Oxide.

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Silver(II) Oxide

AgO

[1301-96-8] · AgO · Silver(II) Oxide · (MW 123.87)

(oxidizing reagent for conversion of hydroquinone ethers[1] and alkoxy anilines[5] to quinones, of alcohols to aldehydes or ketones,[11] of allylic alcohols to conjugated acids,[12] of aldehydes to acids, of amines to azo compounds, and of amino acids to aldehydes;[13] radical coupling reactions;[8,9] utilized in oxidative decarboxylation of carboxylic acids[10])

Physical Data: dec above 100 °C; *d* 7.483 g cm^{-3}.

Solubility: insol H_2O; sol alkali; sol NH_4OH (with decomposition and evolution of N_2).

Form Supplied in: charcoal-gray powder; widely available.

Handling, Storage, and Precautions: protect from light. Highly irritating to skin, eyes, mucous membranes, and respiratory tract. Avoid contact with skin, organic matter, strong ammonia, and alkali.

Oxidation of Hydroquinone Ethers and Alkoxy Anilines.

This reagent effects the oxidative demethylation of hydroquinone ethers to afford *para*-quinones in acidic media (eq 1).[1] A mechanism has been proposed in which oxidative hydration takes place at the aromatic carbon.

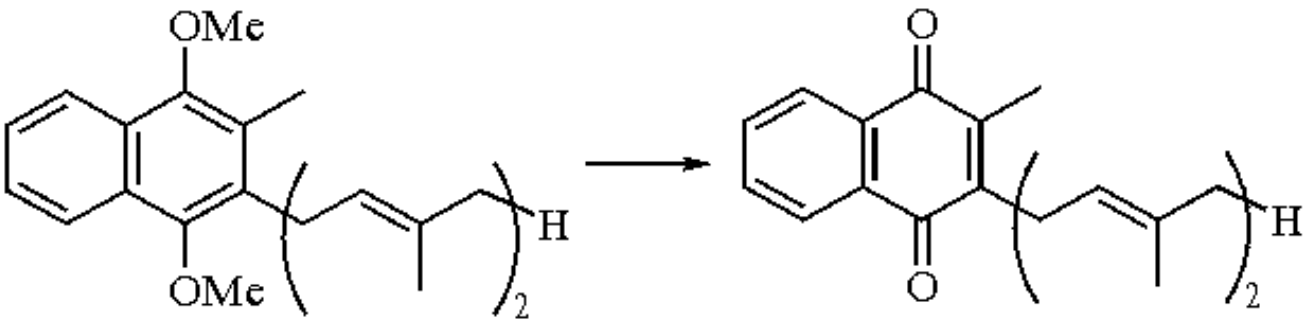

(1)

AgO in dioxane-nitric acid solution also oxidizes hydroquinone mono- and diesters to the corresponding quinones (eq 2).[2] The order of reaction is 4-acetoxyphenols > hydroquinone dimethyl ethers > hydroquinone diacetates.[2]

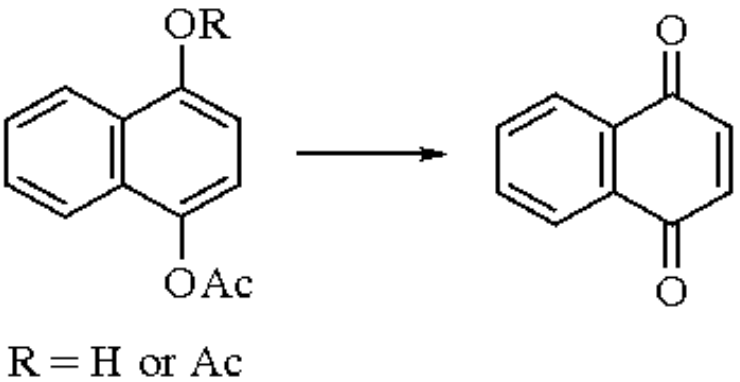

(2)

AgO is effective in oxidizing electron-deficient 1,4,5-trimethoxy-9,10-anthraquinone to the corresponding diquinone, an intermediate in anthracyclinone synthesis (eq 3).[3] This bifunctional dienophile undergoes the Diels-Alder reaction at the internal double bond with

electron-rich dienes (e.g. 2-ethoxybutadiene), and at the external double bond with slightly electron-poor or unsubstituted dienes (e.g. 1,3-butadiene and 2-acetoxybutadiene).[4]

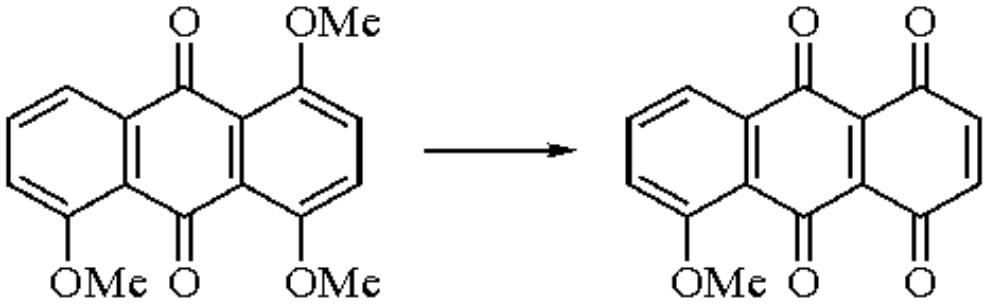

(3)

In the presence of AgO in aqueous nitric acid, *p*-methoxyanilines are oxidized with hydrolysis to quinones (eq 4).[5]

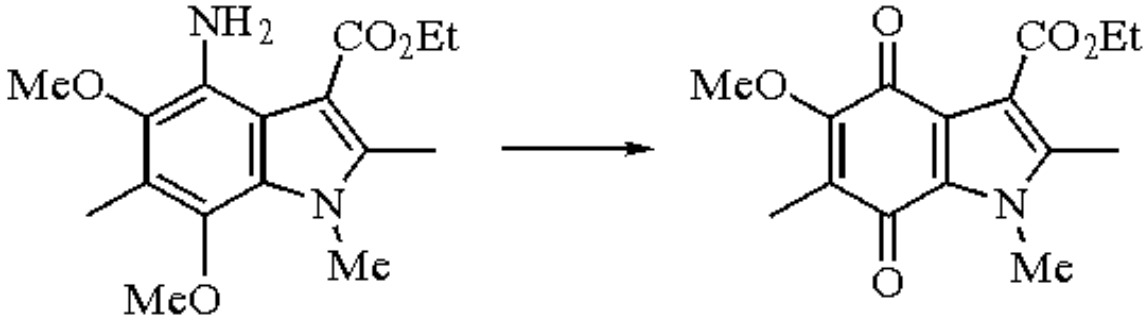

(4)

Tautomerization of a tetracyclic keto quinone obtained from AgO oxidation affords an aromatized anthracycline intermediate (eq 5).[6] The crude product subsequently undergoes tautomerization at rt in acetone with a few drops of concd. HCl.

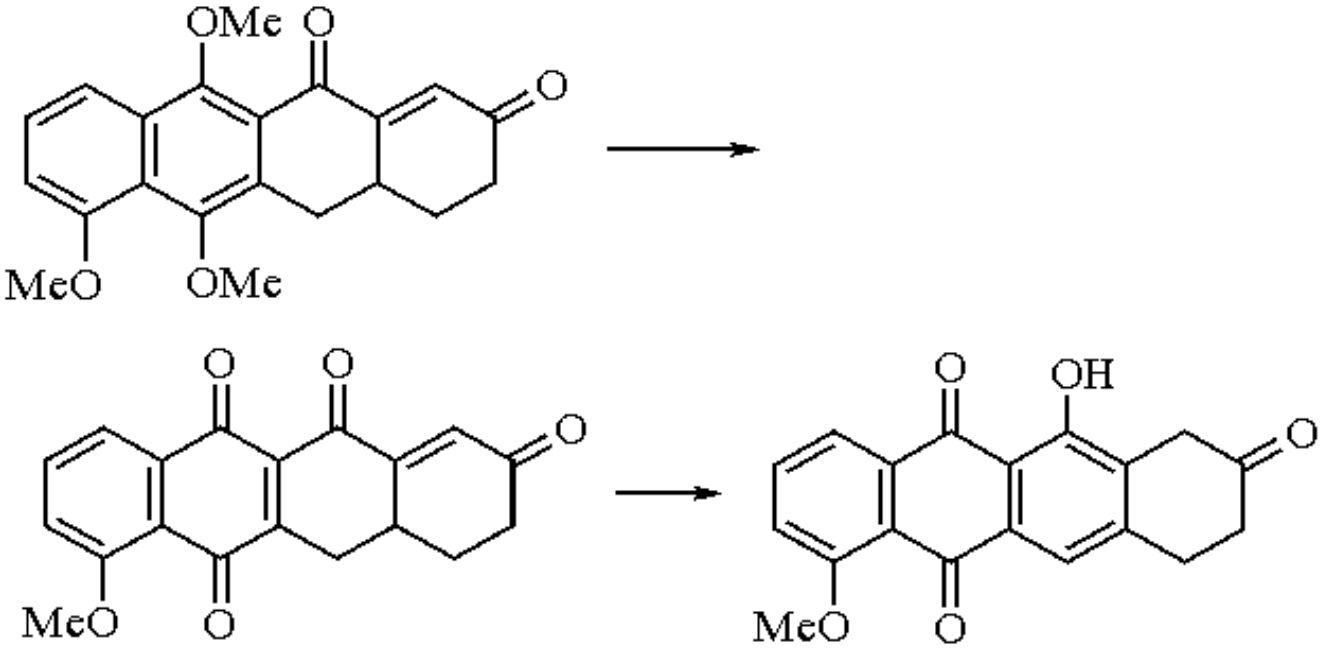

(5)

The trimethoxyphenyl lactam derivatives of hydroquinone methyl ethers are oxidized by AgO in an acidic milieu to give the lactam-substituted quinones (eq 6).[7]

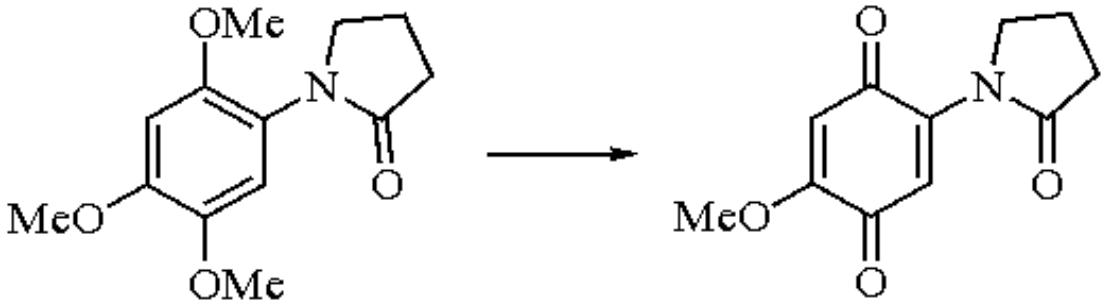

(6)

Radical Coupling Reactions.

The addition of acetone to terminal alkenes is accomplished by the action of AgO (eq 7).[8] 2-Alkanones are formed in 73-83% yield. Internal alkenes are less reactive. A radical mechanism is proposed for this transformation in which AgO acts as a heterogeneous initiator for the hydrogen atom abstraction from acetone to generate an acetonyl radical; this is followed by the addition of this radical to the alkene.

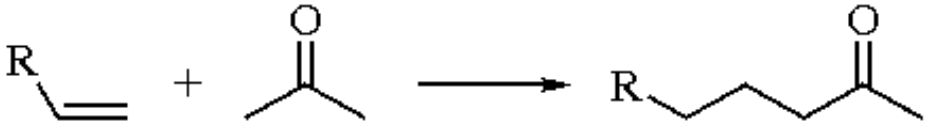

(7)

R = H, alkyl

The oxidative dimerization of 2-(vinyloxy) phenols by AgO under anhydrous conditions proceeds with rearrangement. A [3,3]-sigmatropic process involving an intermediate cyclohexadienol radical has been proposed (eq 8).[9]

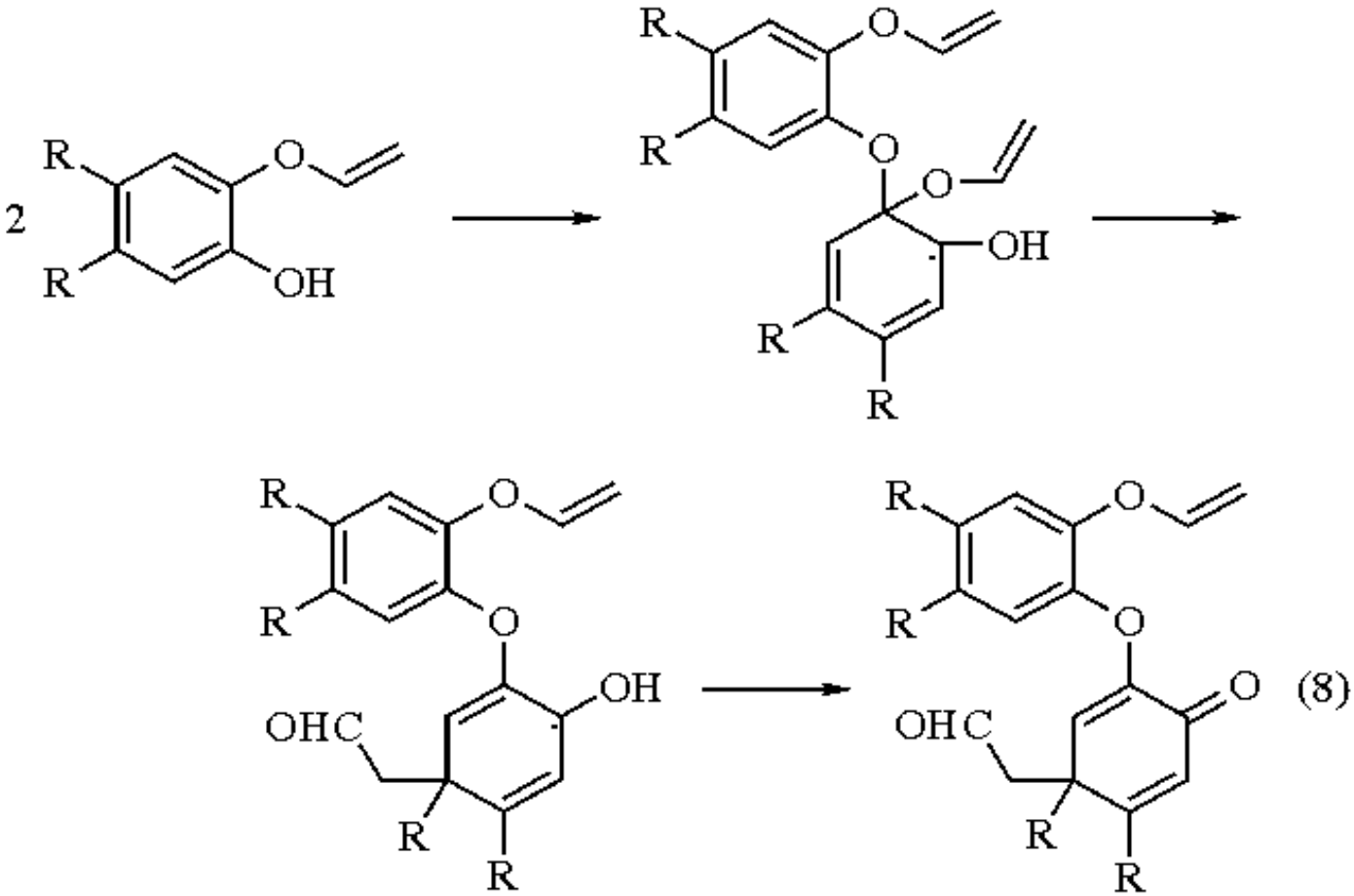

(8)

R = OMe or 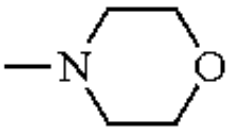

Other Oxidation Reactions.

AgO has been utilized in the oxidative decarboxylation of carboxylic acids such as pivalic acid, isobutyric acid, and *n*-butyric acid.[10] The reaction proceeds significantly faster when acetonitrile is utilized as a cosolvent. AgO oxidizes primary alcohols to aldehydes, secondary alcohols to ketones,[11] allylic alcohols to conjugated acids,[12] aromatic hydrocarbons to aromatic aldehydes and ketones, α-amino acids and α-amino esters to aldehydes (with decarboxylation), aldehydes to acids,[13] and amines, aniline, *p*-toluidine, and *N*,*N*-dimethyl-*p*-phenylenediamine to the corresponding azo derivatives.[14]

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Silver(I) Perchlorate[1]

$AgClO_4$

[7783-93-9] · $AgClO_4$ · Silver(I) Perchlorate · (MW 207.32)

(cyclization, dehydration, glycosylation, rearrangement of strained systems, solvolysis of halides)

Physical Data: mp 486 °C (dec); *d* 2.806 g cm^{-3}.[2]

Solubility: sol aniline, benzene, chlorobenzene, ethanol, glycerol, nitrobenzene, nitromethane, pyridine, toluene, water.[2,3]

Form Supplied in: white crystalline anhydride; white crystalline monohydrate *[14242-05-8]*.

Purification: dissolve 1g of the monohydrate per 6mL of benzene and heat at reflux under Dean-Stark conditions until the water is removed. Allow to cool and dilute with 4 mL of pentane per gram of the perchlorate. Filter the precipitate and place it in a desiccator containing P_2O_5 under high vacuum (1 mmHg) for 24 h.[4]

Handling, Storage, and Precautions: the anhydrous crystal readily forms the monohydrate, which is stable up to 43 °C and therefore should be stored in a desiccator. The salt is irritating to the skin and mucous membranes, corrosive, shock sensitive, and can be explosive in the presence of organic compounds.[3,4]

Cyclization Reactions.

The thiophilicity of silver perchlorate has been exploited in two types of cyclization processes. Nicolaou and co-workers[5] have developed a thioacetal cyclization strategy for oxocene synthesis that employs a silver perchlorate-sodium bicarbonate system to effect the transformation (eq 1). This protocol shows a marked increase in efficiency over other methods of oxocene construction. Similar tactics have been applied to the macrolide ring closure in eq 2 by Nimitz and Wollenberg,[6] and to the synthesis of the BCD ring framework of brevetoxin A developed by Nicolaou and co-workers.[7]

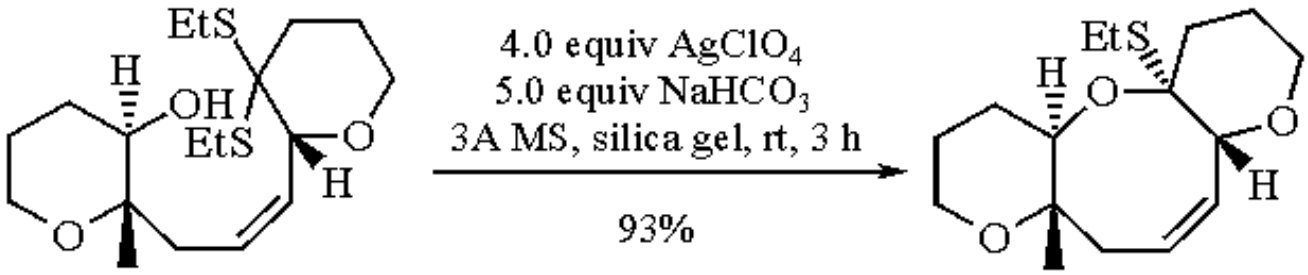

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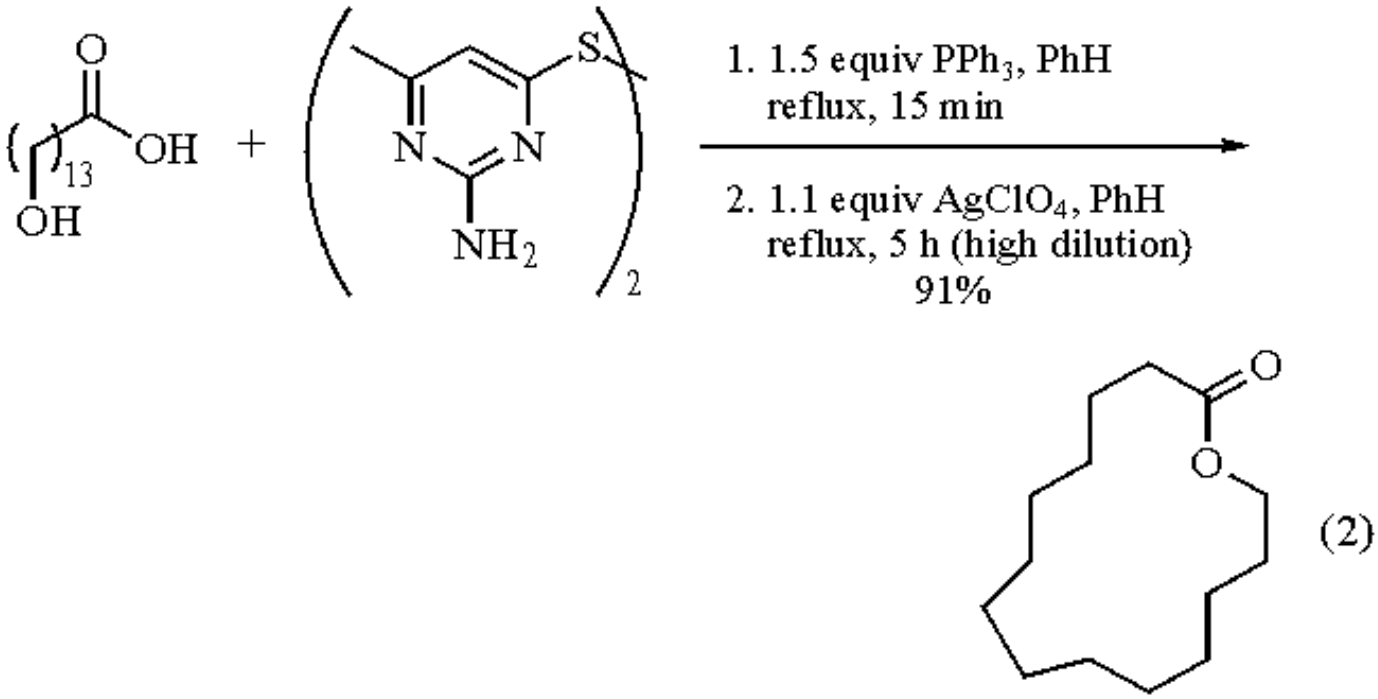

Dehydration.

Various secondary and tertiary alcohols can be efficiently dehydrated to their corresponding alkenes by the action of silver perchlorate in refluxing benzene,[8] as a milder alternative to treatment with strong acid. It has also been demonstrated that α-hydroxy thioacetals[9] (eq 3) and α-hydroxy ketones (eq 4)[10] are easily dehydrated to cyclopentenones by this reagent in the presence of water and under anhydrous conditions, respectively. In the investigation of α-hydroxy thioacetals, silver perchlorate was demonstrated to be a very potent reagent for the cleavage of thioacetals to ketones.

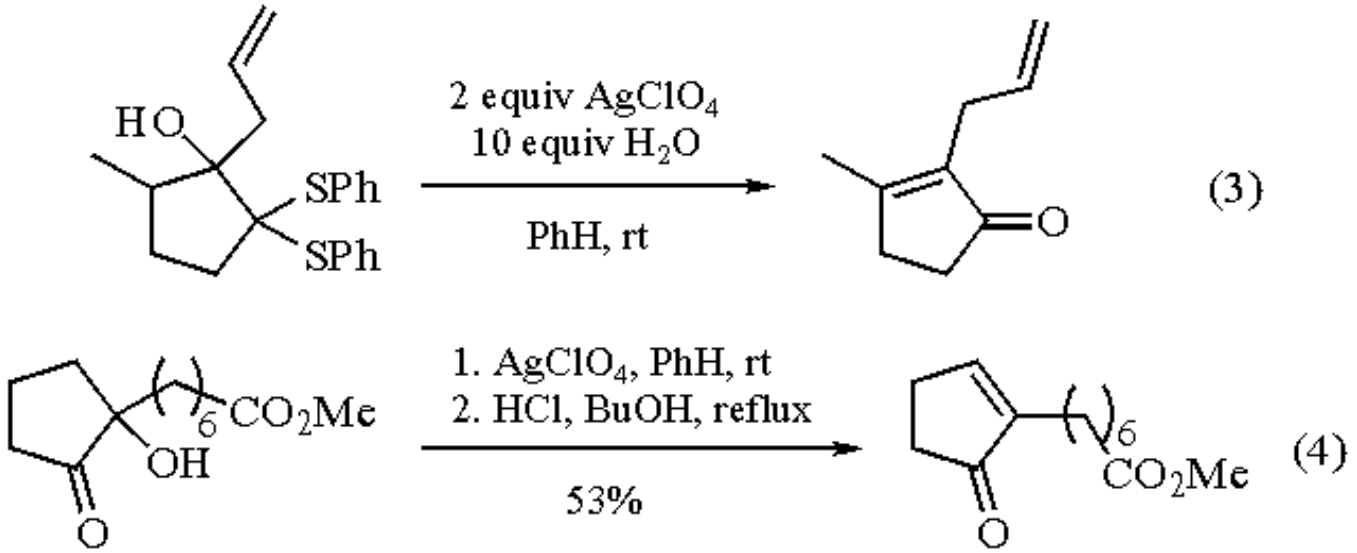

Glycosylation.

Silver perchlorate has been employed in a large variety of ways to form glycosidic linkages.[1c,d] In concert with various Lewis acids,[11,12] silver perchlorate catalyzes the glycosylation of 1-*O*-acetyl-D-glucose to produce a glucoside with a high degree of stereoselectivity (eq 5). Similar success has been achieved in both the stoichiometric and catalytic coupling of glycosyl fluorides,[13-22] dimethylphosphothionates,[23] and imidazolylcarbonyls[24,25] with various silver perchlorate systems.

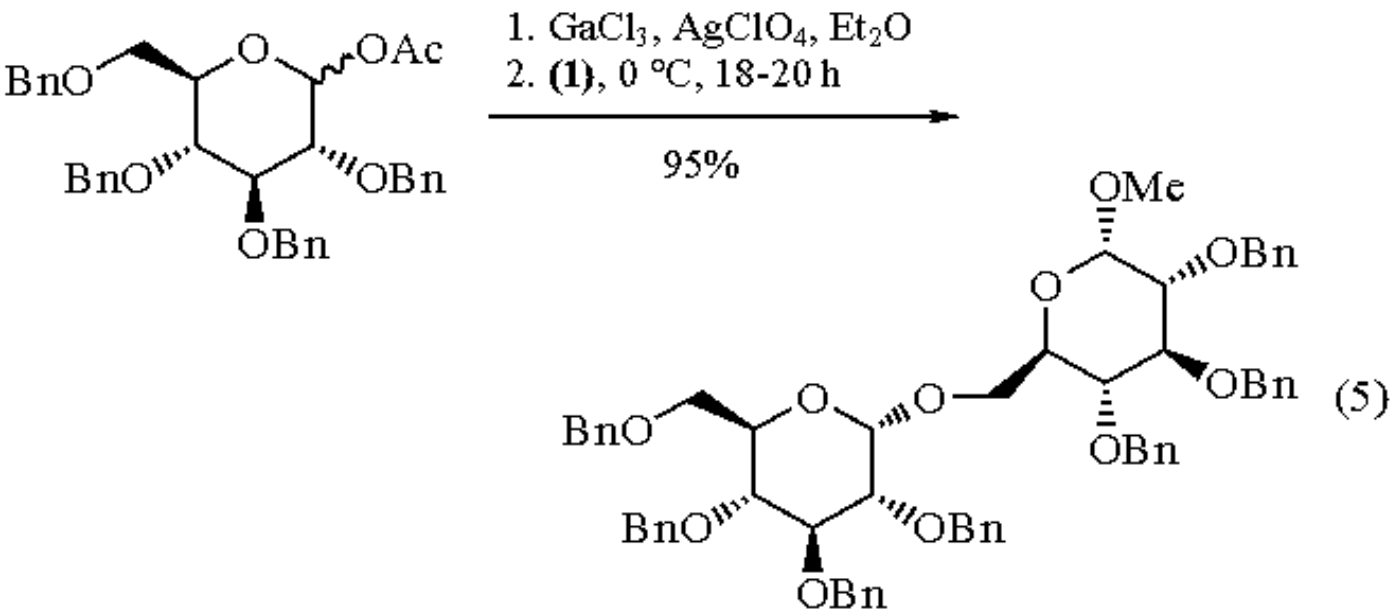

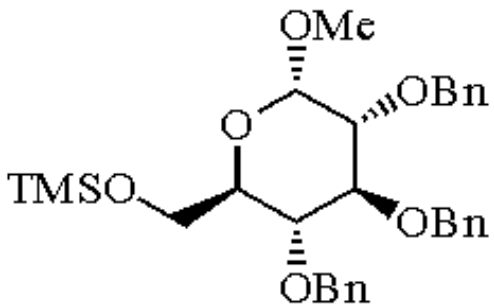

(1)

Rearrangement and Electrocyclic Reactions.

Rearrangements in a wide range of strained molecules can be triggered by silver perchlorate.[1a,b] Bicyclobutanes are readily transformed into butadienes[26,27] in high yield, as evidenced in eq 6; cyclopropanes, particularly those in quadricyclane structures, display similar reactivity (eq 7).[28-30] Padwa et al.[31] have demonstrated that cyclopropenes can be manipulated by Ag^+ into interesting structures (eq 8). Silver perchlorate has also been implemented in the rearrangement of propargyl acetates to allenes.[32] Hiyama[33] used a modification of this procedure to access protected substituted furanones (eq 9) that are complementary to those formed by the mercury-catalyzed process. Finally, 2-(trimethylsiloxy)allyl cations have been generated in the presence of silver perchlorate and furan to generate 4-pyrones via a [3 + 4] cycloaddition process (eq 10).[34]

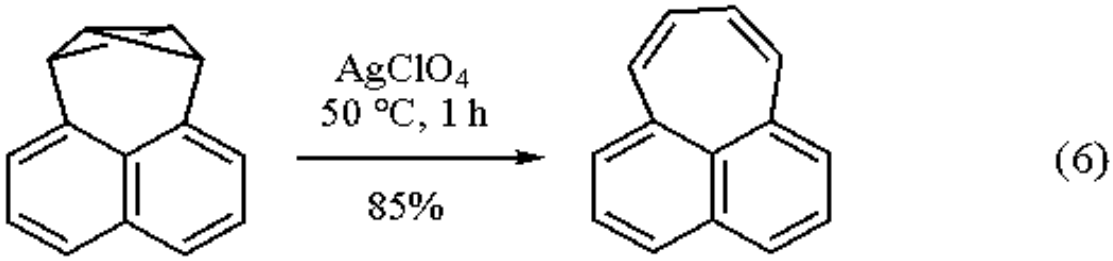

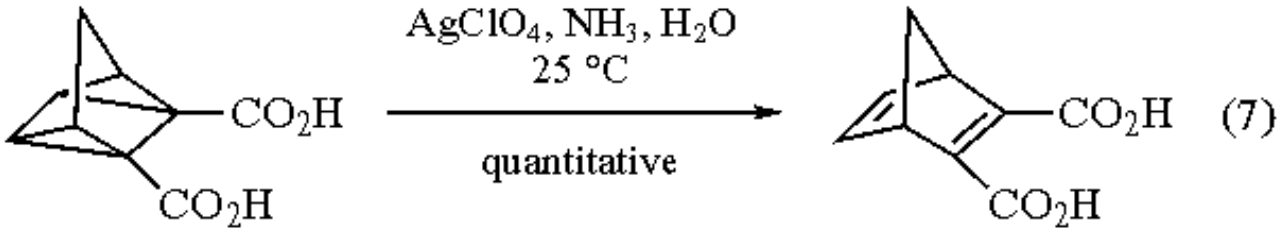

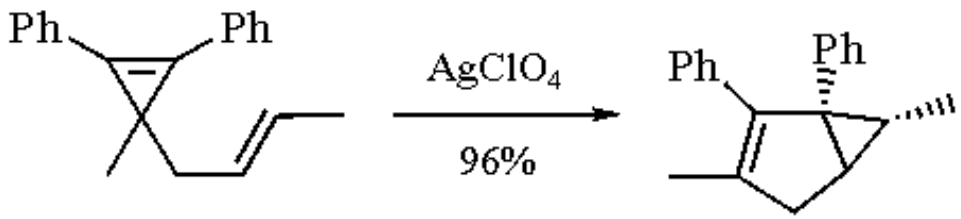

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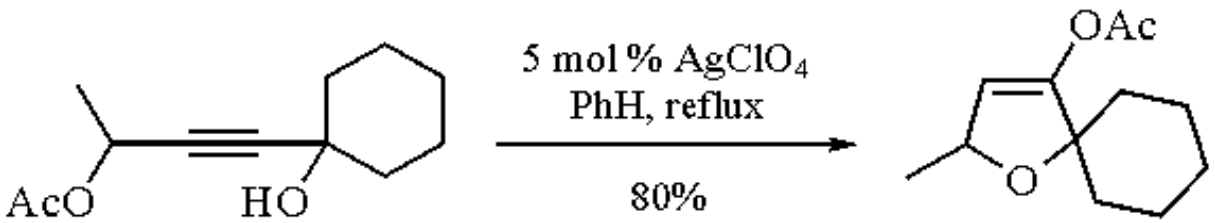

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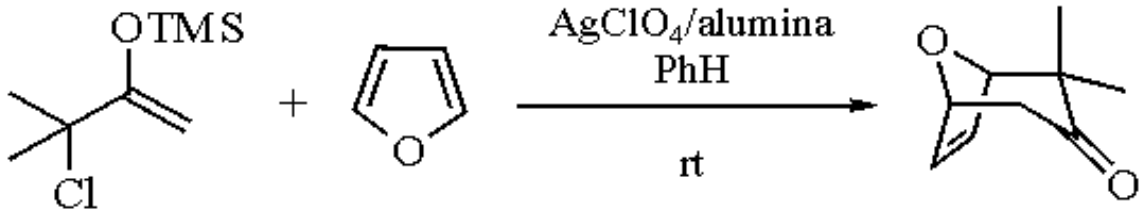

(10)

Solvolysis of Halides.

Wynberg[35] and colleagues have observed an interesting quasi-Favorskii rearrangement when they treated 4-bromoadamantanone with silver perchlorate in acetone-water (eq 11); solvolysis with retention is observed, however, in the case of *trans*,*trans*-2-bromodecalin in refluxing acetonitrile (eq 12).[36] Finally, Reese et al.[37] have examined the silver perchlorate-facilitated methanolysis of dihalocarbene adducts in the context of synthetic routes to functionalized medium-ring cycloalkanes.

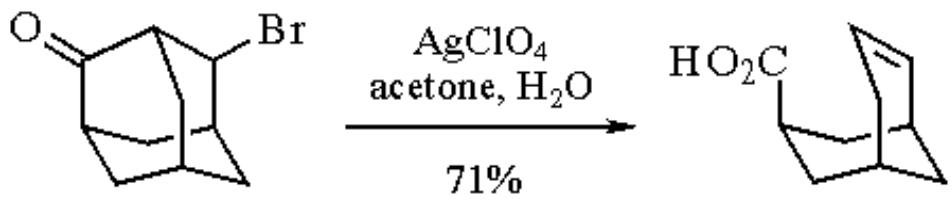

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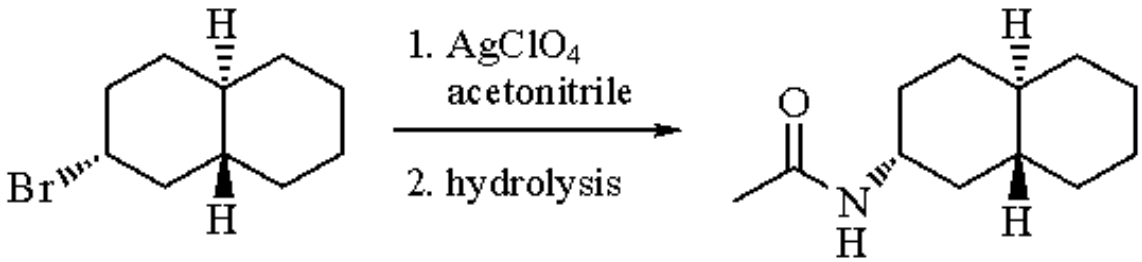

(12)

Related Reagents.

Tin(II) Chloride-Silver(I) Perchlorate.

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Silver(I) Phosphate

Ag_3PO_4

[7784-09-0] · Ag_3O_4P · Silver(I) Phosphate · (MW 418.58)

(basic halophilic salt capable of accelerating the rate of palladium-catalyzed Heck reactions,[1,2] exhibiting large effects on enantio- or diastereoselectivity, and suppressing product alkene isomerization[3,4])

Physical Data: mp 849 °C; *d* 6.37 g cm^{-3}.

Solubility: slightly sol H_2O, acetic acid; freely sol nitric acid; ammonia.

Form Supplied in: yellow, odorless powder.

Handling, Storage, and Precautions: protect from light.

Palladium-Catalyzed Heck Reactions.

Rate Enhancement.

The rate of Heck reactions of aryl or alkenyl halides is typically increased upon addition of silver salts with nonnucleophilic or weakly nucleophilic counterions, including NO_3^-, OTf^-, CO_3^{2-}, OAc^-, and PO_4^{3-}. Silver phosphate is among the most effective of these salts, and its relative efficiency has been attributed to the basicity of the anion. Its role is likely two-fold. First, the Ag^+ likely abstracts the halide from the Pd^{II} complex which is generated by oxidative addition of the aryl or alkenyl halide. Halide abstraction produces a cationic Pd^{II} complex which binds more efficiently to the alkene which is inserted in the next step of the process.[1,2] Secondly, the PO_4^{3-} is an efficient base for scavenging the proton generated by the β-hydride elimination which terminates the process.

Suppression of Product Isomerization.

Alkene isomerization is frequently a problem in Heck reactions and is undoubtedly caused by readdition-elimination of a palladium hydride species to the product alkene. The removal of the hydrohalic acid by silver phosphate prevents such a readdition and thus effectively suppresses alkene isomerization (eq 1). Silver phosphate is typically the most effective silver salt in the suppression of alkene isomerization.[3,4]

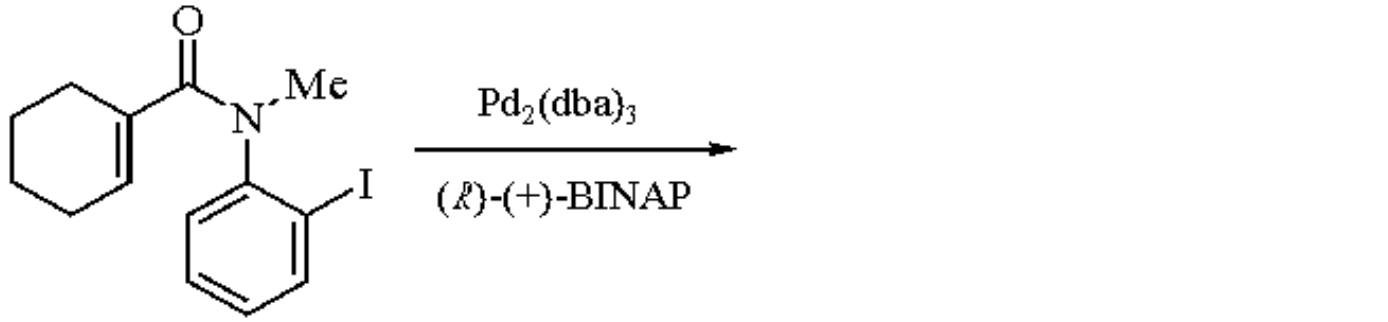

Ag_3PO_4	74% (*S*) 79-81% ee	8%
1,2,2,6,6-pentamethylpiperidine	45% (*R*) 89-95% ee	44%

Effect on Diastereoselectivity.

The diastereoselectivity of Heck reactions can be markedly affected by the presence of silver phosphate (eqs 2 and 3). Such an effect was attributed to coordination of a remote alkene to the cationic palladium complex generated in a silver phosphate-promoted cyclization.[5]

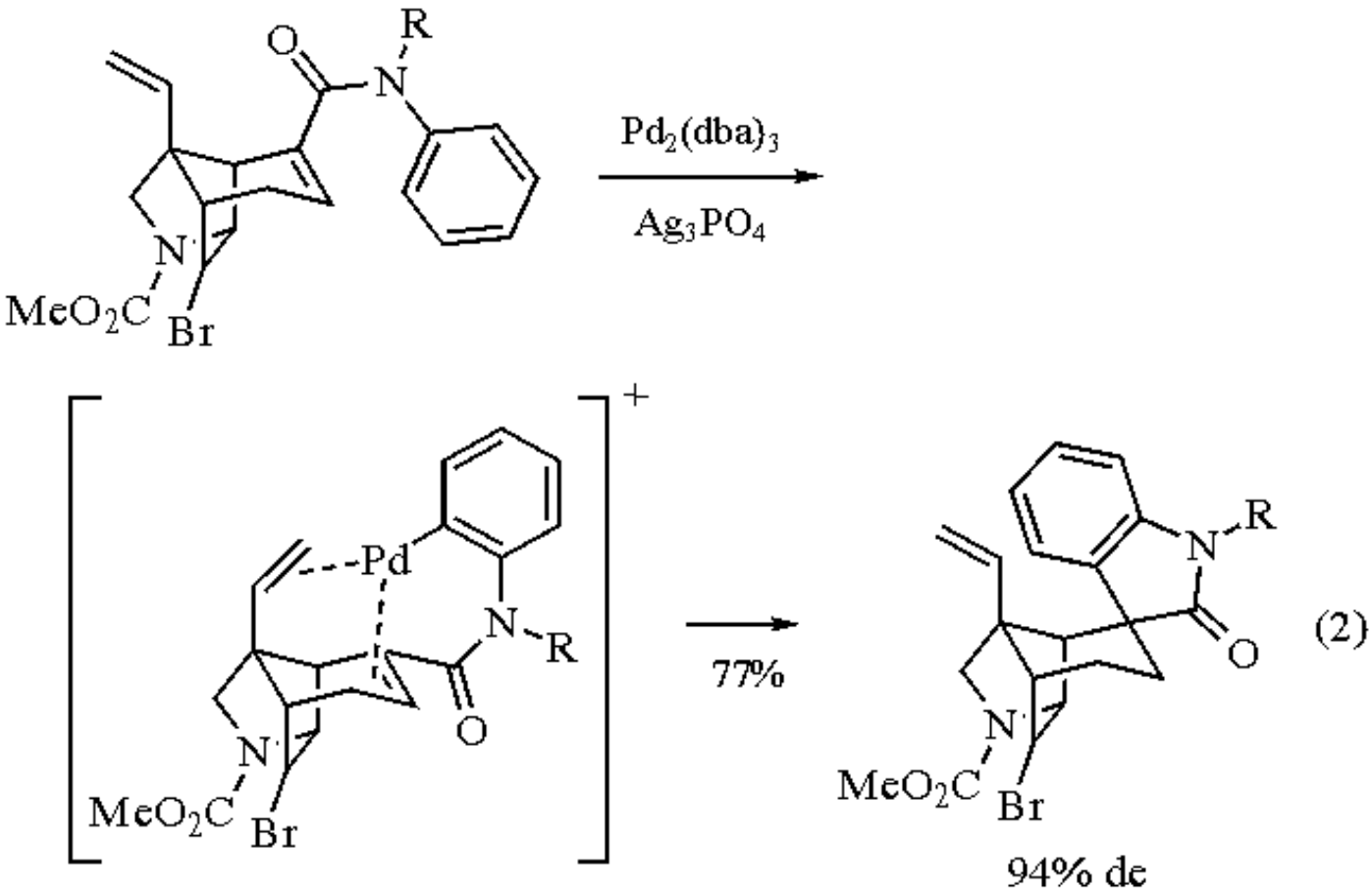

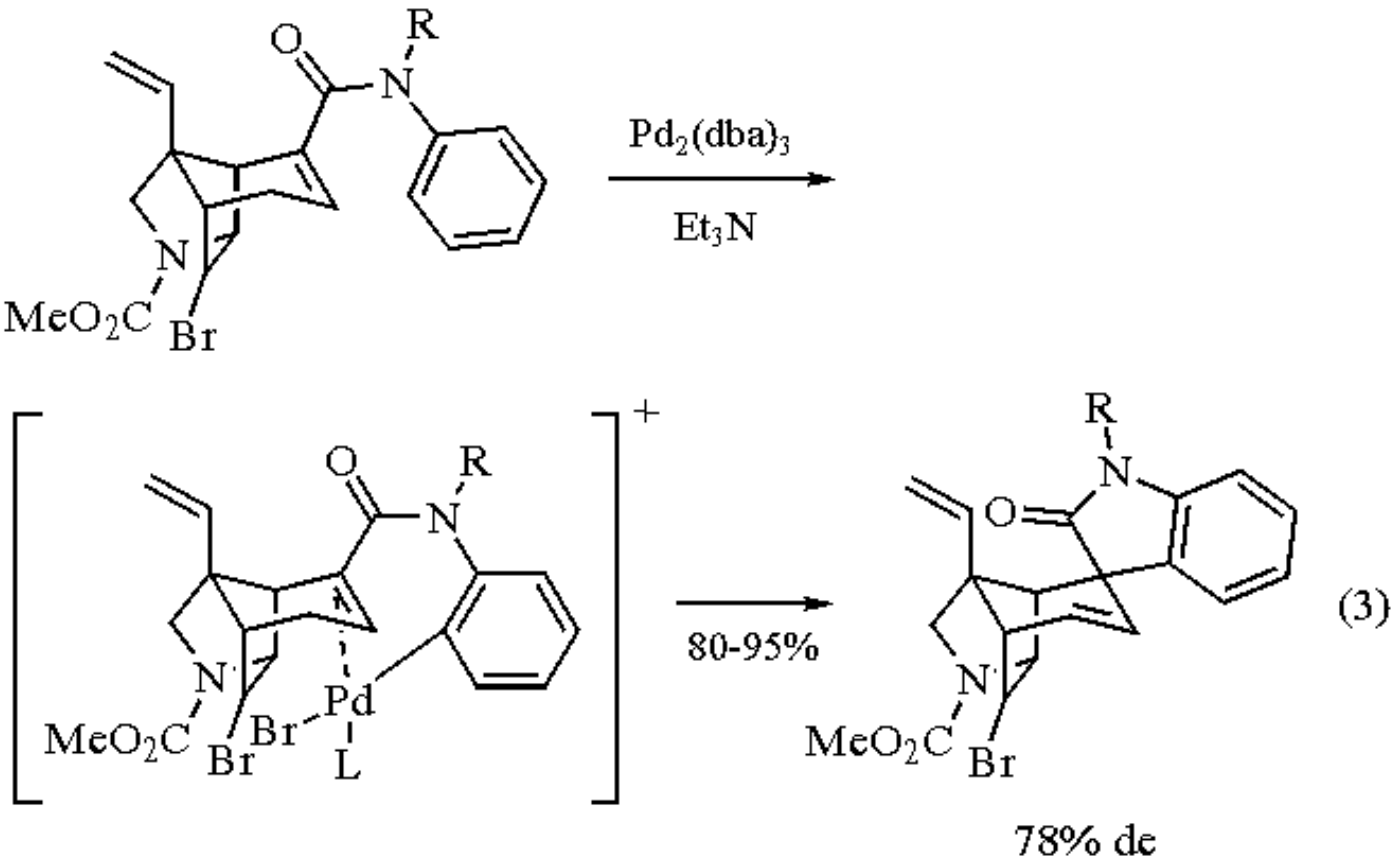

(3)

Effect on Enantioselectivity.

Silver phosphate has been used in the catalytic asymmetric synthesis of *cis*-hydrindanes[6] and *cis*-decalins[7,8] by Heck reactions (eqs 4 and 5). Enantioselectivities with silver phosphate generally exceed those of other silver salts and of non-silver-catalyzed reactions. In one study (eq 1), the addition of silver phosphate completely reversed the absolute stereochemistry of the products with respect to the enantioselectivity observed in the non-silver-catalyzed reaction. Less basic silver salts afforded virtually no asymmetric induction in this study.[4]

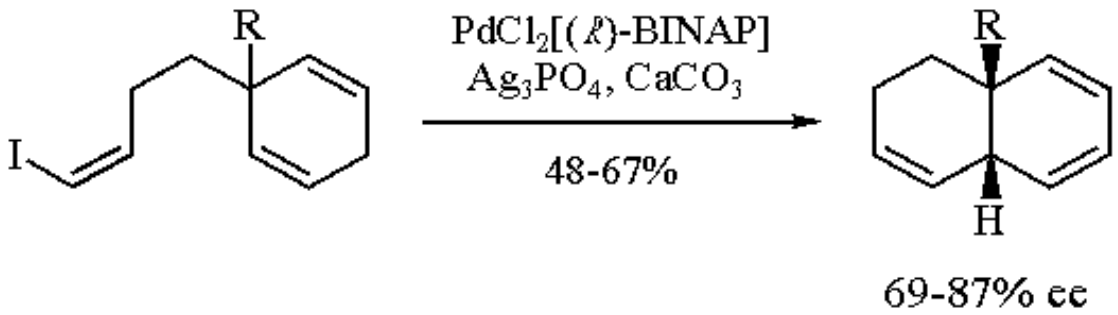

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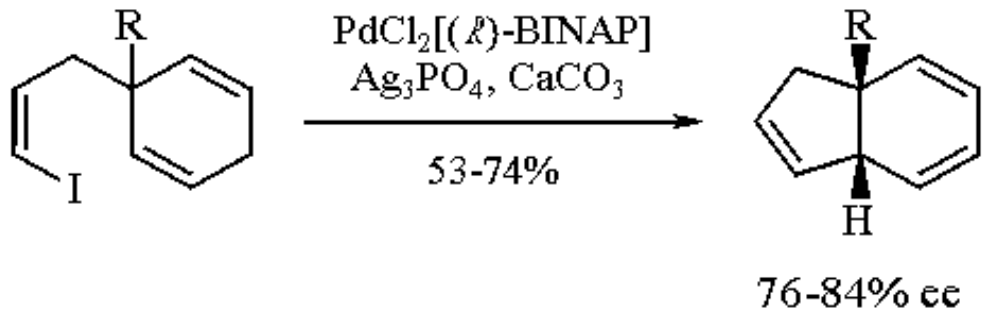

(5)

Related Reagents.

Silver(I) Acetate; ***Silver(I) Carbonate***; ***Silver(I) Nitrate***; ***Silver(I) Trifluoromethanesulfonate***.

1. Karabelas, K.; Westerlund, C.; Hallberg, A. *JOC* **1985**, *50*, 3896.
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Silver(I) Tetrafluoroborate

$AgBF_4$

[14104-20-2] · $AgBF_4$ · Silver(I) Tetrafluoroborate · (MW 194.68)

(mild Lewis acid with a high affinity for organic halides)

Physical Data: mp 200 °C (dec).

Solubility: sol benzene, toluene, nitromethane, diethyl ether, water.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: contents of Ag can be assayed conveniently by volumetric titration of Ag^I.

Preparative Method: can be prepared by reacting ***Silver(I) Fluoride*** with ***Boron Trifluoride*** in nitromethane.[1]

Handling, Storage, and Precautions: should be protected from light and moisture; very hygroscopic.

Introduction.

This reagent has replaced ***Silver(I) Perchlorate*** to a large extent because of the sensitivity of perchlorates.

Activation of Acyl Chlorides.

In several cases, $AgBF_4$ has been used to increase the reactivity of acyl chlorides towards nucleophiles.[2] For example, *N*-acylammonium salts were prepared for the first time by the reaction of a tertiary amine and an acyl chloride in the presence of $AgBF_4$ (eq 1).[3]

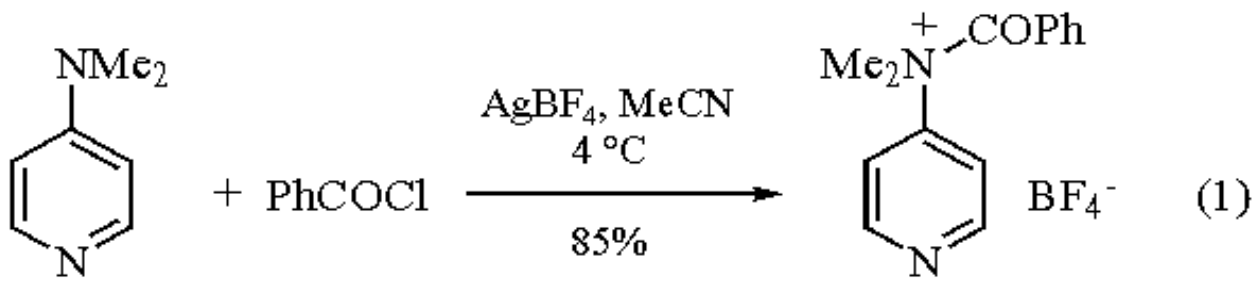

(1)

Nucleophilic Substitution on Alkyl Halides by Heteroatoms.

A number of more or less activated alkyl halides, such as benzyl halides[4] and allyl halides,[5] undergo substitution reactions mediated by $AgBF_4$ in the presence of a heteroatom nucleophile. For example, treatment of pentamethylcyclopentadienyl bromide with $AgBF_4$ in the presence of a nucleophile gives the corresponding substituted product (eq 2). Thiols, amines, and alcohols have been used as nucleophiles.[6]

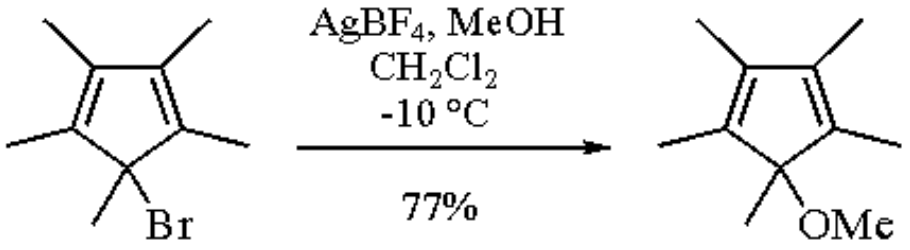

(2)

Adenine analogs are prepared stereoselectively from cyclopentene derivatives using a two-step procedure (eq 3). The reaction probably involves a seleniranium salt as an intermediate.[7]

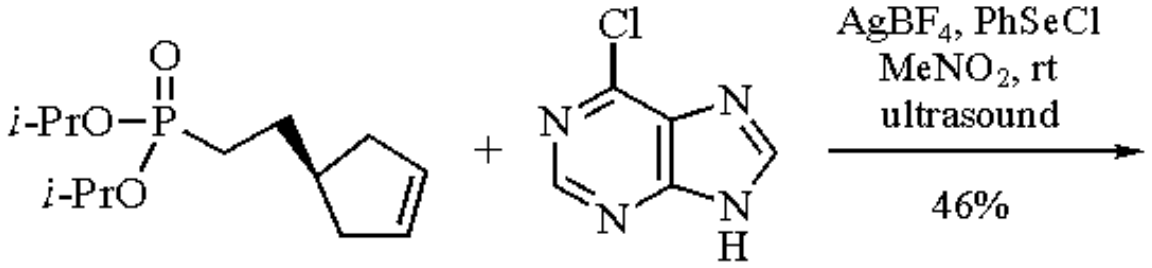

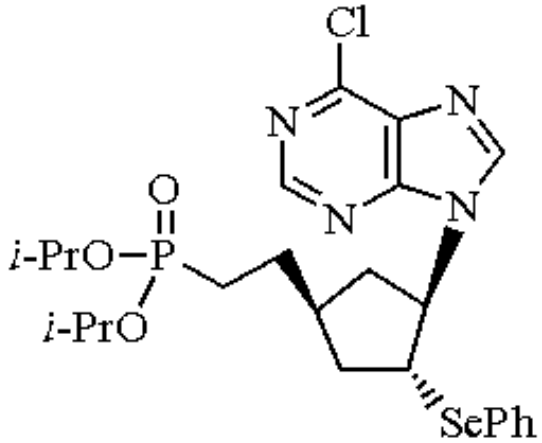

(3)

Intramolecular substitutions mediated by Ag^+ do not seem to require activated halides.[8] For example, o-chloro amides react with $AgBF_4$, giving products from intramolecular attack of the amide oxygen. Depending on the structure of the amide, imino lactones,[9] imino lactonium salts,[10] or lactone hydrazones (eq 4)[11] are obtained as products. Fluorination of α-bromo ketones using $AgBF_4$ has also been reported.[12]

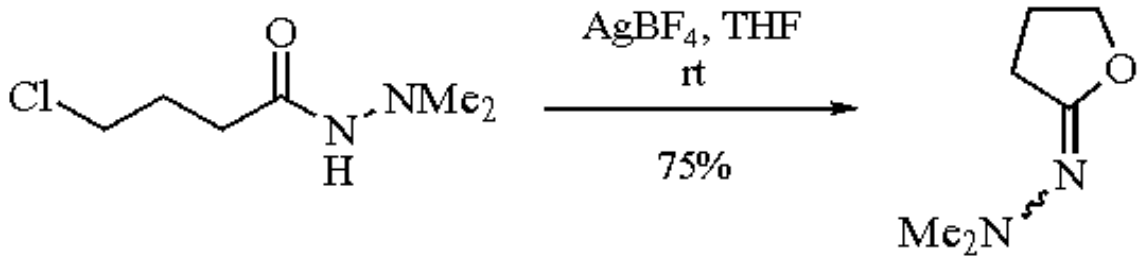

(4)

Nucleophilic Aromatic Substitution.

In one case, it has been reported that $AgBF_4$ promotes the nucleophilic substitution of an aromatic chloride (eq 5).[13] This is not due to activation of the halide, but apparently to suppression of halide-promoted decomplexation of the arene-manganese derivative.

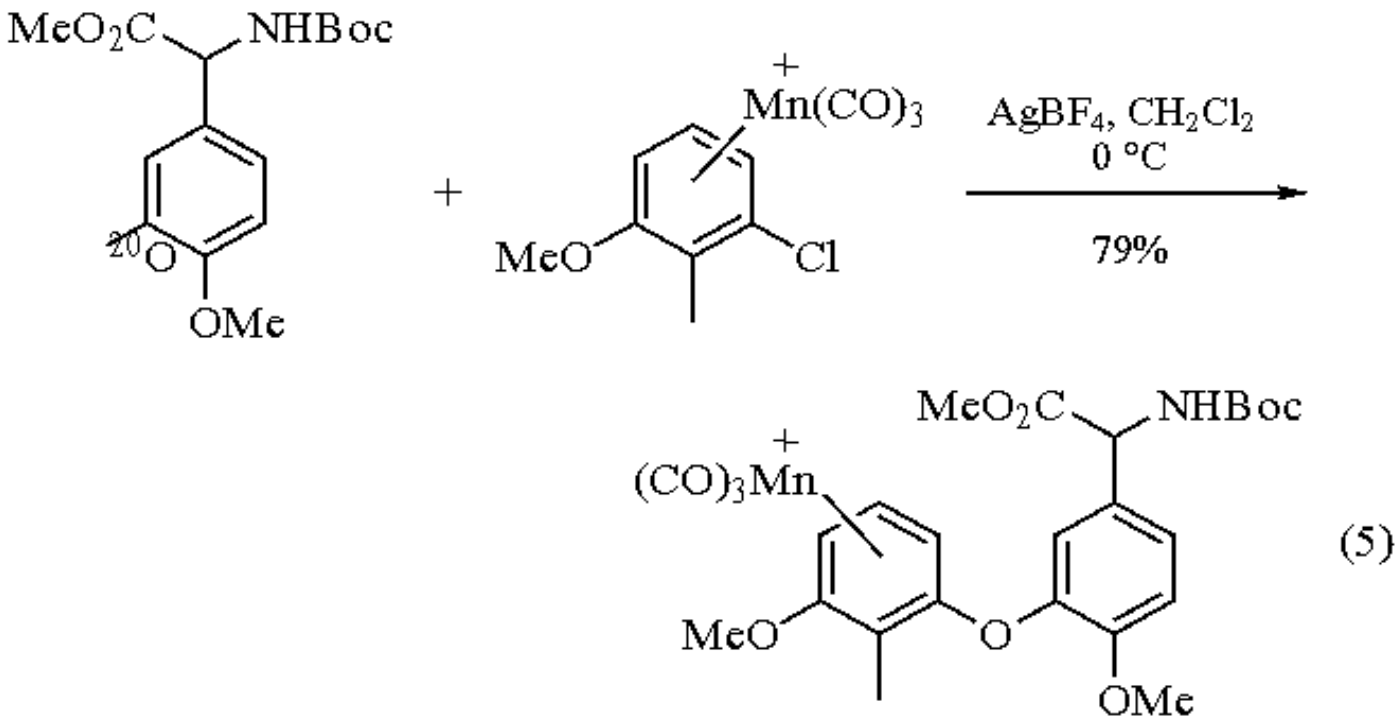

Carbon-Carbon Bond Formation via Cationic Intermediates.

In analogy with the heteroatom substitutions described above, certain aliphatic halides undergo substitution reactions with carbon nucleophiles promoted by $AgBF_4$. For example, Eschenmoser and co-workers used $AgBF_4$ in order to transform α-chloro nitrones into 1,3-dipoles which react with ordinary alkenes in a cycloaddition manner (eq 6).[14]

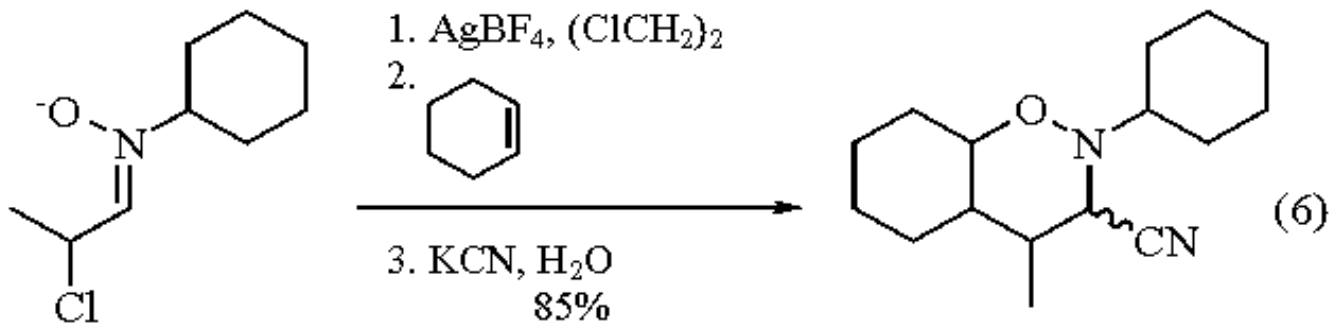

Livinghouse and co-workers have shown that acylnitrilium ions, prepared from isocyanides and an acid chloride followed by treatment with $AgBF_4$, are useful intermediates in the synthesis of nitrogen-containing heterocycles (eq 7).[15]

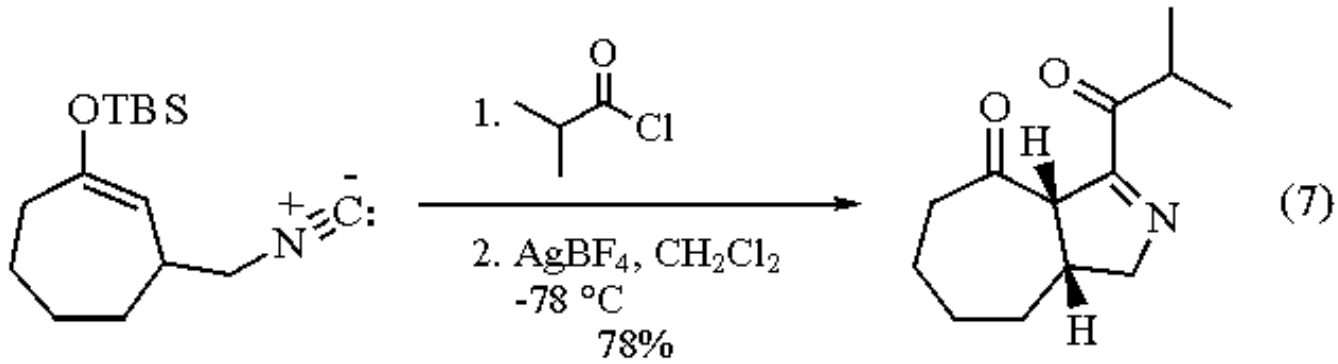

In certain cases, allylsilanes[16] and trimethylsilyl enol ethers[17] react with alkyl halides with the formation of a new carbon-carbon bond. α-Bromo imidates[18] (eq 8) and β-chloro imines[19] have been reported to undergo electrophilic aromatic substitution on relatively electron-rich aromatics in the presence of $AgBF_4$.

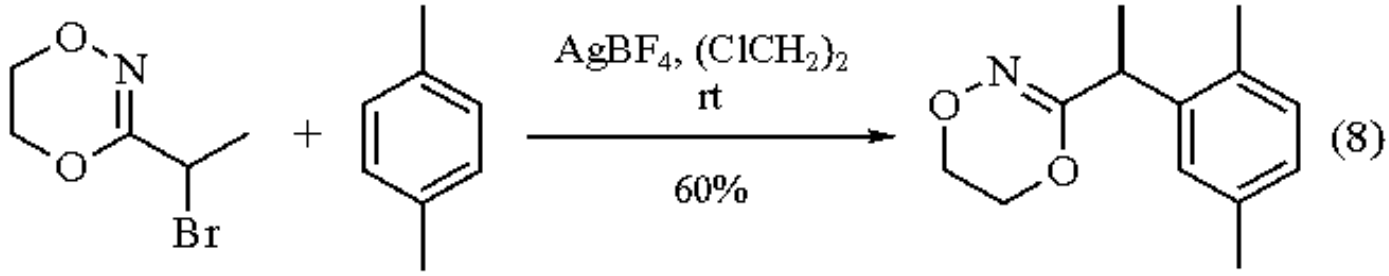

Synthesis via Iminium Ions.

α-Cyano amines react with $AgBF_4$ with the formation of an intermediate iminium ion.[20] This has been used synthetically as a method for removal of the cyano group either by a consecutive reduction[21,22] to the amine (eq 9) or by elimination to the imine[23] or enamine.[24]

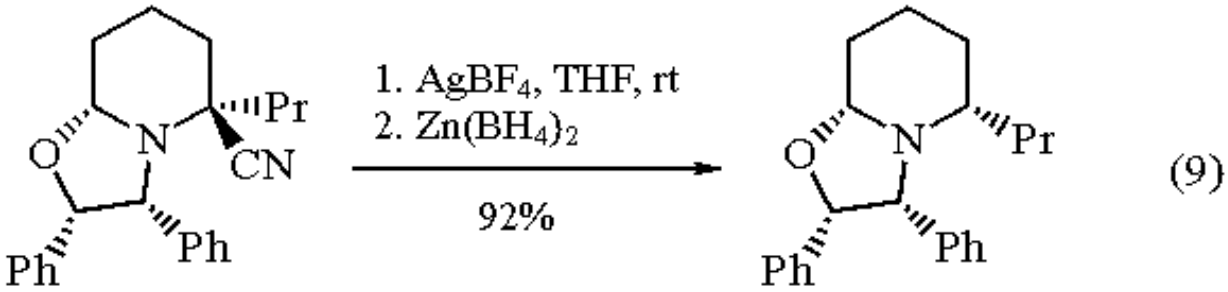

Rearrangements.

A number of strained alkyl and/or reactive halides, such as cyclopropyl[25] and bicyclic[26,27] chlorides, rearrange on treatment with $AgBF_4$. For example, β-bromotetrahydropyrans rearrange to tetrahydrofurans stereoselectively on treatment with $AgBF_4$ (eq 10).[28] Other examples include the rearrangement of α-haloalkyl aryl ketones into arylacetic acid derivatives,[29] and the rearrangement of α-haloalkylsilanes upon treatment with $AgBF_4$.[30]

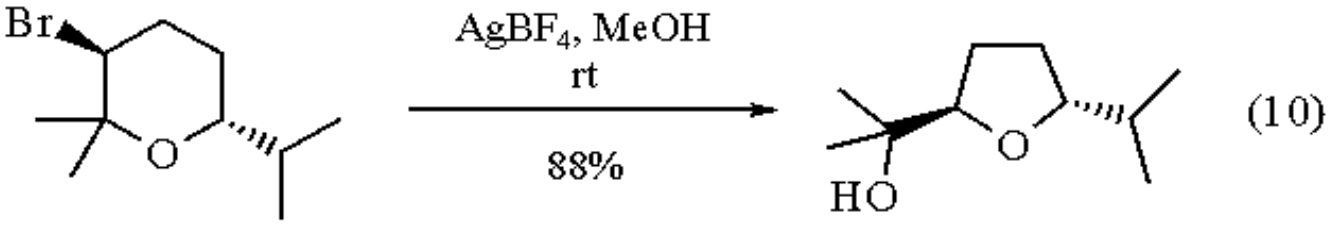

In the presence of strained hydrocarbons, $AgBF_4$ functions as a mild Lewis acid and causes rearrangements.[31-33] For example, the tricyclic hydrocarbon (**1**) rearranges upon treatment with a catalytic amount of $AgBF_4$ to the less strained hydrocarbon (**2**) (eq 11).[34]

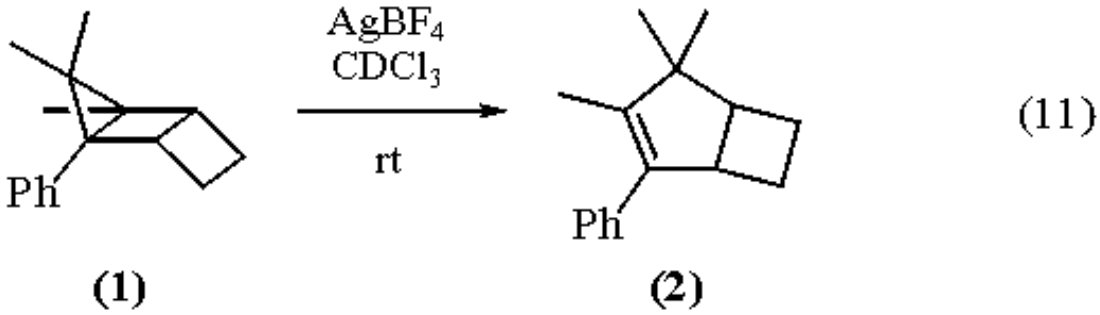

Numerous examples include the rearrangement of propargyl esters into allenyl esters (see also ***Silver(I) Trifluoromethanesulfonate***)[35] or to dihydrofurans,[36] the Claisen rearrangement of aryl allenylmethyl ethers,[37] and the rearrangement of silyloxycyclopropanes (eq 12, also effected by ***Copper(II) Tetrafluoroborate***).[38]

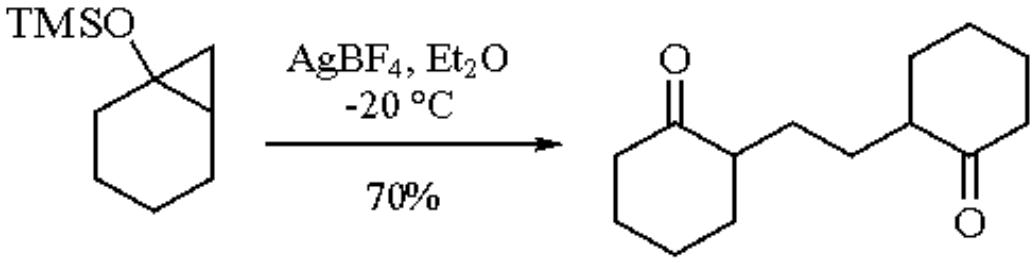

(12)

Activation of Thiol Esters.

Pyridyl thiol esters are converted into esters on treatment with $AgBF_4$ and an alcohol.[39] Acylation of alkynylsilanes can also be carried out using thiol esters in the presence of $AgBF_4$.[40]

Alkylation of Thioethers.

Thioethers can be methylated by ***Iodomethane*** in the presence of $AgBF_4$.[41] Benzylation of thioethers in the presence of $AgBF_4$ has also been reported.[42]

Electrophilic Aromatic Substitution.

Electrophilic nitration using a combination of NO_2Cl and $AgBF_4$ has been reported.[43] Conversion of arylsilanes into iodides and bromides has been achieved using a combination of the halogen and $AgBF_4$ (eq 13).[44]

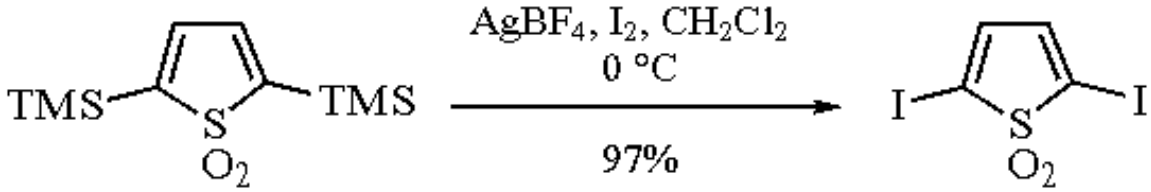

(13)

Catalysis of Cycloadditions.

Addition of catalytic amounts of $AgBF_4$ greatly increases the selectivity of [2 + 4] cycloadditions of benzyne.[45]

Related Reagents.

Dimethyl Sulfoxide-Silver Tetrafluoroborate.

---

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Silver(I) *p*-Toluenesulfonate

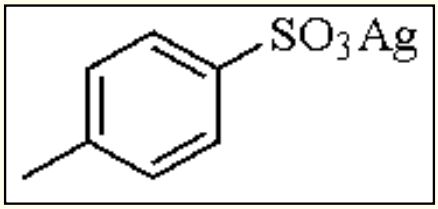

[16836-95-6] · $C_7H_7AgO_3S$ · Silver(I) *p*-Toluenesulfonate · (MW 279.08)

(mild Lewis acid with a high affinity for organic halides)

Solubility: sol acetonitrile, diethyl ether, water.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: contents of Ag can be assayed conveniently by volumetric titration of Ag^I.

Preparative Method: can be prepared by mixing aqueous solutions of ***Silver(I) Nitrate*** and sodium tosylate and filtering off the precipitate.

Handling, Storage, and Precautions: should be protected from light.

Conversion of Alkyl Halides into Tosylates.

Treatment of primary alkyl halides, in most cases bromides and iodides, with silver tosylate in acetonitrile, gives good yields of the corresponding tosylates.[1,2] Tertiary and benzylic tosylates, even though they are very prone to dissociate, have been prepared using a similar procedure.[3]

Solvolysis of Reactive Halides.

In analogy with other silver(I) salts, this reagent has been used for solvolysis of reactive bromides. Thus treatment of bicyclic geminal dibromocyclopropanes leads to ring-enlarged products (eq 1). The stereoselectivity observed indicates that a concerted electrocyclic ring opening is involved.[4] Analogously, benzylic bromides have been shown to give styrenes on treatment with AgOTs in dichloromethane.[5]

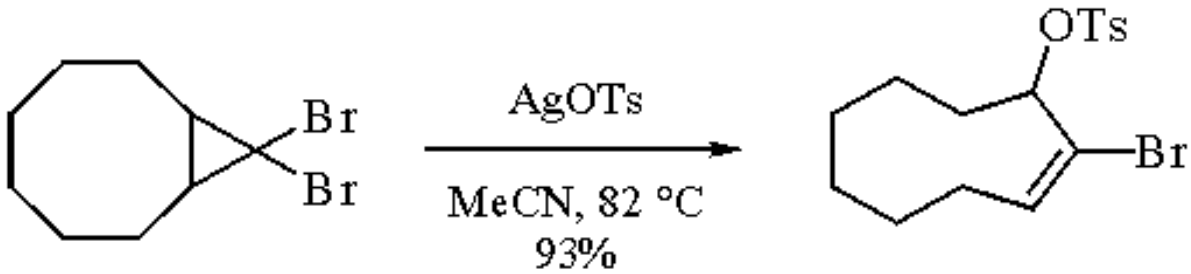

(1)

Synthesis via Benzeneselenenyl Tosylate.

Treatment of ***Benzeneselenenyl Chloride*** with AgOTs in acetonitrile gives the unstable benzeneselenenyl tosylate. This reagent (prepared in situ) adds to alkynes to give β-(phenylseleno)vinyl tosylates (eq 2).[6]

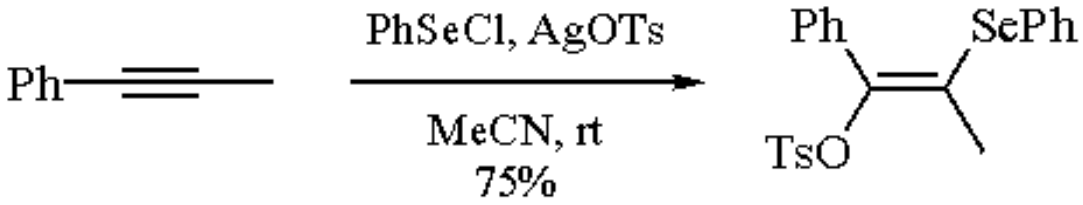

(2)

Related Reagents.

Silver(I) Tetrafluoroborate.

---

1. Emmons, W. D.; Ferris, A. F. *JACS* **1953**, *75*, 2257.
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Silver(I) Trifluoroacetate

$AgOCOCF_3$

[2966-50-9] · $C_2AgF_3O_2$ · Silver(I) Trifluoroacetate · (MW 220.89)

(mild Lewis acid with a high affinity for aliphatic halides)

Physical Data: mp 257-269 °C (dec).

Solubility: sol benzene, diethyl ether, water.

Form Supplied in: white solid; widely available.

Analysis of Reagent Purity: contents of Ag can be assayed conveniently by volumetric titration of Ag^I.

Preparative Method: can be prepared by extraction of an aqueous solution of ***Silver(I) Nitrate*** and $NaOCOCF_3$ with ether.[1]

Handling, Storage, and Precautions: should be protected from light.

Solvolysis of Reactive Halides.

Like other silver(I) salts, this reagent has been used for solvolysis of reactive halides. Thus treatment of methoxyallyl bromide with $AgOCOCF_3$ yields the corresponding allyl cation which can be captured as its cycloadduct with furan (eq 1).[2]

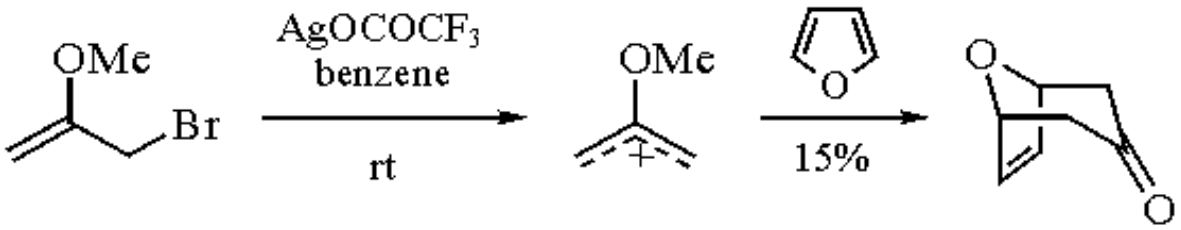

(1)

Geminal dibromocyclopropanes, as well as dibromocyclobutanes, are easily hydrolyzed using this reagent.[3,4] In the case of substrates containing a side-chain with a nucleophilic hydroxy or carboxylic acid group, products from ring opening of the cyclopropane followed by nucleophilic ring closure (eq 2) have been observed.[5]

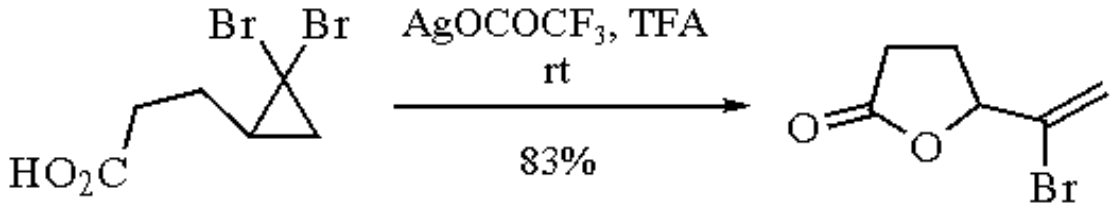

(2)

Alkylation of Silyl Enol Ethers.

Primary and secondary iodides,[6] as well as allylic bromides,[7] react with silyl enol ethers in the presence of $AgOCOCF_3$ to give products of alkylation (eq 3). In the case of 2-trimethylsilyloxyfuran, exclusive attack on the 5-position is observed (eq 4).[8,9]

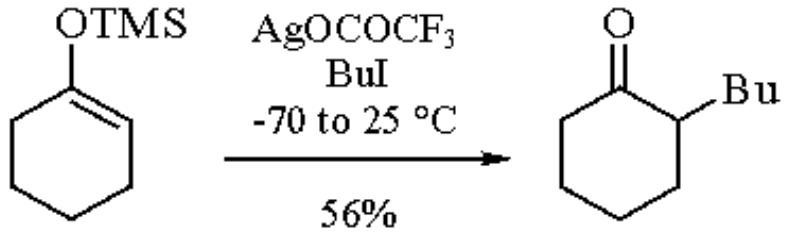

(3)

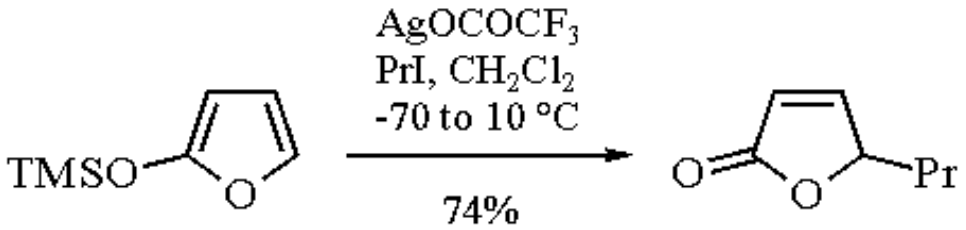

(4)

Activation of Thiol Esters.

Thiol esters can be converted into *O*-esters on treatment with the corresponding alcohol and $AgOCOCF_3$, $HgOCOCF_3$, or copper salts (eq 5).[10] Similarly, β-keto thioesters react with amines in the presence of $AgOCOCF_3$ to give β-keto amides (eq 6).[11]

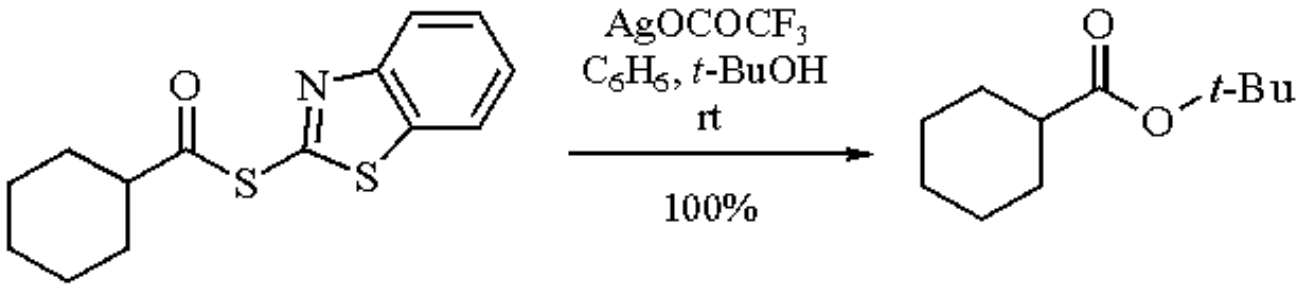

(5)

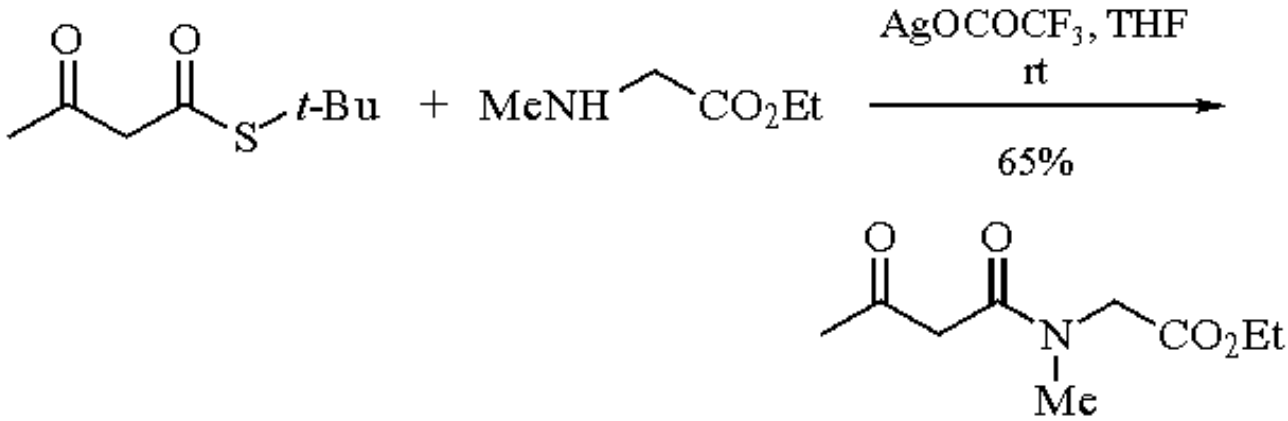

(6)

Rearrangements of Alkynes.

Propargylic esters rearrange to 1,3-dienyl esters in the presence of a catalytic amount of $AgOCOCF_3$ (eq 7).[12,13] For similar transformations, see ***Silver(I) Tetrafluoroborate***.

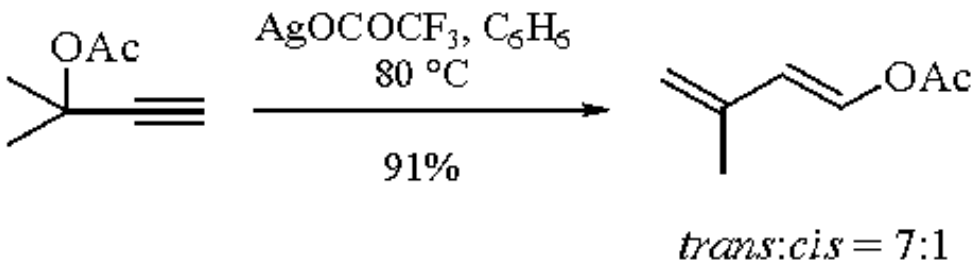

(7)

Oxidation of Dihydrazones.

Newman and Reid found that $AgOCOCF_3$ is an excellent reagent for the oxidation of aromatic dihydrazones into 1,2-diarylacetylenes (eq 8).[14]

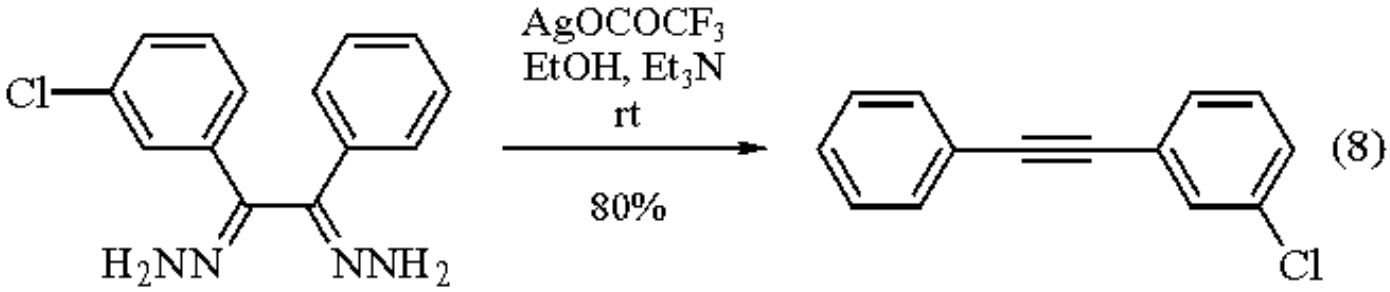

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Lars-G. Wistrand

Nycomed Innovation, Malmö, Sweden

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Silver(I) Trifluoromethanesulfonate

$AgOSO_2CF_3$

[2923-28-6] · $CAgF_3O_3S$ · Silver(I) Trifluoromethanesulfonate · (MW 256.95)

(reactive triflating agent and source of soluble silver ions useful for formation of electrophilic onium species,[1] and promotion of Friedel-Crafts,[2] nucleophile-alkene cyclization,[3] and esterification[4] reactions)

Alternate Name: silver triflate.

Physical Data: mp 356 °C.

Solubility: sol typical organic solvents.

Form Supplied in: white solid; widely available.

Preparative Method: can be prepared from the barium salt via treatment with dil H_2SO_4 followed by neutralization with Ag_2CO_3.[5]

Handling, Storage, and Precautions: light sensitive; irritant. Use in a fume hood.

Oxonium (Iminium) Reactions.

Oxygen- and nitrogen-containing molecules bearing an α-nucleofuge such as a halide or sulfur are converted by AgOTf to highly electrophilic onium (eq 1)[1] or iminium (eq 2)[6] species. The intermediacy of a planar cation is substantiated by the formation of the same diastereomer from either substrate isomer in some cyclization reactions (eq 1).

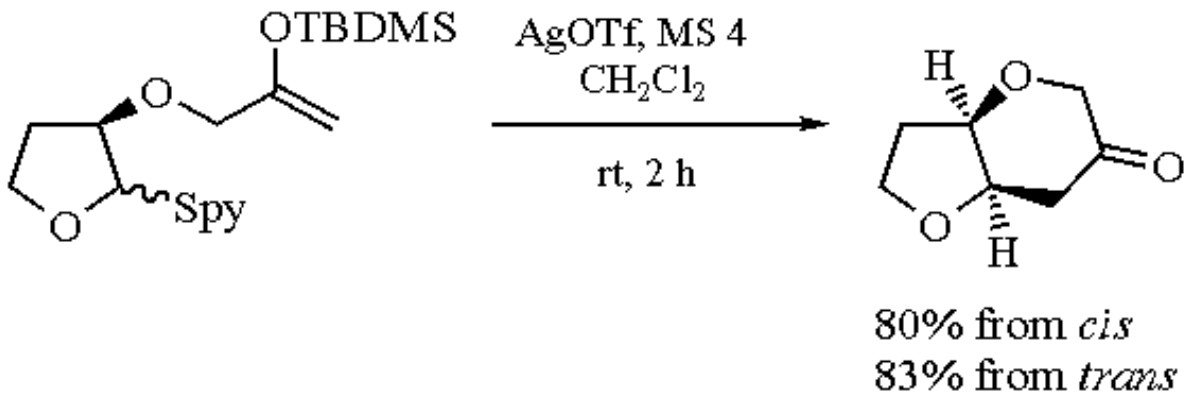

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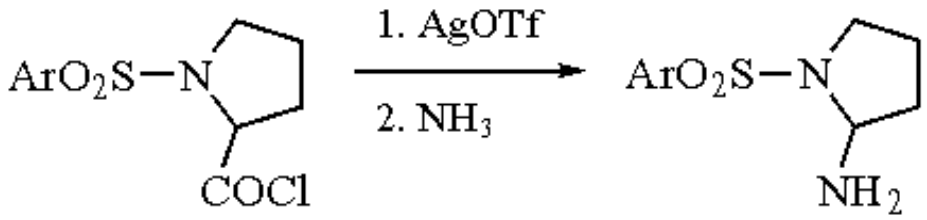

(2)

This reaction type has enjoyed wide application in carbohydrate chemistry, as anomeric carbons can be easily functionalized with high stereospecificity by silyl enol ethers (eq 3, R´ = Ph,[7] H[8]) and other nucleophiles.

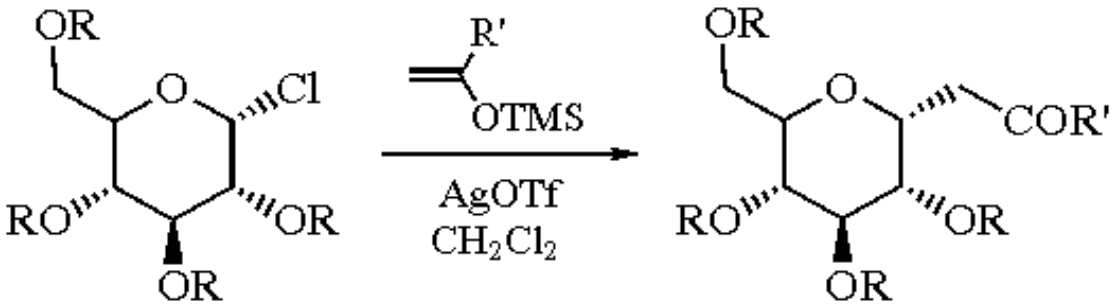

(3)

R = Bn

R' = Ph, 88%
R' = H, 81%

Friedel-Crafts (and Other Aromatic Functionalization) Reactions.

When treated with AgOTf, alkyl,[2] acyl (eq 4),[9] and sulfonyl[10] halides are converted to extremely electrophilic triflate species that react rapidly with even deactivated[11] aromatic rings in the absence of catalysis. Benzylic chloroformates participate similarly (eq 5).[12] Aromatic rings are also efficiently vinylated[13] and iodinated[14] via AgOTf-promoted processes.

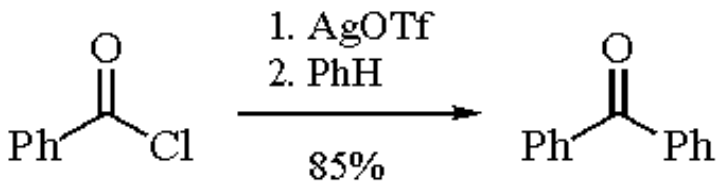

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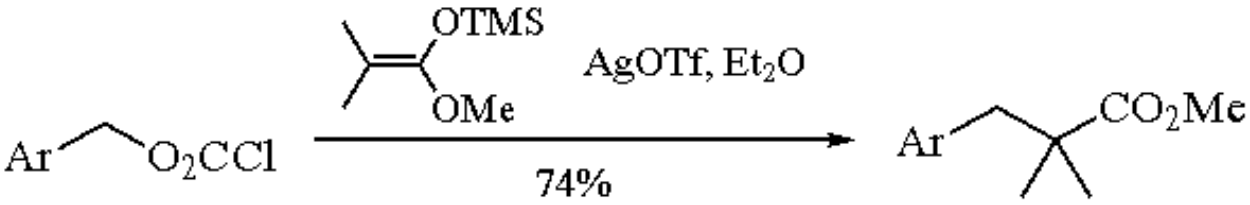

(5)

Ar = *p*-$MeOC_6H_4$-

Miscellaneous Reactions.

AgOTf induces a highly diastereoselective cyclization of amino ketenes wherein asymmetry is induced by an adjacent stereogenic center and is dependent upon silver concentration (eq 6).[3] Acetylenic oxy-Cope rearrangements are also facilitated by AgOTf (eq 7),[15] and a mild, high-yield esterification utilizes AgOTf in the presence of ***Titanium(IV) Chloride*** (eq 8).[4]

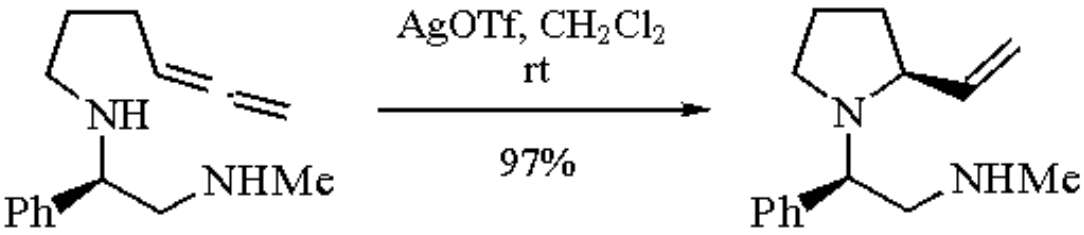

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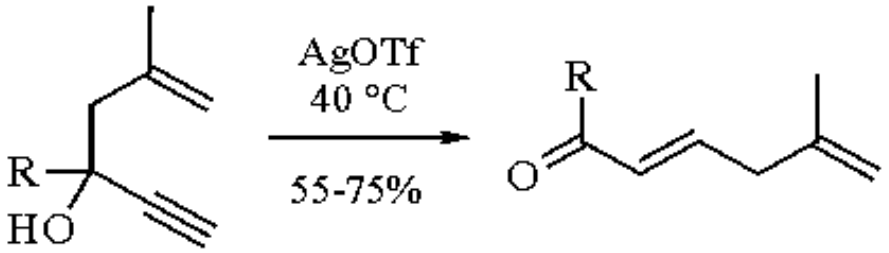

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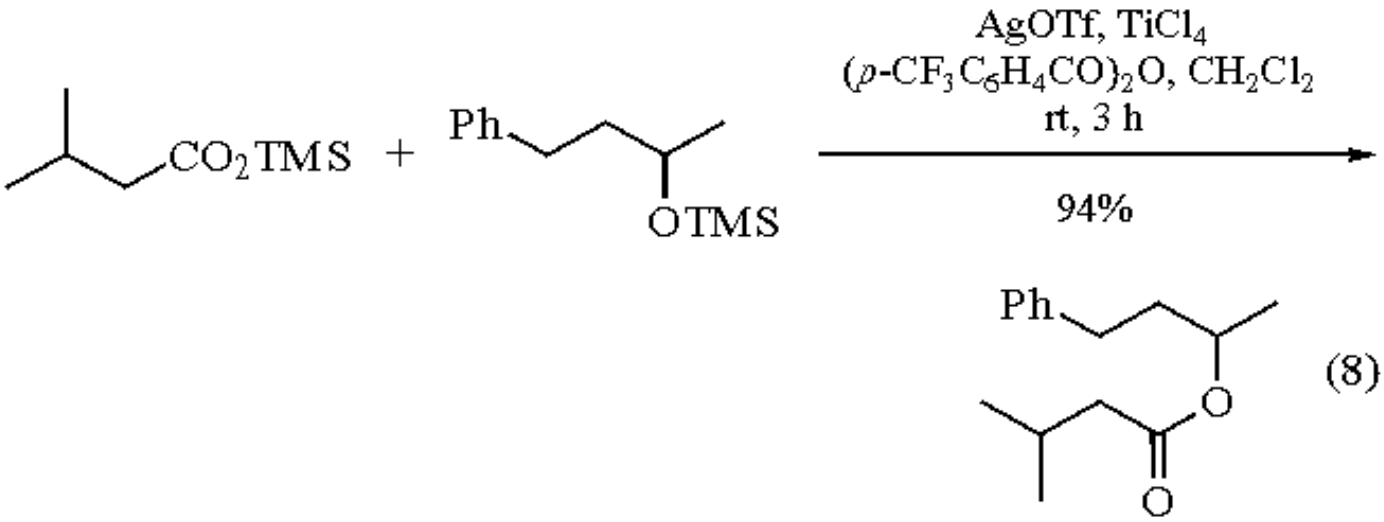

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Singlet Oxygen

[7782-44-7] · O_2 · Singlet Oxygen · (MW 32.00)

(electrophilic oxidizing agent for oxygenation of cisoid 1,3-dienes, many types of heterocyclic systems, enamines, alkenes containing allylic hydrogen atoms, sulfides, carbon-phosphorus double bonds, and other electron-rich unsaturated organic compounds)

Physical Data: singlet oxygen ($^1O_2$) is the first excited electronic state of molecular oxygen ($^1\Delta_g$), lying 22.4 kcal mol^{-1} above the ground state triplet. The second singlet state (^{1}&SSigma;+g), 37 kcal mol^{-1} above the ground state, is relatively short-lived in solution (10^{-12} s) due to a rapid spin-allowed transition to the longer-lived (10^{-3}-10^{-6} s) first excited state. Because of the short lifetime of the ^{1}&SSigma;+g state, the more stable singlet oxygen species ($^1\Delta_g$) is considered to be the reactive intermediate in the oxygenation of organic compounds in solution.[1]

Solubility: sol aqueous and organic solvents.

Form Supplied in: singlet oxygen is an unstable, short-lived species and must be prepared in situ or immediately prior to use.

Preparative Methods: among the methods for generating singlet oxygen in solution are: (a) the dye-sensitized photooxidation of triplet oxygen;[2] (b) the decomposition of phosphite ozonides;[3] (c) the decomposition of transannular peroxides such as 9,10-diphenylanthracene peroxide;[4] (d) the reaction of ***Hydrogen Peroxide*** with ***Sodium Hypochlorite***;[5,6] and (e) subjecting gaseous oxygen to electrodeless discharge.[7] In the following section, the procedures for generating singlet oxygen by the methods (a)-(d) above are discussed, and some typical reactions of singlet oxygen with organic compounds are reviewed.

Handling, Storage, and Precautions: the initial peroxidic products formed in $^1O_2$ reactions usually undergo decomposition or rearrangement under the conditions of workup, but in some cases (certain transannular peroxides or dioxetanes) they may remain in the reaction mixture as potentially explosive materials. Unless the peroxides are sought as reaction products, they may be deoxygenated by the action of ***Dimethyl Sulfide***, diphenyl sulfide, or ***Triphenylphosphine***.

Preparative Methods.

Generation by Dye-Sensitized Photooxygenation.[2]

The most common method for generating $^1O_2$ in solution is the dye-sensitized photochemical excitation of triplet oxygen. The mechanism for generating $^1O_2$ in this way involves the excitation of an appropriate dye with visible light to form the corresponding excited singlet state. Rapid intersystem crossing generates the excited triplet state of the sensitizer (E_T > 22.4 kcal mol^{-1}) which undergoes energy transfer with triplet oxygen to form singlet oxygen, regenerating the ground state of the sensitizer (eq 1). Among the sensitizers which can be utilized in solution are methylene blue, Rose Bengal, eosin yellow, chlorophyll, riboflavin, zinc tetraphenylporphyrin, bis-naphthalenothiophene, erythrosin B, and hematoporphyrin. In addition to the soluble, homogeneous sensitizers, polymer-bound dyes such as Rose Bengal have been used for the photochemical generation of $^1O_2$.[8]

$$\text{Sens} \xrightarrow{h\nu} {}^1(\text{Sens}^*) \xrightarrow{\text{ISC}} {}^3(\text{Sens}^*) \xrightarrow{{}^3O_2} {}^1O_2 + \text{Sens} \quad (1)$$

Singlet oxygen may be generated in a wide range of solvents, the choice of solvent being dictated by the solubility of substrate and sensitizer and by solvent properties that influence ease of workup. The lifetime of $^1O_2$ varies from 2 µs in H_2O to approximately 700 µs in CCl_4 (Table 1) and is considerably longer when the solvent is deuterated (the lifetime of $^1O_2$ is almost always increased by a factor of ten when the solvent is perdeuterated).[9]

Table 1 Lifetimes of Singlet Oxygen in Various Solvents[9]

Solvent	Lifetime (ms)	Solvent	Lifetime (ms)
H_2O	2	MeCN	30
MeOH	7	$CHCl_3$	60
EtOH	12	CS_2	200
C_6H_{12}	17	$CDCl_3$	300
D_2O	20	C_6F_6	600
C_6H_6	24	CCl_4	700
MeCOMe	26	Freon-11	1000

The light sources used are generally high intensity lamps which emit light in the visible range. Sun lamps have been employed in certain instances but they may bring about competing UV-promoted reactions and rearrangements. Among the lamps used as light sources are Sylvania 500 W tungsten halogen,[10] Osram-Vialox 250 W,[11] 500 W Halogen-Argaphoto,[12] 500 W Toshiba JD,[13] 200 W halogen,[14] 650 W tungsten halogen,[15] 100 W tungsten halogen,[16] and 500 W high pressure sodium.[17]

Generation from Phosphite Ozonides.[3]

Triphenyl Phosphite is treated with ***Ozone*** at -78 °C (dry ice-acetone) in methylene chloride until the blue color of excess ozone is observed. Ozonization is then discontinued and the solution is purged with dry nitrogen to remove the excess oxidant. A cold solution of the acceptor in methylene chloride is then added, and mixing is effected by the nitrogen stream. The -78 °C bath is then removed and replaced with a -25 °C bath (ice-methanol). Alternatively, the reaction mixture is permitted to warm to rt and then worked up by concentration and chromatography.

Generation by the Decomposition of 9,10-Diphenylanthracene Endoperoxide. Oxidation of an Oxazole to a Triamide.

In contrast to dialkyl peroxides, which usually undergo oxygen-oxygen bond cleavage on pyrolysis, many aromatic endoperoxides break down on heating with release of oxygen in the singlet state.[18] Among the available endoperoxides, 9,10-diphenylanthracene peroxide (**1**) has been found to be a particularly efficient donor of $^1O_2$ in this type of decomposition. It can easily be prepared as a stable product (dec 180-181 °C, mp 254 °C) by irradiation of a cold solution of 9,10-diphenylanthracene in carbon disulfide for 48 h in a stream of oxygen using a 275 W Sylvania RS lamp.[19]

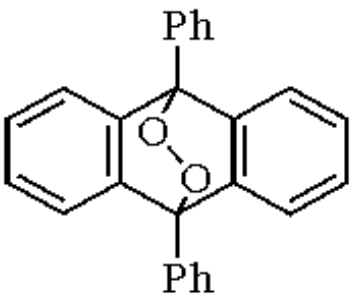

(1) DPAP

A typical singlet oxygen reaction using this peroxide is illustrated in the conversion of 2,5-diphenyl-4-methyloxazole to *N*-acetyldibenzamide (eq 2).[18] In this oxidation, an anhydrous benzene solution containing the peroxide and the oxazole is stirred at reflux temperature in the dark for 94 h under a positive pressure of nitrogen. Removal of benzene and chromatography on silica gel yields the triamide (92%), as well as some diamide formed during chromatography, in addition to 9,10-diphenylanthracene.[4]

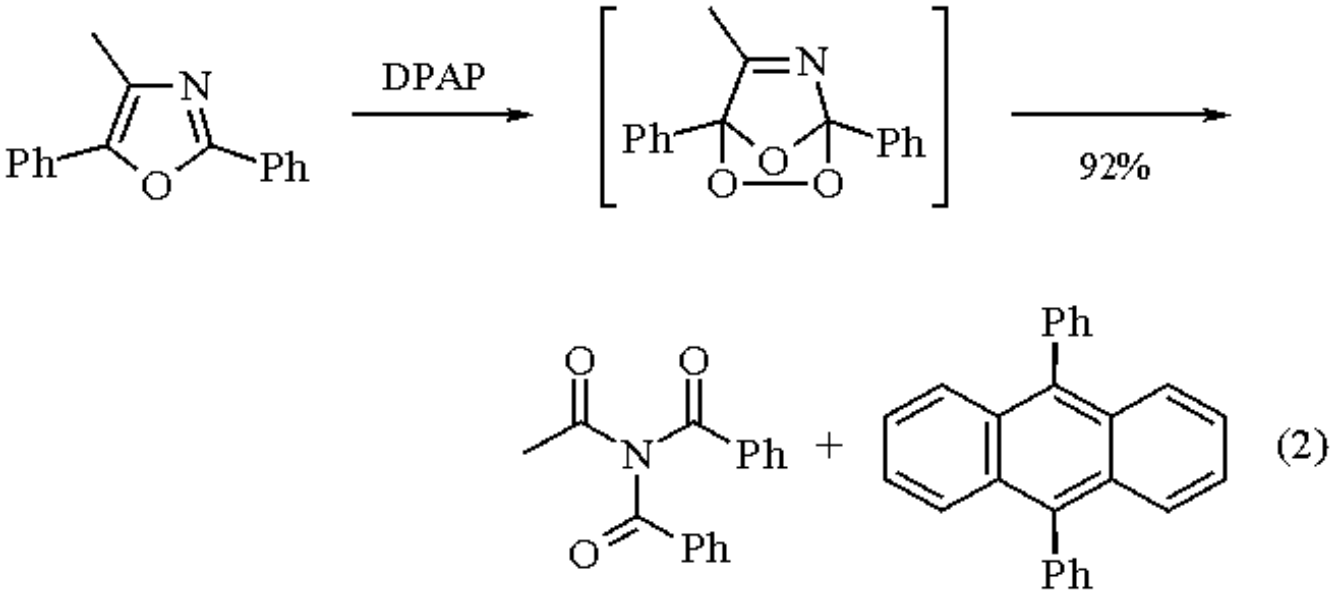

Generation of $^1O_2$ by Hypochlorite-Hydrogen Peroxide Oxygenation.[5]

In this procedure, illustrated by the conversion of 2,3-dimethylbutene to the allylic hydroperoxide (eq 3), a methanolic solution of the substrate is treated with 3 equiv of 30% ***Hydrogen Peroxide*** and stirred at 10 °C. To this mixture, aqueous ***Sodium Hypochlorite*** is slowly added (2.5 equiv). The solution is then diluted with water, extracted with ether, and worked up.

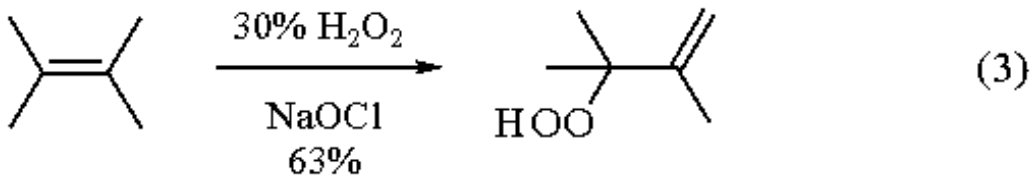

Oxygenations with $^1O_2$.

Singlet oxygen undergoes three classes of reaction with alkenes: an ene type of reaction forming allylic hydroperoxides; 1,4-cycloaddition with cisoid 1,3-dienes; and 1,2-cycloaddition with electron-rich or strained alkenes. In addition, $^1O_2$ reactions take place with many types of heterocyclic compounds including furans, pyrroles, oxazoles, indoles, imidazoles, and thiophenes.[20,21] Other types of $^1O_2$ reaction take place with sulfides, carbon-phosphorus double bonds, and electron-rich aromatic systems. In many cases, competition exists between different modes of oxidation, as in the reaction of dihydropyran with $^1O_2$ (eq 4), which takes place either by 1,2-dioxetane formation and subsequent cleavage, or by an ene reaction forming a hydroperoxide which undergoes O-O bond fission by a β-elimination. In this case, it is found that the ratio of products (**2**) to (**3**) varies over a 58-fold range depending on the solvent used (Table 2), with polar solvents favoring 1,2-dioxetane formation over the ene reaction.[22]

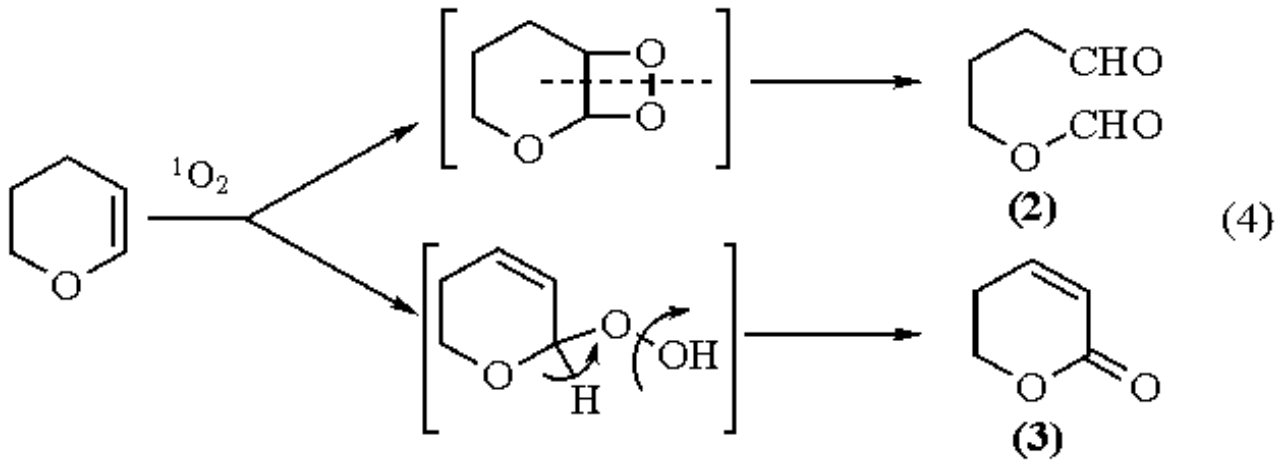

Table 2 Dependence of Reaction Mode on Solvent in the $^1O_2$ Oxidation of Dihydropyran

Solvent	Product ratio (**2**)/(**3**)
Benzene	0.094
Acetone	0.50
Methylene chloride	2.67
Acetonitrile	5.51

The Singlet Oxygen Ene Reaction.

The reaction of alkenes containing at least one allylic hydrogen with singlet oxygen, yielding a hydroperoxide with accompanying shift of the double bond, bears a close resemblance to the Alder ene reaction (eq 5). This ene type of oxidation has been extensively used in synthesis. Reduction of the allylic hydroperoxide yields the corresponding allylic alcohol. An analogous reaction of enol silyl ethers yielding silylperoxy esters is assumed to take place by the same mechanism (eq 6).[23] Formation of allylic hydroperoxides is not stereoselective, as is shown by the intermediates in the garrya and atisine alkaloid syntheses (eqs 7 and 8).[24]

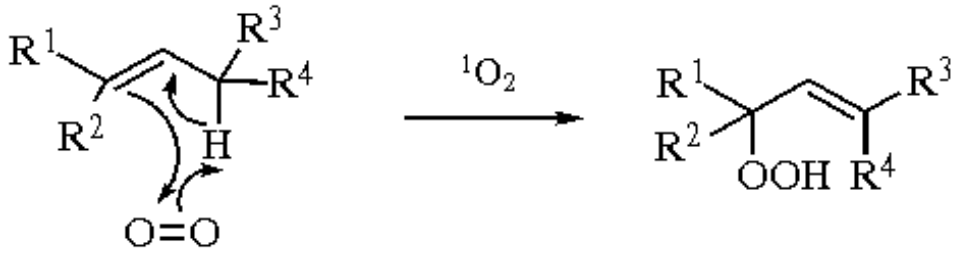

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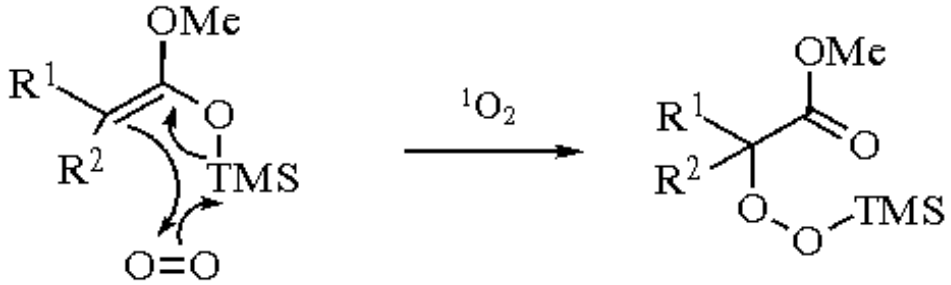

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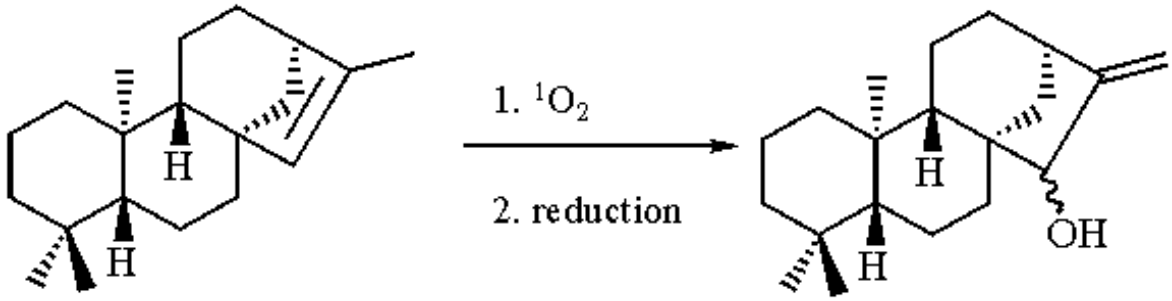

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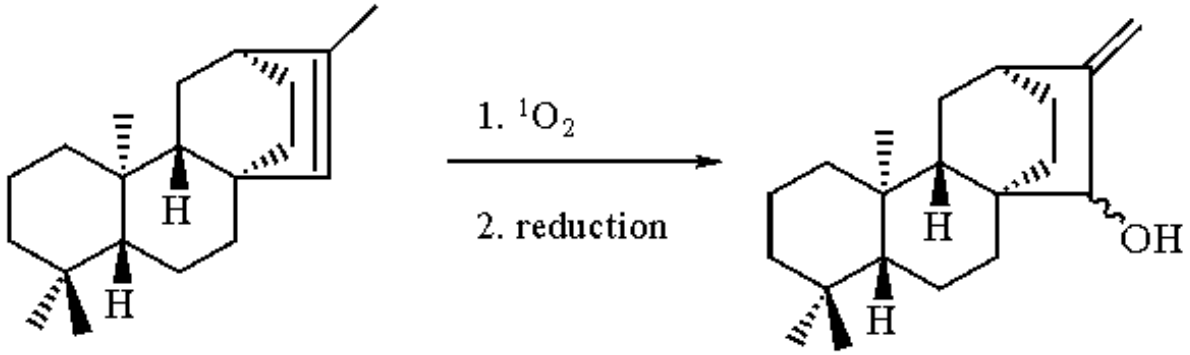

(8)

The photooxygenation of Δ^9-octalin followed by reduction with hydrazine yields $\Delta^{1(9)}$-10-octalol, a key intermediate in the synthesis of *trans*-cyclodecenone (eq 9).[25] The ene reaction has also been used for the contrathermodynamic isomerization of an alkene (eq 10)[26] and in the formation of allylic alcohols for later conversion to α,β-unsaturated ketones (eq 11).[27]

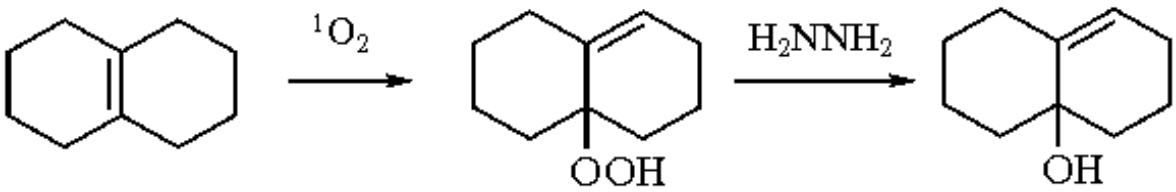

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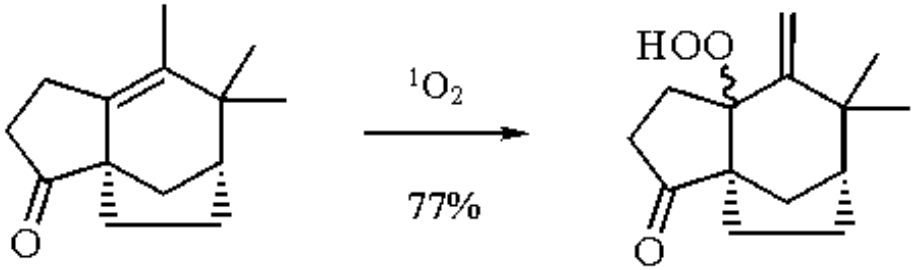

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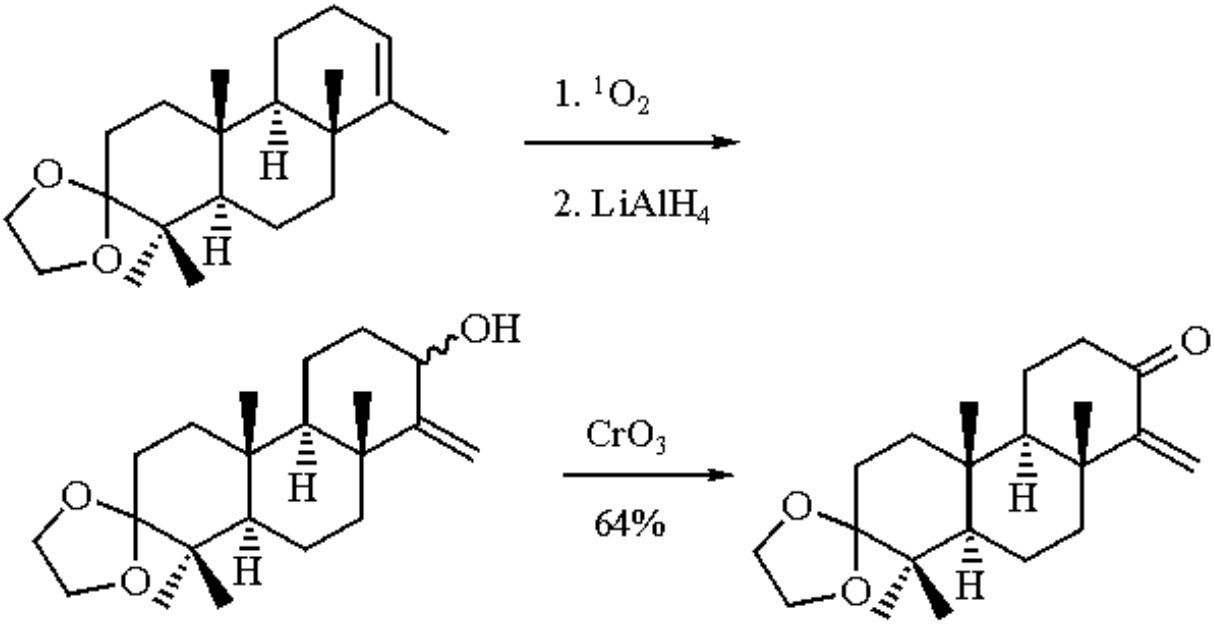

(11)

An interesting use of the ene $^1O_2$ reaction in conjunction with the Diels-Alder type of $^1O_2$ addition is found in the dye-sensitized photooxidation of neoabietic acid.[28] The first step involves an ene reaction at the more highly substituted double bond, generating a hydroperoxide along with the shift of the double bond to form a *cis*-1,3-diene. The second-stage [2 + 4] addition yields a transannular peroxide which undergoes a β-elimination and reduction to form the product (eq 12).

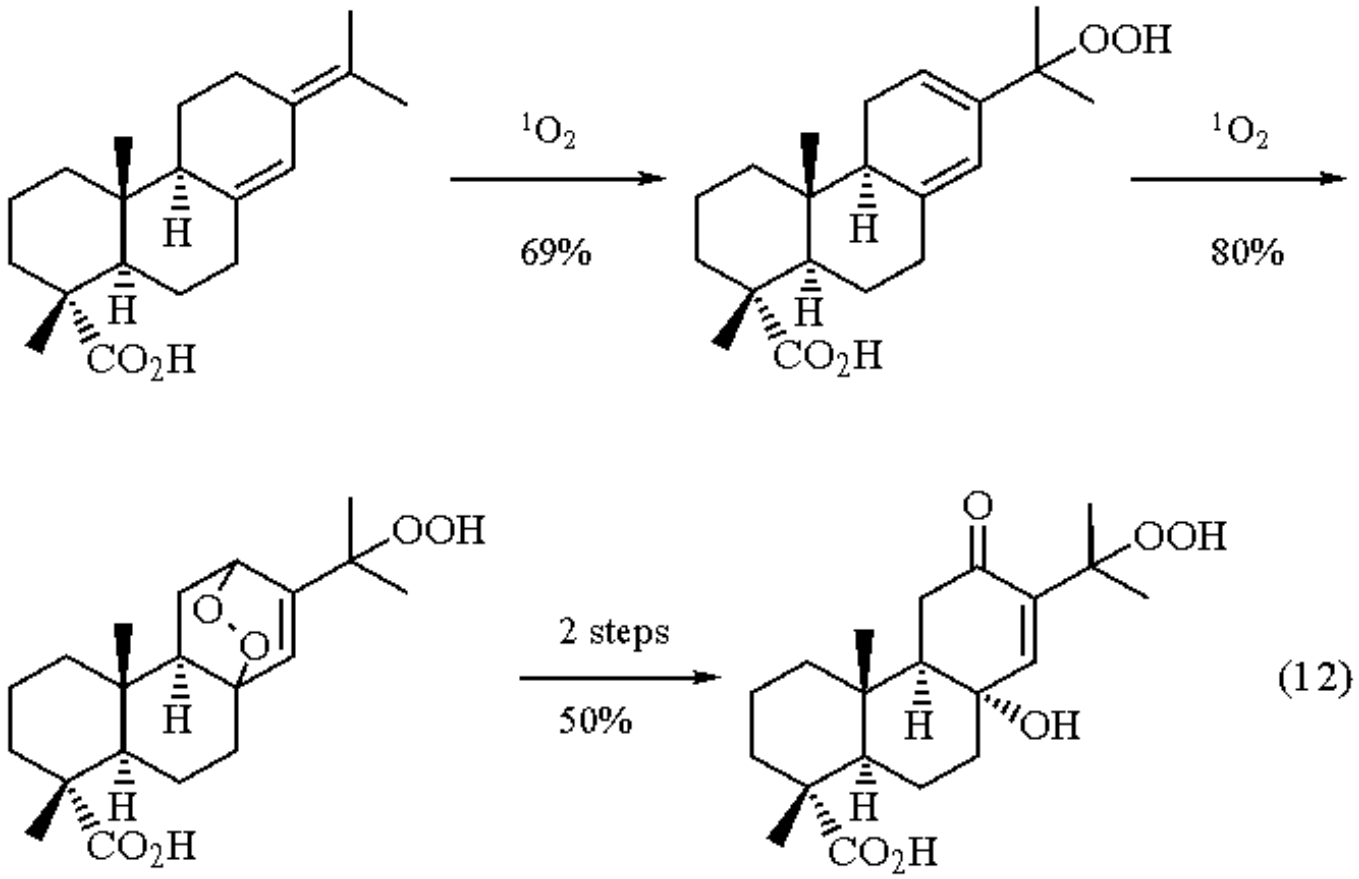

(12)

In the final steps of a total synthesis of tetracycline, the anhydro derivative is converted to a hydroperoxide in high yield by a singlet oxygen addition in the ene mode (eq 13). The reaction is very sensitive to overoxidation and succeeds only when the dye-sensitized photooxidation is terminated after a few minutes.[29]

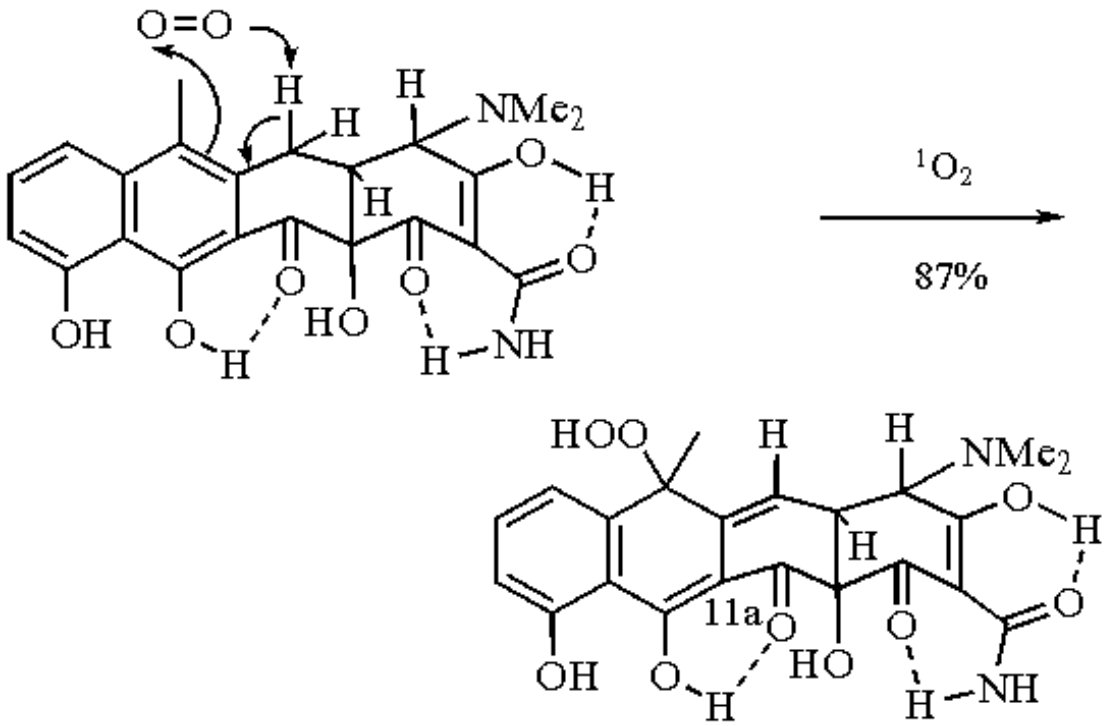

(13)

1,4-Cycloaddition.

The reaction of singlet oxygen with cisoid 1,3-dienes takes place in both carbocyclic and heterocyclic systems. In general, the formation of 1,4-cycloaddition products from 1,3-dienes is the hallmark of singlet oxygen reactivity, in contrast to other less well-defined oxidation processes effected by oxygen in the ground state. The early synthesis of (±)-ascaridol by the dye-sensitized photooxygenation of α-terpinene is a classic case of 1,4-addition by singlet oxygen (eq 14).[30] The Schenck synthesis of cantharidine[31] also makes use of an endoperoxide formed by a Diels-Alder type cycloaddition of singlet oxygen (eq 15). In another application, the formation of bis-epoxides by thermolysis of 1,4-endoperoxides generated in a singlet oxygen addition is employed in the synthesis of (±)-crotepoxide (eq 16).[32]

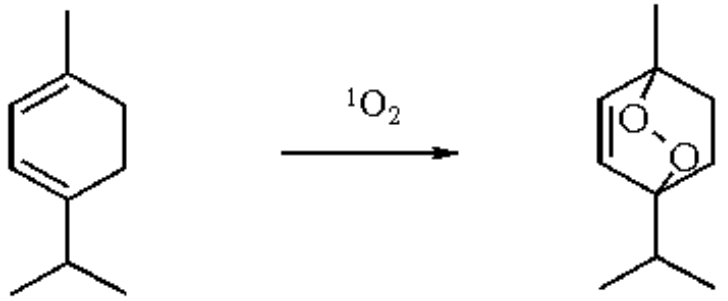

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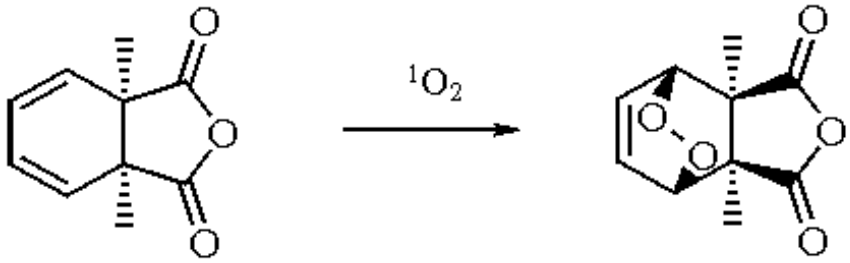

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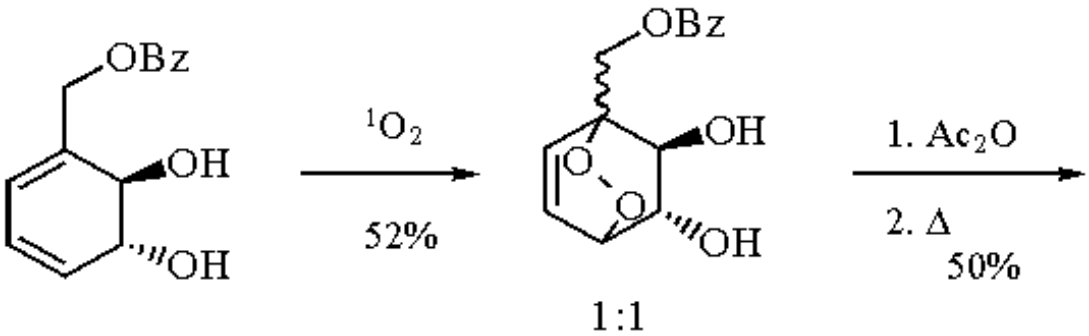

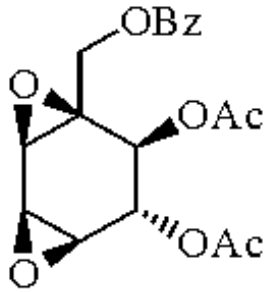

(16)

Furan photooxidation by 1,4-cycloaddition of $^1O_2$ has been widely used as a means of generating carbonyl compounds from transannular peroxide intermediates. In an early example, 2-furfural was converted by $^1O_2$ to the unsaturated lactone intermediate (eq 17) in a synthesis of camptothecin.[33] Likewise, oxidation of 3-methyl-2-furoic acid yields the corresponding methyl derivative used as a key component in a synthesis of (±)-strigol (eq 18).[34] These transformations most probably take place by solvolysis of the intermediate endoperoxide followed by fragmentation, as shown in eq 19. Examples have been reported of singlet oxygen reactions with styrene derivatives where a benzene ring acts as part of a 1,3-diene system (eq 20).[35,36]

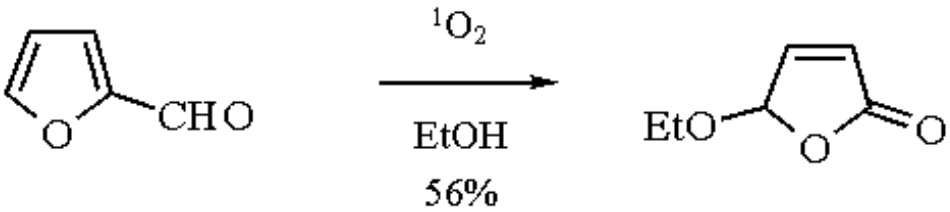

(17)

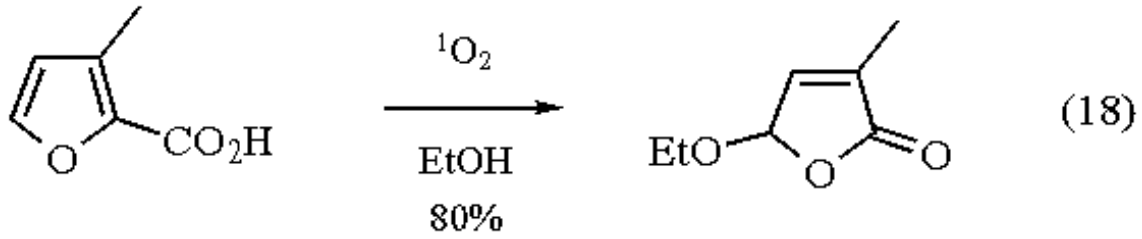

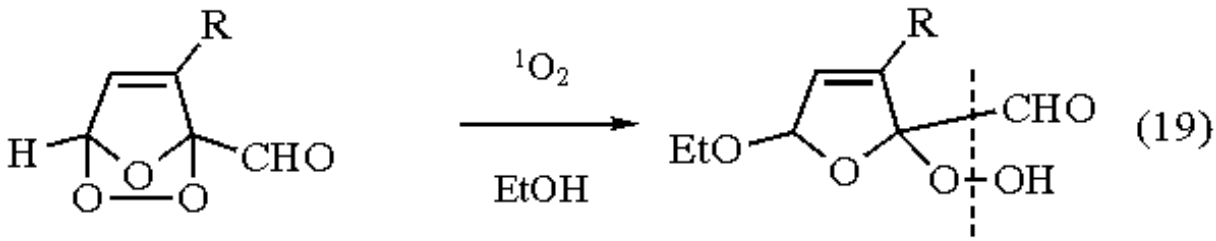

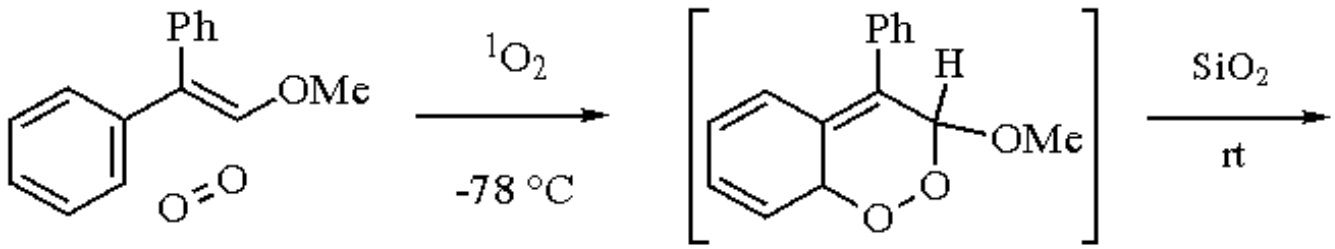

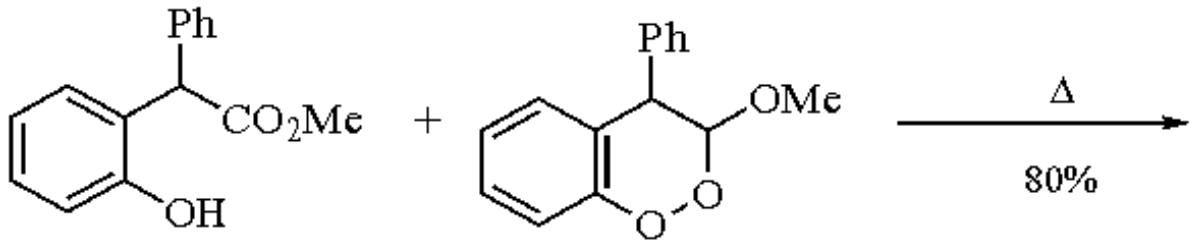

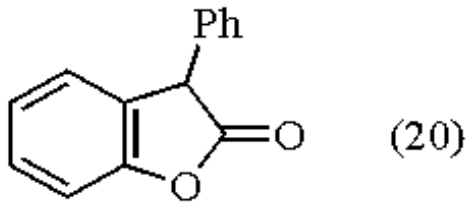

A recent example of 1,4-addition of singlet oxygen to a pyrrole involves the dye-sensitized photooxidation of 2-carboxy-4-methoxy-5-(methoxycarbonyl)-1-methylpyrrole (eq 21). The intermediate endoperoxide undergoes fragmentation by decarboxylation and cleavage of the O-O bond to give 5-hydroxy-4-methoxy-5-(methoxycarbonyl)-1-methyl-3-pyrrolin-2-one).[37]

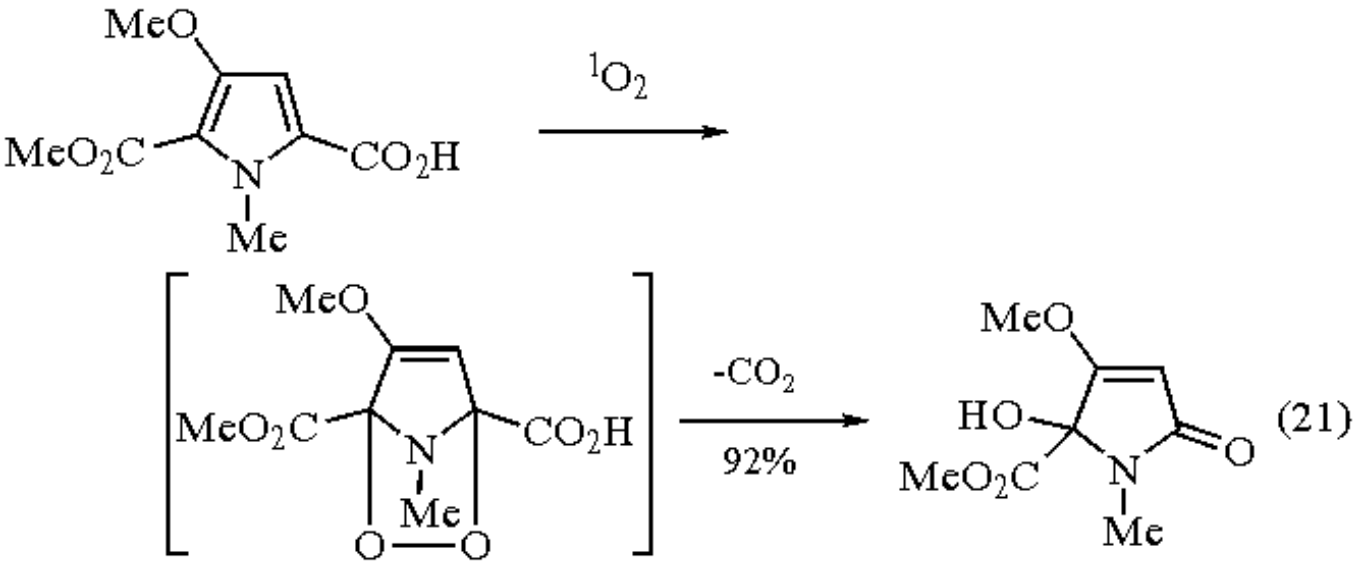

Addition of Singlet Oxygen to Alkenes Activated by Electron-Releasing Groups.

The addition of singlet oxygen to alkenes occurs in the presence of amino or alkoxyl groups in the absence of active allylic hydrogens in the same molecule. The addition takes place stereospecifically by *cis* addition to form dioxetanes as isolable products. These, in turn, undergo thermolysis to form electronically excited carbonyl compounds with accompanying chemiluminescence. Thus photooxidation of 1,1,2,2-tetramethyoxyethylene sensitized by either zinc tetraphenylporphyrin or dinaphthalenothiophene proceeds smoothly to give an isolable clear, pale-yellow liquid shown to be the tetramethoxydioxetane (eq 22).[38] On the other hand, the crystalline *cis*-dioxetane, formed on dye-sensitized photooxidation of *cis*-diethoxyethylene in fluorotrichloromethane at -78 °C under irradiation with a 500 W lamp for 25 min, explodes on warming to rt (eq 23).[39]

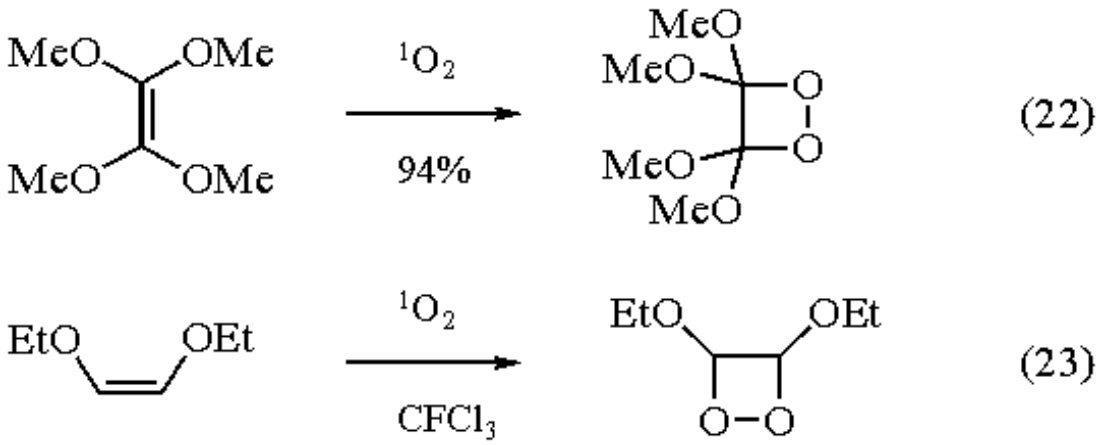

Reactions of Enamines with Singlet Oxygen.

Reactions of enamines with $^1O_2$ take place readily to form the carbonyl products expected from the cleavage of dioxetane intermediates. In the case of the piperidine enamine of methyl isopropyl ketone, the reaction is carried out in benzene using zinc tetraphenylporphyrin as sensitizer (eq 24).[40] In related work, photooxygenation of the 22-morpholine enamine of 3-oxobisnor-4-cholen-22-al in DMF at 15 °C using Rose Bengal as sensitizer yields a quantitative yield of progesterone (eq 25).[41] Likewise, $^1O_2$ cleavage of the highly electron-rich enamines formed from the silyl enol ethers of azetidinecarboxylic esters provides a route to β-lactams (eq 26).[42]

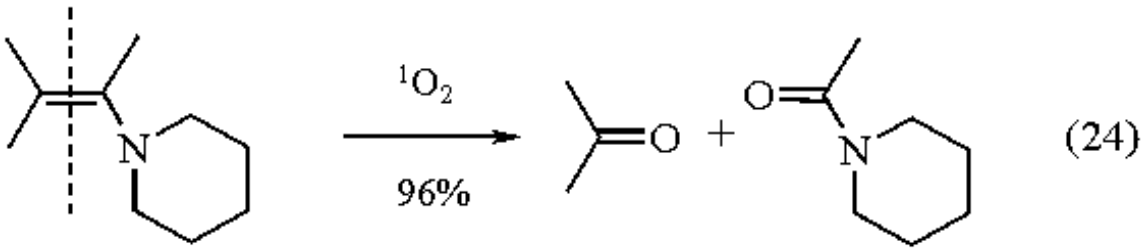

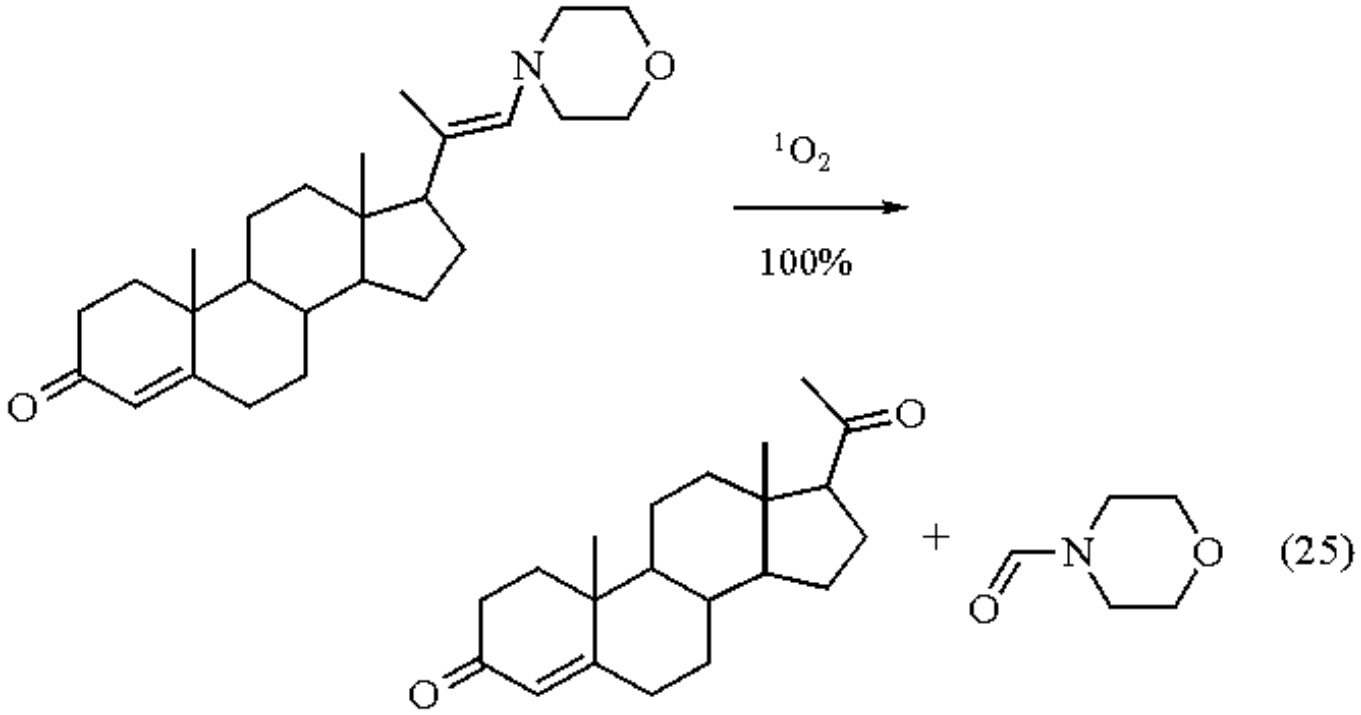

(25)

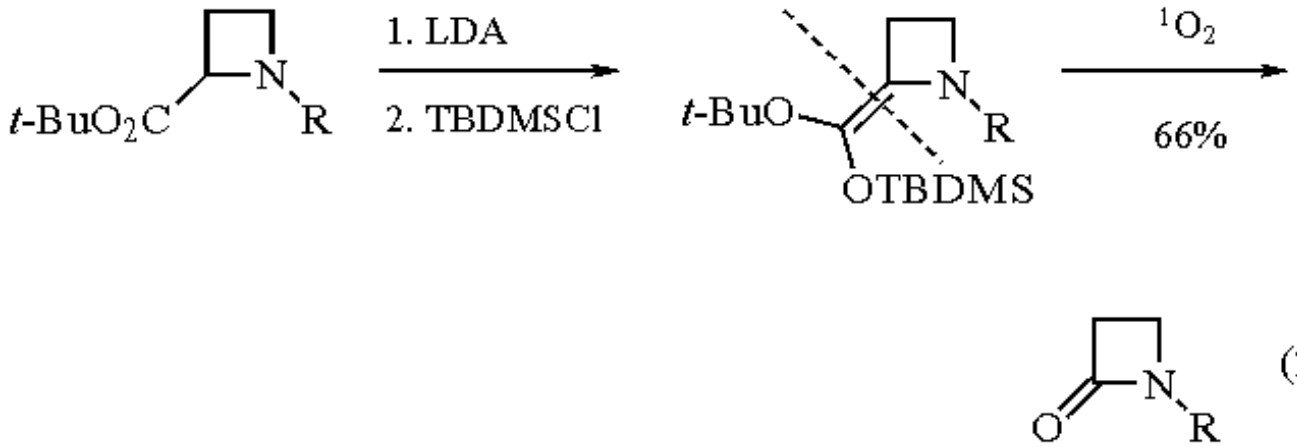

(26)

Reactions of Enols with $^1O_2$.

As electron-rich alkenes, enols react with singlet oxygen along the lines of the ene reaction to give unstable intermediate hydroperoxides which undergo further transformations. The reactions are enhanced by the presence of fluoride ion, presumably by the formation of a strong hydrogen bond between the enol-OH and the fluoride.[43] Thus 1,3-cyclohexanedione reacts with $^1O_2$ in the presence of fluoride ion to give pyrogallol (eq 27). 4-Hydroxycoumarin, which is normally relatively inert toward $^1O_2$, readily undergoes oxygen uptake with $^1O_2$ in the presence of fluoride ion (eq 28).

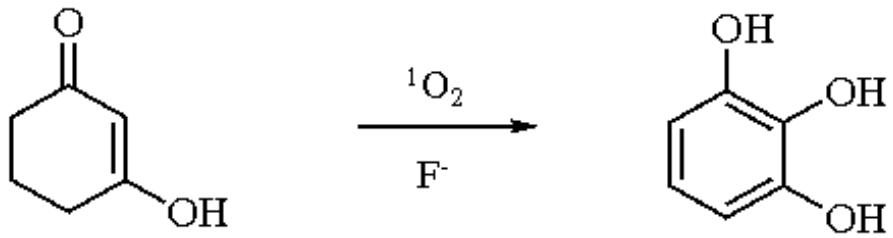

(27)

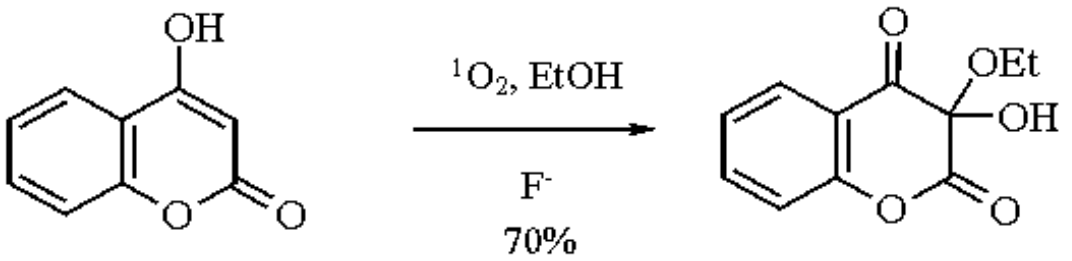

(28)

While it has generally been assumed that alkenes with electron-withdrawing groups are inert to $^1O_2$, it has recently been shown that α,β-unsaturated ketones which are constrained in the *s-cis* conformation are rapidly oxidized by $^1O_2$. Systems which prefer the *s-trans* conformation react slowly or not at all.[44,45] For example, compound (**4**) yields 88% of the hydroperoxide (eq 29) while compound (**5**) shows no reaction toward $^1O_2$. The difference is accounted for in terms of an initial [4 + 2] cycloaddition of $^1O_2$ to form a 1,2,3-trioxine (eq 30),[44] which then undergoes further transformations.

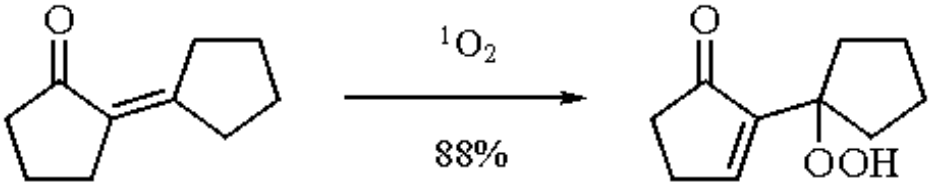

(29)

(4)

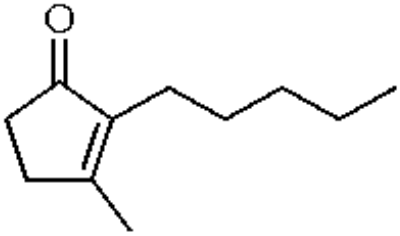

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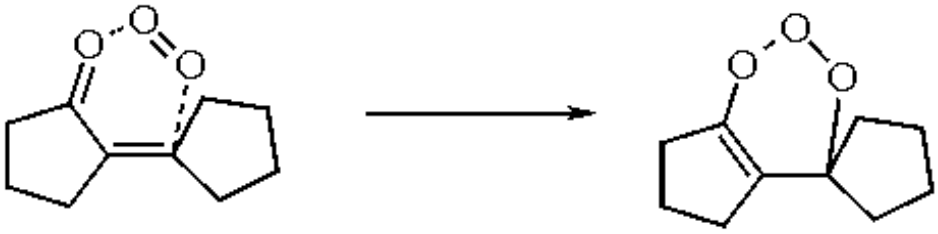

(30)

Oxidation of Sulfides.

Sulfides react with singlet oxygen to form sulfoxides and sulfones.[46-49] The reaction takes place through intermediate persulfoxides. The rate of uptake of $^1O_2$ appears to be relatively independent of solvent and temperature. Other reaction paths have been observed. Thus although the $^1O_2$ oxidation of the linear sulfide yields the expected mixture of sulfoxide and sulfone (eq 31), oxidation of the thiazolidine with singlet oxygen, followed by deoxygenation with Me_2S or Ph_3P, gives a quantitative yield of the product of α-hydroxylation (eq 32). Formation of this alcohol is considered to take place by a Pummerer-type of rearrangement of an intermediate persulfoxide.[50]

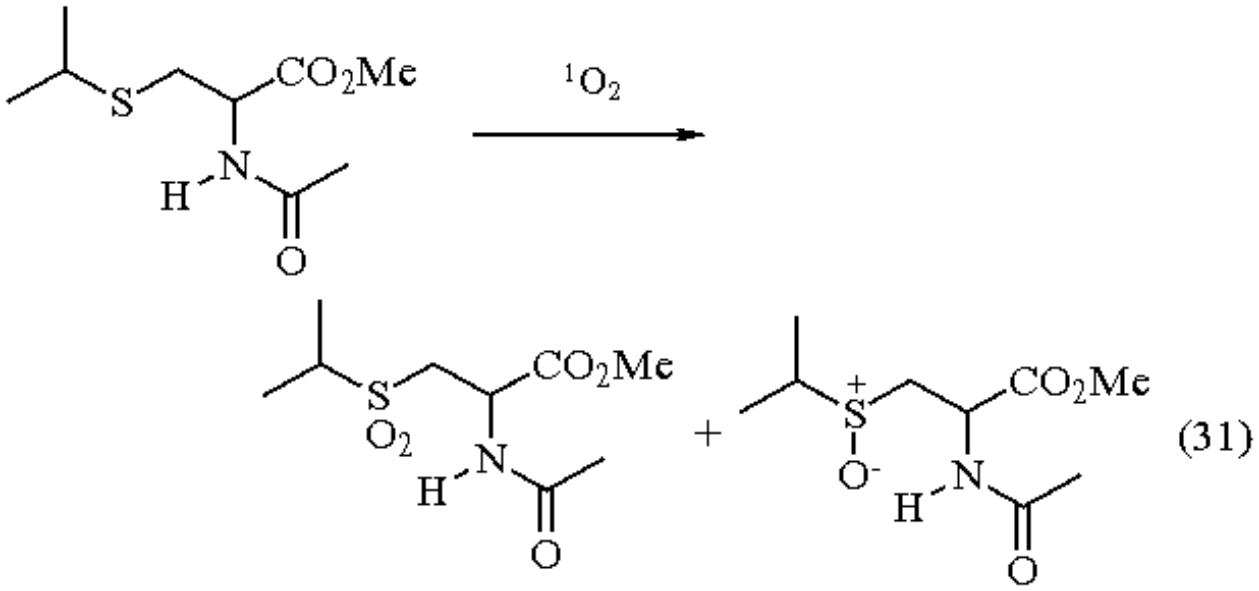

(31)

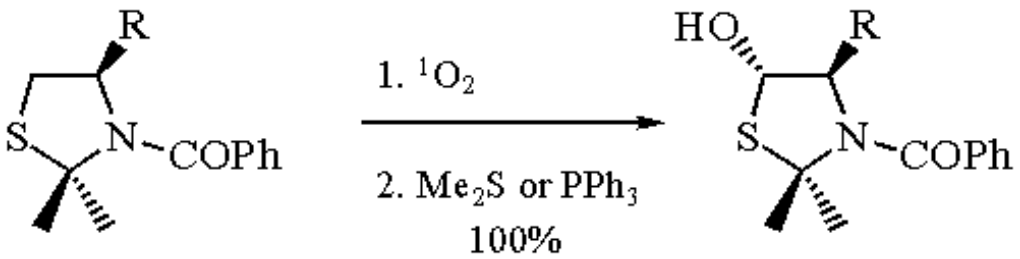

(32)

Cleavage of Carbon-Phosphorus Double Bonds by Singlet Oxygen.

Singlet oxygen cleaves phosphorus ylides to form carbonyl compounds and the corresponding phosphine oxide (eq 33).[51] The reported procedure involves dye-sensitized photooxidation of the phosphorane in a solvent such as chloroform, benzene, or methanol using *meso*-tetraphenylporphyrin or Rose Bengal as sensitizer with irradiation from a 500 W tungsten filament lamp while oxygen is bubbled through the solution. This method has recently been employed in one of the procedures for oxidizing phosphoranes to tricarbonyl compounds (eq 34).[52]

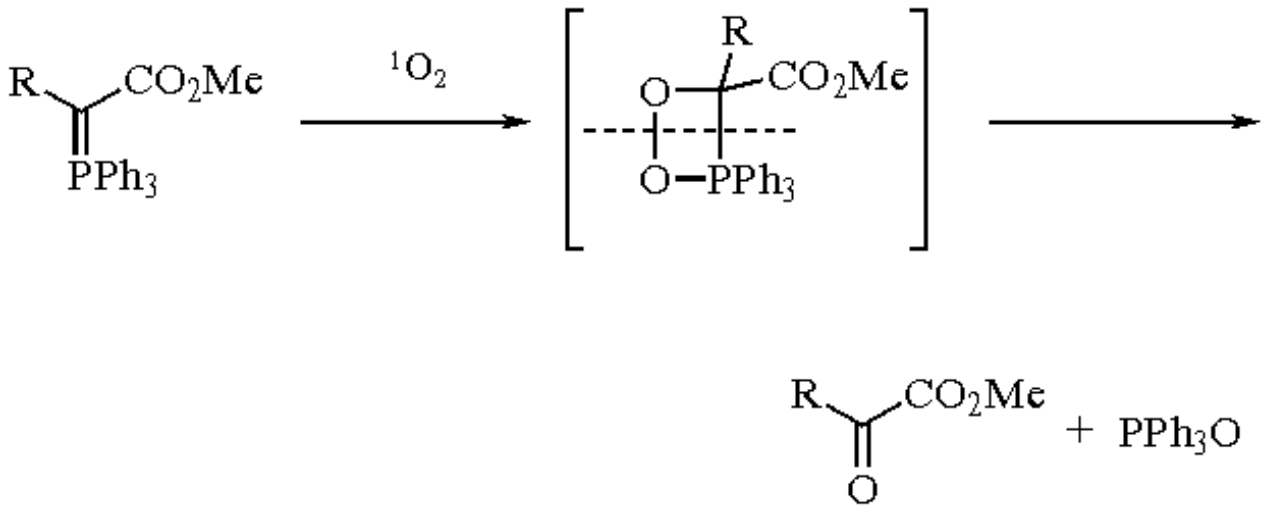

(33)

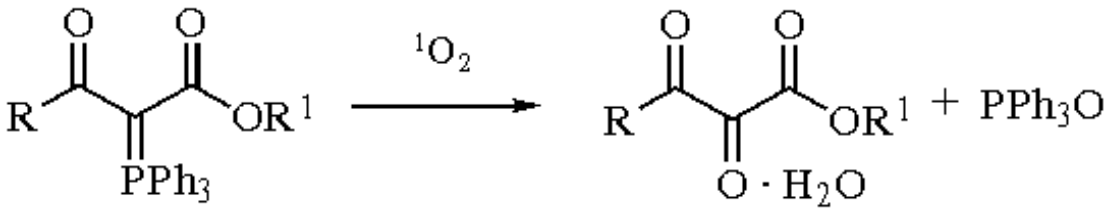

(34)

Trapping Dioxetanes and Other Peroxidic Singlet Oxygen Oxidation Products.

In certain cases, dioxetane intermediates and other peroxidic species may be deoxygenated by reaction with diphenyl sulfide, a species which is unreactive toward $^1O_2$.[48] As an example,[53] the dye-sensitized photooxygenation of tetraphenylimidazole normally yields the dibenzoyl derivative in nearly quantitative yield, presumably through the dioxetane (eq 35). In the presence of diphenyl sulfide, a product of rearrangement is also formed along with diphenyl sulfoxide. Other studies on trapping agents for peroxidic intermediates have included the use of pinacolone for perepoxides[54] and dimethyl sulfide or triphenylphosphine for persulfoxides.[55]

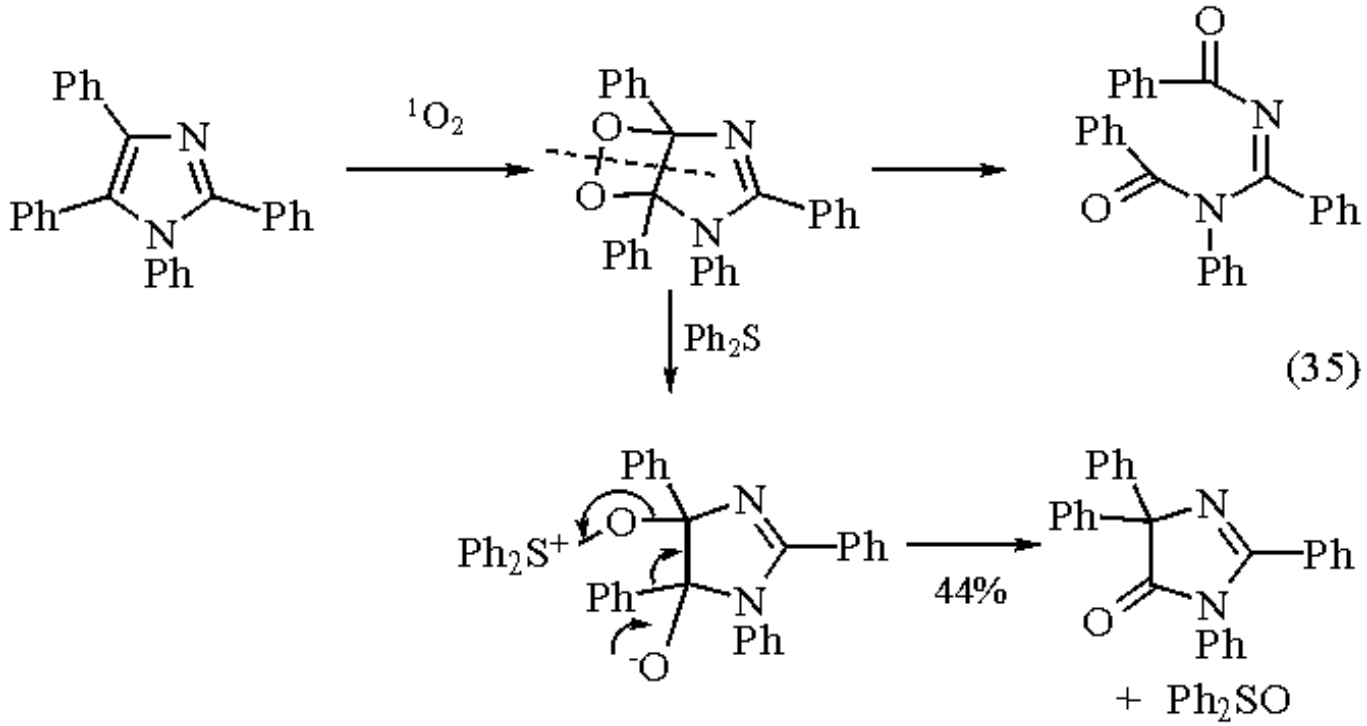

(35)

Sensitivity of $^1O_2$ Reactions to the Environment.

The reactions of singlet oxygen with organic substrates are very sensitive to the experimental environment. Temperature, reaction time, substituents, solvent, and dissolved solutes may all affect the oxidations, resulting in mixtures of products of varied composition. This phenomenon is well illustrated in the studies on the sensitized photooxidation of a 5,6-disubstituted 3,4-dihydro-2*H*-pyran, in which solvent effects lead to widely varying product distributions (eq 36).[56] Table 3 illustrates these effects.

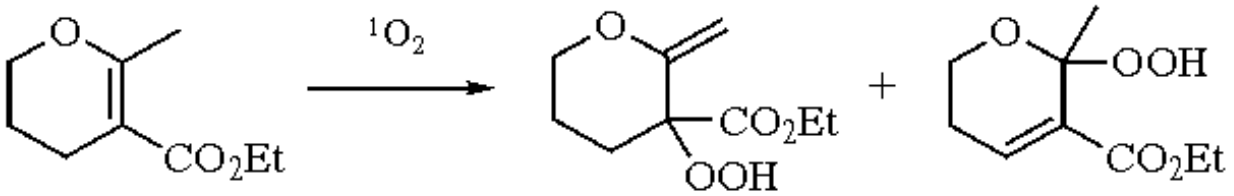

(36)

(6) (7)

Table 3 Solvent Effects in the $^1O_2$ Ene Reaction

Solvent/sensitizer	Time (h)	% (**6**)	% (**7**)	(**6**):(**7**)
Benzene/TPP	9	10	90	0.11
CCl_4/TPP	7	17	83	0.18
$CHCl_3$/TPP	5	45	55	0.82
CH_2Cl_2/TPP	5	50	50	1.00
MeCN/MB	3.5	65	35	1.86

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Sodium[1]

Na

[7440-23-5] · Na · Sodium · (MW 22.99)

(powerful one-electron reducing agent for most functional groups;[1] reductively couples ketones and esters to unsaturated carbon atoms;[2] reductively eliminates and couples halogens and other groups; can be used to generate alkoxides)

Physical Data: mp 97.8 °C; *d* 0.968 g cm^{-3}.

Solubility: sol liquid NH_3; slightly sol ethereal solvents; dec in alcohols; reacts violently in H_2O.

Form Supplied in: silver-white or gray solid in brick, stick, or ingot form; more commonly as 3-8 mm spheres or as a dispersion in various inert oils.

Purification: surface oxide can be removed by heating in toluene;[3] oxide impurities can usually be ignored.

Handling, Storage, and Precautions: the dry solid quickly oxidizes when exposed to air and in very moist air is potentially flammable. The highly corrosive sodium vapor ignites spontaneously in air, and is a severe irritant to eyes, skin, and mucous membranes. Utmost care should be taken to keep sodium away from halogenated solvents, oxidants, and aqueous mineral acids. Fires should be quenched with a dry powder such as Na_2CO_3, NaCl, or NaF; water, CO_2, Halon, and silica gel should be avoided. Excess sodium is best disposed of by slow introduction into a flask of isopropanol, possibly containing 1% water, taking care to vent liberated H_2, and neutralizing the resulting solution with aqueous acid. Sodium stored under oil is best weighed by rinsing freshly cut pieces with hexane and after evaporation adding to a tared beaker containing hexane.

Reaction Conditions.

Sodium, along with the other commonly used alkali metals ***Lithium*** and ***Potassium***, is an extremely powerful one-electron reductant. Historically, solutions of sodium in ammonia have been used to reduce a wide variety of functional groups (see also ***Sodium-Ammonia*** for some of these transformations, particularly the Birch reduction of aromatic rings).[4] These reductions are usually carried out in the presence of proton donors, normally simple alcohols or NH_4Cl, though occasionally these are added prior to workup. Many reductions are performed with solutions of sodium in refluxing alcohols; here a large excess of sodium is often required due to its gradual decomposition to alkoxides and H_2. It is sometimes simpler to add a mixture of alcohol and substrate to a dispersion of sodium in an inert solvent such as toluene. HMPA is also occasionally employed as a solvent;[5] solutions of sodium in HMPA behave similarly to those in ammonia.[6] While sodium is insoluble in solvents such as DME or THF, naphthalene is usually included, and a green solution of the ***Sodium Naphthalenide*** radical anion forms.[7] Though the reduction potential of this system is similar to that of sodium in other solvents (a half-wave potential of -2.5 V[8] vs. -2.96 V in HMPA[6b] and -2.59 V in NH_3[1b]), side reactions are often minimized, and reductions are sometimes titrated to color end-point. Other additives such as anthracene and benzophenone result in solutions with decreased, more selective, reducing power, though this has been rarely exploited.[8]

Reduction of Unsaturated Bonds.

The classical reduction of ketones with sodium in alcohol, along with the mechanistically similar reduction in ammonia with added proton donors, still finds use in certain systems where the desired stereochemistry cannot be generated by metal hydrides (see also ***Lithium***).[1d-g] The ammonia system is preferred, minimizing epimerization of ketones and equilibration of product alcohols. NH_4Cl has been recommended as proton donor to suppress hydrogen transfer,[9] though this requires a large excess of sodium;[10] using several equivalents of a primary alcohol also minimizes this side reaction.[11] Alcohols, ethers, amines, carboxylic acids, and isolated internal double bonds are unaffected, but most other functional groups have reduction potentials less negative than aliphatic ketones. Aromatic ketones and α-heteroatom-substituted ketones are generally unsuitable substrates for these reductions.

Reductions are kinetically controlled, though the literature contains several mistaken assumptions on this point; stereochemistry is determined by pyramidalization of the ketyl and subsequent carbanion intermediates, and prediction of the stereochemical result is in

most cases extremely difficult. Study of certain systems does allow a few general remarks to be made. Unhindered cyclohexanones usually give larger equatorial:axial ratios than can be obtained with metal hydrides or by equilibration.[12] Generation of equatorial alcohols from hindered cyclohexanones often requires the use of dissolving metals, while metal hydrides can give exclusively the axial product (eqs 1 and 2).[13] Bicyclo[2.2.1]heptan-2-ones always provide an excess of the *endo*-alcohol (eq 3).[14,15]

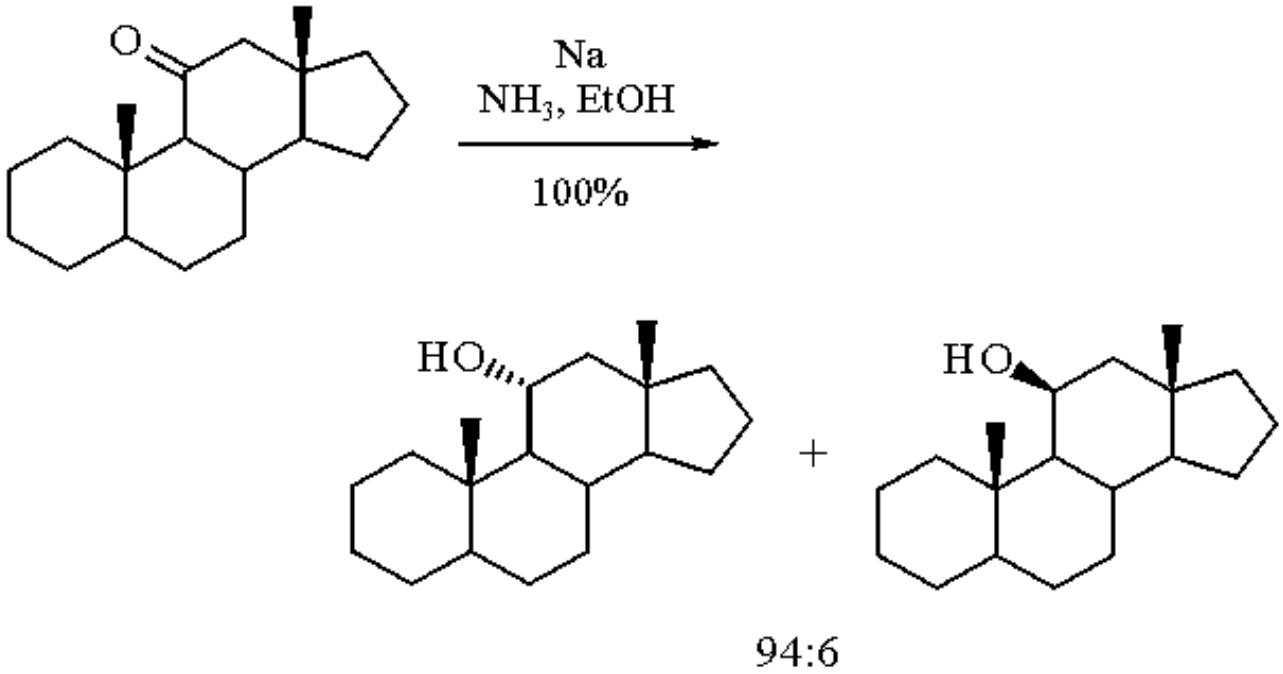

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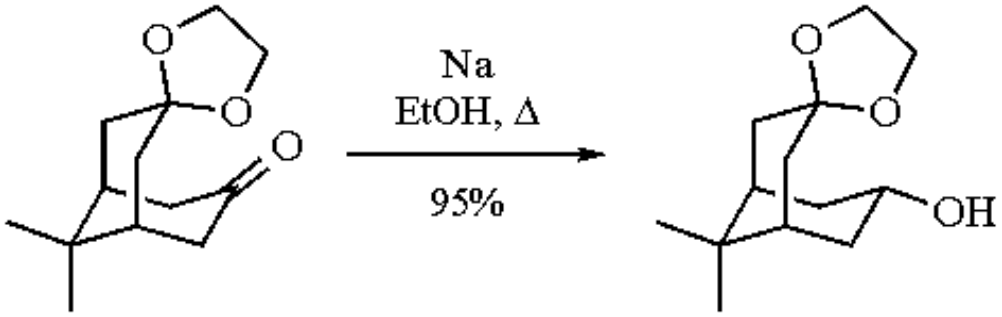

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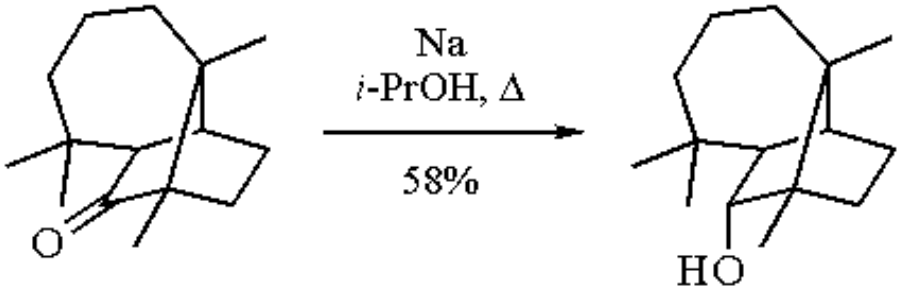

(3)

Imines are reduced to amines in good yield by sodium in alcohols, probably through a similar mechanism. In the absence of proton donors, reductive dimerization dominates.[16] 1,3-Diimines, which exist as tautomeric enamino imine mixtures, are reduced to diastereomeric mixtures of diamines (eq 4).[17] Allylic imines have been reduced to alkenes.[18] Reduction of oximes by sodium in alcohol is particularly useful,[19] since ***Lithium Aluminum Hydride*** can produce Beckmann rearrangements or aziridines.[20,21] Bicyclo[2.2.1]heptan-2-one and tricyclo[2.2.1.0^{2,6}]heptan-3-one oxime reductions yield predominantly *endo*-amines (eq 5).[21,22]

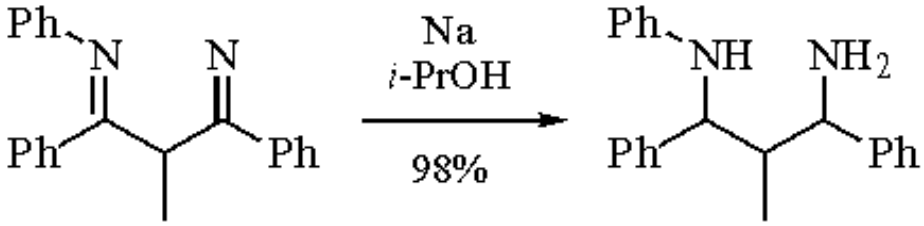

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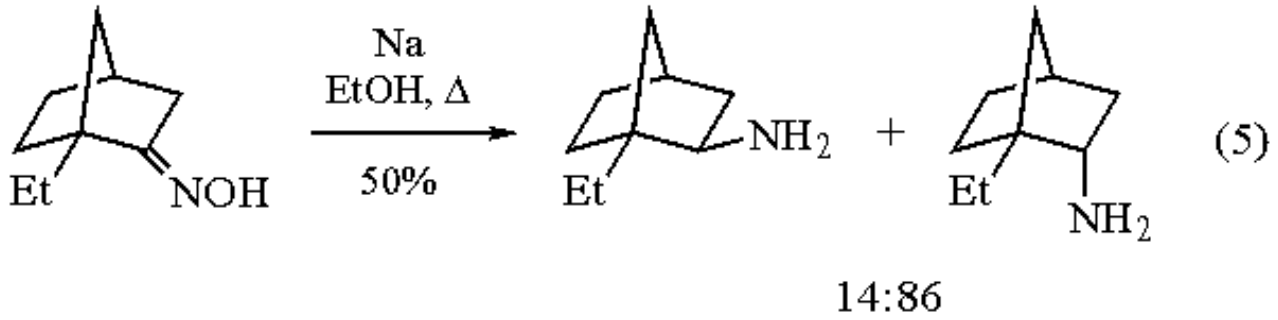

The reduction of esters to alcohols with sodium in alcohol (Bouveault-Blanc reduction)[23] has been all but supplanted by the use of metal hydrides. Where an ester must be reduced in the presence of an acid, an improved procedure run in ammonia can be used effectively (eq 6).[24]

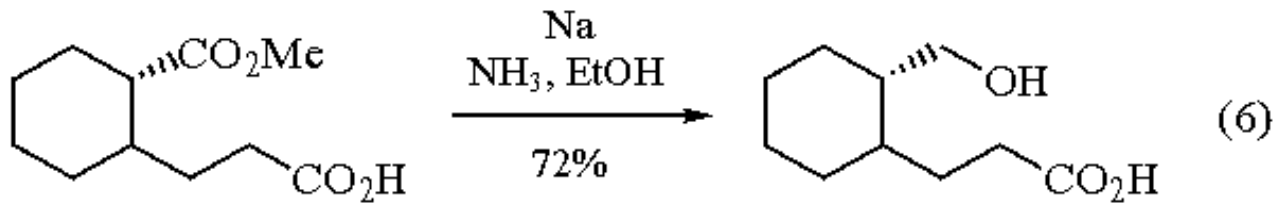

Dissolving metal reductions of α,β-unsaturated carbonyl compounds are almost always performed with lithium in ammonia (see ***Lithium***),[1d] though sodium is occasionally used without any particular change in result. Selected examples of enone reduction with sodium in HMPA have been examined;[6b,25] these are most notable for the fact that they tend to produce product mixtures enriched in the less stable epimer, compared to reactions run in ammonia (eq 7).[25a,1e]

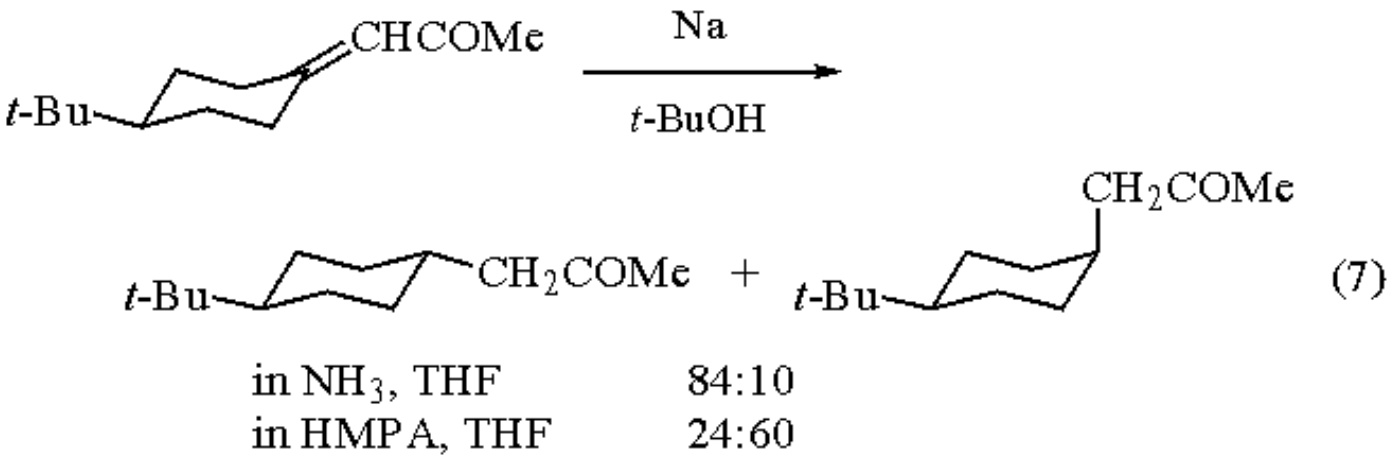

The reduction of internal acyclic alkynes to *trans*-alkenes by sodium in ammonia is well known.[1b] Complications in reducing terminal alkynes result from deprotonation by $NaNH_2$, formed in situ. This can be exploited by addition of an equivalent of $NaNH_2$,[26] or overcome by addition of ammonium salts.[27] Medium-ring cyclic alkynes often give mixtures of *cis*- and *trans*-alkenes, resulting from partial isomerization by $NaNH_2$ to allenes,[28] which in turn give *cis*/*trans* mixtures dependent on product stability and the presence or absence of proton donors.[29] Sodium in HMPA/*t*-BuOH has been shown to reduce alkynes;[30] internal monoalkenes, inert under most conditions, give near-equilibrium mixtures of alkanes with this system (eqs 8 and 9).[31] Conjugated dienes are reduced via a *cis*-radical anion,[32] while, with lithium, *trans*-dianions may play a role. Dimerization and regioisomer formation usually preclude the use of sodium, though exceptions exist.[33] A few reports of homoconjugated diene reduction have appeared.[34]

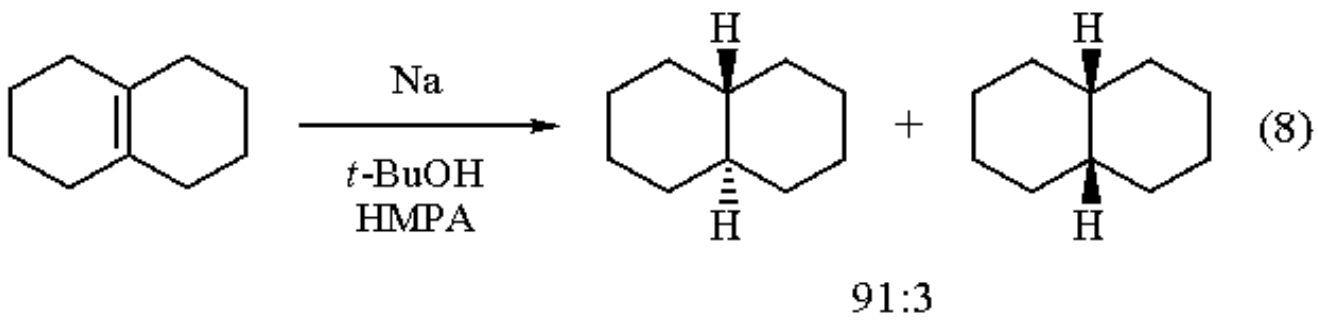

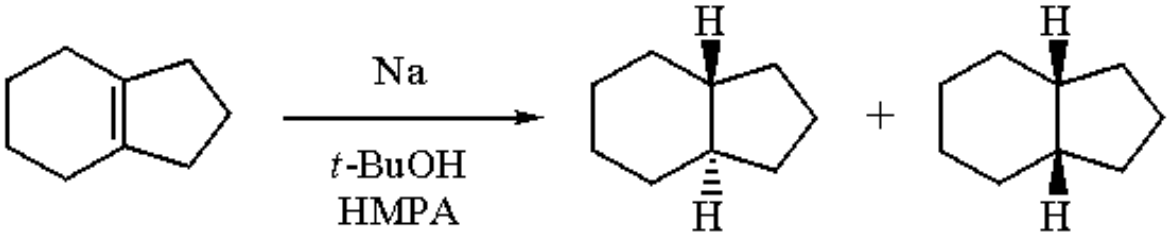

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Pinacol Coupling Reactions.

In the absence of proton donors, reductions of carbonyl compounds often lead to significant amounts of reductively coupled products, but the intentional pinacol coupling of ketones with sodium in inert solvents is typically a low-yielding, unselective process. Milder conditions utilize lanthanoids and low-valent transition metals, particularly titanium.[35] Sodium is used only in cases where no other functional groups are present.[36] Sodium is often employed in related intramolecular couplings with unsaturated carbon-carbon bonds, forming five- and six-membered rings regio- and (often) stereoselectively.[37] Ketyls cyclize onto allylic systems with *anti* displacement (eqs 10 and 11).[38] Transannular cyclizations have also been demonstrated.[39] Alkynes are cyclized similarly (eq 12),[40] usually with ***Sodium Naphthalenide***.[41] With allenes, the *exo* closure product is obtained (eq 13),[42] though prolonged reaction can scramble the position of the resulting double bond.[43]

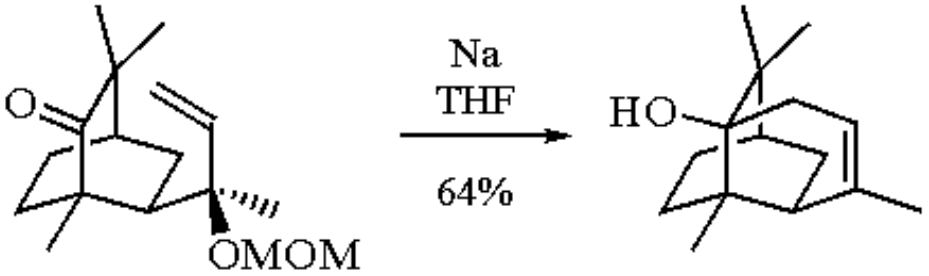

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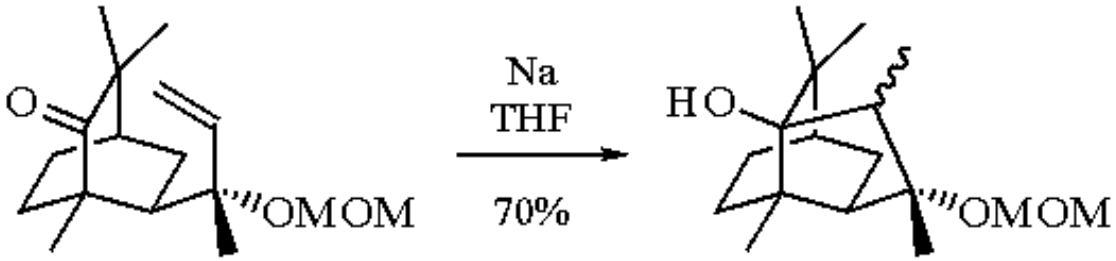

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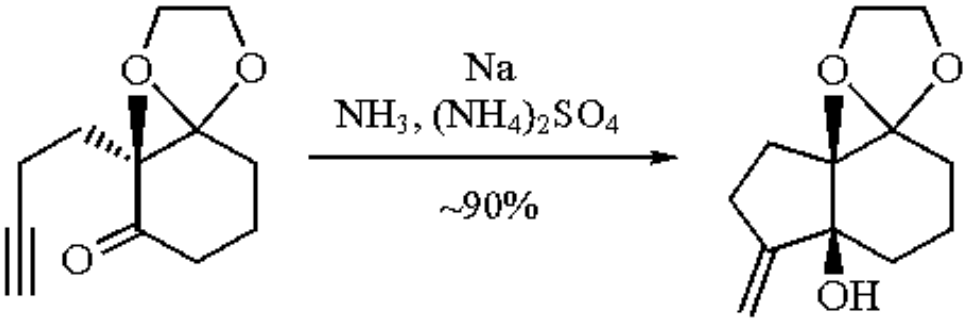

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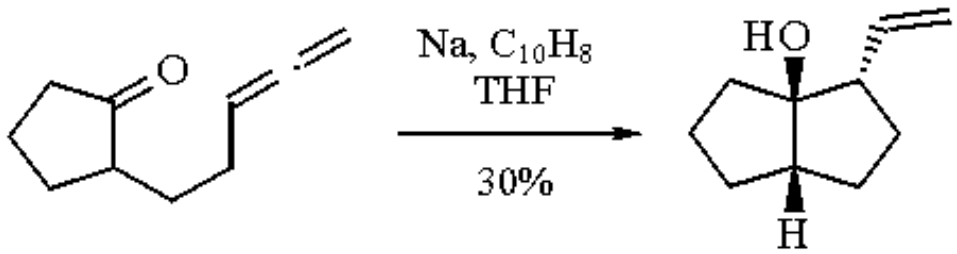

(13)

Acyloin Couplings.

Reductions of esters under aprotic conditions, usually refluxing toluene or xylene, result in α-hydroxy ketones, also called acyloins.[2] ***Sodium-Potassium Alloy*** alloy is also used and allows reaction at lower temperatures. Rigorous exclusion of oxygen during reaction and workup is essential. Base-catalyzed side reactions are suppressed by the coaddition of substrate and ***Chlorotrimethylsilane***, so as to trap the enediolate and alkoxide products, though good yields can sometimes be obtained regardless.[2,44] Workup is greatly simplified, and the acyloins can be freed by treatment with aqueous acid or deoxygenated methanol. Couplings can be performed on esters with leaving groups at the β-position (eq 14),[45] resulting in a useful cyclopropanone hemiacetal synthesis (eq 15).[46]

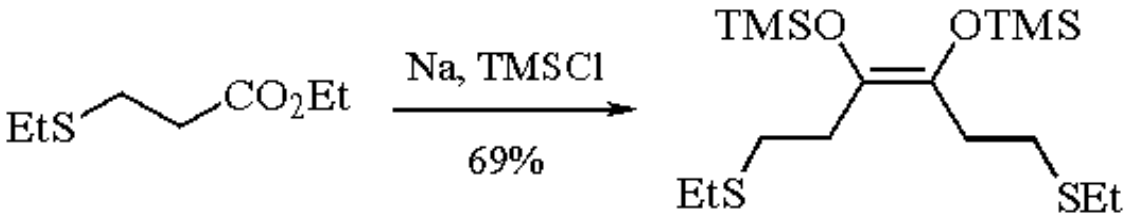

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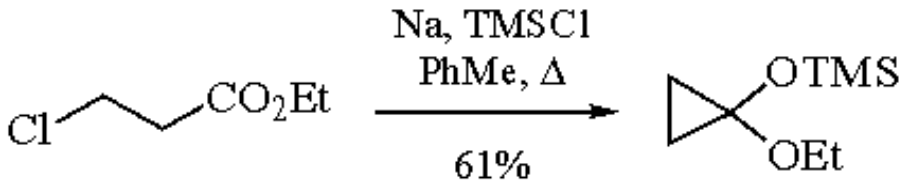

(15)

Intramolecular acyloin couplings are an enormously successful method for forming four-membered rings.[47] Highly strained products can undergo subsequent thermal ring opening (eq 16); Na/K is sometimes more effective in these cases. Hindered diesters can undergo α,α-bond cleavage prior to reduction.[2] Five- and six-membered rings are routinely generated, often without employing TMSCl. Larger rings, more difficult to form by other methods, are also closed in good yields,[48] including several polycyclic frameworks (eq 17).[49] Rings containing 12, 24, and 42 carbon atoms,[50] paracyclophanes, and rings containing N, O, S, and Si atoms have been formed.[51]

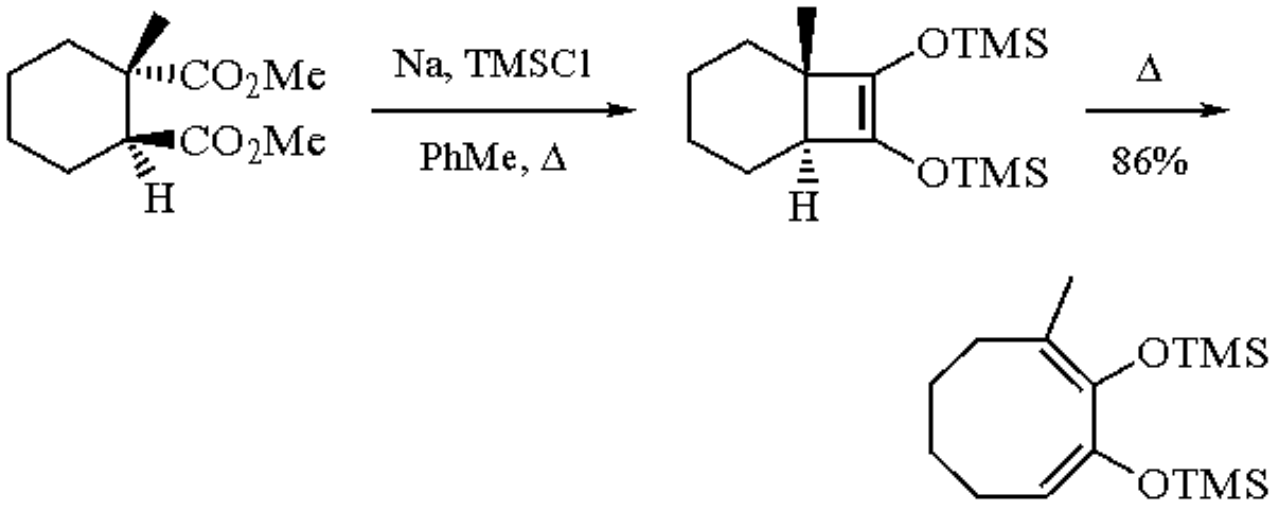

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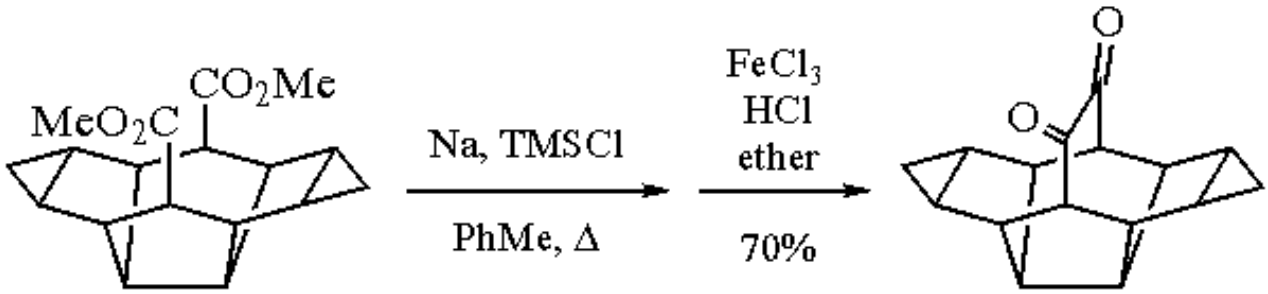

(17)

Reduction of Saturated Bonds.

Typical Birch reduction conditions dehalogenate aryl, vinyl, bridgehead, and cyclopropyl halides, though side reactions are often

troublesome.[52] Alkyl fluorides are not reduced by sodium under any conditions, requiring a K/crown ether system.[53] Sodium in alcohol/THF is an effective substitute for Birch conditions;[54,55] these conditions can also reduce simple alkyl halides (eq 18).[36b] A simpler procedure employing refluxing ethanol is superior in some cases (eq 19).[56]

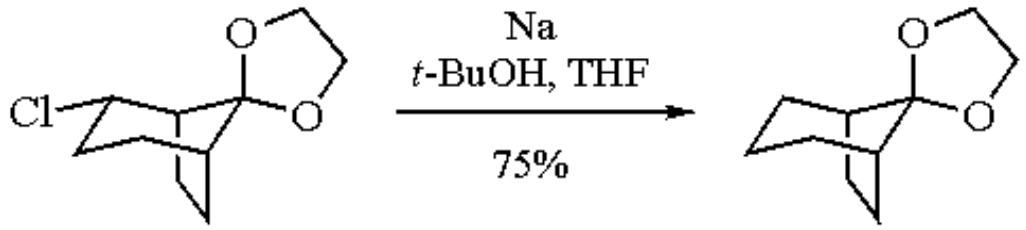

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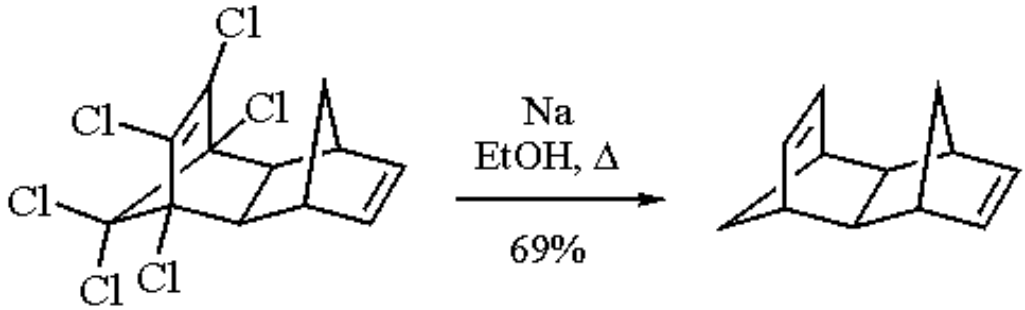

(19)

Alcohols are usually derivatized and reduced with metal hydrides, though other methods have received attention.[57] Among dissolving metal techniques, lithium or potassium in amines are most often used to hydrogenolyze various esters. Sodium in HMPA gives nearly quantitative yields of alkanes from tertiary esters.[58] Sodium in ammonia can cleave alkyl mesylates (eq 20),[59] while phosphate esters or mesylates of phenols are similarly reduced to aromatic hydrocarbons.[60] Like metal hydrides, sodium in ammonia cleaves epoxides to give the more substituted alcohols, with the exception of aryl-substituted epoxides (eq 21).[61] Lithium and second-row metals, particularly calcium, are also effective for epoxide cleavages.

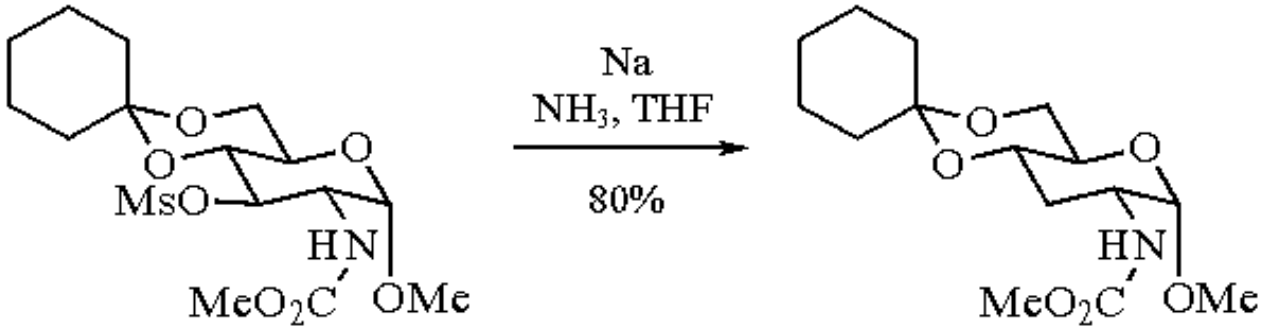

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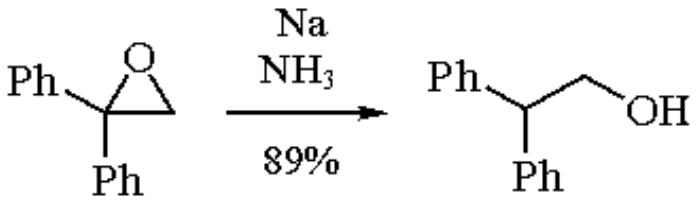

(21)

Most other aliphatic ethers are inert to dissolving metals, but benzyl ethers (as well as esters, amines, and thioethers) are readily debenzylated by sodium in ammonia. This is a common deprotection method in peptide and carbohydrate chemistry.[62] Substituted trityl ethers have been used to protect hydroxyl groups in nucleotides. The differing reduction potentials for the *p*-methoxytrityl[63] and α-naphthyldiphenylmethyl[64] groups allow for selective deprotection using sodium/aromatic hydrocarbon systems (eqs 22 and 23). Simple phenyl ethers are cleaved by sodium only with great difficulty.

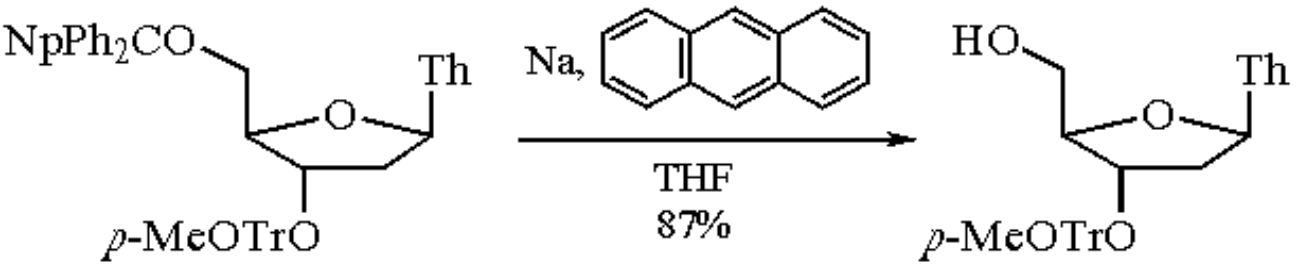

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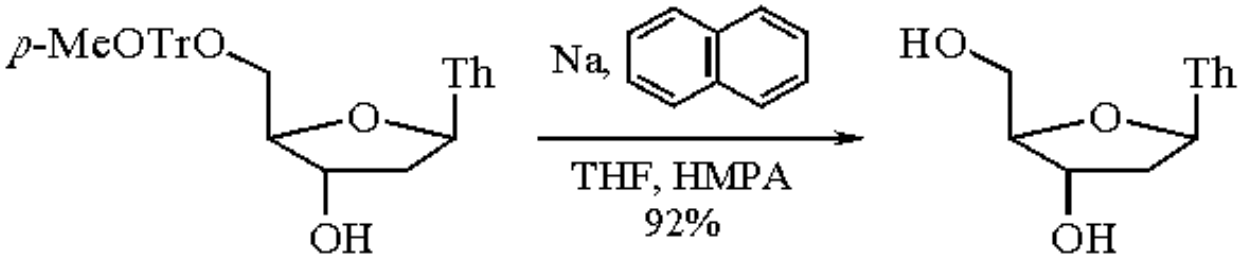

(23)

While many desulfurizations by alkali metals are known,[65] use of sodium is generally restricted to alkyl aryl thioethers. These are cleaved in the presence of aryl ethers by sodium in HMPA.[66] Phenyl thioethers are more often cleaved in refluxing alcohols (eq 24).[67] By substituting TMSCl for the proton source, alkyl or vinyl silanes can be isolated (eq 25).[68] Sodium in ammonia has been used in a deoxy sugar synthesis where more typical reagents (***Raney Nickel***, ***Nickel Boride***, ***Tri-n-butylstannane***) fail.[69]

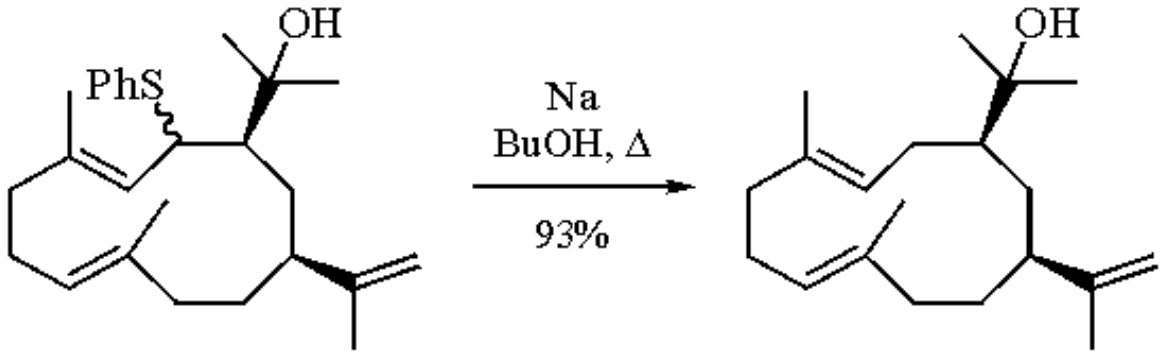

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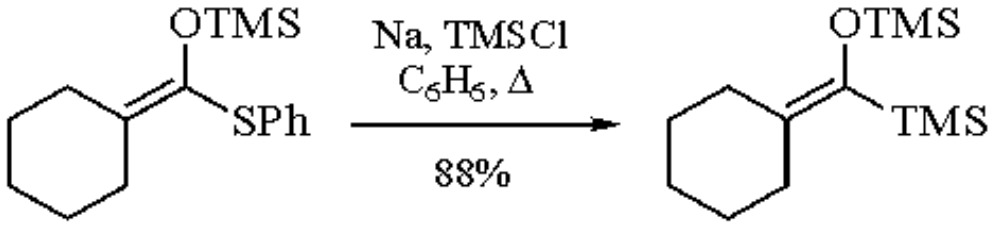

(25)

Sulfones are hydrogenolyzed by sodium in ethanol.[70] This method is again most often used where commonly preferred methods fail (eq 26),[71] and includes a rare application to an α-substituted carboxylic acid (eq 27).[72] Aryl sulfonamides are readily cleaved to amines with sodium naphthalenide and ***Sodium Anthracenide***.[73] Tosylates[74,62] and *N*-tosylsulfoximines[75] are similarly reduced to alcohols and sulfoximines, respectively.

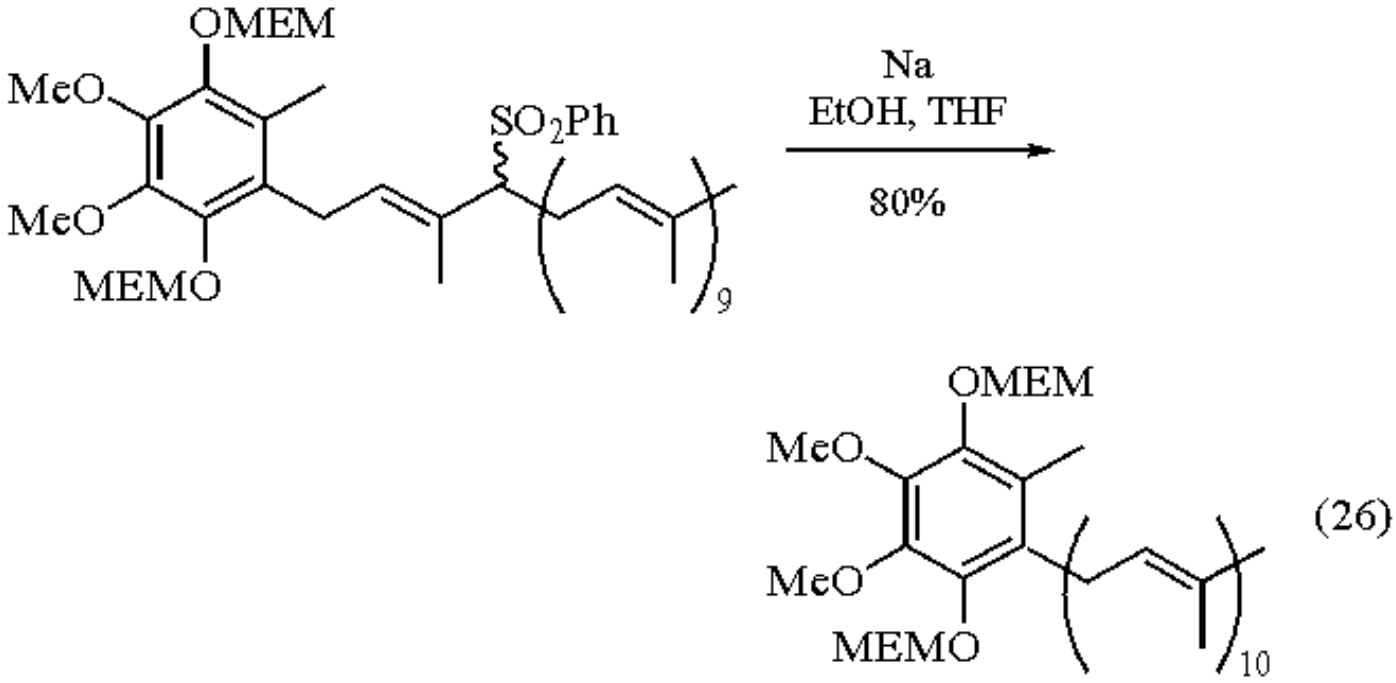

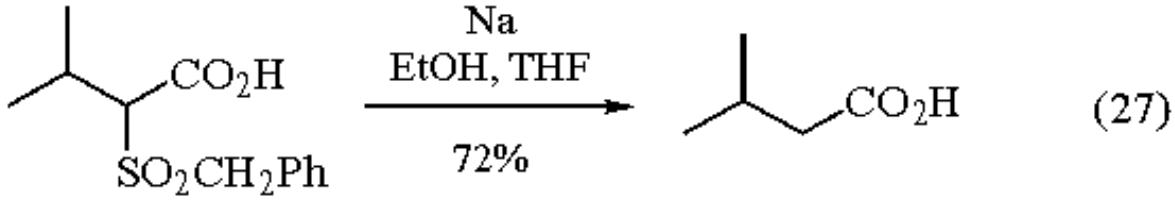

Reductive decyanation is effectively performed with sodium in ammonia.[76] This method complements ***Sodium Borohydride***, which is sometimes ineffective with α-amino nitrile substrates and provides products with inversion of configuration (eq 28).[77] An alternative method employing sodium or preferably potassium in HMPA/*t*-BuOH also smoothly removes nitriles.[78] Isocyanides are reduced to hydrocarbons, providing an effective deamination method (eq 29).[79] Rearrangements are largely avoided but, with acyclic substrates, loss of optical activity results. Finally, one last common application of the sodium/ammonia system is the reductive cleavage of acylated N-N bonds (eq 30).[80]

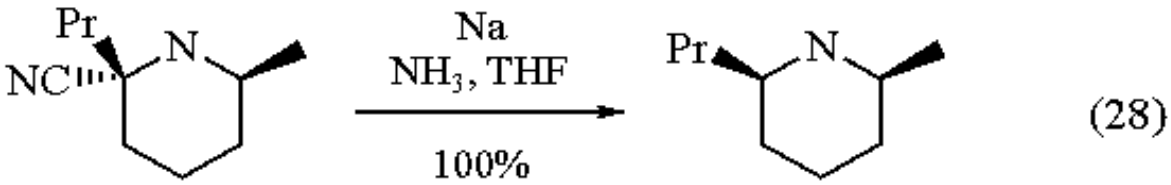

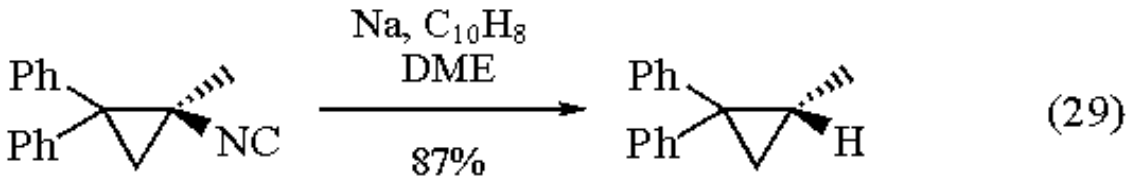

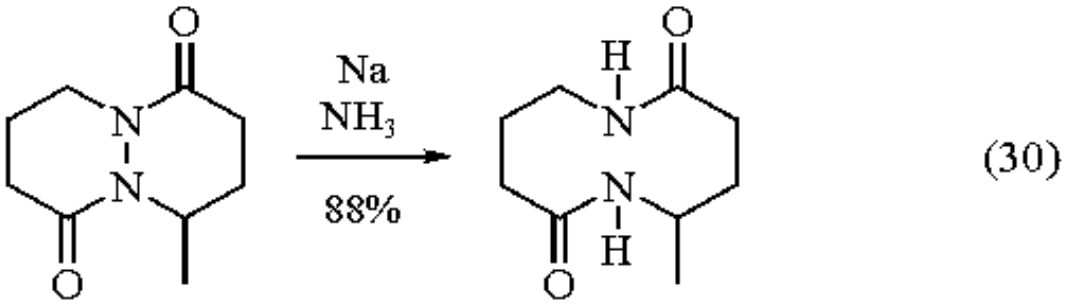

Reductive Eliminations.

When a leaving group is situated adjacent to a reducible functionality, elimination results. It is generally agreed that at the site of the initially reduced carbon atom, an anion is generated which then displaces the leaving group. Highly strained alkenes have been generated in this way. Usually *vic*-dihalides are the immediate precursor (eq 31),[81] though *vic*-dimesylates have also been used.[82] Alkenes have also been generated from *vic*-dinitriles[83] and more exotic combinations of functional groups.[84] Fragmentations of β-chloro ethers,[85] β,γ-epoxy nitriles,[86] and β-hydroxy nitriles[87] have also been demonstrated, the last undergoing subsequent double bond reduction (eqs 32-34).

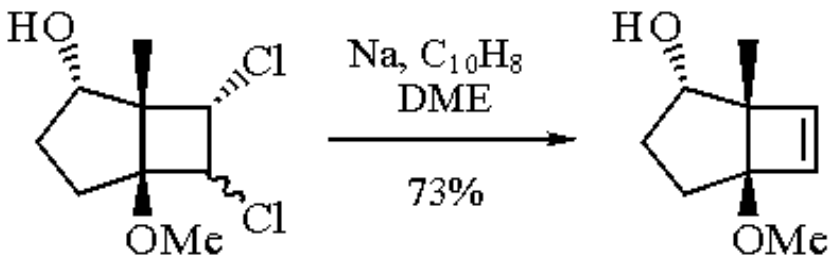

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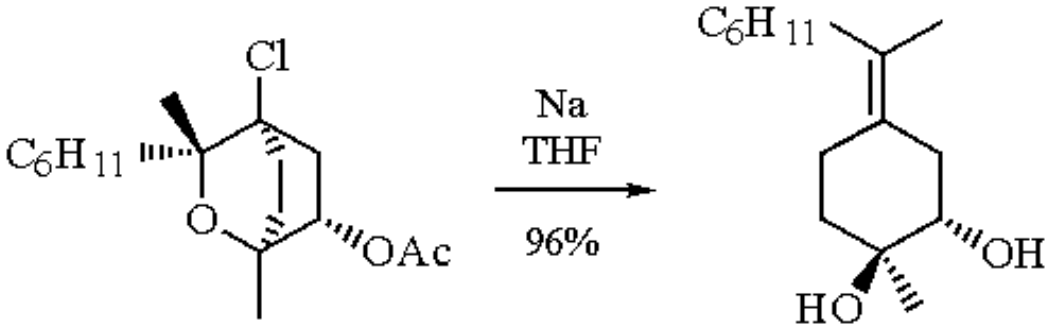

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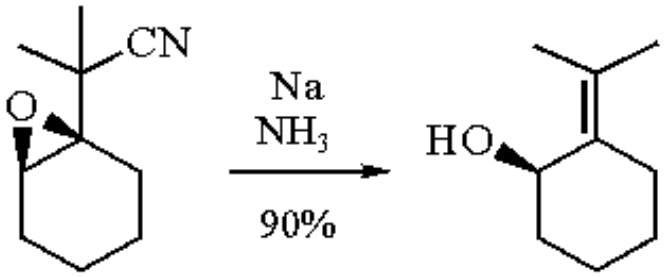

(33)

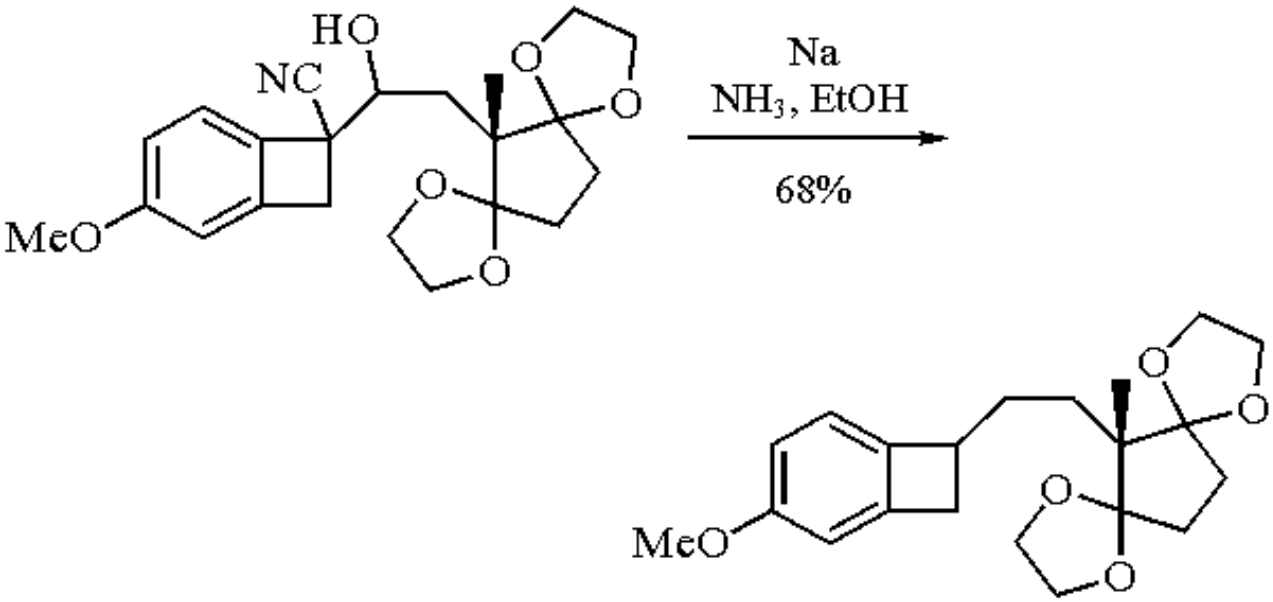

(34)

Wurtz Reaction.

The classical intermolecular coupling of halides with sodium, mechanistically related to the eliminations noted above, is of limited use.

Cross couplings lead to mixtures of desired and homocoupled products, while dimerizations are of little synthetic value. Magnesium, lithium, and copper reagents are normally employed here.[88] Intramolecular couplings frequently employ sodium, however. Ring closure to form [2.2]phanes is effective when tetraphenylethylene (TPE) is used catalytically (eq 35).[89] Greatest utility is found in the formation of cyclopropanes (eq 36),[90] and to a lesser extent cyclobutanes (eq 37),[91] where ***Zinc*** is preferred.

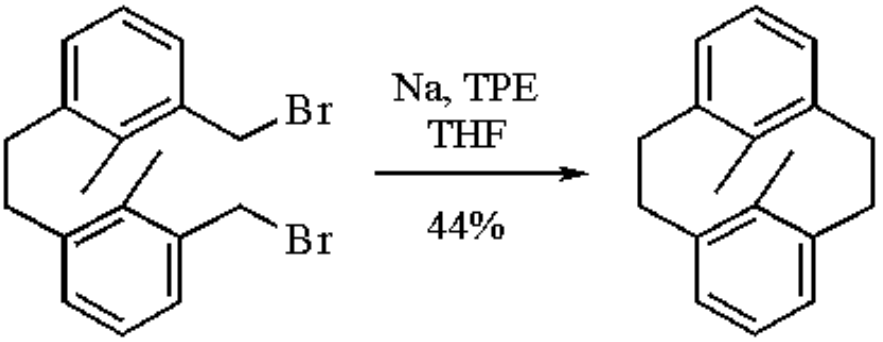

(35)

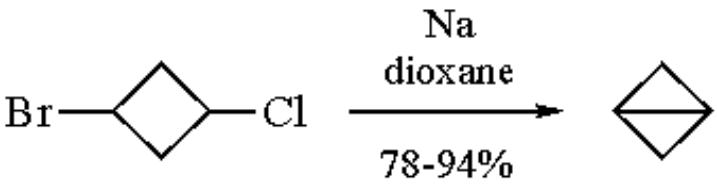

(36)

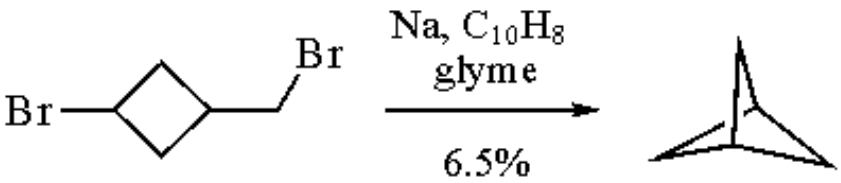

(37)

Use as a Base.

Sodium reacts slowly with alcohols to give solutions of alkoxides. While sodium alkoxides are far more commonly generated by ***Sodium Hydride***, or obtained commercially, the older method is still occasionally used. The protic Bamford-Stevens reaction uses sodium to generate alkoxides from ***Ethylene Glycol***, present as solvent.[92] Sodium methoxide can be substituted, but the original conditions are usually employed. Regioselectivity can be a problem; while the more substituted regioisomer usually predominates, prediction is difficult.[93] Rearrangements of cationic intermediates also limit its use, though many successful examples of this reaction do exist (eq 38).[94]

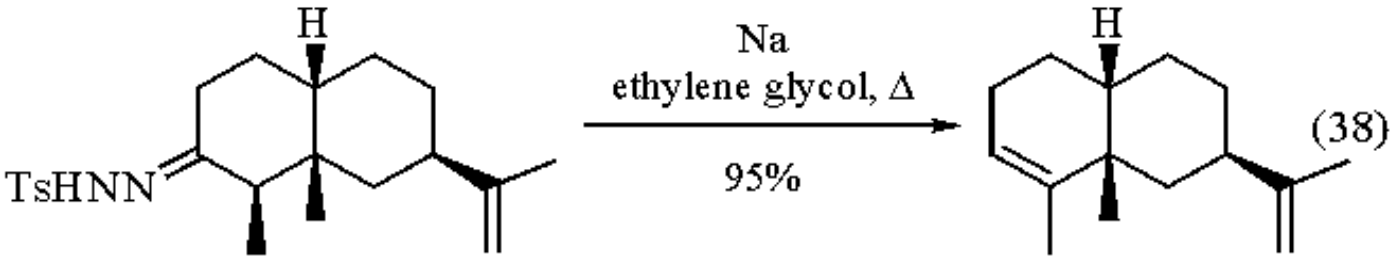

(38)

Related Reagents.

Sodium-Alcohol; ***Sodium-Alumina***; ***Sodium-Ammonia***.

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Sodium-Alcohol[1]

Na-ROH

(Na)

[7440-23-5] · Na · Sodium-Alcohol · (MW 22.99)

(reducing agent for esters, amides, ketones, oximes, nitriles, sulfonamides, aromatic hydrocarbons, certain alkenes, ethers, and carbon-halogen bonds; moderately strong base)

Physical Data: Na: mp 97.5 °C; bp 880 °C; *d* 0.97 g cm^{-3}. EtOH: mp -117.3 °C; bp 78.5 °C; *d* 0.7893 g cm^{-3}.

Form Supplied in: Na: silvery white, soft metal. EtOH and other alcohols: liquid. *Drying:* absolute ethanol can usually be employed without further drying. Most other common alcohols can be dried by storing over anhydrous calcium sulfate followed by distillation.

Handling, Storage, and Precautions: ***Sodium*** metal is a water-reactive, flammable solid. In case of contact with water, the heat of the reaction is usually sufficient to ignite the product hydrogen. Ethanol and other alcohols likely to be encountered in these reductions are flammable liquids. Use in a fume hood.

Reduction of Esters and Carboxamides.

Though often replaced by the use of more modern hydride reagents, the Bouveault-Blanc reduction has long been known to convert esters to alcohols by refluxing the former reagents with sodium in alcohols.[2] For example, ethyl hydrocinnamate is converted to hydrocinnamyl alcohol in good yields (eq 1).[2] Numerous examples of reductions of mono-[3] and diesters[4] can be found in the literature. The major improvement in the procedure over the years has been the use of stoichiometric amounts of ester, alcohol, and toluene or xylene added to sodium in xylene.[5] Treatment of unsaturated esters with sodium in alcohols reduces conjugated double bonds[2] but not unconjugated alkenes (eq 2).[6] Less common have been reductions of carboxamides to amines by sodium in alcohols. For example, a number of primary, secondary, and tertiary amides have been reduced to their corresponding amines in good yields by sodium in propanol.[7]

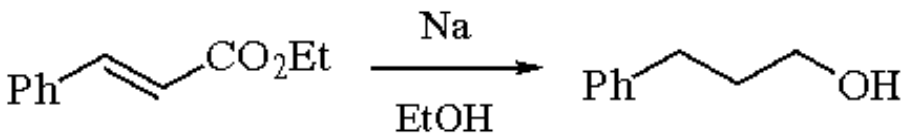

(1)

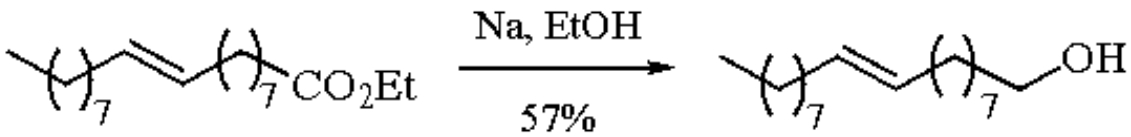

(2)

Reduction of Ketones and Derivatives.

Aliphatic ketones and phenones are readily converted to alcohols by sodium in alcohols,[8] as illustrated by the thermodynamically controlled reduction shown in eq 3, which forms part of a recently described synthesis of taxol and its analogs.[8d]

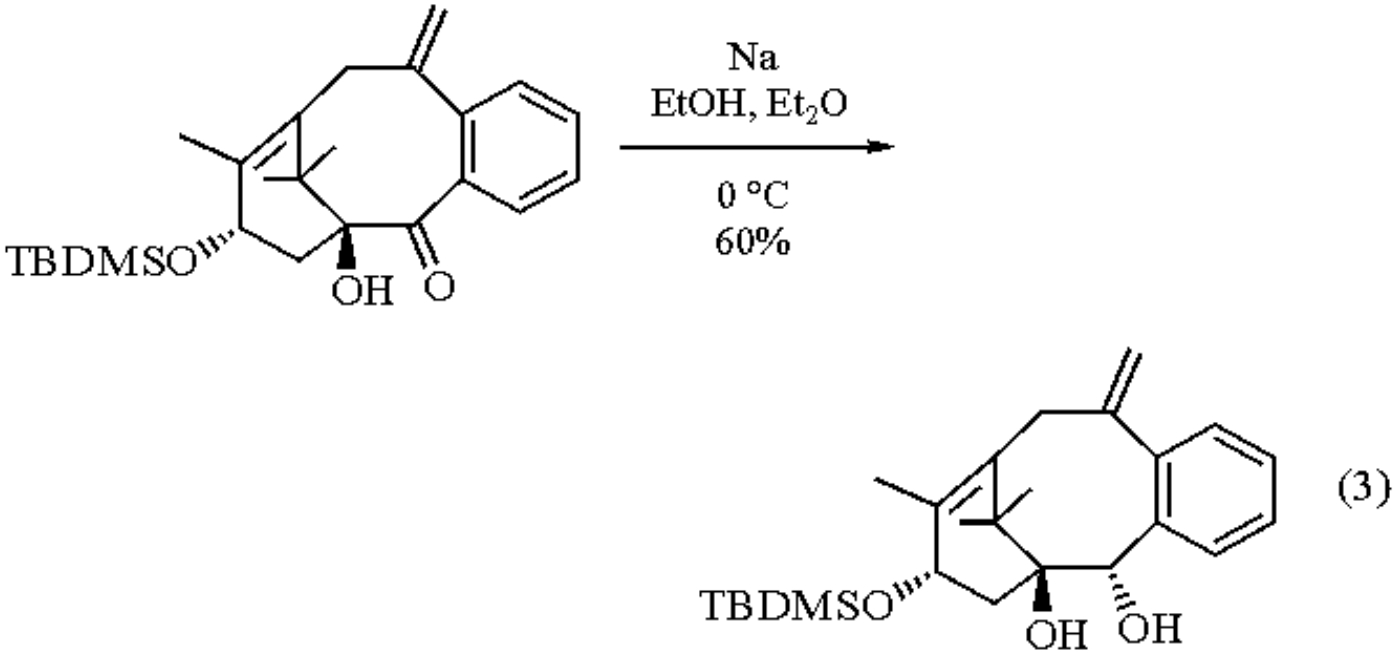

Reduction by sodium in alcohols of α,β-unsaturated ketones affords saturated alcohols (eq 4),[9] while similar reductions of diaryl ketones give methylene derivatives (eq 5).[10]

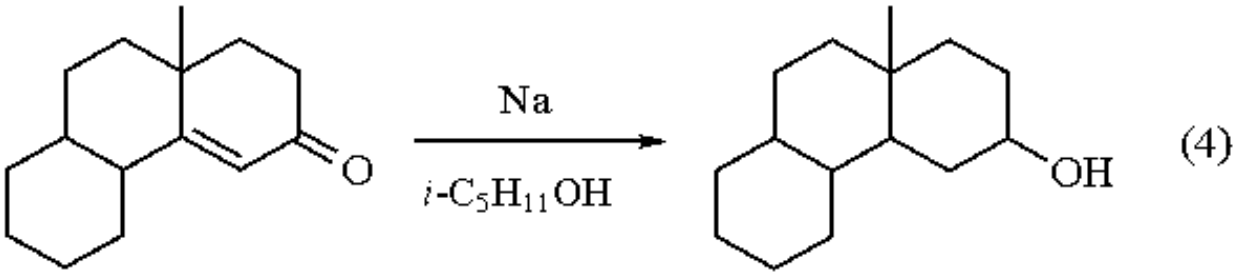

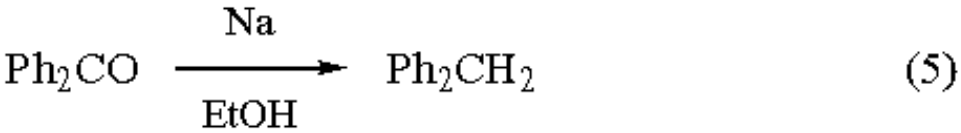

Oximes are conveniently converted to amines by sodium in alcohols.[11] For example, the oxime of 2-phenylcyclohexanone is reduced by sodium in ethanol to the corresponding amine in quantitative yield (eq 6).[11b] The use of higher molecular weight alcohols has been reported to afford better yields of products.[11d]

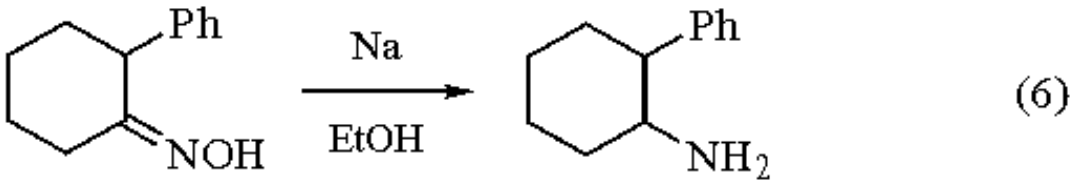

Reduction of Nitriles.

Aliphatic nitriles are also reduced to amines in satisfactory yields by sodium in *n*-butyl alcohol[12a] or ethanol and toluene (eq 7).[12b]

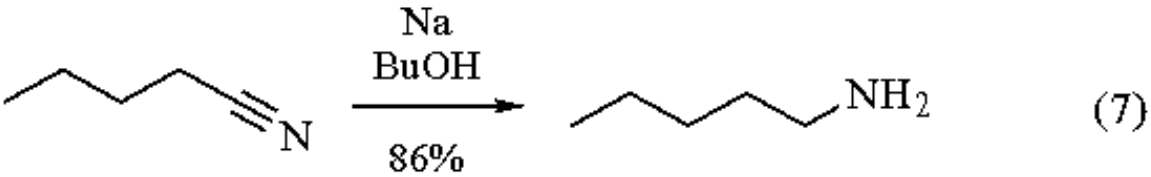

Reduction of Sulfonamides.

Both aliphatic and aromatic sulfonamides are converted to sulfinic acids and amines by sodium in isopentyl alcohol.[13] This reduction has been employed in the preparation of azetidine (eq 8).[13b]

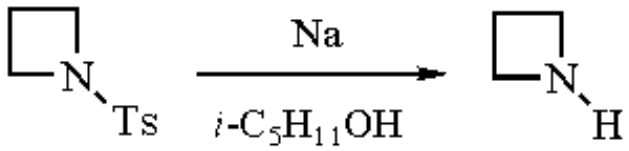

(8)

Reduction of Aromatic Hydrocarbons.

Naphthalene and higher aromatic hydrocarbons, as well as certain amino, ether, and carboxyl derivatives, are reduced to more saturated derivatives by sodium in numerous alcohols.[1a,14] Thus while naphthalene itself is converted by sodium in ethanol and benzene to the 1,4-dihydro derivative,[14b] β-naphthylamine and β-alkoxynaphthalenes are reduced to tetrahydro-β-naphthylamine (eq 9)[14a] and β-tetralone (eq 10),[14c,d] respectively.

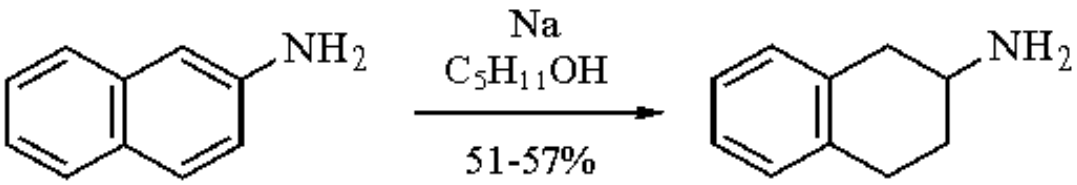

(9)

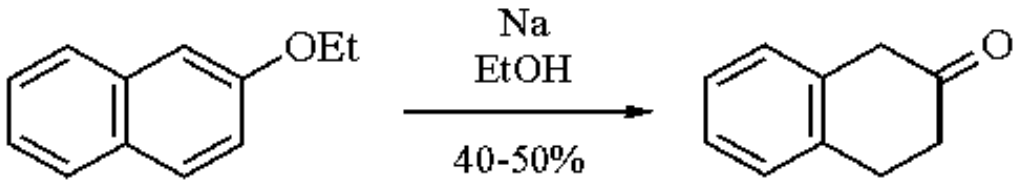

(10)

Interestingly, sodium/isopentyl alcohol reduction of salicylic acid gives pimelic acid (eq 11).[14e] In the case of biphenyl substituted with a carboxyl group on one ring and a methoxy group on the other, the ring bearing the carboxyl group is converted to its hexahydro derivative (eq 12).[14f]

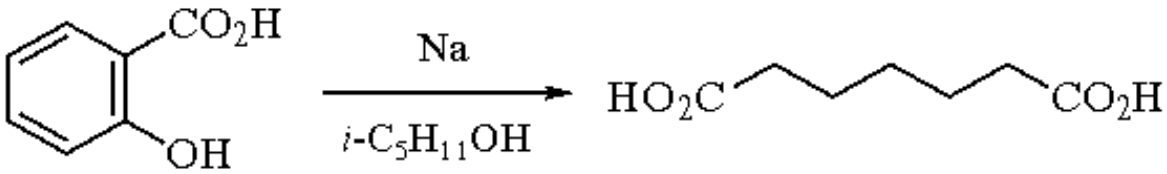

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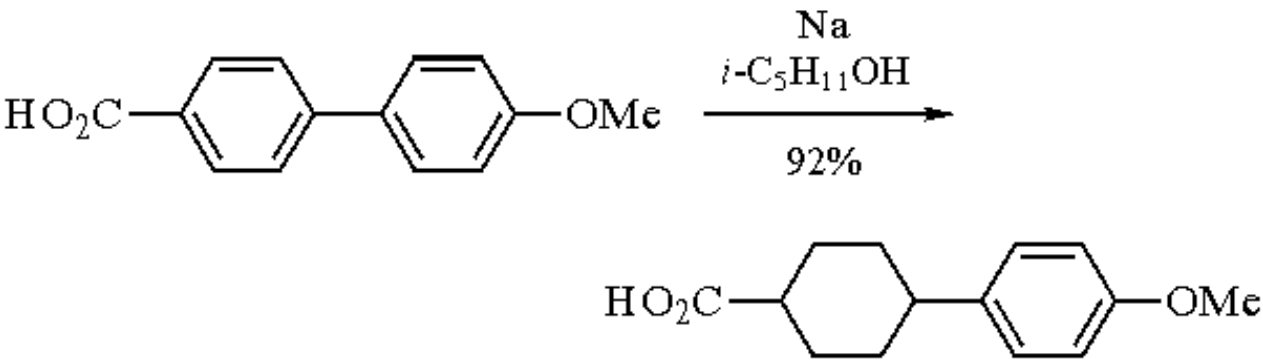

(12)

Pyridine derivatives are also reduced by sodium in ethanol[15] or in pentyl alcohol.[11b] For example, benzo[*f*]quinoline is converted to the *trans*-amine (eq 13).[11b]

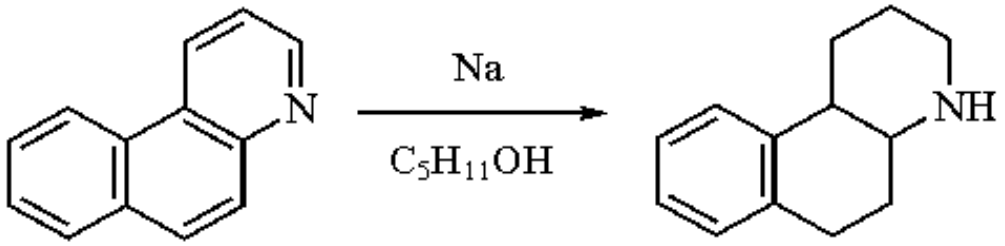

(13)

Reduction of Alkenes.

Perhaps surprisingly, numerous examples of alkenes conjugated with aromatic rings have been converted to alkanes by sodium in alcohols.[1a] For example, cinnamyl alcohol is conveniently reduced by this method (eq 14).[16]

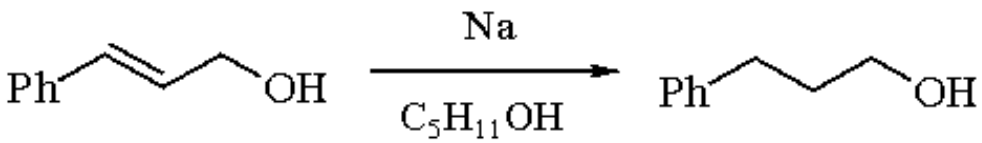

(14)

Cleavage of Ethers.

4-Phenyl-*m*-dioxane has been reduced to 3-phenyl-1-propanol by sodium in isobutyl alcohol.[17] Similar examples include demethoxylations of methyl aryl ethers (eq 15)[18a,b] and debenzylations of benzyl derivatives of certain sugars.[18c]

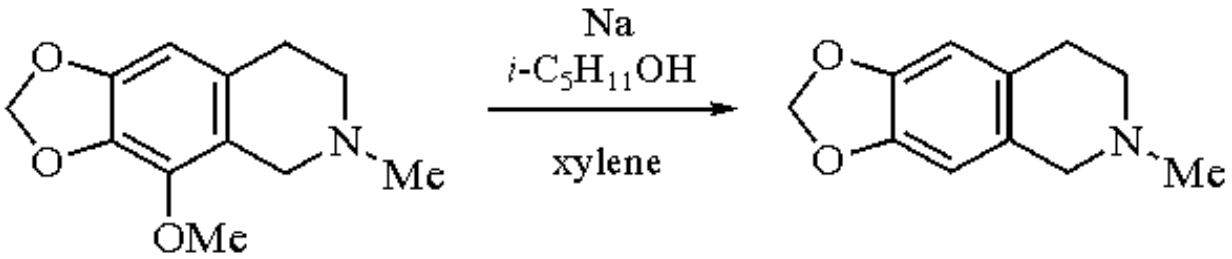

(15)

Reduction of Carbon-Halogen Bonds.

gem-Dibromides are reduced by sodium in wet methanol to the parent hydrocarbons (eqs 16 and 17).[19] Both vinylic and allylic chlorides, but not methyl ether moieties, are similarly reduced by sodium in *t*-butyl alcohol and THF (eq 18).[20]

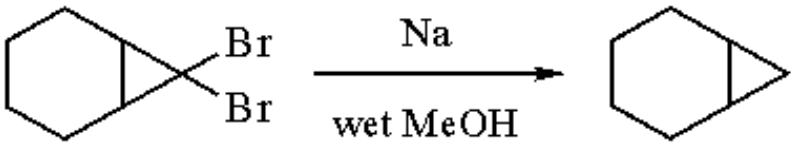

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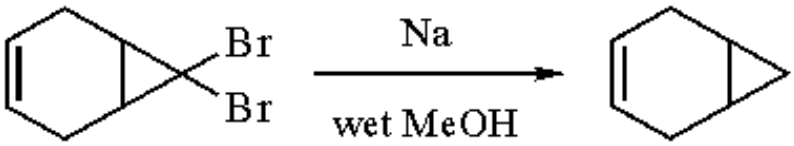

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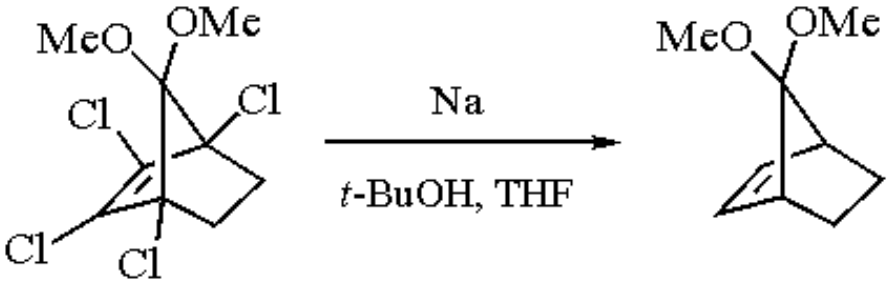

(18)

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Sodium-Alumina

Na/Al_2O_3

(Na)

[7440-23-5] · Na · Sodium-Alumina · (MW 22.99) (Al_2O_3)

[1344-28-1] · Al_2O_3 · Sodium-Alumina · (MW 101.96)

(isomerization of alkenes;[1] isomerization of amines;[2] a form of high surface area sodium metal[3])

Physical Data: sodium: mp 97.8 °C; *d* 0.968 g cm^{-3}. Alumina: *d* 3.97 g cm^{-3}.

Preparative Method: basic ***Alumina*** is dried at 150-200 °C and vigorously stirred with ***Sodium*** metal under an inert atmosphere until cool. The 2-10% sodium on alumina mixtures (as typically used for alkene isomerization) are free flowing, nonpyrophoric solids ranging from bright to dark gray; the color intensity markedly increases with increasing metal content.[1,4-6]

Handling, Storage, and Precautions: sodium metal reacts violently with water to produce flammable H_2 gas. High sodium-containing Na/Al_2O_3 catalysts may be pyrophoric. In case of fire, do not expose to water, CO_2, or vaporizable liquids. The activity of the catalyst is lost upon exposure to air or moisture.

Alkene Isomerization.

Isomerization of alkenes may be accomplished under mild conditions. Thus methylenecyclobutane is converted to methylcyclobutene in nearly quantitative yield, avoiding the formation of isoprene, common with higher temperature routes (eq 1).[4] Both 1-butene and 1-pentene have been isomerized to the internal alkene with this catalyst.[5,7] The system operates under kinetic control, favoring the initial formation of the *cis*-isomer over the *trans*-isomer (eq 2). When cyclic dialkenes are treated with Na/Al_2O_3, dehydrogenation can follow the reversible C=C bond shift (eq 3).[1] More forcing conditions can cause skeletal rearrangement (eq 4).[1]

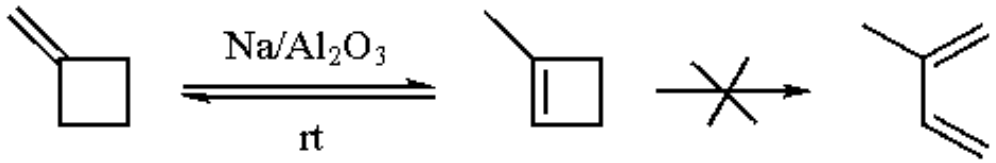

(1)

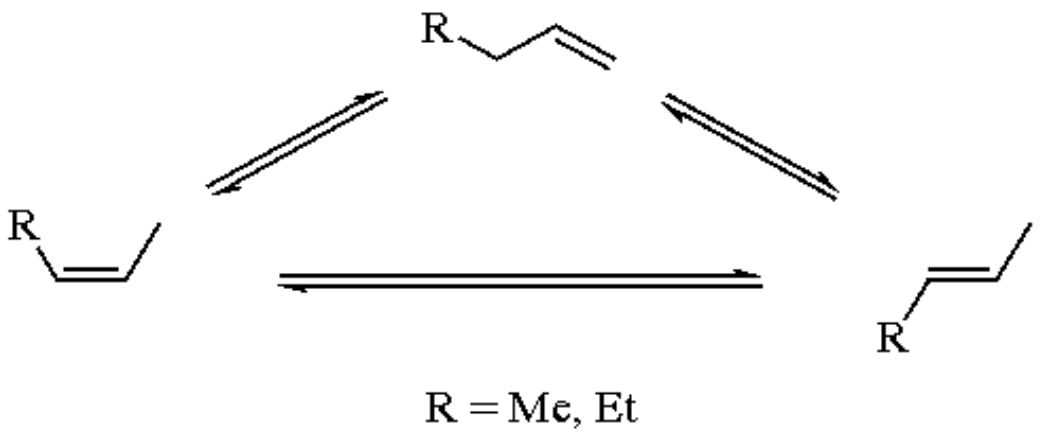

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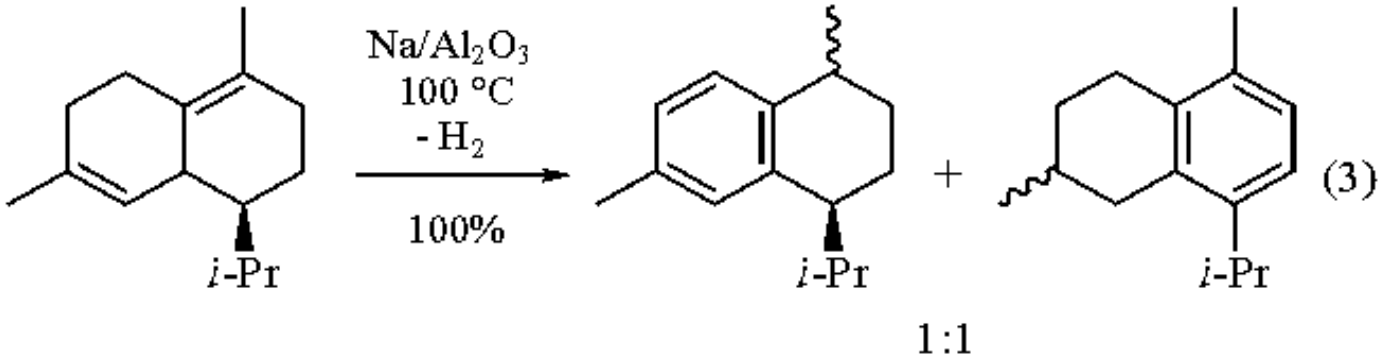

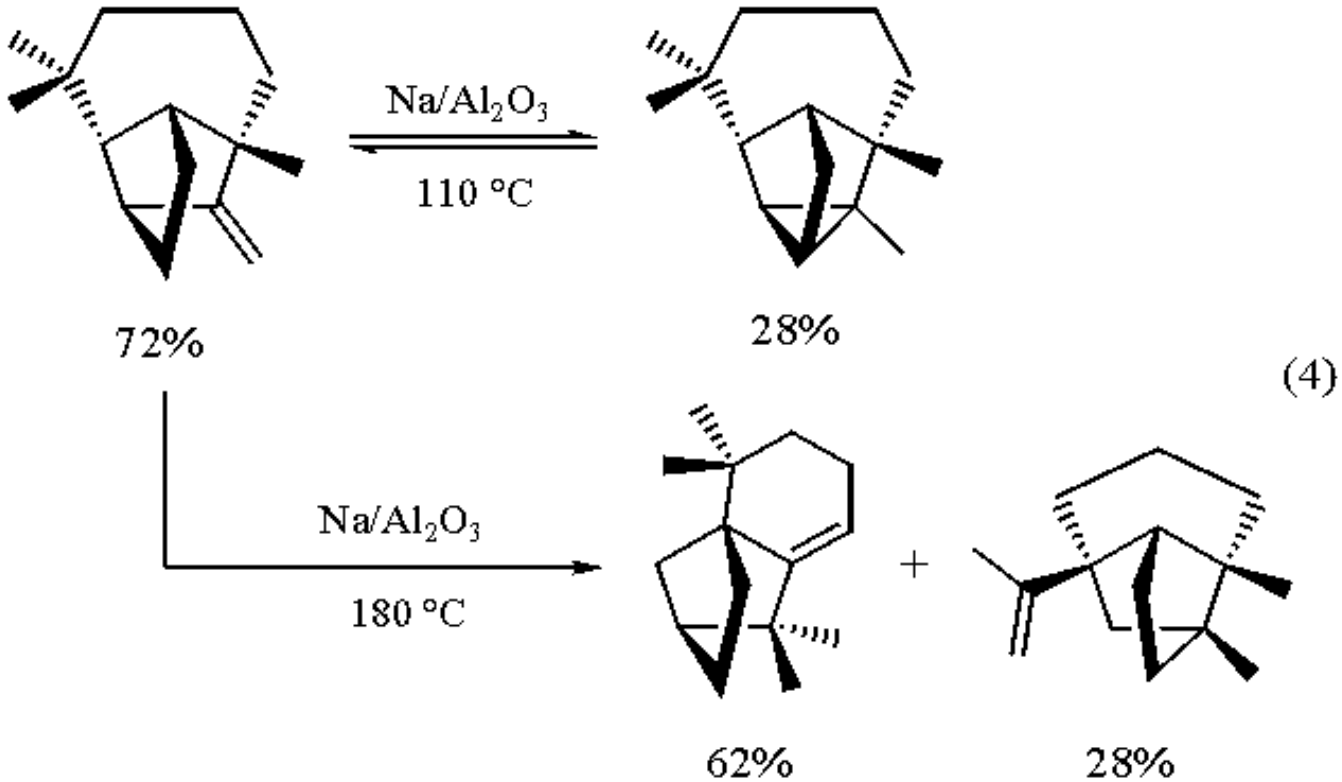

Miscellaneous Uses.

This catalyst has also been used to racemize optically active benzyl amines.[2] Na/Al_2O_3 has also been used as a sodium metal source in the large scale preparation of sodium cyclopentadienide.[3] Recently, this method has been abandoned for the use of oil-free ***Sodium Hydride***, avoiding the need to filter Al_2O_3 from the product.[8]

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Dean R. Lagerwall

Occidental Chemical Corp., Grand Island, NY, USA

Sodium Aluminum Hydride

$NaAlH_4$

[13770-96-2] · AlH_4Na · Sodium Aluminum Hydride · (MW 54.01)

(reducing agent similar in activity to $LiAlH_4$;[1] deoxygenative dimerization of carbonyls and alcohols;[11a] hydroalumination of alkenes and alkynes[11b])

Physical Data: mp 180-183 °C (dec with evolution of H_2); *d* 1.28 g cm^{-3}.

Solubility: sol THF, DME, diglyme; insol ether, hydrocarbons.

Form Supplied in: white crystalline solid.

Analysis of Reagent Purity: iodometric titration;[10b] H content determined by gas evolution analysis; Al content determined by EDTA-$Zn(OAc)_2$ back titration at pH 4 using dithizone as an indicator.[9a]

Purification: recrystallization from a THF-benzene solvent mixture by addition of benzene, followed by partial removal of the solvent under vacuum. The white solid is collected and dried under vacuum before dissolving in freshly distilled THF.

Handling, Storage, and Precautions: severe fire and explosion hazard in contact with oxidizing agents and water, forms caustic and irritant compounds; stable in dry air at room temperature. Solutions in THF or diglyme appear to be stable for at least several months if not exposed to air. To preserve reactivity it is best to store wet with toluene than to store dry. Use in a fume hood.

Functional Group Reductions.

This reagent reduces aldehydes, ketones, carboxylic acids, esters, and acid chlorides to give alcohols. Amides, nitriles, and aliphatic nitro compounds give amines. Aromatic nitro compounds yield azo compounds. Yields are usually within 10% of those reported for ***Lithium Aluminum Hydride***.[1] $NaAlH_4$ is about 10-11 times less reactive than $LiAlH_4$ in the reduction of ketones.[2] Heterogenous reductions of esters in diethyl ether, benzene, toluene, or heptane give good yields of the alcohols.[1a,3] Hydrogenolysis of alkyl halides occurs at a rate considerably slower than with $LiAlH_4$.[1,4a,b] Aromatic iodides and bromides are readily reduced in THF but diglyme is a better solvent for chlorides.[4c] Ethers and double and triple bonds are normally stable to this reagent. Under controlled conditions, the reaction with esters, dialkylamides, and aromatic nitriles can provide aldehydes in good yields.[5] Aliphatic nitriles proceed mainly to the amines with only 15-25% yield of the aldehydes. Best yields are obtained by inverse addition of the hydride at low temperatures. Certain lactones can be partially reduced.[6a] Phthalic anhydrides are sluggishly converted to the lactones and substituent effects on regioselectivity have been studied.[6b] Quaternary pyridinium iodides are reduced to piperidines.[7] Reduction of *N*-cyclopropylimines gives the cyclopropylamines as well as the *n*-propylamines resulting from ring cleavage.[8]

Stereoselective Reductions.

$NaAlH_4$ gives a slightly smaller extent of axial addition to 4-*t*-butylcyclohexanone than is observed for $LiAlH_4$ (88% and 92%, respectively).[9] The stereochemical features of a number of ketone reductions by this reagent have been examined.[9,10] Greater degrees of stereoselectivity are generally found with $LiAlH_4$. In the case of cyclic α-amino ketones, larger amounts of *trans*-isomers are produced compared to $LiAlH_4$ (eq 1).[10d-f]

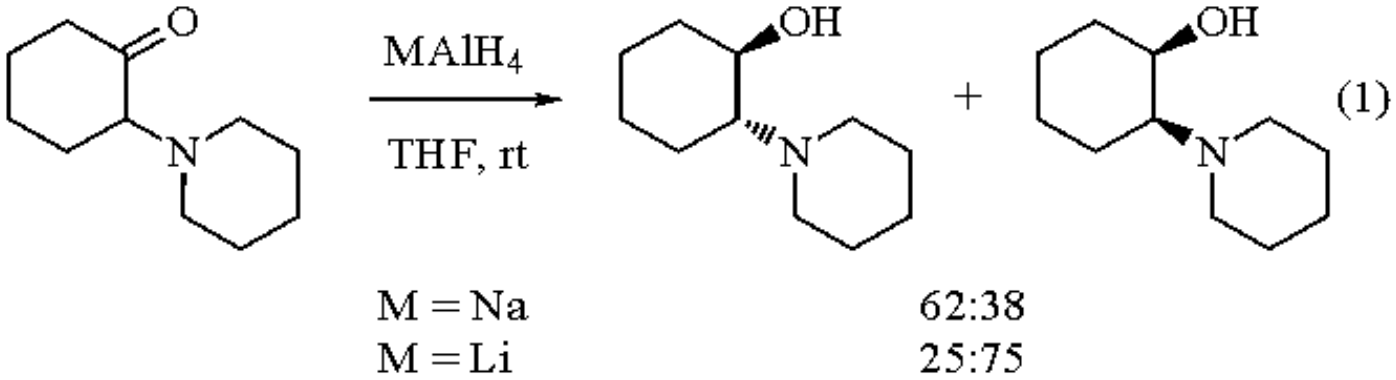

Deoxygenative Dimerization Reactions.

In the presence of $NaAlH_4/NbCl_5$, aromatic carbonyl compounds undergo deoxygenative dimerization to yield alkenes (56-99%).[11a] Purely aliphatic carbonyls give trace to low yields of alkenes. Allylic and benzylic alcohols form symmetrical coupling products (eq 2). Allylic rearrangements occur in some cases. Under these conditions, epoxides can be deoxygenated to give the corresponding alkenes.

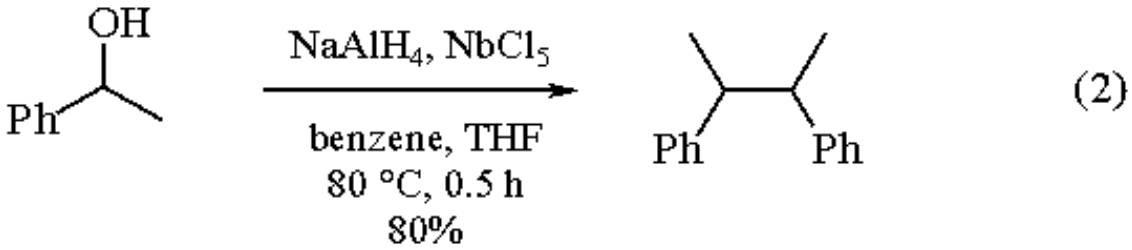

Hydrometalation.

Internal alkynes are converted to (*Z*)-alkenes with high stereoselectivities (>20:1) using the $NaAlH_4/NbCl_5$ system.[11a] Terminal alkenes and internal alkynes are reduced rapidly and in high yield by $NaAlH_4$ in the presence of a catalytic amount of ***Dichlorobis(cyclopentadienyl)titanium***.[11b] The reduction of 2-alkyn-1-ols by $NaAlH_4$ via a cyclic alanate provides β- or γ-substituted allyl alcohols, depending on the solvent and the electronic character of the substituent.[12]

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Sodium Amalgam

Na(Hg)

[11110-52-4] · Na · Sodium Amalgam · (MW 22.99)

(used in the preparation of alkenes and alkynes; to reductively cleave C-S and N-O bonds; for the reductive cleavage of quaternary phosphonium and arsonium salts; selective dehalogenation of aryl halides; also for the reduction of a variety of other functional groups)

Physical Data: the consistency and mp vary with the sodium content; 1.2% sodium is a semisolid at room temperature and melts completely at 50 °C; 5.4% sodium melts above 360 °C.

Solubility: sodium amalgams are decomposed by water but more slowly than sodium.

Form Supplied in: crushed solid; limited commercial availability.

Analysis of Reagent Purity: the amalgam can be analyzed for sodium by titration with 0.1 N sulfuric or hydrochloric acid.

Preparative Methods: several procedures for the preparation of sodium amalgam have been reported.[1-4] Amalgams containing 2-6% sodium are the most commonly employed for synthetic work. The safest and most convenient procedure for the preparation of 2% sodium amalgam is the addition of ***Mercury(0)*** to ribbons of ***Sodium*** metal.[5,6] No external heating is required with this protocol. The resulting solid can be crushed and stored indefinitely in a tightly stoppered container.

Handling, Storage, and Precautions: moisture sensitive; keep tightly closed.

Alkyne Synthesis.

Reductive cleavage of the triflate salts of vinyl phosphonium triflates with 2% sodium amalgam affords pure alkynes in good to excellent yield (eqs 1 and 2).[7] This represents a significant improvement in yield and purity over the method involving thermal cleavage of acyl ylides. The highest yields are obtained when one group is aryl (eq 2). Alkynes are also obtained in respectable yields by the reductive elimination of enol phosphates of β-oxo sulfones with the reagent (6%) in DMSO-THF (eq 3).[8]

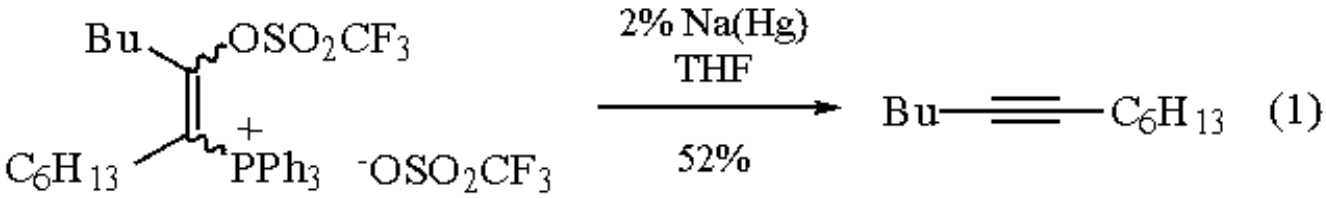

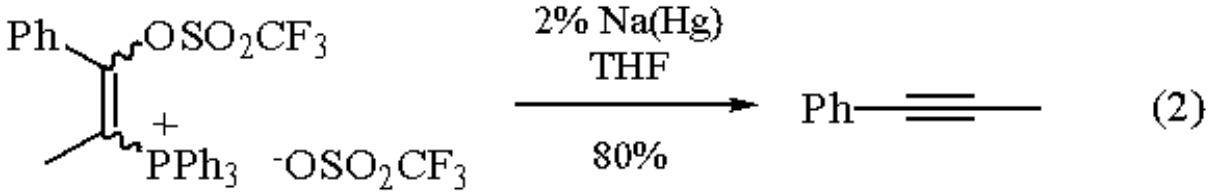

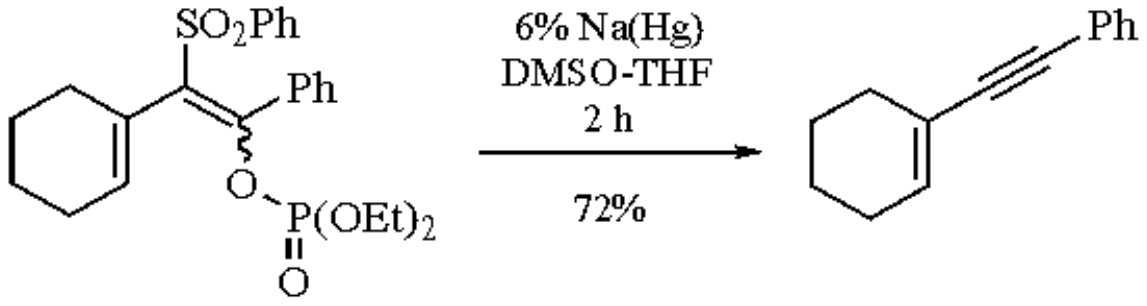

(3)

Longer reaction times are required for nonconjugated enol phosphates. Aromatic *cis*- and *trans*-enediol diesters are reported to give the corresponding diaryl alkynes in modest yield by reductive elimination with the reagent (eq 4).[9] This procedure has been modified to provide for a one-pot operation in which 4 equiv of an aromatic acyl chloride is treated with an excess of the reagent in ether.[9]

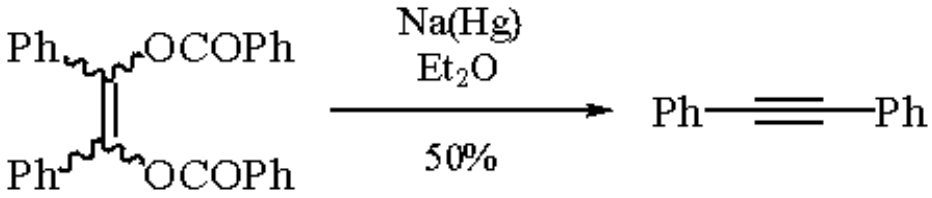

(4)

Alkene Synthesis.

The preparation of *trans*-alkenes from the reaction of β-alkoxy or acyloxy sulfones with sodium amalgam has been reported (eq 5).[10] Trisubstituted and tetrasubstituted precursors generally give disappointing results. Stereoselective introduction of the double bond in a total synthesis of diumycinol was accomplished with this method (eq 6).[11] This protocol is effective when other standard conditions fail.

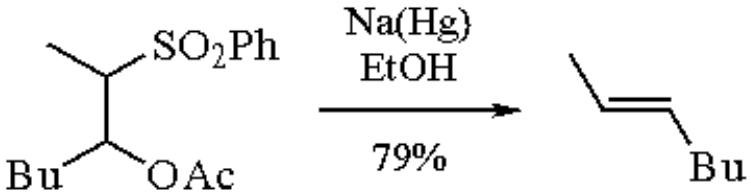

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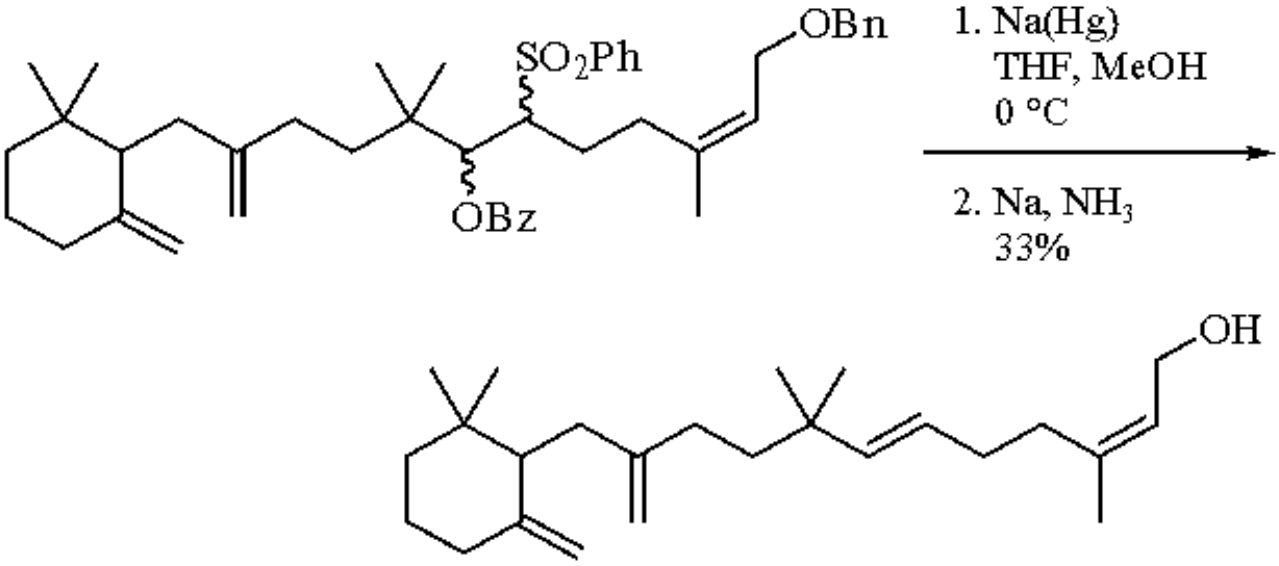

(6)

Desulfurization.[12-17]

This reaction has perhaps found the widest use of the reagent. The value of sulfides, sulfoxides, and sulfones in organic synthesis is increased by the ease with which their removal is accomplished. For example, sulfones are conveniently hydrogenolyzed with 6% reagent in boiling ethanol (eq 7).[12] The use of disodium hydrogen phosphate is recommended as a buffer with the reagent in some applications with allylic sulfones and β-keto sulfides (eqs 8 and 9).[15]

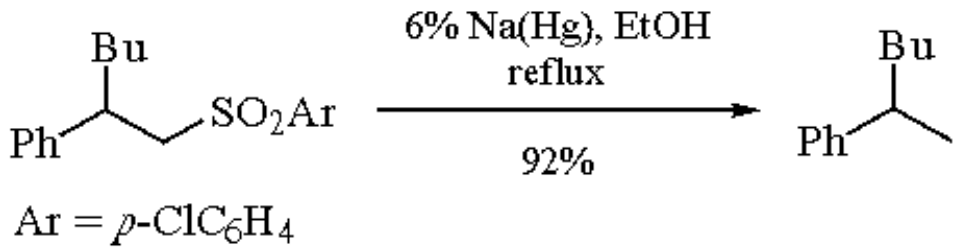

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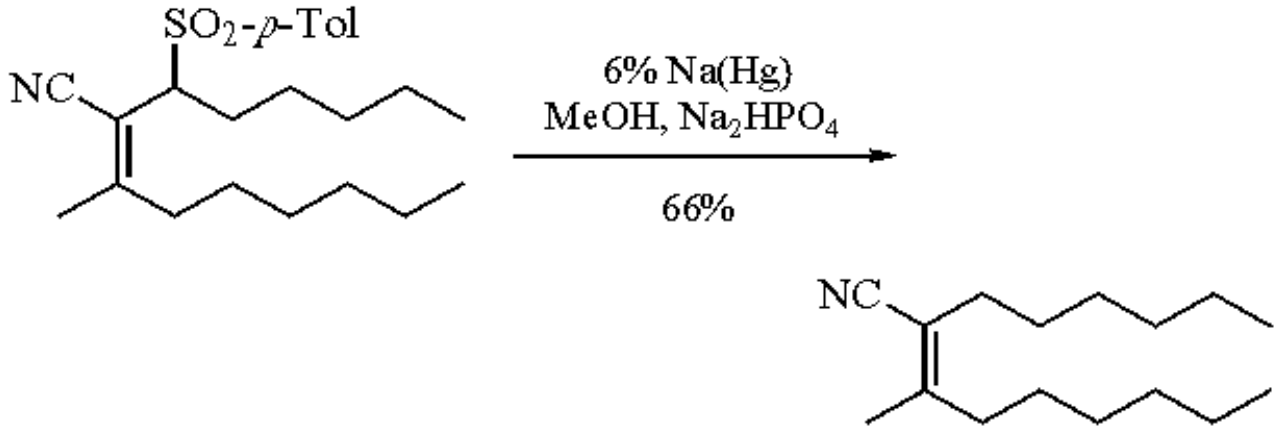

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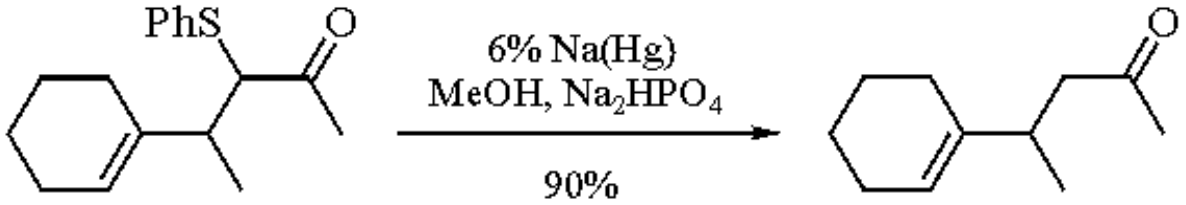

(9)

Desulfonylation of unsaturated α,β-unsaturated acetals with the reagent in buffered methanolic medium gives the reduced products as a mixture of isomers (eq 10).[17] Hydrolysis of the mixture affords the desired α,β-unsaturated ketone as the major product. β-Hydroxynitriles have been prepared in good yield and with retention of stereochemistry by the action of the 2% reagent in wet THF on sulfonylisoxazolines (eqs 11 and 12).[18] The addition of aqueous phosphate buffer is sometimes required to prevent further hydrogenolysis (eq 12).

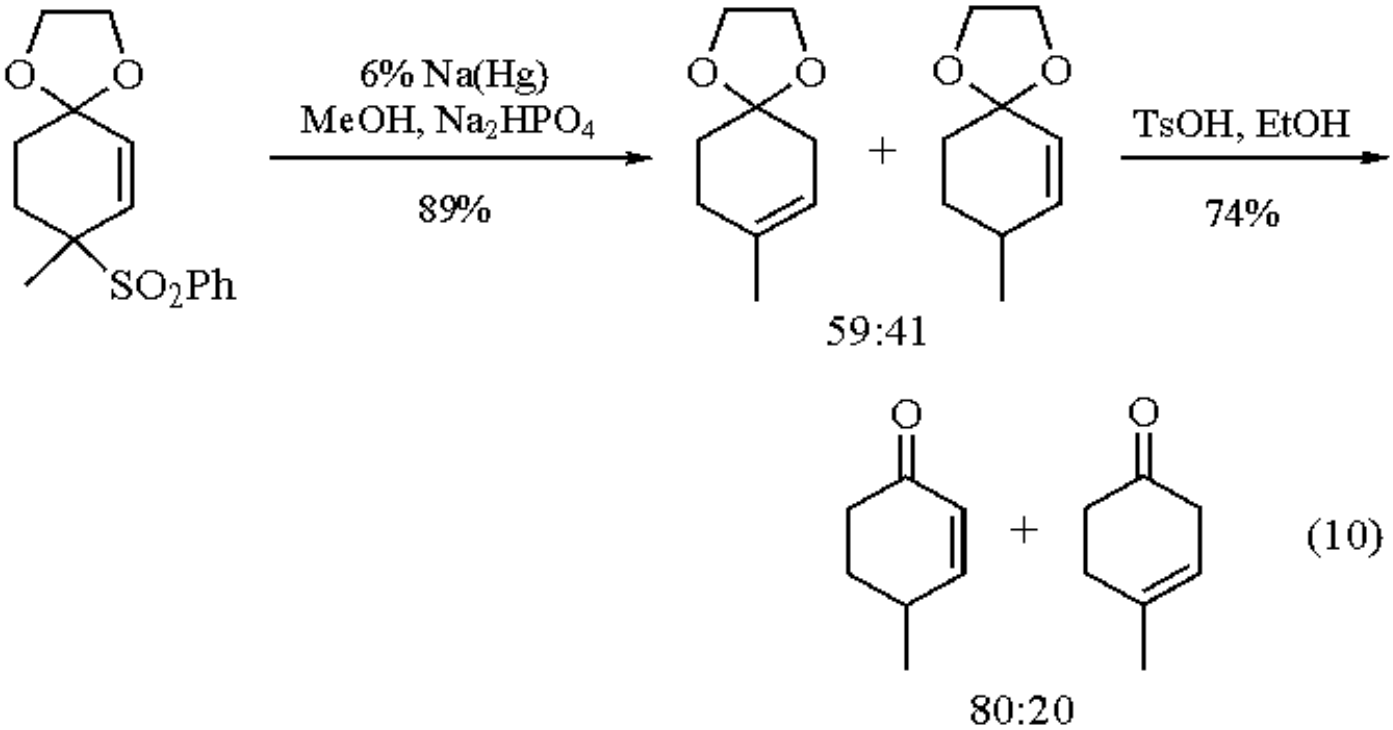

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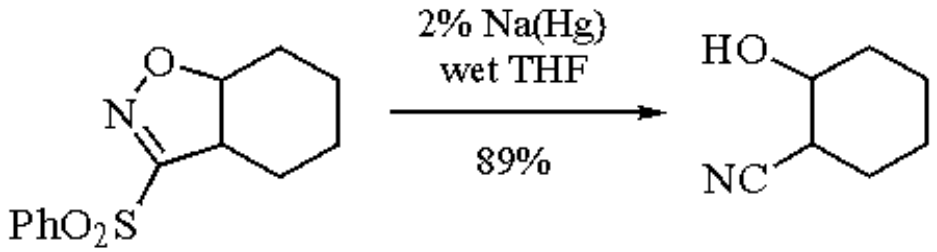

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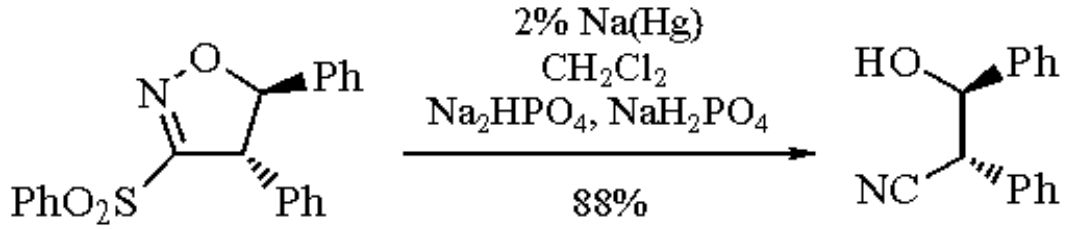

(12)

Enantiomerically pure 4,5-dihydroisoxazoles are available by selective desulfurization of 3-*p*-tolylsulfinylmethyl-4,5-dihydroisoxazoles with the reagent in a buffered medium (eq 13).[19] Further treatment of the products with ***Raney Nickel*** affords the corresponding amino alcohols. Selective desulfurization of methyl 3,4,6-tri-*O*-benzyl-2-*O*-(methylsulfonyl)-α-D-mannopyranoside derivatives was accomplished with 6-7% reagent in 2-propanol and ether (eq 14).[20] Treatment with ***Nickel*** in ethanol, ***Sodium Naphthalenide*** in THF, or ***Sodium-Ammonia*** resulted in removal of the benzyl groups as well.

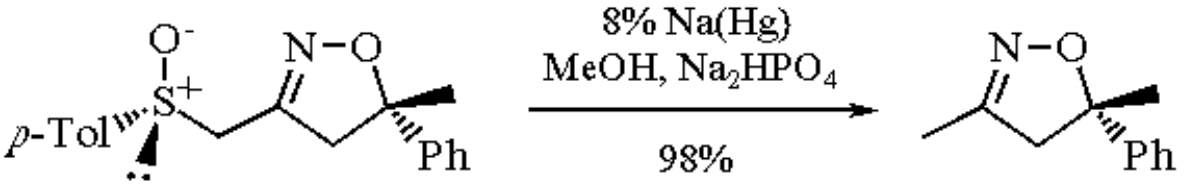

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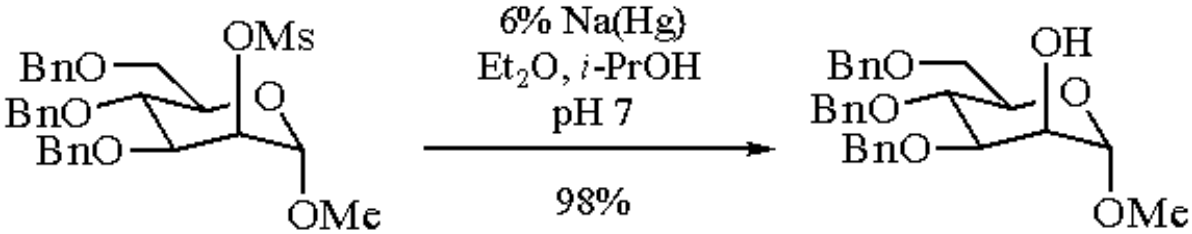

(14)

N-O Bond Hydrogenolysis.

Reductive cleavage of N-O bonds is easily accomplished with the reagent (eqs 15 and 16). Keck reported the facile hydrogenolysis of the intramolecular Diels-Alder acyl-nitroso cycloadduct with excess reagent in a buffered alcoholic medium to yield a hydroxy lactam (eq 15).[21] Similarly, Jager subjected dihydroisoxazoles to hydrogenolysis with 6% sodium amalgam to afford the corresponding 1,3-amino alcohols (eq 16).[22] The *syn* and *anti* stereoselectivity is reported to be lower with this reagent than with ***Lithium Aluminum Hydride***. This method of N-O bond reduction is less common than those using either ***Aluminum Amalgam*** or LAH.

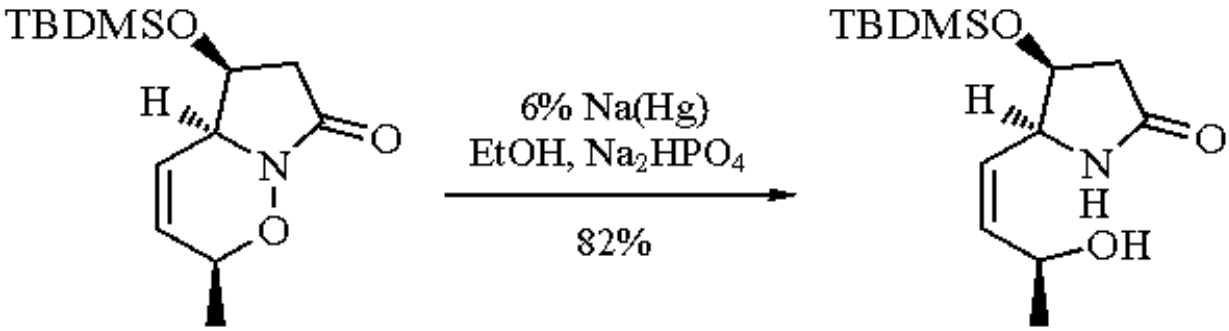

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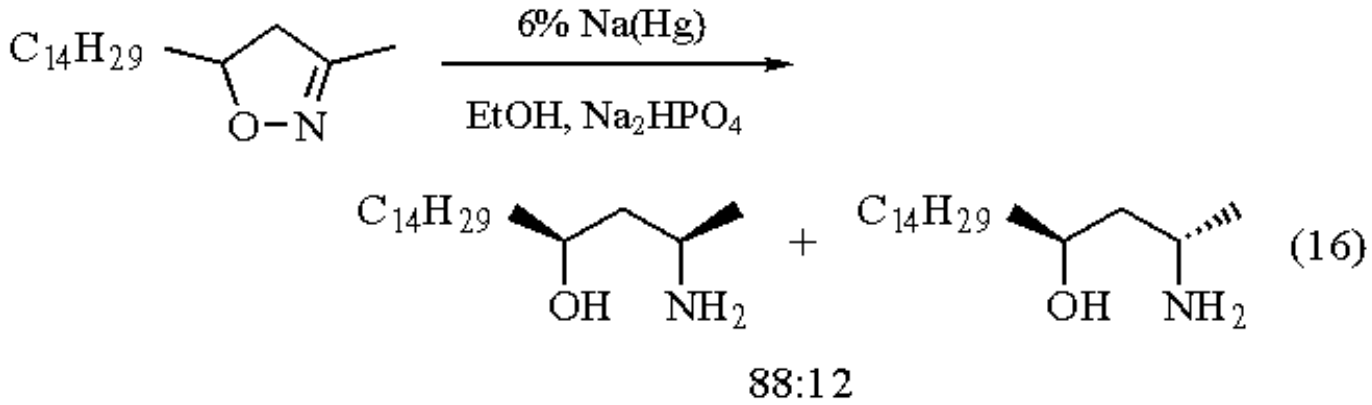

Reductive Cleavage of Quaternary Phosphonium and Arsonium Salts.

Reductive cleavage of achiral and optically active quaternary and phosphonium salts with the reagent affords tertiary phosphines and arsines in high yields and with retention of configuration (eq 17).[23]

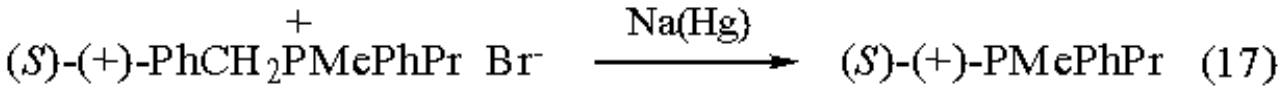

Selective reductive cleavage of the *t*-butyl group occurs in substrates containing both the *t*-butyl and benzyl substituents. The present method is reported to be superior to the conventional cathodic cleavage. Emde degradation of the quaternary ammonium chloride succeeds where the Hofmann method is unsuccessful (eq 18).[24] In a similar fashion, hemimellitene was prepared by treating an aqueous suspension of the benzyltrimethylammonium iodide with a large excess of the reagent (eq 19).[3]

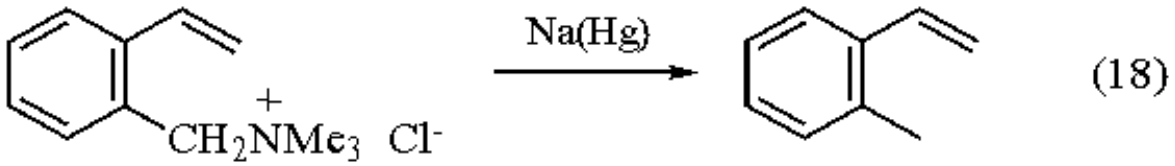

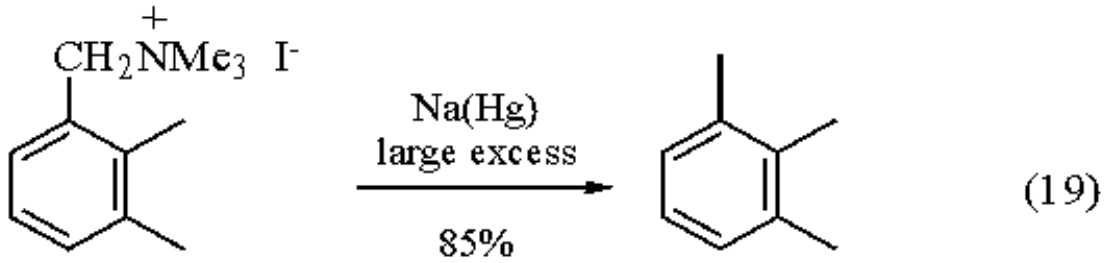

Dehalogenation of Aryl Halides.

Selective dehalogenation of aryl halides with the reagent in liquid ammonia has been found (eqs 20 and 21).[25]

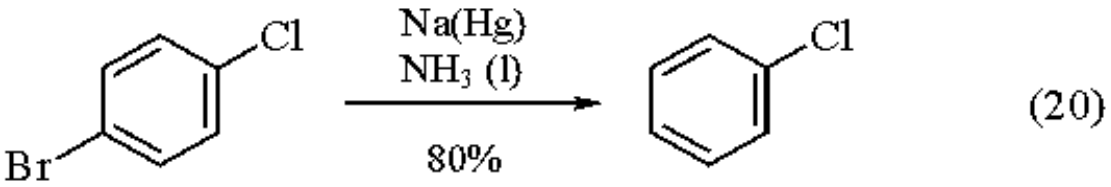

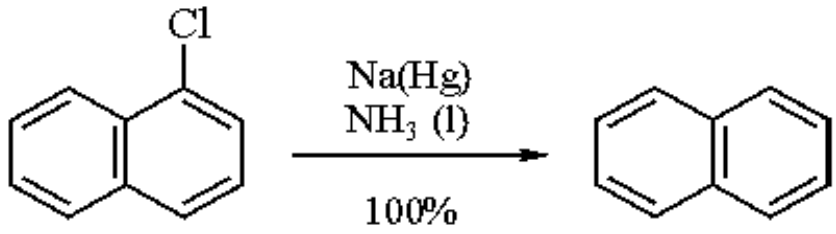

(21)

Reduction of Miscellaneous Functional Groups.

Many additional functional groups react readily with the reagent to afford, in generally good yields, the corresponding reduced products. For example, phthalic acid reacts with the 3% reagent to yield *trans*-1,2-dihydrophthalic acid in good yield (eq 22).[4] α,β-Unsaturated carboxylic acids are also readily reduced by the reagent. Thus cinnamic acid is reduced to hydrocinnamic acid with 2.5% reagent in aqueous base (eq 23).[4]

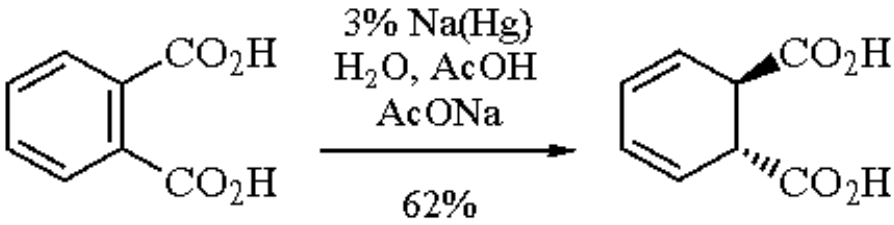

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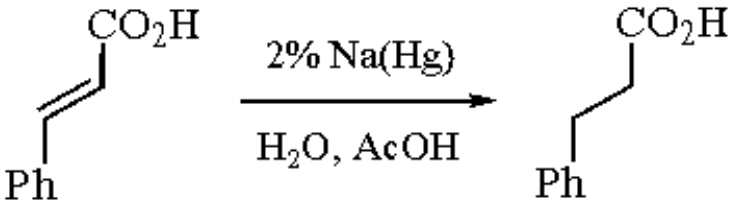

(23)

The product from the condensation of vanillin and creatinine is reduced by 3% reagent in water (eq 24).[26] Xanthone was reduced to xanthydrol with the reagent in ethanol (eq 25).[1] Triphenylchloromethane is converted to triphenylmethylsodium by action of the 1% reagent (eq 26).[2] Oximes are reduced to primary amines with the 2.5% reagent with acetic acid in ethanol (eq 27).[27] One of the oldest applications of sodium amalgam involves the reduction of aldonolactones to aldoses (eq 28).[28]

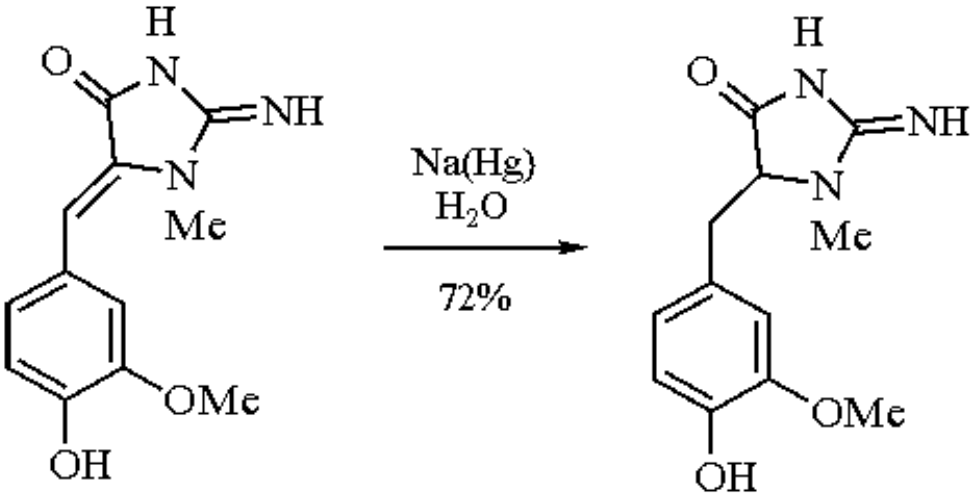

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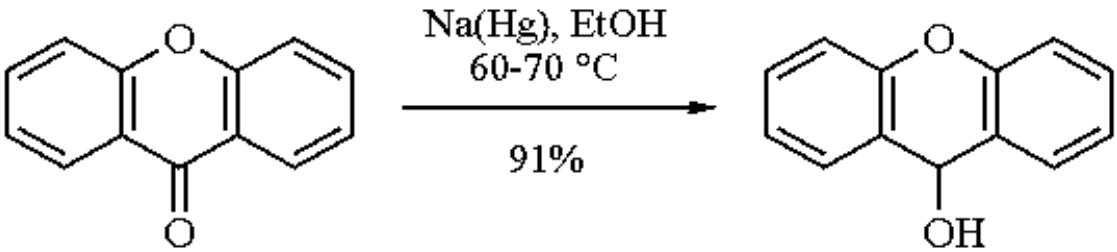

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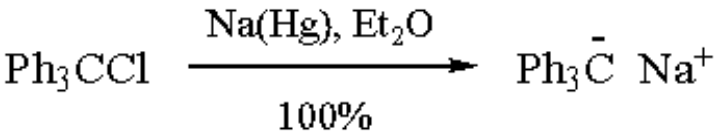

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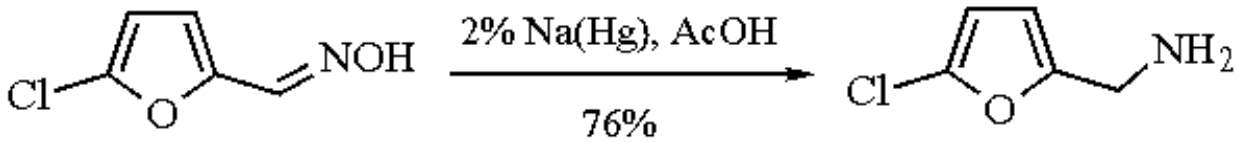

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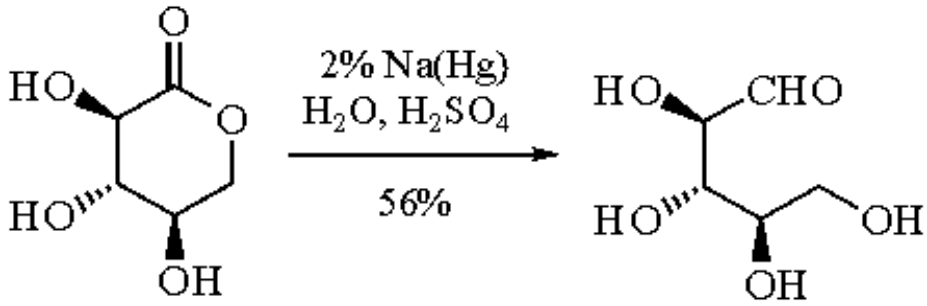

(28)

Other Applications.

Several recent useful miscellaneous applications have been reported. They include the use of the 3% reagent for the reduction of 1-ethyl-4-methoxycarbonylpyridinium iodide in acetonitrile to produce a stable radical (eq 29);[29] the use of the reagent as a catalyst to initiate aromatic radical nucleophilic substitution reactions;[30] and the use of the reagent for the preparation of novel titanium catalysts for the stereoselective cyclization of diynes to (*E*,*E*)-exocyclic dienes.[31]

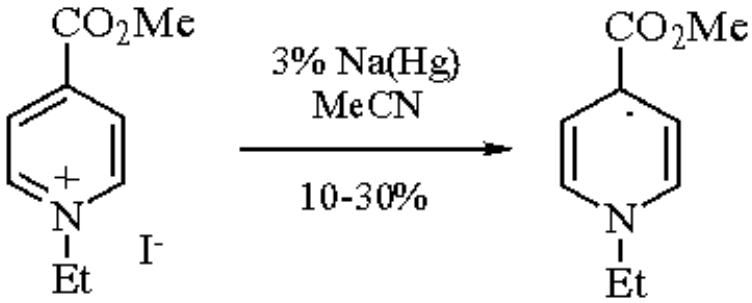

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Sodium Amide

$NaNH_2$

[7782-92-5] · H_2NNa · Sodium Amide · (MW 39.02)

(strong base;[3] strong nucleophile[3b])

Alternate Name: sodamide.

Physical Data: mp 210 °C; bp 400 °C/760 mmHg.

Solubility: sol liq ammonia (~1 mol L^{-1} at -33 °C).[1]

Form Supplied in: commercially available as a powder; easily prepared in the laboratory.

Preparative Methods: combination of ***Ammonia***, small quantities of an iron(III) salt, and ***Sodium*** leads to formation of a black catalyst, whereupon the remainder of the sodium is added. Published procedures differ in details.[2]

Handling, Storage, and Precautions: flammable; corrosive; when opened to air, decomposes and forms a potentially explosive yellow byproduct.[1]

Reaction as a Base.

Sodamide often serves as a base to generate reactive anions.[3] In DMSO in the presence of various bases, including sodamide, carbohydrates are benzylated in good yield with ***Benzyl Chloride***.[3a] Reaction of (**1**) and (**2**) in the presence[3b] of sodamide gives (**3**) (eq 1). Sodamide is effective in generating the acetonitrile anion for reaction with sulfines.[4] Deprotonation of phenylacetic esters in the presence of sodamide allows aldol reaction with benzaldehyde derivatives to afford 2,3-diaryl-3-hydroxypropionic acids.[5] Similarly, reaction of acetophenone and ethyl chloroacetate (eq 2) gives the Darzens' product (**4**).[6] Treatment of primary anilines and cyanopyridines with sodamide leads to good yields of carboxamidines.[7] Oxygenation of hindered 4-alkylphenols in the presence of sodamide provides a convenient source of quinols.[8]

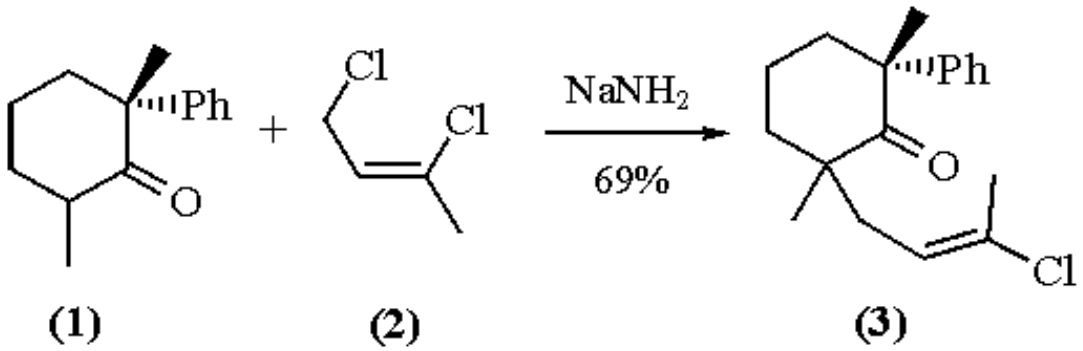

(1)

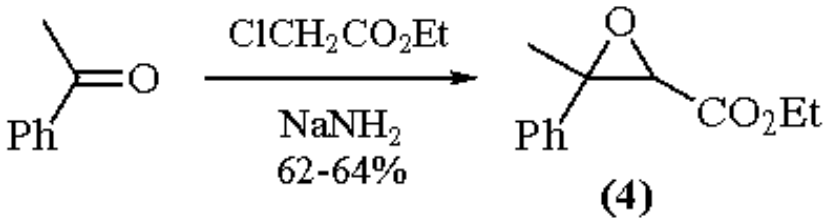

(2)

Sodamide in THF with boric acid neutralization has proven effective for the deconjugation of conjugated unsaturated steroids.[9] The

presence of sodamide in liquid ammonia at low temperature facilitates interconversion of 1,4- and 1,3-cyclohexadienes.[10] Deprotonation of 2-bromothiophenes and 2-halothianaphthalenes affords the 3-halo isomers via a series of complex equilibria.[11] Cyclopropenes, which possess an acidity comparable to alkynes, are rapidly metalated by sodamide (and other alkali amides) to produce reactive intermediates for alkylation.[12] Selective deprotonation occurs with a wide variety of acidic methyl, methylene, and methine hydrogens adjacent to carbonyls or attached to heterocycles. For example, 2,4-lutidine (**5**) undergoes deprotonation (eq 3) to (**6**) followed by reaction with ethyl benzoate to yield (**7**).[13a] Deprotonation followed by reaction with electrophiles is a powerful method for generating complex carbon skeletons.[13] Examination of the role of bases, including sodamide, on the stereochemistry (including isomerization) of products formed in the Michael reaction has been reported.[14] In the racemization of the single stereogenic center in nicotine, sodamide was inferior to ***Potassium t-Butoxide***.[15]

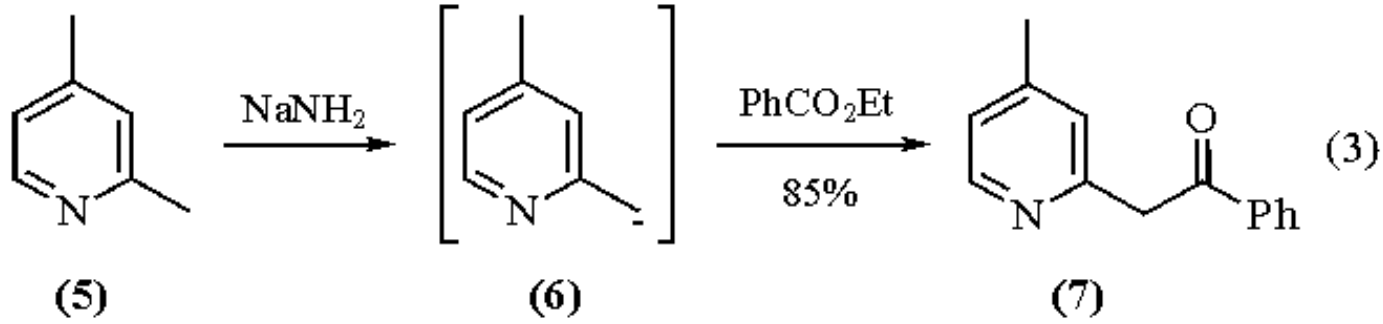

Dianion Generation.

Numerous early investigations into dianion chemistry[16] employed sodamide as the base. Conversion of the simple heterocycle (**8**) into the corresponding dianion with sodamide in liquid ammonia followed by reaction with benzonitrile (eq 4) led to an interesting rearrangement product (**9**).[17] β-Dicarbonyl dianions are routinely prepared by reaction with sodamide. These strongly nucleophilic species undergo regioselective alkylation (eq 5) by reaction of disodioacetylacetone (**10**) (much more soluble in liquid ammonia than its dipotassium counterpart[16a]) with 11-bromoundecanoic acid to give (**11**)[18] and reaction of (**10**) (eq 6) with diphenyliodonium chloride to yield (**12**).[19]

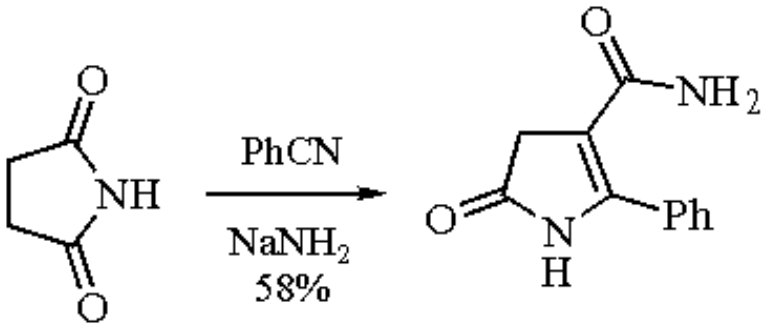

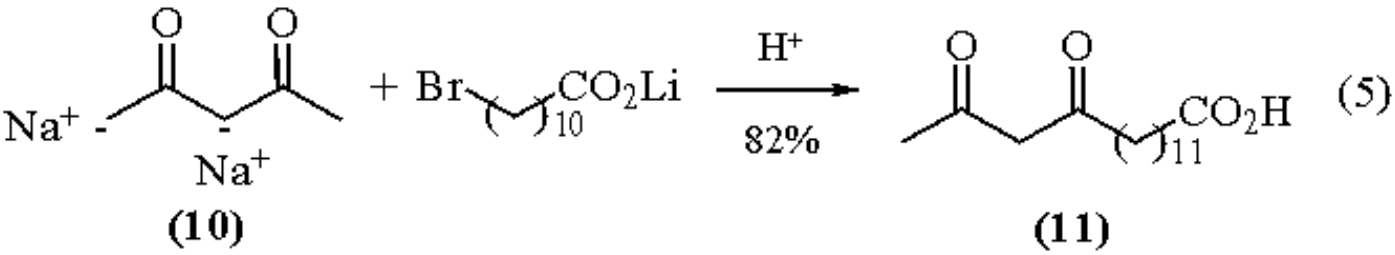

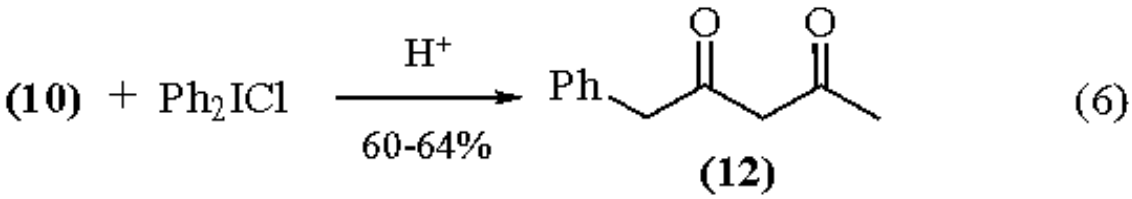

Elimination Reactions.

Sodamide's utility as a reagent for elimination reactions is illustrated by the following selected examples. Methiodide (**13**) undergoes facile loss of HI and diethylmethylamine to generate methyl vinyl ketone.[20] Five isomeric alkenes and a cyclopropane result from treatment of 2-benzyl-3-phenylpropyltrimethylammonium iodide with sodamide.[21] Upon reaction with sodamide, various thioamides eliminate hydrogen sulfide to form ynamines in fair yield.[22] In the presence of sodamide, *cis*-1,4-dichloro-2-butene (**14**) yields mainly *trans*-1-chloro-1,3-butadiene (**15**) (eq 7) while *trans*-1,4-dichloro-2-butene gives a preponderence of *cis*-1-chloro-1,3-butadiene (**16**) (eq 8).[23] Upon warming a mixture of methallyl chloride (**17**) and sodamide (eq 9), there is formed methylenecyclopropane (**18**) and 1-methylcyclopropene (**19**).[24] Sodamide, ***Sodium Hydride***, and ***Sodium Methoxide*** all have utility in the Bamford-Stevens reaction for the conversion of tosylhydrazones into alkenes.[25]

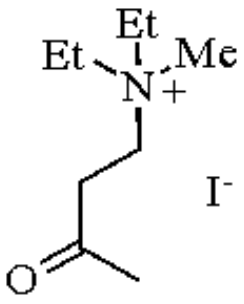

(13)

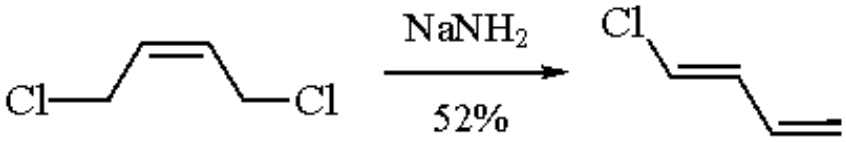

(7)

(14) **(15)**

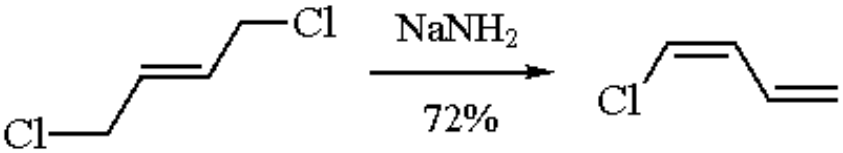

(8)

(16)

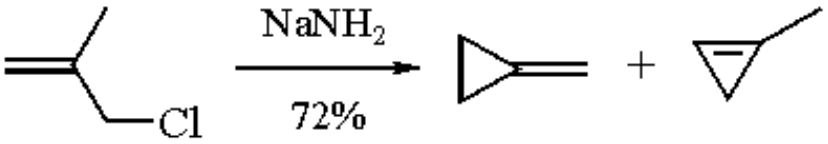

(9)

(17) **(18)** **(19)**

Preparation of Alkynes.

Sodamide-mediated elimination of one or two moles of HX from a suitable substrate is a classical method for the synthesis of alkynes. For example, β-bromostyrene with sodamide in liquid ammonia provides an excellent source of phenylacetylene.[26] Cyclohexylpropyne (**21**) can be generated by reaction (eq 10) of vinyl bromide (**20**) with 3 equiv (excess) of sodamide.[27] Oleic acid (**22**) can be transformed into stearolic acid (**23**) by a straightforward sequence (eq 11) involving bromination followed by reaction with excess sodamide.[28] Similar methodology has been employed to synthesize many other alkynes.[29] Dehydrohalogenation with concomitant ether cleavage provides an efficient route to complex alkynes. For example, reaction of (**24**) with sodamide (eq 12) provides the hydroxylic terminal pentyne (**25**).[29j] Alkyne-allene isomerization has been accomplished with sodamide.[30]

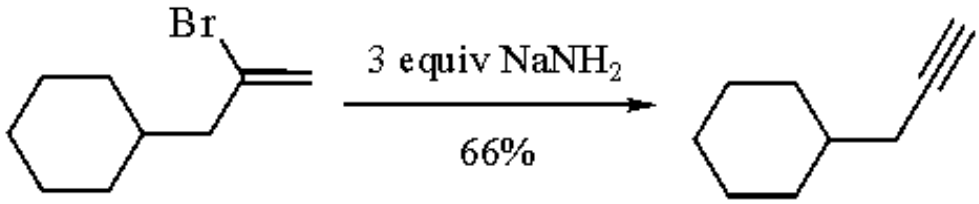

(20) (21) (10)

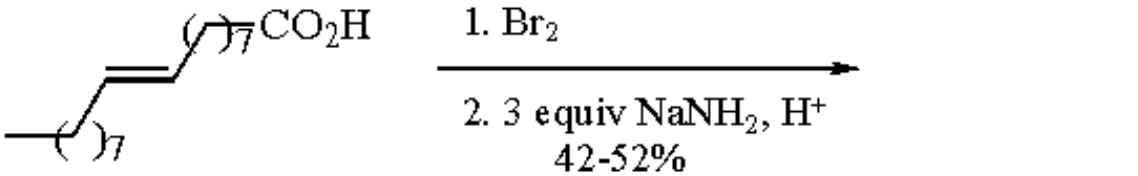

(22) (23) (11)

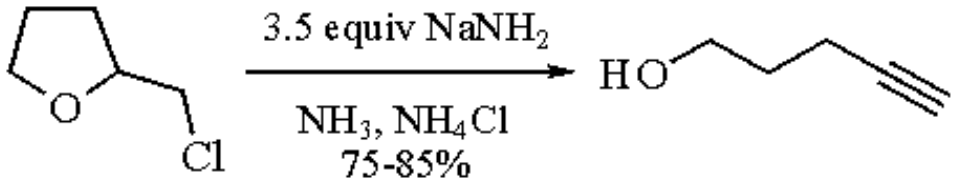

(24) (25) (12)

Aryne Chemistry.

Among the many existing methods for the generation of arynes,[31] reaction of a halobenzene derivative with sodamide (as in the example (eq 13) of (**26**) going to (**27**)[32a]) is a commonly employed procedure.[32] The highly reactive intermediate arynes can be made to undergo reaction with nucleophiles other than amide anion. Thus bromobenzene (**28**) is converted (eq 14) into aryl sulfide (**29**).[33a] Sodamide-generated arynes have also been reacted with more complex species,[34] as illustrated by the transformation (eq 15) of (**30**) into (**31**) followed by cyclization to (**32**).[34a] Intramolecular benzyne reactions involving sodamide have been used successfully in the synthesis of aporphine alkaloids.[35]

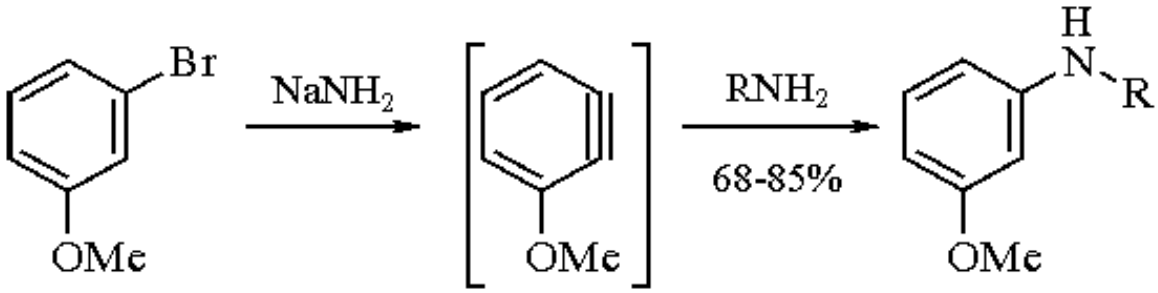

(26) (27) (13)

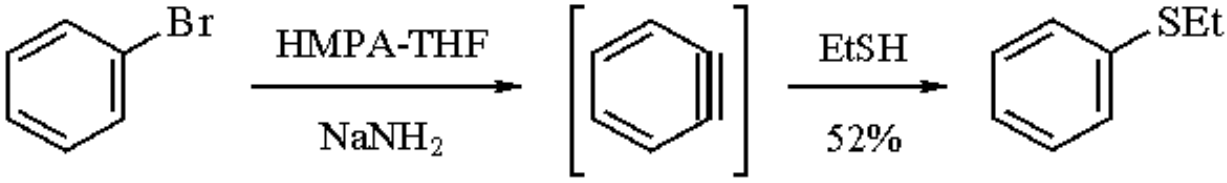

(28) (29) (14)

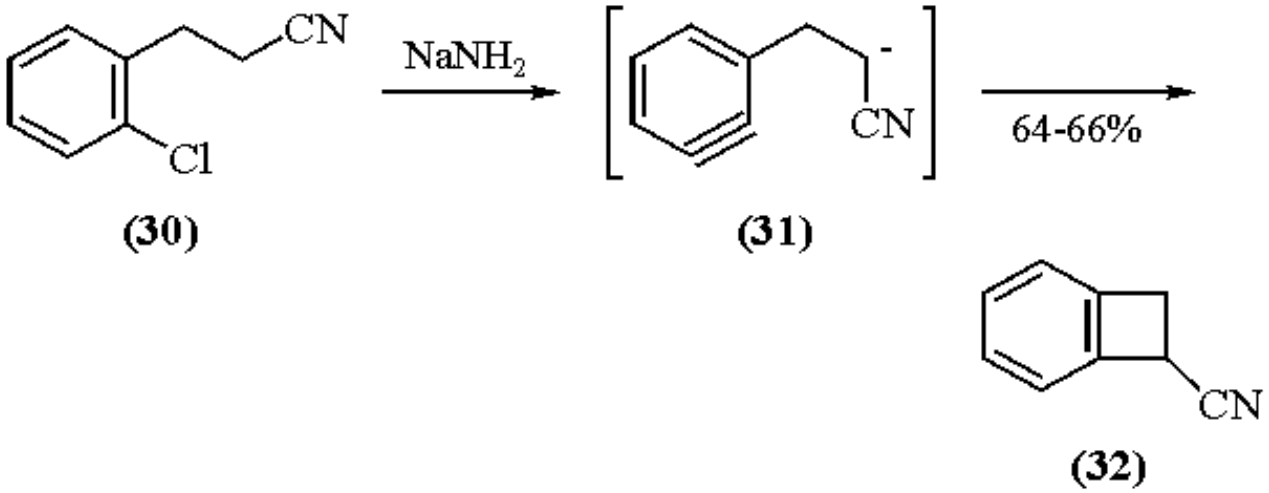

(30) (31) (32) (15)

Generation of Ylides.

Sodamide is a common base for the generation of ylides in the Wittig reaction.[36] The commercially available instant ylide consists[37a] of a 1:1 stoichiometric mixture of ***Methyltriphenylphosphonium Bromide*** and sodium amide (eq 16).[37b]

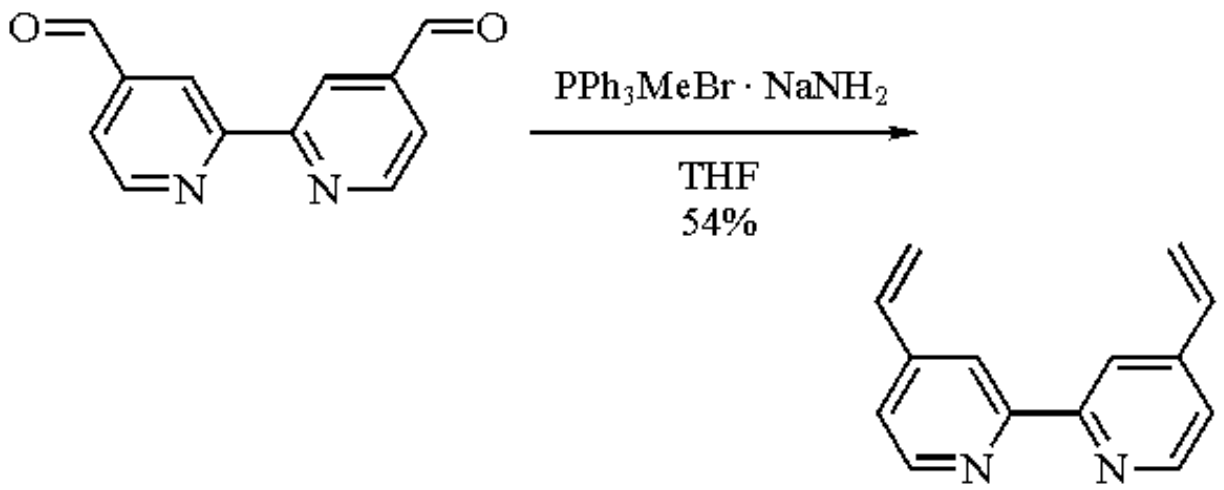

(16)

Reaction as a Nucleophile.

Nucleophilic addition reactions are a major feature of sodamide chemistry. Addition followed by intramolecular attack provides a convenient methodology for the construction of unusual adducts.[38] Sodamide, sodamide/potassamide mixtures, and other alkali metal amides have been found to catalyze the amination of alkenes.[39] The Chichibabin reaction and its variants[40] provide a useful route to numerous substituted heterocycles. The addition-elimination reaction of sodamide on a heterocyclic substrate is nicely illustrated by the transformation (eq 17) of (**33**) into 6-methylisocytosine (**34**).[41] Nucleophilic addition reactions to nitro-substituted aromatic substrates have been observed.[42] Also intriguing are the various reaction pathways observed for heterocycles containing an appended trifluoromethyl group.[43] Photochemically assisted additions of sodamide have been reported (eq 18).[44] Sodamide is also an effective reagent for accomplishing *N*-dealkylations (eq 19)[45a] and *N*-deacylations.[45b]

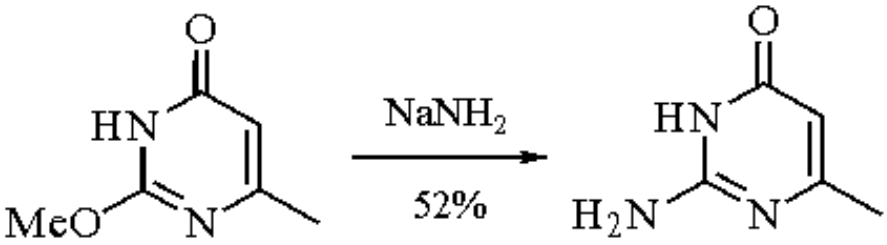

(33) (34) (17)

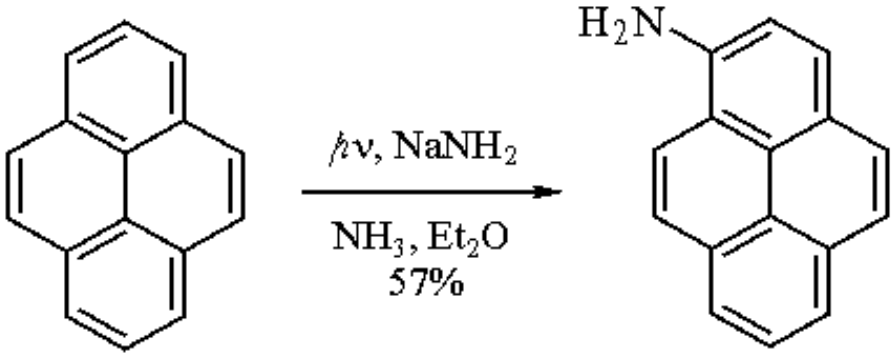

(18)

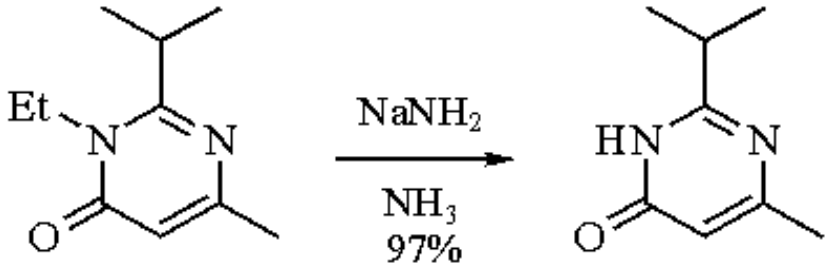

(19)

Cleavage and Rearrangement.

Sodamide is involved in many cleavage and rearrangement reactions. Cleavage reactions,[46] with specific reference to the Haller-Bauer reaction,[47] exemplified by (**35**) going to (**36**) (eq 20),[47d] are a convenient synthetic transform. It is significant that the addition of ***1,4-Diazabicyclo[2.2.2]octane*** (DABCO) permits the Haller-Bauer reaction to be performed with commercial sodamide.[47d] Rearrangement reactions involving sodamide are well-known,[48] with several being common name reactions such as the Truce-Stiles,[49] the Sommelet-Hauser,[50a] and the Stevens[50a] reactions. A typical Sommelet-Hauser rearrangement is illustrated by (**37**) going to (**38**) (eq 21).[50b] Vinylpyridines undergo polymerization in sodamide/liquid ammonia.[51]

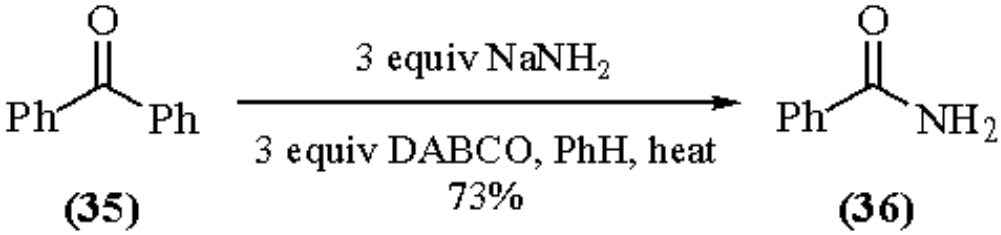

(35) (36)

(20)

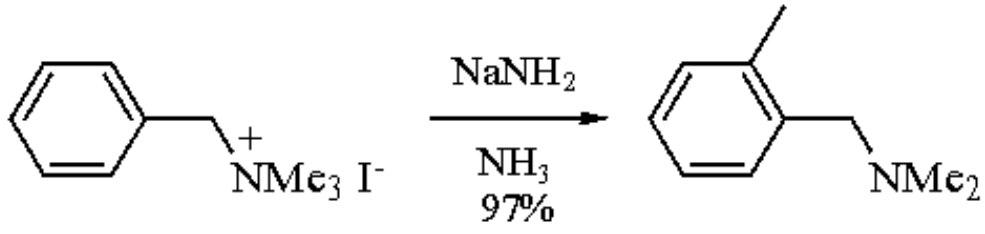

(37) (38)

(21)

In recent years, sodamide has been combined with other bases (especially with alkali metal *t*-butoxides) to create a whole family of so-called complex bases with exceptional properties (see ***Sodium Amide-Sodium t-Butoxide***).[52] Typical applications of these bases are in the *syn* elimination depicted[52d] by (**39**) going to (**40**) and (**41**) (eq 22) and the carbanion alkylation involving the conversion of (**42**) to (**43**) (eq 23).[52f]

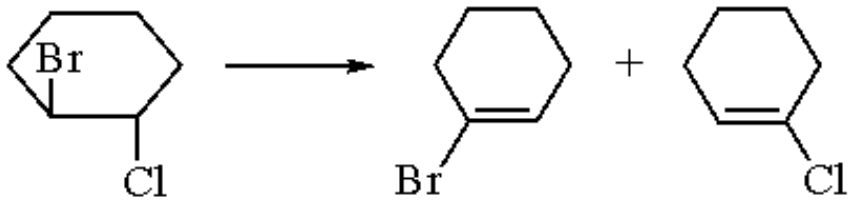

(22)

(39) (40) (41)

$NaNH_2$, *t*-BuONa, 87% 65:35
$NaNH_2$, *t*-BuONa, 15-crown-5, 76% 3:97

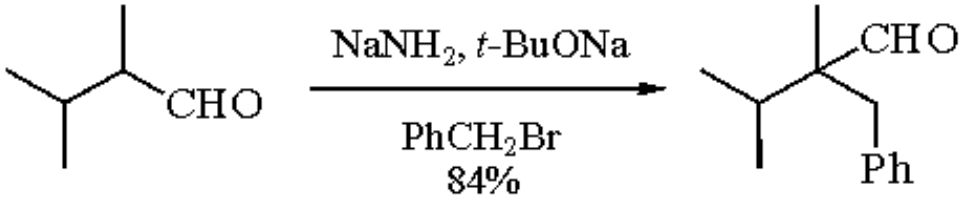

(23)

(42) (43)

Related Reagents.

Lithium Amide; ***Potassium Amide***; ***Potassium t-Butoxide***; ***Sodium Amide-Sodium t-Butoxide***; ***Sodium-Ammonia***; ***Sodium Hydride***.

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Sodium Amide-Sodium *t*-Butoxide[1]

$NaNH_2$-RONa

($NaNH_2$)

[7782-92-5] · H_2NNa · Sodium Amide-Sodium *t*-Butoxide · (MW 39.02) (R = *t*-Bu)

[865-48-5] · C_4H_9NaO · Sodium Amide-Sodium *t*-Butoxide · (MW 96.12) (R = $Et(OCH_2CH_2)_2$)

[52382-21-5] · $C_6H_{13}NaO_3$ · Sodium Amide-Sodium Ethoxyethoxyethoxide · (MW 156.18)

(strong bases, very efficient for *syn* eliminations of organic halides, useful in aromatic, heteroaromatic, and cycloalkenyl elimination-addition reactions; initiate anionic polymerizations)

Physical Data: sodium amide complex bases have not been characterized structurally. They are generated in situ, or commercial preparations are used as received. They are white or light yellow suspensions in the reaction solvent.

Solubility: poorly sol THF or DME.

Preparative Methods: complex bases $NaNH_2$-RONa (2:1) are conveniently prepared by the reaction of an alcohol (ROH, 1 equiv) with $NaNH_2$ (3 equiv) in ethereal solvents (THF, DME, etc.) or in hydrocarbons; *t*-BuOH and $Et(OCH_2CH_2)_2OH$ are distilled from sodium. Complex bases (2:1) contain 2 equiv $NaNH_2$ and 1 equiv RONa (activating agent).

Form Supplied in: suspensions in THF: NABUT (~0.8 mol L^{-1}, *d* 0.915-0.920 g mL^{-1}); NAMEDEG (~0.7 mol L^{-1}, *d* 0.928-0.933 g mL^{-1}).

Handling, Storage, and Precautions: complex bases must be handled and stored under inert atmosphere (N_2 or Ar). Hydrolysis is performed by slow addition of cold water.

Proton Abstractions.

Complex bases $NaNH_2$-RONa (2:1) abstract protons from very weak organic acids. Condensation of the resulting carbanions with electrophiles takes place in excellent yields, as exemplified in eq 1.[2]

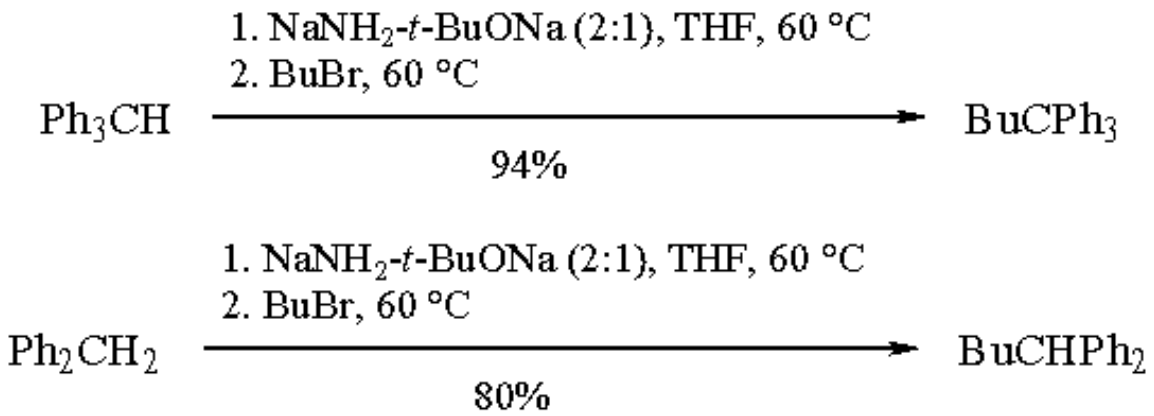

(1)

Complex bases strongly favor monoalkylation of activated methylenes, a property used to perform monoalkylation of carboxylic acid derivatives on an industrial scale.[3]

$NaNH_2$-*t*-BuONa or $NaNH_2$-$Et(OCH_2CH_2)_2ONa$ (the strongest of the sodium amide-containing complex bases) may conveniently replace

organolithium reagents or lithium amides in the synthesis of diazaphospholanes[4] as well as in the thiomethylation of ketones (eq 2).[5]

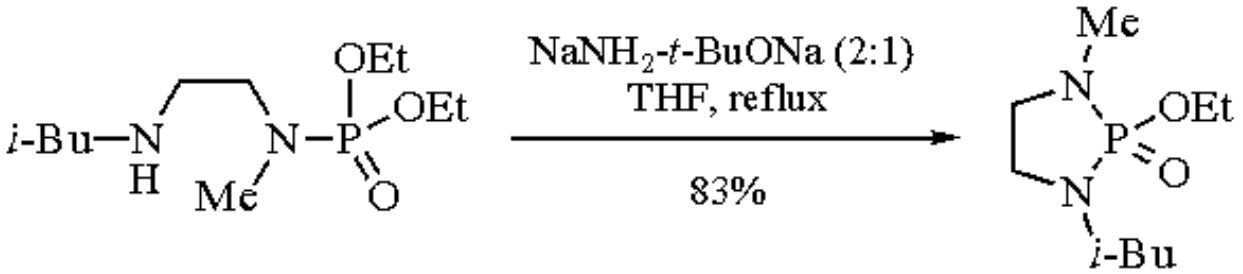

(2)

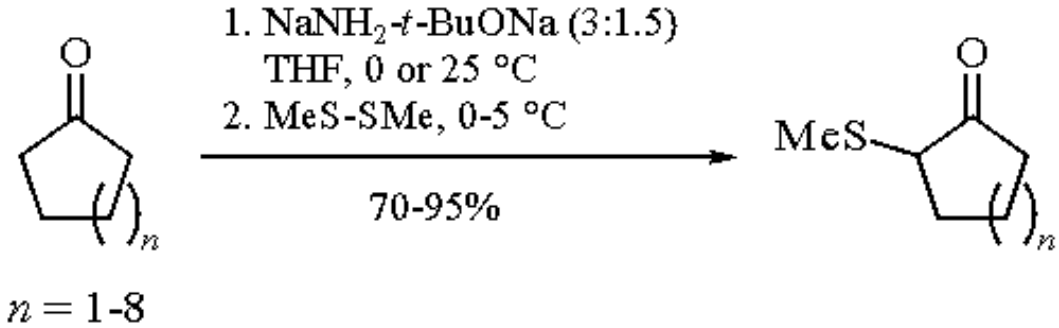

Elimination Reactions.

Complex bases are efficient in usual elimination reactions and they conveniently replace more expensive and/or less accessible bases. Thus $NaNH_2$-*t*-BuONa may be used instead of ***Potassium Amide*** in the preparation of methylenecyclopropane (eq 3).[2b]

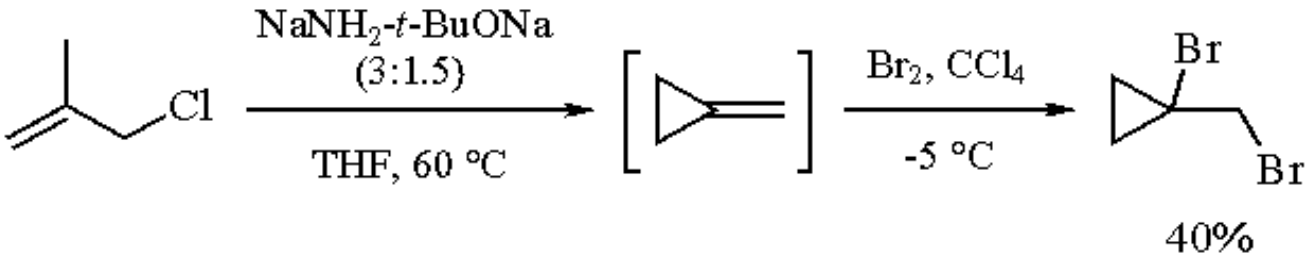

(3)

The complex base $NaNH_2$-*t*-BuONa (2:1) promotes *syn* eliminations under mild conditions (eq 4).[6]

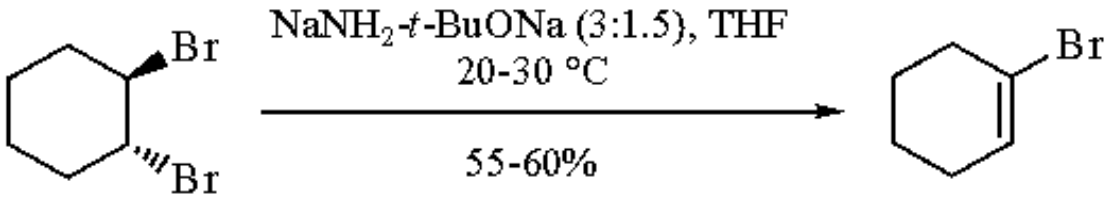

(4)

The poorer leaving group is preferentially eliminated in reactions of *trans*-dihalocyclohexanes with $NaNH_2$-*t*-BuONa (1:1).[7] Advantage may be gained from the strong propensity of $NaNH_2$-*t*-BuONa (2:1) to effect *syn* eliminations in the synthesis of linear[8] and cyclic alkynes.[9]

Elimination-Addition Reactions.

Nucleophilic arynic substitutions may be performed in etheral solvents such as THF or DME due to the facile generation of arynes from aryl halides and $NaNH_2$-*t*-BuONa or $NaNH_2$-Et$(OCH_2CH_2)_2$ONa. Such reactions are more convenient than condensations usually performed in liquid NH_3 and the scope of applications is more extended.

Thus amines and sodium thiolates are condensed with aryl halides (including fluorides) under mild conditions and in very good yields, as exemplified in eq 5.[10]

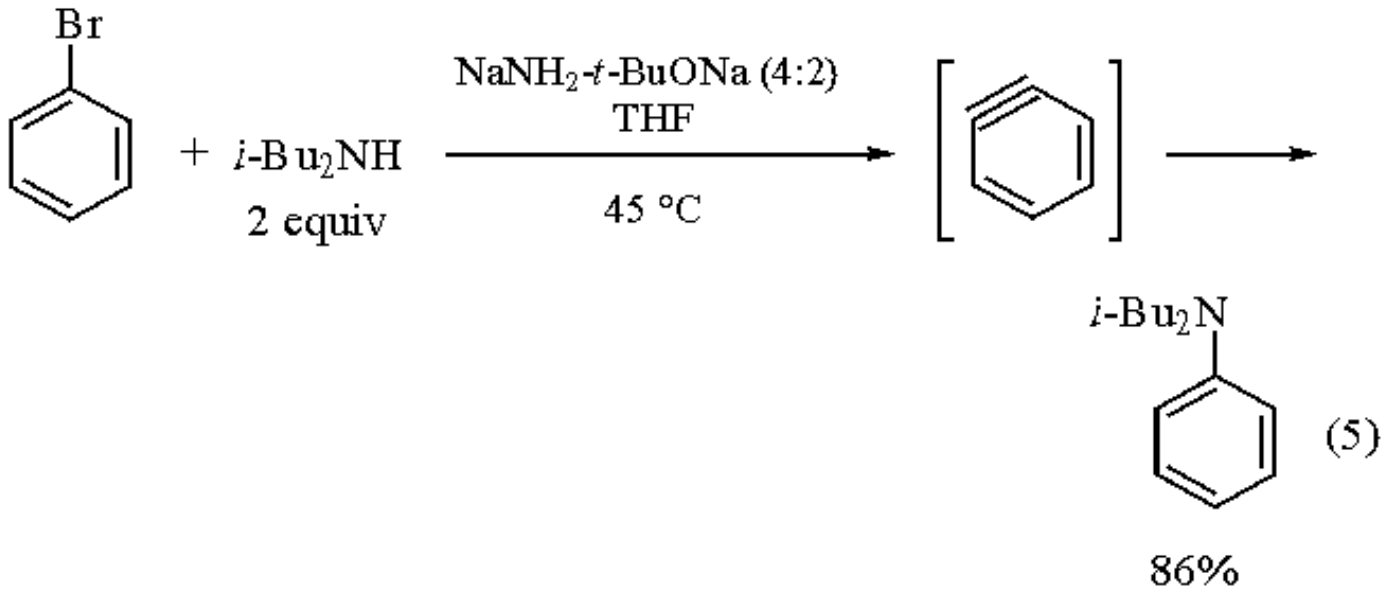

(5)

Such reactions may be also performed with polyhalogenobenzenes[11] and used in the synthesis of nitrogen containing heterocycles (eq 6).[11d]

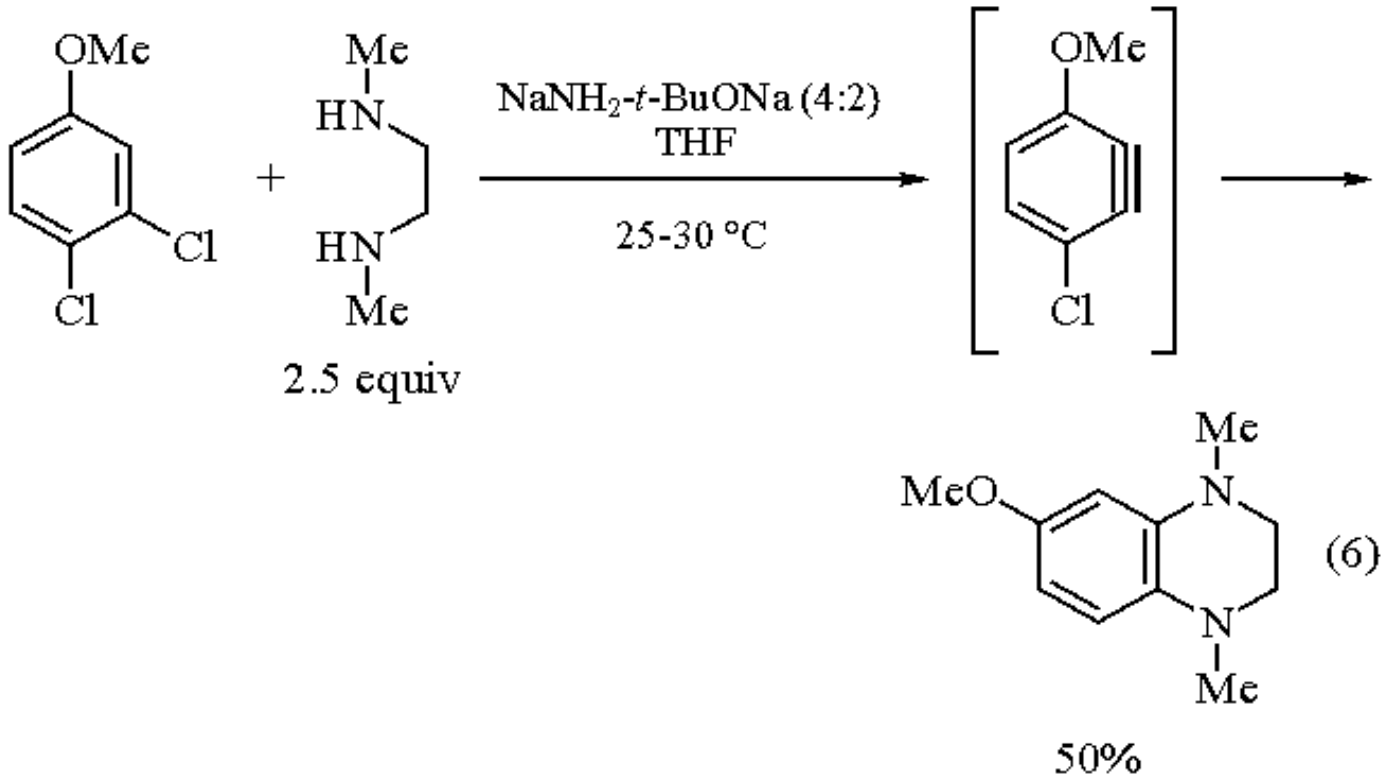

(6)

Use of the complex base $NaNH_2$-$Et(OCH_2CH_2)_2ONa$ provides a good solution to the difficult monoarylation of nitriles (eq 7).[12]

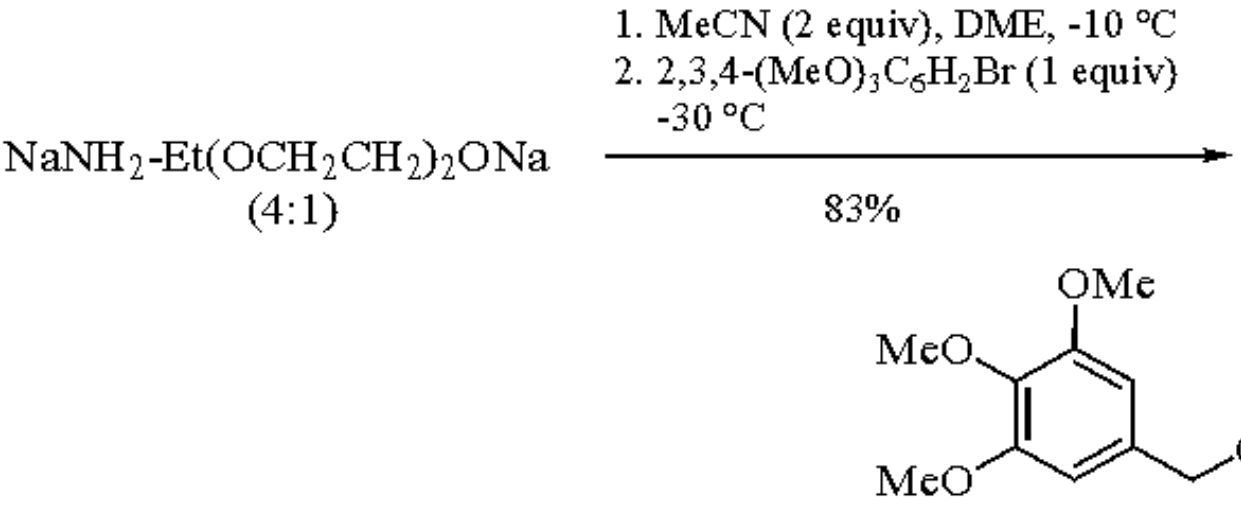

(7)

Arynic condensations of ketone enolates which cannot be performed in the presence of sodium amide alone, are easily performed with $NaNH_2$-*t*-BuONa. Thus 1,2-diketone monoacetals are condensed with bromobenzene to give benzocyclobutenol derivatives in good yields (eq 8).[5b,13]

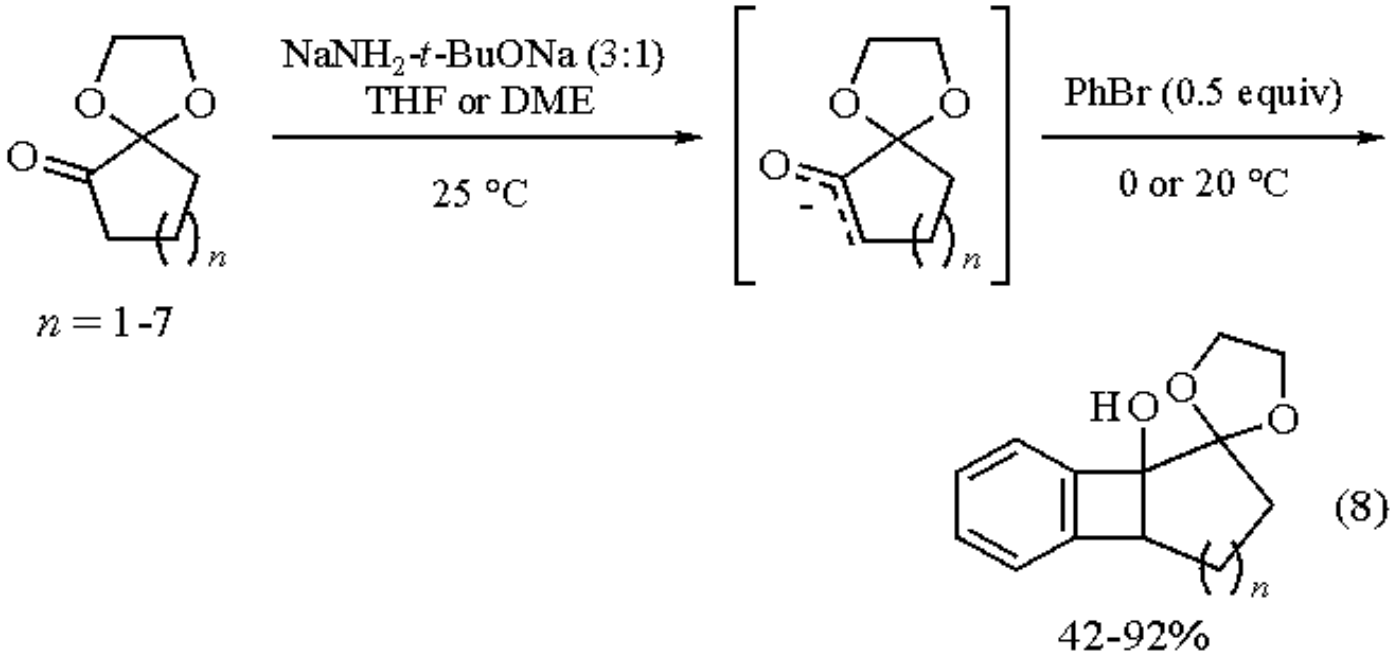

(8)

In the same way, one-step syntheses of naphthalenes, tetralones, indanones, and dihydronaphthocyclobutenols are easily performed via arynic condensation of α,β-unsaturated ketone enolates with aryl halides in the presence of $NaNH_2$-*t*-BuONa.[14]

$NaNH_2$-*t*-BuONa is also an efficient reagent for generating cyclopropabenzynes (eq 9),[15] while classical conditions in liquid NH_3 are unsuccessful.

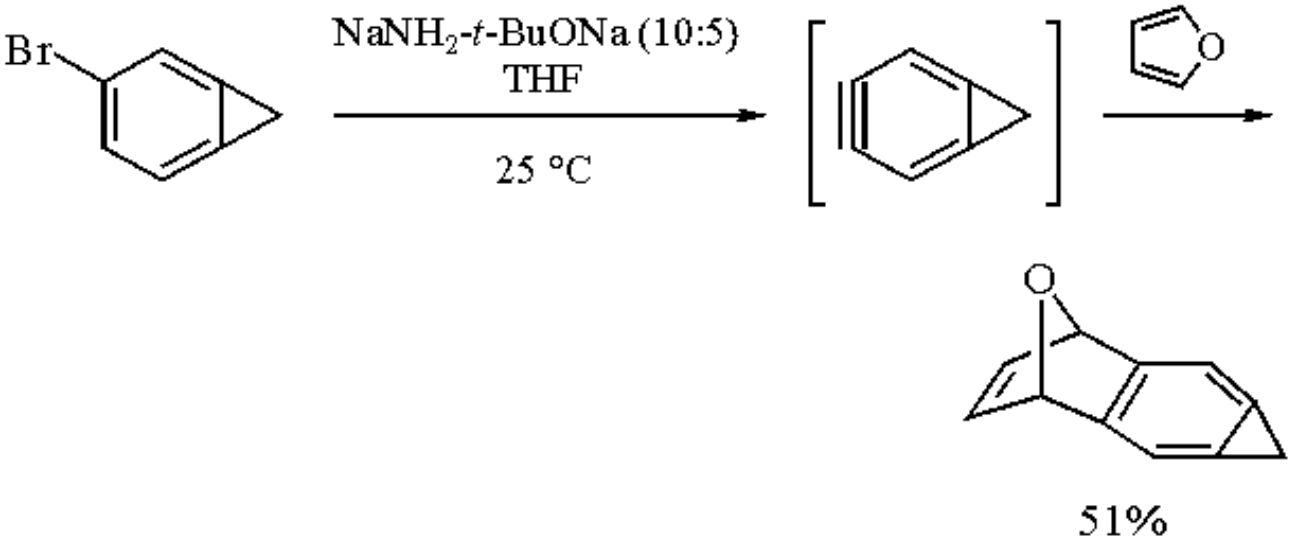

(9)

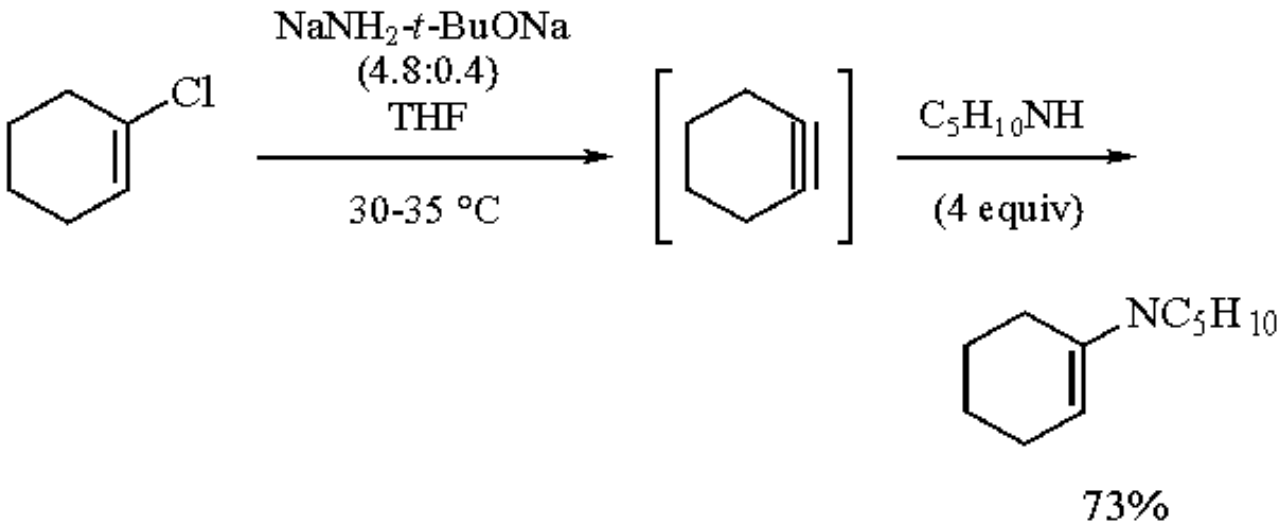

$NaNH_2$-*t*-BuONa easily generates pyrid-3-yne, allowing hetarynic condensations with nucleophiles.[16]

Finally, strained cycloalkynes and cycloalka-1,2-dienes are generated under mild conditions from the corresponding 1-halocycloalkenes and $NaNH_2$-*t*-BuONa and condensed with nucleophiles (eq 10).[17]

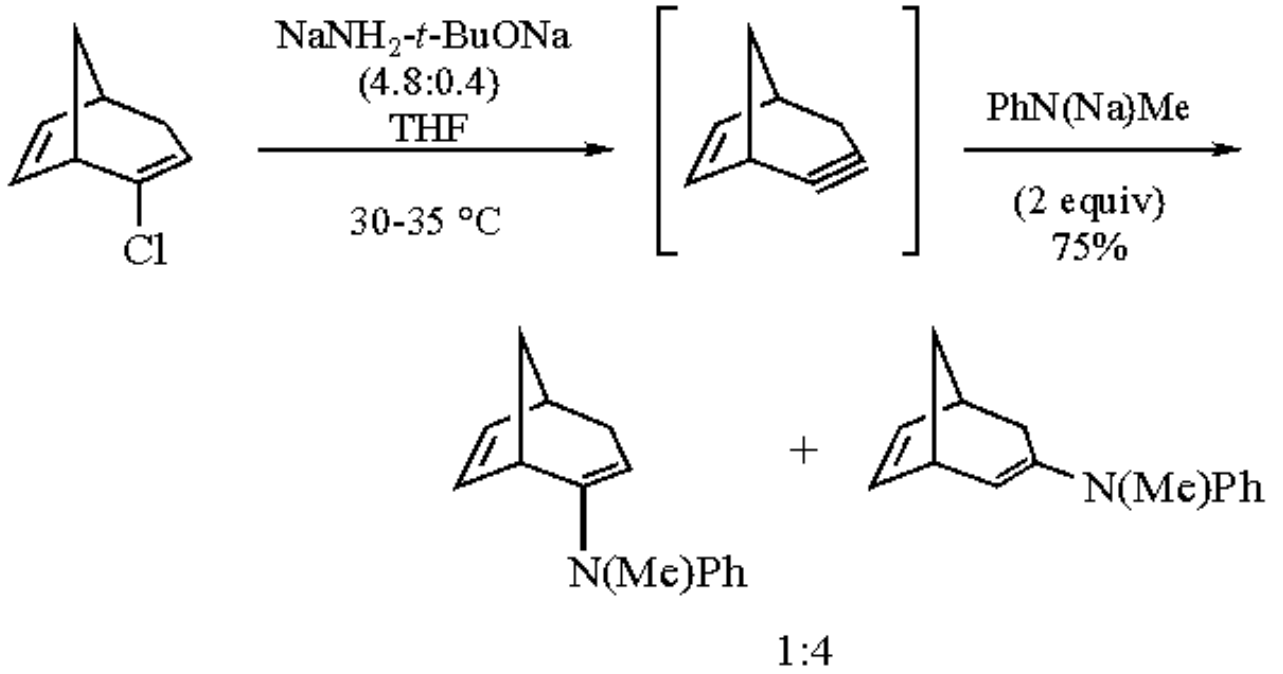

(10)

Such reactions have found a large number of extensions and applications.[1b,d,18]

Anionic Polymerizations.

The complex bases $NaNH_2$-*t*-BuONa and $NaNH_2$-Et$(OCH_2CH_2)_2$ONa are very efficient in initiating anionic polymerizations of acrylic and methacrylic derivatives as well as styrene and vinylpyridine.[1c] These reactions can be performed in solution or in the absence of solvent.

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Sodium-Ammonia[1]

Na-NH_3

(Na)

[7440-23-5] · Na · Sodium-Ammonia · (MW 22.99) (NH_3)

[7664-41-7] · H_3N · Sodium-Ammonia · (MW 17.04)

(strong reducing agent; reduces polyunsaturated hydrocarbons, carbonyl compounds, and other electron acceptors by electron transfer; strongly basic medium)

Physical Data: sodium: mp 97.8 °C; *d* 0.968 g cm^{-3}. Ammonia: mp -77.7 °C; bp -33.4 °C.

Solubility: sodium is soluble to the extent of 25 g in 100 g ammonia at -33 °C.

Form Supplied in: sodium: flammable, metallic solid. Ammonia: compressed gas.

Purification: sodium: by melting and removal of oxide shell.[2] Ammonia: by distillation from alkali metal solutions or passage through a drying tube containing barium oxide.[1o]

Handling, Storage, and Precautions: ***Sodium*** reacts violently with water (frequently explosively) and many other protic or halogenated solvents. While it is best handled under an inert atmosphere, it is usually stored under oil and common practice is to rinse the metal with hydrocarbon solvent and weigh it in air. ***Ammonia*** is a corrosive gas with a pungent odor, and must be handled in a good fume hood.

Sodium-Ammonia Solutions.

Sodium dissolves in liquid, anhydrous ammonia to form a deep-blue solution.[3] At high concentrations, the solution separates into two liquid phases: the more dilute lower phase retains the deep-blue color while the upper phase has a metallic bronze appearance. Sodium reacts slowly with ammonia to produce sodium amide and hydrogen (eq 1), and this reaction is catalyzed by metals such as iron, cobalt, and nickel. The addition of trace amounts of iron salts to sodium-ammonia solutions is a convenient method for the preparation of ***Sodium Amide***. Sodium-ammonia solution serves as an excellent reducing agent, with a half-wave potential of -2.59 V at -50 °C.[1f]

$$Na + NH_3 \longrightarrow NaNH_2 + 1/2\ H_2 \qquad (1)$$

Birch Reduction of Aromatic Rings.

A major use of the sodium-ammonia reagent is the Birch reduction of aromatic rings to cyclohexadienes or sometimes higher levels of unsaturation.[1,4,5] With benzene and less reactive aromatics (electron donor substituents), a proton donor is necessary and alcohols such as ethanol and *t*-butyl alcohol are commonly used. With more reactive aromatics (electron-withdrawing substituents and polynuclear aromatics), alcohols are generally unnecessary and are often deleterious.[1n] The kinetically controlled regiochemistry[6] affords 1,4-dihydroaromatics (1,4-cyclohexadienes), with preference for the regioisomer with the maximum number of alkyl and/or alkoxy groups located on the remaining double bonds (i.e. the Birch rule).[1h,7] Due to the limited solubility of many aromatic compounds in ammonia, cosolvents are often included in amounts of 25-35% relative to the volume of ammonia. While the most common cosolvents are ethers, such as diethyl ether and THF, protic solvents are sometimes used as both cosolvent and proton source. The range of metal concentrations is usually 0.1-0.5 g metal per 100 mL of ammonia, and highly concentrated solutions producing so-called metallic or bronze phases are generally avoided for Birch reductions.

Benzenes containing alkyl or ether substituents, especially where these substituents may be attached to vinyl positions in the product, are reduced in high yields by sodium-ammonia solution in the presence of ethanol or *t*-butyl alcohol (eq 2).[8] The reduced ethers are useful in synthesis since subsequent acid hydrolysis leads to either nonconjugated or conjugated ketones; alternatively, products may be used directly in Diels-Alder reactions without hydrolysis (eq 3).[9]

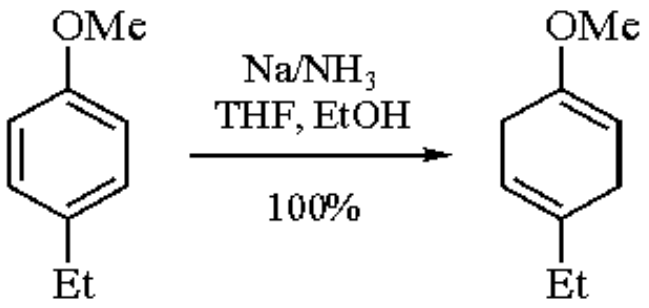

(2)

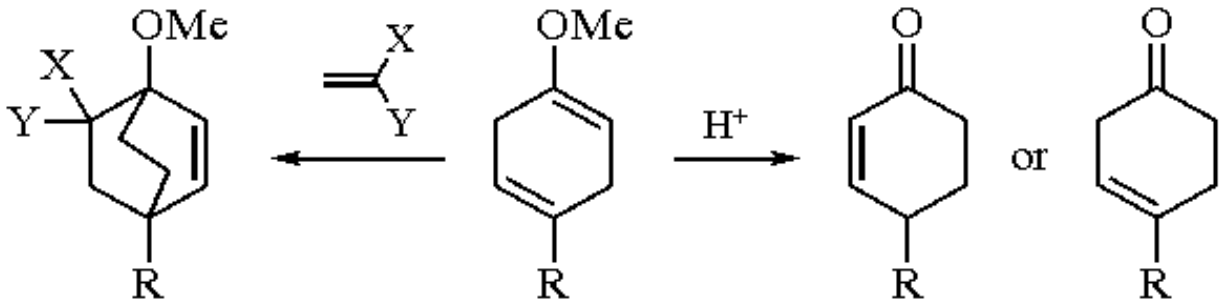

(3)

In cases where this substitution pattern does not apply, however, reduction may be more difficult. For example, while 6-methoxytetralin is reduced smoothly by sodium-ammonia (eq 4), 5-methoxytetralin requires the use of ***Lithium*** with the alcohol added last (eq 5).[5a,10,11] This latter procedure is known as the Wilds and Nelson modification,[11] and is useful for less reactive substrates.

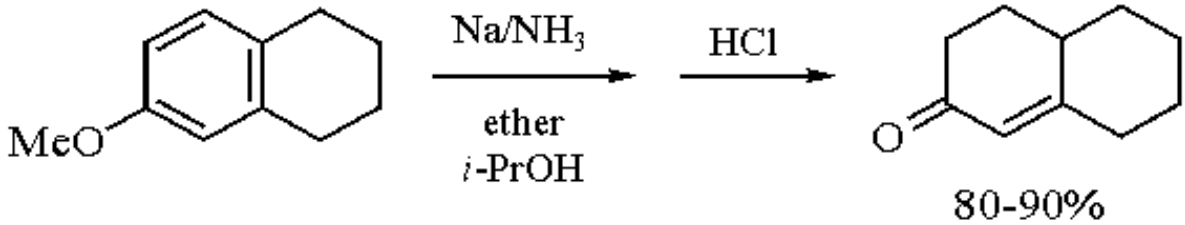

(4)

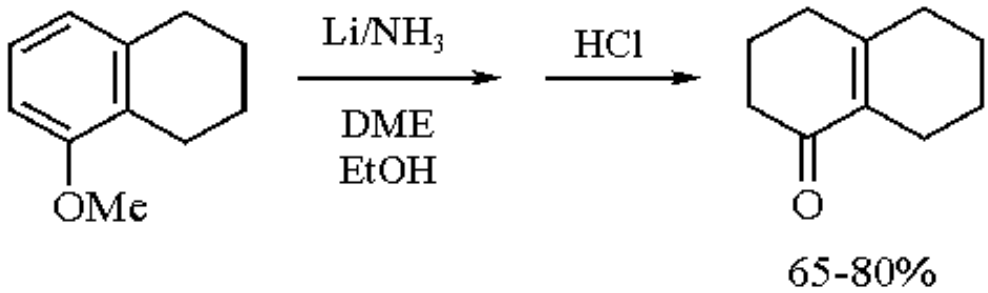

(5)

In polynuclear aromatics, regiochemistry generally follows protonation at the positions bearing the highest coefficients in the HOMO of the anionic intermediates, with sometimes little influence from substituents.[1g,m] Both anthracene (eq 6) and naphthalene (see below) are reduced in nearly quantitative yields by sodium-ammonia solution, provided that highly acidic quenching agents such as water or ammonium chloride are used rather than alcohols. However, some reductions of polynuclear aromatics are hard to control even under these conditions, and iron salts have been used to keep the reaction to a single stage. Such is the case with chrysene (eq 7) and phenanthrene.[1o]

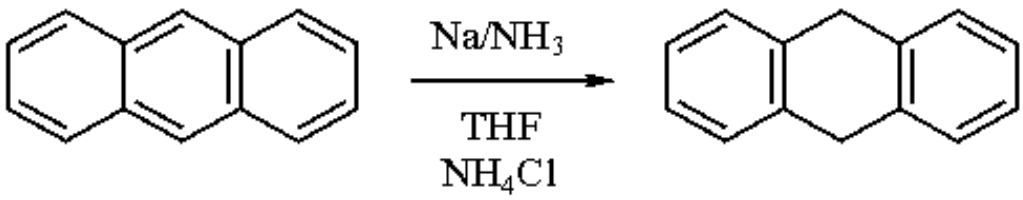

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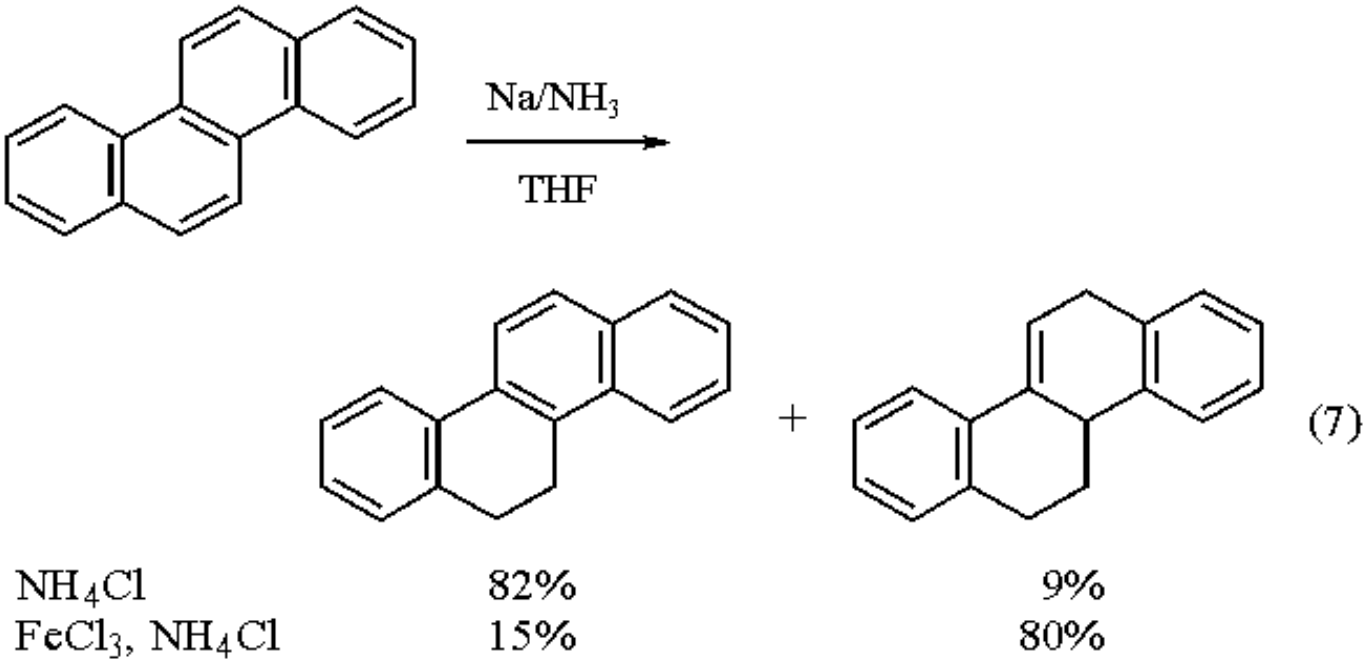

Sodium vs. Lithium.

While sodium and lithium are the most commonly employed metals in Birch reduction (and ***Potassium*** to a lesser extent), the choice between these two metals is not always obvious due to the relative lack of comparison data. Although lithium is the most reactive due to its greater heat of solvation of the cation, its reactivity relative to sodium has probably been overestimated. Early experiments with sodium-ammonia solutions containing impurities in either the metal or ammonia probably showed diminished reactivity due to the greater sensitivity of sodium to amide formation catalyzed by trace contaminants.[1f] Thus metal selection may be based on expense, reactivity, or demonstrated superiority with a particular substrate. With very small scale reactions, the higher atomic weight of sodium may make it more practical due to accuracy in weighing. Lithium is the metal of choice when greater reactivity is required, but greater reactivity can sometimes lead to overreduction, whereupon sodium becomes the reagent of choice.

In many cases (eq 8)[12,13] the results are comparable with either metal. However, a comparison of the two metals in the reduction of naphthalene[14] shows best results with sodium at low temperatures (eq 9). At higher temperatures, and especially with lithium, protonation of the intermediates and subsequent isomerization of the 1,4-dihydro product to the 1,2-dihydro isomer leads to appreciable overreduction. The reductive methylation of naphthalene shows even greater differences between the metals, with lithium affording monoalkylation (95%) and sodium dialkylation (93%).[14,15] This is due to a second alkylation via proton abstraction by amide ion during the alkylation step, a process that does not occur with lithium due to the relative lack of solubility of lithium amide in ammonia as compared to sodium amide. Similar results are observed for biphenyl, where lithium provides 99% monomethylation and sodium leads to 40% dimethylation with 10% trimethylation.[16]

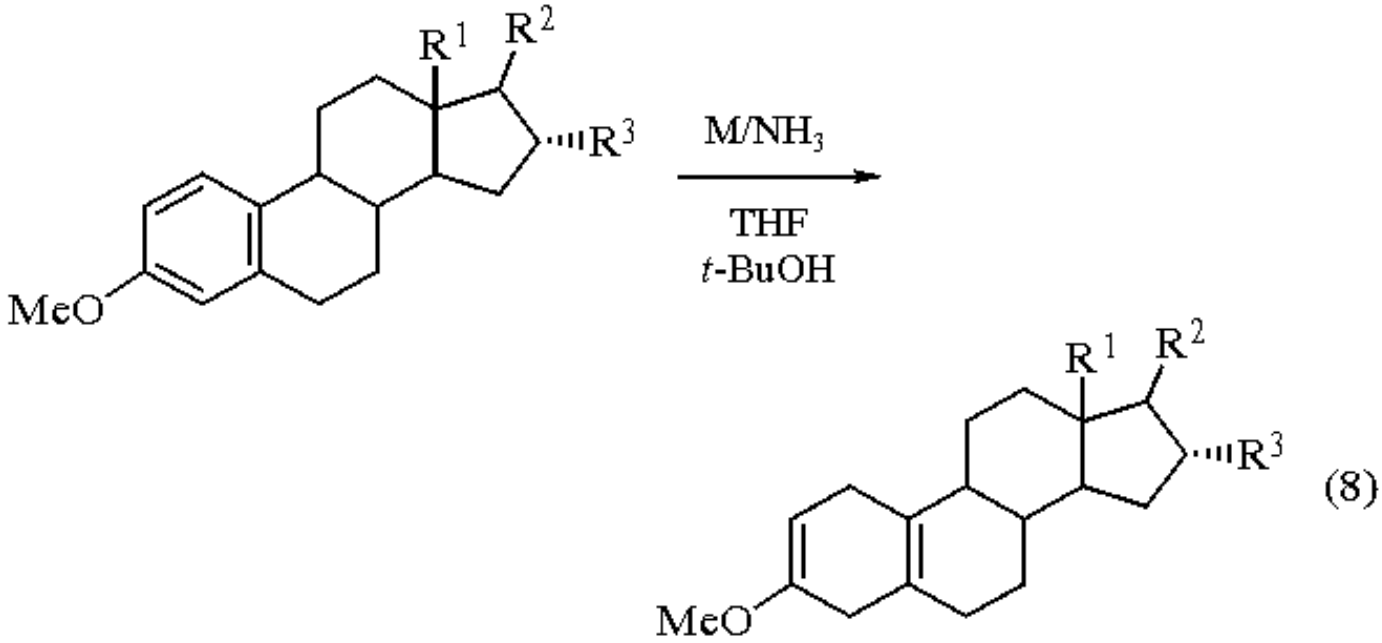

$M = Li, R^1 = CH_2CHMeOH, R^2 = R^3 = H, 89\%$
$M = Na, R^1 = Me, R^2 = OH, R^3 = Et, 87\%$

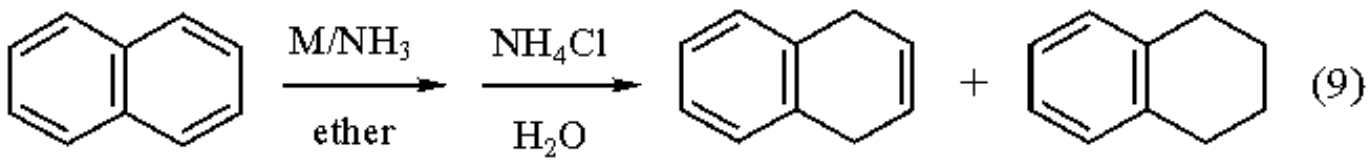

M = Li, -33 °C	40%	55%
M = Li, -78 °C	81%	14%
M = Na, -33 °C	83%	17%
M = Na, -78 °C	96%	2%

Regioselectivity and Stereoselectivity.

The regiochemistry of Birch reduction is generally driven by electron densities in the radical anions, dianions, and monoanions that serve as intermediates in the reaction. An attempt has been made to control regiochemistry by use of trimethylsilyl substituents.[17] For example, while 1-methylnaphthalene reduces exclusively in the unsubstituted ring, 1-methyl-4-trimethylsilylnaphthalene reduces in the silylated ring, and subsequent removal of the silyl group affords a misoriented Birch product (eq 10).

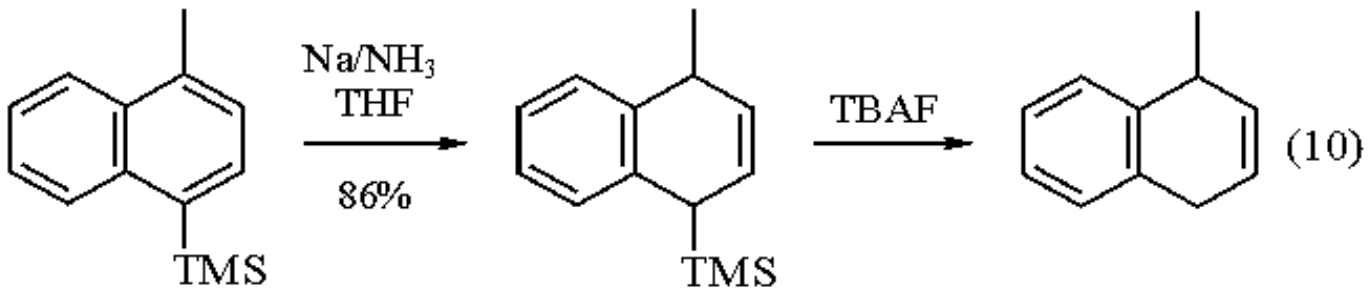

Excellent diastereoselectivities have been accomplished in the reductive methylation of benzoic acids where L-proline has been introduced as a chiral auxiliary (eq 11).[18] Results with a variety of derivatives appear to give comparable results with sodium, lithium, or potassium.

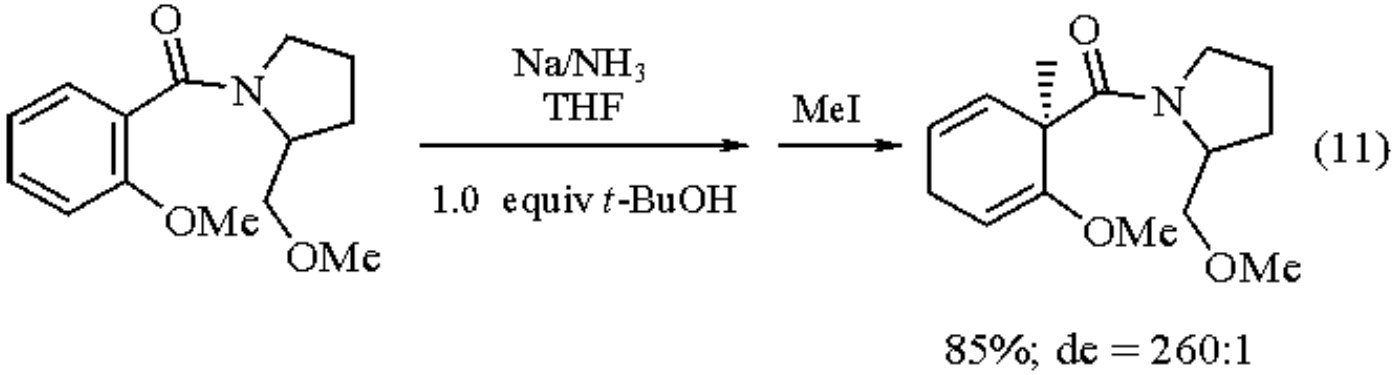

(11)

Reduction of Carbonyl Functions.

The sodium-ammonia reduction of cyclic aliphatic ketones has some utility for the preparation of the more stable epimeric alcohols (such as 11α-hydroxy steroids) derived from sterically hindered ketones.[11,m] In other cases, product mixtures resemble those obtained with reagents such as borohydride. Similarly, esters may be reduced (Bouveault-Blanc reduction), but there is little advantage except with monoesters of diacids where the acid carbonyl remains unreduced (eq 12).[19] Carboxamides are reduced by sodium-ammonia, often affording rather good results, as illustrated with the L-asparagine derivative (eq 13).

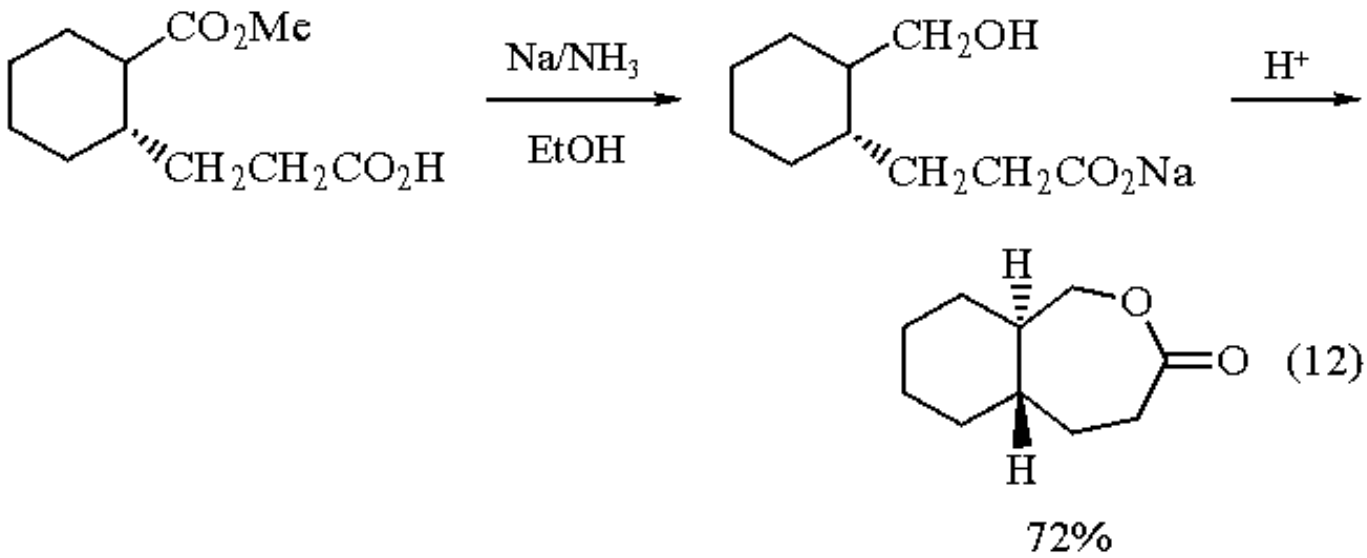

(12)

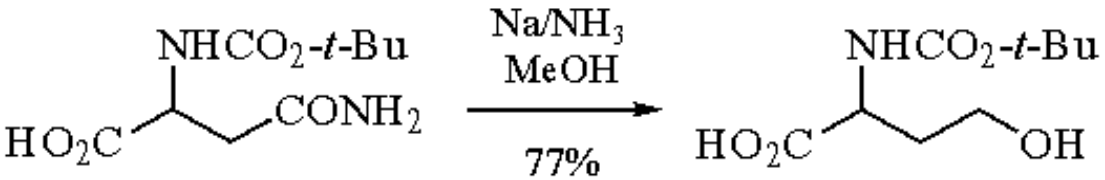

(13)

The most common use of sodium-ammonia reagent for the reduction of carbonyl compounds is the reduction of α,β-unsaturated ketones, and an extensive list of examples has been provided by Caine.[1k] Of special interest are bicycloalkenones, where the α,β-double bond is exocyclic to the second ring (eq 14).[20] In these cases, stereochemistry is dictated by the protonation at the β-position, and the most favored transition states are those involving protonation of an axial anionic center; this most often results in the formation of *trans* products, although the stereochemistry can be reversed by 6β- and 7α-substituents. α,β-Unsaturated acids and esters can also be reduced, and reductive alkylation can be achieved by adding alkylating agents before the protic quench. However, Li and K have more often been used for the latter process.

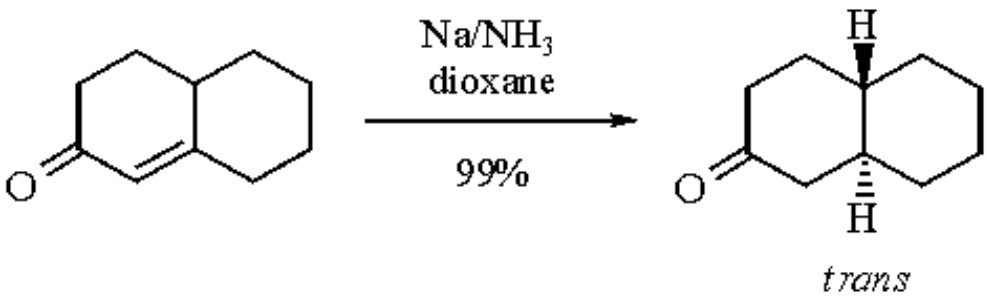

(14)

Reductive Cleavage.

The sodium-ammonia reagent is effective in cleaving a variety of bonds including carbon-carbon (especially when strained), carbon-sulfur, carbon-nitrogen (especially positively charged nitrogen), and carbon-halogen; also allylic and benzylic alcohols, ethers and esters, epoxides, and many phenol ethers. While most halides are cleaved, vinyl halides are cleaved stereospecifically (eqs 15 and 16).[21,22]

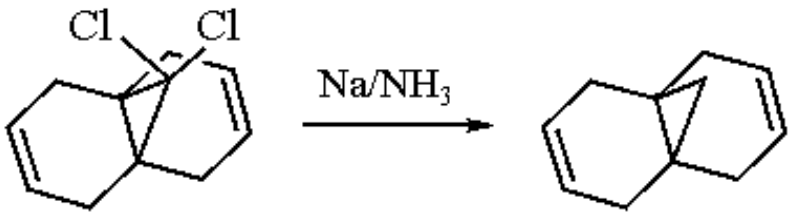

(15)

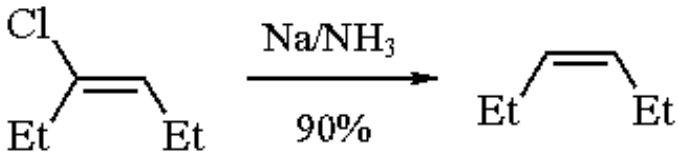

(16)

Cleavage of the hydrazine derivative in eq 17 represents an especially useful application since ***Zinc-Acetic Acid***, ***Aluminum Amalgam***, and ***Raney Nickel*** all give no reduction.[23] An interesting example of carbon-carbon bond cleavage is provided by an important step in the synthesis of (C_2)-dioxa-C_{20}-octaquinane (eq 18),[24] and sulfur-sulfur bond cleavage is illustrated with the mercaptosulfinate synthon shown in eq 19.[25] In the latter example, both sodium hydride and ***Sodium Borohydride*** gave poor results.

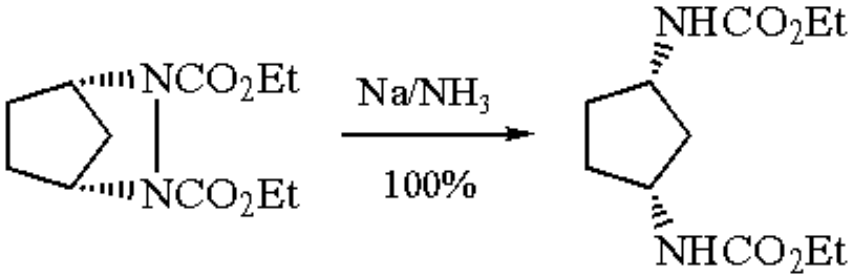

(17)

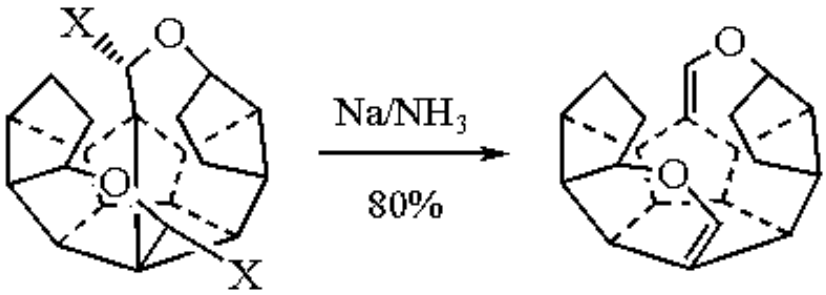

(18)

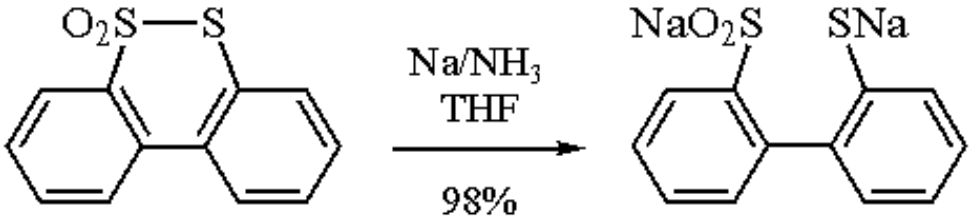

(19)

Reduction of Alkenes and Alkynes.

Conjugated polyenes are reduced by sodium-ammonia, although complications such as dimerization generally limit good results to cyclic systems and styrenes.[1f] The reduction of alkynes to *trans*-alkenes is well-known,[1f,h] the stereochemistry presumably resulting from the *trans* nature of the intermediate radical anion. Terminal alkynes can be protected by removal of the acidic proton by sodium amide, allowing synthetically useful strategies (eq 20).[26]

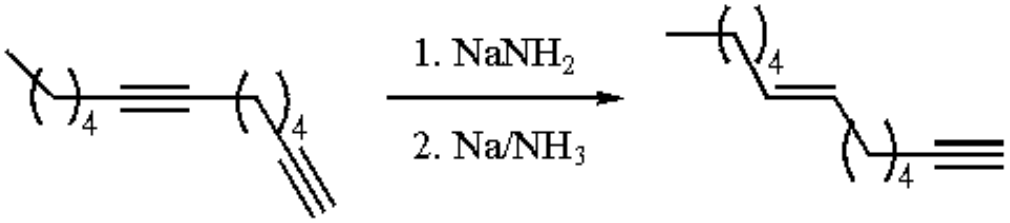

(20)

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Sodium Anthracenide

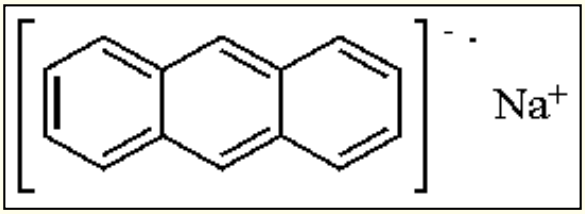

[12261-48-2] · $C_{14}H_{10}Na$ · Sodium Anthracenide · (MW 201.23)

(reductive cleavage of N-S,[1,2] O-S,[3] O-P,[4] and C-O[5-7] bonds)

Solubility: sol THF, DME, HMPA.

Preparative Methods: a 0.1 M solution of the reagent in THF (or DME) is prepared by stirring sodium metal (1.0 equiv) and anthracene (1.1 equiv) in anhydrous solvent for 24 h under an argon atmosphere.[2] The resulting solution exhibits the characteristic dark green color of the radical anion. The preparation time can be significantly reduced by ultrasound irradiation of the reaction.[1,8]

Handling, Storage, and Precautions: sodium anthracenide is both air- and moisture-sensitive. However, stock solutions of the reagent are stable for several weeks at rt when stored under an argon atmosphere. The reagent is flammable and should be handled with care. Excess reagent can be neutralized by the slow addition of isopropyl alcohol.

Reductive N-S Cleavage.

Sulfoximines unsubstituted at nitrogen are readily prepared by the titration of *N*-tosylsulfoximines with sodium anthracenide (eq 1).[1] Alternative reagents employed to cleave the tosyl group (e.g. ***Sulfuric Acid***, *h*υ, and ***Sodium-Ammonia***) are less efficient (yields of 7-60% in eq 1).

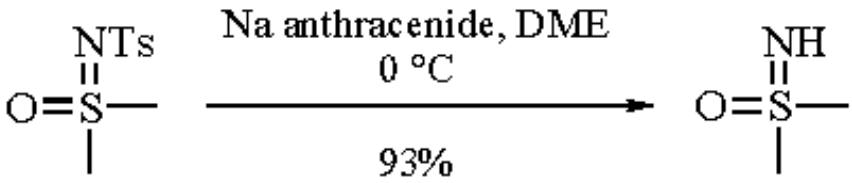

(1)

Secondary arenesulfonamides are reductively cleaved by sodium anthracenide to provide the corresponding amines.[2] *N*-Arenesulfonyl aziridines can be reduced to free aziridines without concomitant homolytic ring opening (eq 2).[2c] Primary arene- and methanesulfonamides are deprotonated, rather than reduced.

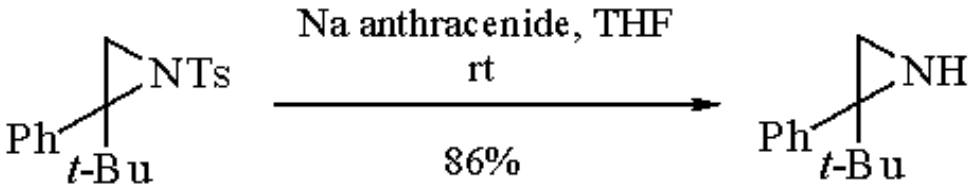

(2)

Reductive O-S Bond Cleavage.

Sodium anthracenide converts arene mesylates to the corresponding phenols (eq 3).[3] More powerful reducing agents such as ***Sodium Naphthalenide*** and Na/NH_3 tend to produce competitive C-O bond cleavage.

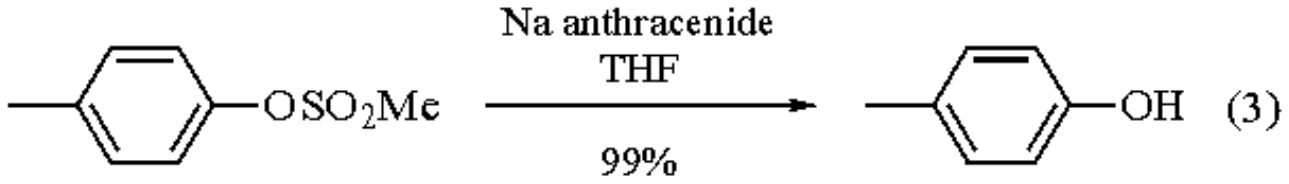

Reductive O-P Bond Cleavage.

Aromatic phosphate esters are reduced to the corresponding phenols upon treatment with sodium anthracenide (eq 4).[4] Extensive C-O bond cleavage can occur with sodium naphthalenide or Na/NH_3.

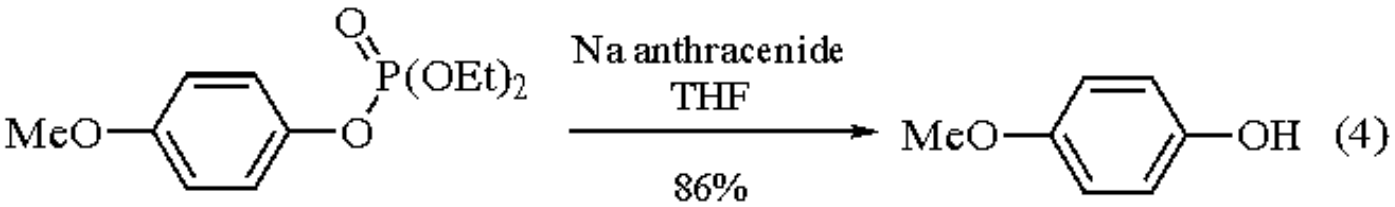

Reductive C-O Bond Cleavage.

The α-naphthyldiphenylmethyl group is selectively cleaved by sodium anthracenide in the presence of the *p*-methoxytrityl protecting group (eq 5).[5] No discrimination between the triarylmethyl ethers is observed with sodium naphthalenide. The order of reactivity is reversed for hydrolytic (aqueous acid) deprotection.

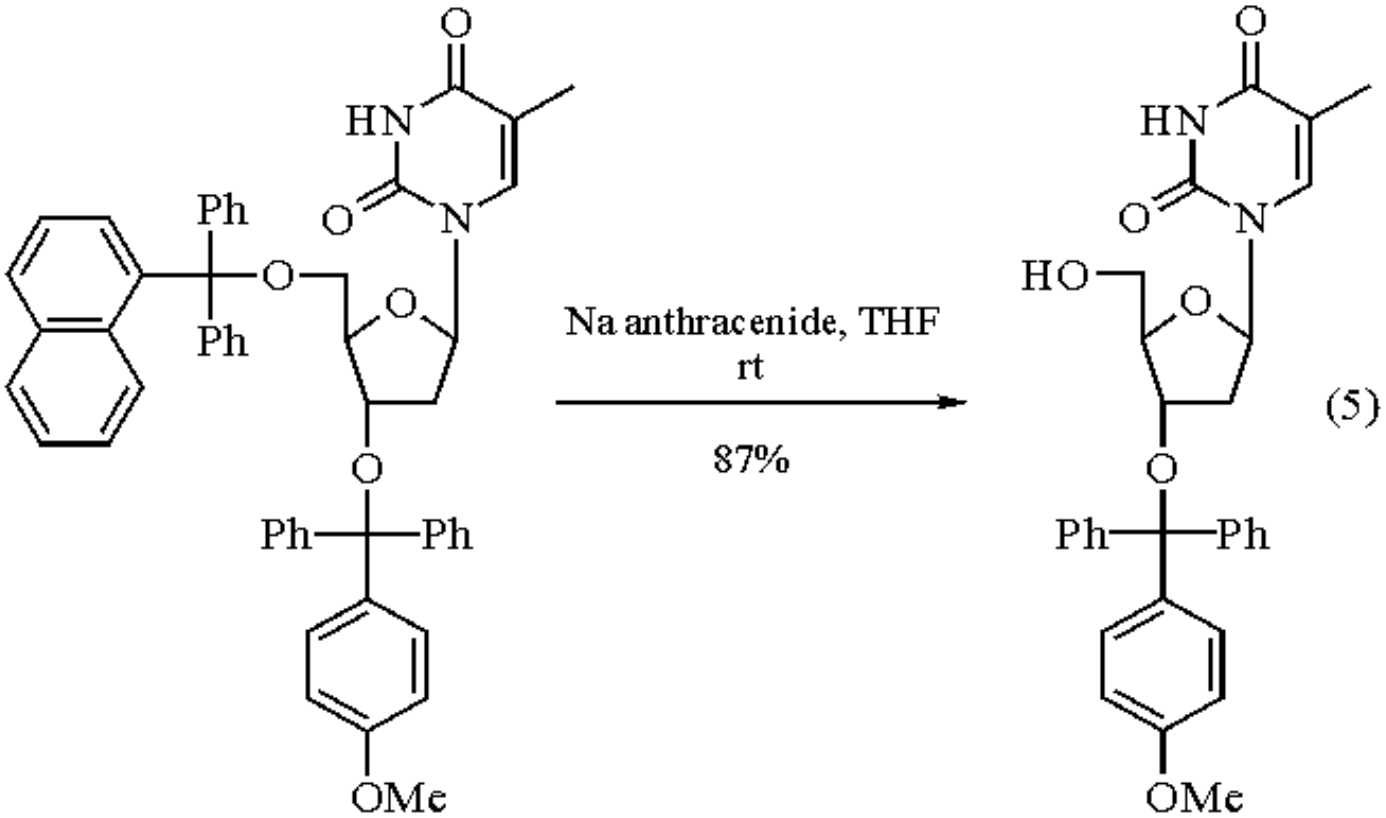

The dimesylates of vicinal diols are efficiently reduced to the corresponding alkenes upon treatment with sodium anthracenide (eq 6).[6] In acyclic substrates, the product contains a mixture of alkene isomers.

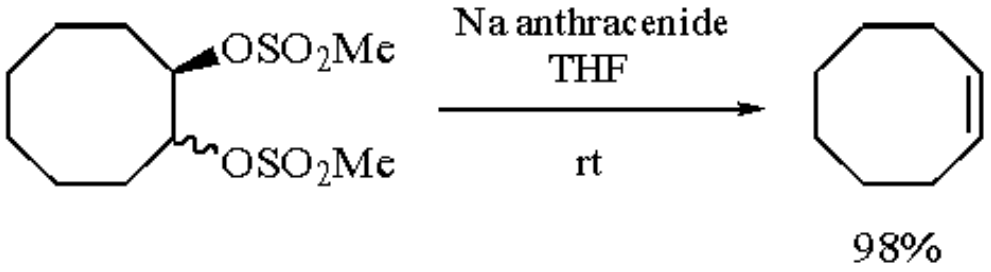

(6)

The reductive cleavage of a cyclic ether to an alcohol with sodium anthracenide has been reported (eq 7). The enone moiety is undisturbed.[7]

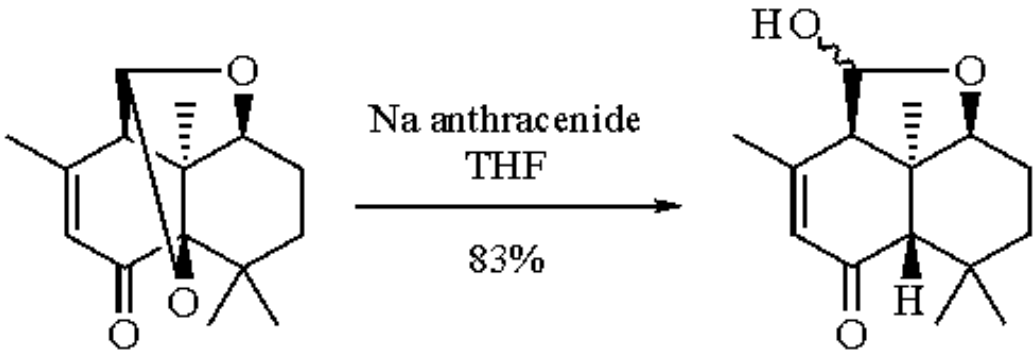

(7)

Related Reagents.

Sodium Phenanthrenide.

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Sodium Azide[1]

NaN_3

[26628-22-8] · N_3Na · Sodium Azide · (MW 65.02)

(nucleophilic azide source for organoazide preparation;[2] precursor to reagents such as hydrazoic acid,[3] halogen azides,[4] trimethylsilyl azide,[5] tosyl azide,[6] and diphenyl phosphorazidate[7])

Physical Data: dec ca. 300 °C; *d* 1.850 g cm^{-3}.

Solubility: sol water (39 g/100 g at 0 °C, 55 g/100 g 100 °C); slightly sol alcohol; insol ether.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: while relatively insensitive to impact, the solid can decompose explosively above its melting point. It forms highly explosive azides with metals such as Cu, Pb, Hg, Ag, Au, their alloys and compounds, and reacts with acids to form hydrazoic acid (HN_3) which is a toxic, spontaneously explosive gas. Explosive *gem*-diazides can be formed in CH_2Cl_2 or other chlorinated solvents and shock or heat sensitive metal azidothioformates in CS_2. All work with NaN_3 and other azides should be conducted on a very small scale behind a shield, in a fume hood. Excess NaN_3 on flasks, paper, etc. can be destroyed in a fume hood by soaking with acidified ***Sodium Nitrite*** or by oxidation with ***Cerium(IV) Ammonium Nitrate***.[8]

Introduction.

The reaction of NaN_3 with I_2 (releasing N_2) is catalyzed by thiols and thiones and this has been used as a spot test for such compounds.[9] NaN_3 has been used to assess the interactions between charged sites in myoglobin.[10]

Preparation of Organic Azides.

Organic azides can be reduced readily to amines, utilized for amine, azide or diazo transfer, act as nitrene or nitrenium precursors, and undergo Curtius and Schmidt rearrangements, cycloadditions and Staudinger reactions.[1b] They are prepared most often by nucleophilic displacement of a leaving group by azide ion (commonly NaN_3) (eq 1). Various leaving groups have been used, including halides, sulfonates (mainly OTs, OMs, or OTf, although brosylates[11] and nosylates[12] have been employed), sulfites,[13] and anhydrides.[14] Displacement of allylic acetates (and related species),[15] with ***Tetrakis(triphenylphosphine)palladium(0)*** as catalyst, and groups such as nitro,[16] phosphine sulfides (from thiaphosphonium species),[17] and phenylseleninates[18] has been reported.

$$R\text{-}X + NaN_3 \longrightarrow R\text{-}N_3 \qquad (1)$$

Eliminative azidation to form α-azidovinyl ketones occurs on NaN_3 treatment of some dibromo ketones (eq 2).[19] This approach also works well for the preparation of α-azidostyrenes from styrene.[20] Usually, *gem*-dihalo compounds react with NaN_3 to give *gem*-diazides;[21] however, an unusual nitrile formation has been reported (eq 3) under these conditions.[22] An interesting, stereospecific, solvent-dependent, azide-induced ring opening reaction of a dioxaphospholane has been observed (eq 4).[23]

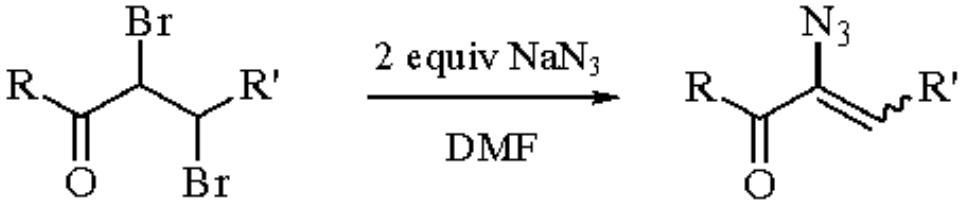

(2)

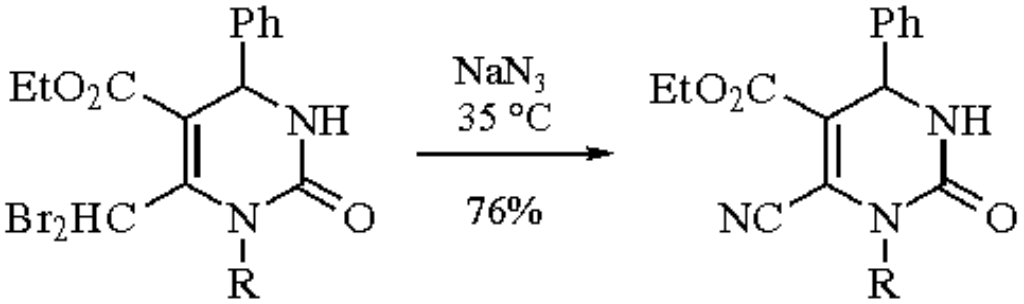

(3)

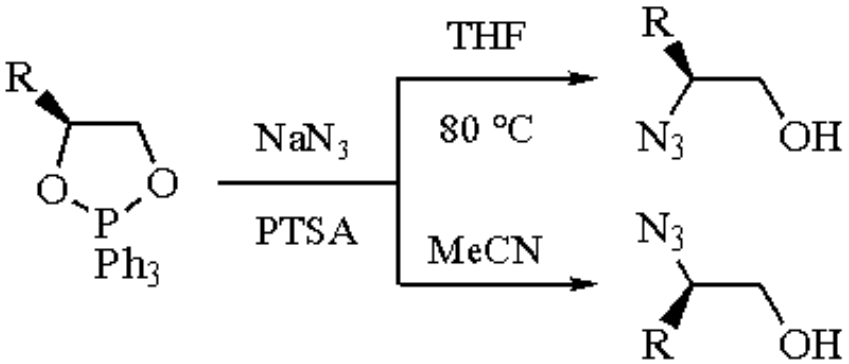

(4)

Displacements can occur at the carbon atom of alkyl (primary, or secondary; tertiary requires ***Zinc Chloride*** or ***Zinc Iodide*** catalysis[24]), allyl, benzyl, acyl,[25] activated vinyl,[26] aryl,[27] or heteroaryl[28] species, and aryl diazonium salts (ArN_2^+, from $ArNH_2/HNO_2$),[29] or at the heteroatom of, amongst others, organosulfonyl, silyl and phosphoryl halides. Of the latter, ***p-Toluenesulfonyl Azide*** ($PTSN_3$),[6] ***Azidotrimethylsilane*** ($TMSN_3$),[5] and ***Diphenyl Phosphorazidate***, $(PhO)_2P(O)N_3$ (DPPA),[7] are the most common and the last two are commercially available.

Nucleophilic azide ion displacements are enhanced by polar, aprotic solvents (e.g. DMSO) with which high yield, aryl halide displacement to form even mononitrophenyl azides can occur.[27] Phase-transfer catalysis[30] (permitting the use of less polar solvents) or ultrasonication (for activated primary halides)[31] has also been used. Under such conditions, S_N2 inversion of configuration occurs and this has been observed also for alcohols under Mitsunobu conditions (***Triphenylphosphine***, ***Diethyl Azodicarboxylate***, HN_3).[32] Retention is possible where a neighboring group is present.[33]

Tertiary alcohols are converted directly to azides using NaN_3/***Sulfuric Acid*** or HN_3/***Boron Trifluoride*** or ***Titanium(IV) Chloride*** (eq 5),[34] and the carboxylic acid to acyl azide transformation (often en route to Curtius rearrangements to isocyanates) occurs with DPPA[7,1b] or via activation with DMF/***Thionyl Chloride***.[35]

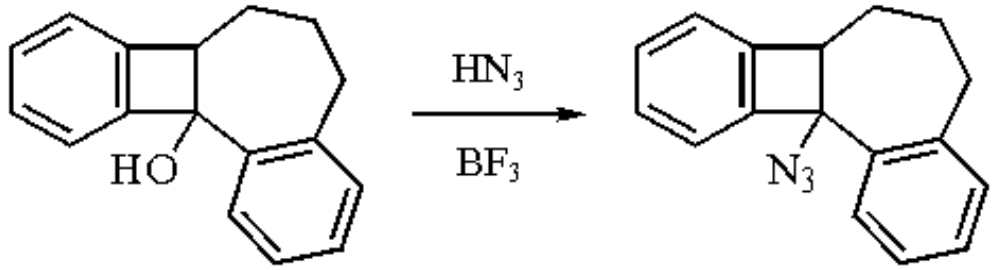

(5)

NaN_3 reacts with epoxides at 25-30 °C (pH 6-7) to give azido alcohols.[36] Usually, inversion of stereochemistry takes place and attack at the least hindered site is preferred. The regio- and stereoselectivity of the reaction can often be enhanced by using $TMSN_3$ with a Lewis acid.[37] High selectivity was shown by NaN_3 on a calcium cation-exchanged Y-type zeolite (CaY) (eq 6),[38] but less so with NaN_3 on silica or alumina or the NaN_3/NH_4Cl system. $NaN_3/ZnCl_2$ gave lower yields than $TMSN_3/BF_3.OEt_2$ for the ring opening of 1,2-

epoxysilanes;[39a] selective azide opening at the site of silyl substitution has been reported.[39b] With a $PhSO_2$ group attached to the epoxide, azidation-elimination occurs to form the corresponding azidoaldehydes.[40] Reaction of the epoxy ester (**1**) with NaN_3 under more vigorous conditions gave (**2**) in 60% yield (eq 6).[41]

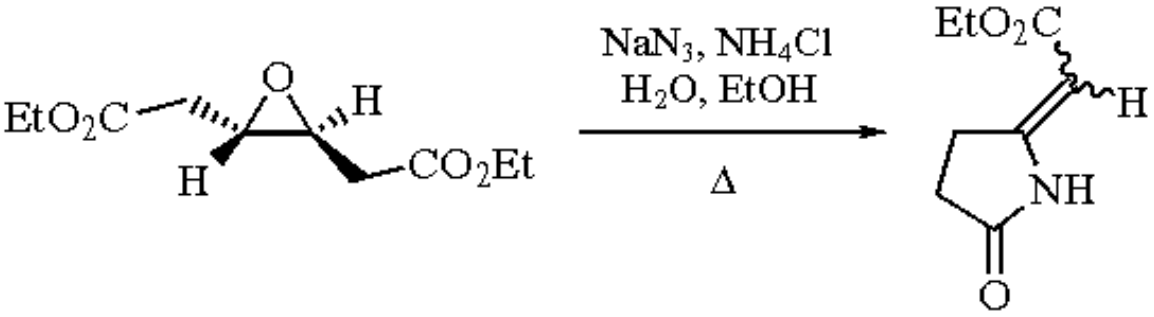

(6)

(1) **(2)**

Hydrazoic acid (HN_3; NaN_3/H^+) reacts with alkenes to form azidoalkanes.[42] Alkenes bearing a phenyl group or two geminal alkyl groups require a Lewis acid ($TiCl_4$ is best). Mono- or 1,2-dialkyl alkenes do not react and Michael additions occur with α,β-unsaturated alkenes.[26b] Enol ethers and silylenol ethers give azido ethers[42] and a similar process occurs with ***Trifluoroacetic Acid*** catalysis[43] or from acetals[44] or aldehydes with $TMSN_3$.[43] Interestingly, $TiCl_4$-catalyzed HN_3 addition to silyl enol ethers in the presence of primary or secondary alcohols gives the azido ethers shown (eq 7).[42] Recently, it has been found that (**3**) reacts with NaN_3/CAN to form the α-azido ketone (**4**) (eq 8).[45]

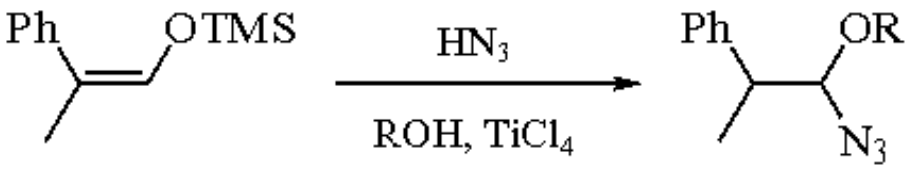

(7)

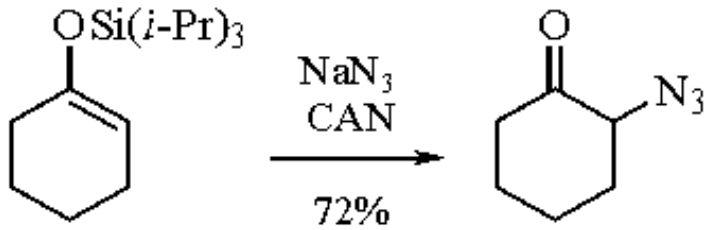

(8)

(3) **(4)**

Other oxidative double bond azidations have been reported. Thus an azidohydrin was formed from pregnenolone acetate and chromyl azide (NaN_3, ***Chromium(VI) Oxide***)[46] and steroidal dienones reacted with $TMSN_3$/***Lead(IV) Acetate***[47] to give diazido compounds. Vicinal diazides also result from alkenes and Fe^{III},[48] ***Manganese(III) Acetate*** (eq 9),[49] or ***Iodosylbenzene*** and NaN_3.[50] Anti-Markovnikov selenoazido products were prepared from the reaction of azide ion with alkenes and ***(Diacetoxyiodo)benzene***/***Diphenyl Diselenide*** (eq 10);[51] α-keto azides (with $TMSN_3$) are formed without PhSeSePh.[52]

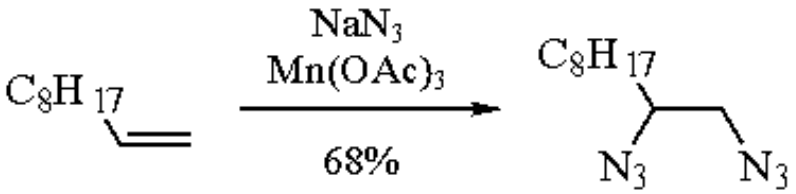

(9)

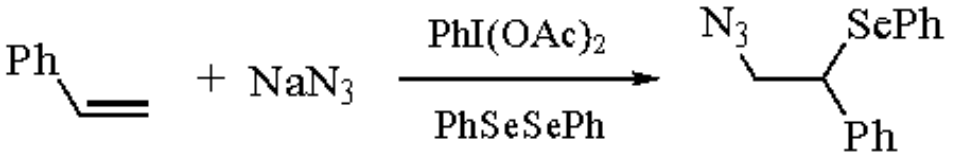

(10)

Azide ion (or congener) attack upon nonconjugated alkenes is aided by the use of ***Dimethyl(methylthio)sulfonium Tetrafluoroborate***.[53] *Trans* products are obtained and, in general, the amount of anti-Markovnikov product increases with increased azide nucleophilicity, and vice versa. Monosubstituted alkenes favor anti-Markovnikov addition, whereas the opposite occurs with trisubstitution. 1,1-Disubstituted alkenes can give either orientation.

Schmidt Reactions.[54]

This term is used for several transformations, general examples of which are shown in eqs 11 and 12. The former is used infrequently due to the drastic conditions required compared to the analogous Curtius and Hoffmann rearrangements and the discovery that DPPA effects the transformation under mild conditions.[7,1b] $TMSN_3$ has been used frequently.

$$RCO_2H \xrightarrow[H^+]{NaN_3} RNH_2 \qquad (11)$$

$$RCOR \xrightarrow[H^+]{NaN_3} RCONHR \qquad (12)$$

The ketone to amide transformation (eq 12) is still of considerable utility (with the provisos regarding the hazards associated with HN_3) and various acids have been employed, including H_2SO_4 (the most common), ***Polyphosphoric Acid***, and ***Methanesulfonic Acid***. With an unsymmetrical ketone a mixture of amide products can result although preferential migration of an aryl group (over alkyl) has been reported. In one case, the amount of aryl migration product (**6**) (R = H, 75%) was greater (80%) starting from the 7-nitroketone (**5**) (R = NO_2) and lower (70%) from the 7-amino species (**5**) (R = NH_2) (eq 13).[55] Aldehydes usually give nitriles under Schmidt conditions.[56]

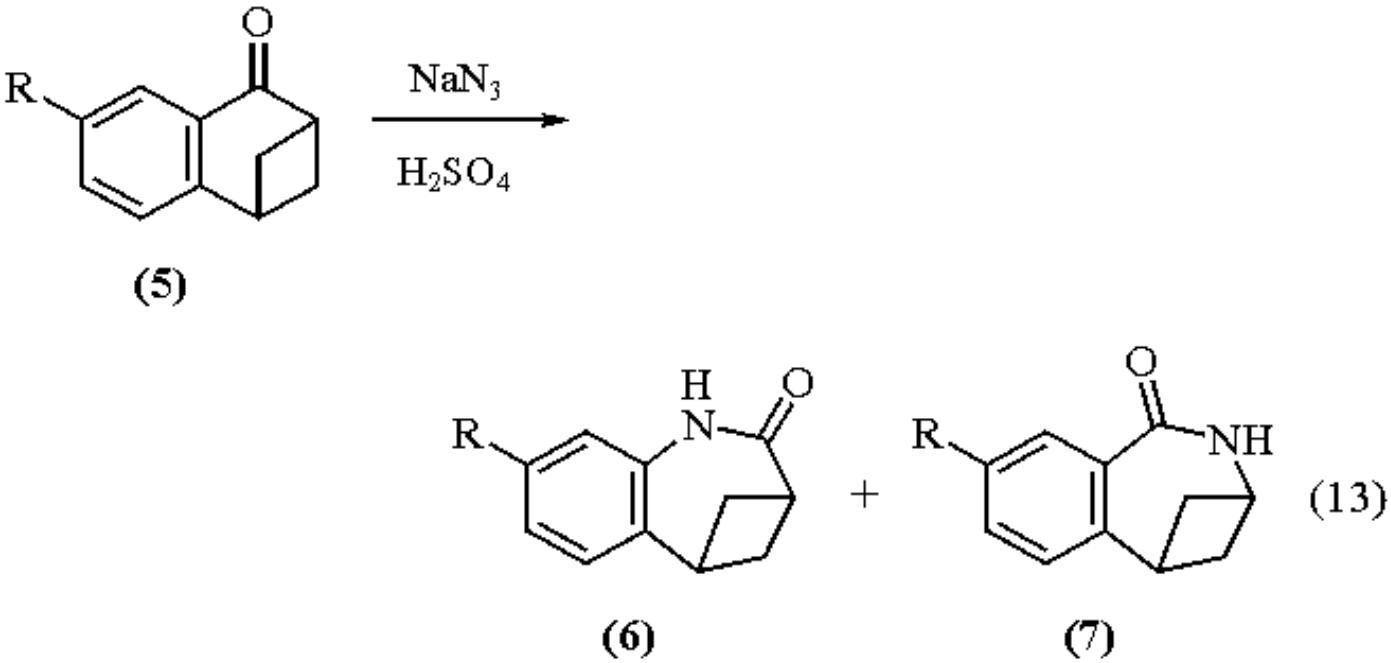

Curtius Reaction.[57]

The Curtius reaction involves conversion of an acid chloride (or anhydride) to an isocyanate (eq 14). Trapping of the isocyanate is possible in the presence of a nucleophile. Some cyclic anhydrides react to give isocyanates which can cyclize subsequently.

$$RCOCl \xrightarrow[2.\ \Delta]{1.\ NaN_3 \text{ or } TMSN_3} RNCO \qquad (14)$$

Preparation of Heterocycles.

As mentioned, heterocycles can be obtained via Schmidt or Curtius reactions. In addition, organic azides react with alkenes to form triazolines (triazoles from alkynes), aziridines, or other heterocycles.[58] In situ triazoline generation and subsequent cleavage can lead to other heterocycles (see eq 15).[59] Reaction of NaN_3 with other α,β-unsaturated alkenes (or alkynes) provides different heterocycles dependent on the substituents. Such reactions are too numerous to mention in detail and only selected examples are shown in eqs 16-18.[60-62]

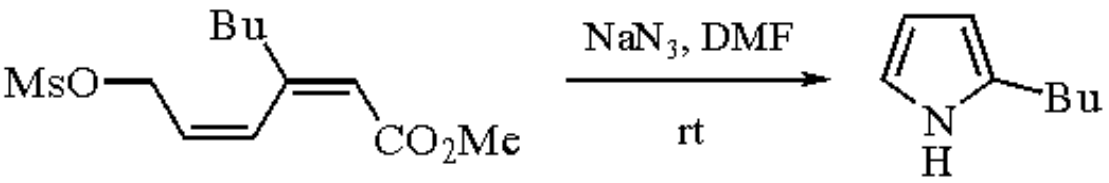

(15)

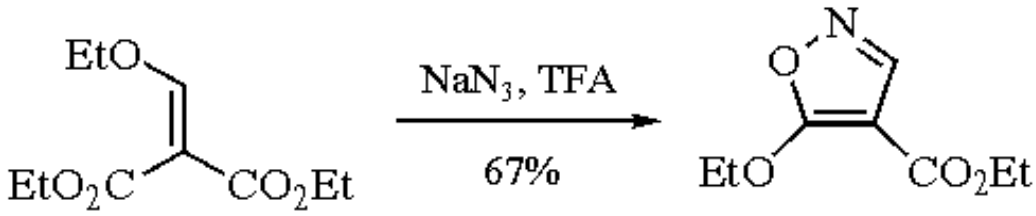

(16)

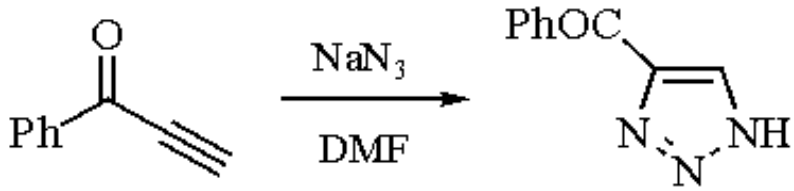

(17)

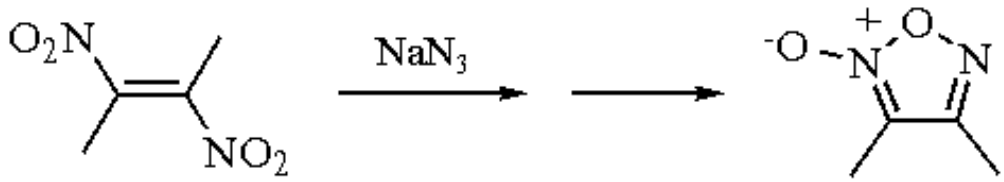

(18)

A useful tetrazole preparation is the addition of NaN_3 (under acidic conditions) to nitriles.[63] Similar processes occur with ***Tri-n-butyltin Azide*** or $TMSN_3$.[64]

Related Reagents.

Azidotrimethylsilane; ***N-Bromosuccinimide-Sodium Azide***; ***Hydrazoic Acid***.

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Sodium Benzenesulfinate[1]

RSO_2Na

(**1**; R = Ph)

[873-55-2] · $C_6H_5NaO_2S$ · Sodium Benzenesulfinate · (MW 164.17) (**1**).$2H_2O$

[25932-11-0] · $C_6H_9NaO_4S$ · Sodium Benzenesulfinate · (MW 200.21) (**2**; R = *p*-Tol)

[824-79-3] · $C_7H_7NaO_2S$ · Sodium *p*-Toluenesulfinate · (MW 178.20) (**2**).$2H_2O$

[7257-26-3] · $C_7H_{11}NaO_4S$ · Sodium Benzenesulfinate · (MW 214.24)

(formation of saturated and unsaturated sulfones;[2] synthesis of thiosulfonates;[3] preparation of *p*-tolylsulfonyldiazomethane[4] and *p*-tolylsulfonylmethyl isocyanide[5])

Physical Data: (**1**) mp >300 °C; (**2**) mp >300 °C.

Solubility: sol H_2O.

Form Supplied in: white solids; widely available.

Analysis of Reagent Purity: (**1**) 97-98% purity; (**2**) 97-98% purity containing 9-18% H_2O; anhydrous reagent commercially available.

Handling, Storage, and Precautions: both sodium sulfinates can be dried in a vacuum oven at 140 °C overnight to remove the water of hydration.

Preparation of Sulfones.

Sodium benzenesulfinate (**1**) and sodium *p*-toluenesulfinate (**2**) are ambident nucleophiles that react with soft electrophiles, such as alkyl halides, to form sulfones as the major product. Hard electrophiles, such as diazomethane, react to yield predominantly sulfinic esters, although substantial quantities of sulfone may be produced (eq 1).[6,7] (Sulfinic esters are best produced by alternate procedures; see ***Methyl Benzenesulfinate***.) The amount of sulfinic ester impurity, typical in the preparation of a sulfone, can be reduced greatly by performing the alkylation under phase-transfer conditions,[8] or by preforming the tetrabutylammonium sulfinate salt.[9] Numerous reactions of arenesulfinates with simple electrophiles to form sulfones have been reported in the early literature.[10]

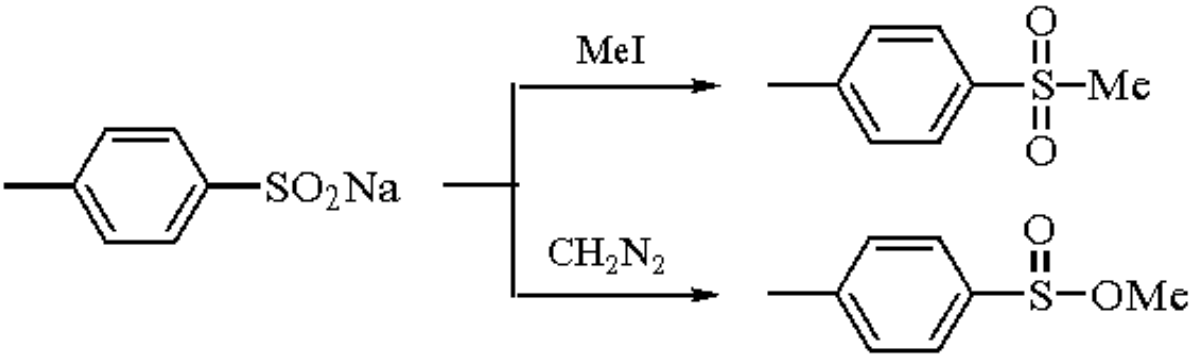

(1)

Aryl alkyl sulfones can readily form α-sulfonyl carbanions by treatment with Grignard reagents or alkyllithium reagents;[11,12] other bases that have been used include ***Lithium Diisopropylamide***, ***Lithium Amide*** and ***Sodium Amide***, ***Sodium Hydride***, and potassium alkoxides.[11] Reagent (**2**) has been used to introduce a sulfone as an activating group for the Michael addition of a benzyl group to

acrylonitrile; the sulfonyl group was removed easily by reductive cleavage with ***Sodium Amalgam*** (eq 2).[13]

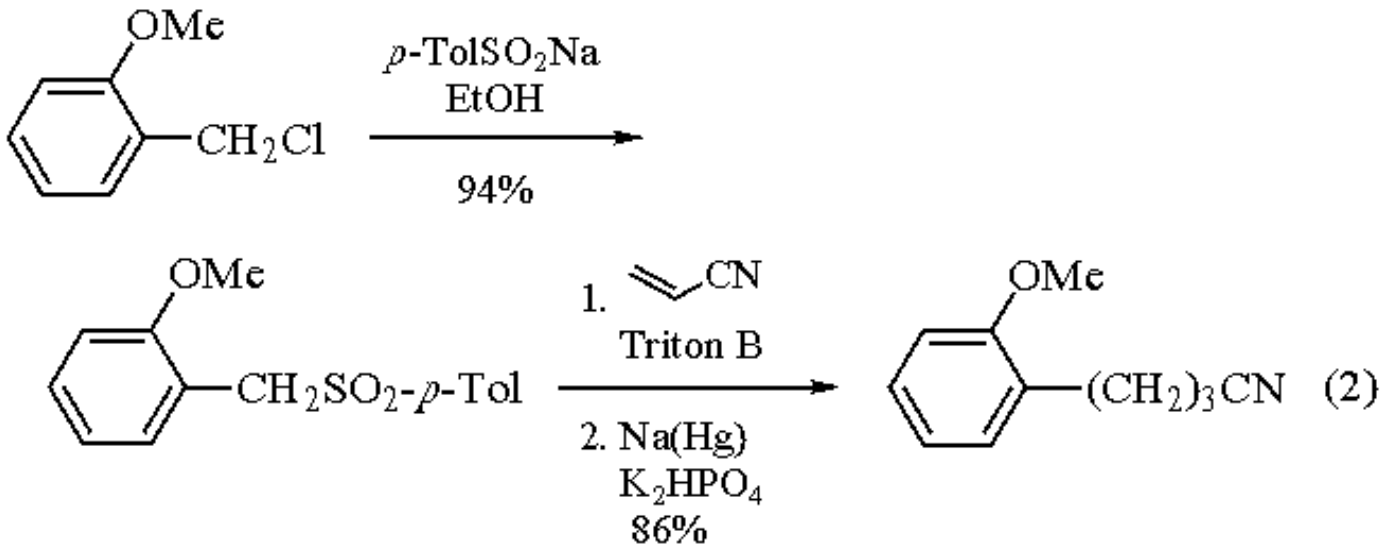

Reagent (**2**) can add to α,β-unsaturated ketones in the presence of AcOH to form γ-oxo sulfones.[14] These intermediates are useful for the β-alkylation of α,β-unsaturated ketones since the sulfonyl group can be eliminated easily with base to reform the double bond (eq 3).

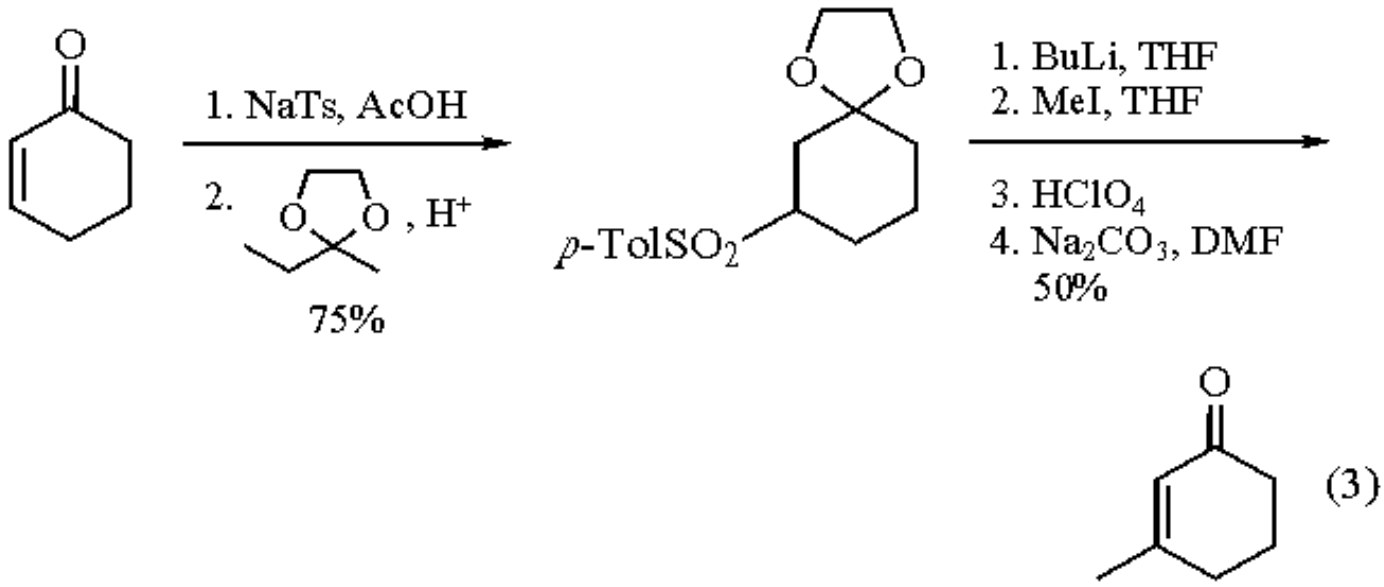

Allylic sulfones are useful synthetic intermediates that can be prepared from either (**1**) or (**2**) and a variety of allylic starting materials.[15] Allylic nitro compounds undergo denitro-sulfonylation in the presence of (**1**)/AcOH,[16] or in the presence of ***Tetrakis(triphenylphosphine)palladium(0)***;[17,18] the latter reaction occurs with high regioselectivity to afford the product from direct displacement of the nitro group (eq 4).

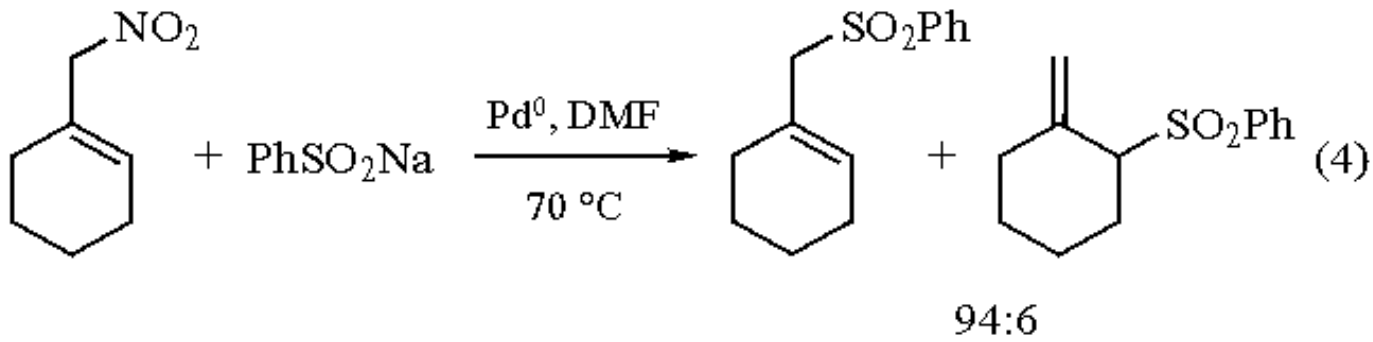

Allylic bromides reportedly react with (**1**) or (**2**) to form sulfones via a classical S_N2' mechanism, but equilibrate to the more thermodynamically stable compound in the presence of catalytic amounts of the same sulfinate.[19] A general synthesis of 1,5-dienes via coupling of an allylic halide and an allylic sulfone followed by reductive cleavage of the sulfone has been reported (eq 5).[20] In this account, ***Lithium-Ethylamine*** was found to be preferred to Na(Hg) for removal of the sulfonyl group, since the use of Na(Hg) resulted in

double-bond migration.

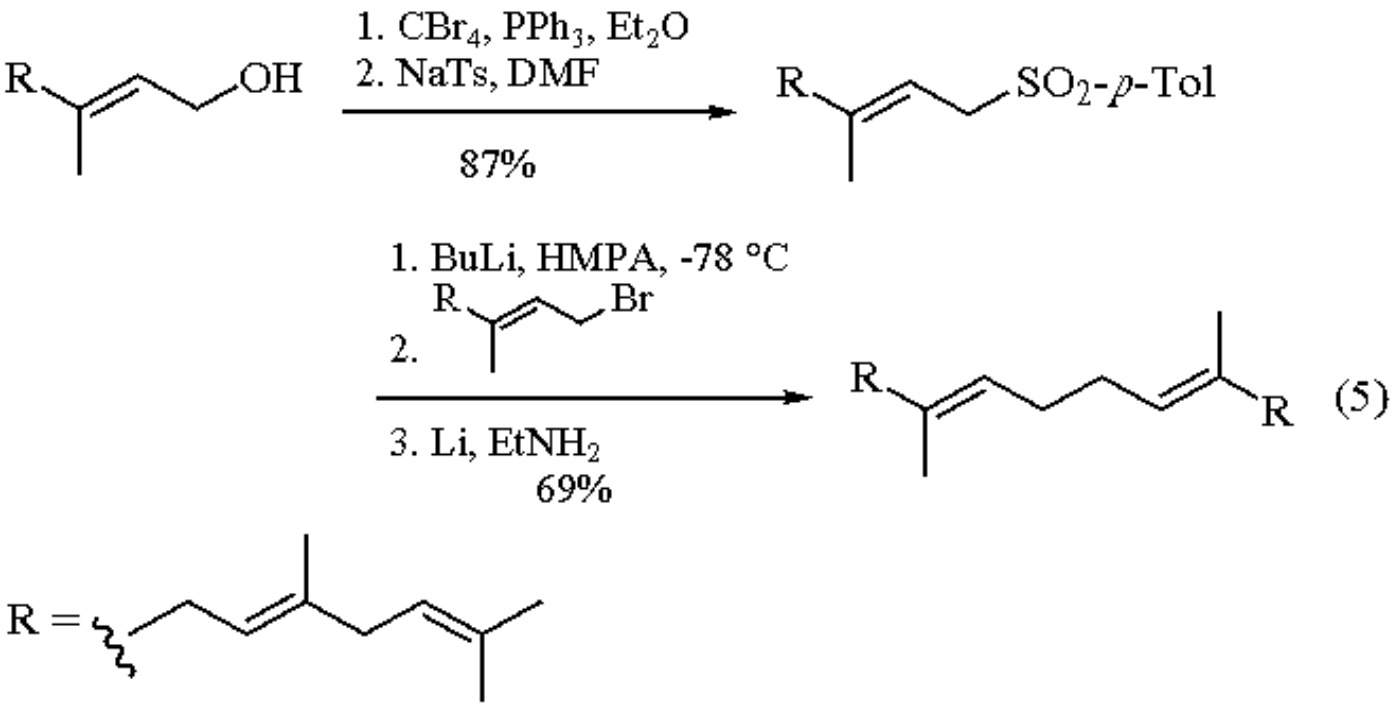

Unsaturated sulfones can be prepared via iodosulfonylation of alkenes and conjugated dienes with (**1**) or (**2**) in the presence of ***Iodine***.[21,22] Alkenes react stereospecifically with (**1**)/I_2 to form 2-iodo sulfones, while 1,3-dienes react to form δ-iodo allylic sulfones. The iodo functionality can be substituted by various nucleophiles or undergo dehydrohalogenation to form allylic sulfones or 1-sulfonyl-1,3-dienes, respectively (eq 6).

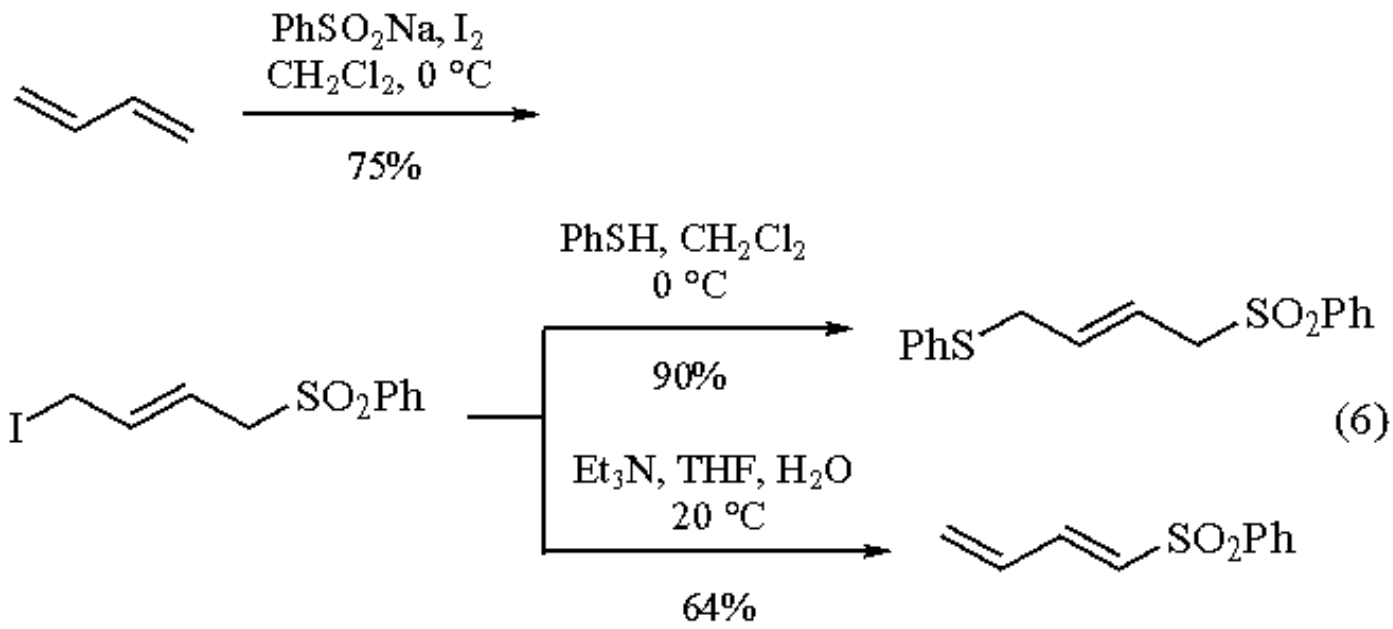

Alternatively, addition of (**1**) to a 1,3-diene in the presence of ***Mercury(II) Chloride*** results in the formation of 2-(phenylsulfonyl)-1,3-dienes (eq 7).[23] These versatile intermediates can participate in Michael-type additions and cycloaddition reactions.[24-26]

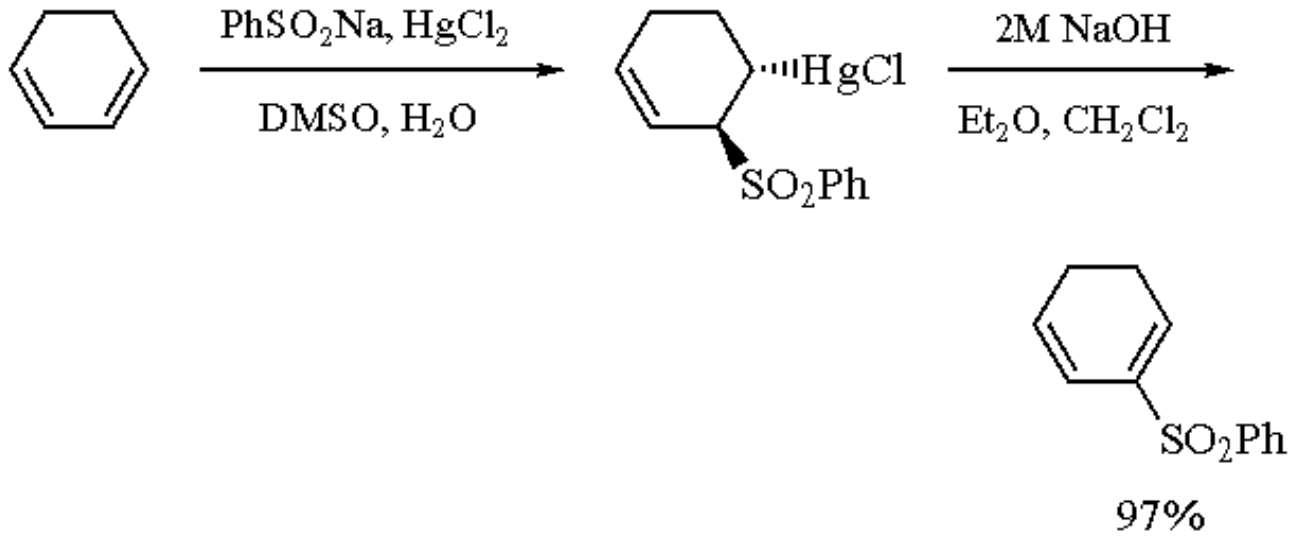

(7)

Substituted vinyl sulfones also may be prepared by addition of (**1**) to alkynyl esters in the presence of ***Boric Acid*** (eq 8).[27] These vinyl sulfones serve as excellent dienophiles in Diels-Alder reactions, containing useful functionality for further transformation.[28] In general, vinyl sulfones serve as valuable synthetic intermediates.[29]

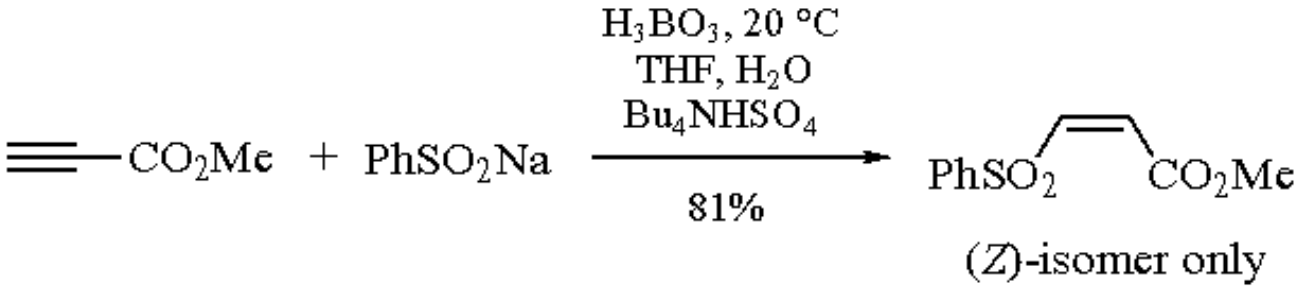

(8)

Catalytic quantities of (**1**) have also been used in a highly efficient [3 + 2] cyclization-elimination reaction of (phenylsulfonyl)allene in the presence of α,β-unsaturated compounds to produce cyclopentenyl-substituted sulfones; other nucleophiles such as cyanide or nitrite will work as well (eq 9).[30]

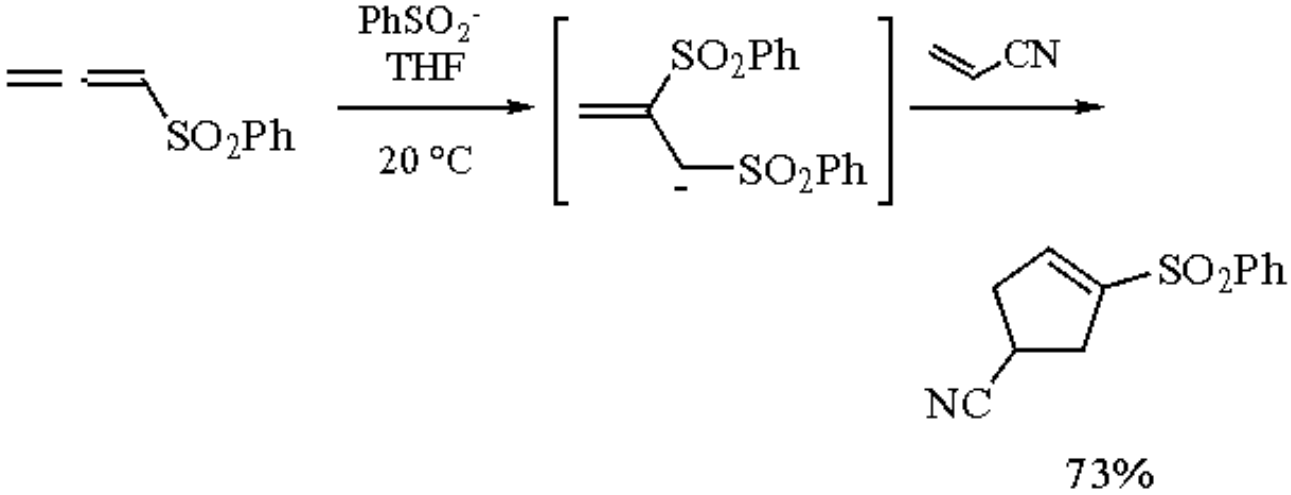

(9)

Preparation of Thiosulfonates.

(**1**) or (**2**) react with elemental sulfur in various amines or liquid ammonia to produce thiosulfonate salts.[3] These salts can be alkylated to form thiosulfonate esters in good yield (eq 10); these compounds are useful sulfenylating agents (eq 11).[31]

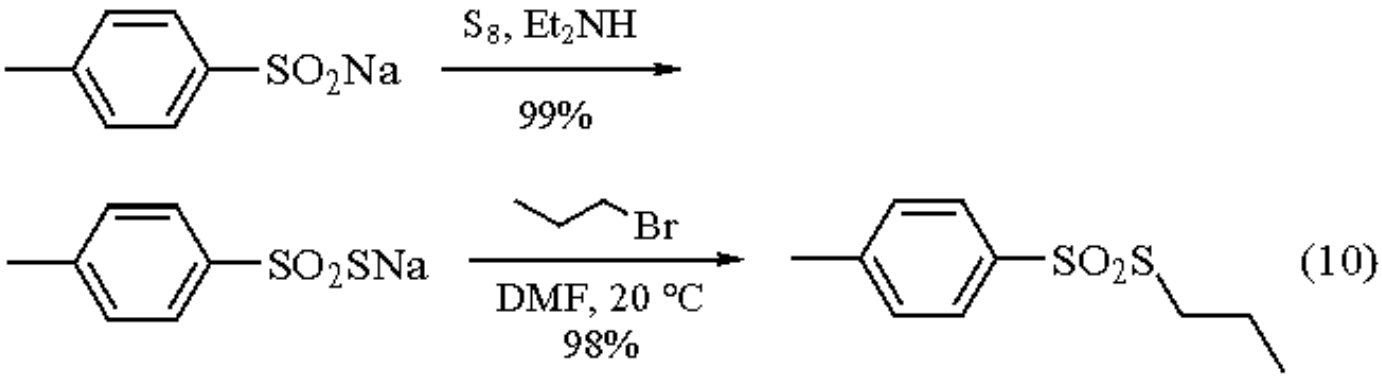

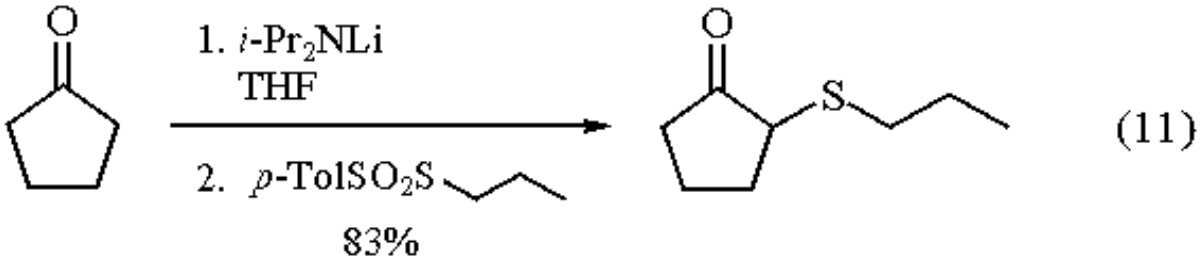

Preparation of *p*-Tolylsulfonyldiazomethane.

(**2**) has been used for preparing *p*-tolylsulfonyldiazomethane,[4] a useful reagent for the synthesis of trisubstituted-methane derivatives,[32] and the conversion of allylic alcohols to homoallylic alcohols.[33] This α-diazo sulfone also reacts with alkenes to provide sulfonyl-substituted cyclopropanes (eq 12).[32,34]

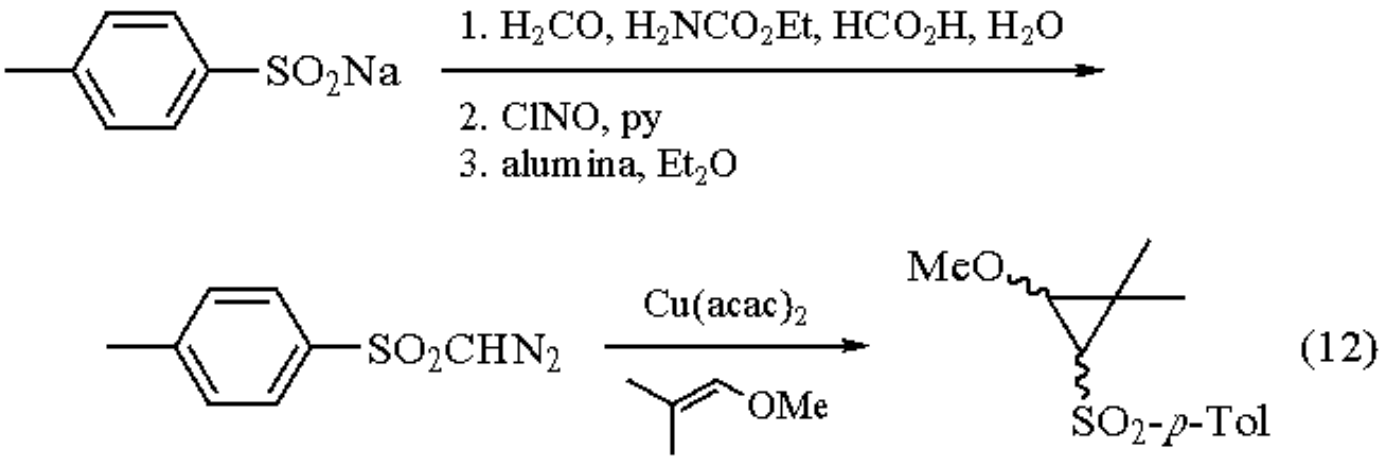

Preparation of *p*-Tolylsulfonylmethyl Isocyanide.

(**2**) also has been utilized for the preparation of ***p-Tolylsulfonylmethyl Isocyanide*** (TosMIC),[5] a useful reagent for the formation of various azole ring systems.[35] Base-induced addition of the C-N=C moiety into the C=O functionality of an aldehyde, for example, produces oxazoles in excellent yield (eq 13).[36] Other ring systems such as imidazoles, thiazoles, pyrroles, and 1,2,4-triazoles can be manufactured via reaction with C=S-, C=C-, C=O-, and N=N-containing substrates, respectively. This reagent also has been utilized for the conversion of ketones into cyanides,[37] and the synthesis of α-hydroxy aldehydes.[35]

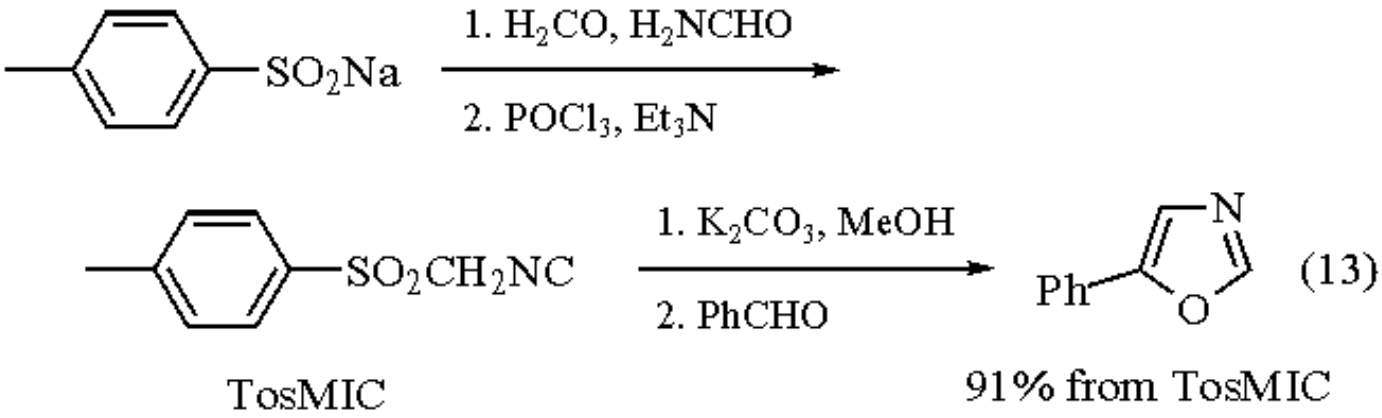

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Sodium Benzylate

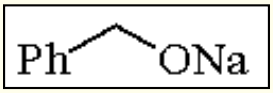

[20194-18-7] · C_7H_7NaO · Sodium Benzylate · (MW 130.13)

(nucleophilic metal alkoxide; infrequently used as the base in Favorskii rearrangements[1])

Solubility: the saturated solution in benzyl alcohol is 3.6 M.[1]

Preparative Methods: usually formed in situ by the reaction of sodium with neat benzyl alcohol[1] or by the reaction of NaH with 1.0 equiv of benzyl alcohol in an ethereal solvent.[2,3]

Handling, Storage, and Precautions: use the same precautions as for other alkali metal alkoxides (e.g. ***Potassium t-Butoxide***); avoid contact of the neat salt or solutions with the eyes, skin, and clothing; carry out preparation and conduct reactions under an inert nitrogen or argon atmosphere. Use in a fume hood.

Substitution and Transesterification Reactions.

$PhCH_2ONa$ is a useful nucleophile in S_N2 reactions of alkyl halides (eq 1).[2] It reacts with acid chlorides to give benzyl esters and participates in transesterification reactions with esters and thioesters. Thiophenyl carbamates are converted into benzyl carbamates with the reagent (eq 2).[4] The reagent also effects slow desilylation of TBDMS-protected alcohols;[4] the low yield of the product in eq 2 is attributable to partial desilylation of TBDMS-protected 3´- and 5´-hydroxyl groups.[4]

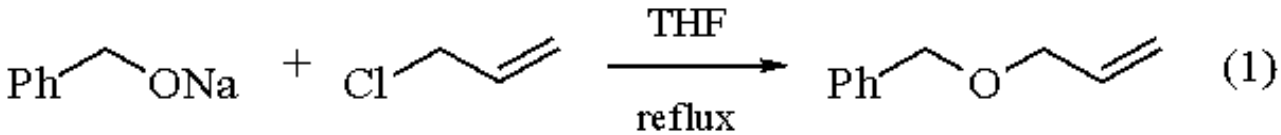

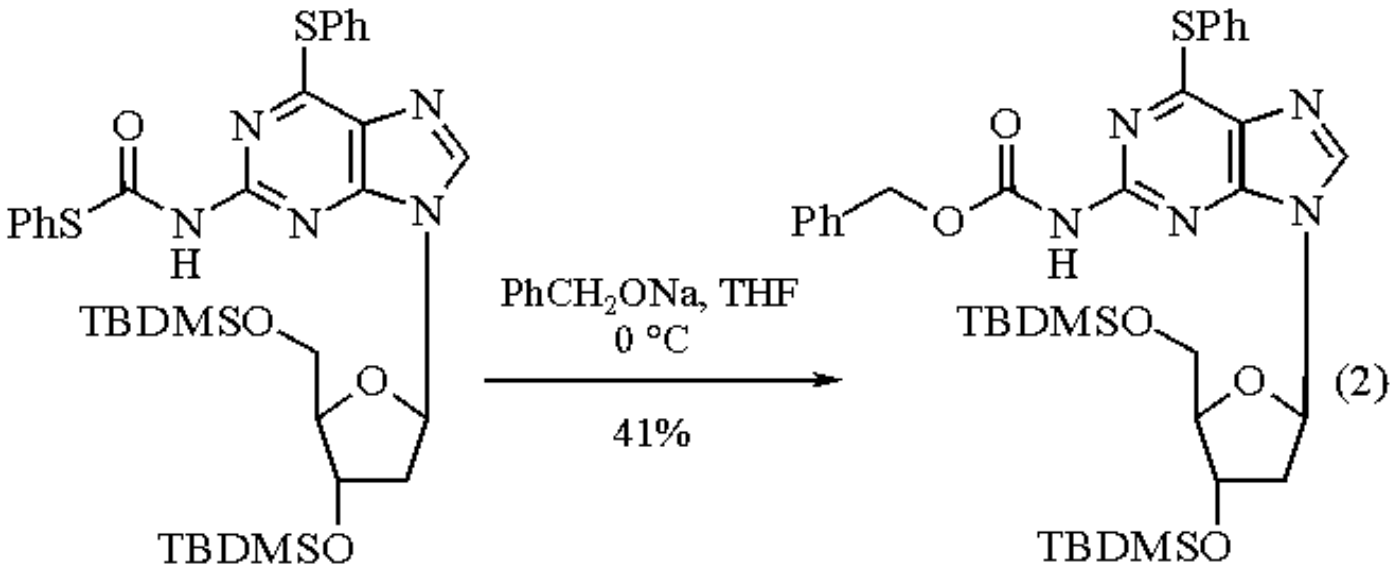

The reagent is capable of effecting demesylation of certain mesylate esters by attacking at the sulfur atom and displacing the alkoxide group with retention of configuration, rather than attacking at the carbon atom and displacing the mesylate group (eq 3).[5] Such reactions are termed S_N2S-type reactions.[6]

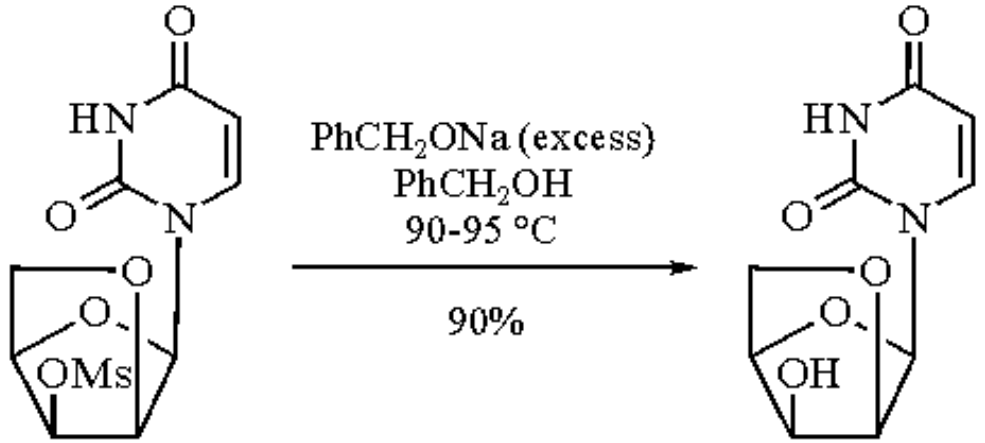

(3)

The reagent acts as a nucleophile in nucleophilic aromatic substitution reactions. The reaction of the 2,6-diacid chloride of 4-chloropyridine with excess $PhCH_2ONa$, which first yields the 2,6-dibenzyloxycarbonyl derivative of 4-benzyloxypyridine, provides an example (eq 4).[7] $PhCH_2ONa$ displaces the chlorine of 3-phenyl-5-chloroisoxazole to give the 5-benzyloxy compound (eq 5).[8] An *ipso* nucleophilic aromatic substitution reaction is also involved in the $PhCH_2ONa$-induced cleavage reactions of the methylenedioxy rings of various aromatic compounds containing appropriately located electron-withdrawing groups in $PhCH_2OH$/DMSO.[9]

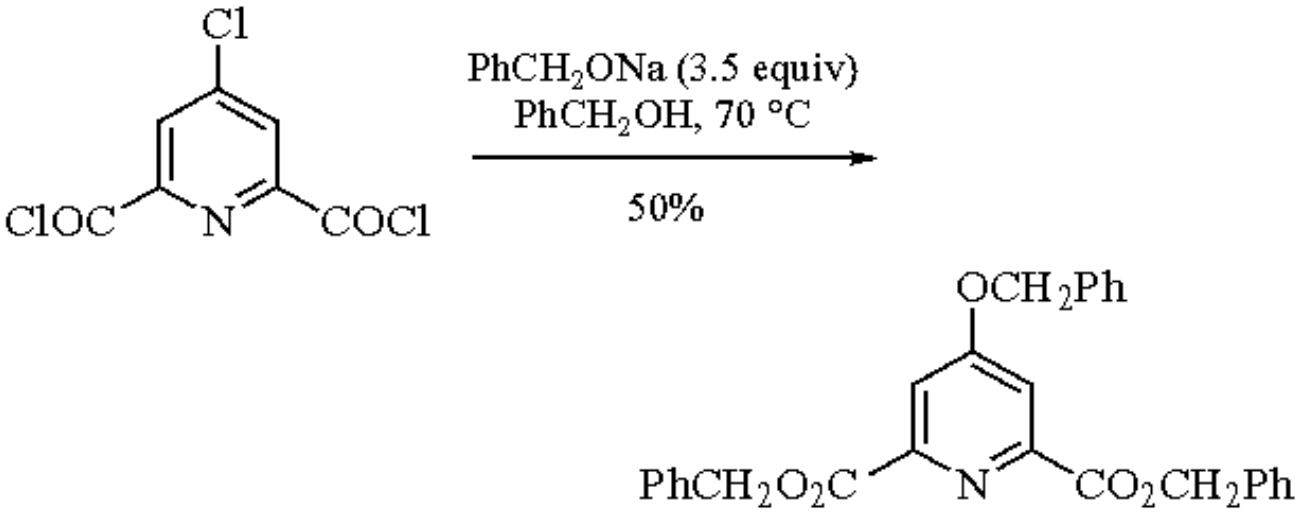

(4)

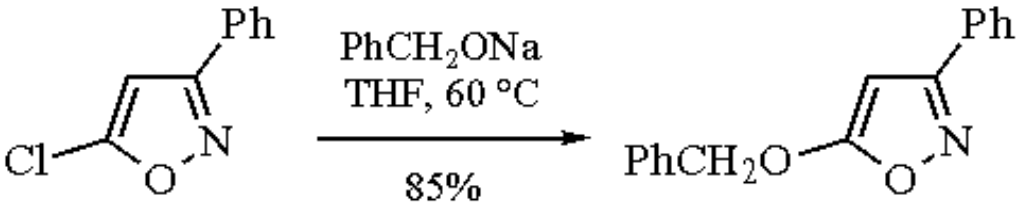

(5)

Addition Reactions.

$PhCH_2ONa$ undergoes conjugate addition to α,β-unsaturated methyl esters and simultaneously exchanges methoxy groups with benzyloxy groups to form benzyl esters. The reaction illustrated in eq 6 is somewhat stereoselective.[10] The conjugate addition reaction occurs more slowly with $PhCH_2ONa$ than with ***Sodium Methoxide*** or ***Sodium Ethoxide***. The strained α-chloro-α,β-unsaturated ester shown in eq 7 also undergoes conjugate addition and ester exchange with the reagent in $PhCH_2OH$.[11] A lower yield was obtained using $PhCH_2OK$ as the nucleophile.[11]

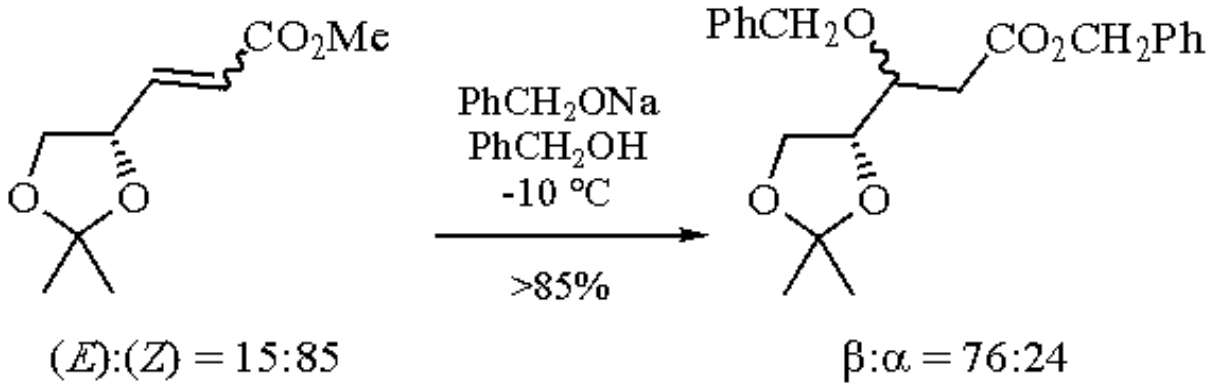

(6)

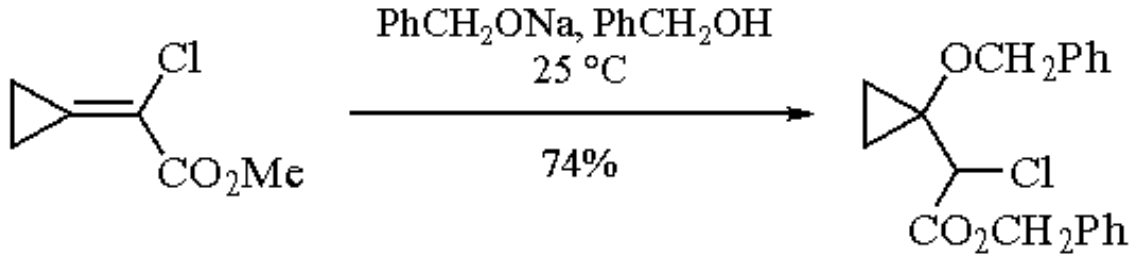

(7)

α,β-Unsaturated nitro compounds yield conjugate addition products upon reaction with $PhCH_2ONa$ in THF. Quenching of the nitronate anion with acetic acid at low temperature yields *anti* β-benzyloxy nitro compounds stereoselectively (eq 8).[3] $PhCH_2OLi$ and $PhCH_2OK$ additions occur with the same degree of stereoselectivity as $PhCH_2ONa$, but the yields of adducts are somewhat lower. Catalytic reduction of the nitro group and hydrogenolysis of the benzyloxy group yields the corresponding β-amino alcohols.[3]

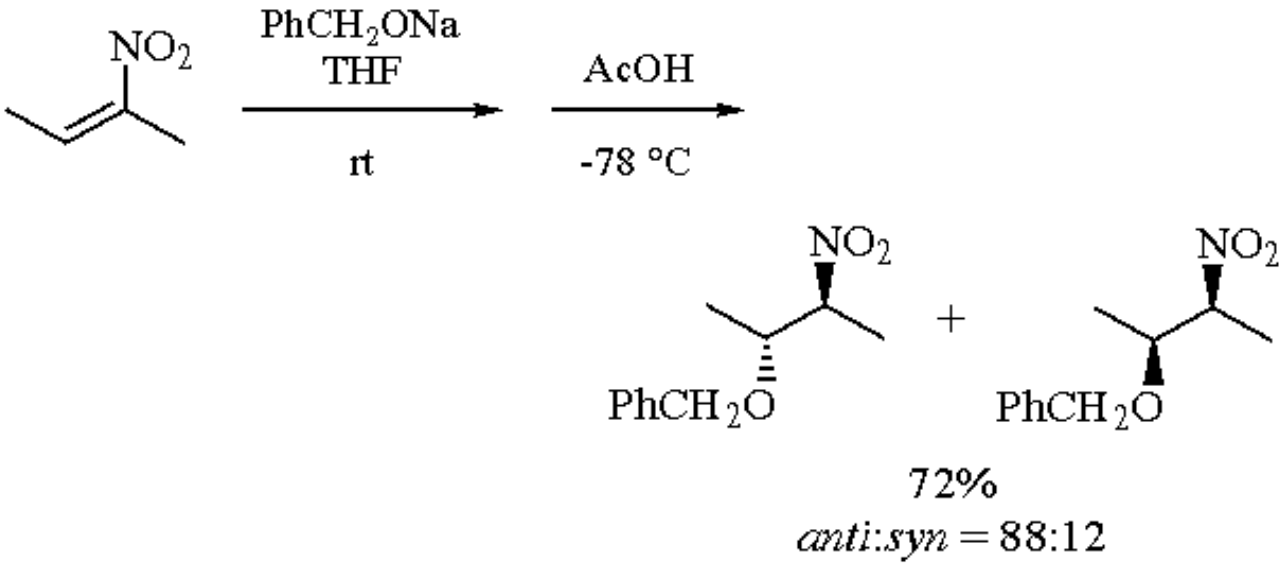

(8)

Favorskii Rearrangements.

The lower molecular weight alkoxides such as MeONa and EtONa are generally employed for the Favorskii rearrangement of α-halo ketones to esters.[12] However, when used as a suspension in Et_2O, $PhCH_2ONa$ is more effective than MeONa, EtONa, or *i*-PrONa for the stereospecific rearrangement of *cis*- and *trans*-1-acetyl-1-chloro-2-methylcyclohexane to the corresponding benzyl esters, in which the new carbon-carbon bond has the opposite configuration to the departing halogen.[1] A solution of the base in DME is highly effective for the stereospecific rearrangement of *cis*-1-acetyl-1-chloro-2-*p*-methoxyphenylcyclohexane into the corresponding benzyl ester (eq 9).[13]

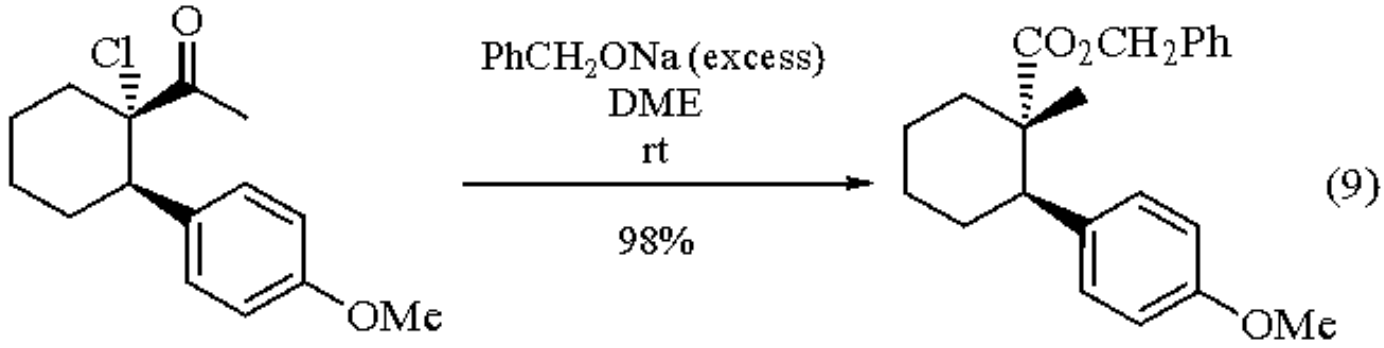

Related Reagents.

Lithium t-Butoxide; ***Potassium t-Butoxide***; ***Sodium Ethoxide***; ***Sodium Methoxide***.

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Sodium Bis(dimethylglyoximato)(pyridine)cobaltate[1]

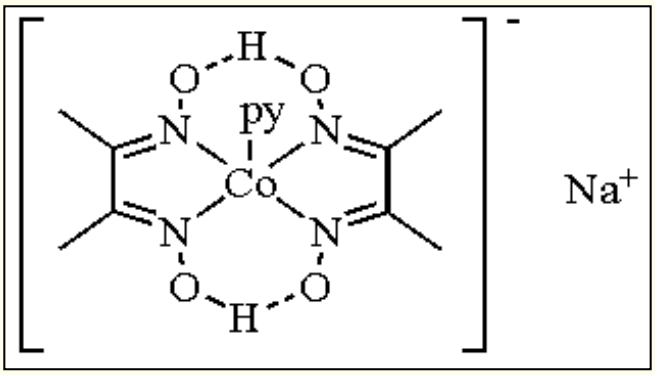

[75699-52-4] · $C_{13}H_{19}CoN_5NaO_4$ · Sodium Bis(dimethylglyoximato)(pyridine)cobaltate · (MW 391.29)

(supernucleophilic cobalt complex;[1] reagent for preparation of alkylbis(dimethylglyoximato)(pyridine)cobalt(III) complexes (alkylcobaloximes)[2] and for formation of metal-cobalt bonds;[3] reducing agent; reagent for reductive formation of carbon-carbon bonds,[4] initializing ring expansions from cyclic halomethyl derivatives[5] and cleavage of *N*-terminal protecting groups of peptides[6])

Alternate Name: sodium cobaloxime(I).

Physical Data: dark purple to brown solid; no melting point has been reported; UV/vis in methanol: λ_{max} = 641, 550, 458 nm.

Solubility: sol oxygen-free alcohols (ethanol, methanol), pyridine; insol ethers (THF, diethyl ether).

Preparative Methods: the reagent is prepared in situ from ***Cobalt(II) Chloride***, butane-2,3-dione dioxime (dimethylglyoxime, $dmgH_2$), ***Pyridine***, ***Sodium Hydroxide*** and ***Sodium Borohydride*** in methanol at temperatures between -78 °C and rt. Addition of triethanolamine and its hydrochloride buffers solutions for base-labile alkylating reagents. Pyridine can be replaced by other heterocyclic nonreducible bases such as substituted pyridines, phosphines, anilines, imidazoles, trialkylamines, thioethers, arsines, or stibines. Water is an especially useful leaving group in alkylcobaloximes(III) for axial ligand exchange as it can fine tune the reactivity or solubility of the cobalt complex.[7]

Another convenient preparation of cobaloximes(I) uses cobalt(II) chloride, dimethylglyoxime, and an excess of sodium hydroxide. The strong basic reaction conditions lead to disproportionation of cobaloxime(II) to cobaloxime(I) and cobaloxime(III), both as their aqua complexes. Alkylation of the nucleophilic cobaloxime(I) with nonbase-labile alkyl halides or sulfonates yields alkylbis(dimethylglyoximato)(aqua)cobalt(III).[8] Alkylaqua complexes of cobalt(III) are more soluble in alcohols or water than their pyridine derivatives, and thus are well suited for introducing any ligand which is more prone to bind to coordinated cobalt(III) than water (the latter property is in general well correlated with the nucleophilicity of the axial ligand in question) (eq 1).

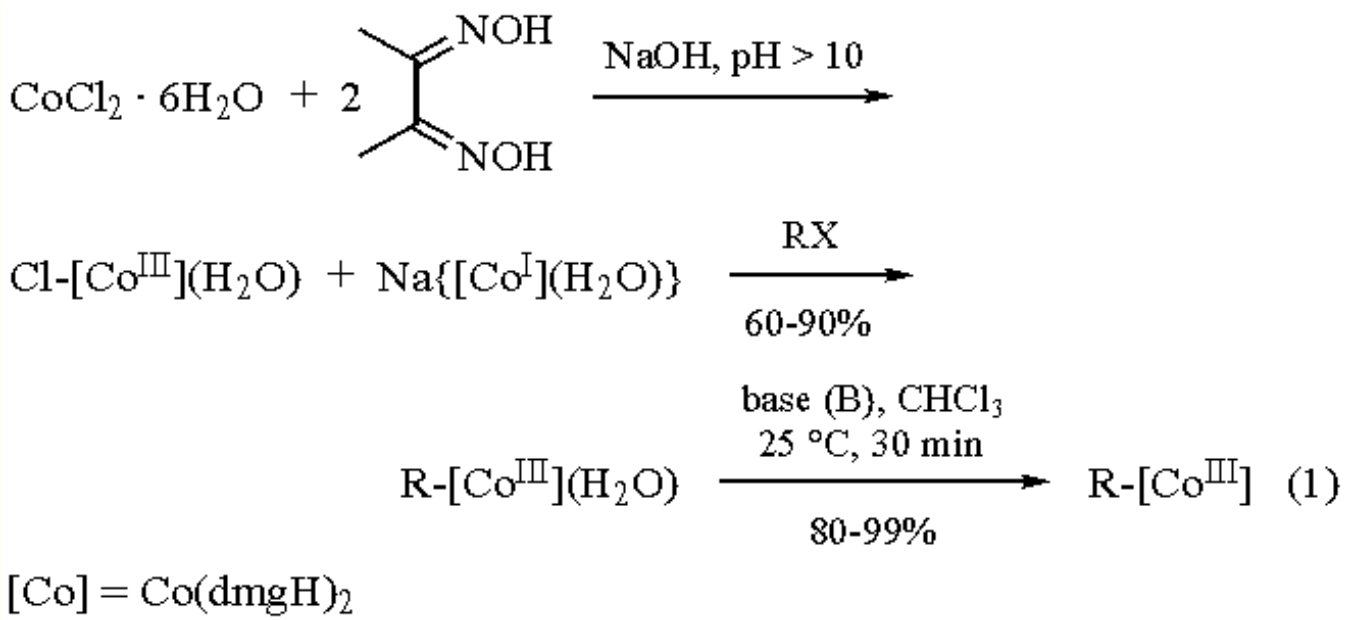

The reagent can also be synthesized by alkali borohydride or alkali amalgam reduction of previously isolated and recrystallized halogenocobaloximes(III).[9] This process is of interest whenever high purity cobaloxime(I) solutions are needed. Some applications of cobaloxime(I) require nonbasic conditions. Thus reacting cyanoethylcobaloxime with potassium *t*-butoxide leads to acrylonitrile elimination and potassium cobaloxime(I)[10] (eq 2).

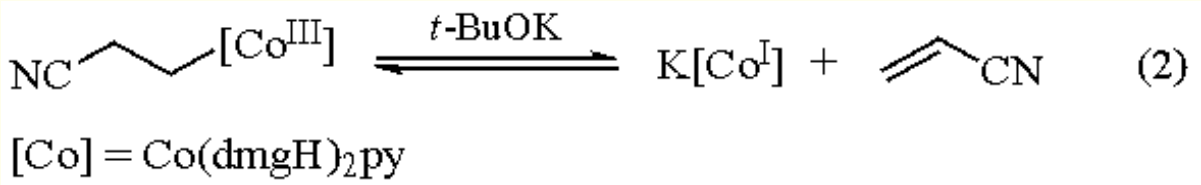

Handling, Storage, and Precautions: extremely air- and acid-sensitive; the reagent should be used as prepared in oxygen-free solutions at temperatures between -78 °C and rt by adding oxygen-free alkyl halides or sulfonates. Solid reagents, i.e. alkylating reagents, should be dissolved in acetone for best results, with halogenated solvents, i.e. carbon tetrachloride or methylene chloride, being avoided as they lead to the immediate formation of chloromethylbis(dimethylglyoximato)(pyridine)cobalt(III).[2e]

Cobalt is the catalytic center of vitamin B_{12} and therefore an essential trace element. However, care should be taken while handling inorganic cobalt(II) salts because they are potential carcinogens on parenteral application (i.e. bypassing the digestive system). Use in a fume hood.

Alkylcobaloximes(III).

Alkylation of supernucleophilic sodium cobaloxime(I) has been reported for a variety of primary and secondary alkyl halides,[2a,b] sulfonates,[2c] epoxides,[2d] electron-deficient alkenes,[2e] or perfluoroalkyl iodides.[2f] Sodium cobaloxime(I) adds in a Michael fashion to acrylic acid derivatives or acrylonitrile (eq 3).

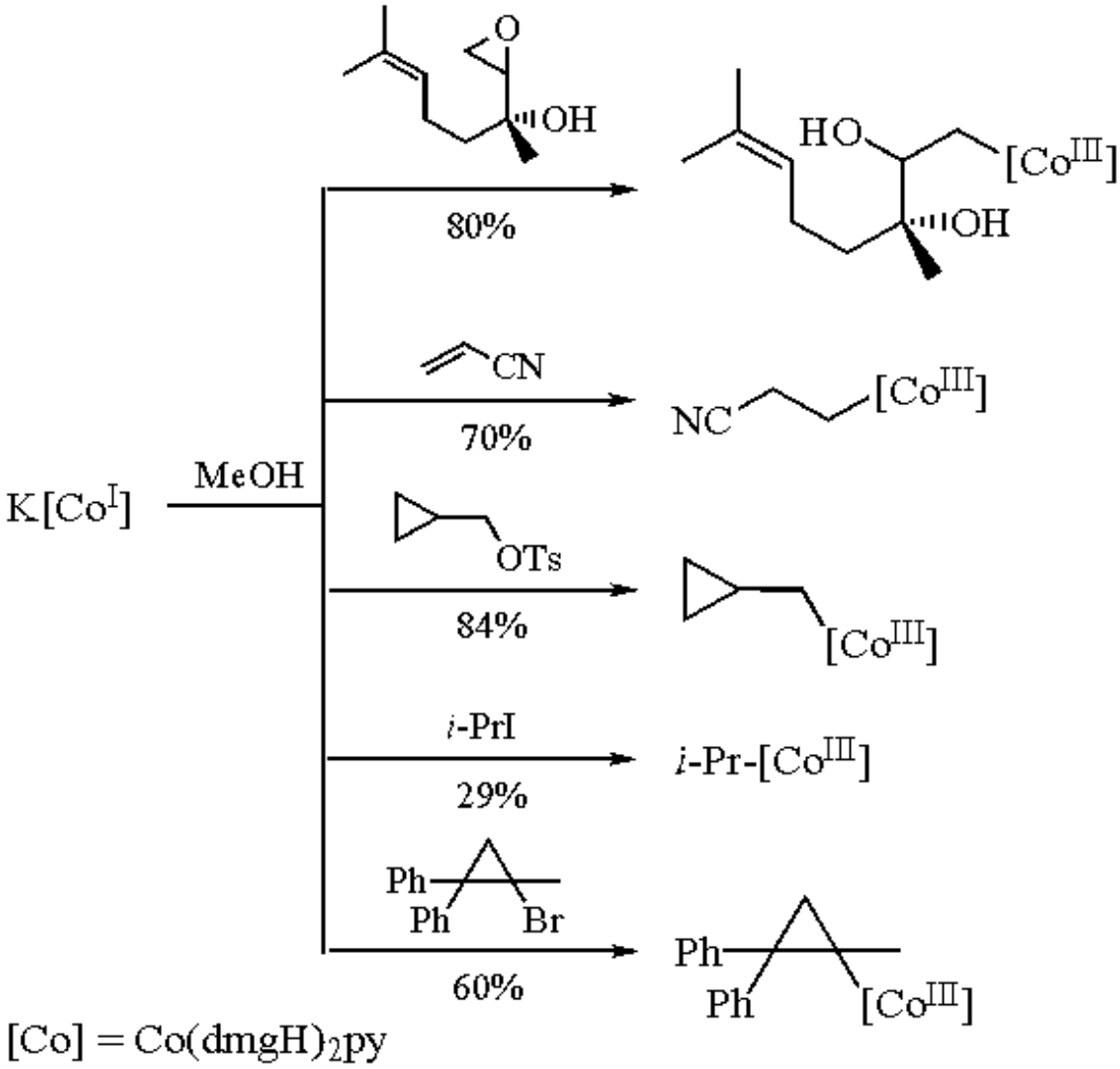

(3)

Hydridocobaloxime can be prepared from cobaloxime(II) or sodium cobaloxime(I) under a hydrogen atmosphere. Hydridocobaloxime adds to α,β-unsaturated carbonyl compounds or aryl substituted alkynes with the opposite regioselectivity of that of sodium cobaloxime. This process can be used for selective isotope labeling (eq 4),[11] when the reaction is carried out in deuterated media under a deuterium atmosphere.

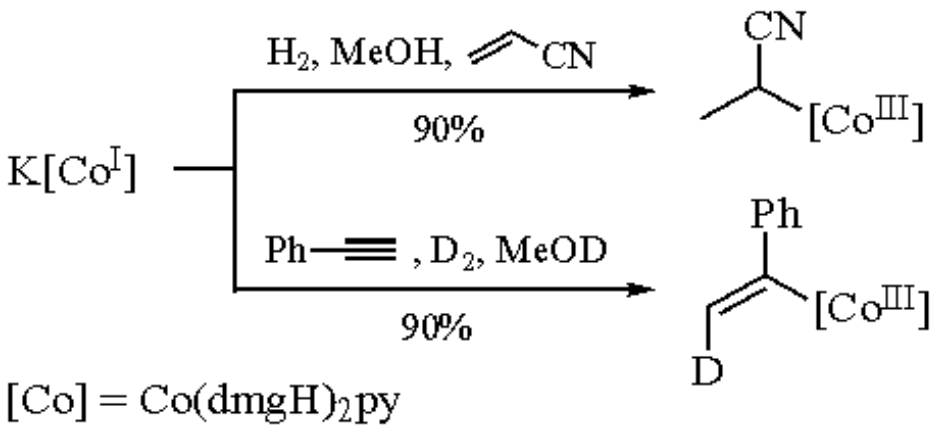

(4)

The stereochemistry of the alkylation reaction is largely governed by the substrate. Kinetic data indicates an S_N2 mechanism operating for simple primary and secondary alkyl bromides.[1] In other cases, reaction pathways are derived from product distributions via S_N2 reactions, e.g. for 4-substituted *t*-butylcyclohexanes (eq 5)[12] and SET reactions of glycosyl halides showing either selective[13a] or nonselective[13b] substitution of the halide (eq 6).

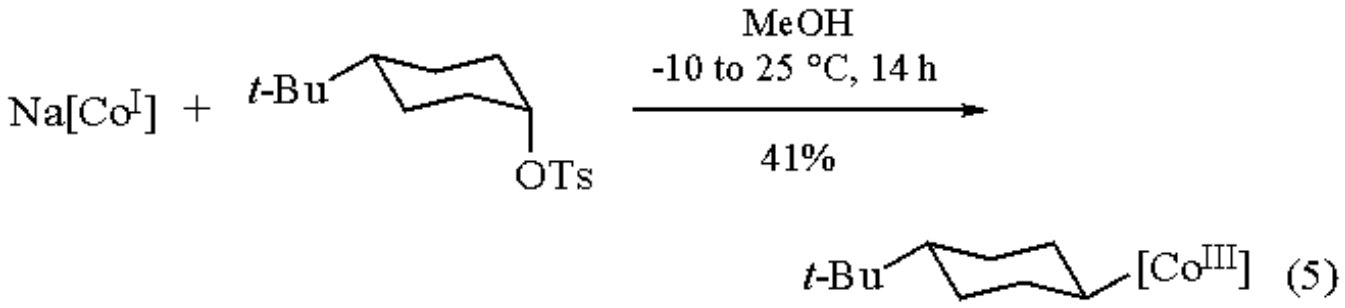

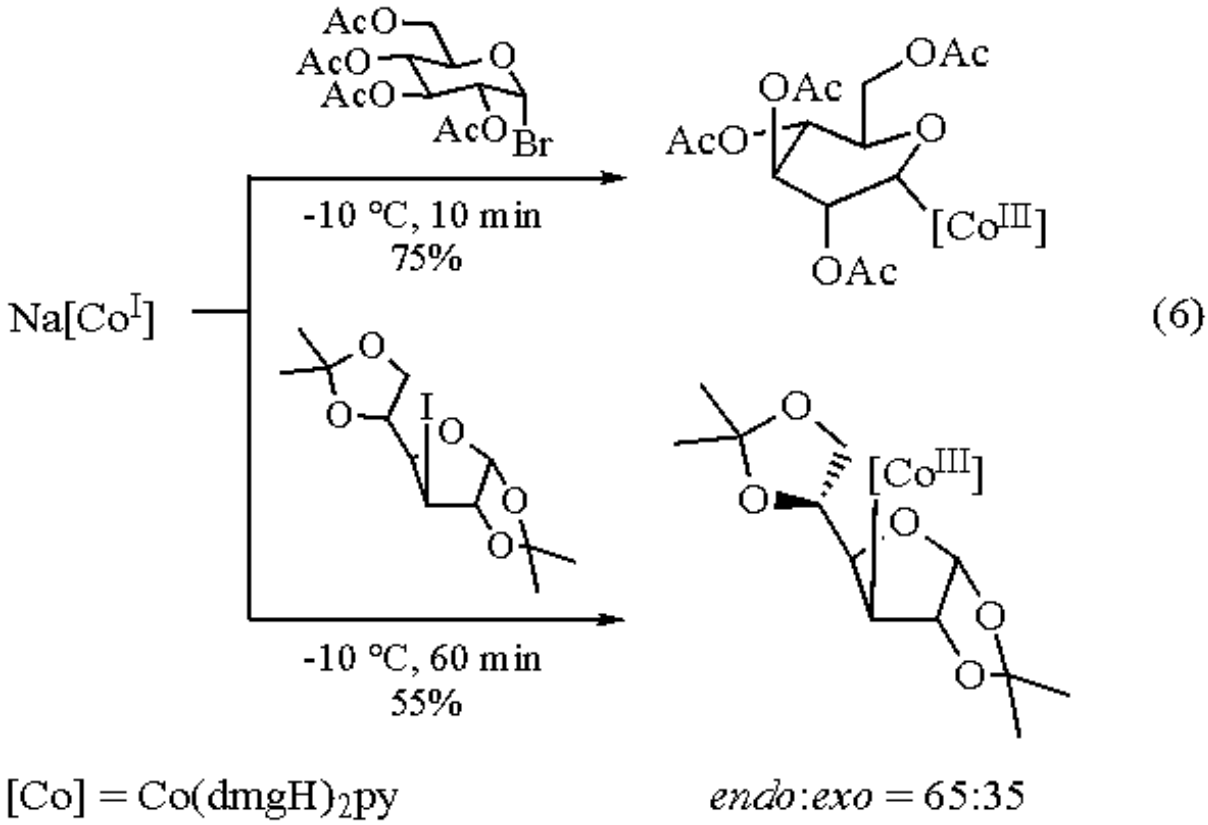

Glycosyl cobaloximes have been employed as building blocks for KDO[13a] and as precursors for amino sugars.[13c] Tertiary alkyl cobaloximes(III) are limited to a few examples, but bridgehead positions are favorable sites for stable tertiary alkyl cobaloxime(III). A synthesis has been designed which takes advantage of the labile intermediate tertiary cobaloxime in the ring expansion of iodomethyl penicillin to a 3:2 mixture of exomethylene cepham to Δ^2-cephem (eq 7).[5]

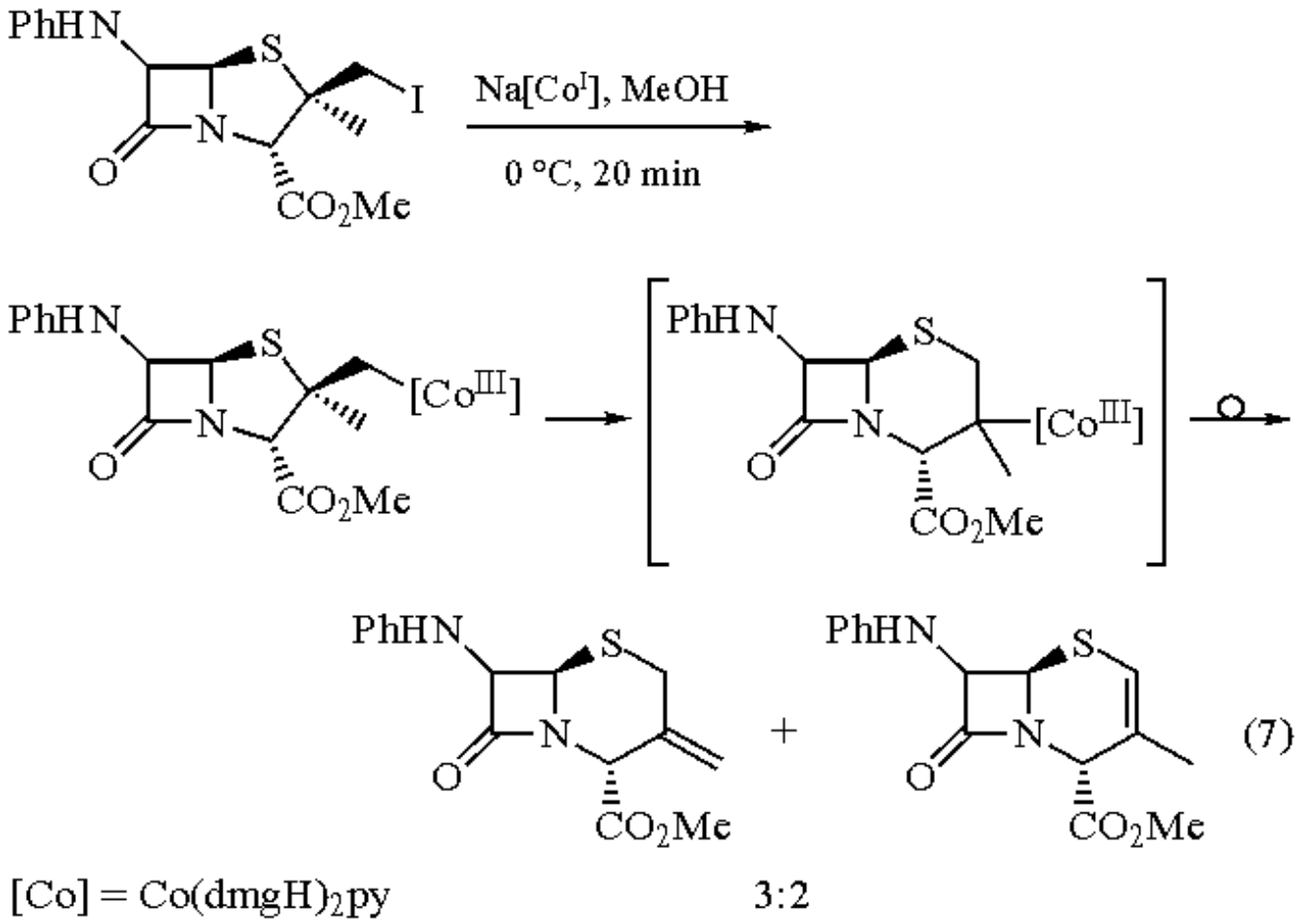

Vinyl triflates react with sodium cobaloxime(I) within 10 min at 0 °C in aqueous methanol to yield vinyl cobaloximes(III) (eq 8). Transformation of isomeric (*E*)- and (*Z*)-vinyl triflates results in stereoconvergence. Application of this methodology to alkynylvinyl triflates leads to σ-butatrienyl- (eq 9) and σ-enynylcobaloximes(III)[14]

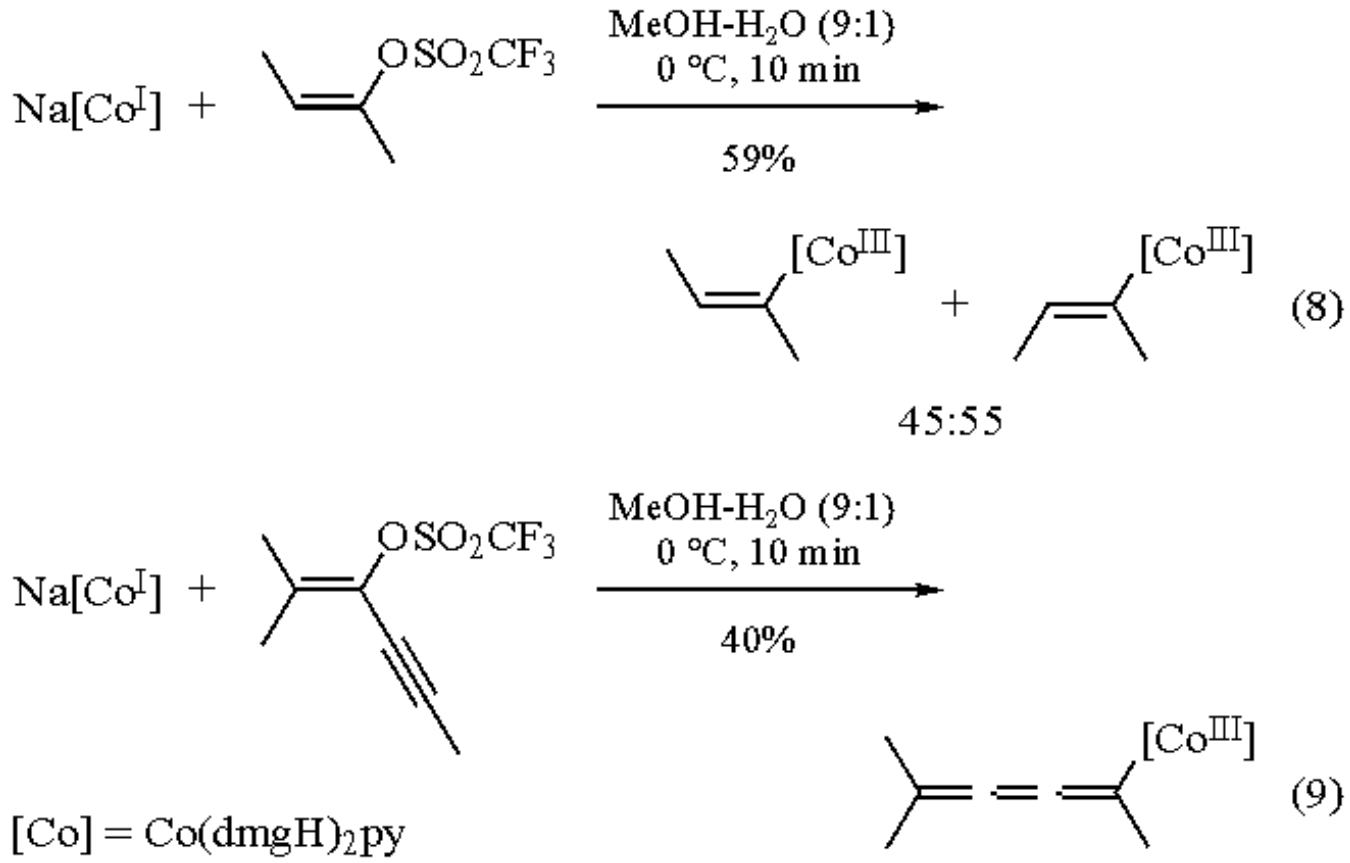

Although arylation of halogenocobaloximes(III) by Grignard reagents is the method of choice for the synthesis of aryl cobaloximes, successful reactions of aryl bromides and cobaloxime(I) have been reported. An electron-withdrawing group in the *para* position (CF_3, CO_2Me) is

required. Bromobenzene is unreactive (eq 10).[15]

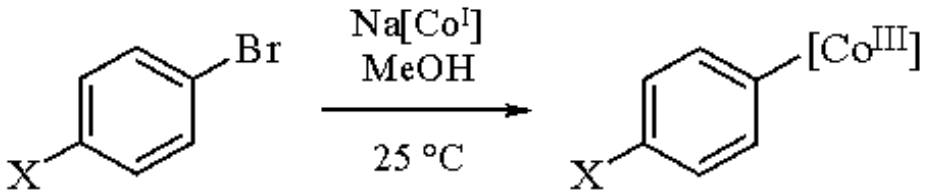

(10)

$X = CF_3, CO_2Me$
$[Co] = Co(dmgH)_2py$

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Sodium Bis(2-methoxyethoxy)aluminum Hydride[1]

$NaAlH_2(OCH_2CH_2OMe)_2$

[22722-98-1] · $C_6H_{16}AlNaO_4$ · Sodium Bis(2-methoxyethoxy)aluminum Hydride · (MW 202.19)

(reducing agent for many functional groups;[1] methylation reagent for aryl-activated compounds;[19] can function as a base;[21] can hydroaluminate alkenes and alkynes[22])

Alternate Names: SMEAH, Red-Al®, Vitride.

Physical Data: fp 4 °C (3.4 M toluene solution); *d* 1.036 g cm^{-3} (3.4 M toluene solution), *d* 1.122 g cm^{-3} (solid); highly viscous liquid at rt; thermally stable up to 205 °C, upon which vigorous decomposition starts.

Solubility: sol aromatic hydrocarbons, ether, THF, DME; insol aliphatic hydrocarbons.

Form Supplied in: 3.4 M solution in toluene. 145 g contains 1 mol of active hydride. The pure compound is a slightly yellow, glassy solid.

Analysis of Reagent Purity: concentration can be determined by iodometric titration.

Handling, Storage, and Precautions: highly flammable; moisture sensitive; reacts less strongly with H_2O than $LiAlH_4$; potent skin irritant. Use in a fume hood.

Functional Group Reductions.

SMEAH has reducing properties fully comparable to ***Lithium Aluminum Hydride***, making it a valuable alternative reducing reagent.[1,2] Some practical advantages of SMEAH are that it does not ignite when exposed to moist air or O_2, has greater solubility in aromatic solvents and ethers, and reactions can be carried out at higher temperatures (up to 200 °C). Carboxylic esters, acids, acid chlorides, anhydrides, aldehydes, and ketones are efficiently converted to the alcohol. Cyclic anhydrides and lactones yield diols. Carboxylic esters are not reduced at -78 °C and *t*-Bu and Ph esters are generally stable to SMEAH at low temperature.

Nitriles, amides, imines, azido compounds, nitro compounds, isocyanates, urethanes, sulfonamides, oximes, lactams, and imides can be reduced to the amine. The formation of aziridines can complete with simple reduction of ketoximes and their *O*-alkyl derivatives. Nitroarenes form azoxyarenes, azoarenes, or hydrazoarenes depending on reaction conditions.[3]

Alkanesulfonates can be converted to alkanes or to alcohols. Phosphate esters afford the alcohol.[4] Some epoxides can be reduced to the alcohol (temperatures above 0 °C are required). Disulfides give thiols while sulfoxides yield sulfides. Sulfones are generally inert or give low yields of sulfides. Haloalkanes, haloarenes, and organosilicon halides undergo hydrogenolysis to the alkane, arene, and silane, respectively.[5] Benzylic aldehydes or alcohols, aryl alkyl or diaryl ketones, and aryl acids containing strong electron donating groups in the *ortho* or *para* position also undergo hydrogenolysis at 120-140 °C.[6] Acetals are usually stable toward hydrogenolysis or elimination at 0-20 °C, except in the presence of a conjugated double bond and bromide (eq 1)[7a] or in certain quinone monoacetal systems.[6b]

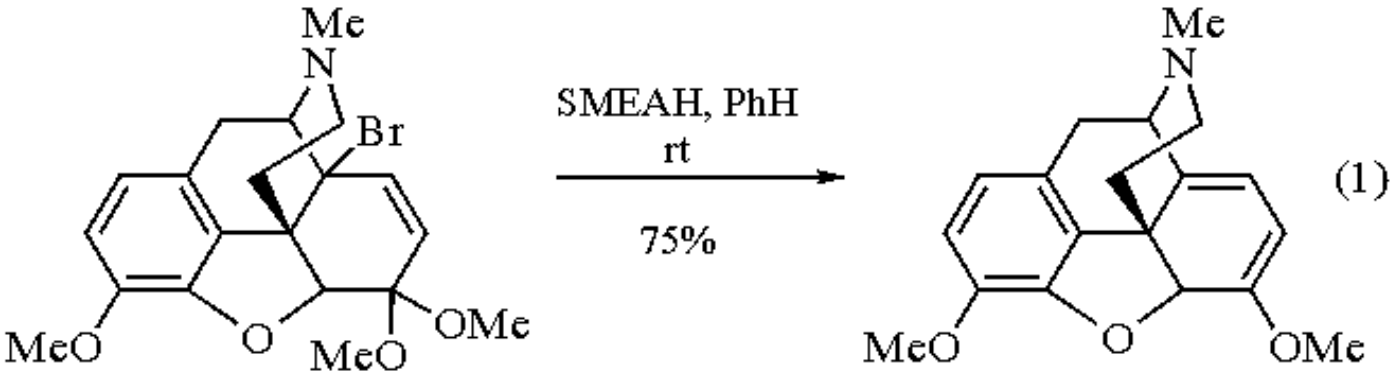

Partial Reductions.

Low-temperature conditions or the use of alcohol or amine-modified SMEAH have proven especially valuable for partial functional group reductions.[1,2] Carboxylic esters, nitriles, and amides can be reduced to the aldehyde at low temperatures. The morpholine or *N*-methylpiperazine modified reagent also yields aldehydes at -55 to 0 °C.[8,9] Lactones are converted to lactols by unmodified SMEAH at -70 °C[2b] or with the EtOH, pyridine, or *i*-PrOH modified reagent at 0 °C. *N*-Substituted cyclic imides provide hydroxylactams upon reduction at -78 °C.[10] It is the reagent of choice for the reduction of Cp_2ZrCl_2 to Cp_2ZrClH.[11]

Selective Reductions.

Vinylogous amides have been selectively reduced to the β-ketoamine (eq 2).[12a] SMEAH is superior to $LiAlH_4$ for the reduction of acetal-protected cyanohydrins to the aldehyde.[12b] It chemoselectively reduces α-formyl ketones to the α-hydroxymethyl ketone.[12c] Lactones are stable in the presence of ketone or aldehyde functionality at low temperatures. SMEAH modified by alcohols or in pyridine solvent selectively reduces lactones in the presence of an amide or ester.[13a] Ester groups in amidoesters undergo selective reduction at 0 °C and short reaction times.[13b] SMEAH gives higher yields than $LiAlH_4$ in the reduction of some hydroxy-substituted carbonyl compounds (eq 3).[13c] 5,5-Disubstituted hydantoins are selectively reduced at the 4-position[13d] and keto aldehydes have been cleanly reduced to the keto alcohol.[13e] Optically active α-alkoxy carboxamides have been reduced to the α-alkoxy aldehydes without racemization.[13f]

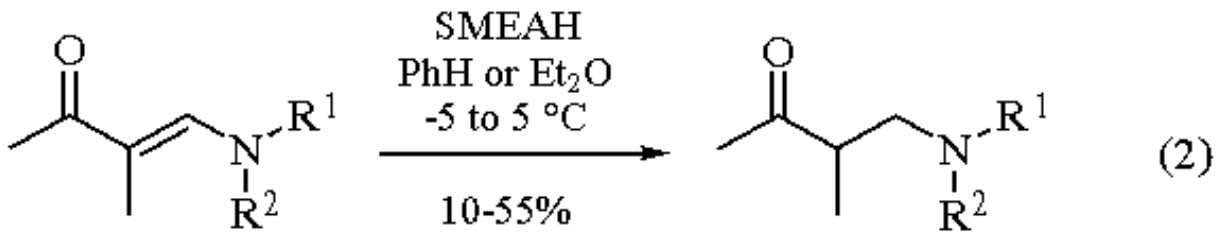

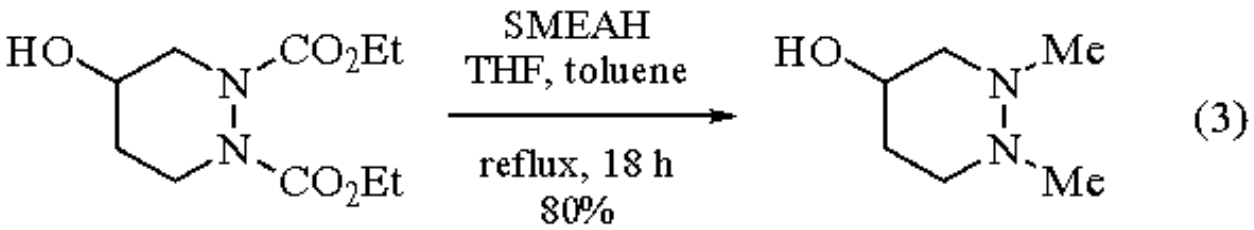

1,2-vs. 1,4-Reductions.

The structure of the enone, solvent, relative initial concentrations, temperature, and softness or hardness of the hydride reagent all play a role in controlling the mode of addition to enone systems. SMEAH typically acts as a hard hydride, favoring 1,2-addition in these reactions. High yields of the allylic alcohol have been reported by inverse addition of the hydride to aliphatic or alicyclic α,β-unsaturated aldehydes and esters.[14a,b] It favors 1,2-addition to cyclic α-enones and is the reagent of choice for the low-temperature reduction of enol esters of alicyclic 1,3-diketones (eq 4).[14c] Alkyl esters are not reduced under these conditions. The SMEAH/CuBr/2-butanol reagent is extremely efficient for 1,4-reduction.[15] Nitrile and ester functions are stable under the conditions of the conjugate reduction, while aldehydes, ketones, and bromides are attacked by the complex.

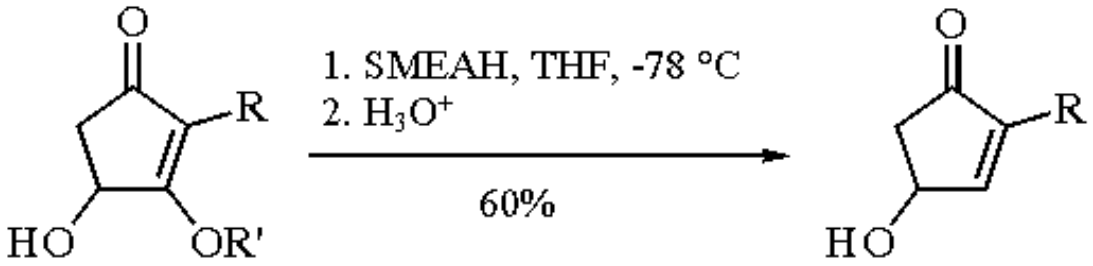

(4)

$R = (CH_2)_6CO_2Me$
$R' = i\text{-Pr, PhCO, ArSO}_2$

Stereoselective Reductions.

The stereochemistry of reductions often varies, depending on the solvent. A possible factor is the degree of solvation. In some cases, complete reversal of stereochemistry has been observed by using SMEAH in benzene versus THF.[1] In comparison to other reducing agents, SMEAH often shows stereoselectivity opposite to that of $LiAlH_4$, ***Sodium Borohydride***, or lithium trialkoxyaluminum hydrides. Unsymmetrical epoxides are attacked preferentially at the least-substituted carbon atom to give the more highly substituted alcohol as the major product.[16a] Exceptionally high regioselectivity in the reduction of α,β-epoxy alcohols to the 1,3-diol has been observed (eq 5).[16b-e] Substituents at the α-carbon reverses the selectivity and decreases the reaction rate. The reduction of α-silyloxy ketones produces *syn*-vicinal diols with high levels of diastereoselectivity.[16f,g]

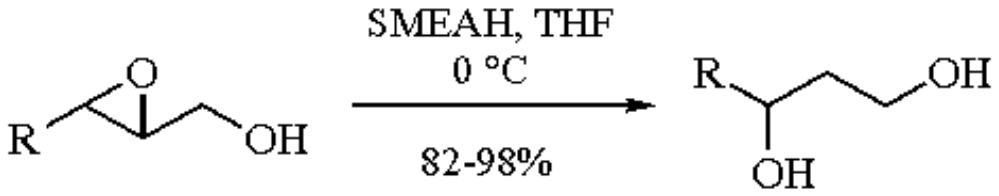

(5)

SMEAH reacts with bridged bicyclic ketones from the less hindered side of the carbonyl.[17a] Reduction of *gem*-dihalocyclopropanes gives *anti*-monohalides as the major product.[17b] It reduces α-alkynic alcohols to *trans*-allylic alcohols with high selectivity.[18a-d] Alkynyl ethers give almost exclusively *O*-alkyl enol ethers with the (*E*) configuration with SMEAH, but with alcohol-modified SMEAH reagent (*Z*)-enol ethers are obtained (eq 6).[18e]

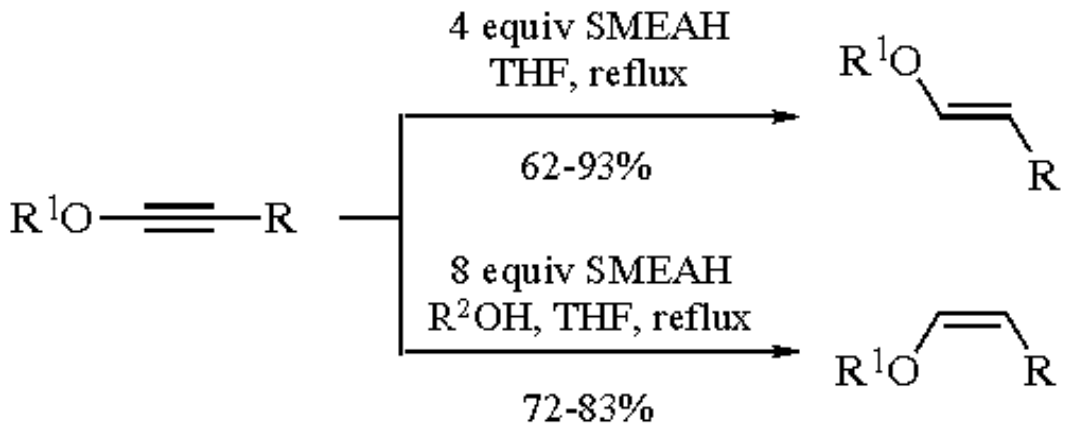

(6)

R = alkyl
R^1, R^2 = alkyl, alicyclic

Methylation Reagent.

The reduction of aryl-conjugated double bonds yields selective methylation at the more highly arylated carbon atom.[19] The Me group originates from the hydride OMe group. Aryl-activated alkanes undergo methylation by this reagent. Diaryl and condensed aromatic ketones undergo hydrogenolysis and subsequent methylation at the benzylic carbon.

Reductive Cleavage of Ethers.

Ethers are usually stable at temperatures below 100 °C. At higher temperatures, cleavage of the ether linkage occurs. SMEAH is a useful reagent for debenzylation and deallylation of aryl benzyl and aryl allyl ethers (eq 7).[20] The reaction is enhanced by a vicinal methoxy group. This method is recommended for debenzylation and deallylation of phenolic ethers that are labile to acid or catalytic hydrogenolysis.

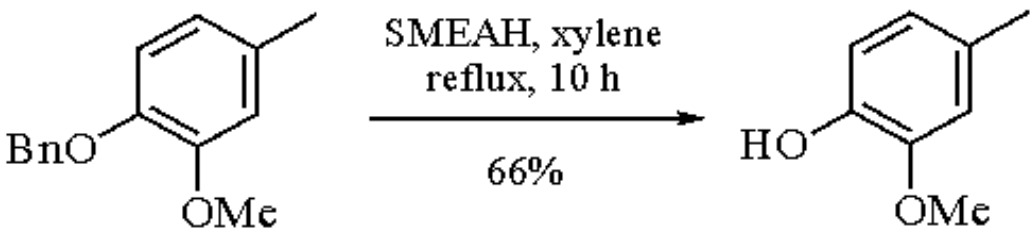

(7)

Use as a Base.

SMEAH can act as a strong base. It is known to promote isomerization and dehydrogenation of aromatic hydrocarbons by a base-catalyzed reaction.[21a,b] The Stevens rearrangement of berbine methiodide affords the spiroisoquinoline derivative in high yield.[21c]

Hydroalumination Reagent.

Double and triple bonds undergo catalytic hydroalumination with a number of aluminum hydride reagents.[22] The effectiveness of SMEAH in this reaction is comparable to that of $LiAlH_4$, $NaAlH_4$, $NaAlHMe_3$, $LiAlH_2(NR_2)_2$, or $NaAlH_2(NR_2)_2$.

Related Reagents.

Copper(I) Bromide-Sodium Bis(2-methoxyethoxy)aluminum Hydride.

---

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Sodium Bismuthate[1]

$NaBiO_3$

[12232-99-4] · $BiNaO_3$ · Sodium Bismuthate · (MW 279.97)

(selective oxidant for cleavage of 1,2-diols[1])

Physical Data: somewhat uncertain composition corresponding to around 85% $NaBiO_3$.

Solubility: insoluble in common solvents.

Form Supplied in: amorphous powder.

Oxidative Cleavage.

Sodium bismuthate is a selective reagent for the oxidative cleavage of 1,2-diols, somewhat similar in scope to periodate or ***Lead(IV) Acetate***.[1] The reagent, an insoluble powder, is used as a suspension in aqueous or organic solvents, normally acidified with ***Acetic Acid*** or ***Phosphoric Acid***. The color and reactivity of commercial samples is somewhat variable. 1,2-Diols are rapidly cleaved to the corresponding carbonyl compounds by sodium bismuthate at moderate temperatures. Like lead tetraacetate but unlike periodate, sodium bismuthate also cleaves α-hydroxy carboxylic acids and some α-hydroxy ketones.[2,3] The general cleavage reactions of sodium bismuthate include the transformations of eqs 1-3 (R = H or alkyl).

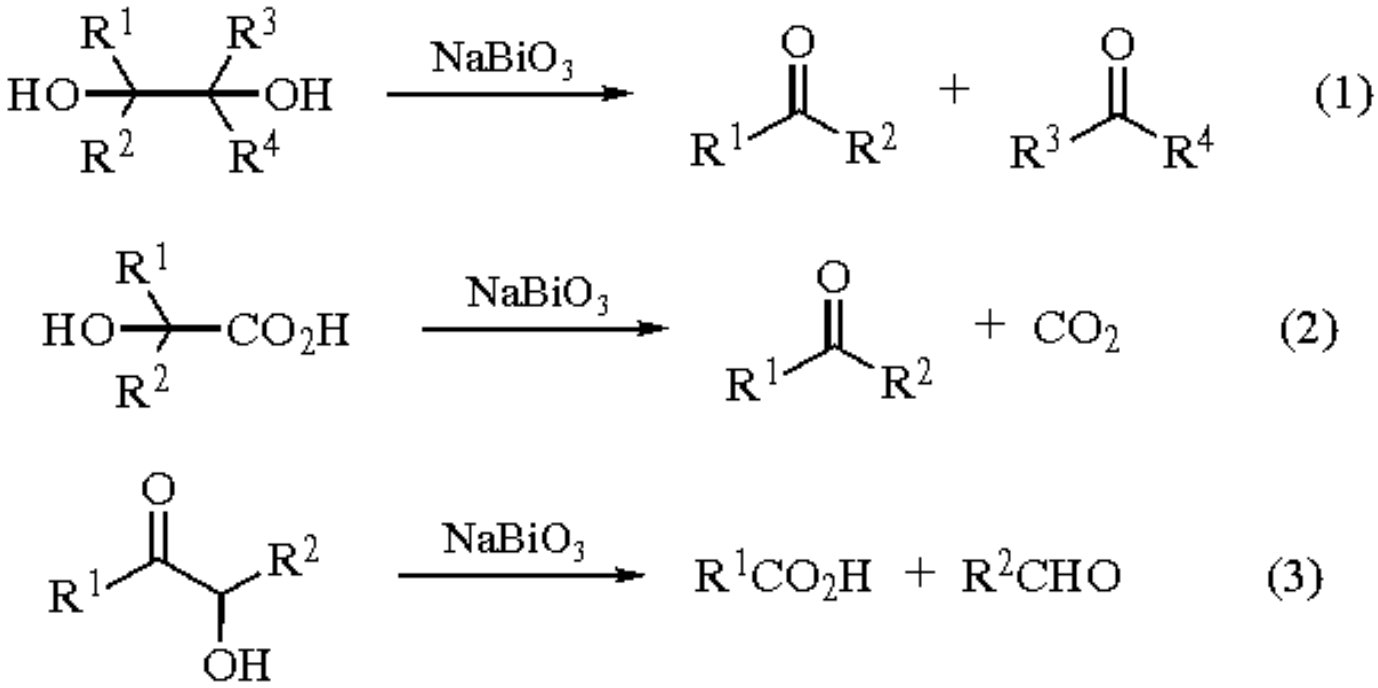

Sodium bismuthate is sometimes preferred to lead tetraacetate because anhydrous conditions are not required for its use. The diol fission reactions of sodium bismuthate are carried out in an excess of acetic or phosphoric acid. When acetic acid is used, a reddish brown suspension, assumed to be bismuth(V) oxide, is formed initially and gradually disappears as the reaction proceeds, leaving a solution of bismuth triacetate. When the reagent is used in combination with phosphoric acid, an orange yellow suspension of unknown composition forms initially. As the oxidation takes place, this gives way to a white precipitate

of bismuth triphosphate.

Even analytical-grade samples of sodium bismuthate display an oxidizing capacity which corresponds to about 85% $NaBiO_3$. Reactions may be carried out in 100% or aqueous acetic acid at, or slightly above, room temperature. A clear colorless solution remains when reaction is complete. Bismuth may be conveniently removed from the reaction by precipitation as the phosphate. Complete reaction may take from a few minutes to several hours.

One application of sodium bismuthate which has received considerable attention is the analytical determination of urinary corticosteroids.[4] This technique relies on the selective cleavage of the corticosteroid side chain. Analysis of the reaction products for 17-keto steroids and formaldehyde is then used to identify the corticosteroids originally present.

Other Oxidations.

Various other oxidation reactions of sodium bismuthate have been studied in addition to 1,2-diol and related cleavage processes. The reagent has been studied, although not widely used, for the oxidation of phenols. Either radical coupling products (typical of one-electron oxidation) or quinonoid products (typical of two-electron oxidation) may be formed, depending on the reaction conditions.

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Sodium Borohydride

$NaBH_4$

[16940-66-2] · BH_4Na · Sodium Borohydride · (MW 37.84)

(reducing agent for aldehydes and ketones, and many other functional groups in the presence of additives[1])

Physical Data: mp 400 °C; *d* 1.0740 g cm^{-3}.

Solubility: sol H_2O (stable at pH 14, rapidly decomposes at neutral or acidic pH); sol MeOH (13 g/100 mL)[1b], and EtOH (3.16 g/100mL),[1b] but decomposes to borates; sol polyethylene glycol (PEG),[2a] sol and stable in *i*-PrOH (0.37 g/100 mL)[3] and diglyme (5.15 g/100 mL);[1b] insol ether;[1b] slightly sol THF.[1c]

Form Supplied in: colorless solid in powder or pellets; supported on silica gel or on basic alumina; 0.5 M solution in diglyme; 2.0 M solution in triglyme; 12 wt % solution in 14 M aqueous NaOH. Typical impurities are sodium methoxide and sodium hydroxide.

Analysis of Reagent Purity: can be assessed by hydrogen evolution.[4]

Purification: crystallize from diglyme[3] or isopropylamine.[4]

Handling, Storage, and Precautions: harmful if inhaled or absorbed through skin. It is decomposed rapidly and exothermically by water, especially if acid solutions are used. This decomposition forms toxic diborane gas and flammable/explosive hydrogen gas, and thus must be carried out under a hood. Solutions in DMF can undergo runaway thermal reactions, resulting in violent decompositions.[5] The addition of supported noble metal catalysts to solutions of $NaBH_4$ can result in ignition of liberated hydrogen gas.[5]

Reduction of Aldehydes and Ketones.

Sodium borohydride is a mild and chemoselective reducing agent for the carbonyl function. At 25 °C in hydroxylic solvents it rapidly reduces aldehydes and ketones, but it is essentially inert to other functional groups such as epoxides, esters, lactones, carboxylic acid salts, nitriles, and nitro groups. Acyl halides, of course, react with the solvent.[1a] The simplicity of use, the low cost, and the high chemoselectivity make it one of the best reagents for this reaction. Ethanol and methanol are usually employed as solvents, the former having the advantage of permitting reductions in homogeneous solutions with relatively little loss of reagent through the side reaction with the solvent.[1a] Aprotic solvents such as diglyme greatly decrease the reaction rates.[1a] On the other hand, $NaBH_4$ in polyethylene glycol (PEG) shows a reactivity similar to that observed in EtOH.[2a] Although the full details of the mechanism of ketone reduction by $NaBH_4$ remain to be established,[6] it has been demonstrated that all four hydrogen atoms can be transferred. Moreover, the rate of reduction was shown to slightly increase when the hydrogens on boron are replaced by alkoxy groups.[1a,c,d] However, especially when $NaBH_4$ is used in MeOH, an excess of reagent has to be used in order to circumvent the competitive borate formation by reaction with the solvent. Ketone reduction has been accelerated under phase-transfer conditions[7] or in the presence of HMPA supported on a polystyrene-type resin.[8]

The isolation of products is usually accomplished by diluting the reaction mixture with water, making it slightly acidic to destroy any excess hydride, and then extracting the organic product from the aqueous solution containing boric acid and its salts.

Kinetic examination of the reduction of benzaldehyde and acetophenone in isopropyl alcohol indicated a rate ratio of 400:1.[1a] Thus it is in principle possible to reduce an aldehyde in the presence of a ketone.[9a] Best results (>95% chemoselectivity) have been obtained using a mixed solvent system (EtOH-CH_2Cl_2 3:7) and performing the reduction at -78 °C,[9a] or by employing an anionic exchange resin in borohydride form.[10] This reagent can also discriminate between aromatic and aliphatic aldehydes. On the other hand, reduction of ketones in the presence of aldehydes can be performed by $NaBH_4$-***Cerium(III) Chloride***. $NaBH_4$ in MeOH-CH_2Cl_2 (1:1) at -78 °C reduces ketones in the presence of conjugated enones and aldehydes in the presence of conjugated enals.[9]

Conjugate Reductions.

$NaBH_4$ usually tends to reduce α,β-unsaturated ketones in the 1,4-sense,[1d] affording mixtures of saturated alcohol and ketone. In alcoholic solvents, saturated β-alkoxy alcohols can be formed as byproducts via conjugate addition of the solvent.[11] The selectivity is not always high. For example, while cyclopentenone is reduced only in the conjugate fashion, cyclohexenone affords a 59:41 ratio of allylic alcohol and saturated alcohol.[1d] Increasing steric hindrance on the enone increases 1,2-attack.[11] Aldehydes undergo more 1,2-reduction than the corresponding ketones.[1c,1d] The use of pyridine as solvent may be advantageous in increasing the selectivity for 1,4-reduction, as exemplified (eq 1) by the reduction of (*R*)-carvone to dihydrocarveols and (in minor amounts) dihydrocarvone.[12]

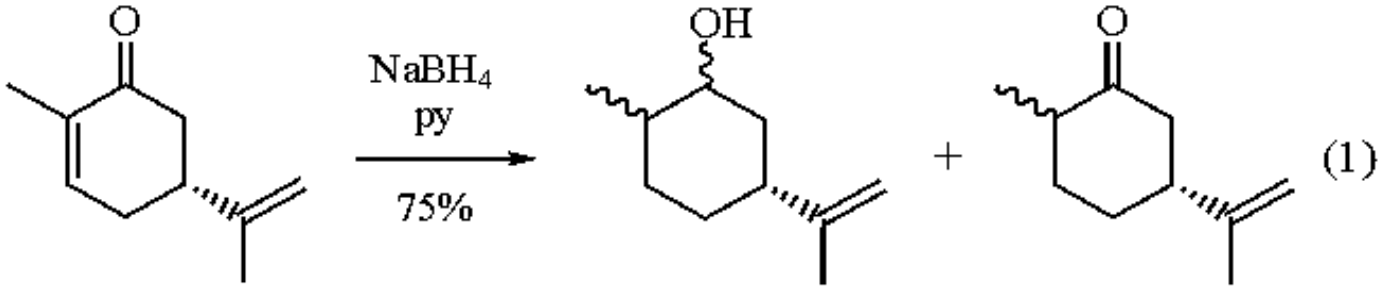

Trialkyl borohydrides such as ***Lithium Tri-s-butylborohydride*** and ***Potassium Tri-s-butylborohydride*** are superior reagents for the chemoselective 1,4-reduction of enones. On the other hand, 1,2-reduction can be obtained by using $NaBH_4$ in the mixed solvent MeOH-THF (1:9),[13] or with $NaBH_4$ in combination with $CeCl_3$ or other lanthanide salts.[14]

$NaBH_4$ in alcoholic solvents has been used for the conjugate reduction of α,β-unsaturated esters,[15] including cinnamates and alkylidenemalonates, without affecting the alkoxycarbonyl group. Conjugate nitroalkenes have been reduced to the corresponding nitroalkanes.[16] Saturated hydroxylamines are obtained by reducing nitroalkenes with the ***Borane-Tetrahydrofuran*** complex in the presence of catalytic amounts of $NaBH_4$, or by using a combination of $NaBH_4$ and ***Boron Trifluoride Etherate*** in 1:1.5 molar ratio.[17] Extended reaction can lead also to the saturated amines.[17]

Reduction of Carboxylic Acid Derivatives.

The reduction of carboxylic esters[1c,1d] by $NaBH_4$ is usually slow, but can be performed by the use of excess reagent in methanol or ethanol[18] at room temperature or higher. The solvent must correspond to the ester group, since $NaBH_4$ catalyzes ester interchange. This transformation can also be achieved at 65-80 °C in *t*-BuOH[19] or polyethylene glycol.[2b] Although the slow rate and the need to use excess reagent makes other stronger complex hydrides such as ***Lithium Borohydride*** or ***Lithium Aluminum Hydride*** best suited for this reaction, in particular cases the use of $NaBH_4$ allows interesting selectivity: see, for example, the reduction of eq 2,[20] where the β-lactam remains unaffected, or of eq 3,[21] where the epoxide and the cyano group do not react.

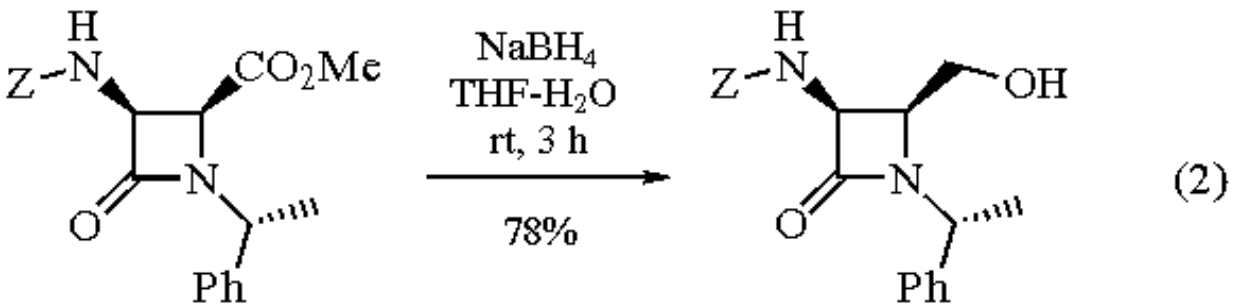

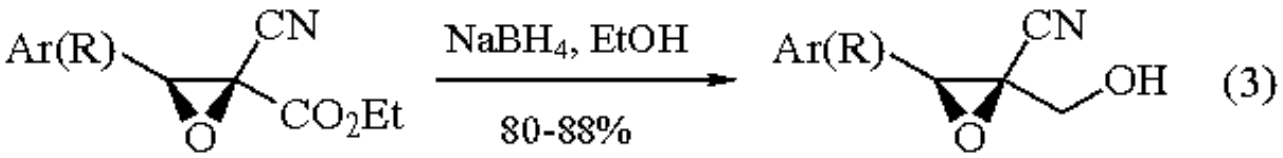

Borohydrides cannot be used for the reduction of α,β-unsaturated esters to allylic alcohols since the conjugate reduction is faster.[18b] The reactivity of $NaBH_4$ toward esters has been enhanced with various additives. For example, the system $NaBH_4$-$CaCl_2$ (2:1) shows a reactivity similar to $LiBH_4$.[18b] Esters have also been reduced with $NaBH_4$-***Zinc Chloride*** in the presence of a tertiary amine,[22] or with $NaBH_4$-***Copper(II) Sulfate***. The latter system reduces selectively aliphatic esters in the presence of aromatic esters of amides.[23] Finally,

esters have also been reduced with $NaBH_4$-***Iodine***.[24a] In this case the reaction seems to proceed through diborane formation, and so it cannot be used for substrates containing an alkenic double bond. A related methodology, employing ***Borane-Dimethyl Sulfide*** in the presence of catalytic $NaBH_4$,[25] is particularly useful for the regioselective reduction of α-hydroxy esters, as exemplified by the conversion of (*S*)-diethyl malate into the vicinal diol (eq 4).

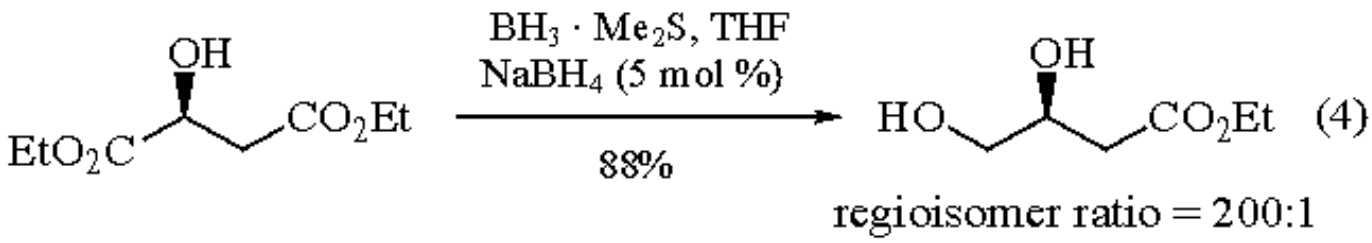

Lactones are only slowly reduced by $NaBH_4$ in alcohol solvents at 25 °C, unless the carbonyl is flanked by an α-heteroatom functionality.[1d] Sugar lactones are reduced to the diol when the reduction is carried out in water at neutral pH, or to the lactol when the reaction is performed at lower (~3) pH.[26] Thiol esters are more reactive and are reduced to primary alcohols with $NaBH_4$ in EtOH, without reduction of ester substituents.[27]

Carboxylic acids are not reduced by $NaBH_4$. The conversion into primary alcohols can be achieved by using $NaBH_4$ in combination with powerful Lewis acids,[1k,28] ***Sulfuric Acid***,[28] ***Catechol***,[24b] ***Trifluoroacetic Acid***,[24b] or I_2.[24a] In these cases the actual reacting species is a borane, and thus hydroboration of double bonds present in the substrate can be a serious side reaction. Alternatively, the carboxylic acids can be transformed into activated derivatives,[29] such as carboxymethyleneiminium salts[29a] or mixed anhydrides,[29b] followed by reduction with $NaBH_4$ at low temperature. These methodologies tolerate the presence of double bonds, even if conjugated to the carboxyl.[29a]

Nitriles are, with few exceptions,[21] not reduced by $NaBH_4$.[1k] Sulfurated $NaBH_4$,[30] prepared by the reaction of sodium borohydride with sulfur in THF, is somewhat more reactive than $NaBH_4$, and reduces aromatic nitriles (but not aliphatic ones) to amines in refluxing THF. Further activation has been realized by using the ***Cobalt Boride*** system, ($NaBH_4$-$CoCl_2$) which appears to be one of the best methods for the reduction of nitriles to primary amines. More recently it has been found that ***Zirconium(IV) Chloride***,[31] Et_2SeBr_2,[32] $CuSO_4$,[23] ***Chlorotrimethylsilane***,[33] and I_2[24a] are also efficient activators for this transformation. The $NaBH_4$-Et_2SeBr_2 reagent allows the selective reduction of nitriles in the presence of esters or nitro groups, which are readily reduced by $NaBH_4$-$CoCl_2$.

$NaBH_4$ in alcoholic solvents does not reduce amides.[1a,1c-d] However, under more forcing conditions ($NaBH_4$ in pyridine at reflux), reduction of tertiary amides to the corresponding amines can be achieved.[32] Secondary amides are inert, while primary amides are dehydrated to give nitriles. Also, $NaBH_4$-Et_2SeBr_2 is specific for tertiary amides.[32] Reagent combinations which show enhanced reactivity, and which are thus employable for all three types of amides, are $NaBH_4$-$CoCl_2$, $NaBH_4$ in the presence of strong acids[34] (e.g. ***Methanesulfonic Acid*** or ***Titanium(IV) Chloride***) in DMF or DME, $NaBH_4$-Me_3SiCl,[33] and $NaBH_4$-I_2.[24a]

An indirect method for the reduction of amides to amines by $NaBH_4$ (applicable only to tertiary amides) involves conversion into a Vilsmeier complex [$(R_2N{=}C(Cl)R)^+Cl^-$], by treatment with ***Phosphorus Oxychloride***, followed by its reduction.[35] In a related methodology, primary or secondary (also cyclic) amides are first converted into ethyl imidates by the action of ***Triethyloxonium Tetrafluoroborate***, and the latter reduced to amines with $NaBH_4$ in EtOH or, better, with $NaBH_4$-***Tin(IV) Chloride*** in Et_2O.[36]

In addition to the above-quoted methods, tertiary δ-lactams have been reduced to the corresponding cyclic amines by dropwise addition of MeOH to the refluxing mixture of $NaBH_4$ and substrate in *t*-BuOH,[37] or by using trifluoroethanol as solvent.[38] This reaction was applied during a synthesis of indolizidine alkaloid swainsonine for the reduction of lactam (**1**) to amine (**2**) (eq 5).[38]

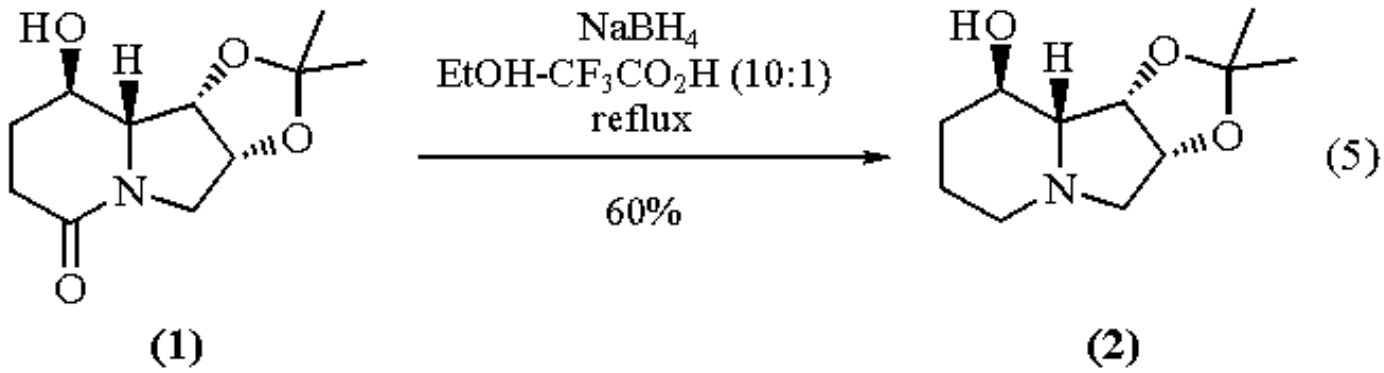

Acyl chlorides can be reduced to primary alcohols by reduction in aprotic solvents such as PEG,[2a] or using $NaBH_4$-***Alumina*** in Et_2O.[39] More synthetically useful is the partial reduction to the aldehydic stage, which can be achieved by using a stoichiometric amount of the reagent at -70 °C in DMF-THF,[40] with the system $NaBH_4$-***Cadmium Chloride***-DMF,[41] or with ***Bis(triphenylphosphine)copper(I) Borohydride***.

Alternative methodologies for the indirect reduction of carboxylic derivatives employ as intermediates 2-substituted 1,3-benzoxathiolium tetrafluoborates (prepared from carboxylic acids, acyl chlorides, anhydrides, or esters)[42] and dihydro-1,3-thiazines or dihydro-1,3-oxazines (best prepared from nitriles).[43] These compounds are smoothly reduced by $NaBH_4$, to give acetal-like adducts, easily transformable into the corresponding aldehydes by acidic hydrolysis. Conversion of primary amides into the *N*-acylpyrrole derivative by reaction with 1,4-dichloro-1,4-dimethoxybutane in the presence of a cationic exchange resin, followed by $NaBH_4$ reduction, furnished the corresponding aldehydes.[44]

Cyclic anhydrides are reduced by $NaBH_4$ to lactones in moderate to good yields. Hydride attack occurs principally at the carbonyl group adjacent to the more highly substituted carbon atom.[45] Cyclic imides are more reactive than amides and can be reduced to the corresponding α´-hydroxylactams by using methanolic or ethanolic $NaBH_4$ in the presence of HCl as buffering agent.[1c] These products are important as precursors for *N*-acyliminium salts. The carbonyl adjacent to the most substituted carbon is usually preferentially reduced[46] (see ***Cobalt Boride***). *N*-Alkylphthalimides may be reduced with $NaBH_4$ in 2-propanol to give an open-chain hydroxy-amide which, upon treatment with AcOH, cyclizes to give phthalide (a lactone) and the free amine. This method represents a convenient procedure for releasing amines from phthalimides under nonbasic conditions.[47]

Reduction of C=N Double Bonds.

The C=N double bond of imines is generally less reactive than the carbonyl C=O toward reduction with complex hydrides. However, imines may be reduced by $NaBH_4$ in alcoholic solvents under neutral conditions at temperatures ranging from 0 °C to that of the refluxing solvent.[1c,1d,48] Protonation or complexation with a Lewis acid of the imino nitrogen dramatically increases the rate of reduction.[1i] Thus $NaBH_4$ in AcOH (see ***Sodium Triacetoxyborohydride***) or in other carboxylic acids is an efficient reagent for this transformation (although the reagent of choice is probably ***Sodium Cyanoborohydride***). Imines are also reduced by ***Cobalt Boride***, $NaBH_4$-***Nickel(II) Chloride***, and $NaBH_4$-$ZrCl_4$.[31] Imine formation, followed by in situ reduction, has been used as a method for synthesis of unsymmetrical secondary amines.[48] Once again, $Na(CN)BH_3$ represents the best reagent.[1c,1d,48] However, this transformation was realized also with $NaBH_4$,[48,49] either by treating the amine with excess aqueous formaldehyde followed by $NaBH_4$ in MeOH, or $NaBH_4$-CF_3CO_2H, or through direct reaction of the amine with the $NaBH_4$-carboxylic acid system. In the latter case, part of the acid is first reduced in situ to the aldehyde, which then forms an imine. The real reagent involved is $NaB(OCOR)_3H$ (see ***Sodium Triacetoxyborohydride***). Reaction of an amine with glutaric aldehyde and $NaBH_4$ in the presence of H_2SO_4 represents a good method for the synthesis of *N*-substituted piperidines.[49c] Like protonated imines, iminium salts are readily reduced by $NaBH_4$ in alcoholic media.[1c,50] *N*-Silylimines are more reactive than *N*-alkylimines. Thus α-amino esters can be obtained by reduction of *N*-silylimino esters.[51] α,β-Unsaturated imines are reduced by $NaBH_4$ in alcoholic solvents in the 1,2-mode to give allylic amines.[52] Enamines are transformed into saturated amines by reduction with $NaBH_4$ in alcoholic media.[48,53]

The reduction of oximes and oxime ethers is considerably more difficult and cannot be realized with $NaBH_4$ alone. Effective reagent combinations for the reduction of oximes include sulfurated $NaBH_4$,[30] $NaBH_4$-$NiCl_2$, $NaBH_4$-$ZrCl_4$,[31] $NaBH_4$-MoO_3,[54] $NaBH_4$-$TiCl_4$,[55] and $NaBH_4$-***Titanium(III) Chloride***.[56] In all cases the main product is the corresponding primary amine. $NaBH_4$-$ZrCl_4$ is efficient also for the reduction of oxime ethers. $NaBH_4$-MoO_3 reduces oximes without affecting double bonds, while $NaBH_4$-$NiCl_2$ reduces both functional groups. The reduction with $NaBH_4$-$TiCl_3$ in buffered (pH 7) aqueous media has been used for the chemoselective reduction of α-oximino esters to give α-amino esters (eq 6).[56]

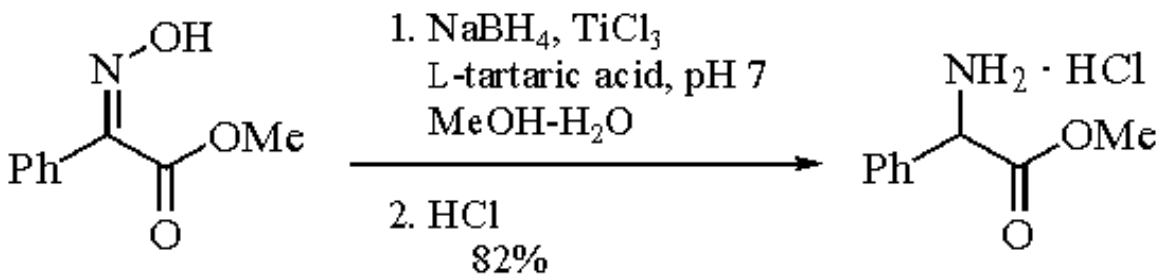

(6)

$NaBH_4$ reduces hydrazones only when they are *N*,*N*-dialkyl substituted. The reaction is slow and yields are not usually satisfactory.[57] More synthetically useful is the reduction of *N*-*p*-tosylhydrazones to give hydrocarbons,[1c,1d,58] which has been carried out with $NaBH_4$ in refluxing MeOH, dioxane, or THF.[58] Since *N*-*p*-tosylhydrazones are easily prepared from aldehydes or ketones, the overall sequence represents a mild method for carbonyl deoxygenation. α,β-Unsaturated tosylhydrazones show a different behavior yielding, in MeOH, the allylic (or benzylic) methyl ethers.[58c] The reduction of tosylhydrazones with $NaBH_4$ is not compatible with ester groups, which are

readily reduced under these conditions. More selective reagents for this reduction are $NaBH(OAc)_3$ and $NaCNBH_3$.

Reduction of Halides, Sulfonates, and Epoxides.

The reduction of alkyl halides or sulfonates by $NaBH_4$ is not an easy reaction.[1d] It is best performed in polar aprotic solvents[59] such as DMSO, sulfolane, HMPA, DMF, diglyme, or PEG (polyethylene glycol),[2a] at temperatures between 60 °C and 100 °C (unless for highly reactive substrates), or under phase-transfer conditions.[60a] The mechanism is believed to be S_N2 (I > Br > Cl and primary > secondary). Although the more nucleophilic ***Lithium Triethylborohydride*** seems better suited for these reductions,[59b] the lower cost of $NaBH_4$ and the higher chemoselectivity (for example esters, nitriles, and sulfones can survive)[59a] makes it a useful alternative. Also, some secondary and tertiary alkyl halides, capable of forming relatively stable carbocations, for example benzhydryl chloride, may be reduced by $NaBH_4$. In this case the mechanism is different (via a carbocation) and the reaction is accelerated by water.[59a,b] Primary, secondary, and even aryl iodides and bromides[1d] have been reduced in good yields by $NaBH_4$ under the catalysis of soluble polyethylene- or polystyrene-bound tin halides (PE-$Sn(Bu)_2Cl$ or PS-$Sn(Bu)_2Cl$).[61] Aryl bromides and iodides have also been reduced with $NaBH_4$-***Copper(I) Chloride*** in MeOH.[62]

$NaBH_4$ reduces epoxides only sluggishly.[1d] Aryl-substituted and terminal epoxides can be reduced by slow addition of MeOH to a refluxing mixture of epoxide and $NaBH_4$ in *t*-BuOH,[63] or by $NaBH_4$ in polyethylene glycol.[2b] The reaction is regioselective (attack takes place on the less substituted carbon), and chemoselective (nitriles, carboxylic acids, and nitro groups are left intact).[63] The opposite regioselectivity was realized by the $NaBH_4$-catalyzed reduction with diborane.[64]

Other Reductions.

Aromatic and aliphatic nitro compounds are not reduced to amines by $NaBH_4$ in the absence of an activator.[1d] The $NaBH_4$-$NiCl_2$ system (see ***Nickel Boride***) is a good reagent combination for this reaction, being effective also for primary and secondary aliphatic compounds. Other additives that permit $NaBH_4$ reduction are $SnCl_2$,[65] Me_3SiCl,[33] $CoCl_2$ (see ***Cobalt Boride***), and MoO_3 (only for aromatic compounds),[66] Cu^{2+} salts (for aromatic and tertiary aliphatic),[23,67] and ***Palladium on Carbon*** (good for both aromatic and aliphatic).[68] Also, sulfurated $NaBH_4$[30] is an effective and mild reducing agent for aromatic nitro groups. In the presence of catalytic selenium or tellurium, $NaBH_4$ reduces nitroarenes to the corresponding *N*-arylhydroxylamines.[69]

The reduction of azides to amines proceeds in low yield under usual conditions, but it can be performed efficiently under phase-transfer conditions,[60b] using $NaBH_4$ supported on an ion-exchange resin,[70] or using a THF-MeOH mixed solvent (this last method is well suited only for aromatic azides).[71]

Tertiary alcohols or other carbinols capable of forming a stable carbocation have been deoxygenated by treatment with $NaBH_4$ and CF_3CO_2H or $NaBH_4$-CF_3SO_3H.[72] Under the same conditions,[72] or with $NaBH_4$-***Aluminum Chloride***,[73] diaryl ketones have also been deoxygenated.

Cyano groups α to a nitrogen atom can be replaced smoothly by hydrogen upon reaction with $NaBH_4$.[74] Since α-cyano derivatives of trisubstituted amines can be easily alkylated with electrophilic agents, the α-aminonitrile functionality can be used as a latent α-amino anion,[74a] as exemplified by eq 7 which shows the synthesis of ephedrine from a protected aminonitrile. The reduction, proceeding with concurrent benzoyl group removal, is only moderately stereoselective (77:23).

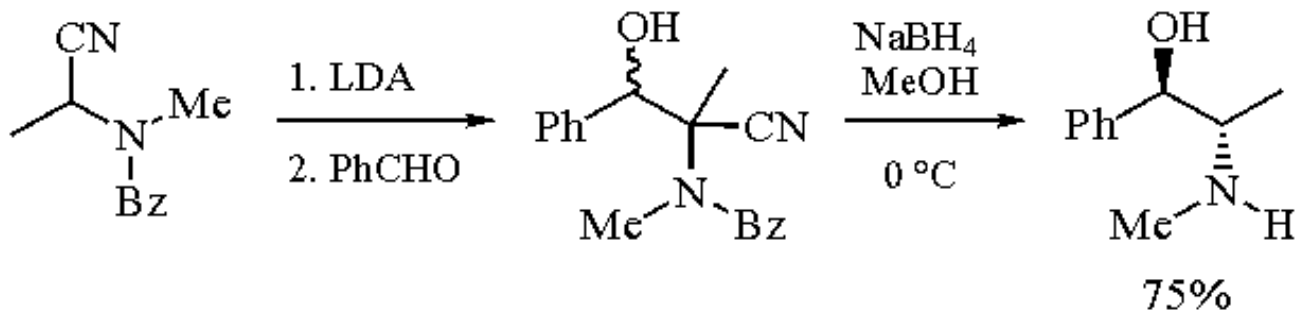

(7)

Primary amines have been deaminated in good yields through reduction of the corresponding bis(sulfonimides) with $NaBH_4$ in HMPA at 150-175 °C.[75] $NaBH_4$ reduction of ozonides is rapid at -78 °C and allows the one-pot degradation of double bonds to alcohols[1b] (see also ***Ozone***). The reduction of organomercury(II) halides (see also ***Mercury(II) Acetate***) is an important step in the functionalization of double bonds via oxymercuration-or amidomercuration-reduction. This reduction, which proceeds through a radical mechanism, is not stereospecific, but it can be in some cases diastereoselective.[76] In the presence of ***Rhodium(III) Chloride*** in EtOH, $NaBH_4$ completely saturates arenes.[77] $NaBH_4$ has also been employed for the reduction of quinones,[78] sulfoxides (in combination with ***Aluminum Iodide***[79]

or Me_3SiCl[33]), and sulfones (with Me_3SiCl),[33] although it does not appear to be the reagent of choice for these reductions. Finally, $NaBH_4$ was used for the reduction of various heterocyclic systems (pyridines, pyridinium salts, indoles, benzofurans, oxazolines, and so on).[1c,1d,48,80] The discussion of these reductions is beyond the scope of this article.

Diastereoselective Reductions.

$NaBH_4$, like other small complex hydrides ($LiBH_4$ and $LiAlH_4$), shows an intrinsic preference for axial attack on cyclohexanones,[1c,1d,81] as exemplified by the reduction of 4-*t*-butylcyclohexanone (eq 8).[81a] This preference, which is due to stereoelectronic reasons,[82] can be counterbalanced by steric biases. For example, in 3,3,5-trimethylcyclohexanone, where a β-axial substituent is present, the stereoselectivity is nearly completely lost (eq 9).[81a]

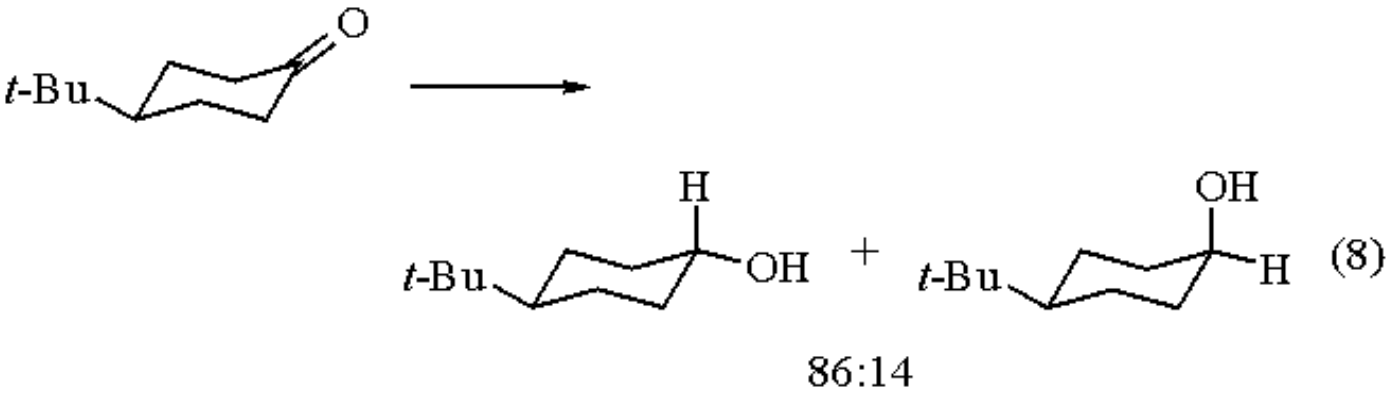

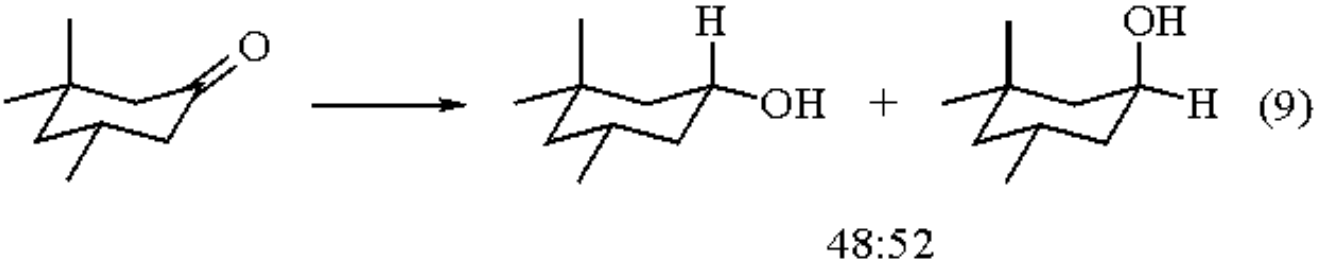

Also, in 2-methylcyclopentanone[81c] the attack takes place from the more hindered side, forming the *trans* isomer (dr = 74:26). In norcamphor,[81a] both stereoelectronic and steric effects favor *exo* attack, forming the *endo* alcohol in 84:16 diastereoisomeric ratio. In camphor, however, the steric bias given by one of the two methyls on the bridge brings about an inversion of stereoselectivity toward the *exo* alcohol.[81a]

The stereoselectivity for equatorial alcohols has been enhanced by using the system $NaBH_4$-***Cerium(III) Chloride***, which has an even higher propensity for attack from the more hindered side,[83] or by precomplexing the ketone on ***Montmorillonite K10*** clay.[84] On the other hand, bulky trialkylborohydrides (see ***Lithium Tri-s-butylborohydride***) are best suited for synthesis of the axial alcohol through attack from the less hindered face.

$NaBH_4$ does not seem to be the best reagent for the stereoselective reduction of chiral unfunctionalized acyclic ketones. Bulky complex hydrides such as $Li(s\text{-}Bu)_3BH$ usually afford better results.[1c,1d] When a heteroatom is present in the α- or β-position, the stereochemical course of the reduction depends also on the possible intervention of a cyclic chelated transition state. Also, in this case other complex hydrides are often better suited for favoring chelation (see ***Zinc Borohydride***). Nevertheless, cases are known[85] where excellent degrees of stereoselection have been achieved with the simpler and less expensive $NaBH_4$. Some examples are shown in eqs 10-15.

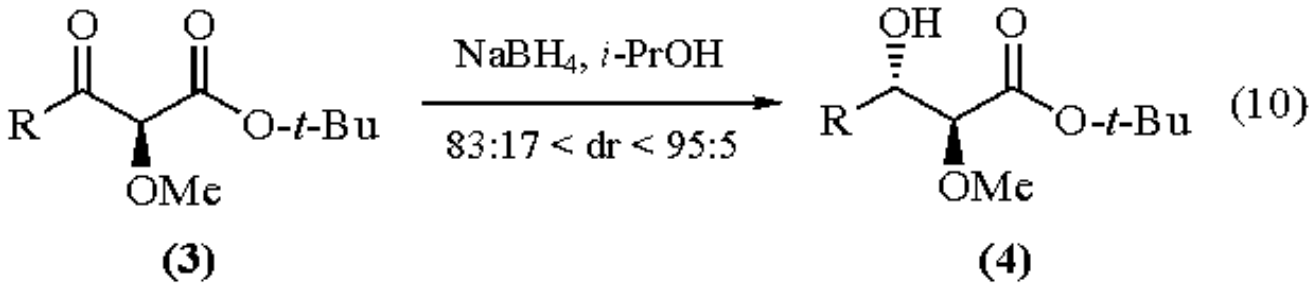

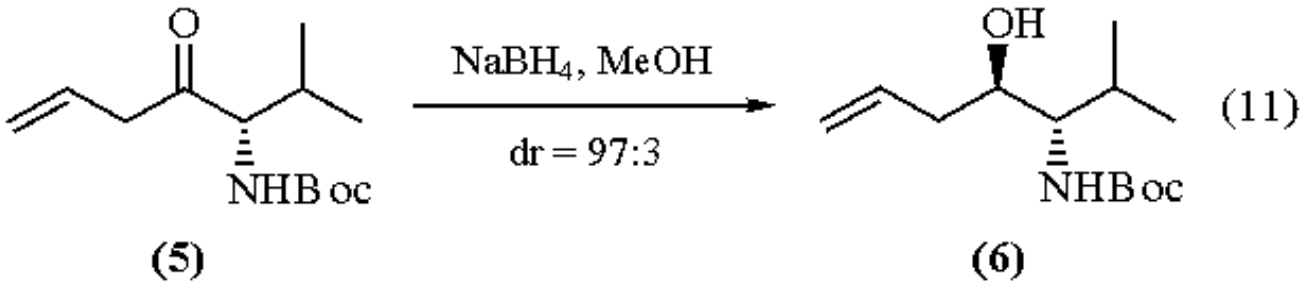

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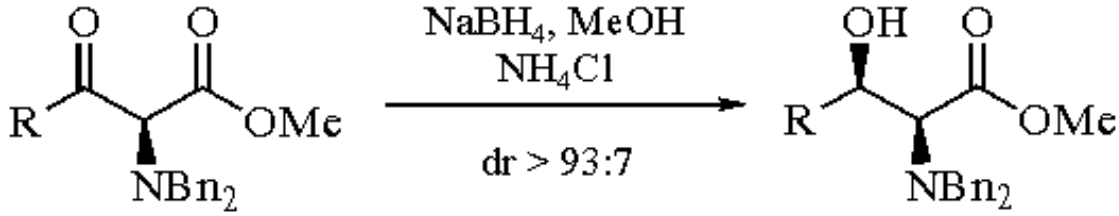

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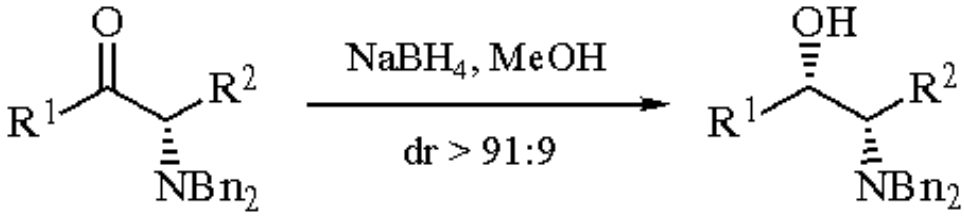

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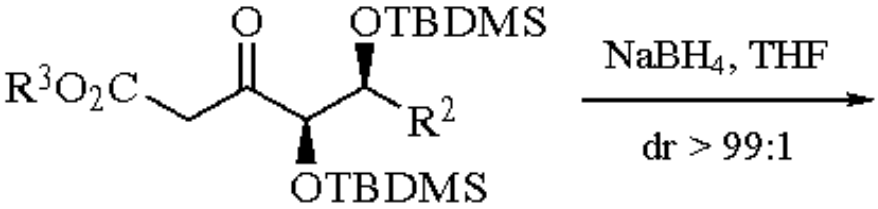

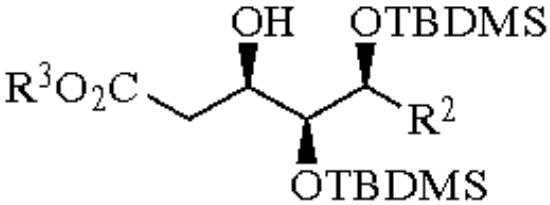

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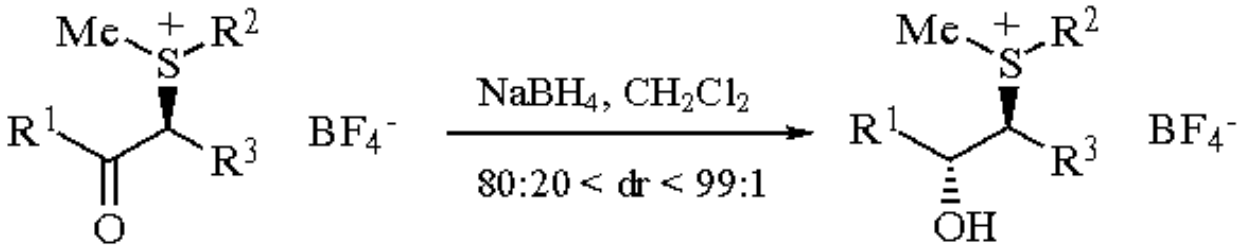

(15)

The stereoselective formation of *anti* adduct (**4**) in the reduction of ketone (**3**) was explained through the intervention of a chelate involving the methoxy group,[85a] although there is some debate on what the acidic species is that is coordinated (probably Na^+). A chelated transition state is probably the cause of the stereoselective formation of *anti* product (**6**) from (**5**).[85b] Methylation of the NH group indeed provokes a decrease of stereoselection. On the other hand, when appropriate protecting groups that disfavor chelation are placed on the heteroatom, the reduction proceeds by way of the Felkin model where the heteroatomic substituent plays the role of large group, and *syn* adducts are formed preferentially. This is the case of α-dibenzylamino ketones (eqs 12 and 13)[85c,d] and of the α-silyloxy ketone of eq 14.[85e] Finally, the sulfonium salt of eq 15 gives, with exce llent stereocontrol, the *anti* alcohol.[85f] This result was explained by a transition state where the S^+ and carbonyl oxygen are close due to a charge attraction.

The reduction of a diastereomeric mixture of enantiomerically pure β-keto sulfoxides (**7**) furnished one of the four possible isomers with good overall stereoselectivity (90%), when carried out under conditions which favor epimerization of the α chiral center (eq 16). This outcome derives from a chelation-controlled reduction (involving the sulfoxide oxygen) coupled with a kinetic resolution of the two

diastereoisomers of (7).[86]

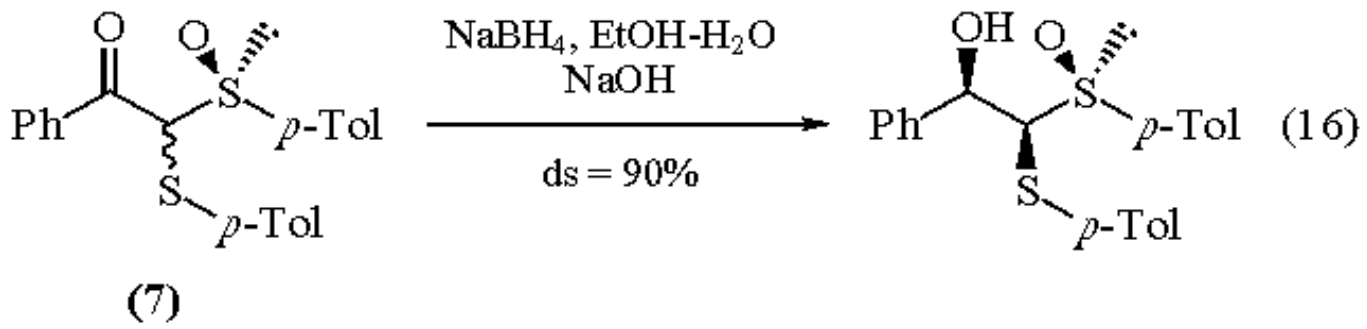

The reduction of cyclic imines and oximes follows a trend similar to that of corresponding ketones. However, the tendency for attack from the most hindered side is in these cases attenuated.[1c,1d,57,87] In the case of oximes, while $NaBH_4$-MoO_3 attacks from the axial side, $NaBH_4$-$NiCl_2$ attacks from the equatorial side.[88] An example of diastereoselective reduction of acyclic chiral imines is represented by the one-pot transformation of α-alkoxy or α,β-epoxynitriles into *anti* vicinal amino alcohols (eq 17) or epoxyamines. The outcome of these reductions was explained on the basis of a cyclic chelated transition state.[89]

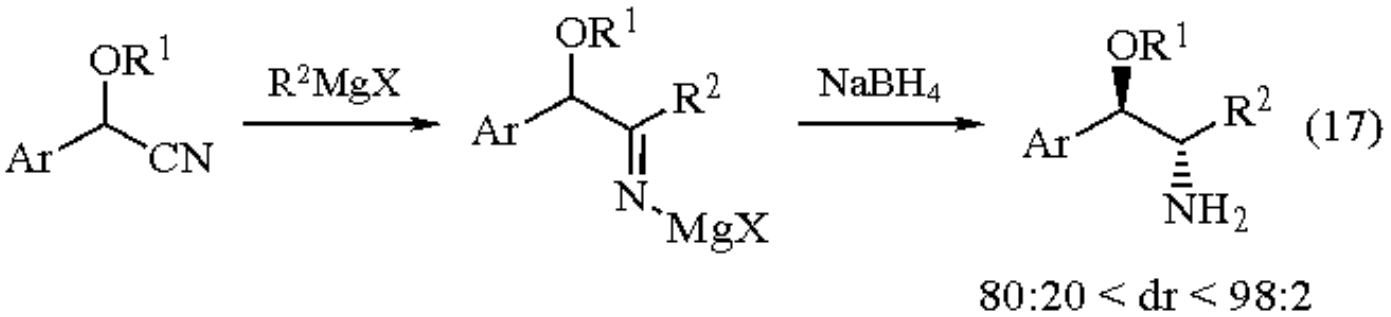

Enantioselective Reductions.

$NaBH_4$ has been employed with less success than $LiAlH_4$ or BH_3 in enantioselective ketone reductions.[1d,90,91] Low to moderate ee values have been obtained in the asymmetric reduction of ketones with chiral phase-transfer catalysts, chiral crown ethers,[91a] β-cyclodextrin,[91b] and bovine serum albumin.[91c] On the other hand, good results have been realized in the reduction of propiophenone with $NaBH_4$ in the presence of isobutyric acid and of diisopropylidene-D-glucofuranose (ee = 85%),[91d] or in the reduction of α-keto esters and β-keto esters with $NaBH_4$-L-tartaric acid (ee &egt;86%).[91e]

Very high ee values have been obtained in the asymmetric conjugate reduction of α,β-unsaturated esters and amides with $NaBH_4$ in the presence of a chiral semicorrin (a bidentate nitrogen ligand) cobalt catalyst.[92] Good to excellent ee values were realized in the reduction of oxime ethers with $NaBH_4$-$ZrCl_4$ in the presence of a chiral 1,2-amino alcohol.[93]

Related Reagents.

Cerium(III) Chloride; ***Nickel Boride***; ***Potassium Triisopropoxyborohydride***; ***Sodium Cyanoborohydride***; ***Sodium Triacetoxyborohydride***.

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Sodium Bromate

$NaBrO_3$

[7789-38-0] · $BrNaO_3$ · Sodium Bromate · (MW 150.89)

(in combination with CAN, oxidizes alcohols to carbonyl compounds;[1] oxidizes other functional groups; promotes oxidative cleavage of ethers[2])

Physical Data: mp about 381 °C decomposing with evolution of oxygen; *d* 3.34 g cm^{-3}.

Solubility: sol 2.5 parts water, 1.1 parts boiling water; almost insol alcohol; sodium bromate is more soluble in water than potassium bromate.

Form Supplied in: colorless crystals or white granules or powder; widely available. *Drying:* for analytical work dry at 100-110 °C for 1 h.

Handling, Storage, and Precautions: sodium bromate is a strong oxidizing agent (standard potential is 1.44 V); toxicity is low; should be kept from contact with mineral acids and organic compounds during storage.

Oxidation of Alcohols.

Sodium bromate, when used with catalytic amounts of cerium(IV) salts, oxidized arylmethanols to the corresponding ketones and aldehydes (eq 1).[3] The sodium bromate serves to continuously replenish the more expensive oxidant, ***Cerium(IV) Ammonium Nitrate*** (CAN).

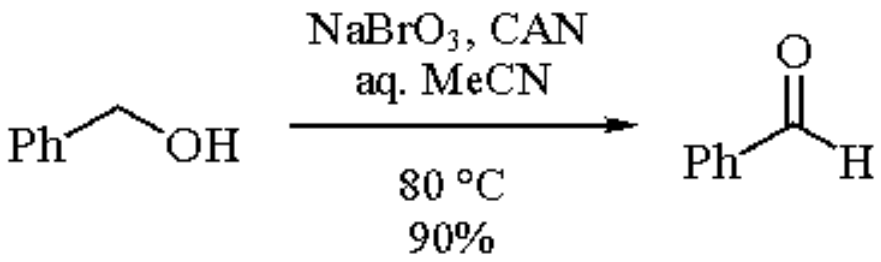

(1)

Sodium bromate was superior to other oxidants in the transition metal-catalyzed oxidation of alcohols to carbonyl compounds.[1] Primary alcohols were recovered practically unchanged. Selective oxidations were observed in mixed primary/secondary alcohol systems (eq 2). However, alkenic moieties even several carbon atoms removed from the hydroxyl group interrupted the oxidation.[1] Oxidations using polymer-supported Ce^{IV}, which are not affected by the alkene moiety in the substrate, provide a useful extension of this method.[4]

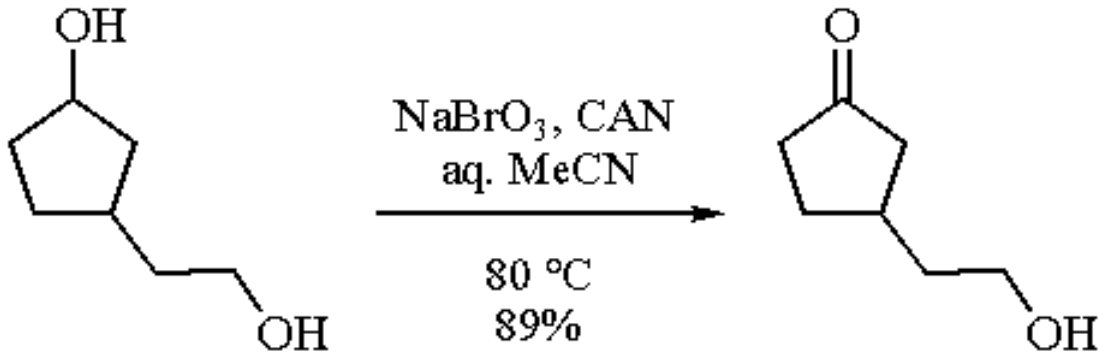

(2)

Secondary alcohols could also be oxidized using ruthenium derivatives in combination with sodium bromite.[1] Oxidation of primary alcohols to aldehydes could be achieved without overoxidation using sodium bromate and dodecacarbonyltriruthenium(0) or sodium bromate and buffered ***Ruthenium(III) Chloride***.[1] Metal-catalyzed oxidation technology has recently been reviewed.[5] Secondary alcohols are oxidized to ketones with ***Sodium Bromite*** in aqueous acetic acid in the absence of a metal catalyst.[6] Oxidative esterification of primary alcohols to the corresponding ester occurs in good yield with sodium bromite.[6]

Oxidation of hydroquinone derivatives to produce the quinones has been reported with sodium bromate in acetic acid.[7] Oxidations of hydroquinones using sodium bromate and CAN in the solid state[8] and in solution[9] have also been reported (eq 3).

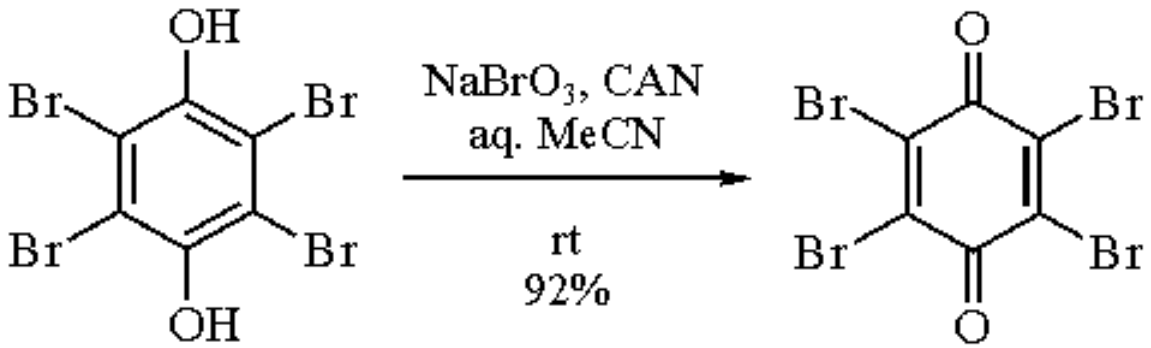

(3)

Oxidation of Other Functional Groups.

The oxidation of sulfides to sulfoxides has been reviewed.[10] A mixture of sodium bromate and bromide in hydrochloric acid solution, which generates a solution of bromine, oxidized sulfides to the sulfoxides.[11] ***Potassium Bromate*** in the absence of added bromide also oxidized thiophenol to diphenyl disulfide or benzenesulfonic acid depending on the conditions.[12] 4,4-Dinitrodiphenyl sulfide was oxidized to the sulfone in excellent yield.[12]

Catalytic amounts of CAN and sodium bromate have been shown to oxidize diaryl sulfides and dialkyl sulfides to the corresponding sulfoxide without overoxidation to the sulfone.[9] In contrast, using CAN alone, dialkyl sulfides were found to undergo the Pummerer rearrangement.[13] Sodium bromite also oxidizes alkyl and aryl sulfides to the sulfoxide.[6]

Catalytic ring opening of epoxides has been reported using polymer-supported cerium(IV) catalysts (eq 4).[14] A mixture of sodium bromate in nitric acid is used to regenerate the catalytic activity. Potassium bromate also oxidizes dialkylhydrazine derivatives to the tetraalkyltetrazenes.[15] Benzaldehyde has been oxidized to benzoic acid using potassium bromate.[16] However, sodium bromate and CAN were not effective for the oxidation of 1,4-dihydropyridines to the pyridine derivatives.[17]

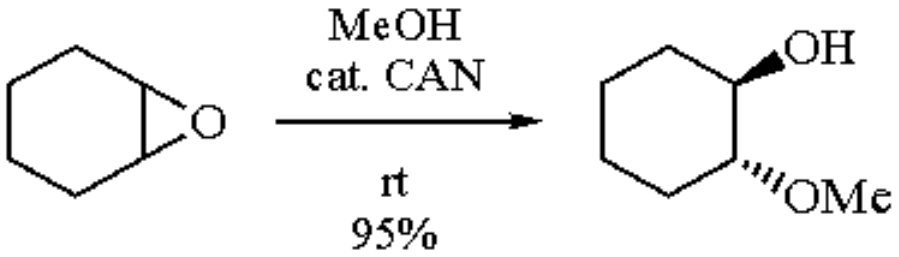

(4)

Oxidative Cleavage of Ethers.[18]

Methyl, ethyl, trimethylsilyl, and *t*-butyldimethylsilyl ethers readily undergo oxidative cleavage to afford the corresponding carbonyl compounds with a catalytic amount of CAN and a molar equivalent of sodium bromate (eq 5).[2] The reaction proceeds smoothly in refluxing aqueous acetonitrile. The reactivity of sodium bromate and CAN approaches that of Jones/KF (see ***Chromic Acid***) and PDC/Me_3SiCl/CH_2Cl_2 (see ***Pyridinium Dichromate***) for the oxidative deprotection and oxidation of alcohols.[18] The selectivity of $NaBrO_3$/CAN for the oxidation of alcohols in the presence of silyl ethers, or the selective oxidation of primary or secondary silyl ethers, has not been extensively explored.[18]

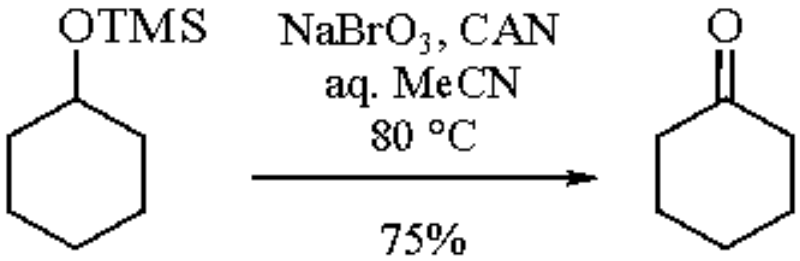

(5)

A selective oxidation of a primary alcohol in the presence of a *t*-butyldimethylsiloxy group has been reported with sodium bromite.[19]

Related Reagents.

Cerium(IV) Ammonium Nitrate-Sodium Bromate.

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Sodium Bromide

NaBr

[7647-15-6] · BrNa · Sodium Bromide · (MW 102.89)

(source of bromide ion as nucleophile; precursor to bromine electrophiles)

Physical Data: mp 755 °C; *d* 3.21 g cm^{-3}.

Solubility: very sol water; sol methanol, ethanol.

Form Supplied in: colorless, odorless crystals, granules, or powder. *Drying:* is hygroscopic and should be dried at 140 °C for applications that require the anhydrous salt.

Handling, Storage, and Precautions: should be taken directly from the oven when dryness is required. NaBr is of low toxicity.

Source of Bromide Nucleophile.

Sodium bromide is an inexpensive source of bromide anion for service as a nucleophile or nucleophilic catalyst. In alcoholic and dipolar aprotic solvents, NaBr converts the sulfonate esters of primary and secondary alcohols to the corresponding alkyl bromides.[1] Sodium bromide cleanly converts primary alkyl chlorides to bromides, provided that a large excess of ethyl bromide or dibromomethane is added as a chloride ion scavenger.[2] In the presence of Dowex-50 ion exchange resin, NaBr opens epoxides to bromohydrins.[3] ***Bromotrimethylsilane*** can be generated in situ from ***Chlorotrimethylsilane*** and NaBr, and then used to convert aldehydes and ketones to silyl enol ethers under mild conditions with significant regio- and stereoselectivity.[4]

Precursor to Bromine Electrophiles.

Chemical or electrochemical oxidation of sodium bromide generates reactive electrophilic bromine species, which can effect a variety of useful transformations. A mixture of NaBr and ***Peracetic Acid*** oxidizes secondary alcohols to ketones, primary benzylic alcohols to aldehydes, primary aliphatic alcohols to dimeric esters, and α,o-diols to lactones.[5] The reaction conditions, which appear to involve the formation of acetyl hypobromite, provide an inexpensive and less toxic alternative to chromium oxidants. By combining NaBr and $NaBrO_2$, it is possible to generate hypobromite ion without using elemental bromine. This mixture of salts effects the Hofmann degradation of primary amides to generate amines and promotes the bromoform reaction of methyl ketones to generate carboxylic acids.[6] Organoboranes are brominolyzed to bromoalkanes or bromoalkenes upon treatment with bromine

chloride, which can be generated by reaction of NaBr with ***Chlorine***, ***Chloramine-T***, or ***N-Chlorosuccinimide***.[7] This procedure allows the preparation of radiobrominated organic compounds from radioactive NaBr. Sodium bromide is useful as an electrolyte in electrochemical oxidations, generating electrophilic bromine species which can react with organic substrates. Under suitable conditions, alkenes are epoxidized,[8] alcohols are oxidized,[9] and methyl ketones are converted to methyl esters.[10]

Miscellaneous Uses.

Raney Nickel modified with tartaric acid and NaBr is an inexpensive catalyst, suitable for the large-scale reduction of methyl ketones and 1,3-dicarbonyl compounds to optically active alcohols in moderate enantiomeric excesses.[11]

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Sodium Bromite[1]

$NaBrO_2$

[7486-26-2] · $BrNaO_2$ · Sodium Bromite · (MW 134.89)

(selective oxidant; oxidizes secondary in preference to primary alcohols, and α,o-diols to lactones; sulfides oxidized to sulfoxides; can be used for Hofmann degradation)

Solubility: sol H_2O (28 g/100 mL at 0 °C; 91 g/100 mL at 100 °C); insol most organic solvents.

Form Supplied in: aqueous solution.

Analysis of Reagent Purity: titration with Na_3AsO_3.

Preparative Methods: the commercial reagent is concentrated under reduced pressure below -30 °C to produce the trihydrate. Anhydrous material is obtained by crystallization from aqueous 2N NaOH followed by drying (20 °C/5 mmHg).

Purification: crystallization as above.

Handling, Storage, and Precautions: refrigerate, thermally labile; handle in a fume hood.

Oxidation of Alcohols.

Sodium bromite oxidizes a range of secondary alcohols to the corresponding ketones (eq 1) in aqueous acetic acid.[2] If the reagent is used in the presence of ***Alumina***, other solvents can be used, in particular dichloromethane, thereby simplifying product isolation (eq 2).[3] Selective oxidation of a primary-secondary diol results in the formation of the hydroxy ketone (eq 3),[2] whereas oxidation of a primary alcohol produces the ester rather than the corresponding aldehyde (eq 4).[4] Following this pattern of reactivity, α,o-diols give good yields of lactones (eq 5).[4]

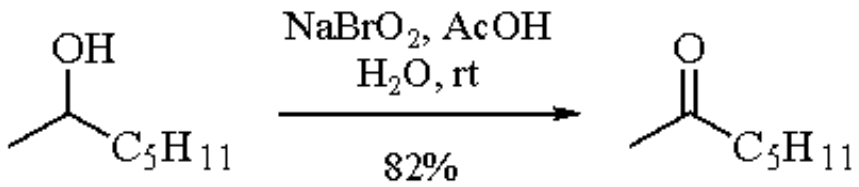

(1)

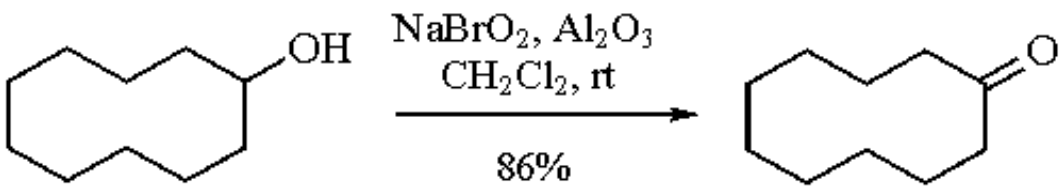

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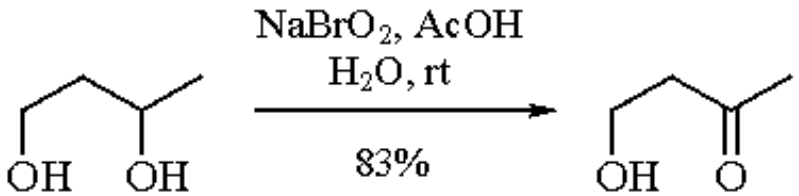

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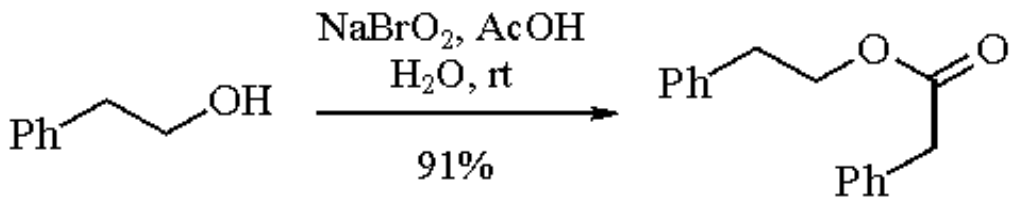

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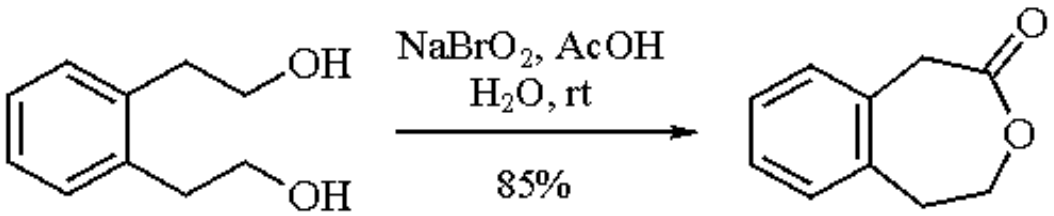

(5)

A catalytic quantity of metals and metal salts (such as Cu, Cu^{2+}, Fe^{3+}, Al^{3+}) has been reported to improve the oxidation of various types of alcohols to ketones, lactones, and diones.[5] Sodium bromite has been used as the stoichiometric oxidant in oxidations of alcohols catalyzed by *N*-oxyl compounds such as (**1**), conditions which allow for the oxidation of primary alcohols to aldehydes (eqs 6 and 7) or acids depending on the conditions (eq 8).[6] Primary alcohols are oxidized in preference to secondary alcohols (eq 9).

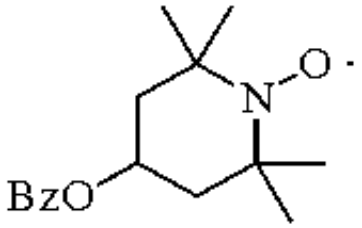

(1)

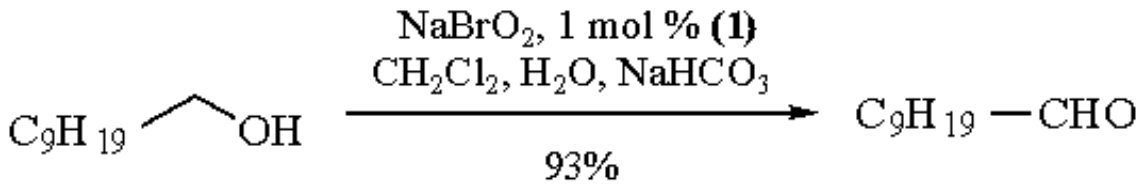

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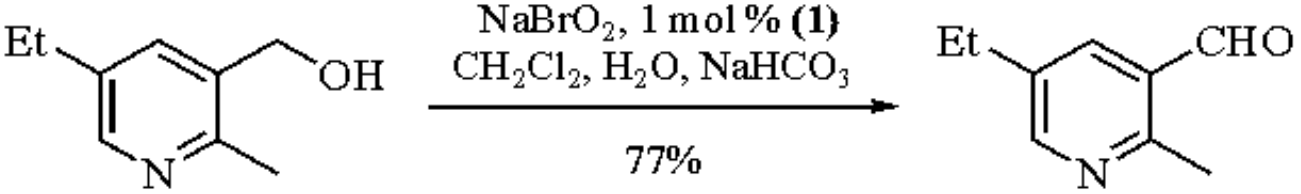

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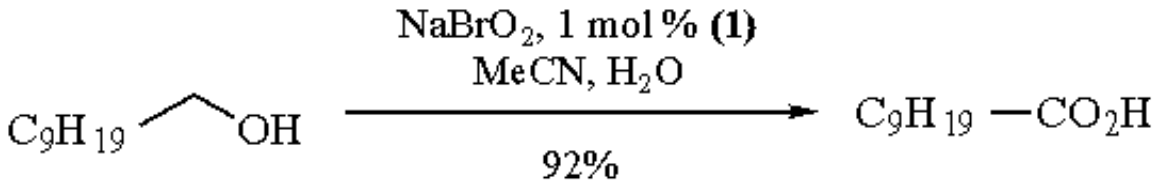

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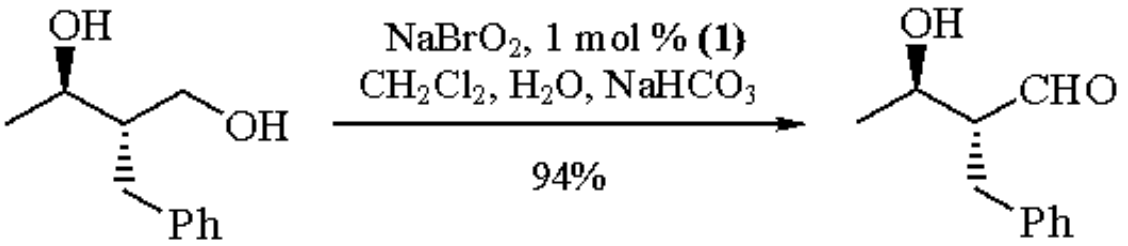

(9)

Oxidation of Sulfides to Sulfoxides.

The oxidation of sulfides to sulfoxides with sodium bromite is often highly selective, with little or no sulfone being produced, and it is possible to avoid oxidation of other potentially reactive functional groups (eqs 10 and 11).[2] This oxidation can be performed very effectively in the presence of wet ***Montmorillonite K10*** (eq 12).[7]

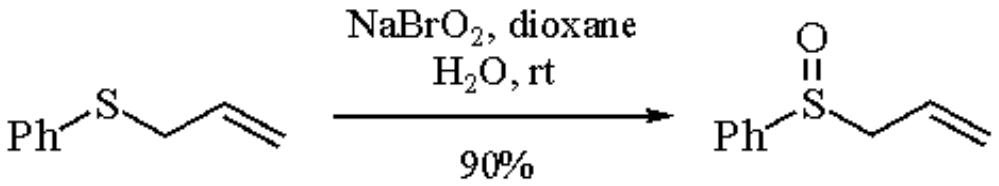

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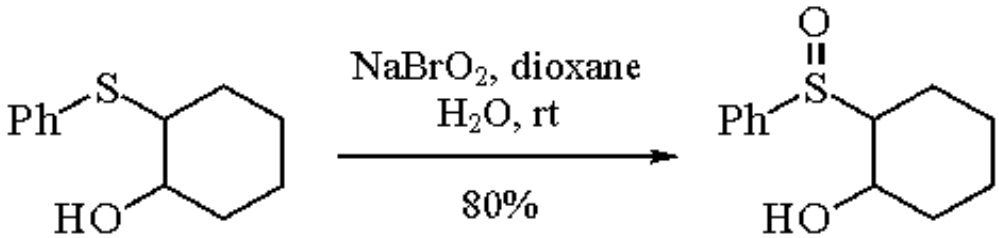

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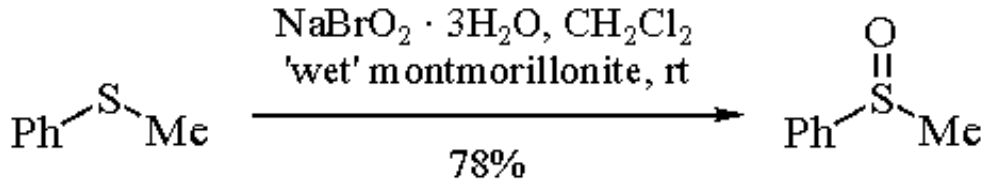

(12)

Other Applications.

Sodium bromite has been used for a number of other oxidations, including the generation of nitrile oxides for dipolar cycloadditions (eq 13),[8] the conversion of alkenes to α-bromo ketones (eq 14),[9] the preparation of *N*-bromoamides (eq 15),[10] and the Hofmann degradation (eq 16).[11]

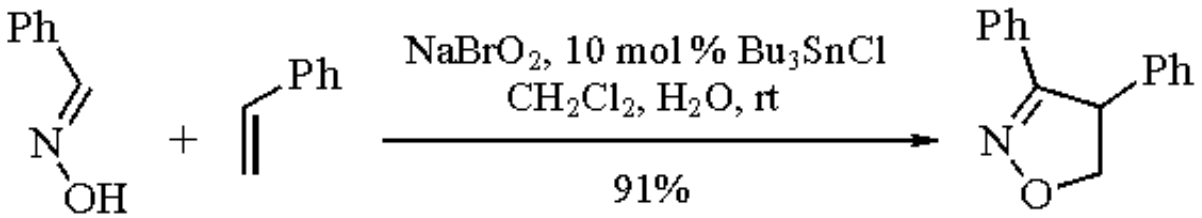

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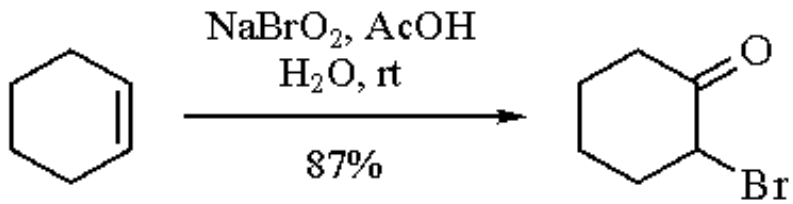

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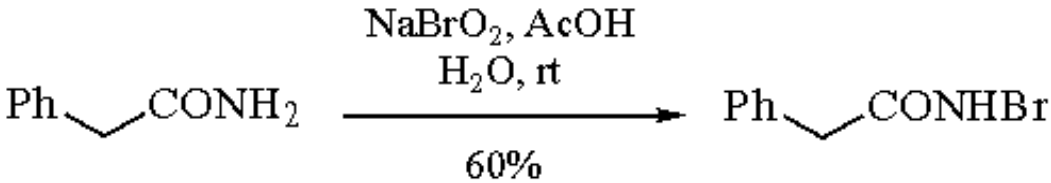

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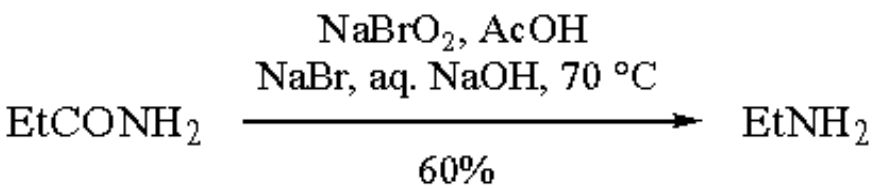

(16)

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Sodium Carbonate

Na_2CO_3

[497-19-8] · CNa_2O_3 · Sodium Carbonate · (MW 105.99)

(widely used base)

Physical Data: mp 851 °C; *d* 2.532 g cm^{-3}.

Solubility: sol glycerol, water.

Form Supplied in: white powder.

Handling, Storage, and Precautions: moderately toxic; severe irritant; noncombustible; stable; decomposition occurs slowly above 400 °C to give carbon dioxide and sodium oxide; incompatible with strong acids and aluminum; hygroscopic.

Selective Hydrolysis.

Cyanoethylated β-keto esters can be hydrolyzed with aqueous sodium carbonate to the corresponding δ-keto nitrile (eq 1).[1] The use of sodium hydroxide in this reaction leads to hydrolysis of the nitrile, affording the keto acid.

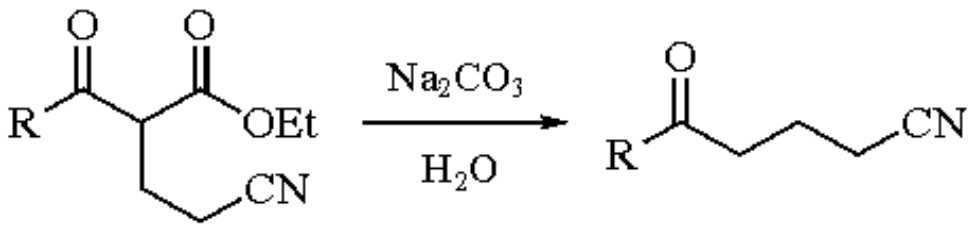

(1)

The selective hydrolysis of esters in the presence of acetyl-protected amines can be achieved with aqueous sodium carbonate (eq 2).[2]

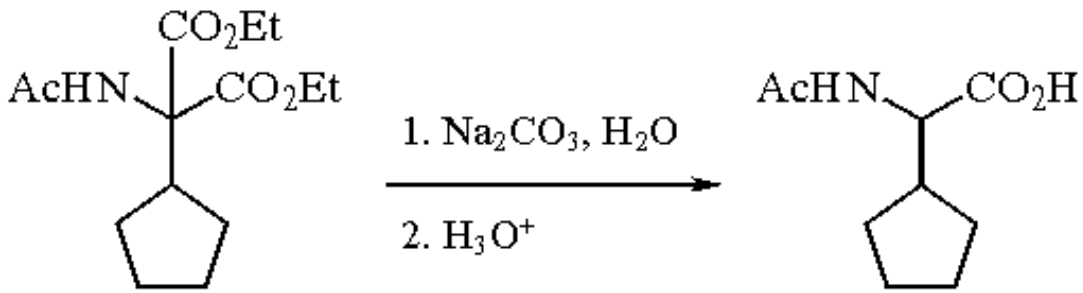

(2)

McFadyen-Stevens Reduction.

The decomposition of sulfonylhydrazines to aldehydes was achieved using sodium carbonate as base. The sulfonylhydrazine was heated in ethylene glycol to 150 °C, and 4-6 equiv of sodium carbonate added. The reaction is complete in approximately 30 s. This reaction has been applied to the formation of aromatic,[3] heterocyclic,[3] and aliphatic aldehydes (eq 3).[4]

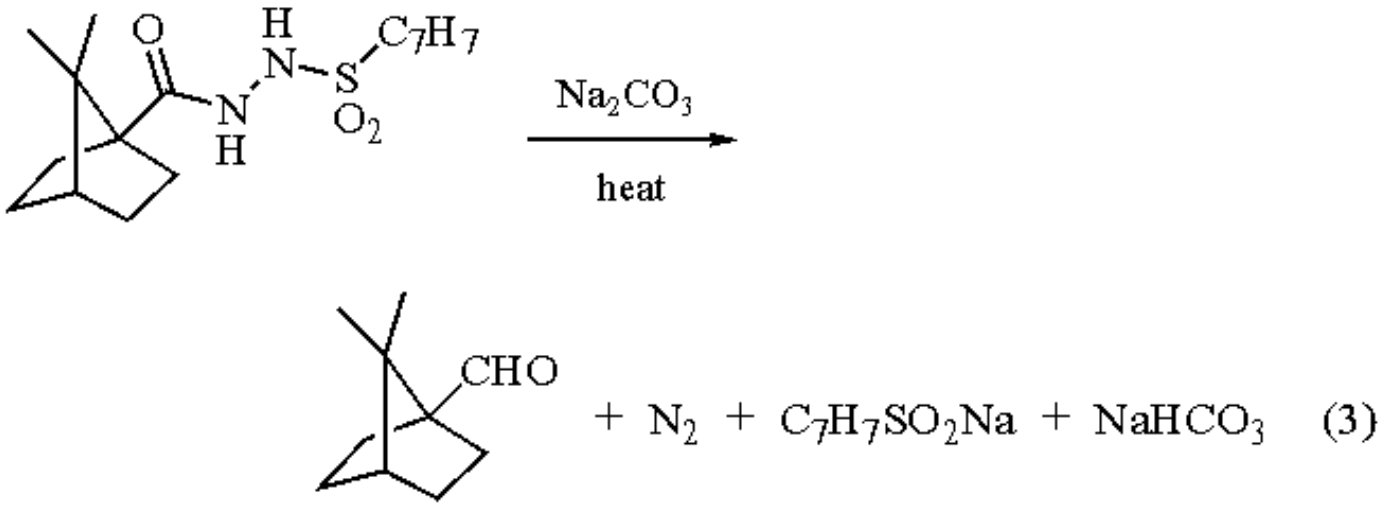

Carbon-Carbon Bond Forming Reactions.

The reaction of β-keto esters with α,β-unsaturated aldehydes in the presence of sodium carbonate and a phase-transfer catalyst afforded the Michael addition product (eq 4).[5] The use of sodium hydroxide in this reaction led to substantial decomposition.

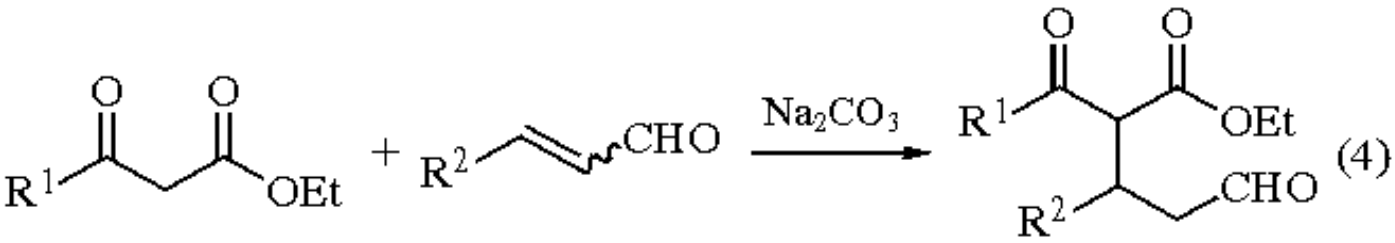

This methodology was used to prepare 3-oxo-5-phenyl-1-cyclohexene from ethyl acetoacetate and cinnamic acid (eq 5).[5] Under the same conditions, β-cyano esters and α,β-unsaturated aldehydes undergo Knoevenagel condensation (eq 6).[5]

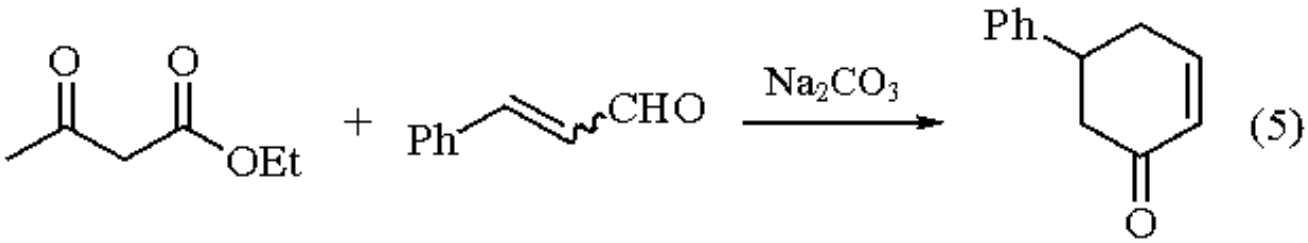

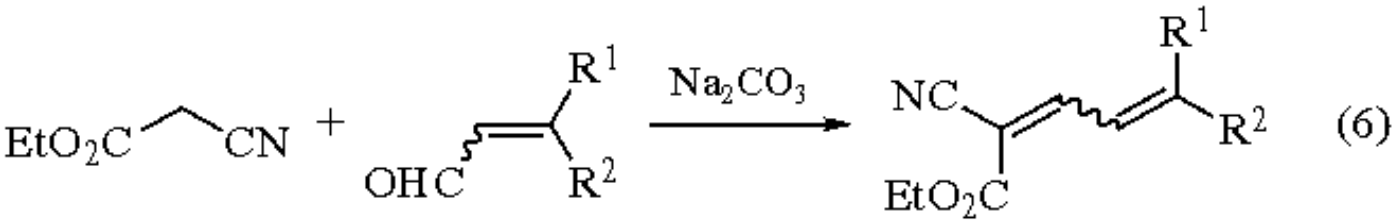

Hydrogenation.

Sodium carbonate is an effective acid scavenger for hydrogenations. The hydrogenation of *m*-nitro-*O*-benzoylmandelate with ***Raney Nickel*** and sodium carbonate in ethanol at 180 °C afforded the ethyl ester of *m*-aminophenylacetic acid (eq 7).[6] Other bases were found to be less effective in removing the benzoic acid, resulting in slow and incomplete reactions. Sodium carbonate is also used in the sodium hydrophosphite hydrogenations of many functional groups.[7]

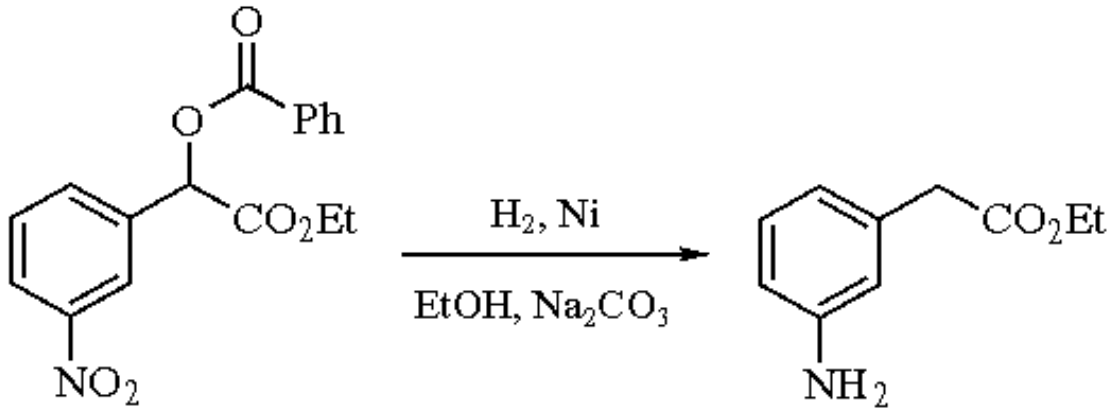

(7)

Synthesis of Phenyliodonium β-Diketonates.

β-Diketones react with ***(Diacetoxyiodo)benzene*** in the presence of sodium carbonate to afford phenyliodonium β-diketonates (eq 8).[8] Ozonolysis of the phenyliodonium β-diketonates provides an efficient synthesis of triketones.

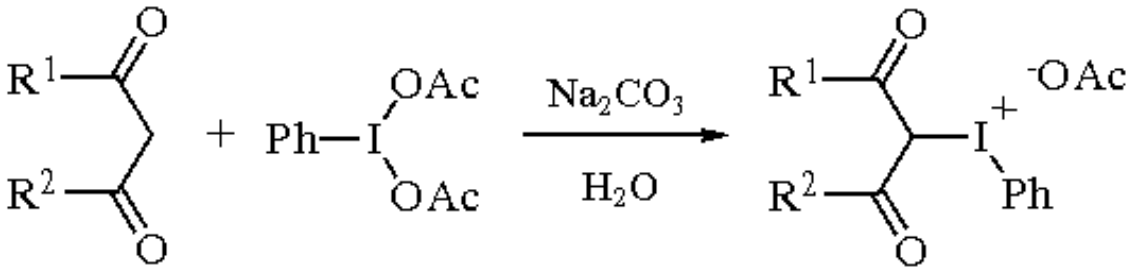

(8)

Other Applications.

Sodium carbonate is used in the alkylation of amines,[9] debromination,[10] hydrolysis,[11] imidazoline synthesis,[12] as a buffer,[13] and a neutralization agent.[14]

Related Reagents.

Barium Hydroxide; ***Cadmium Carbonate***; ***Calcium Carbonate***; ***Cesium Carbonate***; ***Lithium Carbonate***; ***Potassium Carbonate***; ***Potassium Hydroxide***; ***Sodium Hydroxide***.

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Sodium Chlorite[1]

$NaClO_2$

[7758-19-2] · $ClNaO_2$ · Sodium Chlorite · (MW 90.44)

(mild and selective reagent for the oxidation of all types of aldehydes to carboxylic acids at room temperature[16,17])

Physical Data: mp 180-200 °C (dec).

Solubility: 39 g/100 ml H_2O (17 °C); slightly sol MeOH.

Form Supplied in: white solid; widely available as technical grade material (ca. 80%; the rest is mainly NaCl).

Analysis of Reagent Purity: iodometric titration at pH 2.

Purification: technical grade material can be used as received. Crystallization from H_2O gives $NaClO_2.3H_2O$ which dehydrates at >37 °C.

Handling, Storage, and Precautions: decomposition at >175 °C is highly exothermic. The reagent is not shock sensitive unless contaminated with organic materials. Causes severe irritation or burns to skin and eyes. Acute oral LD_{50} 180 mg kg^{-1} (rat, 80% assay material).

Oxidation of Aldehydes to Carboxylic Acids.

First employed in cellulose chemistry,[2] the reagent is now widely used for the oxidation of saturated,[3-8] α,β-unsaturated,[9-15] aromatic,[8,13,16,17] and heteroaromatic[13] aldehydes to the corresponding carboxylic acids (eq 1). The high yields, selectivity, mild conditions, and ease of workup make this the method of choice for most RCHO to RCO_2H conversions. For example, with allylic primary alcohols[13] it is advantageous to carry out a two-step $MnO_2/NaClO_2$ process instead of a direct oxidation using Cr^{VI} or Ag^{I} because of higher purity and yield. The hypochlorite formed (eq 1) may interfere with the substrate or the product, or react with the reagent to give ClO_2 (eq 2), which also may have an adverse effect.

$$RCHO + HClO_2 \longrightarrow RCO_2H + HOCl \qquad (1)$$

$$HOCl + 2\,ClO_2^- \longrightarrow 2\,ClO_2 + Cl^- + OH^- \qquad (2)$$

To eliminate the various unwanted positive Cl species present, the reaction is therefore usually conducted in the presence of a scavenger (Table 1). The use of resorcinol has the drawback that the byproduct formed (4-chlororesorcinol) must be removed from the carboxylic acid in a separate step.

Table 1 The Reported Areas of Applicability and Functional Group Tolerances or Incompatibilities of Various ClO_2 Oxidation Procedures[a]

	Cl scavenger					
	H_2NSO_3H	Resor-cinol	$Me_2C=CHMe$	H_2O_2	DMSO	None
R CHO		(+)[3]	(+)[4 7]			(+)[8]
C=C CHO	(-)[15]	(+)[9,10]	(+)[11 14]	(+)[15]	(+)[15]	(-)[8]
C° C CHO, Het CHO				(+)[15,b]		
Ar CHO	(+)[16,17]	(+)[16]		(+)[15]	(+)[8,15]	(+)[8]
Isolated C=C		yes[10]	yes[7,23]	no[15]		
Conj. diene; acetal			yes[7]			
Cyclopropane			yes[23]			
s-OH		yes[9]	yes[7]			no[18]
R_2CH N_3			yes[19]			
p-HO Ar	yes[16,17]	yes[16]		no[15]	yes[15]	yes[8]
o-HO Ar	yes[17]			no[15]	yes[8]	no[8]
p-H_2N- or *p*-MeS Ar				no[15]		
MOM ether			yes[5]			
$PhCH_2$ ether		yes[3]	yes[12]			
TBDMS ether			yes[11,12]			
Allyl ether			yes[11]			
Ester		yes[3,9]	yes[4,7,14]			
Epoxy			yes[4]			
a-Boc-NH ester			yes[6]			
Ketone	yes[17]	yes[9]				yes[8]
b-Lactam, $ArNO_2$		yes[3]				

[a] (+) oxidized in good yield; (-) not oxidized or decomposes; 'yes' = compatible functionality; 'no' = functionality oxidized or compound decomposes. [b] Not pyrrole.

The alkene double bond is retained in oxidations of unsaturated alcohols. In an enantiospecific synthesis[19] of L-amino acids in >92% ee, intermediate chloroboronic esters (obtained from the alkyl Grignards) were directly oxidized to the acids, thus circumventing the problematic

prior conversion to the aldehydes (eq 3).

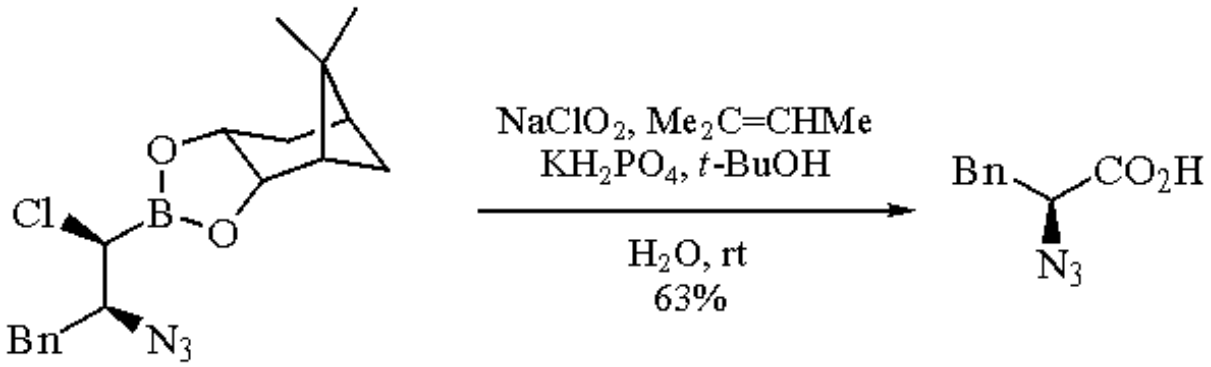

(3)

Other Oxidations.

Dithiocarbamates are oxidized to isothiocyanates,[20] ArSMe to ArSOMe,[21] RCH_2NO_2 to RCHO, and $R_2CH\text{-}NO_2$ to R_2CO (eq 4).[22]

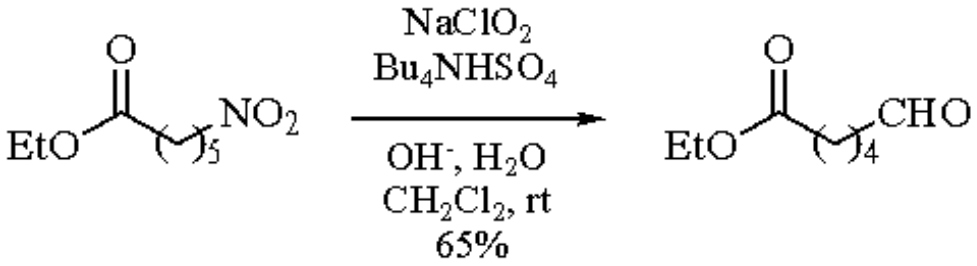

(4)

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Sodium Chlorodifluoroacetate

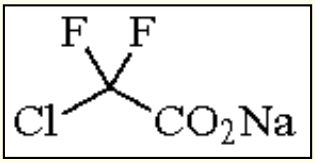

[1895-39-2] · $C_2ClF_2NaO_2$ · Sodium Chlorodifluoroacetate · (MW 152.46)

(generation of difluorocarbene and the synthesis of difluorocyclopropanes and difluoroalkenes)

Physical Data: mp 196-198 °C.

Solubility: sol DME, diglyme (0.60 g mL^{-1}), triglyme, DMF.

Preparative Methods: the salt is prepared by careful neutralization of 130.5 g (1.0 mol) of chlorodifluoroacetic acid in 300 mL of Et_2O with 53 g (0.5 mol) of anhydrous Na_2CO_3. The Et_2O and water are removed under reduced pressure. The salt is then dried in a vacuum desiccator over P_2O_5.[1]

Handling, Storage, and Precautions: is an irritant and is hygroscopic.

Cyclopropanation.

The thermal decomposition of sodium chlorodifluoroacetate produces difluorocarbene, which will react with alkenes to form the difluorocyclopropane. Cyclohexene reacts (eq 1) with the carbene to form the difluorocyclopropane in 11% yield.[2]

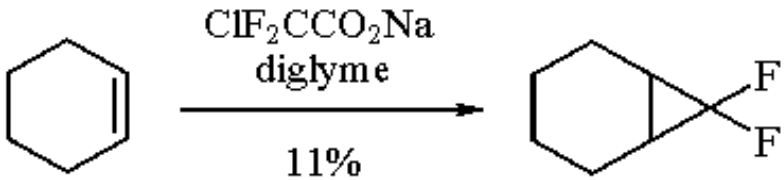

(1)

There are times when a change from the sodium salt to the lithium salt results in a higher yield of the cyclopropane (eq 2). In addition to the higher yields, the reaction with the lithium salt was also reported to be cleaner. No stereochemistry for the products of this reaction was reported.[3]

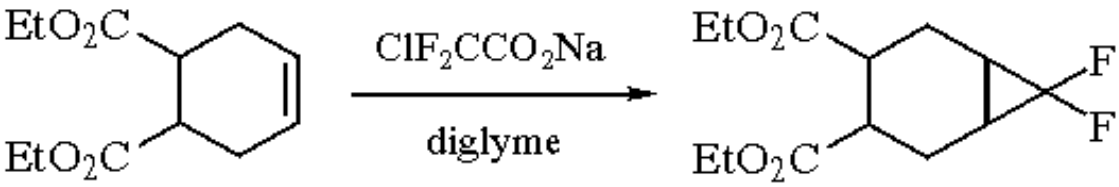

(2)

M = Na^+, 26 %; Li^+, 51%

A change from sodium to lithium can also alter the course of the reaction. The reaction of an *o*-quinone (eq 3) with the sodium salt produces the carbonate, while the lithium salt provides the hydroxy ketone. The exact reason for the different paths followed by the two salts is not known for certain. One explanation was that the sodium salt produced the difluorocarbene directly by a one-step α-elimination and then the carbene underwent a 1,4-addition to the *o*-quinone. The carbonate was then produced by hydrolysis, which would require only 0.05% water to be present in the diglyme.[4]

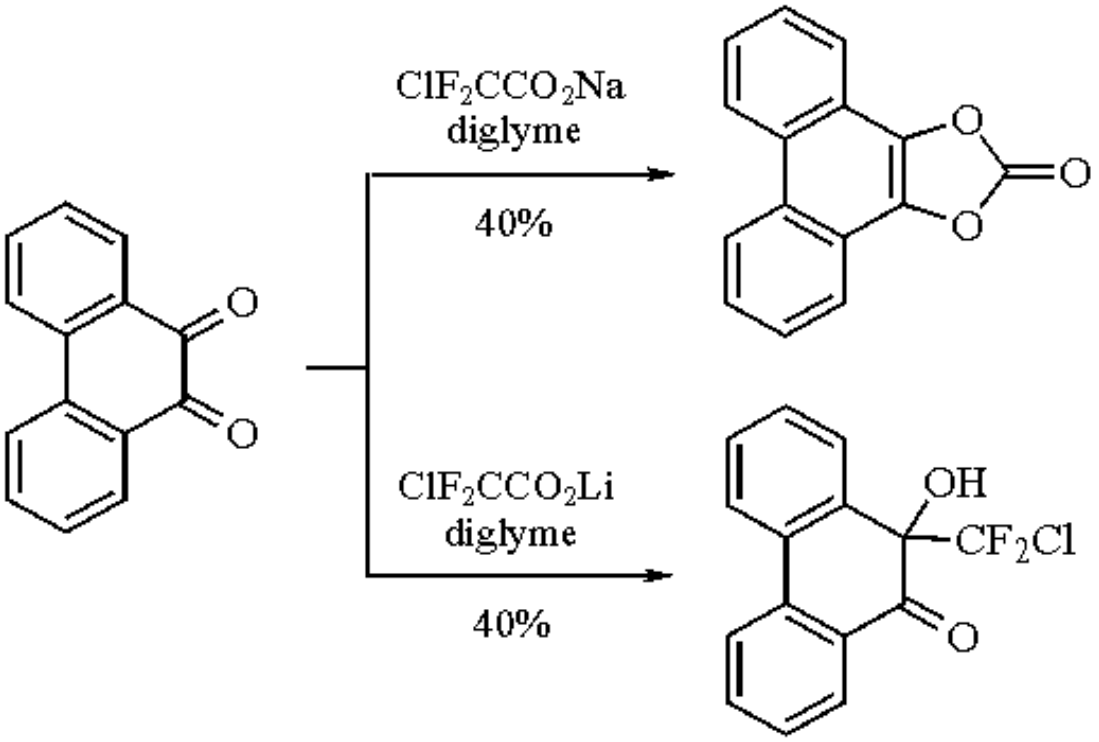

(3)

A 1,4-addition had been previously observed in the reaction of a *cisoid* β-methoxy enone (eq 4). This reaction affords the 1,4-adduct as a mixture of 3´-methoxy isomers.[5]

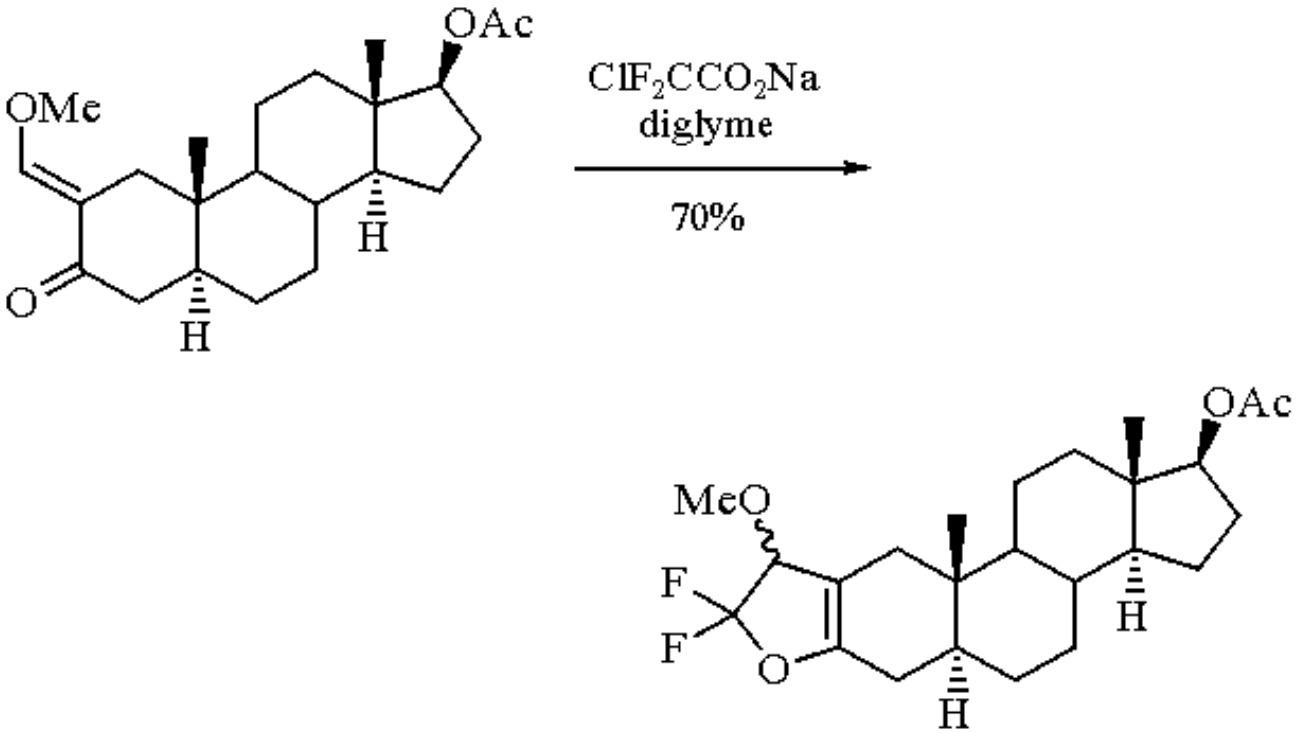

(4)

Transoid enones produce the cyclopropane derivatives. The α,β-unsaturated ketone (eq 5) only underwent addition at a temperature of 150 °C, even though the salt was observed to decompose at 125 °C.[6] In the case of a trienone (eq 6), the reaction selectively took place at the carbon-carbon double bond furthest removed from the carbonyl.[7]

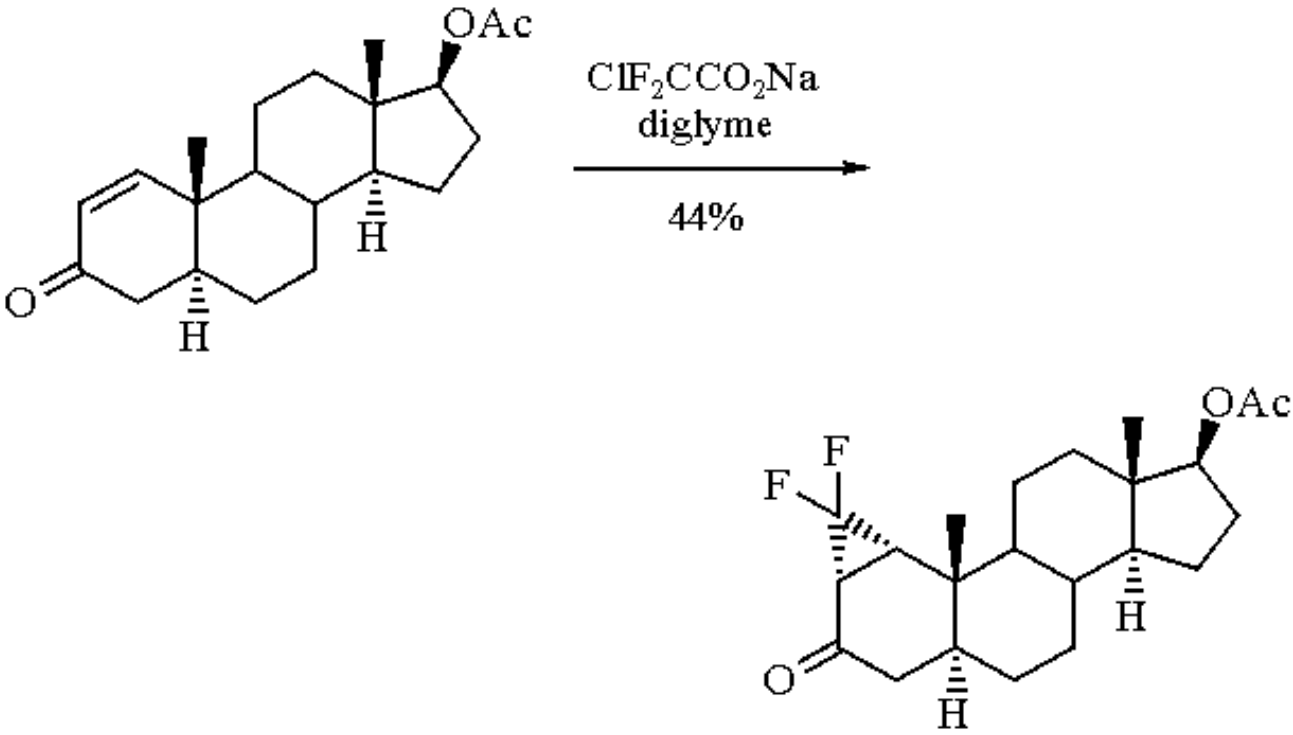

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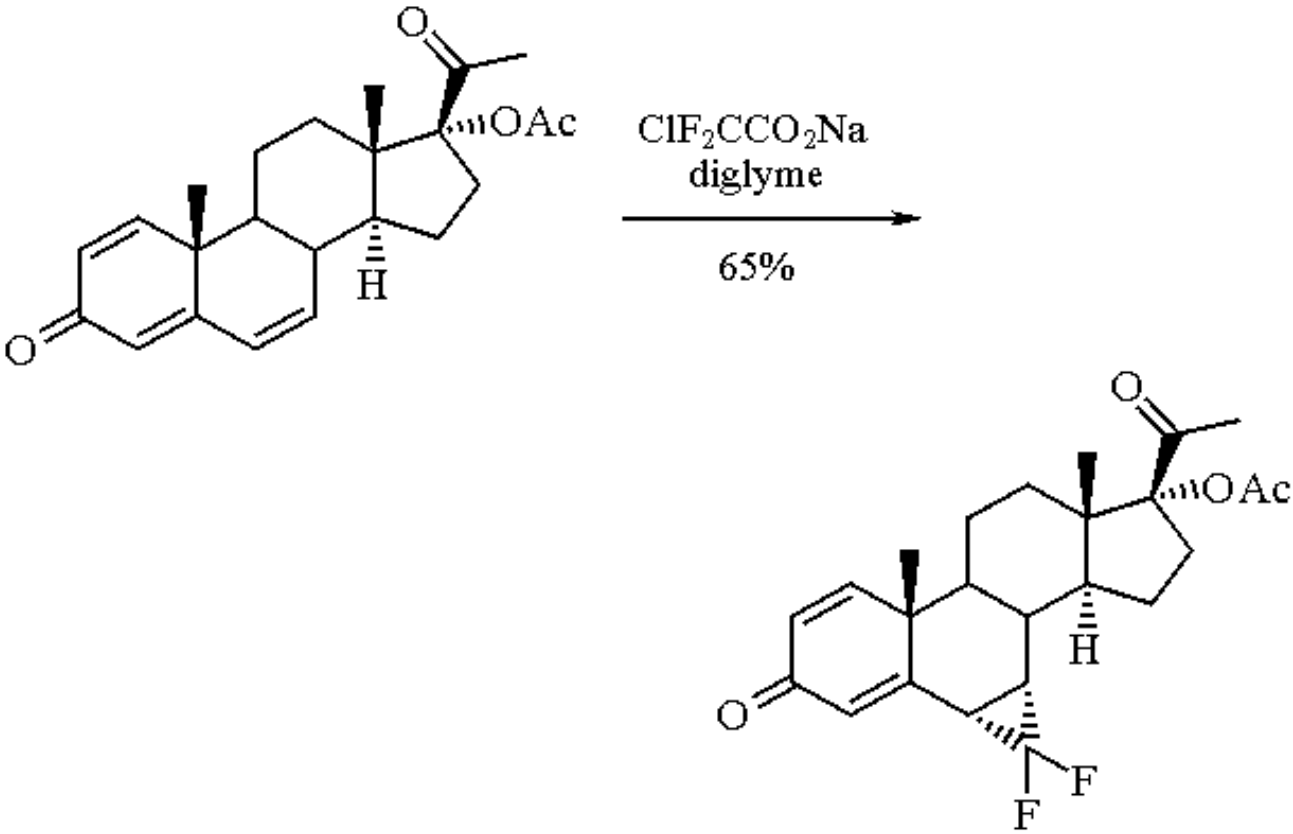

(6)

Similar regiospecificity has been seen in the reaction of a dienone (eq 7) from the prostaglandin area. Again, reaction at the more remote double bond was observed. The reaction was not stereoselective in this case, providing a mixture of stereoisomeric cyclopropanes.[8]

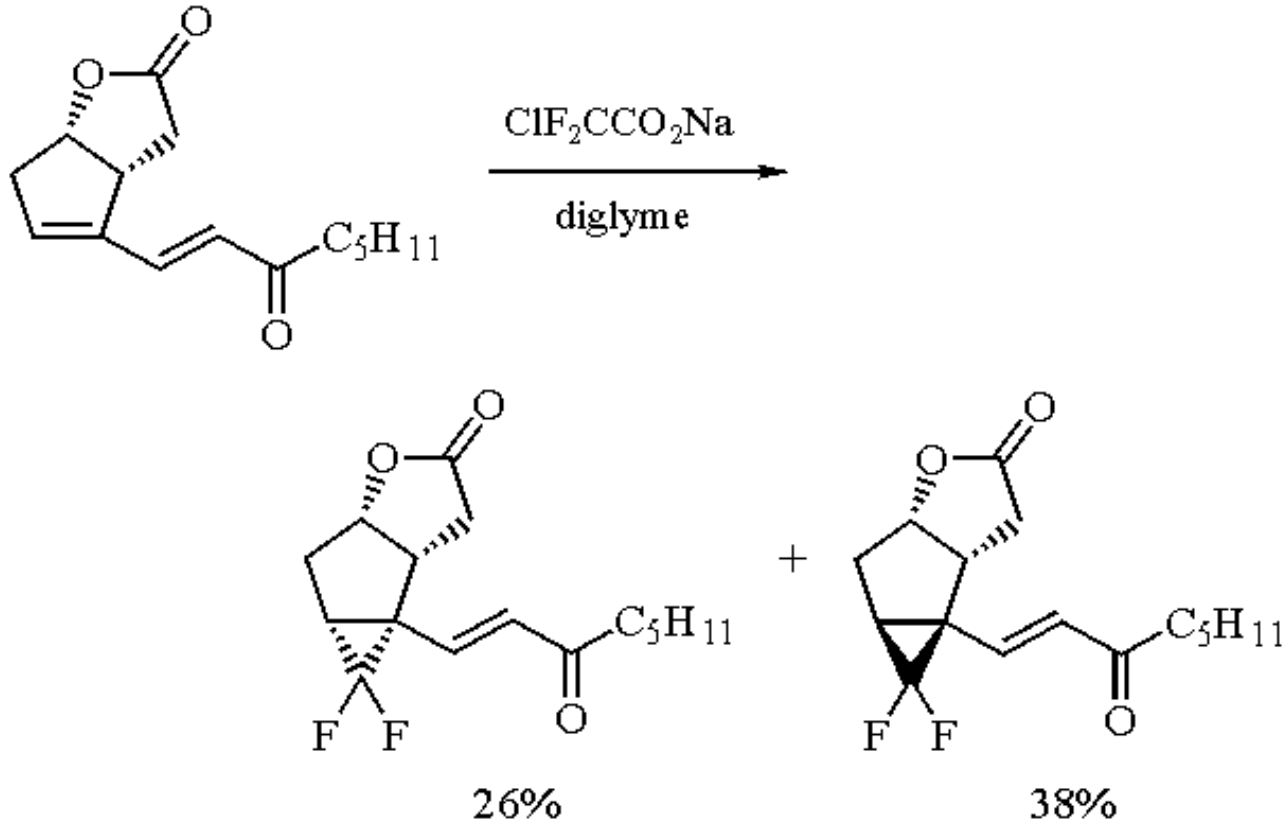

(7)

A mixture of cyclopropanes was also observed for the reaction of a diene lactone with the sodium salt in triglyme (eq 8). Cyclopropanation of the more remote double bond is again preferred.[9]

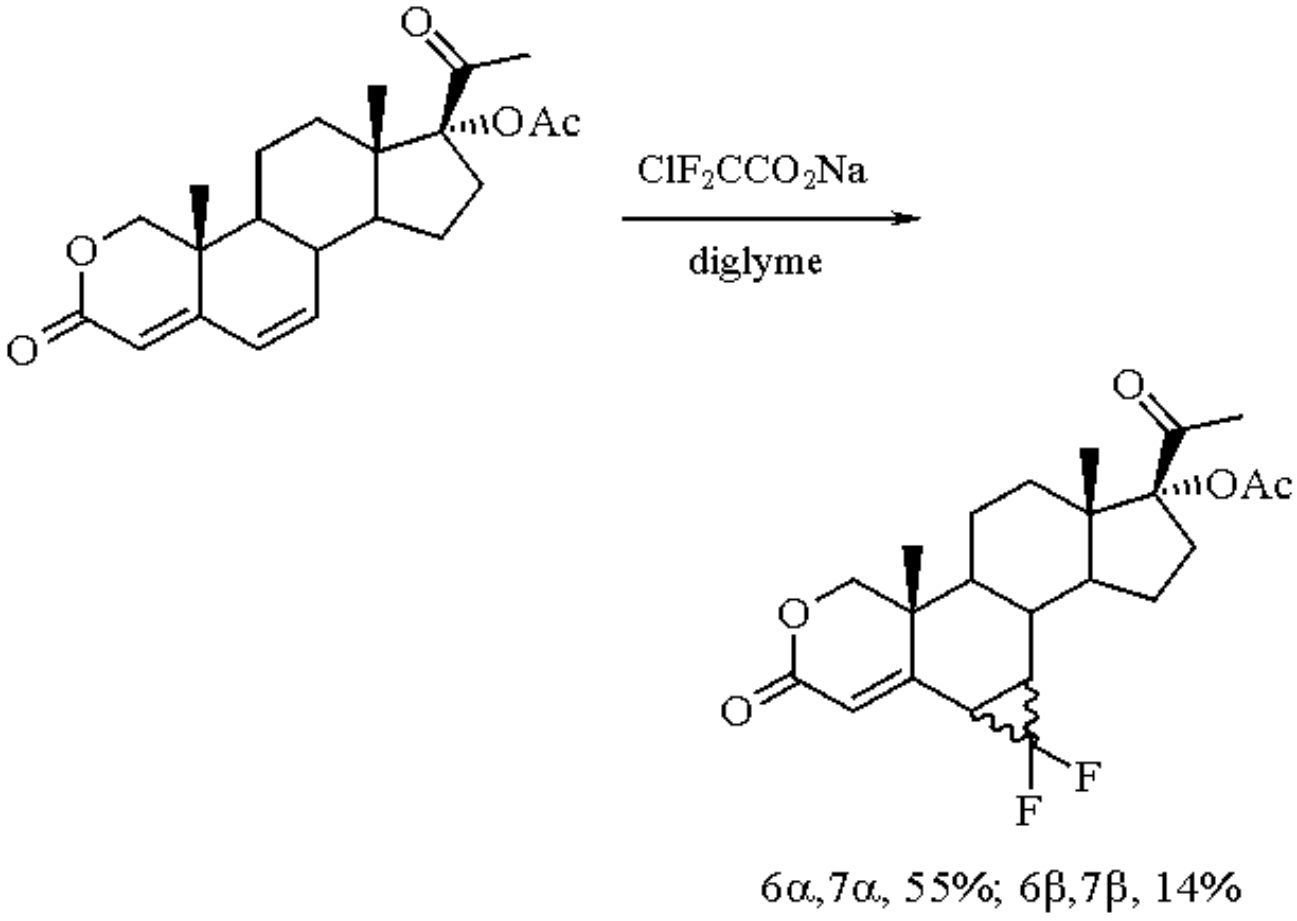

(8)

The selective difluorocyclopropanation of an α-methylene lactone over an unsaturated ketone was also achieved by reaction with sodium chlorodifluoroacetate. Helenalin acetate (eq 9) afforded a mixture of three products, all resulting from cyclopropanation of the α-methylene group.[10]

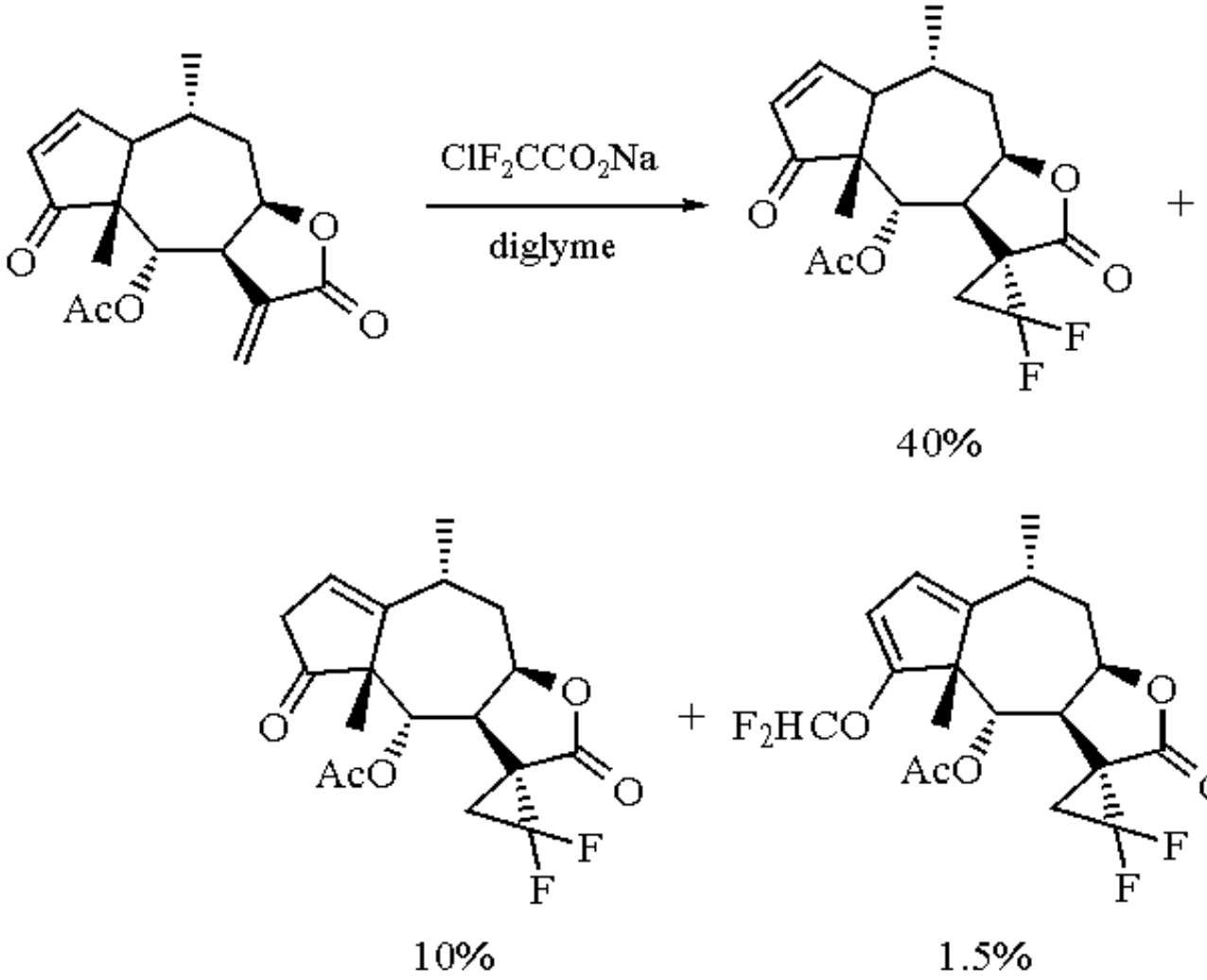

(9)

Enol acetates will react with difluorocarbene. The enol acetate of diisobutyl ketone (eq 10) leads to the formation of an unspecified 2:1 mixture of acetoxy difluorocyclopropanes.[11] The enol acetate (eq 11) was selectively cyclopropanated over the 5,6-double bond by controlling the amount of the sodium salt used (~10 mol equiv). The yield in this reaction was 34%, with 53% of the starting enol acetate being recovered.[12]

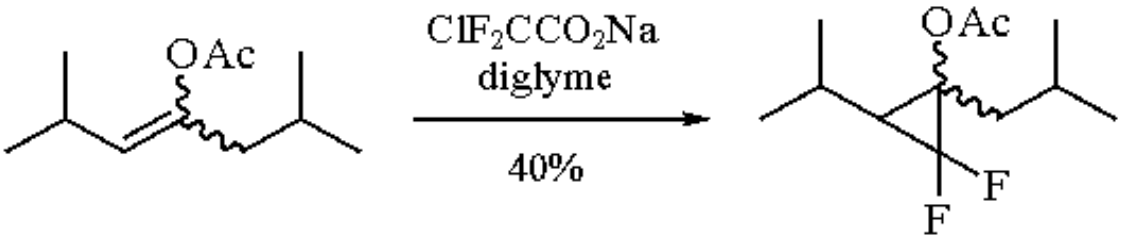

(10)

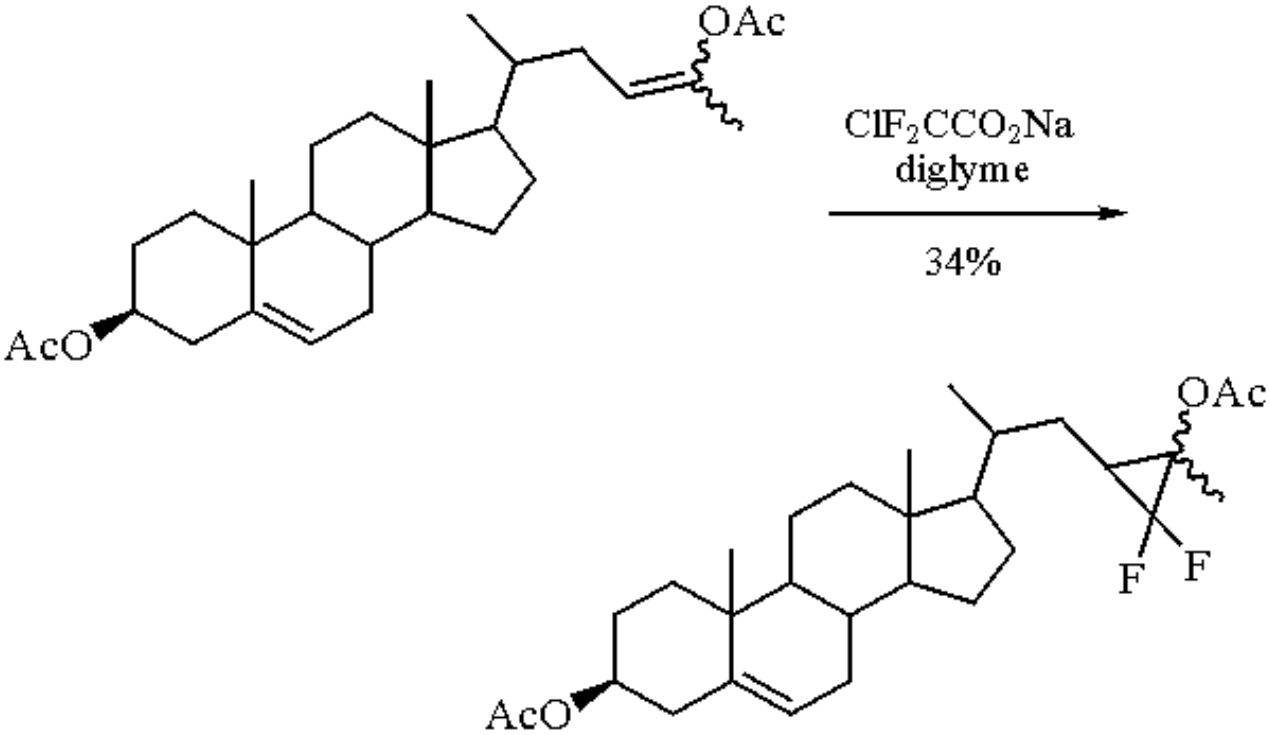

(11)

Silyl enol ethers react readily with difluorocarbene. In the case of an α,α-difluoro ketone, the enol acetate was unreactive toward difluorocarbene generated by thermal decomposition of the salt. The trimethylsilyl enol ether reacted rapidly with the carbene to produce the trimethylsilyloxycyclopropane (eq 12). Some of the enol ether underwent hydrolysis to return the ketone under the reaction conditions. The *t*-butyldimethylsilyl enol ether was stable to hydrolysis but reacted at a much slower rate that the trimethylsilyl enol ether.[13]

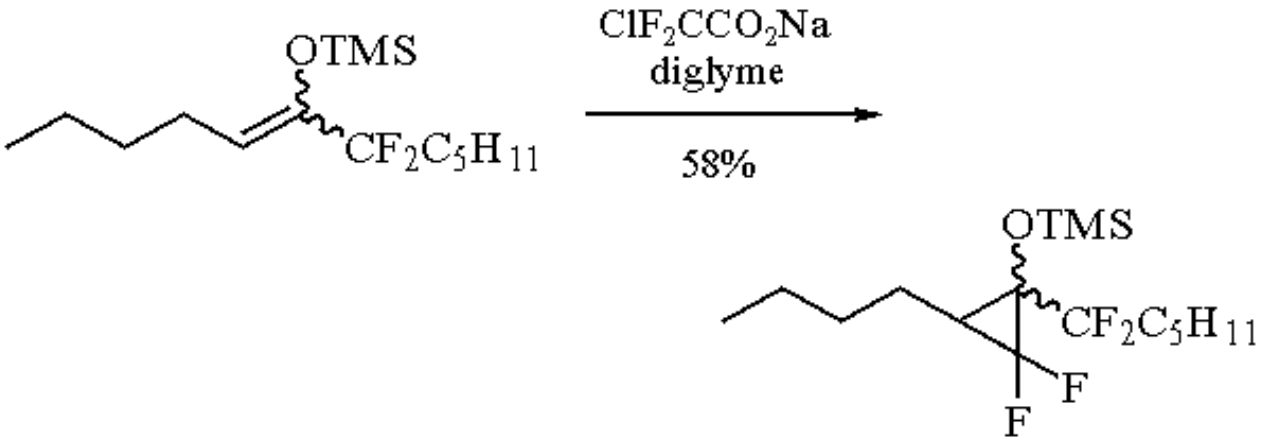

(12)

A comparison of methods for difluorocarbene formation has shown the thermal decomposition of the salt to be one of the two most effective for the cyclopropanation of butyl (*Z*)-propenyl ether (eq 13). The reaction of the enol ether and 2 equiv of the salt in triglyme at 165 °C for 0.5 h results in a 42% yield of the cyclopropane. The *cis* relationship of the groups on the double bond appears to be maintained in the final product. By using 4 equiv of the salt, the yield could be raised to 53%. The only method found to be superior in terms of yield was the fluoride ion-induced decomposition of (bromodifluoromethyl)triphenylphosphonium bromide.[14]

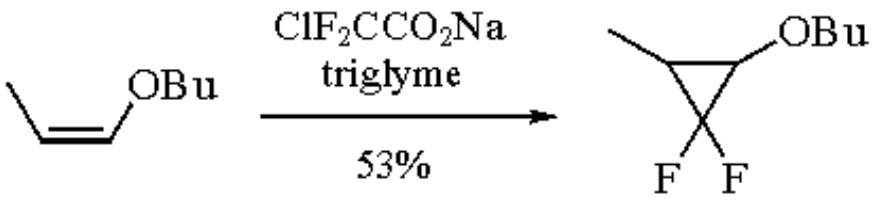

(13)

Wittig Alkenation.

In the presence of ***Triphenylphosphine***, sodium chlorodifluoroacetate produces the intermediate difluoro ylide. Treatment of benzaldehyde (eq 14) with this reagent combination delivers the difluoroalkene in 74% yield.[15] The reaction reportedly does not work well for ketones when triphenylphosphine is used. Substitution of ***Tri-n-butylphosphine*** and changing the solvent to *N*-

methylpyrrolidone allows cyclohexanone (eq 15) to be transformed in 46% yield to the difluoroalkene.[16]

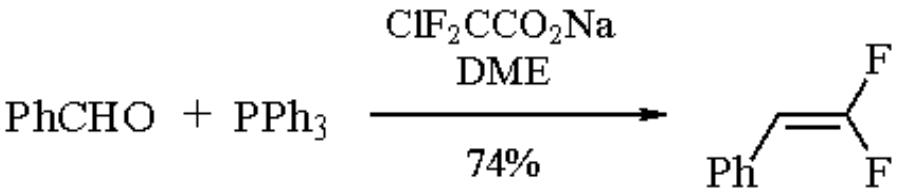

(14)

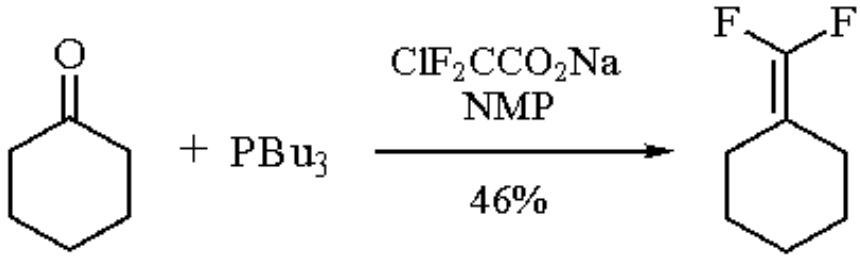

(15)

With fluorines on the α-carbon of the carbonyl, the reaction with the salt and triphenylphosphine in DME provides the perfluoroalkenes in good yield. Treatment of 2,2,2-trifluoroacetophenone under these conditions affords the alkene (eq 16) in 68% yield.[1] Changing solvents to DMF causes a dramatic increase in the rate of decomposition of the salt. It also results in an improvement in yield to 84%.[17]

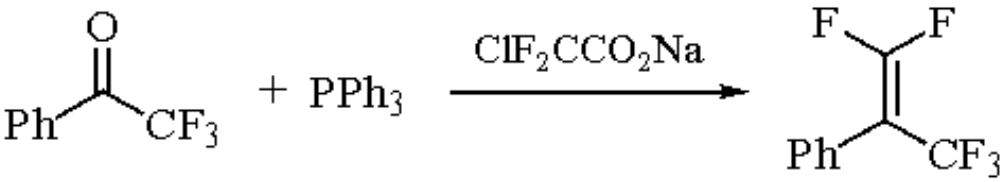

(16)

DME, 3 h	68%
DMF, 0.5 h	84%

When the perfluoroalkyl chain of the ketone is two or more carbons, fluoride ion-catalyzed rearrangement of the initially produced alkene can occur (eq 17). In these cases, the use of the lithium salt is recommended in order to suppress rearrangement.[18]

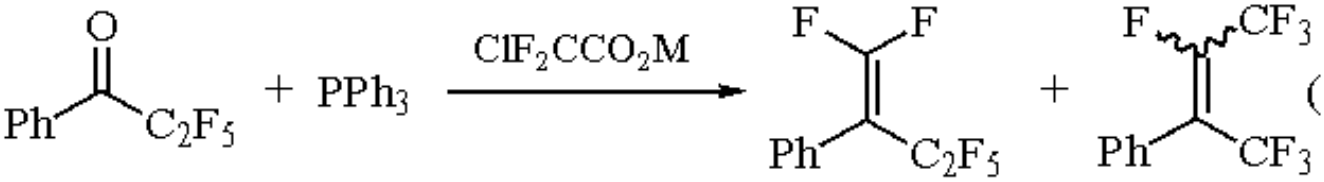

(17)

M = Na^+, 6.5 h	42%	2%
M = Na^+, 20 h	6%	54%
M = Li^+, 0.5 h	48%	0%

Miscellaneous.

The acyl hypochlorite of chlorodifluoroacetic acid can be prepared by reaction of the sodium salt and Cl-F at low temperature.[19] A substitution product has been isolated from the reaction of a tungsten dihydride with the salt.[20] The crystal structures of the products from the reaction of Vaska's complex, $IrCl(CO)(PPh_3)_2$, with the salt have also been reported.[21] An iridobetaine intermediate has been proposed to account for the observed products.[21c]

---

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Sodium Cyanide[1]

NaCN

[143-33-9] · CNNa · Sodium Cyanide · (MW 49.01)

(preparation of nitriles,[2] cyanohydrins,[3] α-amino nitriles,[4] methyleneamino acetonitriles;[5] catalyst for benzoin condensation[6])

Physical Data: mp 563.7 °C; vp_1 1.0 mmHg (817 °C).

Solubility: sol water; slightly sol ethanol; the aq soln is strongly alkaline and rapidly decomposes.

Form Supplied in: white powder with chunks; widely available.

Purification: Perrin and Armarego[7] for general procedure.

Handling, Storage, and Precautions: highly toxic; severe eye irritant; hygroscopic; readily absorbed through skin. Avoid breathing dust particles. Can be fatal if inhaled, swallowed, or absorbed through skin. Exposure can cause lung irritation and cyanosis (orl-hmn LDLo: 2857 μg kg^{-1}; orl-rat LD_{50}: 6440 μg kg^{-1}). Store in a dry area; use only in a fume hood. Incompatible with acids, strong oxidizing agents, and carbon dioxide. May decompose on exposure to moist air or water. Thermal decomposition produces toxic fumes of hydrogen cyanide, carbon monoxide, carbon dioxide, and nitrogen oxides.

Nitrile Synthesis.

Nitriles can be readily prepared from activated alcohols and halides by treatment with NaCN in an appropriate solvent. The reactivity of NaCN closely parallels ***Potassium Cyanide*** and the review of the latter reagent should also be considered for general reaction conditions. A difference in reactivity, however, was observed in the reaction of NaCN with alkyl chlorides in DMSO.[8] Increased yields and lower reaction times were seen for NaCN compared to KCN (eq 1). The conversion of alkyl bromides to nitriles using NaCN is accomplished under phase-transfer conditions employing primary, secondary, or tertiary amines as catalysts.[9]

$$\text{BuCl} \xrightarrow[93\%]{\text{NaCN, DMSO}\ 140\ ^\circ\text{C}} \text{BuCN} \qquad (1)$$

NaCN has also proved to be the most favorable reagent for the preparation of sodium dicyanocuprate. The cyanocuprate generated in situ reacts readily with vinyl and aryl halides to afford the corresponding nitrile (eq 2).[10] Aryl cyanation can also be effected with NaCN in the presence of catalytic ***Tetrakis(triphenylphosphine)palladium(0)***.[11] This method requires the use of neutral ***Alumina*** either as a support for NaCN or as a cocatalyst.

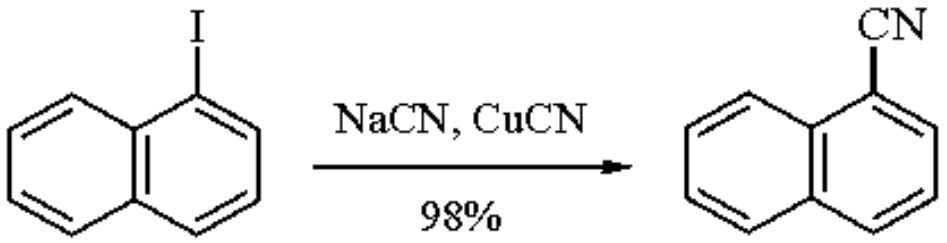

(2)

Aldehydes can be converted to nitriles by treating the *N*-tosyl imines with NaCN in HMPA (eq 3).[12] Tetrahydropyranyl ethers have also been shown to react with NaCN in the presence of ***Triphenylphosphine Dibromide*** to yield a nitrile (eq 4).[13]

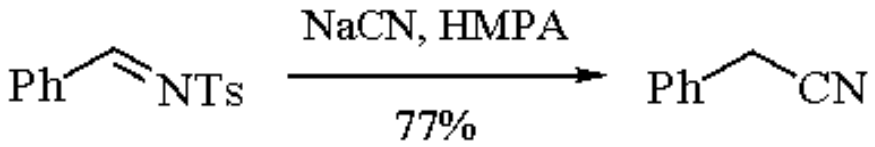

(3)

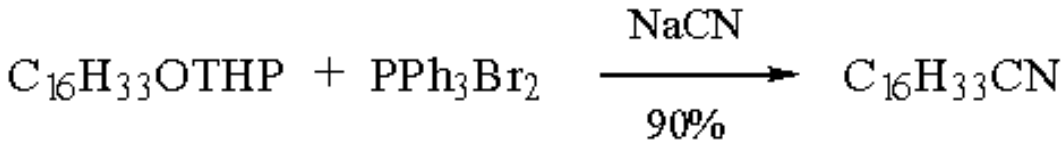

(4)

The reaction of NaCN with aryl nickel compounds also provides a facile route to aromatic nitriles in high yields (eq 5).[14]

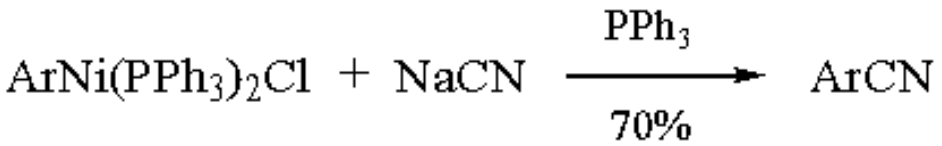

(5)

Cyanohydrin Synthesis.

Cyanohydrins are versatile synthetic intermediates which can be prepared by the reaction of NaCN with aldehydes, although benzoin condensations often compete. The reactions of NaCN with ketones,[15] acid chlorides,[16] and epoxides[17] are much more general. A novel preparation of aryl cyanohydrin esters involves treatment of an acid chloride with NaCN, ***Sodium Borohydride***, and catalytic ***Tetra-n-butylammonium Bromide*** (eq 6).[18] The cyanohydrin anion generated by reduction of the acyl cyanide is immediately captured by any anhydrides or acid chlorides present.

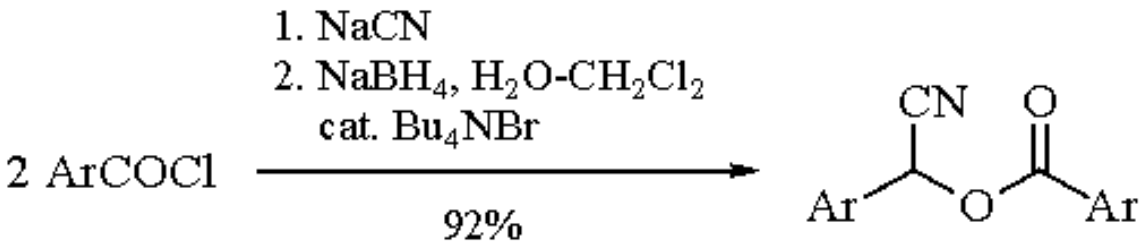

(6)

α-Amino Nitriles.

Cyclopropane hemiacetals can undergo a one-pot modified Strecker synthesis under sonication to provide α-amino nitriles (eq 7).[19] The reaction is high yielding and does not suffer significant polymerization or ring-opening side reactions. Since the cyanide group is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids.

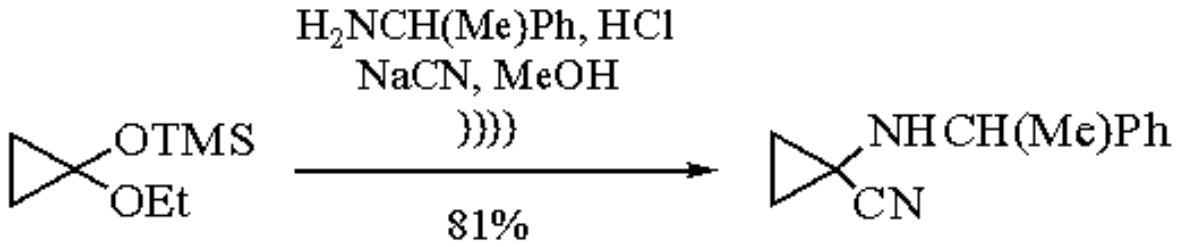

(7)

Acyl Cyanides.

α-Cyanoalkyl aryl ketones can be obtained from arylhydrazones by heterogeneous reaction with aq NaCN, an inert organic solvent, and acetic acid in the presence of air with catalytic quaternary ammonium salts (eq 8).[20] Air oxidation of the initial adduct is followed by alkaline-induced decomposition affording the α-cyanoalkyl ketone.

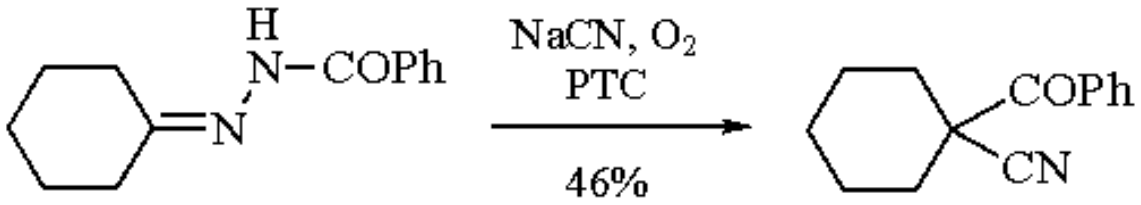

(8)

Ring Opening/Forming.

NaCN in DMSO has been used to nucleophilically open geminally activated cyclopropanes (eq 9).[21] Conversely, the reaction of NaCN on a dimethylene heptanedionate yields a cyano-oxobicyclo[3.2.1]octanecarboxylate via a novel double-ring closure (eq 10).[22]

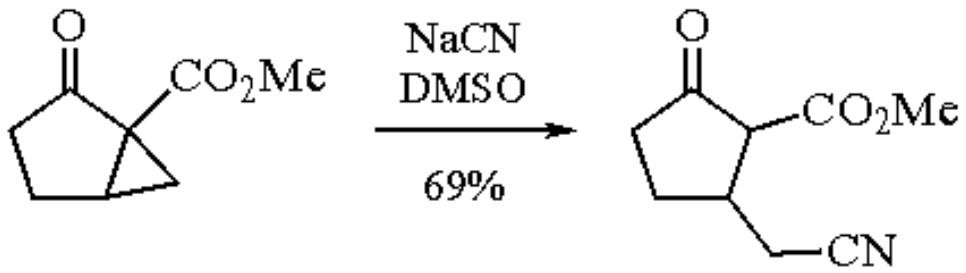

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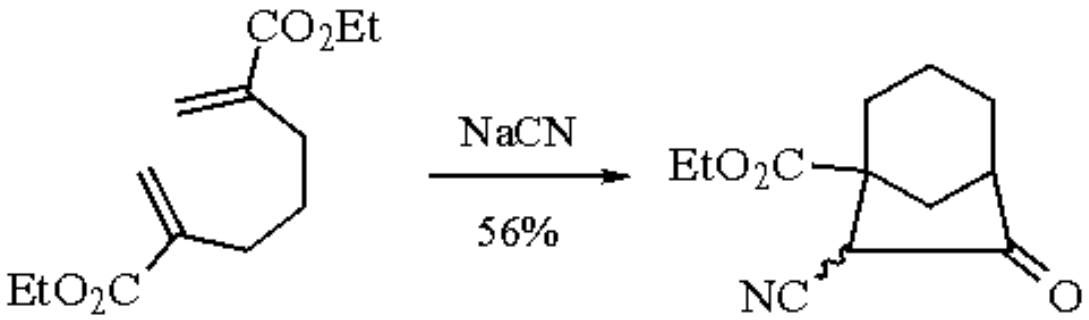

(10)

Reducing Agent.

Deethoxycarbonylation of geminal diesters can be effected with NaCN in DMSO (eq 11).[23] The same reaction in HMPA can selectively cleave methyl esters in the presence of ethyl esters.[24]

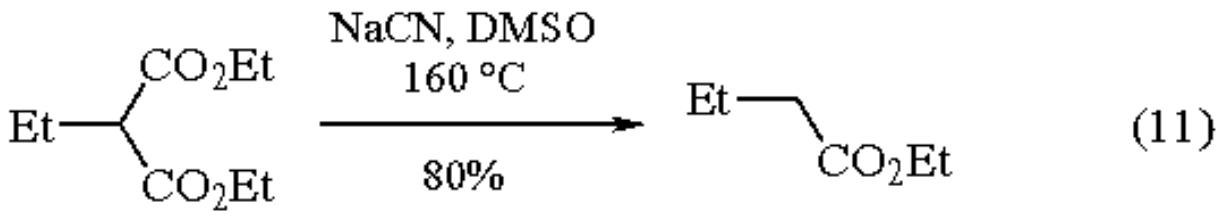

(11)

The reaction of benzil with NaCN in DMSO has been shown to produce a *trans*-α,α´-stilbenediol dibenzoate (eq 12).[25] The proposed mechanism assumes cleavage of the central C-C bond in benzil, generating a resonance stabilized carbanion. In the presence of a proton donor this carbanion is forced to attack a second benzil molecule, forming the stilbene product.

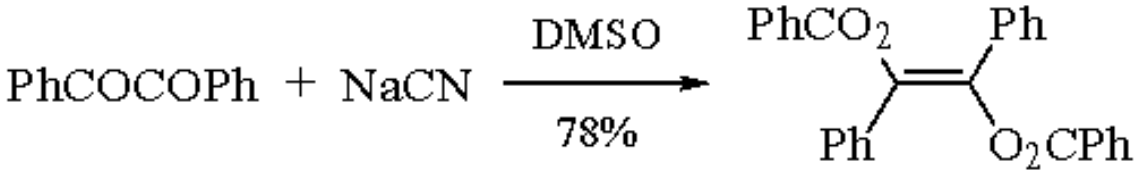

(12)

NaCN has also been used in the desulfurization of dialkyl disulfides in DMSO or DMF to give the corresponding monosulfide (eq 13).[26] Under similar conditions, thiophenols react with NaCN to afford methyl thioethers (eq 14).

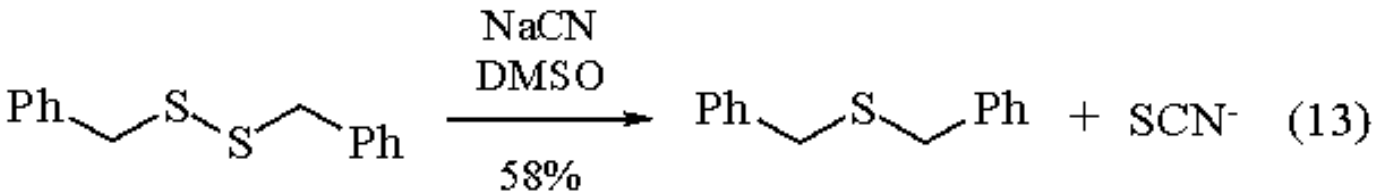

(13)

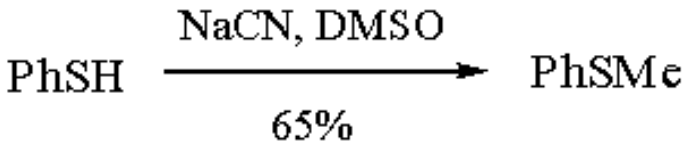

(14)

Oxidations.

The oxidation of α,β-unsaturated aldehydes to the corresponding methyl esters can be accomplished with NaCN (eq 15).[27] The cyanohydrin generated in situ is susceptible to further oxidation by ***Manganese Dioxide*** to an acyl cyanide, leading finally in an alcoholic medium to an ester. Aside from the simplicity and convenience of this procedure, the high yield and lack of *cis-trans* isomerization of the α,β-alkenic linkage is also noteworthy compared to traditional methods such as ***Silver(I) Oxide*** oxidation.

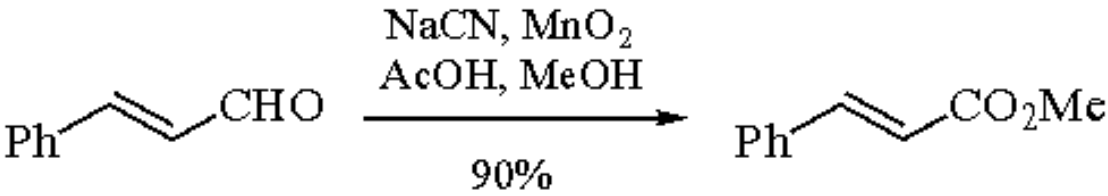

(15)

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Sodium Cyanoborohydride[1]

$NaBH_3CN$

[25895-60-7] · CH_3BNNa · Sodium Cyanoborohydride · (MW 62.85)

(selective, mild reducing reagent for reductive aminations of aldehydes and ketones, reductions of imines, iminium ions, oximes and oxime derivatives, hydrazones, enamines; reductive deoxygenation of carbonyls via sulfonyl hydrazones, reductions of aldehydes and ketones, polarized alkenes, alkyl halides, epoxides, acetals, and allylic ester groups)

Physical Data: white, hygroscopic solid, mp 240-242 °C (dec).

Solubility: sol most polar solvents (e.g. MeOH, EtOH, H_2O, carboxylic acids) and polar aprotic solvents (e.g. HMPA, DMSO, DMF, sulfolane, THF, diglyme); insol nonpolar solvents (e.g. ether, CH_2Cl_2, benzene, hexane).

Form Supplied in: widely available; the corresponding deuterated (or tritiated) reagent is available via acid-catalyzed exchange with D_2O (or T_2O).[1a,2]

Handling, Storage, and Precautions: store under dry N_2 or Ar.

Functional Group Reductions: General.

The chemoselectivity available with $NaBH_3CN$ is remarkably dependent on solvent and pH. Under neutral or slightly acidic conditions (pH > 5), only iminium ions are reduced in protic and ether (e.g. THF) solvents.[2] Most other functional groups including aldehydes, ketones, esters, lactones, amides, nitro groups, halides, and epoxides are inert under these conditions.

Reductive Aminations.

The relative inertness of aldehydes and ketones toward $NaBH_3CN$ at pH > 5 allows reductive aminations with amine and amine derivatives (usually in MeOH) via in situ generation of iminium ions which are then reduced to amines (eqs 1 and 2).[2-4] This protocol is compatible with most other functional groups, can be used to prepare N-heterocycles with stereochemical control (eqs 3 and 4),[5,6] and serves as a methylation process using CH_2O as the aldehyde (eq 5).[7,8] For difficult cases (e.g. aromatic amines, hindered and trifluoromethyl ketones), yields may be greatly improved by prior treatment of the carbonyl and amine with ***Titanium(IV) Chloride*** (eq 6)[9] or ***Titanium Tetraisopropoxide***.[10a] A reagent system prepared from $NaBH_3CN$ and ***Zinc Chloride*** also is also effective for reductive aminations[10b] (see also ***Sodium Triacetoxyborohydride*** and ***Tetra-n-butylammonium Cyanoborohydride***).

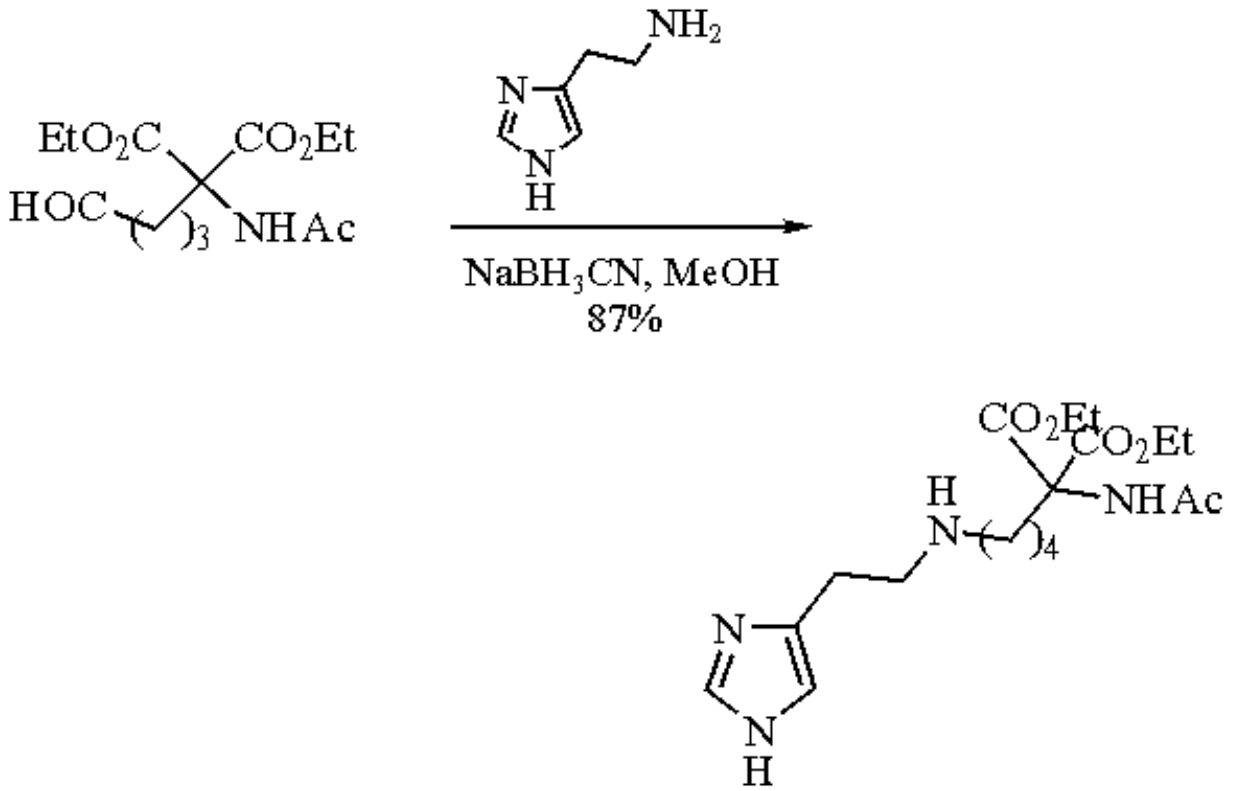
EtO2C
CO2Et
HOC
NHAc
NH2
N
N
H
NaBH3CN, MeOH
87%
CO2Et
CO2Et
H
N
NHAc
N
N
H

(1)

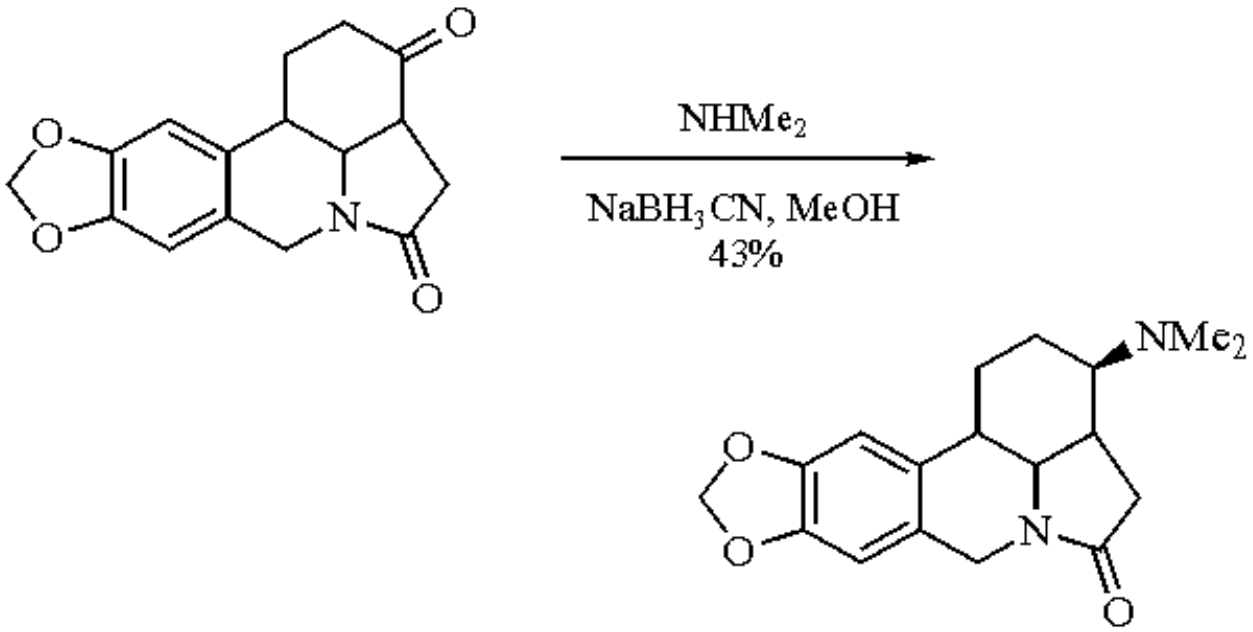
O
O
O
N
O
NHMe2
NaBH3CN, MeOH
43%
NMe2
O
O
N
O

(2)

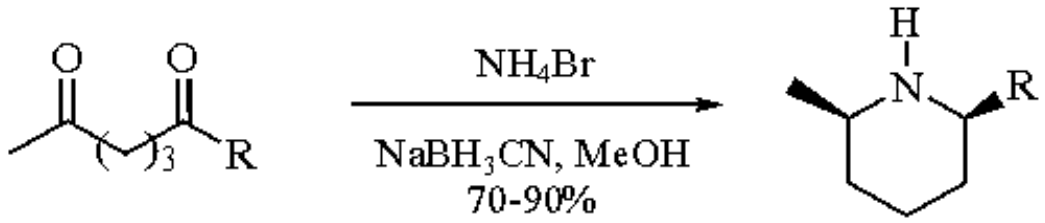
O
O
R
NH4Br
NaBH3CN, MeOH
70-90%
H
N
R

(3)

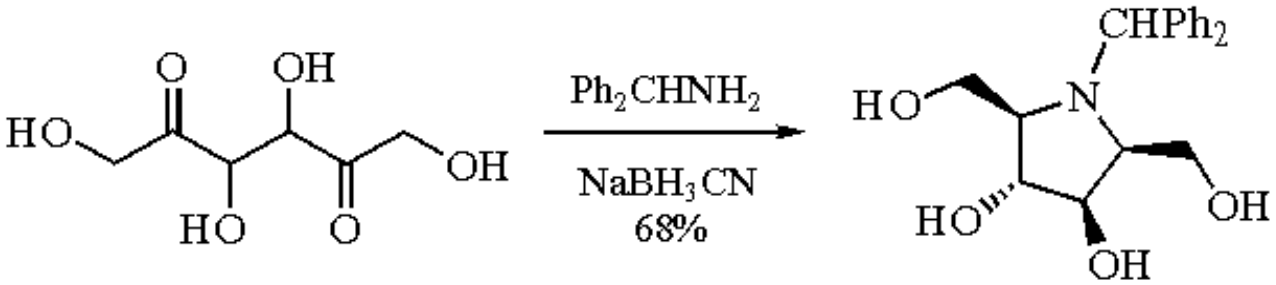
O
OH
HO
OH
HO
O
Ph2CHNH2
NaBH3CN
68%
CHPh2
HO
N
HO
OH
OH

(4)

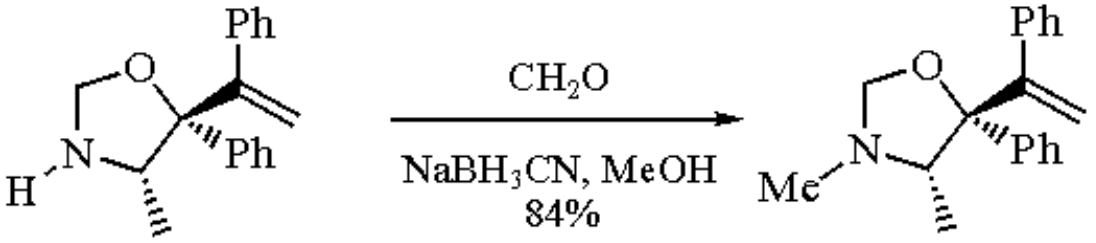

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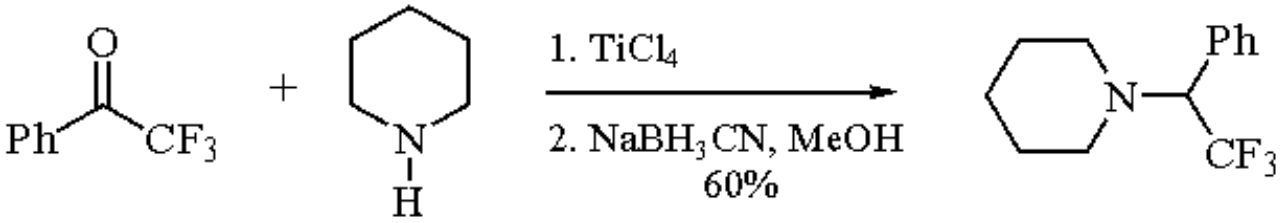

(6)

Reductions of Imines and Derivatives.

Preformed imines (eq 7),[2,11,12] iminium ions (eq 8),[2,11,13] oximes (eq 9),[2,14] oxime derivatives (eqs 10 and 11),[15,16] hydrazones (eq 12),[17] and other *N*-heterosubstituted imines (eqs 13 and 14)[18,19] are reduced to the corresponding amine derivatives by $NaBH_3CN$, usually in acidic media (see also ***Lithium Aluminum Hydride*** and ***Sodium Borohydride***).

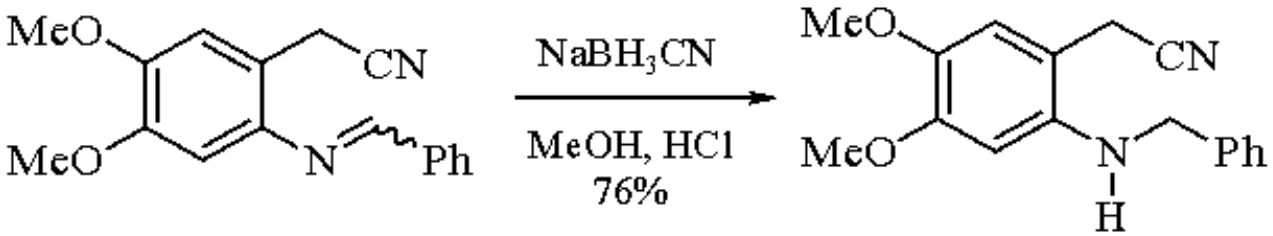

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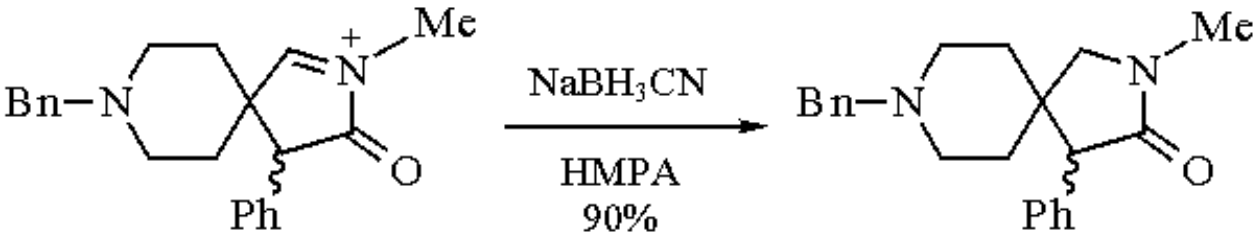

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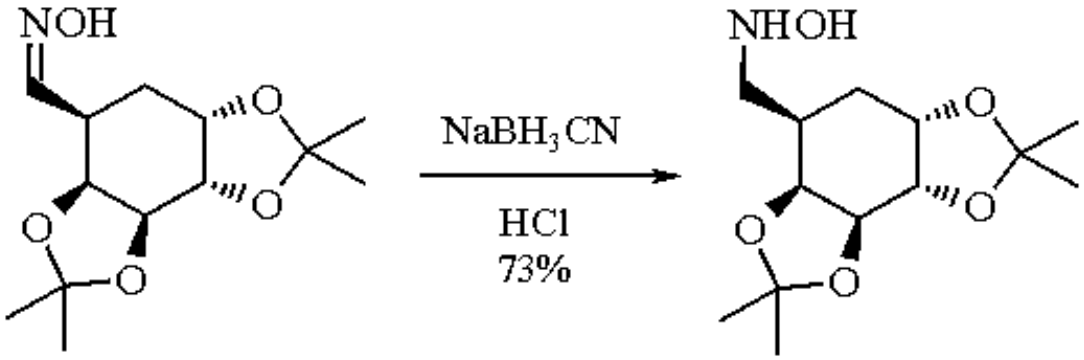

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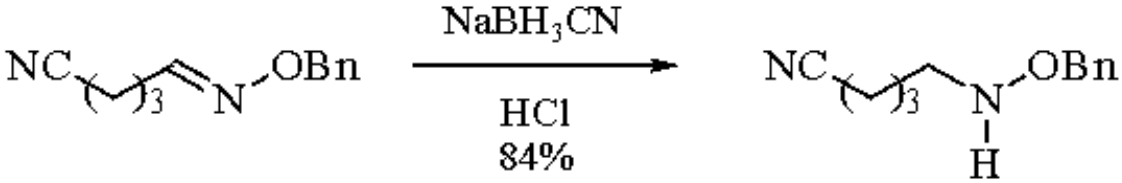

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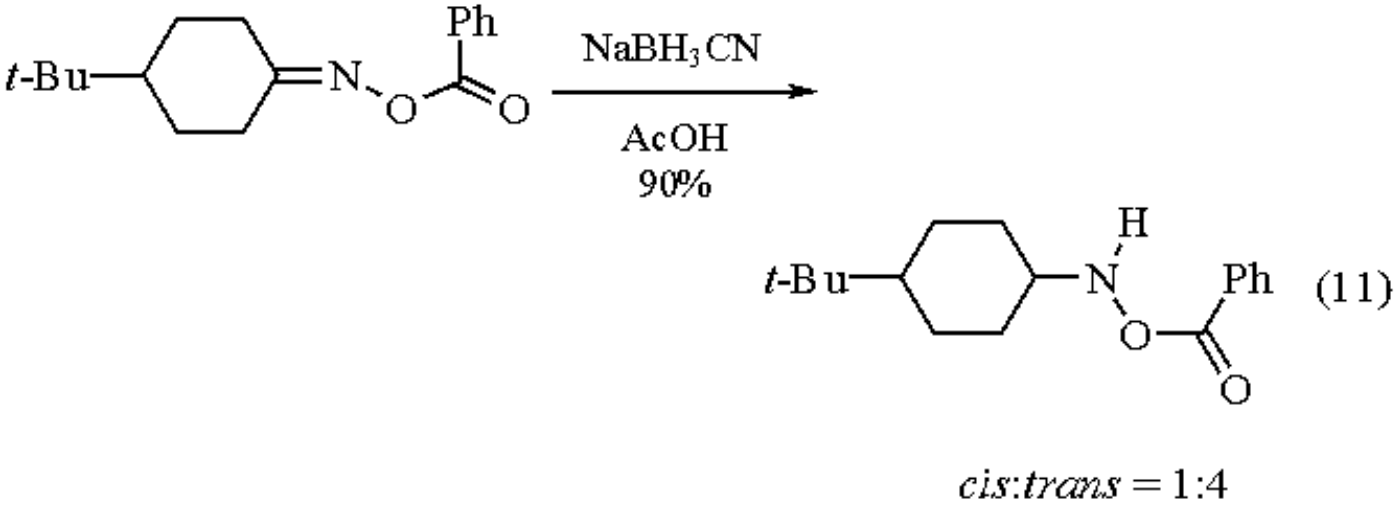

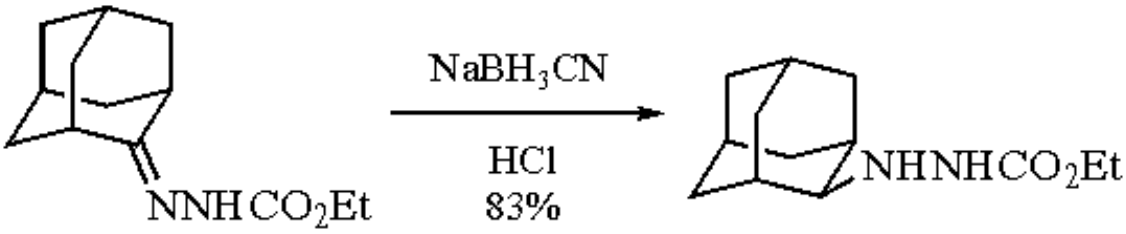

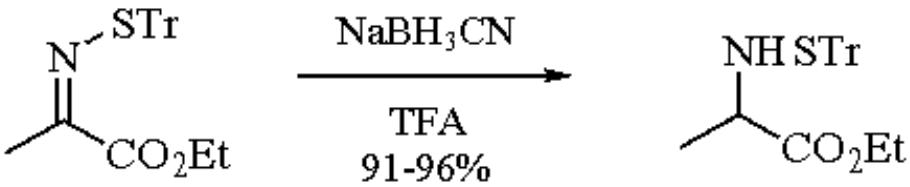

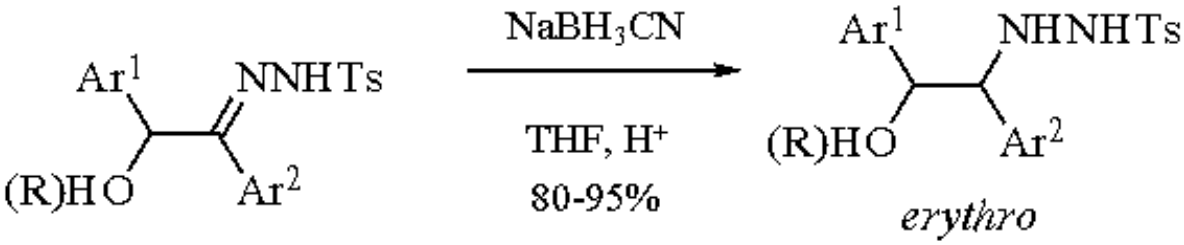

Also under acidic conditions, enamines are reduced to amines via iminium ions by $NaBH_3CN$ (eq 15).[2,20] This type of conversion is also effected with $NaBH_3CN/ZnCl_2$.[10b] Pyridines and related nitrogen heterocycles are reduced by $NaBH_3CN/H^+$ to di- or tetrahydro derivatives (eq 16).[1e,21] Likewise, pyridinium and related salts (e.g. quinolinium, isoquinolinium) are reduced. With 4-substituted derivatives, 1,2,5,6-tetrahydropyridine products are produced (eq 17).[22]

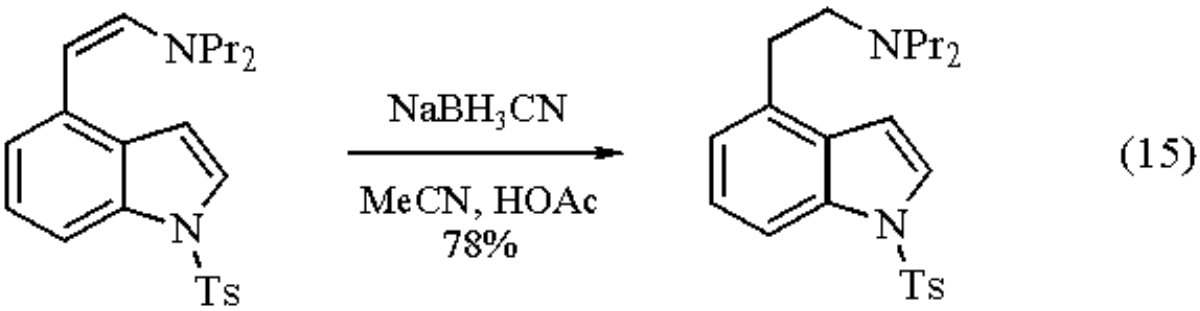

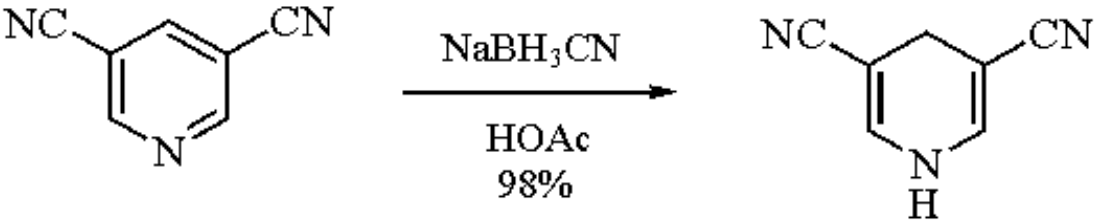

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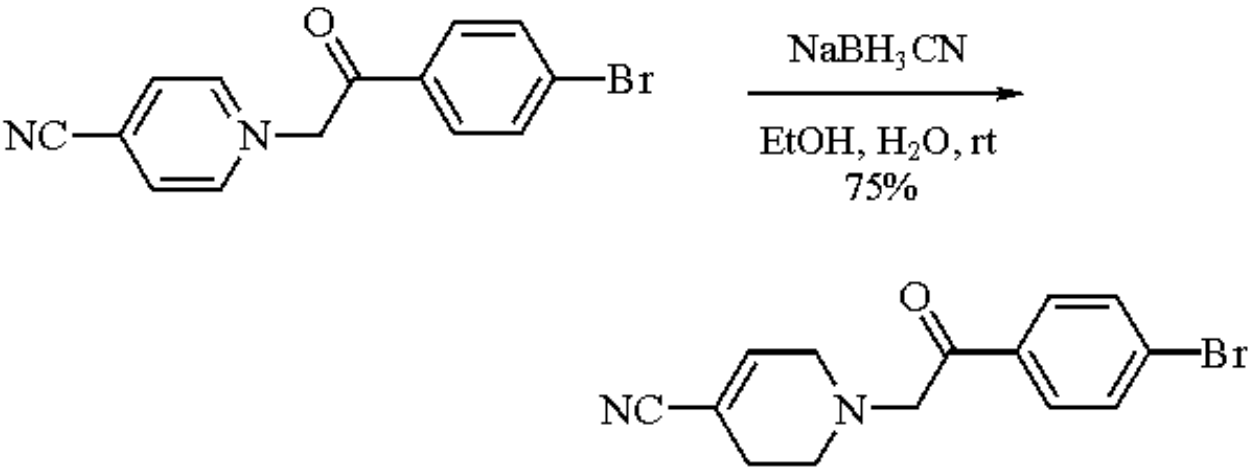

(17)

Reductive Deoxygenation of Aldehydes and Ketones.[23,24]

p-Toluenesulfonylhydrazones (tosylhydrazones), generated in situ from unhindered aliphatic aldehydes and ketones and tosylhydrazine, are reduced by $NaBH_3CN$ in slightly acidic DMF/sulfolane (ca. 100-110 °C) to hydrocarbons via diazene intermediates (eq 18).[24] With hindered examples the tosylhydrazones must be preformed and large excesses (5-10×) of $NaBH_3CN$ used in more acidic media (e.g. pH < 4) (eq 19).[24,25] Likewise, aryl tosylhydrazones are nearly inert to the reagent, but exceptions are known.[26] Reduction of tosylhydrazones to hydrocarbons also occurs with $NaBH_3CN/ZnCl_2$ in refluxing MeOH. This combination also gives poor yields with aryl systems.[10b]

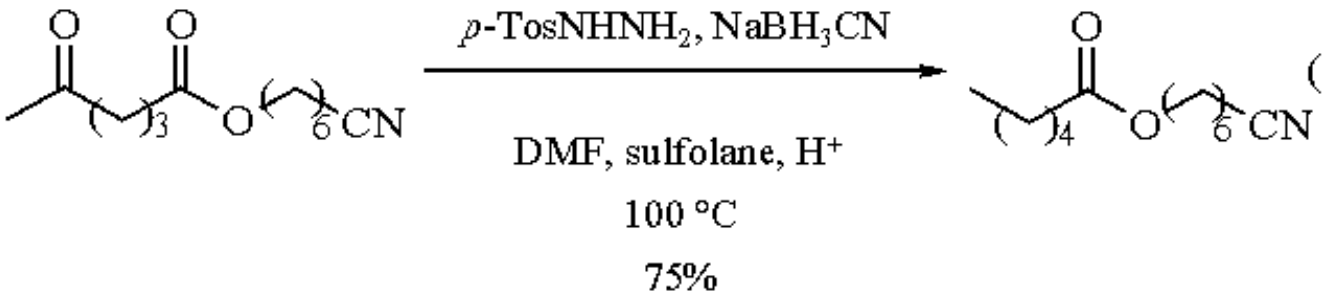

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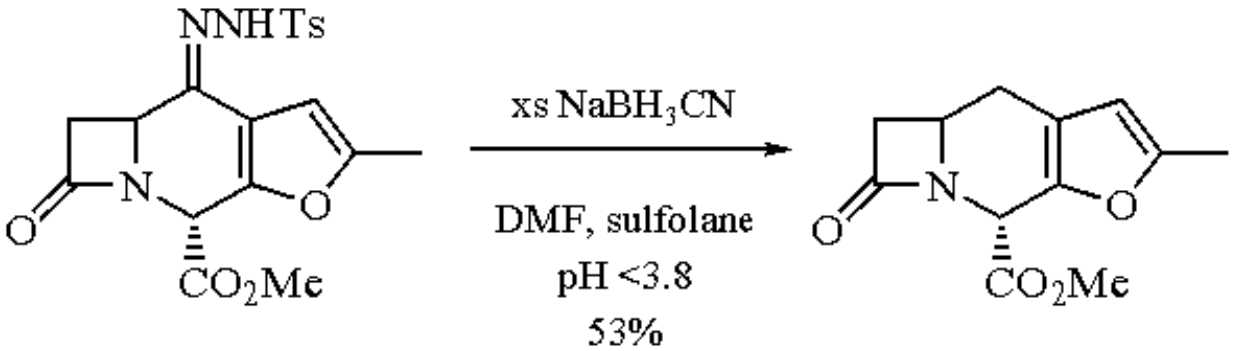

(19)

Reductive deoxygenation of most α,β-unsaturated tosylhydrazones with $NaBH_3CN$ cleanly affords alkenes in which the double bond migrates to the former tosylhydrazone carbon (eq 20).[24,27,28] However, the process gives mixtures of alkenes and alkanes with cyclohexenones[27] (see also ***Bis(triphenylphosphine)copper(I) Borohydride***, ***Catecholborane*** and ***Sodium Borohydride***).

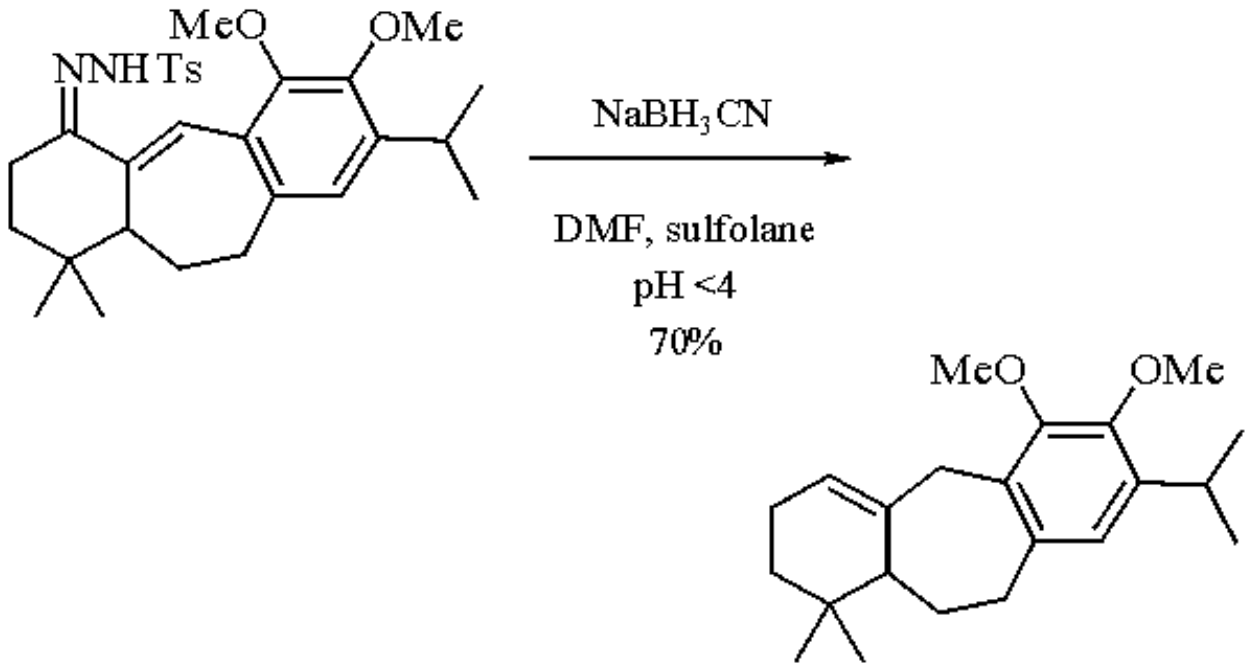

(20)

Reduction of Other π-Bonded Functional Groups.

In acidic media (i.e. pH < 4), aldehydes and ketones are selectively reduced to alcohols (eq 21).[2a,28] α,β-Unsaturated ketones are reduced primarily to allylic alcohols (eq 22)[29] except cyclohexenones, which give mixtures of allylic and saturated alcohols. Allylic ethers are also produced concomitantly with substrates further conjugated with aryl rings.[29]

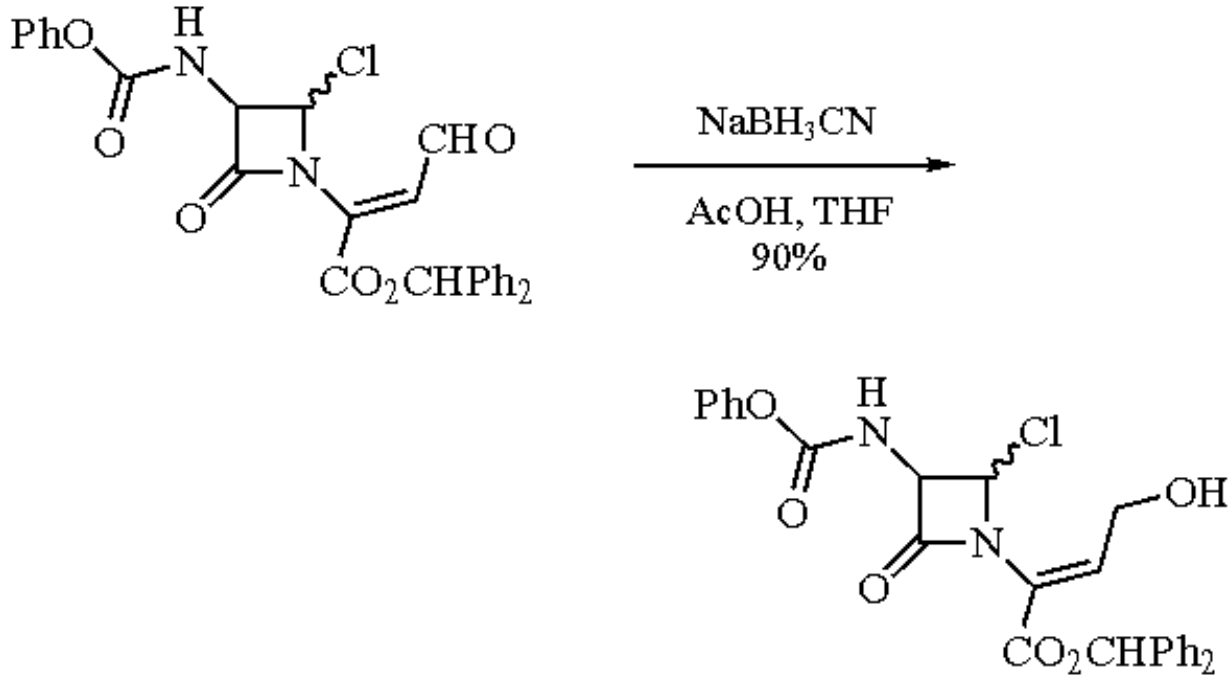

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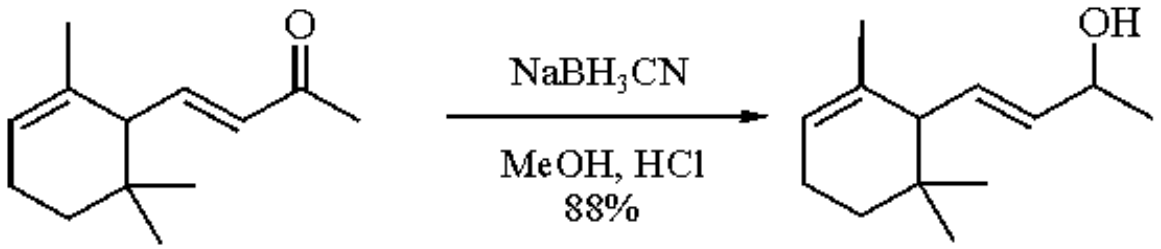

(22)

The combination of $NaBH_3CN/ZnCl_2$ in ether also reduces aldehydes and ketones to alcohols.[10b] With 5% H_2O present, cyclohexanones are selectively reduced in the presence of aliphatic derivatives.[30a] With $NaBH_3CN$/***Zinc Iodide***, however, aryl aldehydes and ketones are

converted to aryl alkanes.[30b]

While isolated alkenes are inert toward $NaBH_3CN$, highly polarized double bonds (i.e. containing an attached nitro or two other electron-withdrawing groups) are reduced to hydrocarbons in acidic EtOH (eq 23).[31,32] Reductions of iron carbonyl-alkene complexes to the corresponding alkyl complexes also occurs readily with $NaBH_3CN$ in MeCN.[33]

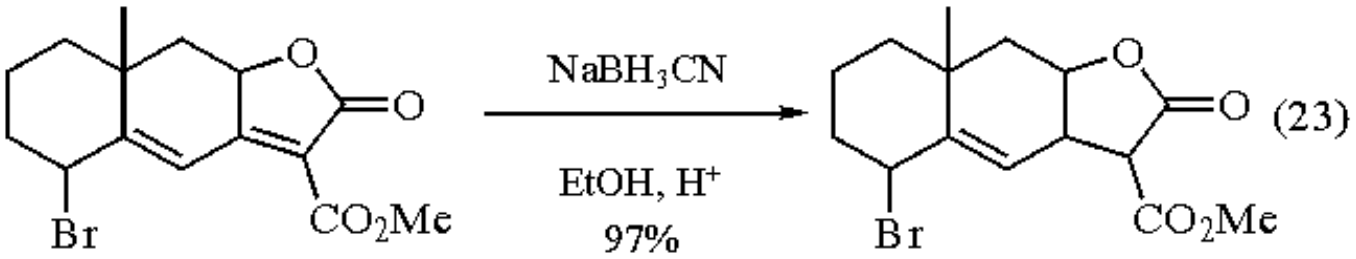

Nitriles are inert toward $NaBH_3CN$ even under strongly acidic conditions. However, methylation with $Me_2Br^+SbF_6^-$ and subsequent reduction with $NaBH_3CN$ affords the corresponding methylamine (eq 24).[34]

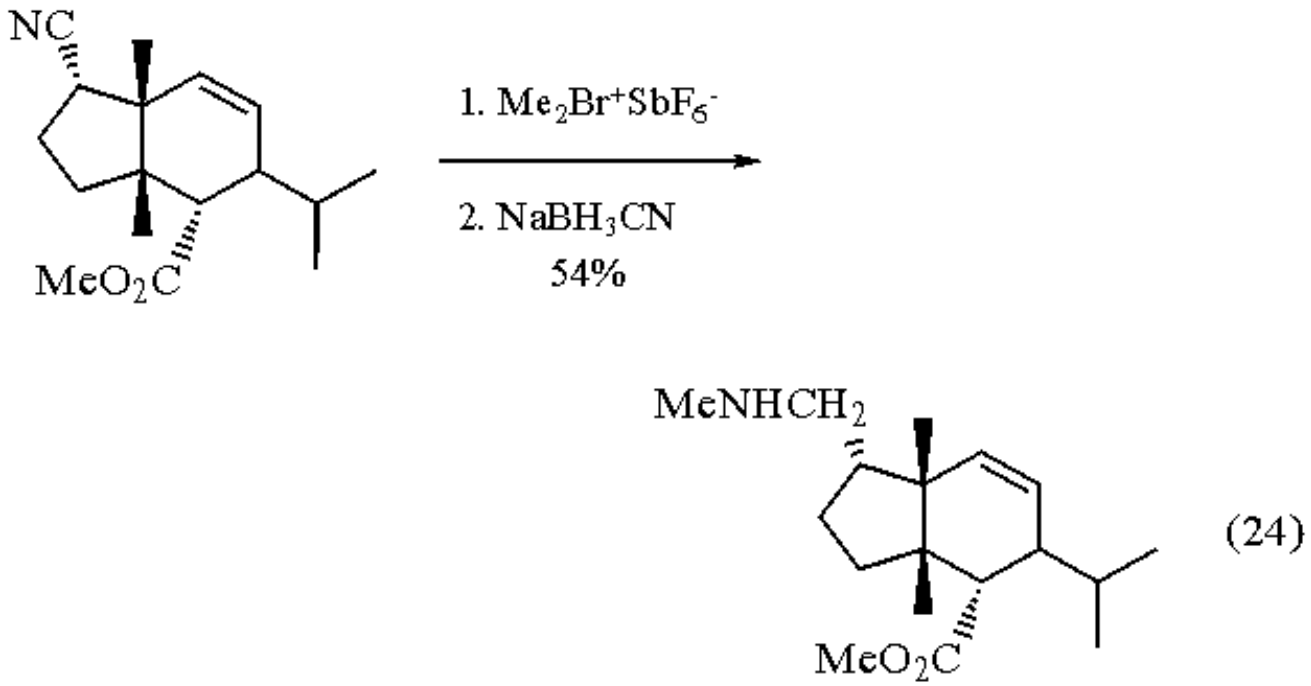

Reduction of σ-Bonded Functional Groups.

In S_N2 rate enhancing polar aprotic solvents (e.g. HMPA, DMSO), primary and secondary alkyl, benzylic and allylic halides, sulfonate esters (eqs 25 and 26),[35a] and quaternary ammonium salts[36] are reduced to hydrocarbons. As expected for an S_N2-type process, the order of reactivity is I > Br, RSO_3 > Cl.[35a] In addition, primary alcohols are reduced to hydrocarbons via in situ conversion to iodides with ***Methyltriphenoxyphosphonium Iodide*** (MTPI) and subsequent reduction (eq 27).[35a,37] On the other hand, the combinations $NaBH_3CN$/***Tin(II) Chloride***[38a] or $NaBH_3CN/ZnCl_2$[38b] reduce tertiary, allylic, and benzylic halides but are inert toward primary, secondary, and aryl derivatives (eq 28)[38] (see also ***Lithium Aluminum Hydride***, ***Lithium Tri-s-butylborohydride*** and ***Sodium Borohydride***).

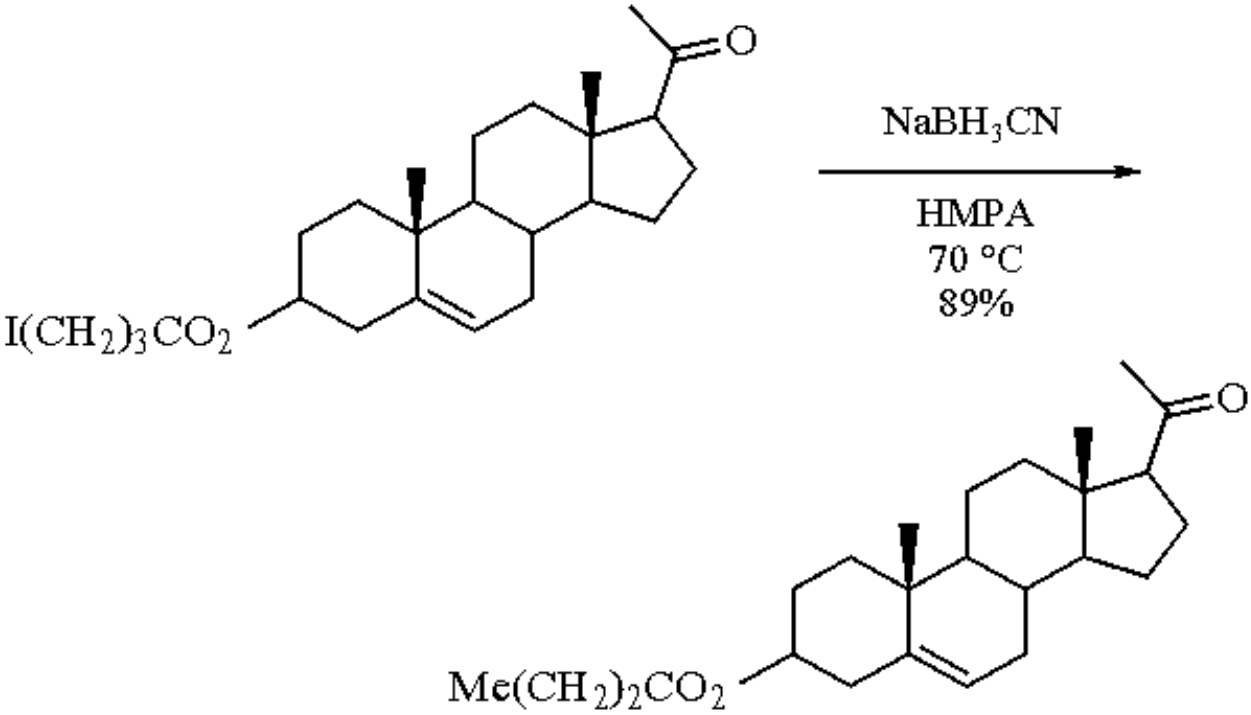

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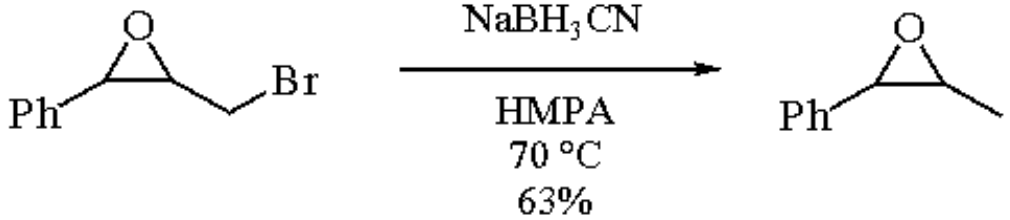

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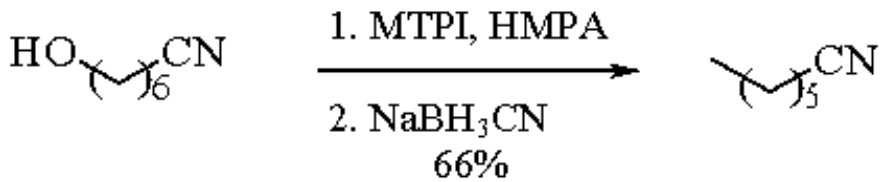

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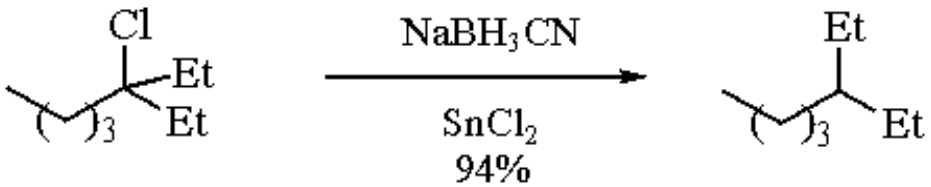

(28)

In the presence of ***Boron Trifluoride Etherate***, $NaBH_3CN$ reduces epoxides to alcohols[39] with attack of hydride at the site best able to accommodate a carbocation. Epoxide opening occurs primarily *anti* (eq 29).[39] Acetals are also reduced to ethers by $NaBH_3CN$ in acetic media (eq 30).[40]

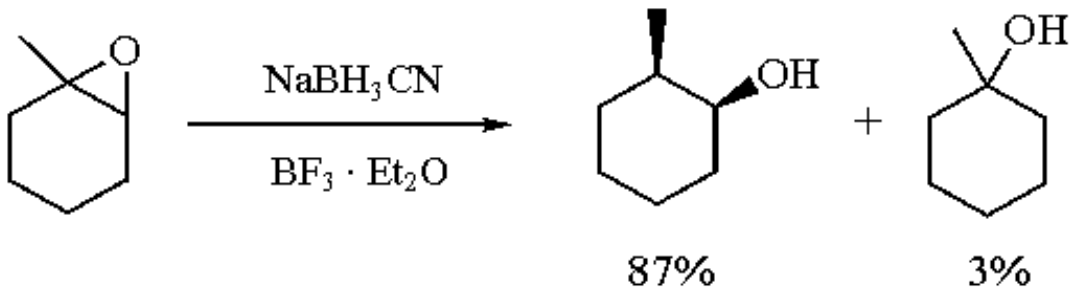

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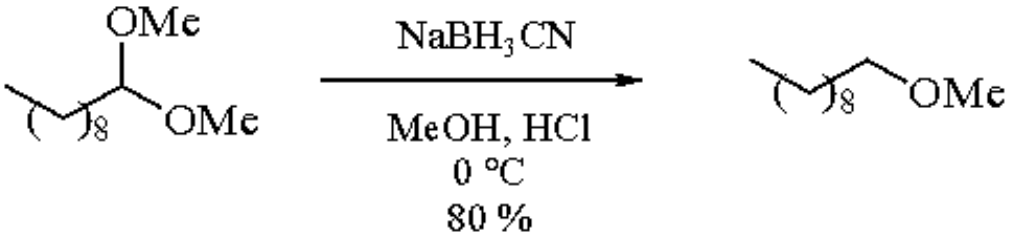

(30)

Allylic groups that are normally not displaced by hydrides (e.g. carboxylates, ethers) are effectively activated via Pd^0 complexation to give π-allyl complexes which are reduced by $NaBH_3CN$ to alkenes (eq 31).[41]

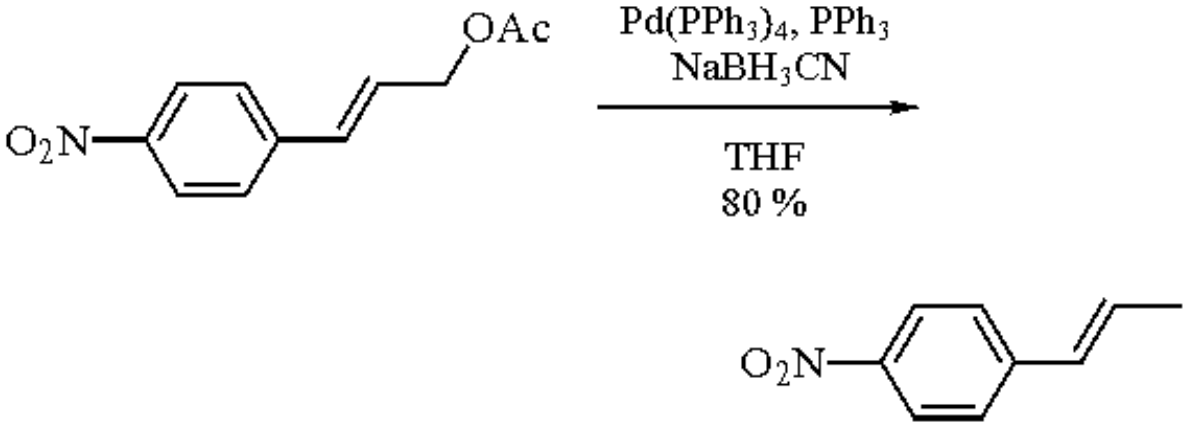

(31)

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Sodium Dicarbonylcyclopentadienylferrate

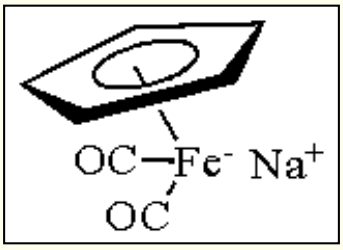

[12152-20-4; 12107-09-4] · $C_7H_5FeNaO_2$ · Sodium Dicarbonylcyclopentadienylferrate · (MW 199.96)

(nucleophilic source of iron;[1] precursor to iron alkene complexes;[1] precursor to η^1-allyliron and η^1-propargyliron complexes; precursor to acyliron complexes;[2] precursor to iron carbenes;[3] with subsequent oxidation will carbonylate alkyl halides or sulfonates[4])

Solubility: sol ethereal organic solvents (Et_2O, THF).

Preparative Methods: to ***Mercury(0)*** (70 mL) stirring under nitrogen in a 500 mL flask with a stopcock in the bottom is slowly added ***Sodium*** metal (7.2 g), cut into small pieces, under a strong flow of nitrogen. The resulting amalgam is cooled to room temperature, and THF (100 mL) is added, followed by ***Bis(dicarbonylcyclopentadienyliron)*** (35.4 g, 0.1 mol). The mixture is stirred for 40 min, and the mercury is drained through the stopcock. The resulting $Na[Fe(CO)_2Cp]$ is used without further purification.[5] An alternative preparation using sodium dispersion in THF at reflux has also been reported.[6]

Handling, Storage, and Precautions: generally prepared and used immediately; it is destroyed by protic solvents.

Organoiron Reagents.

The reagent, NaFp (the $[Fe(CO)_2Cp]$ unit is commonly abbreviated Fp), is a highly nucleophilic source of iron which readily substitutes alkyl halides or pseudohalides.[7] The reaction occurs with inversion at a chiral center, and substrate reactivity, as well as yields, are as expected for S_N2 substitutions (primary > secondary >> tertiary). Benzyl and allyl halides also react easily (eq 1), while propargyl substrates give the expected propargyl-Fp complexes if the remote alkyne terminus is substituted (eq 2)[7b] and σ-bonded iron allenes (by formal S_N2') if unsubstituted (eq 3).[7c] Epoxides react readily but undergo subsequent rearrangement. Acid chlorides or anhydrides are attacked by NaFp to give useful yields of acyl iron complexes (eq 4).[8] β-Chloroenones undergo addition-elimination with NaFp to afford β-Fp enones.[9]

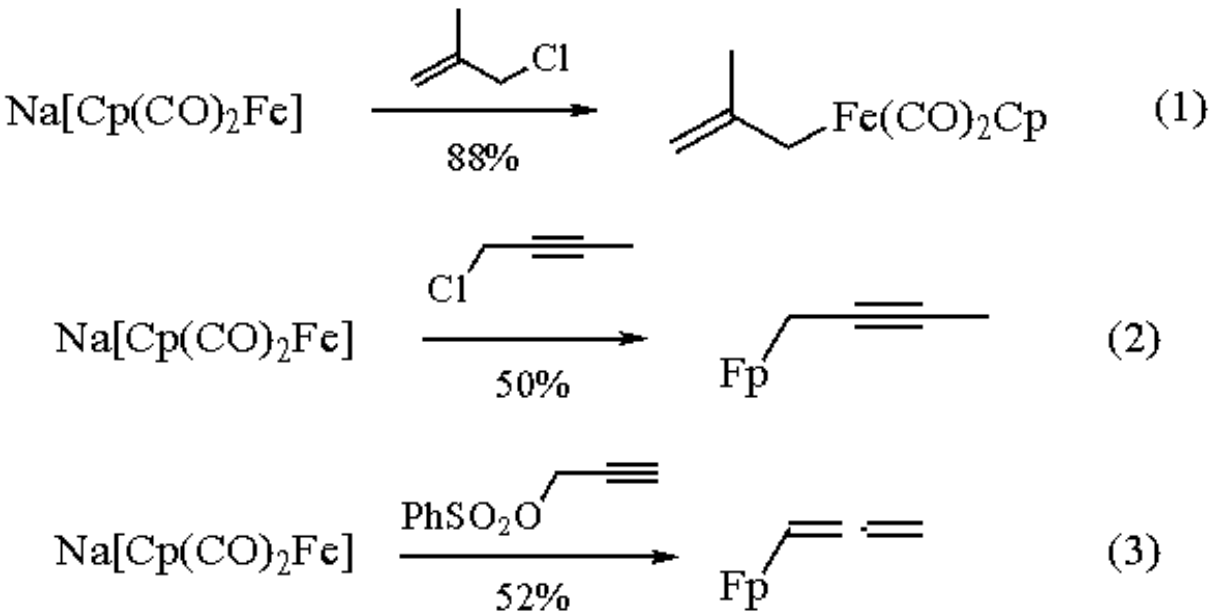

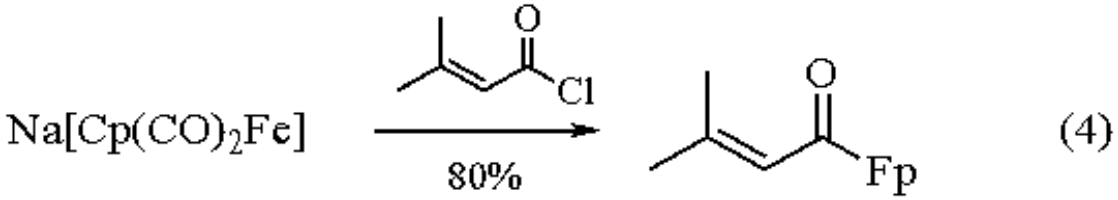

Iron Alkene Complexes.[1]

Epoxides suffer nucleophilic attack by NaFp, and give cationic iron alkene complexes upon protonation with strong acid. Iodide ion in acetone liberates the free alkene, giving an overall stereospecifically *syn* reduction of epoxides (eq 5). Pyrolysis of the iron alkoxide intermediate gives the other alkene isomer (eq 6), allowing access to either isomer from one epoxide. Stereospecificity is high for diaryl or dialkyl epoxides, but isomeric mixtures are obtained in the preparation of enones.[10]

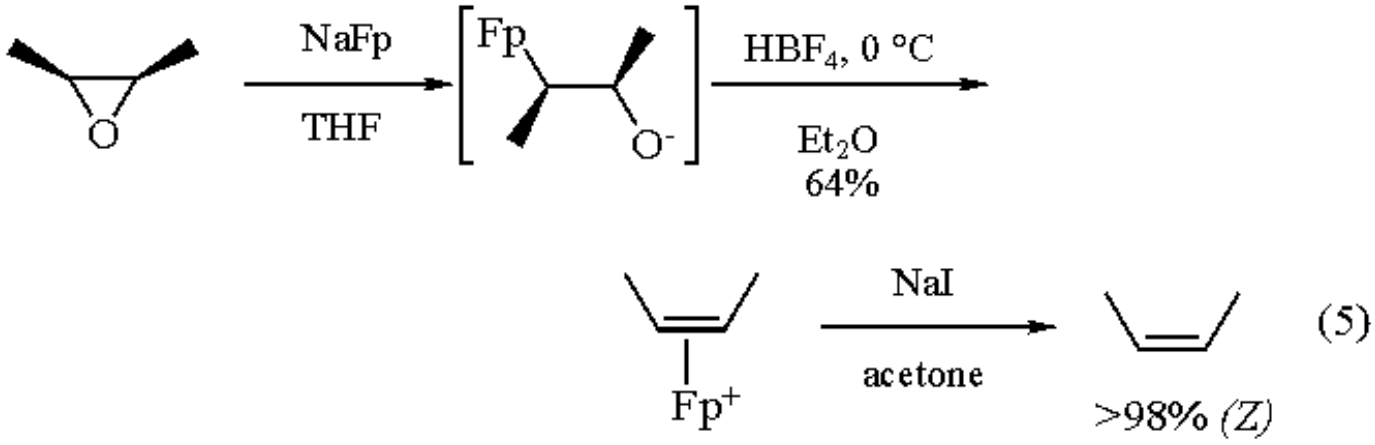

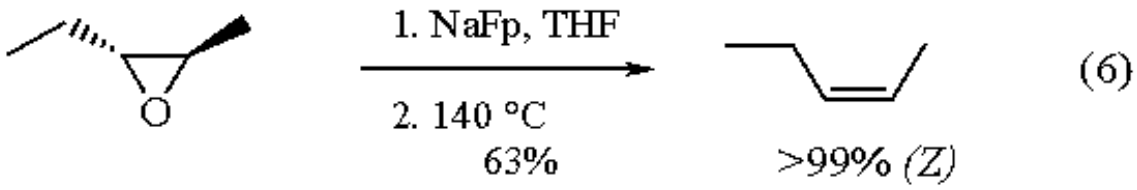

The cationic enone-iron complexes made by the above procedure undergo highly regioselective β-nucleophilic attack. They have been shown to be reactive as Michael acceptors with enolates or silyl enol ethers and may serve as Robinson ring annulation precursors (eq 7).[11]

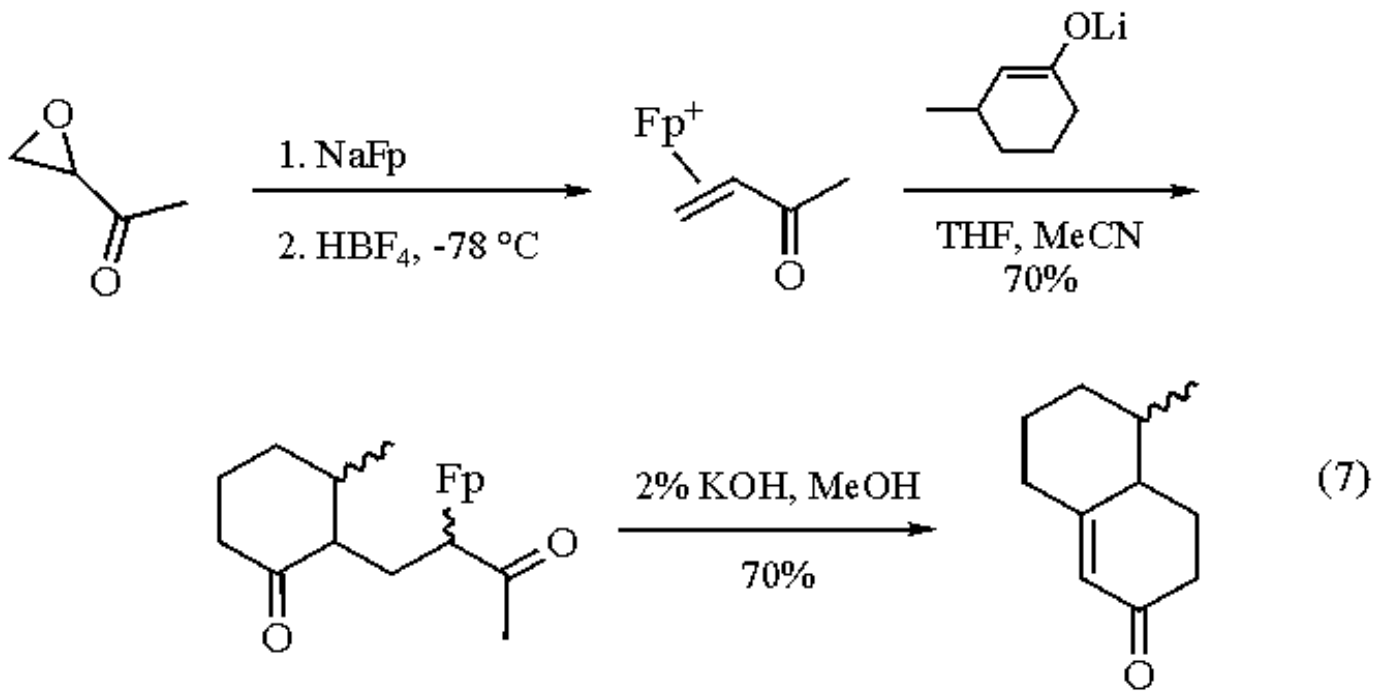

The attack of NaFp upon α-bromo acetals, followed by acid- or trityl cation-induced loss of alkoxide, gives cationic Fp-vinyl ether

complexes (eq 8).[12,13] These compounds react with enolates α to the alkoxy unit, regardless of additional substituents; subsequent treatment with strong acid and iodide ion gives overall vinylation of the enolate.[13] The complex of ethyl α-ethoxyacrylate (**1**) serves in a closely analogous manner in the three step synthesis of α-methylene-γ-lactones (eq 9).[13b]

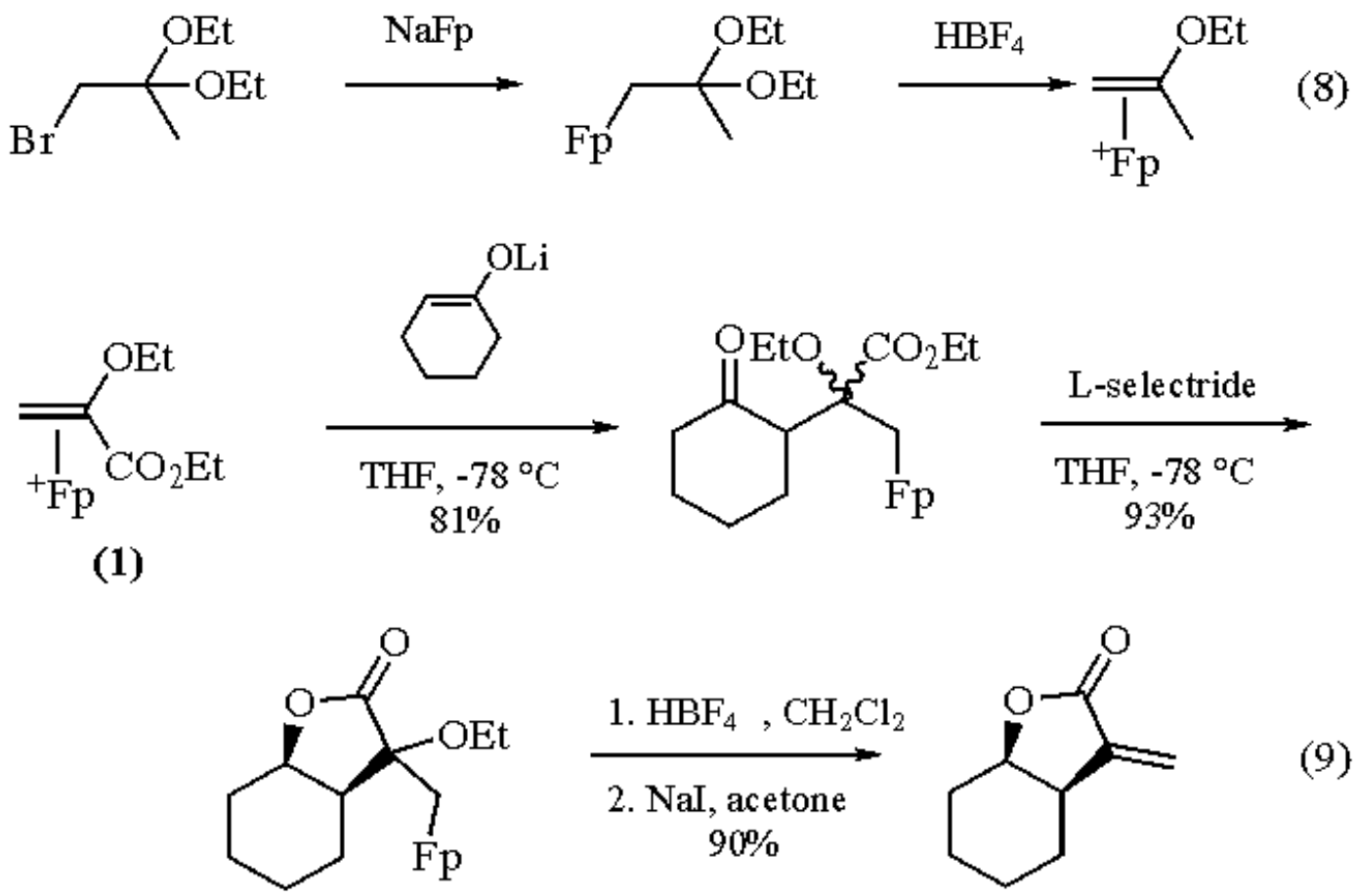

Alkene Synthesis.

Aliphatic alkyl halides or pseudohalides may be converted into alkenes by a three-step process involving nucleophilic substitution by NaFp, hydride abstraction by ***Triphenylcarbenium Tetrafluoroborate***, and ***Sodium Iodide***-induced decomposition of the iron alkene (eq 10). Hydride abstraction is selective, such that both 1-haloalkenes and 2-haloalkenes normally afford terminal alkenes; 3-haloalkenes normally give (*Z*)-alkenes as products, but yields are modest.[14]

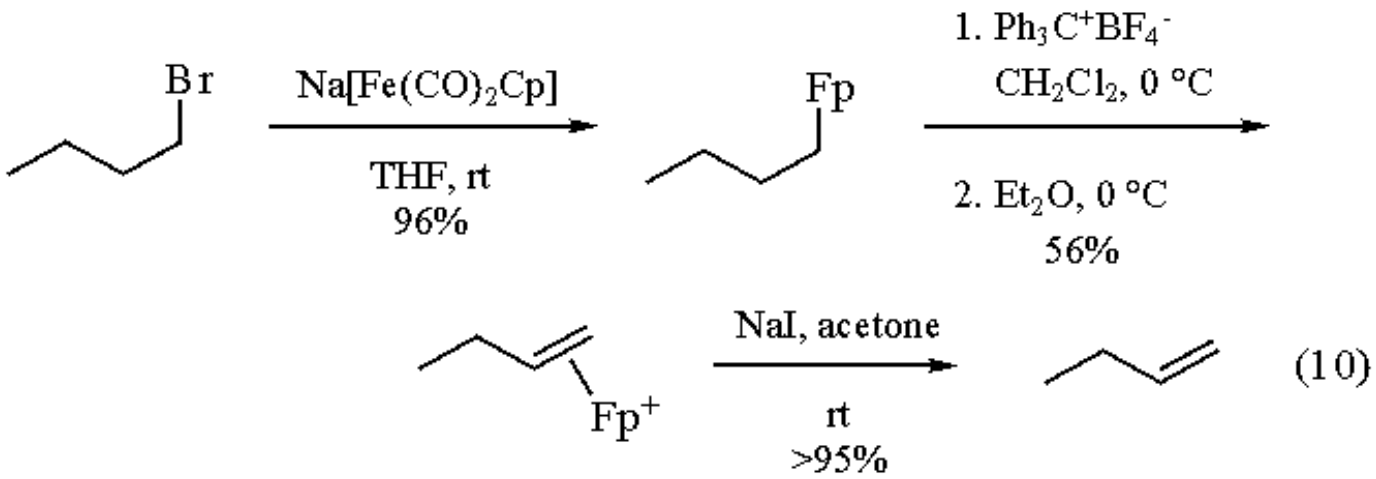

η^1-Allyliron Complexes.

η^1-Allyliron complexes, prepared by the nucleophilic substitution of NaFp on allyl halides or pseudohalides, are nucleophilic allylation reagents for aldehydes, ketones, and acid chlorides in the presence of Lewis acids (eq 11).[15]

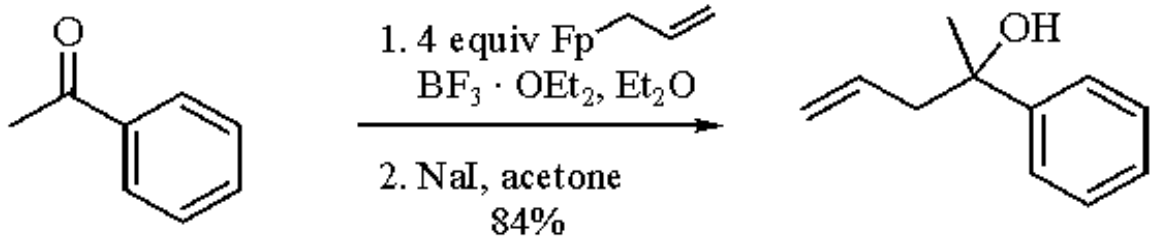

(11)

They are reactive with a variety of other cationic species, including strong acids, and this route has been employed for the preparation of more complex alkene-Fp cations.[7b] Reaction occurs at the end of the allyl unit remote from iron; this fact has been used to convert allyl alcohols to terminal alkenes through the intermediacy of Fp-allyl complexes (eq 12).[16]

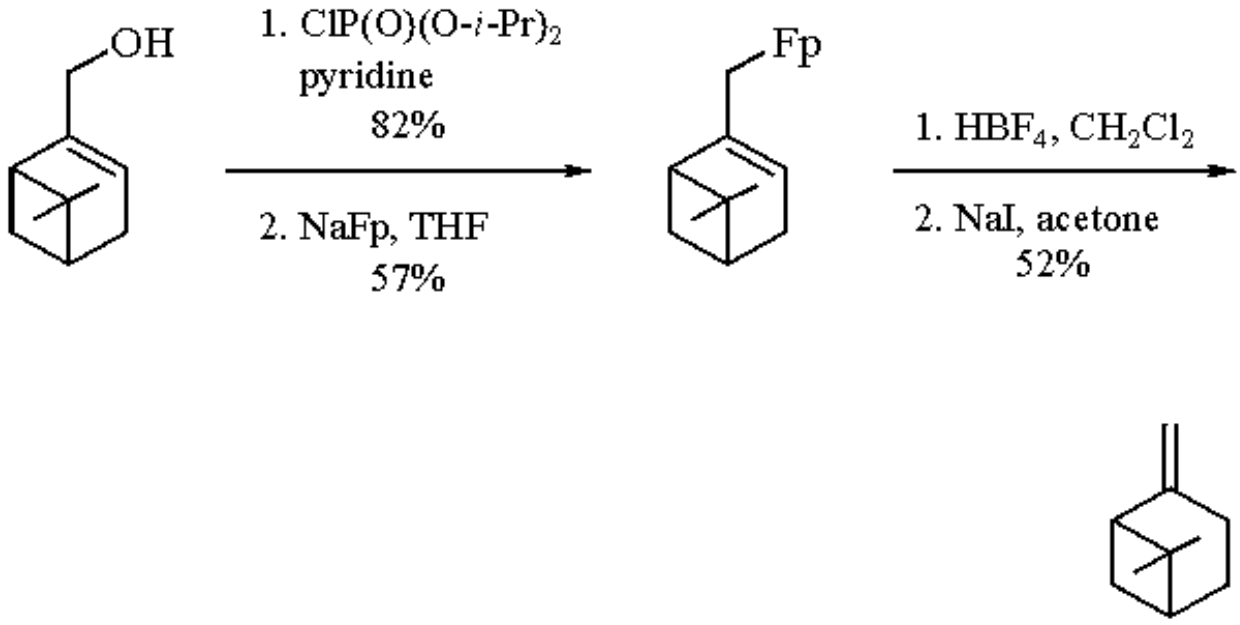

(12)

η^1-Allyliron and η^1-propargyliron complexes, as well the Fp-allene complex, react with electron-deficient alkenes in a stepwise [3 + 2] cycloaddition; the result is a cyclopentane or cyclopentene ring annulation (eq 13). The most reactive substrates include α,β-unsaturated esters or nitriles possessing two electron-withdrawing groups, whereas simple enones will react in the presence of a Lewis acid.[7b,17,18] Heteroatom-based double-bonded systems such as isocyanates, hexafluoroacetone, *N*-sulfonylurethane, and S_2O (generated in situ)[19] participate in these cycloadditions, but the resulting Fe-C bond usually has not been further manipulated (S_2O adduct excepted). Also reactive is the uncomplexed double bond of tropyliumiron tricarbonyls, which ultimately form the fused 5,7 ring systems of hydroazulenes (eq 14).[20]

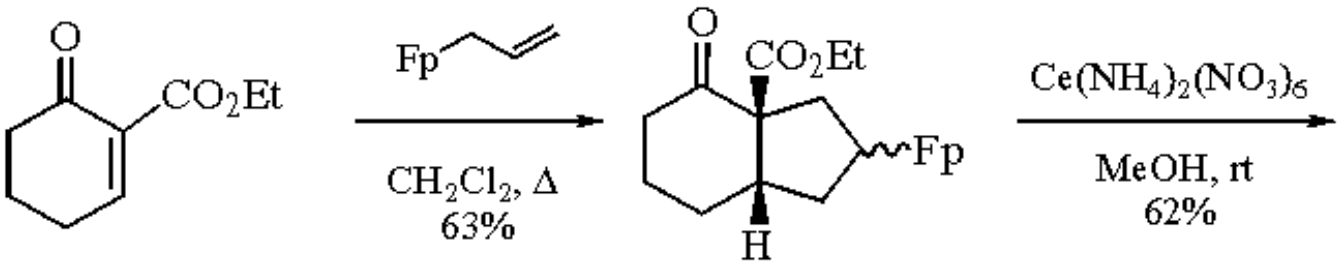

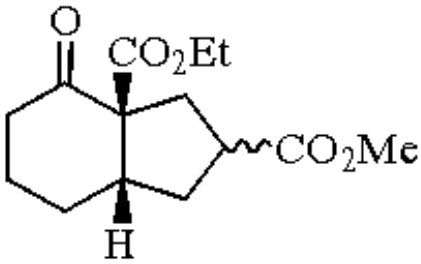

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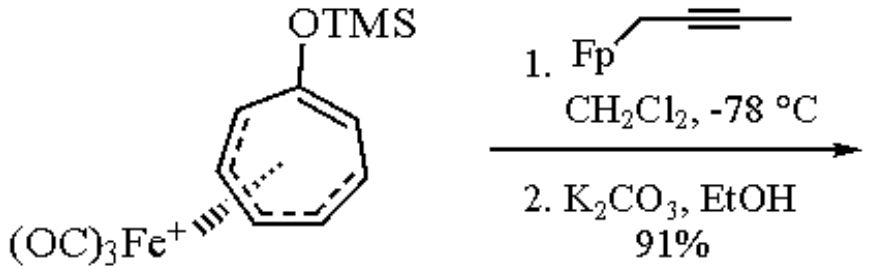

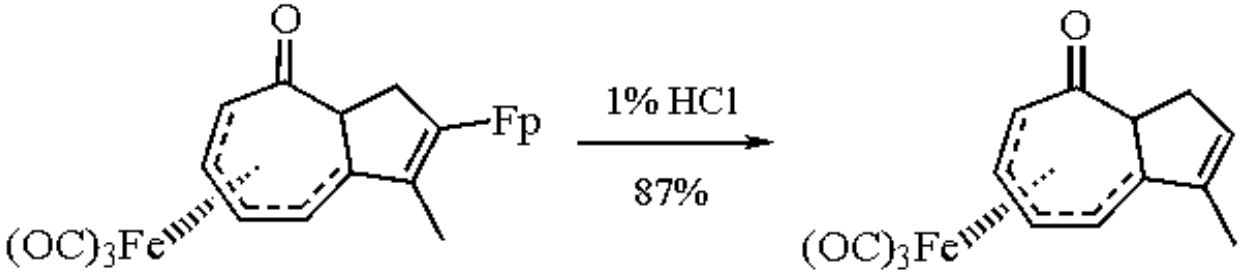

(14)

Acyliron Complexes.

α,β-Enoyl-Fp complexes, available by NaFp attack on acid chlorides (eq 4), are susceptible to conjugate addition by amine or thiol nucleophiles. The amine adducts may be oxidatively demetalated to give β-lactams (eq 15).[21] Allylstannanes react with α,β-enoyl-Fp complexes in a highly regio- and stereoselective [3 + 2] cycloaddition (eq 16).[2] The tin residue of the product is invariably *trans* to the acyliron function, whereas either *cis* or *trans* crotylstannanes result in a methyl function *trans* to the tin unit. Subsequent conversion of the acyliron function to an ester and conversion of the tin unit to a hydroxy group gives moderate overall yields of cyclopentanes which may be quite highly functionalized. The use of dimethoxycarbenium tetrafluoroborate instead of ***Aluminum Chloride*** results in conjugate addition without cyclization.[2]

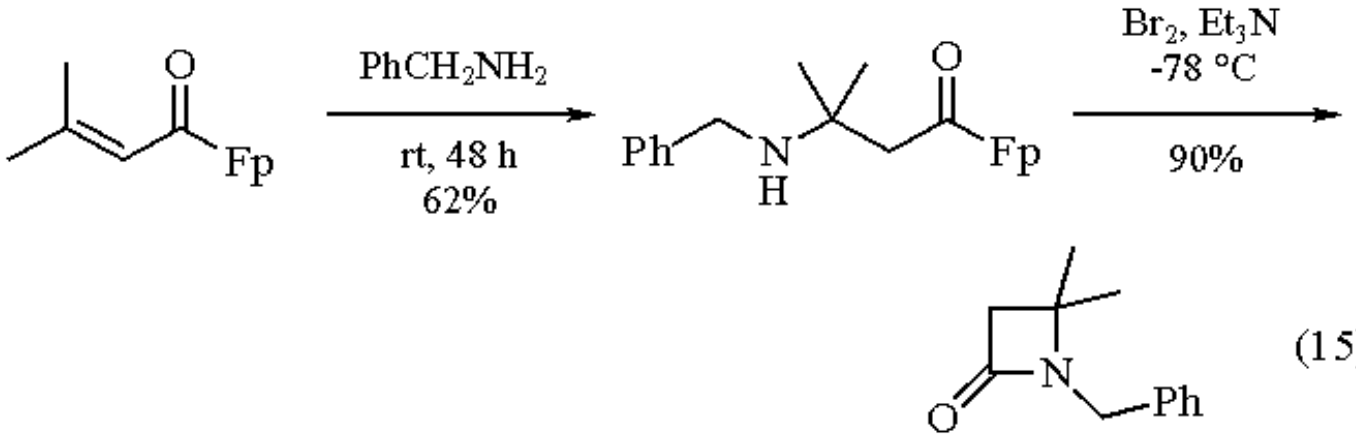

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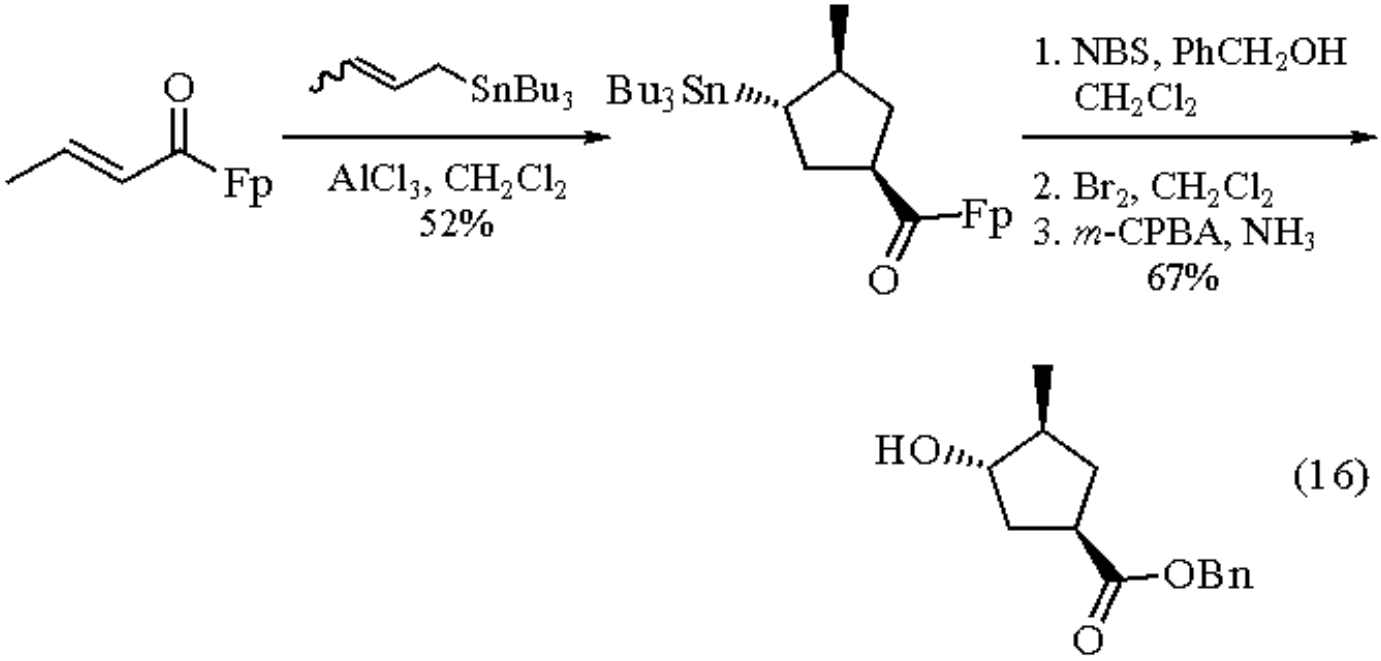

(16)

The chiral acyl-Fe(CO)(PR_3)Cp complexes are not generally accessible by phosphine substitution of acyl-Fp complexes (see ***(S)-Aceto(carbonyl)(cyclopentadienyl)-(triphenylphosphine)iron***). The nicotinyl or dihydronicotinyl acyliron substrates do substitute phosphine ligands successfully, however, and complexes such as (**2**) prepared in this manner have been shown to be useful in the enantioselective reduction of ethyl benzoylformate to ethyl mandelate.[22]

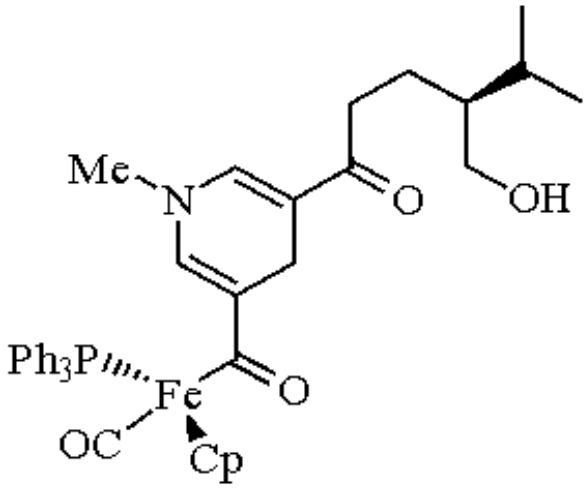

(2)

Iron Carbene Reagents.[2]

NaFp reacts with α-chloro ethers and α-chloro thioethers to afford α-methoxy- or α-alkylthioalkyliron complexes (**3**), respectively (eq 17).[23-26] Acyliron complexes undergo an *O*-methylation-reduction sequence which also gives (**3**; R = OMe) (eq 18). Alternatively, the reaction of NaFp with aldehydes, followed by *O*-silylation, gives α-trimethylsiloxyalkyliron complexes (**3**; X = $OSiMe_3$) (eq 19).[27] When treated with protic or (more often) Lewis acids, these compounds (**3**) are converted to cationic iron carbene complexes (**4**) (eq 20), which in turn react with alkenes to form cyclopropanes.

$$Na[Fe(CO)_2Cp] + ClCH(R)X \longrightarrow Cp(CO)_2FeCH(R)X \qquad (17)$$

(3) X = OMe, SMe, SPh

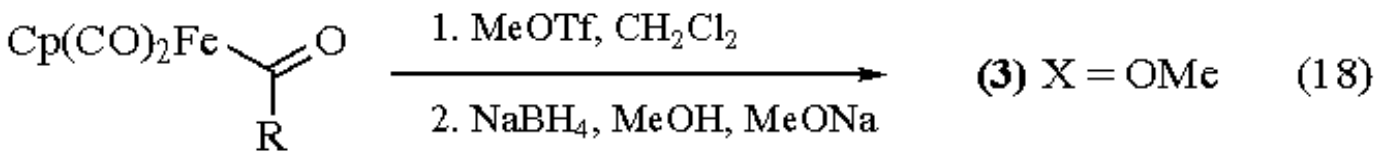

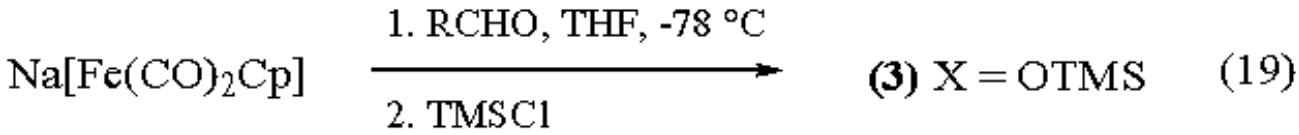

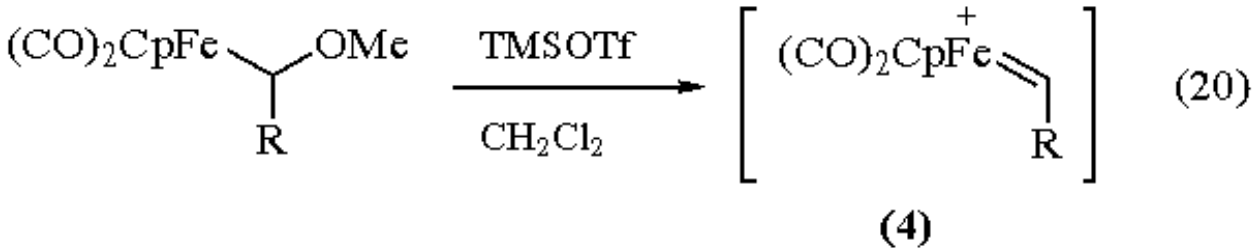

Addition to the alkene is stereospecifically *cis* with respect to alkene geometry. The α-methoxyalkyliron and trimethylsiloxyalkyliron complexes are the most reactive and the most stereoselective at any newly formed chiral centers; substituents on the carbene normally enter *cis* with respect to alkene substituents (&egt;4:1) (eq 21). The α-alkylthioalkyliron complexes (X = SMe, SPh) are less *cis* stereoselective, but are more suitable for transfer of a methylene group (R = H) (eq 22). For intermolecular cases, yields are best for methyl-, aryl-, or cyclopropyl-substituted carbenes;[28] vinyl substituents give lower yields, and *n*-alkyl- or dialkyl-substituted carbenes, regardless of precursor, do not give synthetically useful yields. Intramolecular cyclopropanations have also been reported, but yields are variable and both C-H insertion and cationic cyclization may compete.[29]

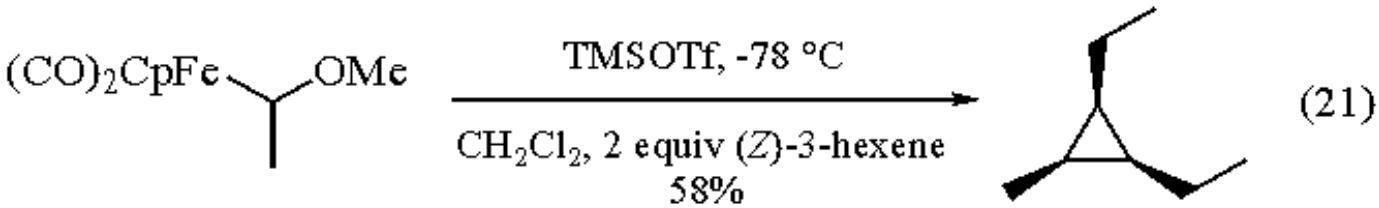

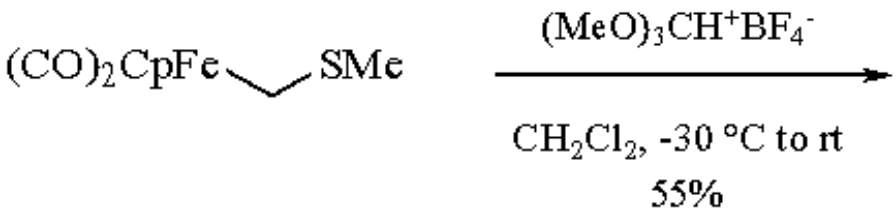

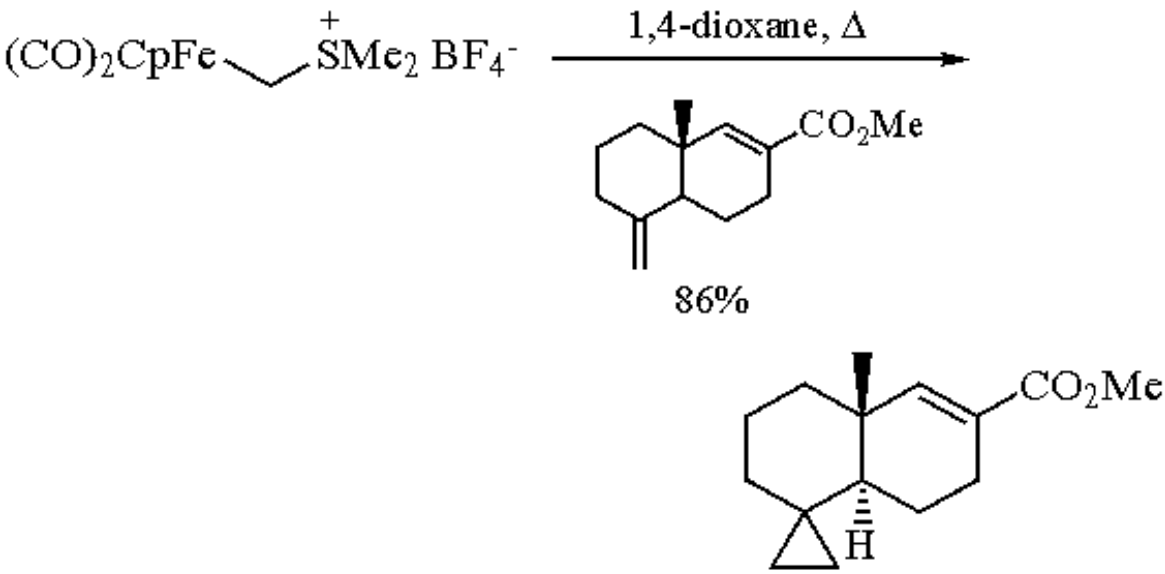

Iron carbenes with α-bridgehead carbon atoms decompose by alkyl group migration to give bridgehead alkene-iron complexes, provided the alkene strain is below 88 kJ mol^{-1}. The decomplexed alkene was isolated in one case (eq 23).[30]

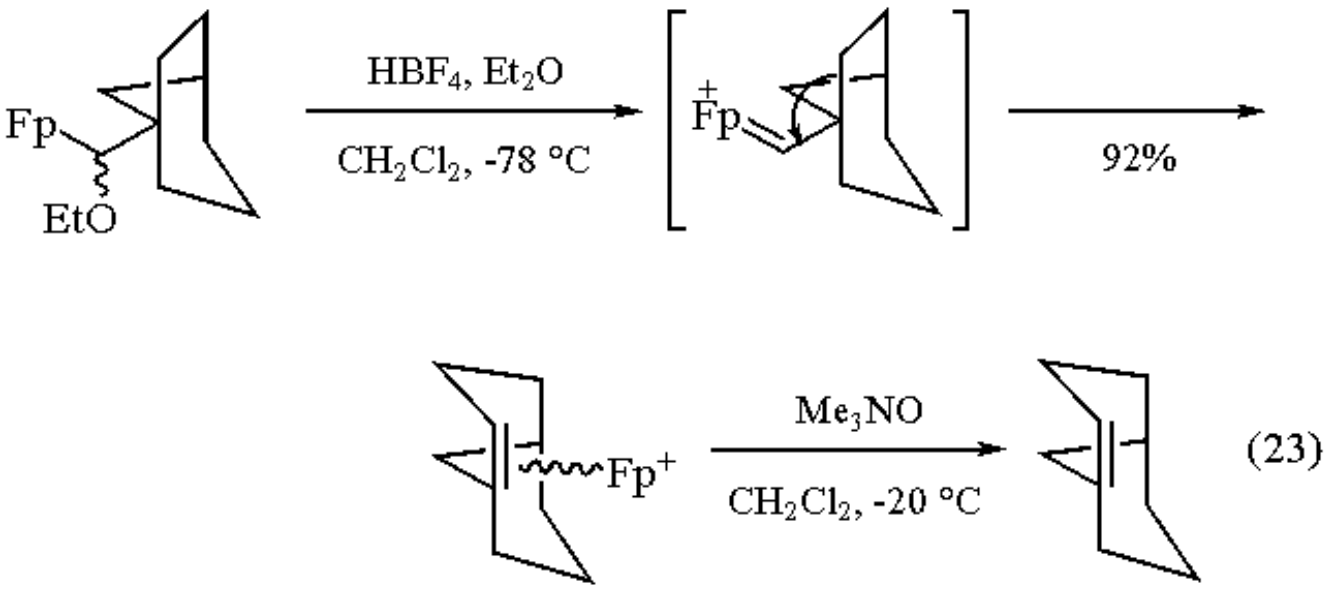

Carbonylation.

Substitution of alkyl halides or sulfonates by NaFp, followed by oxidative carbonyl insertion by Br_2 in methanol, gives good yields of carbonylation products (eq 24). The use of NaFp allows milder reaction conditions to be used relative to ***Sodium Tetracarbonylcobaltate***, and ethers, esters, and free hydroxyl groups are tolerated.[3] Although applied synthetically for primary halides or pseudohalides, secondary substrates give overall inversion of configuration.[31] Carbonyl insertion is also induced by the addition of a ligand, most commonly PPh_3; this route is the one of choice for the preparation of racemic acetyl(carbonyl)cyclopentadienyl(triphenylphosphine)iron (eq 25).[32]

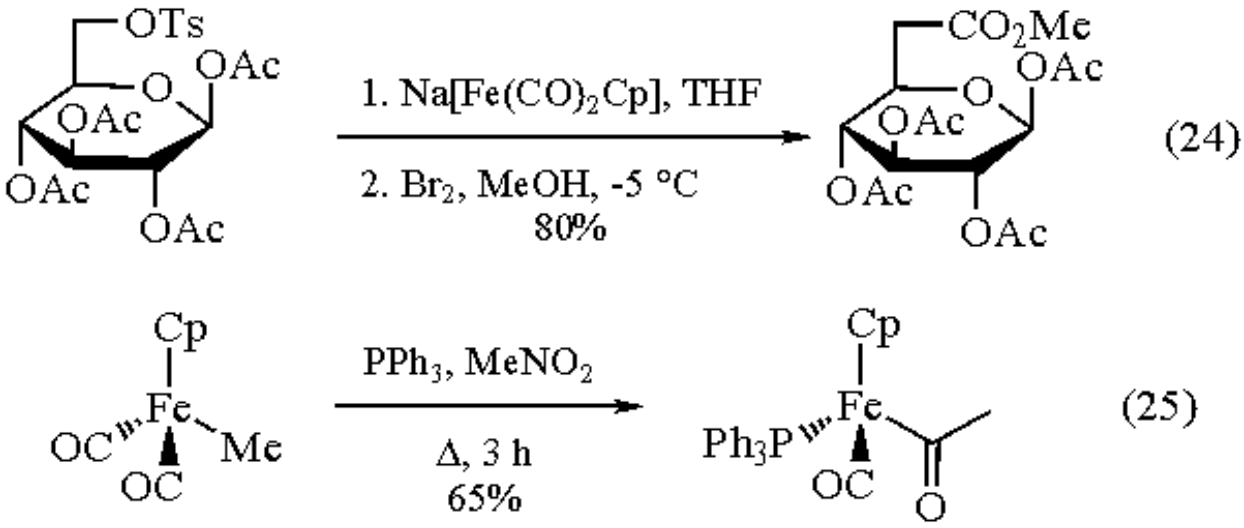

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Sodium Dichlorofluoroacetate

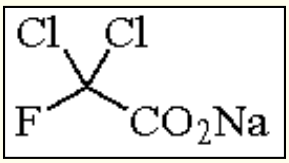

[2837-90-3] · $C_2Cl_2FNaO_2$ · Sodium Dichlorofluoroacetate · (MW 168.91)

(reagent for generation of chlorofluorocarbene and the synthesis of chlorofluorocyclopropanes and chlorofluoroalkenes)

Solubility: sol DME, diglyme, triglyme, *N*-methylpyrrolidone.

Preparative Methods: prepared by careful neutralization of 80 g (0.54 mol) of dichlorofluoroacetic acid in 150 mL of Et_2O with 29 g of anhydrous Na_2CO_3. The Et_2O and water are removed under reduced pressure. The salt is then dried overnight at 50 °C at a pressure of less than 4 mmHg.[1]

Handling, Storage, and Precautions: is an irritant and is hygroscopic.

Wittig Reactions.

The thermal decomposition of sodium dichlorofluoroacetate in the presence of ***Triphenylphosphine*** and benzaldehyde in triglyme results in the formation of a mixture of (*E*)- and (*Z*)-chlorofluoroalkenes in 49% yield (eq 1). A ratio of triphenylphosphine:sodium salt:carbonyl of 1.5:1.5:1.0 is recommended. The choice of solvent had little effect on the ratio of alkene isomers obtained. However, in terms of overall yield, triglyme was the solvent of choice. Simple ketones generally do not react well under these conditions, the exceptions being when there are fluorine substituents on the α-carbon (eq 2).[1]

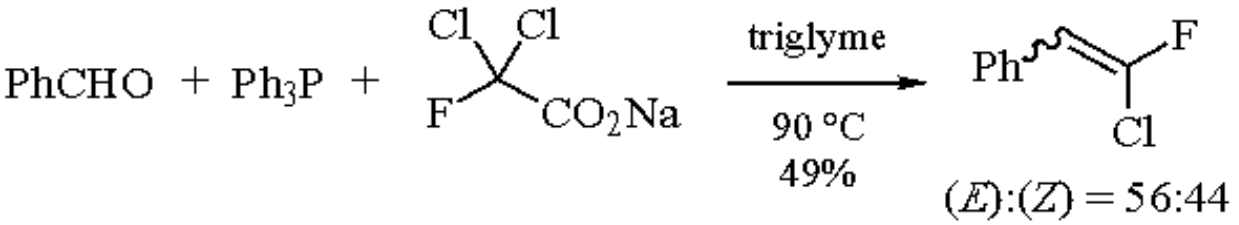

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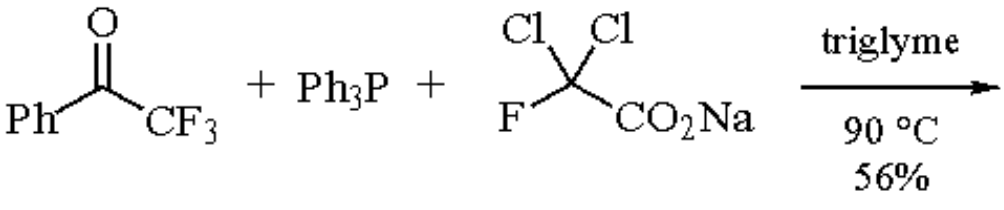

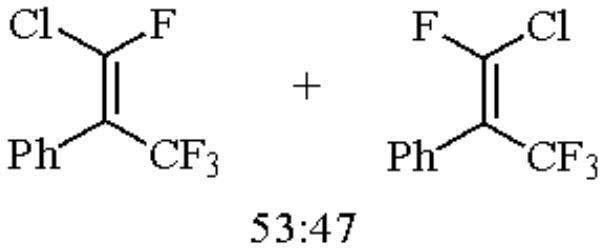

(2)

Substitution of ***Tri-n-butylphosphine*** for triphenylphosphine produced a less stable but more reactive ylide that was capable of reacting with cyclopentanone (eq 3). The yield in the cyclopentanone reaction was comparable to the haloform method of carbene formation and subsequent ylide generation. In general, the yields of chlorofluoroalkenes using the decarboxylation method for generating chlorofluorocarbene were superior to the haloform method.

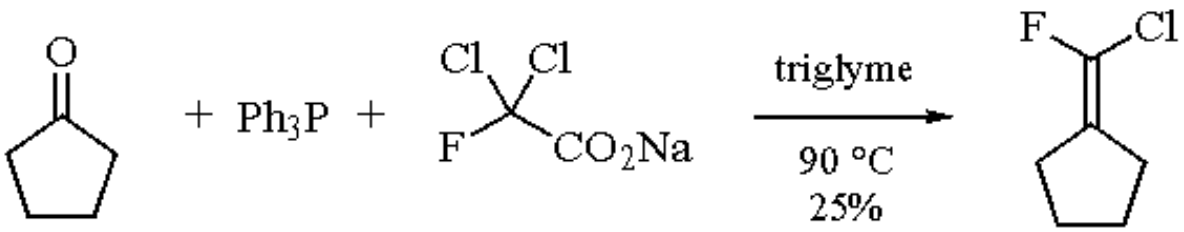

(3)

Cyclopropanation.

The reaction of tetramethylethylene with the sodium salt in triglyme at 85 °C leads to the formation of the chlorofluorocyclopropane in 37% yield (eq 4). In the presence of triphenylphosphine, no cyclopropane was observed. Tetramethylethylene and triphenylphosphine have been shown to be comparable in reactivity toward chlorofluorocarbene generated using the haloform method. Thus it appears that the carbene may not be the precursor for the ylide in the decarboxylation method.[1]

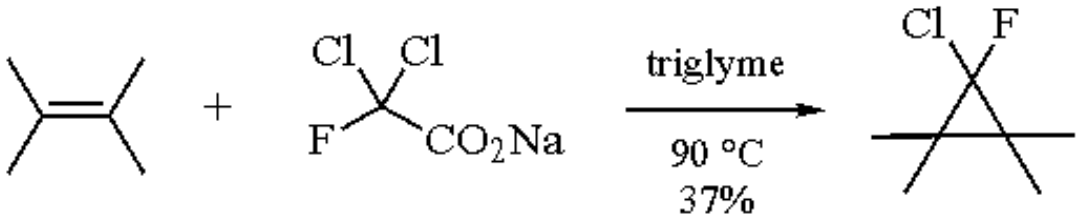

(4)

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Sodium Dichromate[1]

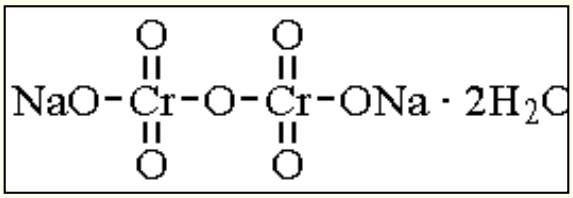

[7778-12-0] · $Cr_2Na_2O_7$ · Sodium Dichromate · (MW 298.02)

(reagent for oxidizing alkylaromatics to carboxylic acids, oxidizing benzylic methylene groups to carbonyl groups, oxidizing alkenes to form α,β-unsaturated compounds, and for converting alcohols to carbonyl compounds)

Physical Data: mp (loses $2H_2O$ at 100 °C) 356.7 °C (anhydr); d = 2.52 g cm^{-3}.[13]

Solubility: sol H_2O (238 g/100 mL at 0 °C), acetic acid, DMSO.

Form Supplied in: red crystals.

Handling, Storage, and Precautions: highly toxic and a cancer suspect agent. All chromium(VI) reagents must be handled with care in a fume hood. The mutagenicity of Cr^{VI} compounds is well documented.[2]

Introduction.

Sodium dichromate, which contains three oxygen equivalents per mol, has a wide range of oxidizing powers which are dependent on the solvent systems and experimental conditions.

Oxidation of Alkylaromatics to Carboxylic Acids.

Aqueous sodium dichromate selectively oxidizes arylmethanes and heteroarylmethanes to the corresponding carboxylic acids in excellent yields.[3] For example, 1-methylnaphthalene is oxidized to 1-naphthoic acid in 95% yield (eq 1). Aromatic dicarboxylic acids are also available from dialkyl-substituted aromatic nuclei. In general, the lower the pH the more likely is attack on the aromatic nucleus.

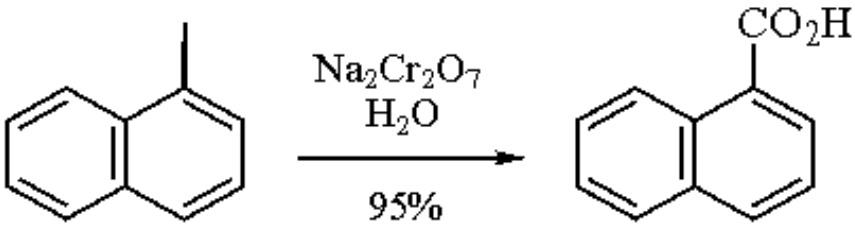

(1)

Oxidation of Benzylic Methylene Groups to Carbonyl Groups.

Sodium dichromate in acetic acid oxidizes 3-ethyl-2,6-dimethylpyrazine to 3-acetyl-2,6-dimethylpyrazine (57%).[4] The heterocyclic ring is essentially destroyed under these experimental conditions. 2-Acetylfluorene is oxidized to the fluorene-2-carboxylic acid by sodium dichromate in acetic anhydride/acetic acid (eq 2)[5] and acenaphthene is converted to acenaphthenequinone with sodium dichromate in anhydrous acetic acid in the presence of cerium(IV) acetate catalyst (eq 3).[6] The octahydrophenanthrene derivative (**1**), an intermediate in the synthesis of morphine analogs, is oxidized to the benzylic ketone by sodium dichromate in sulfuric acid (eq 4).[7]

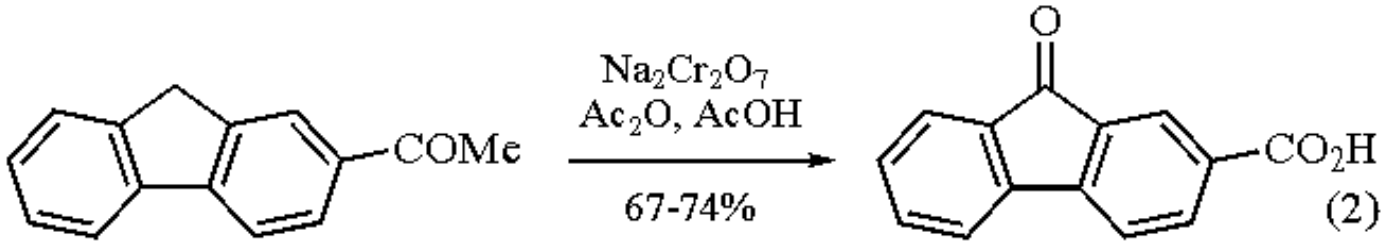

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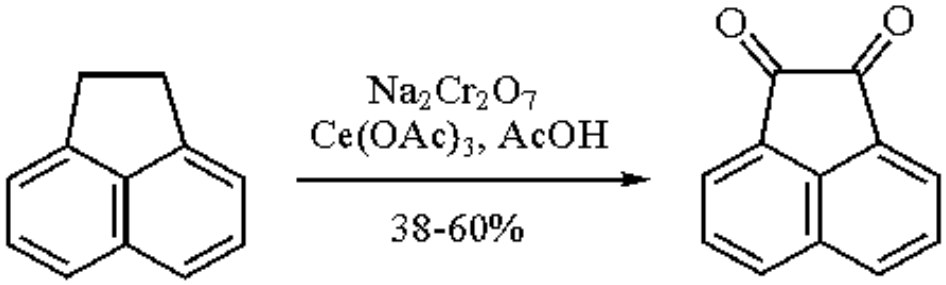

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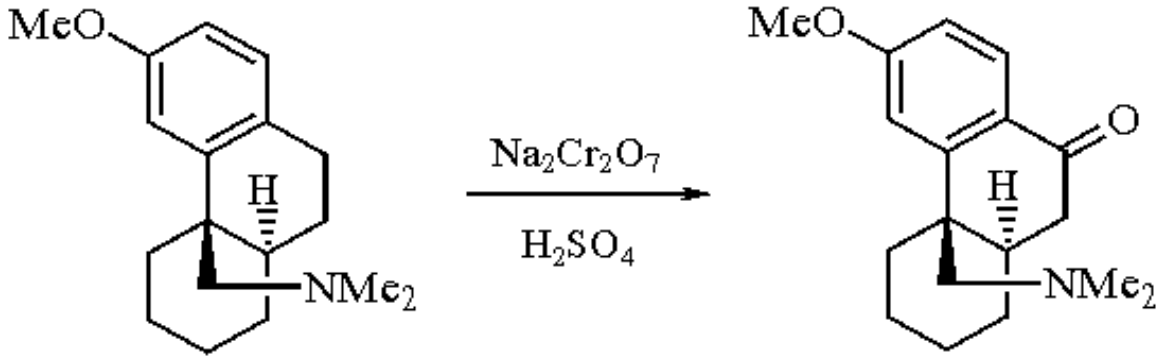

(4)

(1)

Allylic Oxidation of Alkenes to α,β-Unsaturated Compounds.

Sodium dichromate, ***Dipyridine Chromium(VI) Oxide*** (Collins reagent), ***Chromium(VI) Oxide-3,5-Dimethylpyrazole*** (DMP/CrO_3), ***Di-t-butyl Chromate***, and sodium chromate are very useful for oxidizing polycyclic alkenes, especially terpenes and steroids, to α,β-unsaturated compounds. Limitations may include side reactions such as cleavage of the carbon-carbon double bond and lack of regiochemistry in the oxidation. Sodium dichromate in acetic acid oxidizes methyl acetyloleanolate to the 11-keto derivative (eq 5).[8]

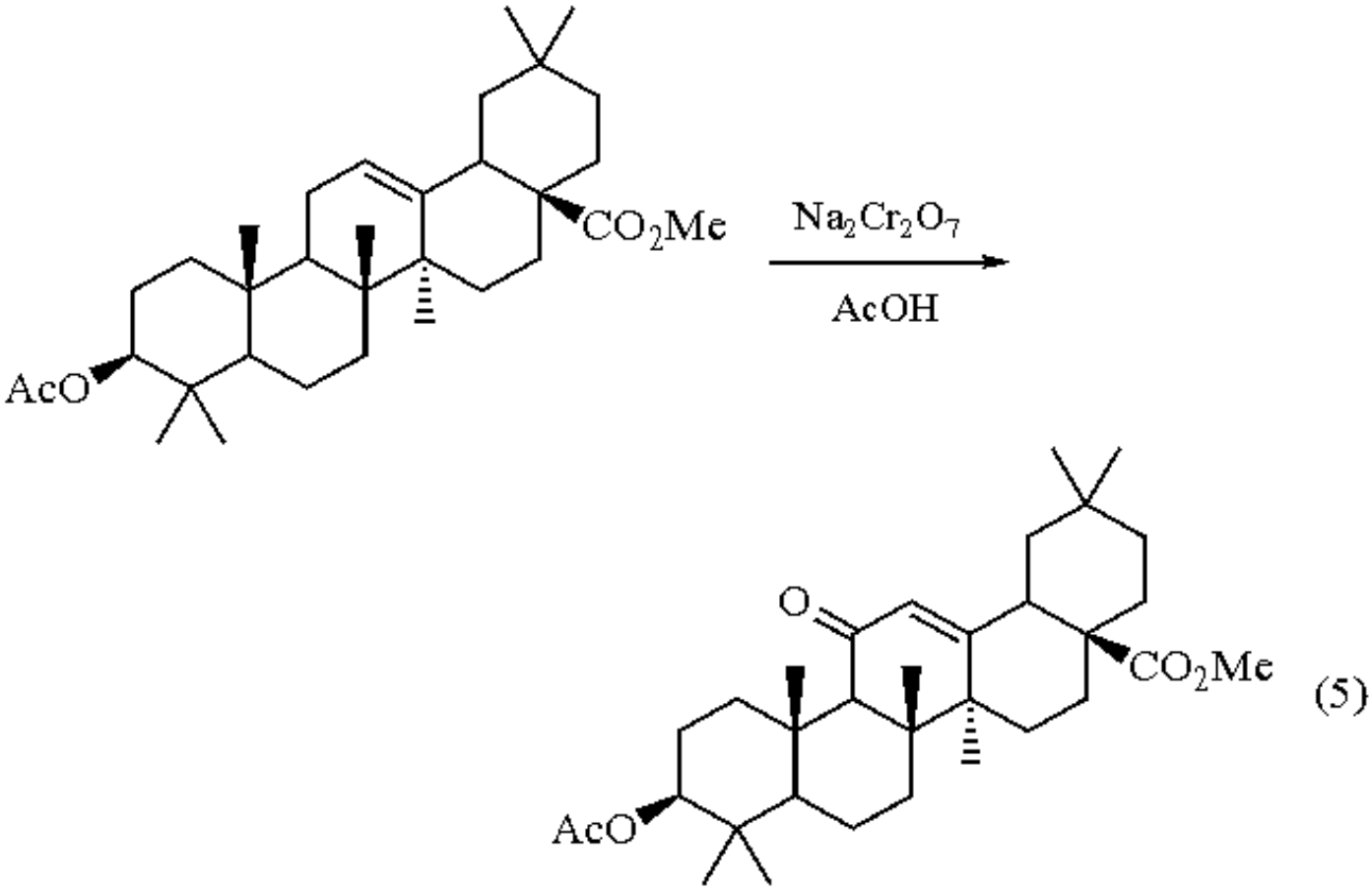

Oxidation of Alcohols to Carbonyl Compounds.

Primary alcohols are oxidized to aldehydes in excellent yields by ***Chromium(VI) Oxide-Silica Gel***, chromium(VI) oxide/graphite, chromium(VI) oxide/Kieselguhr, and other chromium oxidants. Primary alcohols are oxidized to aldehydes, acids, and esters by sodium dichromate.[9-13] Removal of the low molecular weight aldehyde as fast as it is formed increases the yield.[9,10] α,β-Unsaturated aldehydes may be prepared (35-50%) by stirring the α,β-unsaturated alcohols in aqueous sulfuric acid with sodium dichromate, followed by extraction of the product.[14-16] Benzyl alcohols are oxidized to aromatic aldehydes in good to excellent yields.[17] 4-Hydroxymethyl-3-methyl-5-phenylisoxazoles are oxidized to 3-methyl-5-phenylisoxazole-4-carbaldehydes by sodium dichromate in sulfuric acid/DMSO (eq 6).[18] Sodium dichromate in DMSO containing small amounts of sulfuric acid oxidizes primary and secondary saturated, allylic, and benzylic alcohols to carbonyl compounds (80-90%).[19]

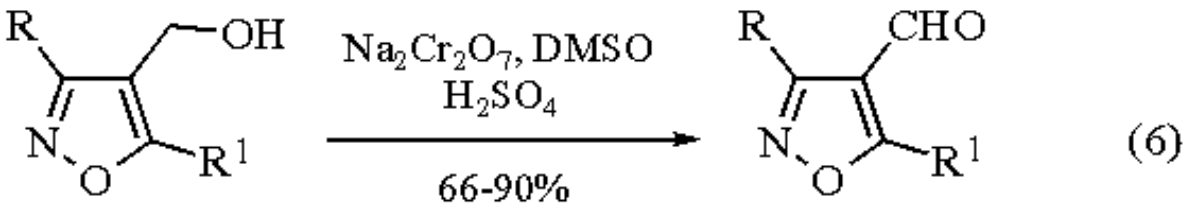

Oxidation of Secondary Alcohols to Ketones.

Secondary alcohols are generally oxidized by sodium dichromate to ketones in excellent yields.[19-22] A two-phase procedure using sodium dichromate, acetic acid, and benzene oxidized a *cis*/*trans* mixture of 1,5-dihydroxydecalins to a *cis*/*trans* mixture of decalin-1,5-diones (71-76%).[23] This system oxidizes 2,5,5-trimethylcyclohex-2-en-1-ol to 2,5,5-trimethylcyclohex-2-en-1-one in 91% yield.[24] A two-phase system of sodium dichromate, sulfuric acid, water, and ether oxidizes (-)-menthol to (-)-menthone in 97% yield.[25,26] The latter procedure has been used for the selective oxidation of steroidal 16β,20α-diols to 16-keto-20α-ols.[27] Dichloromethane has also been used as the organic phase in the sodium dichromate/sulfuric acid oxidation of a *cis*/*trans* mixture of 2-cyclopentene-1,4-diol to the 2-cyclopentene-1,4-dione.[28] The organic phase protects the product from undesirable side reactions such as oxidation and epimerization. Of the three organic solvents, ethyl ether appears to be the one of choice owing to the ease of product isolation. Other examples of the two-phase sodium dichromate oxidation of alcohols are shown in eqs 7 and 8.[29] Addition of a phase-transfer catalyst improves the two-phase transfer procedures.[30,31]

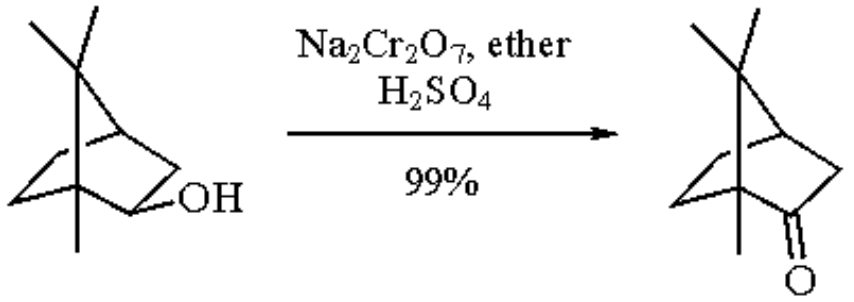

(7)

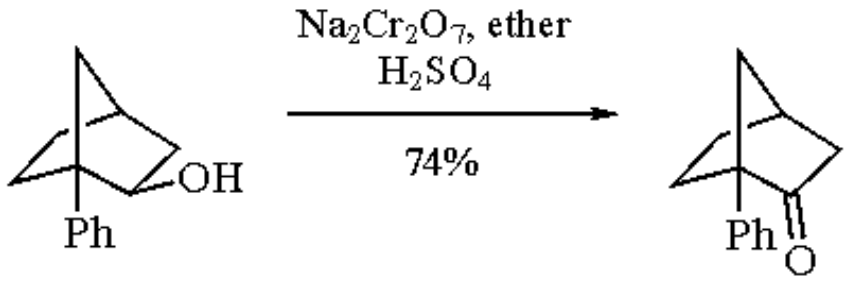

(8)

Other Applications.

Sodium dichromate in aqueous sulfuric acid oxidizes phenols, anilines, and aminophenols to *p*-quinones.[32,33] 3-Iodo-4-aminophenol is oxidized to 2-iodobenzoquinone in 95% yield. Sodium dichromate in acetic acid/sulfuric acid oxidizes phenols with an alkyl group *para* to the oxygen function to quinones and coupling products (eq 9).[34] The minor product arises from oxidative elimination of the tertiary alkyl group from the *para* position. Sodium dichromate in acetic acid, sulfuric acid, and water (Kiliani reagent)[35,36] oxidizes the triol digitogenin to digitogenic acid (a 13-keto-2,3-dioic acid).[35]

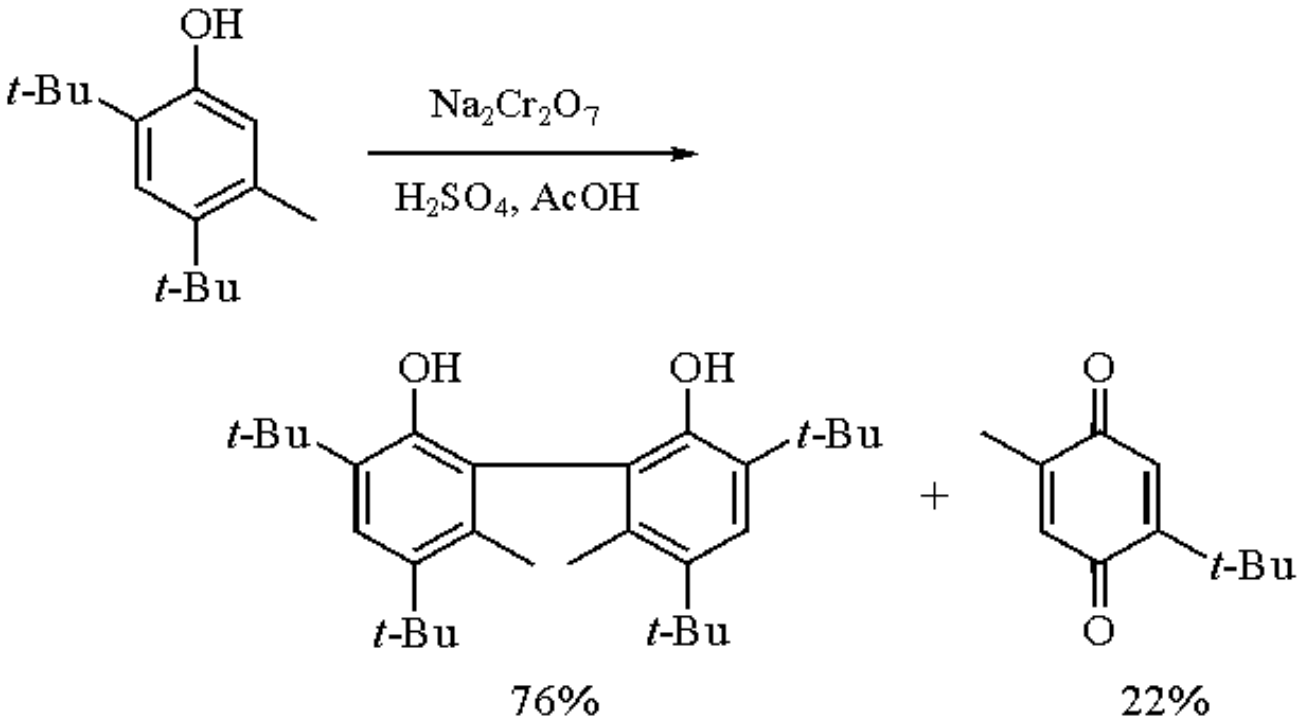

(9)

Borinate esters derived from the hydroboration of homoallylic alcohols were oxidized with sodium dichromate in aqueous sulfuric acid to racemic and enantiomeric γ-butyrolactones (2-oxotetrahydrofurans).[37] Hydroboration of 1-alkyl- and 1-aryl-1-indenes followed by sodium dichromate oxidation leads to the corresponding 1-alkyl- and 1-aryl-2-indanones (70-80%).[38]

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Fillmore Freeman

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Sodium *O,O*-Diethyl Phosphorotelluroate

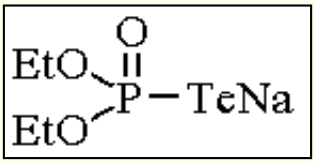

[65857-68-3] · $C_4H_{10}NaO_3PTe$ · Sodium *O,O*-Diethyl Phosphorotelluroate · (MW 287.69)

(deoxygenation of epoxides,[1] dehalogenation of α-bromo and α-chloro ketones,[2] debromination of vicinal dibromides,[3] and for use in the preparation of sulfones[4])

Physical Data: white solid;[1] NMR data (^{31}P and ^{1}H) have been reported.[1]

Solubility: sol ethanol, tetrahydrofuran.[1]

Preparative Methods: [1] generated in situ by addition of ethanolic sodium diethyl phosphite to metallic tellurium. When made separately, the reagent is best formed in THF. This solvent can then be replaced by ethanol, which is the best solvent for epoxide deoxygenation.

Handling, Storage, and Precautions: the reagent is extremely air sensitive and is preferably made just before use or, more simply, generated in situ.[1]

Deoxygenation of Epoxides.[1]

Sodium *O,O*-diethyl phosphorotelluroate and the lithium salt, which is more reactive, deoxygenates epoxides to the corresponding alkenes. The reaction occurs in ethanol solution but in THF is too slow to be useful. Reaction takes place most easily with terminal epoxides and it can be run for these cases, as well as for certain others, by using much less than a stoichiometric amount (e.g. 2-20 mol %) of tellurium. For such experiments, sodium diethyl phosphite is added to a stirred mixture of the epoxide, ***Tellurium***, and ethanol. When used stoichiometrically, the reagent is made in THF, and the solvent is evaporated and replaced by ethanol. The deoxygenation is stereospecific and epoxides derived from (*Z*)-alkenes are more reactive than those from (*E*)-alkenes. Reaction occurs more easily with cyclohexene oxide than with cyclopentene oxide. Typical deoxygenations are shown in eqs 1-4.

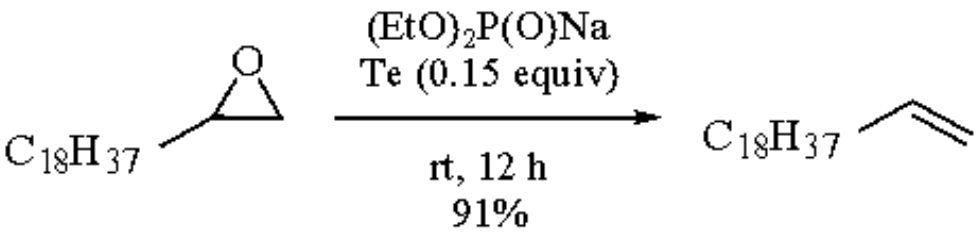

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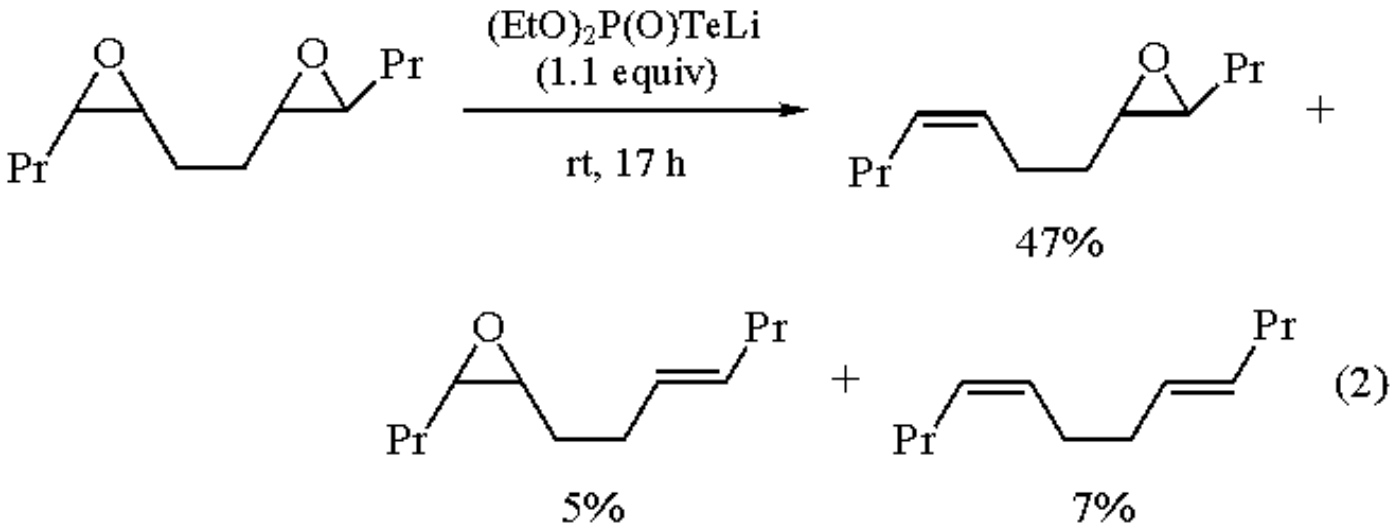

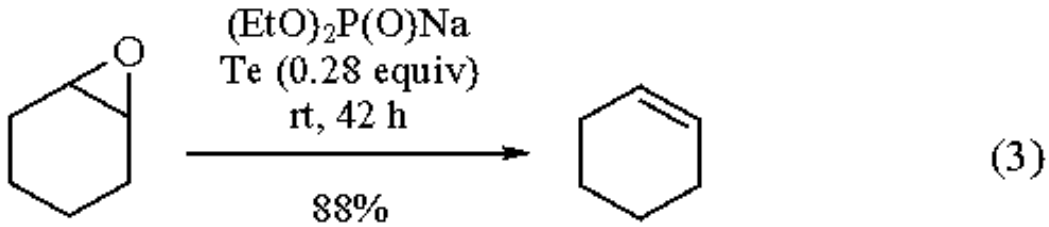

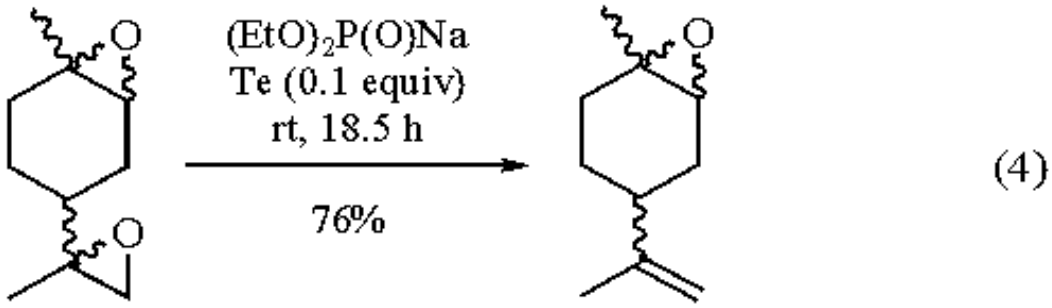

Dehalogenation of α-Bromo and α-Chloro Ketones.[2]

α-Bromo and α-chloro ketones, on treatment with sodium *O,O*-diethyl phosphorotelluroate in ethanol or THF, are converted into the parent ketone. Reaction proceeds in the temperature range 25-80 °C and reaction times vary from 45 min to 15 h. For highest yields, a stoichiometric amount of reagent is best, but a catalytic amount of tellurium and a stoichiometric amount of sodium diethyl phosphite can also be used. The catalytic mode is possible because sodium *O,O*-diethyl phosphate reacts only slowly with α-bromo ketones, but rapidly with tellurium, and the reagent itself reacts rapidly with α-halo ketones. The selenium analog, sodium *O,O*-diethyl phosphoroselenoate, does not appear to dehalogenate α-bromo ketones,[2] the selenium atom merely being alkylated. Typical results with the tellurium reagent are shown in eqs 5 and 6.

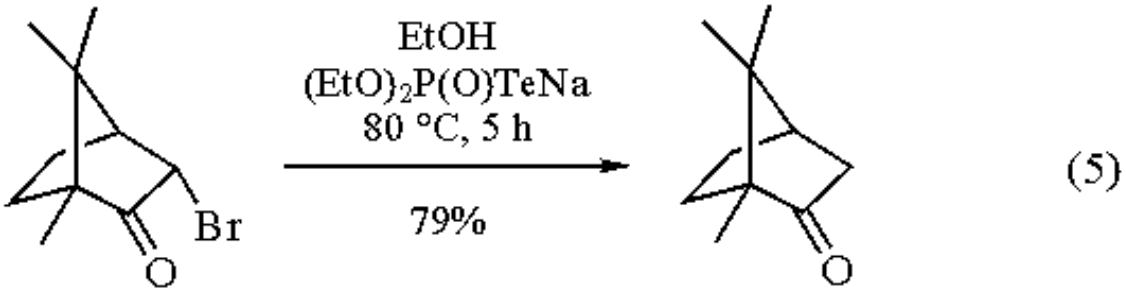

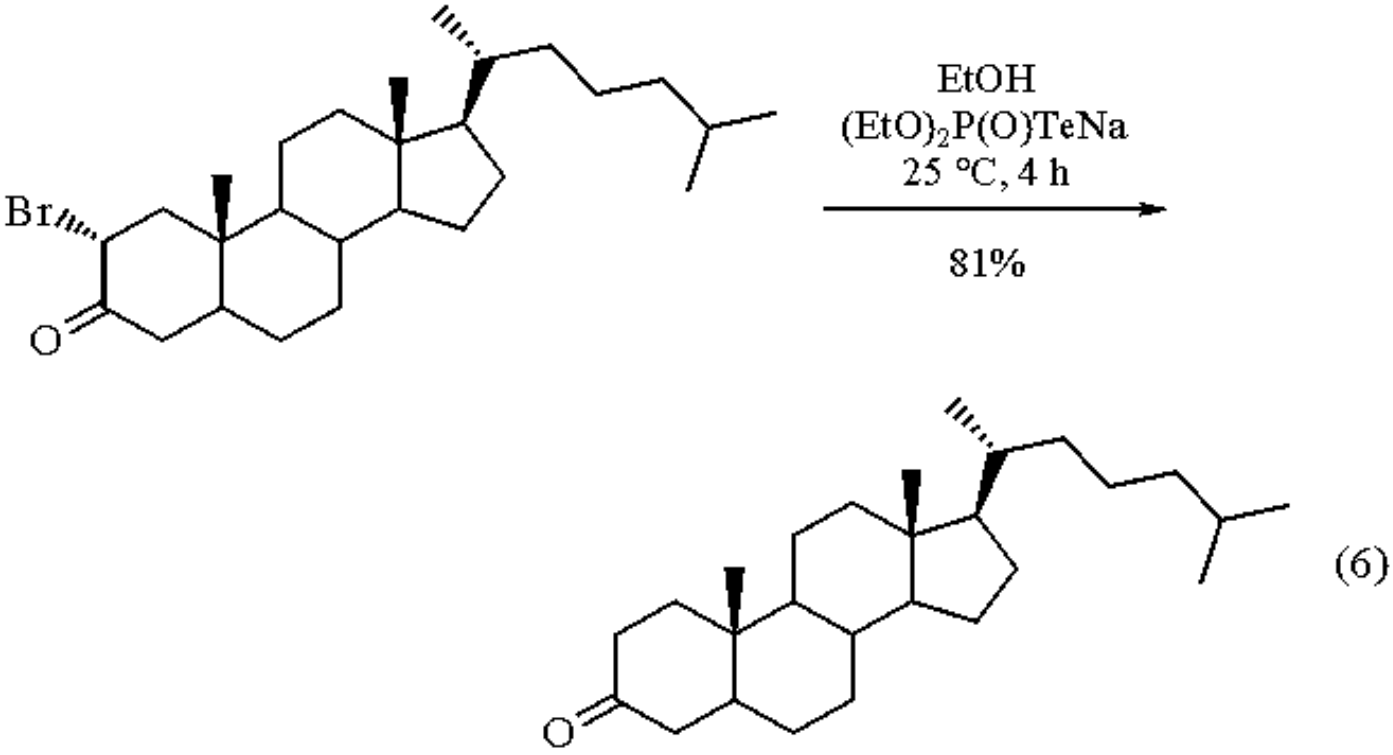

Debromination of Vicinal Dibromides.[3]

Vicinal dibromides are converted (2.5-10 h at rt; 64-88% yields) into the corresponding alkenes by treatment in ethanol with sodium diethyl phosphite and a catalytic amount of tellurium (eqs 7 and 8). The alkene geometry corresponds to removal of the bromine from an antiperiplanar conformation.

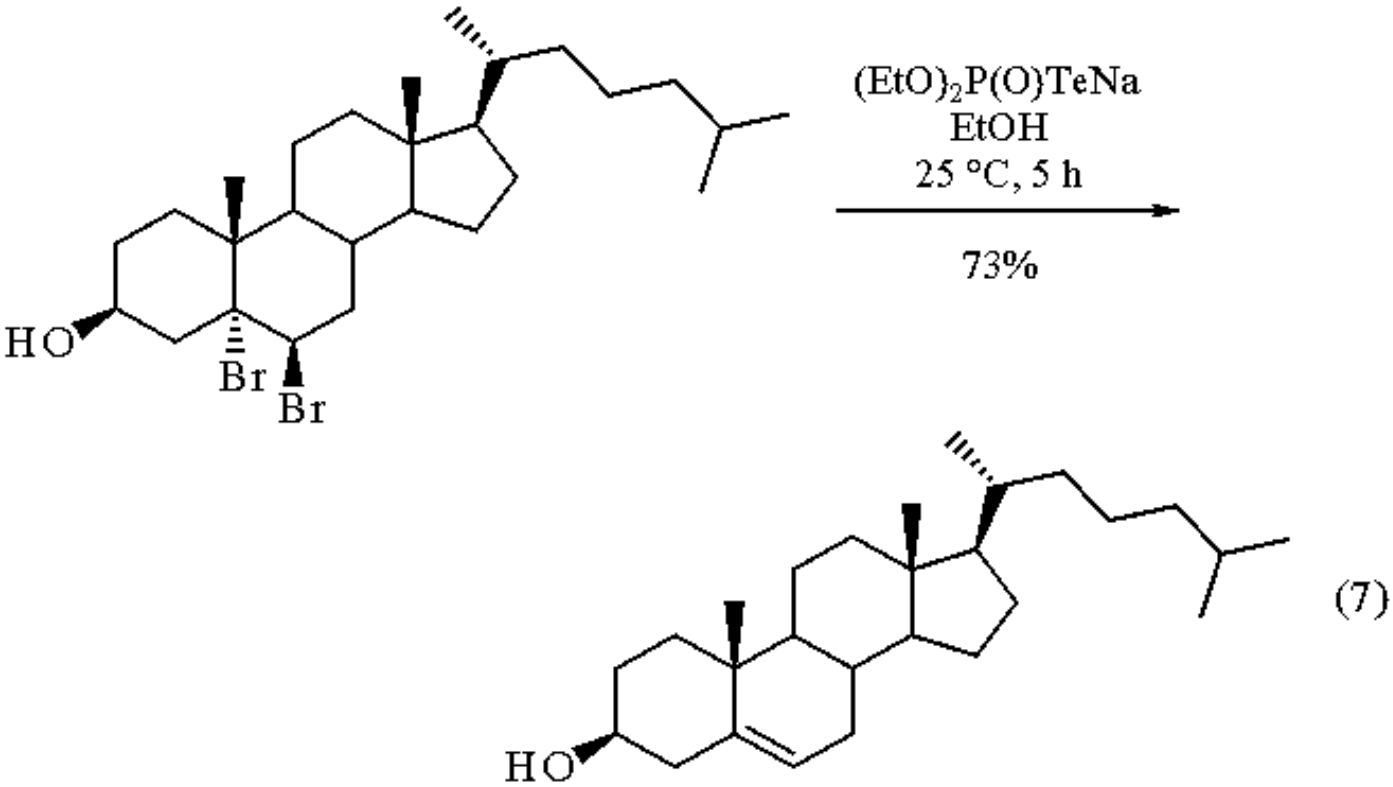

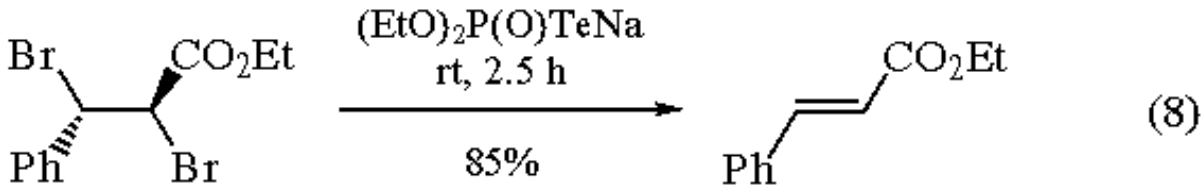

Formation of α,β-Unsaturated Ketones.[4]

2-Bromoacetophenone has been converted into a series of α,β-unsaturated ketones (eq 9) by treatment with an aldehyde in ethanol in the presence of sodium *O,O*-diethyl phosphorotelluroate (77-93% yield).

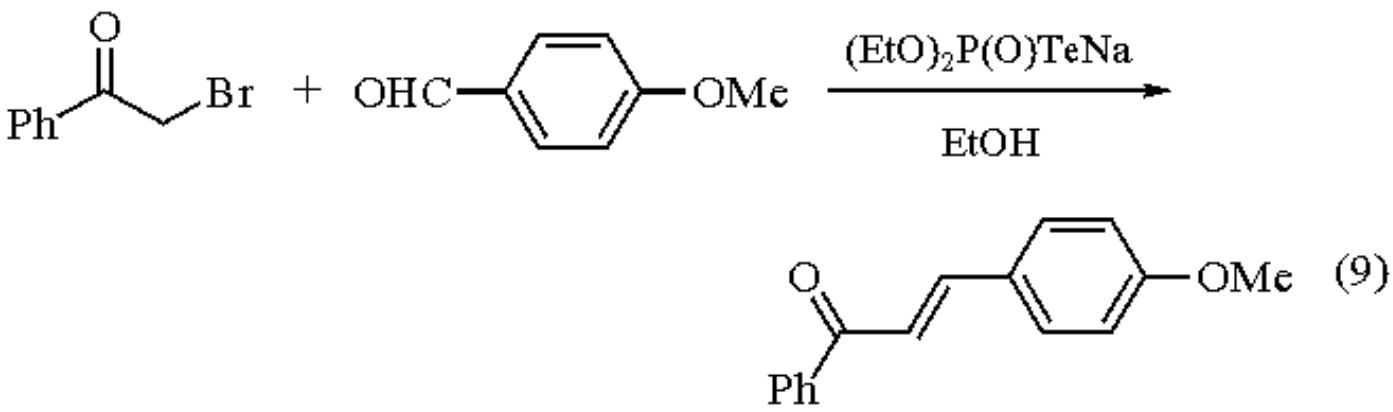

Conversion of Arenesulfonyl Chlorides into Sulfones.[5]

Aryl sulfonyl chlorides are converted by sodium *O,O*-diethyl phosphorotelluroate into the corresponding sodium sulfinates. These then react in situ with alkyl halides to afford sulfones in 77-94% yield (eq 10).

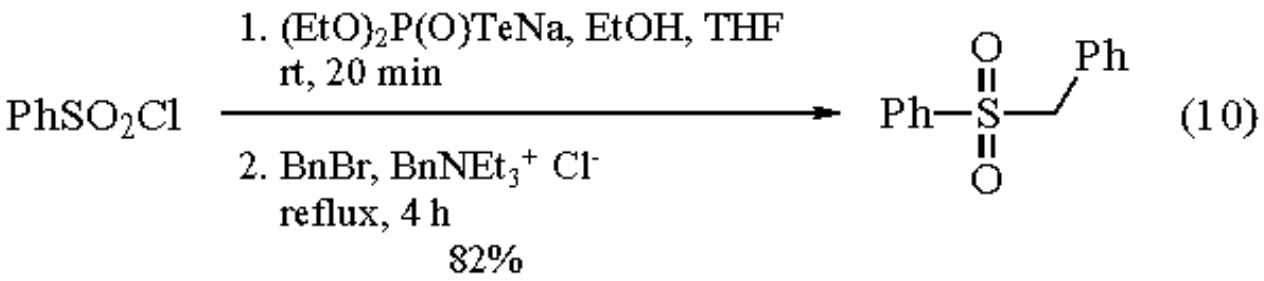

Related Reagents.

Chromium(II) Chloride; ***Chromium(II) Sulfate***; ***Diphenylphosphine***; ***3-Methyl-2-selenoxobenzothiazole***; ***Sodium Dicarbonylcyclopentadienylferrate***; ***Sodium Iodide***; ***Sodium Nitrite***; ***Sodium Selenide***; ***Tellurium***; ***Tetrakis(triphenylphosphine)palladium(0)***; ***Tin(II) Chloride***; ***Tungsten(VI) Chloride-n-Butyllithium***; ***Zinc/Copper Couple***.

---

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Sodium 4,6-Diphenyl-1-oxido-2-pyridone

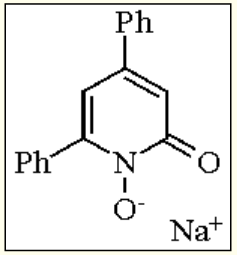

[65218-74-8] · $C_{17}H_{12}NNaO_2$ · Sodium 4,6-Diphenyl-1-oxido-2-pyridone · (MW 285.29)

(nonhydrolytic conversion of alkyl and benzyl halides to aldehydes and ketones)

Alternate Name: pyridona.

Physical Data: white solid, mp 299-301 °C.

Solubility: sol methanol, DMF, ethanol.

Preparative Methods: the reagent is not commercially available. It can be synthesized by treatment of ethyl benzoylacetate with ***Sulfuric Acid*** to give 4,6-diphenyl-2-pyrone,[1] which is converted by reaction with ***Hydroxylamine*** followed by base to the title compound (eq 1).[2,3]

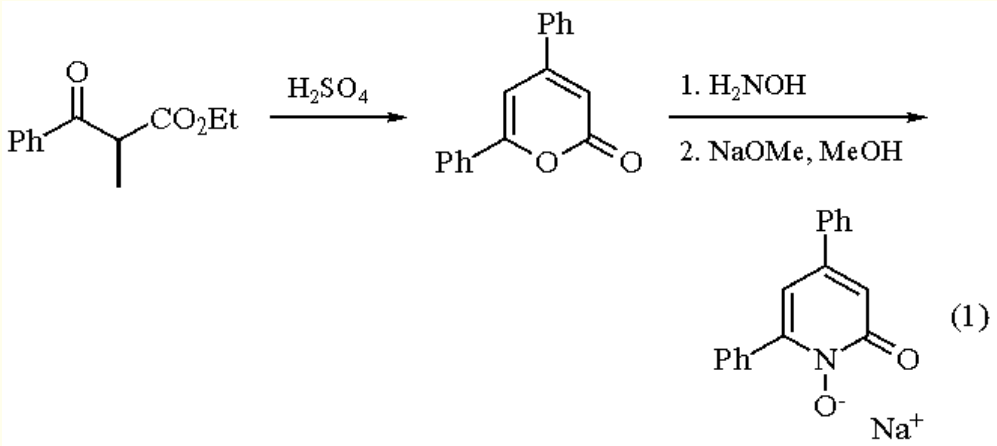

Purification: the salt is used without purification. The *N*-hydroxy precursor, mp 162 °C, is recrystallized from benzene light petroleum.

Analysis of Reagent Purity: ^{1}H NMR (DMSO-d_6) δ (ppm) 6.4 (1H, s), 6.5 (1H, s), 7.5 (10H, m).

Handling, Storage, and Precautions: store protected from moisture.

Oxidation of Alkyl and Benzyl Halides.

A disadvantage of most of the methods of accomplishing this transformation[4] (e.g. the Kröhnke and Kornblum oxidations) is the need for strongly hydrolytic conditions which may be deleterious to sensitive functionality. Furthermore, many of these alternative methods are limited to activated (allylic or benzylic) halides. The reaction employing pyridona developed by Katritzky et al. avoids these problems.[3,5-7] This oxidation takes place in two steps. First, the halide and title reagent are allowed to react together in a solvent (usually DMF but also MeOH and EtOH), giving the *N*-alkoxy-2-pyridone derivative. On thermolysis or photolysis, this compound then undergoes homolytic decomposition to the carbonyl compound and the 2-pyridone (eq 2).

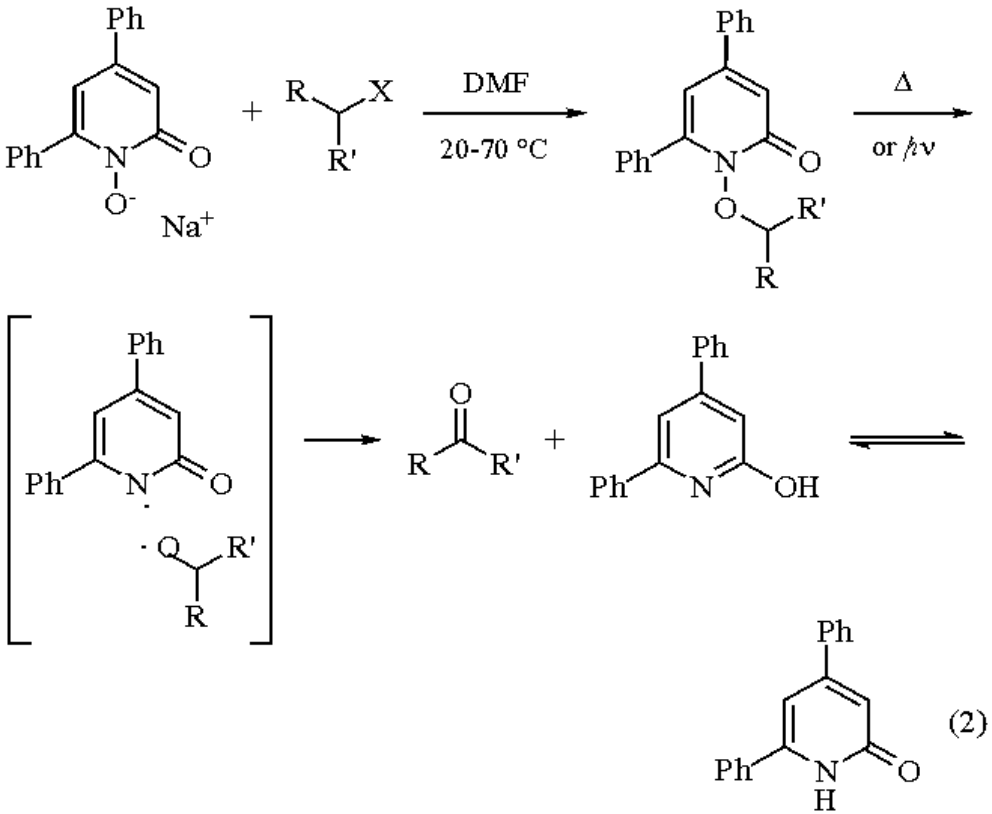

As can be seen from Table 1, the reaction proceeds very smoothly for benzylic halides. For certain aliphatic halides a significant amount of the alcohol is produced as a byproduct in the second step.

Table 1 Conversion of Halides to Carbonyl Compounds using Pyridona

R	R¢	X	Yield, 1st step (%)	Yield, D (%)	Temp (°C)	Yield, hn (%)
Ph	H	Br	94	73	200	80
4-$NO_2C_6H_4$	H	Br	99	79	190	53
2,4,6-$(NO_2)_3C_6H_2$	H	Cl	72	93	140	
Pr	H	Br	94	59	240	
C_7H_{15}	H	I	94	37[a]	240	47
MeCH=CH	H	Cl	96	53	200	
Me	CH_3	Br	94	32	220	
Bn	H	Br	99	49	220	30

[a] 13% alcohol isolated.

The thermolysis is usually performed neat, and the carbonyl compound is obtained as it is formed by distillation from the reaction mixture. The alternative photolysis procedure is conducted with a medium-pressure mercury lamp through a pyrex filter, usually in ethyl acetate or benzene (eq 3). A limitation of the method is the further fragmentation of certain substrates.[6]

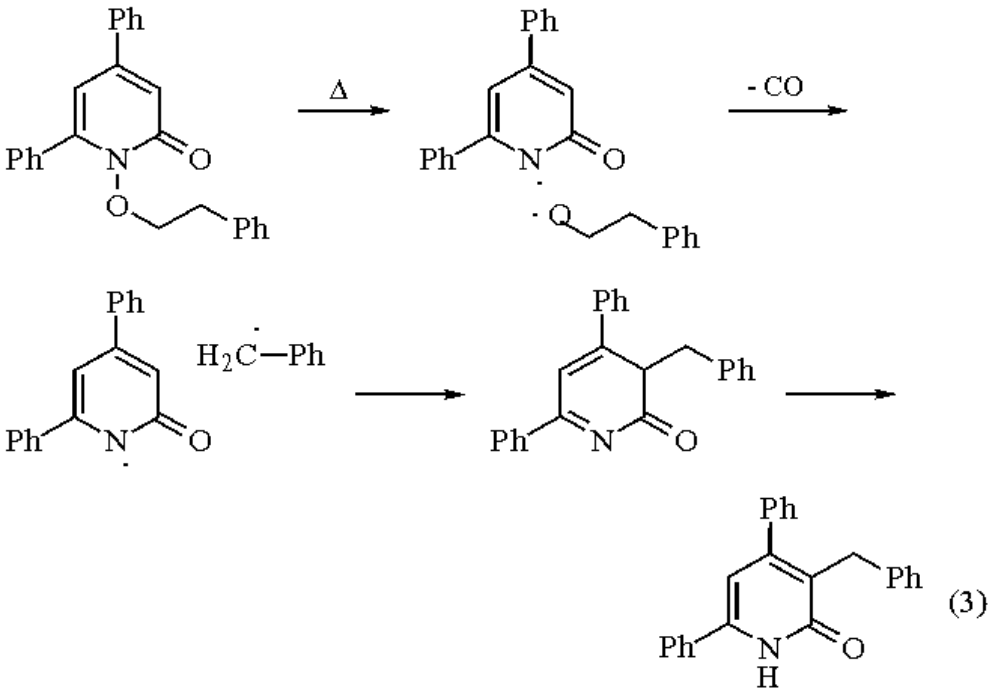

The oxidation may be performed with comparable results with the alternative reagents (**1**) and (**2**).[8]

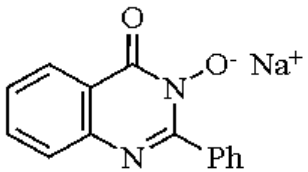

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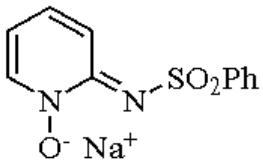

(2)

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S. Nicholas Kilényi

Sanofi Research, Brussels, Belgium

Sodium Diselenide[1]

Na_2Se_2

[39775-49-0] · Na_2Se_2 · Sodium Diselenide · (MW 203.90)

(nucleophilic agent for synthesis of organic diselenides[1,2])

Alternate Name: disodium diselenide.

Physical Data: mp about 495 °C.

Solubility: readily sol water, forming a red solution which easily decomposes on contact with air, separating selenium; sol ethanol, liquid ammonia; sparingly sol THF.

Form Supplied in: dull gray-black, microcrystalline material; used in solution or suspension without isolation.

Preparative Methods: heat equimolar amounts of ***Sodium*** and ***Selenium*** under nitrogen at 500 °C, or reduce Se with Na in liquid ammonia.[4] ***Sodium Hydroxymethanesulfinate*** (rongalite) in water[5] and ***Sodium Borohydride*** in water or ethanol[6] are used as reducing agents. ***Hydrazine*** in aqueous alkali also reduces Se, giving Na_2Se_2 or K_2Se_2 solutions as a source of Se_2^{2-}.[7,8] A combination of electrochemical reduction of Se and ultrasound will produce the Se_2^{2-} anion in THF, acetonitrile, or DMF.[9] A suspension of Na_2Se_2 (or K_2Se_2) can be produced in high-boiling polar aprotic solvents, such as DMF, HMPA, or NMP by the direct reaction of selenium powder with sodium or ***Potassium***.[10] A similar reduction in THF, carried out in the presence of catalytic amounts of naphthalene, is the best way to prepare of a suspension of Na_2Se_2 or K_2Se_2 in this solvent.[2]

Handling, Storage, and Precautions: very hygroscopic; decomposes in moist air, turning red. It should be used as prepared without isolation. Use in a fume hood.

Synthesis of Diselenides.

The diselenide anion Se_2^{2-} derived from Na_2Se_2 or K_2Se_2 is an excellent nucleophilic agent used for the synthesis of dialkyl diselenides from alkyl halides or sulfates.[2,4-8,11] The alkylating agent is added directly to the alkali metal diselenide solution or suspension and the dialkyl diselenide is formed, usually in high yield (eq 1).[2] Nucleophilic aromatic substitution with the Se_2^{2-} anion is achieved on activated aromatic halides, such as 2-nitrochlorobenzene (eq 2).[12]

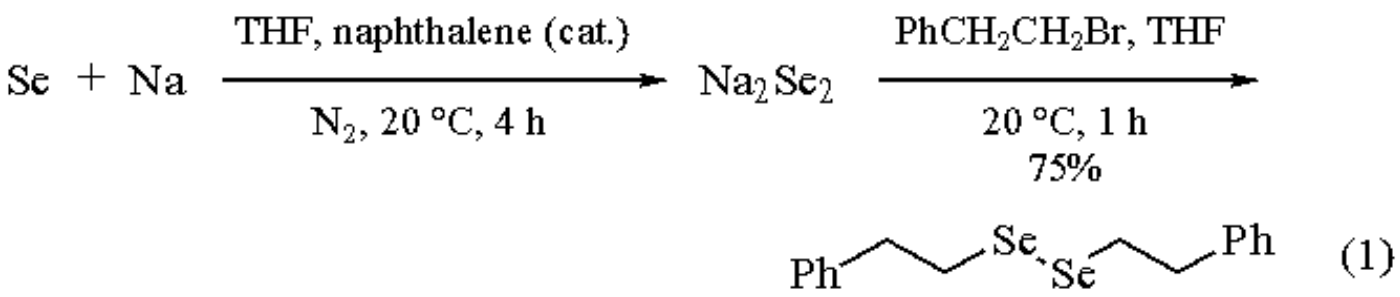

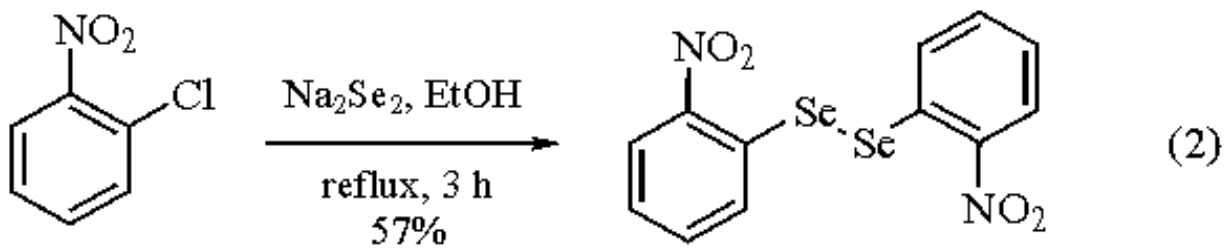

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12. (a) Bogert, M. T.; Stull, A. *JACS* **1927**, *49*, 2011. (b) Battistoni, P.; Bompadre, S.; Bruni, P.; Fava, G. *G* **1981**, *111*, 505. (c) Rheinboldt, H. *MOC* **1955**, *9*, 993.

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Sodium Disulfide[1]

Na_2S_2

[22868-13-9] · Na_2S_2 · Sodium Disulfide · (MW 110.12)

(nucleophilic agent for synthesis of organic disulfides and selective reducing reagent for the nitro group[1-3])

Alternate Name: disodium disulfide.

Physical Data: mp about 495 °C; *d* 2.01 g cm^{-3}.

Solubility: readily sol water; sol ethanol.

Form Supplied in: light yellow, microcrystalline, very hygroscopic powder; gradually darkens on heating. $N_2S_2.6H_2O$, cream colored needles. Alkali metal disulfides are not commercially available.

Preparative Methods: Na_2S_2 preparations are cumbersome and sometimes afford mixtures containing the polysulfides Na_2S_4 and Na_2S_5. They involve reduction of ***Sulfur*** with ***Sodium*** in liquid ammonia,[4] heating Na with S in a vacuum at 500 °C,[4] or heating Na_2S_4 with Na in absolute ethanol under inert gas.[4,5] Na_2S_2 is formed in situ by heating the aqueous or alcoholic ***Sodium Sulfide*** solution with elemental sulfur.[6-9]

Handling, Storage, and Precautions: can be stored for a limited period under anhydrous and oxygen-free conditions, but generally it is used directly as prepared as the aqueous or ethanolic solution.

Organic Disulfides Formation.

Alkylation of Na_2S_2 with alkyl halides or sulfonates is a good synthesis of symmetrical disulfides.[1,2,9-11] For example, when 1-bromopentane is treated with Na_2S_2 (generated in situ from Na_2S and S), bis(*n*-pentyl) disulfide is formed in satisfactory yield (eq 1).[12]

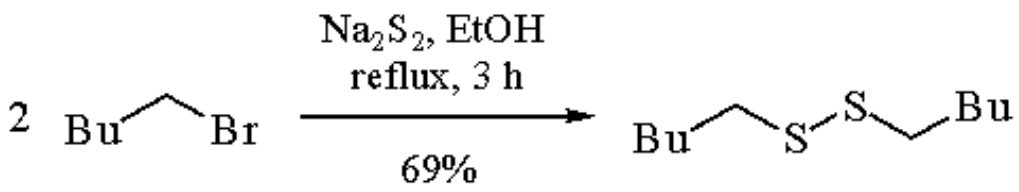

(1)

Activated aryl halides treated with Na_2S_2 produce disulfides in high yields and numerous examples, among them the preparation of bis(2-nitrophenyl) disulfide (eq 2), have been reported.[1,2,13]

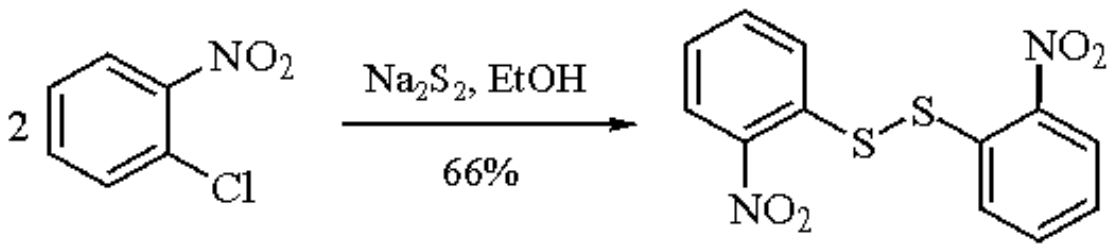

(2)

The Sandmeyer-type displacement of the diazonium group by S^{2-} anion gives aryl disulfides. Reaction of this type is used for synthesis of thiosalicyclic acid (eq 3).[6] Although many arenediazonium salts arylate Na_2S_2, one should beware of possible explosions, probably caused by an accumulation of diazosulfides.[1,2]

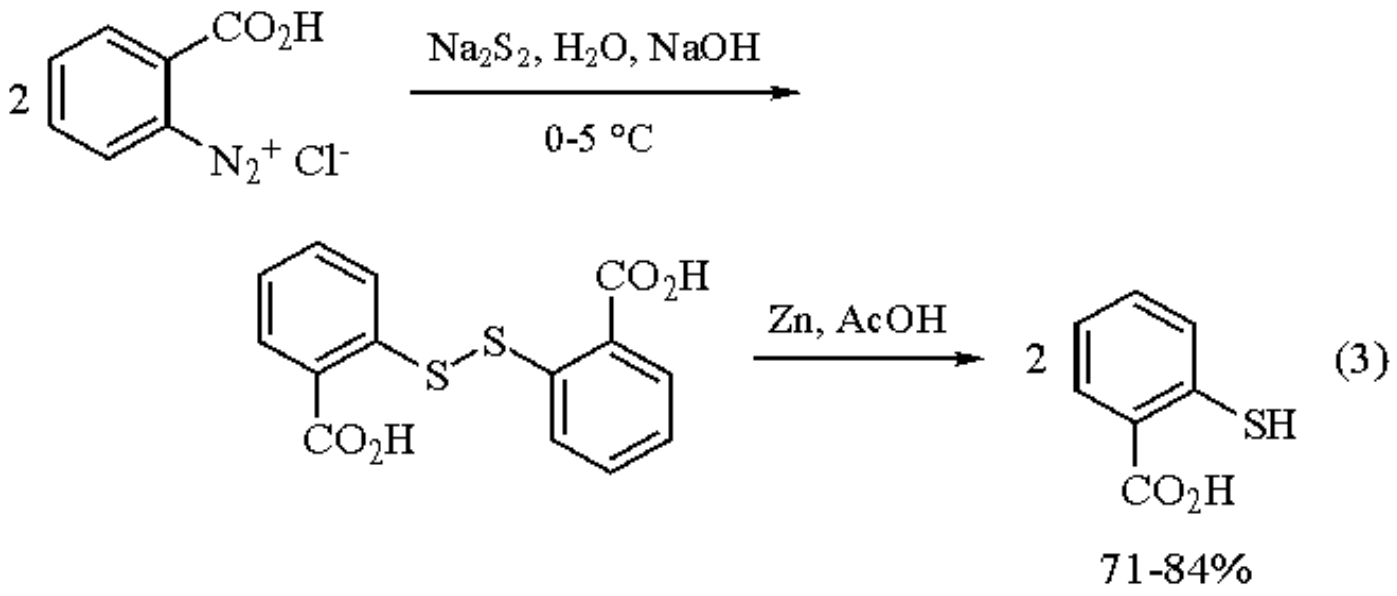

Selective Reduction of Nitro Groups.

Na_2S_2 is a useful reducing reagent for the nitro group in the presence of other functional groups. It is used for selective reduction of 3-nitrobenzonitrile to 3-aminobenzonitrile, and of one nitro group in 4,6-diamino-1,3-dinitrobenzene (eq 4).[7] The reaction of 4-nitrotoluene with Na_2S_2 and polysulfides, generated in situ from Na_2S and S, involves an interesting disproportionation. The methyl group is oxidized to formyl, and the nitro group is reduced to NH_2. Finally, 4-aminobenzaldehyde is obtained as a product (eq 5).[8]

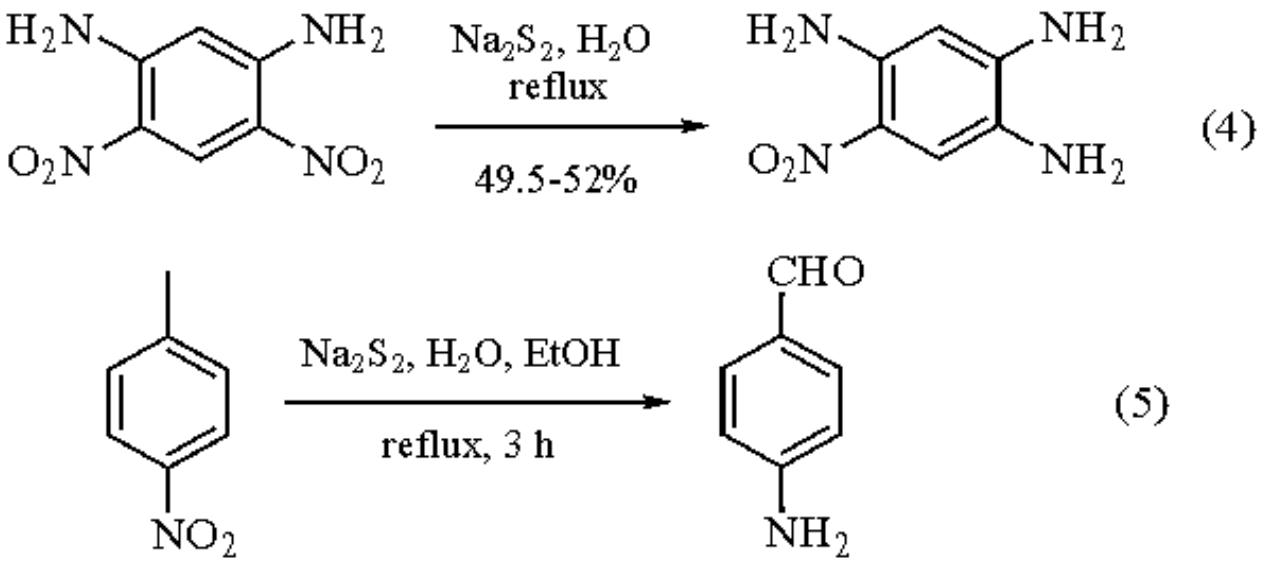

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Sodium Dithionite[1]

$Na_2S_2O_4$

[7775-14-6] · $Na_2O_4S_2$ · Sodium Dithionite · (MW 174.12)

(versatile reagent for reduction of aldehydes,[2] ketones,[2-6] unsaturated conjugated ketones,[7,8] quinones,[9-10] diunsaturated acids,[11] azo,[12] nitro,[13] and nitroso compounds,[14,15] imines,[16] oximes,[17] tropylium salts,[18] pyridinium salts,[19] pyrazine,[20] and vinyl sulfones;[21] intramolecular Marschalk cyclizations,[22,23] dehalogenation of *vic* dibromides[24] and α-halo ketones,[25] Claisen rearrangement of allyloxyanthraquinones[26] and for the synthesis of 8-arylaminopurines[27,28])

Alternate Name: sodium hydrosulfite.

Physical Data: mp 52 °C (dec).

Solubility: very sol water; sol alcohol.

Form Supplied in: white or gray-white crystalline powder.

Preparative Methods: by the action of ***Sulfur Dioxide*** on ***Sodium Amalgam*** in alcoholic solution.[29,30]

Handling, Storage, and Precautions: flammable; moisture sensitive.

Reduction of Aldehydes and Ketones.[2]

Sodium dithionite is an alternative and less expensive reducing agent than metal hydrides. The reactions are performed in water for soluble substrates, otherwise a 50:50 mixture of water and dioxane or DMF can be used; sodium bicarbonate is added to keep the reaction mixture basic. Examples are hexanal to 1-hexanol (67%), benzaldehyde to benzyl alcohol (84%), cyclohexanone to cyclohexanol (80%),[3] and acetophenone to α-hydroxyethylbenzene (94%).[2] Reduction of methylcyclohexanones by $Na_2S_2O_4$ in benzene-water using adogen (commercial mixture of methyl trialkyl C_8-C_{10} ammonium chloride) as a phase-transfer agent afforded good yields of isomeric mixtures of the corresponding methylcyclohexanols.[3] Reduction using $Na_2S_2O_4$ proceeds with stereoselectivity[4-6] similar to that obtained with metal hydrides (***Sodium Borohydride***) and opposite to dissolving metals reductions, e.g. the reductions of 3α-hydroxy-7-keto-5β-cholanic acid to diols (eq 1).

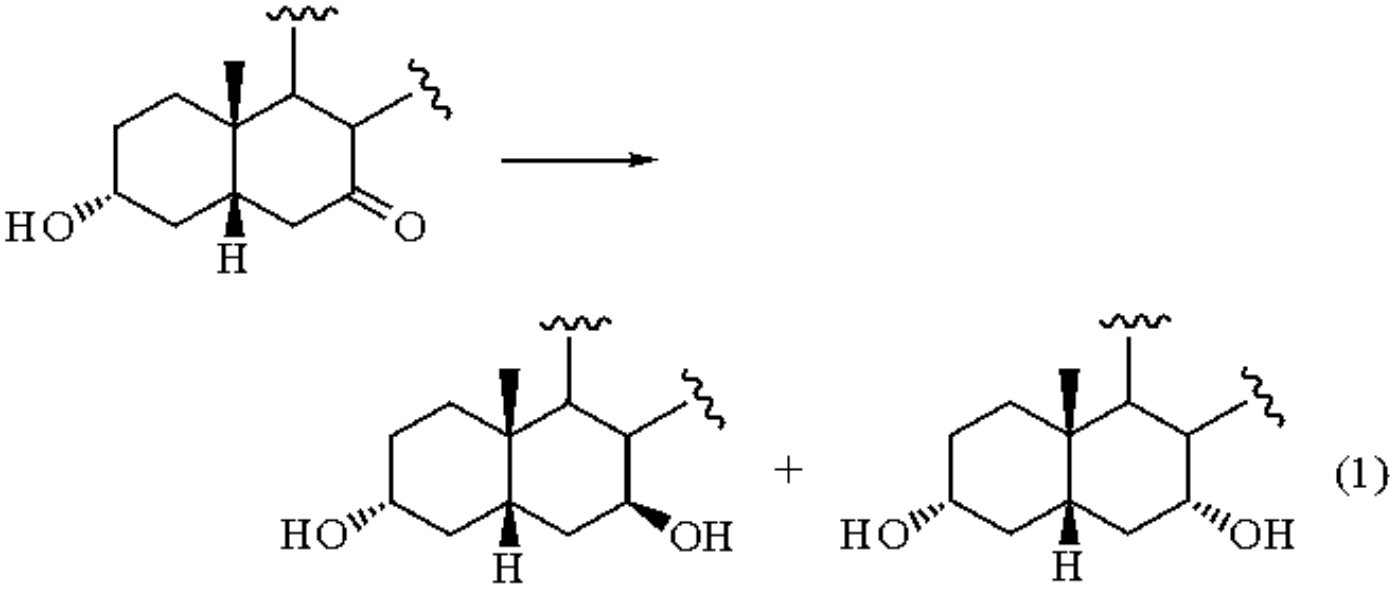

Na, 100%	85:15
K, 100%	94:6
$Na_2S_2O_4$, 100%	4:96
$NaBH_4$, 100%	6:94

Regiospecific Reduction of Unsaturated Conjugated Ketones.[7,8]

Exclusive reduction of conjugated carbon-carbon double bonds is achieved with $Na_2S_2O_4$ to afford the corresponding saturated carbonyl compound. A two-phase (benzene-water) system using adogen as the phase-transfer catalyst is used. The isolated carbon-carbon double bond remains unaffected. No alcohols are detectable (eqs 2-4).

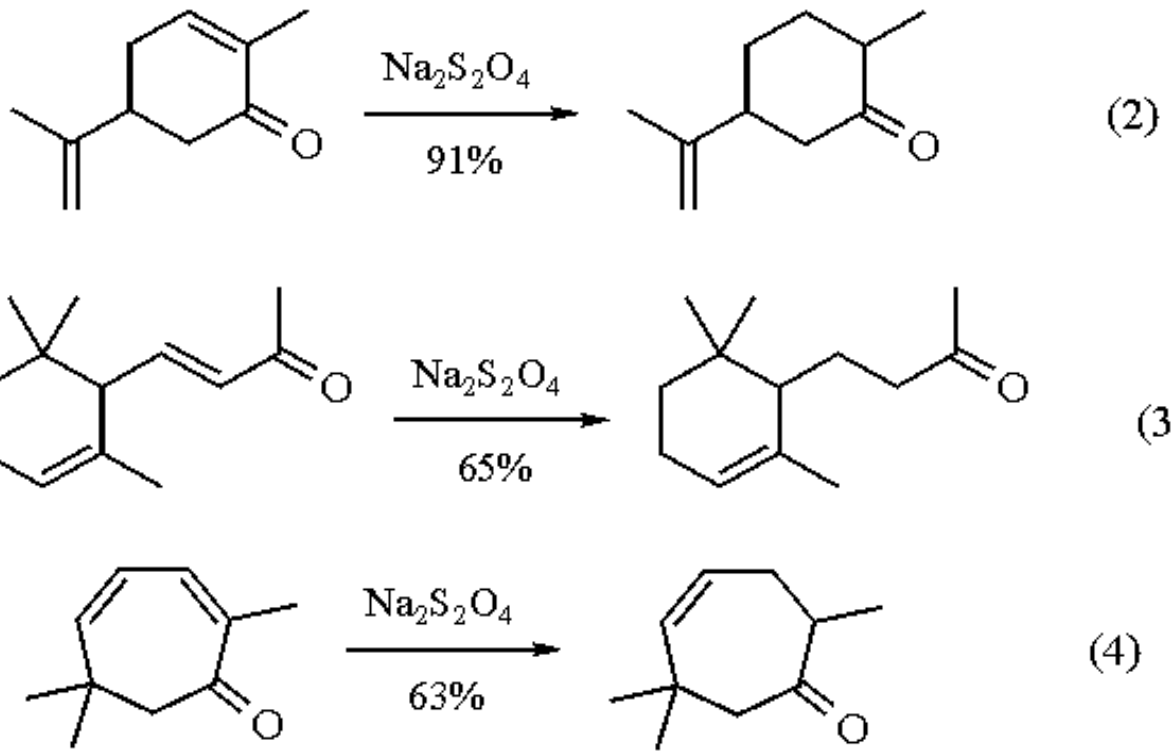

Quinones to Hydroquinones.[9]

Most quinones are reduced by sodium dithionite to hydroquinones. Naphthacenequinone and higher linear benzologs are exceptional in that they are not reduced by alkaline sodium dithionite.[10] Sodium dithionite reduces anthraquinone to anthrone.

Conjugated Diunsaturated Acids (and Esters) to Monounsaturated Acids (and Esters).[11]

α,β;γ,δ-Unsaturated acids are reduced by $Na_2S_2O_4$ in an alkaline medium (NaOH or $NaHCO_3$) to a mixture of (*Z*)- and (*E*)-β,γ-unsaturated acids (and esters) (40-75% yield) (eq 5).

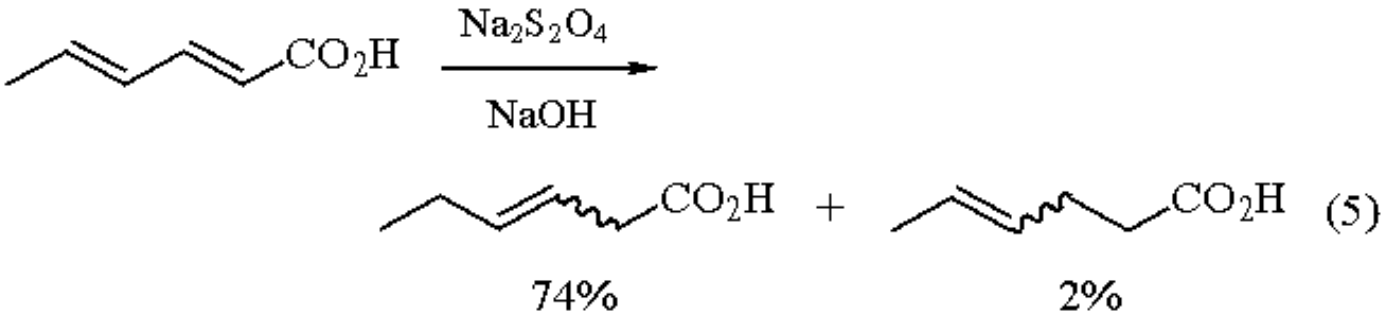

Azo to Amine.[12]

Azobenzene is reduced to aniline by sodium dithionite. This reaction is used to introduce an amino group into a phenolic compound by first coupling with an aromatic diazonium salt and then reducing the resulting hydroxyazo derivatives with $Na_2S_2O_4$, e.g. 2- and 4-amino-1-naphthols can be prepared from 1-naphthol.

Nitro to Amine.[13]

Various aromatic nitro compounds are reduced conveniently to the corresponding aniline derivatives with sodium dithionite using dioctyl viologen as an electron-transfer catalyst in a two-phase system (CH_2Cl_2-H_2O), e.g. 1-nitronaphthalene to 1-naphthylamine.

Nitroso to Amine.

Nitroso compounds are reduced to amines by sodium dithionite, e.g. nitrosouracil to diaminouracil (eq 6).[14] Reduction of *N*-nitrosodibenzylamine[15] with $Na_2S_2O_4$ is accompanied by liberation of N_2 and rearrangement to dibenzyl. Mixed benzylaryl or diaryl-*N*-nitrosoamines are reduced to hydrazines (eq 7).

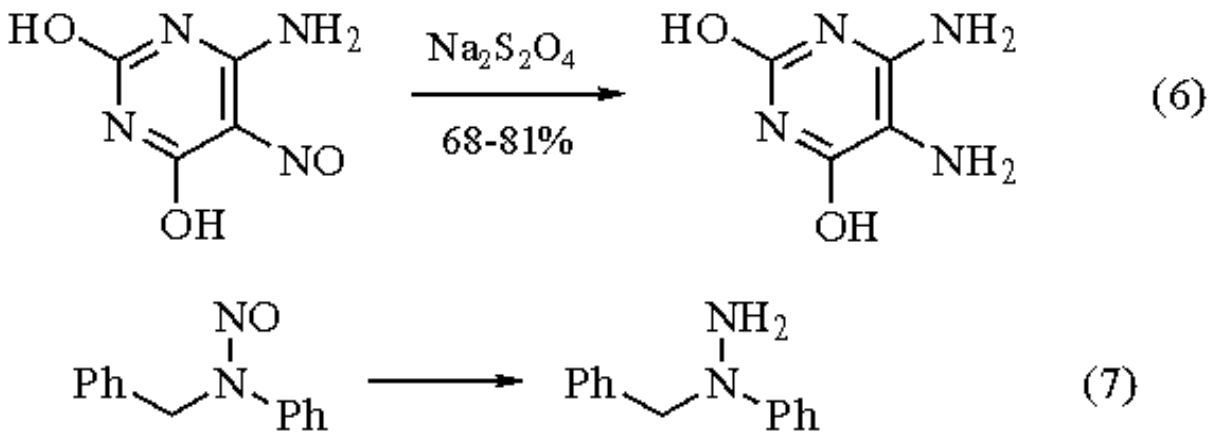

Imines to Amines.

Sodium dithionite in DMF reduces imines[16] to *N*-alkylamines at 110 °C with yields ranging from 40 to 73%. Heating *N*-cyclohexyldibenzylamine, sodium dithionite, and $NaHCO_3$ in DMF for 30 min at 110 °C gives 73% benzylcyclohexylamine.

Oximes to Amines.[17]

Oximes are readily reduced to amines by sodium dithionite. Substituted phenylethylamines are key intermediates required for the synthesis of isoquinoline derivatives. They are readily obtained from aryl alkyl ketones by nitrosation of the alkyl group followed by the reduction of the resulting oxime derivatives by sodium dithionite (eq 8).

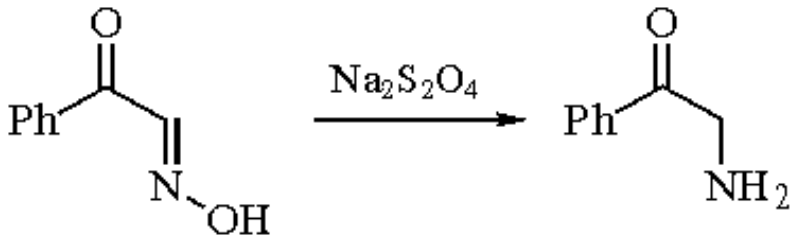

(8)

Cleavage of Oximes.[16]

Both aldehydes and ketones are regenerated from their oxime derivatives with aqueous sodium dithionite either alone or in the presence of Na_2CO_3 at 25 °C, e.g. cyclohexanone oxime to cyclohexanone (95%) and benzaldehyde oxime to benzaldehyde (96%).

Reduction of Tropylium and Cyclopropenium Halides.[18]

$Na_2S_2O_4$ in acetonitrile at 25 °C reduces the tropylium halides to ditropyl (eq 9) and triphenylcyclopropenium halides to bicyclopropenyl sulfones (eq 10).

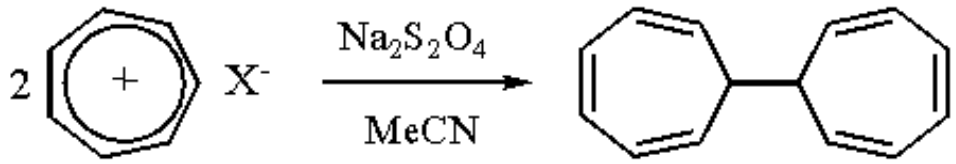

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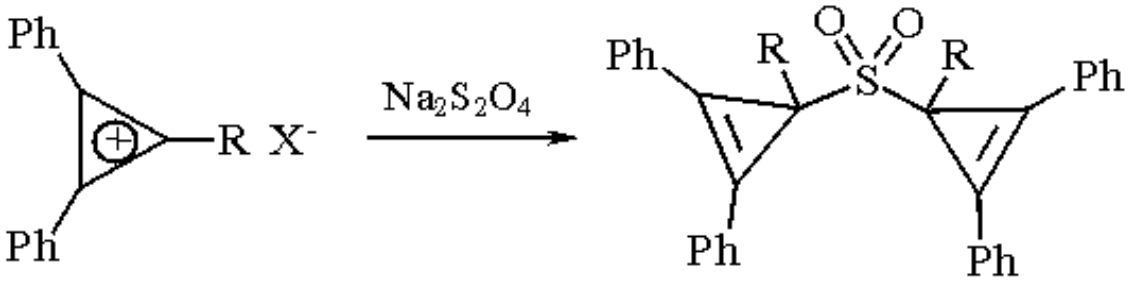

(10)

R = H, Ph

Reduction of Pyridinium Salt.[19]

Sodium dithionite has been extensively used for the reduction of *N*-methylpyridinium-3-carboxamide to *N*-methyl-1,4-dihydropyridine-3-carboxamide (eq 11), which is a model of reduced dihydrophosphopyridine nucleotide (DPNH).

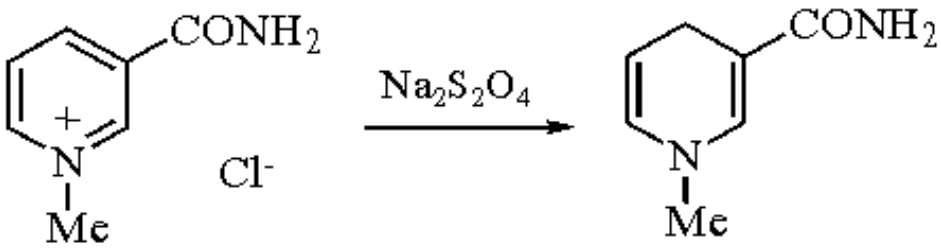

(11)

Reduction of Pyrazine Derivatives.[20]

2,3,5,6-Tetraethoxycarbonyl-1,4-dihydropyrazine is prepared from 2,3,5,6-tetraethoxycarbonylpyrazine using sodium dithionite as

reducing agent (eq 12). It is a more convenient and simpler method than catalytic hydrogenation and no saponification of esters occurred during this reduction process.

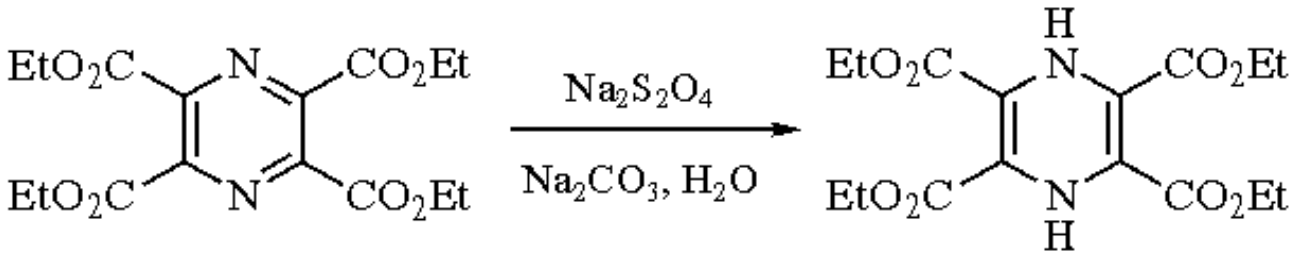

(12)

Reduction of Vinyl Sulfone.

An insect phermone, (*Z*)-8-dodecenyl 1-acetate,[21] is readily obtained by the reduction of corresponding vinyl sulfone in aqueous ethanol with retention of configuration (eq 13). The mechanism involves the Michael addition of SO_2^- to the vinylic sulfone, accompanied by protonation and expulsion of SO_2 and sulfinate ion to give the alkene.

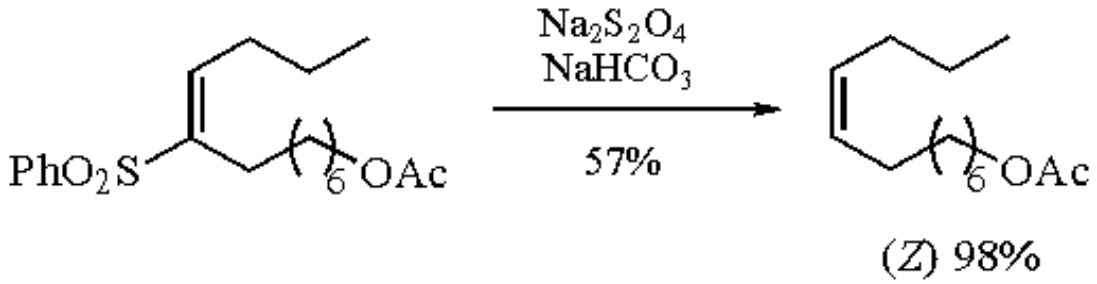

(13)

Intramolecular Marschalk Cyclization.[22,23]

This cyclization reaction is a key step in the total synthesis of daunomycinone, the aglycon of an anthracycline antibiotic. Treatment of the anthraquinone derivative with sodium dithionite and sodium hydroxide in dioxane at 25-90 °C gives the anticipated cyclized product in 52% yield (eq 14).

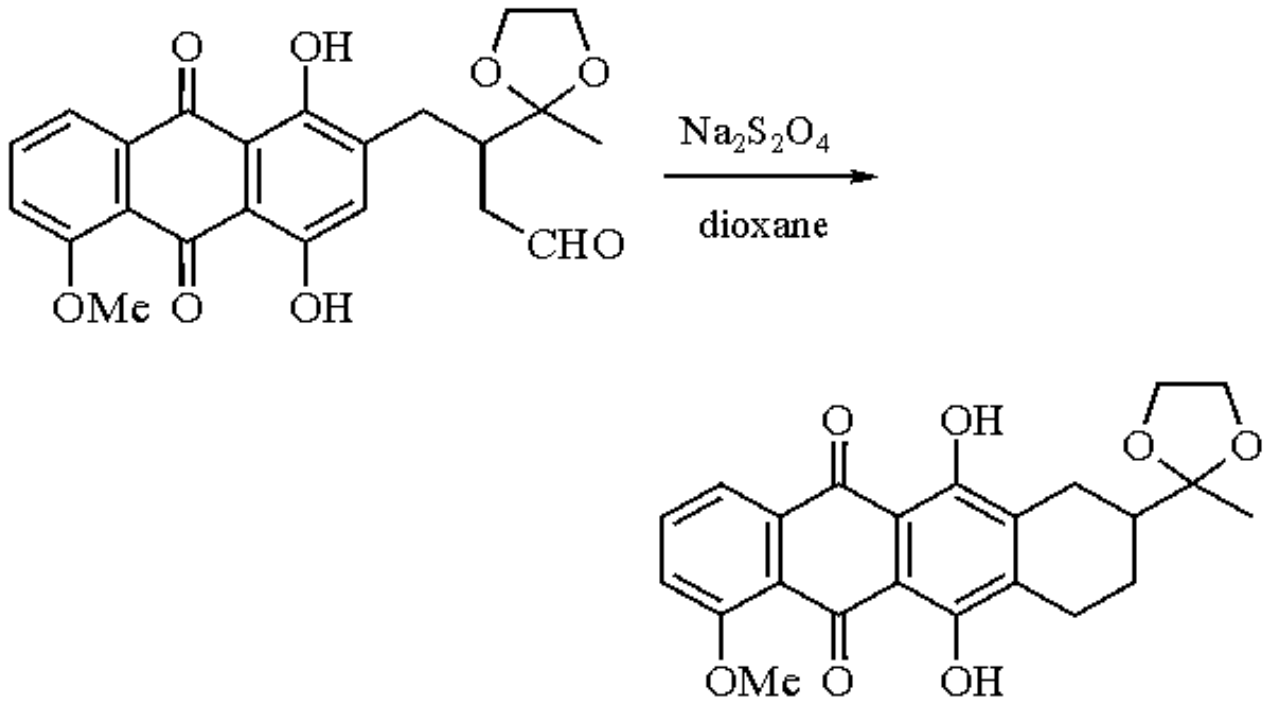

(14)

Dehalogenation of *vic*-Dibromides, α-Bromo and α-Chloro Ketones.

Vicinal dibromides are debrominated[24] with $Na_2S_2O_4$ in DMF (140-145 °C). The yields are moderate to high but the reaction is not

stereospecific. Both *meso*- and (±)-2,3-dibromobutane give 1:1 mixtures of *cis*- and *trans*-2-butene. The dehalogenation[25] of α-bromo or α-chloro ketones can be effected with $Na_2S_2O_4$ in aqueous DMF at 25-90 °C in yields of 50-95%. The rate can be enhanced by addition of $NaHCO_3$.[25]

Claisen Rearrangement of Allyloxyanthraquinone.[26]

1-Allyloxyanthraquinones rearrange to 1-hydroxy-2-allylanthraquinones in high yields when heated in DMF-H_2O containing 1.3-1.8 equiv $Na_2S_2O_4$. 1,4-Bis(allyloxy)anthraquinone rearranges slowly under these conditions, but more readily if 4 equiv NaOH is added (eq 15).

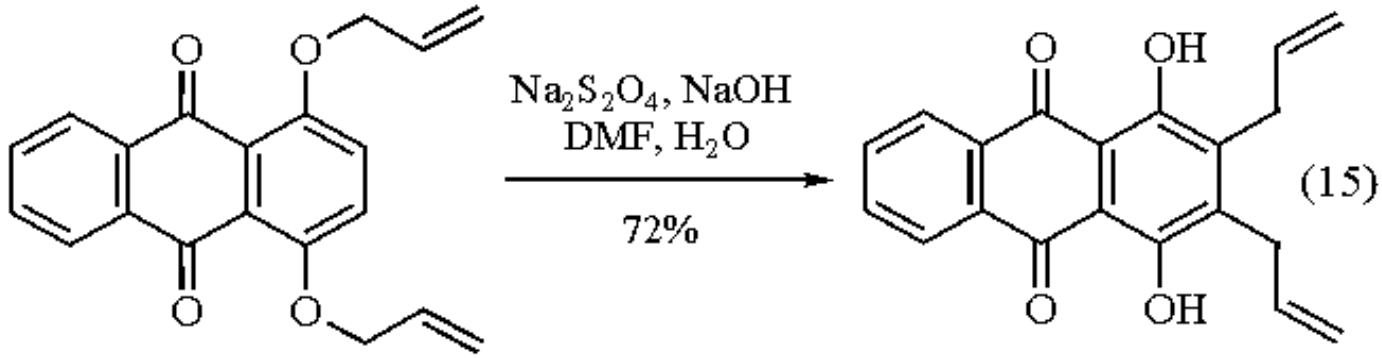

Synthesis of 8-Arylaminotheophyllines.[27,28]

Treatment of 5-arylazo-1,3-dimethyl-6-ethoxymethyleneaminouracil with $Na_2S_2O_4$ in formic acid gives 8-arylaminotheophyllines (eq 16). The key intermediates required for this reaction are prepared by reaction of the appropriate 6-amino-5-arylazo-1,3-dimethyluracils with a mixture of ***Triethyl Orthoformate*** and DMF at 180 °C for 5 h.

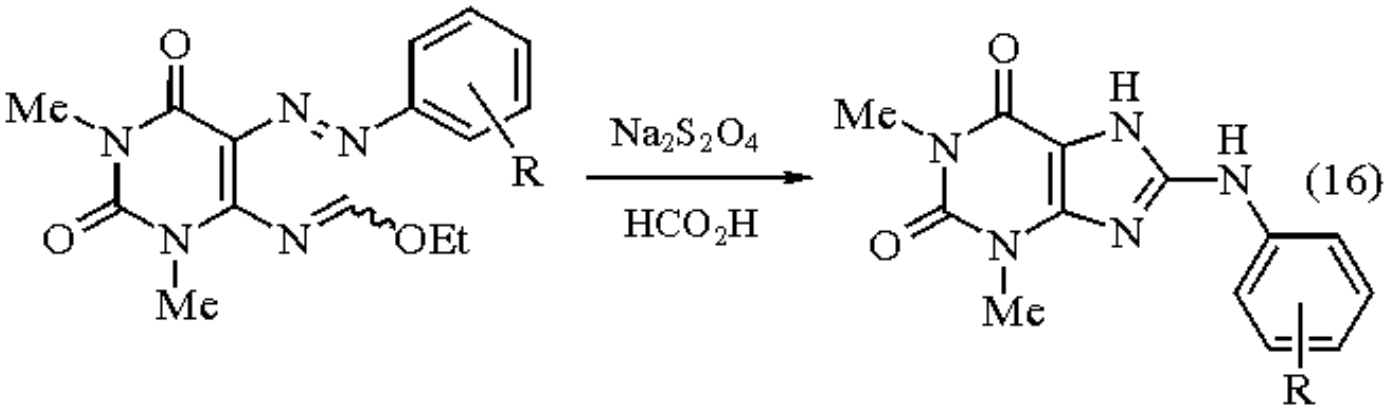

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Sodium Dodecyl Sulfate

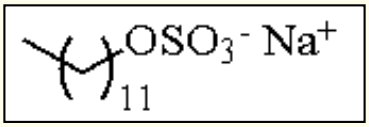

[151-21-3] · $C_{12}H_{25}NaO_4S$ · Sodium Dodecyl Sulfate · (MW 288.38)

(used in surfactant-based reaction media)

Alternate Names: SDS; sodium lauryl sulfate; SLS.

Physical Data: mp 204-207 °C.

Solubility: sol H_2O; insol Et_2O; critical micelle concentration (CMC) in H_2O (25 °C) = 8.1 mM.[1]

Form Supplied in: colorless or white solid.

Analysis of Reagent Purity: commercially available sodium dodecyl sulfate generally contains 1-dodecanol,[2] which yields a minimum at the CMC in plots of surface tension vs. concentration. The presence of 1-dodecanol can be detected by an HPLC method.[3] Impurities can also include surfactant homologs and electrolytes,[2] which yield low surface tension values above the CMC.

Preparative Methods: by sulfation of 1-dodecanol with ***Sulfur Trioxide***, followed by neutralization of the resultant dodecylsulfuric acid with ***Sodium Hydroxide***.[4]

Purification: recrystallization from H_2O and EtOH.[5]

Handling, Storage, and Precautions: harmful if inhaled or swallowed and is irritating to the eyes and skin; should be stored under nitrogen.[2b]

General Considerations.

In H_2O, SDS forms micelles above its CMC. Aqueous micellar solutions solubilize neutral organic compounds that would otherwise be insoluble in H_2O alone. Synthetic applications of micellar SDS have generally involved its ability to solubilize simultaneously both H_2O-insoluble organic substrates and H_2O-soluble (inorganic) reagents, and thus to facilitate their reactions under homogeneous conditions. An organic compound with even modest polarity is normally solubilized within a micelle in a preferred time-averaged orientation with the polar portion near or at the micelle-H_2O interface and the nonpolar portion directed into the micelle's hydrocarbon interior. In several of the examples given below, regioselectivity has resulted from these orientational effects. The features and principles of micellar catalysis have been reviewed,[6] including coulombic attraction and repulsion of ionic reagents from charged micelle-H_2O interfaces. SDS can also be used to form microemulsions, which are isotropic, optically transparent dispersions of oil (hydrocarbon) in water or water in oil. Microemulsions are formed from specific proportions of a surfactant, a cosurfactant (usually a low molecular weight alcohol), H_2O, and a hydrocarbon. Compared to aqueous micellar solutions, microemulsions can solubilize greater amounts of H_2O-insoluble organic compounds and thus offer greater reaction capacity.

Electrophilic Aromatic Substitution.

Micellar SDS has been used as a reaction medium for the chlorination and bromination of alkyl phenyl ethers[4,5a,7] and phenol[7b,8] by several halogenating agents (eq 1). Compared to reactions in H_2O alone, the *para*:*ortho* product ratio increased for pentyl, nonyl, and dodecyl phenyl ether, and decreased for anisole. Enhanced *ortho* relative to *para* substitution was obtained with phenol. In each case the observed regioselectivity derived at least in part from alignment of the substrate at the micelle-H_2O interface and resultant differential steric shielding of the *para* and *ortho* positions by the micelle superstructure.

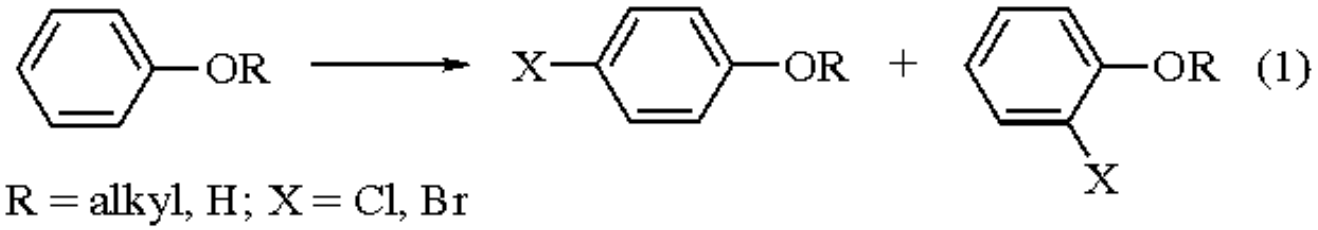

Electrophilic Addition to Alkenes.

Hydroxy- and alkoxymercurations of alkenes have been performed in micellar SDS.[9] Hydroxymercuration of (**1**) with ***Mercury(II) Acetate***, followed by reduction with ***Sodium Borohydride***, gave a greatly enhanced yield of (**2**) in micellar SDS (90%) relative to that obtained in THF-H_2O (20-25%) (eq 2).[9a] Also, the reactions of (**1**) and the related limonene[9a] gave greater cyclic ether:diol product ratios in the SDS environment than in aq THF. Both the enhanced yields and ratios were attributed to anisotropic solubilization of the alkylmercurial intermediate in a relatively H_2O-poor micellar microenvironment. The hydroxymercuration of an aromatic diene, *p*-diallylbenzene, did not display enhanced chemoselectivity (mono vs. diol formation) in micellar SDS relative to THF-H_2O.[9b] This result suggests that the micellar solubilization sites of aromatic substrates and reaction intermediates are more H_2O-rich than those of aliphatic systems.

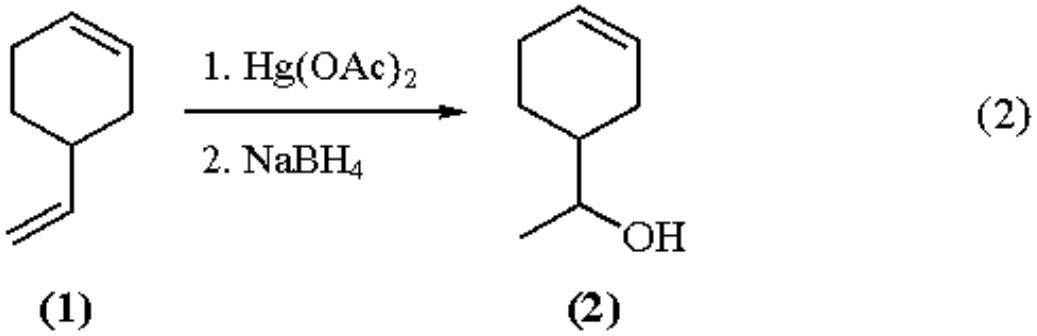

Alkoxymercuration of 1-octene in micellar SDS by added primary alcohols gave 2-octyl alkyl ethers.[9b] Thus when a given alcohol cannot be employed as both the reactant and solvent in the alkoxymercuration of an alkene, the use of micellar SDS-alcohol could be an attractive option.

Oxidation and Reduction.

Hypochlorite oxidations of alcohols to aldehydes and acids and of primary amines to nitriles have been performed in micellar SDS.[10,11] A microemulsion composed of SDS, 1-butanol, H_2O, and cyclohexane has been used for the very rapid oxidation of ethyl 2-chloroethyl sulfide to the corresponding sulfone by hypochlorite.[12] SDS has been used as a catalyst in the oxidations of 3,6-dimethoxydurene and xylenes by ***Cerium(IV) Ammonium Nitrate*** under two-phase conditions.[13] Selective reductions of α,β-unsaturated aldehydes and ketones have been performed with $NaBH_4$ in micellar SDS.[14] Compared to reactions in EtOH and H_2O, greater fractions of unsaturated alcohols were obtained, relative to saturated alcohols.

Cyclization.

The acid-catalyzed cyclization of (+)-citronellal (**3**) in H_2O gives diols (**4**) and (**5**) (2:1 ratio) as the major products (eq 3).[15a] In micellar SDS, the product ratio increases to 5:1 and the rate of cyclization also increases.[15a] The product and rate effects in micellar SDS are consistent with orientational effects for reactive conformations of (**3**) at the micelle-H_2O interface. Furthermore, the cyclization can be performed in micellar SDS with concentrations of (**3**) far above its solubility in H_2O alone. Micellar SDS significantly altered the ratio of acyclic to cyclic alcohol products in the acid-catalyzed solvolysis of linalyl acetate.[15b]

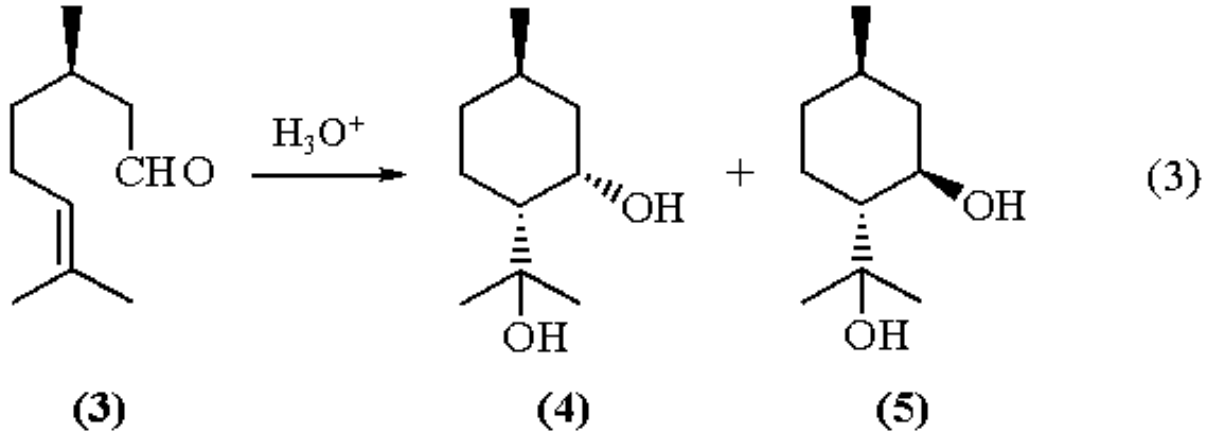

In micellar SDS and vesicular dipalmitoylphosphatidylcholine (DPPC), the aggregate-H_2O interfaces induce stereoselectivity in the radical cyclization of bromohydrin (**6**) (eq 4).[16] In C_6H_6 and pH 10 buffer the (**7**):(**8**) ratios are 0.77 and 1.03, respectively, whereas in the pH 10 buffer with SDS and DPPC the (**7**):(**8**) ratios are 2.29 and 2.39, respectively. These results are consistent with differential stabilization at the aggregate-H_2O interfaces of the diastereomeric transition states leading to (**7**) and (**8**).

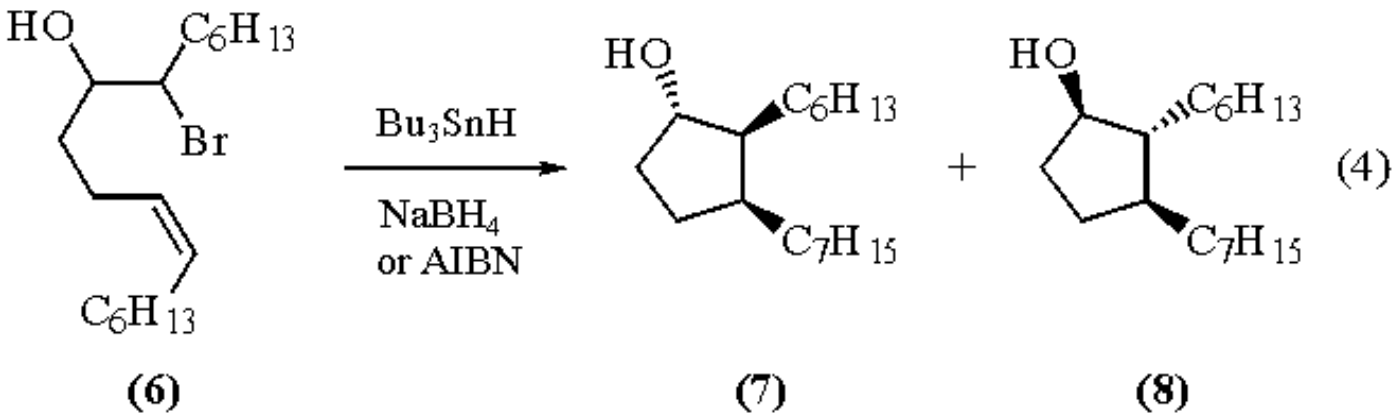

Miscellaneous.

Diazonium ion (**10**), formed from amine (**9**) (eq 5), in the presence of H_3PO_2 gives (**11**) with, and (**12**) without, micellar SDS.[17]

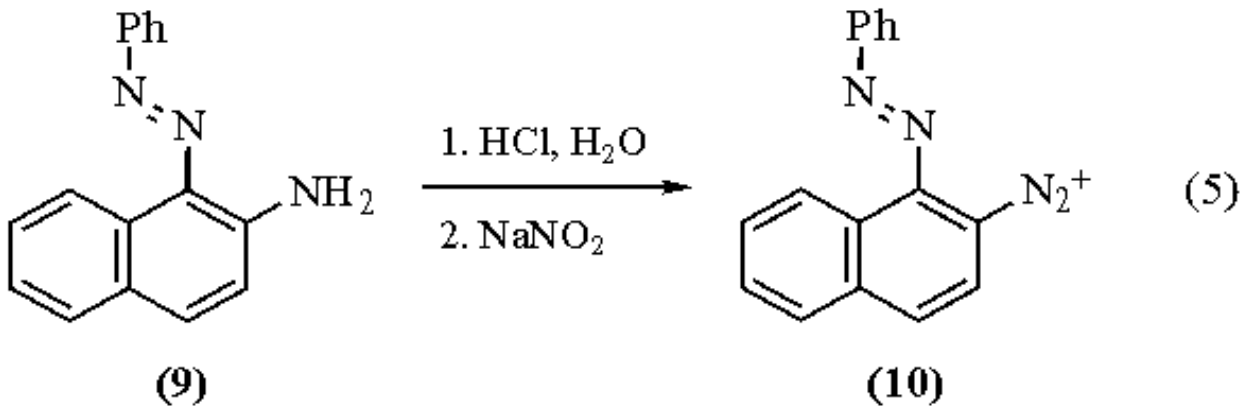

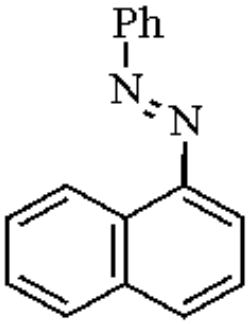

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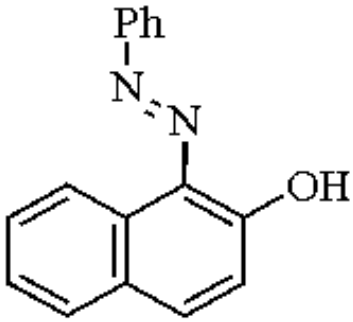

(12)

There have been many other reports of reactions of organic substrates performed in micellar SDS under conditions that would not be synthetically useful.[6] Generally, the focus of these studies has been kinetics and/or regio- and stereoselectivity. However, the clear potential exists for the application of their results to organic synthesis. The conditions under which SDS undergoes acid- and base-catalyzed hydrolyses (eq 6) are generally more severe than those used in reactions performed in micellar SDS;[18] thus the hydrolysis of SDS can usually be neglected.

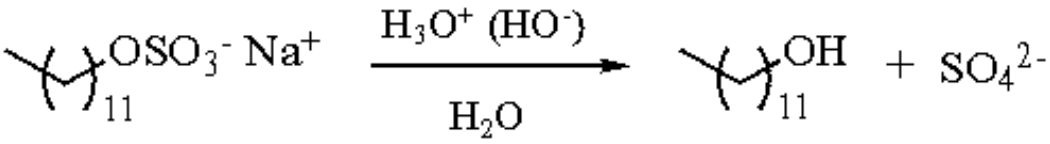

(6)

Synthetic Application of Other Surfactants.

In most cases, other anionic surfactants would be expected to offer results comparable to those obtained above with SDS. Cationic surfactants such as hexadecyltrimethylammonium bromide catalyze reactions involving anionic reagents.[6] In general, the isolation of organic products from surfactant-based reaction media can be facilitated by the use of cleavable surfactants.[19] A cleavable surfactant can be converted into nonsurfactant products after its use in a surfactant-based reaction solvent, thereby eliminating problems resulting from the presence of a surfactant during workup, such as the formation of persistent emulsions.

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Sodium Ethoxide[1]

NaOEt

[141-52-6] · C_2H_5NaO · Sodium Ethoxide · (MW 68.06)

(used as a base for the α-deprotonation of carbonyl-containing compounds for subsequent intermolecular[2] or intramolecular[1f] condensations, displacements,[3] or skeletal rearrangements,[1d,4] arylacetonitriles,[5] nitro-containing aliphatic compounds,[6] sulfonium salts,[3j,7] for the dehydration of carbinolamines[8] and for dehydrohalogenation,[1b,9] for the *N*-deprotonation of amides,[10a-d] tosylamines,[10e] amine hydrochlorides[1c] or toluenesulfonates,[10f] cyanamide,[10g] and the *S*-deprotonations of sulfides,[1c,11] often followed by cyclizations;[1c,10b,10g,11] can be used as a nucleophile in *ipso* substitution reactions of vinyl sulfides,[12a] aromatic halides,[12b-i] sometimes catalyzed by copper[12c] or palladium,[12h,i] aryl sulfones,[12j] and aromatic nitro compounds,[12k] in the Williamson ether synthesis,[13a-c] in displacements of halo,[13d-h] nitro,[13e] thiooxy,[13g,h] and phenoxy[13g] groups from dichloromethane and chloroform analogs, in a novel transesterification-conjugate addition protocol of acrylic esters,[14] with α-nitro epoxides to form α-ethoxy ketones,[15] in the nucleophilic attack on nitriles[1e,16] and polyhaloalkenes,[17] in reaction with chlorodiphenylphosphine to form Arbuzov precursors,[18] and with Grignard reagents to form organomagnesium ethoxides[19])

Physical Data: mp >300 °C.

Solubility: sol ethanol, diethyl ether.

Form Supplied in: white or yellowish powder or as 21 wt % solution in ethanol; widely available.

Preparative Methods: it is often necessary to prepare sodium ethoxide immediately prior to its use. Preparation of a 6-10% solution in ethanol: to commercial absolute ethanol is added the required amount of ***Sodium*** in lumps or slices with or without stirring and with or without a nitrogen atmosphere and the solution is cooled or heated as required until the metal is dissolved. The evolved hydrogen should be vented into a hood. Addition of ethanol to sodium is also reported. Alcohol-free reagent can also be prepared.[1a]

Handling, Storage, and Precautions: is a hygroscopic, flammable, corrosive, and toxic solid which will decompose upon exposure to air. The solid or solution reagent should be tightly sealed under an inert atmosphere in a dark bottle.

General Discussion.

Kinetic studies of the proton transfer reaction between bis(4-nitrophenyl)methane and alkoxide base systems reveal that sodium ethoxide is a kinetically faster (k_H = 2.16 M^{-1} s^{-1}) base than either sodium isopropoxide (k_H = 0.280 M^{-1} s^{-1}) or sodium *t*-butoxide (k_H = 1.05 M^{-1} s^{-1}) (eq 1).[20a] Reaction between alkali alkoxides and *p*-nitrophenyl methanesulfonate have revealed the following order of reactivity: LiOEt< NaOEt < CsOEt &AApprox; KOEt &AApprox; KOEt + 18-crown-6 < KOEt + [2.2.2]cryptand.[20b]

$$Ar_2CH_2 + RONa \rightleftharpoons Ar_2CHNa + ROH \qquad (1)$$

Condensations of esters with the enolate of acetone can be effected using sodium ethoxide as a base to yield products such as acetylacetone[2a] and the precursor to chelidonic acid depicted in eq 2.[2b] The corresponding enolates of methyl aryl ketones can similarly be utilized.[2c,1f]

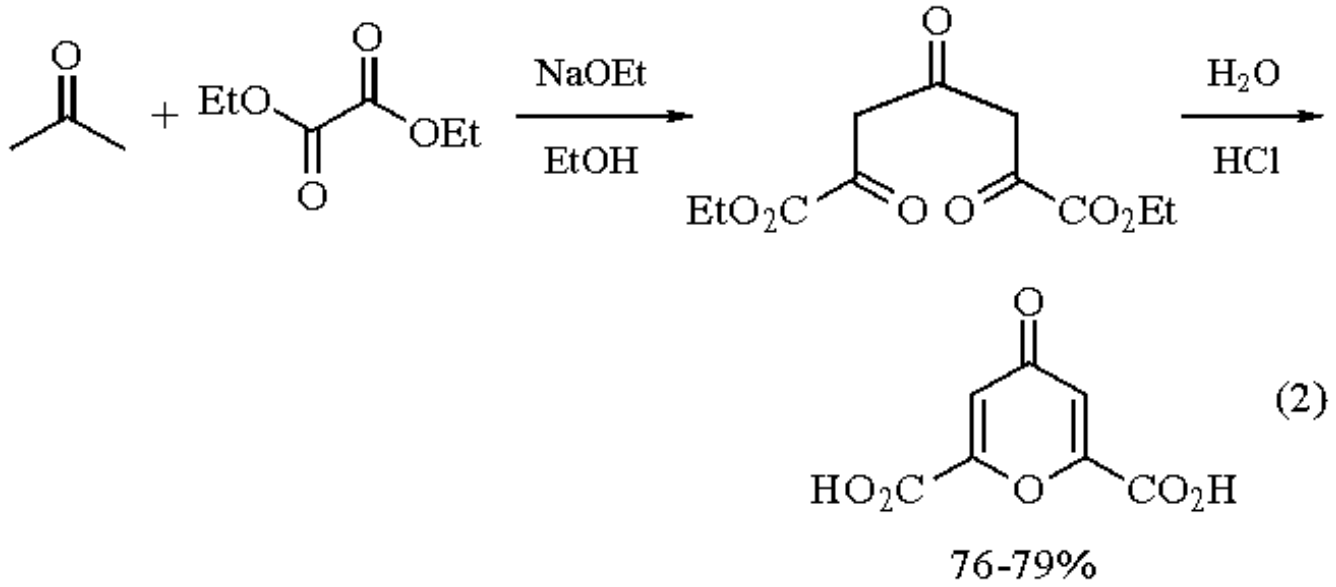

(2)

Condensation of the sodium ethoxide-generated enolate of cyclohexanone with ethyl formate yields 2-hydroxymethylenecyclohexanone which, upon treatment with hydrazine monohydrate, forms indazole in excellent yield (eq 3).[2d]

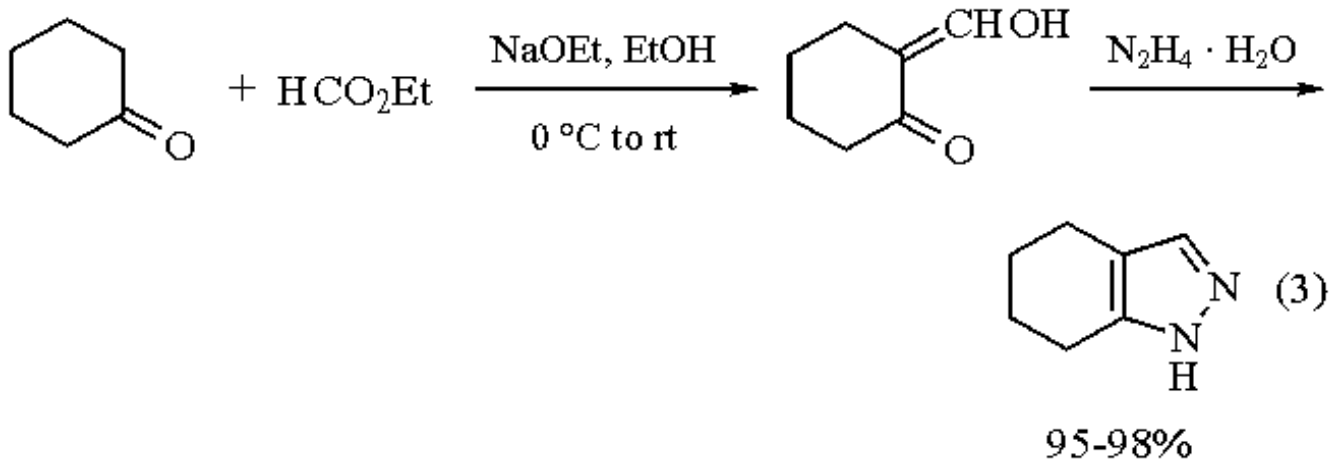

(3)

Sodium ethoxide is often the base of choice in the α-acylation[2e-i] and alkylation[3h] of esters. Interesting intramolecular cyclizations sometimes follow in good yield (eq 4).

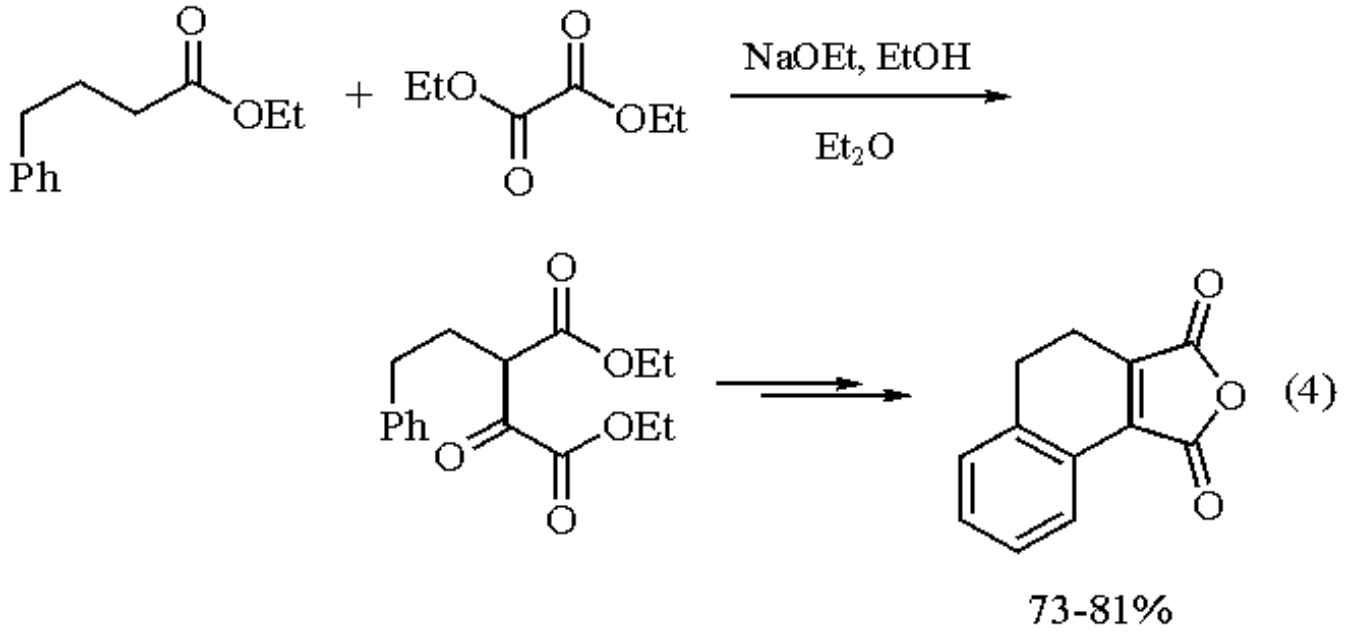

(4)

Alkylation of malonate esters through the intermediacy of enolates generated using sodium ethoxide is quite common.[3] Subsequent decarboxylation to the carboxylic acid can then be induced, as depicted in eq 5.[3d]

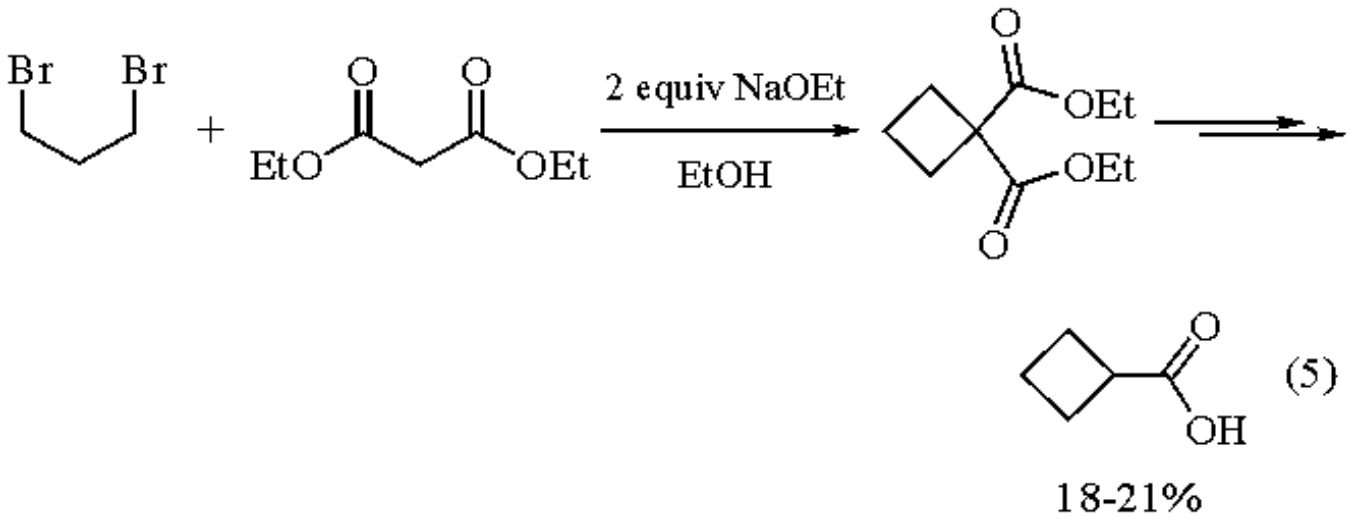

Sodium ethoxide and ***Sodium Hydroxide*** have both proven effective in the cyclopropanation of various γ,δ-epoxy ketones, as illustrated in eq 6. Adducts are generated in good to excellent yields.[4]

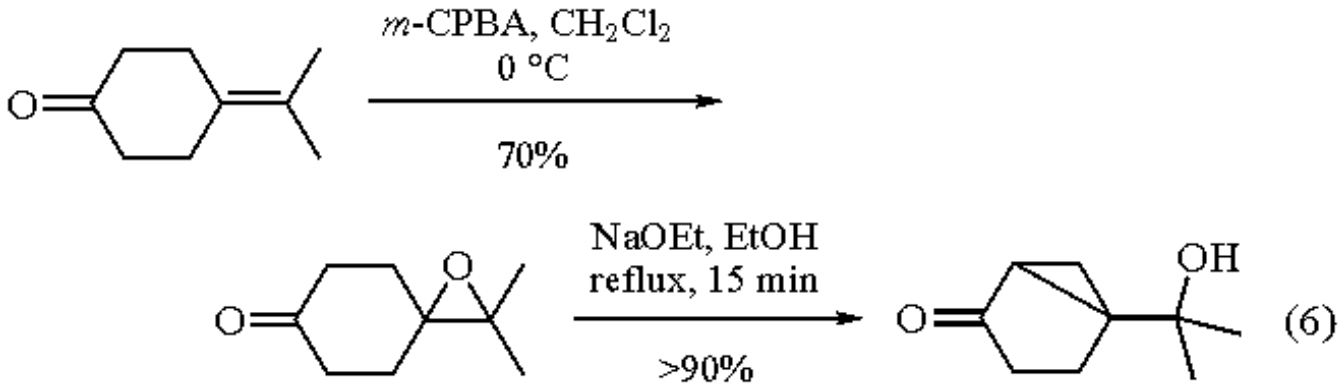

Deprotonation α to nitriles has been found to be strongly influenced by the purity of the sodium ethoxide used[5a] and can be done selectively over α-deprotonation of an ester.[5b] Reactions with aromatic aldehydes lead to condensation adducts (eq 7).[5c]

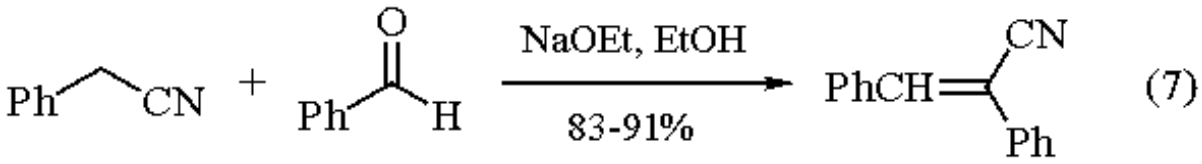

Deprotonations α to nitro functionalities have been found to proceed with greater ease using sodium ethoxide rather than ***Sodium Methoxide***.[6] The in situ generated anion of 2-nitropropane transforms a benzylic bromide to its aromatic aldehyde derivative in good yield (eq 8).[7a]

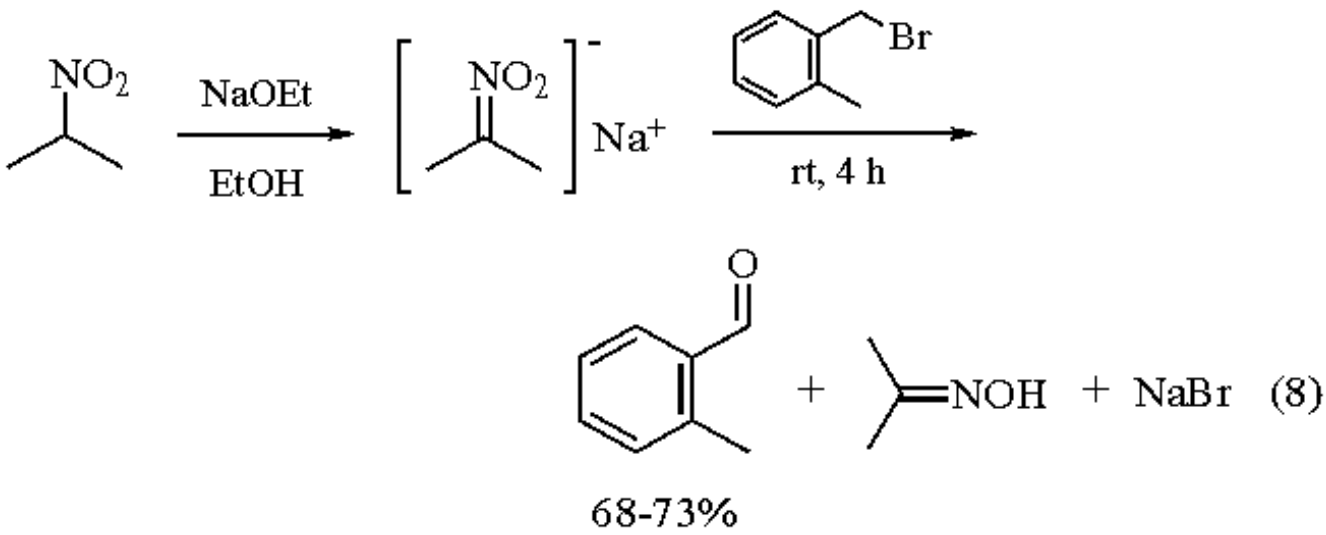

Sodium ethoxide serves as a multipurpose base to generate both the ylide of dimethyl-2-propynylsulfonium bromide and the anion of acetylacetone in the synthesis of 3-acetyl-2,4-dimethylfuran illustrated in eq 9.[3j] The intermediacy of an allene has been suggested.[7b]

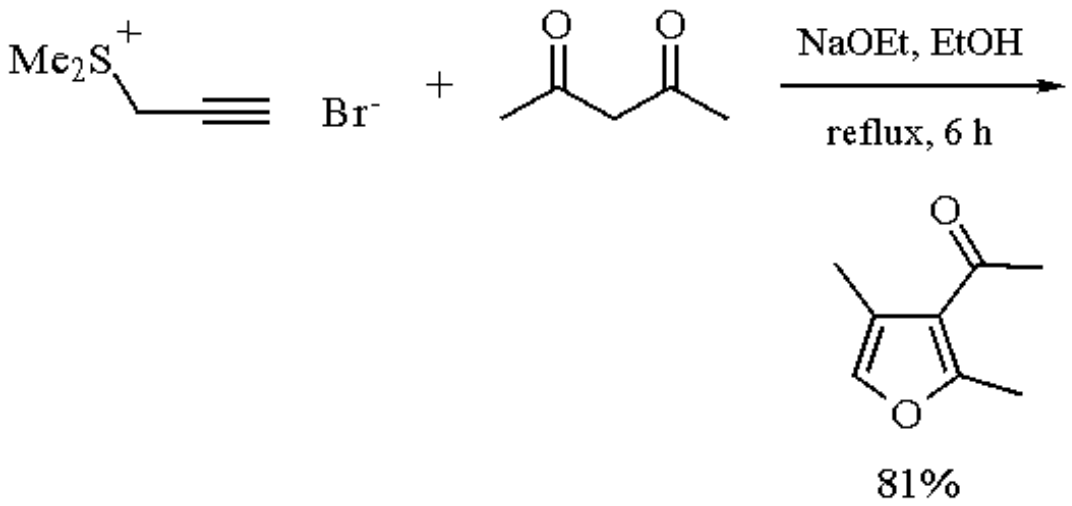

(9)

Sodium ethoxide both dehydrates and nucleophilically assists in the deacylation of the carbinolamine intermediate depicted in eq 10.[8] Furthermore, sodium ethoxide-mediated dehydrohalogenation in DMSO solvent has been achieved in excellent yield (eq 11).[1b,9]

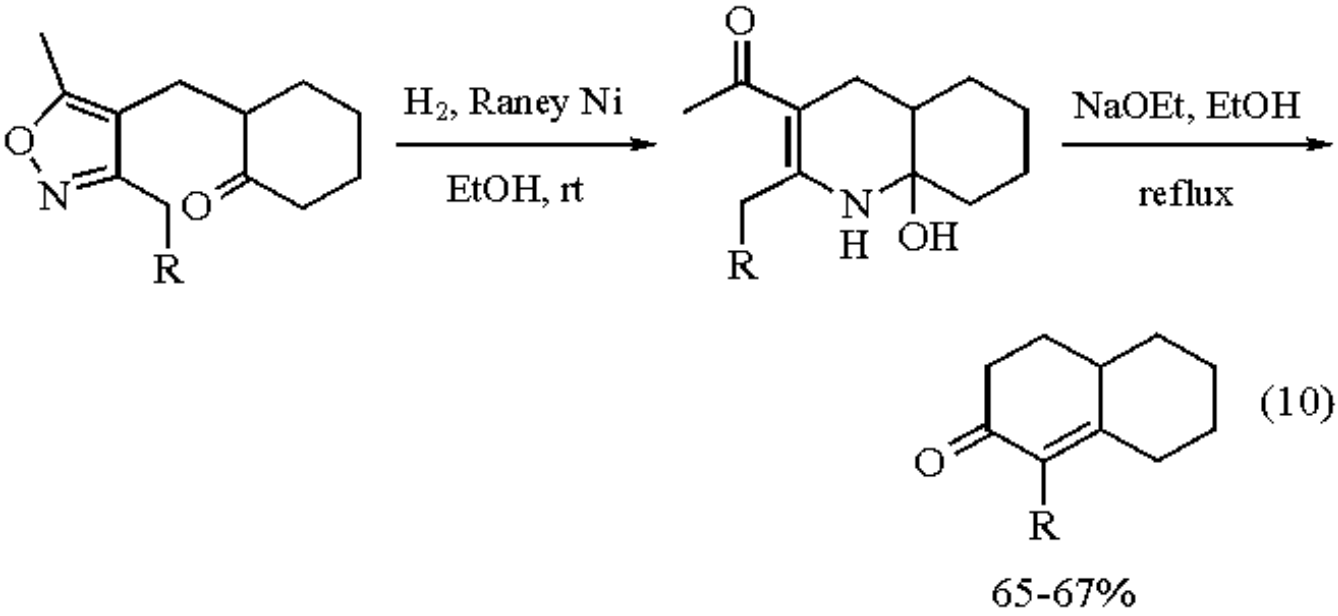

(10)

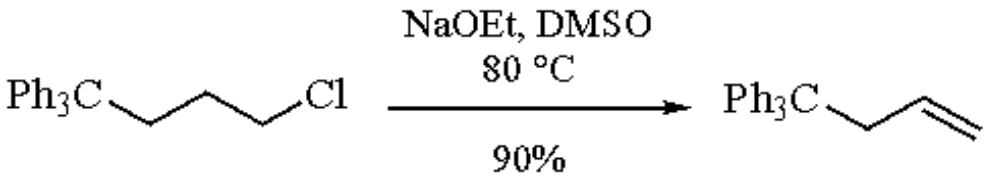

(11)

Heteroatom deprotonations using sodium ethoxide as the base are also quite common. Sodium ethoxide serves as an effective base when the nitrogen of cyanoacetamide must be condensed on an ester. Subsequent intramolecular cyclization proceeding via α-deprotonation to the nitrile leads to excellent yield of the dicyanoglutarimide shown in eq 12.[10a]

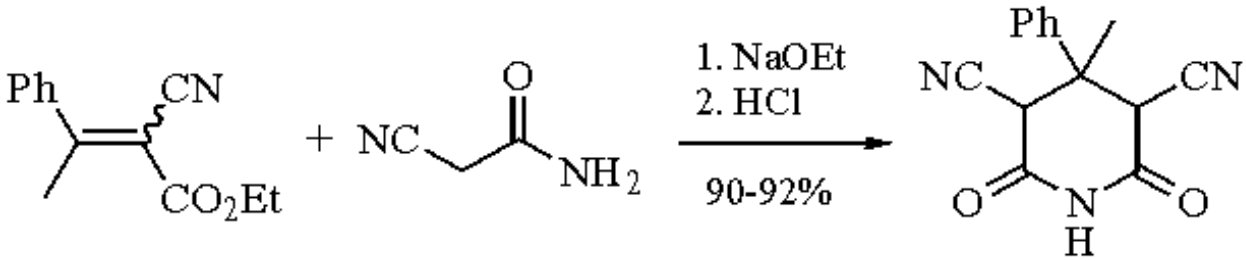

(12)

Other *N*-deprotonations include that of urea,[10b] thiourea,[10c] succinimide,[10d] tosylamines,[10e] cysteamine hydrochloride (eq 13),[1c] ribofuranosylamine toluenesulfonate,[10f] and cyanamide (eq 14).[10g] Similarly, *S*-deprotonations of sulfides (eq 13)[1c,11] have been reported. Often, adducts can be used in subsequent cyclizations.[1c,10b,g,11]

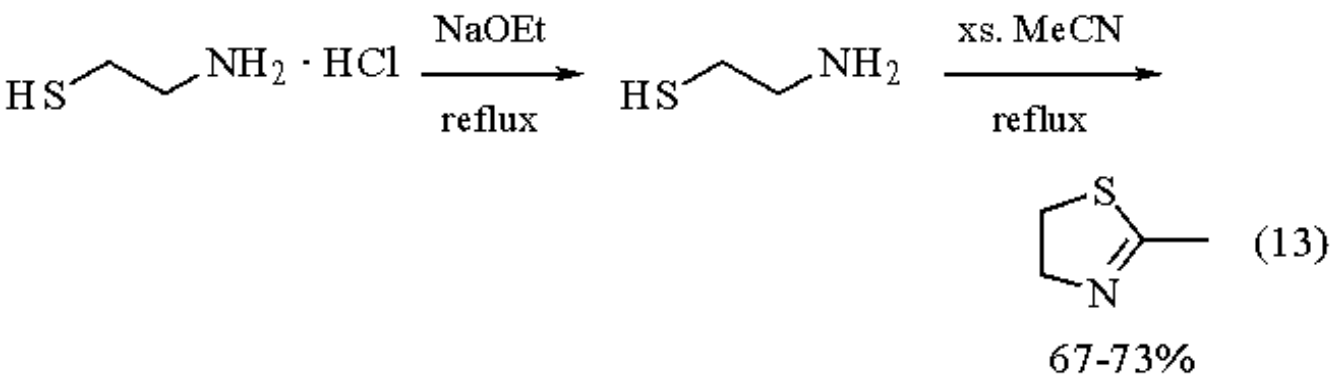

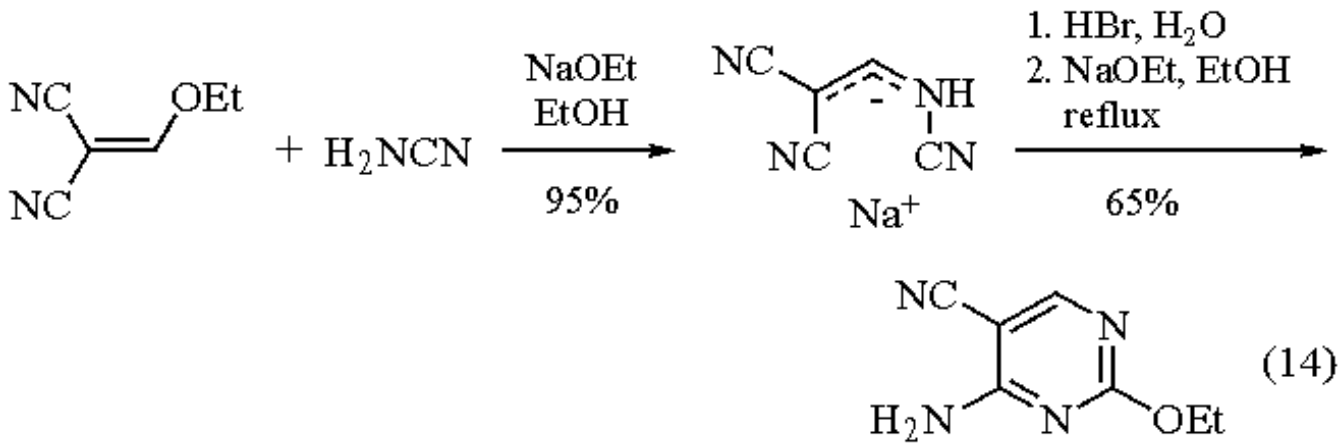

The synthesis of 6,6-dialkoxyfulvenes from 6,6-bis(methylthio)fulvene has been reported in good yield via treatment with sodium ethoxide or related nucleophiles, followed by thermolysis (eq 15).[12a]

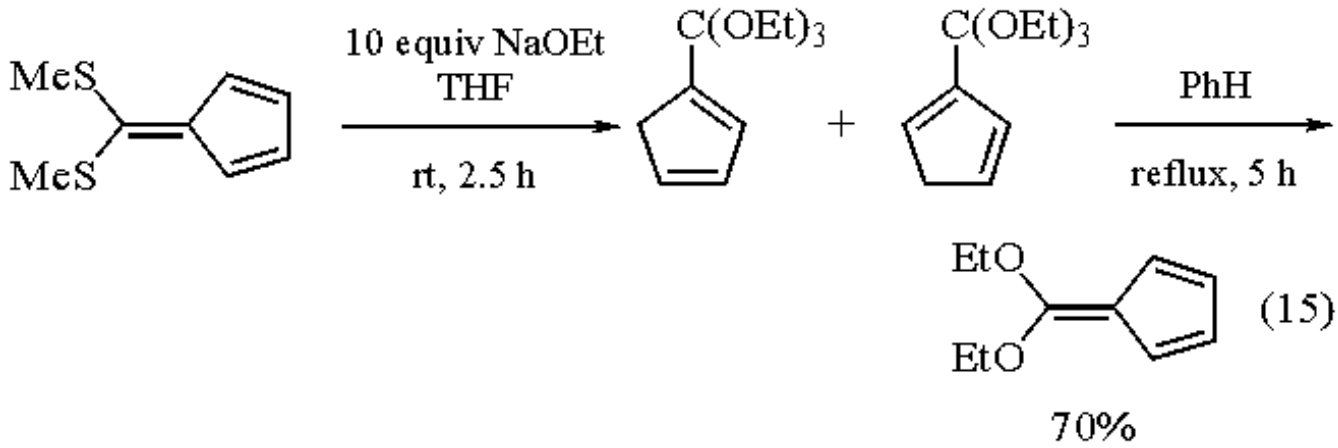

Addition of a large excess of sodium ethoxide or methoxide to 11-chloro[5]metacyclophanes leads to good yields of *ipso* alkoxy-substituted adducts.[12b] Sodium ethoxide proves to be the fastest of a series of nucleophiles in *ipso* substitution reactions of aromatic bromides employing a ***Copper(I) Bromide*** catalyst (eq 16). Once again, purity of alkoxide seems to be important.[12c] Substitution of aryl iodides is also known.[12d]

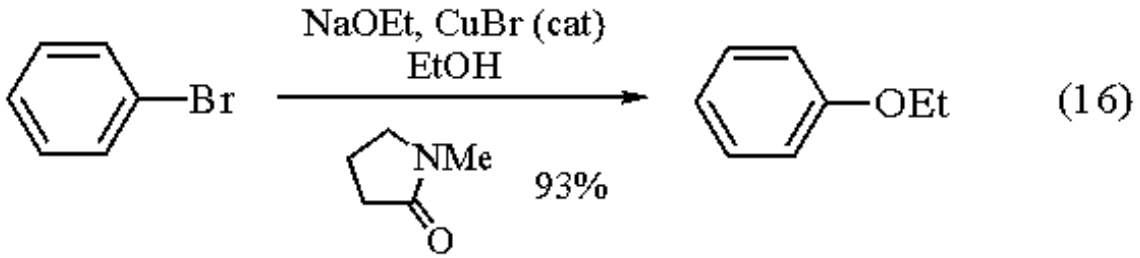

Ipso ethoxy substitutions of halo-pyrimidines,[10g] -purines (eq 17),[12e] -thiophenes,[12c,f] -furans,[12c] and -triazines[12g] using sodium ethoxide have

also been reported in good yield.

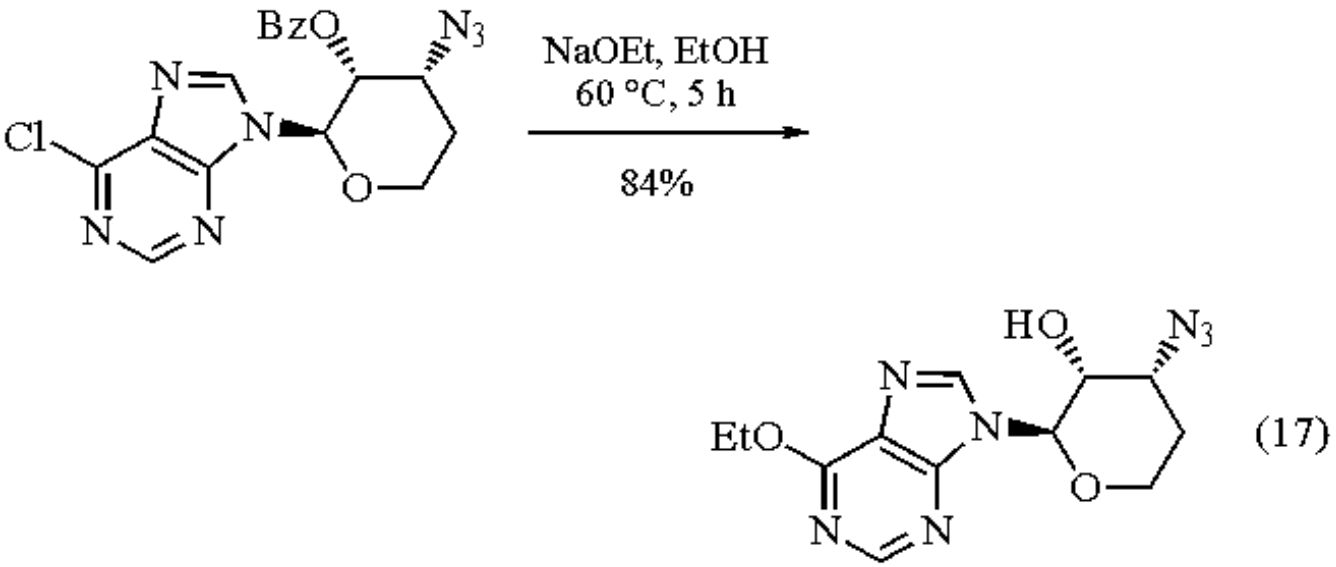

Aryl iodides, vinyl bromides, and tricarbonyl(chloroarene)chromium complexes have been found to react under mild conditions with sodium alkoxides in the presence of catalytic dichlorobis(triphenylphosphine)palladium(II) (see ***Palladium(II) Chloride***) to afford the corresponding benzoate esters as the major products (eq 18).[12h,i] It has been rationalized that the higher base strength of sodium ethoxide compared to that of sodium methoxide allows the former to successfully decarbonylate ethyl formate, whereas the latter proves more sluggish, yielding poorer results.

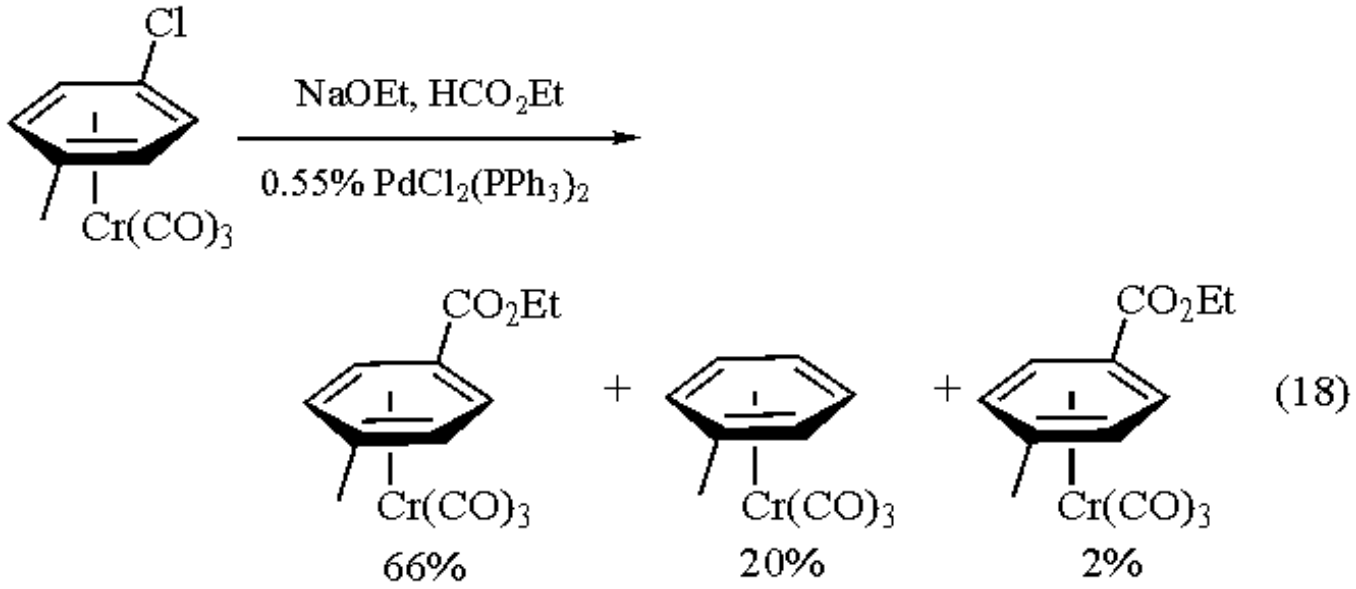

Ipso substitution of 2- and 4-pyridyl sulfones is also possible using a variety of nucleophiles, including sodium ethoxide. The sulfone moiety is preferentially displaced over a chlorine substituent also present on the aromatic ring (eq 19). The same reaction utilizing sulfoxides gives mixed results, while sulfides fail to react.[12j]

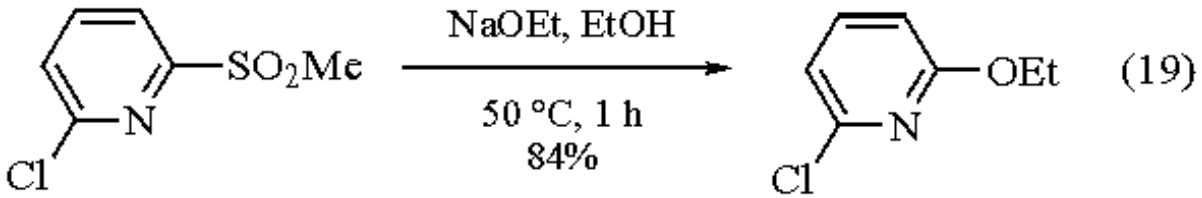

It has been suggested that displacement of the nitro group of the radical anion of *p*-nitrobenzophenone by sodium ethoxide is followed by chain transfer from the resulting *p*-ethoxybenzophenone radical, resulting in the adduct pictured in eq 20.[12k]

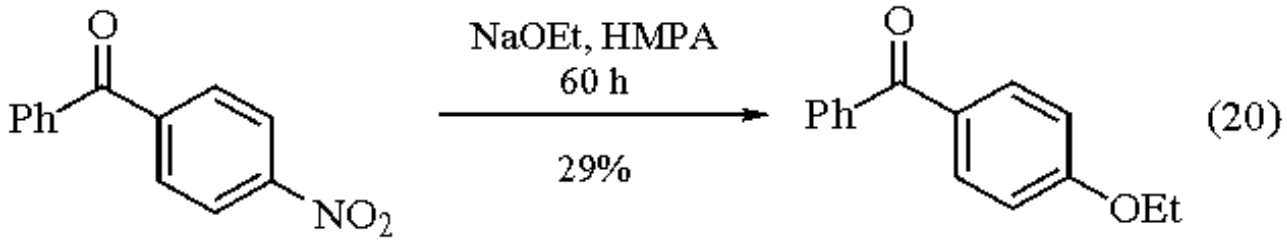

Sodium ethoxide is frequently employed as the nucleophile in the Williamson ether synthesis,[13a-c] as illustrated in eq 21. Furthermore, polydisplacements of halo,[13d-h] nitro,[13e] thiooxy,[13g,h] and phenoxy[13g] groups of dichloromethane and chloroform analogs have been realized by the use of sodium ethoxide as the nucleophile. This methodology has been used in the syntheses of ethyl orthocarbonate (eq 22) and ethyl diethoxyacetate (eq 23) in moderate to good yields.

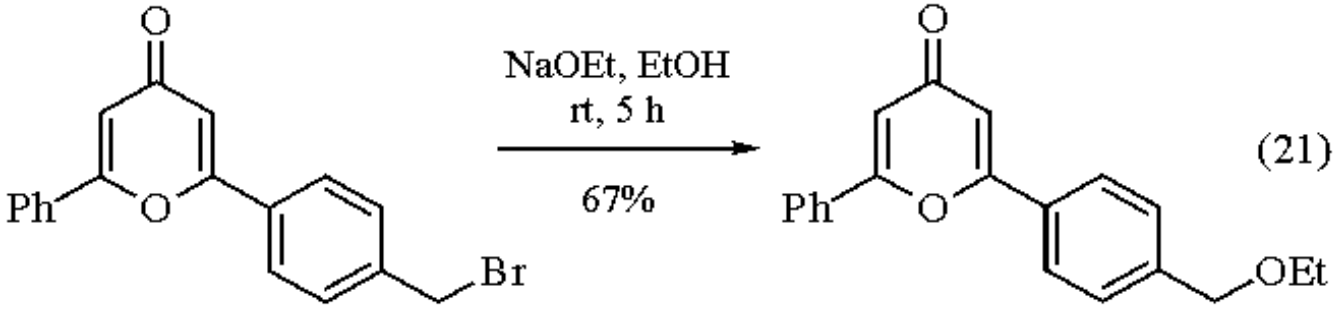

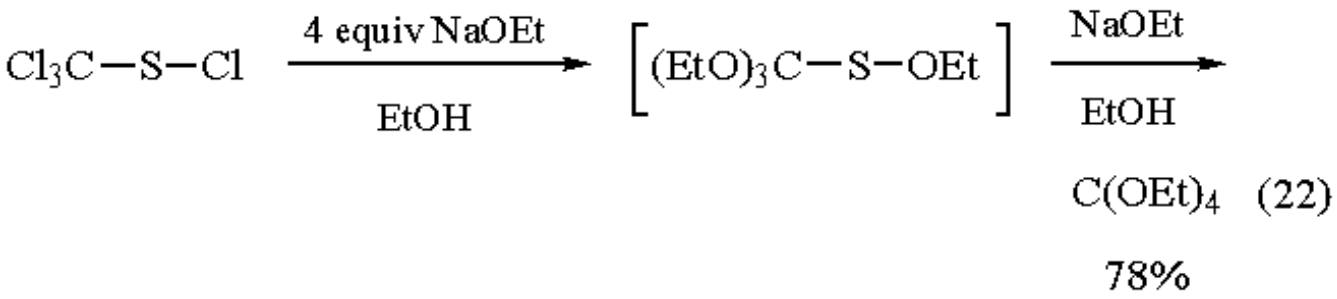

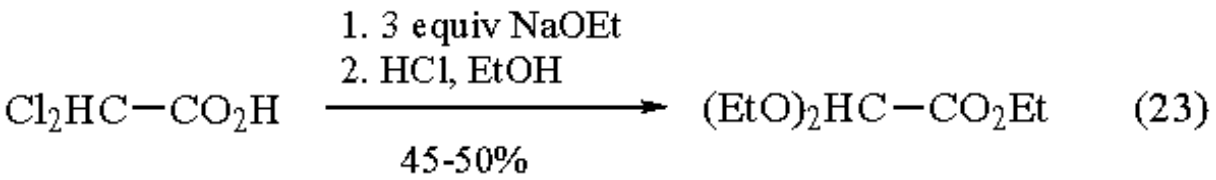

Sodium ethoxide has been employed for a transesterification-conjugate addition protocol, which takes advantage of the *syn*-selective addition of sodium alkoxides to acrylic esters such as the one depicted in eq 24.[14]

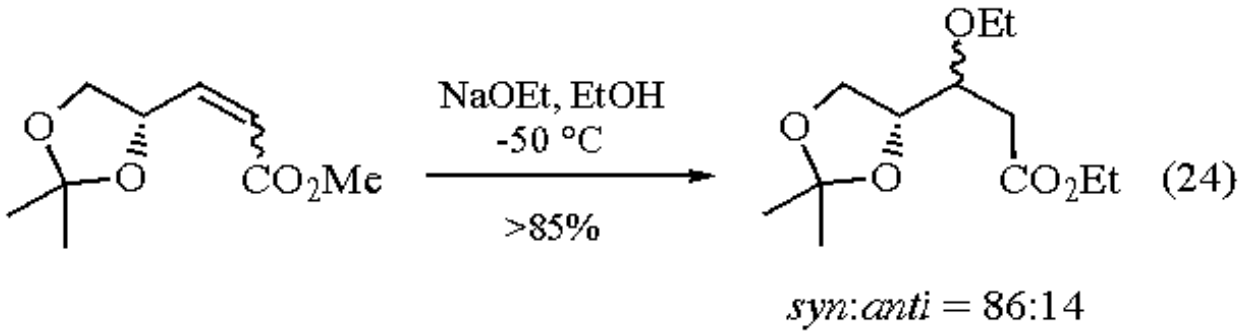

An interesting synthesis of α-ethoxy ketones employs nucleophilic reaction of sodium ethoxide with α-nitro epoxides. The reaction appears to be quite general and a variety of nucleophiles may be employed (eq 25).[15]

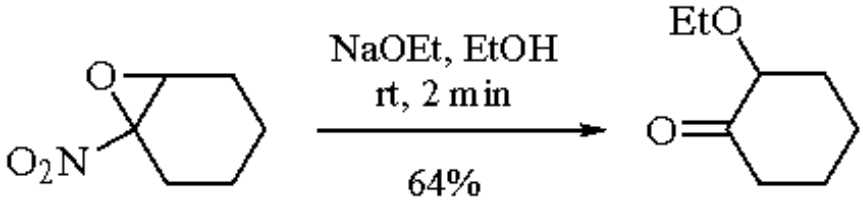

(25)

Nucleophilic attack of sodium ethoxide on 3,4- or 2,3-cyanomethyl cyanopyridines followed by cyclization provides access to amino alkoxy naphthyridines (eq 26).[1e,16] The reaction is believed to proceed through an imidate intermediate.[16a] Unfortunately, treatment of the analogous carbocyclic 2-cyanobenzyl cyanides under similar conditions leads to dimerization of starting material, and cyclization must be achieved under acidic conditions.[16b]

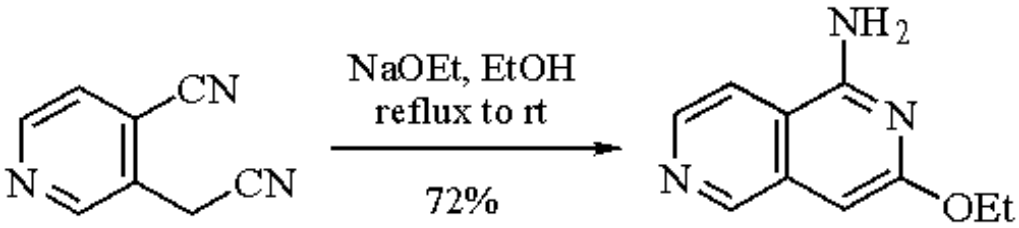

(26)

Sodium ethoxide is also known to nucleophilically add to polyhaloalkenes with preferential attack on the methylene with the highest degree of fluorine substitution (eqs 27 and 28).[17] Excess nucleophile unveils an ethyl ester (eq 28).

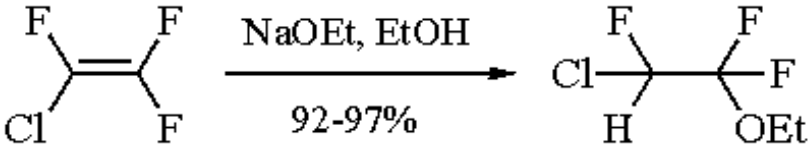

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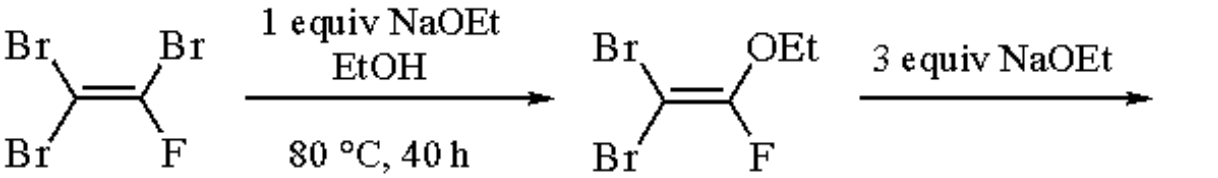

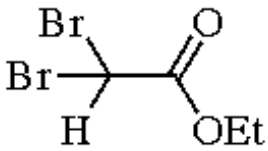

(28)

80-85%

Reaction of sodium ethoxide with chlorodiphenylphosphine provides access to Arbuzov precursors, which can be further reacted with suitable electrophiles to form phosphine oxides (eq 29).[18]

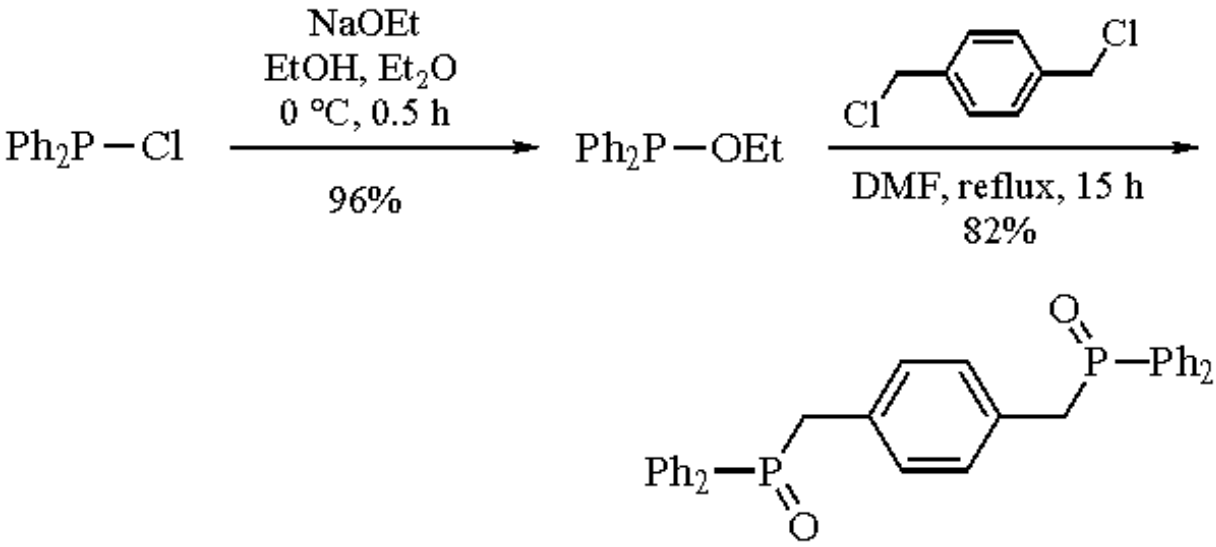

(29)

Treatment of Grignard reagents (RMgBr) with sodium ethoxide offers a synthetic route to organomagnesium ethoxides (RMgOEt).[19] No yields are reported for this reaction.

Related Reagents.

Potassium t-Butoxide; ***Potassium 2-Methyl-2-butoxide***; ***Sodium Hydroxide***; ***Sodium Methoxide***.

---

1. (a) *FF* **1967**, *1*, 1065. (b) *FF* **1969**, *2*, 157. (c) *FF* **1972**, *3*, 265. (d) *FF* **1974**, *4*, 451. (e) *FF* **1977**, *6*, 540. (f) *FF* **1986**, *12*, 402.
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4. (a) Gaoni, Y. *T* **1972**, *28*, 5525. (b) Gaoni, Y. *T* **1972**, *28*, 5533.
5. (a) Horning, E. C.; Finell, A. F. *OSC* **1963**, *4*, 461. (b) Coan, S. B.; Becker, E. I. *OSC* **1963**, *4*, 174. (c) Womack, E. B.; McWhirter, J. *OSC* **1955**, *3*, 714.
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7. (a) Hass, W. B.; Bender, M. L. *OSC* **1963**, *4*, 932. (b) Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *JCS(P1)* **1973**, 65.
8. McMurry, J. E. *OSC* **1988**, *6*, 781.
9. Norman, R. O. C.; Thomas, C. B. *JCS(C)* **1967**, 1115.
10. (a) McElvain, S. M.; Clemens, D. H. *OSC* **1963**, *4*, 662. (b) Sherman, W. R.; Taylor, Jr., E. C. *OSC* **1963**, *4*, 247. (c) Ulbricht, T. L. V.; Okuda, T.; Price, C. C. *OSC* **1963**, *4*, 566. (d) Crockett, G. C.; Koch, T. D. *OSC* **1988**, *6*, 226. (e) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *OSC* **1988**, *6*, 652. (f) Espie, J. C.; Lhomme, M. F.; Morat, C.; Lhomme, J. *TL* **1990**, *31*, 1423. (g) Schmidt, H.-W.; Koitz, G.; Junek, H. *JHC* **1987**, *24*, 1305.
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Sodium Fluoride[1]

NaF

[7681-49-4] · FNa · Sodium Fluoride · (MW 41.99)

(halogen replacement by fluorine)

Physical Data: mp 993 °C; *d* 2.56 g cm^{-3}.

Solubility: sol 42.2 g L^{-1} H_2O; sol HF; insol EtOH.

Form Supplied in: white solid, widely available.

Handling, Storage, and Precautions: moderately toxic with LD_{50} = 0.18 g kg^{-1} in rats. People are severely affected after injesting less than one gram of NaF.

Introduction.

Although NaF can be used to replace other halogens with fluorine, ***Potassium Fluoride*** is the research chemist's reagent of choice because NaF is less efficient and much less soluble in commonly used solvents. This is not meant to imply that NaF is ineffective. Where the previously listed disadvantages are not critical, NaF is less hygroscopic and cheaper.[2] In general, laboratory syntheses use KF and, upon scaleup to a plant procedure, NaF is substituted if possible.

Displacement of Halogen with Sodium Fluoride.

Traditionally, compounds containing a reactive chlorine bonded to carbon, sulfur, or phosphorus can be converted to the corresponding fluorides with NaF in tetramethylene sulfone, MeCN, or DMF, as shown in Table 1.[1] Pentachloropyridine and NaF in tetramethylene sulfone gave 3,5-dichlorotrifluoropyridine.[3] In a similar way, 2,4,6-trifluoro-1,3,5-triazine can be formed from the trichloro- or a mixture of chloro- and fluoro-1,3,5-triazines.[4] The rate and efficiency of the reaction can be improved by the addition of a phase-transfer catalyst. This is illustrated by the conversion of benzyl halides to benzyl fluoride or carboxylic acid halides to carboxylic acid fluorides.[5]

Table 1 Conversion of Organic Chlorides to Fluorides with NaF and Tetramethylene Sulfone.

Reactant	Product	Conversion to fluoride (%)
CCl_3SCl	CF_3SCl	47
$ClCH_2OMe$	FCH_2OMe	47
$ClCO_2Me$	FCO_2Me	33
$(COCl)_2$	$(COF)_2$	60
MeCOCl	MeCOF	48
PhCOCl	PhCOF	62
$SOCl_2$	SOF_2	77
SO_2Cl_2	SO_2F_2	85
$PhPSCl_2$	$PhPSF_2$	65

Although a halomethyl ether can be converted to a fluoromethyl ether (Table 1), an unusual reaction incorporates the use of NaF, with the reactant and product as the solvent, under supercritical reaction conditions, to displace halogen with fluoride (eqs 1 and 2). KF is equally effective.[6]

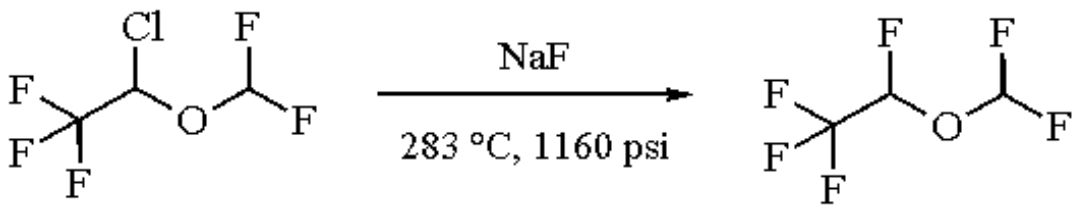

(1)

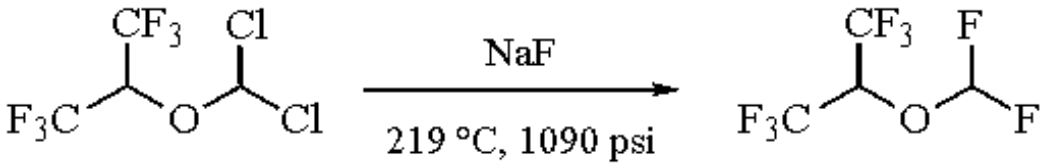

(2)

Generally speaking, the choice of NaF in place of KF is based on economics. There is no cited synthetic advantage of NaF over KF other than that NaF is easier to obtain and maintain in the anhydrous state.

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Donald F. Halpern

Murray Hill, NJ, USA

Sodium Hexamethyldisilazide[1]

$NaN(SiMe_3)_2$

[1070-89-9] · $C_6H_{18}NNaSi_2$ · Sodium Hexamethyldisilazide · (MW 183.42)

(useful as a sterically hindered base and as a nucleophile)

Alternate Names: NaHMDS; sodium bis(trimethylsilyl)amide.

Physical Data: mp 171-175 °C; bp 170 °C/2 mmHg.

Solubility: sol THF, ether, benzene, toluene.[1]

Form Supplied in: (a) off-white powder (95%); (b) solution in THF (1.0 M); (c) solution in toluene (0.6 M).

Analysis of Reagent Purity: THF solutions of the reagent may be titrated using 4-phenylbenzylidenebenzylamine as an indicator.[2]

Handling, Storage, and Precautions: the dry solid and solutions are flammable and must be stored in the absence of moisture. These should be handled and stored under a nitrogen atmosphere. Use in a fume hood.

Introduction.

Sodium bis(trimethylsilyl)amide is a synthetically useful reagent in that it combines both high basicity[3] and nucleophilicity,[4] each of which may be exploited for useful organic transformations such as selective formation of enolates,[5] preparation of Wittig reagents,[6] formation of acyl anion equivalents,[7] and the generation of carbenoid species.[8] As a nucleophile, it has been used as a nitrogen source for the preparation of primary amines.[9,10]

Sterically Hindered Base for Enolate Formation.

Like other metal dialkylamide bases, sodium bis(trimethylsilyl)amide is sufficiently basic to deprotonate carbonyl-activated carbon acids[5] and is sterically hindered, allowing good initial kinetic vs. thermodynamic deprotonation ratios.[11] The presence of the sodium counterion also allows for subsequent equilibration to the thermodynamically more stable enolate.[5f] More recently, this base has been used in the stereoselective generation of enolates for subsequent alkylation or oxidation in asymmetric syntheses.[12] As shown in eq 1, NaHMDS was used to selectively generate a (*Z*)-enolate; alkylation with ***Iodomethane*** proceeded with excellent diastereoselectivity.[12a] In this case, use of the sodium enolate was preferred as it was more reactive than the corresponding lithium enolate at lower temperatures.

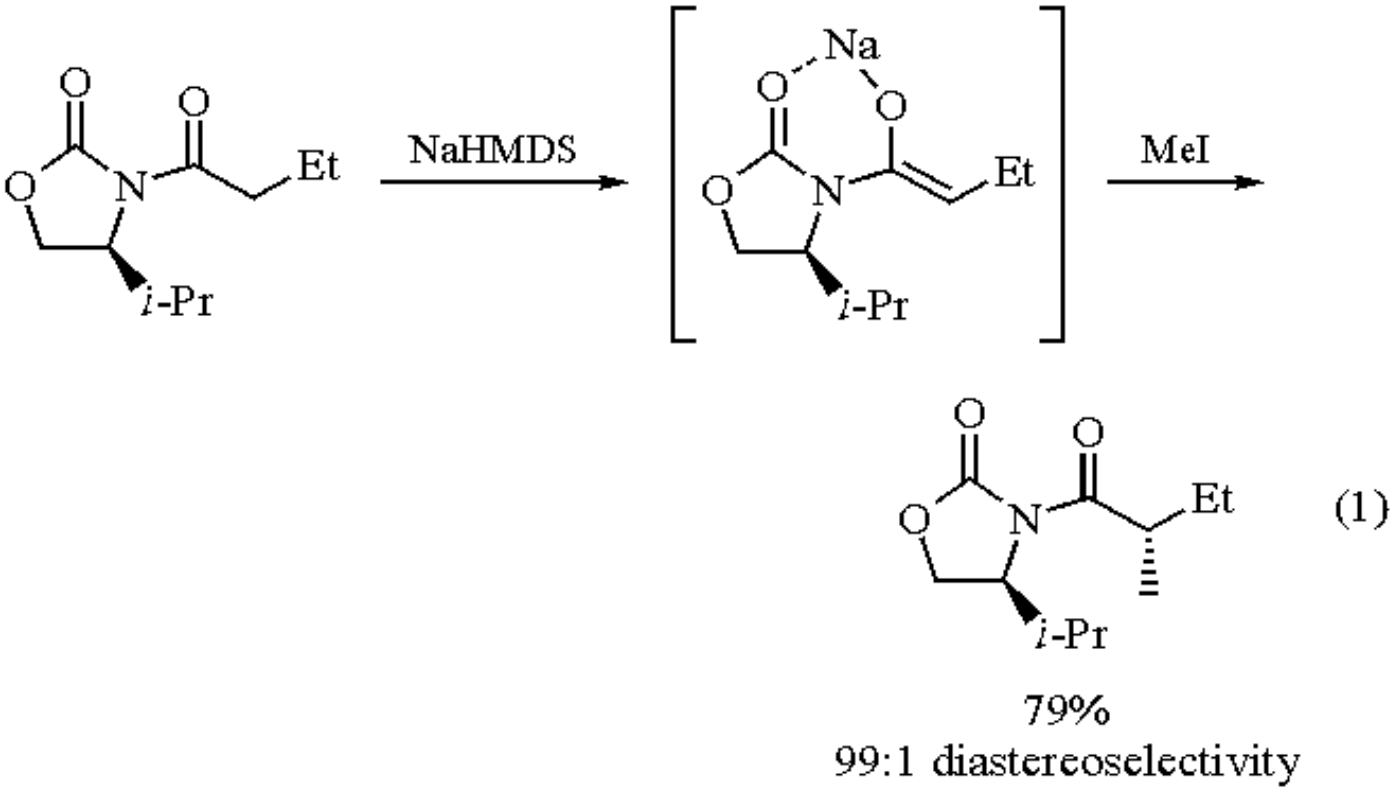

The reagent has been used for the enolization of carbonyl compounds in a number of syntheses.[13] For ketones and aldehydes which do not have enolizable protons, NaHMDS may be used to prepare the corresponding TMS-imine.[14]

Generation of Ylides for Wittig Reactions.

In the Wittig reaction, salt-free conditions have been shown to improve (*Z*):(*E*) ratios of the alkenes which are prepared.[15] NaHMDS has been shown to be a good base for generating ylides under lithium-salt-free conditions.[6] It has been used in a number of syntheses to selectively prepare (*Z*)-alkenes.[16] Ylides generated under these conditions have been shown to undergo other ylide reactions such as *C*-acylations of thiolesters and inter- and intramolecular cyclization.[6] Although Wittig-based syntheses of vinyl halides exist,[17] NaHMDS has been shown to be the base of choice for the generation of iodomethylenetriphenylphosphorane for the stereoselective synthesis of (*Z*)-1-iodoalkenes from aldehydes and ketones (eq 2).[18]

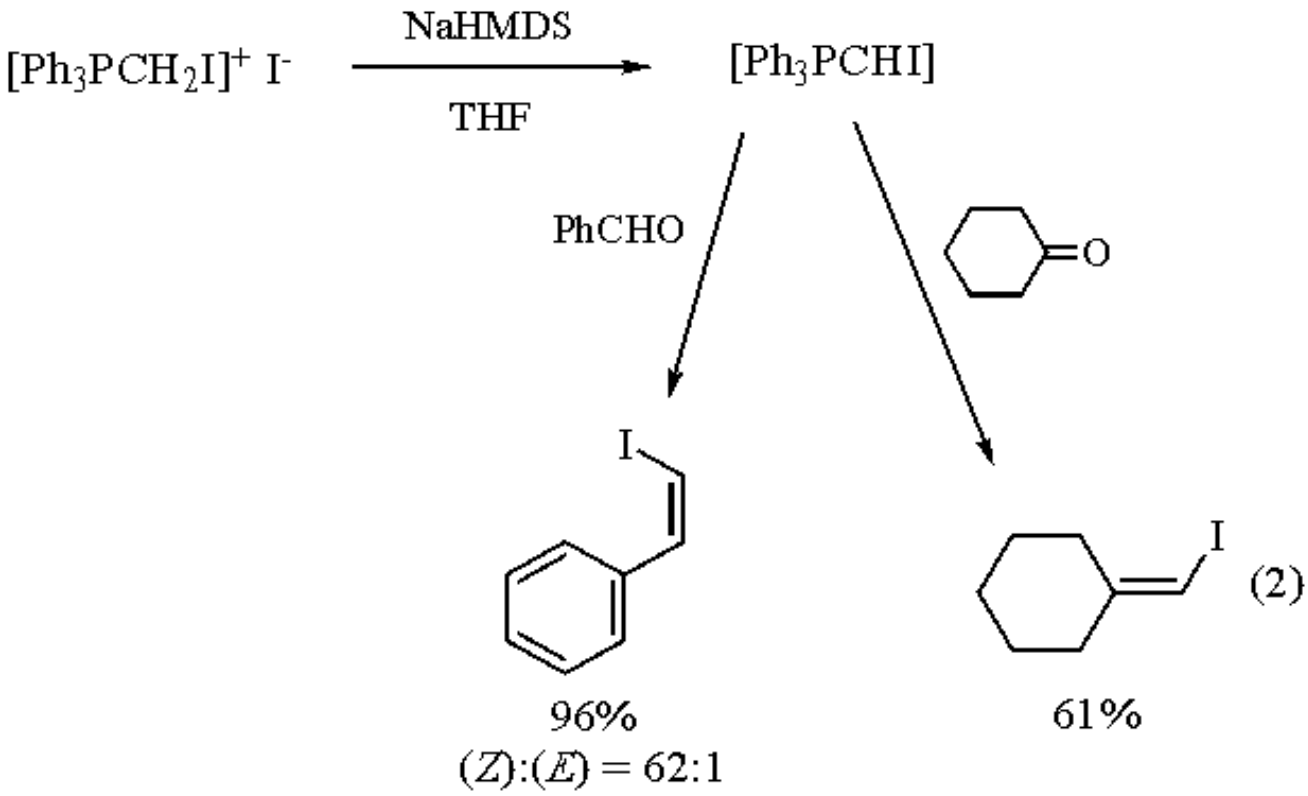

NaHMDS has been shown to be the necessary base for the generation of the ylide anion of sodium cyanotriphenylphosphoranylidenemethanide, which may be alkylated with various electrophiles and in turn used as an ylide to react with carbonyl compounds.[19] NaHMDS was used as the base of choice in a Horner-Emmons-Wadsworth-based synthesis of terminal conjugated enynes.[20]

Intramolecular Alkylation via Protected Cyanohydrins (Acyl Anion Equivalents).

Although NaHMDS was not the base of choice for the generation of protected cyanohydrin acyl carbanion equivalents in the original references,[21] it has been shown to be an important reagent for intramolecular alkylation using this strategy (eqs 3 and 4).[7,22] The advantages of this reagent are (a) that it allows high yields of intramolecularly cyclized products with little intermolecular alkylation and (b) the carbanion produced in this manner acts only as a nucleophile without isomerization of double bonds α,β to the anion or other existing double bonds in the molecule. Small and medium rings as well as macrocycles[22a] have been reported using this methodology (eqs 3 and 4).

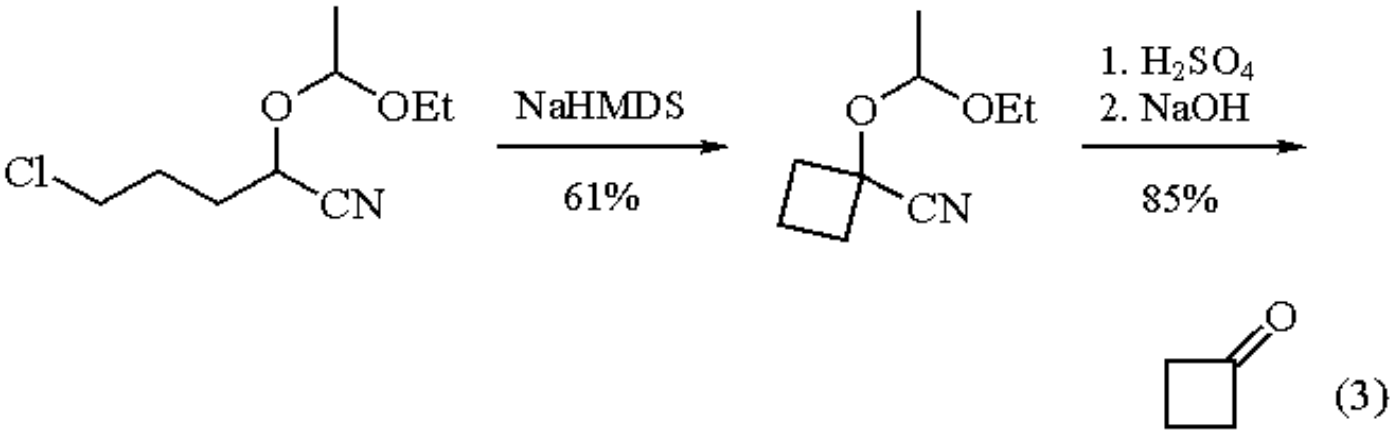

(3)

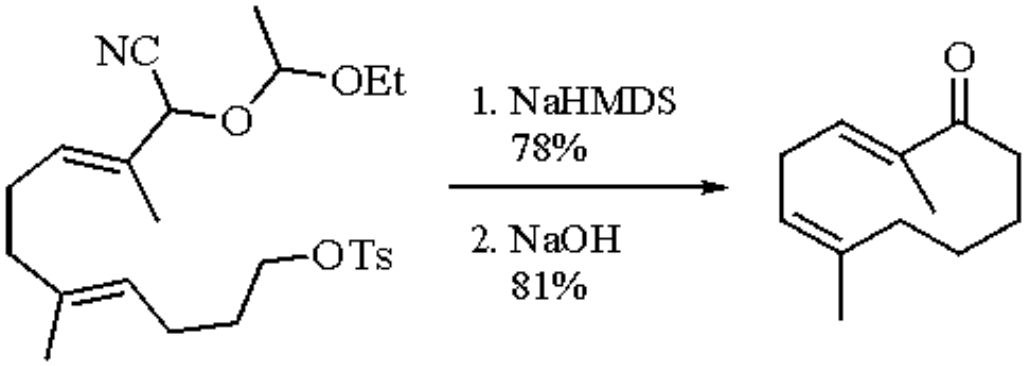

(4)

Generation of Carbenoid Species.

Metal bis(trimethylsilyl)amides may be used to effect α-eliminations.[23] It is proposed that these nucleophilic agents undergo a hydrogen-metal exchange reaction with polyhalomethanes to give stable carbenoid species.[23b] NaHMDS has been used to generate carbenoid species which have been used in a one-step synthesis of monobromocyclopropanes (eqs 5 and 6).[23c,d] NaHMDS has been shown to give better yields than the corresponding lithium or potassium amides in this reaction.

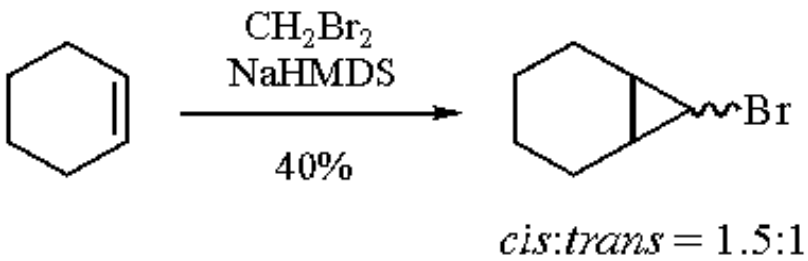

(5)

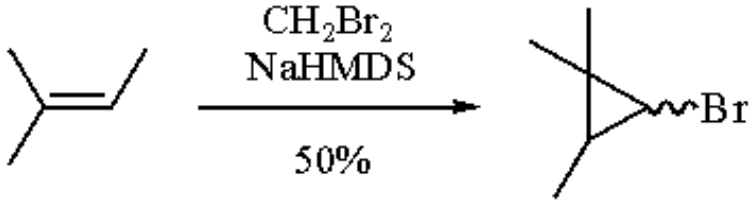

(6)

A similar study which evaluated the use of NaHMDS versus ***n-Butyllithium*** for the generation of the active carbenoid species from 1,1-dichloroethane and subsequent reaction with alkenes, forming 1-chloro-1-methylcyclopropanes, suggested that the amide gave very similar results to those with *n*-butyllithium.[24]

In an initial report, the carbenoid species formed by the treatment of diiodomethane with NaHMDS was shown to react as a nucleophile, displacing primary halides and leading to a synthesis of 1,1-diiodoalkanes; this is formally a 1,1-diiodomethylene homologation (eq 7).[25] This methodology is limited in that electrophiles which contain functionality that allows facile E2 elimination (i.e. allyl) form a mixture of the desired 1,1-diiodo compound and the iododiene. In the case of ***Allyl Bromide***, addition of 2 equiv of the sodium reagent allows isolation of the iododiene as the major product.

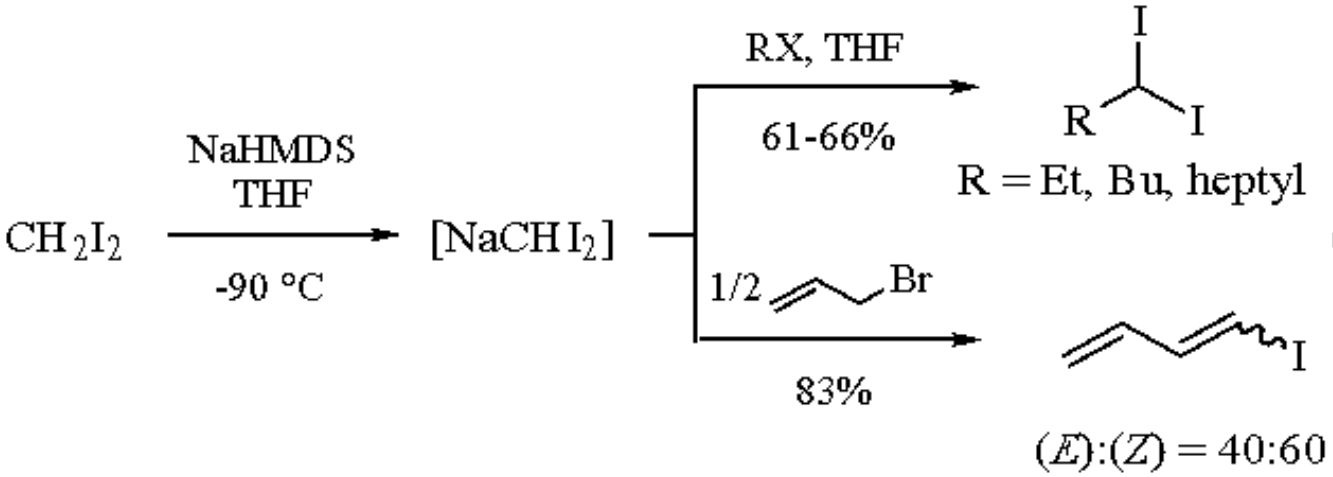

(7)

Synthesis of Primary Amines.

The nucleophilic properties of this reagent may be utilized in the S_N2 displacement of primary alkyl bromides, iodides, and tosylates to form bis(trimethylsilyl)amines (**1**) (eq 8).[9a] HCl hydrolysis of (**1**) allows isolation of the corresponding hydrochloride salt of the amine, which may be readily separated from the byproduct, bis(trimethylsilyl) ether. In one example a secondary allylic bromide also underwent the conversion with good yield.

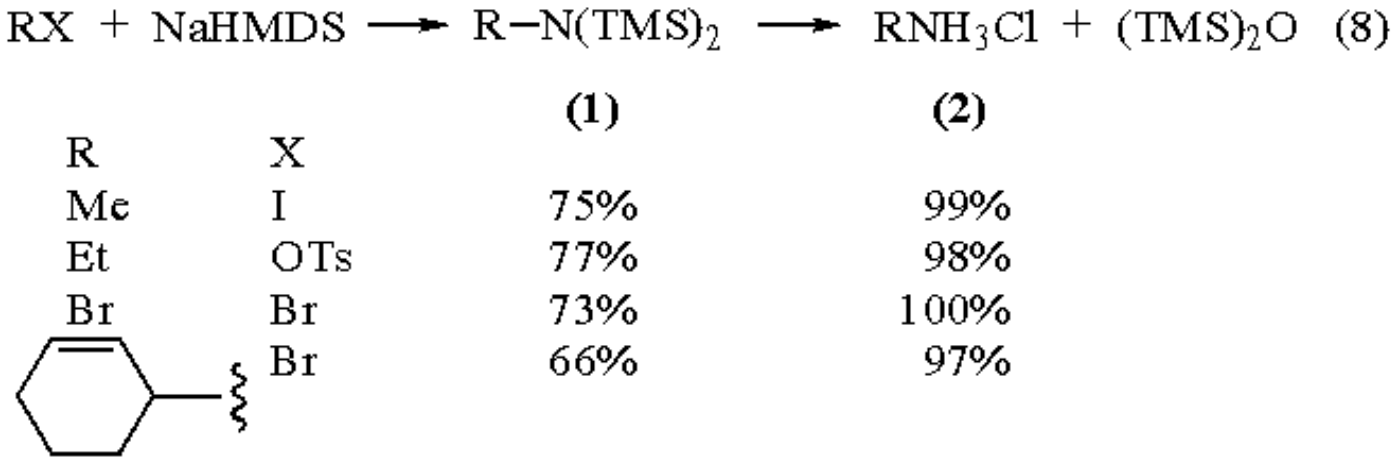

(8)

Aminomethylation.

NaHMDS may be used as the nitrogen source in a general method for the addition of an aminomethyl group (eq 9).[10] The reagent is allowed to react with chloromethyl methyl ether, forming the intermediate aminoether. Addition of Grignard reagents to this compound allows the displacement of the methoxy group, leaving the bis(trimethylsilyl)-protected amines. Acidic hydrolysis of these allows

isolation of the hydrochloride salt of the corresponding amine in good yields.

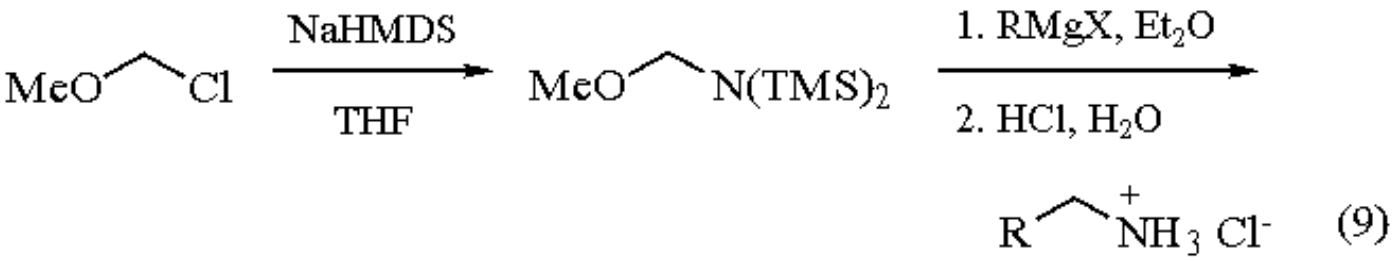

R = Me, 89%; allyl, 76%; Cy, 75%; Ph, 78%; propargyl, 66%

Related Reagents.

Lithium Hexamethyldisilazide; ***Potassium Hexamethyldisilazide***.

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Sodium Hydrazide[1]

$NaHNNH_2$

[16657-57-1] · H_3N_2Na · Sodium Hydrazide · (MW 54.04)

(capable of nucleophilic addition to alkenes,[2] alkynes,[3] and nitriles[4] to give hydrazines, hydrazones, or amidrazones; reacts by nucleophilic substitution with electrophilic heteroarenes[5] to give hydrazines[5] or amines[6] and with benzene halides[7] or benzene sulfonates[8] to give hydrazines; reacts with 1,3-dienes in presence of hydrazine to give dehydrogenated hydrazine derivatives;[9] further reaction modes include reduction of unsaturated hydrocarbons[10] and reductive dehalogenation,[11] cleavage of C=C double bonds affording a hydrocarbon and a hydrazone,[12] and selective cleavage of tertiary amide bonds[13])

Physical Data: IR spectrum.[14]

Solubility: moderately sol H_2NNH_2, liquid NH_3.

Preparative Methods: obtained as a suspension of pale yellow crystals by action of ***Sodium Amide*** on anhydrous ***Hydrazine*** under pure N_2 at rt in ether or at -33 °C in liquid NH_3 in a special apparatus.[2a] The method of preparation using Na/H_2NNH_2 often leads to explosion, even if O_2 is strictly excluded.[15]

Handling, Storage, and Precautions: **explodes violently and regularly** in contact with O_2; storage is not recommended. A protective plexiglass screen (thickness 1 cm) is absolutely necessary in front of the apparatus as $NaHNNH_2$ is prepared and reacted. In reactions with organic compounds, moderate heating (max 60 °C) is allowed. Hydrolysis of the reaction mixture is possible by very slow addition (avoidance of local overheating) of water under ice-cooling. Use in a fume hood.

Nucleophilic Addition.

The high tendency of $NaHNNH_2$ to add by a special mechanism[2a] to unsaturated organic compounds enables the transformation of alkenes such as styrene[2] to alkyl hydrazines, of alkynes[3] to hydrazones, and of nitriles[4] to amidrazones at low temperatures in ether (eqs 1-5). For the reaction of eq 1, only a catalytic amount of $NaHNNH_2$ is necessary.

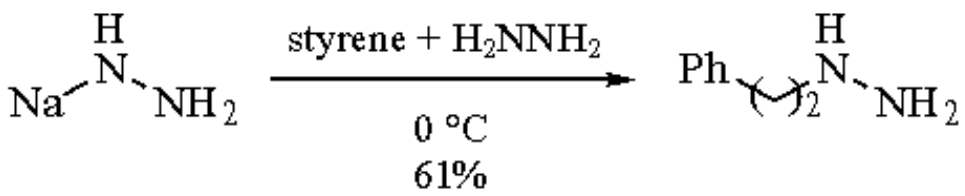

(1)

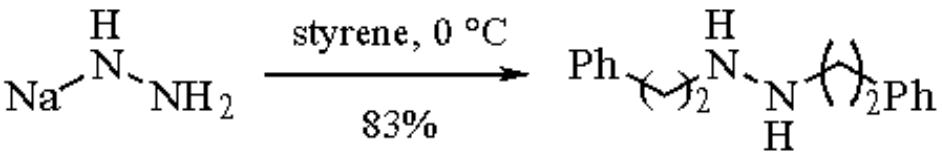

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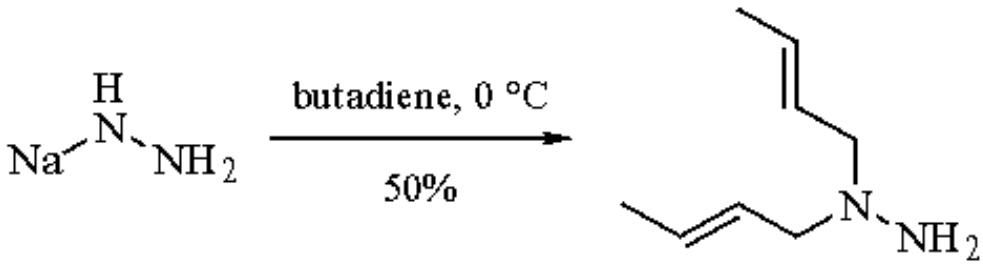

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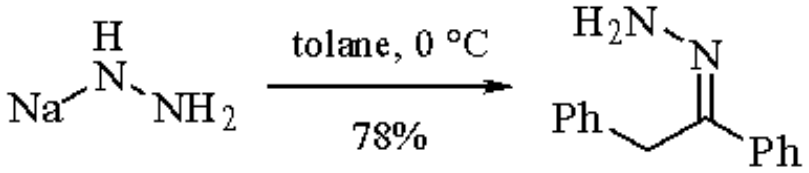

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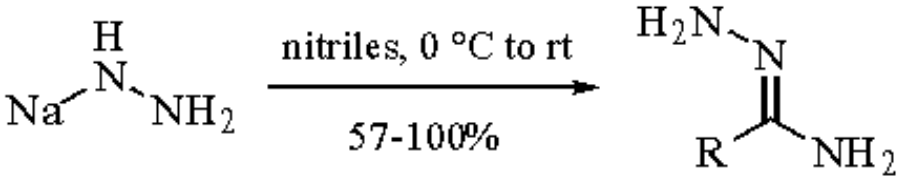

(5)

Nucleophilic Substitution.

$NaHNNH_2$ reacts with electrophilic heteroarenes such as pyridine[5a] and isoquinoline[5b,5c] by substitution of hydrogen. In ether, reactions in the presence of H_2NNH_2 produce mono(heteroaryl)hydrazines, whereas in the absence of H_2NNH_2, *N,N′*-bis(heteroaryl)hydrazines are generated (eqs 6 and 7). In the case of acridine and phenanthridine the substitution product is an amino heteroarene.[6] Treating *p*-tolyl halides[7] with $NaHNNH_2/H_2NNH_2$ yields tolyl hydrazines by an addition-elimination mechanism (eq 8) or aryne mechanism (eq 9). Sodium *p*-tolylsulfonate[8] reacts under the same conditions to give *p*-tolylhydrazine.

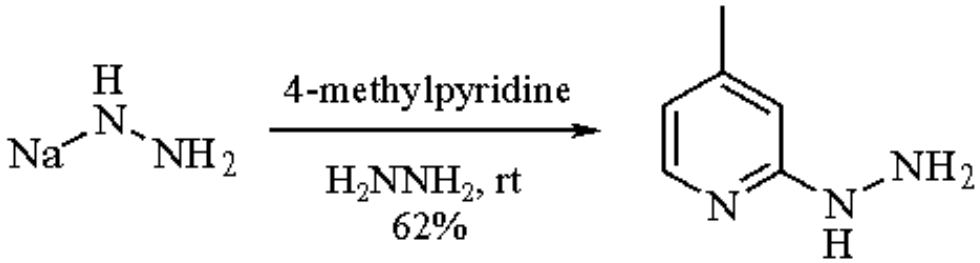

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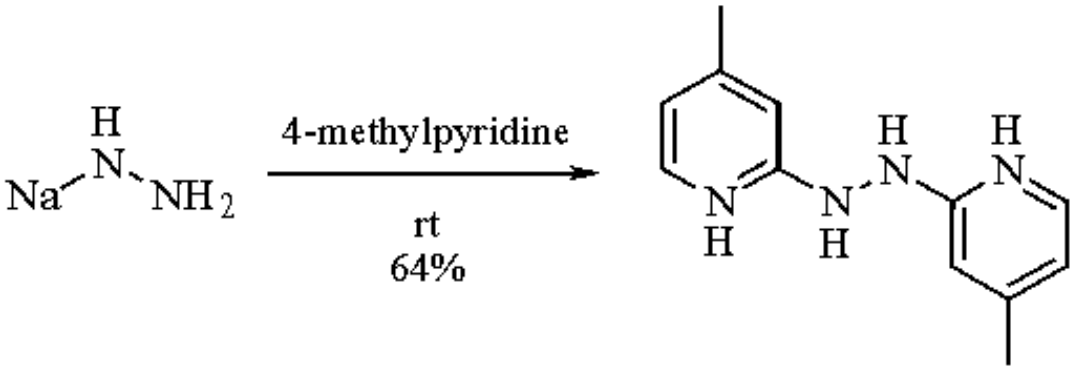

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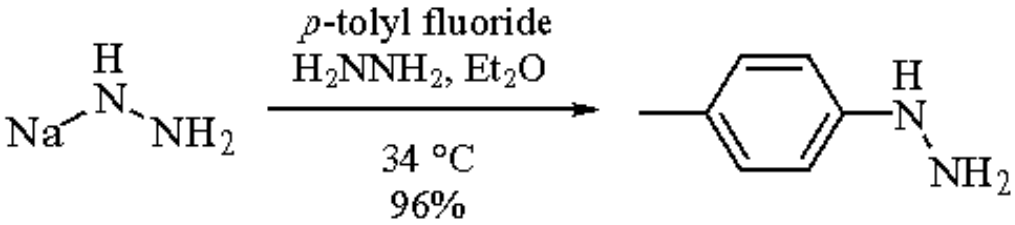

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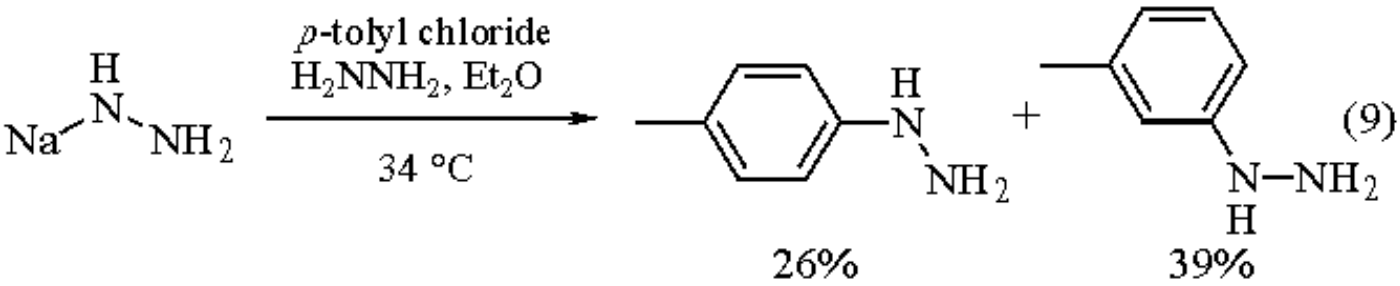

(9)

Oxidative Hydrazination.

Hydrazination with subsequent dehydrogenation to give azines or pyrazoles occurs by simultaneous action of $NaHNNH_2$ and H_2NNH_2 in ether on 1,3-dienes (eqs 10 and 11).[9]

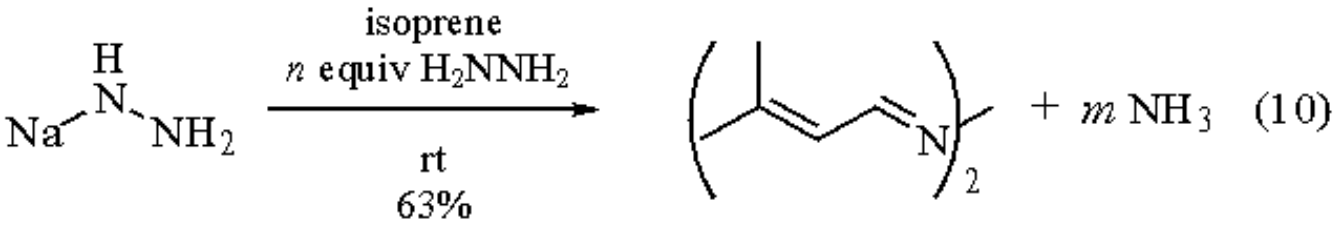

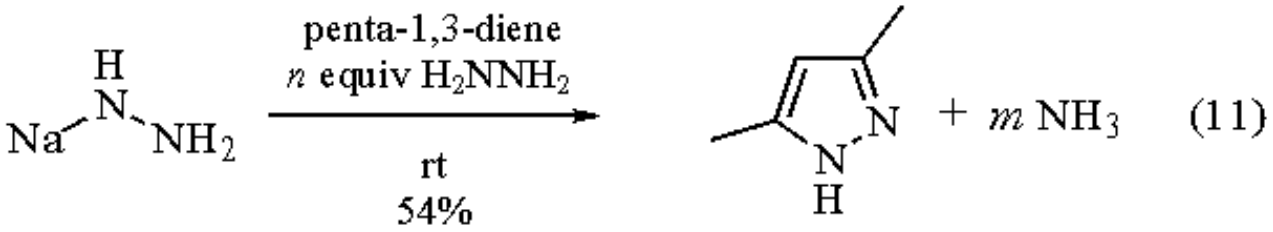

Reduction and Reductive Hydrazination.

Treatment of unsaturated hydrocarbons (e.g. stilbene), unsaturated nitrogen compounds, or polycyclic arenes with $NaHNNH_2/H_2NNH_2$ leads frequently to reduction of the substrate[10] (e.g. eq 12). The initially formed $NaHNNH_2$ adduct is believed to eliminate sodium diimide in these cases. Naphthalene is reduced to the 1,2-dihydro derivative, which affords 2-hydrazino-1,2,3,4-tetrahydronaphthaline[2b] by addition of $NaHNNH_2$ (eq 13). A further type of reduction is reductive dehalogenation.[11]

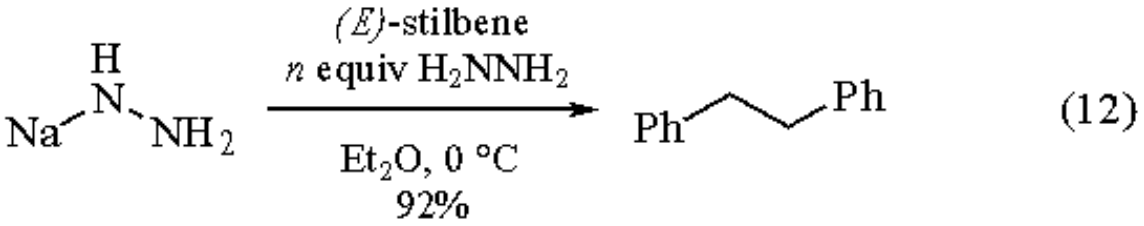

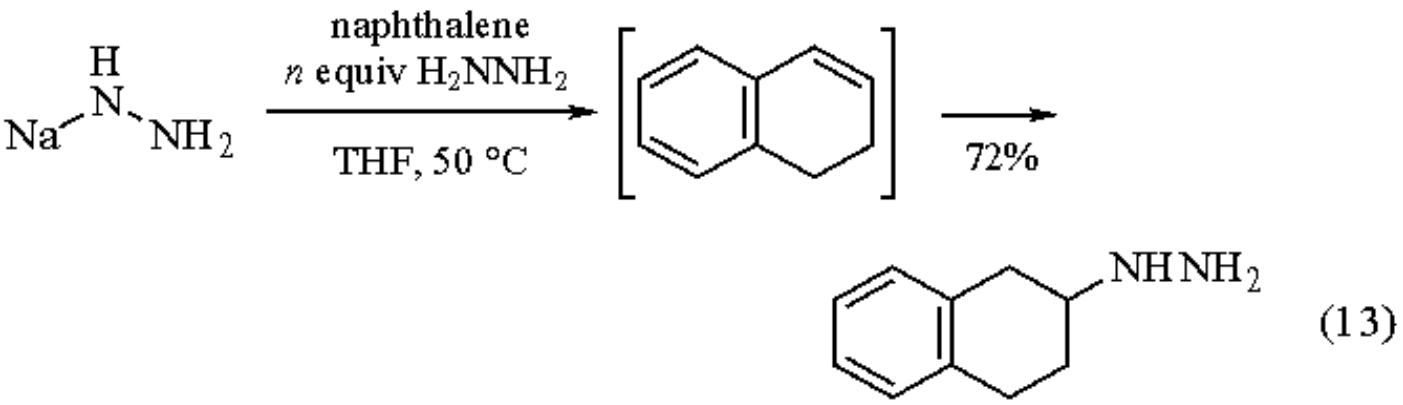

Alkene Hydrazidolysis.

$NaHNNH_2$ is capable of cleaving C=C double bonds[12] which are activated by an adjacent aryl residue (eq 14). This reaction is analogous to the reaction of aldehydes and ketones with H_2NNH_2 to give H_2O and a hydrazone. By subsequent treatment of the hydrazone of eq 14 with aq acid, a formal hydrolysis (eq 15) of a C=C double bond is achieved. Alternatively, subsequent treatment of the hydrazone with NaOH under Wolff-Kishner conditions gives rise to formal reductive cleavage (eq 16).

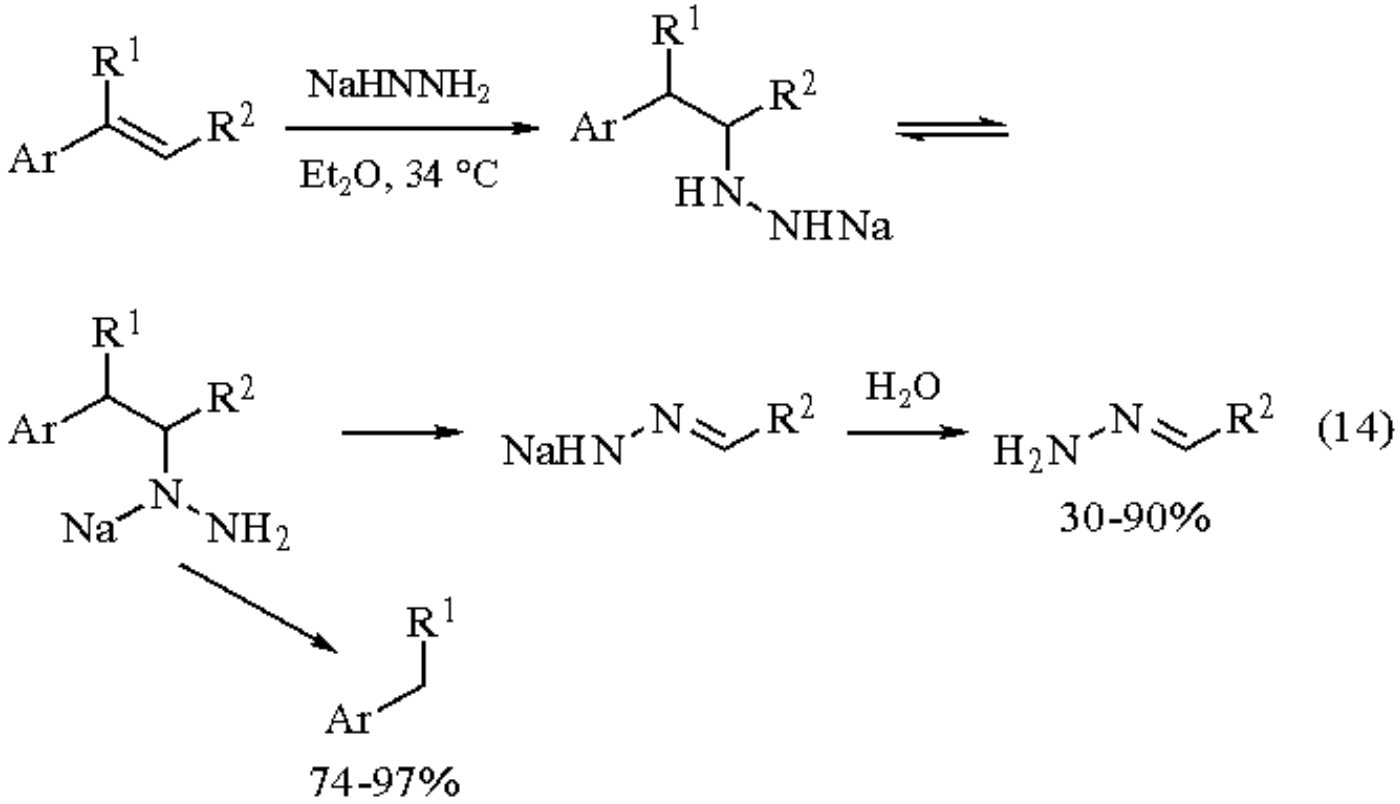

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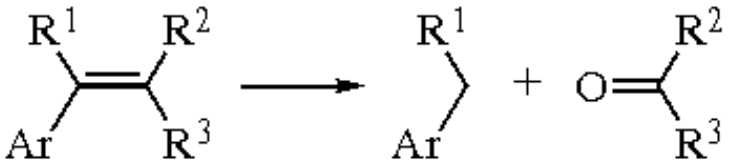

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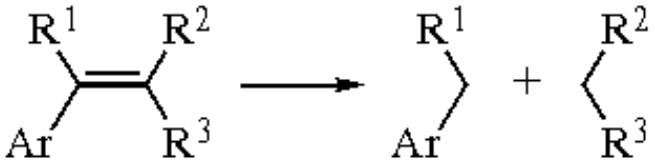

(16)

A related cleavage reaction (eq 17)[12c] was observed by reacting 2 equiv $NaHNNH_2$ with β-halogen phenylalkanes in the presence of hydrazine.

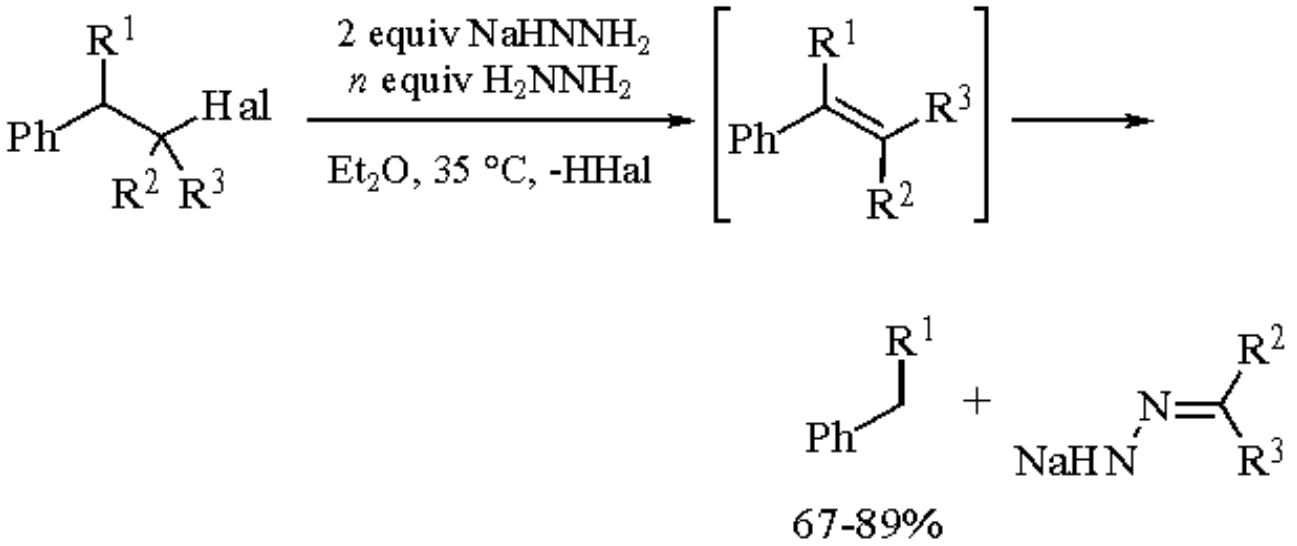

(17)

Regiospecific or Regioselective Peptide Hydrazidolysis.

In the presence of hydrazine, $NaNHNH_2$ cleaves tertiary amide groups, whereas secondary and primary amide groups (which form

mesomeric anions) are stable under these conditions. This allows a quantitative regiospecific hydrolysis of diglycyl-L-proline (eq 18).[13] By reacting $NaHNNH_2/H_2NNH_2$ with insulin, which contains only one tertiary amide bond, selective fission was possible to give the peptide Pro-Lys-Ala-CO_2H (ca. 70%).

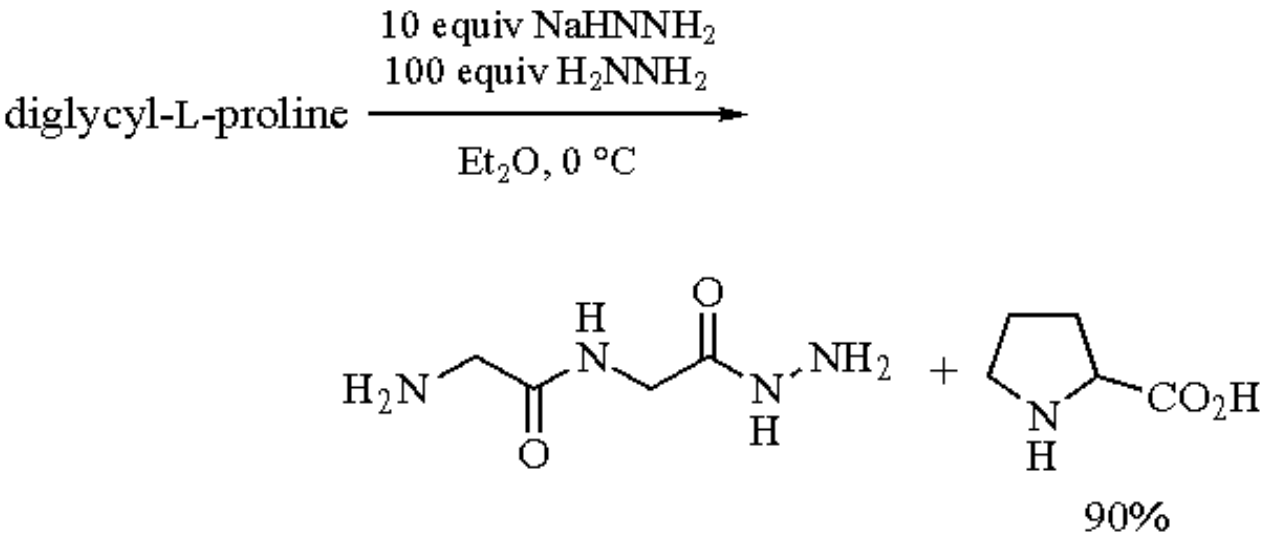

(18)

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Sodium Hydride[1]

NaH

[7646-69-7] · HNa · Sodium Hydride · (MW 24.00)

(used as a base for the deprotonation of alcohols, phenols, amides (NH), ketones, esters, and stannanes; used as a reducing agent for disulfides, disilanes, azides, and isoquinolines)

Physical Data: mp 800 °C (dec); *d* 1.396 g cm^{-3}.

Solubility: decomposes in water; insol all organic solvents; insol liq NH_3; sol molten sodium.

Form Supplied in: free-flowing gray powder (95% dry hydride); gray powder dispersed in mineral oil.

Handling, Storage, and Precautions: the dispersion is a solid and may be handled in the air. The mineral oil may be removed from the dispersion by stirring with pentane, then allowing the hydride to settle. The pentane/mineral oil supernatant may be pipetted off, but care should be exercised to quench carefully any hydride in the supernatant with a small amount of an alcohol before disposal. The dry powder should only be handled in an inert atmosphere.

Sodium hydride dust is a severe irritant and all operations should be done in a fume hood, under a dry atmosphere. Sodium hydride is stable in dry air at temperatures of up to 230 °C before ignition occurs; in moist air, however, the hydride rapidly decomposes, and if the material is a very fine powder, spontaneous ignition can occur as a result of the heat evolved from the hydrolysis reaction. Sodium hydride reacts more violently with water than sodium metal (eq 1); the heat of reaction usually causes hydrogen ignition.

$$NaH + H_2O \longrightarrow NaOH + H_2 \qquad (1)$$

Introduction.

The following is arranged by reaction type: NaH acting as a base on oxygen, nitrogen, germanium/silicon, and carbon acids, and as a reducing agent.

Oxygen Acids (Alcohol Deprotonation).

Sodium hydride may be used as a base in the Williamson ether synthesis in neat benzyl chloride,[2] in DMSO,[3] or in THF (eq 2).[4] Phenols may also be deprotonated and alkylated in THF.[4b]

$$Ph_3COH + NaH + MeI \xrightarrow[85\%]{THF} Ph_3COMe \qquad (2)$$

Curiously, tertiary propargylic alcohols may be alkylated in preference to either axial or equatorial secondary alcohols, using sodium hydride in DMF (eq 3).[5]

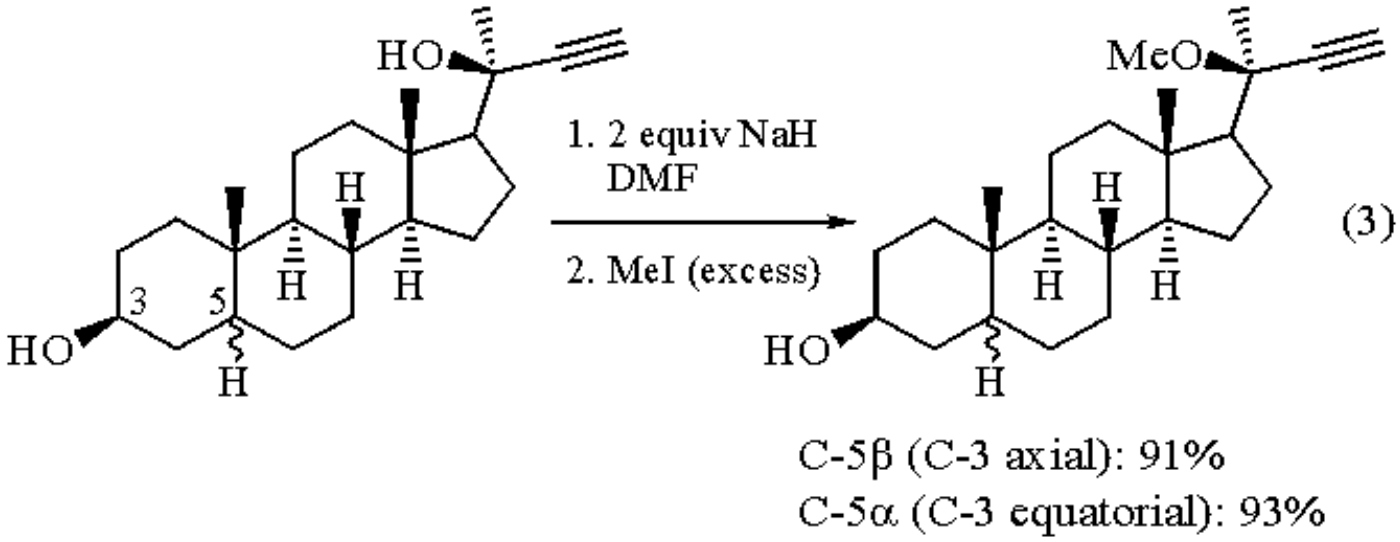

Sodium hydride in DMF is also used to deprotonate carbohydrate derivatives, for methylation or benzylation (eq 4).[6]

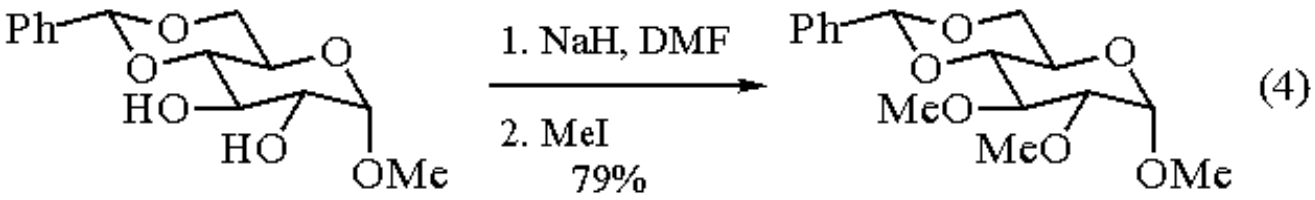

Unstable benzyl tosylates may be made by deprotonation of benzyl alcohols and acylation with ***p-Toluenesulfonyl Chloride*** (eq 5).[7]

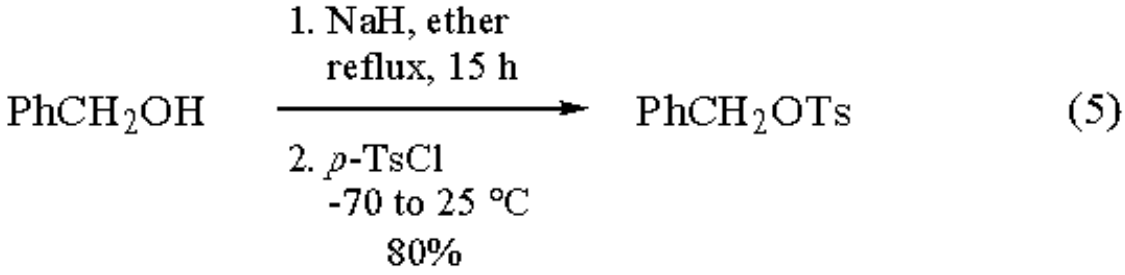

An interesting conformational effect is seen when *p-t*-butylcalix[4]arene is tetraethylated. When ***Potassium Hydride*** is used as the base, the partial cone conformation predominates (i.e. one of the aryl groups is inverted), whereas with sodium hydride, the cone is produced exclusively (eq 6).[8]

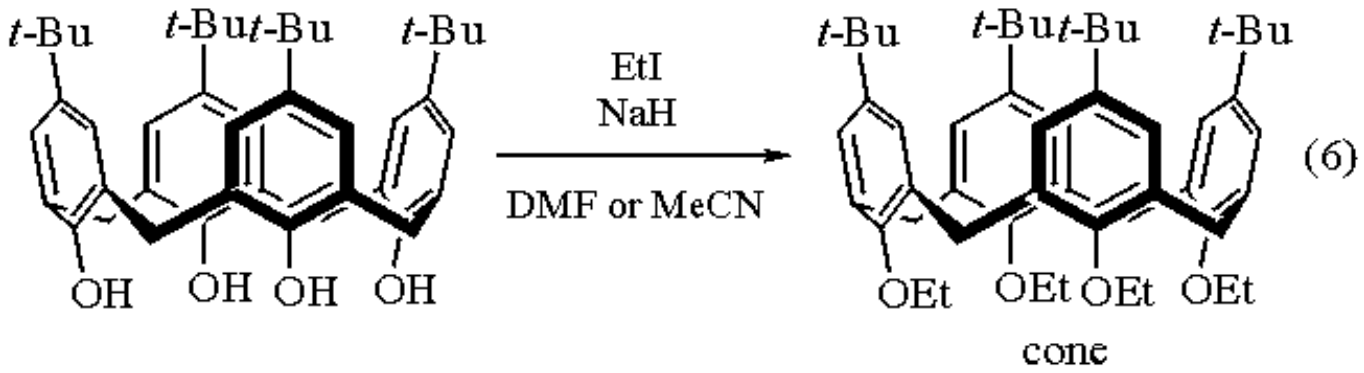

Deprotonation of vinylsilane-allylic alcohols using sodium hydride in HMPA is followed by an essentially quantitative C -> O silicon migration (eq 7).[9]

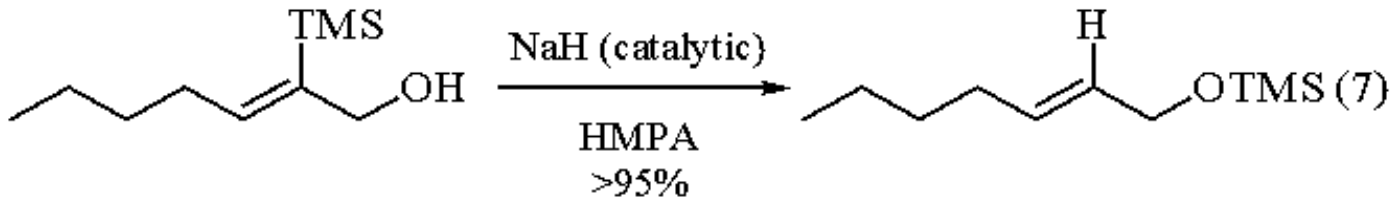

Nitrogen Acids.

Sodium hydride in DMSO, HMPA, NMP, or DMA assists the transamination of esters (eq 8).[10]

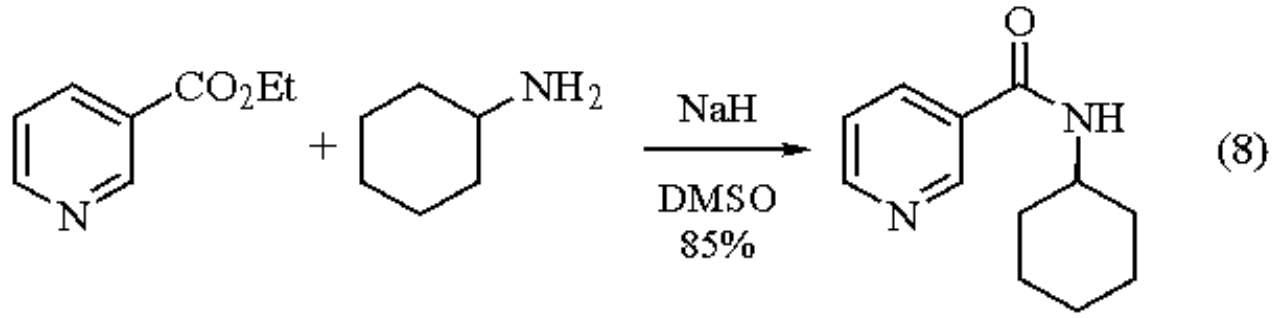

Acyl amino acids and peptides may be alkylated on nitrogen using sodium hydride, with no racemization (eq 9).[11] A slight change of reaction conditions allows simultaneous esterification.[12]

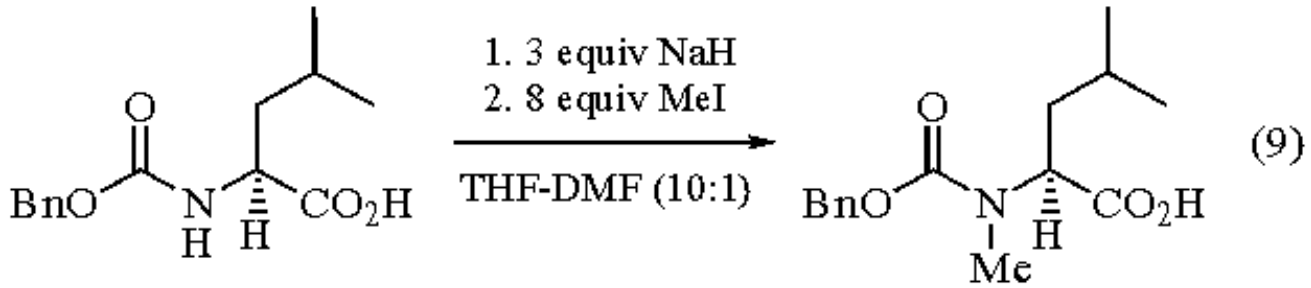

A similar intramolecular alkylation has been used to make β-lactams (eq 10).[13]

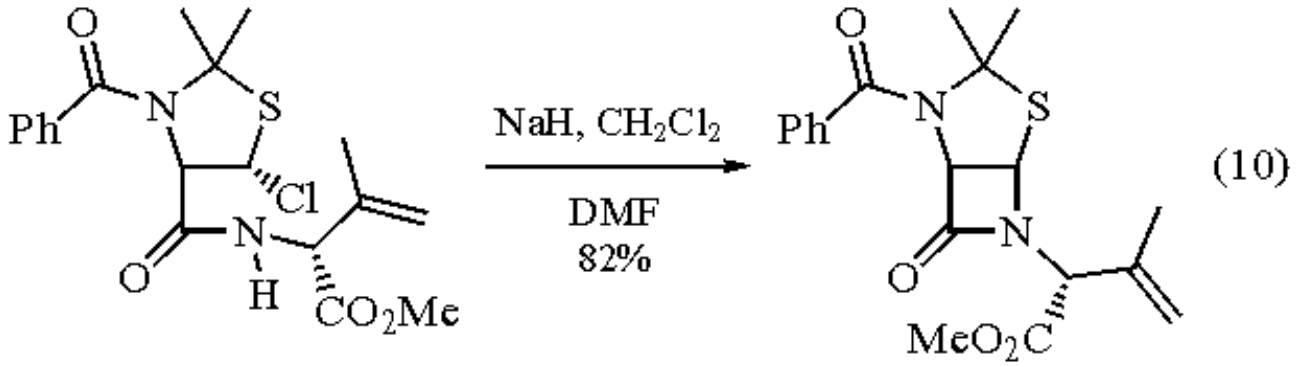

Germanium/Silicon Acids.

Germanium-hydrogen and silicon-hydrogen bonds are quantitatively cleaved with sodium hydride in ethereal solvents (eq 11).[14]

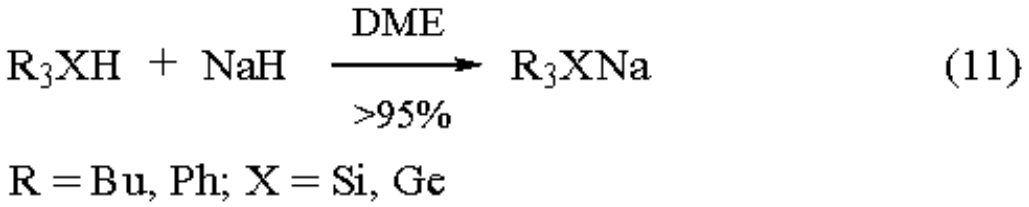

Carbon Acids.

Active methylene compounds, such as malonates and β-keto esters, can be deprotonated with sodium hydride and alkylated on carbon (eqs 12 and 13).[15] Alkylation of Reissert anions is also facile with sodium hydride (eq 14).[16]

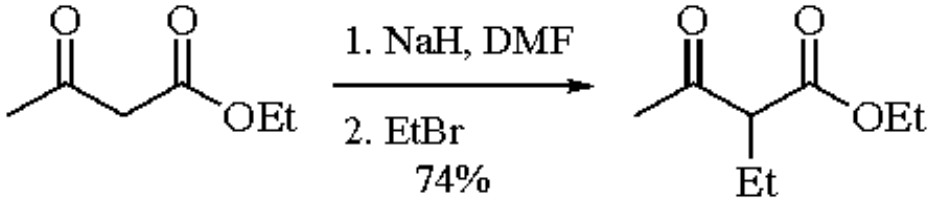

(12)

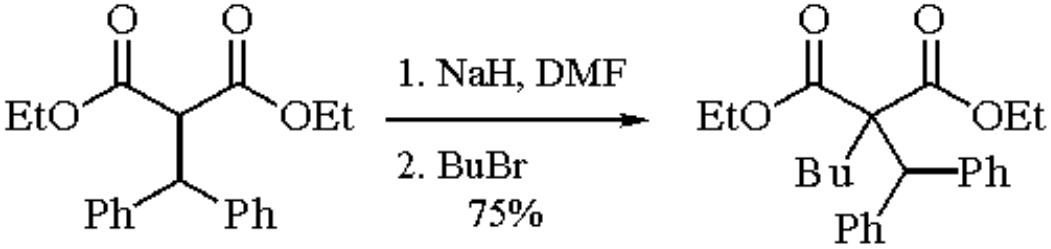

(13)

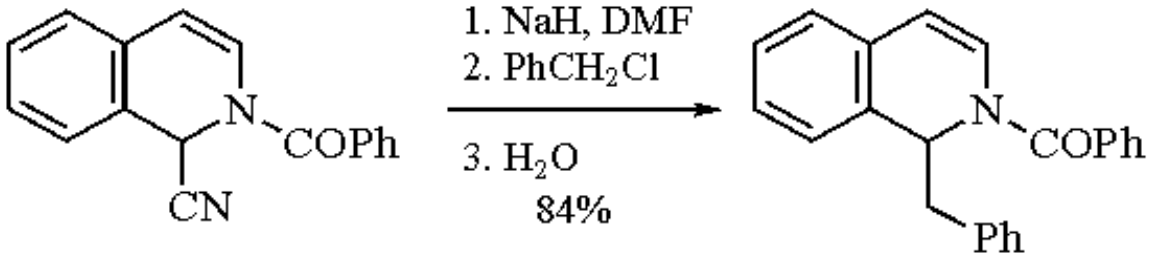

(14)

Normally, sodium enolates of ketones alkylate on oxygen. A superactive form of sodium hydride is formed when butylsodium is reduced with hydrogen; superactive sodium hydride is an excellent base for essentially quantitative deprotonation of ketones, trapped as their silyl ethers.[17] For example, cyclododecanone is converted to its enol ether (containing a hyperstable double bond) in 92% yield (eq 15).

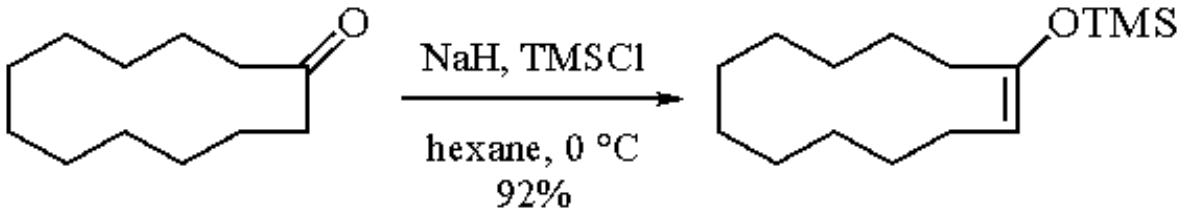

(15)

More commonly, sodium hydride is used as a base for carbonyl condensation reactions. For example, Claisen condensations of ethyl acetate[18] and ethyl isovalerate[19] are effected by sodium hydride. Condensations of cyclohexanone with methyl benzoate[19] and ethyl formate (eq 16)[20] are also facile.[21] Sodium hydride can also doubly deprotonate β-diketones, allowing acylation at the less acidic site (eq 17).[22]

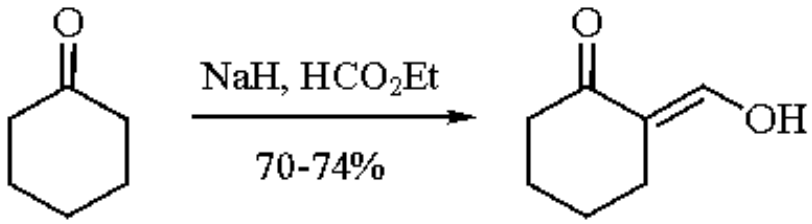

(16)

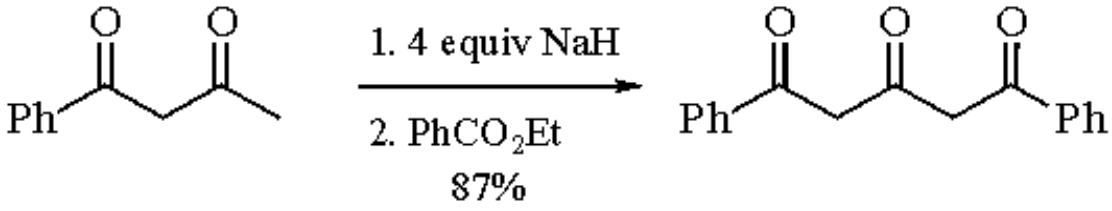

(17)

An undergraduate experiment using sodium hydride involves the crossed condensation of ethyl acetate and dimethyl phthalate (eq 18).[23] Sodium hydride is also effective as a base in the Stobbe condensation[24] and the Darzens condensation.[25] It is also effective in a stereoselective intramolecular Michael reaction (eq 19).[26]

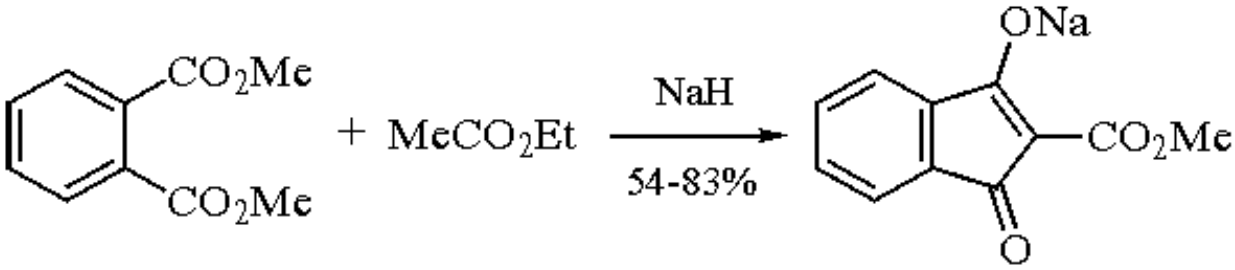

(18)

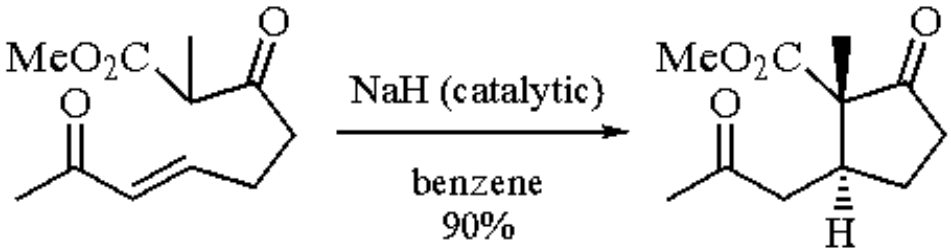

(19)

The Dieckmann condensation of esters[27] and thioesters[28] is mediated by sodium hydride (eq 20). Conditions for the latter are significantly more mild than for the former, and the yields are higher.

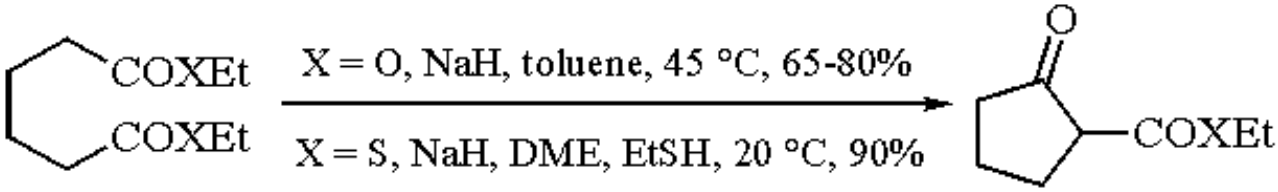

(20)

Sodium hydride may be used to cleave formate esters and formanilides (eqs 21 and 22).[29] The mechanism apparently involves removal of the formyl proton and loss of carbon monoxide.

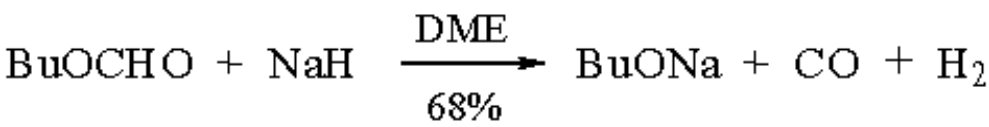

(21)

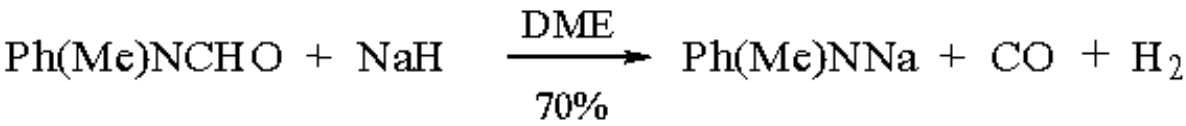

(22)

Dehydrohalogenation with sodium hydride is a means of making methylenecyclopropanes (eq 23).[30]

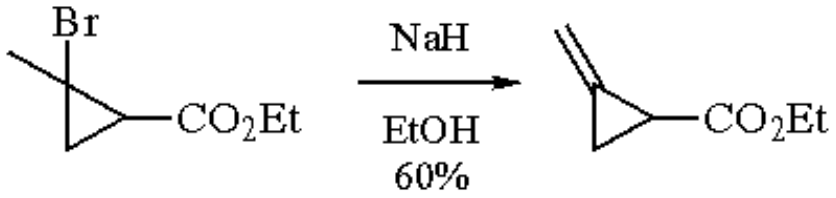

(23)

Enolate formation apparently accelerates the Diels-Alder cycloaddition/cycloreversion, shown in eq 24, which occurs at room temperature.[31]

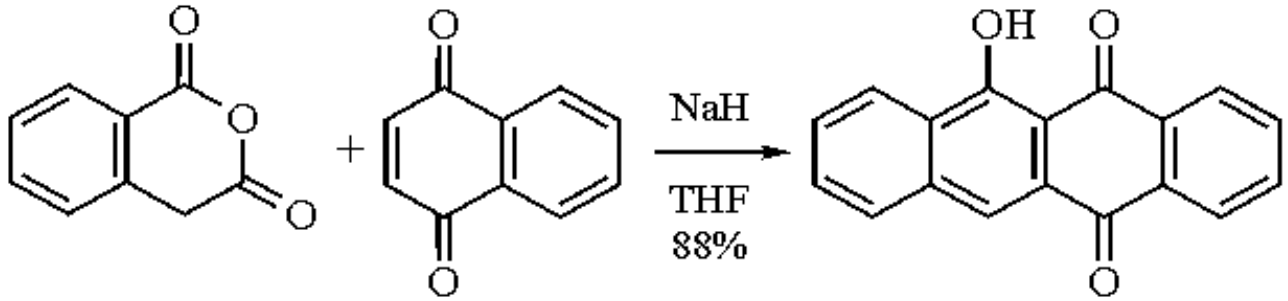

(24)

An unusual cyclization of *N*-allyl-α,β-unsaturated amides is mediated by sodium hydride in refluxing xylene (eq 25).[32] The reaction is thought to proceed by intramolecular 1,4-addition of the dianion shown.

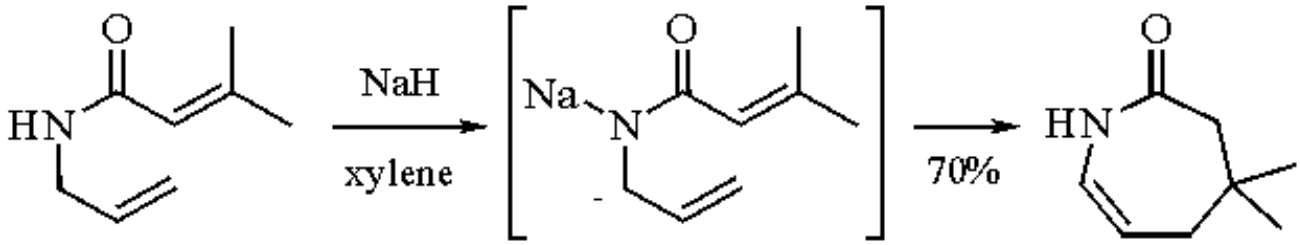

(25)

Reductions.

The sodium salt of trimethylsilane is produced quantitatively by reduction of hexamethyldisilane with sodium hydride (eq 26).[33]

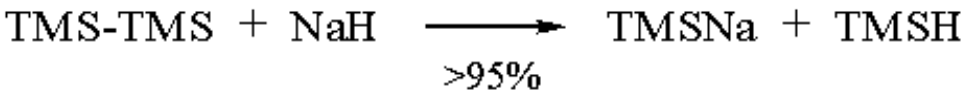

(26)

Sodium hydride in DMSO is an effective medium for the reduction of disulfide bonds in proteins under aprotic conditions.[34] When the molar ratio of hydride to 1/2 cystine residues exceeds 2:1, essentially complete reduction of the disulfide bonds of bovine serum albumin is achieved.

Azides are reduced to amines by sodium hydride, although the yields are moderate (eq 27).[35] Sodium hydride also reduces isoquinoline to 1,2-dihydroisoquinoline in good yield (eq 28).[36]

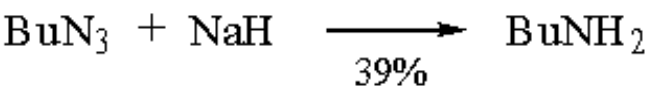

(27)

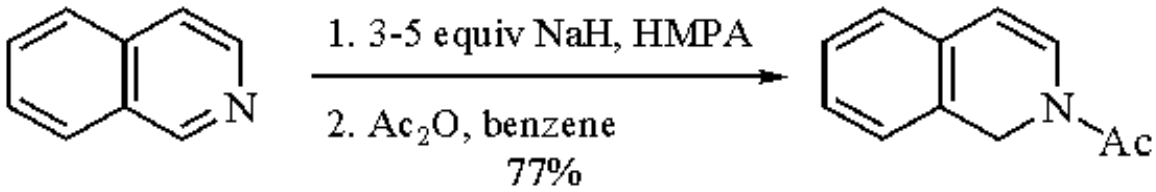

(28)

Related Reagents.

Calcium Hydride; ***Iron(III) Chloride-Sodium Hydride***; ***Lithium Aluminum Hydride***; ***Potassium Hydride***; ***Potassium Hydride-s-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine***; ***Potassium Hydride-Hexamethylphosphoric Triamide***; ***Sodium Borohydride***; ***Sodium Hydride-Copper(II) Acetate-Sodium t-Pentoxide***; ***Sodium Hydride-Nickel(II) Acetate-Sodium t-Pentoxide***; ***Sodium Hydride-Palladium(II) Acetate-Sodium t-Pentoxide***; ***Tris(cyclopentadienyl)lanthanum-Sodium Hydride***.

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Sodium Hydride-Copper(II) Acetate-Sodium *t*-Pentoxide

NaH + $Cu(OAc)_2$ + NaO-*t*-C_5H_{11}

(NaH)

[7646-69-7] · HNa · Sodium Hydride-Copper(II) Acetate-Sodium *t*-Pentoxide · (MW 24.00) ($Cu(OAc)_2$)

[142-71-2] · $C_4H_6CuO_4$ · Sodium Hydride-Copper(II) Acetate-Sodium *t*-Pentoxide · (MW 181.65) (NaO-*t*-C_5H_{11})

[14593-46-5] · $C_5H_{11}NaO$ · Sodium Hydride-Copper(II) Acetate-Sodium *t*-Pentoxide · (MW 110.15)

(a complex reducing agent (CRA) that converts aromatic halides to hydrocarbons; can act as a coupling agent[1,2])

Physical Data: see ***Sodium Hydride*** and ***Copper(II) Acetate***; the *t*-pentoxide salt is prepared in situ.

Solubility: sol THF, DME.

Preparative Methods: from NaH, *t*-pentanol, and $Cu(OAc)_2$ in THF. Addition of *t*-pentanol begins at 40 °C, as it is very important not to exceed 45 °C throughout the process. After 3 h of stirring at 45 °C, the catalyst is ready for use.[3,4]

Handling, Storage, and Precautions: store under argon in airtight bottles; moisture sensitive. Use in a fume hood.

Reduction of Aromatic Halides.

The title reagent is an example of a series of complex reducing agents (CRAs) obtained by treating NaH and an alcohol (in this case, *t*-pentanol) with a metallic acetate salt (in this case, copper(II) acetate). These CRAs exhibit reducing abilities which can be varied by changing the solvent, the alkoxide, or the reaction temperature. In eq 1, reduction of 1-bromonaphthalene to the hydrocarbon is accompanied by coupling to produce 1,1´-binaphthyl.

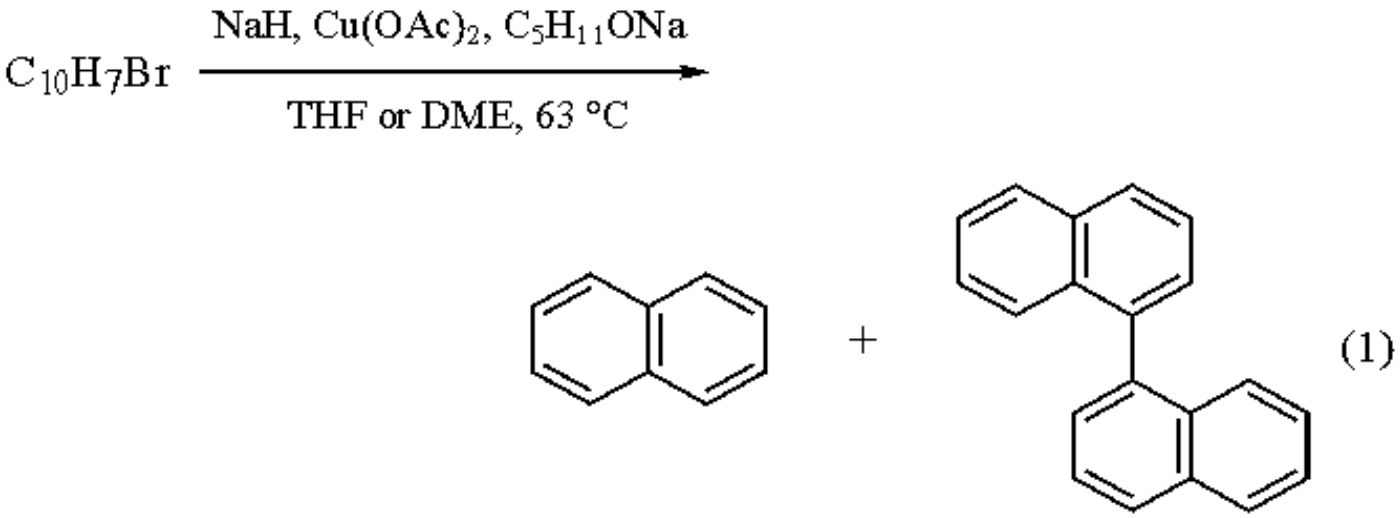

Both THF and DME can be used as solvent. In THF, reaction after 17 h yielded 60-65% naphthalene and 20% 1,1´-binaphthyl. In DME, after 20 h, 80-85% naphthalene and 5-10% 1,1´-binaphthyl were formed. With other salts ($Co(OAc)_2$, $Ni(OAc)_2$, $Zn(OAc)_2$), hydrocarbon yields were 85-95% within 5 min-2 h, with no coupling product observed.

Reduction of Primary Alkyl Halides.

The reagent was not effective in the reduction of primary alkyl halides. When reacted with *n*-octyl bromide, it afforded mainly 1-octene along with small amounts (5-20%) of octane.

Related Reagents.

Nickel Complex Reducing Agents; ***Sodium Hydride***; ***Sodium Hydride-Nickel(II) Acetate-Sodium t-Pentoxide***; ***Sodium Hydride-Palladium(II) Acetate-Sodium t-Pentoxide***; ***Zinc Complex Reducing Agents***.

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Sodium Hydride-Nickel(II) Acetate-Sodium *t*-Pentoxide

$NaH + Ni(OAc)_2 + NaO\text{-}t\text{-}C_5H_{11}$

(NaH)

[7646-69-7] · HNa · Sodium Hydride-Nickel(II) Acetate-Sodium *t*-Pentoxide · (MW 24.00) ($Ni(OAc)_2.4H_2O$)

[6018-89-9] · $C_4H_{14}NiO_8$ · Sodium Hydride-Nickel(II) Acetate-Sodium *t*-Pentoxide · (MW 248.87) ($NaO\text{-}t\text{-}C_5H_{11}$)

[14593-46-5] · $C_5H_{11}NaO$ · Sodium Hydride-Nickel(II) Acetate-Sodium *t*-Pentoxide · (MW 110.15)

(highly active and selective nickel hydrogenation catalyst at atmospheric pressure; allows semihydrogenation of alkynes to *cis*-alkenes[1,2] and stereoselective reduction of ketones[9])

Physical Data: see ***Sodium Hydride*** and ***Nickel(II) Acetate***; the *t*-pentoxide salt is prepared in situ.

Solubility: sol THF, DME.

Preparative Methods: the nickel catalyst (referred to as NiC) is easily prepared by addition of the alcohol, the sodium salt of which has been chosen as an activating agent (in this case, sodium *t*-pentoxide), to a stirred suspension of $Ni(OAc)_2$ and a calculated excess of NaH in THF at 45 °C. Before hydrogenation, EtOH is used to wash NiC to eliminate excess soluble alkoxide.

Handling, Storage, and Precautions: when long storage is required, the excess sodium hydride must not be neutralized, but rather destroyed before use in hydrogenation. Simple washing with EtOH can eliminate excess alkoxide. Store under argon. Use in a fume hood.

Hydrogenation.

It was observed that, at room temperature and atmospheric pressure, alkenes and alkynes could be reduced to alkanes and *cis*-alkenes, respectively, over this NiC catalyst. Until most of the alkyne is converted to the alkene, only minor amounts of alkane are formed, even when further hydrogenation of the alkene is the faster reaction.[1,2] It was also found that NiC could promote hydrogenation of carbonyl compounds under ambient conditions. In reductions of ethylenic unsaturations, NiC catalysts are very sensitive to steric hindrance about the carbonyl groups (eqs 1-4).[3]

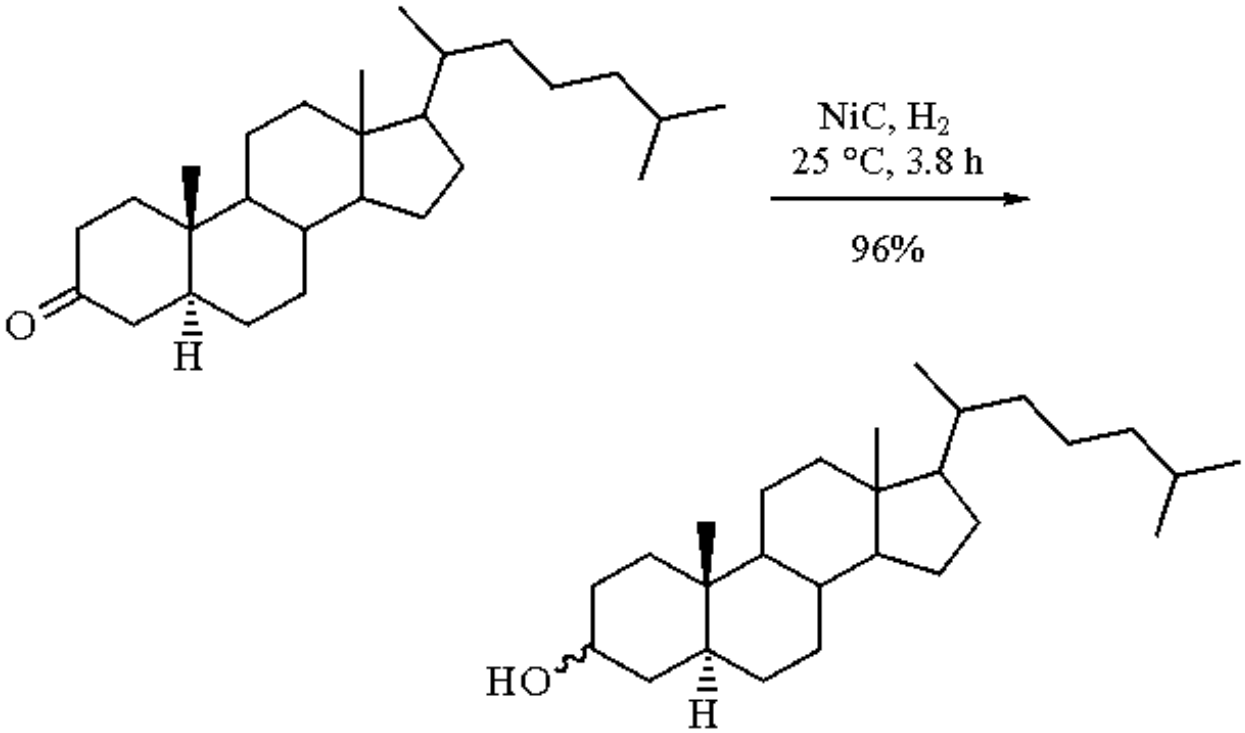

(1)

3α:3β = 67:33

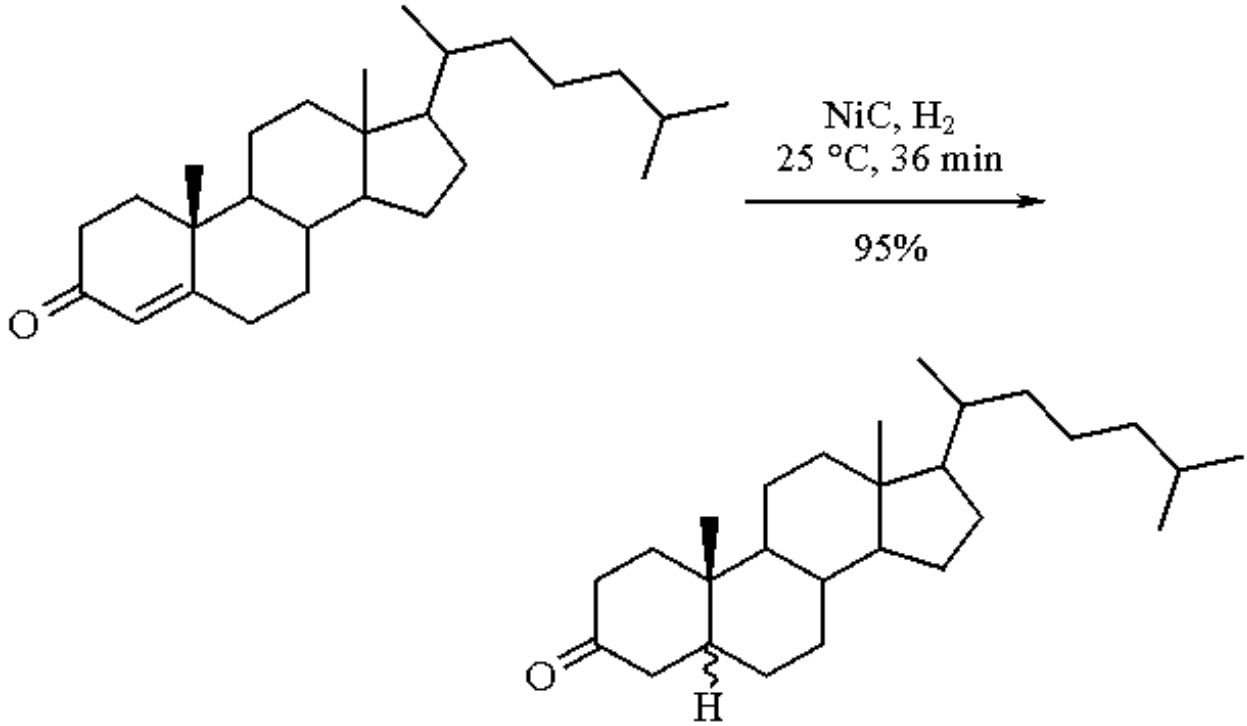

(2)

5α:5β = 13:87

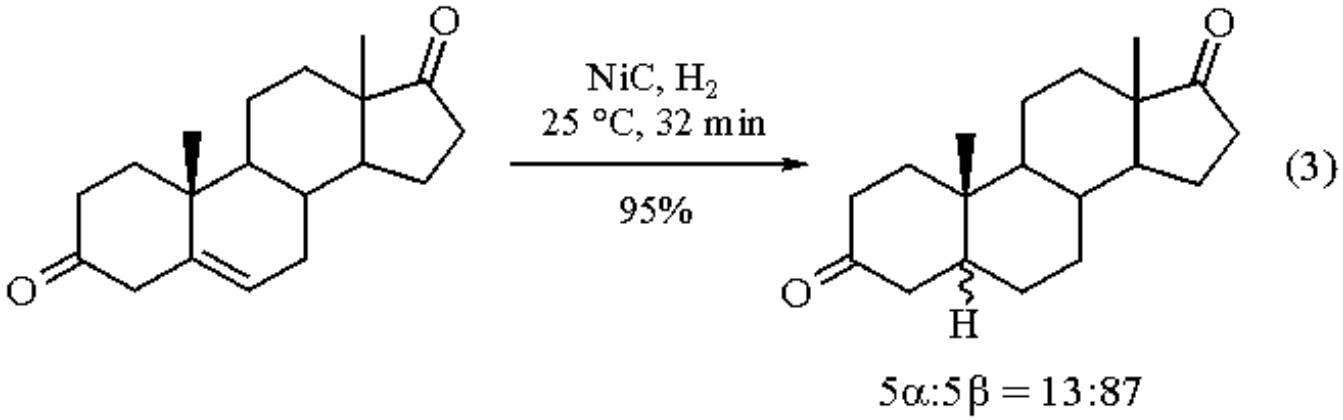

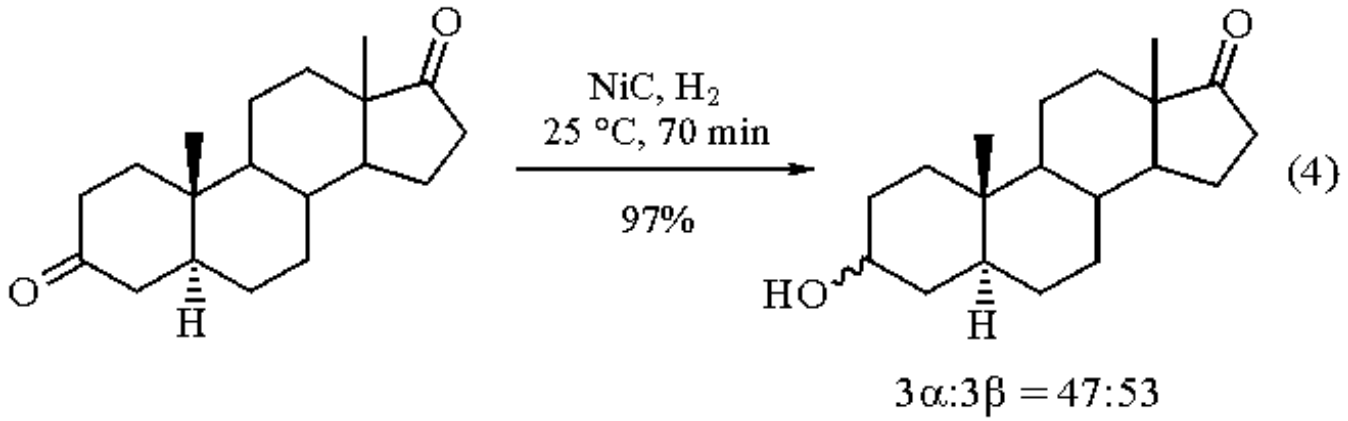

Other Reductions.

NiC can also be activated by ***Chlorotrimethylsilane***; selective reduction of polyunsaturated ketones is easily performed with this reagent.[4] NiC is useful in desulfurizing organic compounds such as sulfur-containing heteroaromatic substrates, aryl thioethers, dithioacetals, sulfoxides, and sulfones.[5,8] NiC combined with 2,2´-bipyridine (the nickel complex reducing agent NiCRA-bipy) is also very efficient in the desulfurization of organic compounds.[8]

Homocoupling of aryl bromides and chlorides is effected with NiCRA-bipy; the presence of alkali iodides improves the procedure. Yields are very high; however, a number of functional groups in the substrate may cause loss of reactivity.[6] NiCRA-bipy is the first nickel-containing reagent that allows Ullmann-type cross-coupling to occur in good yield and under mild conditions.[7]

NiCRAs and other metal complex reducing agents are among the reagents known for epimerization of alcohols. By varying the metal used, and by using additives such as ***Magnesium Bromide*** or Me_3SiCl, preferential formation of axial and equatorial alcohols from ketones is achieved. NiCRAs may be used to transform a given alcohol into its thermodynamically less stable epimer.[9] This method, complementary to the familiar Meerwein-Ponndorf-Verley-Oppenauer and Raney nickel processes, employs substrate-activated agents ((SA)NiCRA) or other additives (eq 5) (DMHDNa = sodium salt of 2,5-dimethylhexane-2,5-diol).

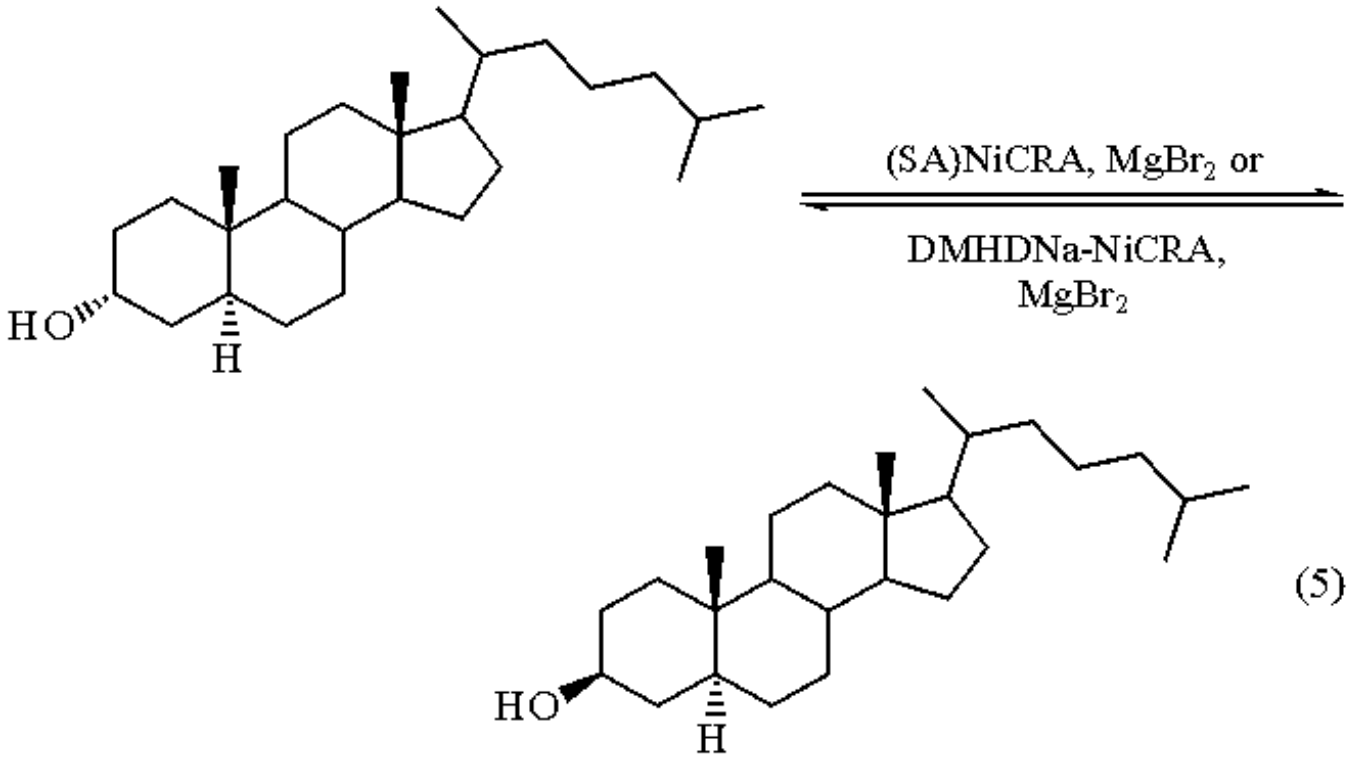

Related Reagents.

Nickel Complex Reducing Agents; ***Sodium Hydride***; ***Sodium Hydride-Copper(II) Acetate-Sodium t-Pentoxide***; ***Sodium Hydride-Palladium(II) Acetate-Sodium t-Pentoxide***; ***Zinc Complex Reducing Agents***.

---

1. Brunet, J. J.; Gallois, P.; Caubere, P. *TL* **1977**, 3955.
2. Brunet, J.-J.; Gallois, P.; Caubere, P. *JOC* **1980**, *45*, 1937.
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Sodium Hydride-Palladium(II) Acetate-Sodium *t*-Pentoxide

NaH + $Pd(OAc)_2$ + NaO-*t*-C_5H_{11}

(NaH)

[7646-69-7] · HNa · Sodium Hydride-Palladium(II) Acetate-Sodium *t*-Pentoxide · (MW 24.00) ($Pd(OAc)_2$)

[3375-31-3] · $C_4H_6O_4Pd$ · Sodium Hydride-Palladium(II) Acetate-Sodium *t*-Pentoxide · (MW 224.52) (NaO-*t*-C_5H_{11})

[14593-46-5] · $C_5H_{11}NaO$ · Sodium Hydride-Palladium(II) Acetate-Sodium *t*-Pentoxide · (MW 110.15)

(complex reducing agent; reduction of aromatic halides;[1] self-terminating semihydrogenation of alkynes[2])

Physical Data: see ***Sodium Hydride*** and ***Palladium(II) Acetate***; the *t*-pentoxide salt is prepared in situ.

Solubility: sol THF, DME, ethanol, hydrocarbon solvents.

Preparative Methods: from NaH, *t*-pentanol, and $Pd(OAc)_2$ in THF. Add the *t*-pentanol at 40 °C, as it is very important not to exceed 45 °C throughout the process. After 3 h of stirring at 45 °C, the catalyst is ready for use.[1,3,4]

Handling, Storage, and Precautions: store under argon in air-tight bottles; moisture sensitive; use in a fume hood.

Reduction of Aromatic Halides.

The reagent can be an effective reducing agent for converting aromatic halides to the corresponding hydrocarbons, as illustrated by the bromonaphthalenes (eq 1).[1] Both THF and DME can be used as solvent with a reaction temperature of 63 °C. With THF, the reaction time is 5 min (90-95% yield); with DME, the reaction time increases to 30 min (85-90% yield).

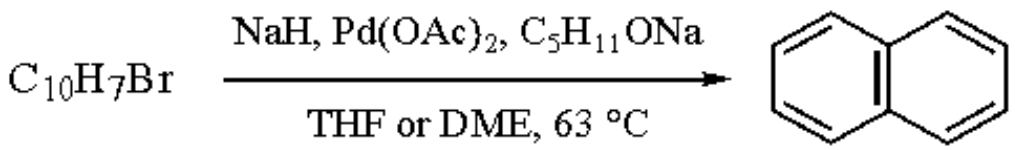

(1)

Self-Terminating Semihydrogenation of Alkynes.

This palladium complex reducing agent (Pd CRA) allows semihydrogenation of alkynes to *cis*-alkenes at atmospheric pressure. For the semihydrogenation of monosubstituted alkynes, reactions must be conducted in solvents such as hexane or octane, whereas the semihydrogenation of disubstituted alkynes are conducted in ethanol, ethanol/hydrocarbon mixtures, or ethanol/THF mixtures. Moreover, in all cases, the presence of ***Quinoline*** as a catalyst modifier was necessary (eq 2).[2]

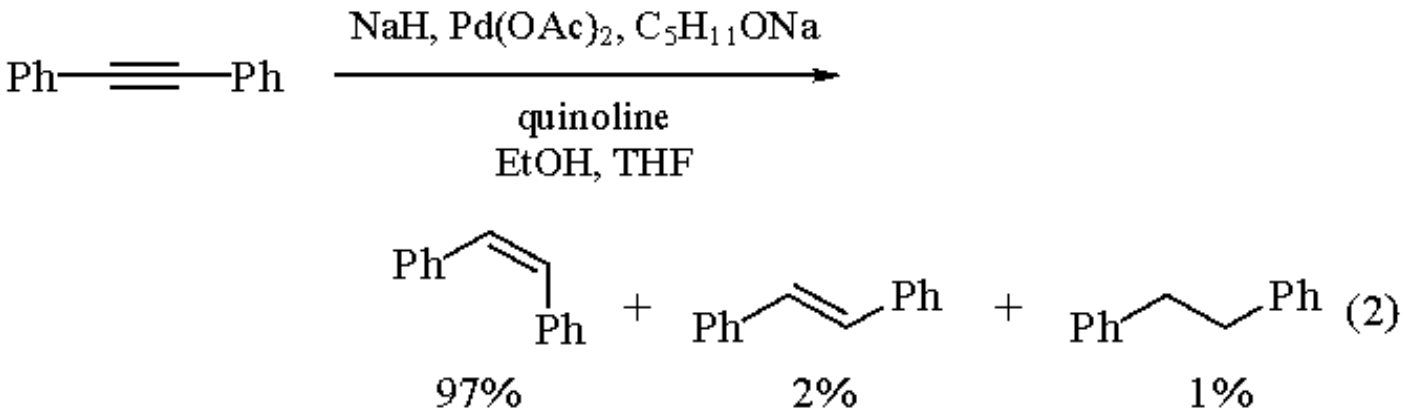

Related Reagents.

Nickel Complex Reducing Agents; ***Sodium Hydride***; ***Sodium Hydride-Copper(II) Acetate-Sodium t-Pentoxide***; ***Sodium Hydride-Nickel(II) Acetate-Sodium t-Pentoxide***; ***Zinc Complex Reducing Agents***.

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1. Brunet, J. J.; Vanderesse, R.; Caubere, P. *JOM* **1978**, *157*, 125.
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4. Brunet, J.-J.; Gallois, P.; Caubere, P. *JOC* **1980**, *45*, 1937.

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Sodium Hydrogen Selenide[1]

NaHSe

[12095-50-5] · HNaSe · Sodium Hydrogen Selenide · (MW 102.96)

(nucleophilic agent for introduction of selenium by substitution reactions; mild reducing agent[1])

Solubility: sol water, ethanol.

Form Supplied in: white crystals; very unstable in moist air.

Preparative Methods: reaction of ***Hydrogen Selenide*** with ***Sodium Ethoxide*** in anhydrous conditions under nitrogen.[2] Aqueous or ethanolic solutions of NaHSe can be prepared by treatment of NaOEt, NaOH, or Na_2CO_3 solutions with H_2Se.[3-5] The most convenient procedure involves reduction of ***Selenium*** with ***Sodium Borohydride***.[6] It allows the rapid and easy preparation of NaHSe without the necessity of generating dangerously toxic H_2Se. A suspension of NaHSe in DMF is produced similarly.[7]

Handling, Storage, and Precautions: unstable compound; decomposes in moist air with the formation of polyselenides and precipitation of Se. It should be used directly as prepared in solution or suspension without isolation. Use in a fume hood.

Introduction of Se.

NaHSe reacts with acyl chlorides to give diacyl diselenides after oxidation (eq 1).[3] Aromatic aldehydes are converted into benzyl diselenides when treated with NaHSe in the presence of ***Piperidine*** hydrochloride followed by reduction with $NaBH_4$.[8]

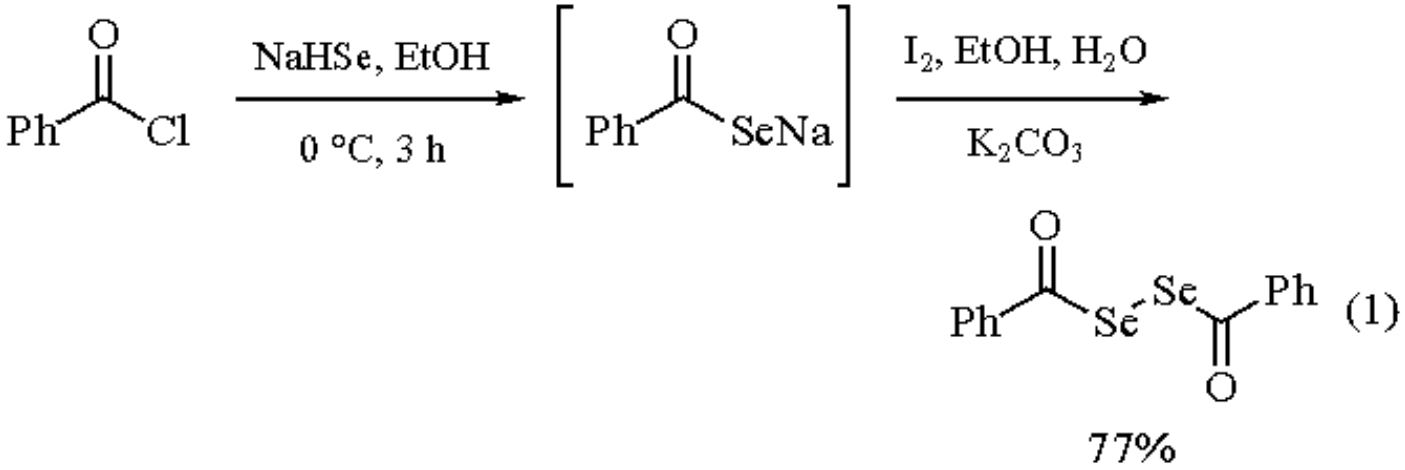

Selenoamides can be obtained from thioamides treated with NaHSe,[9] whereas tetrasubstituted selenoureas are prepared by the reaction of NaHSe with methylthiouronium salts (eq 2).[5] An efficient method for synthesis of selenoesters consists in transforming *N*,*N*-dimethylamides into *N*,*N*-dimethylimidoyl chlorides and treatment of these with NaHSe in ethanol (eq 3).[10] Selenoformates are also prepared in this way.[11] Carboxylic esters are easily cleaved into carboxylic acids and selenols by treatment with NaHSe in DMF or EtOH.[7,12] Alkyl halides react with NaHSe to form selenides (eq 4)[6] or selenols.[13]

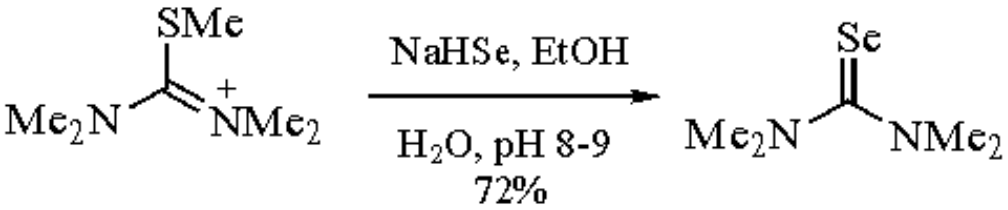

(2)

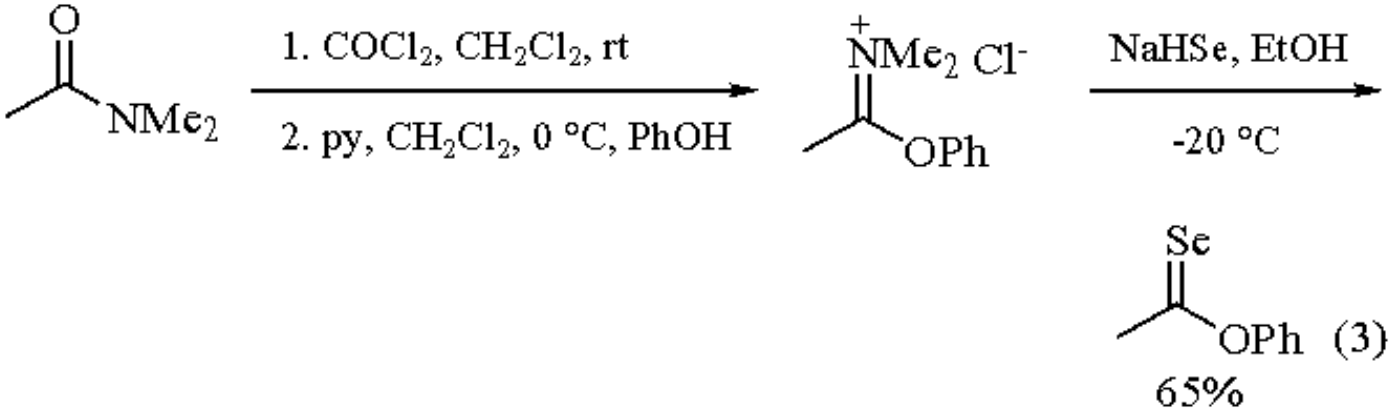

(3)

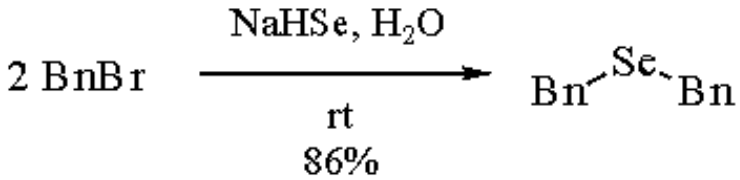

(4)

Reducing Reagent.

NaHSe functions as an efficient agent for reductive elimination of vicinal dihalides. Chalcone dibromides undergo debromination when treated with NaHSe in boiling ethanol to give chalcones in 53-65% yield.[14] NaHSe has been shown to be an effective reagent for reduction of alkyl, aryl, aralkyl, and functionally substituted disulfides to thiols under mild conditions in protic solvents.[15]

Related Reagents.

Hydrogen Selenide; ***Lithium Selenide***; ***Sodium Selenide***.

---

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15. Woods, T. S.; Klayman, D. L. *JOC* **1974**, *39*, 3716.

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Sodium Hydrogen Sulfide

NaSH

(anhyd)

[16721-80-5] · HNaS · Sodium Hydrogen Sulfide · (MW 56.07) (hydrate)

[140650-84-6]

(a nucleophile and reducing agent derived from H_2S; a reagent for the synthesis of thiols[1] and other divalent sulfur compounds,[2] including thiocarbonyl derivatives;[3] reduces aromatic nitro groups to amines[4])

Physical Data: mp (hydrate) 52-54 °C; anhyd, 350 °C; *d* 1.79 g cm^{-3}; pK_a (HS^- &ibond; S^{2-} + H^+) 14.15.

Solubility: v sol H_2O; sol EtOH, DMF (colored solution).

Form Supplied in: yellow chips ($NaSH.xH_2O$, may be principally $NaSH.2H_2O$); also available anhydrous; may contain Na_2S, $Na_2S_2O_3$ Na_2CO_3.

Analysis of Reagent Purity: iodometric titration.[5]

Preparative Methods: saturation of ethanolic ***Sodium Hydroxide*** with ***Hydrogen Sulfide***;[5] anhydrous NaSH is obtained by precipitation with ether. Saturation with H_2S shifts the equilibrium, 2NaSH &ibond; Na_2S + H_2S, to the left, as does operation in a solvent less polar than water or addition of $NaHCO_3$ to Na_2S.

Handling, Storage, and Precautions: store in cool, dry place under nitrogen. Exposure to air forms $Na_2S_2O_4$ and Na_2CO_3; very hygroscopic. Flammable; produces SO_2 on combustion. Stench. A reducing agent. Incompatible with acids (produces H_2S), with strong oxidizing agents, and with Zn, Al, and Cu. Corrosive (NaSH + H_2O &ibond; NaOH + H_2S). Use in a well-ventilated fume hood. Toxicity like that of Na_2S. Extremely destructive to mucous membranes, eyes, upper respiratory tract, and skin. Can cause blindness; inhalation can be fatal. Decontamination with $FeCl_3$ (production of insoluble iron sulfides).

Thiols.[1]

Treatment of halides, sulfonate esters, epoxides (eq 1),[6a] and aziridines with NaSH yields thiols. Saturation with H_2S helps to prevent sulfide formation. Near quantitative yields of thiols are obtained from primary alkyl bromides in DMSO.[6b] Primary substrates are best; tertiary substrates undergo elimination reactions. Aliphatic thiols are readily desulfurized by ***Raney Nickel***, thus providing a method for reduction of alcohols to alkanes (eq 2).[7] Activated aromatic or heteroaromatic halides (eq 3)[8] also are satisfactory, but nitro groups and cyano groups are likely to be incompatible due to reduction (or substitution) and addition reactions, respectively. Michael additions of SH^- to activated double and triple bonds also yield thiols or thiolates; sulfides may be obtained by further reaction of the thiolate (eq 4).[9] Thiol acids (RCOSH) are obtained from NaSH and acid chlorides or anhydrides (eq 5).[10]

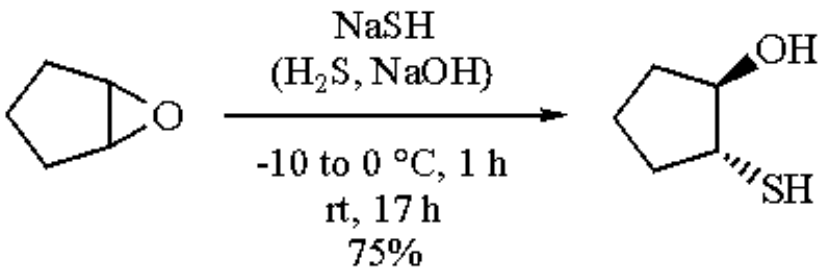

(1)

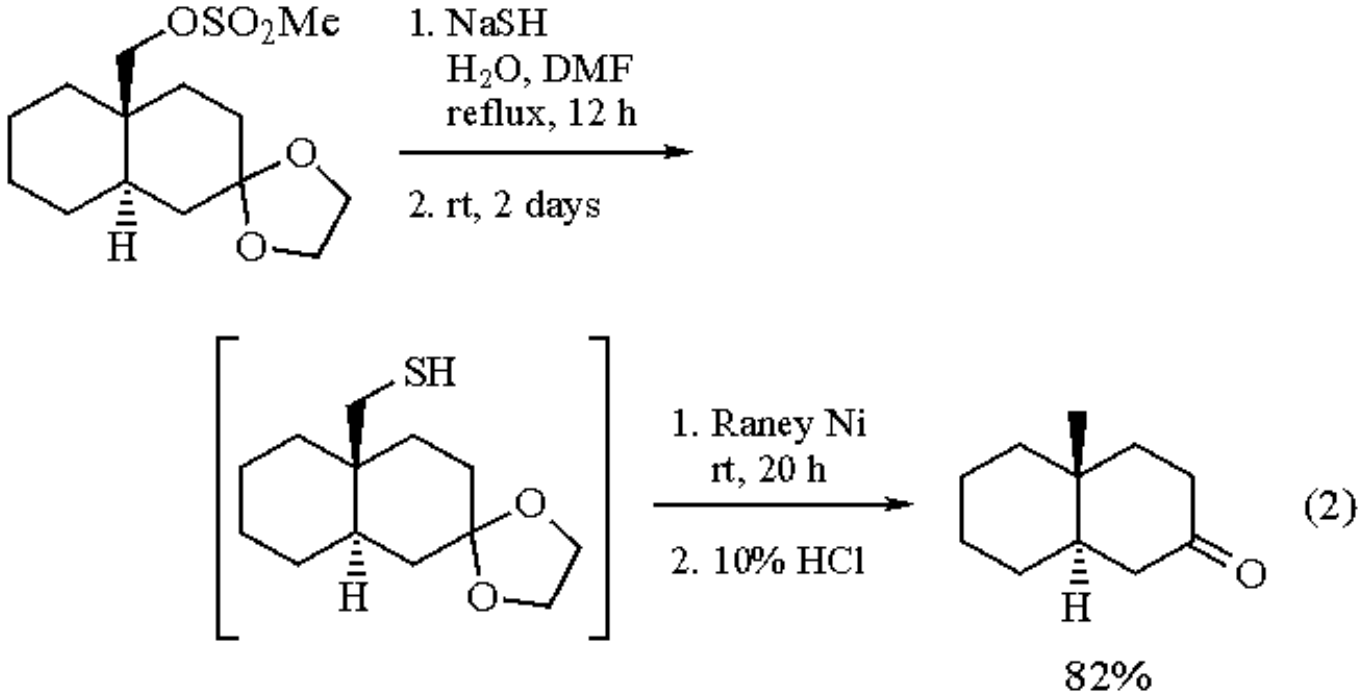
OSO2Me
1. NaSH
H2O, DMF
reflux, 12 h
2. rt, 2 days
SH
1. Raney Ni
rt, 20 h
2. 10% HCl
(2)
82%

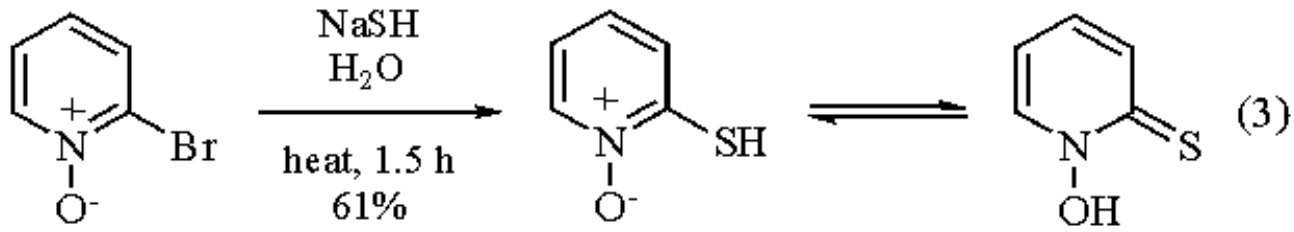
NaSH
H2O
heat, 1.5 h
61%
Br
SH
(3)

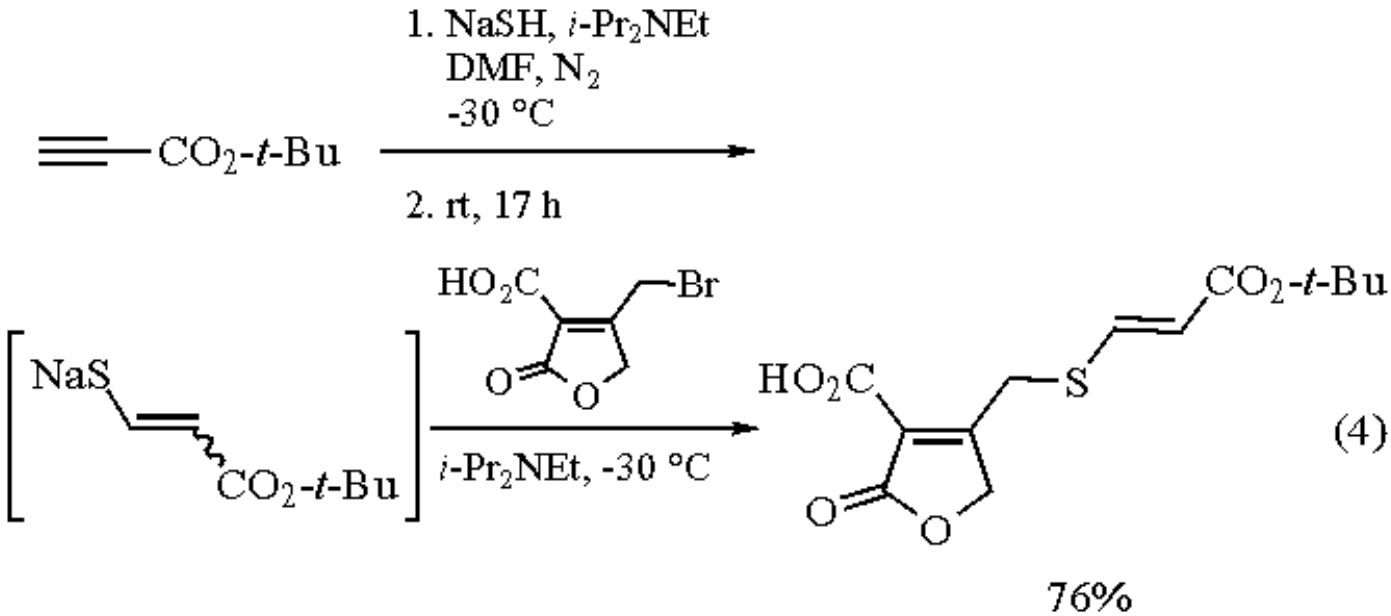
1. NaSH, i-Pr2NEt
DMF, N2
-30 °C
CO2-t-Bu
2. rt, 17 h
HO2C
Br
NaS
CO2-t-Bu
i-Pr2NEt, -30 °C
(4)
76%

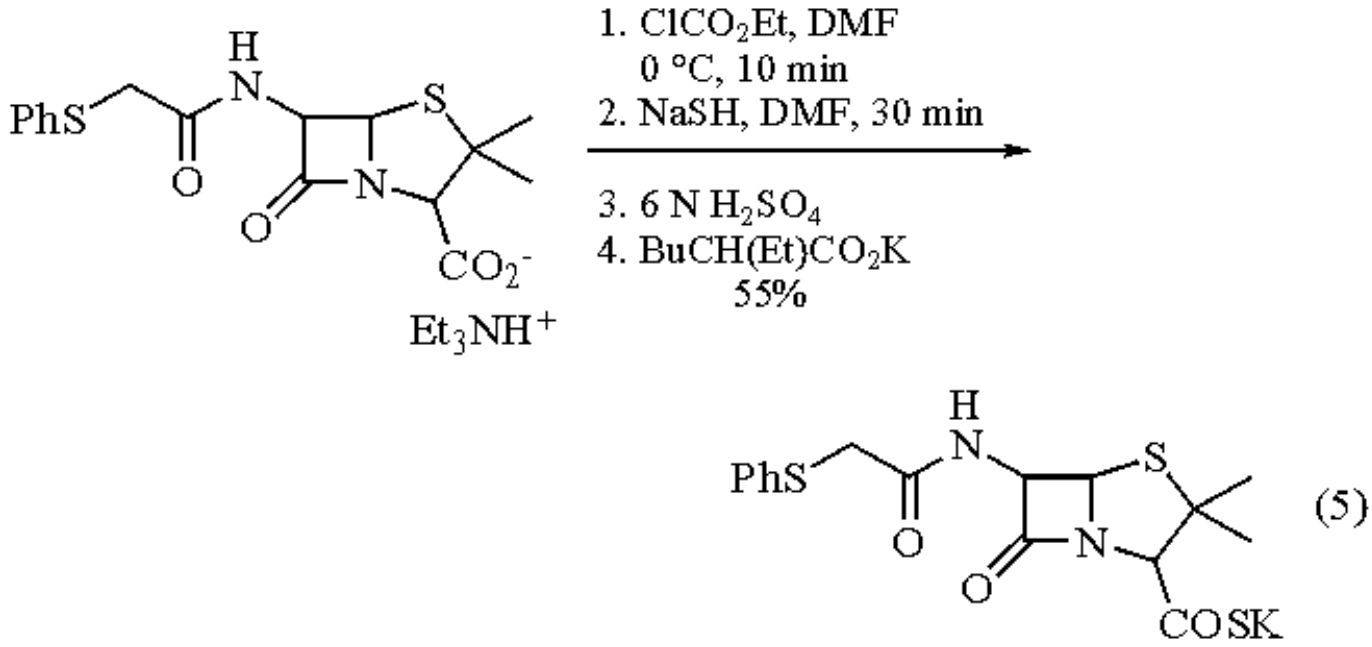

Thioethers (Sulfides).[2]

Sodium sulfide and sodium thiolates are more commonly used to prepare thioethers (eq 4), but NaSH has been applied to the synthesis of heterocyclic compounds of sulfur. Both the facile addition of NaSH to alkynic bonds[9a,11] and its desilylating ability are exemplified in eq 6.[11a] The addition of NaSH in liquid NH_3 to phenylacetylene gave both (*Z*,*Z*)- and (*E*,*Z*)-distyryl sulfide (in a ratio of 2.5:1), unlike $Na_2S.9H_2O$ which gave principally the (*Z*,*Z*) isomer (ratio 20:1).[11d]

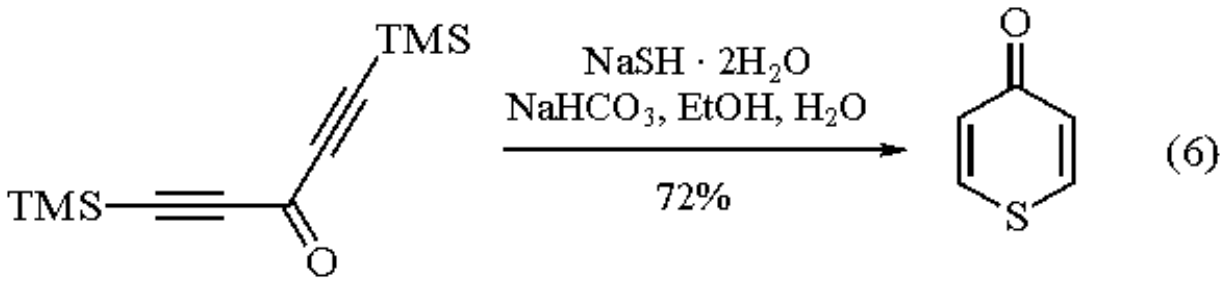

Thiocarbonyl Compounds.[3]

Addition of NaSH to iminium salts (Vilsmeier intermediates) (eq 7)[12] and related compounds[13] results in introduction of the thiocarbonyl group. Thioamides are obtained by addition to the triple bond of nitriles.

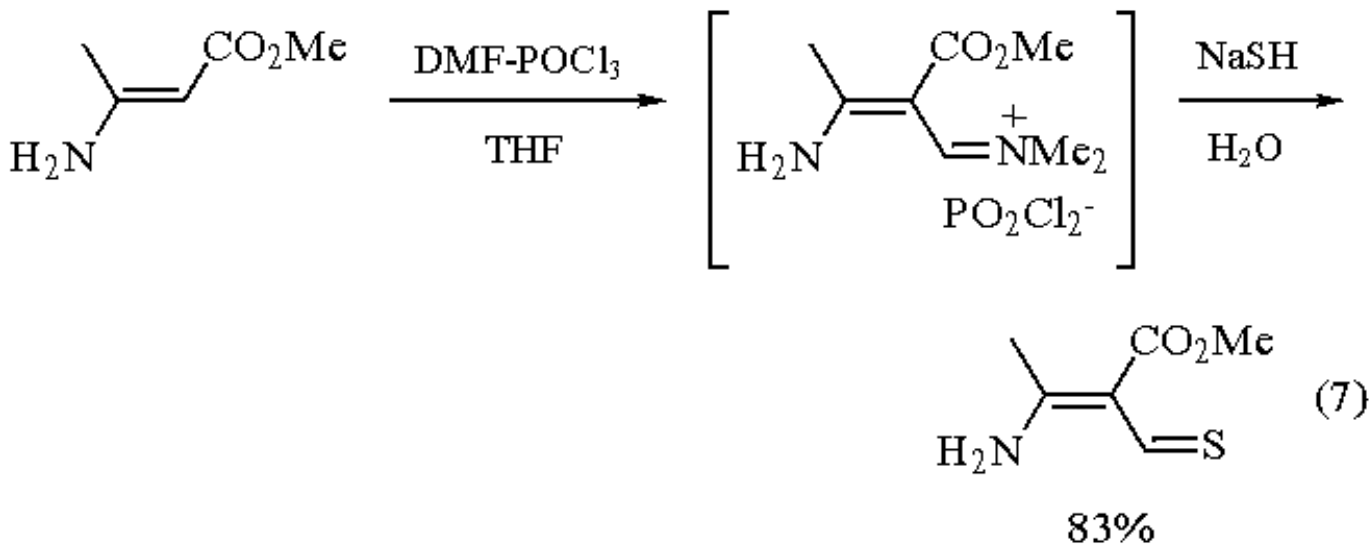

Reductions.

Aromatic, but not aliphatic, nitro groups are reduced by NaSH to amino groups,[4,14] often selectively,[15] as shown in eq 8. Favorable steric factors and the presence of an *ortho* phenolic hydroxyl group facilitate the reduction of one nitro group in preference to others. Further reductions are the dehalogenation of α-halo ketones and α-halo esters mediated by ***Tin(II) Chloride***[16] and the conversion of ArN=NAr to $ArNH_2$[17] (a nitro group is reduced preferentially[18]).

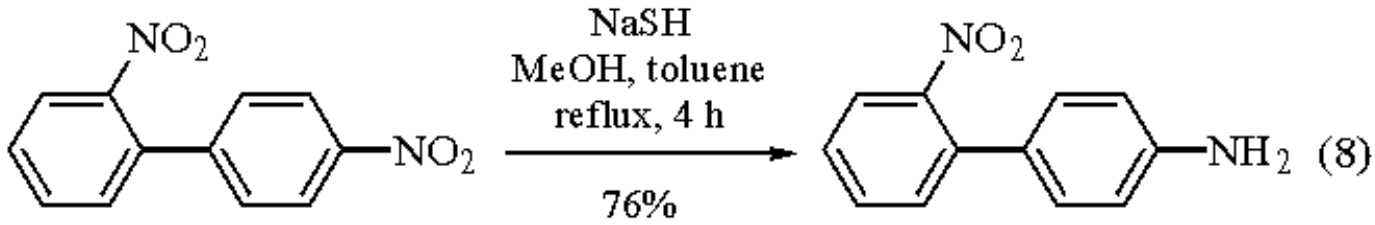

Miscellaneous.

Anti debromination of *gem*-dibromides by NaSH (or Na_2S) yields alkenes (eq 9).[19] 2-Pyranthiones are isomerized to 2-thiopyrones by NaSH.[20] A solution of NaSH at pH 8 selectively removes the acetyl group from menthyl *O*-acetylmandelate.[21]

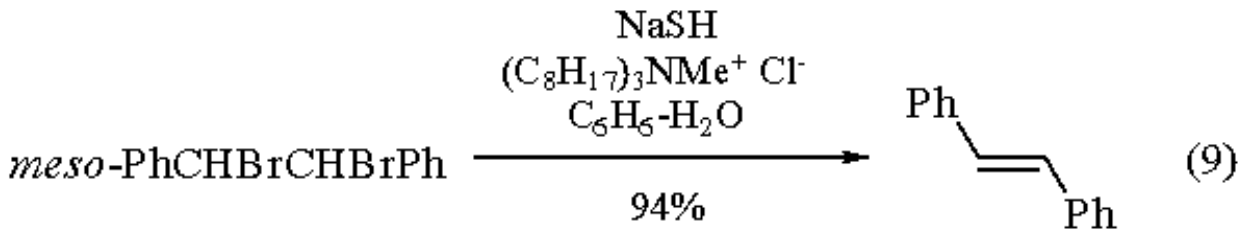

Related Reagents.

Potassium Hydrogen Sulfide; ***Sodium Sulfide***; ***Sodium Telluride***.

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Sodium Hydroxide[1]

NaOH

[1310-73-2] · HNaO · Sodium Hydroxide · (MW 40.00)

(inorganic source of hydroxide ion for the saponification of carboxylic acid derivatives;[3,4] alkylation of phenols,[7] alcohols,[13] aldehydes,[18] and ketones;[19] transformation of amides to amines,[11] generation of dichlorocarbenes;[22] also useful for removing water from amines[27])

Physical Data: mp 318.4 °C; *d* 2.13 g cm^{-3}.

Solubility: in water: 0.42 g mL^{-1} at 0 °C; 3.47 g mL^{-1} at 100 °C.

Form Supplied in: pellets or standard aqueous solutions of variable concentrations.

Purification: dissolve in dry ethanol, 100 g L^{-1}, filter solution through a fine frit. Concentrate the solution under vacuum until a thick slurry is formed. Place slurry on a coarse sintered-glass disk, remove mother liquor and wash several times with dry ethanol. Vacuum dry crystals with mild heating for 30 h to give fine white powder.

Handling, Storage, and Precautions: hygroscopic; keep in a sealed container in a dry environment. Keep away from flame. Avoid contact and ingestion.

Hydrolysis of Carboxylic Acid Derivatives.

The hydrolysis of esters, amides, nitriles, and ureas to the corresponding carboxylic acid can be accomplished with NaOH as hydroxide source, although milder methodology is available.[2] Ester hydrolysis is typically carried out in combinations of 1 N NaOH and either ethanol or methanol.[3] The hydrolysis of amides, nitriles and ureas is usually accomplished using excess NaOH in refluxing ethylene glycol with trace amounts of water.[4]

Dehydration of Sulfoxides and Selenoxides.

Thiophenes and selenophenes can be generated by the dehydration of the corresponding sulfoxides[5] and selenoxides[6] using 40% and 50% NaOH (aq), respectively.

Alkylation Reactions.

The NaOH-promoted conversion of phenols and carboxylic acids to their corresponding ethers[7] and esters[8] is accomplished in almost quantitative yield when excess ***Hexamethylphosphoric Triamide*** (HMPA) is added. The procedure calls for substrate, alkylating agent, 25% NaOH (aq), and HMPA to be combined at room temperature (eq 1).

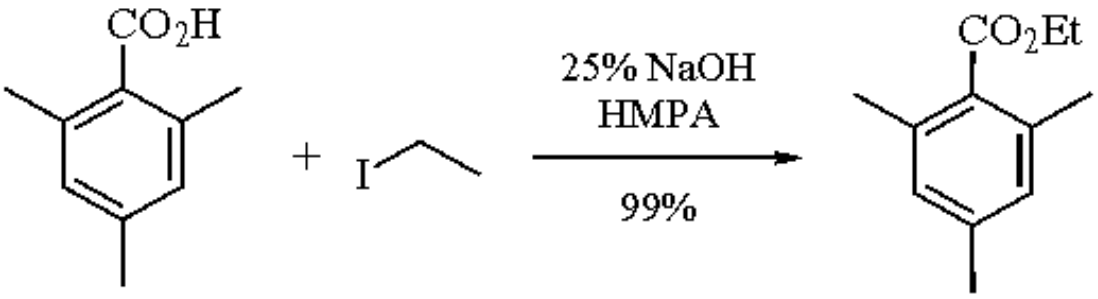

(1)

Phenols can be methylated with dimethyl sulfate,[9] and epoxides can be derived from halohydrins[10] using NaOH to generate the phenolate and alcoholate anions.

Conversion of Amides to Amines.

The conversion of amides to amines containing one less carbon, the Hoffman reaction, is accomplished by the combination of bromine (or chlorine) with NaOH followed by heating (eq 2).[11] The reaction works well with aliphatic, aryl, and heterocyclic amides. The reaction can also be carried out in alcohol solutions, and the resulting urethane hydrolyzed in a subsequent step.

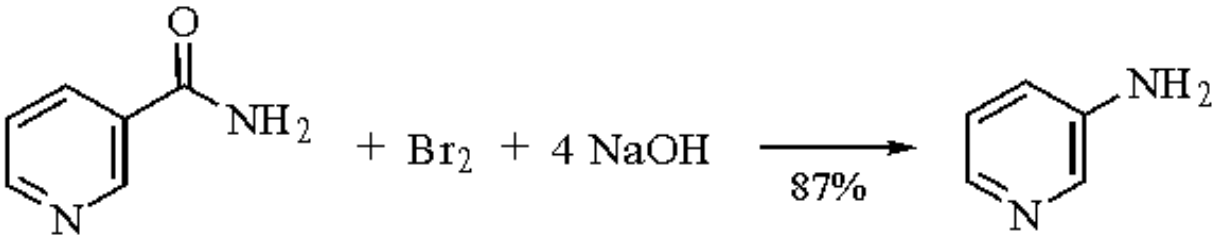

(2)

Phase-Transfer-Catalyzed Alkylation Reactions.

The use of phase-transfer-catalyzed two-phase reactions introduces hydroxide ion into organic solvent.[12] Under these conditions, hydroxide acts as a powerful base that efficiently promotes many transformations. Phase-transfer methodology is superior to the traditional Williamson synthesis of ethers (eq 3).[13]

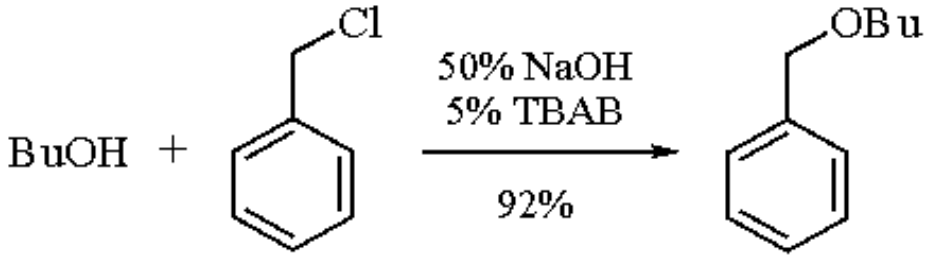

(3)

Reaction conditions consist of a fivefold excess of 50% NaOH (aq), alcohol, excess alkyl chloride, and 3-5 mol % tetrabutylammonium bisulfate (TBAB). This method does not work with secondary alkyl halides but was successful with secondary alcohols. Alcohols can also be methylated under phase-transfer conditions using ***Dimethyl Sulfate***, 50% NaOH (aq), alcohol, and ***Tetra-n-butylammonium Iodide*** (TBAI) with methylene chloride or petroleum ether as the second phase.[14] This method works well for primary alcohols, is sluggish for secondary alcohols, and works not at all for tertiary alcohols. The use of a chiral phase-transfer catalyst gave alkylation of racemic alcohols[15] and ring closure of racemic chlorohydrins[16] with only moderate enantiomeric excess. Diphenylphosphinic hydrazide was alkylated in high yield using a mixture of solid K_2CO_3, NaOH, and tetra-*n*-butylammonium sulfate in boiling benzene.[17]

The combination of TBAI and 50% NaOH (aq) promotes aldehyde alkylation in modest yield.[18] The use of *N*-benzylcinchonine salts as phase-transfer catalysts results in excellent yield and good enantioselectivity in the alkylation of indonanes (eq 4).[19]

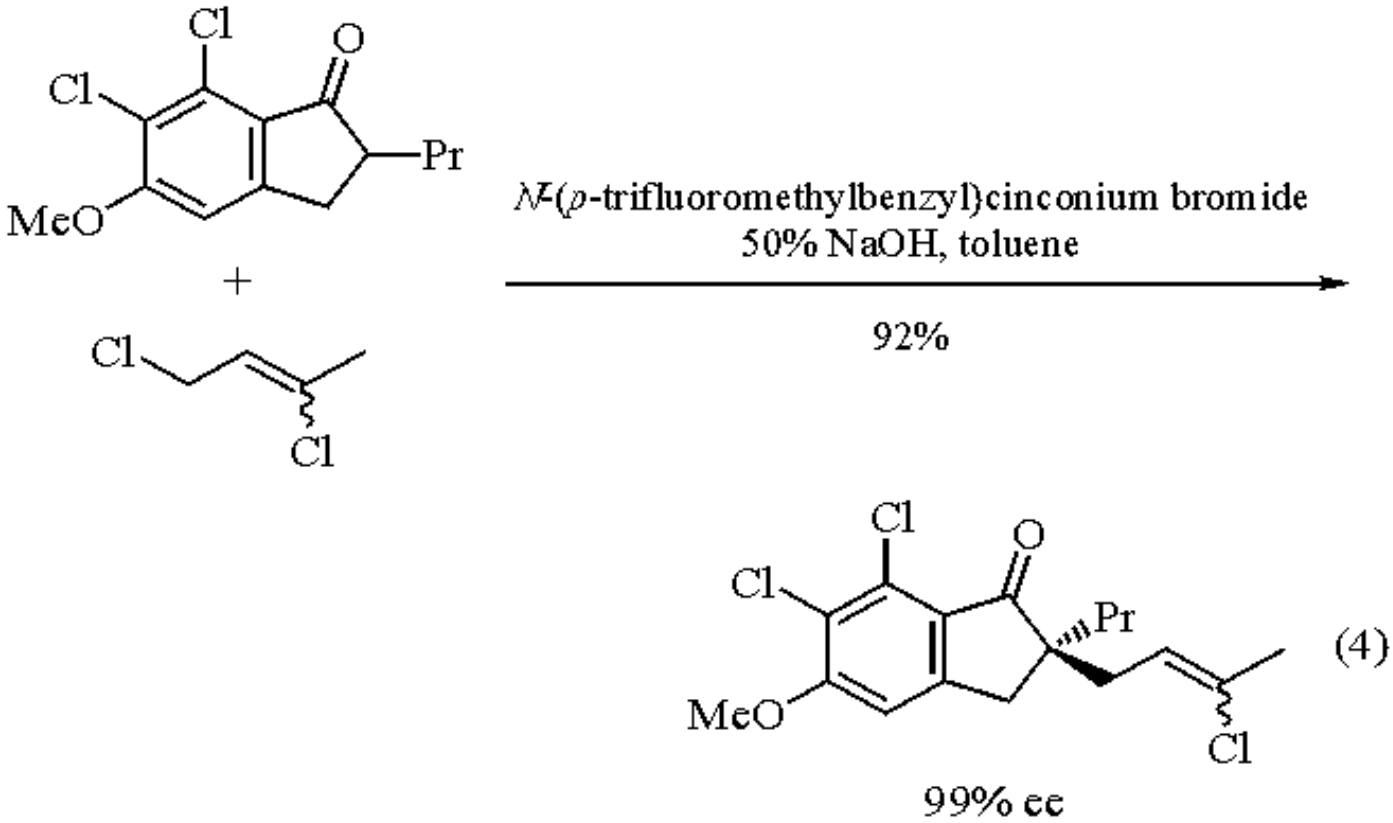

Phase-Transfer-Catalyzed Ylide Chemistry.

Wittig reactions can be done by combining 50% NaOH (aq), TBAI, a phosphonium salt, and a ketone in CH_2Cl_2. Benzylic phosphonium salts are converted to alkenes in good yields, but no stereoselectivity is observed (eq 5).[20]

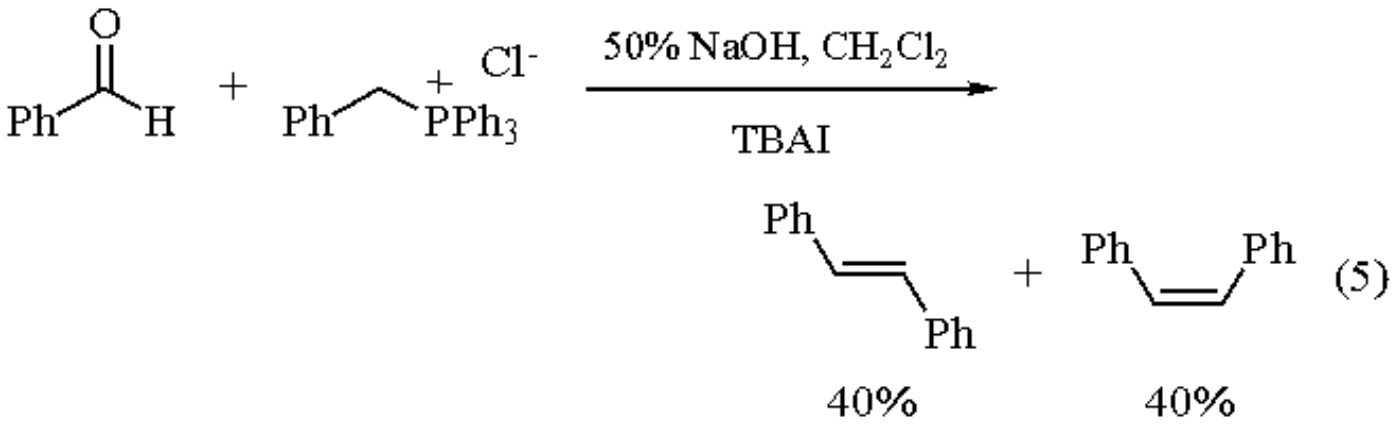

Similarly, trimethylsulfonium iodide (eq 6) and trimethyloxosulfonium iodide (eq 7) are converted to the corresponding sulfur ylides.[21]

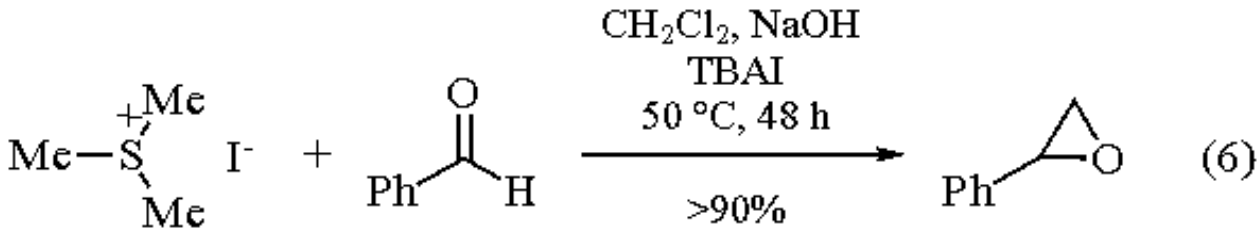

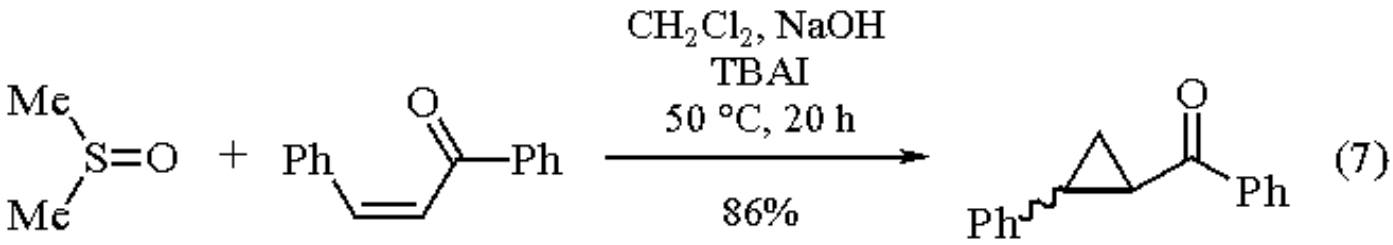

Phase-Transfer-Catalyzed Carbene Chemistry.

Dichlorocarbene can be generated from chloroform using 50% NaOH (aq) with 1-5% phase-transfer catalyst. This methodology can be used for dichlorocyclopropanation (eq 8),[22] C-H insertion (eq 9)[23] and the conversion of primary amines into isocyanides.[24]

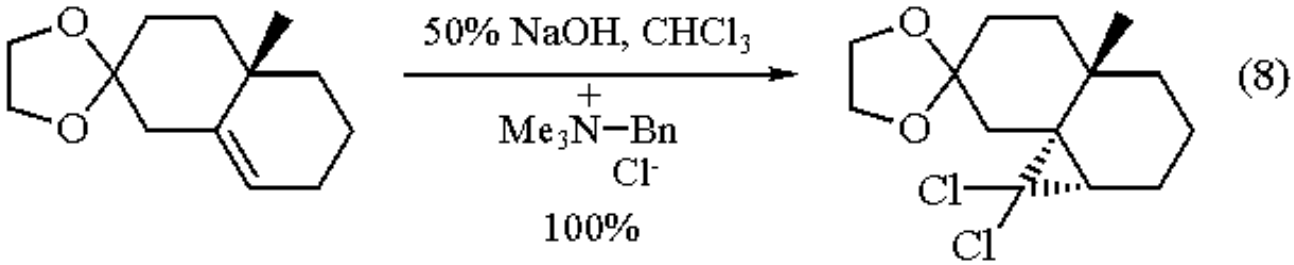

Micelles have been shown to give increased yields compared to tetraalkylammonium salt phase-transfer catalysts.[25] Similiar reactions can be done using bromoform, but the ease with which dibromocarbene undergoes hydrolysis makes this methodology less useful than the generation of dichlorocarbene.[26]

Related Reagents.

Potassium Carbonate; ***Potassium Hydroxide***; ***Sodium Carbonate***.

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Sodium Hydroxymethanesulfinate

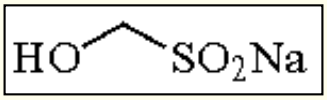

[149-44-0] · CH_3NaO_3S · Sodium Hydroxymethanesulfinate · (MW 118.10) (dihydrate)

[6035-47-8] · CH_7NaO_5S · Sodium Hydroxymethanesulfinate · (MW 154.14) (Zn salt)

[24887-06-7]

(reducing agent for elemental selenium and tellurium, diselenides, α-halo ketones, and aromatic aldehydes; yields symmetrical sulfones with primary halides and with Michael acceptors; a source of SO_2^-&bdot; and SO_2^{2-})

Alternate Names: Rongalite; sodium formaldehyde sulfoxylate.

Physical Data: mp (dihydrate) 64.5 °C; *d* 1.75 g cm^{-3}.

Solubility: v sol H_2O; sol aq EtOH, formamide, DMSO; sl sol DMF; insol abs EtOH, ether, CS_2, benzene.

Form Supplied in: the white, crystalline dihydrate is available commercially with a purity of 90% or greater. May contain up to 5% Na_2SO_3 or $NaHSO_3$.

Analysis of Reagent Purity: iodometric titration.[1]

Purification: recrystallization from H_2O and vacuum drying.

Handling, Storage, and Precautions: thermally unstable ($2HOCH_2SO_2Na$ -> $2CH_2O + Na_2SO_3 + S + H_2O$). Slowly decomposes in air. Above 80 °C in air the odor of hydrogen sulfide becomes apparent. Keep refrigerated and airtight. Hygroscopic. In aqueous solutions the decomposition products include $HOCH_2SO_3Na$, Na_2SO_3, $Na_2S_2O_3$, HCO_2Na, H_2S, CH_2O. Stability is greatest between pH 6 and 9. Low toxicity (oral LD_{50} (mouse) 4 g kg^{-1}). Can be handled without unusual precautions. Incompatible with oxidizing agents and acids.

Reduction of Se and Te.

Elemental ***Selenium***[2] and ***Tellurium***[2a,3] are reduced by Rongalite to ***Sodium Selenide*** and ***Sodium Telluride***. Colored solutions are common and indicate the presence of Na_2Se_n (red-brown) or Na_2Te_n (red-purple), probably existing mainly as Na_2Se_2 and Na_2Te_2. Solutions of Na_2Te_n obtained from Rongalite are capable of converting tosylates of primary, optically active glycidols to optically active secondary and tertiary allylic alcohols; however, these same solutions perform sluggishly with secondary tosylates, for which solutions of telluride ions produced via reduction with a borohydride are required.[4] It is suggested that borane byproducts in the reduction of Te with borohydrides catalyze the telluride reaction with the sterically more hindered secondary tosylates.

Reductions of Organic Compounds.

Reductions performed by Rongalite are sensitive to solvent, temperature, and the presence or absence of base. The reduction of diselenides is a useful method of producing selenide anions (RSe^-) in situ for further reaction with electrophilic reagents (eq 1).[5] The reductive dehalogenation of phenacyl chlorides and bromides occurs smoothly, but aliphatic analogs are less reactive.[6] The addition of a nucleophilic catalyst (***Sodium Iodide***) in the reduction of phenacyl chloride under anhydrous conditions gives the symmetrical 1,4-dione as the major product instead of acetophenone (eq 2).[6b] 2,4-Dinitrobenzyl bromide yields 2,4-dinitrotoluene; perfluorinated aromatic and aliphatic iodides (Ar_FI, R_FI) are reduced to Ar_FH and R_FH by Rongalite.[7] Reduction of aromatic aldehydes to benzyl alcohols (60-77%)[8] and benzils to benzoins (62-75%)[8,9] occurs best in DMF solvent at 100 °C. Simple ketones are reduced very slowly, and cyano groups are unaffected. 7,7,8,8-Tetracyanoquinodimethane, fumaronitrile, and fumaric acid are reduced to *p*-phenylenedimalononitrile (71%),

succinodinitrile (49%), and succinic acid (no yield given), respectively.[10] Rongalite is used widely in the reduction of vat dyes.

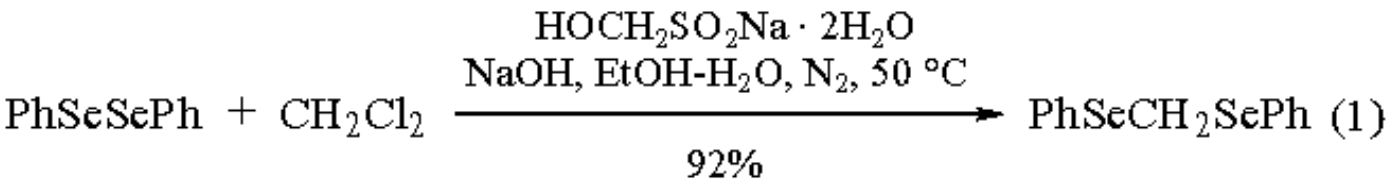

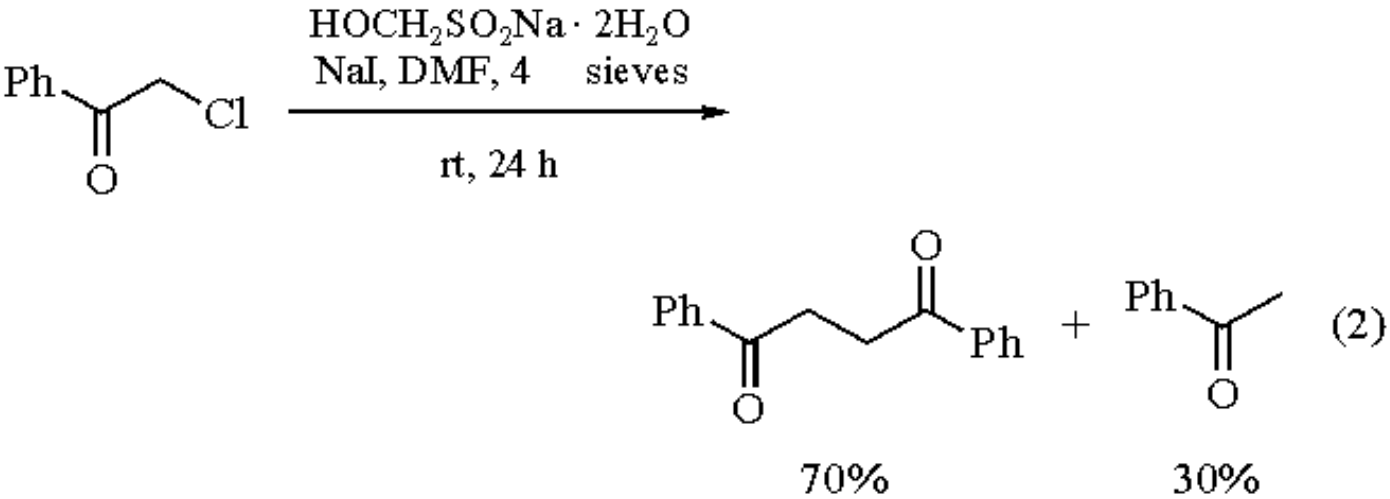

Sulfones and Sulfinates.

Symmetrical sulfones are obtained by treatment of primary halides with Rongalite, presumably by way of intermediate sulfinate salts. Benzyl halides give the best yields (45-88%) (eq 3);[6b,11] di-*n*-butyl sulfone is obtained from *n*-butyl bromide (46%), thiacyclohexane 1,1-dioxide from 1,5-dibromopentane (43%), and diallyl sulfone from allyl bromide (20%).[6b] Phenacyl halides yield sulfones when the reaction is conducted in the presence of ***Sulfur Dioxide*** (eq 4).[6b] When α,α´-dibromo-*o*-xylene is treated with a slurry of Rongalite in DMF at 0-25 °C, a cyclic sulfinate (sultine) is obtained. If sulfur dioxide is passed through the reaction mixture at 70 °C, the cyclic sulfone is obtained (eq 5).[12] Sulfones are also obtained by the reaction of Rongalite via SO_2^{2-} or HSO_2^- with activated double bonds. Mannich bases[13] and α,β-unsaturated carbonyl, nitrile, sulfonyl, or pyridyl derivatives yield symmetrical sulfones (eq 6).[14] Treatment of anilines with Rongalite, ***Formaldehyde***, and concentrated aqueous HCl produces *p*-aminobenzyl sulfones.[15] Sodium sulfinates (R_FSO_2Na) are isolated in the reaction of perfluorinated alkyl iodides (R_FI) with Rongalite in acetonitrile or DMF; reduction to R_FH occurs in ethanol or dioxane.[7b,16]

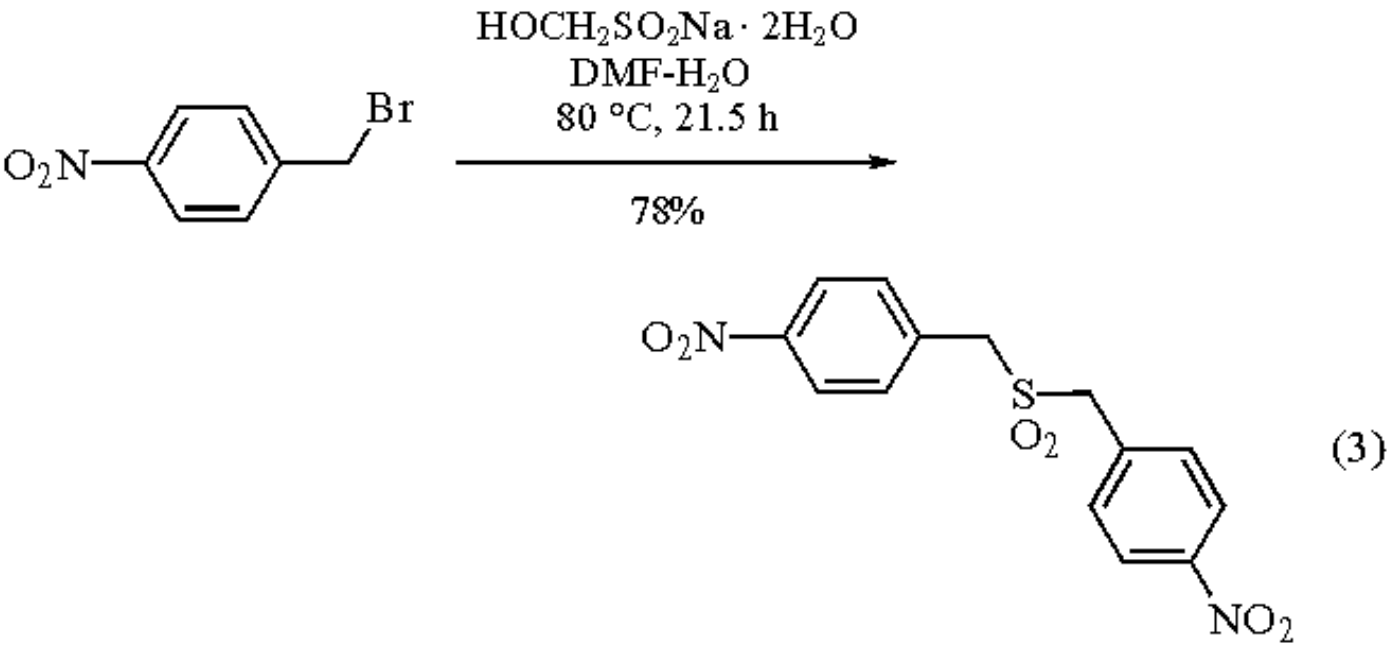

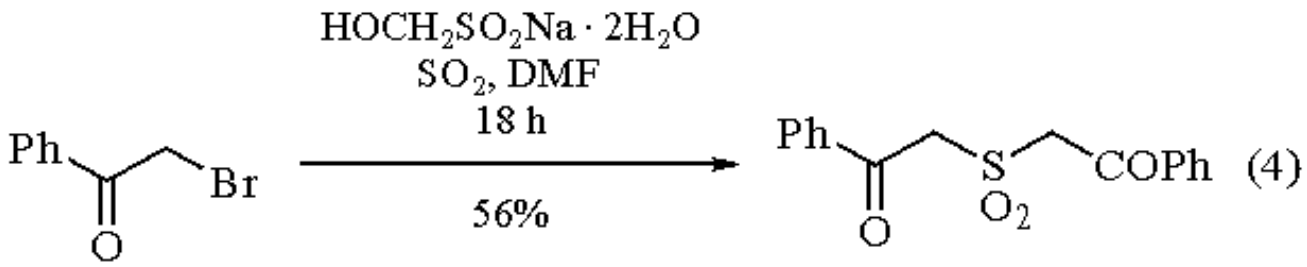

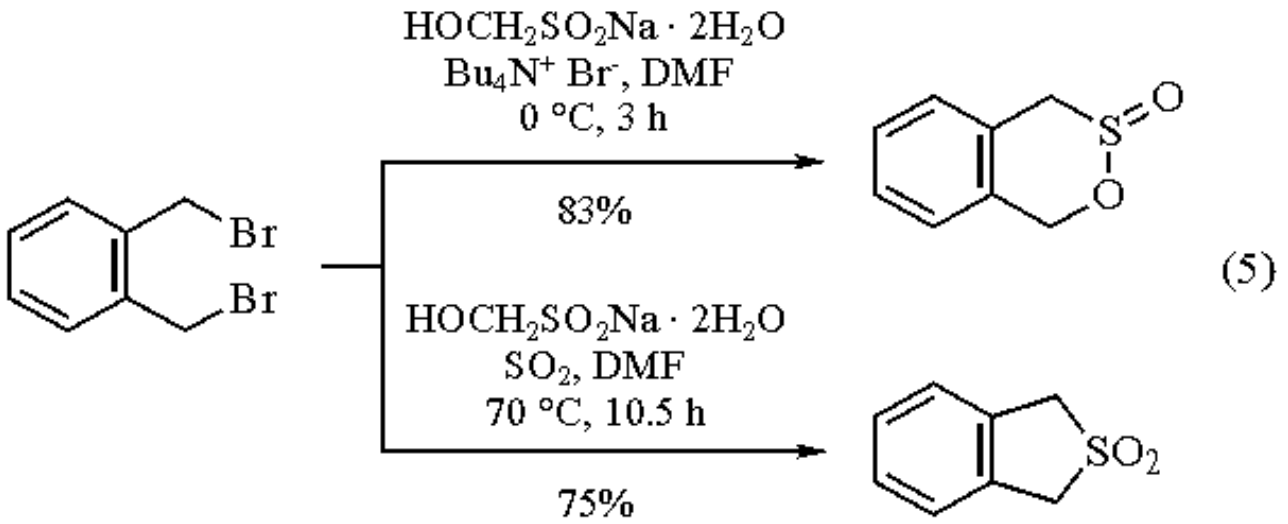

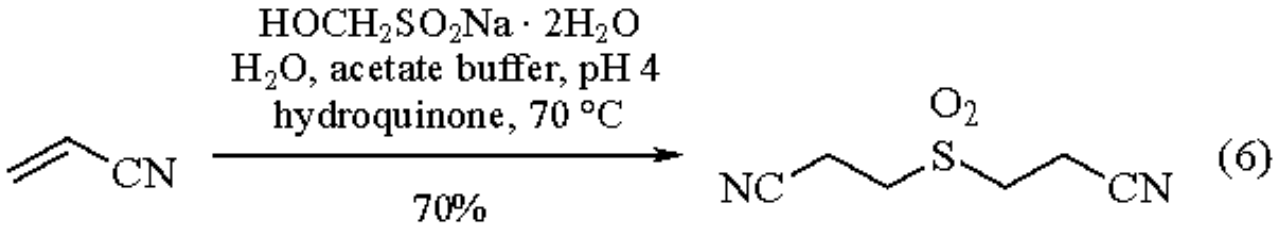

Perfluoroalkylation Reactions.

Perfluoroalkyl radicals are generated from perfluoroalkyl iodides or bromides and the anion radical, SO_2^-&bdot;, obtained from Rongalite. Additions of the perfluoroalkyl radicals to disulfides (eq 7),[17] pyridines,[18] coumarins (eq 8),[19] and other alkenes[20] give good yields of perfluoroalkyl derivatives. Cyano, amino, and ester groups are unaffected.

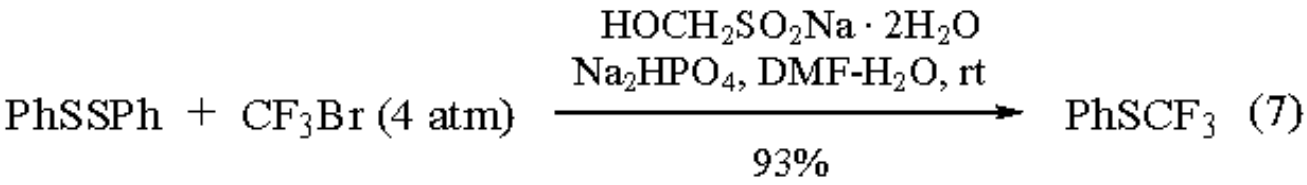

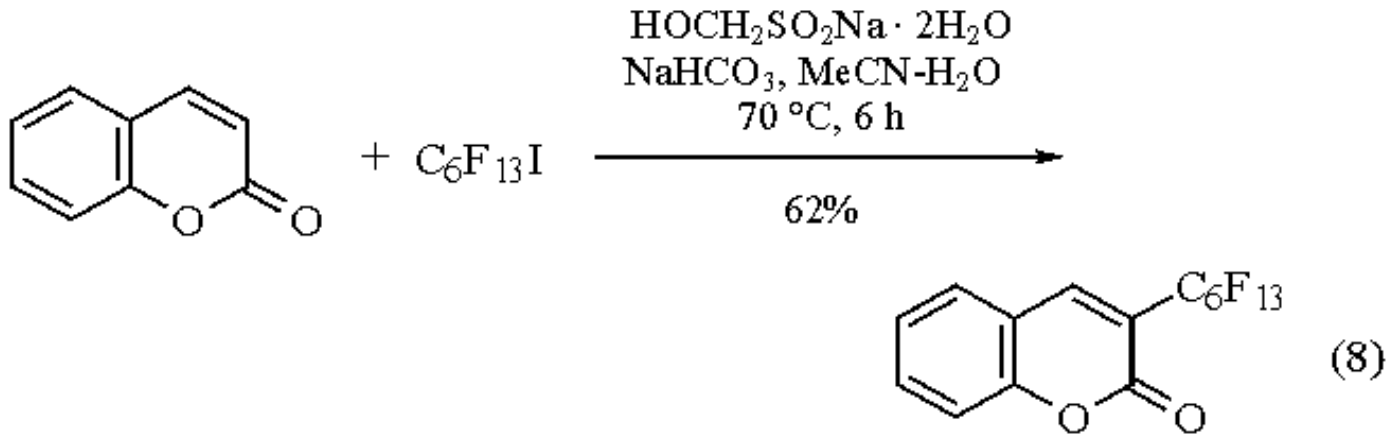

Miscellaneous.

The hydrolysis of primary perfluoroalkyl iodides or bromides with Rongalite-$NaHCO_3$ in aqueous DMF or DMSO gives perfluoro carboxylates (51-86%).[21]

Related Reagents.

Sodium Dithionite.

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Sodium Hypochlorite[1]

NaOCl

[7681-52-9] · ClNaO · Sodium Hypochlorite · (MW 74.44)

(versatile and easily handled oxidizing agent;[1] can oxidize alcohols,[2] aldehydes,[3] electron deficient alkenes,[4] amines,[5] and transition metal catalysts;[6] reagent for *N*-chlorination,[7] oxidative coupling,[8] and degradation reactions[9])

Physical Data: most commonly used in aqueous solution; $NaOCl.5H_2O$: mp 18 °C.

Solubility: pentahydrate: 293 g L^{-1} in H_2O (0 °C).

Form Supplied in: commercially available as aqueous solutions with 5.25-12.5% available oxidant (w/v) (0.74-1.75 M). Concentration is expressed in % available chlorine, since half of the chlorine in bleach is present as NaCl. The pH of commercial bleach is typically 11-12.5, and it may be adjusted and buffered.[6a]

Analysis of Reagent Purity: active oxidant may be assayed by iodometric[10] or potentiometric[11] titration.

Preparative Methods: solutions may be generated in situ by passing ***Chlorine*** gas through aq ***Sodium Hydroxide*** solution,[12] or electrochemically.[13]

Purification: commercial solutions are generally used without purification.

Handling, Storage, and Precautions: higher concentration sodium hypochlorite (12.5%), sometimes referred to as swimming pool chlorine, tends to decrease in concentration by 20% per month upon storage and therefore should be titrated prior to use.[1b] The concentration of oxidant in household bleach (5.25%) tends to remain constant upon prolonged storage; titration is generally not necessary with brand names (e.g. Clorox®). Solid NaOCl is explosive as the pentahydrate or the anhydride, and therefore it is very rarely employed in those forms. Aqueous solutions are very stable. Bleach is a household item, and it is quite easy and safe to handle. Still, it is a strong oxidant, and precaution should be taken to avoid prolonged skin exposure or inhalation.[14] May react violently with NH_3.

Composition of Aqueous Solution as a Function of pH.

The equilibrium composition of aqueous solutions of NaOCl is pH-dependent (eqs 1 and 2), and so pH control can be a critical consideration in many oxidation and chlorination reactions. Under strongly alkaline conditions (pH > 12), OCl^- is the predominant form of positive chlorine. Because hypochlorite ion is insoluble in organic solvents, phase transfer catalysts are needed at this pH to effect oxidation reactions in biphasic media.[15] In general, tetraalkylammonium salts have been the phase-transfer catalysts of choice for such applications. Below pH 11, the equilibrium amount of HOCl becomes significant,[6a] and this form of positive chlorine is soluble in polar organic solvents such as CH_2Cl_2. No phase-transfer catalyst is necessary to effect oxidation of substrates or catalysts dissolved in the organic phase of biphasic reactions in the pH range 10-11.[6a] Below pH 10, molecular chlorine becomes a significant component of aqueous bleach solutions, and the reactivity of these solutions can be attributed to that of Cl_2.[1b]

$$ClO^- + Cl^- + H_2O \rightleftharpoons Cl_2 + 2\,OH^- \qquad (1)$$

$$ClO^- + H_2O \rightleftharpoons HOCl + OH^- \qquad (2)$$

Oxidation of Alcohols.

Oxidation of alcohols by NaOCl can be effected under a variety of conditions, and useful yields and selectivities are attainable for

conversion of primary alcohols to aldehydes or carboxylic acids, or of secondary alcohols to ketones. The advantages of NaOCl oxidations over methods that employ stoichiometric Cr^{VI} include simplified waste disposal and lower toxicity and cost. The earliest application of NaOCl as a practical synthetic reagent for alcohol oxidation involved its use in a two-phase system with a phase-transfer catalyst,[16] or in association with ***Ruthenium(VIII) Oxide***.[17] More recently, two improved methods for bleach-mediated oxidation of alcohols have been developed, one of which employs acetic acid as solvent in a monophasic system,[18] and the other uses catalytic amounts of ***2,2,6,6-Tetramethylpiperidin-1-oxyl*** (TEMPO) in a buffered biphasic medium.[2b] These variants are highly complementary and can offer significant advantages over alternative methods for alcohol oxidation.

Secondary alcohols are cleanly oxidized to ketones with NaOCl in acetic acid in the absence of added catalyst (eq 3).[18] Either swimming pool chlorine or household laundry bleach can be used with similar success.[19] Excess hypochlorite is quenched with sodium bisulfite, and essentially pure ketone is obtained simply by extraction of the product into dichloromethane or ether.

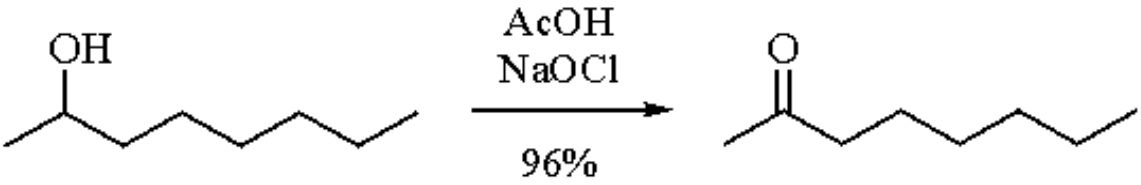

(3)

Under these conditions, secondary alcohols can be oxidized in the presence of primary alcohols with essentially absolute selectivity (eq 4).[20] No epimerization is observed in the oxidation of alcohols bearing β-stereocenters (eq 5). Kinetic studies have led to the proposal that molecular chlorine is the active oxidant under conditions of low pH such as those employed for these reactions.[21]

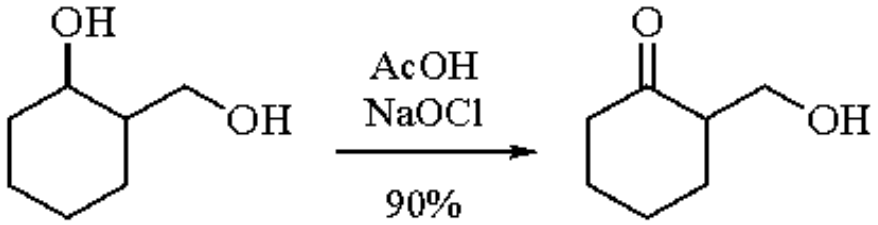

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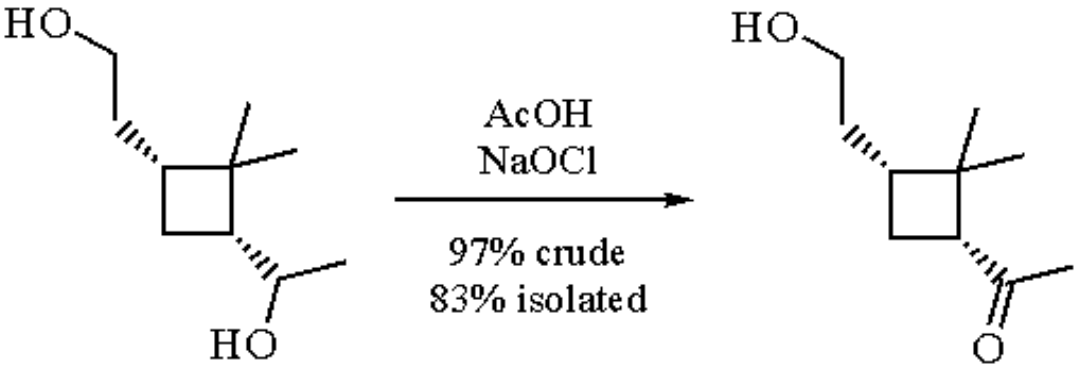

(5)

Primary and secondary alcohols can be oxidized by oxoammonium salts;[22] hypochlorite oxidation of the reduced nitroxyl radical regenerates the active oxoammonium salt. Thus the nitroxyl radical agent TEMPO can be employed as an alcohol oxidation catalyst, with NaOCl as the stoichiometric oxidant.[2b] This protocol has rapidly achieved widespread use due to its selectivity, ease of application, and versatility. A biphasic system is employed consisting of CH_2Cl_2 or toluene as the organic phase, and commercial bleach buffered to pH ~9 with $NaHCO_3$ and containing substoichiometric levels of KBr or NaBr (eq 6).[23] Reaction times are longer in the absence of bromide salts, indicating that HOBr is the agent that oxidizes TEMPO to the nitrosonium ion. Without added phase transfer catalyst, primary alcohols are oxidized with excellent selectivity to the corresponding aldehydes.[24] High stirring rates (>1000 rpm) help to minimize overoxidation to the carboxylic acid.[23] The stereospecificity of TEMPO-catalyzed oxidations of primary alcohols bearing β-stereocenters has been investigated in detail, and it is absolute in all cases reported thus far (eqs 7-9).[23,24]

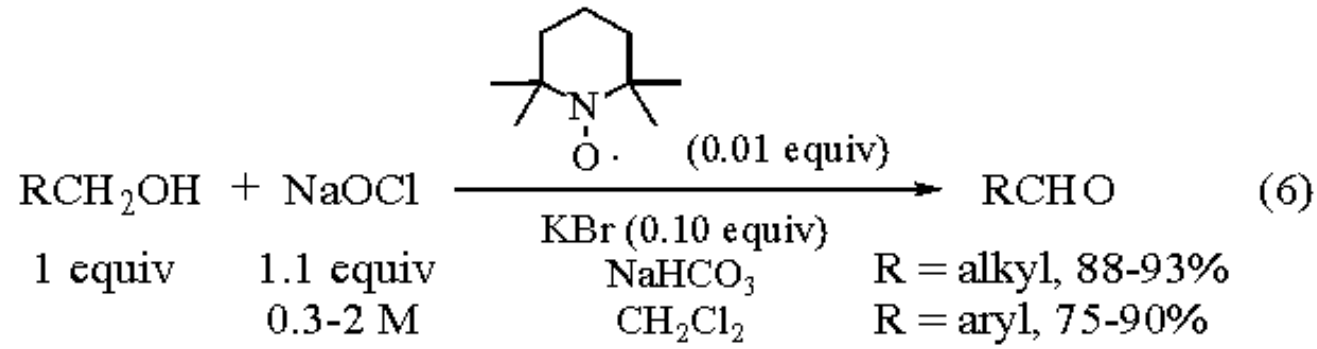

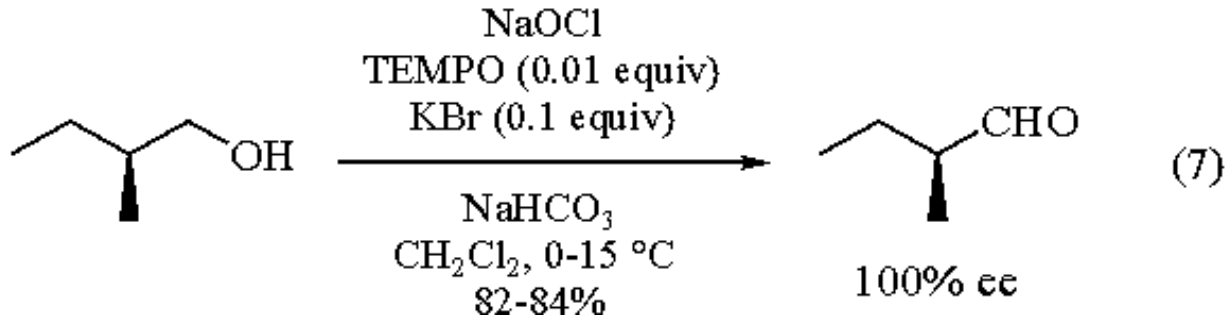

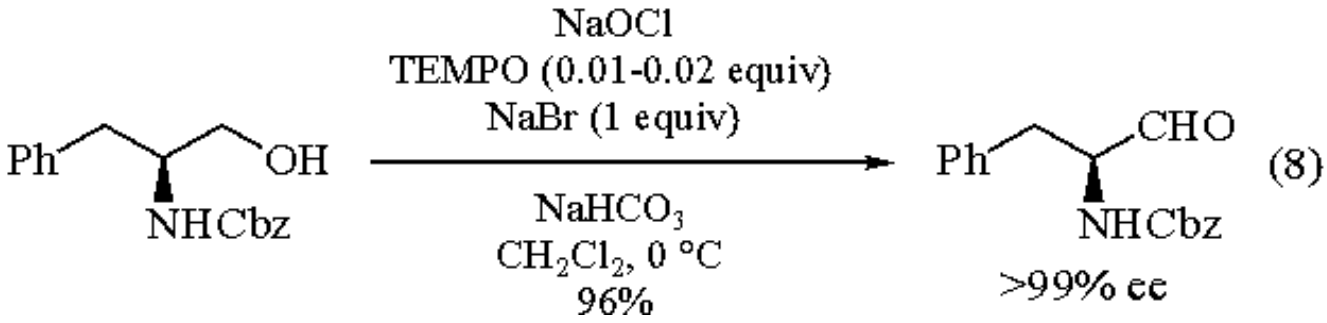

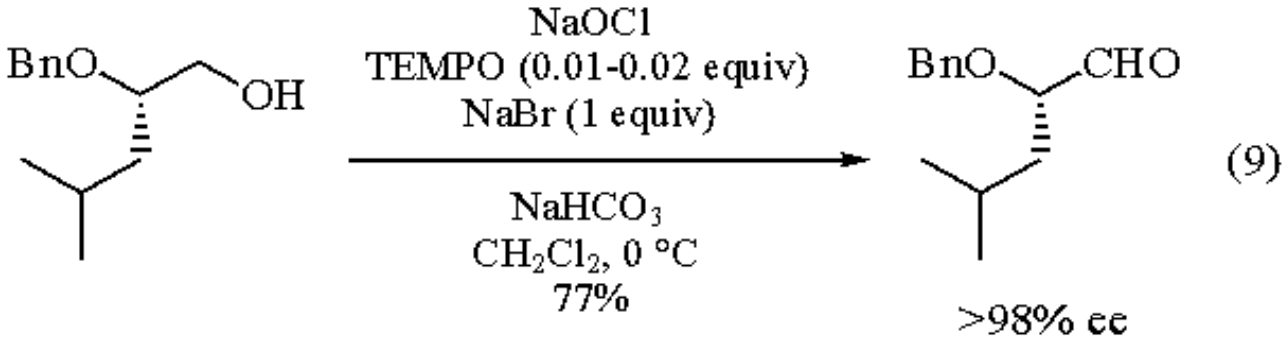

Although both primary and secondary alcohols are oxidized with this catalyst system, moderate-to-good selectivity for the primary position is obtained in oxidation of diols (eq 10).[25] The diol must have nearly complete solubility in the organic phase for these oxidations to occur cleanly. This selectivity for primary alcohols is in direct contrast with monophasic NaOCl oxidations in acetic acid (see above). Thus, proper choice of reaction conditions allows selective oxidation by NaOCl of either or both the primary or the secondary carbinol in diols.

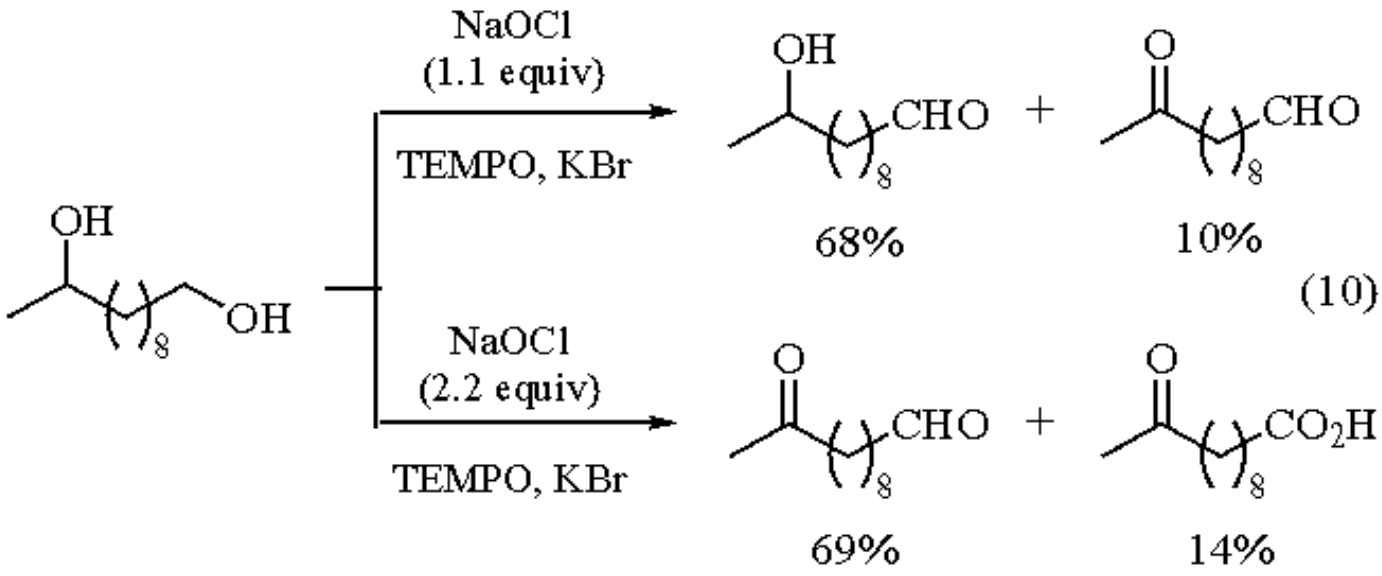

(10)

Molecular chlorine generated from NaOCl appears to have a detrimental effect on the oxidizing power of the *N*-oxoammonium salt in these reactions.[26] A similar protocol to the one described above, but using ***Sodium Bromite*** ($NaBrO_2$) in place of NaOCl may be superior in this context. Despite this caveat, there is ample precedent for the successful application of the NaOCl/TEMPO system with a variety of substrates, and the use of commercial bleach solutions has significant practical advantages.

For further discussion of this oxidizing system, see: ***2,2,6,6-Tetramethylpiperidin-1-oxyl***. See also ***Dimethyl Sulfoxide-Oxalyl Chloride***, ***Pyridinium Chlorochromate***, ***Pyridinium Dichromate***, ***Potassium Permanganate***, ***Dipyridine Chromium(VI) Oxide***, and ***Tetra-n-propylammonium Perruthenate***.

Oxidation of Primary Alcohols to Carboxylic Acids.

Simple incorporation of a tetraalkylammonium chloride phase-transfer catalyst (PTC) to the catalyst recipe outlined above for aldehyde synthesis leads to a useful protocol for oxidation of primary alcohols to the corresponding carboxylic acids (eq 11).[2b] Similar selectivity for primary alcohols over secondary alcohols is observed as in the absence of PTC.[25] This has been exploited in the oxidation of unprotected monosaccharide derivatives to the corresponding uronic acids (eq 12).[27]

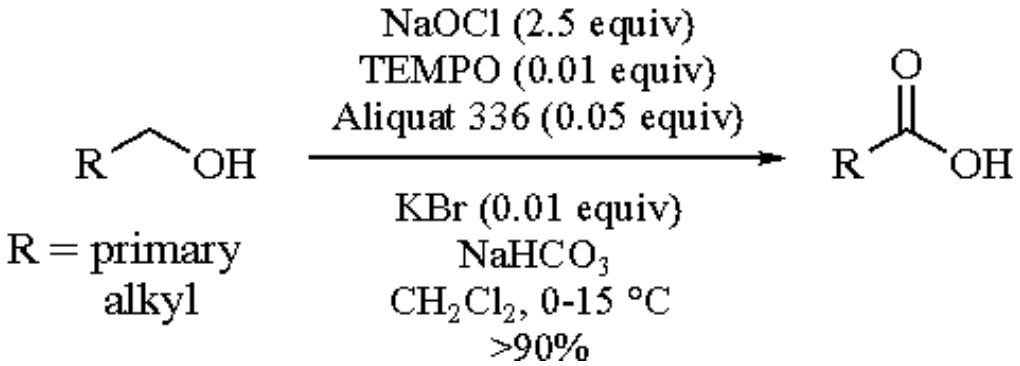

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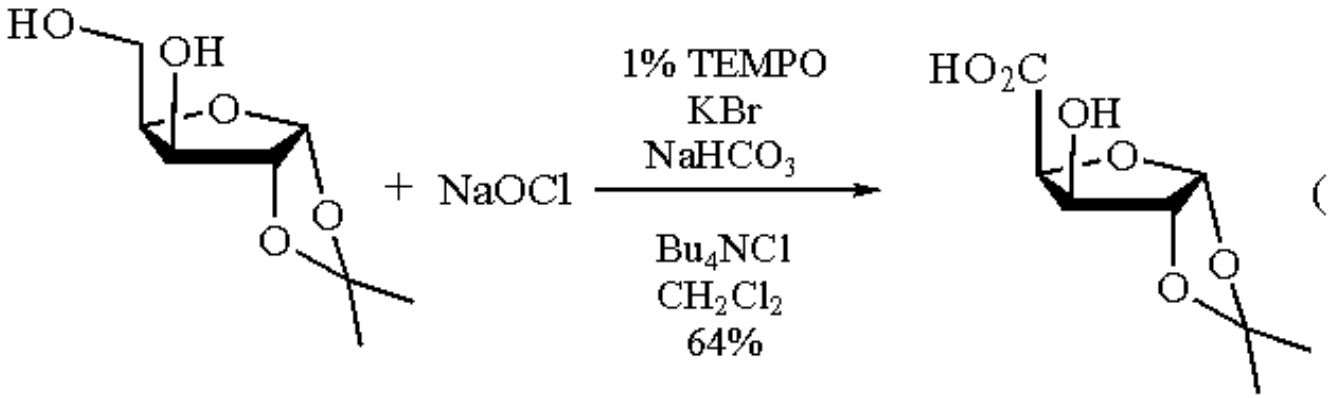

(12)

The mildness of the oxidizing medium in TEMPO-catalyzed oxidations by NaOCl is illustrated by the high yield oxidation of (2-hydroxyethyl)spiropentane to the corresponding acid (eq 13).[28] Jones oxidation conditions lead to extensive decomposition of the

spiropentane residue of the same substrate.

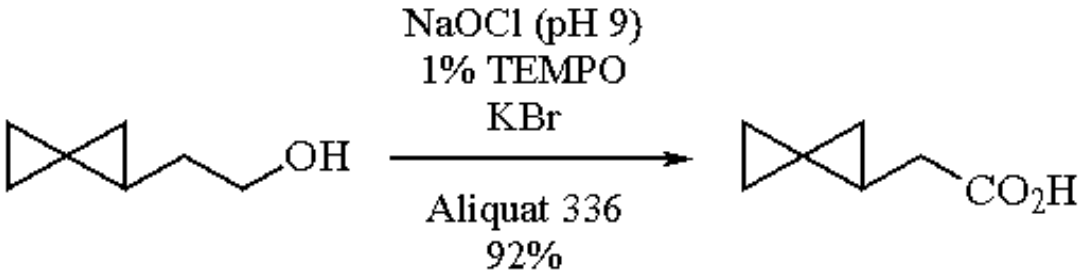

(13)

See also: ***Chromium(VI) Oxide***, ***Potassium Dichromate***, ***Potassium Permanganate***, and ***Oxygen-Platinum Catalyst***.

Oxidation of Aldehydes.

Sodium hypochlorite oxidizes aromatic aldehydes to the corresponding acids in the presence of a phase-transfer catalyst.[3] Best results are obtained at pH 9-10 with Bu_4NHSO_4 as phase-transfer catalyst (eq 14). In this pH regime, HOCl is present in significant concentrations, and phase-transfer catalysts are generally not necessary.[6a] It has been suggested that in this system, however, the phase-transfer catalyst helps to solubilize HOCl in the organic phase through hydrogen bonding.[3] Direct oxidation of aliphatic and aromatic aldehydes to the corresponding methyl esters is accomplished with methanol in acetic acid and 1-2 equiv of NaOCl.[20] This reaction, which affords esters in moderate-to-good yield, probably proceeds via oxidation of equilibrium concentrations of methyl hemiacetals. Poor results are obtained with electron-rich aromatic aldehydes and unsaturated aldehydes, each of which undergo competitive chlorination.[20]

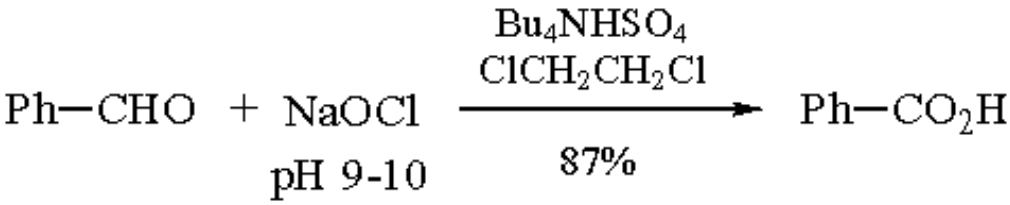

(14)

See also: ***Potassium Permanganate***, ***Ozone***, and ***N-Bromosuccinimide***.

Epoxidation.

Sodium hypochlorite is an effective, although infrequently utilized, reagent for epoxidation of enones and polycyclic arenes. Careful control of pH is necessary for good yields in these reactions. Polycyclic aromatics can be oxidized to epoxides at pH 8-9 (eq 15).[29] Phenanthridine is oxidized to the corresponding lactam, presumably via an oxaziridine intermediate (eq 16), without formation of *N*-oxide.[29] The optimum pH for this reaction is 8-9, and phase transfer catalysts are required.

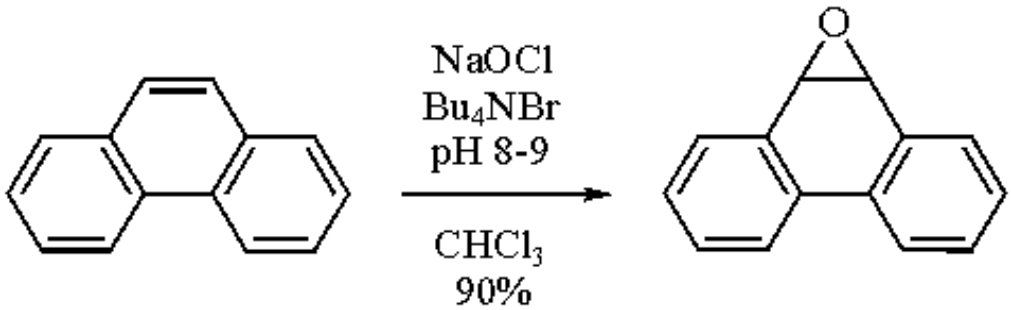

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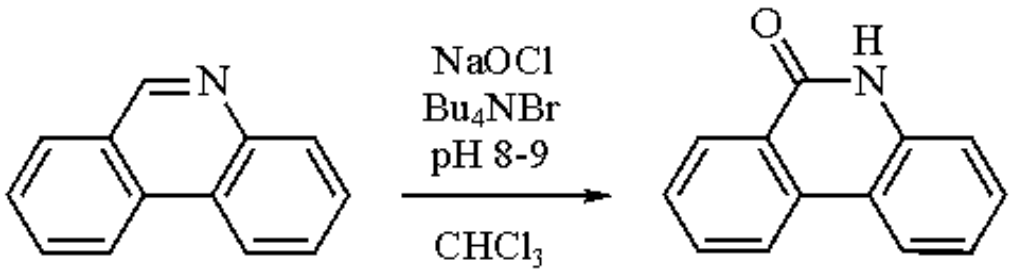

(16)

Enones,[4,30] particularly chalcones,[31] also react with sodium hypochlorite to form epoxides (eqs 17-19). These reactions generally exhibit

a strong dependence on the pH of the aqueous phase; chlorination reactions can be competitive.[30a] The mechanism for these reactions has been proposed to involve production of the ClO**.** radical species; this proposal was made on the basis of data from the chlorination of hydrocarbons, selectivity of epoxidation reactions, and Hammett ρ values for the chlorination of toluene.[32]

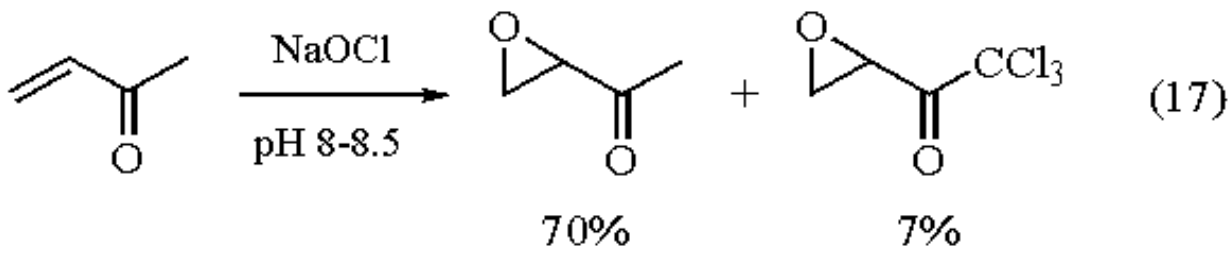

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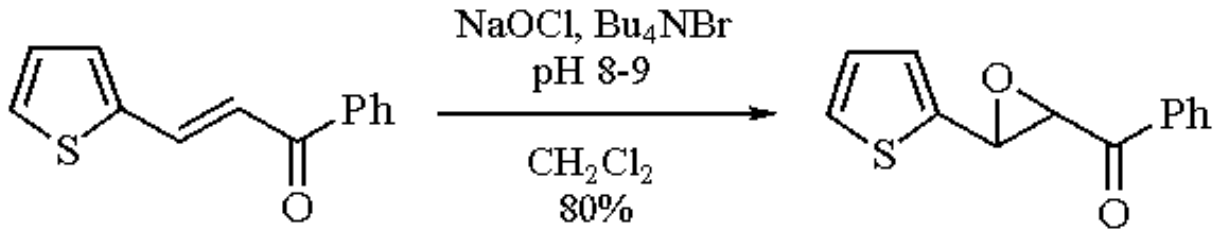

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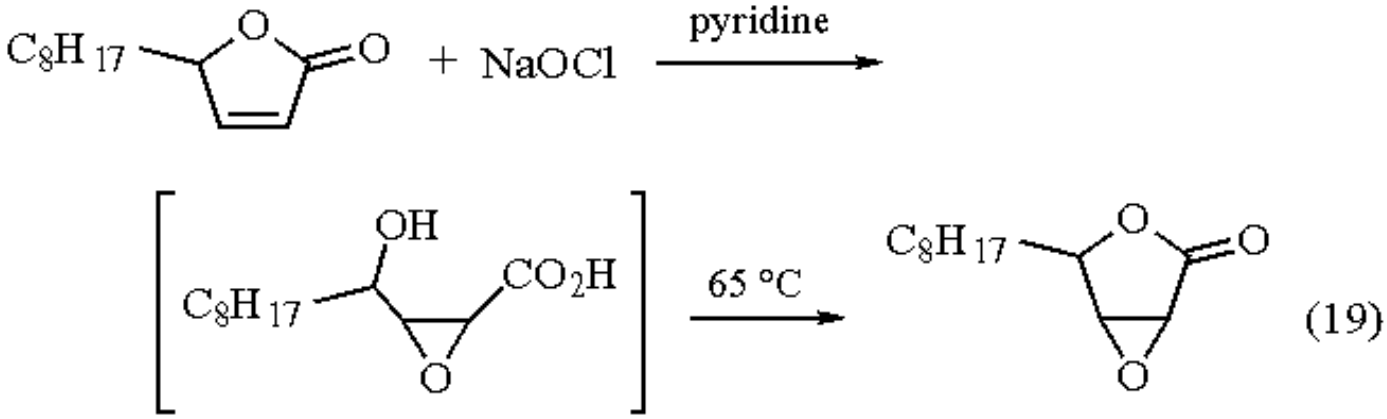

(19)

See also: ***Sodium Hypochlorite-N,N´-Bis(3,5-di-t-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) Chloride***, ***Hydrogen Peroxide***, ***t-Butyl Hydroperoxide***, and ***Dimethyldioxirane***.

Other Oxidation Reactions.

Several other substrate classes also undergo oxidation reactions with sodium hypochlorite. Diketones may be oxidatively cleaved to give the corresponding diacids (eq 20).[33] Oxidation of hydroquinones and catechols[34] and oxidative cyclization of phenols (eq 21)[8] have also been realized.

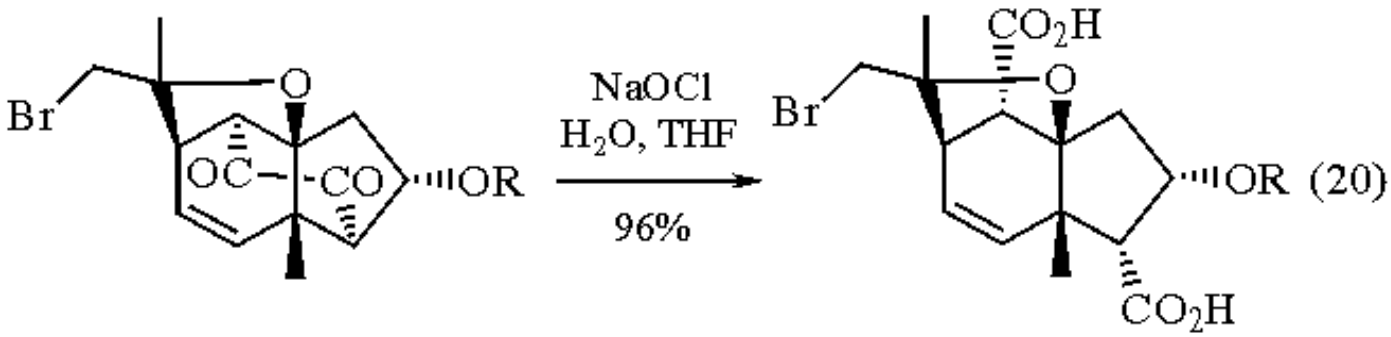

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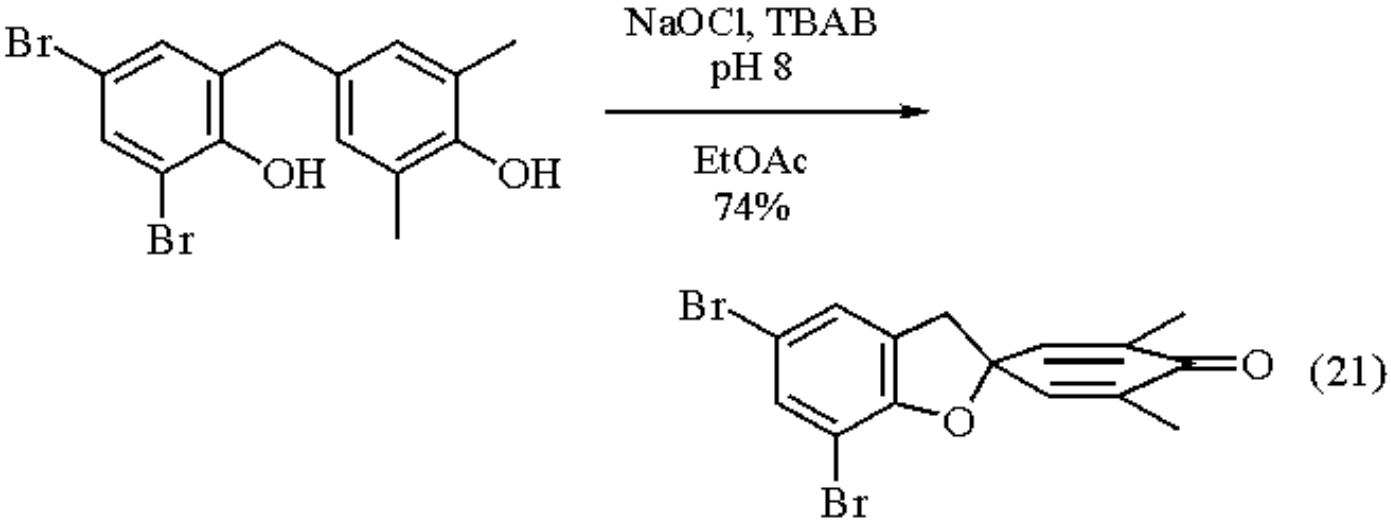

Oxidative Degradation.

Treatment of carboxylic acids with sodium hypochlorite can lead to decarboxylation to afford aldehydes with one less carbon atom (eq 22).[35] The mechanism of this reaction is likely to involve methylene oxidation to the chloride or the alcohol followed by decarboxylation and oxidation to the aldehyde. This method has primarily been applied to sugar degradation (eq 23).[9,36]

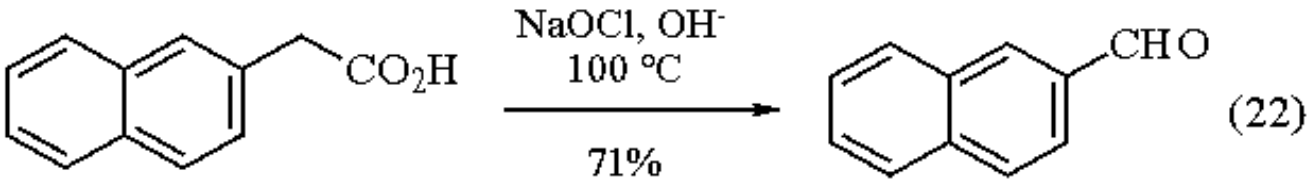

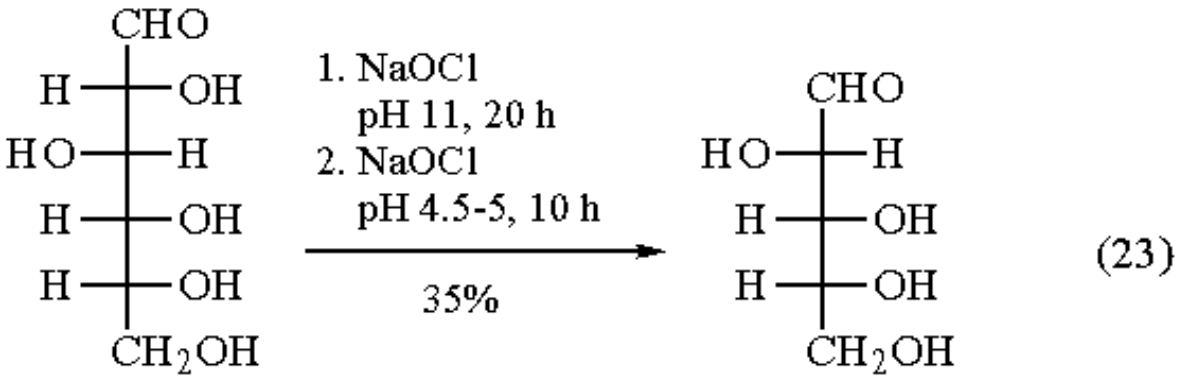

Reaction with Amines.

Reactions of sodium hypochlorite with amines can yield ketones, cyclization products, or, in the case of amino acids, degradation products. The mechanism of each of these processes involves initial *N*-chlorination.[37] Chlorinated intermediates have been identified spectroscopically, and in some cases isolated, providing access to chlorination products as well. Treatment of aliphatic amines under phase transfer conditions yields ketones or nitriles.[15,16a] The initial product is the *N*-chloro imine, with the carbonyl being released upon hydrolytic workup (eq 24).

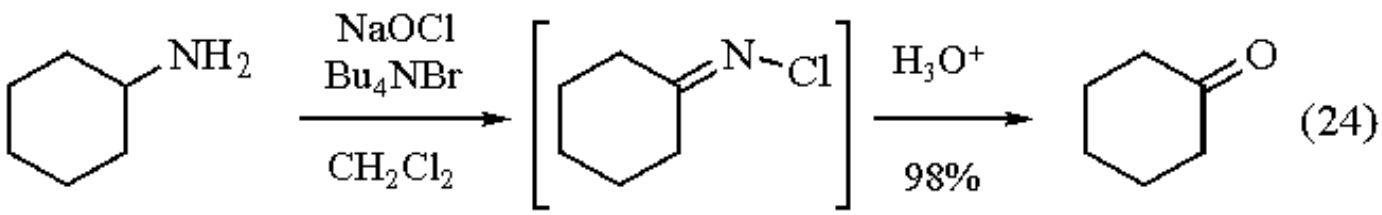

Reaction of α- or β-amino acids with NaOCl leads to the corresponding aldehyde or methyl ketone containing one less carbon.[38] The mechanism postulated for this Strecker-type degradation of amino acids again involves *N*-chlorination, followed by decarboxylation to

yield the imines. Aldehydes and ketones are released by hydrolysis (eq 25).[39] This method has been applied to degradation of α-methyl DOPA (eq 26).[40]

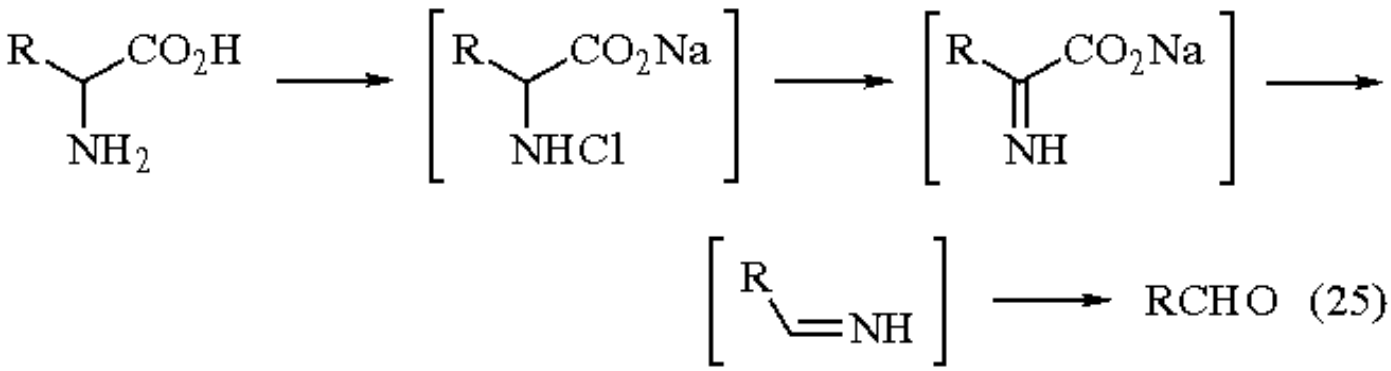

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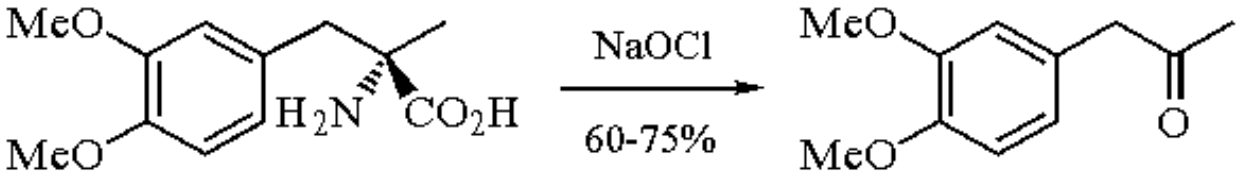

(26)

Oxidative Cyclization of Amines.

Treatment of nitro anilines with sodium hypochlorite under alkaline conditions affords benzofuroxans as cyclization products (eq 27).[41] Spectroscopic evidence suggests an initial chlorination of the amino group, followed by cyclization. In addition, chlorinated intermediates have been prepared independently and submitted to the reaction conditions to show that cyclization products are formed.[37] The cyclization reaction requires addition of base, as azo products are formed at neutral pH. Oxadiazoles (eq 28)[42] and chlorodiazirines (eq 29)[43] are also formed by oxidative cyclization in moderate-to-good yields. The key intermediate for both of these reactions is also proposed to be an *N*-chloro imine.

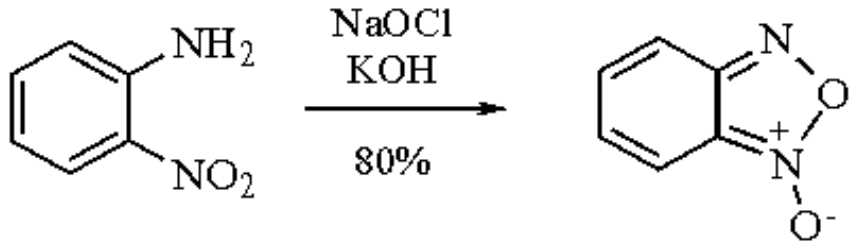

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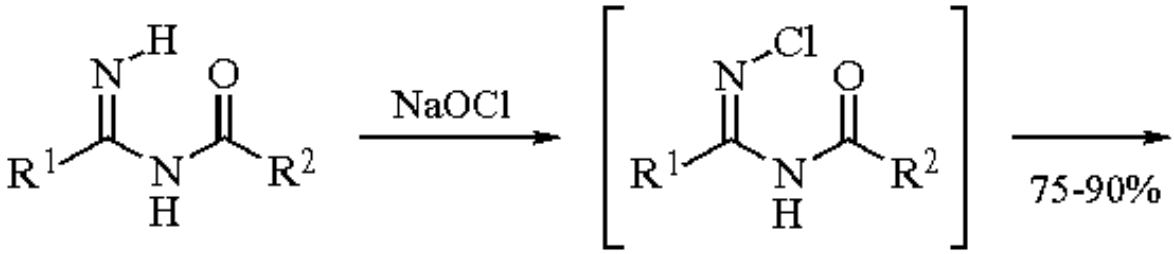

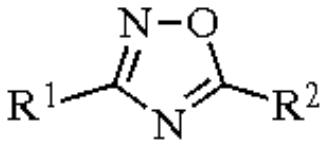

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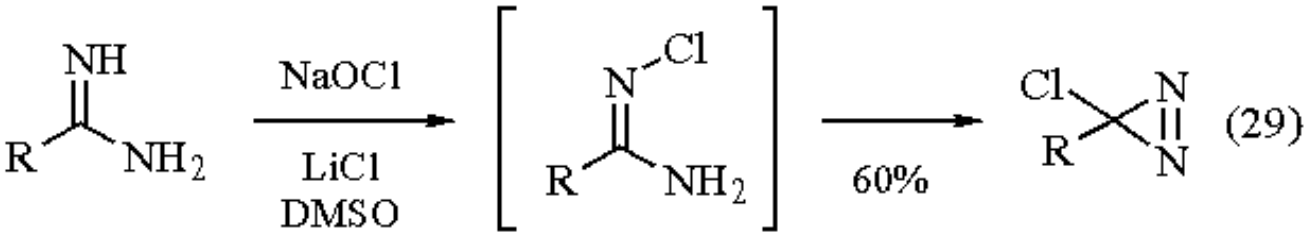

Amine Coupling Reactions.

Hydrazines[44] and alkylhydrazines (eq 30)[45] are formed by the action of bleach and amines. Azoethanes are toxic, and therefore care should be taken in their production and handling.

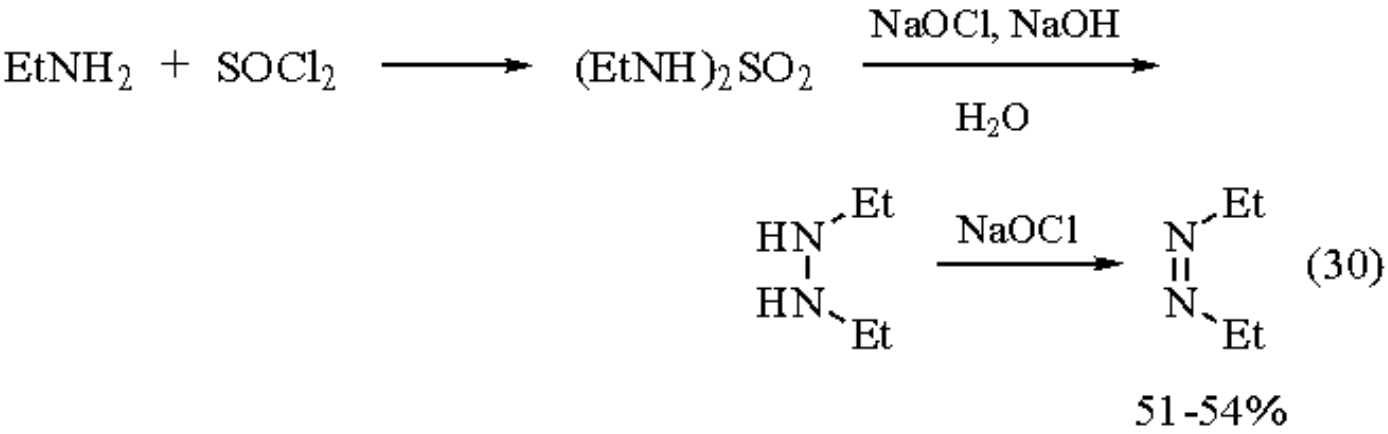

Chlorination.

Several types of organic nucleophiles undergo reaction with sodium hypochlorite to afford chlorination products. *N*-Chlorination of primary and secondary amines is a representative and widely-used example of this reaction class (eq 31).[46] Either mono- or dichlorinated products can be obtained selectively through control of the relative stoichiometry of the amine and NaOCl.[47] A two-step chlorine-shuttle pathway for the selective chlorination of electron-rich aromatics has been developed which relies on initial *N*-chlorination with NaOCl.[46] Intramolecular cyclization of amines via the Hofmann-Loffler reaction may also be accomplished by effecting the requisite *N*-halogenation with NaOCl (eq 32).[48]

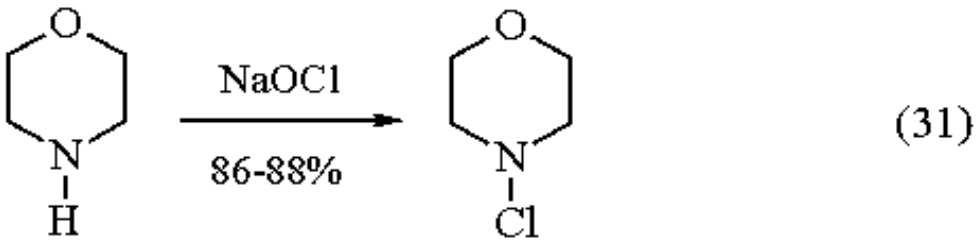

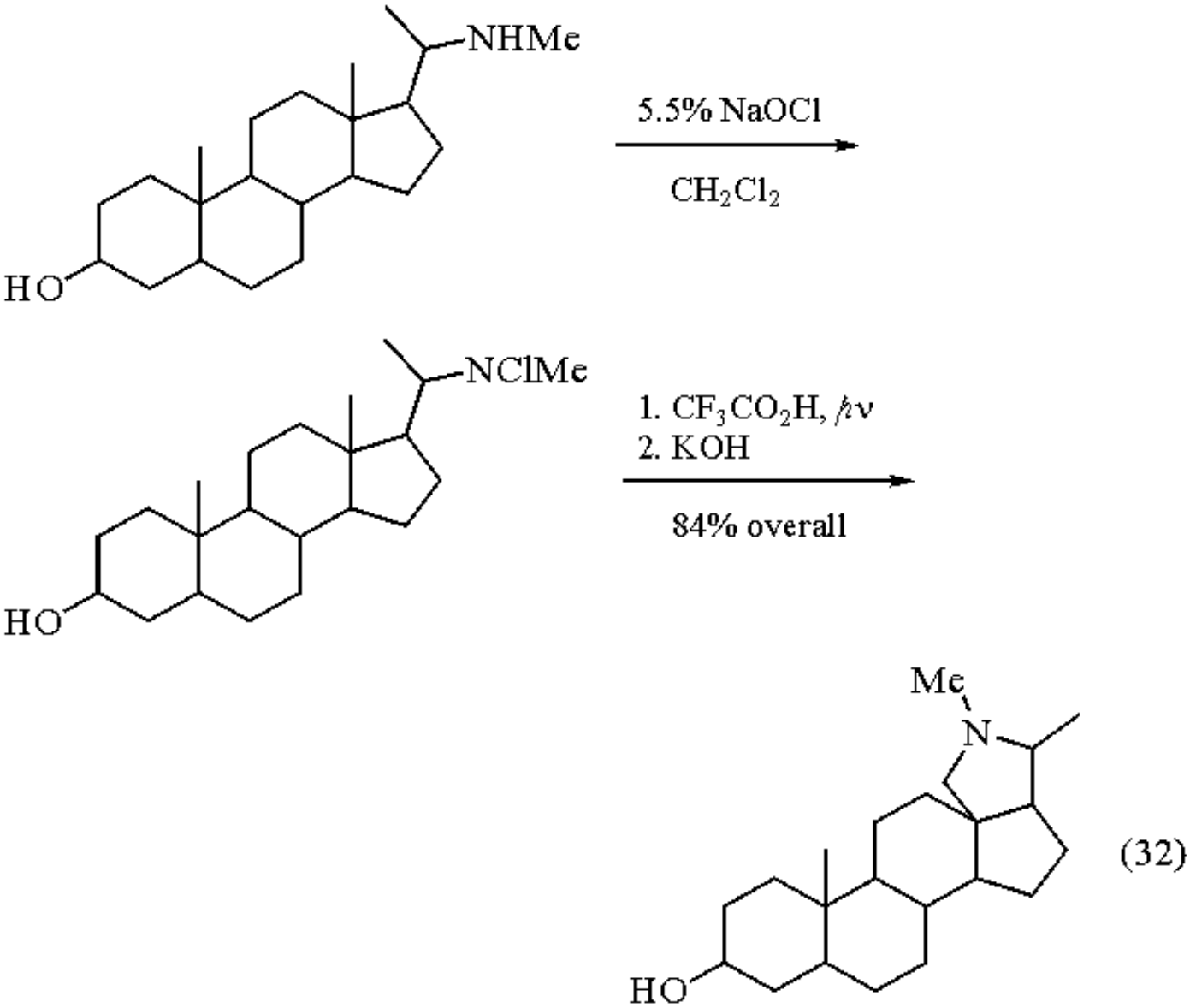

(32)

Chlorination of indoles (eq 33),[7,49] amides, and ureas[50] occurs at the nitrogen center, while oximes[51] are chlorinated at carbon. Selective chlorination of nicotinic acids (eq 34),[52] chromones,[53] and polymers[54] has also been achieved. Substitution of chlorine for other halides occurs upon treatment of certain aromatic halides with sodium hypochlorite solution.[55]

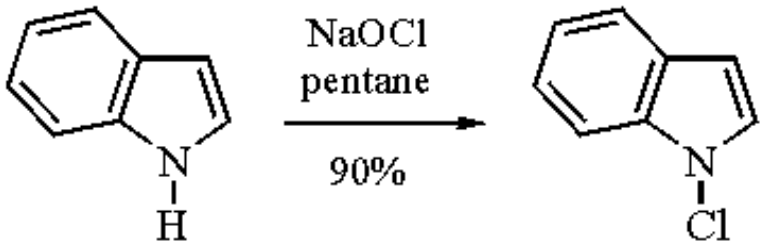

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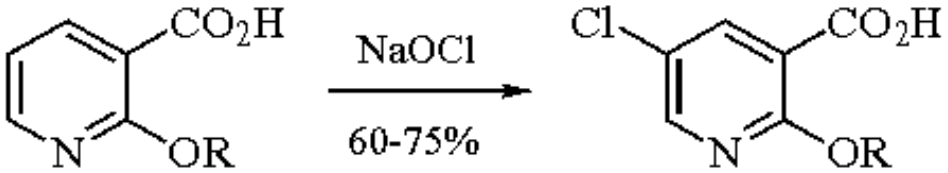

(34)

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Sodium Hypochlorite-*N,N´*-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) Chloride[1]

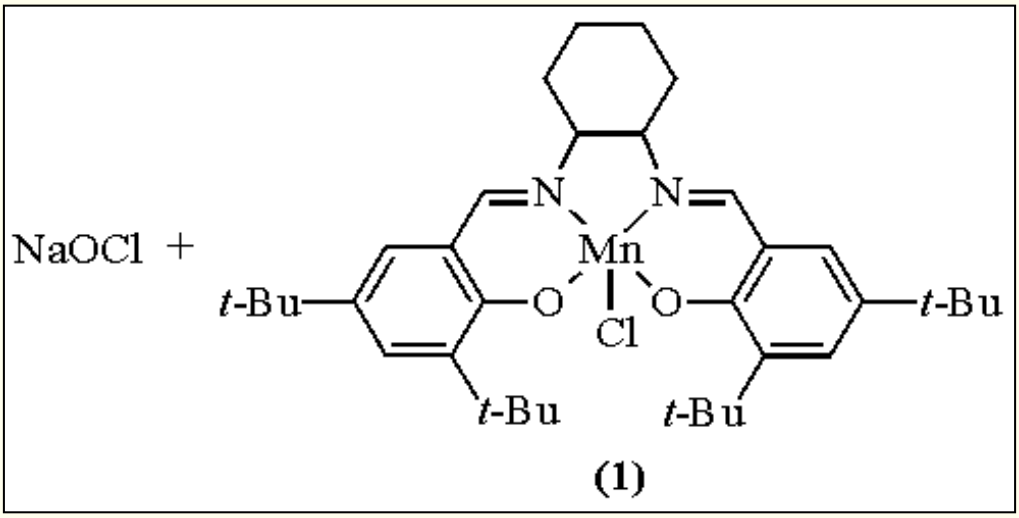

(NaOCl)

[7681-52-9] · ClNaO · Sodium Hypochlorite-*N,N´*-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) Chloride · (MW 74.44) (*R,R*)-(**1**)

[138124-32-0] · $C_{36}H_{52}ClMnN_2O_2$ · Sodium Hypochlorite-*N,N´*-Bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) Chloride · (MW 635.29) (*S,S*)-(**1**)

[135620-04-1]

(catalytic system for enantioselective epoxidation of unfunctionalized alkenes[2])

Physical Data: NaOCl: see ***Sodium Hypochlorite***. (**1**): mp 330-332 °C.

Solubility: (**1**) freely sol CH_2Cl_2, *t*-butyl methyl ether, acetonitrile, ethyl acetate.

Form Supplied in: both enantiomers of (**1**) are commercially available as brown powders, 98%; synthetic preparations may contain up to one solvated molecule of ethanol or DMF for each manganese.

Analysis of Reagent Purity: (salen)Mn^{III} complexes are paramagnetic and do not provide readily interpretable NMR data. (**1**): R_f = 0.63 (SiO_2, ethanol); purity may be established by elemental analysis.

Preparative Methods: over 100 chiral manganese(III) salen complexes have been reported;[1] the general procedure for their preparation involves condensation of a 1,2-diamine with 2 equiv of a salicylaldehyde derivative, followed by addition of $Mn(OAc)_2$ in the presence of air.[3] Yields of (salen)Mn^{III} complexes usually exceed 90%.

Purification: (**1**) can be recrystallized from toluene or CH_2Cl_2/heptane. The solvent content of (**1**) and related complexes does not influence their effectiveness as epoxidation catalysts,[4] but heating to >80 °C for 3 h under vacuum results in liberation of solvated molecules.

Handling, Storage, and Precautions: (**1**) is sensitive to acid, but indefinitely stable to air, moisture, and light.

Epoxidation Method.

Epoxidation of a variety of conjugated and nonconjugated alkenes may be effected in a biphasic reaction system consisting of aqueous bleach at pH &egt; 9.5 and an organic phase bearing catalytic levels of a soluble manganese(III) complex.[4,5] The ideal pH range appears to be 10.5-11.5 for most applications, with nonwater-miscible solvents such as CH_2Cl_2, *t*-butyl methyl ether, or ethyl acetate as the organic solvent. At pH <= 11.5, no phase transfer catalysts are necessary for epoxidation to occur, due to the presence of significant equilibrium concentrations of HOCl.[5] At low pH, equilibrium levels of Cl_2 can produce chlorinated byproducts. Reactions with alkenes are carried out in air, without the need for precautions to exclude moisture or trace impurities. The substrate and catalyst are dissolved in the organic solvent and combined with the bleach solution at 0 °C or room temperature. Catalyst turnover numbers and product yields may be improved in the epoxidation of certain substrates by the addition of substoichiometric levels of a pyridine *N*-oxide derivative (Table 1).[3a,6] Isolation of the epoxide is accomplished by separation of the organic phase and purification by distillation, crystallization, or chromatography.

Table 1 Asymmetric Epoxidation of Representative Alkenes by Catalyst **(1)**

Alkene	*N*-Oxide[a] (mol %)	**(1)** (mol %)	Yield (%)	ee of major epoxide (%)
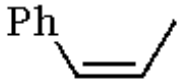	0	4	84[b]	92
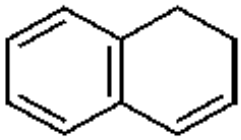	20	4	67	86
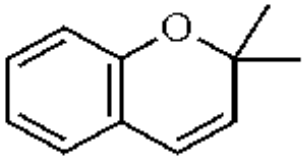	0	2	87	98
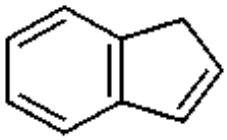	0	1	80	88
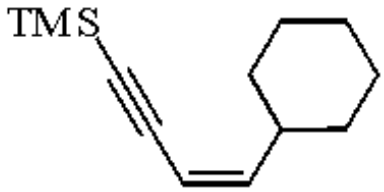	0	4	65[c]	98
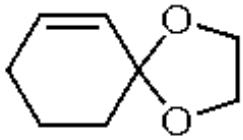	20	15	63	94
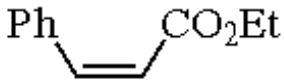	20	8	67[d]	97

[a]*N*-Oxide employed is 4-phenylpyridine *N*-oxide. [b]Isolated yield of epoxide mixture (*cis*:*trans* = 11.5:1). [c]Isolated yield of epoxide mixture (*cis*:*trans* = 1:5.2). [d]Isolated yield of epoxide mixture (*cis*:*trans* = 5:1).

Substrate Scope.

Best results in the (salen)Mn^{III}-catalyzed epoxidation reaction have been obtained with *cis*-disubstituted, conjugated alkenes (Table 1). Epoxidation of 2,2-dimethylchromene derivatives occurs with especially high selectivity (&egt;97% ee).[7] *trans*-Disubstituted alkenes are epoxidized with low selectivity (20-50% ee), as are simple alkyl-substituted alkenes.

Mechanistic Considerations.

A stepwise mechanism involving a nonpolar intermediate has been proposed for the oxygen atom transfer event in (salen)Mn^{III}-catalyzed epoxidations (eq 1).[6a,8] Consistent with this proposal, acyclic *cis*-alkenes afford mixtures of *cis*- and *trans*-epoxides, and conjugated alkenes are 1-2 orders of magnitude times more reactive than isolated alkenes.[1] In the case of dienes and enynes, the *trans*-epoxide can in fact constitute the major product.[7]

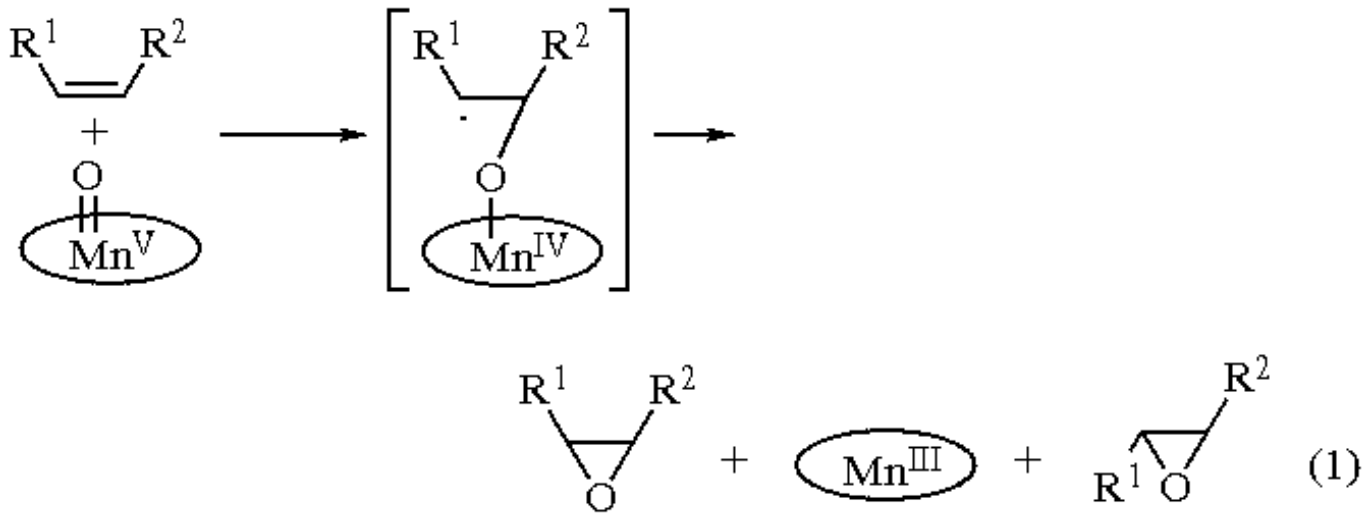

In the case of 1,2-disubstituted alkenes, the nonstereospecificity of the epoxidation reaction results in formation of diastereomeric epoxides. In contrast, for terminal alkenes the *trans* pathway results in partitioning to enantiomers. Thus, diminished enantioselectivity observed in the epoxidation of terminal alkenes such as styrene (50-70% ee) relative to sterically similar *cis*-disubstituted alkenes can be attributed to enantiomeric leakage due to the *trans* pathway. Suppression of this pathway has not been accomplished successfully, and synthetically useful enantioselectivities with terminal alkenes have not yet been achieved using the chiral (salen)Mn^{III} systems.

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Sodium Hypophosphite

NaH_2PO_2

[7681-53-0] · H_2NaO_2P · Sodium Hypophosphite · (MW 87.98)

(source of hydrogen in heterogeneous catalytic transfer reductions;[1-10] synthesis of phosphonous acids via hydrophosphorylation of terminal alkenes[11])

Physical Data: decomposes upon strong heating with release of phosphine, which is highly flammable in air.

Solubility: sol water, alcohol; insol ether.

Form Supplied in: monohydrate, white solid.

Handling, Storage, and Precautions: explodes when triturated with chlorates or other oxidizing agents.

Functional Group Reductions.

Sodium hypophosphite is a very effective and mild hydrogen-transfer reagent capable of reducing a wide range of functional groups when utilized with the appropriate catalyst. The reductions of aldehydes to alcohols,[1] alkynes to alkenes,[2] azides to amines,[1] benzoquinones to dihydrobenzoquinones,[3] epoxides to alcohols,[1] alkyl or aryl halides to alkanes or arenes,[1,4] ketones to alcohols,[1] nitriles to aldehydes,[5] nitroalkenes to oximes,[6] nitroarenes to aryl amines,[7] *N*-oxides to amines,[1] alkenes to alkanes,[8] oximes to ketones,[1,9] and phenols to arenes,[10] as well as the hydrogenolysis of benzylic ethers,[1] have all been effected. Reactions have been carried out in solvent systems ranging from aqueous to anhydrous organic solvents, typically at elevated temperatures (50-75 °C), with excess sodium hypophosphite and most often ***Palladium on Carbon*** as the catalyst. Reaction workup generally involves filtration of the catalyst, extraction if appropriate, and removal of solvent.

Studies on polyfunctional molecules have shown the reduction to be tunable; while treatment of cinnamonitrile (**1**) with sodium hypophosphite and 5% Pd/C yields 87% of dihydrocinnamonitrile (**2**),[1] reduction with sodium hypophosphite and ***Raney Nickel*** gives only cinnamaldehyde (**3**)[5] (eq 1). A more profound demonstration of selectivity is seen in the conversion of (**4**) to (**5**) (eq 2), intermediates in the synthesis of (+)-pilocarpine.[5b]

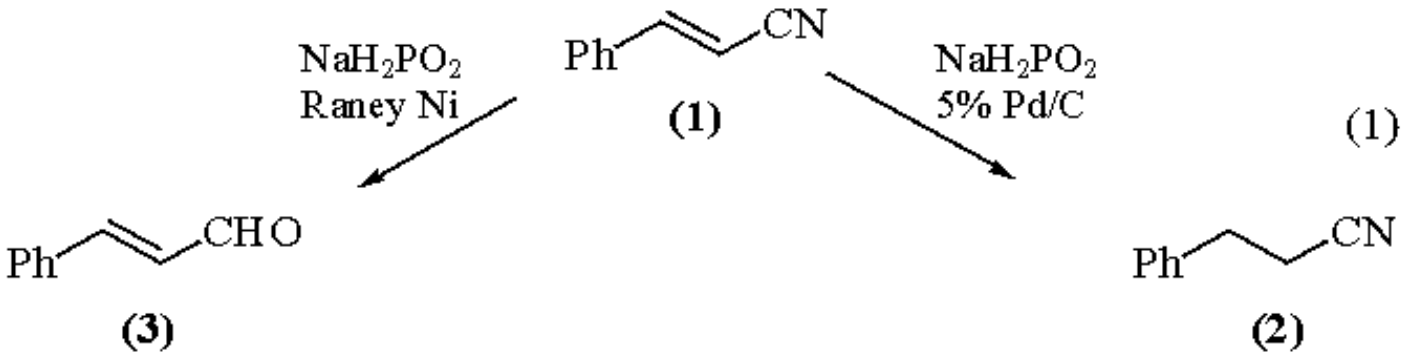

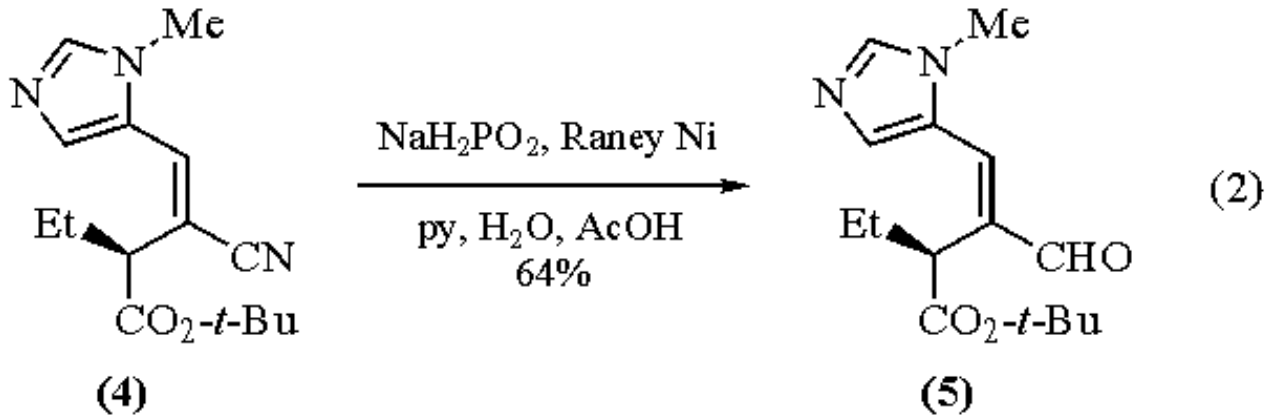

Hydrophosphorylation of Alkenes.

Terminal alkenes (**6**), when treated with sodium hypophosphite in the presence of ***Azobisisobutyronitrile***, yield phosphonous acids (**7**) (eq 3).[11]

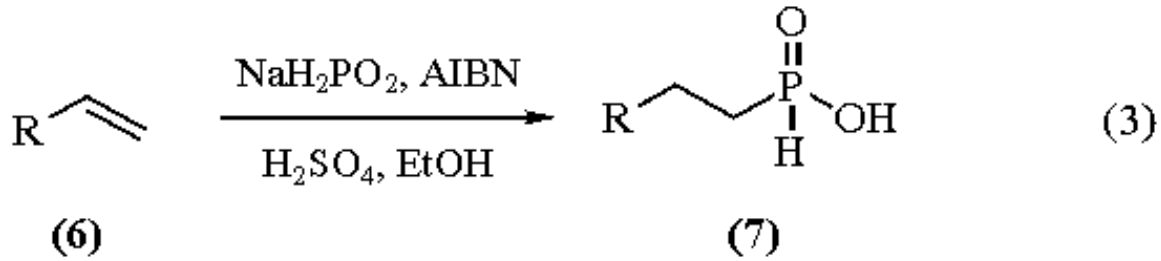

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Sodium Iodide[1]

NaI

[7681-82-5] · INa · Sodium Iodide · (MW 149.89)

(source of iodide ion for nucleophilic displacement reactions in the preparation of alkyl iodides[4-10] and aryl iodides[11-13] from halides and sulfonates; in combination with Zn, reduces sulfonates;[14,15] converts *vic*-dihalides and *vic*-disulfonates to alkenes;[16-20] dehalogenates α-halo ketones[21-23] and α-bromo enones;[27] converts acyl chlorides to acyl iodides;[24] cleaves aryl methyl[25,26] and some dialkyl ethers;[27-32] deoxygenates epoxides;[31] in combination with TMSCl/MeCN, generates TMSI in situ;[33-35] catalyzes phosphorylations;[36] reduces ene dicarbonyl compounds;[37] converts acetylenic ketones to vinyl iodides;[38] in combination with TMSCl/MeCN/0.5 H_2O, generates anhydrous HI;[40] with various co-reagents, reduces sulfoxides[41-43] and *N*-oxides;[43a,44,45] with oxidizing agents, iodinates organoboranes,[46] phenols,[47,48] and aromatic compounds[49])

Physical Data: mp 661 °C; bp 1304 °C; *d* 3.667 g cm^{-3}.

Solubility: very sol cold H_2O (184 g/100 mL, 25 °C), hot H_2O (302 g/100 mL, 100 °C), alcohol (42.57 g/100 mL, 25 °C), acetone (39.9 g/100 mL, 25 °C); sol glycerin.[2] Also sol acetic acid, acetonitrile, DMF, DMSO, formic acid, HMPA, methyl ethyl ketone.

Form Supplied in: white solid (crystalline, granular, or powder); widely available. *Drying:* can be dried under vacuum at 70 °C.[3]

Handling, Storage, and Precautions: deliquescent in moist air (gradually absorbs up to ca. 5% (0.5 mol) H_2O in air), and upon long exposure to air will turn brown due to liberation of iodine; storage in a dry or inert atmosphere is recommended.

Introduction.

Sodium iodide and potassium iodide are used in organic synthesis as sources of iodide. NaI is more commonly used due to greater solubility in organic solvents and slightly lower cost. Tetraalkylammonium iodides have also been used as organic-soluble sources of iodide. See also ***Potassium Iodide*** and ***Tetra-n-butylammonium Iodide***.

Displacement Reactions.

NaI reacts with alkyl chlorides, bromides, and sulfonates (e.g. mesylates and tosylates[4]) to provide the corresponding alkyl iodides.[5] The conversion of alkyl halides to iodides using NaI in acetone is known as the Finkelstein reaction.[6] Though usually an S_N2 displacement, radicals have been implicated in some cases.[6b] Displacement reactions using NaI are numerous in the literature, and representative examples (eqs 1 and 2)[7,8] are shown below. In some cases the iodo compound is not isolated but reacts with another nucleophile present (eq 3).[9] NaI has been used catalytically in such reactions.[10]

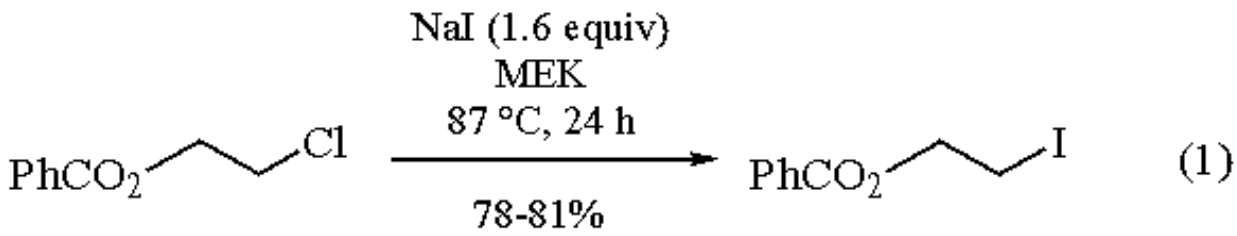

(1)

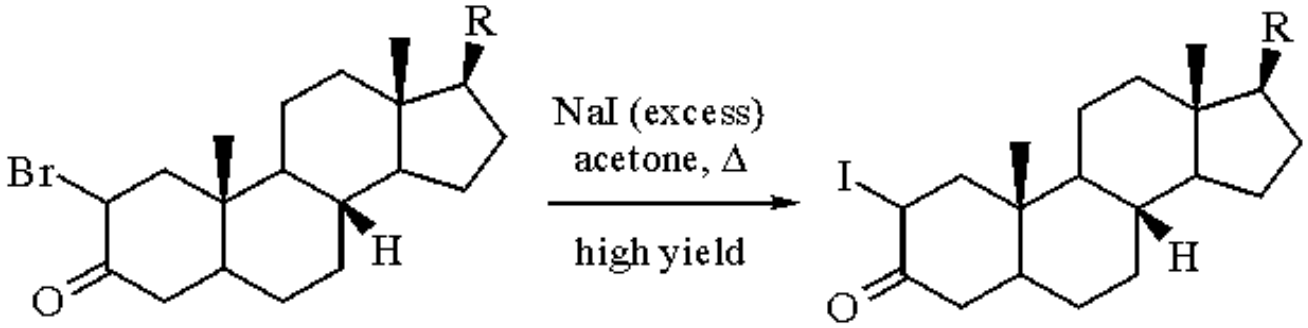

(2)

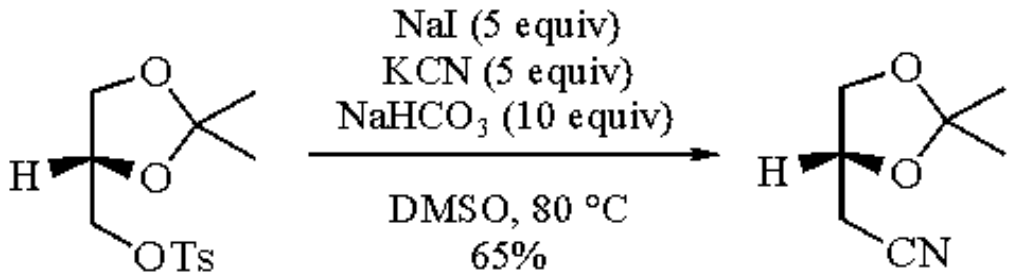

(3)

NaI reacts with electron-deficient aryl halides in a formal S_NAr reaction (e.g. with 2,4-dinitrochlorobenzene)[11] to give aryl iodides; however, with aryl diazonium compounds the reaction proceeds via electron transfer and involves an aryl radical.[12] The latter process has been applied to the Pschorr phenanthrene synthesis[13] (eq 4).[13b]

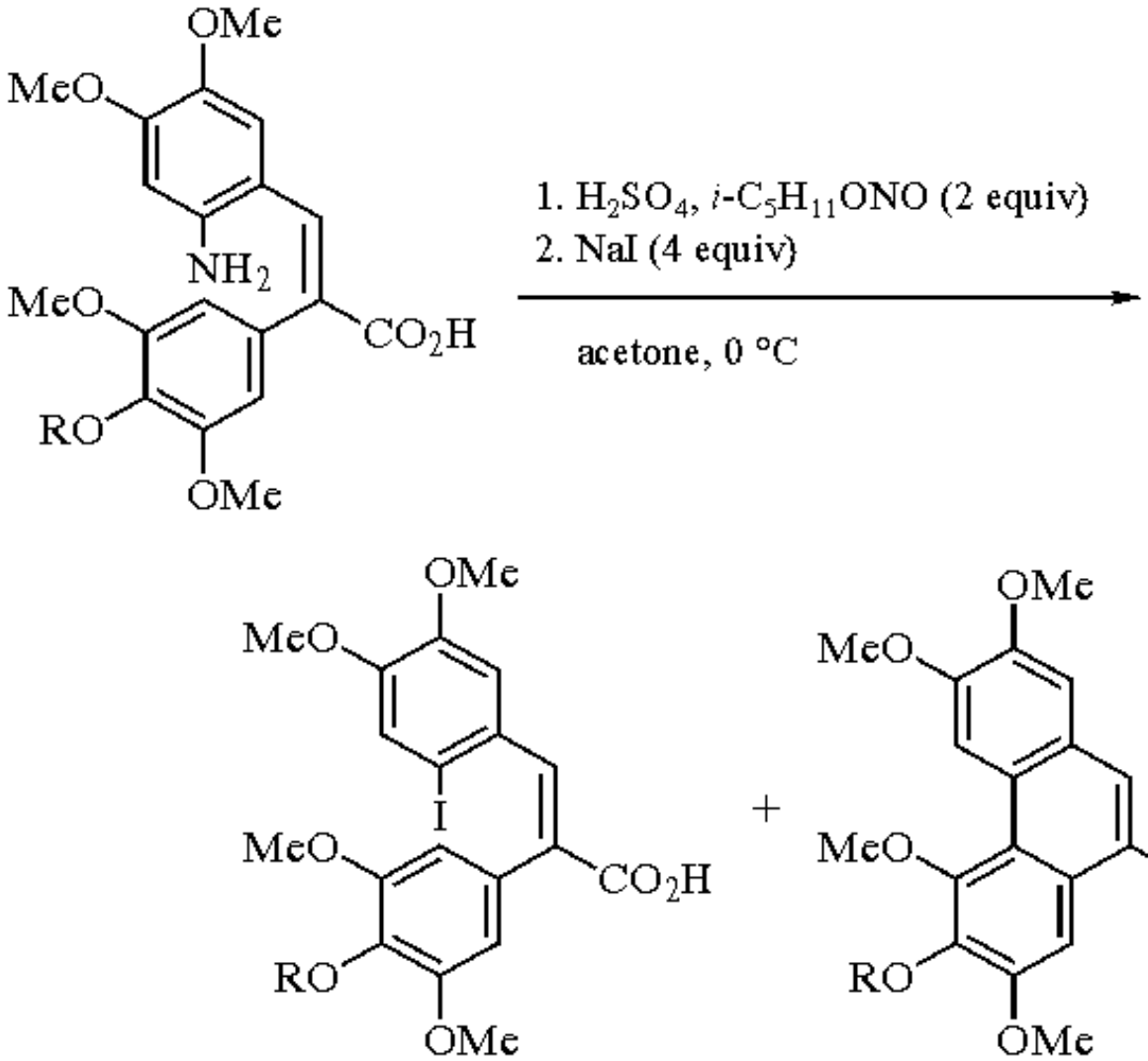

(4)

R = CH_2Ph	20%	45%
R = SO_2Ph	few %	71%

Reductive Cleavage of Sulfonates.

NaI/***Zinc*** has been used to reduce alkyl tosylates and mesylates to the corresponding alkanes (eq 5).[14] This procedure complements ***Lithium Aluminum Hydride*** reductions of sulfonates since, in some cases, $LiAlH_4$ produces both the alkane and the alcohol. However, with secondary mesylates and tosylates a large amount of the alkene elimination product is often obtained using NaI/Zn. NaI/Zn/D_2O (or T_2O) in dimethoxyethane has been used to replace primary and secondary hydroxyl groups with deuterium (or tritium).[15]

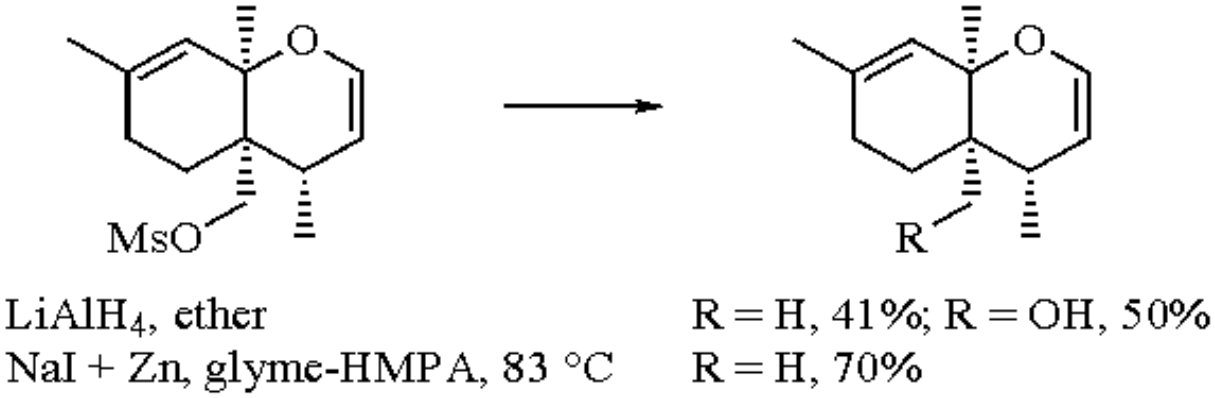

Conversion of *vic*-Halides and *vic*-Sulfonates to Alkenes.

NaI reacts with *vic*-dibromides, *vic*-bromochlorides, and *vic*-dichlorides to give the corresponding alkenes.[16] This reaction can be utilized for alkene *cis*/*trans* isomerization (eq 6).[17] *vic*-Bromochlorides and *vic*-dichlorides give predominantly *cis*-products while dibromides give predominantly *trans*-alkenes. *vic*-Dimesylates[17] and *vic*-ditosylates[18,19] also give alkenes when treated with sodium iodide, via initial displacement of one sulfonate group followed by attack of iodide on the iodine of the *vic*-iodosulfonate. This reaction has been carried out under phase-transfer conditions.[20]

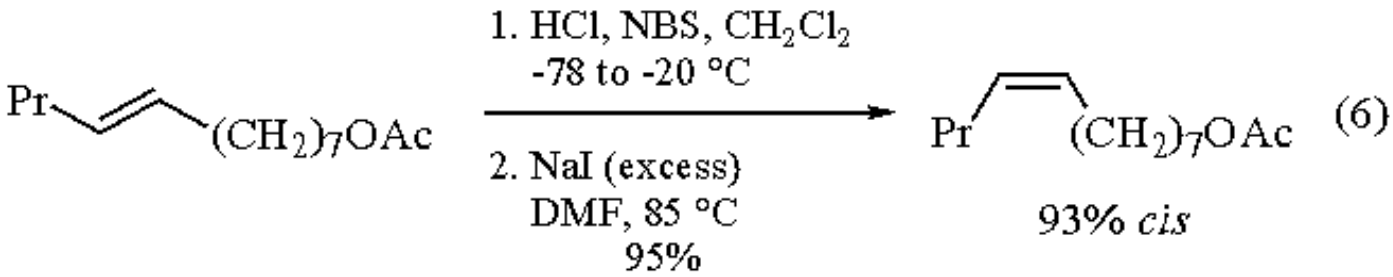

Dehalogenation of α-Halo Ketones.

NaI will reductively dehalogenate some α-halo ketones in acidic aqueous THF or dioxane (eq 7)[21] or in AcOH.[22] This reaction may not be general for all α-halo ketones.[21] NaI/***Sulfur Trioxide-Pyridine*** in acetonitrile has also been used to carry out this transformation.[23]

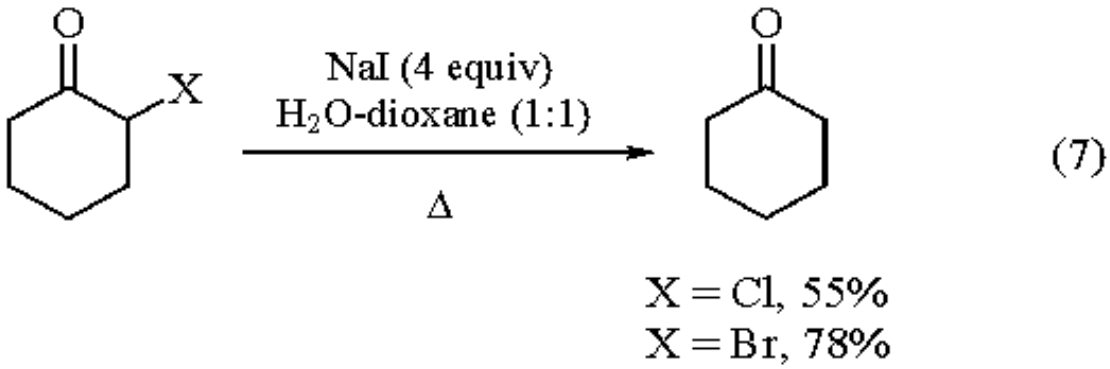

Preparation of Acyl Iodides.

NaI reacts with acyl chlorides in anhydrous acetonitrile to give acyl iodides in high yield.[24] Diacyl diiodides[24b] and iodoformates[24c] have

also been prepared in this fashion.

Demethylation of Aryl Methyl Ethers.

NaI reacts with aryl methyl ethers in acetic or formic acid to give the corresponding phenolic derivatives and methyl iodide.[25] In one study, KI was found to give slightly higher yields (eq 8).[26] See also NaI/Me_3SiCl/MeCN below.

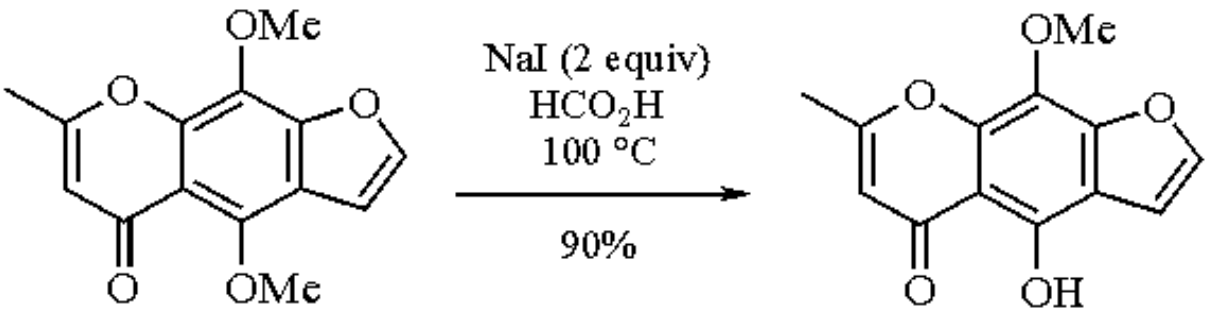

(8)

Other Ether Cleavage Reactions.

NaI/***Boron Trifluoride Etherate*** cleaves some alkyl ethers[27] and acetals,[27b] and converts keto epoxides to enones.[27c] Some primary and secondary alkyl methyl ethers are cleaved by NaI/***Boron Tribromide***/***15-Crown-5*** in CH_2Cl_2.[28] Cyclic (e.g. THF and THP) and acyclic dialkyl ethers are cleaved at the less substituted carbon by NaI in the presence of acyl chlorides.[29] For example, 2-methyltetrahydrofuran gives the pivalate derivative of 5-iodo-2-pentanol when treated with NaI/*t*-BuCOCl in acetonitrile. Similarly, 2-iodoethyl esters are produced from acyl chlorides, ***Ethylene Oxide***, and NaI (eq 9).[30] NaI/***Trifluoroacetic Anhydride*** has been used to deoxygenate epoxides with retention of configuration: trifluoroacetyl iodide is generated in situ and reacts with the epoxide in the presence of NaI to give a *vic*-iodo trifluoroacetate, which decomposes in the presence of excess NaI to give the alkene.[31] NaI/NaOAc has been reported to reduce α,β-epoxy ketoses to β-hydroxy ketoses, presumably via the α-iodo-β-hydroxy ketone (eq 10).[32]

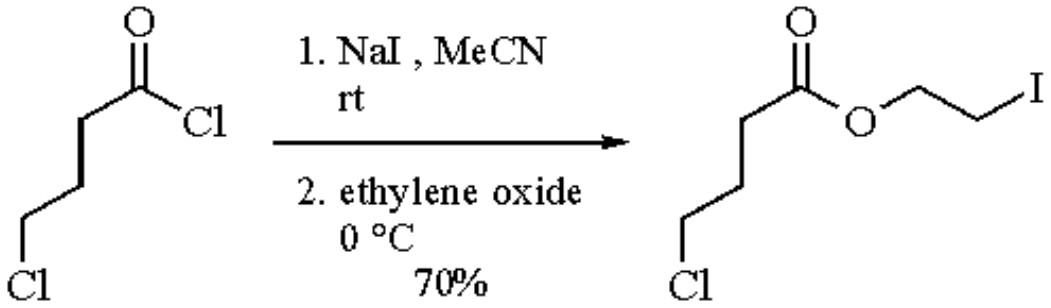

(9)

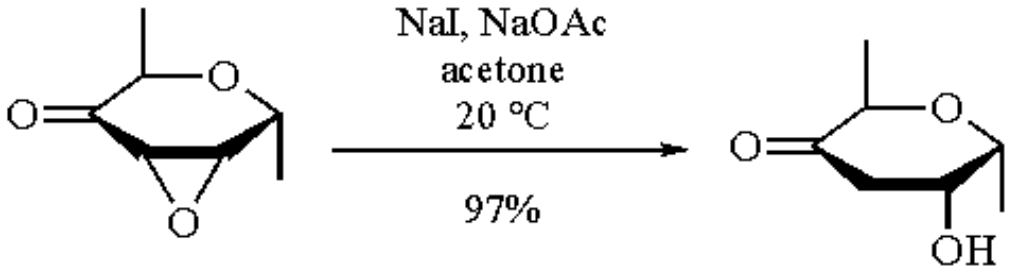

(10)

In Situ Generation of Trimethylsilyl Iodide.

NaI/***Chlorotrimethylsilane***/MeCN has been widely used as a convenient substitute for ***Iodotrimethylsilane***.[33-35] For example, this reagent removes benzylic hydroxyl groups,[34] cleaves methoxyethoxymethyl (MEM),[35] aryl methyl, and aryl ethyl ethers, deoxygenates sulfoxides (and *N*-oxides in the presence of zinc), converts some alcohols to iodides, and dehalogenates α-halo ketones.[33a]

Catalysis of Phosphorylation.

NaI catalyzes the phosphorylation of nucleosides by chlorophosphates, pyrophosphates, and triazolides.[36] The rate of phosphorylation is greatly enhanced by addition of 1 or 2 equiv of NaI. For example, 3´-*O*-benzoylthymidine is phosphorylated over 10 times faster with

Diethyl Phosphorochloridate when 1 equiv of NaI is added, and over 300 times faster when 2 equiv of NaI are added.

1,4-Addition to α,β-Unsaturated Carbonyl Compounds.

NaI has been used to reduce the carbon-carbon double bond of 2-ene-1,4-dicarbonyl compounds, presumably via conjugate addition of iodide followed by reduction of the newly formed α-iodo carbonyl compound (eq 11).[37] The reaction is specific to 1,4-diketones or keto aldehydes, and fails with 1,4-diacids, 1,4-diesters, and α,β-unsaturated monocarbonyl compounds. However, NaI apparently does add to enones under some conditions since NaI/BF_3.OEt_2 dehalogenates α-bromo enones (via the *vic*-bromoiodide).[27c] Furthermore, NaI in TFA reacts with α,β-acetylenic ketones to give (*E*)-β-iodovinyl ketones, while NaI in AcOH gives predominantly the (*Z*)-isomer (eq 12).[38] The reaction tolerates both terminal and substituted alkynes.

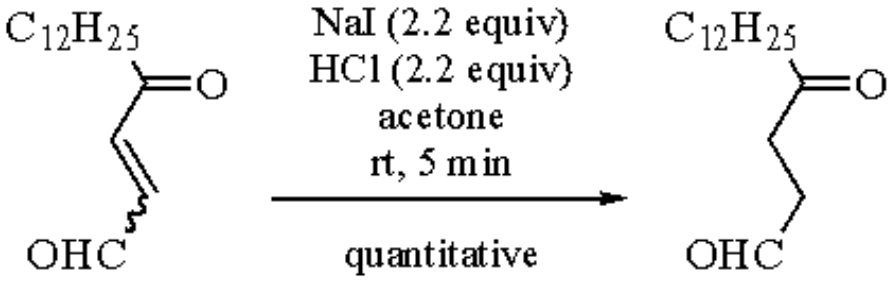

(11)

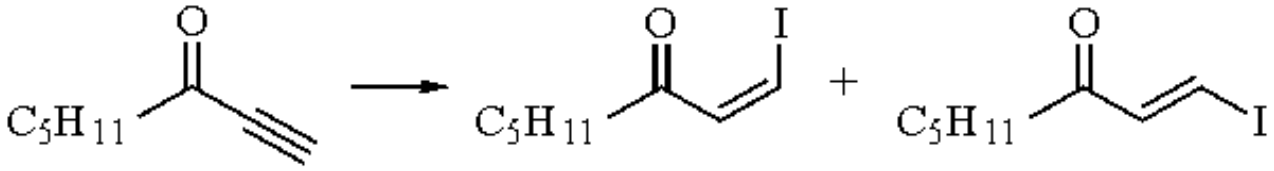

(12)

NaI, TFA	30 min	-	95%
NaI, AcOH	30 min	70%	17%
NaI, AcOH	21 h	-	94%

Conversion of Allylic, Benzylic, and Tertiary Alcohols to Iodides.

NaI/BF_3.OEt_2 in acetonitrile converts allylic, benzylic, and tertiary alcohols to iodides in good yield.[39,40] NaI/Me_3SiCl/MeCN/0.5 H_2O (anhydrous HI) has been used to convert allylic alcohols to allylic iodides, with allylic rearrangement if the alcohol is secondary or tertiary.[40]

Reduction of Sulfoxides.

NaI/$(CF_3CO)_2O$ in acetone,[41] NaI/BF_3.OEt_2 in acetonitrile,[42] NaI/I_2/***Hexamethylphosphorous Triamide*** in acetonitrile,[43a] NaI/***Oxalyl Chloride*** in acetonitrile,[43b] NaI/Me_3SiCl in acetonitrile,[43c] NaI/I_2/Me_2NEt.SO_3 in acetonitrile,[43d] and NaI/pyridine.SO_3 in acetonitrile[43d] all reduce sulfoxides to sulfides in high yield.

Reduction of *N*-Oxides and Nitrones.

NaI/$(CF_3CO)_2O$ in acetonitrile deoxygenates various heteroaromatic *N*-oxides and nitrones in very high yield.[44] NaI/pyridine.SO_3 deoxygenates di-*N*-oxides of quinoxalines and phenazines.[45] NaI/I_2/$(Me_2N)_3P$ in acetonitrile deoxygenates azoxides.[43a]

Iodinations of Phenols and Organoboranes.

NaI/***Chloramine-T*** has been used as an in situ source of ***Iodine Monochloride*** for iodinations of organoboranes[46] and phenols.[47] For example, methyl 5-iodosalicylate is prepared from methyl salicylate in 78% yield.[47] Iodinated carbohydrates have been prepared via iodination of organoboranes (eq 13).[46b] Recently, NaI/***Sodium Hypochlorite*** in methanol has been used to iodinate phenols in high yield with good regioselectivity.[48] The yield and regioselectivity with phenol (80% *para*, 10% *ortho*, 4% *ortho,para*) are different than those obtained with ICl or NaI/Chloramine-T. Simple aromatic hydrocarbons are iodinated with NaI/O_2/cat. ***Nitrosonium Tetrafluoroborate*** in

CH_2Cl_2/TFA.[49] This iodination fails with electron-deficient aromatics.

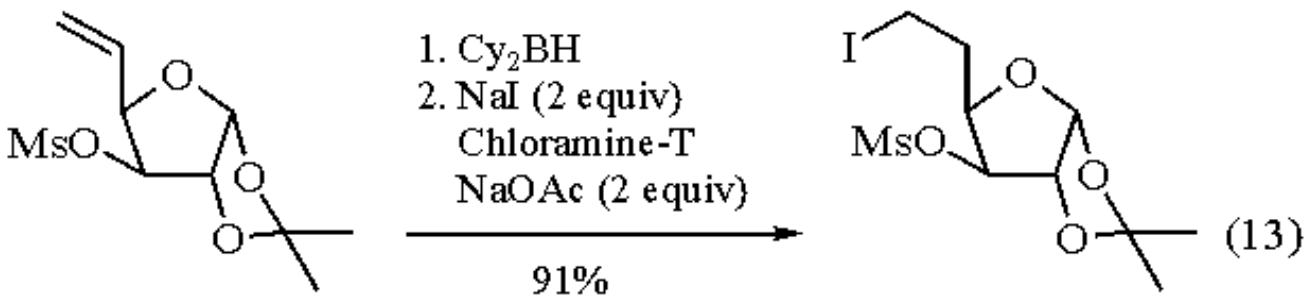

Related Reagents.

Sodium Iodide-Copper; ***Trifluoroacetic Anhydride-Sodium Iodide***.

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Sodium Iodide-Copper[1]

NaI/Cu

(NaI)

[7681-82-5] · INa · Sodium Iodide-Copper · (MW 149.89) (Cu)

[7440-50-8] · Cu · Sodium Iodide-Copper · (MW 63.55)

(mild two-electron reductant, capable of generating weakly electrophilic sodium oxyallyl cations from α,α´-dibromo ketones; capture of nucleophilic 1,3-dienes affords seven-membered unsaturated ketones)

Physical Data: NaI: mp 661 °C; bp 1304 °C; *d* 3.67 g cm^{-3}.

Solubility: NaI: sol water, alcohol, acetone, acetonitrile.

Form Supplied in: NaI: white odorless, deliquescent crystals or granules. *Drying:* sodium iodide (together with commercially available copper powder) is dried in a flame-dried reaction flask for 3 h at 150 °C under reduced pressure (oil pump).

Handling, Storage, and Precautions: NaI: gradually absorbs up to ca. 5% (0.5 mol) moisture when exposed to air. Slowly becomes brown in air due to liberation of iodine. Keep well closed and protected from light.

Sodium Oxyallyl Intermediates.

Sodium oxyallyl cations, conveniently generated from α,α´-dibromo ketones and anhydrous ***Sodium Iodide*** in the presence of ***Copper*** powder in anhydrous acetonitrile, are weak and selective electrophilic intermediates, which combine with nucleophilic 1,3-dienes to give 4-cycloheptenones. Iodide ion (2 equiv) functions as a two-electron reductant. Molecular iodine liberated during the reaction (eq 1) is removed efficiently by metallic copper powder (eq 2), while the reaction solution assumes a characteristic oatmeal color.[1-3]

$$2\,I^- \longrightarrow I_2 + 2\,e^- \qquad (1)$$

$$I_2 + 2\,Cu \longrightarrow 2\,CuI \qquad (2)$$

The mode of workup is important, in order to avoid decomposition of sensitive cycloadducts. The reaction mixture is cooled, and remaining copper and sodium salts are suction filtered. Filtration through silica gel is also helpful at this stage. Usually, the acetonitrile mother liquor (which can be concentrated further under reduced pressure at 0 °C) contains dissolved CuHal and is taken up in ice-cooled dichloromethane. The combined organic phase is washed with ice-cold ammonia, until the blue color disappears. (In aqueous solution, Cu^I disproportionates: 2 Cu^I -> Cu + Cu^{II}; the reaction is driven by complexation of Cu^{II} with NH_3). Standard workup (evaporation of solvent, chromatography on silica gel, and, in the case of the major α,α-configurated stereoisomer, crystallization) affords the oxa-bridged seven-membered ketone (eq 3).[2] Among cyclic dienes, ***Furan*** (bp 31 °C) is especially useful, because it can be used in excess without problems, serves as a solvent for the α,α´-dibromo ketone, and is removed easily on workup.

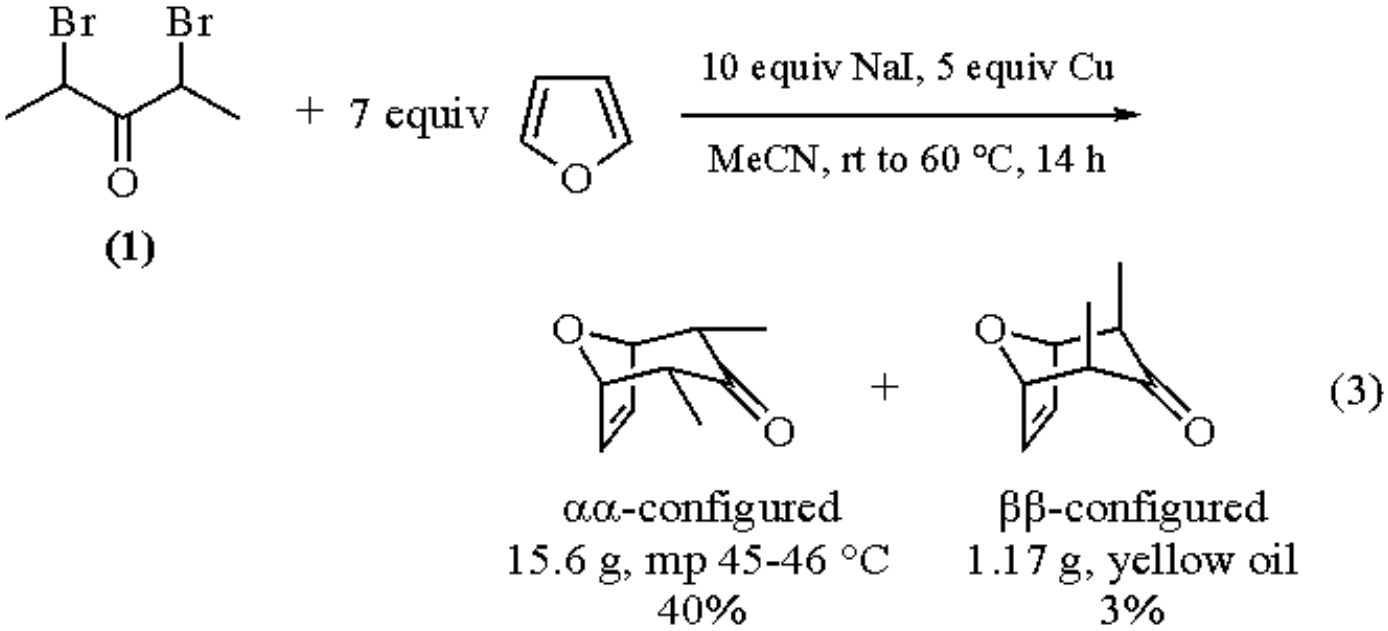

In place of furan (eq 3), other cyclic dienes have been reacted with ***2,4-Dibromo-3-pentanone*** (**1**), including ***Cyclopentadiene***, ***6,6-Dimethylfulvene***, and 6-acetoxyfulvene.[4] These give (**2**), (**3**), and (**4**), respectively; only the major stereoisomer with α,α-configured dimethyl groups is shown. The bicyclic dione (**5**), the hypothetical adduct of cyclopentadienone, has been prepared by hydrolysis and oxidation of 8-acetoxymethylene-2,4-dimethylbicyclo[3.2.1]oct-6-en-3-one (**4**) (eq 4)[4] (the minor stereoisomer is α,β-configurated in this case).

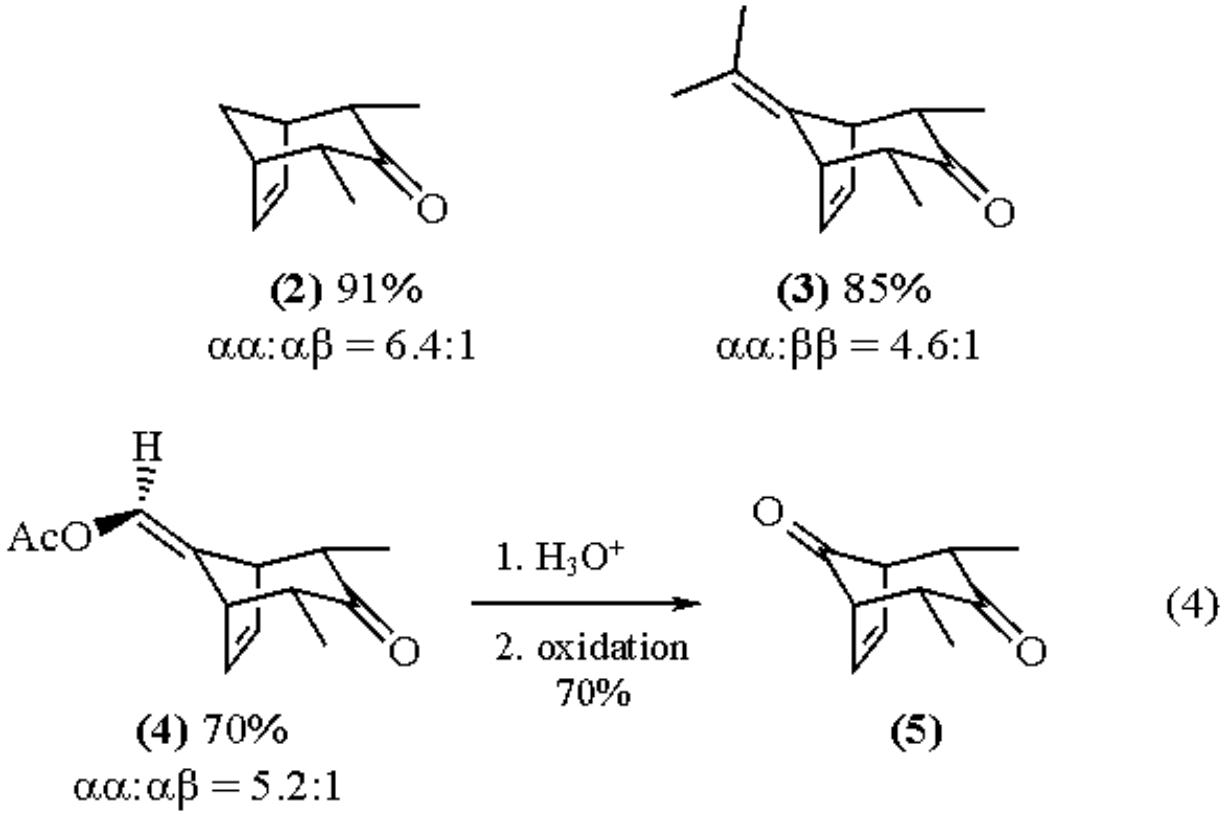

α-Alkylated 2,6-dibromocyclohexanones and NaI/Cu also enter into reductive intermolecular cyclodehalogenation, giving unsaturated tricyclic ketones.[5,6] The preparation of 1-isopropyl-7-methyl-11-oxatricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (**6**) from furan and α,α´-dibromomenthone has been optimized.[6,7]

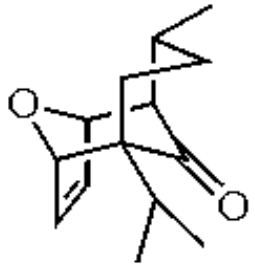

(6) 36%
5.5 g isolated

The reaction of dibromo ketones derived from (5*R*)- and (5*S*)-menthone affords enantiomerically pure tricyclic compounds (eqs 5 and 6).[3]

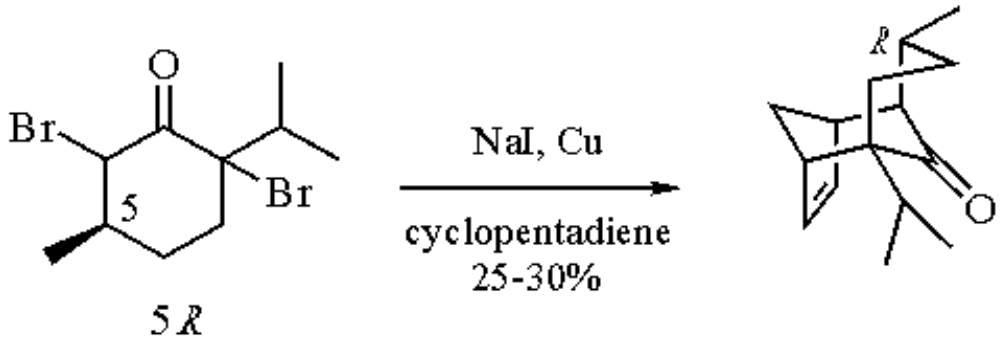

(5)

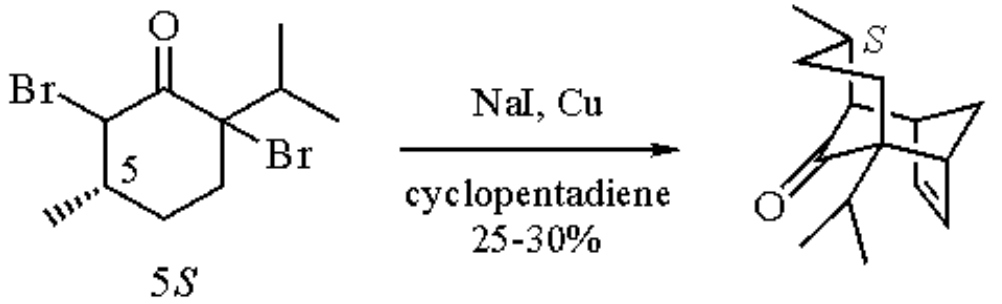

(6)

For cycloadditions with ***Cyclopentadiene***, it is advantageous to precool the cyclopentadiene to -78 °C and to add it slowly by syringe to the reaction mixture, synchronously with the α,α´-dibromo ketone which is added with another syringe.[5] Other tricyclic compounds (**7**) and (**8**) have been prepared in similar fashion.[5,7,8]

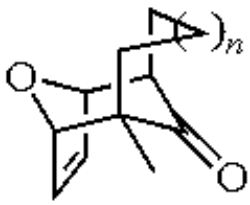

(7)
$n = 1$, 25%
$n = 2$, 21%
$n = 3$, 13%

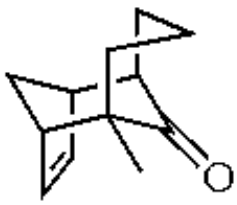

(8) 25%

The series of cycloadducts (**9**)-(**11**) derived from 2,6-dibromo-2,6-dimethylcyclohexanone is of interest, because the ketone is flanked by two quaternary carbon atoms.[5,6]

(9) 22%

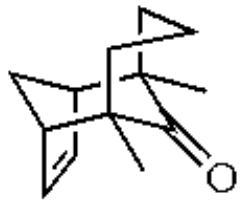

(10) 18%

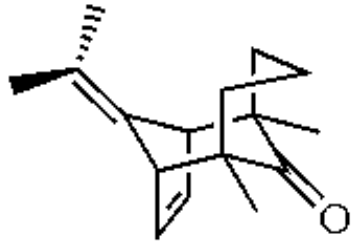

(11) 23%

Starting from the acyclic ditertiary dibromo ketone (**12**) and the secondary-tertiary dibromo ketone (**13**), the furan and cyclopentadiene adducts are accessible in good yield (eqs 7 and 8). In these cases the NaI/Cu procedure is the recommended alternative[9] to the ***Zinc/Copper Couple*** and the ***Nonacarbonyldiiron*** procedures, which have been used more frequently in the past.[3,10,11]

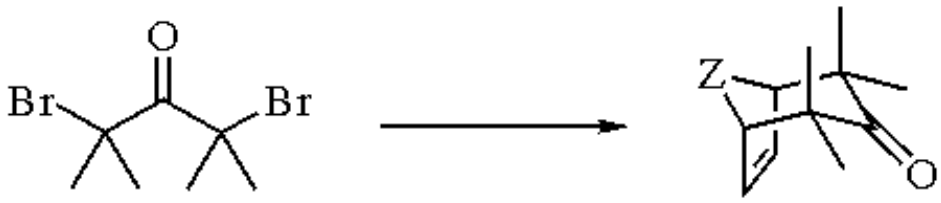

(7)

(12)

Z = O, 50%, 2.70 g
Z = CH_2, 37%, 1.98 g

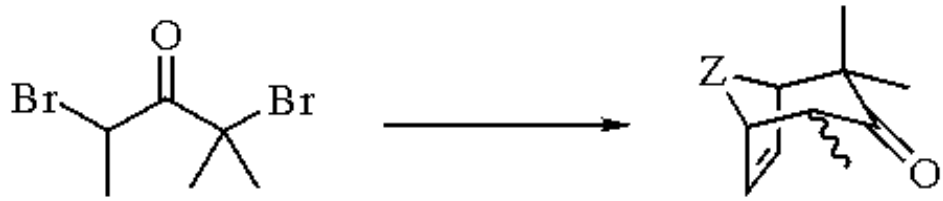

(8)

(13)

Z = O, 71%, 23.6 g; α:β = 5.25:1
Z = CH_2, 70%, 17.2 g; α:β = 19:1

Pyrroles and alkylated pyrroles afford unsaturated β-amino ketones (**14**)-(**16**) (bicyclic Mannich bases) in a simple one-pot procedure.[12,13] Temporary tethering of the sodium cation by the ethoxycarbonyl group of the pyrrole is thought to facilitate the formation of the azabicyclic compound (**16**), which has been obtained in high isolated yield.[13] From the point of view of substitution pattern, the oxyallyl cation route to 6,7-dehydrotropinones complements the well-known synthesis of the alkaloid (±)-tropinone (*N*-methyl-9-azabicyclo[3.2.1]octan-3-one) by Robinson[14a] and Schöpf.[14b,15]

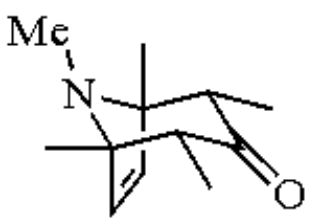

(14) 74%

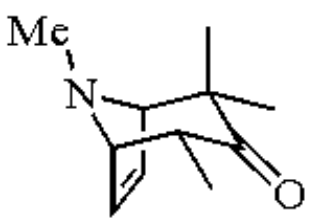

(15) 70%

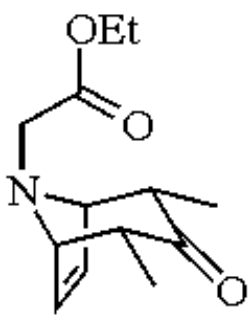

(16) 76%
1.65 g, mp 31-32 °C

Reaction of ***Isoprene*** with the isoprenoid primary-tertiary α,α´-dibromo ketone (**17**) affords monoterpenoid ethers on extractive workup. Claisen rearrangement of the major isomer at higher temperature (E_a = 33.6 kcal mol^{-1}) yields 2,2,4-trimethyl-4-cycloheptenone, while the minor ether gives karahanaenone (eq 9).[20a] The two isomeric seven-membered ketones are obtained directly and more easily from isoprene

and more electrophilic isoprenoid metal oxyallyl cation intermediates.[3,20b]

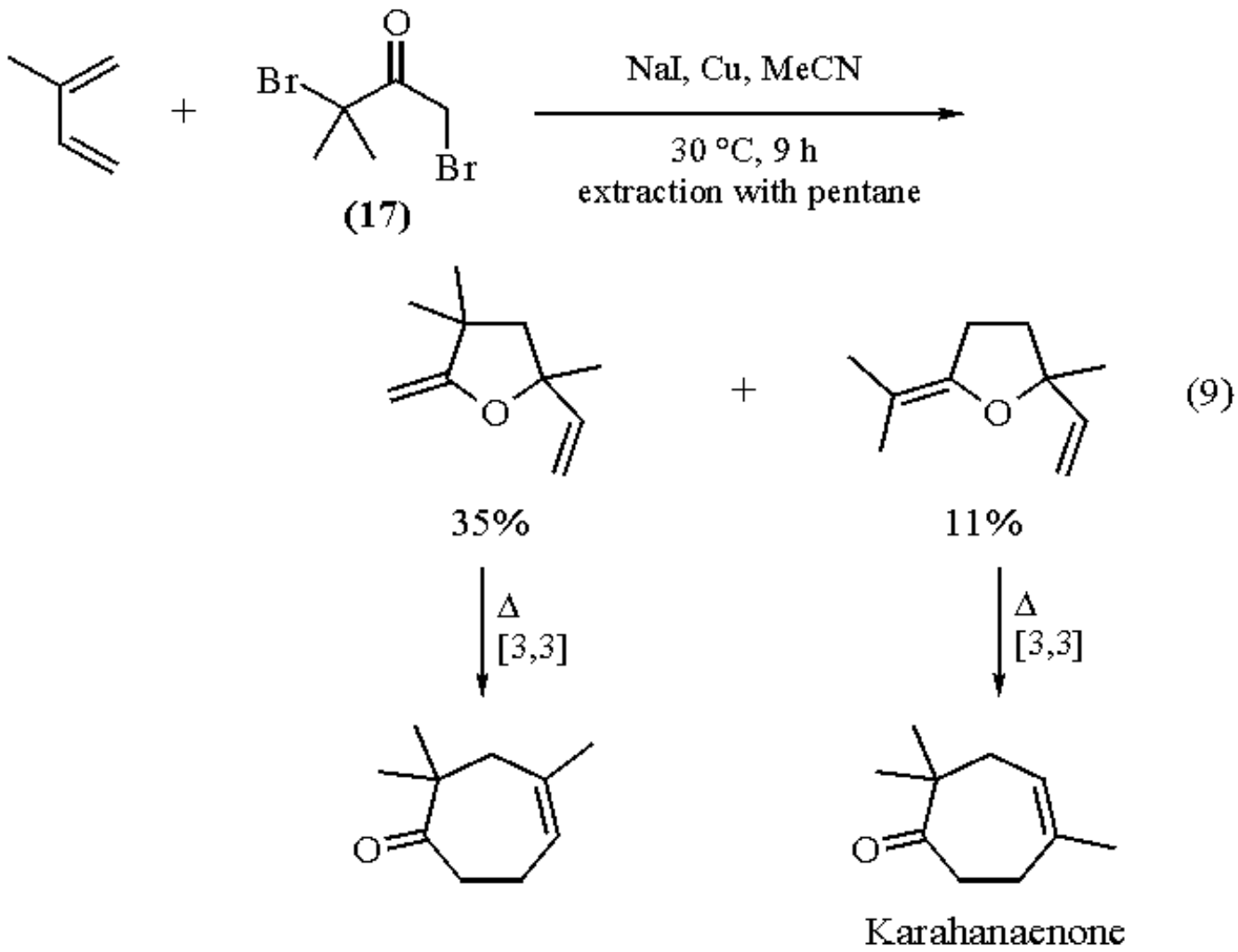

(9)

In summary, NaI/Cu in acetonitrile is a simple and inexpensive reagent that allows the generation of sodium oxyallyl cation intermediates from a number of α,α´-dibromo ketones, as exemplified by the disecondary (**1**), ditertiary (**12**), and secondary-tertiary (**13**) dibromo ketones. These intermediates have been trapped with nucleophilic dienes to give seven-membered rings. For structurally and electronically more demanding cycloadditions, other methods for generating allyl cations are required. Frequently, but not necessarily, a preformed allylic halide or ester, with a donor substituent at the central allyl carbon atom, is treated with a Lewis acid in the presence of the diene at low temperature.[21-24] In all cases, the electrophilicity of the allyl cation and, equally important, its hidden nucleophilicity (cf. stepwise class B reactions[3]) must be tailored carefully to match the reactivity of the diene.

Acyl Iodides and Related Derivatives.

Sodium iodide in acetonitrile (in the presence or absence of copper powder) is the reagent of choice for preparing acyl iodides from acyl chlorides (eq 10) A wide variety of acyl chlorides react in excellent yield, including sterically hindered pivaloyl chloride (80%), adamantanecarbonyl chloride (93%), and aromatic derivatives. The reaction is monitored by precipitation of sodium chloride. Acyl iodides are surprisingly lipophilic, due to the large iodine atom, and are isolated by continuous extraction from the mother liquor with pentane, using the low temperature reactor-extractor[25] (cf. eq 9). The structure of the acyl iodides is indicated by the diagnostic ^{13}C NMR upfield shift of the iodocarbonyl atom (heavy atom effect).[25]

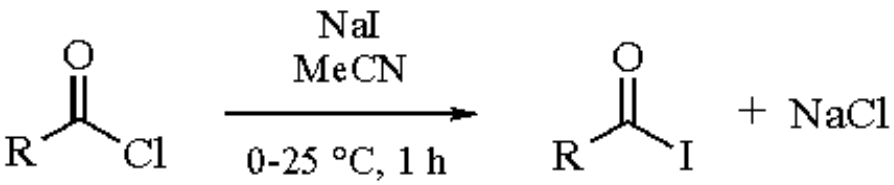

(10)

Using the same methodology, Hoffmann and his co-workers have also prepared dicarboxylic acid iodides. For example, hexanedioyl diiodide (from the dichloride of adipic acid) has been isolated as heavy, snow-white crystals by extraction into pentane. When exposed to air the compound is oxidized readily, first turning yellow and then brown with simultaneous fuming.[26] Under the same conditions,

chloroformates have been converted into iodoformic esters.[27]

---

1. Ashcroft, M. R.; Hoffmann, H. M. R. *OSC* **1988**, *6*, 512. The results shown (eq 3) correspond to scale-up by a factor of 2.5, using 256 mmol of 2,4-dibromo-3-pentanone: Nowakowski, M., unpublished results.
2. The β,β-adduct is the minor isomer (3%) in the NaI/Cu procedure. Using more electrophilic metal oxyallyl cation intermediates, one may increase the yield of this stereoisomer at the expense of the α,α-configured adduct. See Ref. 3, sections 4.2 and 4.3.
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14. Succinic dialdehyde, methylamine, and acetonedicarboxylic acid are condensed in biomimetic fashion: (a) Robinson, R. *JCS* **1917**, 762. (b) Schöpf, C.; Lehmann, G.; Arnold, W. *AG* **1937**, *50*, 783.
15. The parent 6,7-dehydrotropinone can be prepared with more electrophilic oxyallyl cation intermediates and an *N*-acceptor-substituted pyrrole, e.g. *N*-methoxycarbonylpyrrole.[10,16,17] Probably the method of choice for preparing parent [3.2.1]bicyclic ketones (from tetrabromoacetone) is the triethyl borate/zinc procedure.[18,19] Monoalkylated derivatives are available by the same procedure.[18]
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20. (a) Chidgey, R.; Hoffmann, H. M. R. *TL* **1978**, 1001. (b) Chidgey, R.; Hoffmann, H. M. R. *TL* **1977**, 2633.
21. For example: (a) Hoffmann, H. M. R.; Matthei, J. *CB* **1980**, *113*, 3837. (b) Henning, R.; Hoffmann, H. M. R. *TL* **1982**, *23*, 2305. (c) Hoffmann, H. M. R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *T* **1988**, *44*, 3899.
22. (a) Kaiser, R.; Föhlisch, B. *HCA* **1990**, *73*, 1504. (b) Föhlisch, B.; Herter, R. *CB* **1984**, *117*, 2580.
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Sodium Pentacarbonylmanganate[1,2]

$NaMn(CO)_5$

[$NaMn(CO)_5$]

[13859-41-1] · C_5MnNaO_5 · Sodium Pentacarbonylmanganate · (MW 217.98) [$LiMn(CO)_5$]

[15689-01-7] · C_5LiMnO_5 · Lithium Pentacarbonylmanganate · (MW 201.93) [$(Ph_3P)_2N$][$Mn(CO)_5$]

[52542-59-3] · $C_{41}H_{30}MnNO_5P_2$ · Bis(triphenylphosphoranylidene)ammonium Pentacarbonylmanganate · (MW 733.60) [$Mn(CO)_5$]$^-$

[14971-26-7]

(strong nucleophile for the preparation of alkyl-, acyl-, and silylmanganese compounds[1,2])

Physical Data: gray or white powder when dried; usually prepared and used as cloudy gray-green solution in THF.

Solubility: Na, K, and Li salts: sol THF. PPN salt: very sol THF, CH_2Cl_2; sparingly sol benzene, diethyl ether; insol hexane.

Form Supplied in: not commercially available

Analysis of Reagent Purity: IR: M[$Mn(CO)_5$][3,4] (M = Na, Li, K; THF, cm^{-1}) 1897 ± 1 (s), 1862 ± 1 (s). PPN[$Mn(CO)_5$][5] (nujol, cm^{-1}) 1892 (s), 1856 (s), 1839 (m).

Preparative Methods: reduction of ***Decacarbonyldimanganese*** with ***Sodium Amalgam*** in THF (eq 1);[6-8] the resulting solution is contaminated with approximately 10% $(CO)_5Mn$-Hg-$Mn(CO)_5$.[7] Use of ***Sodium-Potassium Alloy*** ($NaK_{2.8}$) provides mostly K[$Mn(CO)_5$].[4] Treatment of $Mn_2(CO)_{10}$ with 2.5 equiv ***Lithium Triethylborohydride*** in THF affords clean Li[$Mn(CO)_5$] (eq 2).[3] The potassium salt may be prepared similarly with ***Potassium Tri-s-butylborohydride*** (eq 3).[3]

$$Mn_2(CO)_{10} + 2\ Na/Hg \xrightarrow{THF,\ rt} Na[Mn(CO)_5] \qquad (1)$$

$$Mn_2(CO)_{10} + 2.5\ LiBEt_3H \xrightarrow{THF,\ 0\ ^\circ C} Li[Mn(CO)_5] \qquad (2)$$

$$Mn_2(CO)_{10} + 2.5\ KB(s\text{-}Bu)_3H \xrightarrow{THF,\ 0\ ^\circ C} K[Mn(CO)_5] \qquad (3)$$

Purification: usually used without purification; the PPN salt (PPN = $[(Ph_3P)_2N]^+$) may be obtained as large yellow crystals by treatment with PPNCl and recrystallization from THF and petroleum ether.[3-5]

Handling, Storage, and Precautions: solutions of the pentacarbonylmanganate anion decompose rapidly upon exposure to air or moisture, and are usually used immediately after generation. The PPN salt may be handled in air in the solid state, but darkens after several days exposure. Use in a fume hood.

Reactions with Electrophiles.

$[Mn(CO)_5]^-$ is highly nucleophilic, reacting at the metal center with a variety of electrophiles (eq 4). Most important are reactions with

alkyl, acyl, and silyl halides,[1-3,9-11] giving organomanganese complexes that undergo subsequent insertion or decarbonylation reactions (see also ***Pentacarbonylmethylmanganese***, ***Pentacarbonylphenylmanganese***, and ***Pentacarbonyl(trimethylsilyl)manganese***). $[Mn(CO)_5]^-$ also reacts cleanly with elemental iodine,[6] Sn and Ge halides,[5] $TlNO_3$ (giving $Tl[Mn(CO)_5]_3$),[12] and strongly electron-deficient vinyl halides.[13,14]

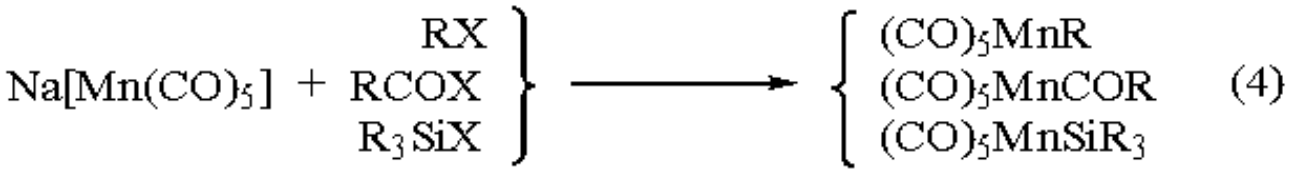

Generation of Ketenes.

Reaction of α-bromoacyl halides with $[PPN][Mn(CO)_5]$ in chloroform comprises a convenient method for the generation of pure solutions of ketenes (eq 5).[15]

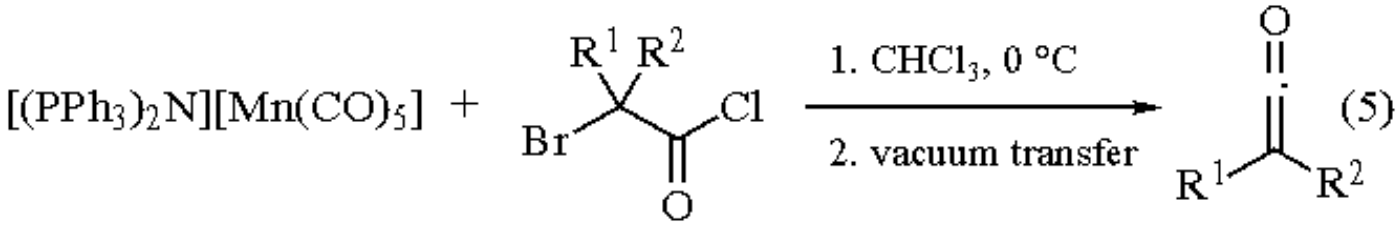

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Sodium Methoxide

NaOMe

[124-41-4] · CH_3NaO · Sodium Methoxide · (MW 54.03)

(highly basic solid capable of catalyzing numerous reactions, including condensations, dehydrohalogenations, and other base-catalyzed mechanisms; also acts as a nucleophile in S_N2 and S_NAr reactions)

Physical Data: mp >300 °C.

Solubility: sol methanol, ethanol, pentane, and DMSO, as well as a wide variety of other solvents; insol hydrocarbon solvents.

Form Supplied in: widely available commercially as a free flowing white powder of 95% purity.

Handling, Storage, and Precautions: flammable solid which spontaneously combusts at 70-80 °C; corrosive; sensitive to and may decompose upon contact with air and moisture; harmful if swallowed, inhaled, or absorbed through the skin; store in a cool, dry place. Capable of creating a dust explosion; keep away from heat, sparks, and flame; incompatible with chlorinated solvents; reacts violently with water and acids.

Basicity of Sodium Methoxide.

The basicity of sodium methoxide is highly dependent on the solvent medium. Solvation and separation of the sodium cation from the methoxide anion affects base strength,[1] as does the degree of hydrogen bonding between the solvent and methoxide ion. Base strength and rates of base-catalyzed reactions may increase by several orders of magnitude in going from a polar protic solvent like methanol to a polar aprotic solvent like DMSO[1,2] (see ***Potassium Methoxide-Dimethyl Sulfoxide***). In comparison to other metalmethoxides, the basicity of sodium methoxide in methanol is greater than that of lithium methoxide but less than that of potassium methoxide.[3] The same basicity order has also been found for solutions of the metal methoxides in DMSO.[1]

Uses as a Base.

Sodium methoxide is the preferred base in the Kolbe electrolytic coupling reaction in methanol.[4] Methoxide ion is generated at the cathode, so only catalytic amounts of NaOMe are required.[5] Sodium methoxide is the preferred base here because of its low cost and the low cost of methanol from which the methoxide is regenerated. Tashiro and co-workers[6] have used the Kolbe electrolysis to synthesize 4-phenylbutyric acid (eq 1). Sodium methoxide has also found use as the preferred base for forming dichlorocarbene from ***Ethyl Trichloroacetate***.[4] An example is the reaction with dihydropyran (eq 2).[7]

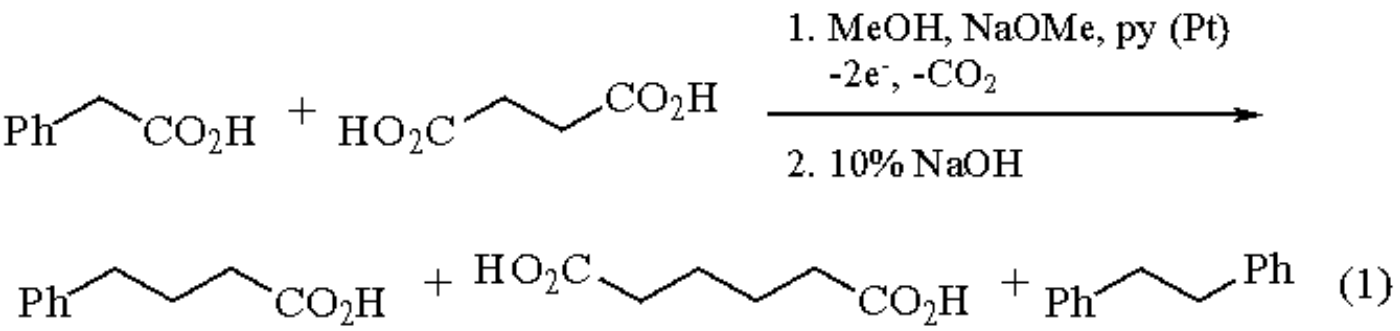

(1)

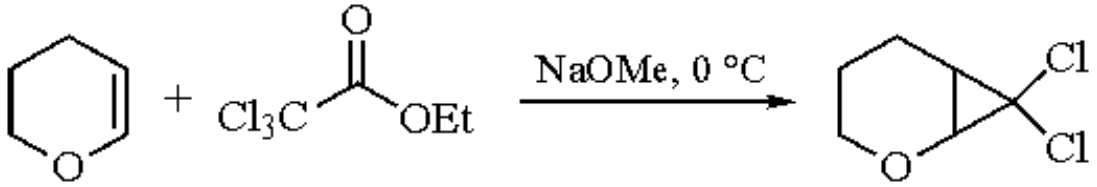

(2)

As a base, sodium methoxide may also perform dehydrohalogenation reactions. Benzalacetophenone dibromide may be treated in this way with sodium methoxide (eq 3).[8] The mechanism of this reaction involves first the nucleophilic displacement of bromide,[4] followed by E2 elimination.[4] Acid hydrolysis then gives dibenzoylmethane.[8] Sodium methoxide also catalyzes the Favorskii rearrangement (eq 4). The first step of the reaction is dehydrochlorination, followed by S_N2 attack of methoxide on the bicyclic intermediate.[9] These examples illustrate one drawback of using sodium methoxide as a base for dehydrohalogenation, namely that NaOMe may also act as a nucleophile, often causing a competition between E2 and S_N2 reactions. Sodium methoxide is not as efficient for E2 reactions as a sterically bulky base might be (see ***Potassium t-Butoxide***).

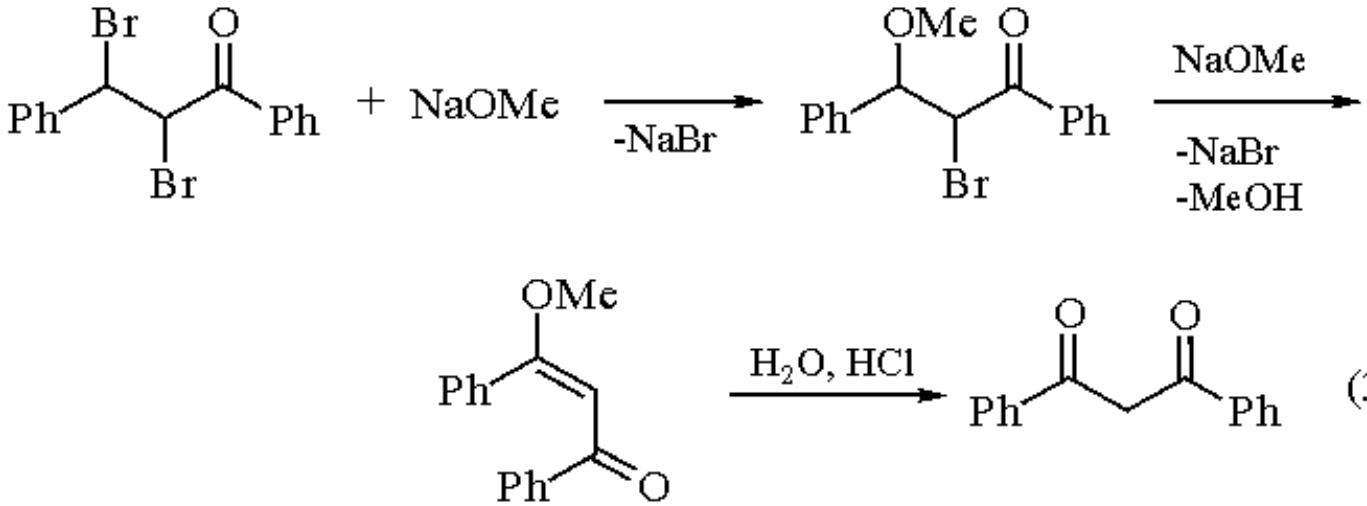

(3)

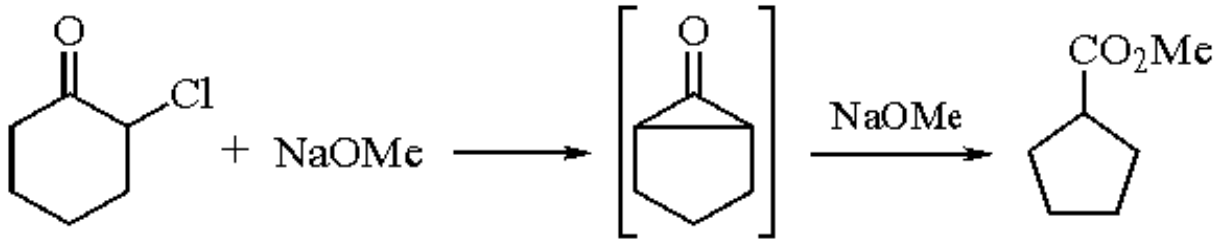

(4)

Sodium methoxide is a basic condensation catalyst typically employed in the aldol condensation reaction as a means of generating the enolate (eq 5).[10] Metal hydroxides do not have sufficient base strength to convert a substantial fraction of the aldehyde or ketone to the enolate, so the equilibrium lies far to the left.[10] For condensation reactions that are difficult to drive forward, as in the condensation of ketones, a stronger base must be used, such as ***Lithium Diisopropylamide***. Although NaOMe is not as strong as LDA in generating the enolate, it has the advantages of lower cost, longer shelf life, and ease of handling, storage, and preparation.[10] It is also used in the Robinson annulation reaction (eq 6).[10] Sodium methoxide has been used to catalyze the condensation of γ-butyrolactone as the first step in the synthesis of dicyclopropyl ketone (eq 7).[11]

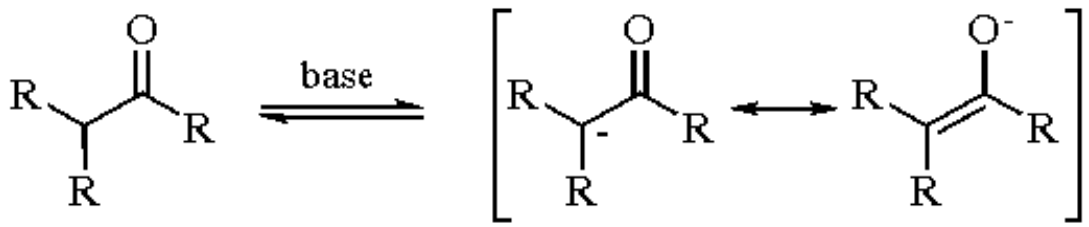

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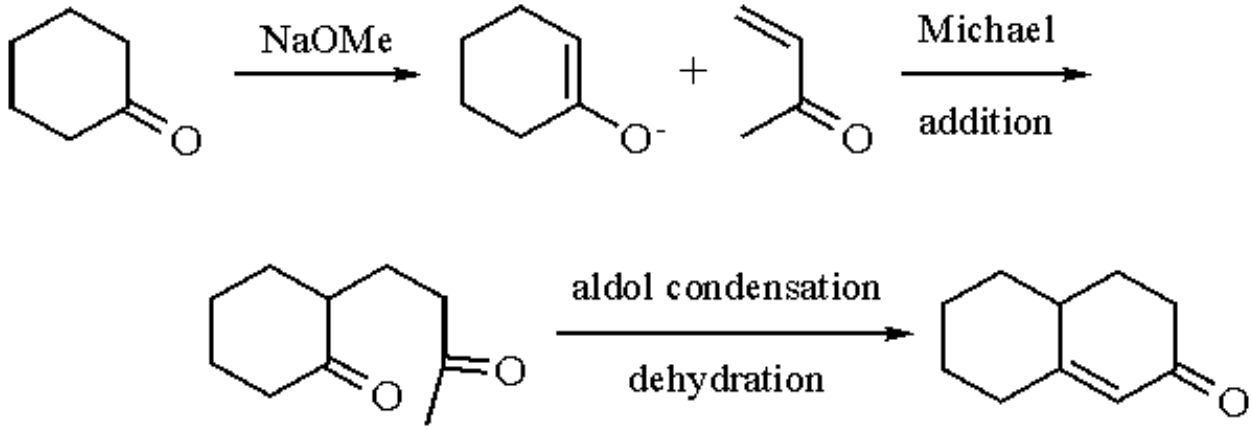

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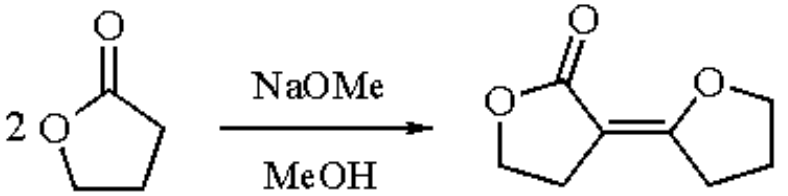

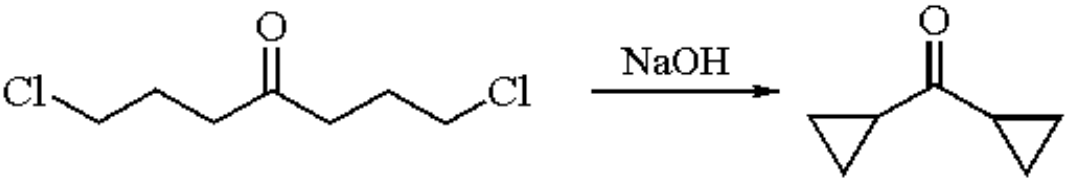

(7)

Seus and Wilson have used sodium methoxide as the basic catalyst for synthesis of stilbene, 2-stilbazole, 2-styrylfuran, and 2-styrylthiophene (eq 8).[12] This method of synthesis provides good yields (75-85%) of the *trans*-alkenes, and is a more convenient procedure than the Wittig alkene synthesis.[12] Sodium methoxide has also been used to condense methyl *N,N*-dimethylsebacamate to give *N,N,N´,N´*-tetramethyl-9-methoxycarbonyl-10-oxononadecanediamide, which, after further processing, yields nonadecanoic acid (eq 9).[13]

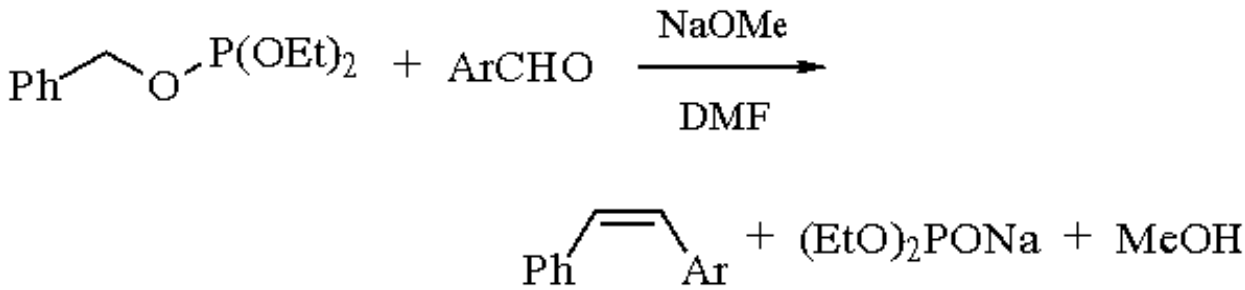

(8)

Ar = Ph, 2-pyridyl, 2-furyl, 2-thienyl

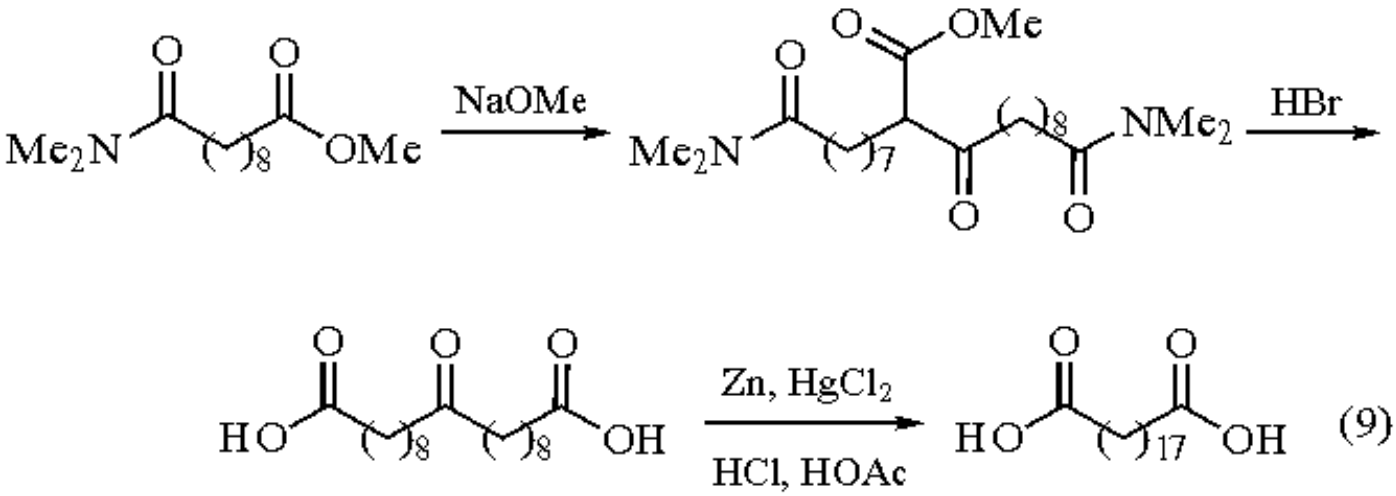

(9)

Sodium methoxide has found use as a condensation catalyst for a particularly interesting category of reactions, namely the synthesis of various heterocycles.[4] For example, 2-amino-4-anilino-6-chloromethyltriazine may be synthesized from phenylbiguanide hydrochloride and ethyl chloroacetate in one step (eq 10).[14] Also, 2-thio-6-methyluracil may be synthesized in a similar reaction from ***Ethyl Acetoacetate*** and ***Thiourea*** (eq 11).[15] A final example is the condensation of ***Urea*** and ***Diethyl Oxalate*** to generate parabanic acid (eq 12).[16]

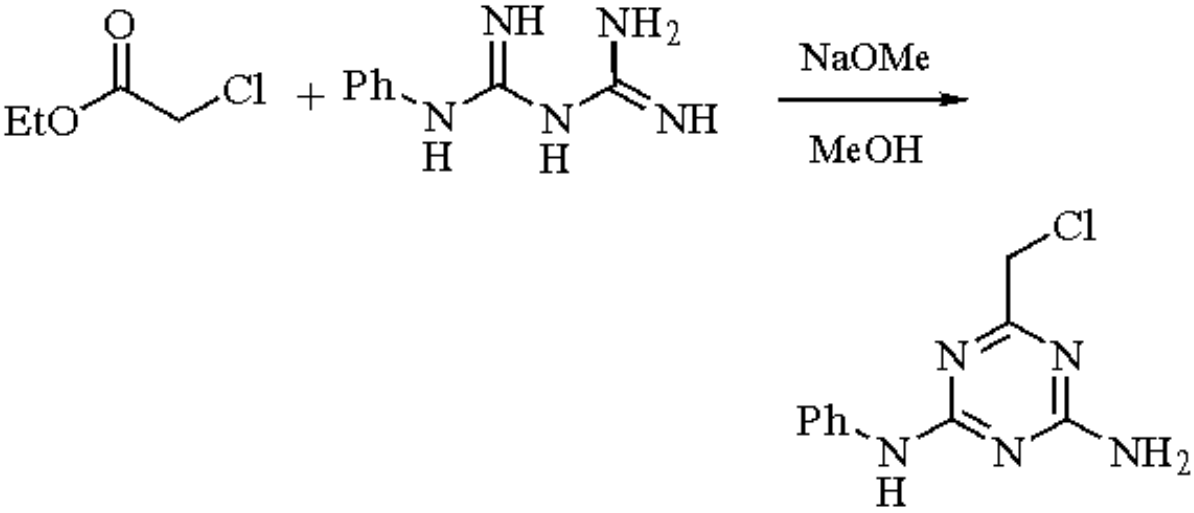

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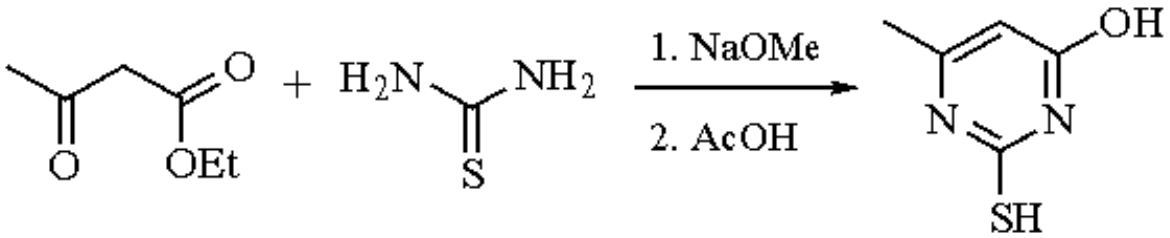

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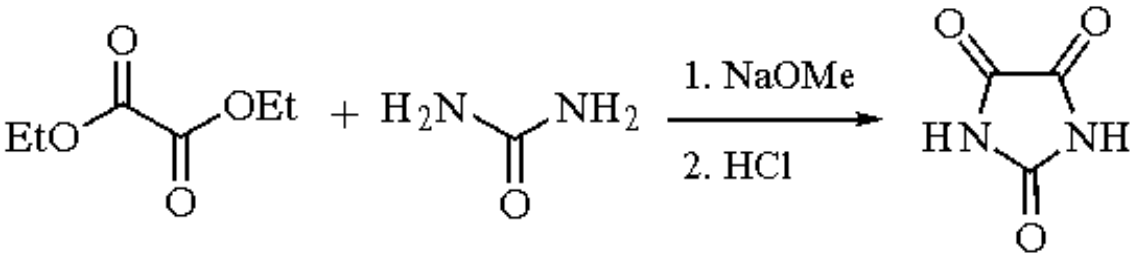

(12)

Carbanion Formation.

Sodium methoxide is also useful for generating carbanions. The synthesis of anthraquinones provides an example (eq 13).[17] Sodium methoxide in HMPA is also capable of cleaving carbon-silicon bonds, resulting in a carbanion (eq 14) that is useful in the synthesis of alkenes.[18] When the carbanion is reacted with a carbonyl compound, the alkene results (eq 15).

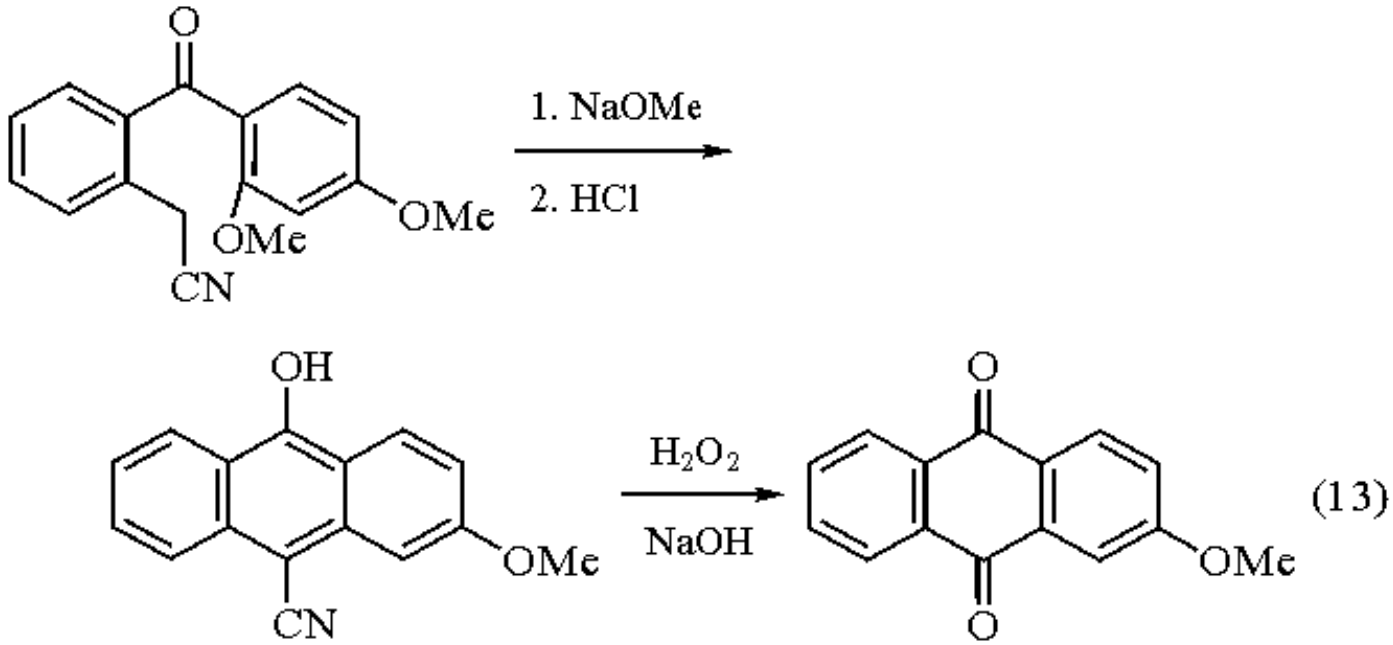

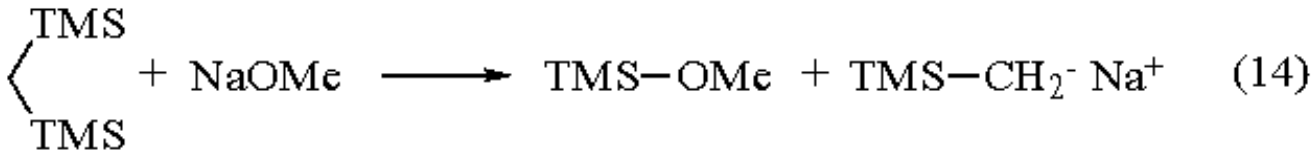

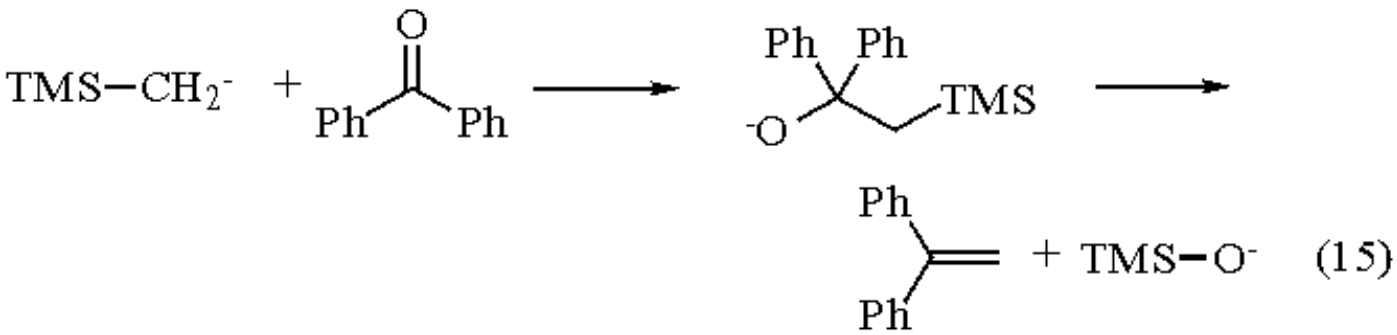

Nucleophile.

Sodium methoxide solvates to produce a relatively small nucleophile. As previously shown, it may displace halogens from an sp^3 carbon in a typical S_N2 reaction. A wide variety of such methoxylations are possible.[19] One interesting use of sodium methoxide as a nucleophile is in the synthesis of secondary amines from aminosilanes.[20] Typical methods of secondary amine synthesis involve reaction of ammonia or a primary amine with an alkyl halide. This method, however, is not highly selective since the alkylation of the ammonia or amine will not stop at the secondary amine stage and will proceed to yield tertiary amines. Ando and Tsumaki have reported a simple and selective synthesis of secondary amines[20] in which nucleophilic attack of methoxide on the silicon atom of the aminosilane is the first step (eq 16), followed by nucleophilic attack of the amide anion on the alkyl halide of choice (eq 17).

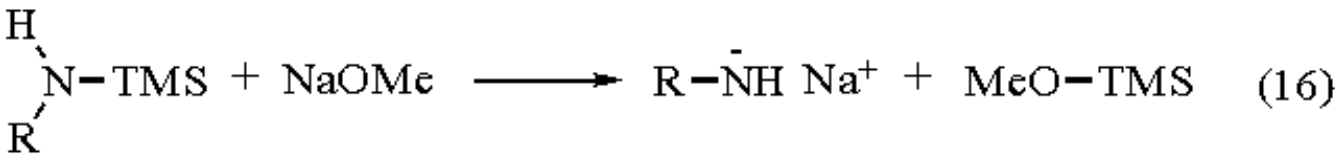

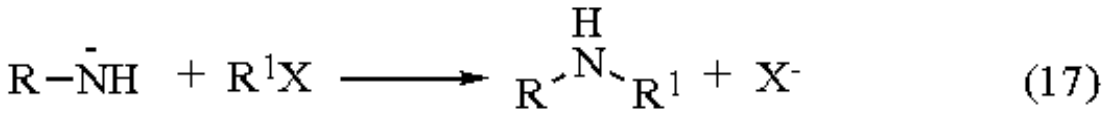

Sodium methoxide is also used as a nucleophile in the simple and efficient synthesis of phloroglucinol from 1,3,5-tribromobenzene (eq 18).[21] Nucleophilic attack of methoxide proceeds by an S_NAr mechanism, and the trimethoxybenzene is then hydrolyzed to give a high yield (~80%) of phloroglucinol.[21] This method has the advantage over the old synthesis in that only two steps are required and no toxic

wastes are produced. Sodium methoxide may also be employed in nucleophilic aromatic substitution reactions to synthesize phenols, anisoles, and methoxyphenols from unactivated aryl halides (eq 19)[22] or 3,5-dinitroanisole from 1,3,5-trinitrobenzene (eq 20).[23]

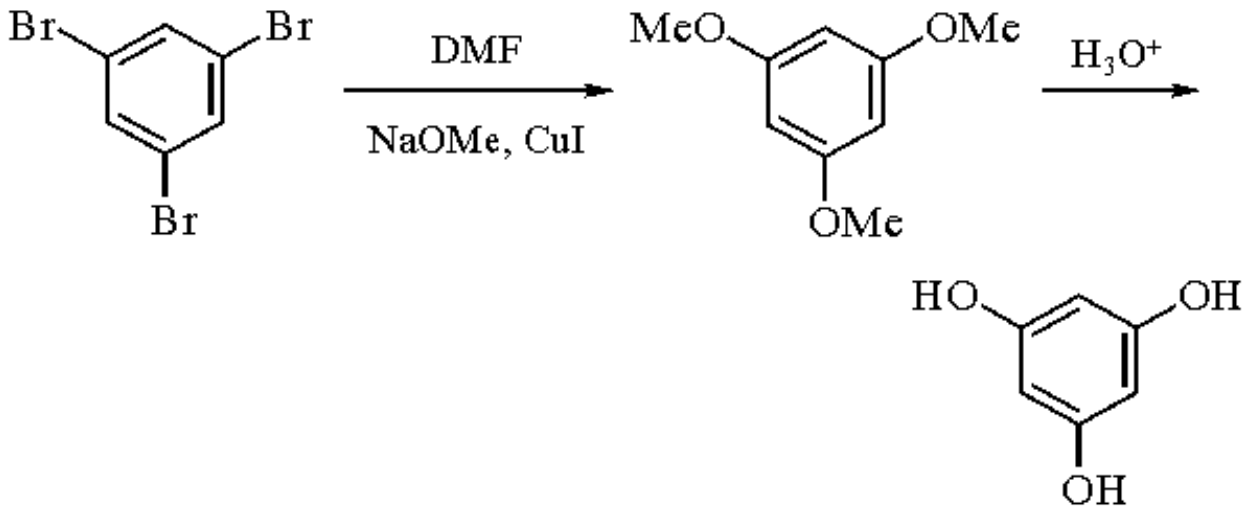

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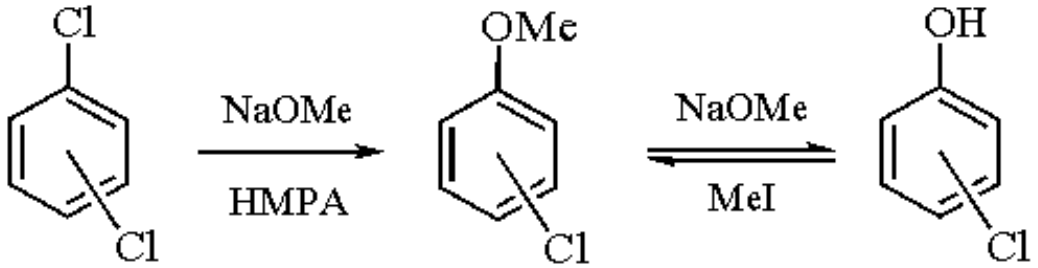

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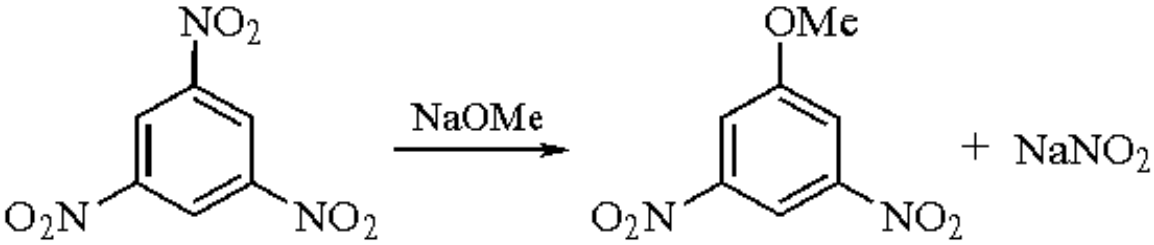

(20)

Other Reactions.

Sodium methoxide may be used to perform selective dealkylation of bis(alkylthio)benzenes.[24,25] Depending on whether sodium methoxide or sodium methanethiolate is used, removal of either the more branched or the less branched alkyl group is possible. If sodium methanethiolate is used, then the less highly substituted alkyl group is eliminated (eq 21). The postulated mechanism[24] for this involves the methanethiolate anion (which is a much better nucleophile than the methoxide anion) attacking the less highly substituted alkyl group in an S_N2 reaction to displace the substituted phenyl group.[24] If sodium methoxide is used, however, then the more highly substituted alkyl group is removed in an elimination reaction, which produces propene and the thiolate with the less substituted alkyl group (eq 22).[24] The reaction may be performed in HMPA[24] or DMF.[25]

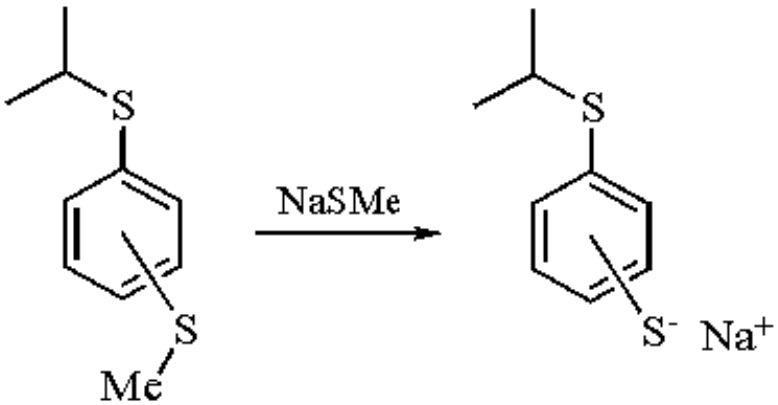

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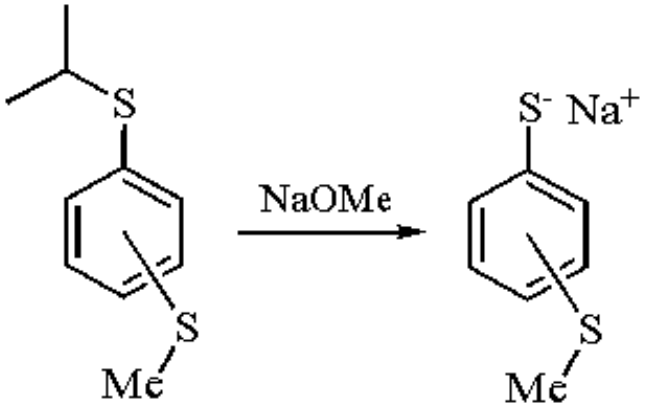

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Another interesting reaction performed by sodium methoxide is the methylation of fluorene. Heating a mixture of fluorene, methanol, and sodium methoxide together in a bomb results in the formation of 9-methylfluorene (eq 23).[26]

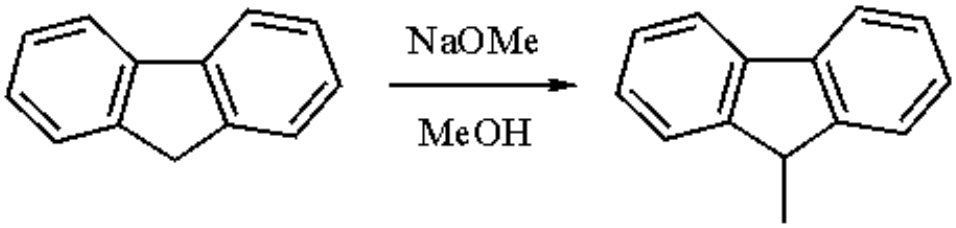

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Sodium Methylsulfinylmethylide[1]

NaDMSO

[15590-23-5] · C_2H_5NaOS · Sodium Methylsulfinylmethylide · (MW 100.13)

(strong base and nucleophile; very useful for the introduction of the methylsulfinylmethyl group[1])

Alternate Names: sodium dimsylate; dimsylsodium.

Solubility: sol DMSO.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: titration with formanilide using triphenylmethane as indicator.[2]

Preparative Method: prepared by the reaction of ***Sodium Hydride*** with ***Dimethyl Sulfoxide*** for 1 h at 70 °C. ***Sodium Amide*** may also be used as base.[3]

Handling, Storage, and Precautions: this reagent is not exceptionally stable over long periods of time. Modifications in preparation and storage have led to an increased shelf life.[4] However, it is probably best prepared as needed and used quickly. Hydrogen is emitted during the preparation of this reagent and decomposition occurs at elevated temperatures.[5] Due caution should be exercised in the preparation, particularly on a large scale. Reports have been made of explosions during the large scale preparation of this reagent or its attempted isolation.[1,6]

Introduction.

The pK_a of DMSO is 35. Consequently, one might expect its conjugate base to be a potent Brønsted base and this is indeed the case. In addition to the sodium salt, both the lithium and potassium salts of DMSO have found widespread use in synthesis (see ***Lithium Methylsulfinylmethylide*** and ***Potassium Methylsulfinylmethylide***). After its introduction by Corey,[2] explorations of the chemistry of sodium methylsulfinylmethylide (NaDMSO) blossomed and are summarized nicely in two reviews.[1]

Sodium Methylsulfinylmethylide as Base.

Generation of Ylides.

NaDMSO as a solution in DMSO has been used extensively in the preparation of phosphorus and sulfur ylides.[1,7,8] This medium is often the one of choice for the generation and reaction of Wittig reagents (eq 1).[7,9] A less common application of Wittig reagents generated with NaDMSO is in an oxidative coupling of a bis-ylide to form a cyclic alkene (eq 2).[10]

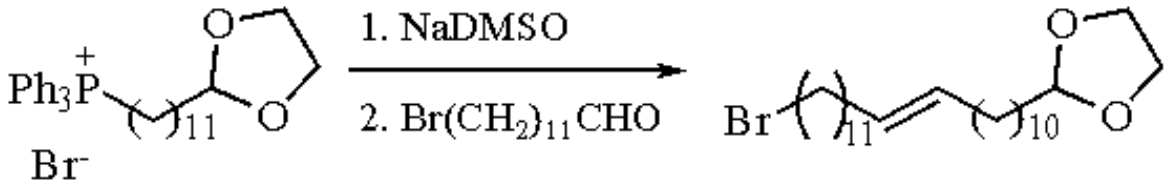

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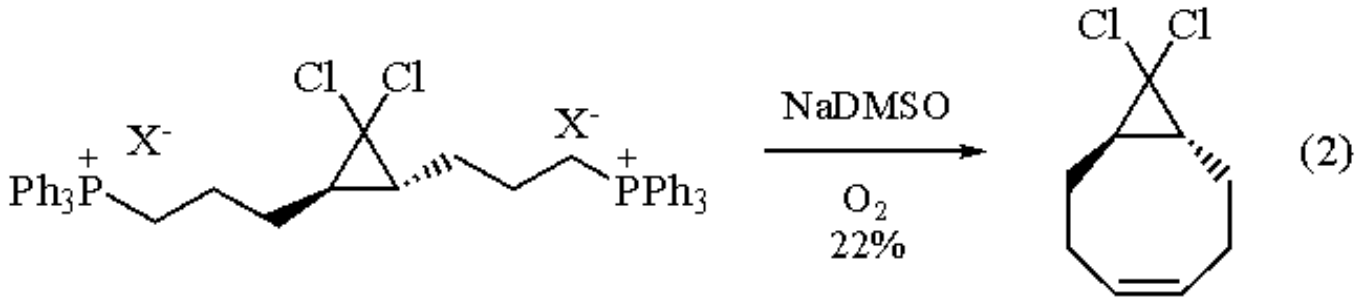

The methylene transfer reagents ***Dimethylsulfonium Methylide*** and ***Dimethylsulfoxonium Methylide*** are conveniently generated with NaDMSO in DMSO.[11] These and other sulfonium ylides are useful in the synthesis of epoxides and cyclopropanes (eqs 3 and 4).[8,11] Also intriguing is the use of dimethyloxosulfoxonium methylide to give dienes (eq 5).[12]

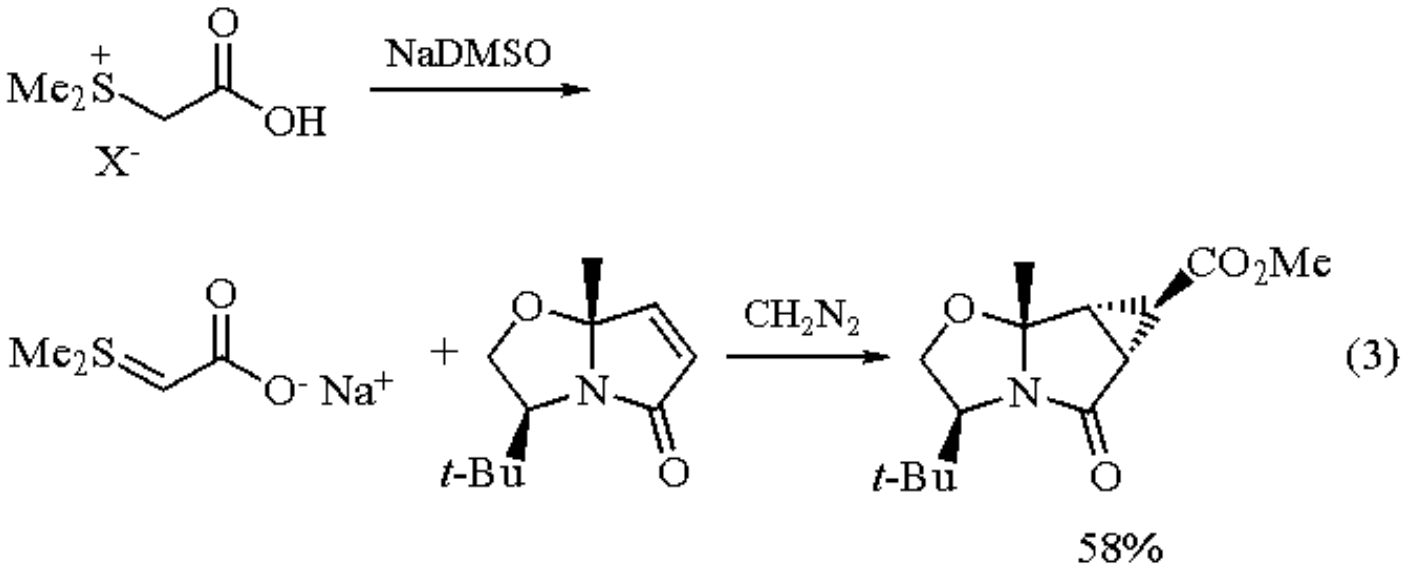

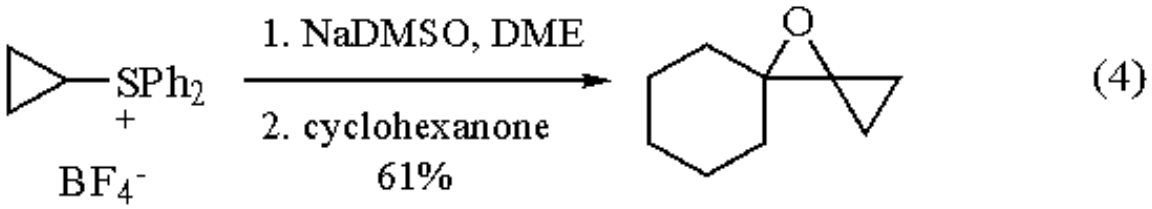

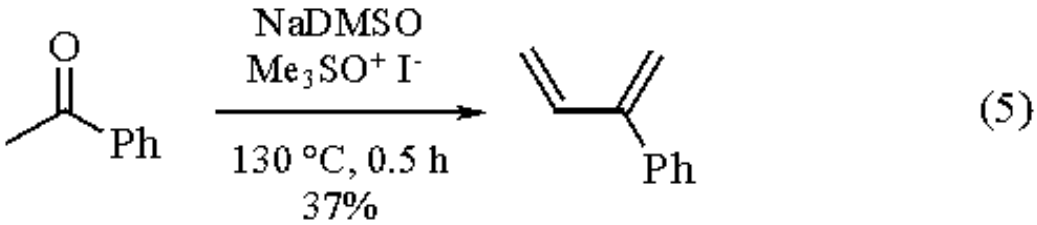

Diaminosulfonium salts can be deprotonated with NaDMSO to give rearrangement products or epoxides upon reaction with aldehydes (eq 6).[13] A variety of ammonium ylides have been generated using NaDMSO.[14,15] These species are disposed to undergo Wittig, Stevens, or Sommelet-Hauser rearrangements, depending on their specific constitution (eqs 7 and 8). Changes in base and other reaction conditions can change product distributions.[14a,b]

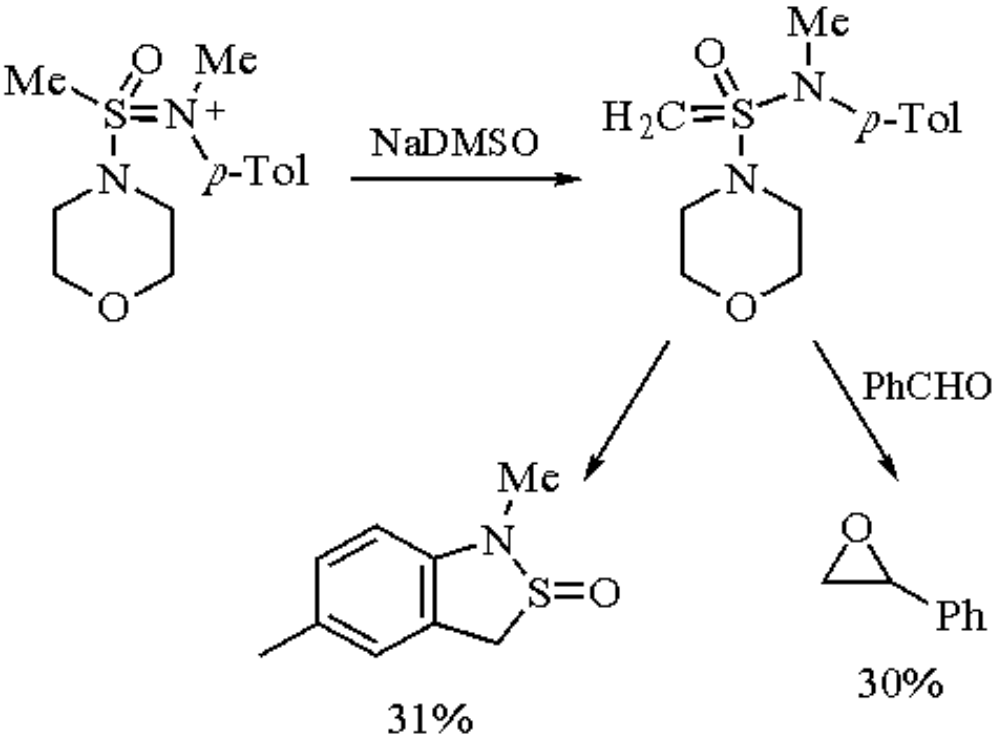

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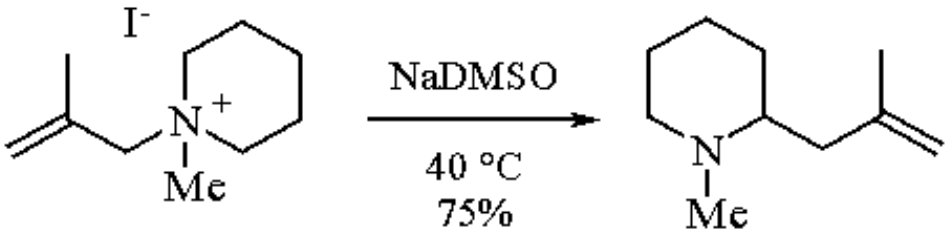

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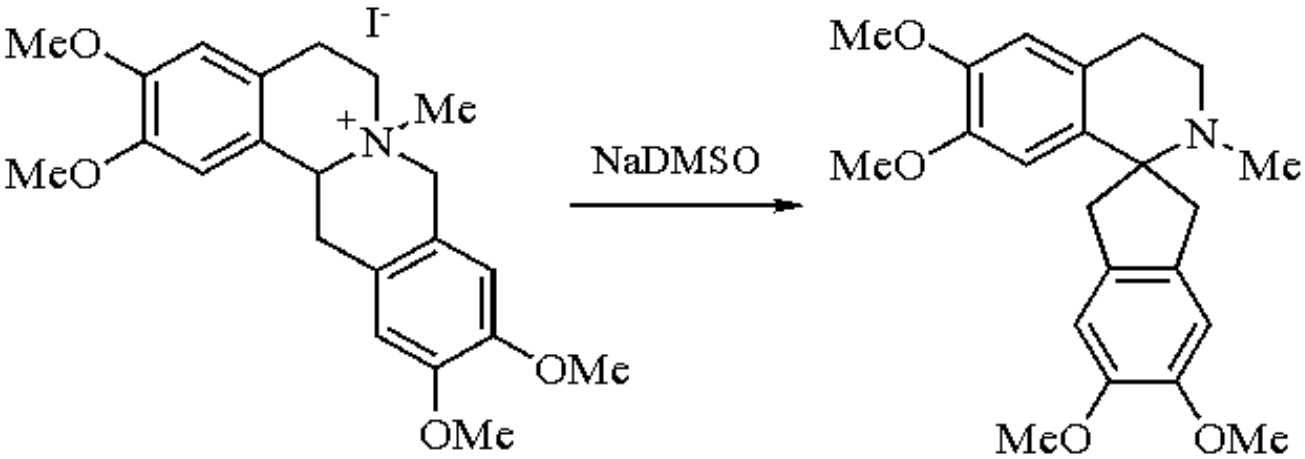

(8)

Eliminations.

Elimination reactions using NaDMSO have apparently not been extensively investigated, although the use of metal alkoxides in DMSO has received considerable attention.[16] Whether the active agent in such mixtures is NaDMSO is not clear. Eliminations clearly mediated by NaDMSO are known.[17] For example, treatment of (**1**) with NaDMSO at 25 °C gives the elimination product (**2**) in 91% yield (eq 9).[17a] Longer reaction times result in addition of DMSO to the newly formed double bond. Heating results in isolation of a dealkylation product (**4**), a clear example of the diverse reactivity associated with NaDMSO. Alkynes are generated by the reaction of 1,2-dibromoalkanes with excess NaDMSO.[18] Aryl halides can give benzynes in the presence of NaDMSO (eq 10).[19] Further, addition of DMSO is possible, leading to a unique mode of functionalization (eq 11).[19c]

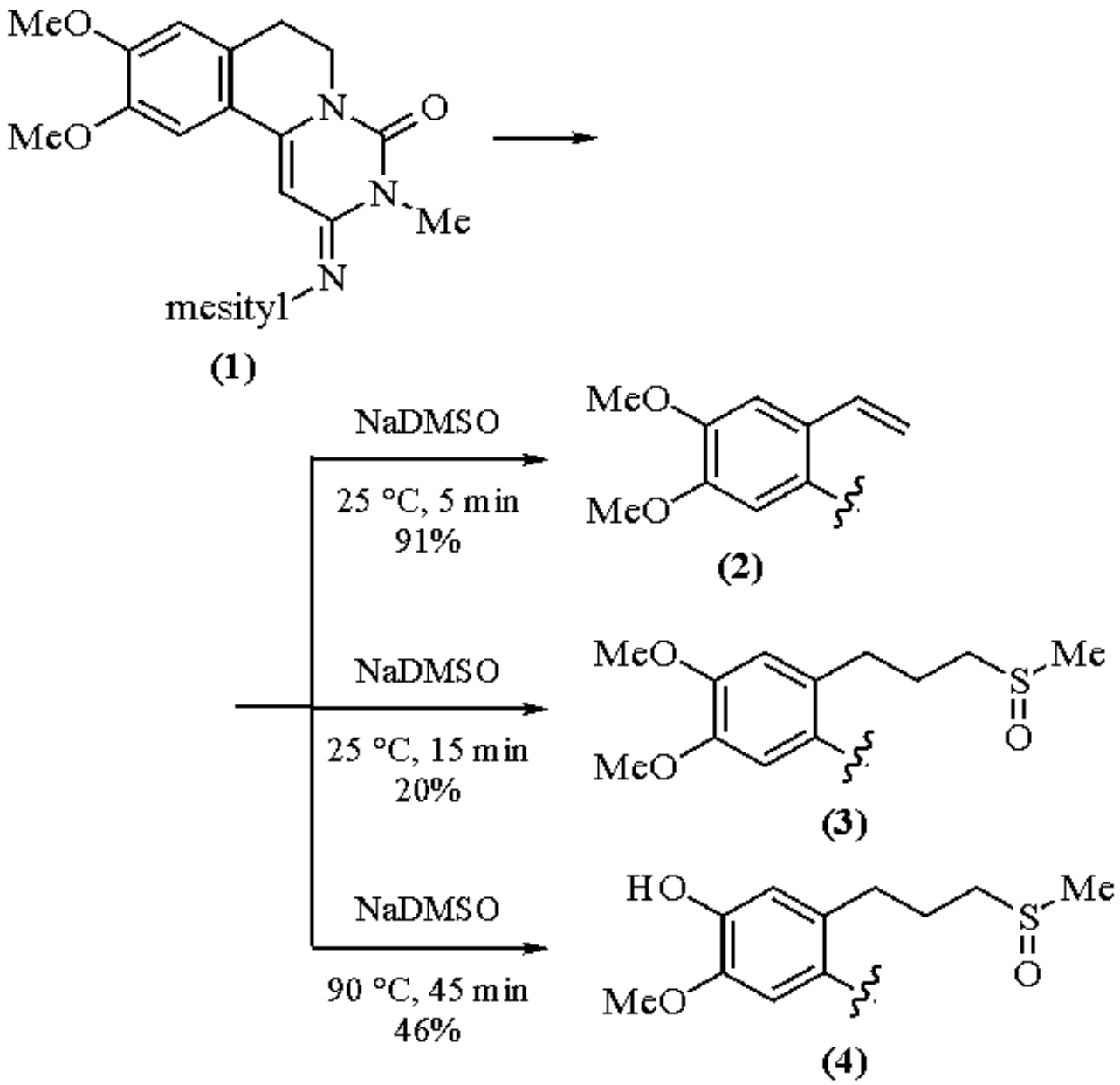
MeO
MeO
N
O
N
Me
N
mesityl
(1)
NaDMSO
25 °C, 5 min
91%
MeO
MeO
(2)
NaDMSO
25 °C, 15 min
20%
MeO
MeO
S
Me
O
(3)
NaDMSO
90 °C, 45 min
46%
HO
MeO
S
Me
O
(4)

(9)

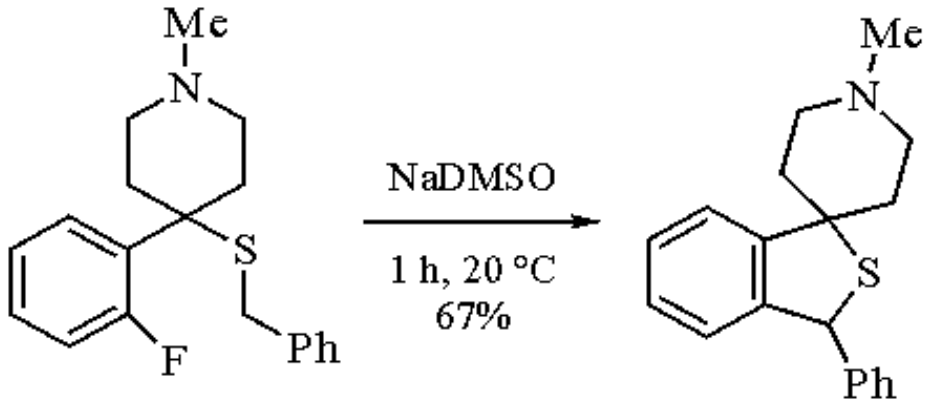
Me
N
S
F
Ph
NaDMSO
1 h, 20 °C
67%
Me
N
S
Ph

(10)

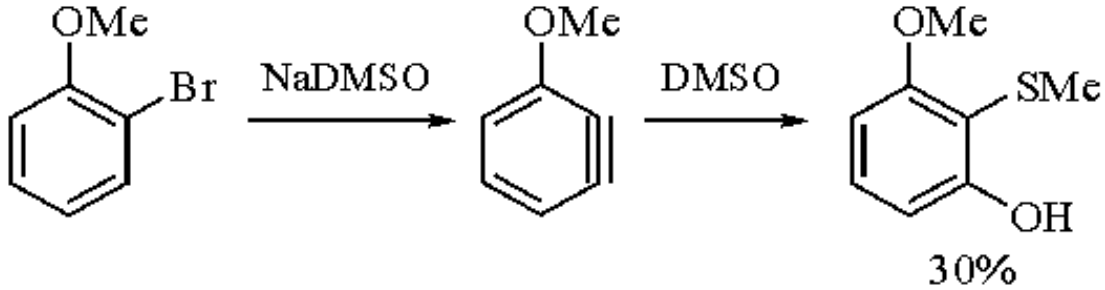
OMe
Br
NaDMSO
OMe
DMSO
OMe
SMe
OH
30%

(11)

Rearrangements.

NaDMSO has been used to promote double bond isomerization, leading to aromatization in the case shown (eq 12).[20] An anionotropic rearrangement of a cyclohexadienone to a substituted hydroquinone has been reported (eq 13).[21] The use of NaDMSO in DMSO has been described as an optimal choice for executing the carbanion accelerated Claisen rearrangement (eq 14).[22] Grob-type fragmentations mediated by NaDMSO have been used in total synthesis (eq 15).[23]

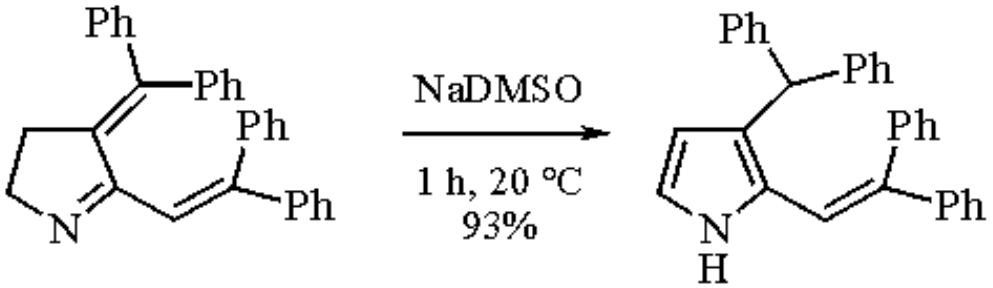

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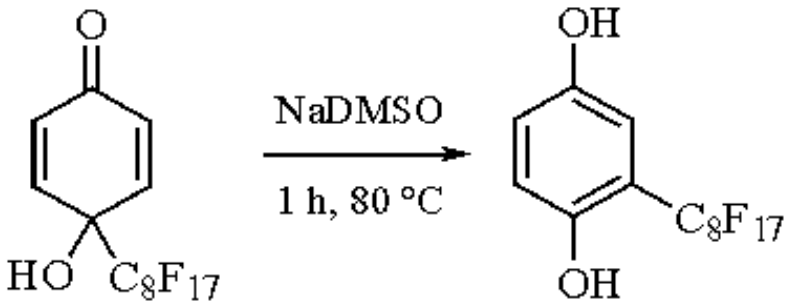

(13)

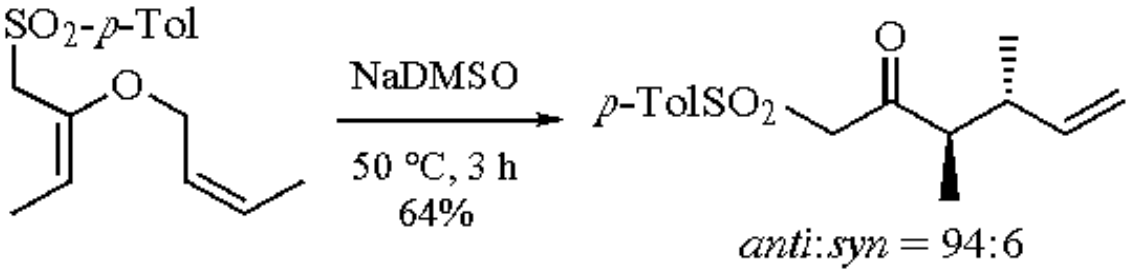

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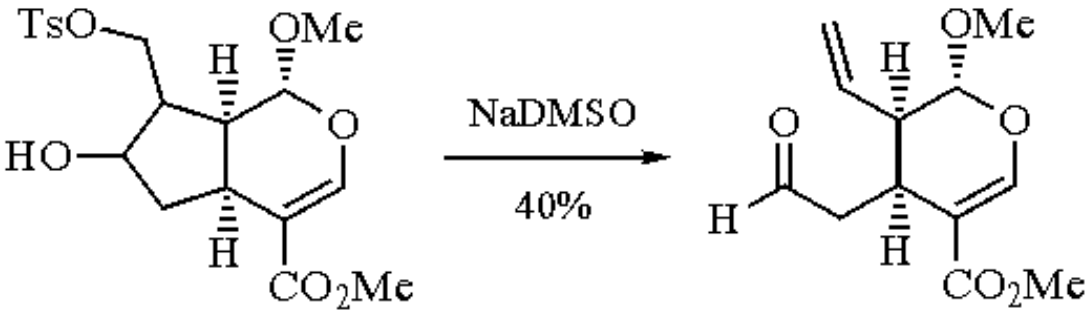

(15)

Anion Alkylation and Acylation.

NaDMSO has been used as a base to create new anions or carbanions, which then can be functionalized via normal alkylation or acylation procedures. Intramolecular aminolysis of an ester mediated by NaDMSO has been reported (eq 16).[24] A tandem double Michael-Dieckmann condensation leading to a complex tricyclic structure has been developed (eq 17).[25] Generation of a ketone enolate with NaDMSO followed by an intramolecular alkylation has been a part of a number of total syntheses.[26] Alkylations of sulfoximine and sulfone (Ramberg-Bäcklund rearrangement) carbanions derived from NaDMSO are known.[27] The intramolecular oxidative coupling of nitro-stabilized carbanions can lead to highly functionalized cyclopropanes which are potentially useful as high energy materials (eq 18).[28]

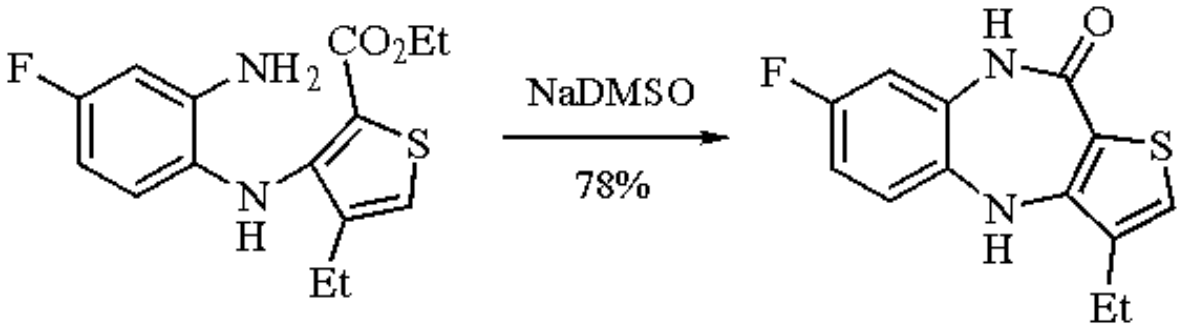

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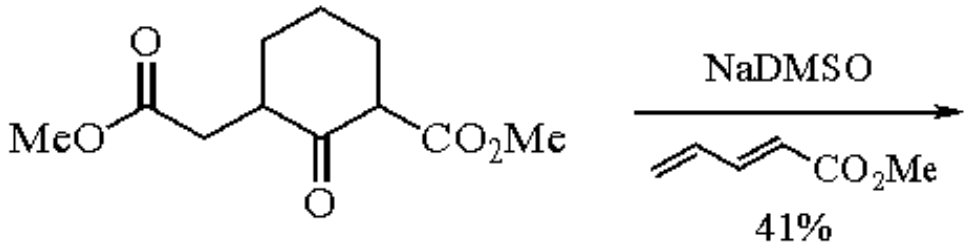

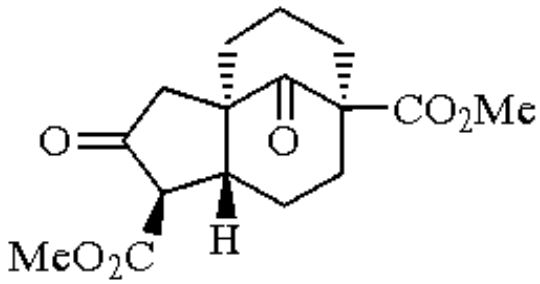

(17)

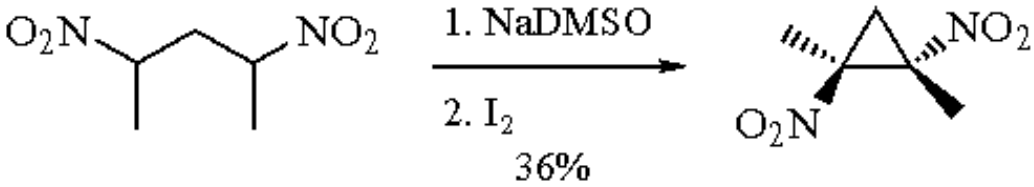

(18)

Ether Synthesis.

The application of NaDMSO to the Williamson ether synthesis has been documented.[29] The potential for alkoxide fragmentation exists and some discretion must be exercised in using this base for ether formation.[30] An intramolecular version of the Williamson reaction mediated by NaDMSO leads to an oxetane in high yield.[31] The preparation of otherwise difficulty accessible xanthates has been realized using NaDMSO.[32] Very common is the modification of oligo- and polysaccharides via Williamson ether synthesis (Hokomori reaction) to facilitate handling and analysis of these compounds.[33] Other hydroxylic polymers can also be functionalized in this way.[34]

Sodium Methylsulfinylmethylide as Nucleophile.

Reactions with Esters.

Perhaps one of the most useful reactions of NaDMSO is its condensation with esters to produce β-keto sulfoxides. The rich chemistry of these difunctional compounds makes accessible a wide variety of other organic compounds.[1,35] One of the most straightforward applications of NaDMSO is the synthesis of methyl ketones from esters (eq 19).[36] Thermal elimination of methylsulfenic acid after alkylation leads to α,β-unsaturated ketones (eq 20).[37] Among the wide variety of possible transformations of β-keto sulfoxides, another which stands out is the Pummerer reaction, which allows for the formation of carbon-carbon bonds via an umpolung of the reactivity adjacent to the carbonyl group (eq 21).[38] A synthesis of ninhydrin was developed based on this type of chemistry.[38c] Methacrylate polymers have been modified by reaction with NaDMSO.[39]

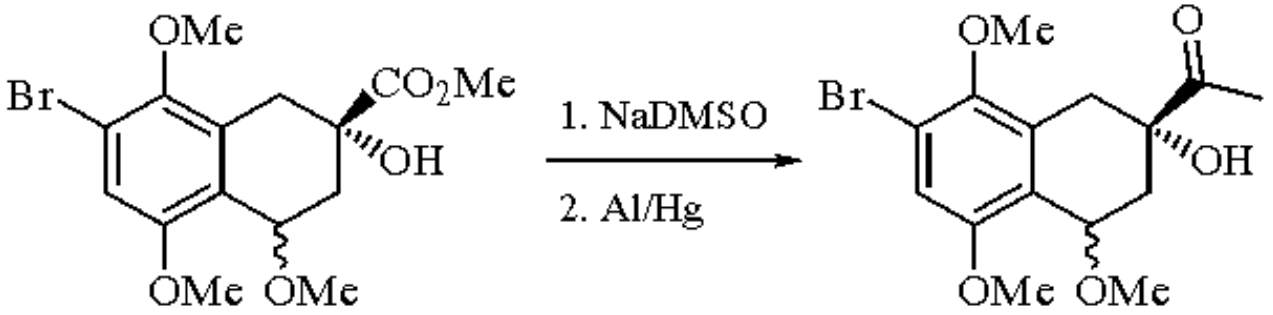

(19)

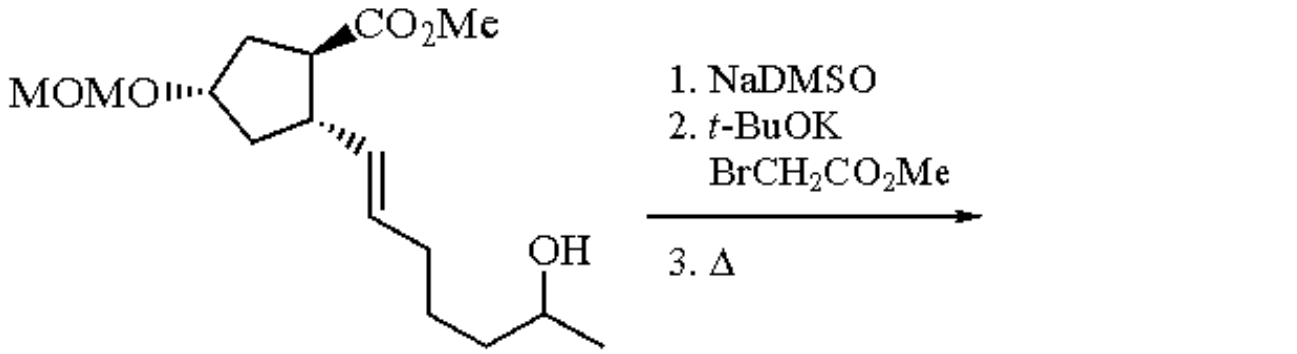

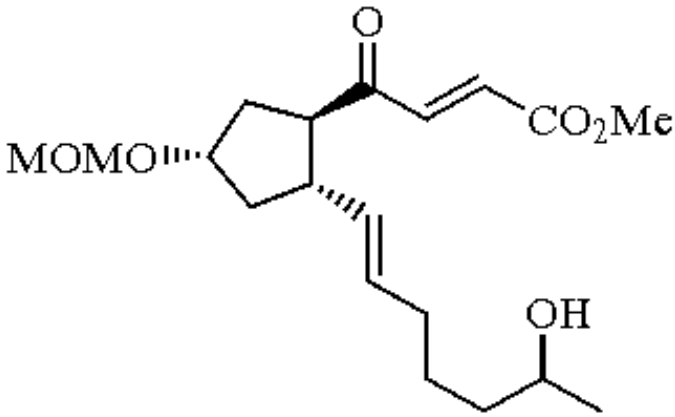

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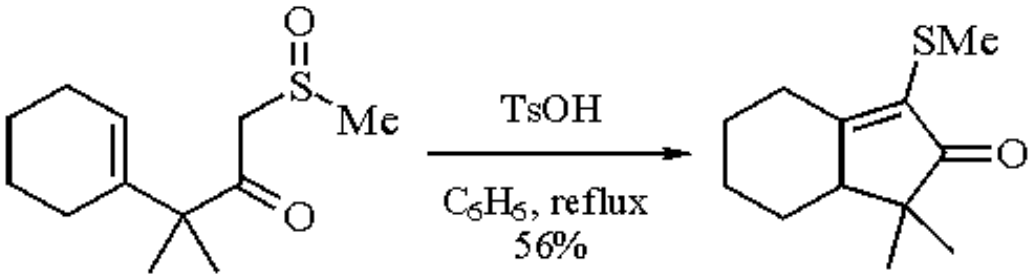

(21)

Reactions with Aldehydes and Ketones.

The reaction of nonenolizable ketones and aldehydes with NaDMSO generally proceeds smoothly to give β-hydroxy sulfoxides.[1] The chemistry of the latter is not as rich as that of β-keto sulfoxides, to which they can be converted. However, dehydration leads efficiently to α,β-unsaturated sulfoxides which can be transformed to the corresponding sulfides or sulfones.[40] A one-pot procedure using ***Sodium*** metal to produce NaDMSO and serve as a reductant leads to α,β-unsaturated sulfides directly.[41] Interestingly, a dianion of DMSO can be prepared from the reaction of DMSO with 2.2 equiv of $NaNH_2$. Reaction with benzophenone gives the expected adduct, albeit in only modest yield (eq 22).[3] A unique synthesis of 3-phenylindole based upon the reaction of NaDMSO with 2-aminobenzophenone has been reported (eq 23).[42]

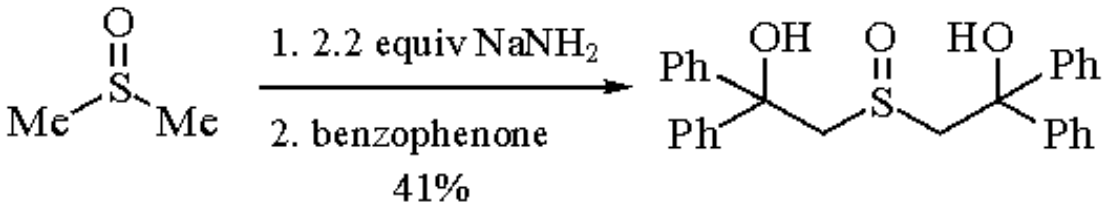

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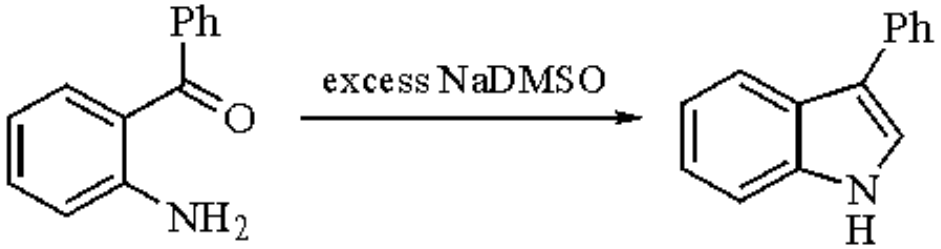

(23)

Enolizable ketones and aldehydes often give enolates upon reaction with NaDMSO as well as the expected addition products, limiting the utility of the reagent with these systems. Several unusual reactions of NaDMSO with enolizable ketones have been reported. For example, treatment of 4-heptanone with NaDMSO at elevated temperatures results in diene formation (eq 24).[43] Similarly, the reaction of cyclopentanone with NaDMSO gives a diene resulting from condensation followed by nucleophilic addition of NaDMSO and fragmentation (eq 25).[44]

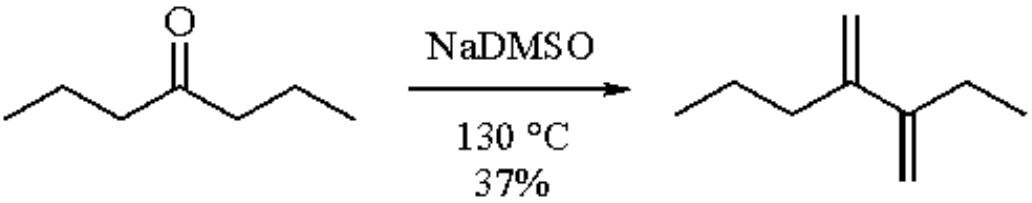

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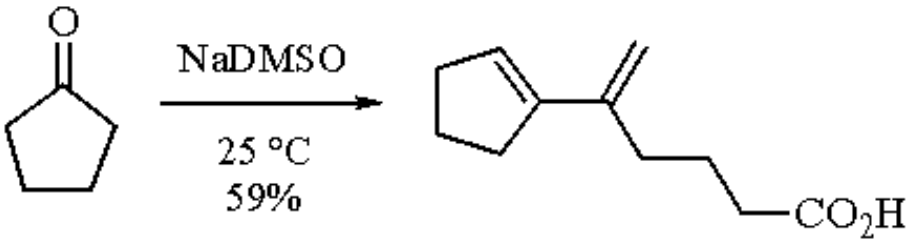

(25)

Reactions with Imines and Related Compounds.

The reaction of imines with NaDMSO has not been extensively studied.[2] However, several interesting applications with heterocycles at least formally possessing imine functional groups have been reported. Treatment of 1-methylquinoline with excess NaDMSO results in a tandem 1,4-1,2 addition to give a unique β-amino sulfoxide (eq 26).[45] A mechanistically intriguing synthesis of phenanthrene is the result of the reaction of a benzoquinoline *N*-oxide with NaDMSO (eq 27).[46] Finally, a synthesis of dibenzo[*a*,*f*]quinolizines has been developed based on the addition of NaDMSO to an imine followed by trapping of the resulting amide with a pendant benzyne (eq 28).[47]

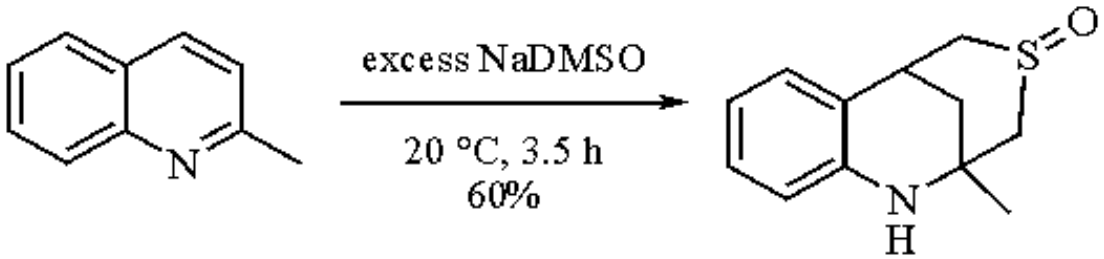

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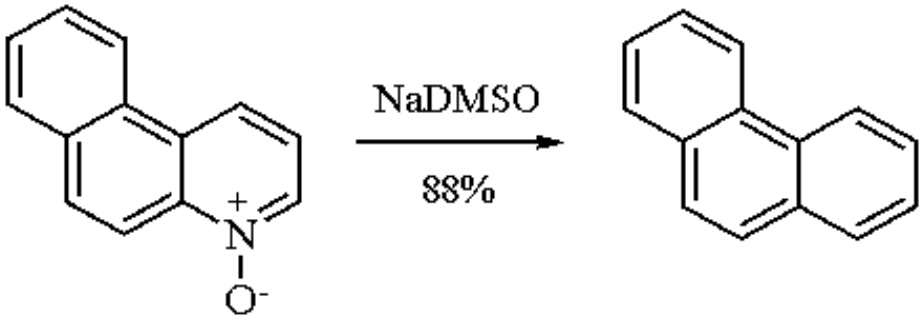

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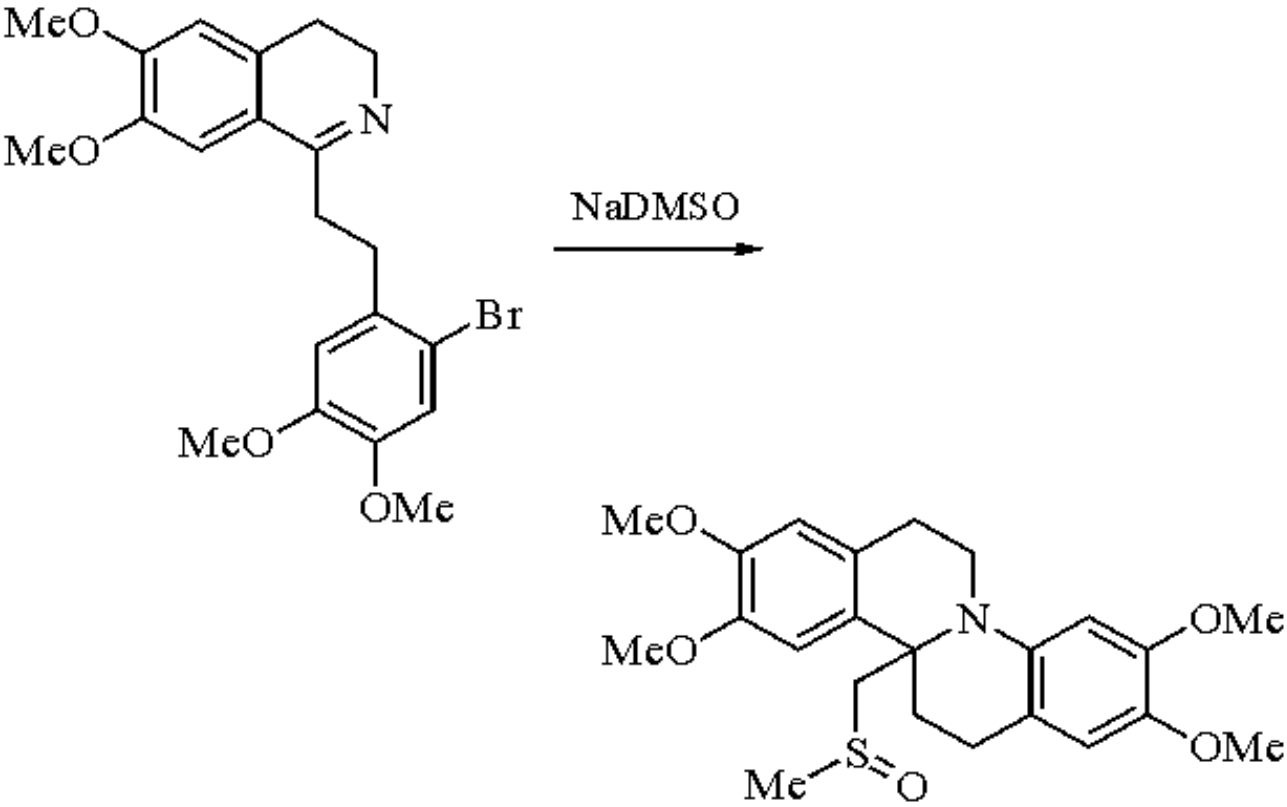

(28)

Reactions with Alkenes and Alkynes.

The reaction of NaDMSO with alkenes or alkynes conjugated to an aryl ring or alkene is well known.[1] 1,1-Diphenylethene gives a 1:1 addition product in quantitative yield upon reaction with NaDMSO.[48] From a synthetic perspective, one of the most useful of these reactions is the alkylation, especially the methylation, of stilbenes (eq 29).[49] This occurs by initial attack of NaDMSO on the unsaturated system followed by the elimination of methanesulfenic acid and isomerization. Dienes and other polyenes are subject to the same type of chemistry, but yields are modest and isomer formation can be a problem (eq 30).[50] Reaction of NaDMSO with diphenylacetylene can lead to either simple addition products or those based on an addition-elimination sequence, depending on the reaction conditions (eq 31).[51] Addition of NaDMSO to unsaturated systems has been used in polymer synthesis.[52]

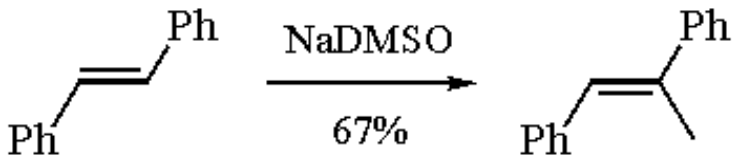

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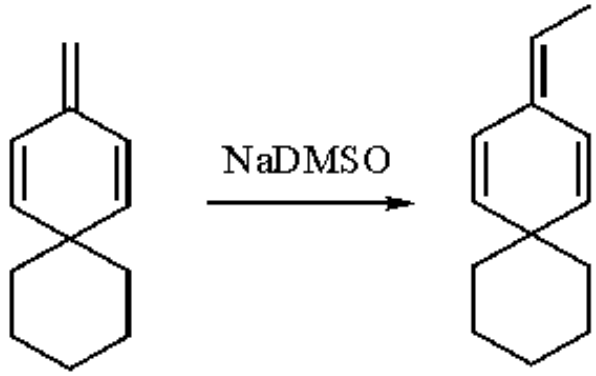

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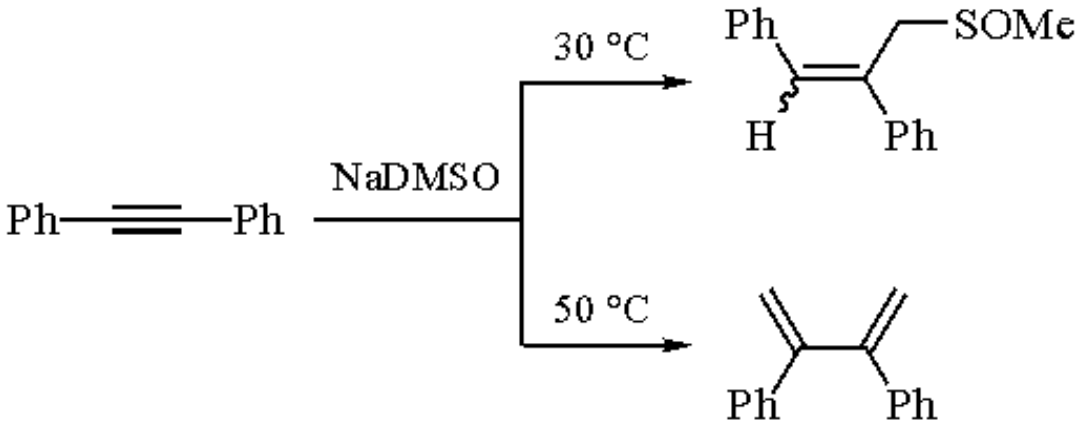

(31)

Reactions with Aromatics.

The reactions of NaDMSO with aromatic electrophiles can be categorized as occurring through either benzyne or addition-elimination mechanisms. Reaction of NaDMSO with chlorobenzene gives a mixture of sulfoxides, presumably via a benzyne intermediate (eq 32).[53] This chemistry has been used in the modification of polystyrenes.[54] Various fluoroaromatics react with NaDMSO to produce substitution products via addition-elimination (eq 33).[55] A variety of condensed aromatics (e.g. anthracene) undergo methylation analogous to that of stilbene upon reaction with NaDMSO (eq 34).[56]

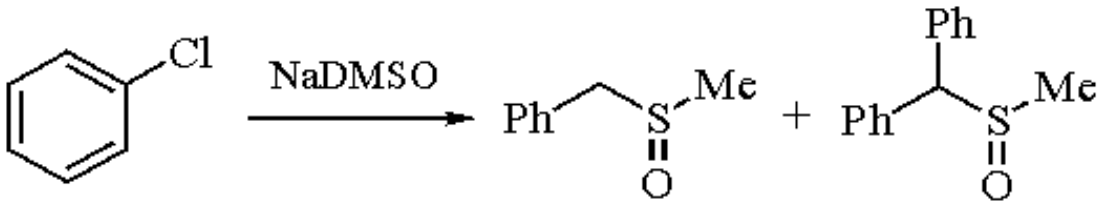

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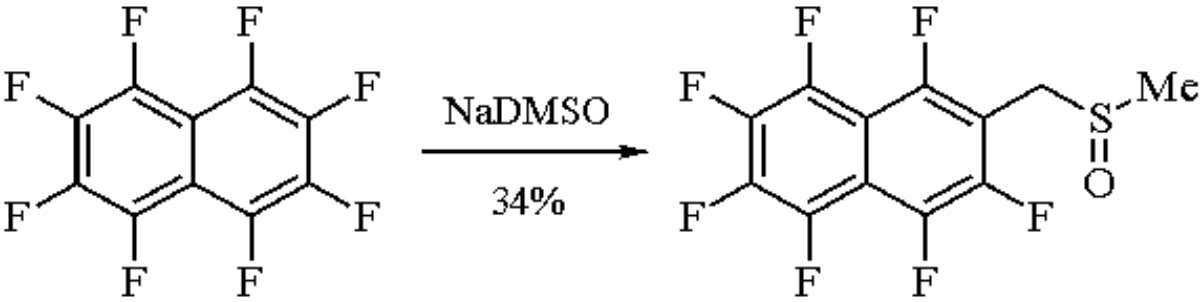

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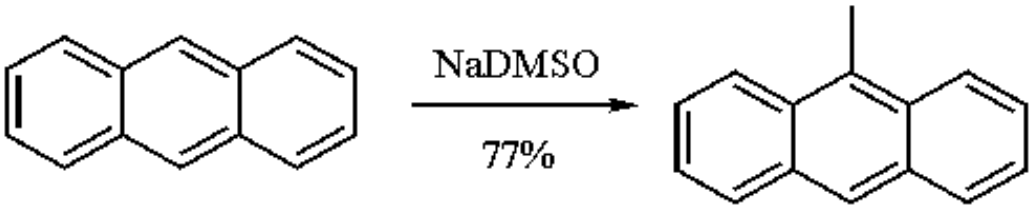

(34)

Reactions with Halides and Related Compounds.

Alkylation of NaDMSO with primary halides and tosylates results in the formation of the expected sulfoxides.[57] However, reaction with benzyl chloride gives stilbene as the major product, suggesting that the basicity of NaDMSO must be considered even with reactive electrophiles.[2] More hindered systems favor elimination. 1,2,5,6-Tetrabromocyclooctane debrominates to 1,5-cyclooctadiene upon reaction with NaDMSO (eq 35).[58] With ***Potassium t-Butoxide*** in DMSO the major product is one of elimination, namely cyclooctatetraene. Monodebromination also occurs with *gem*-dibromocyclopropanes.[59] In a process which presumably proceeds via S_N2 substitution, reaction of imidates with NaDMSO leads to amides (eq 36).[60]

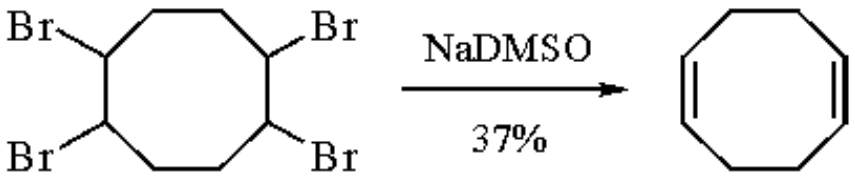

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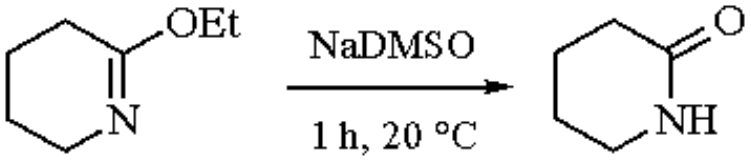

(36)

Reactions with Epoxides.

The reaction of NaDMSO with epoxides does not appear to have been widely investigated. Nevertheless, some synthetically useful transformations have been documented. Ring opening with NaDMSO followed by thermal alkene formation was developed as a route to an optically pure secondary allylic alcohol (eq 37).[61] A related transformation involves the reaction of trimethylsilyl-substituted epoxides (eq 38).[62] Ring opening at the TMS-substituted carbon, followed by desilylation and sulfenate elimination, leads to allyl alcohols in good yield in a one-pot process.

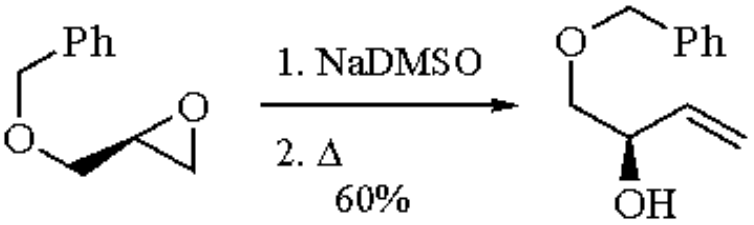

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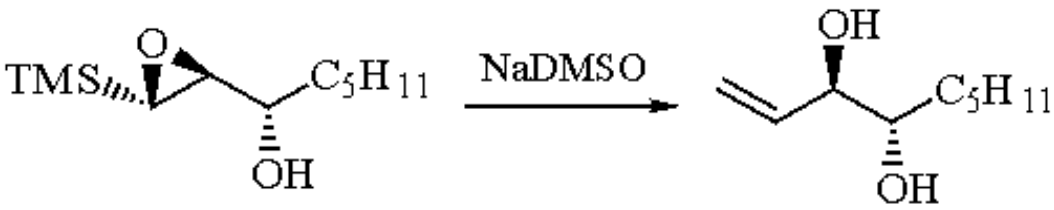

(38)

Reactions with Phosphorus and Sulfur Electrophiles.

A one-pot synthesis of α,β-unsaturated sulfoxides begins with the reaction of NaDMSO with ***Diethyl Phosphorochloridate*** to give a Horner-Emmons reagent which reacts with aldehydes in an efficient manner (eq 39).[63] Bis-sulfoxides are prepared by the reaction of NaDMSO and a diastereomerically pure methyl sulfinate ester.[64] Some kinetic resolution is observed in this reaction. The thiophilic addition of NaDMSO to sulfines also leads to bis-sulfoxides (eq 40).[65]

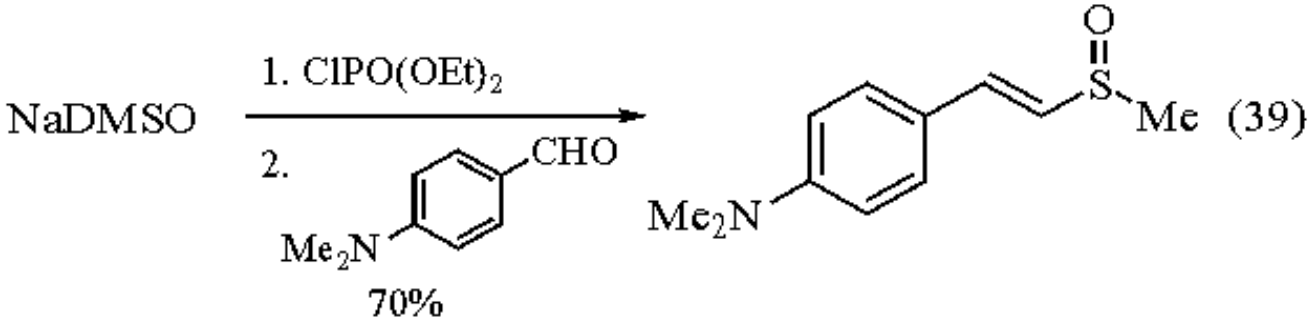

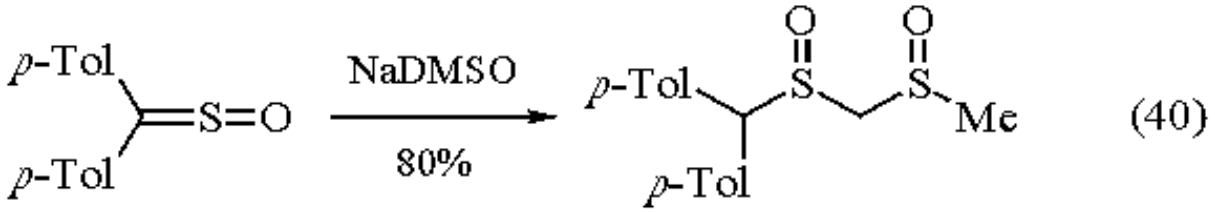

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3. Kaiser, E. M.; Beard, R. D.; Hauser, C. R. *JOM* **1973**, *59*, 53.
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5. Price, C. C.; Yukuta, T. *JOC* **1969**, *34*, 2503.
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Sodium Naphthalenide

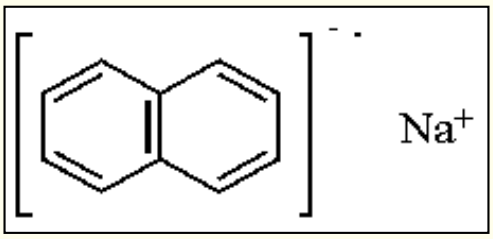

[3481-12-7] · $C_{10}H_8Na$ · Sodium Naphthalenide · (MW 151.17)

(one-electron donor promoting ketyl-alkene[3] and ketyl-alkyne[2] radical cyclizations; facilitates coupling of ketone[4] and thiocarbonyl[5] functionalities; removes mesylate, tosylate, and benzyl protecting groups[11,13-15] to generate the corresponding alkene or alcohol)

Solubility: sol diethyl ether, THF; forms complexes with diethyl ether and THF.

Preparative Method: typically prepared from the reduction of naphthalene by ***Sodium*** metal in THF solvent.[1]

Handling, Storage, and Precautions: stability is a matter of contention.[1] THF apparently contributes substantially to the stability of the complex by solvating the resulting ion pairs.

Reductive Cyclization.

Sodium naphthalenide is a good electron donor and promotes the reductive cyclization of steroidal acetylenic ketones in high yield (eq 1).[2] The resulting allylic alcohol is the only observed product and no overreduction occurs as with more powerful reducing agents.

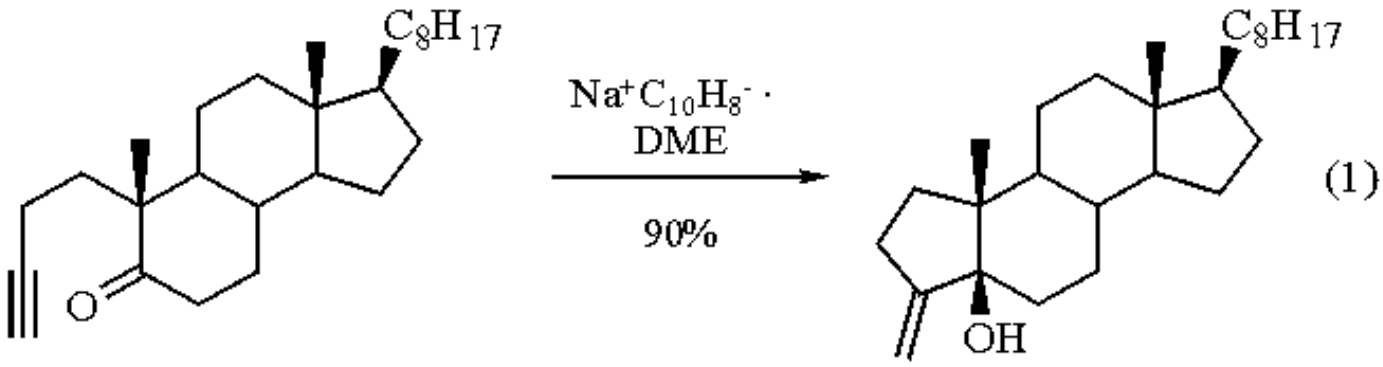

Similarly, radical cyclization of an alkenyl aldehyde with sodium naphthalenide provides the product resulting from 5-*exo* ring closure in moderate yield. This method has been utilized in the synthesis of a key intermediate leading to α-cuparenone, which presents a challenge synthetically because of the steric congestion around the cyclopentane ring (eq 2).[3]

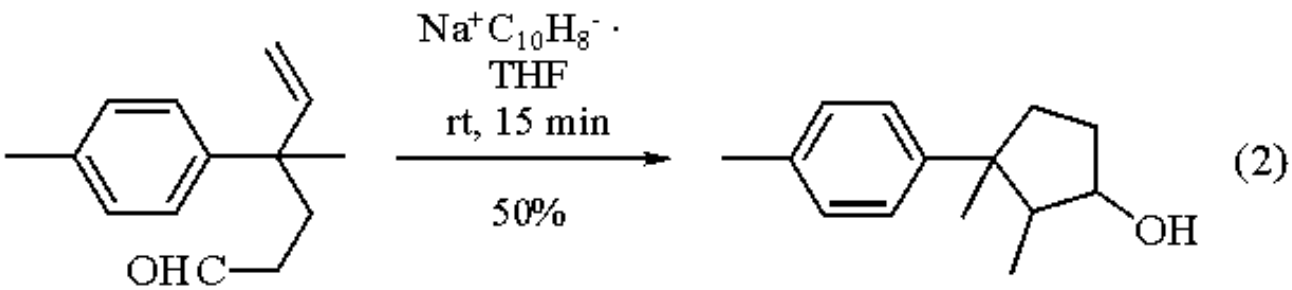

Ketone and Thiocarbonyl Coupling.

More recently, sodium naphthalenide in conjunction with ***Titanium(IV) Chloride*** has been used to perform a McMurry-like coupling reaction in an intramolecular process, providing a bicyclic structure in good yield (eq 3).[4]

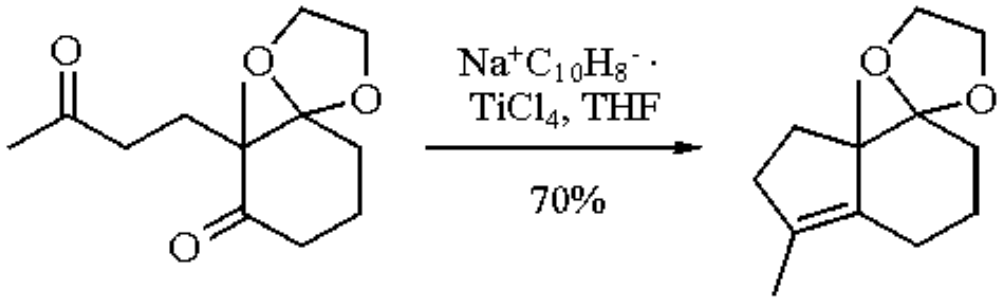

(3)

Sodium naphthalenide further provides a method for the bridging of macrocycles. Nicolaou has recently used this method in the preparation of *cis*- and *trans*-fused oxabicyclic and oxapolycyclic systems, which are common structural components of marine and other natural products (eq 4).[5] This process is thought to proceed by initial electon transfer to the thiocarbonyl group of the macrodithionolide system generating the radical anion; this initiates a sequence leading to the bridged product which is quenched with methyl iodide to generate the more stable disulfide. The disulfide may then be further transformed chemically to either the *cis*- or *trans*-fused polycycle.

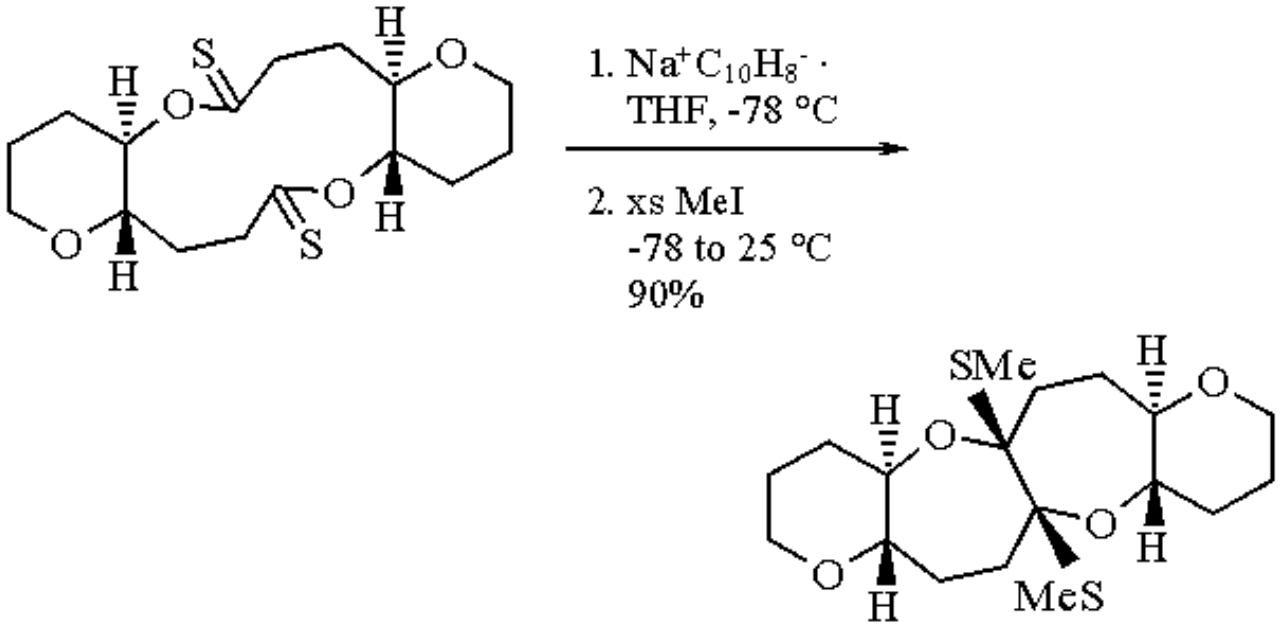

(4)

Reduction of Epoxides.

The ability to relocate the allylic alcohol moiety within a molecule is another synthetic strategy for which sodium naphthalenide has been found useful. This ability is demonstrated in the transformation of geraniol to linalool (eq 5) by epoxidation of the allylic alcohol, mesylation, and subsequent treatment with sodium naphthalenide to produce the allylic alcohol in good yield.[6] Similarly, this method has been utilized in the synthesis of isocarbacyclin, a therapeutic agent for cardiovascular disease. Treatment of the epoxidized and protected allylic alcohol with sodium naphthalenide provides the desired allylic alcohol with the exocyclic double bond as a mixture of diastereomers (eq 6).[7] Apparently, the *t*-butyldimethylsilyl ether is unaffected under these reaction conditions.

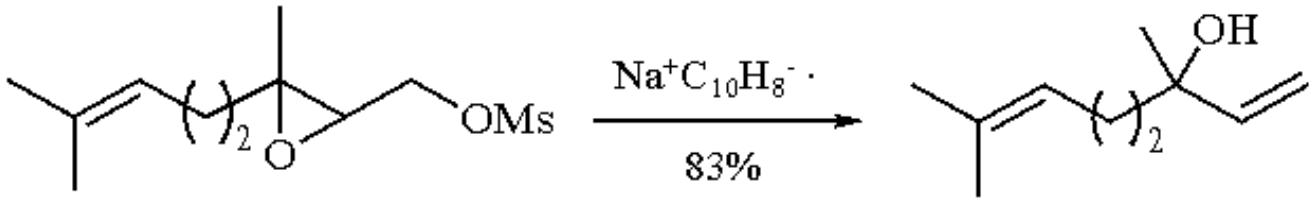

(5)

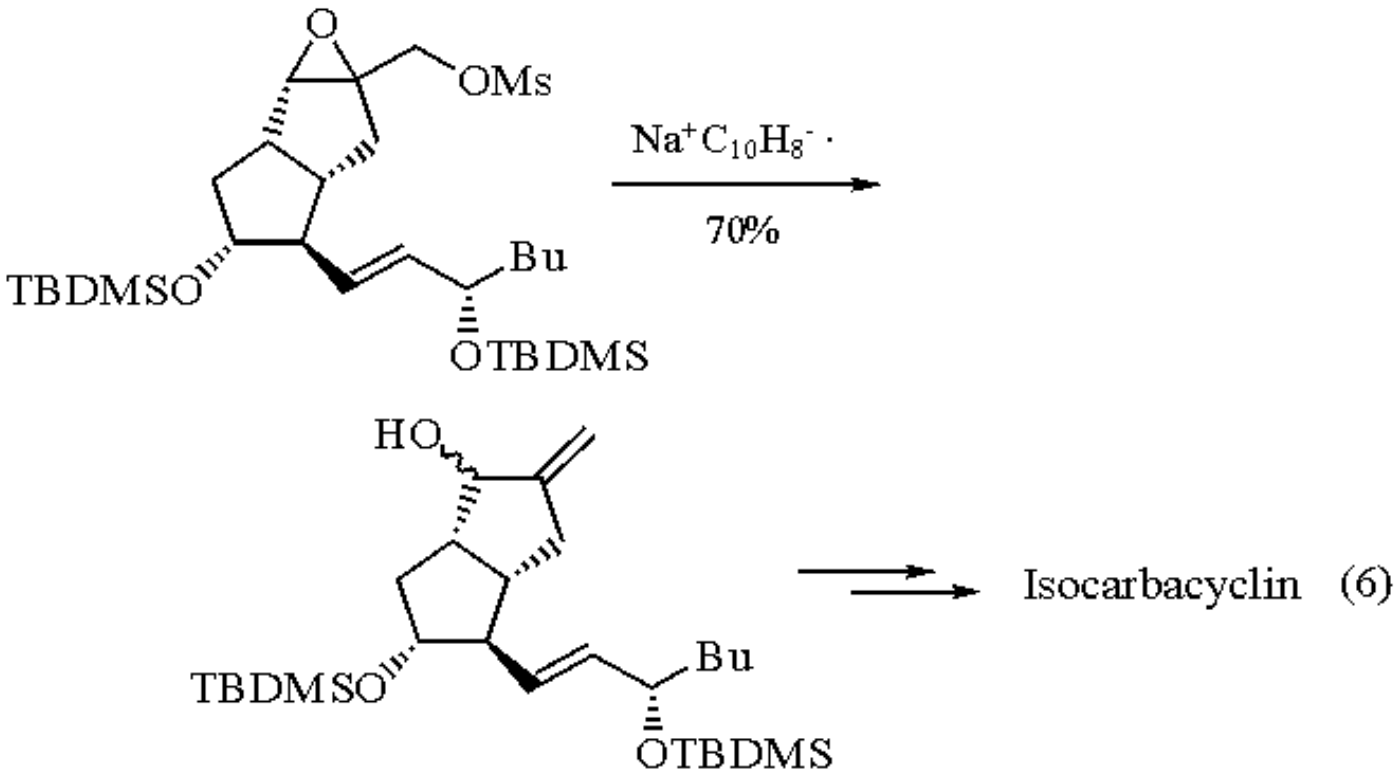

Sodium naphthalenide with ***N,N,N´,N´-Tetramethylethylenediamine*** effects a carbon-carbon bond-forming reaction between carboxylic acids and conjugated alkenes (eq 7) to produce the substituted carboxylic acid in moderate yield.[8,9] This method has been utilized in the preparation of dihydrolavandulol (eq 8) in fair yield.[8]

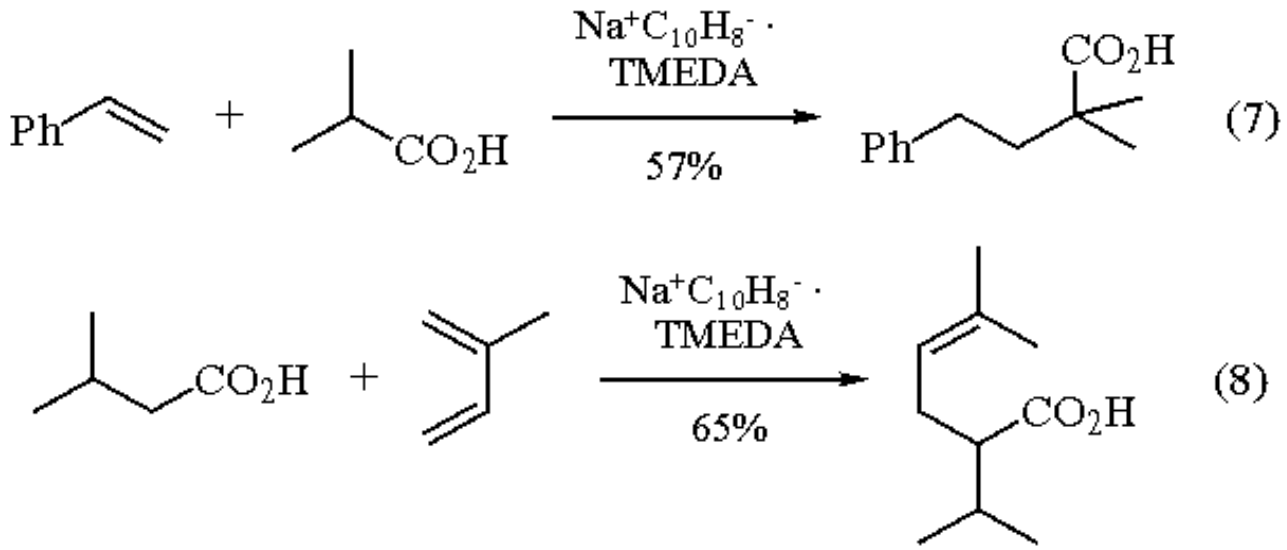

Treatment of benzimidazoline-2-thione with alkyl halide and sodium naphthalenide in THF affords the 1-alkyl-2-(alkylthio)benzimidazoles in excellent yield. These substrates may be further transformed by additional sodium naphthalenide to provide the 1-alkylbenzimidazoline-2-thiones in high yield (eq 9).[10] Thus, sodium naphthalenide provides an alternative to other known methods which generally proceed in much lower yield and require longer reaction times and more vigorous reaction conditions.

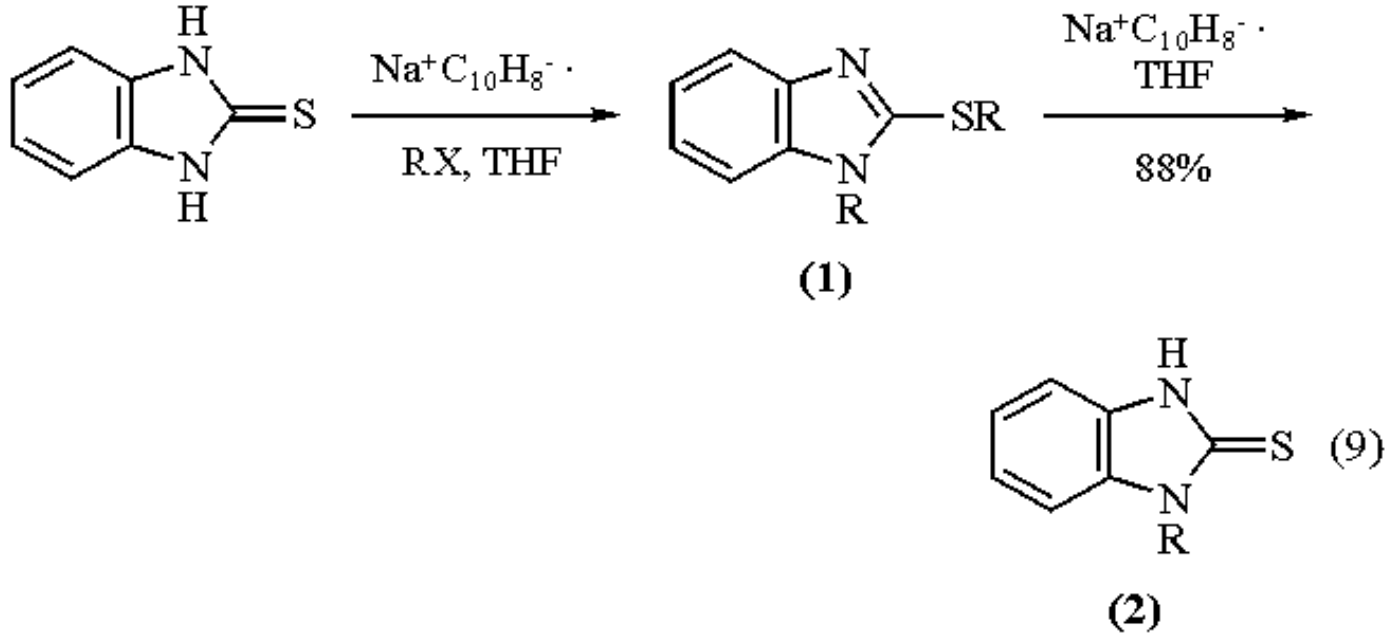

R	(1) (%)	(2) (%)
Me	97	88
Et	100	94
Allyl	100	92
Benzyl	100	93

Protecting Group Removal; Alkene Formation.

Sodium naphthalenide also facilitates the removal of protecting groups. It has been utilized in the debenzylation of nucleosides (eq 10).[11] Sodium naphthalenide also effects the reductive cleavage of toluenesulfonates. Both menthyl tosylate and bridged bicyclic tosylates are quantitatively reduced under mild reaction conditions (eqs 11 and 12).

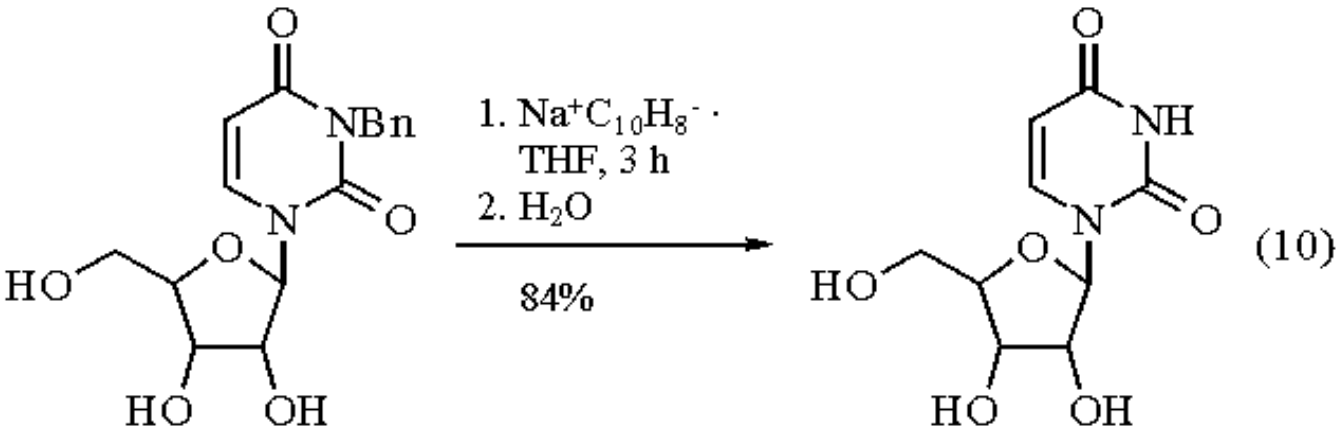

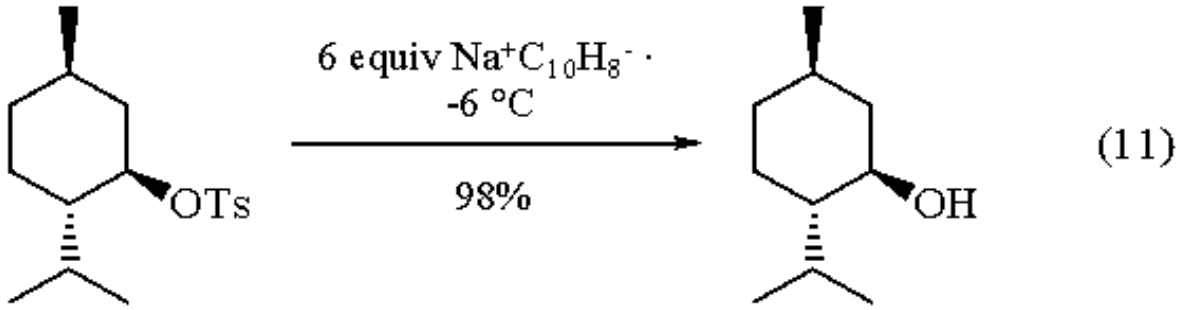

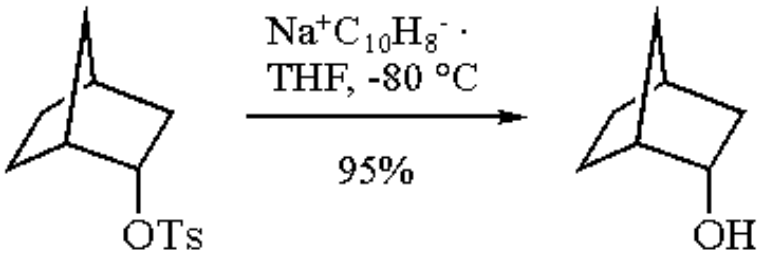

(12)

Cyanohydrins with α-methyl thiomethyl ether or α-methyl thiomethyl sulfone substituents are converted regio- and stereospecifically to the corresponding alkenes (eqs 13 and 14).[12] The *cis*-substituted cyanohydrin undergoes elimination to generate the *cis*-alkene while the *trans*-substituted cyanohydrin provides the *trans*-alkene upon treatment with sodium naphthalenide/HMPA. This provides an excellent method for the preparation of either *cis*- or *trans*-alkenes in large ring systems.

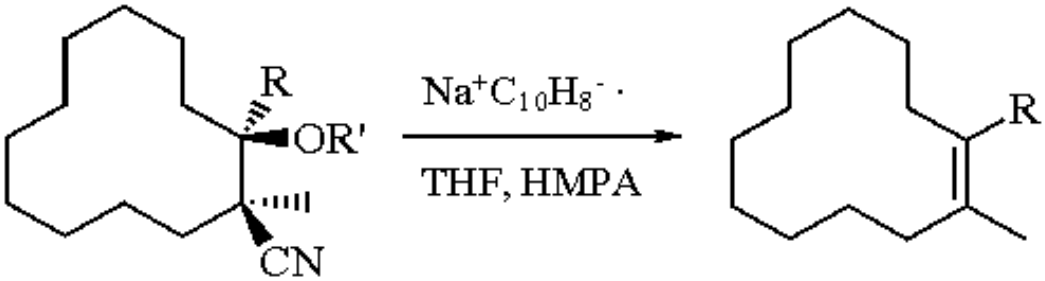

(13)

R = H, 85%; Me, 74%
R' = CH_2SMe or CH_2SO_2Me

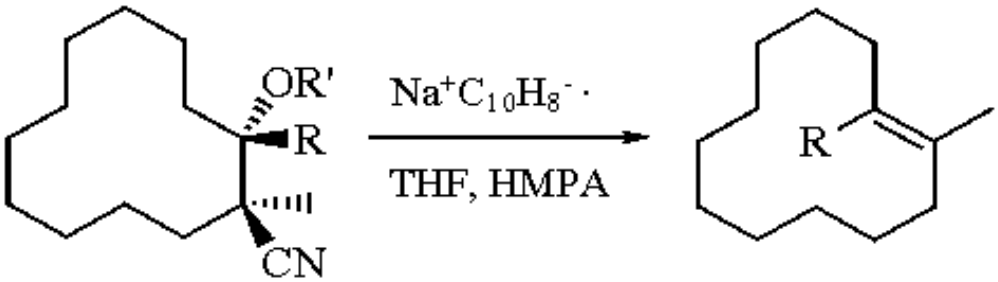

(14)

R = H, 60%; Me, 83%
R' = CH_2SMe or CH_2SO_2Me

Treatment of methanesulfonates of vicinal diols with sodium naphthalenide in THF or DME results in the rapid and high conversion to the alkene (eqs 15 and 16).[13] Although the reaction is highly regiospecific, the more stable alkene generally predominates in close to the equilibrium ratio. This method has recently been utilized in the synthesis of (±)-20-deethylcatharanthine (eq 17) in which the diol is converted to the dimesylate followed by subsequent treatment with sodium naphthalenide, providing the desired alkaloid analog in good yield.[14]

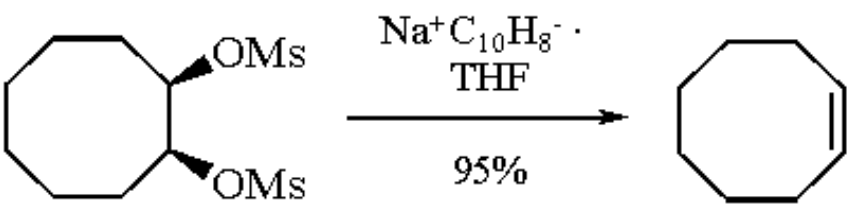

(15)

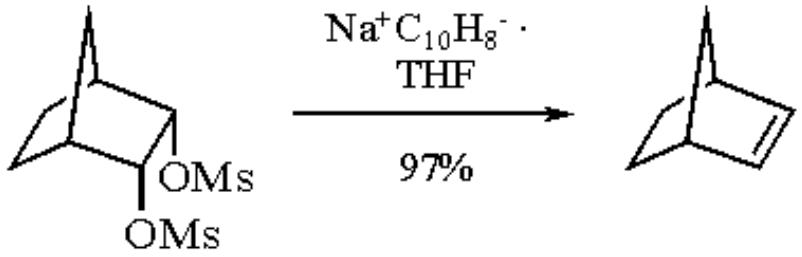

(16)

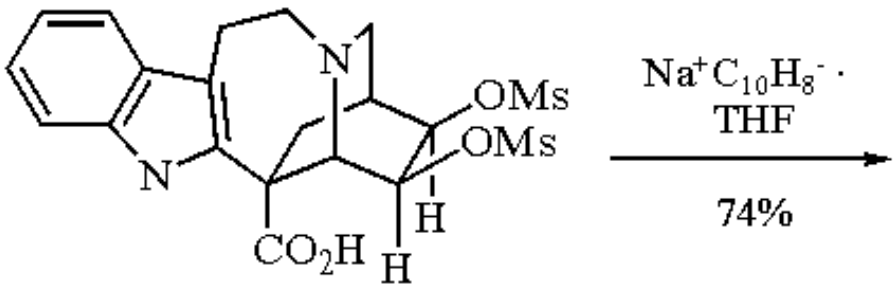

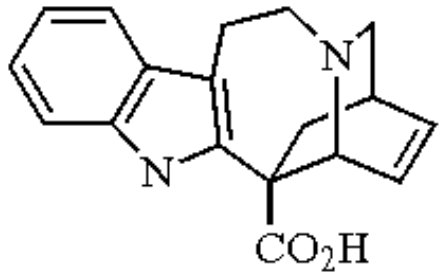

(17)

Similar conversion of the bicyclic vicinal diol to the dimesylate followed by treatment with sodium naphthalenide provides an efficient strategy for the deoxygenation of the vicinal diol to form an immediate precursor to the natural product (+)-(1*S*,5*R*,7S)-exobrevicomin (eq 18).[15] This method provides significantly higher yield than xanthate formation followed by reduction with ***Tri-n-butylstannane***.

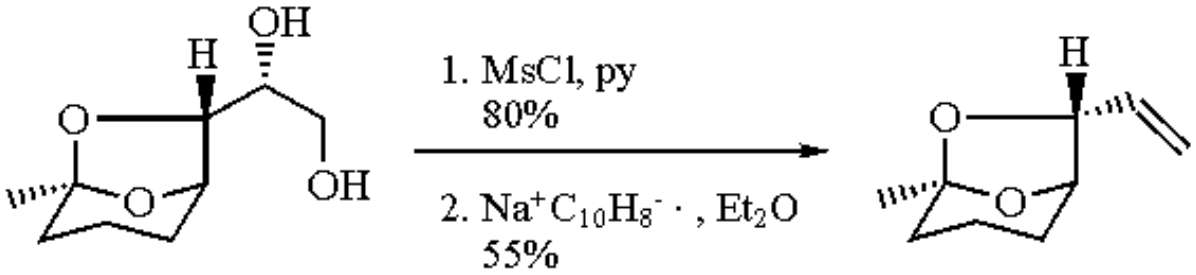

(18)

Sodium naphthalenide further affords a useful procedure for the conversion of cyclic sulfates into alkenes, providing an efficient synthesis of deoxygenated vicinal diols (eq 19).[16] This reaction is highly regiospecific but, in examples where (*E*)/(*Z*) isomerization is possible, the thermodynamically preferred alkene predominates. Additionally, carbonyl functionalities and other easily reduced species are incompatible with these reaction conditions.

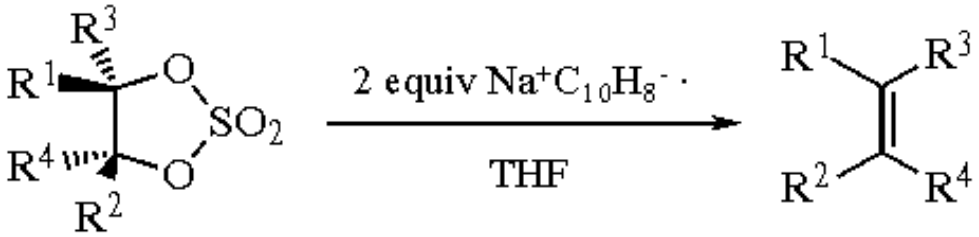

(19)

$R^1, R^2, R^3, R^4 = H, Ph, Ph, H$; 86%
$R^1, R^2, R^3, R^4 = (CH_2)_9Me, H, H, H$; 88%

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Sodium Nitrite[1]

$NaNO_2$

[7632-00-0] · $NNaO_2$ · Sodium Nitrite · (MW 69.00)

(diazotization of primary aliphatic and aromatic amines;[1] *N*- and *C*-nitrosating agent;[2,3] reacts with alkyl halides to form aliphatic nitro compounds[4])

Physical Data: mp 271 °C; dec. above 320 °C; *d* 2.17 g cm^{-3}.

Solubility: very sol water (0.815 g mL^{-1}, 15 °C); sol DMSO, DMF; slightly sol Et_2O, MeOH, EtOH.

Form Supplied in: white crystalline, hygroscopic solid; reagent grade 97%+; widely available.

Handling, Storage, and Precautions: should be kept dry in tightly closed containers. Nitrites undergo slow oxidation to the nitrate in air. Aqueous solutions of $NaNO_2$, which are alkaline (ca. pH 9), are unstable on prolonged storage and should be made up fresh prior to use. $NaNO_2$ decomposes in the presence of weak acids with the evolution of brown fumes of N_2O_3. Since $NaNO_2$ is classified as toxic, oral ingestion should be avoided.

Introduction.

In many synthetic applications, $NaNO_2$ is used as a convenient precursor of the unstable nitrous acid HONO which is generated in situ on treatment with a variety of mineral and carboxylic acids. Reactions involving HONO are complex because, in solution, it exists in equilibrium with a variety of other reactive species, including N_2O_3, nitrosyl halides, and the nitrosonium ion ON^+. Although $LiNO_2$ and KNO_2 will also react in a similar fashion to the sodium salt, the latter is preferred on the basis of price and availability. Diazotization and nitrosation reactions can also be carried out using a variety of reagents including ***Nitrosyl Chloride*** and alkyl nitrites.

Reactions with Amines and Related Compounds.

In such reactions, a solution or suspension of the amine in dilute hydrochloric acid (2.5 molar equiv per mole of amine) is treated with a molar equiv of $NaNO_2$ solution at 0-10 °C. Reactions are normally rapid and in many cases quantitative.[1] The reaction outcome depends markedly on the nature of the amine. With primary aliphatic amines, the reaction (usually described as diazotization) produces the corresponding diazonium ion (**1**) as the first significant intermediate. This can subsequently eliminate either a molecule of nitrogen to generate a carbocation, or H^+ to give a diazoalkane (eq 1).[5] In the diazotization of simple primary aliphatic amines with sodium nitrite in dilute mineral acid, the former process predominates resulting in rapid evolution of N_2, an observation which forms the basis for the characteristic chemical test for primary aliphatic amines.

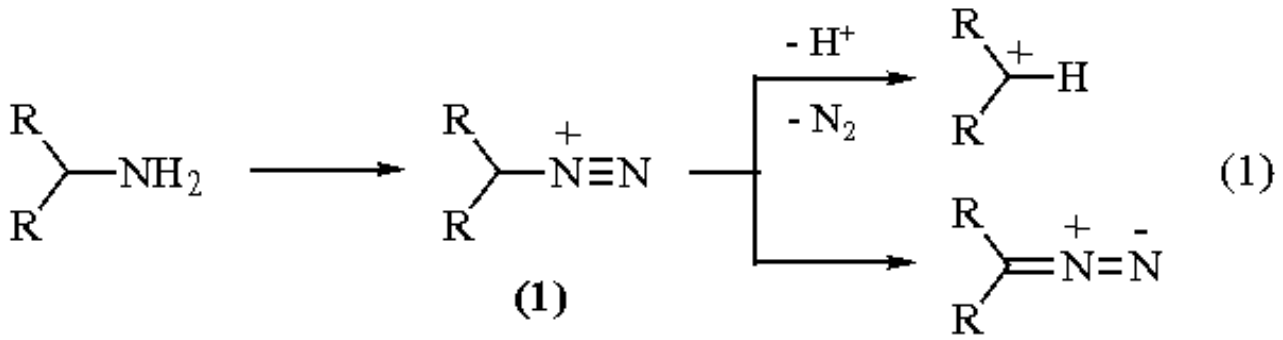

Cycloalkylamines (ring sizes C_4 and C_6-C_8) can undergo ring contraction on diazotization (eq 2); conversely, cycloalkylmethylamines (ring sizes C_3-C_8) undergo ring expansion under similar conditions (Demjanov rearrangement) (eq 3).[6] Ring expansions of certain

alkanolamines (ring sizes C_4-C_8) also occur on diazotization, affording cyclic ketones (Tiffeneau-Demjanov rearrangement) (eq 4).[7] Product yields from the latter reaction are generally superior to those from the corresponding simple Demjanov rearrangements.

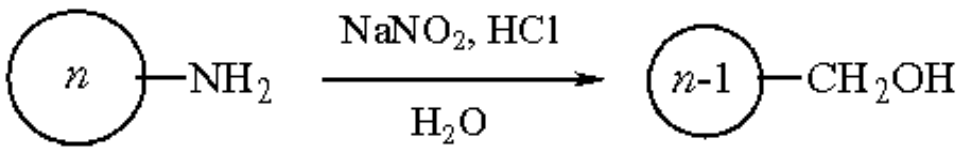

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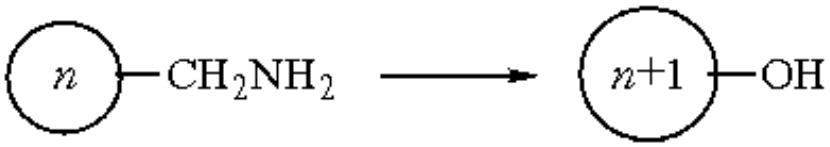

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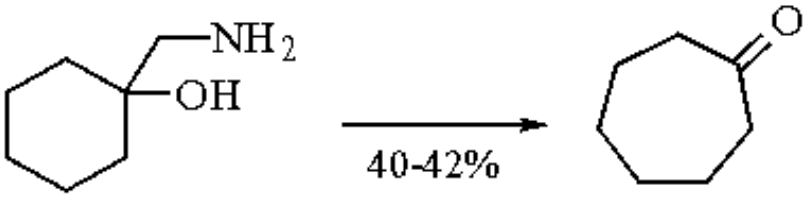

(4)

Diazotization of amino acids using $NaNO_2$ in HCl affords the corresponding α-chloro carboxylic acids in moderate yield and with almost complete retention of configuration (95-98% ee) (eq 5).[8] Analogous deamination/halogenation transformations have also been effected on 6β-aminopenicillanic acid (**2**) with inversion of configuration.[9] In the presence of ***Bromine***, the corresponding geminal dibromide (ca. 30%) is obtained;[10] yields can be increased to 80% if a two-phase solvent system is used (eq 6).[11] The *S*,*S*-dioxide derivative of (**2**) affords the corresponding geminal dibromide in good yield and high purity with methanol, rather than water, as solvent.[12]

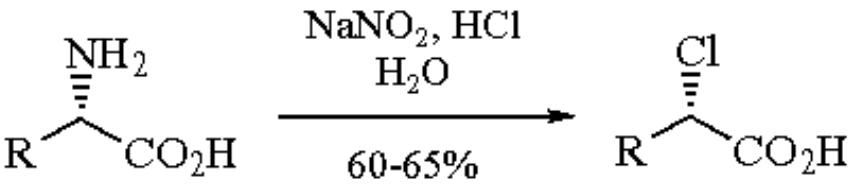

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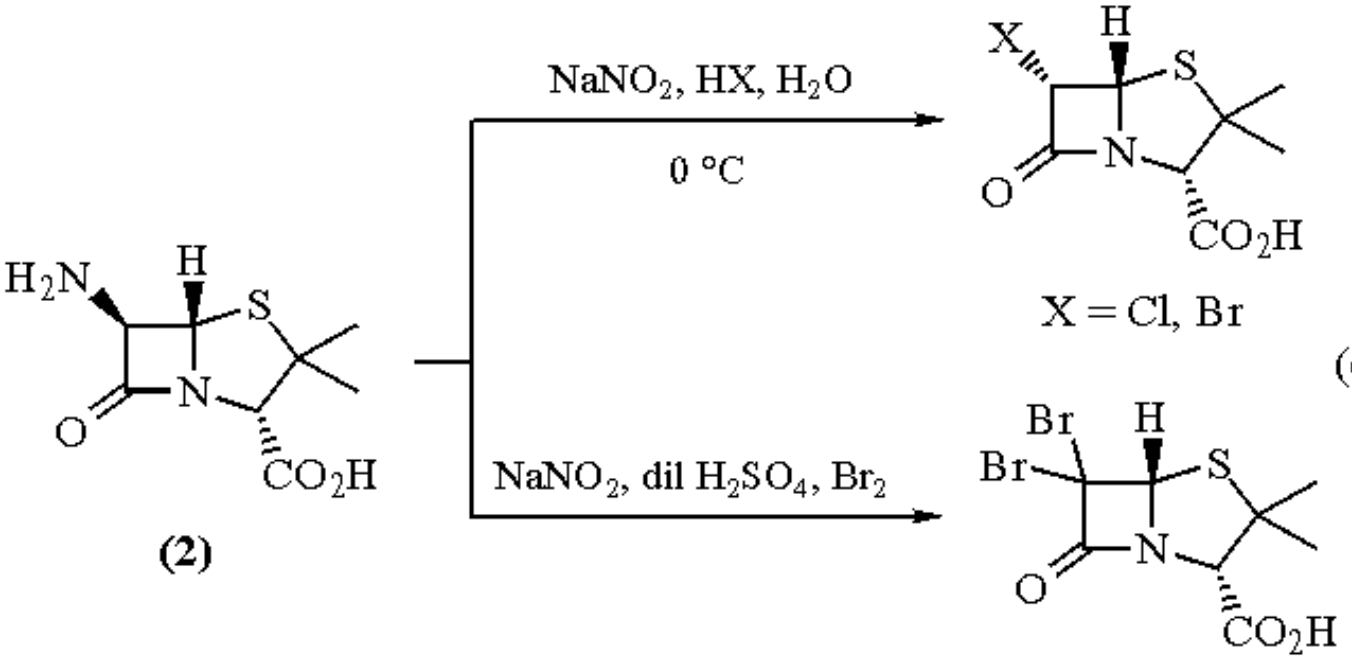

(6)

When primary aliphatic amines with strongly electron-withdrawing substituents attached to the amino carbon atom are diazotized, the corresponding diazoalkanes can be isolated.[5,13] Diazotization of 2,2,2-trifluoroethylamine affords the corresponding diazoalkane in 70% yield.[14] Treatment of glycine ethyl ester hydrochloride with sodium nitrite in dilute sulfuric acid affords the important synthetic intermediate ***Ethyl Diazoacetate*** (eq 7).[15] The benzyl ester of acid (**2**) has also been transformed into the corresponding α-diazo derivative using sodium nitrite in aqueous acetone.[16] Attempted diazotization of 2-aminocyclohexanone results in deamination and

rearrangement to cyclopentanecarboxylic acid (57%).[17]

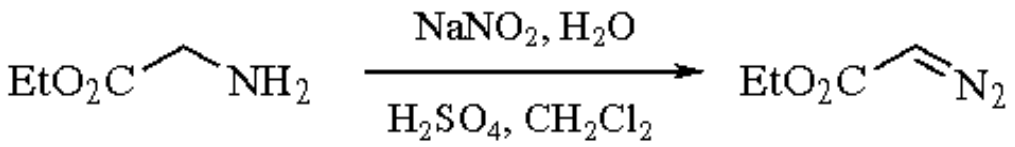

(7)

Primary aromatic amines readily undergo diazotization to give the corresponding diazonium salts, which are generally stable in solution at temperatures below 0 °C.[1] These are important intermediates in electrophilic aromatic substitution reactions, e.g. the formation of azo dyes, and a variety of coupling/displacement reactions including the Sandmeyer, Balz-Schiemann, and Gomberg reactions. Amines with strongly acidic groups are best diazotized by the slow addition of a solution of the amine and $NaNO_2$ in dilute alkali to the acid with vigorous stirring.[1a] To avoid hydrolysis of the diazonium salt, amines with strongly electron-withdrawing groups should be diazotized in concentrated acid.[1a,18] The transformation of aromatic 1,2-diamines to bis-diazonium salts should also be carried out in concentrated acid. In dilute or weak acid, the mono-diazonium ions derived from 1,2-phenylenediamines cyclize to give 1,2,3-benzotriazoles (eq 8).[1a,b,19] By analogy, diazotization of *p*-nitro-*o*-toluidine affords 5-nitroindazole under similar conditions.[20]

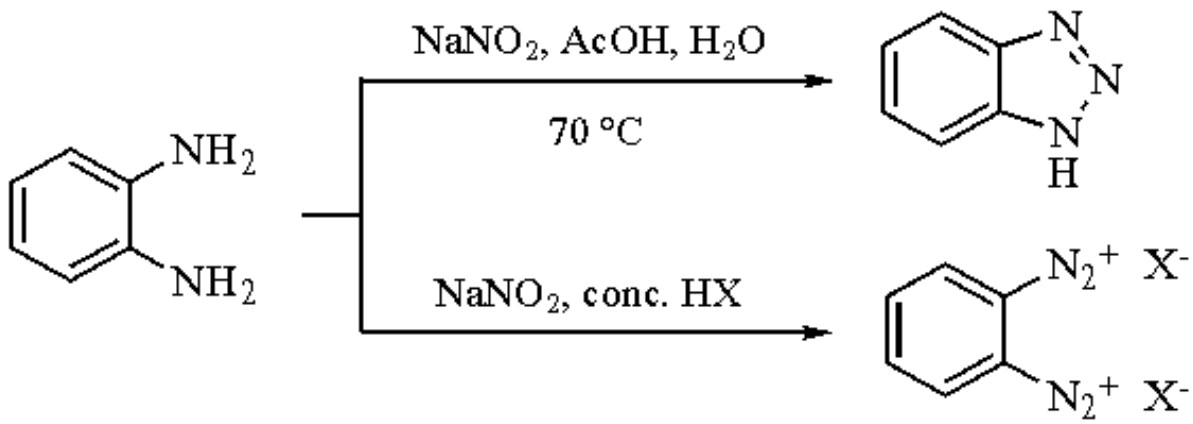

(8)

Treatment of diazonium salts, preferably the tetrafluoroborates, with $NaNO_2$ in the presence of a Cu^I catalyst at pH > 7 results in the formation of the corresponding aromatic nitro compounds (cf. the Sandmeyer reaction).[21] For analogous reactions involving amines with strongly electron-withdrawing groups, a Cu^I catalyst is not required.[22]

Heteroaromatic amines also undergo diazotization on treatment with sodium nitrite in acid; for example, 3-aminopyridines give isolable diazonium salts whereas the 2- and 4-derivatives afford either the corresponding pyridones in dilute acid[23] or halopyridines in concentrated HCl or HBr (eq 9).[24] Diazotization of 2-aminopyrimidine in concentrated HCl produces 2-chloropyrimidine.[25]

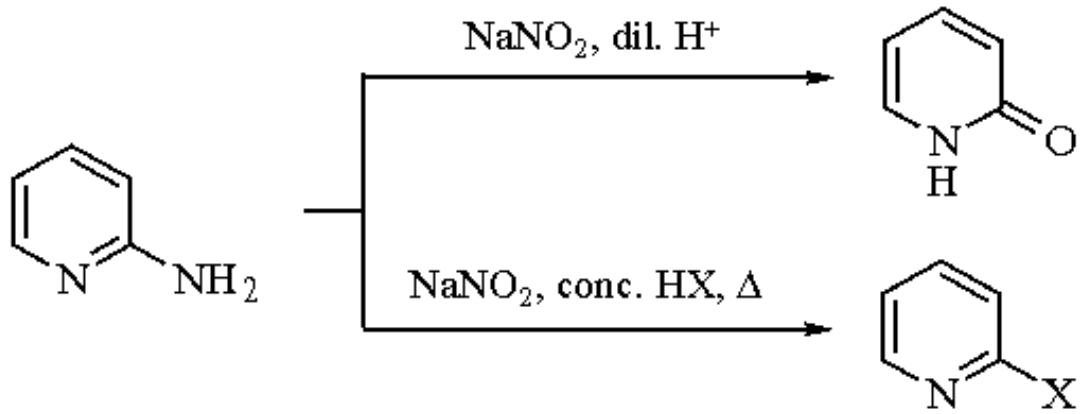

(9)

Treatment of secondary dialkyl-, diaryl-, and alkylarylamines with sodium nitrite in mineral acid with gentle heating usually results in the formation of the corresponding *N*-nitrosamines which, being unable to lose a proton, are comparatively stable to further reaction (eq 10).[2,26] Secondary amides will also undergo *N*-nitrosation.[27]

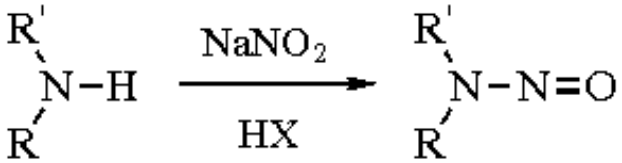

(10)

Although erroneously considered to be inert towards nitrosation,[28] tertiary amines do undergo nitrosative dealkylation when treated with $NaNO_2$ in aqueous acetic acid at 90 °C to give mixtures of products including dialkyl-*N*-nitrosamines, carbonyl compounds, and nitrous oxide (eq 11).[29] A diterpenylalkanolamine was found to lose a terpenyl substituent selectively on nitrosation with $NaNO_2$ in acetic acid.[30]

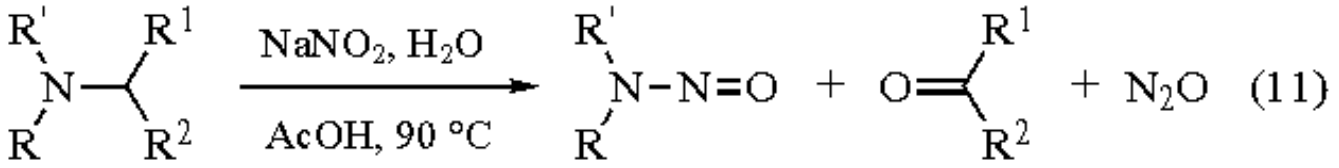

Nitrosation of hydrazine derivatives using $NaNO_2$ in acid solution provides a convenient method of preparing the corresponding azide derivatives.[31] For example, phenyl azide can be prepared by treating a suspension of phenylhydrazine hydrochloride in dilute HCl with $NaNO_2$ at 0 °C in a two-phase water/ether system (eq 12).[32] Highly substituted hydrazines undergo nitrosative dealkylation in an analogous fashion to give tertiary amines.[33] Hydrazinium salts, derived from *N*,*N*-dimethylhydrazine and an alkyl halide, are deaminated on treatment with $NaNO_2$ in HCl (4 M) to yield tertiary amines (eq 13).[34] Like simple hydrazines, hydrazides can be converted into the corresponding acyl azides by reaction with $NaNO_2$ in dilute HCl at low temperature.[31,35]

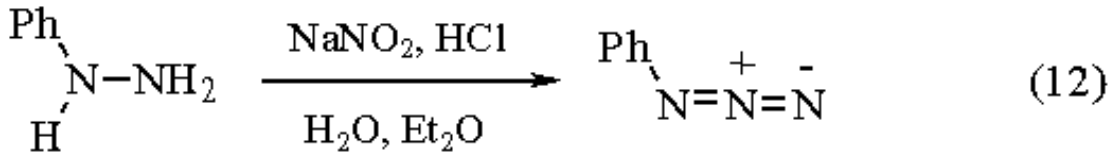

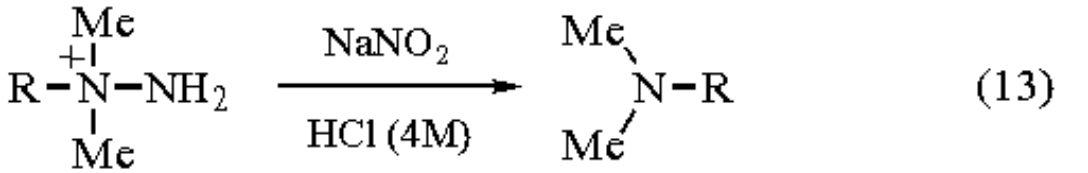

C-Nitrosation Reactions.

Aliphatic carbon centers in alkanes do not readily undergo *C*-nitrosation with nitrous acid unless activated by an electron-withdrawing substituent such as acyl, aroyl, carbonyl, carboxyl, nitro, cyano, imino, or aryl.[3] The usual products are *C*-nitrosamines or oximes, depending on the degree of substitution at the carbon center in question (eq 14). Detailed procedures have been reported for the preparation of the oximes derived from the active methylene compounds ***Ethyl Acetoacetate*** and ***Diethyl Malonate***.[36,37] The unstable β-chloro- and bromopyruvaldoximes have been obtained by treatment of the appropriate γ-haloacetoacetyl chlorides with $NaNO_2$ in ether-water via a reaction sequence which involves hydrolysis and nitrosation of the resulting β-keto acid followed by decarboxylation.[38]

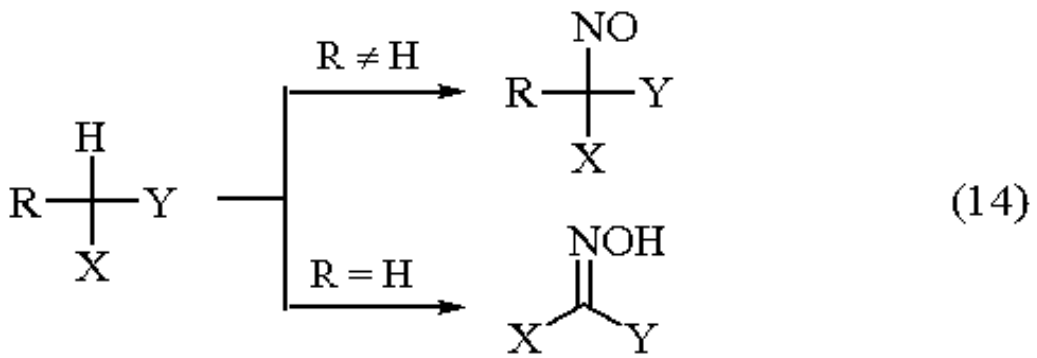

Although gaseous NOCl is generally the reagent of choice for the direct nitrosation of alkenes, the simultaneous addition of concentrated solutions of $NaNO_2$ and hydrochloric acid to limonene in isopropanol (t < 10 °C) affords the corresponding chloro oxime in good yield (eq 15).[39] The rate of nitrosation of alkenes using $NaNO_2$ and aqueous hydrochloric acid can be accelerated to a significant extent by bromide and chloride ions.[40] Tetracyclone undergoes *cis*-dihydroxylation on treatment with $NaNO_2$ in acetic acid; the reaction is thought to proceed via a cycloaddition of N_2O_3 to one of the double bonds (eq 16).[41a] Under similar conditions, methyl methacrylate and tricyclone are nitrated at unsubstituted sp^2 carbon centers, and 2,5-disubstituted furans ring open to unsaturated diketones.[41b] Isopropylidene and terpene alkenes undergo dehydromethylation to give alkynes in moderate to good yield on reaction with $NaNO_2$ in acetic acid; the reaction is complex and the Me group is lost as CO_2 (eq 17).[42] Mucobromic acid in ethanol is transformed to the sodium

salt of nitromalonaldehyde, a useful building block for the synthesis of pyrimidines, by the action of aqueous $NaNO_2$.[43]

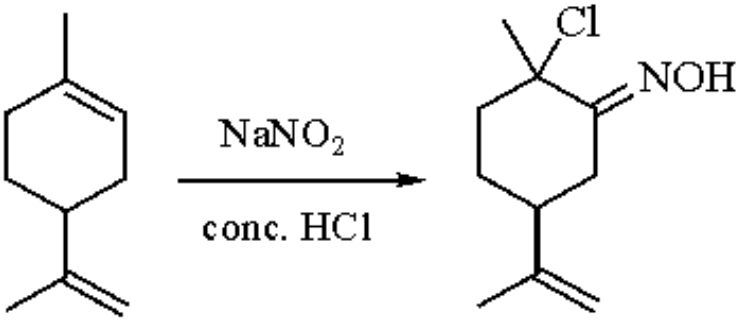

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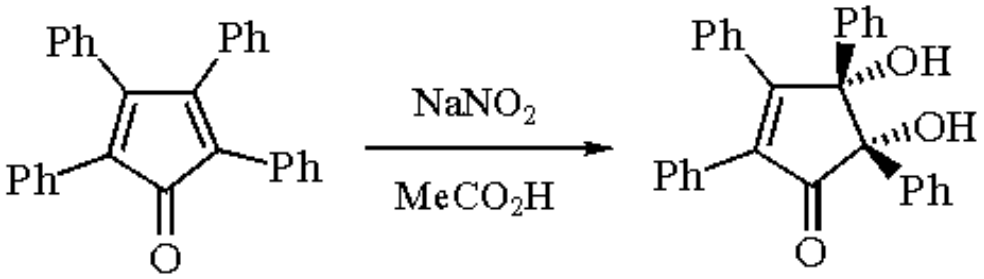

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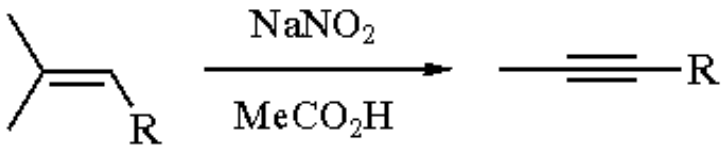

(17)

Nitrosation of phenols using $NaNO_2$ in hydrochloric acid generally results in formation of the corresponding nitroso compound.[44] Thus, for example, phenol yields 4-nitrosophenol, together with a small quantity of the 2-isomer (ca. 10%) (eq 18),[44] and 2-naphthol produces 1-nitroso-2-naphthol.[45] Treatment of phenols with buffered nitrous acid ($NaNO_2$ in large excess compared to HCl) in aqueous acetone results in the formation of diazonium salts.[46]

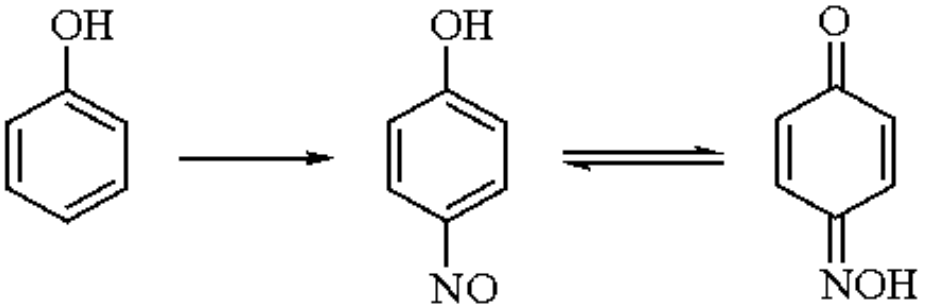

(18)

Although anisole and diphenyl ether are readily nitrosated, they both give rise to 4-nitrosophenol.[47] 4-Nitrosoanisole is, however, obtained in 57% yield from anisole if the nitrosation reaction is carried out in CH_2Cl_2/CF_3CO_2H under argon at 0 °C.[48] Nitration of simple aromatic compounds is reported to be readily achieved by reaction with $NaNO_2$ in ***Trifluoroacetic Acid*** at 25 °C; isomer ratios are similar to those expected from electrophilic aromatic substitution reactions.[49] Hydroquinones are conveniently oxidized to quinones by excess $NaNO_2$ in acetic acid.[50] Reaction of 2,3,5-trisubstituted pyrroles and 3,5-disubstituted pyrazoles with buffered nitrous acid gives rise to diazo compounds.[51]

Oxidation Reactions.

$NaNO_2$ in various acidic media, including dilute HCl, acetic acid, and CF_3CO_2H, oxidatively cleaves C=N bonds in oximes,[52] semicarbazones,[53] and hydrazones,[54,55] thereby regenerating the carbonyl group under mild reaction conditions (eq 19). 2,4-Dinitrophenylhydrazones, which are normally resistant to hydrolysis, are transformed to carbonyl compounds in ca. 80% yield.[55] Reaction of secondary or tertiary thioamides with $NaNO_2$ in HCl (4 M) affords the corresponding amides in good yield (70-90%).[56]

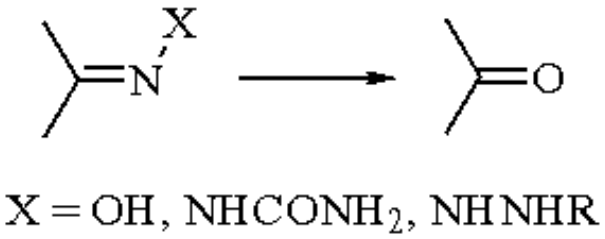

(19)

α-Nitro esters[57] and sulfones[58] are readily converted into their respective α-oximino derivatives on reaction with $NaNO_2$ in aqueous ethanol and DMF, respectively. Reactions between secondary aliphatic nitro compounds and mixtures of $NaNO_2$ and alkyl nitrites give ketones in good yield;[59] with primary aliphatic nitro compounds, carboxylic acids are obtained in low yield.[60] Carboxylic acids can undergo oxidative decarboxylation with concomitant formation of cyano compounds (50-70%) on treatment with a mixture of $NaNO_2$ and ***Trifluoroacetic Anhydride*** (1:3) in CF_3CO_2H.[61] Benzylic alcohols can be oxidized to aldehydes with $NaNO_2$ in aqueous CF_3CO_2H.[62] Diazotization of benzylamine with $NaNO_2/CF_3CO_2H$ in dry DMSO at 100 °C results in the formation of benzaldehyde (60-80%); poorer yields are obtained from the analogous isoamyl nitrite reaction.[63]

Nitroalkanes and Nitrite Esters.

Since the nitrite ion is bidentate, nucleophilic displacement reactions with alkyl halides can take place through either nitrogen or oxygen to give nitro compounds or nitrite esters respectively (eq 20). $NaNO_2$ in either DMF or DMSO reacts readily with primary and secondary alkyl bromides or iodides to yield the corresponding nitro compounds; ***Silver(I) Nitrite*** gives better yields with primary alkyl halides.[64] It is important that significant quantities of both the nitrite and the halide are in solution or the reaction does not take place. Secondary nitrosation reactions can be minimized by the addition of a nitrite scavenger such as phloroglucinol.

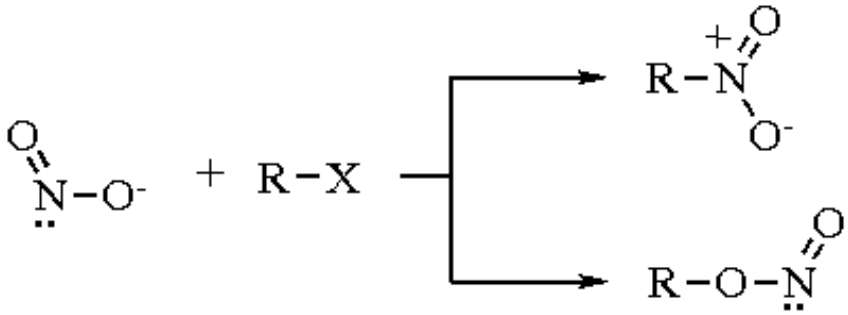

(20)

Simple alkyl nitrites can be prepared by direct esterification of the appropriate alcohol with aqueous $NaNO_2$ in sulfuric acid at 0 °C. The preparations of methyl,[65] ethyl,[66] and butyl nitrites[67] have been described in detail. ***Isopentyl Nitrite*** is obtained in high yield by treatment of a mixture of the alcohol and $NaNO_2$ with aluminum sulfate.[68] Propargyl bromides have been transformed into 3-nitroisoxazoles (20-60%) using $NaNO_2$ in DMF (eq 21).[69]

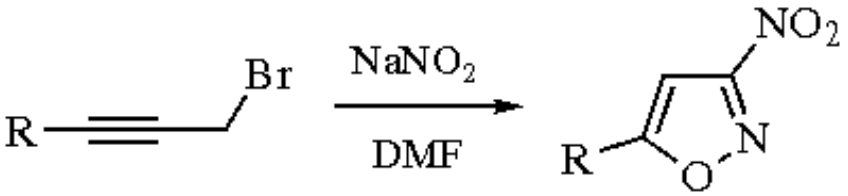

(21)

Fremy's Salt.

Potassium Nitrosodisulfonate, a useful reagent for the selective oxidation of phenols and aromatic amines to quinones (Teuber reaction), has been prepared by the reaction of $NaNO_2$ with $NaHSO_3$ and SO_3 followed by electrolysis using a stainless steel anode in alkaline solution.[70] Fremy's salt has also been generated in situ as a marker in ESR spectroscopy by bubbling O_2 through an equimolar mixture of $NaNO_2$ and $NaHSO_3$ in alkaline solution (pH 9).[71]

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Sodium Octacarbonylhydridodiferrate

$NaHFe_2(CO)_8$

[60308-01-2] · $C_8HFe_2NaO_8$ · Sodium Octacarbonylhydridodiferrate · (MW 359.78)

(reduction of α,β-unsaturated carbonyl compounds)

Physical Data: X-ray structure of the $HFe_2(CO)_8^-$ ion as the PPN^+ salt has been reported.[1]

Solubility: sol THF.

Form Supplied in: prepared as a solution in THF; not commercially available.

Analysis of Reagent Purity: IR (THF) 1987 (s), 1940 (s), 1880 (s), 1852 (s), 1770 (m) and 1730 cm^{-1} (w); ^1H NMR (THF, C_6D_6) δ -8.47 (32 °C).

Preparative Method: $Na_2Fe_2(CO)_8$ (0.764 g, 2.00 mmol)[2] is taken into a test tube equipped with a magnetic stir bar. With a pipet, 20 mL of dry THF is added; 0.112 mL of HOAc (2.00 mmol) is then added and the test tube is sealed with a serum stopper, removed from the dry box, and immediately placed in an ice bath. The sample is centrifuged for 5-10 min. This procedure gives about 12-13 mL of a yellow-brown homogeneous 0.10 M $NaHFe_2(CO)_8$ solution.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2) to exclude oxygen and moisture; solutions in THF slowly decompose at ambient temperature; the solutions are stable for a few days in a -22 °C freezer.

Reaction with CO and Ph_3P.

Added ***Carbon Monoxide*** cleaves the metal-metal bond in $NaHFe_2(CO)_8$ and forms the products shown in eq 1. The addition of other ligands such as ***Triphenylphosphine*** to $NaHFe_2(CO)_8$ in THF also results in iron-iron bond cleavage. The reaction gives significant amounts of $NaHFe(CO)_4$, $Fe(CO)_3(Ph_3P)_2$, $Fe(CO)_5$, and some $Fe(CO)_4Ph_3P$, but not $NaHFe(CO)_3Ph_3P$. The reaction stoichiometry, precise to ±15%, is shown in eq 2.

$$NaHFe_2(CO)_8 + CO \xrightarrow{THF} NaHFe(CO)_4 + Fe(CO)_5 \quad (1)$$

$$NaHFe_2(CO)_8 + Ph_3P \xrightarrow[25\ °C]{THF} NaHFe(CO)_4 + 0.4\ Fe(CO)_5 + 0.4\ Fe(CO)_3(Ph_3P)_2 + 0.2\ Fe(CO)_4Ph_3P \quad (2)$$

Reaction with MeCOCl.

The addition of ***Acetyl Chloride*** to $NaHFe_2(CO)_8$ in THF gives 18% of acetoxymethylenediiron heptacarbonyl and 20-25% acetaldehyde (eq 3).[3]

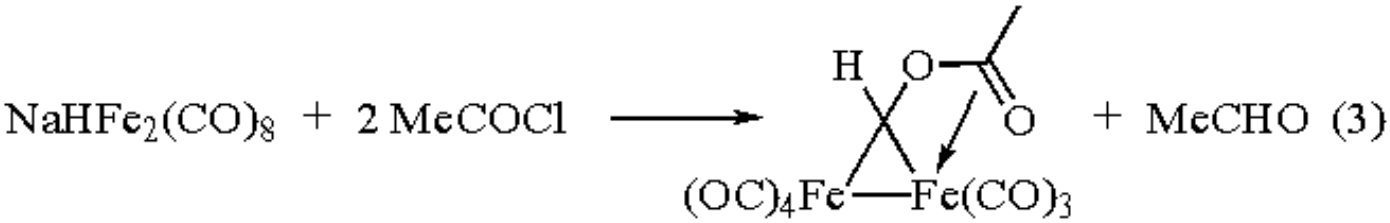

Selective Reductions.

A solution of $NaHFe_2(CO)_8$ and HOAc in THF reduces the alkenic bond in α,β-unsaturated carbonyl compounds in high yield.[2] The double bonds in unsaturated esters, ketones, aldehydes, nitriles, amides, and lactones are all reduced without concurrent carbonyl reductions, demonstrating the mild conditions of these reductions. Carvone is reduced without isomerization or concurrent reduction of the isopropenyl group (eq 4). This is in contrast to Wilkinson's catalyst[4] (***Chlorotris(triphenylphosphine)rhodium(I)***), which preferentially hydrogenates the isopropenyl group in carvone.

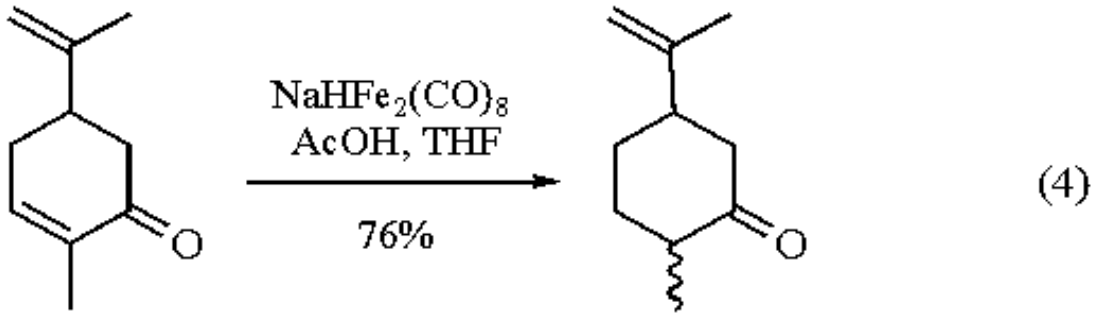

$\Delta^{1,9}$-2-Octalone is reduced to 2-decalone with a *cis*:*trans* ratio of 4:1 (eq 5). The selectivity is better than that of Noyori's reduction[5] based on ***Pentacarbonyliron*** and NaOH in methanol, which yields products with a *cis*:*trans* ratio of 1:2. A bulky substrate such as testosterone is also reduced with a *cis*:*trans* ratio of 10:1 (eq 6). However, the yield of this reaction is poor.

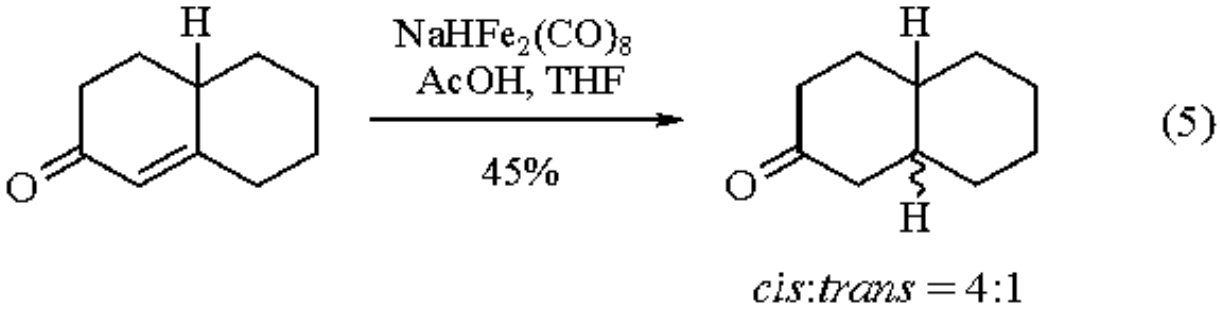

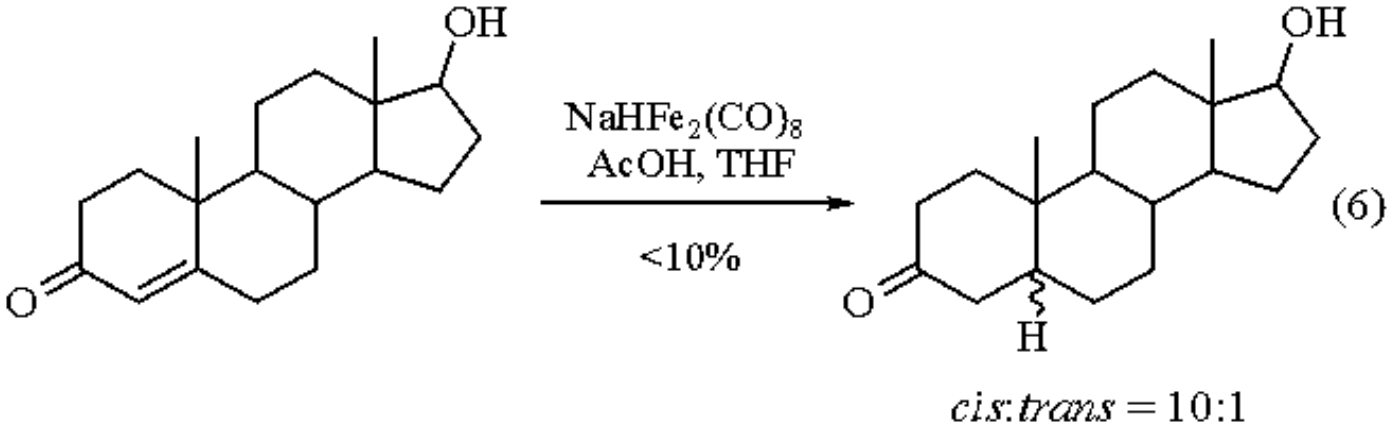

Except for exceptionally active substrates like ***Dimethyl Maleate*** and mesityl oxide, 2 or more equiv of $NaHFe_2(CO)_8$ are required to reduce 1 equiv of substrate. Compared to acetic acid, the weak, insoluble acid NH_4Cl increases yields, while the stronger acid ***Trichloroacetic Acid*** decreases yields. This reagent is a better reducing agent for the alkenic bond in α,β-unsaturated carbonyl compounds than ***Sodium Borohydride***, which is limited primarily to double bonds activated by two carbonyls.[6] The reagent also has the advantage of greater selectivity and mildness over heterogeneous hydrogenation.[7]

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Sodium Perborate

$NaBO_3.4H_2O$

[10486-00-7] · BH_8NaO_7 · Sodium Perborate · (MW 153.88)

(oxidizing agent for a variety of functional groups)

Physical Data: mp 60 °C (dec.); bulk density 0.74-0.82 g cm^{-3}.

Solubility: sol water (~23 g L^{-1} at 20 °C, ~37 g L^{-1} at 30 °C; pH of 1% solution ~10.4); sol acetic acid, lower alcohols.

Form Supplied in: colorless, crystalline, odorless, free-flowing powder; widely available; 96% minimum sodium perborate tetrahydrate; 10% minimum available oxygen.

Handling, Storage, and Precautions: safe when handled correctly. It should be stored in a cool, dry place (below 40 °C) protected from direct heat and humidity.

Sodium perborate tetrahydrate, $NaBO_3.4H_2O$, has the 1,4-diboratetraoxane structure (**1**). This structure is disrupted in polar protic solvents such as water, alcohols, and carboxylic acids, and various types of oxidizing species can be generated, from the perhydroxyl anion to protonated perboric acid, depending on the pH. The reagent is most commonly used in acetic acid at temperatures between ambient and 60 °C; peracetic acid is produced at appreciable rates at higher temperatures. Detailed mechanisms for the various perborate oxidations have yet to be established. In most of its applications, sodium perborate is recommended as a cheap, safe, and convenient alternative to oxidants such as ***Hydrogen Peroxide***, ***Peracetic Acid*** and ***m-Chloroperbenzoic Acid***, especially for large scale operations.

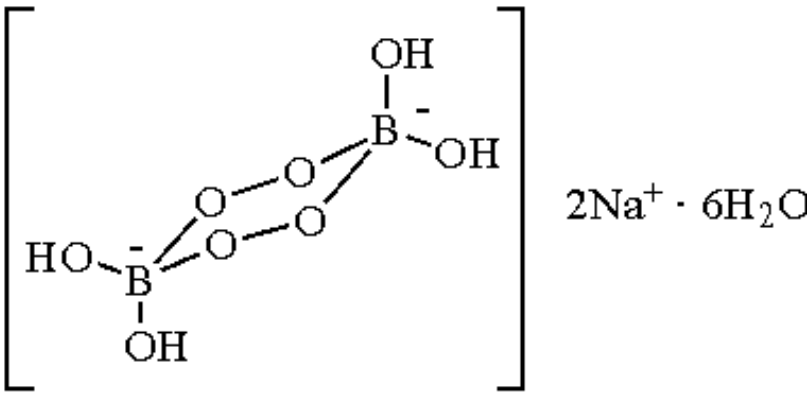

(1)

Functional Group Oxidations.

Sulfur and Selenium.

Thiols (RSH) and selenols (RSeH) are smoothly oxidized in high yield to disulfides (RSSR) and diselenides (RSeSeR).[1] Many sulfides, including a range of heterocyclic sulfur compounds, have been oxidized cleanly to sulfones with excess reagent (eq 1).[2-5] Conversion of sulfides into sulfoxides also proceeds in high yield when 1 equiv of oxidant is used, although in most cases small amounts of sulfones are also formed.[2,6] Chiral sulfoxides are obtained from appropriate precursors (eq 2).[7] Oxidation at sulfur and selenium is faster than at most other functional groups and hence it is not usually necessary to protect amino, hydroxyl, or alkenic centers. In the presence of ***Acetic Anhydride***, sodium perborate is an effective reagent for the preparation of α,β-unsaturated carbonyl compounds by oxidative deselenylation of α-phenylselenocarbonyl derivatives (eq 3).[8]

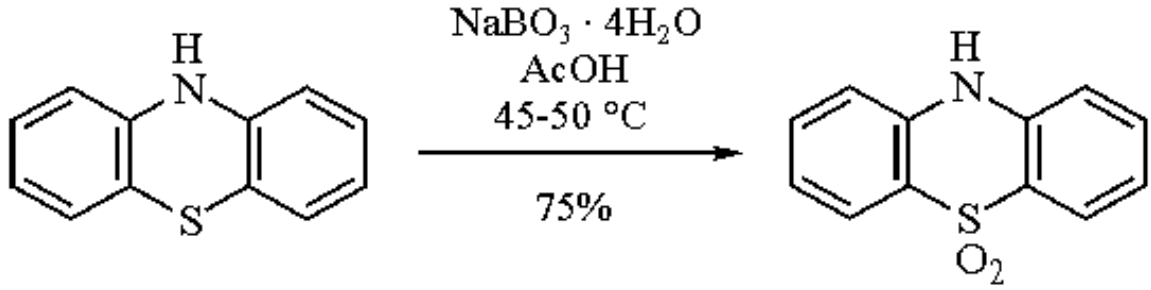

(1)

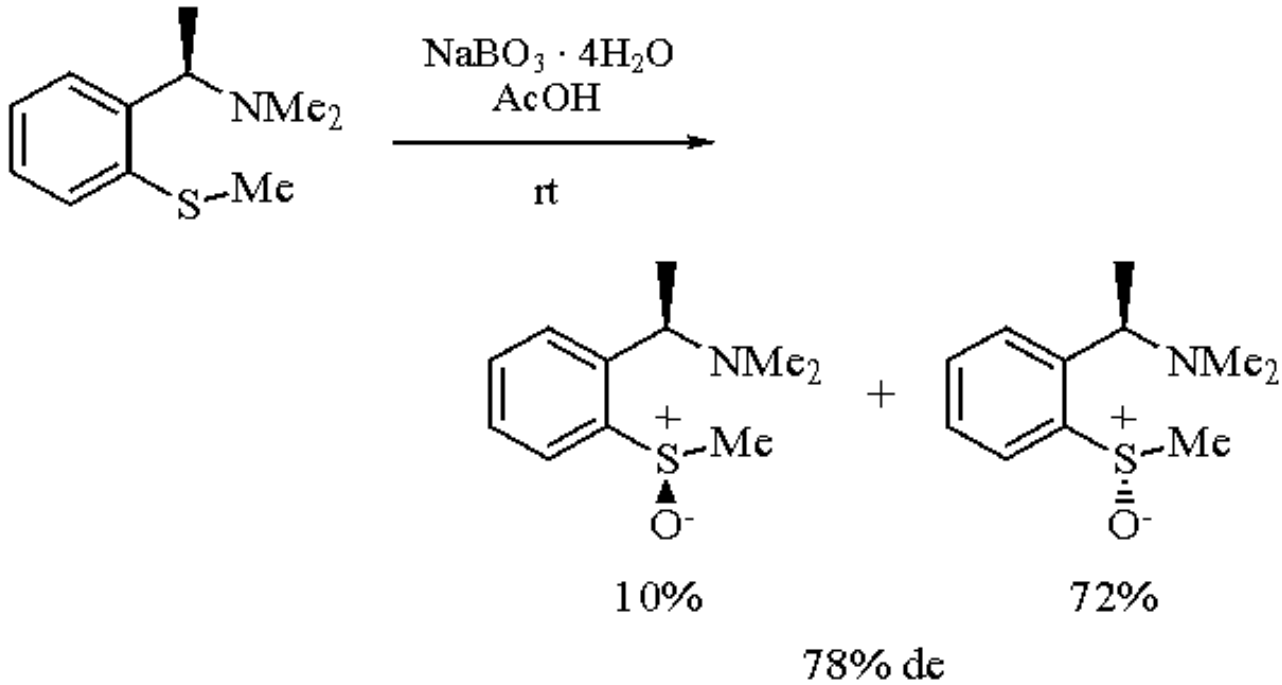

(2)

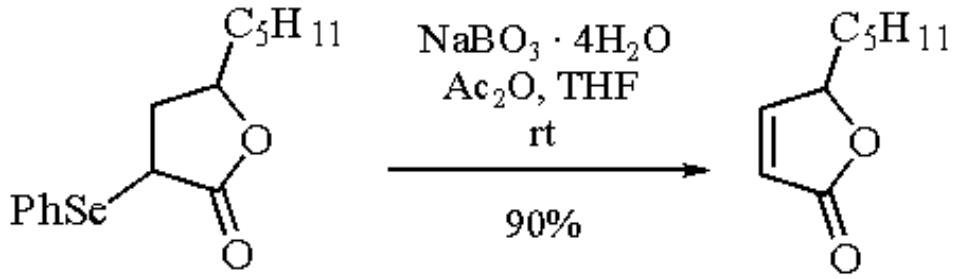

(3)

Nitrogen.

Oxidation of π-deficient azines (substituted pyridines, pyrazines, and quinolines; isoquinoline) with sodium perborate in acetic acid gives good yields of the corresponding *N*-oxides.[5,9] The reactions of anilines are particularly interesting. Depending on the reaction conditions, they can be converted into the corresponding azo,[10-12] azoxy,[13] or nitro[2,14] compounds (eq 4). The latter transformation is particularly useful for anilines which contain powerful electron-withdrawing groups in the *ortho* or *para* positions (eq 5).[2] Excellent yields are obtained of products which are very difficult, or impossible, to prepare by standard aromatic substitution reactions. Primary aliphatic amines are oxidised to *C*-nitroso compounds[15] (isolated in good yield as the dimers), while oximes give moderate yields of the corresponding nitro compounds.[16] *N*,*N*-Dialkylhydrazones are cleaved to the ketones in good to excellent yield.[2,17]

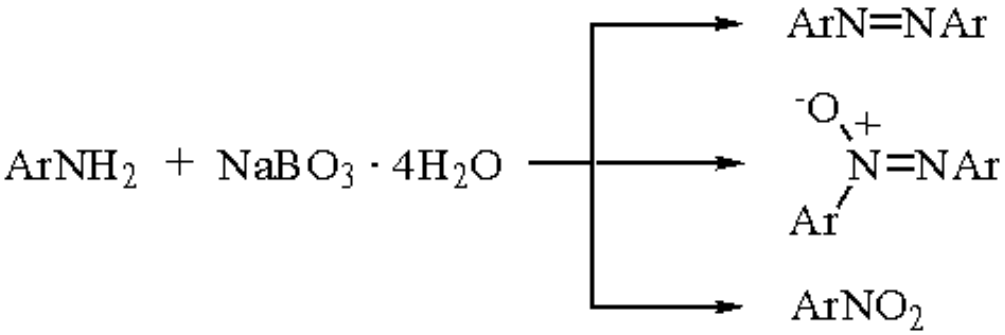

(4)

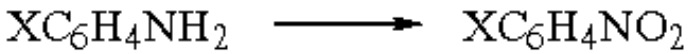

(5)

X = 4-CF_3, 86%; 2-O_2N, 76%; 4-NC, 91%

Alkenes and Alkynes.

Most types of alkenes react rather sluggishly with sodium perborate in acetic acid and this process is of little use for epoxidation. A mixture of the perborate with acetic anhydride, however, apparently generates peroxybis(diacetoxyborane), $(AcO)_2B\text{-}O\text{-}O\text{-}B(OAc)_2$, which does epoxidize alkenes in good yield (eq 6).[18] Use of the same reagent system with ***Sulfuric Acid*** catalysis gives 1,2-diol monoacetates (eq 7). Similar types of products are obtained from a series of α-substituted styrenes with perborate in acetic acid (eq 8),[19] while terminal alkynes give 1-acetoxyalkan-2-ones with added ***Mercury(II) Acetate*** as catalyst.[20] Epoxidation of α,β-unsaturated ketones can be effected in excellent yield either under phase-transfer conditions[21] or simply by using sodium perborate in a two phase water-THF system (eq 9).[22] Epoxidation of quinones has been described,[23] but in most cases yields are low.

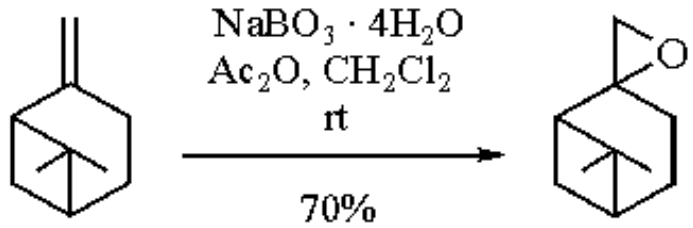

(6)

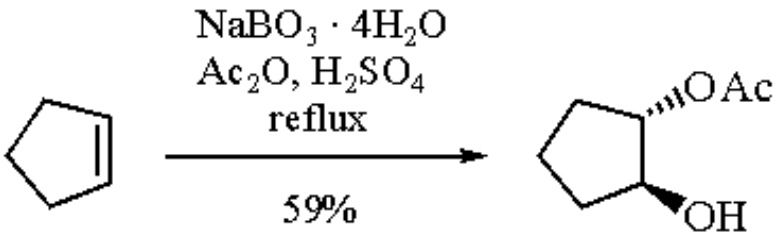

(7)

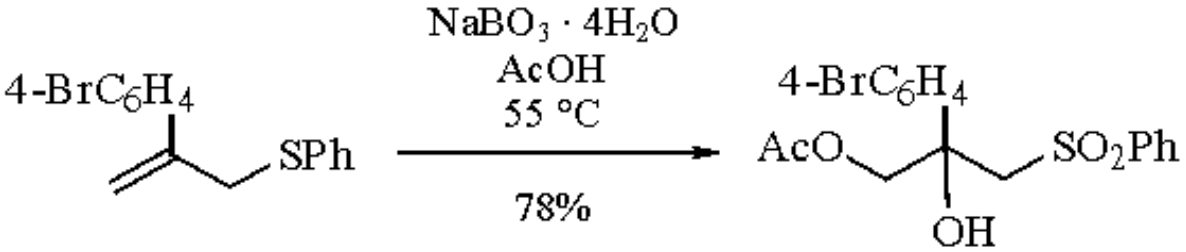

(8)

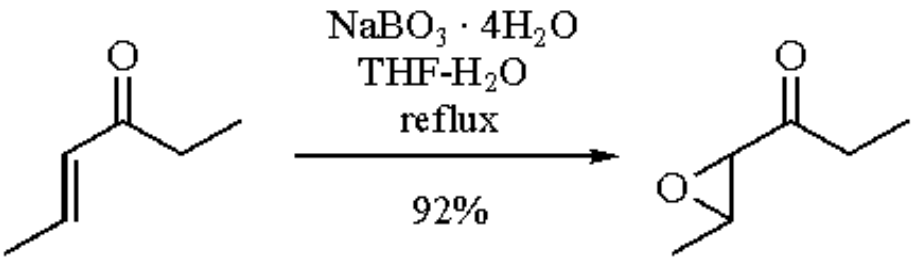

(9)

Alcohols, Aldehydes, Ketones, Phenols, and Nitriles.

Simple alcohols react only very slowly with sodium perborate and, as indicated below, aqueous alcohol serves as a very suitable solvent for the hydration of nitriles. Benzylic alcohols are oxidized to aldehydes, ketones, and/or carboxylic acids only at temperatures higher than 60 °C.[24] α-Hydroxy acids are oxidized to ketones or carboxylic acids, 1,2-diols are cleaved to acids and ketones, and α-diketones also give carboxylic acids.[25] Room temperature Baeyer-Villiger oxidation of ketones proceeds smoothly (eq 10),[2] while perborate/acetic acid at 45-50 °C is an excellent reagent for the high yield oxidation of a wide range of aromatic aldehydes to the corresponding carboxylic acids.[5,26] Hydroquinones and certain highly substituted phenols are oxidized in good yield to quinones.[2] The phenol oxidations may involve initial electrophilic hydroxylation of the electron-rich rings.[11,27] Although not formally an oxidation, the hydration of nitriles by perborate is a clean and high yielding reaction.[5,28,29] Interestingly, there is no reaction when acetic acid is used as solvent, but use of water, aqueous methanol, or a water-dioxane system gives excellent results.

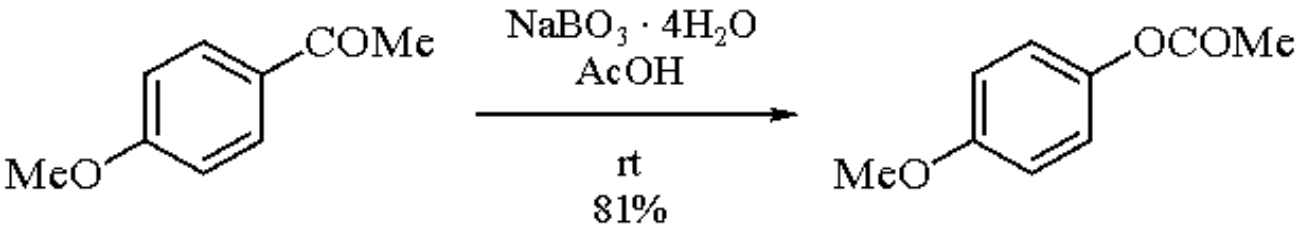

(10)

Boron, Iodine, Phosphorus.

Trialkyl- and triarylboranes are efficiently converted into alcohols and phenols on treatment at room temperature with sodium perborate in a water-THF system.[30,31] Oxidation at boron is even faster than oxidation at sulfur (eq 11), and the perborate oxidation is as good as, or better than, the conventional peroxide/base procedure. It is particularly useful for the clean, high yield conversion of alkenylboranes into aldehydes and ketones.[32] Iodoarenes are readily oxidised by sodium perborate. Use of acetic acid as solvent gives good yields of (diacetoxyiodo)arenes (eq 12),[5] while (dichloroiodo)arenes, $ArICl_2$, are obtained in 60-98% yield when hydrochloric acid is used.[33] Sodium perborate has been recommended as a viable alternative to hydrogen peroxide for the large scale oxidative decomposition of toxic organophosphorus ester wastes.[34-36]

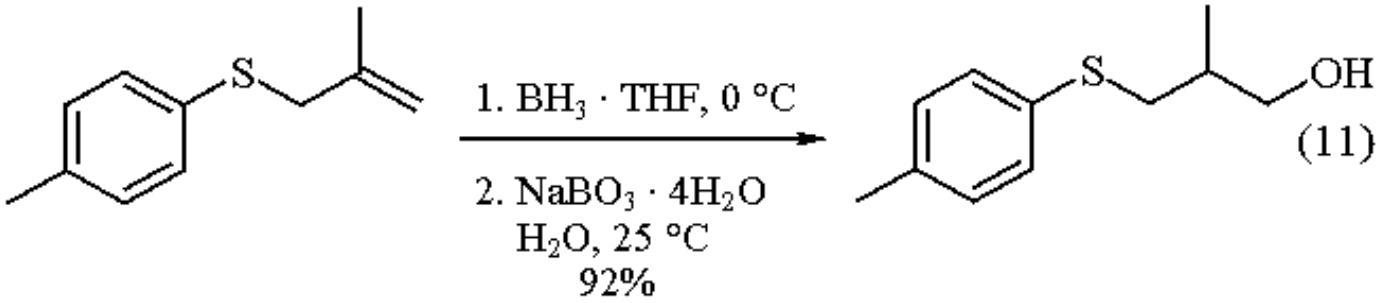

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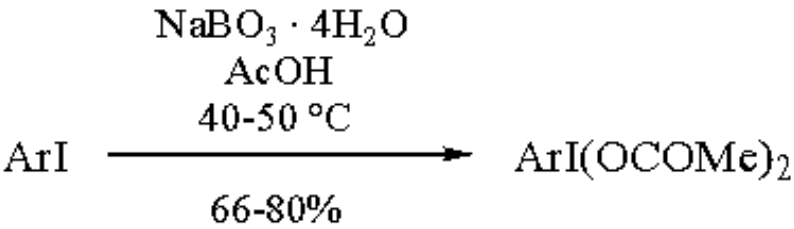

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Sodium Periodate[1]

$NaIO_4$

[7790-28-5] · $INaO_4$ · Sodium Periodate · (MW 213.89)

(oxidative cleavage of 1,2-diols;[2] oxidation of sulfides,[3] selenides,[4] phenols,[5] indoles,[6] and tetrahydro-β-carbolines[7])

Alternate Name: sodium metaperiodate.

Physical Data: mp 300 °C (dec); specific gravity 3.865.

Solubility: sol H_2O (14.4 g/100 mL H_2O at 25 °C; 38.9 g/100 mL at 51.5 °C), H_2SO_4, HNO_3, acetic acid; insol organic solvents.

Form Supplied in: colorless to white tetragonal, efflorescent crystals; readily available.

Handling, Storage, and Precautions: irritant; gloves and safety goggles should be worn when handling this oxidant; avoid inhalation of dust and avoid contact of oxidant with combustible matter.

Introduction.

Sodium periodate is widely used for the oxidation of a variety of organic substrates and as a cooxidant in other oxidation reactions (see ***Sodium Periodate-Osmium Tetroxide*** and ***Sodium Periodate-Potassium Permanganate***).[8] The $NaIO_4$ oxidation is usually conducted in water; however, for organic substrates that are insoluble in water, an organic cosolvent (e.g. MeOH, 95% EtOH, 1,4-dioxane, acetone, MeCN) is used. Alternatively, the oxidation can be conducted either with phase-transfer catalysis (PTC) using quaternary ammonium[5] or phosphonium[9] salts in a two-phase system, or in an organic solvent if the oxidant is first coated on an inert support.[10]

Oxidative Cleavage of 1,2-Diols.

$NaIO_4$ is widely used for the oxidative cleavage[2] of a variety of 1,2-diols to yield aldehydes or ketones (eq 1). In this respect, it complements the ***Lead(IV) Acetate*** method for oxidation. 1,2-Diols have been shown to be chemoselectively cleaved by $NaIO_4$ in the presence of a sulfide group.[11] $NaIO_4$ coated on wet silica gel efficiently oxidizes 1,2-diols to the aldehydes (eq 2).[10a] This method is particularly useful for the preparation of aldehydes which readily form hydrates, and it is also convenient to conduct because isolation of the product involves simple filtration of the reaction mixture and evaporation.

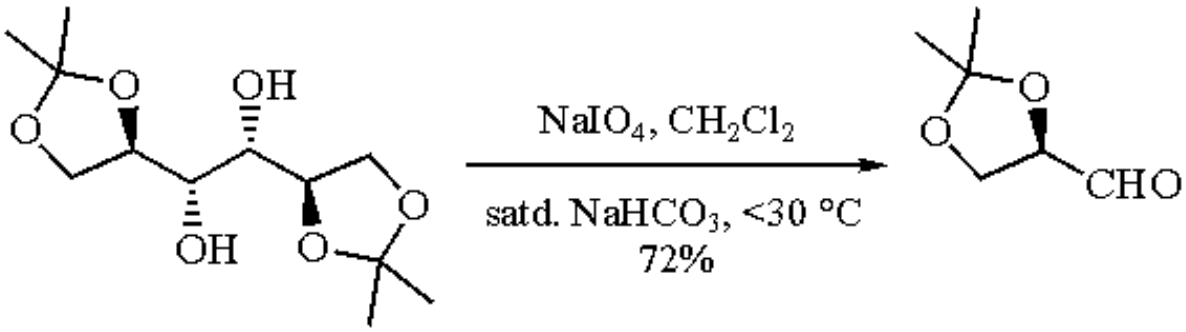

(1)

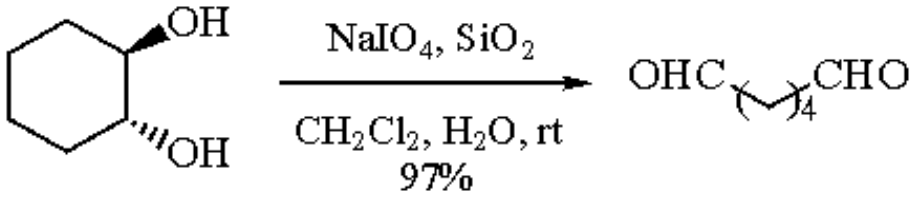

(2)

Oxidation of Sulfides to Sulfoxides.

The selective oxidation of sulfides to sulfoxides is an important transformation because sulfoxides are useful intermediates in synthesis.[12] The reaction is conducted using an equimolar amount of $NaIO_4$ in aqueous methanol at 0 °C (eq 3).[3] Higher reaction temperatures or the use of an excess of $NaIO_4$ result in overoxidation to give sulfones. $NaIO_4$ supported on acidic alumina (eq 4)[10b,c] or silica gel[10d] is effective for the selective oxidation of sulfides, at ambient temperature, to afford good yields of sulfoxides. Phase transfer-catalyzed $NaIO_4$ oxidation of sulfides also results in the selective formation of sulfoxides.[9]

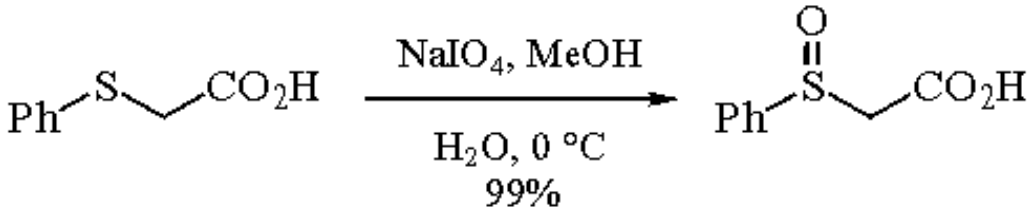

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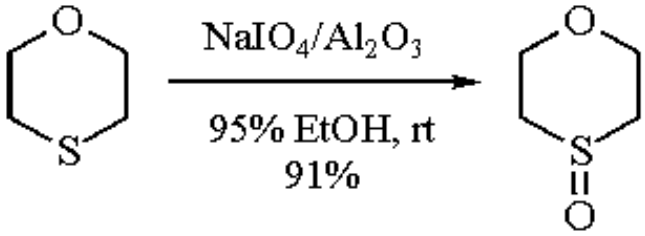

(4)

α-Phosphoryl sulfoxides, useful for the preparation of vinylic sulfoxides,[13] are prepared in high yields by the oxidation of α-phosphoryl sulfides using $NaIO_4$.[14] Vinylic sulfoxides can also be prepared in good yields by the oxidation of vinylic sulfides using $NaIO_4$ (eq 5).[15] Poor yields of sulfoxides are obtained in the $NaIO_4$ oxidation of acetylenic sulfides.[15a]

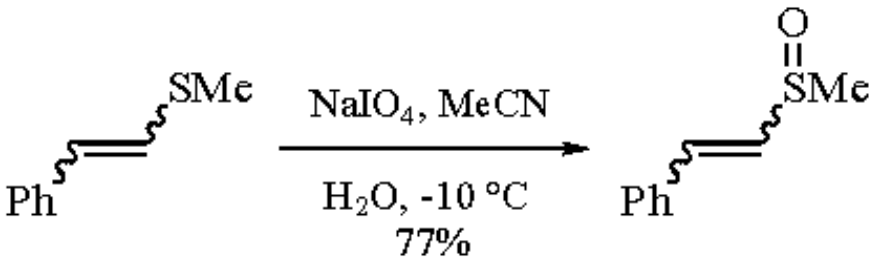

(5)

2-Substituted 1,3-dithianes are stereoselectively oxidized to the *trans*-1-oxide by $NaIO_4$ at low temperatures.[16] Dimethyl dithioacetals of aldehydes and ketones suffer $NaIO_4$-mediated hydrolysis to give carbonyl compounds.[17] This method could be useful for the deprotection of dimethyl dithioacetals. Oxidation of dithioethers such as 1,4-dithiacycloheptane using $NaIO_4$ at 0 °C furnishes the 1-oxide in modest yield.[18] The use of ***m-Chloroperbenzoic Acid*** for this oxidation leads to an appreciable amount of the 1,4-dioxide. Oxidation of a naphtho-1,5-dithiocin using an excess of $NaIO_4$ at rt results in a high yield of the *cis*-1,5-dioxide.[19] The sulfide unit in thiosulfoxides is selectively oxidized to the *S,S*-dioxide in good yields using an equimolar amount of $NaIO_4$ at 0 °C.[20] Unsymmetrical thiosulfinic *S*-esters are efficiently converted to the thiosulfonic *S*-esters, without concomitant cleavage of the S-S bond, by $NaIO_4$ oxidation.[21] $NaIO_4$ is effective for the selective oxidation of the sulfide moiety in (**1**) to the sulfoxide in the presence of a disulfide linkage (eq 6).[22] Other oxidants such as CrO_3 in acetic acid, H_2O_2, and *m*-CPBA, which are useful for the oxidation of simple sulfides, only cause the decomposition of (**1**).

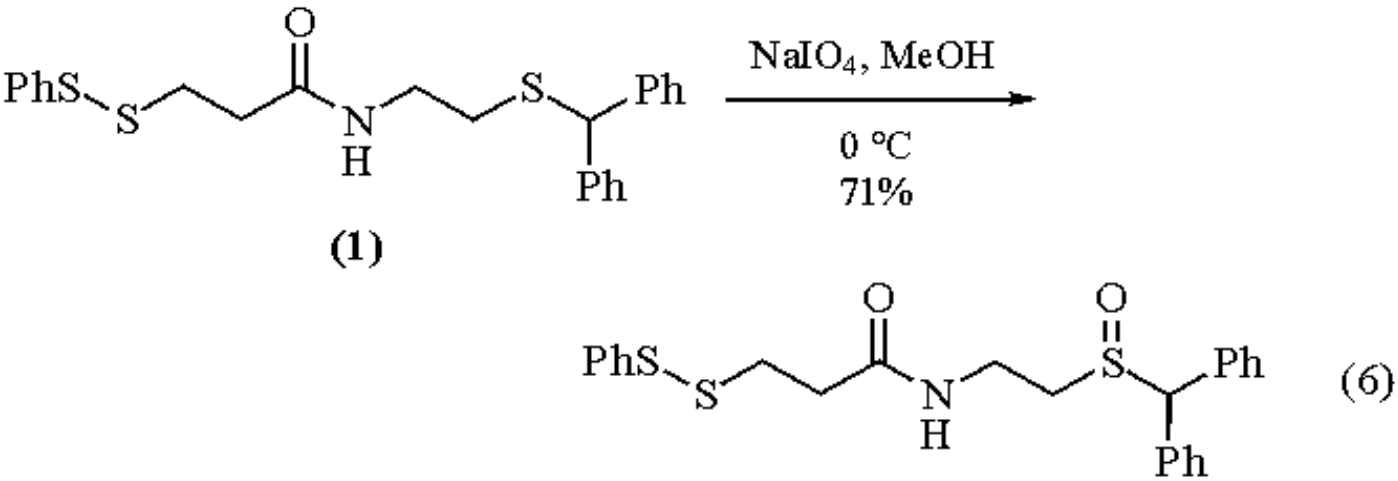

Oxidation of Selenides to Selenoxides.

Diaryl, dialkyl, and aryl alkyl selenides are oxidized[4] to the corresponding selenoxides in high yields using a slight excess of $NaIO_4$ at 0 °C (eq 7).[4a] The presence of an electron-withdrawing substituent in diaryl selenides inhibits the oxidation of the selenium center. Vinylic selenides can be oxidized[23] with $NaIO_4$ to give high yields of vinylic selenoxides (eq 8).[23a] In contrast, oxidation with ***Hydrogen Peroxide*** results in the cleavage of the double bond to give carboxylic acids. The oxidation of organoselenides possessing β-hydrogens results in the formation of highly unstable organoselenoxides that undergo facile *syn* elimination, often at room temperature, to give alkenes (eq 9).[24,25] Such a process constitutes a useful method for the introduction of a double bond into organic molecules.

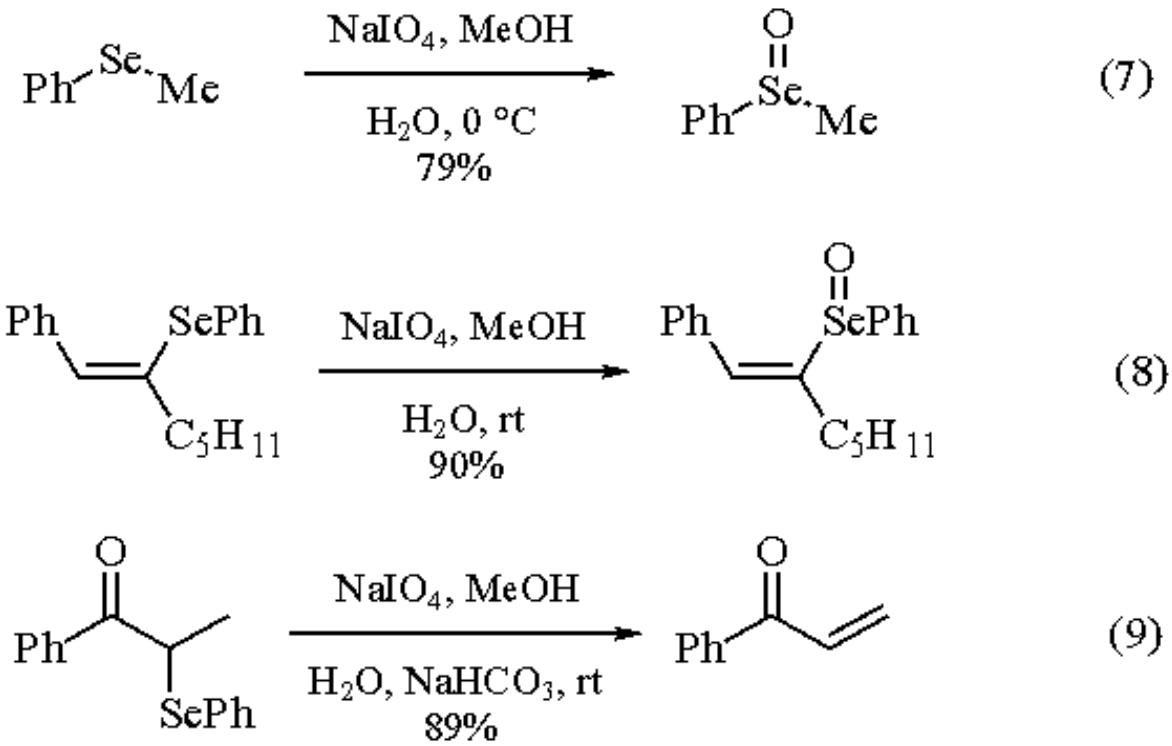

Oxidation of Phenols and Its Derivatives.

Dihydroxybenzenes are oxidized to give high yields of the corresponding quinones using $NaIO_4$ supported on silica gel (eq 10)[10a] or under PTC (see also ***Tetra-n-butylammonium Periodate***).[5] Treatment of *p*-hydroxybenzyl alcohol with $NaIO_4$ in aqueous acetic acid results in the formation of *p*-benzoquinone, albeit in low yield (23%).[26] On the other hand, *o*-(hydroxymethyl)phenols possessing at least one bulky group at the C-4 position are efficiently oxidized to give spiroepoxy-2,4-cyclohexadienones (eq 11).[27] In the absence of a bulky group, self-dimerization of the spiroepoxycyclohexadienone via Diels-Alder reaction occurs. In the case of *o*-(hydroxymethyl)phenols that are substituted with one or two aryl groups at the benzylic carbon, a novel oxidative rearrangement occurs to yield benzylidene protected catechols in modest yields (eq 12).[28] However, this oxidative rearrangement is only successful if substituents are present in the C-2 and C-4 positions of the phenol unit, because oxidation of α-(2-hydroxyphenyl)benzyl alcohol only results in the formation of a dimer.

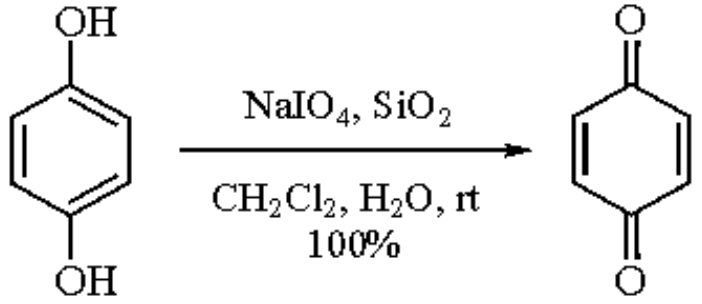

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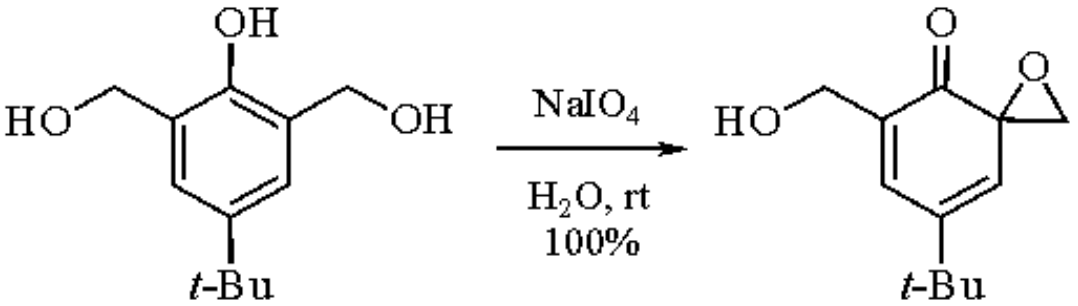

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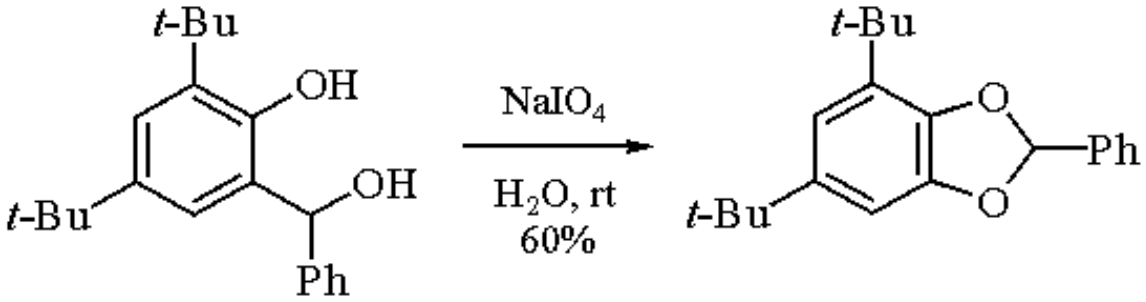

(12)

Oxidation of Indoles and Tetrahydro-β-Carbolines.

The indolic double bond in 2,3-dialkyl- and 3-alkylindoles is readily oxidized by 2 mole equiv of $NaIO_4$ at room temperature to give *o*-amidoacetophenone derivatives in good yields (eq 13).[6] However, the oxidation of 2,3-diphenylindole under the same conditions results in a lower yield of the oxidative cleavage product.[29] Interestingly, the oxidation of 2-alkylindoles results in the formation of a mixture of products comprised of indoxyl derivatives.[29] Tetrahydrocarbazoles are also efficiently oxidized by $NaIO_4$ to afford benzocyclononene-2,7-dione derivatives.[6] Tetrahydro-β-carbolines have also been subjected to $NaIO_4$ oxidation.[7] Thus, in the oxidation of the tetrahydro-β-carboline-3-carboxylates, the type of product that is formed depends upon the degree of substitution at C-1 of the starting material (eqs 14 and 15).[7a]

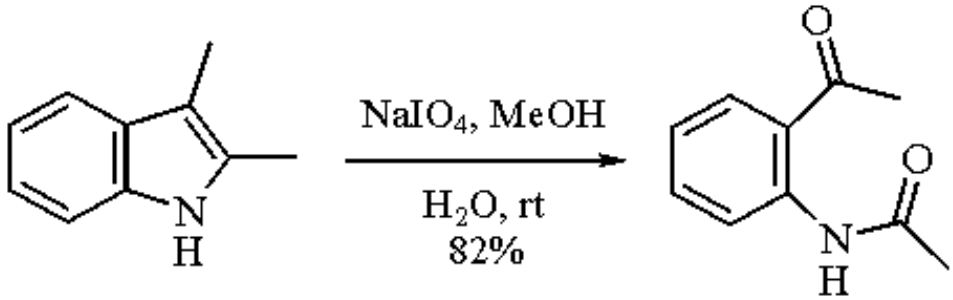

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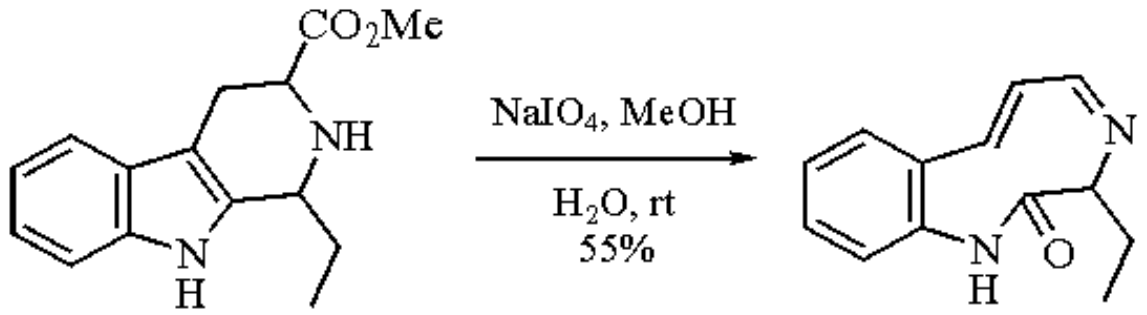

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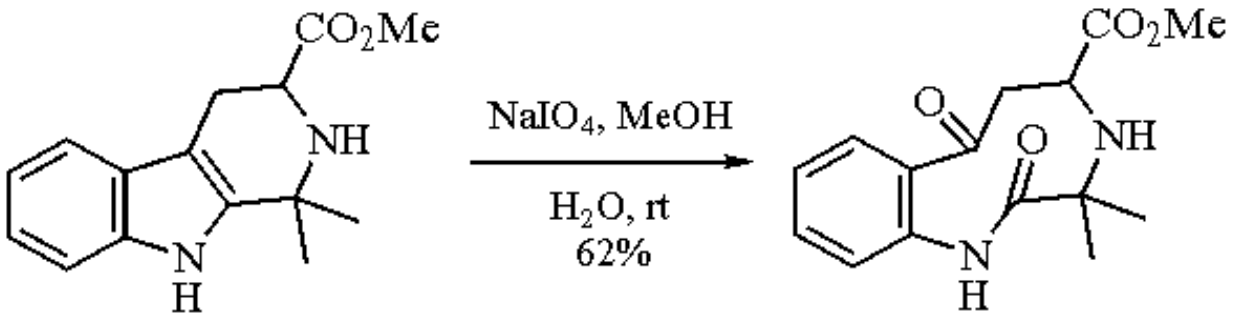

(15)

Other Applications.

1,3-Cyclohexanedione and its 3-substituted derivatives are oxidized with $NaIO_4$, with concomitant loss of the C-2 carbon unit, to give glutaric acid in good yields.[30] 1,3-Cyclopentanediones react more slowly under the same conditions, and aromatic diketones such as 1,3-indandione give poor yields of the dicarboxylic acid product. α-Hydroxy carboxylic acids undergo oxidative decarboxylation to give aldehydes (eq 16)[31] upon treatment with aqueous $NaIO_4$; however, long reaction times are required. The use of PTC[9] or Bu_4NIO_4 allows for shorter reaction times without adversely affecting the yield. The oxidation of hydrazine with $NaIO_4$ in the presence of trace amounts of aqueous ***Copper(II) Sulfate*** and ***Acetic Acid*** results in the formation of ***Diimide***. The in situ generation of diimide by this method has been successfully applied to a one-pot procedure for the reduction of alkenes (eq 17).[32]

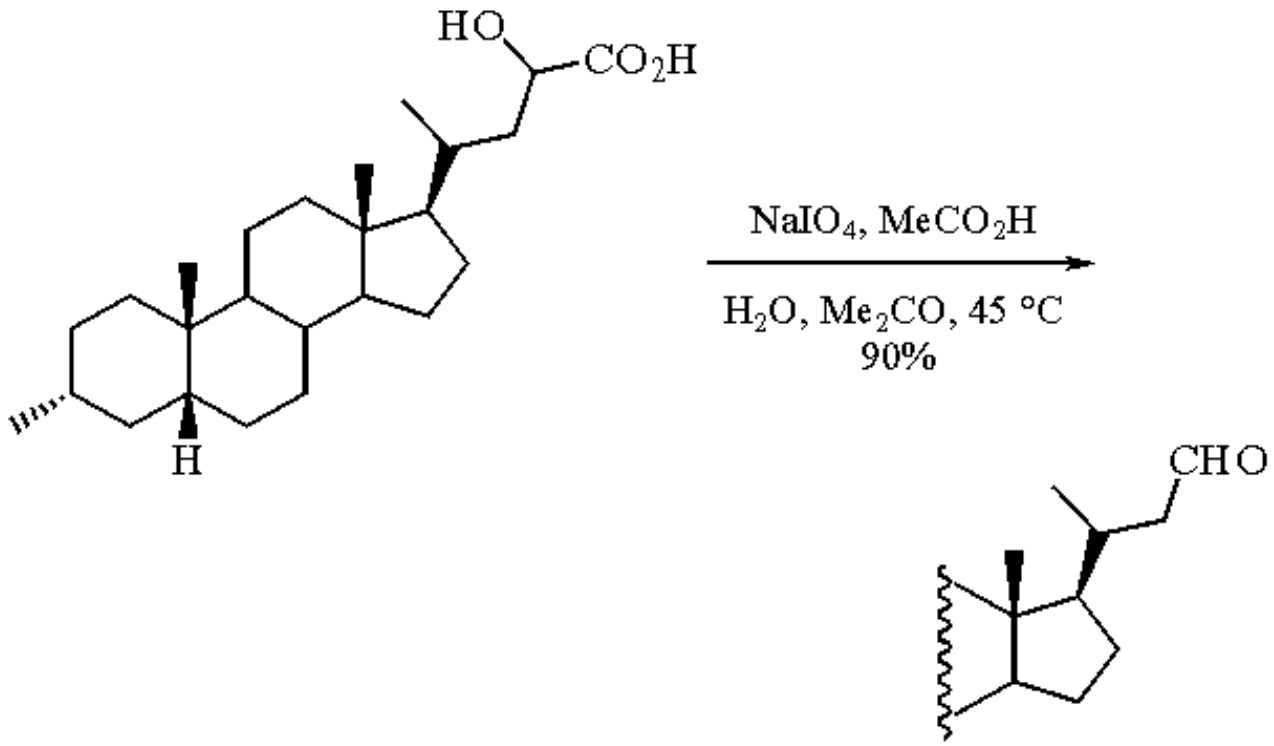

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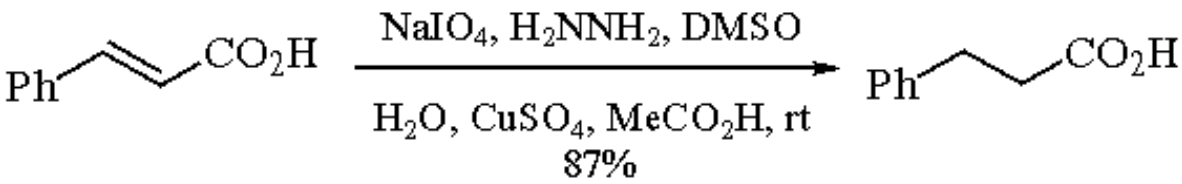

(17)

A secondary amide is obtained by selective oxidation of a tertiary carbon center in adamantane with $NaIO_4$ in the presence of iron(III) perchlorate in acetonitrile (eq 18).[33] Dimethylhydrazones undergo periodate induced hydrolysis, at pH 7, to give carbonyl compounds in high yields (eq 19).[34] However, these conditions are unsuitable for the hydrolysis of dimethylhydrazones derived from aromatic or α,β-unsaturated aldehydes because mixtures of aldehydes and nitriles are formed.

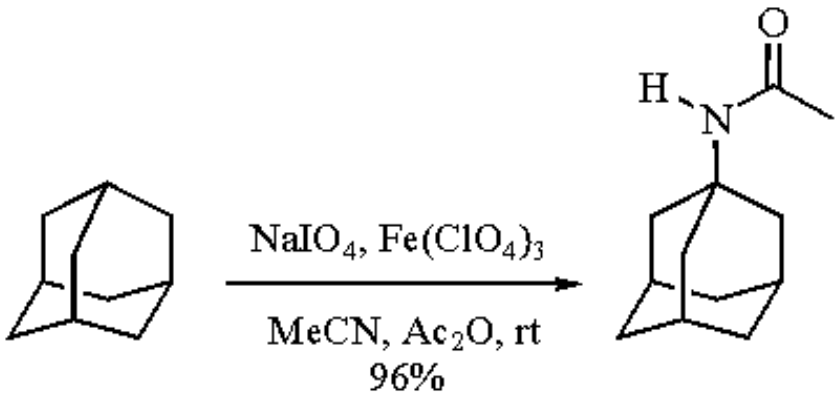

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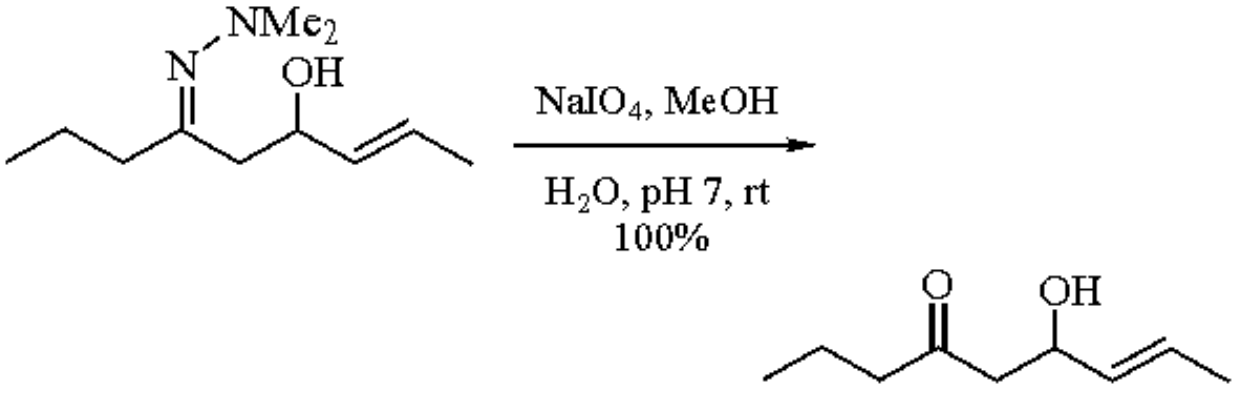

(19)

Acylphosphoranes are oxidized to α,β-dicarbonyl compounds in fair yields using aqueous $NaIO_4$ (eq 20).[35] This method complements other methods such as the ***Potassium Permanganate***[36a] or ***Ruthenium(VIII) Oxide*** oxidation[36b] of alkynes. $NaIO_4$ is also used for the oxidation of hydroxamic acids and *N*-hydroxycarbamic esters at pH 6 to generate highly reactive nitroso compounds.[37] The oxidations are usually conducted in the presence of conjugated dienes so that the nitroso intermediates are trapped as their Diels-Alder cycloadducts (eq 21).

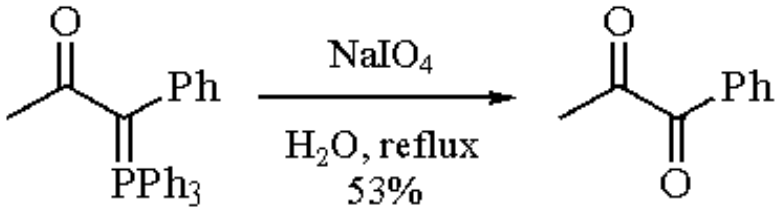

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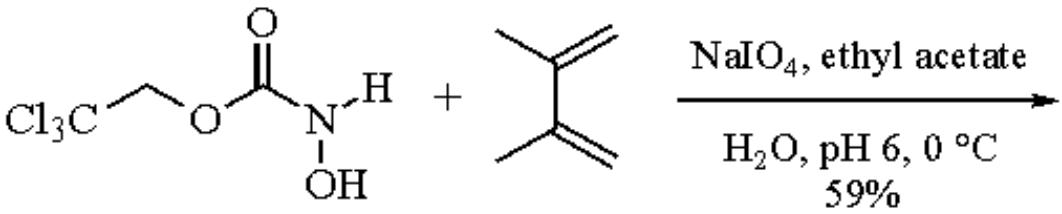

(21)

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Sodium Periodate-Osmium Tetroxide[1,2]

$NaIO_4$-OsO_4

($NaIO_4$)

[7790-28-5] · $INaO_4$ · Sodium Periodate-Osmium Tetroxide · (MW 213.89) (OsO_4)

[20816-12-0] · O_4Os · Sodium Periodate-Osmium Tetroxide · (MW 254.20)

(oxidizing agent for oxidative cleavage of carbon-carbon double bonds[3] to give aldehydes and ketones)

Physical Data: $NaIO_4$: mp 300 °C (dec); specific gravity 3.865. OsO_4: bp 130 °C; mp 40 °C; specific gravity 4.900 at 22 °C.

Solubility: $NaIO_4$: sol H_2O (14.4 g/100 mL H_2O at 25 °C; 38.9 g/100 mL at 51.5 °C), H_2SO_4, HNO_3, acetic acid; insol organic solvents. OsO_4: sol alcohol, Et_2O, benzene, CCl_4, NH_3, $POCl_3$, H_2O (25%).

Form Supplied in: $NaIO_4$: colorless to white tetragonal, efflorescent crystals. OsO_4: colorless to pale yellow crystals contained in ampules. Both reagents are readily available.

Handling, Storage, and Precautions: $NaIO_4$: irritant; gloves and safety goggles should be worn when handling this oxidant; avoid inhalation of dust and avoid contact of oxidant with combustible matter. OsO_4: acrid, chlorine-like odor; irritant; highly corrosive; causes burns to skin, eyes, and respiratory tract; gloves and safety goggles must be worn and this reagent must be handled in a well ventilated fume hood.

Introduction.

In 1956, Lemieux, Johnson, and co-workers first described[3] the use of sodium periodate-osmium tetroxide for the direct oxidation of alkenic bonds to give carbonyl compounds. This reaction combines the hydroxylating properties of ***Osmium Tetroxide*** with the glycol cleavage capabilities of ***Sodium Periodate***. Additionally, sodium periodate serves to regenerate osmium tetroxide during the reaction, thereby permitting the use of only catalytic amounts of the expensive and toxic osmium tetroxide. This oxidation complements the classical method of ozonization of double bonds followed by reductive cleavage. The reaction is usually carried out in a mixed aqueous solvent system such as aqueous dioxane, aqueous THF, aqueous acetone, or aqueous DME. Water is required in this reaction for the hydrolysis of the intermediate osmate ester. In reactions where the carbonyl products are prone to self-condensation, the use of the ether-water system is found to be highly satisfactory.

Oxidative Cleavage of Double Bonds to Give Carbonyl Compounds.

The oxidation of acyclic alkenes and stilbene in aqueous 1,4-dioxane using sodium periodate in the presence of catalytic amounts of osmium tetroxide ($NaIO_4$-cat. OsO_4) yields the corresponding aldehydes in good yields (eqs 1 and 2).[3,4] In contrast, the oxidation of cyclohexene under the same conditions gives only a low yield of adipaldehyde. The low yield is attributed to the tendency of adipaldehyde to undergo self-condensation. The use of an ether-water system for the oxidation circumvents this problem. Under the modified conditions, the oxidation of cyclohexene gives a good yield of adipaldehyde (eq 3).[3] Similarly, cyclopentene is oxidized to afford glutaraldehyde in good yield. 1-Methylcyclohexene, however, is oxidized very slowly under the optimum conditions found for cyclohexene; only a small amount of an uncharacterized carbonyl compound is obtained. Nevertheless, this outcome suggests that $NaIO_4$-cat. OsO_4 can be employed for the selective cleavage of unhindered double bonds in the presence of hindered ones. This type of selective oxidation is effectively applied to the cleavage of a vinyl group in the presence of a more hindered alkenic bond in the etorphine ring system (eq 4).[5]

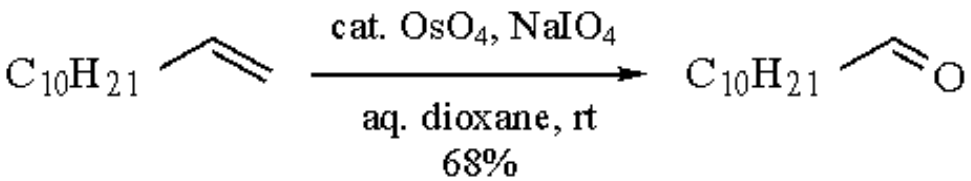

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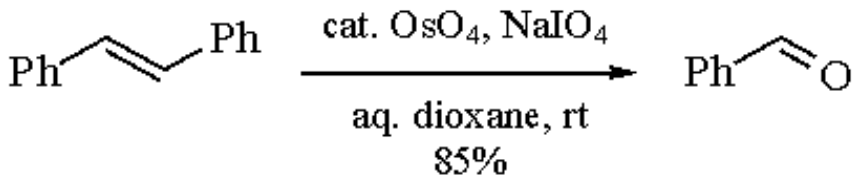

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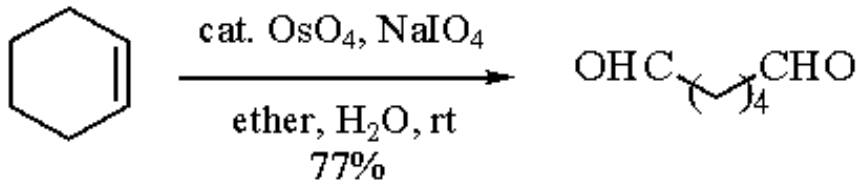

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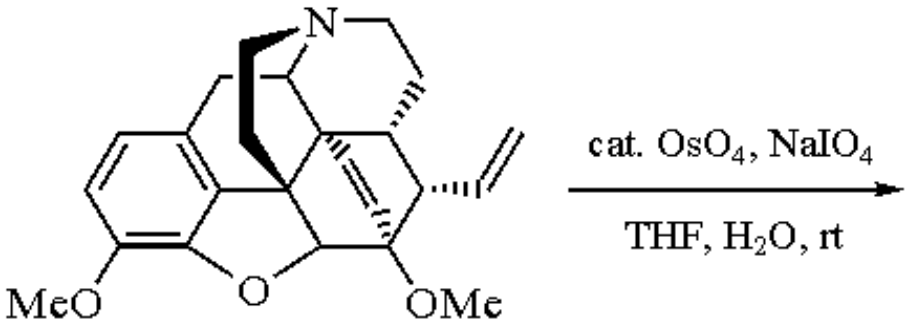

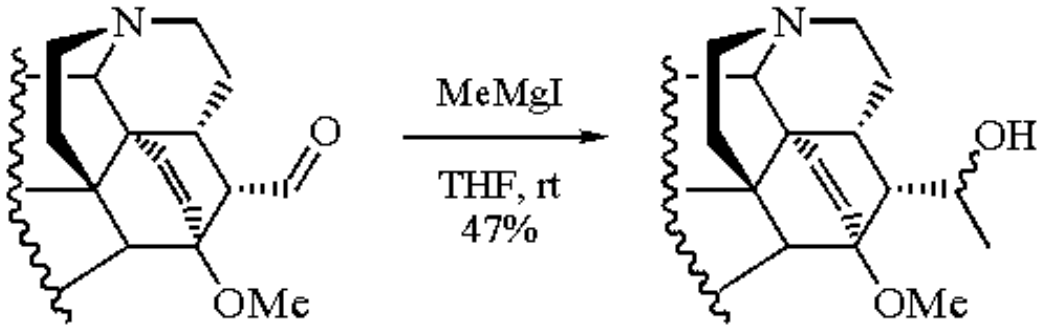

(4)

Alkenic compounds are rapidly and efficiently cleaved to carbonyl compounds using $NaIO_4$ in the presence of polymer-supported OsO_4 (P-OsO_4) (eqs 5 and 6).[6] Cyclohexene is oxidized to give a fairly good yield of adipaldehyde (eq 7). This provides a useful alternative to oxidation in the ether-water system[3] alluded to earlier. α,β-Unsaturated carbonyl compounds are oxidized at the double bond to give aldehydes in good yields (eq 8). A notable feature of this method[6] is that a particular oxidation can be easily repeated, at least 10 times, by simply adding new portions of substrate and sodium periodate.

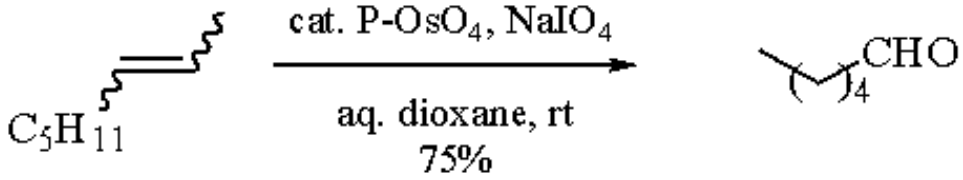

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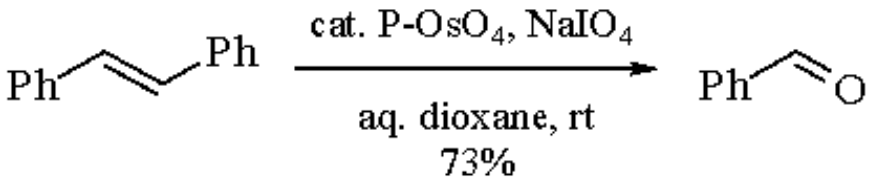

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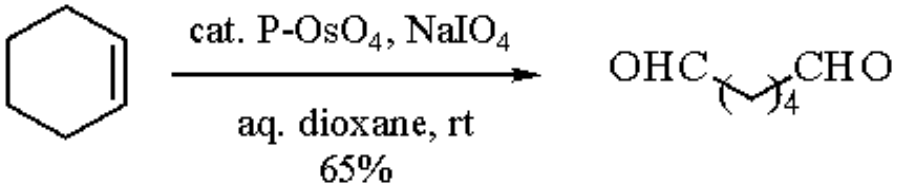

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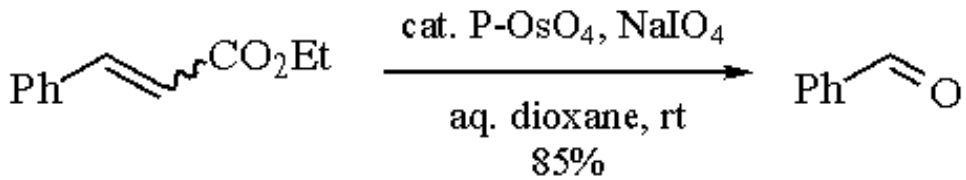

(8)

The double bond in alkyl, cycloalkylmethyl, and arylmethyl allyl ethers can be oxidatively cleaved using $NaIO_4$-cat. OsO_4. The oxidation of (**1**) in aqueous dioxane containing trace amounts of acetic acid affords a good yield of the benzyloxy aldehyde (eq 9).[7] On the other hand, oxidation of similar systems[8] in aqueous dioxane results in only low yields of aldehydes. Higher yields are obtained when the oxidation is carried out using the ether-water system (eq 10).

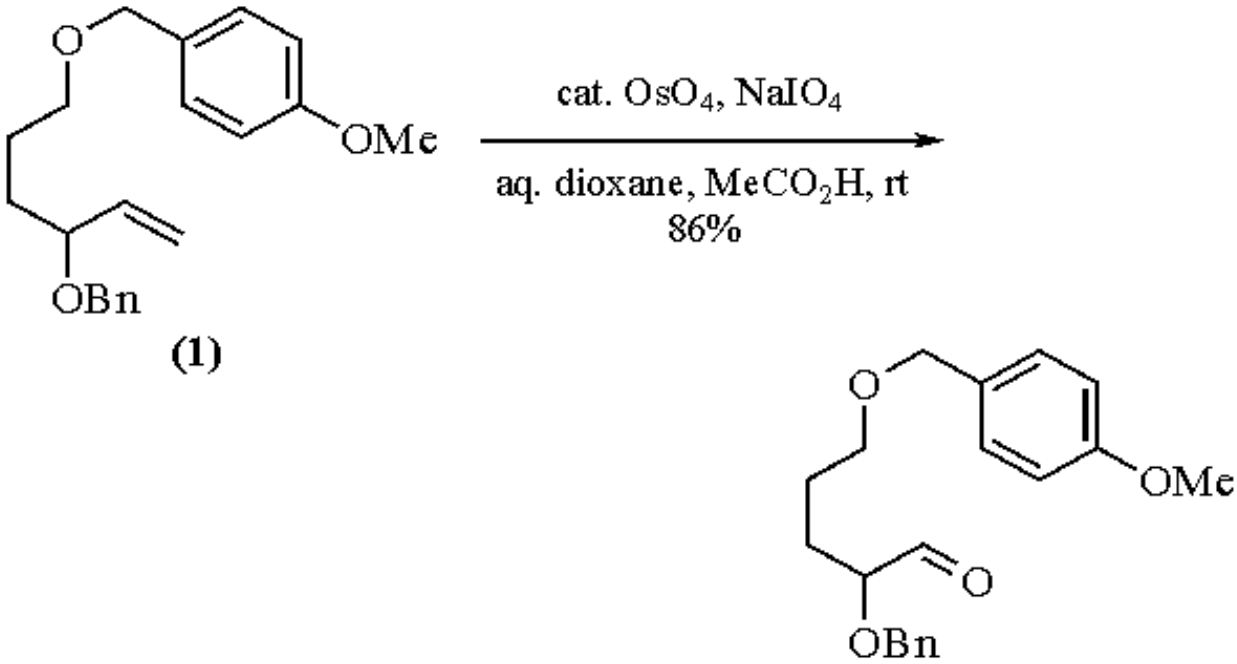

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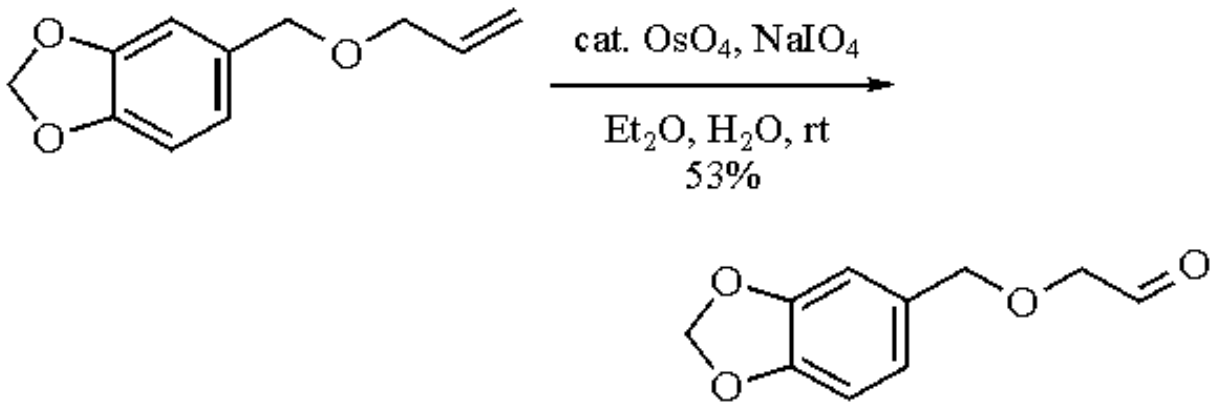

(10)

Allylic alcohols are oxidized using $NaIO_4$-cat. OsO_4, with concomitant loss of two carbon units, to furnish good yields of the expected aldehyde (eq 11).[9] The double bond in hydroxy alkenes, such as in (*R*)-(+)-citronellol, is selectively oxidized to give the corresponding hydroxy aldehydes which, upon subsequent Wittig alkenation, give the α,β-unsaturated esters (eq 12).[10]

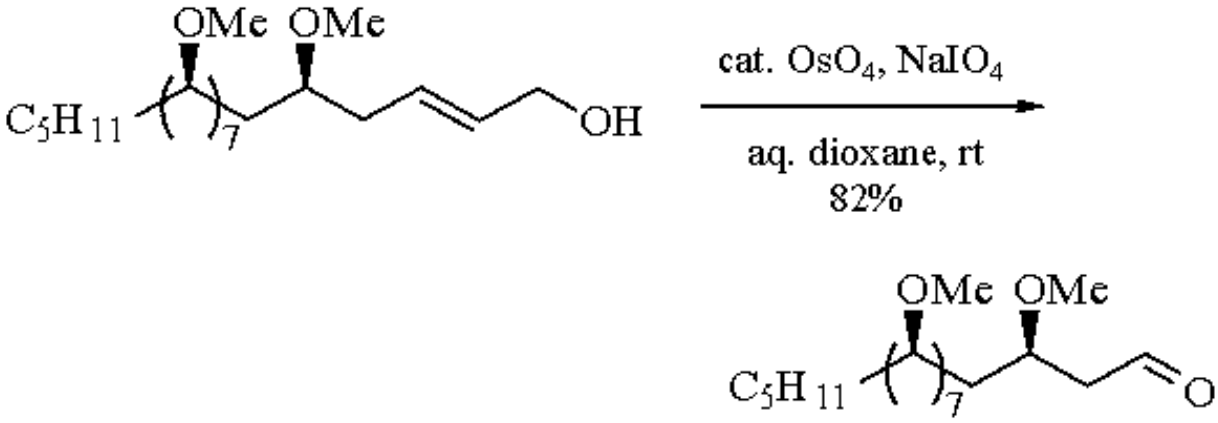

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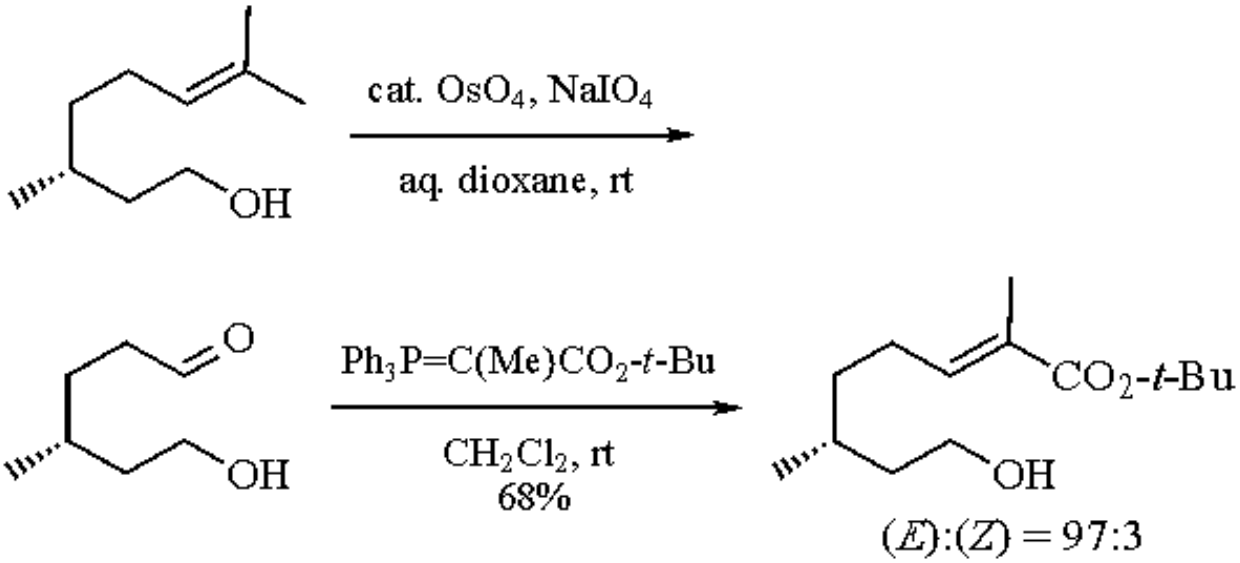

(12)

The oxidation of γ,δ-unsaturated carbonyl substrates using $NaIO_4$-cat. OsO_4 is a practical method for the preparation of synthetically useful 1,4-dicarbonyl compounds.[11] For example, oxidation of the double bond of the allyl moiety in (**2**) yields the aldehyde in good yield (eq 13).[11a] Subsequent base-catalyzed aldol condensation of the keto aldehyde furnishes the spirocyclopentenone derivative, albeit in low yield. Such a protocol has been employed for the preparation of key cyclopentenone intermediates used in natural products synthesis, e.g. in the syntheses of phytuberin (eq 14),[12] aphidicolin (eq 15),[13] and bakkenolide (eq 16).[14]

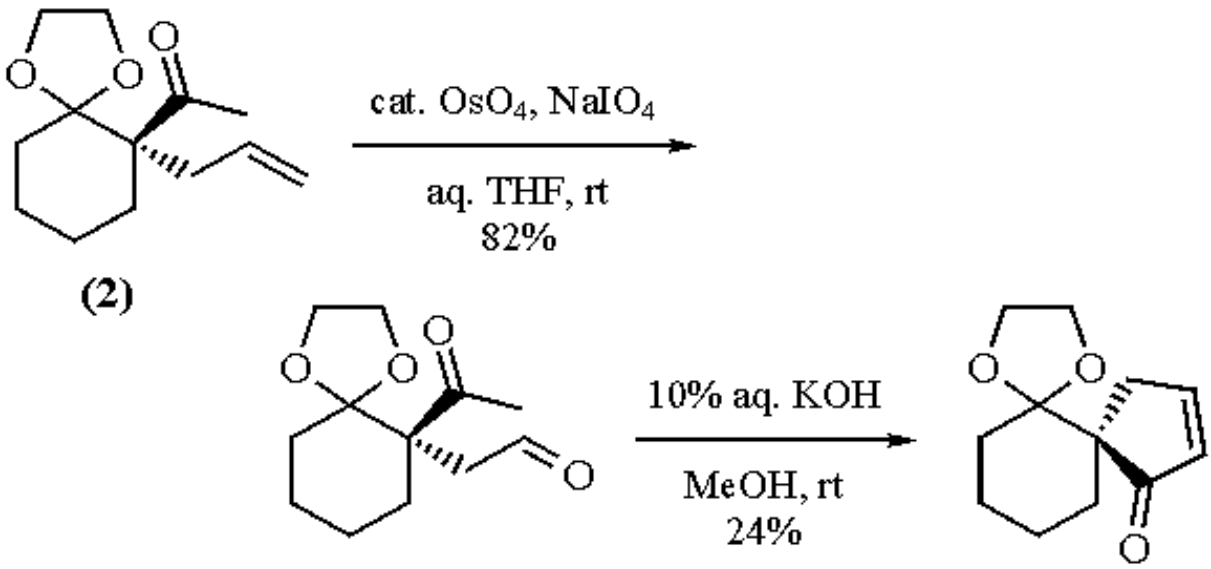

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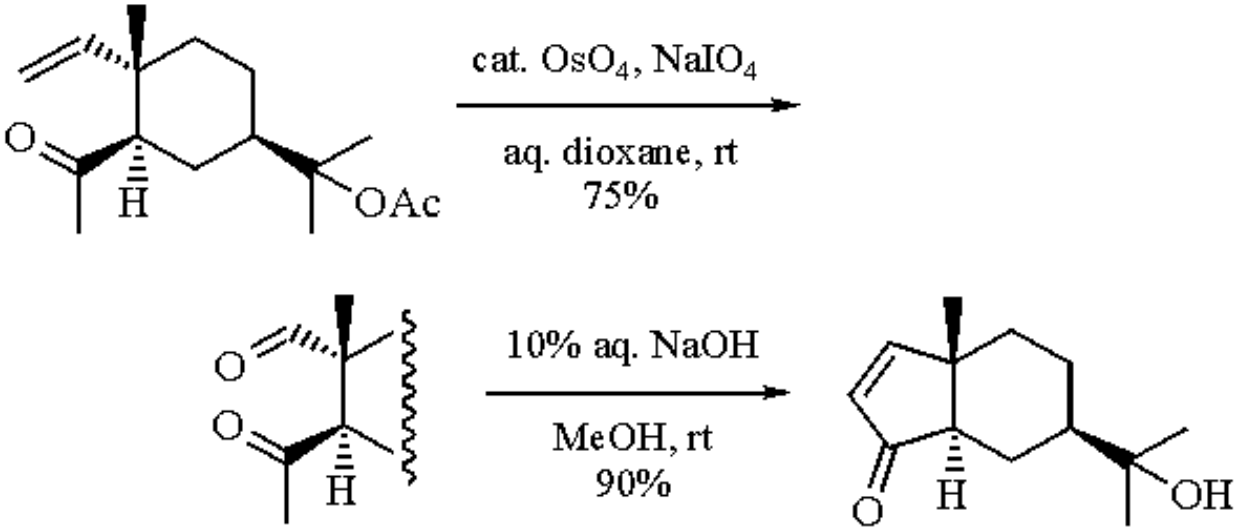

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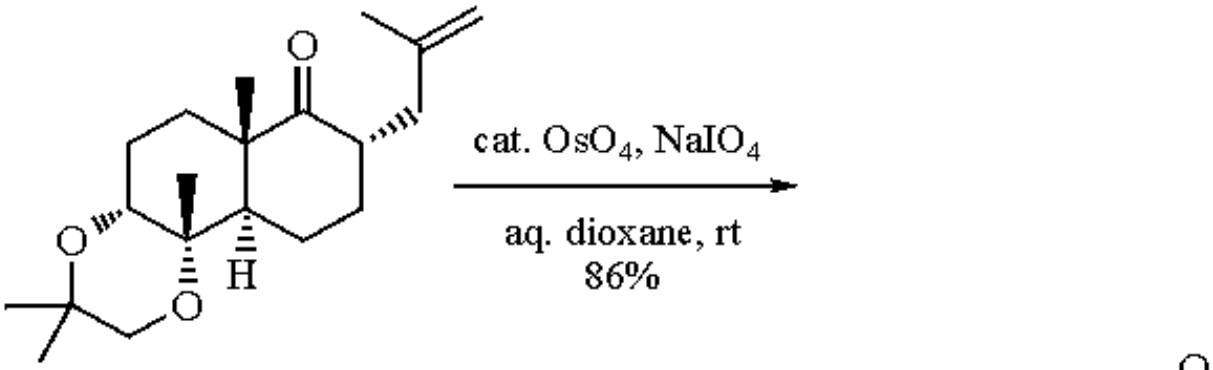

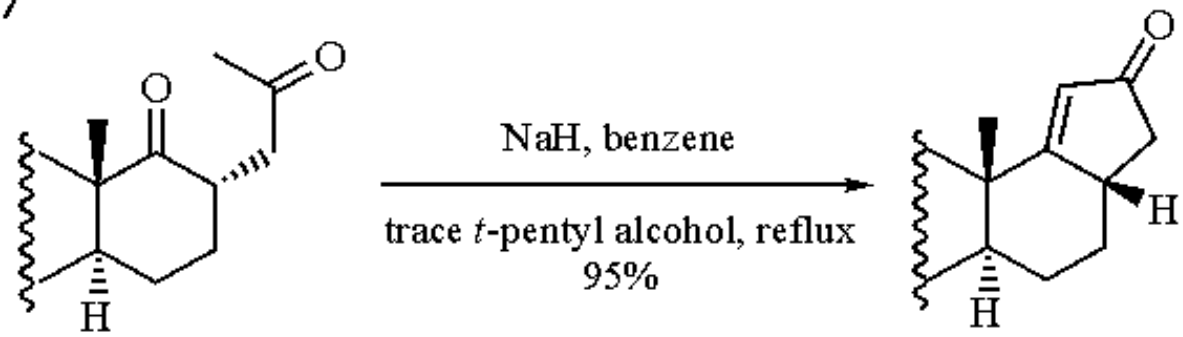

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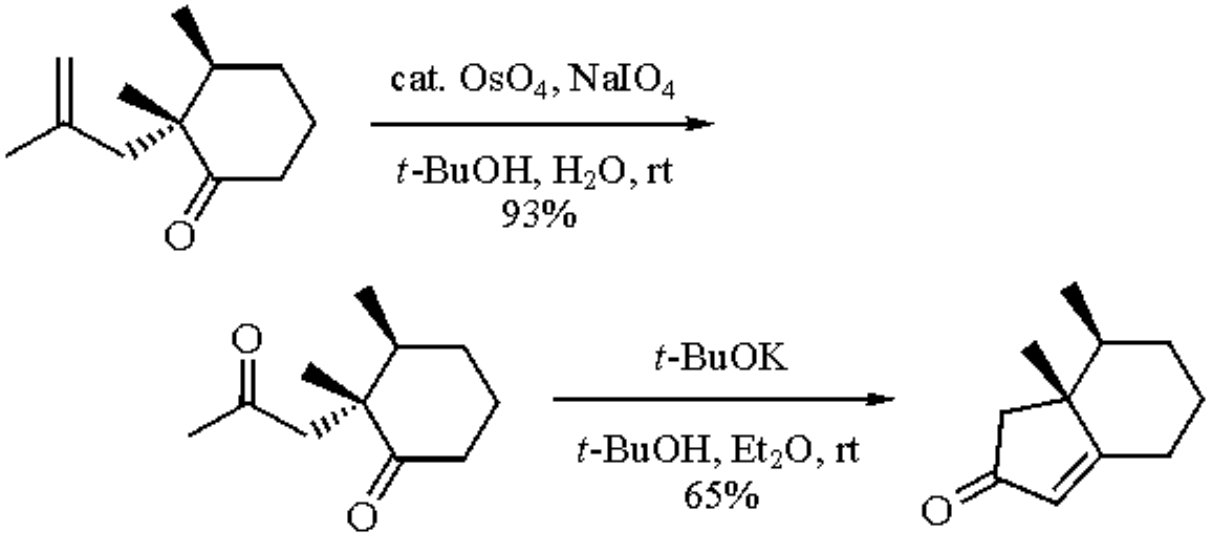

(16)

The 1-methylvinyl group can be used as a latent acetyl unit in synthesis. This is exemplified in the synthesis of a key intermediate required for the construction of the polyether antibiotic carbamonensin (eq 17).[15] The acetyl group is subsequently utilized for the stereospecific installation of the acetate moiety via Baeyer-Villiger oxidation. Double bonds present in polyoxygenated systems have also been efficiently oxidized to the aldehydes in high yields (eq 18).[9]

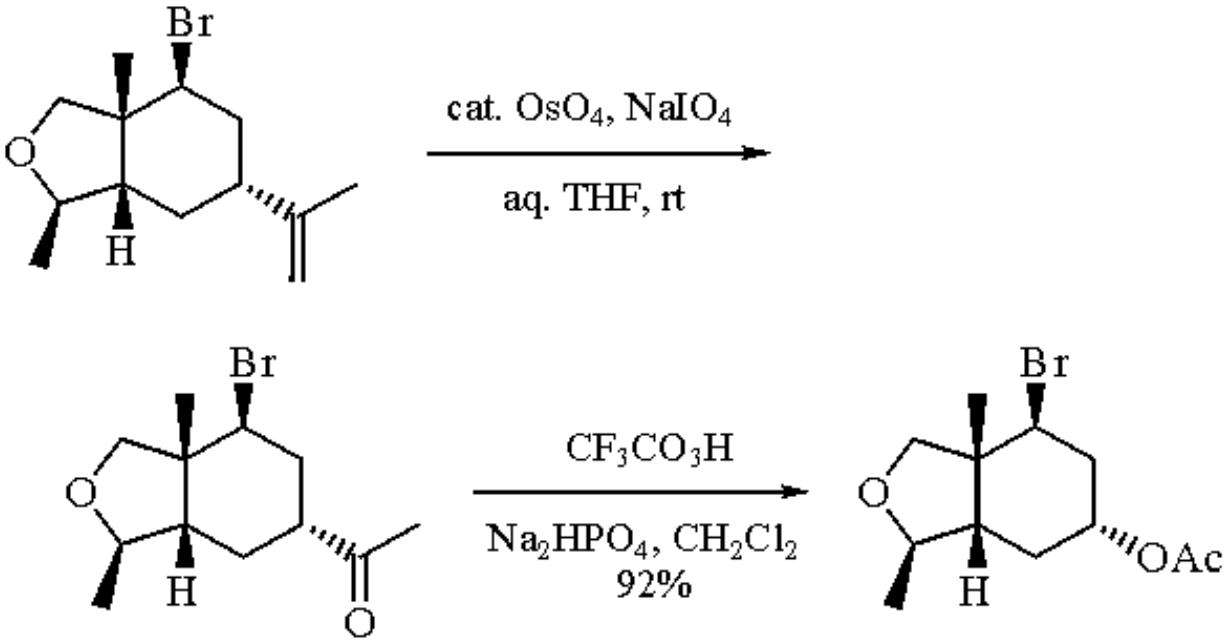

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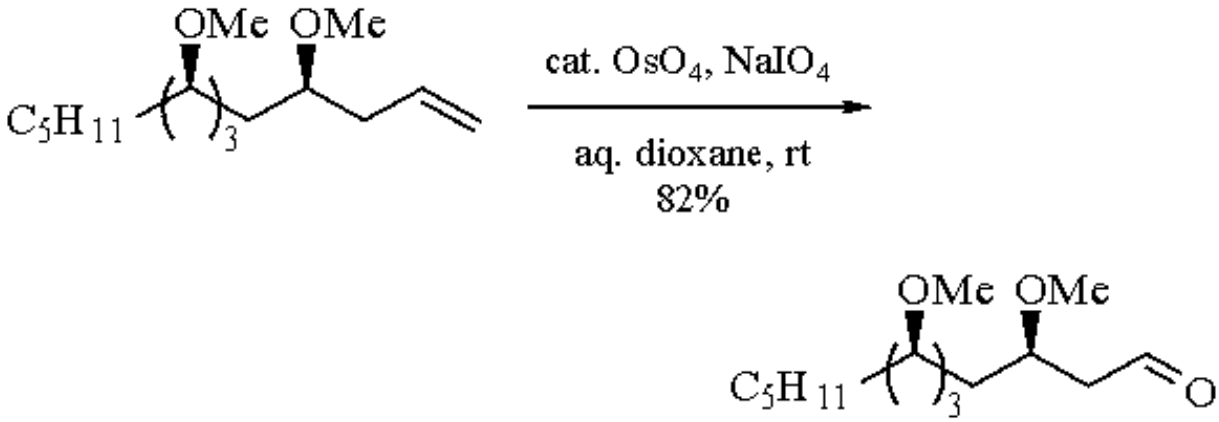

(18)

The reaction conditions used for the $NaIO_4$-cat. OsO_4 oxidation are mild and this permits the oxidation of double bonds in the presence of acid or base labile groups such as the ester (eq 19),[11b] carbamate, acetal (eq 20),[16] silyl ether (eq 21),[17] and carbonate (eq 22)[18] functions.

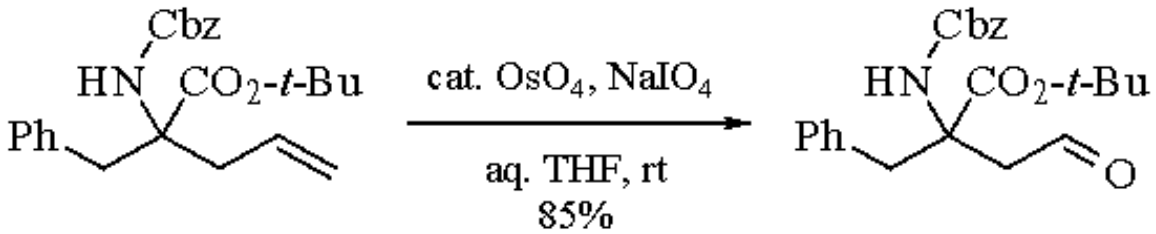

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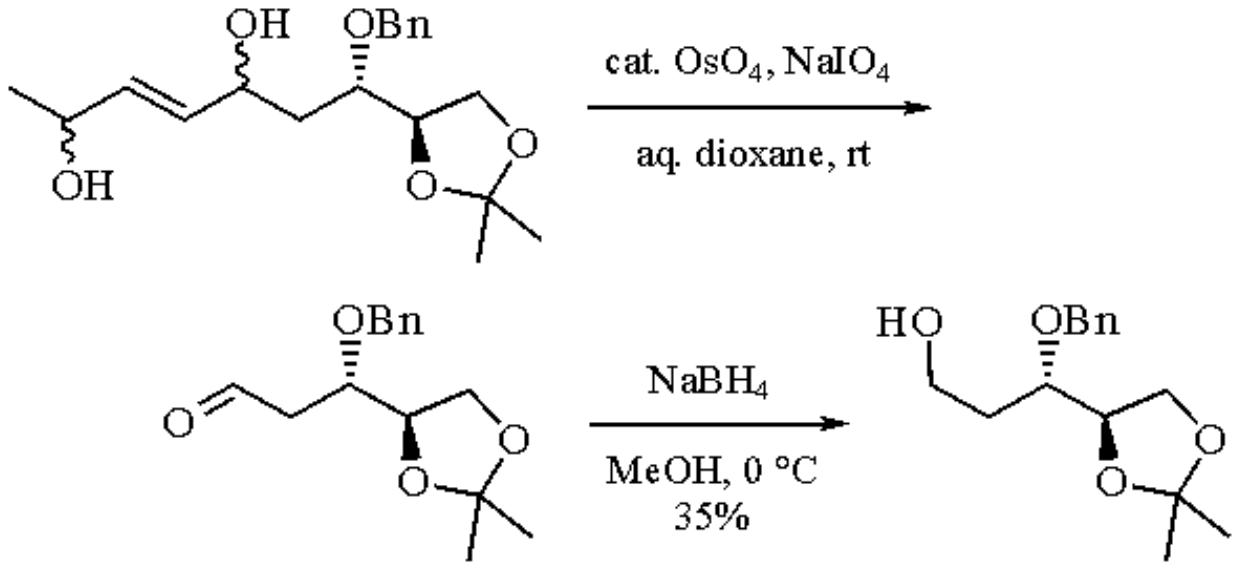

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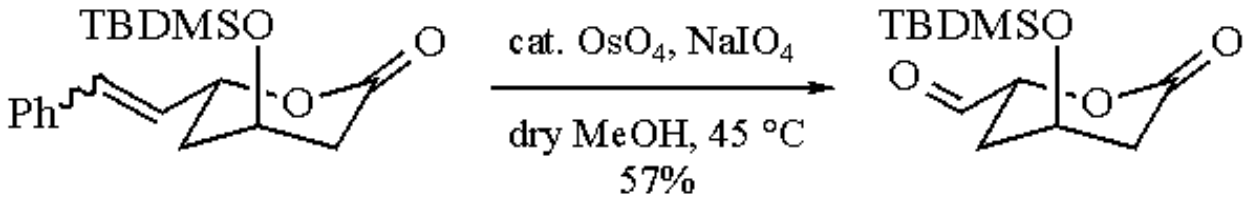

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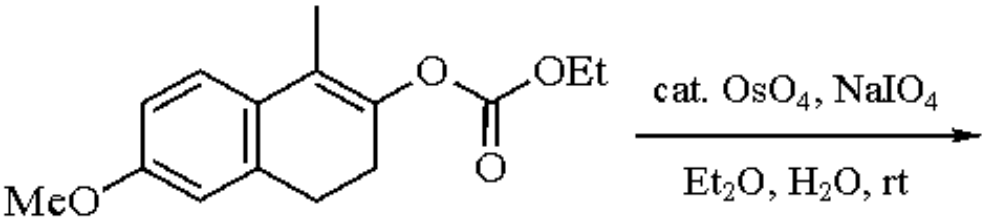

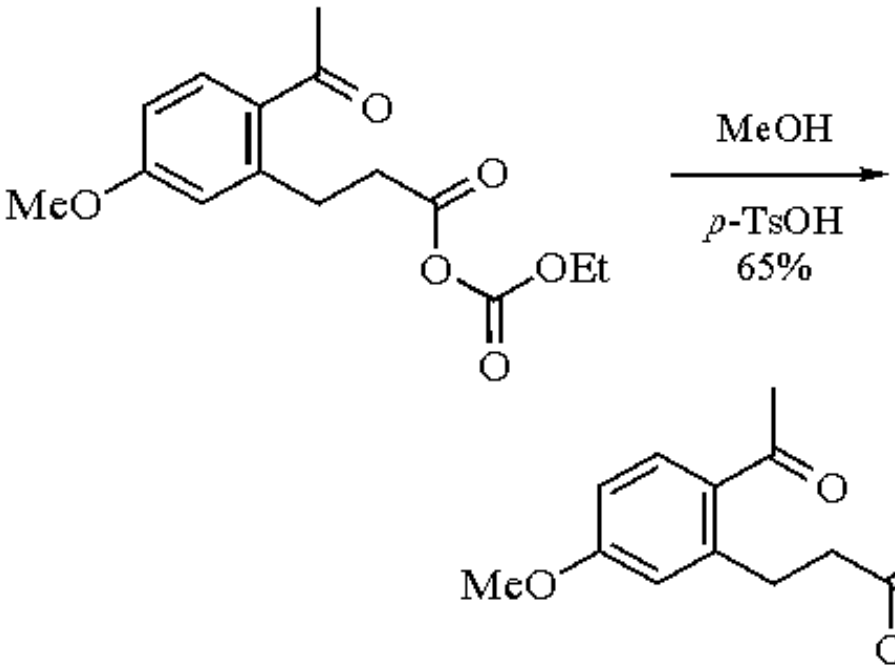

(22)

Cyclobutanones have been prepared from alkylidene- or arylidenecyclobutanes via the $NaIO_4$-cat. OsO_4 oxidation.[19] The oxidation of benzylidenecyclobutane with $NaIO_4$-cat. OsO_4 gives cyclobutanone, albeit in low yields (17%).[19a] This outcome, however, is better than the ozonolysis method, which does not yield any cyclobutanone. The $NaIO_4$-cat. OsO_4 oxidation of 3-methylenecyclobutanecarboxylic acid is more successful and a good yield of 3-oxocyclobutanecarboxylic acid is obtained (eq 23).[19b] This protocol for the preparation of cyclobutanone from methylenecyclobutane has been used in natural product synthesis (eq 24).[20]

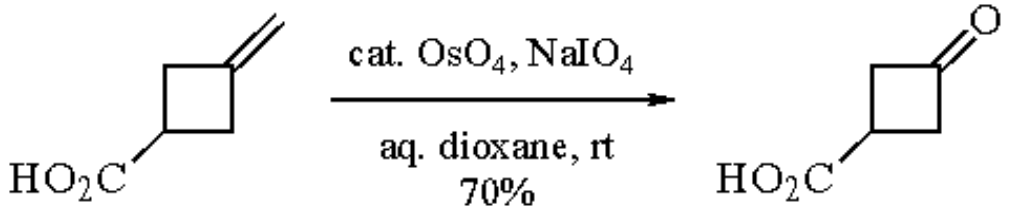

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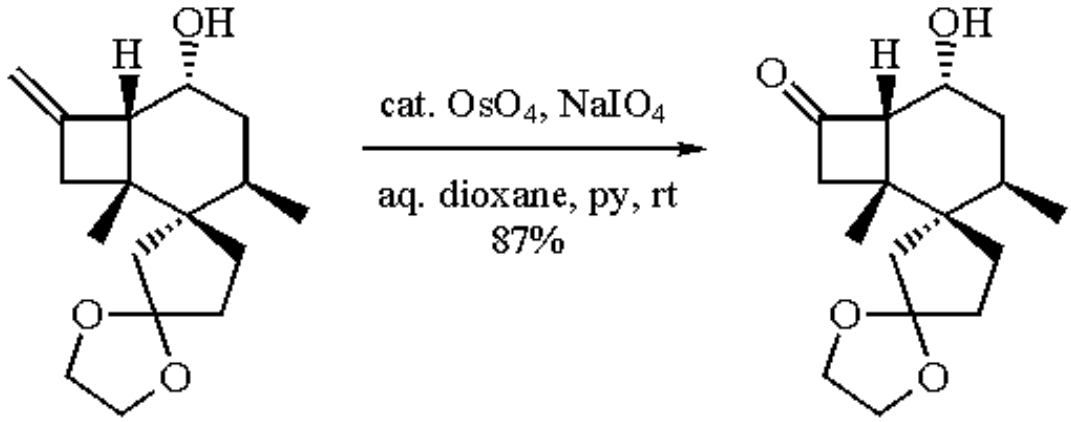

(24)

Alkenic bonds in heterocyclic molecules have also been oxidatively cleaved using $NaIO_4$-cat. OsO_4. Oxidation of the methylenecyclobutane moiety in the 2-quinolone derivative affords a good yield of the cyclobutanone derivative (eq 25).[21] 1-Substituted 2-nitroimidazole-5-carbaldehydes are prepared in useful yields by the action of $NaIO_4$-cat. OsO_4 on 5-vinylimidazole precursors (eq 26).[22] This method is better than the two-step procedure, namely, ***Potassium Permanganate*** hydroxylation followed by $NaIO_4$ oxidation of the 1,2-diol, which gives a lower yield of the product. Previous attempts to prepare 2-nitroimidazole-5-carbaldehydes such as by the ozonolysis of 5-vinylimidazoles and by the direct oxidation of 5-methyl-2-nitroimidazoles with CAN or SeO_2 were unsuccessful. $NaIO_4$-cat. OsO_4 is effective for the oxidation of double bonds in 2-azetidinone derivatives to give a good yield of the co rresponding aldehydes (eq 27).[23]

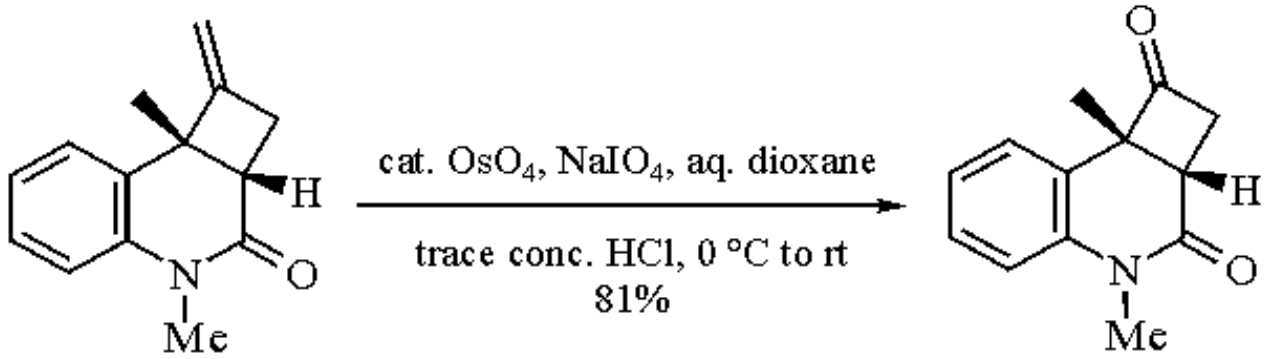

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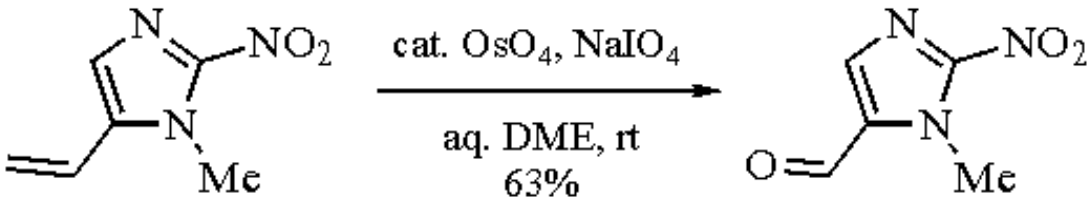

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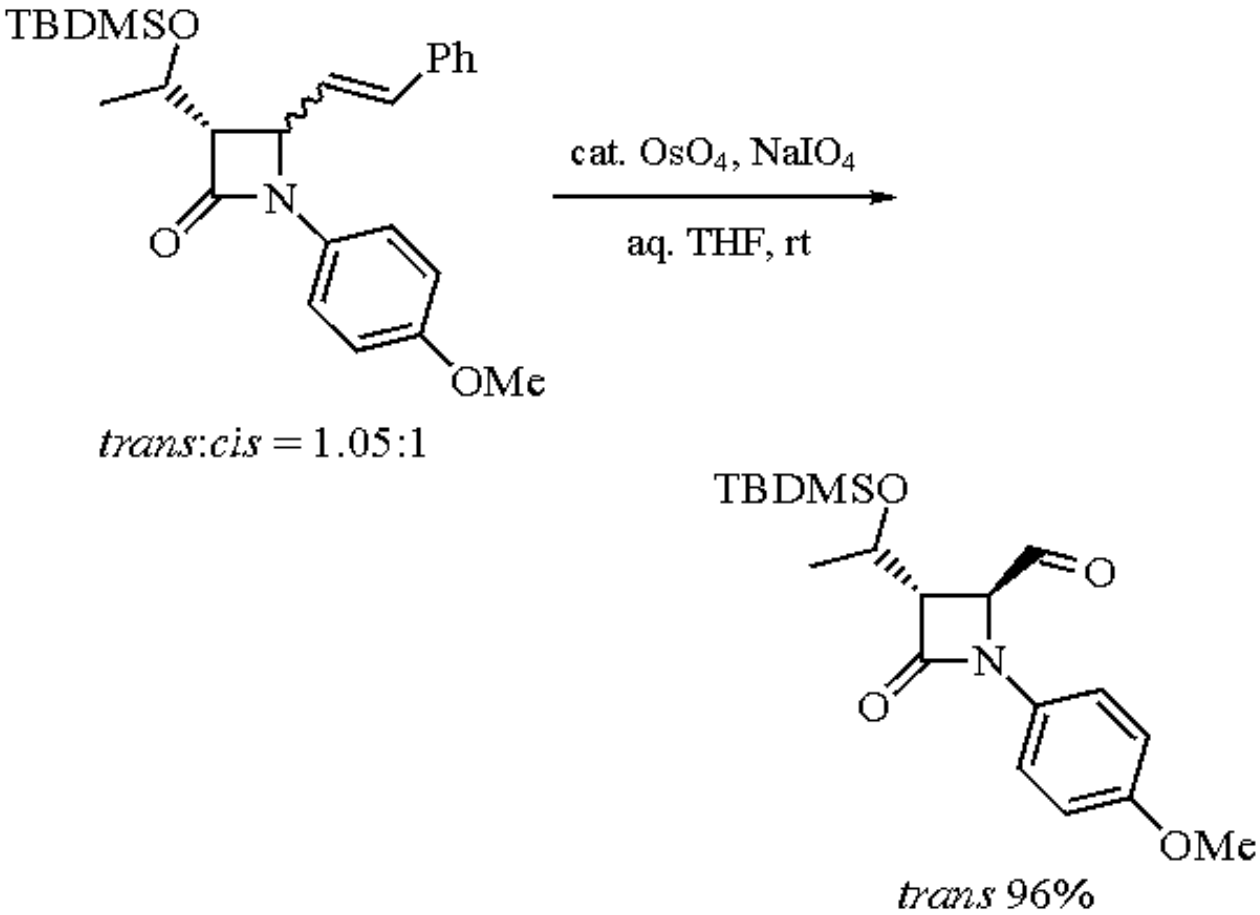

(27)

Other Applications.

$NaIO_4$-cat. OsO_4 is a mild oxidizing agent and does not oxidize aryl groups. However, pyrene has been oxidized using $NaIO_4$-cat. OsO_4 to afford two major products arising from oxidation at the 4,5-double bond (eq 28).[24] The use of OsO_4-H_2O_2 gives only a low yield of the 4,5-quinone and most of the starting material is recovered. RuO_2-$NaIO_4$ oxidation is less specific and a mixture of products, resulting from attack at positions other than the 4,5-double bond, is obtained.

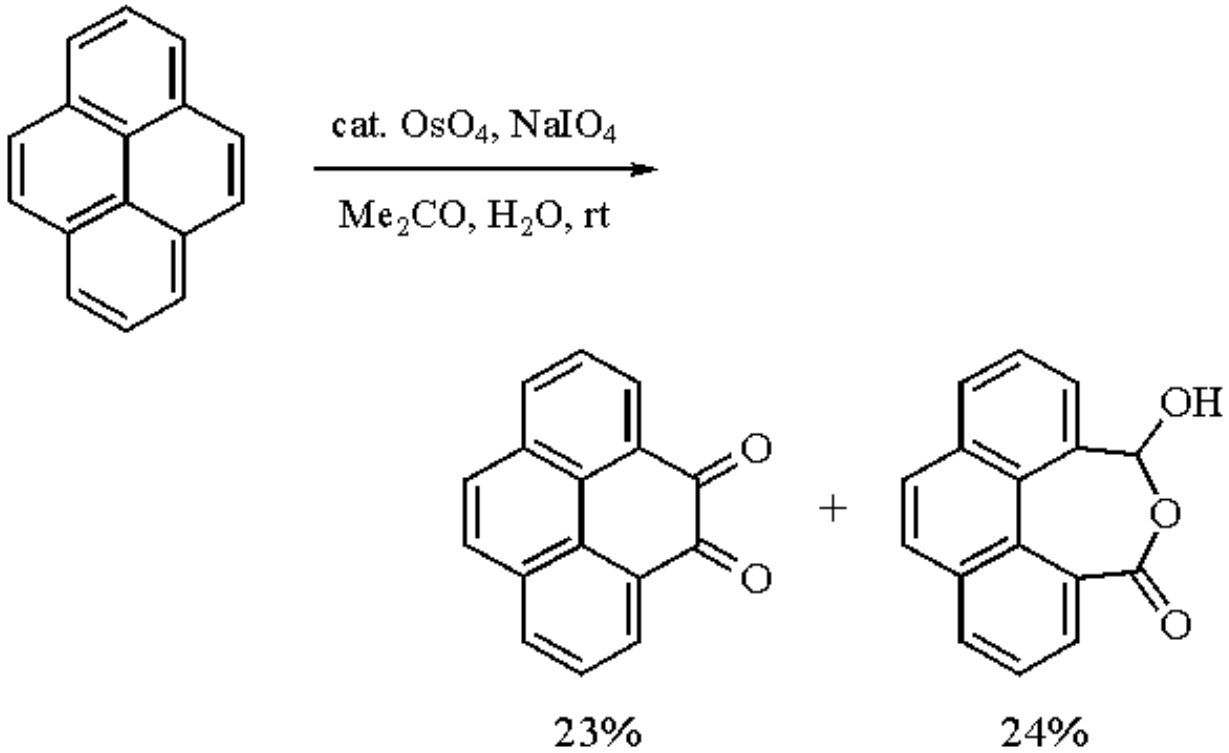

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Sodium Periodate-Potassium Permanganate

$NaIO_4$-$KMnO_4$

($NaIO_4$)

[7790-28-5] · $INaO_4$ · Sodium Periodate-Potassium Permanganate · (MW 213.89) ($KMnO_4$)

[7722-64-7] · $KMnO_4$ · Sodium Periodate-Potassium Permanganate · (MW 158.04)

(oxidant for the cleavage of carbon-carbon double bonds[1])

Physical Data: $NaIO_4$: mp 300 °C (dec); specific gravity 3.865. $KMnO_4$: mp 240 °C (dec); specific gravity 2.703.

Solubility: $NaIO_4$: sol H_2SO_4, HNO_3, $MeCO_2H$, hot water; slightly sol cold water. $KMnO_4$: sol MeOH, acetone, hot water; slightly sol cold water.

Form Supplied in: $NaIO_4$: white to colorless efflorescent solid. $KMnO_4$: dark purple crystals. Both reagents are widely available and can be used as supplied.

Handling, Storage, and Precautions: gloves and safety goggles must be worn during handling; avoid inhalation of dust and contact with combustible matter.

Introduction.

The oxidative cleavage of carbon-carbon double bonds to give carboxylic acids using a catalytic amount of ***Potassium Permanganate*** in the presence of ***Sodium Periodate*** was first reported by Lemieux and von Rudloff.[2] The reaction is usually carried out under buffered reaction conditions and, depending on the pH of the solution, either a 1,2-diol (at pH 9-10) or a 1,2-ketol (at pH 7-8) is initially formed. Oxidative cleavage of either of these intermediates by periodate yields the corresponding aldehyde, which is oxidized by permanganate to give the carboxylic acid. Permanganate is continually being regenerated from its reduced state (manganate) by the periodate. The reaction can be carried out in an aqueous medium or in mixed solvents (e.g. *t*-BuOH-H_2O, pyridine-H_2O) and proceeds optimally in the pH range between 7 and 10. Ketones and esters are not oxidized by $NaIO_4$-$KMnO_4$, whereas alcohols are oxidized slowly to carboxylic acids. Acyclic and cyclic alkenes are efficiently oxidized by $NaIO_4$-$KMnO_4$ to the carboxylic acids (eqs 1 and 2).[1,3] α,β-Unsaturated ketones are oxidized smoothly to give keto acids with loss of one carbon atom (eq 3).[4]

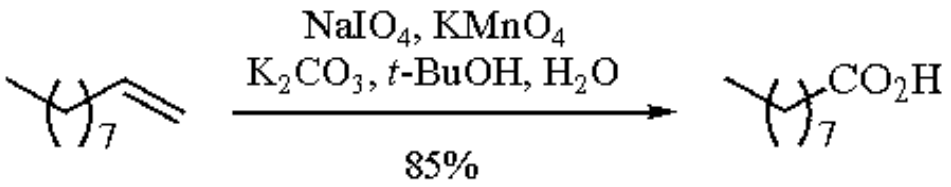

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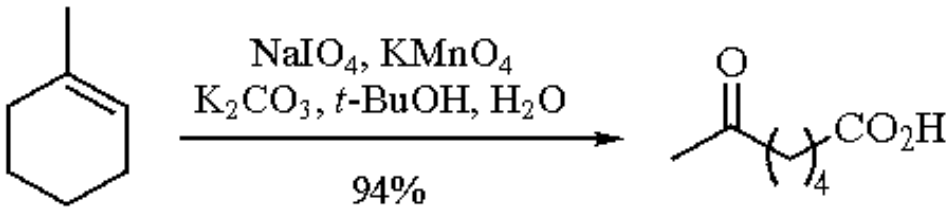

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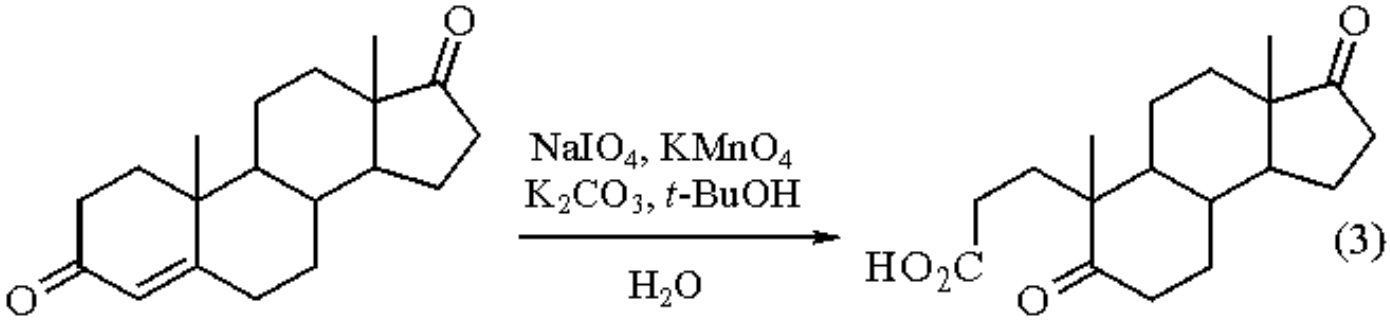

Double bonds located in the side chain of a ring are more easily oxidized than those situated in the ring (eq 4).[5] Also, double bonds in hydroxy alkenes can be selectively cleaved in the presence of a hydroxyl group.[5b,c] Thus (*R*)-(+)-citronellol is oxidized with $NaIO_4$-$KMnO_4$ to give (*R*)-(+)-6-hydroxy-4-methylhexanoic acid (eq 5).[5c] The oxidation of cyclic conjugated dienes[6] with $NaIO_4$-$KMnO_4$ can lead to products arising from hydroxylation[7] and epoxidation[5a] of the double bonds, as well as the expected oxidative cleavage of the double bonds (eq 6).[7a]

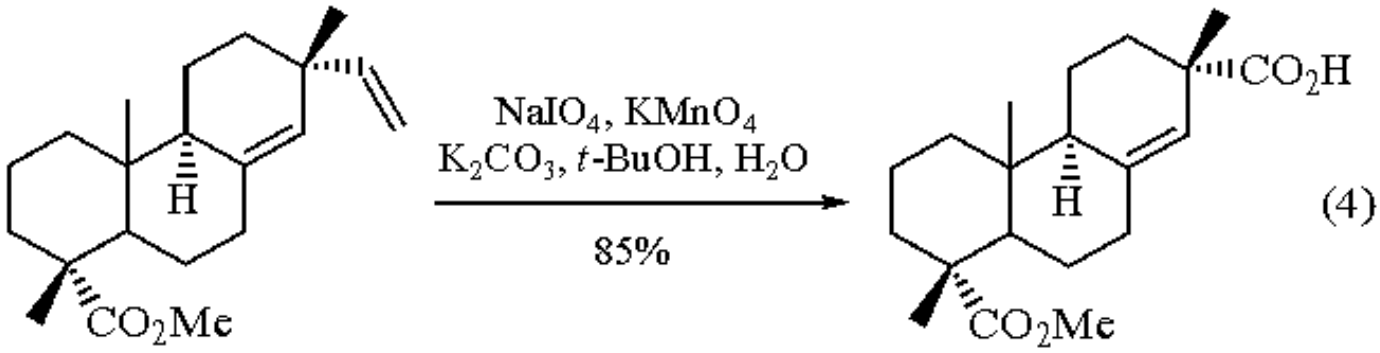

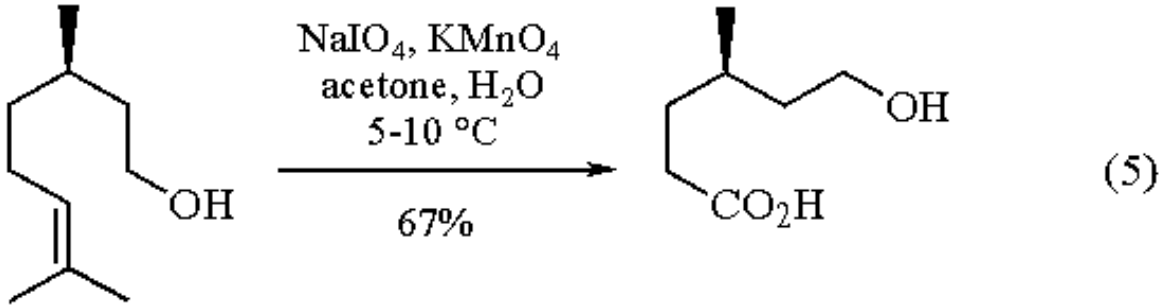

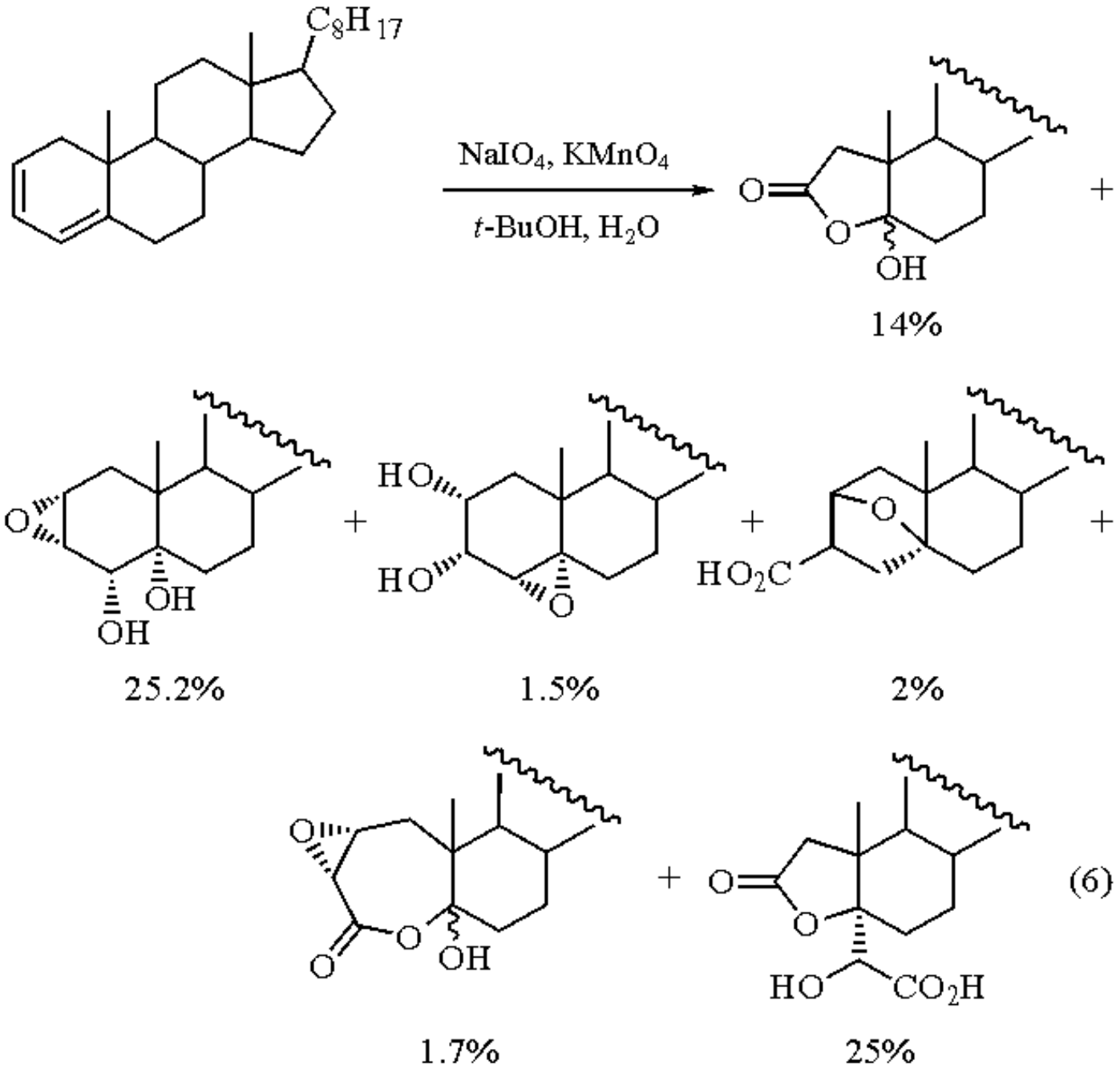

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Sodium Permanganate

$NaMnO_4.H_2O$

[10101-50-5] · H_2MnNaO_5 · Sodium Permanganate · (MW 159.95)

(oxidant; capable of converting secondary alcohols into ketones, primary alcohols and aldehydes into carboxylic acids, sulfides into sulfones, and amines into the corresponding nitro compounds; less effective oxidant for unsaturated alcohols; unreactive toward alkanes, alkenes, alkynes, and epoxides)

Physical Data: solid; decomposes with evolution of oxygen at 170 °C; *d* 2.46 g cm^{-3}.

Solubility: sol water; insol hexane.

Form Supplied in: purple solid; commercially available.

Handling, Storage, and Precautions: oxidant; store in glass vessel at rt.

Introduction.

When dissolved in water, the chemical properities of sodium permanganate are very similar to those of ***Potassium Permanganate***; when used heterogeneously, it is a slightly less reactive oxidant than ***Copper(II) Permanganate*** heptahydrate. In common with $Cu(MnO_4)_2$, anhydrous sodium permanganate is not a good heterogeneous oxidant.

Oxidation of Alcohols.

When 3 mmol of an alcohol in 15 mL of hexane is stirred with 1.92 g (12 mmol) of $NaMnO_4.H_2O$ at reflux for 2.5 h, the resulting ketone or carboxylic acid can be easily isolated by filtering the mixture and flash evaporating the solvent.[1] The yields for allylic alcohols are lower. Typical examples of this oxidation are shown in eqs 1-4.

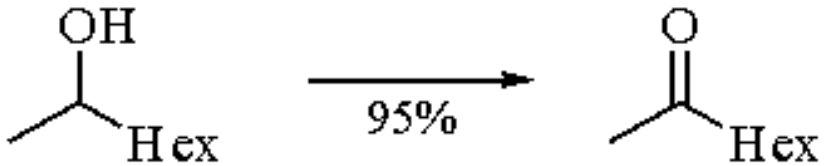

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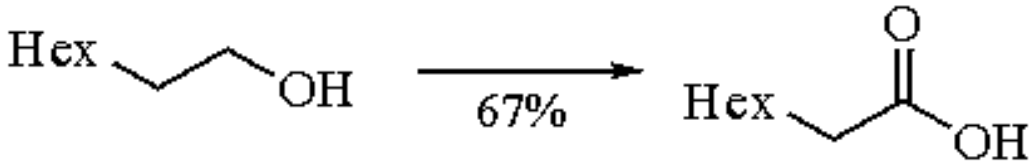

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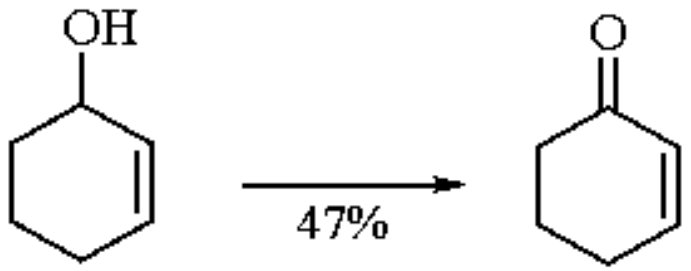

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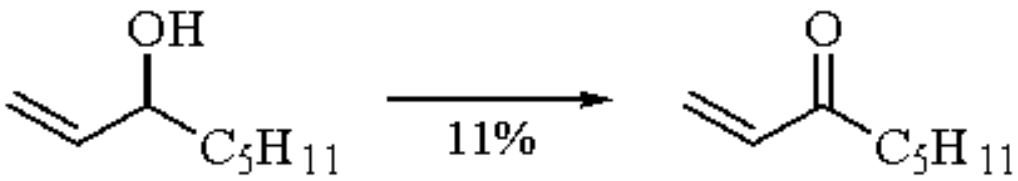

(4)

Oxidation of Sulfides.

Dialkyl sulfides are converted to the corresponding sulfones under similar conditions (eq 5).[1]

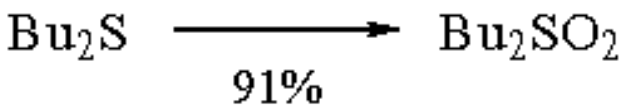

(5)

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Sodium Phenanthrenide

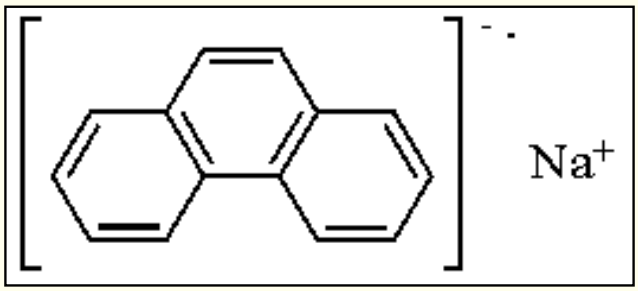

[96229-74-2] · $C_{14}H_{10}Na$ · Sodium Phenanthrenide · (MW 201.23)

(dehalogenation of vicinal dichlorides[1])

Solubility: sol THF

Preparative Method: prepared by adding 1.0 equiv of ***Sodium*** to a solution of 1.1 equiv of phenanthrene in dry THF. The resulting dark-green solution is stirred for 18 h at rt.[1]

Handling, Storage, and Precautions: should be used as prepared, under anhydrous conditions; the dry solid and solutions are flammable.

Dehalogenation Agent.

Sodium phenanthrenide is a useful reagent for the dehalogenation of vicinal dichlorides, resulting in the formation of alkenes. An isomeric mixture of *cis*- and *trans-exo,exo*-3,4-dichlorotetracyclo[4.4.2.0^{2,5}.0^{7,10}]dodeca-8,11-diene is easily converted to *exo,exo*-tetracyclo[4.4.2.0^{2,5}.0^{7,10}]dodecatriene in the presence of sodium phenanthrenide in THF (eq 1).[1]

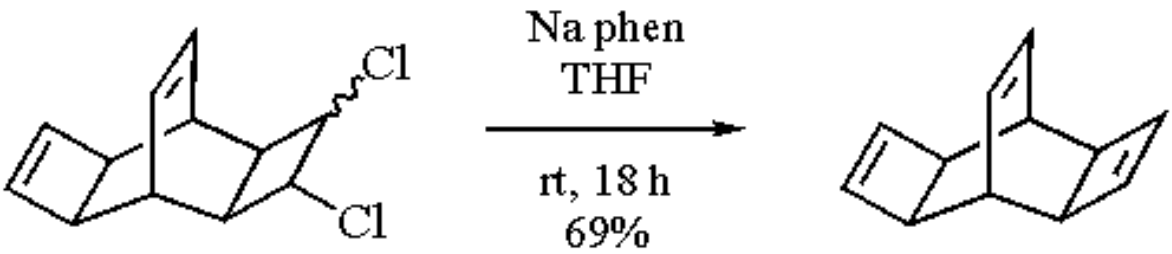

(1)

In addition to sodium phenanthrenide, disodium phenanthrenide,[2] zinc metal,[3] chromium dichloride,[4] titanium trichloride/lithium aluminum hydride,[5] sodium sulfide nonahydrate,[6] and activated nickel complexes[7] have also been employed in dehalogenations of 1,2-dihalides.

Related Reagents.

Chromium(II) Chloride; ***Disodium Phenanthrenide***; ***Lithium 4,4´-Di-t-butylbiphenylide***; ***Lithium Naphthalenide***; ***Potassium Naphthalenide***; ***Sodium Anthracenide***; ***Sodium Naphthalenide***; ***Sodium Sulfide***; ***Titanium(III) Chloride-Lithium Aluminum Hydride***; ***Zinc***.

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Sodium-Potassium Alloy

Na-K

[11135-81-2] · KNa · Sodium-Potassium Alloy · (MW 62.09)

(preparation of organopotassium compounds;[1] in combination with TMSCl, greatly enhances acyloin condensations;[2] dehalogenation of dihalides;[3] preparation of γ, δ-unsaturated alcohols via fragmentation of γ-halo ketones;[4] in combination with crown ethers is a useful reducing agent for alkynes[5,6] and alkyl fluorides[7,8])

Physical Data: mp -11 °C.

Form Supplied in: available in two alloy forms: 56% K, 44% Na; 78% K, 22% Na.

Preparative Method: can be prepared by mixing 1 part ***Sodium*** and 5 parts ***Potassium*** (by weight) in refluxing xylene until melted. The melt is then carefully mixed with a glass stirring rod, keeping the alloy in one large globule. Upon cooling to room temperature, the alloy will remain liquid and can easily be transferred via a glass pipet.[1]

Handling, Storage, and Precautions: flammable solid; handle under inert atmosphere.

Organopotassium Compounds.

Potassium derivatives can be generated from a number of organic substrates via the action of Na-K alloy (eqs 1-3).[1] The generated organopotassium adducts are soluble and stable in anhydrous diethyl ether. Similarly, the treatment of either organosodium or organolithium compounds with Na-K alloy results in the more reactive organopotassium species.

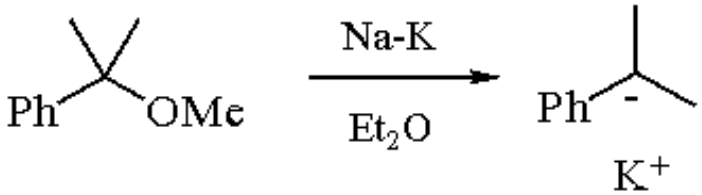

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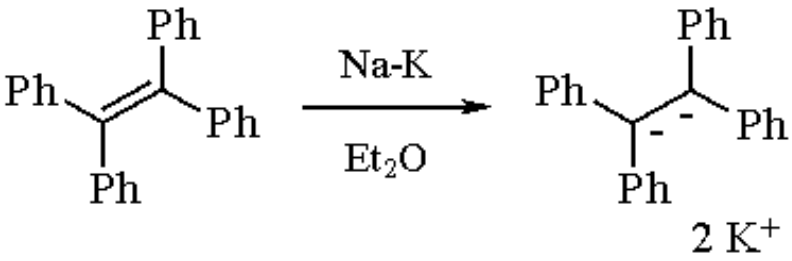

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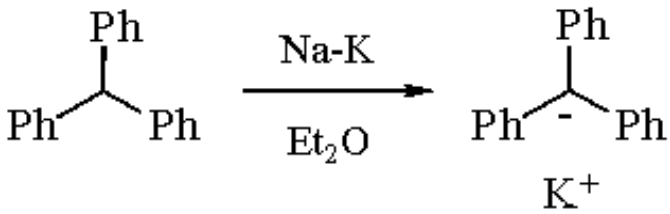

(3)

Acyloin Condensation.

The combination of ***Chlorotrimethylsilane*** (TMSCl) with Na-K alloy greatly facilitates the acyloin condensation.[2] This action results in smooth conversion of diesters to disiloxenes (eqs 4 and 5). Sodium metal can also be used, with similar results, to facilitate the acyloin condensation.

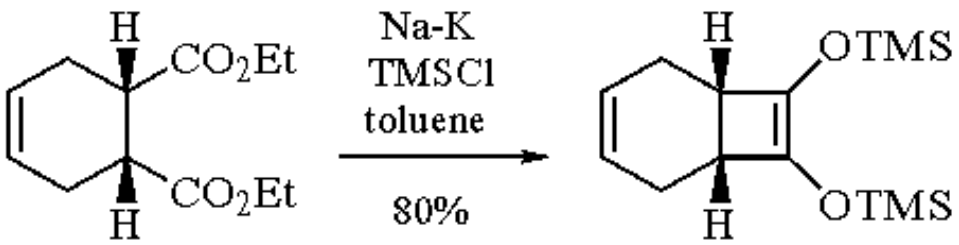

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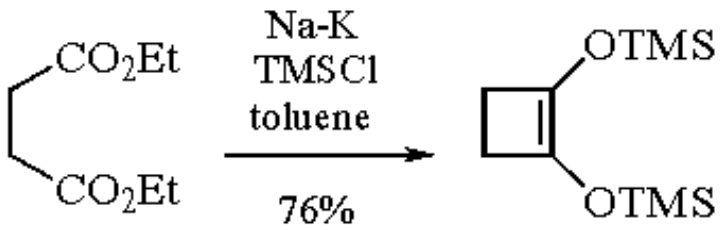

(5)

Dehalogenations.

Sodium-potassium alloy is also useful in the dehalogenation of dihalides. Sodium-potassium alloy in ethanol reacts with 1,4-dibromobicyclo[2.2.2]octane to give the Grob fragmentation product, 1,4-dimethylenecyclohexane (eq 6). However, the use of an inert solvent such as cyclohexane affords bicyclo[2.2.2]octane in modest yield (eq 7).[3]

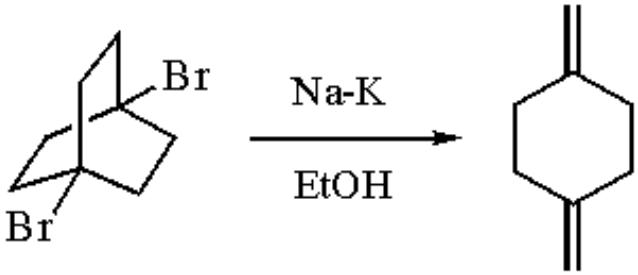

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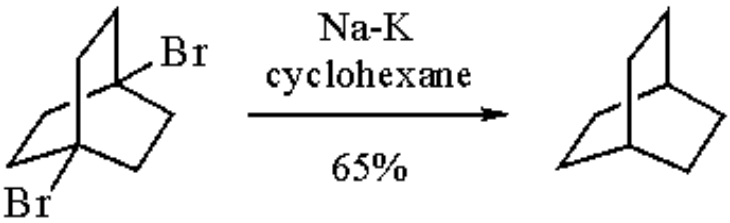

(7)

Fragmentation of γ-Halo Ketones.

The reaction of γ-halo ketones with Na-K alloy in anhydrous ether gives rise to products where 1,4-reductive elimination of halide proceeds with cleavage of the 2,3 carbon-carbon bond.[4] Under these conditions, 1-chloroadamantan-4-one is converted to 7-methylbicyclo[3.3.1]nonan-2-ol (eq 8).

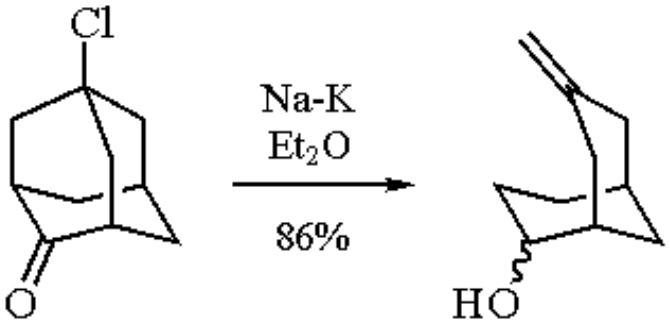

(8)

Reduction of Multiple Bonds.

The dissolving metal reduction of alkynes typically involves an alkali metal in liquid ammonia.[5] However, it has been demonstrated that dissolving metal reductions utilizing *t*-butyl alcohol and Na-K alloy in THF with catalytic amounts of ***18-Crown-6*** proceed smoothly.[6] The solubility of alkali metals in THF can be greatly increased with the aid of an appropriate crown ether or cryptate. Thus 4-octyne can be reduced to the corresponding octene (3:1 mixture of *trans*:*cis*) (eq 9).

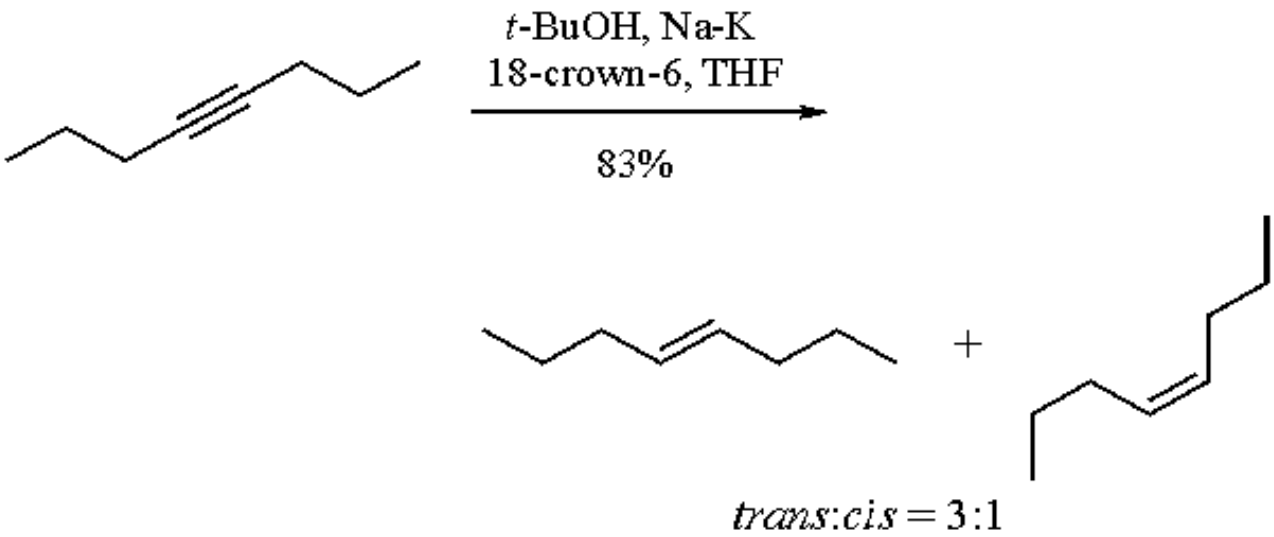

(9)

Reduction of Alkyl Fluorides.

The reductive cleavage of unactivated C-F bonds is a difficult transformation in organic synthesis. The carbon-fluorine bond is known to strongly resist the usual reductive conditions.[7] However, the use of sodium-potassium alloy and ***Dicyclohexano-18-crown-6*** in diglyme is effective in the reductive cleavage of unactivated carbon-fluorine bonds.[8] Thus 3β-fluorocholest-5-ene is successfully reduced to cholest-5-ene in high yield (eq 10).

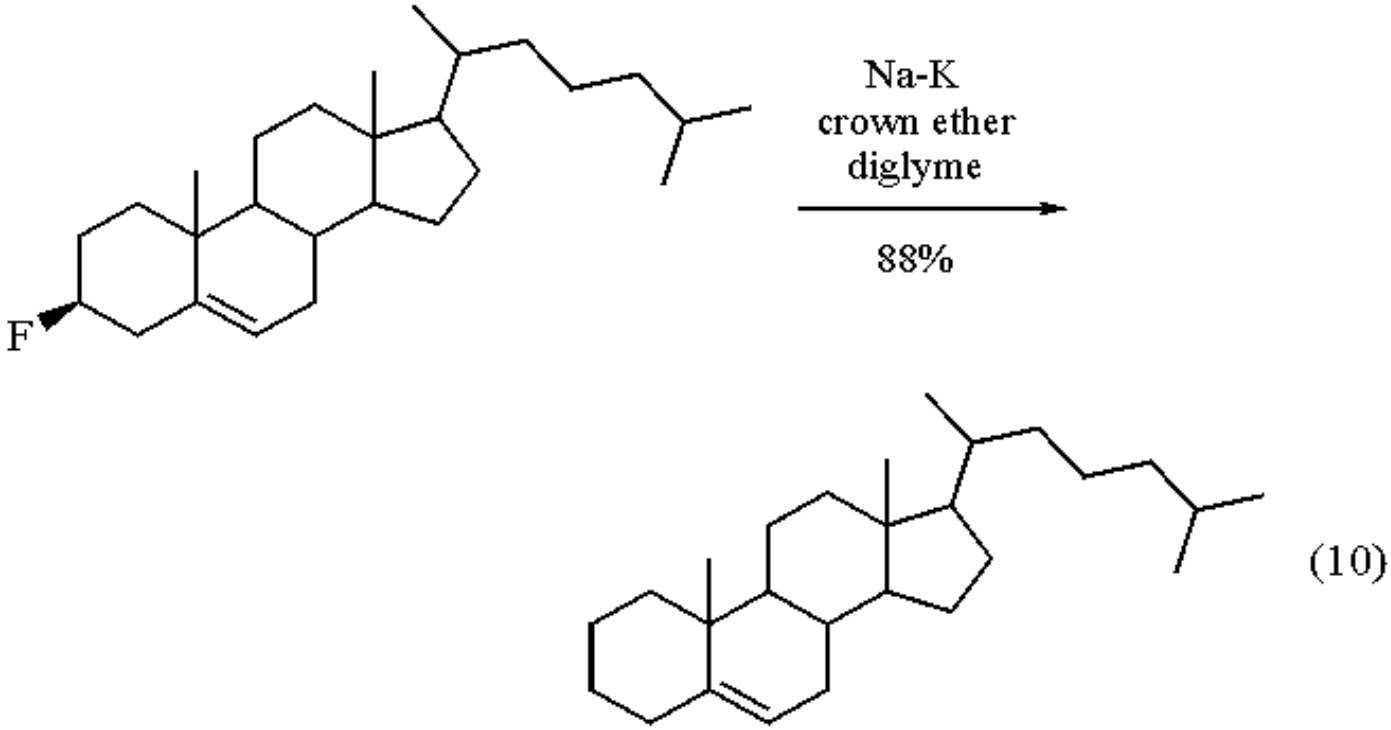

Related Reagents.

Sodium Phenanthrenide.

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Sodium Selenide[1]

Na_2Se

[1313-85-5] · Na_2Se · Sodium Selenide · (MW 124.94)

(nucleophilic agent for synthesis of organic selenides[1])

Physical Data: mp 845 °C; *d* 2.58 g cm^{-3}.

Solubility: readily sol water; sol ethanol, liquid ammonia; sparingly sol THF.

Form Supplied in: white, fine hygroscopic crystals.

Preparative Methods: prepared by reduction of ***Selenium*** with ***Sodium*** (molar ratio 1:2) in liquid ammonia. It can be used in solution[2b,c] or isolated by evaporation of ammonia.[2a] In aqueous medium, Na_2Se is obtained by reduction of Se with ***Sodium Hydroxymethanesulfinate*** (rongalite)[3] or by reduction of Na_2Se_2 with ***Sodium Dithionite***.[4] Na_2Se (or K_2Se) can also be produced by the direct reaction of Se with Na (or K) in high-boiling, polar, aprotic solvents, such as DMF, HMPA, and NMP[5] or in THF in the presence of naphthalene as a catalyst.[6] A combination of electrochemical reduction and ultrasound is used to produce the Se^{2-} anion in THF, DMF, and acetonitrile.[7]

Handling, Storage, and Precautions: hygroscopic crystals; rapidly turns red in moist air because of the formation of polyselenides and separation of Se. From water solution, red Se separates rapidly on contact with air. It can be stored under anhydrous and oxygen-free conditions, although usually it is used as prepared without isolation. Use in a fume hood.

Sodium and potassium selenides are good nucleophiles for the synthesis of dialkyl selenides from alkyl halides or sulfates.[2b,3,4,7] The alkylating agent is added directly to Na_2Se (or K_2Se) in solution or suspension (eq 1).[7] Aliphatic diacyl selenides are obtained in 58-90% yield from the reaction of acyl chlorides with Na_2Se suspended in ethyl ether.[8]

$$\mathrm{Se} + 2\,\mathrm{Na} \xrightarrow[\mathrm{N_2,\ rt,\ 4\ h}]{\mathrm{THF,\ naphthalene\ (cat)}} \mathrm{Na_2Se} \xrightarrow[\mathrm{reflux,\ 4\ h}]{\mathrm{PhCH_2CH_2Br,\ THF}} \underset{78\%}{(\mathrm{PhCH_2CH_2})_2\mathrm{Se}} \qquad (1)$$

A general method for the preparation of symmetrical diaryl selenides involves treatment of arenediazonium salts with Na_2Se or K_2Se,[9] or with sodium or potassium polyselenide (Na_2Se_x or K_2Se_x) produced by heating elemental Se with NaOH (or KOH) (eq 2).[1b,10] Bis(nitroaryl) selenides are prepared in a similar way from nitroaryl halides.[1b,11]

$$\mathrm{Se} \xrightarrow[\mathrm{2.\ H_2O}]{\mathrm{1.\ KOH,\ \Delta}} \mathrm{K_2Se_x} \xrightarrow[\mathrm{H_2O}]{\mathrm{PhN_2Cl}} \underset{86\%}{\mathrm{PhSePh}} \qquad (2)$$

Diphenyl selenide is formed from Na_2Se and iodobenzene in liquid ammonia under photochemical activation. This selenide is easily reduced to the benzeneselenolate anion ($PhSe^-$) by addition of an excess of Na, and this provides a route to aryl methyl selenides (when ***Iodomethane*** is added) and unsymmetrical diaryl selenides (by photostimulated reaction with aryl iodides).[2c]

Sodium selenide is also used in the synthesis of divinyl selenides. Alkylation with diethyl iodomethylphosphate forms a selenide which gives bis(2-phenylvinyl) selenide by Horner-Wittig reaction with benzaldehyde (eq 3).[12] Treatment of *N*-phenyldichloroimine with Na_2Se gives phenyl isoselenocyanate.[13]

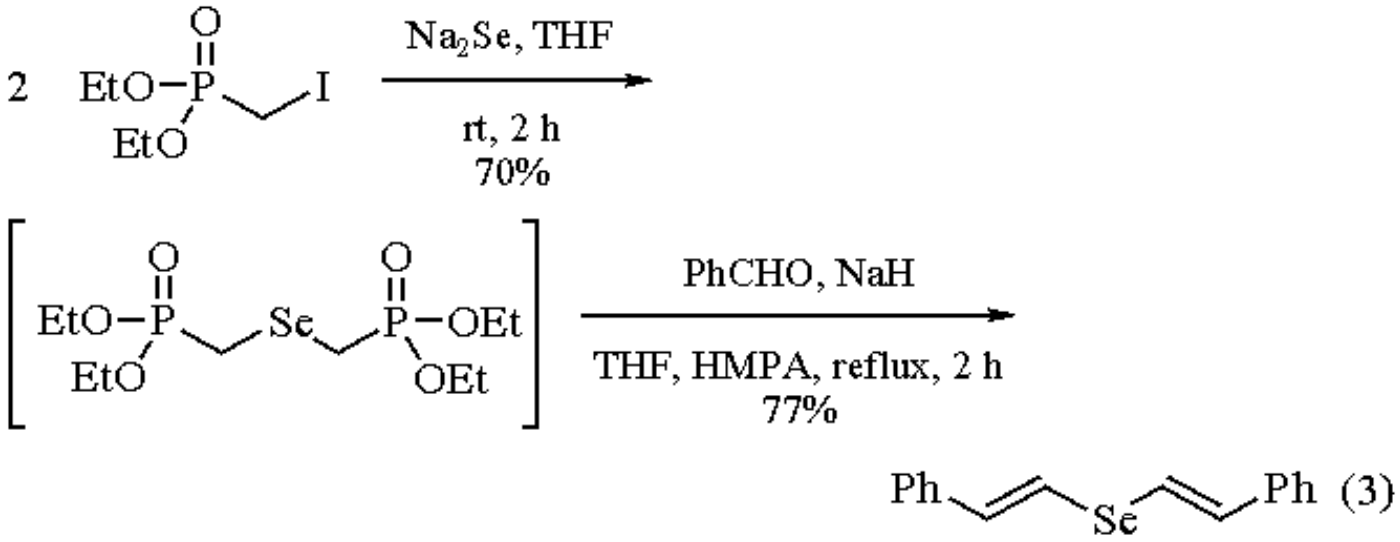

Related Reagents.

Hydrogen Selenide; ***Lithium Selenide***; ***Sodium Sulfide***.

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Sodium Sulfide[1]

$Na_2S.9H_2O$

(nonahydrate)

[1313-84-4] · $H_{18}Na_2O_9S$ · Sodium Sulfide · (MW 240.18) (anhydrous)

[1313-82-2] · Na_2S · Sodium Sulfide · (MW 78.05)

(nucleophile and reducing agent derived from H_2S; reagent for the synthesis of thiols,[2] thioethers,[3] and disulfides;[4] reduces aromatic nitro compounds to amines[5])

Physical Data: mp ~50 °C (hydrate, loses most of its water below 100 °C); mp 1180 ± 10 °C (pure Na_2S); *d* 1.43 g cm^{-3} (anhydrous 1.86 g cm^{-3}); E_0 (S^{2-} -> S + 2e) +0.48 V.

Solubility: v sol cold and hot water; somewhat sol methanol, ethanol; insol acetone, benzene, ether.

Form Supplied in: colorless or pale yellow crystalline solid. May contain NaSH and small amounts of $Na_2S_2O_3$, Na_2SO_3, NaOH, Na_2CO_3, NaCl, $Na_2S_2O_4$, and Na_2SO_4. Also available as essentially anhydrous fused chips of 60% Na_2S. The form used in synthesis is not always specified. A pentahydrate is also known.

Analysis of Reagent Purity: titration methods (e.g. iodometric) are available.

Handling, Storage, and Precautions: light (discolors) and air sensitive. Produces H_2S on exposure to air. Corrosive; flammable; deliquescent. Refrigerate. Incompatible with oxidizing agents and strong acids. Destructive of mucous membranes, eyes, skin. Absorbed through the skin. Inhalation can be fatal. Use a well-ventilated hood, goggles, and gloves.

Preparation of Na_2S_2, Na_2S_x.

Refluxing sodium sulfide with elemental ***Sulfur*** in 95% ethanol or aqueous sodium hydroxide yields solutions of ***Sodium Disulfide***, Na_2S_3, and Na_2S_x.[6]

Thiols.

Although treatment of halides, epoxides, aziridines, and sulfonate esters with ***Sodium Hydrogen Sulfide*** or ***Potassium Hydrogen Sulfide*** is usually more advantageous (Na_2S often gives the thioether), the use of Na_2S_2 followed by reduction of the disulfide has found application (eq 1).[6b,d] Sulfide or disulfide ions can cleave a disulfide to a thiolate ion,[7] and nitro aromatic halides have been observed to yield the thiolate under conditions in which Na_2S_2 may be formed from Na_2S.[7b] Best results are obtained at room temperature with anhydrous Na_2S, in DMF or DMSO (eq 2).[8a] Reduction of the nitro group[8b] does not occur. What appears to be a direct synthesis of a thiol via $Na_2S.9H_2O$ occurs in the formation of 6-mercaptopteridine (84% yield) from 6-chloropteridine,[9a] and 3-aryl-1,2,3,4-thiatriazolium-5-thiolates (30-34% yields) from 5-ethoxy-3-aryl-1,2,3,4-thiatriazolium tetrafluoroborates.[9b] Na_2S cleaves thiocyanates to the thiols.[10] Tertiary thiols are obtained from tertiary nitro compounds by treatment with Na_2S_x (Na_2S + S) in DMSO (eq 3),[11] but the reaction is limited to tertiary derivatives. Addition of ***Methanethiol*** to acetaldehyde in the presence of Na_2S gives the dithiohemiacetal in 38% yield.[12]

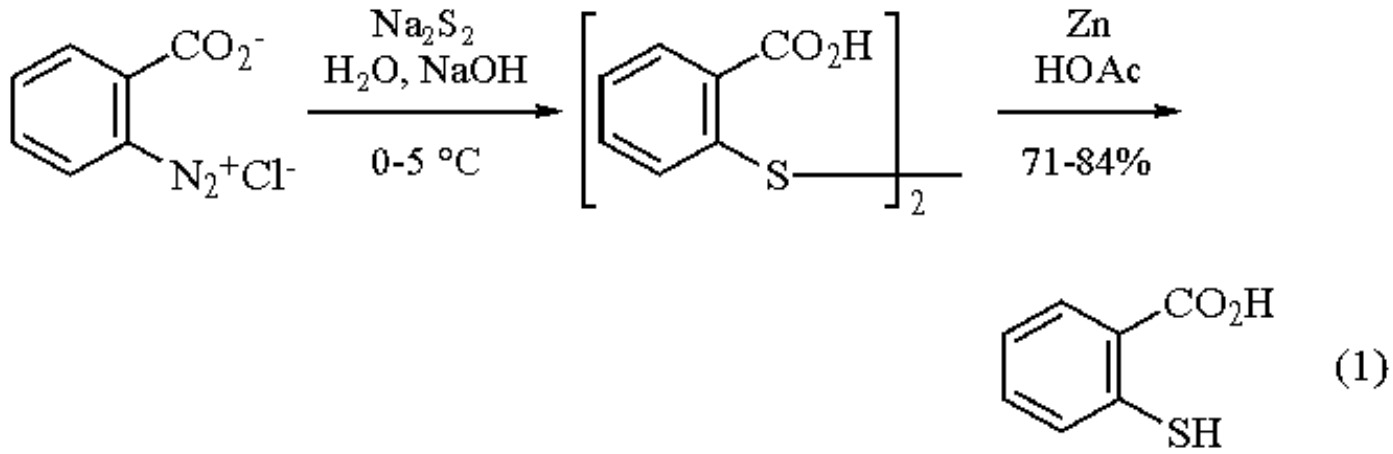

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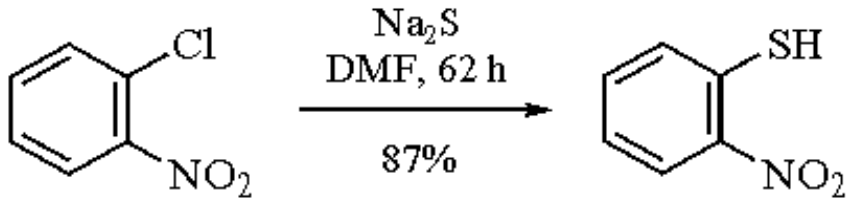

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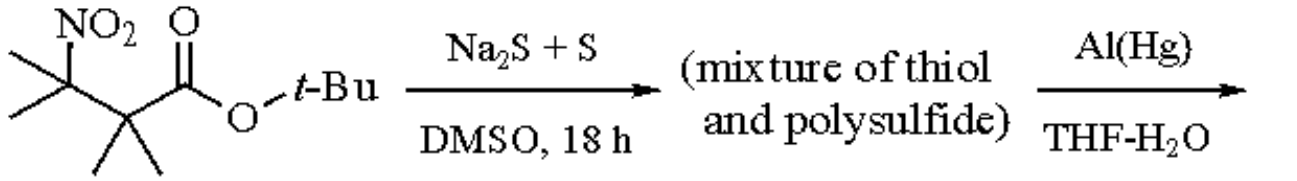

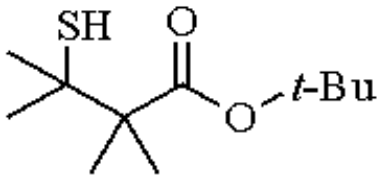

(3)

85%

Thioethers (Sulfides).

Symmetrical primary and secondary acyclic thioethers are obtained from the corresponding halide, sulfonate, or sulfate ester.[13] Oxiranes and aziridines are also useful substrates but ***Hydrogen Sulfide***, NaSH, and KSH are more commonly used with this class of compound.[3] Secondary starting materials may yield some alkene, particularly if Na_2S is prepared in situ from H_2S and alkali. The yield of di-*n*-octyl sulfide from *n*-octyl bromide is increased from 20% to 97% when Na_2S is supported on neutral ***Alumina***.[14] The use of phase-transfer catalysis is beneficial.[15] In the absence of catalyst, the yield of bis(3-penten-2-yl) sulfide from 4-chloro-2-pentene and $Na_2S.9H_2O$ is 14%; in the presence of polyglycol or ***Tetra-n-butylammonium Bromide*** it is 98% and 94%, respectively (eq 4).[15a] The α-trimethylsilyl sulfide (**1**) is a source of the useful $MeSCH_2^-$ synthon (eq 5),[16] ***Bis(trimethylsilyl) Sulfide*** is available (96% yield) by treatment of ***Chlorotrimethylsilane*** with anhydrous Na_2S at 240 °C in a sealed tube.[17a] Treatment of this silyl sulfide[17b] with ***Methyllithium*** yields highly active Li_2S that is useful in the synthesis of six- to twelve-membered sulfur heterocycles without the need for high dilution techniques.[17c] Addition of the sulfide anion to Michael acceptors such as acrylonitrile is another route to acyclic sulfides.[18]

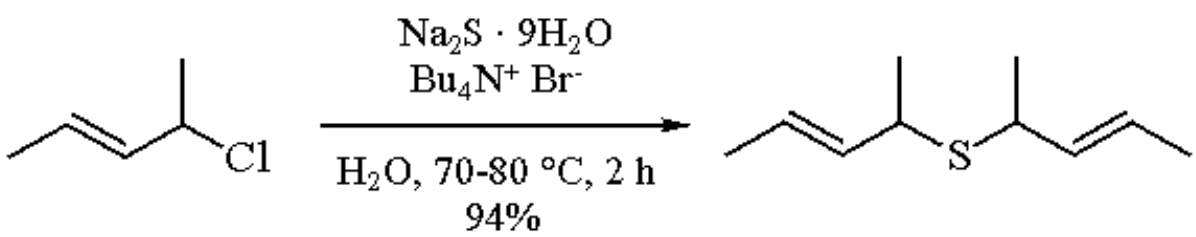

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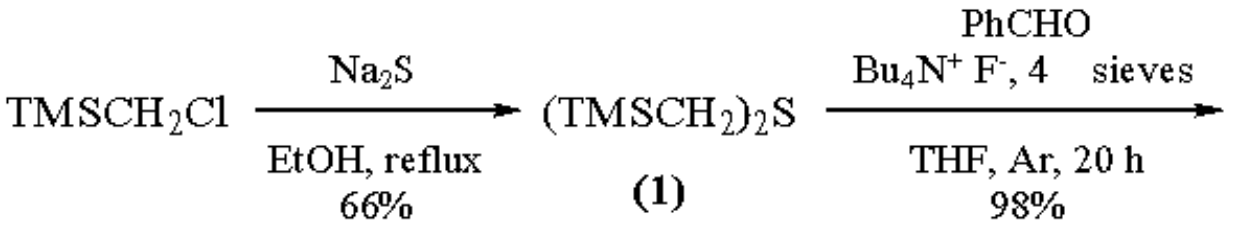

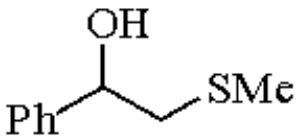

(5)

Cyclic sulfides in small to large ring sizes are readily obtained from dihalides, bissulfonates, or other compounds that are capable of reacting with Na_2S at two sites with formation of a ring. The formation of thiiranes[19] from 1,2-dihalides and Na_2S frequently fails due to polymerization or elimination to the alkene. However, use of α-halo or thiocyanato thiocyanates or disulfides with Na_2S can circumvent this limitation (eq 6).[19,20] Thietanes are conveniently prepared from 1,3-dihalides and related compounds (eq 7).[21] Cyclizations involving mesylates or tosylates are conducted under anhydrous conditions to avoid hydrolysis.[22] Even the cyclization of 1,4-dichlorobutane to thiolane gives better yields if fused 60% Na_2S is used instead of the nonahydrate.[23] Examples of the synthesis of five- and six-membered sulfur heterocycles are shown in eqs 8-10.[24-26] The dithiin synthesis in eq 11 demonstrates the ability of sulfide ion to add to an acetylenic bond.[27] Macrocyclic sulfides are readily prepared (eq 12).[28]

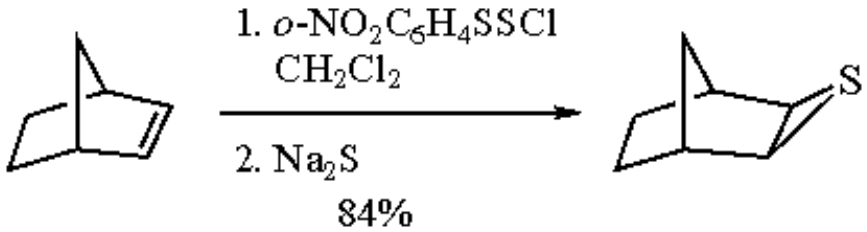

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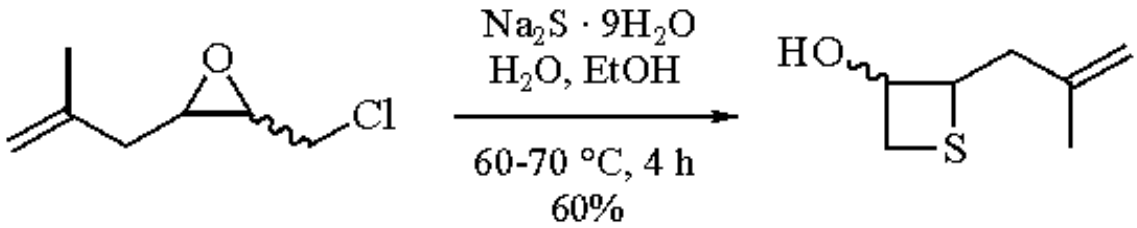

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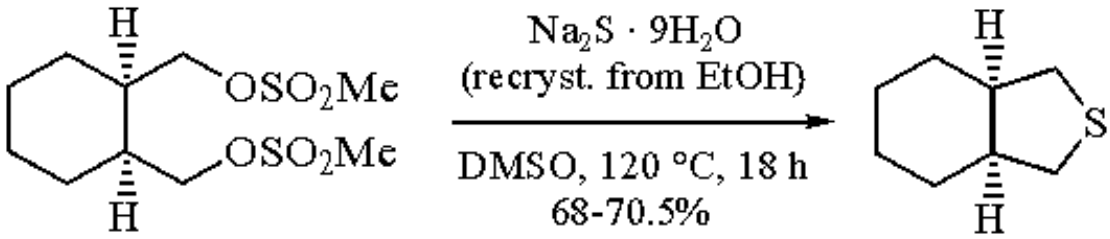

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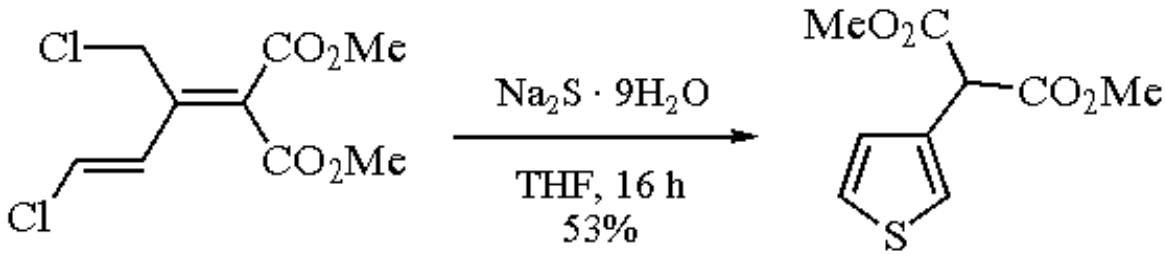

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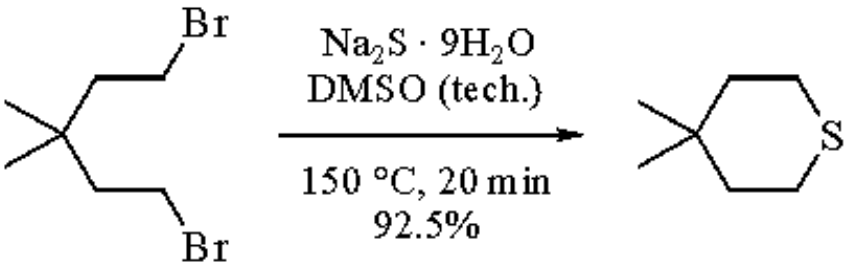

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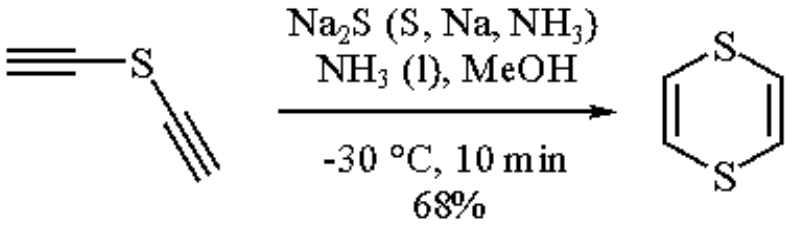

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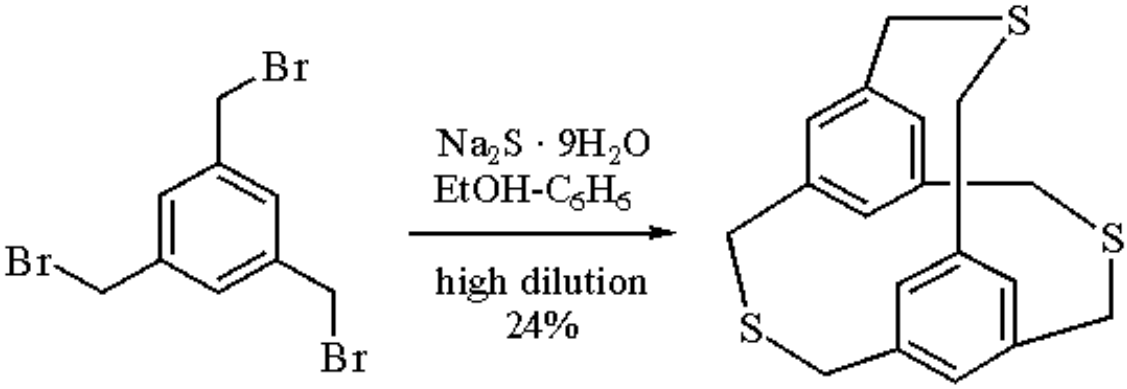

(12)

Aryl sulfides are obtained by S_NAr-type reactions of sulfide ion with activated aryl halides;[3] a nitro group also may be displaced,[29a] even in preference to halogen.[29b] Phase transfer catalysts, including crown ethers, are useful (eq 13).[30] The yields in the substitution reaction are sensitive to the medium. The yield of sulfide from 4-chlorobenzonitrile is 99% in DMF but only 14% in toluene.[30] In ethanol, 2,4-dinitrochlorobenzene yields the sulfide (79%) with $Na_2S.9H_2O$ and the disulfide when the same reaction is done in the presence of elemental sulfur.[31] It should be noted that nitro groups may be reduced by sulfide or polysulfide ions.[5]

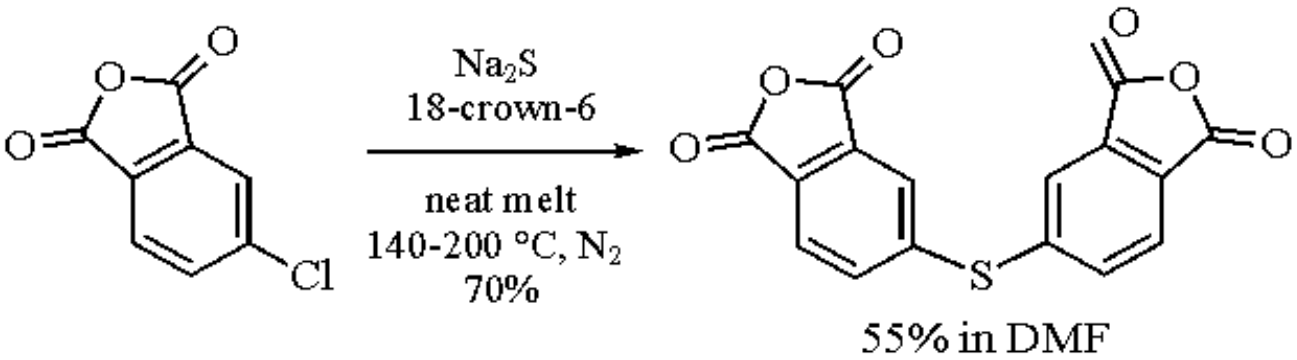

(13)

Di- and Polysulfides.

These are derived from Na_2S_2 (or Li_2S_2, Na_2S_x) and halides (or their equivalents) (eq 14)[4,6a,c-e,32,33] or aryl diazonium salts (eq 1).[6b] With some substrates, especially those that contain sulfur, Na_2S itself may be used (eq 15).[33]

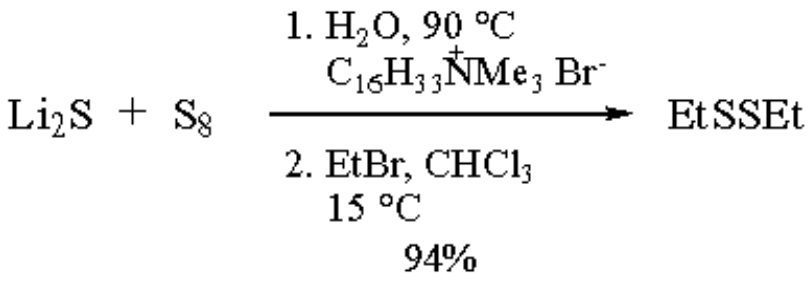

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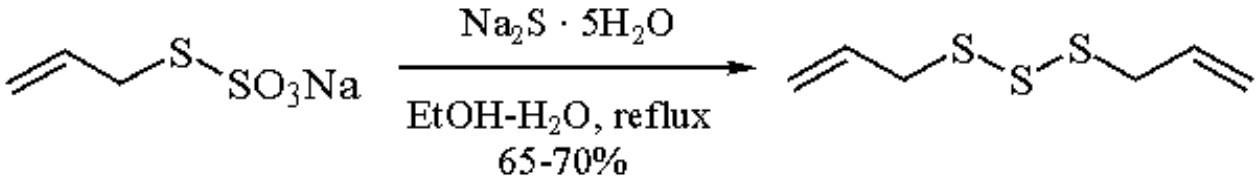

(15)

Reductions.

Sodium sulfide and polysulfides are better reducing agents than H_2S and have been widely used in the reduction of aromatic nitro groups to amino groups (the Zinin reaction).[5,6c,f,7c,34] The reduction can be selective for one nitro group of several. In the reduction shown in eq 16, Na_2S reduces the *o*-nitro group whereas ***Tin(II) Chloride*** reduces the *p*-nitro group.[34a] The Zinin reaction is especially useful in the presence of groups sensitive to acid that preclude the use of a metal-acid reducing reagent. Aliphatic nitro groups are unreactive (eq 17),[35] although elimination of nitrous acid has been observed with tertiary aliphatic derivatives. Differences are observed depending on whether $Na_2S.9H_2O$ or anhydrous Na_2S is used. Treatment of *p*-nitrotoluene with Na_2S_x-NaOH results in a remarkable oxidation-reduction reaction (eq 18).[6c,36] Partial reduction of 2,2´-dinitrobiphenyl by Na_2S gives a benzocinnoline (eq 19),[37a] whereas Na_2S_x gives the monoamino derivative.[37b] Refluxing 2-nitro-4,5-dimethoxybenzophenone with methanolic sodium sulfide yields the anthranil (**2**) (eq 20).[37c] A quinone dioxime is reduced to the diamine by $Na_2S.9H_2O$,[38] and nitrite esters are reduced to alcohols.[39] In β-nitrostyrenes, the nitro group is replaced by hydrogen on treatment with $Na_2S.9H_2O$-PhSH.[40] Other functionalities that are reduced by Na_2S are as follows (product in parentheses): nitroxide (amine),[41] chlorosulfonyl (sulfinic acid),[42] disulfide (thiol),[20,43] α-halo (with $SnCl_2$) and α-phenylthio ketones (ketone),[44] aldehydes (alcohols; requires Na_2S-Al_2O_3 which does not reduce nitro groups, ketones, or esters) (eq 21),[45] carbon-Hg bonds (hydrocarbon) (elimination may be a serious side reaction) (eq 22),[46] tetravalent tellurium- and selenium-halogen bonds (divalent tellurides, selenides) (eq 23).[47]

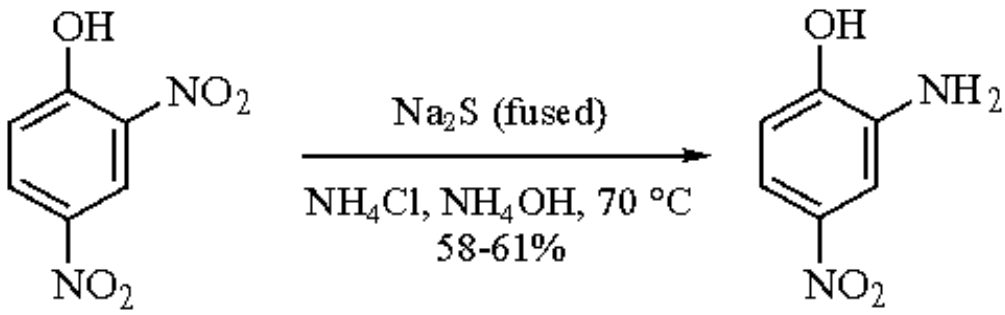

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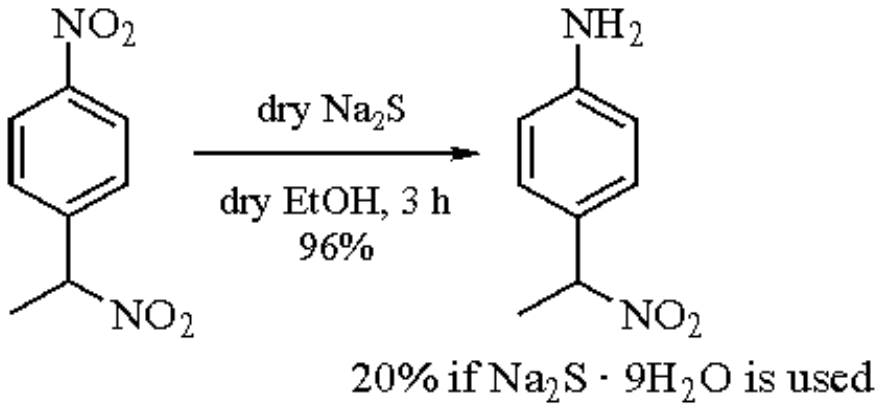

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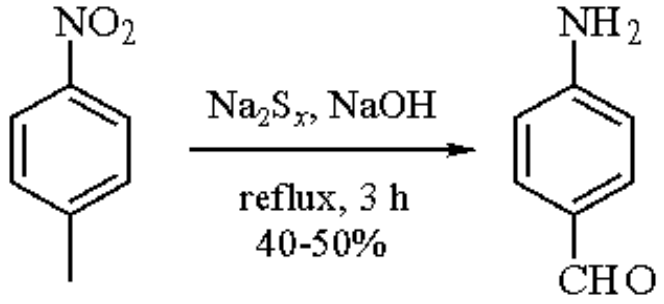

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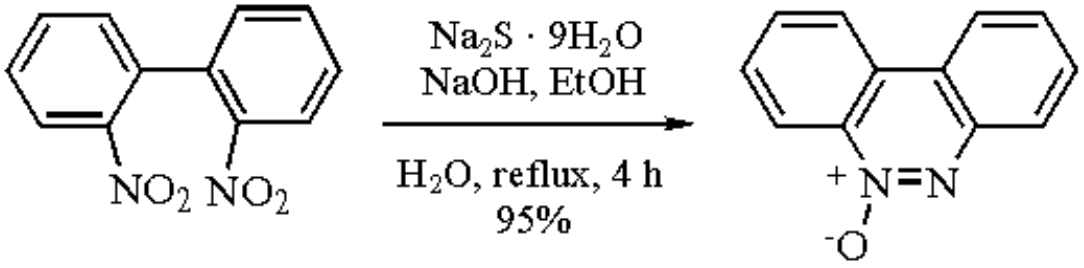

(19)

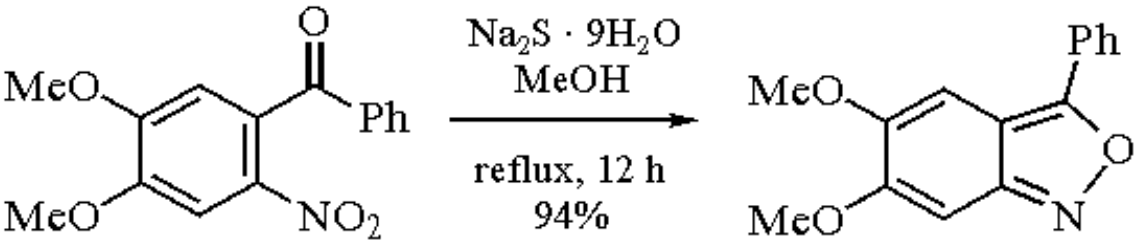

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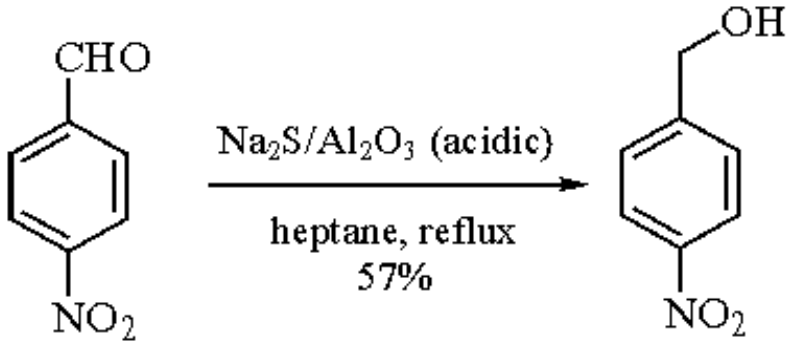

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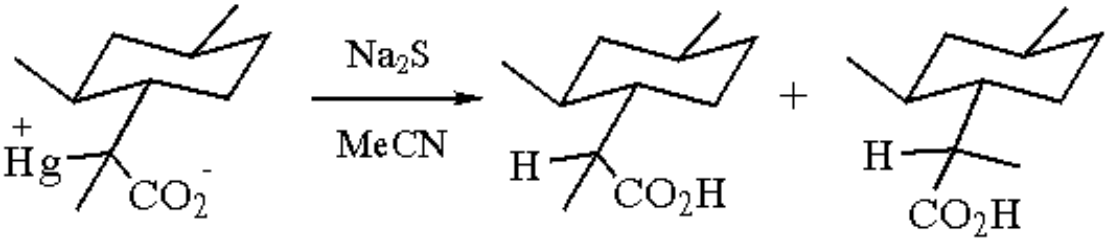

(22)

10:90

50:50 with aq Na_2S

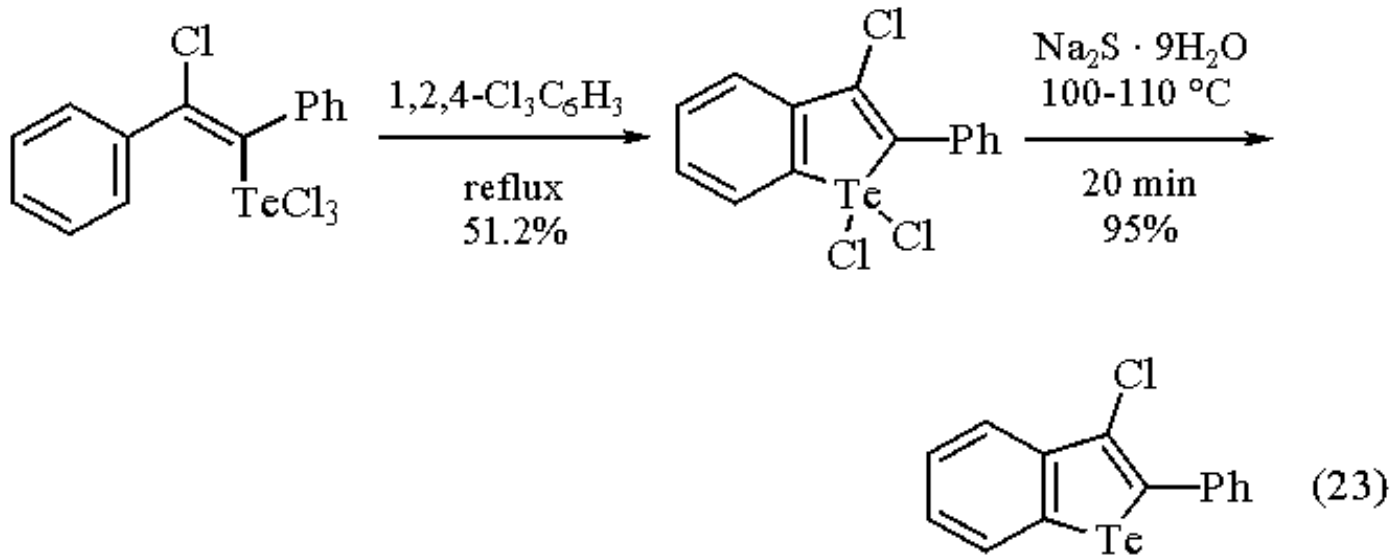

(23)

Miscellaneous.

Na_2S has been used in the synthesis of thiocarbonyl compounds, but H_2S is more widely applicable. A combination of $Na_2S.9H_2O$ and H_2S with a phase-transfer catalyst converts nitriles to thioamides (46-98% yields),[48] and the combination of Na_2S with ***Phosphorus(V) Sulfide***, which performs the same transformation, is notable in that a nitro group is not reduced (eq 24).[49] A convenient isothiazole synthesis uses thioenaminones obtained by addition of $Na_2S.9H_2O$ to ArC(Cl)=CHCH=+NMe_2 ClO_4^-.[50] A cyclopropenethione is obtained by addition of Na_2S to a chlorocyclopropenium salt,[51a] a thioester by addition to a dialkoxy carbocation,[51b] and 4*H*-thiopyran-4-thiones by addition to 6a-thiathiophthenes.[51c] The usefulness of ***2-Chloroacrylonitrile*** as a dienophile is enhanced by the conversion of the chloro nitrile adducts to ketones by $Na_2S.9H_2O$, which is superior to KOH (eq 25).[52] A thioketone is presumed to be an intermediate. This renders 2-chloroacrylonitrile into a dienophilic ketene equivalent. An improved synthesis of ***Sodium Trithiocarbonate*** utilizes a phase-transfer catalyst in the reaction of $Na_2S.9H_2O$ with CS_2.[53] Sodium sulfide also has been used to effect elimination reactions from 1,2-dihalides (*anti*),[54] 1,2-dinitro compounds,[55a] β-halo tellurium(IV) derivatives (*anti*),[55b] and β-nitro sulfones,[55c] and to assist in hydration of alkynes.[56] Carboxylic acids protected as their cyanomethyl[57a] or 4-chlorobutyl[57b] esters are readily deprotected by treatment with Na_2S, thus avoiding strongly acidic or basic conditions (eq 26).

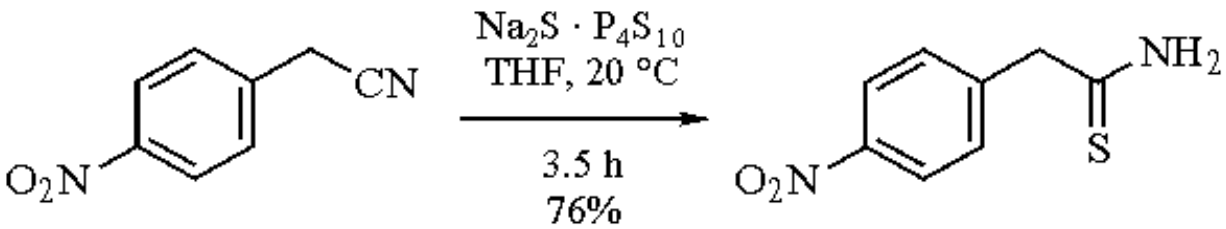

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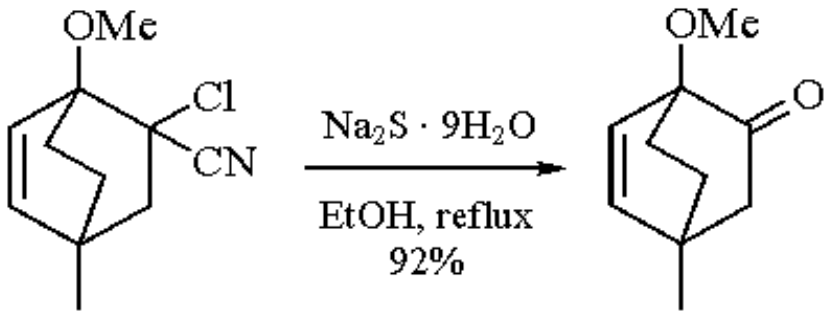

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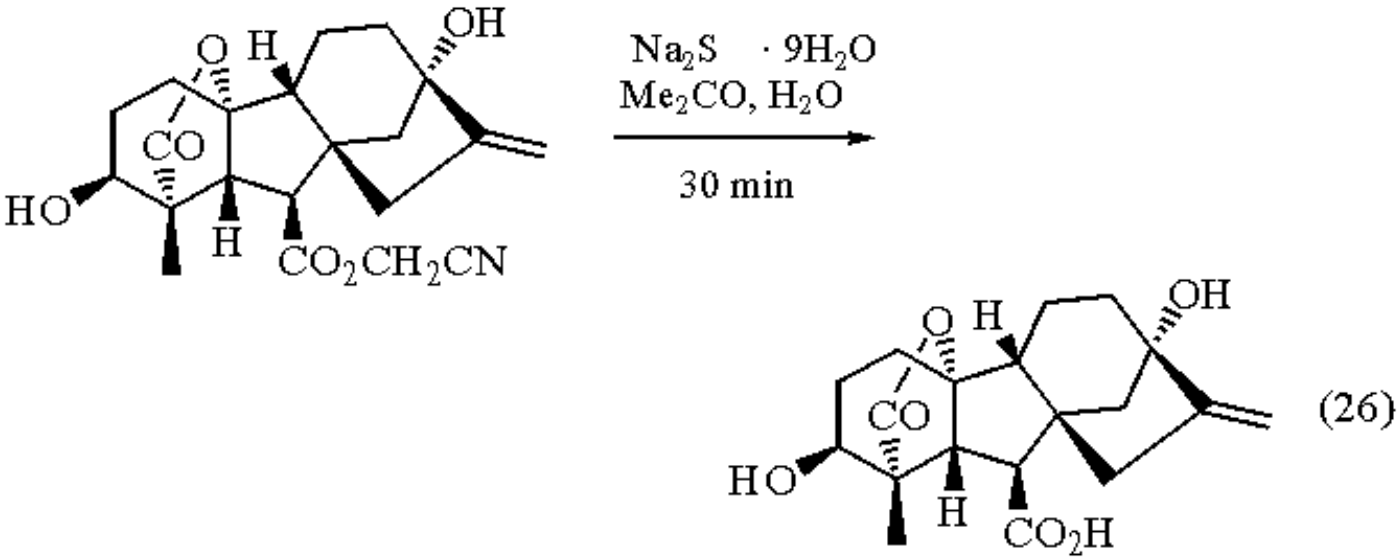

Related Reagents.

Hydrogen Selenide; ***Hydrogen Sulfide***; ***Hydrogen Telluride***; ***Potassium Hydrogen Sulfide***; ***Sodium Hydrogen Sulfide***.

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Sodium Telluride[1]

Na_2Te

(Na_2Te)

[12034-41-2] · Na_2Te · Sodium Telluride · (MW 173.58) (NaHTe)

[65312-92-7] · HNaTe · Sodium Hydrogen Telluride · (MW 151.60) (Li_2Te)

[12136-59-3] · Li_2Te · Lithium Telluride · (MW 141.48) (K_2Te)

[12142-40-4] · K_2Te · Potassium Telluride · (MW 205.80)

(telluride ion and its conjugate acid, TeH^-, are reducing agents and powerful nucleophiles that accomplish nucleophilic reductions;[2] reduction of nitro groups,[3] *N*-oxides,[4] imines,[5] azides,[6] enones,[7] alkenes,[7b,8] α,β-epoxy ketones,[9] and carbon-halogen[10] or carbon-sulfur[11] bonds; conversion of optically active glycidyl sulfonate esters to allylic alcohols;[2] ester cleavage;[12] reductive alkylation of amines;[13] Reformatsky reaction;[14] synthesis of tellurium compounds[1b])

Physical Data: mp 953 °C (dec); *d* 2.90 g cm^{-3}; pK_a (HTe^{-}&b;&ibond; $H^+ + Te^{2-}$) 10.8; E_0 (Te^{2-} -> Te + 2e) +0.95 to 1.14 V.

Solubility: sol H_2O; insol. THF; purple solutions of sodium polytellurides (Na_2Te_n) occur in H_2O, THF, DMF, and methanol.

Preparative Methods: prepared[1b,e] in situ (often as a suspension) by reduction of elemental ***Tellurium*** with ***Sodium Hydroxymethanesulfinate*** ($HOCH_2SO_2Na$) in aqueous base, ***Sodium Borohydride*** in protic or dipolar aprotic (DMF) solvents,[1f] ***Lithium Triethylborohydride*** in THF, ***Thiourea Dioxide*** in aqueous basic THF, ***Sodium Hydride*** in dipolar aprotic solvents, ***Sodium*** in liquid ammonia or DMF, aqueous ***Sodium Dithionite***, ***Sodium Naphthalenide*** in THF, or ***Hydrazine*** hydrate in aqueous base or in DMF, or by electrolysis of elemental tellurium. Often, only catalytic amounts of tellurium are required in the reductions of various organic compounds. Buffering solutions of Na_2Te with acetic acid provides NaTeH. The latter also is obtained by decreasing the amount of $NaBH_4$ in reduction with that reagent.

Handling, Storage, and Precautions: sodium telluride is a white, crystalline, hygroscopic solid that decomposes to elemental tellurium on exposure to air. Traces of oxygen immediately produce pink to purple solutions of polytelluride anions that are not necessarily harmful for subsequent use. Operation in an inert atmosphere is essential, and degassing of solvents is advised. Avoid strong acids that produce noxious ***Hydrogen Telluride***. The reaction with oxidizing agents may be highly exothermic. All reactions should be carried out in a good fume hood to avoid exposure to possible toxic and malodorous organic tellurium products or byproducts. Decontamination of apparatus or spills is effected by treatment with oxidants such as Chlorox or hydrogen peroxide.

Reductions.

Aromatic mono- and polynitro compounds are reduced to amines by catalytic amounts of Na_2Te (eq 1).[3a] The method is useful when acid sensitive groups are present and is said to give fewer side reactions than does ***Sodium Sulfide***. Use of NaH in DMF to reduce Te gives azobenzenes,[3a,b] and use of sodium borohydride gives arylhydroxylamines.[3c] Sodium hydrogen telluride produces azoxybenzene derivatives.[3e] The latter reagent also reduces amine oxides[4] and imines[5] to the free amines. Sulfoxides are difficult to reduce and phosphine oxides are inert.[4c] The in situ formation and reduction of imines by NaTeH is a variation of the reductive alkylation of amines (eq 2).[13] Reductions of imines may proceed via iminium salts and are pH sensitive.[5b] At pH 6, *N*-methylpyridinium iodide is reduced to *N*-methylpiperidine, whereas at pH 10-11 a 2:1 mixture of *N*-methyl-1,2- and -1,4-dihydropyridine is obtained. Azides are selectively reduced to amines by NaTeH,[6] thus providing a useful synthesis for the pyrazine (**1**) (eq 3),[6a] but the method is not applicable to primary azido ketones. For the selective reduction of the double bond of enones[7] and of certain α,β-unsaturated sulfones,[11a,15] NaTeH is superior to Na_2Te (eq 4).[7c] In the sulfone case, reduction of the carbon-sulfur bond may occur (eq 5).[15] The triple bond of dimethyl acetylenedicarboxylate and of methyl phenylpropiolate is reduced partially.[16] Carbon-carbon double bonds conjugated with aromatic systems are reduced by NaTeH (and also PhTeH).[7b,8] Addition of HTe^- to an isolated, unconjugated double bond followed by reduction with ***Nickel Boride*** effects the reduction of alkenes.[17a]

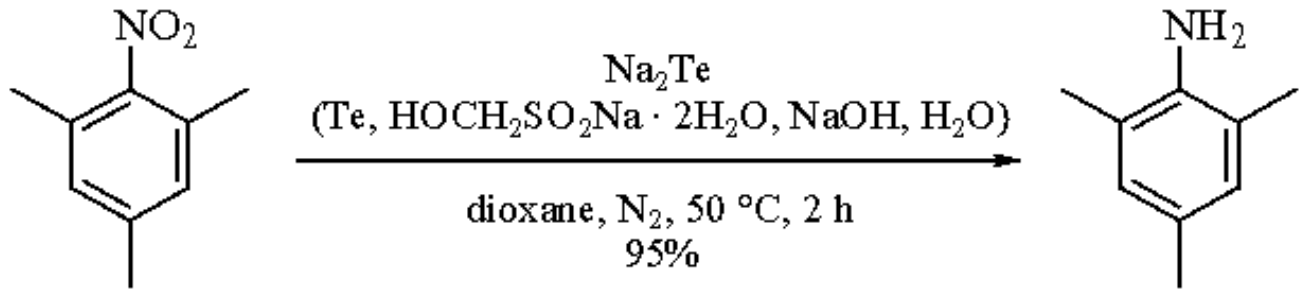
NO2
Na2Te
(Te, HOCH2SO2Na · 2H2O, NaOH, H2O)
dioxane, N2, 50 °C, 2 h
95%
NH2

(1)

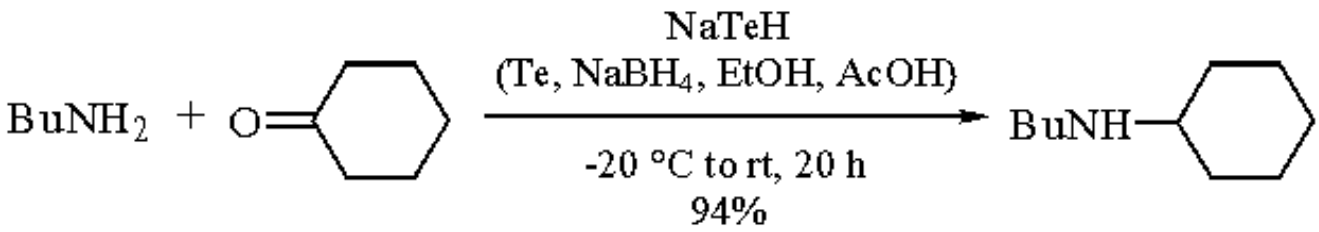
BuNH2 +
O
NaTeH
(Te, NaBH4, EtOH, AcOH)
-20 °C to rt, 20 h
94%
BuNH

(2)

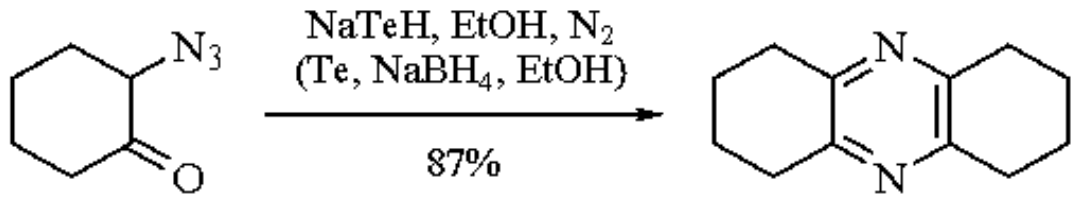
N3
O
NaTeH, EtOH, N2
(Te, NaBH4, EtOH)
87%
N
N

(3)

(1)

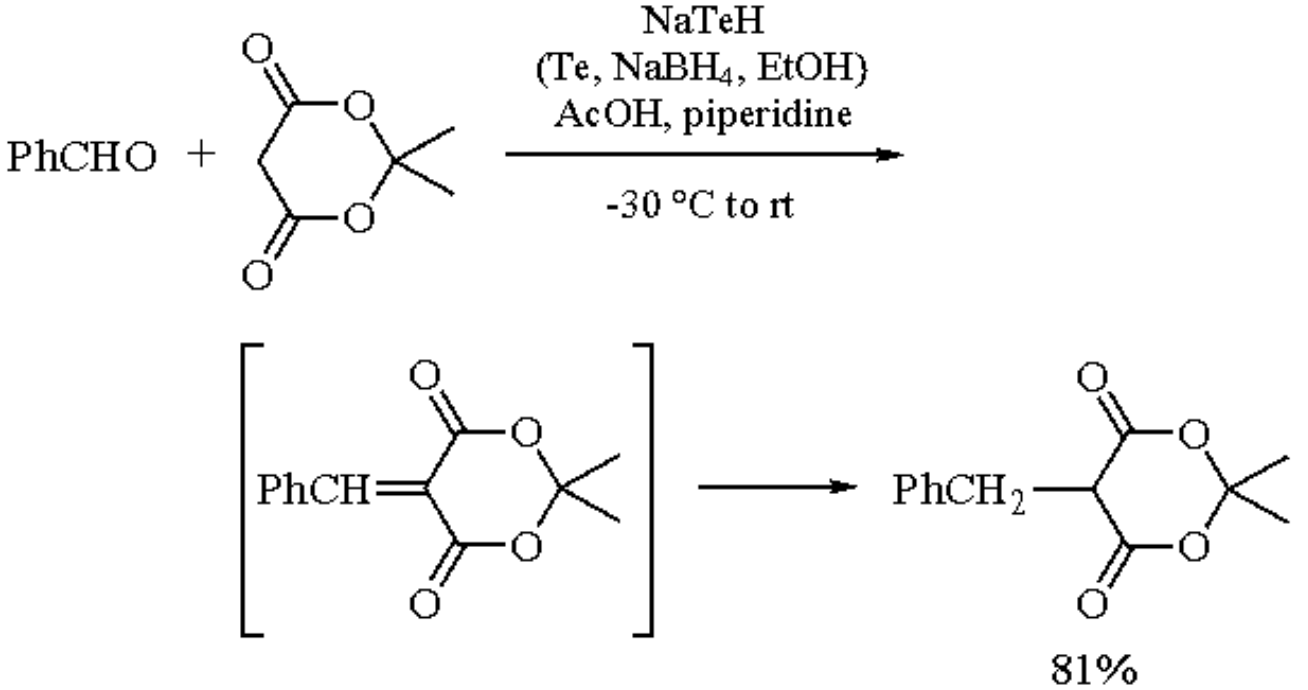
PhCHO +
O
O
O
O
NaTeH
(Te, NaBH4, EtOH)
AcOH, piperidine
-30 °C to rt
PhCH
PhCH2
81%

(4)

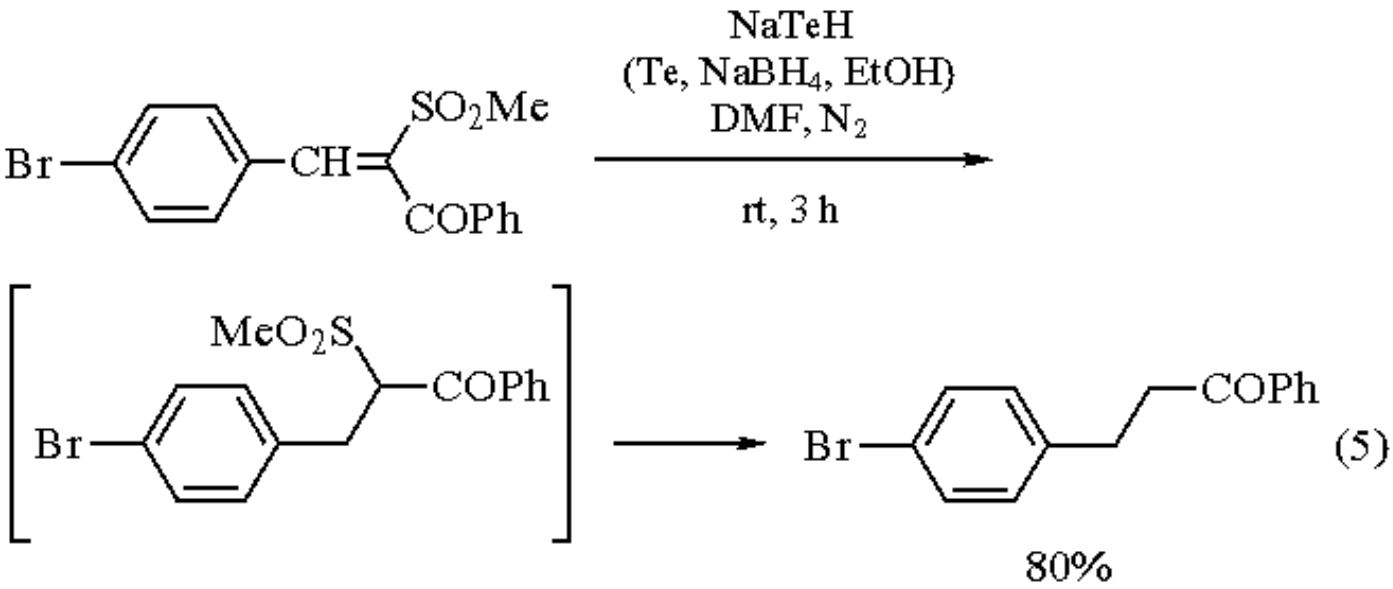

One carbonyl group in 1,2-diketones is reduced to the alcohol,[4c] and aromatic thioketones are reduced to the alkane.[3a] Aromatic aldehydes and ketones are reduced to alcohols (34-89% yields) by Na_2Te (Te, NaH) in ***1-Methyl-2-pyrrolidinone*** (NMP).[17b] Other groups that are reduced are as follows: the carbon-carbon bond of certain *C*-allyl compounds,[18] the α-carbon-oxygen bond of α,β-epoxy ketones (eq 6),[9] carbon-sulfur bonds of sulfides and sulfones (eqs 5, 7 and 8),[11,15b,19] the carbon-nitrogen bond of tertiary nitro compounds,[20] *gem*-diamino compounds,[21] and carbamate esters,[22] carbon-halogen bonds,[10] sulfonyl chlorides (to the sulfinate anion),[23] and the sulfur-sulfur bond of disulfides and thiosulfates.[24]

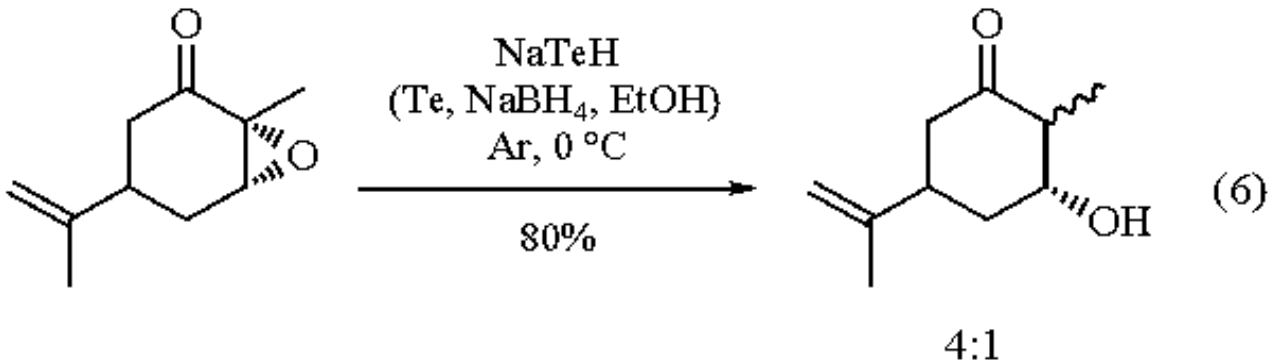

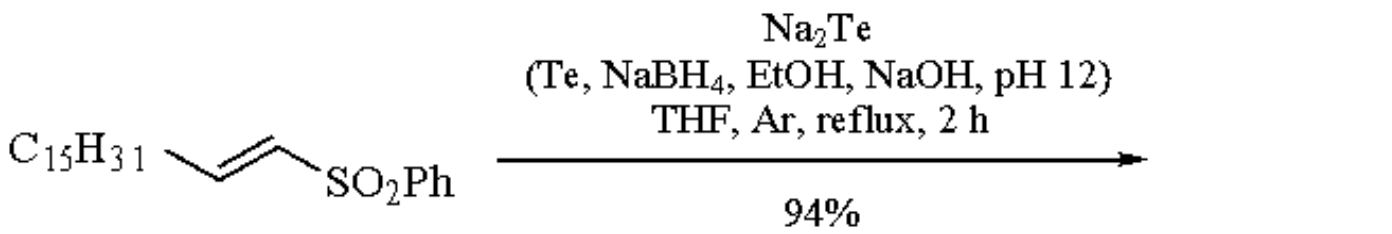

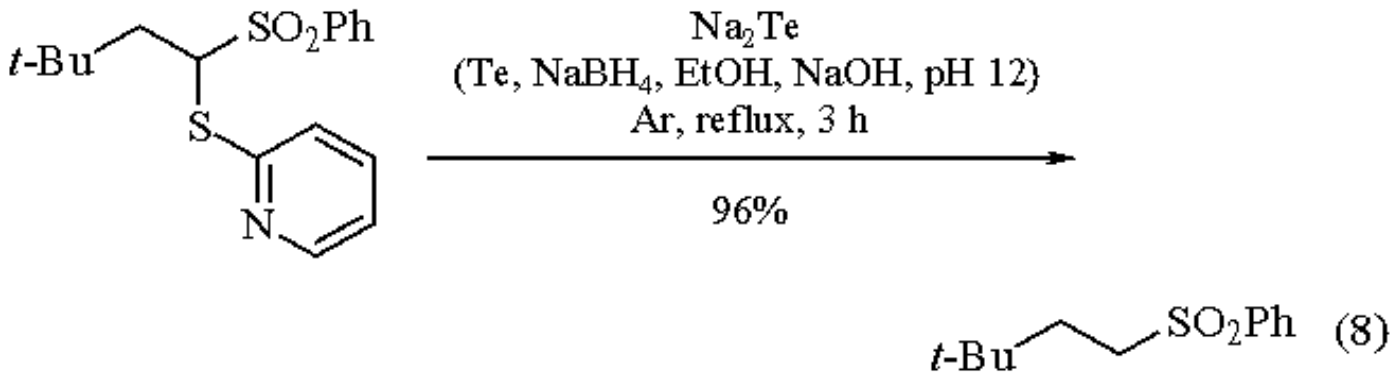

The reduction of α-halo carbonyl compounds leads to a variant of the Reformatsky reaction (eq 9).[14] Wurtz-type couplings have been

observed with halides.[25] The reduction of optically active glycidyl tosylates and mesylates (obtained via a Sharpless asymmetric epoxidation) by Na_2Te to allylic alcohols is accompanied by a transposition of the hydroxy function and the former double bond that enables the synthesis of optically active secondary and tertiary allylic alcohols without the necessity of a resolution (eq 10).[2] Epichlorohydrins are transformed to allylic alcohols by treatment with telluride ion.[26] Simple epoxides may be reduced to alkenes by a two-step procedure involving nucleophilic opening of the epoxide by NaTeH to a β-hydroxy tellurol and conversion of the alcohol function to a tosylate which, in the presence of pyridine, decomposes to the alkene and elemental tellurium.[27]

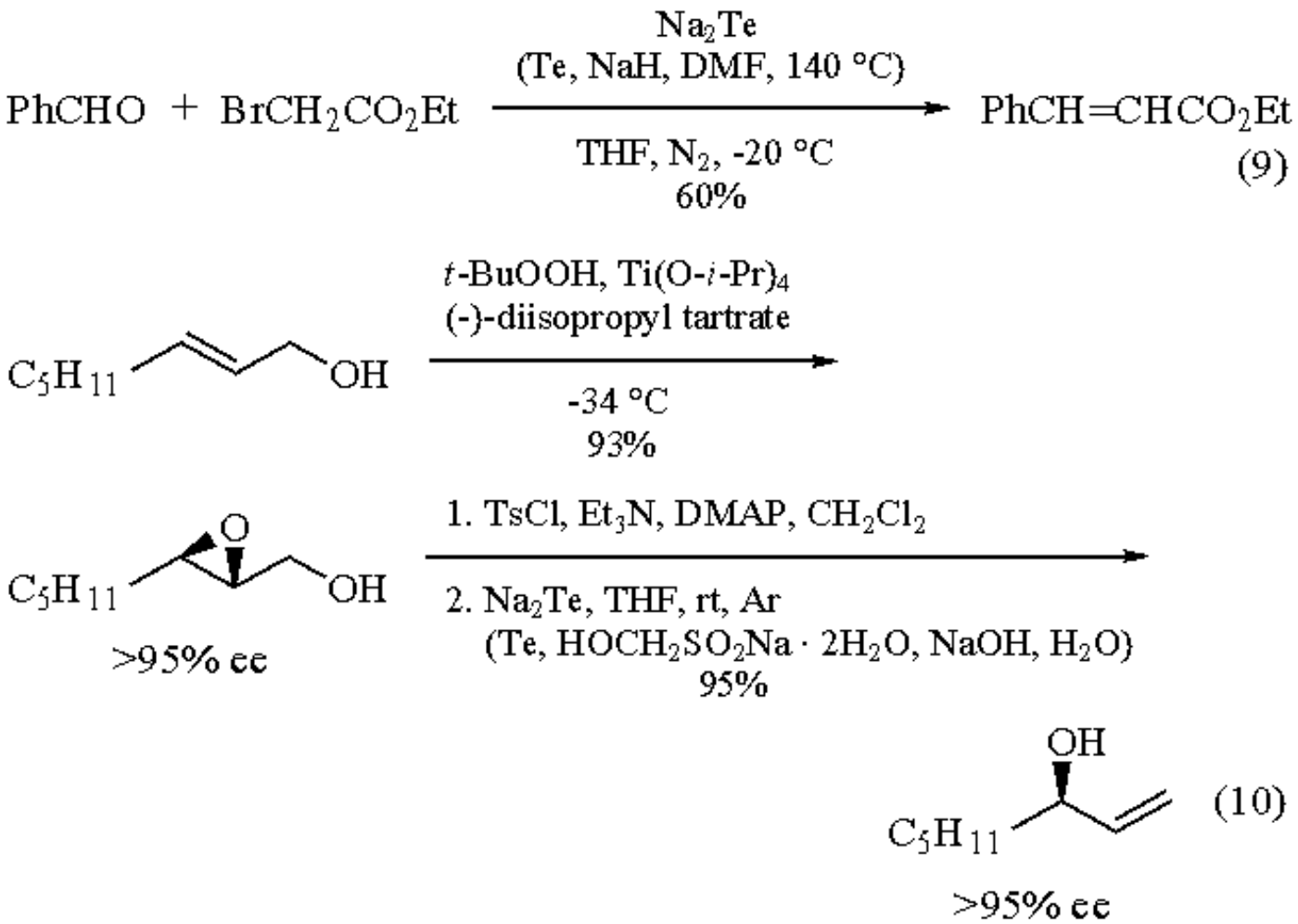

Deprotection of Functional Groups.

Deprotection of various esters to yield carboxylic acids is effected with either Na_2Te or NaTeH.[12,28] β-Halo alkyl esters are especially reactive (eq 11);[12a,b,28c] methyl, ethyl, phenacyl,[12d,28a] and allyl esters[12c] also are dealkylated readily. Phenols protected as acetate, benzoate,[28b] carbonate,[29] or chloroacetate[28c] esters or as allyl ethers[12c] can be regenerated. Amines have been freed from quaternary ammonium salts,[27] and diols, from cyclic acetals.[30]

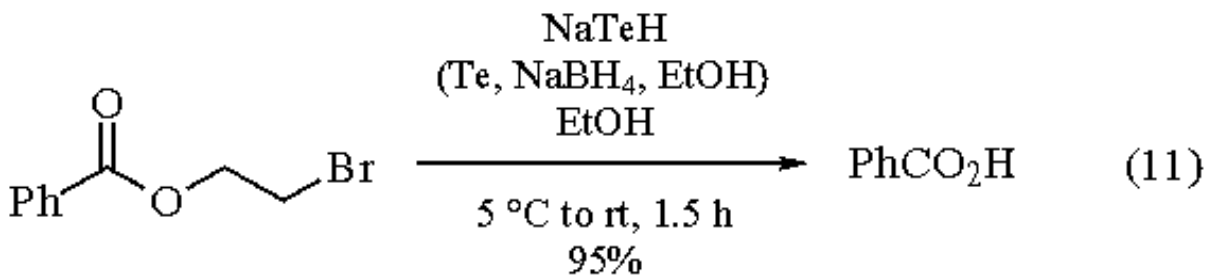

Heterocyclic Compounds.[31]

Addition of telluride ion to the triple bonds of 1,3-dialkynes such as 1,4-bis(trimethylsilyl)-1,3-butadiyne is a convenient synthesis of tellurophenes (eq 12);[32] six-membered ring systems containing tellurium can likewise be obtained from the appropriate dialkyne.[33] A tellurophene synthesis (eq 13) that involves reaction of telluride ion with an acetylenic epichlorohydrin is related to the nucleophilic reduction-transposition reaction exemplified in eq 10.[34]

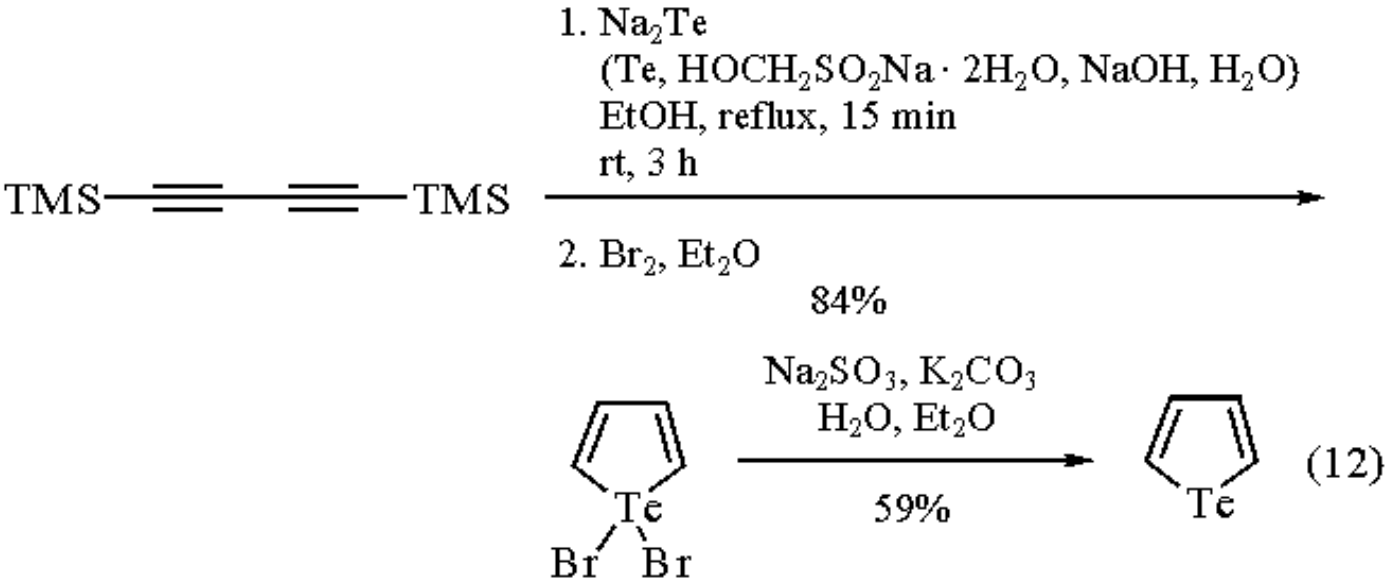

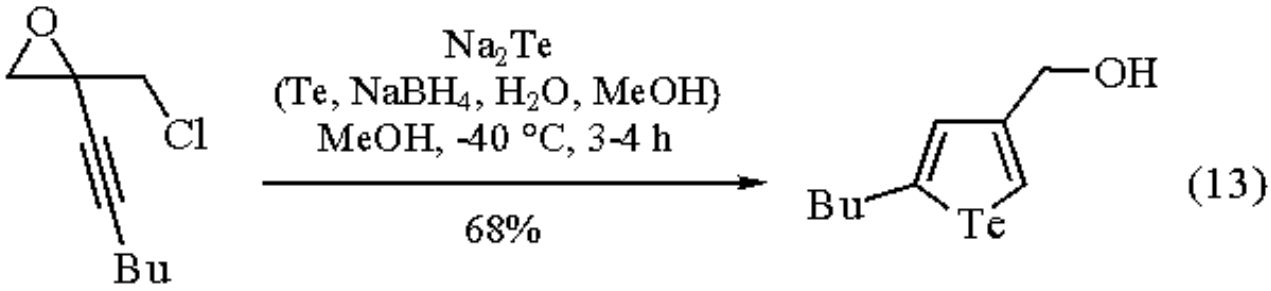

Tellurols and Tellurides.[35]

Reactions of Na_2Te and NaTeH with organic halides have found limited use in the synthesis of sodium salts of tellurols. However, a wide variety of symmetrical tellurides are obtained from halides, alkynes, and related compounds with Na_2Te (eqs 14 and 15).[36a-d] Tellurocarboxylates, $RCOTe^-$, are obtained from the acid chloride.[36e]

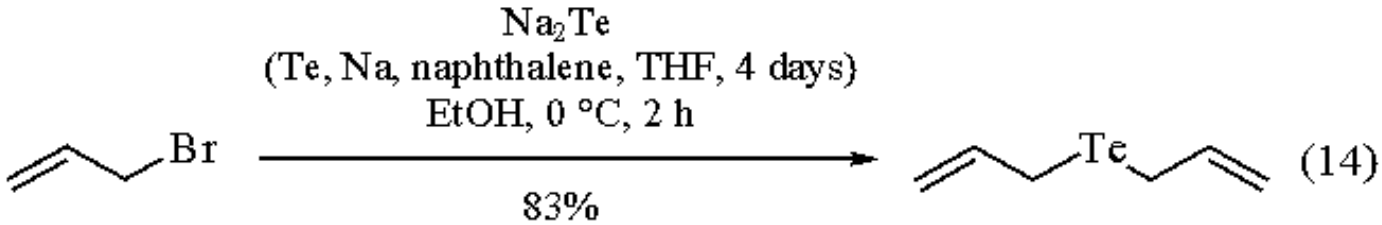

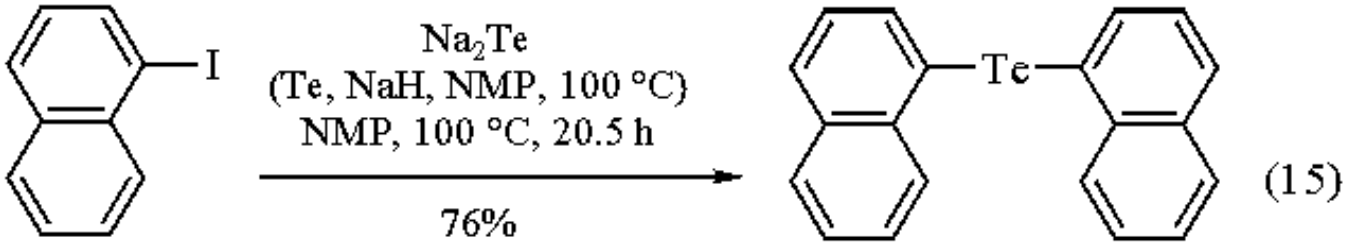

Miscellaneous.

Elimination reactions yielding alkenes are observed when the following are treated with NaTeH or Na_2Te: 1,2-dihalides,[8b,37] 1,2-dinitroalkanes,[3e] β-nitro sulfones,[38] and β-bromo azides.[6a] Conversion of an alcohol to a benzyl ether has been accomplished by addition of NaTeH to an iminium ester derivative of the alcohol.[39a,b] Lithium telluride is used in the preparation of $(Bu_3Sn)_2Te$ (from Bu_3SnCl) which is an intermediate for $(Me_2Al)_2Te$, useful in the synthesis of highly reactive telluroaldehydes and telluroketones.[40]

Related Reagents.

Hydrogen Selenide; ***Hydrogen Telluride***; ***Sodium Diselenide***; ***Sodium Hydrogen Sulfide***; ***Sodium Selenide***; ***Tellurium***.

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Sodium Tetraborate

$Na_2B_4O_7$

[1330-43-4] · $B_4Na_2O_7$ · Sodium Tetraborate · (MW 201.22) (decahydrate)

[1303-96-4]

(source of boric acid at low concentration in aq soln;[1] desilylation of trimethylsilyl alkynones[2])

Physical Data: mp 743 °C, 720 °C, 663 °C (α, β, and γ crystals); bp 1575 °C; *d* 2.367 g cm^{-3}.

Solubility: slowly sol water (1 g in 91 mL at 0 °C; 1 g in 11.4 mL at 40 °C); sol methanol, ethylene glycol.

Form Supplied in: powder or glasslike plates that turn opaque on exposure to air. Commonly supplied as the decahydrate (borax). However, borax is insoluble in alcohol.

Handling, Storage, and Precautions: hygroscopic; absorbs water up to 300 °C; dehydrates completely at 700 °C. Slow decomposition will occur above 900 °C. Eye, skin, and upper respiratory tract irritant. Incompatible with strong oxidizing agents.

Introduction.

$Na_2B_4O_7$ is most commonly available as its decahydrate (borax) and is sometimes referred to as fused borax. Below 10% relative humidity, borax will irreversibly decompose to the dihydrate (metakernite); between 10-50% relative humidity there is reversible decomposition to the pentahydrate (tincalconite).[3] In aqueous solution, $Na_2B_4O_7$ dissociates into a number of different boron species depending upon the pH, temperature, concentration of boron, and concentration of any added salt.[1] At low concentration (i.e. [B] < 0.025 M), $Na_2B_4O_7$ dissociates exclusively into ***Boric Acid***, $[B(OH)_3]$, and monoborate ion, $[B(OH)_4^-]$, to yield an alkaline solution that buffers around pH 9.[4] At higher boron concentrations, polyborates predominate.[1]

Desilylation.

The high yields and low cost make $Na_2B_4O_7$ an attractive reagent for the desilylation of trimethylsilyl alkynones to yield monosubstituted alkynes (eq 1).[2,5]

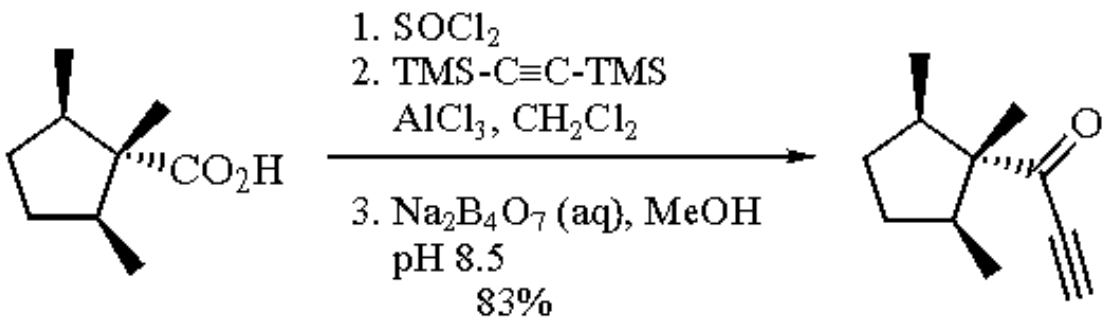

(1)

Nef Reaction.

The original Nef reaction involves hydrolysis of the conjugate base of a primary or secondary nitro compound to the corresponding aldehyde or ketone with ***Sulfuric Acid***.[6] Many alternatives exist for carrying out this reaction. One approach is to oxidize the conjugate base.[6] When an alkaline ***Potassium Permanganate*** solution is used, it has been shown that addition of $Na_2B_4O_7$ will improve yields (eq 2).[7]

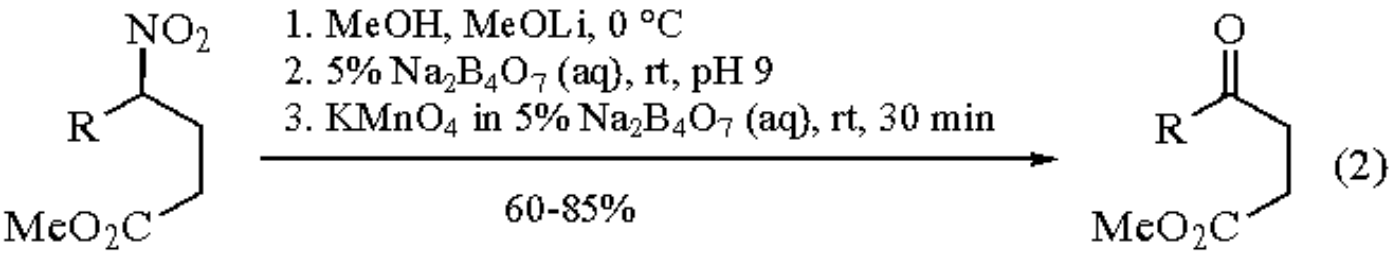

R = alkyl, aryl containing acid sensitive functionalities

Substitution and Addition.

$Na_2B_4O_7$ in methanol creates a mild source of methoxide ion for carrying out stereoselective substitutions α to a carbonyl function (eq 3).[8,9]

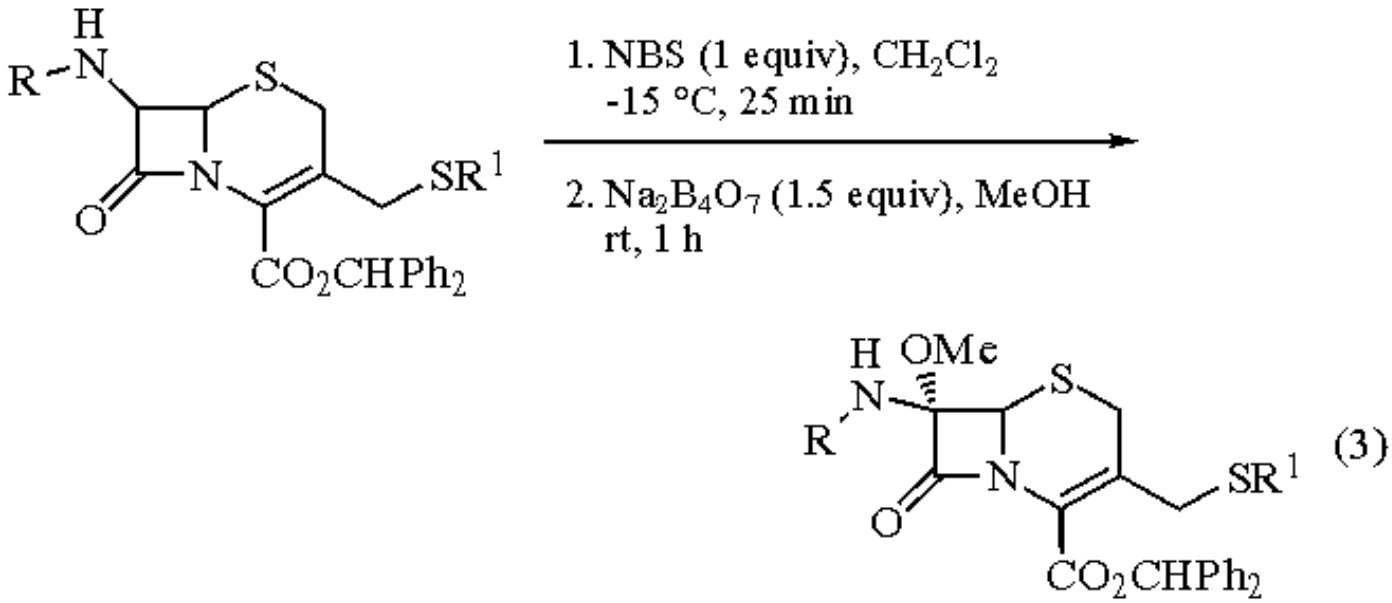

$Na_2B_4O_7$ affects the reactivity of α,β-unsaturated esters in two ways: (i) suppression of 1,2 attack;[10] and (ii) enhancement of 1,4 addition especially by thioalkanes.[11] The combined effects have been used succesfully as a method to selectively reduce isolated alkenes in the presence of conjugated alkenes (eq 4).[12]

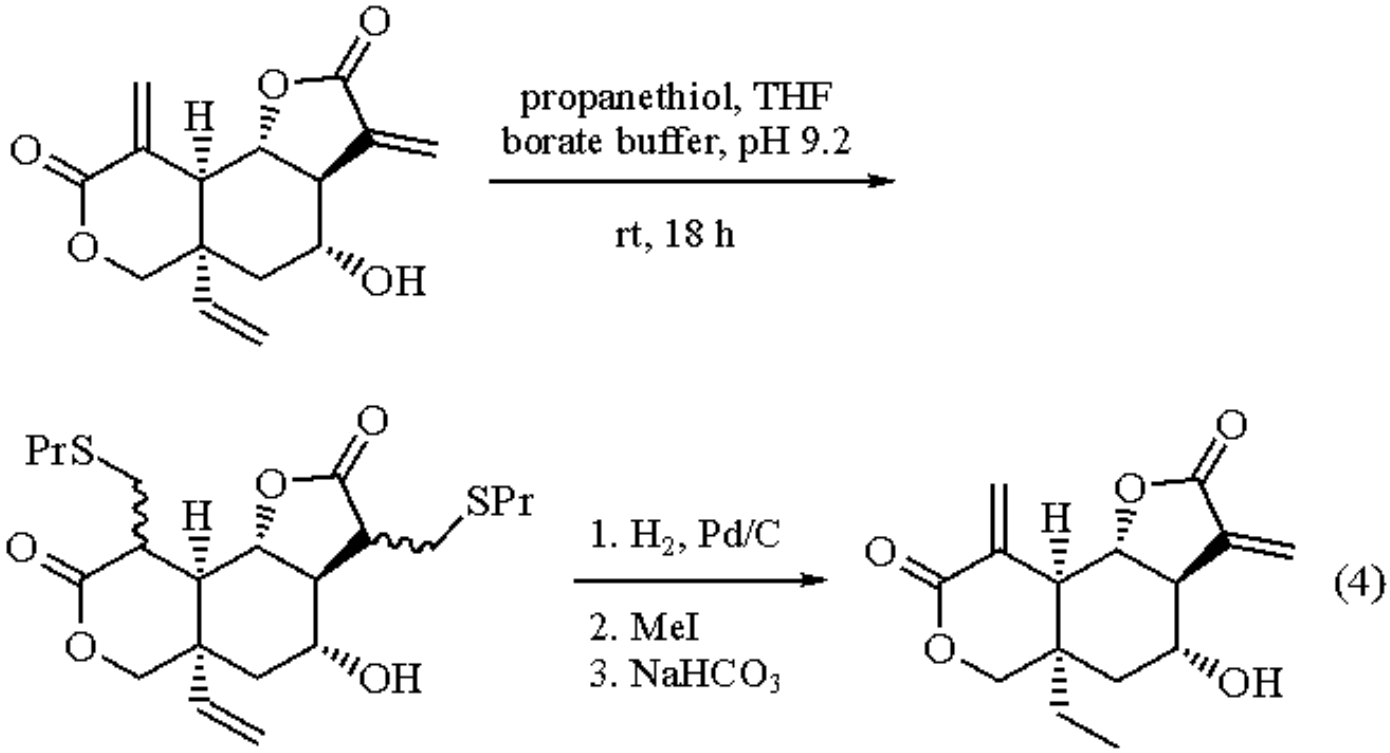

Protecting Group For Vicinal Diols.

The ability of $Na_2B_4O_7$ to complex with vicinal diols provides a convenient protecting group that can be easily removed under acidic conditions.[13] The selective methylation of methyl gallate illustrates the simplicity of the method (eq 5).[14]

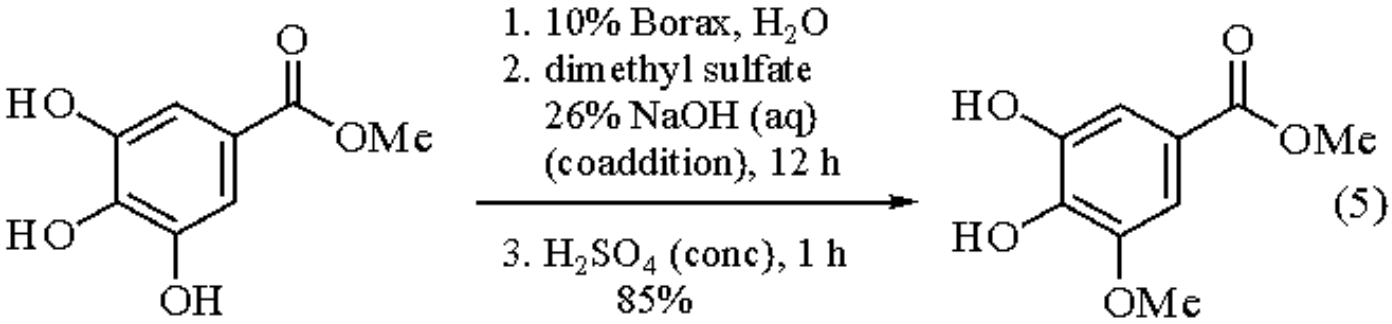

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Sodium Tetracarbonylcobaltate

$NaCo(CO)_4$

($NaCo(CO)_4$)

[14878-28-5] · C_4CoNaO_4 · Sodium Tetracarbonylcobaltate · (MW 193.96) ($HCo(CO)_4$)

[16842-03-8] · C_4HCoO_4 · Tetracarbonylhydridocobalt · (MW 171.98) ($KCo(CO)_4$)

[14878-26-3] · C_4CoKO_4 · Potassium Tetracarbonylcobaltate · (MW 210.07) ($LiCo(CO)_4$)

[15616-75-8] · C_4CoLiO_4 · Lithium Tetracarbonylcobaltate · (MW 177.91) ($TlCo(CO)_4$)

[38991-21-8] · C_4CoO_4Tl · Thallium Tetracarbonylcobaltate · (MW 375.35) ($[CuCo(CO)_4]_4$)

[94024-70-1] · $C_{16}Co_4Cu_4O_{16}$ · Tetracopper Tetrakis(tetracarbonylcobaltate) · (MW 938.08)

(catalyst for carboxylation reactions of alkyl,[46] benzyl,[49] aryl,[55] and vinyl halides;[55] reagent for single and double carbonylation of benzyl halides[17a,b] and alkene oxides;[65] mediates butenolide synthesis from alkynes and acid chlorides;[73] mediates alkyl halide hydrogenolysis,[77] coupling of *gem*-dihalides to give tetrasubstituted alkenes,[5b] formation of symmetrical ketones,[80] formation of alkylcobalt tetracarbonyl complexes and alkylidynetricobalt nonacarbonyl complexes;[82,84] the conjugate acid, $HCo(CO)_4$, is the true hydroformylation catalyst;[31] $HCo(CO)_4$ is also a reagent for hydrogenation of alkenes conjugated to aldehydes,[108a] ketones,[111a] or arenes[111a] and for alkene isomerization;[93b,c] $HCo(CO)_4$ is an effective acid catalyst for a variety of organic transformations; tetracarbonylcobaltate with a range of counter ions mediates an array of organic transformations)

Physical Data: white solid. No other documented literature values. The $Co(CO)_4^-$ anion has a distorted tetrahedral structure.[1]

Solubility: sol heptane, hexane, benzene, toluene, dichloromethane, THF, ether; alcohols are the most effective solvents for reactions of the title compound.

Form Supplied in: off-white powder; commercially available.

Analysis of Reagent Purity: IR;[2] ^{59}Co NQR;[3] Raman.[2f,g]

Preparative Methods: conveniently prepared in a variety of ways.[4] Reacting ***Octacarbonyldicobalt*** with ***Sodium Amalgam*** (1%) in THF,[5] ether,[6] hexane,[7] or benzene[8] under N_2 or CO gives $NaCo(CO)_4$ in up to 94% yield.[8] High yields can also be achieved using alternative reducing agents with $Co_2(CO)_8$ under mild conditions. ***Sodium Hydride*** (98% yield),[9] ***Sodium Naphthalenide*** (90% yield),[10] ***Sodium-Potassium Alloy*** (product isolated as the Ph_3Sn derivative in 96% yield),[11] and ***Sodium-Ammonia*** (95% yield)[12] have all been used to prepare the required anion. Octacarbonyl(mercury)dicobalt ($Hg[Co(CO)_4]_2$) (see also ***Octacarbonyl(zinc)dicobalt***) has also been efficiently used as the $Co(CO)_4$ source with either Na(Hg)[7] or aqueous ***Sodium Sulfide***.[13] When required under stringently dry and deoxygenated conditions, $NaCo(CO)_4$ is most conveniently and rapidly formed from $Co_2(CO)_8$ with ***Sodium Hydroxide*** in dry THF under N_2.[14] Furthermore, this technique does not require the preformation or handling of Na(Hg) or $Hg[Co(CO)_4]_2$. Less widely used methods involving electrochemical[15] or photochemical techniques[16] have also been reported. In addition to the techniques already described, $NaCo(CO)_4$ is commonly prepared in situ either from $Co_2(CO)_8$ under basic phase-transfer conditions[17] or under reductive conditions from simple cobalt salts and CO (e.g. $CoCl_2/NaBH_4$,[18] $CoBr_2$/Na naphthalenide,[19] and $Co(acac)_2$/Na naphthalenide[20]).

The potassium, lithium, and thallium analogs, $KCo(CO)_4$[13,14] (IR[2i,j]), $LiCo(CO)_4$[14] (white crystalline solid, IR[2h-j]), and $TlCo(CO)_4$[21-23] (recrystallized from H_2O,[21] volatile, air-sensitive,[22] bright yellow crystalline solid, mp 120-130 °C (dec),[21] IR,[21] MS,[21] X-ray structure[23]), are also available by similar techniques, as well as by alternative routes using KH,[24] K- and L-Selectride,[25] C_8K,[26] and Li wire in THF with $Co_2(CO)_8$.[27] It is also worth noting that an efficient aqueous, low-pressure

synthesis of the potassium species has been reported from simple cobalt halides, KOH, and KCN in the presence of CO.[28] This procedure is more convenient than a similar earlier synthesis from $Co(NO_3)_2$.[29] In addition to the species already mentioned, the copper analog, $CuCo(CO)_4$, exists as an orange-red crystalline tetramer (X-ray structure[30]) and is readily synthesized from $NaCo(CO)_4$ and CuCl.[30]

Tetracarbonylhydridocobalt,[31] $HCo(CO)_4$, (hydrogen tetracarbonylcobaltate, cobalt tetracarbonyl hydride, cobalt hydrocarbonyl; white to light yellow solid or liquid; mp -33 °C;[28a,29,32] bp 10 °C (estimate),[33] bp 47 °C;[34] decomposes thermally to $Co_2(CO)_8$ and H_2;[29,32,35] intolerable odor;[29] sol hexane, toluene, ethanol; sparingly sol in H_2O; IR,[36] ^1H NMR,[1h,37] ^{59}Co NQR,[3] MS;[38] X-ray structure,[39] central Co surrounded tetrahedrally by four CO groups with H lying in one face of the tetrahedron and bonded to three CO groups[39,40]) is the conjugate acid of the title compound and will also be discussed here. The metal hydride is not readily available commercially but is prepared by a variety of techniques with and without the requirement for high gas pressures. Methods where CO and H_2 pressure are not required include reaction of salts containing the $Co(CO)_4^-$ anion (usually the readily prepared pyridinium salt) with protic acids[40a] or the similar reaction of acid with the disproportionation product of $Co_2(CO)_8$ with DMF under 1 atm of CO.[41] A further simple route to $HCo(CO)_4$ is by reaction of preformed $KCo(CO)_4$ with HCl.[28a,29,32] In a much less common route, reaction of a range of other transition metal hydrides with $Co_2(CO)_8$ yields the cobalt hydride.[36l] Routes to $HCo(CO)_4$ from common cobalt salts are available but require high pressures (approx. 200 atm) of CO with, in most cases, H_2.[33,40a,42] Similarly, $Co_2(CO)_8$ can be converted to $HCo(CO)_4$ under CO/H_2 pressure at elevated temperatures.[43] An electrochemical route from $Co(acac)_2$ at milder CO/H_2 pressures has also been reported.[44] Yields in the higher pressure reactions are generally lower than the atmospheric pressure reactions and offer no obvious advantage. General purification techniques for $HCo(CO)_4$ are given by Moore et al.[45]

Handling, Storage, and Precautions: the title compound decomposes readily in air. Can be handled and stored as a solid or solution in the organic solvents quoted above under inert gas (argon or nitrogen). The conjugate acid, $HCo(CO)_4$, is an unpleasantly odorous gas at room temperature with a toxicity predicted as being equivalent to that of $Ni(CO)_4$.[29] This material is usually prepared as required.

Carboxylation and Related Reactions.

Carboxylation of halogen compounds with $Co_2(CO)_8$, which is considered to involve $^-Co(CO)_4$, is well known and is discussed elsewhere (see ***Octacarbonyldicobalt***). Additionally, the reaction of alkyl halides, sulfates, or sulfonates and carbon monoxide (atmospheric pressure) in alcohol solution in the presence of base with a catalytic amount of $NaCo(CO)_4$ gives alkoxycarbonylation in good yields (eqs 1 and 2).[46] The initially formed alkylcobalt tetracarbonyl undergoes carbon monoxide addition to form the acylcobalt tetracarbonyl and finally gives the ester by alcoholysis.[47] When the reactions are carried out at 50 °C or below, only the expected ester, where the halogen has been directly replaced by the methoxycarbonyl group, is obtained. Therefore, at low temperatures, the mixture of isomers formed by the analogous $Co_2(CO)_8$ carboxylation is avoided. Further studies have shown that isomerization of acylcobalt carbonyls is possible and is dependent on solvent, atmosphere, and the acyl group structure.[28b,48]

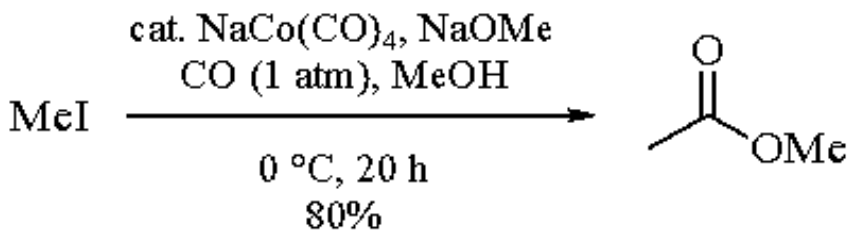

(1)

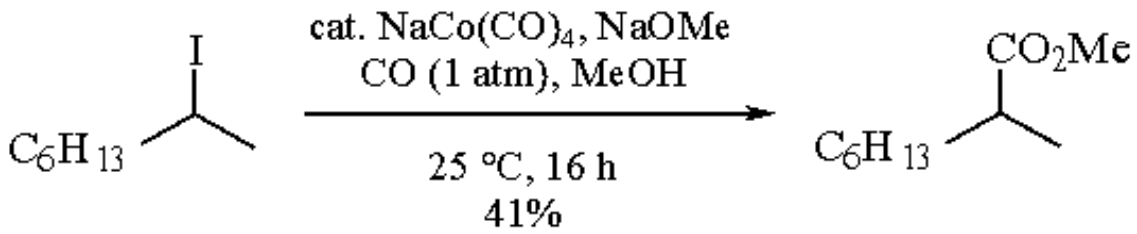

(2)

Benzyl halides also undergo carboxylation reactions under both homogeneous (eq 3)[49] and phase-transfer conditions (PTC) (eq 4).[17a,b,50] Anion-exchange resins have also been used effectively, in a similar way to PTC, to heterogenize the cobaltate anion.[51] Additionally, the tetracarbonylcobaltate anion has been prepared in situ from simple cobalt salts and CO under reductive conditions, and reacted with benzyl halides to give the products of both carboxylation and carbonylation/cyclization in good yields (eqs 5 and 6).[18-20,52]

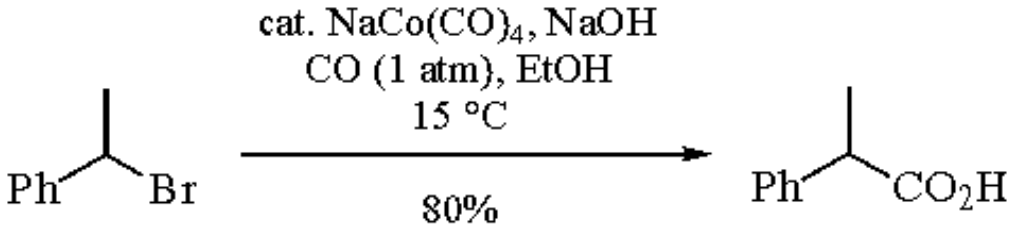

(3)

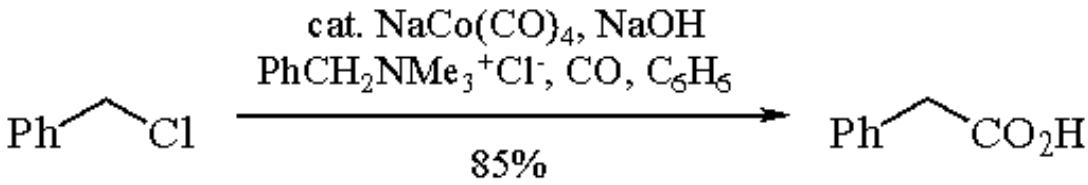

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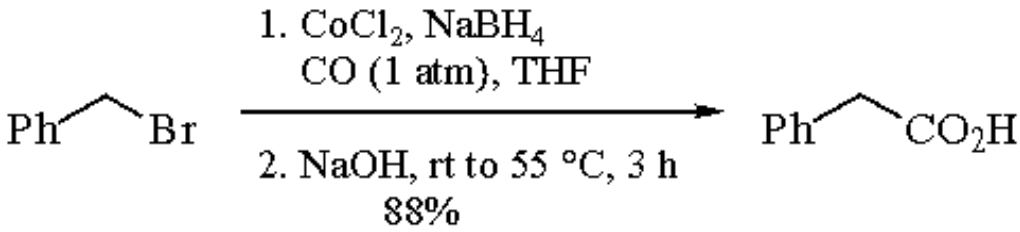

(5)

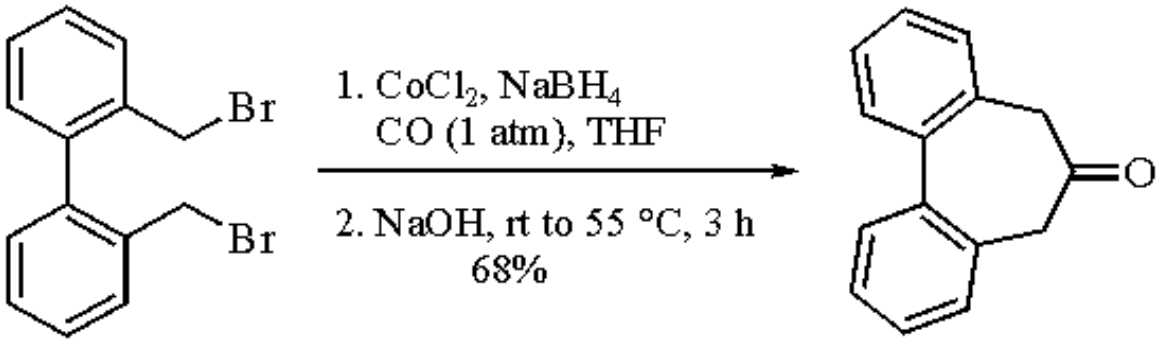

(6)

Following the initially reported reactions, PTC have been used extensively in reactions involving the tetracarbonylcobaltate anion.[17c,53] Under such conditions the Co anion is considered to be more nucleophilic than under more conventional techniques[50b] and, in carboxylation reactions, the PTC allow the product and catalyst to be easily separated in the aqueous and organic phase respectively.[54] Furthermore, in most cases when PTC are used, the $(CO)_4Co^-$ is generated in situ from $Co_2(CO)_8$ and base under a CO atmosphere. The efficiency of the phase-transfer techniques is illustrated by the carboxylation of aryl and vinyl halides (eqs 7 and 8).[55] Subsequently, the carboxylation of vinyl, aryl, and heteroaryl halides, using a variety of techniques for the generation and reaction of the tetracarbonylcobaltate anion, have been reported. These include the in situ preparation of activated alkyltetracarbonylcobalt complexes,[20,56] the similarly prepared Co/complex reducing agent/CO (CoCRACO) system,[9,57] and the more routine use of $KCo(CO)_4$.[58]

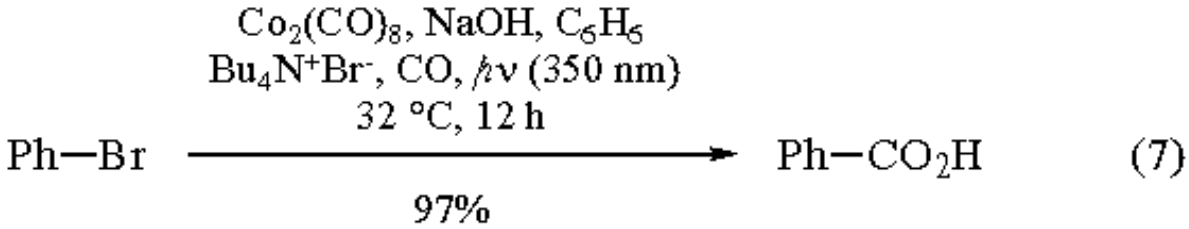

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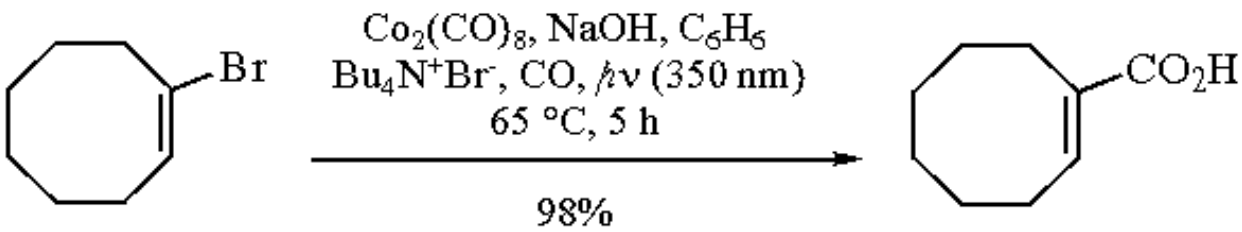

(8)

The products of double CO insertion can also predominate in the two-phase system. This is illustrated by the reaction of (1-

bromoethyl)benzene (eq 9)[17a,b] in *t*-pentyl alcohol (cf. Alper and Des Abbayes[50b]). The distribution of single and double carbonylation products is dependent on solvent,[17a,b,50b] aromatic substitution,[59] and, remarkably, the stirring speed of the reaction.[59] Furthermore, when aromatic hydrocarbons replace alcoholic solvents under PTC, the products of benzyl coupling predominate (eq 10).[17a,b]

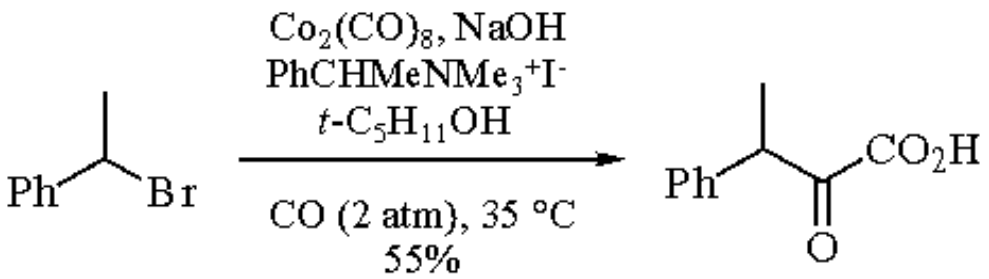

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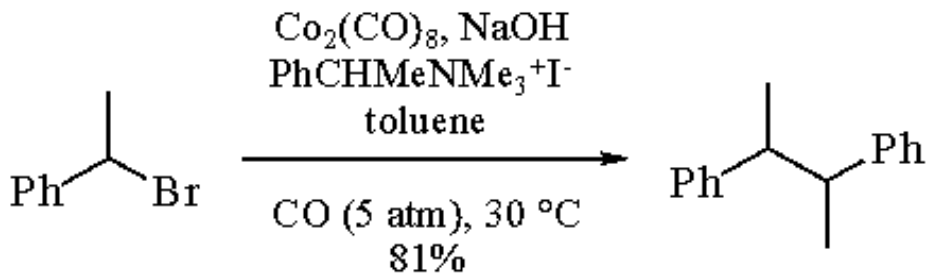

(10)

In a further variation to the phase-transfer techniques already presented, aryl methyl ketones result when the reactions are carried out in the presence of an excess of ***Iodomethane*** (eq 11).[60] When the cobaltate anion is generated in a homogeneous mixture, carboxylic acids or α-keto acids, the products of double carbonylation, result.[61] Again, the product distribution is both solvent and base dependent.[61,62] When the tetracarbonylcobaltate anion is generated in situ from $CoCl_2$, the α-keto acids again predominate, even when an excess of MeI is used (eq 12).[63]

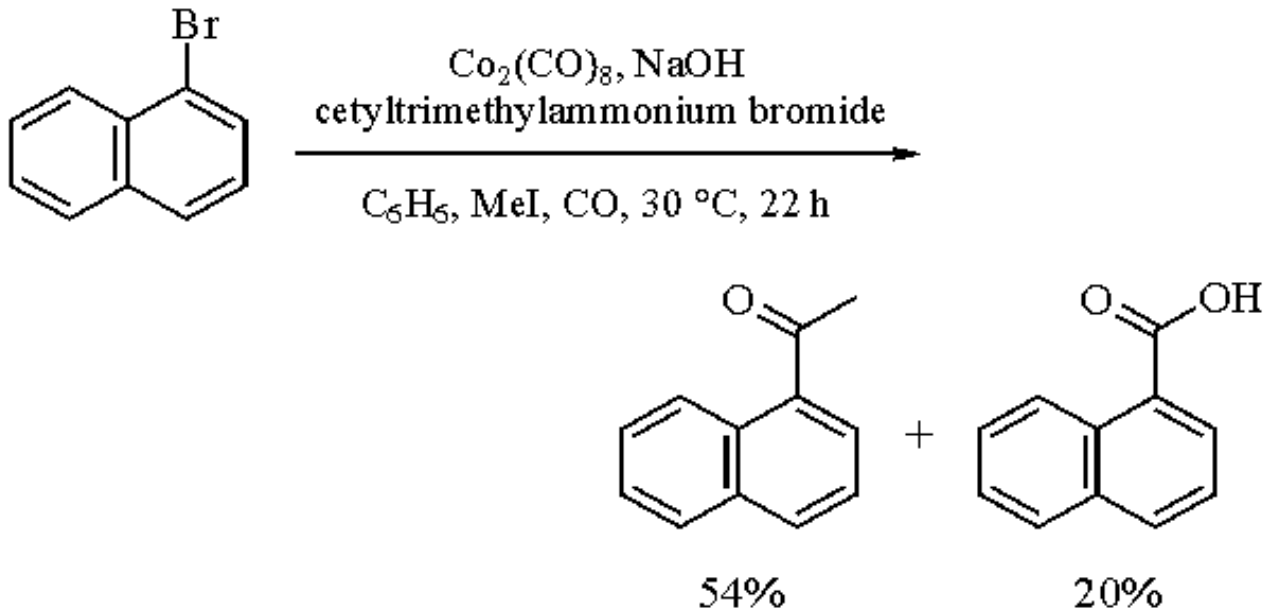

(11)

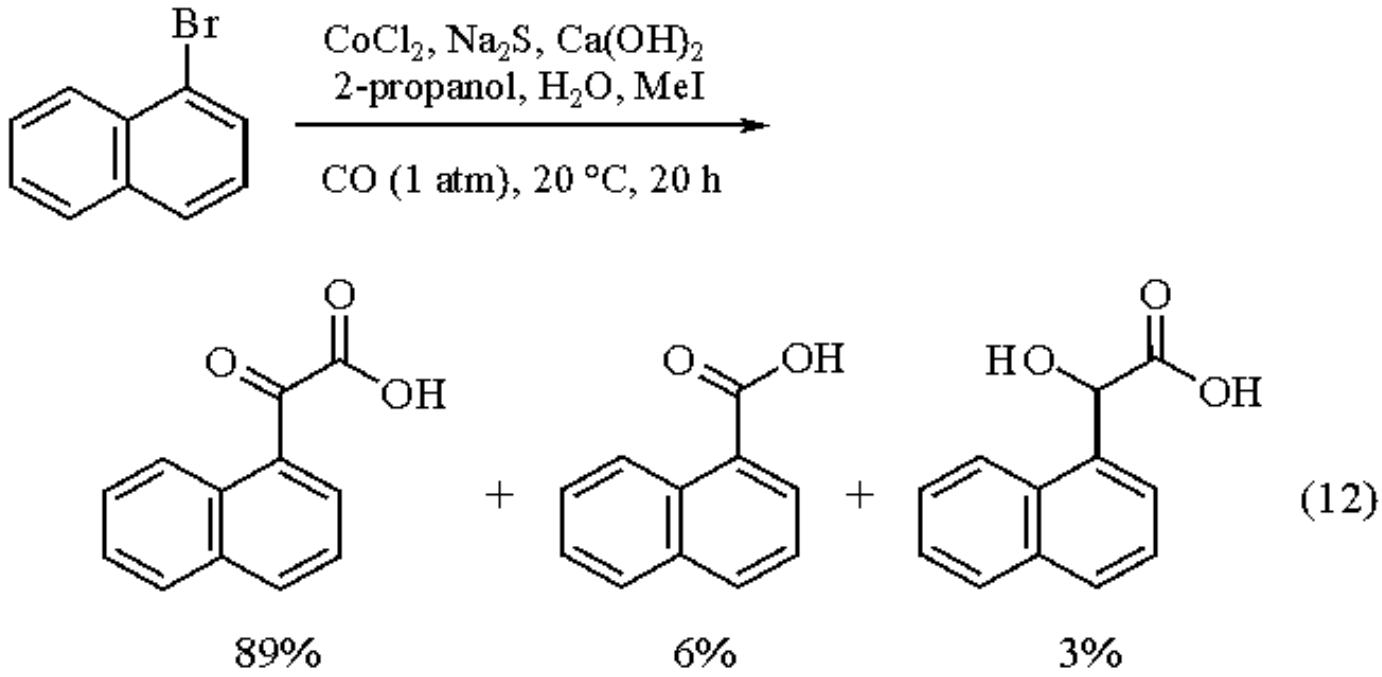

In an extension of the photostimulated phase-transfer studies, it has been shown that benzolactones and lactams can be prepared (eqs 13 and 14)[58] using techniques which compare favorably with the equivalent Pd methods.[64] Again, activated alkyltetracarbonylcobalt complexes, prepared in situ have been used to prepare similar products.[56]

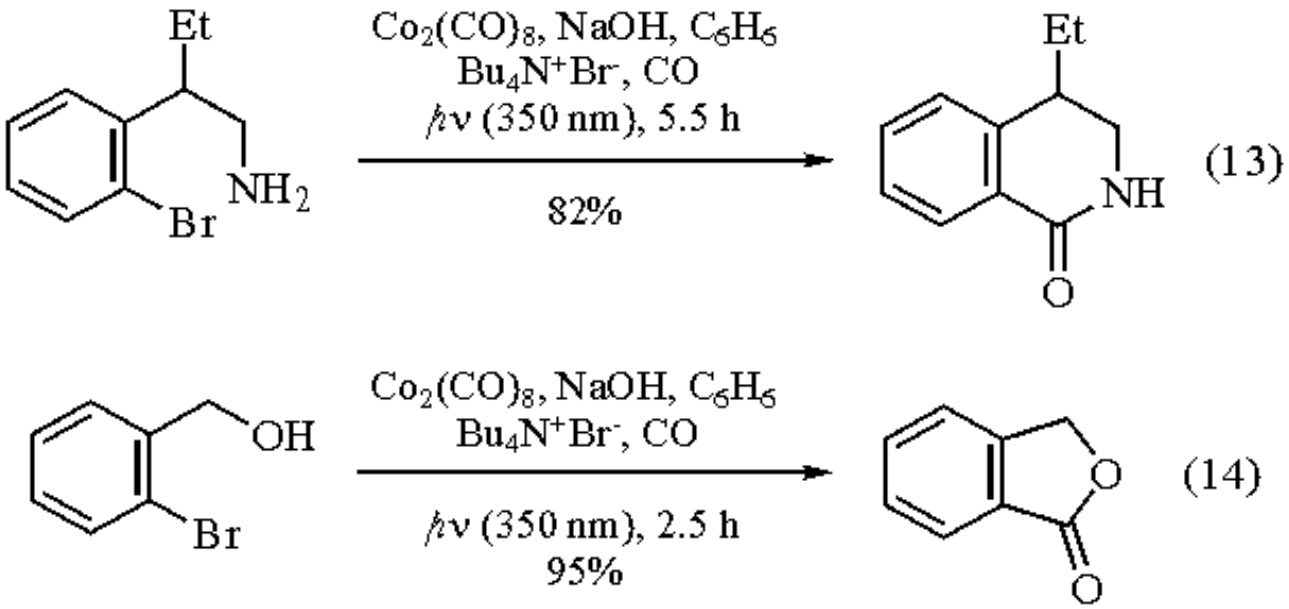

In a similar fashion to $Co_2(CO)_8$ (see ***Octacarbonyldicobalt***), despite low yields being common, regioselective carboxylation of epoxides can be achieved using $NaCo(CO)_4$.[65] The yields are improved in a number of specific examples (e.g. eq 15)[66] or, alternatively, by either employing $KCo(CO)_4$[67] or by the in situ formation of the cobaltate anion from $Co_2(CO)_8$ and K_2CO_3 under a CO atmosphere.[68] Again, under PTC, double CO insertion products can result. To date, this type of reaction is only known for styrene oxides in the presence of methyl iodide (eq 16).[69] Alternatively, under similar conditions, styrene sulfides simply give the products of single CO insertion.[70] It should also be noted here that, under certain conditions, $NaCo(CO)_4$ (and $Co_2(CO)_8$) can deoxygenate epoxides to give the alkenic products with good stereoselectivity.[71]

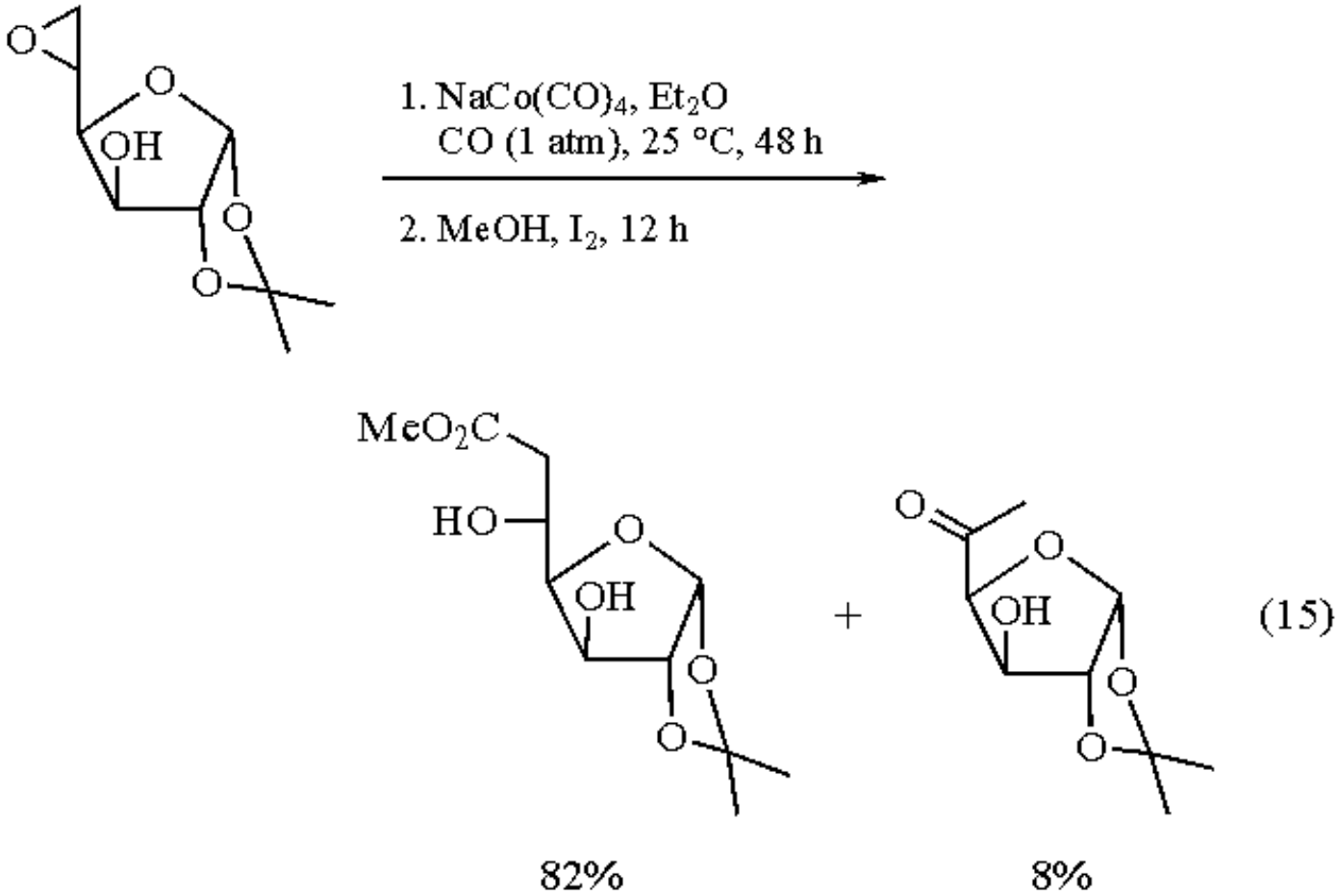

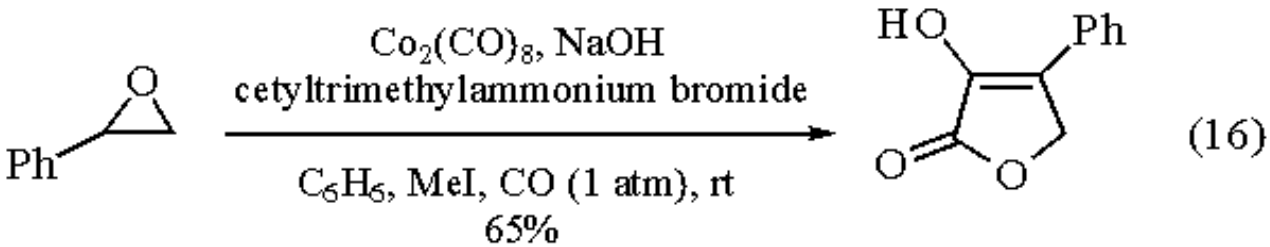

Alkoxycarbonylation of allyl acetates with $NaCo(CO)_4$, in combination with Pd, has also been demonstrated. Here, the cobaltate anion attacks the initially formed (π-allyl)palladium species and, following CO insertion and methanolysis, gives the corresponding ester (eq 17).[72]

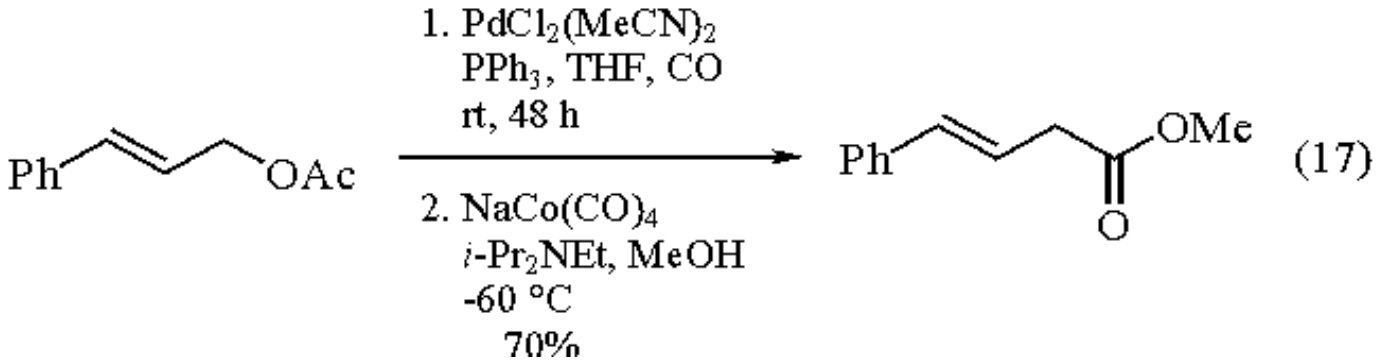

In studies which follow on from the original Co-catalyzed formation of butenolides from acylcobalt tetracarbonyls and alkynes,[47a,73] acid chlorides have been used with stoichiometric quantities of $NaCo(CO)_4$ to form the acylcobalt species in situ which, in turn, react with disubstituted alkynes to give 3,4,5-trisubstituted 3-buten-2-olides.[74] Unsymmetrically substituted alkynes where the substituents are sterically similar give rise to mixtures of regioisomers. In contrast, 2,2-dimethyl-3-pentyne undergoes reaction with propionyl chloride and $NaCo(CO)_4$ to give predominantly one regioisomer (eq 18). Under these conditions, terminal alkynes do not react cleanly. However, in a similar transformation this is overcome by the use of mild PTC.[75] Furthermore, butadienolides are also available using the title compound when acid chlorides which contain a leaving group in the α-position (e.g. chloroacetyl chloride) (eq 19)[76] are employed.

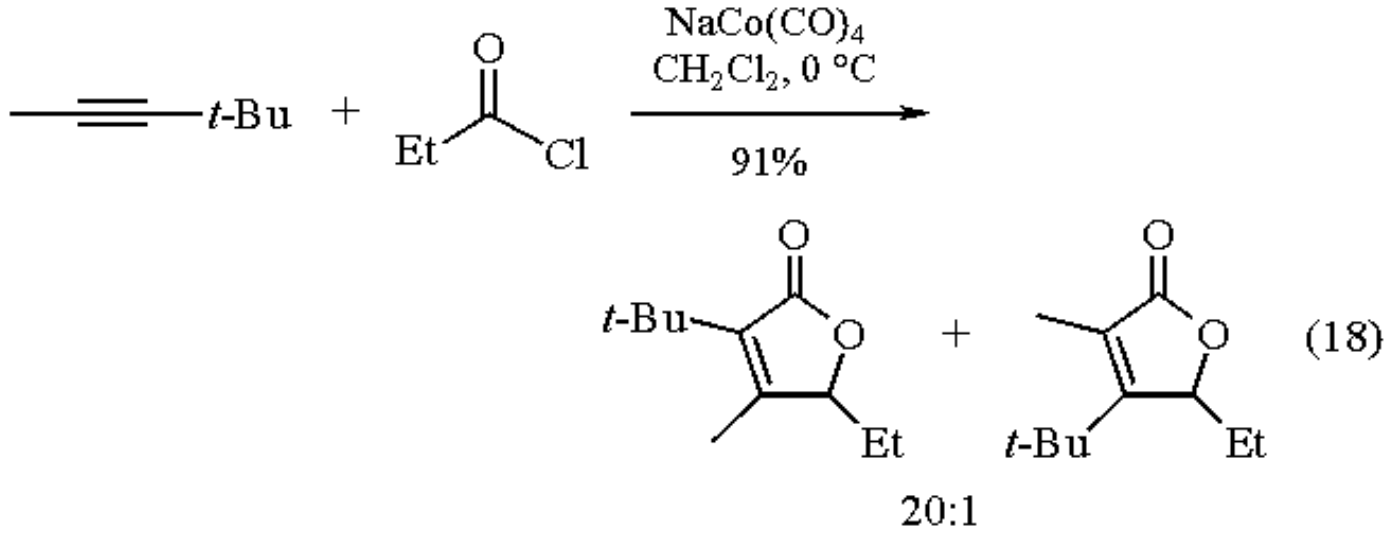

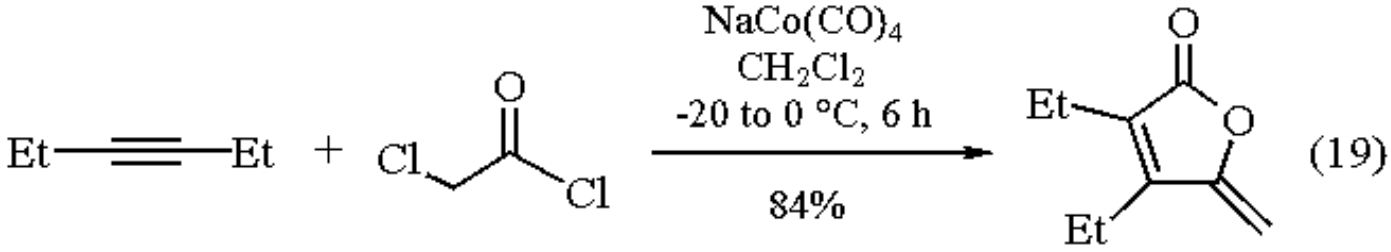

Other $NaCo(CO)_4$-Mediated Reactions.

In contrast to the carboxylation reactions, which occur when the cobaltate anion is either formed or simply used under basic conditions, hydrodehalogenation can be achieved in the presence of acid (eq 20) (anion formed in situ).[77] The yields of the hydrogenated products are often poor. Additionally, the reaction rate depends on the structure of the alkyl halide, and the hydrogenolysis of the C-X bond is often accompanied by aldehyde formation.

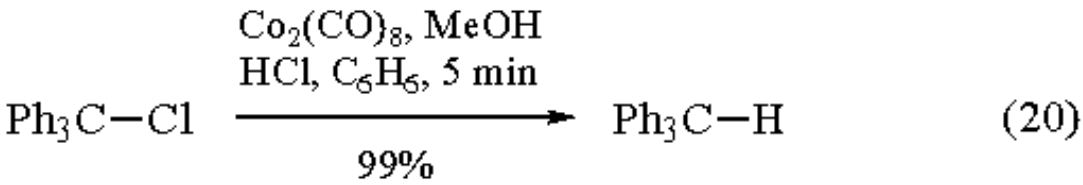

Coupling of *gem*-dihalides has also been achieved using the title compound to produce tetrasubstituted alkenes in good yield (eq 21).[5b] ***Octacarbonyldicobalt*** also mediates this reaction in comparable yield, whilst the related metal-cobalt carbonyl species $Hg[Co(CO)_4]_2$ (see ***Octacarbonyl(zinc)dicobalt***) is effective when UV irradiation is employed.[5b] In a related reaction, vicinal dihalides are dehalogenated using $NaCo(CO)_4$ (eq 22) or $Co_2(CO)_8$.[5b]

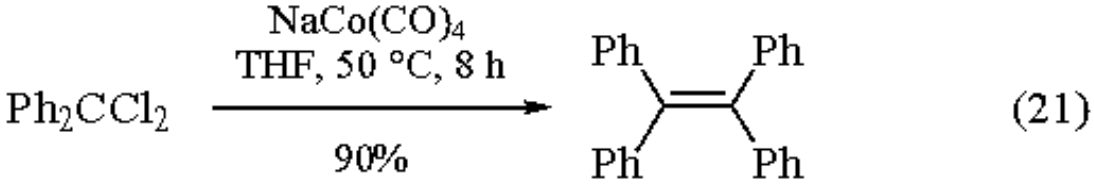

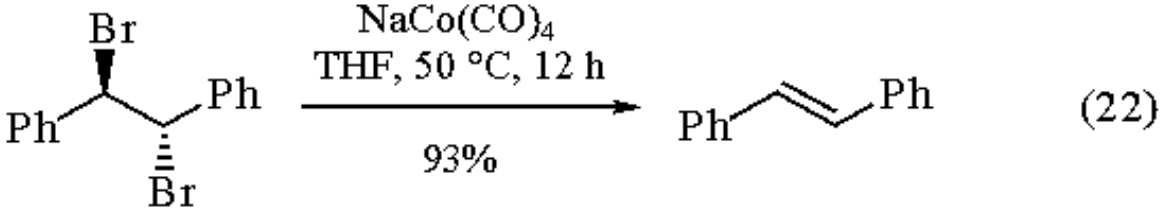

In a transformation which is complementary to the synthesis of symmetrical diaryl ketones using $Hg[Co(CO)_4]_2$,[78] dialkyl ketones can be

formed by the reaction of $NaCo(CO)_4$ (formed in situ[19]) with a dialkyl-BI species[79] followed by basic oxidative workup.[80] This procedure is illustrated for the formation of di-*n*-octyl ketone (eq 23).

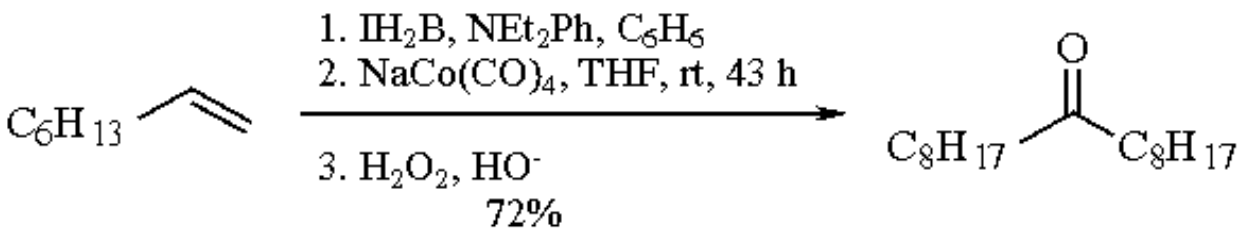

(23)

In an isolated example, $NaCo(CO)_4$ (in combination with $Co(NO)_2Cl$) has been shown to catalyze the dimerization of butadiene to afford 4-vinylcyclohexene (eq 24).[81] On the other hand, the alternative sodium-metal species, $Na[Fe(CO)_3NO]$, with various metal halides, mediates this transformation more efficiently in up to 100% yield under similar reaction conditions.[81]

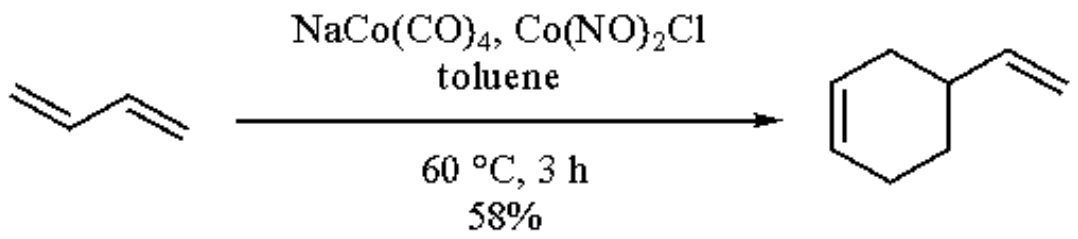

(24)

Alkylcobalt tetracarbonyl complexes, $RCo(CO)_4$, are readily formed from the tetracarbonylcobaltate anion and organic halides or tosylates. These species readily insert CO under mild conditions to give the corresponding acylcobalt complexes, $RCOCo(CO)_4$. The acylcobalt species react readily with 1,3-dienes to give (π-allyl)cobalt complexes by insertion of the diene into the Co-acyl bond. In turn, when these complexes are treated with base, acyl dienes result.[82] Phase-transfer techniques have also been used in this area.[75] These transformations are illustrated by the last step of a one-pot reaction sequence in which the acyl(π-allyl)cobalt complex (**1**) reacts with a stabilized carbanion to give 1,4-acylation/alkylation products from 1,3-dienes (eq 25).[83]

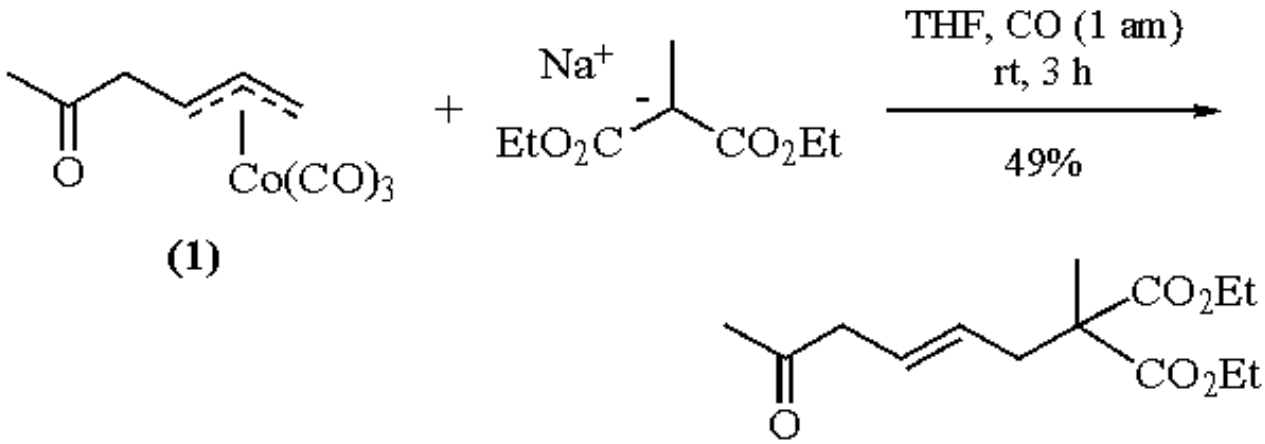

(25)

Alkylidynetricobalt Nonacarbonyl Complexes.[4b,5a,84]

Trinuclear compounds of the general structure $RCH_2C[Co_3(CO)_9]$ are formed directly from $Co_2(CO)_8$ with terminal alkynes at 85 °C[85] or by reaction of the terminal alkyne complex (RC&tbond;CH)$[Co_2(CO)_6]$ with H_2SO_4 in MeOH.[86] More general syntheses of trinuclear alkylidyne complexes of general structure $RCCo_3(CO)_9$ are available by treating trihalomethane derivatives of type RCX_3 with $Co_2(CO)_8$ or $Co_4(CO)_{12}$.[4b,87] The significance of the tetracarbonylcobaltate anion in the latter synthetic strategy has been supported by the preparation of $MeCCo_3(CO)_9$ from $NaCo(CO)_4$ and $MeCCl_3$ in refluxing THF.[4b] Furthermore, fluorinated tricobalt complexes of the type $RC[Co_3(CO)_9]$, where R = F, CF_3, CF_3CF_2, and CHF_2, have been prepared by the reaction of fluoroalkyltetracarbonylcobalt compounds with $NaCo(CO)_4$ (e.g. eq 26).[88] The fluoroalkyl complexes are themselves conveniently prepared by treatment of the corresponding fluorinated acid chloride with $NaCo(CO)_4$.[5a,27,89]

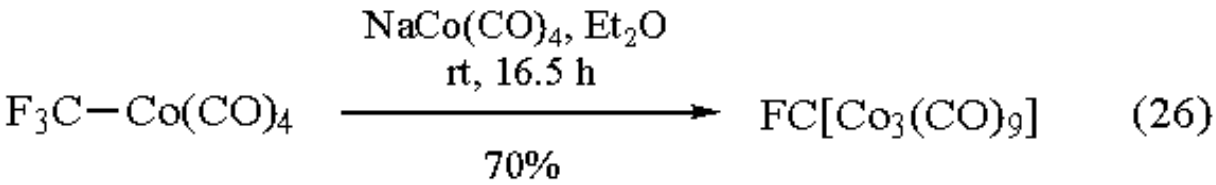

Three other routes to complexes of the general structure $RC[Co_3(CO)_9]$ are worth noting. In the first, $NaCo(CO)_4$ reacts with ***N-Dichloromethylene-N,N-dimethyliminium Chloride*** to give the complex where R = NMe_2 in good yield.[90] In the second example, $TlCo(CO)_4$ is reacted with CCl_4 in benzene to give the compound where R = Cl.[91] Lastly, PTC have been employed with $Co_2(CO)_8$ to generate the anion in situ and prepared a number of complexes from trihalomethane derivatives.[92] Alkylidynetricobalt nonacarbonyl complexes are deep violet/purple crystalline compounds which are soluble in organic solvents (insoluble in H_2O) and appear to be some of the most air-stable of all cobalt carbonyl derivatives.[4b] The chemistry of these compounds is reviewed by Seyferth.[84a]

Reactions of the Conjugate Acid, Tetracarbonylhydrocobalt, $HCo(CO)_4$.

In the hydroformylation reaction of alkenes with $Co_2(CO)_8$, CO, and H_2, it has been demonstrated that the true catalyst is $HCo(CO)_4$.[31,41a,43,93] Hydroformylation reactions catalyzed by cobalt are covered elsewhere (see ***Octacarbonyldicobalt***). Nonetheless, by using the title compound (and its deuterium equivalent), it has been shown that this transformation is a *cis* process.[94] Further studies have also shown that, with catalytic hydroformylation, the reaction rate is increased by the addition of organic bases[95] (e.g. pyridine, quinoline, or Et_3N) or oxygenated compounds (e.g. ketones or alcohols).[96] Under stoichiometric conditions using $HCo(CO)_4$, the reaction rate and yield are increased and the isomerization of excess alkene is greatly reduced by the addition of benzonitrile.[97] Alternative nucleophiles have been shown to be less effective in promoting hydroformylation. Additionally, product ratios have been optimized using modified catalysts; for example, phosphine ligands enhance straight-chain products.[98] Hydrogenation reactions are also possible when $HCo(CO)_4$ is reacted with alkenes (see below). However, it should be noted that mixtures of hydrogenation and hydroformylation products can result, with product ratios being dependent on both reaction atmosphere composition and pressure,[99] as well as on temperature and catalyst activator.[100]

As with $Co_2(CO)_8$ and $NaCo(CO)_4$, the hydrocobalt species is also known to mediate the hydroformylation of alkene oxides to give β-hydroxy aldehydes.[96,101] Furthermore, these reactions are accelerated by addition of small amounts of inorganic salts, the best of those used being ***Copper(I) Oxide***.[102] In related examples, $HCo(CO)_4$ has been shown to react with aziridines with CO insertion to give β-aminoacyl complexes.[103] More recently, the alkoxycarbonylation of vinylsilanes has been significantly improved. When compared to previous examples,[104] the hydroesterification reactions can be performed with Co catalysis and display high α-stereoselectivity[105] (cf. the use of Pd catalysis for β-selectivity). Again, stoichiometric quantities of $HCo(CO)_4$ are active in this process. In one final carbonylation related example, the rarely used Co-mediated homologation of alcohols (see ***Octacarbonyldicobalt***), the active species is believed to be $HCo(CO)_4/^-Co(CO)_4$.[106]

When catalytic hydroformylation is performed at elevated temperatures (approx. 185 °C), the aldehydes are believed to be reduced under the reaction conditions and alcohols are isolated as the principal products.[107] On the other hand, when reactions are performed using $HCo(CO)_4$ under stoichiometric conditions, aldehydes are only reduced very slowly and in low overall yield.[108] Indeed, in only a limited number of cases have stoichiometric reductions of carbonyl groups been successfully performed using mononuclear Co complexes[109] (e.g. formaldehyde in eq 27).[110]

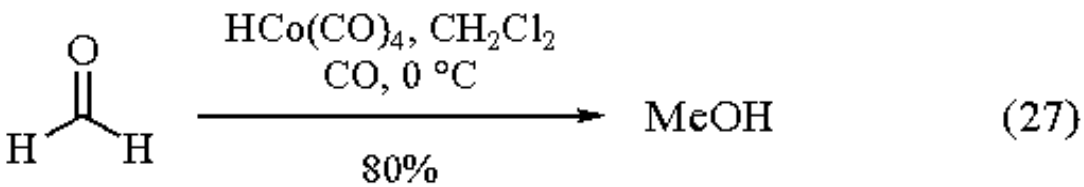

In contrast to the reduction of carbonyl groups, double bonds conjugated to aldehydes,[108a,111] ketones,[111a,112] or arenes[111a,113] are readily reduced under mild stoichiometric conditions (cf. less mild catalytic conditions).[114] Two illustrative examples are shown in eqs 28 and 29.[108a,113a] Hydrogenation using $HCo(CO)_4$[31,93d,115] has been shown, like the similar hydroformylation, to be a *cis* process[113h,i] and proceeds under H_2, N_2, or CO atmospheres. Reaction rates under CO, which retards the breakdown of $HCo(CO)_4$, are faster.[108,111a,113a] With only one recorded exception,[116] α,β-unsaturated esters undergo hydroformylation in preference to hydrogenation.

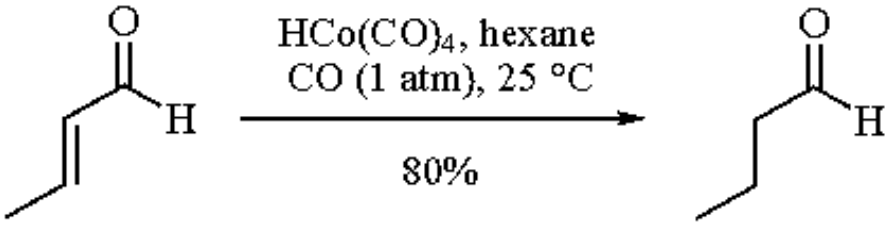

(28)

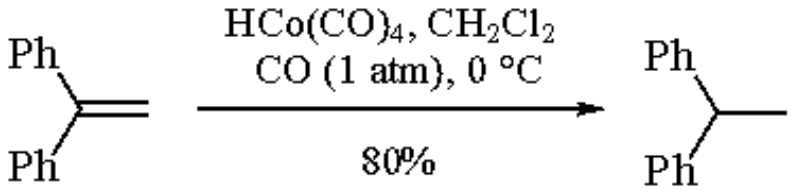

(29)

Cobalt-catalyzed dihydroformylation of conjugated butadienes is not successful, especially when compared to the substantial yields which can be achieved with Rh catalysts.[117] Normally with $HCo(CO)_4$ as the reactive species, butadienes are hydrogenated to butenes which then undergo hydroformylation or alkoxycarbonylation to give C_5 products.[115b,118] Reactions of conjugated dialkenes with $HCo(CO)_4$ can also readily give π-methallyl complexes.[119] Furthermore, it has been demonstrated that $HCo(CO)_4$ readily isomerizes alkenes to give more highly substituted double bonds.[93b,c,111b,115b,120] Tetrasubstituted allenes give mixtures of both isomerized and hydrogenated products when treated with $HCo(CO)_4$.[121]

At elevated temperatures (180-220 °C), $HCo(CO)_4$ catalyzes the hydrogenolysis of diaryl glycols to diarylethanes with high selectivity.[93a,122] Additionally, in contrast to $Co_2(CO)_8$ which in reaction with acetylene gives fumaric, acrylic, and succinic acid esters under hydroformylation conditions,[123] $HCo(CO)_4$ simply gives the acetylenehexacarbonyldicobalt complex under similar conditions.[124]

Despite being often termed as a cobalt hydride, $HCo(CO)_4$ is a stronger acid than $MeSO_3H$ and 2,4,6-trinitrophenol and all other transition metal hydrides which have been examined, and is comparable in acid strength with HCl and HNO_3[33,36a,k,45,125] (pK_a 8.3 in MeCN,[45] bond dissociation energy 280 kJ mol^{-1} [126]). It is also mildly reducing in character.[127] In terms of organic synthesis, the acidic Co hydride has been utilized to mediate a number of acid-catalyzed reactions including the pinacol rearrangement to pinacolone,[128] the formation and hydrolysis of acetals,[129] the homologation of alcohols,[130] and the reactions of vinyl ethers,[131] as well as the course of the reaction of $HCo(CO)_4$ itself with cyclohexene oxide.[132] Finally, in an isolated series of examples, $HCo(CO)_4$ has been shown to mediate the cyclization and coupling of aryl imines with vinyl ethers.[133] Electron-releasing substituents favor formation of the quinoline products (e.g. eq 30) but, in other examples, mixtures of products often result. When THF is used as solvent, only the quinoline products result, albeit with a drop in yield.

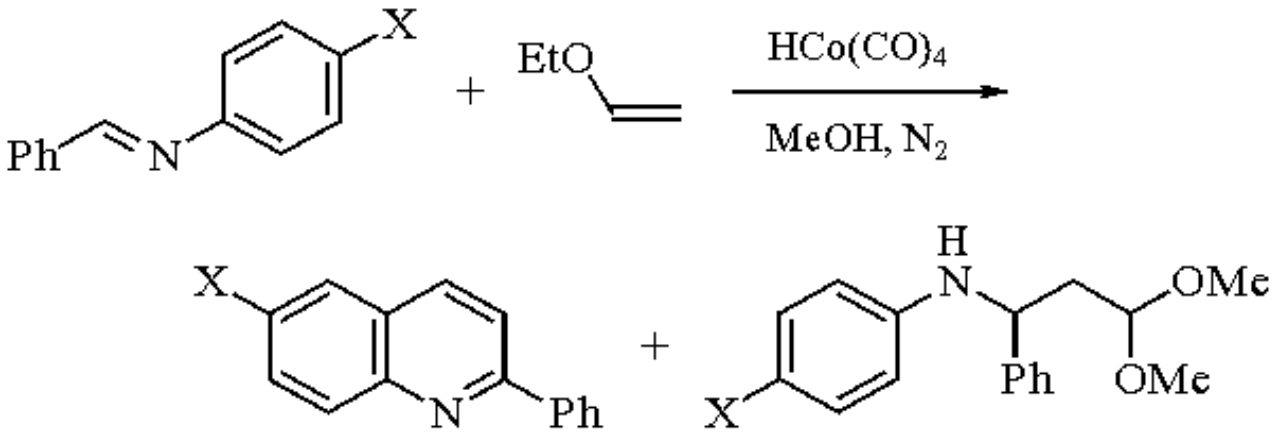

(30)

X = Cl	0%	73%
X = OMe	86%	0%

Tetracarbonylcobaltate with Alternative Counter Ions.

When the tetracarbonylcobaltate moiety is combined with counter ions other than Na^+ (Li^+, K^+, Tl^+) or H, a considerable variety of reactivity has been observed. In the simplest example, where the counter ion is the pyridinium ion, $C_5H_5NH^+$, higher catalytic activities in reactions involving CO, e.g. hydroformylation and hydrocarboxylation, are observed.[134] When readily formed[135] ytterbium/cobalt

clusters, such as $Cp_2YbCo(CO)_4$, are used under hydroformylation conditions, compared to $Co_2(CO)_8$ a considerably higher conversion of starting alkene into aldehydes results.[136] Similar processes using lutetium[137] and uranium[138] have also been reported.

With other counter ions, reactions which have not been reported with the simple cobaltate systems have been observed. In the first example, the results can be directly compared with the $NaCo(CO)_4$ carboxylation of epoxides. When cobalt hexaalcohol counter ions are used as the reagents, ketones are formed in good yields.[139] The methanol (eq 31) and isopropyl alcohol complexes have been used to give comparable yields of products. A similar reaction using $Sn[Co(CO)_4]_4$ under high CO pressure has also been reported.[140]

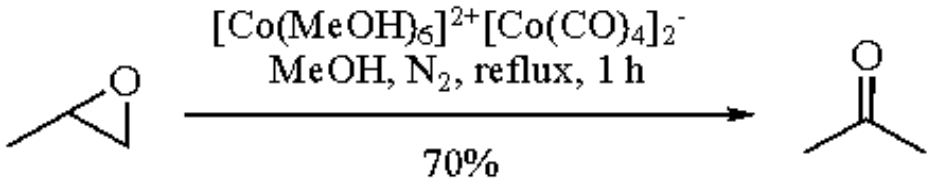

(31)

Another reaction which can readily be compared with those of other Co species, in particular $CpCo(CO)_2$, $Co_2(CO)_8$, and $Hg[Co(CO)_4]_2$, is the cyclotrimerization of alkynes using $[Ph_3PC_5H_4Co(CO)_2]^+$ $[Co(CO)_4]^-$.[141] This complex is readily formed by reaction of $Co_2(CO)_8$ and triphenylphosphinocyclopentadienide (Cp^--PPh_3^+) and is reacted in refluxing THF to give good yields of aromatic products (e.g. eq 32).

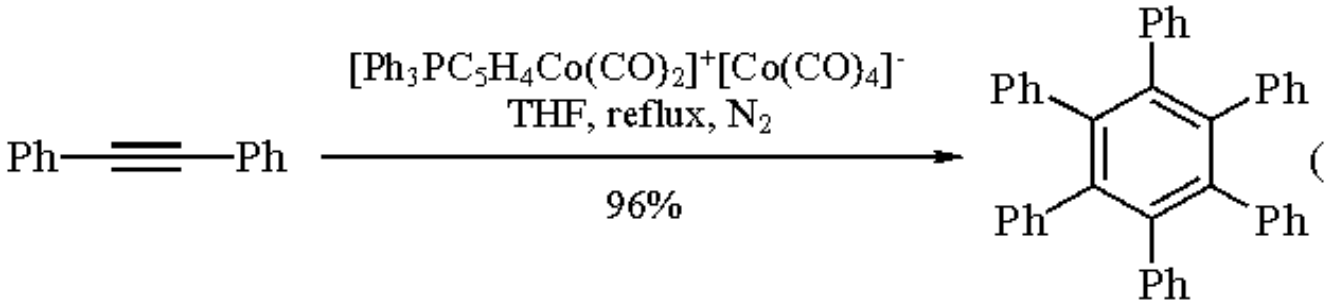

(32)

Novel silyl carbocyclization reactions with double CO incorporation have been observed[142] using $(t\text{-BuNC})_4RhCo(CO)_4$[143] as catalyst. When dipropargylallylamines are reacted with this catalyst, the main product (**2**) is accompanied by a small amount of a single CO incorporation product (**3**) (eq 33). When $Rh_4(CO)_{12}$ is used as the catalyst (at ambient CO pressure), ketone (**3**) is the sole product (81%). Cyclopentenone formation can also be achieved using the same Rh/Co catalyst (eq 34).[142] Alternative Rh and Rh/Co catalysts have also been reported for this latter cyclization. Mixed Rh/Co complexes also catalyze silylcarbonylation (the Si version of hydroformylation) and hydrosilylation of alkynes,[144] as well as the synthesis of 2-arylethanols from benzyl halides.[145]

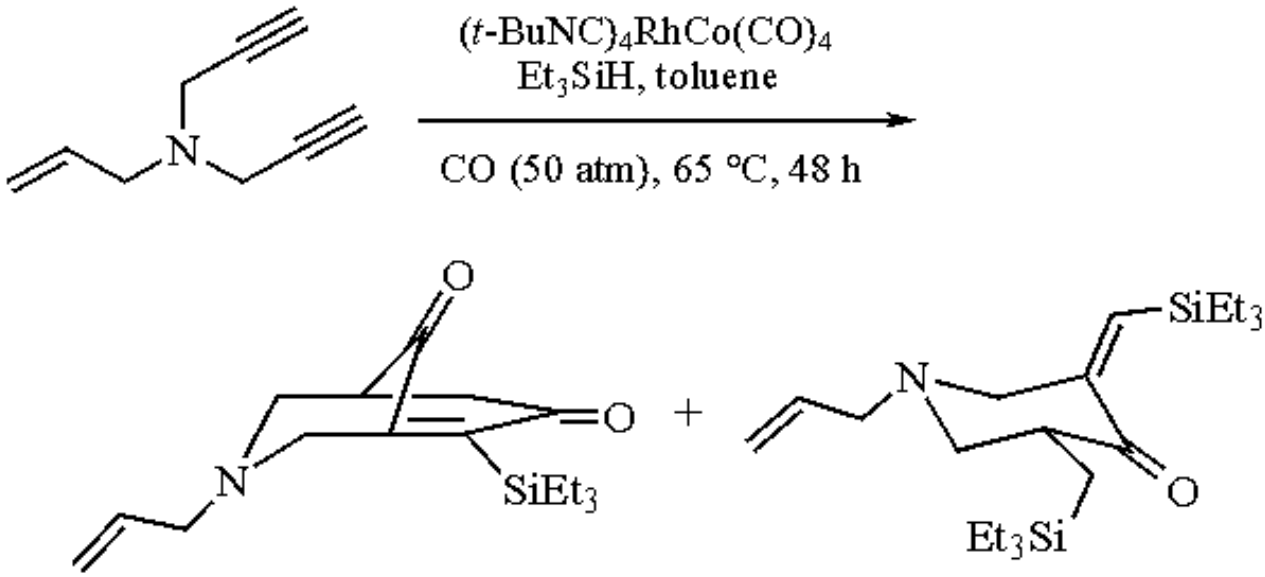

(33)

(2) 62% **(3)** <2%

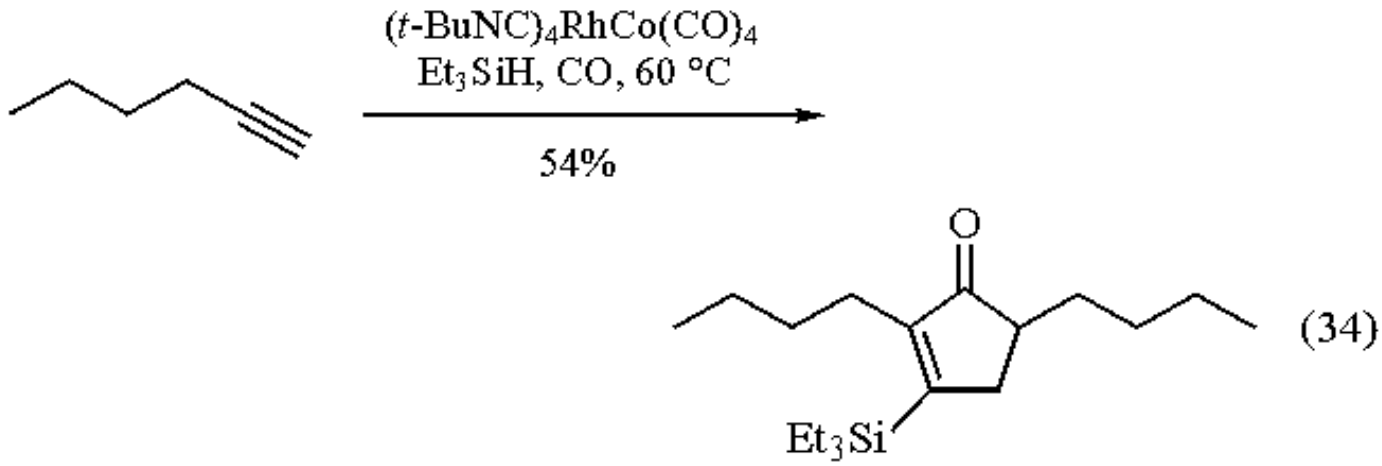

(34)

When the tetracarbonylcobaltate anion was being studied as a potential desulfurization agent, it was found that tetraarylethylenes are formed as the principal organic products from reaction of $(Ph_3P)_2N^+\ ^-Co(CO)_4$ with thioketones (eq 35).[146] The same study showed that higher yields in this reaction can be achieved by using $Co_2(CO)_8$ and that desulfurization to give hydrocarbons can be realized by using the $HFe(CO)_4^-$ anion.

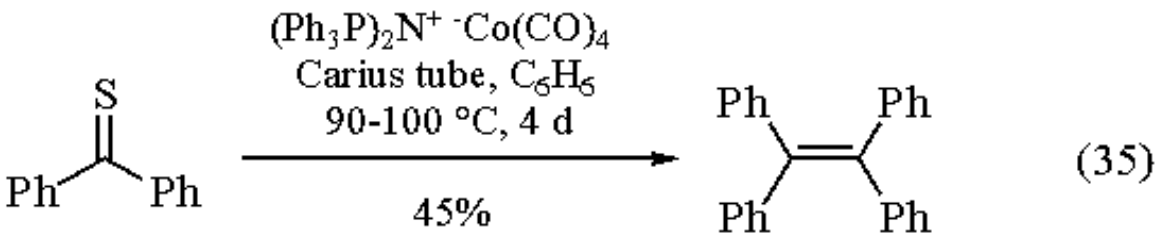

(35)

The structurally simple ammonium tetracarbonylcobalt species, $NH_4Co(CO)_4$, is formed by reaction of $HCo(CO)_4$ with ammonia and reacts with aromatic aldehydes to give aromatic imines.[147] Finally, it is also worth noting that the tin tetracobaltate species, $Sn[Co(CO)_4]_4$, is an active catalyst for the hydrolysis of carbonates[148] (as is $Co_2(CO)_8$) and for hydroformylation and acetalization reactions.[149]

Related Reagents.

Octacarbonyldicobalt; ***Octacarbonyl(zinc)dicobalt***.

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Sodium Tetracarbonylhydridoferrate

$NaHFe(CO)_4$

[53558-55-7] · $C_4HFeNaO_4$ · Sodium Tetracarbonylhydridoferrate · (MW 191.89)

(alkylation of carbonyl compounds and amines with aldehydes; reduction of α,β-unsaturated carbonyl compounds, enamines, and nitro compounds; carbonylation of alkenes)

Physical Data: X-ray structure of the $HFe(CO)_4^-$ ion as the PPN^+ salt has been reported.[1]

Solubility: sol THF, ethanol, methanol.

Form Supplied in: prepared as a solution in THF or in methanol.

Analysis of Reagent Purity: IR (THF) 1997 (m), 1903 (sh), 1878 (s), 1851 (sh) cm^{-1}; ^1H NMR (THF, C_6D_6) δ -8.74 (32 °C).

Preparative Methods: Method A. To a stirred suspension of ***Sodium Amalgam*** (100 g of mercury and 0.76 g of sodium) in dry THF (50 mL), ***Pentacarbonyliron*** (1.5 mL, 11 mmol) is added dropwise under argon. The mixture is stirred for 2 h at room temperature, and the excess of amalgam is removed through a sidearm. The suspension is treated with water (0.2 mL, 11 mmol) and the resulting $NaHFe(CO)_4$ is used immediately. Method B. To a stirred solution of ***Sodium Hydroxide*** (33 mmol) in methanol (50 mL), pentacarbonyliron (1.5 mL, 11 mmol) is added under nitrogen or argon. The mixture is stirred for 2 h under reflux and the resulting solution of $NaHFe(CO)_4$ is used immediately. The corresponding potassium salt of $HFe(CO)_4^-$ is prepared similarly from ***Potassium Hydroxide***.

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar or N_2).

Dimerization.

When the light yellow aqueous solution of $NaHFe(CO)_4$ is allowed to stand for a few days, it becomes dark red due to the formation of a dimeric anion (eq 1). The dimer slowly gives off hydrogen and forms a dinuclear iron carbonyl anion.[2]

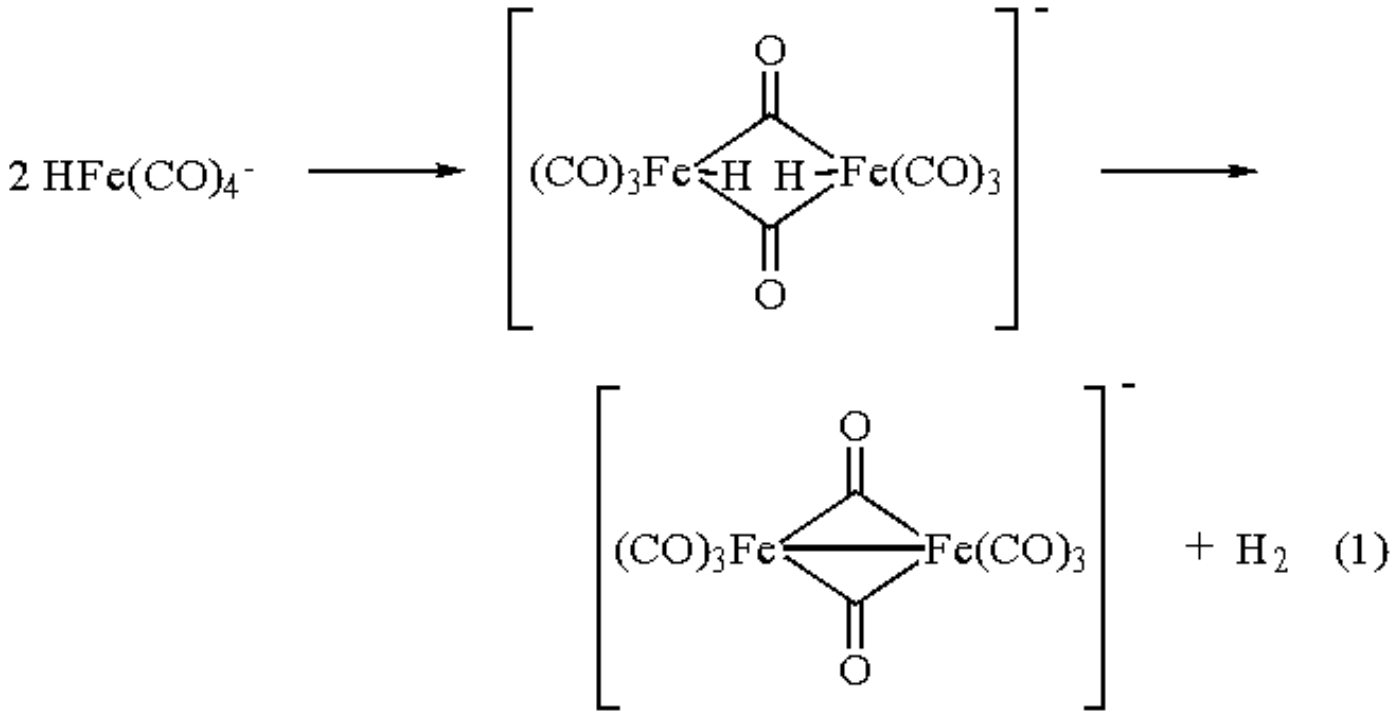

Reaction with Acetylene.

Reaction of an alkaline aqueous solution of $HFe(CO)_4^-$ with acetylene followed by acidic workup provides $H_2[HC{=}CHFe_2(CO)_8]$.[3] The structure of the complex has been determined on the basis of chemical and spectroscopic evidence.[3,4] Analogous complexes are obtained from propyne and 2-butyne by essentially similar methods.[4] In an aprotic solvent such as methylene chloride, the $HFe(CO)_4^-$ ion (prepared as $[N(PPh_3)_2][FeH(CO)_4]$ from $KHFe(CO)_4$ and bis(triphenylphosphine)iminium chloride in methanol) reacts with methyl propiolate, dimethyl acetylenedicarboxylate, ethynyl methyl ketone, and propiolaldehyde to give (η^3-acryloyl)tricarbonylferrates by *trans* addition of the hydride to the acetylenic bond (eq 2).[5]

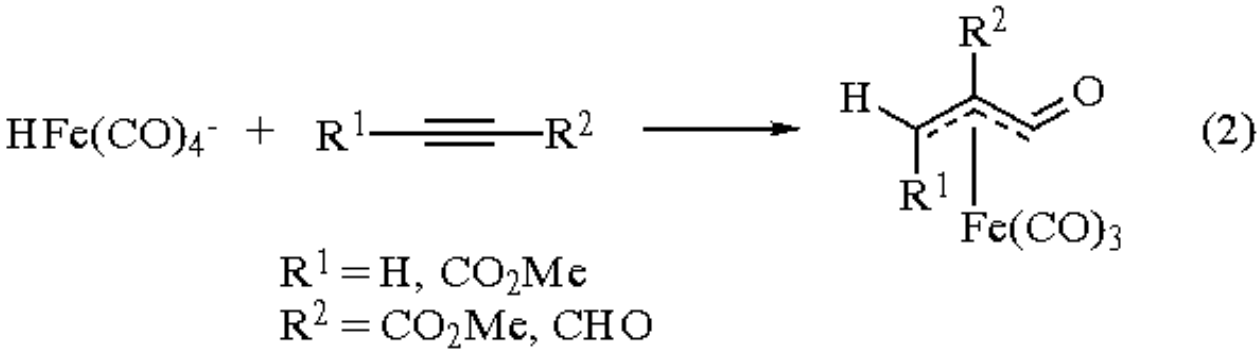

Alkylation of Carbonyl Compounds and Amines with Aldehydes.

Treatment of an aldehyde or a ketone with formaldehyde in the presence of $HFe(CO)_4^-$ in ethanol or water results in reductive methylation of the carbonyl compounds in high yield (eq 3).[6] The reaction also occurs with carbonyl compounds and alkyl, aryl, and heterocyclic aldehydes in the presence of $HFe(CO)_4^-$ to provide a variety of substituted carbonyl compounds.[7]

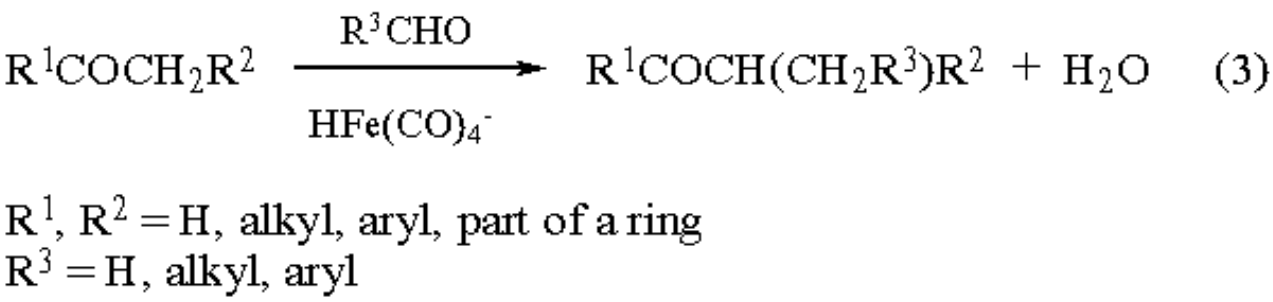

Indole can also be reductively alkylated or arylated in the 3-position by aliphatic or aromatic aldehydes using the same procedure (eq 4).[8] The facile alkylation and arylation of primary and secondary amines and of ammonia by aldehydes in the presence of $HFe(CO)_4^-$ has also been reported (eq 5).[9] A practical advantage of this method is the possibility of obtaining a predominantly mono- or dialkyl derivative by using a 1:1:1 or 1:2:2 molar ratio of amine, aldehyde, and $HFe(CO)_4^-$, respectively.

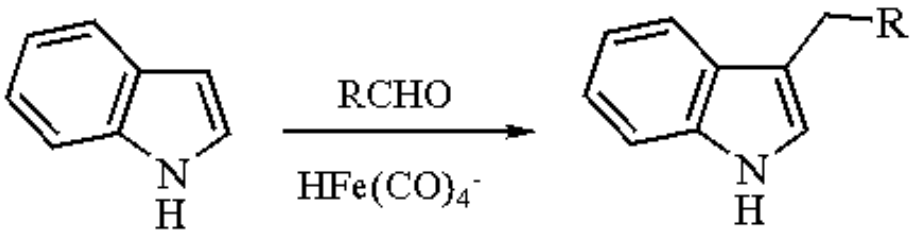

(4)

R = H, Me, Pr, Ph, *p*-ClC_6H_4, *p*-MeC_6H_4

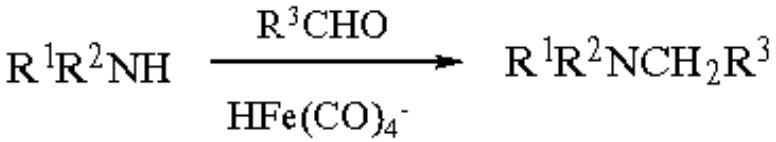

(5)

R^1, R^2 = H, alkyl, aryl, part of a ring
R^3 = H, alkyl, aryl

Reduction of α,β-Unsaturated Carbonyl Compounds.

Treatment of unsaturated carbonyl derivatives (ketones, aldehydes, esters, lactones, nitriles) with $HFe(CO)_4^-$, generated in situ from iron pentacarbonyl and NaOH in methanol, gives the corresponding saturated derivatives in high yield.[10] The method is very mild and possesses the following characteristics: (1) overreduction of the ketonic groups is negligible; (2) ester functions are not reduced; (3) reductive coupling of ketones to pinacols, frequently encountered with Birch conditions, is not observed; (4) no skeletal rearrangement, often observed during Clemmensen reduction, takes place; (5) phenyl and furyl groups are not affected; and (6) the rate of reduction is influenced by steric environments around double bonds; reduction is slower for a sterically hindered double bond. As to the stereochemistry of the reduction, cholest-4-en-3-one is converted selectively into the corresponding 5β-cholestanone having *cis* stereochemistry (eq 6), whereas $\Delta^{1,9}$-2-octalone is reduced to afford a stereoisomeric mixture of 2-decalones (eq 7).

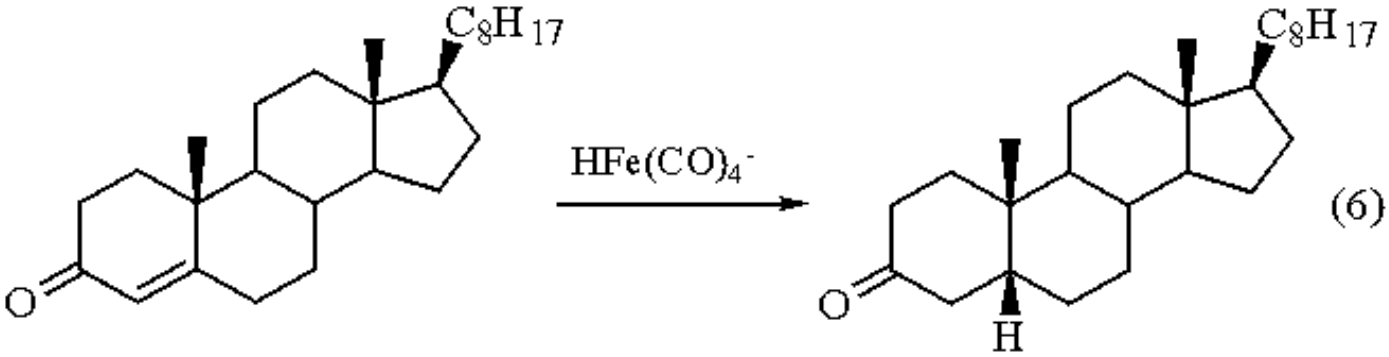

(6)

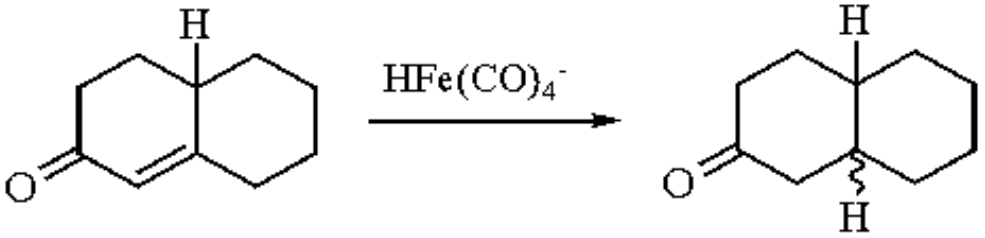

(7)

cis:*trans* = 37:63

In an aprotic solvent under ambient conditions, α,β-unsaturated esters selectively insert into the hydrogen-iron bond of $HFe(CO)_4^-$

(prepared by protonation of $Na_2[Fe(CO)_4]$ in THF with 1 equiv of acetic acid) to give alkyl-iron complexes (eq 8). On treatment with alkyl iodide, the alkyl complexes give the corresponding hydroacylated products (eq 8).[11]

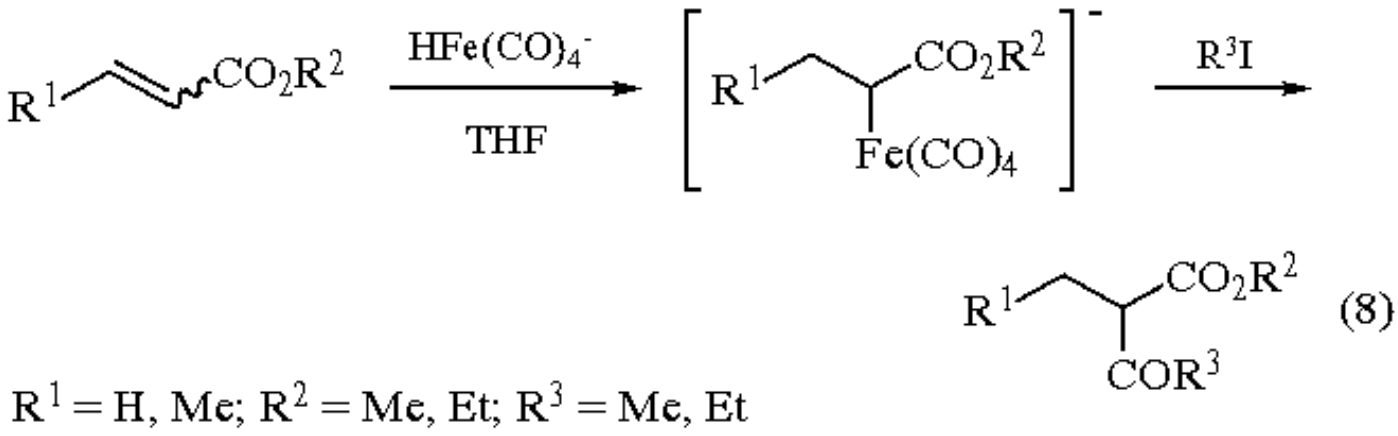

The $HFe(CO)_4^-$ derivatives prepared from triethylenediamine (33 mol), deionized water (33 mmol), and pentacarbonyliron (11 mmol) are effective in reducing α,β-unsaturated carbonyl compounds to the saturated alcohols.[12] With prochiral compounds the reaction proceeds stereospecifically. For example, $HFe(CO)_4^-$, generated in situ in THF, reacts with (+)-carvone at 60 °C for 9 days under an argon atmosphere to give (-)-neodihydrocarveol in almost quantitative yield (eq 9). Similarly, (+)-neodihydrocarveol is obtained exclusively from (-)-carvone.

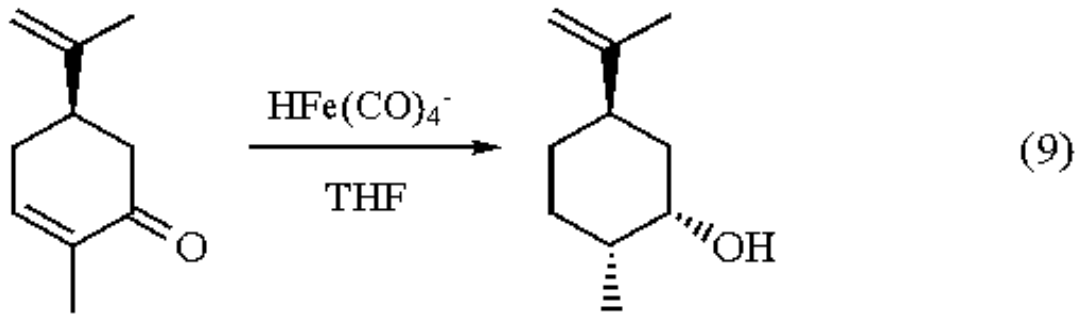

Reduction of Enamines and Nitro Compounds.

Enamines are converted to the corresponding saturated tertiary amines.[13] For example, enamines such as *N*-(1-cyclohexenyl)morpholine, *N*-(1-phenylvinyl)morpholine, and *N*-(2-methyl-1-propenyl)piperidine readily react with an alcoholic solution of $HFe(CO)_4^-$ with the absorption of CO at room temperature to give the corresponding amines in high yield (eqs 10-12).

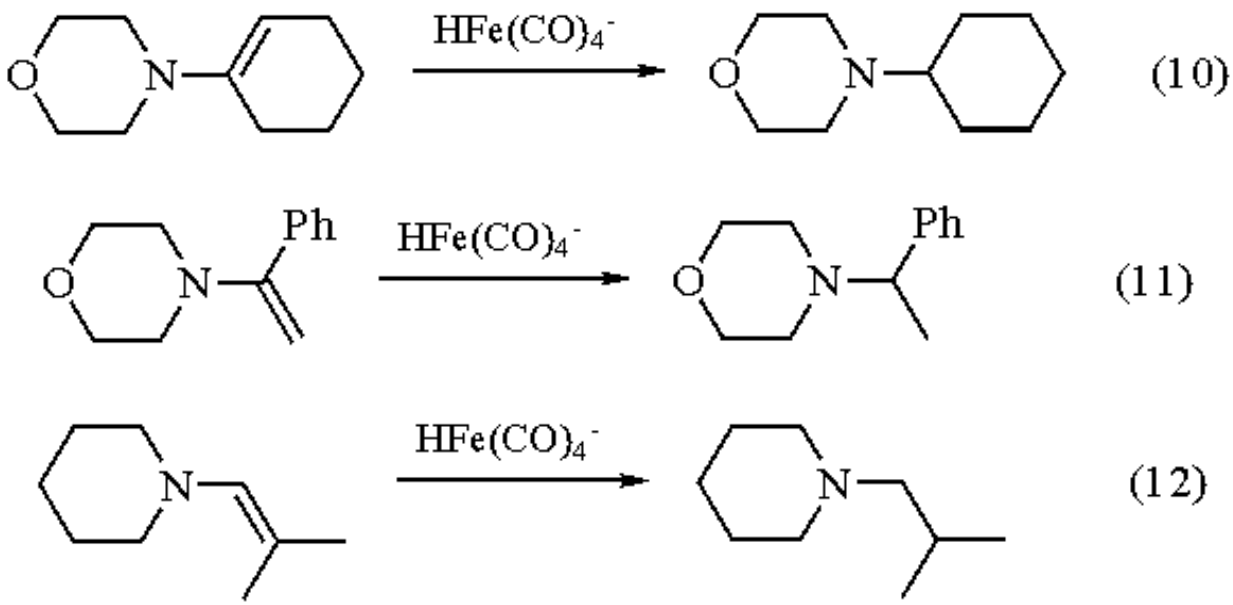

An application of $HFe(CO)_4^-$ as a reducing reagent in the preparation of primary amines from nitro compounds, mainly substituted

nitrobenzenes, has also been reported (eq 13).[14] The reduction is exothermic and gives the corresponding amines in excellent yields. The ferrate has also high reactivity for nitrosobenzene and moderate reactivity for azobenzene.[14] Nitrocyclohexane reacts slowly to provide cyclohexylamine in good yield.[14]

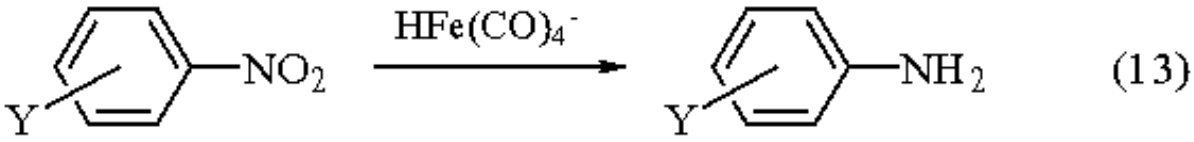

Y = Cl, Me, CO_2H, OH, NH_2

Carbonylation of Alkenes.[15]

$HFe(CO)_4^-$ reacts with ethyl acrylate at 40-70 °C under an atmosphere of carbon monoxide to give methylmalonate in high yield after treatment of the reaction mixture with alcoholic iodine and hydrogen chloride solutions (eq 14). Both crotonate and 3-butenoate give ethylmalonate as a major product and methylsuccinate and glutarate as minor ones (eq 15). Styrene, on treatment with iron ferrate under CO, yields two isomeric aldehydes, α- and β-phenylpropionaldehyde (eq 16). Ethyl caproate and enanthate are obtained from 1-pentene and 1-hexene, respectively, in poor yield.

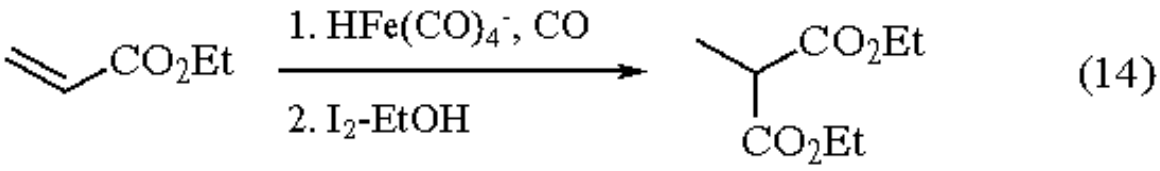

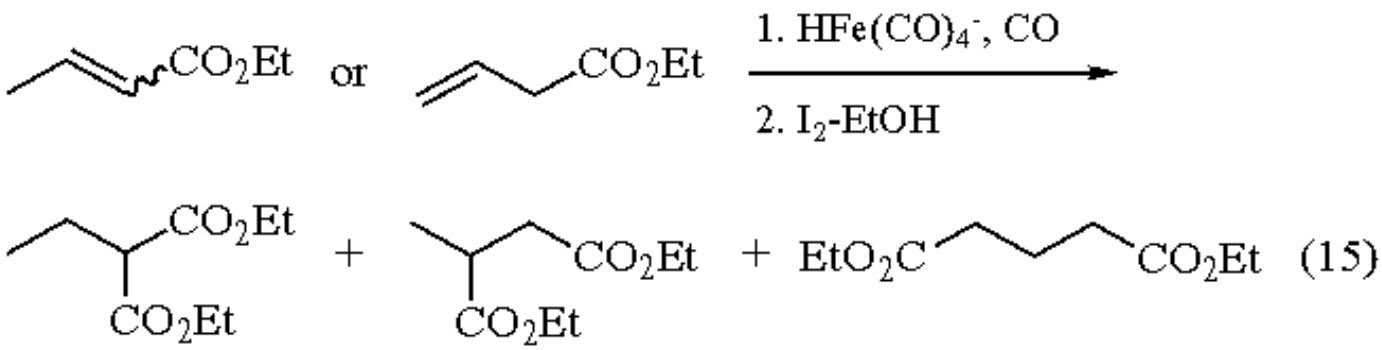

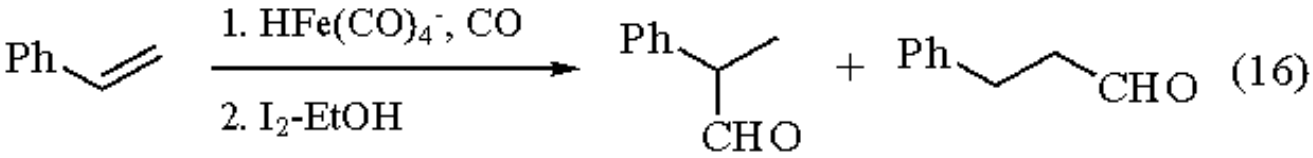

Other Reactions.

The reaction of $HFe(CO)_4^-$ with [$M(CO)_3$(α-diimine)Br] yields novel heterodinuclear hydride species (eq 17).[16] The structure of these bimetallic compounds has been determined by X-ray crystallography. The $HFe(CO)_4^-$ anion is also an effective catalyst for the steam gasification of Miike coal.[17] It is also used for hydrodimerization of acrylonitrile to provide adiponitrile.[18] With $Na_2S.9H_2O$, it provides iron carbonyl sulfide clusters.[19]

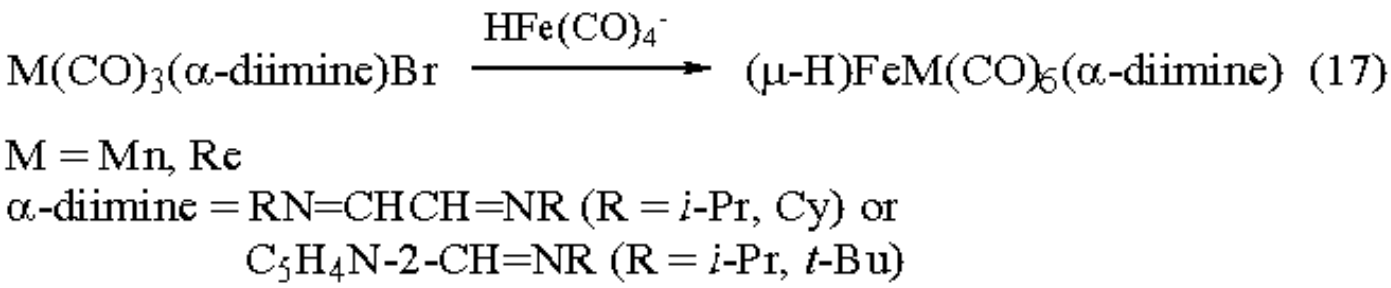

Related Reagents.

Potassium tetracarbonylhydridoferrate is prepared and used in a similar fashion to the sodium salt.[6,9,20,21] Tetramethylammonium tetracarbonylhydridoferrate is readily prepared by reaction of pentacarbonyliron with KOH and Me_4NBr in aqueous solution. Similar transformations may be performed with this reagent, including high yielding reduction of acid chlorides to aldehydes.[22]

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Sodium Tetrachloroaluminate[1]

$NaAlCl_4$

[7784-16-9] · $AlCl_4Na$ · Sodium Tetrachloroaluminate · (MW 191.77)

(dehydrating and dehydrogenating agent; Friedel-Crafts acylating agent)

Alternate Name: sodium aluminum chloride.

Physical Data: mp 100-150 °C, depending on composition. The initial melting point depends on the ratio of NaCl to $AlCl_3$ and on the coarseness of the mixture. Once the mixture has melted, the temperature may be lowered, with solidification beginning about 100 °C. The 1:2 (NaCl-$AlCl_3$) mixture is a strong Lewis acid because it contains excess $AlCl_3$. The 1:1 mixture is much less acidic.

Solubility: used as a solvent itself; appears to dissolve compounds with nucleophilic groups (carbonyl, hydroxyl); incompatible with water.

Form Supplied in: not supplied commercially, but easily formed from NaCl and $AlCl_3$ in the heated reaction vessel. The reagent can be prepared in advance and stored.[2]

Analysis of Reagent Purity: can be done electrochemically,[1] but this is rarely necessary. The purity of the reagent depends entirely on the purity of the NaCl and $AlCl_3$ used. In the 1:1 melt, excess $AlCl_3$ markedly changes the acidity of the reagent, but excess NaCl has little effect on the acidity. The properties of the 1:2 reagent (excess $AlCl_3$) do not change greatly with small differences in composition.

Handling, Storage, and Precautions: similar to ***Aluminum Chloride***, except that the molten salt is capable of producing thermal burns, as well as severe burns from $AlCl_3$. The melt may spatter when organic reagents are added, and spattering is common when the reaction mixture is poured over ice. HCl fumes are evolved during most reactions, and large amounts of HCl are evolved when the mixture is poured over ice. Use in a fume hood.

Friedel-Crafts Acylation.

In the presence of sodium tetrachloroaluminate, acids acylate activated aromatic rings (eq 1).[3] Yields of ketones from these acylations are often best with intramolecular reactions (eq 2).[3,4] Anhydrides also can be used as acylating reagents (eq 3).[5,6]

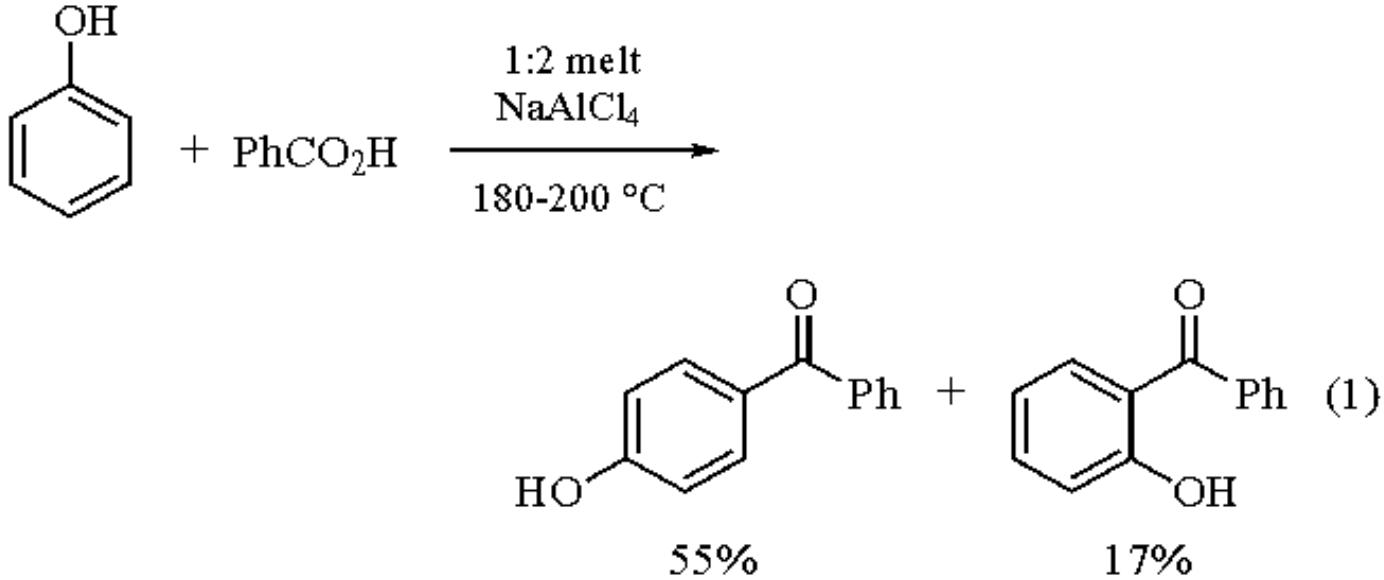

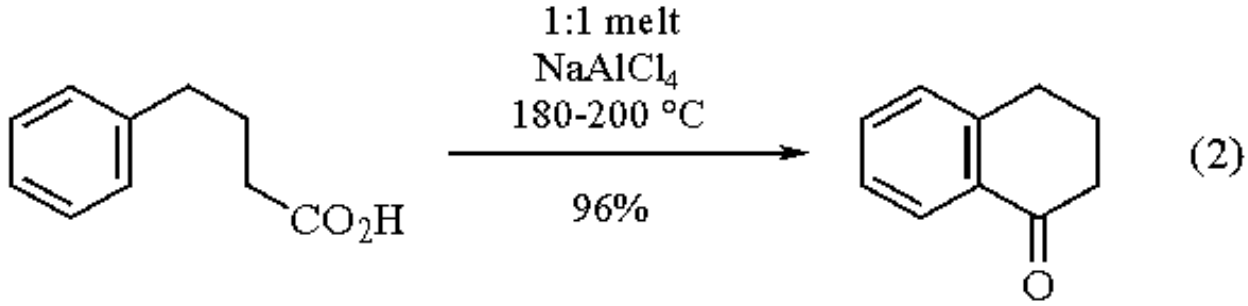

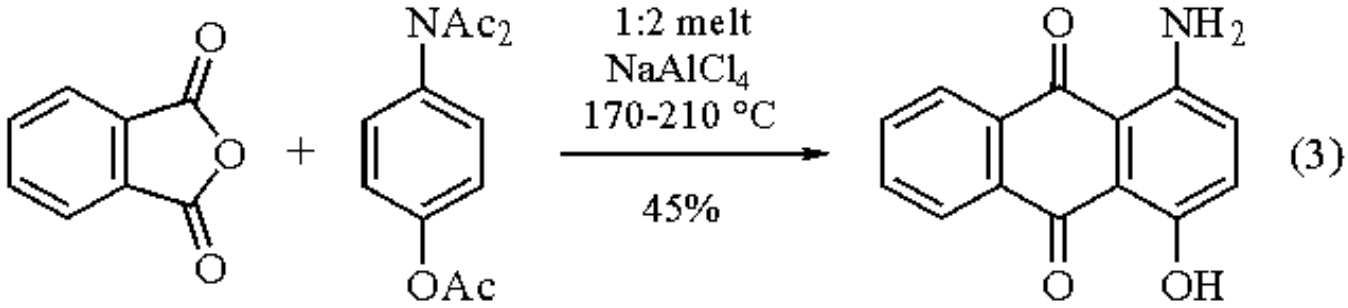

Acylation can also take place via the Fries rearrangement (eq 4).[3] A seven-membered ring can be formed by cyclodehydration (eq 5).[3,7] Aryl vinyl ketones may isomerize to give products resulting from aromatic substitution (eq 6).[3]

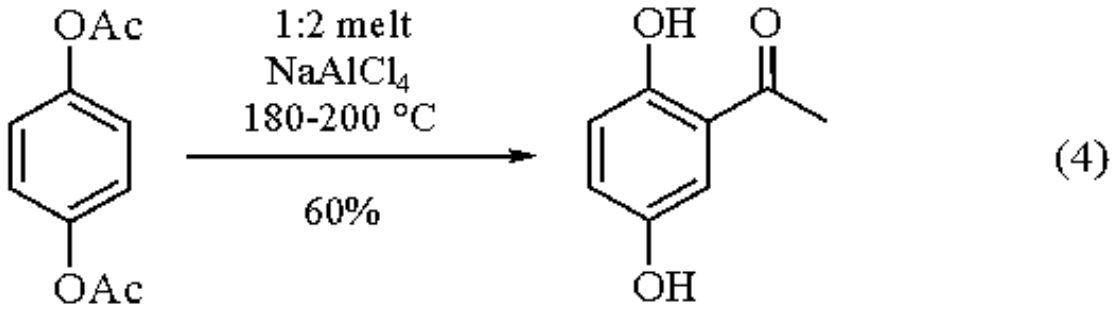

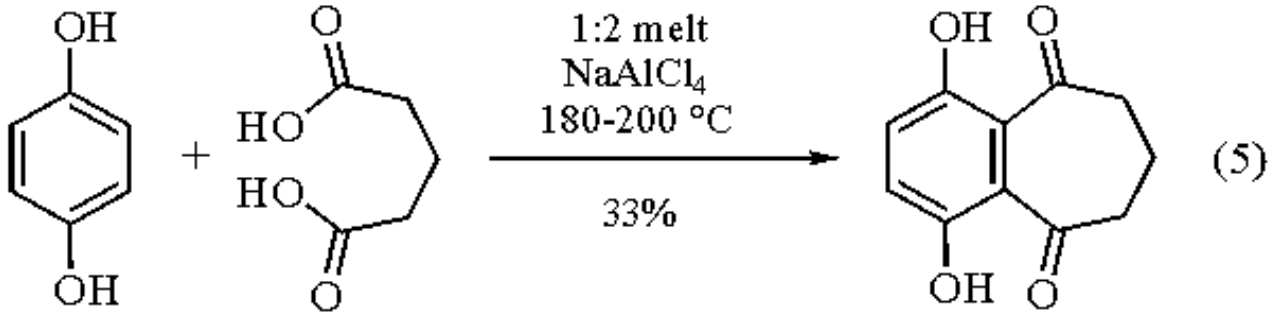

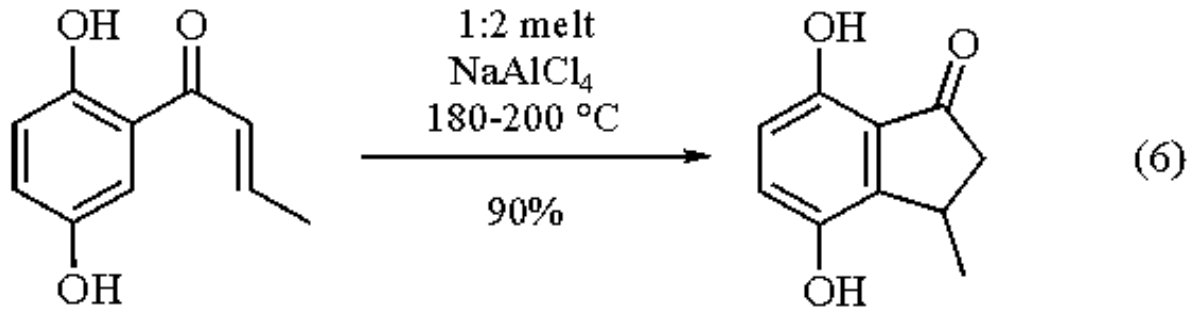

The reagent promotes the cyclization of *N*,*N*′-diphenylmalonamide by a cyclodeamination that may proceed via a ketene intermediate (eq 7).[8,9] Sodium tetrachloroaluminate dehydrates simple amides to nitriles (eq 8).[2]

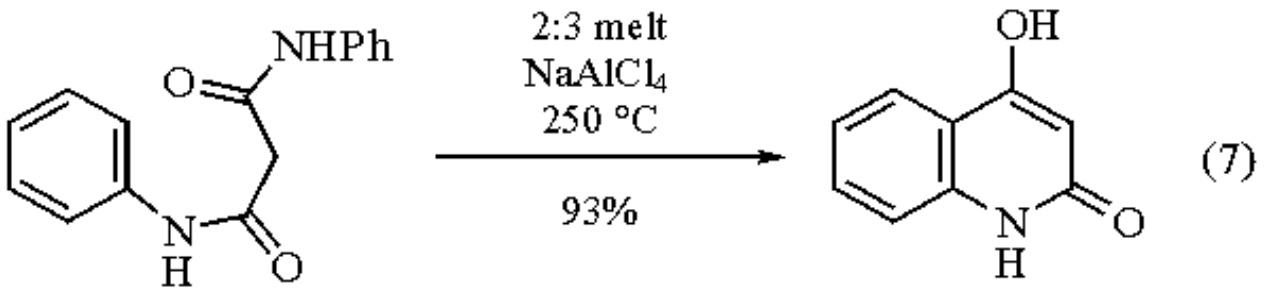

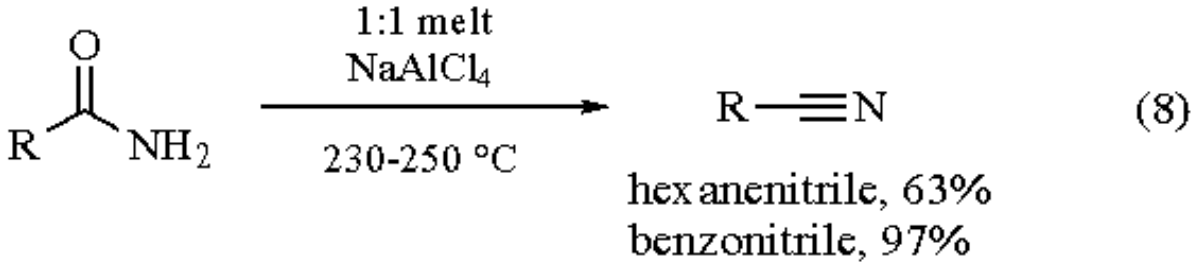

The Scholl reaction, an aromatic cyclodehydrogenation known to take place with aluminum chloride,[10] also takes place with sodium tetrachloroaluminate. Examples are known using polynuclear aromatics (eq 9),[11] benzophenones (eq 10),[12] quinazolines,[13] and benzothiophene-based heterohelicenes.[14]

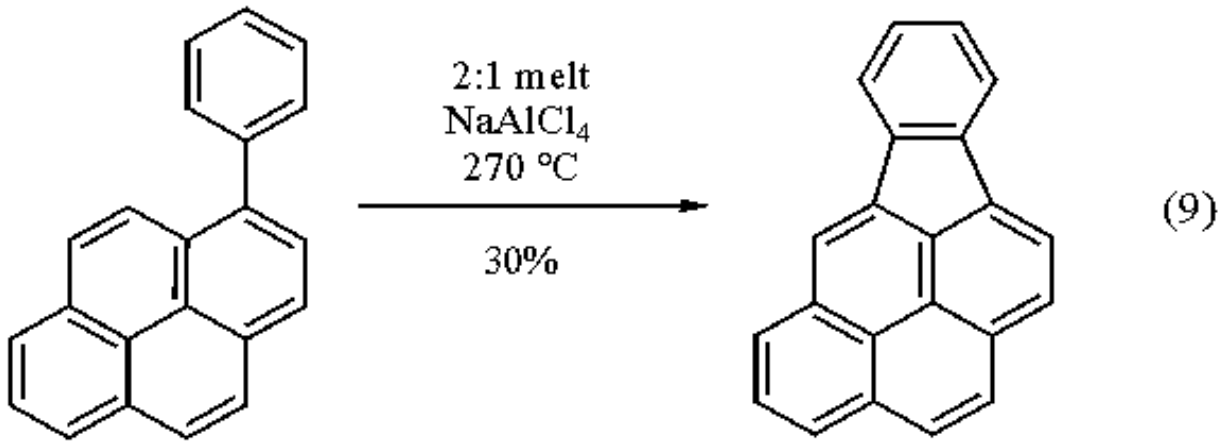

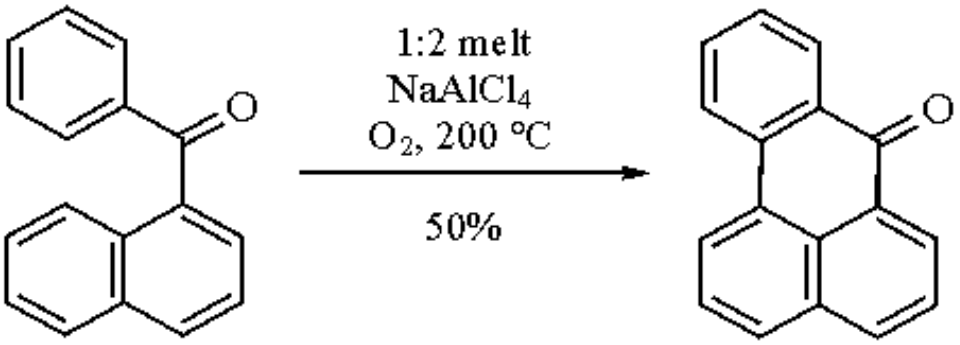

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Sodium Tetrachloroaurate(III)

$NaAuCl_4.2H_2O$

($NaAuCl_4.2H_2O$)

[13874-02-7] · $AuCl_4H_4NaO_2$ · Sodium Tetrachloroaurate(III) · (MW 397.80) ($NaAuCl_4$)

[15189-51-2] · $AuCl_4Na$ · Sodium Tetrachloroaurate(III) · (MW 361.76) ($KAuCl_4$)

[13682-61-6] · $AuCl_4K$ · Potassium Tetrachloroaurate(III) · (MW 377.87) ($HAuCl_4$)

[16903-35-8] · $AuCl_4H$ · Hydrogen Tetrachloroaurate(III) · (MW 339.78)

(catalyst precursor for the hydrochlorination of acetylene,[1] oxidation of sulfides,[2] and the synthesis of isoxazoles[3])

Physical Data: mp 100 °C (dec).

Solubility: sol water, alcohols; sparingly sol diethyl ether.

Form Supplied in: golden-yellow crystalline solid.

Preparative Method: prepared from $HAuCl_4$ (which is formed when $AuCl_3$ is dissolved in HCl or when Au is dissolved in aqua regia) and NaCl to give orange-yellow crystals.

Handling, Storage, and Precautions: air stable.

Hydrochlorination.

Addition of hydrogen chloride to acetylene to afford vinyl chloride (eq 1) is a well established industrial process, currently accounting for 6% of the total world production of this versatile monomer. Although the industrial process utilizes ***Mercury(II) Chloride*** as the catalyst source,[4] recent work demonstrates that gold(III) catalysts can also be employed for this transformation.[1] Catalysts comprised of $HAuCl_4$ supported on activated carbon are particularly active.

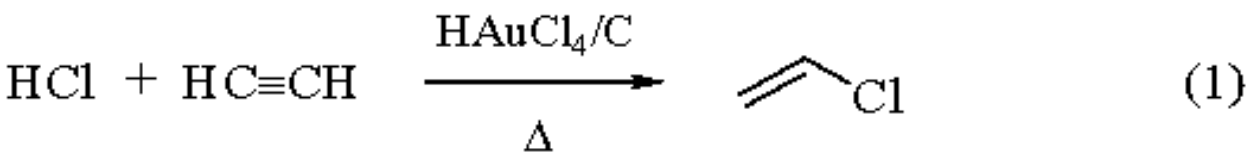

Oxidation of Sulfides.

Sulfoxides are important intermediates in organic synthesis and recent work has focused on improving their method of preparation.[5] While it is well known that gold(III) halides oxidize organic sulfides to sulfoxides and sulfones,[6-8] early work was stoichiometric in gold. More recently, studies have shown that $AuCl_4^-$ can be employed in catalytic amounts

under phase-transfer conditions to affect this reaction (eq 2). Oxidation under these conditions takes place selectively at the sulfur atom even in the presence of other oxidizable moieties such as vinyl, tertiary amino, hydroxy, and diol groups.

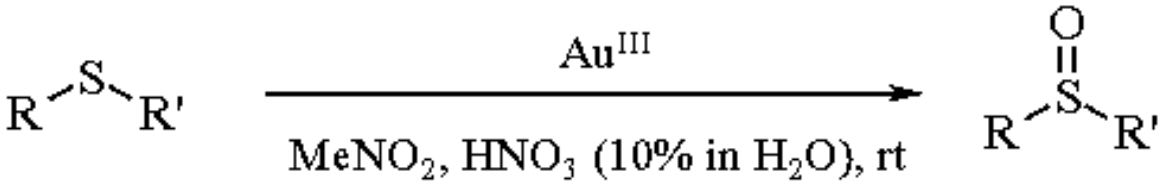

(2)

Reactions with unsymmetric disulfides are completely regiospecific, affording monosulfoxides where the more reactive sulfur has been oxidized. Symmetric disulfides afford monosulfoxides upon oxidation in higher yields than those obtained using traditional oxidizing agents such as ***Bromine***.[6] The greater activity of the analogous tetrabromoaurate(III) catalyst is exemplified in the oxidation of hindered dialkyl sulfides and aryl alkyl sulfides, as well as diaryl sulfides, which are not readily oxidized under mild conditions using $AuCl_4^-$.[7] In a related study, a number of gold complexes were found to catalyze the oxidation of carbon monoxide at low temperatures.[8]

Synthesis of Isoxazoles.

Terminal alkynes react with nitric acid under biphasic conditions and in the presence of a catalytic amount of $TBA^+AuCl_4^-$ to give 3,5-disubstituted isoxazoles (eq 3).[3] There appears to be no limitations on the nature of the R group and yields of isolated products range from 35-50%. Poor results are obtained using different metal chloride catalysts, and a biphasic system of nitromethane/water seems to be unique in promoting this transformation.

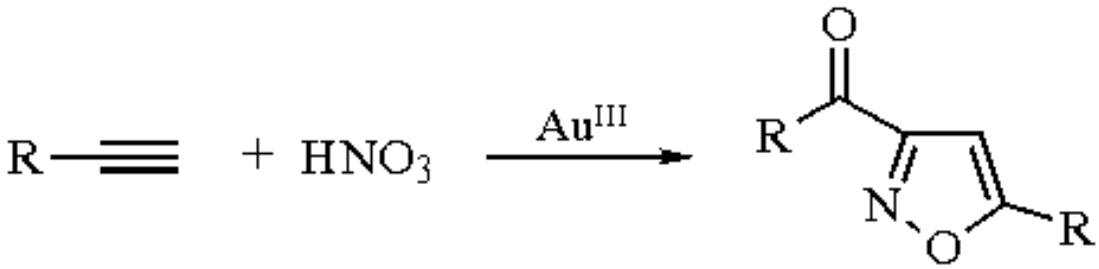

(3)

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Sodium Thiocyanate[1]

NaSCN

[540-72-7] · CNNaS · Sodium Thiocyanate · (MW 81.08)

(thiocyanation or isothiocyanation of organic compounds;[1] with a metal salt, reduces α-halo ketones to ketones[13])

Physical Data: mp 287 °C.

Solubility: v sol H_2O (139 g/100 mL at 21 °C); sol acetone, EtOH; partially sol CH_2Cl_2.

Form Supplied in: colorless to white deliquescent crystals; widely available.

Purification: recrystallization from water, MeCN, or MeOH, followed by washing with ether and drying at 130 °C.

Handling, Storage, and Precautions: contact with acids liberates toxic gas. Keep container well sealed during storage.

General Discussion.

Sodium thiocyanate is primarily a reagent for the thiocyanation or isothiocyanation of organic compounds by nucleophilic chemistry. It acts as a thiocyanating agent by nucleophilic attack via its sulfur while attachment by nitrogen affords isothiocyanates.[1] The ambident character of thiocyanate ion is explained in more detail in the description of ***Potassium Thiocyanate***. Sodium thiocyanate is not often employed for the thiocyanation of organic compounds, although there are some instances of its use.[1] It is preferred over KSCN for the formation of PhSeSCN from PhSeCl,[2] but TMSNCS is the best reagent since the product is not contaminated with thiocyanate ion residues.[3] NaSCN has been employed to introduce a thiocyanate group into a nitroxyl spin label (eq 1).[4] NaSCN is rarely utilized for the thiocyanation of saccharides; potassium, ammonium, silver, and lead thiocyanates are employed instead.[5]

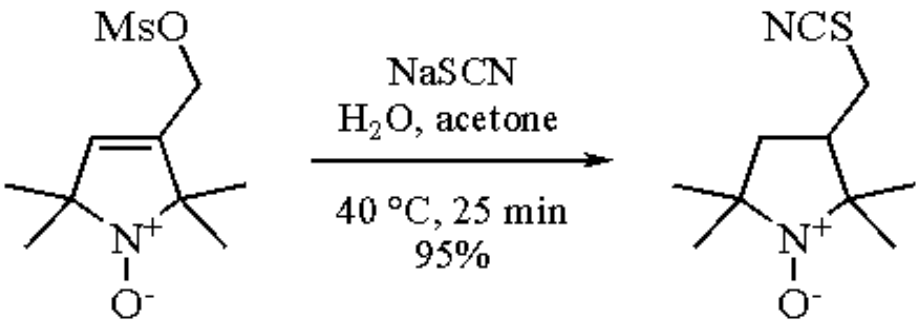

(1)

The primary use of sodium thiocyanate is as a reagent for the isothiocyanation of unsaturated compounds. For instance, the reaction of alkyl carbonochloridothioates with NaSCN followed by an alcohol quench affords *O,O*-dialkyl imidodithiocarbonothioates via an intermediate isothiocyanate. KSCN and NH_4SCN give lower yields (eq 2).[6] The identity of the base is also important in these and related isothiocyanate syntheses.[6,7]

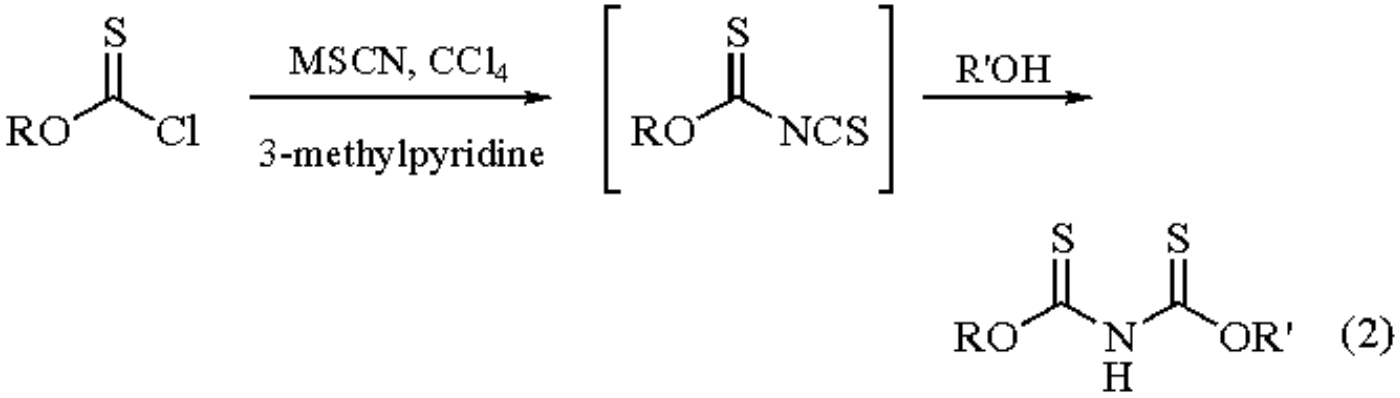

M = Na, 79%; K, 64%; NH_4, 40%

In addition to alkoxycarbonyl halides, compounds such as imidoyl chlorides[8] and aminocarbonyl chlorides[9] react with NaSCN to afford isothiocyanates; in many cases, the isothiocyanates are intermediates on the path to substituted thioureas (eq 3). The reaction of NaSCN with imidoyl chlorides attached to a phosphonium salt affords substituted thioimidazolones by nitrogen attack and cyclization.[10] Thioacyl halides may give the isothiocyanate or the thiocyanate, depending on the reaction conditions.[1,11] In some instances, the organic thiocyanate can be converted to the isothiocyanate by thermolysis.[1]

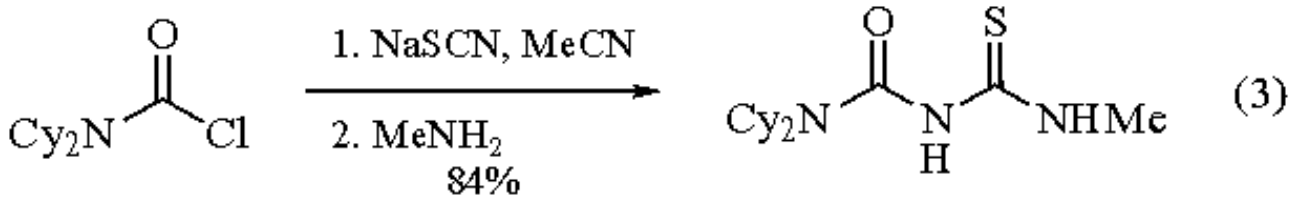

The reaction of 2 equiv of NaSCN with aryl and alkyl dichloromethyl disulfides is an effective means of synthesizing 2-alkyl(aryl)thio-4λ^4-[1,2,4]dithiazolo[1,5-*b*][1,2,4]dithiazoles (eq 4).[12]

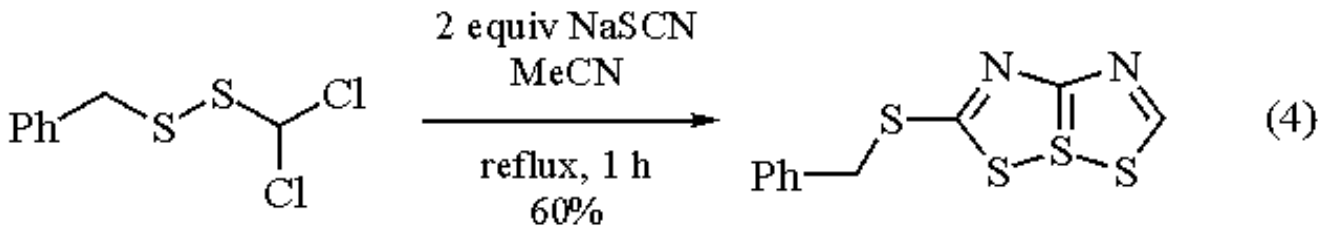

NaSCN is one of a collection of pseudohalides or halides that has been used in conjunction with a metal halide for the reductive dehalogenation of α-halo ketones (eq 5).[13] NaSCN does not seem to have any particular advantage over the other reagents; all achieve the reduction in >90% yield.

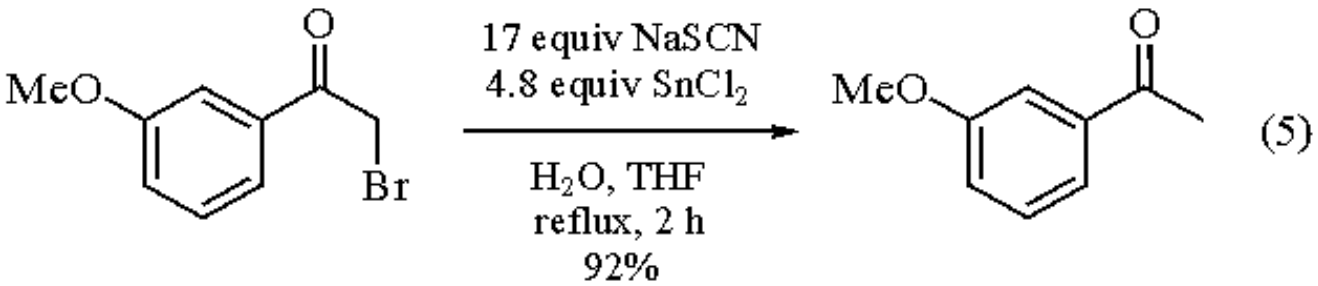

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Sodium Thiosulfate[1]

$Na_2S_2O_3$

($Na_2S_2O_3$)

[7772-98-7] · $Na_2O_3S_2$ · Sodium Thiosulfate · (MW 158.12) ($Na_2S_2O_3.5H_2O$)

[10102-17-7] · $H_{10}Na_2O_8S_2$ · Sodium Thiosulfate · (MW 248.22)

(general reducing agent; reagent for nucleophilic introduction of sulfur[2])

Physical Data: mp (pentahydrate) 40-45 °C; *d* 1.73 g cm^{-3}.

Solubility: insol alcohol; v sol water.

Form Supplied in: both the pentahydrate and anhydrous form are widely available as white solids.

Handling, Storage, and Precautions: reported to be an irritant. The anhydrous form is hygroscopic.

Functional Group Reductions.

$Na_2S_2O_3$ is a sufficiently powerful reducing agent to effect a number of useful synthetic transformations. Vicinal dibromides are efficiently dehalogenated to the corresponding alkenes in warm DMSO.[3] Anilines are obtained by reduction of aryl nitroso compounds[4] or aryl azides,[5] and nitrosamides can be reduced to amides.[6] Peroxides are reduced to the corresponding alcohols[7] when exposed to aqueous $Na_2S_2O_3$, and reductive workup of an ozonolysis with NaI/$Na_2S_2O_3$ has been employed in the isolation of a ketone.[8] Saturation of activated alkenes by $Na_2S_2O_3$ has been reported, including the reduction of a quinone[9] and of 1,2-dibenzoylethylene.[10]

Introduction of Sulfur.

Nucleophilic attack by thiosulfate on alkyl halides results in the formation of *S*-alkyl thiosulfates, commonly known as Bunte salts. Extensive reviews on the preparation and classical reactions of Bunte salts have appeared.[2] In addition to alkyl halides, thiosulfate has been reported to add to epoxides,[2b] oxetanes,[11] activated alkenes,[2b] and even acylaziridines.[12] Probably the most well-known classical application of Bunte salts is their conversion to thiols, which can be accomplished via acidic hydrolysis[13] or reduction.[11] Extension of this methodology to the synthesis of aryl thiols is possible by the addition of $Na_2S_2O_3$ to quinones (eq 1).[14] When the hydrolysis is performed under oxidative conditions, sulfonic acids or sulfonyl chlorides are obtained.[2,15]

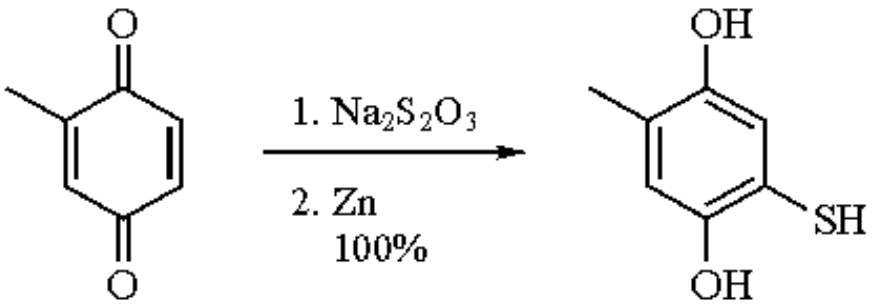

(1)

Much of the useful chemistry of Bunte salts results from the leaving group potential of the sulfite moiety. Nucleophilic displacement by thiolates results in the synthesis of unsymmetrical disulfides (eq 2).[16] In a mechanistically similar manner, symmetrical trisulfides are available by the reaction of Bunte salts with sodium sulfide.[17]

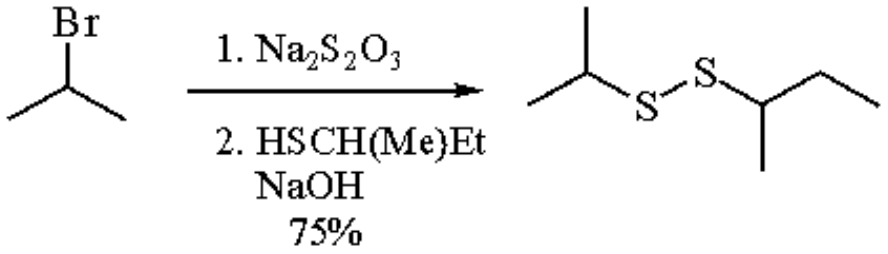

(2)

The sulfite group of Bunte salts may also function as a leaving group via an E2 elimination, comprising a convenient and mild method for generating thiocarbonyl compounds. This reaction was first noted when the carbamoyl derivatives $RNHCOCH_2SSO_3Na$ were reacted with primary and secondary amines R'_2NH, affording thiooxamides $RNHCOCSNR'_2$.[18] Dimerization of the reactive thiocarbonyl intermediates to 1,3-dithietanes has also been observed.[19] The thiocarbonyl group is a good dienophile and will trap 1,3-dienes at low temperatures.[20] The resulting cycloadducts can be rearranged stereoselectively under basic conditions to cyclopentenyl sulfides (eq 3).[21]

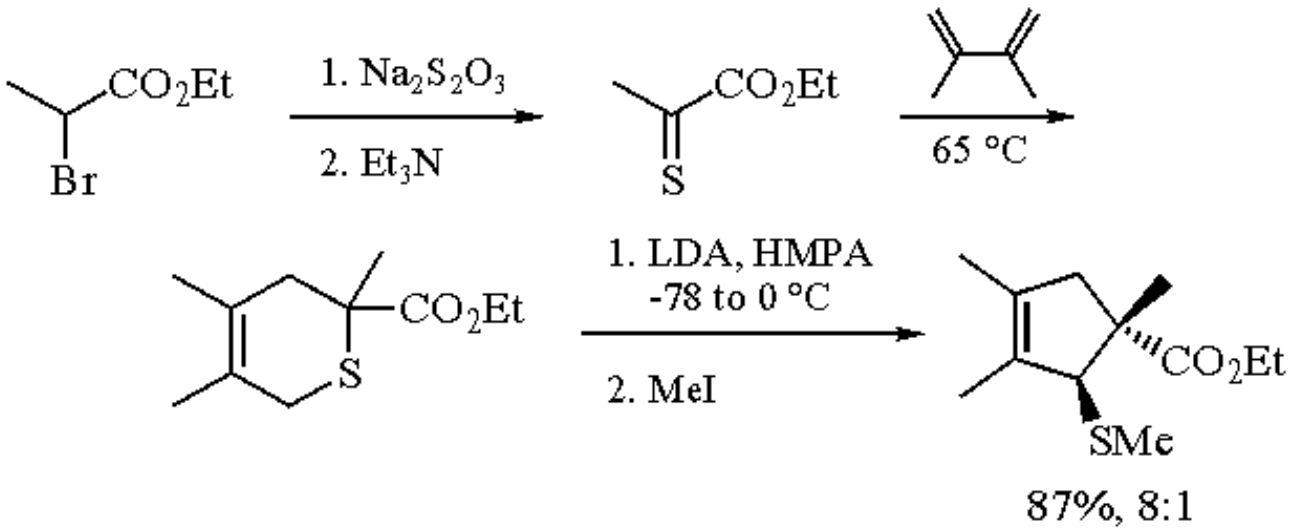

(3)

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Sodium Triacetoxyborohydride[1]

$NaBH(OAc)_3$

[56553-60-7] · $C_6H_{10}BNaO_6$ · Sodium Triacetoxyborohydride · (MW 211.96)

(the prototype of a class of $NaBH(OCOR)_3$ reagents that are selective reducing agents for a number of functional groups[1] and heterocycles;[1] alkylation of amines;[1-4] hydroboration[1])

Physical Data: mp 116-120 °C (dec); the related $NaBH_3OAc$ has not been fully characterized.

Solubility: $NaBH(OAc)_3$ and related acyloxyborohydrides are rapidly destroyed by H_2O and protic solvents; H_2 is liberated. Cosolvents that have been employed are benzene, toluene, THF, dioxane, CH_2Cl_2, $ClCH_2CH_2Cl$.

Form Supplied in: $NaBH(OAc)_3$ and the related ***Tetramethylammonium Triacetoxyborohydride*** are commercially available as colorless powders.

Preparative Method: $NaBH(OAc)_3$ and $NaBH_3OAc$ can be easily prepared in situ from the appropriate amount of acetic acid and $NaBH_4$.

Analysis of Reagent Purity: $NaBH(OAc)_3$ has been characterized by elemental analysis, IR, and ^1H, ^{13}C, and ^{11}B NMR.

Handling, Storage, and Precautions: because H_2 is liberated during the preparation of these reagents, all handling and storage of acyloxyborohydrides should take place under an inert atmosphere.

Functional Group Reductions.

$NaBH(OAc)_3$ selectively reduces aldehydes but not ketones[5,6] (eqs 1 and 2),[7,8] even with excess reagent. However, α- and β-hydroxy ketones are reduced to the *anti*-diols by hydroxy-directed hydride delivery[6,9,10] (eqs 3 and 4).[11,12] Diastereoselectivities are generally excellent, although $Me_4NBH(OAc)_3$ seems to be a superior reagent in this regard.[9] Several recent examples of $NaBH(OAc)_3$ in the stereoselective reduction of hydroxy ketones attest to the power of this reagent.[13]

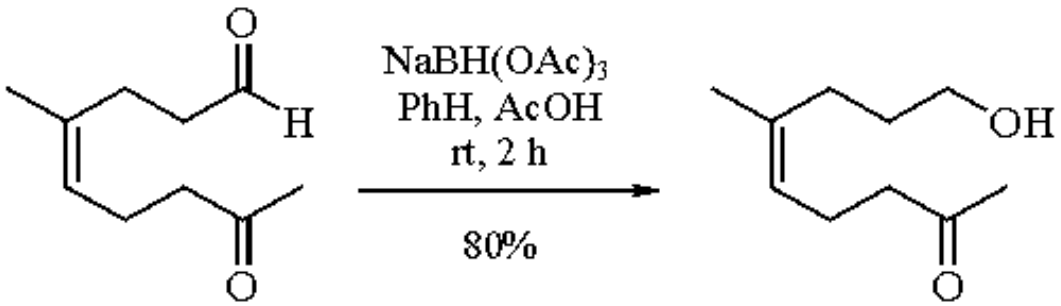

(1)

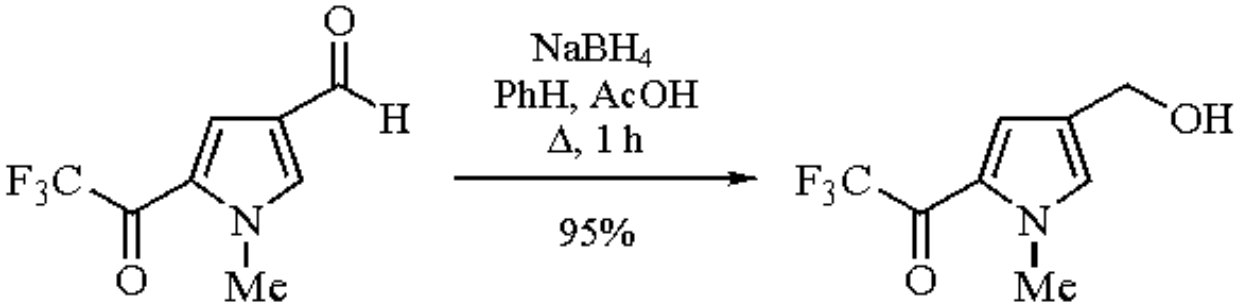

(2)

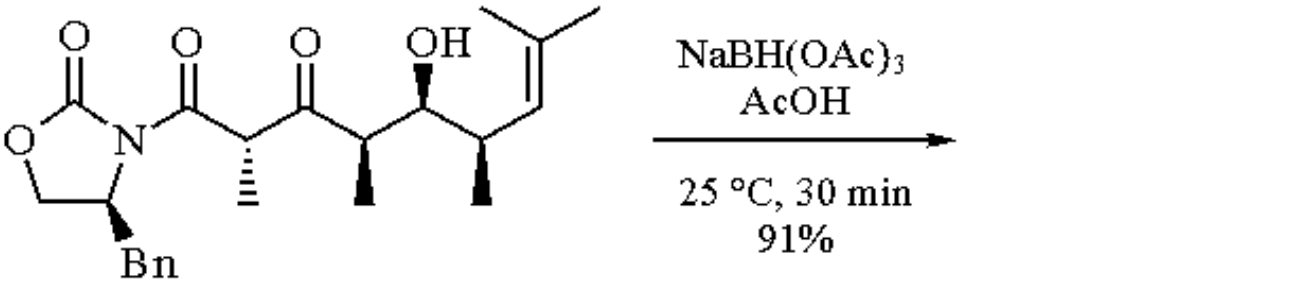

(3)

anti:*syn* = >30:1

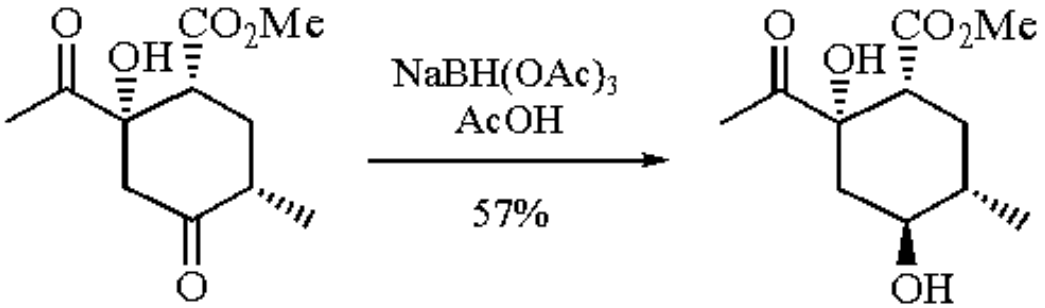

(4)

The hydroxy-directed $NaBH(OAc)_3$ reduction of an imide has been described.[14] The more reactive $NaBH_3OAc$ reduces enones to allylic alcohols,[15] and some ketones can be reduced to alcohols with ***Sodium Borohydride***-tartaric acid.[16] The combination of $NaBH_4$ or ***Sodium Cyanoborohydride-Acetic Acid*** serves to deoxygenate tricarbonyl systems (eq 5)[17] and tosylhydrazones of ketones and aldehydes (eq 6).[18] Primary and secondary amides are reduced to amines by the action of $NaBH_3OAc$ (eq 7),[19,20] while tertiary amides require ***Sodium Trifluoroacetoxyborohydride***.

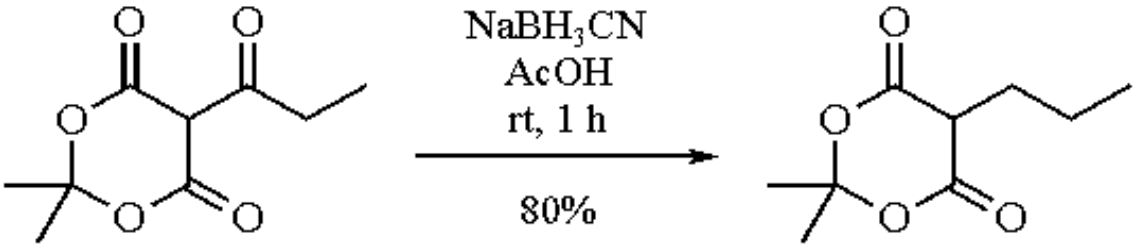

(5)

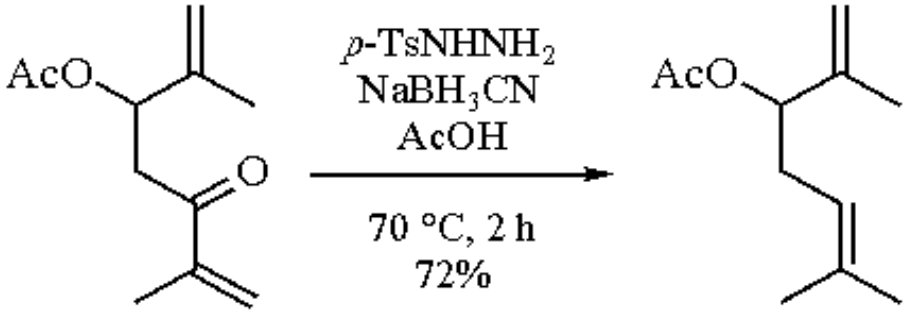

(6)

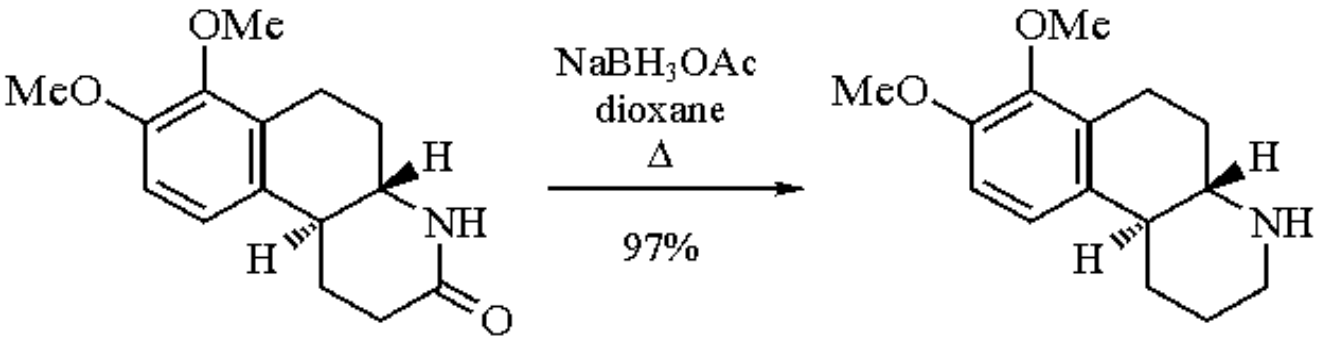

(7)

Amine Alkylation (Reductive Amination).

By a pathway that may involve the generation of free aldehyde, the combination of $NaBH_4$ and carboxylic acids is capable of *N*-alkylation of amines.[1-4] Recent examples abound (eqs 8-11). At lower temperature, monoalkylation is generally observed (eq 8),[21] while at 50-55 °C, primary and secondary amines are converted into tertiary amines (eqs 9 and 10).[22,23] Neat carboxylic acid (eqs 8 and 9) or a cosolvent (eq 10) may be used. In the latter event, solid carboxylic acids function well (eq 11).[24] ***Formic Acid*** may be employed for *N*-methylation.[1,25] A useful variation is the reductive amination of aldehydes and ketones (eqs 12-14),[1,26-29] a method which is claimed to be superior to that using $NaBH_3CN$-MeOH.[26] ***Paraformaldehyde*** serves as a convenient source of HCHO for *N*-methylation in this protocol.[30,31]

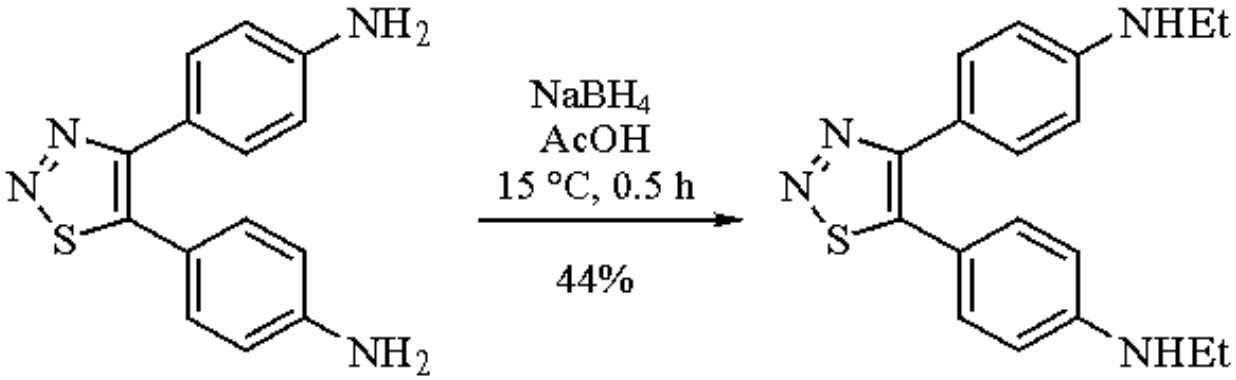

(8)

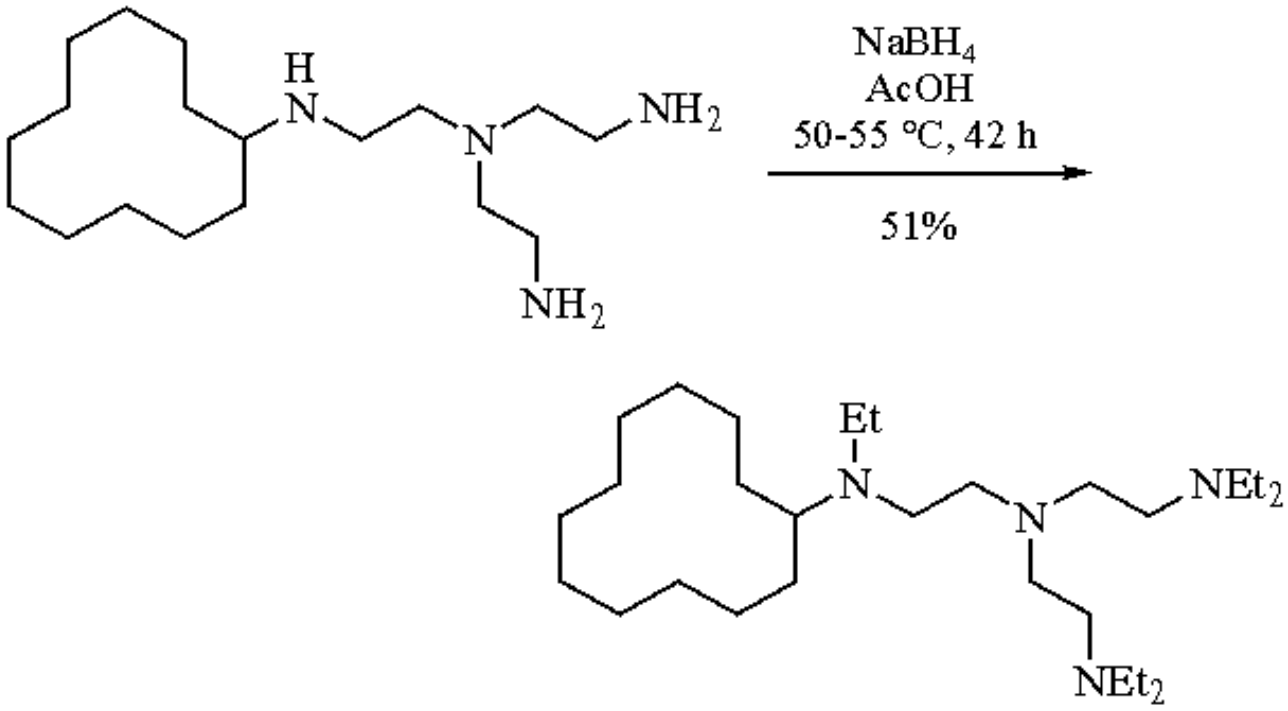
H
N
N
NH2
NH2
NaBH4
AcOH
50-55 °C, 42 h
51%
Et
N
N
NEt2
NEt2

(9)

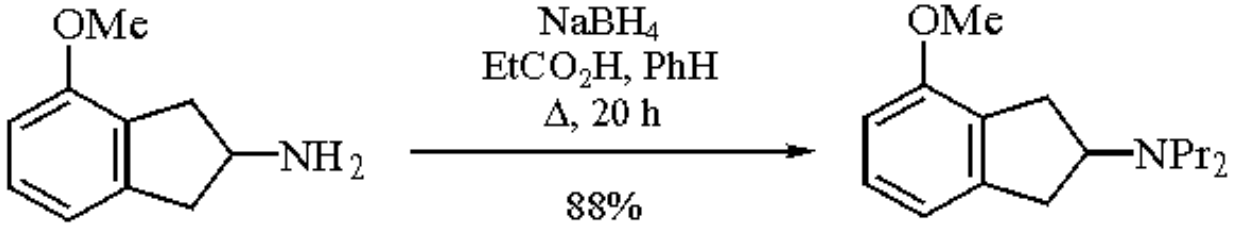
OMe
NH2
NaBH4
EtCO2H, PhH
Δ, 20 h
88%
OMe
NPr2

(10)

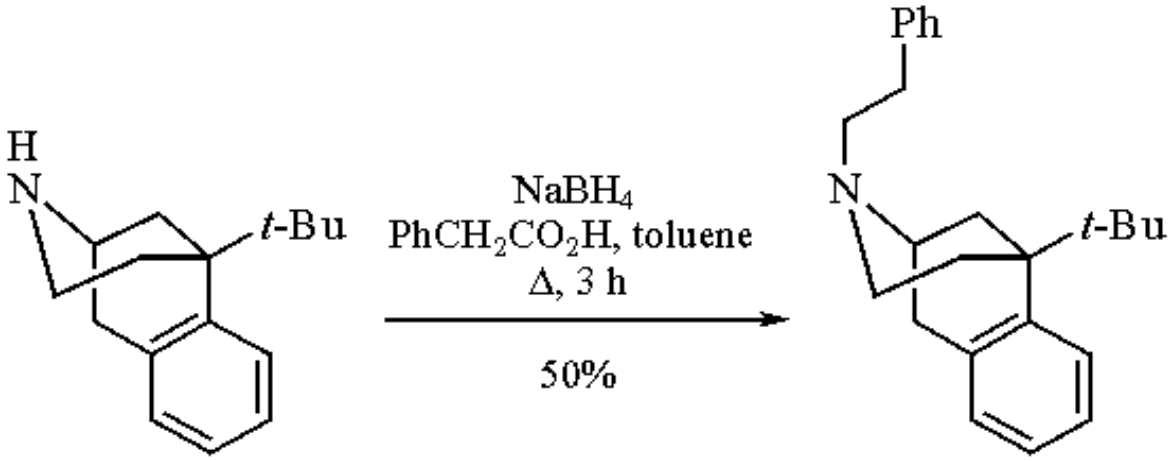
H
N
t-Bu
NaBH4
PhCH2CO2H, toluene
Δ, 3 h
50%
Ph
N
t-Bu

(11)

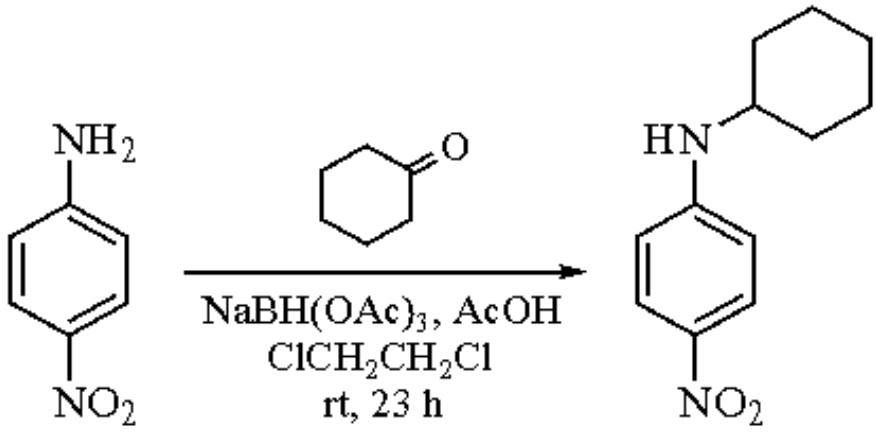
NH2
NO2
O
NaBH(OAc)3, AcOH
ClCH2CH2Cl
rt, 23 h
66%
HN
NO2

(12)

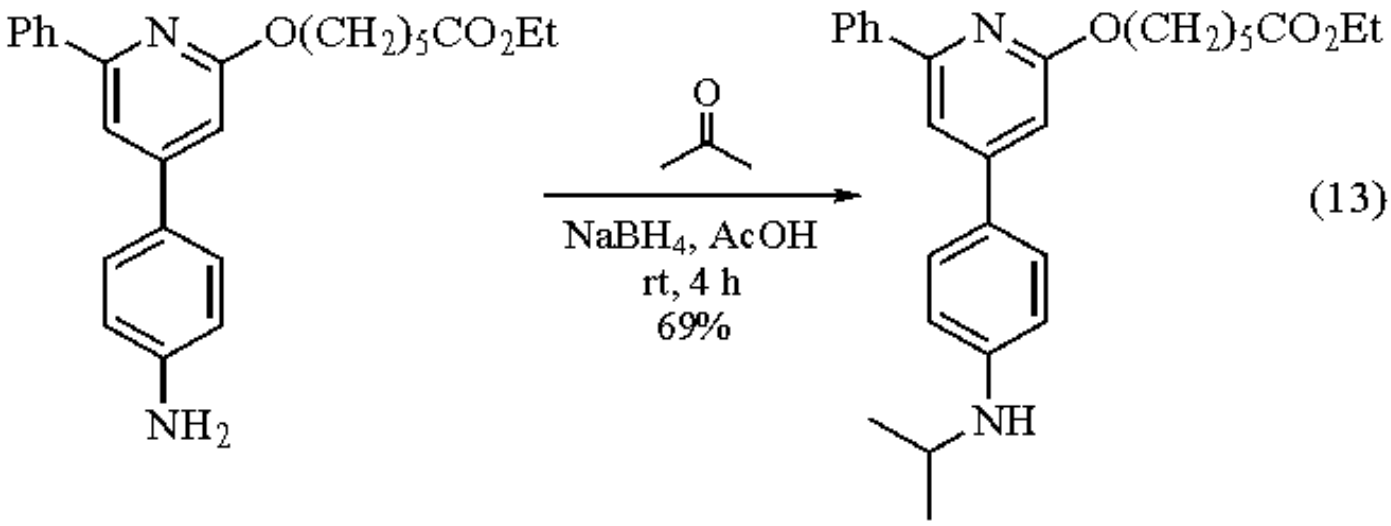

(13)

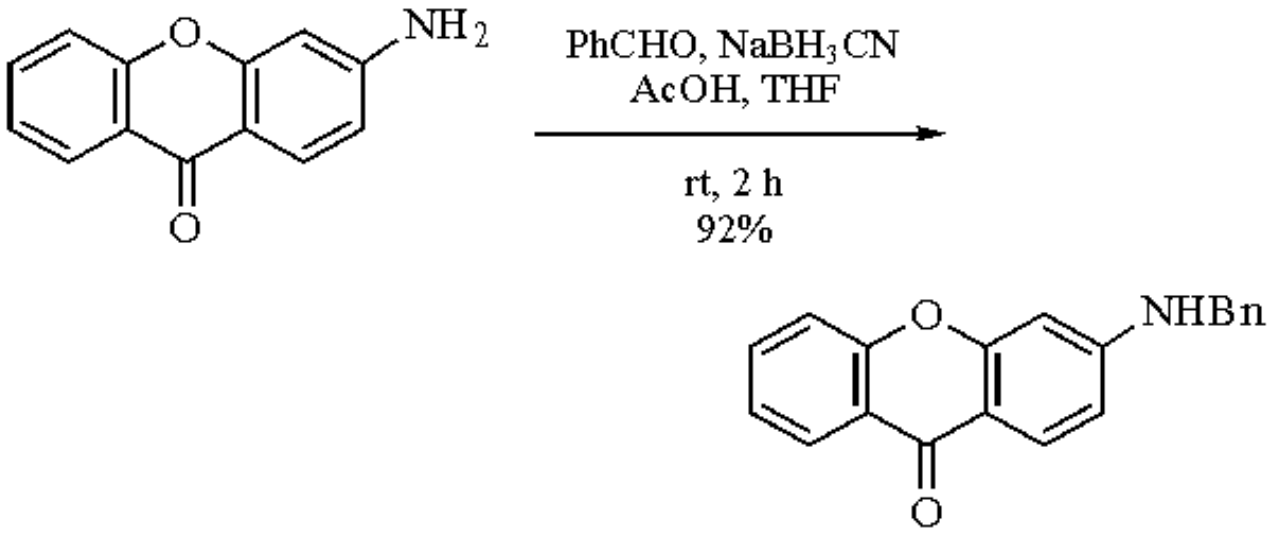

(14)

Carboxylic acids are reduced to alcohols with $NaBH_4$ in THF,[32] although the use of CF_3CO_2H in this regard is superior, and there is one report of an ester reduction to a primary alcohol with $NaBH_4$-HOAc.[33]

Enamine, Imine, Iminium Ion, and Enamide Reduction.

The first reported use of $NaBH_4$-HOAc was in the reduction of dienamines,[34] and this application has found extensive use in synthesis[1] (eqs 15-19).[35-39]

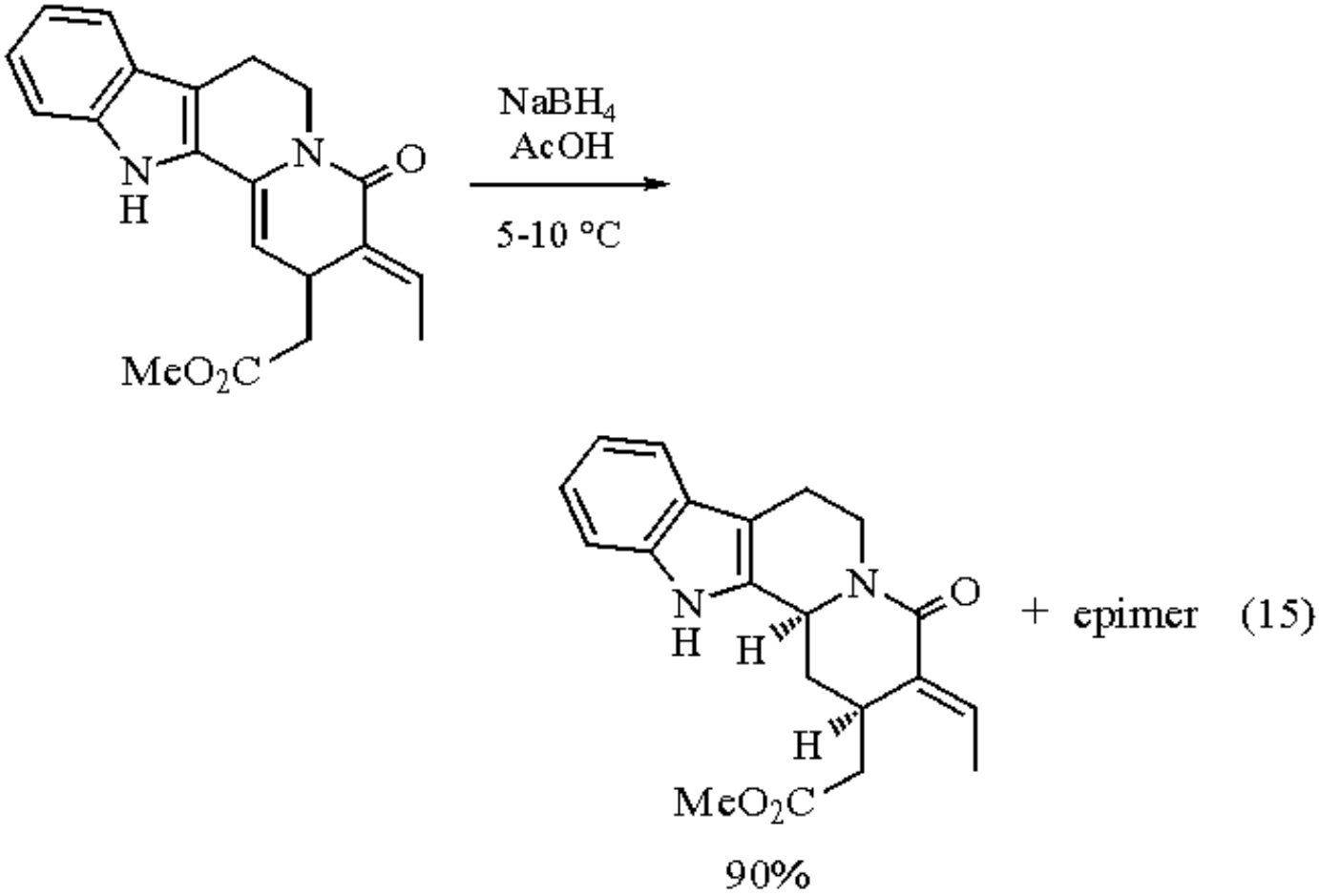
NaBH4
AcOH
5-10 °C
MeO2C
+ epimer
90%

(15)

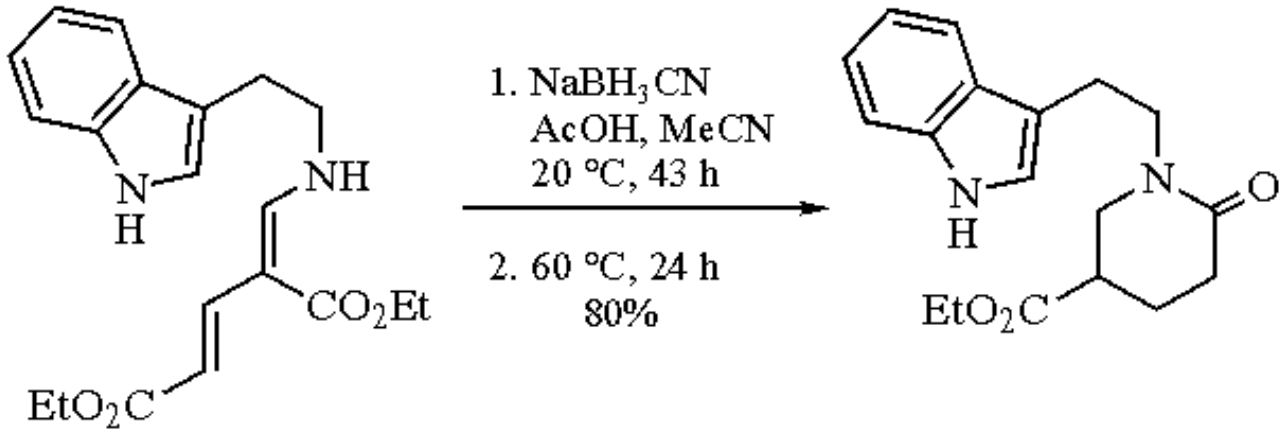
1. NaBH3CN
AcOH, MeCN
20 °C, 43 h
2. 60 °C, 24 h
80%
CO2Et
EtO2C

(16)

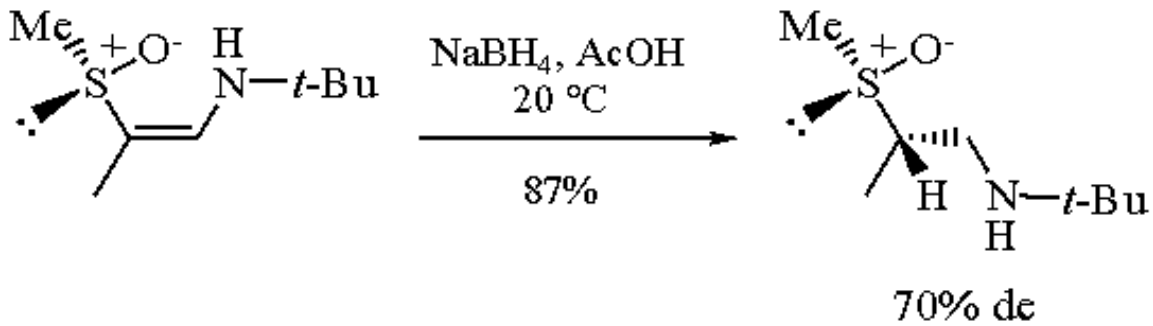
NaBH4, AcOH
20 °C
87%
t-Bu
70% de

(17)

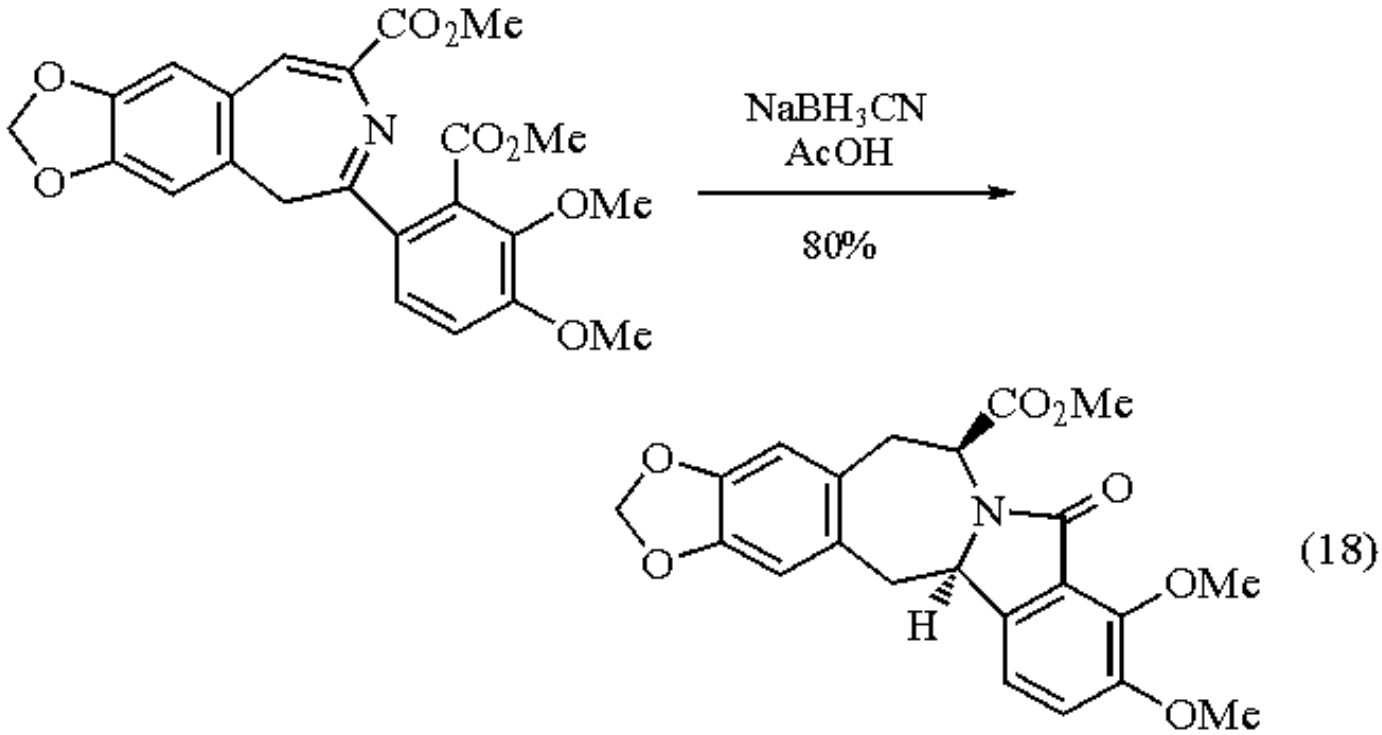

(18)

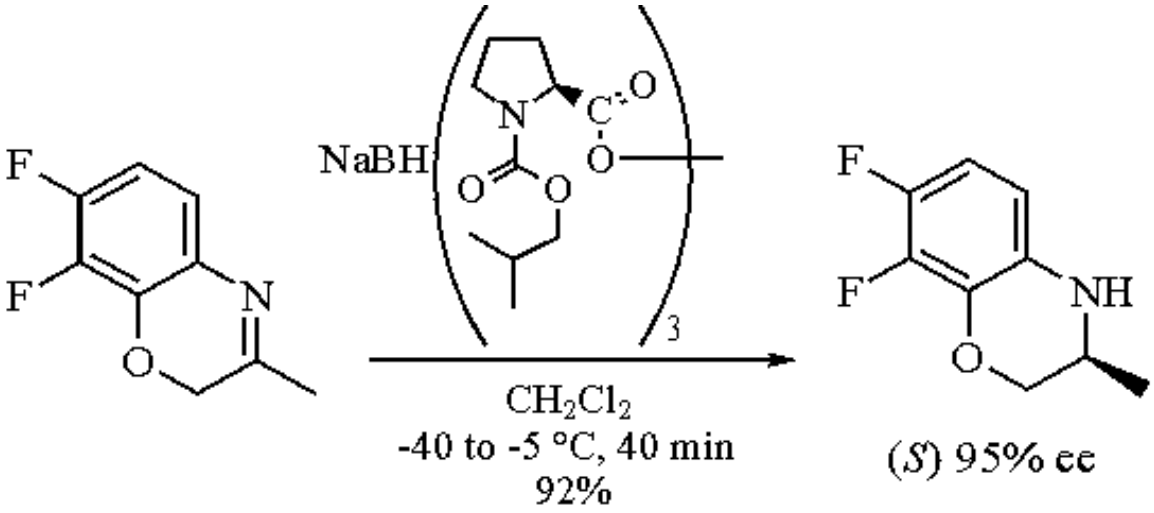

(19)

Indole Reduction.

Indole is smoothly reduced to indoline under the influence of $NaBH_3CN$-HOAc;[2] the reaction is quite general[1,40] and has been employed often (eqs 20-22),[41-43] especially in the synthesis of CC-1065, PDE, and analogs where only the more basic indole ring is reduced (eq 23).[44,45] *N*-Substituted indoles are reduced to indolines with $NaBH_4$-HOAc,[1,2] and the action of $NaBH_4$-RCO_2H on *N*-unsubstituted indoles affords *N*-alkylindolines by *N*-alkylation of the initially formed indoline.[1,2]

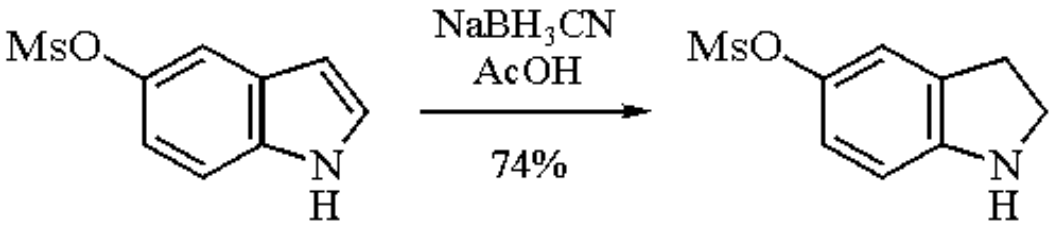

(20)

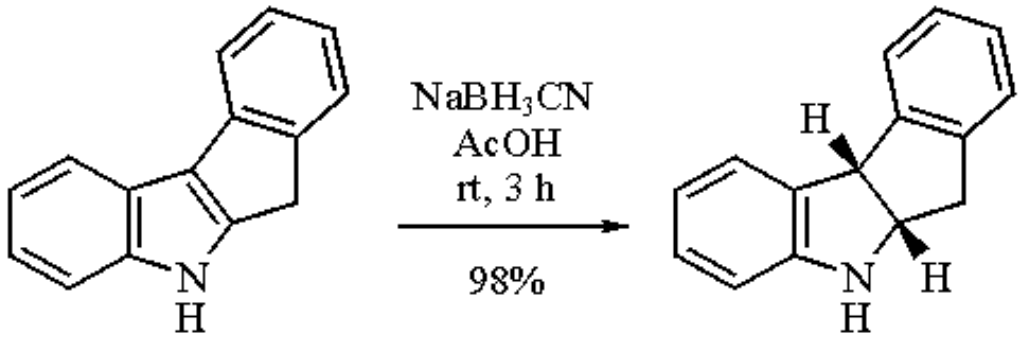

(21)

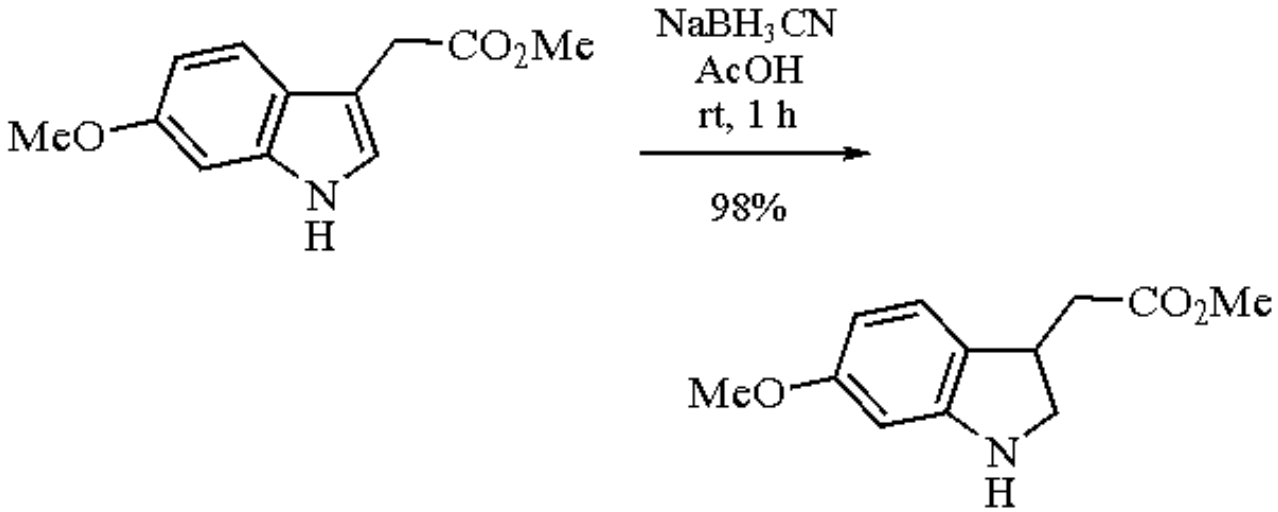

(22)

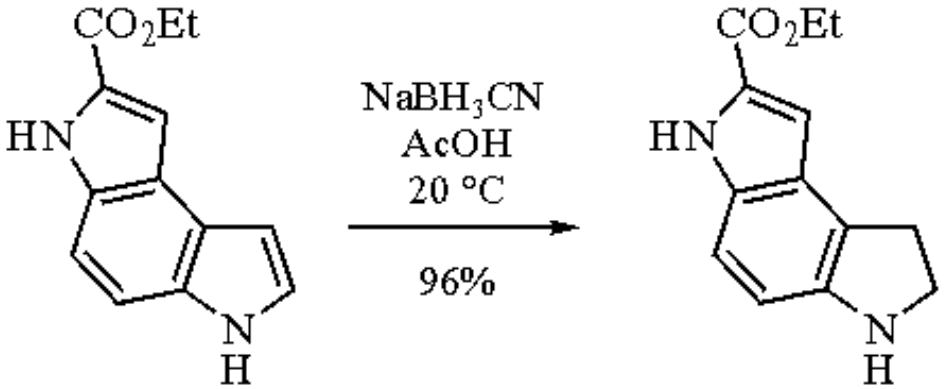

(23)

Reduction of Other Heterocycles.

Quinolines and isoquinolines are reduced to the corresponding tetrahydro derivatives with $NaBH_3CN$ or $NaBH_4$-RCO_2H, the latter combination affording the *N*-alkylated compounds.[1,46] Related heterocycles have been subjected to this protocol (eqs 24 and 25).[47]

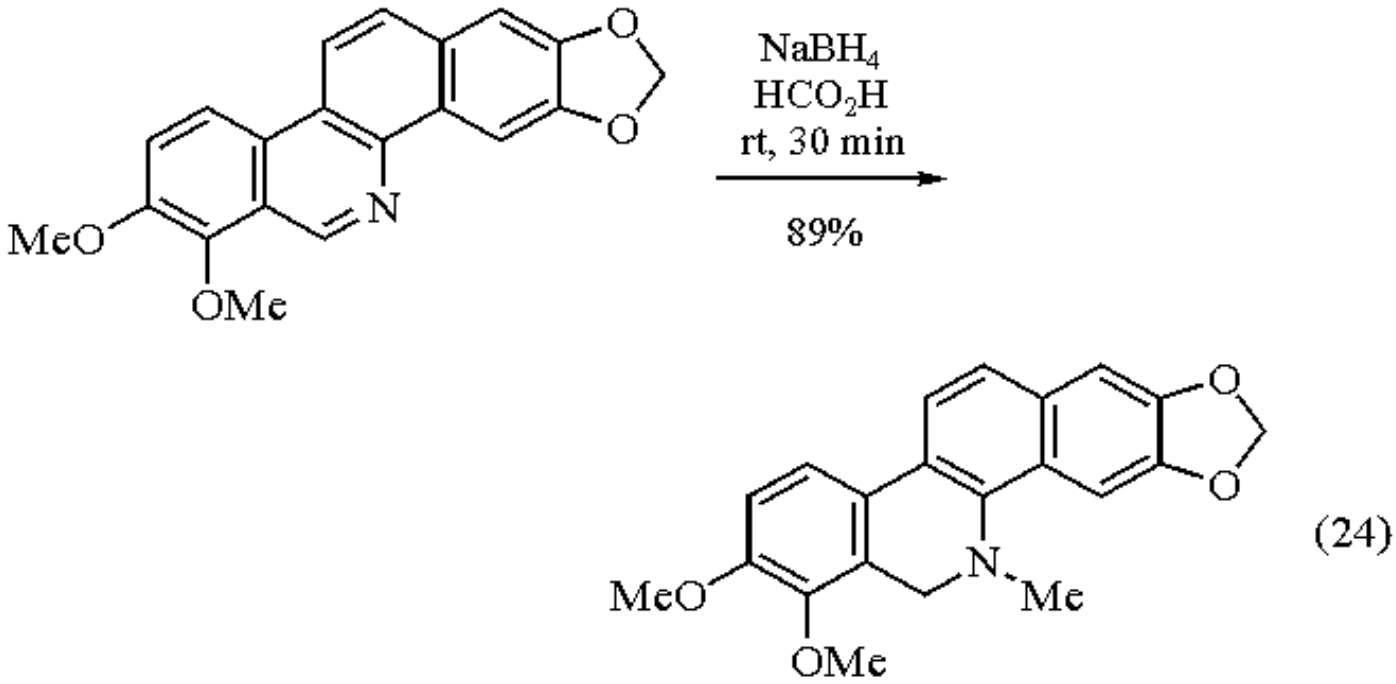

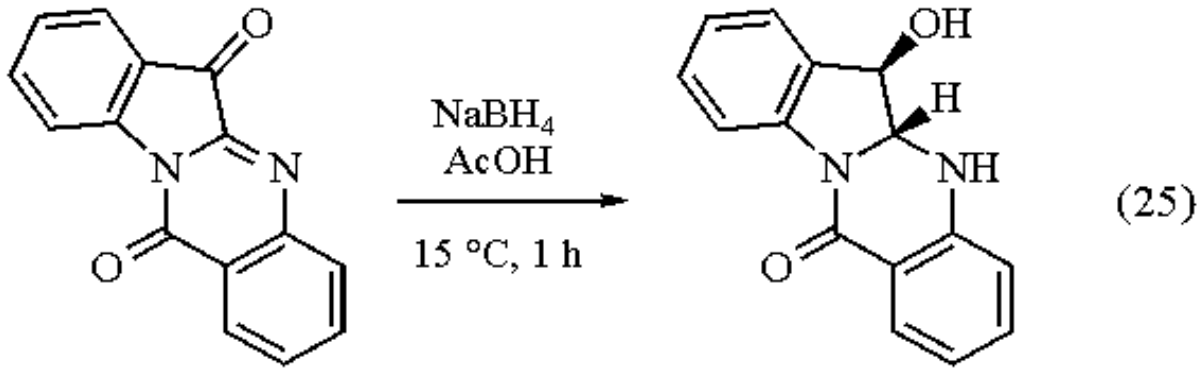

The reduction of pyrylium salts (eq 26),[48] the reductive cleavage of benzoxazoles (eq 27)[49] and of saturated nitrogen heterocycles (eqs 28 and 29),[1,50,51] and the reduction of other π-deficient nitrogen heterocycles[1] are known.

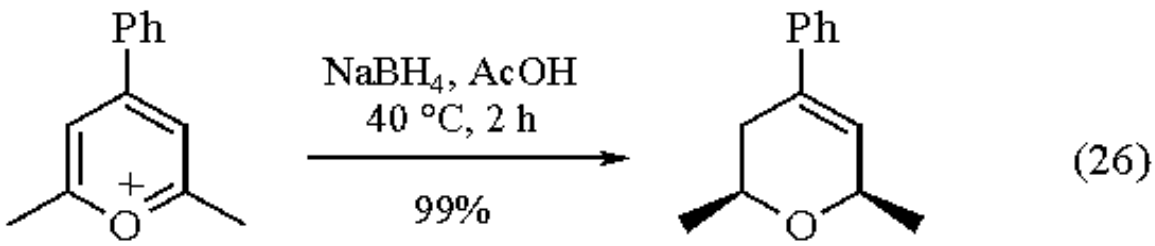

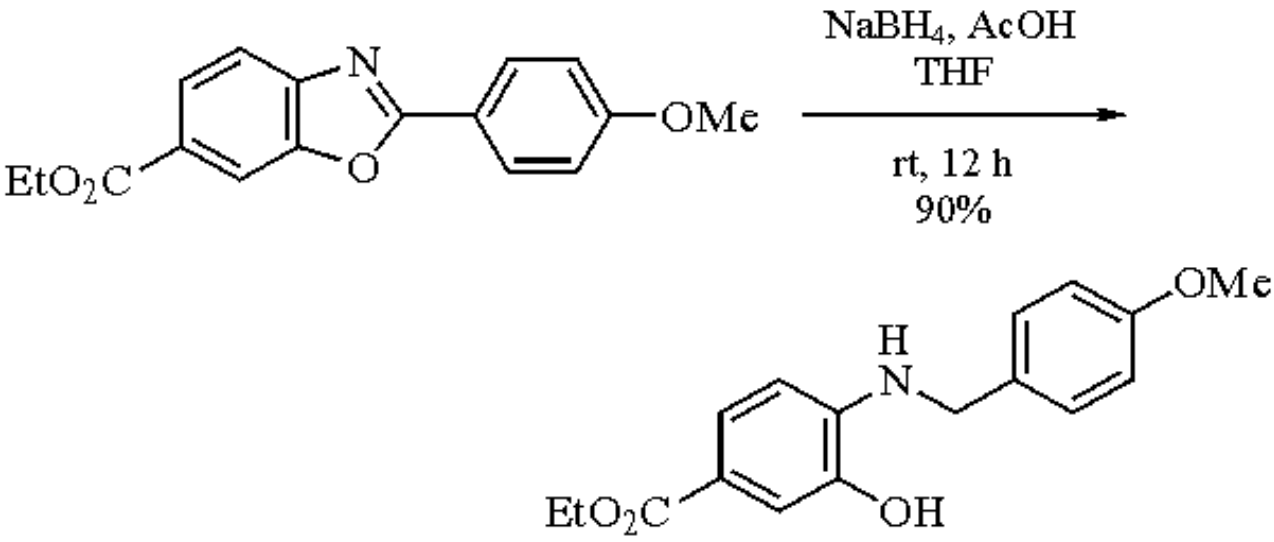

(27)

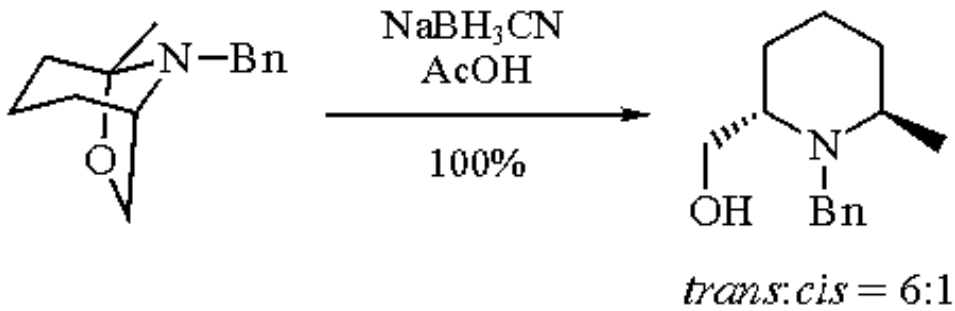

(28)

trans:*cis* = 6:1

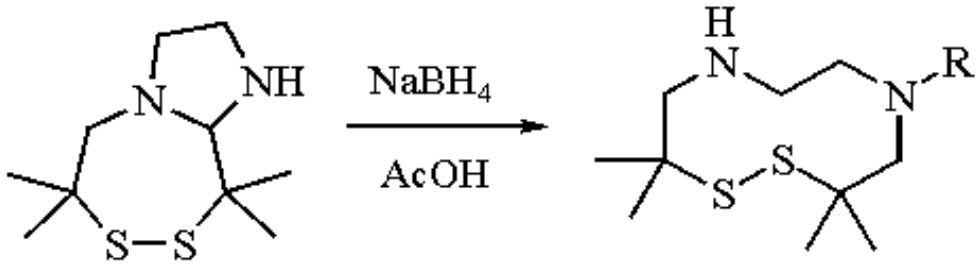

(29)

R = H, 61%; Et, 34%

Reduction of Oximes.

Oximes can be alkylated or reduced, depending on whether $NaBH_4$ or $NaBH_3CN$ is employed, to give hydroxylamines[1,52] (eqs 30 and 31).[52,53] Oxime ethers are also reduced under these conditions,[1,54] and the hydroxy-directed reduction of oxime ethers has been reported using $Me_4NBH(OAc)_3$.[55] Nitriles are converted into primary amines by the tandem action of acyloxyborohydrides and alkyllithium reagents (eq 32).[56]

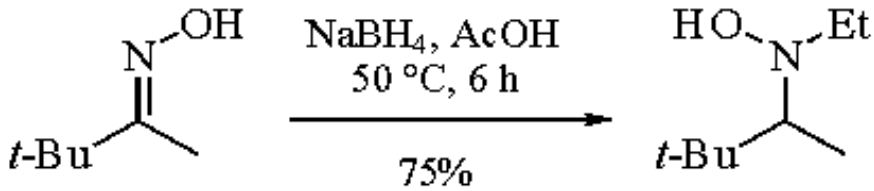

(30)

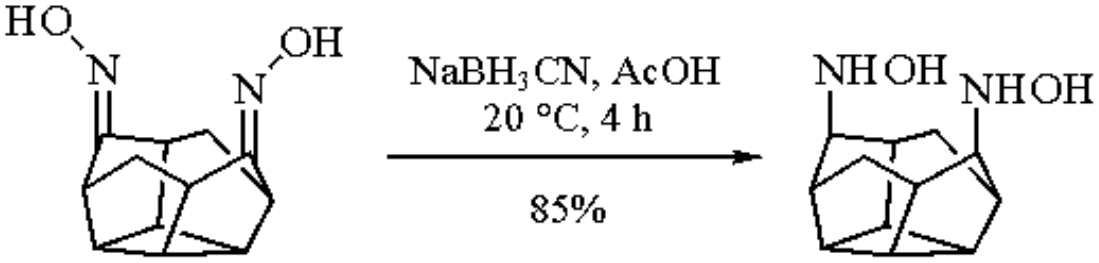

(31)

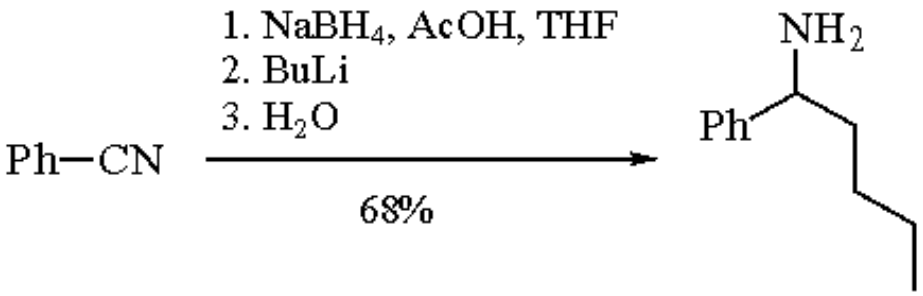

(32)

Hydroboration of Alkenes.

The second reported reaction of acyloxyborohydrides was the hydroboration of alkenes,[1,57] and this reaction has been further refined.[58] In a similar vein, the reduction of organomercurials by $NaBH(OAc)_3$ has been described.[59]

Related Reagents.

Sodium Borohydride; ***Sodium Cyanoborohydride***; ***Sodium Trifluoroacetoxyborohydride***; ***Sodium Tris(trifluoroacetoxy)borohydride***; ***Tetramethylammonium Triacetoxyborohydride***.

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Sodium Trichloroacetate

$Cl_3C\text{-}CO_2Na$

[650-51-1] · $C_2Cl_3NaO_2$ · Sodium Trichloroacetate · (MW 185.36)

(generation of the trichloromethyl anion and dichlorocarbene)

Physical Data: mp >300 °C.

Solubility: sol DME, diglyme.

Preparative Method: a methanol solution of ***Trichloroacetic Acid*** is neutralized with freshly prepared ***Sodium Methoxide*** to the phenolphthalein end point while keeping the temperature below 20 °C. The methanol is removed on the rotary evaporator at 20 °C. The salt is then dried in a vacuum oven at 50 °C for 20 h. The yield is nearly quantitative.[1]

Handling, Storage, and Precautions: is an irritant and is hygroscopic.

Cyclopropanations.

It was discovered that dichlorocarbene could be generated under essentially neutral conditions by heating a solution of sodium trichloroacetate. If this was done in the presence of an alkene, the corresponding dichlorocyclopropane was obtained (eqs 1 and 2). Cyclohexene and cycloheptatriene yielded the cyclopropyl derivatives in 65% and 47% yield, respectively.[2]

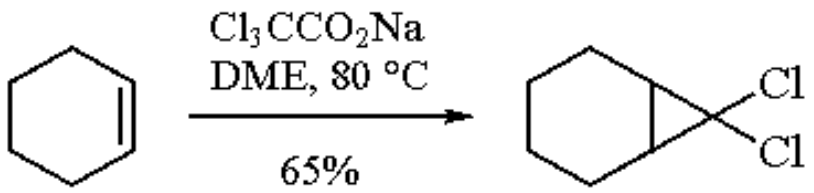

(1)

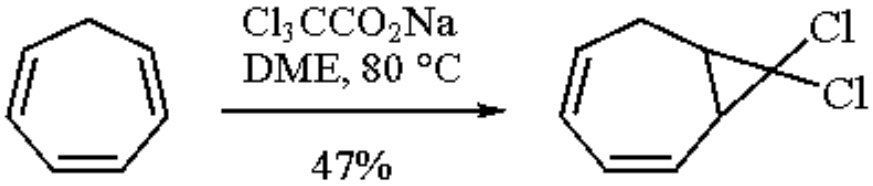

(2)

This was found to be the preferred method for the cyclopropanation of ***Trichloroethylene*** (eq 3). Although the yield was modest (22%), this was counterbalanced by the overall simplicity of the method.[3] This yield was later improved to 47% by reducing the amount of ***1,1-Dimethoxyethane*** (DME) used in the reaction by one half. The reduction in the amount of DME slowed the decomposition of the salt and cut down on the byproducts produced from the reaction of DME with dichlorocarbene. Hundreds of grams of the cyclopropane can be prepared in this way.[4]

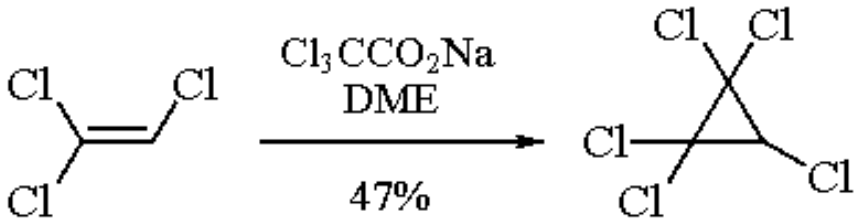

(3)

Another modification in the way the reaction can be run is to use a combination of tetrachloroethylene, which is very unreactive,[5] and DME. By using a 10:2.5 ratio of tetrachloroethylene:DME, the entire amount of the salt could be added at the start rather than in portions. In this solvent mixture, only a portion of the salt dissolves. This helps control the rate of CO_2 evolution and hence the rate of carbene formation. Under these conditions, the yield of the *cis*-biscyclopropyl derivative of 1,5-cyclooctadiene (eq 4) rose to 62%. A small amount of the *trans*-bis-adduct was also formed, but was easily removed by recrystallization. If the solvent was tetrachloroethylene alone, none of the desired product was formed.[6]

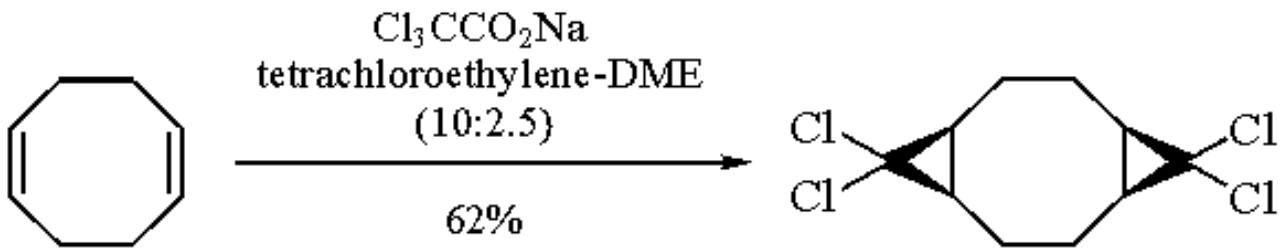

(4)

Allene reacts with dichlorocarbene generated from the salt to afford the methylenecyclopropane derivative (eq 5).[7]

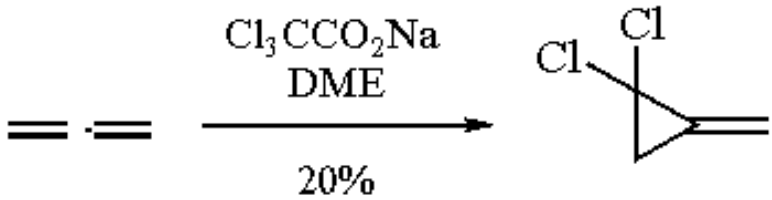

(5)

In an attempted cyclopropanation of ***Bis(trimethylsilyl)acetylene*** with sodium trichloroacetate (eq 6), the cyclobutenone was produced instead of the cyclopropane. The reaction with ***Phenyl(trichloromethyl)mercury*** resulted in ill-defined material.[8]

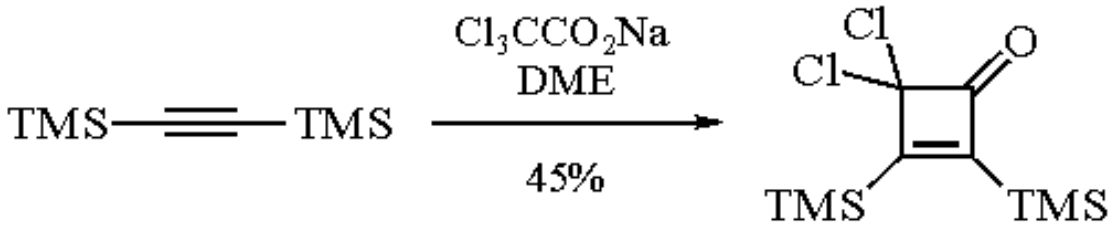

(6)

An effort to prepare diaziridines from azodicarboxylates and dichlorocarbene was thwarted by a rearrangement. The reaction of ***Diethyl Azodicarboxylate*** with sodium trichloroacetate in refluxing DME (eq 7) produced the rearranged compound in 69% yield. The same reaction with $PhHgCCl_2Br$ as the carbene precursor provided the same compound in 87% yield.[9]

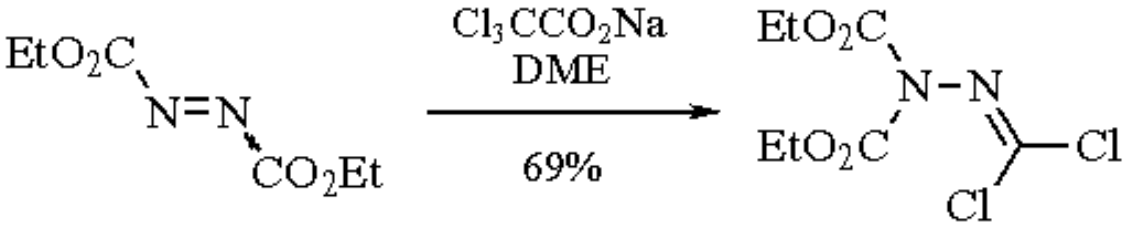

(7)

The use of phase transfer conditions can provide an effective set of reaction conditions in some cyclopropanation reactions, with tetraheptylammonium bromide and Aliquat® 336 being the most effective.[10] In addition, crown ethers were found to accelerate the loss of CO_2, but at the same time result in somewhat lower yields.[11]

Insertion Reactions.

Dichlorocarbene has been shown to be capable of inserting into a C-H bond of alkyl-substituted aromatics. Thus the reaction of cumene with sodium trichloroacetate (eq 8) in refluxing DME resulted in a 33% yield of β,β-dichloro-*t*-butylbenzene. Only a 0.5% yield of insertion product was obtained if the dichlorocarbene was formed using ***Chloroform*/*Potassium t-Butoxide***.[12] Prior to this, halocarbenes were not known to attack C-H bonds.

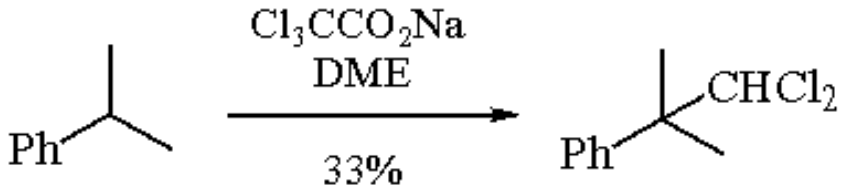

(8)

The insertion into Si-H is also possible. Treatment of ***Triethylsilane*** with sodium trichloroacetate affords the dichloromethylsilane (eq 9) in 32% yield.[13] The insertion of dichlorocarbene into the Si-H bond occurs with retention of configuration at silicon. The reaction of (+)-α-naphthylphenylmethylsilane (eq 10) with sodium trichloroacetate in the presence of ***18-Crown-6*** produces (+)-α-naphthylphenylmethyldichloromethylsilane in 70% yield.[14]

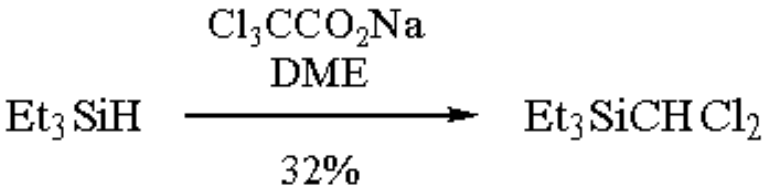

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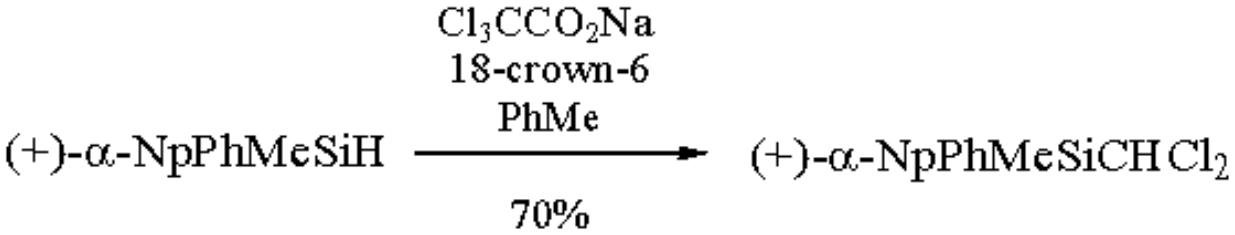

(10)

Trichloromethyl Anion.

The reaction of the tricyclic anhydride with sodium trichloroacetate did not result in any dichlorocyclopropane formation. Instead, the product from the addition of the trichloromethyl anion to the anhydride was produced (eq 11).[1] The reaction of aldehydes (eq 12) and acid chlorides (eq 13) under these conditions also affords products resulting from the reaction of the trichloromethyl anion.[15] The yields for these later two processes were not as good as for the reaction with the anhydride. The presence of the anhydride was found to accelerate the decomposition of the salt.

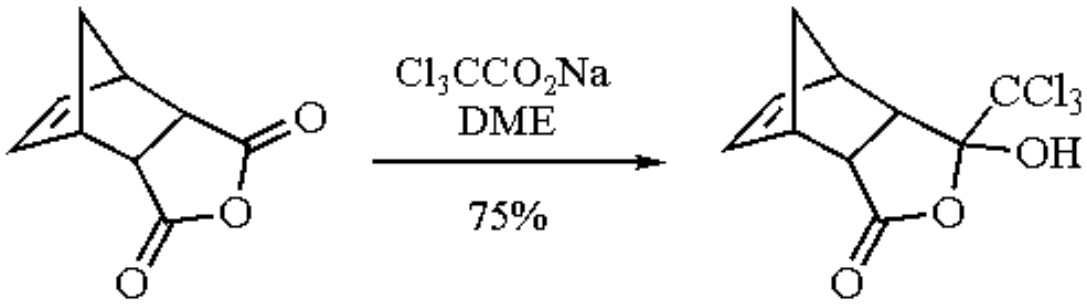

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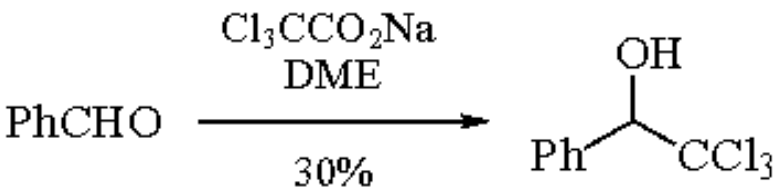

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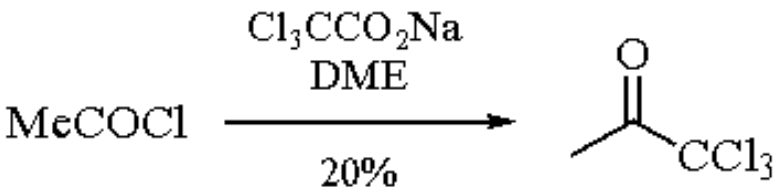

(13)

Miscellaneous.

Sodium trichloroacetate has been employed in the syntheses of trimethylsilyl trichloroacetate[16] and *t*-butyldimethylsilyl trichloroacetate.[17] The trimethylsilyl derivative was prepared from the salt and the silyl chloride in 83% yield in benzene using 18-crown-6 as the catalyst (eq 14). The *t*-butyldimethylsilyl compound was formed in 83% yield in an uncatalyzed reaction between the salt and the silyl chloride in THF (eq 15). These two reagents have found use for the introduction of silyl-protecting groups.[17,18] The trimethylsilyl trichloroacetate has also found application in a simple procedure for the preparation of Mosher's acid.[16]

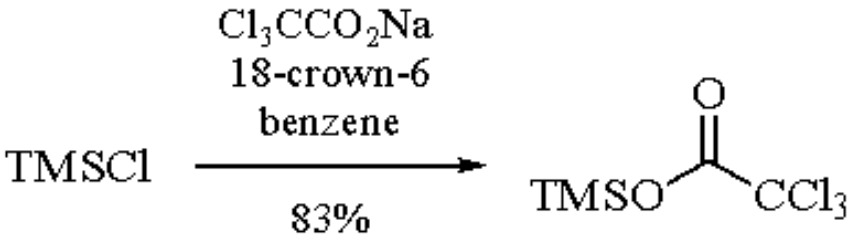

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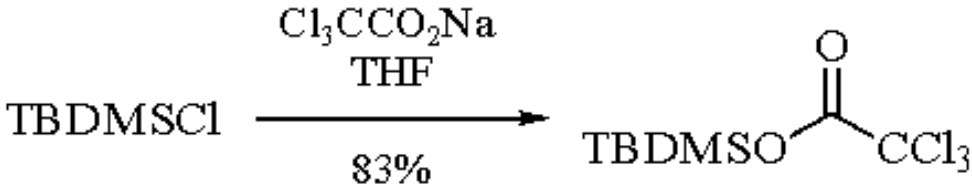

(15)

Dichlorocarbene has been found to mediate carbon-carbon bond formation in the coupling of benzazoles to bis-benzazoles. The yields of the bis-benzazoles were identical using either the sodium trichloroacetate method (eq 16) or the ***Chloroform***/***Sodium Hydroxide***/phase transfer method to generate dichlorocarbene.[19]

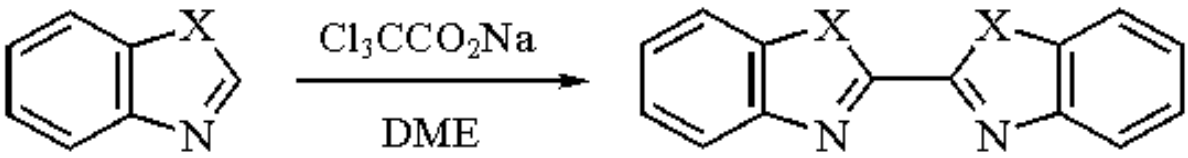

(16)

X = NMe, 30%; S, 60%; O, 24%

In a ring-expansion route for the preparation of [6](2,4)pyridinophanes, the bicyclic pyrrole was heated with sodium trichloroacetate in DME (eq 17) to provide the pyridinophane in 28% yield. An analogous reaction with phenyl(bromodichloromethyl)mercury as the source of dichlorocarbene produced the same compound but only in 20% yield.[20]

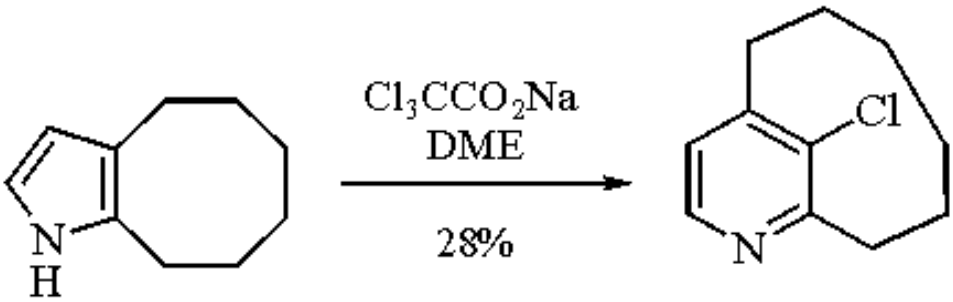

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Sodium Triethylborohydride-Iron(II) Chloride

$NaEt_3BH$-$FeCl_2$

($NaEt_3BH$)

[17979-81-6] · $C_6H_{16}BNa$ · Sodium Triethylborohydride-Iron(II) Chloride · (MW 122.02) ($FeCl_2$)

[7758-94-3] · Cl_2Fe · Sodium Triethylborohydride-Iron(II) Chloride · (MW 126.75)

(reducing agent for thiols;[1] can dimerize diaryl thioketones[2])

Form Supplied in: ***Iron(II) Chloride*** is supplied in anhydrous form as a white powder. Sodium triethylborohydride is available as a 1 M solution in diethyl ether, THF, or toluene.

Desulfurization.

Thiols may be desulfurized to their parent hydrocarbons by the action of a mixture of $FeCl_2$ and $NaEt_3BH$ (eq 1). Normally, a solution of the thiol (1.5 mmol) in THF (2-3 mL) is added to anhydrous $FeCl_2$ (3.0 mmol) in THF (2 mL). THF (8 mL) is added, and after stirring for a short time period, the solution is added to a 1 M solution of $NaEt_3BH$ (6 mmol) in THF at -78 °C. An option exists where the $NaEt_3BH$ mixed with ***Alumina*** allows room temperature reactions and a more convenient reaction workup,[2] but results in some cases in increased amounts of dimerization side products.

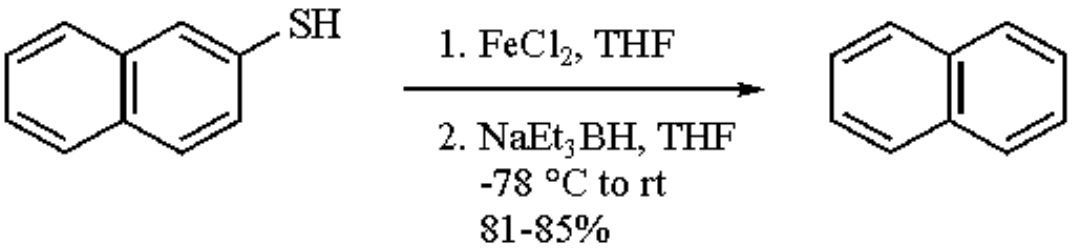

(1)

Dimerization of Diaryl Thioketones.

Diaryl thioketones undergo dimerization to tetraarylalkenes by $NaEt_3BH$-$FeCl_2$ on alumina (eq 2).[2] These heterogeneous conditions give results superior to the homogeneous ones, where a significant amount of reduction to the diarylalkane competes with the desired reaction.

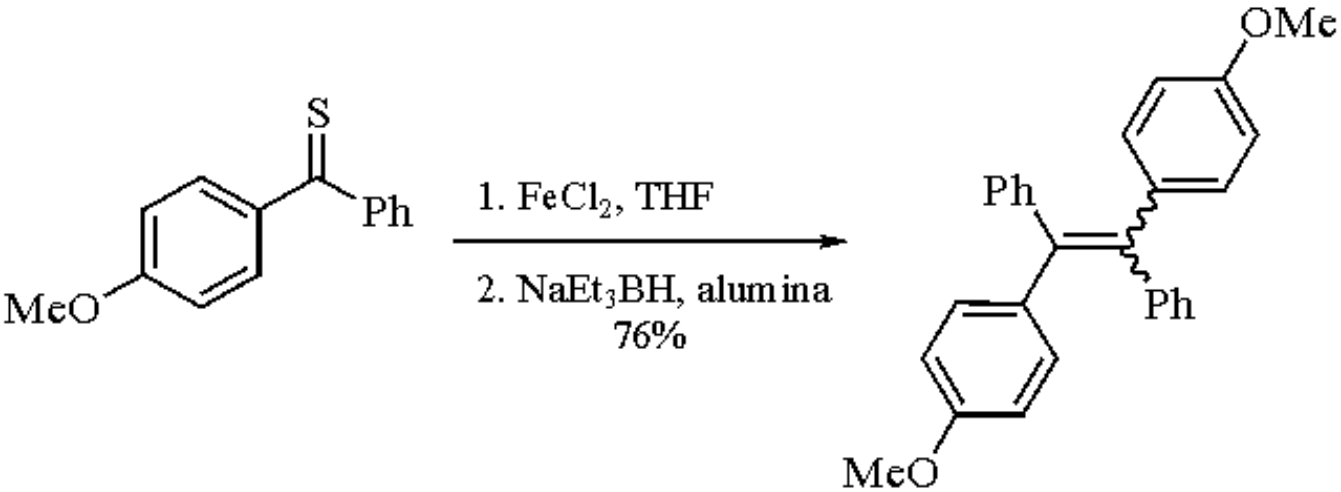

(2)

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Sodium Trifluoroacetoxyborohydride[1]

$NaBH_3OCOCF_3$

[61666-40-8] · $C_2H_3BF_3NaO_2$ · Sodium Trifluoroacetoxyborohydride · (MW 149.85)

(a very selective reducing agent for the reduction of nitriles and amides to amines;[1] may serve as a source of trifluoroacetaldehyde or its equivalent[2])

Solubility: the reagent is rapidly destroyed by H_2O and protic solvents; H_2 is liberated. Common cosolvents for the reactions of this reagent are CH_2Cl_2, THF, toluene, and Et_2O.

Form Supplied in: not commercially available.

Preparative Methods: normally prepared in situ by the reaction of the appropriate amount of ***Trifluoroacetic Acid*** with ***Sodium Borohydride***.[1]

Analysis of Reagent Purity: has not been characterized.

Handling, Storage, and Precautions: the preparation of and all reactions involving this reagent should be conducted under an inert atmosphere because H_2 may be liberated; this is particularly true when $NaBH_4$ powder is used.

Functional Group Reductions.

The combination of strong acid and hydride donor yields a unique and powerful reagent for the reduction of nitriles and amides to amines. The related though less reactive ***Sodium Tris(trifluoroacetoxy)borohydride*** effects the deoxygenation of benzylic alcohols and aryl ketones, the reduction of imines, enamines, oximes, and related double bonds, and the reduction of heterocycles (indoles, pyrroles, and some π-deficient heterocyclic systems). In some of these examples the active reagent may be $NaBH_3OCOCF_3$.

Whereas nitriles and amides are unaffected by $NaBH(OCOCF_3)_3$ ($NaBH_4$ in excess CF_3CO_2H), the action of $NaBH_3OCOCF_3$ on these functional groups leads to amines[3] (eqs 1-7).[4-10] Noteworthy is the survival of the 1,2-oxazine carbamate (eq 3),[6] the diaryl ketone (eq 4),[7] the Boc protecting groups (eq 5),[8] and the diaryl carbinol (eq 7).[10] Thus $NaBH(OCOCF_3)_3$ (in CF_3CO_2H) reduces diaryl carbinols but not amides, while $NaBH_3OCOCF_3$ reduces amides but not diaryl carbinols!

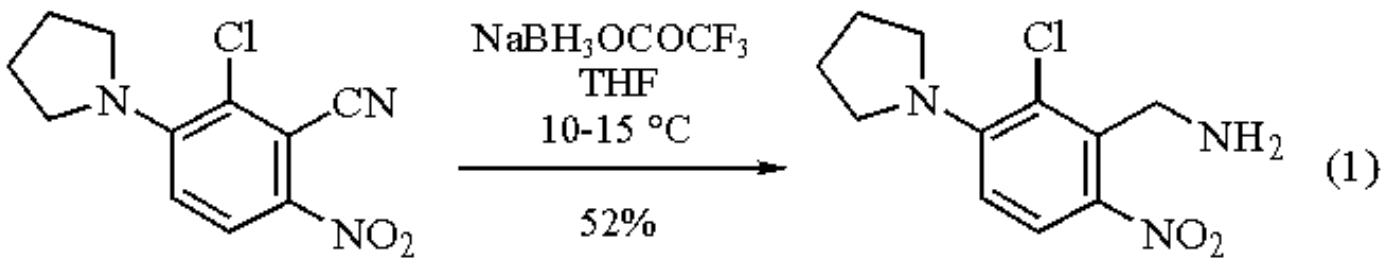

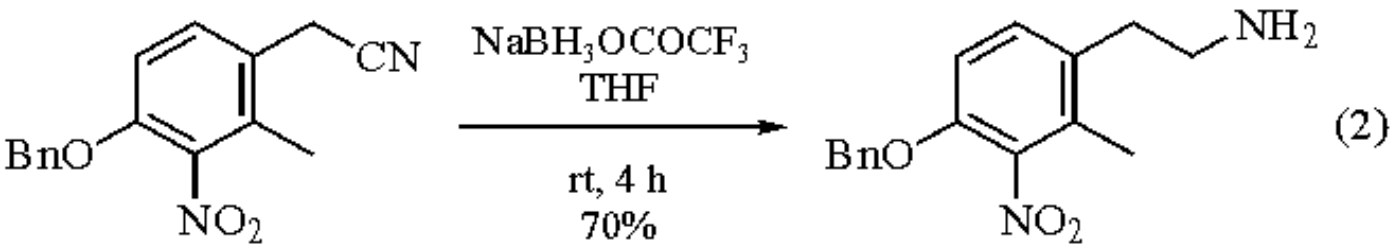

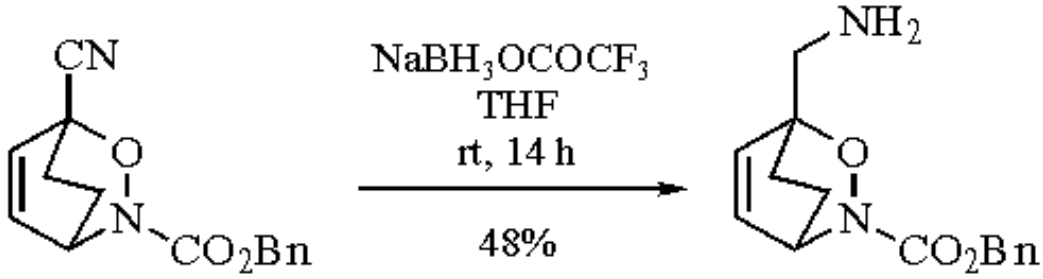

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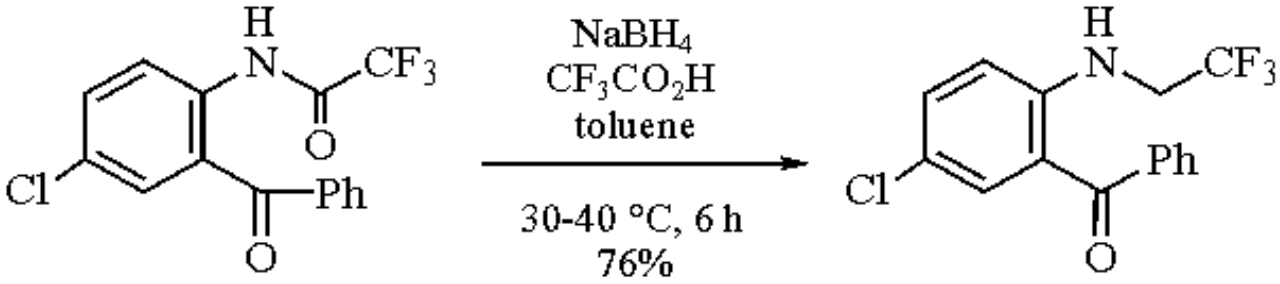

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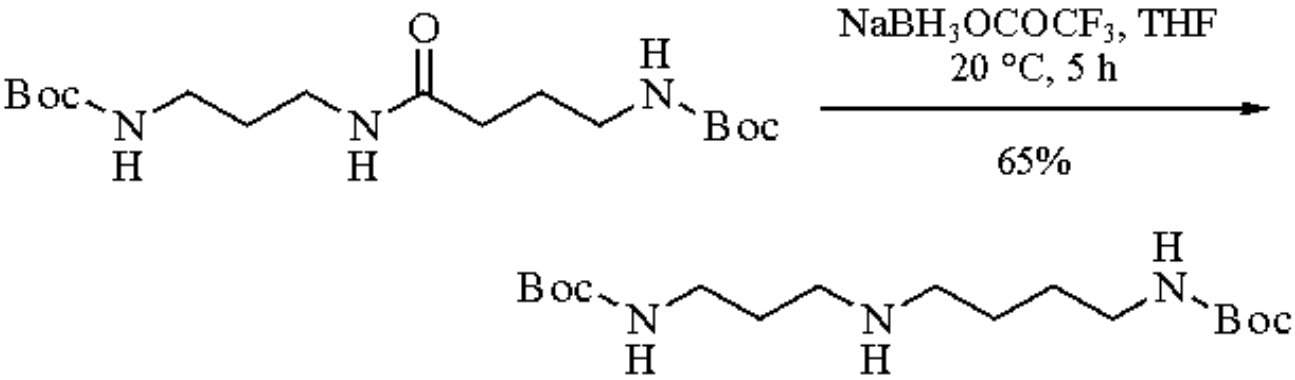

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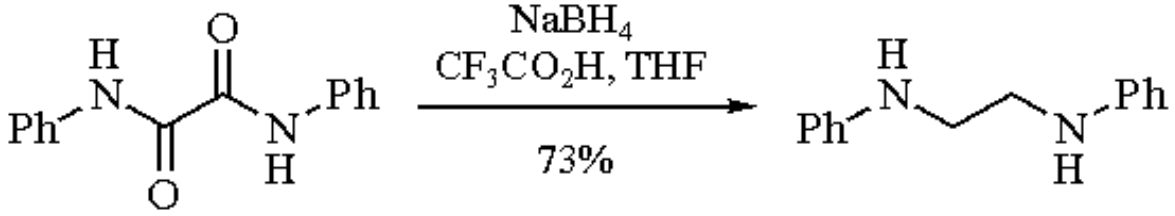

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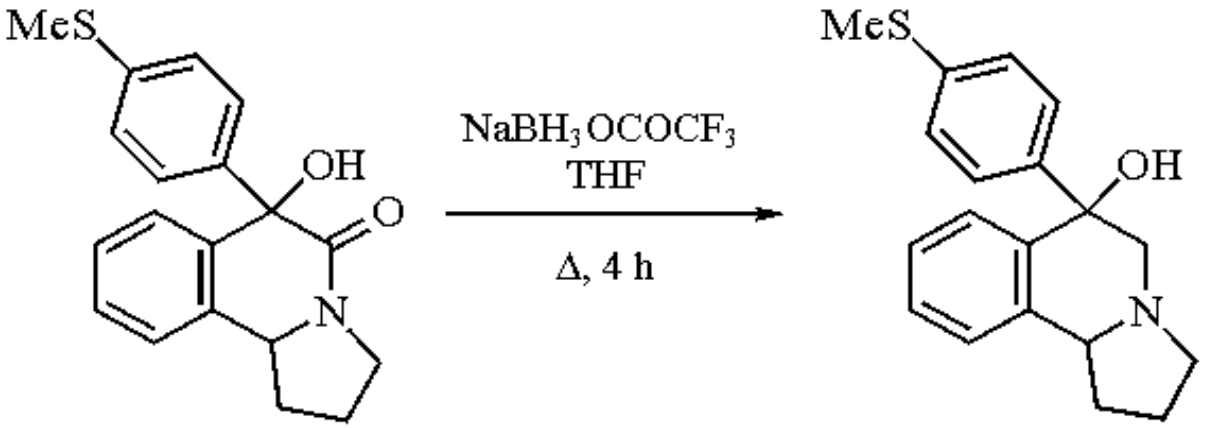

(7)

Carboxylic acids can be reduced to primary alcohols with $NaBH_3OCOCF_3$.[11]

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Sodium Trimethoxyborohydride[1]

$NaBH(OMe)_3$

[16940-17-3] · $C_3H_{10}BNaO_3$ · Sodium Trimethoxyborohydride · (MW 127.93)

(reducing agent for various functional groups;[1,2] dehalogenates vicinal dihalides;[3] assists in coupling of electron-deficient alkenes with organomercurials[4])

Alternate Name: sodium hydrotrimethoxyborate

Physical Data: mp 230 °C (disproportionates).

Solubility: sol isopropylamine, pyridine, morpholine, dioxane, diglyme, and THF,[5] as well as HMPA[2c,d] and methylene chloride.[2c-e] However, it disproportionates rapidly in diglyme to $NaBH_4$ (soln) and $NaB(OMe)_4$ (ppt) or in THF to $NaBH_4$ (ppt) and $NaB(OMe)_4$ (soln).[6] Also, methanol reacts with $NaBH_4$ in THF only to a limited extent, with initially formed methoxyborohydrides disproportionating rapidly to $NaBH_4$ and $NaB(OMe)_4$ and contributing to solubilization of the otherwise insoluble $NaBH_4$.[7] Thus, disproportionation products may account for some reductions attributed to $NaBH(OMe)_3$.

Form Supplied in: white solid.

Preparative Methods: reaction of suitably active ***Sodium Hydride*** with ***Trimethyl Borate*** at reflux;[8] addition of $(MeO)_3B$ to a suspension of NaH in refluxing THF.[2a]

Handling, Storage, and Precautions: the solid material is stable in dry air. It reacts rapidly with strong acids and slowly with water and some alcohols. It is considered relatively safe.

Functional Group Reductions.

The reagent reduces various functional groups.[2a] With diethyl ether as solvent, aldehydes, ketones, acid chlorides, and acid anhydrides are readily reduced to alcohols at 35 °C. Esters and nitriles are more slowly reduced, even at 100-140 °C (dibutyl ether solvent). Carboxylic acids and carboxylates are not affected and nor are alkenes, even those in conjugation with carbonyl groups. The nitro group undergoes reaction at 140 °C but the nature of the product was not investigated. An acyl chloride may be reduced to an aldehyde selectively at -80 °C.[2b]

In HMPA at 70 °C, reductive displacement of halides and sulfonates occurs (***Sodium Borohydride*** gives better results in most cases).[2c,d] Quantum yields in photodechlorination of chlorotoluenes are enhanced by $NaBH(OMe)_3$ or $NaBH_4$.[2e] Birch-type reduction occurs on reaction with cation radicals generated by photoelectron transfer between aromatic hydrocarbons and electron acceptors.[2f]

Selective Reductions.

Conjugated nitroalkenes are reduced to the corresponding nitroalkanes, with accompanying addition of the original reduction products to the parent nitroalkenes to form salts of the corresponding 1,3-dinitroalkanes (eq 1).[9] In most cases, comparable results are obtained with ***Lithium Borohydride***, $NaBH_4$, and ***Lithium Aluminum Hydride***.

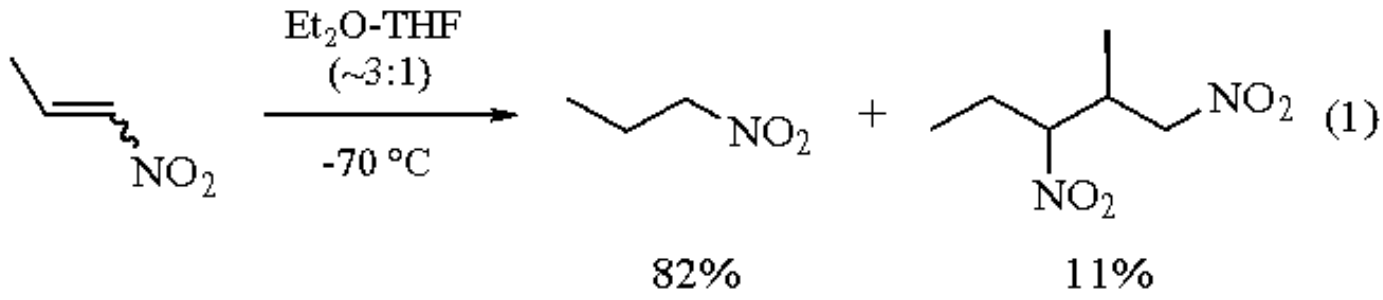

One of two ester functions is reduced selectively (eq 2), since relative rates are primary > secondary > tertiary.[10] Ketones are reduced selectively in the presence of conjugated enones, as demonstrated for conversion of androst-4-ene-3,17-dione to testosterone (eq 3).[11]

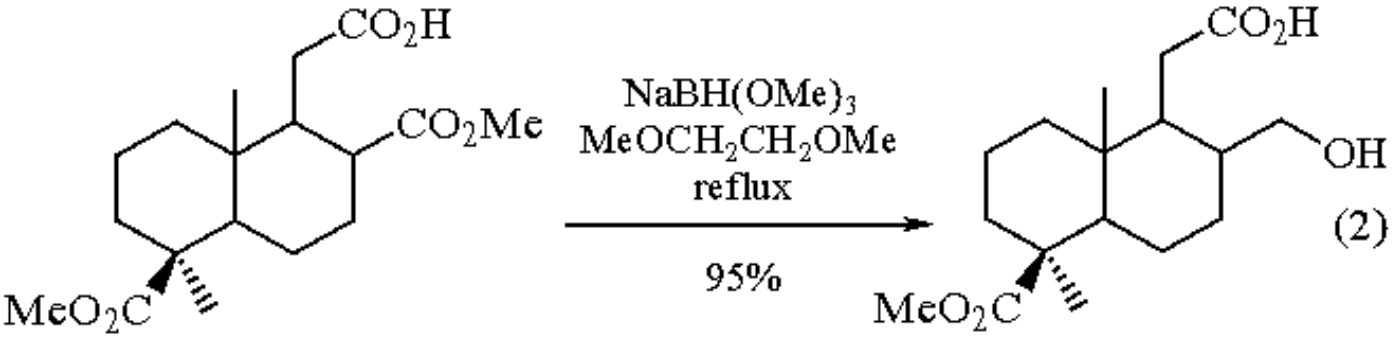

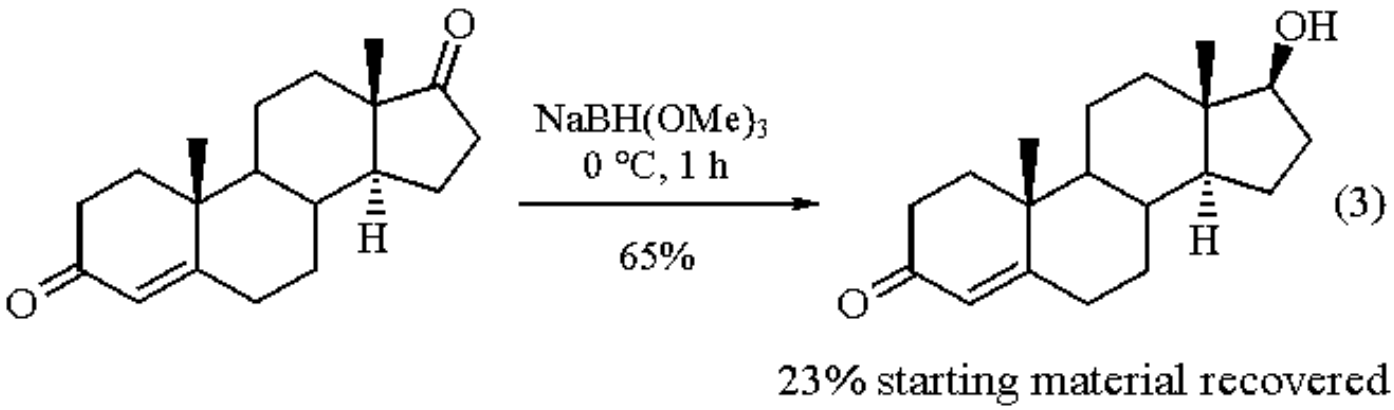

Iodide is displaced selectively in the presence of chloride for some 1-chloro-2-iodoperfluorocycloalkenes (eq 4).[12] Even in the most reactive case (n = 1, yield 72%) there is unreacted starting material, and yields diminish with increasing n.

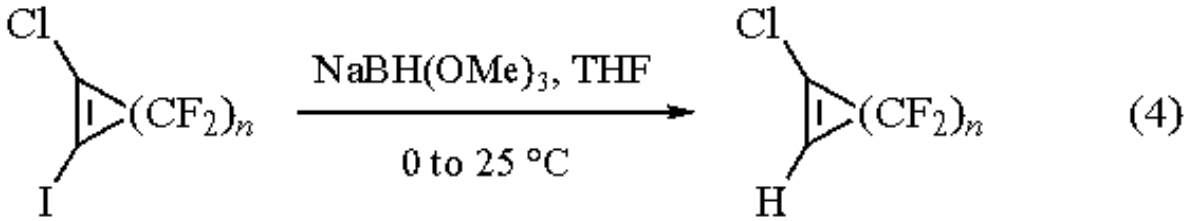

Stereoselective Reductions.

Stereoselectivity is reported in the reduction of some ketones.[13] An example for which in situ formation of $NaBH(OMe)_3$ is postulated[13d] may involve disproportionation.[7] Better selectivity is usually obtained using other hydrides, most of which also are not prone to disproportionation. In stereoselective demercuration, superior results are obtained with $NaBH_4$.[14]

Dehalogenation of Vicinal Dihalides.

While this is not a highly useful synthetic reaction, it is noted that $NaBH(OMe)_3$ gives good results in some cases.[3] For example, 5α,6β-dibromocholestan-3β-ol is converted to cholesterol (diglyme, 24 h, 25 °C, 80%).

Coupling of Alkylmercury(II) Salts with Electron-Deficient Alkenes.

Methoxyalkylmercury(II) chlorides, generated from the corresponding alkenes or cyclopropanes, add to various electron-deficient alkenes in the presence of $NaBH(OMe)_3$ (eqs 5 and 6).[4a,b]

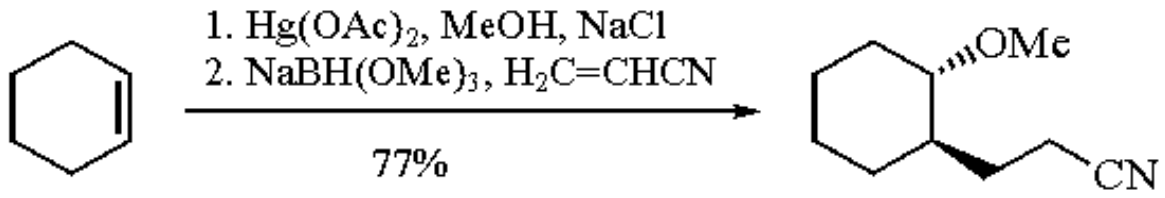

(5)

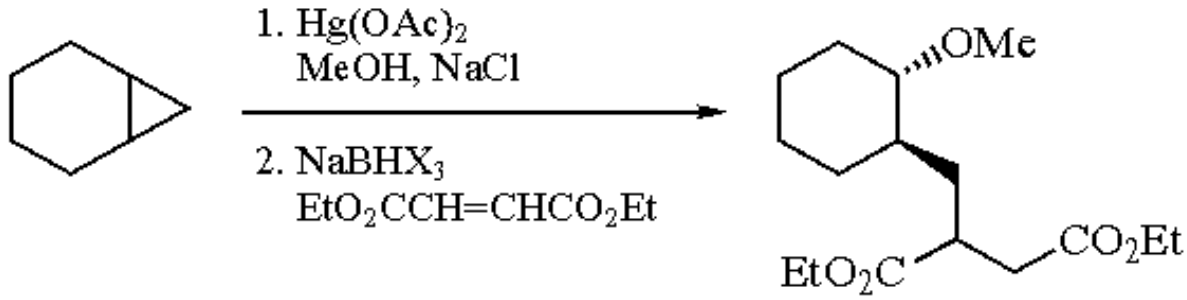

(6)

X = OMe, 76%
X = H, 80%

Yields are improved for coupling with acrylates if a 1:1 ***Mercury(II) Oxide-Mercury(II) Acetate*** mixture is used for mercuration, with the entire sequence carried out in a single flask.[4c,d] The electron-rich alkene may contain a nucleophilic neighboring group (eq 7).[4d] Enones containing isolated double bonds are converted to mercurial enones, which may then undergo reductive cyclization (eq 8).[4e]

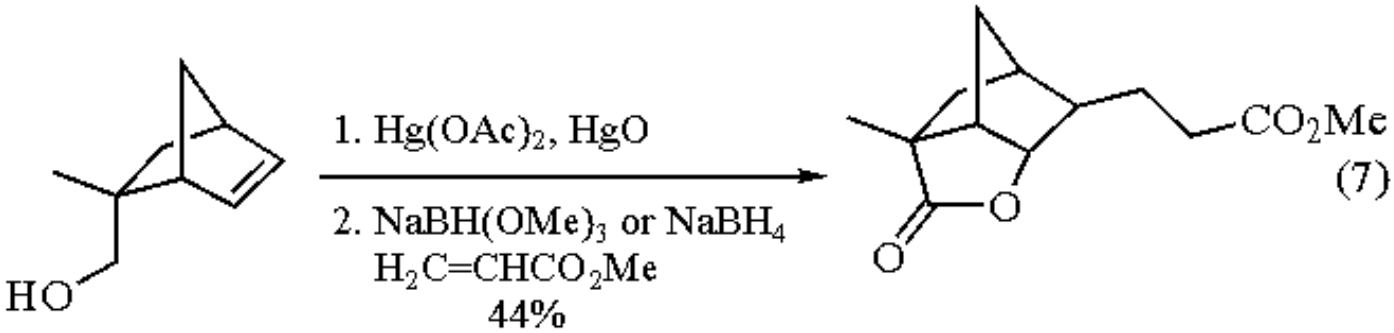

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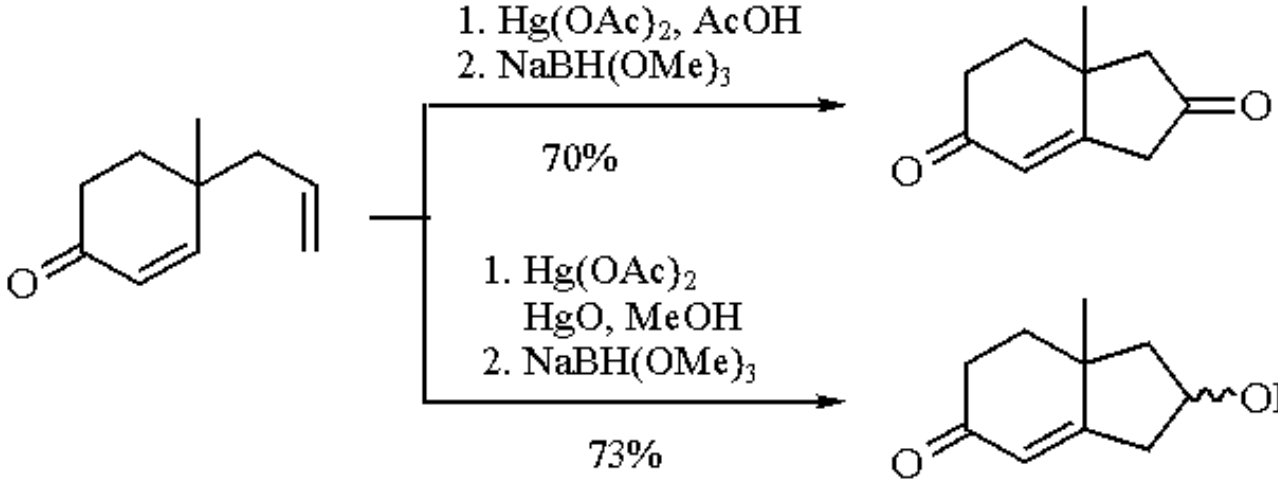

(8)

Related Reagents.

Lithium Borohydride; ***Lithium Tri-t-butoxyaluminum Hydride***; ***Mercury(II) Acetate-Sodium Trimethoxyborohydride***; ***Sodium Borohydride***.

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Sodium Tris(trifluoroacetoxy)borohydride[1]

$NaBH(OCOCF_3)_3$

[76791-24-7] · $C_6HBF_9NaO_6$ · Sodium Tris(trifluoroacetoxy)borohydride · (MW 373.87)

(a reducing agent for many different functional groups and heterocycles;[1] can serve as a source of trifluoroacetaldehyde or its equivalent;[2] is similar to other ionic hydrogenation methods in the facile reduction of benzylic systems[3])

Physical Data: mp 64-66 °C.[4]

Solubility: is rapidly destroyed by H_2O and protic solvents; H_2 is liberated. Common cosolvents for the reactions of this reagent are CH_2Cl_2, THF, toluene, and Et_2O.

Form Supplied in: not commercially available.

Preparative Methods: normally prepared in situ by the reaction of excess ***Trifluoroacetic Acid*** with ***Sodium Borohydride***.[1,4]

Analysis of Reagent Purity: has been characterized by elemental analysis and IR.[4]

Handling, Storage, and Precautions: the preparation of and all reactions involving this reagent should be conducted under an inert atmosphere because H_2 may be liberated; this is particularly true when $NaBH_4$ powder is used; $NaBH_4$ pellets are particularly convenient and safe to use for the preparation of $NaBH(OCOCF_3)_3$.

Functional Group Reductions.

The combination of strong acid and hydride donor provides a unique and powerful reagent for the deoxygenation of benzylic alcohols and aryl ketones, the reduction of imines, enamines, oximes, and related double bonds, and the reduction of heterocycles (indoles, pyrroles, and some π-deficient heterocyclic systems). The deoxygenation of benzylic alcohols via carbocations is limited to diarylcarbinols,[3,5] triarylcarbinols,[3] and a few activated monobenzylic systems (eqs 1-3),[6] but a wide range of functional groups is tolerated by the reaction conditions. Generally, excess CF_3CO_2H is employed and, in these cases, the reducing species is assumed to be $NaBH(OCOCF_3)_3$,[2,3] although in some cases ***Sodium Trifluoroacetoxyborohydride*** may be involved.[5,6] Recent examples abound.[7]

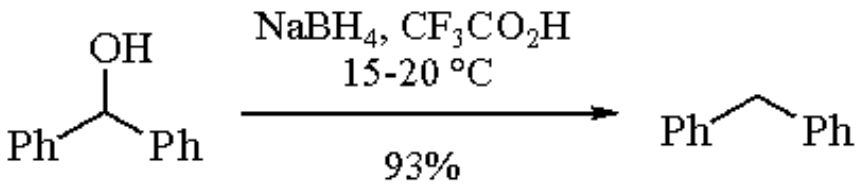

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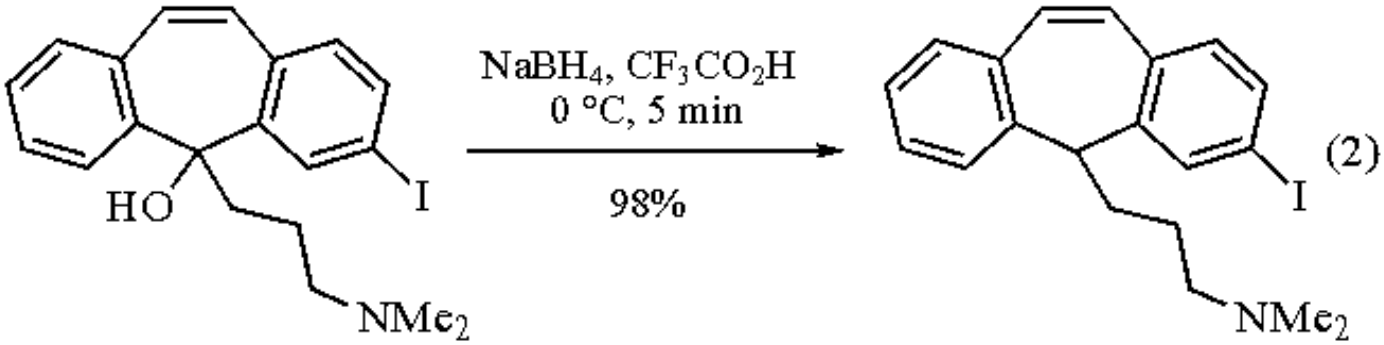

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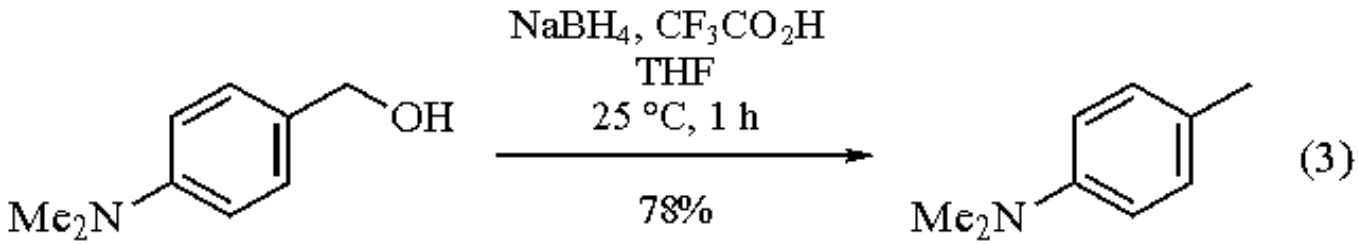

(3)

Diaryl ketones and a few aryl ketones are deoxygenated by $NaBH_4$ in CF_3CO_2H and a wide range of functional groups may be present in the substrate (CO_2Me, CN, NO_2, halogen, CO_2H, CONHPh, NMe_2, OMe).[8] Some examples are shown (eqs 4-8).[9]

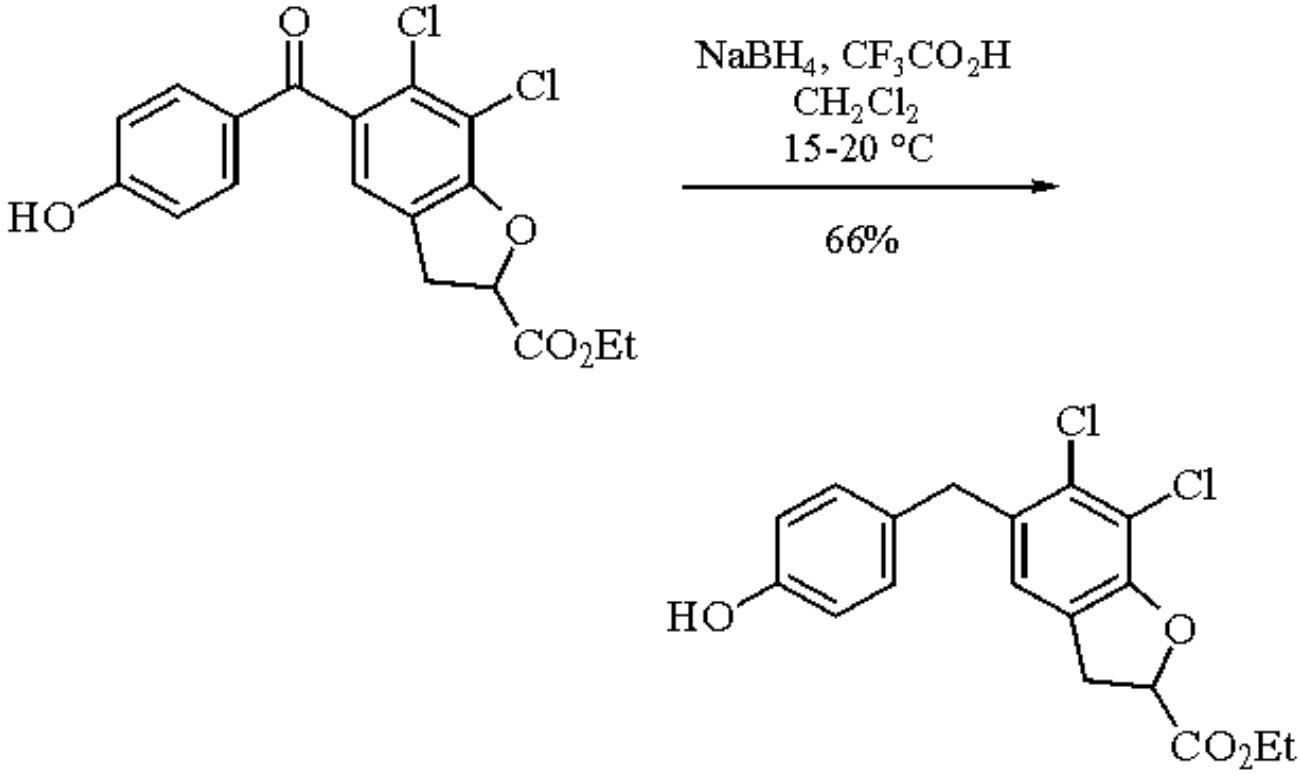

(4)

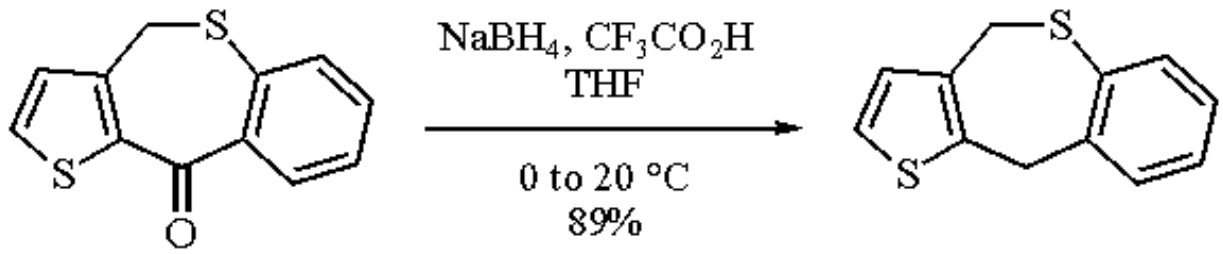

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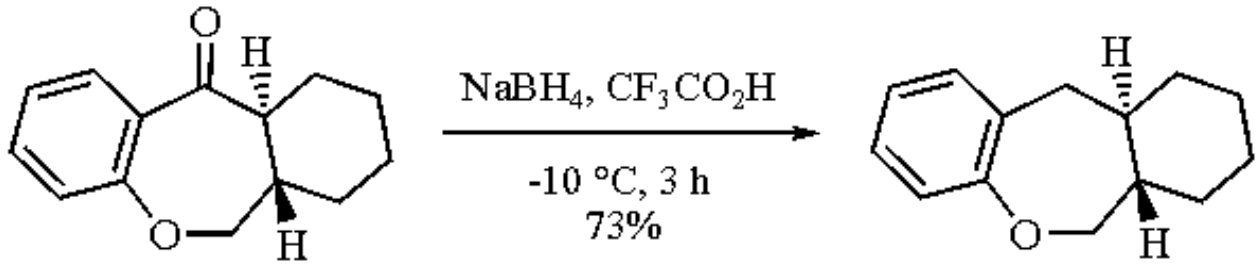

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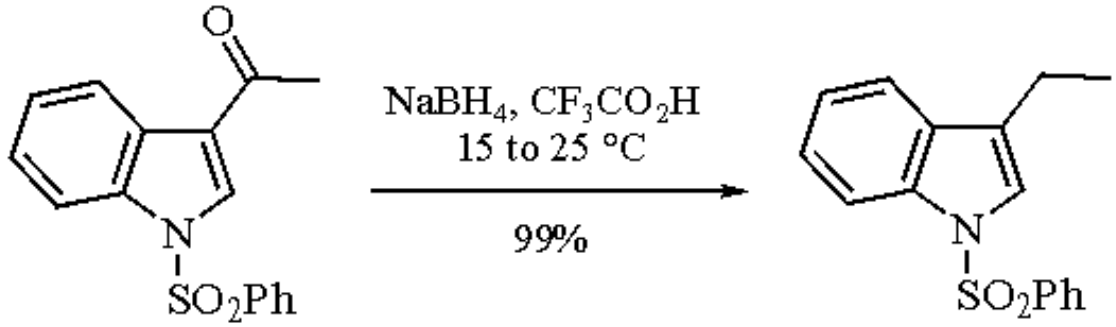

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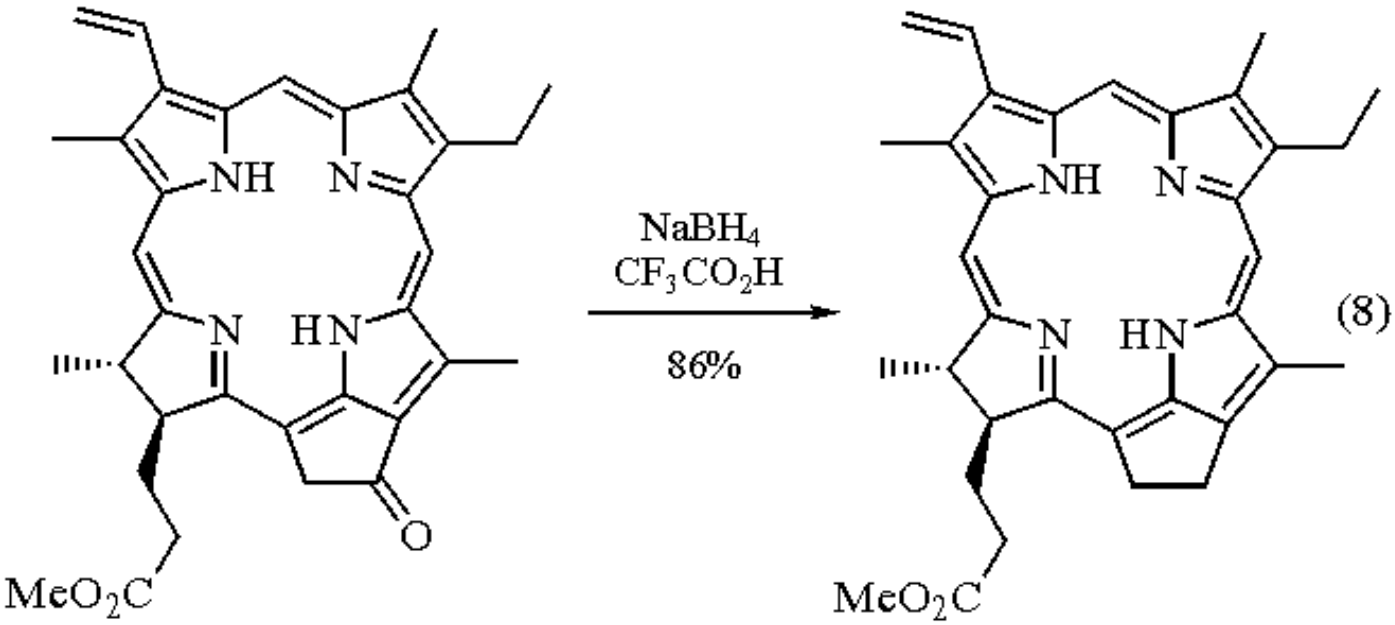

(8)

1,1-Diphenylethylene is reduced to 1,1-diphenylethane in 93% yield,[3] presumably via the carbocation.

Whereas indoles containing a second, basic nitrogen are normally not reduced by ***Sodium Triacetoxyborohydride***, they are reduced by the combination $NaBH_4$ or ***Sodium Cyanoborohydride*** and CF_3CO_2H (eqs 9-11).[10-12]

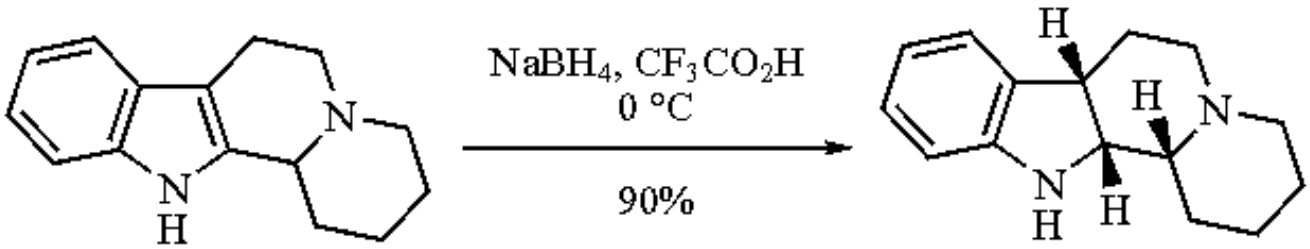

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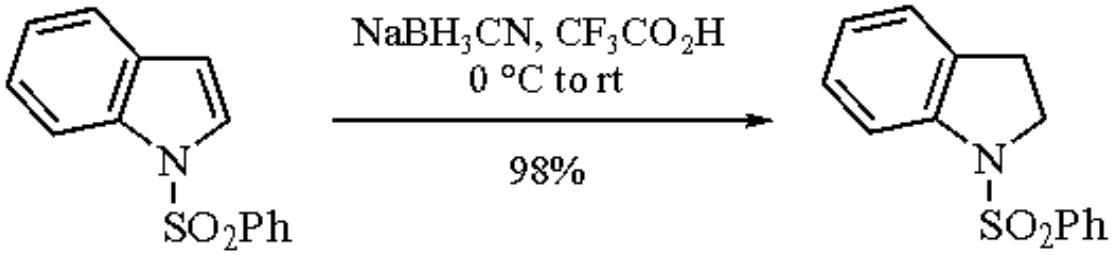

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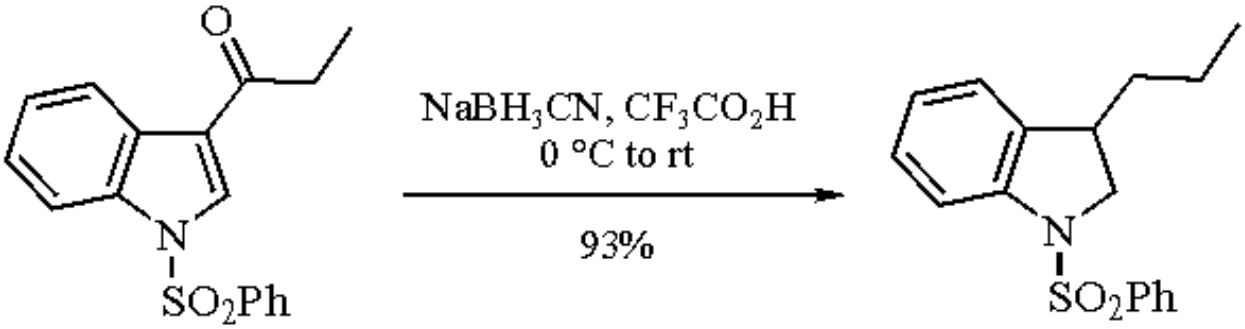

(11)

The combination of $NaBH_3CN$-CF_3CO_2H, which smoothly reduces even deactivated indole rings (eqs 10 and 11),[11] also reduces some pyrroles (eqs 12 and 13).[13]

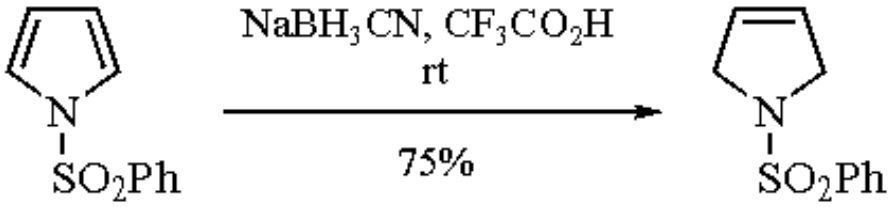

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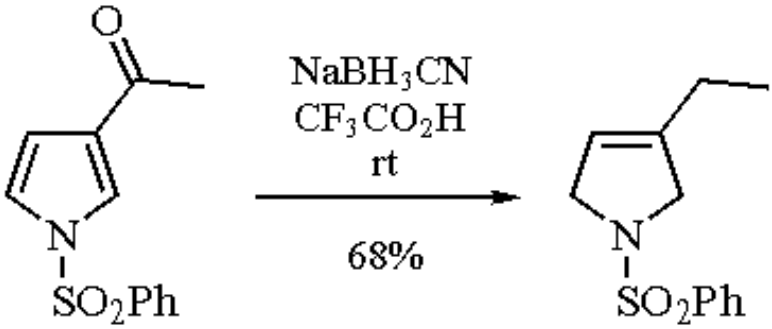

(13)

Benzylic acetals are reductively cleaved with $NaBH_3CN$-CF_3CO_2H[14,15] (eq 14),[15] as are arene 1,4-oxides[16] and ozonides.[17]

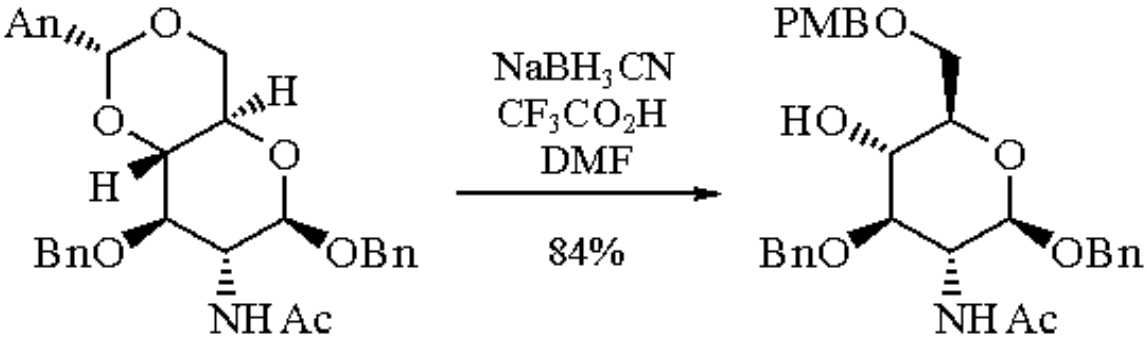

(14)

Iminium ions, whether generated from imines, enamines, or carbinol amines, are readily reduced by $NaBH_4$-CF_3CO_2H (eqs 15-18).[18-21]

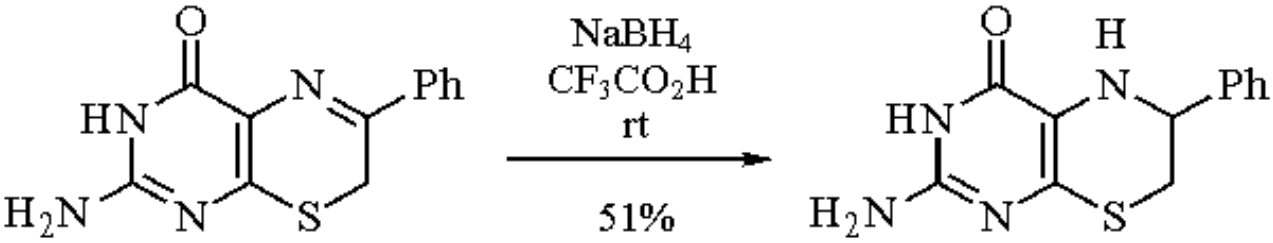

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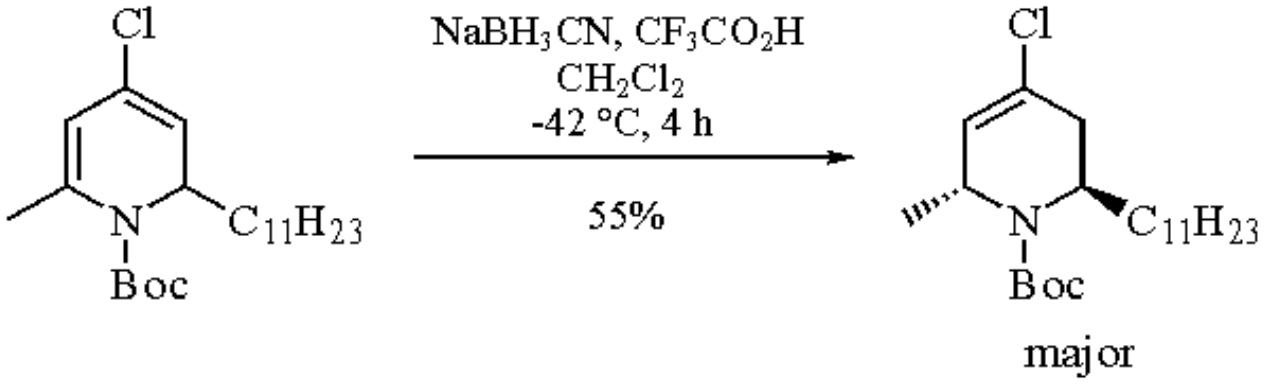

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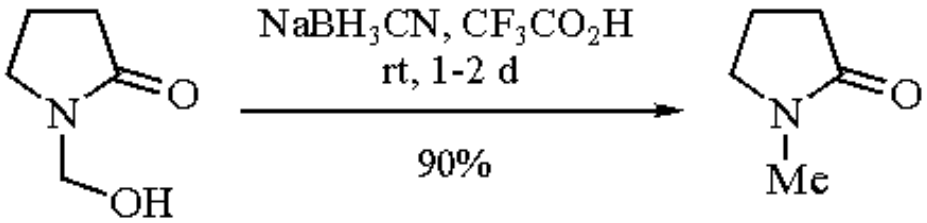

(17)

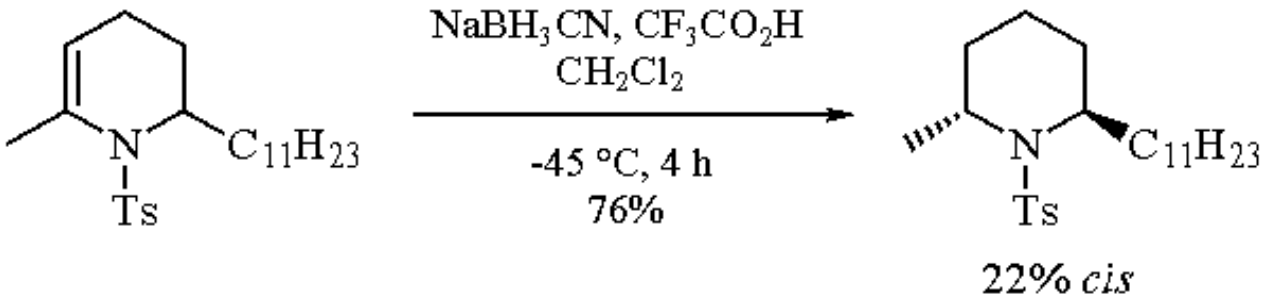

(18)

Oximes are also reduced to amines (eqs 19 and 20).[22-24]

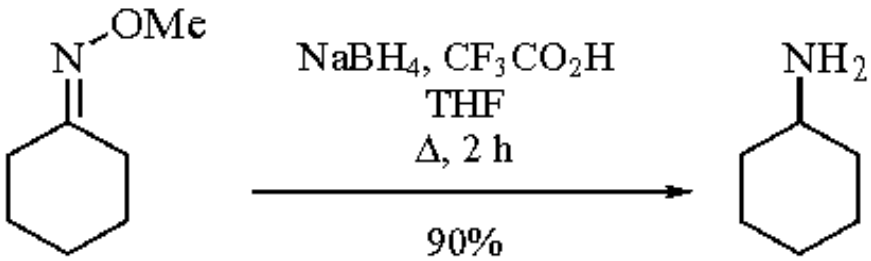

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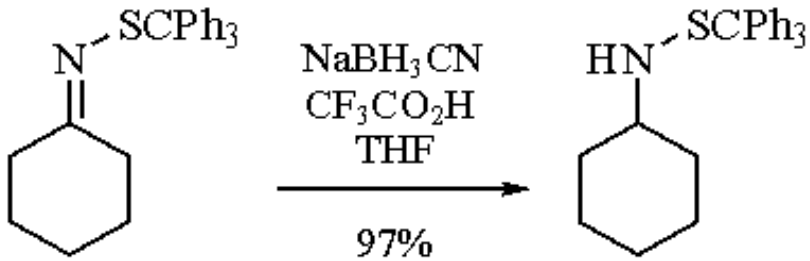

(20)

The *N*-trifluoroethylation of amines occurs with $NaBH_4$-CF_3CO_2H (eq 21),[25] presumably via CF_3CHO or its equivalent,[1,2] and has been observed by several groups.[1] CF_3CO_2H can serve as a useful medium for the $NaBH_4$-***Paraformaldehyde*** methylation of amines (eq 22).[26]

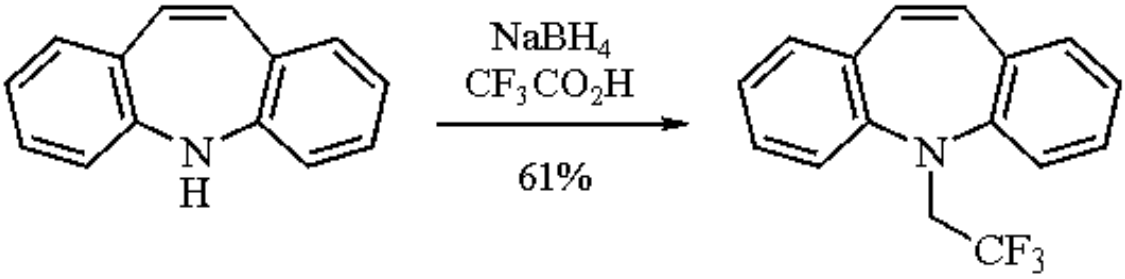

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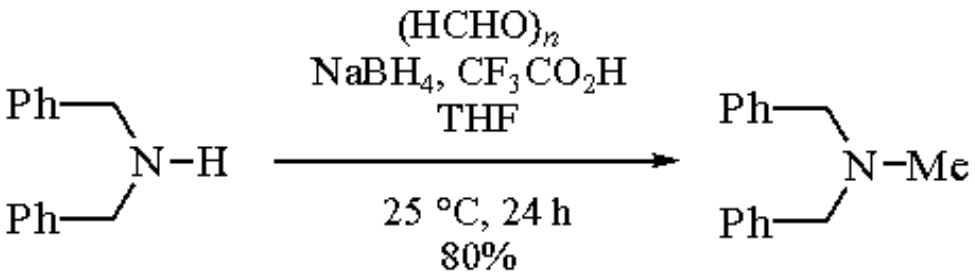

(22)

In a reaction (Baeyer condensation) reminiscent of the classic DDT synthesis, the combination $NaBH_4$-CF_3CO_2H leads to the formation of bis-arenes (eqs 23 and 24).[2,25]

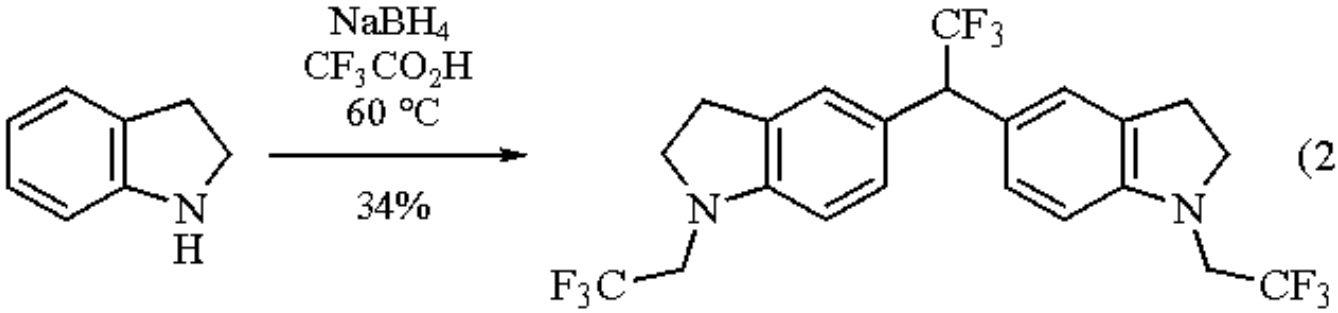

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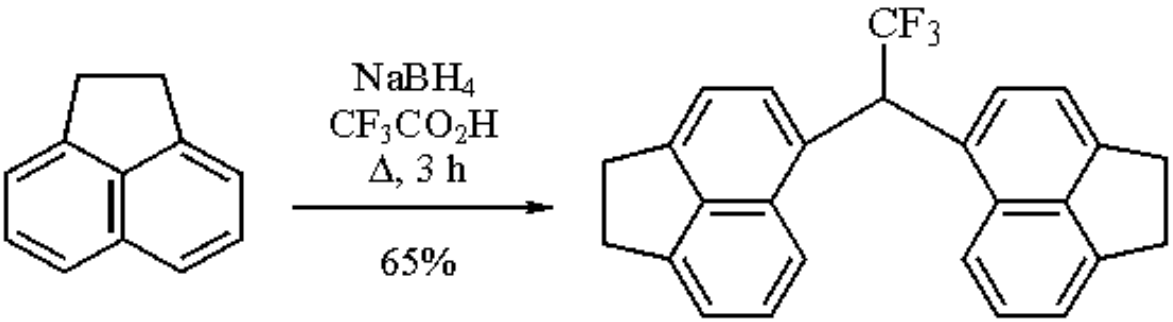

(24)

A few π-deficient heterocycles, such as quinoxaline (eq 25)[27] and pyrido[2,3-*b*]pyrazine (eq 26),[27] are reduced by $NaBH_4$-CF_3CO_2H.

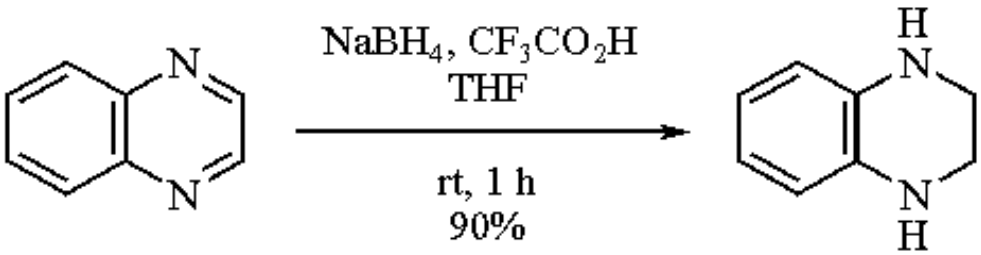

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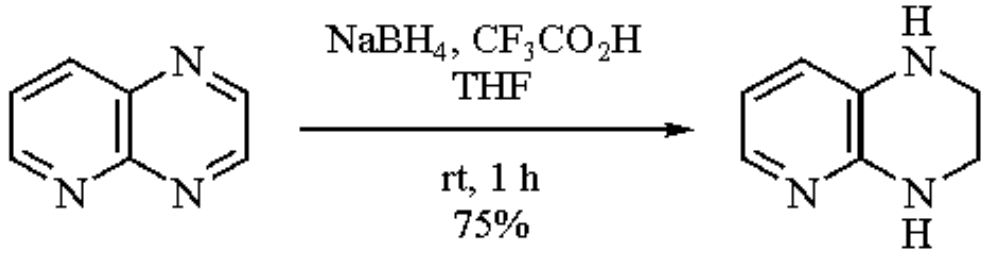

(26)

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Sodium Trithiocarbonate[1]

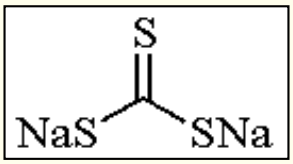

[534-18-9] · CNa_2S_3 · Sodium Trithiocarbonate · (MW 154.20)

(converts alkyl chlorides into thiols;[1] 1,2- or 1,3-dihaloalkanes or dimesylates into cyclic trithiocarbonates[2] or into alkenes;[3] reductively removes chloroethyl ester protecting groups;[4] effective for demercuration[5])

Preparative Method: a 33% aqueous solution is prepared from ***Sodium Sulfide*** and ***Carbon Disulfide*** in H_2O.

Alkyl chlorides can be treated with sodium trithiocarbonate followed by an acidic workup to prepare the corresponding thiol (eq 1).[1a] This methodology was applicable to simple alkyl chlorides (eq 2)[1b] and to β-alkoxy chlorides (eq 3).[1a] It was noted that this method was superior to direct substitution with NH_4SH.

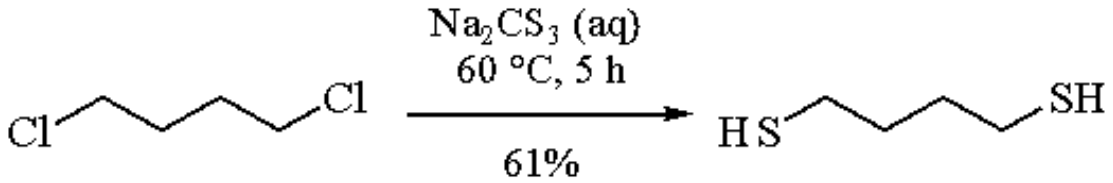

(1)

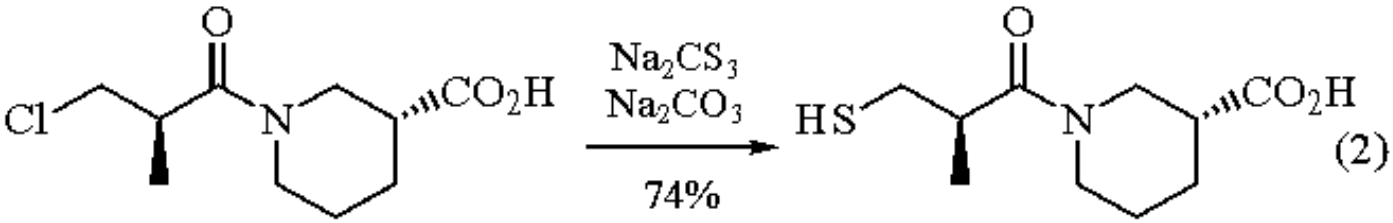

(2)

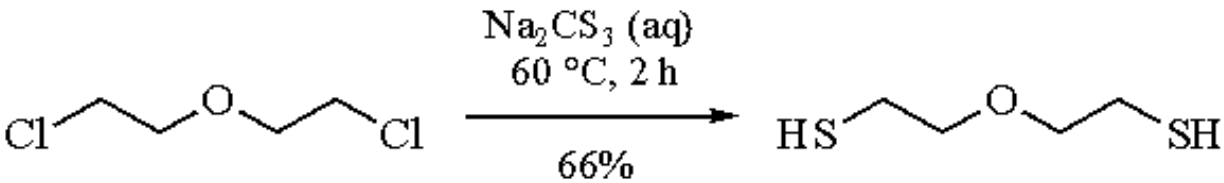

(3)

Sodium trithiocarbonate can be reacted with ***Chloroacetonitrile*** with liberation of carbon disulfide (eq 4).[6] The mercaptoacetonitrile could be reacted further with acid chlorides, providing cyanomethyl thioesters.

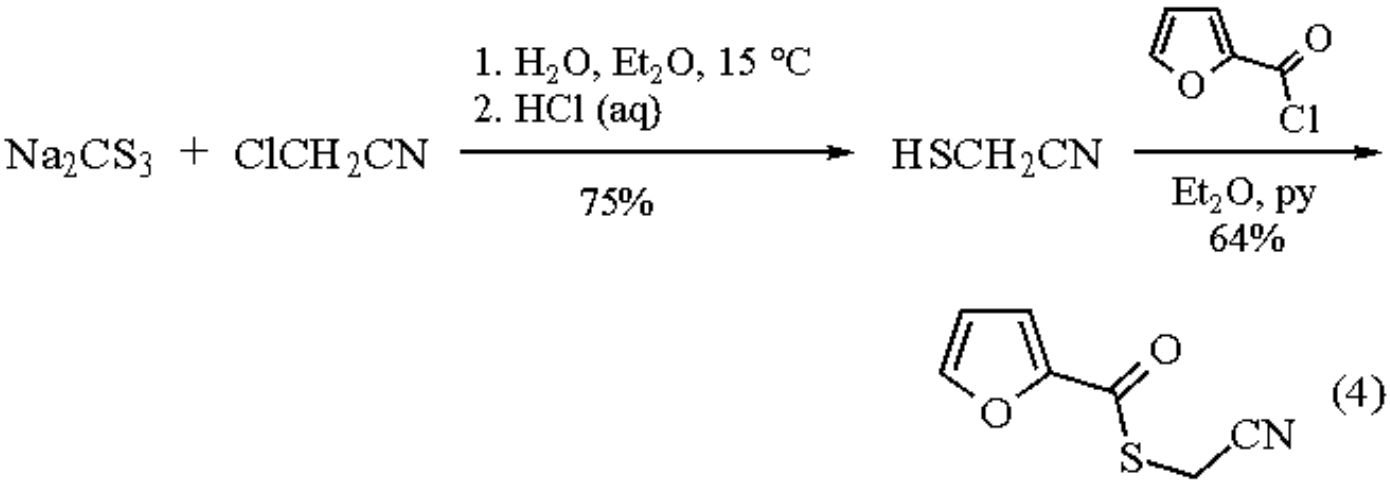

Thioureas have been prepared by reaction of sodium trithiocarbonate, ***2-Chloro-1-methylpyridinium Iodide*** and two equivalents of the appropriate amine.[7] The bis(pyridinium) thiocarbonate intermediate is activated toward nucleophilic attack (eq 5). The authors point out that other methods suffer from severe conditions and toxic reagents (e.g. ***Thiophosgene***). Sterically hindered amines, such as 2,6-dimethylaniline, were accommodated as well.

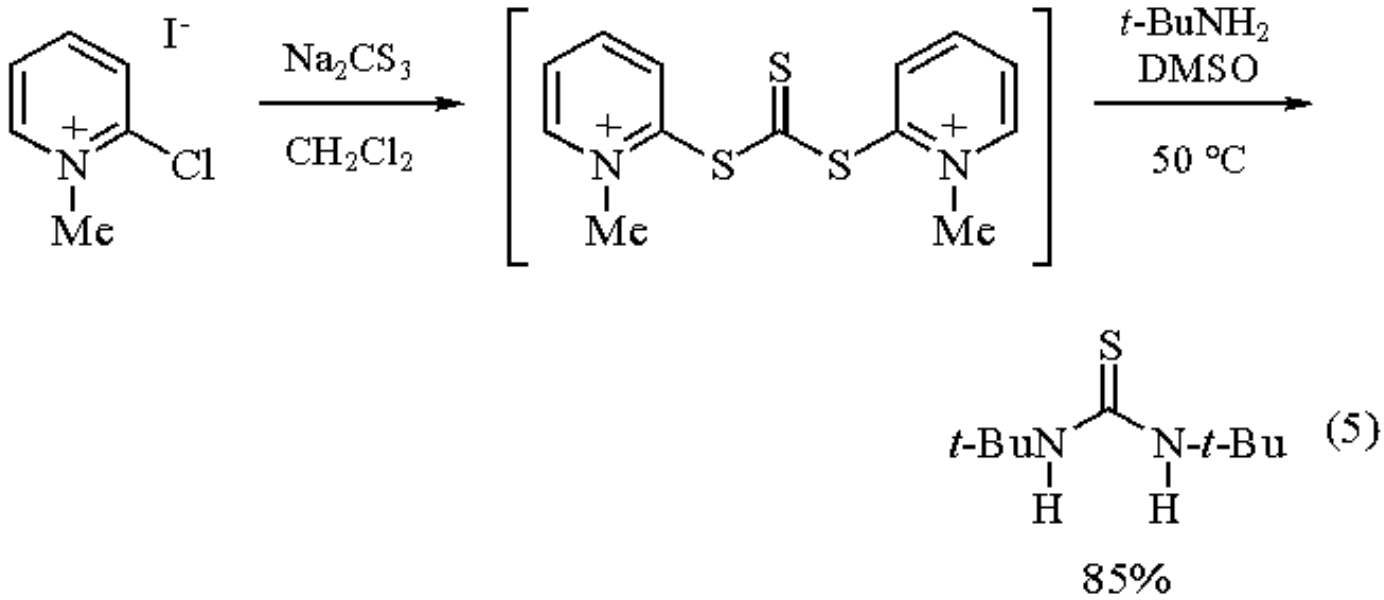

Chloroethyl esters, when treated with sodium trithiocarbonate, are reductively deprotected to liberate the carboxylic acid.[4]

Preparation of Cyclic Trithiocarbonates.

Cyclic trithiocarbonates are important intermediates en route to insecticides and other biologically active compounds.[8] These compounds can be synthesized by a double nucleophilic addition of sodium trithiocarbonate and 1,2- or 1,3-bis(mesylates)[2a] or halides (eqs 6 and 7).[2b] It was found that the reactions of the dibromide compounds were best performed under phase-transfer catalysis with trioctylmethylammonium chloride. In general, the yields were better for five-membered ring formation than for six-membered rings. One limitation for five-membered rings was that R^1 and R^2 need be alkyl groups. When R^1 and R^2 were phenyl or methoxycarbonyl groups, alkenes were isolated in excellent yields by a single electron transfer mechanism.[3]

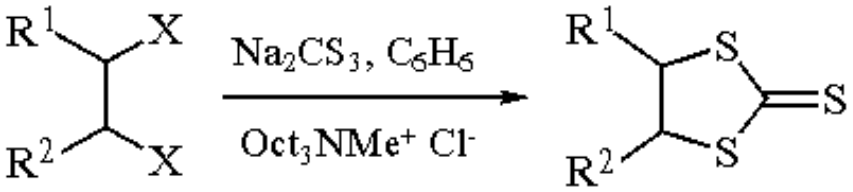

(6)

R^1	R^2	X	Temp (°C)	Time (h)	Cat (equiv)	Yield (%)
H	H	Br	60	8	0	84
H	H	Br	60	8	0.08	97
H	H	SH	80	2	0	90
Me	H	Br	60	20	0.08	81
Me	Me	Br	60	25	0.08	10

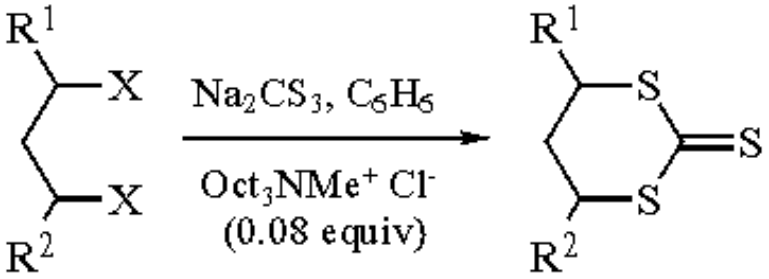

(7)

R^1	R^2	X	Temp (°C)	Time (h)	Yield (%)
H	H	Br	60	1	7
H	H	SH	100	3	45
Me	H	Br	60	5	66
Me	Me	Br	60	20	31

Cyclic trithiocarbonates have been selectively reduced to the dithiol or the thioacetal depending on the choice of reducing agent (eq 8).[9] Thus reduction with ***Lithium Aluminum Hydride*** in toluene at 110 °C provided good yields of the dithiol whereas if ***Diisobutylaluminum Hydride*** was employed, the thioacetal was isolated. The trithiocarbonate could also be desulfurized with aqueous ***Mercury(II) Acetate*** to provide the 1,3-dithiole-2-thione (eq 9).[10]

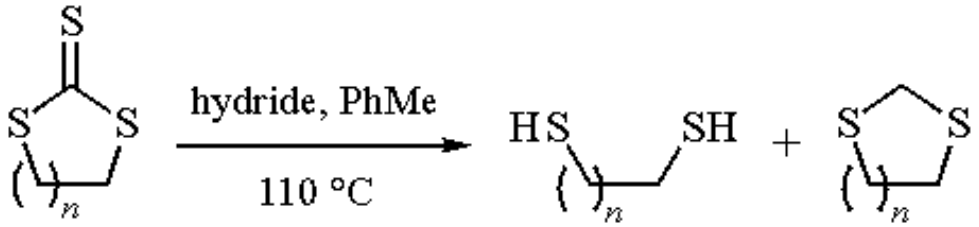

(8)

n	hydride		
1	LAH	86%	0%
1	DIB AL	0%	59%
2	LAH	37%	0%
2	DIB AL	0%	67%

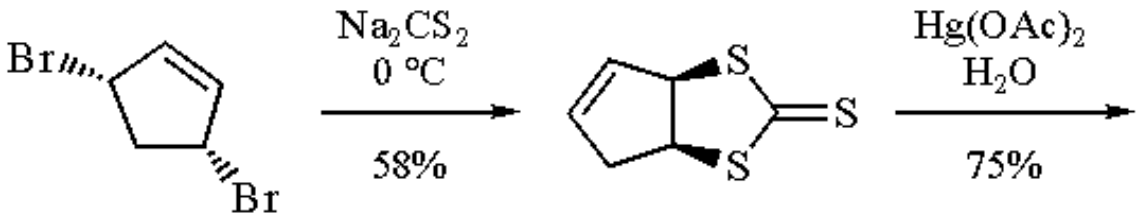

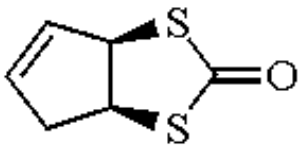

(9)

Demercuration.

A synthetic sequence en route to propionate natural products utilized the regio- and stereoselective oxymercuration[11] of stereodefined enoates. The success of this method hinged upon the stereoselective removal of mercury (eq 10).[5] Previous methods (e.g. ***Sodium Borohydride*** and ***Sodium Sulfide***)[12] gave poor diastereomeric ratios. In this system it was determined that sodium borohydride favored formation of the *threo* isomer and the dithiol reagents gave preferentially the *erythro* product. Sodium trithiocarbonate was slightly less efficient than ***1,3-Propanedithiol*** both in terms of yield and selectivity.

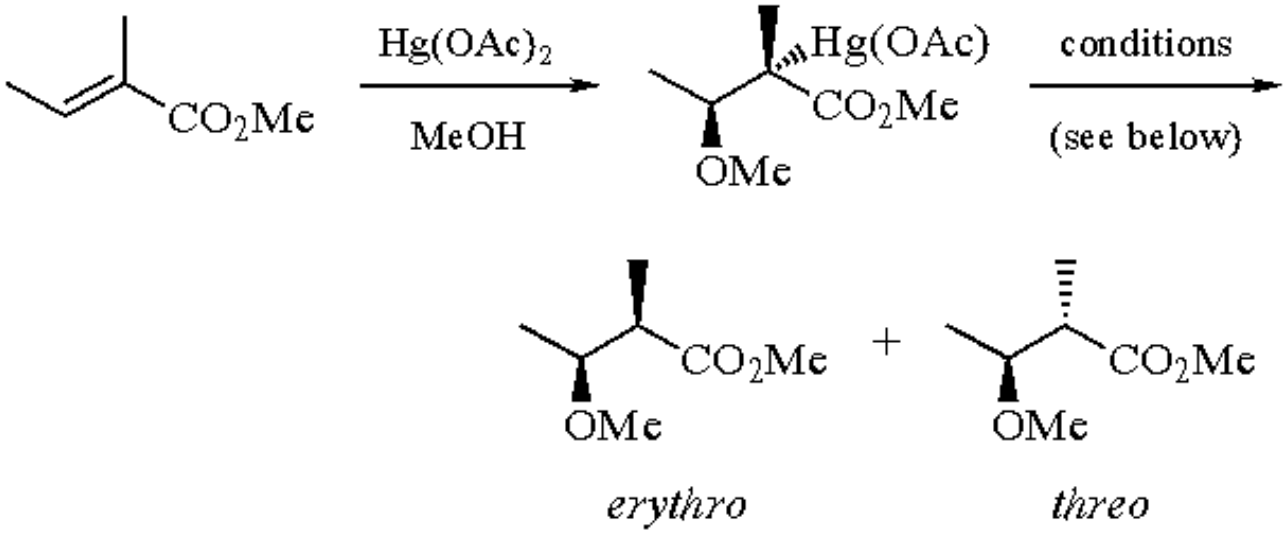

Conditions	Yield (%)	*erythro*:*threo*
$NaBH_4$, EtOH, 0 °C	85	20:80
$HS(CH_2)_2SH$, EtOH	43	90:10
$HS(CH_2)_3SH$, EtOH	99	95: 5
Na_2CS_3, MeOH-H_2O	72	90:10

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(-)-Sparteine[1]

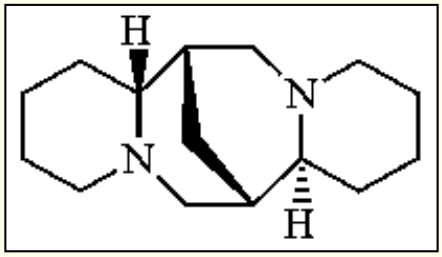

[90-39-1] · $C_{15}H_{26}N_2$ · (-)-Sparteine · (MW 234.43) (sulfate pentahydrate)

[6160-12-9] · $C_{15}H_{38}N_2O_9S$ · (-)-Sparteine · (MW 422.62)

(reagent for chiral modification of organo-lithium, -magnesium, and -zinc reagents[1,2])

Alternate Name: [(7*S*)-(7α,7aα,14α,14aβ)]-dodecahydro-7,14-methano-2*H*,6*H*-dipyrido[1,2-*a*:1´,2´-*e*][1,5]diazocine.

Physical Data: bp 137-138 °C/1 mm Hg; *d* 1.02 g cm^{-3}; $[\alpha]^{20}_D$ -17.5° (*c* = 2, EtOH). X-Ray structures of several complexes of metal salts,[3] alkyllithium derivatives,[4] and of allylpalladium[5] and studies on the conformation in solution[6] and a NMR study on the structure of the 2-propyllithium-ether-(-)-sparteine complex[7] have been reported.

Solubility: 0.3 g/100 ml H_2O at 20 °C; sol ether, hexane.

Form Supplied in: free base: colorless viscous fluid.

Handling, Storage, and Precautions: highly toxic in the digestive tract. Keep in refrigerator at 0 °C. Moderately hygroscopic; dehydration by drying an ethereal solution over ***Calcium Hydride***. Is easily recovered by extraction of alkaline aqueous solutions. Use in a fume hood.

Chiral Modification of Achiral Organometallic Reagents.

The addition of ***n-Butyllithium*** or ***Ethylmagnesium Bromide*** to aldehydes or ketones in the presence of (-)- sparteine resulted in the formation of optically active secondary or tertiary alcohols with 20% ee or lower.[8] Optically active acyl sulfoxides (<=15% ee) were obtained by acylation of ***p-Tolylsulfinylmethyllithium***.[9] The asymmetric Reformatsky reaction of ethyl bromoacetate with benzaldehyde proceeds with 95% ee,[10] in an exceptional case (eq 1).[11]

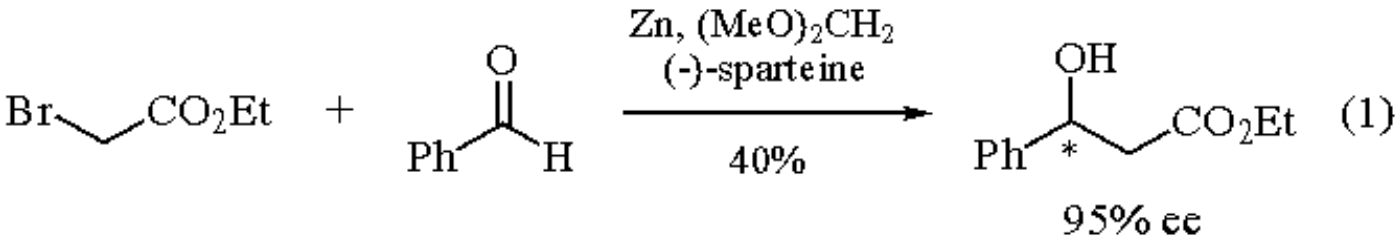

Equilibration of Configurationally Labile Organolithium Reagents.

The equilibration of diastereomeric pairs of alkyllithium-(-)-sparteine complexes and trapping by achiral electrophiles gives enantioenriched products. Examples are α-(*N*,*N*-diisopropylcarbamoyloxy)benzyllithium in ether,[12] not in THF,[13] 1-phenylethyllithium,[8a] and the dilithium salt of *N*-methyl-3-phenylpropanoic acid amide (eq 2).[14]

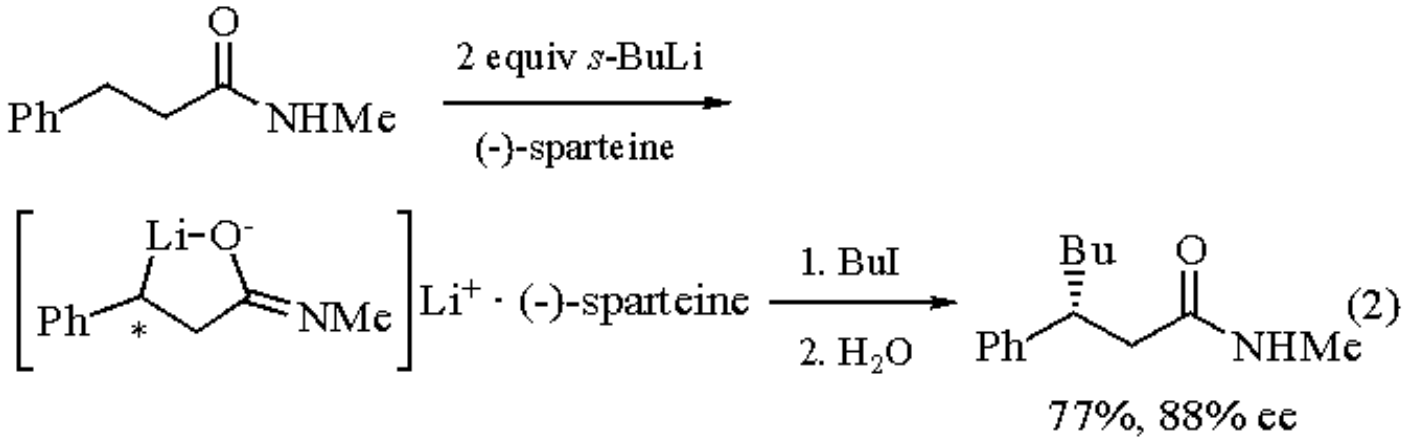

The deprotonation[15] of (*E*)-2-butenyl *N*,*N*-diisopropylcarbamate leads to (1*S*,2*E*)-1-(*N*,*N*-diisopropylcarbamoyloxy)-2-butenyllithium-(-)-sparteine[16] with &egt;90% de after crystallization, combined with a second-order asymmetric transformation (eq 3).[4d] It has been applied in the enantioselective synthesis of γ-lactones,[16] such as (+)-eldanolide (eq 3),[17] dihydroavermectin B_{1b},[18] and doubly branched sugar analogs.[19]

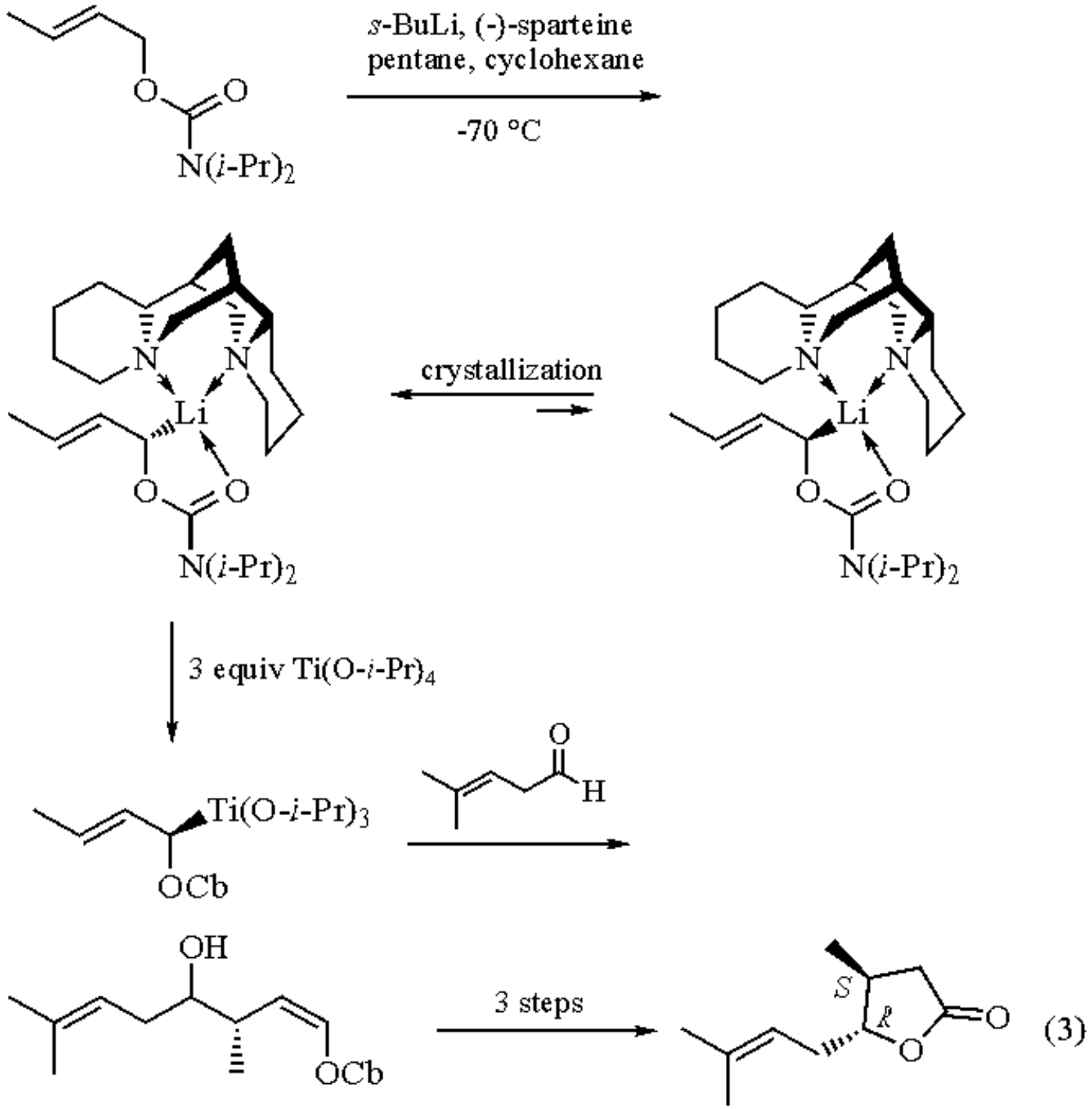

62%, >97% ds, 92% ee

Generation of Enantioenriched, Configurationally Stable Organolithium Reagents.[15,20]

(1*S*,2*E*)-1-(*N*,*N*-Diisopropylcarbamoyloxy)-1-methyl-2-butenyllithium-(-)-sparteine is configurationally stable in solution and is obtained by kinetic resolution of the racemic 2-alkenyl carbamate by *n*-butyllithium-(-)-sparteine with &egt;80% de (eq 4).[21] The enantioenriched allylstannane, obtained on γ-stannylation, was used as chiral homoenolate reagent.[21a] The methoxycarbonylation (α, inversion) yields enantioenriched 3-alkenoates.[21b]

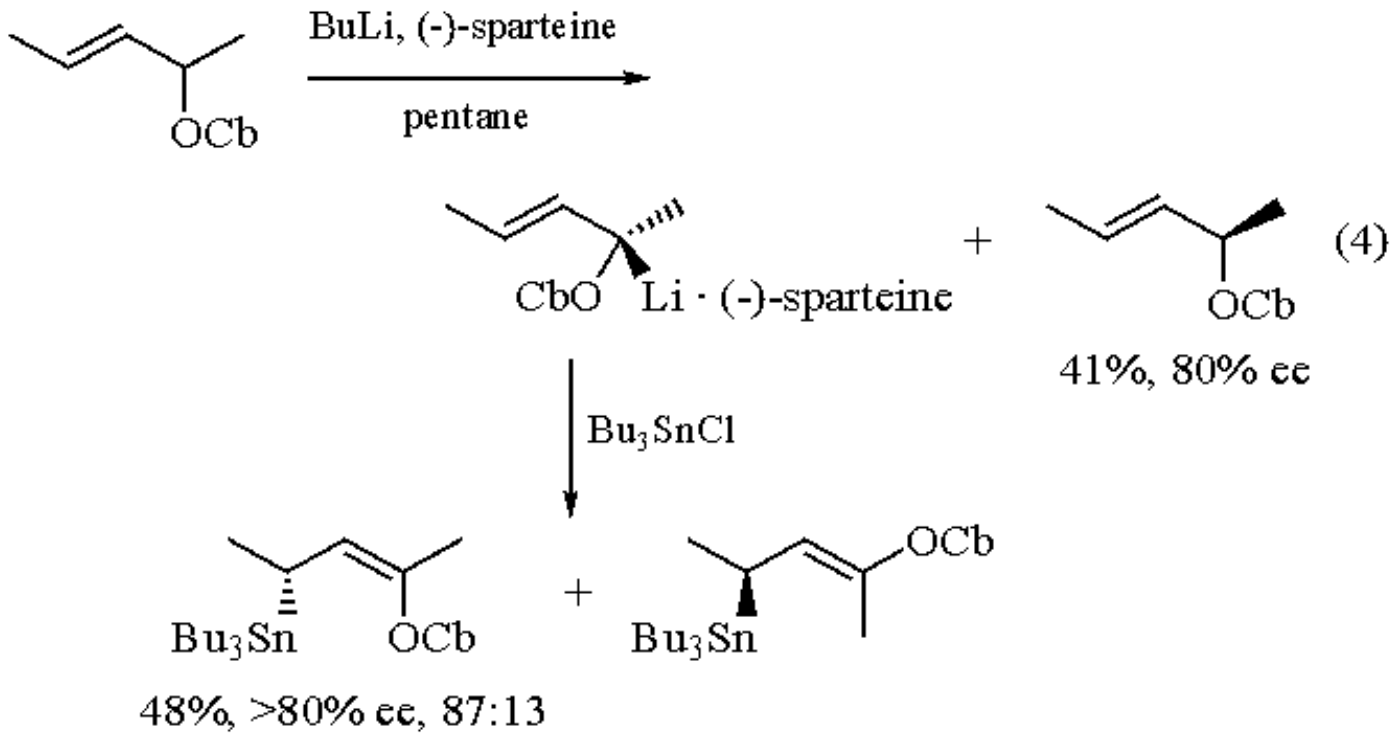

Alkyl carbamates, derived from 2,2,4,4-tetramethyl-1,3-oxazolidine (R-CH_2-OCby), are deprotonated by ***s-Butyllithium***-(-)-sparteine with differentiation between the enantiotopic protons (eq 5).[22,20] The pro-*S* proton is removed with high stereoselectivity and reliability, and, subsequently, stereospecifically substituted by electrophiles with stereoretention to give enantiomerically enriched secondary alcohols (&egt;95% ee) after deprotection.[22b]

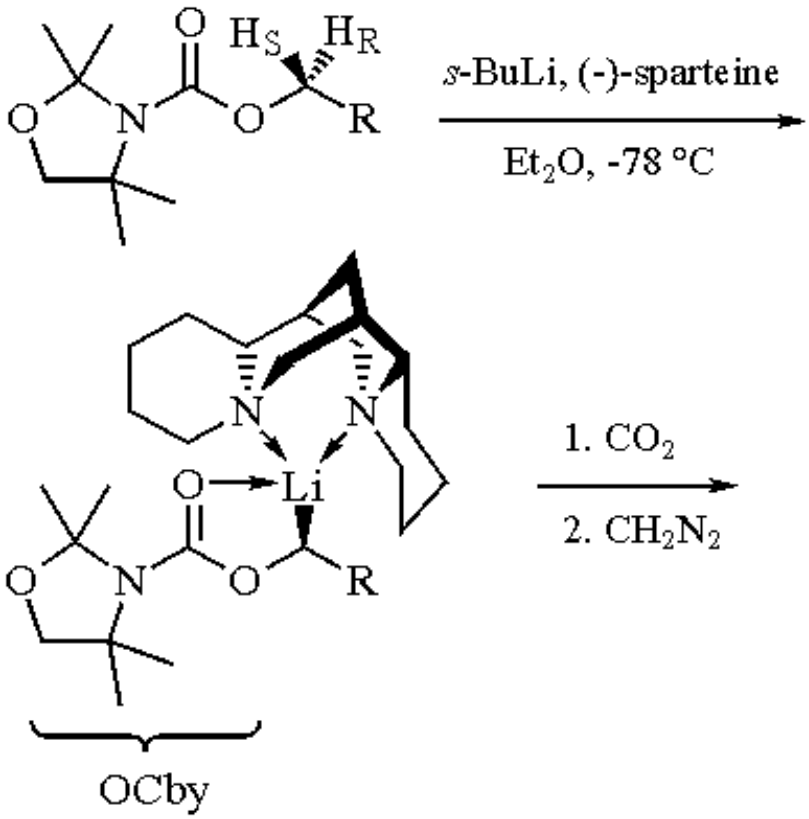

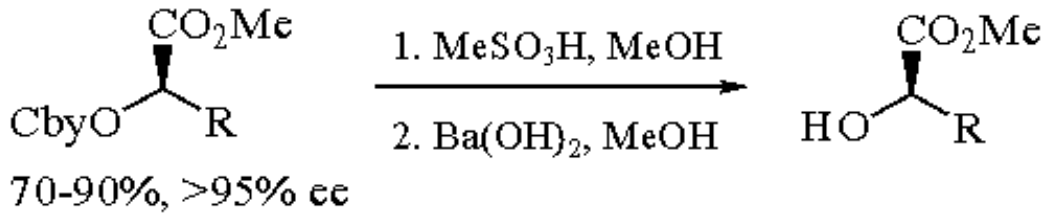

(5)

R = alkyl, Bn_2NCH_2, $Bn_2N(CH_2)_2$, $CbyOCH_2CH_2$

The ee values in the enantioselective deprotonation are independent of the size of the attached alkyl residue. The method tolerates several substituents, e.g. 2-[23] or 3-dibenzylamino,[24] 3- or 4-(*N*,*N*-dialkylcarbamoyloxy),[25] or 4-TBDMSO.[25a] Essentially enantiopure 2-hydroxy acids,[22a] β-amino alkanols,[24] γ-amino alkanols,[23] cyclopropyl carbamates,[25a] and 2-hydroxy-4-butanolides[25a] were obtained. Extraordinary high (>70) kinetic H/D isotope effects were observed in the deprotonation of chiral 1-deuteroalkyl carbamates.[26] Kinetic resolution of racemic alkyl carbamates was achieved.[27]

N-Boc-pyrrolidines are similarly deprotonated and furnish enantioenriched 2-substituted pyrrolidines (eq 6).[28]

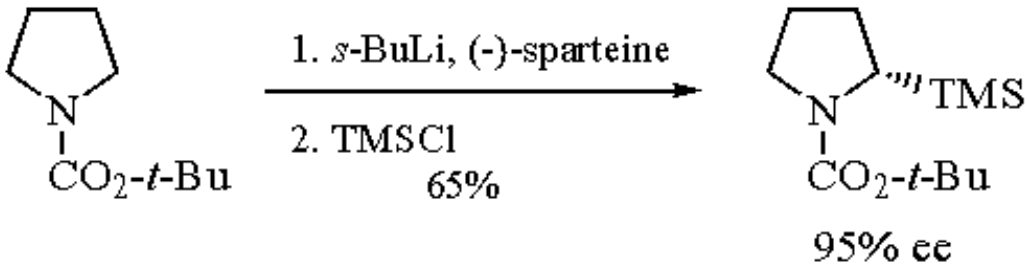

(6)

Further Applications.

Chiral 1,1-diaryl-2-propynols are resolved by mutual crystallization with (-)-sparteine.[29] Low ee values were achieved in Pd-mediated alkylations.[30] Numerous attempts at enantioselective, alkyllithium-catalyzed polymerizations of alkenes in the presence of (-)-sparteine have been reported.[31]

Related Reagents.

(+)-Sparteine (pachycarpine[32]) is best prepared by resolution of (±)-sparteine, obtained from *rac*-lupanine[33] or by total synthesis[34] with (-)-10-camphorsulfonic acid.[35]

---

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Spiro{bicyclo[4.2.0]octa-1,3,5-triene-7,2´-[1,3]-dioxolan}-8-one[1]

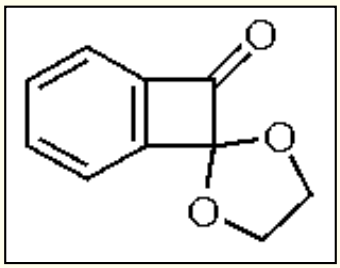

[6383-64-8] · $C_{10}H_8O_3$ · Spiro{bicyclo[4.2.0]octa-1,3,5-triene-7,2´-[1,3]-dioxolan}-8-one · (MW 176.18)

(serves as a 1,4-dipole synthon for synthesis of anthraquinone-related ring systems[2])

Physical Data: mp 109-112 °C.

Preparative Methods: this simple monoethylene acetal of benzocyclobutenedione[3] may be prepared by reaction of the parent dione with ***Ethylene Glycol*** in benzene with a trace of ***p-Toluenesulfonic Acid*** and azeotropic removal of water,[1] or by a three-step method that is essentially a silicon analog of the Kornblum oxidation (eq 1).[4] The latter approach affords control over acetal regiochemistry in systems with unsymmetrical substitution on the aromatic ring.

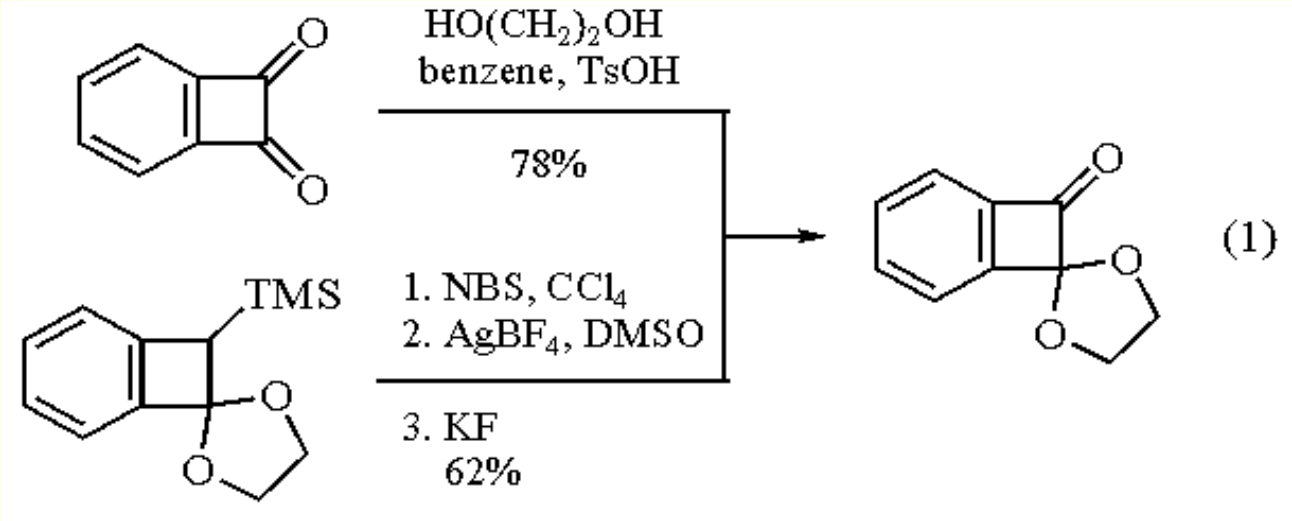

Purification: crystallizes from benzene-hexane; slightly yellow needles.

Annulation Reactions.

Reaction with lithiated quinone bisacetals affords anthraquinone-related structures (eq 2).[2] Studies support a stepwise rather than a concerted mechanism for this 1,4-dipole-type annulation.[5] Thus reaction with a highly functionalized lithioquinone bisacetal followed by hydrolysis and demethylation steps gave the 7-*O*-methyl epimer of the anthracycline aglycons 4-demethoxydaunomycinone (R = H) or daunomycinone (R = OMe) (eq 3).[4] A related strategy was used in a synthesis of α-citromycinone,[6] although the annulation yield was only 30%.

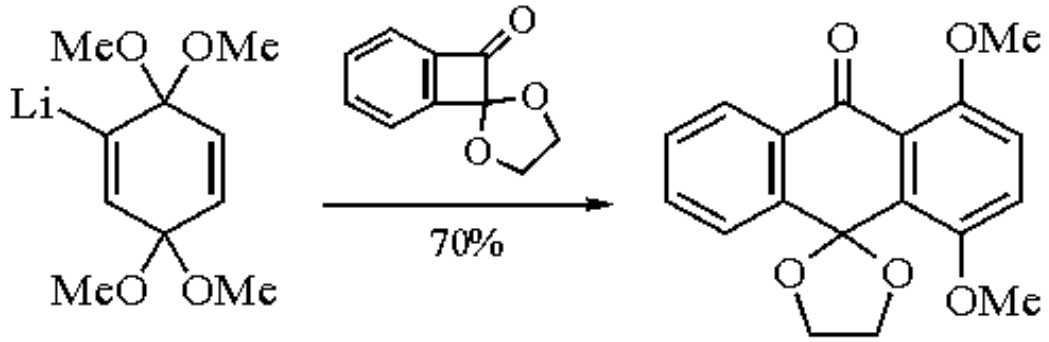

(2)

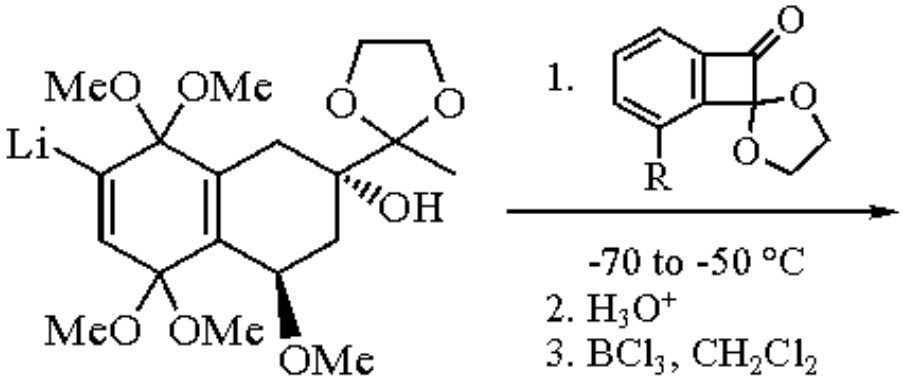

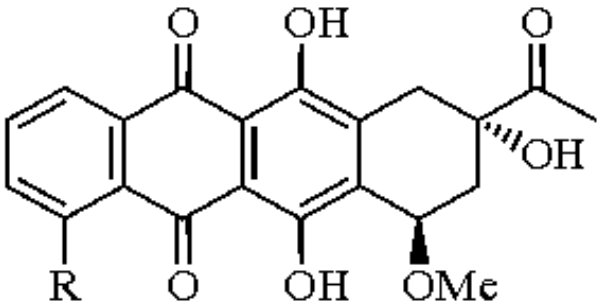

(3)

R = H, 62%; R = OMe, 56%

This method has also been used in an approach to the tetracycline antibiotics,[7] giving an annulation adduct which, after addition of ***Methyllithium***, showed the correct relative configuration at key eventual positions of the tetracycline ring system (eq 4).

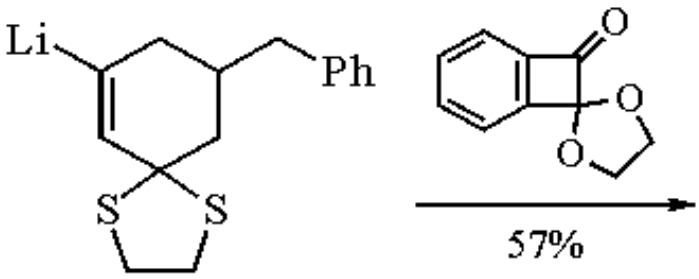

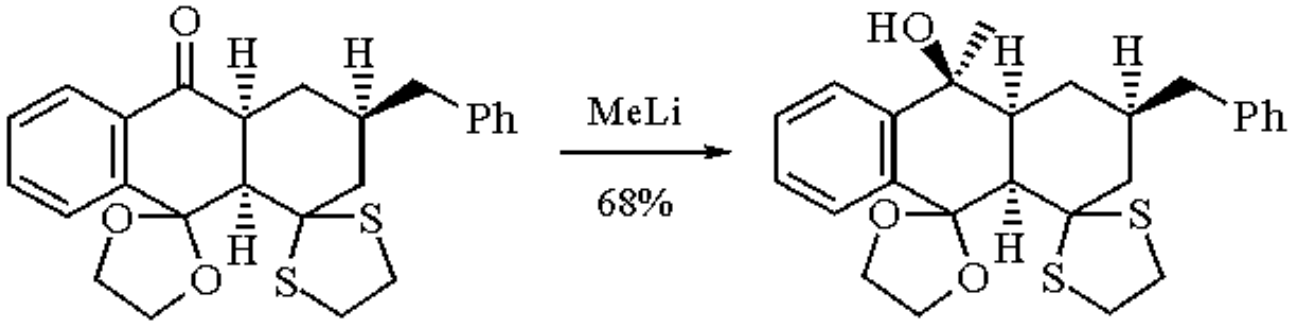

(4)

Ring Expansion.

Reaction with 1-lithioalkynes affords 1,2-adducts which undergo palladium triflate-catalyzed ring expansion to (*Z*)-2-alkylideneindan-1,3-dione monoacetals (eq 5),[8] a methodology that has been used in the synthesis of a benzo analog of the antiviral agent abikoviromycin.[9]

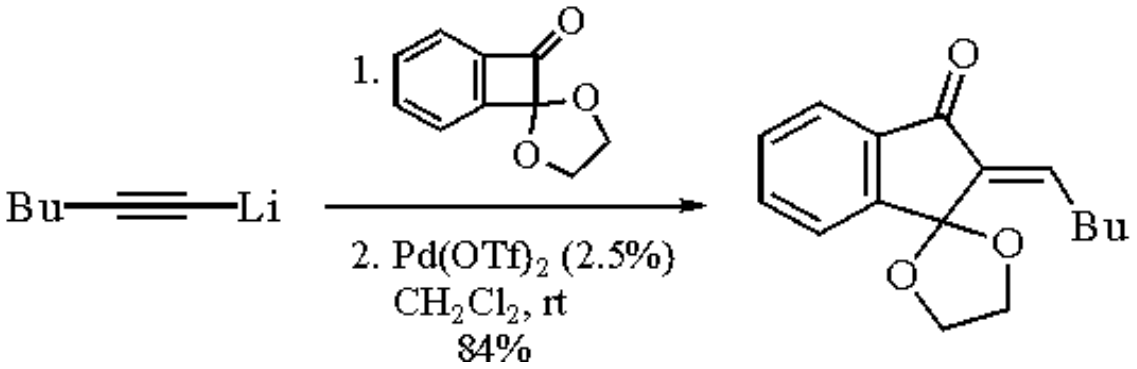

(5)

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Squaric Acid[1]

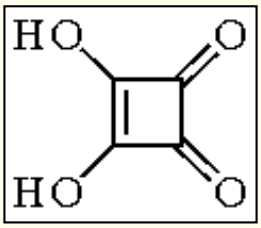

[2892-51-5] · $C_4H_2O_4$ · Squaric Acid · (MW 114.06)

(synthesis of cyclobutenediones, quinones, and hydroquinones[1])

Alternate Name: 3,4-dihydroxy-3-cyclobutene-1,2-dione.

Physical Data: mp >300 °C.

Solubility: sol H_2O.

Form Supplied in: white crystals.

Analysis of Reagent Purity: IR ν 2326 (OH), 1818 (C=O), 1639 (C=C) cm^{-1}.

Handling, Storage, and Precautions: the crystals should be handled with gloves.

Dichlorocyclobutenedione.

Treatment of squaric acid (**1**) with ***Thionyl Chloride*** and a trace amount of ***N,N-Dimethylformamide*** affords dichlorocyclobutenedione (DCCB) (**2**) (eq 1).[2]

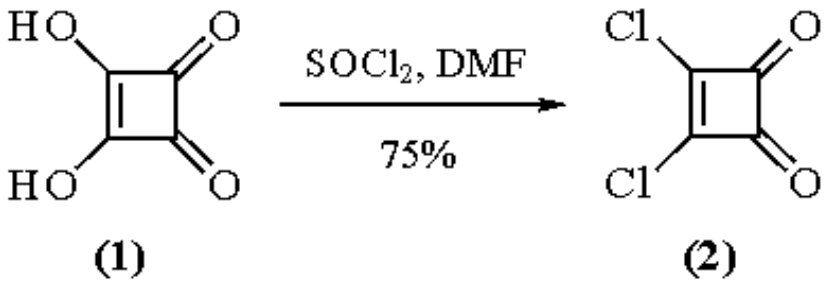

(1)

DCCB (**2**) reacts with nucleophiles by displacement of the chlorine atoms.[1d] For example, reaction of (**2**) with 2-nitroaniline in a solution of *o*-dichlorobenzene at 150 °C for 40 min affords diaminocyclobutenedione (**3**) (eq 2).[3]

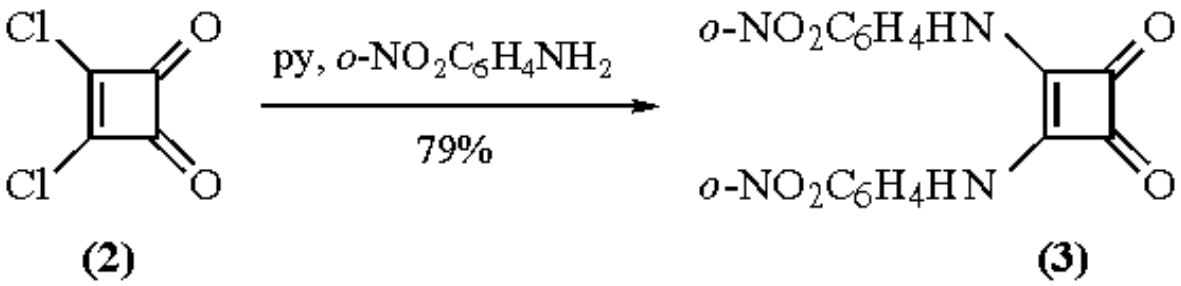

(2)

DCCB reacts similarly with ***Sodium Azide*** at 0 °C to afford chlorocyanoketene,[4] with cyanamides[5] and carbodiimides[6] to afford carboxyimidoyl chlorides, with thiols to afford dithiocyclobutenediones,[7] with tertiary amines, phosphines, arsines, and thioethers to afford betaines,[8] and with carbonylmetallates to afford metallocyclobutenediones.[9]

DCCB also reacts with carbon nucleophiles. For example, treatment with ***Aluminum Chloride*** in benzene affords diphenylcyclobutenedione (**4**) (eq 3).[10] Furthermore, (**2**) reacts with ***Tetrakis(triphenylphosphine)palladium(0)*** and alkynylstannanes to give dialkynylcyclobutenediones in 11-70% yield.[11]

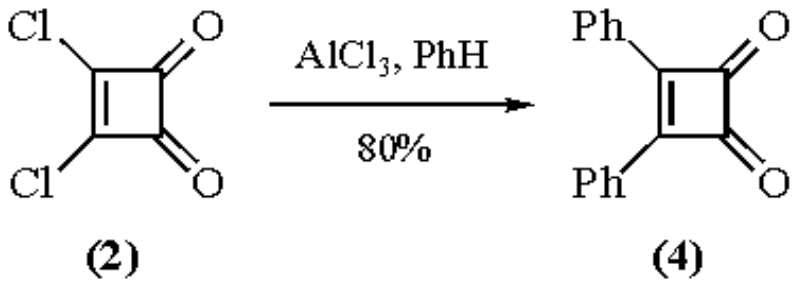

(3)

Dialkoxycyclobutenediones.

Treatment of squaric acid (**1**) with ***Sodium Hydroxide*** followed by ***Silver(I) Nitrate*** affords disilver salt (**5**) (eq 4); this reacts with ***Iodomethane*** to give dimethyl squarate (DMS) (**6a**).[12] Similarly, treatment of (**5**) with *t*-butyl chloride affords di-*t*-butyl squarate (**6b**).[13]

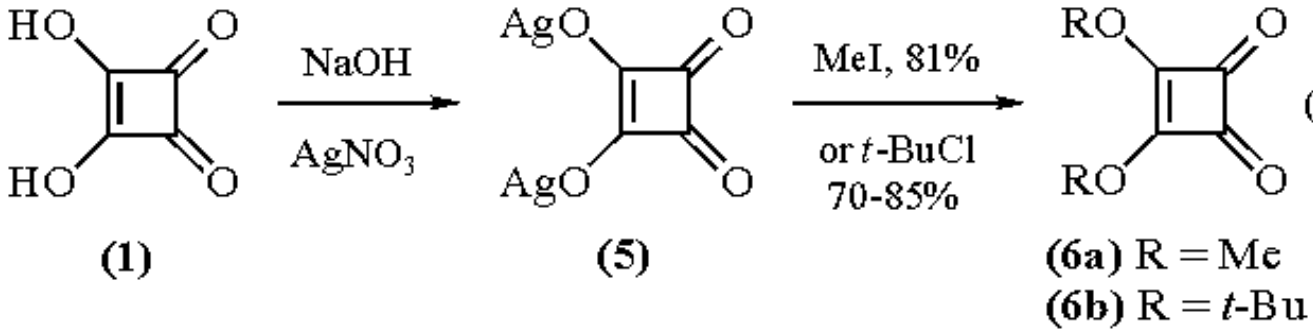

(4)

Other esters can be prepared by refluxing a solution of squaric acid in the appropriate alcoholic solvent.[12] A specific example is given in eq 5, showing the formation of diisopropyl squarate (DIPS) (**7**).[14]

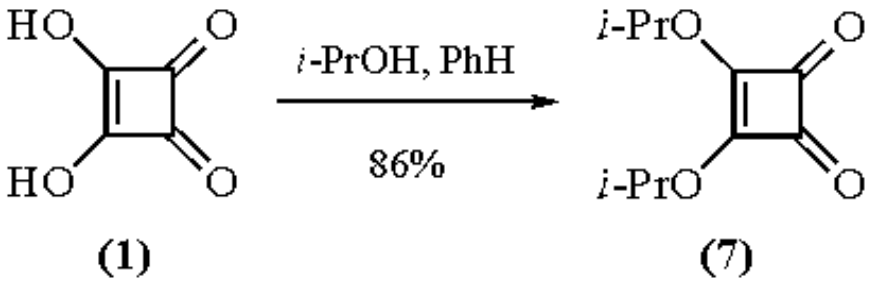

(5)

Cyclobutenediones.

Dialkoxysquarates can be converted to a wide variety of other cyclobutenediones. For example, treatment of (**7**) with ***Methyllithium*** yields methyl adduct (**8**) (eq 6). The crude material is then subjected to acidic hydrolysis to afford dione (**9**) in 89% overall yield.[14] Alternatively, this transformation can be accomplished in a one-pot procedure with comparable yields by treatment of the intermediate lithium alkoxide with ***Trifluoroacetic Anhydride*** followed by an aqueous extraction.[15]

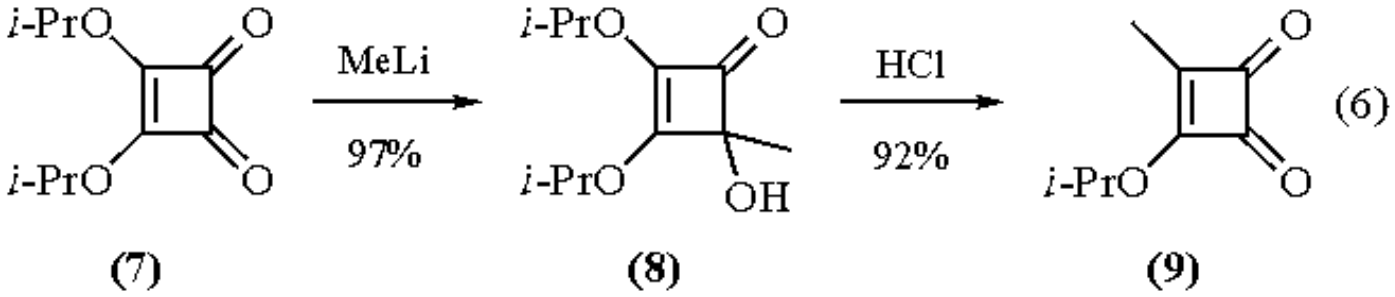

Disubstituted cyclobutenediones can be made by the following procedure. First, a 4-hydroxycyclobutenone such as (**8**) is silylated with ***4-Dimethylaminopyridine*** and ***t-Butyldimethylchlorosilane*** (eq 7).[14] Then, a second lithium reagent is added (e.g. ***n-Butyllithium***) followed by acidic hydrolysis of the crude material to afford dione (**10**) in 79% yield.

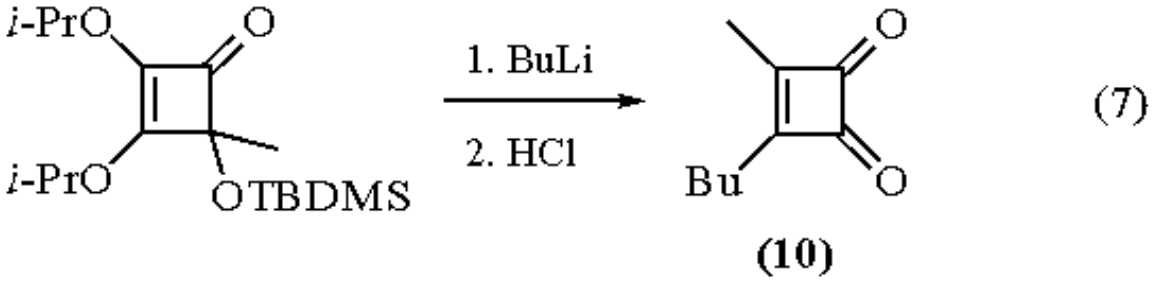

The two carbonyl groups of cyclobutenediones can be differentiated by forming a monoacetal. One such method produces cyclobutenedione ethylene acetal.[16] Another method is described in eq 8. Acetal (**11**) is made from DMS (**6a**) by the addition of ***Phenyllithium*** followed by treatment with TFAA and MeOH. A second lithium reagent (e.g. MeLi) is then added; addition of TFAA and aqueous extraction affords disubstituted acetal (**12**).[17]

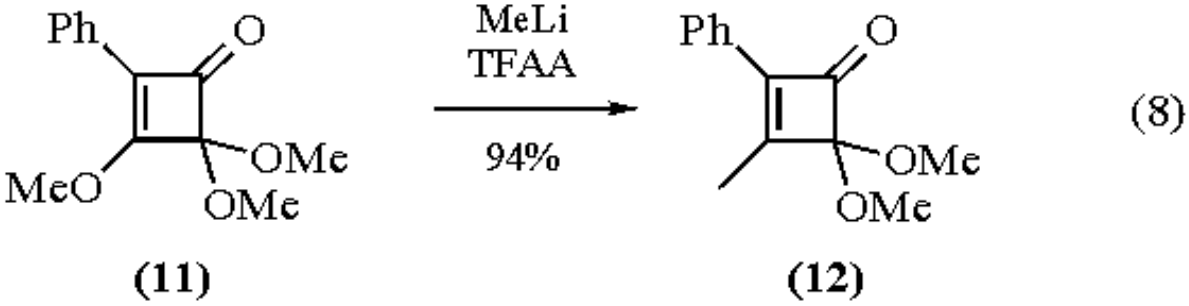

In eq 9, DIPS is treated with *n*-$Bu_3SnSiMe_3$ and a catalytic amount of *n*-Bu_4NCN to afford dione (**13**).[18] Stannylcyclobutenediones are versatile intermediates for the synthesis of other cyclobutenediones, utilizing palladium-catalyzed coupling reactions.[19]

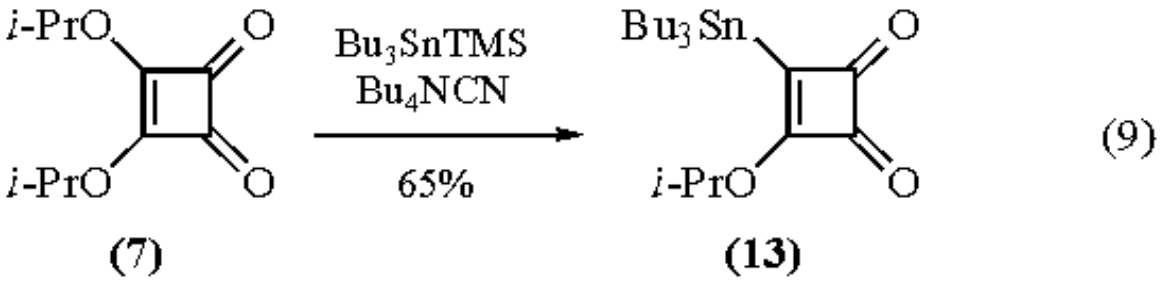

Quinones and Aromatic Compounds.

Lithium anions add to cyclobutenediones and cyclobutenedione monoacetals to afford 4-alkynyl-, 4-aryl-, and 4-alkenylcyclobutenones. When heated, these compounds rearrange to give quinones or related aromatic compounds.[20] The reaction is general and is limited only by the availability of the starting cyclobutenedione. For example, eq 10 depicts the thermolysis of 4-alkynylcyclobutenone (**14**), which was made by the addition of the lithium salt of benzylacetylene to 3-butyl-4-methoxycyclobutenedione, to produce quinone (**15**).[20a] Upon heating, 4-arylcyclobutenone (**16**), which was made from acetal (**12**) by addition of PhLi followed by hydrolysis with HCl, rearranges to afford naphthoquinone (**17**) after oxidation in 70% yield from (**12**) (eq 11).[17] Finally, 4-alkenylcyclobutenone (**18**) is thermolyzed to afford coenzyme Q_0 (**19**) after oxidation (eq 12).[20d]

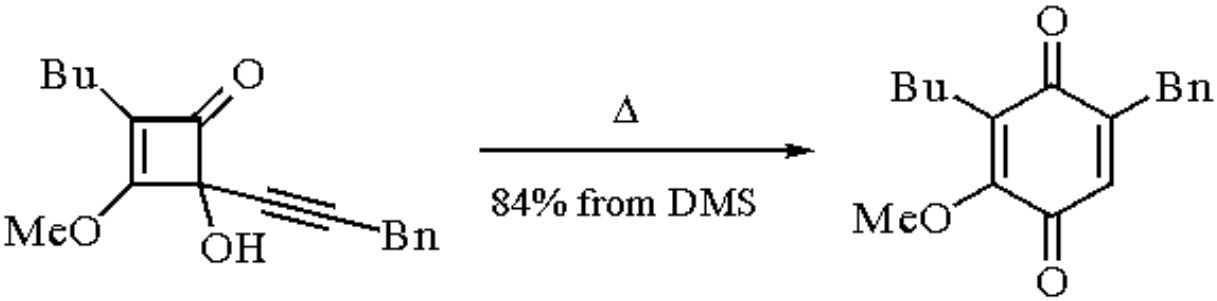

(10)

(14) (15)

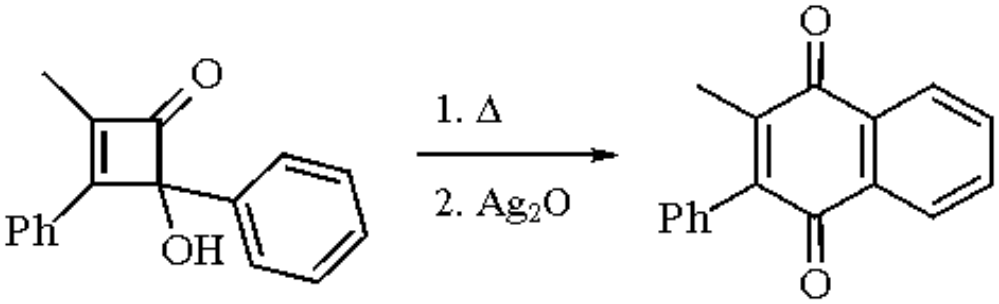

(11)

(16) (17)

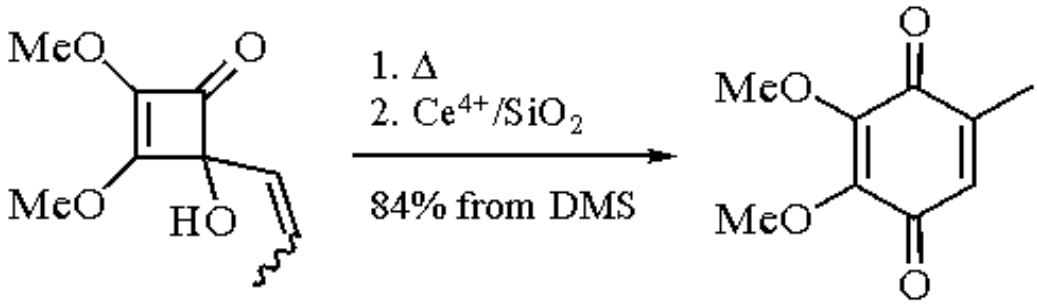

(12)

(18) (19)

Besides the methods described above, another regioselective route to 2,3-disubstituted furano- and naphthoquinones has been developed,[21] as illustrated in eq 13. Cyclobutenone (**20**) is made from 2-methyl-3-isopropoxy-4-methoxy-4-(2-methoxyphenyl)-3-cyclobutenone by reduction with ***Lithium Aluminum Hydride*** followed by treatment with TFAA and aqueous extraction in 54% yield. Thermolysis of (**20**) then produces naphthoquinone (**21**).

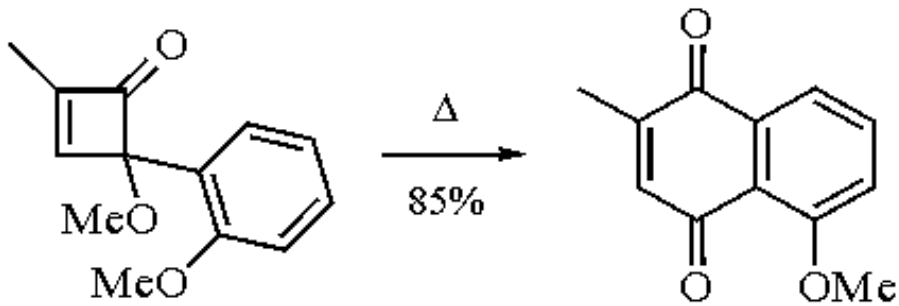

(13)

(20) (21)

A number of unusual classes of quinones are available by the rearrangement of 4-alkynylcyclobutenones. For example, thermolysis of cyclobutenone (**22**) affords silylquinone (**23**) (eq 14).[20a,22] Analogously, thermolysis of cyclobutenones in the presence of ***Tri-n-butyl(methoxy)stannane*** provides stannylquinones in good yields (eq 15).[23]

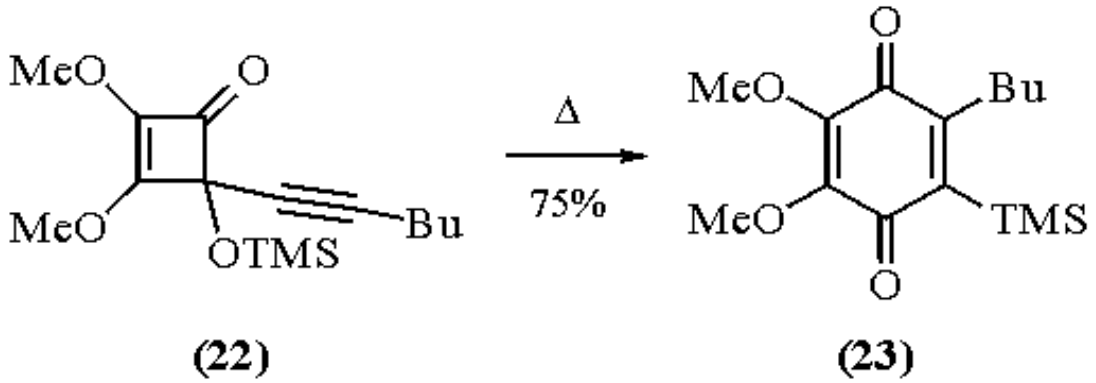

(14)

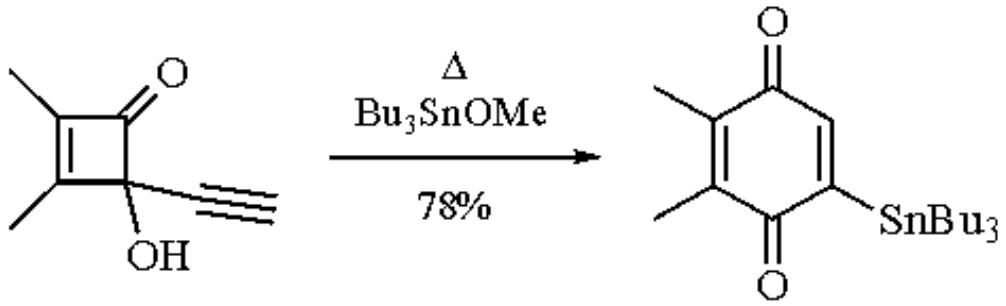

(15)

Cyclobutenone ring expansions have been employed as key steps in the synthesis of a variety of natural products and biologically active molecules such as isoarnebifuranone,[24] nanaomycin D,[24,25] mycophenolic acid,[26] Δ^6-tetrahydrocannabinol,[27] danshenxinkun B,[28] terreic acid,[29] perezone and isoperezone,[29,30] lonapalene,[31] and khellin.[32]

Alkylidenecyclopentenediones.

Treatment of cyclobutenones with ***Palladium(II) Trifluoroacetate*** triggers a ring expansion to alkylidenecyclopentenediones.[33] For example, eq 16 shows the rearrangement of cyclobutenone (**24**). The palladium intermediate can be efficiently trapped with ***N-Bromosuccinimide*** to afford vinyl bromide (**25**) in 77% yield.

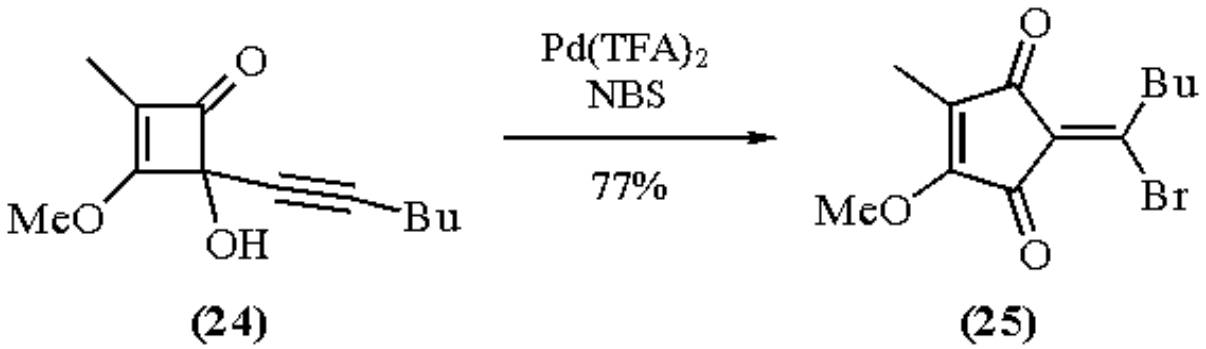

(16)

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30. Enhsen, A.; Karabelas, K.; Heerding, J. M.; Moore, H. W. *JOC* **1990**, *55*, 1177.
31. Perri, S. T.; Moore, H. W. *TL* **1987**, *28*, 4507.
32. (a) Reed, M. W.; Moore, H. W. *JOC* **1987**, *52*, 3491. (b) Reed, M. W.; Moore, H. W. *JOC* **1988**, *53*, 4166.
33. Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *JACS* **1987**, *109*, 7908.

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Succindialdehyde

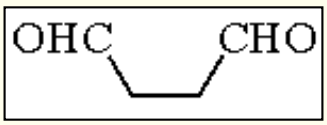

[638-37-9] · $C_4H_6O_2$ · Succindialdehyde · (MW 86.10)

(useful annulating reagent for constructing heterocycles)

Alternate Name: butanedial.

Physical Data: oil, bp 62 °C/14 mmHg.

Solubility: v sol water, alcohol, ether.

Preparative Methods: easily made by acidic hydrolysis of its stable, commercially available synthetic equivalent ***2,5-Dimethoxytetrahydrofuran*** (or its diethoxy analog), followed by extraction with ether and distillation (eq 1).[1]

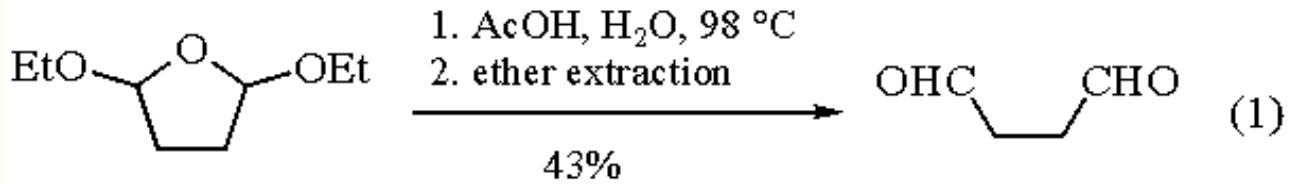

Handling, Storage, and Precautions: succindialdehyde rapidly polymerizes and has to be used immediately after distillation. Use in a fume hood.

Annulations.

Succindialdehyde is largely used as an annulating agent in the synthesis of pyrrole and pyrrolidine derivatives. Use of 2,5-dimethoxytetrahydrofuran as a precursor of the dialdehyde may be preferred in some instances. A familiar example is the Robinson-Schöpf cyclization (eq 2)[2] (for similar reactions see also ***Glutaraldehyde***).

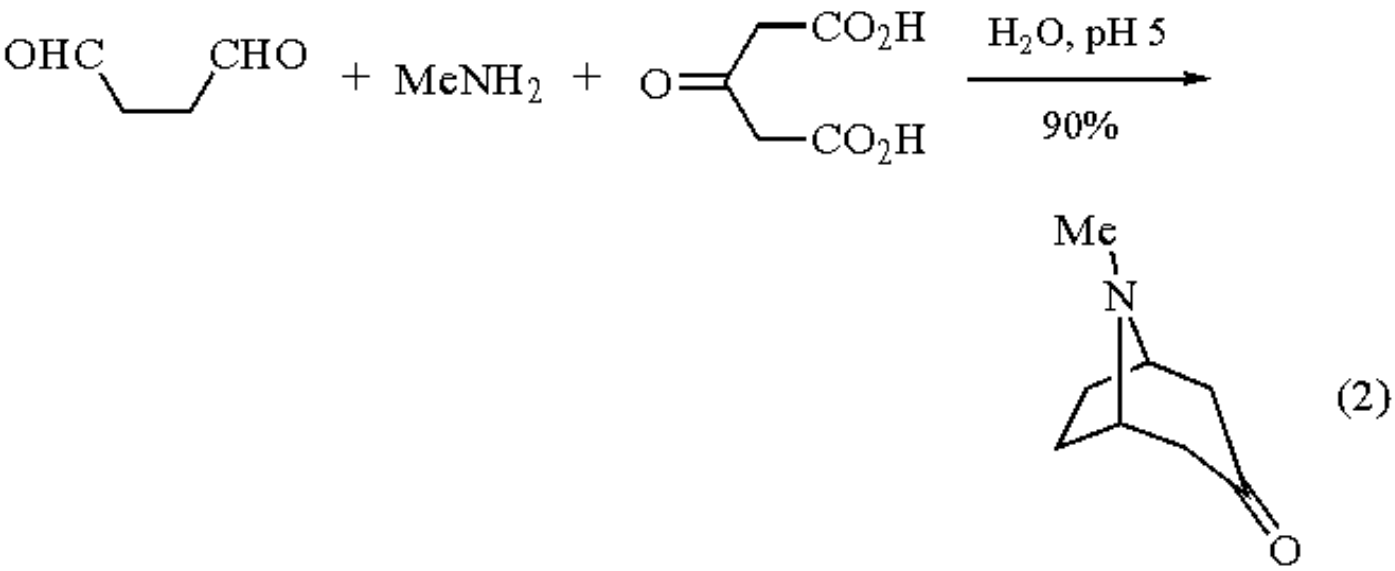

Using the same methodology, 2,5-dicyanopyrrolidines can be prepared with cyanide as nucleophile (eq 3); in this example,

succindialdehyde is used as its bis-sodium bisulfite adduct.[3]

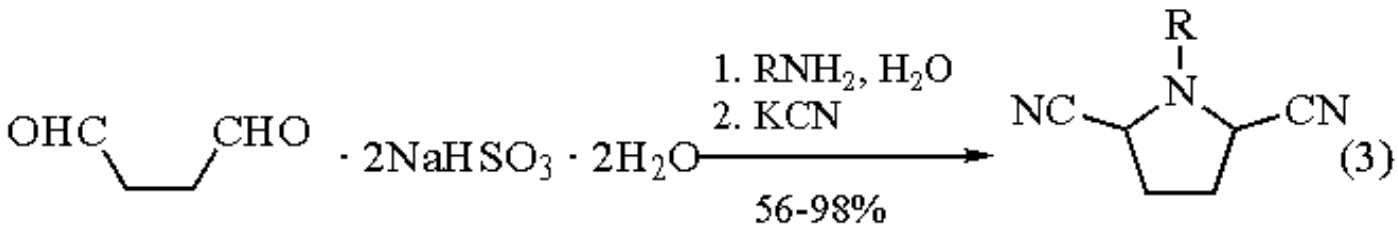

Pyrrolidines are formed by reductive alkylation (eq 4),[4] whereas in the absence of any nucleophilic reagent the double condensation of succindialdehyde with a primary amine gives a pyrrole (eq 5).[5]

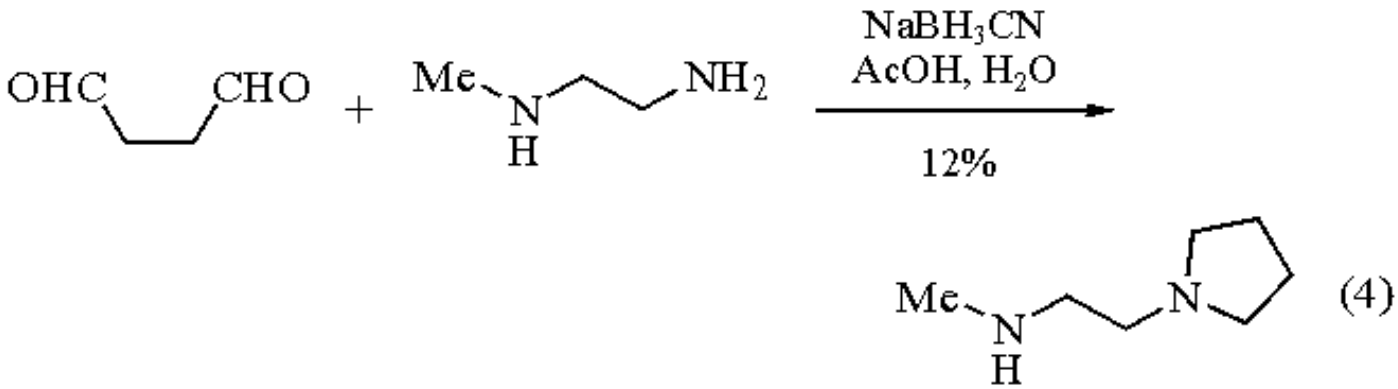

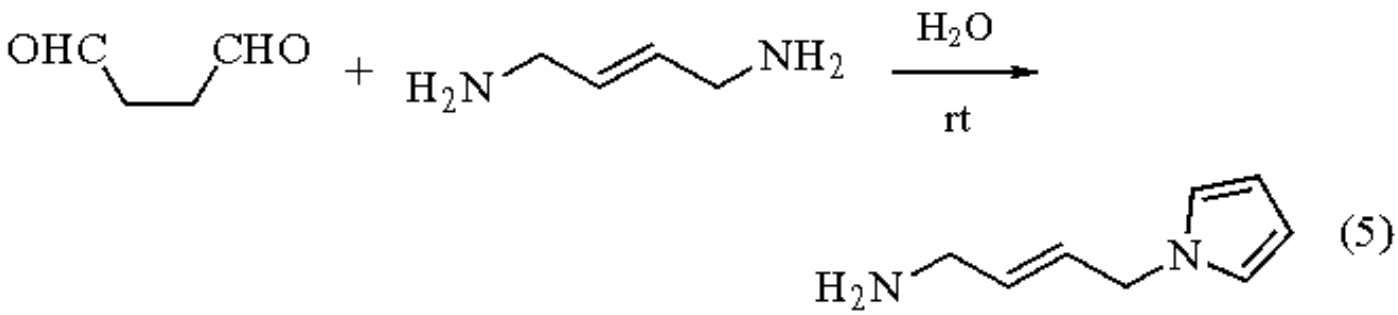

Succindialdehyde can also be considered as a linear C_4 unit useful in the synthesis of natural products. It has been used as starting material in the synthesis of squalene;[6] the first step consists of the addition of a Grignard reagent to both aldehyde functions (eq 6).

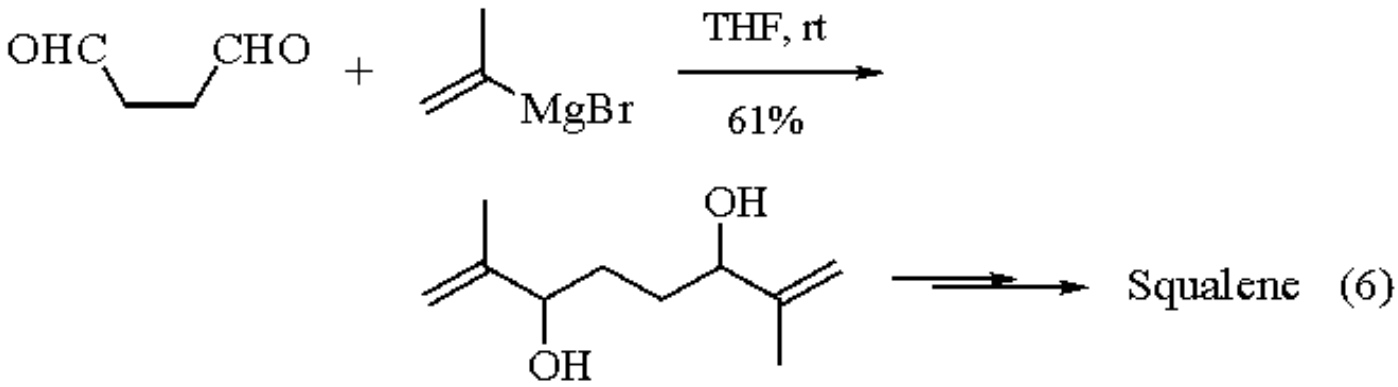

The diol thus obtained can be cyclized to give a 2,5-dialkyltetrahydrofuran, as in the example (eq 7) using Mitsunobu conditions.[7]

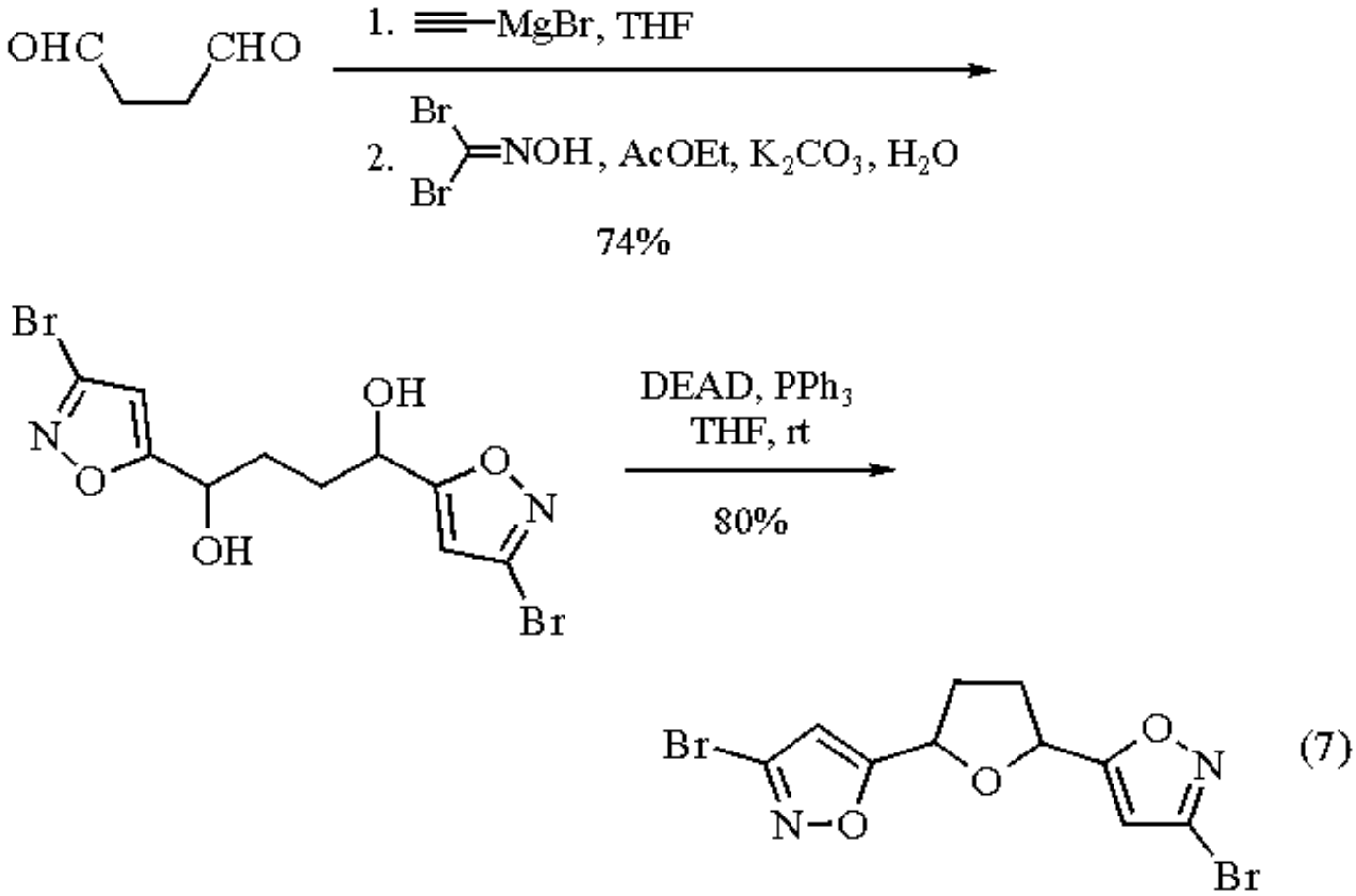

Succindialdehyde has also proved useful in the synthesis of the anthracycline skeleton (eq 8) via two aldol-type reactions.[8]

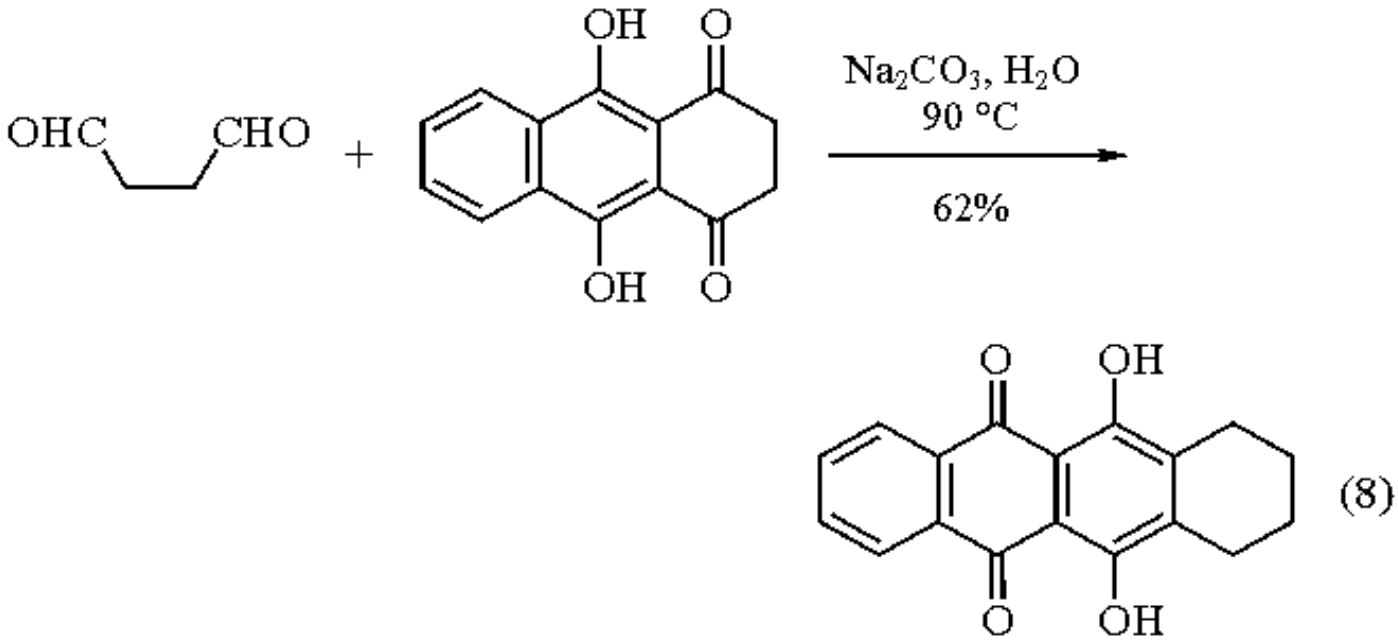

A formal phenyl homologation can be achieved by the double aldol condensation of phthalaldehyde with succindialdehyde. In this example, succindialdehyde is generated in situ from 2,5-dimethoxytetrahydrofuran (eq 9).[9]

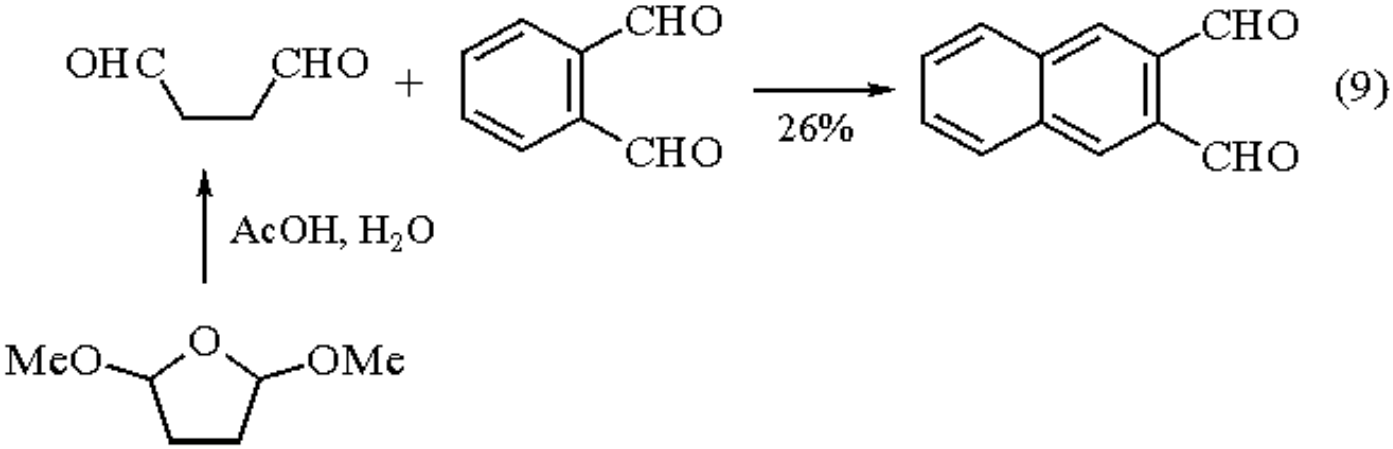

Related Reagents.

Diethyl Succinate; ***Malondialdehyde***.

---

1. Fakstorp, J.; Raleigh, D.; Schniepp, L. E. *JACS* **1950**, *72*, 869.
2. (a) Robinson, R. *JCS* **1917**, *111*, 762. (b) Schöpf, C.; Lehmann, G. *LA* **1935**, *518*, 1.
3. Takahashi, K.; Saitoh, H.; Ogura, K.; Iida, H. *H* **1986**, *24*, 2905.
4. Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. J. *JMC* **1991**, *34*, 181.
5. (a) Hinshaw, J. C. *JOC* **1975**, *40*, 47. (b) Jacobi, P. A.; Buddhu, S. C. *TL* **1988**, *29*, 4823.
6. Faulkner, D. J.; Petersen, M. R. *JACS* **1973**, *95*, 553.
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8. Morris, M. J.; Brown, J. R. *TL* **1978**, 2937.
9. Mallouli, A.; Lepage, Y. *S* **1980**, 689.

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CNRS, Gif-sur-Yvette, France

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Succinic Anhydride

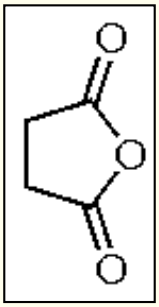

[108-30-5] · $C_4H_4O_3$ · Succinic Anhydride · (MW 100.08)

(acylation reactions,[1-8] lactone synthesis,[9-14] Reformatsky reaction[15])

Alternate Names: succinic acid anhydride; butanedioic anhydride; dihydro-2,5-furandione; succinyl anhydride.

Physical Data: mp 119-120 °C; bp 261 °C; vapor density 3.5; vapor pressure 1 mmHg (92 °C).

Form Supplied in: colorless needles or white flakes.

Solubility: slightly sol water; sol toluene (10.0 g L^{-1} at 30 °C).

Handling, Storage, and Precautions: use only in a chemical fume hood; severe eye irritant; moisture sensitive; store in cool dry place.

Acylation Reactions.

N- and *O*-Acylation.

Succinic anhydride (**1**) is a reactive acylating agent and reacts rapidly with amines. For alcohols, procedures often call for use of ***Pyridine*** or ***4-Dimethylaminopyridine*** as catalyst. The *N*-acylation reaction has been extensively used for the synthesis of chiral succinimides (eq 1),[1a] which are important intermediates in asymmetric synthesis.[1] The *O*-acylation has been widely employed as a facile method for enzymatic resolution of racemic alcohols (eq 2).[2]

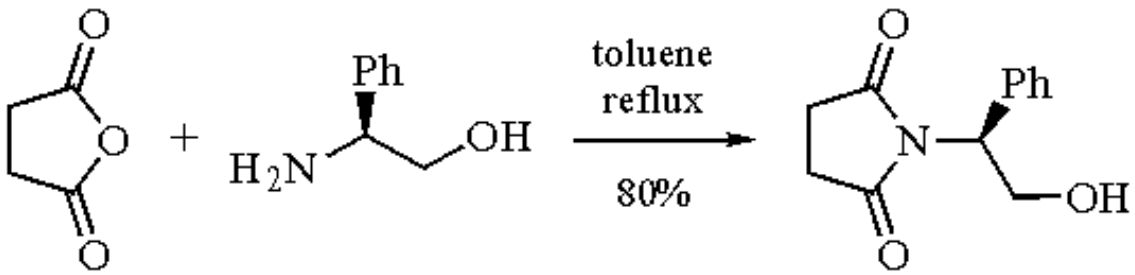

(1)

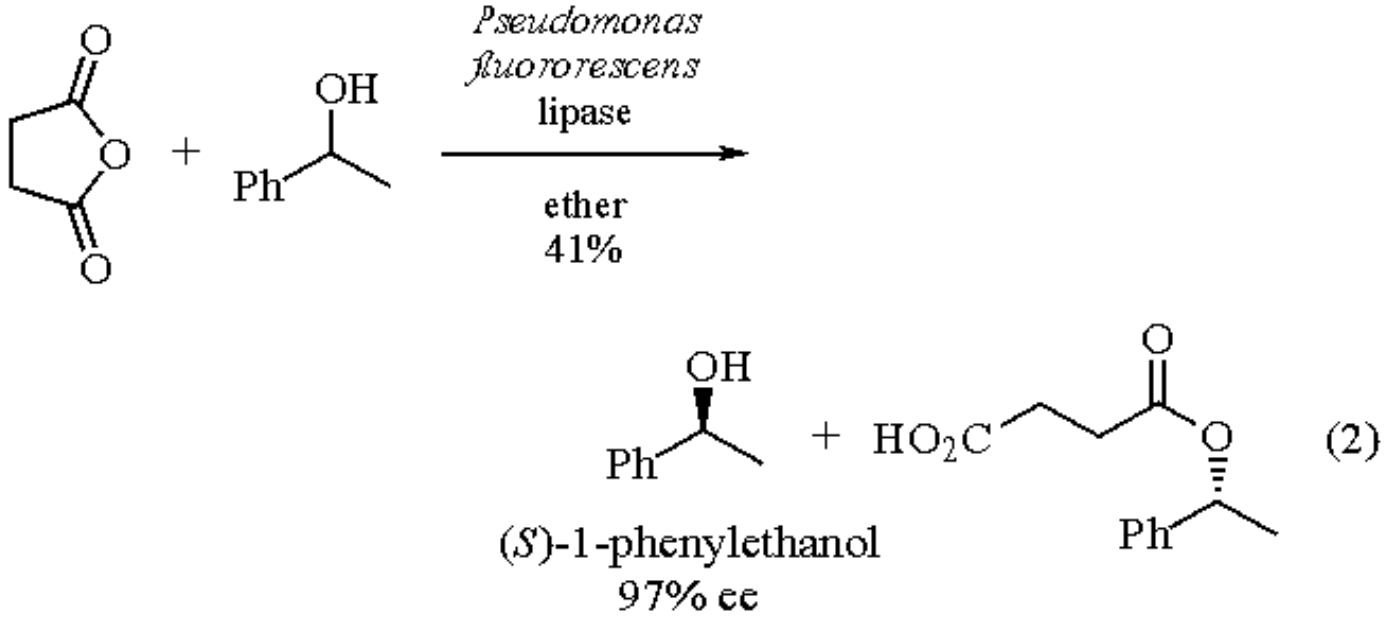

Acylation of Organometallic Agents.

γ-Keto acids can be obtained in good yield by reaction of organomanganese(II) compounds with (**1**) (eq 3).[3]

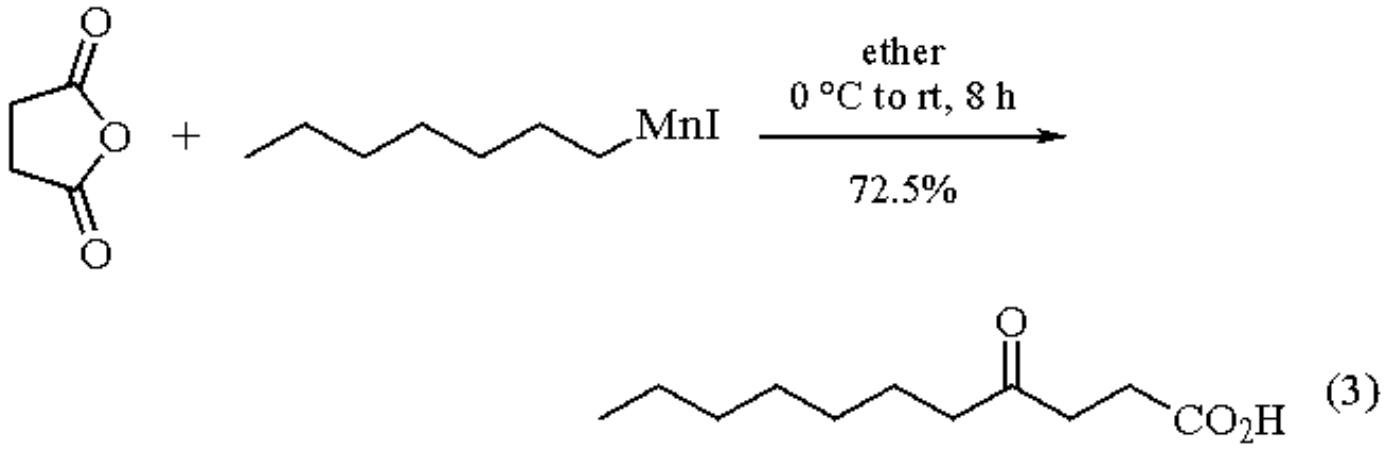

The keto acid intermediate in the khellin total synthesis was readily prepared by addition of (**1**) to the dianion of 3-furoic acid (eq 4).[4] The anion derived from diphenylmethane reacts with (**1**) to form the diphenylmethyl ketone in 63% yield.[5]

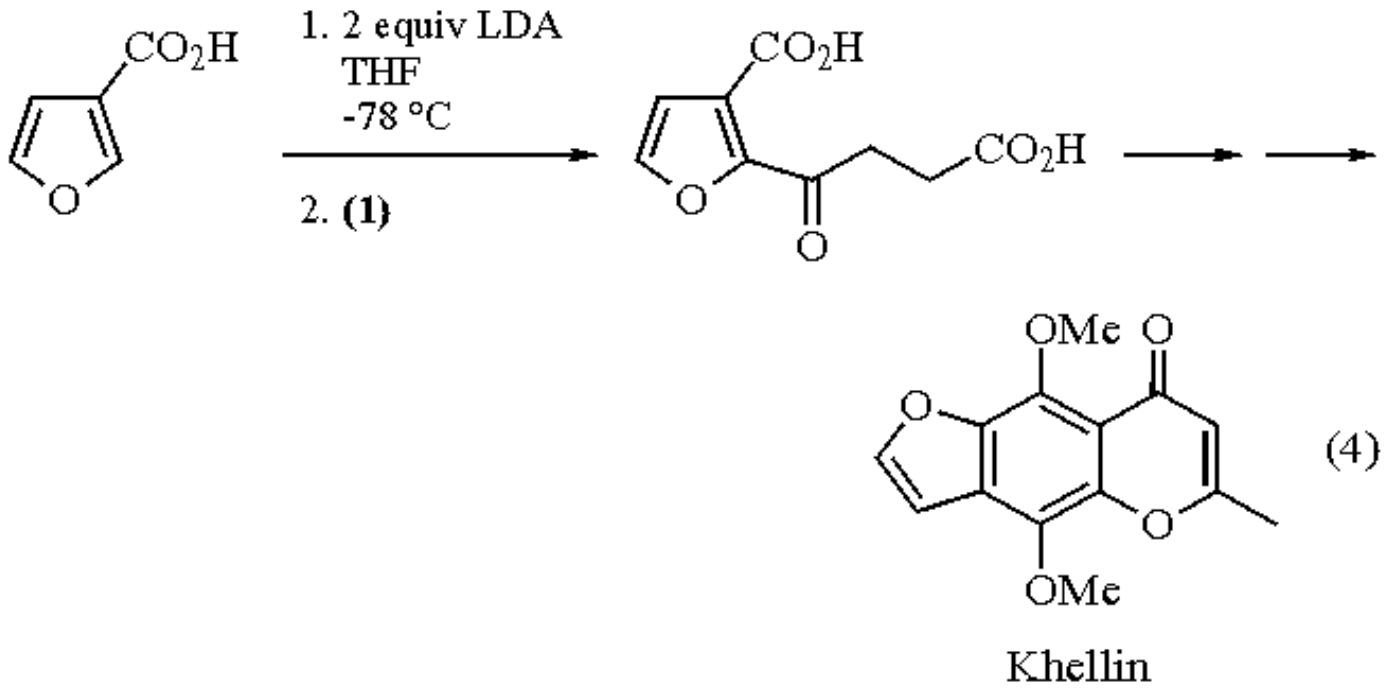

(4)

Acylation of Ketone Enolates.

Aryl 1,3-diketones have been prepared in good yields by quenching the enolate of an aryl methyl ketone with (**1**) (eq 5).[6]

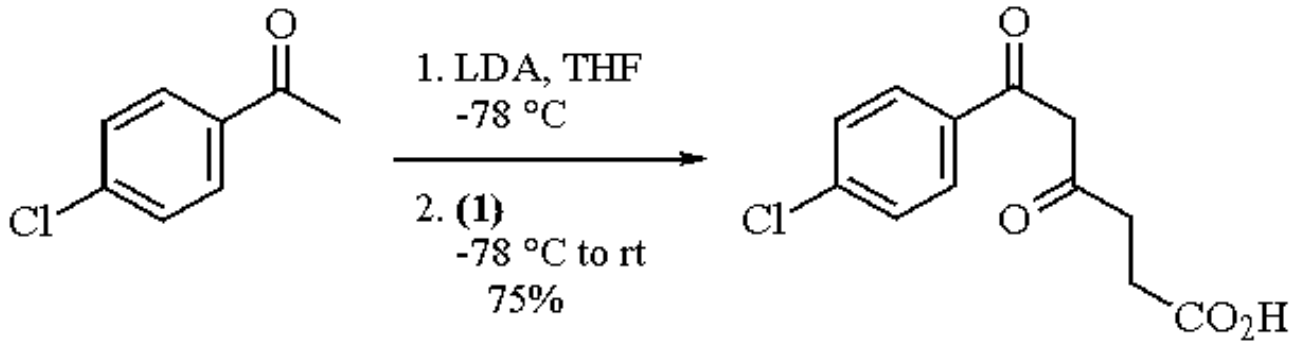

(5)

Friedel-Crafts Acylation.

Alkenes[7] and aromatic[8] compounds react with (**1**) in the presence of Lewis acid catalysts to give various succinoylation products,[8c] which are useful synthetic intermediates. Selected examples are shown in eqs 6 and 7.[7a,8a]

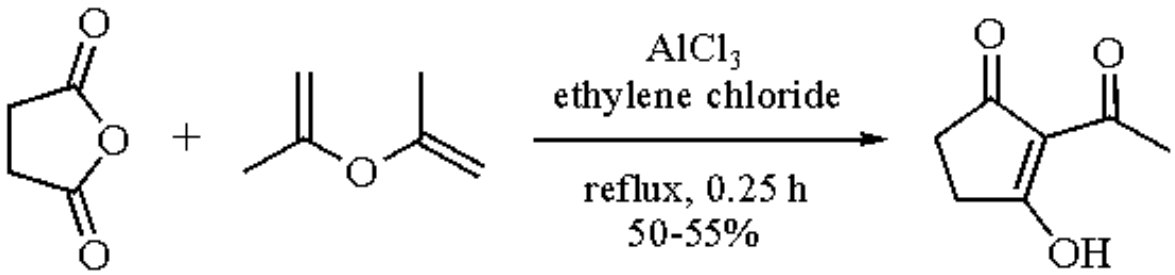

(6)

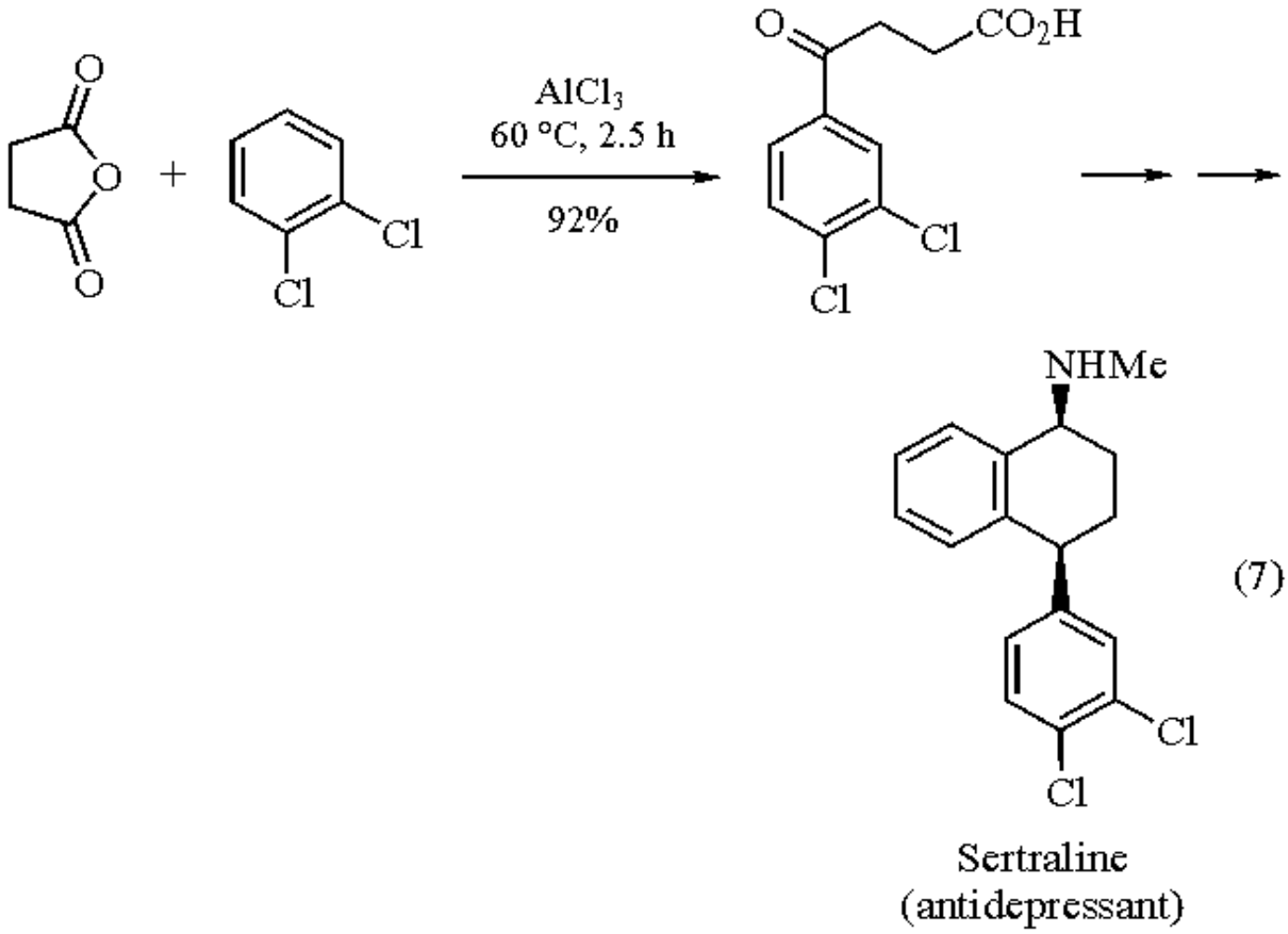

(7)

Lactone Synthesis.

Reduction.

Anhydride (**1**) can be reduced to give γ-butyrolactone by metal oxide catalysts[9a] by catalytic hydrogenation,[9b] and by ***Sodium Borohydride***.[10a] Similar reductions of unsymmetrical succinic anhydrides by hydrogenation $[Ru(PPh_3)_3Cl_2]$,[10b] sodium borohydride,[10a,c] or ***Lithium Aluminum Hydride***[10d] often occur selectively at the more hindered carbonyl group, although some exceptions have been reported.[10e]

Spirolactone Synthesis.

Diaddition of Grignard reagents to (**1**) gives spirolactones in good yield.[11] The reaction has been applied to the preparation of a key intermediate in the synthesis of cubebene (eq 8).[11c] Monoaddition of cerium 3-cerio propoxide to (**1**) gives the oxaspirolactone (eq 9).[12]

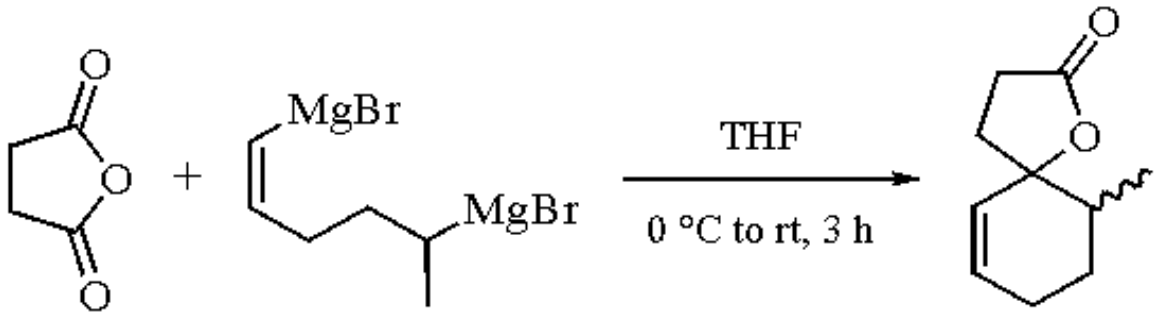

(8)

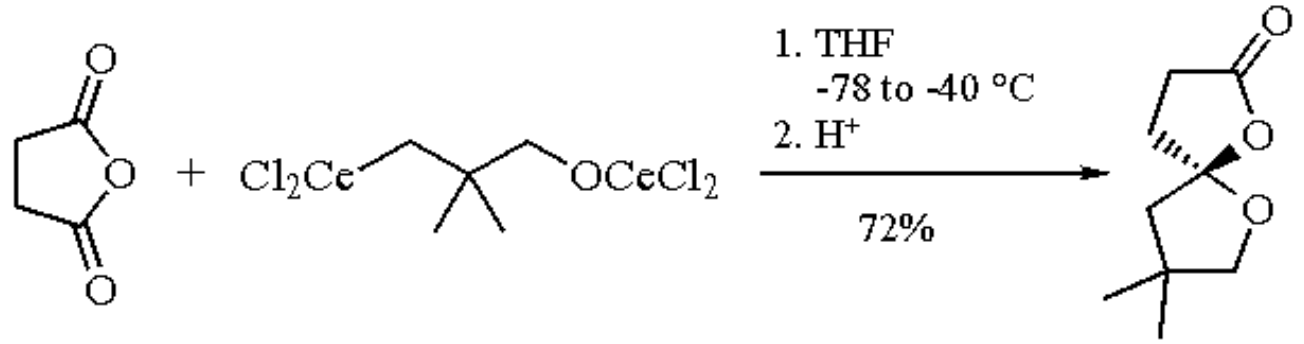

Condensation with Aldehydes and Ketones.

The enolate of (**1**) can be successfully prepared by treatment of (**1**) with a sterically hindered alkoxide, lithium 1,1-bis(trimethylsilyl)-3-methyl-1-butoxide, in THF at -78 °C. The enolate readily reacts with aldehydes and ketones to give γ-butyrolactones (eq 10).[13]

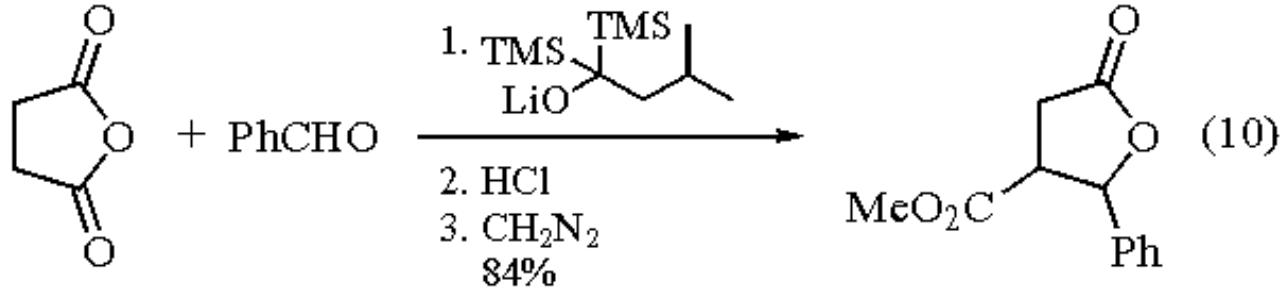

Wittig Reaction.

Enol lactones can be prepared by the Wittig reaction between stabilized phosphoranes and (**1**) (eq 11).[14]

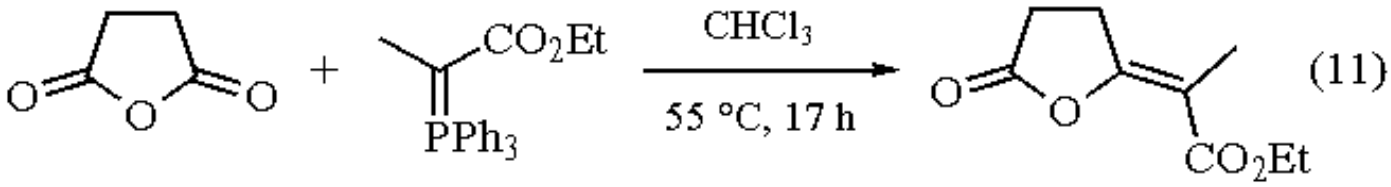

Reformatsky Reaction.

Electrolysis of ethyl 2-bromo-2-methylpropanoate in the presence of (**1**) in DMF gave 1-ethyl 3-oxo-2,2-dimethylhexanedioate in 65% yield (eq 12).[15] This electrochemically assisted procedure circumvented both the problems of zinc activation and the difficulty associated with the uncontrollable exothermic course of the normal Reformatsky reaction of cyclic carboxylic anhydrides.

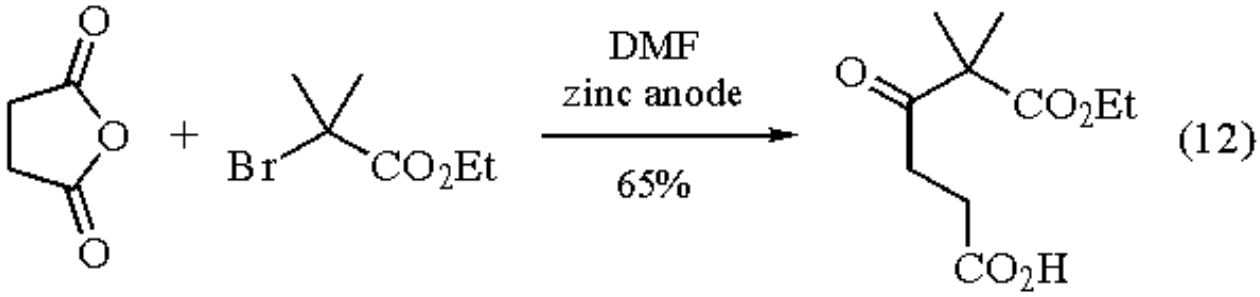

Vinyl Ether Synthesis.

Use of (**1**) as a methanol scavenger, provides an improved procedure for the preparation of vinyl ethers.[16] The method has been used for the synthesis of spiro vinyl ethers (eq 13).[16b]

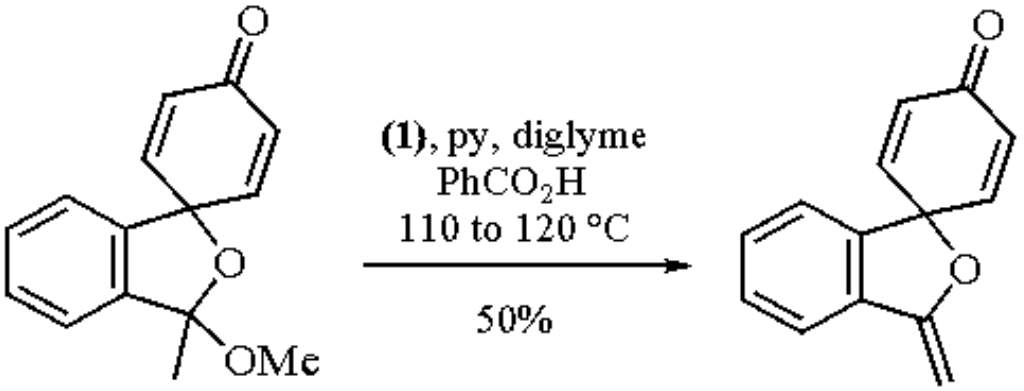

(13)

Related Reagents.

Acetic Anhydride; ***Acetic Formic Anhydride***; ***Benzoic Anhydride***; ***Diethyl Succinate***; ***Itaconic Anhydride***; ***Maleic Anhydride***; ***Succindialdehyde***; ***Succinimide***.

---

1. (a) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *JOC* **1989**, *54*, 4243. (b) Polniaszek, R. P.; Belmont, S. E. *JOC* **1990**, *55*, 4688.
2. (a) Terao, Y.; Tsuji, K.; Murata, M.; Achiwa, K.; Nishio, T.; Watanabe, N.; Seto, K.; Achiwa, K. *CPB* **1989**, *37*, 1653. (b) Ottolina, G.; Carrea, G.; Riva, S. *JOC* **1990**, *55*, 2366. (c) Nicotra, F.; Riva, S.; Secundo, F.; Zucchelli, L. *SC* **1990**, *20*, 679.
3. Friour, G.; Cahiez, G.; Normant, J. F. *S* **1985**, 50.
4. Gammill, R. B.; Hyde, B. R. *JOC* **1983**, *48*, 3863.
5. Bunce, R. A.; Dowdy, E. D. *SC* **1990**, *20*, 3007.
6. (a) Murray, W. V.; Wachter, M. P. *JOC* **1990**, *55*, 3424. (b) *FF* **1981**, *9*, 82.
7. (a) Merényi, F.; Nilsson, M. *OS* **1972**, *52*, 1. (b) Naora, H.; Ohnuki, T.; Nakamura, A. *CL* **1988**, 143.
8. (a) Quallich, G. J.; Williams, M. T.; Friedmann, R. C. *JOC* **1990**, *55*, 4971. (b) Murakami, Y.; Tani, M.; Ariyasu, T. Nishiyama, C.; Watanabe, T.; Yokoyama, Y. *H* **1988**, *27*, 1855. (c) Rao, Y. S.; Kretchmer, R. A. *OPP* **1971**, *3*, 177. (d) Zheng, G-C; Kojima, T.; Kakisawa, H. *H* **1988**, *27*, 1341. (e) Rahman, U.; Torre, M. C. *LA* **1968**, *718*, 136.
9. (a) Takahashi, K.; Shibagaki, M.; Matsushita, H. *BCJ* **1992**, *65*, 262. (b) Hara, Y.; Wada, K. *CL* **1991**, 553.
10. (a) Bailey, D.; Johnson, R. *JOC* **1970**, *35*, 3574. (b) Morand, P.; Kayser, M. *CC* **1976**, 314. (c) Kayser, M.; Morand, P. *CJC* **1980**, *58*, 2484. (d) Bloomfield, J. J.; Lee, S. L. *JOC* **1967**, *32*, 3919. (e) Makhlouf, M. A.; Rickborn, B. *JOC*, **1981**, *46*, 4810.
11. (a) Murty, Y. V. S. N.; Pillai, C. N. *TL* **1990**, *31*, 6067. (b) Canonne, P.; Bélanger, D. *CC* **1980**, 125. (c) Canonne, P.; Boulanger, R.; Angers, P. *TL* **1991**, *32*, 5861.
12. Mudryk, B.; Shook, C. A.; Cohen, T. *JACS* **1990**, *112*, 6389.
13. Minami, N.; Kuwajima, I. *TL* **1977**, 1423.
14. Doyle, I. D.; Massy-Westropp, R. A.; Warren, R. F. O. *S* **1986**, 845.
15. Schwarz, K-H; Kleiner, K.; Lugwig, R.; Schick, H. *JOC* **1992**, *57*, 4013.
16. (a) Buchanan, G.; Gustafson, A. *JOC* **1973**, *38*, 2910. (b) Wang, S.; Morrow, G. W.; Swenton, J. S. *JOC* **1989**, *54*, 5364.

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Succinimide[1]

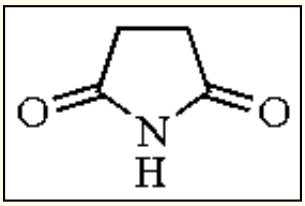

[123-56-8] · $C_4H_5NO_2$ · Succinimide · (MW 99.10)

(building block for synthesis of other heterocyclic compounds, especially via *N*-acyliminium cyclizations[2])

Physical Data: mp 126-127 °C; bp 287-288 °C (slight decomposition); *d* 1.418 g cm^{-3}; dipole moment 1.54 D (dioxane, 20 °C); pK_a 9.656 (H_2O, 25 °C).

Solubility: sol H_2O (1 g/3 mL at 20 °C; 1 g/0.7 mL at bp), ethanol (1 g/24 mL at 20 °C; 1 g/5 mL at 60 °C); insol ether, chloroform.

Form Supplied in: white solid.

Handling, Storage, and Precautions: may be harmful by inhalation, ingestion, or skin absorption; may cause irritation. Use in a fume hood.

Reactions at the Nitrogen Atom.

The most widely used method for direct *N*-alkylation of succinimide is the Mitsunobu condensation[3] with primary[4] or secondary[5] alcohols under the influence of ***Triphenylphosphine*** and dialkyl azodicarboxylates (eq 1).[4] The extraction and purification steps are often tedious, on account of Ph_3PO and $RO_2CNHNHCO_2R$, formed in the reaction. Therefore, reaction of alkali metal salts of succinimide with primary halides or sulfonates is usually more convenient in cases where the electrophile does not give side reactions with the basic substrate (eq 2).[6] The alkali metal salt can be prepared by reaction of ***Sodium Methoxide*** in MeOH, or ***Potassium t-Butoxide*** in *t*-BuOH, and can also be generated from the alkali metal hydride in DMF or HMPA, without isolation of the salt. Solid-liquid phase-transfer catalysis (***Potassium Carbonate***, 0.1 equiv ***18-Crown-6***, reflux in benzene or toluene)[7] is also used for *N*-alkylation of succinimide in high yield. Addition of 0.1 equiv of ***Potassium Iodide*** increases the reaction rate for less reactive halides.

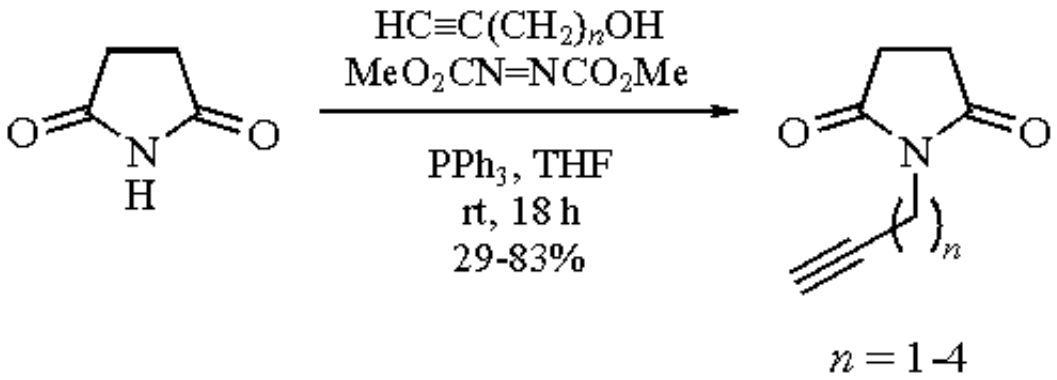

(1)

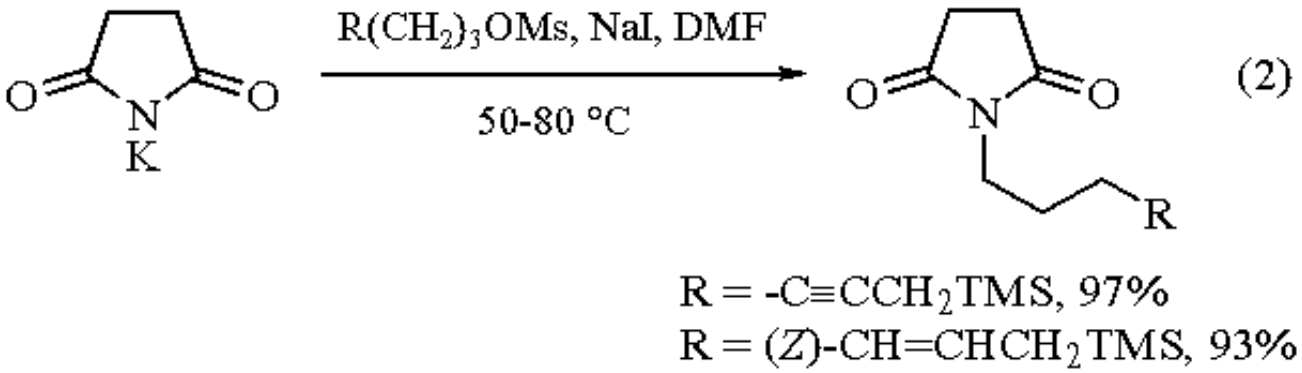

N-Alkenyl and *N*-alkynylsuccinimides are important intermediates in the synthesis of other heterocyclic compounds. Upon partial reduction (***Sodium Borohydride***, EtOH, H^+) to the hydroxylactam and treatment with acid, an *N*-acyliminium cyclization occurs (eq 3).[2]

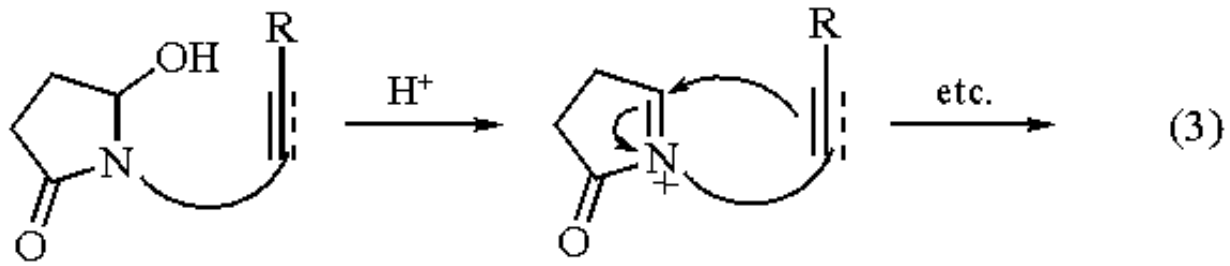

The ***Copper(I) Iodide*** promoted reaction of potassium succinimide with a vinyl bromide in an aprotic solvent affords the *N*-vinyl derivative (eq 4).[8] *N*-Alkoxycarbonyl derivatives can be prepared with the corresponding alkyl chloroformate (eq 5).[9]

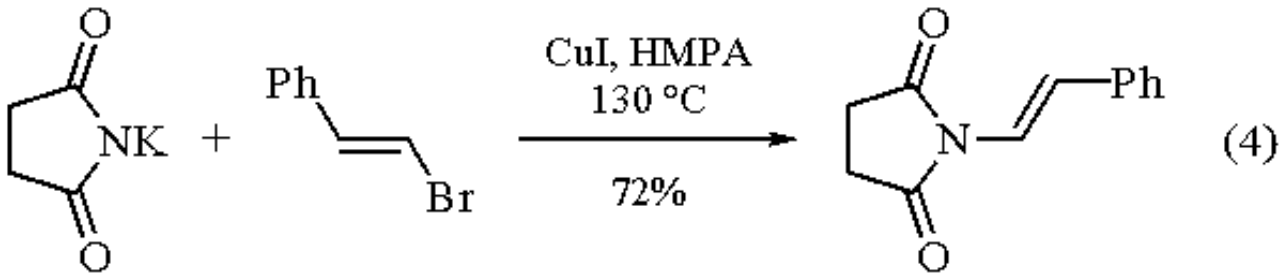

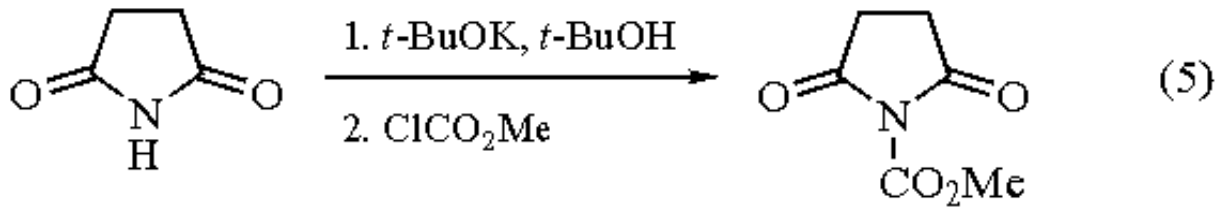

Reactions at the Carbonyl Group.

Addition of Grignard reagents (3 equiv; or first 1 equiv of MeMgCl and then 2 equiv of the more expensive reagent) provides hydroxylactams,[10] which can be reduced with ***Sodium Cyanoborohydride*** at pH 3 to the 5-alkylpyrrolidinone (eq 6).[10a]

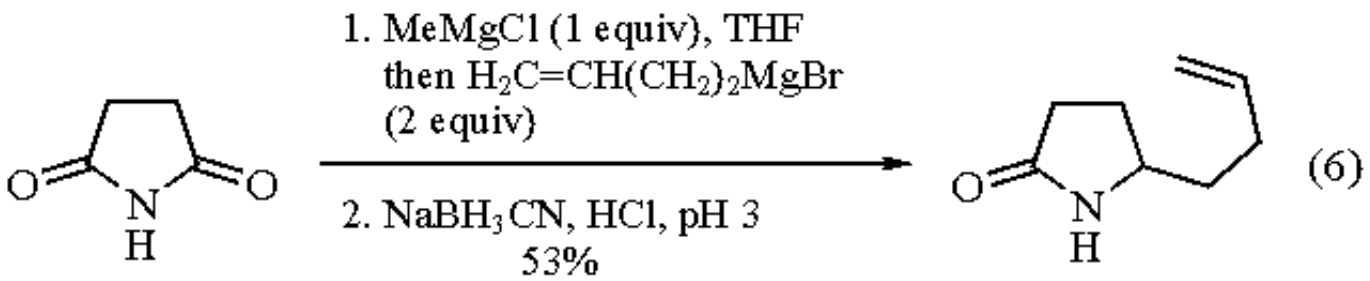

For intermolecular Wittig reactions of succinimide with stabilized phosphoranes, high temperatures are necessary and yields are poor.[11]

The intramolecular reaction proceeds somewhat better and can be applied to the synthesis of pyrrolizidine derivatives. *N*-Alkylation of sodium succinimide with bromophosphorane (**1**) and subsequent intramolecular Wittig reaction affords the pyrrolizidinedione (**2**) (eq 7).[12] Another pyrrolizidine compound is obtained upon reaction of sodium succinimide with cyclopropyl derivative (**3**). The reaction presumably proceeds via nucleophilic opening of the activated cyclopropane ring, leading to a stabilized ylide which then undergoes an intramolecular Wittig reaction (eq 8).[13]

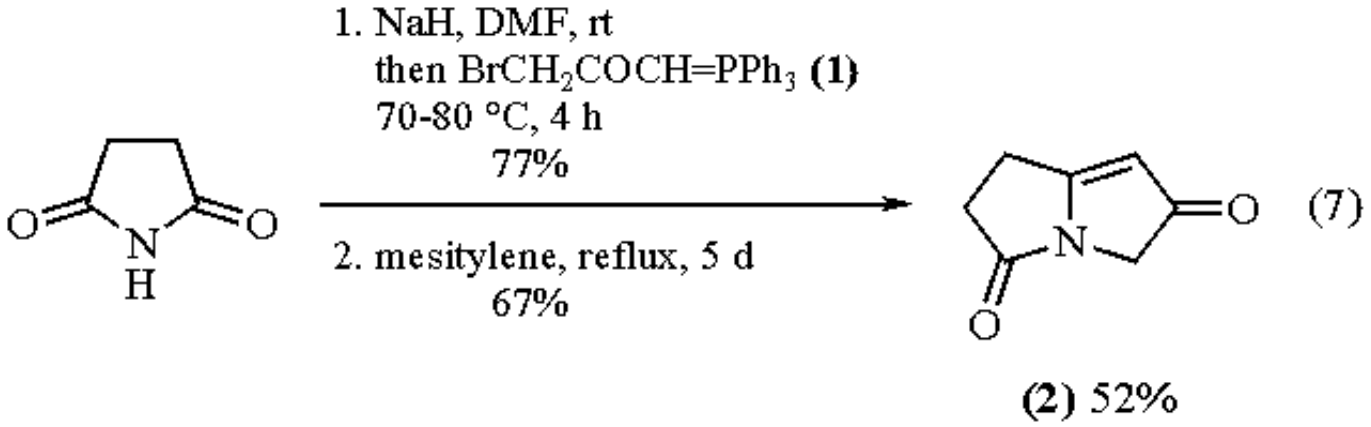

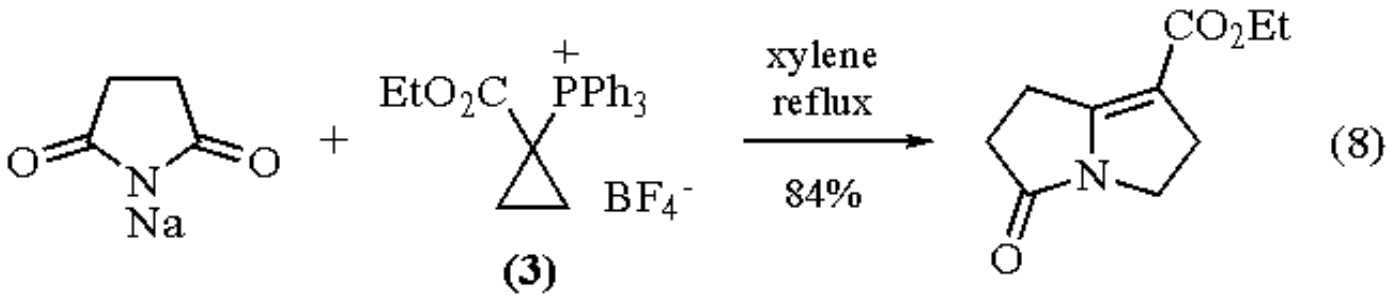

Reactions at the α-Methylene Position.

Upon reaction of the dipotassium or disodium salt of succinimide with electrophiles, such as ***Benzyl Chloride***, benzophenone, or methyl benzoate, 2-substituted succinimide derivatives are obtained in moderate yields (eq 9).[14]

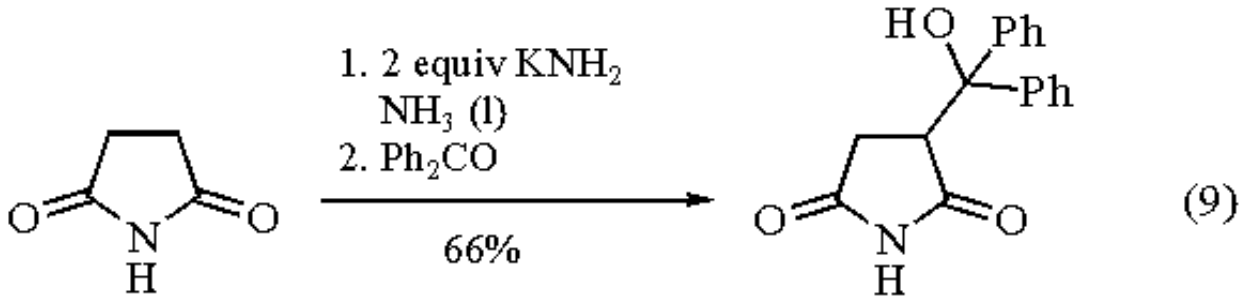

Related Reagents.

Glutarimide; ***Phthalimide***.

---

1. Hargreaves, M. K.; Pritchard, J. G.; Dave, H. R. *CRV* **1970**, *70*, 439.
2. (a) Speckamp, W. N.; Hiemstra, H. *T* **1985**, *41*, 4367. (b) Hiemstra, H.; Speckamp, W. N. *COS* **1991**, *2*, 1047.
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11. Flitsch, W.; Schindler, S. R. *S* **1975**, 685.
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14. Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *S* **1977**, 509.

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Sulfamide[1]

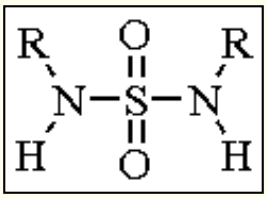

(R = H)

[7803-58-9] · $H_4N_2O_2S$ · Sulfamide · (MW 96.13) (R = Et)

[6104-21-8] · $C_4H_{12}N_2O_2S$ · *N,N´*-Diethylsulfamide · (MW 152.25) (R = *n*-Pr)

[19757-10-9] · $C_6H_{16}N_2O_2S$ · *N,N´*-Dipropylsulfamide · (MW 180.31) (R = *t*-Bu)

[13952-67-5] · $C_8H_{20}N_2O_2S$ · *N,N´*-Di-*t*-butylsulfamide · (MW 208.37) (R = $NO_2C_6H_4$)

[19757-13-2] · $C_{12}H_{10}N_4O_6S$ · *N,N´*-Bis(4-nitrophenyl)sulfamide · (MW 338.33)

(useful for synthesis of substituted 1,2,6-thiadiazine 1,1-dioxides,[3] 1,2,5-thiadiazolidine 1,1-dioxides,[7] sulfamoylamidines,[11] and nitriles[12])

Physical Data: R = H, mp 93 °C, dipole moment 3.9 D; R = Et, mp 67 °C; R = *n*-Pr, mp 118 °C; R = *t*-Bu, mp 140 °C; R = $NO_2C_6H_4$, mp 197 °C.

Solubility: R = H, freely sol water, hot alcohol, acetone; more acidic than urea, and can act as a dibasic acid.

Preparative Methods: N,N´-diethylsulfamide is prepared by addition of a solution of ***Sulfuryl Chloride*** (0.889 mol) in petroleum ether, at -30 °C, to a mixture of ethylamine (2.2 mol) and ***Pyridine*** (1.76 mol) in petroleum ether. Stirring at rt followed by acidic workup affords *N,N´*-diethylsulfamide (45% yield). Large alkyl (C_3 to C_6) sulfamides are prepared by addition of a solution of an alkylamine (2.5 mol) in chloroform to a mixture of pyridine (4 mol) and sulfuryl chloride (1 mol) in chloroform at -5 °C. Similar workup as above gives *N,N´*-dialkylsulfamides in 58-69% yield.[1,2]

Handling, Storage, and Precautions: use in a fume hood.

General Discussion.

Sulfamide reacts with 1,3-diketones (eq 1)[3] and β-amino α,β-unsaturated ketones (eq 2)[4] to provide substituted 2*H*-1,2,6-thiadiazine 1,1-dioxides. The reaction of sulfamide with ***Malononitrile*** (eq 3)[5] or cyanogen (eq 4)[6] under acid catalysis yields 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxides or 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide. 3-Imino-4-substituted 1,2,5-thiadiazolidines[7] can be prepared from sulfamide, aldehydes, and metal cyanides (eq 5).

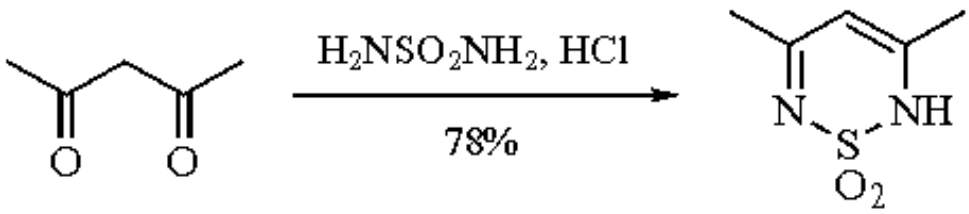

(1)

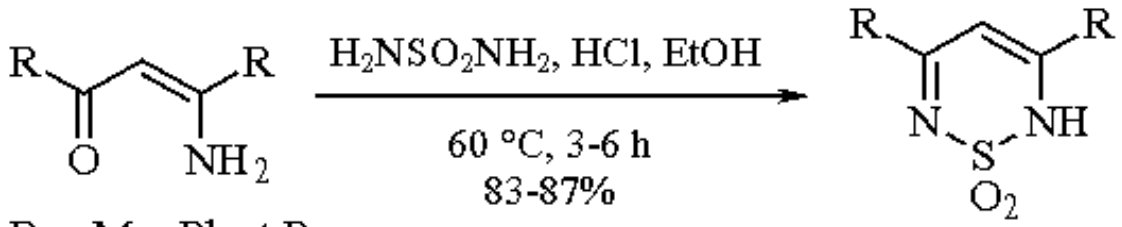

R = Me, Ph, *t*-Bu (2)

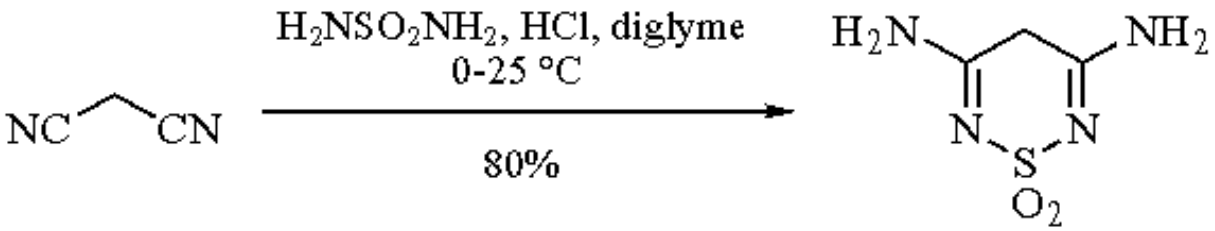

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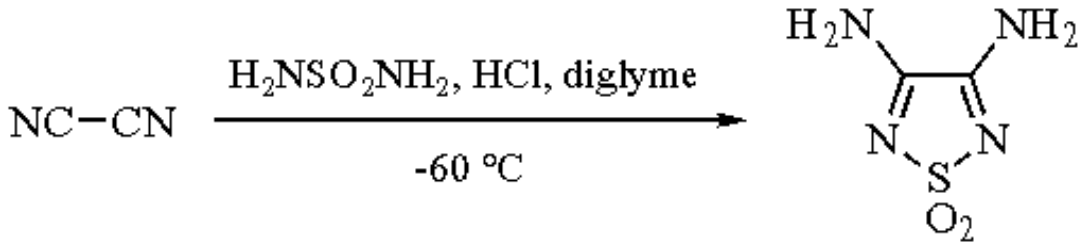

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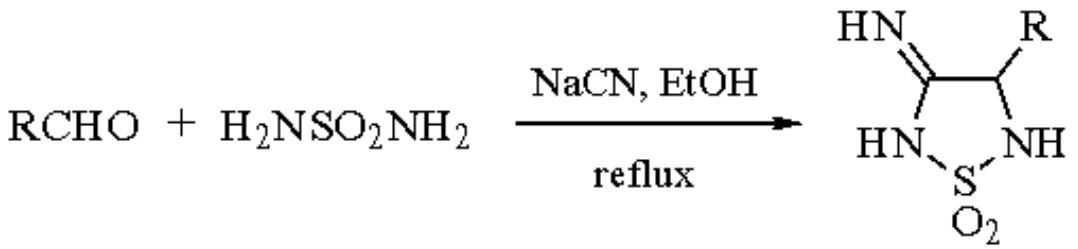

(5)

R	Yield (%)
hexyl	40
4-methoxyphenyl	62
2-pyrrolyl	12

N,*N*′-Cyclic sulfamides are synthesized by heating sulfamide with 1,2- or 1,3-diamines in pyridine or diglyme solvent (eqs 6 and 7).[8,9] Reaction temperature is an important factor in this cyclization, because at lower temperature uncyclized products may be obtained (eq 6).[8]

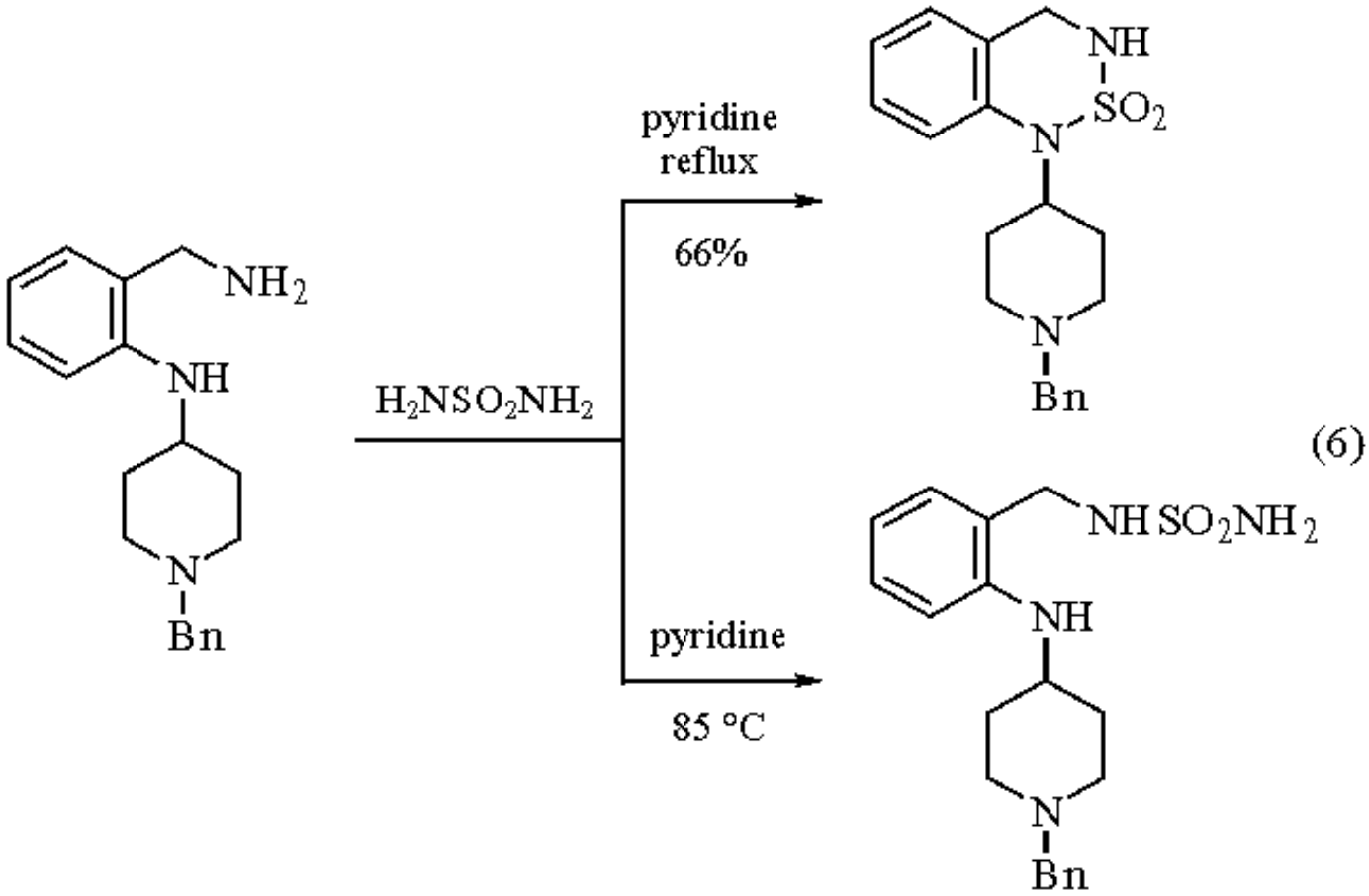

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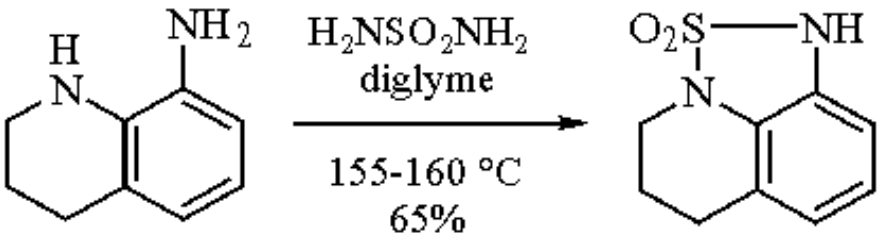

(7)

Sulfamide can be used to form eight-membered heterocyclic compounds[10] and the very toxic tetramethylenedisulfotetramine (eqs 8 and 9).[11]

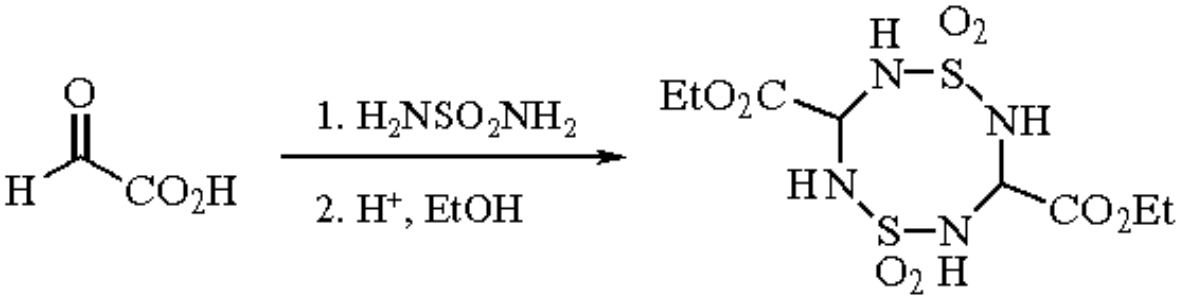

(8)

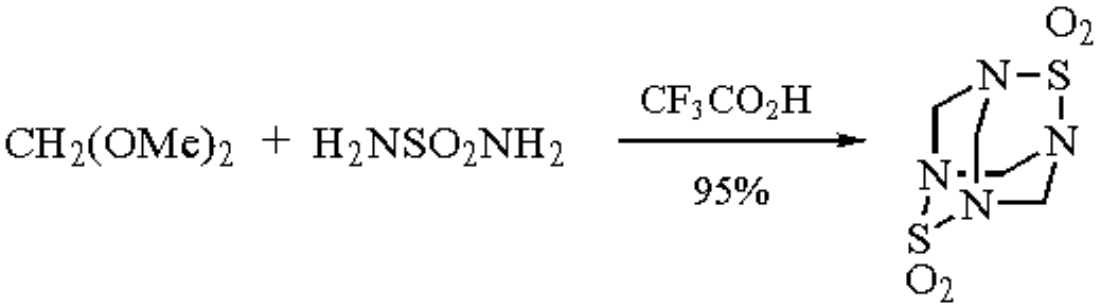

(9)

N-Sulfamoylamidines,[12] nitriles,[13] and azoalkanes[2] have been prepared by using sulfamide or substituted sulfamides (eqs 10-12).

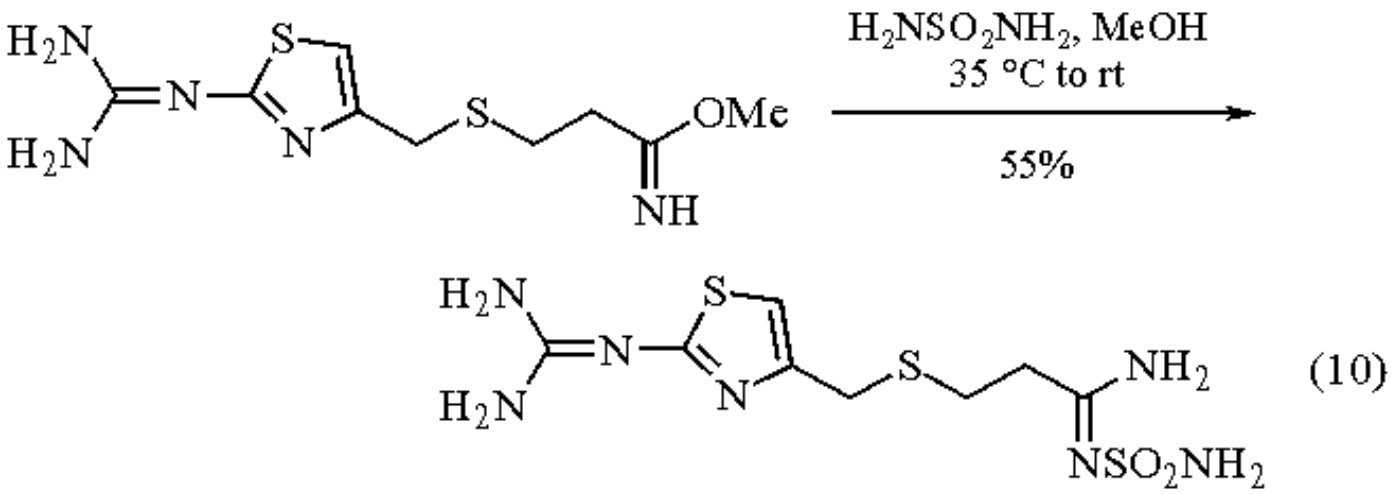

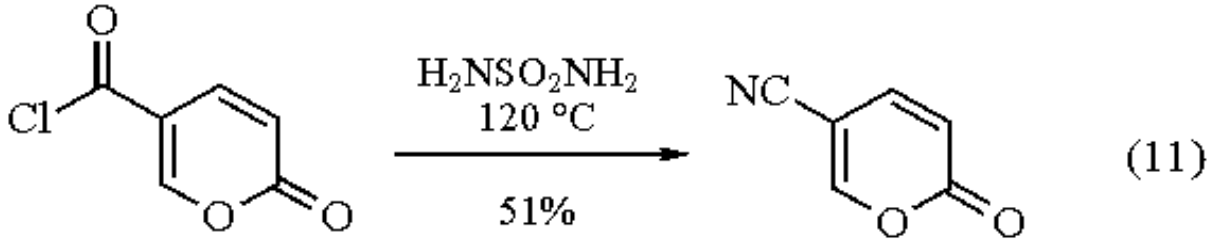

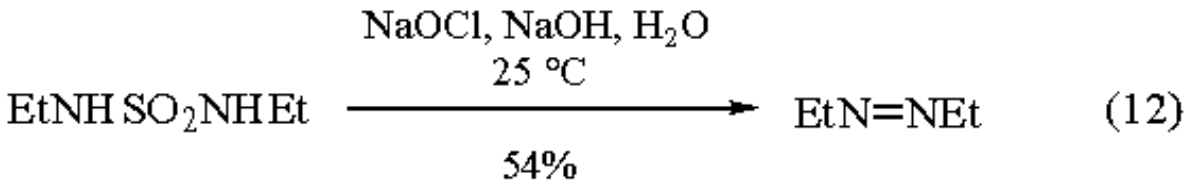

Related Reagents.

Sulfuryl Chloride; ***N,N´-Sulfuryldiimidazole***.

---

1. Hantzsch, A.; Holl, A. *CB* **1901**, *34*, 3420.
2. Ohme, R.; Preuschhof, H; Heyne, H-U. *OSC* **1988**, *6*, 78.
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Sulfene[1]

$H_2C{=}SO_2$

[917-73-7] · CH_2O_2S · Sulfene · (MW 78.10)

(reactive intermediate used for sulfonations and as a partner in [2 + 2], [3 + 2], [4 + 2], [8 + 2], and 1,3-dipolar cycloaddition reactions)

Solubility: sol CH_2Cl_2, THF, Et_2O, MeCN.

Preparative Methods: prepared in situ by reaction of ***Methanesulfonyl Chloride*** and ***Triethylamine*** in a solvent such CH_2Cl_2. The sulfonyl chloride is usually added slowly to a solution of the substrate and Et_3N.[2] Alternatively, sulfene can be generated by the action of fluoride ion on 1-(trimethylsilyl)methanesulfonyl chloride (see ***(Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride***). This method has advantages over the amine method when reagents either have a low reactivity with sulfene or high reactivity with the amine.[3]

Handling, Storage, and Precautions: unstable at rt. It has been observed by IR after trapping at -196 °C.[4] The methanesulfonyl chloride commonly used to generate sulfene is toxic, corrosive, a lachrymator, and moisture sensitive. Use in a fume hood.

Sulfonations.

Although sulfene is not stable, it is still useful for the preparation of methanesulfonate esters and other sulfonyl compounds. It will react with H_2O, alcohols, amines, thiols, sulfonamides, imides, and oximes[1a] The most common use of sulfene is in the synthesis of mesylate esters of hydroxy compounds. These esters are typically prepared via the amine method (eq 1). These conditions will allow for the preparation of reactive mesylates provided the temperature is held at 0 °C.[2]

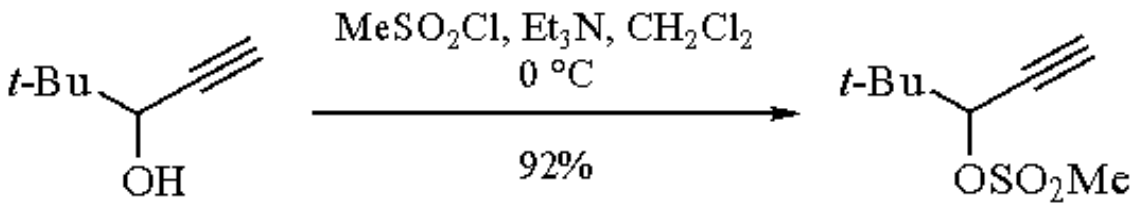

(1)

[2 + 2] Cycloadditions.

The simultaneous discovery that sulfene will undergo cycloaddition with an enamine was one of the first hints at its existence. The reaction with cyclohexanone enamine produced the four-membered ring sulfone (eq 2).[5] The acyclic enamine from propionaldehyde also formed the cyclic sulfone (eq 3).[6]

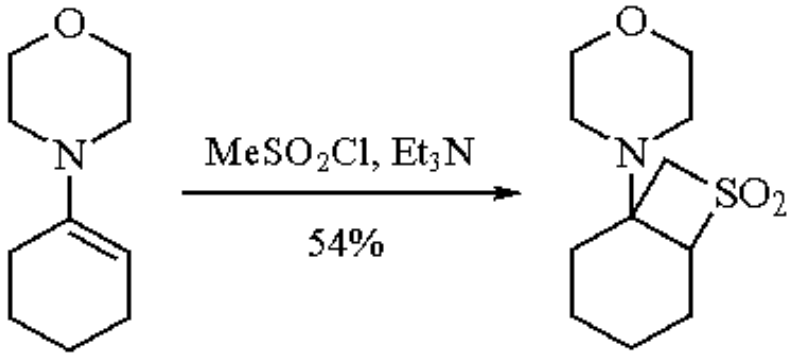

(2)

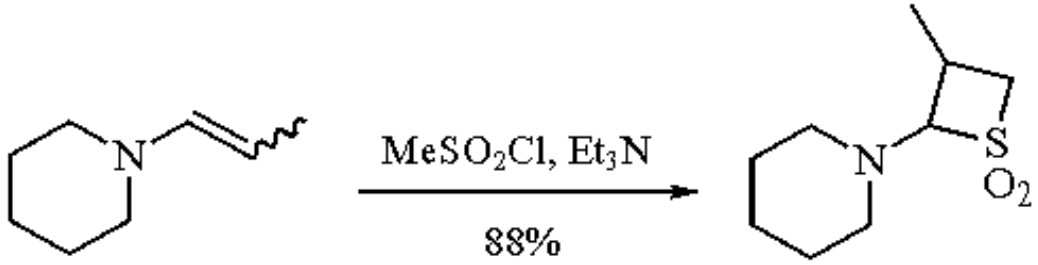

(3)

There is no observed stereoselectivity in the reaction of sulfene with enamines of 4-*t*-butylcyclohexanone. This reaction produces a nearly 1:1 mixture of the two diastereomers (eq 4).[7]

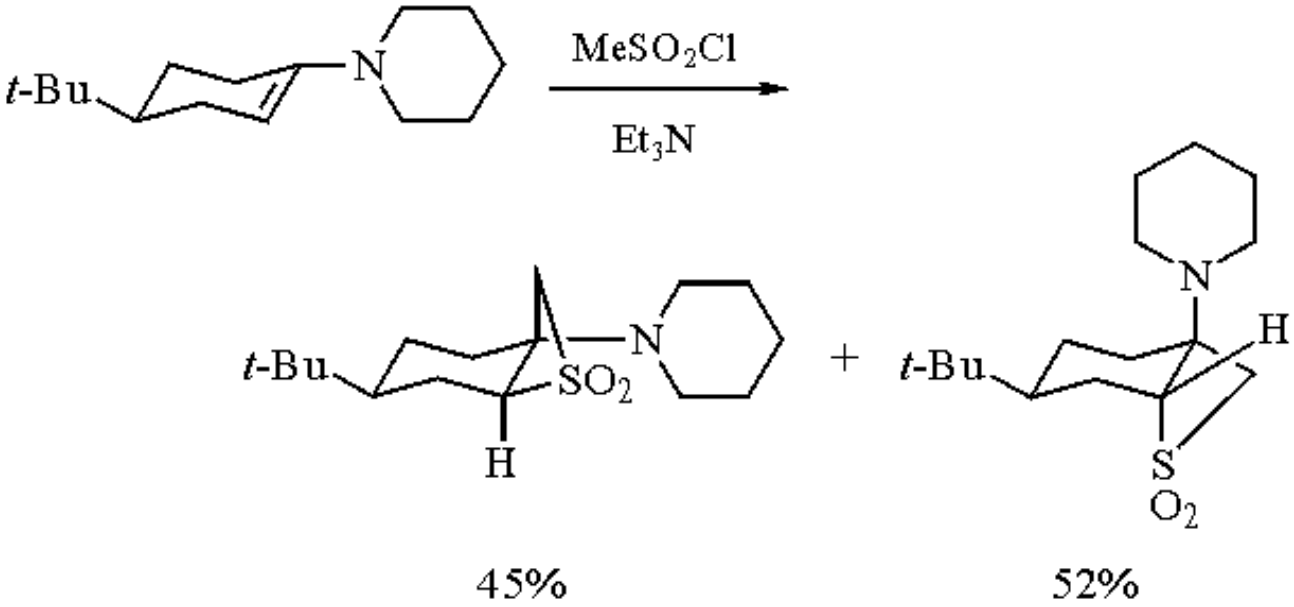

(4)

An investigation of asymmetric induction in the sulfene-enamine condensation with an enamine derived from propionaldehyde and (*R*)-2-methylpyrrolidine was conducted. Following Hofmann elimination, the thiete 1,1-dioxide (eq 5) was obtained in 25% ee. The use of (*R*)-(+)-methyl-α-phenethylamine resulted in an opposite sense of induction but the product only had a 6% ee. Attempts to induce asymmetry by using an optically active tertiary amine to generate sulfene were unsuccessful.[8]

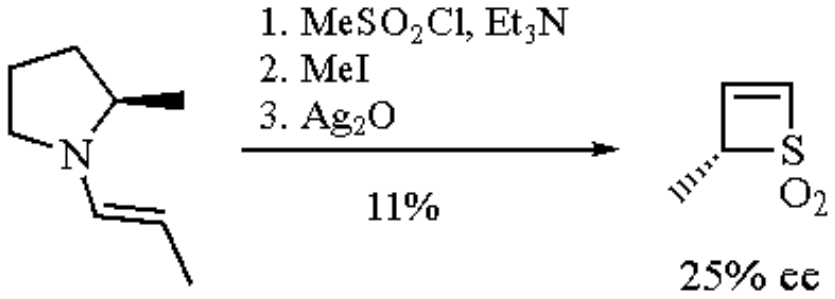

(5)

[4 + 2] Cycloadditions.

Sulfene generated using the amine protocol does not undergo reaction with simple alkenes or dienes. However, when cyclopentadiene was reacted with sulfene prepared using the newly developed fluorodesilylation method, the [4 + 2] cycloadduct was obtained in 64% yield (eq 6).[3] The use of the sulfonic anhydride instead of the chloride gave a 75% yield of the cycloadduct.

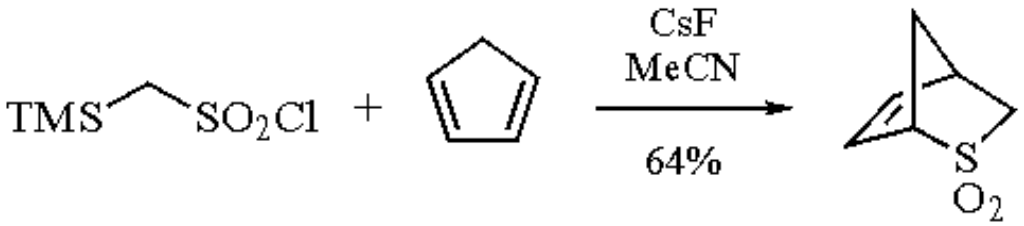

(6)

Miscellaneous.

Recently, an interesting reaction of sulfene with citreamicin η produced the cyclic β-hydroxy sulfonate in addition to forming the mesylate of the hydroxymethyl group (eq 7).[9] A similar result was observed earlier in an attempt to mesylate the α-hydroxy ketone (eq 8). Instead of stopping at the simple mesylate, the intermediate reacted further to afford the unsaturated sultone.[10]

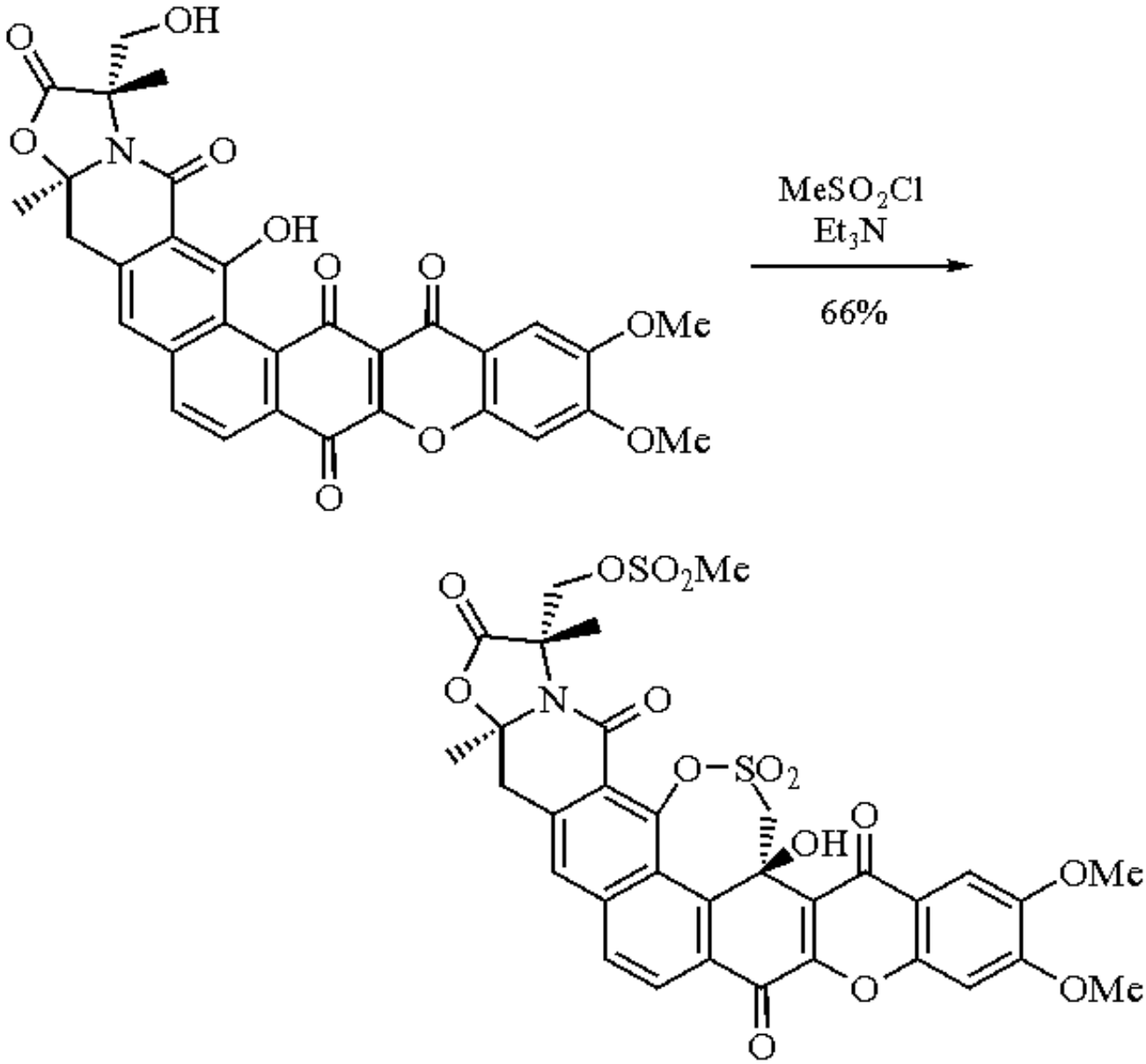

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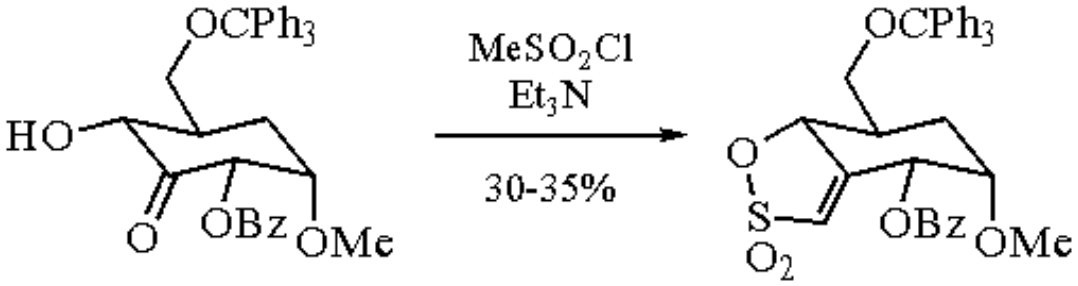

(8)

Related Reagents.

(Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride.

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1. (a) King, J. F.; Rathore, R. *The Chemistry of Sulfonic Acids, Esters, and Their Derivatives*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1991; pp 697-766. (b) King, J. F. *ACR* **1975**, *8*, 10. (c) Opitz, G. *AG(E)* **1967**, *6*, 107.
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N-Sulfinyl-*p*-toluenesulfonamide[1]

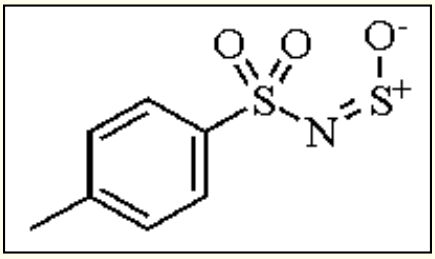

[4104-47-6] · $C_7H_7NO_3S_2$ · *N*-Sulfinyl-*p*-toluenesulfonamide · (MW 217.29)

(used to generate electrophilic *N*-tosyl aldimines;[4-7] can act as an enophile in ene reactions[2,8] and as a dienophile in Diels-Alder reactions;[10,11] participates in Wittig-type reactions[17])

Alternate Name: 4-methyl-*N*-sulfinylbenzenesulfonamide.

Physical Data: mp 53 °C; bp 130-140 °C/0.06 mmHg.

Solubility: sol benzene, toluene, halogenated solvents.

Form Supplied in: bright yellow solid; commercially available.

Preparative Methods: the most common method of preparing *N*-sulfinyl-*p*-toluenesulfonamide (TsNSO) (**1**) is by heating *p*-toluenesulfonamide with excess ***Thionyl Chloride*** in benzene (eq 1).[2]

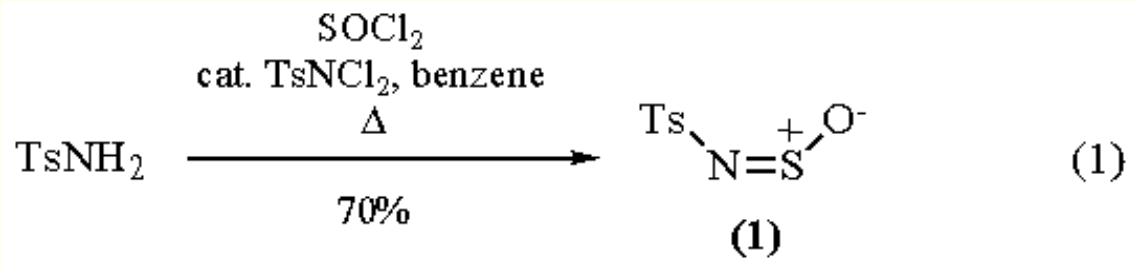

An alternative procedure is the treatment of *p*-toluenesulfonamide with *N*-chlorosulfinylimidazole, which is derived from thionyl chloride and ***Imidazole*** (eq 2).[3] The latter method benefits from shorter reaction times and better yields.

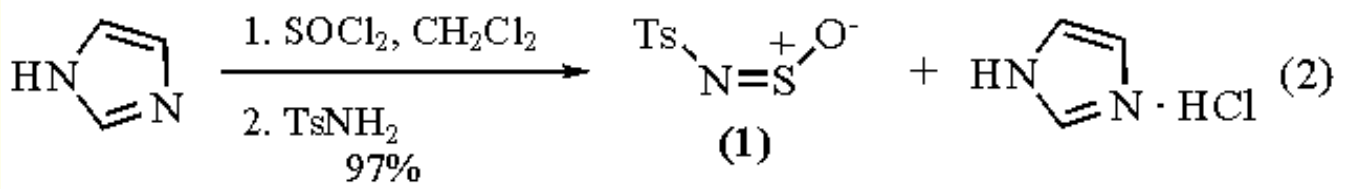

Handling, Storage, and Precautions: should be weighed out in a glove bag or dry box, since it readily hydrolyzes to *p*-toluenesulfonamide. Can be prepared just prior to use and used in situ or stored for extended periods of time in an inert environment.

Formation of *N*-Tosyl Aldimines.

A number of years ago it was reported by Kresze that nonenolizable aldehydes could be converted to the corresponding *N*-tosylimine using the title reagent (**1**) in the presence of a Lewis acid.[4] Recently, it has been shown that this transformation can also be effected with enolizable aldehydes both under Lewis acid catalysis at low temperature and thermally.[5] Thus treatment of propionaldehyde with (**1**) leads to the *N*-tosyl aldimine (**2**) or its Lewis acid complex (eq 3).

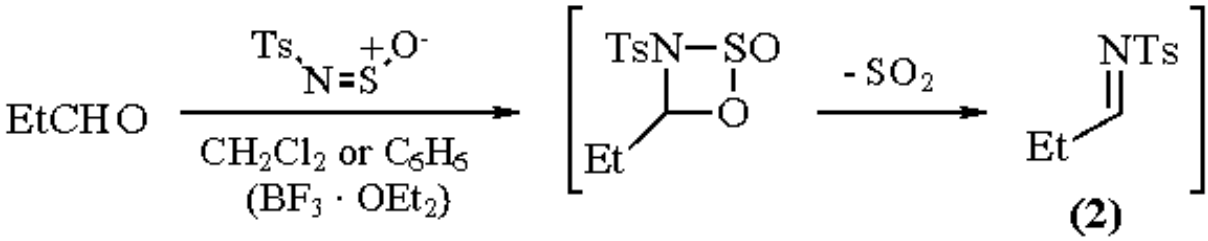

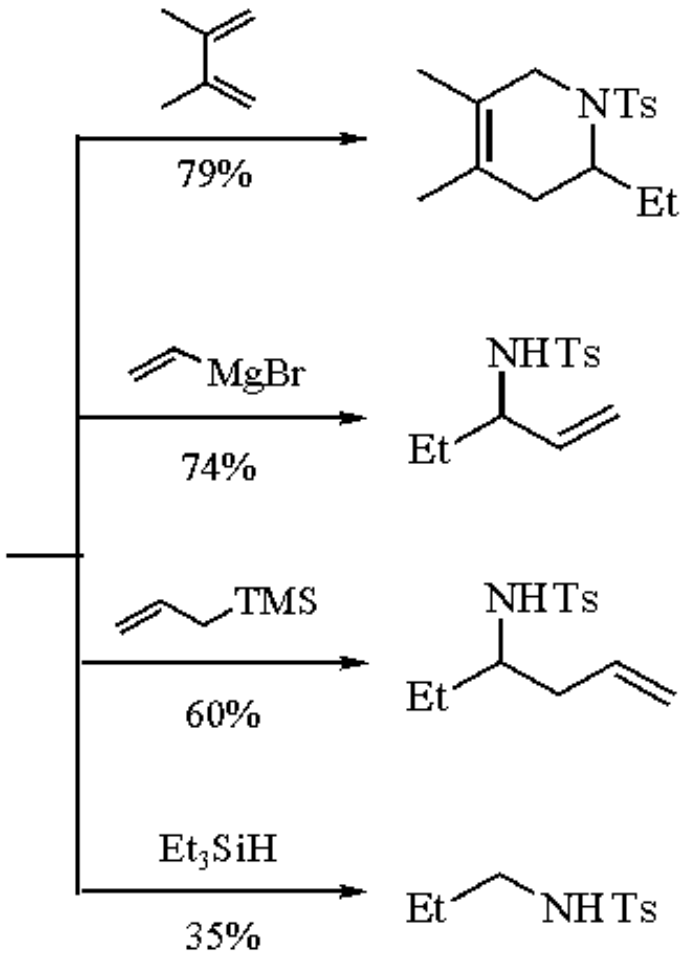

(3)

The imines (**2**) can be trapped in situ with 1,3 dienes,[5a] organometallic reagents,[5b] allyl silanes,[5c] or reduced with ***Triethylsilane*** (eq 3).[5d] Vinyl silanes also add intramolecularly to *N*-tosylimines in the presence of ***Boron Trifluoride Etherate*** or ***Tin(IV) Chloride*** to give cyclohexenylsulfonamides (eq 4).[6]

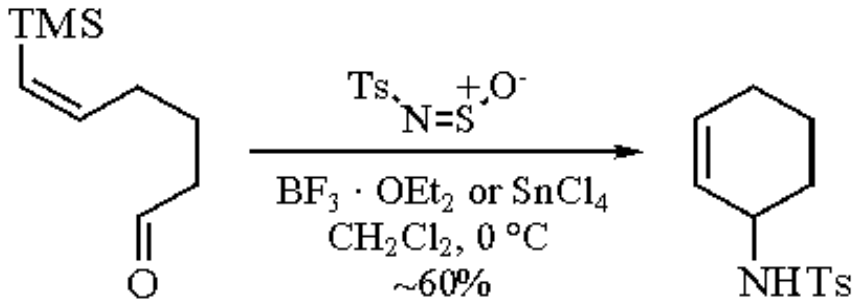

(4)

Intramolecular ene-like reactions of Lewis acid complexed *N*-tosyliminium intermediates can be effected to afford cyclization products, presumably via a cationic, stepwise pathway (eq 5).[7]

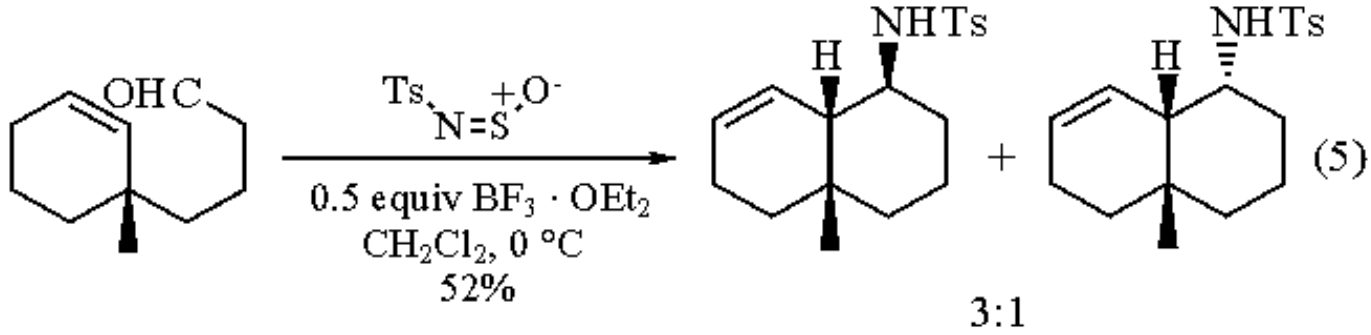

Ene Reaction.

The ene reaction of (**1**) and β-pinene in benzene at rt to give the *N*-tosylsulfinamide (**3**) (eq 6)[2a] is reversible under these conditions and has been exploited specifically to introduce deuterium into the allylic position of an alkene.

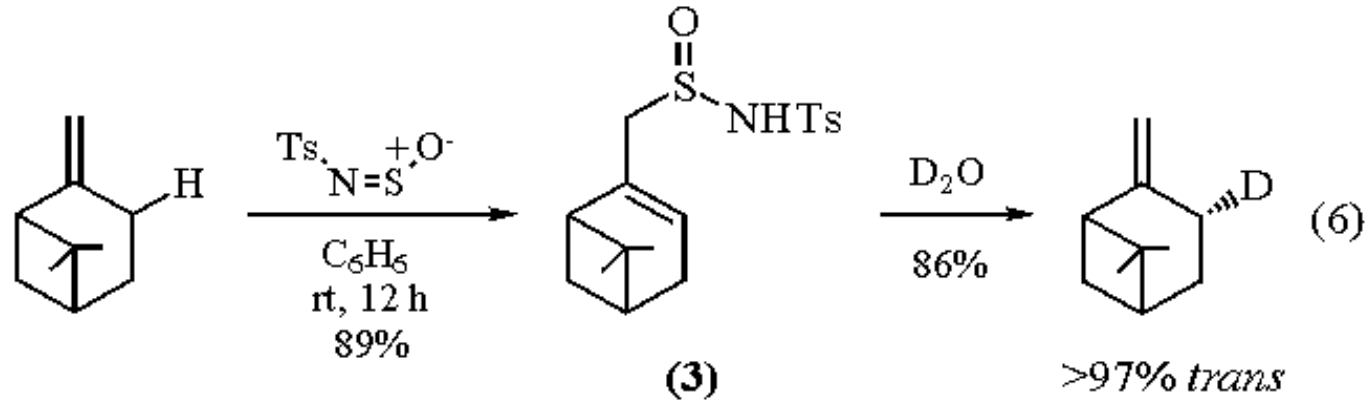

A more reactive *N*-sulfinyl compound, *N*-sulfinylnonafluorobutanesulfonamide, undergoes intermolecular ene reactions with alkenes over 10^3 times faster than the corresponding tosyl derivative (eq 7).[8]

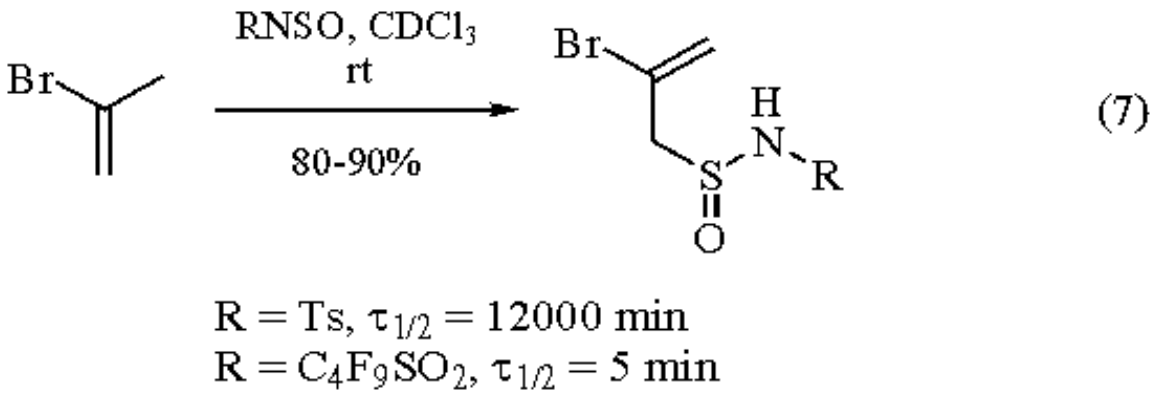

In addition, this perfluoro-*N*-sulfinyl compound undergoes thermal, intermolecular ene reactions with 1-aryl-2-alkanones under neutral conditions to give *N*-sulfinyl-2-oxoalkanesulfonamides in high yields (eq 8).[8a,9]

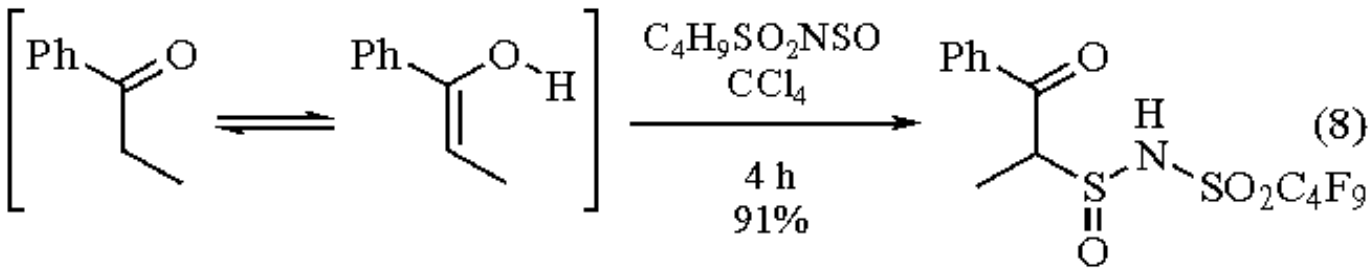

Diels-Alder Reactions.

N-Sulfinyl compound (**1**) is an effective dienophile in the regioselective [4 + 2] cycloaddition of unsymmetrical dienes.[1b,10,11] For example, 2-substituted dienes were found to yield only 5-substituted dihydrothiazine oxides (eq 9). The cycloaddition of (**1**) with simple 1-substituted 1,3-dienes is often dependent on the reaction temperature. At low temperatures, 3-substituted dihydrothiazine oxides are usually formed as kinetic products, but at higher temperatures the more stable 6-substituted heterocycles are produced (eq 10).[12]

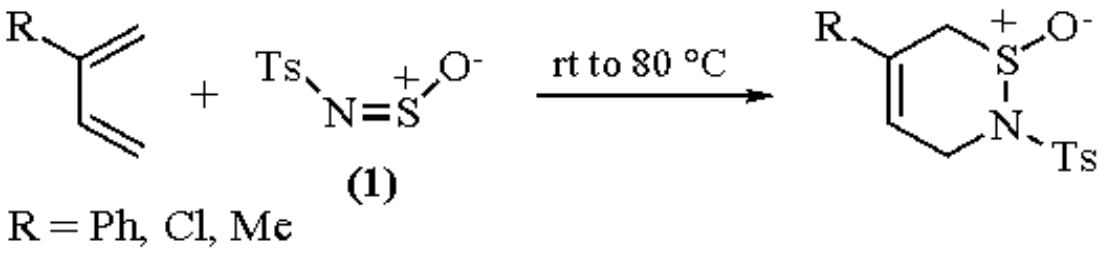

(9)

R = Ph, Cl, Me

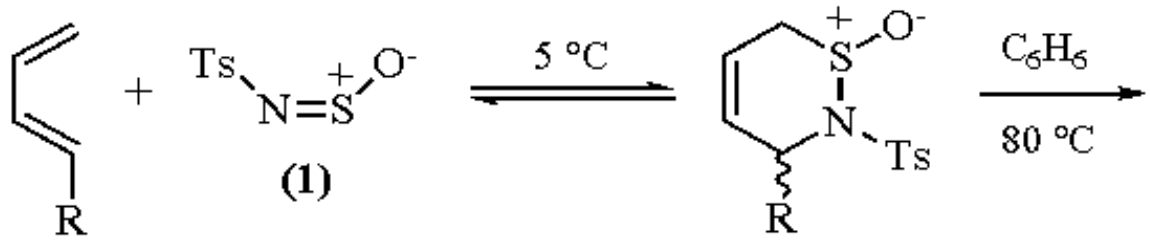

R = Ph, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$, Me

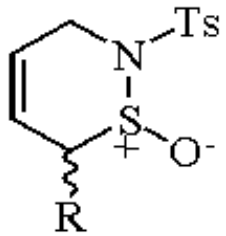

(10)

The dihydrothiazine oxides derived from this hetero Diels-Alder process are valuable synthetic intermediates in constructing homoallylic amines and vicinal amino alcohols in a stereorational manner.[11] For instance, in a system involving the diastereoselective synthesis of unsaturated acyclic amines, (**1**) was combined with (*E*,*E*)-tetramethylbutadiene to give cycloadduct (**4**), whereupon hydrolysis and retro-ene loss of SO_2 via a rigid chair-like transition state afforded exclusively the (*E*)-homoallylic amine derivative (**5**) (eq 11).[11,13] Similarly, (*E*,*Z*)-tetramethylbutadiene produced 3,6-dihydrothiazine oxide (**6**), which was hydrolyzed to give (*E*)-homoallylic sulfonamide (**7**).

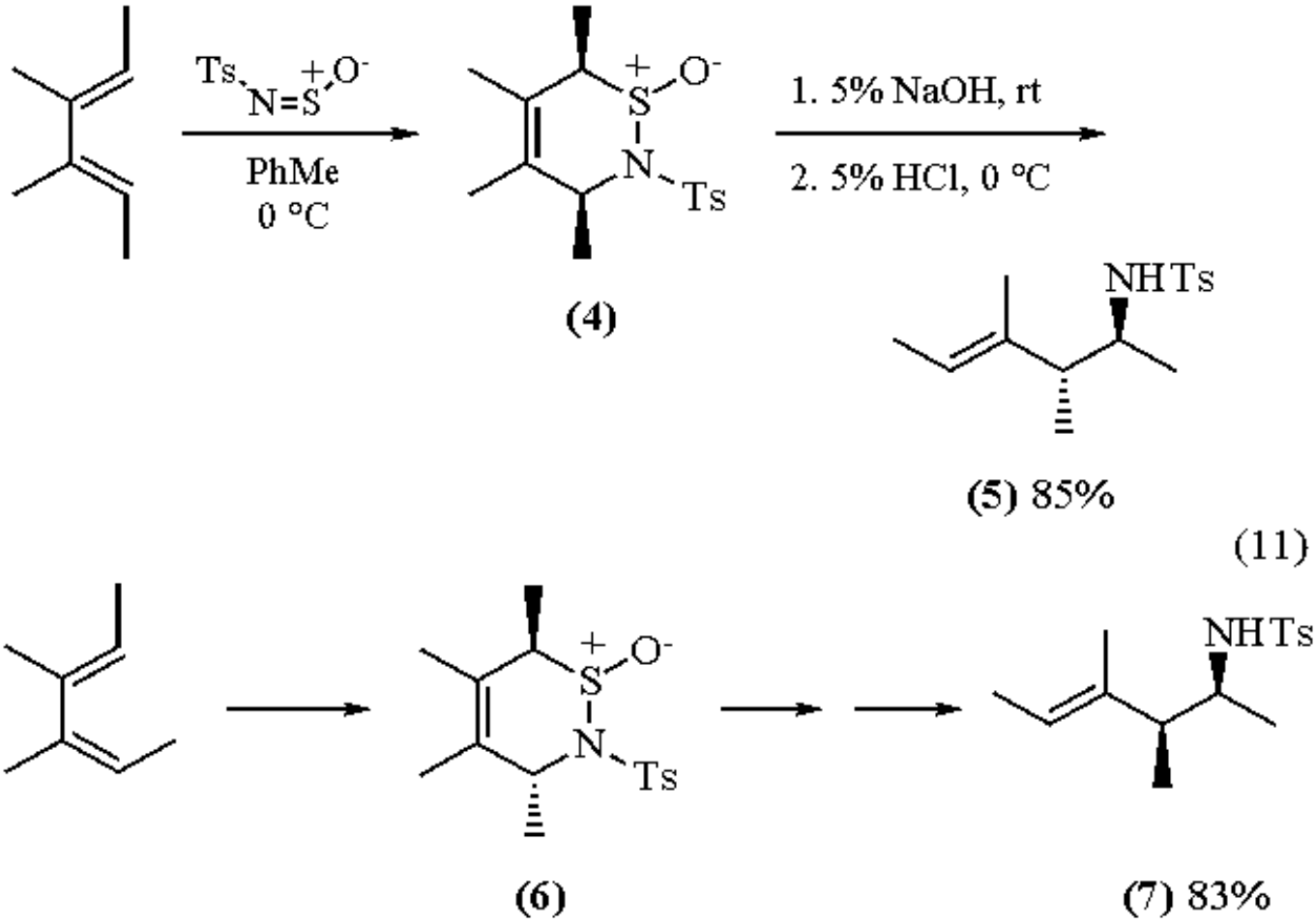

In a related system involving the diastereoselective synthesis of unsaturated vicinal amino alcohols, the Diels-Alder cycloaddition of (*E*,*E*)-hexadiene with benzyl *N*-sulfinylcarbamate[14] gave a 15:1 mixture of epimeric adducts (eq 12). Ring opening of these cycloadducts with ***Phenylmagnesium Bromide***, followed by the [2,3]-sigmatropic rearrangement of the intermediate allylic sulfoxide in the presence of trimethyl phosphite, yielded the (*E*)-*threo* vicinal amino alcohol derivative (**8**). Similarly, (*E*,*Z*)-hexadiene underwent the *N*-sulfinyl Diels-Alder reaction and subsequent steps to give the (*E*)-*erythro* hydroxy carbamate (**9**) exclusively.

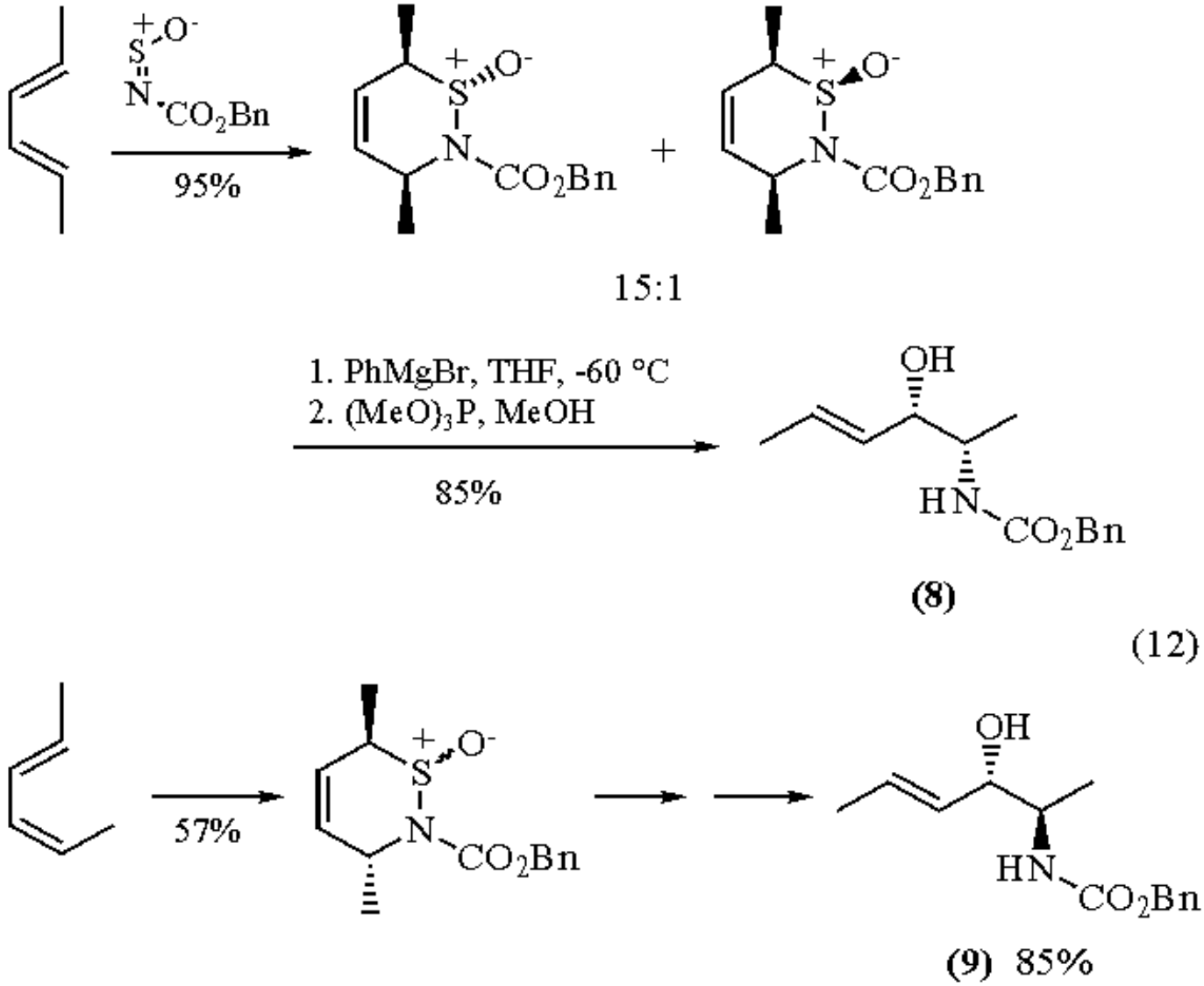

The chiral *N*-sulfinyl carbamate prepared from (+)-camphor (eq 13)[15] displayed high enantioselectivity in the ***Titanium(IV) Chloride*** catalyzed [4 + 2] cycloaddition with 1,3-cyclohexadiene, affording only one cycloadduct. The stereochemistry of compound (**12**) can be rationalized by a cycloaddition occurring through either conformer (**10**) via an *endo* transition state or conformer (**11**) by an *exo* transition state. High levels of asymmetric induction have also been reported in the cycloaddition reactions of *N*-sulfinylcarbamates derived from the chiral auxiliary 8-phenylmenthol.[16]

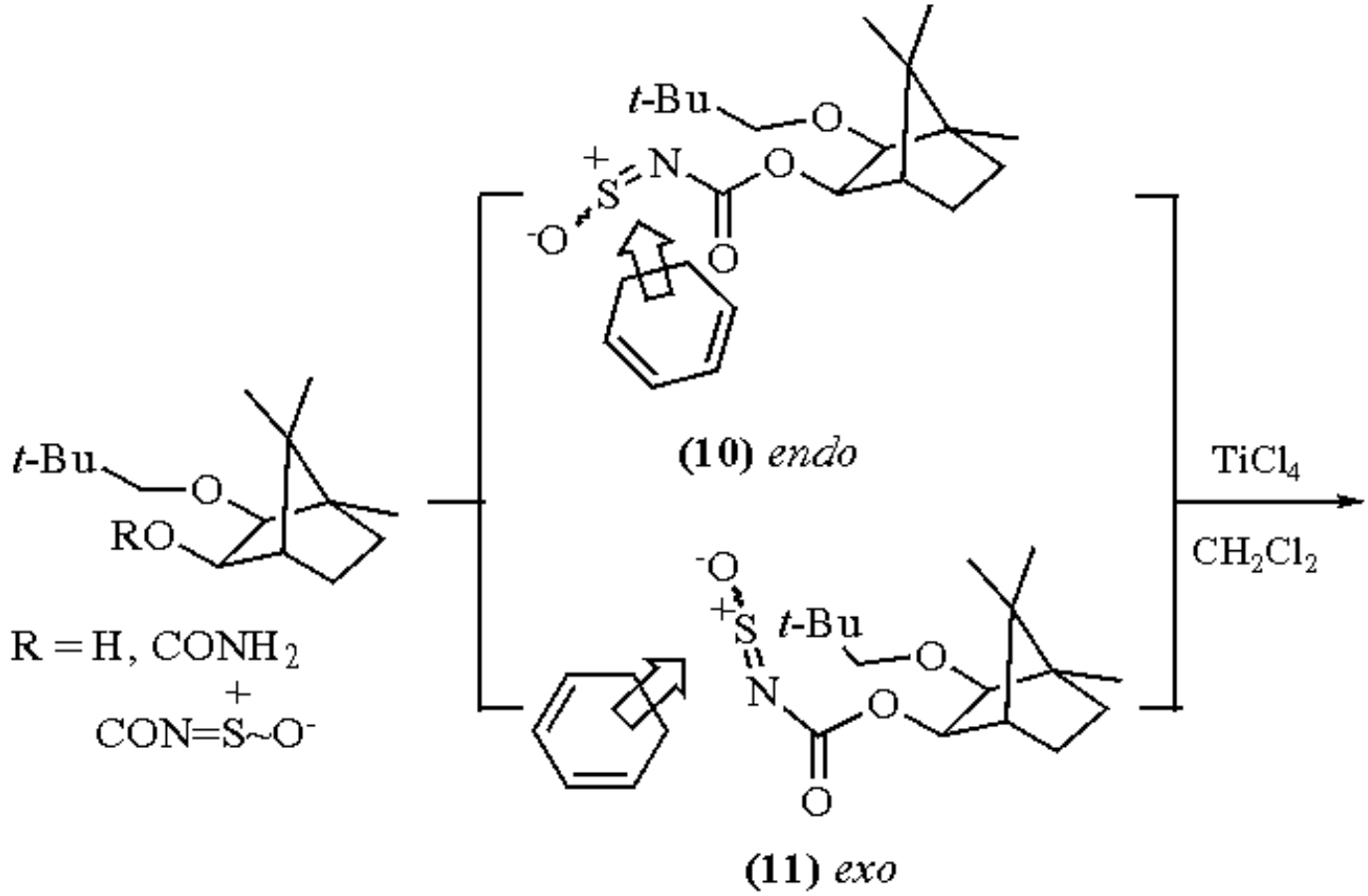

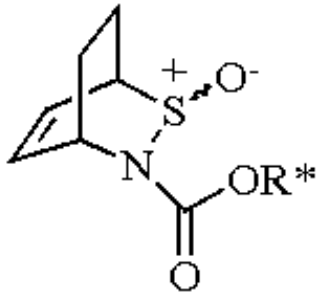

(13)

(12) 75%

Wittig-Type Reaction.

TsNSO undergoes an interesting Wittig-type reaction with triphenylphosphonium fluorenylide to afford thione *S*-imides in good yields (eq 14).[17]

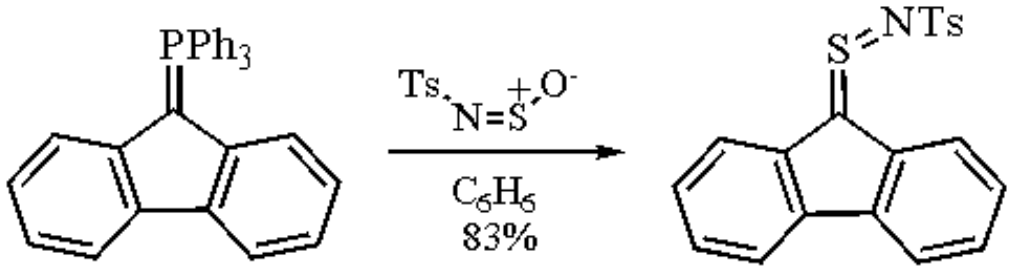

+ Ph_3PO (14)

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9. For uses of related *N*-sulfinyl compounds such as *N*-sulfinyl-(β-(trimethylsilyl)ethyl)sulfonamide and *N*-sulfinyl-(*p*-methylphenyl)methanesulfonamide see: Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *JACS* **1990**, *112*, 3475 and Ref. 5a.
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3-Sulfolene[1]

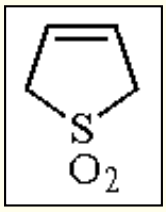

[77-79-2] · $C_4H_6O_2S$ · 3-Sulfolene · (MW 118.17)

(solid source of butadiene and substituted butadienes used in Diels-Alder reactions;[3] undergoes ready addition reactions and alkylation/aldol reactions[21])

Alternate Names: butadiene sulfone; 2,5-dihydrothiophene 1,1-dioxide.

Physical Data: mp 65 °C; dec above ca. 110 °C.

Solubility: sol water, organic solvents.

Form Supplied in: white solid, widely available.

Handling, Storage, and Precautions: nonflammable and nonhygroscopic, odorless, and indefinitely stable; skin irritant and under investigation as a potential carcinogen[2] (RTECS #XM9100000).

Introduction.

3-Sulfolene (**1**) is a convenient solid source for in situ generation of ***1,3-Butadiene***, for example in Diels-Alder reactions (eq 1).[3] It affords ***Sulfur Dioxide*** and butadiene by a concerted disrotatory[4-6] thermal process. The liberated SO_2 may cause acid-catalyzed reactions (eq 2).[7]

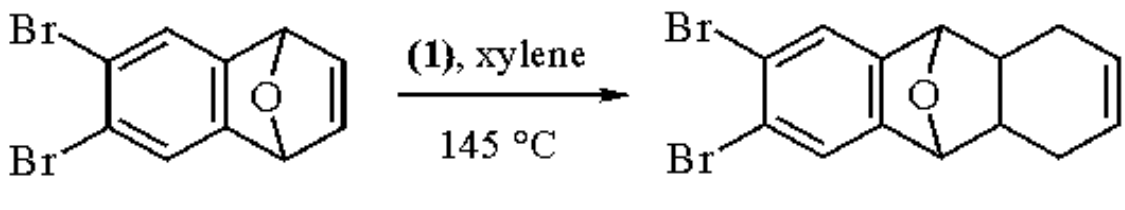

(1)

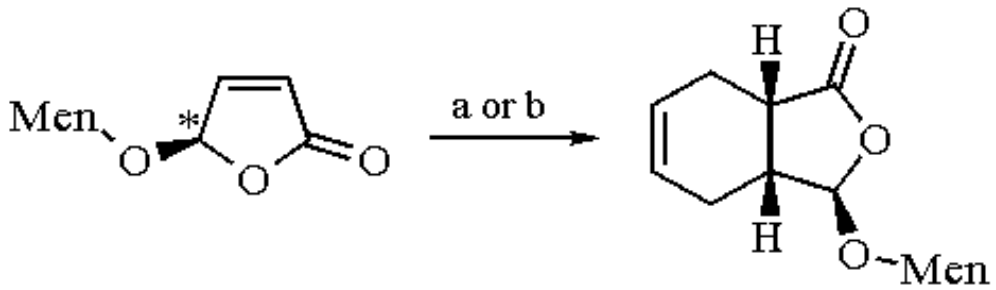

(2)

(a) butadiene, toluene, 110 °C 45%, 96% de, 99% ee
(b) **(1)**, toluene, 110 °C 77%, 73% de, 72% ee

Under mildly basic conditions, equilibrium is established between the 2-isomer (42%) and 3-isomer (58%).[8,9] For substituted rings, the equilibrium concentrations are strongly substituent dependent. Sulfolene serves as a platform for preparing conjugated dienes (eq 3)[10] by

substitution followed by SO_2 elimination. Very sensitive conjugated dienes such as those of the dendralene type (eq 7)[11] can be prepared in this manner.

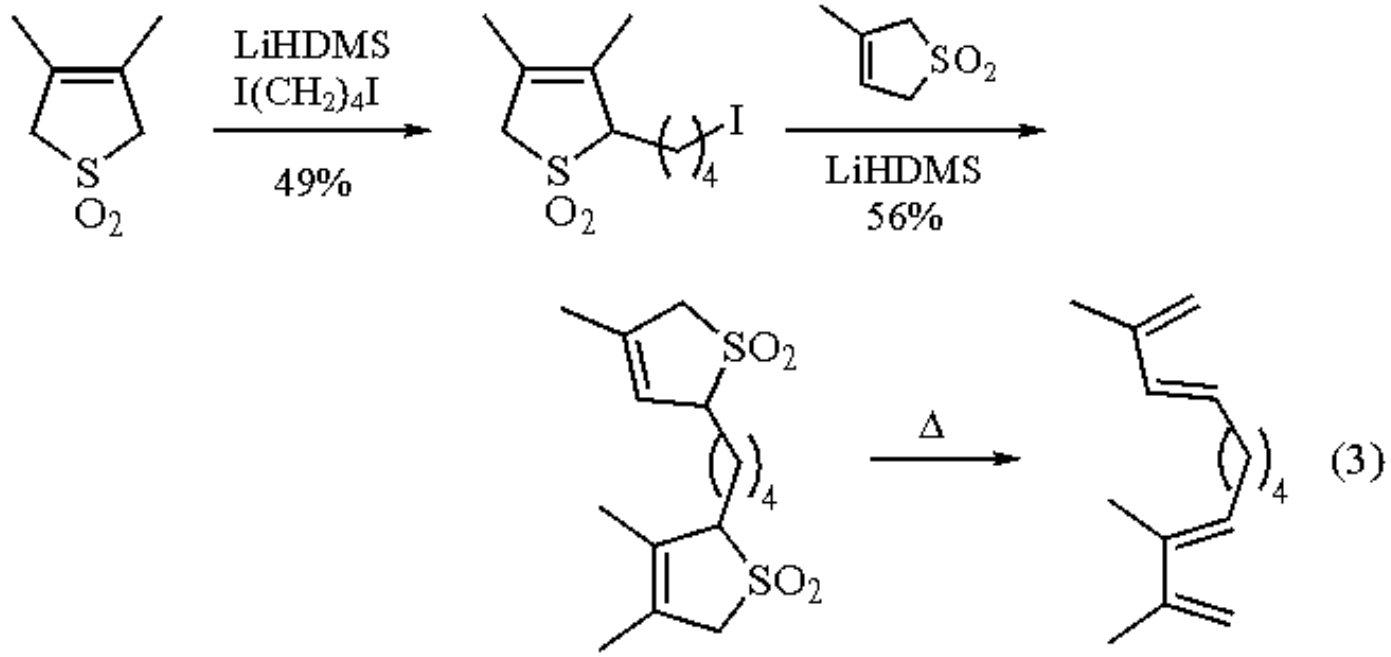

Additions to C=C.

Typical electrophilic additions occur readily. The dibromo derivative is a convenient source of the very reactive thiophene dioxide (eq 4).[12]

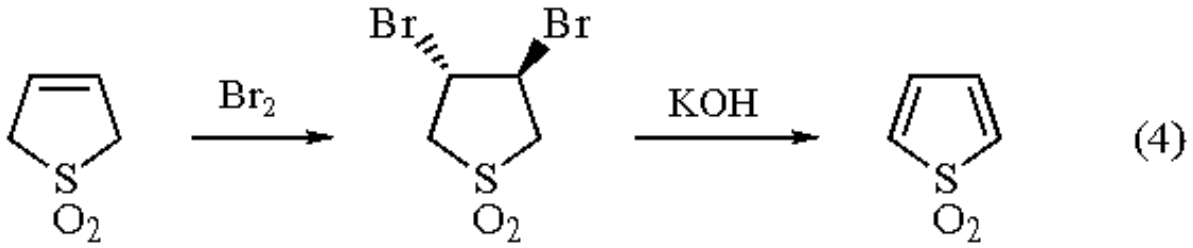

PhSX and PhSeX give *trans* additions and oxidative removal of PhSeOH affords the substituted 3-sulfolene (eq 5).[13] Dienes such as 2,3-bis(phenylthio)butadiene have been prepared by manipulation of the addition products.[14] Products of peracid oxidation or carbene or nitrene addition afford divinyl ethers, 1,4-dienes,[15] divinylamines,[16] or cyclobutenes[17] by thermal extrusion of SO_2 (eq 6).

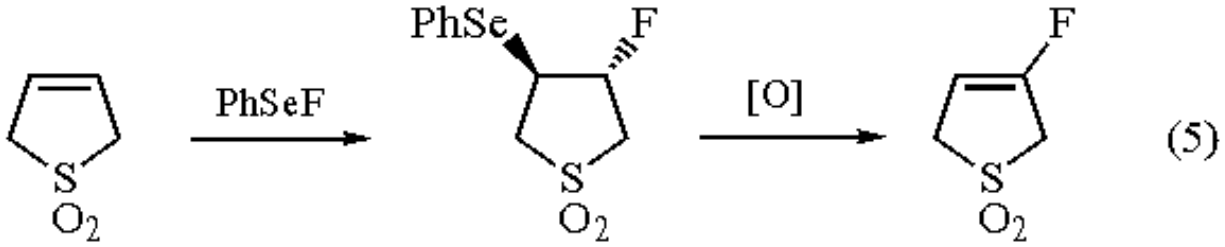

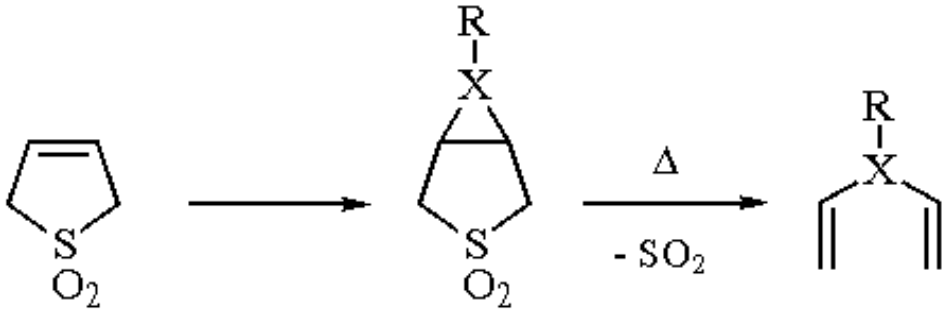

(6)

X = CH, N, O

The epoxides are often elaborated further to regenerate a substituted 3-sulfolene (eq 7).

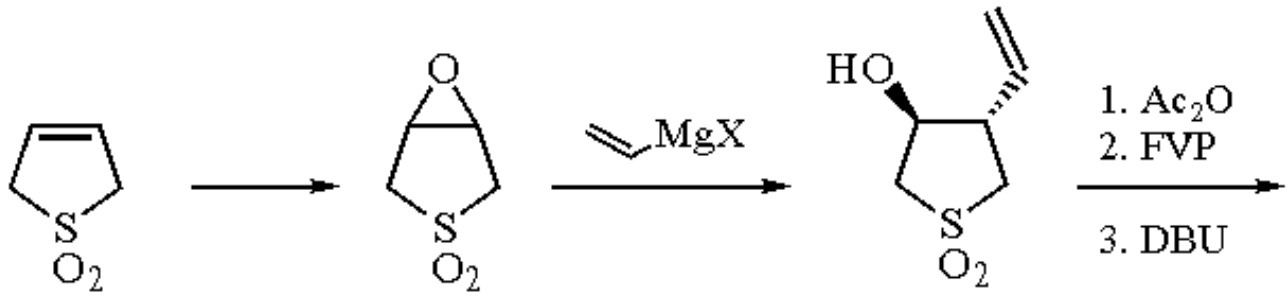

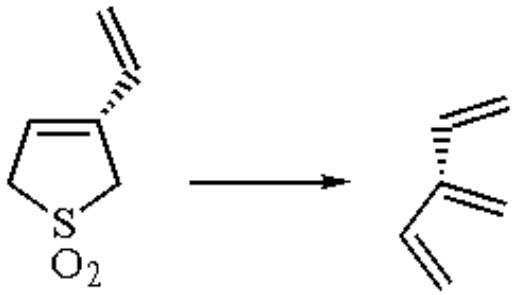

(7)

Apparently anomalous nucleophilic additions actually proceed by prior isomerization to the vinyl sulfone (2-sulfolene) (eq 8). Other processes are also affected by this tautomerism.[8]

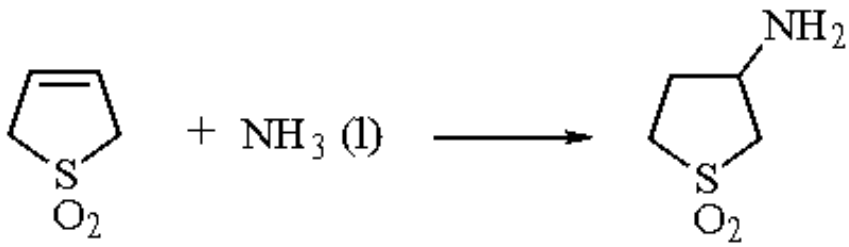

(8)

Alkylations and Aldol Reactions.

Substituted (**1**) can be obtained by addition of SO_2 to dienes or nucleophiles to thiophene dioxides,[1] by alkylations of anions derived from (**1**), or by peracid oxidation of substituted 2,5-dihydrothiophenes which occurs regioselectively at sulfur (eq 9).[18,19] The alkyl-substituted dihydrothiophenes are best prepared from vinylphosphonium salts,[18,19] while functionalized systems can be prepared using vinyl phosphonates.[20]

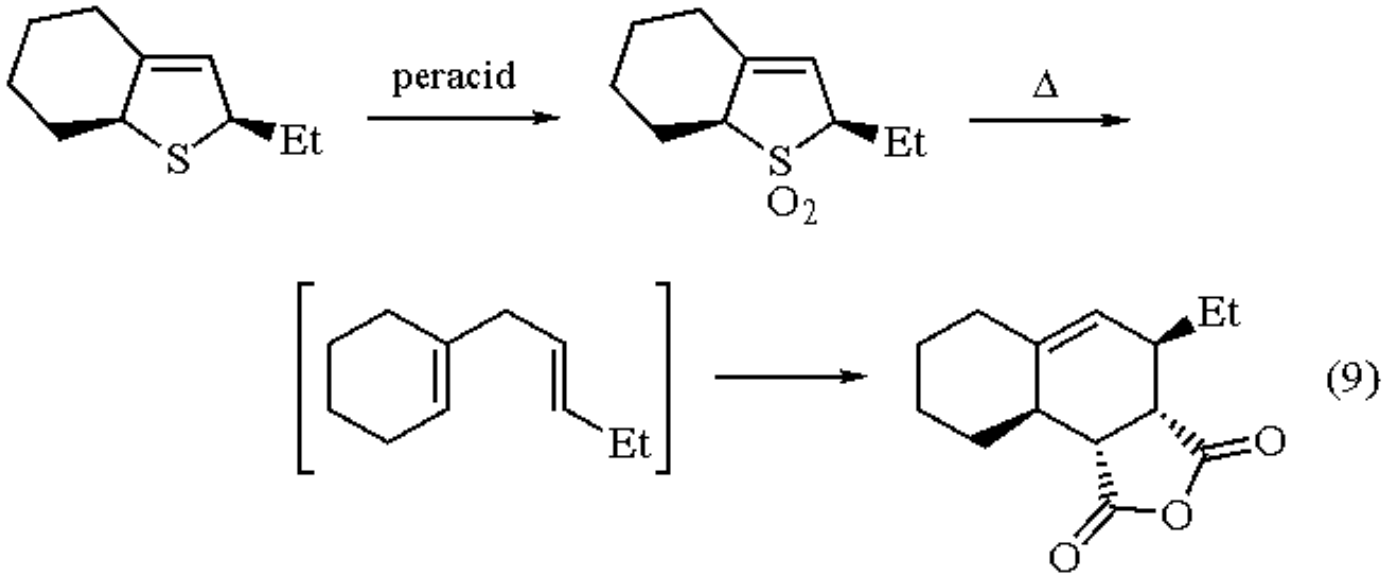

Deprotonation to form a delocalized carbanion occurs under basic conditions. Reactions with electrophiles usually occur α to the sulfone (eq 3) to afford the 2-substituted 3-sulfolene,[21] but electronic and steric effects of existing substituents strongly affect the alkylation regioselectivity.[22] Equilibration with D_2O affords the 2,2,5,5-tetradeutero derivative,[23] which is a convenient source of specifically deuterated butadiene-d_4. This has been used in syntheses of deuterated anthracenes[24] and cyclohexenes,[25] etc. Dialkylation preferentially proceeds to give the 2,5-disubstituted isomer.[26,27] The presence of a 2-trimethylsilyl or -stannyl substituent can be used advantageously to access the 2-monosubstituted or the 2,2-disubstituted system which may be spiro in nature (eq 10).[26,28]

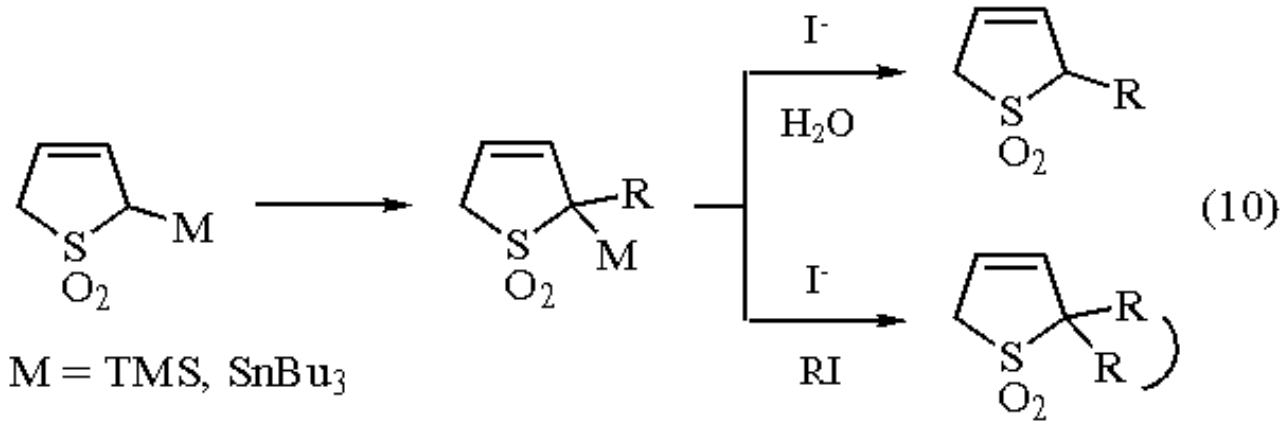

The alkylation stereochemistry controls the geometry of the diene and ultimately the stereochemistry of the Diels-Alder product. The *trans* 2,5-disubstituted isomer is formed fastest but the *cis* isomer is more stable and its thermal decomposition to the (*E*,*E*)-diene is faster than that of the isomeric *trans* isomer to the (*E*,*Z*)-diene. Therefore by heating the *trans* isomer in the presence or absence of small amounts of base, either the (*E*,*E*)- or the (*E*,*Z*)-dienes can be obtained selectively (eq 11).[27]

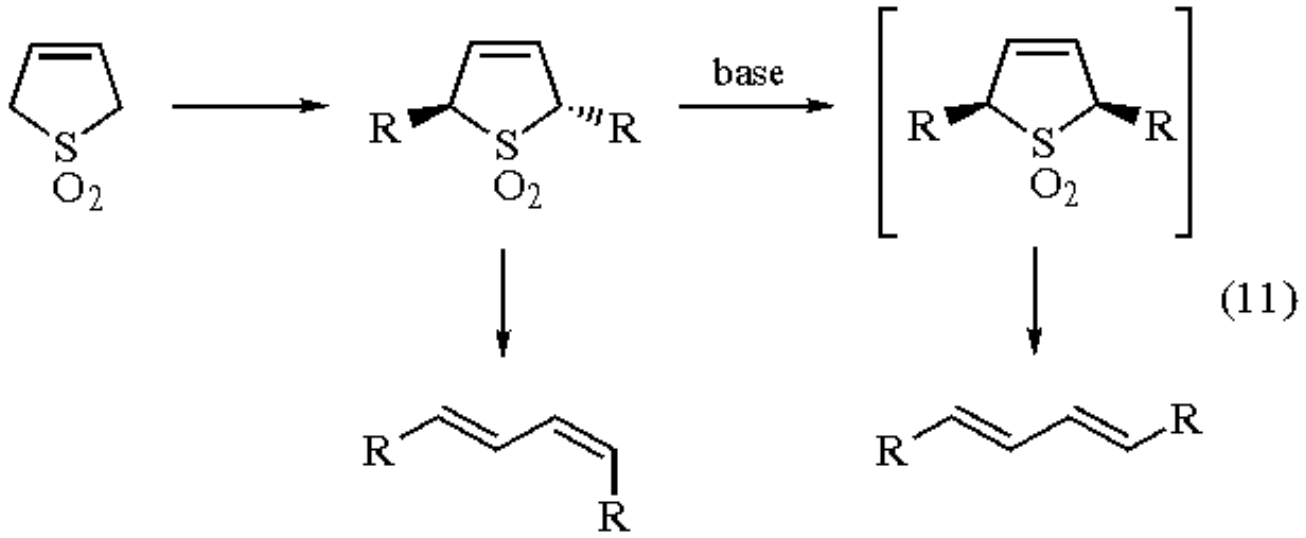

Other methodologies have been used to obtain the *cis* isomer (e.g. eq 12)[29]

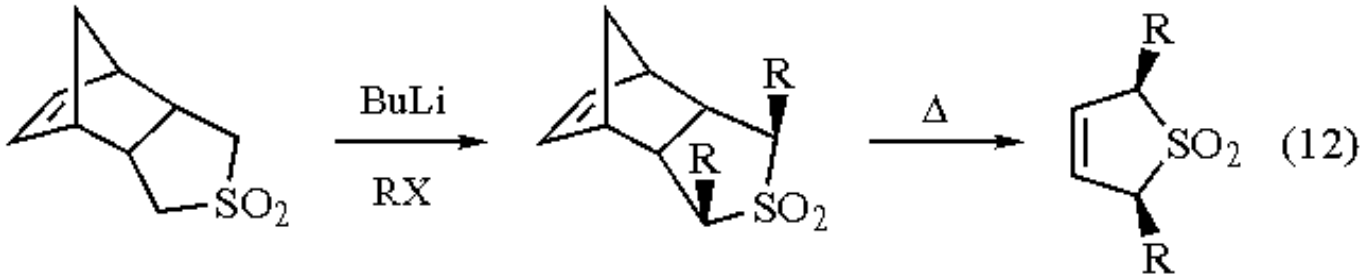

Aldol reactions and acylations[30] occur at the 2-position. Aldol condensations with various heterocyclic aldehydes occur in low yields (ca. 10%), but the products have been used as precursors to conducting polymers (eq 13).[31]

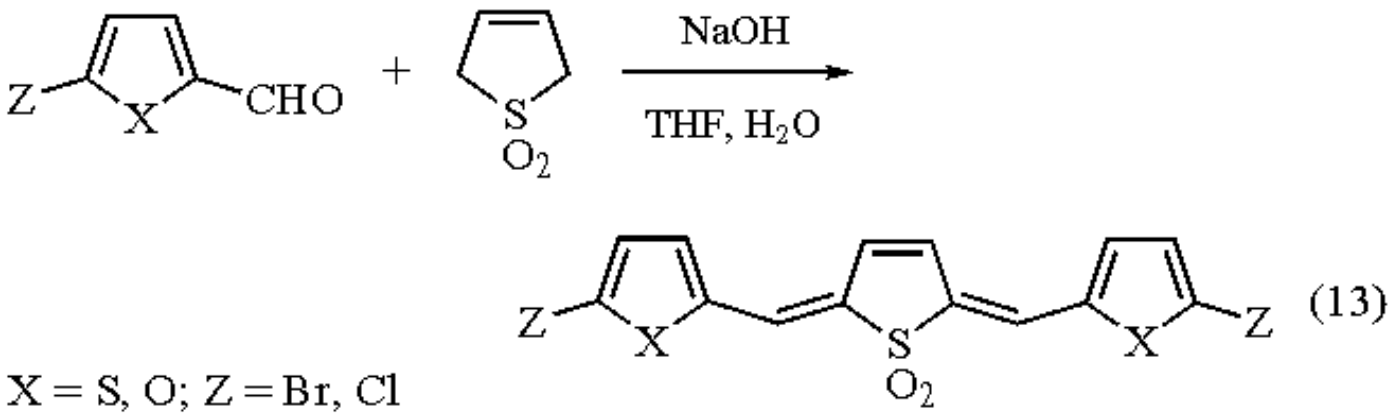

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John M. McIntosh

o-Sulfoperbenzoic Acid

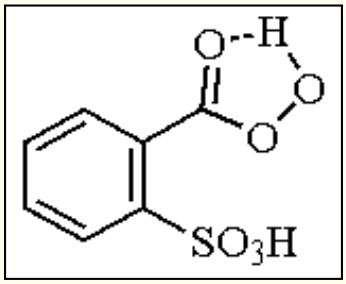

[31652-18-3] · $C_7H_6O_6S$ · *o*-Sulfoperbenzoic Acid · (MW 218.20)

(electrophilic reagent which delivers oxygen to alkenes[1])

Solubility: sol water and aqueous acetone.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: iodometry.[2]

Preparative Method: o-sulfobenzoic anhydride and ***Hydrogen Peroxide*** (30%; 1.3 equiv) react in acetone at -4 to 0 °C to furnish *o*-sulfoperbenzoic acid (**1**) in 65-75% yield (eq 1).

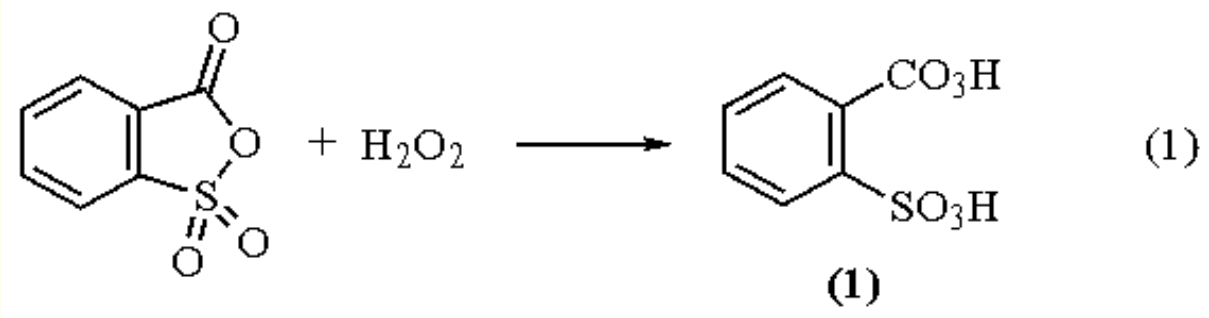

Handling, Storage, and Precautions: an aqueous acetone solution of the reagent is quite stable at rt and loss of active oxygen amounts to 1-2% per week. Since the reagent is a peroxide and potentially explosive, care is required in carrying out reactions with it. During workup, check for peroxides before solvent removal.

Anti Hydroxylation of Alkenes.

Reaction of a peroxycarboxylic acid (RCO_3H) with an alkene (**2**) is *syn* stereospecific;[3] the product is the epoxide (**3**) (eq 2). Under favorable conditions (pH of the reaction medium, temperature) the initially formed epoxide (**3**) undergoes *trans* ring opening due to reaction with RCO_2H and furnishes the diol monoester (**4**) or (**5**) (or a mixture of **4** and **5**); saponification of the diol monoester gives the diol (**6**). Peroxyformic acid (H_2O_2/***Formic Acid***) and ***Trifluoroperacetic Acid*** (TFPAA) are the peroxy acids which are normally used to effect the *anti* hydroxylation of alkenes (**2** -> **6**). *Anti* addition of hydroxyl groups to alkenes can also be effected by Prevost reaction, which involves treating an alkene with one equivalent of ***Iodine*** and two equivalents of the silver salt of a carboxylic acid; the monoester of the diol which is obtained is saponified.[4]

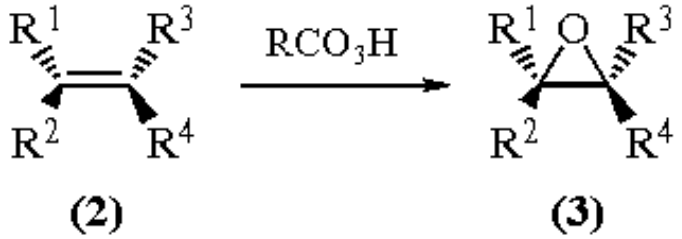

(2)

When an alkene is reacted with the peroxy acid (**1**) in aqueous acetone, the *anti* hydroxylation product is obtained directly. Cyclohexene (**8**) is converted to the *trans*-diol (**9**) (eq 3). Reagent (**1**) has been used for the synthesis of (±) γ-rhodomycinone (**11**) via *trans* hydroxylation of the alkene (**10**) (eq 4).[5]

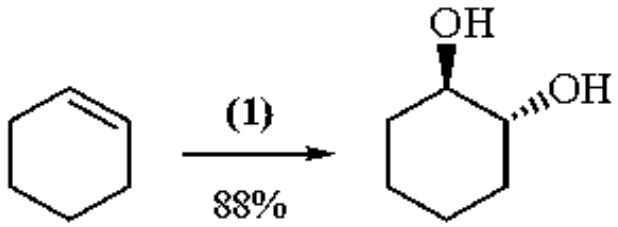

(3)

(8) (9)

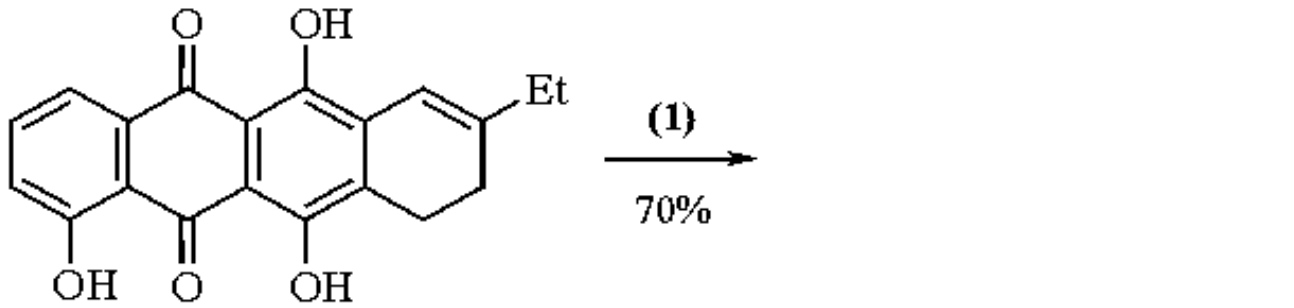

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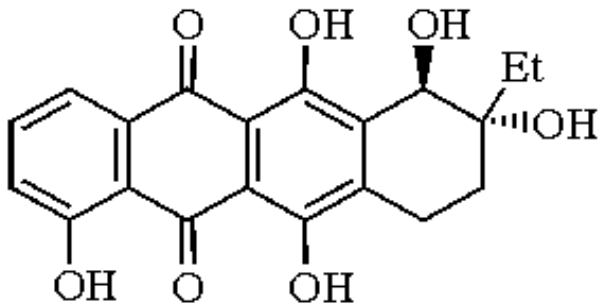

(4)

(11)

It is of interest to note that the electron-deficient alkene maleic acid has been hydroxylated to furnish tartaric acid in 80% yield. Phenylglyceric acid has been similarly prepared from cinnamic acid.

When one of the groups (R^1,R^2,R^3,R^4) attached to the epoxide ring in (**3**) is capable of stabilizing a positive charge on the neighboring carbon, the epoxide can undergo *cis* ring opening.[6]

Epoxidation of Alkenes.

Epoxides have been isolated by reacting alkenes with the peroxy acid (**1**) in the presence of a solid buffer such as ***Sodium Carbonate***. Epoxides have been prepared from α-terpineol and cholesterol in 82% and 89% yields, respectively.

Baeyer-Villiger Reaction.

Baeyer-Villiger reaction of cyclohexanone takes place readily at 0 °C with (**1**) (4-6 h) to furnish hexanolide in 80% yield. Peracid (**1**) did not react with the ketone (**12**) and 4,4-dimethylcholestan-3-one. Reaction of (**12**) with ***Peracetic Acid-Boron Trifluoride Etherate*** furnished the lactone (**13**) in 36% yield.[7]

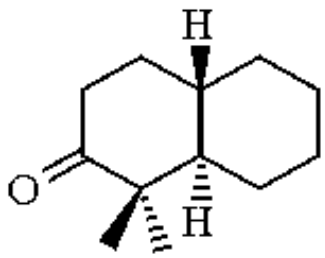

(12)

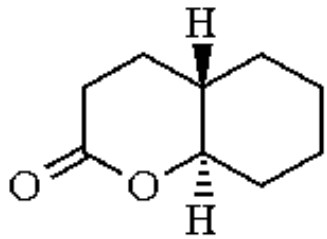

(13)

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Sulfur[1]

[7704-34-9] · S · Sulfur · (MW 32.07)

(mild oxidizing agent used for the Willgerodt reaction[2] and dehydrogenation of various organic compounds;[3] its most recent use has been for the in situ generation of carbonyl sulfide[4] from CO for the synthesis of thiocarbamates[5] and other derivatives)

Physical Data: mp 119 °C; bp 444.6 °C; *d* 2.07 g cm^{-3}.

Solubility: insol water; slightly sol alcohol, ether; sol carbon disulfide, benzene, toluene.

Form Supplied in: powder, flakes.

Handling, Storage, and Precautions: store in a closed bottle at ambient temperatures. Chronic inhalation of dust can cause irritation of the mucous membranes.

Willgerodt Reaction.

The first reaction of this type was carried out by Willgerodt[6] on 1-acetylnaphthalene to give what was later identified as 1-naphthylacetamide (eq 1).[7] This was accomplished by using an ammonium polysulfide solution in a sealed tube at 210-230 °C for 3 or 4 days. The corresponding acid salt always accompanied the amide. Another limitation is that the harsh conditions used in the original procedure gave yields of only 20-50%.

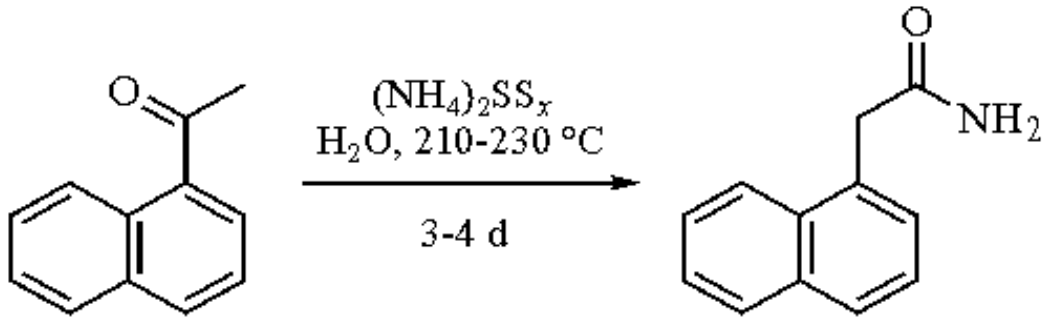

(1)

The Kindler[8] modification of the reaction allows this to be carried out under anhydrous conditions at lower temperatures. The thioamide can be isolated and then hydrolyzed to the acid or reduced to the amine. Even with this important change, the reaction saw little application because it had to be carried out in an autoclave as in eq 2.[9]

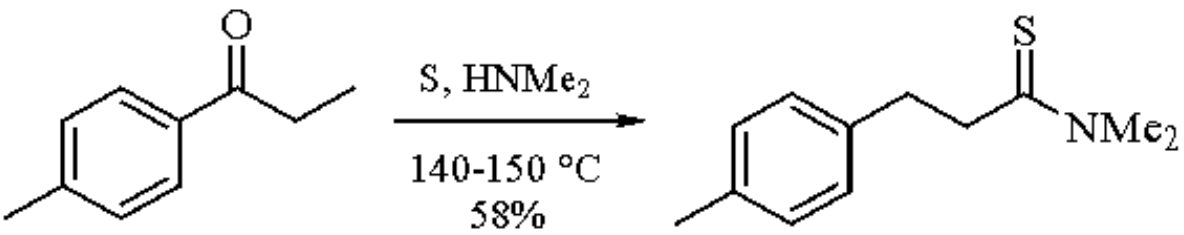

(2)

The adoption of ***Morpholine*** as both the solvent and base led to a procedure that could be used at ambient pressure (eq 3).[10a] With the relatively mild temperatures (bp 129 °C), certain functionalities on the aryl ring like nitro, amino, hydroxy, and acetoxy groups can tolerate these conditions.[10b]

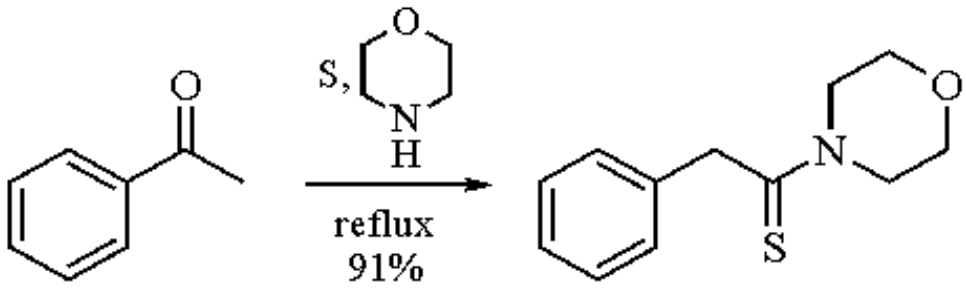

(3)

The original Willgerodt conditions found a use in converting aliphatic aldehydes and ketones to the amides in poor to moderate yields (eqs 4-7).[11]

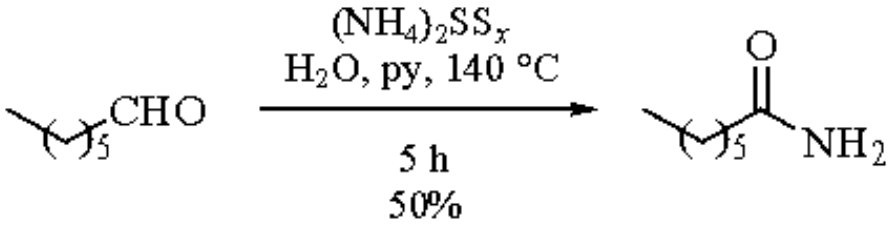

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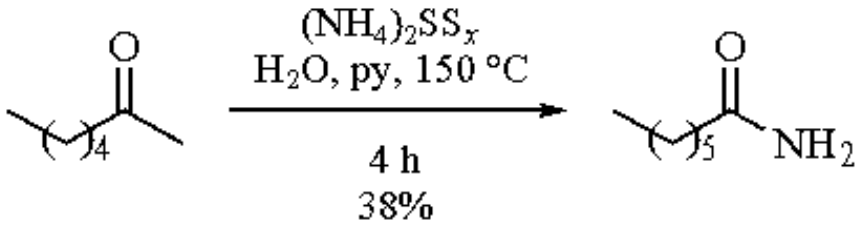

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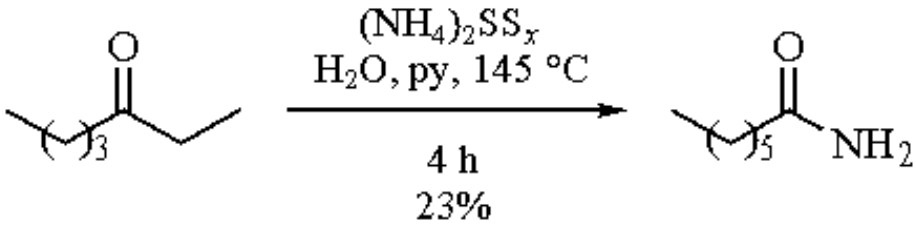

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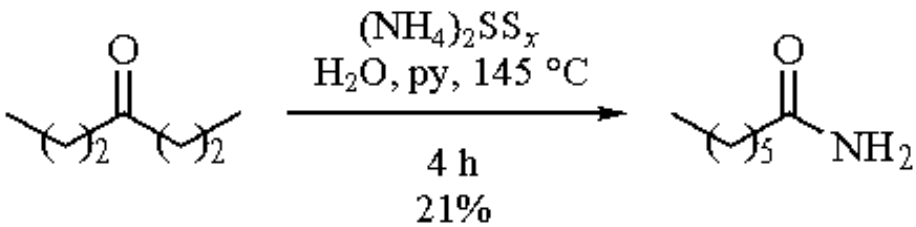

(7)

This reaction can also be applied to unconventional substrates for conversion into thioamides (eq 8).[12] It was found that methylphenylcarbinol, β-phenylethyl alcohol, β-phenylethyl acetate, and methylbenzylcarbinol failed to give appreciable amounts of amide when heated with a typical Willgerodt reagent at 160 °C. Unexpected results were seen with β-substituted acrylic acids (eqs 9 and 10).[13] Apparently, the carboxyl group was eliminated to give an amide with one less carbon atom.

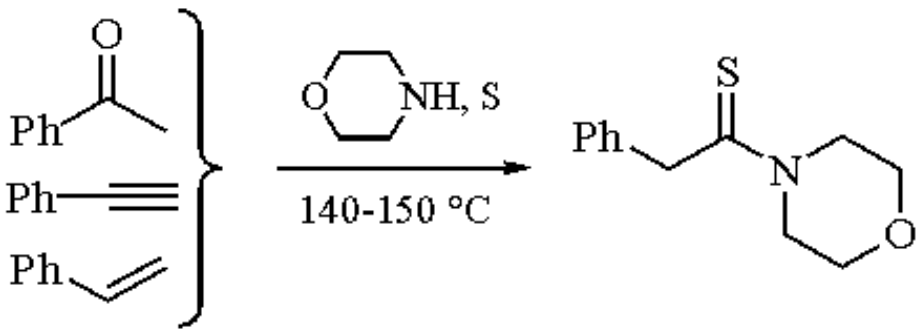

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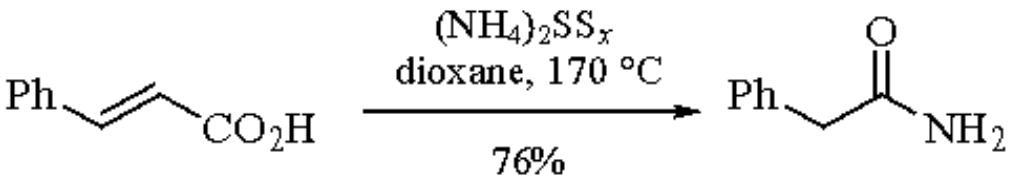

(9)

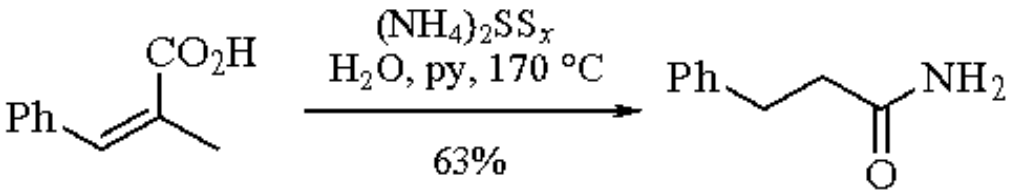

(10)

Other functionalities were found to allow the Willgerodt reaction to work on substrates that yield phenylacetamide in an attempt to elucidate the mechanism.[14] Poor to good yields were obtained. A thorough review of this reaction was written by Carmack and Spielman in 1946.[15]

Dehydrogenation.

This reaction is another important use of elemental sulfur in organic chemistry. Sulfur is the reagent of choice for the dehydrogenation of hydroaromatic compounds because it is simpler than ***Selenium*** and may be preferred over selenium or catalytic dehydrogenation. The following example is from a systematic study that compared the three methods (eq 11).[16]

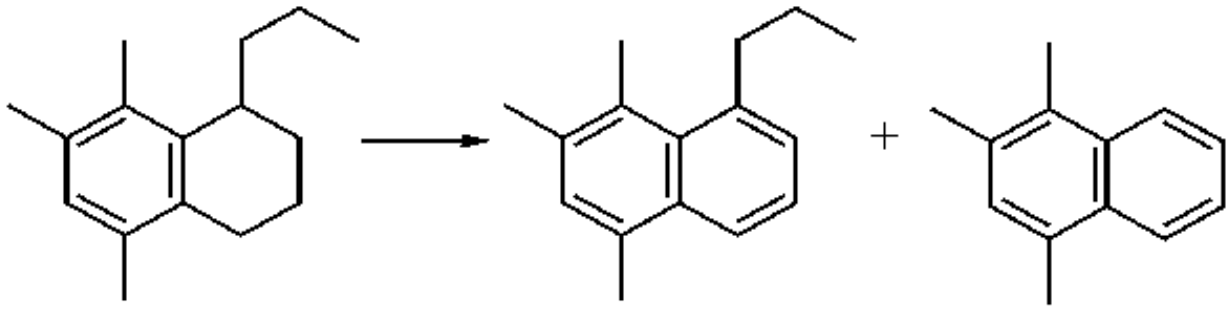

(11)

S	230-240 °C	+	-
Pd/C	260-280 °C	+	+
Se	330-350 °C	-	+

The dehydrogenation of aromatizable hydrocarbons works well enough to have been incorporated into an undergraduate experiment (eq 12).[17]

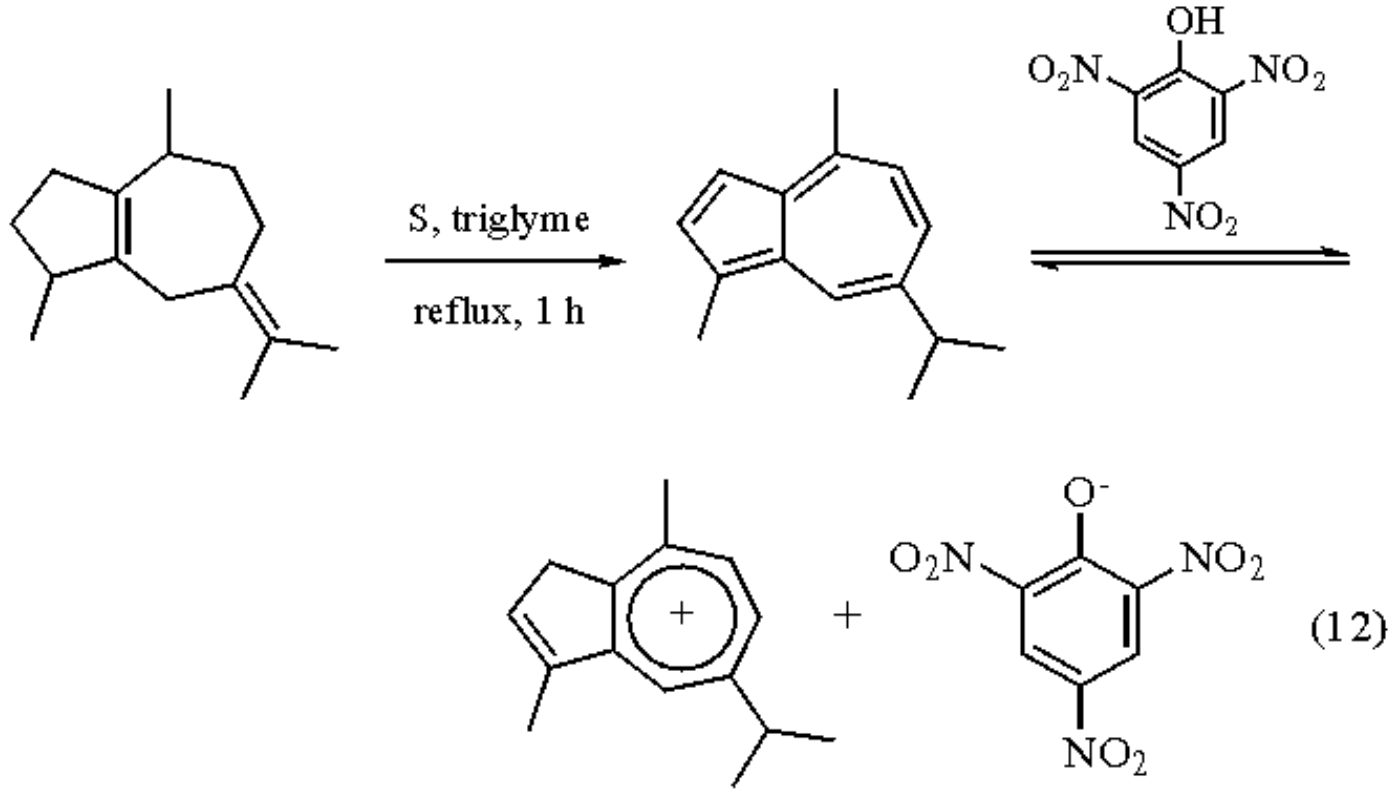

In this experiment it was necessary to use less than the theoretical amount of sulfur because the brilliantly blue product, guaiazulene, reacts with sulfur to form an intractable brown product.

More complex structures can be selectively dehydrogenated to give fair yields of products, as the example from Haede et al. illustrates (eq 13).[18]

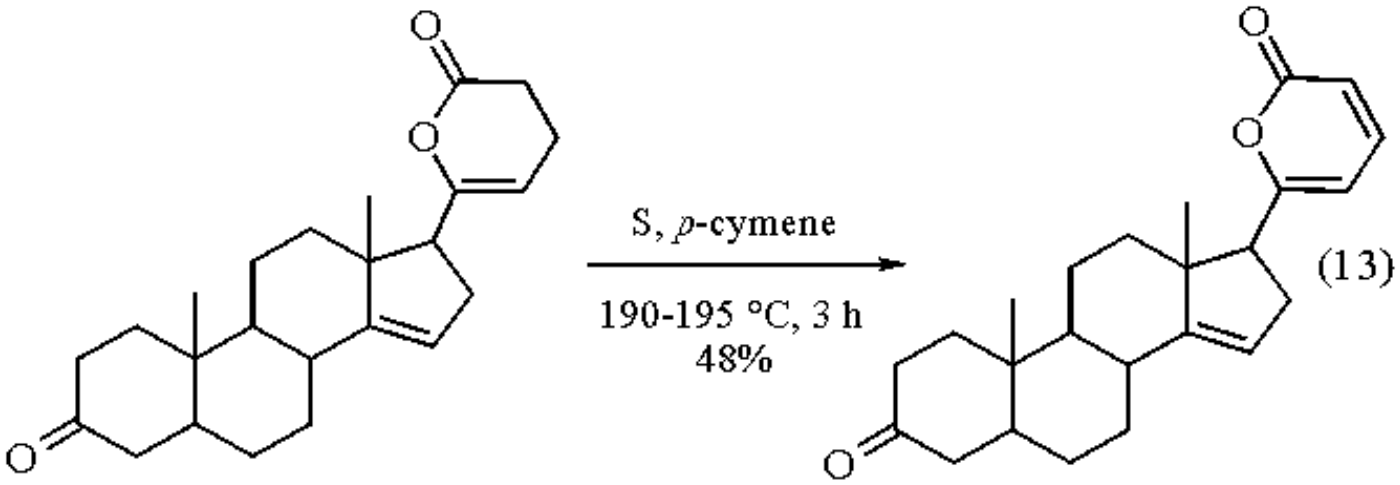

Other heterocycles are good substrates for the dehydrogenation reaction (eqs 14-18).[19-23]

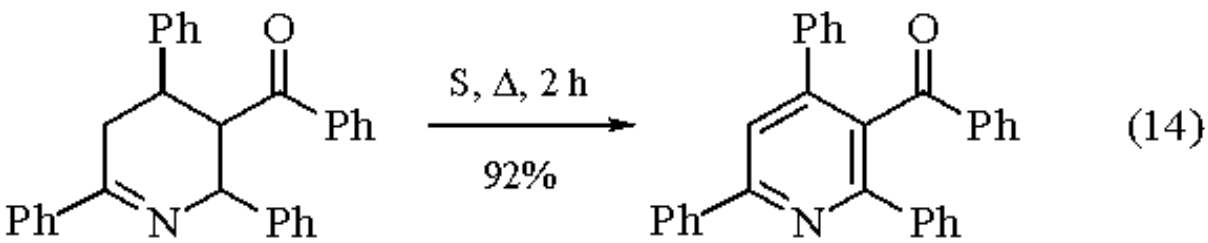

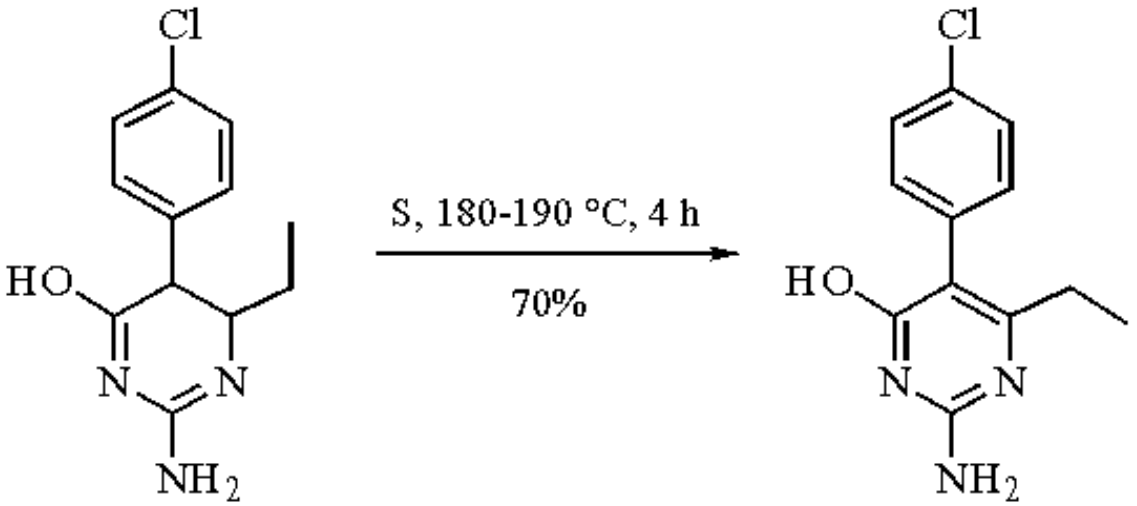

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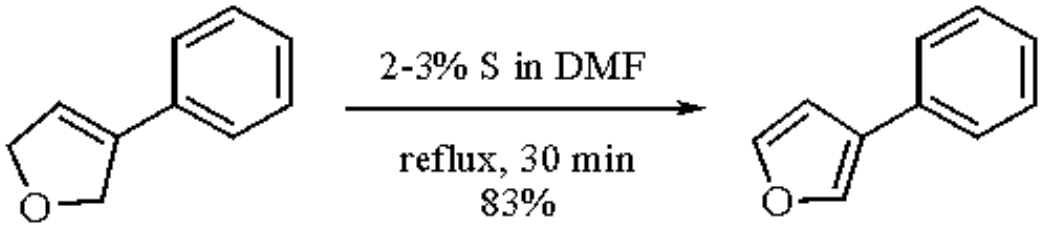

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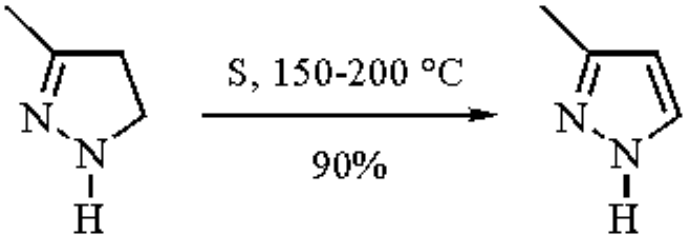

(17)

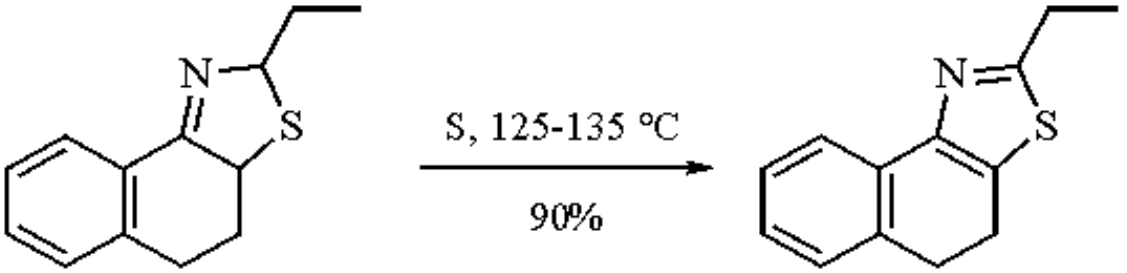

(18)

Carbonyl Sulfide Generation.

The use of ***Carbon Monoxide*** and sulfur leads to the generation of carbonyl sulfide (***Carbon Oxysulfide***), which is electrophilic enough to be attacked by nucleophiles present in the reaction mixture. A new synthesis of ureas based upon this intermediate was put forth (eq 19).[24] This reaction starts out with each of the reactants in a different phase, liquid, gas, and solid, respectively. This simplifies the industrial process, and the in situ oxidation of carbon monoxide leads to a ***Phosgene*** synthon without the formation of ammonium salts as byproducts. In an experiment using only ***Ammonia***, carbon monoxide, and sulfur in methanol, Franz and Applegath[25] found carbonyl sulfide making up about 30% of the product gases when the reaction was run at 150 °C. Ammonium thiocarbamate was obtained in large quantities when the temperature of the reaction was held overnight at 25-30 °C with 700 psi of CO. The isocyanate group was detected by IR in an alcoholic solution of ammonium thiocarbamate (eq 20). This method has also been used to synthesize unsymmetrical ureas, with the authors postulating that aryl isocyanates are formed first which then react with primary or secondary alkyl amines to give the 1-aryl-3-alkyl- or 1-aryl-3-dialkylureas in good yield (eq 21).[26]

(19)

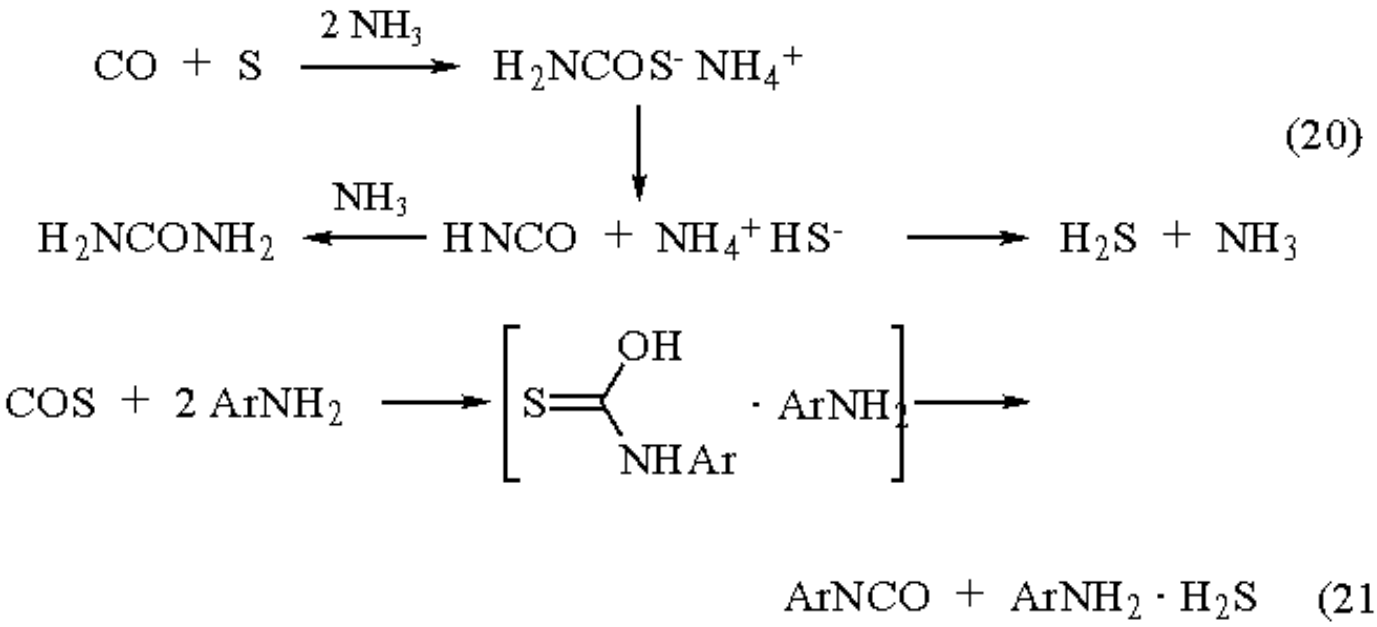

This sulfur-assisted carbonylation has also been applied to the synthesis of 4-hydroxycoumarins,[27] which entails the direct formation of a C-C bond without a transition metal catalyst (eq 22).

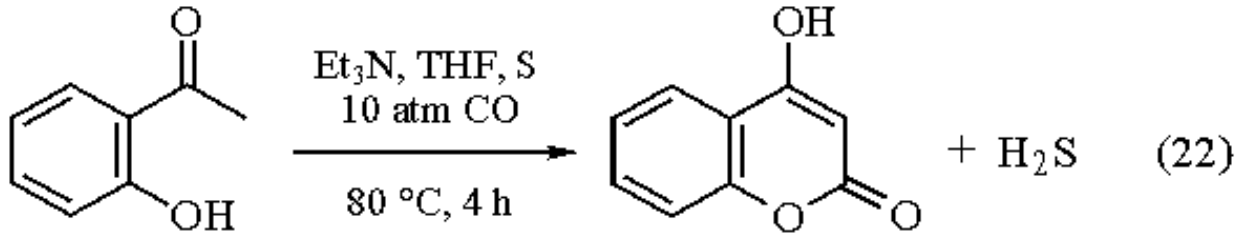

This reaction has also been applied to the synthesis of *S*-alkyl carbonothioates, which requires the use of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** and an alkylating agent (eq 23).[28]

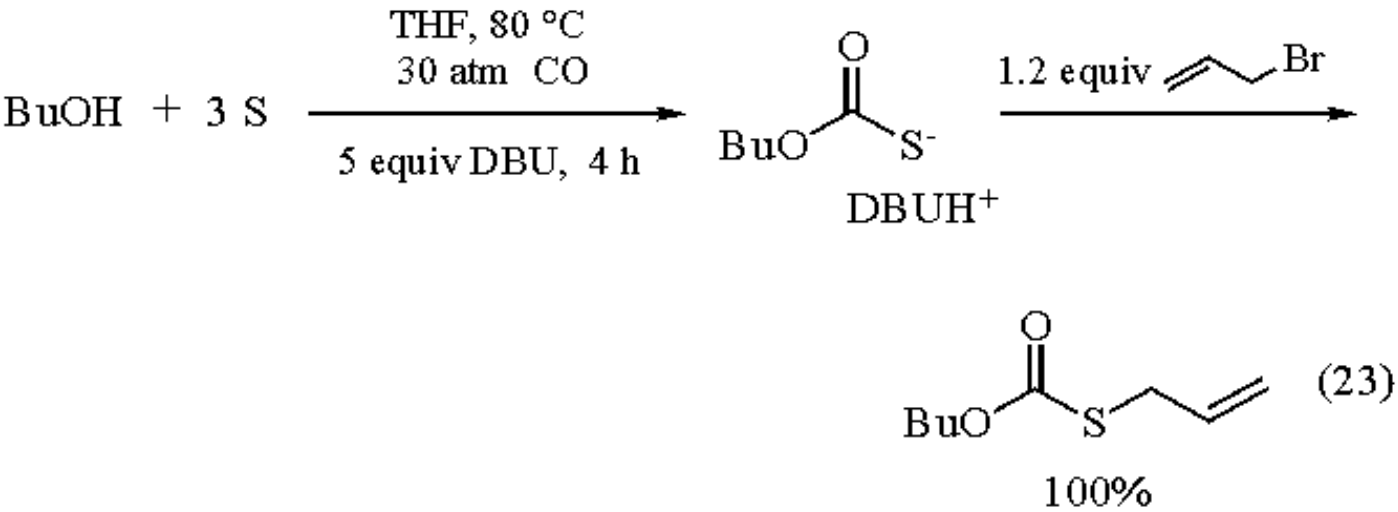

Application to the synthesis of carbonates has been accomplished by inclusion of a stoichiometric amount of ***Copper(II) Chloride*** in the second step (eq 24).[29]

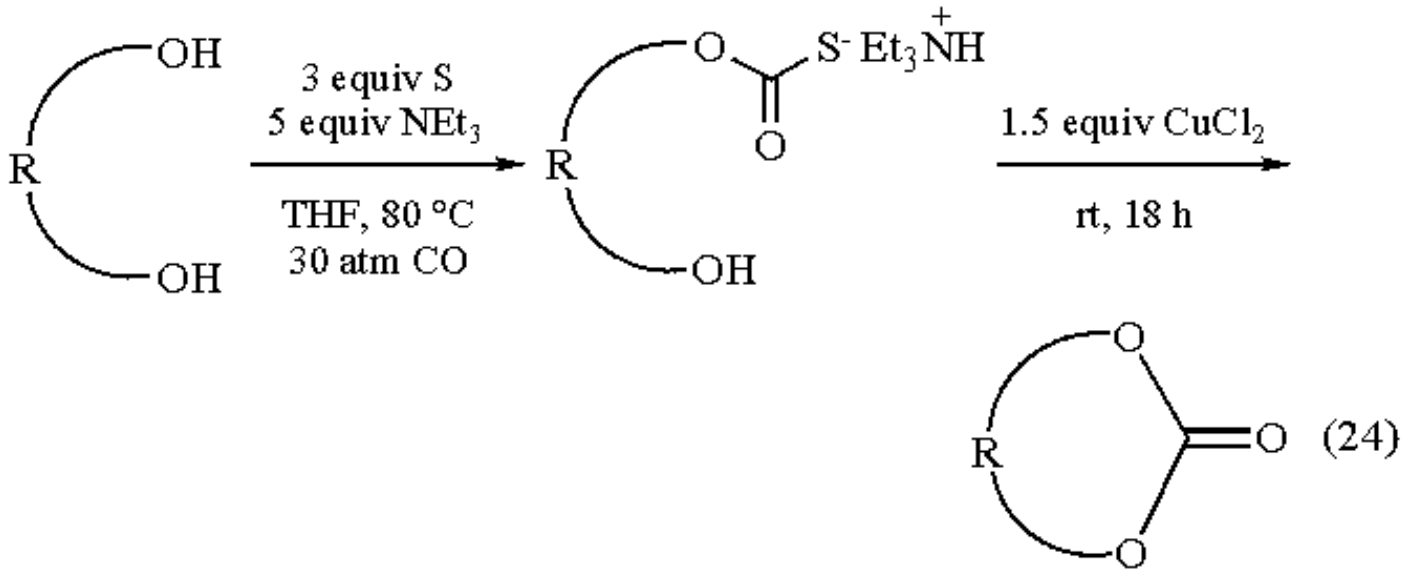

More complex heterocycles like 4-alkylidene-2-oxo-1,3-oxathiolanes have been synthesized by a related method (eq 25).[30]

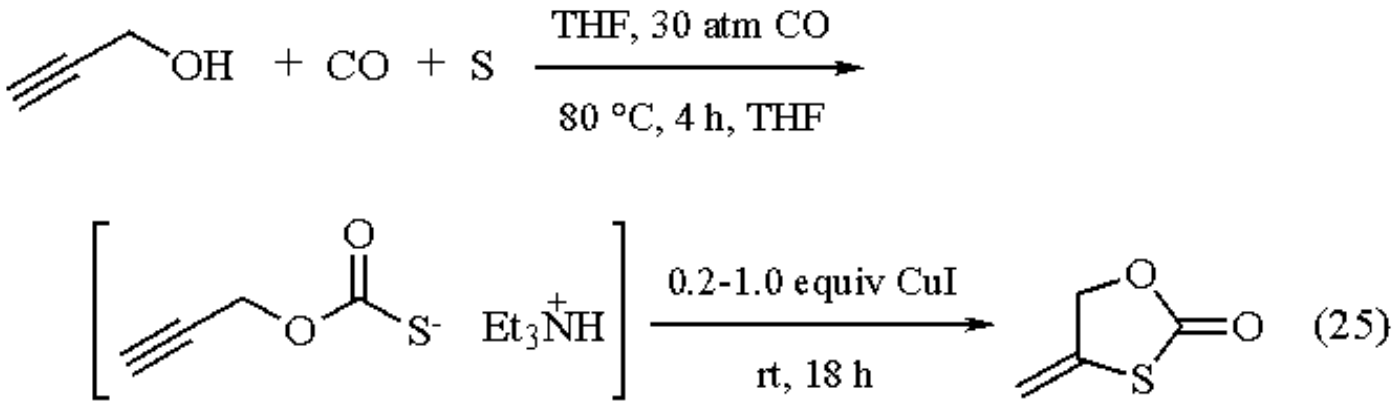

The same group has developed a variation of this technique which provides the *S*,*S*-dialkyl dithiocarbonates from water, sulfur, carbon monoxide, and alkyl halides.[31] The use of a catalytic amount of selenium provides a synthesis of *S*-alkyl thiocarbamates from amines, carbon monoxide, sulfur, and alkyl halides that can be carried out under ambient pressure (eqs 26 and 27).[32] The intermediate (**1**) can undergo decomposition to carbonyl selenide which then undergoes facile exchange with sulfur to give carbonyl sulfide, which will then react as usual. At higher pressures of CO (10 atm) and 1 mol % selenium these authors can synthesize *S*-alkyl carbonothioates.[33]

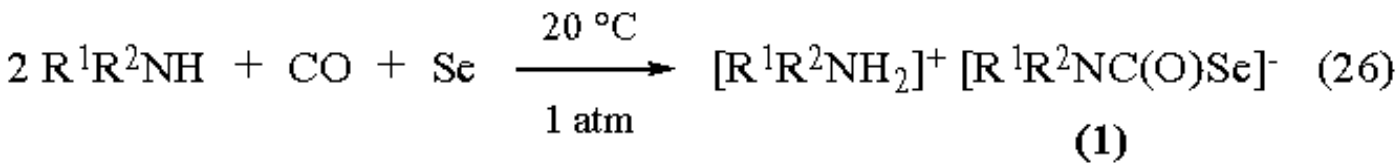

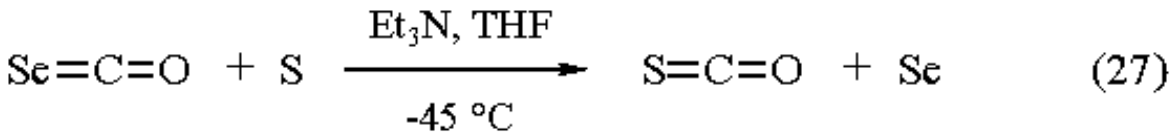

Sulfide and Polysulfide-Derived Reactions.

The largest and broadest application of sulfur in organic synthesis is in the generation of sulfides and polysulfides from elemental sulfur. These polysulfides can act as nucleophiles, reductants, and oxidants. A brief survey of these various aspects of sulfides and polysulfides is in order.

Elemental sulfur is believed to dissociate in liquid ammonia according to the following series of equations (eq 28).

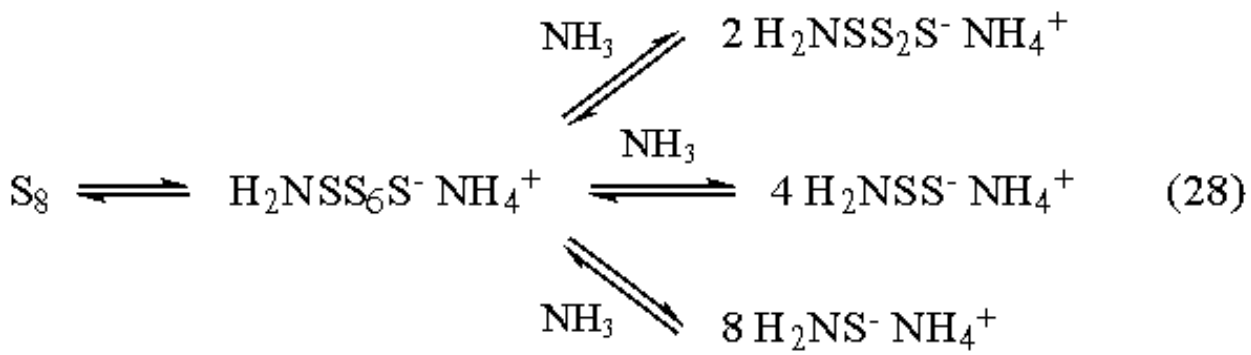

(28)

Sato obtained a mixture of products upon attempted reduction of 4-nitrotoluene in liquid ammonia (eq 29).[34]

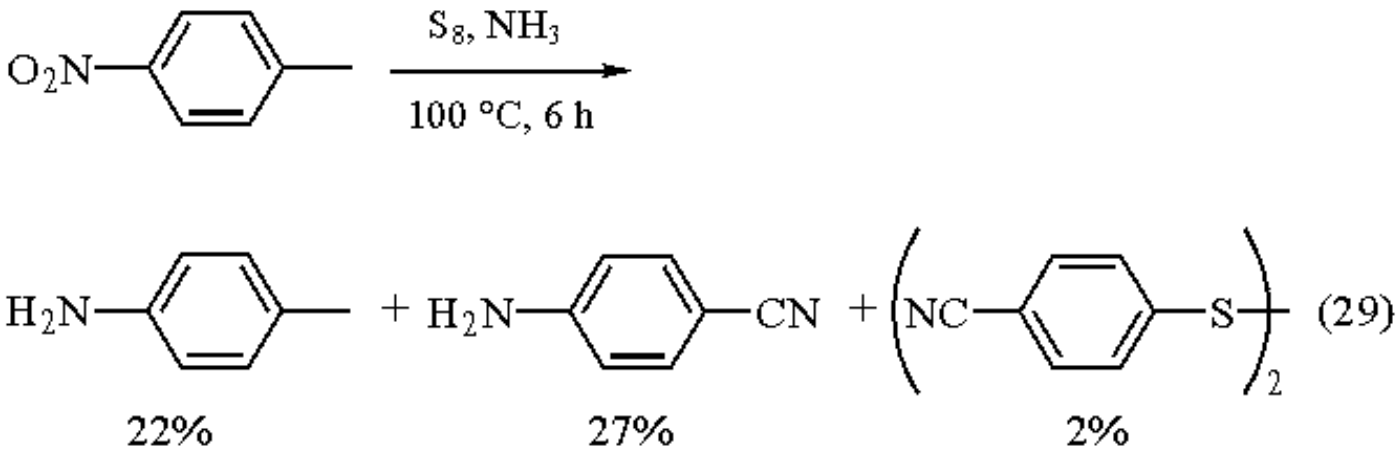

(29)

The use of sulfur as an oxidant is more common and several examples exist. The oxidation of aromatic sulfinates with elemental sulfur in amines gives thiosulfonates almost quantitatively.[35] Oxidation of benzylic carbons to aldehydes is observed with 4-nitrotoluene in a water-ethanol solvent at reflux (eq 30).[36] The oxidation of both methyl groups of *m*- and *p*-xylene gave high yields of isophthalic and terephthalic acids in 87 and 96% yields, respectively (eqs 31 and 32).[37]

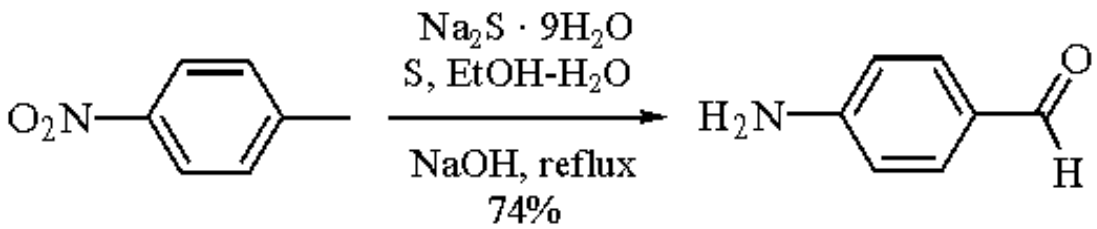

(30)

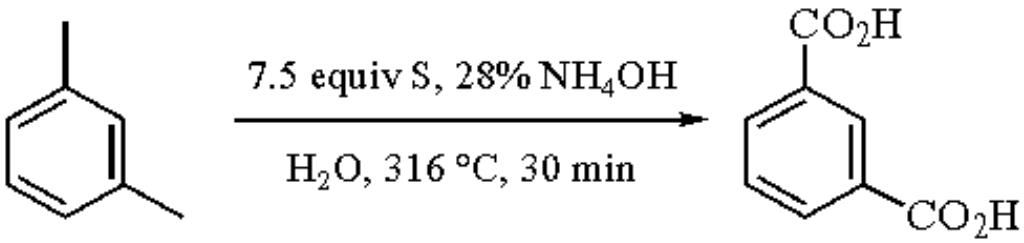

(31)

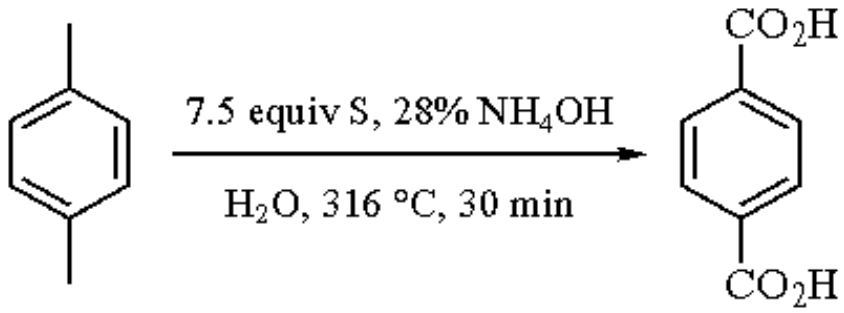

(32)

Strong nucleophiles are generated upon the reaction of excess ammonia and elemental sulfur. These have been used to prepare arenesulfinamides from *S*-(4-nitrophenyl) *S*-substituted phenyl sulfoximides (eq 33).[38] The same conversion has been accomplished using 4-nitrophenyl substituted phenyl sulfoxides.[39]

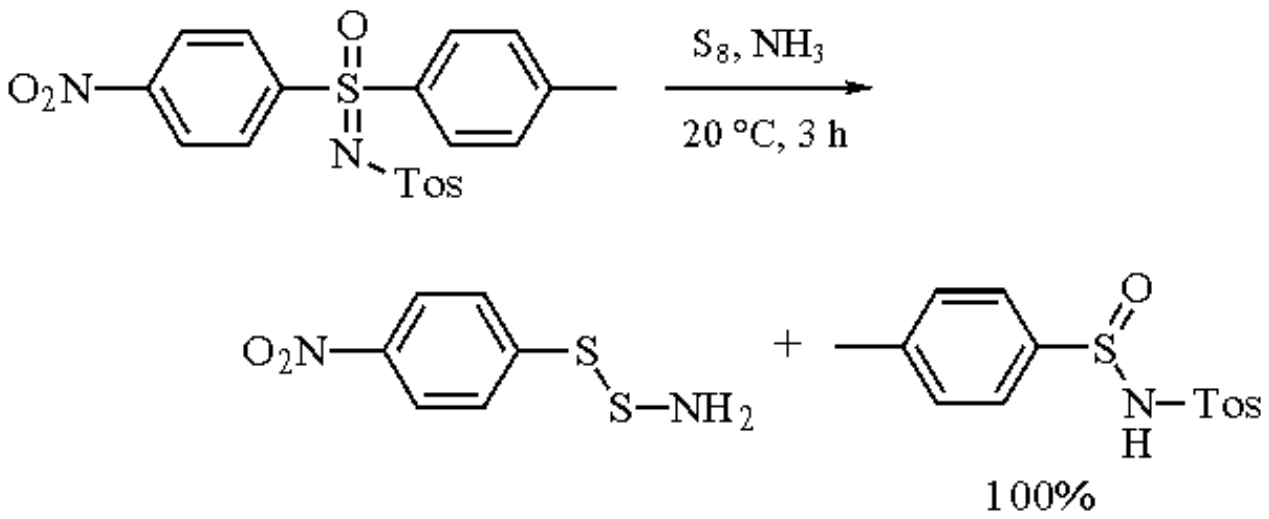

(33)

The generation of anhydrous lithium sulfide is easily accomplished by reaction of two equivalents of ***Lithium Triethylborohydride*** with sulfur in THF at room temperature. This reacts well with a variety of electrophiles that require strictly anhydrous conditions to give good yields of products. The alkali metal disulfides are not commercially available and the methods for their preparation [Li^0, NH_3(l)] are difficult and give mixtures of polysulfide salts. The reaction of one equivalent of the hydride reagent with sulfur yields the lithium disulfide which gives high yields of disulfide products.[40] More recently a phase transfer catalytic method of generating the disulfide in a water/chloroform mixture has been used with electrophiles that can tolerate the presence of water (eq 34).[41]

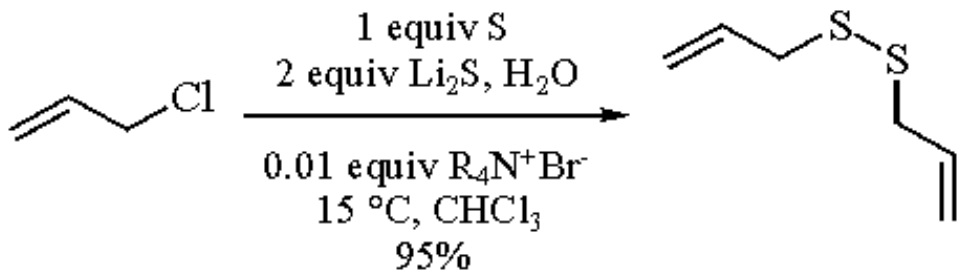

(34)

When sulfur reacts with ***Sodium Borohydride*** in an appropriate solvent such as THF, the sulfurated hydride $NaBH_2S_3$ is formed. The reagent is most useful for its special reactivity and not necessarily as a sulfurating agent (eqs 35 and 36). A synopsis of its range of reactions was published more than 20 years ago.[42]

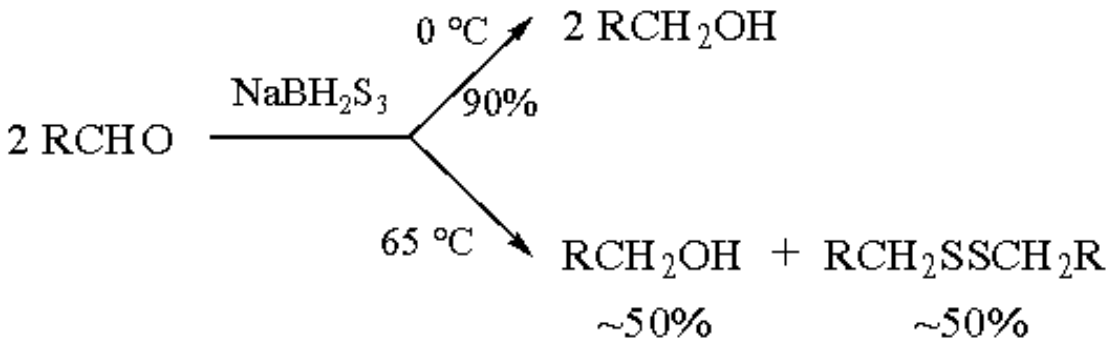

(35)

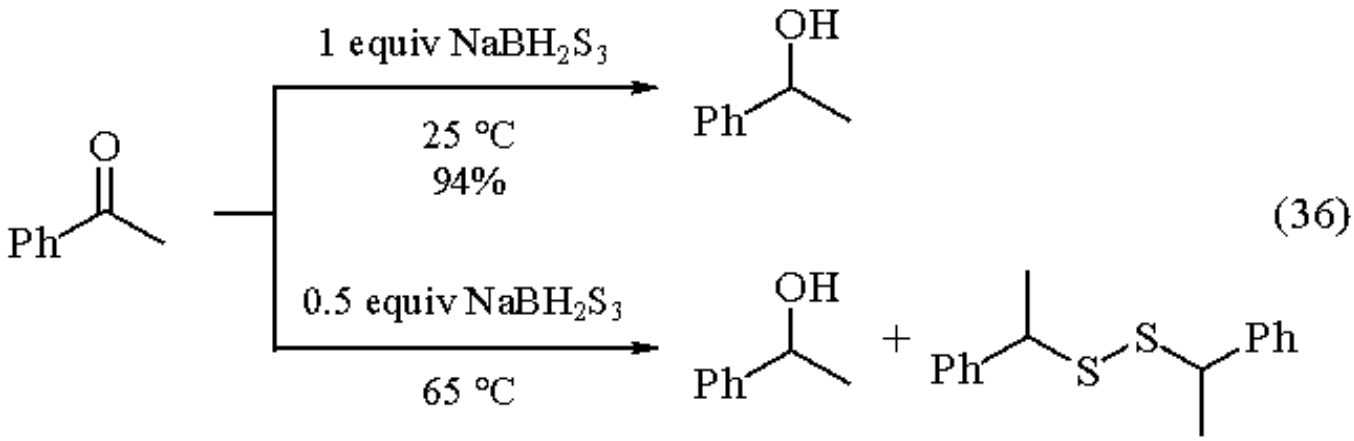

Miscellaneous Reactions.

Sulfur will react with organometallic reagents to replace a metal-carbon bond with a sulfur-carbon bond. Since sulfur is divalent, a thiolate results which is generally not useful. In some cases, however, the thiolate is essential for further reactivity. The utility of lithium thioalkynolates in the synthesis of alkenes is outlined below (eqs 37 and 38).[43]

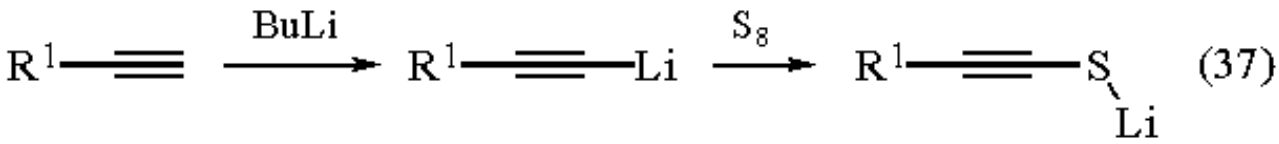

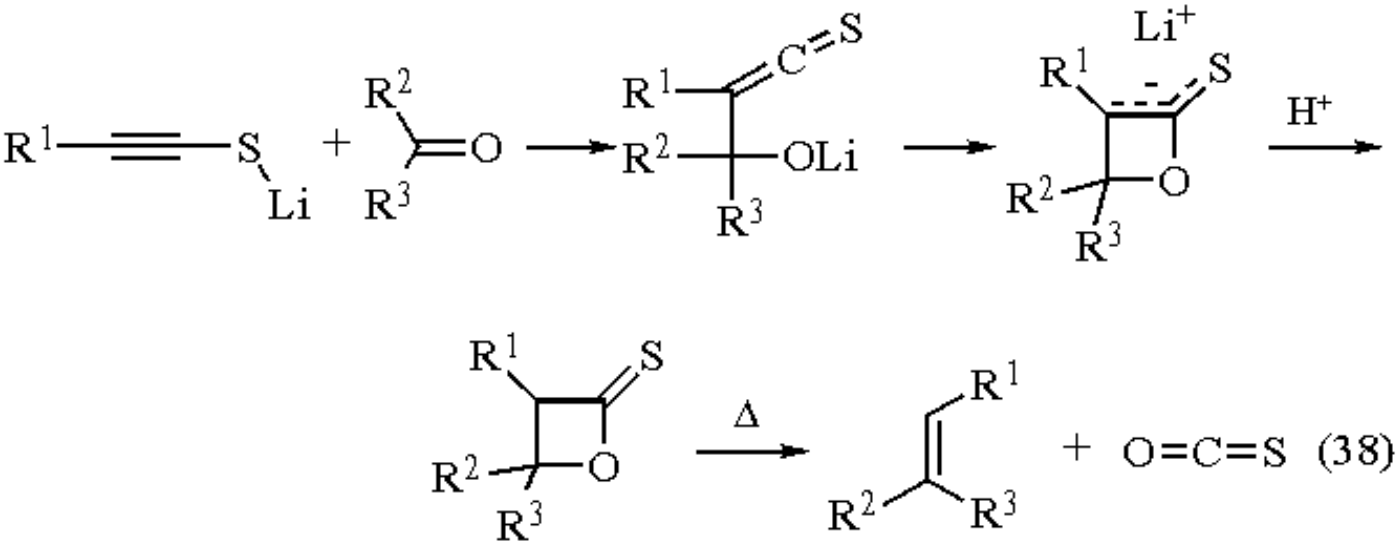

Using the same intermediate alkynylthiolates, one can prepare thioamides (eq 39).[44] This sequence works for selenium derivatives as well.

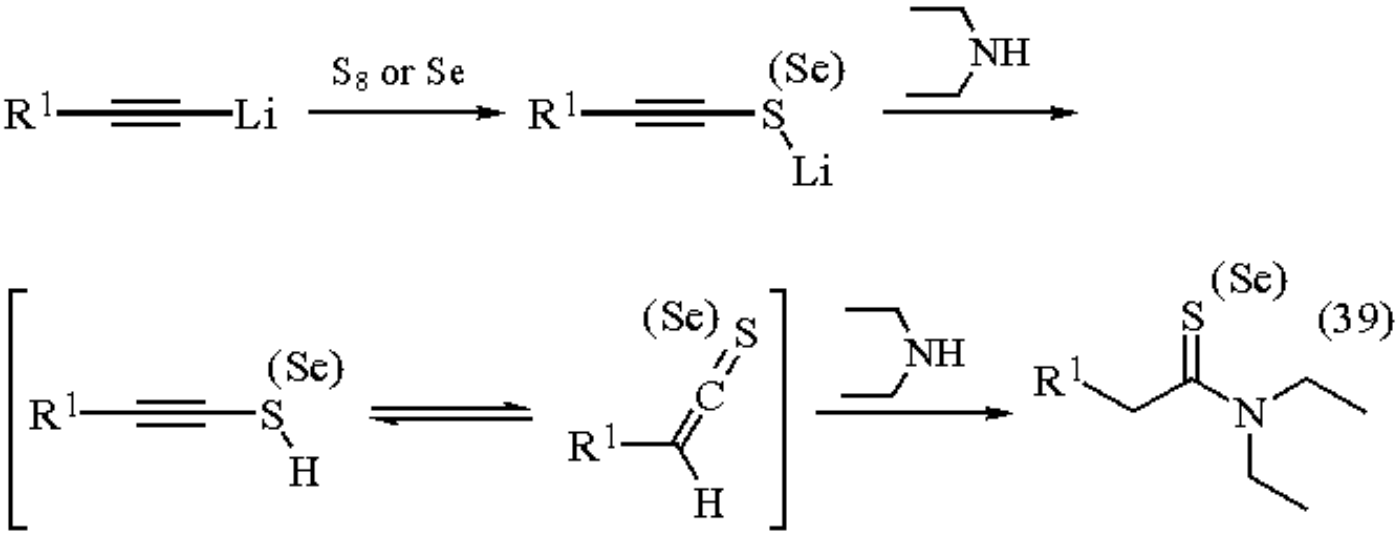

A tetrahydrothiophene synthesis was accomplished by treating the carboalumination product of ***Triethylaluminum*** and terminal alkenes with sulfur (eq 40).[45]

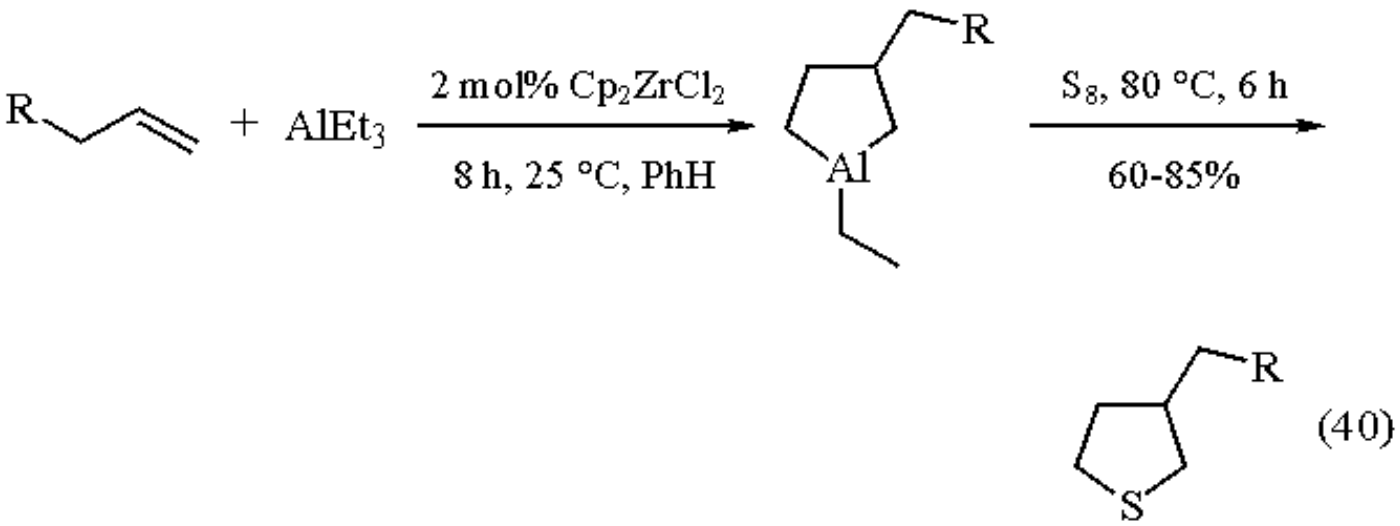

Diazo compounds react with sulfur to give thioketones. Monothioanthraquinones can be synthesized from the reaction of 10-diazoanthrones with sulfur in DMF at 130-150 °C (eq 41).[46]

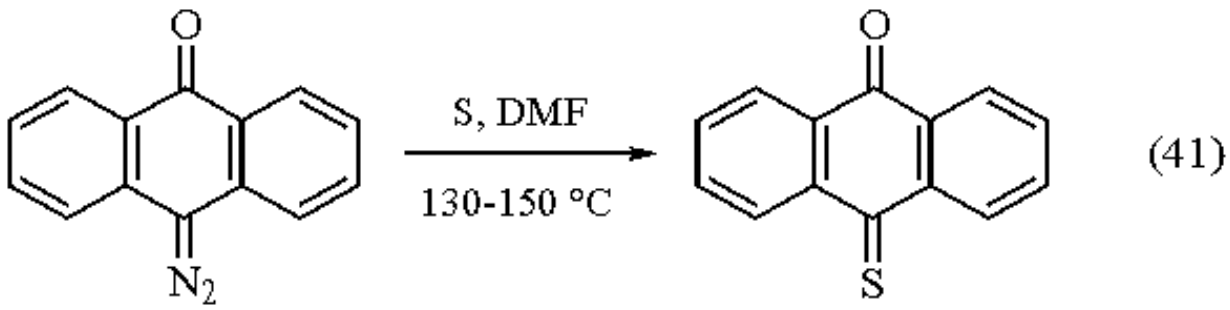

Sulfur is less reactive towards carbenes than selenium and so selenium is used in a catalytic fashion first to react with carbene-like compounds (isocyanides in this case), and then sulfur replaces the selenium to give an isothiocyanate (eq 42).[47] Using this method, cyclohexyl isothiocyanate was synthesized in 89% yield using 5 mol % of Se and 1.2 equiv of S. The reaction could be run with 0.5 mol % Se with only a modest lengthening of the reaction time.

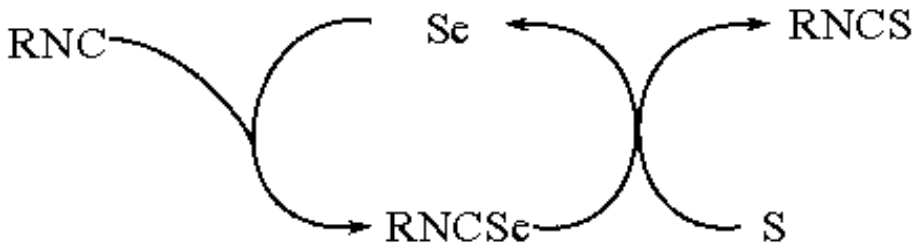

(42)

An unusual aspect of sulfur chemistry is the reaction of alkenes with elemental sulfur (eqs 43 and 44). The reaction of sulfur with norbornene in the presence of ammonia in DMF at 110 °C results in a selective and stereospecific sulfuration.[48] The *exo*-3,4,5-trithiatricyclo[5.2.1.0^{2,6}]decane forms in about 86% yield.

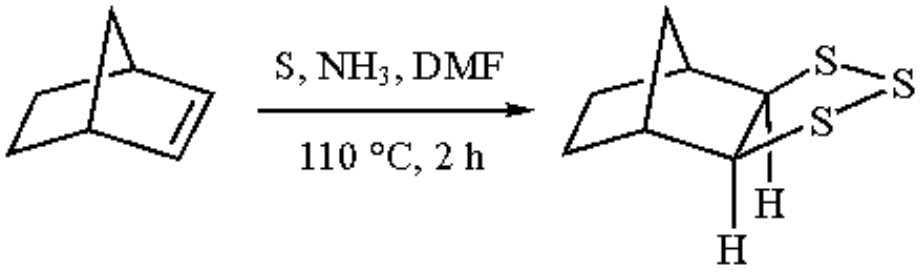

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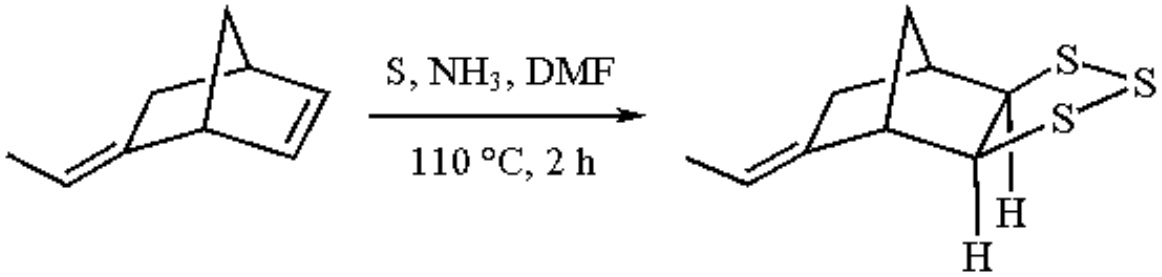

(44)

Sulfur has also been used to oxidize inorganic compounds to increase their electrophilic nature. A simple synthesis of ***Triphenylphosphine*** that does not rely on organometallic reagents has been published by Olah (eq 45).[49] This Friedel-Crafts reaction fails with ***Phosphorus(III) Chloride*** as well as its corresponding oxide. There exists an unfavorable disproportionation between triphenylphosphine, diphenylchlorophosphine, and phenyldichlorophosphine. The oxychloride does not give the triphenylphosphine oxide. The phosphorus sulfochloride gives the corresponding triphenylphosphine sulfide, which is easily reduced.

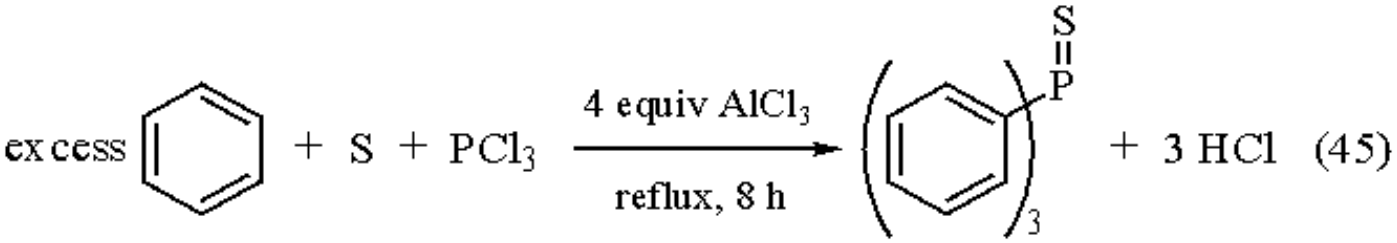

(45)

Olah also used ***Trifluoromethanesulfonic Acid*** catalysis for the electrophilic sulfuration of cycloalkanes.[50] Elemental sulfur was heated in a stainless steel autoclave with excess cyclopentane in triflic acid at 150 °C for 12 h. This gave dicyclopentyl sulfide in 46% isolated yield (eq 46).

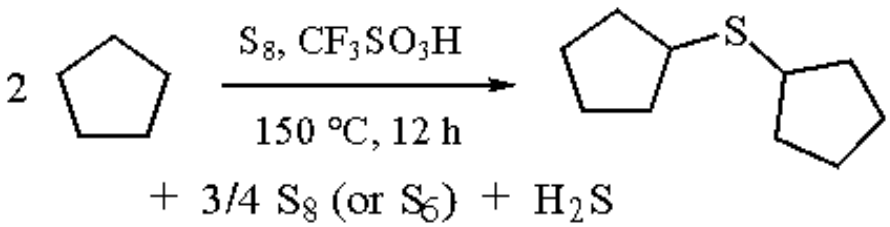

(46)

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Sulfur Dichloride

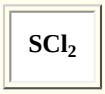

[10545-99-0] · Cl_2S · Sulfur Dichloride · (MW 102.97)

(electrophilic addition to alkenes and dienes;[1] synthesis of heterocycles from eneimines and nitriles;[2] and electrophile for the synthesis of sulfides[3])

Physical Data: mp -121 °C; bp 59 °C; *d* (20 °C) 1.621 g cm^{-3}; *n*20D 1.5570.

Solubility: sol dichloromethane, *n*-hexane, CCl_4, benzene; reacts violently with H_2O, acetone, DMSO, DMF.

Form Supplied in: dark-red liquid. Techgrade (80%), major impurity is S_2Cl_2. Also 1.0 M in CH_2Cl_2. Very pungent, chlorine-like odor. Readily decomposes to S_2Cl_2 and Cl_2.

Preparative Methods: can be synthesized from $S_{(5)}$ or S_2Cl_2.[4]

Purification: pure SCl_2 can be obtained from ***Disulfur Dichloride*** and ***Chlorine*** by distillation from ***Phosphorus(III) Chloride***.

Handling, Storage, and Precautions: distilled SCl_2 is stable for a few days in glass with a few drops of PCl_3. Air and H_2O sensitive. Incompatible with acids, bases, alcohols, plastics, amines. Avoid contact with metals. Corrosive; lachrymator. Harmful if swallowed, inhaled, or absorbed through the skin. Inhalation can be fatal. Possible carcinogen.

Electrophilic Addition to Dienes.

Sulfur dichloride is an extremely reactive electrophile towards alkenes. Under dilute conditions, sulfur dichloride reacts with unconjugated dienes (eq 1) to give dichloro sulfur-bridged bicyclic compounds.[1a-c,5]

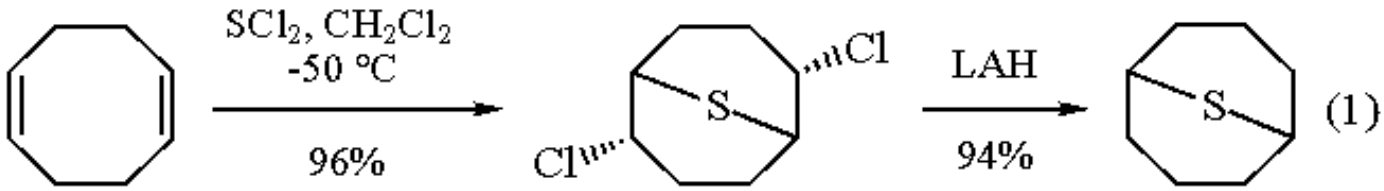

The proposed 1,2-episulfonium ion intermediate (eq 2) explains the selectivity of chlorine addition and their high lability. Yields for the addition of SCl_2 to dienes[1] and for subsequent halide displacements are closely tied to how readily the sterically demanding 1,2-episulfonium ion is formed.[6,7]

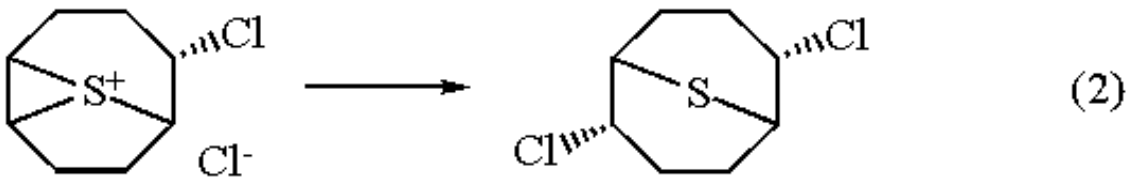

Common transformations of the SCl_2-diene addition products are chloride replacement,[6a] chloride displacement to form episulfides,[6b,7a] and oxidation of the sulfide bridge to a sulfone bridge.[1] In a few cases, the addition of SCl_2 has been extended to conjugated dienes.[8]

The reactivity of sulfur dichloride towards alkenes is exploited in the synthesis of thiaalkanams and thiaisoalkanams in which SCl_2 is used as a sulfur transfer agent to nonconjugated diene systems (eq 3).

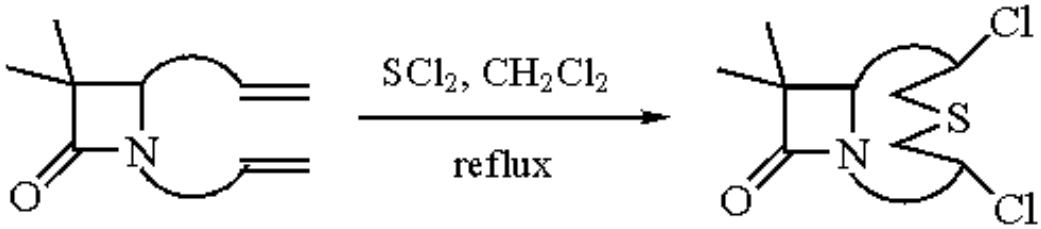

(3)

Select examples of five and seven-membered sulfur-nitrogen heterocycles can be synthesized in modest yield.[9,10]

Reaction with Unsaturated Heteroatom Functionality.

Lewis acid catalysis of sulfur dichloride additions to nitriles leads to the formation of 1,2,4-thiadiazoles.[2] As seen in eq 4, a major side reaction of this process is the chlorination of the aromatic substituents.

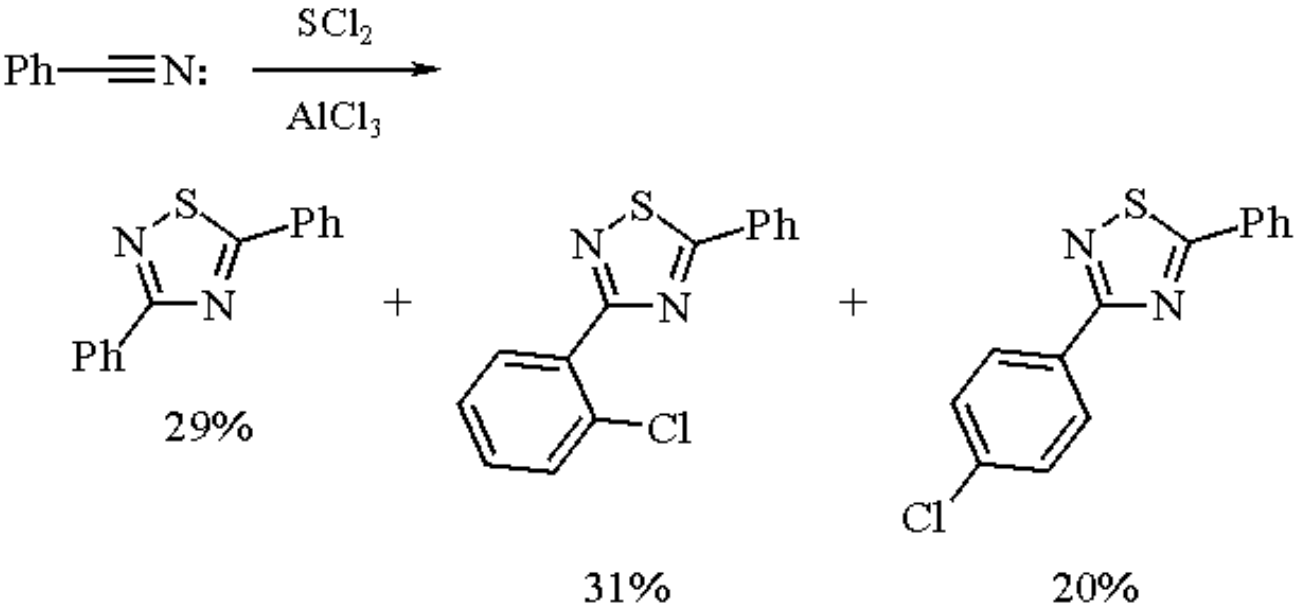

(4)

Lewis acid catalysts for this reaction are ***Tin(IV) Chloride***, ***Aluminum Chloride***, ***Iron(III) Chloride*** and ***Antimony(V) Chloride***. Nitriles with α-hydrogens do not yield any thiadiazole product, but rather give disulfur species from deprotonation (eq 5).[2]

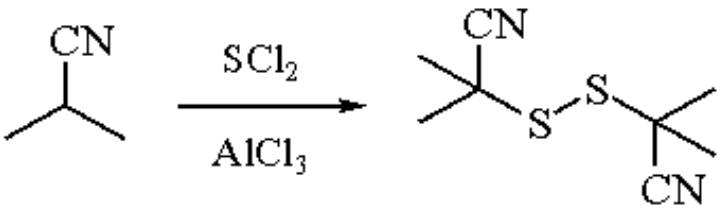

(5)

Conjugated imines such as 1-*t*-butyl-4-phenyl-1-aza-1,3-butadiene react with 0.5 equiv of sulfur dichloride to give isothiazoles[11] in high yield, 86-91%, based on sulfur (eq 6). Spectroscopic evidence verifies that two equivalents of the imine are required to form the 2:1 salt intermediate before cyclization.

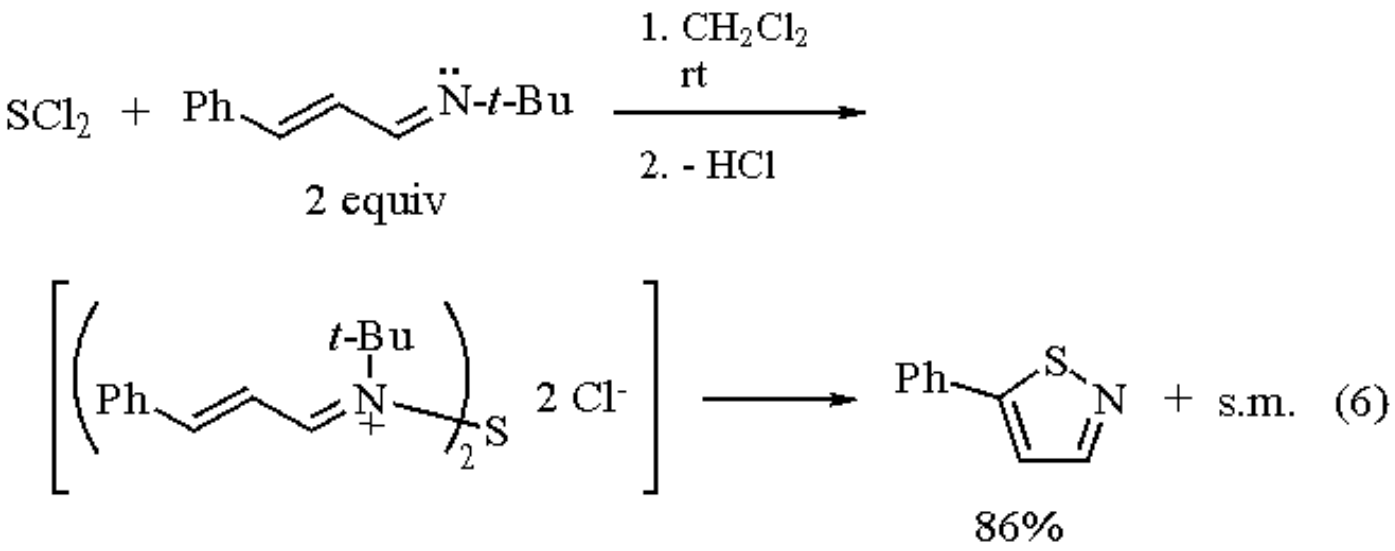

Unlike 1-azadienes, 2-azadienes react with high yields in a 1:1 molar ratio and show no spectroscopic evidence of a 2:1 salt intermediate (eq 7).

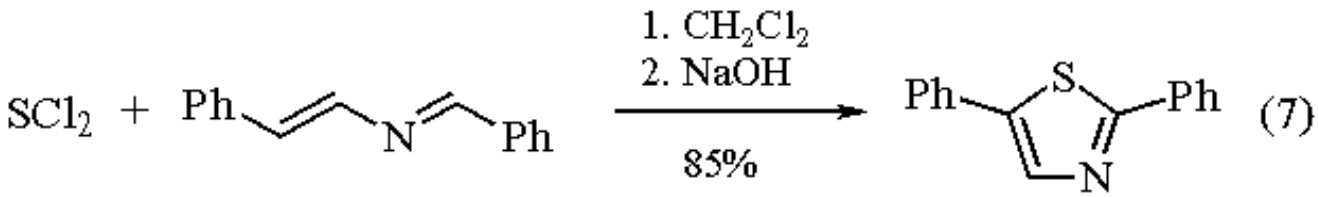

Miscellaneous Applications.

Other applications include the synthesis of dialkynyl sulfides, (RC&tbond;C)S,[12] the heterocyclic adducts of alkynes,[13] the synthesis of novel macrocyclic polysulfur compounds,[13b] and one-pot syntheses of benzothiophenes.[14] Considerable literature has also been devoted to the formation of episulfides from hindered alkenes,[15] with limited success (see also ***Disulfur Dichloride***).

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8. (a) Fieser, M.; Fieser, L. *FF* **1969**, *2*, 391. (b) Lautenschlaeger, F. *JOC* **1968**, *33*, 2627.
9. Komatsu, M.; Ogawa, H.; Mohri, M.; Ohshiro, Y. *TL* **1990**, *31*, 3627.
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15. (a) Taolstikov, G. A.; Lerman, B. M.; Umanskaya, L. I.; Struchkov, Y. T.; Espenbetov, A. A.; Yanovsky, A. L. *TL* **1980**, *21*, 4189. (b) Tolstikov, G. A.; Lerman, B. M.; Umanskaya, L. I.; Struchkov, Y. T. *BAU* **1982**, 588.

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Sulfur Dioxide

O=S=O

[7446-09-5] · O_2S · Sulfur Dioxide · (MW 64.07)

(reacts with 1,3-dienes in reversible cheletropic addition;[2,3] SO_2 extrusion from 2,5-dihydrothiophene 1,1-dioxides generates 1,3-dienes,[9,10] *o*-quinodimethanes;[4,5] inserts into carbon-metal bonds;[14-16] reacts with ylides to give heterocycles;[17,18] electrophilic promoter of Mannich reactions;[20,21] catalyst for isomerization of alkenes,[24] dienes,[22,23] and nitrile oxides;[25] involved in sulfonic acid[26] and sulfonyl chloride synthesis;[27] reacts with Wittig reagents or α-silyl carbanions to give sulfines;[28,29] reacts with polyenes,[30,31] cyclopropanes;[32] reduces pyridine *N*-oxides[36] and ozonides;[37] solvent for superacid-promoted reactions[41])

Physical Data: [1] mp -75.5 °C; bp -10.0 °C; *d* (liquid) 1.434 g cm^{-3} at 0 °C; *d* (vapor, 0 °C) 2.264 g cm^{-3}.

Solubility: sol H_2O, alcohol, acetic acid, sulfuric acid, benzene, acetonitrile.

Form Supplied in: colorless liquid or pungent, nonflammable gas; supplied in small cylinders; widely available.

Handling, Storage, and Precautions: corrosive irritant to respiratory system, skin, eyes; mildly toxic by inhalation; teratogenic; reacts violently with numerous substances; use only in well-ventilated fume hood.[1]

Reversible Cheletropic Addition of SO_2 to 1,3-Dienes and Analogs.

Much of the chemistry of SO_2 involves its reversible cheletropic addition to 1,3-dienes to give 2,5-dihydrothiophene 1,1-dioxides (sulfolenes) (eq 1).[2] Much less commonly observed is the alternative, hetero-Diels-Alder cycloaddition mode, also reversible, leading to the sultine (sulfinic ester) structure.[3] At low temperature this latter mode can be kinetically favored with reactive 1,3-dienes, but the cheletropic addition is generally favored thermodynamically.[3]

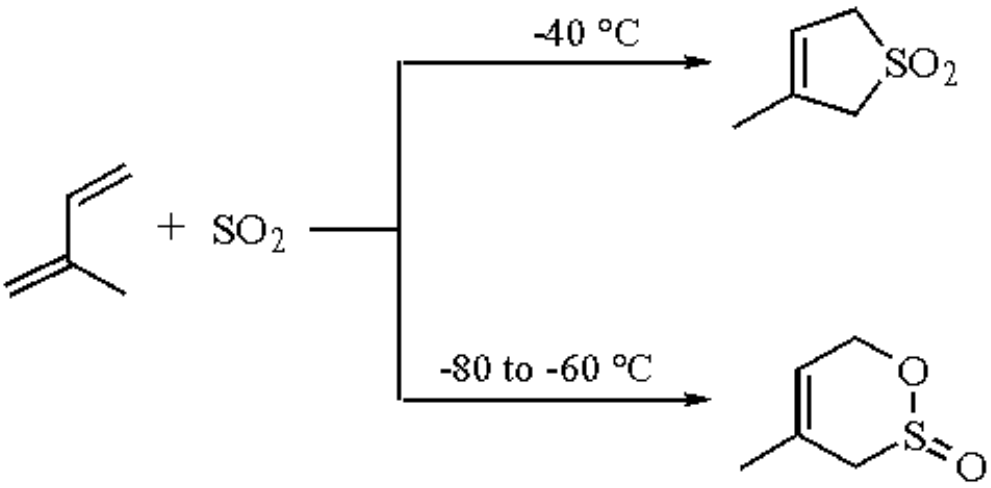

(1)

Trapping and regeneration of reactive *o*-quinodimethanes via cheletropic addition and extrusion of SO_2 has proven useful in heterocyclic (eqs 2 and 3)[4] and carbocyclic systems (eq 4).[5] Thermal extrusion of SO_2 from the cyclic sulfones yielded the reactive *o*-quinodimethanes, which were trapped with various dienophiles.

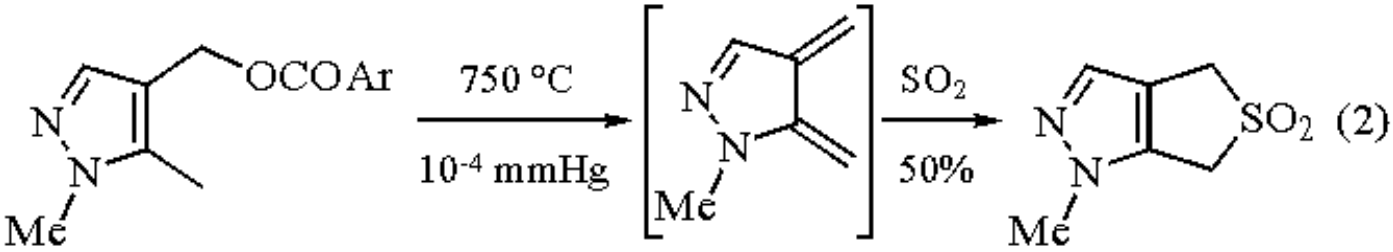

(2)

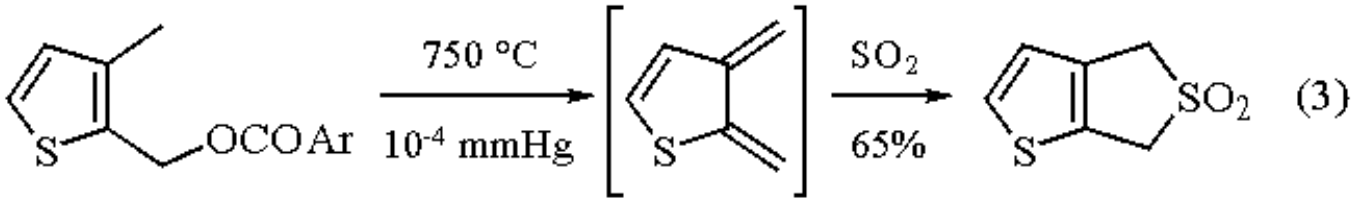

(3)

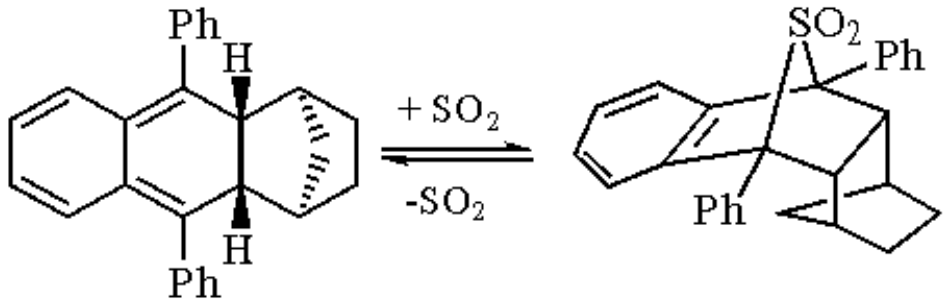

(4)

Linear cheletropic addition of SO_2 to conjugated diallenes affords 2,5-bis(alkylidene)-2,5-dihydrothiophene 1,1-dioxides via the disrotatory process shown (eq 5).[6]

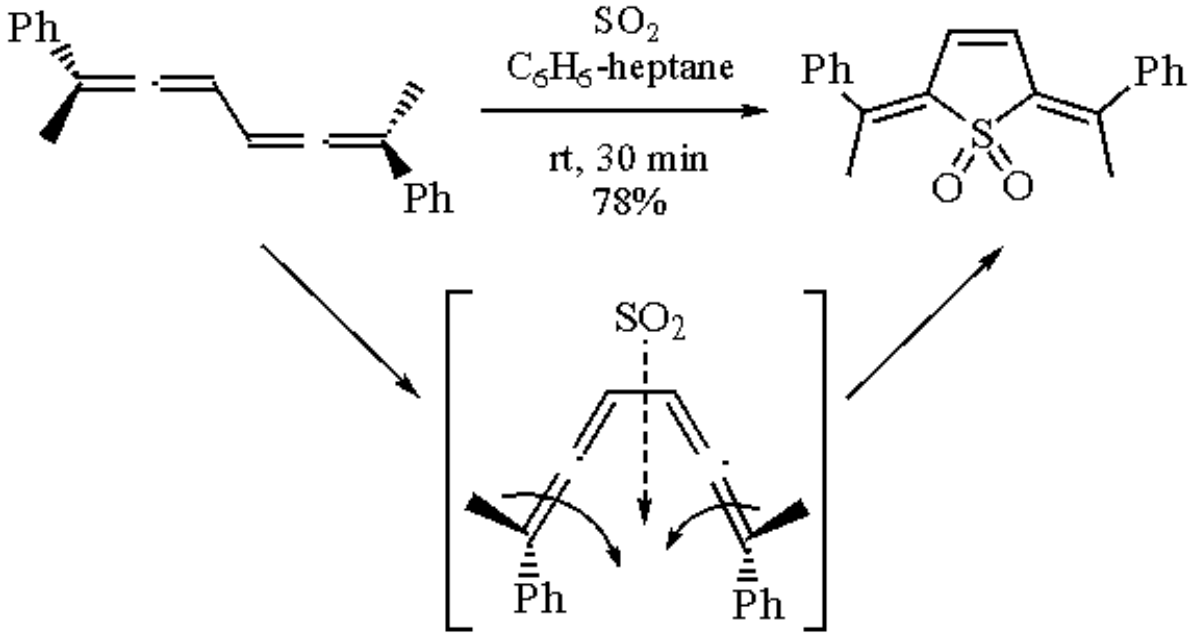

(5)

Similarly, addition of SO_2 to 3-methyl-1,2,4-pentatrienyl-1-phosphonate (eq 6)[7] or 5-methyl-1,3,4-hexatrienyl-3-phosphonate esters (eq 7)[8] affords the corresponding phosphorylated alkylidene-2,5-dihydrothiophene 1,1-dioxides.

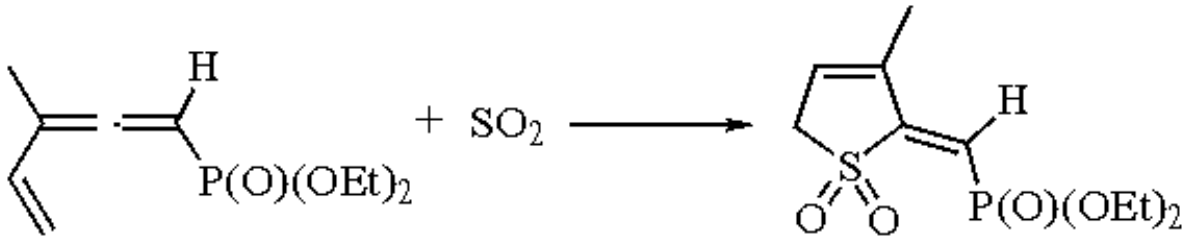

(6)

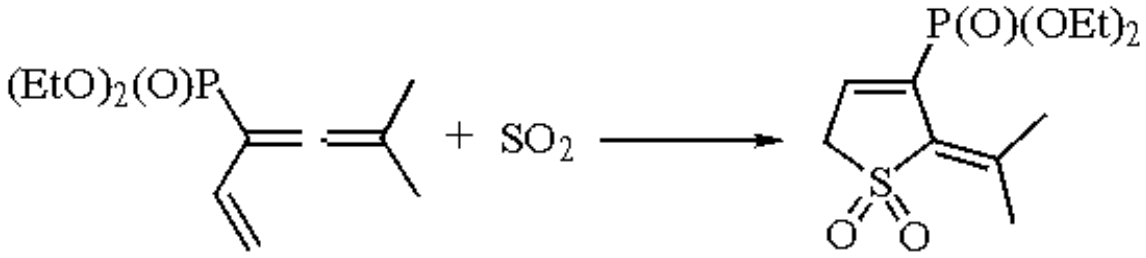

(7)

Chemical separation of a mixture of 1,3-diene geometric isomers was accomplished by selective cheletropic addition of SO_2 to the *trans* diastereomer (eq 8).[9] Chromatographic purification of the dihydrothiophene and thermolysis cleanly afforded *trans*-9,11-dodecadien-1-yl acetate, a sex pheromone of the female red bollworm moth.

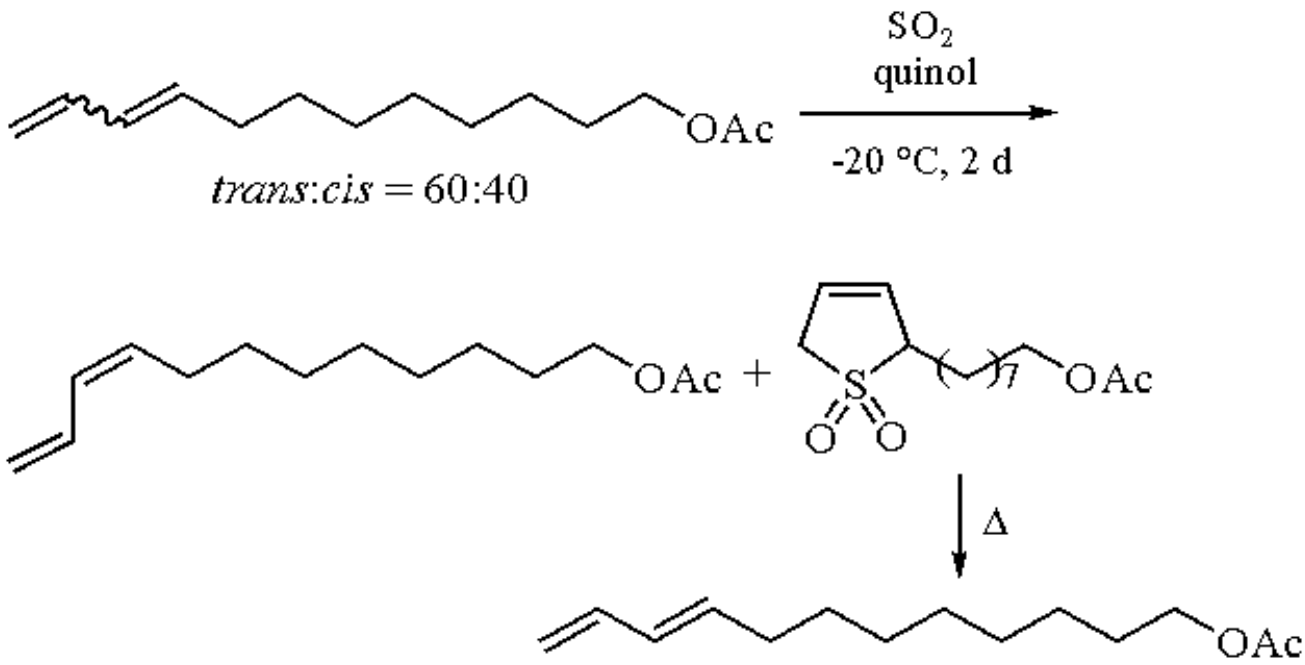

(8)

An elaboration of this tactic is shown in eq 9 for the synthesis of (*E*)-1-substituted 1,3-dienes and (*E*,*E*)-1,4-disubstituted 1,3-dienes.[10] The tricyclic sulfone (**1**) can be metalated and alkylated once or twice, giving (**2**) or (**3**), respectively. Thermolysis in the gas phase at 650 °C resulted in sequential loss of cyclopentadiene and SO_2 to provide the dienes in 91-98% isomeric purity.

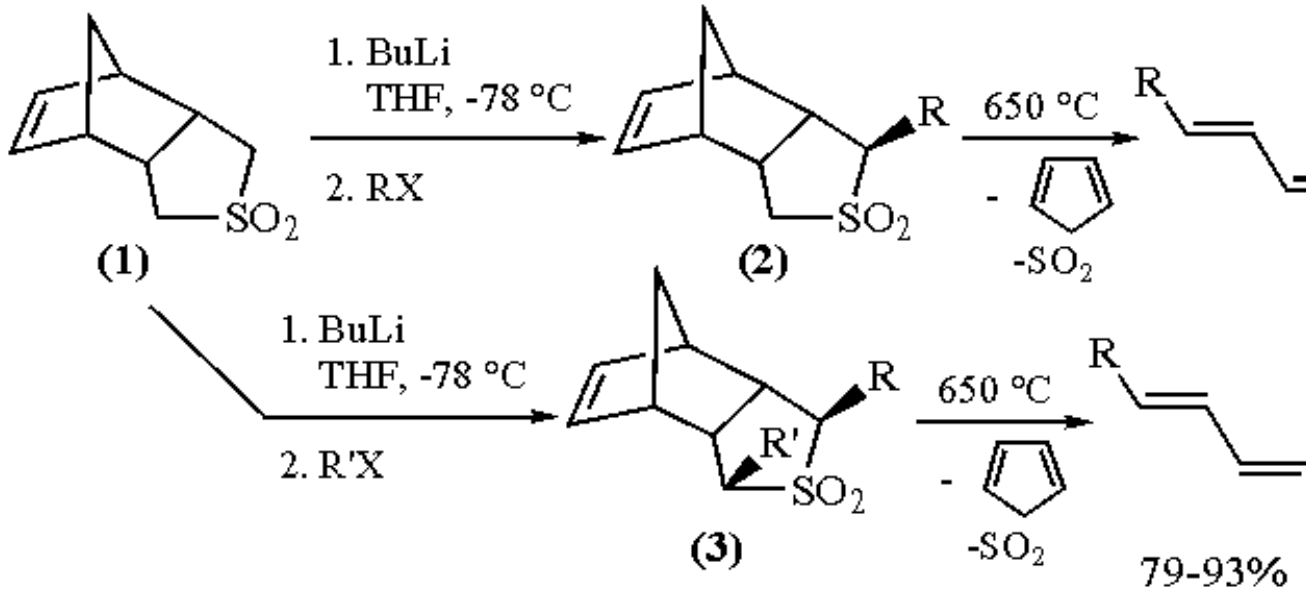

(9)

Acyclic Sulfone Synthesis.

Addition of Grignard and organolithium reagents to SO_2 is known to produce salts of sulfinic acids.[11] An example extending this to the enolate derived from camphor is shown in eq 10.[12] The intermediate β-keto sulfinate was alkylated to afford the β-keto sulfone shown in

modest yield.

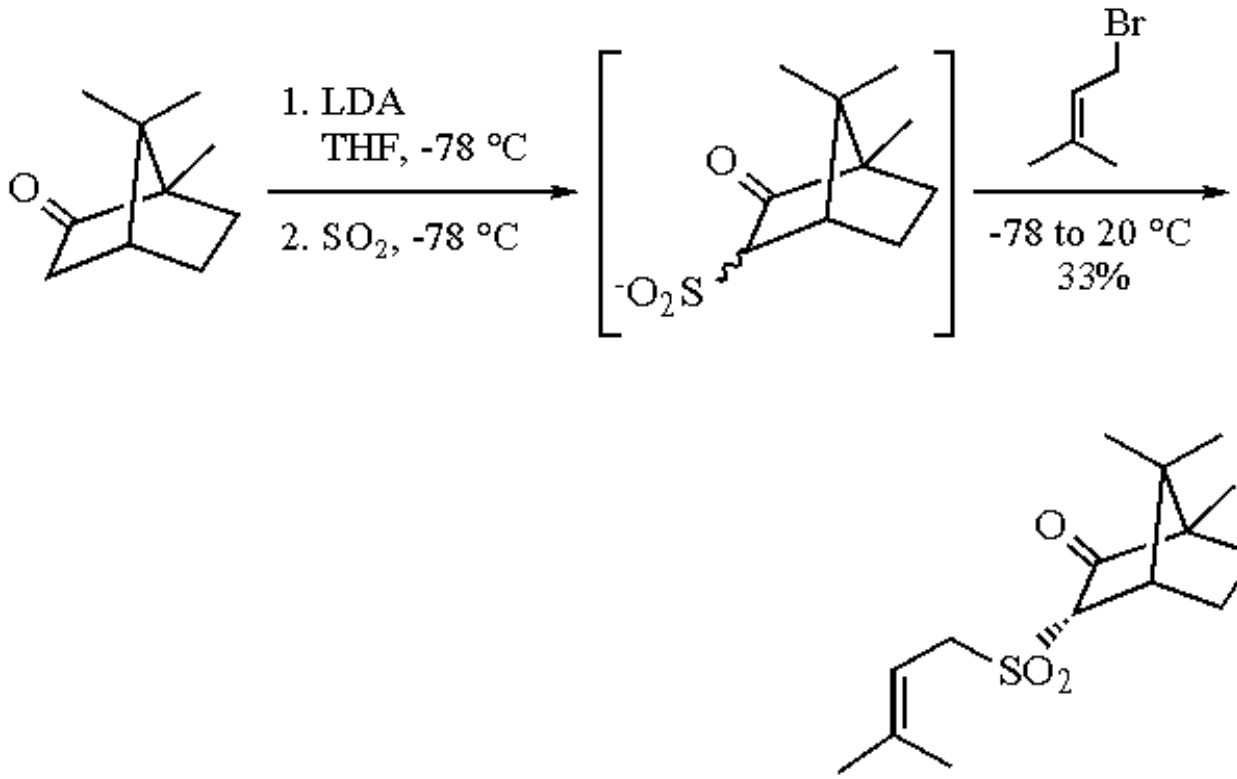

(10)

A high yield synthesis of diphenyl sulfone results from the phenylation of SO_2 with pentaphenylbismuth (eq 11),[13a] which proceeds more readily than the corresponding reaction with ***Triphenylbismuthine***.[13b]

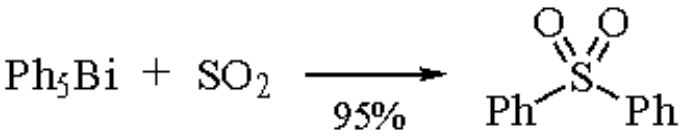

(11)

Insertion of SO_2 into Carbon-Metal Bonds.

Sulfur dioxide inserts into cyclohex-2-enylstannanes in chloroform via a *syn* S_E' process (eqs 12 and 13).[14] The γ-*syn* stereospecificity is lost upon changing the solvent to methanol.

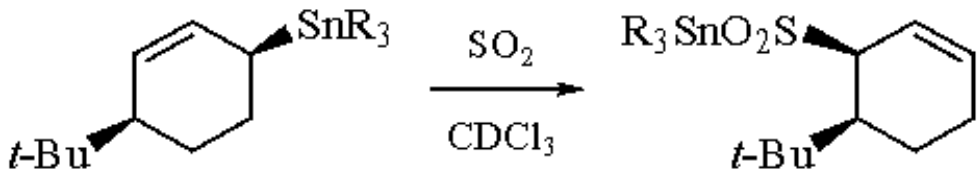

(12)

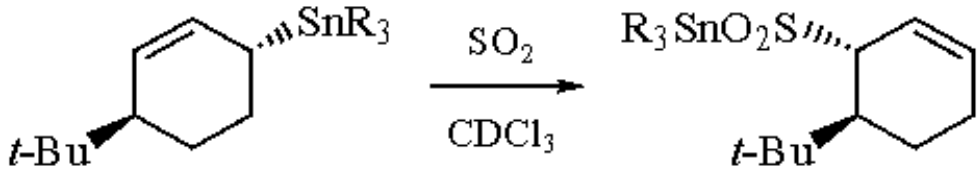

(13)

The bis(η^1,η^3-allyl)palladium phosphine complex in eq 14 inserts SO_2 to provide the *S*-sulfinate derivative, which undergoes reductive elimination to a 1:1 mixture of diallyl and allyl 2-propenyl sulfone upon treatment with ***Carbon Monoxide***.[15]

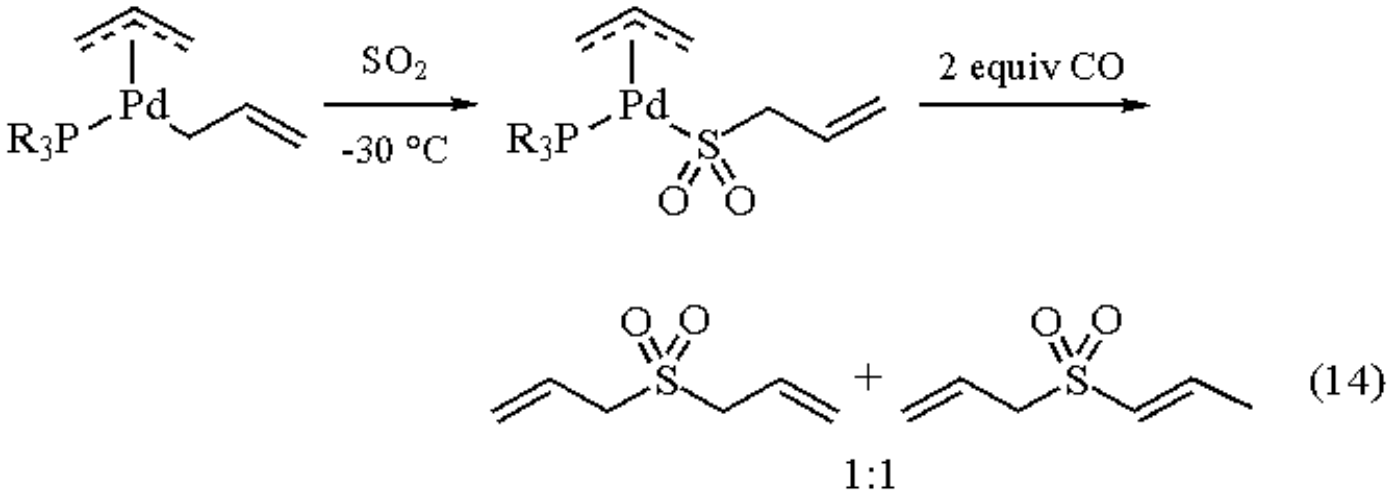

Triethylaluminum etherate reacts with SO_2 to afford the aluminum salt of ethylsulfinic acid (eq 15).[16]

Heterocycle Synthesis.

Combination of a dihaloketene, a Schiff base and SO_2 to give 5,5-dihalo-4-oxo-1,3-thiazolidine 1,1-dioxides is exemplified in eq 16.[17] These products can be dehalogenated or heated to extrude SO_2, yielding β-lactams.

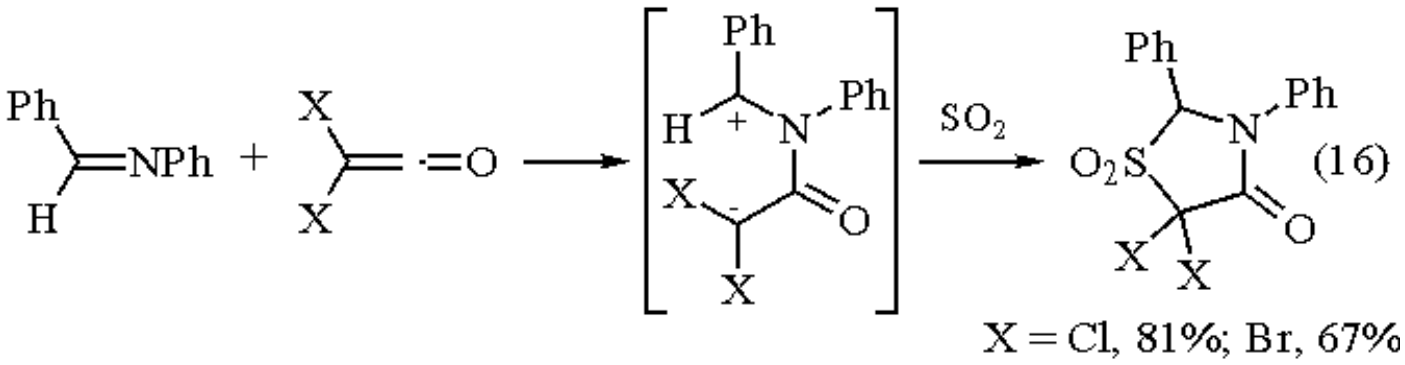

Generation of a thiocarbonyl ylide in liquid SO_2 from a Δ^3-1,3,4-thiadiazoline results in a regioselective 1,3-dipolar cycloaddition, giving 1,2,4-oxadithiolane 2-oxides (eq 17).[18]

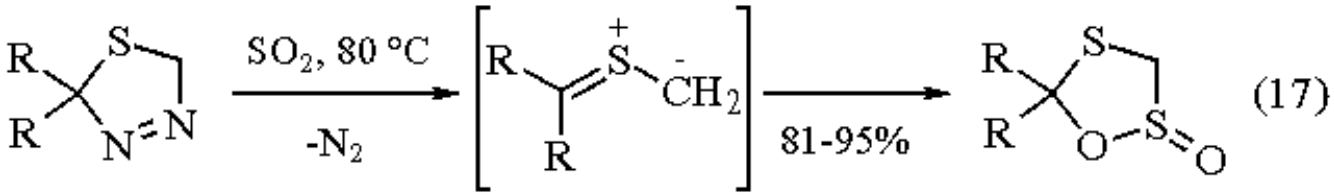

Reaction of the functionalized formamidine in eq 18 with SO_2 in the presence of ***Triethylamine*** affords the 1,2,4-oxathiazole 2-oxide shown.[19]

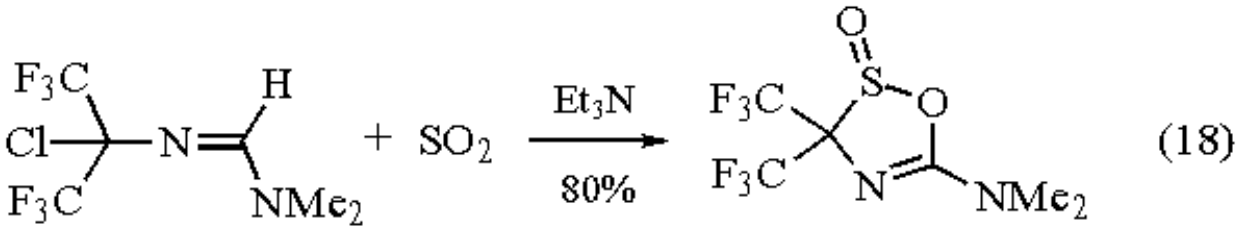

Use of SO_2 in Mannich Reactions.

Treatment of 2,5-dimethylphenol with SO_2 apparently allows the formation of a half-sulfite ester (eq 19). Addition of an aminol ether affords selective *o*-aminoalkylation.[20] Without SO_2, the major pathway of Mannich reaction with 2,5-dimethylphenol leads to the *p*-amino-alkylation product.

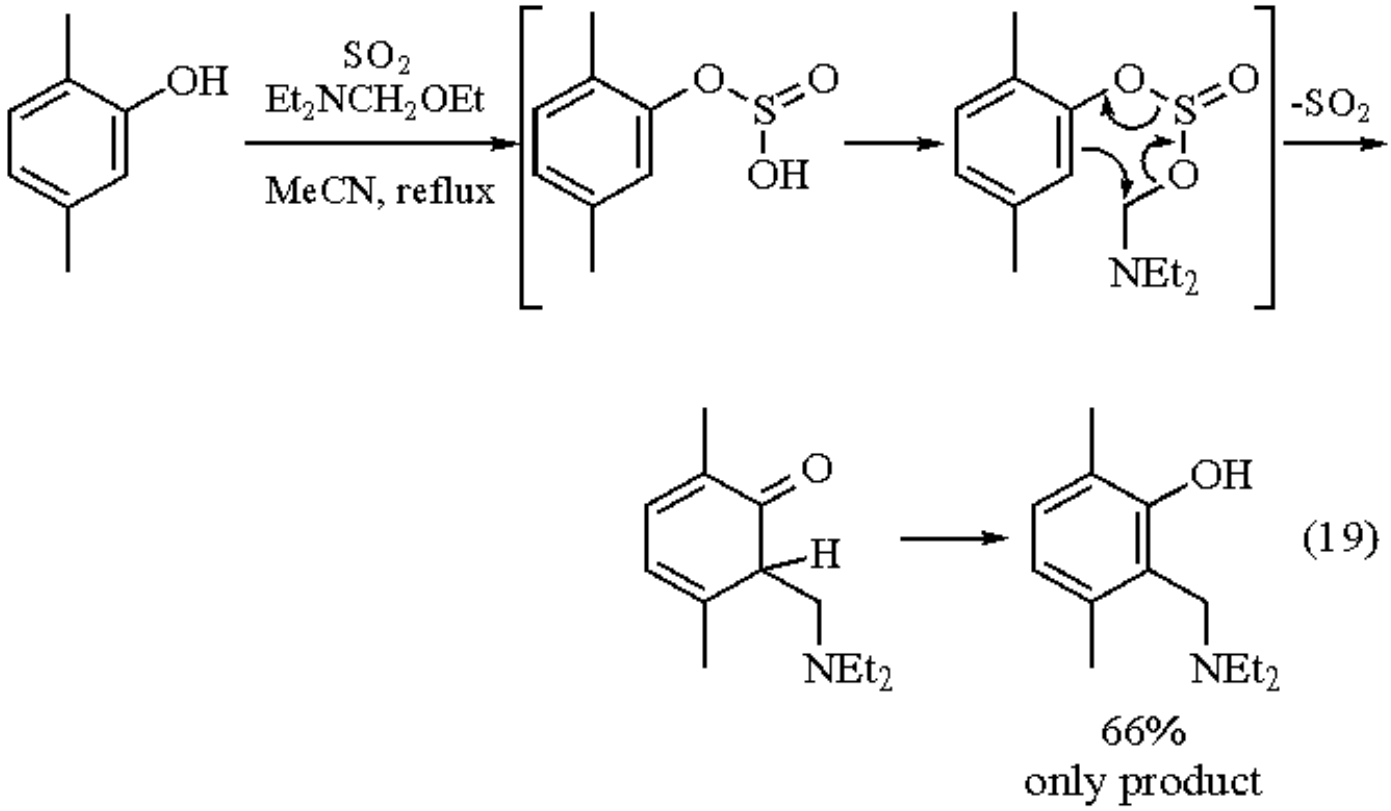

Sulfur dioxide serves as an electrophilic reagent for activating bis(dialkylamino)methanes or alkoxy(dialkylamino)methanes for Mannich reactions with 2-methylfuran (eq 20), *N*-methylpyrrole (eq 21), and indole (eq 22).[21] Dipolar adducts of SO_2 and the bis(amino)methane or alkoxyaminomethane reagents are proposed as intermediates, rather than free iminium salts.

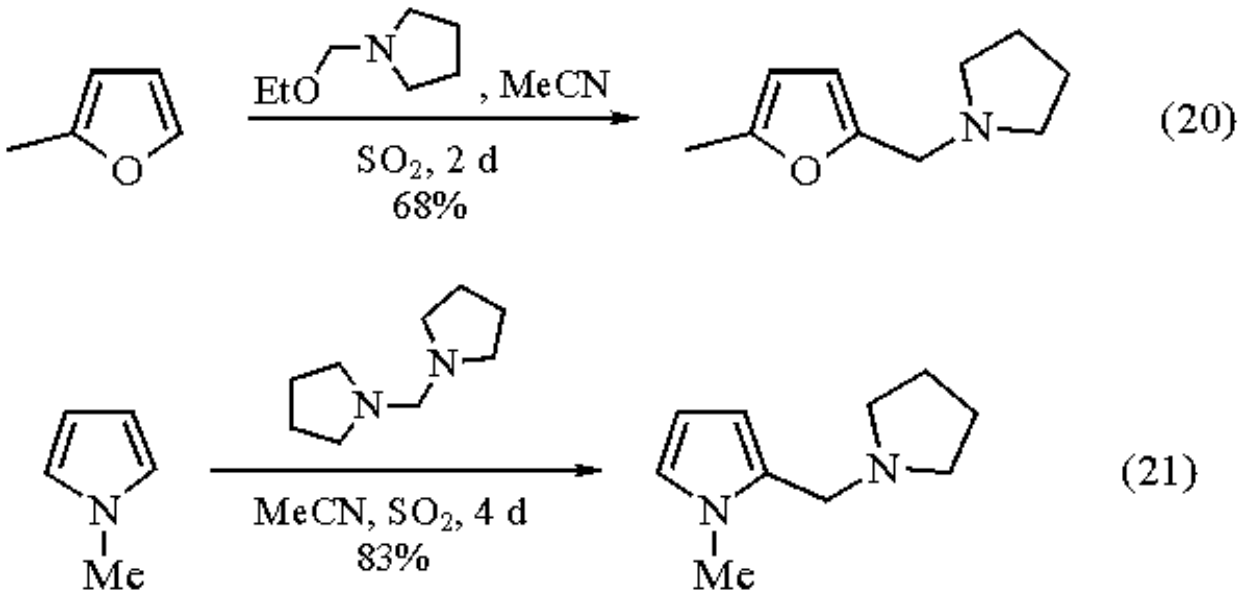

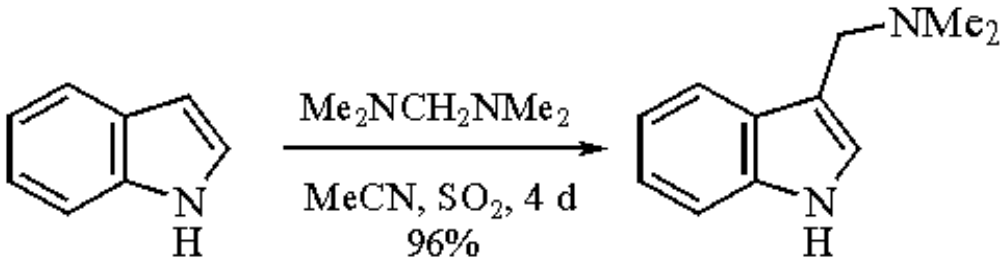

(22)

Isomerization of Dienes, Alkenes, and Nitrile Oxides by SO_2.

Treatment of ergosterol acetate with SO_2 in pyridine causes rearrangement of the 5,7-diene to the 6,8(14)-diene isomer (eq 23).[22] This result is fundamentally different from related sterol diene rearrangements catalyzed by acid. A consistent rationale for this SO_2-induced isomerization is shown.

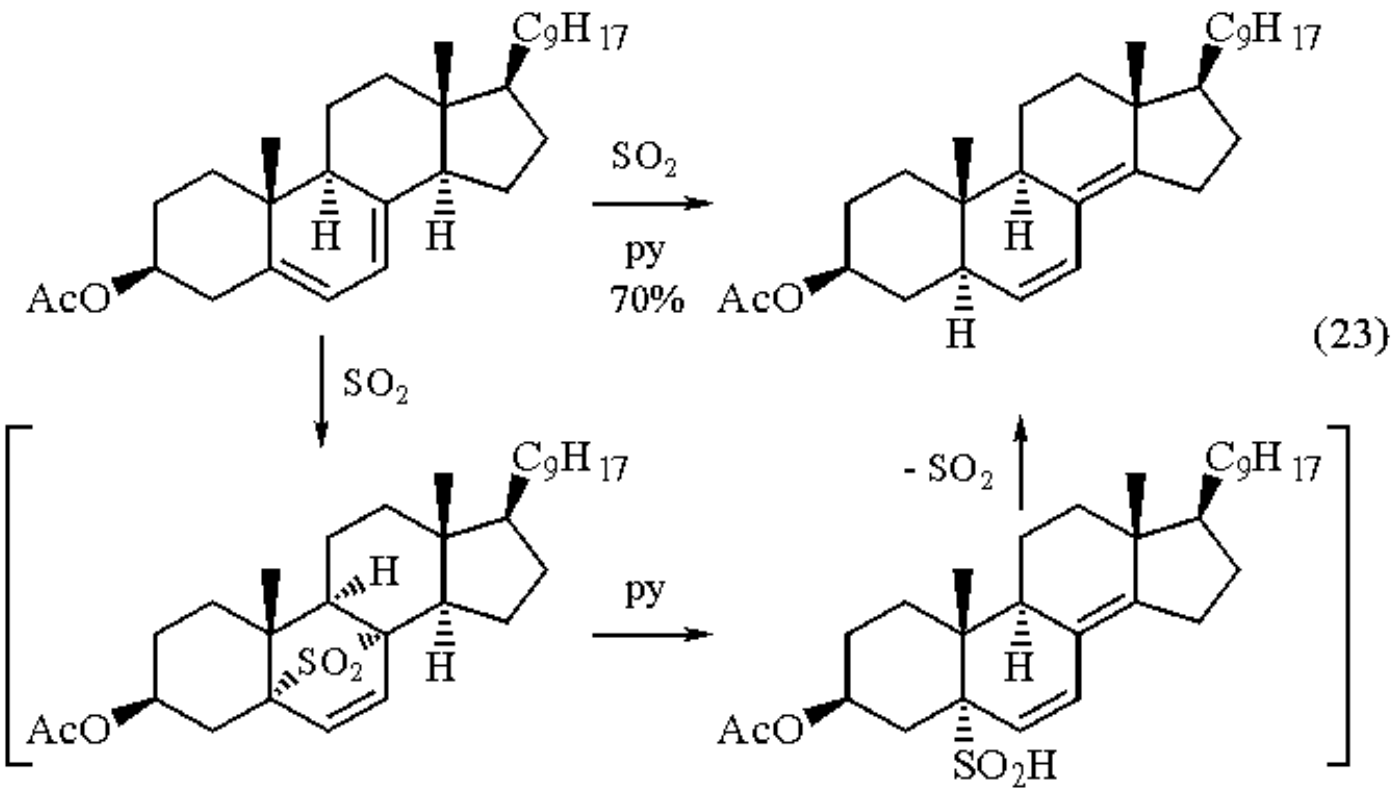

(23)

Addition of SO_2 to (5*Z*)- and (5*E*)-vitamin D_3 (**4**) yields the sulfolene derivatives (**5**) (eq 24).[23] Thermal extrusion of SO_2 from (**5**) affords isotachysterol$_3$ (**6**), alone or mixed with isovitamin D_3 (**7**). Treatment of sulfone (**5**) with methanolic ***Potassium Hydroxide*** or ***Alumina*** results in the formation of (5*E*)-vitamin D_3.

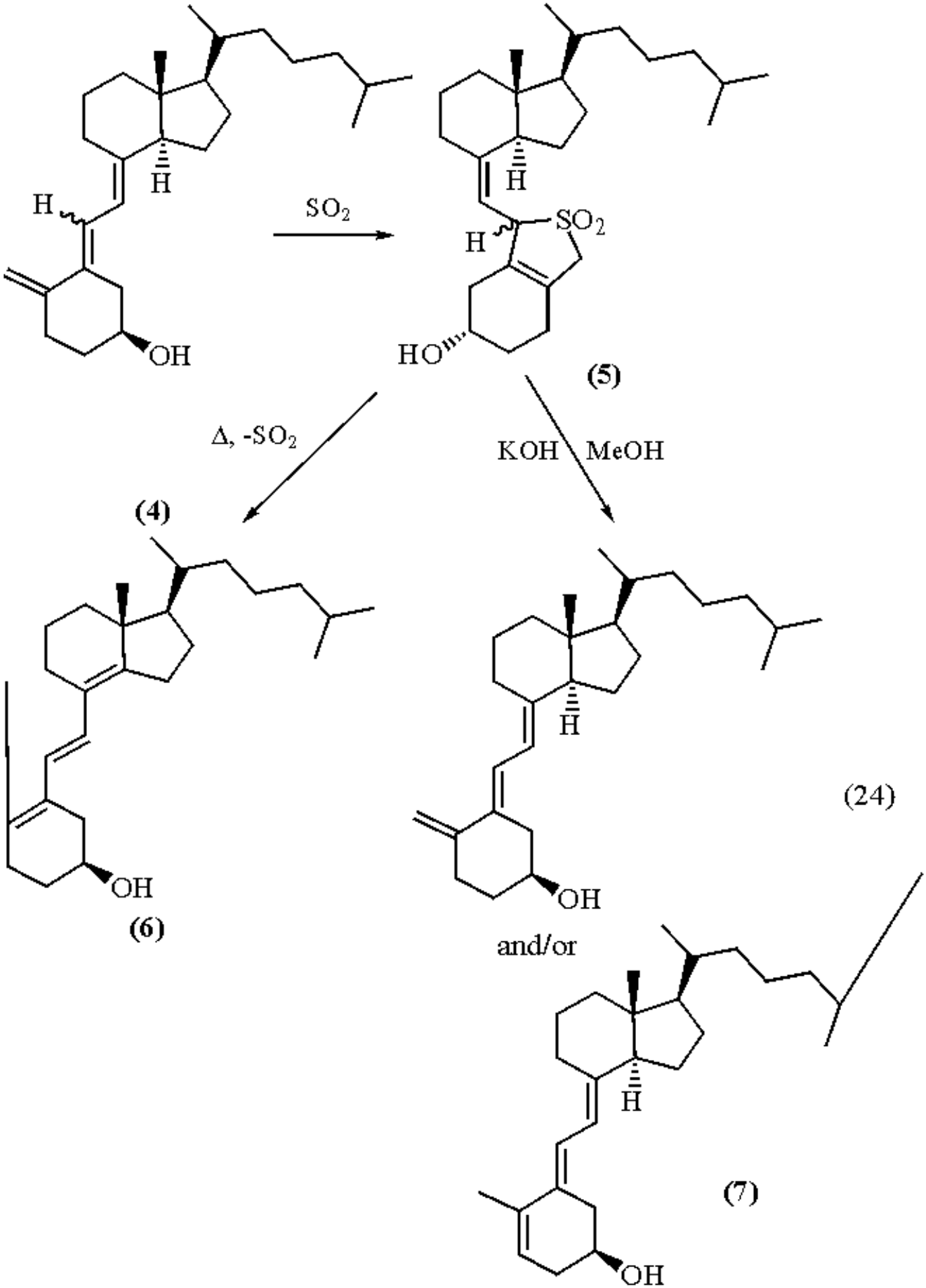

Regiospecific alkene isomerization has been effected by SO_2 with a variety of acyclic and cyclic alkenes, including β-pinene (eq 25) and methylenecyclohexane (eq 26).[24a] The sequence of steps presented in eq 26 has been advanced to rationalize the process. Interestingly, if the reaction is attempted in the presence of D_2O, alkene migration is completely suppressed, and all allylic hydrogens in the substrate alkene are exchanged for deuterium.[24b]

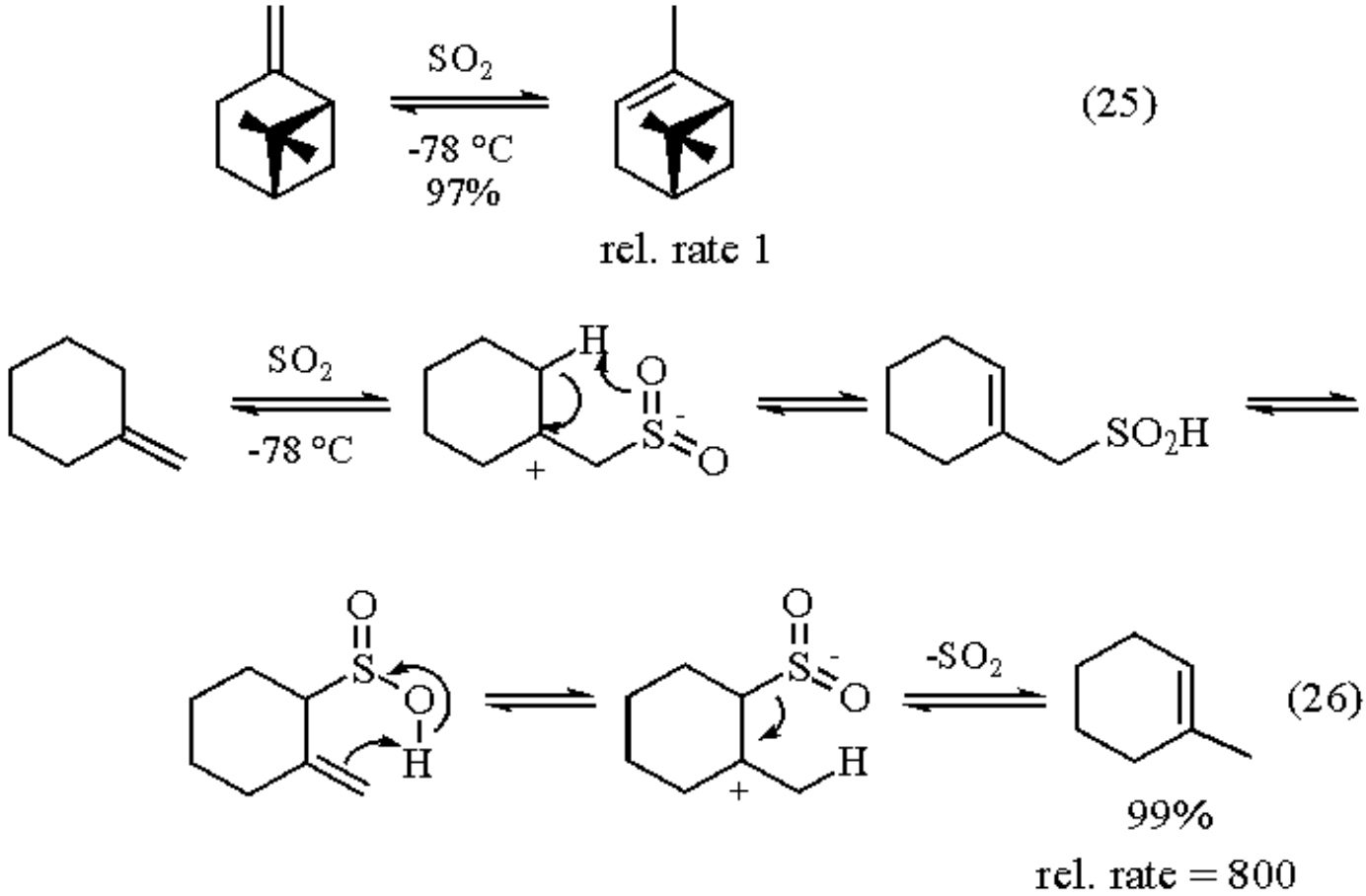

SO_2 catalyzes the conversion of nitrile oxides to isocyanates via a dipolar cycloaddition followed by regioisomeric loss of SO_2 and rearrangement (eq 27).[25] The intermediate 1,3,2,4-dioxathiazole 2-oxides can be isolated, or converted to hydroxamic acids upon hydrolysis.

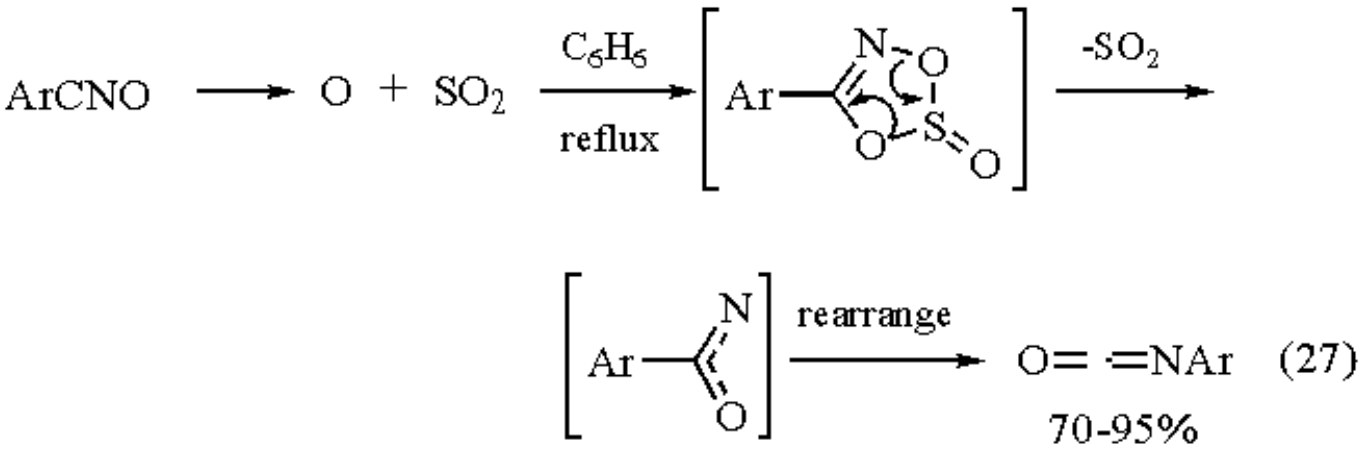

Sulfonic Acid and Sulfonyl Chloride Synthesis.

Condensation of benzimidazole with SO_2 and an aldehyde or ketone results in the formation of benzimidazoylalkylsulfonic acids (eq 28).[26]

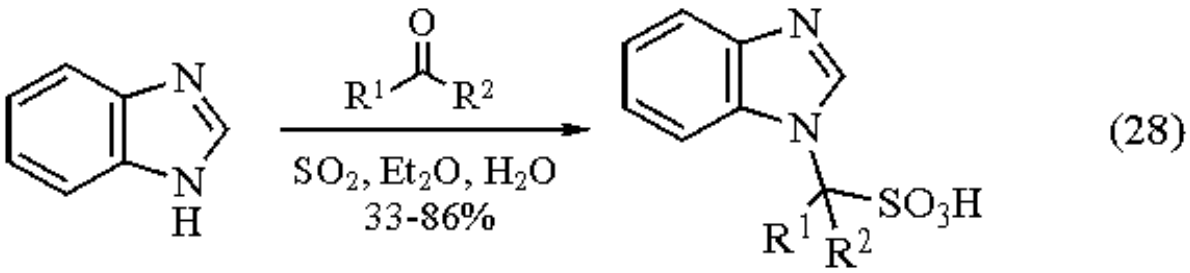

A wide variety of substituted anilines, especially those with electron-withdrawing substituents, can be converted to substituted arenesulfonyl

chlorides via their diazonium salts (eq 29).[27]

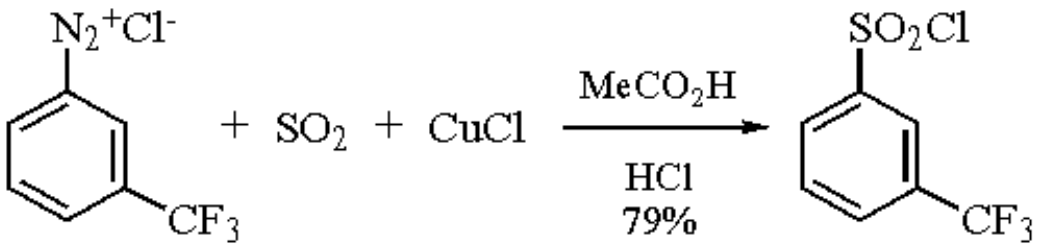

(29)

Synthesis of Sulfines.

Reaction of SO_2 with fluorenylidene-triphenylphosphorane in benzene gave the corresponding sulfine (eq 30).[28] In a related fashion, reaction of SO_2 with an α-silyl carbanion leads to the sulfine product (eq 31).[29] Thus alkylidenation of SO_2 is possible with Wittig or Peterson reagents.

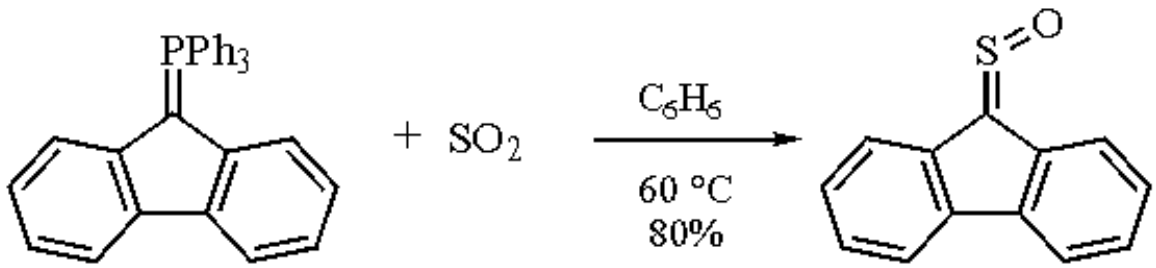

(30)

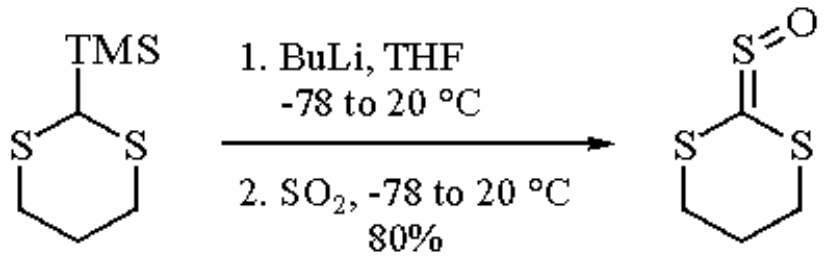

(31)

Miscellaneous Addition Reactions of SO_2.

A 1,6-addition of SO_2 to *cis*-3-hexatriene gives 2,7-dihydrothiepin 1,1-dioxide in high yield (eq 32).[30] Fully unsaturated thiepin dioxides can be elaborated from this and analogous triene-SO_2 adducts, or the triene can be regenerated by thermolysis.

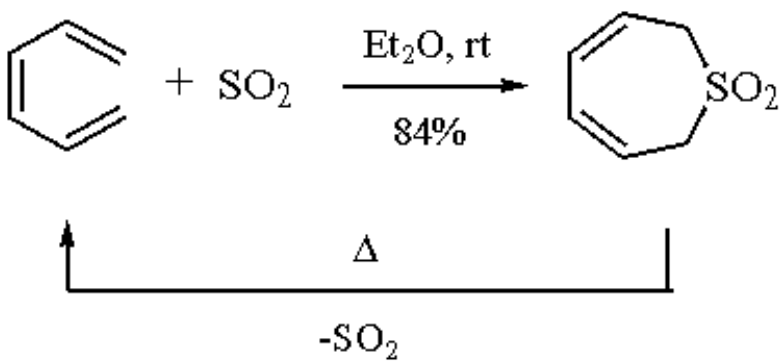

(32)

A cyclo(copolymerization) between dimethyldiallylammonium chloride and SO_2 afforded a 3:1 mixture of the 10- and 20-membered macrocycles containing pyrrolidinium and sulfonyl groups (eq 33).[31]

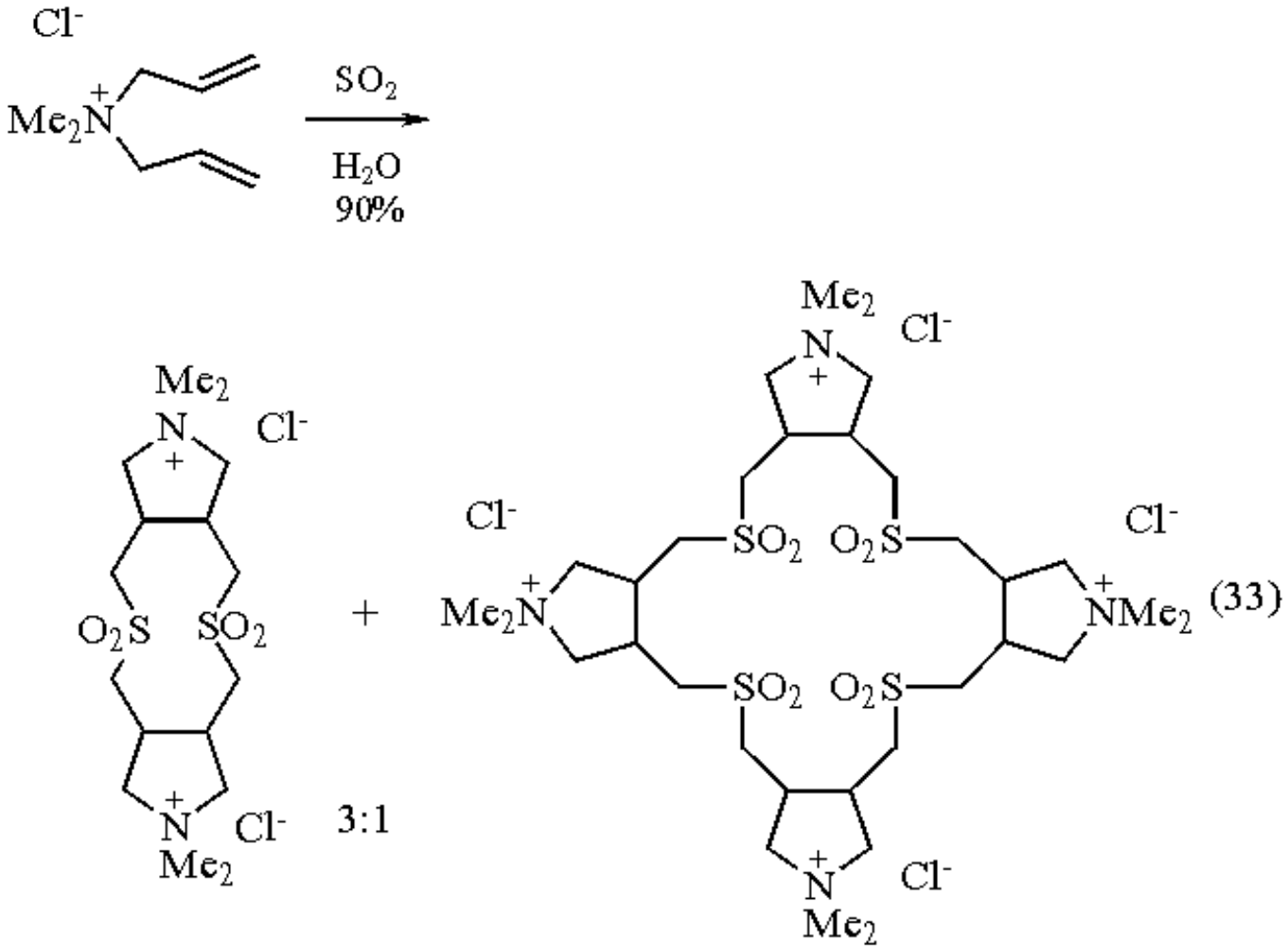

Aryl-substituted cyclopropanes undergo γ-sultine formation when treated with SO_2 in protic acid. The ring opening is regioselective, but the substituted 1,2-oxathiolane 2-oxides are formed as mixtures of diastereomers (eq 34).[32]

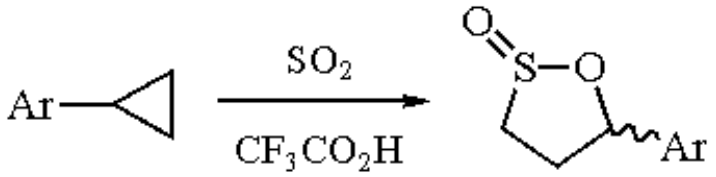

(34)

Bicyclo[5.1.0]octa-2,5-diene reacts with dry SO_2 at 150 °C in toluene to afford a moderate yield of the bicyclic sulfone shown (eq 35).[33]

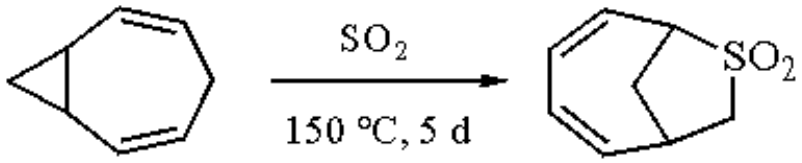

(35)

Photoaddition of 4,5-pyrenedione and SO_2 proceeds to give the cyclic sulfate (eq 36) in high yield.[34]

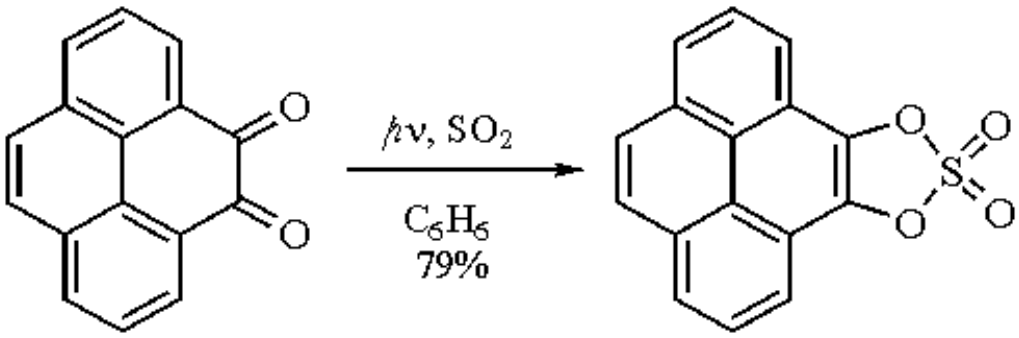

(36)

Cheletropic [$_{\pi}2_s + {}_{\pi}2_s + {}_{o}2_s$] addition of SO_2 to norbornadiene provides a nearly quantitative yield of the tetracyclic sulfone in eq 37.[35] Of several homoconjugated dienes examined, only norbornadiene exhibited this mode of reactivity.

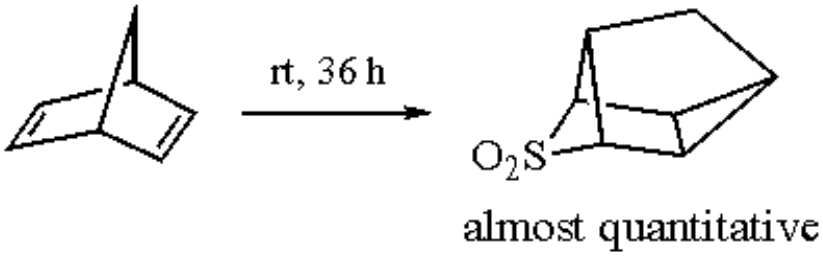

(37)

Miscellaneous Reactions of SO_2.

Two examples of SO_2 serving as a reductant are illustrated in eqs 38 and 39. Pyridine *N*-oxides are deoxygenated under mild conditions in moderate yields.[36] The ozonide derived from sulfolene (itself a product of SO_2 plus butadiene) is reduced by SO_2 to afford the acetal. Treatment of this with ammonium chloride gives 4*H*-1,4-thiazine 1,1-dioxide (eq 39).[37]

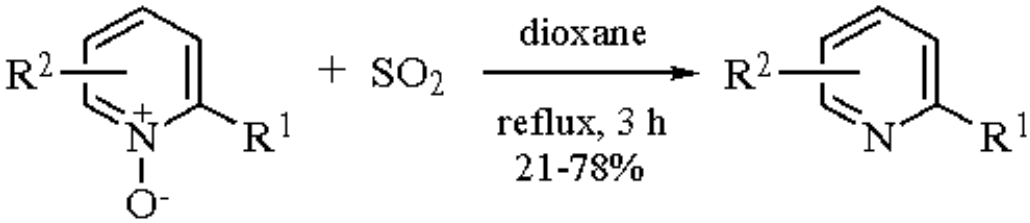

(38)

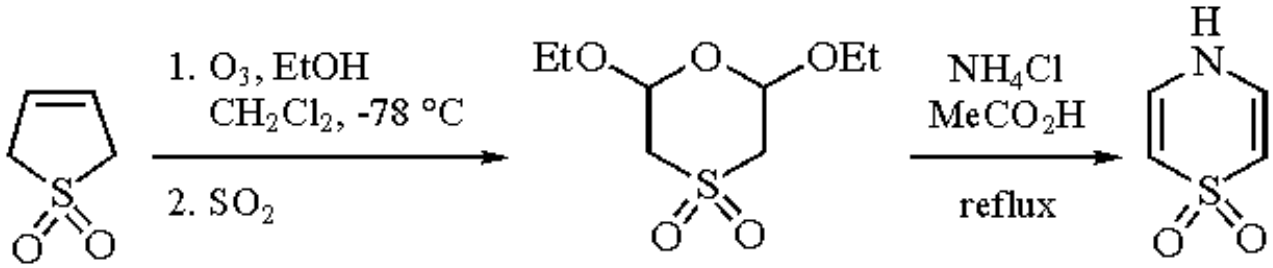

(39)

Vinyldiazomethane reacts with SO_2 leading, via the presumed *cis*-divinyl episulfone intermediate, to the dihydrothiepin 1,1-dioxide through a Cope rearrangement (eq 40).[38]

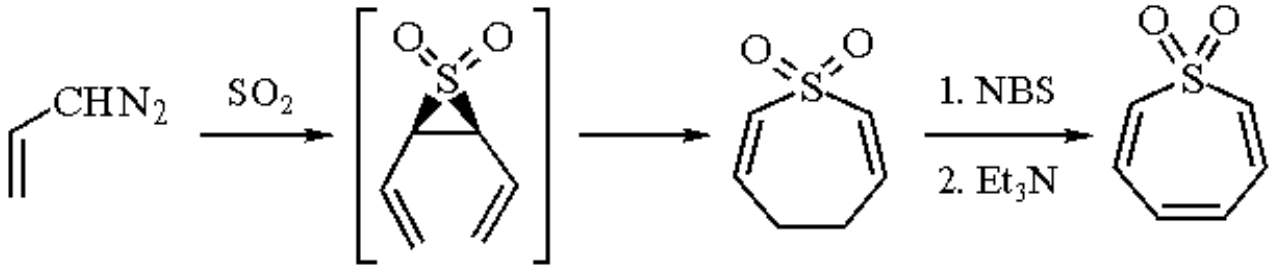

(40)

Sulfur dioxide also serves as an electrophilic agent for the conversion of orthoesters to esters and dialkyl sulfites. For example, ***Triethyl***

Orthoacetate gives only ethyl acetate and diethyl sulfite as products upon treatment with SO_2 (eq 41).[39]

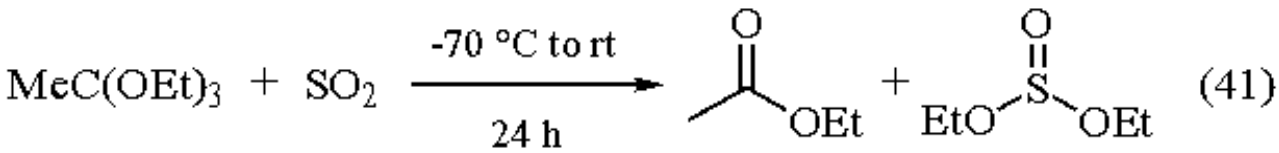

Formation of dithioacetals and *O*,*S*-acetals from ketones and aldehydes can be catalyzed by SO_2, with yields comparable or superior to protic catalysts.[40] Finally, liquid SO_2 has served as a solvent for a variety of superacid-mediated cyclization, rearrangement, and sulfinylation reactions.[41]

Related Reagents.

Copper(I) Chloride-Sulfur Dioxide.

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Sulfuric Acid[1]

H_2SO_4

[7664-93-9] · H_2O_4S · Sulfuric Acid · (MW 98.09)

(widely used protic acid solvent and catalyst;[1] can oxidize aliphatic and aromatic hydrocarbons;[1d] can sulfonate aromatic rings[1b])

Physical Data: mp 3 °C (98% sulfuric acid); bp 290+ °C; *d* 1.841 g cm^{-3} (96-98% sulfuric acid).

Solubility: sol water.

Form Supplied in: liquid sold in aqueous solutions of concentrations 78, 93, 95-98, 99, 100 wt %. Sulfuric acid (fuming) contains 18-24% free ***Sulfur Trioxide***.

Preparative Method: 100% sulfuric acid can be prepared by adding 95-98% sulfuric acid (concentrated sulfuric acid) to fuming sulfuric acid.[2]

Protic Acid Solvent and Catalyst.[3]

Sulfuric acid is an inexpensive, easily handled protic acid, solvent, and catalyst. Typical workup procedures for reactions in H_2SO_4 involve aqueous dilution prior to product separation.

Hydrolyses.

Nitroalkanes are readily available and their hydrolysis is an important synthetic tool. Hydrolysis of primary nitroalkanes with H_2SO_4, the most effective catalyst, gives carboxylic acids.[4] The salts of primary or secondary nitroalkanes, when hydrolyzed with H_2SO_4, form aldehydes or ketones (also see ***Titanium(III) Chloride***).[5] This reaction has been applied to β,γ-unsaturated nitroalkenes as a mild route to α,β-unsaturated aldehydes.[5c] An improved two-layer method treats the nitronate anion with H_2SO_4 in pentane; the product aldehyde dissolves in pentane and avoids contact with acid.[5d]

Vinyl halides are hydrolyzed by H_2SO_4 in the Wichterle reaction, a route to 1,5-diketones in which 1,3-dichloro-*cis*-2-butene serves as a methyl vinyl ketone equivalent.[6] The hydrolysis can be controlled to avoid acid-catalyzed aldol condensation (see condensations, below).[7]

Sulfuric acid is a useful catalyst for cleavage of protecting groups,[8] and has been used to cleave TBDMS protecting groups in the presence of TBDPS groups.[9] A useful method for resolution of chiral ketones involves formation and separation of chiral hydrazones followed by hydrolysis with 10% H_2SO_4.[10]

Hydrations.

Alkyne hydration generally involves mercury(II) ion catalysts.[1b] However, H_2SO_4 hydrates the alkyne (**1**) and also catalyzes a subsequent regio- and stereoselective cyclopentanone annulation via the Nazarov cyclization (eq 1).[11] Nitriles can be selectively hydrated to amides using strong H_2SO_4.[12]

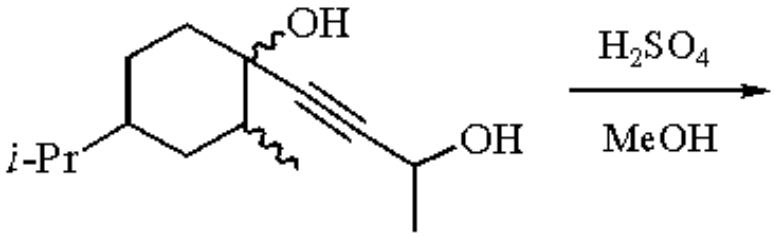

(1)

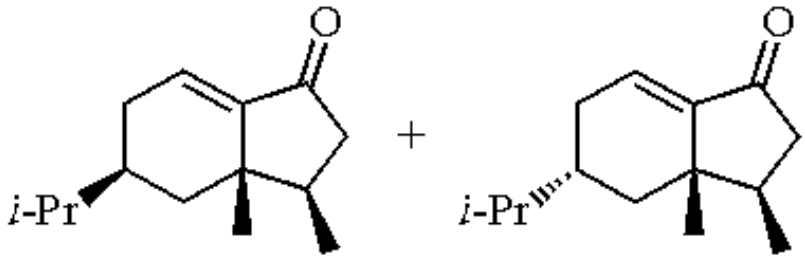

64% 10% (1)

Additions.[1a,b]

The Ritter reaction, in which nitriles add to alkenes in conc H_2SO_4, is a useful procedure for preparation of amides of *t*-alkylcarbinamines.[1b] As applied to the *threo* α-halo alcohol (**2**), retention of stereochemistry is observed (eq 2).[13] H_2SO_4 catalyzes carbonylation of α,β-unsaturated aldehydes in a general synthesis of 3,4-dialkyl-2(5*H*)-furanones (eq 3).[14] Michael additions to conjugated ketones are catalyzed by H_2SO_4 (see condensations, below).[7]

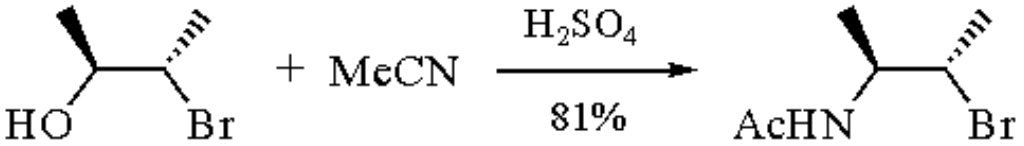

(2) (2)

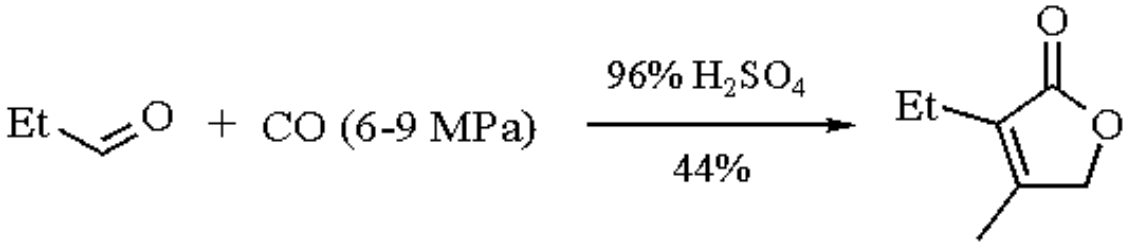

(3)

Sulfuric acid catalyzes the regioselective methoxybromination of α,β-unsaturated carbonyl compounds with ***N-Bromosuccinimide*** (eq 4); ***Boron Trifluoride***, ***Acetic Acid***, and ***Phosphoric Acid*** were unsatisfactory catalysts.[15] Sensitivity to acid catalyst was also noted in the intramolecular diazo ketone cyclization of β,γ-unsaturated diazomethyl ketone (**3**) (eq 5); H_2SO_4 gave a rearrangement product (**4**).[16]

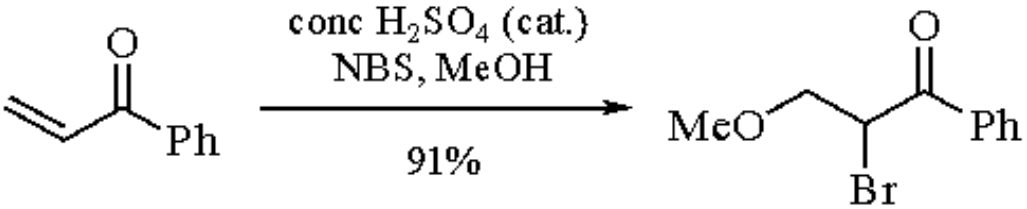

(4)

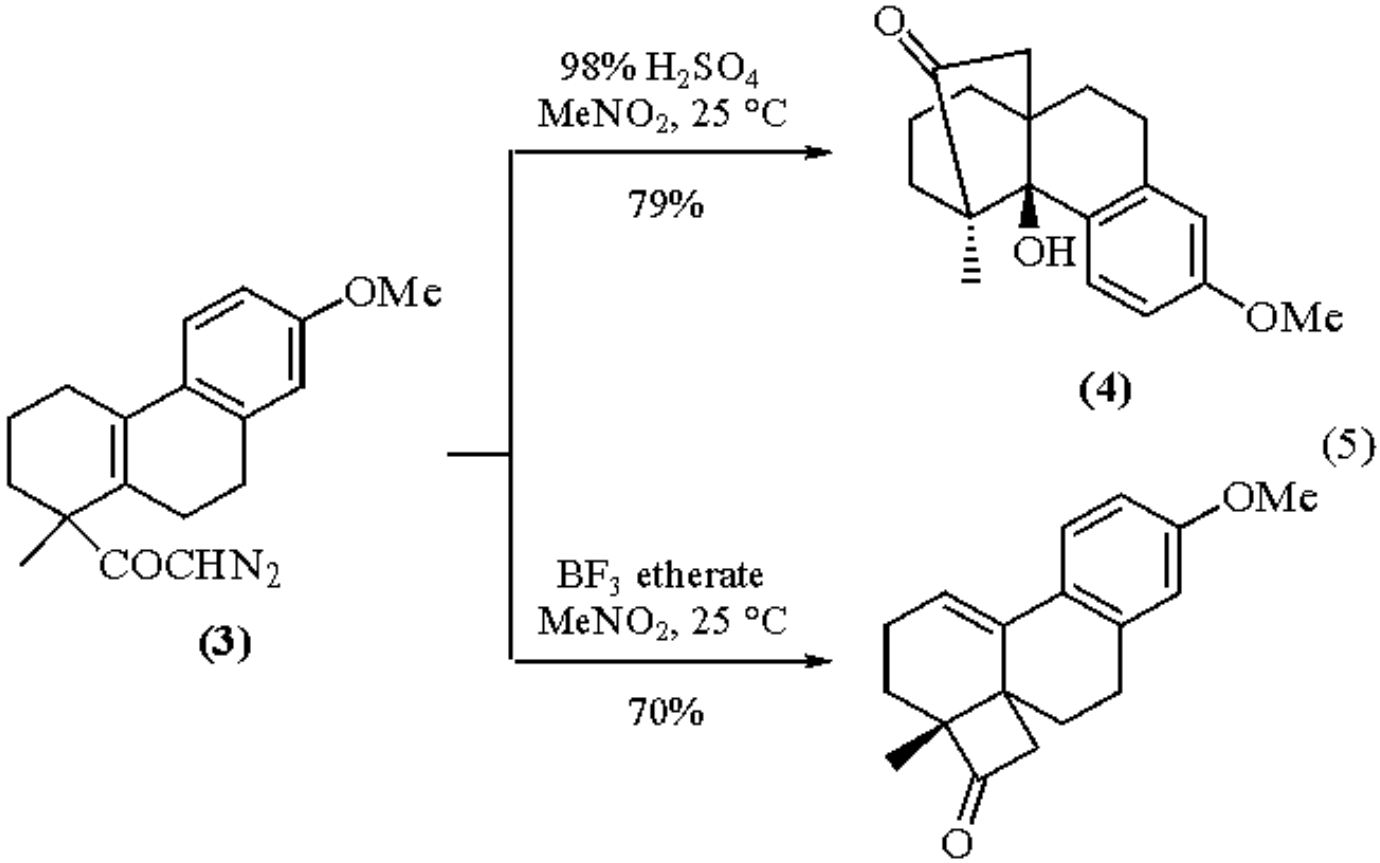

Dehydrations and β-Eliminations.[1b]

Useful stereospecific H_2SO_4-catalyzed *anti* elimination of *threo*-β-hydroxyalkylsilanes is stereoselective for the *cis*-alkene, while ***Potassium Hydride*** mediated *syn* elimination affords selectively *trans*-alkenes (eq 6).[17]

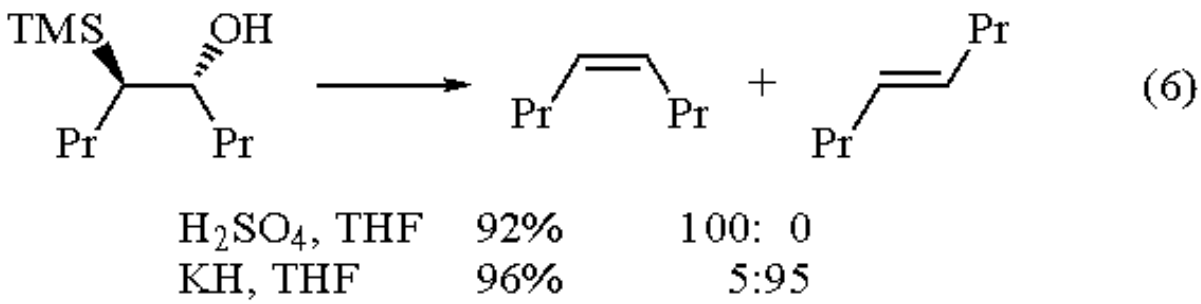

Electrophilic Substitutions.[1a]

Sulfuric acid catalyzes nitration of aromatic carbocycles[1a,b] and heterocycles.[18] Benzenes with *meta*-directing groups can be alkylated by primary and secondary alcohols in H_2SO_4, ***Polyphosphoric Acid***, or 85% phosphoric acid; even nitrobenzene can be alkylated by ethanol.[19] H_2SO_4 catalyzes the α-amidoalkylation reaction[20] and is especially useful for Friedel-Craft ketone synthesis using anhydrides.[1a] For acylations with acids, PPA avoids charring, sulfonation, and ester cleavage and is generally a preferred reagent (***Hydrogen Fluoride*** and ***Trifluoromethanesulfonic Acid***).[21] Keto acids and phenol react selectively to give phenolic esters with PPA, but ring substitution products with H_2SO_4.[22]

The utility of H_2SO_4 as a catalyst for the substitution of alkanes is evidenced in the formation of carboxylic acids by *trans* carboxylation (eq 7);[23] the hydrocarbon must have a tertiary hydrogen and the acid source for CO must be a tertiary alkyl acid.

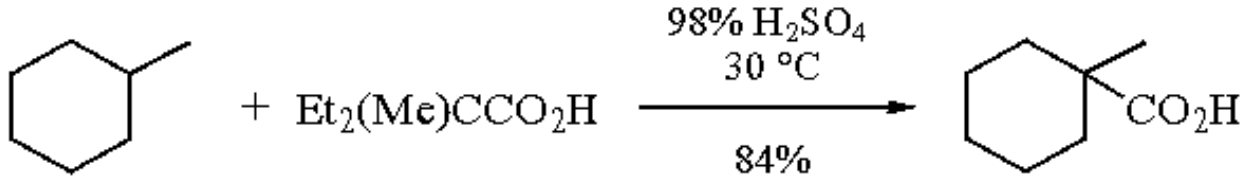

(7)

Carbonyl Reactions.[1a,b]

H_2SO_4 is considerably more effective than ***p-Toluenesulfonic Acid*** for conversion of anthrone to 9-alkoxyanthracenes.[24] A practical procedure for regioselective formation of pyridoxine dimethyl acetal which replaces anhydrous TsOH utilizes 96% H_2SO_4 (eq 8).[25]

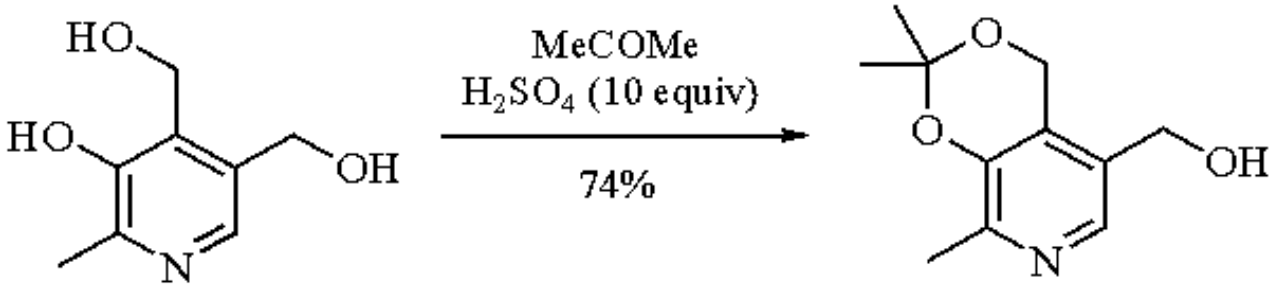

(8)

H_2SO_4 catalyzes esterification of highly hindered aromatic acids,[1b] and it catalyzes the formation of *N*-acylamides from acid anhydrides and amides.[26] A rapid esterification procedure involves reaction of primary, secondary, or tertiary alcohols with acids in H_2SO_4 using ultrasound.[27]

Condensations.

Sulfuric acid is a useful reagent for the synthesis of heterocycles by dehydrative cyclization.[18,28] Yields in the Skraup quinoline synthesis, which utilizes sulfuric acid as the condensing agent, are remarkably sensitive to H_2SO_4 concentration.[29]

Sulfuric acid-catalyzed aldol condensations of 1,5-diketones in H_2SO_4 are under thermodynamical control[30] and products may differ from those of base-catalyzed reactions (eqs 9 and 10).[7,31,32]

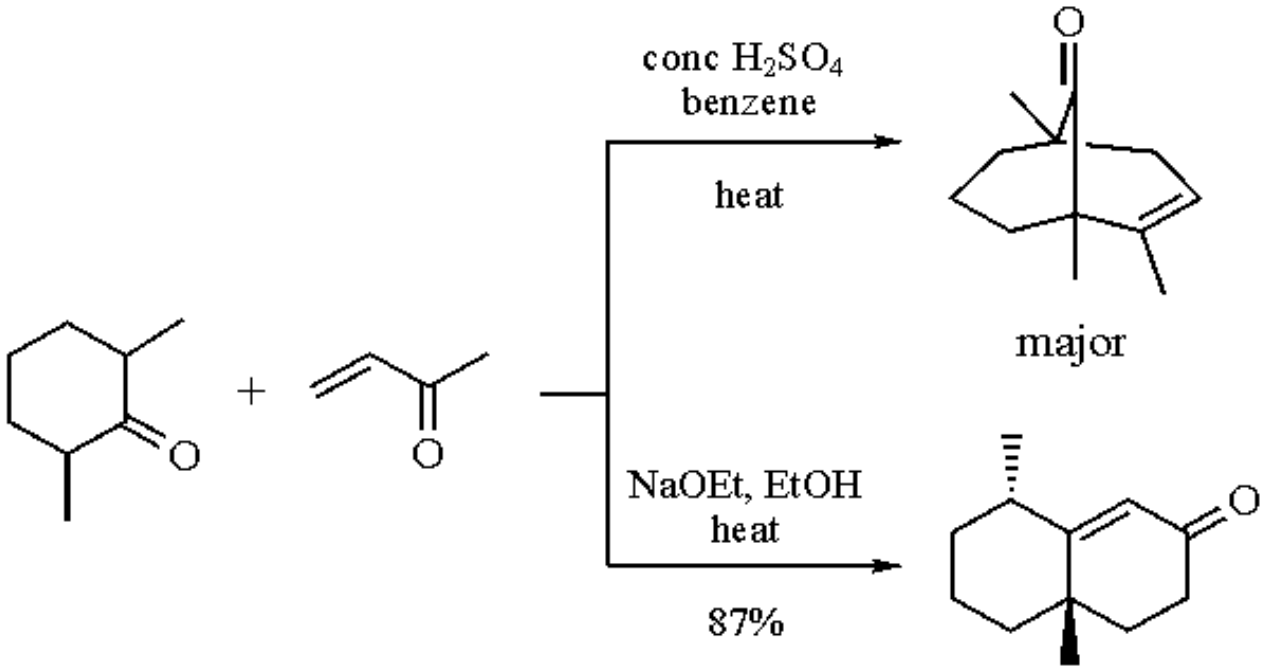

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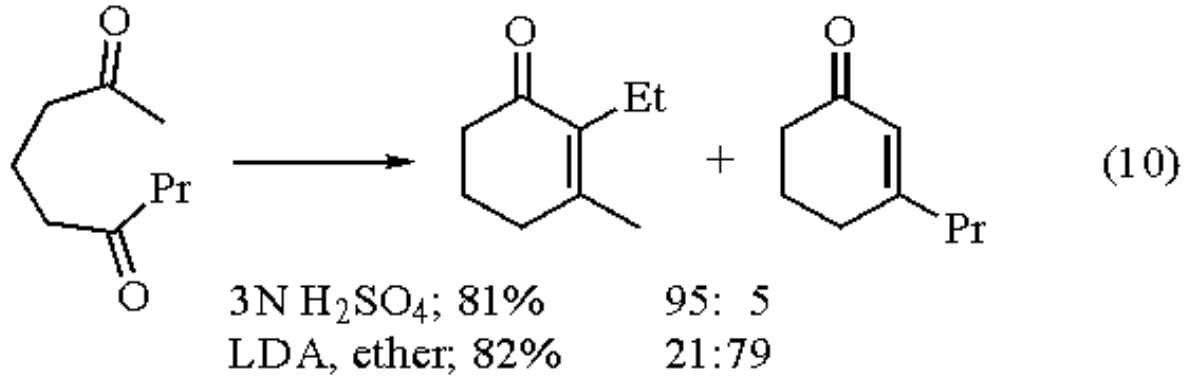

(10)

Rearrangements.

The choice of acid catalyst can influence skeletal rearrangements; for example, H_2SO_4 and H_3PO_4 can afford different products in polyene cyclizations (eq 11).[33] The reductive rearrangement of alcohol (**5**) gave different products in H_2SO_4 and H_3PO_4 (eq 12).[34]

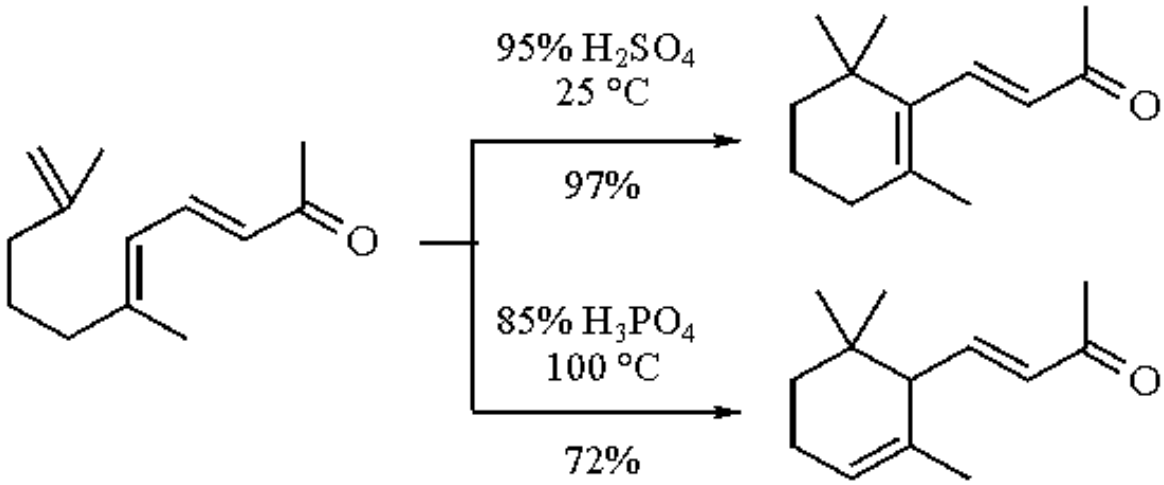

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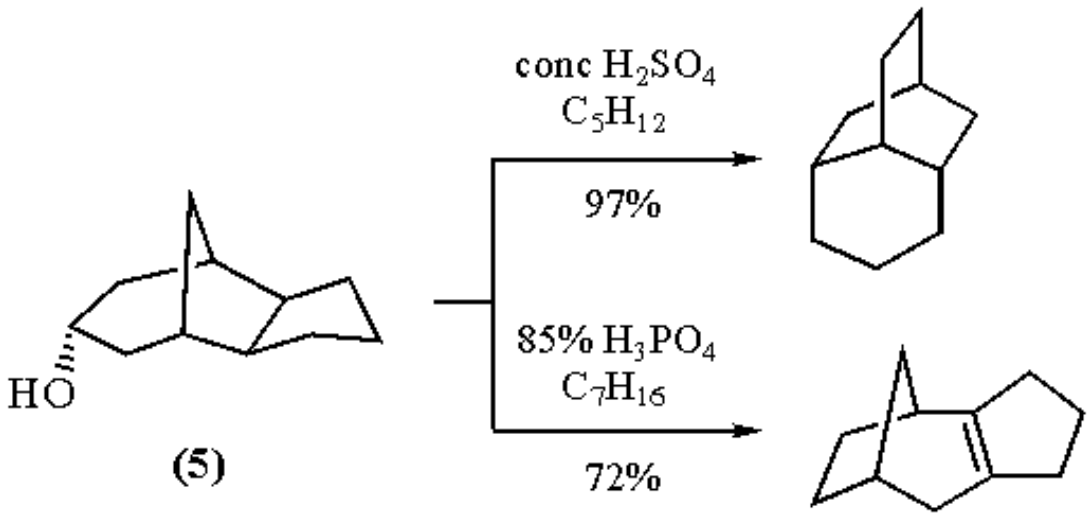

(12)

For functional group isomerizations, H_2SO_4 is useful in the Beckmann rearrangement of oximes and the Hofmann-Loffler-Freytag reaction of *N*-haloamines and amides.[1b] H_2SO_4 is superior to BF_3 in the isomerization of α-epoxycyclopentanones to α-hydroxycyclopentenones (eq 13).[35] The formation of 2-oxoadamantane from bicyclo[3.3.1]nonane-2,6-diol is highly sensitive to acid concentration and requires 95% H_2SO_4 for optimum yield.[36]

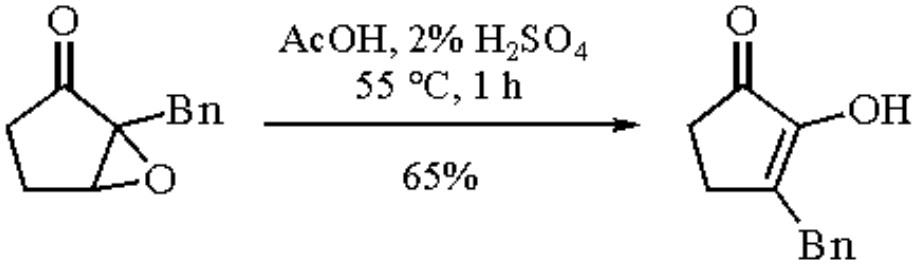

(13)

Choice and strength of acid catalyst can have regiochemical consequences. H_2SO_4-catalyzed Wallach rearrangement of azoxybenzenes provides mainly *p*-hydroxyazobenzenes, while ***Antimony(V) Chloride*** gives mainly *ortho* products.[37] Regiochemistry in the Schmidt reaction of ketones can be dependent upon H_2SO_4 concentration (eq 14).[38]

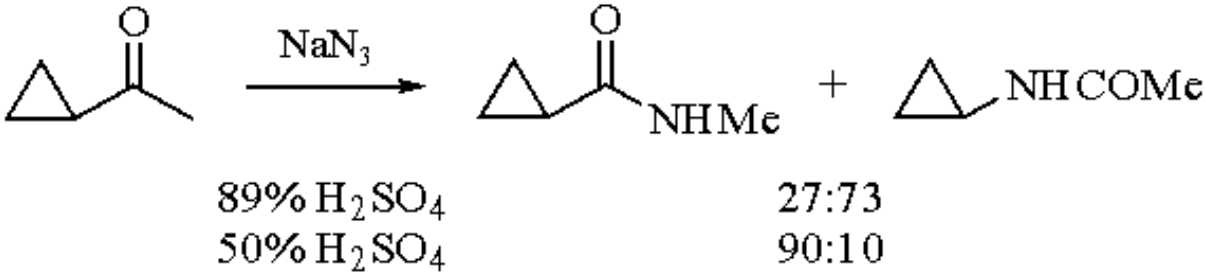

(14)

H_2SO_4 can catalyze stereochemical isomerizations (eq 15); thermodynamic conditions afforded *cis*-lactone (**6**); the diastereomeric *cis*-lactone is formed under kinetic control with ***Formic Acid*** or ***Tin(IV) Chloride***.[39] If a chiral center is present, enantioselective allylic alcohol rearrangement[40] and enantioselective alkene cyclization can be catalyzed by H_2SO_4 (eq 16).[41]

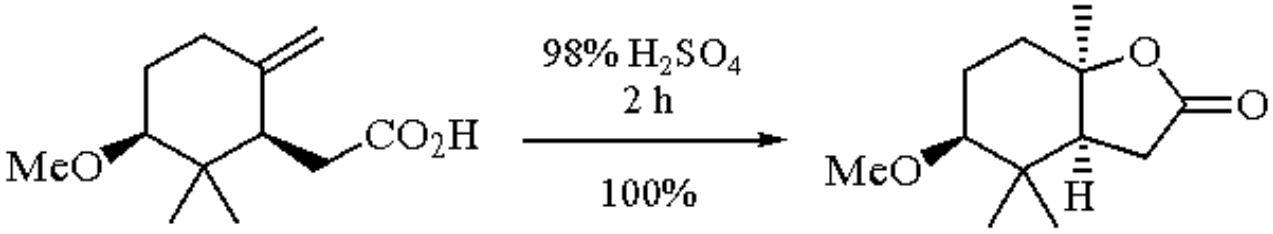

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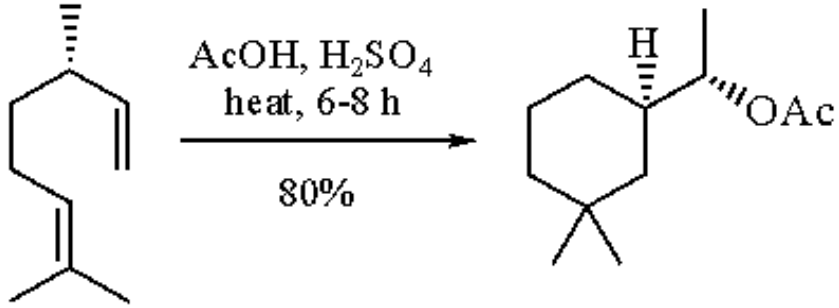

(16)

Catalyzed Oxidations.[1b]

Sulfuric acid is the catalyst of choice for ***m-Chloroperbenzoic Acid*** oxidation of unreactive 11-keto steroids,[42] and it catalyzes the $NaBO_3$ oxidation of alkenes in Ac_2O to *trans*-diols.[43]

Dehydrogenation.

H_2SO_4 acts as solvent, catalyst, and selective oxidizing agent in the formation of 2-pyridones from cyclic cyano ketones (eq 17).[44] Aromatization of unsaturated carbocyclic rings can be effected using H_2SO_4 and heat,[1d] and α-alkylcyclohexanones can be converted to *o*-alkylphenyl acetates by reaction using H_2SO_4 (eq 18).[45] Intermolecular dehydrogenation of an aminonaphthalene to a biphenyl occurs

with 66% H_2SO_4 (eq 19).[46]

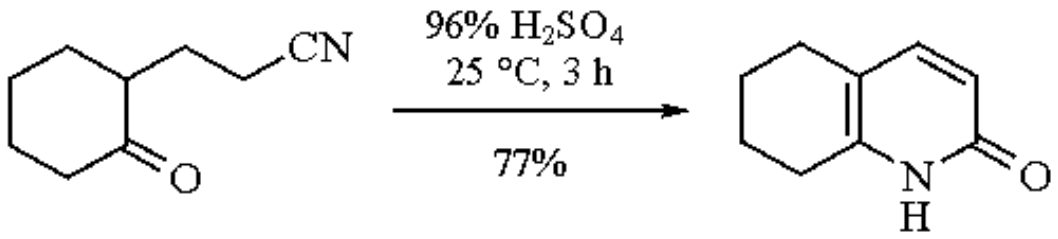

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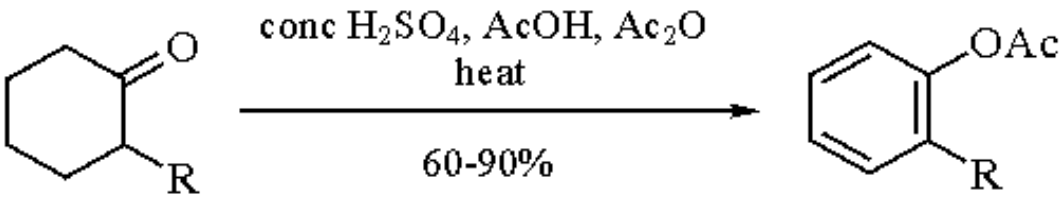

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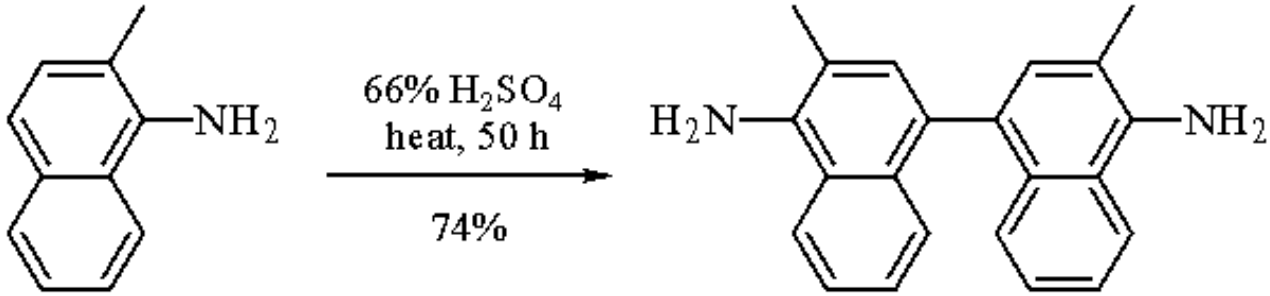

(19)

Hydroxylation.

Hydroxylation of nitro and hydroxyl-substituted fused aromatic rings can be effected with sulfuric acid under forcing conditions.[1d] Adamantanone has been prepared from adamantane using 98% H_2SO_4 as oxidant.[47]

Sulfonation.

Sulfonation of β-carbolines occurs in concentrated H_2SO_4; pyrrole, indole, and carbazole do not sulfonate under the conditions.[48]

Formation of Reducing Agents.

An easily scaled-up method to convert amino acids to amino alcohols without affecting *N*-tosyl or *N*-Cbz groups uses H_2SO_4/***Sodium Borohydride*** (see also ***Aluminum Hydride***).[49]

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Sulfur Tetrafluoride[1]

[7783-60-0] · F_4S · Sulfur Tetrafluoride · (MW 108.07)

(fluorinating agent for many functional groups;[1] can form other fluorinating agents[1])

Physical Data: mp -121.0 °C; bp -38 °C; *d* (liq, -78 °C) 1.95 g cm^{-3}, *d* (solid, -183 °C) 2.349 g cm^{-3}.

Solubility: sol benzene.

Form Supplied in: colorless gas.

Handling, Storage, and Precautions: is about as toxic as phosgene. It is also a strong irritant and a corrosive agent that should be handled with utmost care in a well-ventilated fume hood. Sulfur tetrafluoride reacts violently with water. The reagent can be handled in a well-dried Pyrex glass apparatus up to about 30 °C with only nominal attack. Stainless steel, copper, and nickel are all inert to SF_4 at both ordinary and elevated temperatures. First-aid treatment of hydrogen fluoride burns has been described.[2] A reactor design for safe, routine handling of SF_4 and HF is available.[3]

Introduction.

Sulfur tetrafluoride is one of the more common fluorinating agents. It converts hydroxyl, carbonyl, and carboxylic groups into mono-, di-, and trifluoromethyl groups, respectively (eq 1).

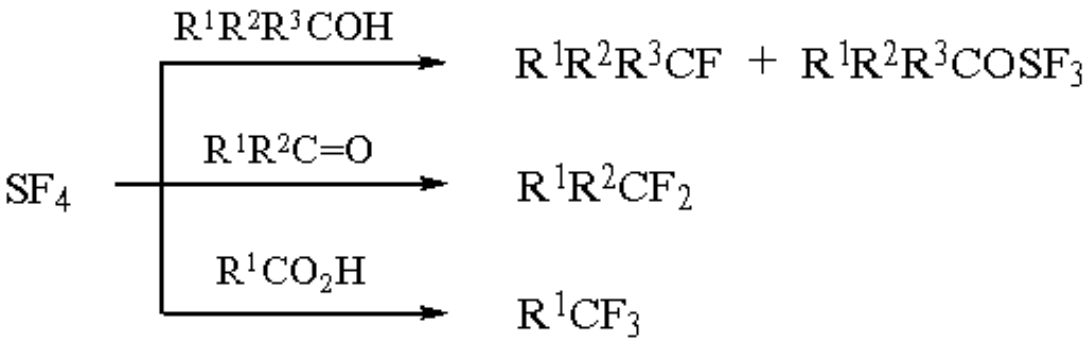

(1)

Fluorination of Alcohols.

Sulfur tetrafluoride is suitable for fluorination of alcohols in high yield, provided that the alcohols are roughly equal to or greater than tropolone in acidity (pK_a = 6.42).[1a] Decomposition is often a problem during SF_4 fluorination of aliphatic alcohols and various alternative fluorinating agents have been introduced, e.g. ***N,N-Diethylaminosulfur Trifluoride*** (DAST),[4] SeF_4-pyridine,[5] and HF.amine (see ***Hydrogen Fluoride***) reagents.[6]

(2-Furyl)methanol and 2-phenylethanol react with SF_4 at -50 °C in the presence of ***Triethylamine*** or ***Pyridine*** in CH_2Cl_2 or cyclohexane to give (2-fluoromethyl)furan and 2-fluoro-1-phenylethane, respectively (eqs 2 and 3).[7]

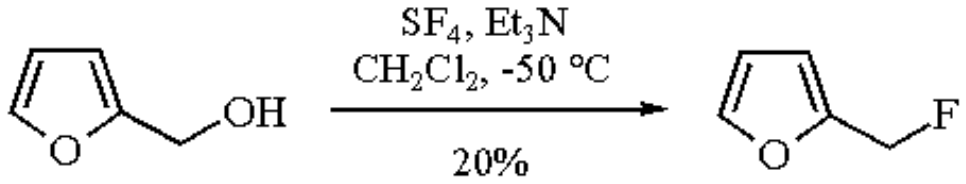

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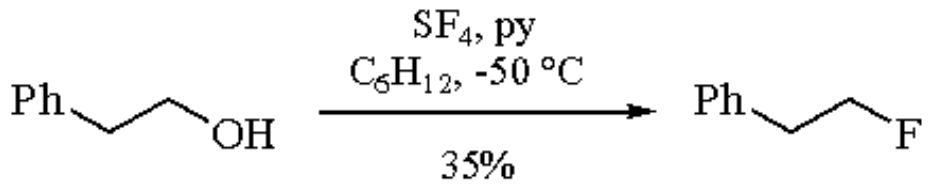

(3)

Fluorination of vicinal diols such as ethanediol and 1,2-propanediol under mild conditions leads to the formation of 2-fluoro fluorosulfites, which are readily hydrolyzed to give the respective fluorohydrins (eqs 4 and 5).[8] A different pattern is observed in the reaction of 3,3,3-trifluoro-1,2-propanediol with SF_4 (eq 6).

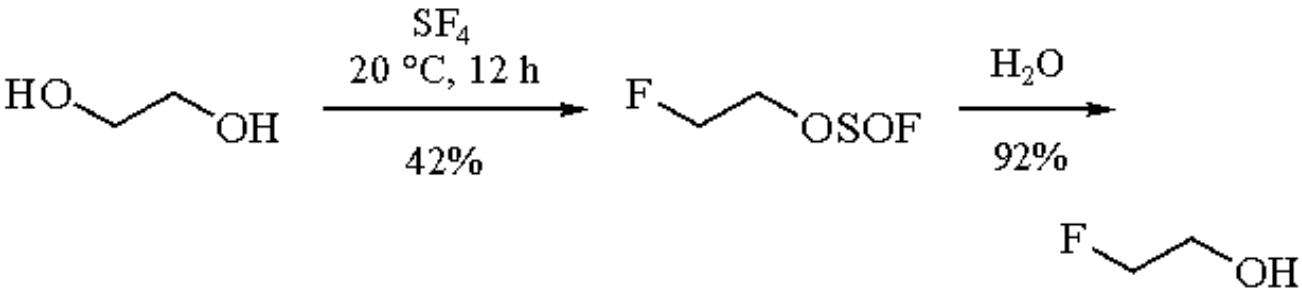

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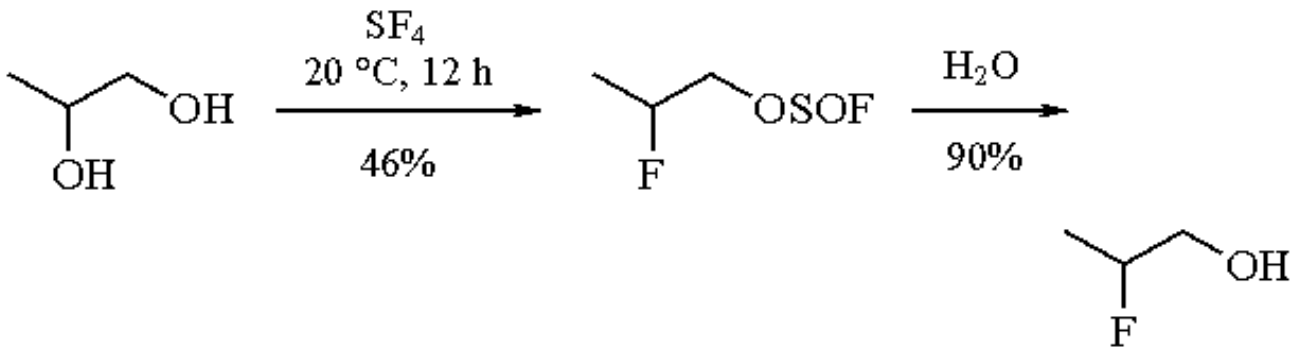

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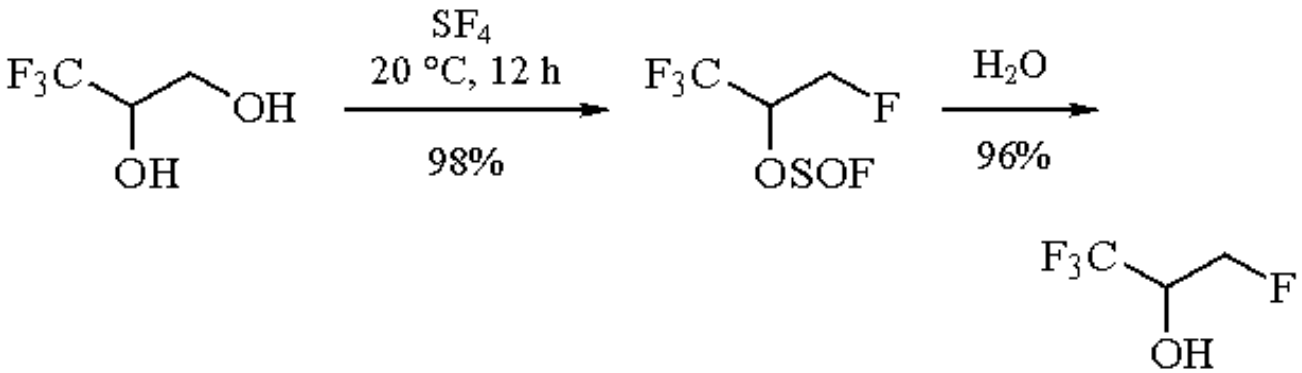

(6)

Selective substitution of the hydroxyl group by fluorine can also be realized in the reactions of SF_4 with 1,3- and 1,4-diols (eqs 7 and 8).[9]

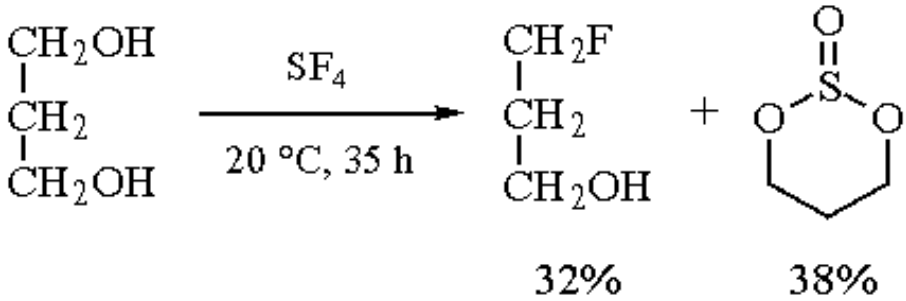

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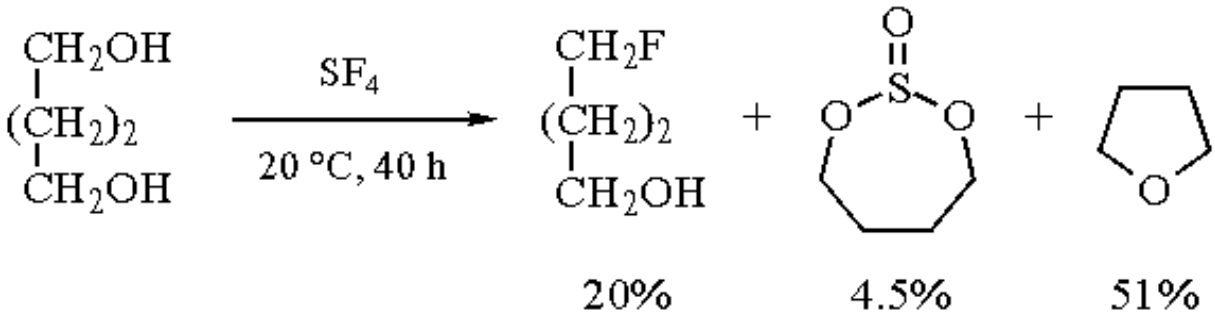

(8)

Reaction of glycerol with SF_4 in anhydrous HF under mild conditions leads unexpectedly to 3-fluoro-1,2-propylene sulfite (eq 9).[10] Treatment of *myo*-inositol with SF_4 and anhydrous HF yields a novel compound, the cyclic sulfite ester of 2β,3β-difluoro-7-oxabicyclo[2.2.1]heptane-5α,6α-diol (eq 10).[11]

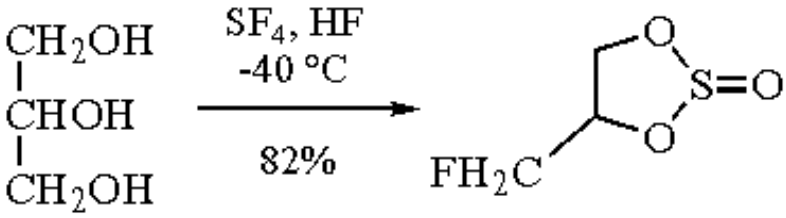

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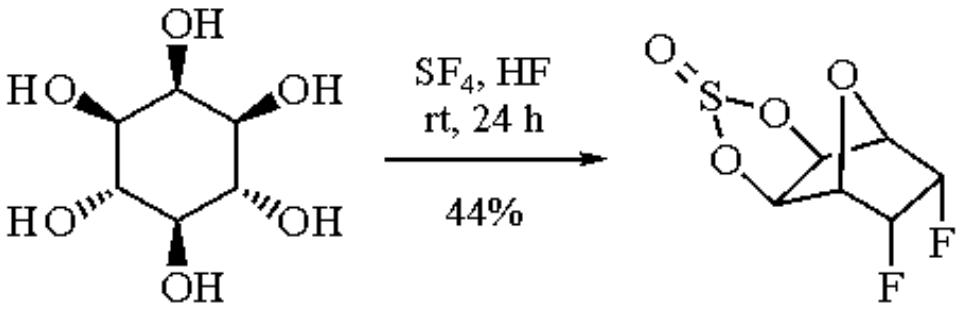

(10)

Fluorination of Aldehydes and Ketones.

Aldehydes lacking α-hydrogens react with SF_4 at high temperatures (150-200 °C) to afford *gem*-difluoride compounds (eq 11).[1a] Aldehydes possessing α-hydrogen atoms can be fluorinated by SF_4 at lower temperatures (to prevent decomposition) and yields of the resulting difluorides are generally low (eq 12).[1a]

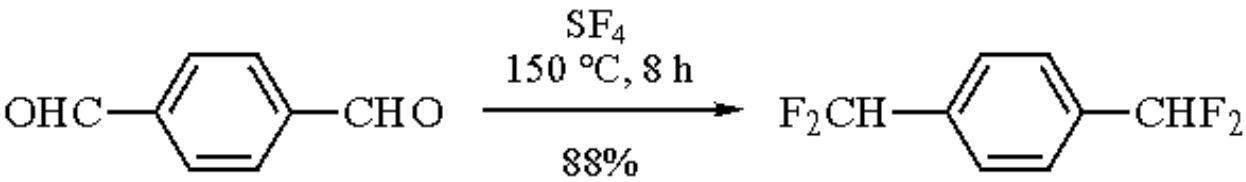

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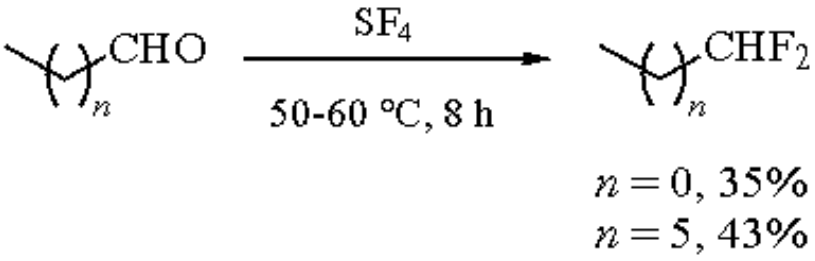

(12)

Fluorination of ketones by SF_4 is exemplified as shown in eq 13.[12] Either one or both carbonyl groups can be converted into difluoromethylene by the control of reaction temperature and time.

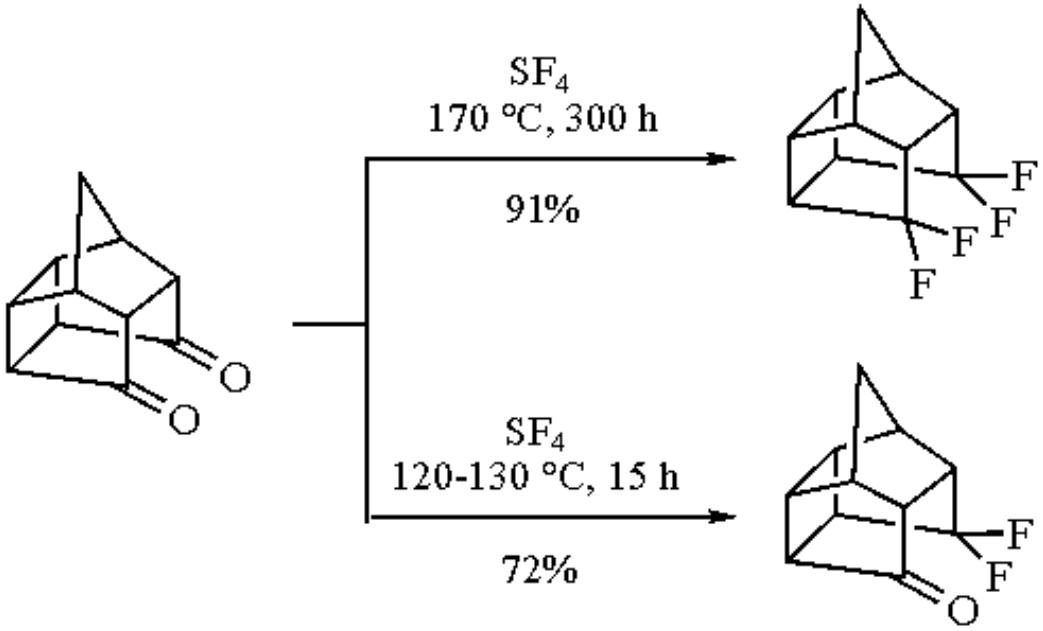

(13)

Aliphatic β-diketones react with SF_4 to form the corresponding di- and tetrafluoro derivatives and also compounds containing double and triple carbon-carbon bonds (eq 14).[13]

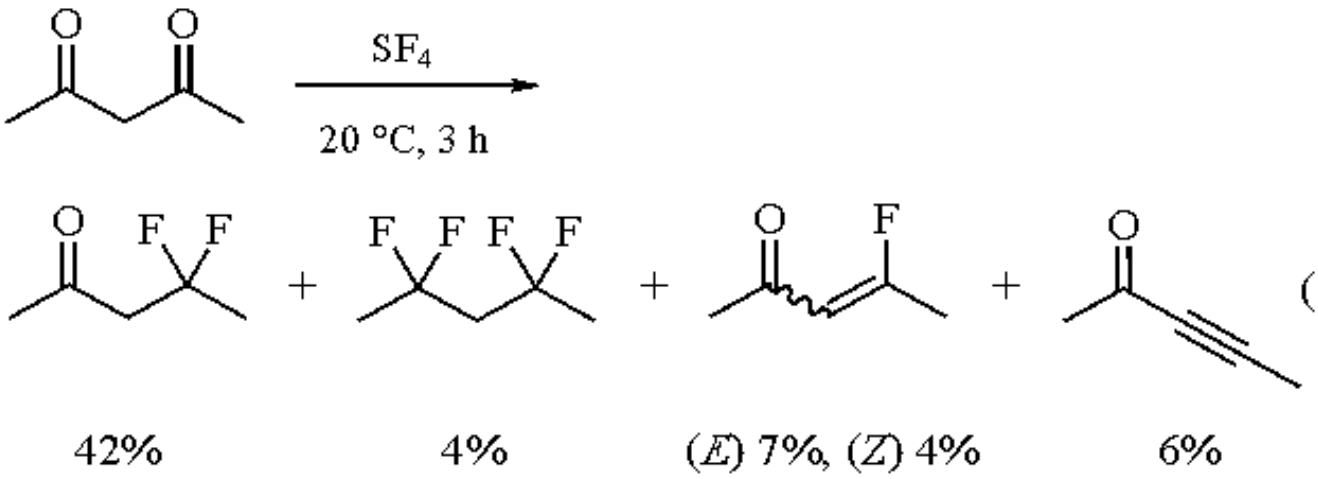

(14)

Fluorination of Carboxylic Acids.

Aliphatic carboxylic acids react with SF_4 at low temperature to give 1,1,1-trifluoroalkanes as well as the unexpected α,α,α´,α´-tetrafluoroalkyl ethers (eq 15).[1b] The yields of tetrafluoroalkyl ethers depend primarily on their stability in the reaction medium because they are subject to protolytic decomposition by HF (eq 16).

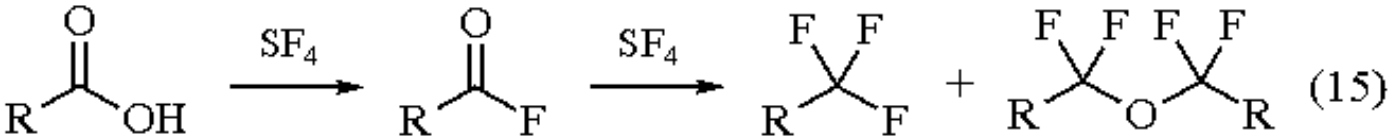

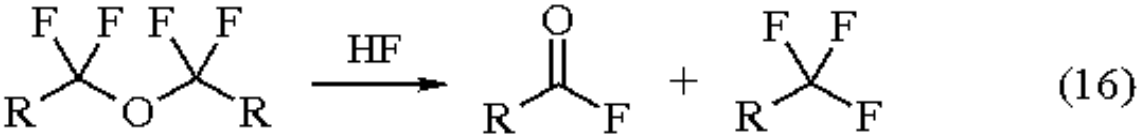

Sulfur tetrafluoride fluorination of aromatic carboxylic acids is the method of choice for introducing the trifluoromethyl substituent (eqs 17-19).[1b,14]

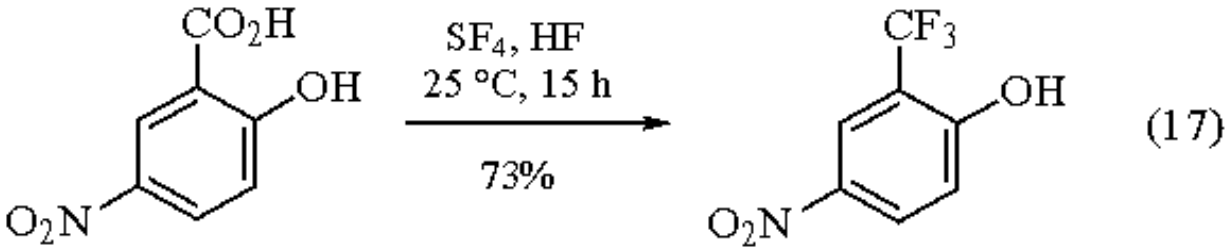

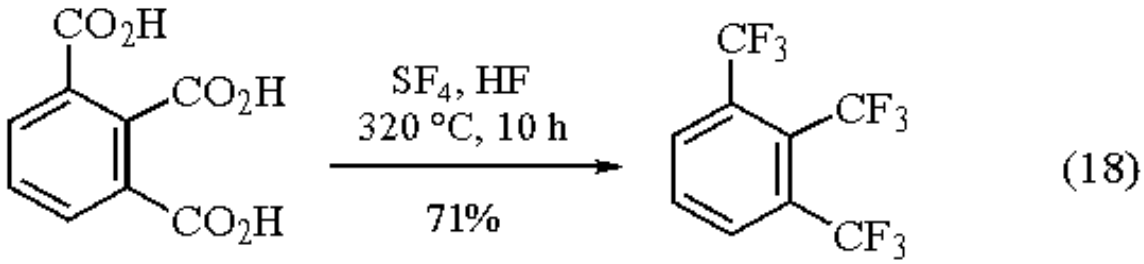

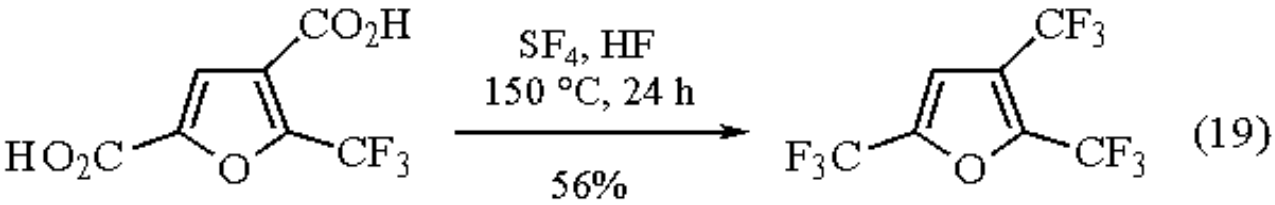

Preparation of Other Fluorinating Agents.

Sulfur tetrafluoride is used to prepare a very useful fluorinating agent, ***N,N-Diethylaminosulfur Trifluoride*** (DAST) (eq 20).[1b]

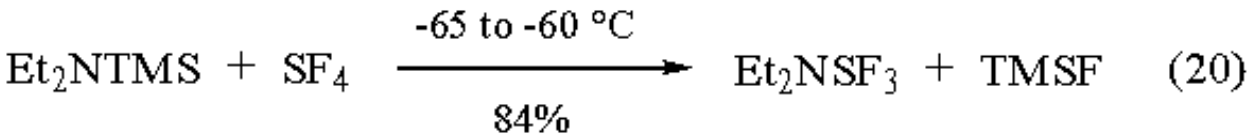

DAST is a convenient reagent to replace the hydroxyl group and carbonyl oxygen of aldehydes or ketones with one and two fluorine atoms, respectively.

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Sulfur Trioxide[1]

[7446-11-9] · O_3S · Sulfur Trioxide · (MW 80.07)

(highly reactive electrophilic agent for replacing (i) a hydrogen atom or other substituent bonded to carbon by an SO_3H or derived sulfo group, forming a carbon-sulfur bond (called sulfonation), (ii) a hydrogen atom bonded to oxygen by an SO_3H group, forming an oxygen-sulfur bond (called sulfation or *O*-sulfonation, and (iii) a hydrogen atom bonded to nitrogen by an SO_3H group, forming a nitrogen-sulfur bond (called sulfamation or *N*-sulfonation);[1a,1b] reagent for cycloaddition to carbon-carbon double bonds;[1a,2] moderate oxidizing agent[3])

Physical Data: mp 16.8 °C; bp 44.7 °C; *d* 1.970 g cm^{-3}.

Solubility: miscible in all proportions with liquid SO_2; sol dichloromethane, chloroform, carbon tetrachloride, 1,1,1-trichloroethane (some react slowly with SO_3, e.g. CCl_4 yields phosgene);[4] SO_3 in dilute solution (<=10 mol %) in SO_2, CCl_3F, and CCl_4 is present as monomer; at higher concentrations the cyclic trimer is also present;[5] sol nitromethane (reacts at 0-15 °C slowly, and at 25-40 °C sometimes violently to give nitromethanesulfonic acid and other compounds);[6] modestly sol 1,4-dioxane; the resulting complex is unstable;[7,8] the solid adduct can decompose violently on standing for some time at rt;[9] reacts violently with water.

Form Supplied in: liquid/solid, containing 1% of stabilizer to prevent polymerization, in sealed glass container.

Handling, Storage, and Precautions: in the absence of a suitable stabilizer, SO_3 shows a strong tendency to polymerize when exposed even to traces of moisture. Use in a fume hood. Keep the container of SO_3 tightly closed and dry. Upon handling open to air, the liquid gives off fumes of a sulfur trioxide-sulfuric acid spray! Reacts violently with water. Causes burns to the skin; is very toxic by inhalation and if swallowed. Contact with combustible material may cause fire. Wear eye and face protection and suitable protective clothing. In case of contact with eyes, rinse immediately with plenty of water, immediately remove all contaminated clothing and seek medical advice.

Organic Sulfur Trioxide Reagents.

Apart from SO_3 and its less reactive addition compounds, formed with suitable Lewis bases[10] such as ***Pyridine***,[11] ***Trimethylamine***,[12] ***Dimethyl Sulfide***,[13] sulfolane,[14] ***Triphenylphosphine***,[15,16] triphenylbismuthine,[16] triphenylphosphine oxide,[17] tricylohexyl-[16] and trimethylphosphine oxide,[17] triethyl phosphate,[18] ***Dimethyl Sulfoxide***,[19] ***N,N-Dimethylformamide***,[20] ***Nitromethane***,[21] 1,4-dioxane,[1a-d] and 1,4-oxathiane,[22] there is a class of sulfonating sulfate ester reagents, e.g. dimethyl polysulfate ($MeOSO_2(OSO_2)_nOMe$)[23] and trimethylsilyl chlorosulfate.[24,25] There are also the protic sulfonating reagents, concentrated aqueous and fuming ***Sulfuric Acid***, and ***Fluorosulfuric Acid***, ***Chlorosulfonic Acid***, and acetylsulfuric acid.[1d] The reactivity order of the Lewis base complexes of SO_3 varies strongly. On the basis of direct experimental evidence[26] and of relative $pK_{B\text{-}SO_3}$[27] and pK_{BH^+}[28] values, the sulfonation reactivity is suggested to increase in the order trimethylamine-SO_3 < ***Sulfur Trioxide-Pyridine***, DMSO-SO_3 < *N,N*-dimethylformamide-SO_3, ***Trimethyl Phosphate***-SO_3 < ***Sulfur Trioxide-1,4-Dioxane*** < sulfolane-SO_3, nitromethane-SO_3.

Aromatic Sulfonation.

Reaction of an arene (ArH) with SO_3 leads to sulfonation with formation of arenesulfonic acids ($ArSO_3H$). Mechanistically two different stages can be recognized, viz. primary and secondary sulfonation.[1f,29,30] In the primary stage, arenepyrosulfonic acids (ArS_2O_6H) are formed. A pyrosulfonic acid is a mixed anhydride, liable to disproportionate to give arenesulfonic anhydride and $H_2S_2O_7$.[30b,31-34] Working up the reaction mixture with water and heating the resulting aqueous mixture to reflux for 15 min leads to complete hydrolysis of the pyrosulfonic acids and sulfonic anhydrides to the corresponding arenesulfonic acids.[31] Sulfonylation to give diaryl sulfones is another possible complication in reaction of arenes with SO_3, especially when using deactivated arenes at high concentrations.[1f]

The steric requirements of a sulfonic acid group are very similar to those of a *t*-butyl group and prevent sulfonation *ortho* to a *t*-butyl group. Sulfonation of *t*-butylbenzene with SO_3 gives 98% of the 4-sulfonic acid (4-S), and that of *m*-di-*t*-butylbenzene gives 98% of the 5-S.[35] Reaction of *p*-di-*t*-butylbenzene with SO_3 in CCl_3F yields 58% of *p*-*t*-butylbenzenesulfonic acid by direct sulfo-de-*t*-butylation.[35]

Sulfonic acid isomer distribution data for the SO_3 sulfonation are available for alkylbenzenes[36] and their halogeno derivatives;[37] phenol and anisole,[31,38] and their methyl,[38,39] halogeno,[38,40] and hydroxy and methoxy derivatives;[32,41] and naphthalene,[36] and its methyl,[42] and hydroxy and methoxy derivatives.[34,43] SO_3 sulfonation isomer distribution data are also available for a number of polycyclic aromatic hydrocarbons and 1,6-methano[10]annulenes, including some alkyl derivatives.[36]

Deviating Sulfonation Behavior of 9-Alkylanthracenes.

Reaction of 9-methylanthracene with SO_3 in dioxane leads exclusively to methyl sulfonation to give sulfonic acid (**1**) quantitatively.[44] Under comparable conditions, 9-*t*-butylanthracene gives δ-sultone (**2**).[45a] Sulfonation of 9-pentylanthracene gives predominantly sulfonic acid (**3**) with some (**4**).[45b] The α-alkenyl-γ-sulfonic acid (**3**) is formed via the corresponding 9-alkenylanthracene as an intermediate.[45c]

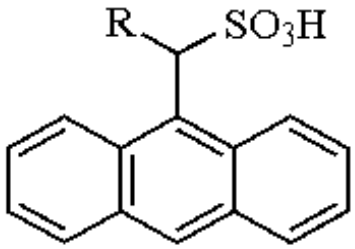

(1) R = H
(4) R = Bu

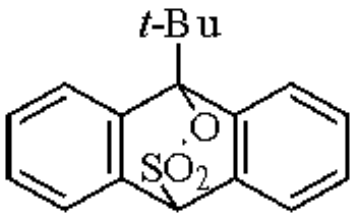

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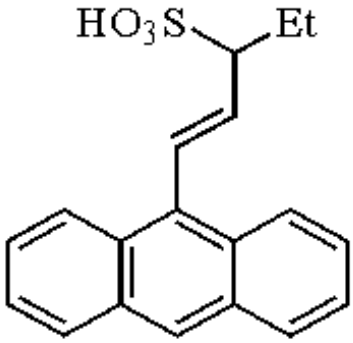

(3)

Positional Selectivity.

Judging from the data for toluene,[46] *o*-xylene,[47] 1-methylnaphthalene,[42a,48] phenol,[38,49] anisole,[38,49] and 2,3-dihydrobenzofuran[50] and -pyran,[50] the positional selectivity is significantly greater for sulfonation with SO_3 than with sulfuric acid containing 90 wt % H_2SO_4.

For the sulfonation of an (alkyl)arene with SO_3 in differing solvents, the variation in the isomer distribution is limited.[14,51] With phenol and anisole the *ortho*:*para* sulfonation ratio is significantly larger when using CH_2Cl_2 than the complex-forming solvents nitromethane and dioxane.[31] With CH_2Cl_2 the SO_3 forms instead a complex with the C(sp^2) oxygen of the substrate which, as result of intramolecular transfer of SO_3, leads to enhanced *ortho* sulfonation. With substituted phenols and anilines, subject to the positions of the other substituents, the positional selectivity changes very significantly on varying the [SO_3]:[substrate] from <=1.0 to &egt;4.0 (Table 1).

Table 1 Sulfonation of Phenol and Aniline Derivatives in Nitromethane at 0 °C

Substrate[a]	SO_3 (equiv)	Product mixture composition (%)[a]
2-MeO-P[41]	1.0	4-S (76) 5-S (24)
	4.0	(19) (81)
	4.0[b]	(<2) (>98)
3,5-Me_2-P[39]	0.9	2-S (89) 4-S (11)
	4.0	(25) (75)
2,6-Me_2-P[40b]	0.9	3-S (<2) 4-S (>98)
	6.0	(77) (23)
2,6-Me_2-A[40b]	1.0	3-S (<2) 4-S (>98)
	8.0	(87) (13)

[a] P, A, and S stand for phenol, aniline, and SO_3H, respectively.
[b] Reversed addition

As for the phenol derivatives, this illustrates the importance of the initial sulfation equilibrium (k_1, k_{-1}) (eq 1). Applying <=1.0 equiv SO_3 the effective substrate species being sulfonated is the hydroxyarene H-Ar-OH (k_2), the OH substituent of which is strongly activating and *para* directing, whereas on using a large excess of SO_3 the entity undergoing sulfonation is the corresponding aryl hydrogen sulfate H-Ar-OSO_3H (k_3), the OSO_3H substituent being deactivating and *para* (+ *ortho*) directing. This may accordingly lead to a different substitution pattern. The sulfation equilibrium (k_1, k_{-1}) constant is temperature dependent. Phenol with 1.0 equiv SO_3 in nitromethane at -35 °C is rapidly sulfated to give phenyl hydrogen sulfate quantitatively, which at &egt;0 °C isomerizes to phenol-4-S as the only eventual product.[38] The increase of both the 2- to 3-S ratio in the reaction of *p*-methoxyphenol with 1.5 equiv SO_3,[41] and the 2- to 4-S ratio in the reaction of 1-naphthol with 1.0 equiv SO_3[43a] with increasing reaction temperature, were ascribed to the increase in the k_{-1}/k_1 ratio.

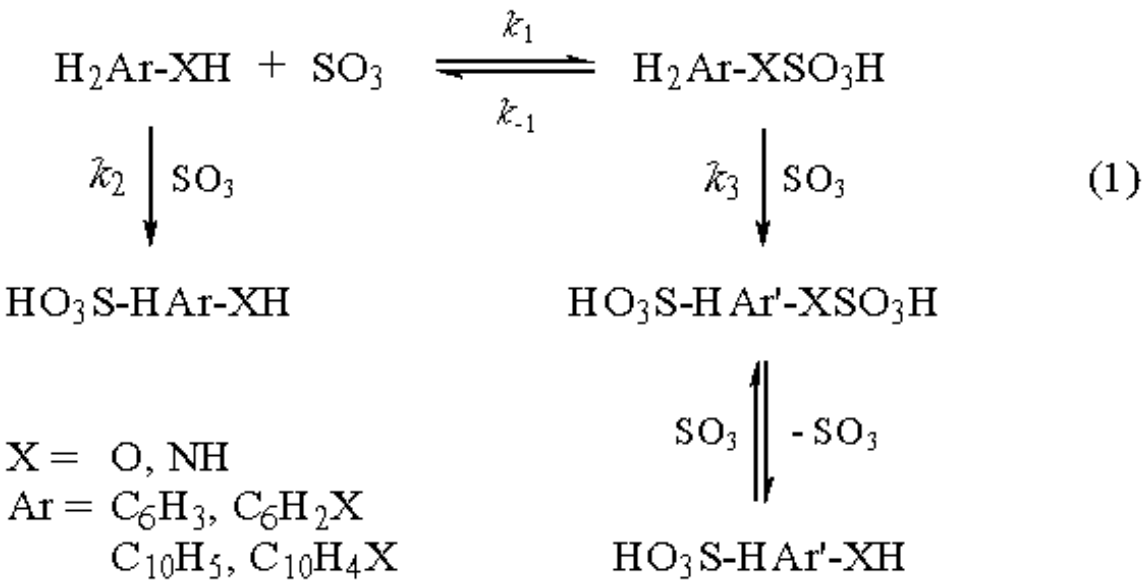

Sulfonation of Unsaturated Aliphatic Compounds.

Sulfur trioxide reacts vigorously with linear[52] and branched[53] alkenes to give rise to β-sultones as the primary sulfonation products.[1a,1b,2] Since neat SO_3 is too reactive, complexes of SO_3 with dioxane[8] or pyridine[11] are used to moderate the sulfonation reaction. The formation of β-sultone is stereo- (*syn*) and regioselective, obeying Markovnikov's rule. However, these β-sultones are thermally unstable at rt and their rearrangement leads to complex mixtures of alkenesulfonic acids and γ- and δ-sultones. Yields of the isolated alkenesulfonic acids (eq 2)[54] and sultones (eq 3)[53] vary considerably with the alkene structure and reaction conditions. Halogenated,[1h] in particular fluorinated,[1i] ethylenes react with SO_3 to give relatively stable halogenated β-sultones. This cycloaddition of SO_3 at the double bond proceeds in a regioselective way (eq 4).[55]

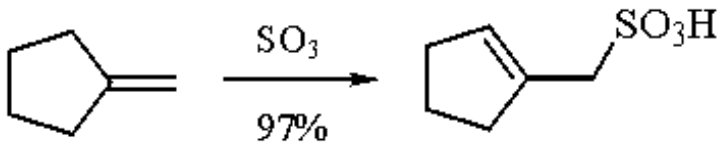

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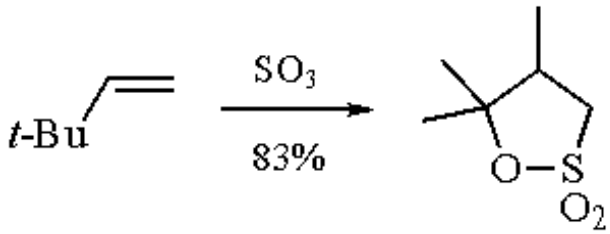

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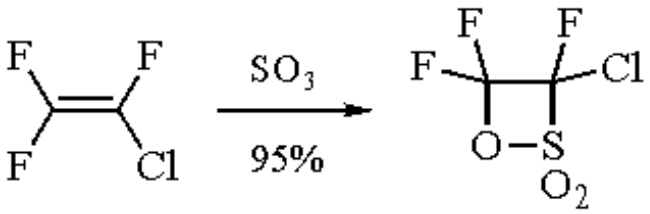

(4)

Reaction of an alkene with an excess of SO_3 gives a cyclic sulfonate-sulfate anhydride, also referred to as carbyl sulfate or pyrosulfate (eq 5).[56] This carbyl sulfate is formed by a slow insertion of SO_3 into the intermediate β-sultone.[52a] The complex of sulfur trioxide with dimethyl sulfide reacts with alkenes and alkynes to afford sulfobetaines in good yields (eq 6).[13,57] These sulfobetaines are produced by nucleophilic attack of the dimethyl sulfide on the initially formed β-sultones.

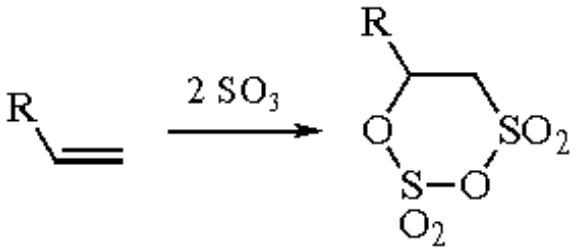

(5)

R = H, 94%; Me, 94%; 2,6-$Cl_2C_6H_3$, 96%

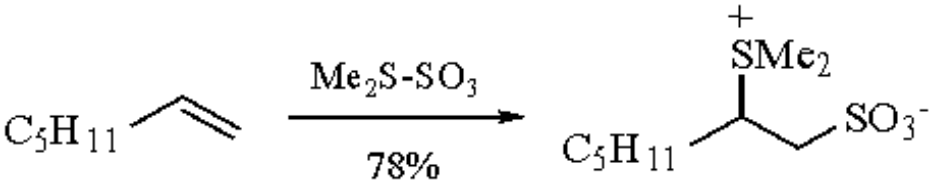

(6)

Conjugated dienes are sulfonated by sulfur trioxide reagents to give β-unsaturated δ-sultones (eq 7). The yields vary strongly; they increase with the number of alkyl substituents at the 2- and 3-positions of the alkadiene.[58]

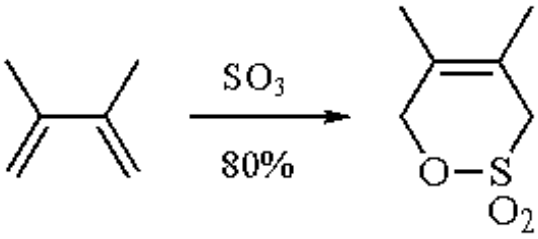

(7)

Functionalized alkenes containing a phenyl or carboxylic acid group at appropriate distance from the double bond undergo intramolecular cyclization during the sulfonation.[59] On reaction of (*E*)-4-hexenoic acid[59a] with SO_3 a sulfo-δ-lactone is formed (eq 8), and a Friedel-Crafts type cyclization is observed on sulfonation of (*E*)-5-phenyl-2-pentene[59b] (eq 9); both cyclizations proceed quantitatively and stereospecifically.

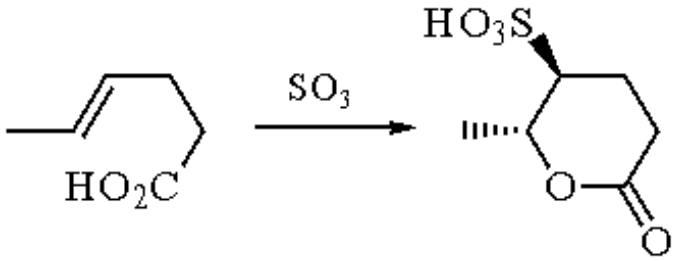

(8)

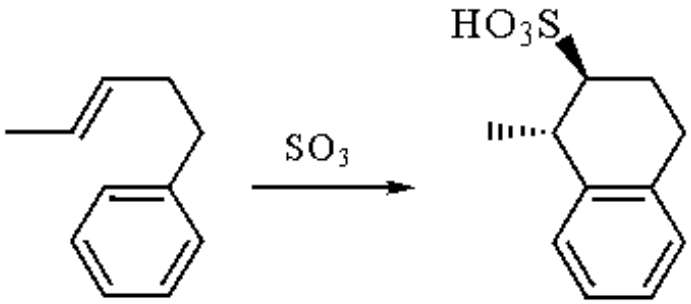

(9)

Sulfonation of Saturated Aliphatic Compounds.

Sulfur trioxide reacts with aliphatic acids[60] or esters[61] to give, initially, insertion of SO_3 into the carboxylic acid or ester group, followed by sulfonation at the α-carbon (eq 10). Reactions of aldehydes and ketones with SO_3 also afford the α-sulfonated products.[62]

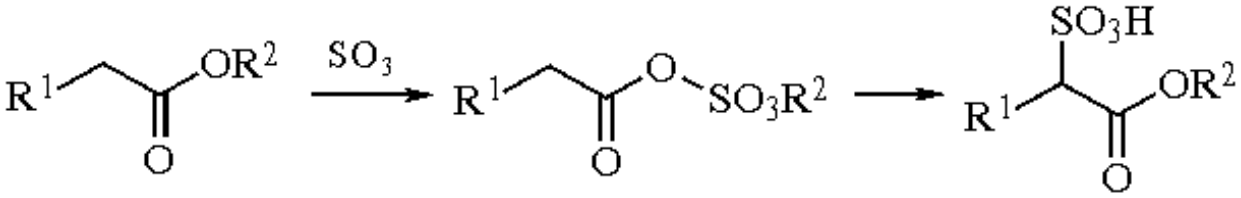

(10)

R^1 = H, alkyl; R^2 = H, alkyl

It should be noted that sulfonation of linear alkylbenzenes, linear long-chain α-alkenes, and fatty esters and the sulfation of fatty alcohols by SO_3-air mixtures are widely applied processes in industry for the production of surfactants.[63]

Related Reagents.

Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine; ***Sulfur Trioxide-1,4-Dioxane***; ***Sulfur Trioxide-Pyridine***.

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Sulfur Trioxide-1,4-Dioxane[1]

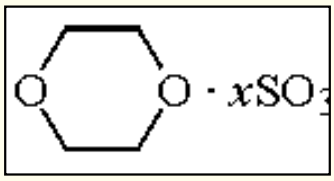

(*x* unspecified)

[54287-50-2] (*x* = 1)

[20769-58-8; 35346-47-5] · $C_4H_8O_5S$ · Sulfur Trioxide-1,4-Dioxane · (MW 168.19) (*x* = 2)

[52922-31-3] · $C_4H_8O_8S_2$ · Sulfur Trioxide-1,4-Dioxane · (MW 248.26) (*x* = 3)

[52922-32-4] · $C_4H_8O_{11}S_3$ · Sulfur Trioxide-1,4-Dioxane · (MW 328.33)

(useful for effecting Beckmann rearrangements;[8] sulfonation of alkenes[11] and arenes[16])

Physical Data: mp 75 °C,[2] but almost never isolated.

Solubility: generated as a solution in dioxane, with or without other solvents.

Preparative Methods: the *Organic Synthesis* procedure[2] involves reaction of ***Sulfur Trioxide*** (as Sulfan B) with dioxane in 1,2-dichloroethane. The complex precipitates and is used immediately. An alternate procedure involves treatment of dioxane with $ClSO_3TMS$,[3] itself prepared by reaction of ***Chlorotrimethylsilane*** and ***Chlorosulfonic Acid***.[4]

Handling, Storage, and Precautions: reacts vigorously with water, alcohols, etc. It has been reported to decompose violently upon standing at rt[2] or upon heating to 75 °C.[5] The chemistry is essentially that of SO_3 with some attenuation in reactivity. Safety precautions in the handling of SO_3, which can be an unexpectedly strong oxidant, should be followed.[1c]

General.

Sulfur trioxide forms addition complexes of varying stability and reactivity with Lewis bases. The stronger the base, the more stable and less reactive is the complex. The reactions of these complexes are essentially those of SO_3 and so it is possible to tune the reactivity of SO_3 to suit the reaction or substrate of interest. Frequently used bases, in order of decreasing reactivity of their SO_3 complexes, are ***N,N-Dimethylformamide***, 1,4-dioxane, ***Pyridine***, and ***Trimethylamine***.[1c] The dioxane adducts are hydrolyzed instantly in cold water, whereas the pyridine adduct is stable in aqueous solution. Dioxane-SO_3 adducts with the stoichiometry of 1:1, 1:2, 1:3, and 1:4 have all been identified. The second and third equivalents of SO_3 in the 1:2 and 1:3 complexes are much more reactive than the first. The following paragraphs refer specifically to the 1:1 complex.

Sulfation Reactions.

Reactions of alcohols proceed with extraordinary ease.[1c] When aromatic nuclei are present, simple control of stoichiometry is sufficient to prevent aromatic substitution. In many cases, reaction of the dioxane-SO_3 complex with amines (sulfamation) is too vigorous to be convenient and a tamer (pyridine-SO_3) complex is preferable. The OH group undergoing sulfation may be part of

another group, e.g. an oxime.[6,7] The oxime-*O*-sulfonate may occasionally be isolated, but more commonly is directly transformed into the amide (Beckmann rearrangement) by heating (eq 1).[8]

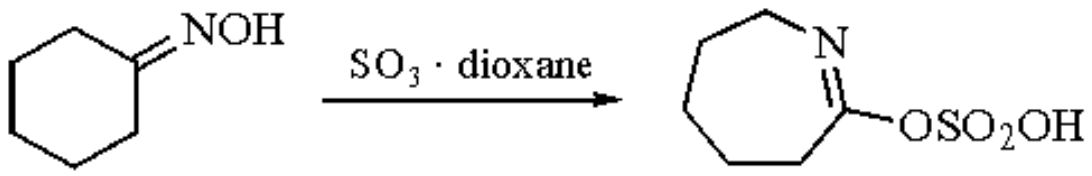

(1)

Sulfonation of Alkenes.

Alkenes undergo sulfonation. The initial product is the cyclic β-sultone which is formed by a concerted mechanism[9] and stereospecifically.[10] These are rapidly hydrolyzed in the presence of water or alcohols. Products range from 2-hydroxysulfonic acids to vinyl or allyl sulfonic acids (eq 2).[1c,11-13]

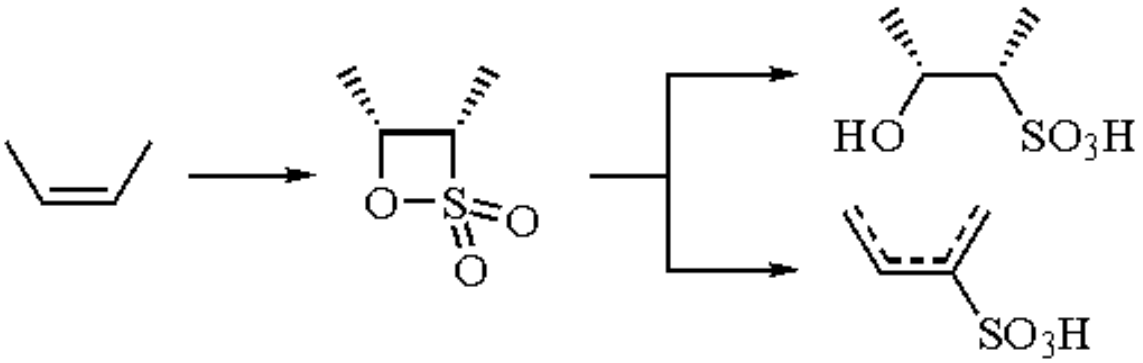

(2)

Sulfonation of Carbonyl Compounds.

Carboxylic acids form acyl sulfates which rearrange into α-sulfo acids. Similarly, aldehydes and ketones sulfonate in the α-position.[14] Aryl-substituted alkanoic acids sulfonate α to the acid without aromatic substitution. This is contrary to their reaction with ***Sulfuric Acid***, which affords ring-sulfonated products.

Sulfonation of Aromatic Compounds.

Cerfontain and co-workers have published many papers dealing with the mechanism of this reaction.[1b,15] Benzene and its derivatives do not react unless highly activated. Polycyclic aromatics react via sultones which may be isolated or may open to give sulfonic acids. For example, anthracene affords the 9-sulfonic acid;[16] 9-alkylanthracenes afford principally side-chain sulfonated materials,[17] whereas alkyl substitution on ring A leads to sultones whose structures depend on the substitution pattern (eq 3).[18] The isomeric composition of the sulfonic acid products may differ substantially from that obtained using sulfuric acid. Dioxane-SO_3 is the reagent of choice for the sulfonation of moderately acid-sensitive aromatics (e.g. thiophene),[19] but it is still too reactive to use with ***Furan*** and pyrrole. The patent literature is replete with references to sulfonation of various polymers using SO_3 in various for ms, but this is beyond the scope of this report.

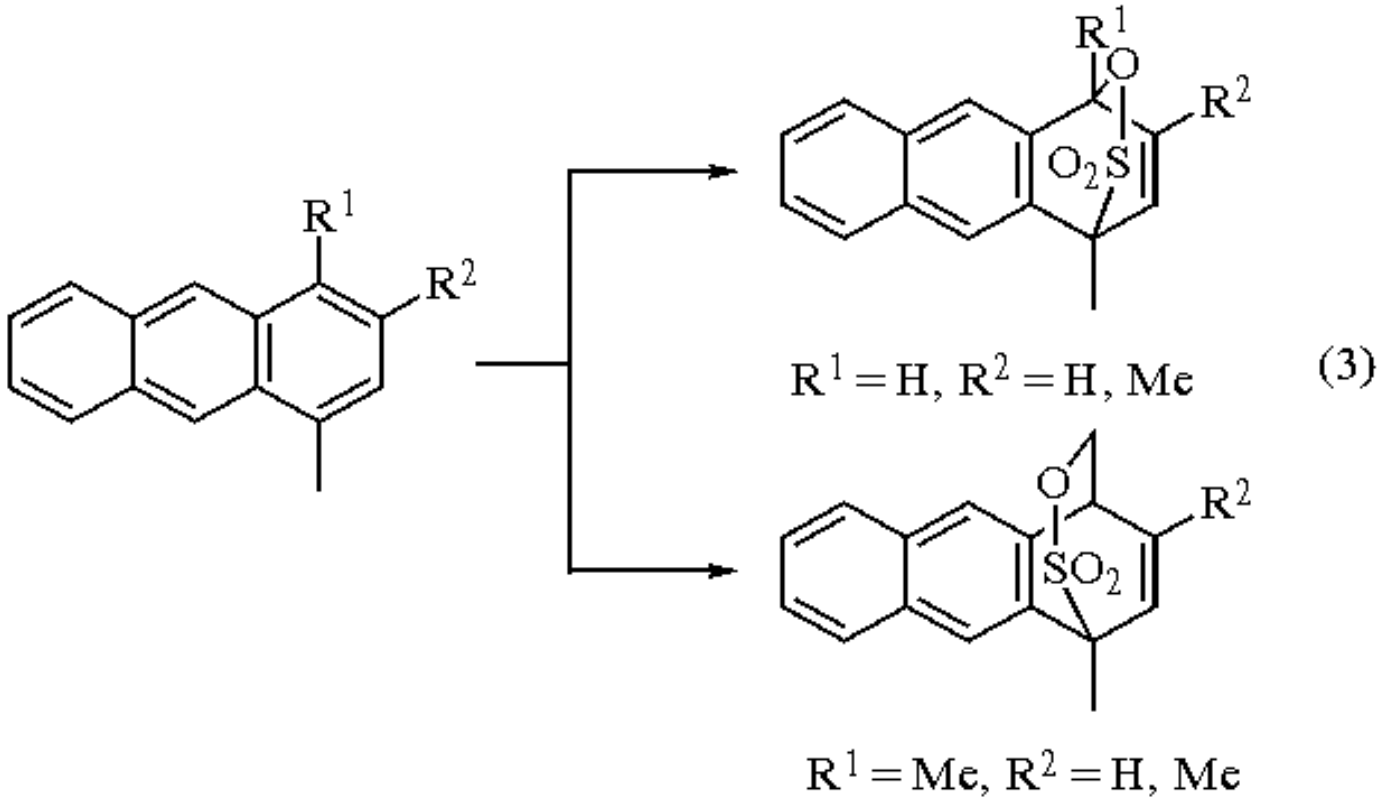

Related Reagents.

Sulfur Trioxide; ***Sulfur Trioxide-Pyridine***.

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Sulfur Trioxide-Pyridine

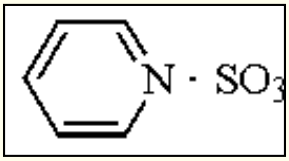

[26412-87-3] · $C_5H_5NO_3S$ · Sulfur Trioxide-Pyridine · (MW 159.18)

(forms sulfate esters which can be displaced with hydride; useful in displacement reactions of allylic alcohols which cannot be converted to halides; used with DMSO for oxidation of alcohols)

Physical Data: mp 175 °C.

Solubility: sol DMSO; slightly sol ether, $CHCl_3$, CCl_4.

Form Supplied in: crystalline white solid; widely available.

Preparative Methods: reaction of ***Chlorosulfonic Acid*** and ***Pyridine*** in $CHCl_3$[1a,b] or reaction of ***Sulfur Trioxide*** and pyridine.[1c]

Handling, Storage, and Precautions: corrosive; reacts quantitatively with hot H_2O to give pyridine and sulfuric acid. Use in a fume hood.

General Discussion.

Addition of the title complex to farnesol (**1**) in THF at 0 °C and stirring of the suspension results in formation of the sulfate (**2**) (eq 1). Addition of ***Lithium Aluminum Hydride*** in THF then gives the hydrocarbon (**3**) (eq 2). [2a] Other alcohols are converted similarly.[2] Reaction with glucose gave glucose-6-sulfate (**4**) isolated as the barium salt (eq 3).[3a] Sulfonation of indole occurs on treatment with the reagent (eq 4).[3b]

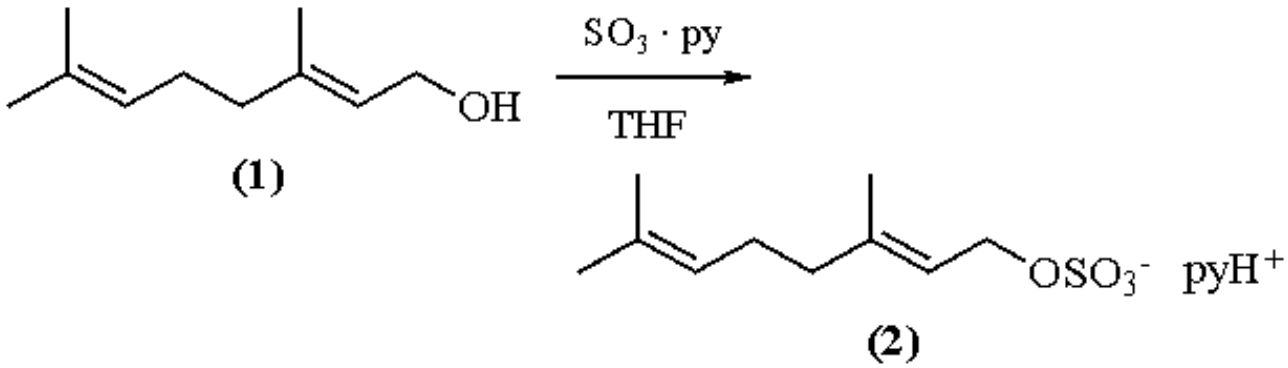

(1)

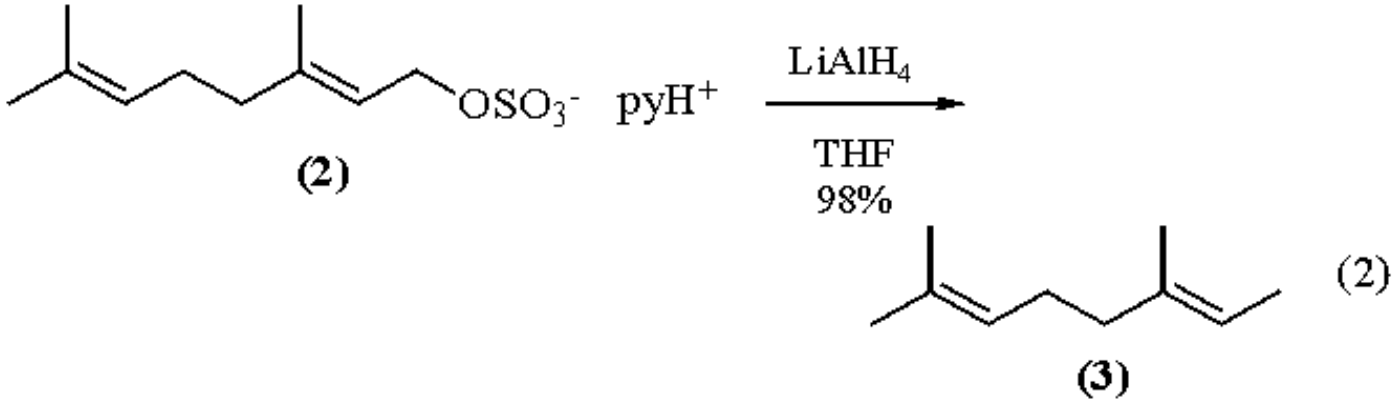

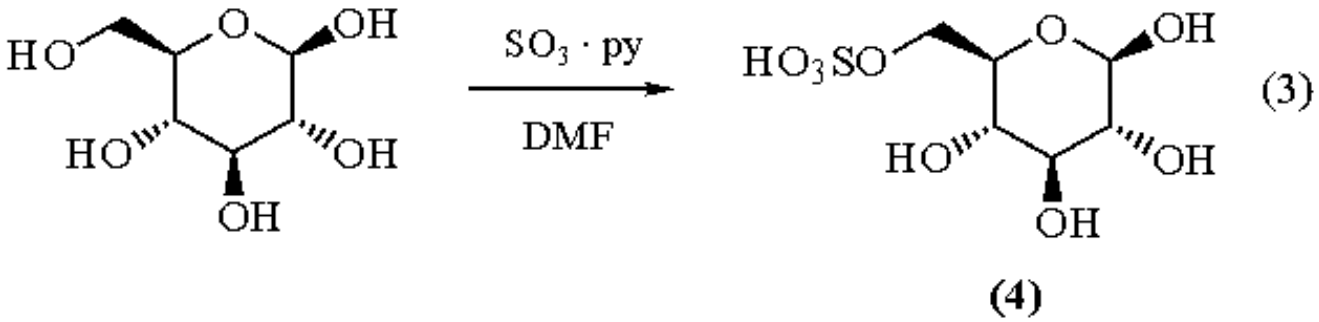

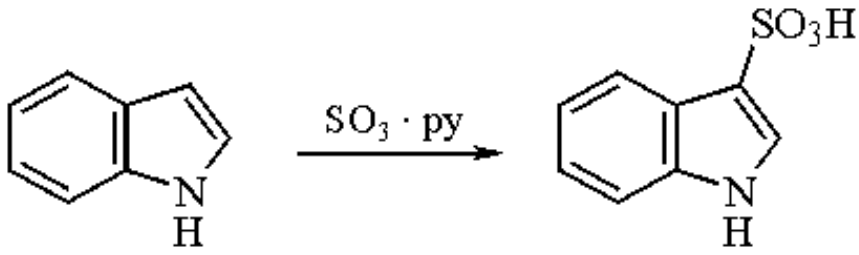

Related Reagents.

Dimethyl Sulfoxide-Sulfur Trioxide/Pyridine; ***Sulfur Trioxide***; ***Sulfur Trioxide-1,4-Dioxane***.

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1. (a) Sisler, H. H.; Audrieth, L. F. *Inorg. Synth.* **1946**, *2*, 173. (b) Fieser, L. F. *JACS* **1948**, *70*, 3232. (c) Baumgarten, P. *CB* **1926**, *59*, 1166.
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Sulfuryl Chloride

SO_2Cl_2

[7791-25-5] · Cl_2O_2S · Sulfuryl Chloride · (MW 134.97)

(widely used chlorinating agent;[1] oxidizing agent;[32] dehydrating agent;[30] esterification catalyst[31])

Physical Data: bp 68-70 °C.

Solubility: miscible with most organic solvents.

Form Supplied in: commercially available in 97-98% purity.

Analysis of Reagent Purity: bp.

Purification: fractional distillation.

Handling, Storage, and Precautions: is highly toxic, corrosive, and acts as a lachrymator. It reacts violently with water to liberate hydrogen chloride gas. Sulfuryl chloride is incompatible with DMSO, DMF, and ethers. This reagent should only be handled in a chemical fume hood using proper protective equipment.

Chlorination of Alkanes.

Hydrocarbons can be chlorinated using sulfuryl chloride by either radical or ionic processes. In the radical mediated process developed by Kharasch and Brown,[1] a mixture containing an excess of the alkane with sulfuryl chloride and a catalytic amount of ***Dibenzoyl Peroxide*** in a suitable solvent such as carbon tetrachloride is heated, initiating chlorination and concomitant evolution of hydrogen chloride and sulfur dioxide. With simple alkanes a mixture of positional isomers is obtained.

Radical chlorination of benzylic positions using sulfuryl chloride proceeds with good selectivity over less activated sites of reaction (eq 1).[1] This reaction can be facilitated by transition metal complexes[2] or zeolites.[3]

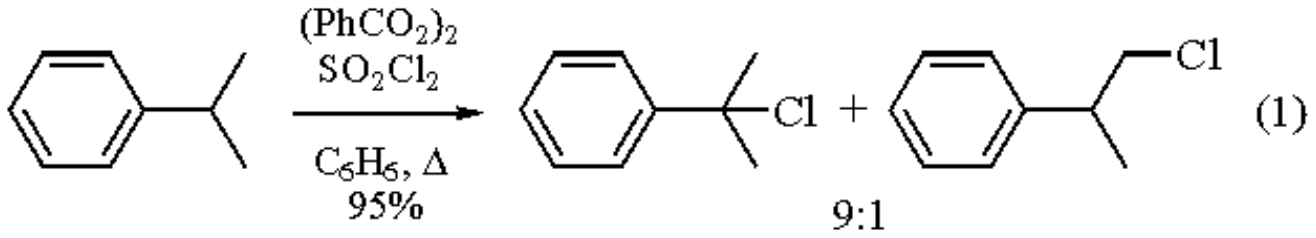

Certain substituted alkanes can also be selectively chlorinated by this method.[4] A good example is Lampman and Aumiller's synthesis of 3-chlorocyclobutanecarboxylic acid (eq 2).[5]

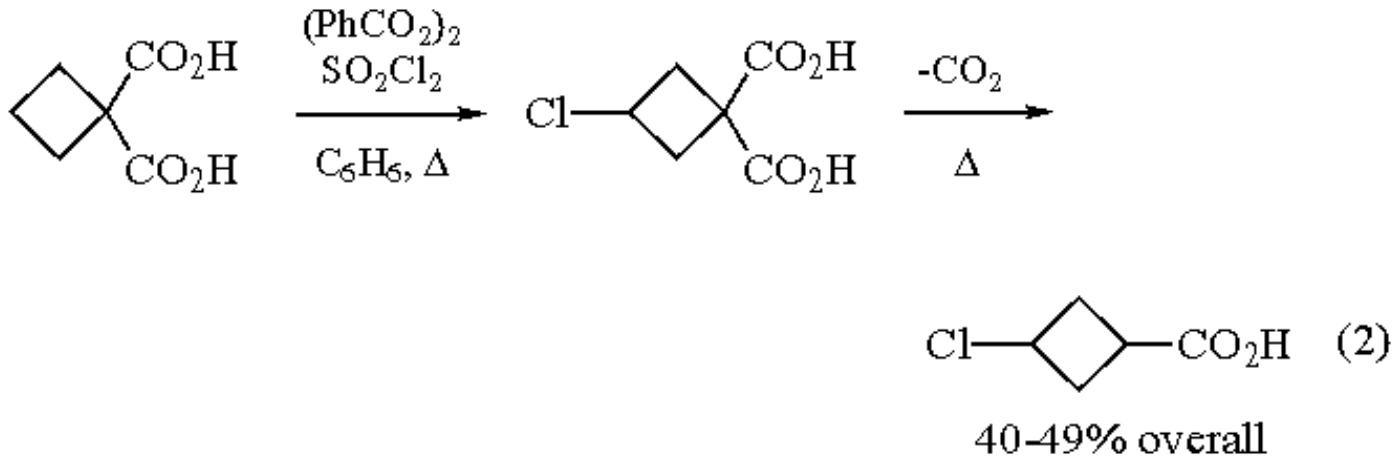

Ionic chlorination of alkanes can be accomplished by heating a mixture of alkane and excess sulfuryl chloride in sulfolane (eq 3).[6] In these chlorinations the reaction mixture is shielded from light to prevent the initiation of radical processes. Since alkanes are more readily chlorinated by this method than sulfolane, competing solvent chlorination is not a problem.

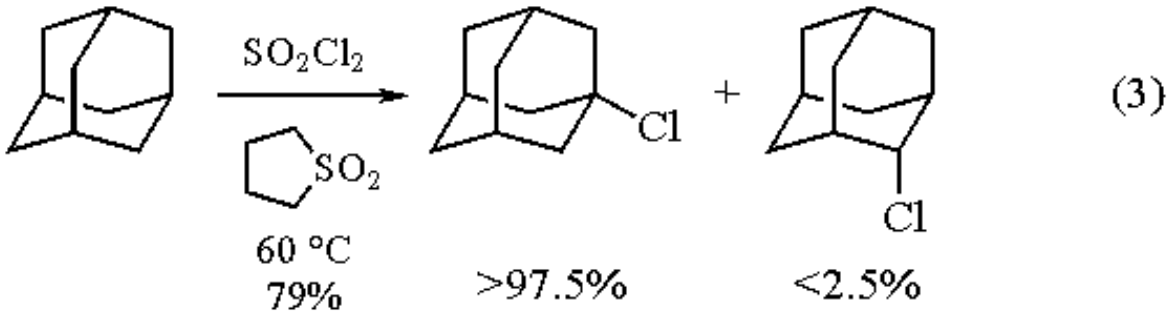

Reactions with Alkenes.

Alkenes react exothermically with sulfuryl chloride to give vicinal dichlorides in generally good yields (eq 4).[7]

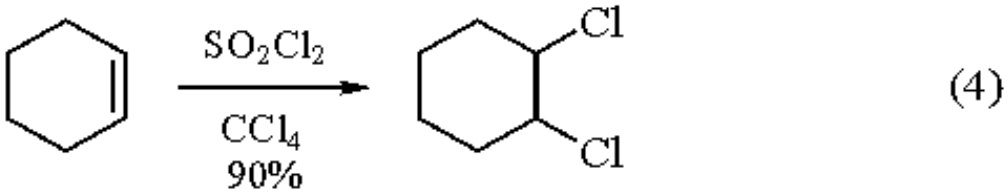

A mixture of sulfuryl chloride and *N*-methylpyrrolidine can be used to convert styrene into styrylsulfonyl chloride (eq 5).[8]

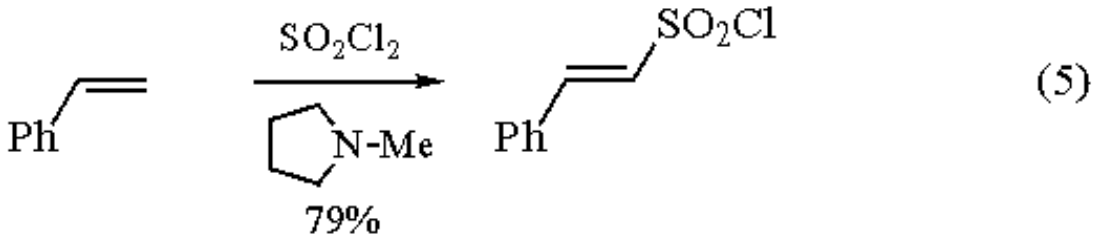

β-Chloro methyl sulfides are produced by the action of ***Dimethyl Sulfide***/sulfuryl chloride/***Dimethyl Sulfoxide*** in acetonitrile on alkenes (eq 6).[9] It is thought that this reagent combination generates methanesulfenyl chloride, which undergoes exclusive *trans* addition to the alkenes. The initially formed anti-Markovnikov adducts slowly rearrange to Markovnikov products.

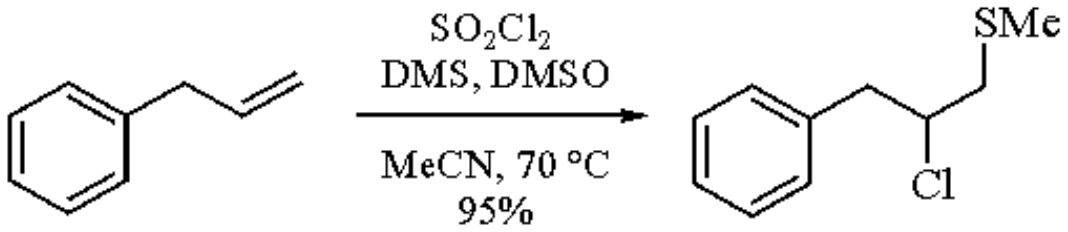

(6)

Chlorination of Epoxides.

Sulfuryl chloride reacts with cyclohexene oxide and ***Pyridine*** in refluxing chloroform to give 99% *cis*-1,2-dichlorocyclohexane in 70% yield.[10]

Chlorination of Alkynes.

Many alkynes react with this reagent via a homolytic pathway to give the corresponding (*E*)- and (*Z*)-dichloroalkenes in good to moderate yields.[11] The ratio of isomers obtained is kinetically controlled and varies depending on the relative size of the alkyne substituents.

Chlorination of Aromatics.

Sulfuryl chloride reacts with aromatic derivatives under mild conditions to afford ring chlorinated products.[12] For example, ethyl 4-hydroxybenzoate reacts at both the 3- and 5-positions when heated with excess sulfuryl chloride. Ester hydrolysis followed by decarboxylation gives 2,6-dichlorophenol (eq 7).[13]

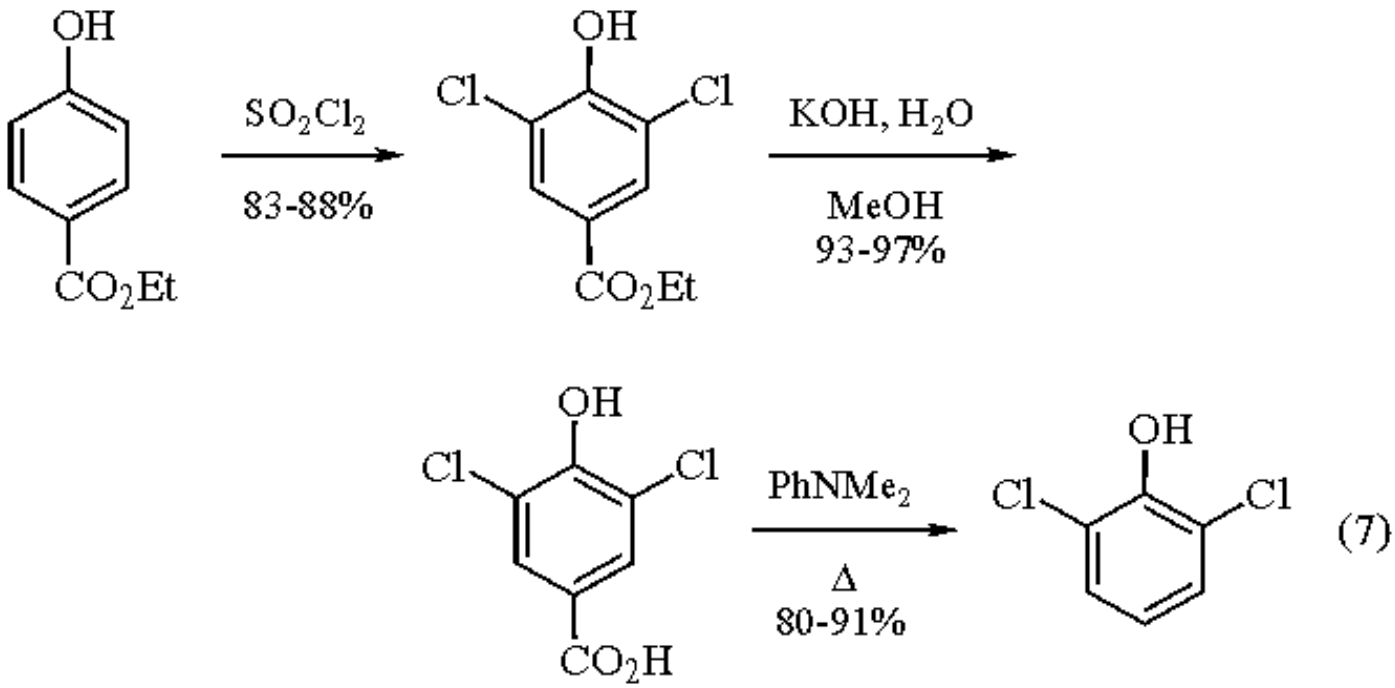

(7)

Regioselective *para*-monochlorination of various phenols has been accomplished using sulfuryl chloride in combination with either ***Aluminum Chloride*** or ***Iron(III) Chloride*** as catalyst.[14]

Thiophenes react with sulfuryl chloride to give 2- or 5-chlorinated products with high selectivity.[15] This reagent has been applied with excellent results to the chlorination of 2-thienylamines. For example, the antihistamine methapyrilene can be converted to chlorothen in 84% yield (eq 8).[16]

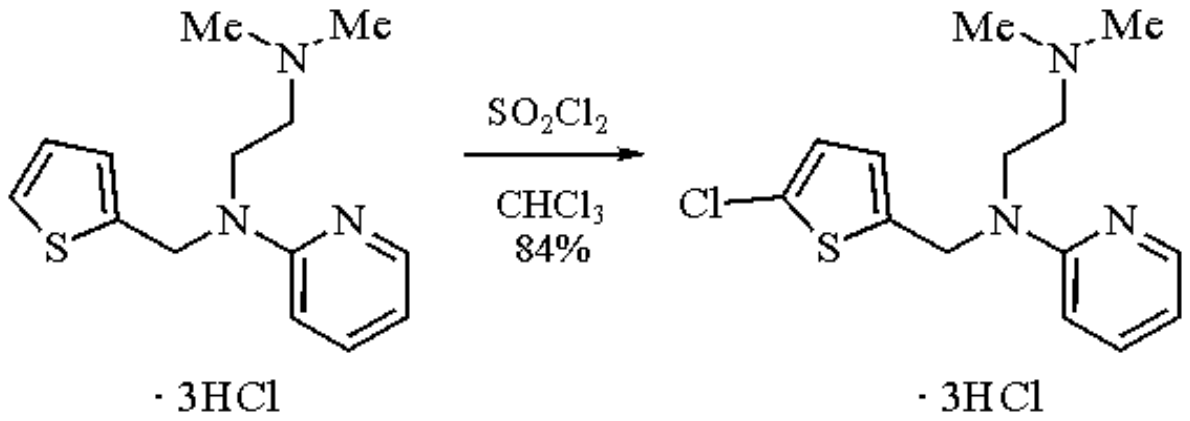

(8)

Aromatic hydrocarbons can be perchlorinated using a reagent composed of sulfur monochloride (5 g), sulfuryl chloride (850 mL), and aluminum trichloride (2.5 g).[17] This reagent combination has been used to prepare highly strained aromatic chlorocarbons, including perchlorotoluene, perchloro-*p*-xylene, and perchlorophenanthrene.

α-Chlorination of Active Methylene Compounds.

Ketones are selectively chlorinated at the α-position with sulfuryl chloride to form products consistent with reaction between the reagent and the thermodynamic enol.[18] For example, only 2-chloro-2-methylcyclohexanone is obtained from 2-methylcyclohexanone (eq 9).[19] Direct chlorination of this ketone with ***Chlorine*** gives mixtures of chloro compounds.[20]

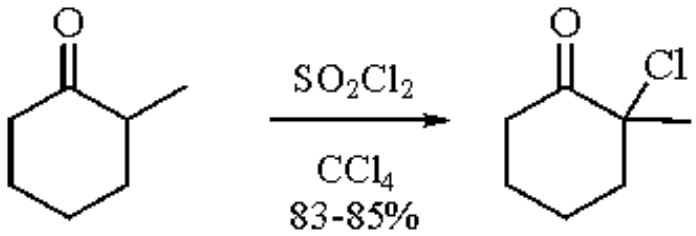

(9)

Many other activated methylene compounds can be α-chlorinated with sulfuryl chloride. Examples include the conversion of ***Ethyl Acetoacetate*** to ethyl 2-chloroacetoacetate in 93-97% yield;[21] the chlorination of pyruvic acid in 96-98% yield;[22] the α-chlorination of ε-benzoylaminocaproic acid;[23] and the transformation of *N*-benzoyl-ε-caprolactam to *N*-benzoyl-α-chloro-ε-caprolactam in 89% yield.[24] Aldehydes react with this reagent to give α-chlorinated products that often react further to form cyclic ether trimers and linear polyethers.[25,26]

4-Ene-3-oxo-steroids react with excess sulfuryl chloride in pyridine solution cleanly to give 4-chloro-4-ene-3-oxo-steroids (eq 10).[27] When testosterone acetate is treated with excess sulfuryl chloride in anhydrous ether, 2α,6β-dichlorotestosterone acetate is obtained as the major product.[28]

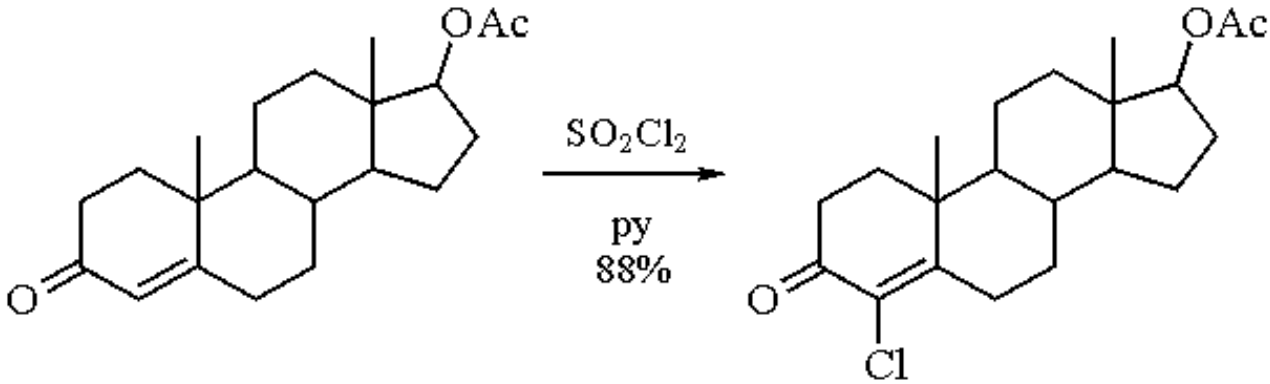

(10)

Conversion of Alcohols to Chlorides.

Kozikowski and Lee[29] report that secondary alcohols can be converted to chlorides with retention of configuration via methyl xanthate formation followed by reaction with sulfuryl chloride (eq 11).

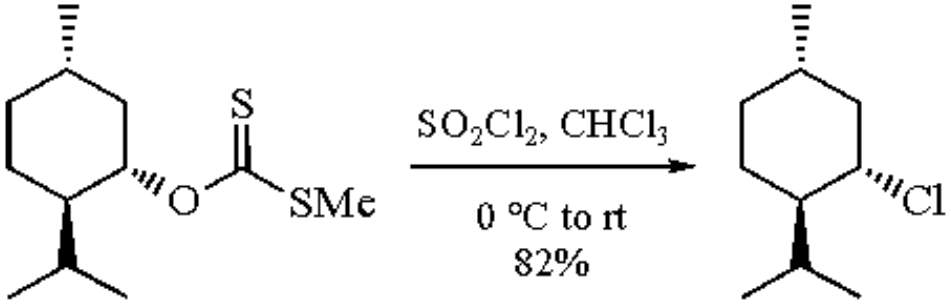

(11)

Dehydrating Agent.

A combination of sulfuryl chloride and pyridine is useful as a dehydrating reagent in the synthesis of shikimic acid derivatives (eq 12).[30]

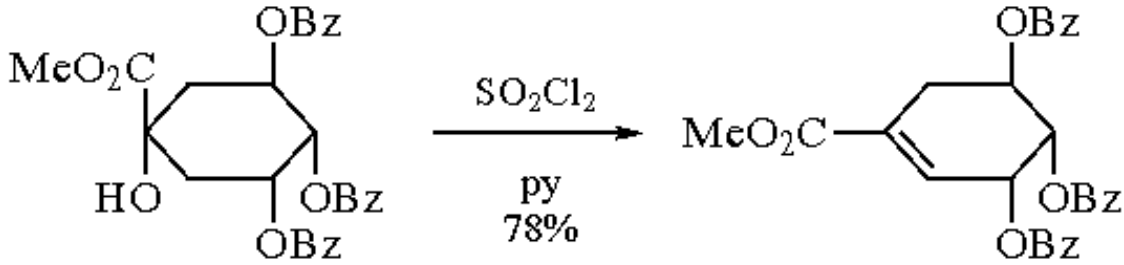

(12)

Esterification Catalyst.

Sulfuryl chloride catalyzes formation of methyl and benzyl esters of *N*-acylated amino acids and peptides at room temperature in yields ranging from 48-98% without causing racemization.[31]

Oxidation of Pyrroles.

This reagent is used to oxidize the methyl group at the 5-position of alkyl 3,4-dialkyl-5-methyl-2-pyrrolecarboxylates. Depending on reaction conditions, one can obtain either the ester (eq 13),[32] the carboxylic acid,[33] the aldehyde,[34] or the dichloromethyl derivative.[35]

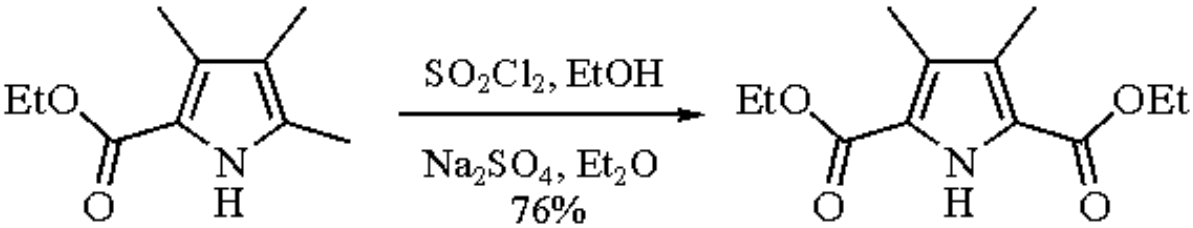

(13)

Reactions with Sulfides.

Sulfuryl chloride reacts with methyl sulfides to give chloromethyl sulfide derivatives (eq 14).[36]

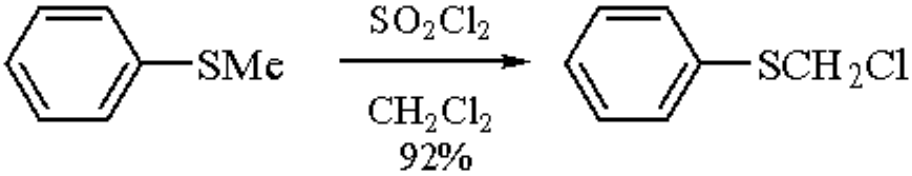

(14)

With α-methylthioalkyl ethers, the corresponding α-chloroalkyl ethers are obtained in high yields.[37] Similarly, α-chloroalkyl esters are obtained from α-phenylthioalkyl esters (eq 15).[38] Styrene is added to remove the benzenesulfenyl chloride that is also formed in the reaction.

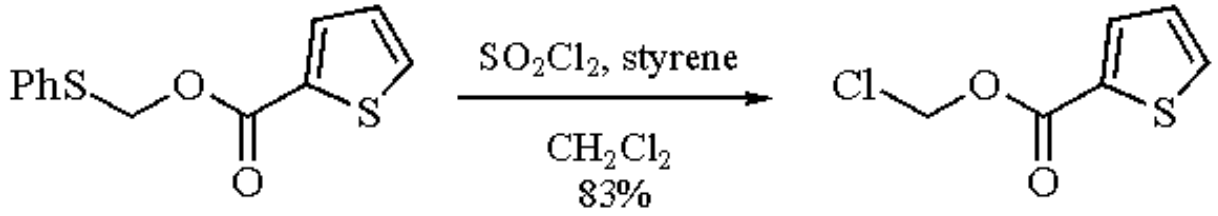

(15)

The facile α-chlorination of sulfides by sulfuryl chloride[39] has been used as a means of dehydrogenating 2,5-dihydrothiophenes.[40] This reaction is successfully employed in the commercial synthesis of the artificial sweetener thiophenesaccharin (eq 16).[41]

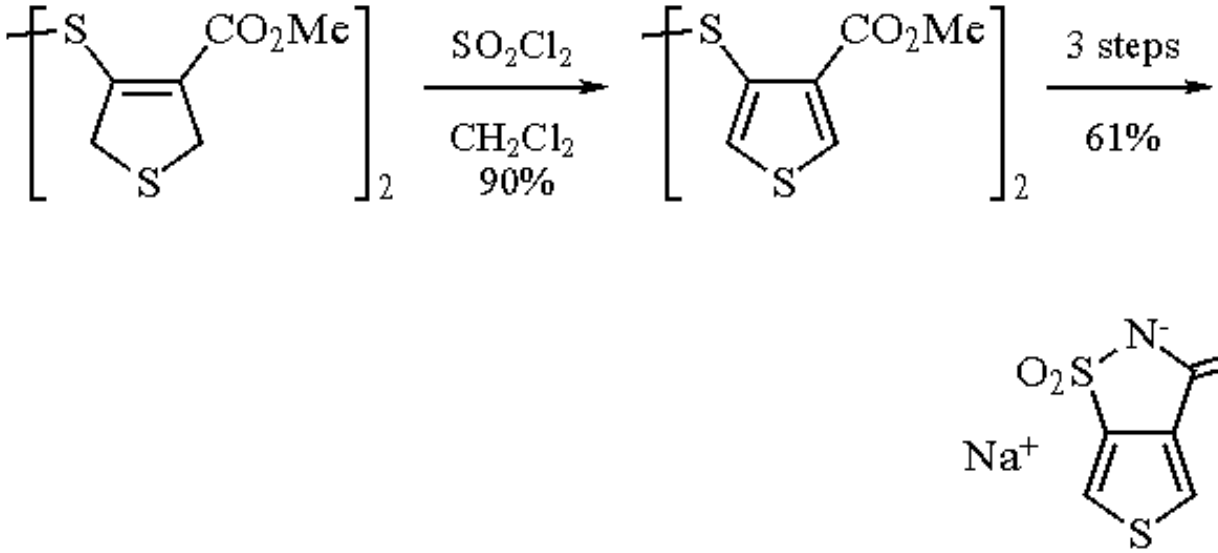

(16)

A reaction sequence involving α-chlorination of dibenzyl sulfides followed by a Ramberg-Bäcklund-like extrusion of sulfur produces diarylethylenes (eq 17).[42]

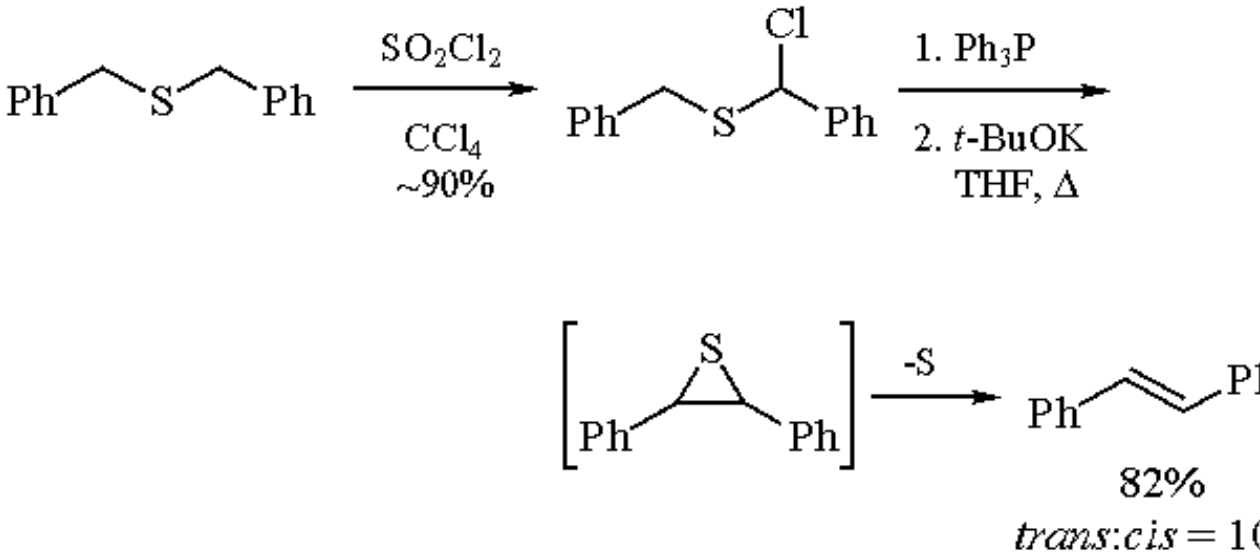

(17)

3-Phenylthio-2-azetidinones are converted to 3-chloro-3-phenylthio-2-azetidinones in 78-95% yield via a Pummerer-type mechanism. Hydrolysis by moist silica gel in the presence of catalytic ***Zinc Chloride*** provides the α-keto-β-lactams in 85-90% yield (eq 18).[43]

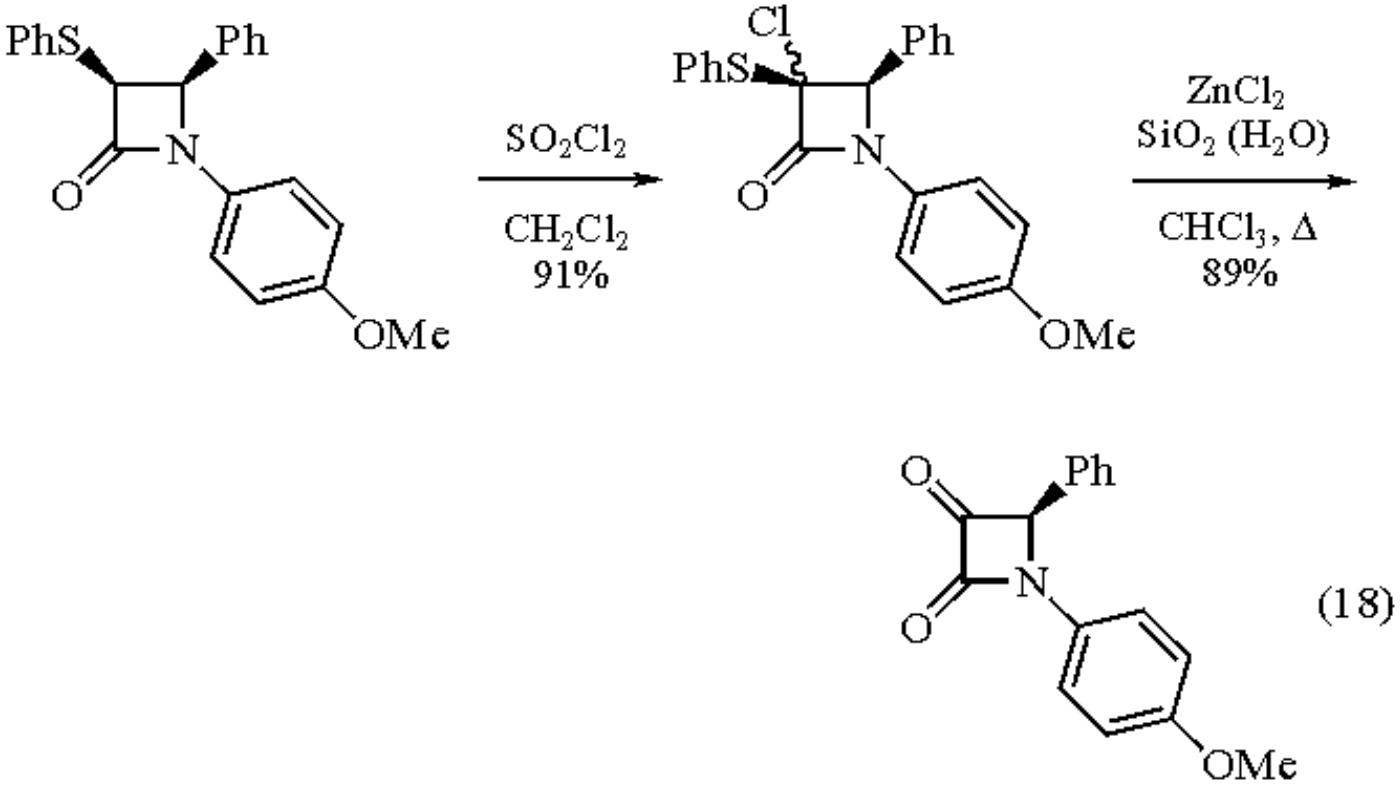

(18)

When alkyl sulfides are treated with sulfuryl chloride at -78 °C, the intermediate chlorosulfonium salts thought to be involved in formation of α-chloro sulfides can be hydrolyzed by treatment with ethanol at -70 °C and then at 25 °C to provide sulfoxides in high yield (eq 19).[44] Alternatively, the oxidation can be performed by dropwise addition of sulfuryl chloride to a stirred mixture of the sulfide and wet silica gel in dichloromethane.[45] The latter method has also been recommended as a convenient means of thioacetal oxidative cleavage, giving the carbonyl compounds in nearly quantitative yields.[46]

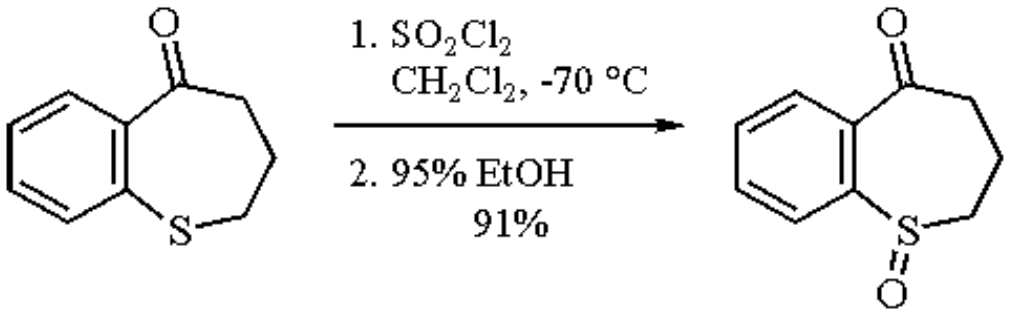

(19)

Reaction of benzyl thioethers with sulfuryl chloride can result in cleavage to form sulfenyl chlorides and benzyl chlorides. An example is Kharasch and Langford's preparation of 2,4-dinitrobenzenesulfenyl chloride (eq 20).[47]

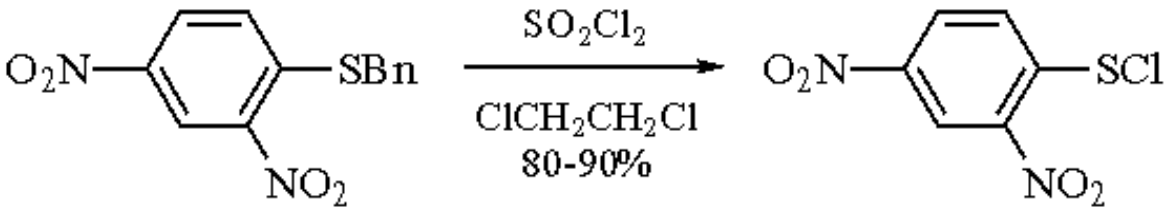

(20)

Reaction with Thiols, Disulfides, and Thioesters.

Sulfinyl chlorides can be conveniently prepared in high yield by the action of sulfuryl chloride in acetic acid on disulfides (eq 21)[48] or thiols[49] at low temperature. Similarly, thioesters are rapidly converted to sulfinyl chlorides in high yields by sulfuryl chloride in acetic anhydride at -10 °C.[50]

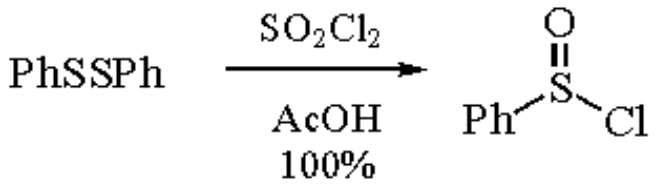

(21)

Similarly, sulfenyl chlorides can be prepared from disulfides in carbon tetrachloride[51] and from thiols in pentane by treatment with sulfuryl chloride[52] in the presence of ***Triethylamine***. The reaction of thioesters with sulfuryl chloride in carbon tetrachloride has been used in the synthesis of optically active sulfenyl chlorides (eq 22).[53]

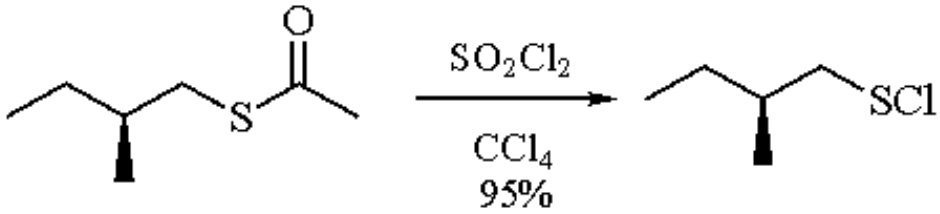

(22)

Chlorination of Sulfoxides.

Sulfoxides are rapidly α-monochlorinated by sulfuryl chloride at -78 to 0 °C in dichloromethane containing CaO.[54] Longer reaction times lead to α,α-dichlorination. Sulfoxides with two available sites of reaction undergo selective chlorination to form the more highly substituted chlorides. α-Chlorination of sulfoxides can also be effected using SO_2Cl_2/pyridine/CH_2Cl_2.[55]

α,β-Unsaturated Ester Synthesis.

β-Hydroxy sulfoxides react with sulfuryl chloride to form alkenes. This reaction has been used to synthesize α,β-unsaturated esters (eq 23).[56] The products obtained from aldehydes in this synthesis have the (*E*) configuration, whereas ethyl methyl ketone gives a 1:1 mixture of geometric isomers.

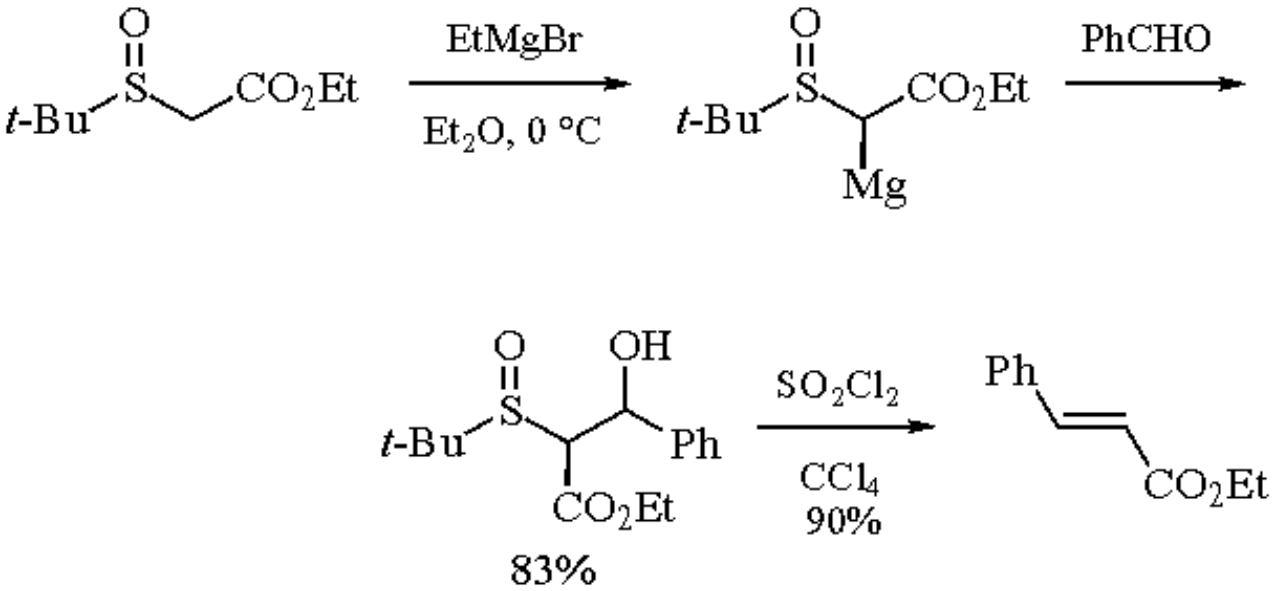

(23)

Chlorination of Sulfones.

Unlike the reaction with sulfides and sulfoxides, chlorination of sulfones using sulfuryl chloride is slow and occurs mostly at β-, γ-, and δ-positions. Sulfolane is quantitatively converted to β-chlorosulfolane (eq 24).[57]

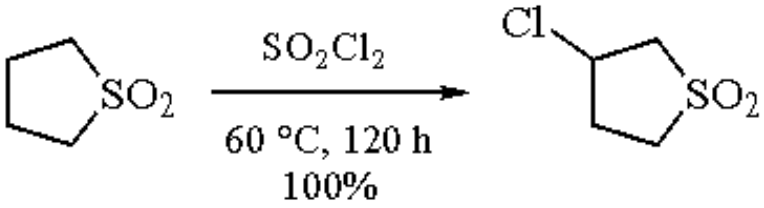

(24)

Synthesis of Sulfonyl Chlorides and Sulfamides.

Alkyllithiums react with sulfuryl chloride in pentane at -65 to -20 °C to give sulfonyl chlorides in moderate yields.[58] Aromatic sulfonyl chlorides can be prepared from aryllithiums by reaction with sulfur dioxide to form the sulfinate salts followed by oxidation with sulfuryl chloride (eq 25).[59]

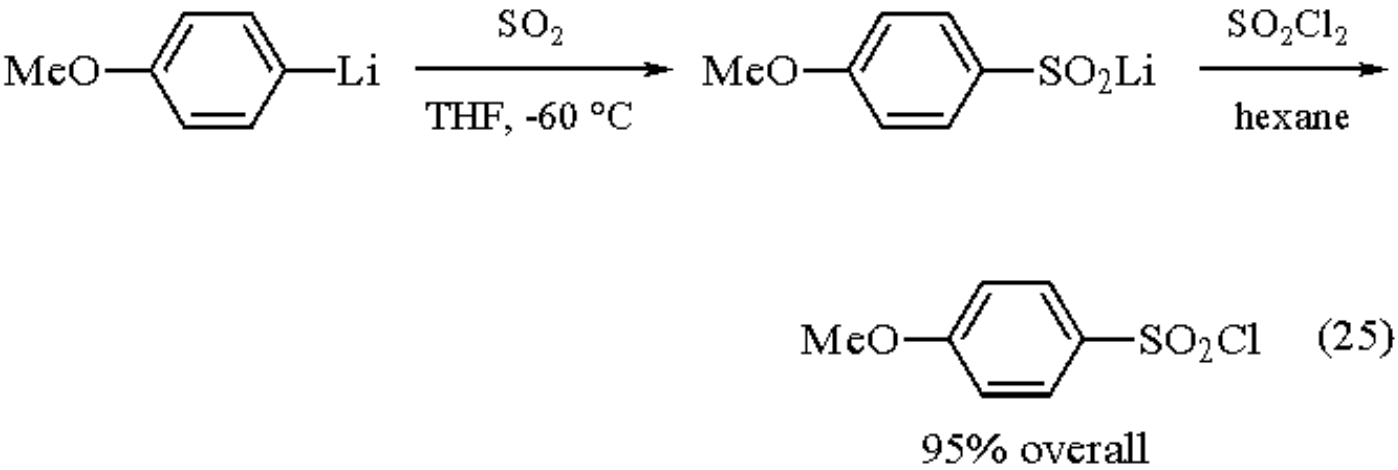

(25)

Sulfuryl chloride oxidizes thiols to sulfonyl chlorides in the presence of potassium nitrate or ***Silver(I) Nitrate*** in ***Acetonitrile*** at 0 °C (eq 26).[60] This transformation probably occurs via initial formation of the sulfenyl chloride followed by conversion to a sulfenyl nitrate and further oxidation.

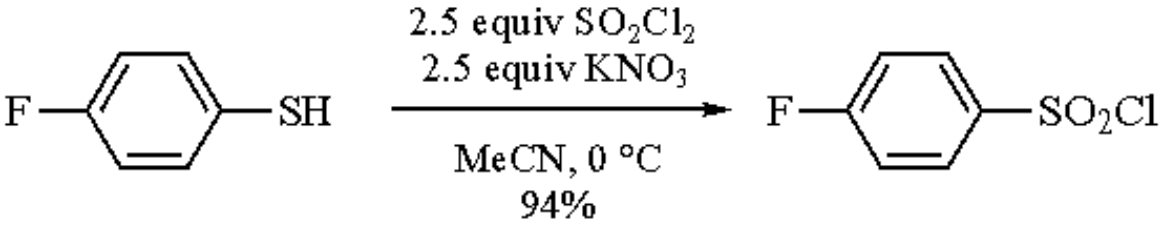

(26)

N-Monoalkyl amidosulfonyl chlorides are produced by the reaction of this reagent with primary amine hydrochlorides in refluxing acetonitrile with an appropriate Lewis acid (eq 27).[61]

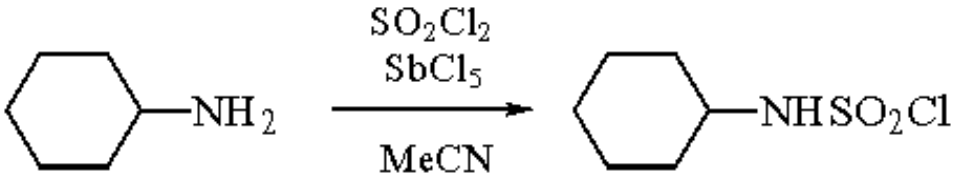

(27)

Treatment of alkylamines[62] or anilines[63] in pyridine with sulfonyl chloride results in formation of the corresponding sulfamides (eq 28).

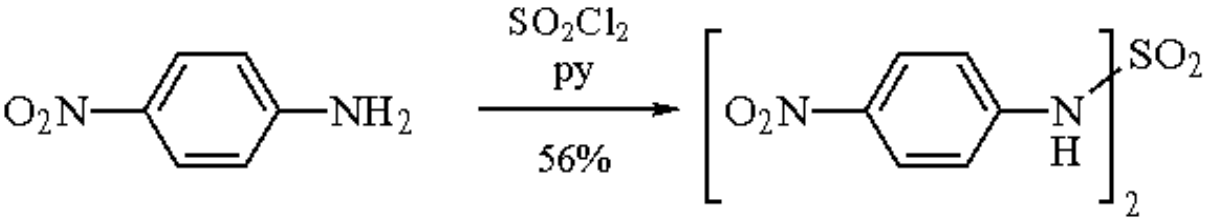

(28)

Synthesis of 2-Aminobenzothiazoles.

Phenylthioureas react with sulfuryl chloride to give 2-aminobenzothiazoles (eq 29).[64]

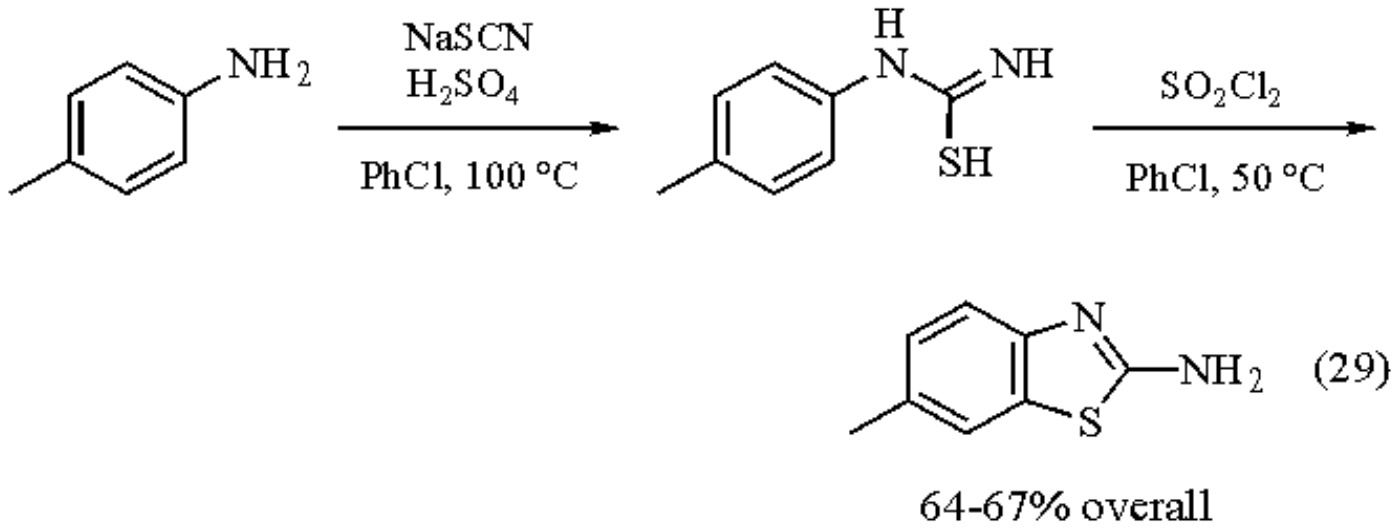

Other Transformations.

Sulfuryl chloride can be used to prepare *n*-butyl sulfate by heating the reagent with 2 equiv of *n*-butyl sulfite and removing the *n*-butyl chloride formed by distillation.[65]

Sulfuryl chloride oxidizes benzoin to benzil via a cyclic dienol ester that decomposes to extrude sulfur dioxide.[66]

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N,N´-Sulfuryldiimidazole[1]

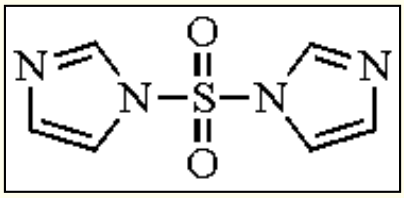

[7189-69-7] · $C_6H_6N_4O_2S$ · *N,N´*-Sulfuryldiimidazole · (MW 198.23)

(reagent for the generation of imidazolylsulfonates which function as leaving groups in S_N2 displacement reactions)

Physical Data: stable crystalline solid, mp 141 °C.

Preparative Method: can be prepared from the reaction of ***Imidazole*** and ***Sulfuryl Chloride*** in THF at ambient temperature.[2]

Purification: recrystallized from ethanol.

Amide Exchange.[3]

In general, tetrasubstituted sulfamides tend to be very unreactive. However, *N,N´*-sulfuryldiimidazole was demonstrated to undergo amide exchange with subsequent rearrangement (eq 1).

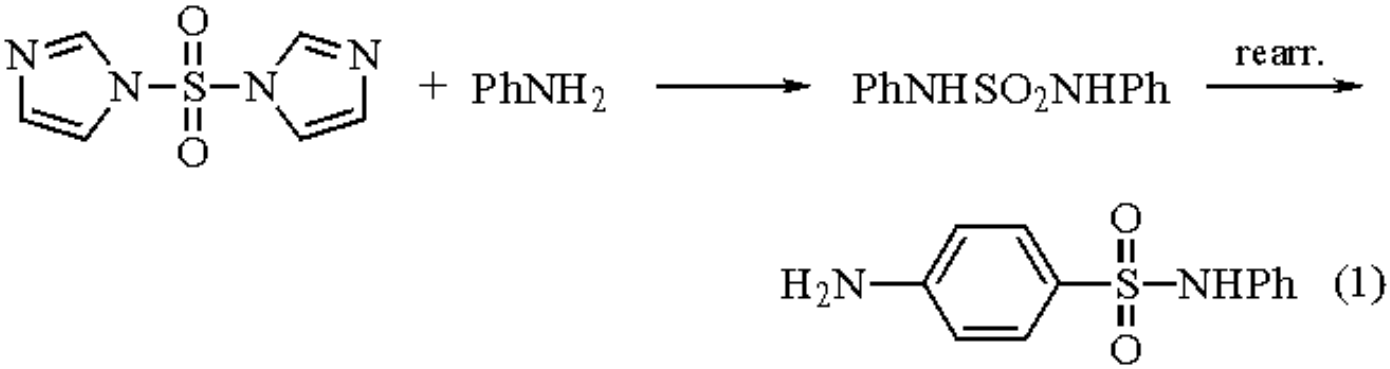

Nucleophilic Displacement Reactions.[4]

Primary and secondary alcohols can be converted to their imidazolylsulfonate esters via the reaction of the corresponding alkoxides (***Sodium Hydride***, ***N,N-Dimethylformamide***) with *N,N´*-sulfuryldiimidazole. Alternatively, the alkoxides were prepared from the action of ***Tetra-n-butylammonium Fluoride*** upon the corresponding trimethylsilyl ethers. Subsequent heating with the title compound in THF at reflux afforded the desired imidazylates. The primary imidazolylsulfonates reacted with azide, fluoride, and iodide at room temperature to provide the displacement products in high yield (eq 2).

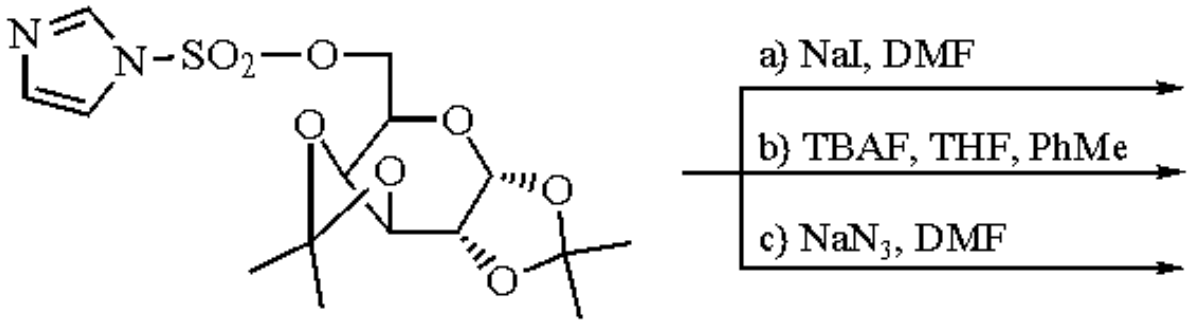

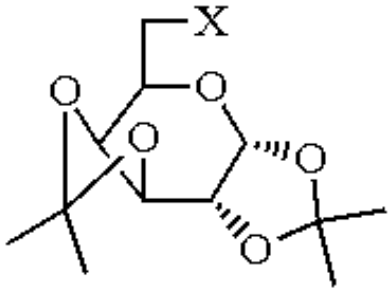

(2)

a) X = I, 81%
b) X = F, 75%
c) X = N_3, 81%

Nucleophilic displacements at the C-2 and C-3 positions of glucopyranosides proved to be equally facile when proceeding through the intermediacy of the imidazylates. Reactions at C-2 have previously been difficult or impossible to effect by other means (eqs 3 and 4).[5,6]

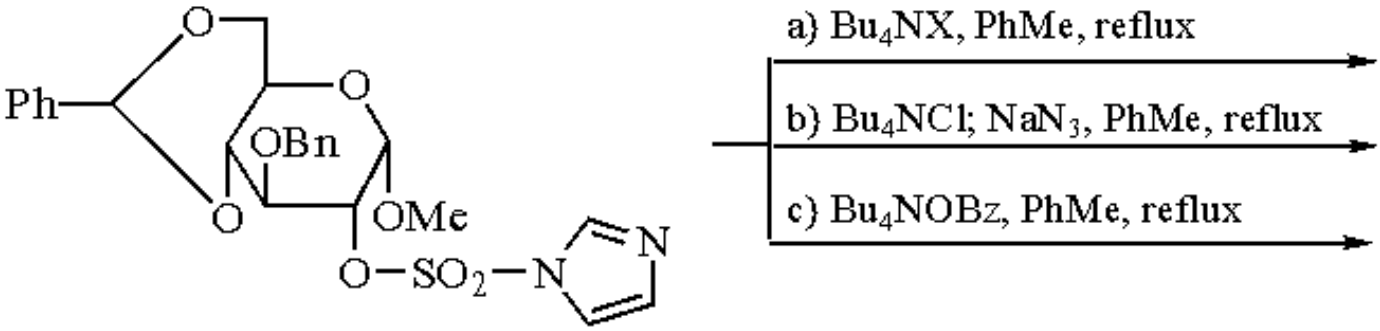

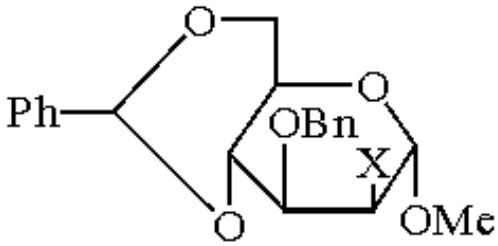

(3)

a) X = Cl, 78%; I, 82%
b) X = N_3, 89%
c) X = OBz, 85%

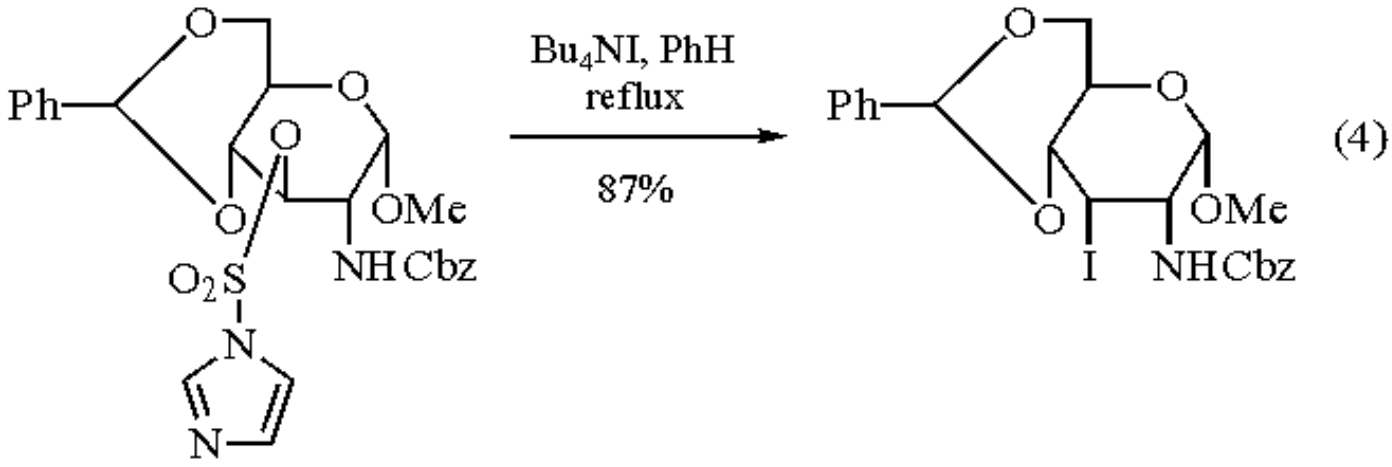

Subsequent reduction of the iodides with ***Tri-n-butylstannane*** and ***Azobisisobutyronitrile*** afforded the deoxyglycosides in good yields.

Cyclic Sulfates.[7]

Cyclic sulfate formation followed by treatment with fluoride ion and subsequent acid hydrolysis provided the fluorinated glucose derivative (eq 5).

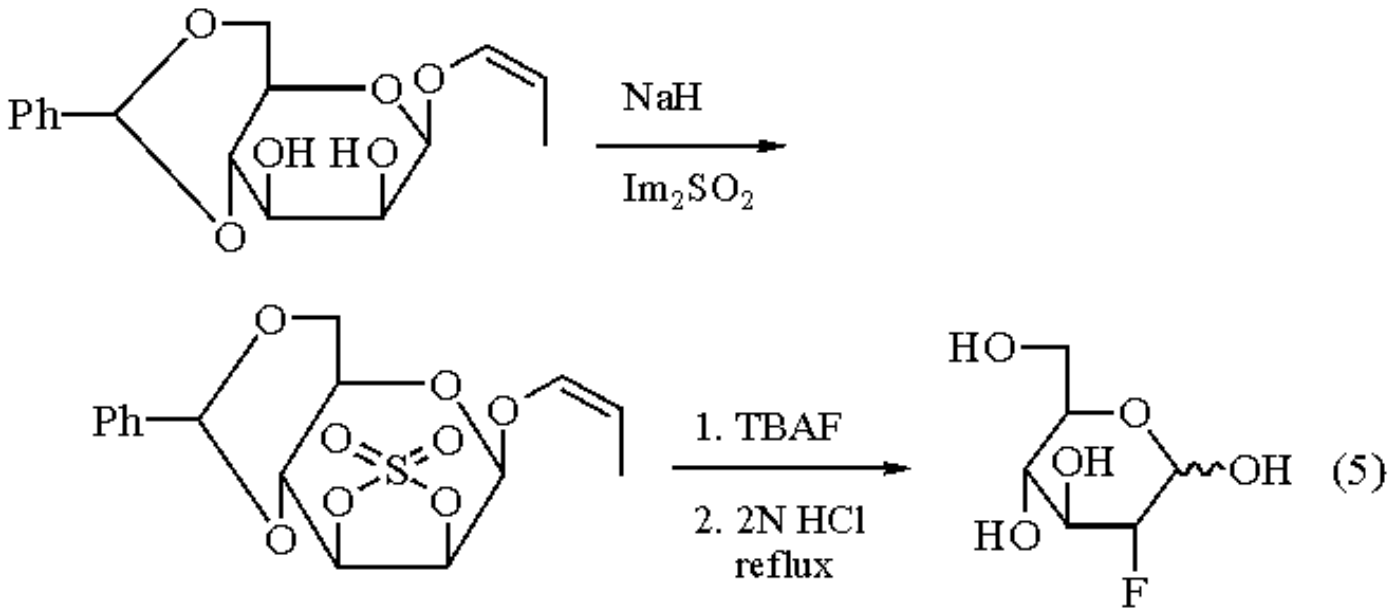

Eliminations.[4]

Alcohol-derived imidazolylsulfonates gave elimination products upon heating with ***Tetra-n-butylammonium Iodide*** in toluene at reflux (eq 6).

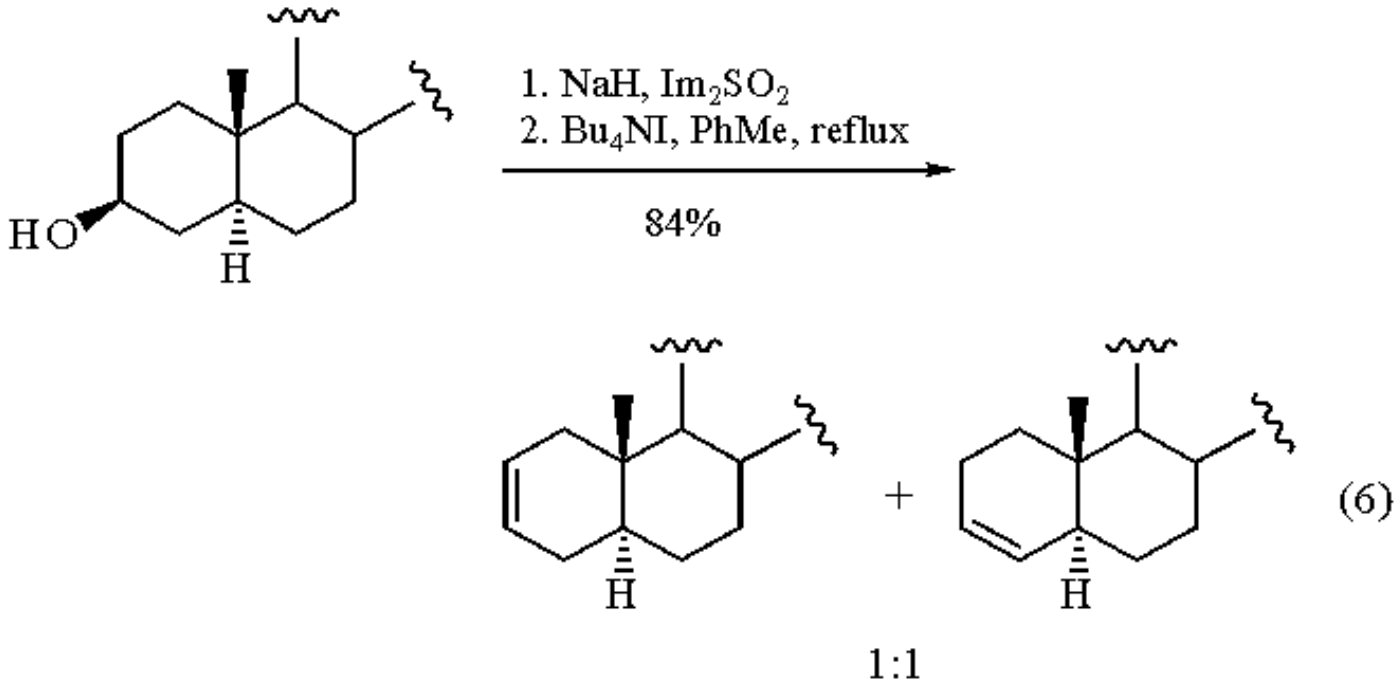

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Tellurium[1]

[13494-80-9] · Te · Tellurium · (MW 127.60)

(*N*-tosylimine synthesis;[5] catalyst for synthesis of alkenes,[6,7] ureas,[8] isothiocyanates,[9] and for reduction of various functional groups[3])

Physical Data: mp 449.8 °C; bp 1390 °C; *d* 6.25 g cm^{-3}.

Solubility: insol any solvent unless tellurium reacts with it.

Form Supplied in: powder, pieces, or ingot.

Preparative Methods: amorphous form of tellurium can be obtained by reduction of tellurous acid (H_2TeO_3) with ***Sulfur Dioxide*** or ***Hydrazine*** hydrate as brown to gray powder.

Handling, Storage, and Precautions: storage under inert atmosphere is recommended since tellurium is oxidized gradually in air at room temperature. Use in a fume hood.

Synthesis of Organotellurium Compounds.[1c,d,2]

Elemental tellurium reacts with organolithium, -sodium, and Grignard reagents to form RTeM (M = Li, Na, MgX) at room temperature. This reaction and reduction of tellurium to its dianion (see below) provide a convenient synthetic route to a variety of organotellurium compounds by combination with appropriate subsequent reactions, as exemplified in eq 1. Tellurium also directly reacts with some organic halides to give diorganyltellurium dihalides, but the synthetic utility of this reaction is limited to the use of alkyl iodides or to the formation of cyclic tellurides from dihaloalkanes.

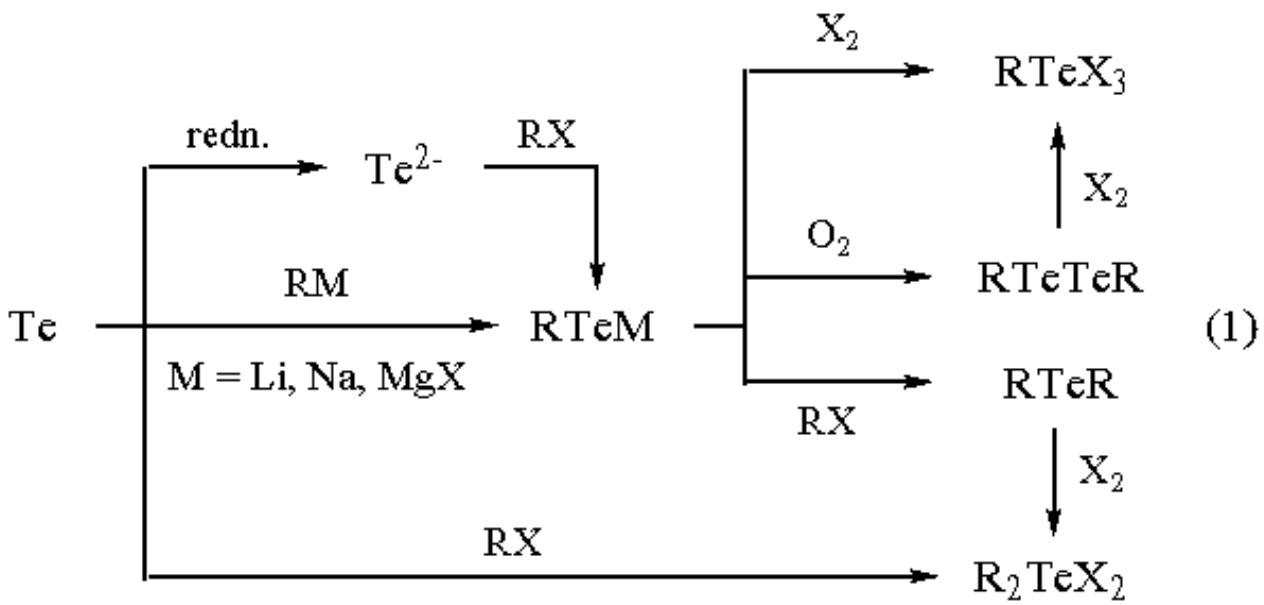

Selective Reduction.[2,3]

Among several methods which have been developed for the reduction of elemental tellurium to its dianion species, synthetically the most convenient are ***Sodium Borohydride*** in EtOH,[2a] ***Lithium Triethylborohydride*** in THF,[2b] rongalite-C (***Sodium***

Hydroxymethanesulfinate) in H_2O,[2c] ***Sodium Hydride*** in DMF[2d] or NMP.[2e] Salts of hydrogen telluride which can be formed (frequently referred to as M_2Te or MTeH where M = Li or Na, see ***Hydrogen Telluride*** and ***Sodium Telluride***) reduce aromatic aldehydes, C-C double bonds conjugated with carbonyl or aryl groups, imines and iminium salts, enamines, thiocarbonyls, epoxides, and a variety of nitrogen-containing functional groups.[3] They also facilitate dehalogenation, desulfurization, desulfonylation, dealkylation or deacylation of carboxylates, deallylation of allylic ethers, etc. Metallic tellurium also reacts with sodium diethyl phosphite in EtOH or THF to give ***Sodium O,O-Diethyl Phosphorotelluroate***, which acts as a reducing agent in a similar manner.[4] These tellurium reagents regenerate elemental tellurium after the reaction, and some reductions have been performed successfully by the use of a catalytic amount of tellurium.

Synthesis of *N*-Tosylimines.[5]

N-Tosylimines have been prepared in excellent yields from aldehydes, ***Chloramine-T***, and 0.5 mol equiv of tellurium (eq 2). This reaction is proposed to involve [2 + 2] cycloaddition of an aldehyde with *N,N´*-ditosyltellurodiimide generated in situ and subsequent cycloreversion.

$$\mathrm{RCHO} + \mathrm{TsN(Cl)Na} \xrightarrow[\text{84-100\%}]{\text{Te, toluene, reflux}} \mathrm{RCH{=}NTs} \qquad (2)$$

Alkene Synthesis by Tellurium-Catalyzed Homocoupling.

Wittig reagents[6] and benzenesulfonylbenzyllithiums[7] undergo homocoupling to yield alkenes in the presence of a catalytic amount of tellurium (eqs 3 and 4). The intermediacy of tellurocarbonyl compounds in the former case was evidenced by the successful trapping with dienes to give telluracyclohexenes.

$$\mathrm{Ph_3P{=}CHPh} \xrightarrow[\text{61\%}]{\text{Te (10 mol\%), toluene, 100 °C, 6 h}} \textit{trans}\text{-PhCH=CHPh} \qquad (3)$$

$$(\mathrm{PhSO_2})\mathrm{PhCHLi} \xrightarrow[\text{90\%}]{\text{Te (ca. 20 mol\%), THF, 25 °C, 3 h}} \underset{(E):(Z) = 80:20}{\mathrm{PhCH{=}CHPh}} \qquad (4)$$

Urea Synthesis by Tellurium-Catalyzed Carbonylation of Amines.[8]

Primary amines are carbonylated with ***Carbon Monoxide*** using tellurium as catalyst to give an equimolar amount of the urea and hydrogen along with formamides (eq 5). Addition of nitrobenzene in the reaction media affords aniline and suppresses the generation of hydrogen and formamides.

$$\underset{\text{100 mmol}}{\mathrm{BuNH_2}} + \underset{\text{30 kg cm}^{-2}}{\mathrm{CO}} \xrightarrow[\text{140 °C, 72 h}]{\text{Te (1 mmol)}} \underset{\text{22.0 mmol}}{\mathrm{(BuNH)_2CO}} + \underset{\text{21.0 mmol}}{\mathrm{H_2}} + \underset{\text{51.8 mmol}}{\mathrm{BuNHCHO}} \qquad (5)$$

Tellurium-Catalyzed Isothiocyanate Synthesis.[9]

Tellurium, like ***Selenium***, catalyzes the synthesis of isothiocyanates from isocyanides and ***Sulfur*** in the presence of a tertiary amine such as ***Triethylamine***, but much more efficiently (eq 6). This reaction is proposed to proceed via isotellurocyanate intermediates.

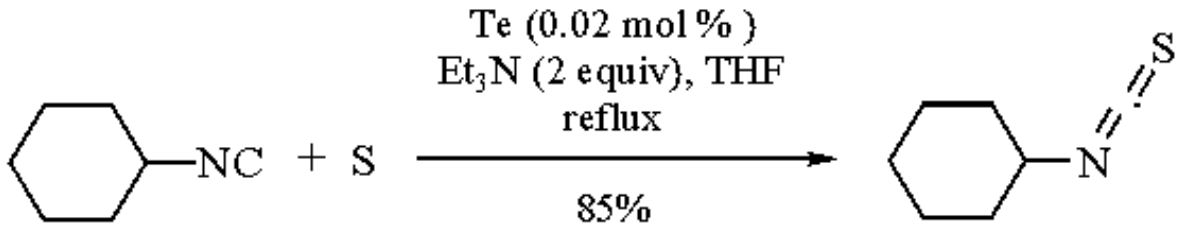

(6)

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Tellurium(IV) Chloride[1]

$TeCl_4$

[65829-99-4] · Cl_4Te · Tellurium(IV) Chloride · (MW 269.40)

(for carbon-carbon bond-forming reactions and functional group manipulation via telluration; Lewis acid for thioacetalization/deacetalization and rearrangements; chlorinating agent)

Physical Data: mp 224 °C; bp 390 °C/755 mmHg; *d* 3.01 g cm^{-3}.

Solubility: insol cyclohexane, hexanes, methylene chloride, chloroform; sol acetonitrile, DMSO, DMF; slightly sol ether, benzene.

Form Supplied in: pale yellow solid; widely available.

Purification: distillation, or, more conveniently, sublimation (200 °C/0.1 mmHg).

Handling, Storage, and Precautions: readily hydrolyzed by water and must be handled and stored in the absence of moisture. The toxicity of tellurium and organotellurium compounds is little investigated. Use in a fume hood.

Carbon-Carbon Bond-Forming Reactions.

Many aromatic compounds undergo electrophilic aromatic substitution with $TeCl_4$ to yield aryltellurium trichlorides and diaryltellurium dichlorides.[2] These compounds can be converted into symmetrical biaryls by treatment with degassed ***Raney Nickel*** in high-boiling ether solvents (eq 1).[3,4] On treatment with ***Tetracarbonylnickel***[5] or ***Carbon Monoxide*** in the presence of a palladium(II) salt,[6] the organotellurium compounds are carbonylated to give benzoic acid derivatives. When $TeCl_4$ is allowed to react with four equiv of 1-alkynyllithium reagents, 1,3-diynes are formed,[7] probably via reductive coupling[8] from intermediate tetrakis(1-alkynyl)tellurium species.

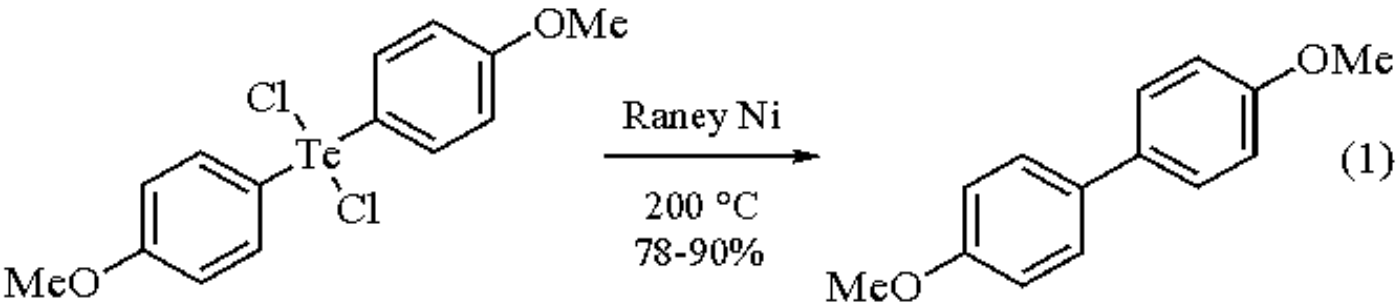

(1)

Functional Group Manipulations.

Tellurium(IV) chloride readily adds to a variety of alkenic substrates to produce β-chloroalkyltellurium trichlorides. In the presence of a radical scavenger, the addition is highly *syn* specific.[9] The *anti* specific ***Sodium Sulfide***-induced elimination of tellurium from this compound has been used for the mild inversion of alkenes (eq 2). $TeCl_4$ undergoes a diastereospecific 1,3-addition to α-substituted allylic esters with 1,2-migration of the acyloxy group.[10] After hydrodetelluration (Raney Ni) and alkaline hydrolysis/ring closure of the resulting chlorohydrin ester, epoxides are formed (eq 3).

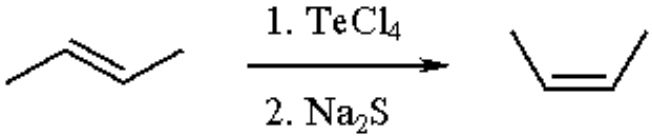

(2)

(Z):(E) = 97:3

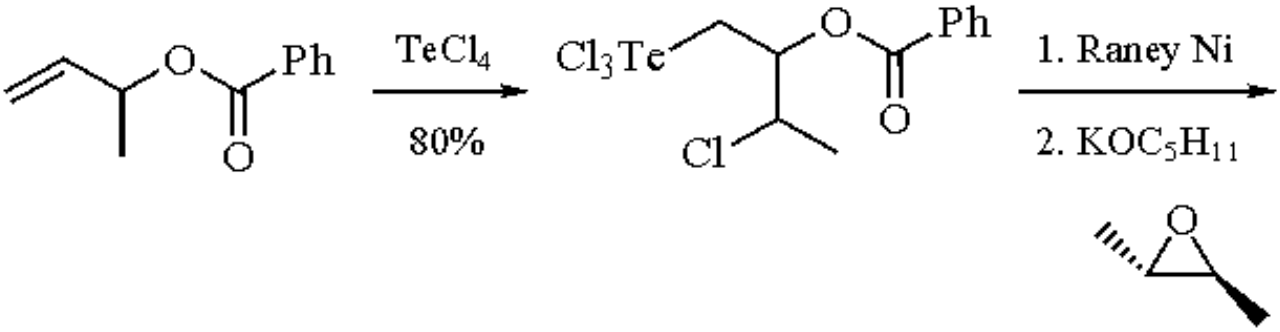

(3)

The reaction of alkenes with $TeCl_4$ and lithium acetate in acetic acid at 120 °C affords products of *syn* diacetoxylation of the double bond.[11] This reaction probably proceeds via *anti* acetoxytellurination followed by acetate-induced cleavage of the C-Te bond with inversion of configuration. The replacement of an alkyl-, alkenyl- or aryl-bound $TeCl_3$ group by chlorine can be induced by heat, light, or oxidation to give *cis*-1,2-dichloroalkanes, *cis*-1,2-dichloroalkenes, and aryl chlorides, respectively.[12]

Lewis Acid Properties.

Aldehydes and ketones react with alkanethiols in the presence of a catalytic amount of $TeCl_4$ to form dithioacetals in good yields. In the presence of a stoichiometric amount of the tellurium reagent, dithioacetals and acetals are easily cleaved by the reagent to regenerate the carbonyl compounds (eq 4).[13,14]

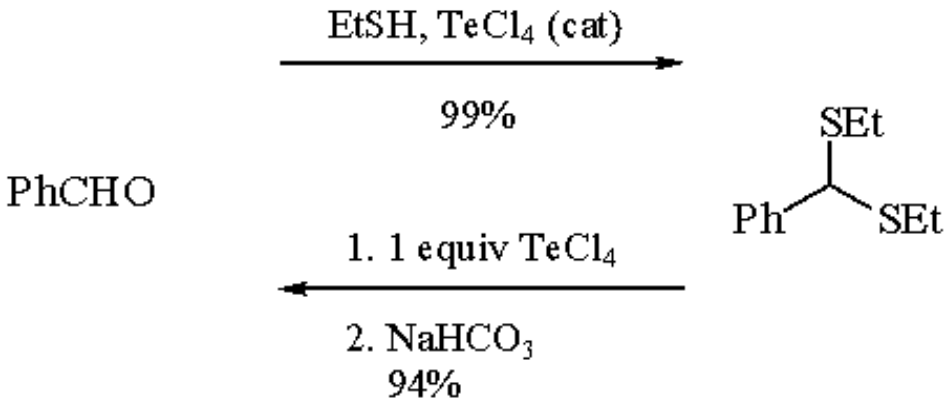

(4)

When the deprotection procedure is applied to five-membered cyclic thioacetals, a facile ring enlargement takes place to give a dihydro-1,4-dithiin.[15] $TeCl_4$ catalyzes the oligomerization of phenylethylenes and benzyl chlorides.[16] Cycloheptatrienes undergo rearrangement with chlorination to give benzyl chlorides in the presence of $TeCl_4$.[17] Alcohols are converted to the corresponding alkyl chlorides when treated with $TeCl_4$ in nonpolar solvents. In aromatic solvents, the tellurium compound acts as a Friedel-Crafts catalyst to give alkylbenzene derivatives.[18] When treated with $TeCl_4$, silyloxycyclopropanes afford β-oxyalkyltellurium trichlorides in high yields.[19] On treatment with ***Dimethyl Sulfoxide*** or amine bases, dehydrotelluration occurs to give α-methylene ketones (eq 5).

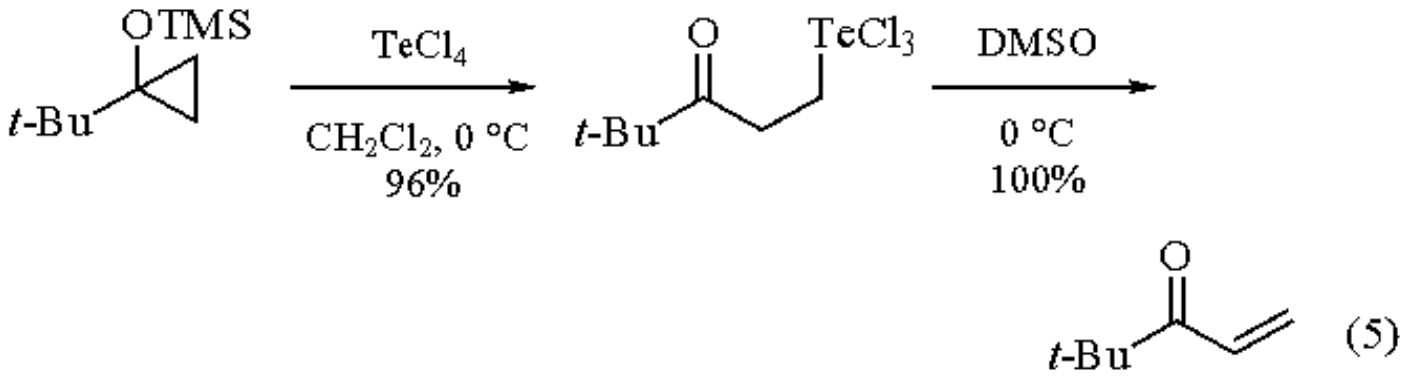

Chlorinating Agent.

Unsaturated or halogenated cyclic or polycyclic hydrocarbons are readily aromatized when heated with $TeCl_4$ at elevated temperature (ca. 80 °C).[20] Chlorinated intermediates were proposed in the reaction. Aromatic compounds are chlorinated by $TeCl_4$[21] and β-ketonitroalkanes are both chlorinated and partly deoxygenated to give α-(hydroxyimino)-α-chloro ketones. The nitriloxides resulting from the latter compounds react with stilbenes to form isoxazolines.[22] It has been reported that the formation of oxamide derivatives, RNHC(O)C(O)NHR, from isocyanides, RNC, in the presence of $TeCl_4$ involves initial insertion of the isocyanide into the Te-Cl bond.[23]

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Tetraacetyl Diborate[1]

$(AcO)_2BOB(OAc)_2$

[5187-37-1] · $C_8H_{12}B_2O_9$ · Tetraacetyl Diborate · (MW 273.82) ($B(OAc)_3$)

[4887-24-5]

(selective acetylating agent for aromatic polyhydroxycarbonyl compounds;[1-3] mild Lewis acid for Diels-Alder reactions of hydroxyquinones[4])

Alternate Names: TADB; boron triacetate; boroacetic anhydride; pyroboroacetate; oxybis(diacetoxyborane).

Physical Data: mp 150-152 °C (sealed tube),[3] 146-147 °C.[5]

Solubility: nearly insol petroleum ether, CCl_4, CS_2, Et_2O; especially sol dry warm benzene, EtOAc, ethylene bromide, and nitrobenzene (can be recrystallized from these solvents).[3]

Preparative Methods: a mixture of 31 g (0.50 mol) of ***Boric Acid*** and 165 mL (1.75 mol) of ***Acetic Anhydride*** is heated slowly with an oil bath under N_2 in a flask equipped with a reflux condenser and a magnetic stirrer. At about 70 °C a vigorous exotherm (CAUTION) occurs and the reaction mixture becomes a clear solution which, upon cooling, deposits crystals of TADB. The supernatant is drawn off and the crystals either washed with dry ether or recrystallized from 200 mL $CHCl_3$/benzene.[5]

Handling, Storage, and Precautions: moisture sensitive.

Structure.

There is some controversy[1,6] whether the mixed anhydride of boric and acetic acid has the structure $(AcO)_2BOB(OAc)_2$ (TADB) or $B(OAc)_3$. The material normally obtained from the reaction of boric acid (H_3BO_3) and acetic anhydride is $(AcO)_2BOB(OAc)_2$, at least in the crystalline state (mp ~150-152 °C).[5,6] Even when prepared under conditions (BH_3 + 3 HOAc) that might be expected to give $B(OAc)_3$,[5,7] the crystalline material isolated is TADB.[5] There is an early report[8] of the preparation of $B(OAc)_3$, mp 121 °C, from boric anhydride (B_2O_3) and Ac_2O. Since TADB is normally employed in excess, the constitution in solution (and the exact molecular weight) is somewhat immaterial to its use.

Selective Acetylation.

The use of TADB/acetic anhydride to acetylate selected hydroxy groups of polyhydroxyquinones was introduced by Dimroth.[2,3] Thus treatment of alizarin (**1**) with a hot mixture of TADB and Ac_2O gives, after workup with cold water, monoacetate (**2**).[2] The reaction proceeds by way of boroacetate complex (**3**), which after acetylation to (**4**) is hydrolyzed to (**2**). Selective preparation of (**6**) from purpurin (**5**) was achieved analogously.[2] If a carbonyl is flanked by two *peri* hydroxyls, only one is protected from acetylation.[2] Thus treatment of (**7**) with TADB/Ac_2O affords (**8**) after hydrolytic workup.[2] Selective monoacetylation of xanthone (**9**) to (**10**) was accomplished similarly.[9] That the product from eq 1 forms a boroacetate derivative was taken as conclusive proof that it possesses structure (**11**) rather than (**12**).[10] In the absence of a flanking carbonyl, a phenol group is not protected from acetylation: reaction of (**13**) with TADB/Ac_2O gives diacetate (**14**).[3] Other compounds or functional group combinations that give boroacetate complexes include salicyclic acid, 8-hydroxyquinoline, *peri*-aminoquinones, and *o*-hydroxyaryl ketones.[1,3]

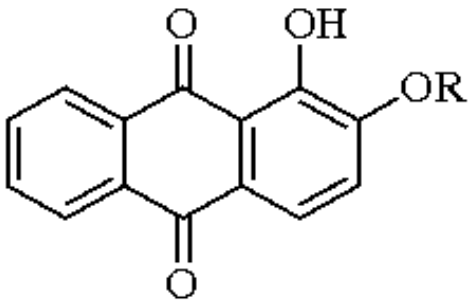

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(2) R = Ac

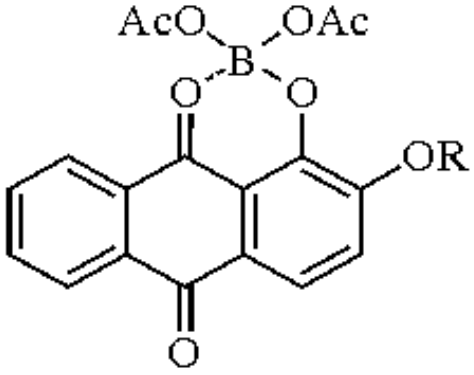

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(4) R = Ac

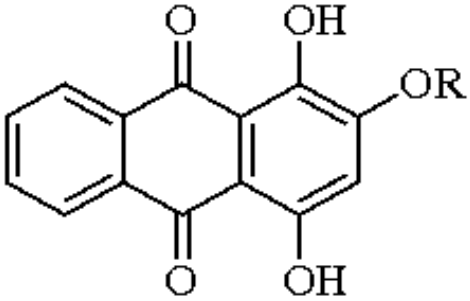

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(6) R = AC

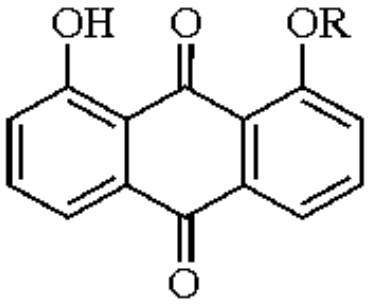

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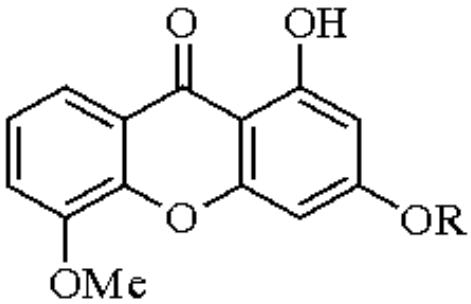

(9) R = H
(10) R = Ac

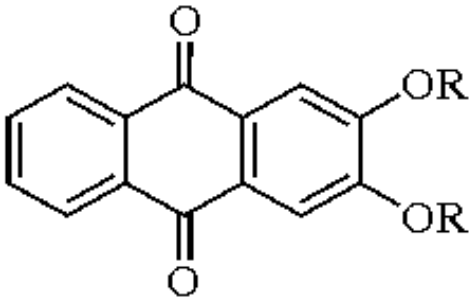

(13) R = H
(14) R = Ac

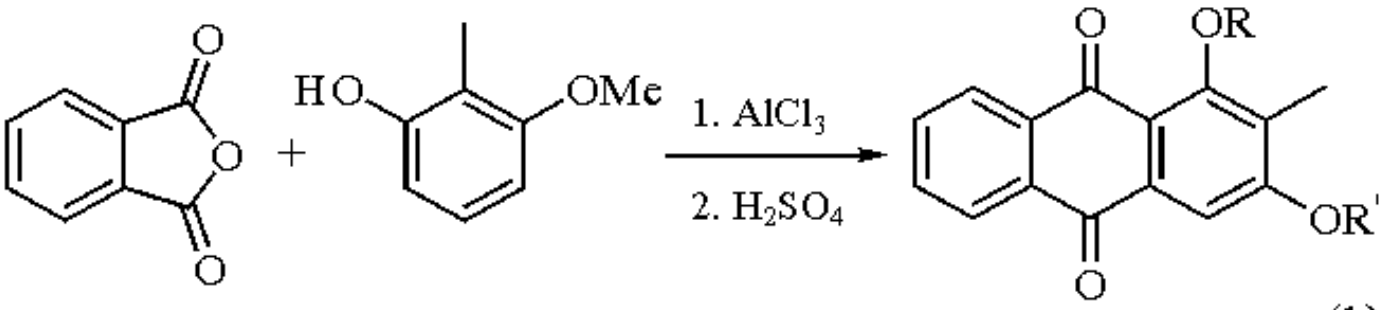

(1)

(11) R = H, R' = Me
(12) R = Me, R' = H

Diels-Alder Reaction Catalysis.

TADB has seen considerable recent use as a catalyst in the Diels-Alder reactions of *peri*-hydroxylated quinones.[4] In addition to usually accelerating[4,11,12] the rate of reaction, it has been employed to advantage to enhance regioselectivity. Thus in the absence of catalyst, (**15**) reacts with (**17**) to give a 45:55 ratio of (**18**) to (**19**).[4] When (**15**) and (**17**) react in the presence of 2 equiv of TADB (via **20**), the ratio of (**18**) to (**19**) is >19:1.[4] In general, with TADB the carbonyl *peri* to the hydroxyl becomes the regiochemical director. Regiochemical control is best achieved with highly polarized dienes;[4] however, in some[11,12] (but not all)[4] cases even ***Isoprene*** reacts with considerable regioselectivity. A frontier molecular orbital explanation for the regiochemical outcome induced by TADB has been advanced.[13] It is to be noted that other Lewis acids can sometimes give a reversal of regiochemistry:[4,11,12] in the absence of catalyst, (**16**) and (**17**) react to give a 40:60 ratio of (**21**) and (**22**), but with 0.5 equiv of ***Magnesium Iodide*** the ratio is 1:>19.[4]

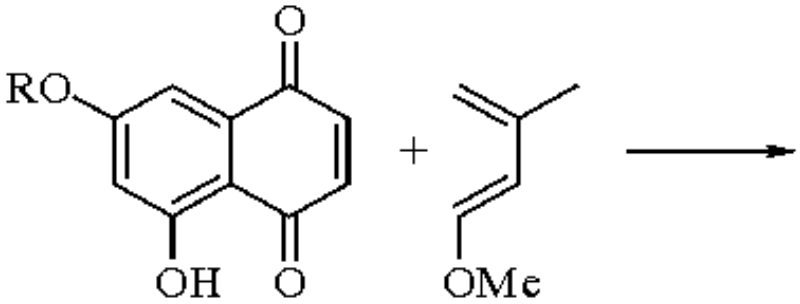

(15) R = H
(16) R = Me

(17)

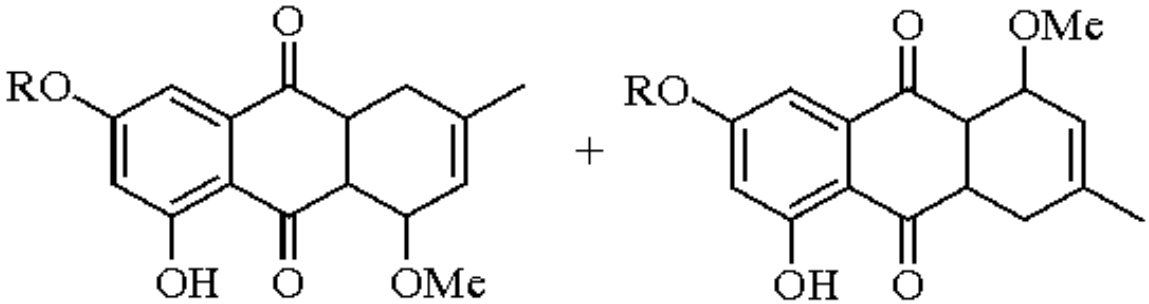

(2)

(18) R = H
(21) R = Me

(19) R = H
(22) R = Me

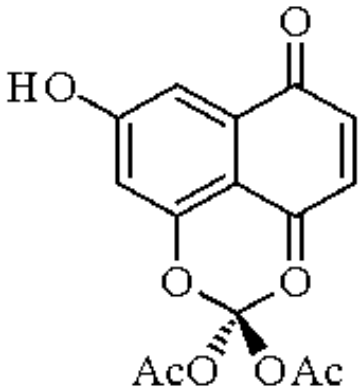

(20)

One of the other virtues of TADB is its relatively noncorrosive nature which, for example, renders it compatible with dienes destroyed by Lewis acids such as ***Boron Trifluoride Etherate***.[4,11] Regiospecific TADB-catalyzed Diels-Alder reactions have been featured in the syntheses of (±)-bostrycin (**23**)[14] (this paper contains experimental details), (±)-altersolanol B (**24**),[15] (±)-ochromycinone (**25**),[16] and (±)-epirubigenone B1 (**26**).[17]

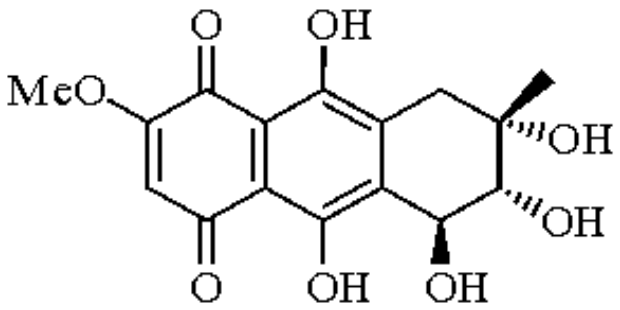

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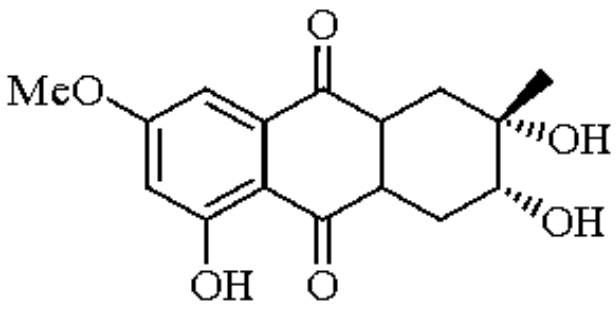

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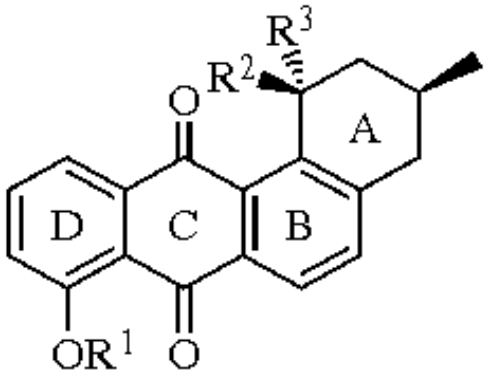

(25) $R^1 = H$, $R^2 = R^3 = O$

(26) $R^1 = Me$, $R^2 = H$, $R^3 = OH$

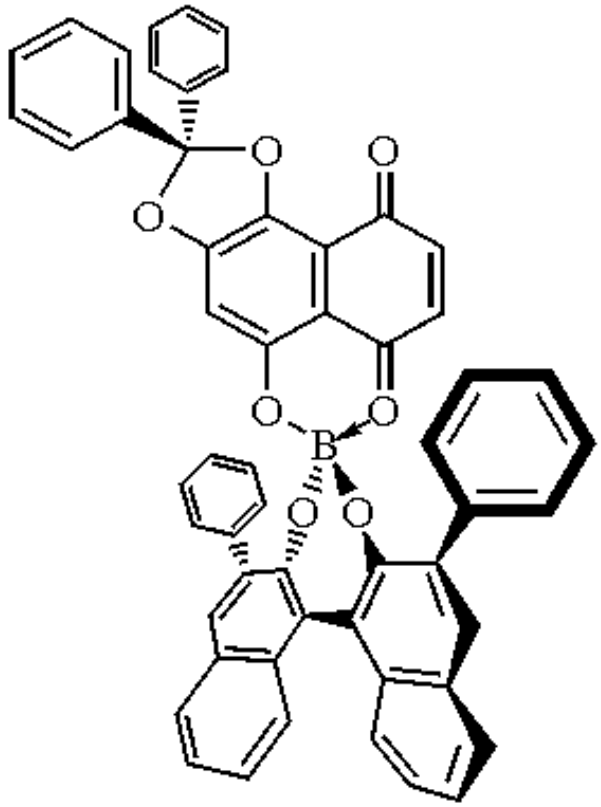

(30)

In the presence of TADB the Diels-Alder reaction between (**27**) and (**28**) proceeds with complete (&egt;98%) facial (and regio-) selectivity (eq 3).[18] Chiral analogs[19,20] (e.g. **30**[19]) of the borate complexes have been used for asymmetric Diels-Alder reactions, including one in an enantioselective synthesis of (-)-bostrycin (**23**).[19] Quinizarin (**31**) does not exhibit any tendency to undergo a Diels-Alder reaction by way of its putative tautomer (**32**) (eq 4),[21] but in the presence of TADB cycloaddition occurs.[22] 1,4-Diaminoanthraquinone behaves similarly.[22] The boroacetate complex of (**32**) also acts as a dipolarophile.[23]

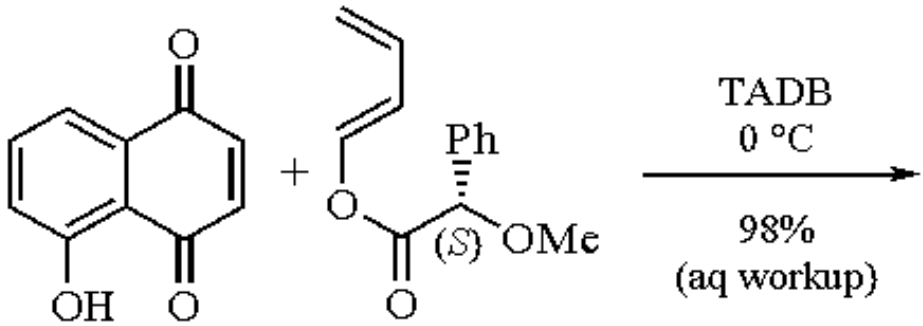

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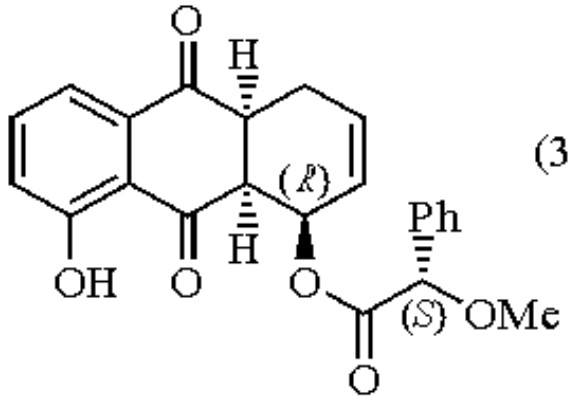

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(29)

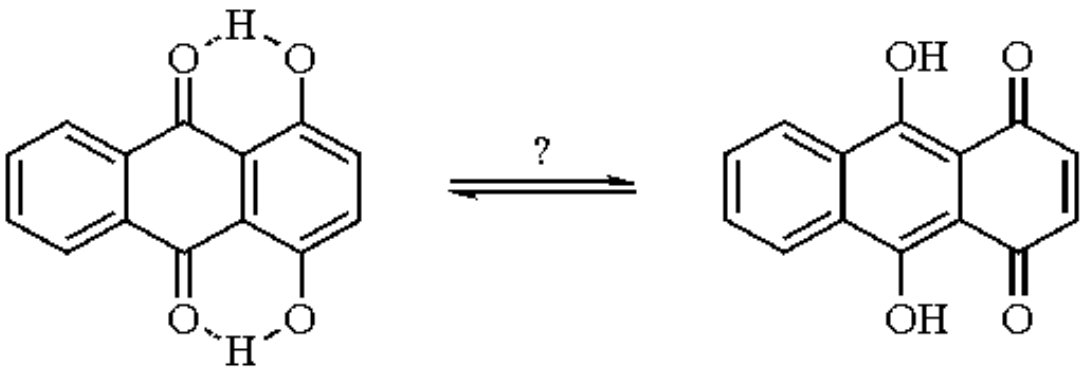

(4)

(31) (32)

Miscellaneous.

TADB has been used for the selective cleavage of cyclic ethers, e.g. (**33**) -> (**34**) (eq 5).[7] In the synthesis of (**26**), TADB was enlisted to aromatize the B ring in (**35**) when acidic and basic treatment gave (**36**).[17]

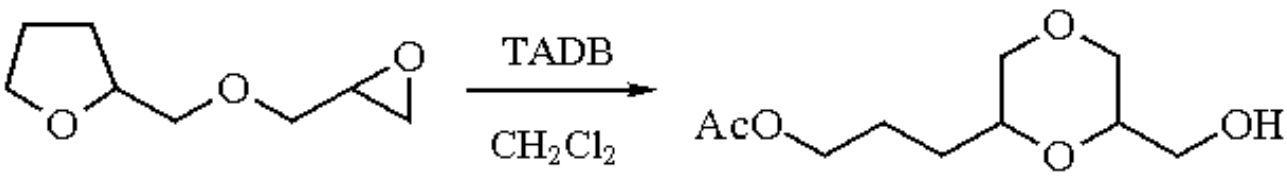

(5)

(33) (34)

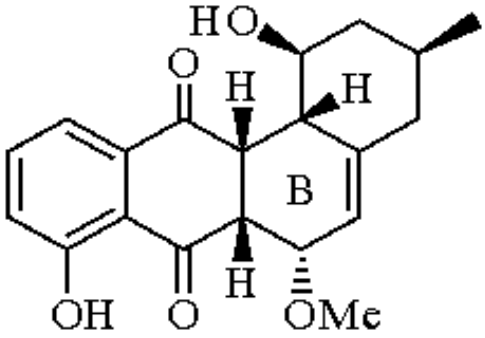

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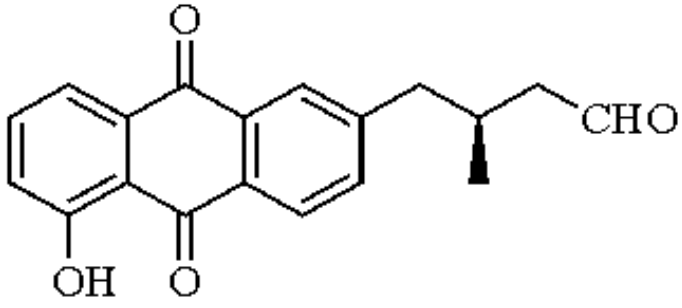

(36)

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Tetraallylstannane[1]

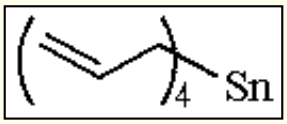

[7393-43-3] · $C_{12}H_{20}Sn$ · Tetraallylstannane · (MW 283.03)

(allyllithium precursor;[2] allyl nucleophile for allyl transfer reactions[3] and Stille coupling[4])

Alternate Name: tetraallyltin.

Physical Data: bp 69-70 °C/1.5 mmHg, 87-88 °C/4 mmHg; *d* 1.179 g cm^{-3}.

Solubility: sol common organic solvents; insol H_2O.

Form Supplied in: widely available as a neat liquid. Major impurities are tin chlorides.

Preparative Methods: synthesized by the reaction of ***Allylmagnesium Bromide*** with ***Tin(IV) Chloride*** in THF.[5]

Analysis of Reagent Purity: shows one spot in the TLC (hexane) and one peak in the GC. ^1H NMR (C_6D_6) can also be informative.

Purification: pure tetraallyltin is a colorless oil. Commercial tetraallyltin is typically obtained as a slightly yellow oil and used without further purification. Large quantities are purified by fractional distillation. Smaller amounts may be filtered through a plug of silica.

Handling, Storage, and Precautions: is an air and water stable oil. No unusual storage precautions are required. Organostannanes are toxic and should only be used in a well ventilated hood. All glassware should be rinsed in a KOH/EtOH bath during cleaning.

Allyllithium.

Allyllithium is formed from transmetalation of tetraallyltin with alkyllithiums. Treatment of a hexane or pentane solution of tetraallyltin with 2.0 equiv of ***n-Butyllithium*** initiates an exchange reaction which is driven by the precipitation of solid allyllithium.[2,6] Removal of solvent by syringe or filtration, followed by washing the allyllithium and dissolution in Et_2O, affords a solution of allyllithium which is stable for long periods if stored under an inert atmosphere. An excess of tetraallyltin is employed because transmetalation is an equilibrium reaction which will not proceed to completion.[2] Ethereal allyllithium solutions are stable for several months at 0 °C. Because of the need to filter solid allyllithium, this approach has been used only sparingly.

Formation of solid allyllithium can be avoided by treatment of an Et_2O solution of tetraallyltin with 4 equiv of ***Phenyllithium***.[2] Removal of tetraphenyltin by filtration (filtration is optional) affords a solution of allyllithium, which also contains LiBr from the PhLi preparation and trace levels of Ph_4Sn (Ph_4Sn is soluble in Et_2O at 0.0010 g mL^{-1} at 20 °C). Allyllithium generated in this manner undergoes conjugate addition with vinyl sulfones in the presence of ***Potassium t-Butoxide*** to give the β-allyl sulfone (eq 1).[7]

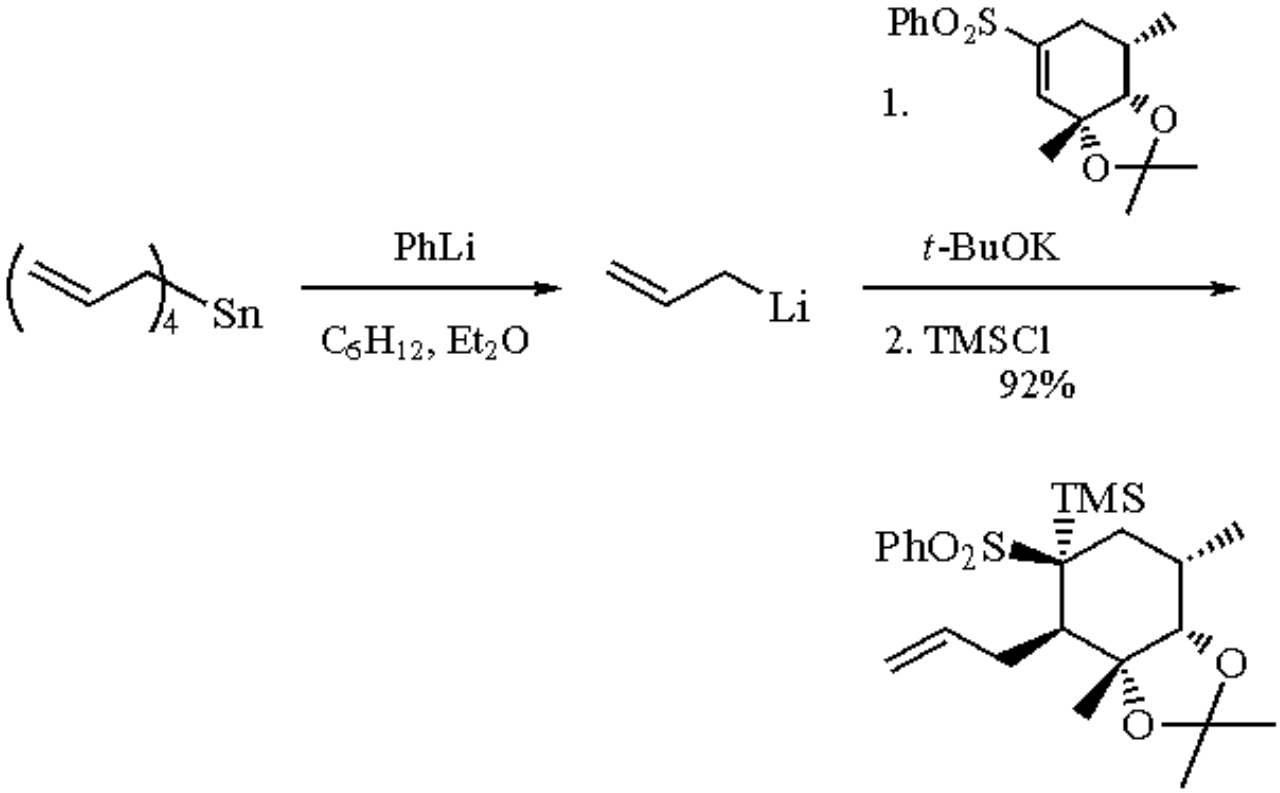

(1)

A solution of allyllithium has also been generated by the reaction of tetraallyltin with 4 equiv of ***Methyllithium*** in Et_2O.[8] Tetraalkylstannanes must not interfere with the ensuing steps. Reaction of allyllithium generated in this manner with 1-naphthyloxazoline afforded, after acid quench, the *trans*-dihydronaphthalene (eq 2).[8]

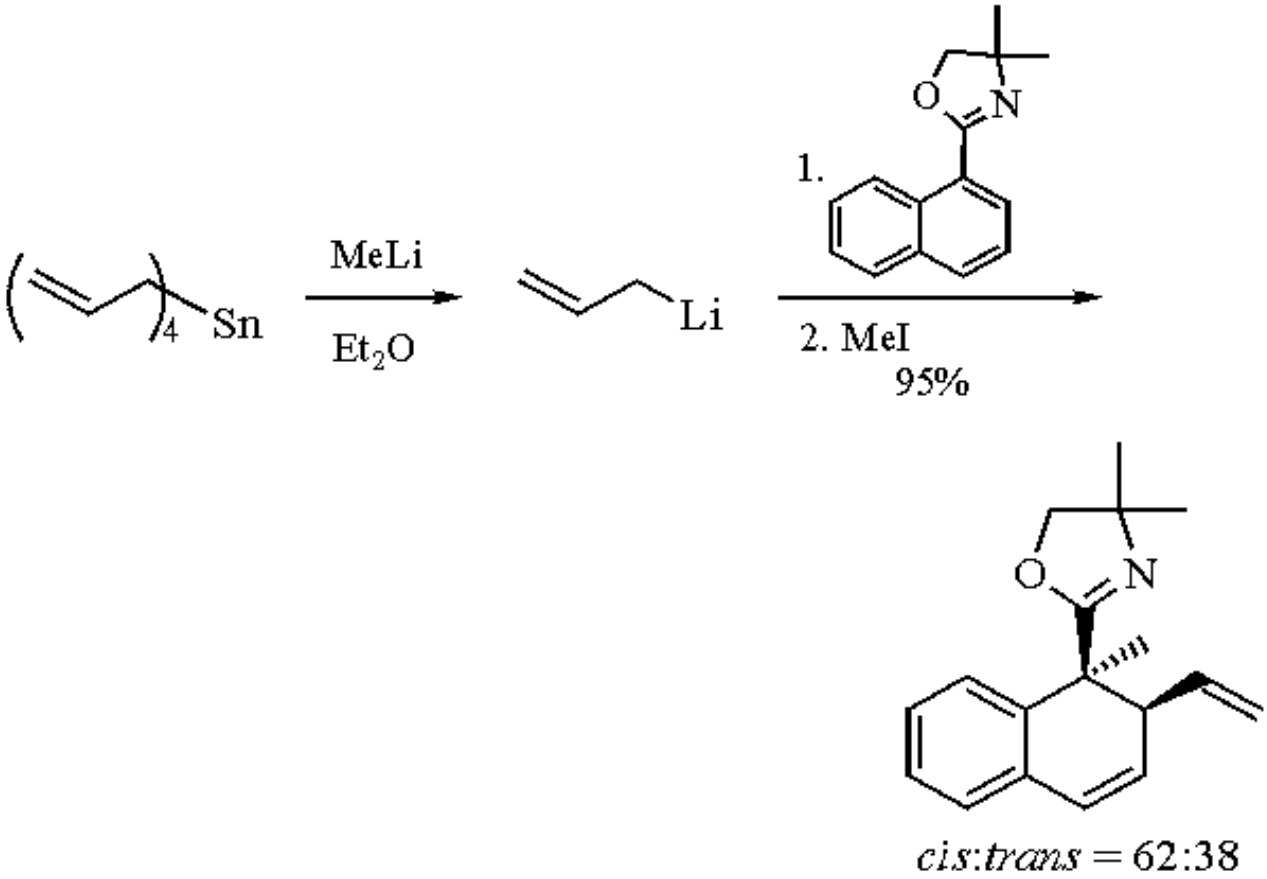

(2)

Disproportionation of tetraallyltin with $SnCl_4$ affords a route to allyltin chlorides.[9]

Allyl Transfer Reactions.

Tetraallyltin is a gentle nucleophile capable of transferring one allyl group to ketones, epoxides, and other reactive electrophiles (eq 3).[3] Nucleophilicity can be enhanced by reaction in the presence of fluoride,[10] or BF_3.[11] Because only one allyl moiety is transferred, ***Allyltributylstannane*** or trimethylallyltin is more commonly used in this reaction.

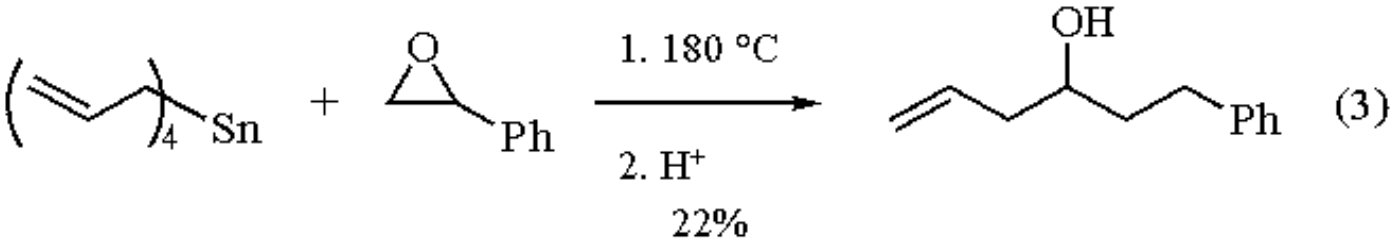

Palladium-Mediated Cross-Coupling Reactions (the Stille Reaction).

Tetraallyltin acts as a nucleophile in palladium-mediated cross-coupling reactions (eq 4).[12] Because the triallyltin halide byproduct is unreactive, tributylallyltin or trimethylallyltin is more commonly used in this reaction. In an interesting variation, treatment of α-halo ketones with ***Tetravinylstannane*** in the presence of catalytic ***Benzylchlorobis(triphenylphosphine)palladium(II)*** affords allyl epoxides (eq 5).[13]

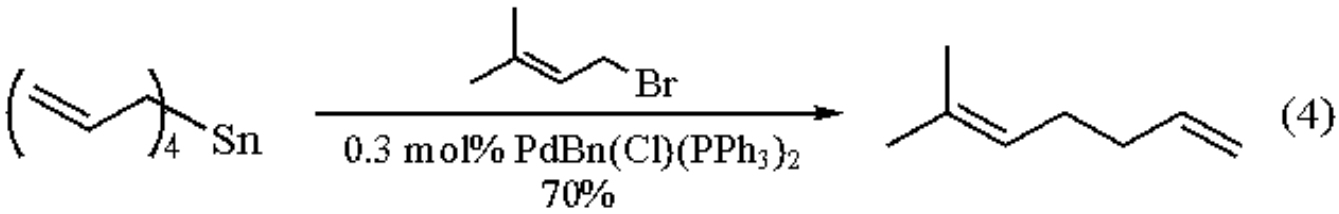

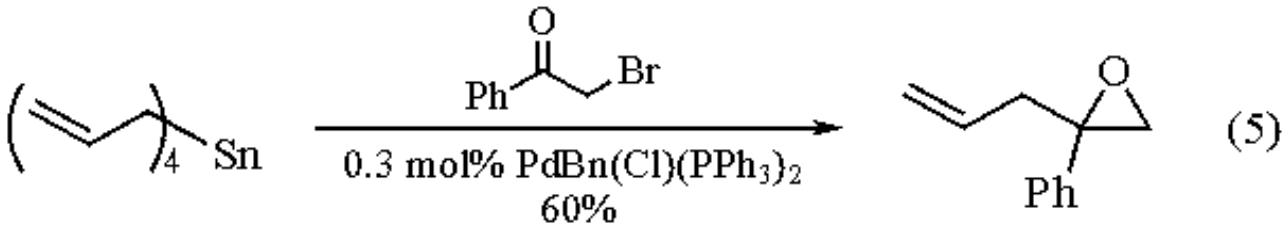

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William J. Scott & Alessandro F. Moretto

Bayer Pharmaceuticals Division, West Haven, CT, USA

1,1,3,3-Tetrabromoacetone[1]

$(CHBr_2)_2CO$

[22612-89-1] · $C_3H_2Br_4O$ · 1,1,3,3-Tetrabromoacetone · (MW 373.65)

(a good source of the 1,3-dibromooxyallyl cation, a synthetic equivalent of the oxyallyl cation; especially useful for [4 + 3] cycloadditions[1])

Alternate Name: 1,1,3,3-tetrabromopropanone.

Physical Data: bp 129-130 °C;[7] mp 37-38 °C.

Solubility: sol moderately polar to polar organic solvents.

Form Supplied in: not commercially available and should be prepared as needed.[2]

Analysis of Reagent Purity: assay by NMR.[2]

Handling, Storage, and Precautions: powerful lachrymator; use in a fume hood. If contact with the skin occurs the affected area should be thoroughly washed with soap followed by a solution of sodium bicarbonate.[3]

[4 + 3] Cycloadditions.

The chemistry of 1,1,3,3-tetrabromoacetone (**1**) is dominated by its ability to form oxyallylic cation (**2**) and related species under a variety of conditions (eq 1). This intermediate has been exploited essentially exclusively as a dienophile in [4 + 3] cycloadditions with dienes, in which it serves as an equivalent of the elusive parent oxyallyl (**3**).[1] 1,1,3,3-Tetrabromoacetone serves as a prototype for other polyhalogenated ketones which exhibit similar chemistry.

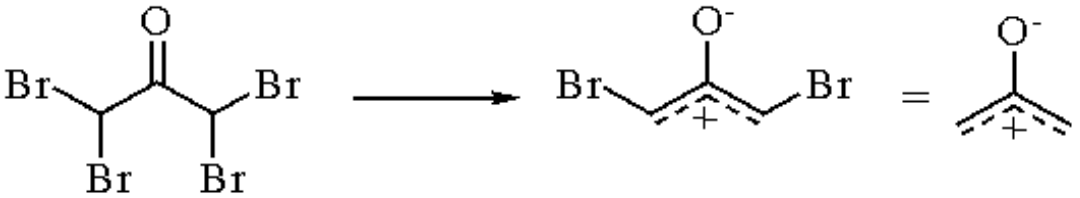

(1) (2) (3) (1)

A number of reagents have been utilized to effect the conversion of (**1**) to (**2**). These include ***Diethylzinc***,[4] ***Nonacarbonyldiiron***,[1d] ***Pentacarbonyliron***,[1c,5] zinc/triethyl borate,[6] ***Zinc/Copper Couple***,[7] and ***Zinc/Silver Couple***.[8] The nature of these reagents precludes the formation of (**2**) in free form and suggests the inclusion of metal counterions which can be expected to attenuate the reactivity of (**2**) in combination with solvent and other effects. It is important to note that 1,3-dibromoacetone has not been successfully used to directly access (**3**).[1c]

The majority of [4 + 3] cycloadditions using (**2**) have involved furans as reaction partners. The reaction of (**2**) with furan to form 8-oxabicyclo[3.2.1]-6-octen-3-one (**4**) is illustrative (eq 2). Nearly all the aforementioned reagents have been used to generate (**2**) for this reaction. Some of the reactions have been conducted quite successfully on a large scale (Table 1).[4,6,8-10] The initial cycloadducts contain bromine, which is removed using a reductive debromination with zinc/copper couple.

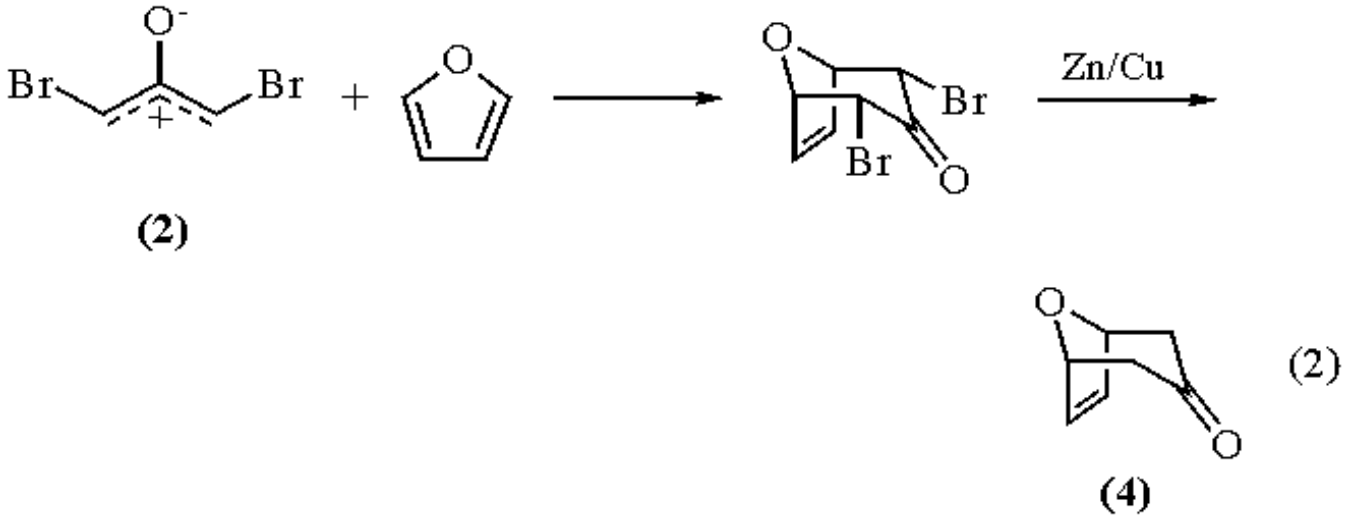

Table 1 Formation of (**3**) from Furan

Reagent	Furan (equiv)	Yield (%)
Et_2Zn[4]	20	57
$Zn/B(OEt)_3$[6,9]	2	54
$Fe_2(CO)_9$[10]	55	63
Zn/Ag[8]	10	55 65

Adducts derived from (**2**) and various furans have been used in the synthesis of analogs of thromboxane,[8] cocaine,[11] and muscarine,[12] among others. A general synthesis of tropanes from such cycloadducts has been developed.[13] For example, nezukone (**6**) could be prepared in fair overall yield in three steps from cycloadduct (**5**) (eq 3).

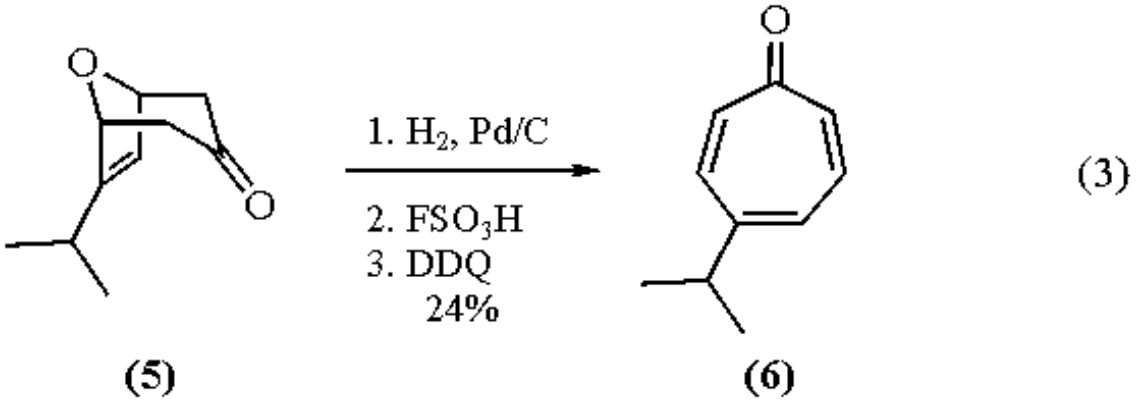

Among the most interesting and important applications of cycloadducts derived from (**2**) has been the synthesis of a family of structurally diverse ribo-C-nucleosides.[14] Examples include (**7**)-(**9**), all of which are ultimately derived from (**1**) and the appropriate furan.[14]

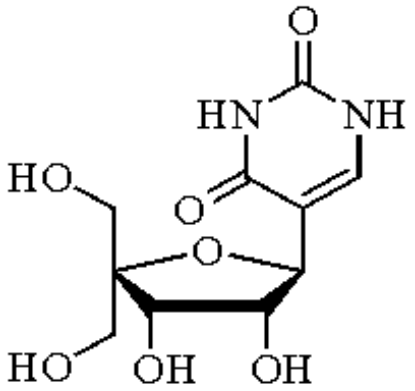

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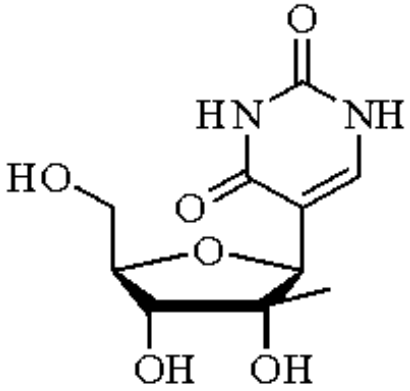

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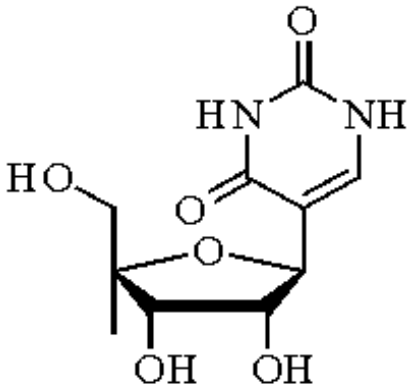

(9)

Oxyallyl (**2**) has also been used in reactions with pyrroles to produce analogs of tropane alkaloids (eq 4).[4,7] Trapping with dienes such as ***Cyclopentadiene***[5,6,9,15] and substituted anthracenes[16] has been studied as well (eqs 5 and 6).

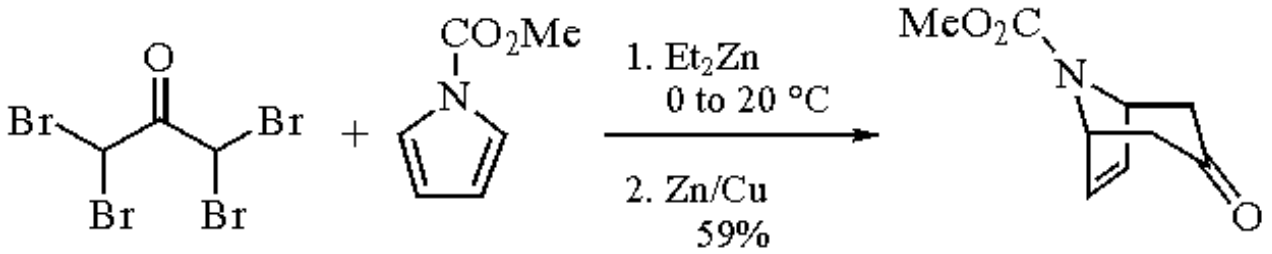

(1)

(4)

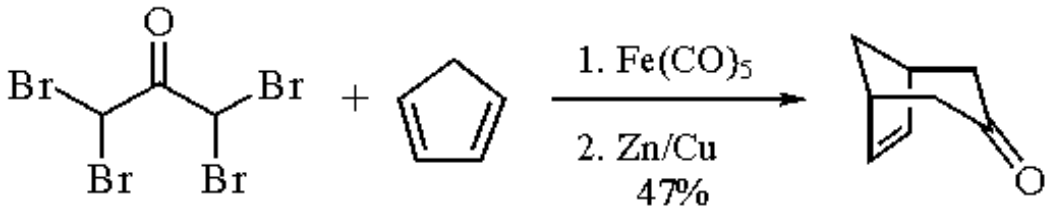

(1)

(5)

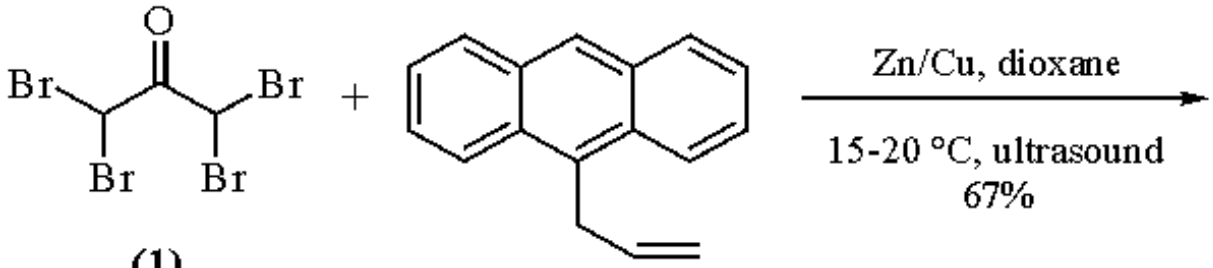

(1)

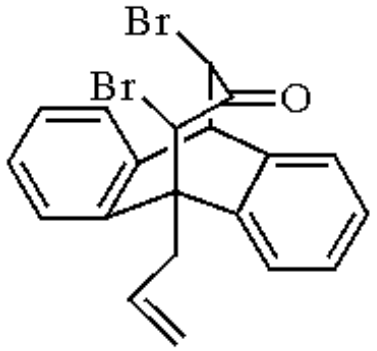

(6)

Other Routes to Equivalents of (3).

Several synthetic routes to equivalents of (**3**) are known. 2-Methoxy-3-bromopropene, for example, undergoes a reaction with ***Furan*** in the presence of silver ion to give (**4**) in low yield (eq 7).[17] Presumably, the cation (**10**) is an intermediate. This intermediate is so reactive that it even gives [4 + 3] cycloaddition products with benzene.[18]

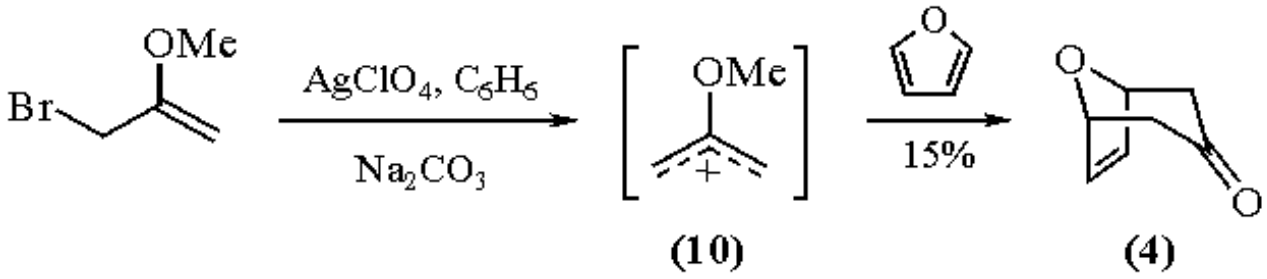

(7)

The reaction of the trimethylsilyl enol ether of 1,3-dichloroacetone (**11**) with furan in the presence of ***Silver(I) Perchlorate*** gave an 80% yield of a mixture of cycloadducts (eq 8).[19] These could undoubtedly be converted to (**3**) via reductive dehalogenation. While the use of silver salts makes this process expensive, the ready availability of (**11**) renders this method attractive.

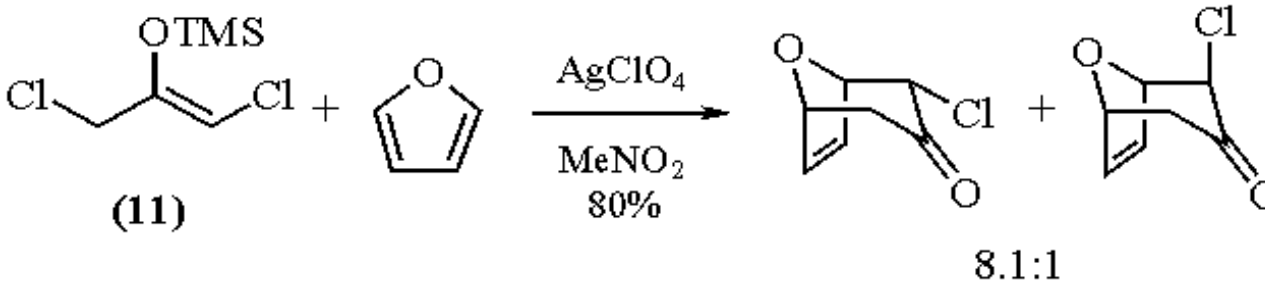

(8)

Finally, tetrachloro- and pentachloroacetone have been shown to give rise to oxyallylic cations capable of [4 + 3] cycloaddition with furan. ***Triethylamine*** in methanol, triethylamine or sodium trifluoroethoxide in trifluoroethanol/furan, and triethylamine in ethereal lithium perchlorate have been used in this reaction (eqs 9 and 10).[20] The cycloadducts in these cases could be dehalogenated to (**4**). This approach has been recognized as particularly convenient, since tetrachloroacetone is more easily handled than (**1**).[1b]

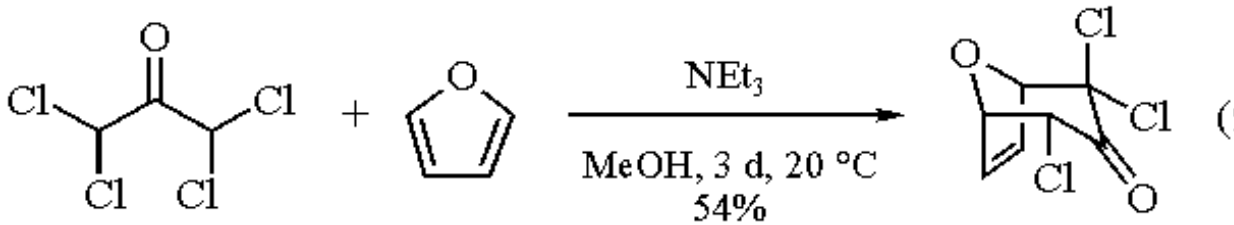

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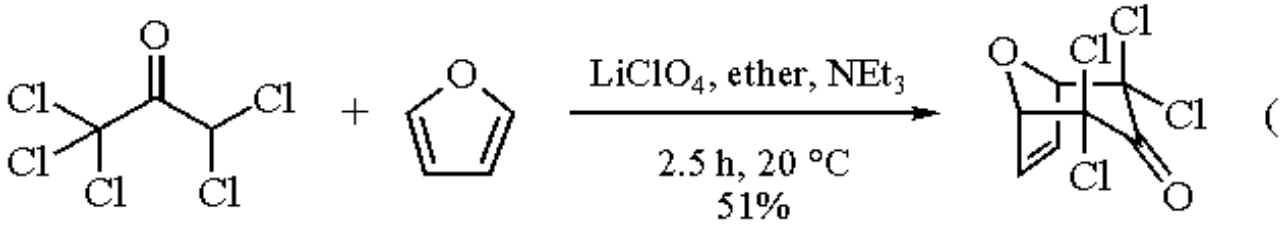

(10)

Favorsky Rearrangement.

Treatment of (**1**) with 1 M sodium bicarbonate resulted in a Favorsky rearrangement to yield β,β-dibromoacrylic acid in good yield (eq 11).[21]

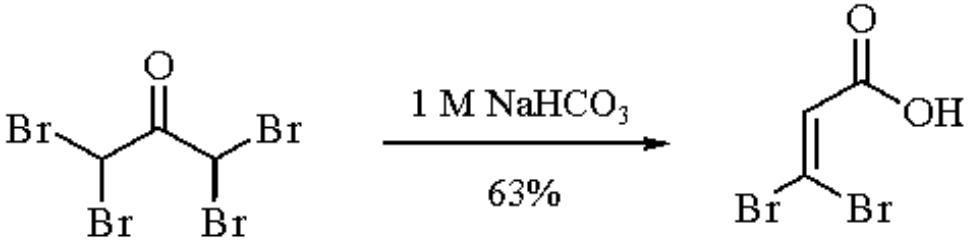

(1) (11)

Related Reagents.

2,4-Dibromo-3-pentanone; ***Diethylzinc***; ***2-Methoxyallyl Bromide***; ***Zinc/Copper Couple***; ***Zinc/Silver Couple***.

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University of Missouri-Columbia, MO, USA

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2,4,4,6-Tetrabromo-2,5-cyclohexadienone[1]

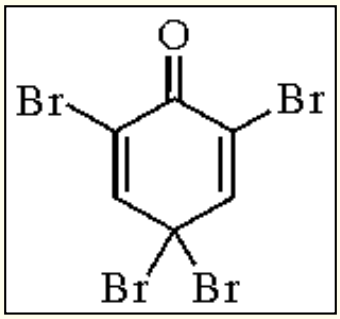

[20244-61-5] · $C_6H_2Br_4O$ · 2,4,4,6-Tetrabromo-2,5-cyclohexadienone · (MW 409.68)

(selective bromination of polyalkenes;[2-4] monobromination of phenols,[5,6] unprotected arylamines,[7,8] and aza heterocycles;[9] oxidation of thiols to disulfides;[10] synthesis of α´-bromo-α,β-unsaturated ketones;[11] electron acceptor in photosensitization reactions;[12] cyclization of alkenols[3,13])

Alternate Name: TBCHD.

Physical Data: mp 125-130 °C (dec).

Solubility: sol CH_2Cl_2, Et_2O, $CHCl_3$, $MeNO_2$, MeOH.

Form Supplied in: crystalline material; commercially available.

Preparative Methods: bromination of 2,4,6-tribromophenol with ***Bromine*** in acetic acid in the presence of sodium acetate (eq 1).[6,7,8,14]

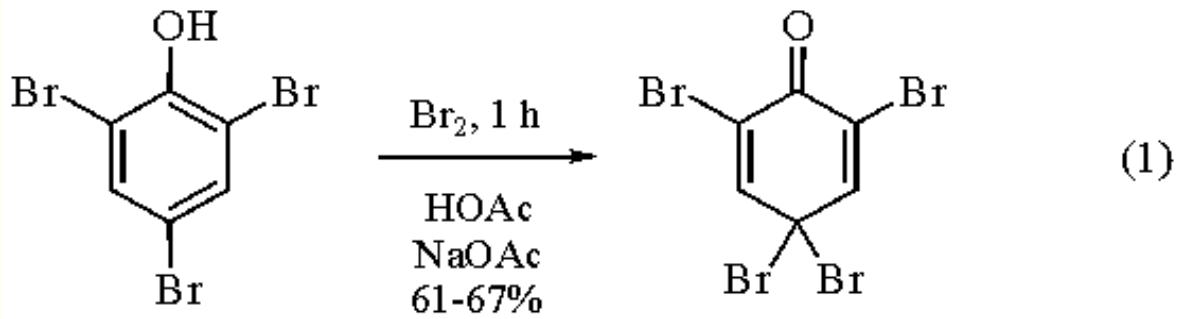

Analysis of Reagent Purity: ^{1}H NMR.

Handling, Storage, and Precautions: the reagent should be kept in a dark vessel, well-protected from light.

Brominative Cyclization of Polyalkenes.

Electrophilic bromination of 1,5-dienes with 2,4,4,6-tetrabromo-2,5-cyclohexadienone results in the formation of brominated six-membered carbocycles. This brominative cyclization does not always proceed in good yield, but has been used for the biomimetic construction of marine natural products.[15] Nerolidol thus reacts with TBCHD to give the monocyclic sesquiterpenes α- and β-snyderol (from the red algae *Laurencia* species) in low yield (eq 2).[2,4] When used as solvent, acetonitrile may participate in the reaction, depending upon the temperature.[16] In a similar fashion, brominative cyclization of methyl farnesate has been used in the total synthesis of acoratriene (eq 3)[16] and 10-bromo-α-chamigrene.[17]

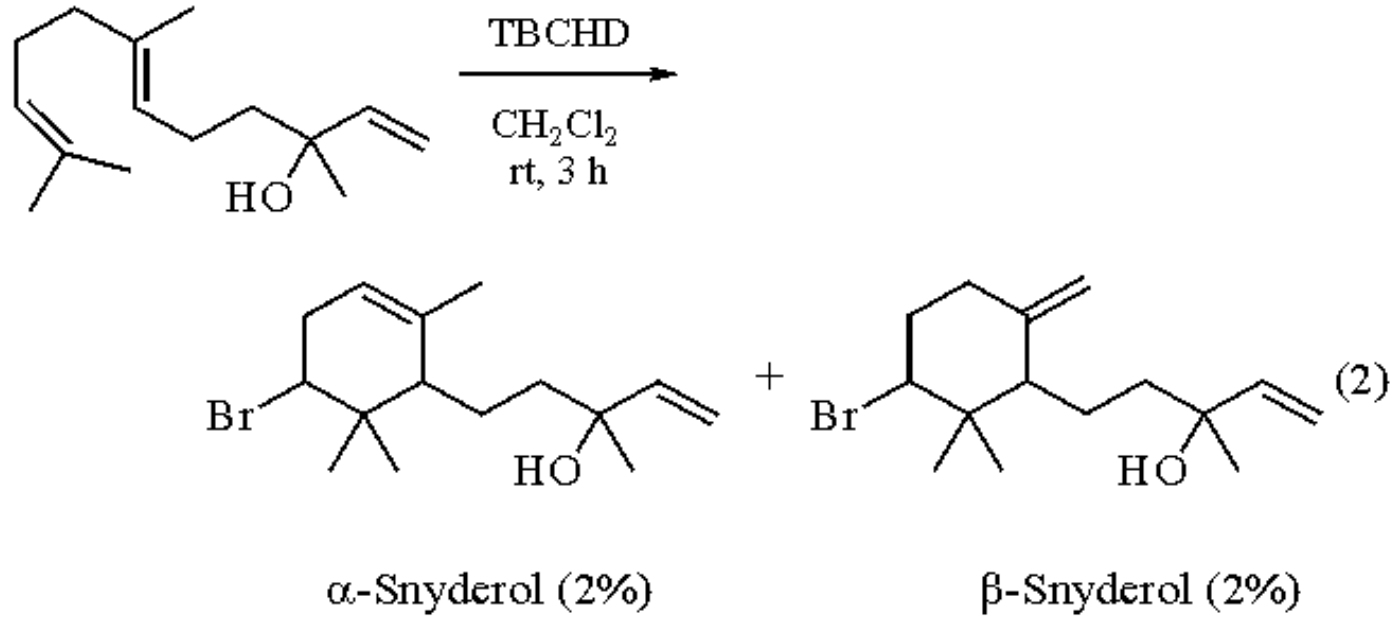

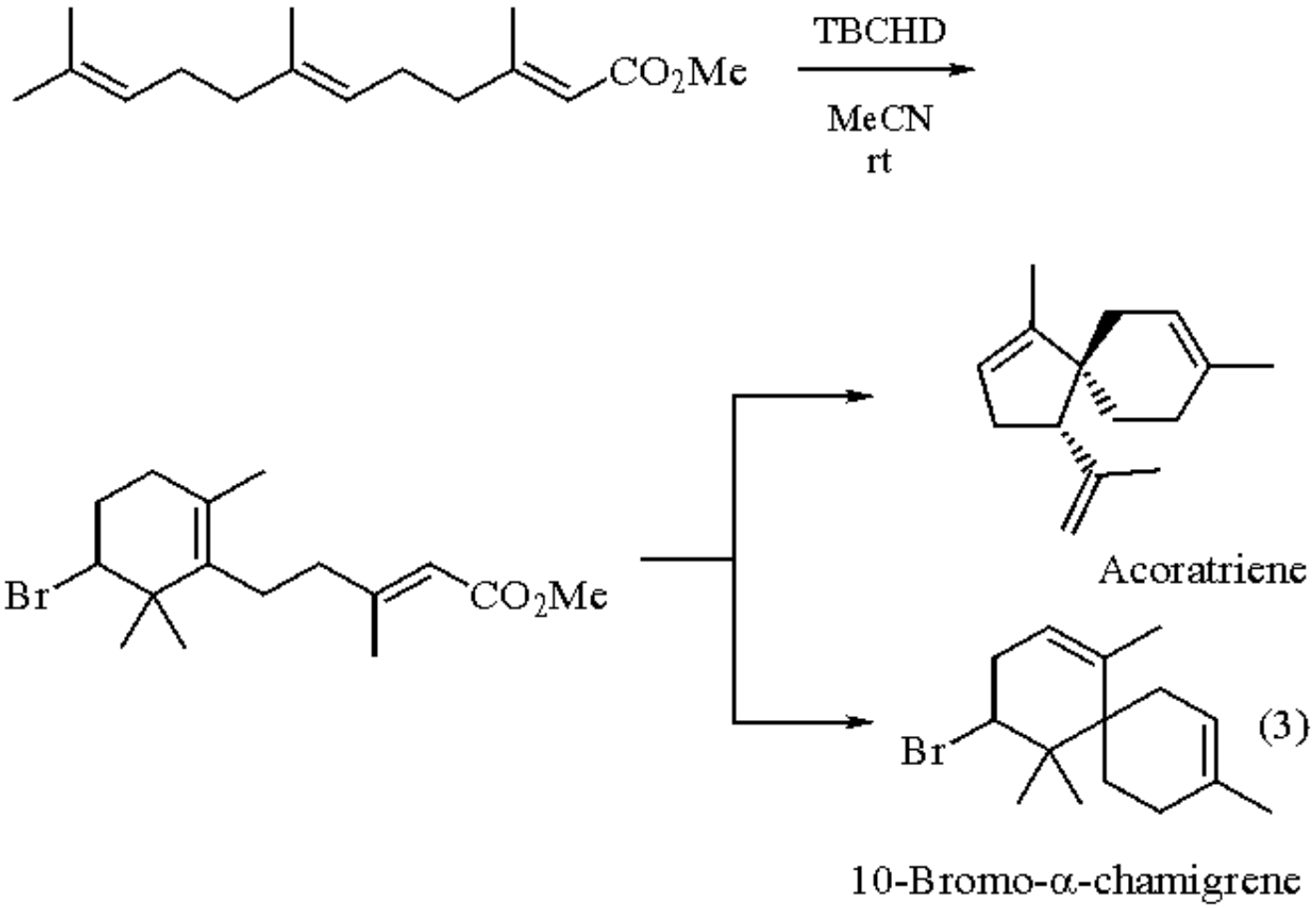

In contrast, geranyl acetate,[17] carvone,[18] and farnesyl cyanide[18] undergo selective bromination to the dibromo adducts with TBCHD (e.g. eq 4). Natural products from *Desmia hornemanni* have been synthesized by bromination of myrcene,[19] and the synthesis of isoconcinndiol has been achieved in a fashion similar to that outlined above.[20]

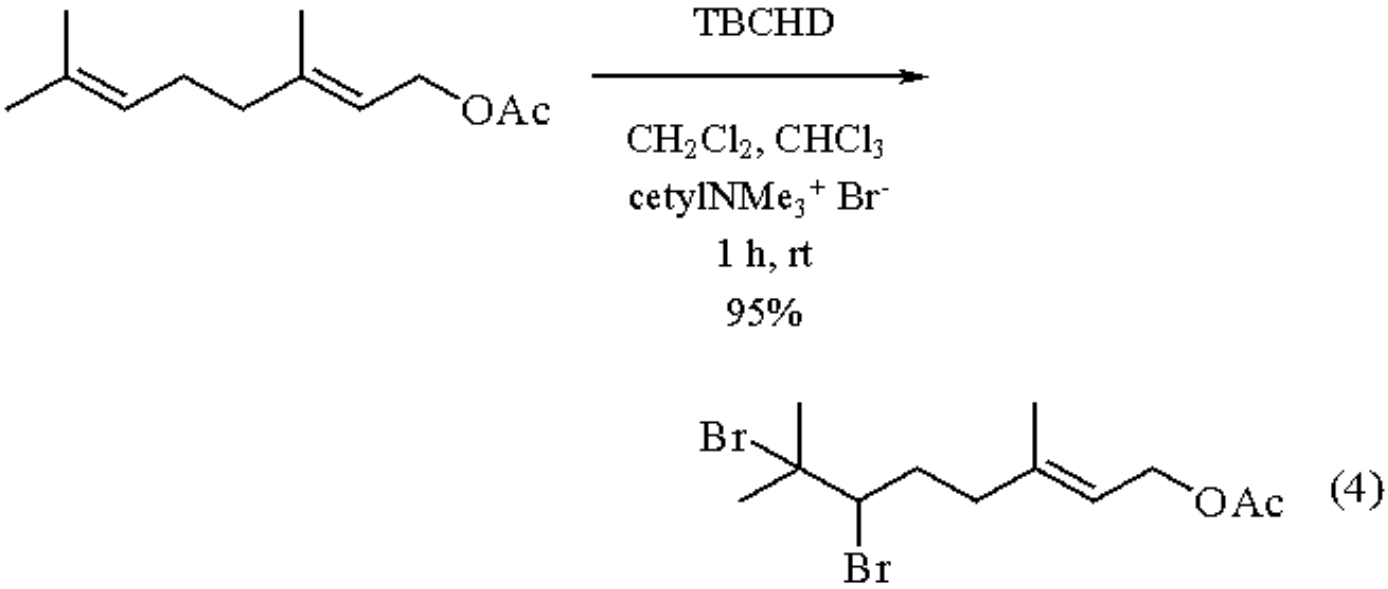

Monobromination of Phenols, Arylamines, and Aza Heterocycles.

Phenols are selectively monobrominated at the *ortho* position by TBCHD.[5,6] Phenol is brominated in CCl_4 to give a 87:13 ratio of *o*-bromo- and *p*-bromophenol (95% yield).[5] Estradiol is brominated at the 2- and 4-positions.[21] Of more potential use is the selective monobromination of anilines at the *para* position (eq 5);[5,7,8,22,28] the following arylamines have been brominated in this fashion: aniline (92%), *N*-methylaniline (94%), *N*,*N*-dimethylaniline (91%), *o*-toluidine (88%), *m*-toluidine (90%), 2,3-dimethylaniline (91%), 2-chloroaniline (86%), 3-chloroaniline (86%), 3-bromoaniline (82%), 2-nitroaniline (91%), *o*-anisidine (85%), 2-aminopyridine (75%), 2-*N*,*N*-dimethylaminopyridine (70%), and 3-*N*,*N*-dimethylaminopyridine (60%). Monobromination of ***Imidazole***, ***N-Methylimidazole*** and indole has also been achieved with TBCHD (eq 6).[9]

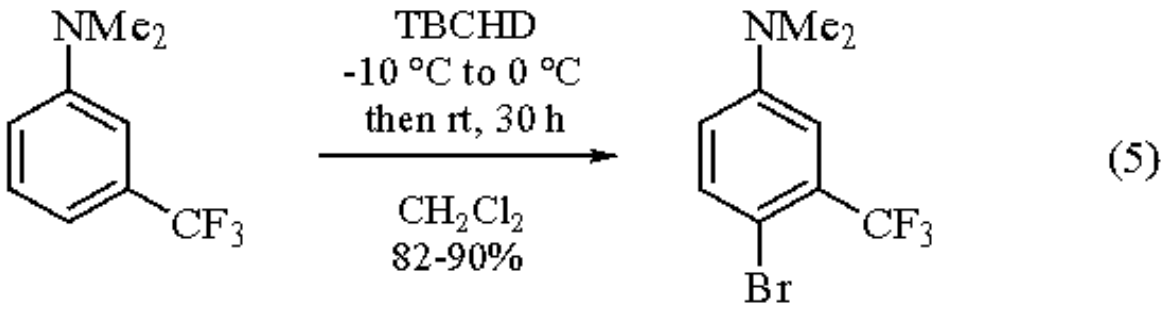

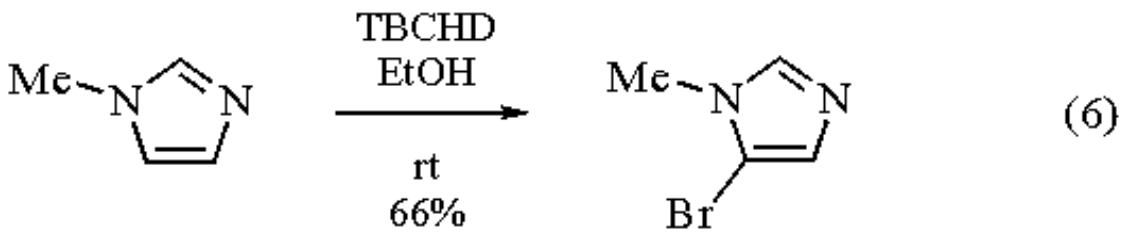

Oxidation of Thiols to Disulfides.

Thiols (as their sodium salts) are oxidized by TBCHD to give disulfides (eq 7).[10] The use of benzene as solvent is particularly recommended as all byproducts are then easily removed as insoluble precipitates. The reagent behaves as an oxidizing agent towards sulfides, converting them into sulfoxides.[23]

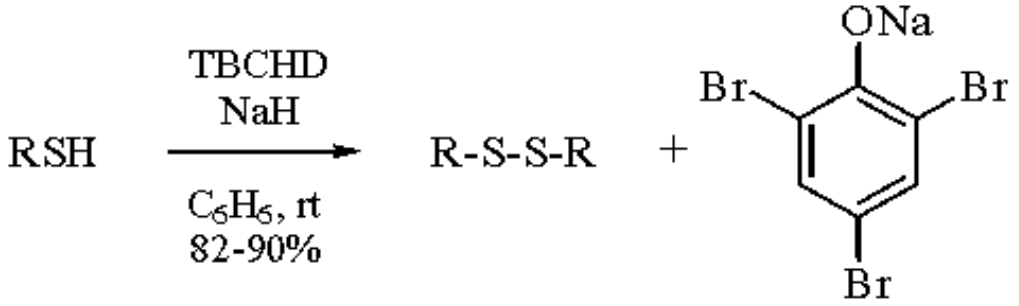

(7)

R = Pr, Bu, Ph, *o*-MeC$_6$H$_4$

Selective α´-Bromination of α,β-Unsaturated Ketones.

Monobromination of α,β-unsaturated ketones at the α´-position without affecting the double bond was performed with TBCHD (eqs 8 and 9).[11,29] The rate of the reaction is very slow, but can be enhanced by the addition of a catalytic amount of gaseous ***Hydrogen Chloride*** or ***Hydrogen Bromide***.

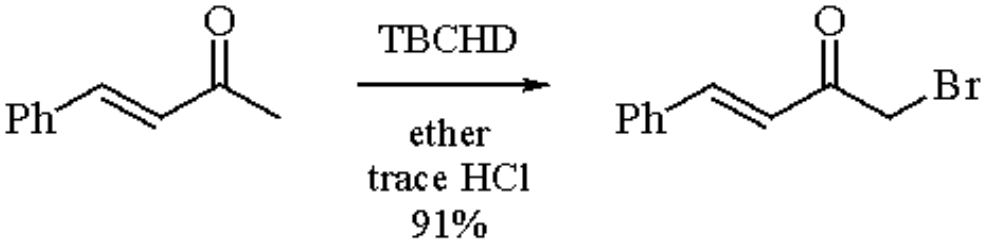

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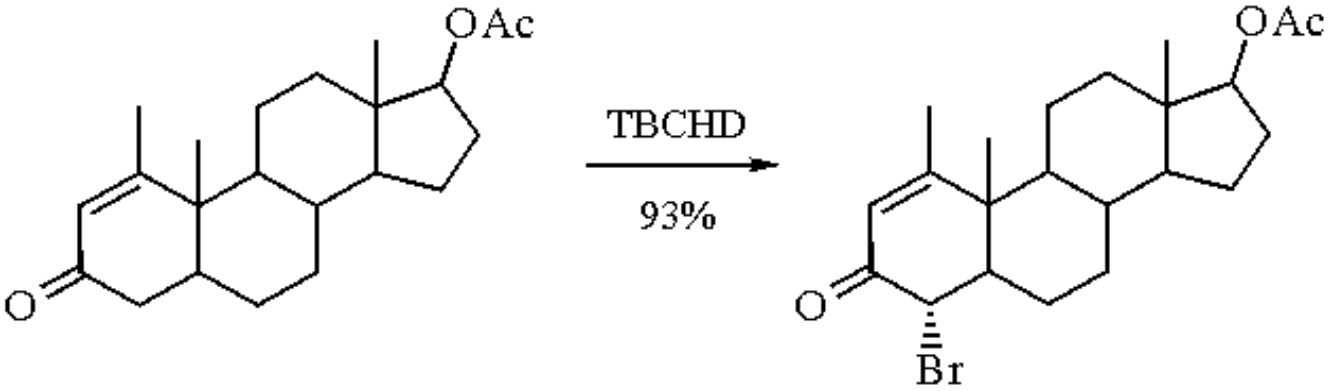

(9)

Electron Acceptor in Photosensitization Reactions.

TBCHD is an electron acceptor in the photosensitized oxidation of unsaturated substrates, e.g. alkynes,[12] stilbene,[12] tetraphenylethylene,[12] α-methylstyrene,[12] dioxenes,[24] and 2,3,5,6-tetraphenyl-*p*-dioxin.[24]

Cyclization of Alkenols.

Cyclization of alkenols with TBCHD gives brominated tetrahydropyrans accompanied by minor amounts of brominated tetrahydrofurans (eq 10).[3,13,25] This reaction has been used for the synthesis of (±)-incensole from (±)-mukulol. In addition, this methodology allows the stereospecific construction of *trans*-2,5-disubstituted tetrahydrofurans by the cyclization of γ,δ-unsaturated alcohols to 3-bromotetrahydropyrans followed by silver-induced ring contraction (eq 11).[13]

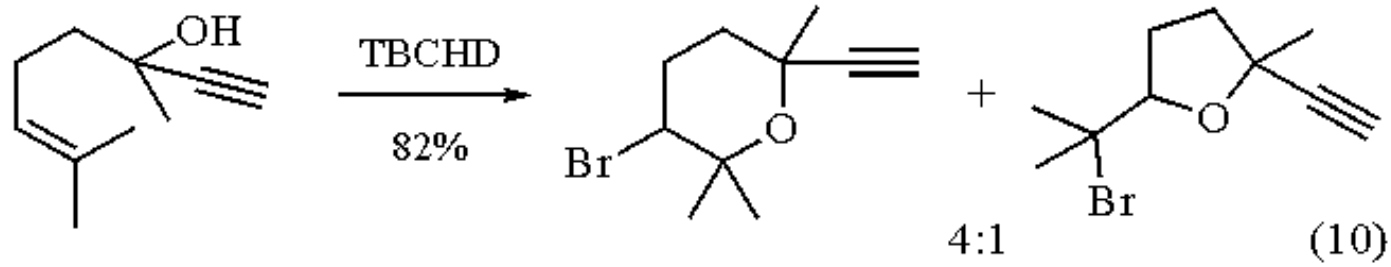

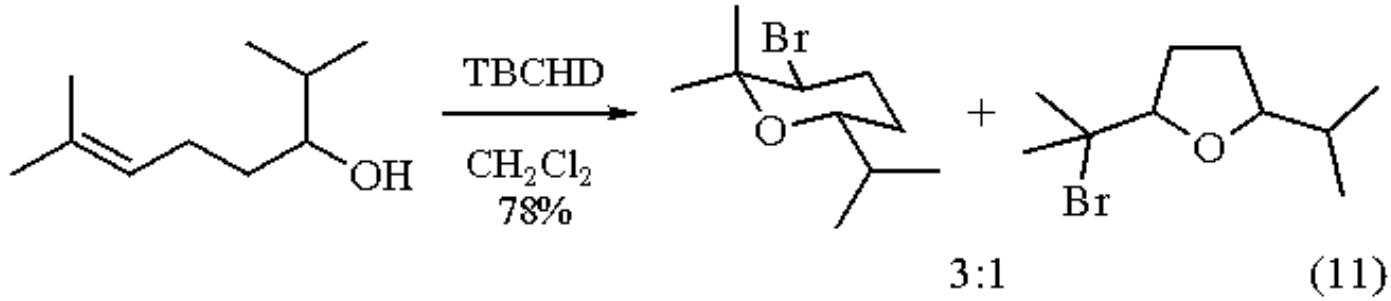

Allylic Bromination and Synthesis of Spiroisoxazolines.

Allylic brominations of cephem derivatives have been achieved with the dienone reagent under irradiation (eq 12).[26] Spiroisoxazolines are formed by oxidative cyclization of *o*-hydroxybenzyl oximes. This methodology was used in the synthesis of the sponge metabolite *cis,cis*-aerothionine (eq 13).[27]

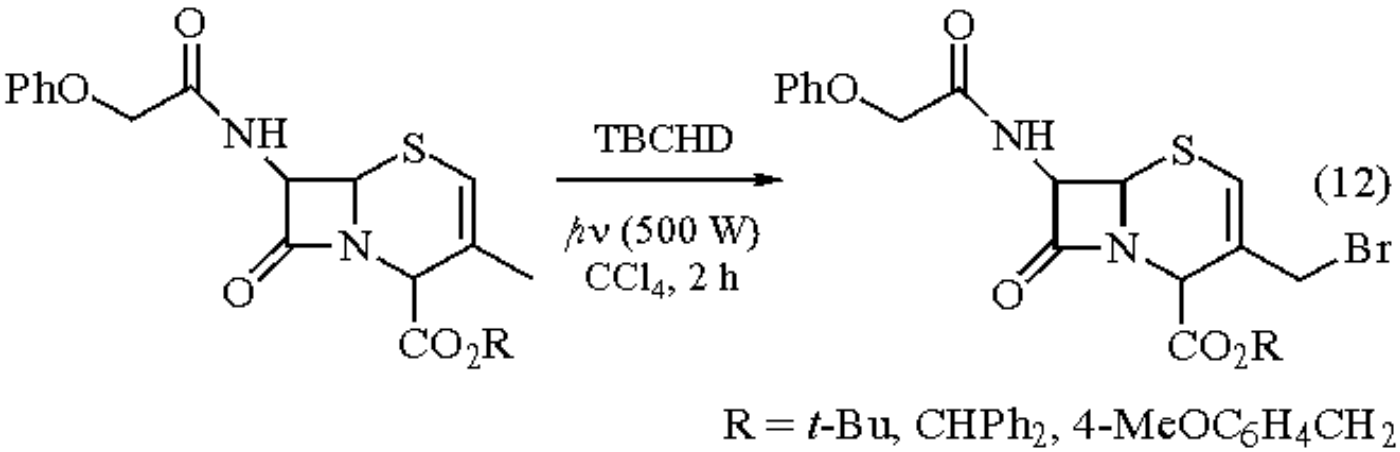

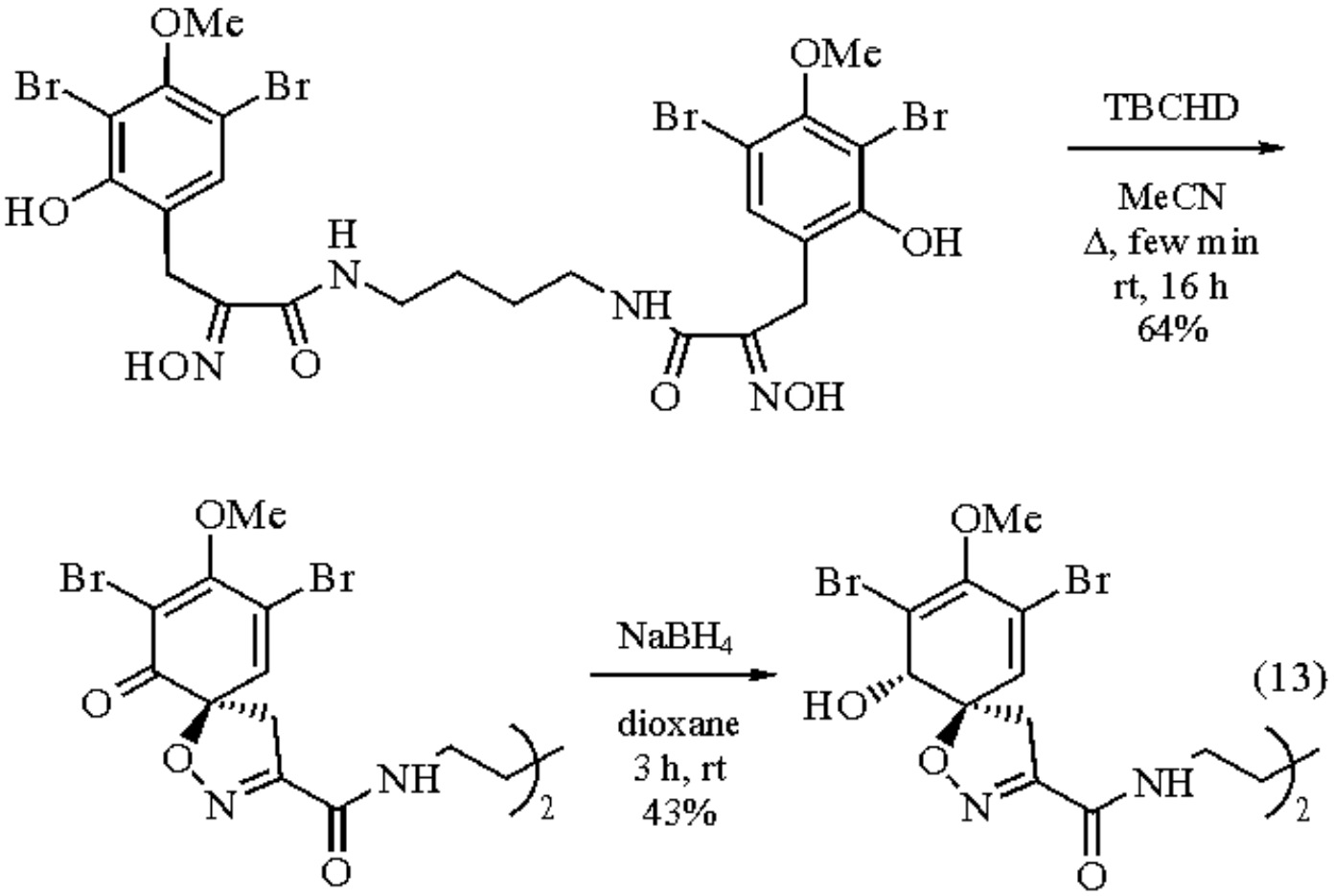

cis,cis-Aerothionine

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Tetra-*n*-butylammonium Acetate

***n*-Bu_4NOAc**

[10534-59-5] · $C_{18}H_{39}NO_2$ · Tetra-*n*-butylammonium Acetate · (MW 301.58)

(nucleophile for S_N2 displacement of sulfonates[1] and allylic halides;[2] mild, soluble base for reduction of tosylhydrazones with catecholborane[3])

Physical Data: mp 114-115 °C (Alfa), 95-98 °C (Aldrich).

Solubility: sol most polar organic solvents (MeCN, acetone, CH_2Cl_2, EtOH); slightly sol benzene.

Form Supplied in: white crystalline solid; widely available.

Purification: recrystallization from a minimum amount of methanol (mp 114-115 °C) or, alternatively, filtration of a benzene solution through basic alumina (activity I) and recrystallization from 5:4:2 benzene-pentane-ethyl acetate at -25 °C (mp 95-98 °C).

Handling, Storage, and Precautions: irritant, hygroscopic; protect from moisture.

Synthesis of Acetate Esters via S_N2 Displacements.

This reagent is an excellent source of nucleophilic acetate ion for S_N2 substitution reactions. Tetraethylammonium acetate functions in a similar fashion. Equatorial steroidal tosylates are displaced to give axial acetates upon treatment with tetra-*n*-butylammonium acetate in refluxing acetone (eq 1).[4] The use of benzene, instead of acetone, results in clean inversion of deuterated *endo*-norbornyl sulfonates without isotopic rearrangement[5] (eq 2).[1] This process may also be carried out in molten reagent (eq 3).[6]

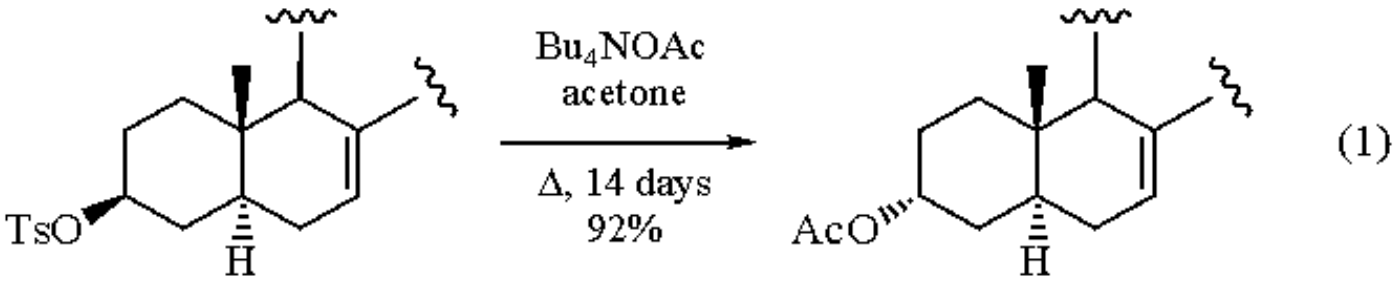

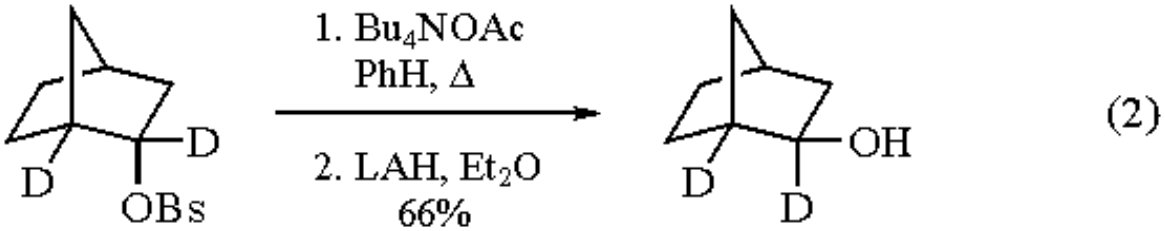

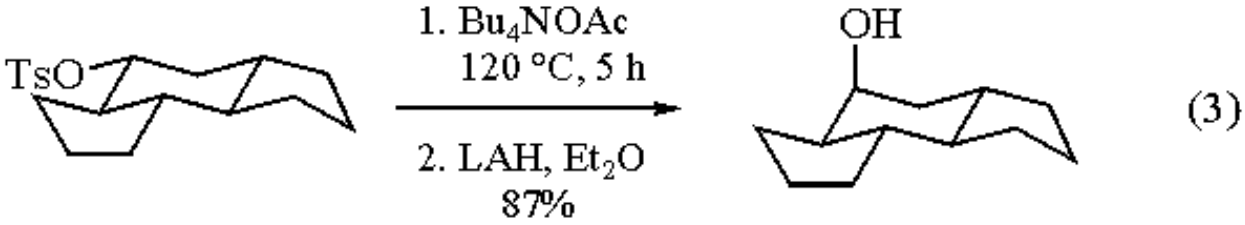

3-Bromomethyl-2-thiacephem derivatives are converted to allylic acetates in excellent yield (eq 4).[2] The use of AcOH as solvent prevents double bond isomerization for related Δ^3-3-bromomethylcephems.[7]

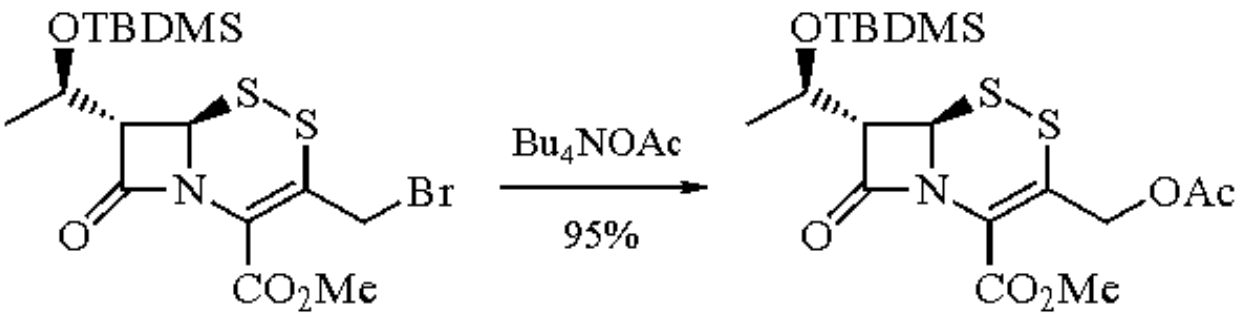

(4)

Other Applications.

The solubility of tetra-*n*-butylammonium acetate in organic solvents makes it an effective replacement for NaOAc. Tetra-*n*-butylammonium acetate is superior to NaOAc for the deoxygenation of aldehydes and ketones by reduction of the corresponding tosylhydrazones with catecholborane (eq 5).[3]

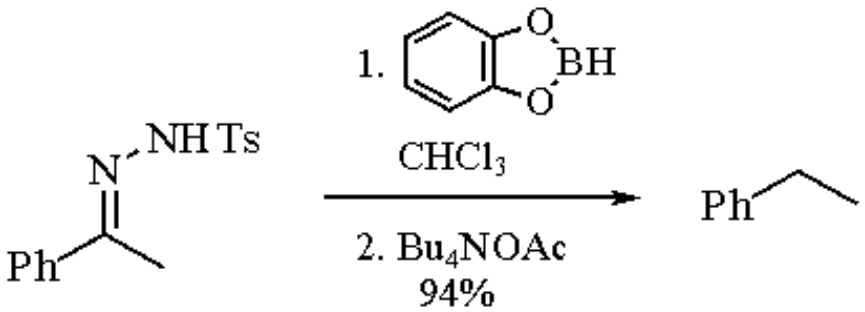

(5)

Use of tetra-*n*-butylammonium acetate in the electrochemical reduction of some *o*-bis(phenylsulfonyl)benzene derivatives affords good yields of dibenzothiophene 5,5-dioxides.[8] Photolysis of 1,2,4,5-tetracyanobenzene in the presence of tetra-*n*-butylammonium acetate yields bis(2,4,5-tricyanophenyl)methane.[9] The reaction between tetra-*n*-butylammonium carboxylates and ***p-Toluenesulfonyl Chloride*** produces mixed *p*-toluenesulfonic carboxylic anhydrides,[10] an alternative to chloroformates.

Tetra-*n*-butylammonium acetate promotes an unexpected elimination of a bromohydrin acetate to produce an alkene.[11] The reagent is also an effective catalyst for the phosphorylation of alcohols by cyclic enediol phosphates in aprotic solvents,[12] as well as for anionic polymerization.[13]

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Tetra-*n*-butylammonium Borohydride

***n*-Bu_4NBH_4**

[33725-74-5] · $C_{16}H_{40}BN$ · Tetra-*n*-butylammonium Borohydride · (MW 257.38)

(selective reducing agent for aldehydes and ketones;[1] soluble in nonaqueous media)

Physical Data: mp 123-128 °C.

Solubility: readily sol CH_2Cl_2, $CHCl_3$; moderately sol benzene; relatively insol ether solvents, H_2O.

Form Supplied in: colorless crystalline solid; commercially available.

Preparative Methods: can be prepared by the reaction between ***Sodium Borohydride*** and tetrabutylammonium chloride.[2] The reagent can also be prepared from the less expensive ***Tetra-n-butylammonium Iodide*** by ion exchange.[1]

Purification: recrystallization from ethyl acetate followed by careful drying under vacuum at 50-60 °C.

Handling, Storage, and Precautions: crystalline samples showed no loss of active hydrogen after storage at rt for more than 1 year.[1] As with other borohydrides, the material reacts rapidly with aqueous acids to produce hydrogen (and, potentially, borane).[2] Use in a fume hood.

General Considerations.

Tetrabutylammonium borohydride, by virtue of its high solubility in organic solvents such as CH_2Cl_2, permits the reduction of aldehydes and ketones to be carried out in high yields in aprotic solvents. The general reactivity of the reagent is analogous to that of sodium borohydride in aqueous or alcoholic media, and reductions are highly selective for the carbonyl groups of aldehydes and ketones relative to unconjugated carbon-carbon multiple bonds. At rt, acid chlorides are reduced very rapidly, aldehydes and ketones are reduced at convenient rates (with half-times of a few hours), and esters are reduced quite slowly. The solubility properties[1,4] of this compound relative to that of other quaternary ammonium borohydrides make it an excellent reagent for reductions of aldehydes and ketones, which sometimes exhibit poor solubility in the protic solvents needed for sodium borohydride reductions.

The tetrabutylammonium reagent is considerably easier to handle and purify[2] than the tetraethylammonium salt, because it is less hygroscopic and is more soluble in organic solvents (although the greater water solubility of most tetraethylammonium salts can facilitate workup of reductions with the latter derivatives). Tetrabutylammonium borohydride was first used to prepare solutions of ***Diborane*** in CH_2Cl_2[2] and was then found to be a mild and selective reagent for the reduction of dioxolenium ions.[5] Subsequently, the reductions were extended to carbonyl reductions in aprotic solvents. Related reductions were reported using ***Tetra-n-butylammonium Cyanoborohydride*** in ***Hexamethylphosphoric Triamide***.[6]

The reactivity of tetrabutylammonium borohydride decreases along the sequence acid chlorides > aldehydes > ketones > esters. The extremes are illustrated by ***Benzoyl Chloride*** (**1**), which is reduced rapidly, even at -78 °C (eq 1),[1] and ethyl laurate (**2**), which undergoes only 25% reduction after 4 d at 25 °C (eq 2).[1]

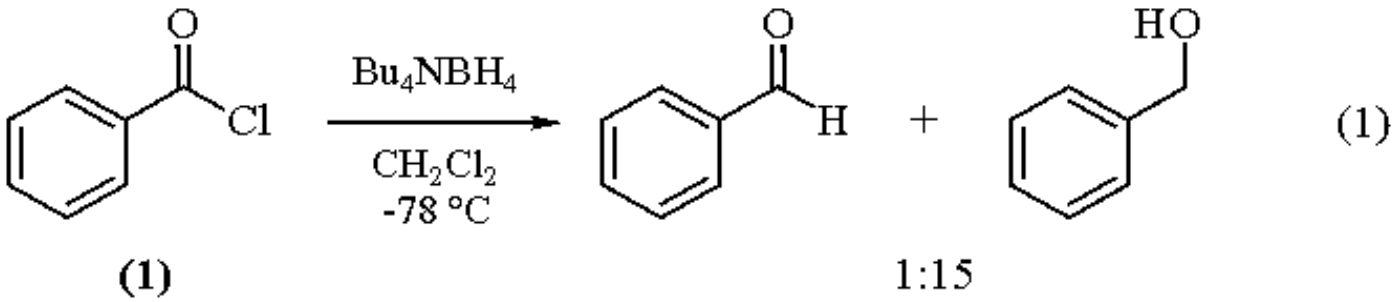

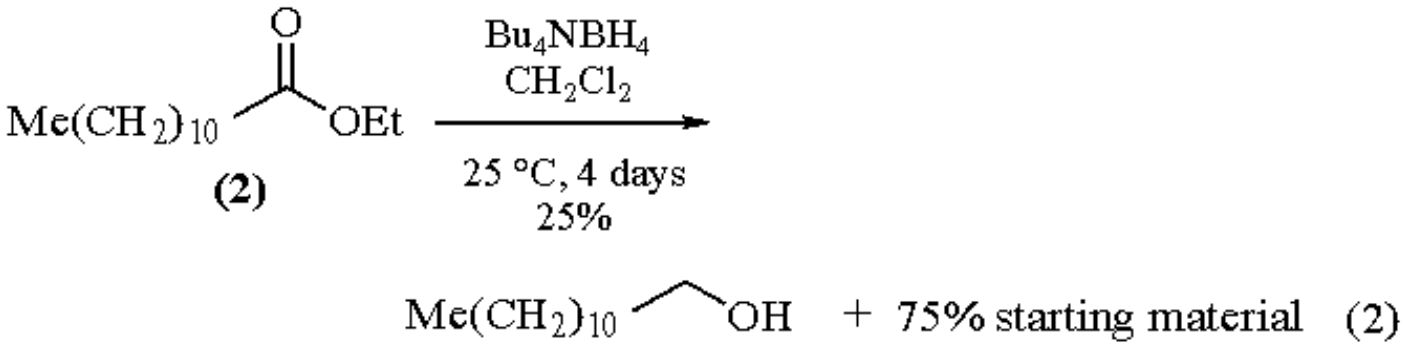

Aldehydes and ketones undergo reduction at 25 °C at convenient rates, which vary with respect to the steric bulk of the substituents. While the reduction of unhindered aldehydes proceeds readily and nearly to completion with only 1 equiv of tetrabutylammonium borohydride, it was found preferable to use 4 equiv of the reducing agent as a general procedure for ketones, where the reaction is otherwise inconveniently slow or does not proceed to completion. The typical reaction time of 2 d for ketone reduction (rt, CH_2Cl_2) can be decreased to several hours if the reduction is carried out at the higher temperature of refluxing $CHCl_3$.[1]

A typical reduction is accomplished by allowing a CH_2Cl_2 solution of the carbonyl derivative (1 M) and tetrabutylammonium borohydride (0.4-1 M) to stand in a stoppered vessel at rt for 0.25-48 h. The reaction mixture is then quenched by stirring for 2 h with alkaline, aqueous ***Hydrogen Peroxide*** (2 vol of 3% hydrogen peroxide and 1 vol of 10% NaOH). After drying the organic layer and evaporating the solvent at reduced pressure, insoluble ammonium salts can be removed by dissolving the crude product in Et_2O and filtering the solution through a short column of alumina. The use of aqueous hydrogen peroxide in the workup not only serves to destroy any unreacted hydride, but also facilitates the hydrolysis of the borate esters formed in the reduction.[7] If this step is omitted, much lower yields result. In order to destroy any peroxides that may have formed during workup, a CH_2Cl_2 solution of the product is washed with aqueous sodium sulfite prior to distillation.

Selective Reductions.

Only the keto group of methyl 3-benzoylpropionate (**3**) was reduced, and the corresponding lactone (formed spontaneously during distillation of the product) was obtained (eq 3).[1]

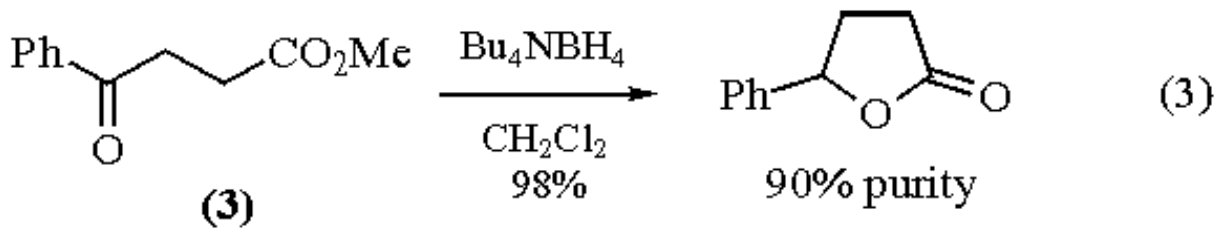

On the other hand, the reactivity differences of aldehyde and ketone carbonyl groups do not appear to be sufficient to allow selective reduction. Although the aldehyde is reduced preferentially, the product distribution in the following example is only 80:20 at best (eq 4).[3]

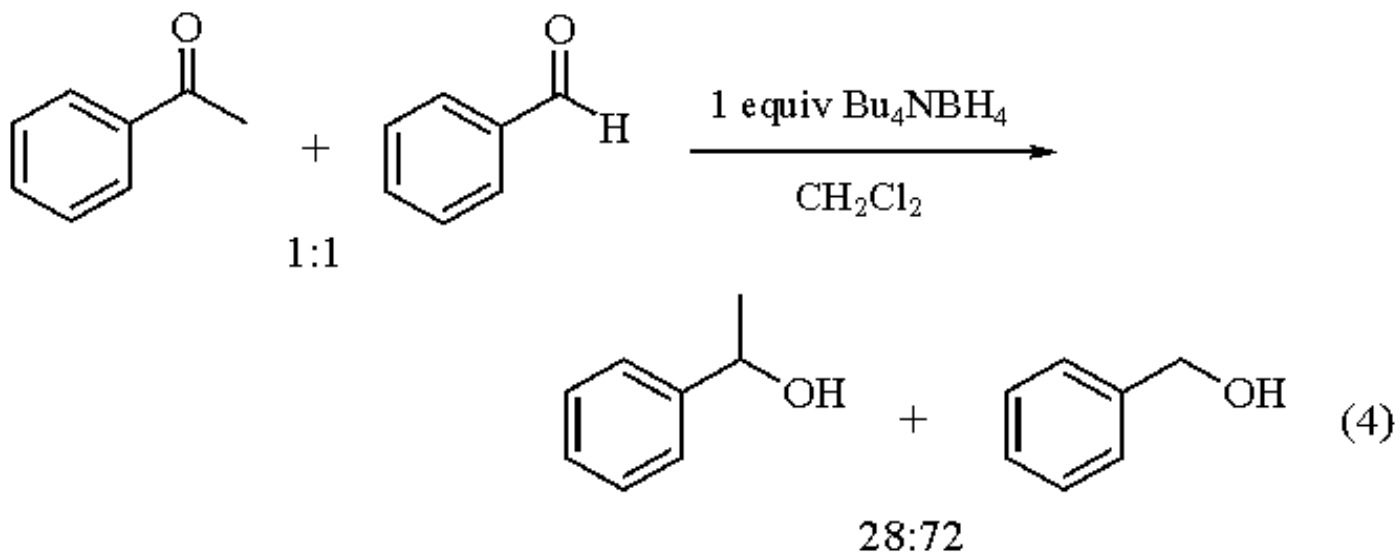

Although diborane is probably formed during the reduction of ketones, hydroboration of the carbon-carbon double bond in 6-methyl-5-hepten-2-one was not observed, and the unsaturated alcohol was isolated in good yield.[1] As with other borohydride reductions,[8,9] there is evidence that the reaction can be assisted by electrophilic catalysis. While not a prerequisite for reduction, the addition of an equivalent amount of ethanol results in an approximate twofold increase in the rate of reduction of cyclohexanone by tetrabutylammonium borohydride in CH_2Cl_2.[1] The identity of the actual reducing agent in reductions performed with Bu_4NBH_4 in CH_2Cl_2 is uncertain. The ability of Bu_4NBH_4 to reduce certain functional groups, such as the cyano group of nitriles,[10] might be due to the presence of diborane in CH_2Cl_2 solutions of this reagent. However, the exact nature of the species present in CH_2Cl_2 solutions of Bu_4NBH_4 is unknown. These solutions are probably complex since it is known[11] that heptahydrodiborate ion ($B_2H_7^-$) is produced in solutions which contain borohydride ion (from Bu_4NBH_4) and diborane.

Tetrabutylammonium borohydride has also been used effectively in aprotic solvents for the reduction of indoles to idolines[12] and for the selective 1,4-reduction of α,β-unsaturated cyclic ketones.[13] Other reports of the use of this reagent that may be of relevance for organic synthesis include deoxy sugar synthesis (in an S_N2 reduction),[14] reduction of thiol esters,[15] stereoselective synthesis of indanols from 2-methyl-2-aryl-1-indanones,[16] preparation of methylboronic acid and trimethylboroxin,[17] the use of borohydrides on solid supports,[18] and synthesis of organic selenides and tellurides.[19]

Related Reagents.

Diborane; ***Sodium Borohydride***; ***Tetra-n-butylammonium Cyanoborohydride***.

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Tetra-*n*-butylammonium Bromide[1]

***n*-Bu$_4$NBr**

[1643-19-2] · $C_{16}H_{36}BrN$ · Tetra-*n*-butylammonium Bromide · (MW 322.43)

(phase-transfer catalyst;[1] source of nucleophilic bromide[1])

Physical Data: mp 103-104 °C.

Solubility: sol H_2O, 1% aq NaOH, CH_2Cl_2, EtOH; slightly sol toluene; insol 20% aq NaOH.

Form Supplied in: anhydrous white solid.

Analysis of Reagent Purity: tetraalkylammonium salts can be titrated with potassium 3,5-di-*t*-butyl-2-hydroxybenzenesulfonate and iron(III) chloride.[1a]

Preparative Methods: several methods are available to recover the quaternary ammonium ion efficiently.[1a]

Purification: all manipulations should be carried out in a dry-box. The salt can be crystallized from benzene (5 mL g^{-1}) at 80 °C by adding 3 vol of hot hexane and allowing to cool. It can also be purified by precipitation of a saturated solution in dry CCl_4 by addition of cyclohexane or by crystallization from a mixture CH_2Cl_2-Et_2O. After filtration, the solid is further dried by heating at 75 °C under vacuo (0.1 mmHg) in the presence of P_2O_5.[2]

Handling, Storage, and Precautions: highly hygroscopic; if used in a reaction requiring anhydrous conditions, it should be manipulated in a glove-bag or in a dry-box.

Catalyst for C-X Bond Formation.

Tetrabutylammonium bromide is undoubtedly one of the most widely used phase-transfer catalysts. It combines the lipophilicity required for an efficient phase-transfer catalyst with the hydrophilicity necessary for efficient catalyst recovery. It has been successfully used in the liquid-liquid or solid-liquid phase-transfer alkylation of the NH groups of anilines,[3] amides,[4] lactams,[5] sulfonamides,[6] and other nitrogen heterocyclic compounds.[7] Sulfur[8] and oxygen-containing functional groups[9] can also be smoothly alkylated under phase-transfer conditions. Several *S*-alkylthioacridines have been prepared by liquid-liquid[10] or solid-liquid[11] phase-transfer catalysis (eq 1).

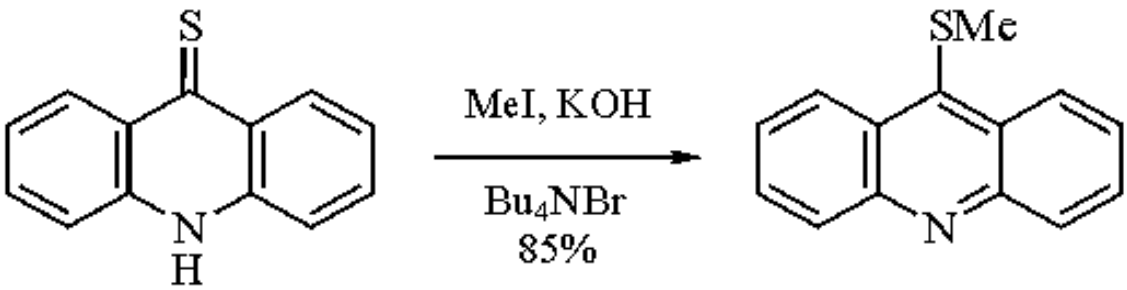

(1)

Carboxylic acids[12] and phenols[13] can also be alkylated in the presence of tetrabutylammonium bromide. Macrolides can be synthesized by an intramolecular S_N2 reaction of a bromo ester via simulated high dilution conditions (eq 2).[14]

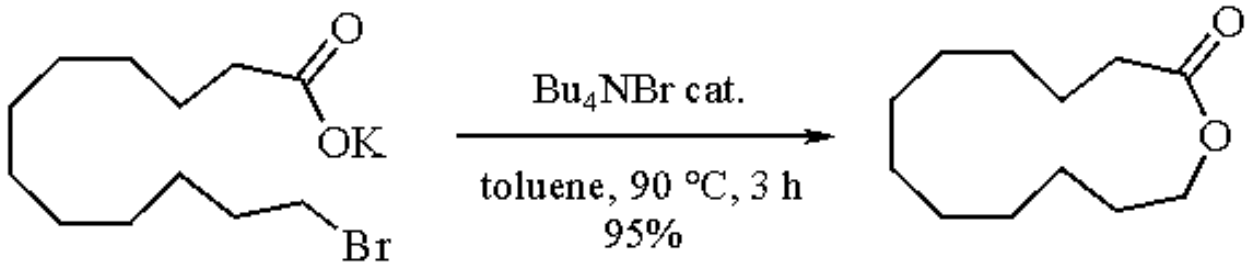

(2)

Bu_4NBr is also very effective in promoting nucleophilic aromatic substitution reactions to produce aryl thio esters,[15] aryl ethers,[16] and *N*-arylbenzodiazepines.[17] Some glycosylations were shown to be efficient only in the presence of Bu_4NBr.[18]

Catalyst for Oxidation Reactions.

Phase-transfer oxidation of alcohols to acids,[19] alkenes to carboxylic acids,[18] sulfides to sulfones,[20] and sulfilimines to sulfoximines[21] have also been carried out in the presence of tetrabutylammonium bromide along with an oxidizing reagent.

Catalyst for C-C Bond Formation.

The presence of Bu_4NBr was shown to be essential in a number of carbon-carbon bond-forming reactions, such as the alkylation of allyl sulfones[22] and of ***Malononitrile***,[23] and in the lead-promoted Barbier-type reaction of propargyl bromide with aldehydes.[24] It has also been used in the efficient synthesis of racemic α-alkyl and α,α-dialkyl α-amino acids by phase-transfer alkylation of Schiff bases (eq 3).[25]

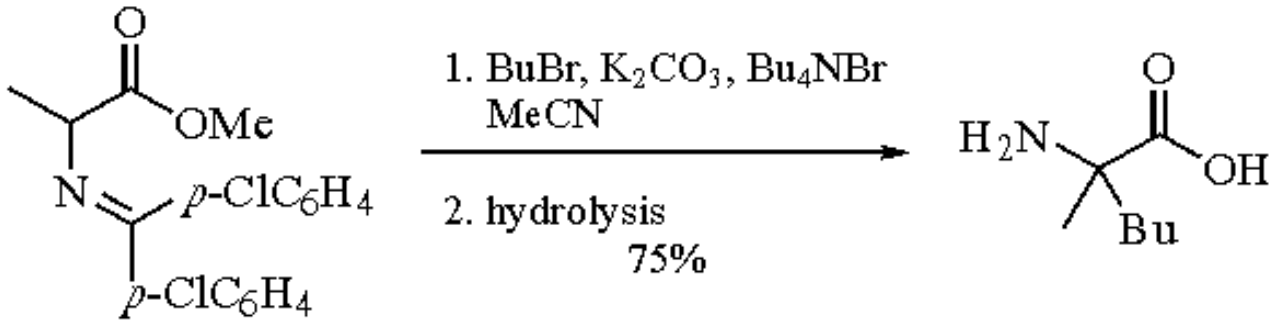

(3)

The presence of Bu_4NBr was shown to be necessary to increase the efficiency of some carbon-carbon double bond forming reactions such as Heck-type couplings,[26] dehydrohalogenations,[27] and Horner-Emmons-Wittig reactions.[28]

Alkyl and Alkenyl Bromides.

Bu_4NBr can be used as a powerful source of bromide for nucleophilic displacement reactions of triflates[29] and iodonium salts.[30]

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Tetra-*n*-butylammonium Chlorochromate[1]

***n*-Bu$_4$N(ClCrO$_3$)**

[54712-57-1] · $C_{16}H_{36}ClCrNO_3$ · Tetra-*n*-butylammonium Chlorochromate · (MW 377.98)

(mild and selective oxidizing agent for benzylic and allylic alcohols;[2] can oxidize thiols[2])

Alternate Name: TBACC.

Physical Data: mp 184-185 °C.

Solubility: sol ethyl acetate, THF, $CHCl_3$, CH_2Cl_2.

Form Supplied in: orange crystalline solid; widely available.

Handling, Storage, and Precautions: the dry solid is nonhygroscopic, but must be stored in the absence of light, since it slowly darkens within weeks, although without losing its oxidizing power. Reaction solvents must be anhydrous and free of reducing impurities. Tetrabutylammonium chlorochromate is reported to be a toxic agent. Use in a fume hood.

Oxidation of Benzylic and Allylic Alcohols.

As is well known, the oxidizing power of heterocycle-chlorochromate salts is inversely proportional to the basicity of the amine counterpart of the chlorochromate anion. Consequently, tetrabutylammonium chlorochromate is described as a neutral, mild, and selective oxidant for benzylic and allylic alcohols. The reagent (3 equiv) very slowly oxidizes these alcohols into the corresponding carbonyl compounds at rt in 68-88% yield (eqs 1-3).[2a] No (*E*)/(*Z*) isomerization is generally observed.

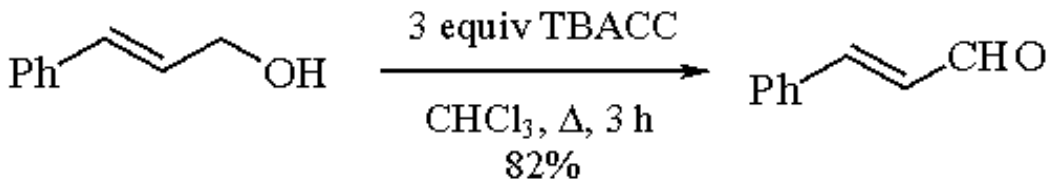

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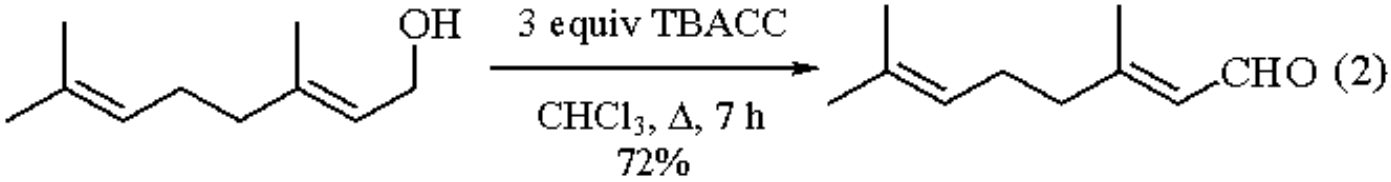

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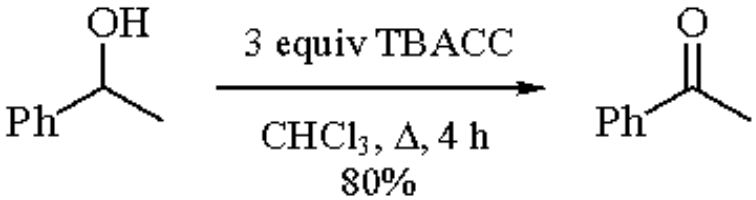

(3)

In refluxing chloroform, the oxidation of benzylic and allylic alcohols is achieved in a reasonable period of time (1-24 h) and in good yields. Using 3 equiv of oxidant, saturated aliphatic alcohols are oxidized to a minimum extent both at rt and in refluxing chloroform. For example, treatment of 1-phenyl-1,3-propanediol with TBACC at 70 °C for 1 h affords 3-hydroxy-1-phenyl-1-propanone in 52% yield (eq 4).[2]

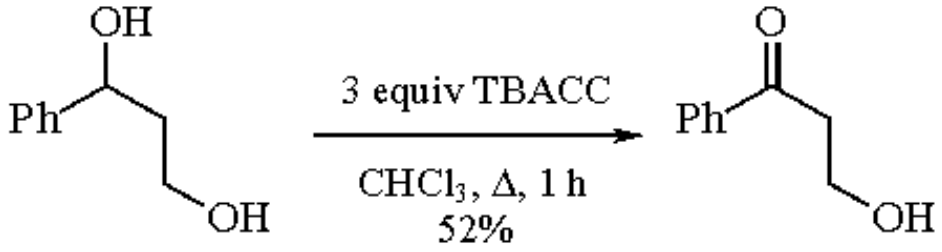

(4)

With a large excess of oxidant (6 equiv), primary and secondary aliphatic alcohols can be oxidized slowly in refluxing chloroform to carbonyl compounds in 50-75% yields.[2a]

Oxidation of Thiols.

TBACC can rapidly perform oxidative coupling of thiols to disulfides in good yield. The reaction can be applied to both alkanethiols and arenethiols, and appears to be superior to ***Pyridinium Chlorochromate*** for this transformation (eq 5).[2]

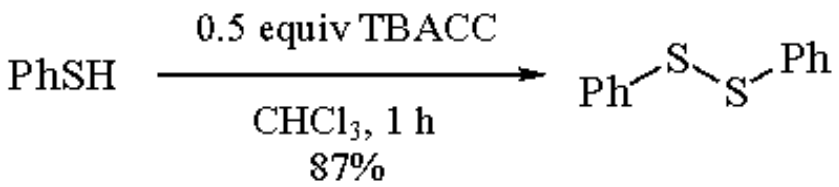

(5)

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Tetra-*n*-butylammonium Cyanoborohydride[1]

***n*-Bu$_4$NBH$_3$CN**

[43064-96-6] · $C_{17}H_{39}BN_2$ · Tetra-*n*-butylammonium Cyanoborohydride · (MW 282.39)

(selective, mild reducing reagent for aldehydes, conjugated aldehydes and ketones, alkyl iodides and bromides; useful for reductive aminations of aldehydes and ketones in nonpolar solvents)

Alternate Name: TBAC.

Physical Data: mp 144-145 °C.

Solubility: sol most polar (e.g. alcohols, carboxylic acids), polar aprotic (e.g. HMPA, DMSO, DMF), and nonpolar (e.g. CH_2Cl_2, benzene, hexane) solvents; sparingly sol H_2O, ether.

Form Supplied in: white, nonhydroscopic solid; commercially available.

Preparative Methods: from *n*-Bu$_4$NHSO$_4$ suspended in H_2O, treated with ***Sodium Hydroxide*** and ***Sodium Cyanoborohydride***, and extracted into CH_2Cl_2; recrystallized from ethyl acetate. Other tetraalkylammonium derivatives are available[3a] (including polymer-supported)[3b] or can be generated in situ from $NaBH_3CN$ and Aliquat 336.[3c]

Functional Group Reductions.

Under neutral conditions in HMPA at ambient temperature, only primary alkyl iodides and allylic bromides are efficiently reduced with TBAC. Most other functional groups, including aldehydes, ketones, esters, amides, nitro groups, and epoxides, are inert. At higher temperatures (e.g. 70-100 °C), benzylic halides, primary and secondary bromides, and naphthalenic iodides and bromides are also reduced (Table 1).[4]

Table 1 Reductions of Alkyl Halides with TBAC in HMPA

Compound	Temp. (°C)	Time (h)	Product	Yield (%)
$Me(CH_2)_9I$	25	21	$Me(CH_2)_8Me$	81
$Me(CH_2)_9Br$	80	24	$Me(CH_2)_8Me$	89
$PhCH{=}CHCH_2Br$	25	3	PhCH=CHMe	64
2,6-$Cl_2C_6H_3CH_2Cl$	70	17	2,6-$Cl_2C_6H_3Me$	91
PhCHBrMe	70	5.25	$PhCH_2Me$	78
1-Bromonaphthalene	100	66	Naphthalene	99

In acidic media, TBAC reduces aldehydes and ketones to alcohols (eqs 1 and 2). However, the greater susceptibility of aldehydes allows selective reductions in the presence of ketones (and halides) at low acid concentrations (eq 3).[1a,5] Alicyclic α,β-unsaturated and α,β-alkynic carbonyls are reduced to allylic and propargylic alcohols, respectively, in acidic media (eq 4).[2]

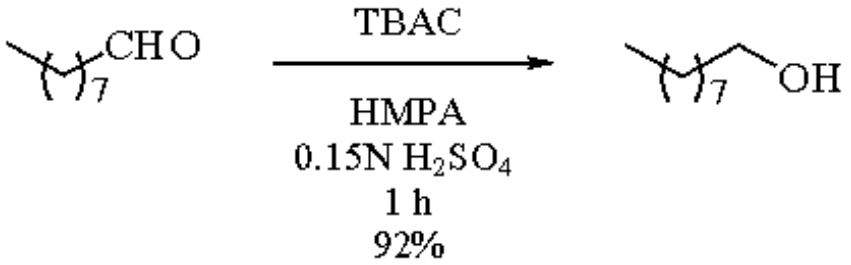

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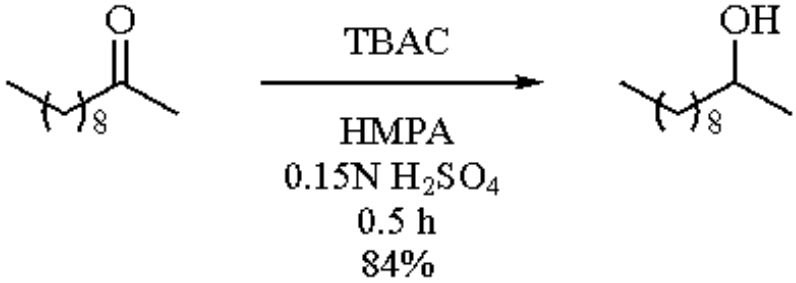

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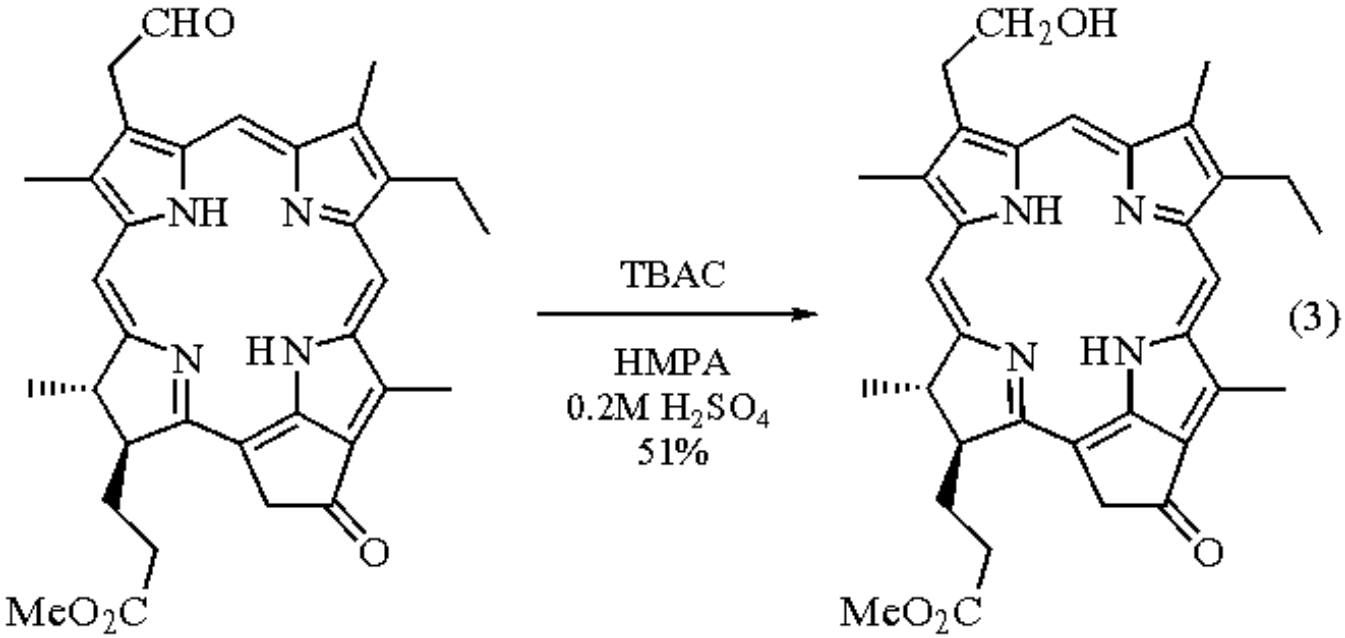

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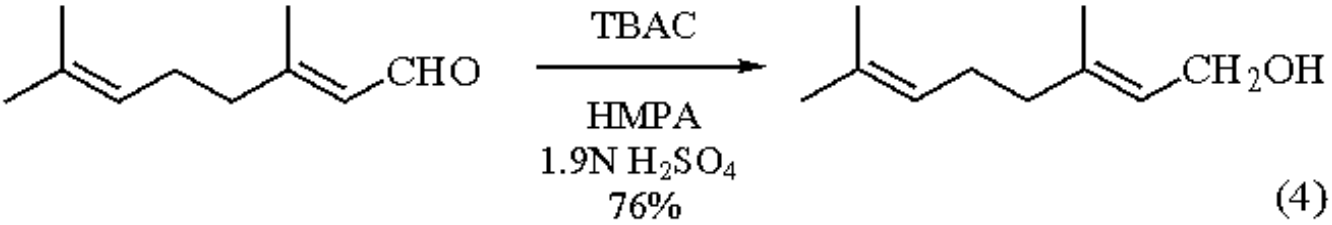

(4)

TBAC is effective for reductive aminations of aldehydes and ketones in nonpolar media including CH_2Cl_2, hexane, THF, and benzene (eq 5).[3c] Alternatively, the combination of ***Sodium Cyanoborohydride*** and Aliquat 336 (methyltrialkylammonium chloride) may be used to generate tetraalkylammonium cyanoborohydride in situ for reductive aminations (eq 6).[3c]

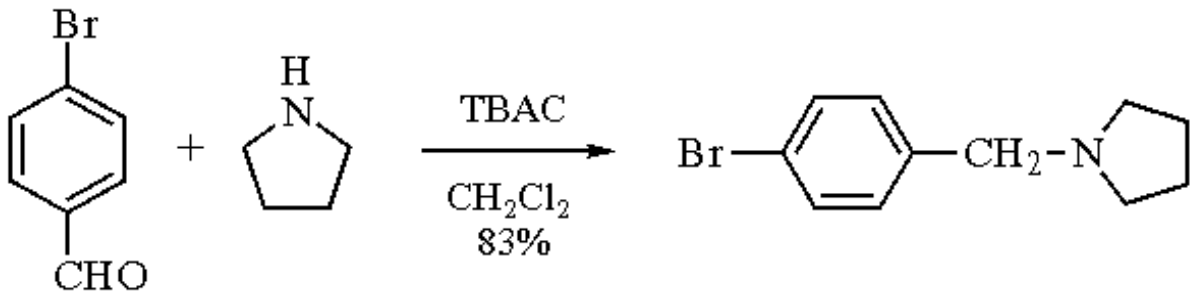

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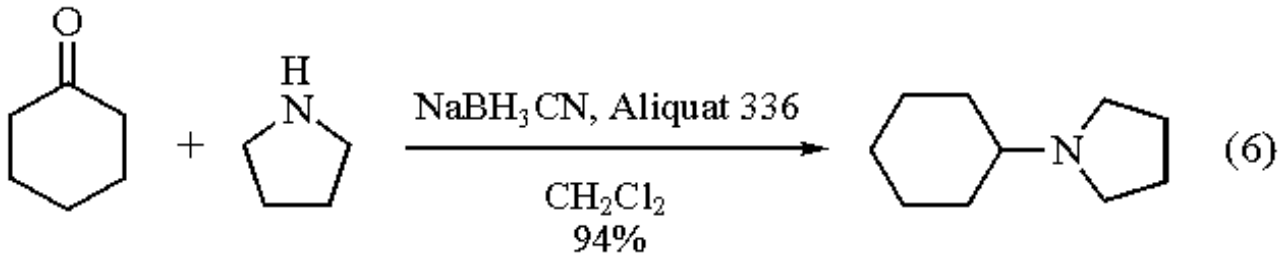

The excellent chemoselectivity available recommends this reagent for reduction of primary alkyl iodides and benzylic bromides at ambient temperature in HMPA since virtually no other functional groups are affected. At higher temperatures, other halides are also reduced chemoselectively. Comparison between TBAC and other cyanoborohydrides (particularly $NaBH_3CN$) for halide reductions is provided by Hutchins.[4] In acidic media, effective chemoselective reductions of aldehydes in the presence of ketones may be obtained.

TBAC allows reductive aminations in nonpolar solvents as an alternative to $NaBH_3CN$, which is used in polar solvents.

Related Reagents.

Sodium Cyanoborohydride; ***Sodium Triacetoxyborohydride***.

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Tetra-*n*-butylammonium Dichlorocuprate(I)[1]

***n*-$Bu_4N^+CuCl_2^-$**

[39926-94-8] · $C_{16}H_{36}Cl_2CuN$ · Tetra-*n*-butylammonium Dichlorocuprate(I) · (MW 376.92)

(homogeneous catalyst for rearrangement of propargyl chlorides to allenyl chlorides;[2] reagent for halogen exchange of halonitrobenzenes[1])

Alternate Name: copper(I) chloride-tetra-*n*-butylammonium chloride.

Physical Data: mp 71-72 °C.

Solubility: sol haloalkanes, haloarenes, ketones, and other polar solvents; poorly sol alkanes.

Preparative Methods: in situ complexation of freshly prepared ***Copper(I) Chloride*** by tetrabutylammonium chloride in appropriate solvent (acetone, chloroform, etc.);[2] pure material can best be prepared by reduction of ***Copper(II) Sulfate*** pentahydrate in aqueous solution with sodium sulfite or ascorbic acid in the presence of tetrabutylammonium hydrogen sulfate and sodium chloride, in the molar ratio 1:2:1:4. The resulting dichlorocuprate salt is extracted into CH_2Cl_2 and may be purified by recrystallization.[3]

Purification: the CH_2Cl_2 solution of the reagent may be dried, the solvent evaporated, and the residue recrystallized from ethyl acetate to yield colorless crystalline rhombic plates.

Handling, Storage, and Precautions: the solid cuprate salt is stable to short-term exposure to air, but should be used immediately or stored under an inert atmosphere.

Chloride Source.

The purified, solid copper(I) chloride-tetrabutylammonium chloride complex has been shown by X-ray crystallography to consist of monomeric, linear $CuCl_2^-$ ions,[4] and is thus best described as tetrabutylammonium dichlorocuprate(I). The reagent appears to function as a source of nucleophilic chloride soluble in common organic solvents. The exact role of the copper(I) is unclear, but the reactivity of the dichlorocuprate does not appear to be a simple extension of that of the chloride ion alone. The nucleophilic reactivity is strongly enhanced over that of tetrabutylammonium chloride alone in the same solvents,[1] and it seems likely that the dichlorocuprate ion coordinates with the substrate during reaction.

The reagent provides a mild alternative to the mixtures of solid and dissolved copper(I) chloride in concentrated hydrochloric acid commonly used to effect rearrangement of propargyl chlorides to the isomeric allenyl chlorides and to effect halogen exchange in activated aryl halides. It is particularly useful where a strongly acidic reaction medium is undesirable, or in kinetic studies in which it is necessary to know the exact concentration of

dichlorocuprate ion.

Use of this reagent promoted rearrangement of a propargyl chloride to the isomeric allene with a high degree of *anti* stereospecificity (eq 1).[2]

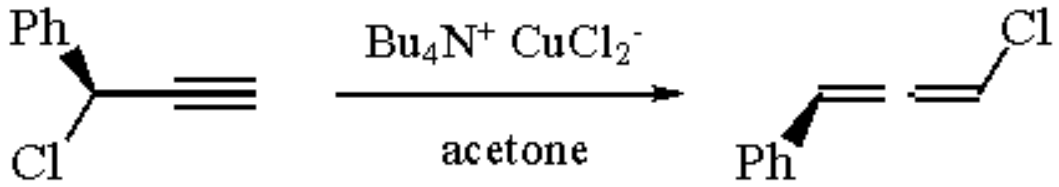

(1)

The purified dichlorocuprate reagent was used in kinetic studies of the halogen exchange reaction of 3-bromo-2-halonitrobenzenes (eq 2).[1,5]

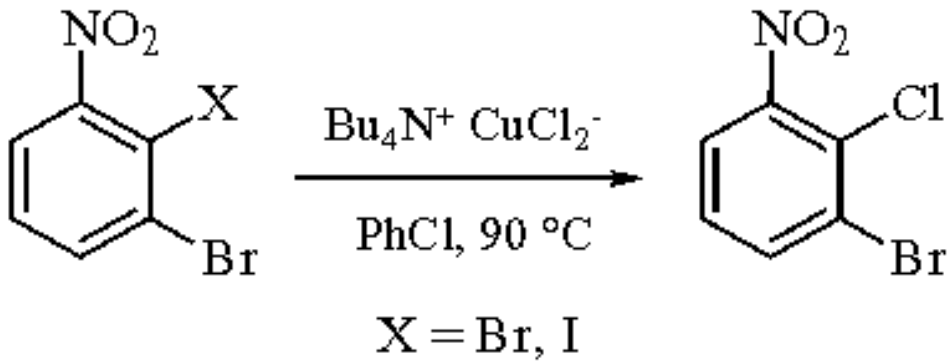

(2)

Both chlorides of the dichlorocuprate are kinetically active, and the observed rate expression was first order in both substrate and chloride ion. Under the conditions of the kinetic study in chlorobenzene solution, the substitution was approximately 90% complete after 5 h, and >99% complete after 24 h reaction time. The 3-bromo-2-chloronitrobenzene product was not reactive with tetrabutylammonium dibromocuprate and tetrabutylammonium diiodocuprate; hence, the above reaction was not reversible. However, 2,3-dibromonitrobenzene and 2-iodo-3-bromonitrobenzene underwent reversible substitutions with the latter two dihalocuprates. Reaction rates for substitution of 2,3-dibromonitrobenzene by tetrabutylammonium dichlorocuprate are enhanced in aqueous DMSO.[5]

Related Reagents.

Copper(I) Chloride; ***Tetra-n-butylammonium Fluoride***.

---

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Tetra-*n*-butylammonium Fluoride[1]

***n*-Bu$_4$NF**

(TBAF)

[429-41-4] · $C_{16}H_{36}FN$ · Tetra-*n*-butylammonium Fluoride · (MW 261.53) (TBAF.3H_2O)

[87749-50-6] · $C_{16}H_{42}FNO_3$ · Tetra-*n*-butylammonium Fluoride · (MW 315.59) (TBAF.*x*H_2O)

[22206-57-1]

(can be used for most fluoride-assisted reactions; deprotection of silyl groups;[1e] desilylation;[2,3] fluorination;[4] used as a base[5,6])

Alternate Name: TBAF.

Physical Data: TBAF.*x*H_2O: mp 62-63 °C.

Solubility: sol H_2O, THF, MeCN.

Form Supplied in: trihydrate, 1.0 M solution in THF, and 75 wt % solution in water.

Preparative Method: aqueous ***Hydrofluoric Acid*** is passed through an Amberlite IRA 410 OH column, followed by an aqueous solution of ***Tetra-n-butylammonium Bromide***. After the resin is washed with water, the combined water fractions are repeatedly evaporated until no water is present. Tetrabutylammonium fluoride is collected as an oil in quantitative yield.

Handling, Storage, and Precautions: use in a fume hood.

Deprotection of Silyl Groups.

Tetrabutylammonium fluoride has been used widely as a reagent for the efficient cleavage of various silyl protecting groups such as *O*-silyls of nucleosides,[7,8] pyrophosphate,[9] *N*-silyls,[10,11] CO_2-silyl, and *S*-silyl derivatives.[1e] These reactions are often carried out under very mild conditions in excellent yields. Thus it has been used in the synthesis of base-sensitive chlorohydrins (eq 1)[12] and β-lactams.[10,13] 2-(Trimethylsilyl)ethoxymethyl groups can also be effectively removed from various substrates (eq 2).[14-18] Silyl ethers can be converted to esters in one pot when they are treated with TBAF, followed by exposure to acyl chlorides[19,20] or anhydride[21] in the presence of base (eq 3). Treatment of triisopropylsilyl enol ethers with ***Iodosylbenzene***/***Azidotrimethylsilane***, followed by desilylation and elimination with TBAF, gives good yields of the α,β-unsaturated ketones (eq 4).[22,23]

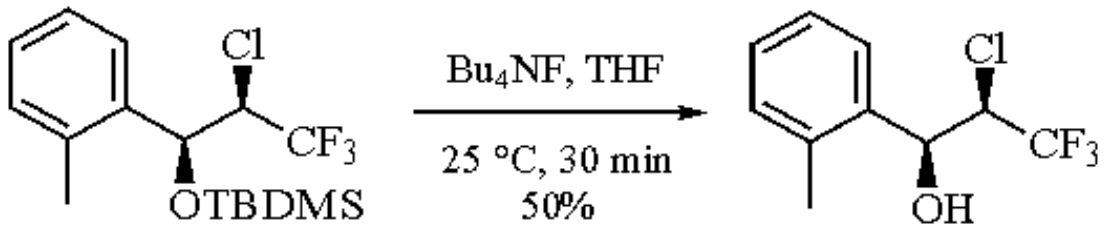

(1)

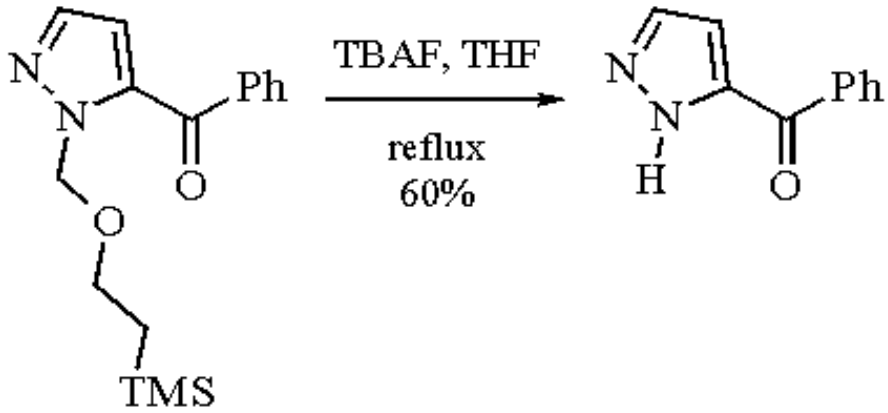

(2)

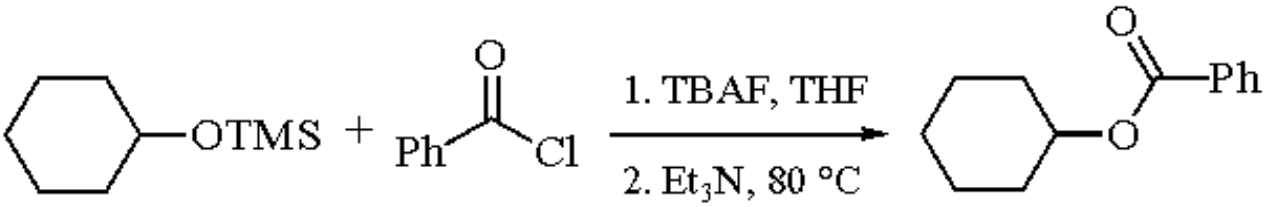

(3)

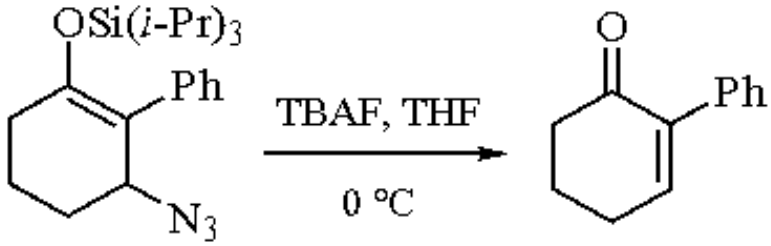

(4)

Cyclobutanone alkyl silyl acetals, obtained from [2 + 2] cycloadditions, can be deprotected with 1 equiv of TBAF in THF to give the open-chain cyano esters in excellent yields (eq 5).[24] When 4-chloro-2-cyanocyclobutane alkyl silyl acetals are used as substrates for this reaction, (*E*/*Z*) mixtures of 2-cyanocyclopropanecarboxylates are obtained by an intramolecular cyclization (eq 6).

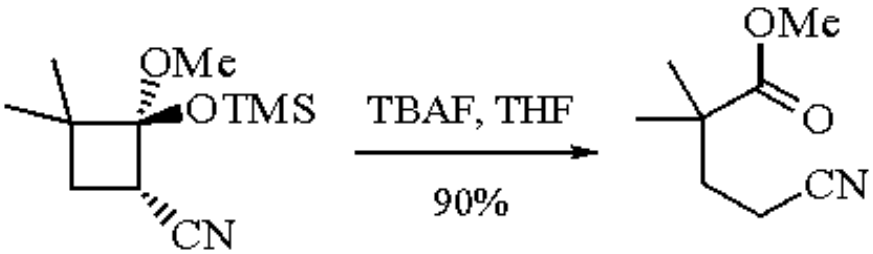

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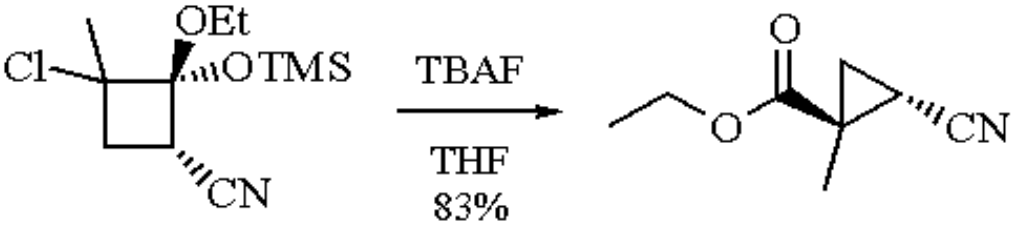

(6)

11-Membered pyrrolizidine dilactones have been synthesized by treating a trimethylsilylethyl ester with TBAF in MeCN to form an anion, which then undergoes cyclization by displacement of the mesylate.

Desilylation Reagent.

Cleavage of carbon-silicon bonds with fluoride has been studied very extensively. TBAF is a very powerful reagent for desilylation of a wide range of silicon-containing compounds, such as vinylsilanes,[2,25,26] alkynylsilanes,[23,27] arylsilanes,[28,29] acylsilanes,[30] β-silyl sulfones,[31-33] and other silane derivatives.[3,34-37] It appears that cleavage of sp-C-Si bonds is more facile than that of sp^2-C-Si and sp^3-C-Si bonds and that substituted groups, such as phenyl and alkoxyl, can often facilitate cleavage. A dimethylphenylsilyl group can be removed from a vinyl carbon by TBAF with retention of the alkene stereochemistry (eq 7).[2] This method has been applied to the synthesis of

terminal conjugated trienes (eqs 8 and 9).[38] The five-membered siloxanes can be desilylated with 3 equiv of TBAF in DMF and this protodesilylation is very sensitive to subtle structure changes (eq 10).[39]

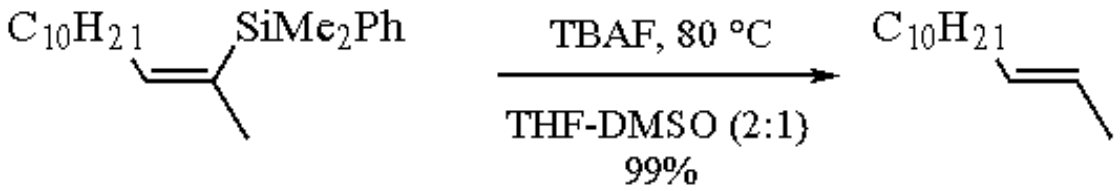

(7)

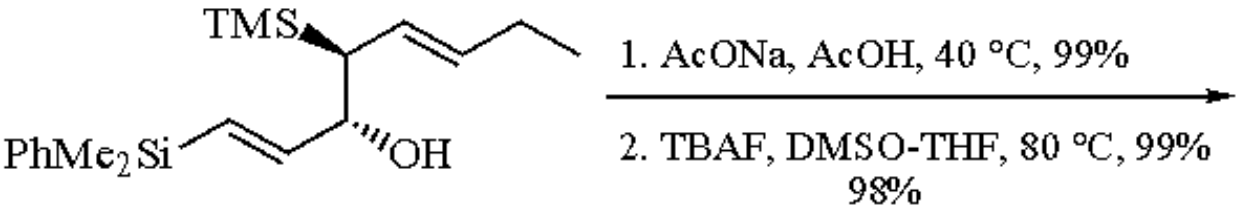

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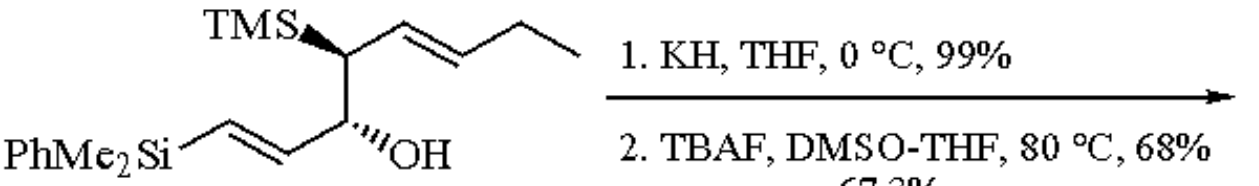

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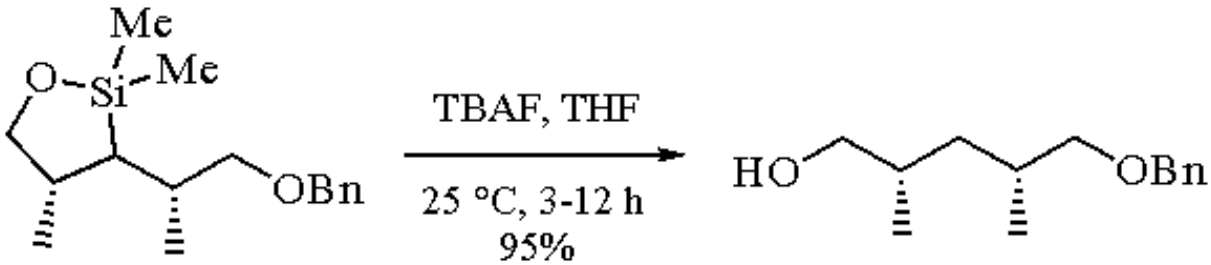

(10)

The anions, generated in situ by desilylation of silylacetylenes,[40,41] allylsilanes,[42-44] propargylsilanes,[45] α-silyloxetanones,[46] bis(trimethylsilylmethyl) sulfides,[47] and other silane derivatives,[48-51] can undergo nucleophilic addition to ketones and aldehydes (eq 11).[52] *N*-(*C*,*C*-bis(trimethylsilyl)methyl) amido derivatives can add to aldehydes followed by Peterson alkenation to form acyl enamines.[48,53] Treatment of 2-trimethylsilyl-1,3-dithianes can generate dithianyl anions, which are capable of carbocyclization via direct addition to carbonyl or Michael addition (eq 12). The fluoride-catalyzed Michael additions are more general than Lewis acid-catalyzed reactions and proceed well even for those compounds with enolizable protons and/or severe steric hindrance (eq 13).[54,55]

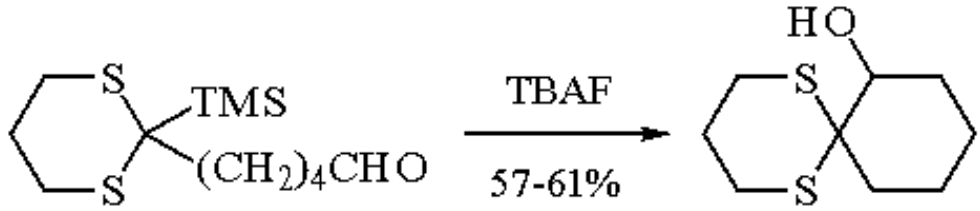

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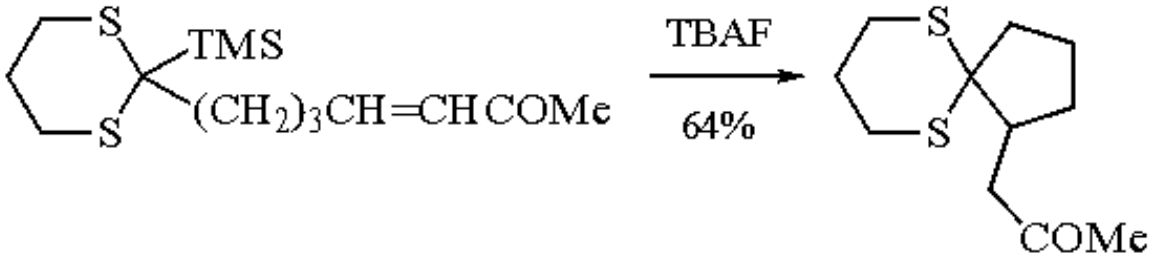

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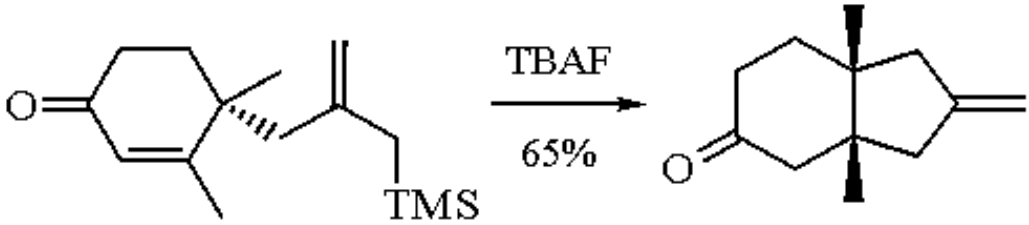

(13)

Direct fluoride-induced trifluoromethylation of α-keto esters (eq 14),[56] ketones,[57] aldehydes,[58,59] and sulfoxides[59] have been reported using ***Trifluoromethyltrimethylsilane*** with TBAF in THF.

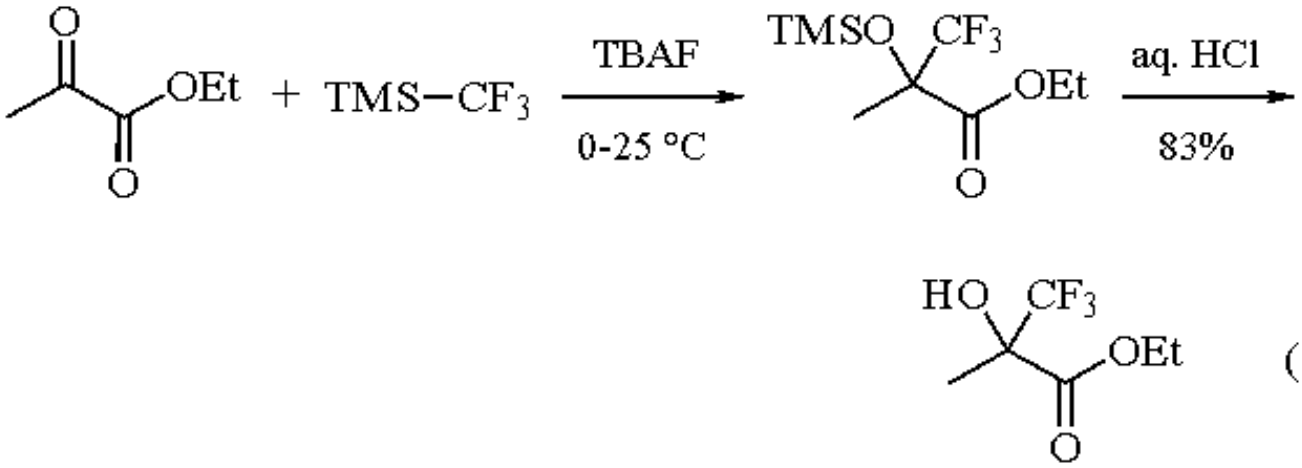

(14)

Desilylation of some compounds can generate very reactive species such as benzynes,[60] pyridynes,[61] xylylenes,[62,63] and benzofuran-2,3-xylylenes.[64] 1,4-Elimination of *o*-(α-trimethylsilylalkyl)benzyltrimethylammonium halides with TBAF in acetonitrile generates *o*-xylylenes, which undergo intermolecular and intramolecular cycloadditions (eq 15).[62-64] Treatment of α-silyl disulfides with ***Cesium Fluoride*** or TBAF forms thioaldehydes, which have been trapped by cycloaddition with cyclopentadiene (eq 16).[65]

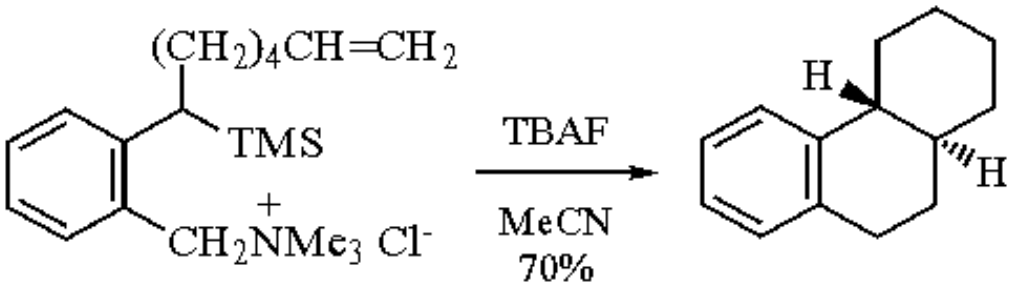

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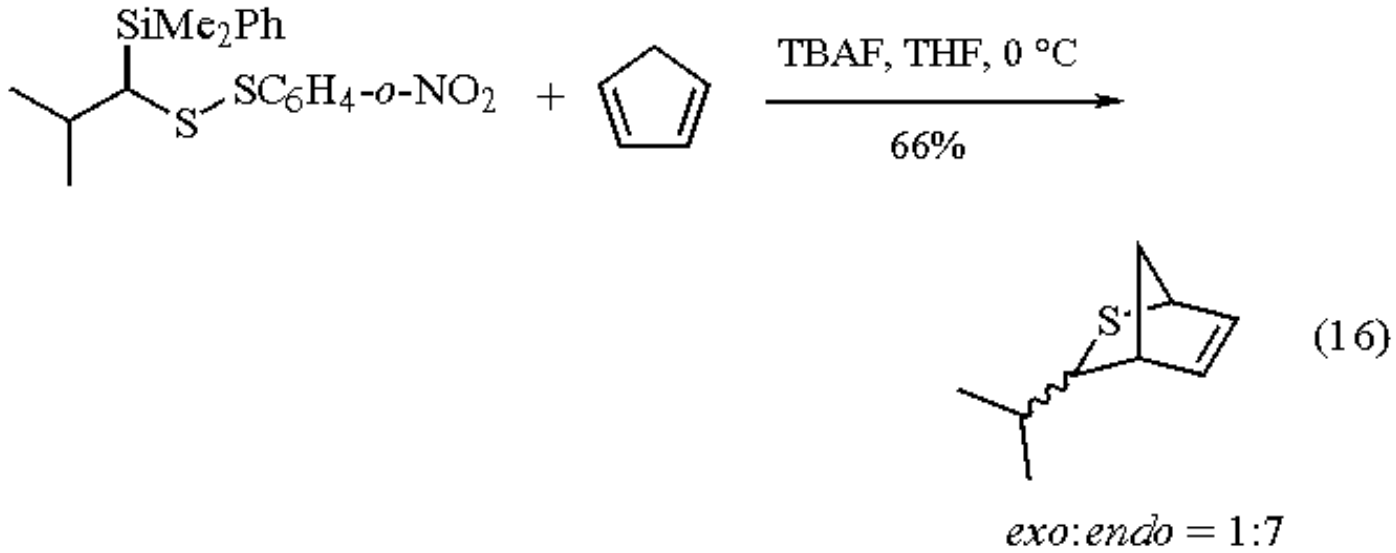

Use as a Base.

TBAF has been widely used for a variety of base-catalyzed reactions such as alkylation,[66] elimination,[67] halogenation,[68] Michael addition,[69-71] aldol condensation, and intramolecular cyclizations.[5,72-74] It is especially useful when other inorganic bases face solubility problems in organic solvents. The reactions are usually carried out below 100 °C due to the low thermal stability of TBAF.[1e]

TBAF is very useful for alkylation of nucleic acid derivatives. Methylation[75] or benzylation[66] of uracil gives almost quantitative yields of alkylated product when using alkyl bromides, dialkyl sulfates (eq 17), trialkyl phosphates, or alkyl chlorides with TBAF. Alkylation of the thiol anions generated from deprotection by 1,2-dibromoethane produces interesting tetrachalcogenofulvalenes.[14] Under phase-transfer conditions, selective mono- and dialkylations of malononitrile have been achieved by using neat TBAF with ***Potassium Carbonate*** or ***Potassium t-Butoxide*** and controlling the amount of alkyl bromides or iodides used (eqs 18 and 19).[76]

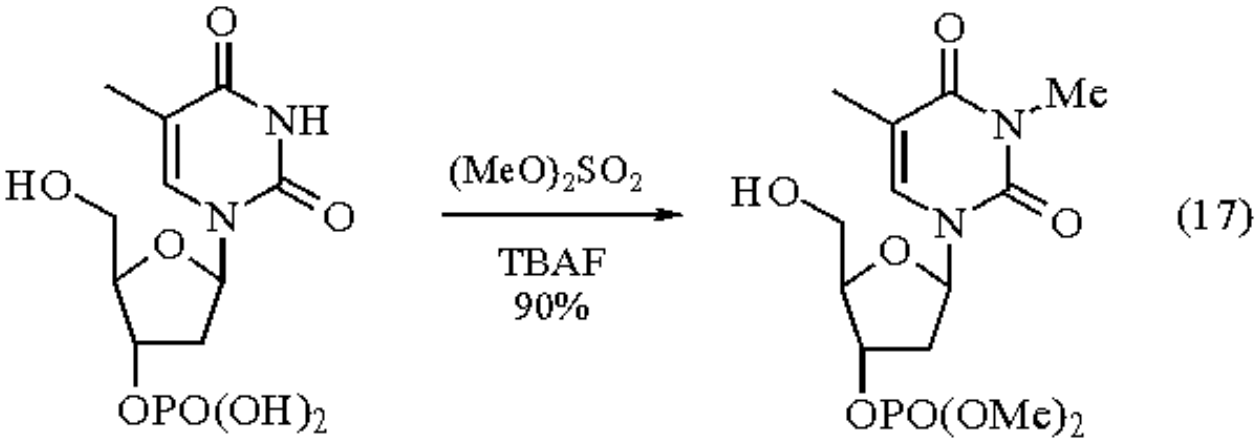

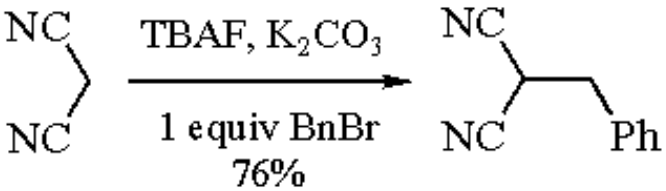

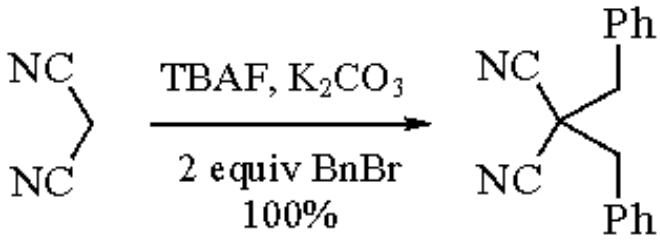

Enol silyl ethers react with aldehydes with a catalytic amount of TBAF to give the aldol silyl ethers in good yields. These reactions generally proceed under very mild conditions and within shorter periods of time than conventional strong acidic or basic conditions. The

products from 4-*t*-butyl-1-methyl-2-(trimethylsilyloxy)cyclohexene and benzaldehyde show very good axial selectivity and a little *anti-syn* selectivity (eq 20).[77] The aldol condensation of ketones and aldehydes can be achieved in one pot when ethyl (trimethylsilyl)acetate is used as a silylation agent with TBAF (eq 21).

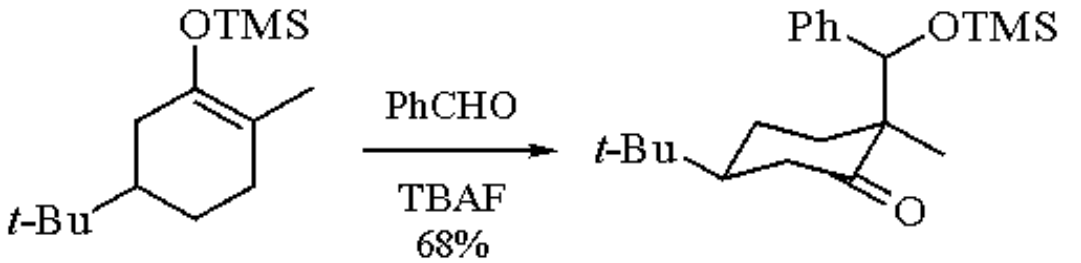

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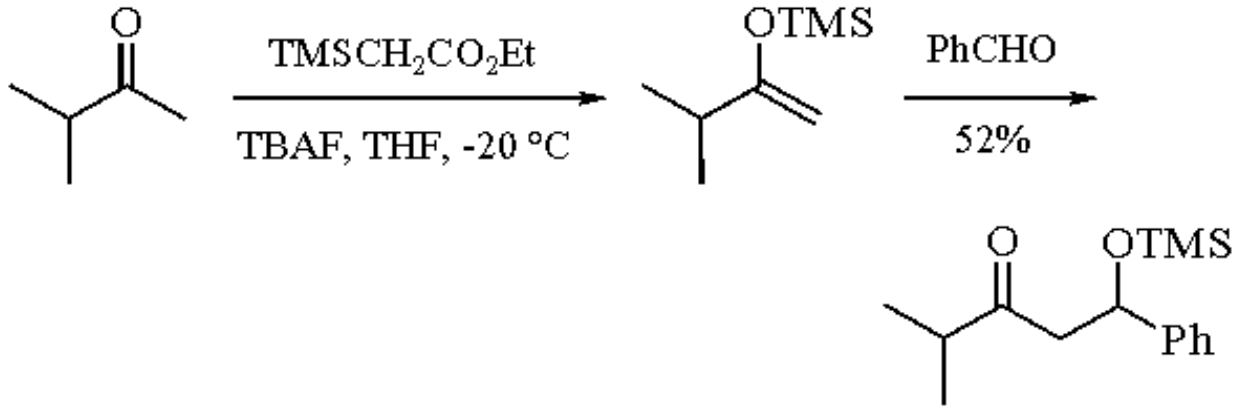

(21)

Silyl nitronates undergo aldol condensation with aldehydes in the presence of a catalytic amount of anhydrous TBAF to form highly diastereoselective *erythro* products, which can be elaborated to give synthetically useful 1,2-amino alcohols (eq 22).[6,78] A one-pot procedure has been developed for direct aldol condensation of nitroalkanes with aldehydes by using TBAF trihydrate with ***Triethylamine*** and ***t-Butyldimethylchlorosilane***.[79] It appears that silyl nitronates are not reactive intermediates in this case, and the reactions proceed by a different mechanism.

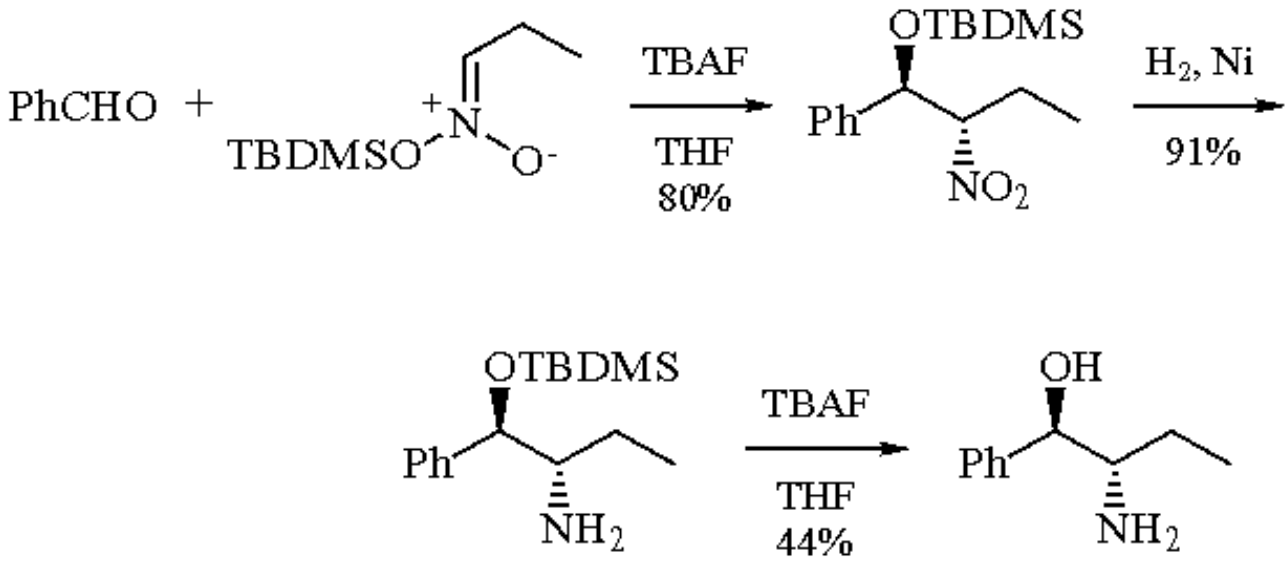

(22)

Miscellaneous.

Fluoride ion from anhydrous TBAF undergoes nucleophilic displacement of tosylates,[4,80] halides,[80] and aryl nitro compounds[81] to give fluorinated products. When used with ***N-Bromosuccinimide***, bromofluorination products are obtained.[82]

Several important peptide-protecting groups such as 9-fluorenylmethyloxycarbonyl,[83] benzyl,[84] 4-nitrobenzyl,[85] 2,2,2-trichloroethyl,[85] and acetonyl (eq 23)[86] can be removed by TBAF under mild conditions.

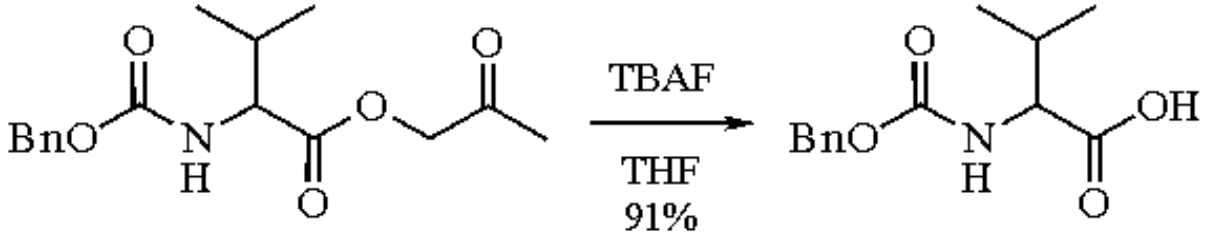

(23)

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Tetra-*n*-butylammonium Fluoride (Supported)[1]

***n*-Bu$_4$NF**

[429-41-4] · $C_{16}H_{36}FN$ · Tetra-*n*-butylammonium Fluoride (Supported) · (MW 261.53)

(can be used for most fluoride-assisted reactions;[1] deprotection of silyl groups;[2] catalysis of Michael addition;[1] alkylation;[3] desilylation;[4] fluorination[5])

Alternate Name: TBAF.

Form Supplied in: on alumina; on silica gel.

Handling, Storage, and Precautions: TBAF/SiO_2 is nonhygroscopic and an air-stable material. Contact with skin may cause irritation.

Desilylation Reagent.

Tetra-n-butylammonium Fluoride is very hygroscopic and absorbed water can greatly effect the reactivity. TBAF/SiO_2 is a nonhygroscopic fluoride ion source, which is also very effective for most fluoride-assisted reactions. Desilylations of allyl, benzyl, and heteroaryl silanes generate carbanions, which undergo nucleophilic addition to an electrophilic center.[4,6] The benzothiazolyl carbanion obtained from treatment of benzothiazolylsilanes with TBAF/SiO_2 or ***Cesium Fluoride*** adds to benzaldehyde to give alcohols (eq 1). When cyclohexen-2-one is used as an electrophile, the 1,4-Michael addition product is obtained in reasonable yield (eq 2). δ-Valerolactone can be opened under these reaction conditions to give the corresponding keto alcohols (eq 3).

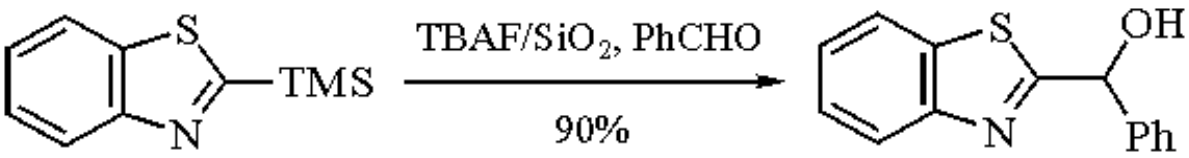

(1)

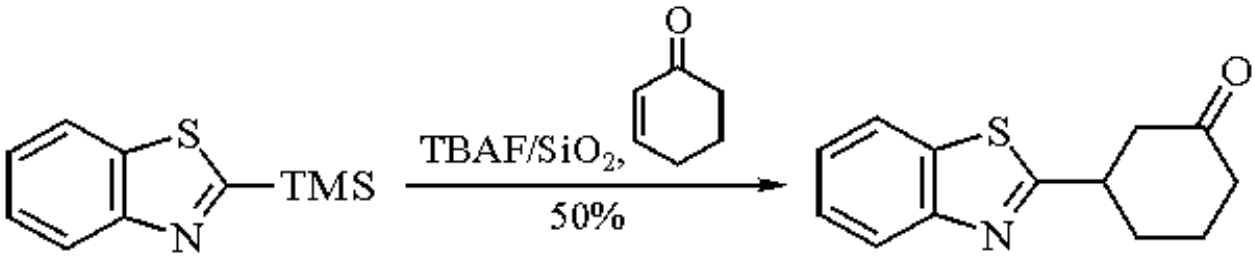

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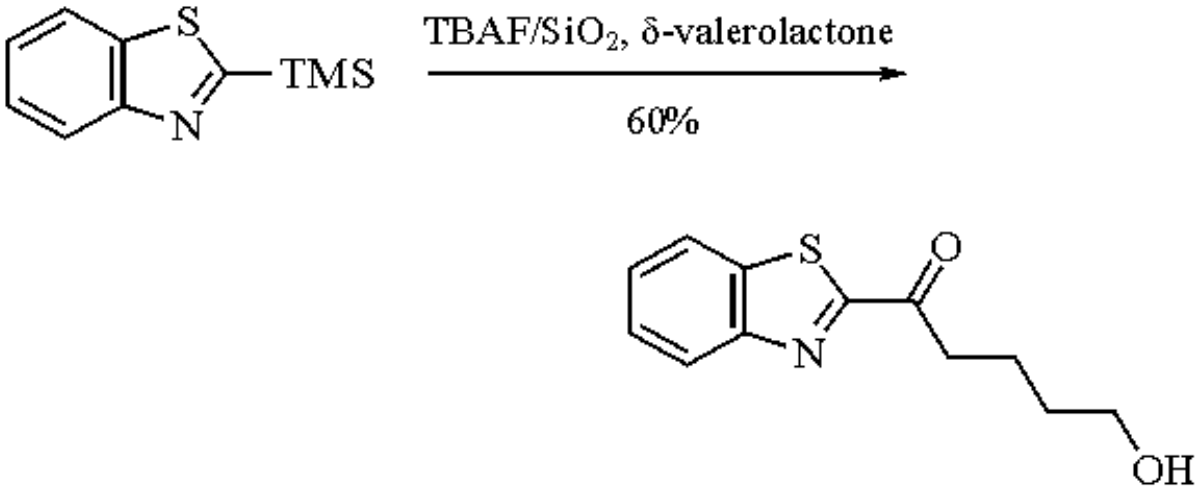

(3)

By using TBAF/SiO_2 or CsF as catalysts with allylsilanes, different products from addition to cyclohexen-2-one have been obtained (eqs 4 and 5). The α-chloroallyl anion made from α-trimethylsilylallyl chloride with TBAF/SiO_2 adds to benzaldehyde with little regioselectivity (eq 6).[7]

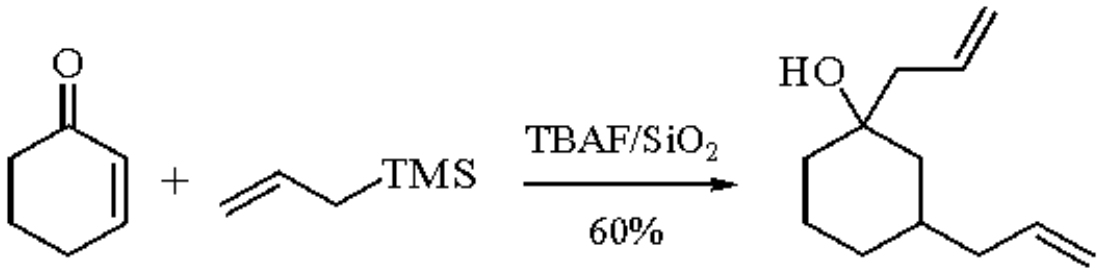

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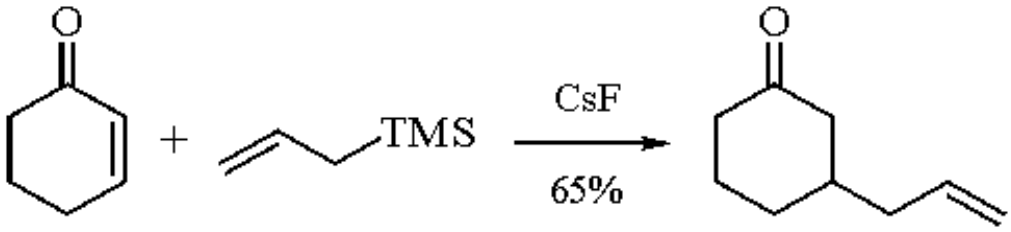

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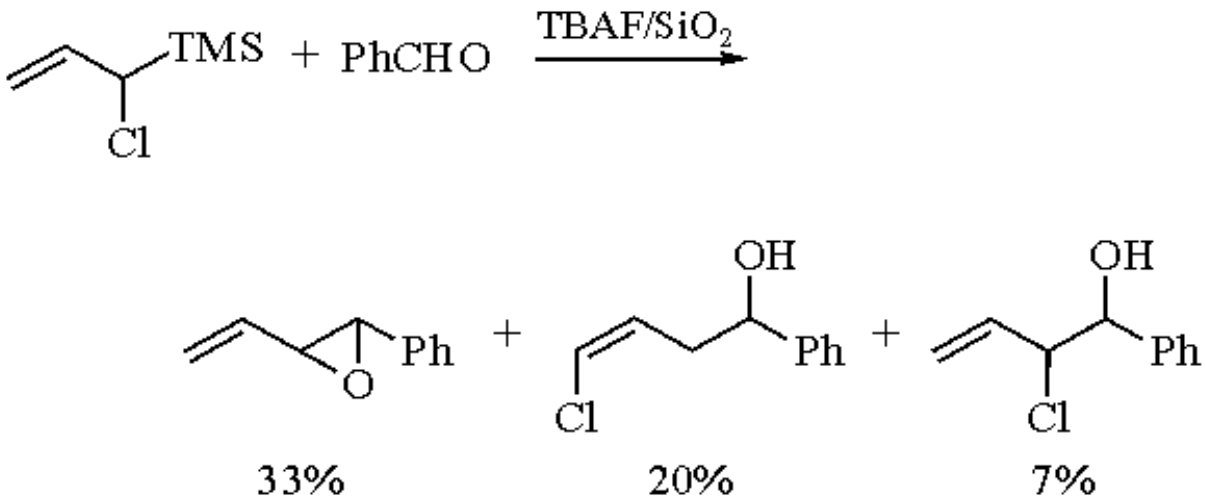

(6)

TBAF/SiO_2 is also effective for deprotecting silyl groups. TBDMS groups of *N*-silylated β-sultam derivatives can be removed by TBAF/SiO_2 using very mild conditions in good yields (eq 7).[2]

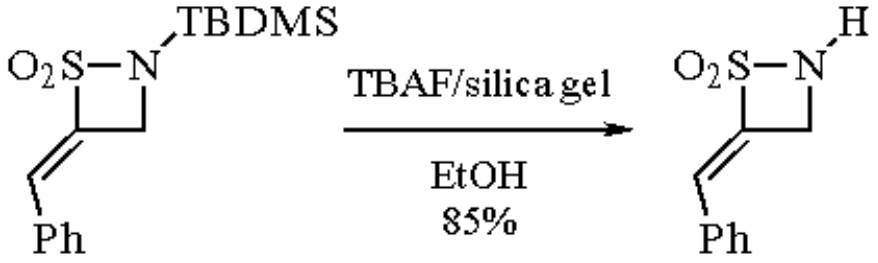

(7)

Fluoride- and Lewis acid-catalyzed intramolecular cyclization of alkylidene 1,3-dioxo compounds with an allylsilane moiety has been observed. It is possible that fluoride cleaves the allylic C-Si bond to give an allylic anion which adds to carbonyl compounds, or more likely, a hypervalent silyl anion is formed as an intermediate (eq 8).[8]

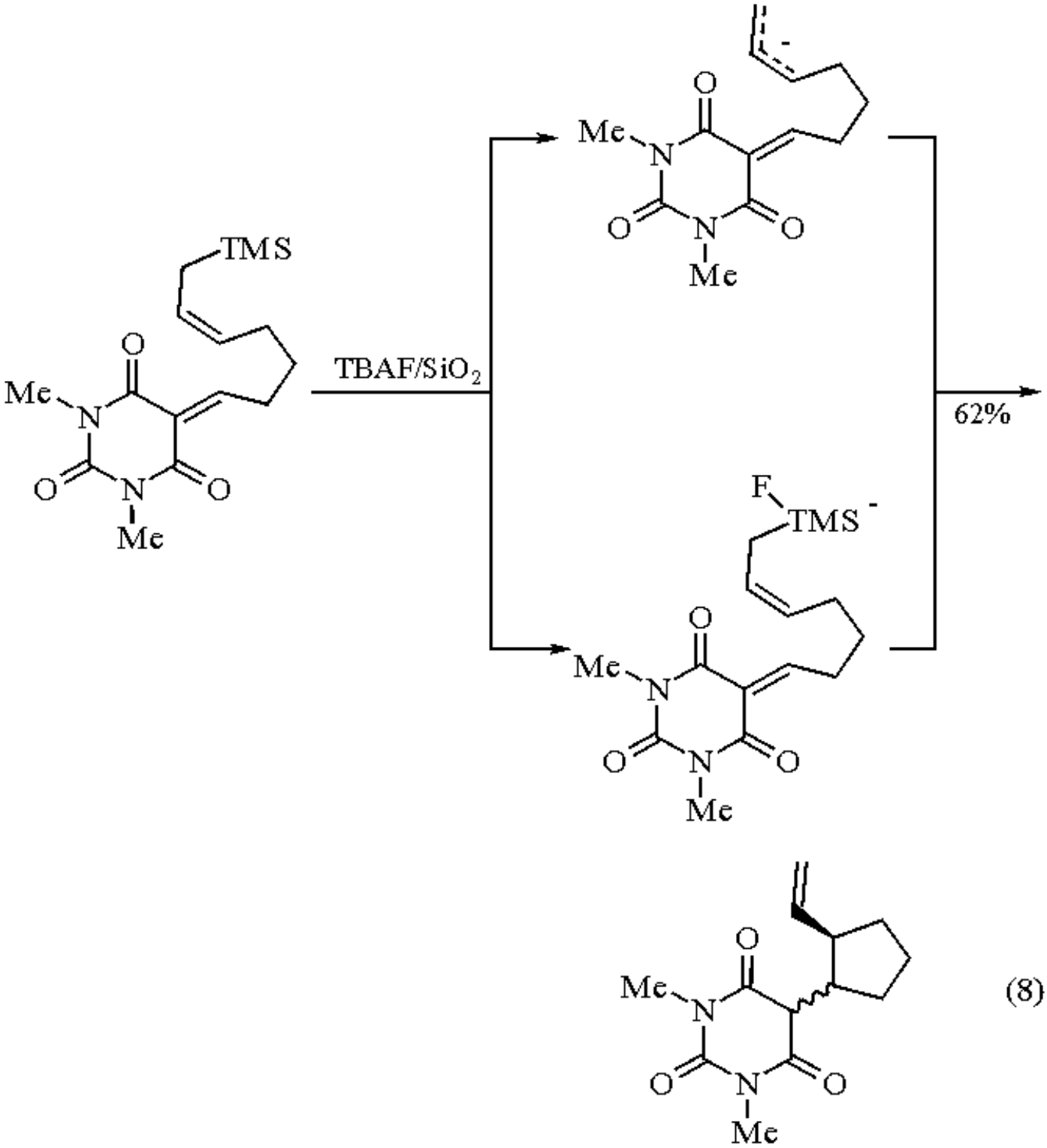

(8)

Fluorination.

Activated nitro groups can be displaced by the fluoride of TBAF or TBAF/SiO_2. This reaction can provide some very useful fluoroaromatic compounds with a very short synthesis. Heating 1-nitrobenzo[*c*]cinnoline with TBAF/SiO_2 in decalin for several hours gave 1-fluorobenzo[*c*]cinnoline in reasonable yield (eq 9).[5]

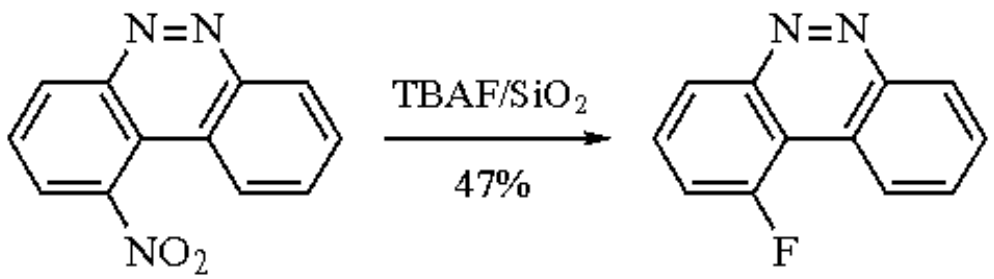

(9)

Use as a Base.

TBAF/SiO_2 is an effective and convenient reagent for catalyzing Michael addition, oxidation, sulfenylation, and alkylation. Nitromethane (eq 10) and PhSH (eq 11) undergo Michael addition very smoothly at rt within a few hours.[1] When a large excess of reagent was used, esterification of acetic acid was achieved (eq 12).

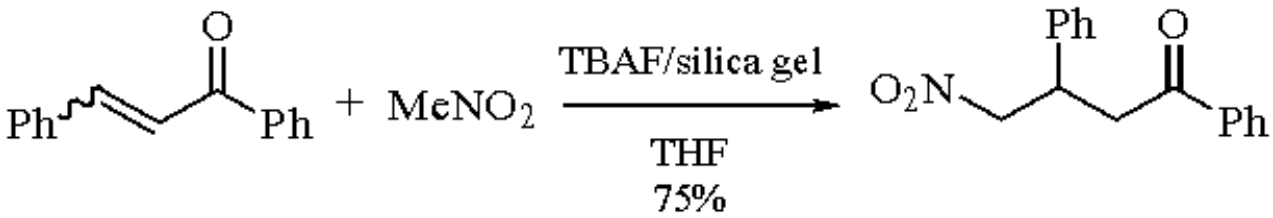

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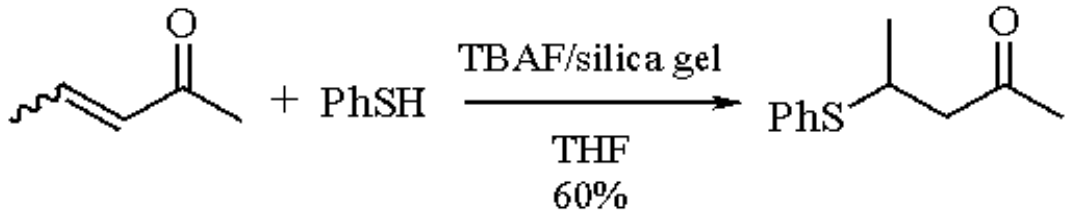

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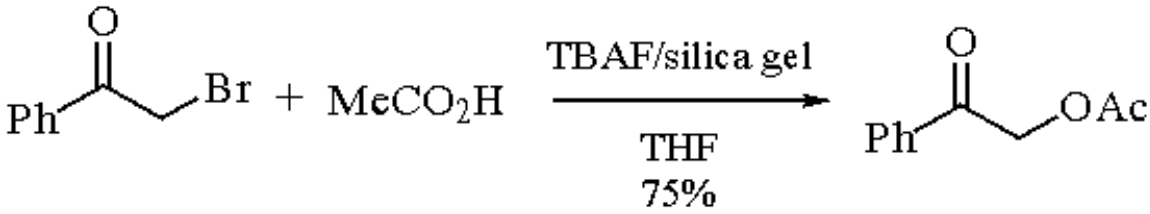

(12)

TBAF/Al_2O_3 is more effective than KF/Al_2O_3 and CsF/Al_2O_3 for methylation of phenol. The reactions are usually complete within a short period of time in quantitative yields (eq 13).[3]

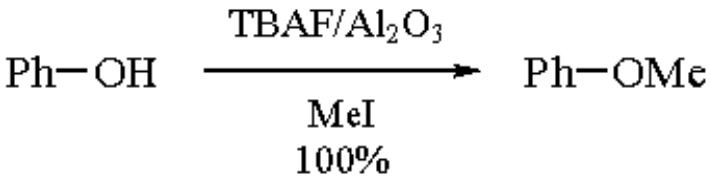

(13)

When using ***Ethyl Trimethylsilylacetate*** (ETSA) as a silylating agent and TBAF/SiO_2 as a catalyst, regioselective formation of silyl enol ethers has been achieved. 2-Methylcyclohexanone is converted to two silyl enol ether isomers where the kinetic product is predominant (eq 14). Exclusive kinetic product with high (*Z*) selectivity has been achieved on 2-methylpentan-3-one (eq 15). These reaction conditions can also be used to silylate alcohols with longer reaction times (eq 16).

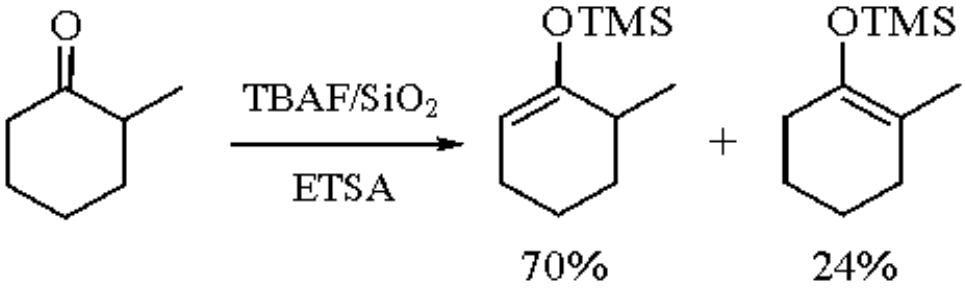

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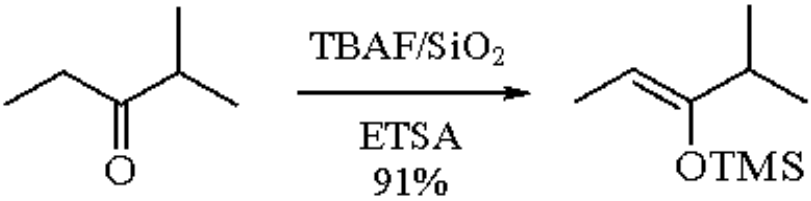

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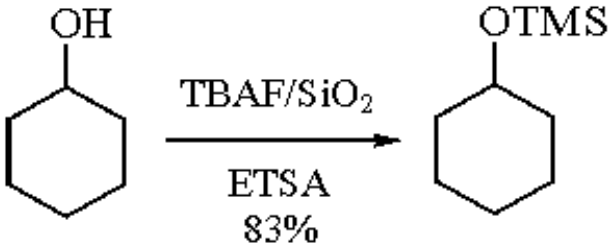

(16)

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Tetra-*n*-butylammonium Hydroxide

***n*-Bu$_4$NOH**

[2052-49-5] · $C_{16}H_{37}NO$ · Tetra-*n*-butylammonium Hydroxide · (MW 259.54)

(quaternary ammonium salt; strong base; phase-transfer catalyst[1])

Alternate Name: TBAH.

Solubility: sol most organic solvents (alcohols, hydrocarbons, aromatics, halogenated solvents), H_2O.

Form Supplied in: 40 wt % solution in H_2O; 1.0 M solution in MeOH. A typical impurity is tributylamine.

Analysis of Reagent Purity: aqueous titration with HCl versus phenolphthalein;[2] nonaqueous titration with benzoic acid in pyridine and thymol blue indicator.[3]

Preparative Method: prepared in situ from ammonium halides.[2]

Handling, Storage, and Precautions: methanol solution is hygroscopic; highly toxic; may decompose on heating.[4]

Alkylations.

Tetrabutylammonium hydroxide (**1**) has been used to effect a variety of organic transformations. A strongly basic catalyst, (**1**) was able to promote alkylation (eq 1)[5] and arylation[6] of nitroalkanes under phase-transfer conditions. The intermediate tetrabutylammonium *aci*-nitronates generated were more reactive than the corresponding lithium salts.

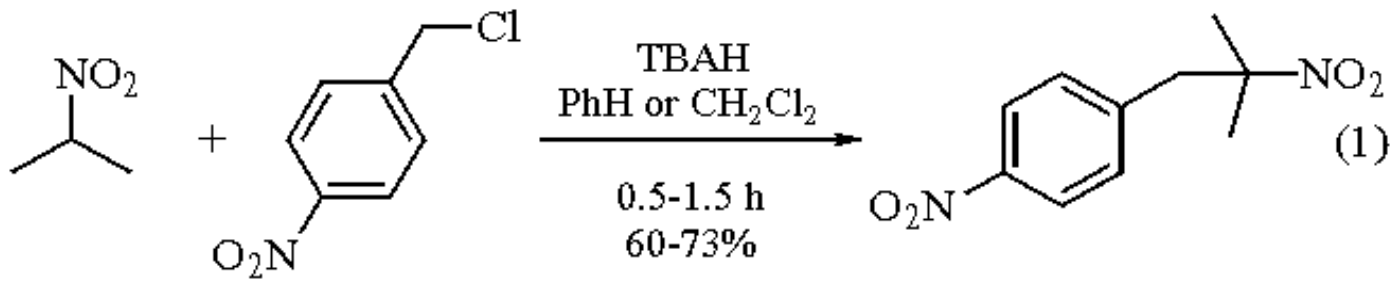

The monoalkylation of cyanomethanephosphonic diamides was reported to occur with high selectivity and good yield (eq 2).[7] Strong amide bases or ***Sodium Hydride*** led to formation of mixtures of mono- and dialkylation products. Alkylations of other active hydrogen compounds have been studied.[8]

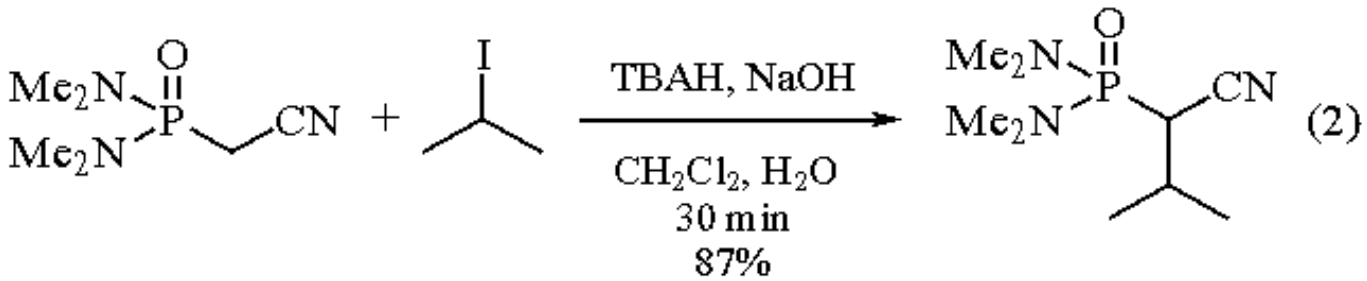

The selective monobenzylation of an indole nitrogen under phase-transfer conditions proceeds in better than 95% yield for a variety of substrates (eq 3).[9] The reaction is procedurally simple when compared to the alkylation of the dianion normally generated under

anhydrous conditions with ***n-Butyllithium*** (***Hexamethylphosphoric Triamide***, THF, 0 °C), which produces only a 60% yield of product.

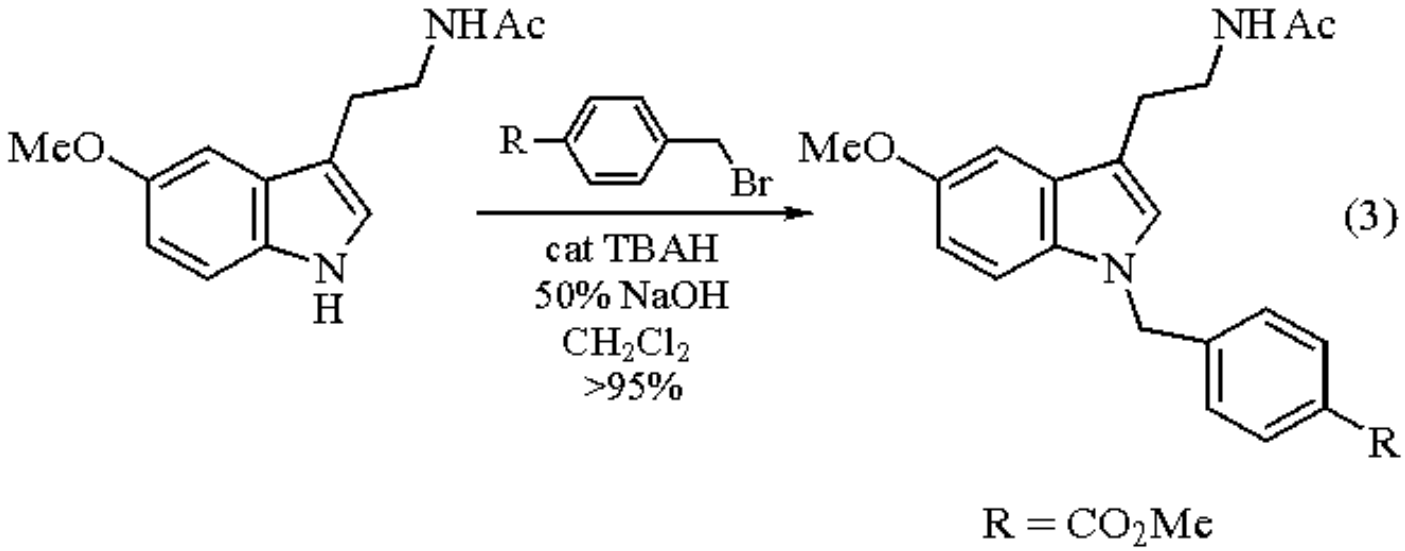

(3)

An extension of this chemistry is seen in the intramolecular alkylations of nitrogen which have been reported in the preparation of dihydropyridones (eq 4).[10]

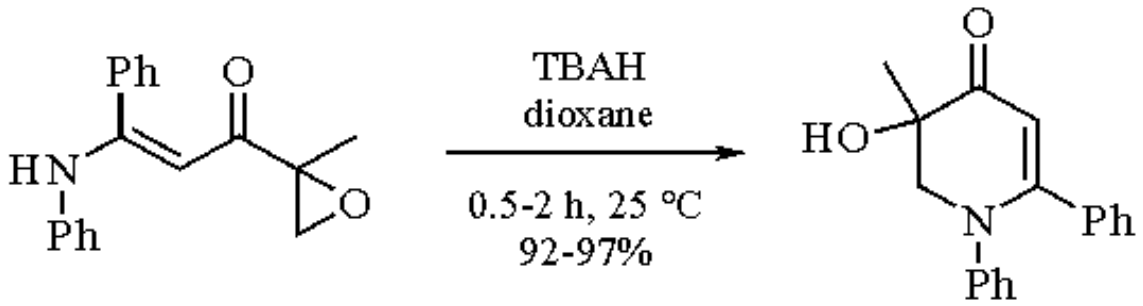

(4)

Tetrabutylammonium hydroxide has also been used in the Robinson annulation of dihydrocarvone with ***Methyl Vinyl Ketone*** in 63% yield, which is reported to improve upon other methods.[11] Dehydration does not occur in the reaction and workup is simplified (eq 5). Similarly, intramolecular Horner-Emmons closure of an activated phosphono ester was used in the synthesis of (±)-silphinene (eq 6).[12]

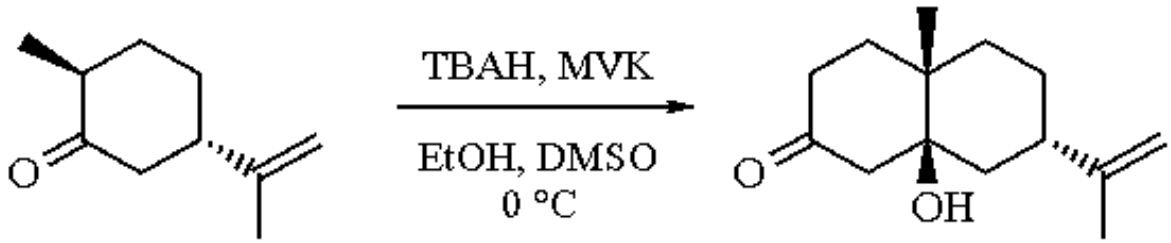

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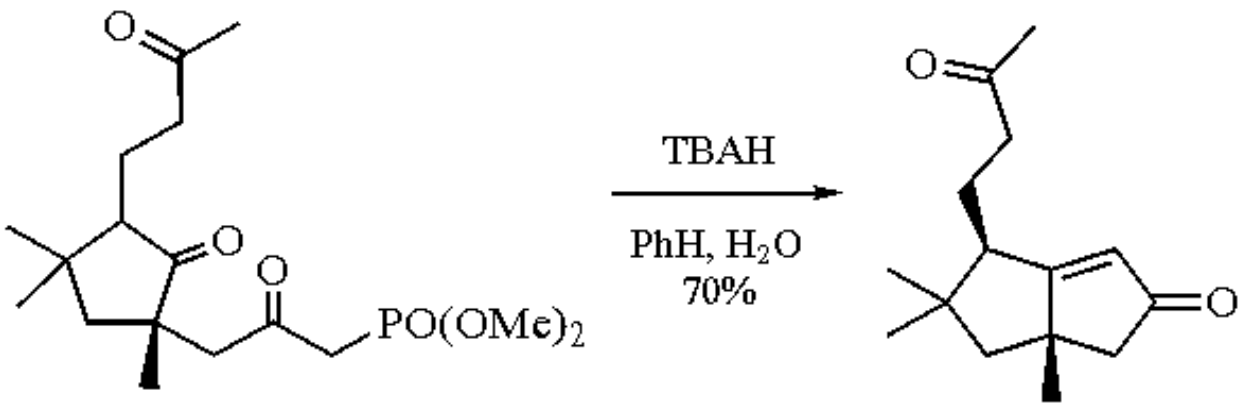

(6)

Dehydrations.

Vicinal dihydro diols of polycyclic aromatic hydrocarbons such as the benzo[*a*]pyrene derivative (**2**) were dehydrated under mild conditions by treatment with TBAH in methanol (eq 7).[13] Alkali hydroxides did not effect the reaction in these cases without a catalyst present (crown ether or ammonium salt), and methanol was necessary as solvent. The regioselectivity for the dehydration (**3:4** = 13:87) was opposite to that from a ***Phosphoric Acid***-catalyzed dehydration (**3:4** = 97:3). The base-catalyzed reaction did not proceed for substrates which lacked aromatization capability. A patent has been obtained for the monodehydration of a fluorinated dihydroxybenzene under similar conditions.[14]

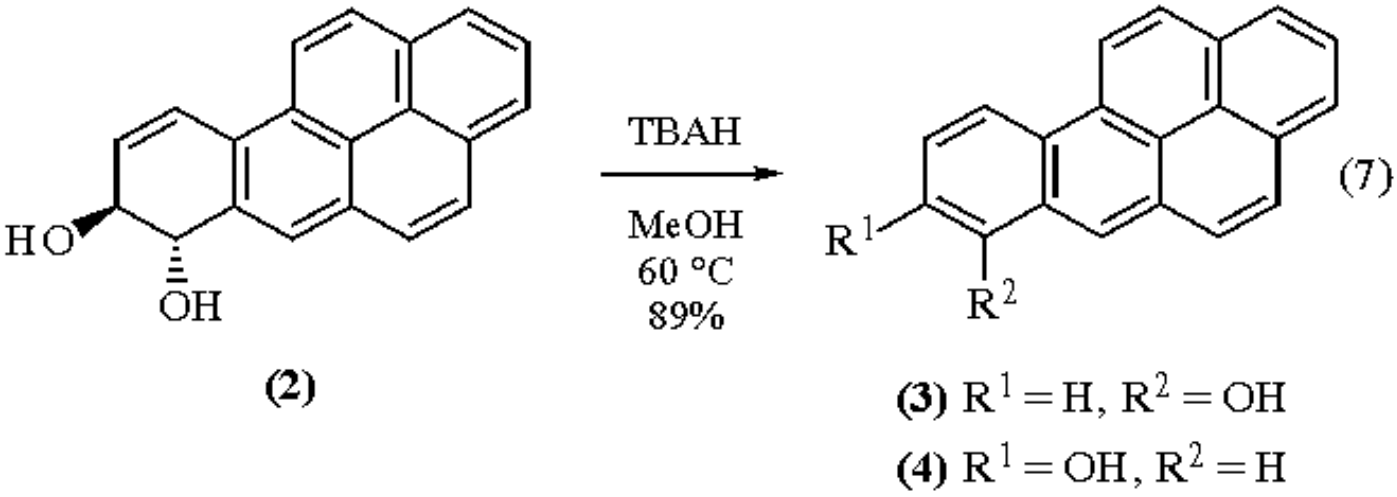

Carbenes.

The reaction of (**1**) with ***Chloroform*** under phase-transfer conditions is a good method for generating dichlorocarbene.[1c] This reaction was used to cleanly generate aldehyde (**6**) from dehydronuciferene (**5**), which is nucleophilic enough to attack dichlorocarbene (eq 8).[15] In contrast, compound (**5**) could not be alkylated with ***Iodomethane***.

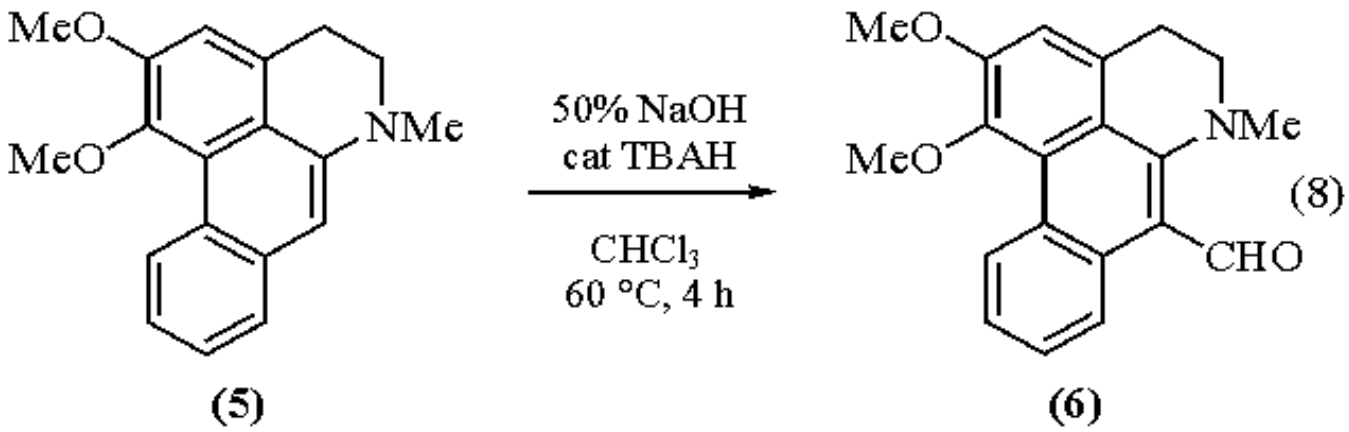

A phase-transfer reaction mediated by tetrabutylammonium hydroxide was found to be most suitable for the halo lactonization of alkynoic acids to prepare halo enol lactones (eq 9).[16] The reaction was carried out with halosuccinimides in the presence of catalytic TBAH, and yields of 70-93% were obtained.

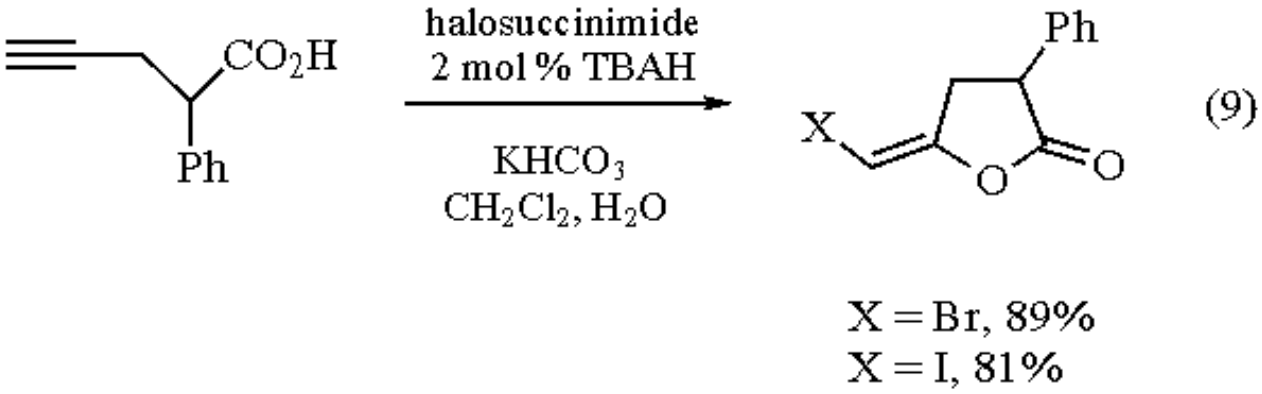

1. For reviews of phase transfer reactions, see (a) Keller, W. E. *Phase Transfer Reactions. Fluka Compendium*; Thieme Verlag: Stuttgart, 1986; Vols. 1 and 2. (b) Dehmlow, E. V. *Phase Transfer Catalysis*; Verlag Chemie: Deerfield Beach, FL, 1980. (c) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis, Principles and Techniques*; Academic: New York, 1978. (d) Dockx, J. *S* **1973**, 441. (e) Dehmlow, E. V. *AG(E)* **1974**, *13*, 170. For a mechanistic review of hydroxide-mediated reactions under PTC conditions, see: (f) Rabinovitz, M.; Cohen, Y.; Halpern, M. *AG(E)* **1986**, *25*, 960.
2. (a) In alcohol using silver oxide and Bu_4I: Cluett, M. L. *Anal. Chem.* **1959**, *31*, 610. (b) In alcohol using ion exchange resin and Bu_4I: Harlow, G. A.; Noble, C. M.; Wyld, G. E. A. *Anal. Chem.* **1956**, *28*, 787.
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Tetra-*n*-butylammonium Iodide[1]

***n*-Bu_4NI**

[311-28-4] · $C_{16}H_{36}IN$ · Tetra-*n*-butylammonium Iodide · (MW 369.43)

(phase-transfer catalyst;[1] ether cleavage;[1] alkyl iodide formation;[1] salt effects[1])

Physical Data: mp 148 °C.

Solubility: sol EtOH, H_2O.

Form Supplied in: anhydrous white solid.

Analysis of Reagent Purity: tetraalkylammonium salts can be titrated with potassium 3,5-di-*t*-butyl-2-hydroxybenzenesulfonate and iron(III) chloride.[1a]

Purification: crystallize from toluene-petroleum ether, CH_2Cl_2-petroleum ether (or hexane), acetone, ethyl acetate, EtOH-ethyl ether, aq EtOH, or H_2O. The solid is then dried at 90 °C under high vacuum for 2 d.[2]

Handling, Storage, and Precautions: highly hygroscopic solid.

Phase-Transfer Catalyst.

Although Bu_4NI is not as widely used as ***Tetra-n-butylammonium Bromide***, it is often used in phase-transfer reactions. It was shown to promote several *N*-alkylation reactions[3] of heterocycles such as pyrroles[4] and of amides[5,6] (eq 1).

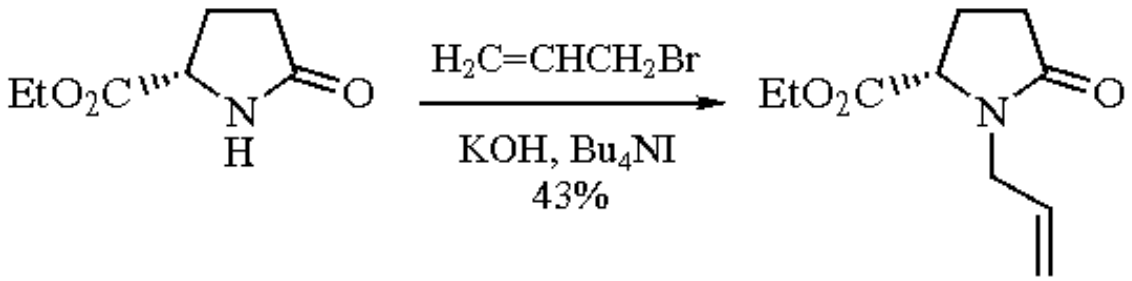

(1)

It has also been used in phase-transfer carbene-mediated cyclopropanation reactions,[7] metal-catalyzed carbonylation reactions of organic halides,[8,9] and Wittig alkenation reactions.[10]

Several *O*-alkylation reactions[11] were shown to proceed much faster if Bu_4NI was added to the reaction mixture. One particularly interesting case is the benzylation of diethyl tartrate in which addition of a catalytic amount of Bu_4NI was shown to be essential for obtaining high yield of the desired product (eq 2).[12]

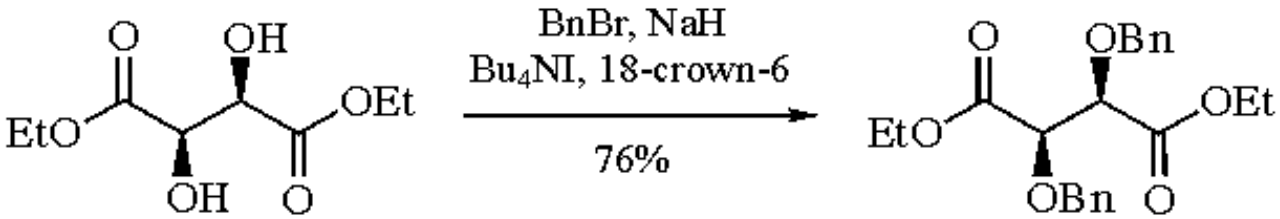

(2)

A mixture of ***Zinc Chloride*** and Bu_4NI catalyzes the synthesis of cyclic carbonates from oxiranes and carbon dioxide at rt and atmospheric pressure.[13]

Ether Cleavage.

Methyl, allyl, and benzyl ethers derived from alcohols and phenols are regioselectively cleaved by a mixture of Bu_4NI and a Lewis acid (***Boron Trifluoride Etherate***[14] or ***Aluminum Iodide***[15]).

Alkyl and Vinyl Iodide.

Bu_4NI can also be used as a source of iodide for nucleophilic displacement reactions. Neopentyl iodides can be prepared via S_N2 displacement of the corresponding triflate (eq 3).[16] Alkenyliodonium tetrafluoroborates can be converted to vinyl iodides upon treatment with Bu_4NI (eqs 4 and 5).[17]

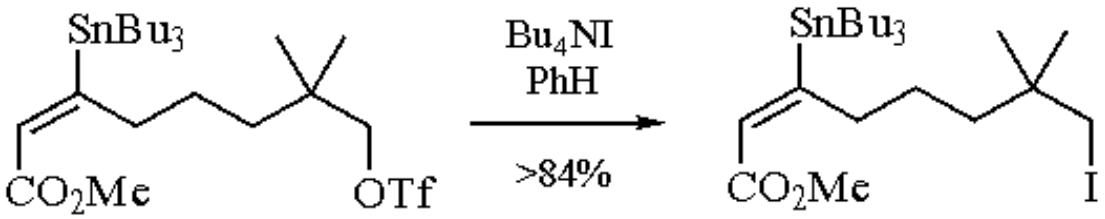

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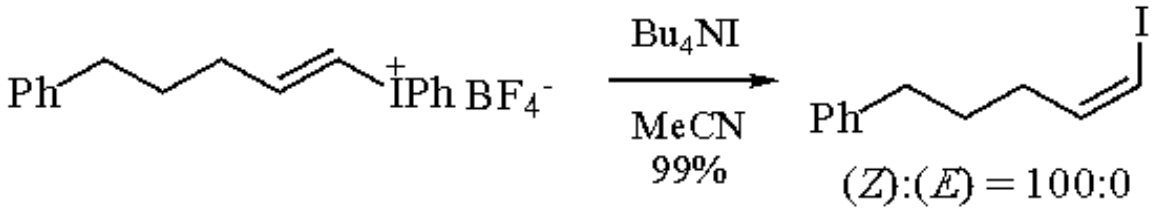

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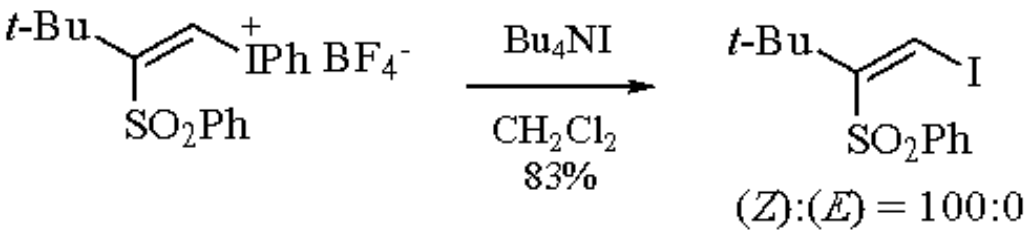

(5)

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Tetra-*n*-butylammonium Periodate

***n*-Bu_4NIO_4**

[65201-77-6] · $C_{16}H_{36}INO_4$ · Tetra-*n*-butylammonium Periodate · (MW 433.43)

(oxidation of sulfides,[1] phenacyl bromides,[1] benzyl halides,[3] phosphites;[7] oxidative decarboxylation;[1] co-oxidant in metal-catalyzed oxidation[1b,5,8])

Physical Data: mp 158-159 °C.

Solubility: sol CH_2Cl_2, $CHCl_3$, benzene, DMSO; insol H_2O, alcohol.

Form Supplied in: white crystalline solid; readily available.

Handling, Storage, and Precautions: tetrabutylammonium periodate is best stored in the dark because it readily turns yellow on exposure to light. There is no loss of oxidizing power on prolonged storage.

Introduction.

Due to its ease of preparation[1] and its solubility in common organic solvents, tetrabutylammonium periodate (**1**) is a useful reagent for the oxidation of organic compounds under homogeneous reaction conditions.

Oxidation of Sulfides to Sulfoxides.[1]

Treatment of sulfides with (**1**) in refluxing $CHCl_3$ selectively provided the sulfoxides in good yields.[1a] Thus, oxidation of methyl *p*-methylphenyl sulfide gave the corresponding sulfoxide in 86% yield. An advantage of this method is that the sulfoxides are readily isolated by simple filtration through a column of silica gel. Oxidant (**1**) and catalytic amounts of *meso*-tetraphenyporphyrinatoiron(III) chloride (**2**) have been found to be effective for the selective oxidation of sulfides to sulfoxides (eq 1).[1b] Sulfides that usually resist oxidation, such as *p*-nitrophenyl phenyl sulfide and di-*t*-butyl sulfide, are also efficiently oxidized to the corresponding sulfoxides. Alkenic bonds are tolerated under the reaction conditions.

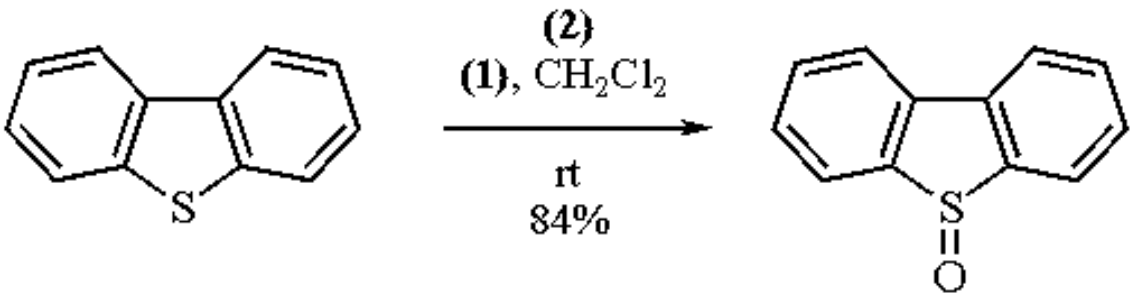

(1)

Oxidative Cleavage of Carbonyl Compounds.

α-Hydroxy carboxylic acids are efficiently oxidized to the aldehydes by treatment with (**1**) in refluxing $CHCl_3$ (eq 2).[1a] Reaction times were found to be shorter than the usual ***Sodium Periodate*** method, which required extended reaction times.

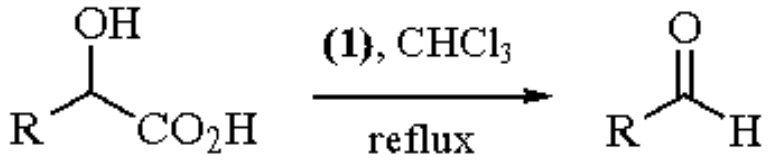

(2)

$R = C_{14}H_{29}$, 90%; Ph, 86%

Benzaldehyde derivatives were also obtained in good yields by the oxidative decarboxylation of arylacetic acids with (**1**) in refluxing 1,4-dioxane.[2] This method was found to be better than the hypochlorite route, which gave over-oxidation products. Treatment of phenacyl bromides with (**1**) in refluxing 1,4-dioxane gave good yields of the corresponding benzoic acids (eq 3).[1a] This oxidation was found to be specific for phenacyl bromides since chloroacetone was not oxidized under the same reaction conditions.

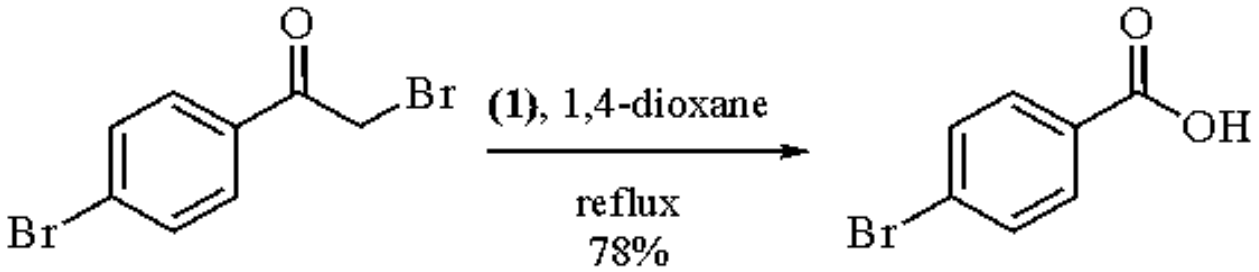

(3)

Other Applications.

Benzyl halides are efficiently converted to benzaldehydes by treatment with (**1**) in refluxing 1,4-dioxane.[3] This oxidation was found to be specific for benzyl halides since compounds such as phenethyl bromide were not oxidized under the same conditions. Oxidant (**1**) has also been shown to be effective for the oxidative cleavage of stannylene derivatives of 1,2-glycols to give high yields of the aldehydes.[4] It was also shown that allylic and benzylic alcohols were oxidized to the corresponding aldehydes by the use of (**1**) and catalytic amounts of either *trans*-$[RuO_2(py)_4][BF_4]_2.H_2O$ (**3**) or *trans*-$[Ru_2O_6(py)_4]$ in CH_2Cl_2 at rt.[5] For example, piperonyl alcohol was oxidized using (**1**) in the presence of (**3**) to give a 99% yield of piperonal. Phenols have been subjected to (**1**) in CH_2Cl_2 at rt to afford good yields of quinones.[6] In the synthesis of oligodeoxynucleotides via the phosphite triester route, oxidant (**1**) was found to be useful for the oxidation of a dinucleoside phosphite to a dinucleoside phosphate under neutral, nonaqueous conditions.[7] The use of a catalytic amount of *meso*-tetraphenylporphyrinatomanganese(III) chloride (**4**) and (**1**), in the presence of 1 equiv of ***Imidazole***, was found[8] to be highly effective for the oxidative desulfurization and deselenation at pentavalent phosphorus (eq 4). The use of (**1**) alone only gave low yields of products.

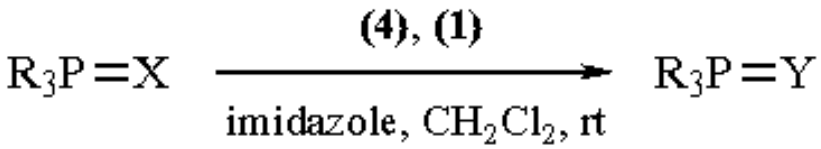

(4)

X = S, R = Ph, Y = O, 81%; X = Se, E = OMe, Y = O, 100%

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Andrew G. Wee

Tetra-*n*-butylammonium Permanganate

***n*-Bu_4NMnO_4**

[35638-41-6] · $C_{16}H_{36}MnNO_4$ · Tetra-*n*-butylammonium Permanganate · (MW 361.47)

(used for the oxidation of polycyclic alkanes,[1] arenes,[1,2] alkenes,[2,3] alcohols,[2,4] and aldehydes[2])

Physical Data: 98 °C (dec).[5]

Form Supplied in: purple solid.

Solubility: sol 0.417 M in CH_2Cl_2, 3.44 × 10^{-4} M in toluene, 2.96 × 10^{-5} M in CCl_4, 2.10 × 10^{-3} M in H_2O; dec $CHCl_3$.[5]

Analysis of Reagent Purity: ε = 2530 ± 30 L mol^{-1} cm^{-1} at 526 nm.[5] IR (KBr) 3420, 2970, 2870, 1470, 1370, 910 cm^{-1}. NMR (CD_2Cl_2) δ 0.35, 0.80, 2.70 ppm.

Preparative Methods: ***Potassium Permanganate*** (3.16 g, dissolved in a minimum of water) is added with stirring to tetra-*n*-butylammonium chloride (6.44 g, dissolved in 200 mL of water) and the purple precipitate collected and washed with water; yields 6.43 g (89%) after drying under vacuum in the presence of P_2O_5.[6]

Purification: recrystallize by dissolving the reagent in a 2:1 solution of CCl_4 and CH_2Cl_2 and drawing a stream of dry air over the mixture to slowly evaporate the solvent. The crystalline product which forms is collected and washed with pentane. It decomposes with ignition at 101 °C when heated in a melting-point tube. The melting point obtained using thermal differential analysis is 98 °C. Highly purified material is not required for most synthetic procedures.

Handling, Storage, and Precautions: oxidant; small quantities may be stored in glass vessels at or below rt. One report states that a violent ignition occurred when 2 g of tetra-*n*-butylammonium permanganate was being weighed onto a glassine paper.[2] Precautions should, therefore, be taken when handling this reagent.

Oxidation of Polycyclic Hydrocarbons.

As illustrated by the following reactions, this reagent shows a substantial preference for the oxidation of tertiary C-H bonds to alcohols as compared to secondary C-H bonds to ketones (eq 1).[1]

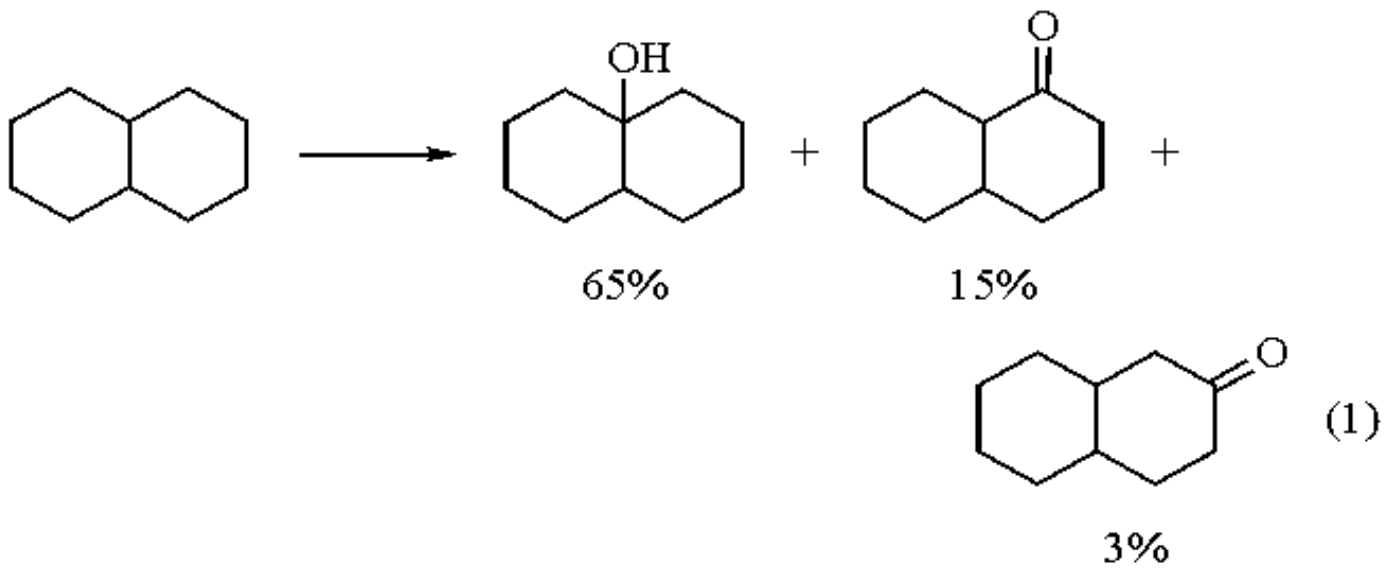

(1)

Oxidation of Arenes.

The oxidation of benzylic methyl groups yields carboxylic acids (eq 2),[2] while more elaborate side chains give alcohols or ketones, depending on the extent of substitution in the benzylic position (eqs 3 and 4).[1]

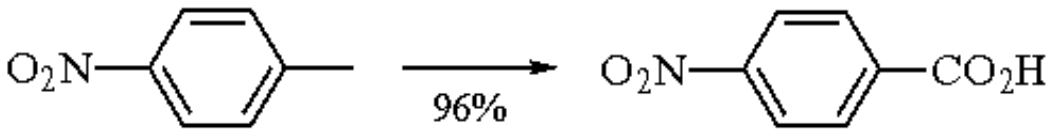

(2)

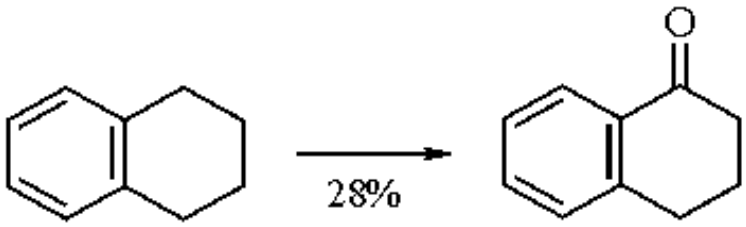

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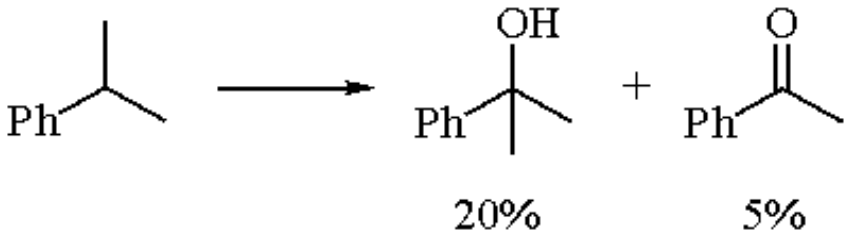

(4)

Oxidation of Alkenes.

Alkenes are either cleaved[2] or converted into 1,2-diols by tetra-*n*-butylammonium permanganate (eqs 5 and 6).

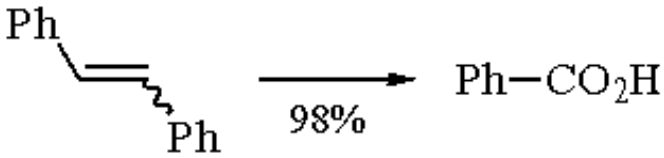

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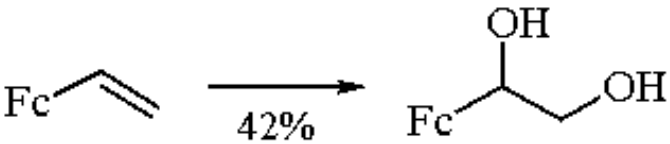

(6)

Fc = ferrocenyl

Oxidation of Alcohols.

Primary alcohols are oxidized to carboxylic acids[2] and secondary alcohols to ketones[2,4] by this reagent (eqs 7-9).

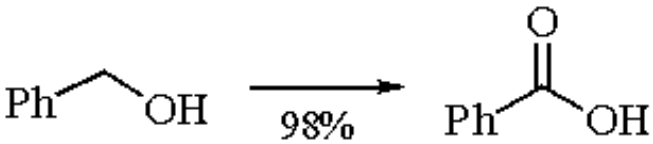

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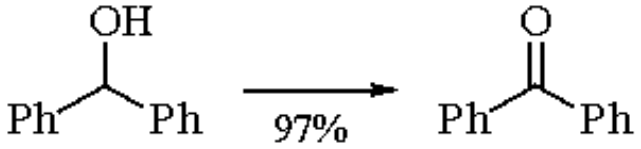

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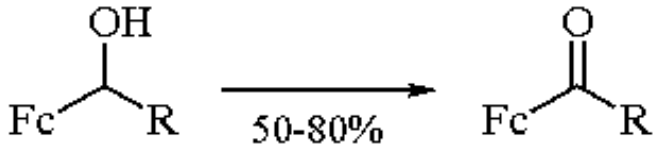

(9)

Fc = ferrocenyl
R = methyl, isopropyl, methoxy or aryl

Oxidation of Aldehydes.

Substituted benzaldehydes are oxidized to the corresponding benzoic acids in good yield.

Other Reactions.

Tetra-*n*-butylammonium permanganate has also been used as an oxidant in certain inorganic syntheses.[7] The reactions of tetra-*n*-butylammonium permanganate are very similar to those of other quaternary ammonium and phosphonium permanganates such as ***Benzyltriethylammonium Permanganate*** and ***Methyltriphenylphosphonium Permanganate***. Similar reactions can also be carried out more simply by use of phase-transfer processes which are described under ***Potassium Permanganate***.

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Tetra-*n*-butylammonium Tribromide

***n*-Bu_4NBr_3**

[38932-80-8] · $C_{12}H_{36}Br_3N$ · Tetra-*n*-butylammonium Tribromide · (MW 482.23)

(mild and efficient brominating agent; useful for synthesis of vicinal dibromides from alkenes and alkynes; synthesis of α-bromo acetals; determination of multiple bonds; oxidation in nonaqueous medium)

Alternate Name: $TBABr_3$.

Physical Data: mp 84 °C (76 °C when crude); λ_{max} (MeCN): 268 nm (67 000), λ 380 nm (810).

Solubility: insol H_2O; sol anhydrous acetic acid (50 g/100 mL), MeCN (300 g/100 mL), $CHCl_3$, trichloroethylene (10 g/100 mL), THF, dioxane; very sol DMF, DMSO; slightly sol alcohols; sol acetone with slow reaction, giving lachrymatory solution.

Form Supplied in: anhydrous, orange nonhygroscopic stable solid; purity more than 98%; stable bromine degree (1 g = 2.07 mequiv Br_2). Red crystals when recrystallized from DMF solution.

Handling, Storage, and Precautions: avoid washing reaction vessels with acetone prior to using with this reagent. Should be handled in a fume hood.

Bromination of Alkenes.

The application of pyridinium, quinolinium, or trimethylphenylammonium tribromide as brominating reagents is known but little used.[1] Tetra-*n*-butylammonium tribromide allows easy double bond bromination under mild conditions and with very good yields (Table 1).[2] For example, an equimolar amount of $TBABr_3$ is slowly added to a solution of alkene in $CHCl_3$ to give, after solvent evaporation, a residue which is washed with 5% aqueous $Na_2S_2O_3$ solution and ethanol, and then filtered and recrystallized. Yields are generally in the range 85-95%.

Table 1 Synthesis of *vic*-Dibromo Compounds at rt

Alkene	*vic*-Dibromide	Reaction time (min)
	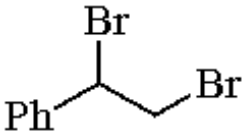	10
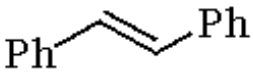	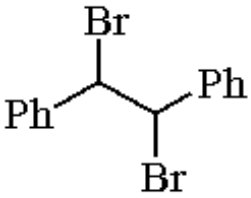 *meso*	15
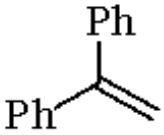	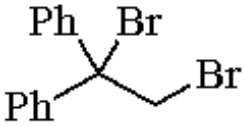	15
	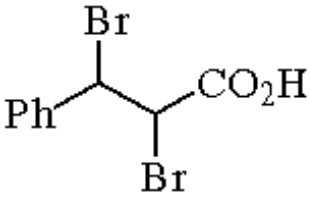 *erythro*	15
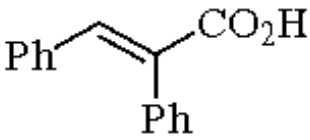	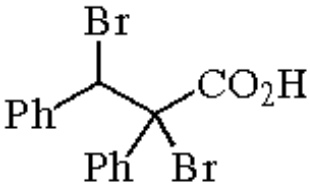 *erythro*	25
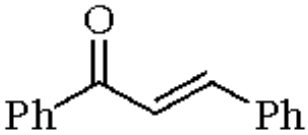	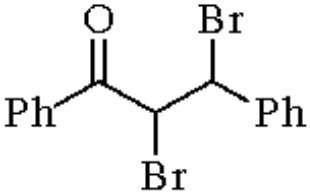	240
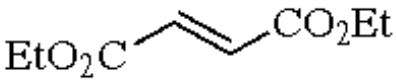	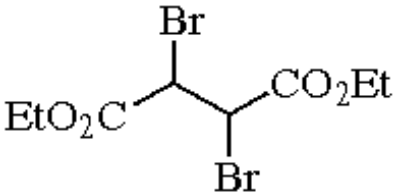	15

Bromination of Alkynes.

The bromination of alkynes is usually difficult and gives mixtures of products.[3] The use of $TBABr_3$ in CCl_4, at rt leads to the (*E*) isomer of 1,2-dibromo alkenes in high yields (85-95%) (Table 2).[4]

Table 2 Synthesis of (*E*)-1,2-Dibromoalkenes at rt

Alkyne	(*E*)-1,2-Dibromoalkene	Reaction time (h)
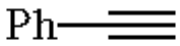	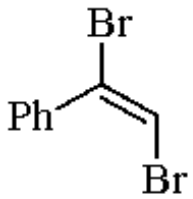	48
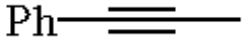	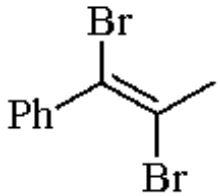	48
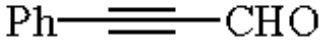	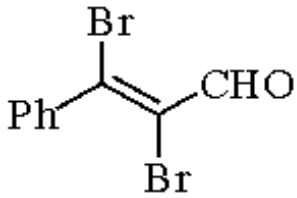	30
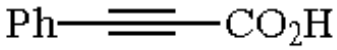	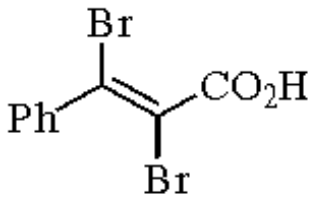	48
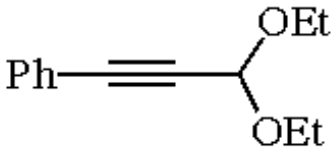	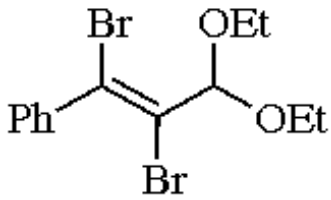	36
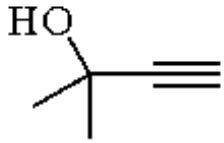	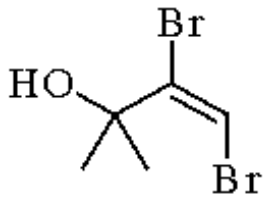	25

Synthesis of α-Bromo Acetals.

α-Bromo acetals are useful reagents for the synthesis of α,β-unsaturated ketones.[5] These derivatives are usually prepared in two steps including

bromination.[5,6] and yields are often poor. $TBABr_3$ is a convenient reagent which gives α-bromo acetals from ketones when used with ethylene glycol.[2] Thus, to a solution of 120 mL of dry ethylene glycol and 0.1 mol of ketone is added an equimolar amount of $TBABr_3$ until the red solution turns yellow (generally 6-10 h). The mixture is then poured into 70 mL of pentane, 70 mL of 10% Na_2CO_3 and 20 mL of 5% aqueous $Na_2S_2O_3$. The organic phase is separated, water washed, dried (Na_2SO_4), and concentrated. The desired α-bromo acetals are obtained in yields of 75-80% (Table 3).

Table 3 Synthesis of α-Bromo Acetals

Ketone	α-Bromo Acetal	Reaction time (h)
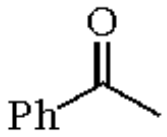	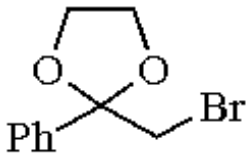	6
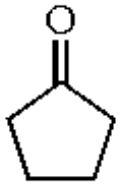	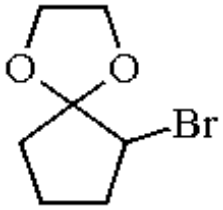	8
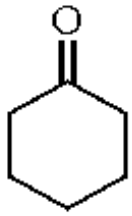	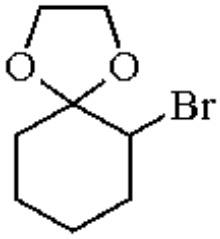	8

Oxidizing Bromination.

4-Bromo-1,1-diphenylbuten-3-one can be prepared in a one-pot synthesis from 1,1-diphenyl-3-ethylenedioxy-1-butanol by the action of $TBABr_3$ in dry $CHCl_3$.[7]

Regioselective Bromination of Aromatic Amines.

The reaction of $TBABr_3$ with aminopyridine and aromatic amines $PhNR^1R^2$ (R^1 = H, Me, Ph, Cy; R^2 = H; R^1 = R^2 = Et) in an aprotic and nonbasic solvent at 20 °C gives exclusively the *para*-brominated compounds in high yields (95%).[8]

Selective Bromination of Phenols.

Phenols were brominated in the *para* position (95%) using $TBABr_3$ in chloroform (or in the *ortho* position if the *para* position was substituted).[8a,9]

Determination of Unsaturation Number.

A method for the determination of the unsaturation number in organic compounds is based on bromination with $TBABr_3$ in nonpolar media followed by electrochemical monitoring of Br_3^-.[10]

1. (a) Marquet, A.; Jacques, J.; Tchoubar, B. *BSF* **1965**, 511. (b) Rosenmund, K. W.; Kuhnhernn, W. *CB* **1923**, *56*, 1262. (c) Rosenmund, K. W.; Kuhnhernn, W.; Lesch, W. *CB* **1923**, *56*, 2042.
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4. Berthelot, J.; Fournier, M. *CJC* **1986**, *64*, 603.
5. Johnson, W. S.; Bass, J. D.; Williamson, K. L. *T* **1963**, *19*, 861.
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7. Berthelot, J.; Fournier, F.; Fournier, M. *SC* **1985**, *15*, 213.
8. (a) Berthelot, J.; Guette, C.; Desbène, P.-L.; Basselier, J.-J.; Chaquin, P.; Masure, D. *CJC* **1989**, *67*, 2061. (b) Berthelot, J.; Guette, C.; Essayegh, M.; Desbene, P. L.; Basselier, J. J. *SC* **1986**, *16*, 1641.
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Tetra-*n*-butylammonium Tricarbonylnitrosylferrate

***n*-$Bu_4N^+[Fe(CO)_3(NO)]^-$**

[96206-23-4] · $C_{19}H_{36}FeN_2O_4$ · Tetra-*n*-butylammonium Tricarbonylnitrosylferrate · (MW 412.42)

(nucleophilic source of iron;[1] mediates electrophilic allylation;[2] can mediate nucleophilic allylation;[2] carbonylation reagent[3])

Physical Data: mp 56-56.5 °C.

Solubility: sol conventional organic solvents such as benzene and THF.

Preparative Method: prepared in 84% yield by the addition of a benzene solution of ***Pentacarbonyliron*** (15 mmol in 5 mL) to a mixture of ***Sodium Nitrite*** (15 mmol) and ***Tetra-n-butylammonium Bromide*** (15 mmol) in water, stirring for 3 h, and separation and concentration of the benzene layer.[1]

Handling, Storage, and Precautions: is less susceptible than sodium tricarbonylnitrosylferrate to air or moisture, allowing handling in the open atmosphere. Storage under inert atmosphere in a glove box is recommended.

Allylic Alkylation.

Tetrabutylammonium tricarbonylnitrosylferrate catalyzes the allylation of malonate anion by allyl carbonates.[1] The reagent serves as a more air-stable substitute (albeit less reactive[5]) for sodium tricarbonylnitrosylferrate. Allylation occurs predominantly without allyl migration, and with a high degree of retention of configuration at a chiral center of the allyl unit (eq 1).[4] Typical conditions employ sodium diethyl malonate (2 equiv), $Bu_4N[Fe(CO)_3(NO)]$ (25 mol %), and the allyl carbonate in THF at reflux under a CO atmosphere. The reaction is thought to proceed by two successive S_N2 reactions, and an η^1-allyliron intermediate.

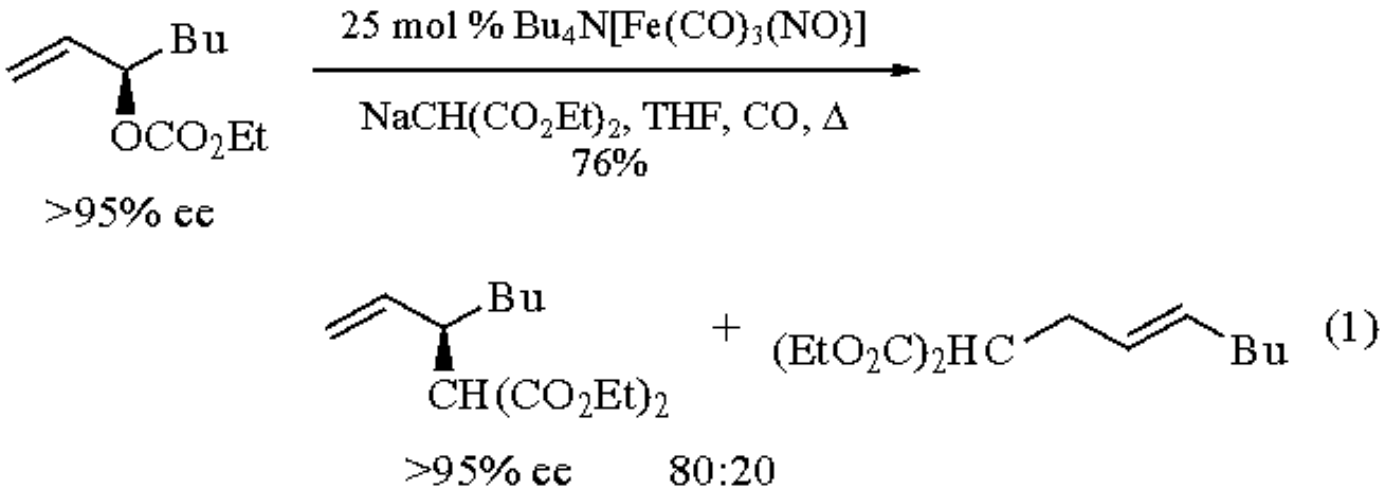

Using stoichiometric amounts of $Bu_4N[Fe(CO)_3(NO)]$, a wider variety of stabilized carbanions (anions of malonates, β-keto esters, dicyanomethane) and enamines have been allylated by allylic halides or mesylates, via an isolated η^3-allyliron intermediate.[2,6] The reaction has been applied to 2-trimethylsiloxyallyl halides and 3-trimethylsiloxyallyl halides to give 1,4-dicarbonyl compounds and 1,5-dicarbonyl compounds, respectively (eq 2).[7] In the stoichiometric reactions, nucleophilic attack is predominantly at the less substituted side of the allyl unit, and *anti* to the face of the allyl unit bearing the iron residue.

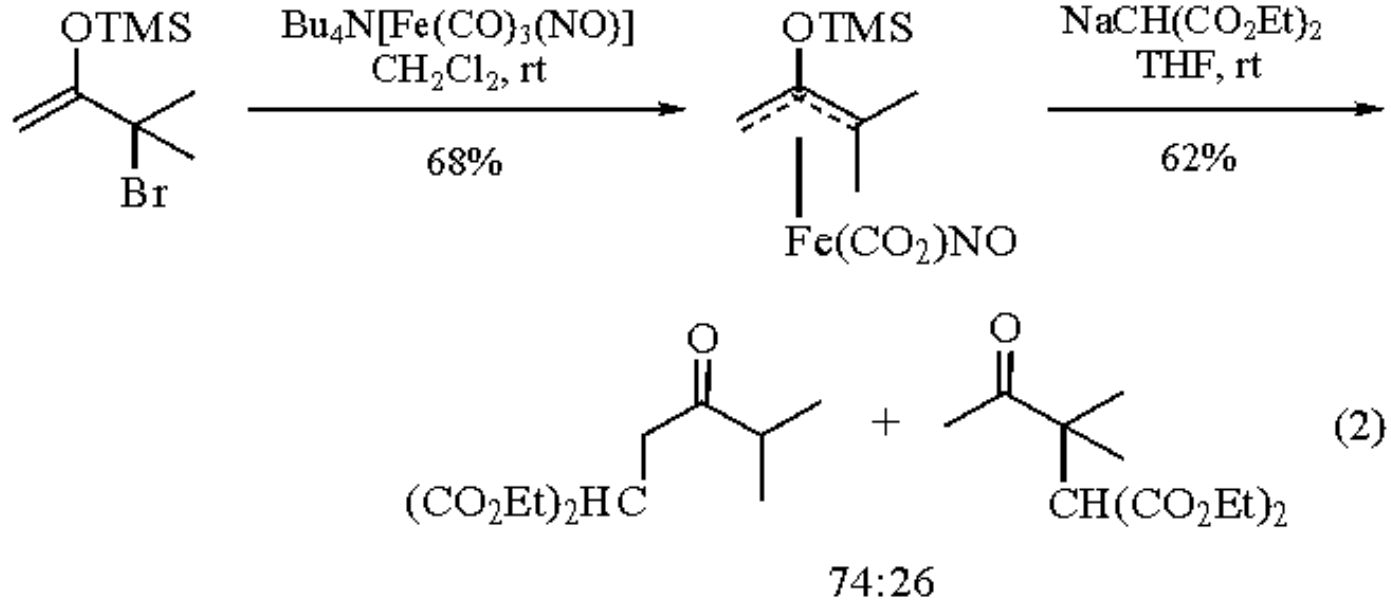

The η^3-allyliron complexes formed from $Bu_4N[Fe(CO)_3(NO)]$ and allyl halides may also function as nucleophiles with allyl or propargyl halides or acid chlorides.[2] The 1-silyloxyallyliron complexes (formed from 3-trimethylsilyloxyallyl iodides) also react in this fashion with allyl or propargyl halides to afford β-allyl or propargyl ketones or esters upon workup, thereby serving as nucleophilic homoenolate equivalents.[6] In these cases the prior addition of ***Triphenyl Phosphite*** gives enhanced yields (eq 3). Regiochemistry of attack is predominantly at the less substituted end of the allyl halide, and attack by the allyl halide is *syn* to iron.

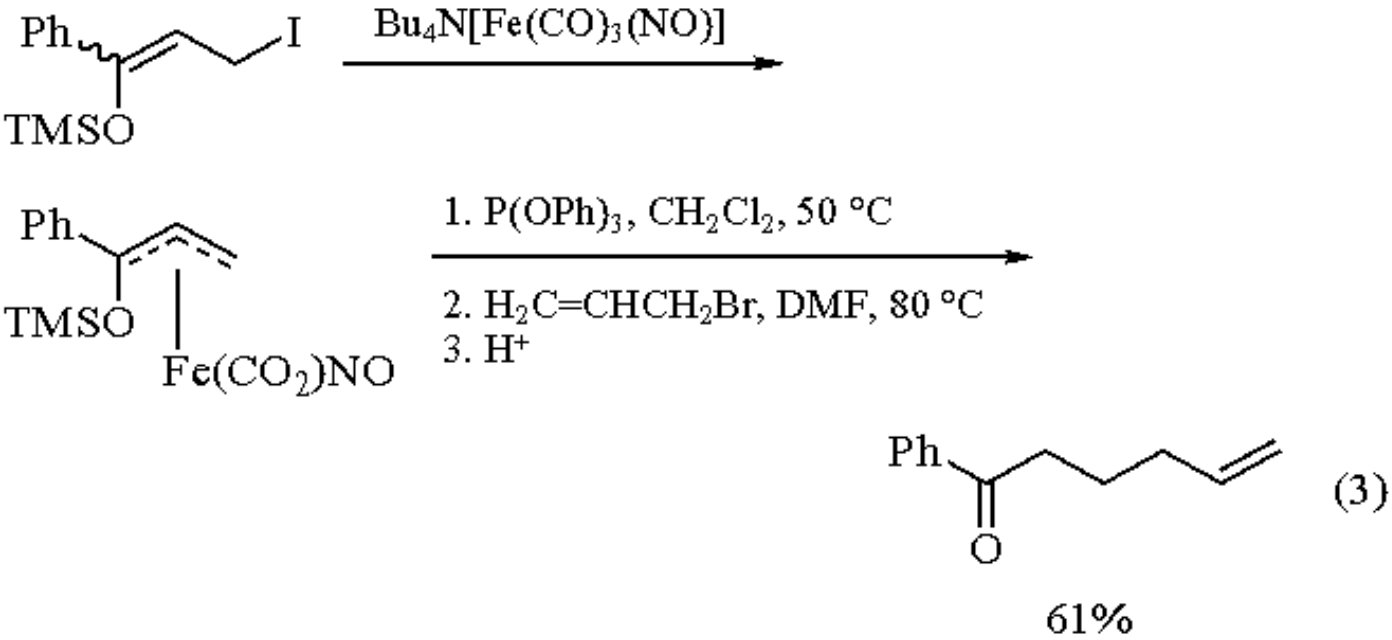

Carbonylation.

Alkyl halides are carbonylated by stoichiometric amounts of $Bu_4N[Fe(CO)_3(NO)]$ in the presence of ***Carbon Monoxide*** (eq 4).[3] Primary benzyl halides react much more efficiently than secondary benzylic ones. Formation of aldehydes may compete in the case of alkyl halides. Allylic halides may be carbonylated in a two-step process featuring the addition of diphos (***1,2-Bis(diphenylphosphino)ethane***) with $Bu_4N[Fe(CO)_3(NO)]$ in the initial step.

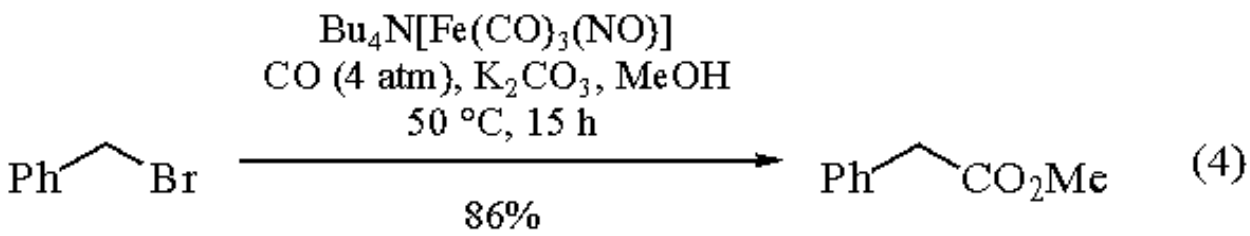

1. Xu, Y.; Zhou, B. *JOC* **1987**, *52*, 974.
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3. Davies, S. G.; Smallridge, A. J.; Ibbotson, A. *JOM* **1990**, *386*, 195.
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7. Itoh, K.; Nakanishi, S.; Otsuji, Y. *BCJ* **1991**, *64*, 2965.

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Tetracarbonylcyclopentadienylvanadium[1]

$CpV(CO)_4$

[12108-04-2] · $C_9H_5O_4V$ · Tetracarbonylcyclopentadienylvanadium · (MW 228.08)

(catalyst for stereoselective alkene oxidation;[1e,3] forms an anionic hydride complex which reduces dibromides;[4] reacts with alkynes to form cyclic ketones[1a,5])

Physical Data: mp 139 °C.[1a]

Solubility: sol benzene, 1,2-dichloroethane, THF; slightly sol hexane.

Form Supplied in: orange air-sensitive solid.

Analysis of Reagent Purity: IR, NMR.[2]

Purification: sublimation at 80-100 °C/0.5 mmHg.[1a]

Handling, Storage, and Precautions: store and handle under an inert atmosphere.

Alkene Oxidation.

$CpV(CO)_4$ catalyzes the stereoselective oxidation of cyclohexene by molecular oxygen to form *cis*-1,2-epoxycyclohexane-3-ol with 99% stereoselectivity.[3a] The yields are good at low conversion rates (e.g. 65% at 10% conversion) and are reasonable at higher conversion rates (eq 1).

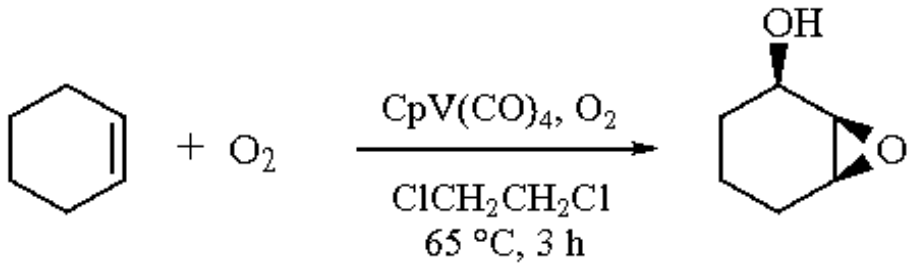

(1)

$CpV(CO)_4$ has also been reported to catalyze the epoxidation of (*Z*)-cyclooct-2-en-1-ol with ***t-Butyl Hydroperoxide***, giving predominantly the *cis*-epoxy alcohol (eq 2).[3b]

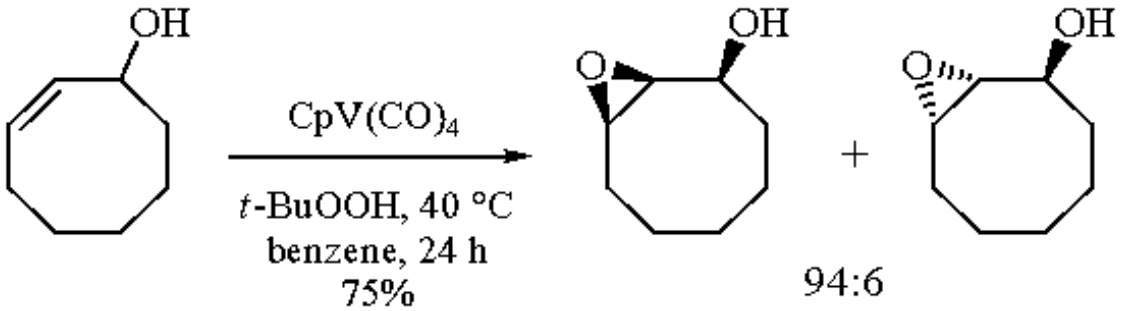

(2)

Reduction of Organic Halides.

The anionic hydride, generated from $CpV(CO)_4$ and ***Sodium*** metal followed by a water quench, has been reported to replace halogen by hydrogen in alkyl, acyl, and vinyl halides by an apparent free radical mechanism (Table 1).[4]

Table 1 Reduction of Organic Halides by $PPN^+ [CpV(CO)_3H]^-$

$$CpV(CO)_4 \xrightarrow[3.\ PPN^+Cl^-]{1.\ Na,\ THF;\ 2.\ H_2O} PPN^+[CpV(CO)_3H]^- \xrightarrow[25\ °C]{R\text{-}X} RH$$

Substrate	Product	Time (h)	Yield (%)
$C_8H_{17}Br$	C_8H_{18}	4	75
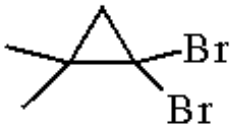	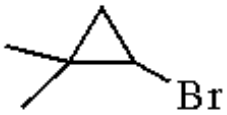	0.5	95
	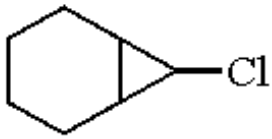	1	95
BnCOCl	BnCHO	<0.1	100
PhCH=CHBr	$PhCH{=}CH_2$	5	46

Alkyne-CO Cooligomerization.

The interaction of $CpV(CO)_4$ with alkynes has been shown to give cyclic ketone products where either one or two CO ligands are incorporated into the organic product. Cyclopentadienones, quinones, and tropones have all been observed as products in these reactions, with the product ratios being dependent upon the reaction conditions and the identity of the substituents on the alkyne. An example of the dependency of the reaction on the alkyne substitution is shown by the contrasting results shown in eqs 3 and 4. The thermal reaction of diphenylacetylene with $CpV(CO)_4$ gives tetraphenylcyclopentadienone as the major organic product (eq 3), while perfluorodiphenylacetylene gives perfluorotetraphenylquinone as the major organic product (eq 4).[5]

$$CpV(CO)_4 + 2\ PhC{\equiv}CPh \xrightarrow[\text{reflux, 12 h; 46\%}]{\text{toluene}} \text{(Ph}_4\text{-cyclopentadienone)} \quad (3)$$

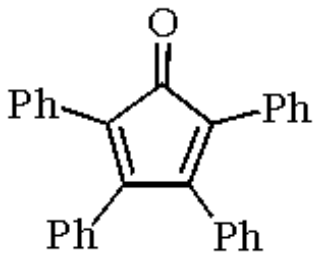

$$CpV(CO)_4 + 2\ C_6F_5C{\equiv}CC_6F_5 \xrightarrow[\text{reflux, 12 h; 61\%}]{\text{toluene}} \text{(}(C_6F_5)_4\text{-quinone)} \quad (4)$$

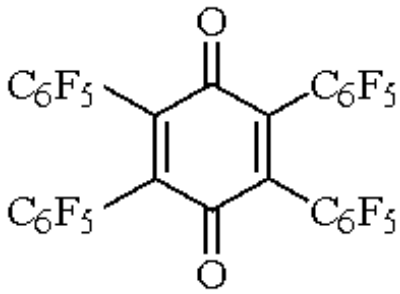

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Tetracarbonyl(di-μ-chloro)dirhodium

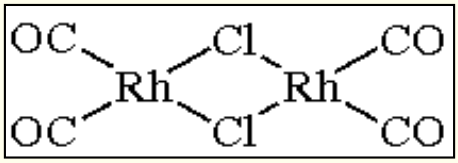

[14523-22-9] · $C_4Cl_2O_4Rh_2$ · Tetracarbonyl(di-μ-chloro)dirhodium · (MW 388.76)

(catalyst or catalyst precursor for rearrangement of strained rings;[1] carbonylative ring expansion;[2] carbonylative coupling of organometallics;[3] hydroformylation;[4] silylformylation[5])

Physical Data: mp 124 °C; sublimes 80 °C/1 mmHg.

Solubility: sol most organic solvents; slightly sol saturated hydrocarbons.

Form Supplied in: red or orange solid; widely available.

Purification: recryst from hexanes.

Handling, Storage, and Precautions: stable in dry air but should be protected from moisture. Solutions decompose in air; solvents should be deoxygenated before dissolving reagent.

Rearrangement of Strained Rings.

Rearrangements of many strained polycyclic hydrocarbons have been carried out with $[Rh(CO)_2(\mu\text{-}Cl)]_2$, but most of these hold more mechanistic interest than synthetic utility.[6] On the other hand, rearrangements of three-membered rings have proven more generally useful. Thermolysis of alkoxy- or siloxycyclopropanes with catalytic $[Rh(CO)_2(\mu\text{-}Cl)]_2$ gives enol ethers,[1a,b] although stereoselectivity is slight (eq 1). Catalyzed rearrangement of 3-acylcyclopropenes yields substituted furans in a regioselective manner (eq 2).[1c,2a] When the reaction is carried out under CO, these same substrates are rearranged with carbonylation to give α-pyrones (eq 3).[2a] In a similar way, vinyl cyclopropenes are carbonylated to give phenols.[2a] Carbonylative ring expansion of aryl aziridines occurs stereo- and regiospecifically to give β-lactams (eq 4); however, the reaction fails in the absence of the aryl substituent.[2b] Cyclopropene (**1**) reacts with 1-hexyne to give oxepin (**2**) in the presence of $[Rh(CO)_2Cl]_2$, which then was isomerized with acid to phenol (**3**) (eq 5) in near quantitative yield.[11]

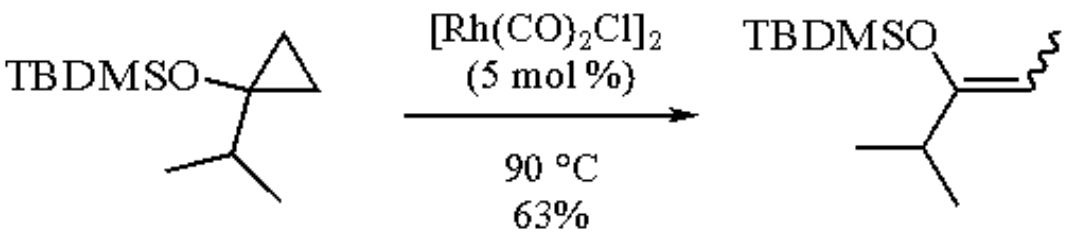

(1)

(*E*):(*Z*) = 70:30

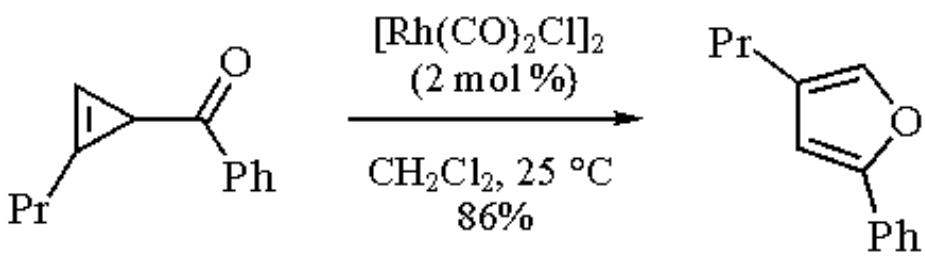

(2)

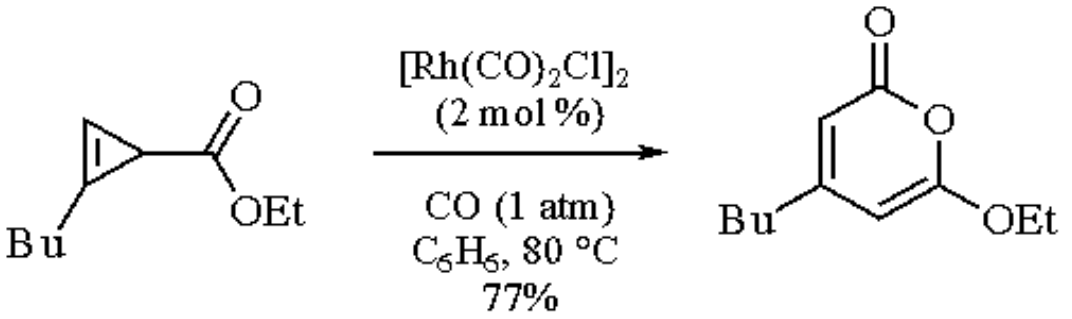

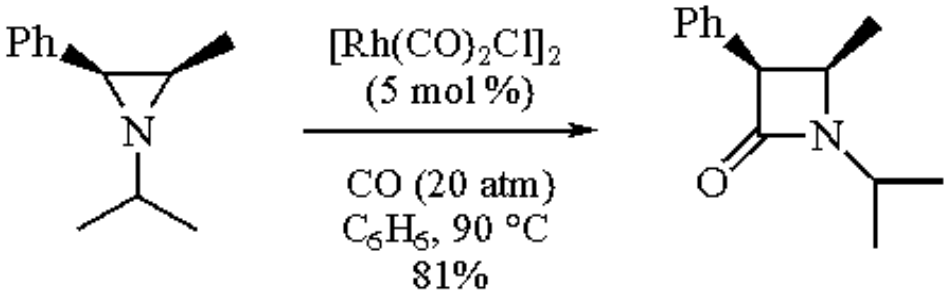

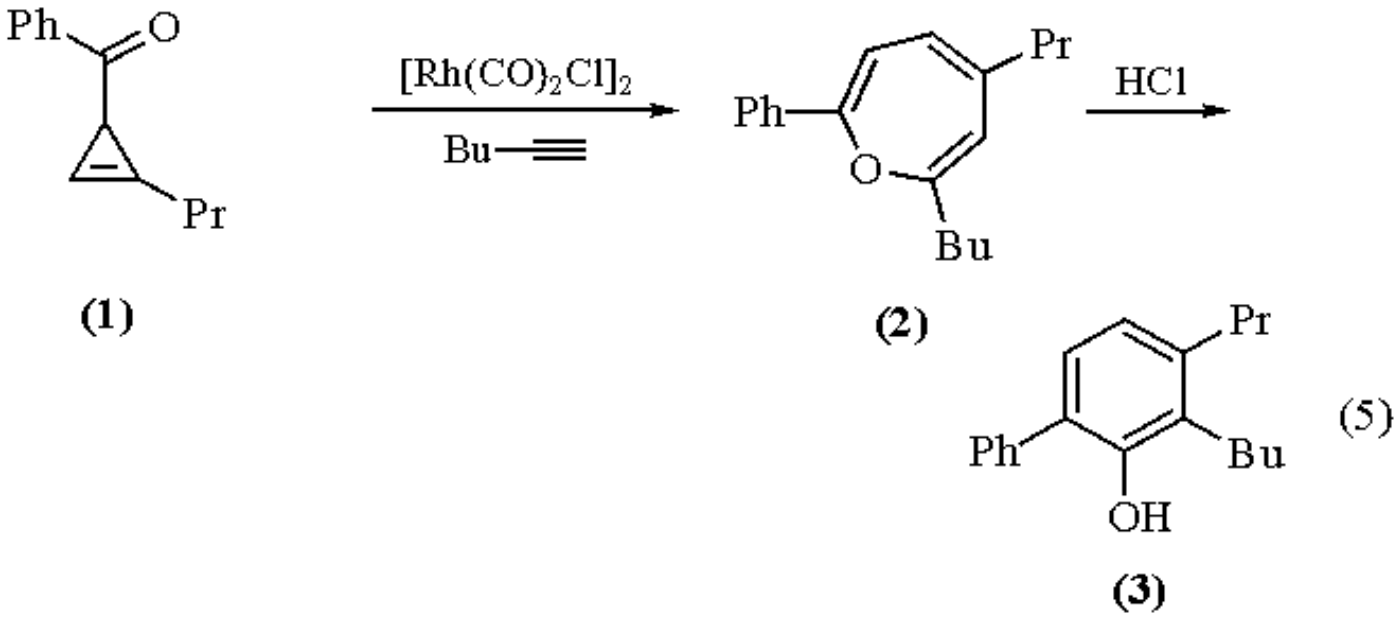

Organometallic Coupling.

The $[Rh(CO)_2(\mu\text{-}Cl)]_2$-catalyzed carbonylative coupling of vinylmercury(II) chlorides provides an efficient synthesis of symmetric divinyl ketones (eq 6).[3a] Arylmercury(II) chlorides or triarylbismuthines[3b] are coupled to give diaryl ketones, while in the absence of CO the mercury reagents are directly coupled to 1,3-dienes and biaryls.[7]

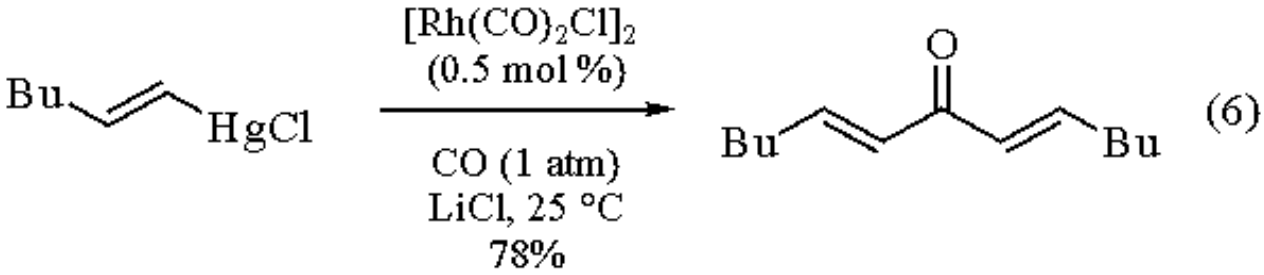

Hydroformylation of Alkenes.

$[Rh(CO)_2(\mu\text{-}Cl)]_2$ is a common catalyst precursor for hydroformylation in the presence of phosphine or phosphite ligands.[4a,b] These reactions are not often used in synthetic schemes because regioselectivity can be poor and alkene isomerization and hydrogenation can

interfere. Nevertheless, with some functionalized alkenes, useful selectivity can be achieved,[4a,c] including modest enantioselectivity (eq 7).[4b,d]

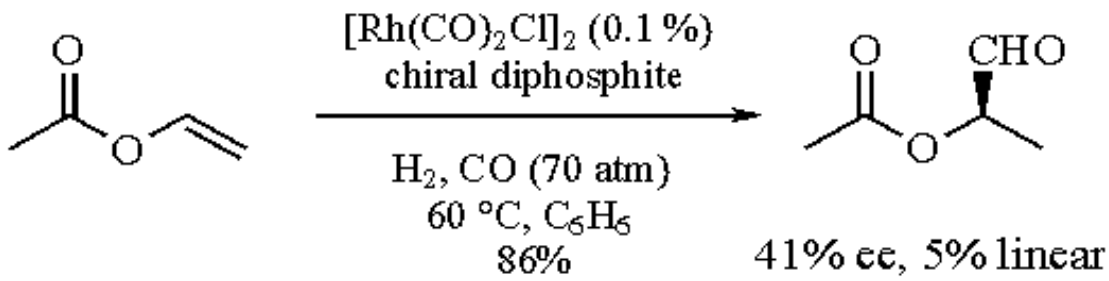

(7)

Silylformylation.

In reactions related to hydroformylation, $[Rh(CO)_2(\mu\text{-}Cl)]_2$ catalyzes the addition of hydrosilanes and CO to enamines, giving silyl enol ethers (eq 8).[5a] Hydrolysis provides α-siloxy ketones. β-Siloxy aldehydes arise stereospecifically from the ring-opening silylformylation of epoxides (eq 9).[5b] As in many of the reactions catalyzed by $[Rh(CO)_2(\mu\text{-}Cl)]_2$, other Rh^I catalysts such as $[Rh(cod)(\mu\text{-}Cl)]_2$ and $Rh(CO)_2(acac)$ can also be used.

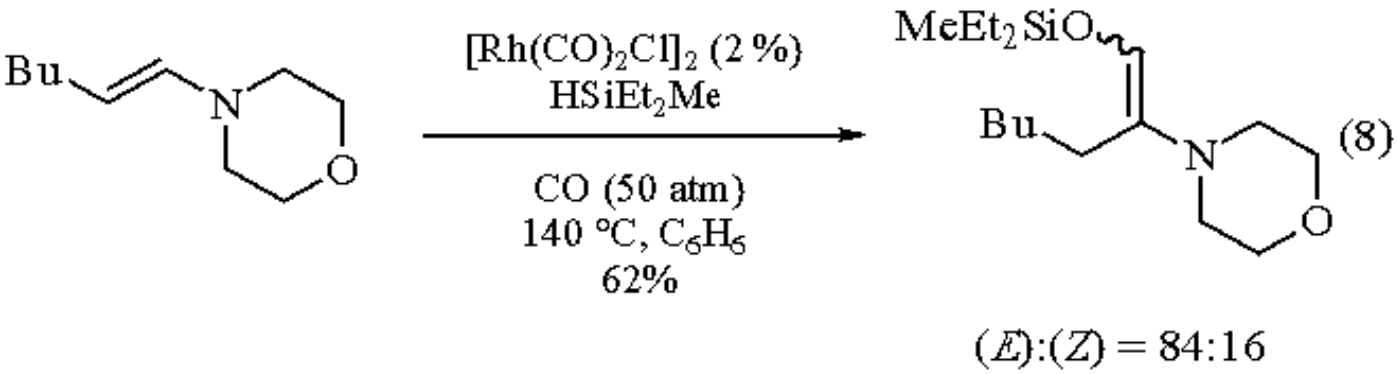

(8)

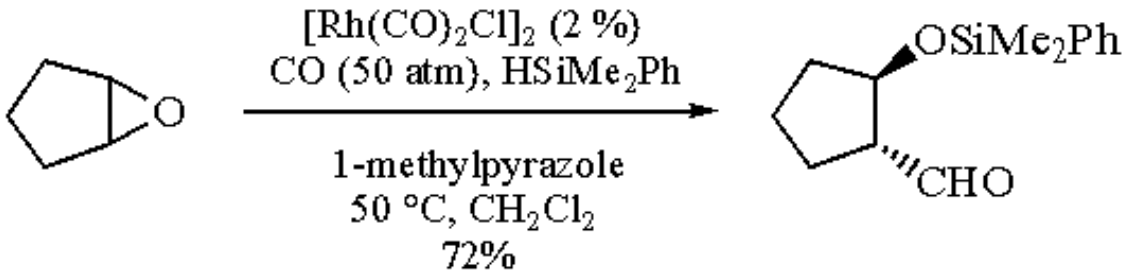

(9)

Catalytic Hydrogenation of Alkenes.

Alkenes are catalytically hydrogenated to alkanes with $[Rh(CO)_2Cl]_2$. The reagent is usually bound to either alumina[8] or phosphine-functionalized polystyrene,[9] although $[[Rh(CO)_2Cl]_2$ has also been used as a heterogeneous catalyst. *trans*-1,3-Pentadiene, for example, has been reduced regiospecifically at the terminal double bond in good yield.[10]

Related Reagents.

Chlorotris(triphenylphosphine)rhodium(I).

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Tetracarbonylnickel[1]

$Ni(CO)_4$

[13463-39-3] · C_4NiO_4 · Tetracarbonylnickel · (MW 170.73)

(oxidation of aryl halides and alkynes; oxidative addition of alkyl and aryl halides; rearrangement and cyclization; carbonylation)

Physical Data: mp -25 °C; bp 43 °C; *d* 1.32 g cm^{-3}; based on calorimetry, the average Ni-C bond strength is 35 kcal mol^{-1}; bond distances Ni-C 1.82 Å and C-O 1.15 Å.

Solubility: insol H_2O; sol most organic solvents.

Form Supplied in: colorless liquid in a lecture bottle or in a cylinder, usually under CO pressure.

Analysis of Reagent Purity: IR spectrum, ν_{CO} = 2040 cm^{-1}; ^{13}C NMR spectrum, δ = 193 ppm; UV spectrum, λ_{max} = 206 nm (ε = 10^5).

Preparative Method: formed from finely divided ***Nickel*** and ***Carbon Monoxide*** gas to give a four-coordinate d^{10} metal complex, with tetrahedral geometry, that satisfies the 18-electron rule.

Handling, Storage, and Precautions: toxic; flammable in air; must be used in a well ventilated fume hood and kept under an inert atmosphere.

Oxidation Reactions.

Upon reaction of $Ni(CO)_4$ with ***Chlorine***, ***Bromine***, or ***Iodine***, the carbonyls are released as carbon monoxide gas and the nickel is oxidized, generating NiX_2 (eq 1). This reaction proves to be a very efficient method for the destruction of excess $Ni(CO)_4$ at the end of a reaction sequence. For example, simply pouring the reaction mixture into a flask containing solid I_2 or by adding an I_2 solution to the reaction mixture, CO gas evolves and the nickel forms NiI_2, which is water soluble.[1]

$$Ni(CO)_4 + X_2 \longrightarrow CO + NiX_2 \qquad (1)$$

A second method for quenching unreacted $Ni(CO)_4$ is to sweep all volatile compounds out of the reaction flask with a stream of nitrogen or argon gas. These volatile compounds are collected in a cold trap and then quenched with ***Nitric Acid***. As with the halogens, the HNO_3 will oxidize the $Ni(CO)_4$, generating carbon monoxide gas and a water-soluble nickel complex.

Reduction Reaction.

The reaction between $Ni(CO)_4$ and an alkali metal, a metal amalgam, or a metal hydroxide generates anionic nickel carbonyl clusters. The major two products are $Ni_5(CO)_{12}^{2-}$ and $Ni_6(CO)_{12}^{2-}$, with the ratio being dependent upon the reaction conditions used.[2] These clusters react with aryl halides[3] (or alkynes[4]) to generate benzoic acid derivatives (eq 2).

$$Ni(CO)_4 + OH^- \longrightarrow Ni_5(CO)_{12}^{2-} \xrightarrow[88\%]{PhBr} PhCO_2H \qquad (2)$$

Nucleophilic Attack.

There are two sites for nucleophilic attack in $Ni(CO)_4$. The first is one of the coordinated carbonyl ligands and the second is the nickel itself, but this can occur only if one of the ligands first dissociates.

Unlike the reaction with hydroxide mentioned above, in the reaction of $Ni(CO)_4$ with a nucleophile such as methoxide, a dialkyl amide, or an alkyllithium, the carbonyl is attacked to give a nickel acylate complex (eq 3). Because these complexes are discussed under ***Lithium Tricarbonyl(n-pentanoyl)nickelate***, it will only briefly be mentioned here that nickel acylate complexes are very air- and water-sensitive, and they react with both alkyl and vinyl halides to form esters, amides, and ketones, respectively.[5-7]

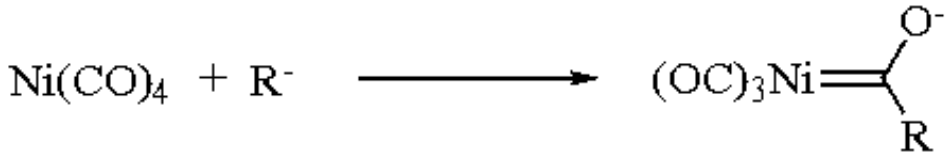

(3)

Poorer nucleophiles do not attack one of the carbonyls. Instead, they coordinate to $Ni(CO)_3$, which is formed readily by the thermal or photochemical dissociation of a carbonyl ligand from the $Ni(CO)_4$.[8] As a specific example, the reaction of $Ni(CO)_4$ with a phosphine (PR_3) is first order in nickel complex and zero order in phosphine.[9] This suggests rate-limiting dissociation of a carbonyl ligand followed by a rapid attack on the $Ni(CO)_3$ by the phosphine (eq 4).

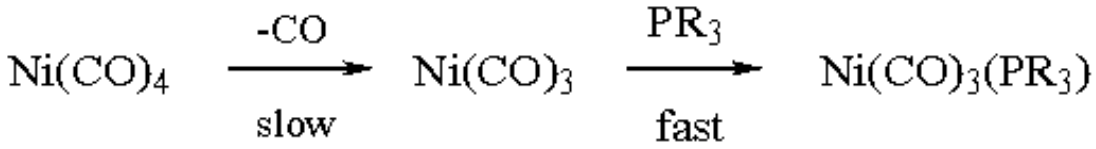

(4)

If an excess of phosphine is used, the $Ni(CO)_3(PR_3)$ complex will react in a similar manner to generate $Ni(CO)_2(PR_3)_2$. Due to the increase in back-bonding from the metal into the π^* orbital of the carbonyl as the number of phosphine ligands increases, removal of a third carbonyl and formation of $Ni(CO)(PR_3)_3$ does not occur.

Halide ions will also react with $Ni(CO)_4$ to form halide-$Ni(CO)_3$ anionic complexes.[8,10] The order of nucleophilicity of the halides is the standard order of $I^- > Br^- > Cl^-$. It is believed that a halide-$Ni(CO)_3$ anionic complex is the actual species which reacts with the acid chloride in the lactone synthesis shown in eq (5).[10]

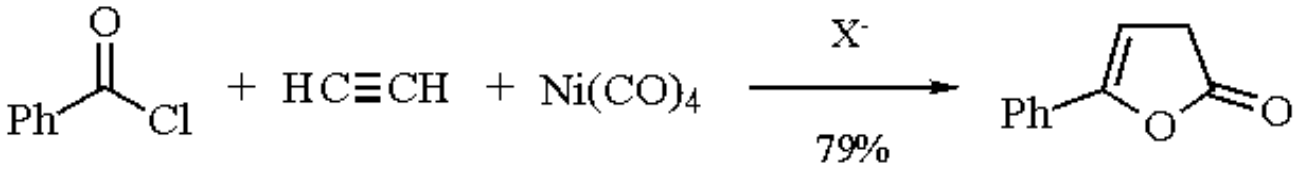

(5)

Oxidative Addition Reactions.

$Ni(CO)_4$, or more specifically $Ni(CO)_3$, will react with alkyl halides in an oxidative addition reaction. (There are a large number of examples of Ni^0 complexes other than $Ni(CO)_4$ undergoing oxidative addition reactions;[1] however, they will not be covered here.) One of the more common reactions of this type is the reaction of $Ni(CO)_4$ with an allyl bromide derivative to form a π-allyl nickel complex (eq 6). These complexes, unlike the analogous palladium complexes, are nucleophilic.[11] In addition, the allyl groups can couple to form a 1,5-hexadiene derivative. For more of the chemistry of allyl nickel complexes, see ***Bis(allyl)di-μ-bromodinickel***.

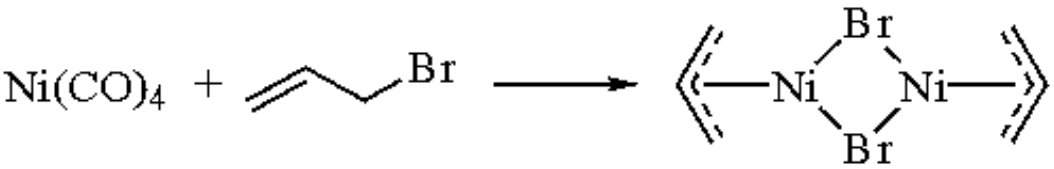

(6)

The reaction of an aryl iodide with $Ni(CO)_4$ generates a 1,2-diketone when THF is used as the solvent, and an ester when methanol is used as the solvent (eq 7). The exact mechanism of this reaction is not known, but a benzoyl-nickel complex has been proposed as a likely intermediate. The reaction of this intermediate with another intermediate forms the diketone or with the alcohol forms the ester.[12]

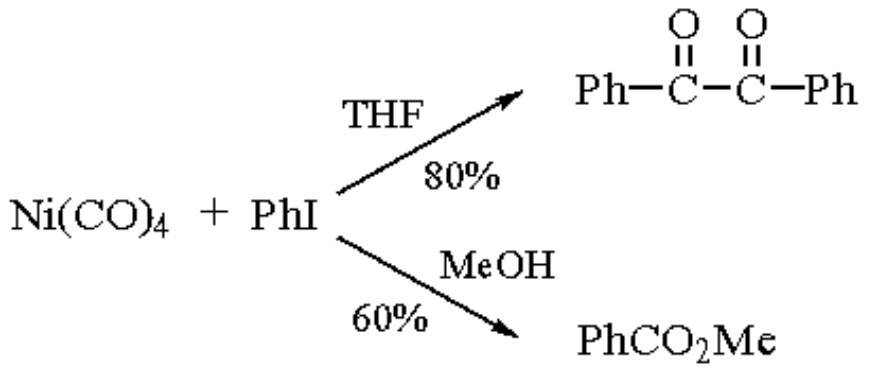

(7)

Similarly, the reaction of an alkyl or vinyl halide with an excess of an alkoxide (RO^-) and $Ni(CO)_4$ in an alcohol solvent at refluxing temperature, generates the corresponding ester in high yield (eq 8). In contrast to the previous reaction, it is speculated that the mechanism involves initial formation of a nickel acylate complex, followed by reaction of the acylate complex with the alkyl or vinyl halide.[6] However, a mechanism in which the nickel carbonyl reacts with the alkyl or vinyl halide to form an acyl nickel complex, and then this is quenched by the alkoxide, cannot be excluded.

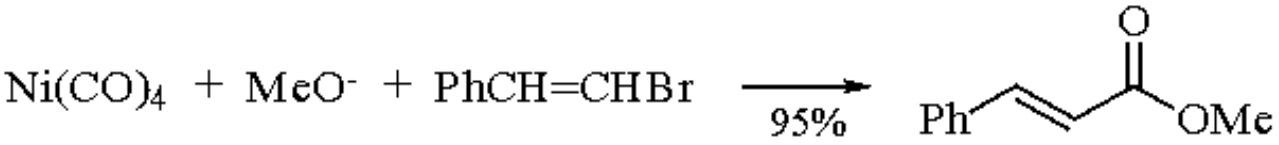

(8)

This general type of reaction also can be performed in the presence of an amine to form an amide as the final organic product (eq 9).[6]

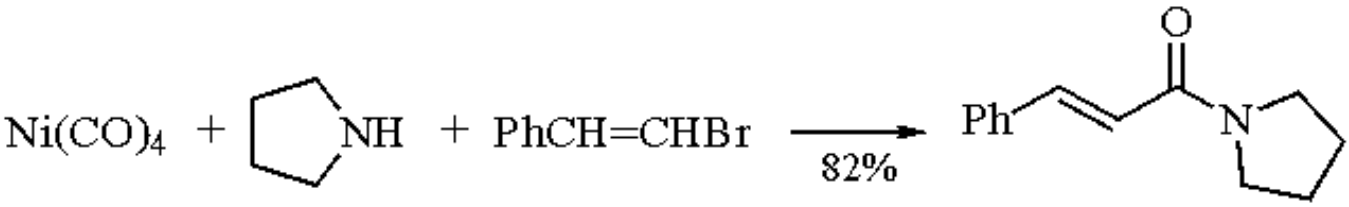

(9)

Intramolecular variations of these two reactions have led to the syntheses of α-methylene lactones and β-lactams. Specifically, the reaction of nickel tetracarbonyl with a molecule possessing a vinyl halide on one end and an alcohol on the other, in refluxing THF with or without added base, can generate a five- or six-membered α-methylene lactone in good yield (eq 10).[13]

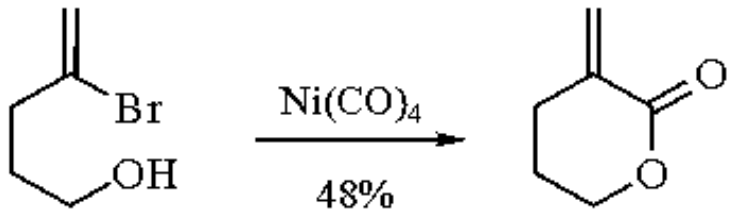

(10)

An aziridine, which is first ring-opened with ***Lithium Iodide***, reacts with nickel tetracarbonyl in a similar cyclization reaction to generate a β-lactam (eq 11).[14]

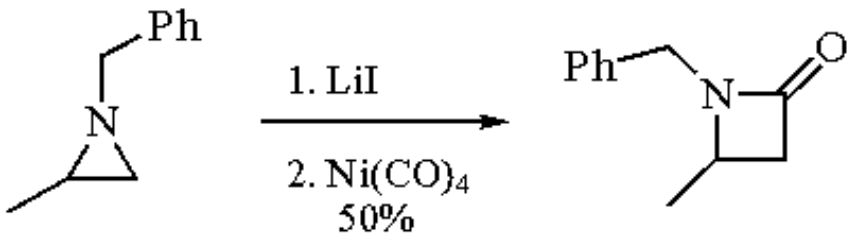

(11)

These two steps must be done individually because, as discussed above, iodide and nickel carbonyl readily react with each other. Because

the first step is an S_N2 reaction, the less substituted carbon-nitrogen bond is carbonylated. This result is complementary to the use of a rhodium complex for the conversion of an aziridine to a β-lactam. In that reaction it is always the more substituted C-N bond which is carbonylated.[15] In addition, it has been shown that when a 2,3-disubstituted aziridine is the starting material, the product β-lactam is generated with retention of stereochemistry.

The oxidative addition of nickel tetracarbonyl has been shown to be an effective method for the formation of an alkene by the removal of two halogens which are *cis*. For example, a *cis*-1,2-dichlorocyclobutane derivative upon reaction with nickel carbonyl generates the corresponding cyclobutene (eq 12).[16] This reaction is compatible with a large variety of R groups; however, the chlorines must be attached to carbon atoms which contain electron-withdrawing groups. If the methoxycarbonyl groups are replaced by electron donors, the starting material is stable to the reaction conditions.[17]

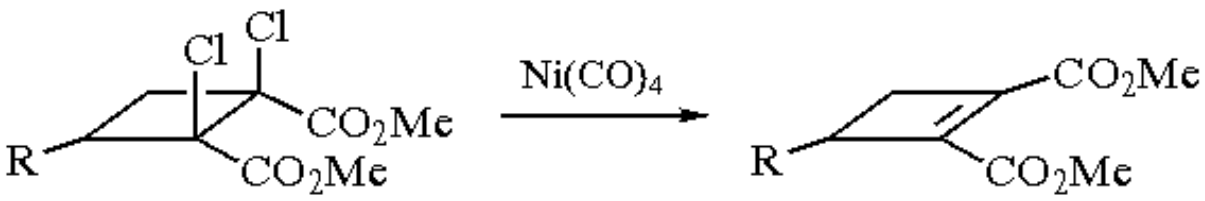

(12)

R = Et, 87%

Rearrangement and Cyclization Reactions.

Nickel carbonyl will catalyze the rearrangement of a vinylcyclobutene to a cyclohexadiene derivative (eq 13).[17] Although a reactive intermediate has not been observed, based upon deuterium-labeling studies, it has been determined that the reaction is unimolecular and that it is the 2,3-bond (and not the 3,4-bond) which is cleaved.

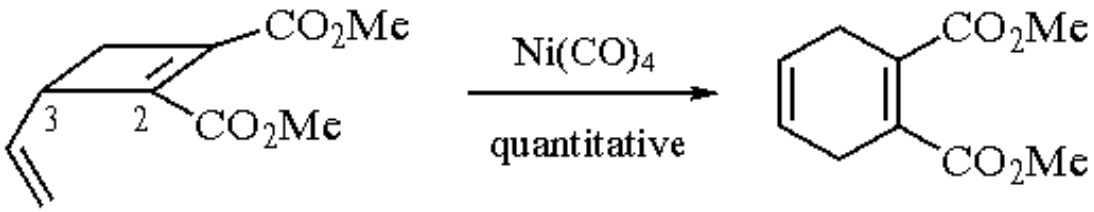

(13)

Nickel tetracarbonyl has initiated a variety of other ring-formation reactions, including the lactone synthesis shown in eq 5.[10] Another is the reaction between an allyl bromide and an alkyne to generate a cyclopentenone derivative (eq 14).[18]

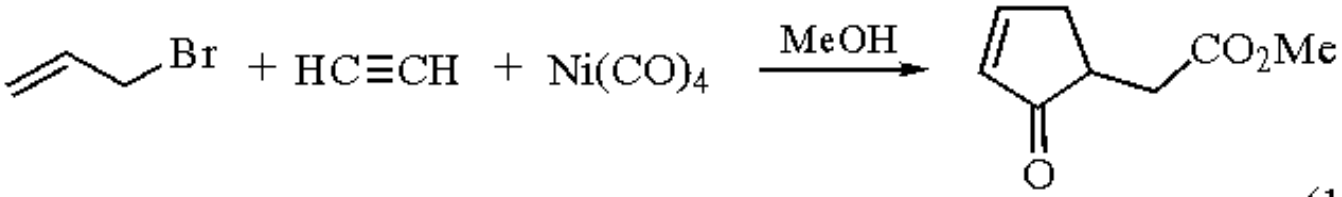

(14)

This reaction is not restricted to allyl bromide itself. A large variety of allyl bromide derivatives have been used, including cyclic derivatives which generate products containing either fused bicyclic or spirocyclic ring systems. In all cases the cyclization reaction gives the five-membered ring rather than the six-membered ring. The alkyne component does not have to be symmetrical. Acetylene itself, terminal alkynes, and unsymmetrical disubstituted alkynes work well. Although the exact mechanism of this reaction is not known, it has been proposed that initially an allyl-nickel complex is formed, followed by alkyne insertion, then carbonyl insertion, and finally ring closure to produce the five-membered ring.[19]

Carbonylation Reactions.

In the absence of any added allyl bromide, an alkyne and nickel carbonyl will react in methanol (excess HCl also is added to this reaction to increase the rate) to give an α,β-unsaturated ester in good yield (eq 15).[20]

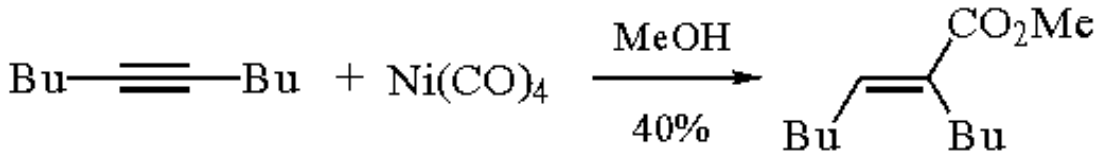

(15)

In addition, it is possible to carbonylate alkenes. This reaction proceeds at a faster rate when the double bond is incorporated into a strained ring system, but almost any alkene will work. 1,5-Hexadiene can be carbonylated to give a *cis*/*trans* mixture of 2,5-dimethylcyclopentanone, as the major product, in good yield (eq 16). Some of the methylcyclohexanone also is generated.[21]

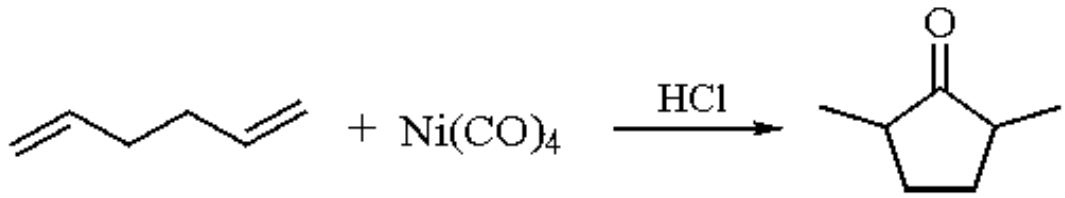

(16)

A substituted dibromocyclopropane, but not the corresponding monobromocyclopropane, can be carbonylated with nickel carbonyl using DMF as the solvent to generate an ester, when the reaction is done in the presence of an alcohol, or an amide, when the reaction is done in the presence of a secondary amine. A large variety of R groups are compatible with these reaction conditions.[22] Where applicable, a *cis*/*trans* mixture of products usually results (eq 17).

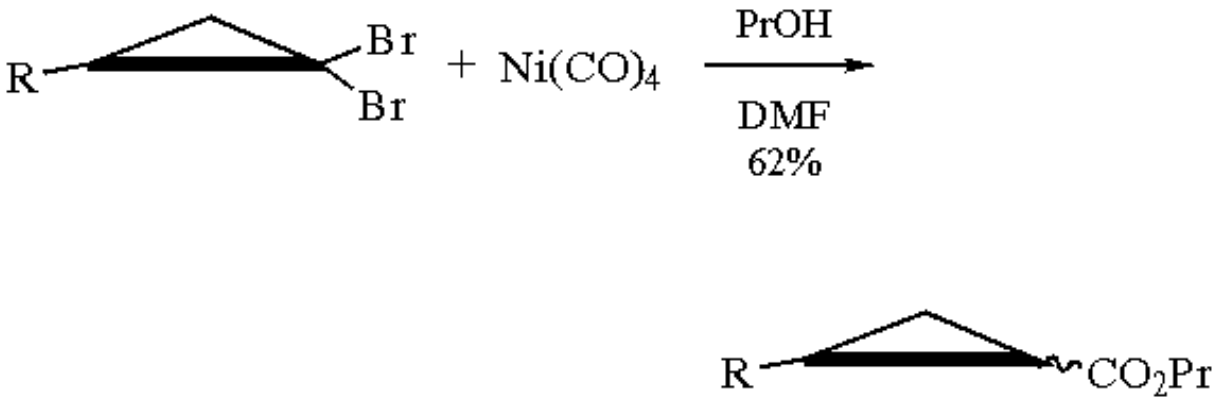

(17)

If one of the R groups is H and the other is CH_2Cl, ring opening of the cyclopropane occurs concomitantly with the carbonylation, again to generate either the ester or the amide (eq 18).[23]

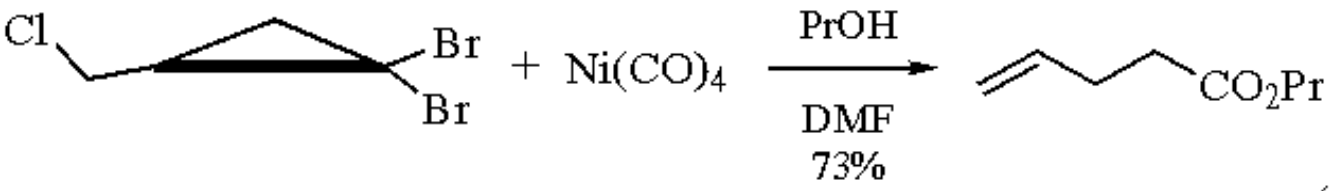

(18)

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Tetrachlorocyclopentadienone

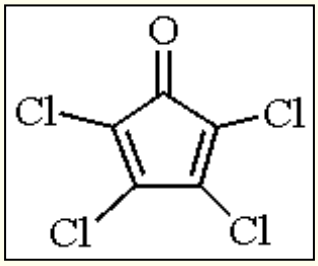

[4723-74-4] · C_5Cl_4O · Tetrachlorocyclopentadienone · (MW 217.85)

(highly reactive diene for Diels-Alder reactions)

Physical Data: unstable as the monomer; matrix-isolated IR spectrum has been recorded.[1]

Form Supplied in: must be prepared in situ.

Preparative Methods: conveniently generated in the presence of dienophiles, starting from hexachlorocyclopentadiene. Treatment of this material with concentrated ***Sulfuric Acid*** at 80 °C affords in good yield the pentachlorocyclopentenone,[2] which is readily dehydrohalogenated with either sodium acetate in MeCN or ***Sodium Iodide*** in 1,2-dimethoxyethane (eq 1).[3]

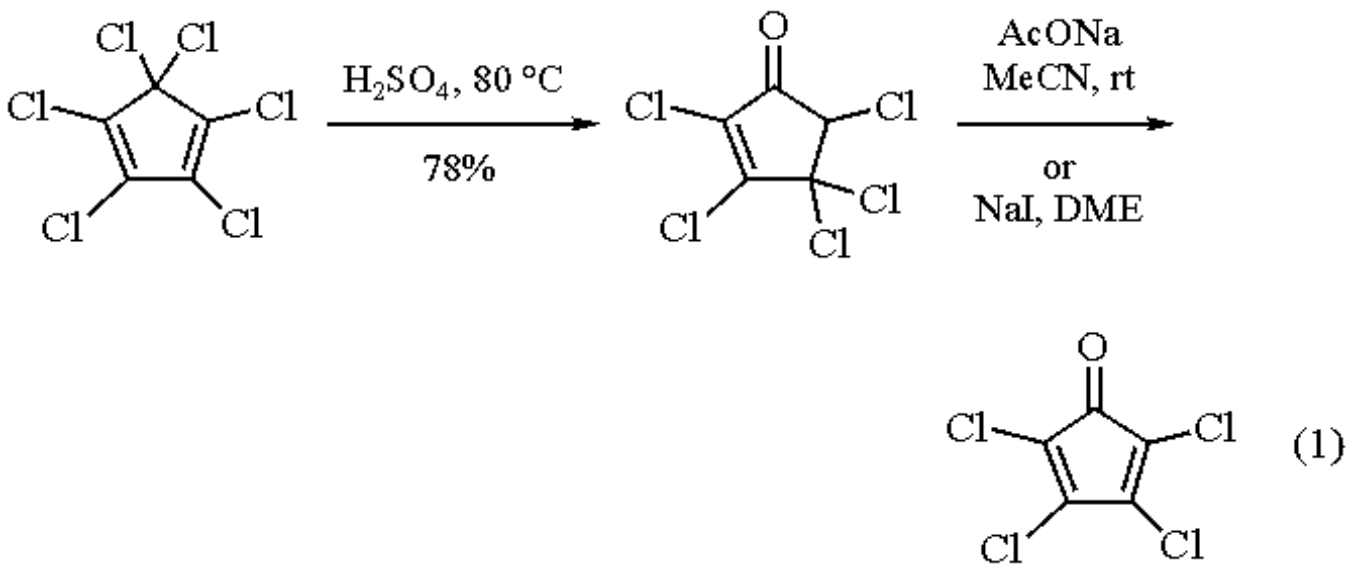

(1)

Reactive Diene.

The utility of tetrachlorocyclopentadienone as a reactive diene has received very little attention. The reagent has only rarely been employed as a trap for dienophiles. Dietsche reported the first Diels-Alder reactions of the reagent with norbornadiene and cyclopentadiene in yields of 80% and 60%, respectively (eqs 2 and 3).[3] The norbornadiene cycloadduct undergoes thermal extrusion of carbon monoxide and subsequent retro-Diels-Alder reaction to give the 1,2,3,4-tetrachlorobenzene (eq 4). Maleic anhydride, acrylonitrile, and less reactive dienophiles such as cyclopentene, cyclohexene, norbornene, and phenylacetylene all fail to react with the reagent; dimerization presumably occurs preferentially.

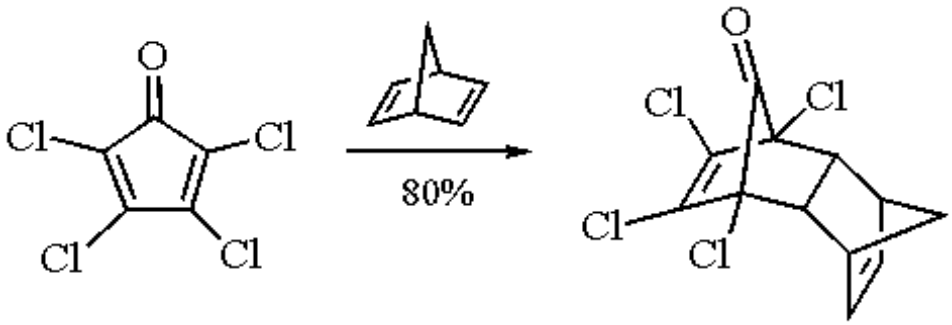

(2)

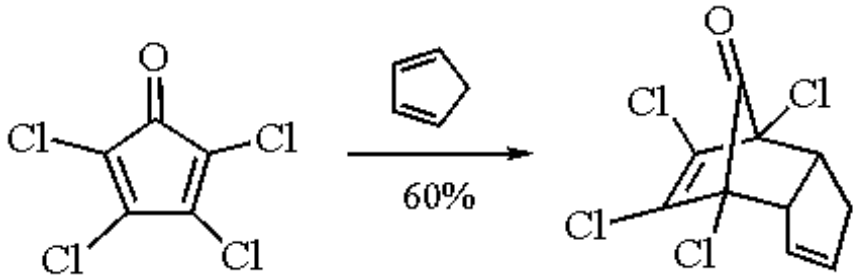

(3)

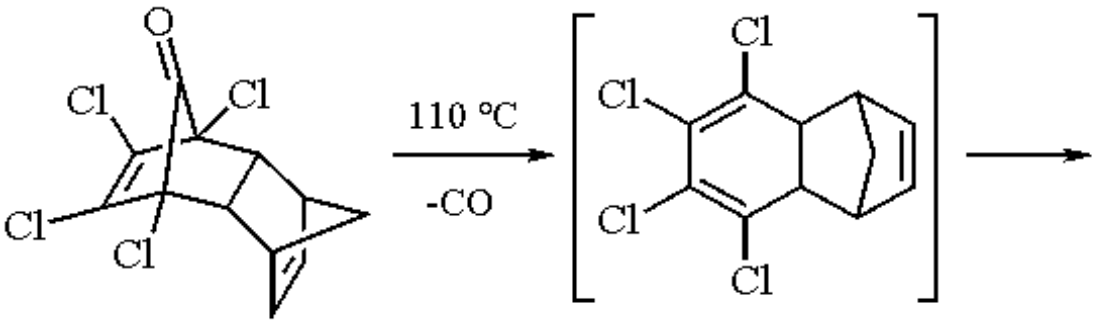

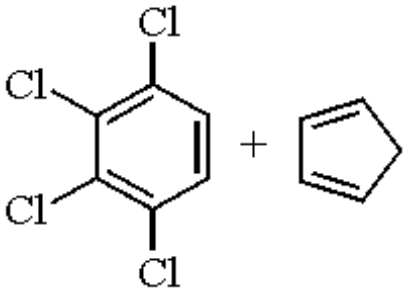

(4)

Fray reported the Diels-Alder reaction of the reagent with acenaphthylene to afford the *endo* and *exo* cycloadducts in a ratio of 4.2:1 (eq 5).[4] Reinvestigation of the reaction with cyclopentadiene gave as the major products the *endo*- and *exo*- adducts in a ratio of about 170:1, along with the Cope-rearranged derivative (eq 6).

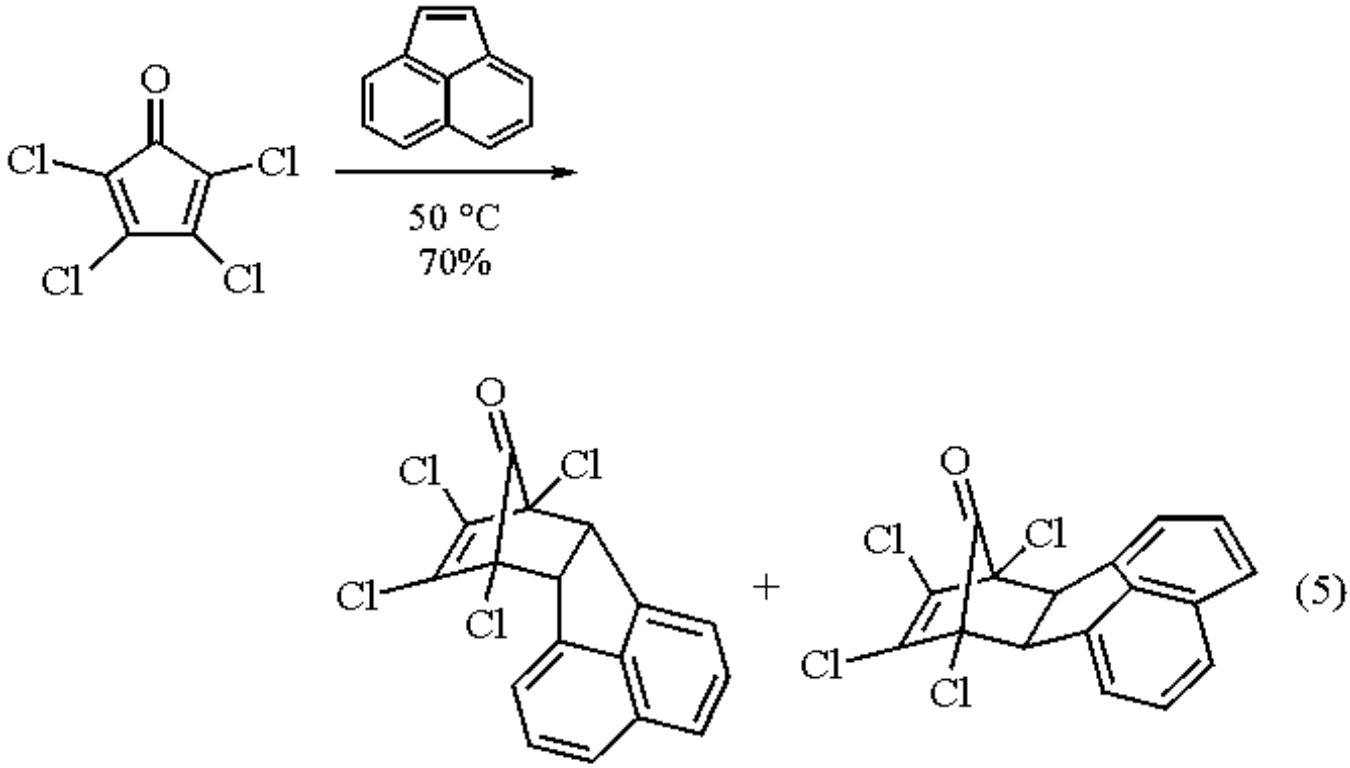

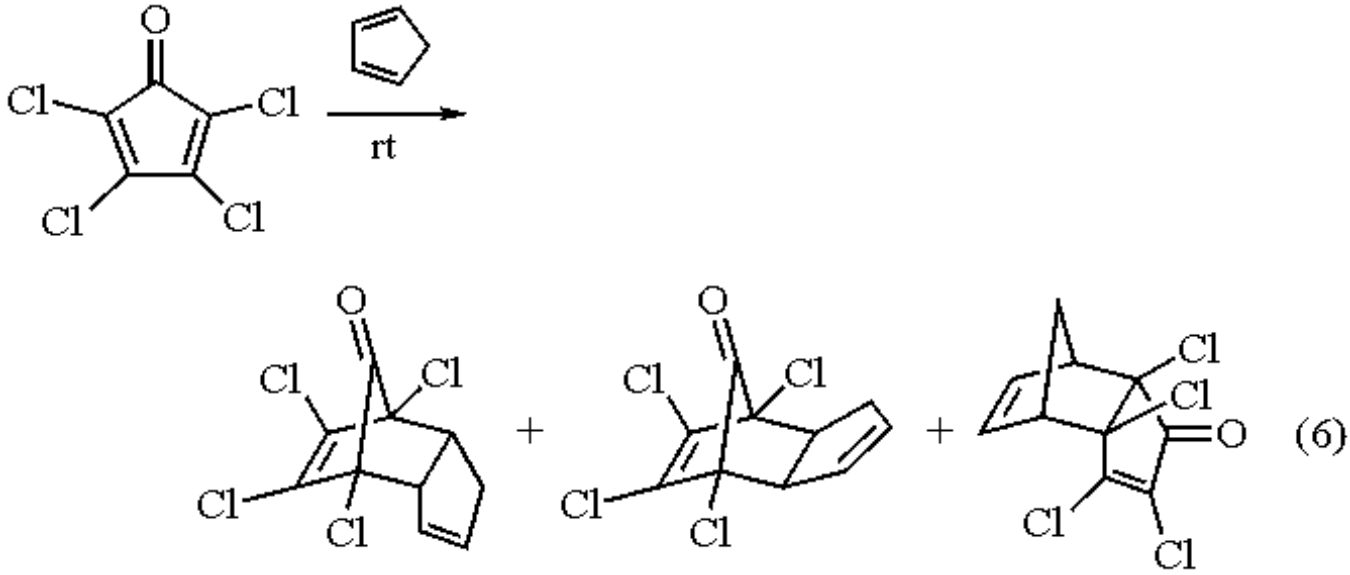

Because of the propensity to dimerize, the reagent is more commonly employed as its dimethyl acetal.[2]

Related Reagents.

Cyclopentadiene; ***2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone***; ***5,5-Dimethoxy-1,2,3,4-tetrachlorocyclopentadiene***; ***Tetrachlorocyclopentadienone Ethylene Acetal***; ***Tetraphenylcyclopentadienone***.

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Tetrachlorocyclopentadienone Ethylene Acetal[1]

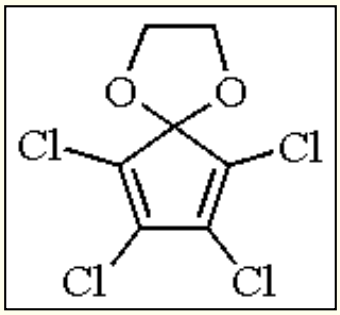

[2082-08-8] · $C_7H_4Cl_4O_2$ · Tetrachlorocyclopentadienone Ethylene Acetal · (MW 261.91)

(Diels-Alder adduct formation;[1-3] employed in the synthesis of condensed polycyclic systems[4,5])

Alternate Name: 6,7,8,9-tetrachloro-2,5-dioxaspiro[4.4]nona-6,8-diene.

Physical Data: mp 65-67 °C; bp 78-80 °C/0.13 mmHg.

Solubility: insol H_2O; sol ether, alcohol, acetone; slightly sol hexane.

Form Supplied in: not available commercially; can be made before use and stored.

Preparative Method: the title reagent can be prepared from hexachlorocyclopentadiene, ***Ethylene Glycol***, and ***Potassium Hydroxide***.

Purification: by distillation followed by recrystallization from ether-pentane.[1]

Handling, Storage, and Precautions: dimerizes in solution within a few months at 0 °C and within 1 h at 100 °C. It is stable for at least 1 year when stored at 0 °C. It is carcinogenic and should be handled in a fume hood.

Diels-Alder Reactions.

The principle use of the title reagent is as a diene in [4 + 2] cycloaddition reactions. It provides 1:1 adducts as shown in eq 1 with dienophiles such as ***Maleic Anhydride***, 2-butene-1,4-diol, ***2,5-Dihydro-2,5-dimethoxyfuran***, allyl alcohol, methyl maleate, indene, ***Vinyl Acetate***, 3-thiolen-2-one,[3a] vinylcyclopropane,[3b] 1,1-diphenyl-2-vinylcyclopropane,[3b] cyclopropene,[3c] 1-methylcyclopropene,[3c] phenylacetylene,[2b] diallylamine, ***Cyclopentadiene***, *cis,cis*-cycloocta-1,3-diene, *cis,cis*-cycloocta-1,5-diene, and cyclooctadeca-1,5,9-triene.[1c] It is notable that reactions occur with both electron-rich and electron-deficient dienophiles. Other alkenes that react with the title reagent include norbornadiene,[5d] 7-*t*-butoxy norbornadiene,[6] cycloheptatriene, tropone, and *p*-benzoquinone.[7] Several of the polyenes afford 2:1 cycloadducts.

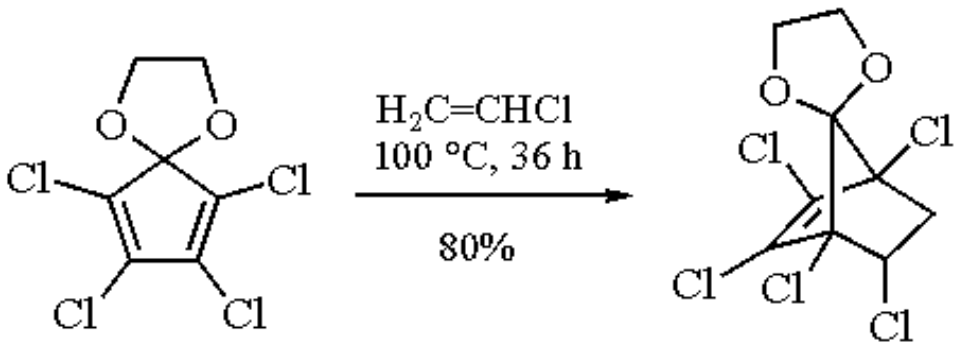

(1)

Cycloadducts with properly selected dienophiles can lead to structures of potential interest by unmasking and manipulating the carbonyl group, and using the chlorides as precursors for other functional groups of interest.[4] For example, the title reagent has been used as a starting material in syntheses of condensed polycyclic systems, as shown in eqs 2 and 3.[5]

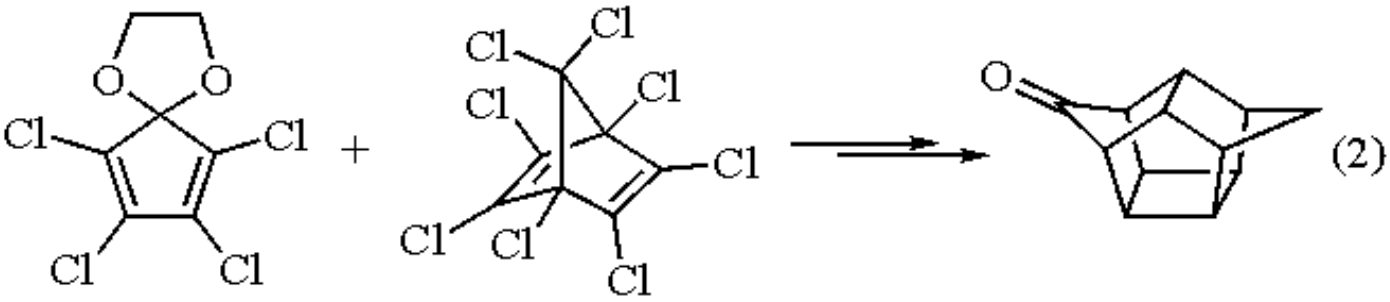

(2)

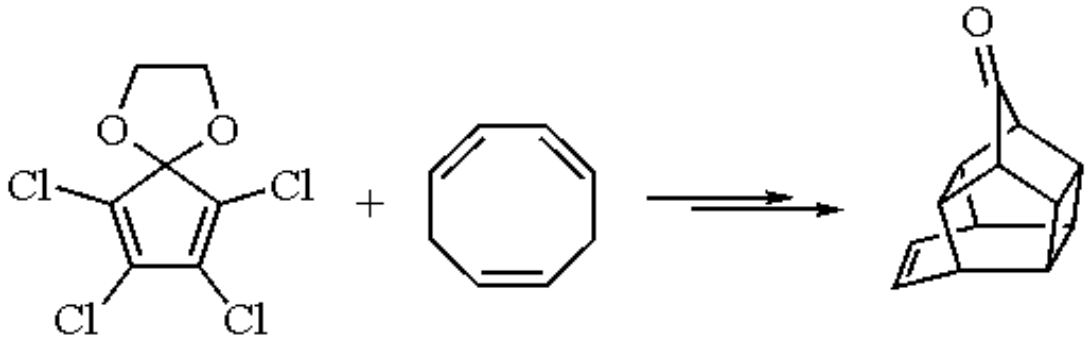

(3)

Miscellaneous Reactions.

The reaction of nitrosobenzene with the title reagent has been reported to give *N*-phenyldichloromaleimide and the unsaturated lactam shown in eq 4.[8] The mass spectra of Diels-Alder adducts of alkenes with the title reagent are much simpler than the spectra of other derivatives, and have been used to determine double bond position and alkene geometry.[9]

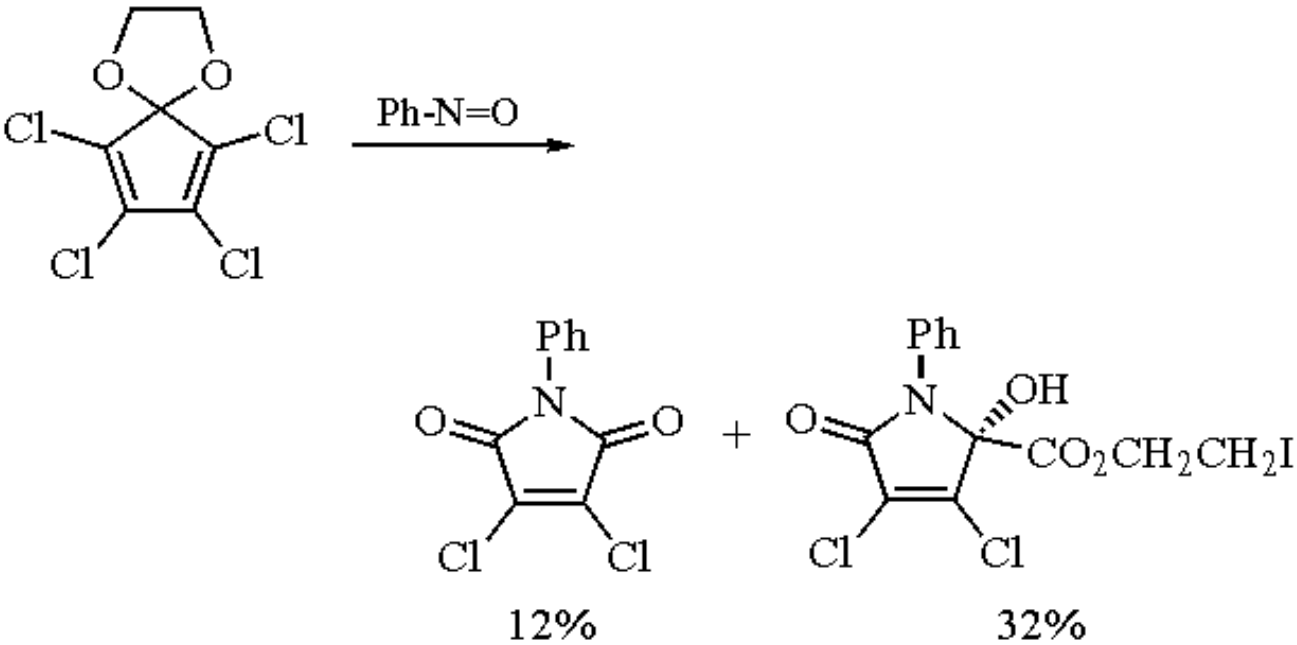

(4)

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Tetrachloro(η^5-cyclopentadienyl)niobium-Magnesium[1]

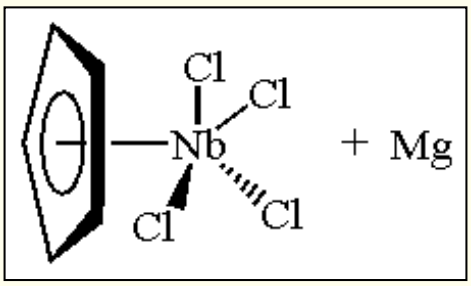

($CpNbCl_4$)

[33114-15-7] · $C_5H_5Cl_4Nb$ · Tetrachloro(η^5-cyclopentadienyl)niobium-Magnesium · (MW 299.81) (Mg)

[7439-95-4] · Mg · Tetrachloro(η^5-cyclopentadienyl)niobium-Magnesium · (MW 24.31)

(catalyst for cyclotrimerization of alkynes[1])

Solubility: sol THF.

Preparative Method: generated, in situ, from $CpNbCl_4$ and ***Magnesium***.

Handling, Storage, and Precautions: is prepared and used under an inert atmosphere of nitrogen or argon.[1] Use in a fume hood.

Cyclotrimerization.

It has been demonstrated[1] that catalytic amounts of $CpNbCl_4$-Mg (i.e. 1 mol %) will effect the cyclotrimerization of terminal alkynes. A mixture of 1,3,5- and 1,2,4-trisubstituted benzenes are obtained as products, with the 1,3,5-trisubstituted isomer being slightly favored (eq 1; Table 1). The reaction proceeds in 83-91% yield with aryl- and alkyl-substituted alkynes; trimethylsilylacetylene, however, does not react. In contrast to the reaction with terminal alkynes, internal alkynes do not undergo cyclotrimerization or polymerization when treated with catalytic amounts of $CpNbCl_4$-Mg.

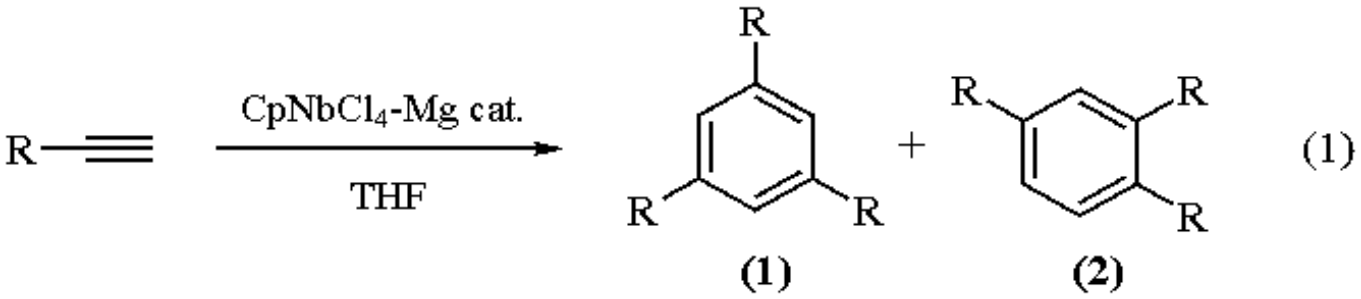

Table 1 Cyclotrimerization of Terminal Alkynes (eq 1)

R	Yield (%)	Ratio (**1**):(**2**)
Ph	90	7
Bu	91	1.2
$(CH_2)_3OTBDMS$	95	1.2
$(CH_2)_2OCO$-*i*-Bu	83	1.2

Alkyne-Diyne Annulation.

$CpNbCl_4$-Mg catalyzes an annulation reaction between diynes and internal alkynes or sterically hindered terminal alkynes (eqs 2 and 3). These annulations, which lead to indanane ring systems, are conducted at 50 °C with 0.35 equiv of $CpNbCl_4$-Mg. Higher reaction temperatures are required because of the less reactive alkyne component, and greater than catalytic amounts of niobium are needed due to decomposition of the niobium intermediates at the higher temperature.

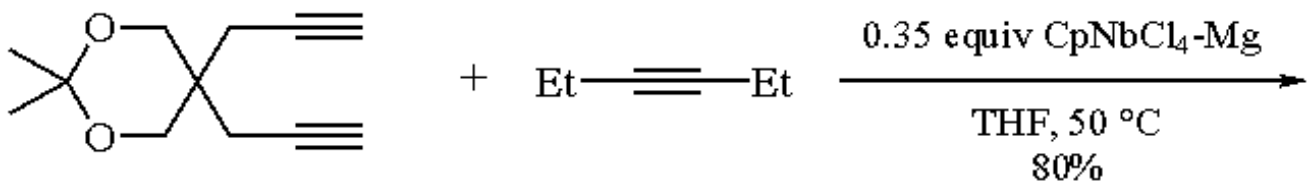

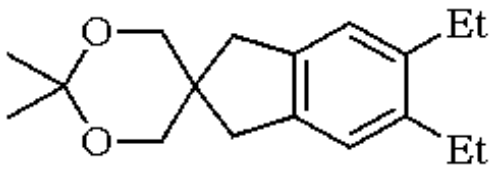

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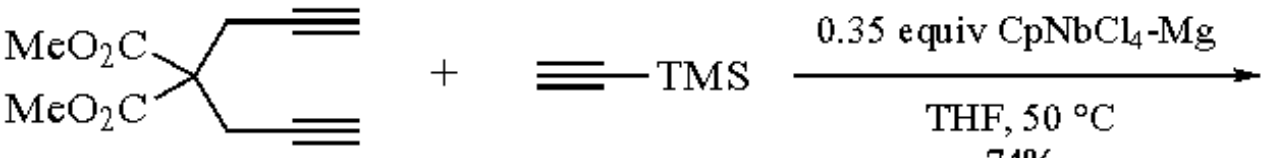

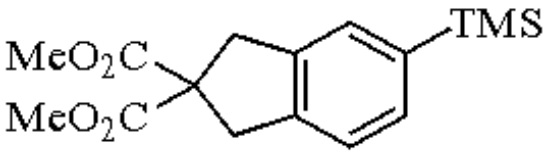

(3)

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Tetrachlorocyclopropene[1]

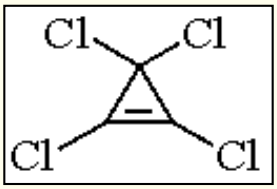

[6262-42-6] · C_3Cl_4 · Tetrachlorocyclopropene · (MW 177.83)

(versatile synthetic building block, based on its ability to react as a cyclopropenium cation,[2] a vinylcarbene,[3] or a dienophile[4])

Physical Data: bp 130-133 °C; *d* 1.450 g cm^{-3}.

Solubility: sol common organic solvents; undergoes ring opening in H_2O at 25 °C and in alcohols at 50-80 °C.[5]

Form Supplied in: colorless liquid; widely available.

Analysis of Reagent Purity: GC, IR.[5]

Preparative Method: from ***Sodium Trichloroacetate*** and ***Trichloroethylene***.[6]

Handling, Storage, and Precautions: lacrymator; must be stored at 4 °C in the absence of moisture; use in a fume hood.

Cyclopropenium Cations.

Tetrachlorocyclopropene (**1**) is widely used as an entry to cyclopropenium cation chemistry. Thus, upon treatment with ***Aluminum Chloride***, (**1**) readily forms the trichlorocyclopropenium salt (**2**) in virtually quantitative yield,[7] which can further be converted to a variety of cyclopropenium cations (**3**) (eq 1).[2] Compound (**2**) has been the starting point for the synthesis of a broad variety of heterocycles, e.g. benzimidazoles or 1,5-benzodiazepines,[8] 2-azacalicenium salts,[9] or indolizines.[10]

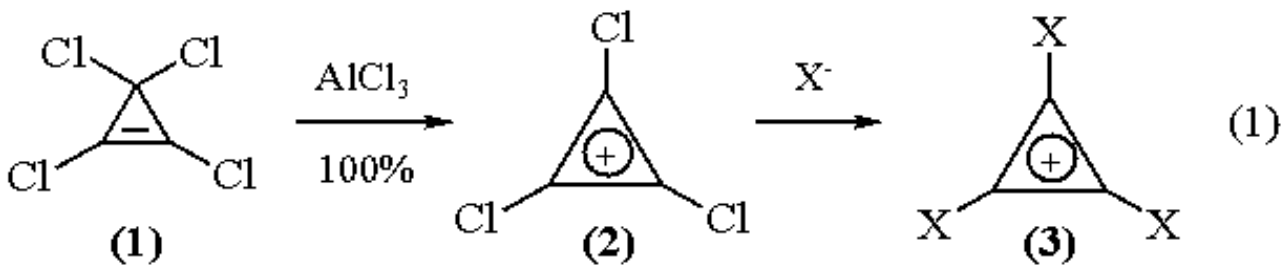

Treatment of (**2**) with arenes and subsequent hydrolysis with alcohols gives rise to arylpropiolates (**4**) in good to excellent yields (eq 2).[11]

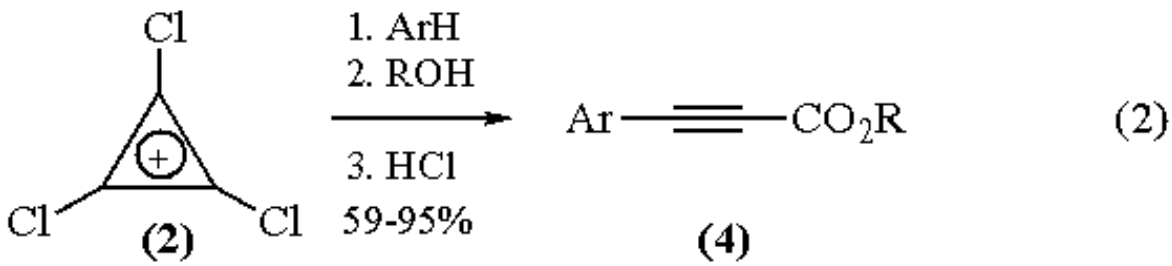

The transformation of (**2**) to substituted cyclopropenones opens up another wide field in synthetic chemistry. For example, vinyl-substituted cyclopropenones derived from (**2**) have been proven to be excellent precursors to α-methylene-γ-butyrolactones.[12]

Another important application of (**2**) was demonstrated with the synthesis of the dialkynyl-substituted cyclopropenone (**5**), which was envisaged as a precursor to new allotropic forms of carbon such as C_{18}, C_{24}, or C_{30}, respectively (eq 3).[13] Moreover, (**5**) can easily be converted to the enediyne (**6**),[13] a structure element which plays a pivotal role in the chemistry of the esperamicin/calicheamicin class of anticancer drugs.[14]

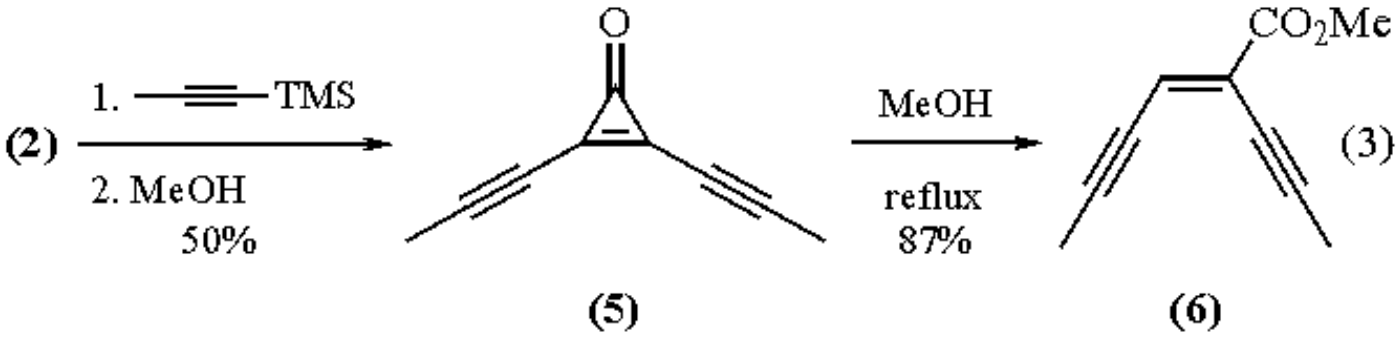

Diarylcyclopropenones (**7**), also readily obtained from (**2**), can be decarbonylated to symmetrically or unsymmetrically substituted alkynes (**8**) in high yields (eq 4).[15]

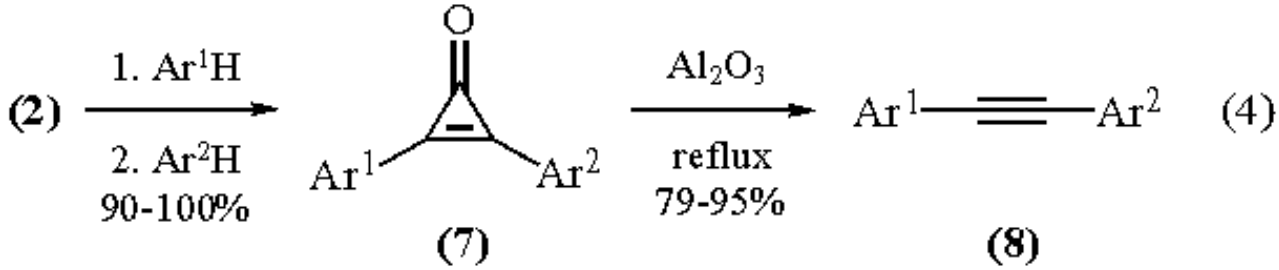

Vinylcarbenes.

Reagent (**1**) undergoes thermal ring opening to perchlorovinylcarbene (**9**), which is efficiently trapped with a large number of alkenes to form 1-chloro-1-trichlorovinylcyclopropanes (**10**).[3] From these intermediates, ethynylcyclopropanes (**11**) as well as cyclopropylideneacetates (**12**) are readily available (eq 5), which have been widely used in natural and nonnatural product synthesis,[16] including α- and β-amino acids,[16d,e] and β-lactams.[16f]

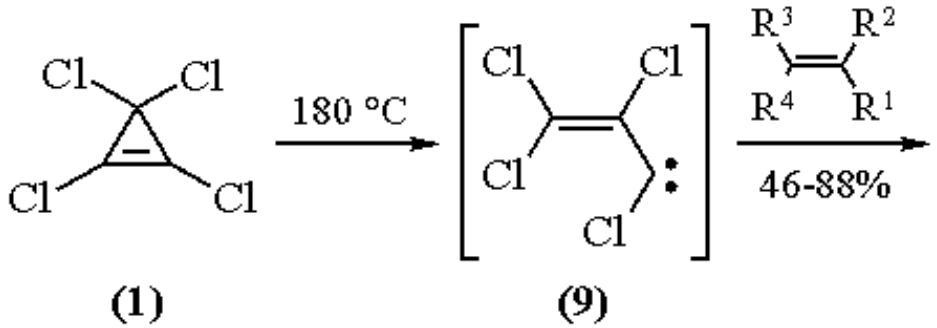

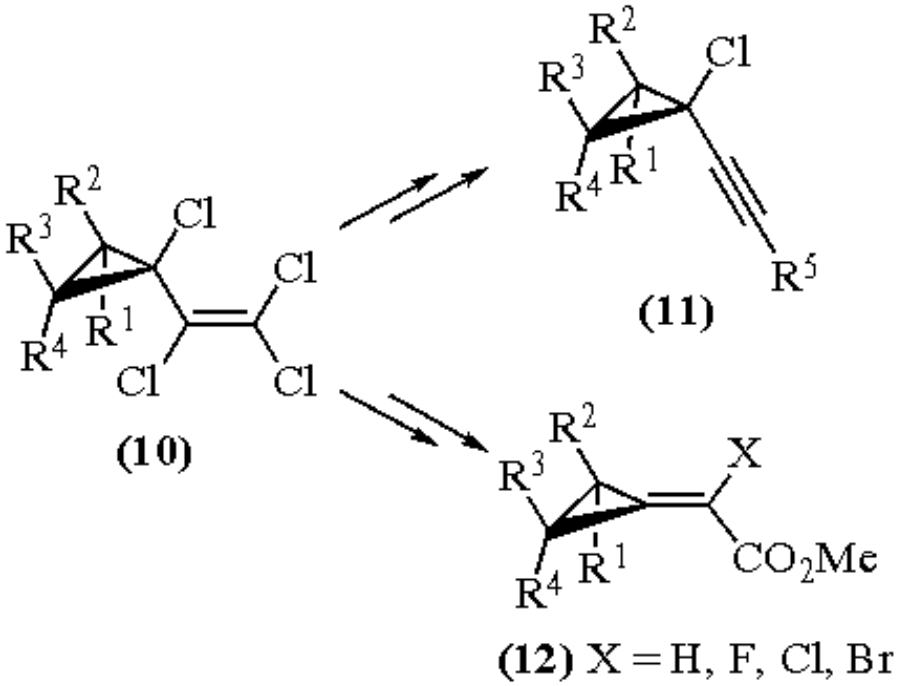

(5)

Cycloadditions.

Reagent (**1**) can react as an electron-poor dienophile in [4 + 2] cycloadditions to yield bicyclo[4.1.0]heptene derivatives (**13**) (eq 6) allowing, for example, the synthesis of tropolones[17] or triafulvalenes.[18] The stereochemical course of such cycloadditions has been investigated.[4]

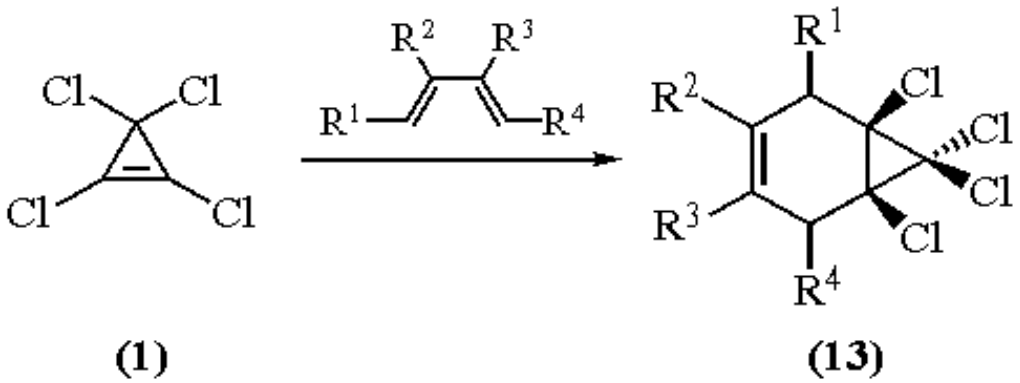

(6)

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Tetrachlorosilane

[10026-04-7] · Cl_4S_2 · Tetrachlorosilane · (MW 169.89)

(precursor of chlorotrialkylsilanes; Lewis acid catalyst)

Physical Data: mp -70 °C; bp 57.6 °C; *d* 1.483 g cm^{-3}.

Solubility: sol benzene, ether, chloroform, petroleum ether, dichloromethane.

Form Supplied in: neat as clear colorless liquid; as 1.0 M solution in dichloromethane.

Handling, Storage, and Precautions: the neat liquid and solutions react violently with water and protic solvents to produce HCl gas. The neat reagent reacts violently and/or explosively with DMSO and DMF. Avoid contact with metals, strong bases, strong acids, and glass. Corrosive; stench; handle and store under N_2; store cool. Use in a fume hood.

Chlorosilane Precursor.

Tetrachlorosilane serves as a useful precursor to tri-, di-, and monosilyl chlorides.[1] Substitution by metal alkoxides and phenoxides,[2] as well as alkyl, vinyl,[3] and aryl organometal nucleophiles, have been reported (eqs 1 and 2). An extremely hindered chlorosilane has been prepared from tri-*t*-butylphenoxide and tetrachlorosilane.[4]

$$2\,ROH + 2\,MeLi \xrightarrow{SiCl_4} (RO)_2SiCl_2 \qquad (1)$$

R = alkyl, aryl

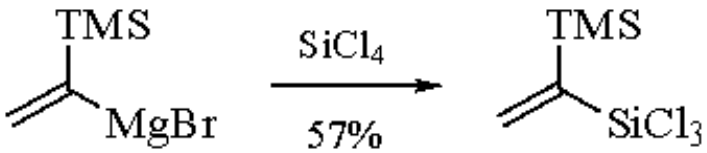

(2)

Treatment of tetrachlorosilane with 4 equiv of a propargyl Grignard reagent afforded, after zirconocene-promoted cyclization and sulfurization, a spiro-fused tetracyclic compound which serves as a precursor to orthogonally fused conducting polymers (eq 3).[5]

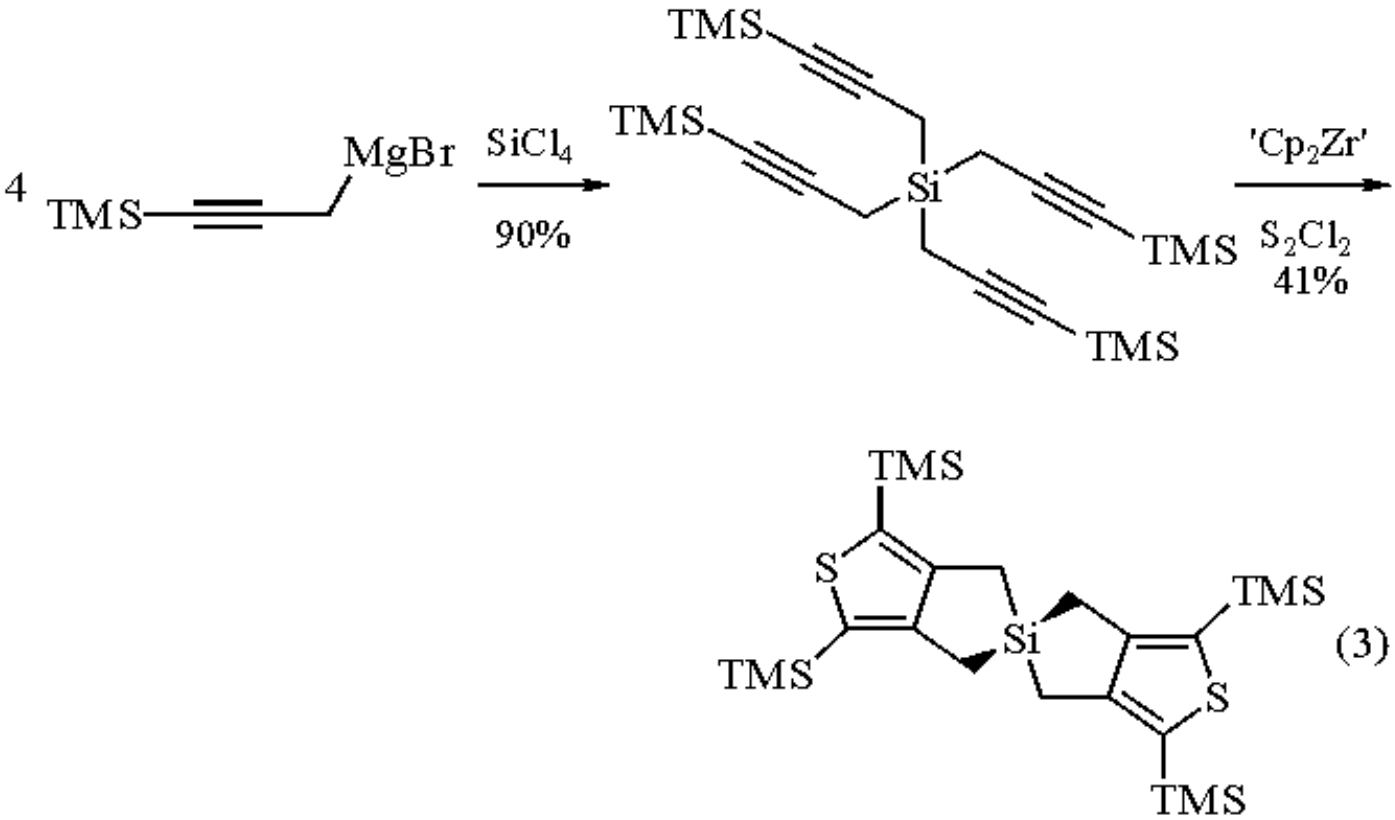

Coupling Reagent for Amide Formation.

Tetrachlorosilane in pyridine has been shown to facilitate amide formation from carboxylic acids and alkyl and aryl amines (eq 4).[6]

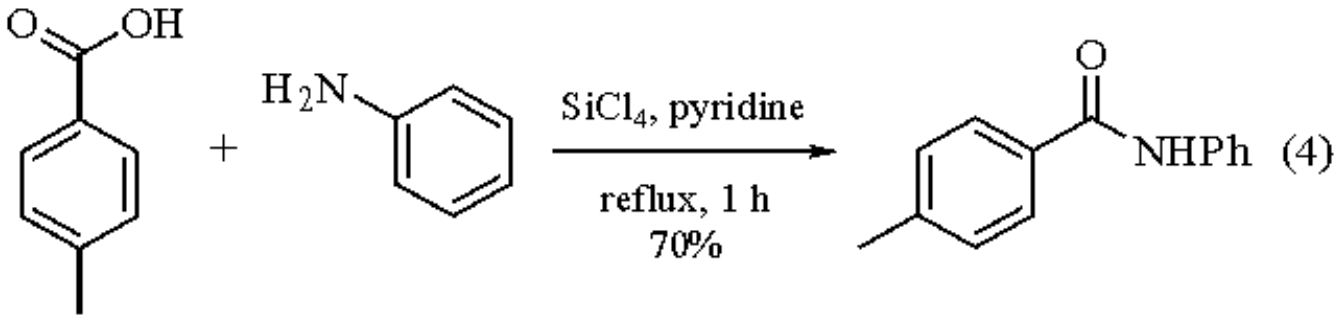

Acetal and Thioacetal Formation.

Tetrachlorosilane has been shown to convert α,β-unsaturated ketones, in the presence of ethylene glycol, to β-chloro acetals (eq 5).[7] Similarly, a propargyl ketone was transformed into the corresponding β,β-dichloro acetal under the same conditions (eq 6).

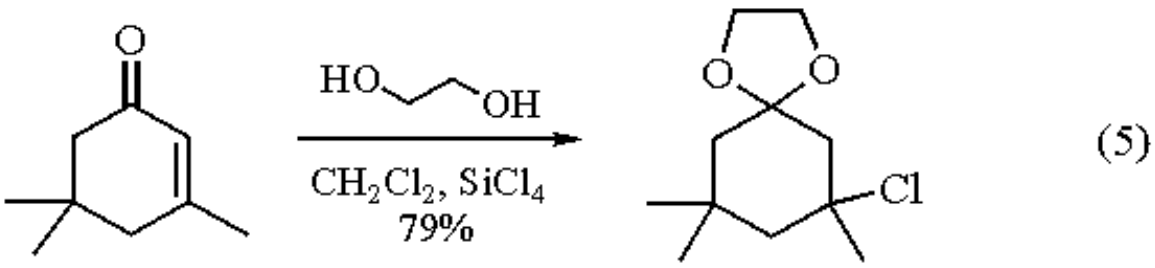

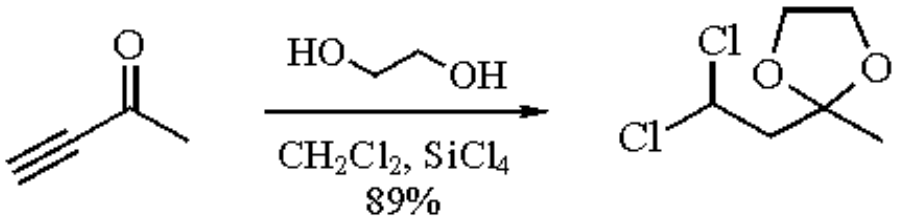

(6)

Dithioacetals of aryl aldehydes are efficiently formed upon treatment with 2 equiv of thiol in the presence of tetrachlorosilane (eq 7).[8] Aryl ketones (e.g. acetophenone or benzophenone) were not converted under the reaction conditions, while treatment of aliphatic ketones with tetrachlorosilane and dimercaptoethane resulted in some vinyl sulfide byproduct, as well as the desired dithioacetal (eq 8).

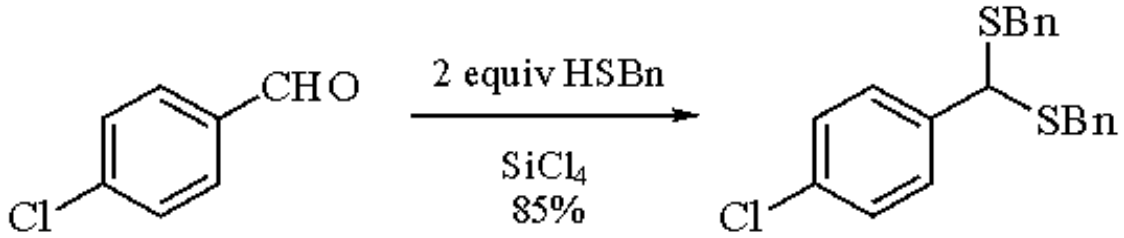

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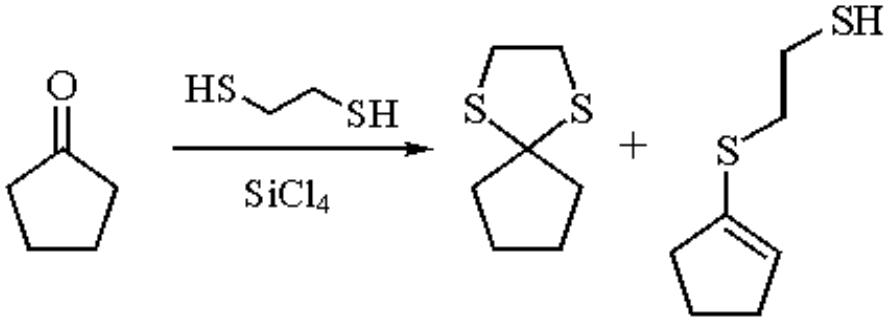

(8)

Cyclization Promoter.

Tetrachlorosilane was the Lewis acid promoter of choice for a critical cyclization step towards the synthesis of the alkaloids julandine and ipalbidine (eq 9).[9] Other Lewis acids evaluated were $TiCl_4$, $SnCl_4$, $BF_3.Et_2O$, $ZrCl_4$, $AlCl_3$, and $FeCl_3$. Tetrachlorosilane, and several other Lewis acids, were evaluated as promoters for Fischer indole synthesis reactions.[10]

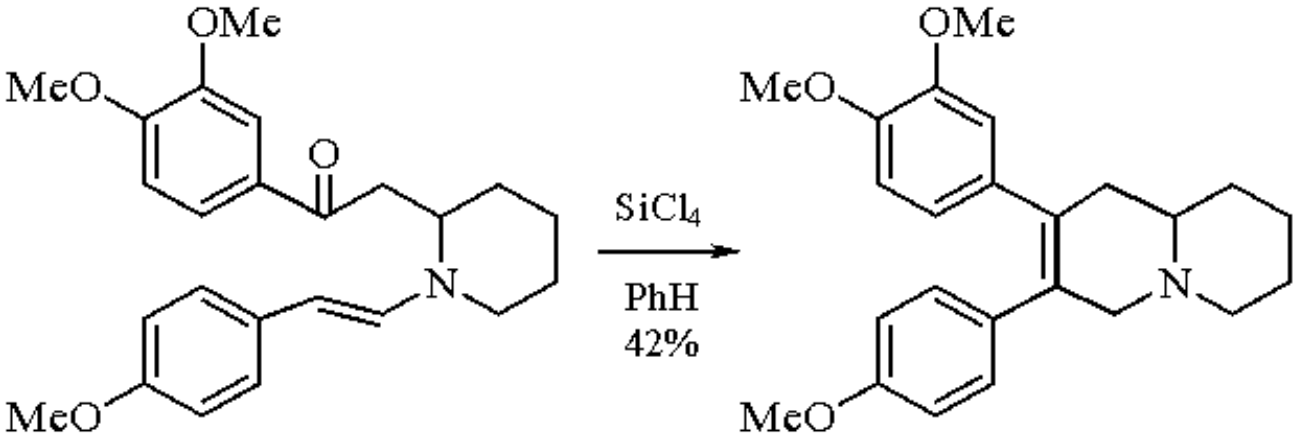

(9)

Disulfide Bond Formation.

In conjunction with diphenyl sulfoxide, tetrachlorosilane in trifluoroacetic acid (TFA) has been shown to effectively facilitate disulfide bond formation in the synthesis of cystine-containing peptides.[11,12] As shown in eq 10, the tetrachlorosilane-diphenyl sulfoxide-TFA system serves to activate the protected SH moiety of cysteine residue side-chains in peptides to afford, after nucleophilic attack of a second protected cysteine thiol, a disulfide bridge. A number of S-protecting groups were employed in the study, including acetamidomethyl (Acm), trimethylacetamidomethyl (Tacm), benzamidomethyl (Bam), *t*-butyl, isopropyl, 4-methoxybenzyl, 4-methylbenzyl, and 4-nitrobenzyl. Similarly, methyltrichlorosilane can be used in place of tetrachlorosilane to effect this transformation and, due to its ease of handling relative to tetrachlorosilane, is recommended by the authors.

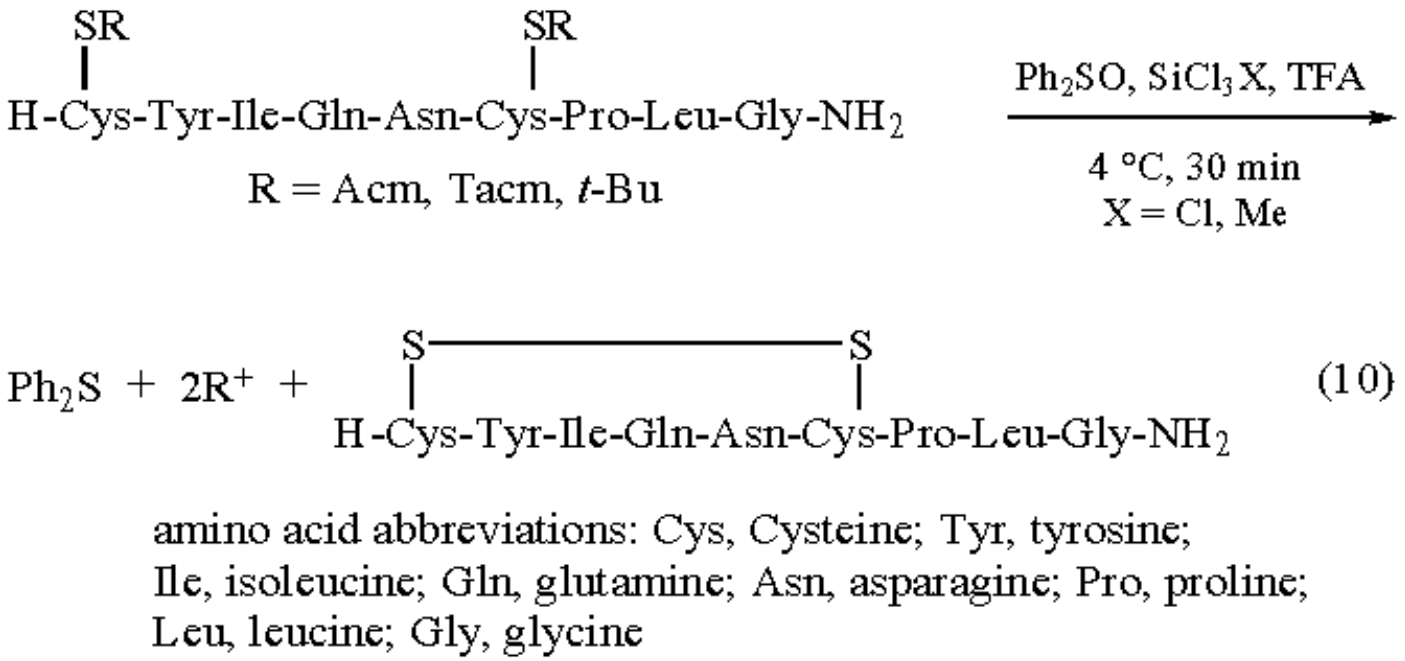

The chlorosilane-diphenyl sulfoxide oxidation system is operationally superior to both air and iodine, which are also used to facilitate peptide disulfide bond formation, due to shorter reaction times and improved regio- and chemoselectivity.

Friedel-Crafts Acylation Catalyst.

Tetrachlorosilane-***Silver(I) Perchlorate*** has been employed as a catalyst to effect the Friedel-Crafts acylation of anisole by hexanoic acid anhydride (eq 11).[13] Other Lewis acids used in combination with $AgClO_4$ which were evaluated in the study and shown to be as effective or better than $SiCl_4$ were $GaCl_4$, $GeCl_4$, $SnCl_4$, BCl_3, and $AlCl_3$. Lewis acids which were not as effective as $SiCl_4$ for this application were $InCl_3$, $SbCl_5$, $TiCl_4$, $ZrCl_4$, and $HfCl_4$.

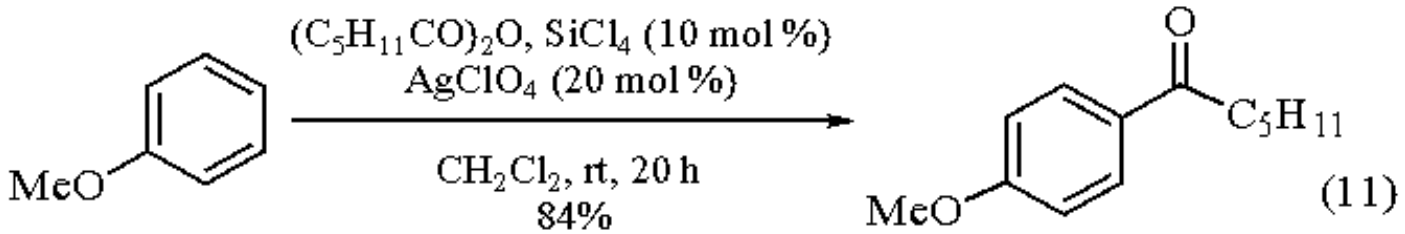

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Tetrachlorotris[bis(1,4-diphenylphosphino)butane]diruthenium

$Ru_2Cl_4(dppb)_3$

[55669-36-8] · $C_{84}H_{84}Cl_4P_6Ru_2$ · Tetrachlorotris[bis(1,4-diphenylphosphino)butane]diruthenium · (MW 1623.44)

(a regioselective hydrogenation and dehydrogenation catalyst for the formation of lactones)

Physical Data: mp 186 °C.[1]

Form Supplied in: light-green solid.[1]

Solubility: insol alcohol, ethyl ether; sol CH_2Cl_2, chlorobenzene.[1]

Preparative Methods: $K_2[RuCl_5(H_2O)]$ (1 mmol) in 2 mL of water is added to a hot ethanolic solution (100 mL) of 1,4-bis(diphenylphosphino)butane (dppb) (4 mmol), and the mixture refluxed for 3 h. The resulting light-green precipitate is washed with diethyl ether and extracted with chlorobenzene. The soluble fraction is crystallized repeatedly from chlorobenzene-diethyl ether.[1]

Handling, Storage, and Precautions: should be handled and stored under an inert atmosphere.

Regioselective Hydrogenation Reactions.

Catalytic amounts of tetrachlorotris[bis(1,4-diphenylphosphino)butane]diruthenium (**1**) have been used to regioselectively hydrogenate unsymmetrically substituted cyclic anhydrides to the corresponding lactones. These reactions have been carried out using as little as 2 mol % of (**1**) with both high regioselectivity and isolated yields (eq 1).[2]

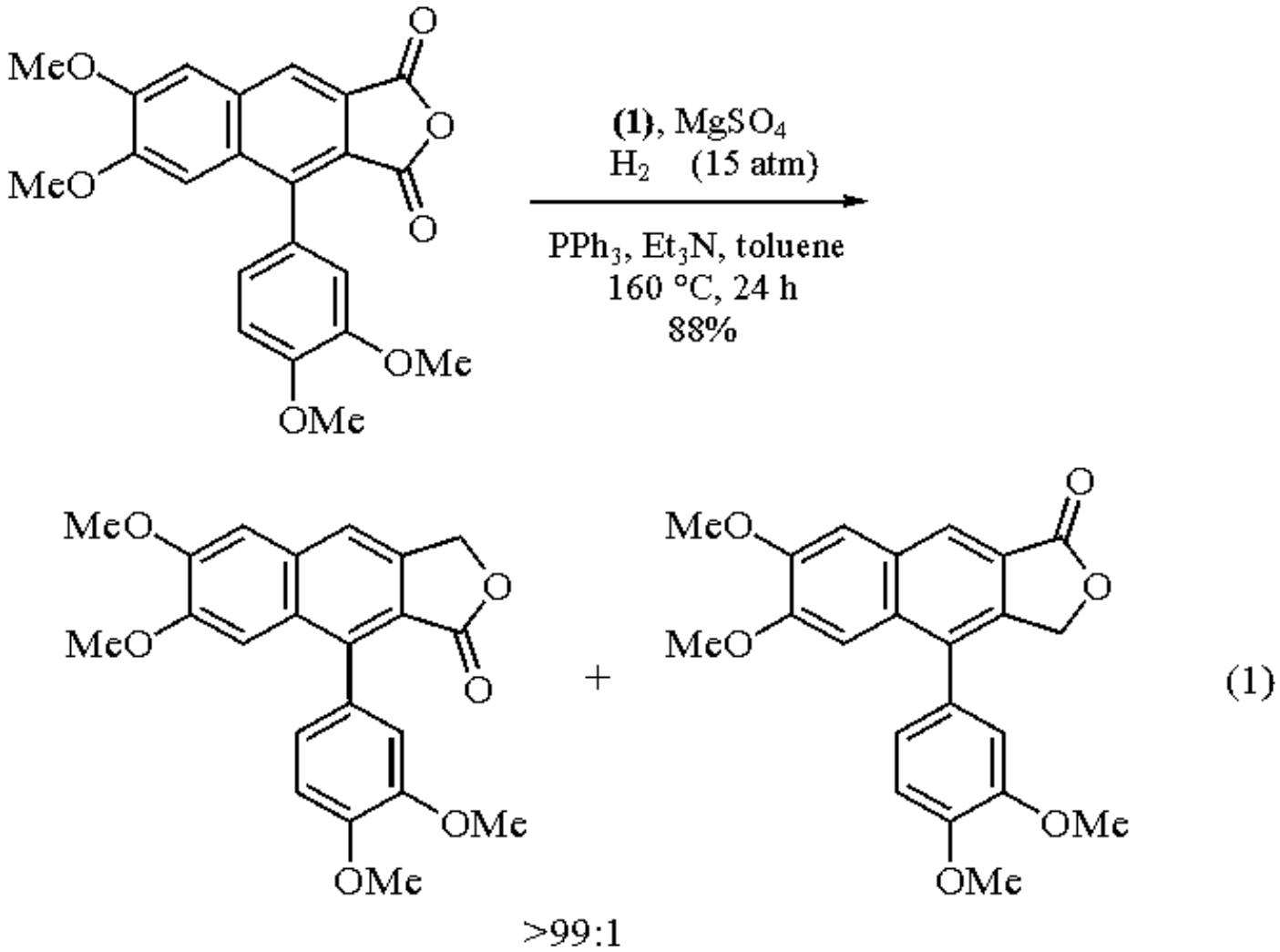

(1)

Attempts to reduce the anhydride of eq 1 with ***Lithium Tri-t-butoxyaluminum Hydride*** resulted in low chemical yields and poor regioselectivity. Use of ***Lithium Aluminum Hydride*** and ***Sodium Borohydride*** resulted in reduction of the more sterically hindered carbonyl group.[2]

Regioselective Dehydration Reactions.

Compound (**1**) also catalyzes the dehydrogenation of α,o-diols to lactones with the use of alkenic hydrogen acceptors (eq 2).[3] This system has several advantages over other reagents and catalysts that could be used in these reactions: it is highly regioselective, can be used catalytically, is less expensive than Ag^{I}, is less toxic than Cr^{VI}, and is safer than peroxides.

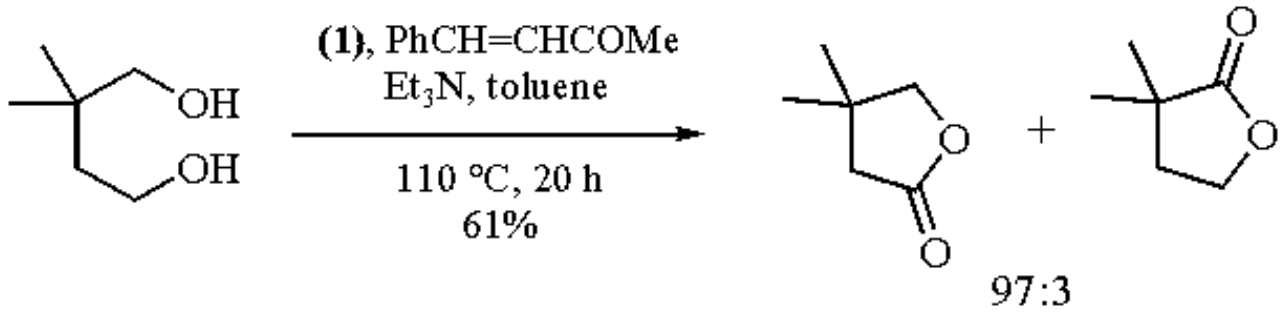

(2)

These hydrogenation and dehydrogenation reactions are sensitive to the size and location of substituents.[3b] With hydrogenations, bulky substituents α to the anhydride give the highest regioselectivity, while with dehydrogenations, bulky substituents β to an alcohol give the highest regioselectivity. Another study has shown that other ruthenium catalysts, e.g. ***Dihydridotetrakis(triphenylphosphine)ruthenium(II)***, can be comparable and in several cases exceed compound (**1**) in both regioselectivity and yield in catalytic dehydrogenations.[3a]

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3. (a) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *JOC* **1986**, *51*, 2034. (b) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *TL* **1983**, *24*, 2677.

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Tetracyanoethylene[1]

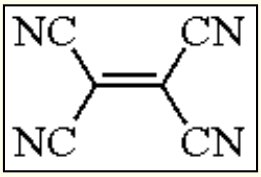

[670-54-2] · C_6N_4 · Tetracyanoethylene · (MW 128.10)

(highly electron-deficient and strongly electrophilic reagent; principal reaction types are addition to its double bond and replacement of the cyano group;[1] forms complexes with organometallic reagents[2])

Alternate Name: TCNE.

Physical Data: mp 200-202 °C (sealed capillary); bp 223 °C/760 mmHg; sublimes at 130 °C/5 mmHg or 60-65 °C/0.2 mmHg.

Form Supplied in: colorless crystals.

Preparative Methods: the preferred synthetic preparation of TCNE involves the debromination of the KBr complex of dibromomalononitrile with Cu powder in boiling benzene (62% yield).[3]

Purification: recrystallize from 1,2-dichloroethane or chlorobenzene, followed by sublimation (130 °C/5 mmHg).

Handling, Storage, and Precautions: extremely toxic and irritant.[4] It must be handled in a well ventilated hood, with rubber gloves, due to appreciable vapor pressure of the reagent at room temperature; sensitive to moist air.

Addition Reactions.

TCNE can be reduced to tetracyanoethane by a variety of reagents (H_2/Pd, HI, H_2S, thiols, $HSCH_2CO_2H$). It was found that, as hydrogen donors, several benzyl alcohols[5] and hydroheterocycles[6] could be dehydrogenated by TCNE (Scheme 1).

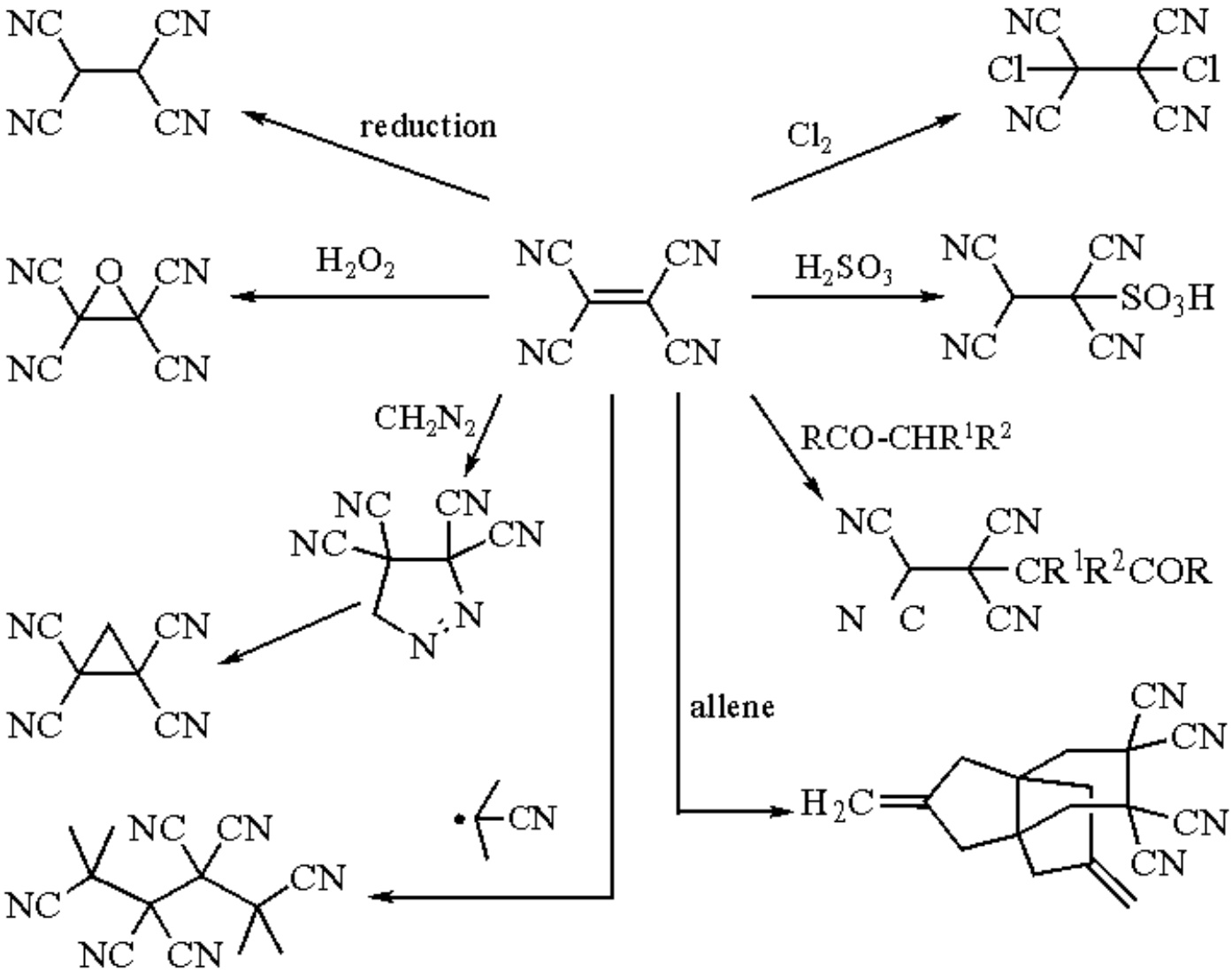

Scheme 1

The chlorination of TCNE leads to the formation of 1,2-dichlorocyanoethane (Scheme 1).[7]

TCNE reacts readily with sulfurous acid to give 1,1,2,2-tetracyanosulfonic acid, of which a number of salts have been reported (Scheme 1).[8]

Diazomethane reacts with TCNE to give a pyrazoline which splits off a molecule of nitrogen to give 1,1,2,2-tetracyanocyclopropane (Scheme 1).[9]

The α-cyanoisopropyl radical reacts with TCNE to give 2,3,3,4,4,5-hexacyano-2,5-dimethylhexane (Scheme 1).[8]

The allene tetramer 1,3,5,7-tetramethylenecyclooctane undergoes an unusual 1,7-addition of TCNE to give 3,3,4,4-tetracyano-8,11-dimethylenetricyclo[4.3.3.0]dodecane (Scheme 1).[10]

TCNE adds to ketones containing an α-hydrogen to give tetracyanopropyl ketones (Scheme 1).[8] It is an acid-catalyzed Michael-type addition. However, the reaction of other active methylene compounds with TCNE depends on the basicity of the reaction medium.[11] Thus the reaction of TCNE with 2,4-pentanedione can give different products (Scheme 2).[12] TCNE can also react with cyclic ketones.[1b]

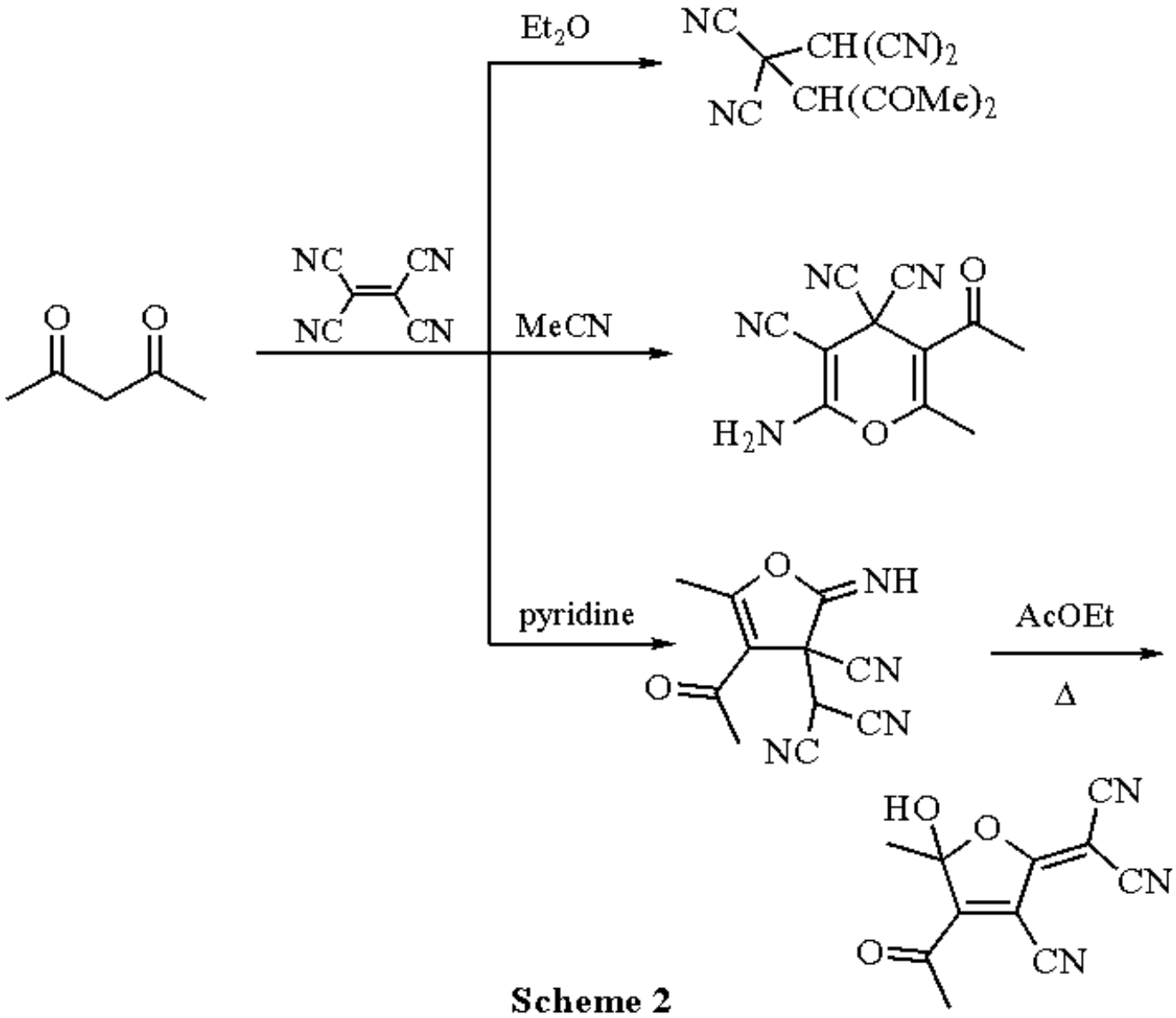

Scheme 2

The oxidation of TCNE with aqueous ***Hydrogen Peroxide*** is the method of choice for the synthesis of tetracyanoethylene oxide (TCNEO) (Scheme 1).[13] The reaction of TCNEO with alkenes proceeds via a 1,3-dipolar cycloaddition pathway.[14] TCNEO can also react with nucleophilic reagents[15] (dialkyl sulfide,[16] nitrogenated tertiary aromatic bases,[14e,15,17] diphenylcyclopropenone, diphenylcyclopropenenethione,[18] or thiophene[19] (Scheme 3).

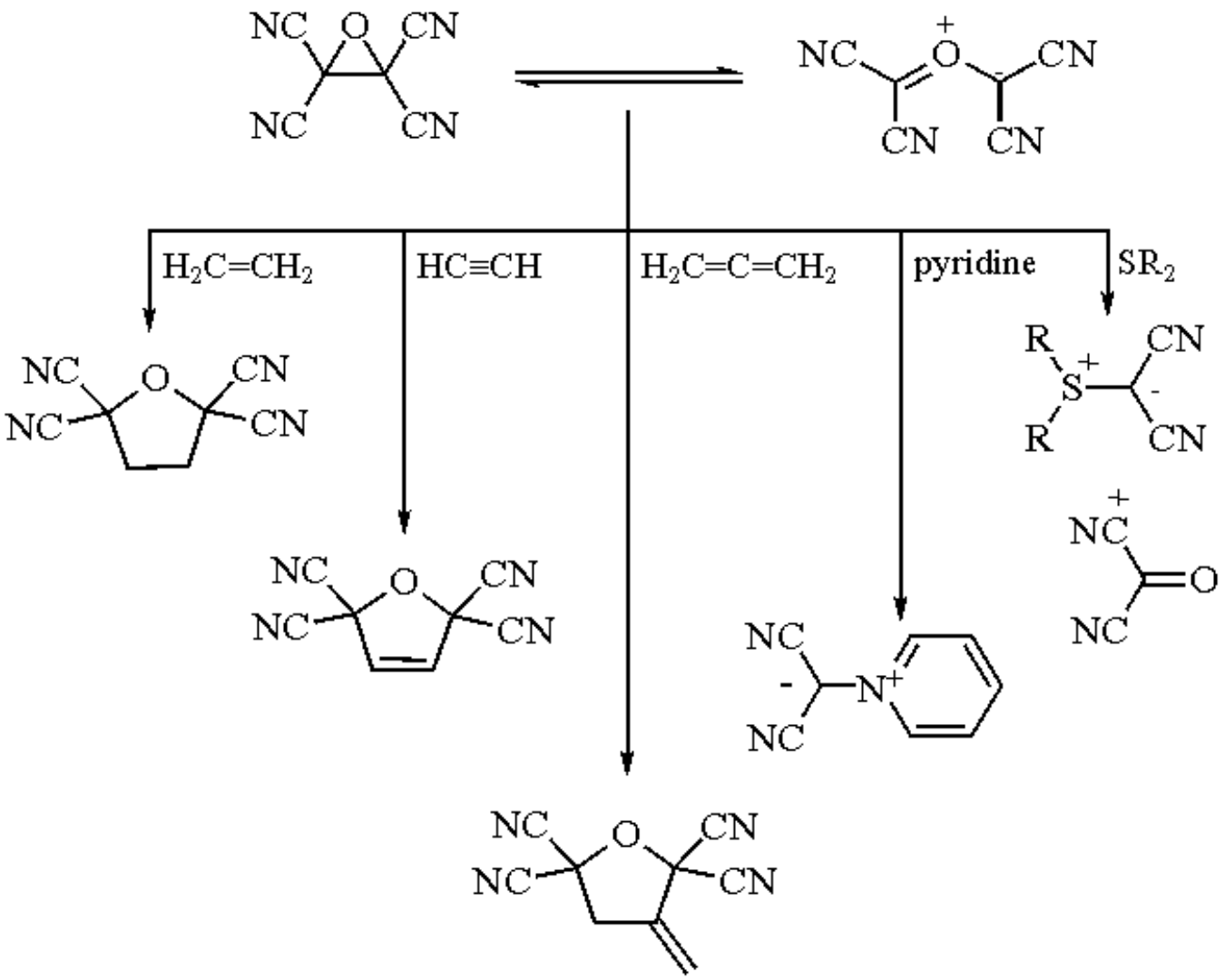

Scheme 3

Synthesis of Heterocycles.

TCNE has proven to be a useful starting material for the synthesis of five- or six-membered heterocycles, including thiophenes, pyrroles,[20] isoxazoles, pyrazoles, pyridines, and pyrimidines.[21] The required reaction partner can be an enolic ketone, amine, imine, hydrazone, or an α,β-unsaturated azo compound. The reaction generally proceeds via a Diels-Alder or 1,3-dipolar cycloaddition. The reaction of TCNE with acyclic ketones yields either 4*H*-pyrans[12] or dihydropyrroles;[22] enolic 1,3-cyclohexanediones with TCNE also produce pyran derivatives.[23] Substituted pyrimidines are obtained from the reaction of barbituric acid with TCNE, and pyrazolopyridines are obtained from aminopyrazoles.[24] Cyclization of 1,1,2,2-tetracyanoethane with substituted azomethines leads to dihydropyrrole or pyrrole derivatives.

Replacement Reactions.

Tricyanovinylation occurs at either the N atom (aliphatic amines) (eq 1) or the *para* position (aromatic amines) (eq 2).[25] (Tricyanovinyl)amines have found widespread interest because of their optical[26] and dyeing[25] properties, and their ability to yield charge-transfer complexes with donors and acceptors.[27] Hassan recently reported that TCNE also forms another tricyanovinylation product, $(PhCH_2)_2NC_6H_4C(CN)=C(CN)_2$, with *N*,*N*-dibenzylaniline.[28]

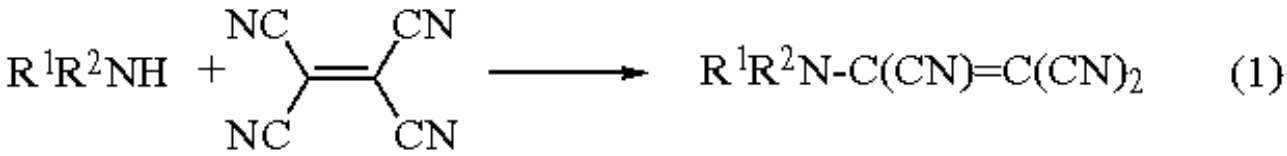

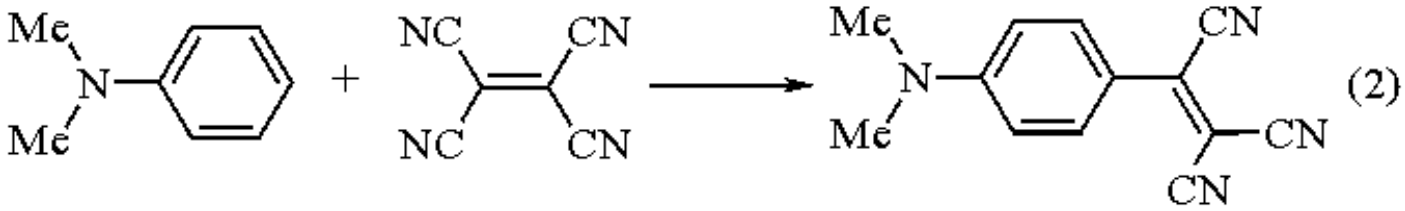

An example of retrograde Michael addition reaction is illustrated by 2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one. Instead of the expected tricyanovinyl derivative, 2-dicyanomethylene-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one was obtained (eq 3).[29]

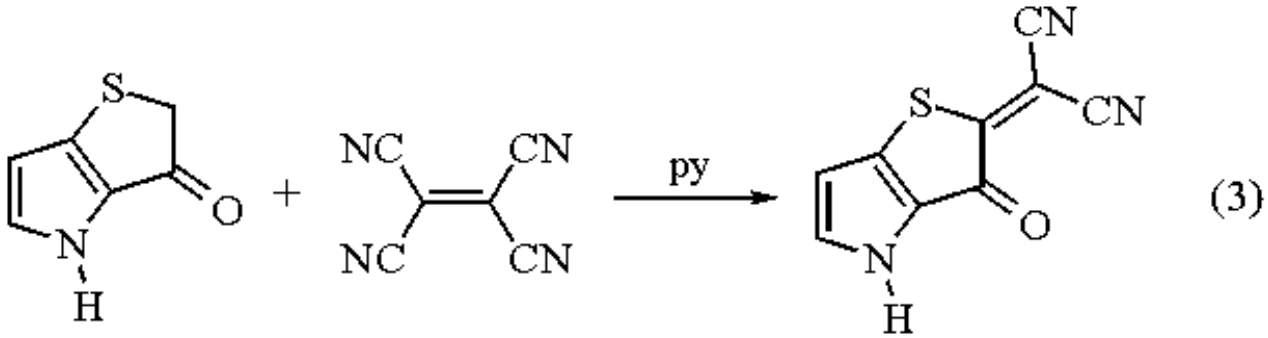

Cycloaddition Reactions.

Diels-Alder and Related [4 + 2] Cycloaddition Reactions.

TCNE is a reactive dienophile and undergoes Diels-Alder type cycloadditions with conjugated dienes. The Diels-Alder reaction of TCNE occurs even with sluggish dienes such as 2-vinylnaphthalene, spontaneously and rapidly, without added catalyst or external heat.[8]

The regiochemistry of concerted, thermal cycloadditions is not fully understood, and the stereoselectivity involves either a torsional preference or π-facial attack on the diene entering the [4 + 2] cycloaddition.[30]

Recently, Fessner et al. have investigated the π-facial diastereoselectivity in the Diels-Alder reaction by studying the directing influence of proximate unsaturation.[31] They used the model dienes (**1**) and (**2**) to differentiate the regioselectivity observed with various dienophiles. Based on steric and electronic considerations, (**1**) is expected to yield the *endo-syn* (*syn* with respect to the four-membered ring) adduct and (**2**) the *endo-anti* product with various dienophiles. Dienophiles such as maleic anhydride and *p*-benzoquinone gave the expected *syn* and *anti* cycloadducts with (**1**) and (**2**), respectively. However, TCNE predominantly gave the *syn* product with both (**1**) and (**2**). The authors attribute this to an *anti* preorienting charge-transfer complex involving the electron-depleted orthogonal π-bonds of the dienophile and the suitably oriented π-moieties of (**2**).

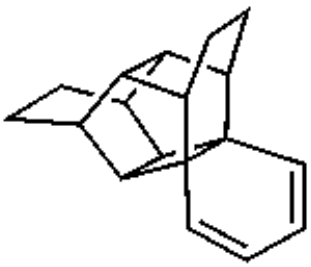

(1)

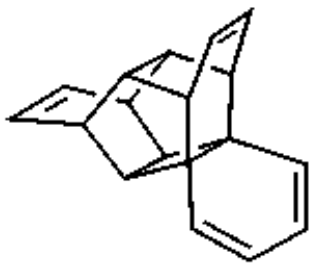

(2)

Porter et al. have investigated the cycloaddition reactions of TCNE with 3-vinylindene, 3-vinylbenzo[*b*]thiophene, and 3-vinylindole.[32] The normal [4 + 2] Diels-Alder cycloaddition reaction is observed with the unsubstituted compounds. However, alkylation of the diene can alter the course of the reaction. Thus (**3**) and (**4**) yield the [2 + 2] cycloadduct (**5**) on reaction with TCNE and a rearrangement accompanies the cycloaddition of TCNE to 2-methyl-3-vinylbenzo[*b*]thiophene (**6**) to give adduct (**7**) (eqs 4 and 5).

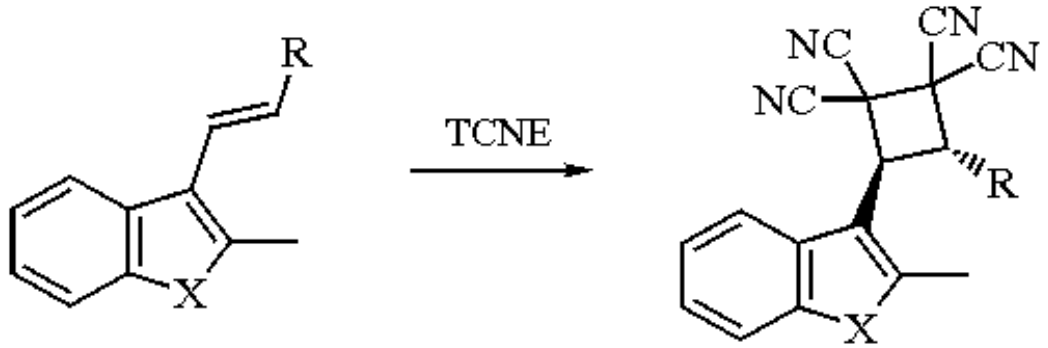

(4)

(3) R = Me, X = S
(4) R = H, X = NMe

(5)

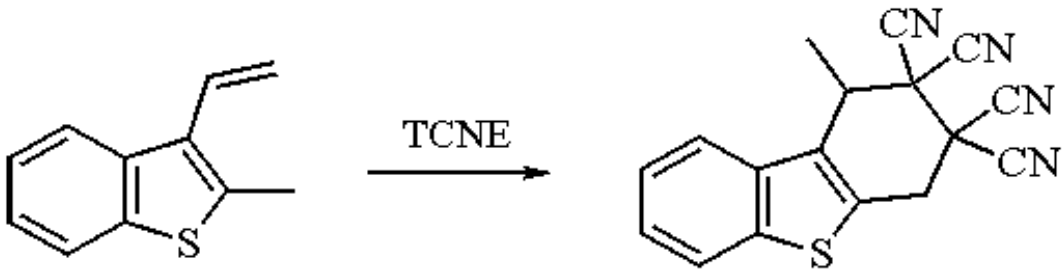

(5)

(6) **(7)**

Pindur et al. have demonstrated the versatility of [4 + 2] cycloaddition and elimination processes of TCNE in their studies of the addition reactions such as 1,4-cycloaddition, cycloreversion, sigmatropic rearrangements, and elimination processes of TCNE with dimethylpyrano[3,4-*b*]indol-3-one and 1-methylpyrido[3,4-*b*]indol-3-one.[33] Pindur et al. have also studied the stereoselectivity and regioselectivity of the Diels-Alder reaction of TCNE with (*E*/*Z*)-2-methoxy-substituted 3-vinylindoles. TCNE reacted with (*Z*)-(**8**) to produce (**9a**):(**10**) in a 1:1 ratio and with (*E*)-(**8**) to give (**9b**):(**10**) in a 1:1 ratio.[34]

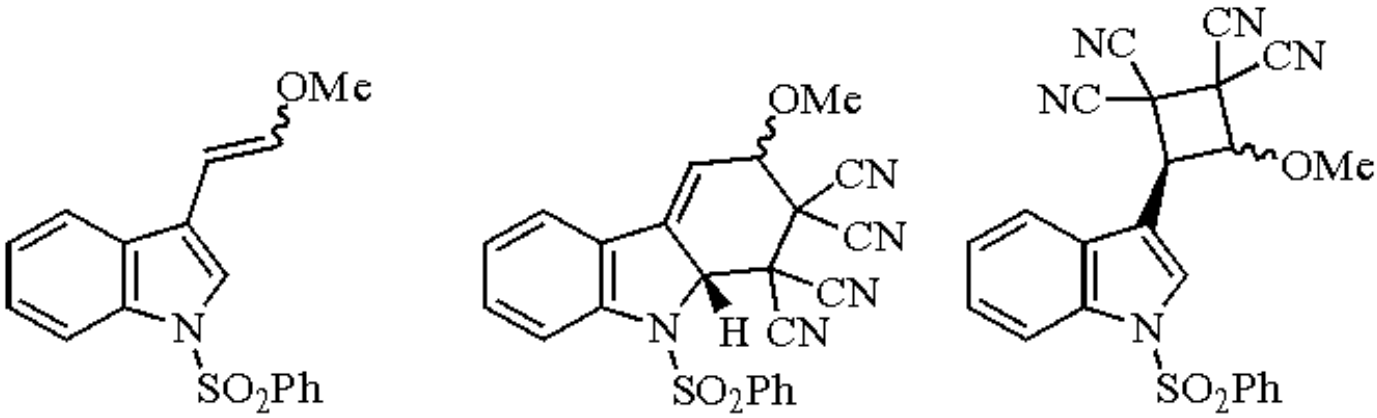

(8) **(9a)** β-OMe **(10)**
(9b) α-OMe

Homo-Diels-Alder Reaction.

The cycloaddition of dienophiles to bridged 1,4-dienes with interrupted conjugation (homo DA reaction) is a useful synthetic reaction for the preparation of tetracyclic compounds (eq 6).[35]

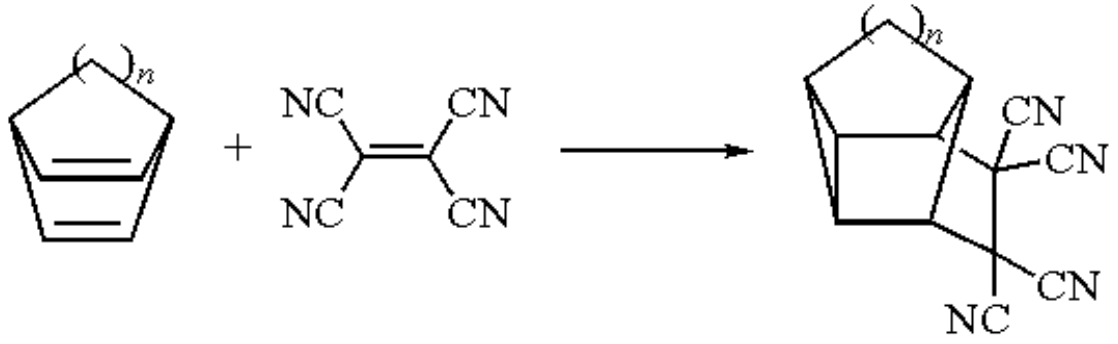

(6)

Alder Ene Reaction.

The ene reaction is the indirect, substituting addition of a compound having a double bond (enophile) to an alkene possessing an allylic hydrogen atom (ene).[36] Trimethyl-substituted isodicyclopentadiene reacts readily with TCNE in an ene reaction involving a zwitterionic intermediate when the reaction is performed in ethyl acetate. However, TCNE adds to isodicyclopentadiene in refluxing xylene to produce the [4 + 2] cycloadduct in 51% yield.[37]

Thermal [2 + 2] Cycloaddition.

It is well established that TCNE undergoes nonconcerted, ionic, thermal, [2 + 2] cycloaddition reactions with electron-rich alkenes (eq 7).[38] The reaction is believed to involve a zwitterion and not a biradical intermediate. This is supported by strong dependency on solvent polarity,[38c] incomplete stereochemistry,[39] and trapping of the zwitterion with alcohol to form an acetal.[40]

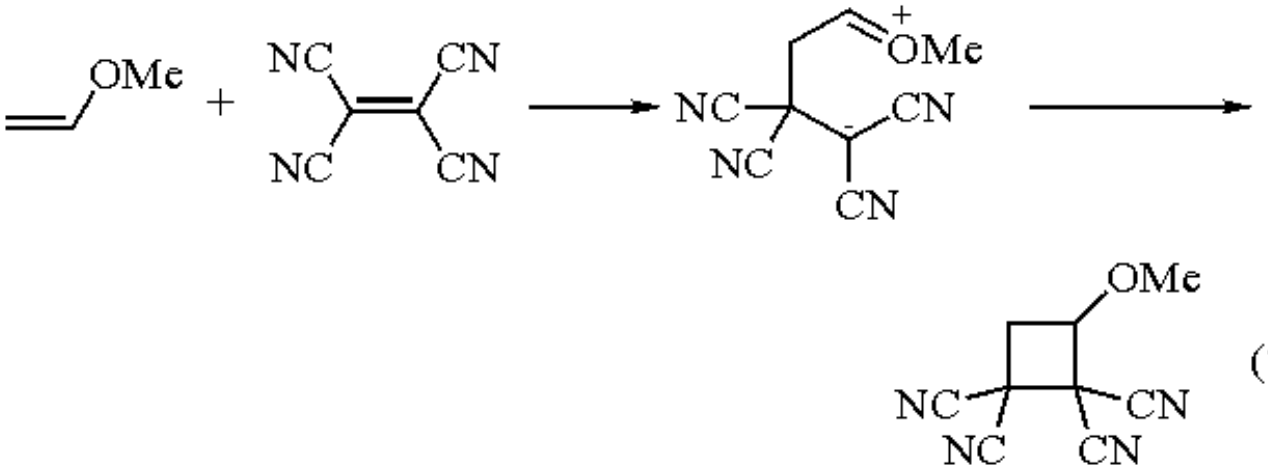

(7)

Other Cycloadditions.

Cyclopropylethylene derivatives have been found to undergo facile cycloadditions with TCNE to form either cyclobutane[41] or cyclopentane derivatives. This thermal, ring-opening cycloaddition was reviewed in 1984.[42]

The reaction of TCNE with substituted 1,3-butadienes leads to competing [4 + 2] and [2 + 2] cycloadditions. The regioselectivity of the reaction depends on substitution of both diene termini, and on solvent polarity. 2,7-Dimethyl-2,4,6-octatriene undergoes cycloaddition with TCNE to give not only the expected Diels-Alder adduct but also the [2 + 2] cycloadduct. Formation of the latter adduct is favored by more polar solvents. The less-substituted 2-methyl-2,4,6-octatriene gives only the [4 + 2] cycloadduct (eq 8).[43]

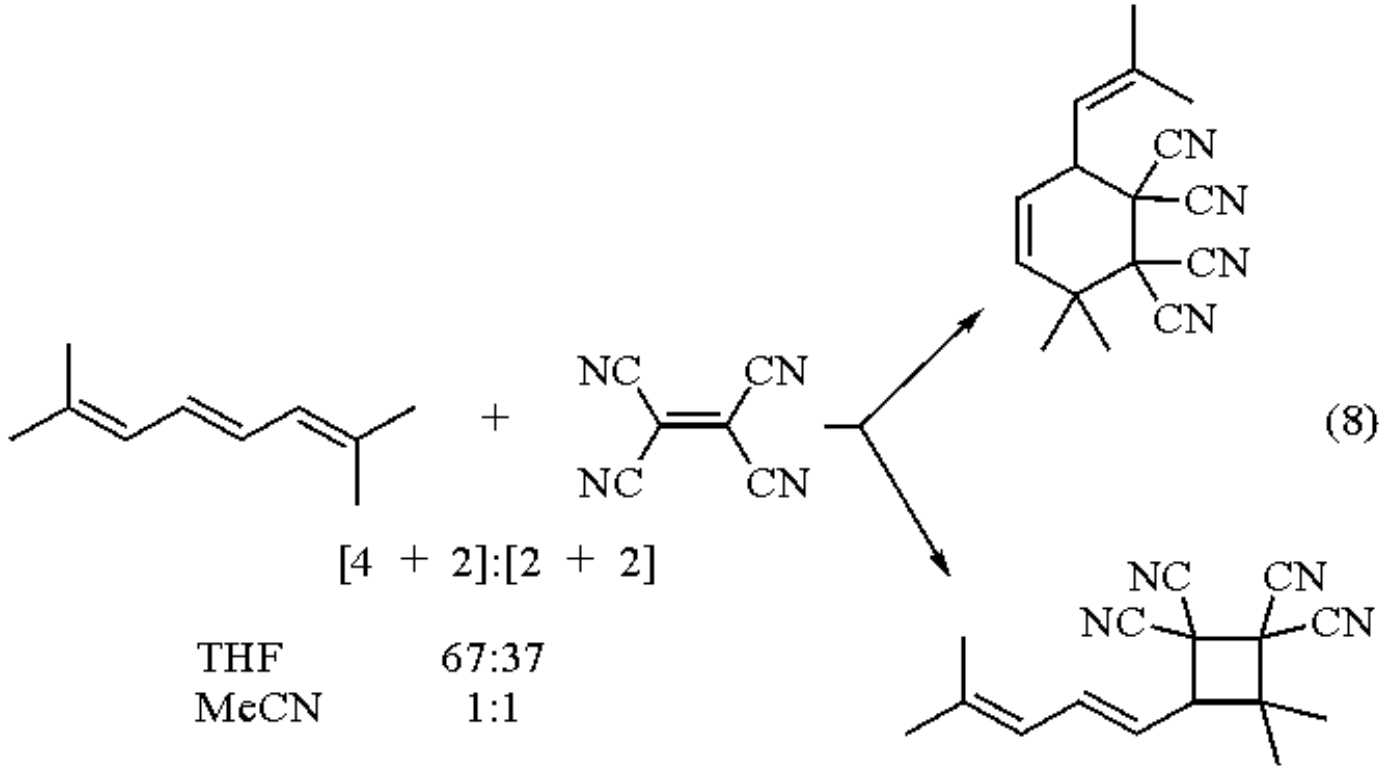

TCNE can react with [4]annulenes, fulvenes, bullvalenes, and cyclooctatetraenes.[1d]

Photochemical Reactions.

Brief reviews on the photochemical reactions of organic compounds in the presence of TCNE are available.[1e,44] The photocycloaddition of alkenes to benzenoids gives a variety of products. Such electron-poor alkenes as α,β-unsaturated acid derivatives generally give [2 + 2] cycloadducts.[45]

Additional cycloaddition type reactions have been described (cycloaddition with aromatic hydrocarbons, cyclophanes, mesoionic compounds, heterocyclic compounds, and stereoselective addition with exocyclic dienes).[1e]

Organometallic Reactions.

With organometallics, TCNE shows interesting properties such as insertion into metal-hydrogen, metal-carbon, and even metal-metal bonds.

Reactions with Main Group Organometallics.

The reaction of TCNE with the main group organometallic compounds generally proceeds by pathways involving the formation of charge-transfer complexes or fragmentation products. Formation of cycloadducts can also be observed.[46] A review on TCNE charge-transfer complexes of phenyl derivatives of silicon, germanium, tin, and lead has been published.[46b]

It has been found that σ-electrons of low ionization energy, such as the Si-Si and Ge-Ge bonds, can be donated to certain π-acceptors, such as TCNE. Charge-transfer complexes of silicon and germanium with TCNE include polymethylpolysilanes,[47] bimetallic compounds $[(Et_3Ge)_2Hg]$,[48] methylphenylsilanes,[49] aryltrisilanes,[50] phenylsilacyclobutanes,[51] 1,2-disilacycloalkanes,[52] silacyclopentenes,[53] cyclopolysilanes,[54] silatranes,[55] trimethylsilyl-substituted benzene,[56] naphthalene, anthracene, and phenanthrene derivatives,[56b] phenylsilanes[57] and -germanes,[57,58] benzylsilanes and -germanes,[59] silicon-containing ethers,[60] and peralkylcyclopropylsilanes.[61] Furans and thiophene containing silyl,[62] germyl, stannyl, and plumbyl have also been examined.[62b]

Reactions of tetraalkyl organometallics derived from silicon, germanium, tin, and lead with TCNE have been described and involve fragmentation of cation radicals following electron transfer.[63]

The Diels-Alder cycloaddition of TCNE to organometallics derived from silicon, germanium, tin, and mercury is not common but has been described.[64] Moreover, the reaction products are not easy to predict.

Reactions with Metallocenes.

Iron metallocenes are regarded as π-bases of high reactivity. They are able to form charge-transfer complexes with TCNE (π-acid) in which the π-cyclopentadienyl rings or the metal can act as an electron donor (eq 9). These complexes have been shown to have a benzenoid structure.[65] In some cases the TCNE radical-anion salt is obtained (complete electron transfer occurs).[66] Neither ruthenocene nor osmocene form stable complexes with TCNE. However, it can proceed smoothly under photochemical activation.[67] Substituted vinylferrocenes react readily with TCNE in a [2 + 2] cycloaddition type reaction.[68]

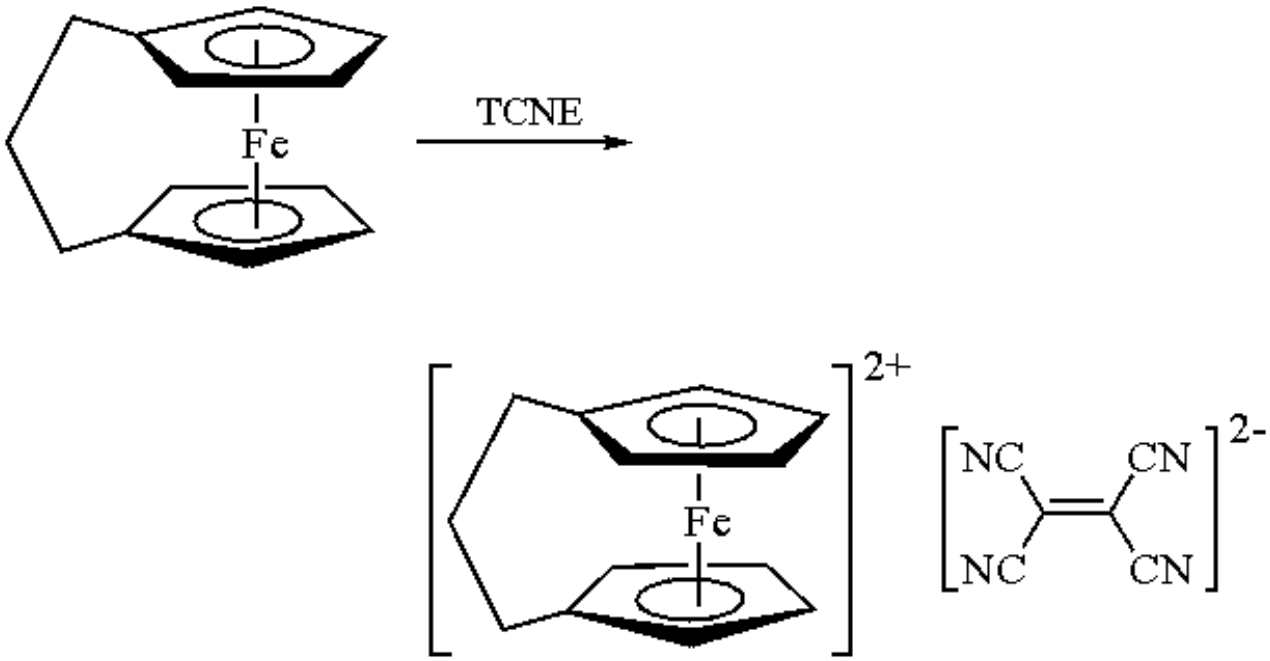

(9)

Reaction with Metal-Coordinated Alkenes and Alkynes.

The electrophile TCNE may act either as a one-electron oxidant towards organotransition metal complexes (eq 10),[69] or undergo a variety of reactions such as metal-carbon insertion (eq 11)[70] and [2 + 2] cycloaddition to coordinated polyalkenes (eq 12).[71]

$$Cr(CO)_2(POMe_3)(\eta^6\text{-}C_6Me_6) + TCNE \xrightarrow{CH_2Cl_2,\ rt} Cr(CO)_2(TCNE)(\eta^6\text{-}C_6Me_6) \qquad (10)$$

$$Ru(CO)_2(POMe_3)[H_2C{=}C(Me)\text{-}(Me)C{=}CH_2] + TCNE \xrightarrow{CH_2Cl_2}$$

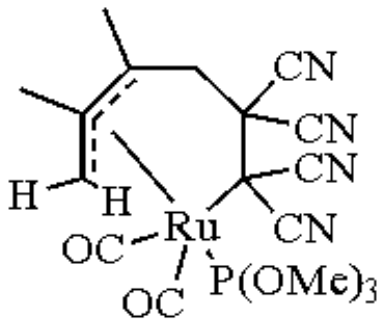

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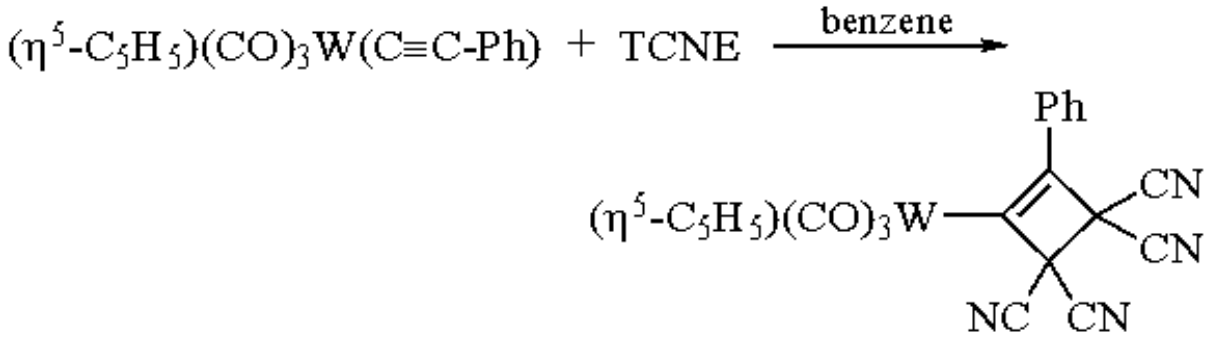

(12)

Additional applications of TCNE in organometallic chemistry include platinum-family complexes with TCNE,[2,72] reactions of tricarbonyliron complexes with TCNE,[2] and diverse behavior of TCNE towards transition metal-carbon σ-bonded complexes.[2]

Related Reagents.

Acrylonitrile; ***1,4-Benzoquinone***; ***Dimethyl Acetylenedicarboxylate***; ***Maleic Anhydride***.

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Tetraethylammonium Cyanide

$R_4N^+CN^-$

(R = Et)

[13435-20-6] · $C_9H_{20}N_2$ · Tetraethylammonium Cyanide · (MW 156.31) (R = *n*-Bu)

[10442-39-4] · $C_{17}H_{36}N_2$ · Tetrabutylammonium Cyanide · (MW 268.55)

(nitrile synthesis; asymmetric cyanohydrin synthesis; catalyst)

Physical Data: R = Et, mp 250 °C; R = *n*-Bu, mp 82-85 °C.

Form Supplied in: white powders, commercially available.

Handling, Storage, and Precautions: highly toxic, irritant solids; very hygroscopic and light sensitive; keep container tightly closed, store in dry and dark area. Use only in chemical fume hood. Incompatible with strong acids and bases. Thermal decomposition may produce hydrogen cyanide.

Nitrile Synthesis.

Primary, secondary, neopentyl, benzylic, and allylic halides are readily converted into the corresponding nitriles by reaction with Et_4NCN in polar aprotic solvents (eq 1).[1,2] The workup of the reaction is simple, since the solvent is removed, and the nitrile is dissolved in ether and filtered from the quaternary ammonium halide byproduct which precipitates out. The same reaction applies to acyl or thioacyl halides, while dihalides furnish dinitriles (eq 2).[1]

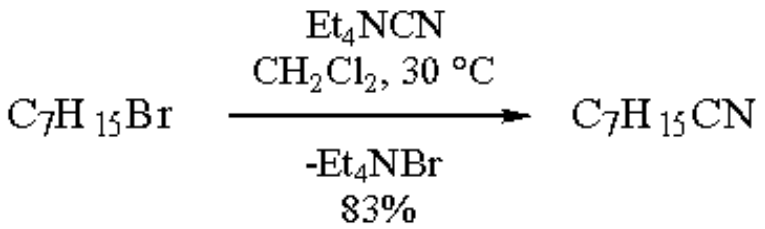

(1)

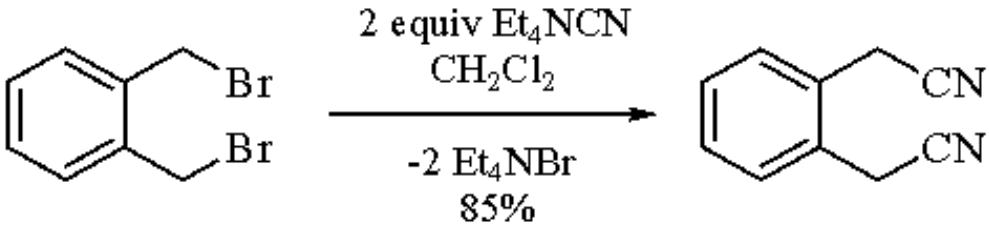

(2)

Aromatic or heteroaromatic halides are less reactive, but their trimethylammonio derivatives react with Et_4NCN under very mild conditions yielding nitriles. In this way, chloropyrimidines and chloroquinazolines are converted smoothly into their carbonitriles (eq 3).[3] The same conditions are applied for the conversion of 6-chloropurines to 6-cyanopurines.[4] Treatment of α-halo ketones with Et_4NCN in CH_2Cl_2 furnishes oxiranecarbonitriles (eq 4)[2] which, under more vigorous conditions, especially with the presence of Et_4NBr, furnish β-keto nitriles (eq 4).

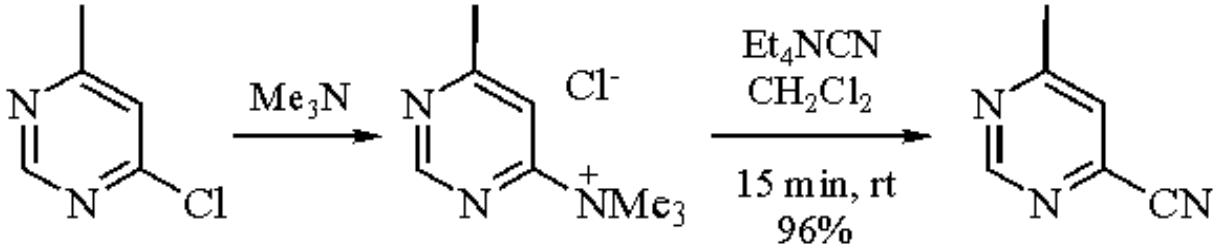

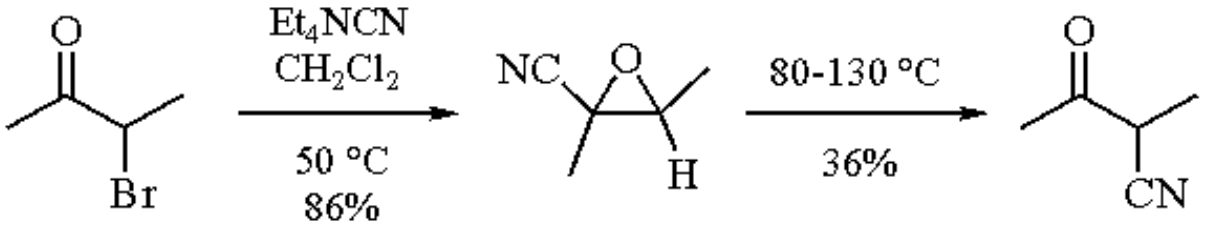

Both methoxymethyl (MOM) and (2-methoxyethoxy)methyl (MEM) ethers are directly converted into cyanomethyl ethers by sequental treatment with ***Bromodimethylborane*** and Bu_4NCN in CH_2Cl_2 at -78 °C (eq 5).[5] The reaction conditions are applicable for the preparation of primary, secondary, or tertiary cyanomethyl ethers, which are being used as excellent acyl anion equivalents in intramolecular alkylation reactions.[6]

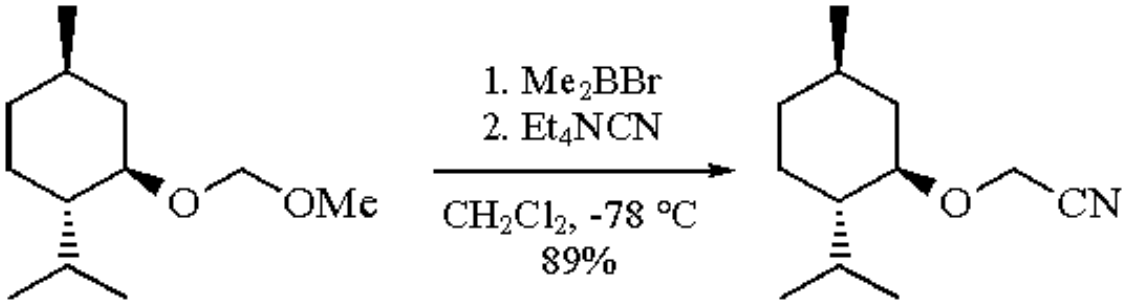

Treatment of *trans*-octahydro-8α-tosyloxymethyl-2(1*H*)-naphthalenone derivatives with Bu_4NCN in THF results in the formation of the nitrile and the simultanous ring closure, yielding the corresponding (4α)-1α-cyano-11-oxatricyclo[7.2.1.0]dodecane derivative (eq 6).[7]

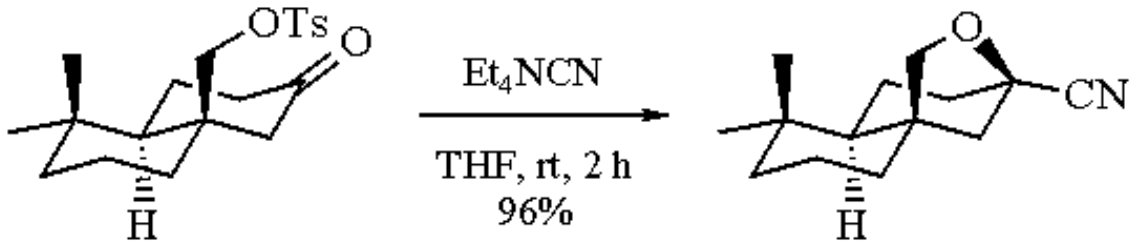

Asymmetric Cyanohydrin Synthesis.

Reaction of racemic or optically active π aldehyde-rhenium Lewis acid complexes $[CpRe(NO)(PPh_3)(\eta^2\text{-}O{=}CHR)]^+ BF_4^-$ with Et_4NCN in CH_2Cl_2 at -80 °C gives cyanohydrin alkoxide complexes, which by treatment with MTPA-Cl and DMAP in C_6H_6 furnish the optically active Mosher esters of the cyanohydrins (eq 7).[8] Analogous reactions of racemic σ methyl ketone complexes leading to the corresponding optically active cyanohydrins are also reported.[8]

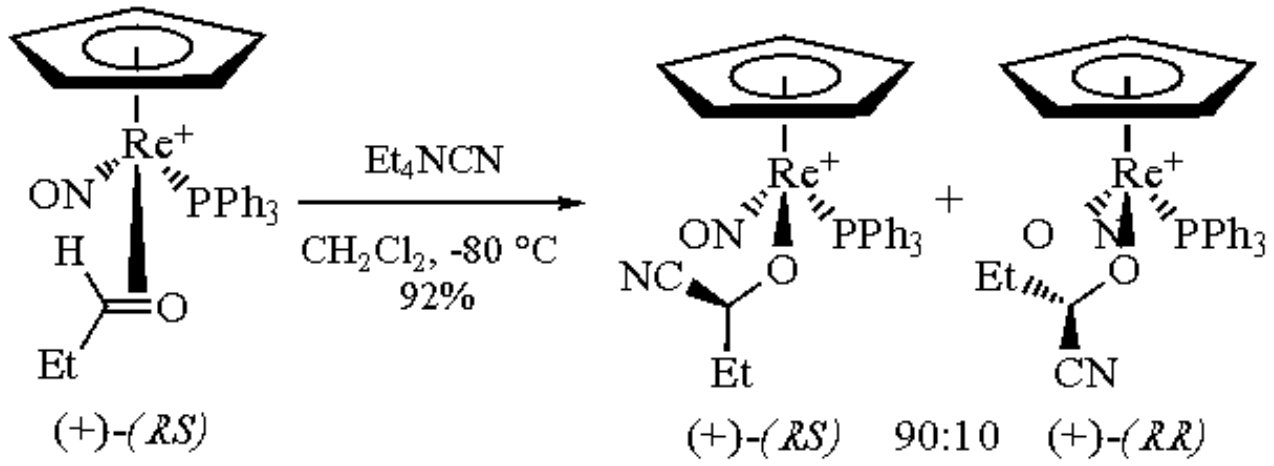

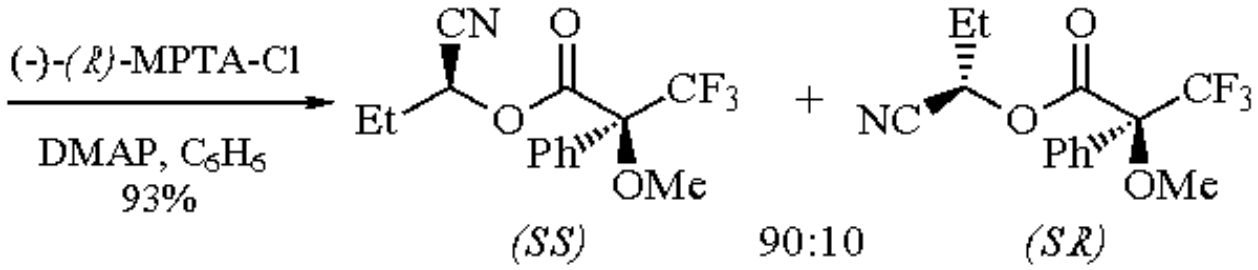

(7)

Use as a Catalyst.

Et_4NCN is formed in situ during the phase transfer catalyzed displacement reactions of alkyl halides (or methansulfonates) with cyanide anion (eq 8).[9]

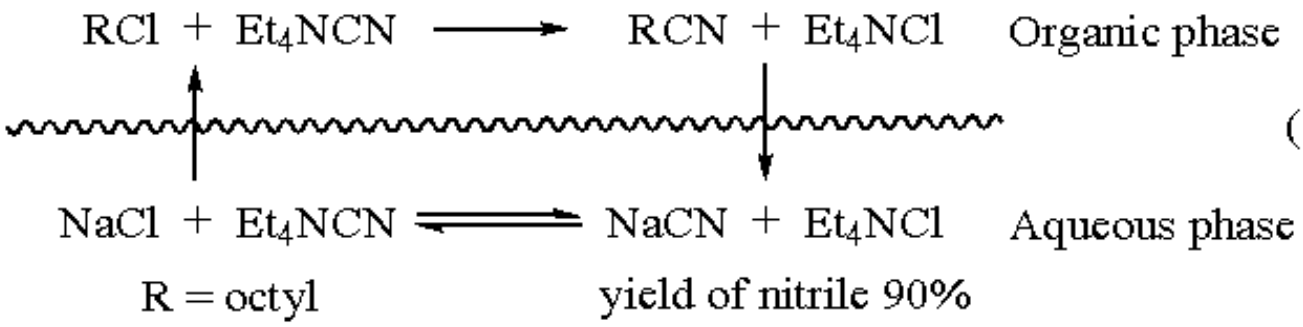

(8)

The complex $Bu_4NCu(CN)_2$ (prepared as a colorless solid by treatment of a slurry of ***Copper(I) Cyanide*** in MeOH with a solution of 1 equiv of Bu_4NCN in MeOH at rt under N_2 and evaporation of the resulting solution to dryness) is used as catalyst for the coupling of vinyllithium components with OBO ester iodides (eq 9).[10]

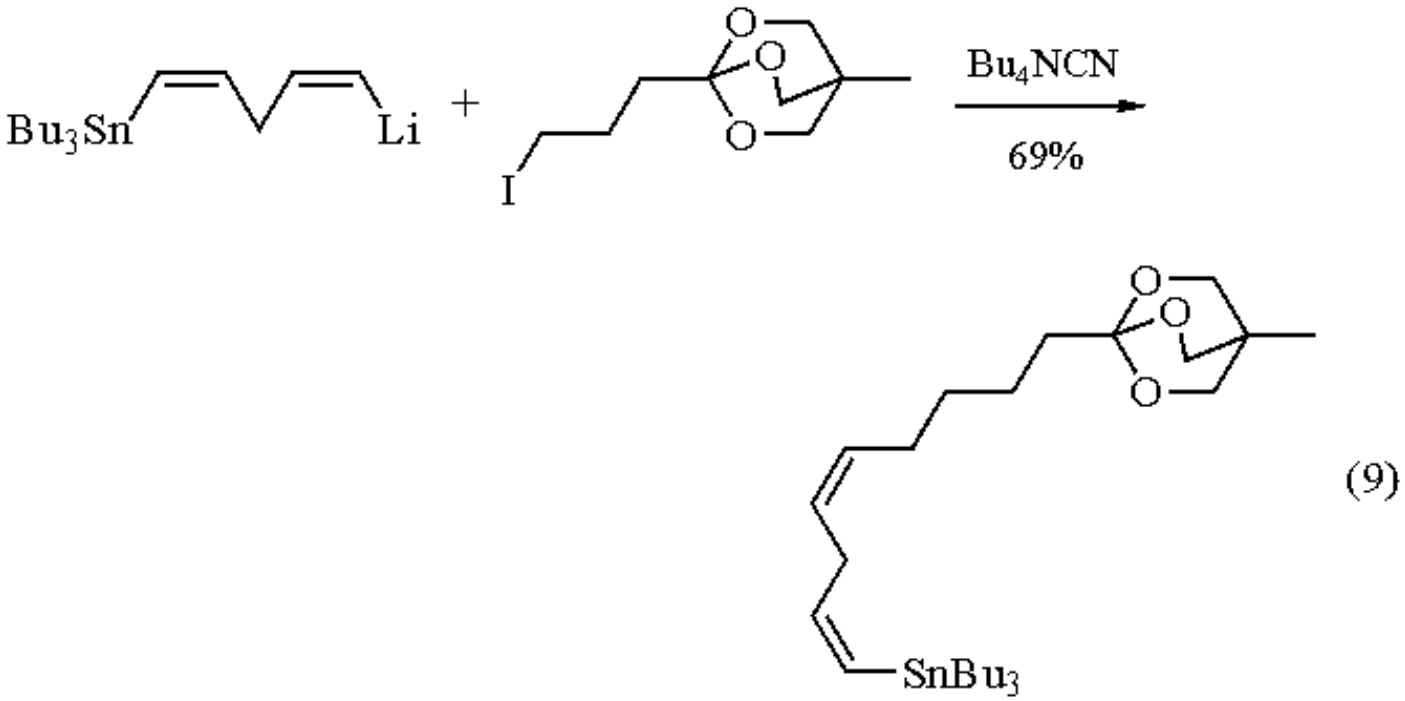

Benzyltrimethylammonium Cyanide.

This related quaternary ammonium cyanide reagent is prepared by dissolving equimolar amounts of $BnNMe_3Cl$ and NaCN in water.[11] It is used for the transformation of alkyl halides to nitriles in aqueous solution. The reaction proceeds in the absence of any organic solvent, and the ammonium salt serves not only as a cyanide source, but also as a surface active agent, thus promoting the reaction rate (eq 10).[12]

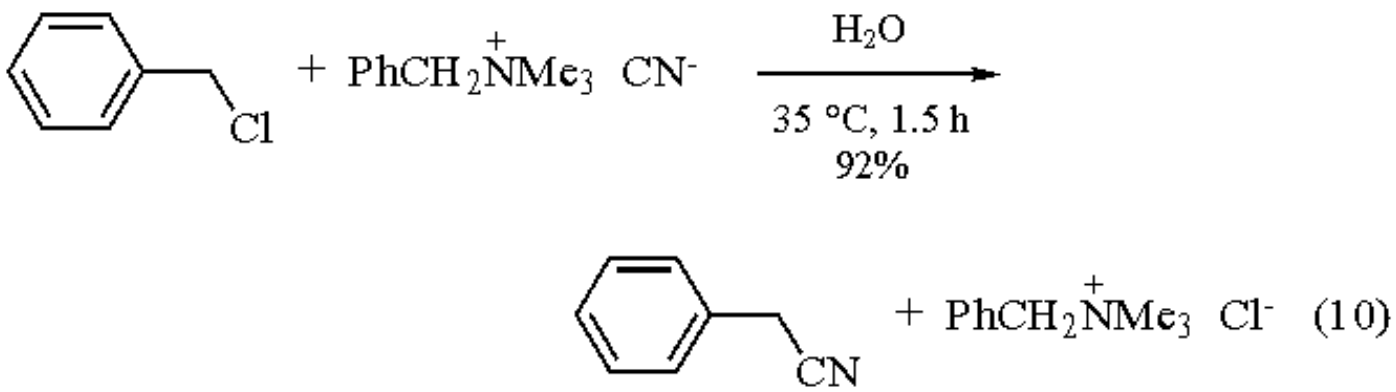

Related Reagents.

Acetone Cyanohydrin; ***t-Butyldimethylsilyl Cyanide***; ***Cyanotrimethylsilane***; ***Diethylaluminum Cyanide***; ***Hydrogen Cyanide***; ***Potassium Cyanide***; ***Sodium Cyanide***.

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Tetraethylammonium Periodate

Et_4NIO_4

[5492-69-3] · $C_8H_{20}INO_4$ · Tetraethylammonium Periodate · (MW 321.19)

(oxidizing agent used for generating nitroso compounds from hydroxamic acids,[1] *N*-hydroxycarbamic esters,[2] and *N*-hydroxyureas[3])

Physical Data: mp 176-177 °C.

Solubility: sol H_2O, $MeCO_2H$, acetone, pyridine, CH_2Cl_2; slightly sol alcohol; insol ethyl acetate, Et_2O, benzene.

Preparative Methods: a solution of periodic acid (H_5IO_6) (7.72 g, 0.034 mol) in water (20 mL) was added slowly to a cooled solution of 25% tetraethylammonium hydroxide (20 mL, 0.034 mol). The resulting solution was evaporated under reduced pressure, the solid residue was extracted with hot *t*-butyl alcohol, and the product was precipitated by addition of diisopropyl ether. Recrystallization from *t*-butyl alcohol yielded a white solid (8.5 g, 82%).[4a] **Caution**: a safety shield should be used since any excess H_5IO_6 present may explode violently during concentration of the aqueous solution and extraction of the crude salt.[4b]

Handling, Storage, and Precautions: the reagent is stable and is best stored in a desiccator in the dark.

Oxidizing Agent.

Tetraethylammonium periodate has similar oxidizing properties to ***Sodium Periodate*** but has the advantage that reactions can be conducted in nonaqueous media and its greater solubility in water may be useful in cases where the use of relatively less soluble periodate salts is problematic.[4] Tetraethylammonium periodate has been used mainly for the oxidation of derivatives of hydroxylamines to yield nitroso compounds. It has been reported[4] that stable nitroso compounds have been obtained from the oxidation of *N*-*t*-alkylhydroxylamines. Tetraethylammonium periodate was found to be a mild oxidant for the selective oxidation of hydroxamic acids,[1] *N*-hydroxycarbamic esters,[2] and *N*-hydroxy ureas[3] in the presence of conjugated dienes (eqs 1-3). The highly reactive nitroso intermediates that were formed readily undergo Diels-Alder cycloaddition to the dienes to give synthetically useful cycloadducts. Further, it was demonstrated[5] that cycloadducts of type (**1**) serve as a good source of highly reactive, transient nitroso species; they undergo facile retro-Diels-Alder reactions on heating to regenerate the nitroso intermediate and 9,10-dimethylanthracene. This method for the regeneration of the nitroso compound has been exploited in inter- and intramolecular nitroso-ene reactions.[5]

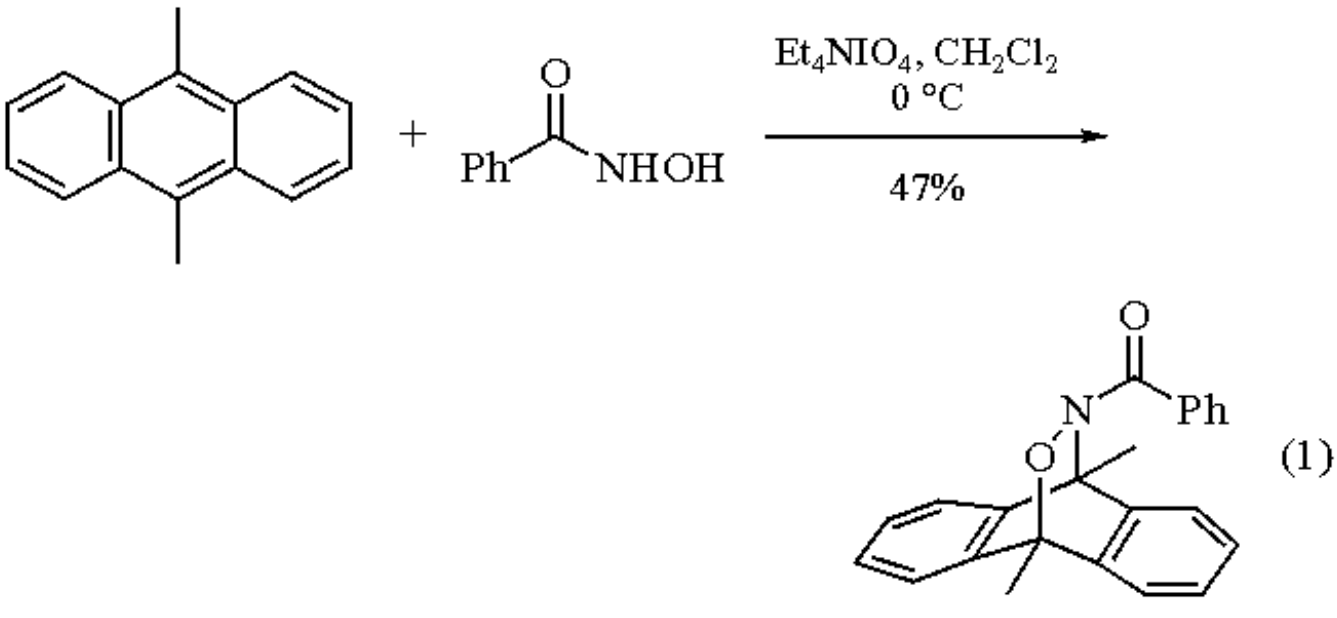

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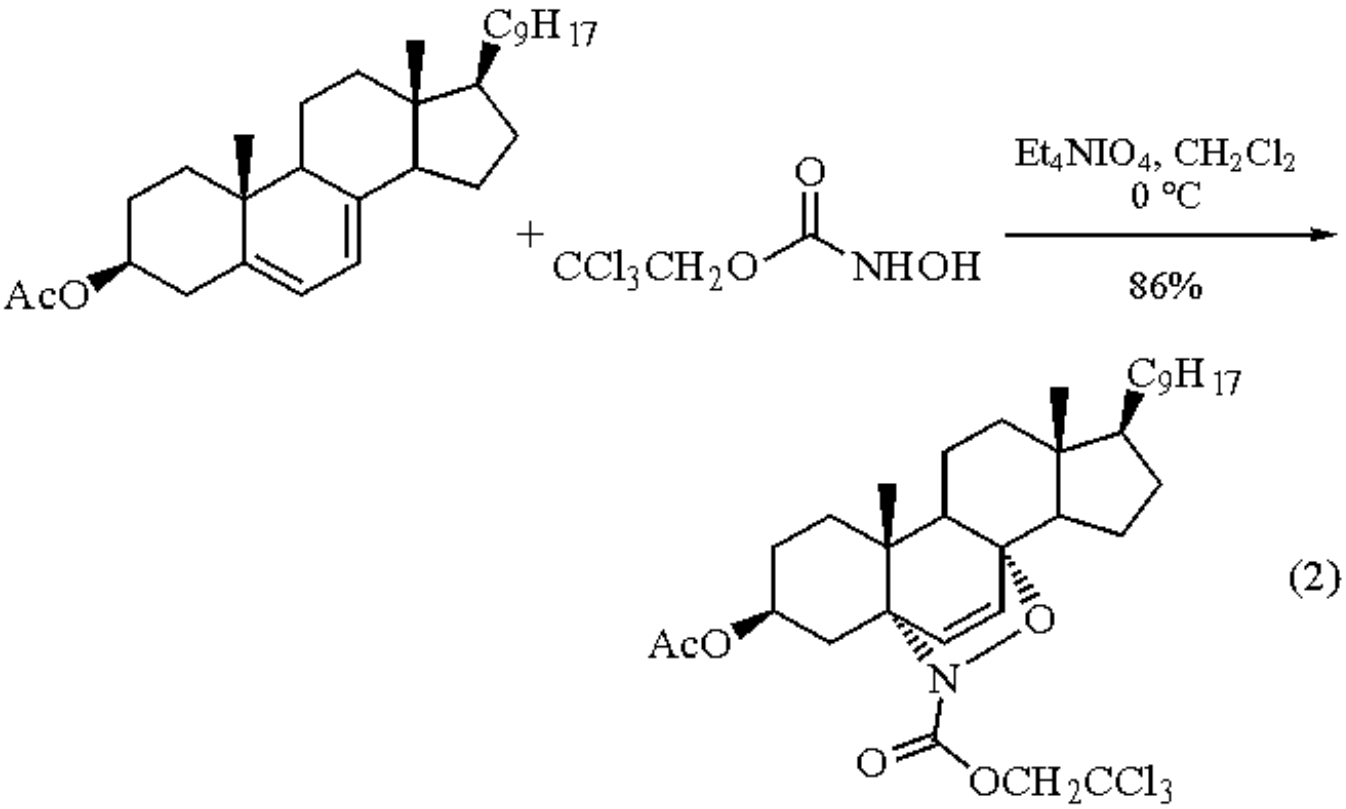

(2)

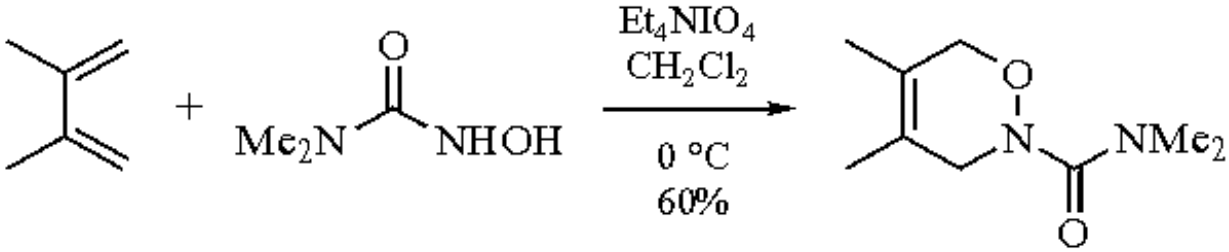

(3)

The generation of nitroso intermediates and trapping of these species by conjugated dienes has found application in natural product synthesis.[6,7] For example, in the stereospecific synthesis of tabtoxin,[6] the key stereochemical defining step involved the cycloaddition of benzyl nitrosoformate, generated in situ by Et_4NIO_4 oxidation of benzyl *N*-hydroxycarbamate, with ethyl 1,3-cyclohexadienecarboxylate (eq 4).

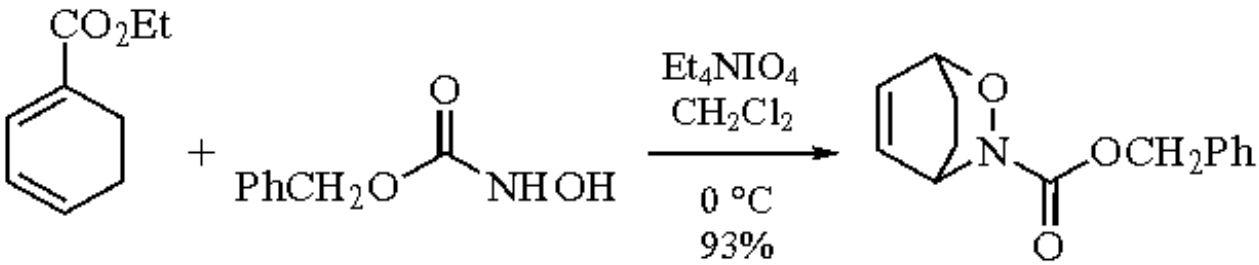

(4)

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Tetraethyl Pyrophosphate

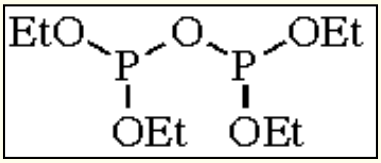

[21646-99-1] · $C_8H_{20}O_5P_2$ · Tetraethyl Pyrophosphate · (MW 258.22)

(peptide synthesis; phosphonylation of ketones, aldehydes, and perfluoroalkyl iodides)

Alternate Name: TEPP.

Physical Data: bp 79-81 °C/0.15 mmHg; *d* 1.057 g cm^{-3}; n_D 1.434.

Solubility: sol acetonitrile, 1,1,2-trichloro-1,2,2-trifluoroethane.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: the most convenient method involves the reaction of diethyl phosphite with diethyl phosphorochloridite. Diethyl phosphorochloridite (223 g) is added rapidly to a solution of diethyl phosphite (138 g) and triethylamine (101 g) in benzene (200 ml). The mixture is filtered and the benzene removed by distillation at reduced pressure. The product is isolated by further distillation at reduced pressure (79-81 °C/0.15 mmHg) in 41% yield.

Analysis of Reagent Purity: product purity is assessed by refractive index.

Handling, Storage, and Precautions: protect from moisture; irritant; handle in a fume hood.

Peptide Formation.[1]

Tetraethyl pyrophosphite will react with amino acids at either the free amine (eq 1) to give amidophosphites, or at the free carboxylic acid (eq 2) to give mixed anhydrides, and both are activated for peptide formation. ***Diethyl Phosphonite*** is a good solvent for amino acids and peptides and so the most convenient procedure for peptide formation involves heating an *N*-protected amino acid with an amino acid ester (eq 3) with an excess of TEPP in diethyl phosphite solution. If the amino acid ester is used as the HCl salt, addition of ***Triethylamine*** is advantageous. The product is precipitated by the addition of water or an organic solvent. No racemization has been observed in this procedure with dipeptide formation; however, variable amounts of racemization are observed in tripeptide formation where Cbz protecting groups are used. TEPP has been successfully used in the synthesis of important medium sized peptides, e.g. oxytocin.[2]

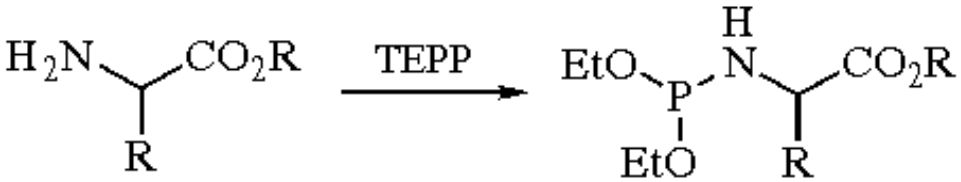

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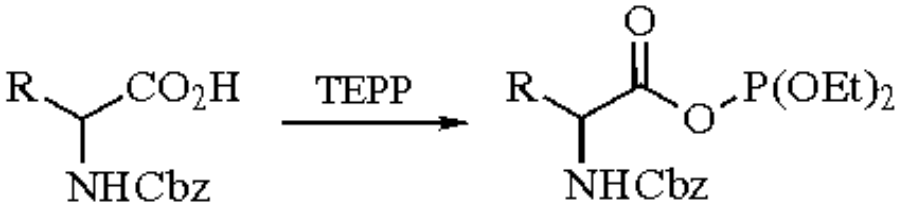

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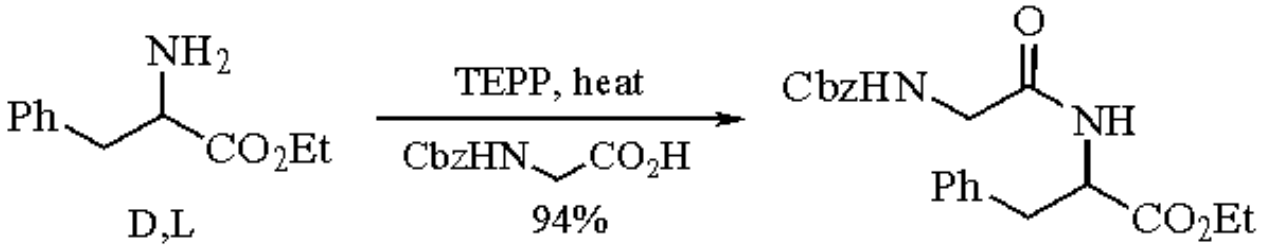

(3)

Phosphonylation.

Tetraethyl pyrophosphite can function as both an electrophile and a nucleophile. The electrophilic behavior is exemplified by the formation of mixed anhydrides from carboxylic acids (eq 4).[3] TEPP shows a nucleophilic character in reaction with carbonyl compounds. Addition of TEPP to aldehydes and ketones (eq 5)[4-6] gives phosphonium alkoxide intermediates, which undergo an intramolecular transfer of phosphite yielding mixed phosphonate-phosphite adducts. A further equivalent of carbonyl reportedly results in further oxidation to phosphonate-phosphate adducts.

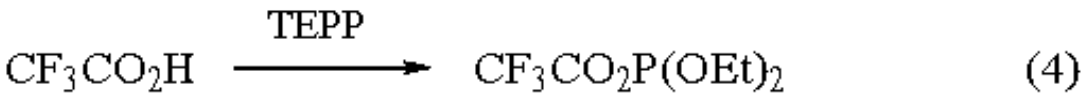

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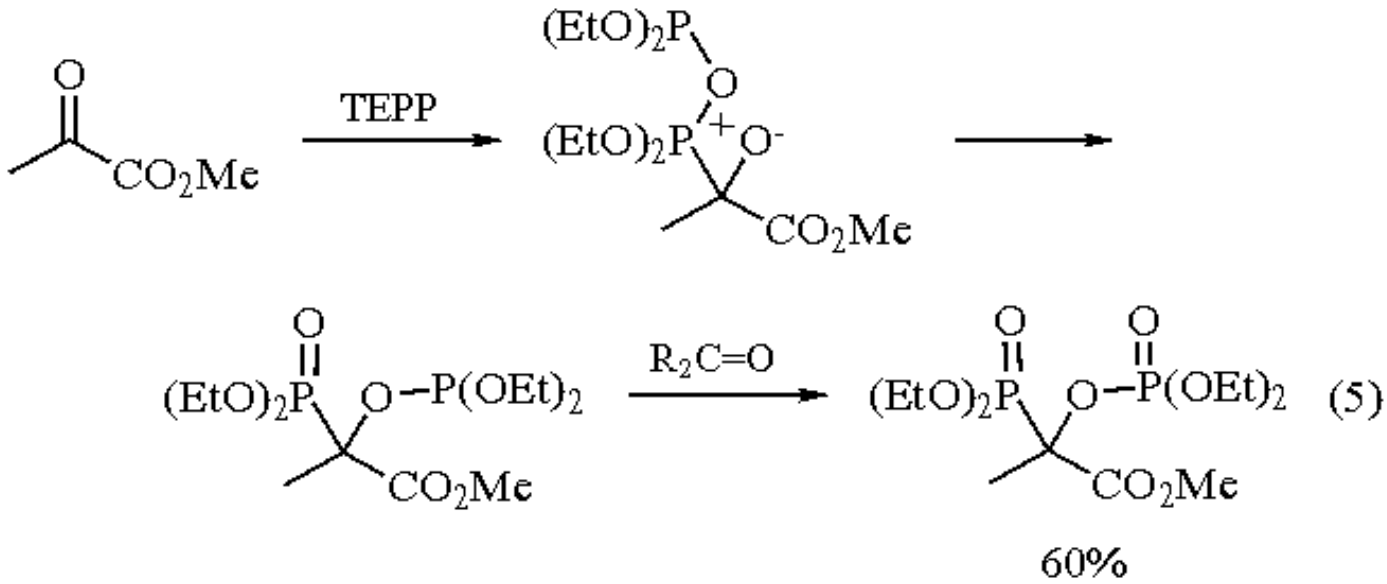

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Reaction of perfluoroalkyl iodides with TEPP and ***1,1-Di-t-butyl Peroxide*** in 1,1,2-trichloro-1,2,2-trifluoroethane gives diethyl phosphonites, which on oxidation with ***t-Butyl Hydroperoxide*** form diethyl perfluoroalkylphosphonates in good yield (eq 6).[7,8] The standard Arbuzov reaction is not generally applicable to fluoroalkyl phosphonates.

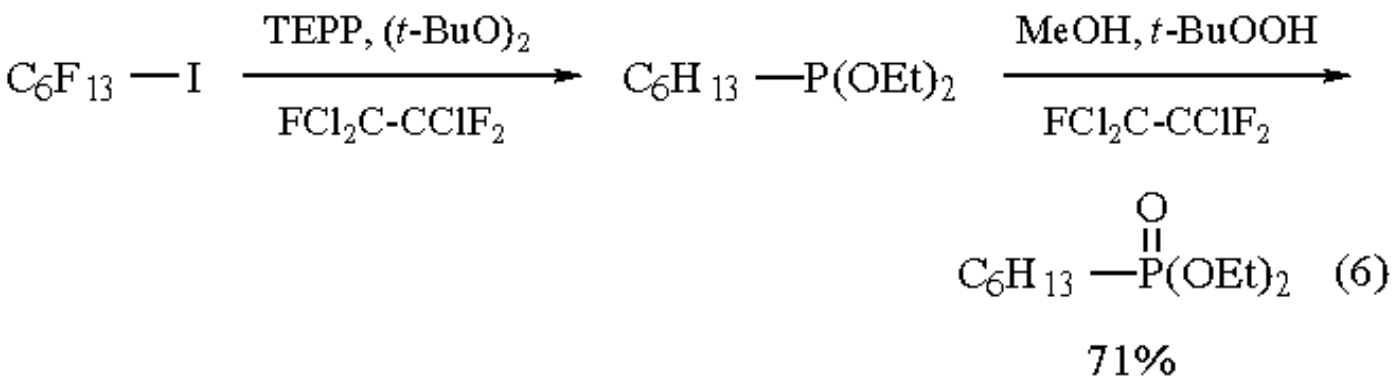

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Tetrafluoroboric Acid

BF_4H

[16872-11-0] · BF_4H · Tetrafluoroboric Acid · (MW 87.82) ($HBF_4.OMe_2$)

[67969-83-9] · $C_2H_7BF_4O$ · Tetrafluoroboric Acid Dimethyl Etherate · (MW 133.90) ($HBF_4.OEt_2$)

[67969-82-8] · $C_4H_{11}BF_4O$ · Tetrafluoroboric Acid Diethyl Etherate · (MW 161.96)

(strong acid with pK_a = -0.44[1] and a noncoordinating counterion[2])

Solubility: sol H_2O, alcohols and ethers.

Form Supplied in: 48% aq solution; diethyl ether complex; dimethyl ether complex.

Purification: commercial 50% solutions can be concentrated by evaporation at 50-60 °C/5 mmHg to give a residue of 11 N total acidity. Water can also be removed by slow addition to ice-cold acetic anhydride (dangerously exothermic reaction: caution is advised!).[3]

Handling, Storage, and Precautions: storage in glass containers is not recommended, although dilute solutions can be used in glass containers over short periods. Poisonous: causes burns to eyes, skin, and mucous membranes and may be fatal if ingested. Use in a fume hood with safety goggles and chemically resistant gloves and clothing. Incompatible with cyanides and strong bases: decomposes to form HF.

General Considerations.

Tetrafluoroboric acid is a useful strong Brønsted acid with a nonnucleophilic counterion. Its solubility in polar organic solvents makes it a useful strong acid under nonaqueous conditions.

Preparation of Arenediazonium Tetrafluoroborates.

Arenediazonium salts can be precipitated as their tetrafluoroborate salts by addition of a cold solution of HBF_4 to a solution of the initial arenediazonium chloride. 4-Methoxybenzenediazonium tetrafluoroborate is thus obtained in 94-98% yield. The arylamine can be diazotized with ***Sodium Nitrite*** in the presence of HBF_4, and the diazonium fluoroborate then precipitates directly. 3-Nitroaniline, when treated in this manner, provides a 90-97% yield of 3-nitrobenzenediazonium tetrafluoroborate (eq 1).[4] Diazotizations of arylamines and heteroarylamines in organic solvents can be conveniently conducted using $HBF_4.OEt_2$ and alkyl nitrites.[5]

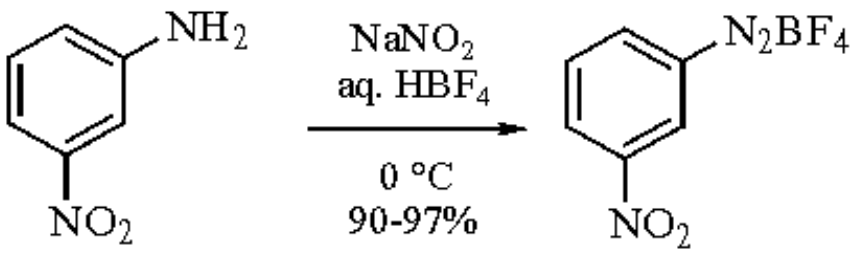

(1)

Protecting-Group Manipulations.

A preparation of monoesters of glutamic and aspartic acids using $HBF_4.OEt_2$ as a catalyst has been developed. The diesters are generally side products when other acids are used, but $HBF_4.OEt_2$ appears to suppress the diesterification. Thus L-glutamic acid γ-benzyl ester was obtained in 94% yield by treatment of the carboxylic acid in BnOH with the $HBF_4.OEt_2$ catalyst and a drying agent.[6]

When di-*t*-butyl carbonate is treated with DMAP.HBF_4, water-soluble Boc-pyridinium tetrafluoroborate is formed.[36] This reagent installs the Boc protecting group onto amino acids in aqueous NaOH. Thus L-proline is converted to its *N*-Boc derivative in nearly quantitative yield in 10 min.

Carbohydrate protection and deprotection reactions are amenable to HBF_4 catalysis; aqueous HBF_4 and $HBF_4.OEt_2$ are complementary in these applications. Transacetalization with benzaldehyde dimethyl acetal and ethereal HBF_4 gives a monobenzylidene product without disturbing the isopropylidene and trityl groups of the substrate (eq 2). Aqueous HBF_4 is useful in selective deprotection reactions, cleaving a trityl group in the presence of other acid-sensitive functionality (eq 3).[7]

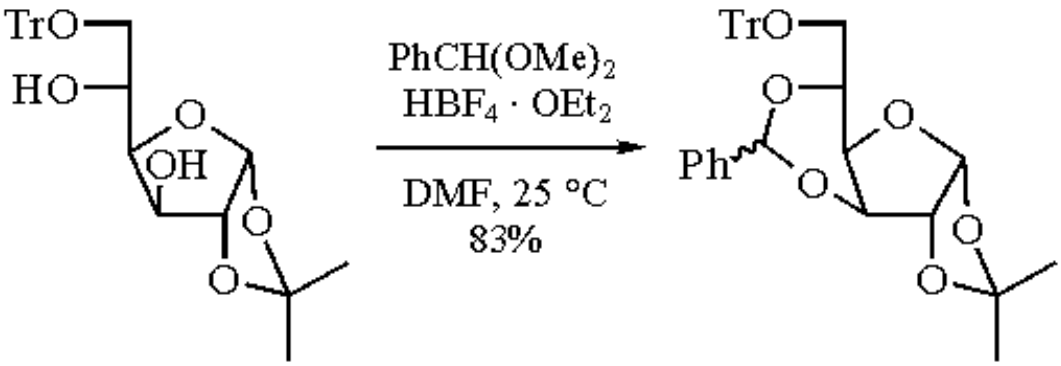

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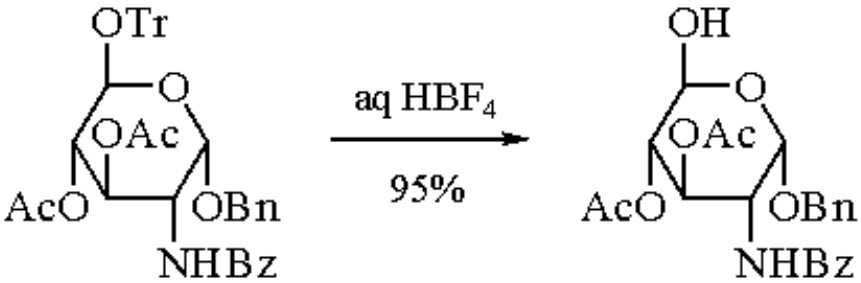

(3)

Recently developed in solid-phase peptide synthesis is the use of HBF_4/thioanisole/*m*-cresol as a general deprotection reagent. Most commonly used groups are cleaved from termini or side chain functionality under mild conditions (1 M HBF_4, 4 °C, 30-60 min) in very high yields. Human glucagon (a 29 residue peptide) has been synthesized as a demonstration of the effectiveness of the method,[8] which has been successful in both solid-phase and solution-phase syntheses.[9]

General Acid Catalysis.

HBF_4 is a versatile acid catalyst which is applicable to many typical acid-catalyzed reactions. Some adducts obtained upon reaction of cyclopropyl phenyl sulfide anion with carbonyl compounds can be rearranged to cyclobutanones under the catalytic influence of HBF_4 (eq 4), although different acids have been required for other substrates.[10] Acid-catalyzed rearrangement of 2-cyclopropylphenyl phenyl ether or sulfide with HBF_4 has been reported (eq 5).[11]

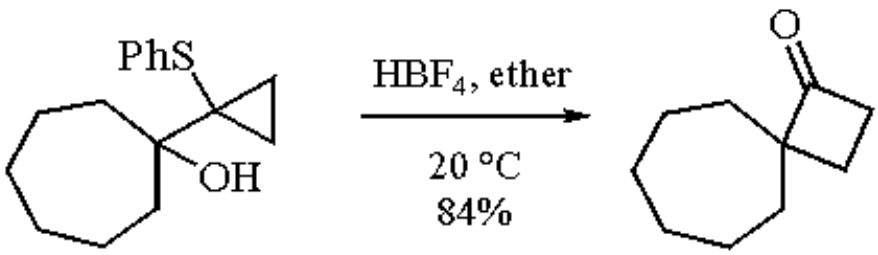

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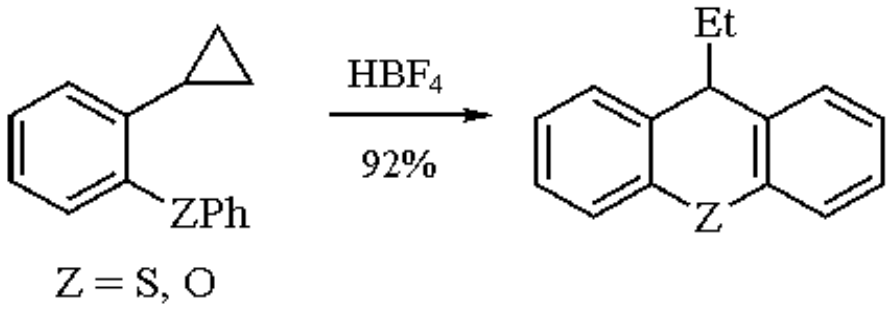

(5)

Acid-catalyzed oxidation of epoxides with $HBF_4.OMe_2$/DMSO results in the formation of α-hydroxy ketones (eq 6).[12] This procedure in an acidic medium complements the α-hydroxylation of ketone enolates under strongly basic conditions.

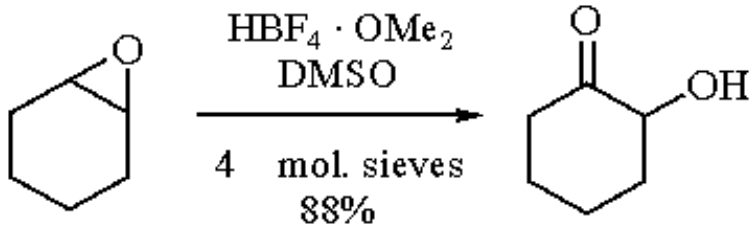

(6)

An intramolecular alkylation of a diazomethyl ketone was achieved with catalysis by HBF_4, providing an angularly fused cyclopentanone hydrofluorene (eq 7).[13]

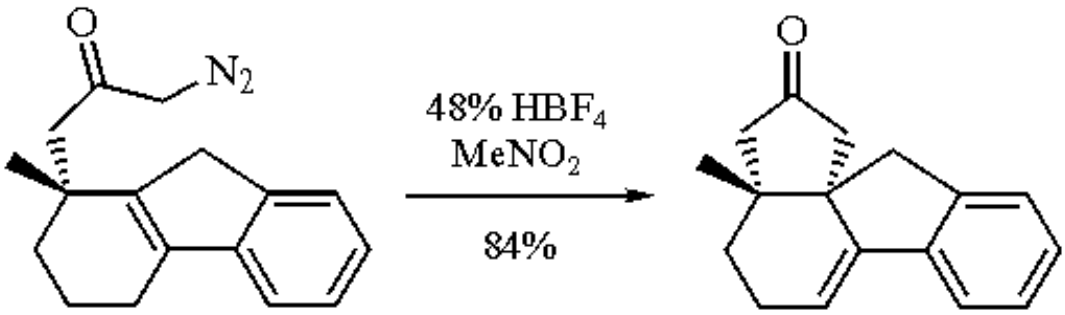

(7)

Other catalytic applications of HBF_4 include alkene isomerizations,[14] alkylation of alcohols with diazoalkanes,[15] preparations of substituted pyridines,[16] hydrolysis of α-hydroxyketene or α-(methylthio)ketene thioacetals to α,β-unsaturated thioesters,[17] and terpene formation from isoprenic precursors.[18]

Preparation of Annulated Triazolones.

Cyclization of the isocyanate in eq 8 in the presence of HBF_4 affords an oxotriazolium tetrafluoroborate, which then rearranges to form a 1,5-heteroannulated 1,2-dihydro-2-phenyl-3*H*-1,2,4-triazol-3-one (eq 8).[19]

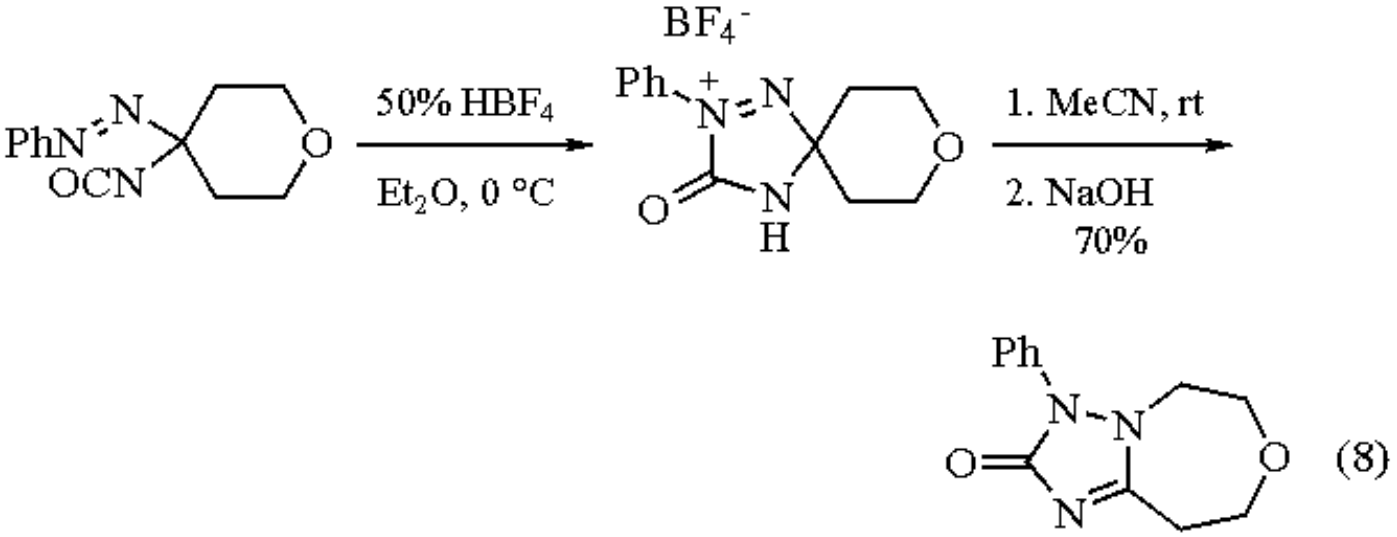

Carbenium Tetrafluoroborate Preparation.

4,6,8-Trimethylazulene is converted by ethereal HBF_4 into 4,6,8-trimethylazulenium tetrafluoroborate.[20] A convenient preparation of tropylium tetrafluoroborate employs HBF_4 to precipitate the product from a solution of the double salt $[C_7H_7]PCl_6.[C_7H_7]Cl$ in ethanol (eq 9). An indefinitely stable, nonhygroscopic, and nonexplosive white solid is obtained, a distinct advantage of a fluoroborate salt.[21]

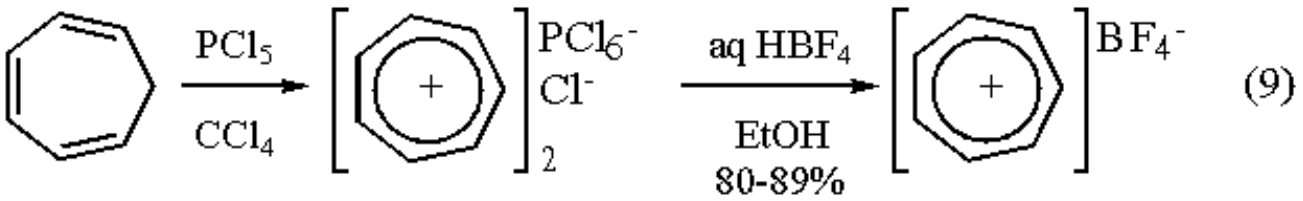

The formyl cation equivalent 1,3-benzodithiolylium tetrafluoroborate can be made in 94% yield by treatment of a dithioorthoformate with HBF_4/Ac_2O (eq 10).[22] 2-Deuterio-1,3-benzothiolylium tetrafluoroborate prepared by this method has been used to produce 1-deuterioaldehydes by homologation.[23] An analogous preparation of a similar formyl cation equivalent, 1,3-dithiolan-2-ylium tetrafluoroborate, employs $HBF_4.OEt_2$ (eq 11) to provide the intermediate salt. Subsequent reaction with a silyl enol ether forms a masked 2-formylcyclohexanone in high yield (eq 11).

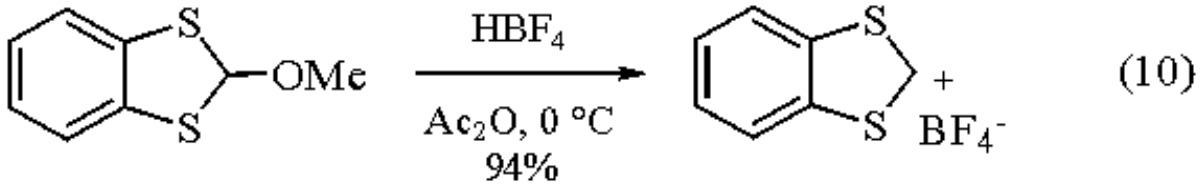

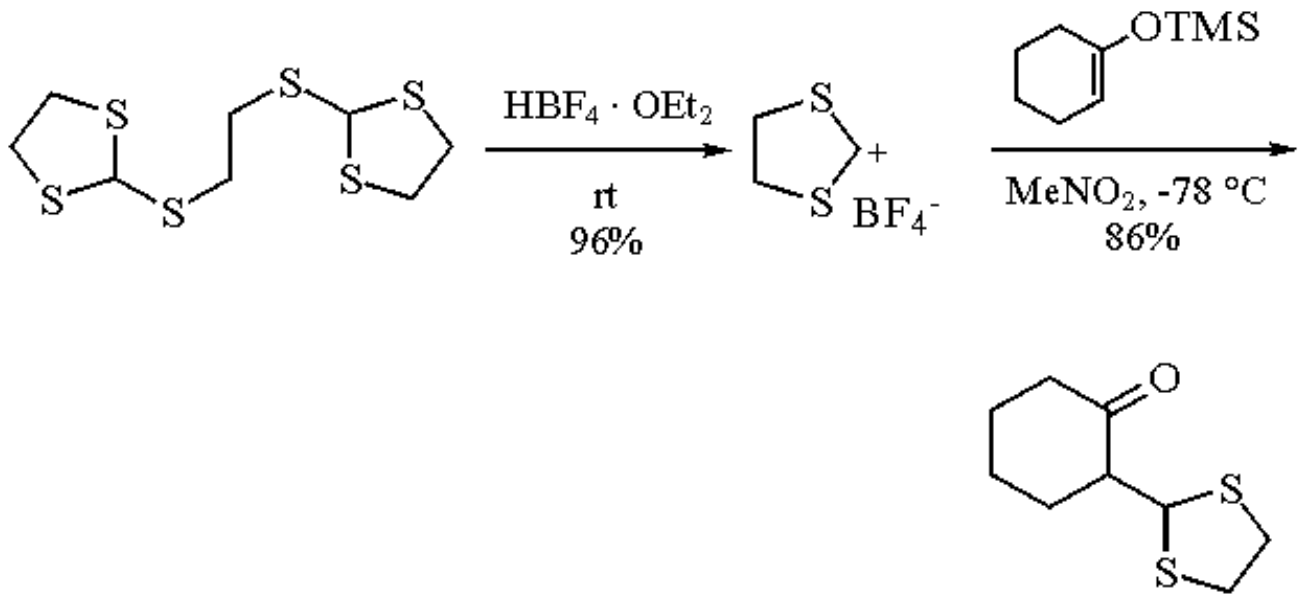

(11)

Ethynylfluorenylium dyes can be obtained by treatment of appropriate tertiary alcohols with HBF_4 (eq 12).[24]

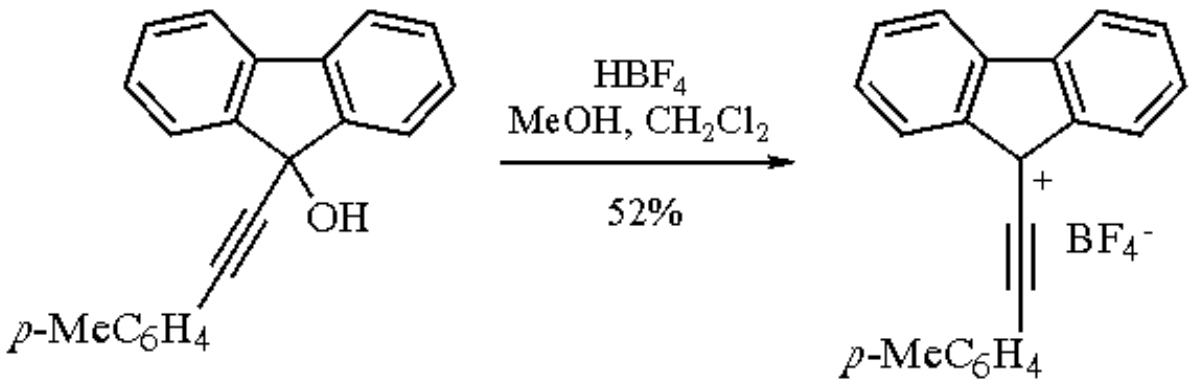

(12)

In addition to the aforementioned carbenium ions and diazonium ions, numerous other organic cations can be obtained as their fluoroborate salts by treatment of appropriate precursors with HBF_4.[25]

Dimerization of Carbodiimides.

Treatment of alkyl carbodiimides with anhydrous $HBF_4.OEt_2$ in CH_2Cl_2 results in rapid dimerization to tetrafluoroborate salts in 95% yield (eq 13). Basification converts the salts to diazetidines.[26] In the same work, aryl carbodiimides undergo a similar reaction, but substituted quinazolines are obtained.

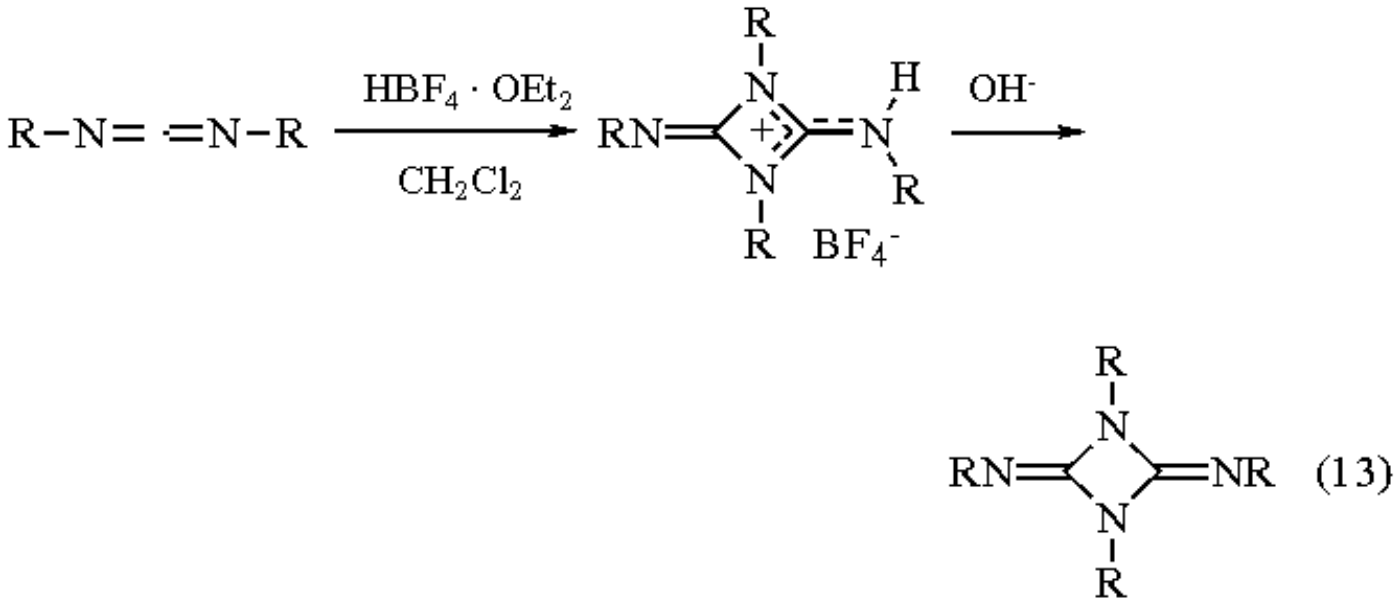

Mercury(II) Oxide/Tetrafluoroboric Acid.

Yellow ***Mercury(II) Oxide*** is added to 48% aqueous HBF_4 to yield, upon solvent removal, $HgO.2HBF_4$ as a hygroscopic white solid.[27] This reagent is useful in applications involving mercuration of alkenes, including diamination of alkenes and preparation of *trans*-cinnamyl ethers from allylbenzene.[28] Alkylations of carboxylic acids[29] and alcohols[30] with alkyl halides are also facilitated by $HgO.2HBF_4$. Mercury(II) oxide and HBF_4 in alcohol effected mild solvolysis of 2-hydroxytrithioorthoesters to yield α-hydroxycarboxylic esters in high yield.[31] See also ***Mercury(II) Oxide-Tetrafluoroboric Acid***.

Preparation of a Useful Hypervalent Iodine Reagent.

When treated with $HBF_4.OMe_2$ at low temperatures, ***Iodosylbenzene*** reacts with silyl enol ethers to form a hypervalent iodine adduct capable of useful carbon-carbon bond formation reactions with alkenes (eq 14).[32]

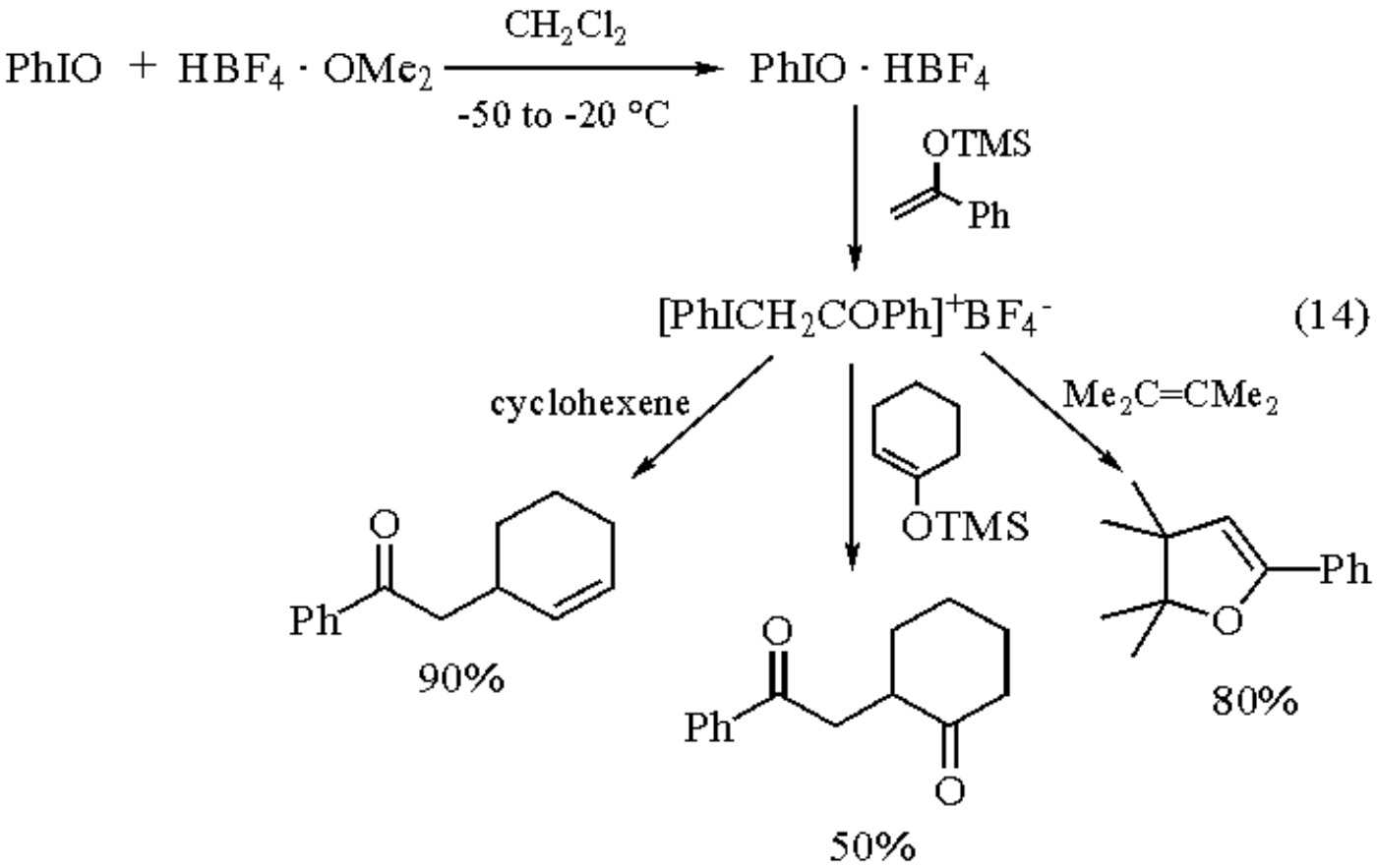

Synthesis of Cationic Organometallic Complexes.

Tetrafluoroborate is frequently encountered as the counterion in cationic organometallic compounds; its lack of nucleophilic reactivity makes HBF_4 and its etherates ideal reagents for delivery of protons without side reactions. The poorly coordinating conjugate base of HBF_4 allows substrates greater opportunity to bind to metals in organometallic reactions requiring the presence of acids.[33]

Propargylium complexes of cobalt, obtained by treatment of propargylic alcohols with $HBF_4.OEt_2$, have been studied with regard to their selectivity as alkylating agents. *N*-Acetyl-3,4-dimethoxyphenethylamine undergoes selective aromatic substitution, whereas the unprotected amine undergoes *N*,*N*-dialkylation but not aromatic substitution (eq 15).[34]

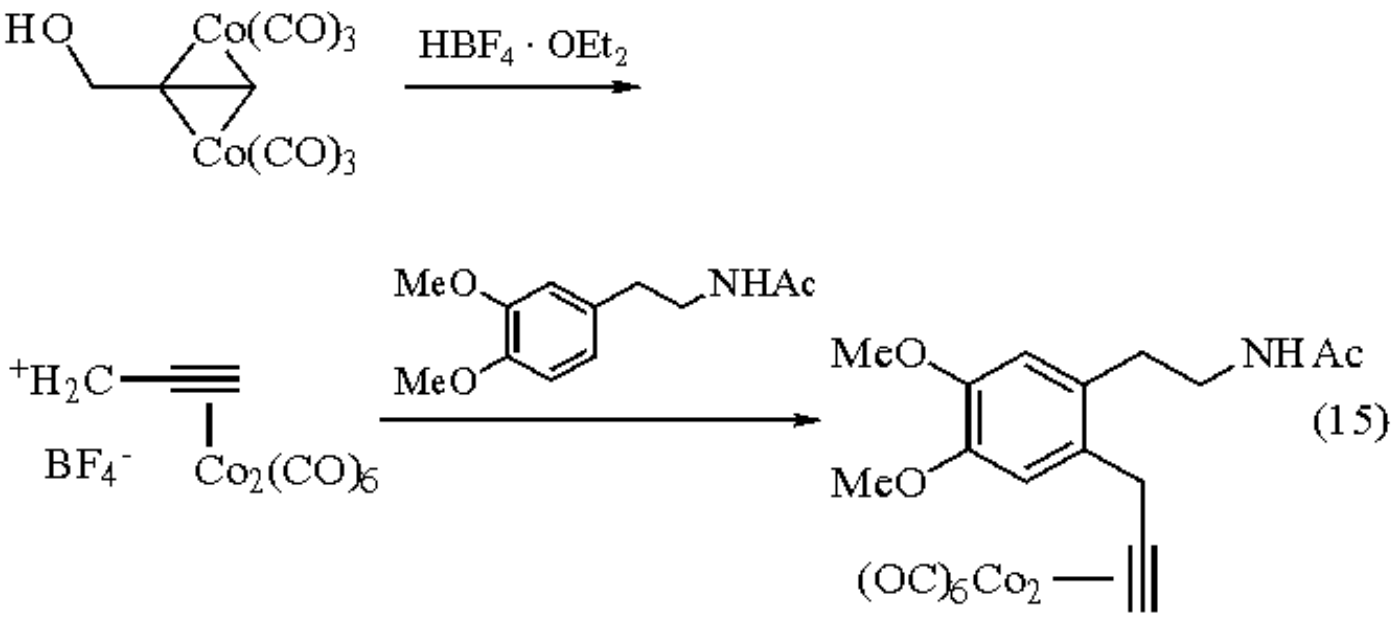

Oxidation.

In a reaction proposed as a model for substrate reactions at metal-sulfur centers of enzymes, HBF_4 apparently functions as an oxidizing agent in a two-electron oxidation of a ruthenium benzenedithiolate complex (eq 16).[35]

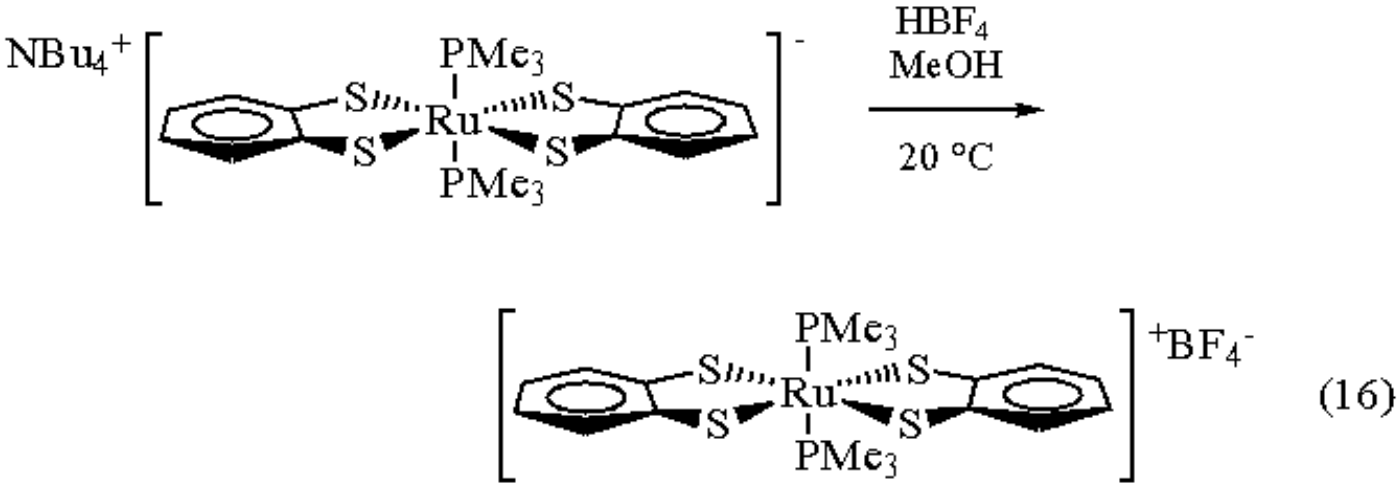

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(3*S*,*cis*)-Tetrahydro-3-isopropyl-7a-methylpyrrolol[2,1-*b*]oxazol-5(6*H*)-one[1]

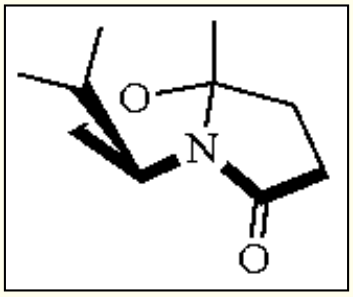

(3*S*,*cis*)

[98203-44-2] · $C_{10}H_{17}NO_2$ · (3*S*,*cis*)-Tetrahydro-3-isopropyl-7a-methylpyrrolol[2,1-*b*]oxazol-5(6*H*)-one · (MW 183.28)
(3*R*,*cis*)

[123808-97-9]

(chiral template for synthesis of enantiomerically pure cyclopropanes, cyclobutanes, cyclopentenones, pyrrolidines, pyrrolidinones, and α,α-disubstituted γ-keto acids[1])

Physical Data: bp 76-80 °C/0.05 mmHg; $[\alpha]_D$ 95.5°.

Preparative Methods: the richly functionalized chiral bicyclic lactam is easily procured by condensation of commercially available (*S*)-valinol and levulinic acid in 86% yield (eq 1).[2] Similar bicyclic lactams have been prepared from other amino alcohols.[3] These bicyclic lactams have served as precursors to a variety of enantiomerically pure compounds that possess quaternary stereocenters. An extensive review on the utility of chiral, nonracemic bicyclic lactams is available.[1]

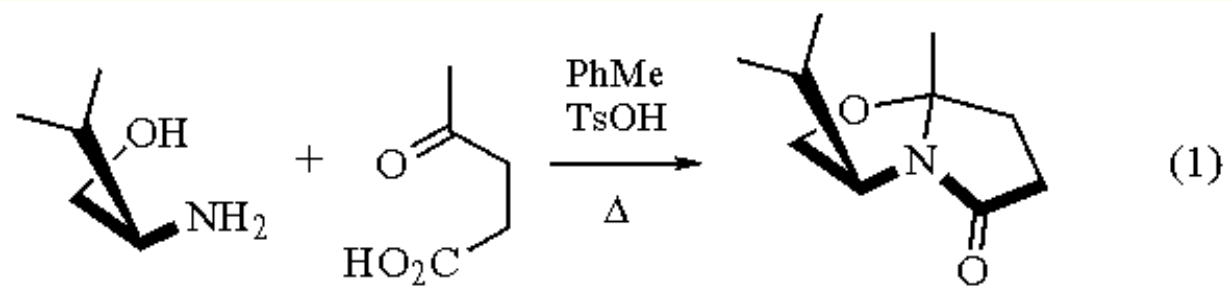

General Considerations.

The title reagent can be sequentially alkylated α to the carbonyl group in a stereocontrolled fashion (eq 2).[1] Lithiation of the parent bicyclic lactam with ***s-Butyllithium*** and reaction with an alkyl halide affords the monoalkylated product. The epimeric mixture is treated again with *s*-BuLi and a second alkyl halide to give the dialkylated bicyclic lactam. The initial epimeric mixture is used directly in the second alkylation since this step proceeds via a planar enolate. It is the second alkylation that dictates the final diastereomeric ratio. The opposite stereochemistry at C-6 can be obtained by inverting the order of electrophile addition.

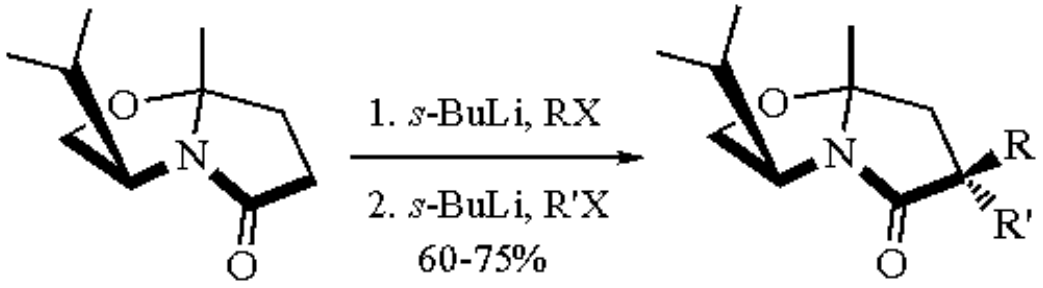

(2)

Reduction and hydrolysis of the bicyclic lactam followed by aldol cyclization affords enantiomerically pure 4,4-dialkyl-2-cyclopentenones (eq 3).[2,4]

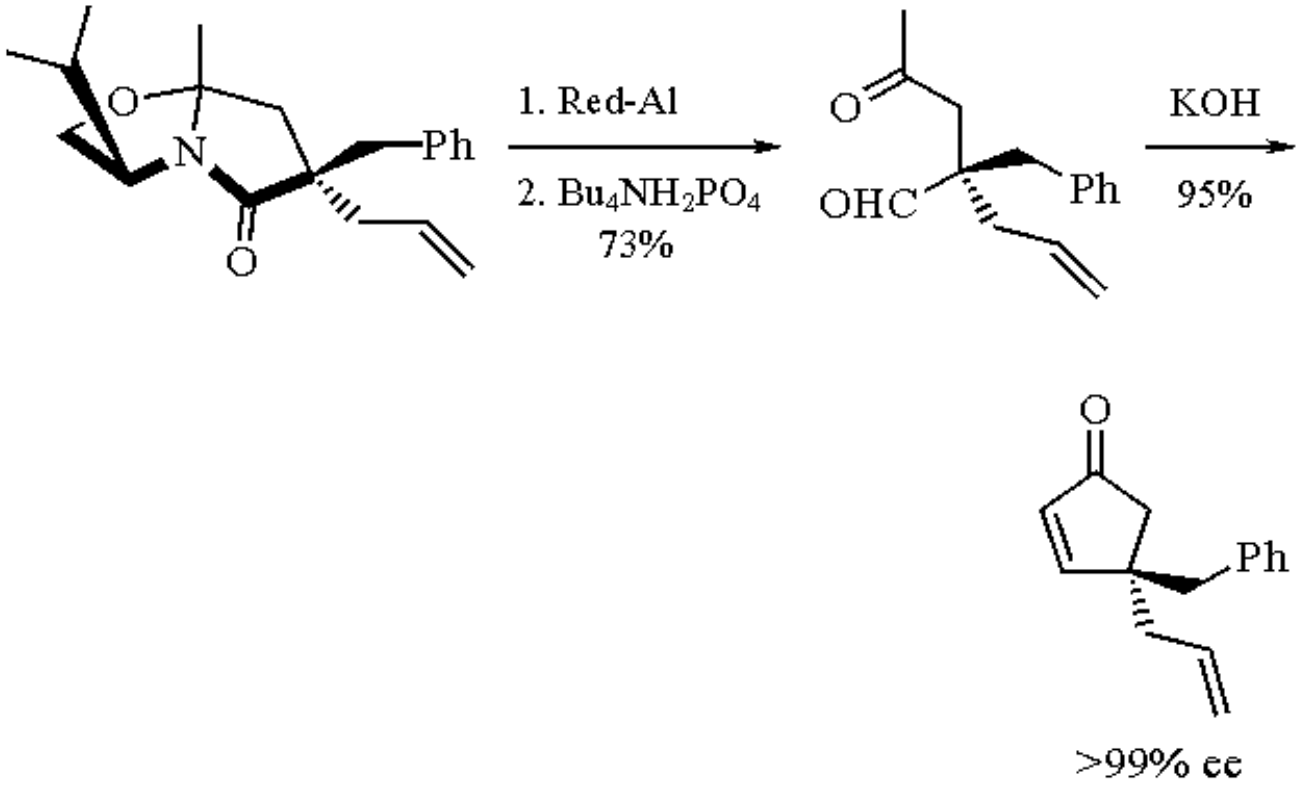

(3)

More highly functionalized cyclopentenones can be accessed by organolithium addition to the carbonyl group instead of hydride reduction with ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al).[5]

α-Substituted γ-keto acids, upon condensation with β-amino alcohols, afford bicyclic lactams containing α-substitutents such as aryl groups. In this case, only one metalation-alkylation sequence is required to form the chiral, nonracemic α,α-disubstituted bicyclic lactam (eq 4).[4b]

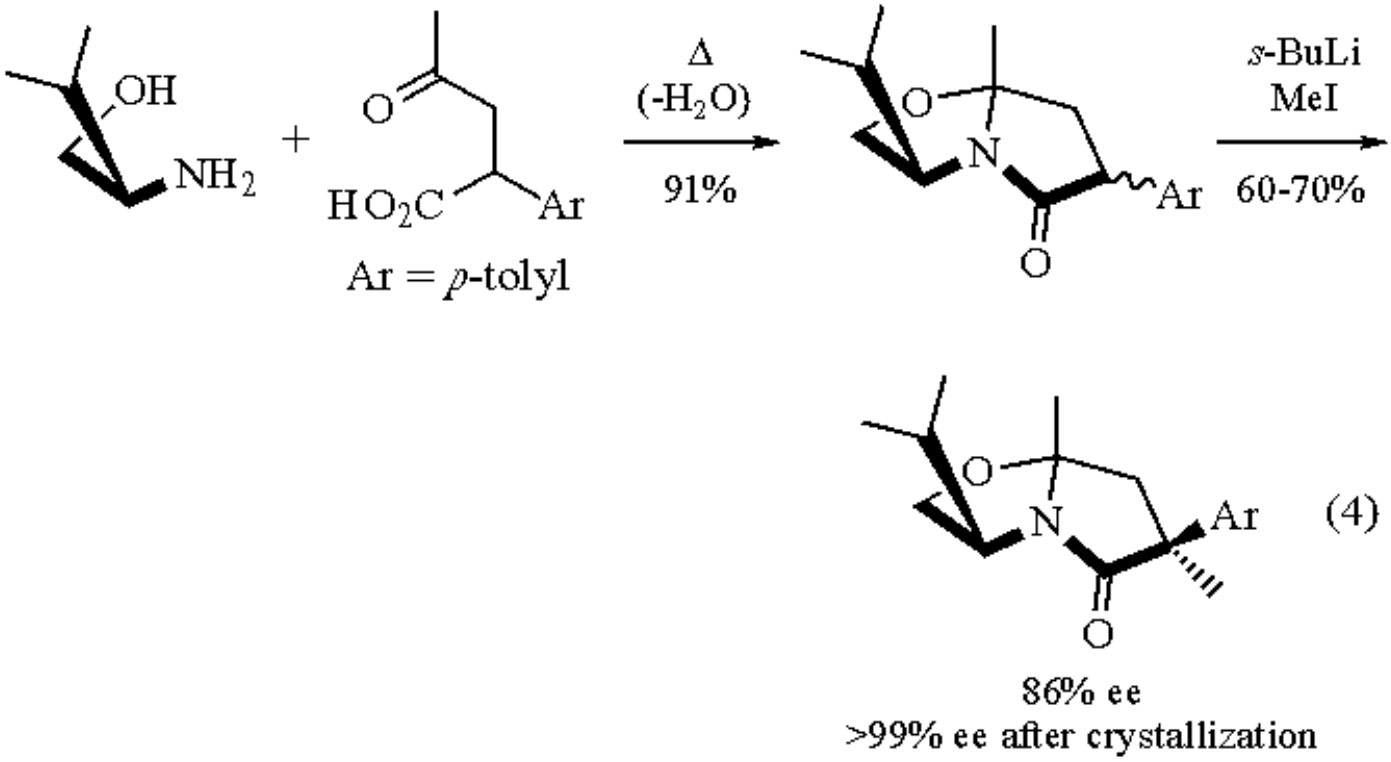

The angular 7a-phenyl bicyclic lactam can be prepared by the cyclocondensation of 3-benzoylpropionic acid and (*S*)-valinol in 85% yield.[6] Dialkylation of this lactam also affords cleanly the α,α-disubstituted compound. Lactam hydrolysis releases chiral, nonracemic α,α-disubstituted γ-keto carboxylic esters (or acids) (eq 5) and 3,3-disubstituted dihydronaphthalenes may be obtained via cyclization.[6]

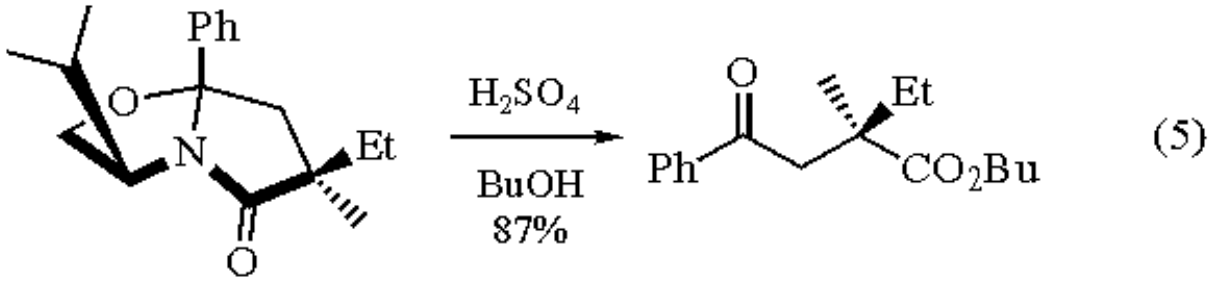

When the bicyclic lactam is substituted with a 3-hydroxypropyl group in the 6-position, acidic hydrolysis gives a bridged bicyclic acetal lactone (eq 6).[7]

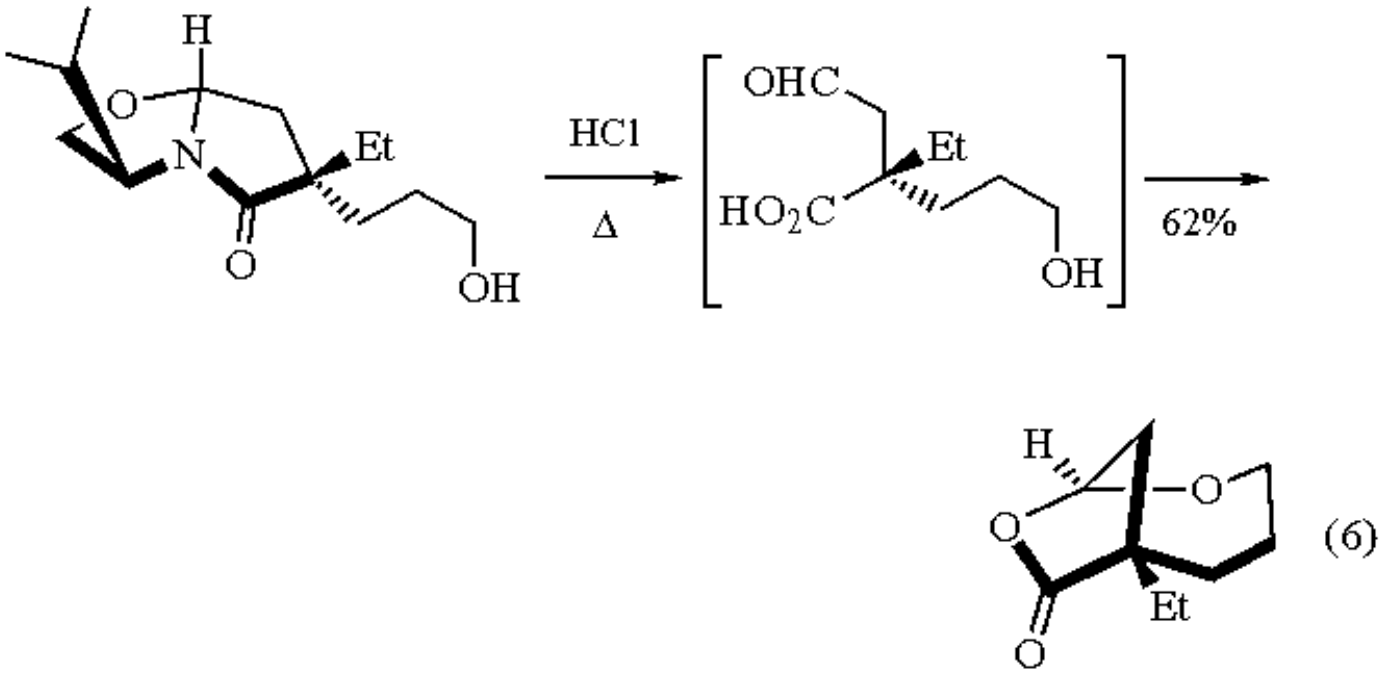

An α-(4-bromobutyl) group can be used as a latent organolithium species by means of bromine-lithium exchange. Intramolecular addition of the organometallic tether to the carbonyl group, followed by lactam hydrolysis and aldol cyclization, affords enantiomerically pure hydrinden-2-ones (eq 7).[8]

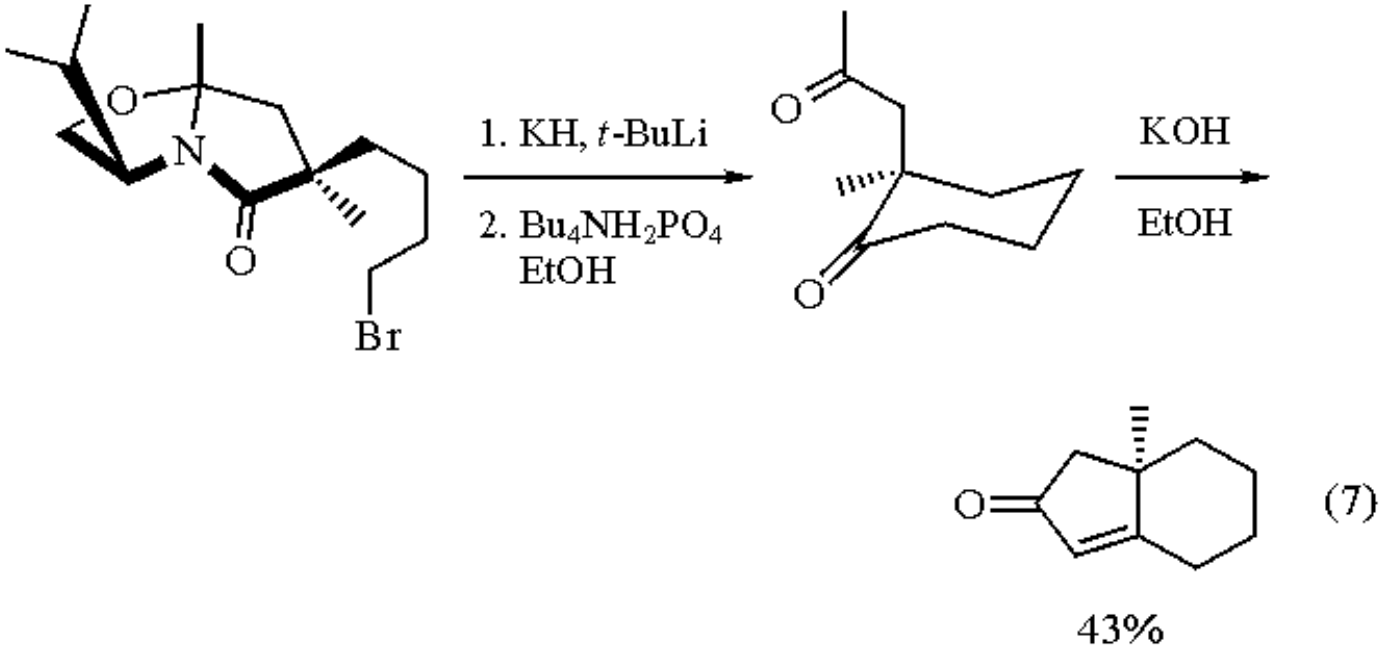

α,β-Unsaturation may be introduced into the bicyclic lactams by standard α-selenation-oxidation methodology. The lactam can now behave as a chiral enone in photochemical [2 + 2] cycloadditions. The lactam moiety can be easily detached owing to its amide and aminal features; thus chiral, nonracemic cyclobutanes are obtained upon hydrolysis (eq 8).[9]

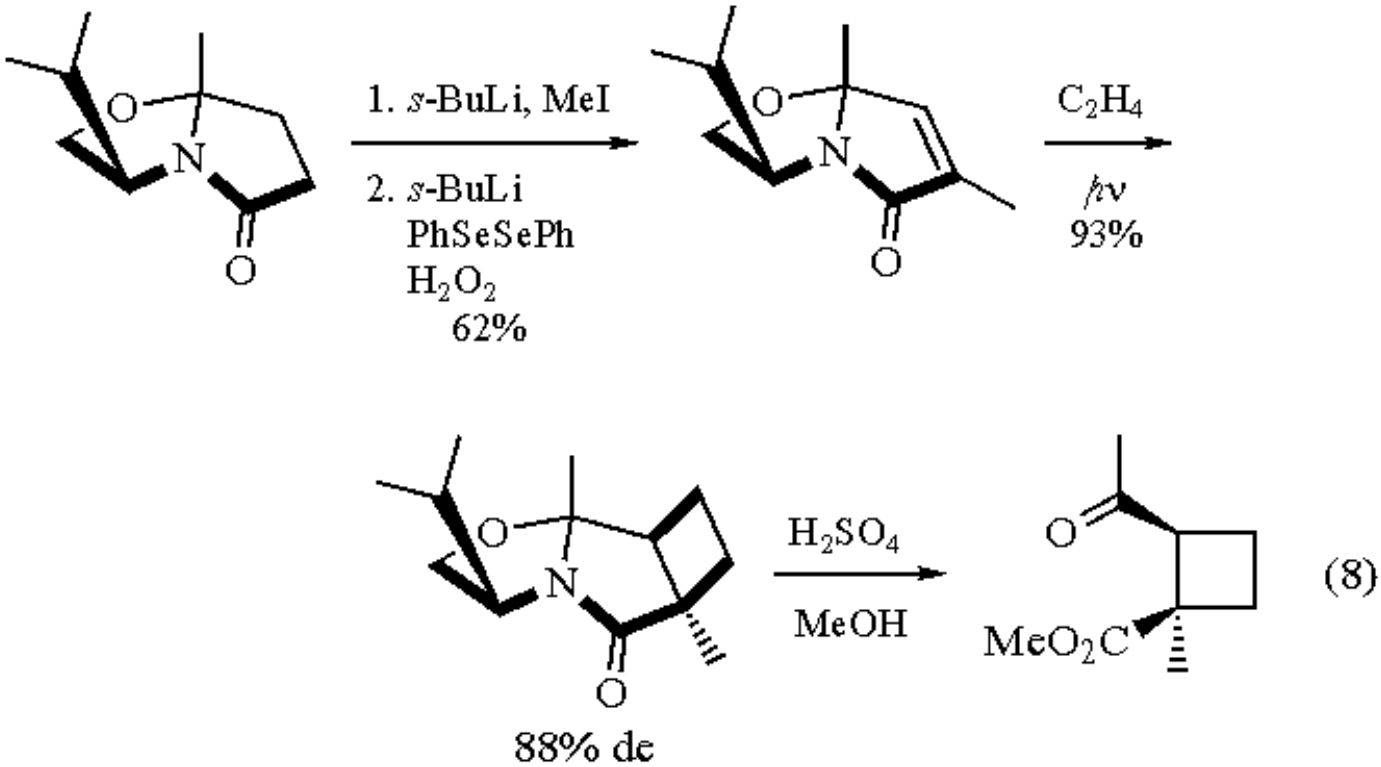

These unsaturated, bicyclic lactams are also precursors to a variety of chiral nonracemic cyclopropanes. Treatment of the parent α,β-unsaturated lactam with ***Dimethylsulfoxonium Methylide*** generates the *endo* cyclopropanated adduct (eq 9).[3b,10]

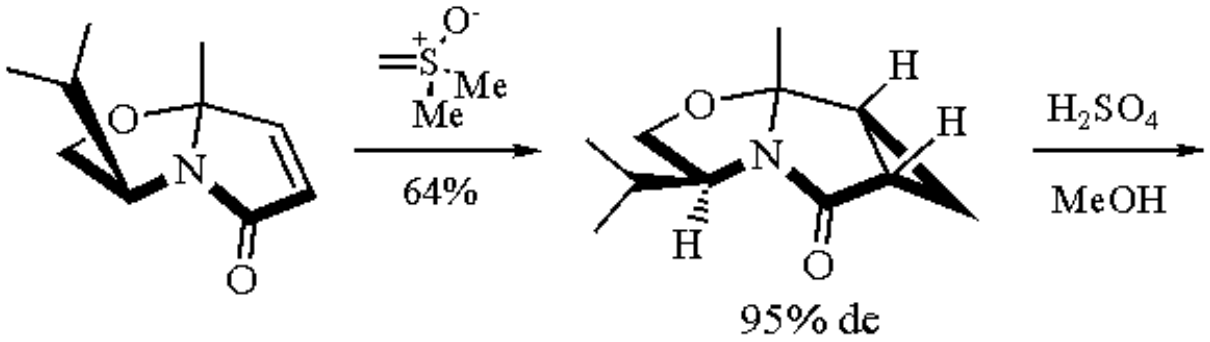

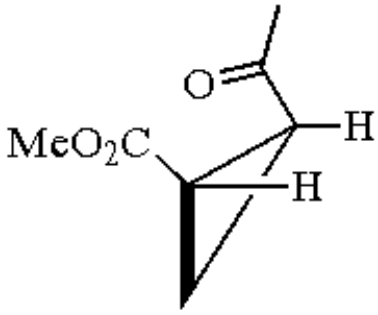

(9)

Diels-Alder cycloadditions occur on the *endo* face when the unsaturated bicyclic lactam is treated with 1,3-dienes such as ***Isoprene*** (eq 10).[11] Ester reduction followed by organolithium addition to the lactam carbonyl group and subsequent hydrolysis affords a variety of enantiopure functionalized cyclohexenes.[11]

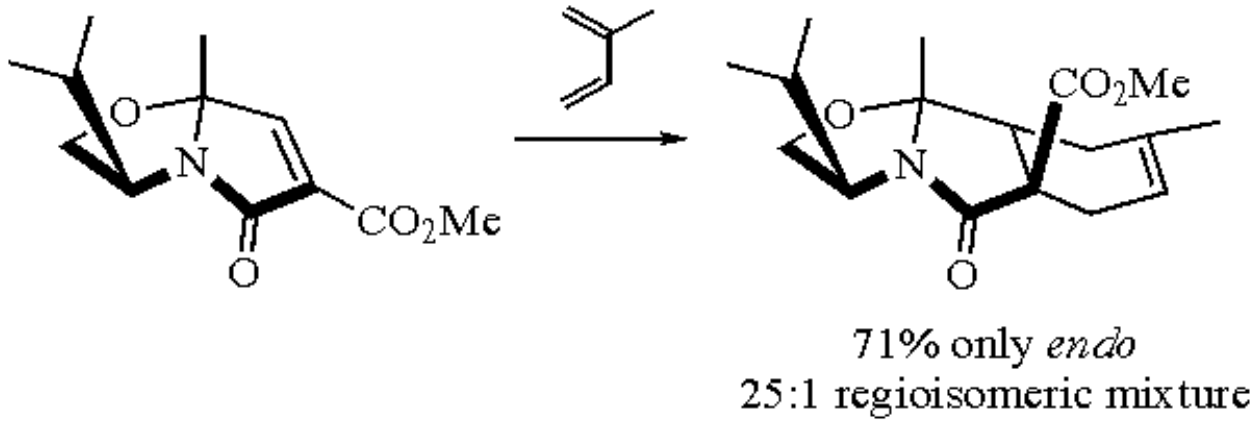

(10)

Cyclopropyl-containing carbocycles can be prepared from the initial [4 + 2] cycloadducts by an *N*-acyliminium ion-enamide rearrangement. The unsaturated bicyclic lactam also undergoes 1,3-dipolar cycloadditions with azomethine ylides.[12] Reduction of the bicyclic lactam with alane followed by hydrogenation affords enantiomerically pure 2-substituted pyrrolidines (eq 11).[13]

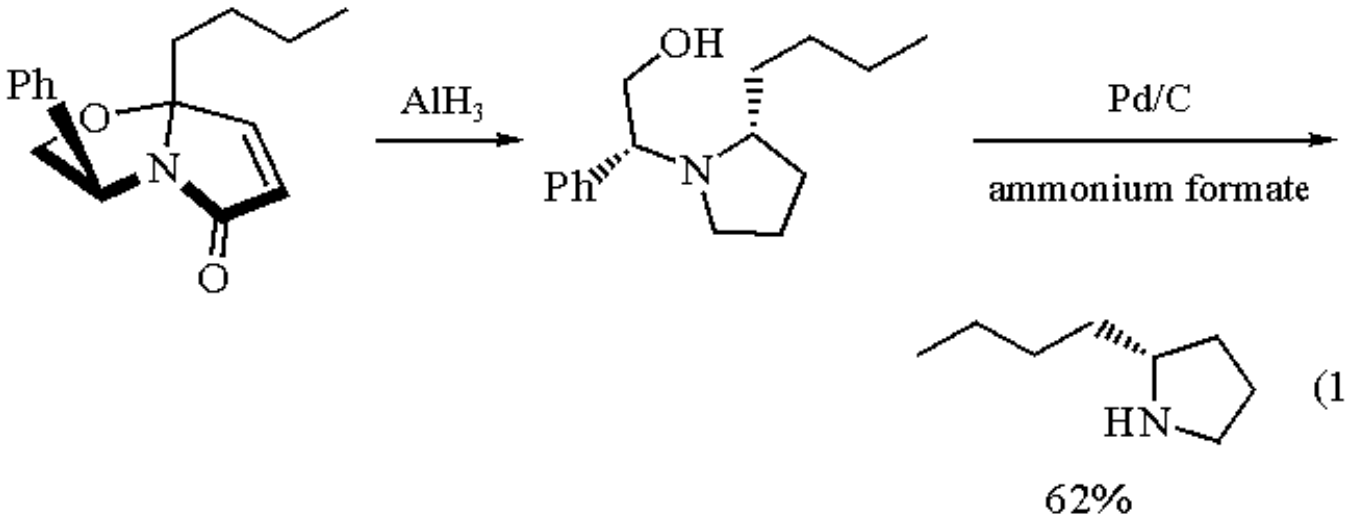

(11)

5,5-Disubstituted pyrrolidinones are formed when the bicyclic lactam is treated with ***Allyltrimethylsilane/Titanium(IV) Chloride***. The remaining phenylglycinol moiety is cleaved with Li/NH_3 (see ***Lithium Amide***) (eq 12).[14] Further reduction with ***Lithium Aluminum Hydride*** affords 2,2-disubstituted pyrrolidines.

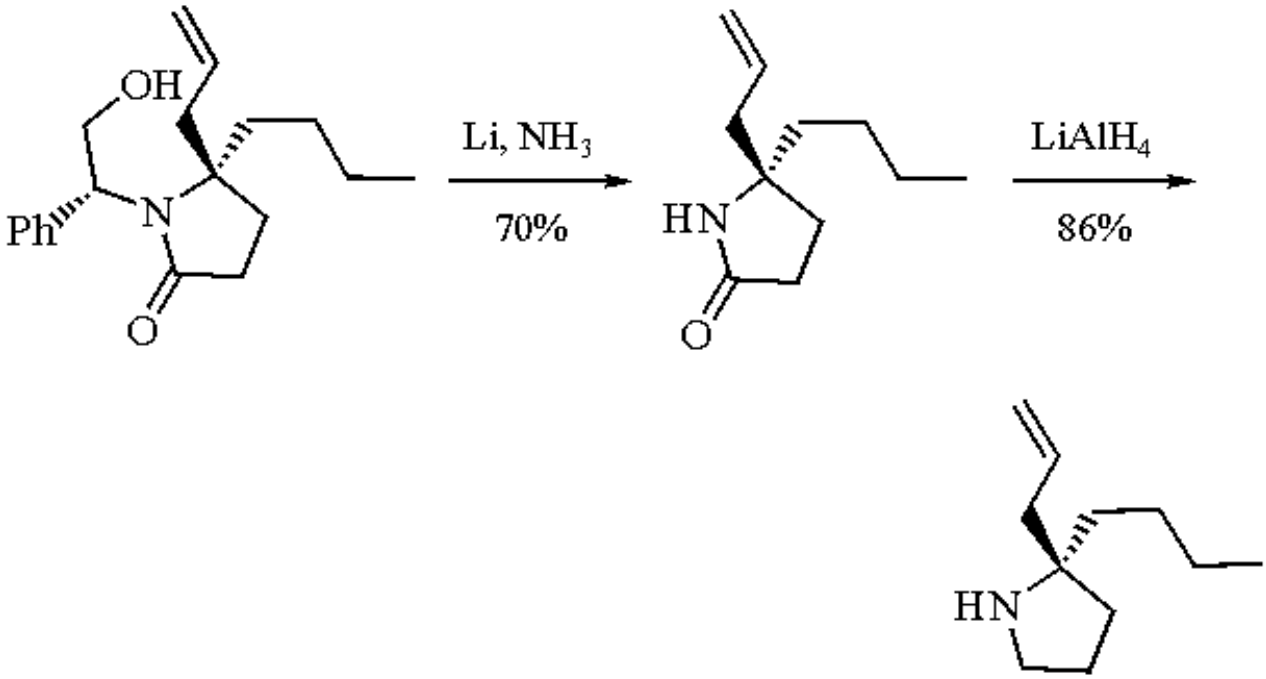

(12)

Reduction with ***Triethylsilane*** allows for the formation of enantiomerically pure 5-substituted pyrrolidinones and 2-substituted pyrrolidines in the same manner.[15]

Conjugate addition of organocuprates to the unsaturated bicyclic lactams (see above) affords rapid access to chiral, nonracemic 3- and 4-substituted pyrrolidines[16] and *trans*-2,3-disubstituted pyrrolidines.[17]

Related Reagents.

(S)-1-Amino-2-methoxymethylpyrrolidine; ***trans-2,5-Bis(methoxymethyl)pyrrolidine***; ***10,2-Camphorsultam***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***(2S)-(2α,3β,8aβ)-Hexahydro-3-(hydroxymethyl)-8a-methyl-2-phenyl-5H-oxazolo[3,2-a]pyridin-5-one***; ***(4S,5S)-4-Methoxymethyl-2-methyl-5-phenyl-2-oxazoline***; ***α-Methyltoluene-2,α-sultam***; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***.

---

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16. Meyers, A. I.; Snyder, L. *JOC* **1993**, *58*, 36.
17. Meyers, A. I.; Snyder, L. *JOC* **1992**, *57*, 3814.

Todd D. Nelson & Albert. I. Meyers

Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole[1]

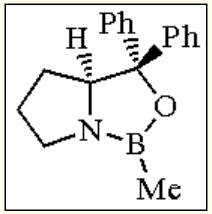

(*S*)

[112022-81-8] · $C_{18}H_{20}BNO$ · Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole · (MW 277.20) (.BH_3)

[112022-90-9] (*R*)

[112022-83-0]

(one of many chiral oxazaborolidines/chiral Lewis acids useful as enantioselective catalysts for the reduction of prochiral ketones,[1-3] imines,[4] and oximes,[2e,f,5] and the reduction of 2-pyranones to afford chiral biaryls;[6] other chiral oxazaborolidines have been used for the addition of diethylzinc to aldehydes,[7] asymmetric hydroboration,[8a,b] the Diels-Alder reaction,[9-11] and the aldol reaction[12,13])

Physical Data: mp 79-81 °C.

Solubility: very sol THF, CH_2Cl_2, toluene.

Preparative Methods: see text.

Purification: Kugelrohr distillation (50 °C/0.001 mbar)

Handling, Storage, and Precautions: the free oxazaborolidine must be rigorously protected from exposure to moisture. The crystalline borane complex is more stable, and is the preferred form to handle and store this catalyst.

Enantioselective Ketone Reduction.

The major application of chiral oxazaborolidines has been the stoichiometric (as the oxazaborolidine-borane complex) (eq 1) and catalytic (in the presence of a stoichiometric borane source) (eq 2) enantioselective reduction of prochiral ketones.[1] These asymmetric catalysts work best for the reduction of aryl alkyl ketones, often providing very high (>95% ee) levels of enantioselectivity.

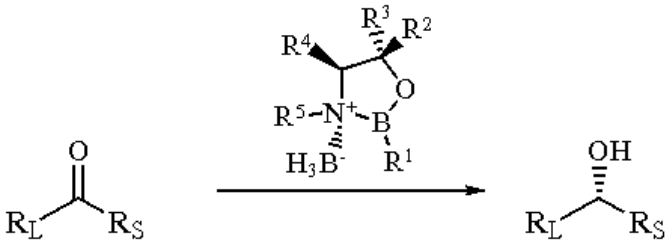

(1)

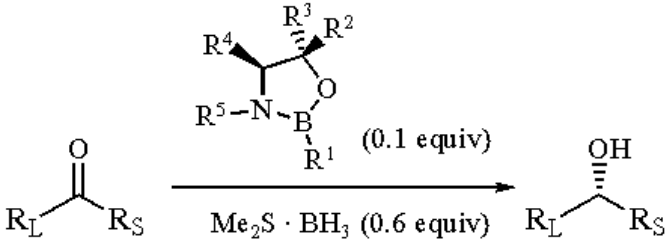

(2)

Following from the work of Itsuno[2] and Corey,[3] over 75 chiral oxazaborolidine catalysts have been reported for the reduction of prochiral ketones [(**1**),[2,3a,14,15a,e,f,16d-f,17b] (**2**),[16d,18b] (**3**),[3,6,19b-e,20,21,26c] (**4**),[16a] (**5**),[1b,16c,22] (**6**),[22b] (**7**),[3d,18a] (**8**),[16b] (**9**),[23] (**10**),[24] (**11**),[24] (**12**),[19a]]. Oxazaborolidines derived from proline (**3**) (see ***α,α-Diphenyl-2-pyrrolidinemethanol***) and valine (**1**; R^4 = *i*-Pr) (see ***2-Amino-3-methyl-1,1-diphenyl-1-butanol***) have received the most attention.

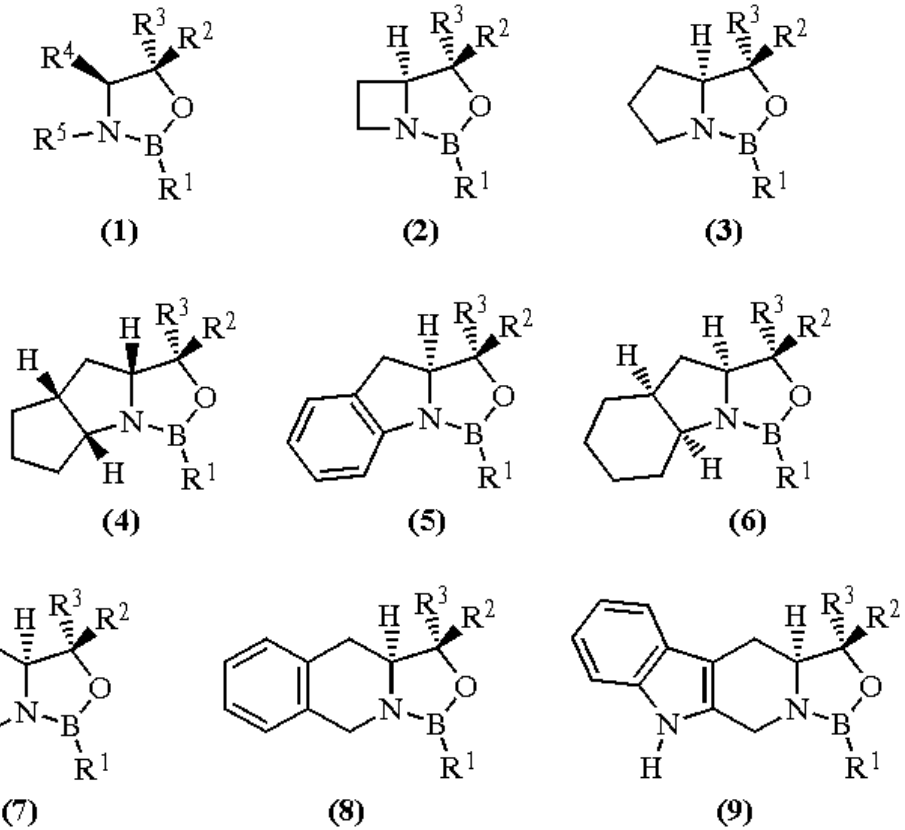

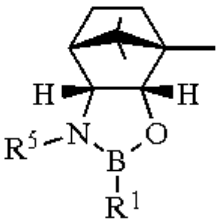

(10)

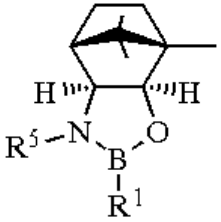

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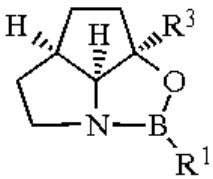

(12)

Unsubstituted (B-H) oxazaborolidines (**16**) are prepared from a chiral β-amino alcohol (**13**) and a source of borane (***Diborane***, ***Borane-Tetrahydrofuran***, ***Borane-Dimethyl Sulfide***, or $H_3B.NMe_3$) via a multistep process (eq 3). Formation of the initial amine-borane complex (**14**) is generally exothermic, and this intermediate can often be isolated. Gentle heating with the loss of one mole of hydrogen results in the formation of (**15**). Continued heating with the loss of a second mole of hydrogen then affords oxazaborolidine (**16**). When R^4 and R^5 are connected, forming a four- or five-membered ring, more forcing conditions (70-75 °C, 1.7 bar, 48-72 h) are required to effect this conversion due to the additional ring strain. [*Caution*: under these conditions, borane or diborane in the vapor phase can begin to decompose.[25]] Finally, additional borane is added to afford the oxazaborolidine-borane complex (**17**).

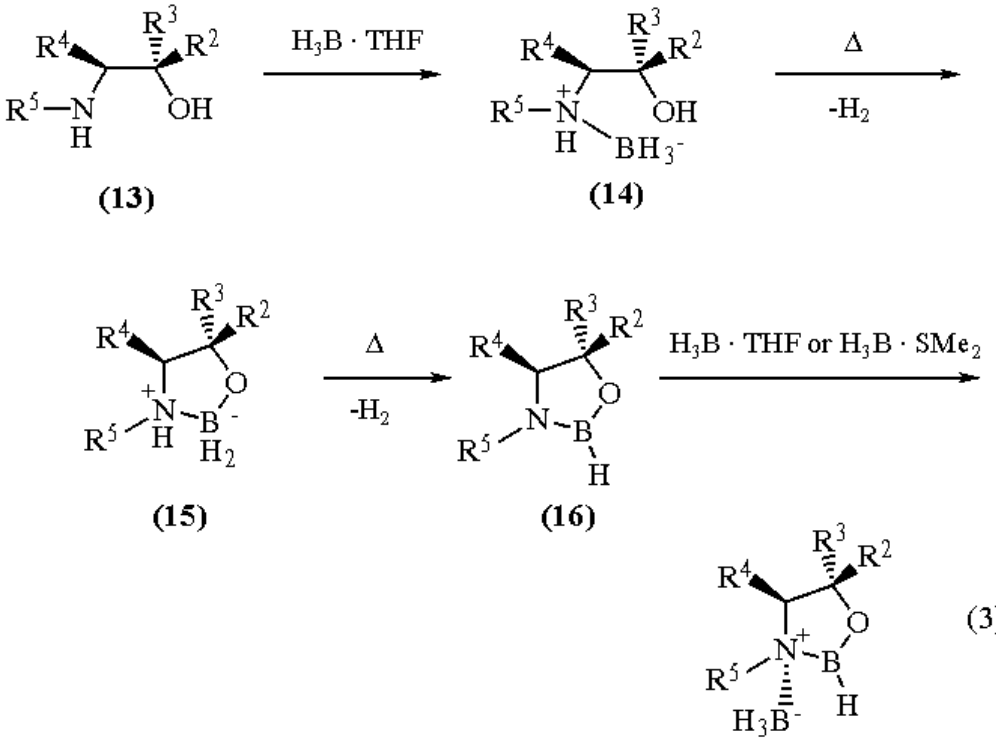

(3)

Free oxazaborolidine (**16**), by itself, will not reduce ketones. Furthermore, (**16**) is not particularly stable, reacting with moisture (H_2O), air (O_2), unreacted amino alcohol, other alcohols,[8c] or, depending on the substituents, with itself to form various dimers.[3a,8c,d,15d,26,27a] This instability is due to the strain of a partial double bond between nitrogen and boron (eq 4). Formation of the oxazaborolidine-borane complex (**17**) tends to release some of this strain. As such, (**16**) and (**17**) are generally prepared and used in situ without isolation; in many cases, they have not been fully characterized.[17c]

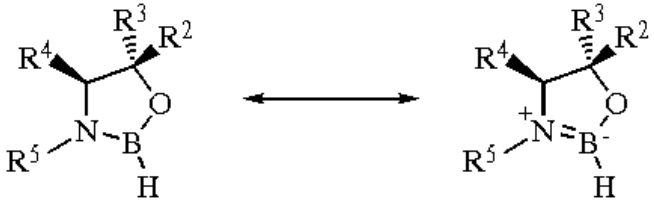

(4)

Oxazaborolidines substituted at boron (**1**; R^1 = alkyl, aryl) are prepared from a chiral β-amino alcohol and the corresponding boronic acid in a two-step process (eq 5).[3b,9] Heat and an efficient method of water removal (i.e. azeotropic distillation, molecular sieves) are required to drive the second step. When R^4 and R^5 are connected, more forcing conditions are necessary, both to complete the second step and to prevent the intermediate from proceeding to an alternate disproportionation product.[21] Alternative procedures using bis(diethylamino)phenylborane (eq 6),[26a,b] trisubstituted boroxines (eq 7),[21,27] and ethyl or butyl bis(trifluoroethyl)boronate esters (eq 8)[19e] have been developed to circumvent these problems. The substituted oxazaborolidines are more stable than unsubstituted (B-H) oxazaborolidines (i.e. they can be handled in the presence of air, and do not form dimers), but are still prone to decomposition by moisture (H_2O).[21] In many cases the substituted oxazaborolidines have been isolated, purified, and characterized.

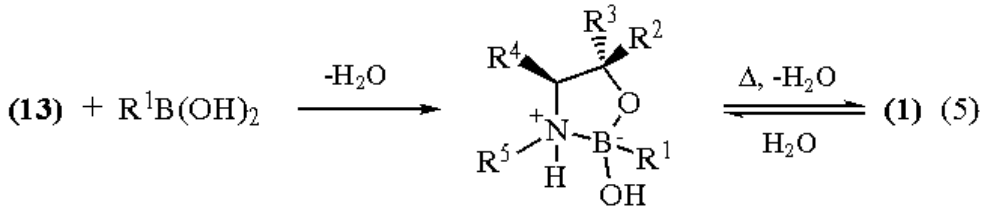

(5)

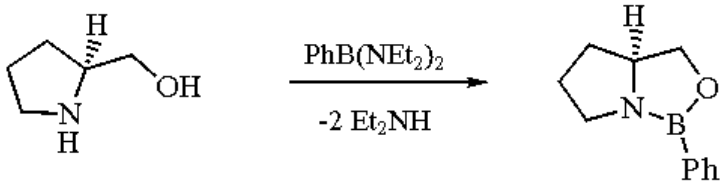

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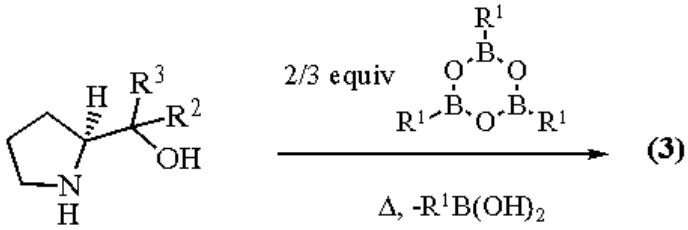

(7)

(18)

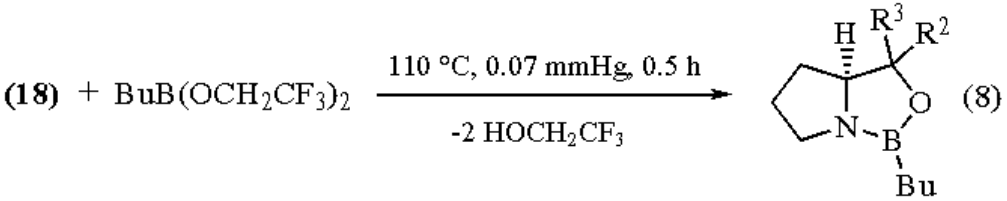

(8)

Substituted oxazaborolidines also react with borane (B_2H_6, $H_3B.THF$, or $H_3B.SMe_2$) to form an oxazaborolidine-borane complex (**19**) (eq 9).[3b,27] The oxazaborolidine-borane complex, by releasing the strain of the partial double bond between the ring boron and nitrogen, is more stable than the free oxazaborolidine, and in many cases exists as a stable crystalline solid.[21c,27,28]

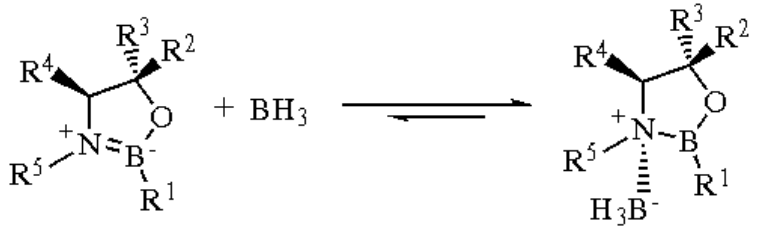

(9)

(19)

The oxazaborolidine-borane complex (**19**) can be used stoichiometrically (eq 1) or catalytically (eq 10) for the enantioselective reduction of prochiral ketones.[27a] When used catalytically, the oxazaborolidine-borane complex (**19**) is the second intermediate in the catalytic cycle (eq 10) proposed to explain the behavior of the oxazaborolidine catalyst.[3a,29] Subsequent coordination between the Lewis acidic ring boron and the carbonyl oxygen activates the ketone toward reduction. Intramolecular hydride transfer from the BH_3 coordinated to the ring nitrogen then occurs via a six-membered ring chair transition state.[17b,27a,30] Following hydride transfer, the alkoxy-BH_2 dissociates, and oxazaborolidine (**1**) is free to begin the cycle again. The diastereomeric transition state model (**20**), leading to the enantiomeric carbinol product, is disfavored due to unfavorable 1,3-diaxial steric interactions between R_L and R^1. Additional work will be required to better understand the catalytic cycle and the intermediates involved to further improve the oxazaborolidine catalysts. The behavior of the catalysts has been the subject of molecular orbital calculations in a series of 12 papers.[31] It should be noted, however, that not all of the results and conclusions are supported by experimental observations.

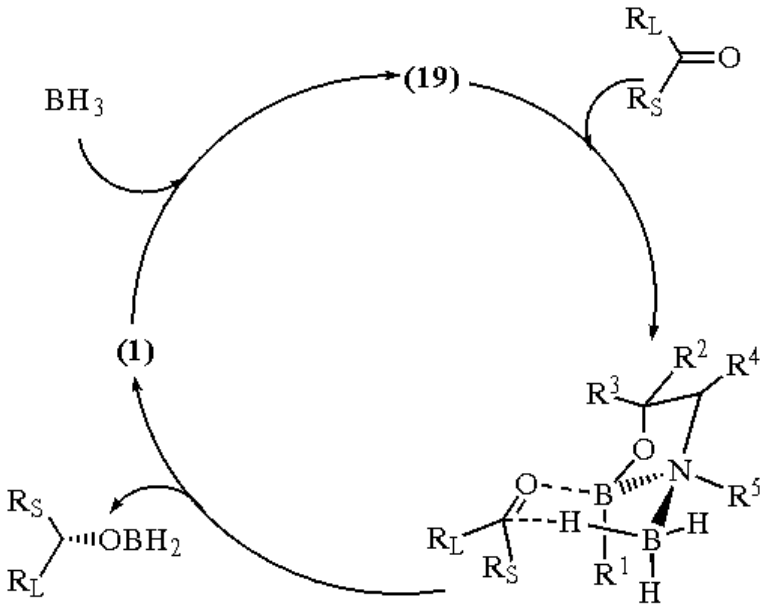

(10)

Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole

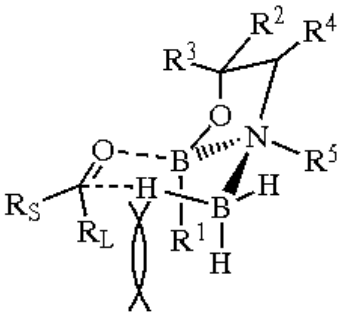

(20)

The enantioselectivities reported for the reduction of acetophenone and 1-tetralone using several representative chiral (4*S*)-oxazaborolidine catalysts are summarized in Table 1. The oxazaborolidines derived from (*S*)-azetidinecarboxylic acid and (*S*)-proline provide the best results. It is interesting to note the reversal in enantioselectivity going from catalyst (**5a**) to (**6a**).

Table 1 Chiral Oxazaborolidine Catalyzed Reduction of Acetophenone and 1-Tetralone

Catalyst	R^1	R^2,R^3	R^4 (mol %)	Catalyst (ee %)	Acetophenone (ee %)	1-Tetralone
(1a)[3a]	H	Ph	*i*-Pr	10	94.7 (*R*)	
(2a)[16d]	H	Ph		10	98 (*R*)	
(3a)[3a]	H	Ph		10	97 (*R*)	89 (*R*)
(3b)[21b]	Me	Ph		10	98 (*R*)	94 (*R*)
(3b)·BH_3[27a]	Me	Ph		5	97.6 (*R*)	99.0 (*R*)
(3b)·BH_3[27a]	Me	Ph		100	99.8 (*R*)	99.2 (*R*)
(5a)[22b]	H	Ph		10	96 (*R*)	79 (*R*)
(6a)[22b]	H	Ph		10	90 (*S*)	79 (*S*)
(7a)[18a]	H	Ph		10	87 (*R*)	
(8a)[16b]	H	Ph		10	71 (*R*)	44 (*R*)
(9a)[23]	H	H		110	88 (*R*)	
(12a)[19a]	Me	Ph		10	97.5 (*R*)	95.3 (*R*)

Oxazaborolidine catalyzed reductions are generally performed in an aprotic solvent, such as dichloromethane, THF, or toluene. When the reactions are run in a Lewis basic solvent, such as THF, the solvent competes with the oxazaborolidine to complex with the borane, which can have an effect on the enantioselectivity and/or rate of the reaction.[27a] The solubility of the oxazaborolidine-borane complex can be the limiting factor for reactions run in toluene, although this problem has been circumvented by using oxazaborolidines with more lipophilic substituents (R^1 = *n*-Bu; R^2, R^3 = 2-naphthyl).[19b-d] We have found dichloromethane to be the best overall solvent for these reactions.[27a]

The reactions are typically performed using $H_3B.THF$, $H_3B.SMe_2$, or ***Catecholborane***[19d] as the hydride source. When using $H_3B.THF$ or $H_3B.SMe_2$, two of the three hydrides are effectively utilized.[27a] This is only true for reactions run at temperatures greater than -40 °C. At lower temperatures,

only one hydride is transferred at a reasonable rate. When two hydrides are used, there is some evidence that the enantioselectivity for transfer of the second hydride is different, and may in fact be lower.[27a] Whether this implies that an alternative catalytic cycle operates, whereby the alkoxy-BH_2 intermediate generated during the first hydride transfer remains coordinated to the oxazaborolidine, and then transfers the second hydride (with a different degree of enantioselectivity), or that some other intermediate present is active, but not as an enantioselective reducing agent, will require further investigation. In any event, the amount of BH_3 used should be at least 0.5 mole per mole of ketone plus an amount equal to the oxazaborolidine catalyst, with the possibility that 1 mole per mole provides slightly higher enantioselectivity. When catecholborane is used as the hydride source, a 50-100% excess of this reagent is used.

The mode of addition and the reaction temperature both affect the enantioselectivity of the reaction. The best results are obtained when the ketone is added slowly to a solution of the oxazaborolidine (or oxazaborolidine-borane complex) and the borane source, at as low a temperature that provides a reasonable reaction rate.[27a] This is in contrast to a previous report that indicated that oxazaborolidine-catalyzed reductions lose stereoselectivity at lower temperatures.[19d] With unsubstituted (R^1 = H) oxazaborolidines, higher temperatures may be required due to incomplete formation of the catalyst, the presence of dimers, and/or other intermediates.[26c]

In their role as enantioselective catalysts for the reduction of prochiral ketones, chiral oxazaborolidines have been used for the preparation of prostaglandins,[3a] PAF antagonists,[3a] a key intermediate of ginkgolide B,[32a] bilobalide,[32b] a key intermediate of forskolin,[32c] (*R*)- and (*S*)-fluoxetine,[32d] (*R*)- and (*S*)-isopreterenol,[19c] vitamin D analogs,[33] the carbonic anhydrase inhibitor MK-0417,[21b] the dopamine D1 agonist A-77636,[20b] taxol,[34] the LTD_4 antagonists L-695,499 and L-699,392,[35] the β-adrenergic agonist CL 316,243,[36] and the antiarrhythmic MK-0499.[37] They have also been used for the synthesis of chiral amines,[38,39] α-hydroxy acids,[19d,40a] benzylic thiols,[40c] the enantioselective reduction of trihalomethyl ketones,[40a,b,d] and ketones containing various heteroatoms.[17a,21b,27a,35,37]

Enantioselective Reduction of Imines and Ketoxime *O*-Ethers.

In addition to the reduction of prochiral ketones, chiral oxazaborolidines have been employed as enantioselective reagents and catalysts for the reduction of imines (eq 11)[4,23] and ketoxime *O*-ethers (eq 12)[2e,f,5] to give chiral amines. It is interesting to note that the enantioselectivity for the reduction of ketoxime *O*-ethers is opposite that of ketones and imines. For more information, see ***2-Amino-3-methyl-1,1-diphenyl-1-butanol***.

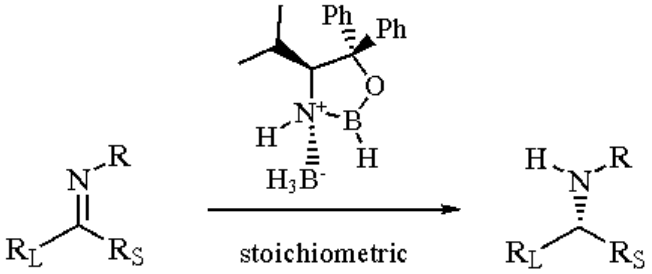

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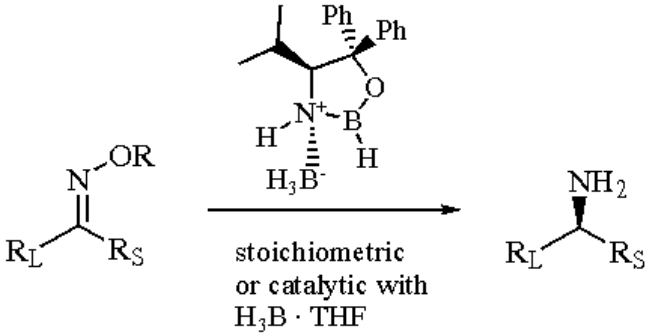

(12)

Enantioselective Addition of Diethylzinc to Aldehydes.

Oxazaborolidines derived from ephedrine have been used to catalyze the addition of ***Diethylzinc*** to aldehydes (eq 13).[7] Both the rate and enantioselectivity are optimized when R^1 = H. Aromatic aldehydes generally react faster than aliphatic aldehydes, and the enantioselectivity for aromatic aldehydes is good to excellent (86-96% ee).

Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole

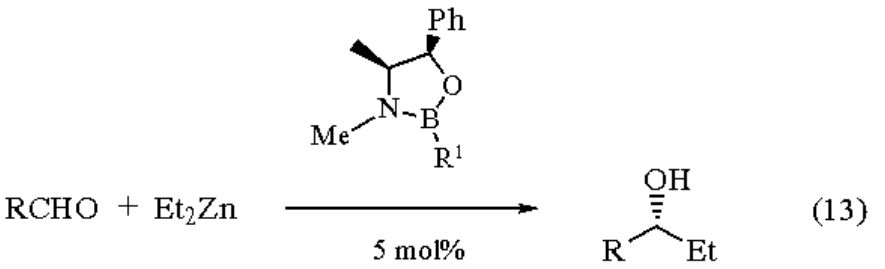

(13)

Other Applications.

Chiral oxazaborolidines derived from ephedrine have also been used in asymmetric hydroborations,[8a,b] and as reagents to determine the enantiomeric purity of secondary alcohols.[8c] Chiral 1,3,2-oxazaborolidin-5-ones derived from amino acids have been used as asymmetric catalysts for the Diels-Alder reaction,[9-11] and the aldol reaction.[12,13]

Related Reagents.

2-Amino-3-methyl-1,1-diphenyl-1-butanol; ***α,α-Diphenyl-2-pyrrolidinemethanol***; ***Ephedrine-borane***; ***Norephedrine-Borane***.

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1-(Tetrahydropyranyloxy)cyclopropanecarbaldehyde[1]

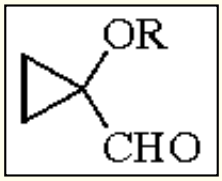

(R = THP)

[83606-32-0] · $C_9H_{14}O_3$ · 1-(Tetrahydropyranyloxy)cyclopropanecarbaldehyde · (MW 170.23) (R = TBDMS)

[90660-09-6] · $C_{10}H_{20}O_2Si$ · 1-(*t*-Butyldimethylsilyloxy)cyclopropanecarbaldehyde · (MW 200.39)

(1-hydroxycyclopropanecarbaldehyde derivatives provide readily 1-donor substituted vinylcyclopropanes, which can undergo ring expansions selectively to four- to eight-membered rings)

Solubility: sol usual organic solvents (ether, THF, CH_2Cl_2).

Purification: by chromatography on silica gel.

Preparative Methods: acyloin condensation of succinic esters by ***Sodium*** in the presence of ***Chlorotrimethylsilane*** provides 1,2-disilyloxycyclobutene.[2] One-pot bromination in CH_2Cl_2 at -10 °C and addition of ice-water gives the 1-hydroxycyclopropanecarboxylic acid.[3] Successive esterification (MeOH, ***Thionyl Chloride***), *O*-protection (***3,4-Dihydro-2H-pyran***, ***Pyridinium p-Toluenesulfonate***.[4] or ***t-Butyldimethylchlorosilane***[5]), reduction with ***Lithium Aluminum Hydride***, and finally oxidation with ***Pyridinium Dichromate***,[6] ***Pyridinium Chlorochromate***,[7] or ***Dimethyl Sulfoxide-Oxalyl Chloride***[8] produce the expected aldehyde in high yields (eq 1).[3b,9]

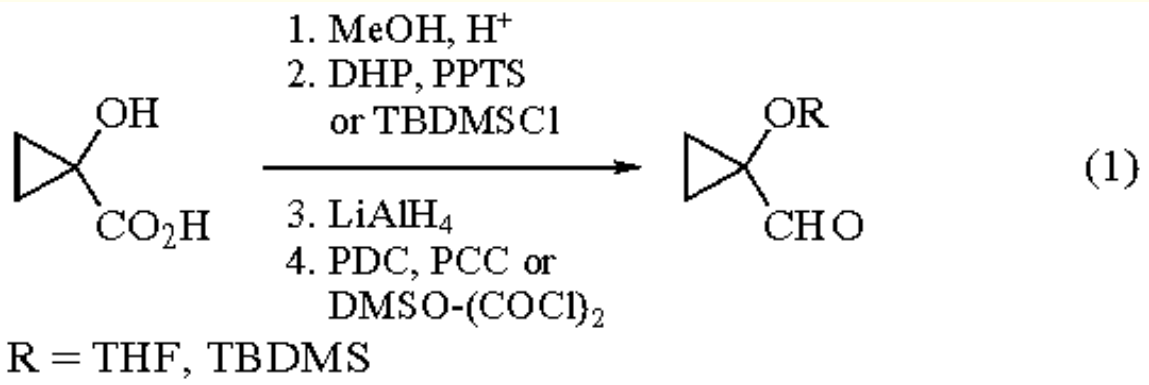

Other routes involve cyclopropanone cyanohydrin as intermediate,[10] or ring closure of 2-chloropropionaldehyde cyanohydrin ethoxyethyl ether with ***Sodium Hexamethyldisilazide***.[11]

Optically active (1*S*,2*R*)- and (1*R*,2*S*)-1-*t*-butyldimethylsilyloxy 2-methylcyclopropanecarbaldehydes (>95% ee) have been prepared by acyloin cyclization of (*R*)- and (*S*)-dimethyl 2-methylsuccinate obtained by enzymatic resolution.[12]

Handling, Storage, and Precautions: must be stored in the absence of oxygen to avoid oxidation into cyclopropanecarboxylic acid. Cleavage of the protective group leads to 2-hydroxycyclobutanone.[1]

Ring Expansions to 2-Vinylcyclobutanones.

Addition of ***Vinylmagnesium Bromide*** and deprotection (PPTS, EtOH)[13] lead to 1-(1-hydroxycyclopropyl)allyl alcohol, which undergoes quantitative C_3 -> C_4 ring expansion to 2-vinylcyclobutanone upon addition of a catalytic amount of ***Boron Trifluoride Etherate*** (eq 2).[3b]

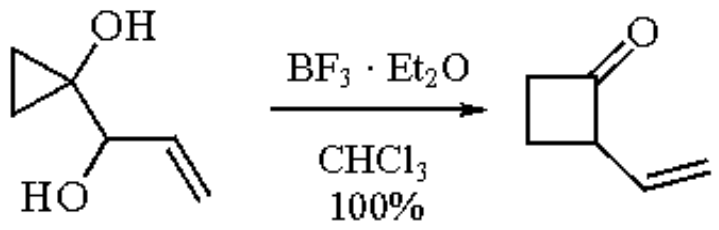

(2)

This rearrangement provides a new synthesis of 2-vinylcyclobutanones;[3b,13,14] these versatile building blocks can undergo further ring expansions leading to five-, six-, or eight-membered ring derivatives in acid, base, thermally, or photochemically induced ring rearrangements.[1b]

Optically active 2-vinylcyclobutanones have been prepared by regio- and stereoselective rearrangement and used in the total synthesis of natural γ-lactones (eq 3).[12]

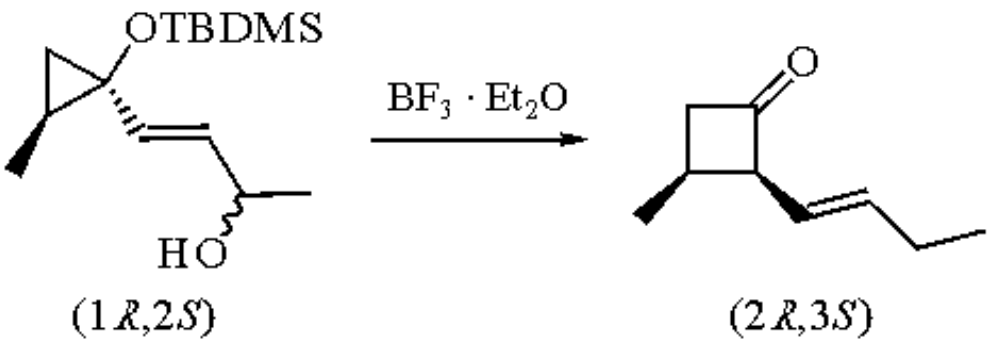

(3)

2-Alkynylcyclobutanones have been also obtained from ring expansion induced by ***Lithium Chloride***.[9b]

C_3 -> C_5 Ring Expansions to Silylated Cyclopentanone Enol Ethers.

Alkenations of the aldehyde (Wittig reaction or successive aldolization and dehydration) provide, after cleavage of the THP group[4] and *O*-silylation,[15] 1-silyloxyvinylcyclopropane derivatives which undergo the thermal vinylcyclopropane-cyclopentane rearrangement[16] to cyclopentanone silyl enol ethers, regioselectively, either on heating neat in a sealed tube or by flash vacuum thermolysis (FVT) (eqs 4-6).

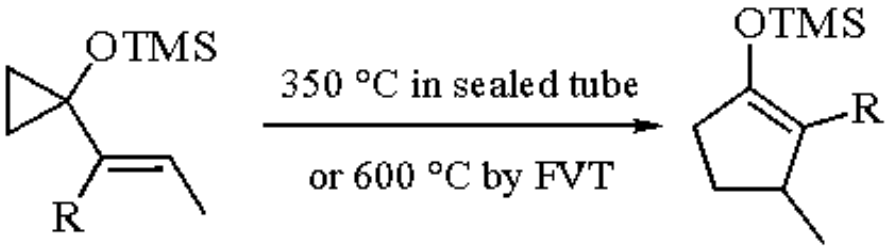

(4)

R = H, 100%; C_5H_{11}, 96%

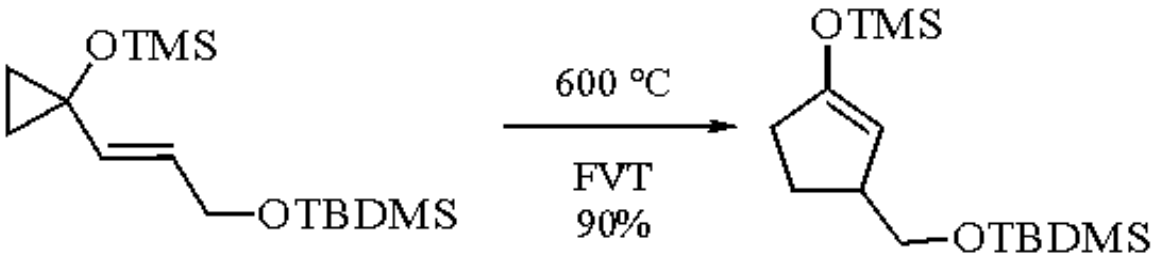

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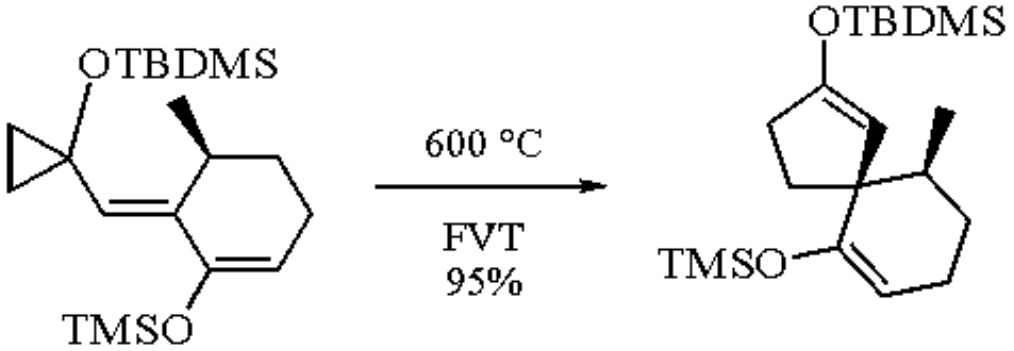

(6)

Total syntheses of *cis*-jasmone and dihydrojasmone[9a] (important raw material as a perfume ingredient), dicranenone A[17] (a new antimicrobial fatty acid containing a cyclopentanone ring), and the spirovetivane framework[9c] (found in sesquiterpenes of the spirovetivane and acorane class) have been performed by the thermal ring enlargement of these readily available vinylcyclopropanes.

Other recent applications of this aldehyde involve the synthesis of eicosanoid compounds[18] (5-lipoxygenase inhibitors), the enantioselective total syntheses of (*R*)-(+)-dodecan-5-olide, and (*S*)-(+)- and (*R*)-(-)-dihydrofuran-2(3*H*)-ones.[19]

Related Reagents.

Cyclobutanone; ***Cyclopropanone***; ***Cyclopropyldiphenylsulfonium Tetrafluoroborate***; ***1-Ethoxycyclopropanol***; ***1-Ethoxy-1-(trimethylsilyloxy)cyclopropane***; ***1-Lithio-1-methoxycyclopropane***.

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3-Tetrahydropyranyloxy-1-propyne

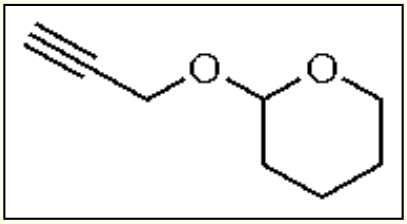

[6089-04-9] · $C_8H_{12}O_2$ · 3-Tetrahydropyranyloxy-1-propyne · (MW 140.20)

(lithium derivative useful as a synthon for preparation of substituted propargylic alcohols;[1] preparation of α-allenic alcohols;[2] synthesis of *trans*-allylic alcohols[3])

Alternate Name: tetrahydro-2-(2-propynyloxy)-2*H*-pyran.

Physical Data: bp 63-65 °C/9 mmHg, 47-50 °C/3.5-5 mmHg; *d* 0.997 g cm^{-3}.

Solubility: insol H_2O; sol benzene, chloroform, 1,2-dichloroethane, ethanol, ether, acetone, dioxane, THF.

Form Supplied in: colorless liquid; commercially available.

Purification: dried over sodium carbonate and distilled under reduced pressure.

Handling, Storage, and Precautions: combustible liquid; harmful if inhaled, or absorbed through skin; causes severe irritation. The THP ether is stable to base but is hydrolyzed by acids or magnesium sulfate, and should be stored under nitrogen in the refrigerator.

Synthesis of Substituted Propargylic Alcohols.

The 2-tetrahydropyranyl (THP) ether of propargyl alcohol can be metalated to form the lithium or magnesium acetylide, which reacts with various electrophiles (eqs 1-7)[1] such as alkyl tosylates,[4] alkyl halides,[5] oxiranes,[6] chloroformates,[7] orthoformates,[8] aldehydes,[9] and ketones.[10] The products have been used to synthesize juvenile hormone (JH-I) (eq 1)[4] and other natural products (eqs 2 and 3).[5,6] Hydroxyalkynoates and protected alkynals are obtained by reactions with chloroformate and orthoformate (eqs 4 and 5).[7,8] Reactions of lithiated propargyl THP ether with ketones or aldehydes provide 2-butyne-1,4-diol derivatives,[9-13] as exemplified in synthetic routes toward (±)-eupenoxide (eq 6)[11] and a benzoquinone (eq 7).[12] Coupling reactions with vinyl halides provide precursors of enediynes (eq 8).[13]

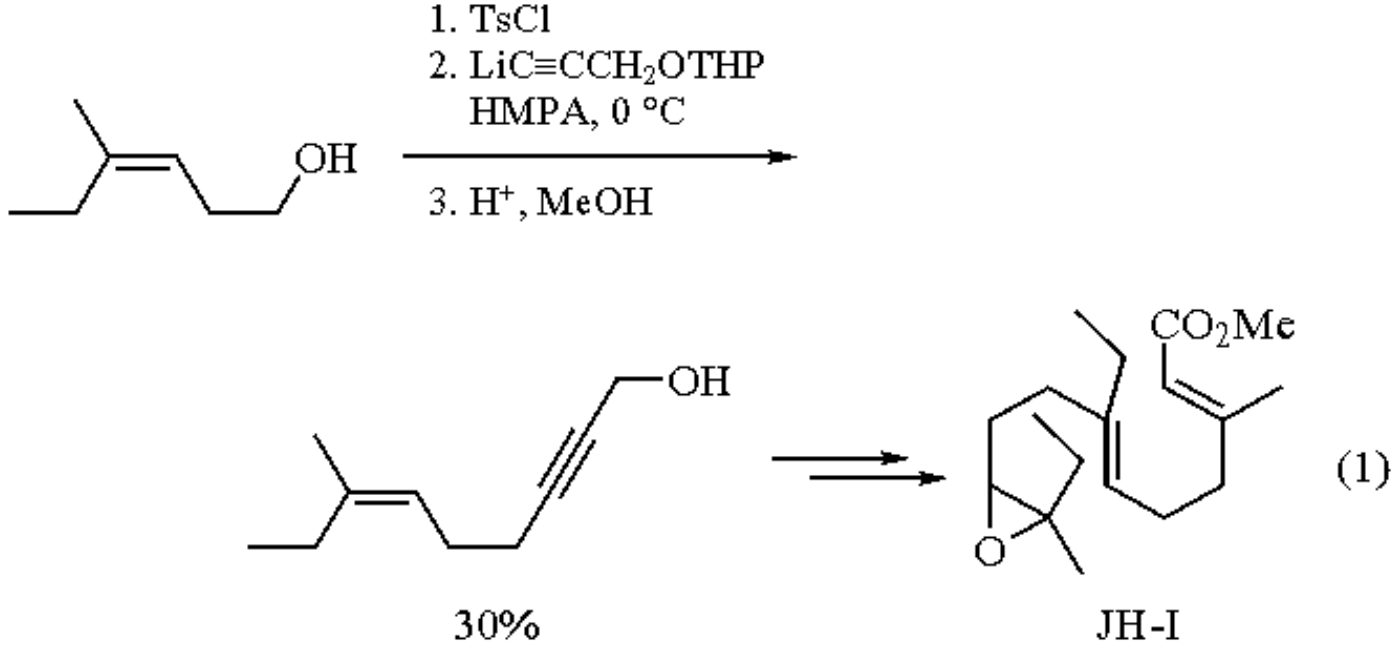
1. TsCl
2. LiC≡CCH2OTHP
HMPA, 0 °C
3. H+, MeOH
OH
OH
CO2Me
O
30%
JH-I
(1)

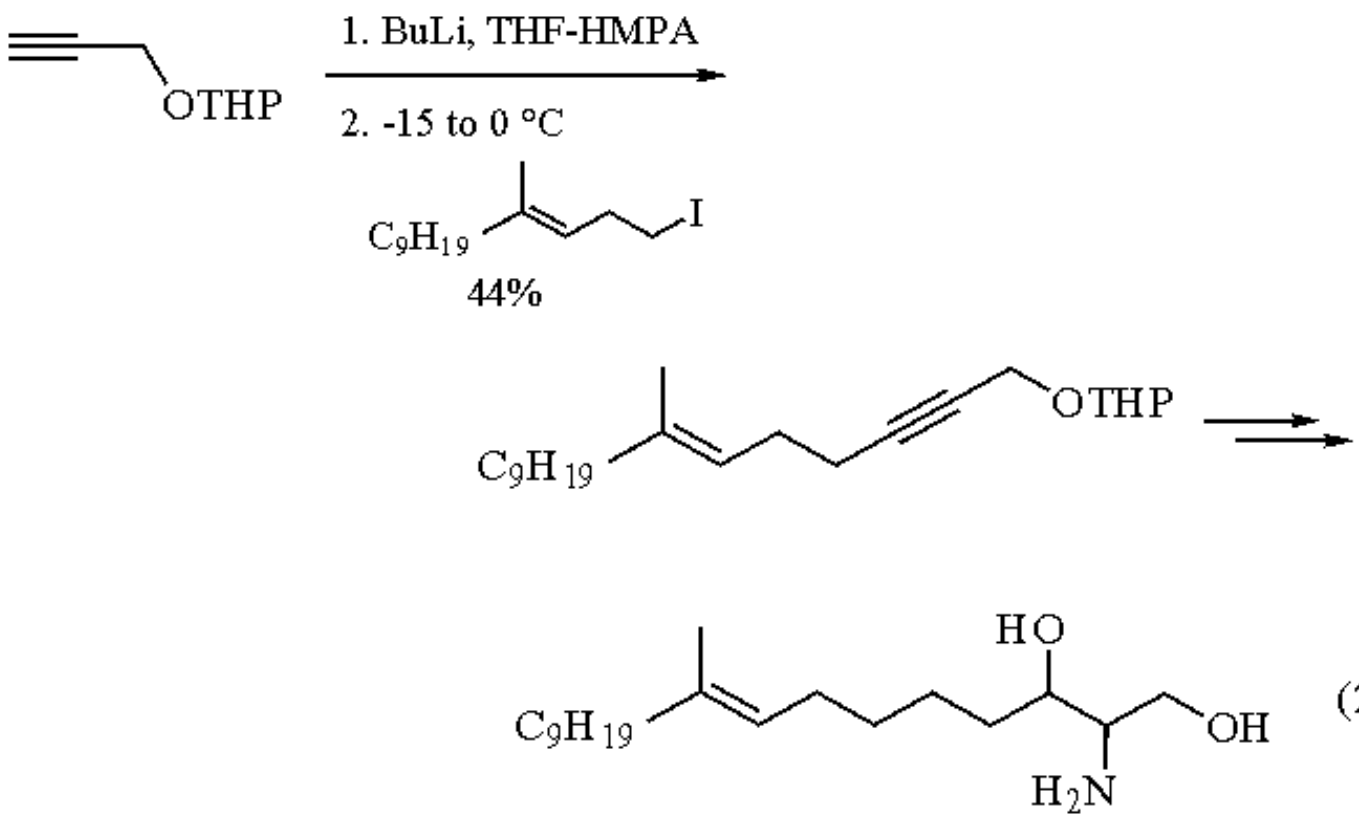
OTHP
1. BuLi, THF-HMPA
2. -15 to 0 °C
C9H19
I
44%
C9H19
OTHP
HO
C9H19
OH
H2N
(2)

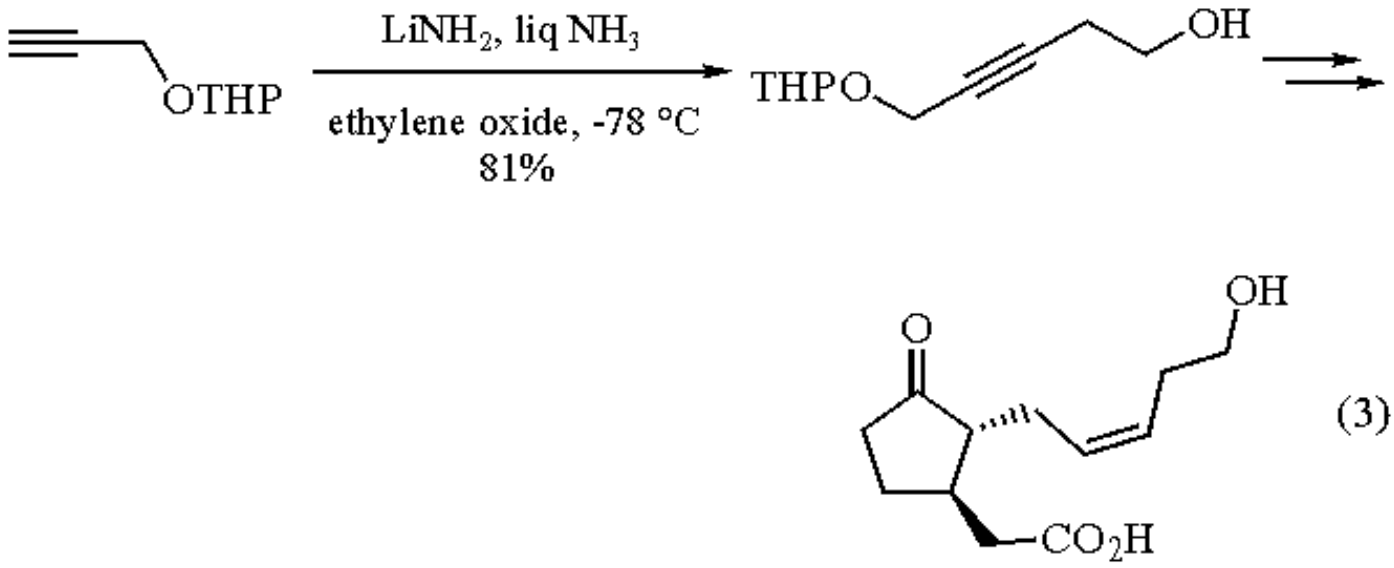

(3)

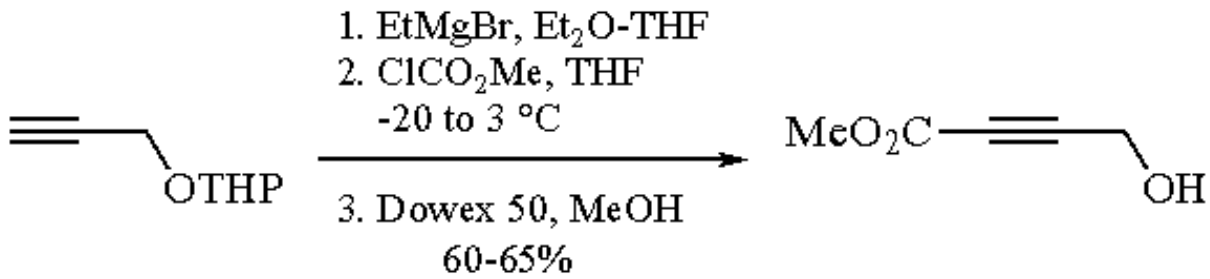

(4)

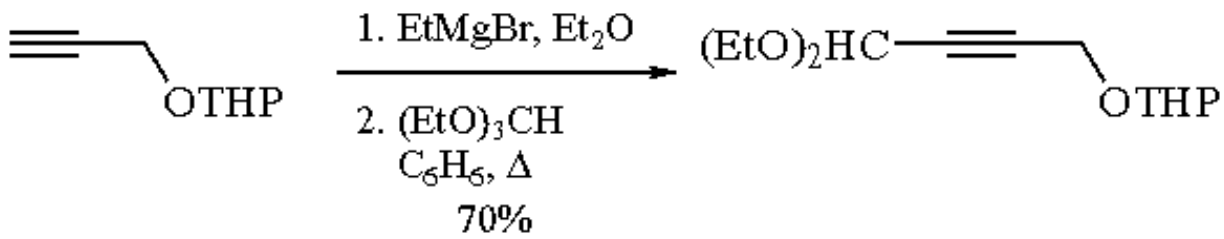

(5)

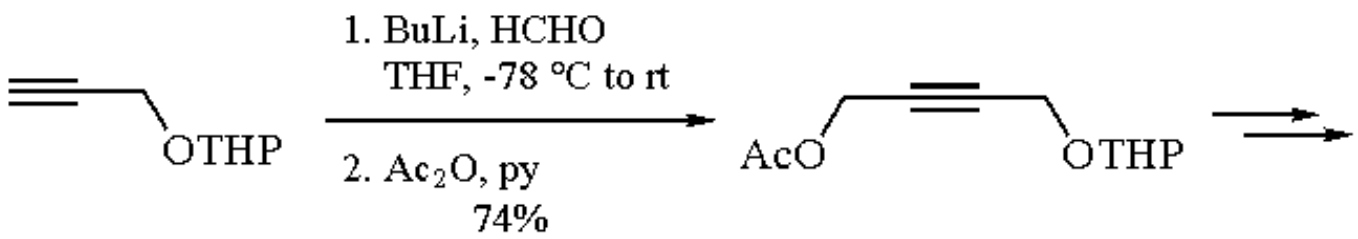

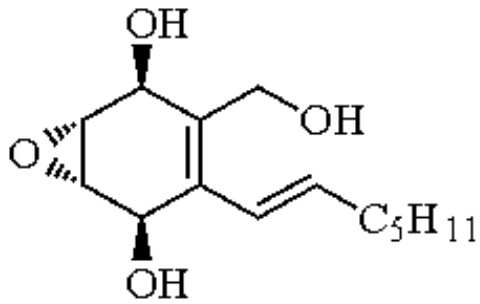

(6)

(±)-Eupenoxide

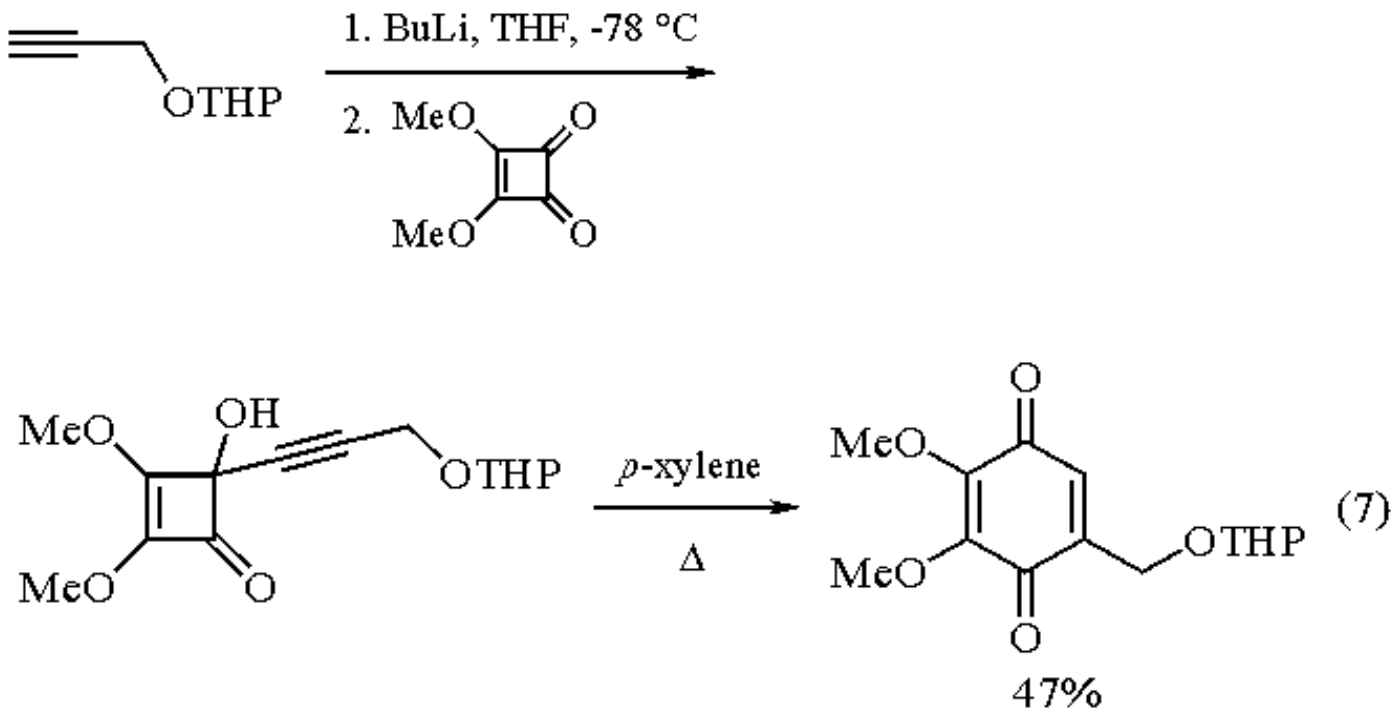

Reduction of the resulting 2-butyne-1,4-diol mono-THP ethers with ***Lithium Aluminum Hydride*** gives α-allenic alcohols (eq 9).[2,14,15] In contrast, Birch reduction of similar substrates gives *trans*-2-butene-1,4-diol mono-THP ethers (e.g. eq 10).[9] Reaction with cuprates affords a mixture of alkylated allenyl and propargyl alcohols (eq 11).[16]

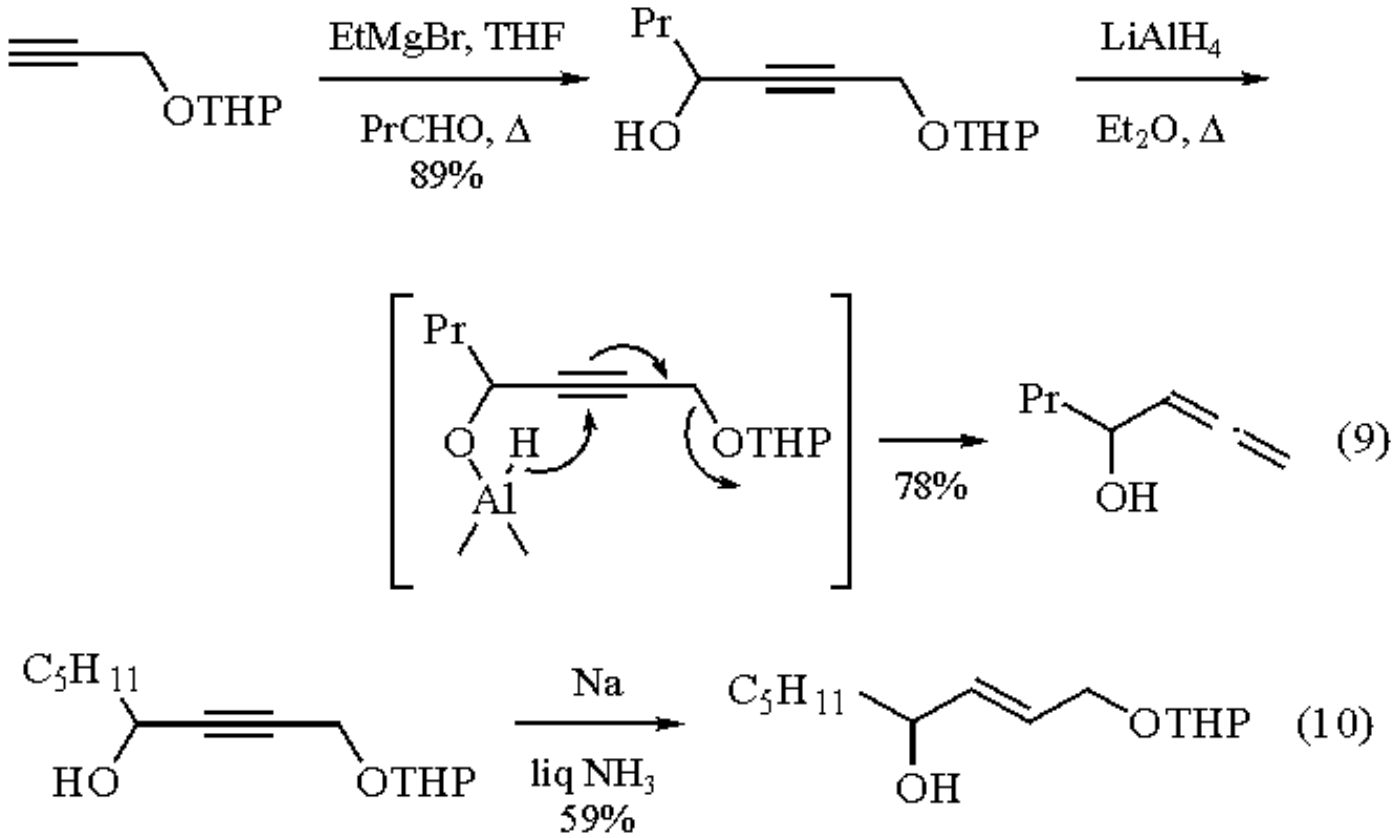

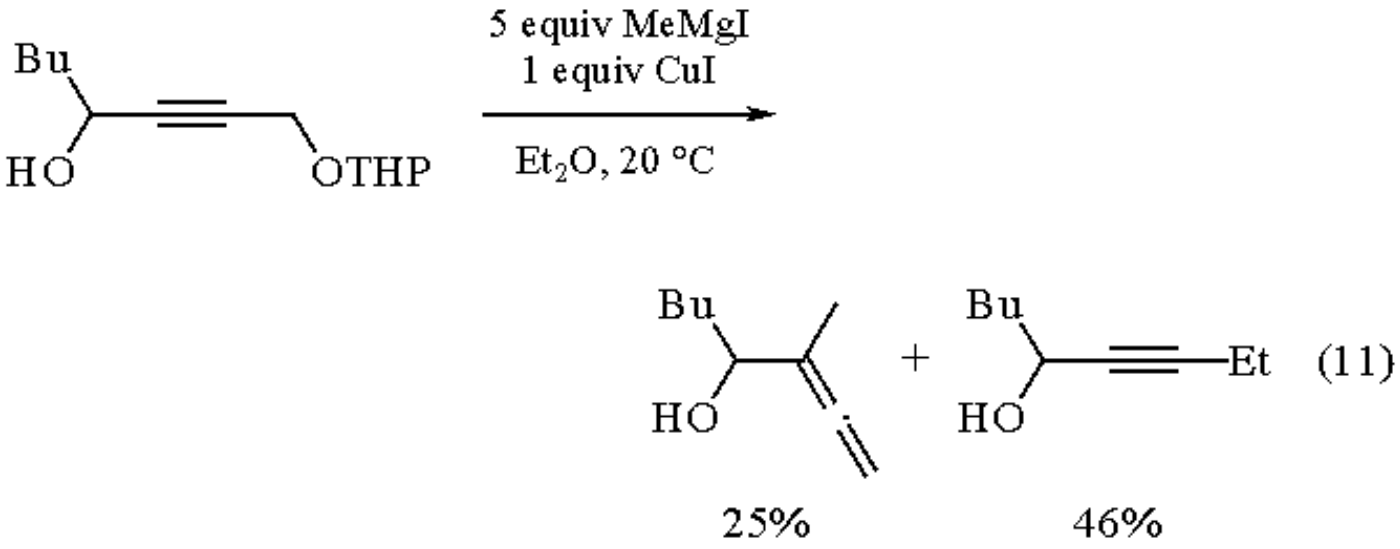

Synthesis of *trans*-Allylic Alcohols via Organotin Reagent.

Radical mediated hydrostannylation of propargyl THP ether gives a vinylstannane which serves as a precursor to the corresponding alkenyllithium reagent (eq 12).[3] The corresponding organocopper compound undergoes conjugate addition to cyclopentenones through a mixed cuprate; this sequence has been applied to the synthesis of 11-deoxyprostaglandin E_2 (eq 13).[3] Cyclic 1,5-dienes are obtained by alkylation of the lithium reagent with α,o-dibromoalkanes followed by deprotection, bromination, and reductive coupling with ***Tetracarbonylnickel*** (eq 13).[3,17]

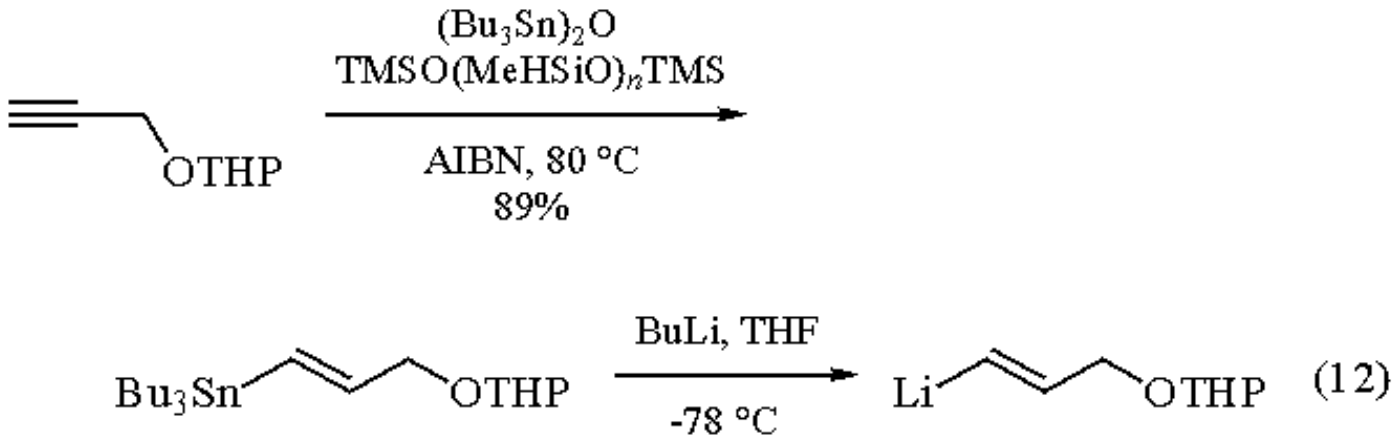

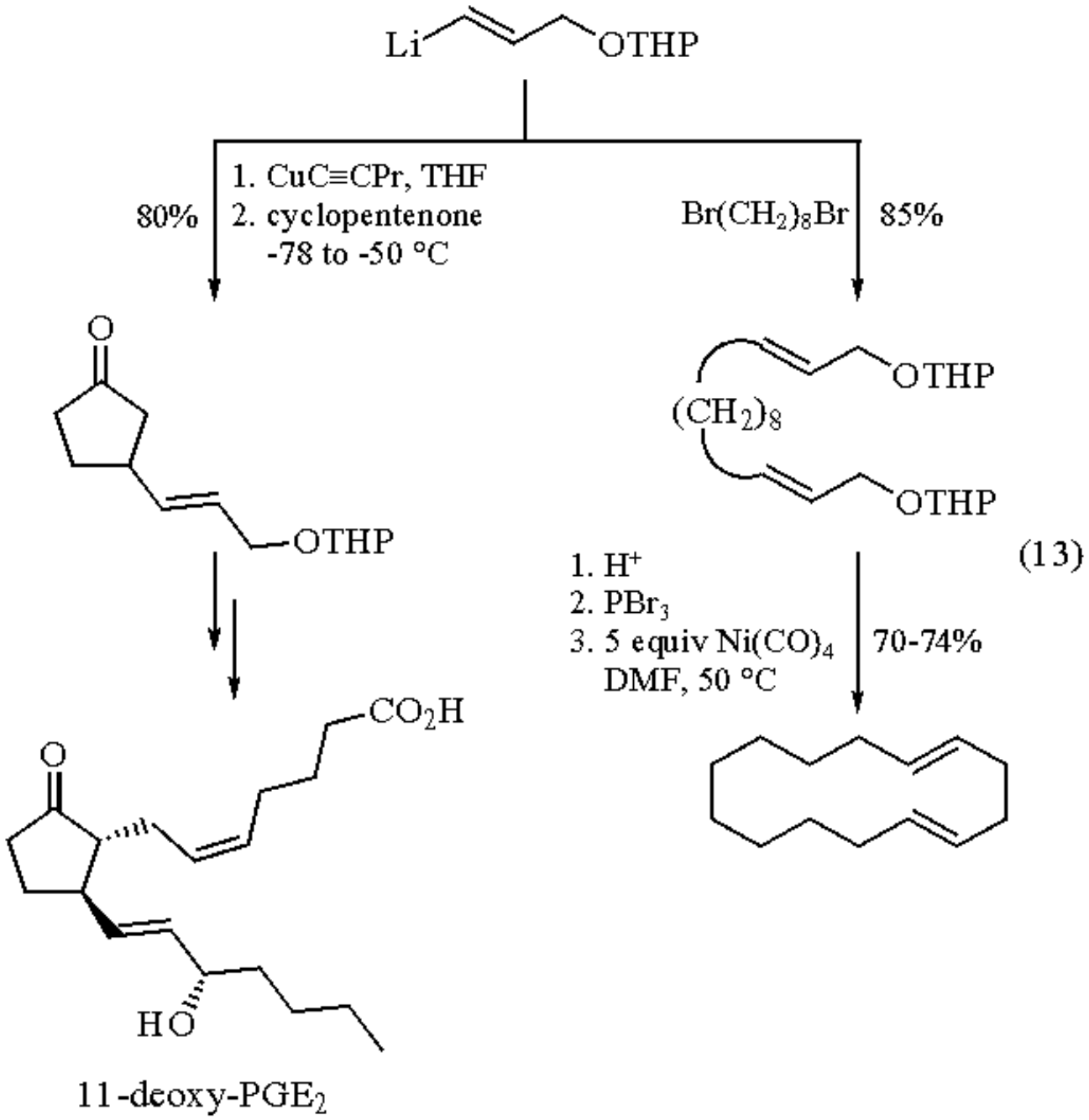

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3-Tetrahydropyranyloxy-1-trimethylsilyl-1-propyne[1]

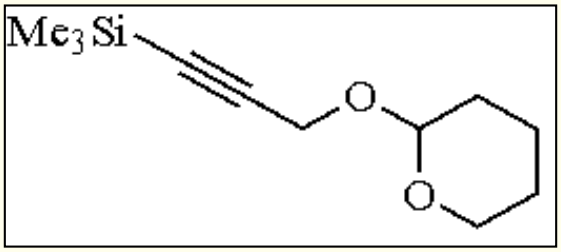

[36551-06-1] · $C_{11}H_{20}O_2Si$ · 3-Tetrahydropyranyloxy-1-trimethylsilyl-1-propyne · (MW 212.40)

(metal derivative is used for 1-alkoxypropargylation;[2,3] used in synthesis of functionalized vinylsilanes[4])

Physical Data: bp 108 °C/11 mmHg; *n*20D 1.4630.[2]

Solubility: sol THF, ether, and most organic solvents.

Preparative Methods: from 2-propynol via tetrahydropyranyl ether formation, deprotonation, and trimethylsilylation;[2,5,6] from 3-trimethylsilylpropynol via tetrahydropyranyl ether formation.[4]

Handling, Storage, and Precautions: store in the absence of air and moisture.

Alkoxypropargylation.

The ambident character of the propargylic anion, which may be in equilibrium with the allenic form, is responsible for its limited use in synthesis. In general the structure and reactivity of the ambident anion depend on the nature of the substrate, the counter cation, and the solvent.[7,8] There is also an *erythro-threo* stereoselectivity problem when alkylated propargylic anions react with aldehydes or unsymmetrical ketones. In contrast, the zinc and titanium reagents derived from the title compound possess the allenic structure and, upon reaction with aldehydes, lead almost exclusively to the β-acetylenic alcohol (eq 1), presumably by a chelate transition state (S_Ei' process).[3,5] The reaction also leads preferentially to the *erythro* diastereomer. The stereoselectivity is highest with titanium as the metal and THF as the solvent.[6,9]

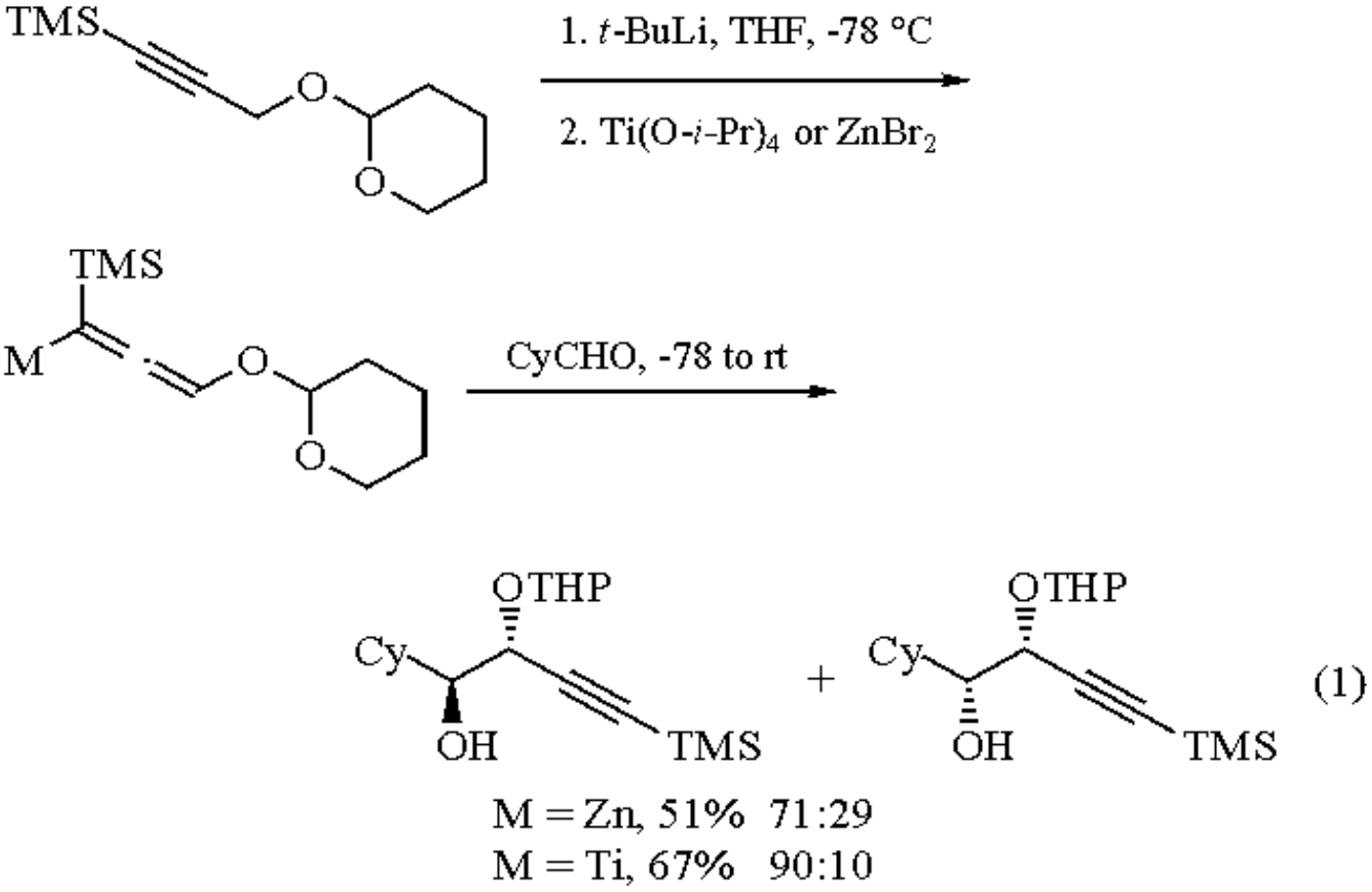

Whereas the titanium reagent is not reactive towards ketones, the zinc derivative has been found to react even with sterically encumbered ketones, such as 17-keto steroids, to yield the β-acetylenic alcohol in good yield (75%).[2]

Synthesis of Vinylsilanes.

The title compound can be used in reductive alkylation sequences for the synthesis of functionalized vinylsilanes with high isomeric purity (eq 2). One sequence consists of a regioselective *cis*-hydroboration, transmetalation, and carbodemetalation.[4,10] In another sequence, ***Diisobutylaluminum Hydride*** reduction-bromination leads to brominated vinylsilanes,[11] which can be further transformed via halogen-metal exchange, followed by reaction with iodides,[12] or with aldehydes and ketones.[13]

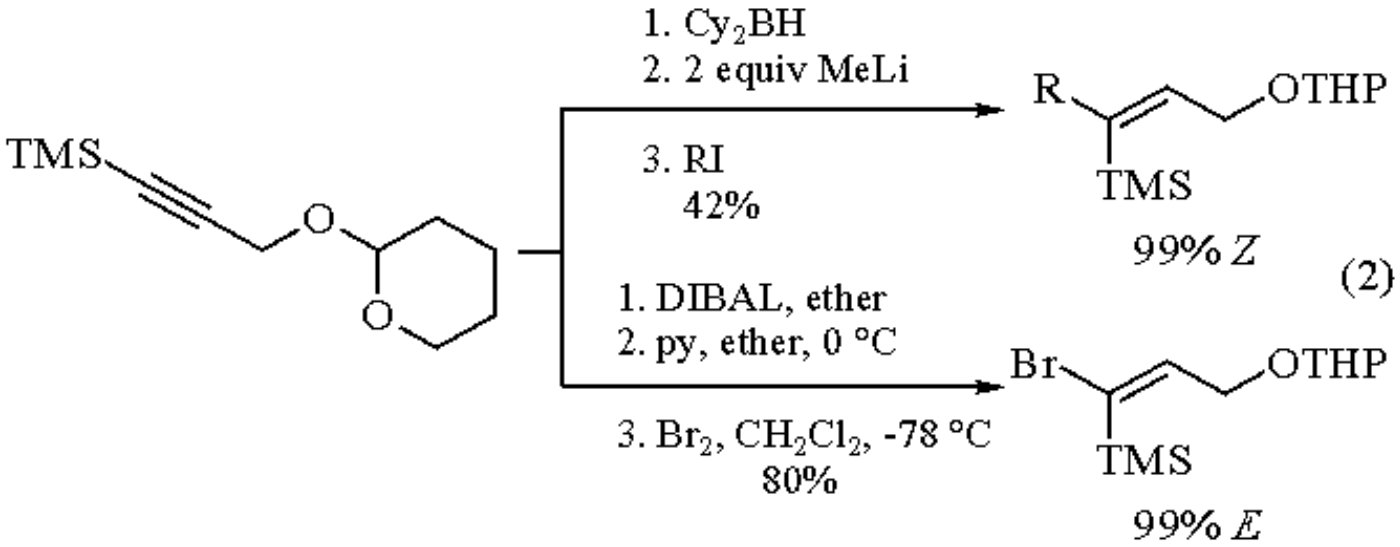

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11. Zweifel, G.; Lewis, W. *JOC* **1978**, *43*, 2739.
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Tetrakis(acetonitrile)copper(I) Perchlorate

$(MeCN)_4Cu^+ ClO_4^-$

[14057-91-1] · $C_8H_{12}ClCuN_4O_4$ · Tetrakis(acetonitrile)copper(I) Perchlorate · (MW 327.24)

(catalyst for Ullmann reaction,[1] cyclopropanation,[4,5] ring expansions of cyclic and cyclopropyl ketones,[2,3] aziridine formation;[7] precursor of other complex catalysts[6])

Physical Data: white crystals that decompose slowly in moist air;[9] mp 164-166 °C;[9] IR ν 2270 (CN), 1092, 622 (ClO_4^-) cm^{-1}.[10]

Solubility: sol toluene, CH_2Cl_2, MeCN.

Form Supplied in: prepared as needed.

Analysis of Reagent Purity: gravimetric determination[9] or EDTA titration[10] of Cu; perchlorate analysis via the tetraphenylarsonium salt.[10]

Preparative Methods: several available, e.g. modification of the known hexafluorophosphate procedure,[11] reaction of ***Copper(I) Oxide*** and ***Acetonitrile*** in perchloric acid,[12] the combination of $CuClO_4$ and MeCN in 2-butanol,[10] and refluxing $Cu(ClO_4)_2$ in MeCN with excess copper powder[9] or turnings.[2]

Purification: can be recryst from MeCN and dried under nitrogen in vacuo at 80 °C for 12 h.[13,14]

Handling, Storage, and Precautions: irritant; moisture sensitive; handle under inert atmosphere. Occasional mild explosions have been reported with dry organic perchlorate salts.[10] Use in a fume hood.

Ullmann Condensation Catalyst.

The title reagent eliminates the induction period in the Ullmann condensation reaction of 1-bromoanthraquinone with 2-aminoethanol. The Cu^I catalyst is first oxidized to a Cu^{II} species by electron transfer from Cu^I to the haloanthraquinone; this Cu^{II} species increases the catalytic activity of the Cu^I catalyst (eq 1).[1]

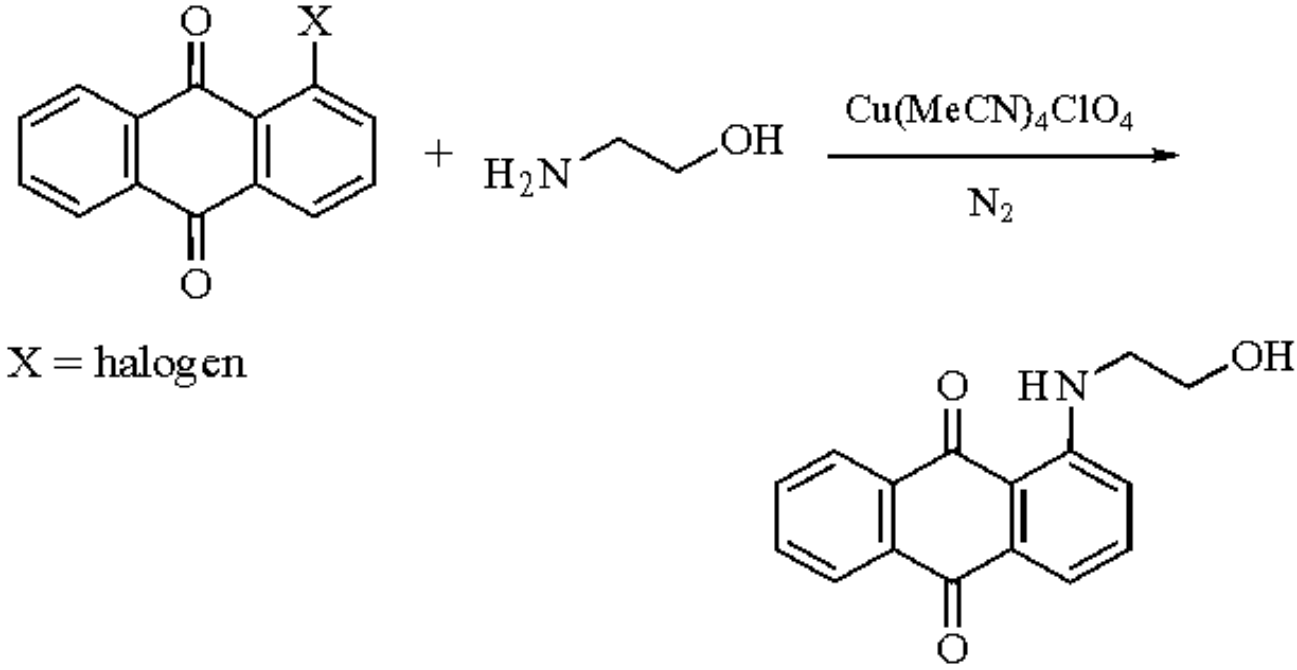

Ring Expansions of Ketones.

The reagent can react with the adducts formed from acyclic or cyclic cyclopropyl ketones and tris(methylthio)methyllithium (see ***Tris(methylthio)methane***); the products have been rationalized via the intervention of epoxide intermediates.[2,3] With acyclic cyclopropyl ketones, C-O epoxide bond cleavage occurs selectively, leading to a cyclopropylcarbinyl carbocation intermediate and subsequent thiomethyl group migration. With more sterically restricted substrates (eq 2), alternative C-O bond cleavage competes.[2]

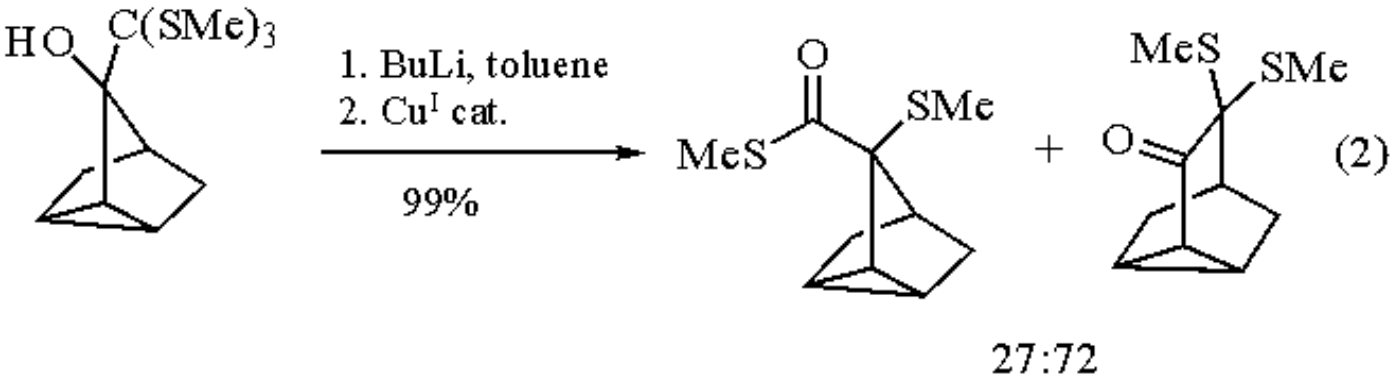

Cyclopropanations.

$Cu(MeCN)_4ClO_4$ can catalyze the cyclopropanation of tetramethylethylene (TME) with ***Ethyl Diazoacetate*** (EDA).[4] High TME/EDA and EDA/catalyst ratios, longer addition periods, and high reaction temperatures increase the product yield.

The reagent has been used to synthesize bis(oxazoline)copper(I) complexes that exhibit high enantioselectivity (up to 94% ee) in the catalytic cyclopropanations of trisubstituted and unsymmetrical *cis*-1,2-disubstituted alkenes.[5] The use of diazoacetates with steric bulk (e.g. R = (-)-menthyl, dicyclohexylmethyl, di- and trimethylpentyl) (eq 3) gives *trans:cis* product ratios as high as 99:1.

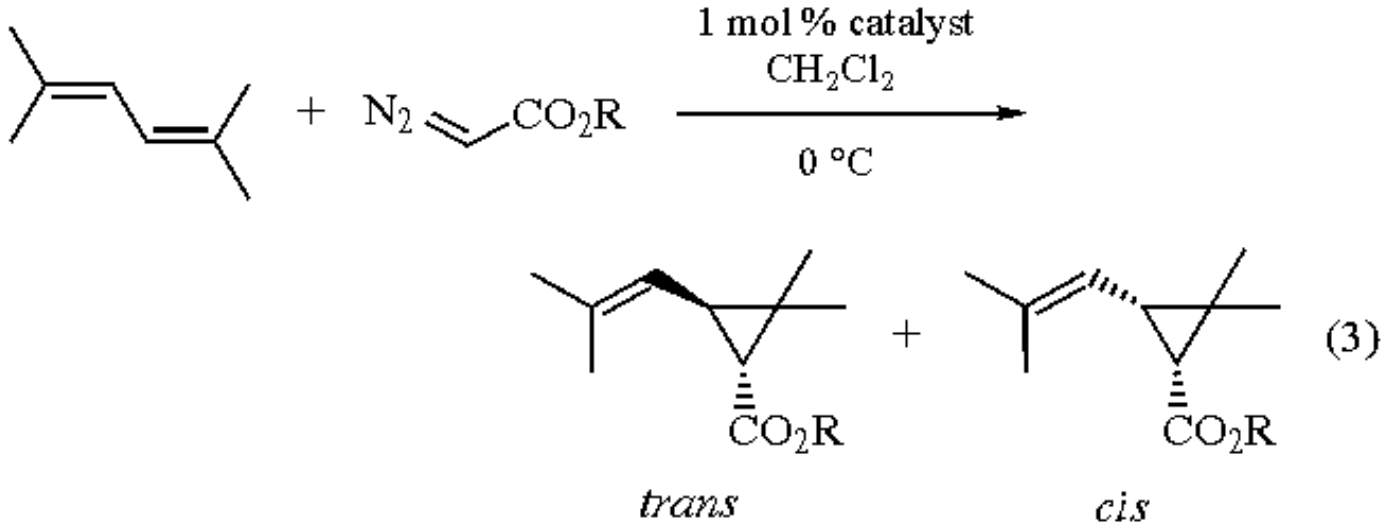

Aziridination Catalyst.

Using PhI=NTs as a nitrene precursor, alkenes are converted to aziridines with $Cu(MeCN)_4ClO_4$ as catalyst (eq 4).[7]

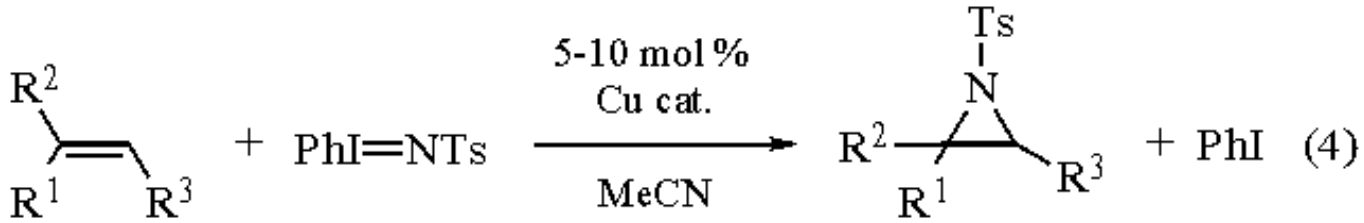

Other Reactions.

This copper(I) complex can serve as the precursor of other synthetically useful catalysts. For example, the addition reaction of tetrachloromethane to 1,5-hexadiene is catalyzed by a copper(I)-butylamine complex[6] prepared from the title reagent. $Cu(MeCN)_4ClO_4$ also catalyzes the intramolecular cycloadditions of ketones with nitrogen heterocycles bearing α-carbonitrile functionality, as illustrated with pyridine-2-carbonitrile (pyCN) (eq 5).[8]

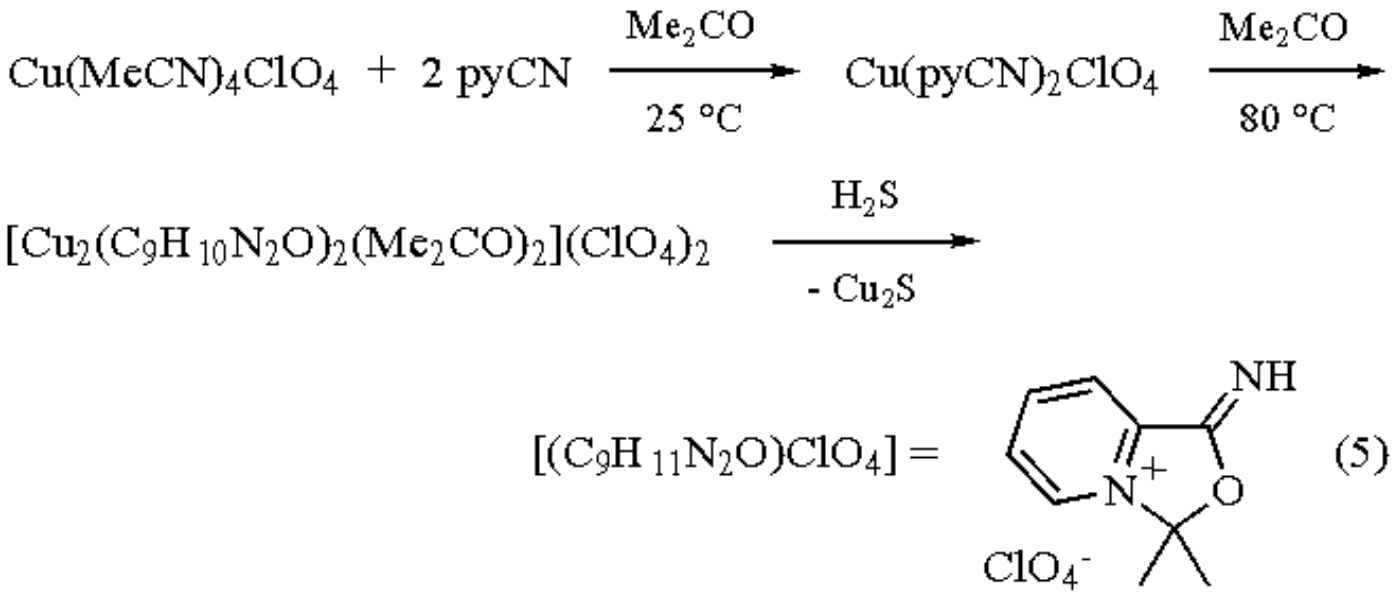

Related Reagents.

Tetrakis(acetonitrile)copper(I) Tetrafluoroborate; ***Tetrakis(pyridine)copper(I) Perchlorate***.

1. Arai, S.; Hida, M.; Yamagishi, T.; Ototake, S. *BCJ* **1977**, *50*, 2982.
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Tetrakis(acetonitrile)copper(I) Tetrafluoroborate

$(MeCN)_4Cu^+ BF_4^-$

[15418-29-8] · $C_8H_{12}BCuF_4N_4$ · Tetrakis(acetonitrile)copper(I) Tetrafluoroborate · (MW 314.60)

(catalyst in Diels-Alder[3] and Ullmann[5] reactions, intramolecular aromatic annulations,[6,7] ring expansions in steroids[8])

Physical Data: white crystals that decompose slowly in moist air[9] to a greenish solid;[10] mp 159-161 °C, dec 270 °C[9] (161-171 °C, sealed tube;[10] 167-169 °C with decomposition[11]); *d* 1.466 g cm^{-3};[10] IR ν 2270, 2290 (CN) cm^{-1}.[9]

Solubility: sol toluene, CH_2Cl_2, MeCN.

Form Supplied in: prepared as needed.

Analysis of Reagent Purity: gravimetric determination of Cu.[9]

Preparative Methods: several available, e.g. modification of the known hexafluorophosphate procedure,[12] addition of ***Acetonitrile*** to the $CuBF_4$-toluene complex,[10] and treatment of ***Copper(I) Oxide*** with ***Boron Trifluoride Etherate*** in MeCN.[11]

Purification: can be recryst from hot MeCN and dried in vacuo at 80 °C for 12 h.[13]

Handling, Storage, and Precautions: irritant; moisture sensitive; handle under inert atmosphere. Use in a fume hood.

Precursor of Redox Catalysts.

Autoxidation of $Cu(MeCN)_4BF_4$ in DMSO, followed by treatment with dioxane, gave $[Cu_2(O)(DMSO)_4(dioxane)]^{2+}$ $2BF_4^-$, a versatile redox catalyst which promotes the oxidation of 2,6-xylenol, benzoin, and 3,5-di-*t*-butylcatechol to poly(2,6-dimethyl-1,4-phenylene ether), benzil, and 3,5-di-*t*-butyl-*o*-benzoquinone, respectively (eq 1).[1,2,4]

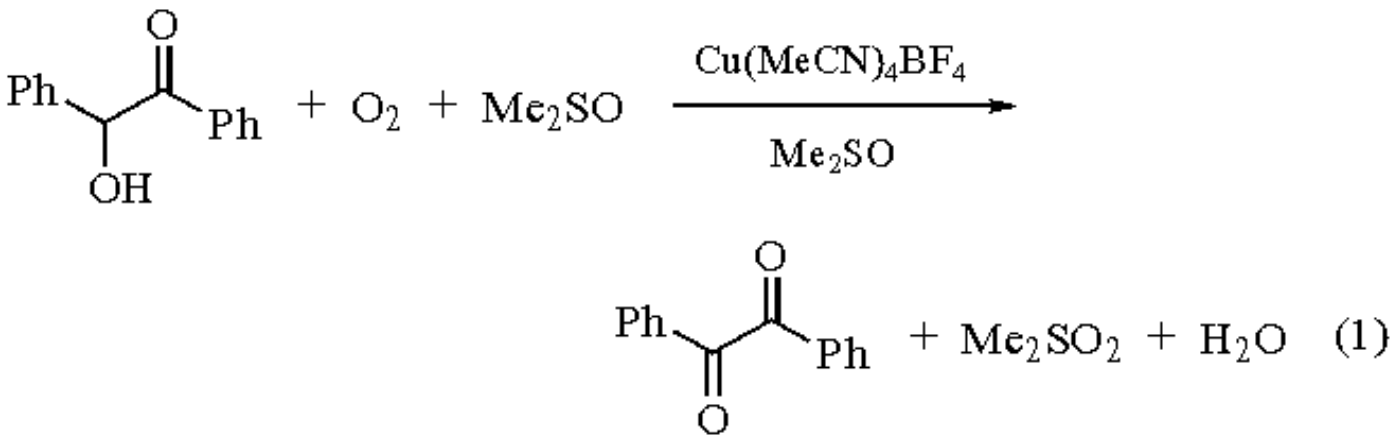

Catalyst for Organic Reactions.

The reagent $Cu(MeCN)_4BF_4$ catalyzes the Diels-Alder reactions of acrylic monomers with furan (eq 2).[3] Lewis acids such as $FeCl_3$, $SnCl_4$, and $ZnCl_2$ led to polymeric products. Many strongly activated dienophiles which are unreactive toward furan in the presence of $Cu(BF_4)_2$-hydroquinone, successfully reacted using the acetonitrile complex. Reactions can be performed at comparatively low temperature (34 °C) without the need for high-pressure apparatus.

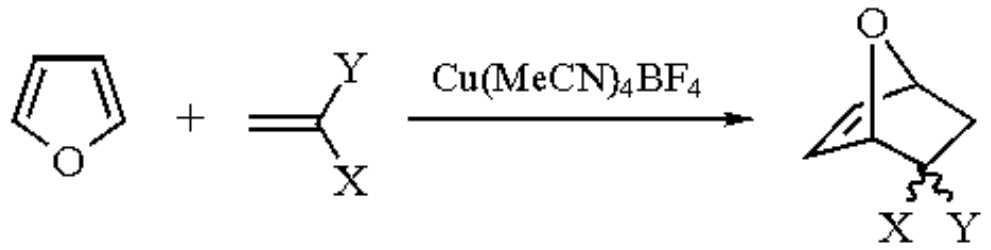

(2)

The title reagent is also responsible for the catalysis of the Ullmann amination of halogenoarenes, the replacement of halogen attached to aromatic nuclei by amines (or ammonia) in the presence of copper salts.[5] Electron-transfer processes and radical formation are mechanisms suggested in discussion of amination and other copper-assisted nucleophilic aromatic substitutions (also see ***Tetrakis(acetonitrile)copper(I) Perchlorate***).

Aromatic Annulation.

As a Lewis acid, $Cu(MeCN)_4BF_4$ promotes cyclization of o-aryl-1,1,1-tris(phenylthio)alkanes, e.g. 4-(*m*-methoxyphenyl)-1,1,1-tris(phenylthio)butane, to the corresponding tetralone in high yield (eq 3).[6] The analogous tris(phenylthio)propane gave uncyclized phenylthio ketone, albeit in 90% yield. ***Silver(I) Trifluoromethanesulfonate*** (and other Lewis acids) gave somewhat lower yields.

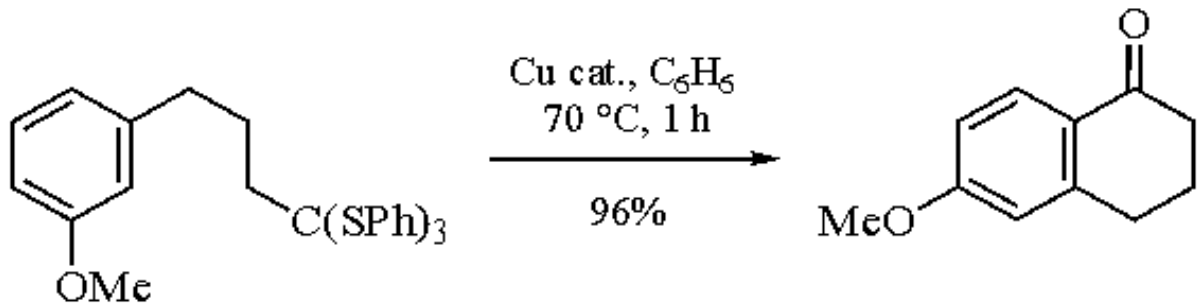

(3)

$Cu(MeCN)_4BF_4$ (in stoichiometric amounts) allows propargyl derivatives of phenylenediamine to undergo cyclization and aromatization to the quinoxaline (eq 4).[7] Attempted intramolecular amination using I_2-THF, CuI-toluene, and bis(collidine)bromonium perchlorate-toluene was unsuccessful.

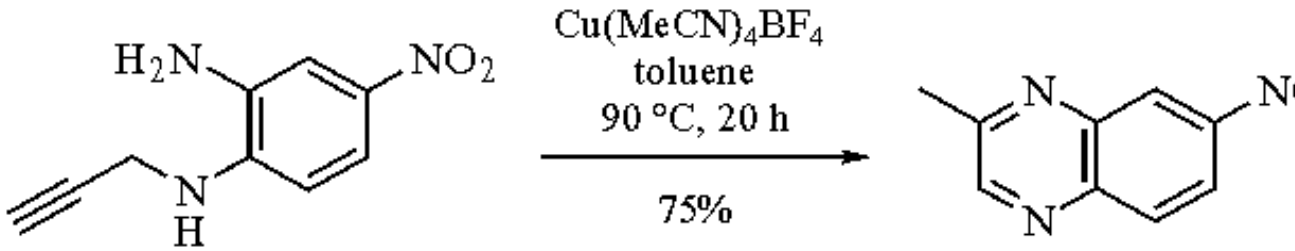

(4)

Steroidal Ring Expansions.

When used in the acid-catalyzed ring expansion reaction of α-hydroxy dithioacetal derivatives of 3-hydroxy-3-acetyl-14α-methyl-4-nor-5α- and -5β-cholest-8-ene (eq 5),[8] exclusive migration of a secondary carbon atom results in the formation of 3,14α-dimethyl-4-oxo steroids. $Cu(MeCN)_4BF_4$ gave the best results compared with $TiCl_4$ and $HgCl_2$-BF_3 etherate.

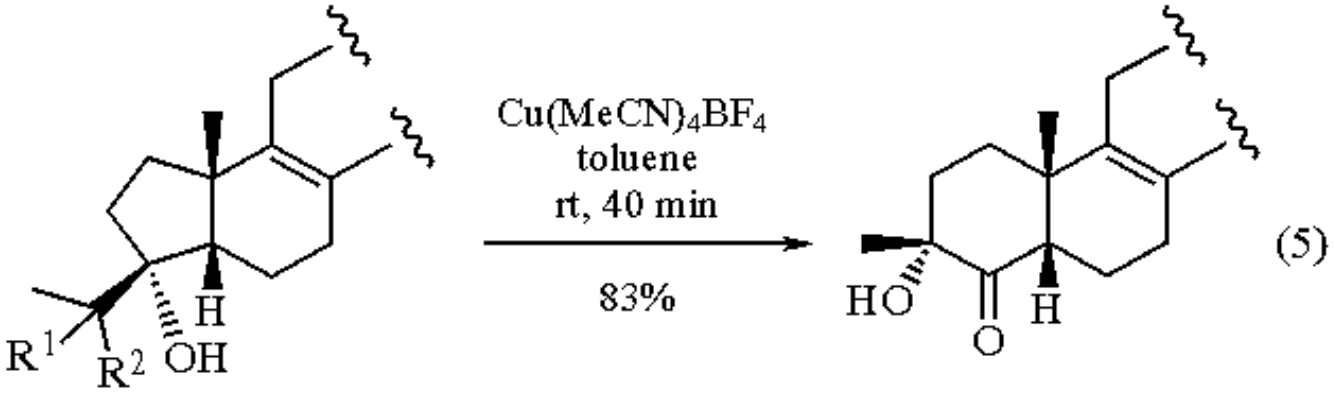

$R^1 = R^2 = SEt$

Related Reagents.

Tetrakis(acetonitrile)copper(I) Perchlorate; ***Tetrakis(pyridine)copper(I) Perchlorate***.

---

1. Gampp, H.; Zuberbuehler, A. D. *C* **1978**, *32*, 54.
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10. Davis, G. D.; Makin, E. C., Jr. *Sep. Purif. Methods* **1972**, *1*, 199.
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13. Simmons, M. G.; Merrill, C. L.; Wilson, L. J.; Bottomley, L. A.; Kadish, K. M. *JCS(D)* **1980**, 1827.

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Tetrakis(acetonitrile)palladium Tetrafluoroborate

$[Pd(MeCN)_4](BF_4)_2$

[21797-13-7] · $C_8H_{12}B_2F_8N_4Pd$ · Tetrakis(acetonitrile)palladium Tetrafluoroborate · (MW 444.28)

(catalyst for isomerization and rearrangement of alkenes[1] and strained carbocycles,[1,2] polymerization of vinyl monomers[1,2] and reagent for preparation of more stable Pd^{2+} complexes[3])

Physical Data: yellow to bright yellow solid; mp 230 °C (dec).

Solubility: sol polar solvents such as MeCN, $MeNO_2$; insol less polar solvents.

Preparative Methods: commercially available but it is easily prepared from either spongy palladium metal[4,5] or ***Palladium(II) Chloride***.[5b,6]

Handling, Storage, and Precautions: air and moisture sensitive.

Double Bond Isomerization and Skeletal Rearrangements.

Double bond isomerizations catalyzed by $[Pd(MeCN)_4](BF_4)_2$ occur mostly at room temperature. Most often, the thermodynamically most stable alkene predominates,[1] but an example has been noted where the product ratio is kinetically controlled (eq 1).[7] The efficacy of this electrophilic catalyst in isomerizations is illustrated by fast skeletal rearrangements of alkenes (eq 2),[1,5b] substituted cyclopropanes (eq 3),[1,5b] and cyclopropenes (eq 4)[5b] at 25 °C.

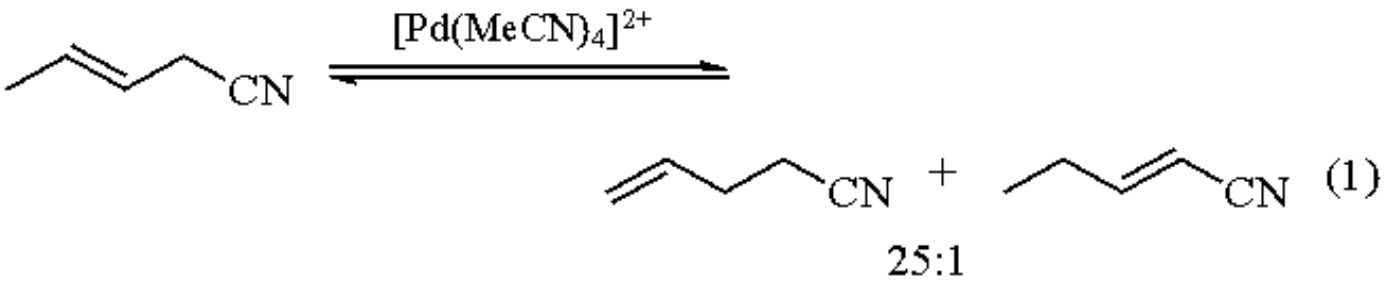

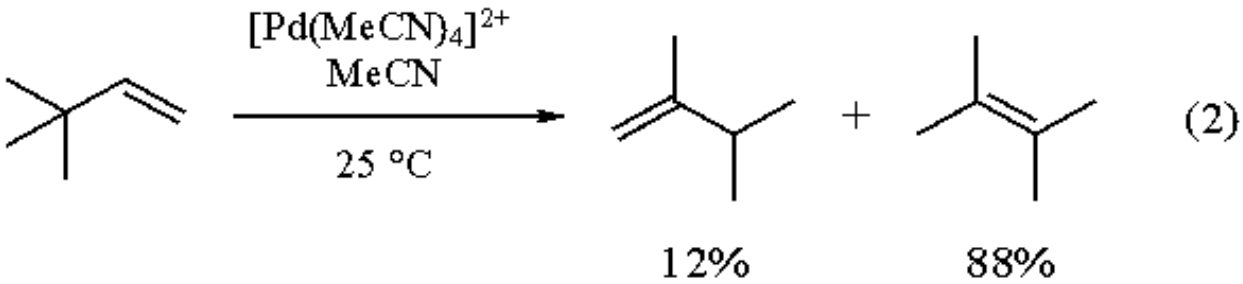

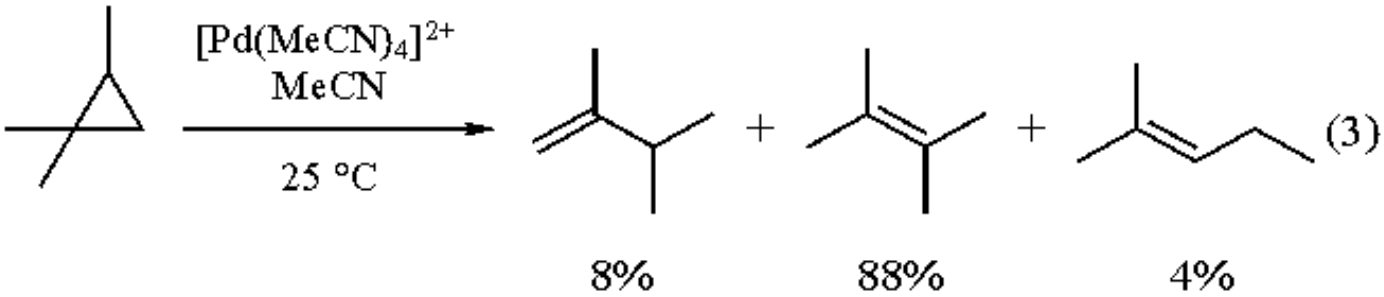

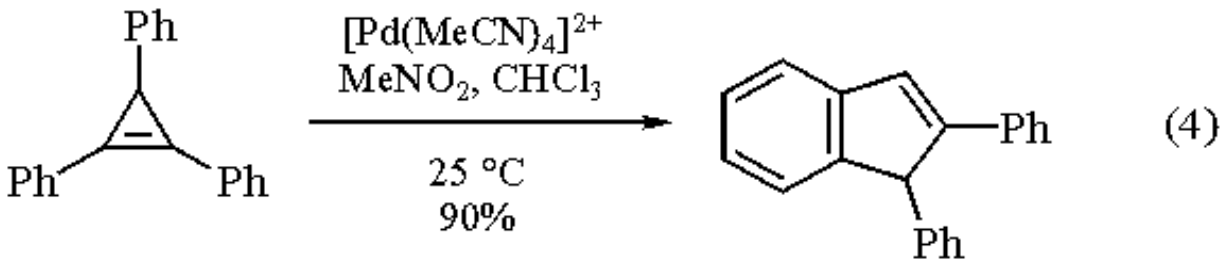

Oligomerization and Polymerization of Vinyl Compounds.

$[Pd(MeCN)_4](BF_4)_2$ has been found to be a very effective catalyst for highly regioselective dimerization of acrylic esters (eq 5) in the presence of ***Lithium Tetrafluoroborate***.[8] It catalyzes the polymerization of vinyl monomers and alkynes at room temperature.[1,5b,9] In the polymerization of norbornene (eq 6)[2,5b,9] and norbornadiene[5b,9] by this catalyst, the bicyclic structure is retained intact. Both cationic[1,5b] and insertion[2] mechanisms have been suggested for these Pd^{2+}-catalyzed processes.

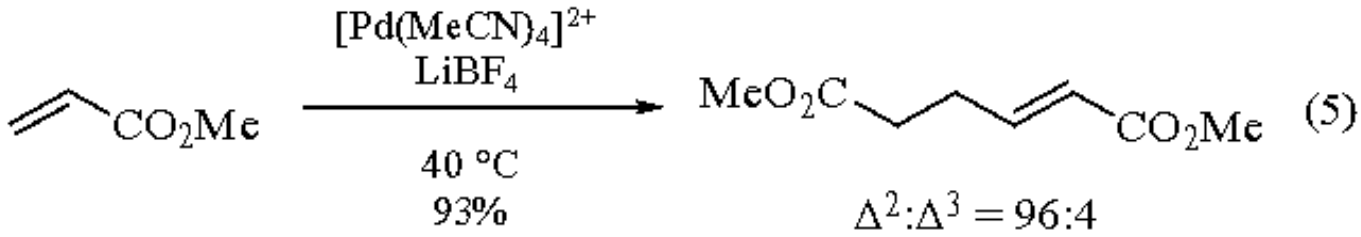

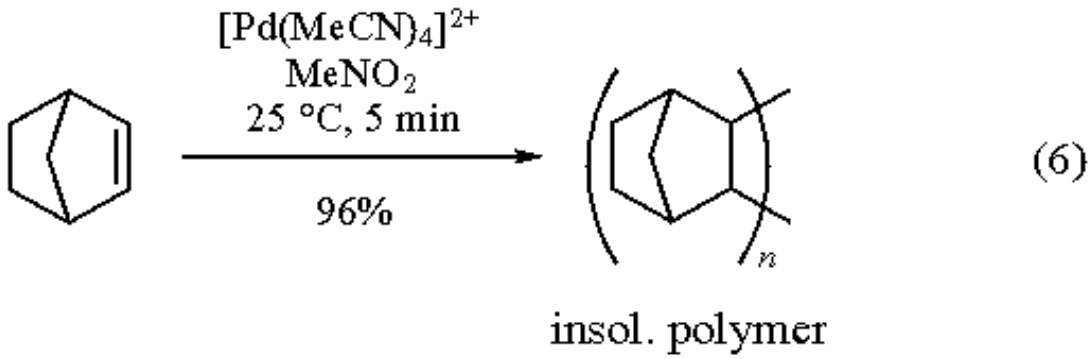

In the presence of ligands which bind more strongly to palladium than MeCN, $[Pd(MeCN)_4](BF_4)_2$ catalyzes the copolymerization of CO with alkenes. The addition of two styrene molecules to CO is highly regiospecific when a solution of this catalyst and styrene in THF is placed under CO and H_2 pressure in the presence of 1,3-diphenylphosphinopropane (dppp) (eq 7).[10] Similarly, CO and ethylene give a polyketone when treated with $[Pd(MeCN)_4](BF_4)_2$ in the presence of a phosphine ligand at room temperature.[11] Cotelomerization of CO_2 with butadiene using the same catalyst and other ligand additives has been reported to give δ-lactones with high selectivity.[12]

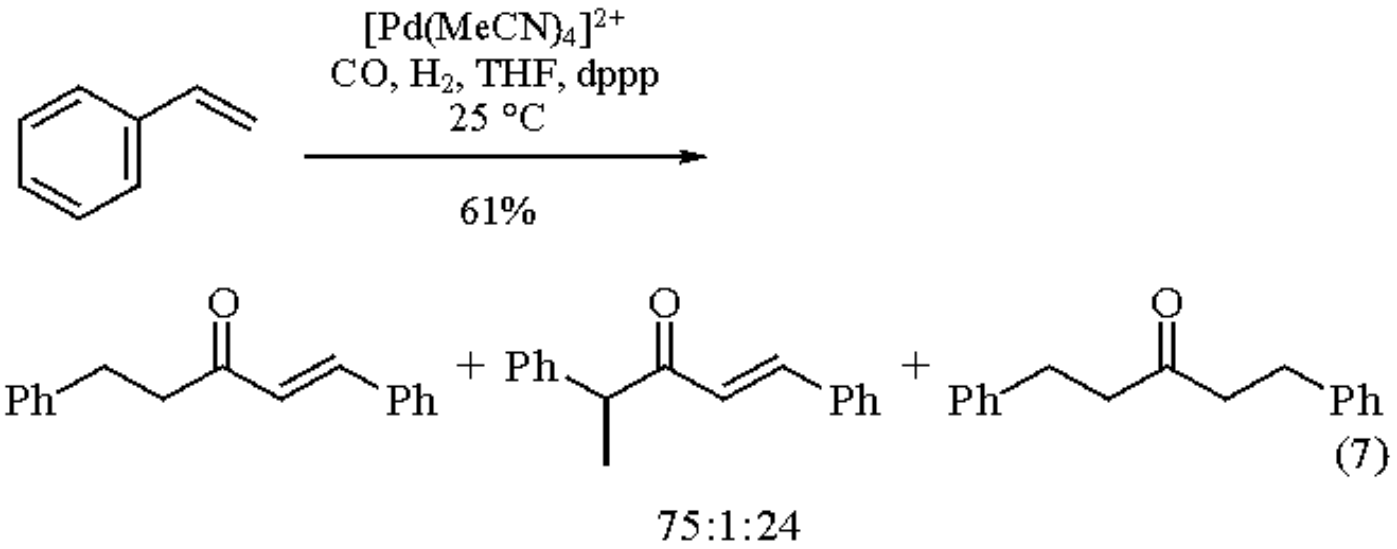

Preparation of More Stable Pd^{2+} Complexes.

Because of the lability of the acetonitrile ligands of $[Pd(MeCN)_4](BF_4)_2$, other cationic and neutral Pd^{2+} complexes are conveniently prepared from it either in a separate step[3] or in situ.[10-12]

---

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2. (a) Mehler, C.; Risse, W. *Macromolecules* **1992**, *25*, 4226; (b) Mehler, C.; Risse, W. *Makromol. Chem., Rapid Commun.* **1991**, *12*, 255; (c) Mehler, C.; Breunig, S.; Risse, W. *Polym. Prepr., ACS Div. Polym. Chem.* **1991**, *32*, 337.
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Tetrakis(pyridine)cobalt(II) Dichromate[1]

$(py)_4Co(HCrO_4)_2$

[139033-95-7] · $C_{20}H_{22}CoCr_2N_4O_8$ · Tetrakis(pyridine)cobalt(II) Dichromate · (MW 609.39)

(oxidizing agent for many functional groups;[1,2,5] dehydrogenative aromatization agent of five-membered N-heterocyclic compounds[6,7])

Alternate Names: TPCD; tetrakis(pyridine)cobalt (II) bis(chromate).

Physical Data: dec. 307 °C

Solubility: sol DMF, DMSO, AcOH, hot H_2O; insol acetone, Et_2O, dichloromethane.

Form Supplied in: deep brown or black crystals; commercially available.

Preparative Methods: to a solution of ***Chromium(VI) Oxide*** (2 equiv) and ***Cobalt(II) Acetate*** (1 equiv) in H_2O is added ***Pyridine*** (4 equiv) at 60 °C. TPCD is collected as brown-colored crystals and washed with acetone. After drying under vacuum, it is available for use.

Handling, Storage, and Precautions: the dry crystals are nonhygroscopic and air stable. The sample stored in a brown-colored bottle under nitrogen over one year will keep its original activity. The reagent should not be heated above its decomposition point without solvent.

Oxidation of Alcohols, Halides, and Amines.[1]

As a neutral Cr^{VI} complex, TPCD oxidizes primary and secondary alcohols, benzylic halides, and benzylamines to their corresponding aldehydes and ketones under essentially neutral conditions. It is very suitable for oxidation of some alcohols with acid-sensitivity and limited solubility (eq 1), for benzylic halides bearing electron-withdrawing substituents (eq 2), and for non-tertiary benzylic amines (eq 3); tertiary amines and quaternary ammonium salts are unaffected by TPCD.

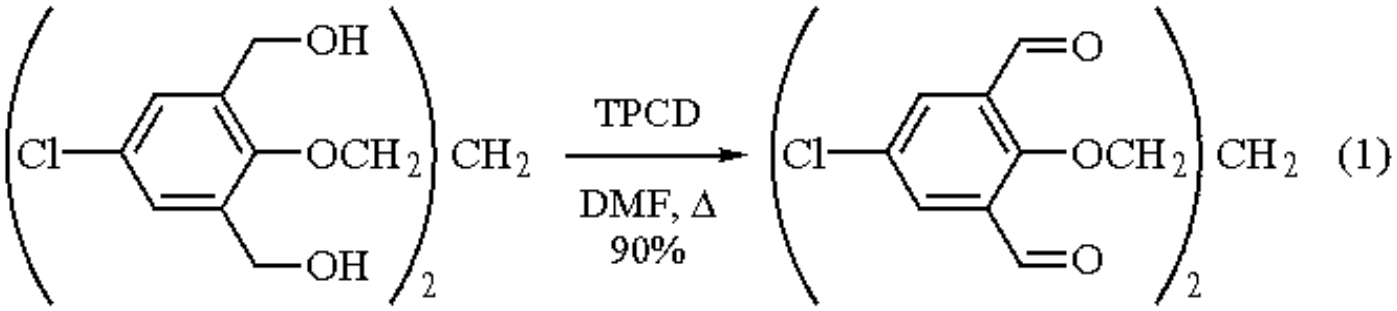

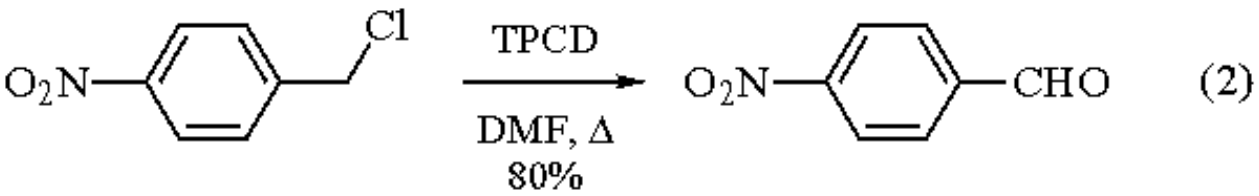

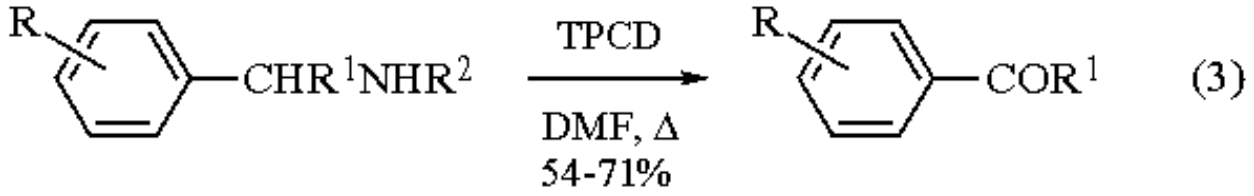

Oxidation of Oxime Compounds.

The behavior of oxime compounds is different and depends on the solvent used. Hence, aromatic aldoximes are converted smoothly into nitriles in DMF or carboxylic acids in aq HOAc (eq 4),[2] in which the dehydro dimer of aldoxime (i.e. a bis-nitrone) is identified as an intermediate. Benzaldoxime dehydro dimer can be trapped by ***Methyl Acrylate*** to yield a 1,3-cycloaddition product.[3] When chalcone oxime is warmed with TPCD at 60 °C, within 1 min an intramolecular 1,3-cycloaddition occurs to give 3,5-diphenylisoxazole (eq 5).[4]

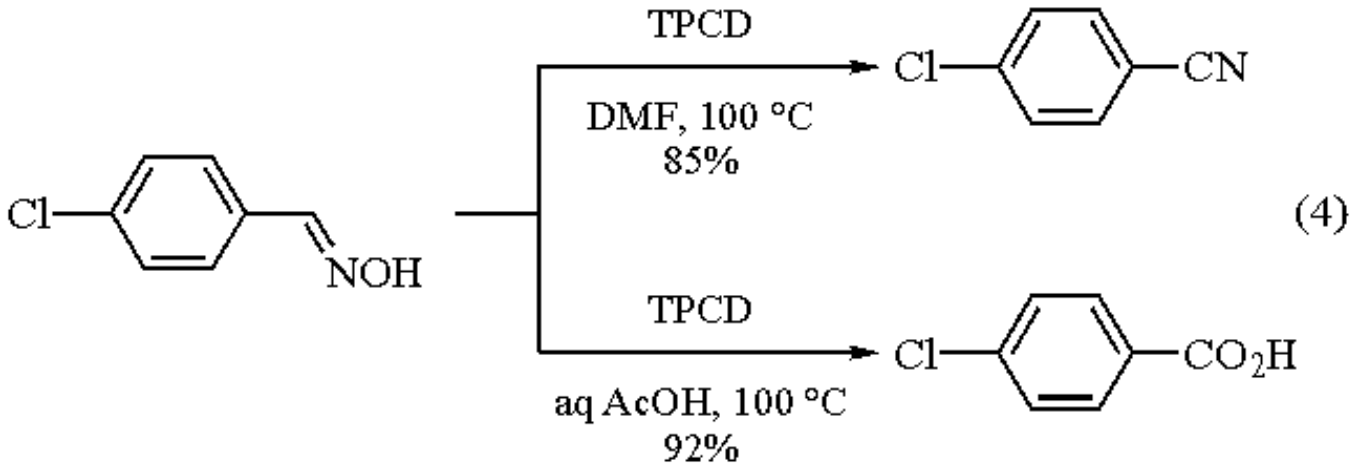

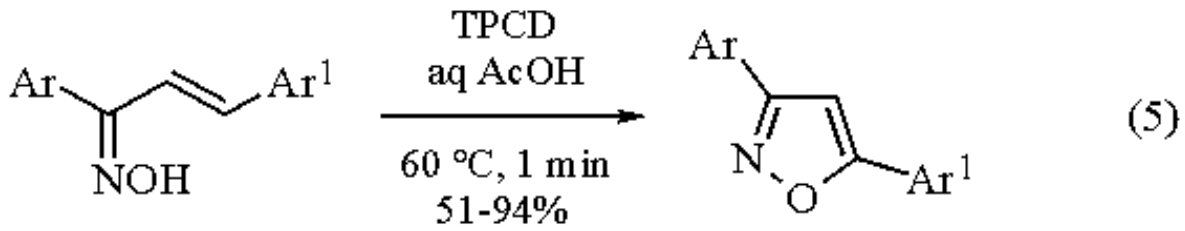

Oxidation of Hydrazides and Hydrazones.

Under the influence of Co^{II}, the behavior of TPCD, as expected, is different from that of other Cr^{VI}-based oxidants. Thus, it can effect the cleavage of hydrazides selectively to generate their acids in the presence of ester or amide groups (eq 6). It also converts benzil dihydrazones into diphenylacetylene derivatives in excellent yields, whereas 1,2-cyclodecanedione dihydrazone affords an 18% yield of cyclodecyne (eq 7).[5]

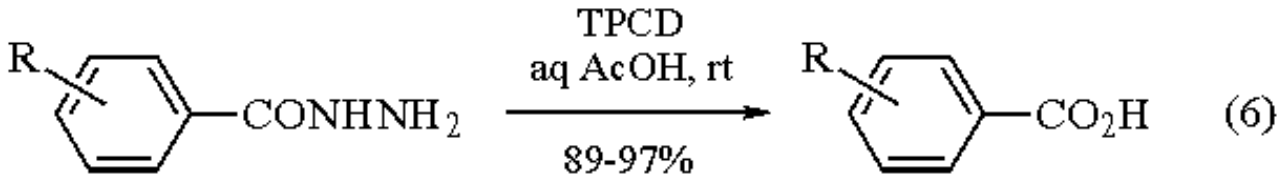

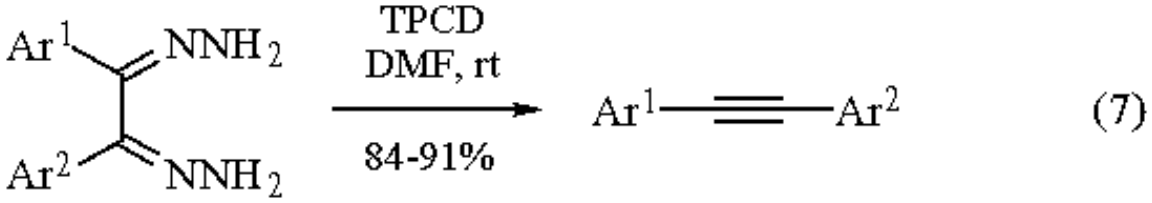

Oxidation of Pyridinium and Related Heterocyclic Ylides.

In the presence of TPCD, derivatives of *N*-acylpyridinium bromides are converted into 1,2,3-triacylindolizines according to a 1,5-dipolar cycloaddition mechanism (eq 8).[6] 1,3-Dipolar cycloaddition of *N*-phenacylpyridinium bromide with alkenes can be accomplished to give the aromatic indolizines in one step (eq 9).[7] Both of these reactions appear to proceed by a dipolar cycloaddition first, followed by a dehydrogenative aromatization. Co^{III} may be regarded as a real oxidant and Cr^{VI} as a reoxidant in these cases.

(8)

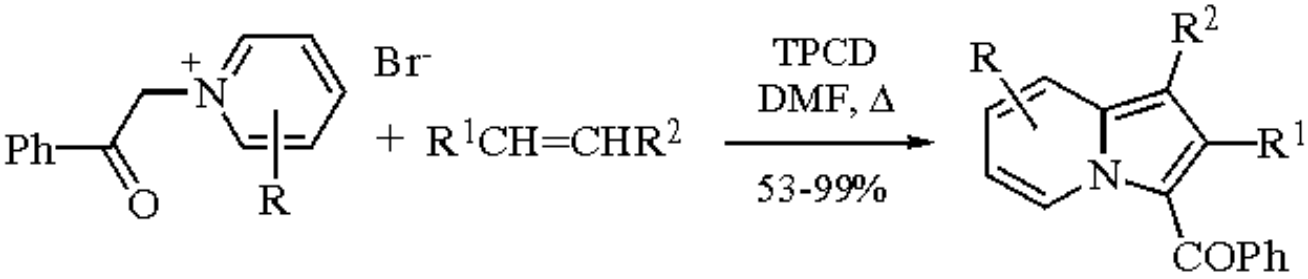

(9)

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Tetrakis(pyridine)copper(I) Perchlorate

$(py)_4Cu^+ ClO_4^-$

[21465-66-7] · $C_{20}H_{20}ClCuN_4O_4$ · Tetrakis(pyridine)copper(I) Perchlorate · (MW 479.44)

(catalyst for the decomposition of diazonium salts)

Physical Data: light yellow crystals;[2,7] *d* 1.47 g cm^{-3};[7] IR ν 1085 (ClO_4^-), 616 (py) cm^{-1}.[2,8]

Solubility: sol pyridine, MeCN.

Form Supplied in: prepared as needed.

Analysis of Reagent Purity: iodometric determination of Cu.[2]

Preparative Methods: conveniently prepared from the tetrakis(acetonitrile) complex[1] by reaction with ***Pyridine*** in a 1:4 molar ratio under nitrogen.[2]

Purification: drying in vacuo at rt.

Handling, Storage, and Precautions: irritant; moisture sensitive; handle under inert atmosphere. Occasional mild explosions have been reported with dry organic perchlorate salts.[9] Use in a fume hood.

Decomposition of Aryl Diazonium Salts.

The homolytic decomposition of aryl diazonium salts can be catalyzed effectively by copper(I) salts. For example, ***Copper(I) Oxide*** accelerates homolytic carbon-nitrogen bond scission and eliminates the competitive heterolytic pathway in the decomposition of 2-diazobenzophenone tetrafluoroborate at 45 °C.[5,6] However, Cu_2O has the disadvantage of being effective only in highly acidic media, due to its insolubility in neutral water. The title reagent was shown[3,4] to be an effective catalyst for diazonium salt decomposition in less acidic media (pH = 6.2). Similar complexes, e.g. ***Tetrakis(acetonitrile)copper(I) Perchlorate*** and ***Tetrakis(acetonitrile)copper(I) Tetrafluoroborate***, disproportionated to Cu^{II} species too rapidly to be useful; nitrate complexes were too unstable to react with the diazonium salt. Many common cuprous salts, as well as CuH, failed to catalyze the reaction.[3]

The nature and concentration of the copper complexes significantly affect the distribution of products shown in eq 1. In the presence of Cu^{II} ions, high yields of 2-hydroxybenzophenone (**1**) could be obtained; with hydrogen-donating solvents such as ethanol, the major product was benzophenone (**2**). A similar heterocyclic amine complex, tris(2-picoline)copper(I) perchlorate, also proved useful as a catalyst, giving a dibenzoylbiphenyl dimer and 9-fluorenone (**3**) as the major products.

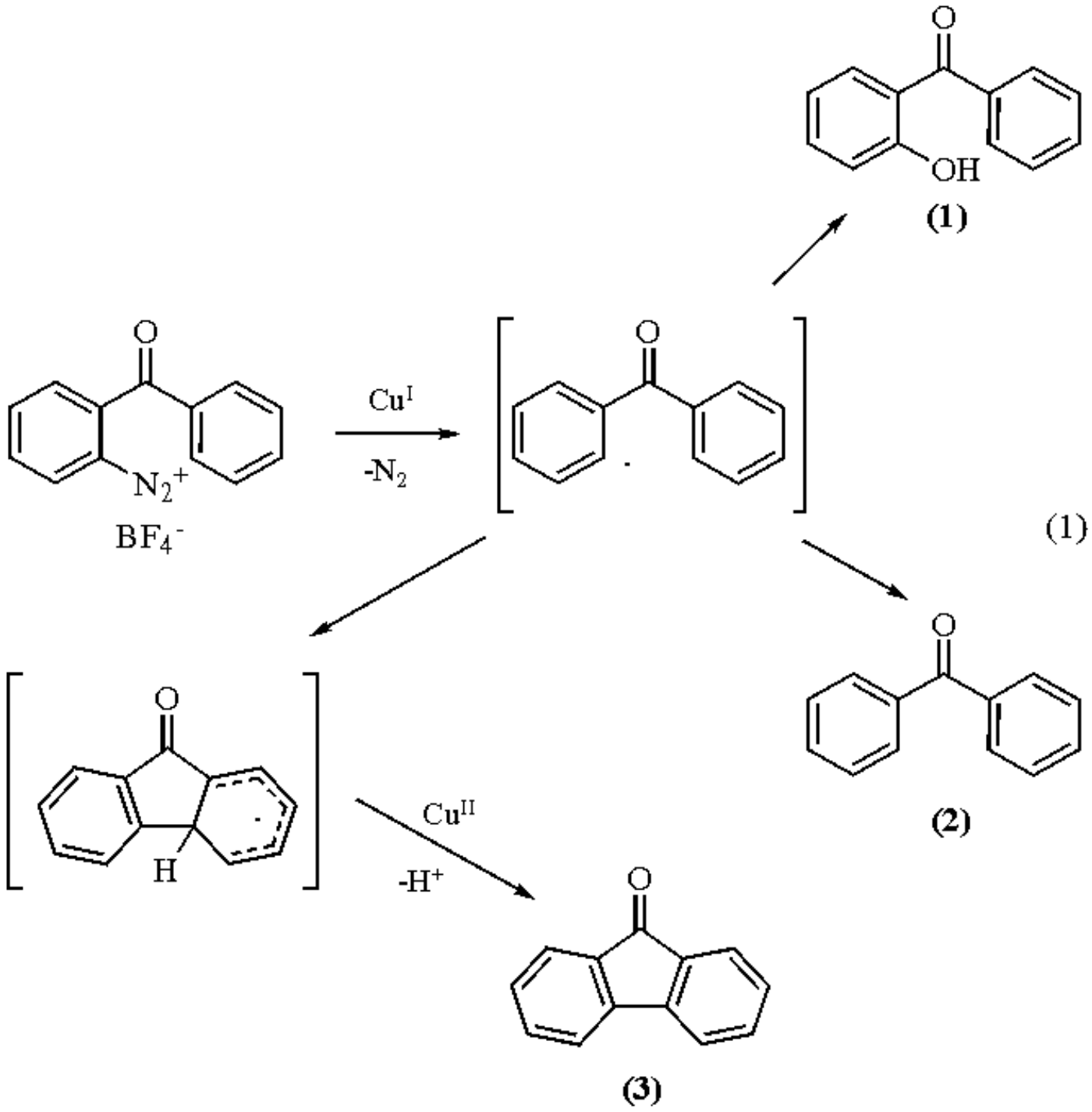

A kinetic study showed the relative rate constants for reduction, phenol formation, and cyclization of the intermediate radical to be 4, 2, and 1, respectively; in solutions containing 15% or more dioxane, however, the rate constant for phenol formation is drastically reduced by micelle formation. A pH-dependent competition between dimerization and cyclization was also observed.[4]

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Tetrakis(trichlorophosphine)nickel(0)[1]

$Ni(PCl_3)_4$

[36421-86-0] · $Cl_{12}NiP_4$ · Tetrakis(trichlorophosphine)nickel(0) · (MW 607.97)

(source of nickel(0) useful for the cyclotetramerization of alkynes[2])

Physical Data: thermochromic crystalline solid that is pale yellow at rt and white at temperatures below -30 °C; mp 120 °C (dec).

Solubility: readily sol benzene, cyclohexane, chloroform, CCl_4, pentane

Analysis of Reagent Purity: ^{31}P NMR: 171.8 ppm (downfield from H_3PO_4).[3] IR (Nujol): 325s, 500s, 570s, 805m, 870m cm^{-1}.[4]

Preparative Methods: the original preparation involved addition of excess ***Phosphorus(III) Chloride*** to ***Tetracarbonylnickel*** (caution: extremely toxic, volatile), whereupon CO was immediately evolved. The reaction was completed by heating the pale-yellow solution to reflux. Distillation removed most of the remaining PCl_3. The pot residue was dissolved in pentane at rt and the resulting solution cooled to -60 °C to crystallize the product as fine crystals, which were dried on a porous plate. Two recrystallizations were sufficient to remove all PCl_3 and gave an 80% yield of $Ni(PCl_3)_4$. All manipulations were carried out under inert atmosphere.[5] The complex may also be prepared by reaction of PCl_3 with $Ni(allyl)_2$.[6]

Handling, Storage, and Precautions: the flammable crystalline solid is stable in air but highly oxygen sensitive in solution. Special inert-atmosphere techniques must be used.[7] Should be stored at 0 °C.

Cyclotetramerization of Alkynes.

The methyl and ethyl esters of propiolic acid can be cyclotetramerized in the presence of catalytic $Ni(PCl_3)_4$ to form cyclooctatetraenes (**1**) (eq 1).[2] For the methyl ester, the remaining product (17%) is the trimerization product (**2**). For the ethyl ester, the selectivity favoring cyclotetramerization reverses, and trimerization accounts for 72% of the product. Attempts to cyclotetramerize a wide variety of other alkynes were unsuccessful. Although the scope of this reaction is extremely limited, $Ni(PCl_3)_4$ is one of only very few compounds that are able to catalyze the cyclotetramerization of substituted alkynes.[8] The order of reactivity of several such catalysts is $Ni(PCl_3)_4$ > $Ni(PF_3)_4$ >> $Ni(PBr_3)_4$ &AApprox; $Ni(PhPCl_2)_4$.

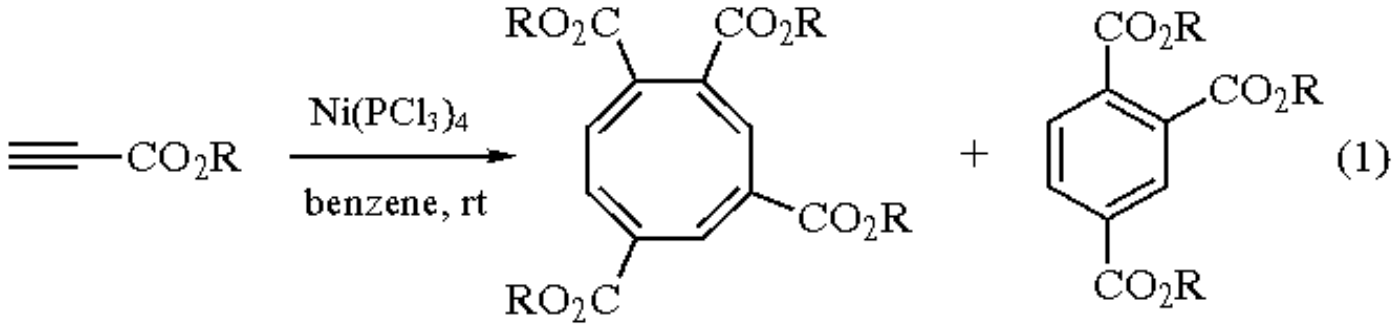

(1) **(2)**

R = Me, 66% 83:17
R = Et, 73% 28:72

Other Uses.

The polymerization of butadiene has been described using a three-component system made up of $Ni(PCl_3)_4$, ***Titanium(IV) Chloride*** and ***Aluminum Chloride***.[9]

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Tetrakis(triethyl phosphite)nickel(0)

$[(EtO)_3P]_4Ni$

[14839-39-5] · $C_{24}H_{60}NiO_{12}P_4$ · Tetrakis(triethyl phosphite)nickel(0) · (MW 723.41)

(catalyst for allylic alkylation;[1] cycloadditions;[2] alkene isomerization;[3] aldol reaction[4])

Physical Data: mp 108 °C; white crystals.

Solubility: sol THF, toluene.

Preparative Methods: easily synthesized by the reaction of ***Triethyl Phosphite***, ***Nickel(II) Chloride***, and Et_2NH.[5]

Handling, Storage, and Precautions: is a cancer suspect agent; air sensitive; reacts with halogenated solvents; should be handled using Schlenk or glovebox techniques.

Allylic Alkylation.

Alkylation of allylic carbonates by 1,3-dicarbonyl compounds under neutral conditions is catalyzed by $[(EtO)_3P]_4Ni$ (eq 1).[1] Alkenyl allyl carbonates undergo an intramolecular decarbonylative allylation with $[(EtO)_3P]_4Ni$ (eq 2).[6]

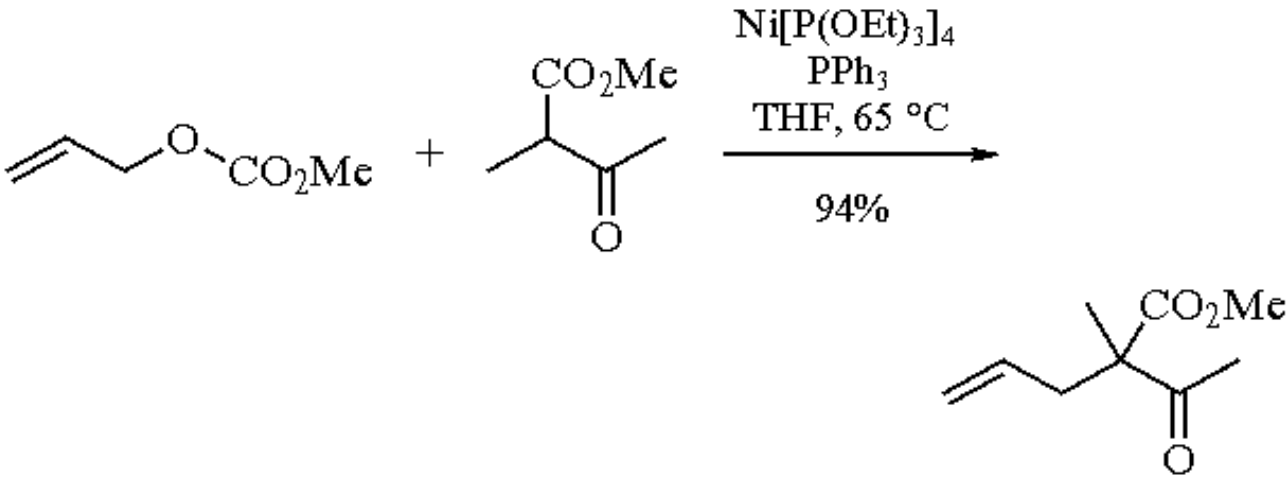

(1)

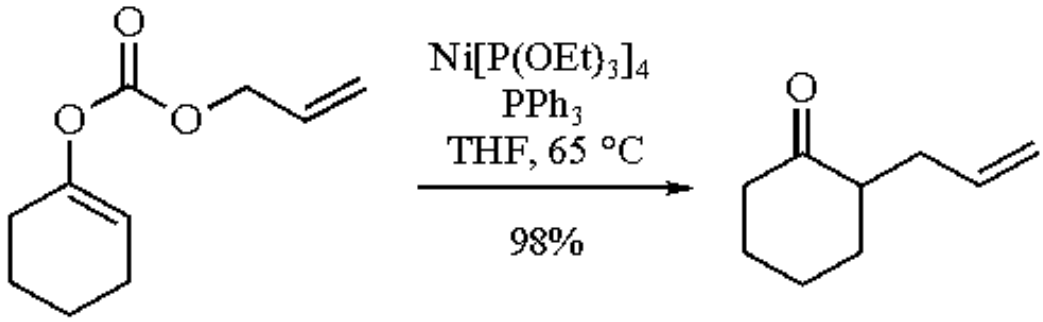

(2)

Cycloaddition Reactions.

The cycloaddition of trimethylenemethane intermediates to imines is catalyzed by $[(EtO)_3P]_4Ni$ to form 4-methylenepyrrolidines (eq 3).[2]

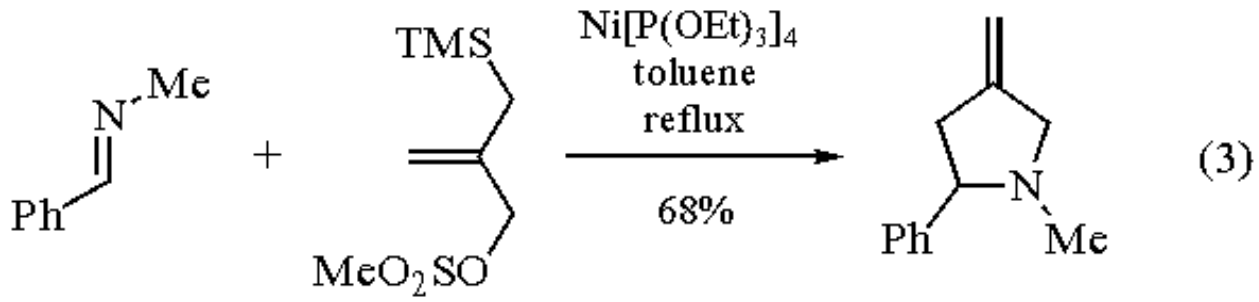

Alkene Isomerization.

$[(EtO)_3P]_4Ni$ catalyzes the isomerization of 1-pentene to a mixture of *cis*- and *trans*-2-pentene (eq 4).[3] At 35 °C, an equilibrium mixture (3:1:1) of *trans*-2-pentene, *cis*-2-pentene, and 1-pentene is formed.

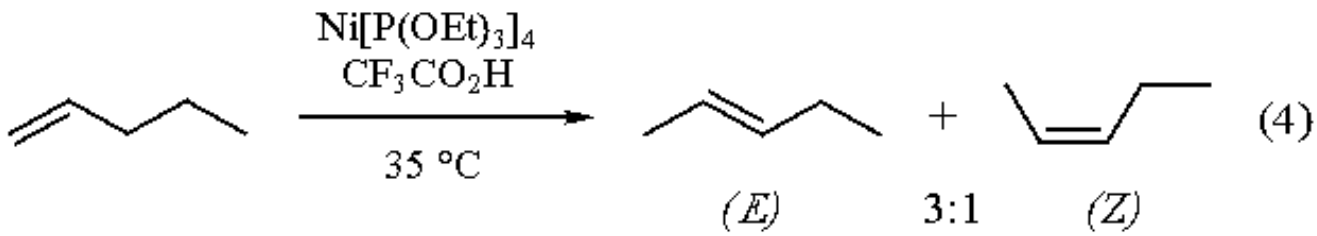

Aldol Reaction.

The reaction of aldehydes with β-keto allyl esters is catalyzed by $[(EtO)_3P]_4Ni$ to form β-hydroxy ketones (eq 5).[4]

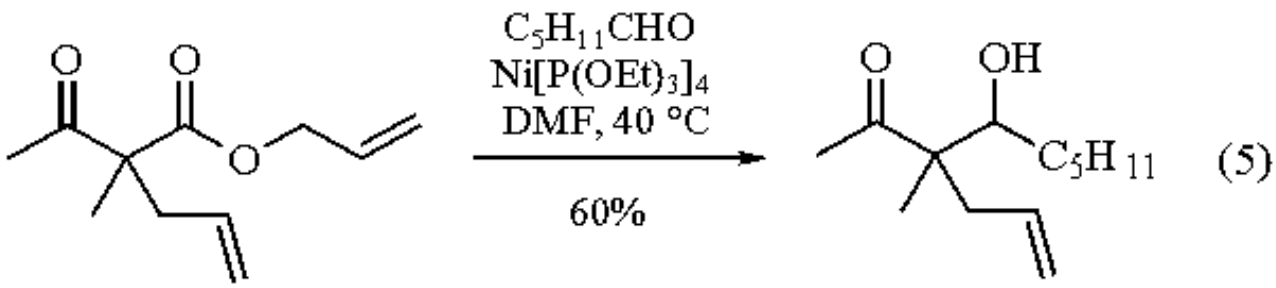

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Tetrakis(triisopropyl phosphite)nickel(0)

$[(i\text{-PrO})_3P]_4Ni$

[36700-07-9] · $C_{36}H_{84}NiO_{12}P_4$ · Tetrakis(triisopropyl phosphite)nickel(0) · (MW 891.77)

(catalyst for hydrazone[1] and alkyne allylation,[2] allyl ester rearrangements,[3] alkene cyclodimerization,[4] and amination[5])

Physical Data: mp 187 °C.

Preparative Methods: most conveniently synthesized by the reaction of ***Bis(1,5-cyclooctadiene)nickel(0)*** with ***Triisopropyl Phosphite***.[6]

Handling, Storage, and Precautions: is a cancer suspect agent; air sensitive; should be handled using Schlenk or glove box techniques. Use in a fume hood.

Catalytic Allylation.

$[(i\text{-PrO})_3P]_4Ni$ efficiently catalyzes the allylation of alkynes and phenylhydrazones with allyl esters. The reaction of phenylhydrazones with allyl acetate using 5 mol % $[(i\text{-PrO})_3P]_4Ni$ produces azo compounds (eq 1).[1] $[(i\text{-PrO})_3P]_4Ni$ was superior to Ni^0 complexes of other alkyl and aryl phosphites.

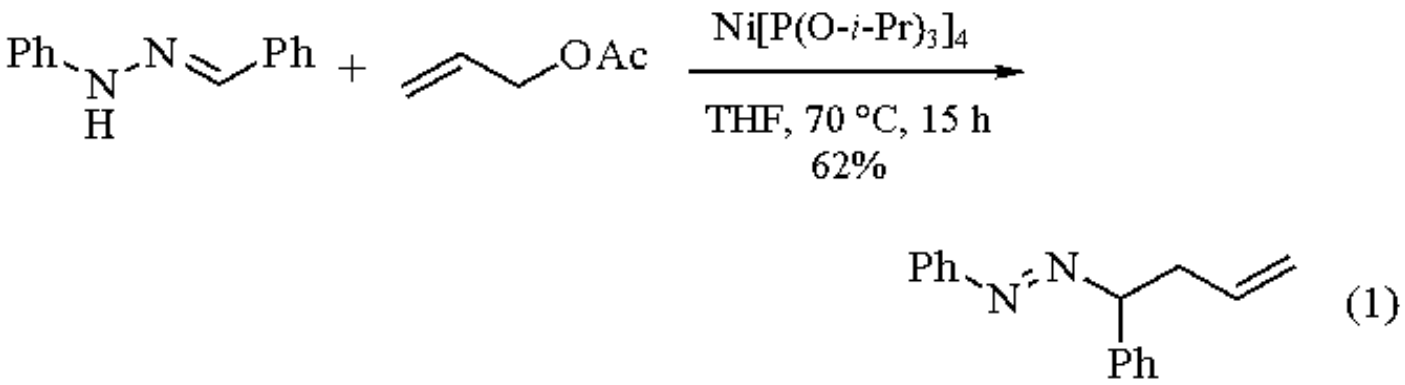

Alkynes react with allyl but-3-enoate in the presence of 2 mol % $[(i\text{-PrO})_3P]_4Ni$ at room temperature to form nonconjugated eneynes in high yield (eq 2).[2] $[(i\text{-PrO})_3P]_4Ni$ was determined to be the optimum catalyst for this transformation.

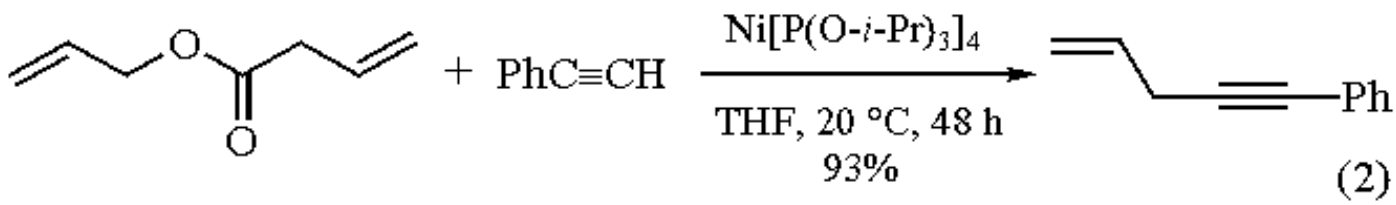

Allyl Ester Rearrangement.

In the absence of alkynes, allyl but-3-enoate is rearranged by $[(i\text{-PrO})_3P]_4Ni$ to a mixture of isomeric heptadienoic acids (eq 3).[3] A 2:1 ratio of isomeric carboxylic acids was formed with $[(i\text{-PrO})_3P]_4Ni$. For comparison, ***Tetrakis(triethyl phosphite)nickel(0)*** gave a 0.8:1 mixture.

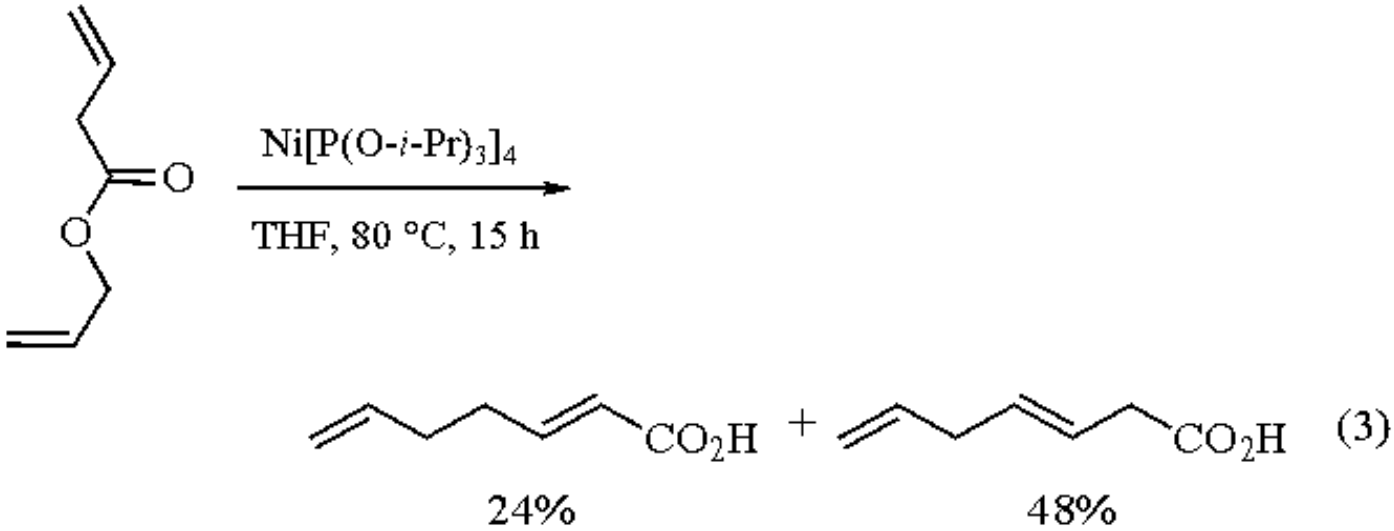

Cyclodimerization Reactions.

Dihydroindoles can be prepared by the dimerization of dipropargylamines with alkynes using catalytic amounts of $[(i\text{-PrO})_3P]_4Ni$ (eq 4).[4] Norbornadiene derivatives can be cyclodimerized with allyl acetate in the presence of $[(i\text{-PrO})_3P]_4Ni$ to give tricyclononane products (eq 5).[7]

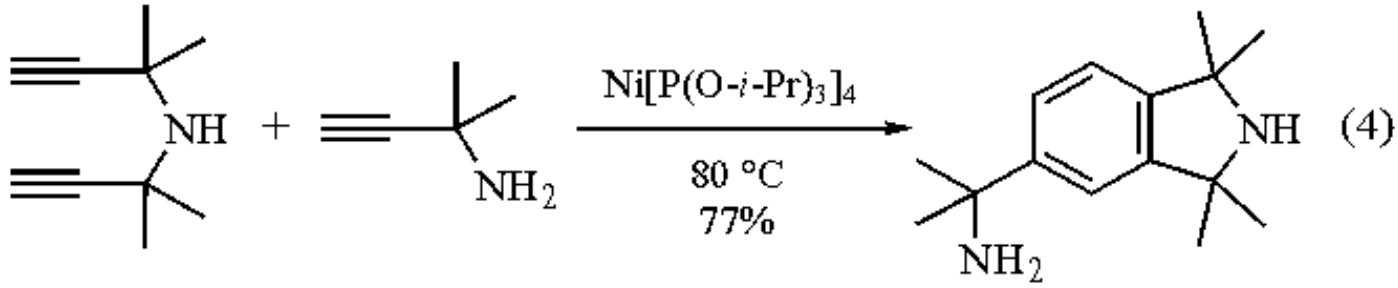

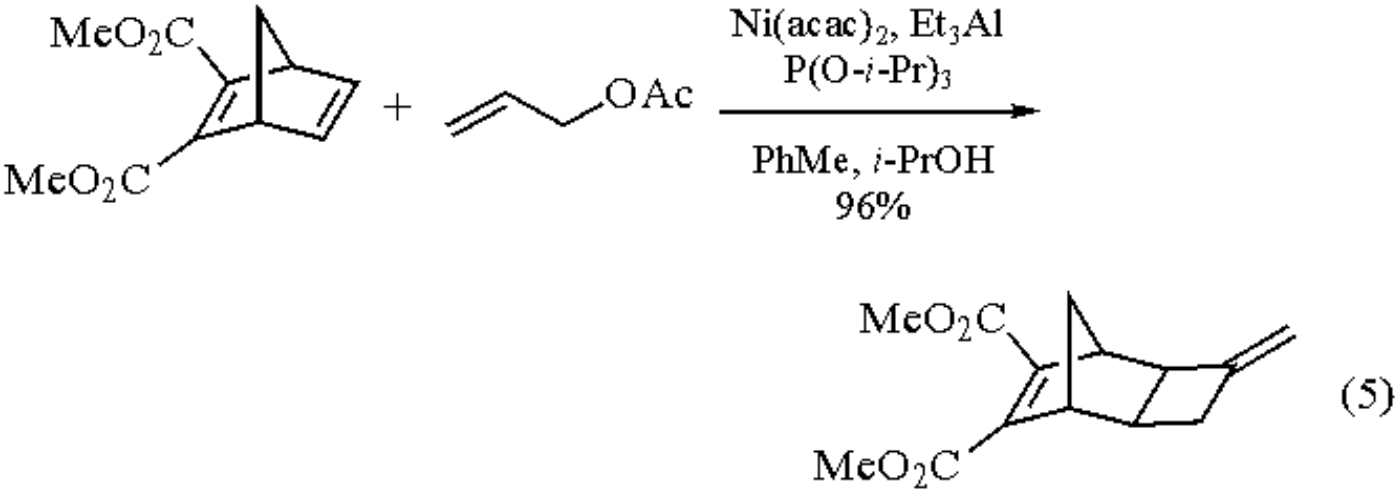

Amination Reactions.

Addition of amines to vinylcyclopropanes is catalyzed by $[(i\text{-PrO})_3P]_4Ni$ to give acyclic allylic amines (eq 6).[5] This reaction is also catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)*** in comparable yield. The reaction of amines with vinyl lactones gave allylamino carboxylic acids.

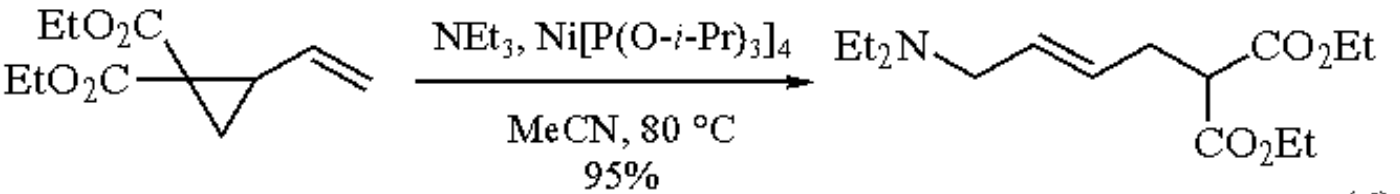

(6)

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Tetrakis(triisopropyl phosphite)palladium(0)

$[(i\text{-PrO})_3P]_4Pd$

[82838-61-7] · $C_{36}H_{84}O_{12}P_4Pd$ · Tetrakis(triisopropyl phosphite)palladium(0) · (MW 939.50)

(catalyst for [4 + 3] and [3 + 2] cycloaddition reactions[1] and nucleophilic additions[2])

Preparative Methods: has only been generated in situ from the reaction of ***Palladium(II) Acetate*** with 2 equiv ***n-Butyllithium*** and 4 equiv ***Triisopropyl Phosphite*** in THF.[2] No reports of the characterization or isolation of $[(i\text{-PrO})_3P]_4Pd$ have appeared.

Handling, Storage, and Precautions: solutions of $[(i\text{-PrO})_3P]_4Pd$ should be generated and used under an argon or nitrogen atmosphere. Use in a fume hood.

Cycloaddition Reactions.

$[(i\text{-PrO})_3P]_4Pd$ has been predominantly utilized in catalytic cycloaddition reactions which involve palladium-trimethylenemethane intermediates. The [3 + 2] cycloaddition of dimethyl 2,3-bicyclo[2.2.1]heptanedicarboxylate with 2-((trimethylsilyl)methyl)allyl iodide gave a single methylenecyclopentene isomer in 63% yield (eq 1).[3] For this particular cycloaddition, $[(i\text{-PrO})_3P]_4Pd$ was reported to be the preferred reagent. Under similar conditions, pyrones undergo selective [4 + 3] cycloaddition to give methyleneoxabicyclononenones (eq 2).[4]

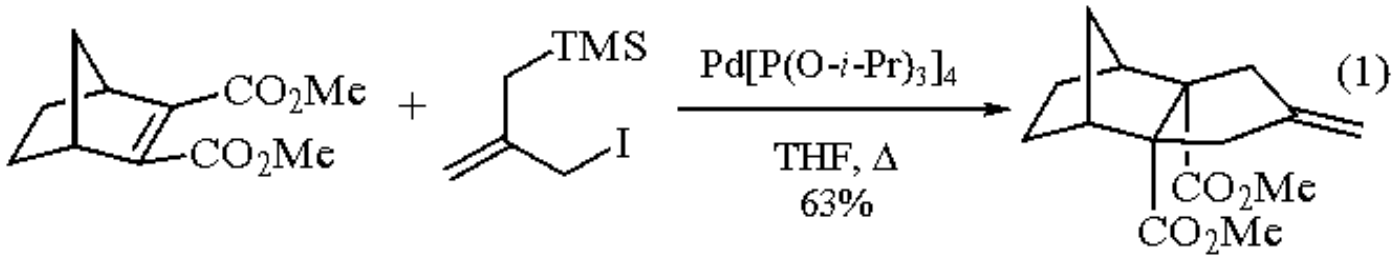

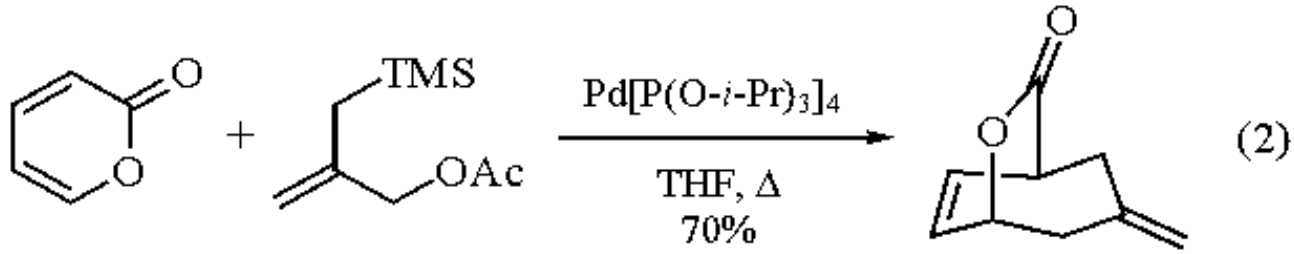

In cycloadditions which involve acyclic dienes, a competition has been observed for formation of five- and seven-membered rings. The reaction of dimethyl (*E*,*E*)-muconate with 2-((trimethylsilyl)methyl)allyl acetate in the presence of a catalytic amount of $[(i\text{-PrO})_3P]_4Pd$ gave a 1.1:1 ratio of methylenecyclopentene and methylenecycloheptene products in 89% combined yield (eq 3).[1] For comparison, ***Tetrakis(triphenylphosphine)palladium(0)*** + ***1,2-Bis(diphenylphosphino)ethane*** in dioxane gave increased selectivity for methylenecyclopentene (3.8:1). Product ratios were also found to be dependent upon diene stereochemistry. The reaction of dimethyl (*Z*,*E*)-muconate with 2-((trimethylsilyl)methyl)allyl acetate using $[(i\text{-PrO})_3P]_4Pd$ gave only cyclopentene products.

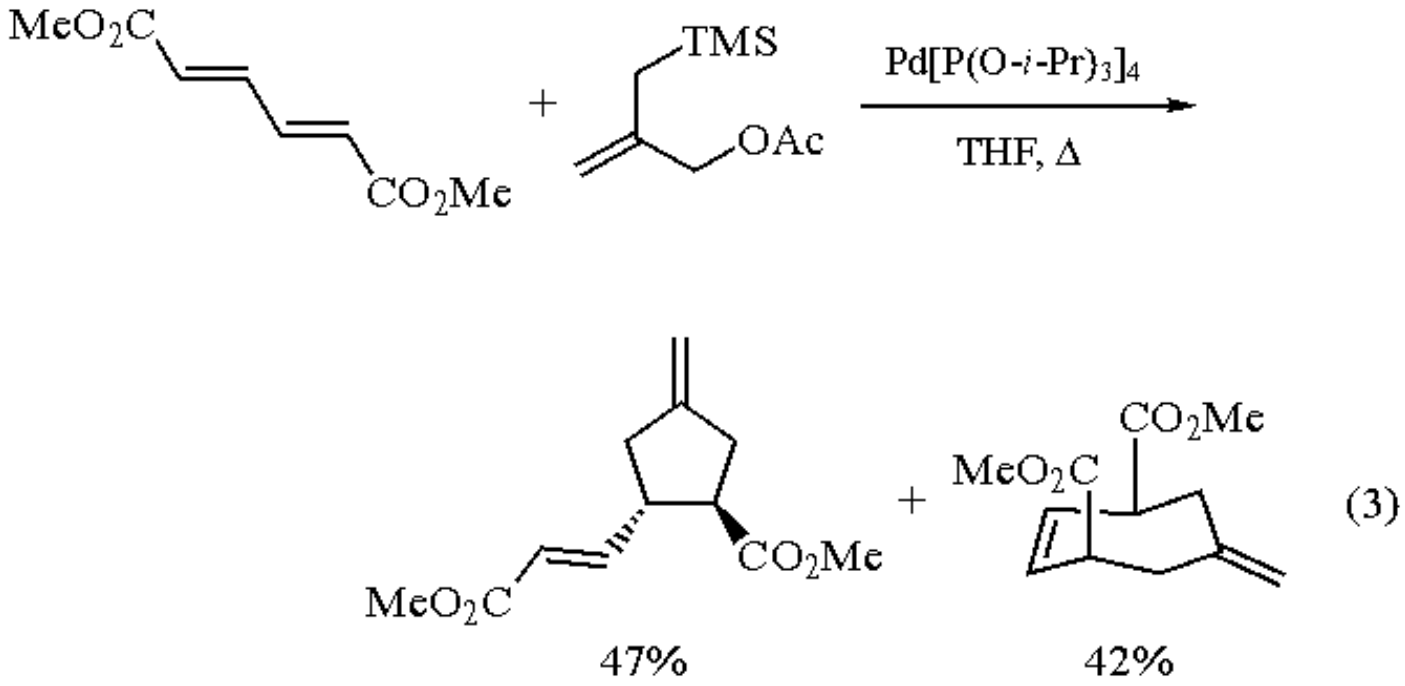

Nucleophilic Additions.

[(i-PrO)$_3$P]$_4$Pd has also been used as a catalyst for nucleophilic addition with high stereo- and regioselectivity. Addition of adenine to epoxides produced a single isomer in 90% yield (eq 4).[1]

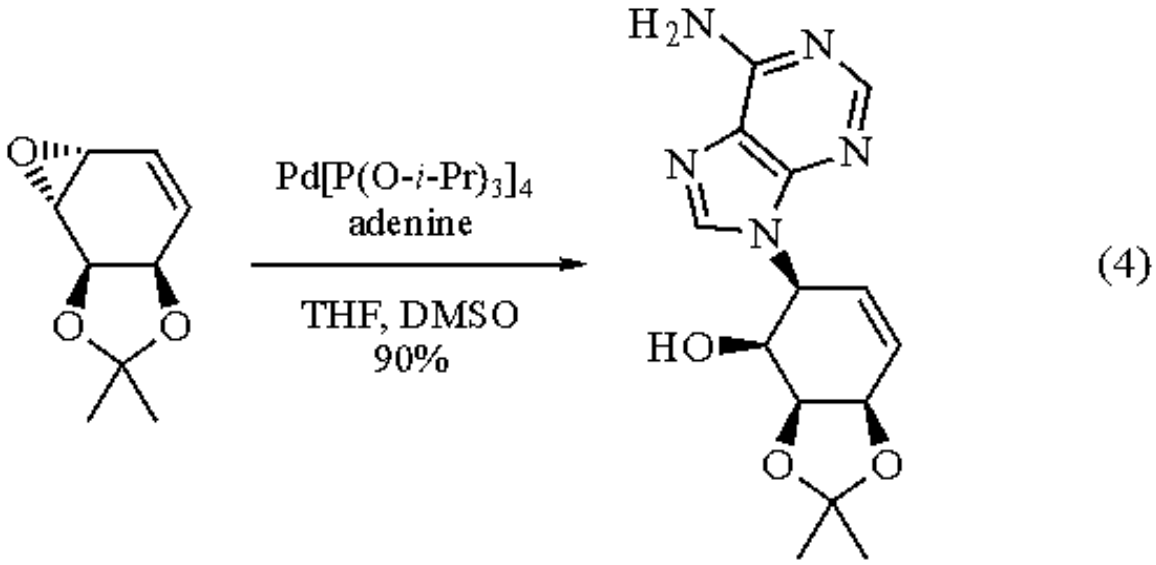

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Tetrakis(triphenylphosphine)nickel(0)[1]

$Ni(PPh_3)_4$

[15133-82-1] · $C_{72}H_{60}NiP_4$ · Tetrakis(triphenylphosphine)nickel(0) · (MW 1107.89)

(a source of nickel(0) useful for coupling reactions of organic halides,[2] and the cyclooligomerization of cumulenes[3])

Physical Data: mp 123-128 °C (N_2).

Solubility: sol DMF, DMA, THF, acetonitrile, benzene; slightly sol Et_2O; very slightly sol *n*-heptane, EtOH.

Form Supplied in: widely available as a red powder of greater than 98% purity.

Preparative Methods: the standard preparation involves the reduction of ***Nickel(II) Acetylacetonate*** with ***Triethylaluminum*** in the presence of ***Triphenylphosphine***. To 21.3 g of anhydrous $Ni(acac)_2$ and 125 g PPh_3 in 800 mL of Et_2O under N_2 at 0 °C is slowly added 28.0 g Et_3Al. The reddish-brown precipitate is collected, washed with Et_2O, and twice dissolved in benzene and reprecipitated by the addition of *n*-heptane to give about 50 g (55%) of $Ni(PPh_3)_4$.[4]

Handling, Storage, and Precautions: highly oxygen sensitive. Special inert-atmosphere techniques must be used.[5] Should be stored at 0 °C. Cancer suspect agent.

Coupling Reactions of Organic Halides.

The zerovalent nickel complex $Ni(PPh_3)_4$ reacts with organic halides by oxidative addition into the carbon-halogen bonds to give organonickel(II) intermediates.[6] These intermediates, which are typically not isolated, can react with a variety of nucleophilic reagents to replace the original halide with another group.[2] With a catalytic amount of $Ni(PPh_3)_4$, aryl halides react with halide salts to give halogen exchange,[7] and with MgH_2 to give hydrogenation.[8] Aryl halides and triflates react with cyanide salts to give nitriles.[9] Aryl bromides and iodides both work well as substrates, and many functional groups are tolerated. However, *o*-substituents tend to slow the reactions down and give lower yields. Oxidative addition to benzylic halides occurs with racemization.[6a] Insertion of an alkene into the organonickel intermediate leads to overall coupling via a β-hydride elimination pathway.[10] This type of reaction has been utilized intramolecularly in the synthesis of indole and oxindole derivatives (eq 1).[11] The organonickel intermediate derived from MeI and $Ni(PPh_3)_4$ can be used for the regioselective alkylation of epoxides.[12]

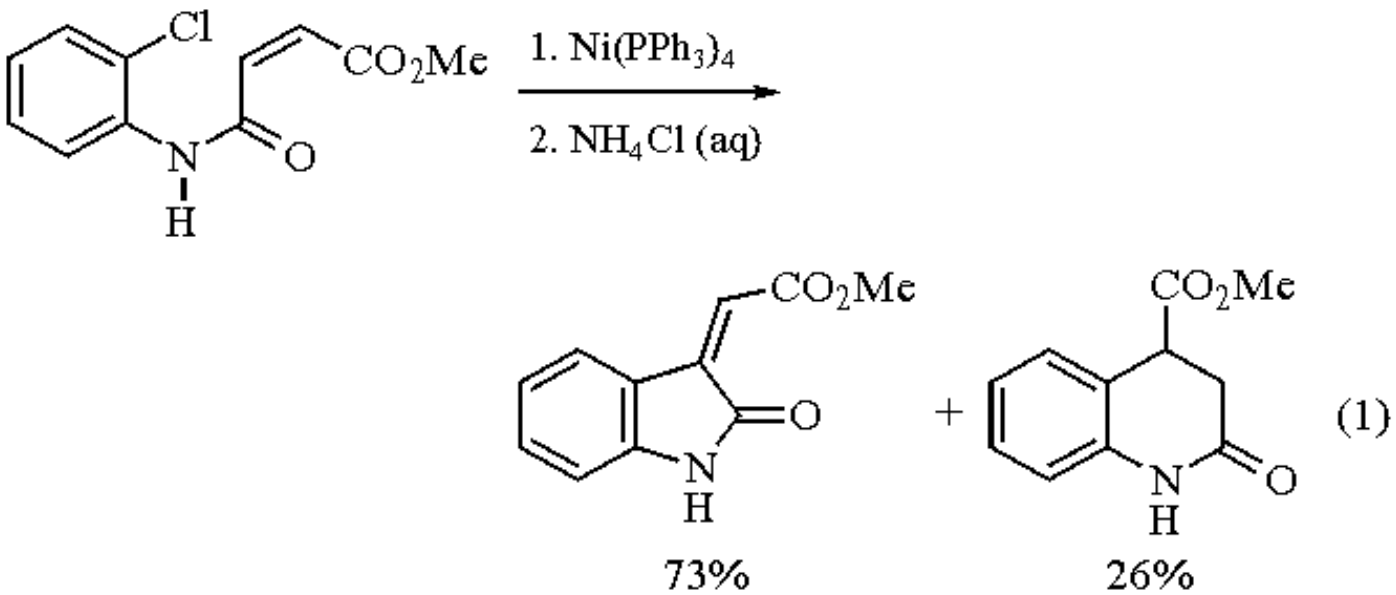

Homocoupling of aryl and alkenyl halides can occur with stoichiometric amounts of nickel(0) (see ***Bis(1,5-cyclooctadiene)nickel(0)***),[13] or catalytically in the presence of an added reducing agent such as zinc (see ***Tris(triphenylphosphine)nickel(0)***).[14] $Ni(PPh_3)_4$ has been used for the homocoupling of 2-halopyridines,[15] and α-halo ketones.[16] Cross coupling of distinct aryl halides by this method is generally not efficient due to extensive symmetrical coupling. Intramolecular couplings of bis(aryl halides), however, do not suffer from this limitation and give cyclized products.[17] These couplings work well for many different tether lengths (eq 2) and this strategy was utilized in the synthesis of the macrocyclic ketone alnusone.[18] The mild conditions of this reaction permit a wide variety of functional groups to be present without concern for the formation of byproducts or decomposition. This is in contrast to the copper catalyzed Ullmann reaction, which often requires harsh thermal conditions (>200 °C).[19]

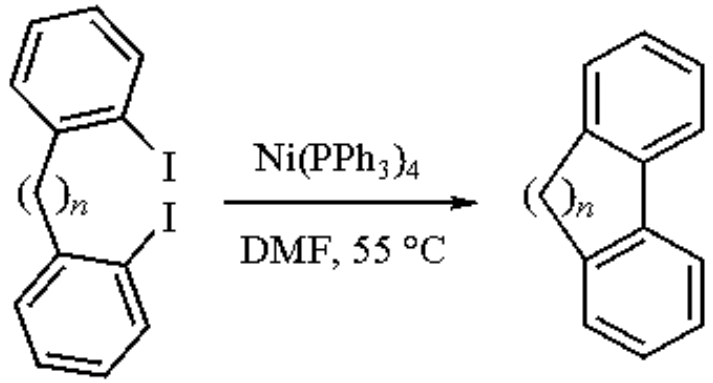

(2)

$n = 2$, 81%; 3, 83%; 4, 76%; 5, 85%; 6, 38%

Coupling Reactions with Organometallic Compounds.

The cross-coupling of aryl and alkenyl halides may be effected by the reaction of organometallic reagents with organic halides in the presence of $Ni(PPh_3)_4$. As before, oxidative addition of Ni^0 to the organic halide is the initial step in the mechanism. The transiently formed organonickel intermediate can then accept an organic group from the added metal reagent through ligand substitution, which leads, upon reductive elimination, to replacement of the original halide with this new group and regeneration of a catalytic nickel(0) species. While initial studies in this area were confined to highly reactive organomagnesium and -lithium reagents,[20] which limited their applicability in synthesis, more recent studies have shown that organic complexes of aluminum, zinc, and zirconium, among others, are all active for the coupling reaction.[21]

Recent uses of Grignard reagents in the presence of $Ni(PPh_3)_4$ include the reaction with trichloroethylene to give 1,1-dichloroalkenes,[22] with 1,2-dichloroethylenes to stereoselectively produce vinyl chlorides,[23] and with phenolic ethers to give arenes,[24] and the reaction of $TMSCH_2MgCl$ with vinyl iodides to give allyl silanes.[25] In addition, lithium enolates have been coupled with aryl halides inter- and intramolecularly.[26]

Alkenylalanes readily couple with aryl and alkenyl halides in the presence of $Ni(PPh_3)_4$ to give styrene and butadiene derivatives in good yields (eq 3).[21] *Trans*-alkenylalanes, which are readily obtainable by the carboalumination of alkynes, couple with retention of configuration at the double bond to provide an efficient route to *trans*-alkenes.[27] (*E*)-1,2-Dichloroethene was coupled with an alkenylalane to give a 1-chloro-(*E*,*E*)-1,3-diene in 80% yield.[28]

Alkenylzirconium reagents are similar to alkenylalanes in that they can be easily prepared by carbometalation of alkynes. They may be coupled with aryl, alkenyl, and alkynyl halides (eq 3).[21] The coupling is facilitated by the presence of added salts containing Zn or Cd such as ***Zinc Chloride***.[29]

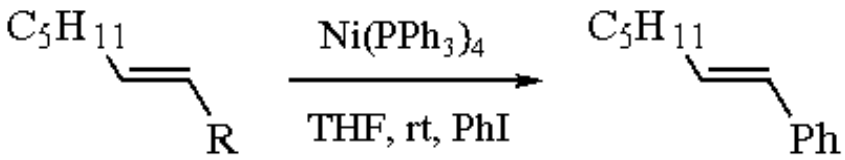

(3)

R = Al(*i*-Bu)$_2$, 91%; $ZrCp_2Cl$, 96%

Arylzinc compounds have also been reacted with aryl halides in good yields with very little homocoupling.[30] This mild coupling method was used with great success in the synthesis of a bisbenzocyclooctadiene lignan, steganone (eq 4).[31] Alkylzincs formed from the Reformatsky reagent also react with aryl halides to give arylacetic acid esters.[32] Benzylzinc compounds react with alkenyl halides in a similar fashion; however, palladium catalysts were found to be more suitable for this reaction due to extensive isomerization to the

conjugated isomers in the presence of nickel.[33] Knochel's (dialkoxyboryl)methylzinc reagents have also been coupled with greater success using palladium catalysts.[34]

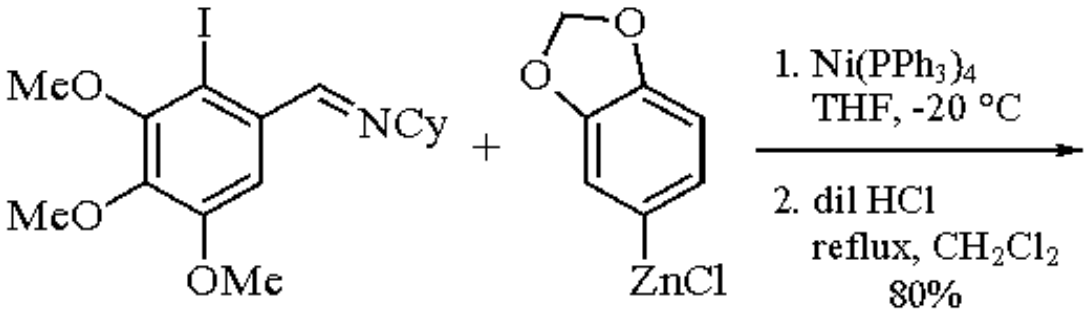

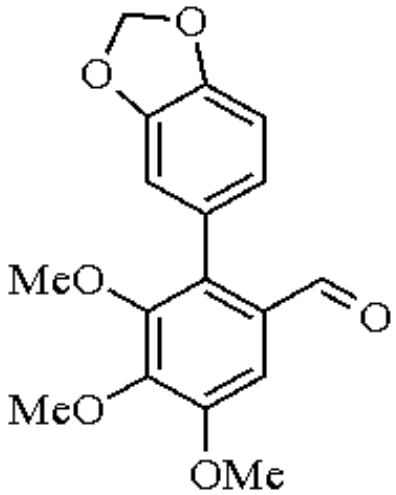

(4)

In general, the coupling reactions of aryl halides may be catalyzed with similar efficiency by palladium catalysts such as ***Tetrakis(triphenylphosphine)palladium(0)*** or $Cl_2Pd(PPh_3)_2$-***Diisobutylaluminum Hydride***. The nickel catalysts tend to be slightly more reactive, however, easily entering into reactions with both organic iodides and bromides, while the palladium catalysts sometimes require activated bromides to react.[30a] In the case of alkenyl halides, the nickel catalysts have shown slight (<=10%) stereochemical scrambling when coupled with alkenylalanes, whereas with the palladium catalysts the stereochemical integrity is &egt;97%.[27b] Palladium catalysts also have the added advantage that they are compatible with the nitro group, which nullifies the catalytic activity of the nickel(0) complexes,[30a] and coupling with boranes is possible.[35]

Cyclooligomerization of Cumulenes.

$Ni(PPh_3)_4$ reacts catalytically with cumulenes via a [2 + 2] cycloaddition to give [4]radialenes[36] and in a [2 + 2 + 2] fashion to give [6]radialenes. The choice of solvent affects the selectivity of some reactions, with benzene providing dimers and DMF leading primarily to the trimeric products.[37] Several extremely strained cyclobutanes have been prepared by this method.[38] Interestingly, the cumulene starting materials (**3**) can be prepared by the Ni^0 mediated coupling of 1,1-dihaloalkenes (**1**) and the subsequent Ni^0 catalyzed elimination of the 2,3-dihalo-1,3-butadiene products (**2**). Thus [4]radialenes (**4**) may be prepared in one step from 1,1-dihaloalkenes (**1**) (eq 5).[39]

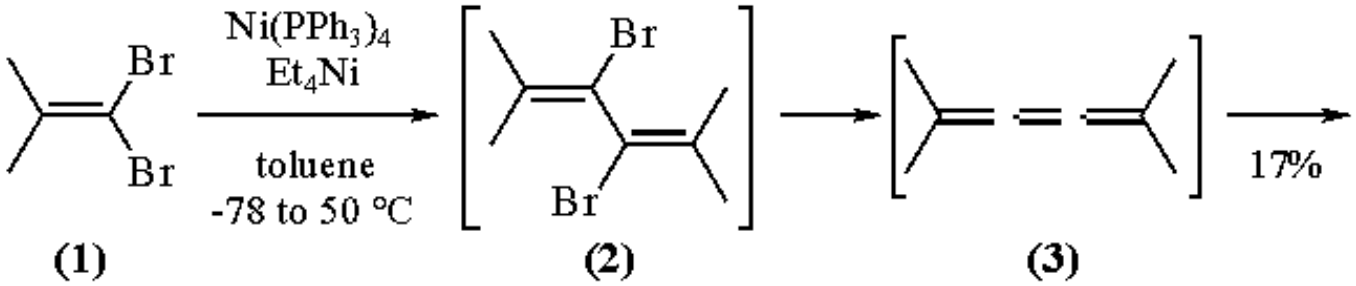

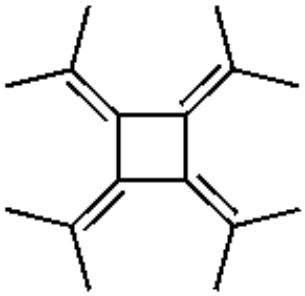

(4)

(5)

Other Uses.

Terminal alkenes may be prepared by the oxidative addition of primary halides to $Ni(PPh_3)_4$ followed by β-hydride elimination.[40] Cyclopropanation of electron-deficient alkenes is possible by the reaction of the complex with *gem*-dibromides or diazoalkanes.[41] Methylenecyclopropane is linearly trimerized selectively in the presence of this catalyst.[42] Tethered diynes react inter- and intramolecularly with alkynes in [2 + 2 + 2] cycloadditions to give tetralins (eq 6).[43]

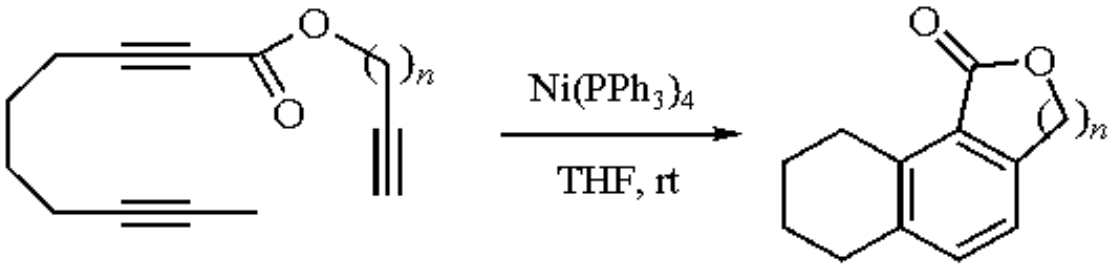

(6)

$n = 1$, 70%; 2, 46%

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43. Bhatarah, P.; Smith, E. H. *JCS(P1)* **1992**, 2163.

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Tetrakis(triphenylphosphine)palladium(0)[1]

$Pd(PPh_3)_4$

[14221-01-3] · $C_{72}H_{60}P_4Pd$ · Tetrakis(triphenylphosphine)palladium(0) · (MW 1155.62)

(catalyzes carbon-carbon bond formation of organometallics with a wide variety of electrophiles;[2] in combination with other reagents, catalyzes the reduction of a variety of functional groups;[3] catalyzes carbon-metal (Sn, Si) bond formation;[4] catalyzes deprotection of the allyloxycarbonyl group[5])

Physical Data: mp has been reported to vary between 100-116 °C (dec) and is not a good indication of purity.

Solubility: insol saturated hydrocarbons; moderately sol many other organic solvents including $CHCl_3$, DME, THF, DMF, PhMe, benzene.

Form Supplied in: yellow, crystalline solid from various sources. The quality of batches from the same source have been noted to be highly variable and can dramatically alter the expected reactivity.

Preparative Methods: readily prepared by the reduction of $PdCl_2(Ph_3P)_2$[6] with ***Hydrazine*** or by the reaction of ***Tris(dibenzylideneacetone)dipalladium*** with ***Triphenylphosphine***.[7]

Handling, Storage, and Precautions: is air and light sensitive and should be stored in an inert atmosphere in the absence of light. It can be handled for short periods quickly in the air but best results are achieved by handling in a glove box or glove bag under argon or nitrogen.

Direct Carbon-Carbon Bond Formation.

One of the most attractive features of $Pd(Ph_3P)_4$ is its ability to catalyze carbon-carbon bond formation under mild conditions by the cross-coupling of organometallic (typically organoaluminum,[2e] -boron,[2f] -copper, -magnesium, -tin,[2b-d] or -zinc[2e] reagents) and unsaturated electrophilic partners (halides or sulfonates such as trifluoromethanesulfonates[2d] (triflates)). Although $Pd(Ph_3P)_4$ is the catalyst of choice in many of these reactions, numerous other Pd^0 and Pd^{II} catalysts have been used successfully.

Symmetrical or unsymmetrical biaryls are efficiently produced by the $Pd(Ph_3P)_4$ catalyzed cross-coupling of aryl halides or aryl triflates (I, Br > OTf in terms of rate of reaction[8a]) with a variety of metalated aromatics such as arylboronic acids,[8] arylstannanes,[9] aryl Grignards[10] and arylzincs[11] (eqs 1 and 2). Reactions employing $ArB(OH)_2$ are carried out in aqueous base (2M Na_2CO_3 or K_3PO_4) while the remainder are conducted under anhydrous conditions. A recent report documents the reaction of $ArB(OR)_2$ with ArBr under nonaqueous conditions in the presence of ***Thallium(I) Carbonate***.[8c] Reactions employing ArOTf and $ArSnR_3$ as coupling partners require greater than stoichiometric amounts of ***Lithium Chloride***.[9a,b] Acceleration of the reaction rate has been noted in the coupling of $ArSnMe_3$ and either ArOTf or ArBr/I by the addition of catalytic ***Copper(I) Bromide***[9c] or stoichiometric ***Silver(I) Oxide***,[9f] respectively. In many cases, one or both of the aromatic species can be heteroaromatic such as pyridine, furan, thiophene, quinoline, oxazole, thiazole, or indole.[8e,9f,g,11] Symmetrical biaryls have been prepared in excellent yields by the $Pd(Ph_3P)_4$-catalyzed homocoupling of ArBr/I under phase transfer conditions.[12]

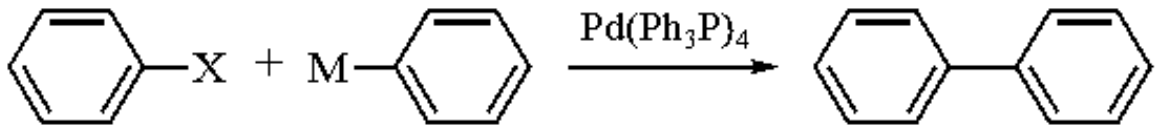

(1)

M = MgBr, X = I 70%
M = ZnCl, X = OSO_2F 95%

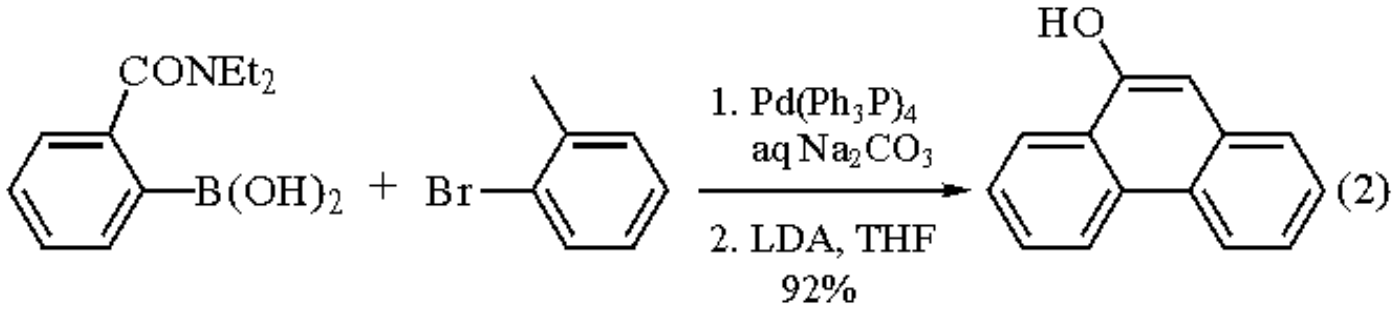

In a similar manner, $Pd(Ph_3P)_4$ catalyzes the cross-coupling of metalated alkenes, such as vinylaluminum reagents,[13] vinylboronates or -boronic acids,[8d,14] vinylstannanes,[15] vinylsilanes,[16] vinylzincs or -zirconates,[17] vinylcuprates[18] or -copper reagents[19] and vinyl Grignards[20] with vinyl halides (I, Br), triflates, or phosphates to form 1,3-dienes (eq 3). Vinylallenes,[17f] dienyl sulfides,[14h] and dienyl ethers[17d] have also been prepared using this strategy. In most instances the dienes are formed with retention of double bond geometry in both reacting partners.[14g] However, the formation of (*E*,*Z*)- and (*Z*,*Z*)-diene combinations has been documented to suffer from poor reaction yields or scrambling of alkene geometry in some cases (eq 4).[14a,b,18-20] A dramatic rate enhancement has been noted in the coupling of vinyl iodides with vinylboronic acids by replacing the aqueous bases that are normally used (NaOEt or NaOH) with ***Thallium(I) Hydroxide***[14f,i] or ***Thallium(I) Carbonate***.[21] LiCl[15a,c] is required when vinyl triflates are used in coupling reactions with vinylstannanes. Intramolecular versions of the vinylstannane-vinyl triflate coupling have been reported[22] and the necessity of adding LiCl in these reactions has been debated.[22a] 1,3-Dienes have been prepared via the $Pd(Ph_3P)_4$-catalyzed reaction between allylic alcohols and aldehydes in the presence of ***Phenyl Isocyanate*** and ***Tri-n-butylphosphine*** (eq 5).[23] (*E*/*E*):(*E*/*Z*) ratios range from 1:1 to 4:1.

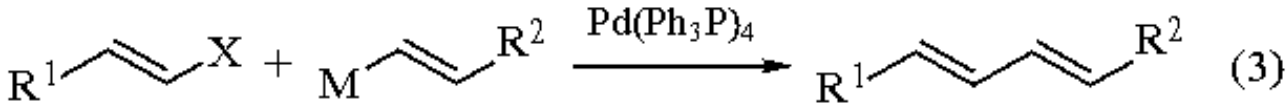

$R^1 = Hex$, $X = Br$; $M = B(DOB)$, $R^2 = Bu$ 86%
$R^1 = Bu$, $X = I$; $M = ZrCp_2Cl$, $R^2 = Hex$ 93%

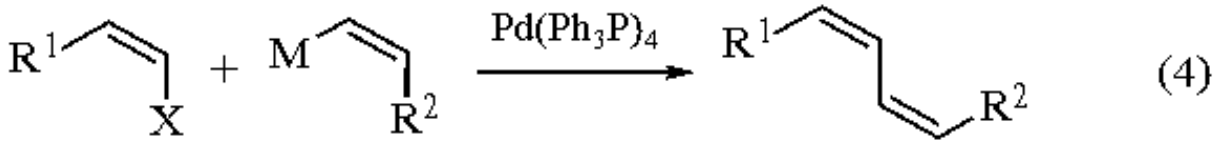

$R^1 = Bu$, $X = Br$; $M = B(sia)_2$, $R^2 = Hex$ 49%
$R^1 = t\text{-}Bu$, $X = I$; $M = Cu \cdot MgCl_2$, $R^2 = Pent$ 53%

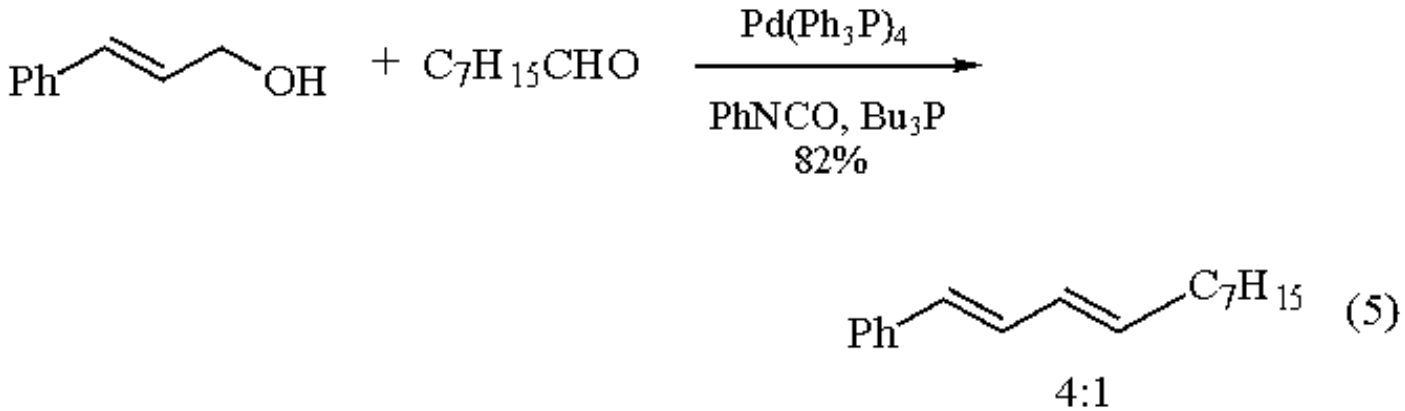

Similar cross-coupling procedures have been used to prepare styrenes by the reaction of metalated aromatics with vinyl halides/triflates[11d,24] or, conversely, metalated alkenes with aromatic halides/triflates[9b,16,25] in the presence of $Pd(Ph_3P)_4$ (eq 6). Typically, ArCl are poor substrates in $Pd(PPh_3)_4$-catalyzed coupling reactions. However, by forming the chromium tricarbonyl complex of the aryl chloride, a facile coupling reaction with vinylstannanes can be achieved (eq 7).[26]

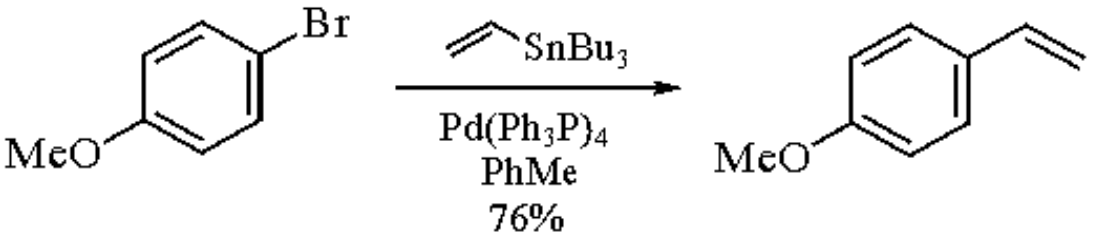

(6)

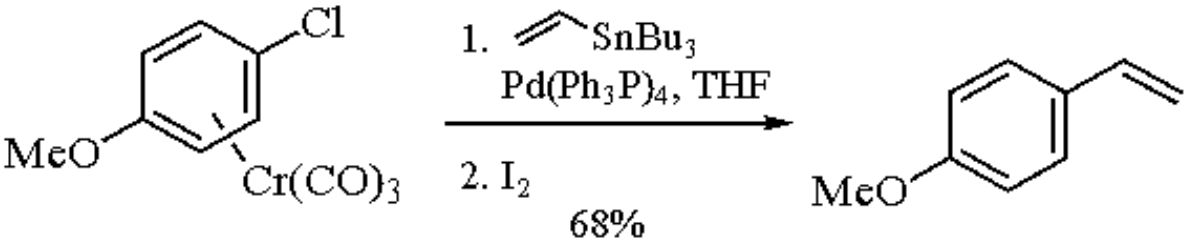

(7)

Enynes and arenynes are available from the $Pd(Ph_3P)_4$-catalyzed coupling of metalated alkynes (Mg,[20] Al,[13,27] Zn,[17f,28] Sn[15a,b,29]) with vinyl or aryl halides, triflates or phosphates (eq 8). Alternatively, 1-haloalkynes and metalated alkenes (B[14c] or Zn[11a,17a]) can be utilized in similar procedures.

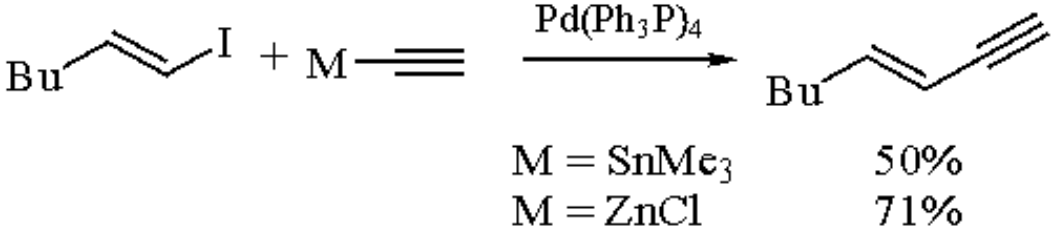

(8)

Enynes and arenynes can also be prepared by the $Pd(Ph_3P)_4$-catalyzed reaction between vinyl halides (I, Br, or Cl) and 1-alkynes in the presence of ***Copper(I) Iodide*** and an amine base such as RNH_2 (R = Bu, Pr), Et_2NH, or Et_3N.[30] A modified procedure employing aqueous base under phase transfer conditions has also been described (eq 9).[31] The arenyne products derived from such coupling reactions provide ready access to substituted indoles (eq 10).[29c,30d]

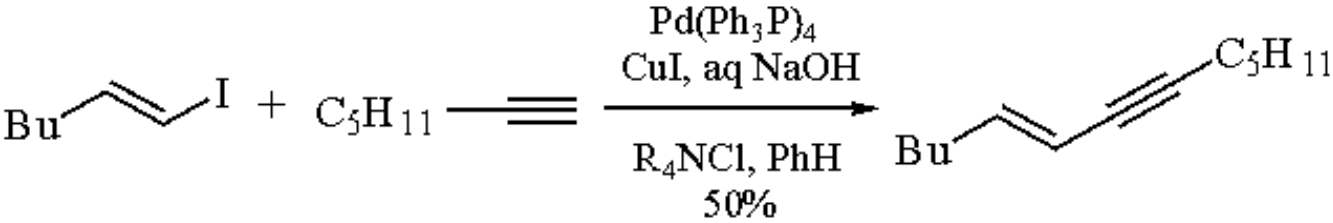

(9)

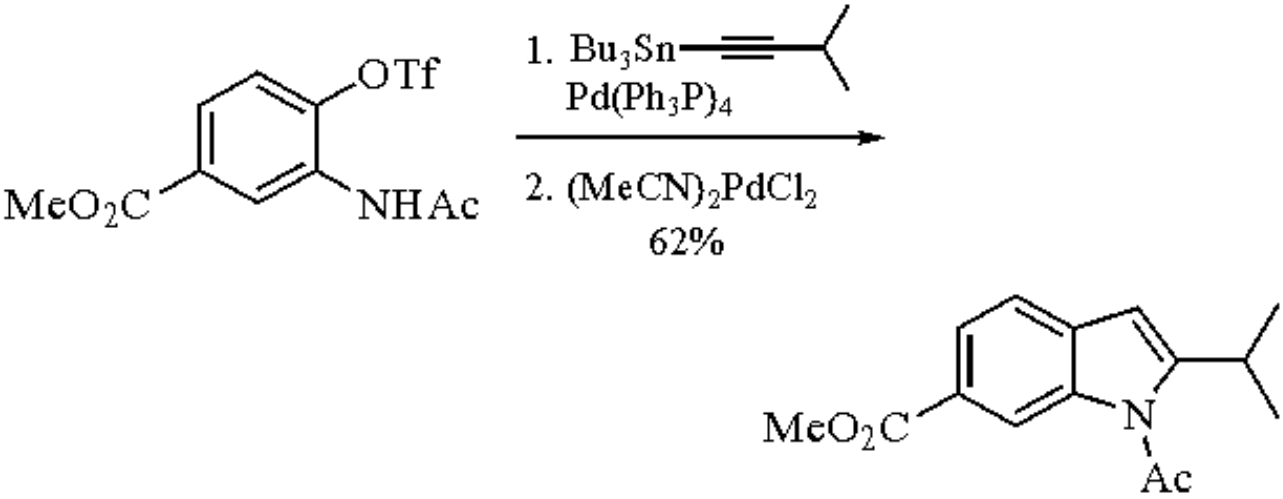

(10)

$Pd(Ph_3P)_4$ catalyzes the coupling of simple alkyl metals and vinyl halides (Br, I) or triflates to form substituted alkenes (eq 11). Alkylboron,[32] alkyl Grignard,[20,33] alkylzinc,[34] and alkylaluminum[13] reagents have been particularly useful in this regard. A variety of functional groups on either reacting partner are tolerated and the reaction proceeds with retention of alkene geometry (usually >98%),

providing stereochemically pure, highly substituted alkenes. For example, allylsilanes (eq 12)[35] and vinylcyclopropanes (eq 13)[36] have been prepared employing ***Trimethylsilylmethylmagnesium Chloride*** and cyclopropylzinc chloride, respectively, as the organometallic partner.

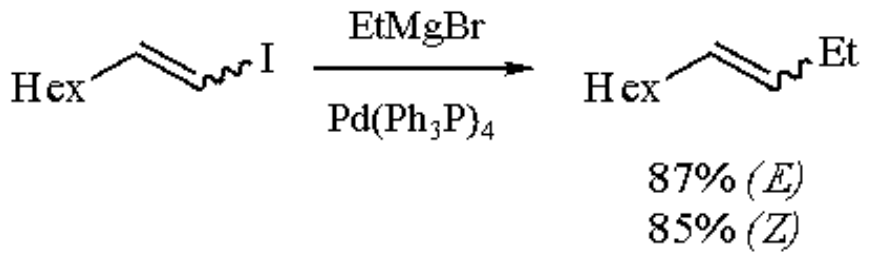

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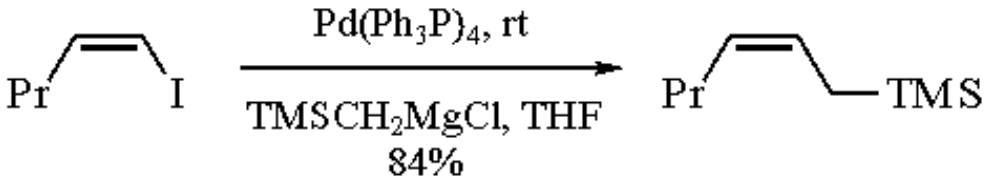

(12)

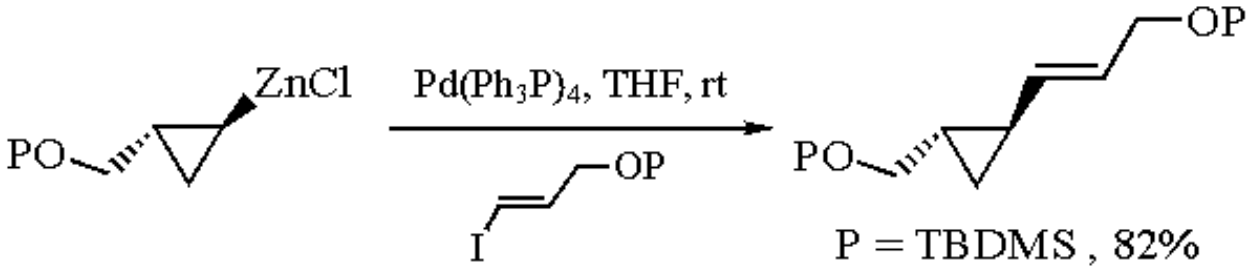

(13)

Ketones are obtained by the $Pd(Ph_3P)_4$-catalyzed coupling of acid chlorides with organometallic reagents (eq 14). Organozinc[37] and organocopper[38] reagents have been used most successfully, while other reports document the utility of R_4Pb (R = Bu, Et),[39] R_4Sn (R = Me, Bu, Ph),[40] and R_2Hg (R = Et, Ph)[41] reagents in this reaction. For those cases in which the organometallic reagent is alkenic, complete retention of alkene geometry is observed (see eq 14). In addition, the formation of tertiary alcohols is not observed under the conditions employed. A modified procedure that substitutes alkyl chloroformates for acid chlorides leads to an efficient preparation of esters (eq 15).[37b,38] In a related reaction, $Pd(Ph_3P)_4$ catalyzes the coupling reaction between substituted aryl- or alkylsulfonyl chlorides and vinyl- or allylstannanes, providing a general route to sulfones (eq 16).[42]

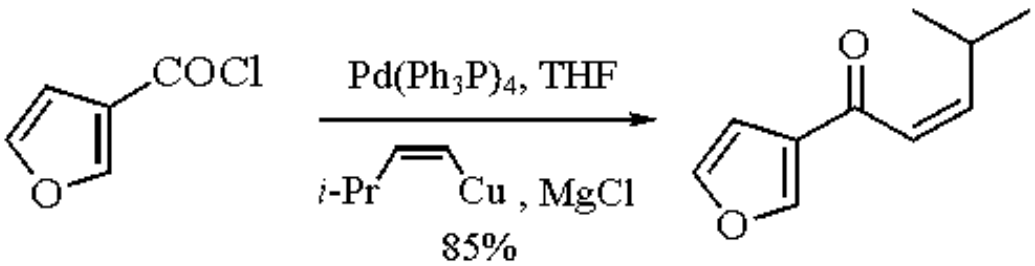

(14)

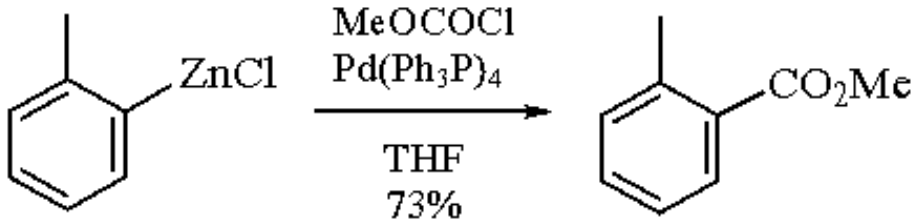

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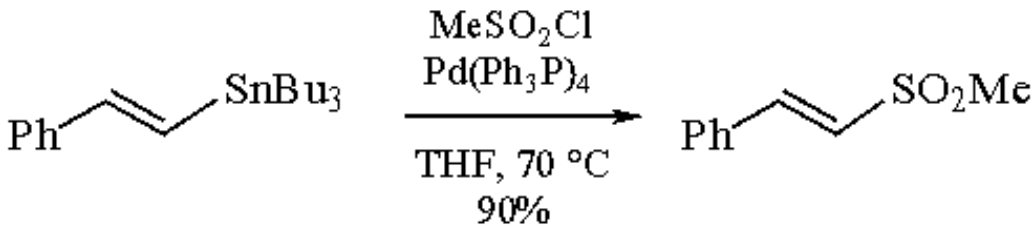

(16)

The $Pd(Ph_3P)_4$-catalyzed reaction of various allylic electrophiles with carbon-based nucleophiles is a very useful method for the formation of C-C bonds under relatively mild conditions (eq 17) and has been extensively reviewed elsewhere.[2a,43] The most commonly used electrophilic substrates for $Pd(Ph_3P)_4$-catalyzed allylic substitution reactions are allylic esters, carbonates, phosphates, carbamates, halides, sulfones, and epoxides. More recently, allylic alcohols themselves have been demonstrated to be useful substrates.[44] Commonly employed nucleophiles include soft stabilized carbanions such as malonate and, to a lesser extent, a variety of organometallic reagents (Al, Grignards, Sn, Zn, Zr). A few selected examples begin to illustrate the scope of this reaction in terms of the general patterns of reactivity with respect to regioselectivity (eqs 18 and 19) and stereoselectivity (eqs 17 and 18). It should be noted that a variety of other Pd catalysts (including ***Palladium(II) Acetate-1,2-Bis(diphenylphosphino)ethane*** and ***Bis(dibenzylideneacetone)palladium(0)***) have been shown to be useful in these alkylations. In addition, certain nitrogen-, sulfur-, and oxygen-based reagents are suitable nucleophilic substrates. The utility of some of these latter reagents are covered in subsequent sections.

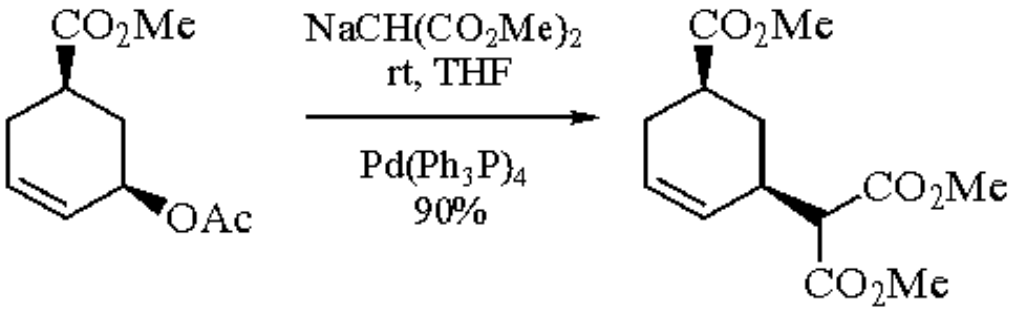

(17)

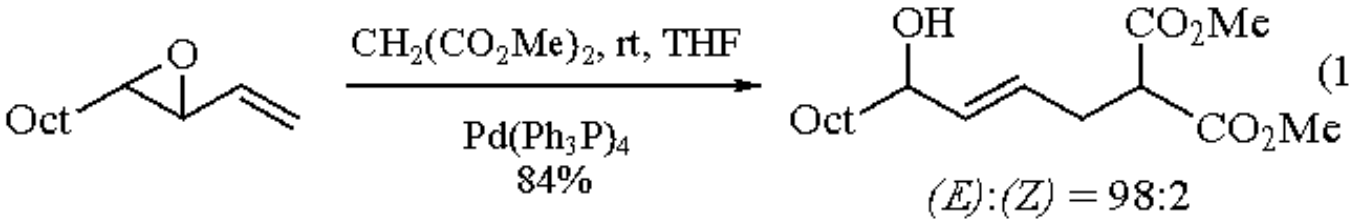

(18)

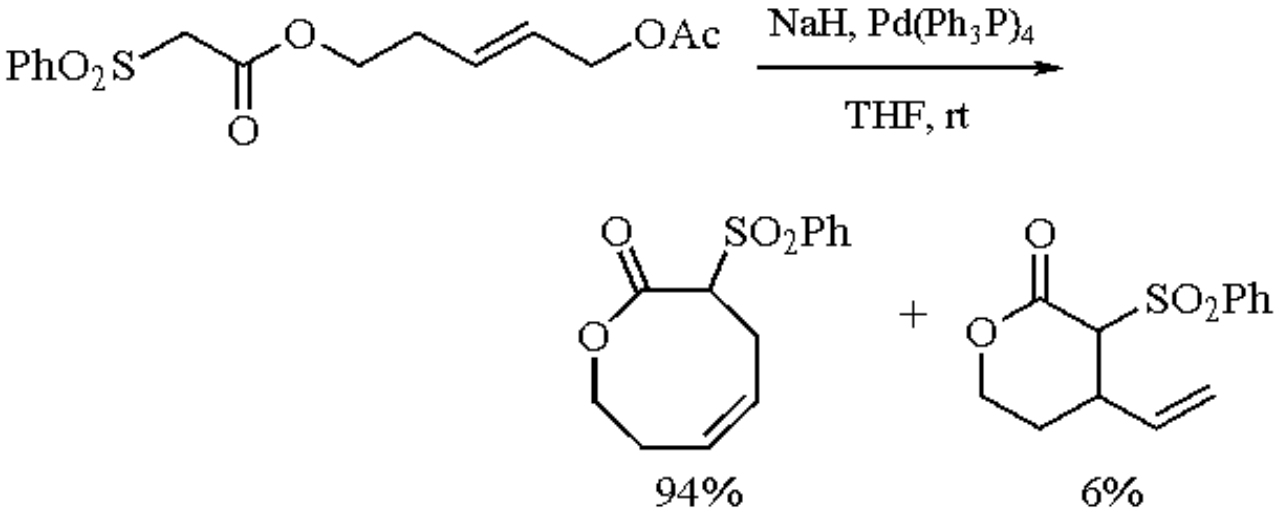

(19)

Aldehydes and α-bromo ketones or esters are efficiently coupled in an aldol reaction in the presence of ***Diethylaluminum Chloride-Tri-n-butylstannyllithium*** (or ***Tin(II) Chloride***) and catalytic $Pd(Ph_3P)_4$, providing β-hydroxy ketones or esters (eq 20).[45]

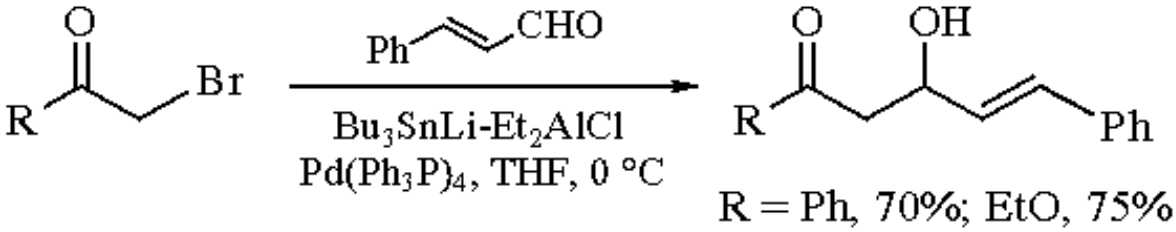

(20)

Carbonylative Carbon-Carbon Bond Formation.

A general, mild (50 °C), and high yielding conversion of halides and triflates into aldehydes via $Pd(Ph_3P)_4$-catalyzed carbonylation (1-3

atm CO) in the presence of ***Tri-n-butylstannane*** has been described (eq 21).[46] The range of usable substrates is extensive and includes ArI, benzyl and allyl halides, and vinyl iodides and triflates. The reaction has been extended to include ArBr by carrying out the carbonylation at 80 °C under pressure (50 atm CO), using poly(methylhydrosiloxane) (PMHS) instead of tin hydride.[47]

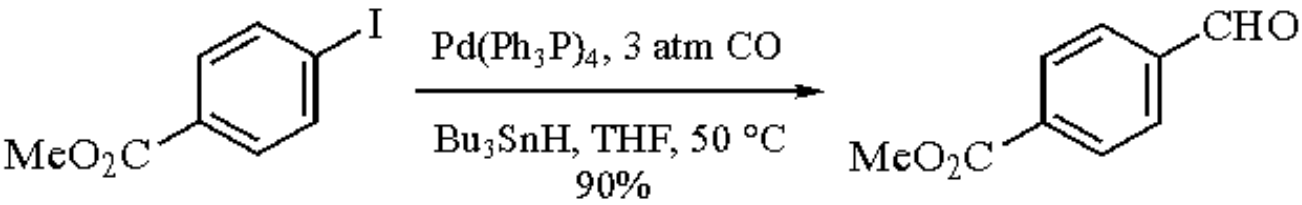

(21)

$Pd(Ph_3P)_4$ catalyzes the carbonylation of benzyl[48a] and vinyl[48b] bromides under phase transfer conditions in the presence of hydroxide to form the corresponding carboxylic acids. A wide variety of substitution is tolerated and the products are formed in moderate to excellent yield at room temperature and at normal pressure (1 atm CO). Extension of the reaction to the formation of esters from aryl, alkyl, and vinyl bromides has been described.[49] These transformations usually require a co-catalyst system of $Pd(Ph_3P)_4$ and $[(1,5\text{-cyclohexadiene})RhCl]_2$ in the presence of either $M(OR)_4$ (M = Ti, Zr) or $M(OR)_3$ (M = B, Al) (eq 22).

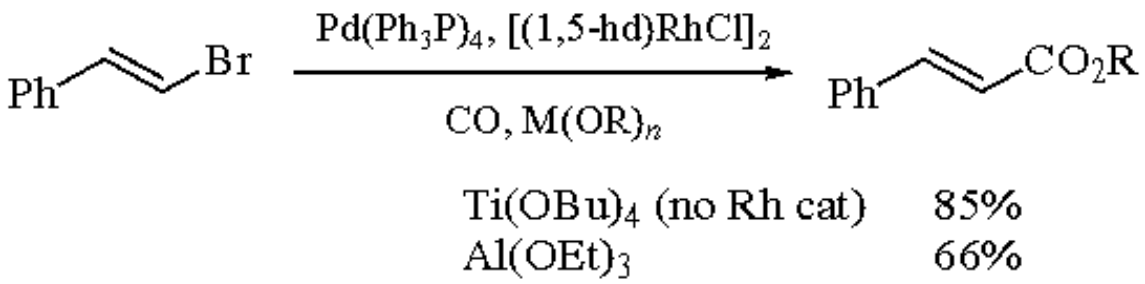

(22)

Vinyl triflates serve as substrates for $Pd(Ph_3P)_4$-catalyzed carbonylation and have been converted into the corresponding esters[50] or ketones[15c,51] (eq 23).

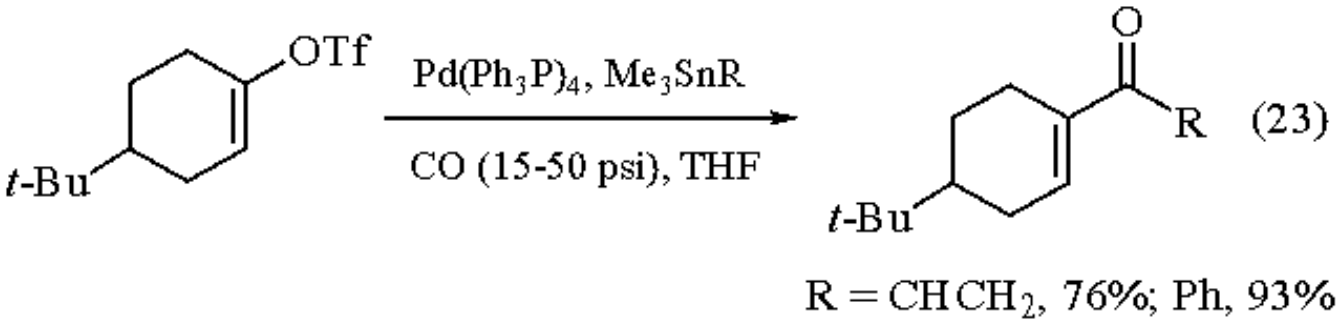

(23)

Aromatic and Vinyl Nitriles.

Aromatic halides (Br, I) have been converted into nitriles in excellent yields by $Pd(Ph_3P)_4$ catalysis in the presence of ***Sodium Cyanide/Alumina***,[52] ***Potassium Cyanide***,[53] or ***Cyanotrimethylsilane***[54] (eq 24). While the latter two procedures require the use of ArI as substrates, a more extensive range of substituents are tolerated than the alternative method employing ArBr. A $Pd(Ph_3P)_4$-catalyzed extrusion of CO from aromatic and heteroaromatic acyl cyanides (readily available from cyanohydrins) at 120 °C provides aryl nitriles in excellent yields (eq 25).[55]

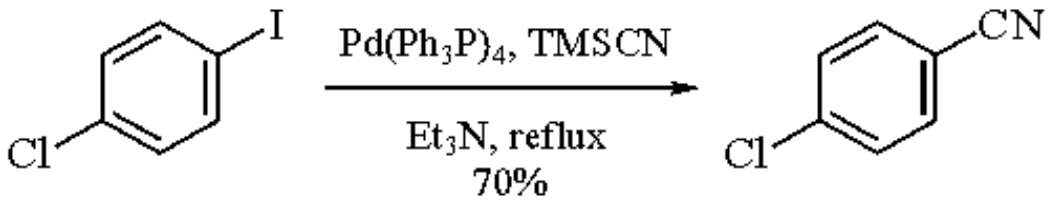

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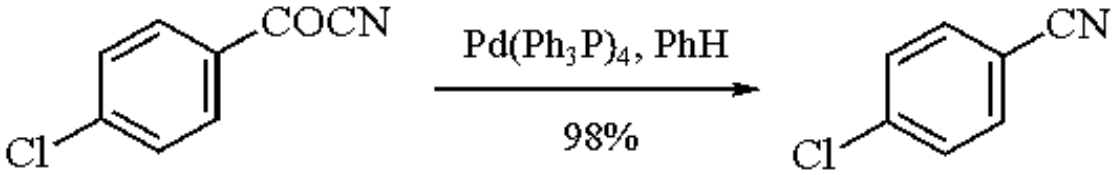

(25)

Similarly, vinyl halides (Br, Cl) provide vinyl nitriles upon treatment with $Pd(Ph_3P)_4$/***Potassium Cyanide/18-Crown-6***.[56]

Carbon-Heteroatom (N, S, O, Sn, Si, Se, P) Bond Formation.

Primary and secondary amines (but not ammonia) undergo reaction with allylic acetates,[57] halides,[58] phosphates,[59] and nitro compounds[60] in the presence of $Pd(Ph_3P)_4$ to provide the corresponding allylic amines (eq 26). A variety of ammonia equivalents have been demonstrated to be useful in this $Pd(Ph_3P)_4$-catalyzed alkylation, including 4,4´-dimethoxybenzhydrylamine,[57c] NaNHTs,[58] and NaN_3[61] (eq 26). Both allylic phosphates and chlorides react faster than the corresponding acetates[58,59a] and (*Z*)-alkenes are isomerized to the (*E*)-isomers.[57a,59a] The use of primary amines as nucleophiles in the synthesis of secondary allyl amines is sometimes problematic since the amine that is formed undergoes further alkylation to form the tertiary amine. Thus hydroxylamines have been shown to be useful primary amine equivalents (eq 27) since the reaction products are easily reduced to secondary amines.[59b]

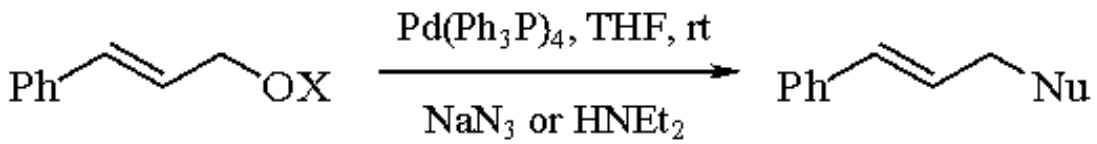

(26)

$X = PO(OEt)_2$, $Nu = NEt_2$ 68%
$X = Ac$, $Nu = N_3$ 88%

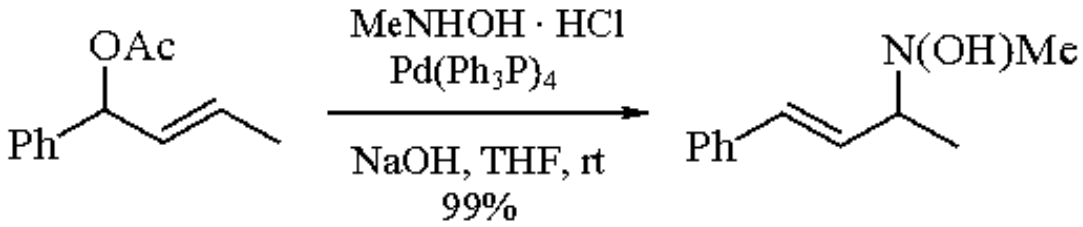

(27)

Allyl sulfones can be obtained by the $Pd(Ph_3P)_4$-catalyzed reaction of allylic acetates[62] and allylic nitro compounds[63,64] with $NaSO_2Ar$ (eq 28). $Pd(Ph_3P)_4$ also catalyzes the addition of HOAc to vinyl epoxides, providing a facile entry into 1,4-hydroxy acetates.[65]

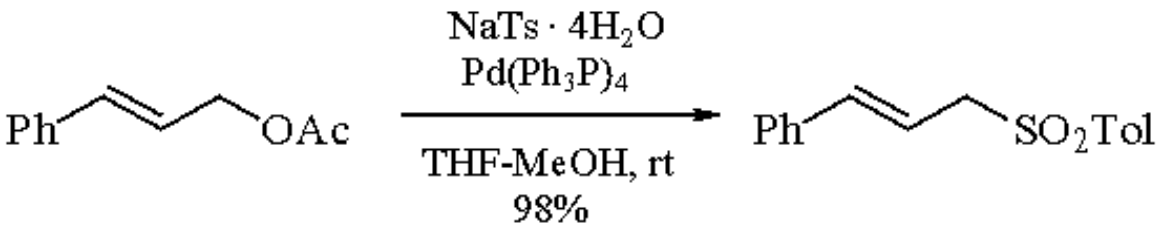

(28)

Aryl halides (Br, I) have been converted in good yields into the corresponding arylstannanes or -silanes by treatment with R_6Sn_2 (R = Bu, Me)[4,66] or ***Hexamethyldisilane***,[67] respectively, in the presence of catalytic $Pd(Ph_3P)_4$ (eq 29). Aryl[9a,b] and vinyl[15b,68] triflates produce aryl- and vinylstannanes under similar conditions, provided ***Hexamethyldistannane*** and LiCl are used as co-reactants. In some cases, the presence of additional Ph_3P has been observed to improve yields.[68] By using the $(Ph_3Sn)_2Zn$-TMEDA complex, vinyl halides can also be converted into vinylstannanes.[69]

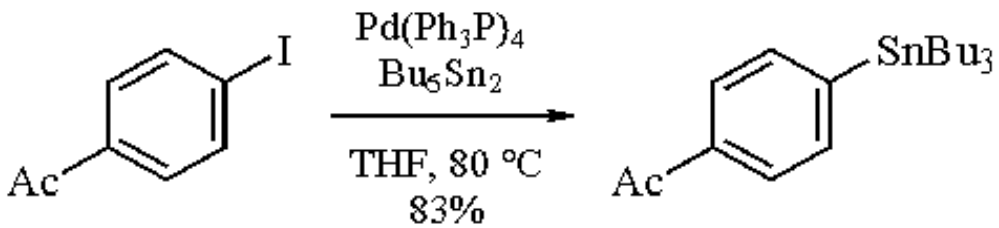

(29)

Acyltrimethylstannanes can be prepared in moderate yields by the treatment of acid chlorides with Me_6Sn_2 and catalytic $Pd(Ph_3P)_4$ in refluxing THF.[70c] However, $Pd(Ph_3P)_2Cl_2$ is a superior catalyst for this transformation when using sterically bulky or electron-poor acyl halides.

$Pd(Ph_3P)_4$ catalyzes the addition of R_6Sn_2,[70] R_6Si_2,[71] Ph_2S_2, and ***Diphenyl Diselenide***[72] across the triple bond of 1-alkynes to provide the respective (*Z*)-1,2-addition products (eq 30). The (*Z*)-distannanes can be partially isomerized to the (*E*)-isomers by photolysis.[70] The reaction cannot be extended to include internal alkynes containing alkyl substituents, but allenes do undergo 1,2-addition of disilane[73] and ditin.[74] In a similar fashion, $Pd(PPh_3)_4$ catalyzes the regio- and stereospecific addition of $R_3Sn\text{-}SiR_3$ to 1-alkynes, the (*Z*)-1-silyl-2-stannylalkene isomers being the sole products (eq 30).[75]

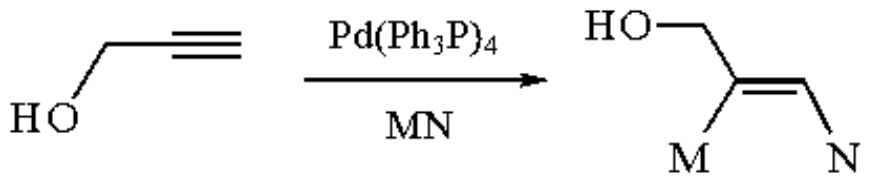

(30)

M = N = SPh	79%
M = N = $SnBu_3$	59%
M = $SnMe_3$, N = TMS	51%

α,β-Acetylenic esters react with R_6Sn_2 in the presence of $Pd(Ph_3P)_4$ at room temperature to provide only the (*Z*)-2,3-distannylalkenoates (eq 31).[76] When heated to 75-95 °C, clean isomerization to the (*E*)-isomers is observed. The corresponding amides are also useful substrates but provide either the (*E*)-isomers directly or (*E*/*Z*)-distannane mixtures.[76] Surprisingly, under similar reaction conditions, α,β-alkynic aldehydes and ketones form (*Z*)-β-stannyl enals and enones in excellent yields (eq 32).[77]

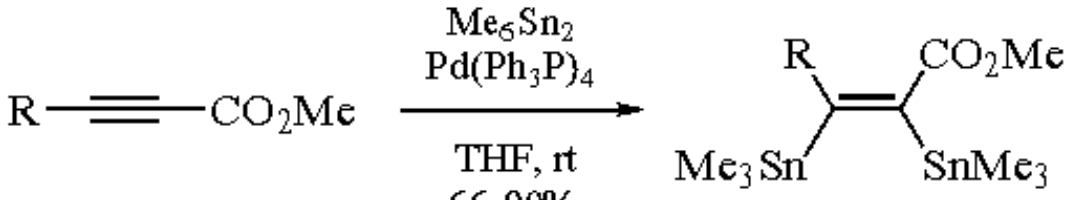

(31)

R = Me, TBDMSOCH$_2$

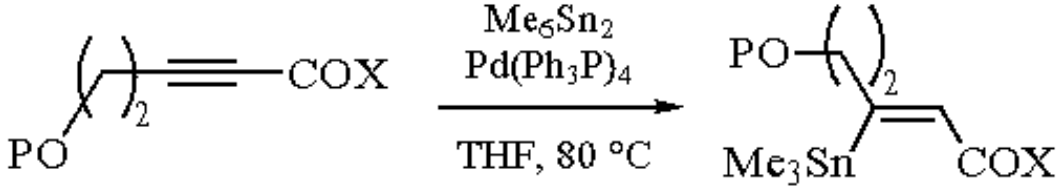

(32)

P = TBDMS X = H, 87%; Me, 90%

The $Pd(Ph_3P)_4$-catalyzed hydrostannylation of 1-alkynes with R_3SnH provides mixtures of vinylstannane regio- and stereoisomers, the ratios depending upon the nature of the alkyne substituents and the R group of the tin reagent.[78] In general, when using alkyl-substituted 1-alkynes, ***Triphenylstannane*** provides (*E*)-1-stannylalkenes[78a] as the major products, while 2-stannylalkenes are obtained predominantly with $(Bu_3Sn)_2Zn$[78c] (eq 33). The $Pd(Ph_3P)_4$ mediated *cis* addition of $R_3Sn\text{-}H$ across symmetrical internal alkynes has also been demonstrated to be generally high yielding.[78b] The hydrostannylation of α,β-unsaturated nitriles with $Bu_3SnH/Pd(Ph_3P)_4$ is regioselective, providing α-stannyl nitriles as the sole products.[79]

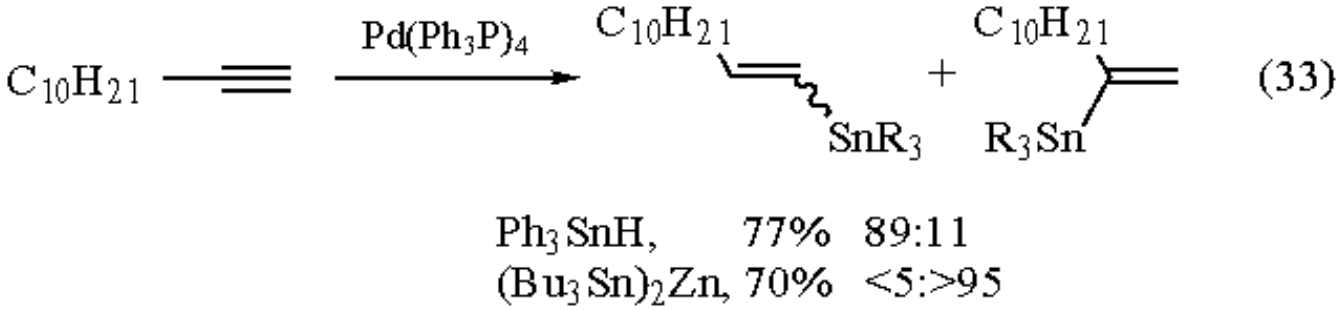

The $Pd(Ph_3P)_4$-mediated preparation of allyl- and benzylstannanes has been achieved by treatment of allylic acetates with $Et_2AlSnBu_3$[80] or by reacting benzyl halides (Br, Cl) with R_6Sn_2.[66c] In a similar fashion, allyl- and benzylsilanes are prepared by the $Pd(Ph_3P)_4$-catalyzed reaction of R_6Si_2 with allylic halides[81] and benzyl halides,[4] respectively. Allylstannanes have also been prepared by the addition of Bu_3SnH to 1,3-dienes in the presence of $Pd(Ph_3P)_4$ (eq 34).[82]

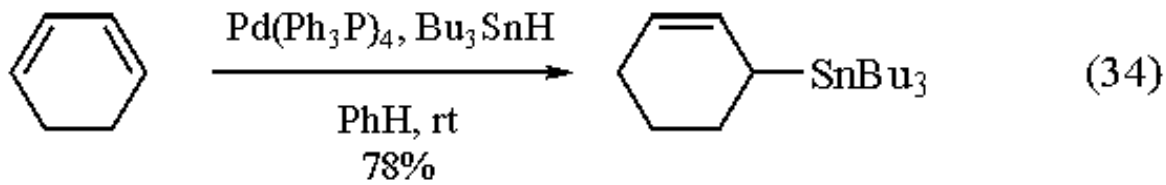

Dialkyl aryl- and vinylphosphonates ($RPO(OR')_2$) are readily prepared in excellent yields by the reaction of aryl or vinyl bromides, respectively, with dialkyl phosphite ($HPO(OR')_2$) in the presence of catalytic $Pd(Ph_3P)_4$ and Et_3N.[83] In a related process, unsymmetrical alkyl diarylphosphinates (ArPhPO(OR)) are obtained in good yields, regardless of aromatic substitution, by the $Pd(Ph_3P)_4$-catalyzed coupling reaction between aryl bromides and alkyl benzenephosphonites (HPhPO(OR)).[84]

Oxidation Reactions.

α-Bromo ketones are dehydrobrominated to produce enones in low to good yields, especially when the products are phenolic, by treatment with stoichiometric $Pd(Ph_3P)_4$ in hot benzene.[85] Primary and secondary alcohols are oxidized in the presence of PhBr, base (NaH or K_2CO_3) and $Pd(Ph_3P)_4$ as catalyst to the corresponding aldehydes or ketones.[86] The practical advantages of these methods to alternative strategies have yet to be demonstrated.

Reduction Reactions.

At elevated temperatures (100-110 °C), ArBr and ArI are reduced to ArH in the presence of catalytic $Pd(Ph_3P)_4$ and reducing agents such as HCO_2Na (eq 35),[3,87] NaOMe,[88] and PMHS/Bu_3N.[3] Aldehydes, ketones, esters, acids, and nitro substituents are unaffected. ArCl are poor substrates unless the aromatic nucleus is substituted with NO_2.[88] ArOTf are reduced in poorer yield under similar conditions; $Pd(OAc)_2$ and $Pd(Ph_3P)_2Cl_2$ are superior catalysts with these substrates.[89] A limited number of examples of the $Pd(PPh_3)_4$-catalyzed reduction of vinyl bromides and triflates to alkenes in the presence of HCO_2Na[3] and Bu_3SnH,[15a,b] respectively, have been described.

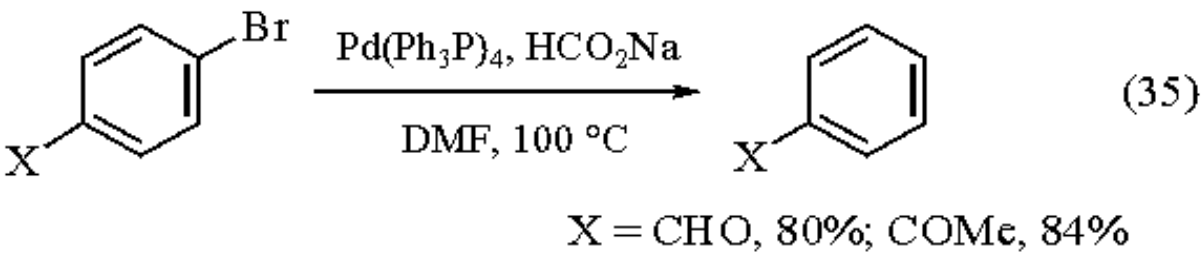

$Pd(Ph_3P)_4$ catalyzes the reductive displacement of a variety of allylic substituents with hydride transfer reagents. Allylic acetates are reduced to simple alkenes in the presence of ***Sodium Cyanoborohydride***,[90] PMHS,[91] ***Samarium(II) Iodide***/*i*-PrOH,[92] or Bu_3SnH[93] (eq 36). $Bu_3SnH/Pd(Ph_3P)_4$ also reduces allylic amines[93] and thiocarbamates.[94] All of these reductive procedures are accompanied by positional and/or geometrical isomerization of the alkene to an extent dependent upon the substrate structure. Interestingly, the $Pd(Ph_3P)_4$-catalyzed reduction of allylic sulfones with ***Sodium Borohydride*** is high yielding with no double bond positional isomerization observed.[95] By using a more bulky reducing agent, ***Lithium Triethylborohydride***, a range of allylic groups, such as methyl, phenyl, and silyl ethers, sulfides, sulfones, selenides, and chlorides, are reduced to alkenes in the presence of $Pd(Ph_3P)_4$ and excess Ph_3P with little or no loss of alkene regio- or stereochemistry (eq 37).[96] An interesting $Pd(Ph_3P)_4$-catalyzed reduction of allylic acetates, tosylates, and chlorides to the

corresponding alkenes has been described that uses *n*-BuZnCl as the hydride source.[97] This procedure proceeds with high levels of regio- and stereospecificity, but the scope has yet to be explored.

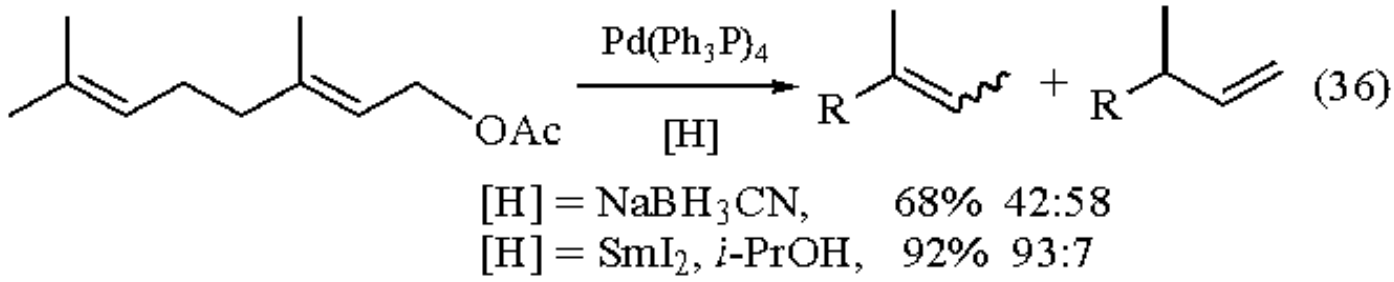

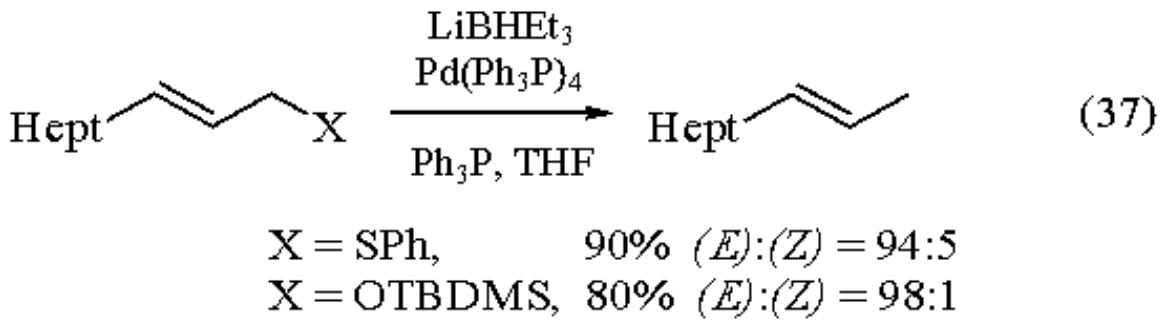

Acid chlorides[98] and acyl selenides[99] are efficiently reduced in the presence of Bu_3SnH under $Pd(Ph_3P)_4$ catalysis to provide the corresponding aldehydes in good to excellent yields without the formation of ester or alcohol byproducts (eq 38). A wide variety of substrate substituents, such as alkenes, nitriles, bromides, and nitro groups, are tolerated.

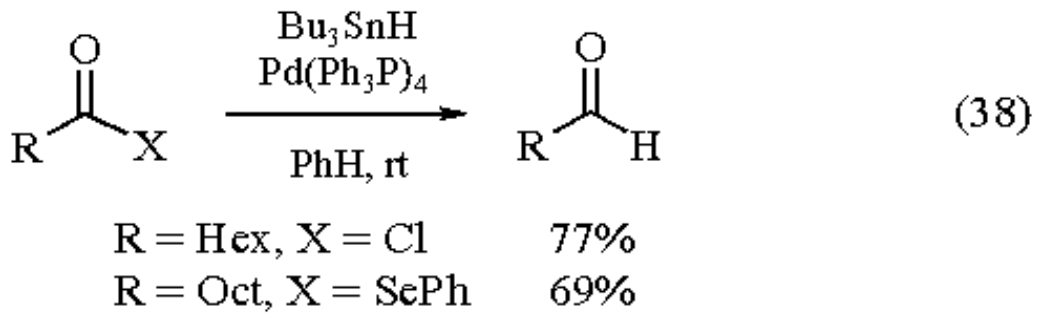

The conjugate reduction of α,β-unsaturated ketones and aldehydes to the saturated analogs can be accomplished in the presence of $Pd(Ph_3P)_4$ and hydride transfer reagents such as Bu_3SnH[100] or mixed systems of Bu_3SnH/HOAc or $Bu_3SnH/ZnCl_2$.[79] A potentially more versatile, general, and selective reduction procedure involves a three-component system of $Pd(Ph_3P)_4/Ph_2SiH_2/ZnCl_2$ (eq 39).[101] α,β-Unsaturated esters and nitriles are untouched using this latter method.

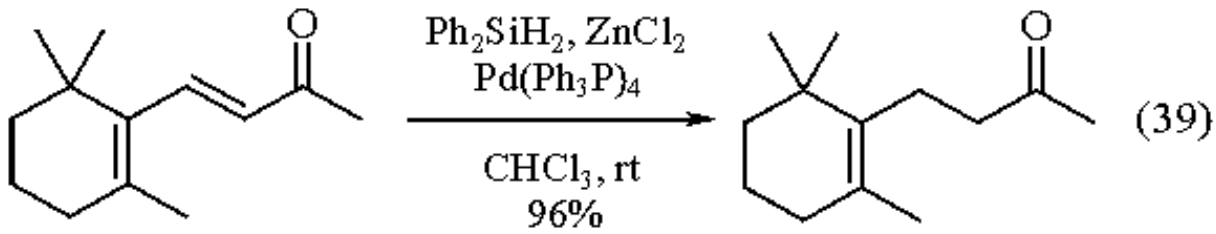

α-Bromo ketones are reductively debrominated to the parent ketones in the presence of $Pd(Ph_3P)_4$ and Ph_2SiH_2/K_2CO_3 at room temperature.[102] However, ***Hexacarbonylmolybdenum*** appears to be a superior catalyst for this conversion. Reductive debromination of α-bromo ketones, acids, and nitriles can also be accomplished by $Pd(Ph_3P)_4$ catalysis using PMHS/Bn_3N,[87b] HCO_2Na,[87b] or Me_6Si_2[103] as hydrogen donors but under much more drastic conditions (110-170 °C).

Removal of Allyloxycarbonyl (Aloc) and Allyl Protecting Groups.

The allyloxycarbonyl protecting group[5] has been used extensively for the protection of a variety of alcohols[104] and amines,[105] including the amines of nucleotide bases,[106] *N*-terminal amines of amino acids and peptides,[107] and amino sugars.[108] $Pd(Ph_3P)_4$ mediates the high

yielding removal of the Aloc group in the presence of nucleophilic allyl scavengers (eq 40) such as Bu_3SnH, 2-ethylhexanoic acid, dimedone, malonate, ***Ammonium Formate***, ***N-Hydroxysuccinimide***, and various amines including ***Morpholine*** and ***Pyrrolidine***. The deprotections are effected at or below room temperature, often in the presence of excess Ph_3P. The mild conditions used in these procedures leave most of the common N or O protecting groups intact, including Boc, TBDMS, MMT, DMT, and carbonates.

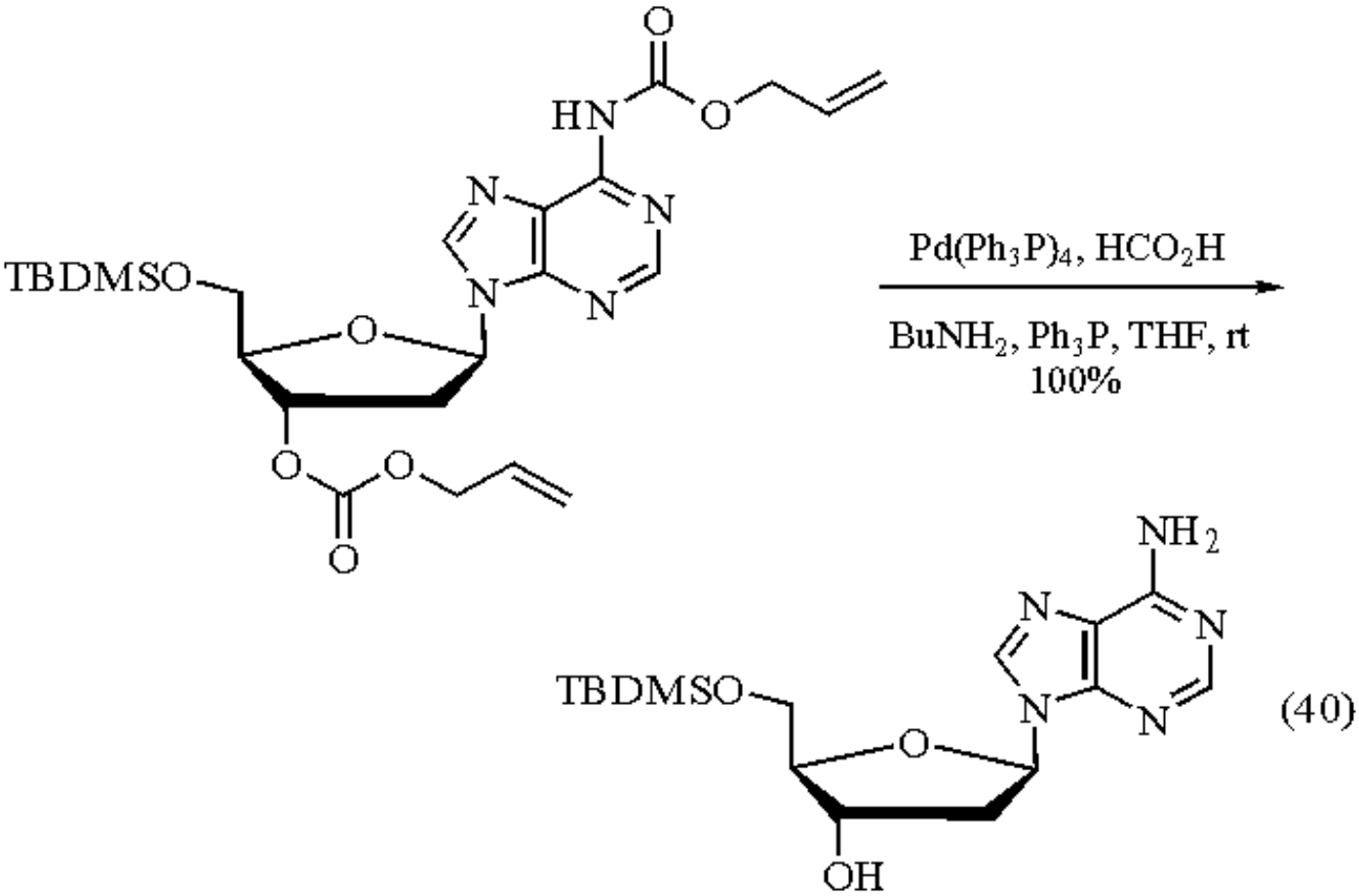

(40)

The $Pd(Ph_3P)_4$-catalyzed removal of the *O*-allyl protecting group has been described for a number of systems.[5] For example, allyl esters are efficiently cleaved to the parent acid in chemically sensitive systems such as penicillins[105,109] and glycopeptides.[110] The internucleotide phosphate linkage, protected as the allyl phospho(III)triester, remains intact upon deprotection under $Pd(Ph_3P)_4$ catalysis.[111] Allyl ethers that protect the anomeric hydroxy in carbohydrates (mono- and disaccharides) are efficiently removed under $Pd(Ph_3P)_4$ catalysis in hot (80 °C) HOAc.[112]

Rearrangements, Isomerizations and Eliminations.

$Pd(Ph_3P)_4$ catalyzes several [3,3]-sigmatropic rearrangements including those of *O*-allyl phosphoro- and phosphonothionates to the corresponding *S*-allyl thiolates (eq 41)[113] and allylic *N*-phenylformimidates to *N*-allyl-*N*-phenylformamides (eq 42).[114] The 3-aza-Cope rearrangement of *N*-allylenamines to γ,δ-unsaturated imines (eq 43)[115] and a Claisen rearrangement but with no allyl inversion[116] have also been described. In general, these $Pd(Ph_3P)_4$-catalyzed rearrangements provide compounds that are either not accessible via thermal reactions or are produced only under much more forcing reaction conditions. For those cases in which the allyl moiety contains substituents that may lead to regioisomers upon rearrangement, the less substituted isomer is usually favoured[113,115] (see eq 41), although exceptions are known.[114]

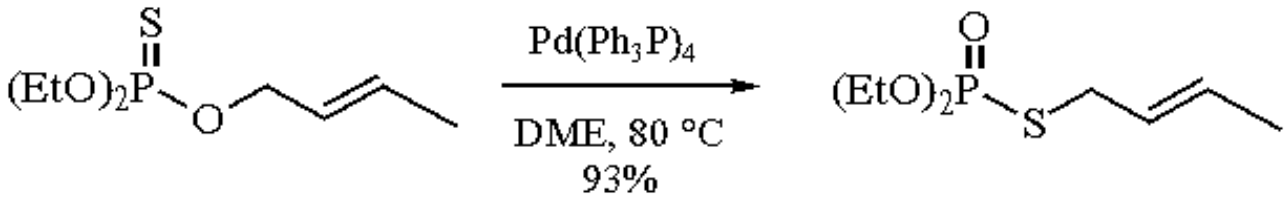

(41)

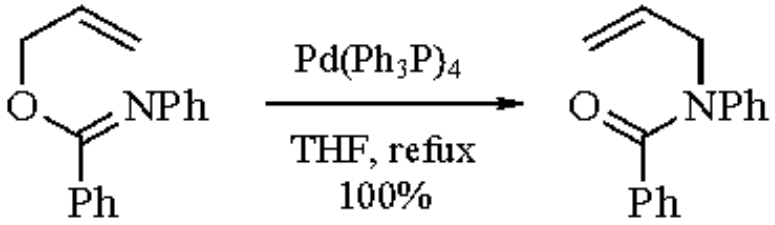

(42)

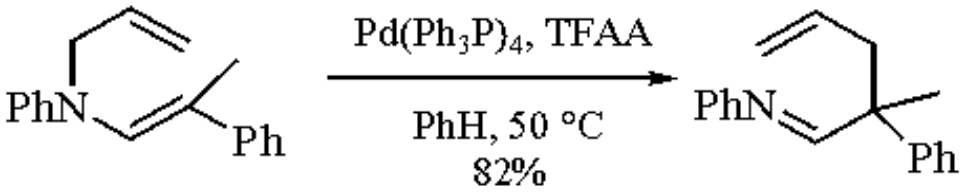

(43)

$Pd(Ph_3P)_4$ catalyzes stereoselective, intramolecular metallo-ene reactions of acetoxydienes in HOAc, efficiently generating a range of cyclic 1,4-dienes (eq 44).[117] The reactions proceed in good to excellent yields and have been extended to include the preparation of pyrrolidines, piperidines, and tetrahydrofurans by incorporating N and O atoms into the bridge that tethers the reactive alkenes.

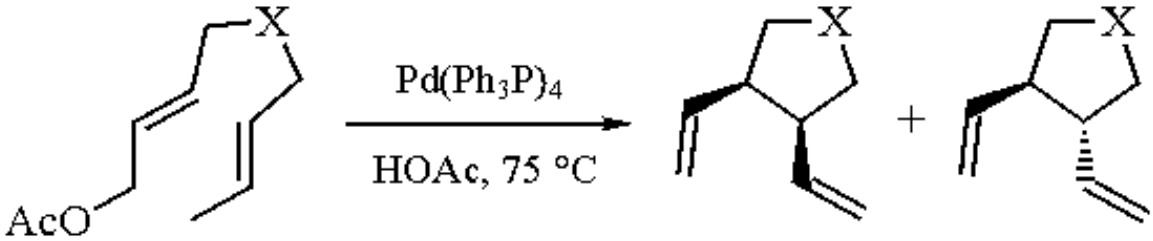

(44)

$X = C(CO_2Me)_2$, 52% 10:90
$X = NCOCF_3$, 67% 28:72

The isomerization of allylic acetates is a useful method for allylic oxygen interconversion. Although these reactions are typically carried out in the presence of Pd^{II} catalysts such as $Pd(OAc)_2$, $Pd(Ph_3P)_4$ has proven to be useful in the 1,3-rearrangement of α-cyanoallylic acetates to γ-acetoxy-α,β-unsaturated nitriles (eq 45).[118] These compounds are conveniently transformed into furans.

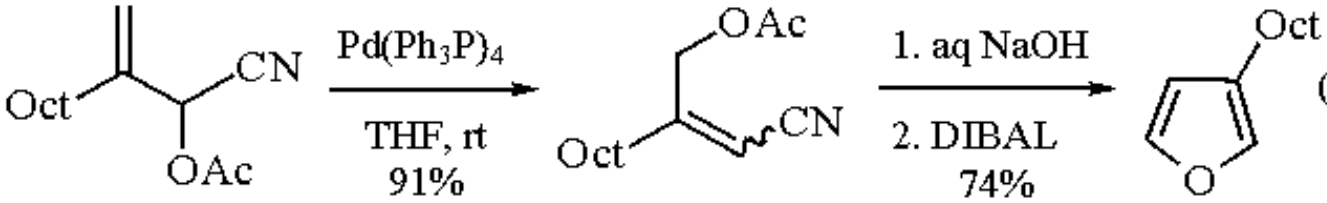

(45)

Several 1,3-diene syntheses involving elimination reactions that are catalyzed by $Pd(Ph_3P)_4$ have been reported. The first involves the Et_3N mediated elimination of HOAc from allylic acetates in refluxing THF.[119] A complementary procedure involves the $Pd(Ph_3P)_4$ catalyzed decarboxylative elimination of β-acetoxycarboxylic acids (eq 46).[120] The substrates are easily prepared by the condensation of enals and carboxylate enolates; irrespective of the diastereomeric mixture, (*E*)-alkenes are formed in a highly stereocontrolled manner. The geometry of the double bond present in the enal precursor remains unaffected in the elimination and the reaction is applicable to the formation of 1,3-cyclohexadienes.

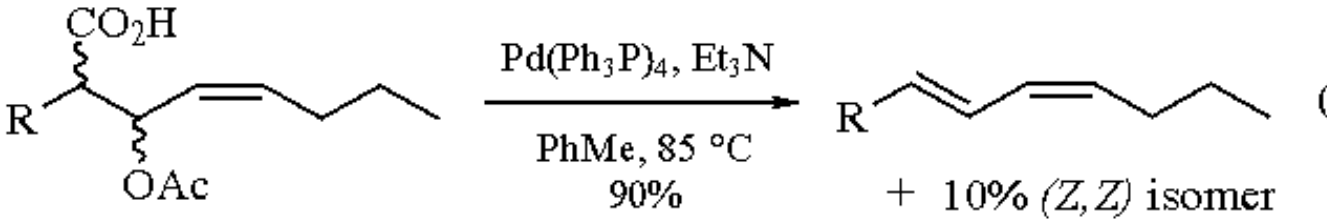

(46)

Monoepoxides of simple cyclic 1,3-dienes are smoothly converted in good yield to β,γ-unsaturated ketones in the presence of $Pd(Ph_3P)_4$ catalyst (eq 47).[121] Other vinyl epoxides, such as those in open chains or in cyclic systems in which the double bond is not in the ring, are converted under similar conditions into dienols.

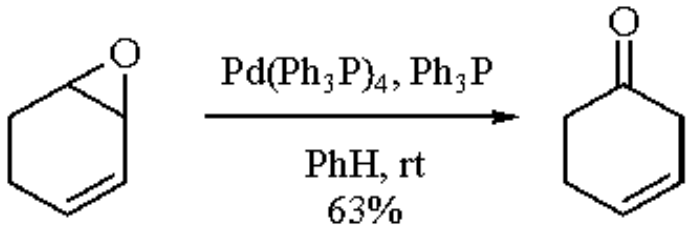

(47)

A mixture of $Pd(Ph_3P)_4$/dppe catalyzes the transformation of α,β-epoxy ketones, readily available via several methods, into β-diketones (eq 48).[122] The reaction is applicable to both cyclic and acyclic compounds, although epoxy ketones bearing an α-alkyl group are poor substrates.

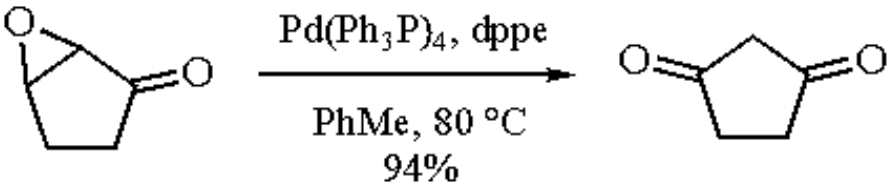

(48)

Related Reagents.

Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride.

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Tetrakis(triphenyl phosphite)nickel(0)

$[(PhO)_3P]_4Ni$

[14221-00-2] · $C_{72}H_{60}NiO_{12}P_4$ · Tetrakis(triphenyl phosphite)nickel(0) · (MW 1299.89)

(catalyst for alkene and alkyne hydrocyanation[1]; styrene dimerization[2])

Physical Data: mp 145 °C (dec).

Solubility: sol THF, toluene.

Form Supplied in: commercially available solid.

Preparative Methods: can be prepared by treating ***Nickel(II) Acetylacetonate*** with ***Sodium Borohydride*** and ***Triphenyl Phosphite***.[3]

Handling, Storage, and Precautions: is a cancer suspect agent; is air sensitive and should be handled using Schlenk or glove-box techniques.

Hydrocyanation of Alkenes and Alkynes.

Hydrocyanation of 1,3-cyclohexadiene is catalyzed by $[(PhO)_3P]_4Ni$ (eq 1).[1] Silylalkynes are hydrocyanated by $[(PhO)_3P]_4Ni$ to give isomeric mixtures of α- and β-silylacrylonitriles.[4] When the bulky Ph_3Si substituent is employed, regiospecific formation of the β-silylacrylonitrile occurs (eq 2). Smaller silyl substituents and alkyl groups give increased amounts of the α-silyl isomer. Aminoalkynes and alkynols have also been hydrocyanated to similar mixtures of acrylonitriles.[5,6]

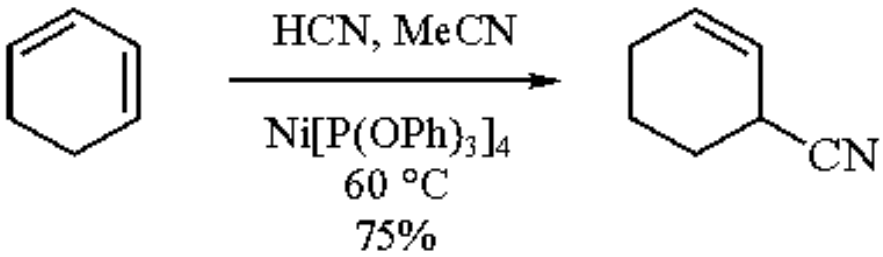

(1)

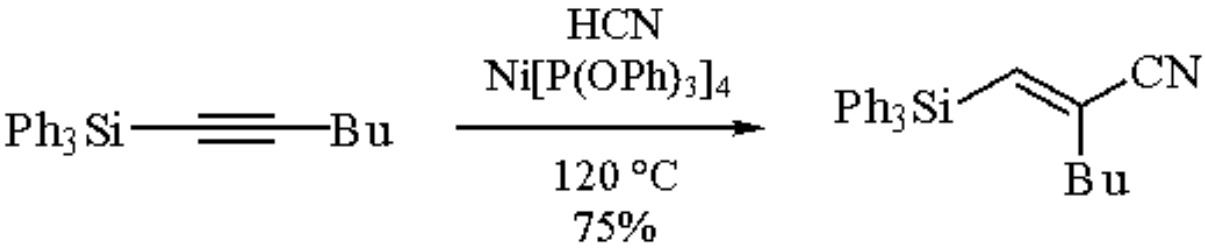

(2)

Styrene Dimerization.

$[(PhO)_3P]_4Ni$, in the presence of ***Trifluoroacetic Acid***, catalyzes the dimerization of styrene (eq 3). The reaction forms only the linear dimer with (*E*):(*Z*) = 5.4.

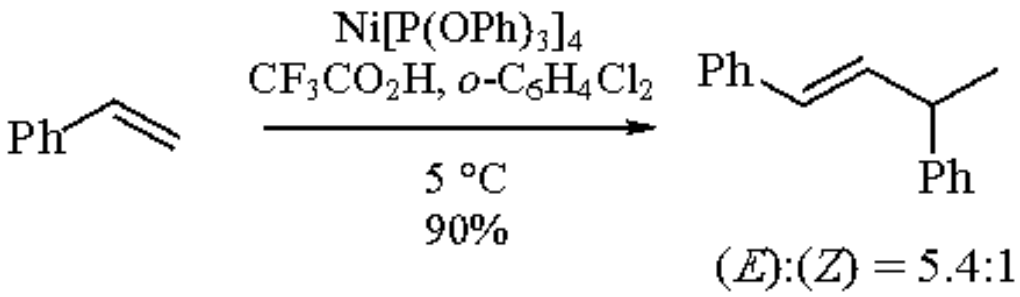

(3)

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α-Tetralyl Hydroperoxide[1]

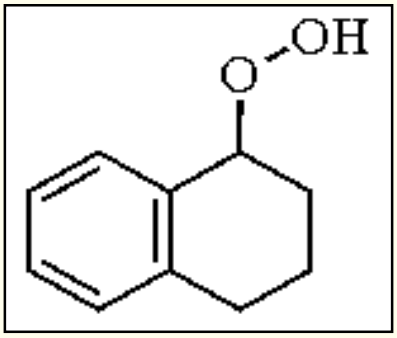

[771-29-9] · $C_{10}H_{12}O_2$ · α-Tetralyl Hydroperoxide · (MW 164.22)

(weak electrophile which delivers oxygen to alkenes when activated by Lewis acids[2])

Alternate Names: tetralin hydroperoxide; THPO; 1,2,3,4-tetrahydro-1-naphthalenyl hydroperoxide.

Physical Data: mp 54-54.5 °C.

Solubility: sol toluene, cyclohexane, $CHCl_3$.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: assay using iodometry.[3]

Preparative Methods: oxygen is passed through pure tetralin maintained at 70 °C until the peroxide content of the reaction mixture is 25-30% (24-48 h). Unreacted tetralin is separated by fractional distillation in an all-glass apparatus in high vacuum (0.2-0.4 mmHg); the pot temperature is not allowed to exceed 70 °C. Crystallization of the pot residue from toluene furnishes THPO (**1**) in 44-57% yield.[4]

Purification: by recrystallization from toluene.

Handling, Storage, and Precautions: remains colorless without appreciable decrease in active oxygen for several months if stored in the dark at or below 0 °C. Since the reagent is a peroxide it is potentially explosive and care is required in handling it (use safety shield). During workup, check for peroxides before solvent removal.

Functional Group Oxidations.

When THPO (**1**) is heated in the presence of cyclohexyl metaborate (CHMB) (**2**) it undergoes facile decomposition at 80 °C.[2] This system (THPO-CHMB) epoxidizes alkenes in high yields. For example, 1-methylcyclohexene (**3**) is thus epoxidized in quantitative yield (eq 1).[2] Epoxidation of *cis*-2-octene at 80 °C furnishes only *cis*-2,3-epoxyoctane in almost quantitative yield. Competitive epoxidations of alkenes have been

studied. It has been observed that the rate of epoxidation increases with the degree of substitution; trisubstituted alkenes react faster than disubstituted alkenes. The reactivity pattern is comparable to that of organic peroxy acids. It has been suggested that the epoxidation proceeds through the transition state (**4**).[2]

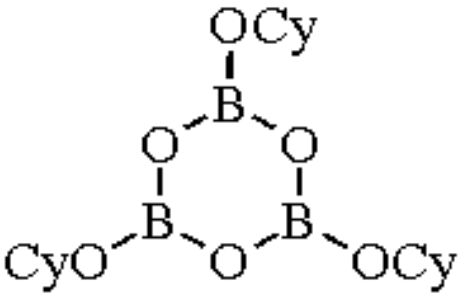

(2)

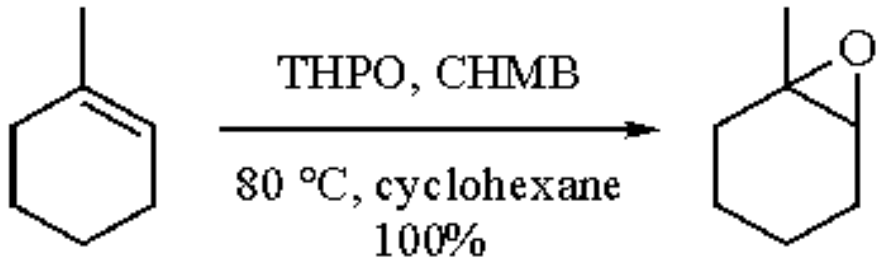

(1)

(3)

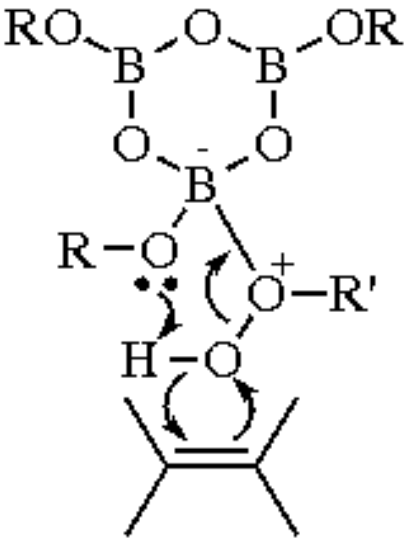

(4)

When cyclodecyne was heated with THPO-CHMB in cyclohexane (reflux, 24 h), a mixture of (**5**), (**6**), and (**7**) was obtained in a 47:23:31 ratio.[5] Similar results are obtained when cyclodecyne is reacted with ***m-Chloroperbenzoic Acid***.

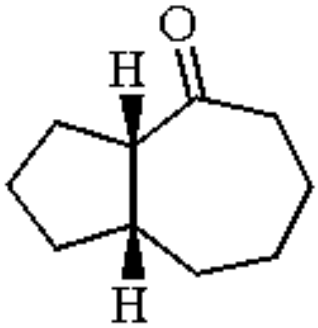

(5)

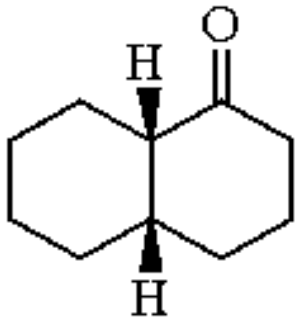

(6)

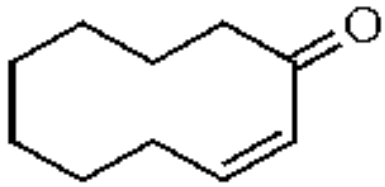

(7)

Asymmetric epoxidation of the allyl alcohol (**8**) has been carried out with six different peroxides at -20 °C with L-(+)-DIPT/***Titanium Tetraisopropoxide*** as catalyst; the yields and ee of the resulting epoxy alcohol (**9**) have been determined.[6] Best results are obtained with ***t-Butyl Hydroperoxide*** (TBHP), which furnishes (**9**) having 90% ee in 45-50% yields. When THPO is used, (**9**) is obtained in 35% yield but the ee of the product is only 14%.

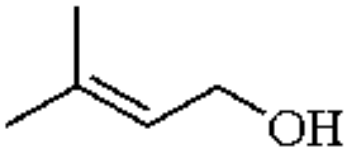

(8)

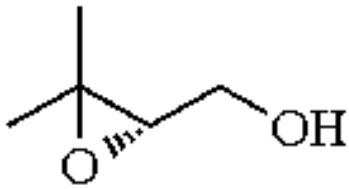

(9)

For preparing epoxides from alkenes lacking directing groups, the widely used reagents are TBHP/Mo[7] and *m*-CPBA.

Other Applications.

2-Thienol (**10**) has been prepared in 10% yield by reacting 2-thienyllithium with THPO;[8a] the same procedure applied to phenyllithium furnishes phenol in 75% yield. THPO oxidation of β-carotene in $CHCl_3$ at rt for 20-22 h furnishes a number of allylic oxidation products, including 4,4´-dihydroxycarotene (**11**) and 4,4´-dioxocarotene (**12**).[8b]

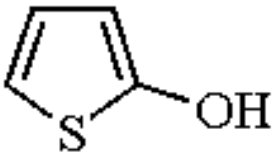

(10)

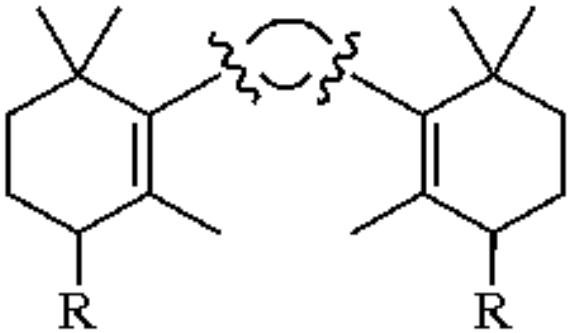

(11) R = OH
(12) R = O

1. *Organic Peroxides*; Hawkins, E. G. E., Ed.; Spon: London, 1961; pp 72-121.
2. Wolf, P. F.; Barnes, R. K. *JOC* **1969**, *34*, 3441.
3. Skellon, J. H.; Wills, E. D. *Analyst* **1948**, *73*, 78.
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8. (a) Hurd, C. D.; Anderson, H. J. *JACS* **1953**, *75*, 5124. (b) Bodea, C.; Nicoara, E.; Tamas, V. *LA* **1959**, *627*, 237.

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Tetramethoxycarbonylpalladacyclopentadiene

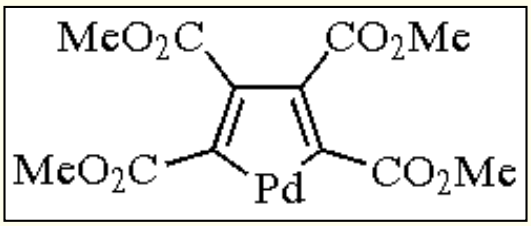

[35279-80-2] · $C_{12}H_{12}O_8Pd$ · Tetramethoxycarbonylpalladacyclopentadiene · (MW 390.66)

(catalyst for intramolecular enyne cyclizations,[1] [2 + 2 + 2] cycloadditions,[1] allene-alkyne cross-condensations,[2] and enyne metatheses[3])

Alternate Name: [1,2,3,4-tetrakis(methoxycarbonyl)-1,3-butadien-1,4-diyl]palladium.

Physical Data: 170 °C (dec); brown, microcrystalline complex which exists as a polymeric structure.[4]

Solubility: very sol complexing solvents (phosphines, benzonitrile); sparingly sol noncomplexing solvents,[4] but will dissolve in benzene and 1,2-dichloroethane upon addition of one equivalent of a phosphine.[1]

Analysis of Reagent Purity: ^{1}H NMR (PhCN) δ 6.23 (s, 6H), 6.34 (s, 6H).[4]

Preparative Methods: synthesized from ***Dimethyl Acetylenedicarboxylate*** and ***Tris(dibenzylideneacetone)dipalladium*** in virtually quantitative yield.[4] The active complex is usually generated by addition of a phosphine ligand to break up the insoluble polymer.[1]

Intramolecular Enyne Cyclization.

In an attempt to observe intermediates in the Pd^{2+} catalyzed cyclization of 1,6-enynes, the title reagent (**1**) was used as an electron-deficient catalyst; an intramolecular carbometalation and subsequent cyclization were observed (eq 1).[1]

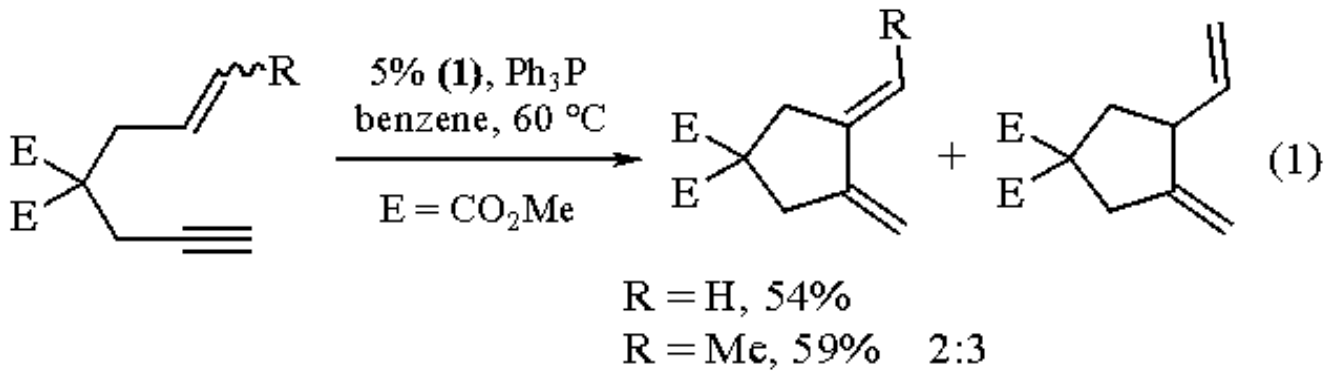

[2 + 2 + 2] Cycloaddition.

When cyclization of a 1,6-enyne was performed in the presence of an acetylene, a [2 + 2 + 2] cycloaddition resulted (eq 2).[1] Further experimentation supported a [2 + 2 + 2] cyclization mechanism rather than a Diels-Alder reaction.[1]

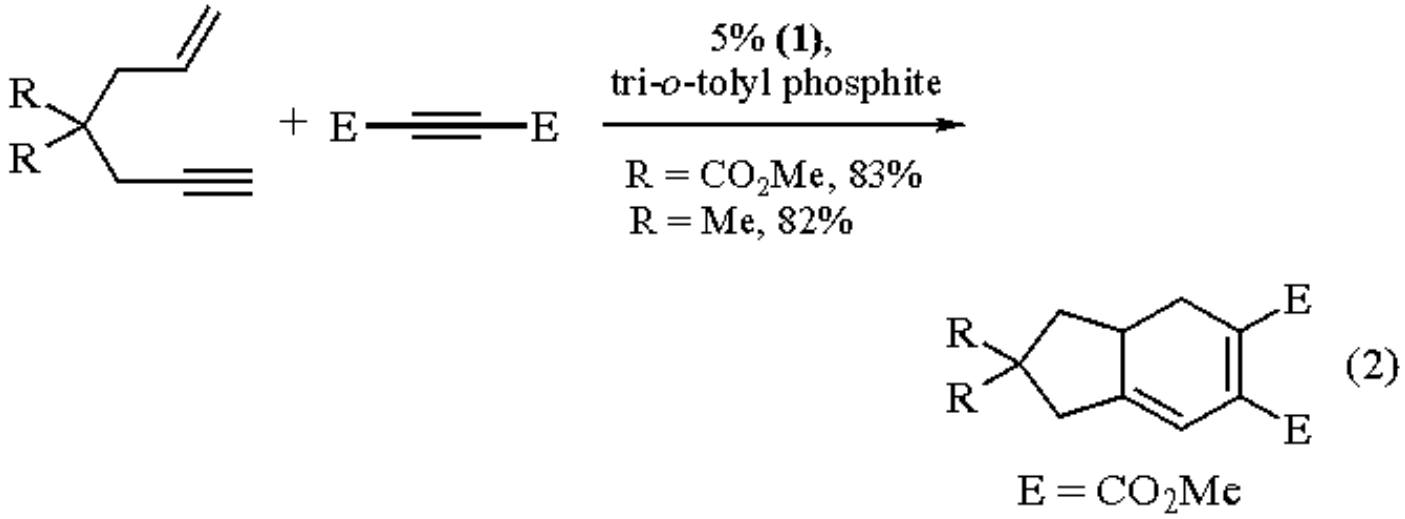

Allene-Alkyne Cross-Condensation.

When (**1**) is exposed to a combination of an allene and an alkyne, a cross-condensation occurs.[2] Regio- and stereocontrol can be obtained by an appropriate choice of ligand (eq 3). Even sterically hindered allenes can be used (eq 4).[2]

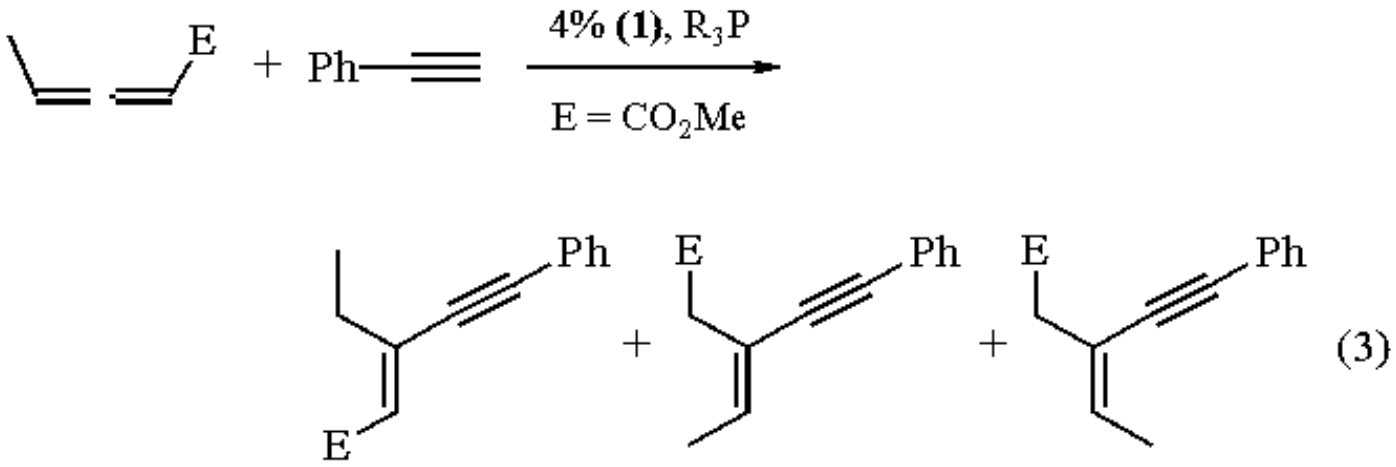

(A)	9%	47%	44%
(B)	42%	37%	21%
(C)	83%	17%	0%

(A) = tris(2,4,6-trimethoxyphenyl)phosphine, 64%
(B) = tris(2,6-dimethoxyphenyl)phosphine, 62%
(C) = triphenylphosphine, 48%

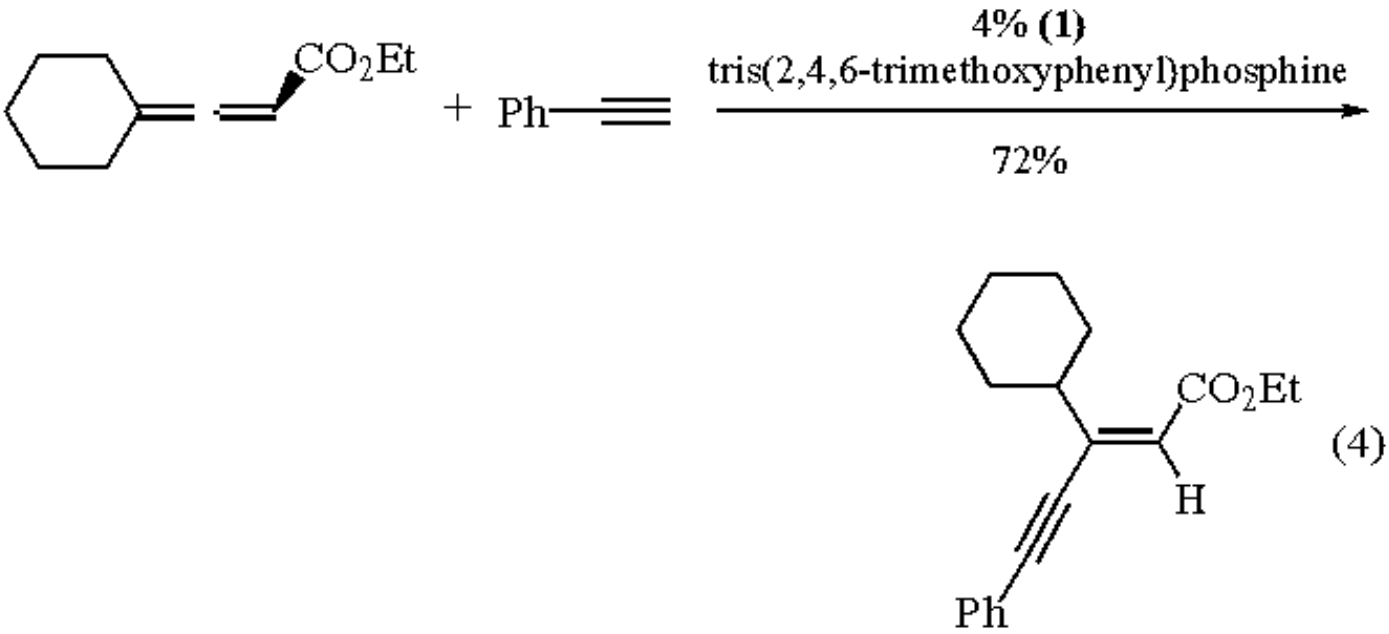

Intramolecular Enyne Metathesis.

By changing the CO_2Me groups to $CO_2CH_2CF_3$ ($TCPC^{TFE}$) or $CO_2CH_2CF_2CF_2CF_3$ ($TCPC^{HFB}$) groups, one obtains a catalyst that effects intramolecular enyne metatheses, accomplishing the installation of a bridgehead alkene within a bridged bicycle (eq 5).[3] The difference in reactivity between (**1**) and $TCPC^{TFE}$ or $TCPC^{HFB}$, shown in eq 6, demonstrates the synthetic utility of this type of catalyst.[3]

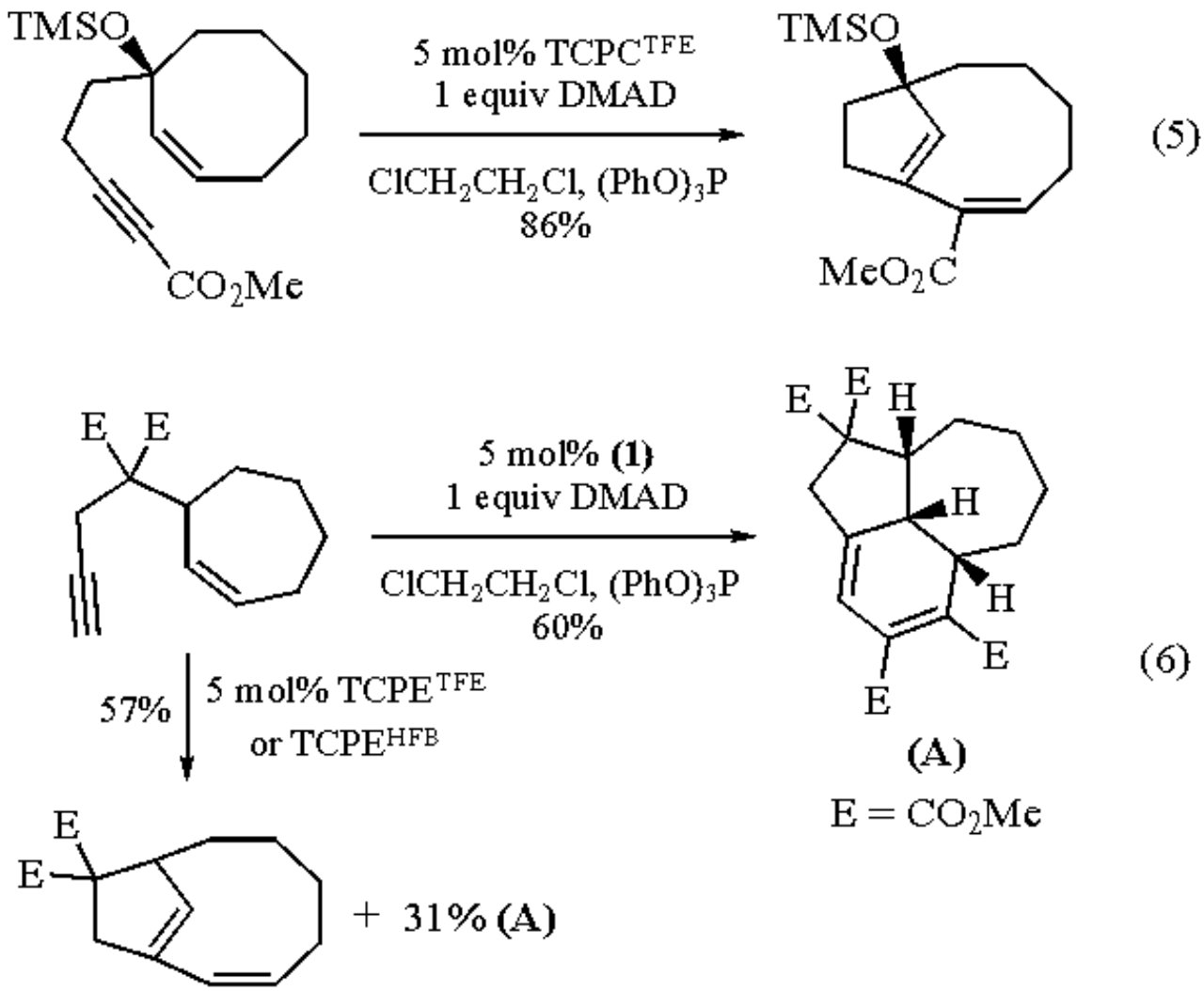

1. Trost, B. M.; Tanoury, G. J. *JACS* **1987**, *109*, 4753.
2. Trost, B. M.; Kottirsch, G. *JACS* **1990**, *112*, 2816.
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Tetramethoxyethylene[1]

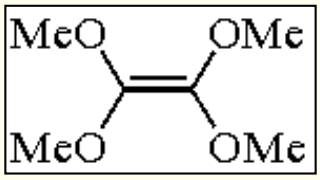

[1069-12-1] · $C_6H_{12}O_4$ · Tetramethoxyethylene · (MW 148.18)

(strong electron-rich ketene acetal which reacts as an oxalyl dication equivalent with a variety of electrophiles).

Physical Data: bp 48 °C/15 mmHg.

Preparative Methods: the best preparative method is from (*p*-chlorophenoxy)dimethoxymethane and ***Sodium Hydride*** (eq 1).[2] This method is also applicable for other tetraalkoxy analogs.

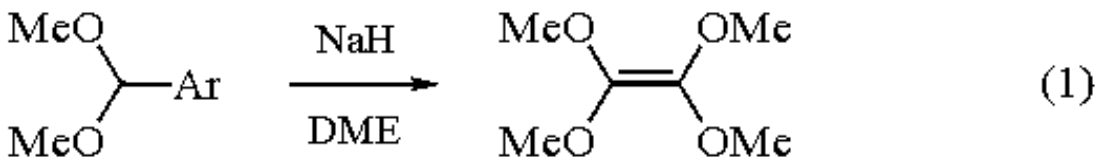

Handling, Storage, and Precautions: the compound should be stored in dry, base-rinsed vessels under nitrogen.

Introduction.

Tetramethoxyethylene, as a very electron-rich alkene, belongs to the class of ketene acetals. Due to its symmetrical electron distribution, its reactivity is generally somewhat lower than the more polarized ketene acetals, e.g. the 1,1-dialkoxyalkenes. The general reactivity towards electrophiles was first explored by Hoffmann et al.[1a] A variety of cationic species such as diazonium salts add to tetramethoxyethylene to yield substituted methyl dimethoxyacetates (eq 2).

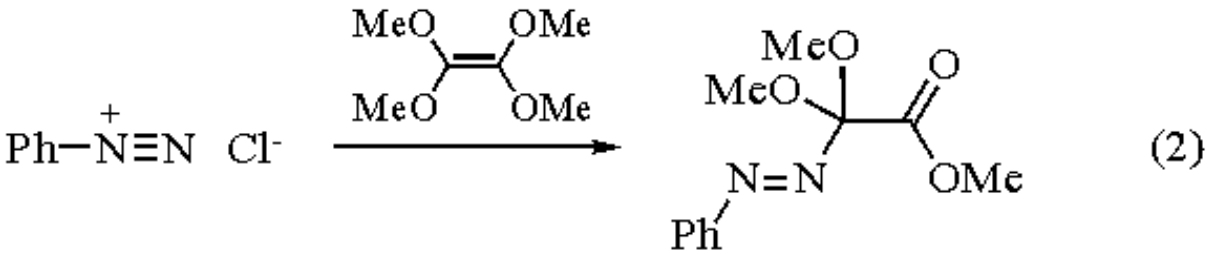

Dihalocarbenes add to give 1,1-dihalotetramethoxycyclopropanes, which upon reaction with ***n-Butyllithium*** are converted into the electron-rich tetramethoxyallene (eq 3).

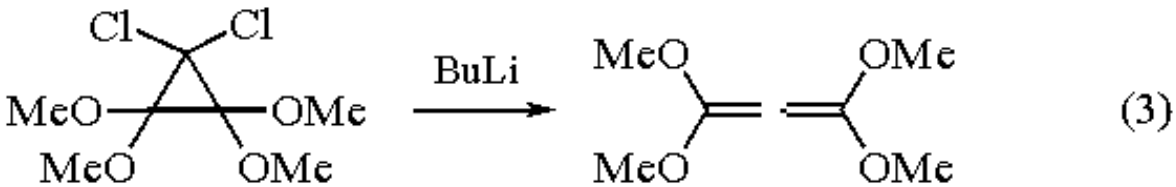

The most important applications are in the field of cycloadditions.[1c] Generally these reactions occur with fewer side products than those of the 1,1-dialkoxyalkenes and the cycloadducts obtained are more stable.

[2 + 2] Cycloadditions.

With a variety of electron-poor alkenes, tetramethoxyethylene reacts to give tetramethoxycyclobutanes.[3] These higly oxygenated cyclobutanes are valuable precursors for the synthesis of α,α-dimethoxy esters,[4] 1-cyano-2-aryl-3,3,4,4-tetramethoxycyclobutenes,[5] 1-cyano-2-arylcyclobutenediones,[6] and 1,1,4,4-tetramethoxybuta-1,3-dienes (eq 4).[7]

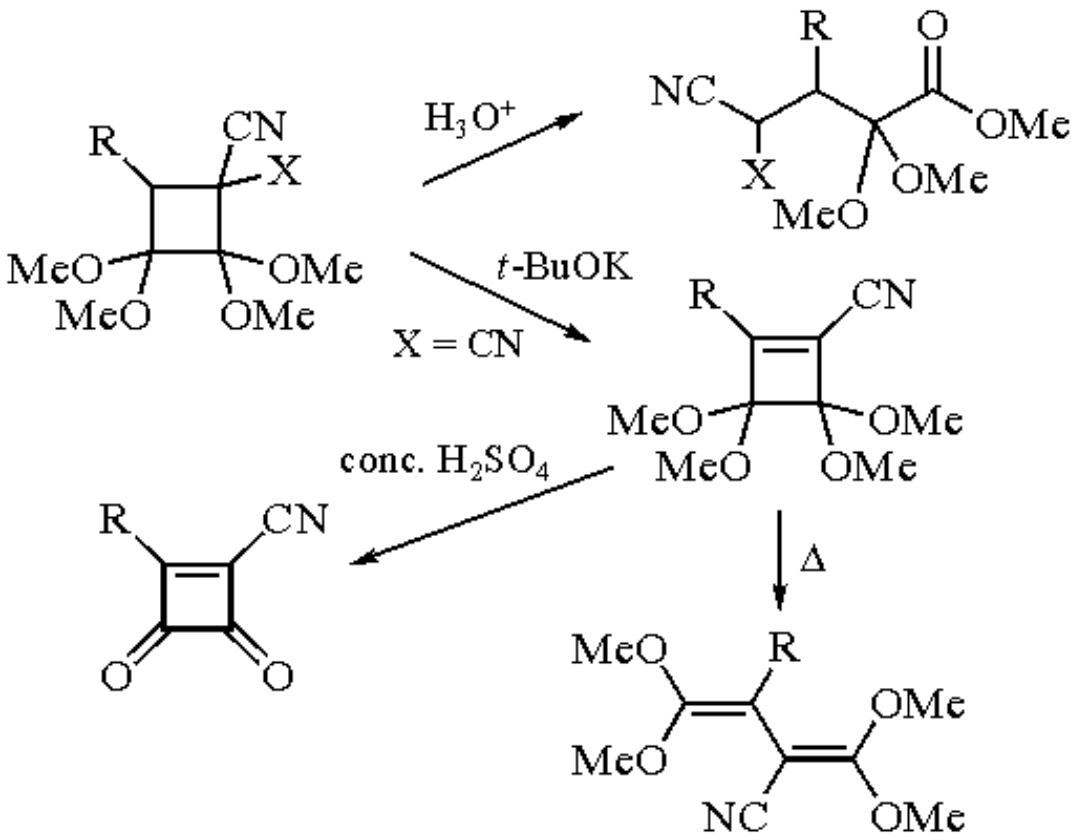

(4)

With aldehydes in the presence of Lewis acids, 2,2,3,3-tetramethoxyoxetanes are formed in good yields (eq 5).[8] These can be easily hydrolyzed to α,α-dimethoxy-β-hydroxy esters.

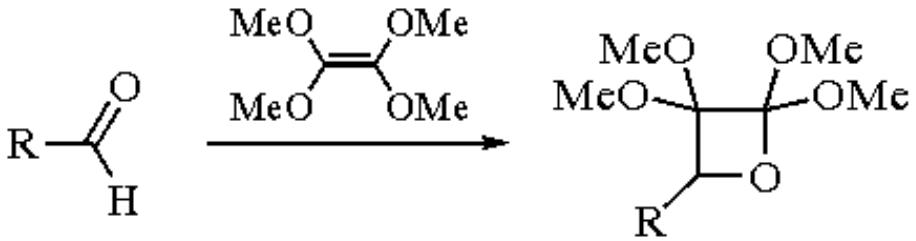

(5)

Under the influence of Lewis acids, α,β-unsaturated carbonyl compounds yield either cyclobutanes or oxetanes depending on the structure of the α,β-unsaturated carbonyl compound (eq 6).[1c,9] These reactions can also be performed at high pressure without Lewis acids.

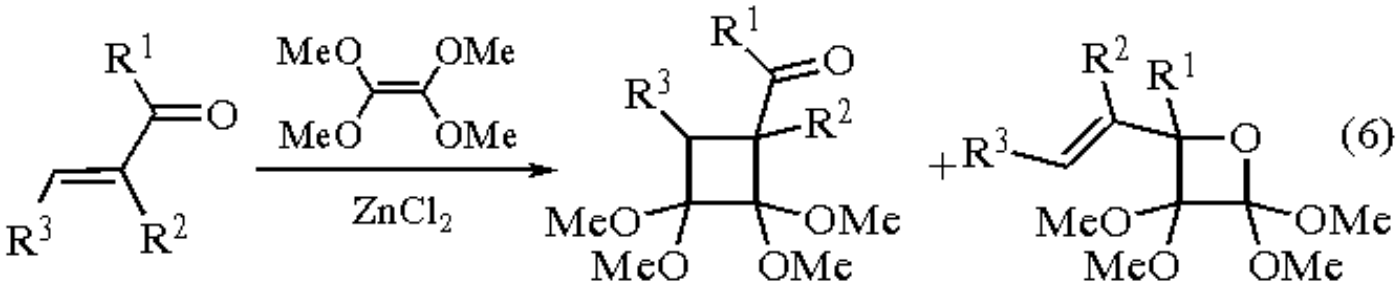

(6)

The thermal reaction with ketene yields mixtures of 2,2,3,3-tetramethoxycyclobutanone and 2,2,3,3-tetramethoxy-4-methyleneoxetane.[10] In the presence of Lewis acids the oxetane is selectively formed.[1c] The cycloadducts from tetraalkoxyethylenes and ketenes have been applied effectively in the synthesis of 1,2-substituted tetramethoxycyclobutenes, 1-substituted 4-oxotrimethoxycyclobutenes, and squaric acid.[11]

Other Cycloadditions.[1c]

Diels-Alder adducts are only obtained from electron-poor dienes or α,β-unsaturated carbonyl compounds having a preferred cisoid conformation. Epoxides behave like 1,3-dipoles when adding to tetramethoxyethylene in the presence of Lewis acids to give 2,2,3,3-tetramethoxy(tetrahydrofurans). Diaryl α-diketones yield [4 + 2] cycloadducts with tetramethoxyethylene (eq 7), whereas electronically asymmetric ketene acetals give oxetanes and bis-oxetanes.

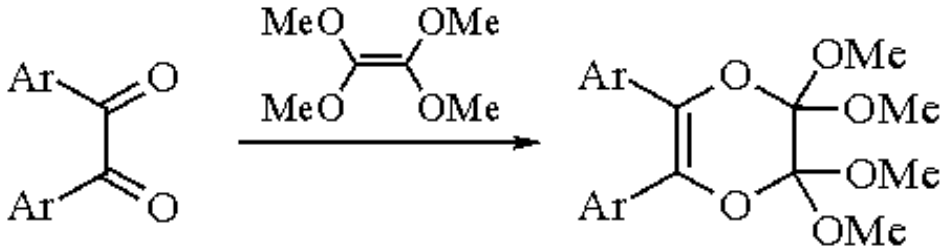

(7)

An inverse demand Diels-Alder reaction is also reported with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (eq 8).[1a]

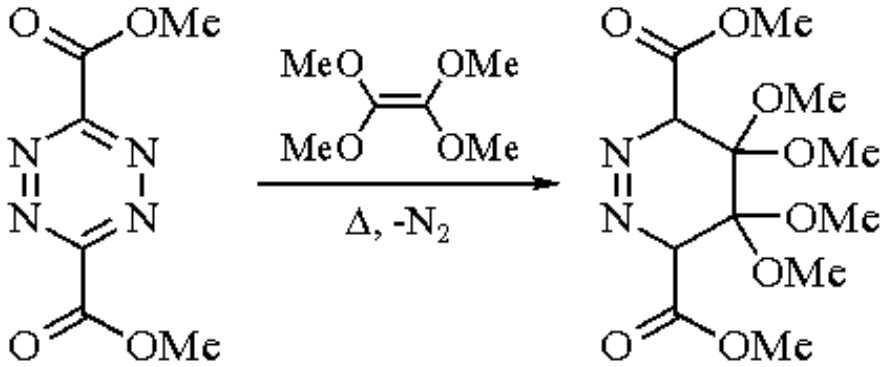

(8)

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene Diethyl Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Methylketene Bis(trimethylsilyl) Acetal***; ***Methylketene Dimethyl Acetal***; ***Tris(trimethylsilyloxy)ethylene***.

---

1. (a) Hoffmann, R. W. *AG* **1968**, *80*, 823; (*AG(E)* **1968**, *7*, 754). (b) Seebach, D. *MOC* **1971**, *B4/4*, 340. (c) Scheeren, J. W. *RTC* **1986**, *105*, 71. (d) Scheeren, J. W. *MOC* **1993**, *BE15*, 1674; (e) *FF* **1969**, *2*, 401; **1975**, *5*, 649.
2. (a) Scheeren, J. W.; Staps, R. J. F. M.; Nivard, R. J. F. *RTC* **1973**, *92*, 11. (b) Bellus, D.; Fischer, H.; Greuter, H.; Martin, P. *HCA* **1978**, *61*, 1784.
3. Scheeren, H. W.; Frissen, A. E. *S* **1983**, 794.
4. Ooms, P. H. J.; Scheeren, J. W.; Nivard, R. J. F. *S* **1975**, 662.
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6. Ooms, P. H. J.; Scheeren, J. W.; Nivard, R. J. F. *S* **1975**, 639.
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10. Hoffmann, R. W.; Bressel, U.; Gehlhaus, J.; Häuser, H. *CB* **1971**, *104*, 873.
11. Bellus, D. *JOC* **1979**, *44*, 1208.

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1,1,1,3-Tetramethoxypropane

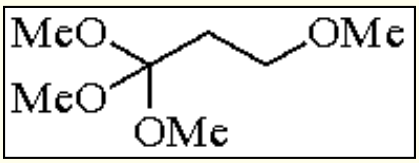

[77197-59-2] · $C_7H_{16}O_4$ · 1,1,1,3-Tetramethoxypropane · (MW 164.23)

(furnishes methyl α-substituted acrylates from allylic alcohols via Claisen orthoester rearrangement and β-elimination[1-5])

Physical Data: bp 89-90 °C/20 mmHg.[1]

Solubility: CCl_4, organic solvents.

Handling, Storage, and Precautions: keep away from moisture; use in a fume hood.

General Discussion.

1,1,1,3-Tetramethoxypropane (**1**) is prepared[1] from β-methoxypropionitrile[6] by the Pinner reaction.[7] It has been used as a synthon for the preparation of methyl α-substituted acrylates via Claisen orthoester rearrangement[8] with allylic alcohols followed by β-elimination of methanol with base. Claisen orthoester rearrangement of allylic alcohols (**2**)-(**4**) with excess (**1**) and a catalytic amount of 2,4,6-trimethylbenzoic acid gave the esters (**5**)-(**7**).[1] Treatment of these esters with one equivalent of ***Potassium t-Butoxide*** in THF (0 °C, 10 min) gave the α-substituted acrylates (**8**)-(**10**).[1]

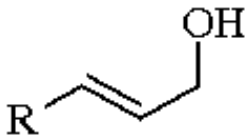

(2) R = Ph
(3) R = $Me_2C{=}CHCH_2CH_2$

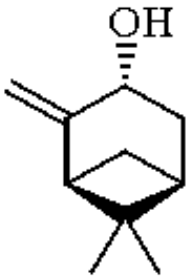

(4)

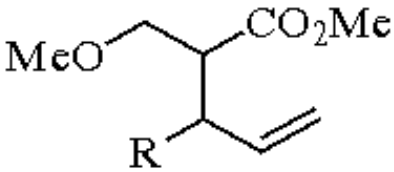

(5) R = Ph
(6) R = $Me_2C{=}CHCH_2CH_2$

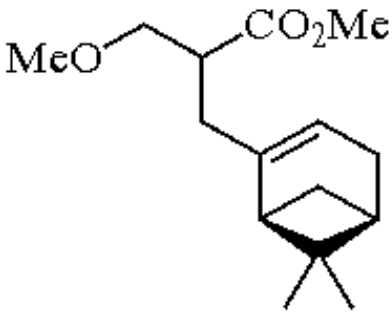

(7)

The conversion of (**11**) to (**12**) and then (**13**) using this methodology has been reported.[5]

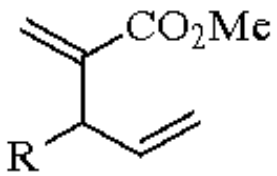

(8) R = Ph
(9) R = $Me_2C{=}CHCH_2CH_2$

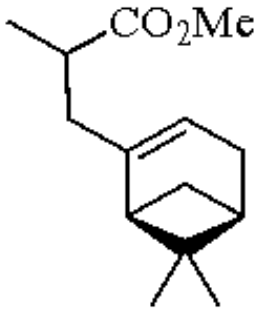

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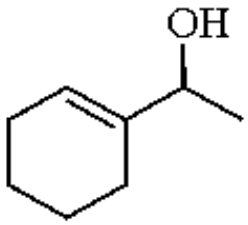

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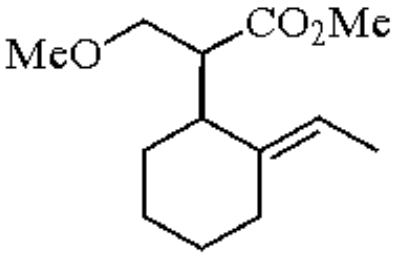

(12)

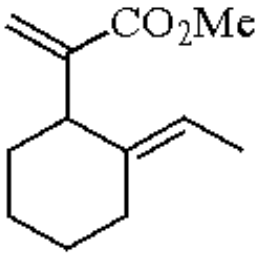

(13)

Another report describes the Claisen rearrangement of (**14**)[1] and (**15**).[2,3] These rearrangements, requiring a larger amount of acid catalyst and longer reaction times, provide the α-substituted acrylates (**16**) and (**17**) directly.

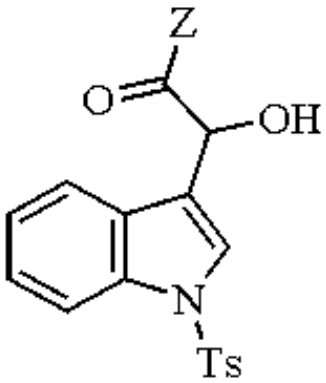

(14) Z = NMe_2

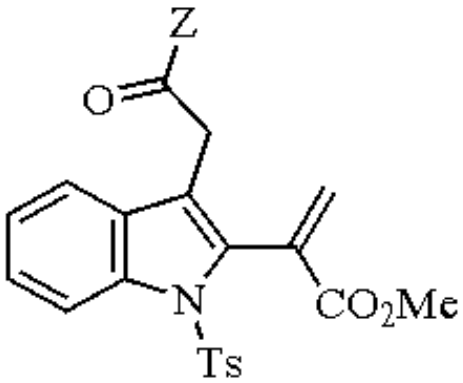

(16) Z = NMe_2

(15) Z = 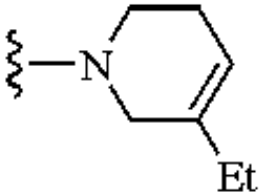

(17) Z = 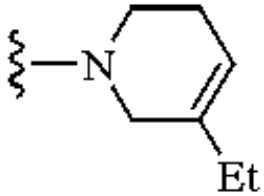

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Stanley Raucher

Tetramethylammonium Bromide[1]

Me_4NBr

[64-20-0] · $C_4H_{12}BrN$ · Tetramethylammonium Bromide · (MW 154.07)

(phase transfer catalyst; source of nucleophilic bromide; cleavage of cyclopropane; salt effects)

Physical Data: mp 230 °C (dec) bp 360 °C (sub. vac.); *d* 1.56 g cm^{-3}.

Solubility: sol H_2O, MeOH.

Form Supplied in: white solid; commercially available.

Analysis of Reagent Purity: tetraalkylammonium salts can be titrated with potassium 3,5-di-*t*-butyl-2-hydroxybenzenesulfonate and iron(III) chloride.[1a]

Purification: the commercially available compound can be recrystallized from EtOH, EtOH-diethyl ether, MeOH-acetone, H_2O, or acetone-EtOH (4:1). It is then dried at 110 °C under reduced pressure for 24 h.

Phase Transfer Catalyst.

It has been generally observed that Me_4NBr is one of the least effective ammonium salts for phase transfer catalysis. A number of studies have shown that increasing the size of the alkyl groups on the nitrogen is generally beneficial for the promotion of phase transfer reactions by ammonium salts. For example, this salt was shown to be inferior to $BuNEt_3Br$ in the *O*- and *C*-alkylation of aryl ketones (eq 1),[2] to ***Tetra-n-butylammonium Iodide*** in the Horner-Emmons alkenation of aldehydes (eq 2),[3] to $(C_8H_{17})_3NMeCl$ in the *S*-alkylation of thiophenol,[4] to Et_4NBr in the oxybromination of aromatic compounds,[5] and to ***Tetra-n-butylammonium Bromide*** and Bu_4PBr in the alkylation of K_2CO_3.[6] Me_4NBr was a very effective phase transfer catalyst for the *N*-alkylation of aromatic heterocyclic compounds (eq 3).[7]

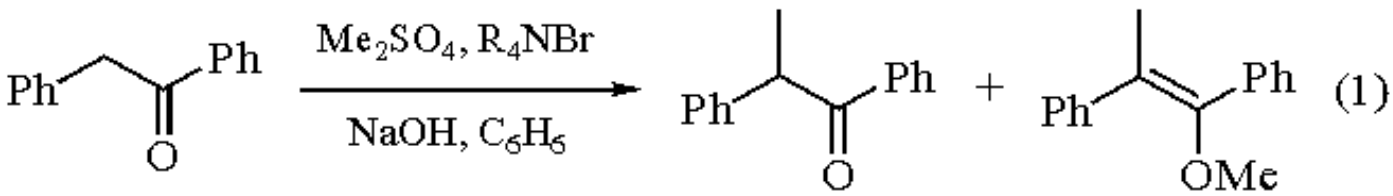

Me_4NBr	21%
$BuNEt_3Br$	100%
Et_4NBr	85%

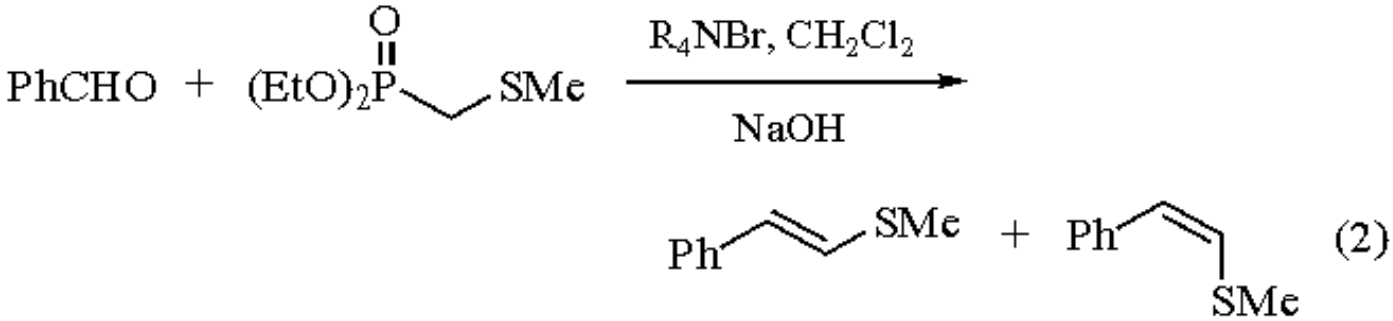

Me_4NBr	77:23
Bu_4NBr	88:19
Et_4NI	83:17

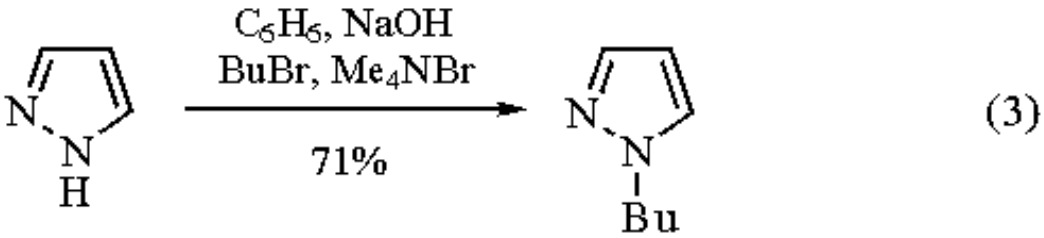

Nucleophilic Opening of Cyclopropyl Ketones.

In combination with acetyl methanesulfonate, Me_4NBr was shown to promote the efficient cleavage of cyclopropyl ketones to produce γ-bromovinyl esters (eqs 4 and 5).[8]

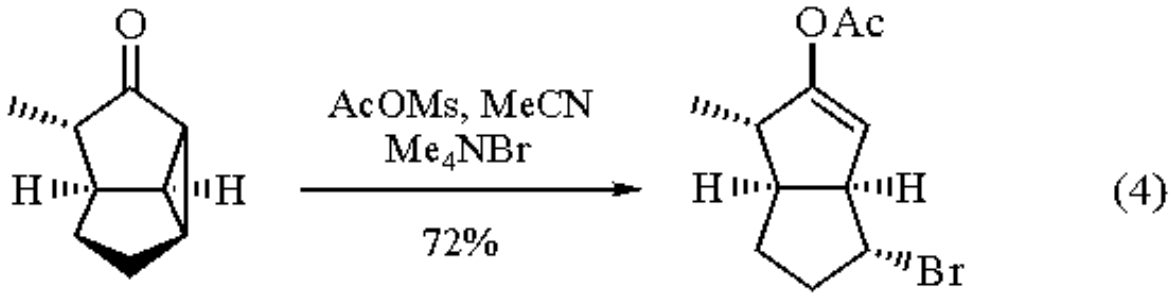

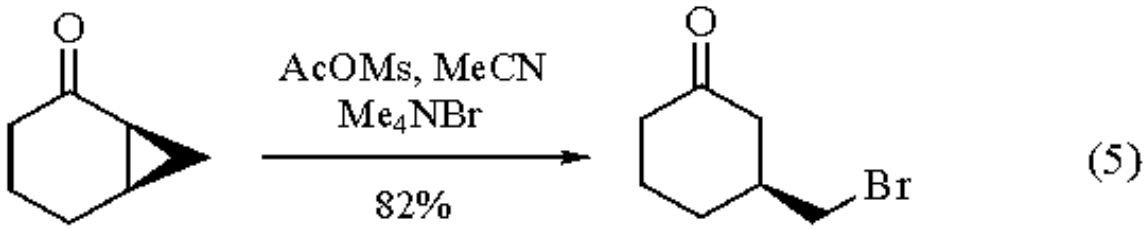

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1. (a) Sjöberg, K. *Aldrichim. Acta* **1980**, *13*, 55. (b) Jones, R. A. *Aldrichim. Acta* **1976**, *9*, 35. (c) Weber, W. P.; Gokel, G. W. *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977. (d) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis*; Academic: New York, 1978. (e) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*; Verlag Chemie: Deerfield Beach, FL, 1980. (f) Loupy, A.; Tchoubar, B. *Salt Effects in Organic and Organometallic Chemistry*; VCH: Weinheim, 1992.
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Tetramethylammonium Dimethyl Phosphate

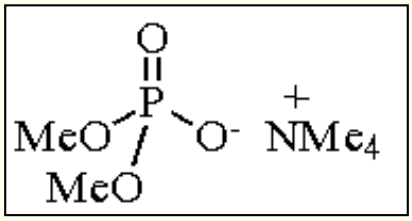

[756-77-4] · $C_6H_{18}NO_4P$ · Tetramethylammonium Dimethyl Phosphate · (MW 199.22)

(dehydrobromination of bromo ketones, bromo aldehydes, and bromoalkanes)

Physical Data: mp 215 °C.

Solubility: sol acetonitrile, DMF, HMPA.

Preparative Methods: prepared[1,2] by reacting an excess of ***Trimethylamine*** (139 g) with ***Trimethyl Phosphate*** (210 g) in acetone solution (400 g) in a sealed glass reactor at ambient temperature. The crystalline product is recovered by filtration in greater than 90% yield.

Analysis of Reagent Purity: the purity is assessed by mp.

Handling, Storage, and Precautions: no data available.

Elimination of Hydrogen Bromide.

Steroidal α-bromo ketones undergo elimination of HBr with tetramethylammonium dimethyl phosphate (**1**) in acetonitrile or DMF at 110 to 150 °C (eq 1) in an autoclave to give α,β-unsaturated ketones in 45-60% yields.[3] Alternative procedures, for example ***Lithium Chloride***/***Lithium Carbonate*** in DMF, are reported to give superior yields.[4]

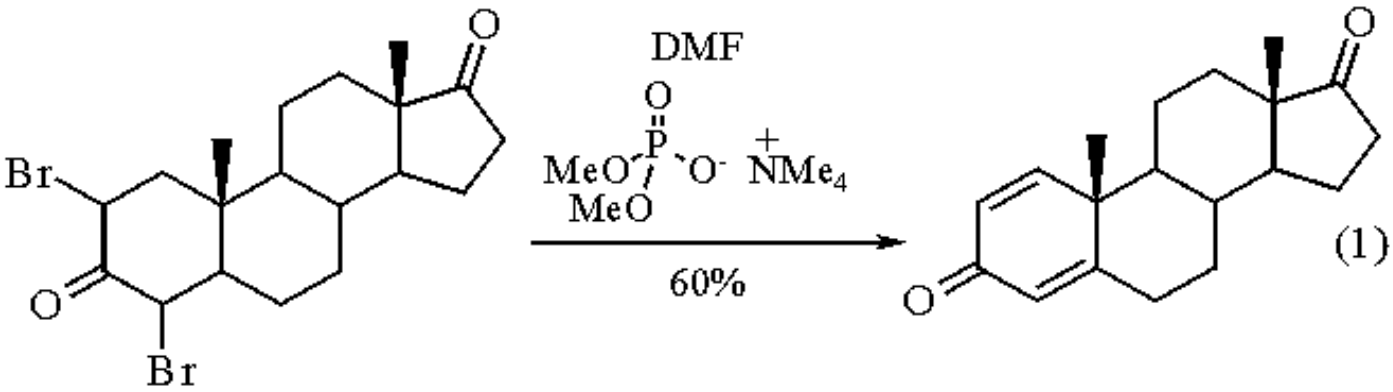

Reaction of less complex α-bromo ketones with (**1**) leads to variable results. 2-Bromocyclopentanone yields exclusively 2-cyclopentenone (60%), whereas 2-bromocyclohexanone and 2-bromocycloheptanone (eq 2) give mixtures of α,β-unsaturated ketones and ketophosphates.[5,6] Additional α-substitution causes elimination to become the predominant pathway; thus 2-bromo-2-methylcyclohexanone gives 2-methyl-2-cyclohexenone in 62% yield.

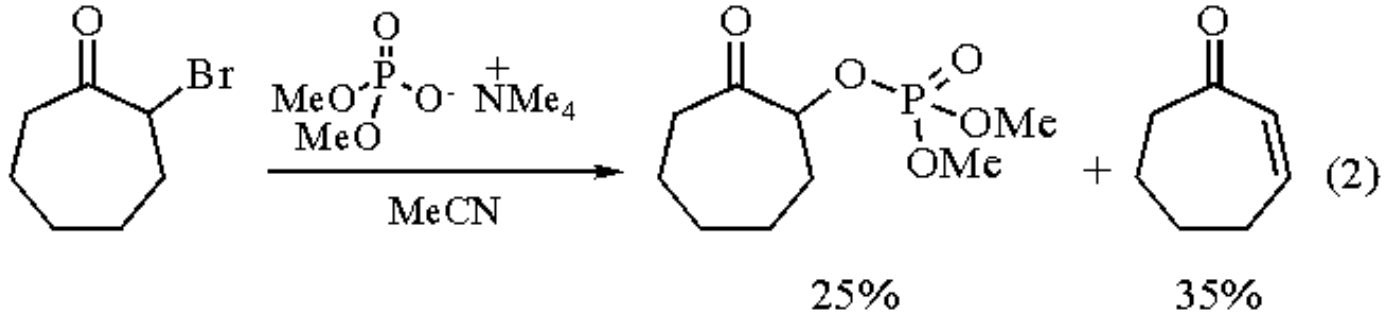

Reaction of (**1**) with α-bromo aldehydes[2] leads predominantly to α-aldophosphates, whereas α-alkyl substituted α-bromo aldehydes[7] give α,β-unsaturated aldehydes by elimination (eq 3). The reaction of alkyl bromides is exemplified by 2-bromopentane in DMF, which forms (*E*)- and (*Z*)-2-pentene, 1-pentene (total alkene 42%), and 2-pentyl dimethyl phosphate (19%).[8]

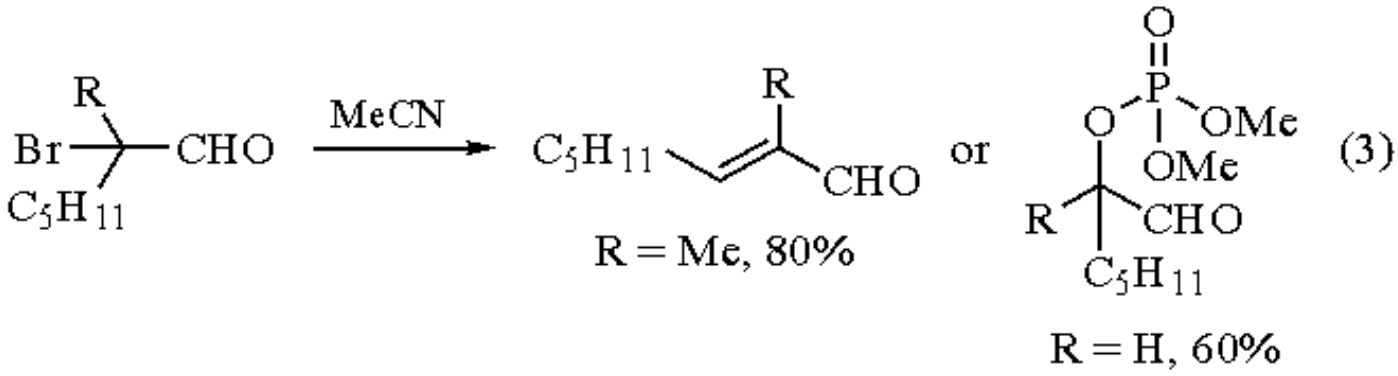

Surprisingly, the steroidal diaxial dibromide (eq 4) gave a quantitative mixture of the $\Delta^{5,7}$-diene and the $\Delta^{4,6}$-diene (1.3:1) upon treatment with (**1**) in HMPA at 130 °C.[9]

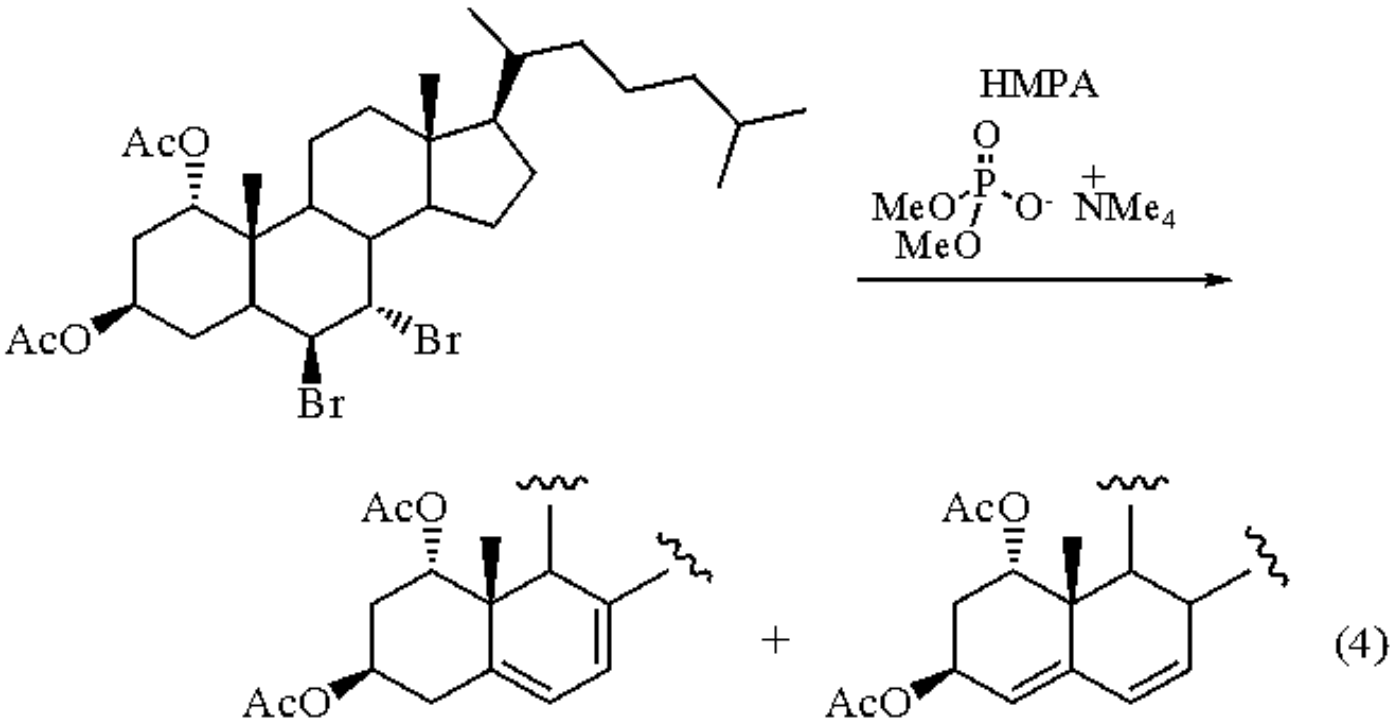

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Tetramethylammonium Hydroxide

$Me_4N^+OH^-$

[75-59-2] · $C_4H_{13}NO$ · Tetramethylammonium Hydroxide · (MW 91.18)

(conversion of hydroperoxyoxiranes to hydroxyalkyl-1,2-dioxetanes; catalyst for transesterification of carboxylic acids; synthesis of phosphorylating agent)

Physical Data: dependent on form supplied in, e.g. 10% aqueous solution has *n*20D 1.3521 and *d* 1.006 g cm^{-3}.

Solubility: sol MeOH, H_2O.

Form Supplied in: commercially available as a solution in water or methanol, or in solid form as the pentahydrate.

Preparative Methods: 1. By heating trimethylacetonylammonium bromide ($MeCOCH_2{+}NMe_3\ Br^-$) to 195-200 °C. The free base is obtained by treating the bromide with warm water.[1] 2. Prepared as a solution in water by electrolysis of tetramethylammonium iodide (at anode), ammonium hydroxide (at cathode), and water (central compartment) in a three-compartment cell.[2] 3. By an ion-exchange method using AV-17 and Me_4NX (X = Cl, Br, I).[3] 4. By treatment of tetramethylammonium iodide with freshly prepared silver(I) oxide in water at 50 °C.[4]

Handling, Storage, and Precautions: decomposes on distillation; stored as solution. It is a very strong base, readily absorbing carbon dioxide from the air. Keep container well closed. Solution is flammable and causes burns.

General Discussion.

Hydroperoxyoxiranes (**2**) are converted to the 3α-hydroxyalkyl-1,2-dioxetanes (**3**) by treatment with tetramethylammonium hydroxide in a two-phase water/diethyl ether medium (eq 1).[5]

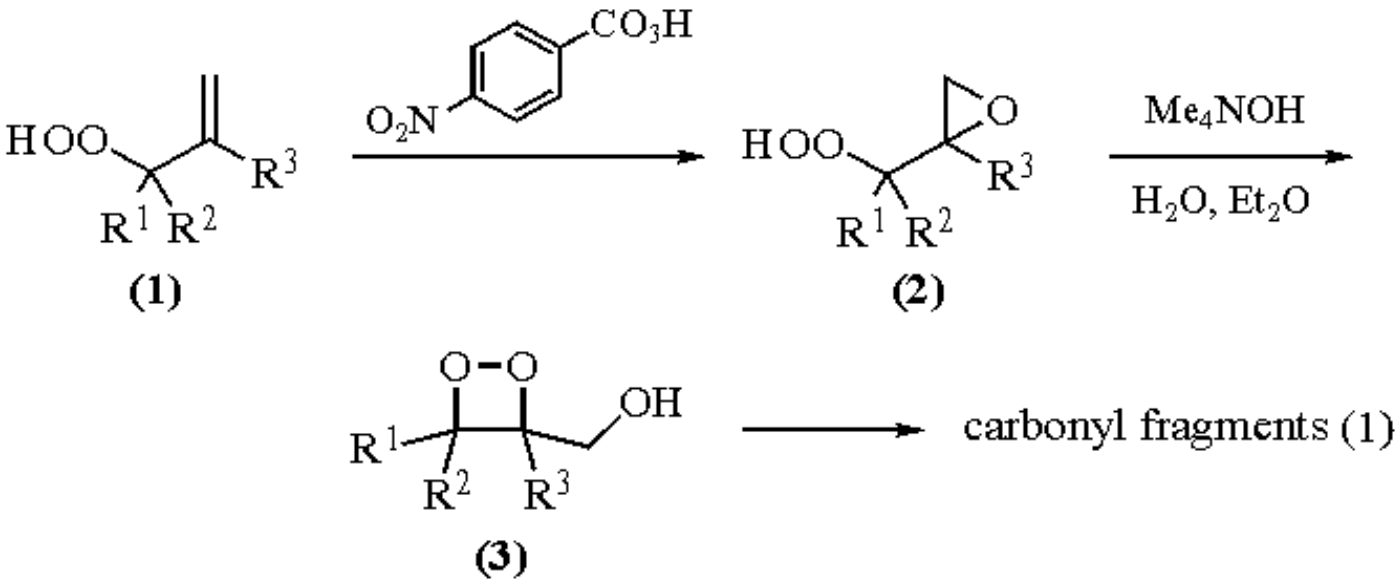

Tetramethylammonium hydroxide in methanol is used to catalyze the transesterification of carboxylic acids. The methyl esters are formed on pyrolysis of the corresponding tetramethylammonium salt when injected into a gas chromatographic unit[6] (methyl esters are popular derivatives for the gas chromatogaphic analysis of fatty acids[7]).

Aqueous solutions of quaternary ammonium hydroxides were used as initiators for the anionic homogeneous polymerization of

acrylonitrile and methylacrylonitrile in DMF.[8]

Aqueous tetramethylammonium hydroxide reacts with di-*t*-butyl phosphite to give tetramethylammonium *t*-butyl hydrogen phosphite (**4**). This is a convenient phosphorylating agent for organic halides. It reacts easily with alkyl iodides and some alkyl bromides in boiling acetone, affording the corresponding alkyl *t*-butyl phosphites (**5**). Treatment with ***Trifluoroacetic Acid*** at room temperature yields monoalkyl hydrogen phosphites (**6**).[9]

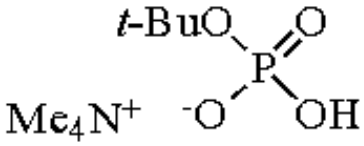

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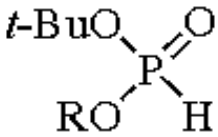

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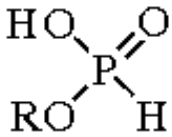

(6)

R = Me, Et, Pr, *i*-Pr, Bu, *s*-Bu, $H_2C{=}CHCH_2$, $Br(CH_2)_4$, EtO_2CCH_2 $PhCOCH_2$, *p*-$BrC_6H_4CH_2$

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Tetramethylammonium Triacetoxyborohydride

$R_4N(AcO)_3BH$

(R = Me)

[109704-53-2] · $C_{10}H_{22}BNO_6$ · Tetramethylammonium Triacetoxyborohydride · (MW 263.14) (R = Bu)

[83722-99-0] · $C_{22}H_{46}BN0_6$ · Tetramethylammonium Triacetoxyborohydride · (MW 431.50)

(reducing agent for the regio- and stereoselective reduction of β-hydroxy ketones, amides, and oximino ethers)[1]

Alternate Name: TABH.

Physical Data: mp 96-98 °C.

Solubility: sol range of organic solvents including CH_2Cl_2, $CHCl_3$, MeCN.

Form Supplied in: hygroscopic white powder; commercially available.

Preparative Methods: experimental procedures are available (eqs 1 and 2).[5a,6]

$$Me_4NOH + NaBH_4 \longrightarrow Me_4NBH_4 \quad (1)$$

$$Me_4NBH_4 + AcOH \longrightarrow Me_4N(AcO)_3BH \quad (2)$$

Purification: recrystallized from CH_2Cl_2-EtOAc.[5a]

Handling, Storage, and Precautions: moisture sensitive; irritant. Stable at 25 °C. Handle in a well ventilated fume hood.

Selective Reduction of Aldehydes.

Tetra-*n*-butylammonium triacetoxyborohydride ($Bu_4N(AcO)_3BH$) reduces aldehydes selectively in the presence of ketones (eq 3).[2] β-Keto aldehydes are reduced to afford the corresponding 1,3-diol adduct; none of the derived primary β-hydroxy ketone is generated. It is proposed that the aldehyde carbonyl group is reduced first and the resulting hydroxyl group directs the delivery of hydride to the ketone site (eq 4).[3]

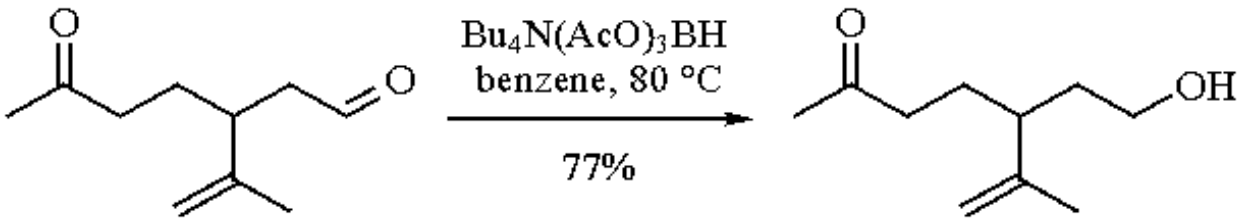

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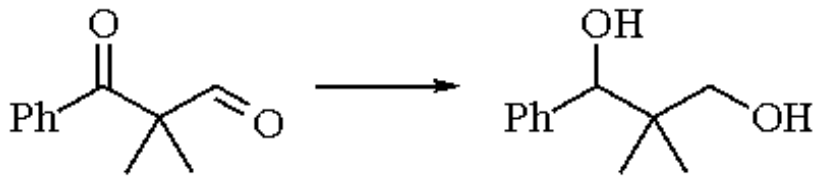

(4)

Similar observations have been reported with ***Sodium Triacetoxyborohydride***.[4] As shown in eq 5, reduction of a cyclic ketone containing a properly disposed hydroxyl function (for hydride delivery) proceeds to afford the derived equatorial alcohol with high diastereoselectivity. In

contrast, an equal mixture of axial and equatorial alcohols are obtained when ***Sodium Borohydride*** is employed as the reducing agent.

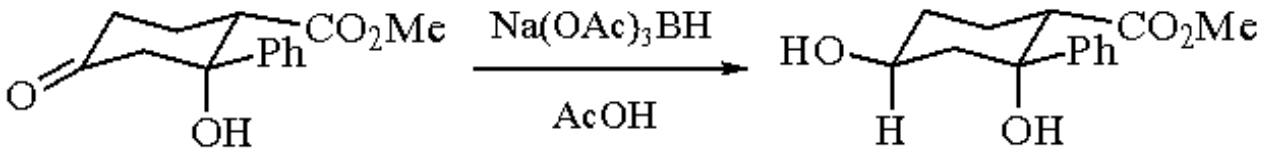

(5)

Directed Reduction of β-Hydroxy Ketones.

Evans has reported that TABH may be employed to effect the stereoselective reduction of β-hydroxy ketones.[5] Several reducing agents under a variety of conditions have been examined (eq 6 and Table 1). The reactivity and selectivity with TABH in AcOH/MeCN are superior to other solvent systems. The presence of HOAc is essential to reaction efficiency, as the protic acid catalyzes the rate determining association between the boron reagent and the resident substrate heteroatom.[5b] Acetonitrile is required since the reduction process may then be performed at lower temperatures without freezing of the reaction mixture; reduced temperatures are critical to obtaining high levels of stereoinduction.

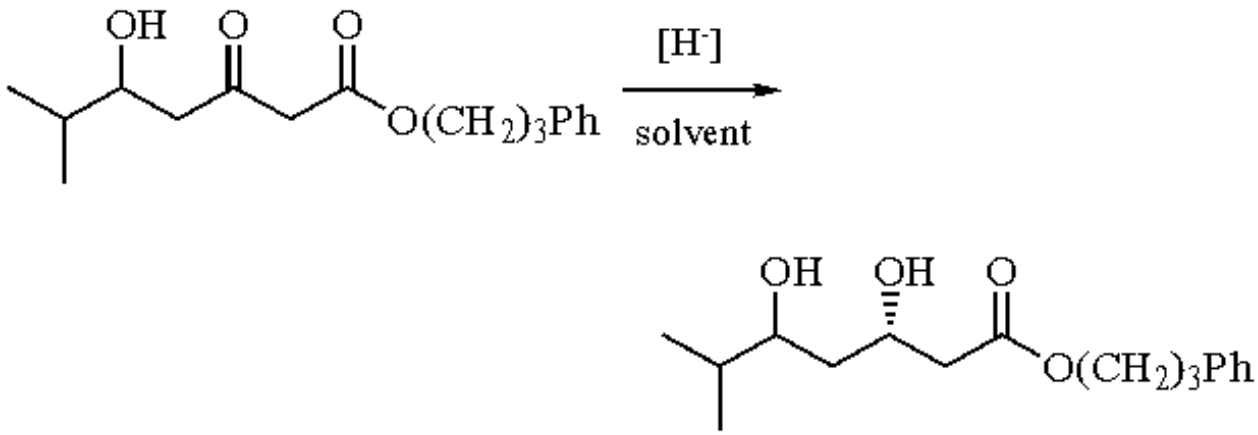

(6)

Table 1 Diastereoselective Directed Reduction of b-Hydroxy Ketones by Various Borohydrides

Hydride	Solvent	Time	Temp (°C)	Ratio (*anti*:*syn*)
$NaBH_4$	AcOH	30 min	25	80:20
$Na(AcO)_3BH$	AcOH	15 min	25	84:16
Me_4NBH_4	AcOH	30 min	25	92:8
$Me_4N(AcO)_3BH$	AcOH	15 min	25	92:8
$Me_4N(AcO)_3BH$	AcOH/MeCN	5 h	- 40	95:5

As illustrated in the directed reductions shown in eqs 7 and 8, the level and sense of diastereoselectivity is independent of the local chirality within the substrate molecule.

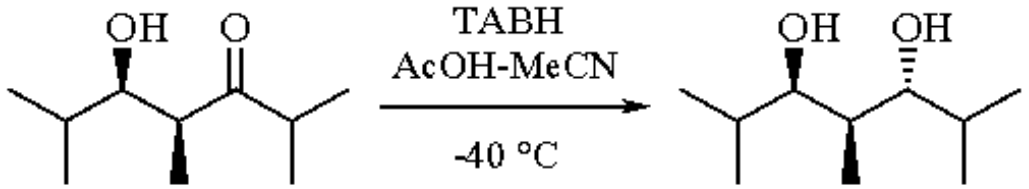

(7)

ds 50:1

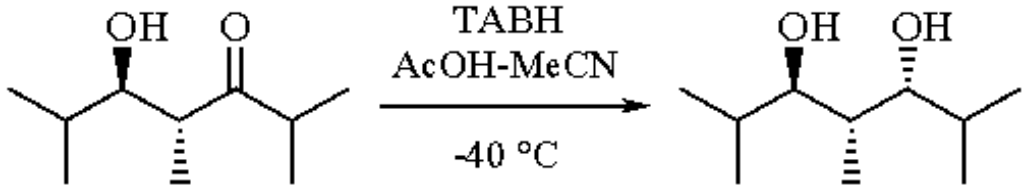

(8)

ds 50:1

Eqs 9 and 10 illustrate two additional important points with regard to the directed borohydride reduction: (1) the hydroxyl unit of an enol function may serve as the directing group (eq 9); (2) the stereoselective intramolecular hydride delivery may be relayed to effect generation of multiple stereogenic sites within an acyclic chain (eq 10).

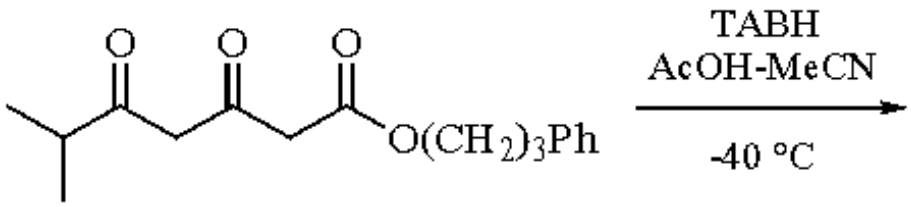

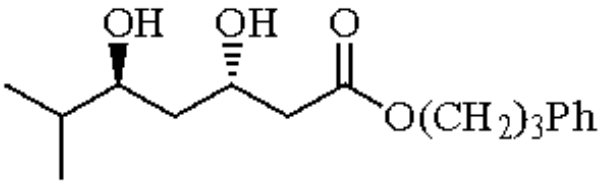

(9)

ds 92:8

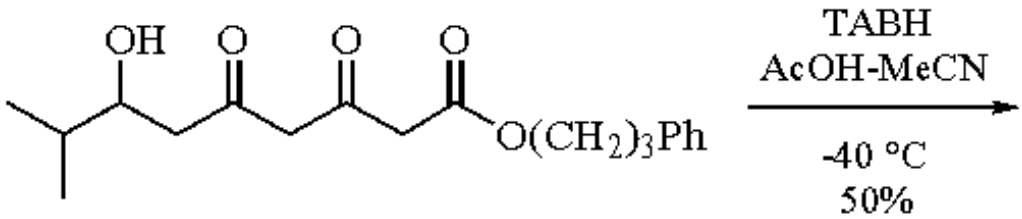

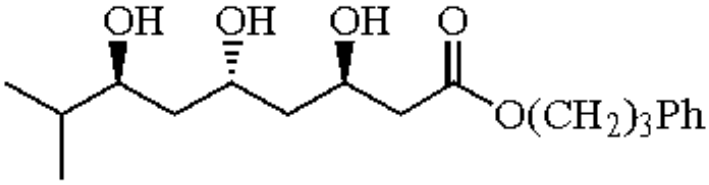

(10)

one stereoisomer

Directed Reduction of Oximino Ethers.

Substrates with β-Hydroxy Substitution.

Stereocontrolled reduction of β-hydroxy oximino ethers has been reported by Williams.[6] Eqs 11 and 12 indicate that whereas (*E*) substrates are

reduced selectively, (*Z*) adducts react with TABH with inferior levels of stereoinduction. As illustrated in eqs 13-16, the stereochemical outcome of reduction of (*E*) oxime ethers is insensitive to the substrate local chirality, whereas the corresponding (*Z*) isomers afford β-hydroxy amines with high selectivity. However, in the latter instance the identity of the major isomer depends on the configuration of the α stereogenic center (eqs 13 and 14). Within the same context, with substrates containing a primary hydroxyl group, the α stereogenic center induces the preferred formation of the *syn* stereoisomer (eq 17). A mechanism-based understanding of the trends in stereoselectivity shown is not yet available.

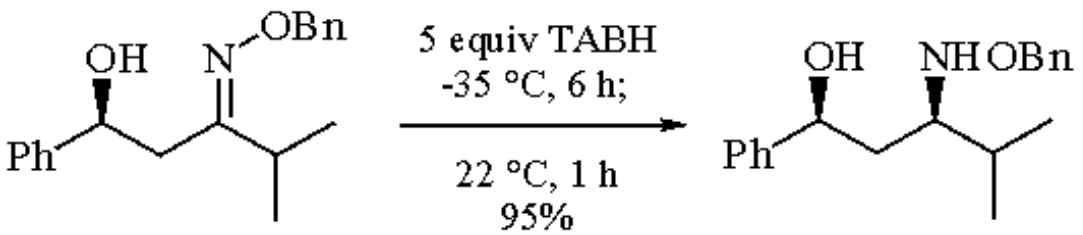

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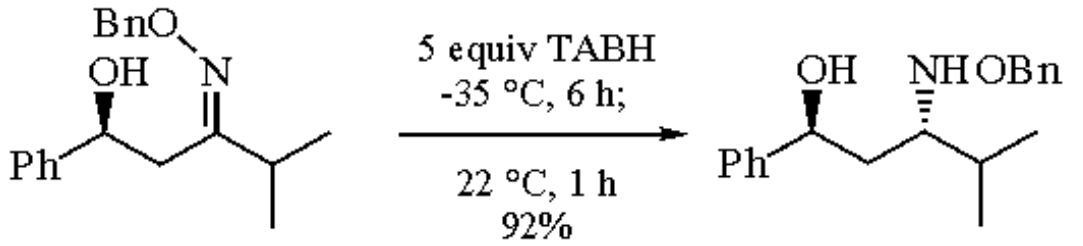

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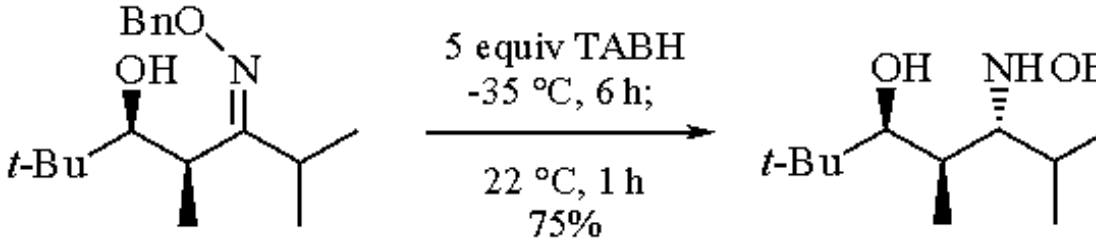

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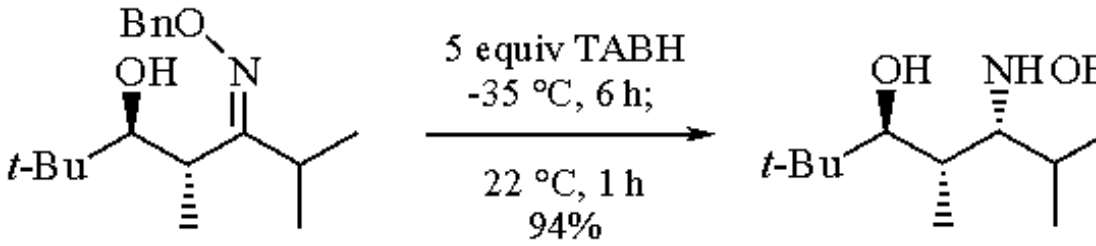

96:4 (14)

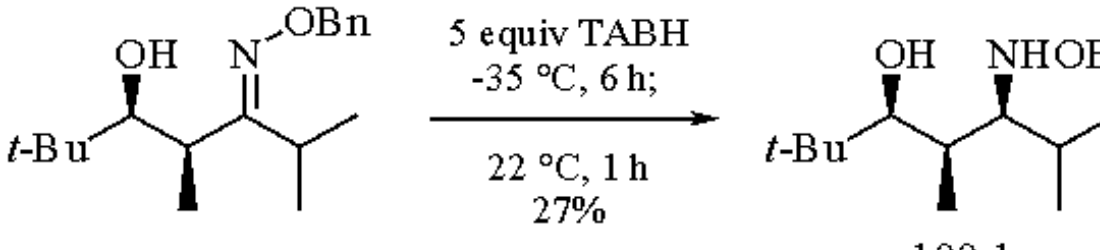

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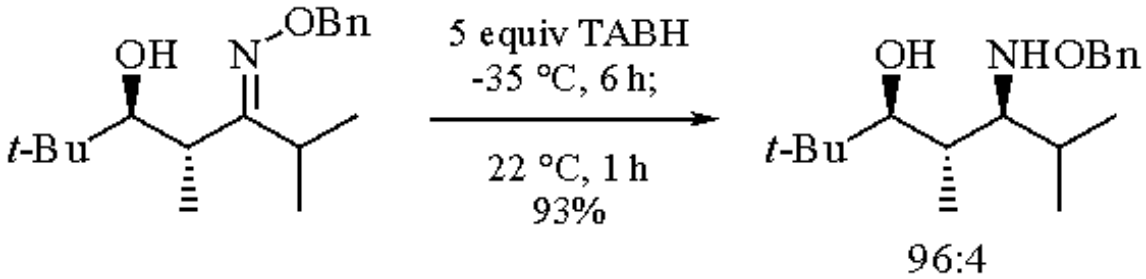

(16)

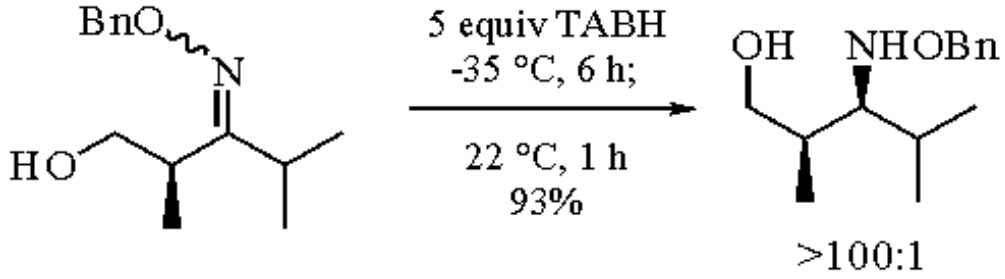

(17)

Substrates with α-Hydroxy Substitution.

Reductions of α-hydroxy oximino ethers with TABH provide *syn*-1,2-hydroxyamines with high diastereoselectivity (eq 18).[7] The observed stereochemical trend complements the previously observed *anti* selectivity achieved with ***Lithium Aluminum Hydride*** (LAH) or ***Diisobutylaluminum Hydride*** (DIBAL)[8] as reducing agents, or when Pd-catalyzed stereoselective hydrogenation is employed.[9] Unlike the case with β-alkoxy oximino ethers (eqs 11-17), neither the stereochemistry at the nitrogen (*E* vs. *Z*) nor that of the methyl group at the β-position has any effect on the stereochemical outcome of the reduction (e.g. eq 19).

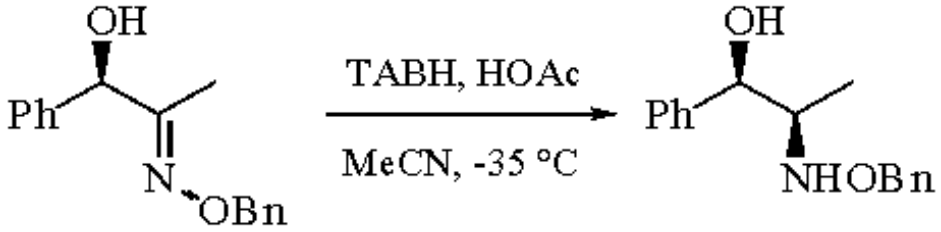

(18)

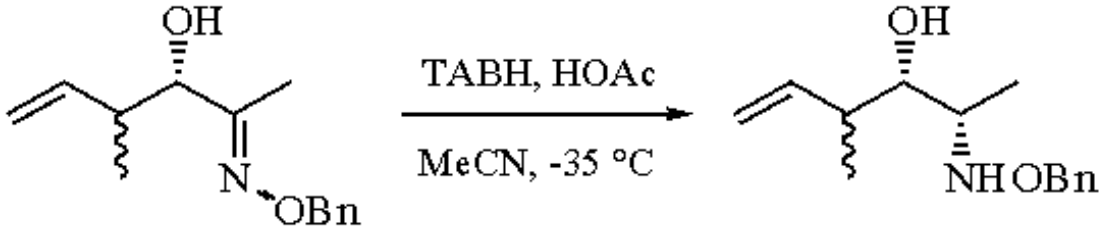

(19)

Directed Reduction of Imides.

As shown in Table 2 and eq 20, imides may undergo directed selective reduction with TABH.[10] The superior levels of stereochemistry obtained with the title borohydride, as opposed to LAH or ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al), may be attributed to the ability of TABH to undergo reduction through the directed pathway exclusively. It is noteworthy that upon protection of the hydroxyl group, no reaction is obtained with TABH. Reduction of the silyl ether with lithium ***Lithium Tri-s-butylborohydride*** (L-Selectride) proceeds with the opposite sense of stereochemical control.

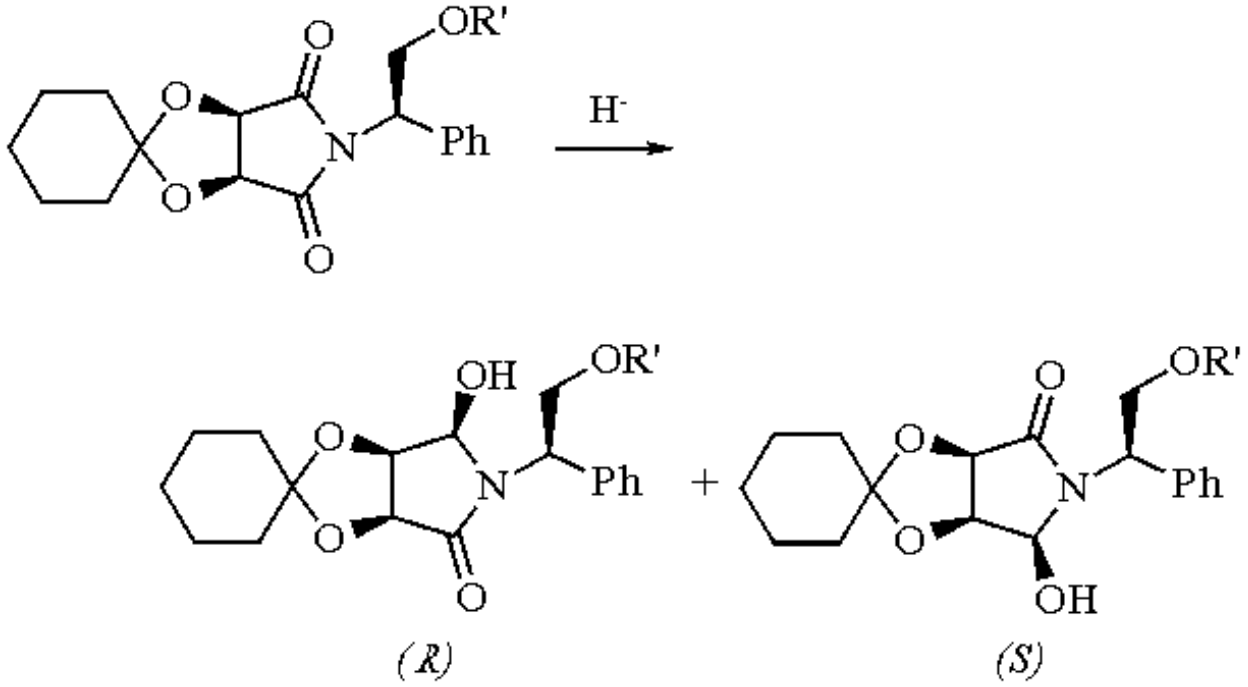

(20)

Table 2 Diastereoselective Directed Reduction of Imides

R¢	Hydride reagent	Yield (%)	(*R*):(*S*)
	LAH	75	61:39
H	Red-Al	80	82:18
	$Me_4N(OAc)_3BH$	63	>99:1
t-$BuMe_2Si$	L-Selectride	98	<1:99
	$Me_4N(OAc)_3BH$	No reaction	

Applications in Synthesis.

The ability of TABH and the corresponding sodium salt to participate in substrate-directed reductions with high levels of diastereoselection renders these reagents as attractive tools in the synthesis of complex molecules. For example, as illustrated in eq 21 in the synthesis of (-)-rocaglamide,[11] the α-hydroxyl group strictly controls (>95%) the stereochemical outcome of the ketone reduction with TABH as the reducing agent. In contrast, hydrogenation (***Palladium(II) Hydroxide*** as catalyst) of the same substrate affords only a 2:1 mixture of isomers. In the total synthesis of (+)-lepicidin A (eq 22), a highly selective β-hydroxy ketone reduction has been achieved (10:1).[12] Stereoselective and directed reductions of β-hydroxy ketones have been employed in the synthesis of subunits of several medicinally important natural products, such as bryostatin I and II, in addition to mevinic acids, compactin, and mevinolin (eq 23, 93% yield, 13:1 selectivity).[13]

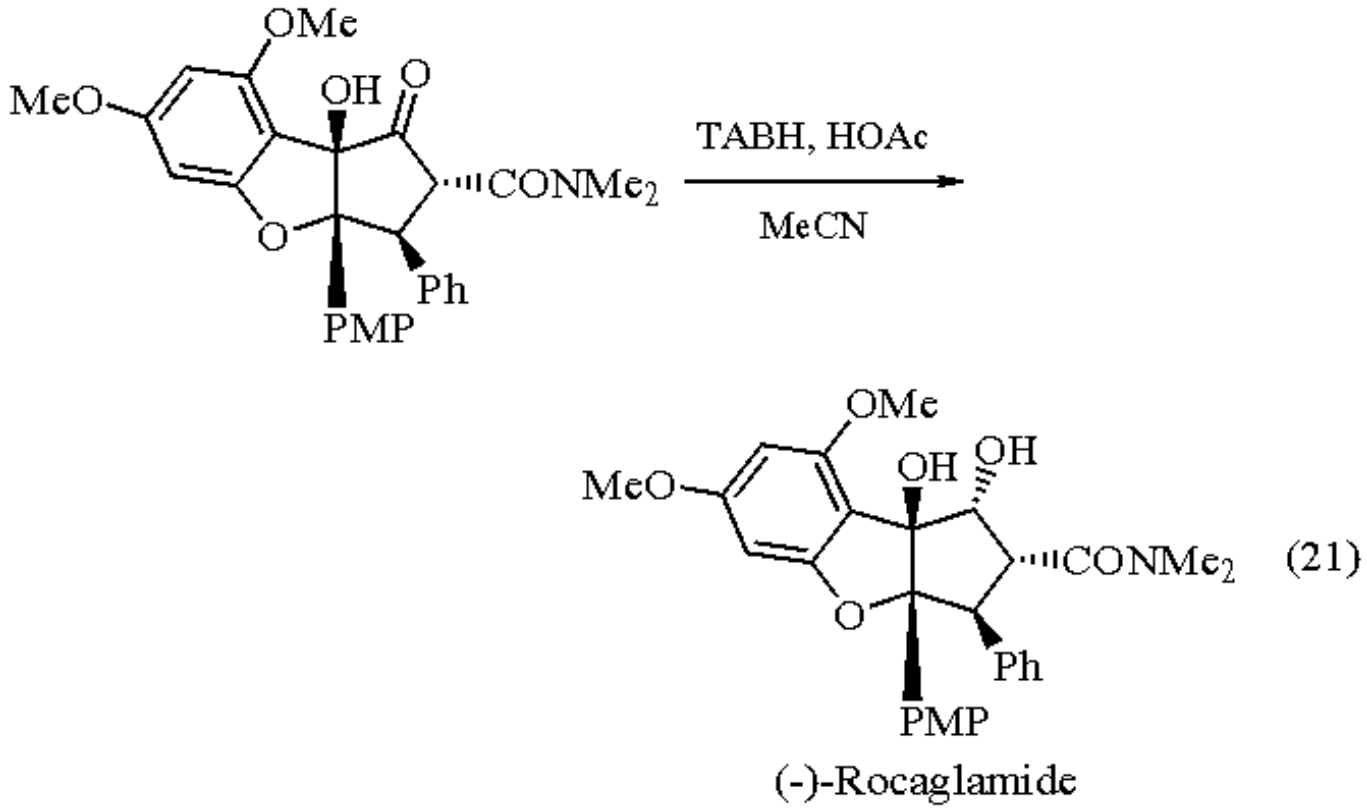

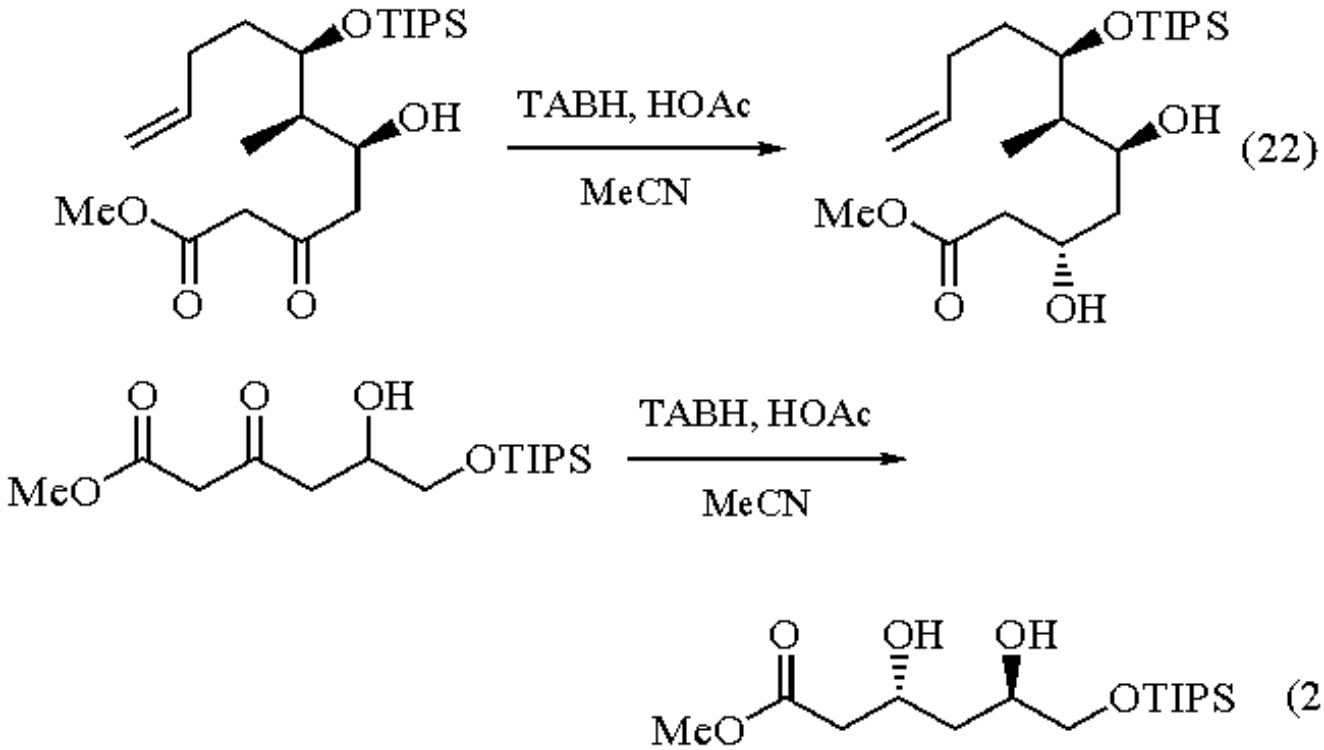

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Tetramethylammonium Tribromide

$Me_4N^+Br_3^-$

[15625-56-6] · $C_4H_{12}Br_3N$ · Tetramethylammonium Tribromide · (MW 313.87)

(mild brominating agent)

Physical Data: mp 118-119 °C.

Solubility: slightly sol H_2O, alcohols, other organic solvents; slowly dissolves in acetone, reacting to form a lachrymatory solution.

Form Supplied in: anhydrous orange powder.

Preparative Methods: tetraalkylammonium salts that have poor stability can be freshly prepared by the procedure in eq 1. Stoichiometric amounts of tetraalkylammonium (methyl, ethyl, butyl…) bromide and sodium bromide are dissolved into hot water (1 L/mol of sodium bromide) and concd nitric acid (2.2 mol/mol NaBr) is slowly added with stirring. The reaction starts after few min and can be quite exothermic. When the temperature of the mixture returns to rt, the orange precipitate is filtered, washed with ethanol and ether, and dried.

$$2\ NaBr + R_4NBr + 4\ HNO_3 \longrightarrow R_4NBr_3 + 2\ NO_2 + 2\ H_2O + 2\ NaNO_3 \quad (1)$$

Purification: by recrystallization from glacial acetic acid.

Handling, Storage, and Precautions: this hygroscopic solid should be stored under dry conditions. Purity more than 98%; stable bromine degree (1 g = 3.18 mequiv Br_2) when correctly handled. Avoid washing reaction vessels with acetone. Less toxic than bromine, but handle in a fume hood.

Bromination of Alkenes.

Application of tetramethylammonium tribromide as a brominating reagent is well known.[1] Tetramethylammonium tribromide allows double bond bromination under mild conditions and with good yields, and in some cases permits the bromination of aryl compounds at the α-position.[2] Cyclohexene leads to 1,2-dibromocyclohexane; toluene gives benzyl bromide. The bromination of fluorene and methylnaphthalene has also been reported.

---

1. (a) Fournier, M.; Fournier, F.; Berthelot, J. *BSB* **1984**, *93*, 157. (b) Berthelot, J.; Fournier, M. *CJC* **1986**, *64*, 603. (c) Berthelot, J.; Fournier, F.; Fournier, M. *SC* **1985**, *15*, 213.
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1,1,3,3-Tetramethylbutyl Isocyanide[1]

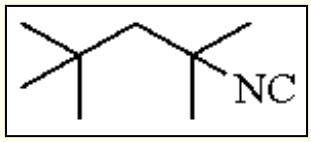

[14542-93-9] · $C_9H_{10}N$ · 1,1,3,3-Tetramethylbutyl Isocyanide · (MW 139.26)

(adds organometallic reagents to give α-metalloaldimines; synthetically useful acyl anion equivalent[2])

Alternate Name: isooctyl isocyanide; 2-isocyano-2,4,4-trimethylpentane; TMBI.

Physical Data: bp 55-57 °C/11 mmHg; *n*20D 1.4220; *d* 0.794 g cm^{-3}.

Solubility: insol water; sol common organic solvents.

Form Supplied in: colorless liquid, commercially available.

Analysis of Reagent Purity: IR ν = 2130 cm^{-1}; ^1H NMR (neat) δ 1.08 (*s*, 9H), 1.43 (t, $J_{^{14}N-H}$ = 2 Hz, 6H) 1.58 (t, $J_{^{14}N-H}$ = 2.3 Hz, 2H).

Preparative Methods: readily available in two steps from 1,1,3,3-tetramethylbutylamine, which is formylated with ***Formic Acid*** (86-90%) followed by dehydration with ***Dimethylchloromethyleneammonium Chloride*** (Vilsmeier reagent).[3]

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: unlike other isocyanides 1,1,3,3-tetramethylbutyl isocyanide is not malodorous, though its sweetish pine odor may become unpleasant after continued inhalation. Since some isocyanides are presumed to be toxic,[4] appropriate precautions are recommended.

Addition of Organometallic Reagents.

Organolithium, Grignard, organocopper, and organozinc reagents add to the NC function of isocyanides that do not possess α-hydrogen atoms to give α-addition products. The α-metalloaldimines formed are useful synthetic equivalents[5] for acyl anions, which are notoriously difficult to prepare.[6] Reaction of α-metalloaldimines with electrophiles followed by hydrolysis of the imine introduces the acyl moiety into the product (eq 1).

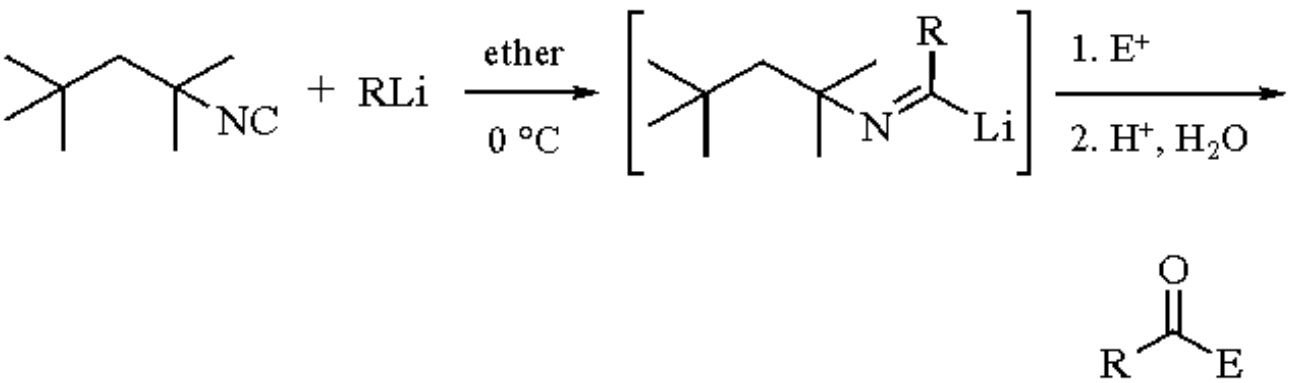

(1)

1,1,3,3-Tetramethylbutyl isocyanide has several advantages over other isocyanides without α-hydrogens.[7] It is easy to prepare from inexpensive starting materials and is not malodorous. Aromatic isocyanides, which could also be considered as precursors to α-metalloaldimines, tend to oligomerize and arylalkyl isocyanides do not form sufficiently stable α-metalloaldimines.

α-Lithioaldimines are generally prepared by addition of organolithium reagents to a solution of 1,1,3,3-tetramethylbutyl isocyanide in ether at

0 °C.[2,7] Aliphatic organolithium reagents add rapidly to produce excellent yields of the products. Aromatic organolithiums usually give lower yields. Grignard reagents also tend to give somewhat lower yields,[2,7] but their use may sometimes be more expedient when organolithiums are not readily available. Anions generated from C-H acids of pK_a < 30 do not add to 1,1,3,3-tetramethylbutyl isocyanide. Reaction with the substituted cyclopropyllithium shown leads to a substituted cyclobutanone as the main product (eq 2).[8]

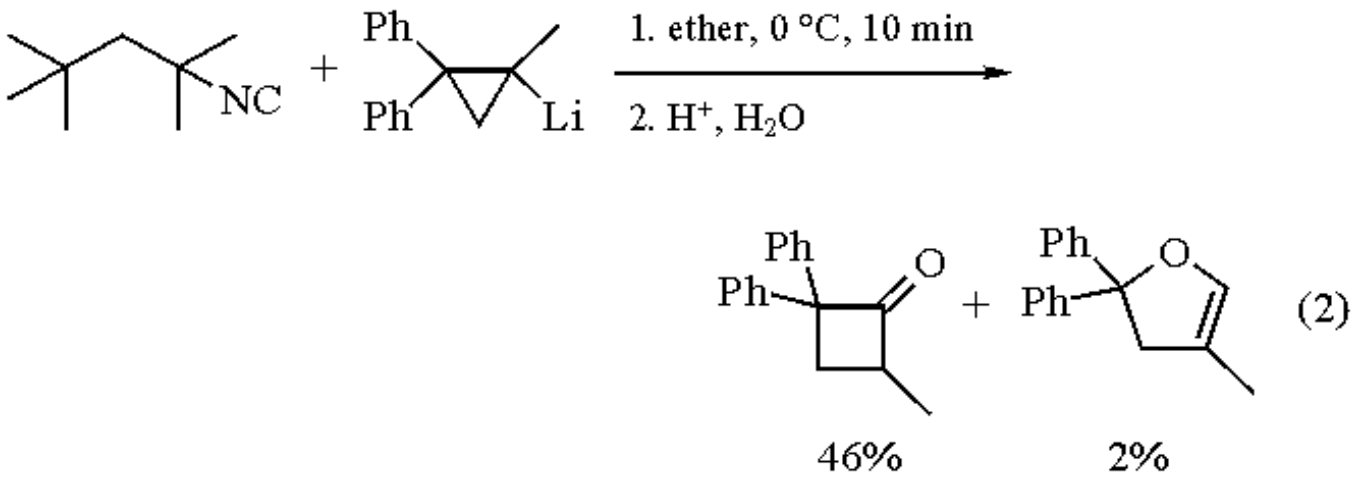

(2)

Preparation of Aldehydes and 1-Deuterio Aldehydes.

While simple protonation of metalloaldimines followed by hydrolysis of the imine provides a facile procedure for the preparation of aldehydes,[2,7] from a synthetic point of view it is much more interesting to utilize this reaction to prepare 1-deuterioaldehydes by using D_2O as a quenching agent (eq 3).[2,3,7]

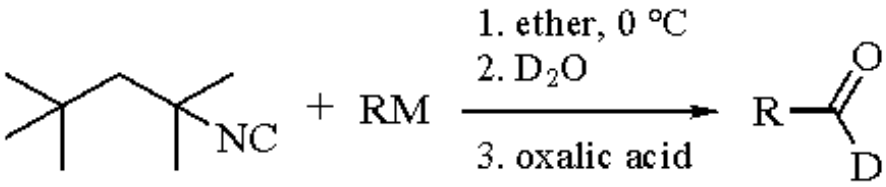

(3)

Yields and deuterium incorporation are higher with organolithiums than with Grignard reagents (Table 1). The products are conveniently isolated by steam distillation from oxalic acid solution.

Table 1 Synthesis of 1-Deuterated Aldehydes from 1,1,3,3-Tetramethylbutyl Isocyanide and Organometallic Reagents

RM	Yield (%)	Deuterium (%)
s-BuLi	92	98
t-BuLi	92	98
s-BuMgBr	67	96
Benzyl MgBr	63	80
Cyclopentyl MgBr	66	89

Reactions with Other Electrophiles.

α-Metalloaldimines react smoothly with ***Carbon Dioxide*** to give, after hydrolysis, α-keto acids (eq 4).[2,7] Similar reaction with ***Ethyl Chloroformate*** leads to α-keto esters.[2]

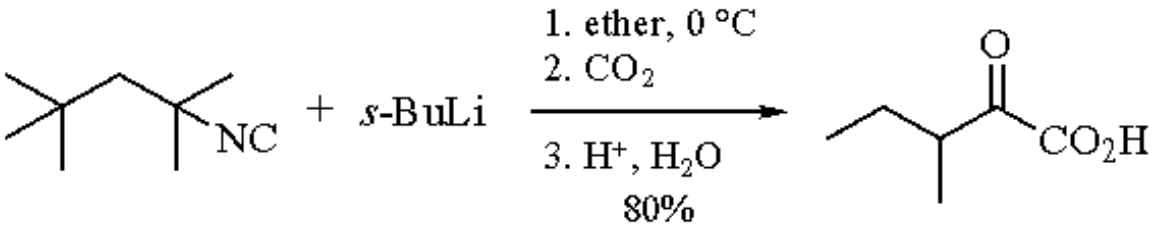

(4)

Alkylation can be performed with primary halides, which leads to unsymmetrical ketones (eq 5).[7b] Benzylic and allylic halides do not give synthetically useful reactions, whereas secondary halides undergo elimination. In the latter case, dialkylchloroboranes were successfully used to overcome this difficulty (demonstrated for *t*-butyl isocyanide).[9]

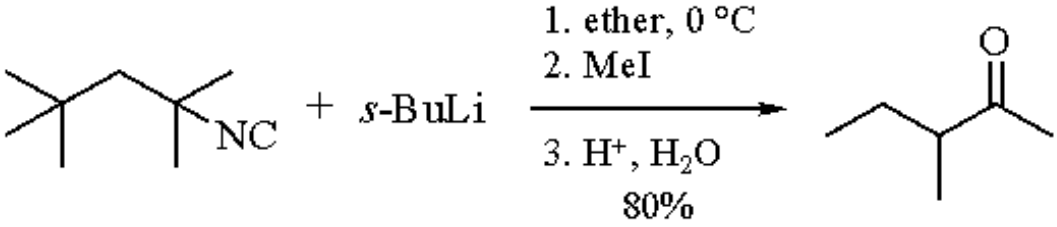

(5)

Addition to nonenolizable aldehydes proceeds smoothly to give, after hydrolysis, α-hydroxy ketones (eq 6), whereas ***Propylene Oxide*** yields β-hydroxy ketones (eq 7) virtually without dehydration.[2,7b]

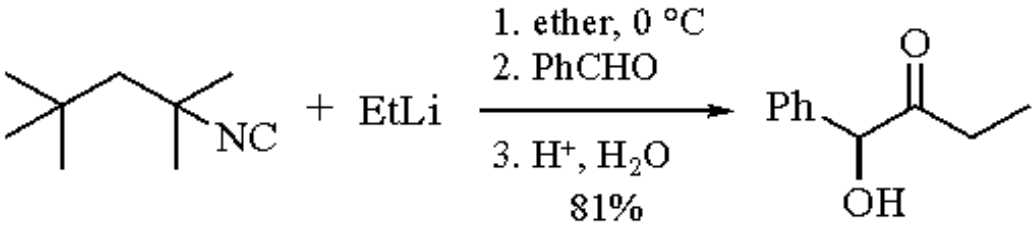

(6)

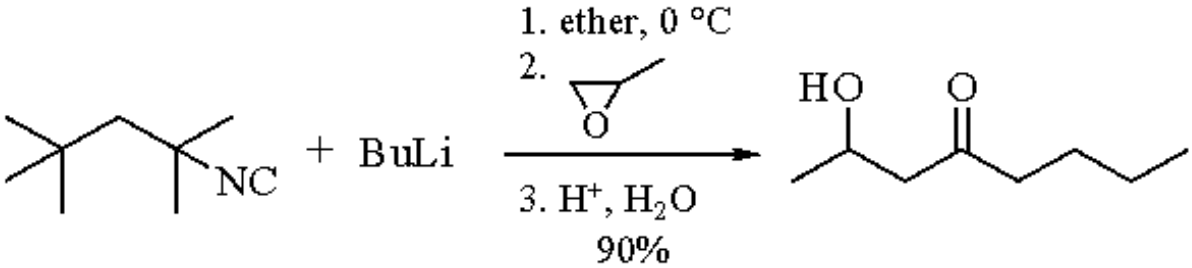

(7)

The mechanism of the reaction with aldehydes has been studied in more detail.[10] It was found that, whereas α-metalloaldimines add to acrolein in a 1,2 fashion, a 1,4-Michael-type addition occurs with ***Methyl Acrylate***.[10]

Reaction of metalloaldimines with ***Chlorotrimethylsilane*** constitutes a simple route to acylsilanes, though the yield is somewhat low due to the difficulties with selective hydrolysis of the intermediate imine (eq 8).[2,7b]

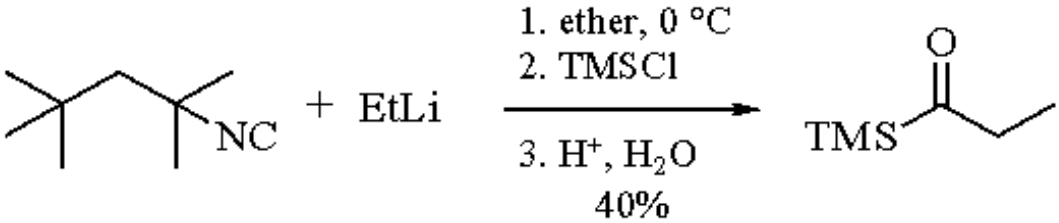

(8)

Coupling of Lithium Aldimines with Aryl, Vinyl, and Alkynyl Halides.

In a reaction unique among acyl anion equivalents, lithium aldimine generated from 1,1,3,3-tetramethylbutyl isocyanide and ***t-Butyllithium***[2] couples with aryl, vinyl, and alkynyl halides to give, after hydrolysis, the corresponding ketones (eqs 9-11).[11]

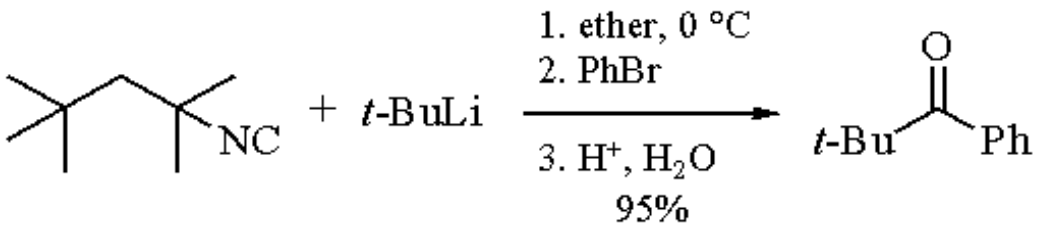

(9)

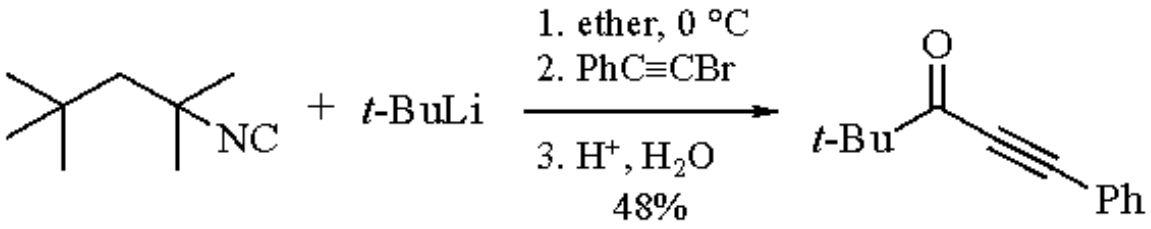

(10)

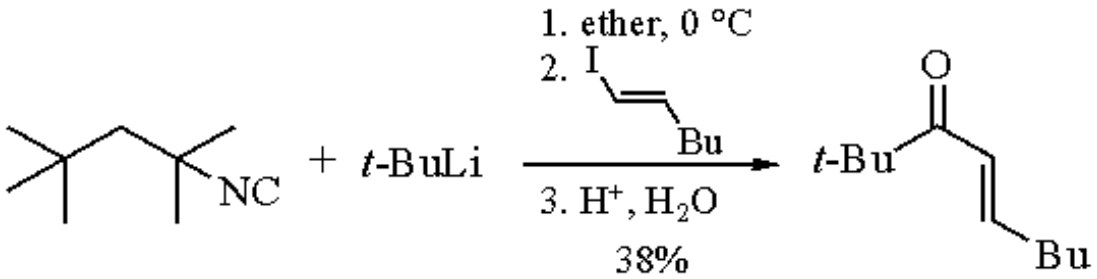

(11)

Aryl halides like iodo- or bromobenzene (but not chlorobenzene) give excellent yields of ketones. This interesting reaction is believed to proceed by halogen-metal exchange to give imidoyl halides and organolithium reagents, which in turn couple to give the product.[11]

Dissociation of Metalloaldimines.

Lithium aldimines are relatively stable; very little dissociation is observed in their reactions. However, their conversion to copper derivatives accelerates the dissociation.[12] Good yields of nitriles are found only when tertiary alkyllithium reagents are used to generate the lithium aldimine (eq 12).

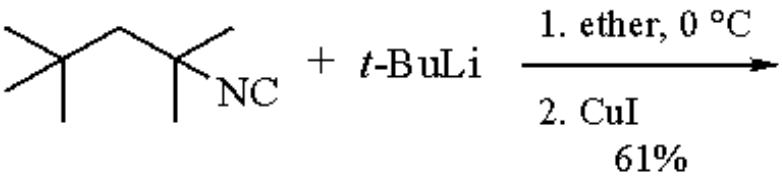

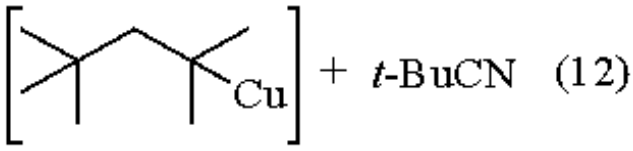

(12)

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12. Periasamy, M. P.; Walborsky, H. M. *JOC* **1974**, *39*, 611.

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1,1,3,3-Tetramethyldisilazane

$(HMe_2Si)_2NH$

[15933-59-2] · $C_4H_{15}NSi_2$ · 1,1,3,3-Tetramethyldisilazane · (MW 133.38)

(intramolecular hydrosilation of allyl alcohols, homoallyl alcohols, and homopropargyl alcohols for the regio- and stereoselective synthesis of polyols)

Physical Data: bp 99-100 °C; *n*20D 1.4040; *d* 0.752 g cm^{-3}.

Solubility: common organic solvents.

Form Supplied in: neat liquid.

Handling, Storage, and Precautions: moisture sensitive but no special precautions necessary for handling in the air for a short period of time. May be stored under nitrogen in a tightly capped bottle in a refrigerator. Use in a fume hood.

Intramolecular Hydrosilation.[1,2]

Allyl and homoallyl alcohols are transformed into 1,3-diols in a highly regio- and stereoselective fashion via intramolecular hydrosilation followed by oxidative cleavage of the silicon-carbon bonds by ***Hydrogen Peroxide***, which proceeds with complete retention of configuration at carbon (eqs 1 and 2).[3,4]

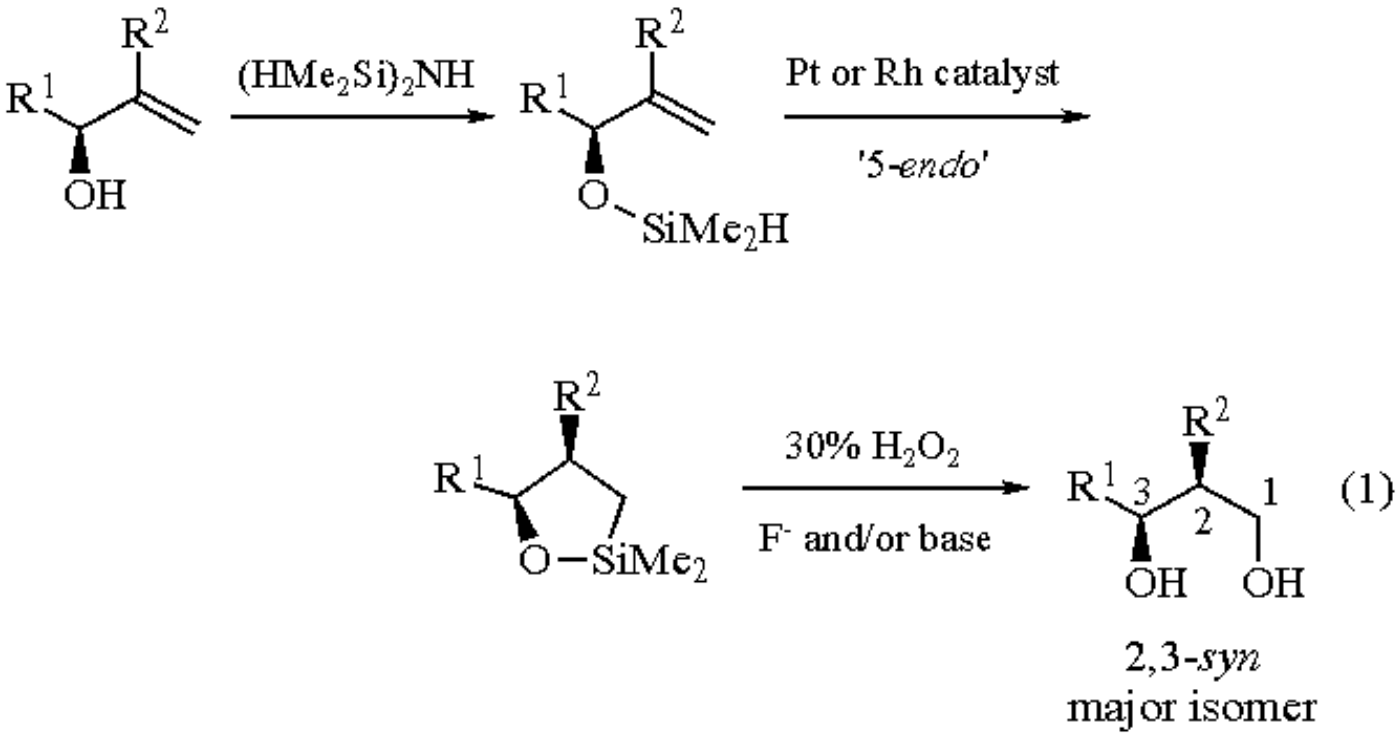

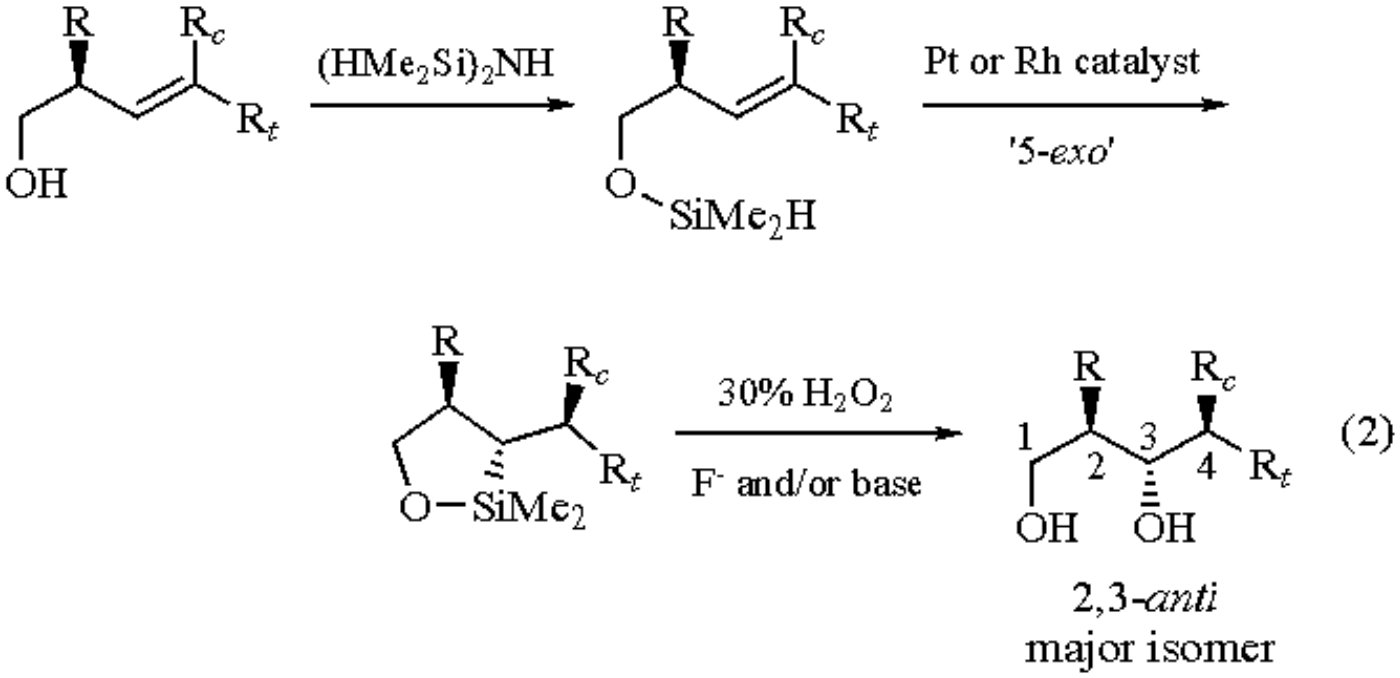

Thus, an alcohol is converted into a hydrodimethylsilyl ether by treatment with 1,1,3,3-tetramethyldisilazane in the absence or presence of a catalytic amount of ammonium chloride as a promoter. The ammonia produced in this reaction and the excess disilazane must be removed prior to the hydrosilation step (see also ***Chlorodimethylsilane*** and ***N,N-Diethylaminodimethylsilane***. The intramolecular hydrosilation can be achieved by using a platinum or rhodium catalyst (<=1 mol %) such as acidic $H_2PtCl_6.6H_2O$ in *i*-PrOH (Speier's catalyst) or THF, neutral $Pt[\{(CH_2{=}CH)Me_2Si\}_2O]_2$ in xylene, or ***Chlorotris(triphenylphosphine)rhodium(I)*** (Wilkinson's catalyst). After the reaction, the catalyst, which causes a rapid decomposition of hydrogen peroxide in the subsequent oxidation step, must be removed by stirring the mixture with crystalline EDTA.2Na or activated carbon followed by filtration.[2] The oxidative cleavage of the organosilane intermediate usually proceeds smoothly at room temperature under the standard conditions shown in the following examples.

The reaction of terminal allyl alcohols proceeds in a 5-*endo* fashion to give five-membered ring compounds regioselectively and stereoselectively. Subsequent oxidation affords 2,3-*syn*-1,3-diols preferentially, regardless of the nature of the catalyst (eq 1).[5] The stereoselectivity increases with increased bulkiness of the allylic substituent R^1 and the nature of the alkene substituent R^2 (see below).[5] 5-*Exo* type cyclization occurs with homoallyl alcohols to form five-membered heterocycles and 1,3-diols after oxidation. Two chiral centers are produced in this reaction. The 2,3-relationship (*anti*) is controlled by the allylic substituent, while the 3,4-relationship is determined by the stereochemistry of the alkene; the hydrosilation occurs by *cis* addition of Si-H to the alkene (eq 2).[5b]

This methodology has been applied to the construction of a variety of stereoisomers of polypropionate skeletons, as exemplified by the formation of a tetraol from a symmetrical bis-allyl alcohol by a sequence involving three intramolecular hydrosilation-oxidation steps (eq 3).[5b]

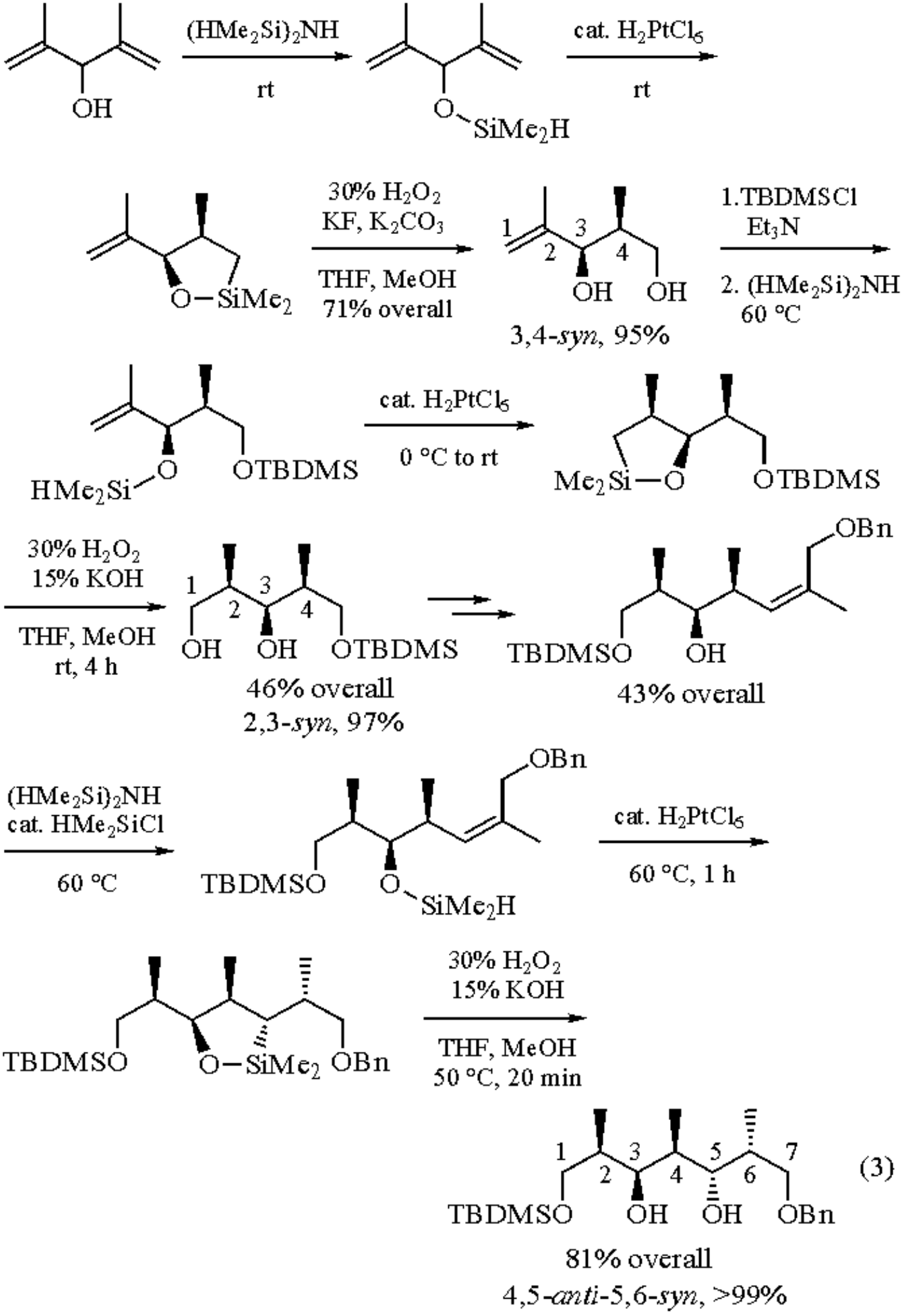
(HMe2Si)2NH
rt
cat. H2PtCl6
rt
OH
O
SiMe2H
30% H2O2
KF, K2CO3
THF, MeOH
71% overall
O—SiMe2
1
2
3
4
OH
OH
3,4-syn, 95%
1.TBDMSCl
Et3N
2. (HMe2Si)2NH
60 °C
HMe2Si
O
OTBDMS
cat. H2PtCl6
0 °C to rt
Me2Si—O
OTBDMS
30% H2O2
15% KOH
THF, MeOH
rt, 4 h
OH
OH
OTBDMS
46% overall
2,3-syn, 97%
OBn
TBDMSO
OH
43% overall
(HMe2Si)2NH
cat. HMe2SiCl
60 °C
TBDMSO
O
SiMe2H
cat. H2PtCl6
60 °C, 1 h
TBDMSO
O—SiMe2
OBn
30% H2O2
15% KOH
THF, MeOH
50 °C, 20 min
5
6
7
TBDMSO
OH
OH
OBn
81% overall
4,5-anti-5,6-syn, >99%

(3)

Extremely high stereoselectivity has been attained in the intramolecular hydrosilation of α-hydroxy enol ethers, leading to 1,2,3-triol derivatives with 2,3-*syn* stereochemistry (eq 4).[6] It has been pointed out, however, that the stereoselectivity largely depends upon the nature of the catalyst, Pt or Rh, and the presence or absence of the disilazane in the Pt case (eq 5).[7]

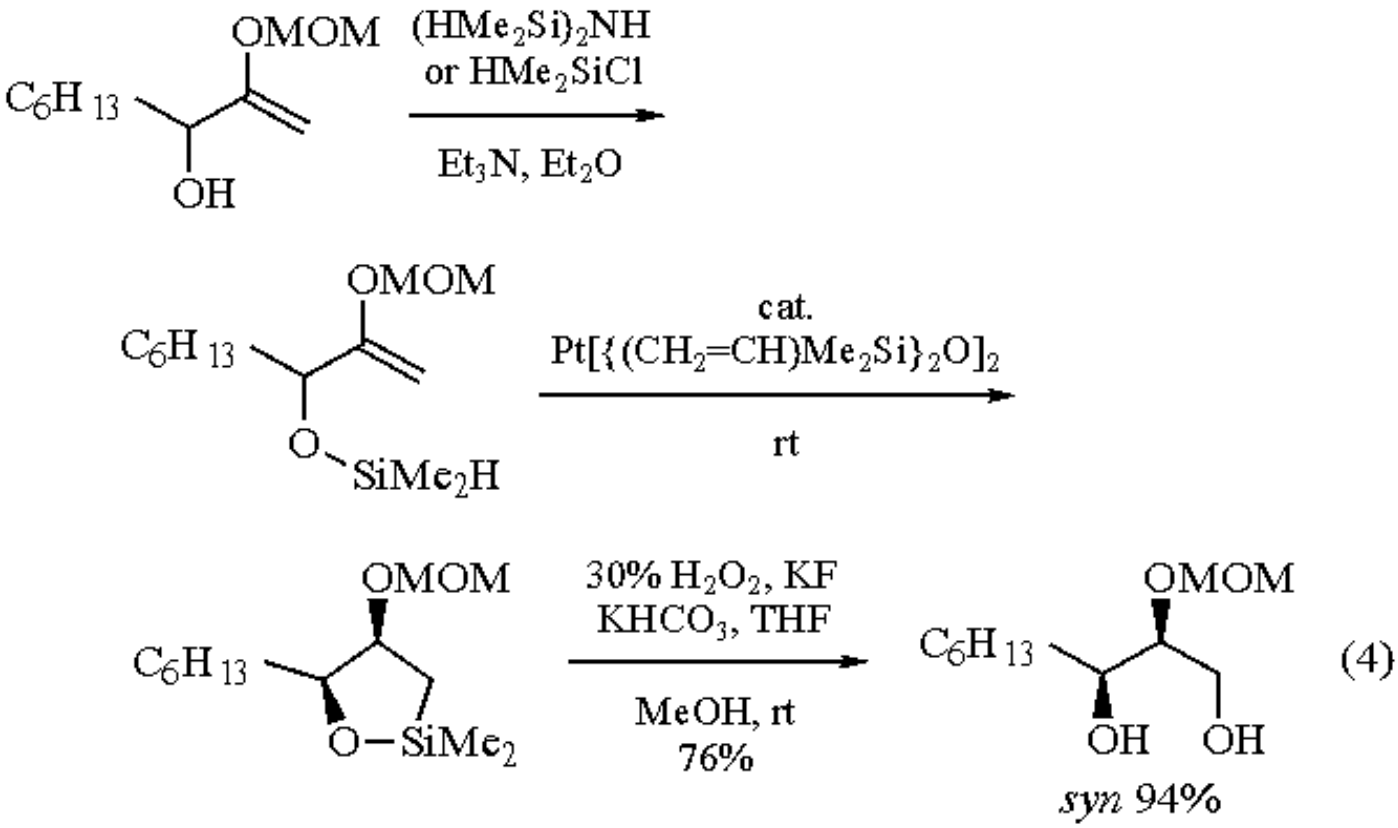

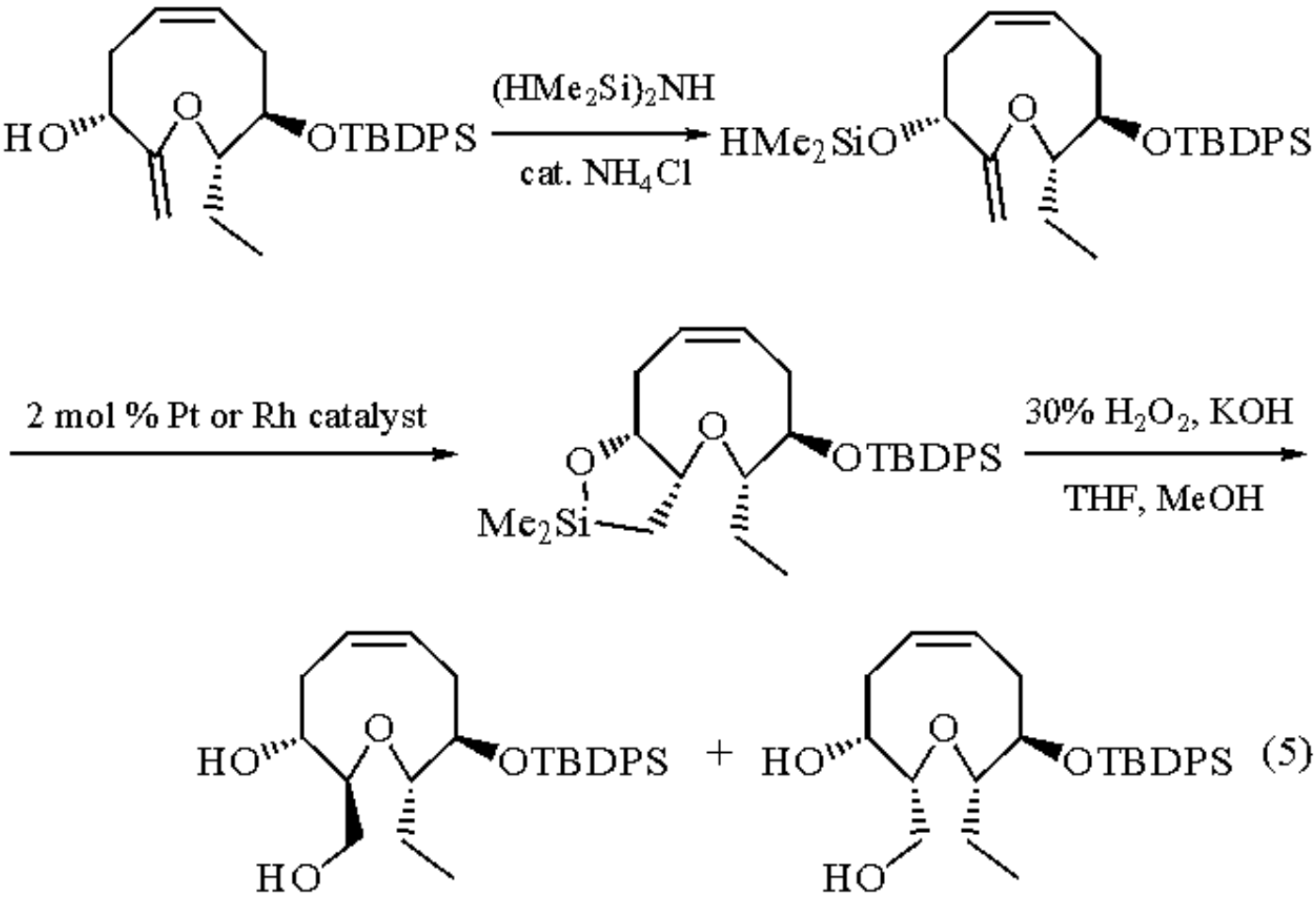

catalyst

$Pt[\{CH_2{=}CH)Me_2Si\}_2O]_2$, 72% 16:84

$Pt[\{CH_2{=}CH)Me_2Si\}_2O]_2$, 72%	16:84
$Pt[\{CH_2{=}CH)Me_2Si\}_2O]_2$ + $(HMe_2Si)_2NH$ (10 mol %), 84%	83:17
Rh(acac)(1,5-cod), 61%	>95:<5

The intramolecular hydrosilation of homopropargyl alcohols also proceeds in a 5-*exo* manner to form five-membered cyclic vinylsilanes exclusively. Subsequent oxidation affords a β-hydroxy ketone (eq 6).[8] The vinylsilane also undergoes a Pd-catalyzed cross-coupling reaction with aryl or alkenyl halides stereoselectively (eq 6).[9] The intramolecular hydrosilation thus provides an efficient methodology for the regio- and/or stereoselective functionalization and carbon-carbon bond formation of the alkyne moiety in homopropargyl alcohol.

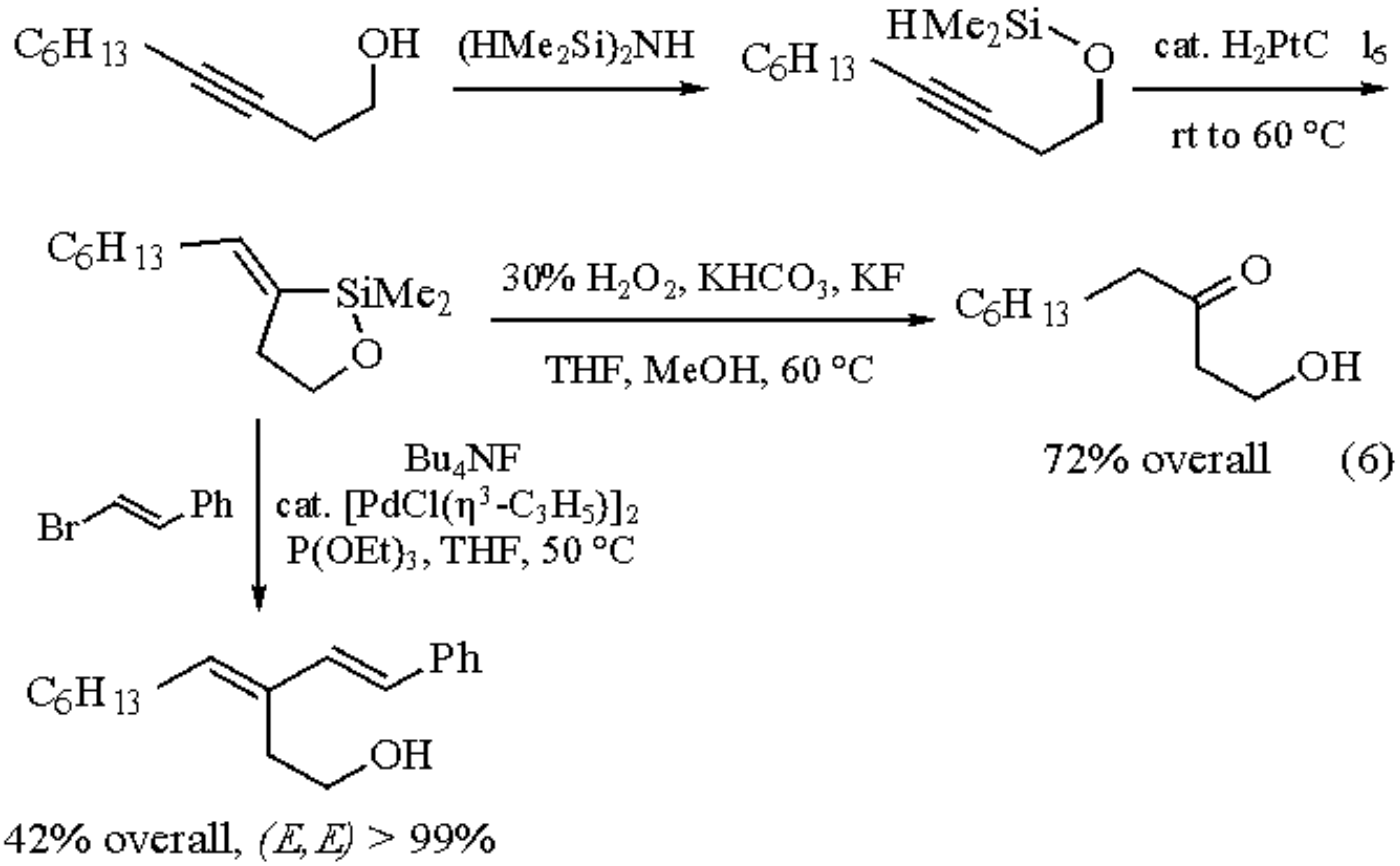

While the five-membered cyclic alkoxysilane moiety has been found to tolerate a wide range of chemical transformations (OsO_4 oxidation, Swern oxidation, Horner-Emmons alkenation, protection conditions such as Tr/py$^+$ BF_4^- and MeI/NaH, and catalytic hydrogenation), the carbon-silicon bond can be cleaved efficiently by ***Tetra-n-butylammonium Fluoride*** in DMF (eq 7).[10]

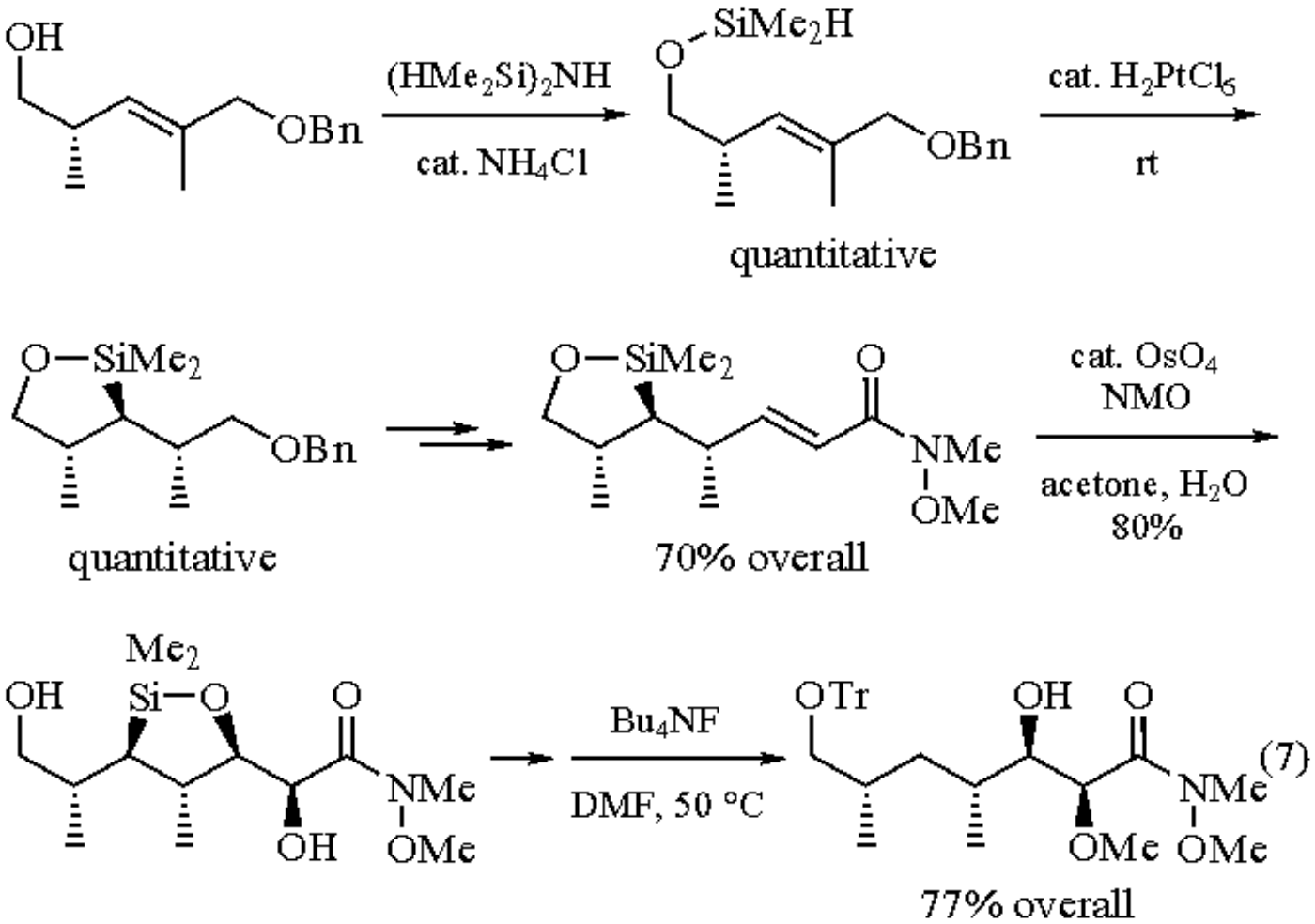

The intramolecular hydrosilation of allyl alcohols containing an ester group at the terminal carbon proceeds in a 5-*endo* fashion to form the five-membered cyclic products with modest stereoselectivity. The silyl group α to the carbonyl group is readily cleaved by a fluoride ion in protic solvents (eq 8).[11]

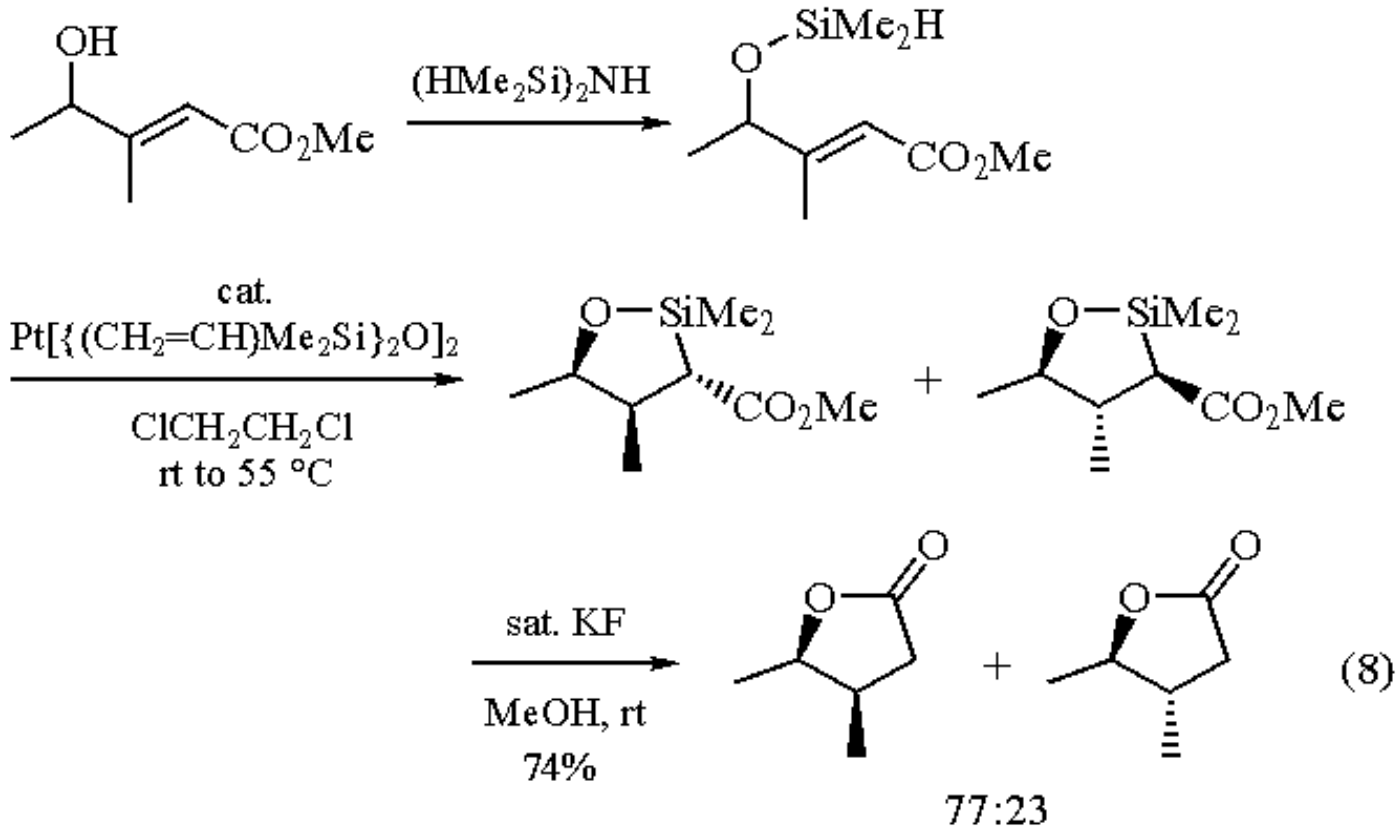

Catalytic asymmetric intramolecular hydrosilation of allyl alcohols has been achieved by using ***Chlorodiphenylsilane***[12] or 1-chloro-1-silacyclohexane[13] as the silylating agent.

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7. (a) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *TL* **1992**, *33*, 671. (b) Curtis, N. R.; Holmes, A. B. *TL* **1992**, *33*, 675.
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N,N,N´,N´-Tetramethylethylenediamine[1]

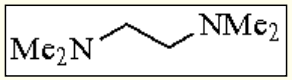

[110-18-9] · $C_6H_{16}N_2$ · *N,N,N´,N´*-Tetramethylethylenediamine · (MW 116.24)

(bidentate tertiary amine Lewis base with good solvating properties; used as an additive to stabilize and activate organometallic reagents and inorganic salts; enhances the rate of metalation of a variety of aromatic and unsaturated systems as well as influencing the regiochemical outcome of these reactions; effective as a neutral amine in base catalyzed reactions)

Alternate Name: TMEDA.

Physical Data: bp 121 °C; *d* 0.781 g cm^{-3}.

Solubility: very sol water, most organic solvents.

Form Supplied in: colorless liquid, typically of 99% purity as obtained commercially. *Drying:* for uses in conjunction with organometallic reagents, moisture exclusion is necessary. Removal of water is best achieved by refluxing over lithium aluminum hydride or calcium hydride for 2 h under nitrogen and distilling immediately prior to use.

Handling, Storage, and Precautions: TMEDA should be used directly after distilling. However, it may be stored under nitrogen and transferred by using a syringe and septum cap as required. For most applications the amine is removed during aqueous workup simply by washing with water owing to its high water solubility. Use in a fume hood.

Lithiation of Difficult Substrates.

TMEDA, through an erstwhile perception of enhanced chelating ability,[1b] but more likely through presentation of a more labile environment, activates organolithium reagents.[1i] ***n-Butyllithium*** forms hexamers in hexane but in the presence of TMEDA exists as a solvated tetramer.[2] Thus the use of the *n*-butyllithium/TMEDA complex in hexane[3] effects the dilithiation of ***Furan*** and thiophene,[4] and lithiation of benzene,[5] in high yields. The allylic deprotonation of unactivated alkenes is normally difficult to achieve with BuLi alone. However, in the presence of TMEDA, propene is monolithiated or dilithiated in the allylic position,[6] and limonene is selectively lithiated at C-10.[7] The resulting allylic carbanion and electrophiles such as ***Paraformaldehyde*** give functionalized products (eq 1).[8]

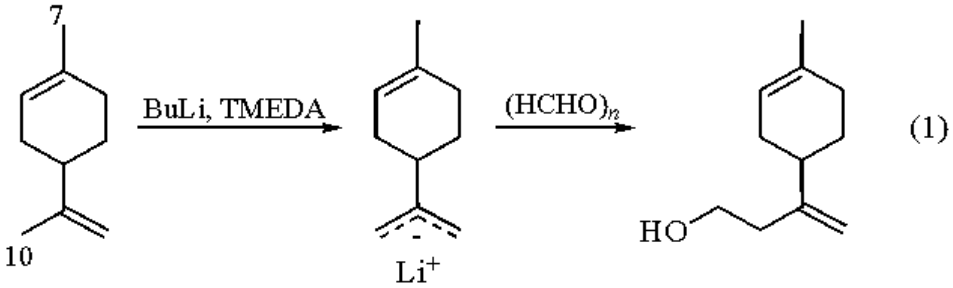

However, when vinylic metalation is desired, competing allylic deprotonation may occur. In general, thermodynamic acidity and the kinetic preference for vinylic deprotonation of cyclic alkenes decrease with increasing ring size.[1h] The stable alkane-soluble reagent ***n-Butyllithium-Potassium t-Butoxide***-TMEDA in hexane[9] metalates ***Ethylene*** with potassium[10] and effects selective vinylic deprotonation of cyclopentene (eq 2),[11] cyclobutene,[12] norbornene, and norbornadiene.[10]

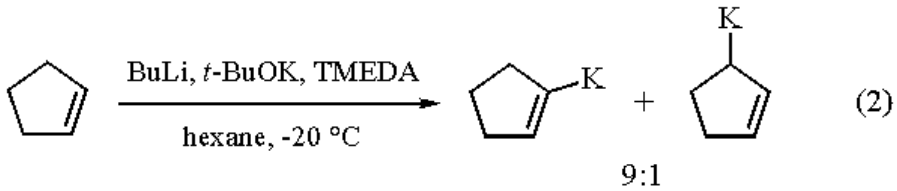

(2)

N-Alkyl- and *N*-arylpyrroles are readily α-lithiated.[1c] For example, *N*-methylpyrrole is deprotonated with ***Ethyllithium***/TMEDA and the lithiated product has been treated with ***Carbon Dioxide*** to give the corresponding carboxylic acid in 70% yield (eq 3).[13]

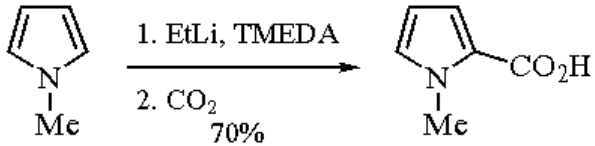

(3)

Numerous examples exist in which TMEDA not only facilitates the lithiation of aromatic and heteroaromatic substrates but also controls the regioselectivity of lithiation.[1c] While tertiary benzamides are susceptible to nucleophilic attack by *n*-butyllithium to give aryl butyl ketones, the use of ***s-Butyllithium***/TMEDA in THF at -78 °C provides the synthetically useful *ortho* metalated tertiary benzamide which may be treated with a large variety of electrophiles (eq 4).[1d,14] Even with compounds having a second more acidic site the above conditions allow *ortho* lithiation to take place under kinetic control. Thus a *p*-toluamide is *ortho* lithiated with *s*-butyllithium/TMEDA in THF at -78 °C, but when ***Lithium Diisopropylamide*** is used as the base in THF at 0 °C the thermodynamically favored benzyllithium species is obtained (eq 5).[15] The very marked influence of TMEDA on the lithiation of naphthyl methyl ether in hydrocarbon solvents is dramatically illustrated in the example in eq 6.[16]

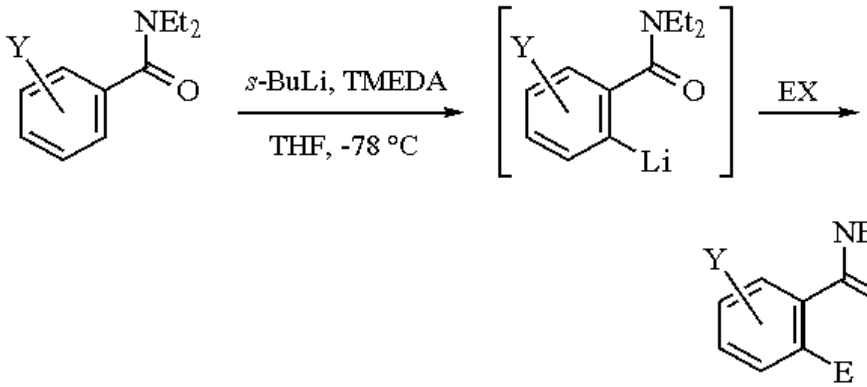

(4)

EX = D_2O, MeI, DMF, CO_2, $(CO_2Et)_2$, ArCHO, I_2, TMSCl, $B(OMe)_3/H_2O_2$, PhNCO, Ph_2CO

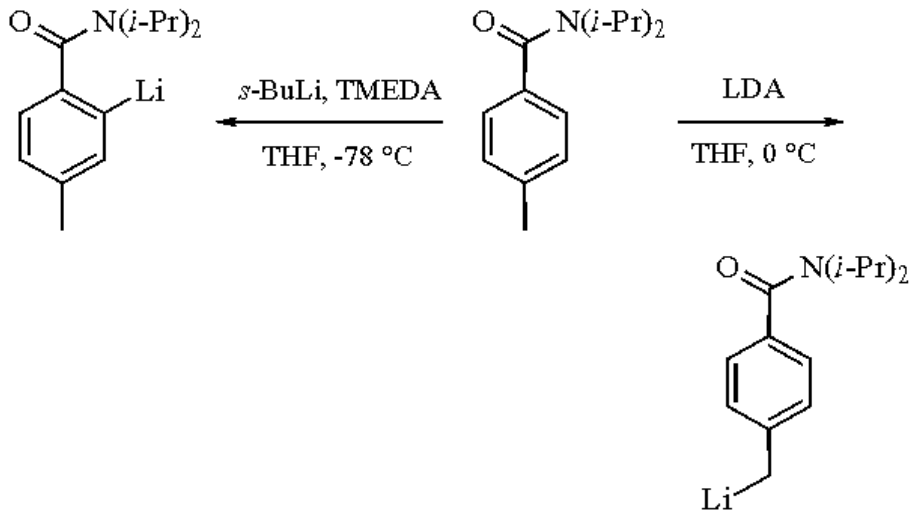

(5)

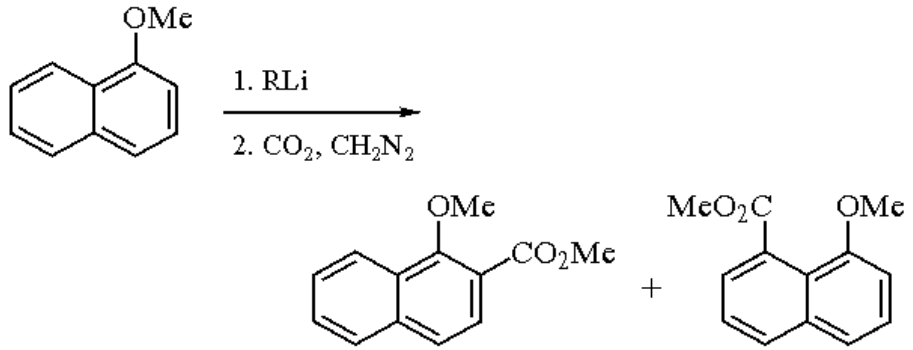

(6)

R = Bu, hexane/TMEDA	>99.3:<0.3	60%
R = *t*-Bu, cyclohexane	1:99	35%

The use of the *s*-butyllithium/TMEDA system in THF at -78 °C is widely employed for the lithiation of amide and thioamide derivatives adjacent to nitrogen.[1f] The resulting lithiated species undergo reaction with a variety of electrophiles such as aldehydes and ketones[17a] and dihalides (eq 7).[17b]

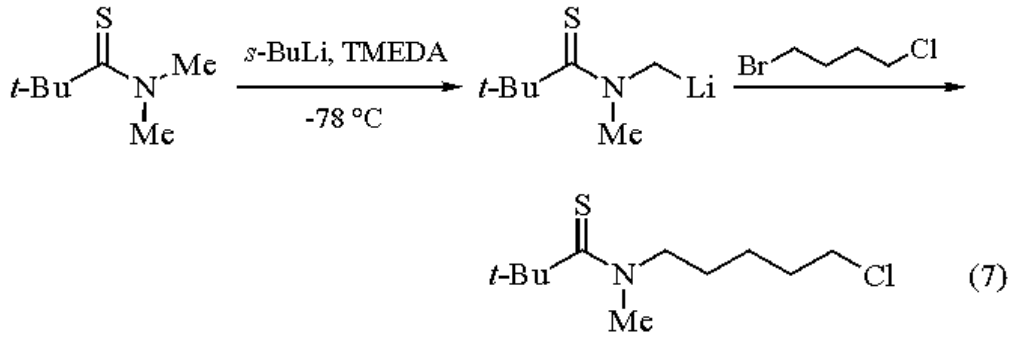

Ligand for Crystallographic Studies.

TMEDA markedly facilitates the isolation of otherwise inaccessible crystalline organolithium reagents suitable for structural determination by X-ray crystallographic means.[18] In most cases, bidentate binding of the TMEDA ligand to the lithium ion is observed.

Control of Regioselectivity and Stereoselectivity.

The recognition by Ireland and co-workers[19] that ***Hexamethylphosphoric Triamide*** has a profound effect on the stereochemistry of lithium enolates has led to the examination of the effects of other additives, as the ability to control enolate stereochemistry is of utmost importance for the stereochemical outcome of aldol reactions. Kinetic deprotonation of 3-pentanone with ***Lithium 2,2,6,6-Tetramethylpiperidide*** at 0 °C in THF containing varying amounts of HMPA or TMEDA was found to give predominantly the (*Z*)-enolate at a base:ketone:additive ratio of ca. 1:1:1, whereas with a base:ketone:additive ratio 1:0.25:1, formation of the (*E*)-enolate was favored (Table 1).[20] This remarkable result contrasts with those cases where HMPA:base ratios were varied towards larger amounts of HMPA, which favored formation of the (*Z*)-enolate.[21]

Table 1 Deprotonation of 3-Pentanone with LiTMP (1.0 mmol) in THF at 0 °C in the Presence of TMEDA or HMPA[19]

3-Pentanone (mmol)	TMEDA (mmol)	HMPA (mmol)	(*E*)-Enolate	(*Z*)-Enolate	Total % yield of silyl enol ether derivatives
0.9	1.0		17	83	70
0.45	1.0		91	9	90
0.25	1.0		95	5	70
0.9		1.0	8	92	89
0.45		1.0	65	35	75
0.25		1.0	66	34	80

However, TMEDA unlike HMPA, does not cause flow over from a carbonyl to conjugate addition manifold for many lithiated systems. For example, lithiated allylic sulfides undergo conjugate (or 1,4) addition to cyclopent-2-enone in the presence of HMPA (see ***Allyl Phenyl Sulfide***), but in the presence of TMEDA, carbonyl addition only is observed.[22] The perception that TMEDA is unable to form solvent-separated ion pairs required for conjugate addition in this case now requires reevaluation.[1j,23] In the reaction of lithio α-trimethylsilylmethyl phenyl sulfide with cyclohexenone, HMPA promotes predominant conjugate addition, whereas TMEDA has little effect on the normal carbonyl addition pathway taken in THF alone (eq 8).[24]

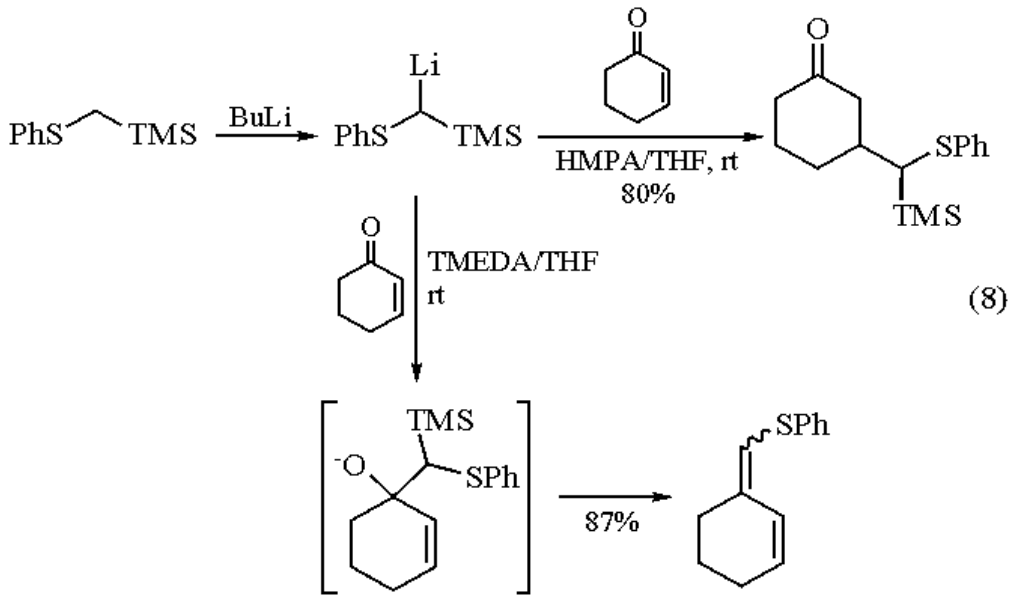

(8)

Likewise, TMEDA in THF has little effect on the stereochemical outcome of the Horner-Wittig reaction of lithiated ethyldiphenylphosphine oxide with benzaldehyde in THF at low temperature compared to the reaction in THF alone: a very slight enhancement in favor of the *erythro* (*anti*) hydroxy phosphine oxide intermediate (*erythro*:*threo* from 85:15 to 88:12), thus leading to slightly enhanced (*Z*)-alkene formation, is observed. By contrast, a reaction in ether alone provides less of the *erythro* product (*erythro*:*threo* 60:40).[25] These examples serve to emphasize current thought that TMEDA is not a good chelating agent for lithium in relation to THF itself.[1i] It is noteworthy that the substitution of methyl in TMEDA by chiral binaphthylmethyl ligands generates a reagent which efficiently catalyzes asymmetric addition of butyllithium to benzaldehyde in ether at low temperature (eq 9).[26]

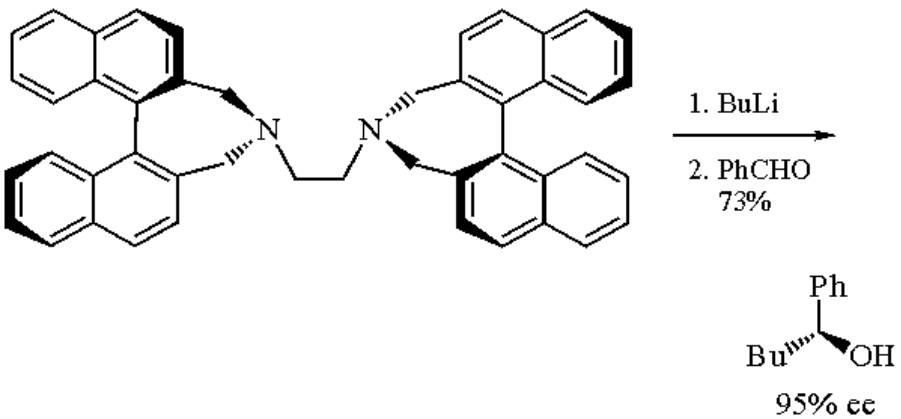

(9)

Butylmagnesium bromide in THF in the presence of excess TMEDA undergoes addition to a chiral crotonamide derivative to give the conjugate adduct in modest diastereomeric excess (67%) compared with 16% in the absence of TMEDA.[27] On the other hand, diastereoselection in the alkylation of enolates of chiral diamides derived from piperazines in THF containing TMEDA was minimal, with better results being provided by HMPA.[28]

Stabilization and Activation of Organometallic Reagents.

The development and use of organocopper reagents as nucleophiles in the conjugate addition to enones is an important area of organic synthesis. It has been found that the reactivity of aryl- and alkylcopper reagents is dramatically improved through the use of ***Chlorotrimethylsilane*** and TMEDA.[29] The TMEDA not only stabilizes and solubilizes the organocopper reagent but also facilitates the trapping of the resulting enolates, thereby affording silyl enol ethers in excellent yields.[29a] Such a role is also played by HMPA[30] and ***4-Dimethylaminopyridine***.[30b] However, the low toxicity and cost of TMEDA makes it an attractive alternative. Conjugate addition of ***Lithium Di-n-butylcuprate*** to methyl 2-butynoate in diethyl ether provides a 74:26 mixture of (*E*)- and (*Z*)-alkylated enoates, whereas in the presence of TMEDA this ratio increases to 97:3. Stereoselectivity of the conjugate addition of the copper reagent derived from butylmagnesium bromide and ***Copper(I) Iodide*** to ethyl pentynoate in diethyl ether is also enhanced when TMEDA or pyrrolidone are used as additives, to give the (*E*)- and (*Z*)-enoates in a ratio of 99:1. In contrast, the use of HMPA affords a selectivity

of only 78:22 for the (*E*)-isomer.[31]

The preparation of a trifluoromethylvinyl anion equivalent has been described in which the vinyl bromide is converted into the zinc reagent with ***Zinc/Silver Couple*** in the presence of TMEDA. The conversion proceeds very cleanly to afford a thermally stable vinylzinc bromide-TMEDA complex which can undergo reactions with electrophiles. TMEDA is essential for the conversion (eq 10).[32]

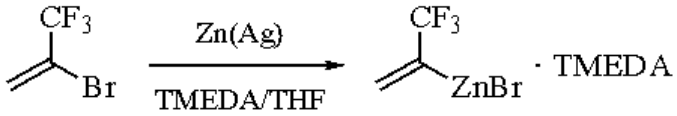

(10)

The intramolecular insertion of unactivated alkenes into carbon-lithium bonds to give cycloalkylmethyllithium compounds provides a high-yielding alternative to analogous radical cyclizations.[1g,33] In many cases the addition of Lewis bases such as TMEDA increases the rate of cyclization[1g,33] and dramatically improves those cyclizations which are otherwise sluggish at room temperature (eq 11).[34]

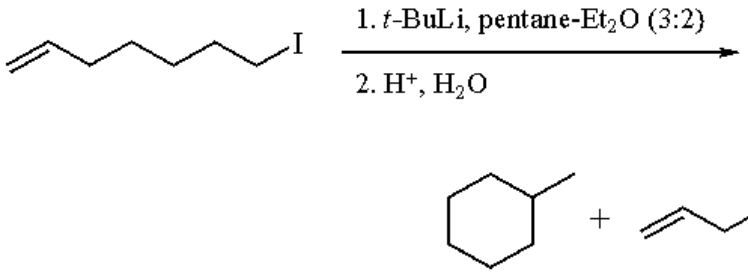

(11)

TMEDA (2 equiv)	68%	31%
no TMEDA	6%	93%

Open chain allylic alcohols add organolithium reagents in the presence of TMEDA. The reactions are regio- and stereoselective; the suggestion is made that the TMEDA complexes the alkoxide lithium counterion, allowing the alkoxide to orientate the incoming organolithium reagent and stabilize the resulting intermediate (eq 12).[35]

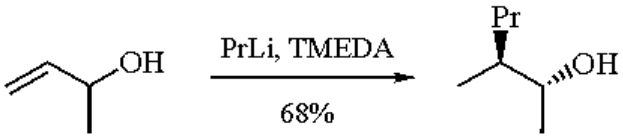

(12)

threo:*erytho* = >50:1

Inorganic Complexes useful in Organometallic Reactions and Organic Synthesis.

The complexing properties of TMEDA have made it possible to prepare and handle salts which are otherwise air and moisture sensitive. Thus ***Zinc Chloride*** in the presence of one equivalent of TMEDA forms a crystalline air stable solid, $ZnCl_2$.TMEDA,[36] which with three equivalents of an alkyllithium reagent is converted into trialkylzinclithium. Likewise, CuI and TMEDA react to form the CuI.TMEDA complex,[29] a stable solid which is used for the preparation of stabilized organocopper reagents. The rate of Cu^I-catalyzed oxidative coupling of terminal alkynes in the presence of oxygen to form diynes is considerably increased by using TMEDA as a solubilizing agent for ***Copper(I) Chloride***.[37] Magnesium hydride, rapidly acquiring widespread recognition as a versatile reducing agent (see ***Magnesium Hydride-Copper(I) Iodide***), is prepared from phenylsilane and ***Dibutylmagnesium*** in the presence of TMEDA to give a very active THF-soluble complex free of halide or impurities derived from the usual reducing agents such as ***Lithium Aluminum Hydride***.[38] TMEDA (see also ***1,4-Diazabicyclo[2.2.2]octane***) forms insoluble adducts with boranes and alanes. In particular, the formation of air-stable adducts with monoalkyl boranes is of synthetic usefulness. The free monoalkyl borane may be regenerated by treating the adduct with ***Boron Trifluoride Etherate*** in THF and filtering off the newly formed TMEDA.$2BF_3$ precipitate.[1e]

Base Catalyzed Reactions.

TMEDA can be monoprotonated (pK_a 8.97) and diprotonated (pK_a 5.85).[39] Titanium enolate formation from ketones and acid derivatives has been achieved by using ***Titanium(IV) Chloride*** and tertiary amines including TMEDA in dichloromethane at 0 °C.[40] The reactive species, which is likely to be a complex with the tertiary amine, undergoes aldol reaction with aldehydes to form *syn* adducts with high stereoselectivity (eq 13).

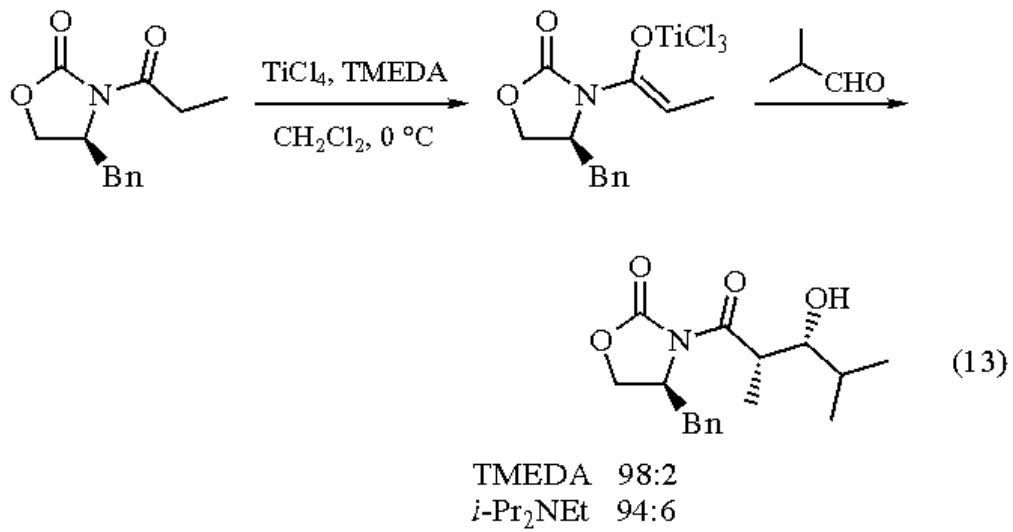

(13)

In the case of TMEDA, stereoselection in favor of the *syn* product (98:2) is enhanced over that achieved with ***Diisopropylethylamine*** (94:6).[40] Along with bases such as ***Triethylamine*** and ethylisopropylamine, TMEDA facilitates the preparation of cyanohydrin trimethylsilyl ethers from aldehydes and ***Cyanotrimethylsilane***.[41] It has been suggested that coordination by nitrogen induces formation of an active hypervalent cyanation intermediate from cyanotrimethylsilane. The conjugate addition of thiols to enones has been successfully catalyzed by using TMEDA in methanol at room temperature, as exemplified by the reaction of 10-mercaptoisoborneol and 4-*t*-butoxycyclopentenone (eq 14).[42] In this case the relative mildness of the reaction conditions prevents subsequent elimination of *t*-butoxide from occurring to give the unwanted enone.

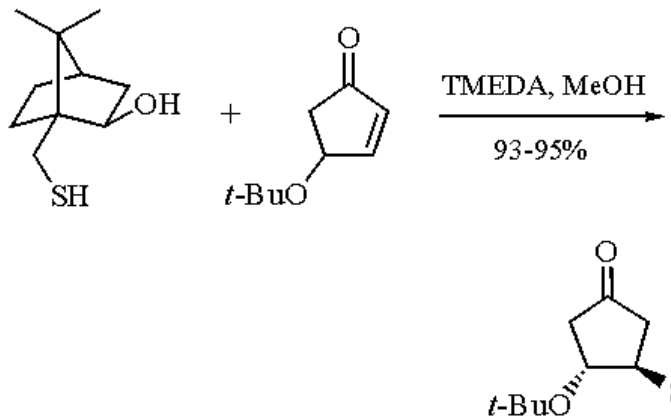

(14)

Related Reagents.

Hexamethylphosphoric Triamide; ***N,N,N´,N´´,N´´-Pentamethyldiethylenetriamine***; ***Potassium Hydride-s-Butyllithium-N,N,N´,N´-Tetramethylethylenediamine***; ***(-)-Sparteine***.

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1,1,3,3-Tetramethylguanidine

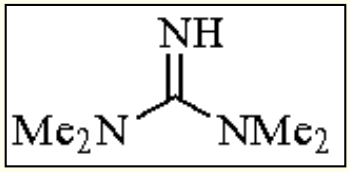

[80-70-6] · $C_5H_{13}N_3$ · 1,1,3,3-Tetramethylguanidine · (MW 115.21)

(strong base used to generate diazo compounds, protected 3β-substituted steroids, amino acid derivatives without racemization, α-nitroalkyl anions, β-glycosylated phenols, amides from acid chlorides; for the selective cleavage of Cbz groups; for cleavage of peptides from a resin; for the catalysis of conjugate addition reactions, as an azide counterion in asymmetric synthesis; for the catalysis of silylation reactions; for the conversion of ketone hydrazones to vinyl iodides)

Alternate Name: TMG.

Physical Data: bp 165 °C, 52-54 °C/11 mmHg; mp 60 °C; *d* 0.918 g cm^{-3}.

Solubility: freely sol most organic solvents; sol water.

Purification: distillation in vacuo.

Handling, Storage, and Precautions: this liquid is corrosive. It is harmful if swallowed, inhaled, or absorbed through the skin. It should be handled in a fume hood; the handler should wear chemical safety goggles, rubber gloves, and a respirator. Bottles of the liquid should be flushed with an inert atmosphere such as nitrogen or argon to minimize exposure to carbon dioxide.

Diazodiphenylmethane Preparation.

1,1,3,3-Tetramethylguanidine is the base of choice for use in the preparation of ***Diphenyldiazomethane*** from the corresponding ketone hydrazone (eq 1).[1]

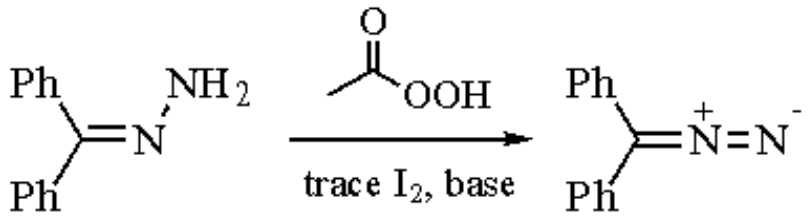

(1)

Base	Yield (%)
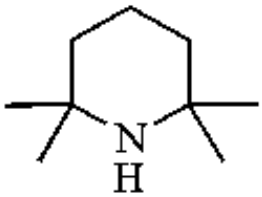	34
TMG	96
$NaHCO_3$ PTC, Bu_4NCl	66

Protected 3β-Substituted Steroids.

Protection of 3β-substituted steroids by conversion to 6-oxo-3α,5-cyclo-5α-steroid derivatives is facile with TMG (eq 2).[2]

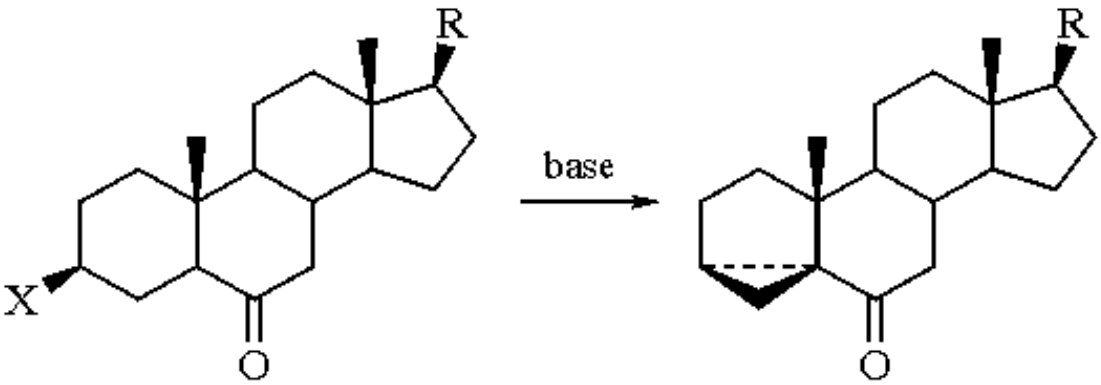

(2)

R	X	Base	Yield (%)
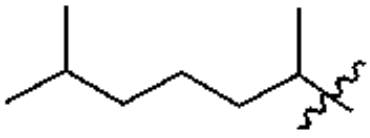	TsO	TMG	98
	Cl	TMG	95
	TsO	NaOEt, EtOH	85
	Cl	NaOEt, EtOH	95
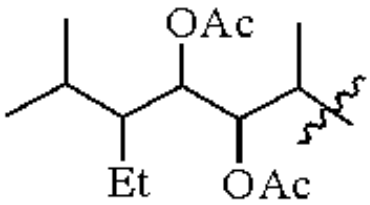	Cl	TMG	90
	Cl	NaOEt, EtOH	NA*

*Transesterification byproducts

*Transesterification byproducts

Amino Acid Derivatives without Racemization.

TMG readily forms soluble salts with numerous amino acids, thus facilitating many reactions. The variety of amino acid derivatives prepared without racemization include *N*-Boc from ***t-Butyl Azidoformate***[3] or from *t*-butyl phenyl carbonate,[4] *N*-trifluoroacetyl,[5] and peptide coupling products (eq 3).[6,7]

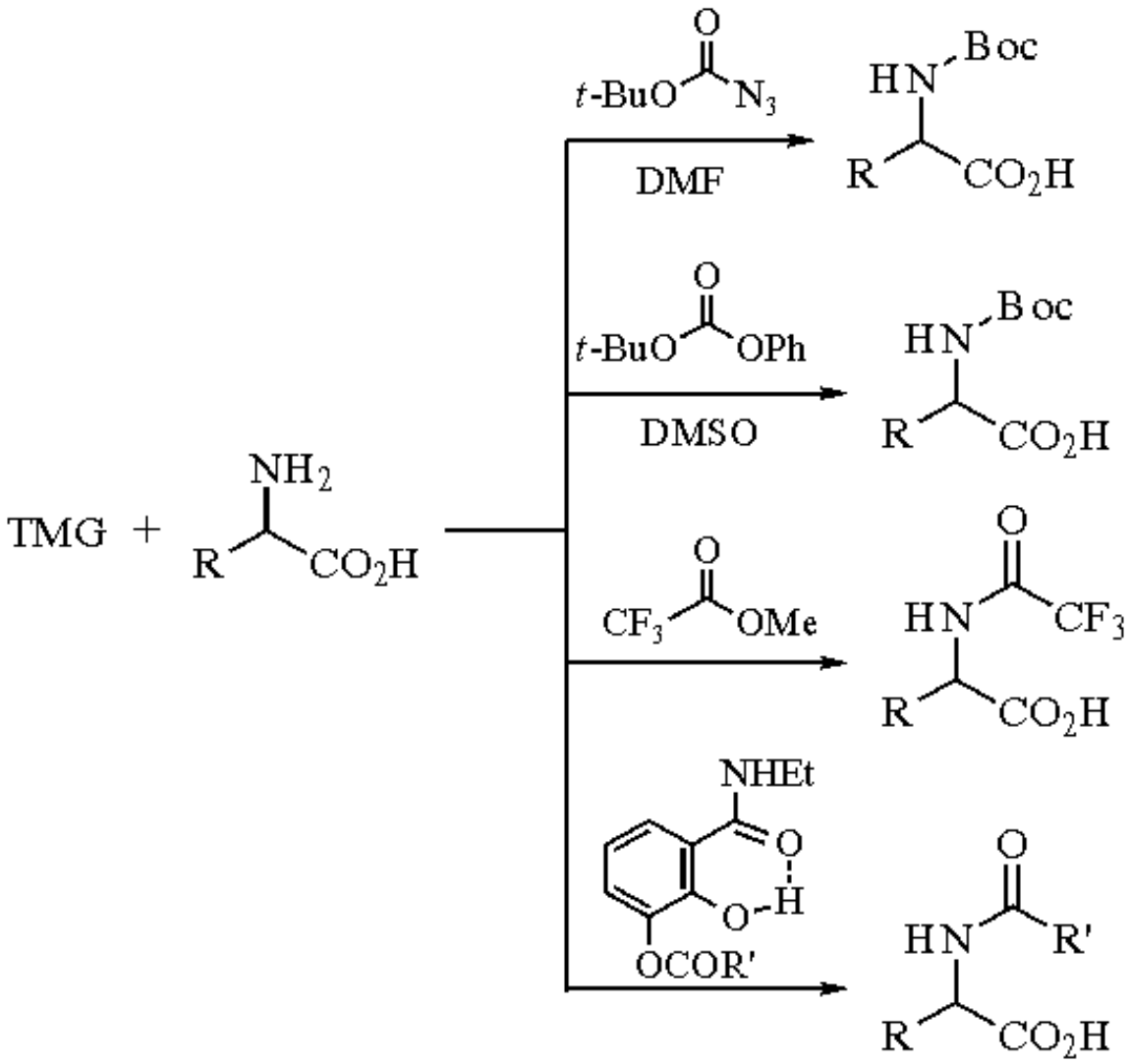

(3)

Insoluble amino acids such as taurine are converted to γ-L-glutamyl taurine with TMG as base (eq 4).[8]

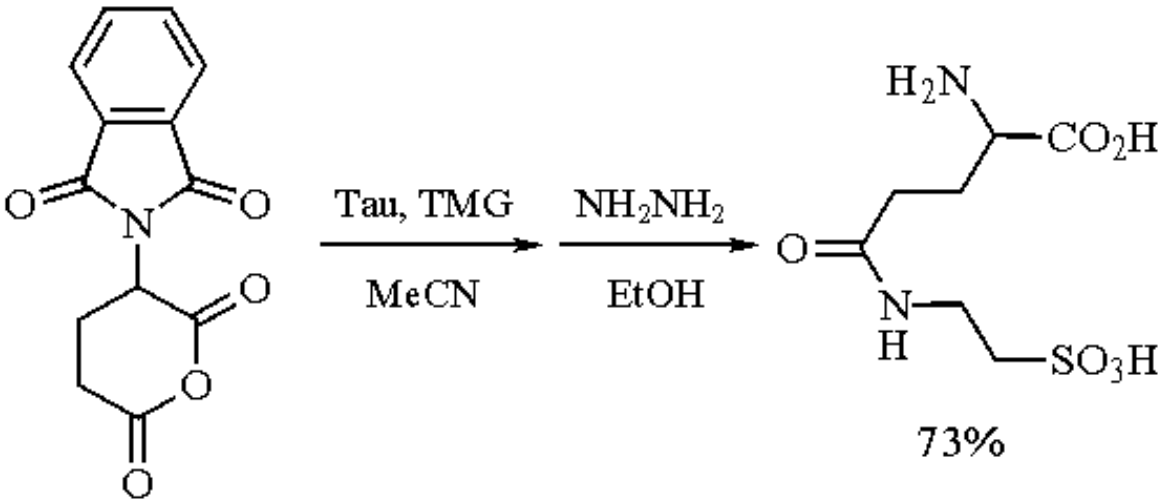

(4)

α-Nitroalkyl Anion Formation.

TMG is often chosen as the basic catalyst for conjugate additions of nitromethane. An early report[9] cited isolation of monomeric addition products to unsaturated esters as a key result (eq 5). Highly selective additions of nitromethane to levoglucosenone afford excellent yields of condensation products (eq 6).[10]

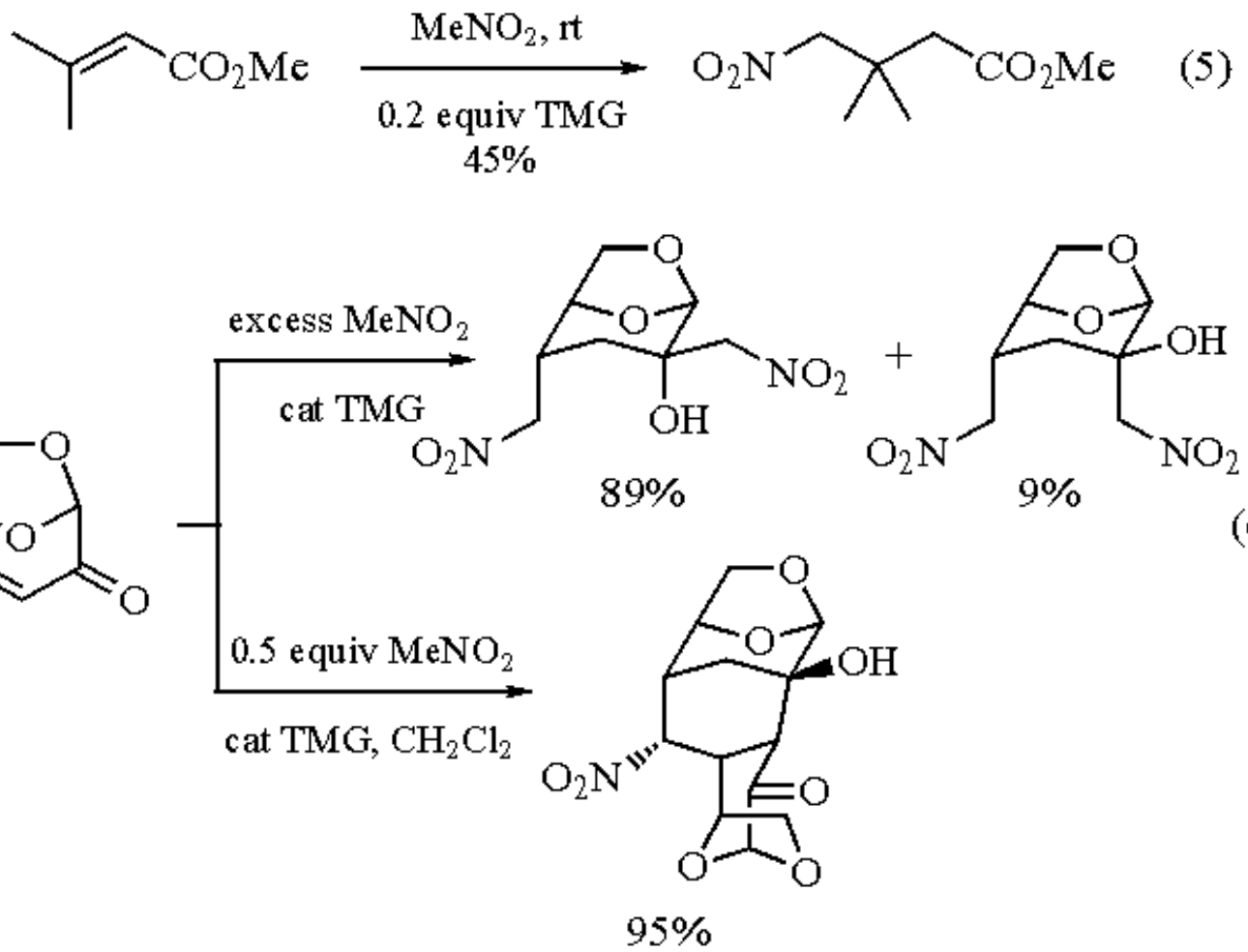

Addition of nitromethane to 4-oxygenated 2-substituted cyclopent-2-enones provides a facile entry to prostaglandin intermediates (eq 7).[11] Precursors of γ-aminobutyric acid analogs are readily available in good yield from nitromethane additions to 2-alkenoic esters (eq 8).[12]

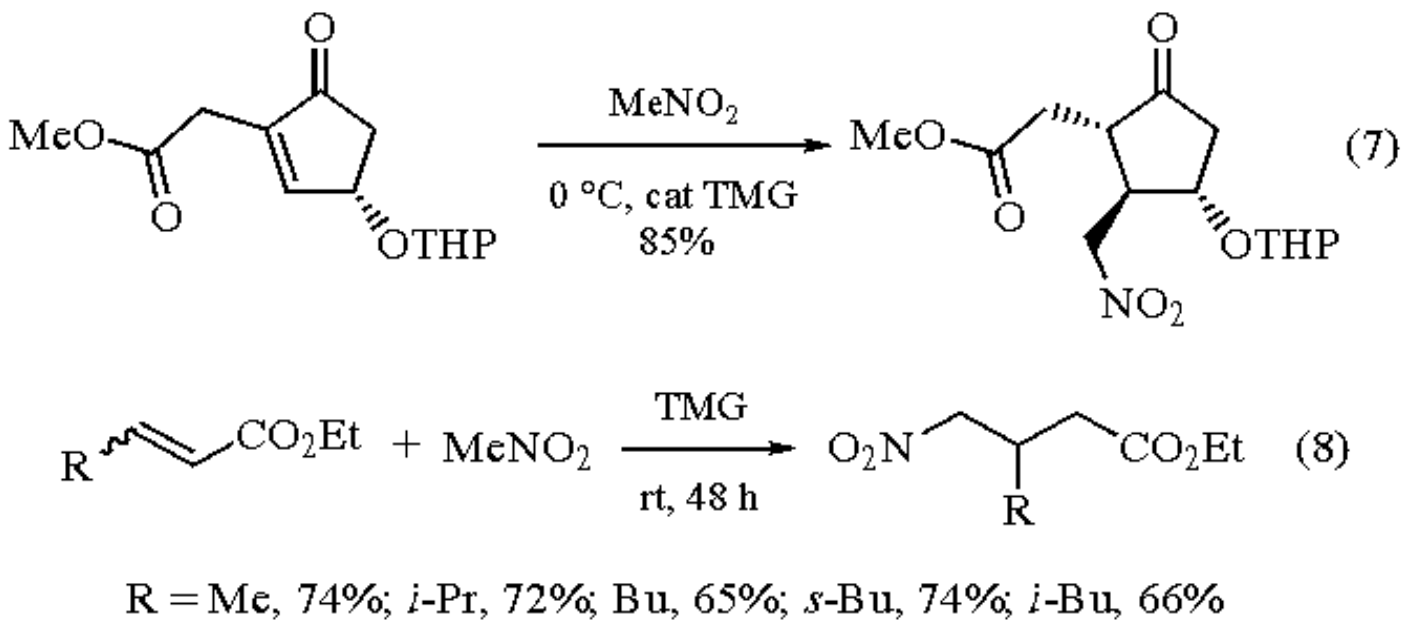

With more hindered nitroalkanes, ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) is required as base for high yields of Michael products (eq 9).[13]

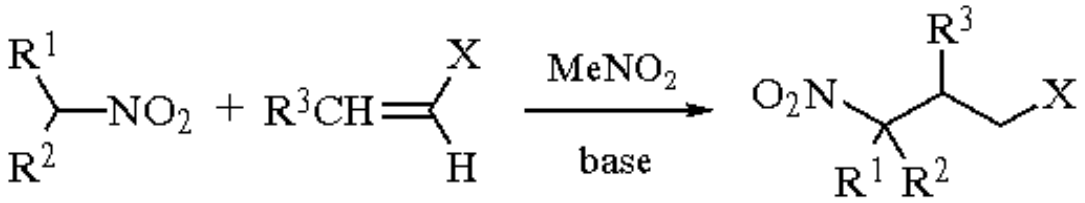

(9)

R^1	R^2	R^3	X	Base	% Product
Me	C_6H_{13}	H	-COMe	TMG	80
Me	*i*-Bu	H	$-CO_2Et$	TMG	80
Me	C_6H_{13}	H	-CN	TMG	82
Me	Me	H	$-SO_2Ph$	TMG	93
Me	Me	Ph	$-CO_2Me$	DBU	90
Bn	Me	Me	-CN	DBU	74
Me	Me	Ph	$-SO_2Ph$	DBU	90

Nitroalkane addition to 3-methylene-2,3-dihydrothiophene *S,S*-dioxide furnishes a new route to 1,3-dienes, including a precursor to ipsenol (eq 10).[14]

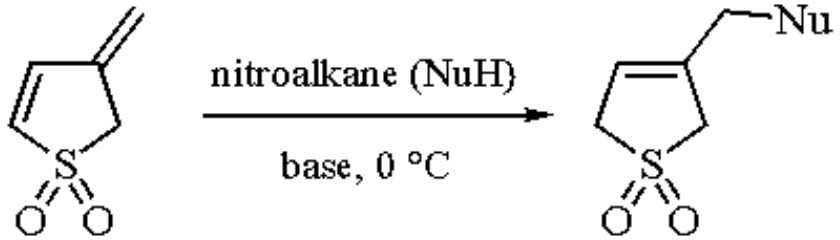

(10)

NuH	base	% Product
$MeNO_2$	DBU	42
$PrNO_2$	TMG	42
i-$PrNO_2$	TMG	78

β-Glycosylated Phenol Formation.

While inorganic bases (CsF, K_2CO_3) or weaker bases such as 2,6-lutidine inhibit the reaction, TMG is especially effective at enhancing β-selectivity in glycosidation of phenols (eq 11).[15]

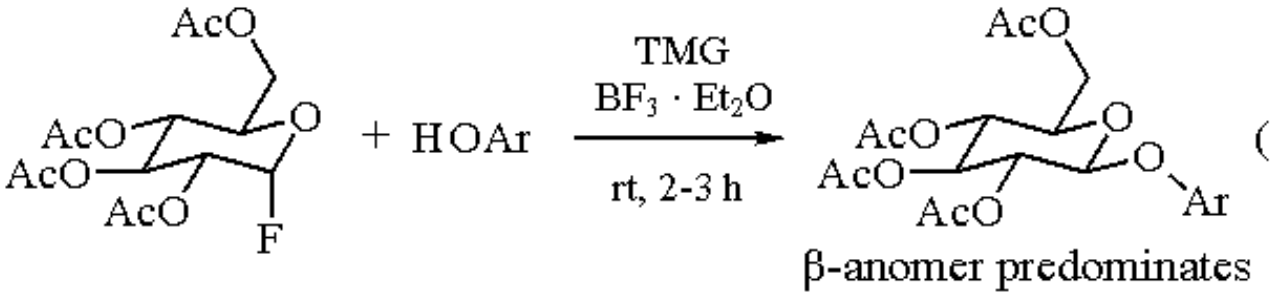

(11)

Ar	α:β ratio Presence TMG	Absence TMG
p-$MeOC_6H_4$	β only	51:49
2,6-$(MeO)_2C_6H_3$	β only	NA
2,6-$Me_2C_6H_3$	β only	NA
o-ClC_6H_4	10:90	80:20
1-Naphthyl	3:97	40:60
p-$O_2NC_6H_4$	32:68	82:18

Amides from Acid Chlorides.

For the preparation of chiral, nonracemic C_2-symmetrical pyrrolidine-derived auxiliaries, TMG is the base of choice (eq 12).[16]

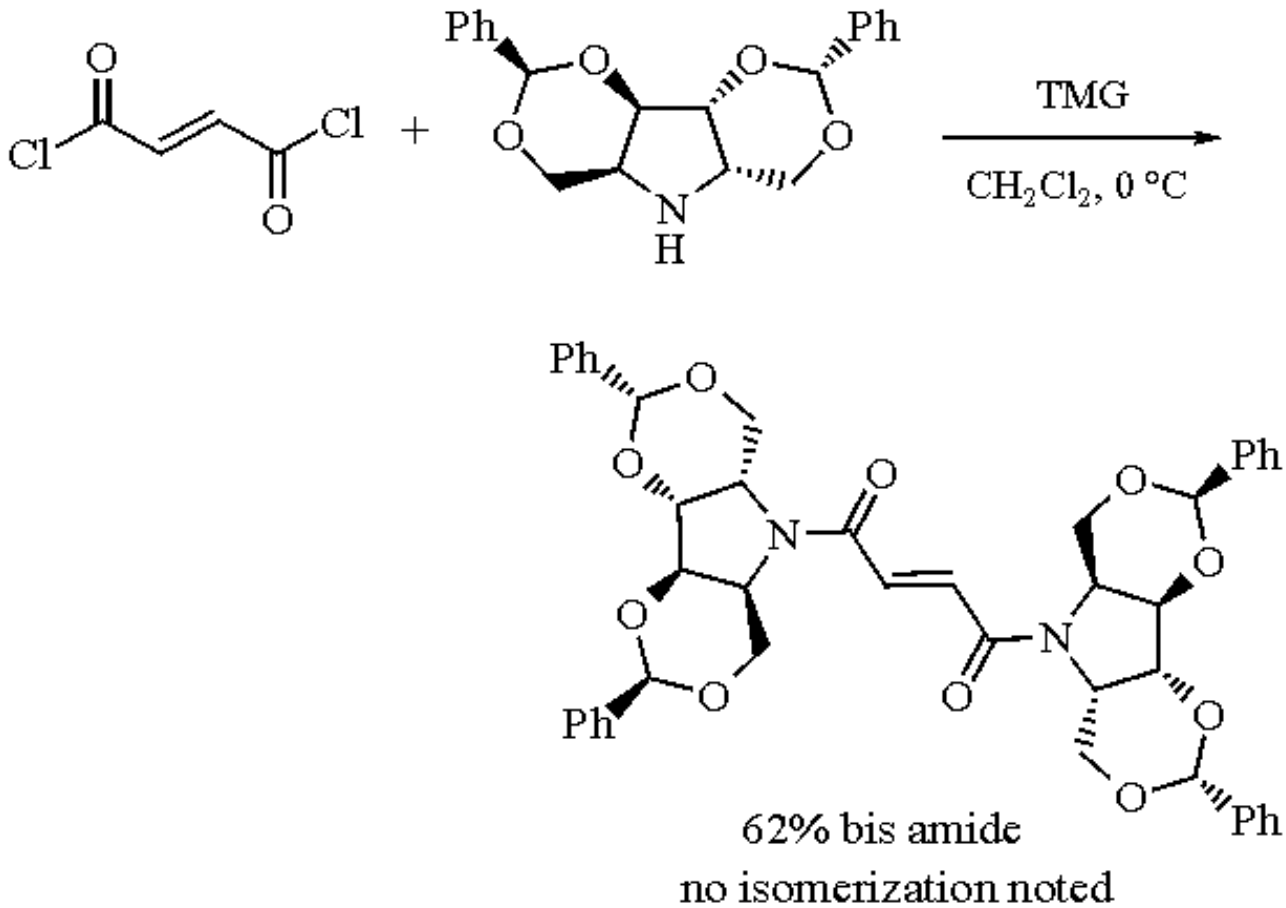

(12)

Selective Cleavage of Z Groups.

Selective removal of a primary benzyloxycarbonyl (Cbz, Z) group in the presence of both primary *t*-butoxycarbonyl (Boc) and secondary Z groups gives primary amines by TMG-catalyzed methanolysis (eq 13).[17,18]

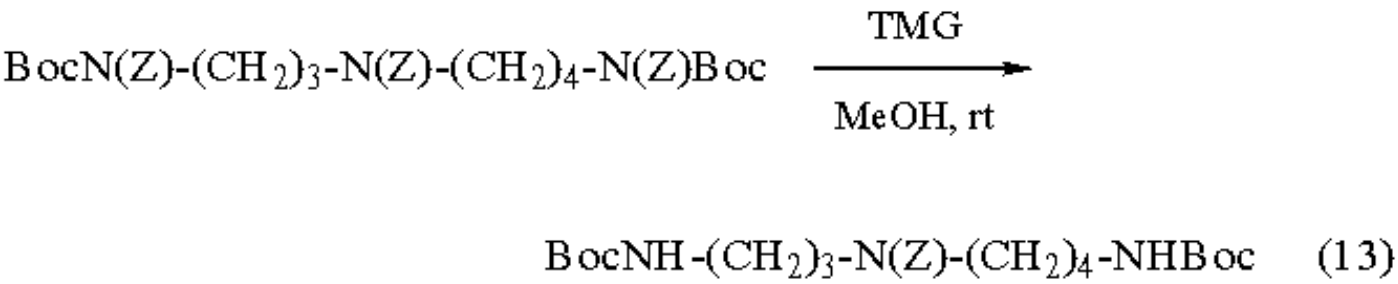

Cleavage of Peptides from a Resin.

TMG-catalyzed elimination effects removal of protected peptides from a 2-[4-(hydroxymethyl)phenylacetoxy]propionyl resin (eq 14).[19]

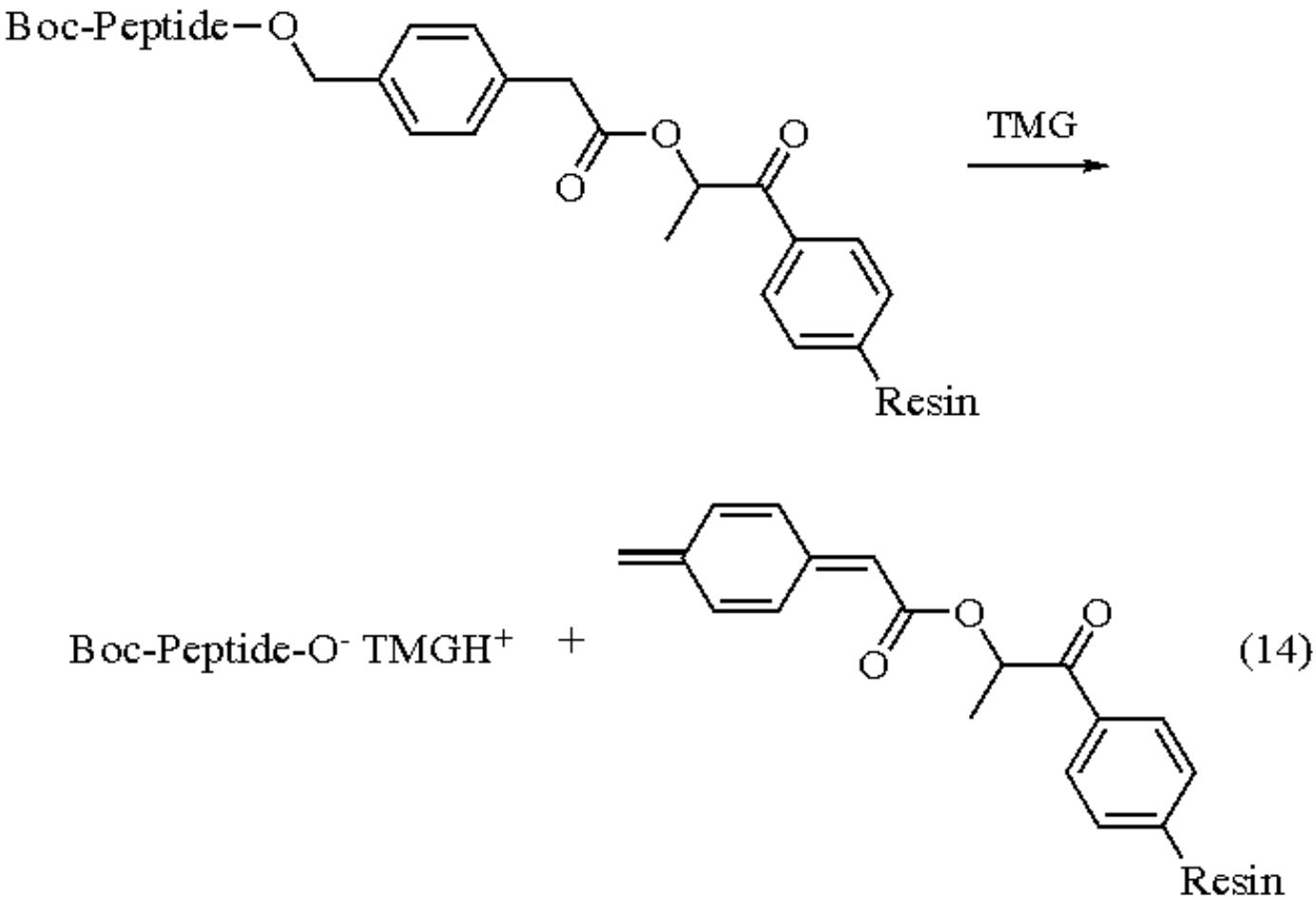

Catalysis of Conjugate Addition Reactions.

Thiol addition to α,β-unsaturated nitroalkenes, in the presence of ***Formaldehyde***, leads to precursors of allyl alcohols in high yields (88-97%) (eq 15).[20] Conjugate addition of hydroxylamine to β-alkoxy acrylonitrile derivatives provides an entry to 4-thiocarbamoyl-5-aminoisoxazoles (eq 16).[21] Conjugate addition of benzyl alcohol catalyzed by TMG provides an adduct with no racemization noted at the initial stereocenter (eq 17).[22]

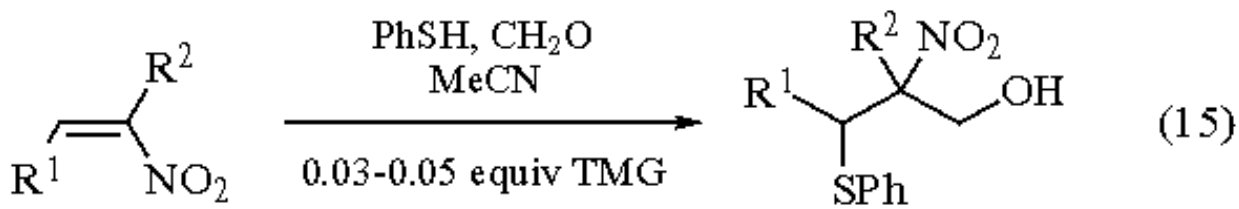

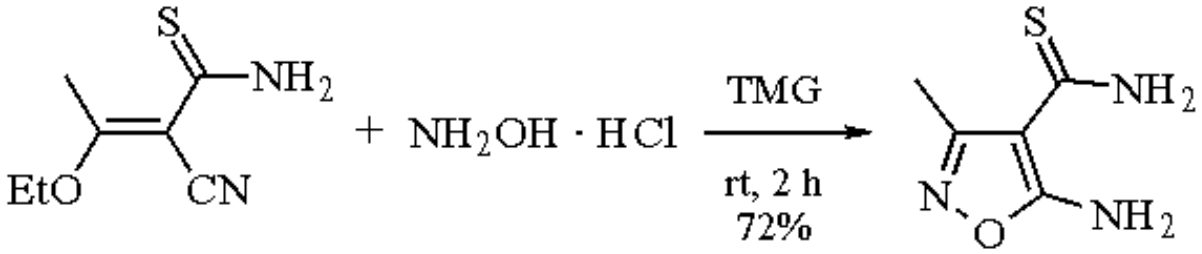

(16)

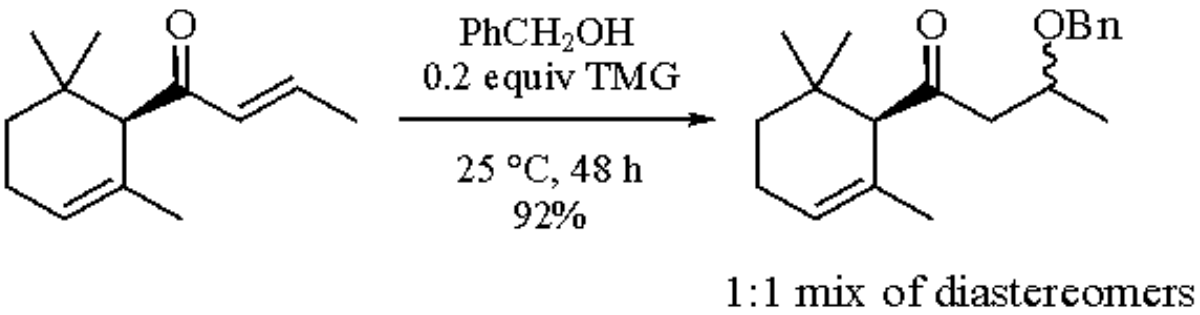

(17)

A practical synthesis of (-)-huperzine A utilizes TMG as the base in a key step involving the assemblage of the tricyclic intermediate (eq 18).[23,24] Enantioselective synthesis of α-allokainoic acid uses tandem conjugate additions catalyzed by TMG (eq 19).[25]

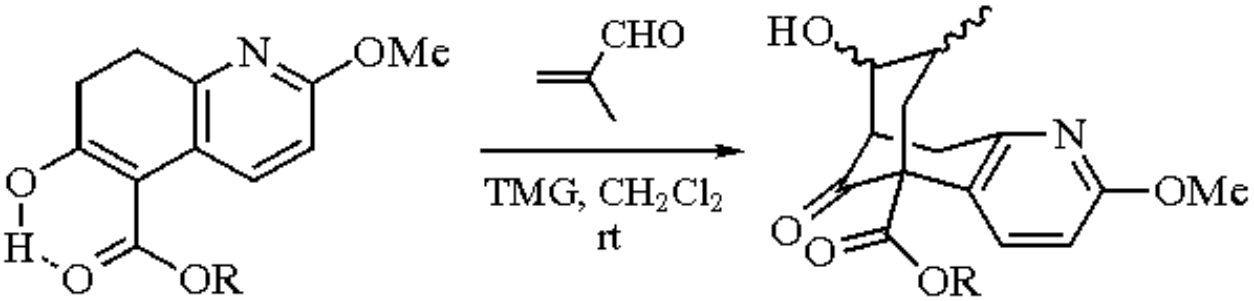

(18)

R = Me, 93%; (-)-8-phenylmenthyl, 91%*

*Major diastereomer of dehydration leads to natural (-)-huperzine

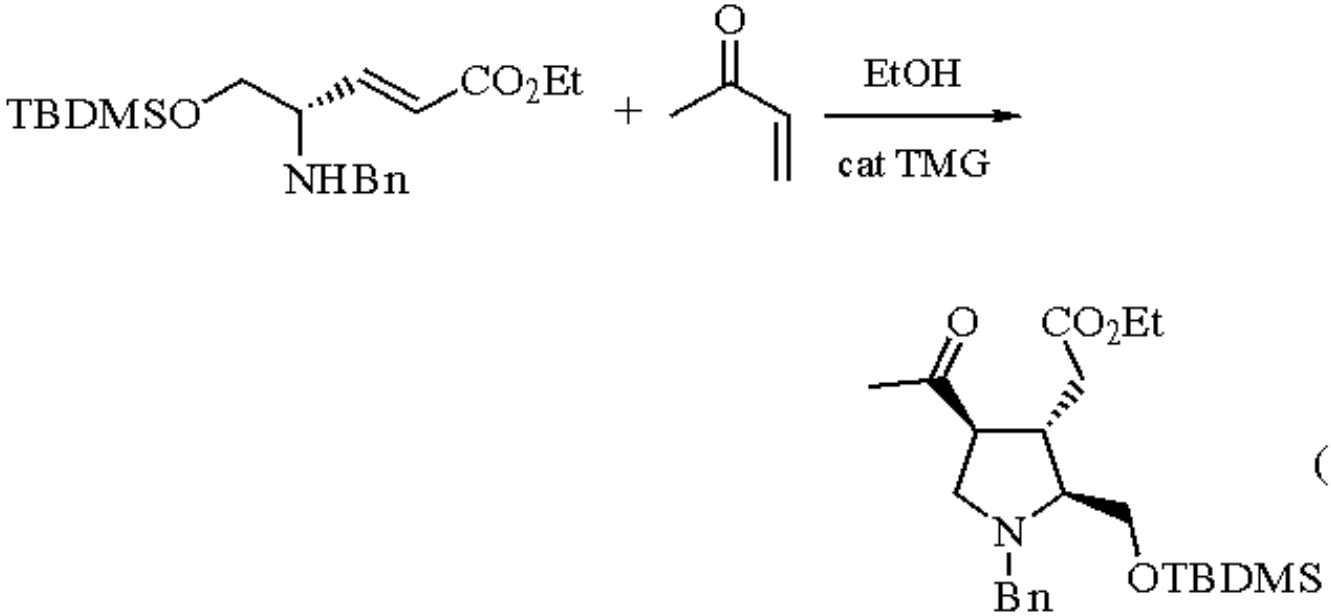

(19)

Azide Counterion in Asymmetric Synthesis.

In the asymmetric synthesis of α-amino acids via the electrophilic azidation of chiral nonracemic imide enolates, stereospecific bromide

displacement by tetramethylguanidinium azide was a high yielding step (eq 20).[26,27]

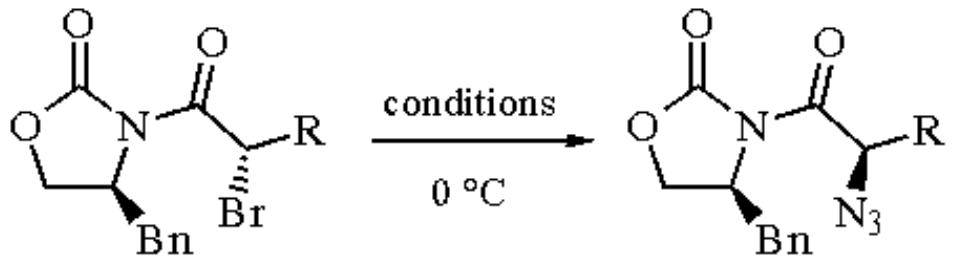

(20)

Conditions	R	Ratio of diastereomers bromide *(R)*:*(S)*[a]	azide *(R)*:*(S)*[a]
NaN_3, DMSO	Bn	95:5	14:86
TMGA,[b] CH_2Cl_2	Bn	95:5	4:96
TMGA,[b] CH_2Cl_2	Ph	78:22	22:78
TMGA,[b] CH_2Cl_2	*i*-Pr	96:4	4:96

[a] Absolute stereochemistry of the carbon bearing the bromide or azide
[b] Tetramethylguanidium azide

Catalysis of Silylation Reactions.

While ***Triethylamine*** is typically used as the HCl scavenger in the formation of *t*-butyldimethylsilyl ethers, TMG as a catalyst tends to accelerate the reaction (eq 21).[28]

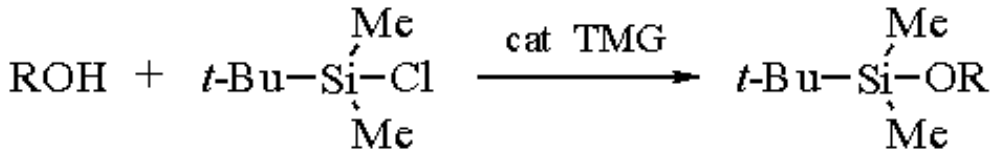

(21)

ROH	Solvent	Time (h)	Yield (%)
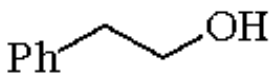	DMF	0.3	95
	MeCN	0.3	96
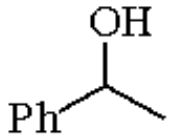	DMF	1.0	93
	MeCN	12.0	96

Conversion of Ketone Hydrazones to Vinyl Iodides.

Oxidation of ketone hydrazones by iodine in the presence of TMG occurs in high yields (eq 22).[29]

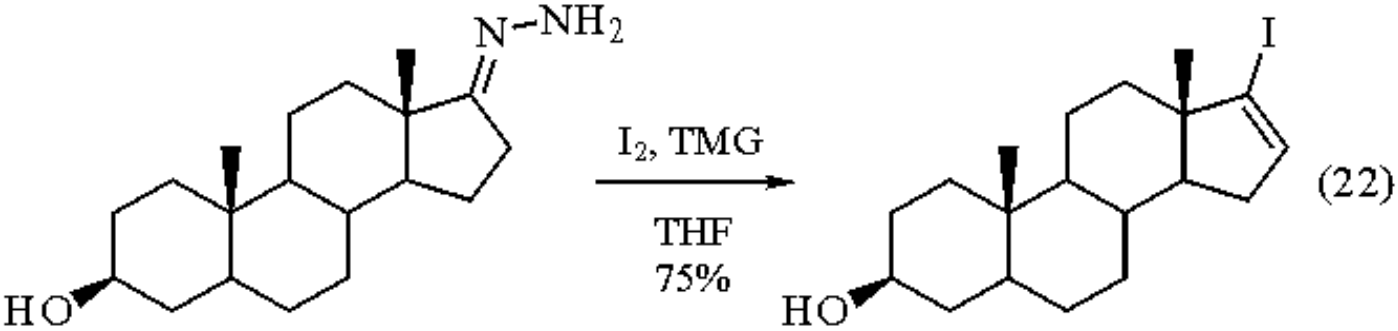

Related Reagents.

t-Butyltetramethylguanidine; ***1,1,2,3,3-Pentaisopropylguanidine***.

---

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Tetramethyl Orthocarbonate

$C(OMe)_4$

[1850-14-2] · $C_5H_{12}O_4$ · Tetramethyl Orthocarbonate · (MW 136.17)

(CO_2 fixation; formation of orthocarbonates from diols; electrophilic introduction of an ester functionality)

Alternate Names: tetramethoxymethane; methyl orthocarbonate.

Physical Data: mp -5.5 °C; bp 114 °C; n_D 1.3864; *d* 1.023 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Preparative Methods: has been prepared by heating a solution of ***Sodium Methoxide*** in methanol with chloropicrin,[1] ***Trichloroacetonitrile***,[2] or thiocarbonyl perchlorate;[1] the best yields have been obtained with the perchlorate. Alternatively, disodium hexamethoxystannate (prepared in situ from sodium methoxide and tetrachlorostannane) can be refluxed with ***Carbon Disulfide*** in methanol to form the orthocarbonate.[3]

Handling, Storage, and Precautions: flammable; moisture sensitive.

Cyanation.

Replacement of one of the methoxy groups of tetramethyl orthocarbonate with a cyano group can be efficiently accomplished by treatment with ***Cyanotrimethylsilane*** in the presence of a Lewis acid such as ***Iron(III) Chloride***,[4] ***Tin(II) Chloride***,[5] or ***Tin(IV) Chloride*** (eq 1).[6]

$$C(OMe)_4 + TMSCN \xrightarrow[69\text{-}83\%]{\text{Lewis acid}} C(OMe)_3CN \qquad (1)$$

CO_2 Fixation.

The title reagent has been employed in the fixation reaction of CO_2 with diethylamine, providing excellent yields of the methyl carbamate (eq 2).[7]

$$Et_2NH + CO_2\ (40\ atm) + C(OMe)_4 \xrightarrow{120\ °C} Et_2NCO_2Me \qquad (2)$$

Protection of Diols.

Tetramethyl orthocarbonate can be used to protect ribonucleosides as their 2´,3´-orthocarbonates, which are stable to basic conditions. The orthocarbonate may also be transformed, under aqueous acidic conditions, into an acid-stable cyclic carbonate protecting group (eq 3).[8]

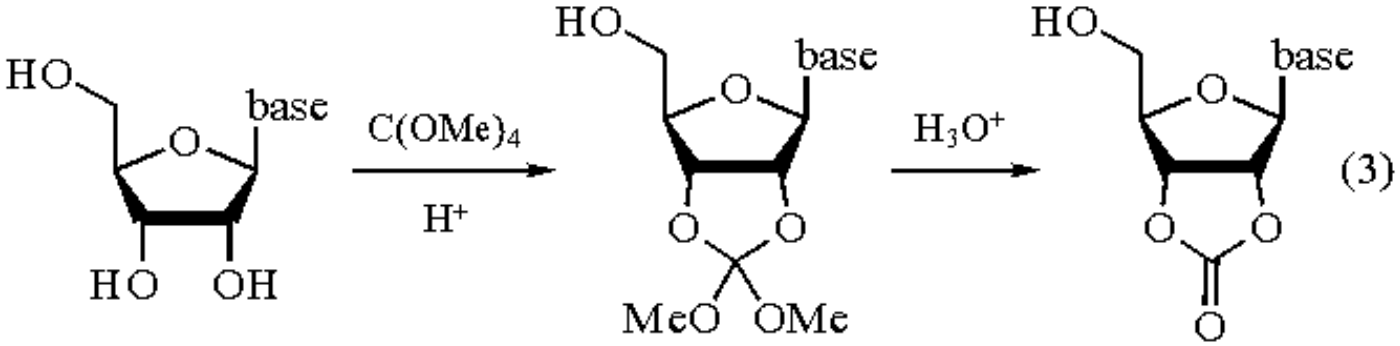

Spiroorthocarbonates.

The acid-catalyzed reaction of tetramethyl orthocarbonate with 2 equiv of a diol at 110 °C affords symmetrical spiroorthocarbonates. Their unsymmetrical counterparts can be prepared via a two-step procedure (eq 4).[9]

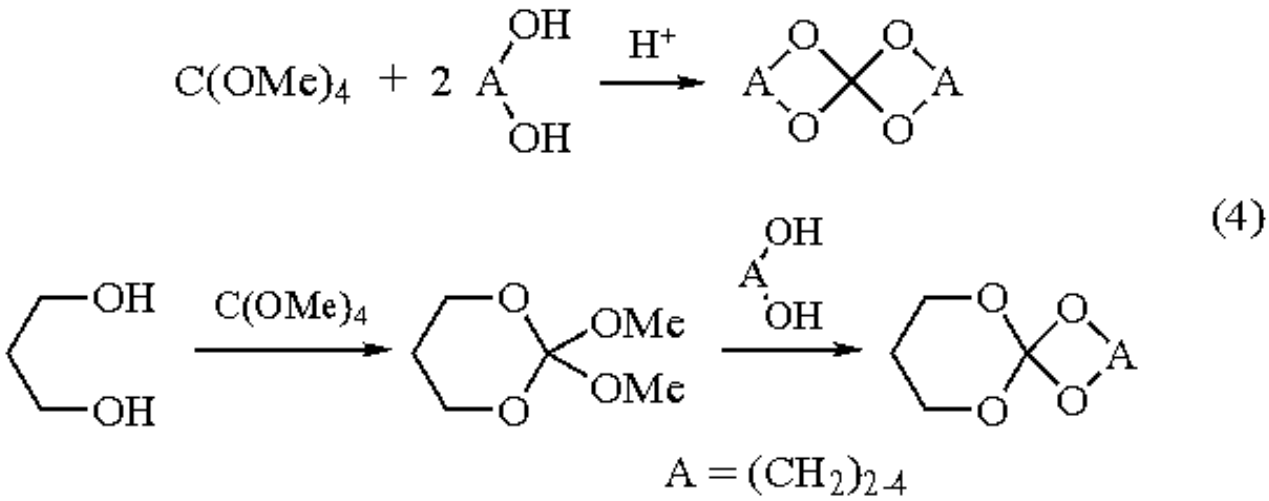

Formation of Thiiranes.

Conversion of 2-mercaptoalcohols to thiiranes can be accomplished with tetramethyl orthocarbonate in the presence of ***p-Toluenesulfonic Acid*** (eq 5).[10]

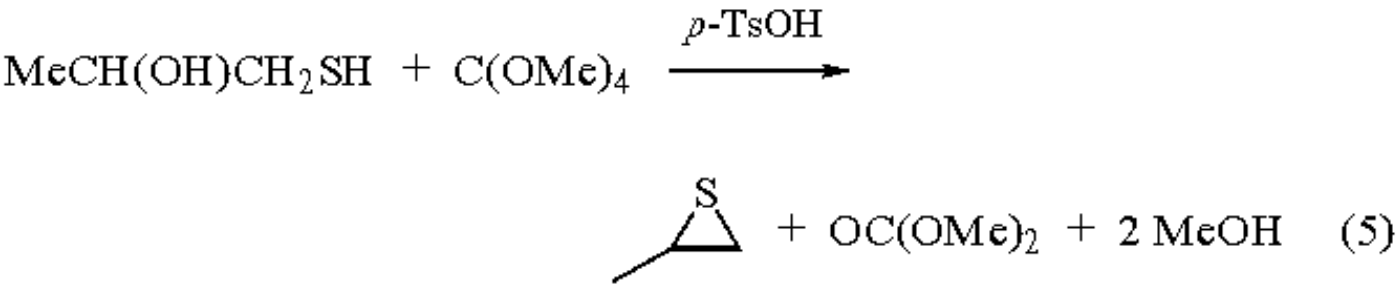

Alkylation.

Tetramethyl orthocarbonate can be used as an electrophile to introduce an ester functionality (eq 6).[11]

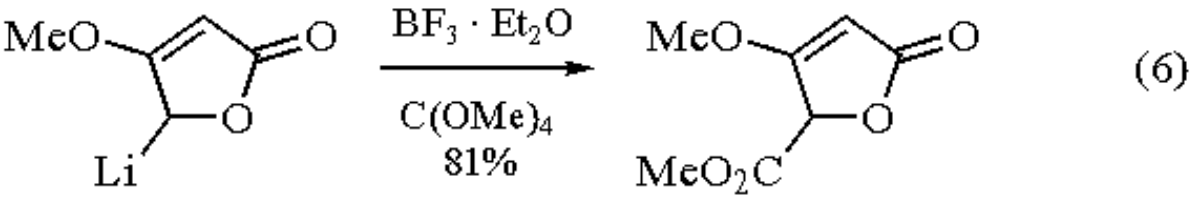

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2,2,6,6-Tetramethylpiperidine

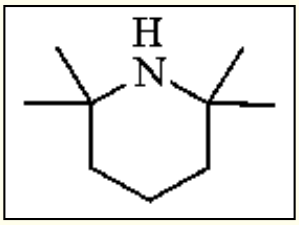

[768-66-1] · $C_9H_{19}N$ · 2,2,6,6-Tetramethylpiperidine · (MW 141.29)

(hindered secondary amine used in preparing metallo-amide bases; selective generation of silylketene acetals)

Alternate Name: TMP.

Physical Data: bp 155.5-156.5 °C; fp 24 °C; *d* 0.837 g cm^{-3}.

Solubility: sol most organic solvents.

Purification: by distillation.

Handling, Storage, and Precautions: liquid is corrosive and flammable. Bottles of 2,2,6,6-tetramethylpiperidine should be flushed with nitrogen or argon to prevent exposure to carbon dioxide. The vapors are harmful and care should be taken to avoid absorption through the skin. Use in a fume hood.

Silylketene Acetal Preparations.

This reagent finds utility in the selective preparation of (*Z*)-silylketene acetals from simple alkyl esters and ***Triethylsilyl Perchlorate*** under kinetic conditions.[1] In a comparison with ***Triethylamine*** and ***Diisopropylethylamine*** (DIPEA), 2,2,6,6-tetramethylpiperidine was found to be the superior base for generating the (*Z*)-silylketene acetal of isopropyl propanoate using triethylsilyl perchlorate in $CHCl_3$ at -70 °C (eq 1). Isomerization (equilibration) is not observed under these reaction conditions (see ***Diisopropylethylamine*** for discussion on similar base-controlled generation of boron enolates).

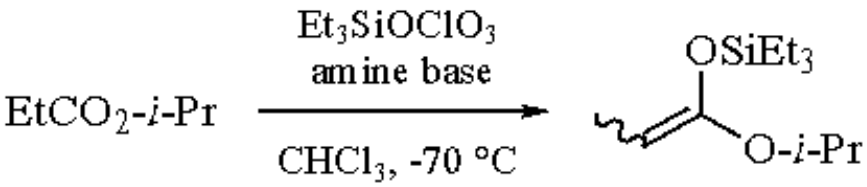

(1)

Amine base	(*E*):(*Z*) ratio
Triethylamine	37:63
DIPEA	10:90
TMP	3:97

Amide Base Preparation.

The hindered base can easily be converted to stronger metallo-amide bases while retaining nonnucleophilic character. Treatment of TMP with organolithium reagents generates ***Lithium 2,2,6,6-Tetramethylpiperidide*** (LTMP),[2] which finds application in synthesis when a strong base (LTMP, pK_a &AApprox; 37.3)[3] is required.[4] However, LTMP has been shown to be somewhat nucleophilic. Treatment of the trifluoromethylamidine (**1**) with a five-fold excess of LTMP in benzene at 50 °C[5] affords the 4-substituted quinazoline (**2**) in 36% yield.

The mechanism involves sequential addition of multiple equivalents of LTMP (eq 2).[6]

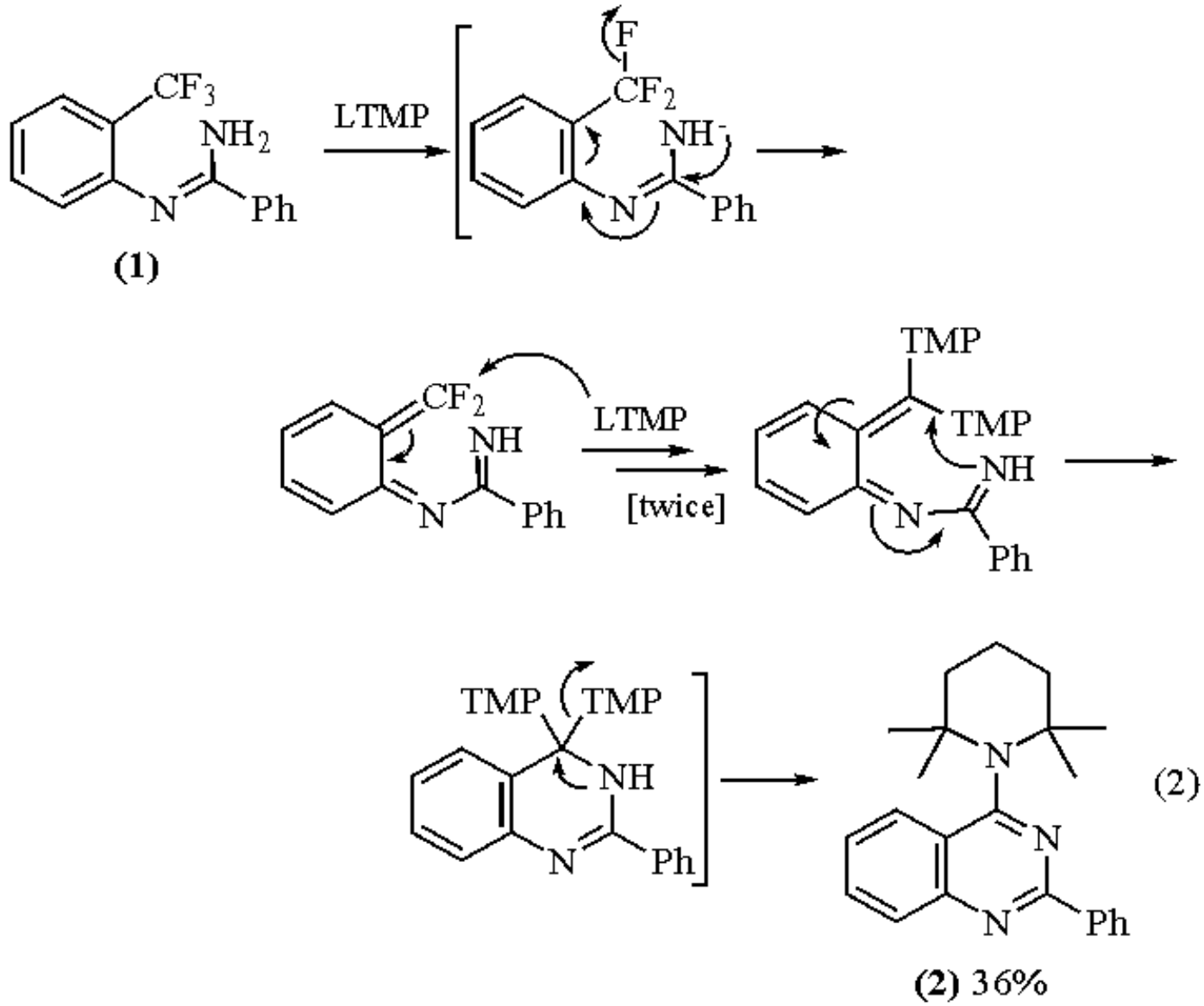

TMP generates, when treated with 1 equiv of ***Ethylmagnesium Bromide*** or 0.5 equiv of ***Dibutylmagnesium*** in refluxing THF, the amido-Grignard reagent *N*-(bromomagnesio)-2,2,6,6-tetramethylpiperidide (TMPMgBr) and the magnesium amide base bis(2,2,6,6-tetramethylpiperidino)magnesium ($(TMP)_2Mg$), respectively. The TMPMgBr base finds use in selective enolate formation,[7] while the bis magnesium base, $(TMP)_2Mg$, succeeds at *ortho* metalation by magnesium of benzamides (eq 3) and aromatic esters (eq 4).[8]

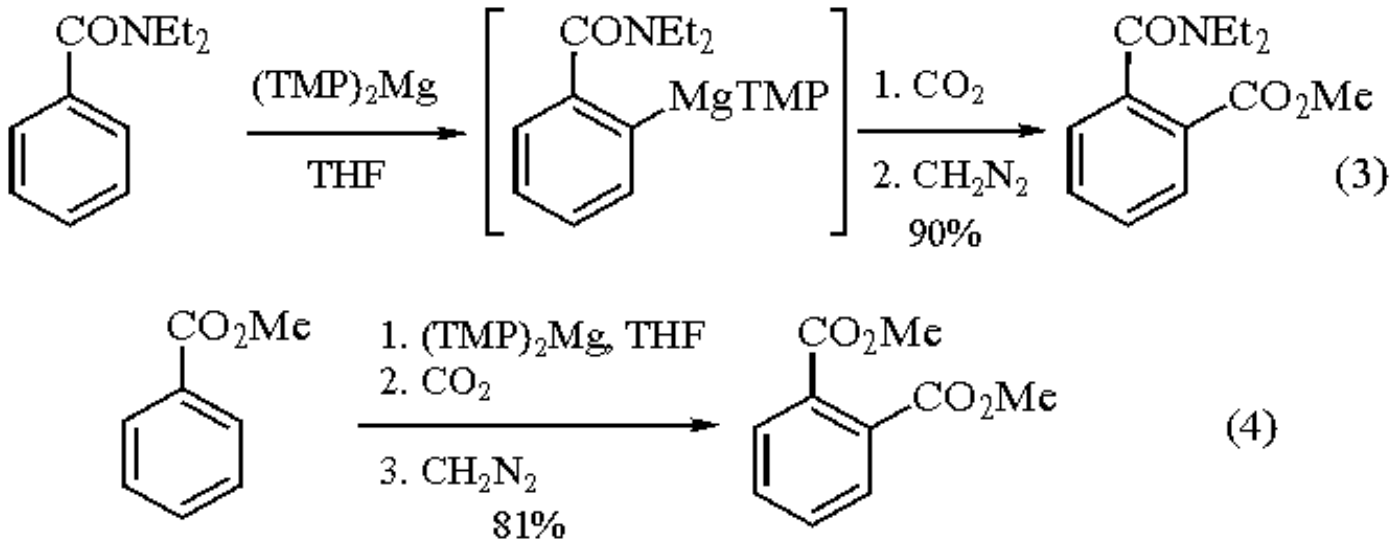

LTMP can be converted to dialkylaluminum amides (e.g. ***Diethylaluminum 2,2,6,6-Tetramethylpiperidide***) by treatment with

dialkylaluminum chloride in toluene. Reaction of LTMP with diisobutylaluminum chloride yields diisobutylaluminum 2,2,6,6-tetramethylpiperidide (*i*-Bu_2AlTMP), which has utility in the diastereoselective cleavage of acetals to chiral nonracemic enol ethers (eq 5).[9]

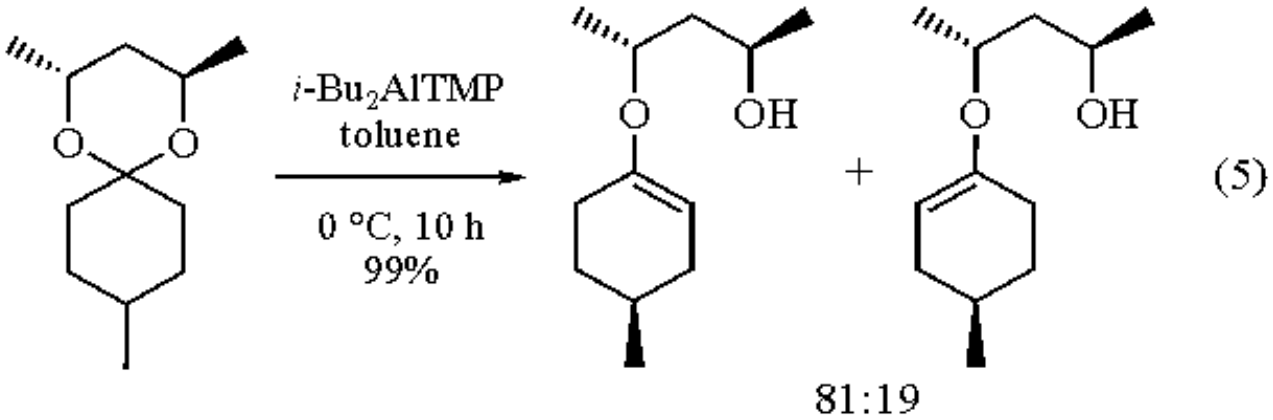

Proton Abstraction.

The nonnucleophilic character of the base TMP makes it an ideal choice in alkylations involving reactive electrophiles. This is evident in the cycloaddition reaction between the trithiadiazepine (**3**) and the highly reactive 1,3-diphenylisobenzofuran involving the intermediacy of the base-induced hetaryne (**4**) (eq 6).[10] Use of TMP in the reaction gives the cycloaddition product (**6**), whereas use of a more nucleophilic base, ***Morpholine***, results in the morpholino derivative (**5**) as the major product. However, when the hetaryne (**4**) reacts with a less reactive diene, such as tetraphenylcyclopentadienone, the major isolated product is the tetramethylpiperdino derivative (**5**) (NR_2 = TMP).[11]

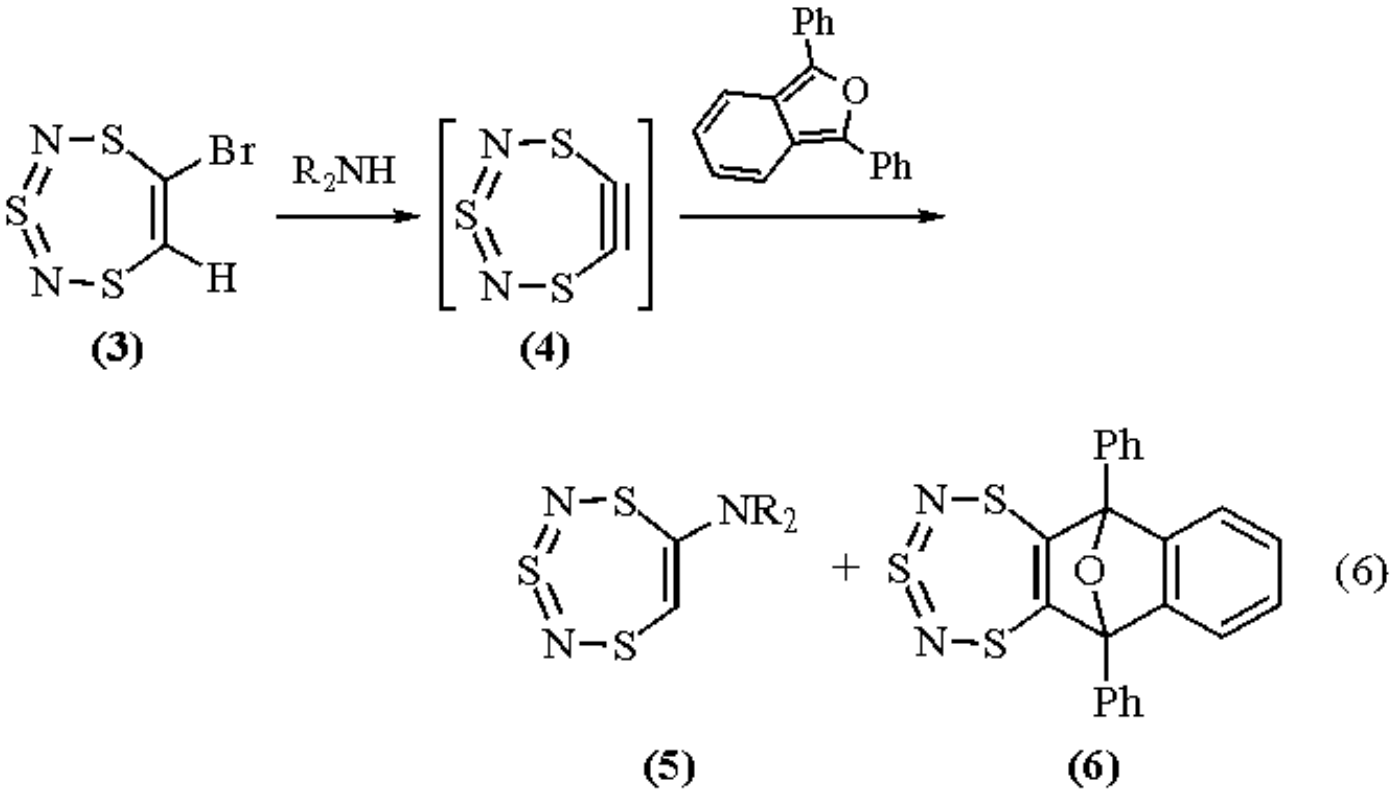

R_2NH	Yield (%) (5)	(6)
Morpholine	74	3
Diisopropylamine	54	11
TMP	0	76

Though TMP is considered nonnucleophilic, it can be alkylated (eq 7)[12] and sulfenylated.[13] Chlorination, using sodium dichloroisocyanurate, leads to *N*-chloro-2,2,6,6-tetramethylpiperidine,[14] which has found limited use in regiospecific chlorinations.[15] Also, treatment of TMP with trifluoroamine oxide produces the *N*-fluoro and *N*-nitroso derivatives,[16] while treatment with ***N,O-***

Bis(trimethylsilyl)acetamide and ***Methyl Chloroformate*** affords the methyl carbamate derivative in 65% yield.[17] The reaction of TMP with diethyl phosphonomethyltriflate in ether at 0 °C for just 30 min leads to the *N*-(diethyl phosphonomethyl)-TMP derivative in excellent yield (eq 7).[18]

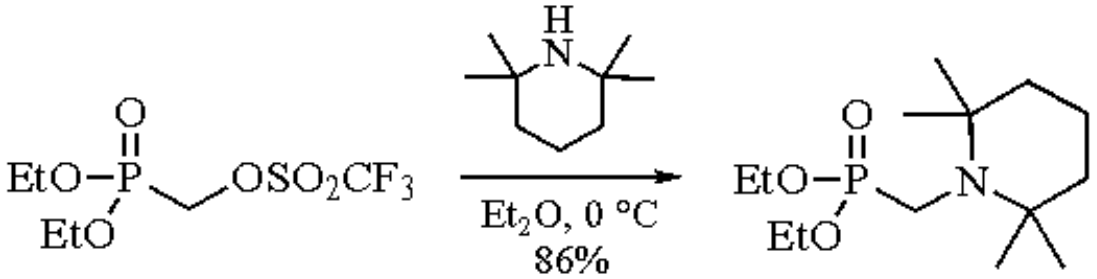

(7)

Oxidation.

N-Hydroxy-2,2,6,6-tetramethylpiperidine is oxidatively converted to the stable nitroxyl radical ***2,2,6,6-Tetramethylpiperidin-1-oxyl***,[19] which is useful as a spin label or trap, and a catalyst for selective oxidation of alcohols.[20]

---

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2,2,6,6-Tetramethylpiperidin-1-oxyl[1]

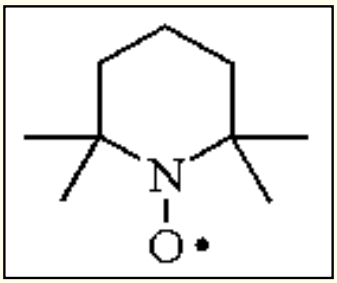

[2564-83-2] · $C_9H_{18}NO$ · 2,2,6,6-Tetramethylpiperidin-1-oxyl · (MW 156.28)

(oxidizing agent for the conversion of primary alcohols to aldehydes[2,3] or carboxylic acids,[2] of secondary alcohols to ketones,[2] and of diols to lactones or hydroxy aldehydes[4])

Alternate Name: TEMPO.

Physical Data: mp 40.0 °C; fp 67 °C.

Solubility: sol all organic solvents and 0.03 mol L^{-1} in H_2O at 25 °C.

Form Supplied in: red orange solid; commercially available.

Analysis of Reagent Purity: IR (Nujol) 1330, 1180, 1060, 975, 950 cm^{-1};[5] UV-Vis, λ (ε) = heptane, 470 nm (10.5), dioxane, 465 nm (10.4), 240-242 nm (2030).[5]

Purification: sublimation.[6]

Handling, Storage, and Precautions: TEMPO is a toxic substance, and a severe irritant which is readily absorbed through the skin.[7] Its toxicity is probably related to the formation of hydroxylamine metabolites.[8]

Oxammonium Salts.

Oxammonium salts (**2**) can be prepared in situ by oxidation of the nitroxide (**1**).[1e] There is evidence that the oxoammonium ion (**2**) is actually the product of an acid-catalyzed disproportionation between two nitroxide molecules (**1**), which produces one oxoammonium ion (**2**) and one hydroxylamine molecule (**3**).[1e] Peracids, for instance, do not oxidize nitroxides to oxoammonium ions, yet do act as the secondary oxidant. The chemical stability of (**2**) depends on the counterion, and this can be easily exchanged; the chloride salt is not very stable. The oxammonium salt is the active species in the oxidation of primary and secondary alcohols to carbonyl derivatives and can be used in stoichiometric or catalytic fashion.[1e] Catalytic procedures require a co-oxidant such as ***Copper(II) Chloride***-O_2,[9] peroxy acids,[10] electrooxidation,[11] or ***Sodium Hypochlorite***.[2-4] Oxammonium salts can be titrated iodometrically.[1e]

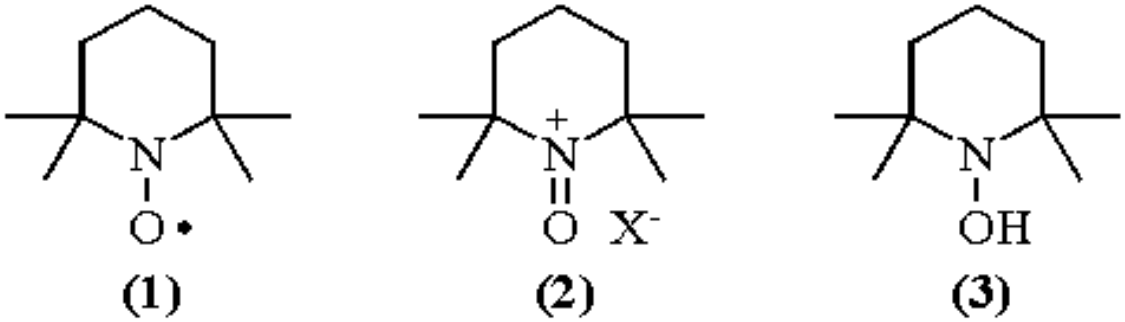

It has been proposed that (**2**) reacts with alcohols, forming carbonyl derivatives and hydroxylamine (**3**).

Oxidation of Alcohols.[2,3,7]

Primary alcohols are converted into aldehydes by the following catalytic system: 0.01-0.002 equiv of TEMPO (or its 4-methoxy derivative), 0.05 equiv of KBr as co-catalyst, and aqueous NaOCl buffered at pH 8.5-9.5 in a CH_2Cl_2/H_2O two-phase system. At this pH, HOCl is the co-oxidant and in the presence of KBr it is likely transformed into HOBr which is more efficient in the oxidation of (**1**) to (**2**). The reaction is exothermic. For reactions carried out on a 1-10 mmol scale the temperature can be easily maintained at 0 °C and conversion is complete in few minutes. On a larger scale, a very efficient cooling system is required. A compromise is to maintain the temperature in the range 10-15 °C with an ice bath; note that higher temperatures lead to fast decomposition of the catalyst. The pH is buffered by adding the appropriate amount of $NaHCO_3$ to the aqueous NaOCl. $NaH_2PO_4.2H_2O$ and $Na_2HPO_4.2H_2O$ have been used as alternatives.[12]

Oxidation of secondary alcohols similarly affords ketones. The oxidation can be applied to saturated alkyl and aryl-alkyl substrates; relatively unstable protecting groups such as acetonide derivatives of diols are not affected. Side reactions occur with substrates with isolated and conjugated double bonds, leading to lower yields. The reaction rates are markedly decreased by the presence of electron-donor groups in the aromatic ring of benzyl alcohol, but they can be speeded up by addition of catalytic amounts of quaternary ammonium salts (Q^+X^-). At the pH of commercial bleach (12.7), reactions are very slow. At lower pH, HOCl is distributed between the aqueous and the organic phase, thus making the phase transfer catalyst unnecessary. Optically active alcohols afford the corresponding aldehydes in good yields and high enantiomeric purity (eq 1).[3,13]

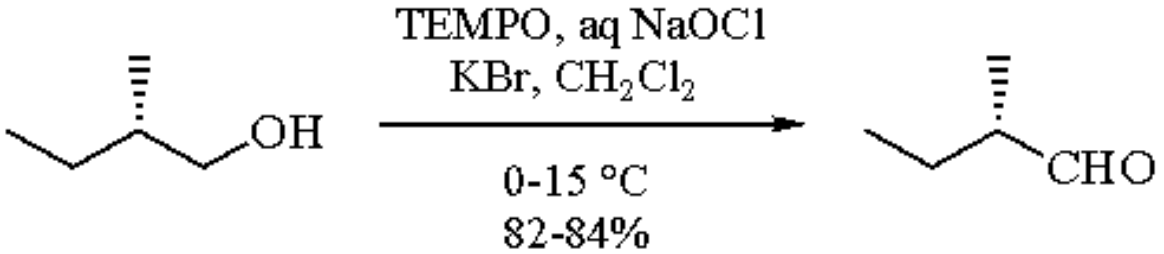

(1)

Oxidation of Diols.

Diols are easily oxidized with this reagent; the nature of the products depends on the amount of oxidant used, the difference in oxidation rates of primary vs. secondary alcohols, the presence of Q^+X^-, and on the relative distance between the OH groups in the aliphatic chain. Under the reaction conditions reported above, primary-secondary diols afford hydroxy or keto aldehydes. In the presence of a catalytic amount of Q^+X^-, primary-secondary diols lead to ketocarboxylic acids. Selectivity in these oxidations also depends on the substituents on the 2,2,6,6-tetramethylpiperidine ring.[14]

Lactones are obtained from 1,4- and 1,5-diols, whereas α,o-diols give unresolvable mixtures of polymeric products.[4] Oxidation of hydrophilic 1,4- and 1,5-diols to γ- and δ-lactones and of hydrophilic alcohols to aldehydes is best conducted using CH_2Cl_2/solid LiOCl in the presence of solid $NaHCO_3$. Commercial LiOCl contains 7% of H_2O so that reaction conditions are those of a pseudo solid-liquid system.[4]

Oxidation of Primary Alcohols and Aldehydes to Carboxylic Acids.[2]

The addition of catalytic amounts of quaternary salt to the oxidizing system leads to the fast and direct formation of carboxylic acids. This oxidation requires the presence, in the organic phase, of ClO^- and/or BrO^- anions which behave as strong bases. Again, electron-donor groups in benzyl alcohol or aromatic aldehydes strongly lower the reaction rates.

---

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Tetramethylstannane[1]

Me_4Sn

[594-27-4] · $C_4H_{12}Sn$ · Tetramethylstannane · (MW 178.87)

(weak nucleophile which reacts with Brønsted and Lewis acids;[2] source of trimethyltin halides;[3] commonly used in Stille coupling[4])

Alternate Name: tetramethyltin.

Physical Data: bp 74-75 °C/760 mmHg; mp -55 °C; *d* 1.315 g cm^{-3}.

Solubility: sol common organic solvents; insol H_2O.

Form Supplied in: widely available as a neat liquid.

Preparative Methods: synthesized by the reaction of methylmagnesium iodide with $SnCl_4$ in Et_2O or THF.[5] Use of higher boiling and/or less Lewis basic solvents, such as toluene or Bu_2O, lessens the need for Vigreux distillation of the product.[6]

Analysis of Reagent Purity: shows one peak in the GC. ^1H NMR (δ 0.1, $J_{H\text{-}^{117}Sn}$ 54.0 Hz, $J_{H\text{-}^{119}Sn}$ 51.0 Hz), ^{13}C NMR (δ -9.5), and ^{119}Sn NMR (Me_4Sn is the common standard) can also be informative.

Purification: commercial tetramethyltin is typically obtained as a colorless oil and is used without further purification. Tetramethyltin is a good solvent for silicone grease;[6b] contamination should be avoided.

Handling, Storage, and Precautions: is an air and water stable oil. Tetramethyltin has a high vapor pressure and containers should be well sealed before storage. Organostannanes are toxic and should only be used in a well ventilated hood. All glassware should be rinsed in a KOH/EtOH bath during cleaning.

Palladium-Mediated Cross-Coupling Reactions (Stille Coupling and Related Reactions).

Tetramethyltin acts as a nucleophile in palladium-mediated cross coupling with electrophiles.[4] The coupling is general for halides with sp or sp^2 centers at or adjacent to the electrophilic center. Aryl and heteroaryl halides (eq 1),[7-9] acid chlorides (eq 2),[10] imidoyl chlorides (eq 3),[11] and some β-ketovinyl iodides (eq 4)[12] have been shown to couple with tetramethyltin. Selectivity for substitution of aryl iodides over aryl chlorides is normally observed.[13] The reaction has been found to be of particular use for the alkylation of the base moiety of nucleosides (eq 5).[14] A variety of Pd^0 and Pd^{II} catalysts may be used to mediate the cross coupling. Variation of the stabilizing ligand from PPh_3 to $(2\text{-furyl})_3P$ (PFu_3) or $AsPh_3$ appears to have little effect on the rate of the reaction.[8] Reactions run at or above the boiling point of tetramethyltin often require use of a sealed flask. Workup is facilitated because the trimethyltin halide byproduct is water soluble.

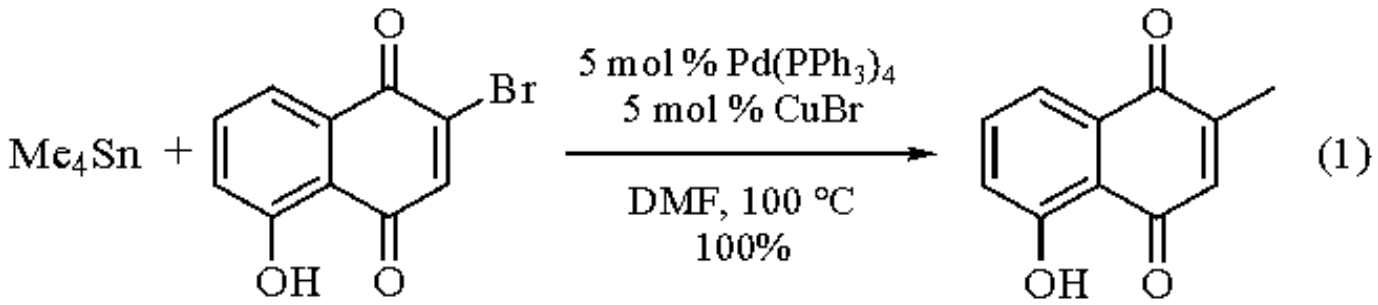

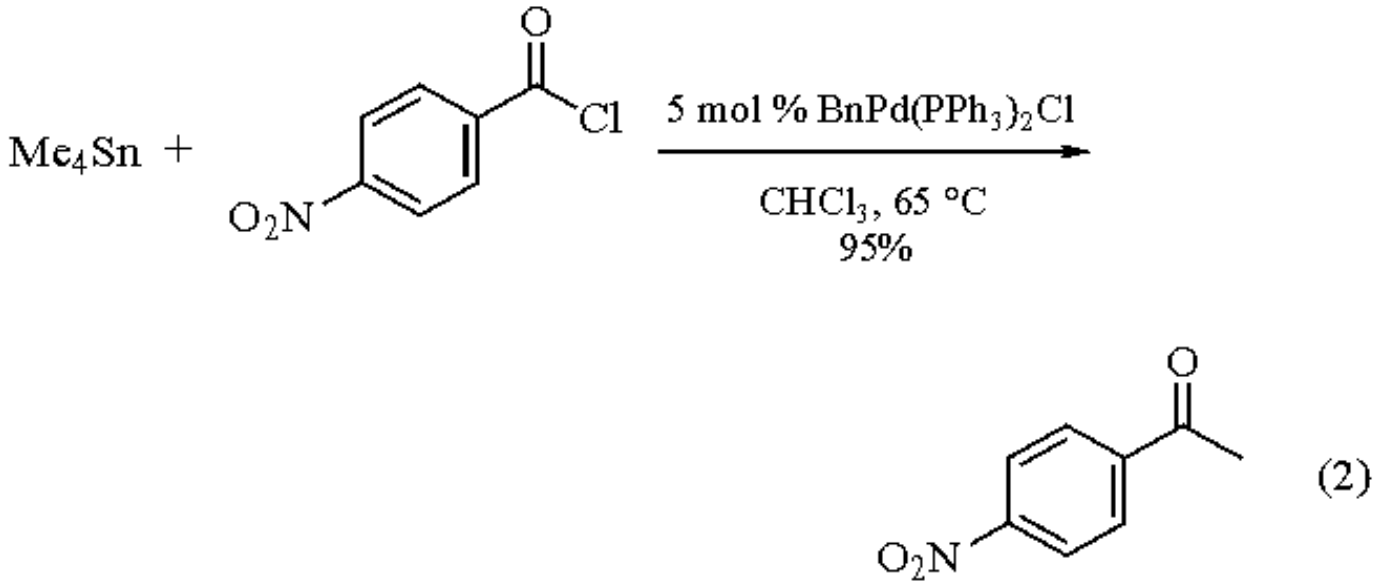

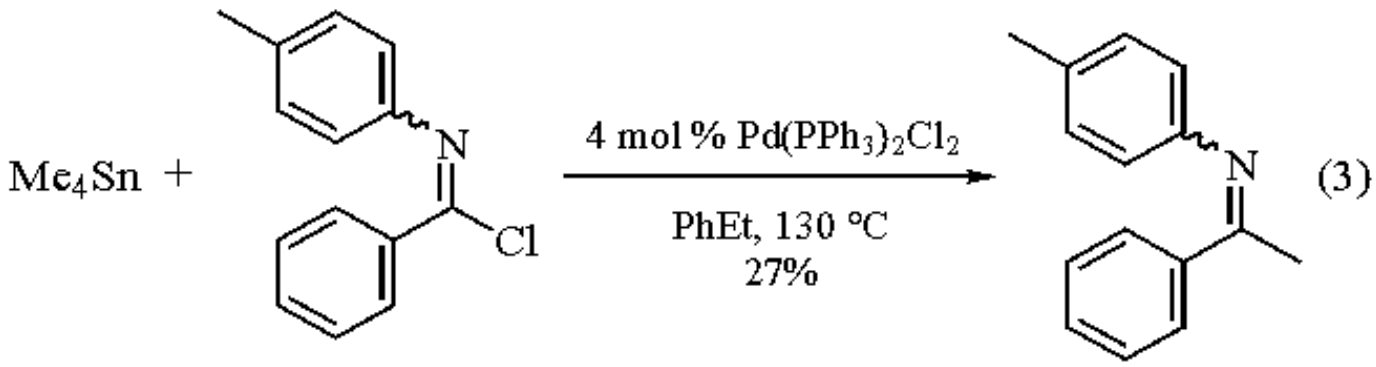

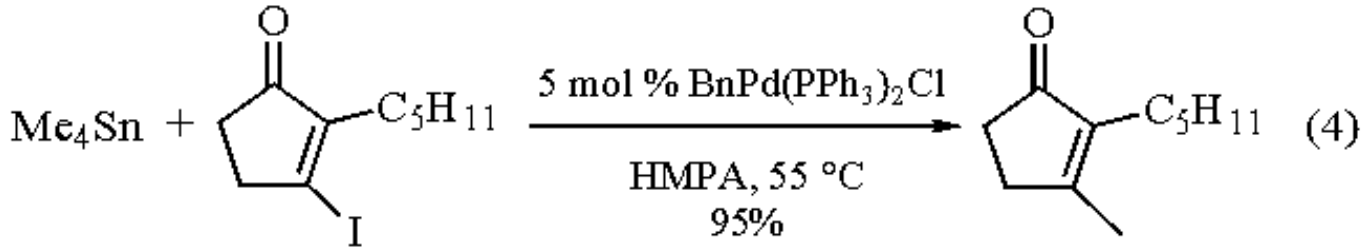

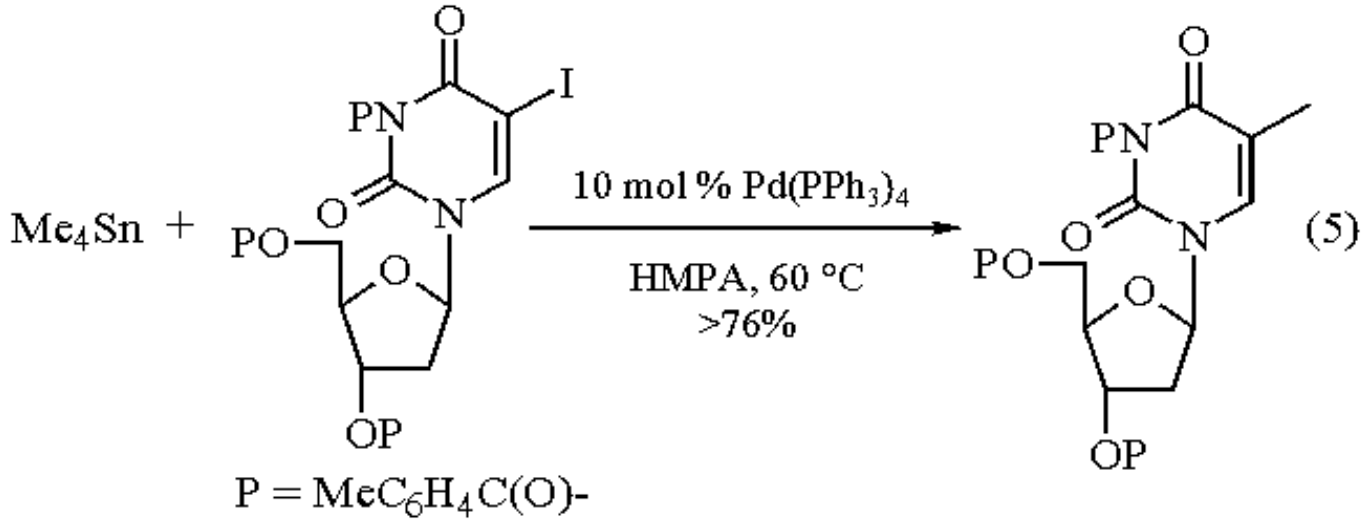

Vinyl and aryl triflates (eq 6) have also proven to be valuable electrophiles in palladium-mediated cross coupling with tetramethyltin.[15,16] An excess of ***Lithium Chloride*** is typically required for the successful coupling. The reaction has found particular value in the synthesis of cephalosporin analogs (eq 7).[17] Palladium catalysts also mediate the cross coupling of tetramethyltin with arylboronic acids,[18] arenediazonium salts,[19] and arylthallium compounds.[20]

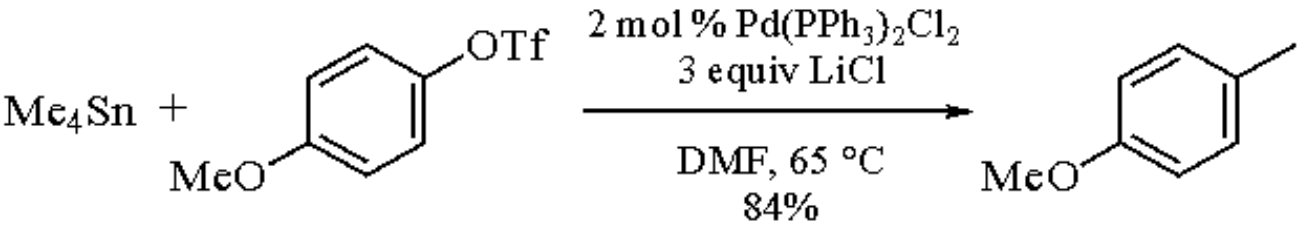

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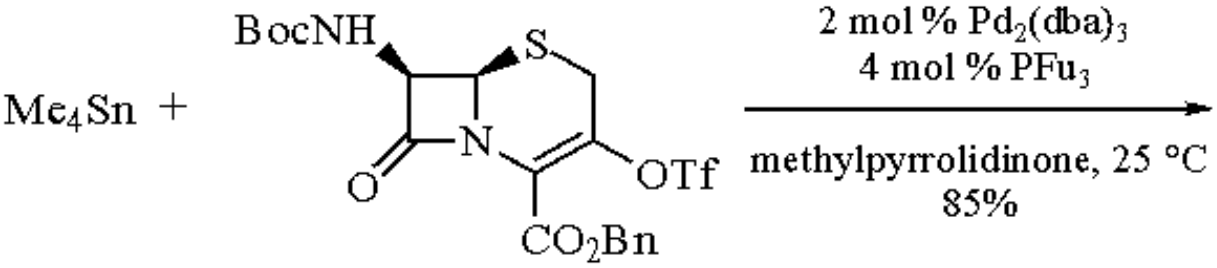

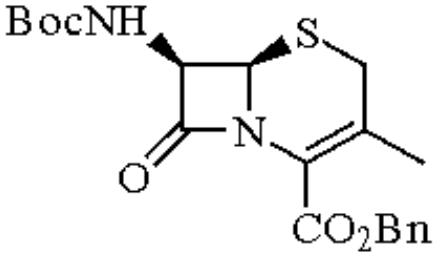

(7)

When conducted under 1-3 atm of carbon monoxide, cross coupling of tetramethyltin with aryl iodides,[21] aryl triflates,[22] and vinyl triflates (eq 8)[23] affords the corresponding methyl ketone. LiCl is typically not required for the reaction to proceed. Occasionally, carbonylative coupling is accelerated by the addition of 1 equiv of anhydrous ***Zinc Chloride***, presumably due to transmetalation to a methylzinc complex. ***Dicarbonylbis(triphenylphosphine)nickel(0)***, a more robust catalyst, has also been reported to mediate a carbonylative coupling.[24]

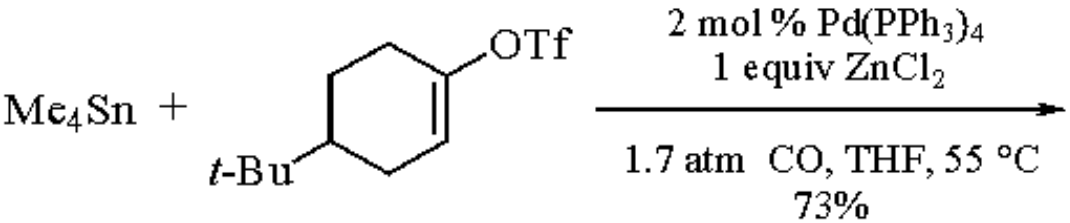

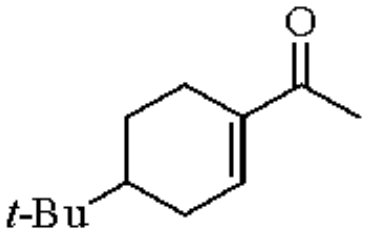

(8)

Reaction with Brønsted and Lewis Acids.

Tetramethyltin reacts with Brønsted and Lewis acids through either homolytic or heterolytic pathways to cleave a methyl-tin bond. Though reaction of ***Mercury(II) Chloride*** with tetramethyltin has been used to generate ***Chlorotrimethylstannane*** and dichlorodimethylstannane,[25] disproportionation is a better route to these compounds. Direct nucleophilic reaction of tetramethyltin with Lewis acids has been effectively utilized to methylate haloboranes (eq 9),[26] thionyl chloride,[27] and antimony halides.[28]

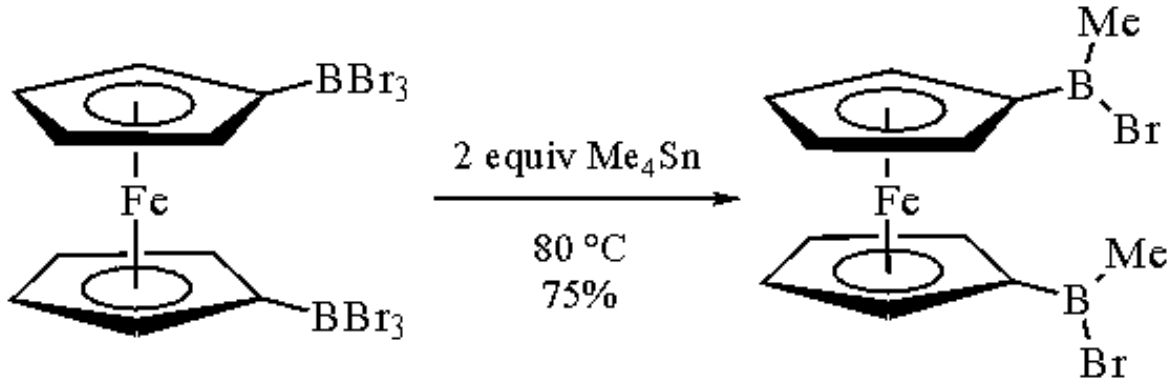

(9)

Disproportionation.

Disproportionation of tetramethyltin with ***Tin(IV) Chloride*** in the absence of solvent provides a simple, quantitative, and relatively inexpensive route to chlorotrimethylstannane.[3]

Related Reagents.

Tungsten(VI) Chloride-Tetramethylstannane.

---

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William J. Scott, J. Howard Jones & Alessandro F. Moretto

Bayer Pharmaceutical Division, West Haven, CT, USA

(*S*)-(+)-2-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic Acid

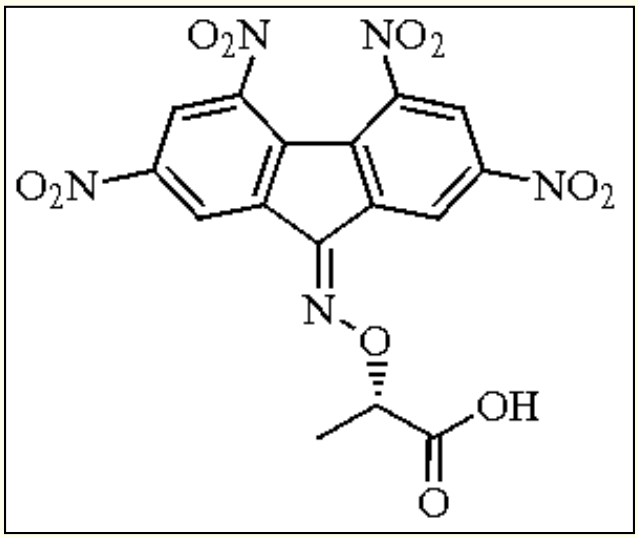

(*S*)-(+)

[50996-73-1] · $C_{16}H_9N_5O_{11}$ · (*S*)-(+)-2-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic Acid · (MW 447.30) (*R*)-(-)

[50874-31-2]

(used as a π-acidic resolving agent for racemic π-bases, especially carbohelicenes[1] and heterohelicenes,[1a,2] and also for resolving certain types of amines[3])

Alternate Name: TAPA.

Physical Data: mp 195 °C (dec.); $[\alpha]^{25}$ +92° (*c* = 1.6, dioxane).

Solubility: sol $CHCl_3$, dioxane, hot acetic acid; slightly sol CH_2Cl_2, toluene.

Form Supplied in: available as the neat solid.

Analysis of Reagent Purity: NMR,[4] mp, [α].

Preparative Methods: prepared from acetone oxime, ethyl 2-bromopropionate, and 2,4,5,7-tetranitrofluorenone.[4] The intermediate racemic 2-(isopropylideneaminooxy)propionic acid is resolved with ***(1R,2S)-Ephedrine***.

Handling, Storage, and Precautions: should be stored under protection from light. No reported toxicity.

Resolving Agent for π-Bases.

The title reagent was originally designed as an agent for resolving hexahelicene, through formation of diastereomeric charge-transfer complexes.[5] It has subsequently been used for resolution of several different types of chiral, racemic π-bases not containing any of the functional groups usually needed to effect resolution by conventional reagents. Carbohelicenes[1] and heterohelicenes (e.g. **1**),[1a,2] [2,2]paracyclophanes,[6] naphthalenophanes,[7] highly substituted alkenes,[8] derivatives of polycyclic aromatic hydrocarbons (e.g. **2**),[9] porphyrin derivatives,[10] an alkyl aryl ether,[11] and an α-aryl ester[11] have been successfully resolved using this reagent, either by chromatographic separation on columns coated with TAPA or by fractional crystallization. Analytical determination of the enantiomeric purity of hexahelicene and several of its derivatives is also possible using HPLC.[12]

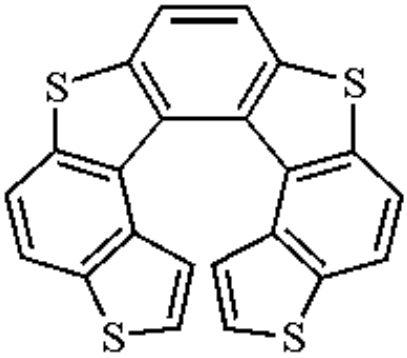

(1)

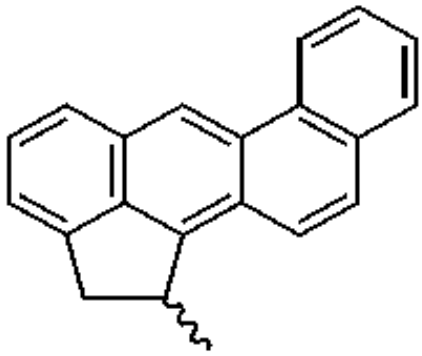

(2)

Resolution of helicenes has been effected using chromatography on other types of chiral stationary phases, including columns derivatized with analogs of TAPA containing larger alkyl groups at the stereocenter, but TAPA is generally the most effective agent.[1]

Resolving Agent for Certain Types of Amines.

TAPA has also been used as resolving agent for some amines that formed either unstable, insoluble, or noncrystalline salts with common resolving acids. Compounds (**3**) and (**4**) were among those resolved with TAPA, whereas camphor-10-sulfonic acid, 3-bromo-8-camphorsulfonic acid, *O*,*O*-di-*p*-toluoyl-(+)-tartaric acid, (+)-tartaric acid, and (+)-camphoric acid could not be used.[3]

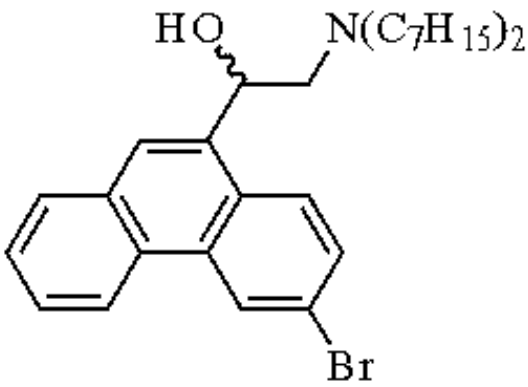

(3)

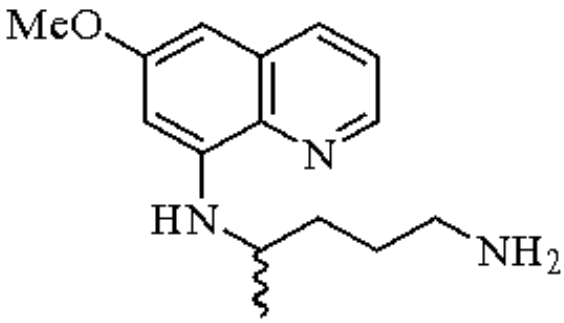

(4)

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Tetraphenylcyclopentadienone[1]

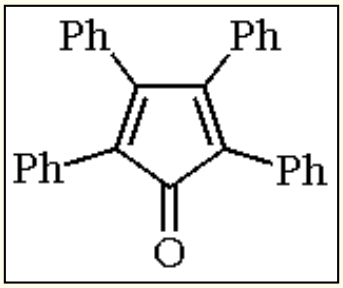

[479-33-4] · $C_{29}H_{20}O$ · Tetraphenylcyclopentadienone · (MW 384.49)

(reactive diene for Diels-Alder reactions)

Alternate Names: tetracyclone; cyclone.

Physical Data: mp 217-220 °C.

Solubility: soluble in ethanol, benzene, xylene, acetic acid.

Form Supplied in: black-violet crystalline solid; commercially available. *Drying:* may be recrystallized from ethanol-benzene.

Handling, Storage, and Precautions: no special precautions; follow manufacturer's label instructions.

General Discussion.

Tetraphenylcyclopentadienone is readily prepared in high yield by the condensation of benzil with dibenzyl ketone under basic catalysis.[2] Less commonly, the reagent has been prepared from the alkaline ***Potassium Ferricyanide*** oxidation of 2,4,5,6-tetraphenyl resorcinol in modest yield.[3] The reagent is most frequently employed as a reactive diene in the Diels-Alder reaction with a large number of vinylic and alkynic dienophiles, especially arynes (eq 1).[1,4] This subject has been reviewed.[1]

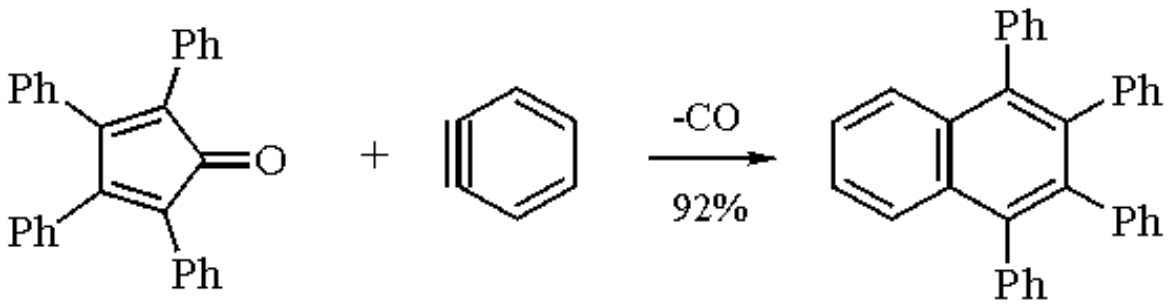

(1)

The reaction can be followed visually by the disappearance of the characteristic intense purple color. Depending on the reaction conditions, the initial cycloadduct may retain the carbonyl bridge (eq 2).[5,6]

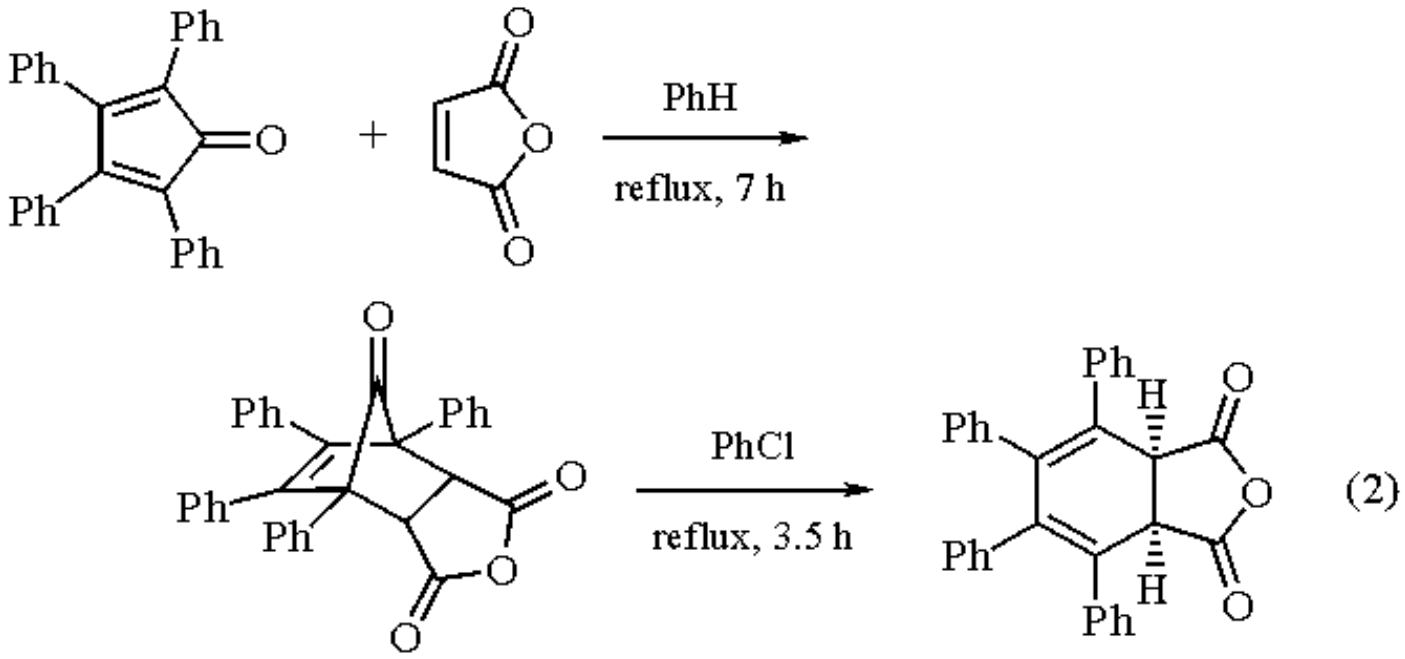

With alkyne dienophiles, loss of CO is universal. The reaction of the reagent with ***Dimethyl Acetylenedicarboxylate*** has been studied extensively in a wide range of solvents (eq 3).[5]

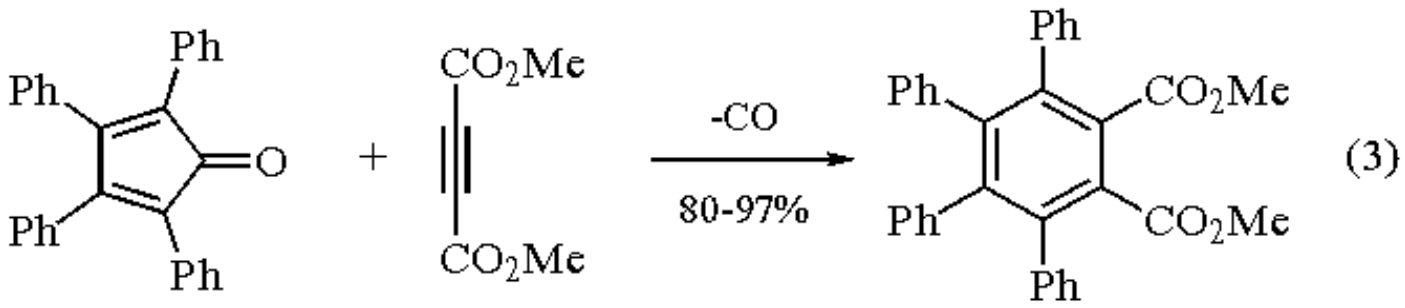

Less common reactions involving the reagent have also been reported. For example, treatment of the cyclooctyne-silver nitrate complex with the reagent affords the decarbonylated cycloadduct in high yield.[7] Reaction of the *O*-tosylhydroxylamine of the reagent with aryl Grignard or lithium nucleophiles gives the corresponding imine, which is converted to the arylamine by treatment with excess ***Hydroxylamine*** in aqueous pyridine.[8] Reduction of the reagent with ***Lithium Aluminum Hydride*** and ***Aluminum Chloride*** (1:1) in ether affords the useful diene tetraphenylcyclopentadiene in excellent yield.[9] The reagent has been used as a scavenger for singlet oxygen.[10]

Related Reagents.

Tetrachlorocyclopentadienone.

---

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Tetraphenylcyclopentadienone Oxime *O*-Tosylate

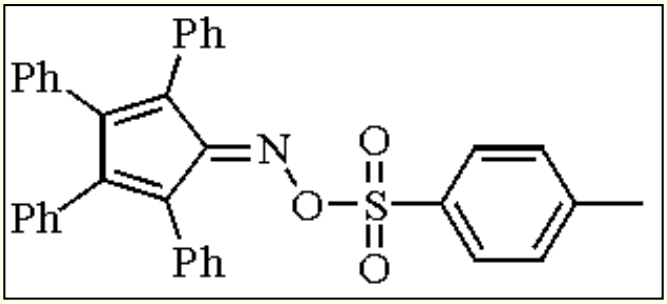

[91550-25-3] · $C_{36}H_{27}NO_3S$ · Tetraphenylcyclopentadienone Oxime *O*-Tosylate · (MW 553.71)

(electrophilic aminating reagent for Grignard reagents[1])

Solubility: sol ether, THF.

Preparative Methods: ***Tetraphenylcyclopentadienone*** (commercially available) reacts with ***Hydroxylamine*** in pyridine to yield the corresponding oxime,[2] and the oxime reacts with ***p-Toluenesulfonyl Chloride*** in an acetone-H_2O basic solution to yield the oxime tosylate.[3]

Electrophilic Amination.

The addition of organometallic reagents to oximes[4] has found limited applicability due to their low electrophilicity and α-deprotonation requiring the use of a considerable excess of organometallic reagent (eq 1). There are various scattered reports of reactions of Grignard reagents and organolithiums with oximes that furnish amines, amino acids, aziridines, β-amino alcohols, and other products.[5] Ketoximes and their *O*-substituted derivatives can also serve as electrophilic aminating reagents for Grignard reagents and organolithiums (eq 2).[5] So far, acetoxime,[6,7] butanone oxime,[6] cyclohexanone oxime,[8] benzaldoxime,[9] isobutyrophenone oxime,[10] ***Acetoxime O-(2,4,6-trimethylphenyl)sulfonate***,[11] and tetraphenylcyclopentadienone oxime *O*-tosylate[1] have been used for amination of Grignard reagents and organolithiums.

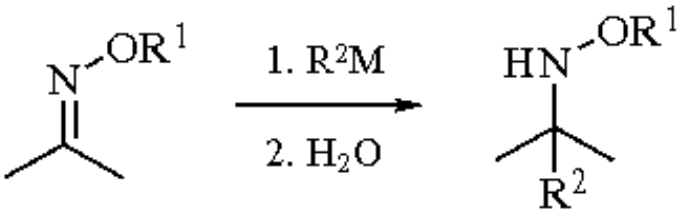

(1)

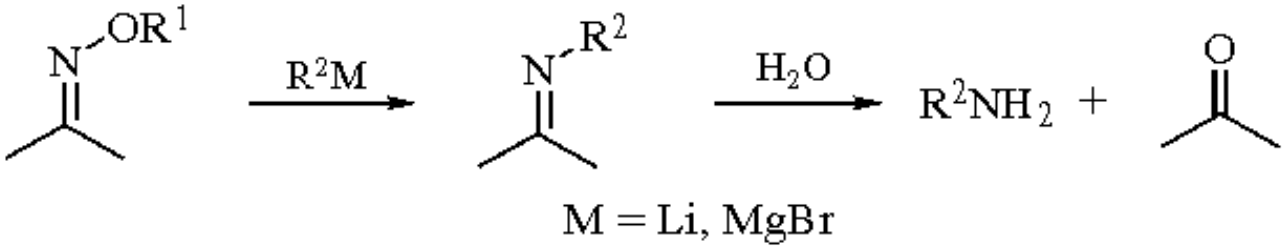

(2)

Tetraphenylcyclopentadienone oxime *O*-tosylate reacts with aryl Grignards and lithiums to give the corresponding imines in good to excellent yields, which are then converted to arylamines by reaction with excess hydroxylamine (eq 3).[3]

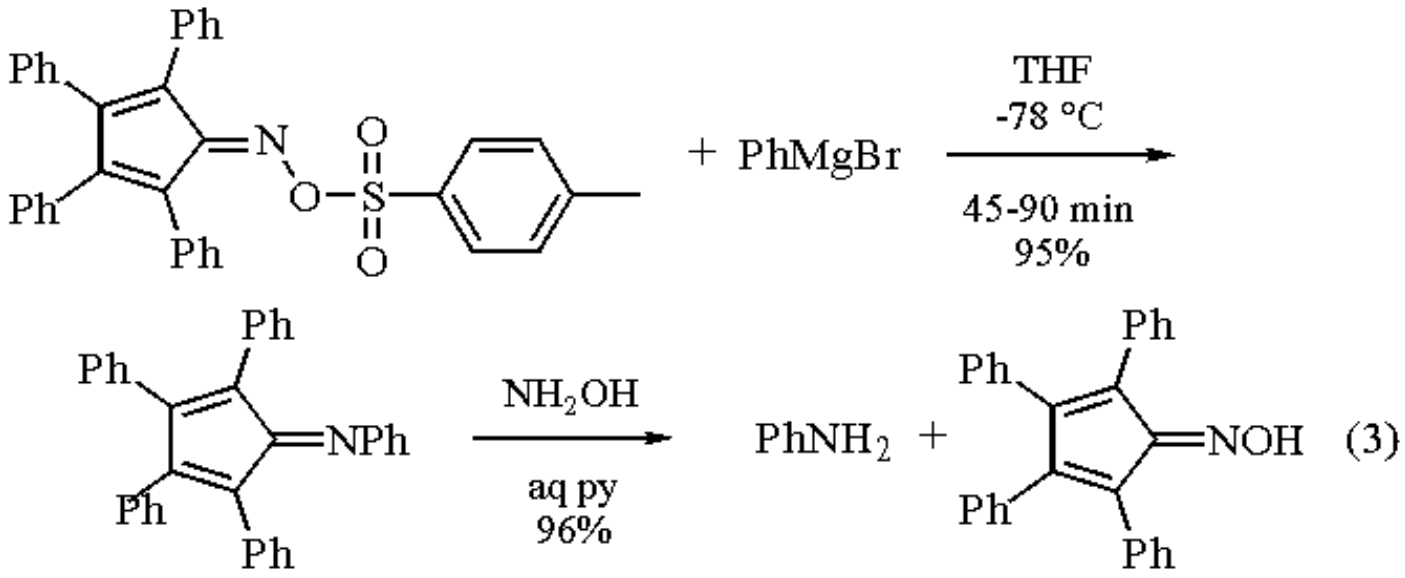

A typical experimental procedure is as follows. The aminating reagent (1 equiv) is added to the aryl Grignard reagent (7 equiv) in THF at -78 °C and the mixture is stirred at -78 °C for 45-90 min. The imine is extracted with benzene, crystallized from benzene-heptane (1:3), and then stirred at rt for 2 h with excess hydroxylamine in aqueous pyridine. The oxime is precipitated on acidification, and, following base treatment, the amine is isolated. Alkyllithiums and Grignard reagents have also been reported to react with the tosylate to yield the corresponding imine, but yields have not been reported.

Significant features of this method are the good yields of aryl amines compared to those obtained by the use of other ketoximes as electrophilic aminating reagents, and the mode of the activating the aminating reagent *O*-tosylhydroxylamine by attacking an auxiliary group (tetraphenylcyclopentadienyl moiety), which then can be removed and efficiently recycled through the sequence.

---

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Ender Erdik

Ankara University, Turkey

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Tetra-*n*-propylammonium Perruthenate[1]

$Pr_4N^+RuO_4^-$

[114615-82-6] · $C_{12}H_{28}NO_4Ru$ · Tetra-*n*-propylammonium Perruthenate · (MW 351.48)

(mild oxidant for conversion of multifunctionalized alcohols to aldehydes and ketones;[1] can selectively oxidize primary-secondary diols to lactones;[2] can cleave carbon-carbon bonds of 1,2-diols[3])

Alternate Name: TPAP.

Physical Data: mp 165 °C (dec).

Solubility: sol CH_2Cl_2, and MeCN; partially sol C_6H_6.

Form Supplied in: dark green solid; commercially available.

Analysis of Reagent Purity: microanalysis.

Handling, Storage, and Precautions: stable at room temperature and may be stored for long periods of time without significant decomposition, especially if kept refrigerated in the dark. The reagent should not be heated neat, as small quantities decompose with flame at 150-160 °C in air.

General Procedures.

TPAP is a convenient, mild, neutral and selective oxidant of primary alcohols to aldehydes and secondary alcohols to ketones.[1] These reactions are carried out with catalytic TPAP at rt in the presence of stoichiometric or excess ***N-Methylmorpholine N-Oxide*** (NMO) as a cooxidant. A kinetic study with 2-propanol as the substrate has shown that these oxidations are strongly autocatalytic.[4] Turnovers of up to 250 are obtainable if activated powdered molecular sieves are introduced to remove both the water formed during oxidations and the water of crystallization of the NMO. Solvents commonly employed are dichloromethane and acetonitrile, or combinations of these. This reagent also works well on a small scale where other methods, such as those employing activated ***Dimethyl Sulfoxide*** reagents, are inconvenient.[1] For large scale oxidations it is necessary to moderate these reactions by cooling and by slow portionwise addition of the TPAP. To achieve full conversion on a large scale, the NMO should be predried (by first treating an organic solution of NMO with anhydrous magnesium sulfate) and the use of 10% acetonitrile-dichloromethane as solvent is recommended.[1]

Oxidation of Primary Alcohols.

Primary alcohols can be oxidized in the presence of a variety of functional groups, including tetrahydropyranyl ethers (eq 1),[1,5] epoxides (eq 2),[1,6] acetals (eq 3),[1,7] silyl ethers,[1,8] peroxides,[9] lactones,[1,10] alkenes,[1,11] alkynes,[1,12] esters,[1,13] amides,[1,14] sulfones,[1] and indoles.[10] Oxidation of substrates with labile α-centers proceeds without epimerization.[1]

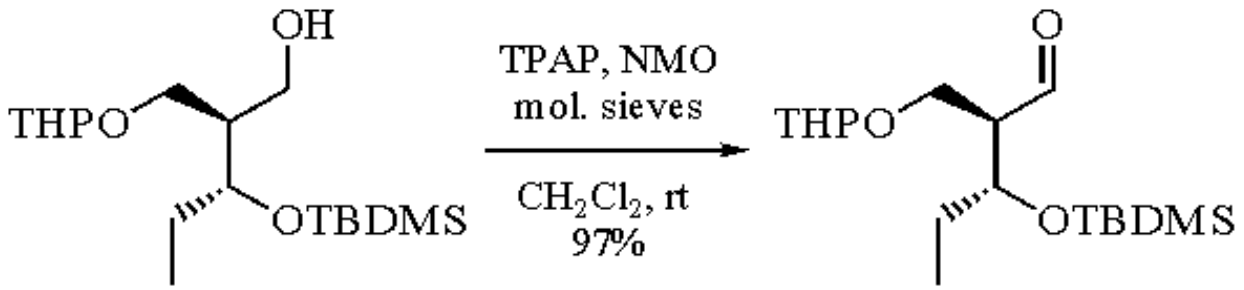

(1)

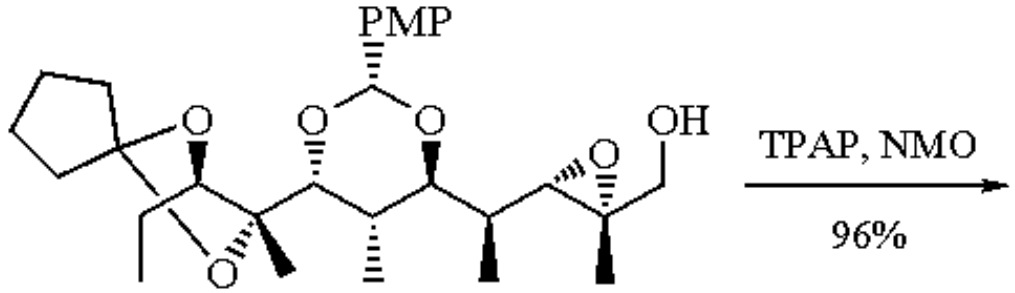

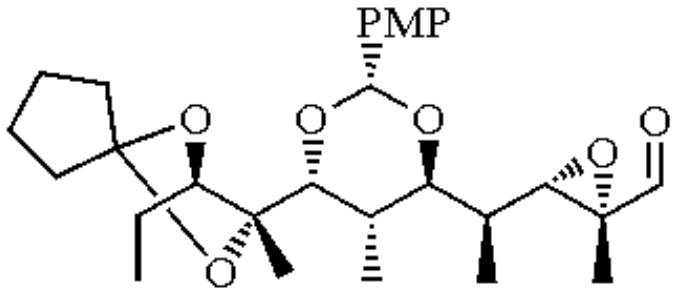

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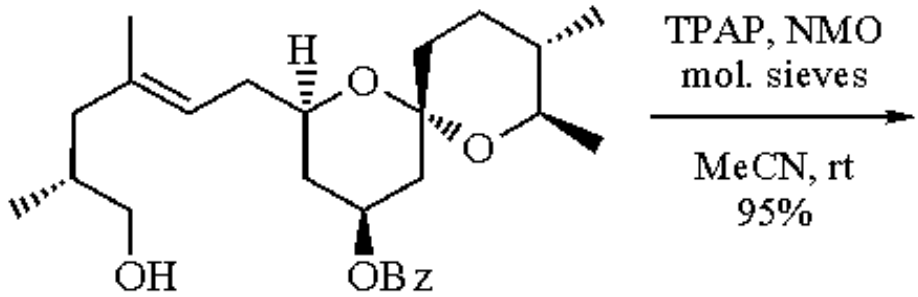

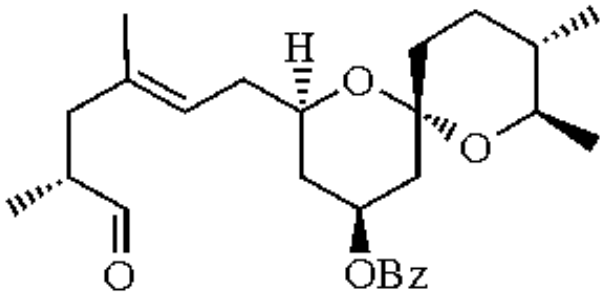

(3)

Oxidation of Secondary Alcohols.

In a similar fashion, multifunctional secondary alcohols are oxidized to ketones (eqs 4 and 5)[9,15] in good yields.[1,5-14]

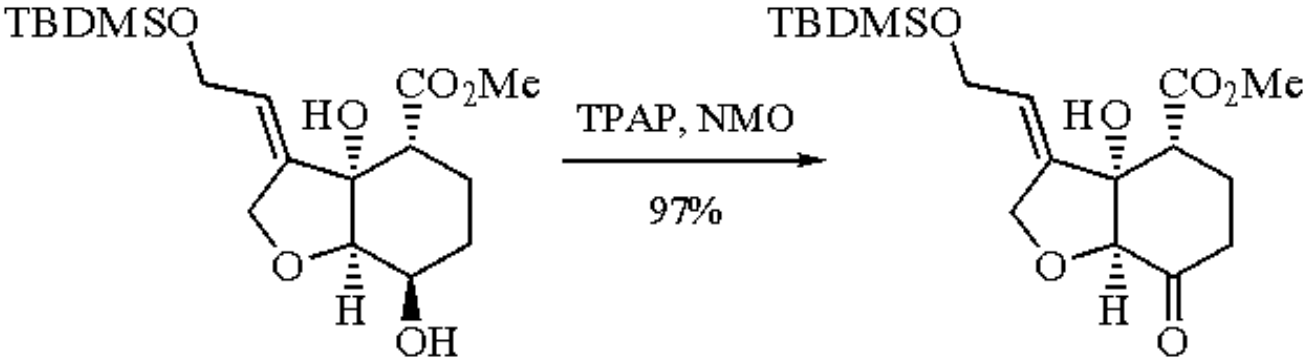

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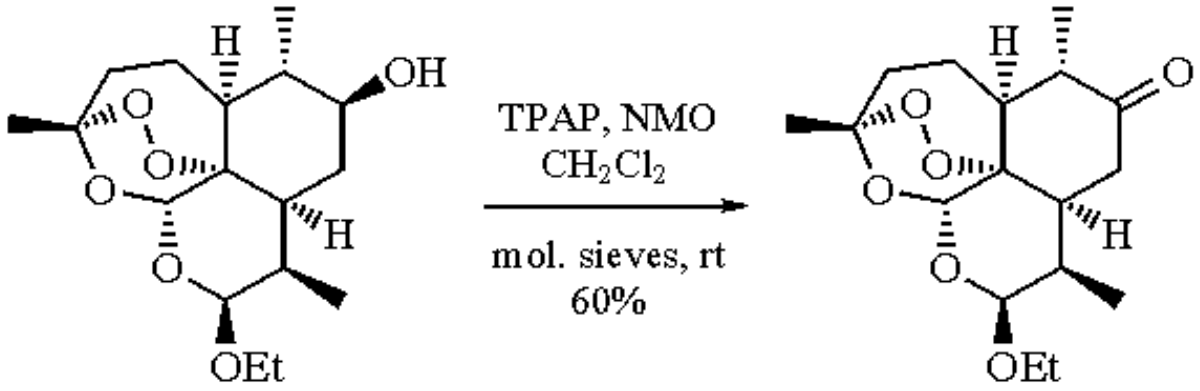

(5)

A particularly hindered secondary alcohol (an intermediate in the latter stages of the synthesis of tetronolide) resisted oxidation with activated DMSO, ***Pyridinium Chlorochromate***, and activated ***Manganese Dioxide***, yet stoichiometric TPAP afforded the ketone in 81% yield.[16]

Allylic Alcohols.

These alcohols are successfully oxidized to the corresponding enones and enals (eq 6).[1,17]

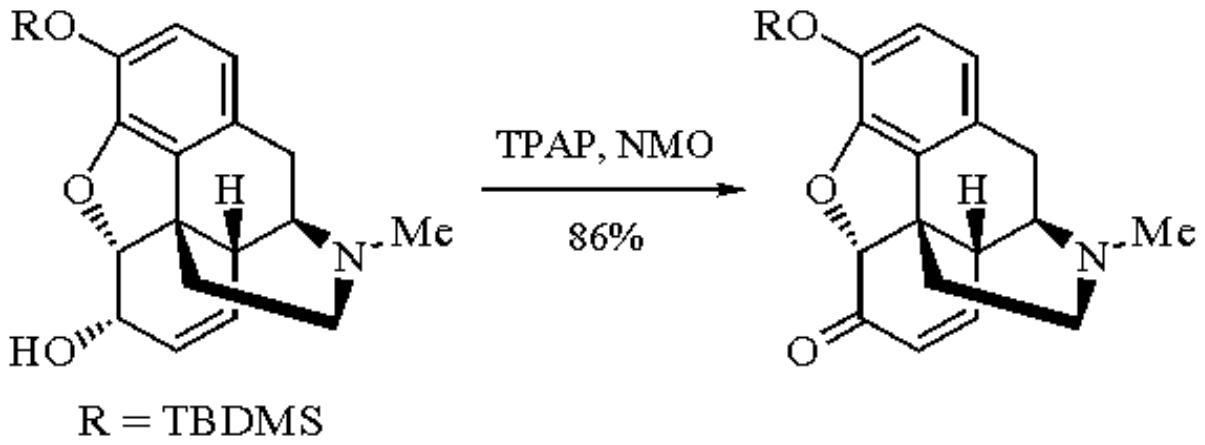

(6)

Oxidation of a primary allylic alcohol over a secondary allylic alcohol has been achieved.[18] Oxidation of the homoallylic alcohol of cholesterol by TPAP and NMO under ultrasonication conditions gives the dienone cholest-4-ene-3,6-dione in 80% yield.[19] This oxidation was subsequently carried out in the presence of a labile TBDMS enol ether group which remained intact, while with both PCC and activated DMSO this protecting group did not survive.[19] Oxidation of homopropargylic alcohols leads to allenones, as with other common oxidants.[20]

Lactols.

Oxidations of lactols to lactones are facile and high yielding; several examples have been reported in the literature (eq 7).[1,21]

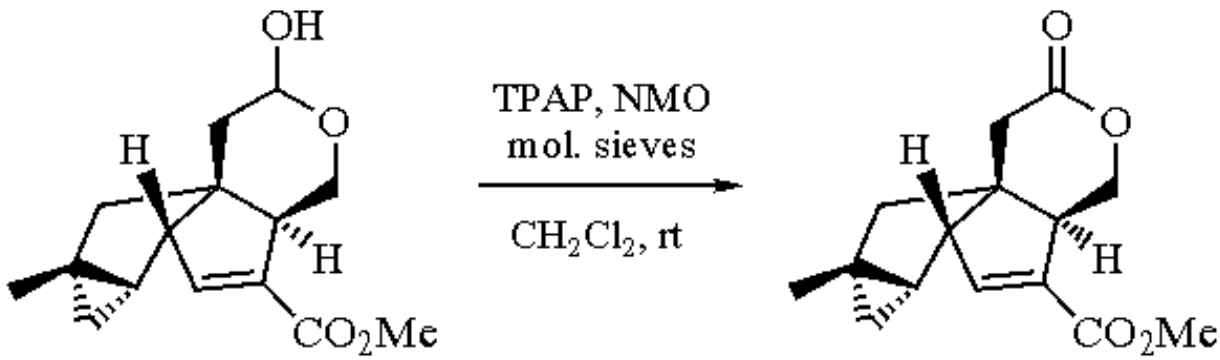

(7)

Selective Oxidations.

The selective oxidation of 1,4 and 1,5 primary-secondary diols to lactones is a valuable application of this reagent.[2] Few general mild reagents for the chemoselective oxidation to the hydroxy aldehyde are available.[22] The most widely known reagents are Pt and O_2, and ***Dihydridotetrakis(triphenylphosphine)ruthenium(II)***.[22] Hydroxy aldehydes, in their lactol form, are then oxidized further to lactones. The use of TPAP is advantageous in that it is commercially available, employs mild catalytic reaction conditions, and reacts with high selectivity in unsymmetrical cases (eq 8).[2] Lactones have also been formed from primary-tertiary diols.[23]

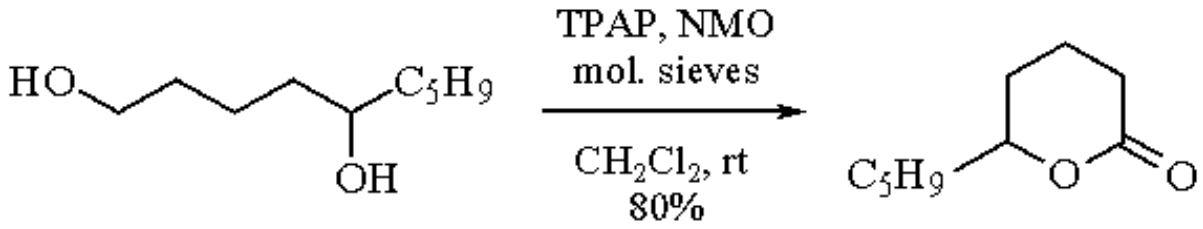

(8)

Functional Group Compatibility.

The neutral conditions of these oxidations have been utilized to provide improved yields with acid sensitive substrates compared to the well established Swern method (eqs 9, 10).[1,16]

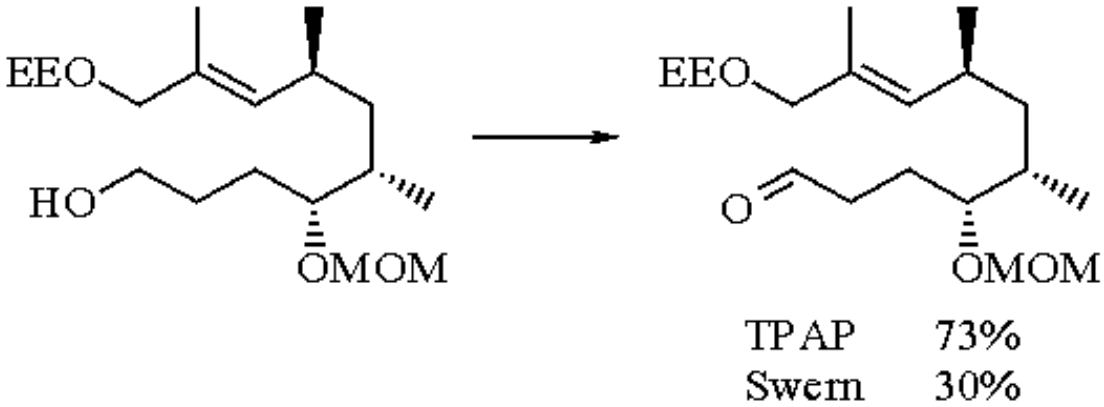

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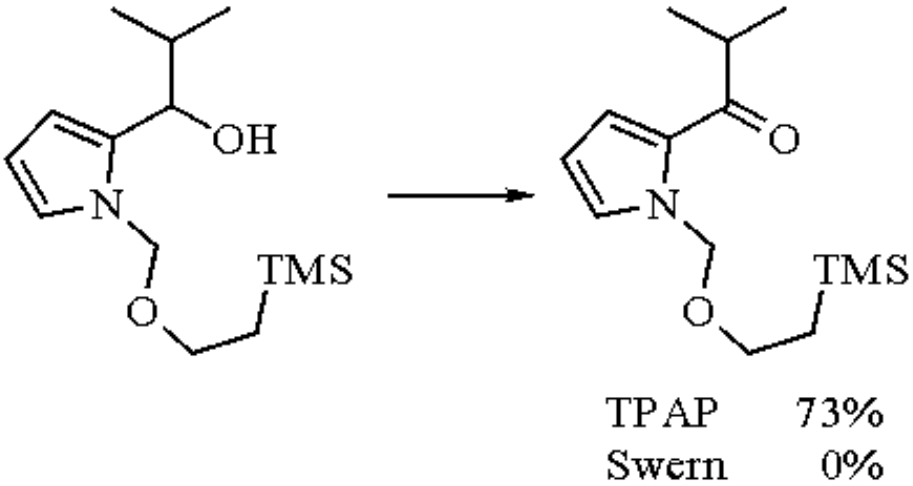

(10)

Highly sensitive alcohols have also been oxidized, albeit in low yield, when most other conventional methods, such as Dess-Martin periodinane (***1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one***),[24] PCC, ***Pyridinium Dichromate***, and DMSO activated with ***Sulfur Trioxide-Pyridine*** have failed (eq 10).[25]

Oxidative Cleavage Reactions.

Among the numerous methods for 1,2-diol cleavage there exist only a few that involve catalytic ruthenium reagents, for example ***Ruthenium(III) Chloride*** with ***Sodium Periodate***.[22] Attempted selective monooxidation of a 1,2-diol to the hydroxy aldehyde with catalytic TPAP and NMO resulted in carbon-carbon bond cleavage to provide the aldehyde (eq 11).[3] Furthermore, attempted oxidation of an anomeric α-hydroxy ester failed; instead, in this case decarboxylation/decarbonylation and formation of the lactone was observed (eq 12). However, ***Dimethyl Sulfoxide-Acetic Anhydride*** provided the required α-dicarbonyl unit.[26] Retro-aldol fragmentations can also be a problem.[27]

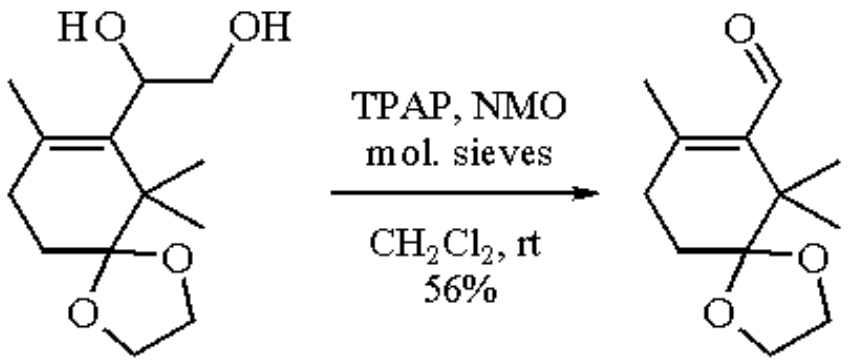

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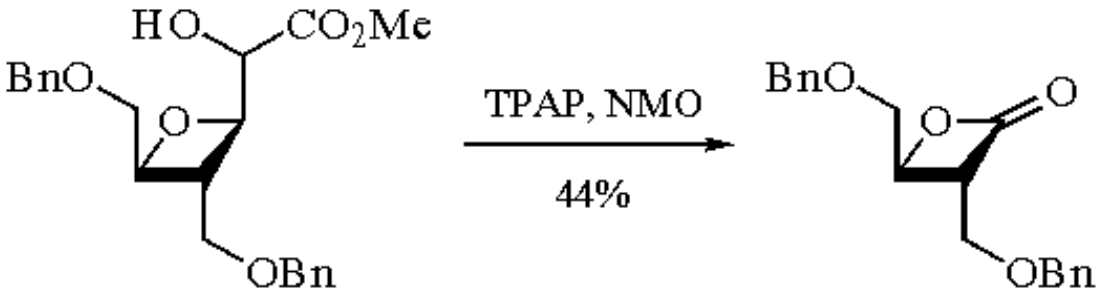

(12)

Heteroatom Oxidation.

Thus far, TPAP has only been used to oxidize sulfur. Oxidation of an oxothiazolidine *S*-oxide to the corresponding *S,S*-dioxide gave only poor results in comparison to the standard RuO_2 with $NaIO_4$ conditions.[28] However, oxidation of sulfides to sulfones in the presence of isolated double bonds has been investigated. The yields with TPAP/NMO range from 61-99% which are higher than to those obtained with ***m-Chloroperbenzoic Acid***, ***Potassium Monoperoxysulfate*** (Oxone®), or ***Hydrogen Peroxide-Acetic Acid***.[29]

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Tetravinylstannane[1]

$(CH_2{=}CH)_4Sn$

[1112-56-7] · $C_8H_{12}Sn$ · Tetravinylstannane · (MW 226.91)

(vinyllithium precursor;[2] vinyl nucleophile source for Stille coupling[3])

Alternate Name: tetravinyltin.

Physical Data: bp 55-57 °C/17 mmHg, 67-70 °C/28 mmHg.

Solubility: sol common organic solvents; insol H_2O.

Form Supplied in: available as a neat liquid. Major impurities are tin chlorides.

Preparative Methods: synthesized by the reaction of ***Vinylmagnesium Bromide*** with ***Tin(IV) Chloride*** in THF.[4]

Analysis of Reagent Purity: shows one spot in the TLC (hexane) and one peak in the GC. ^1H NMR (C_6D_6) can also be informative.

Purification: commercial tetravinyltin is commonly used without further purification. Large quantities are purified by fractional distillation. Smaller amounts may be filtered through a plug of silica.

Handling, Storage, and Precautions: is an air and water stable oil. No unusual storage precautions are required. Organostannanes are toxic and should only be used in a well ventilated hood. All glassware should be rinsed in a KOH/EtOH bath during cleaning.

Vinyllithium.

The primary use of tetravinyltin is for the generation of vinyllithium. There are three common methods used to form vinyllithium. Treatment of a pentane solution of tetravinyltin with 2.0-2.5 equiv of ***n-Butyllithium*** in pentane initiates an exchange reaction which is driven by the precipitation of solid vinyllithium.[2] Removal of solvent by syringe or filtration, followed by washing the vinyllithium and dissolution in Et_2O, affords a solution of vinyllithium which is stable for long periods if stored under an inert atmosphere. An excess of tetravinyltin is employed because the exchange reaction will not proceed to completion.[2] Ethereal vinyllithium solutions are stable for several months at 0 °C. A subsequent study using *n*-BuLi in hexane has shown that the vinyllithium solution can be contaminated with small amounts (<2%) of *n*-BuLi, *n*-hexyllithium, and Bu_4Sn.[5] Vinyllithium formed in this manner has been reacted with 1-chloro-2-methylcyclohexene to afford a substituted bicyclo[4.1.0]heptane (eq 1).[4]

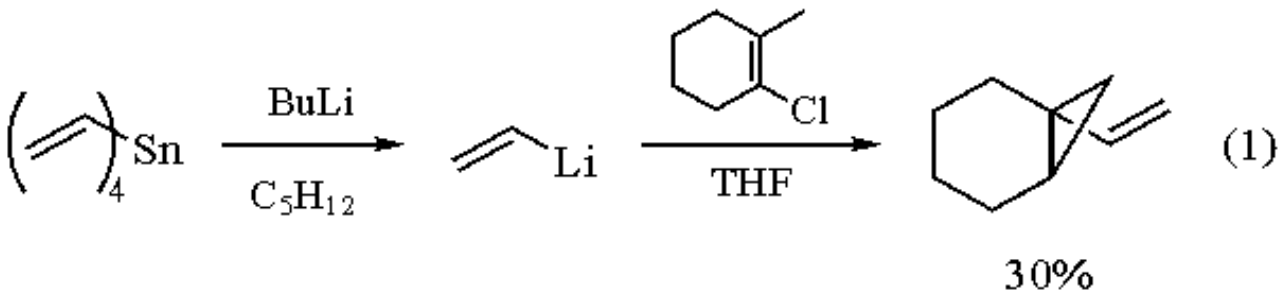

Formation of solid vinyllithium can be avoided by treatment of an Et_2O solution of tetravinyltin with 4 equiv of ***Phenyllithium***.[2] Removal of tetraphenyltin by filtration affords a solution of vinyllithium, which also contains LiBr from the PhLi preparation and trace levels of Ph_4Sn (Ph_4Sn is soluble in Et_2O at 0.0010 g mL^{-1} at 20 °C). Vinyllithium generated in this manner has been reacted with a

sulfonyldihydroisoxazole to afford the vinyldihydroisoxazole (eq 2).[6] Use of Vinylmagnesium bromide afforded the product in low yield.

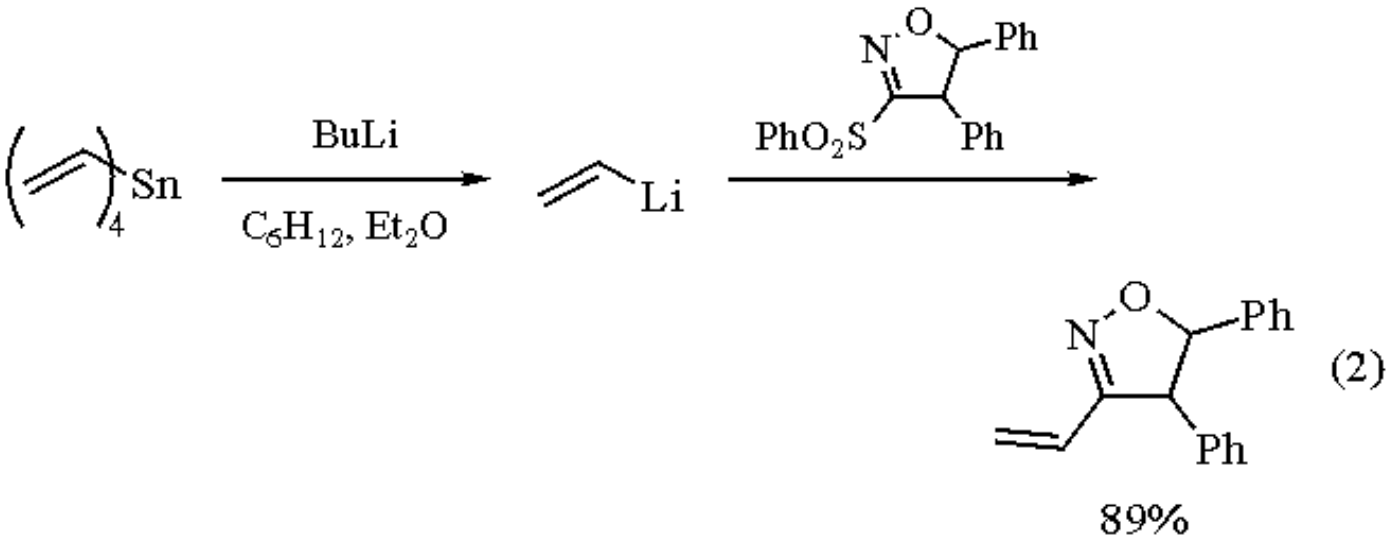

More recently, vinyllithium has been generated by the reaction of tetravinyltin with either 4 equiv of *n*-BuLi in THF[7] or 4 equiv of ***Methyllithium*** in Et_2O,[8] obviating the need for filtration. Tetraalkylstannanes must not interfere with the ensuing steps. This approach has been used to generate lithium vinyltellurolate[7] and vinylcyanocuprate.[8] Reaction of vinyllithium generated in this manner with 1-naphthyloxazoline afforded, after acid quench, the *trans*-dihydronaphthalene (eq 3).[9]

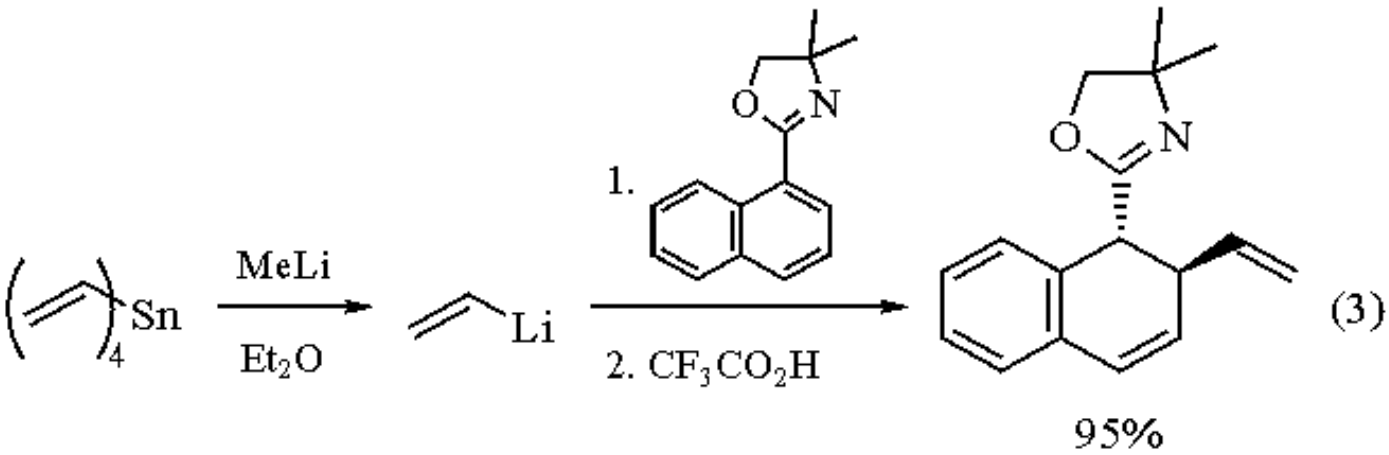

Palladium-Mediated Cross-Coupling Reactions (Stille Reaction).

Tetravinyltin has occasionally been used as a nucleophile in palladium-mediated cross-coupling reactions with acid chlorides,[10] bromo- and iodonucleosides (eq 4),[11,12] and iodoglycals.[13] Because only one vinyl equiv is transferred per tin, vinyltrimethyltin or ***Vinyltributylstannane*** are more commonly utilized in cross-coupling reactions.[3]

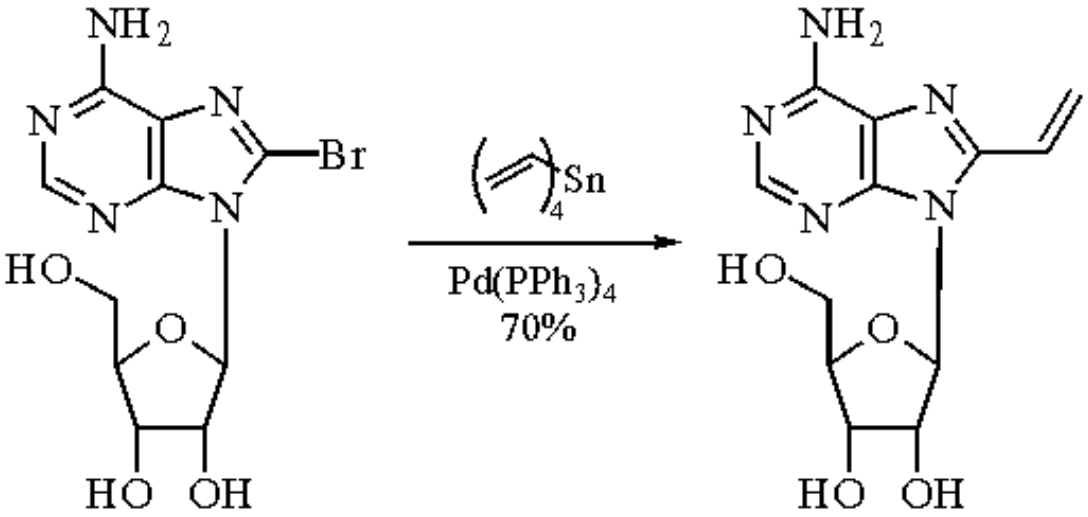

(4)

Protolytic and Halogenolytic Cleavage.

Tetravinyltin reacts once with I_2 to give vinyl iodide and trivinyltin iodide.[14] Similarly, reaction with aqueous HCl affords ethylene and trivinyltin chloride.[15]

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Thallium[1]

[7440-28-0] · Tl · Thallium · (MW 204.38)

(reducing agent, coupling agent)

Physical Data: mp 303 °C, bp 1437 °C, *d* 11.85 g cm^{-3}.

Solubility: insol organic solvents.

Form Supplied in: bluish-white very soft metal, packaged under water; widely available.

Handling, Storage, and Precautions: oxidizes superficially in air, forming a coating of thallium oxide. All thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium is a very soft, abundant, and inexpensive metal. Like a variety of other metals, the utility of thallium in Ullmann-like coupling reactions has been explored. Inactivated thallium metal is very inefficient in coupling reactions of aryl halides. For example, reaction of bromobenzene with thallium under reflux produces <5% of biphenyl (eq 1).[2] The use of mossy or pyrophoric thallium in these coupling reactions does not lead to improvement in yields of the biaryls.

$$2\ ArBr + 2\ Tl \longrightarrow \underset{<5\%}{ArAr} + 2\ TlBr \qquad (1)$$

The use of an activated form of thallium in the preparation of trialkylthalliums from alkyl iodides has been reported (eq 2).[3] The activated thallium was prepared by reduction of thallium(I) chloride with ***Potassium*** in boiling *m*-xylene.

$$Tl + RI \longrightarrow R_3Tl \xrightarrow{HCl} R_2TlCl \qquad (2)$$

Metallic thallium is useful in converting aromatic nitro compounds to azoxy compounds (eq 3).[4] In this reaction, thallium is believed to act as a reducing agent and thallium oxide is the byproduct.

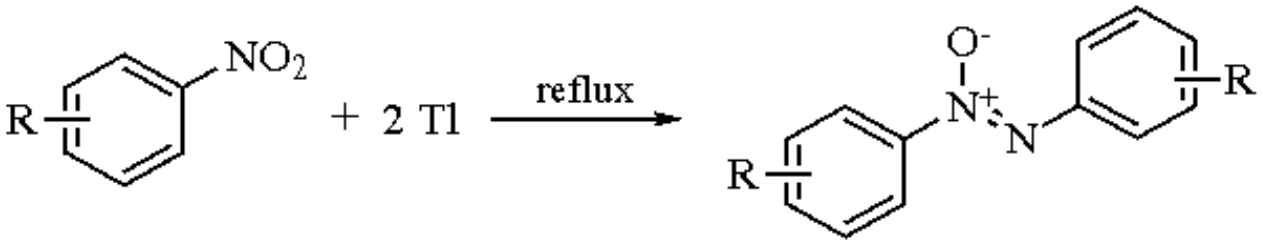

(3)

R = H, 76%; 2-Me, 73%; 3-Me, 77%; 4-Me, 77%; 3-OMe, 80%; 2-Cl, 86%; 3-Cl, 84%; 4-F, 89%

The preparation of azoxy compounds by this route is very efficient and simple. The yields range from good to excellent and a variety of substrates can be used. Aromatic nitro compounds with electron-withdrawing substituents and substrates containing acidic hydrogens such

as OH and NH_2 fail to give azoxy compounds. Bromo- and iodo-substituted nitrobenzenes gave complex products. An interesting coupling reaction using 2,4-dichloronitrobenzene was also reported in this study.[4] This reaction gives a high yield of 2,2´,4,4´-tetrachloroazobenzene as the product (eq 4).

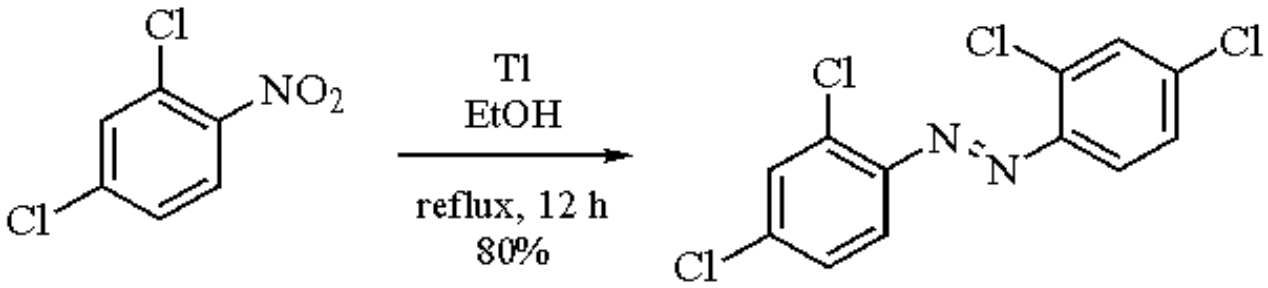

(4)

1. (a) Taylor, E. C.; McKillop, A. *ACR* **1970**, *3*, 338. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465. (c) McKillop, A.; Taylor, E. C. *Chem. Br.* **1973**, *9*, 4.
2. (a) McKillop, A.; Elsom, L. F.; Taylor, E. C. *T* **1970**, *26*, 4041. (b) McHatton, L. P.; Soulal, M. J. *JCS* **1953**, 4095.
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4. McKillop, A.; Raphael, R. A.; Taylor, E. C. *JOC* **1970**, *35*, 1670.

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Thallium(I) Acetate

TlOAc

[563-68-8] · $C_2H_3O_2Tl$ · Thallium(I) Acetate · (MW 263.43)

(inexpensive and stable substitute for Ag^IOAc for iodocarboxylation;[1] stereoselective vicinal diol synthesis;[2] kinetically controlled iodolactonization[3])

Physical Data: mp 110 °C; *d* 3.68 g cm^{-3}.

Solubility: sol water, alcohol, acetic acid.

Form Supplied in: silk-white crystals; widely available.

Handling, Storage, and Precautions: thallium reagents are extremely toxic. The reactions should be carried out in a well-ventilated fume hood, and rubber gloves should be worn. Thallium(I) acetate is reported as a human poison by unspecified routes.[4]

Iodocarboxylation.

As an inexpensive and stable substitute for ***Silver(I) Acetate***, Tl^IOAc reacts with stoichiometric amounts of alkenes and ***Iodine*** in acetic acid to produce *trans*-α-iodoacetates in high yields (eq 1).[1] The reaction can be carried out in a nonhomogeneous system using benzene or CH_2Cl_2 as a solvent, where more than two equiv of the thallium salt are required. This reaction is not highly regioselective for trisubstituted alkenes,[5,6] and no addition was observed for electron-poor alkenes such as methyl cinnamate.[7] When enol acetates are used as alkenes, the corresponding α-iodo ketones are formed (eq 2).[8] This reaction is a mild alternative to the ***N-Iodosuccinimide*** procedure for α-iodination of ketones.

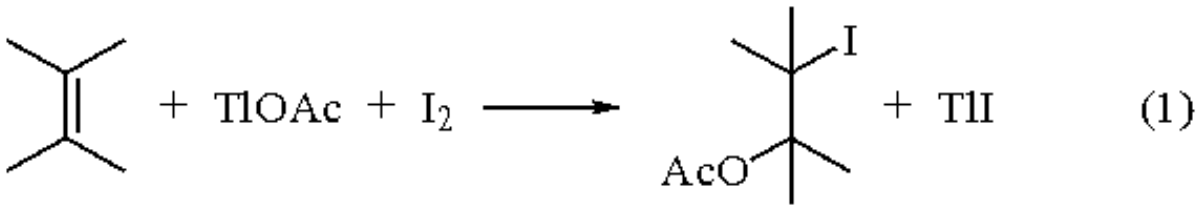

(1)

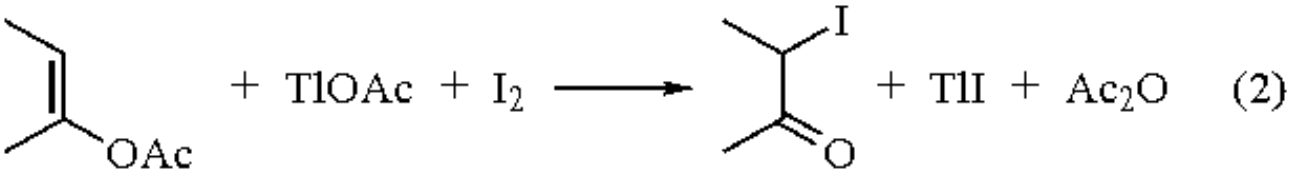

(2)

Thallium acetate can be used in the Prevost reaction[9] (dry) and in the Woodward modification[10] (wet) for stereoselective vicinal diol formation. *trans*-1,2-Diacetoxycyclohexane is obtained when a mixture of TlOAc, I_2, and cyclohexene (a stoichiometric ratio of 2:1:1) is heated at reflux in anhydrous acetic acid.[2] After hydrolysis of the acetyl groups, *trans*-1,2-cyclohexanediol is obtained in 65-70% yields (eq 3). In the Woodward modification the reaction mixture is heated at reflux in aqueous acetic acid to afford *cis*-hydroxyacetate, which, upon hydrolysis, produces *cis*-1,2-cyclohexanediol in 70-75% yields (eq 4).[2]

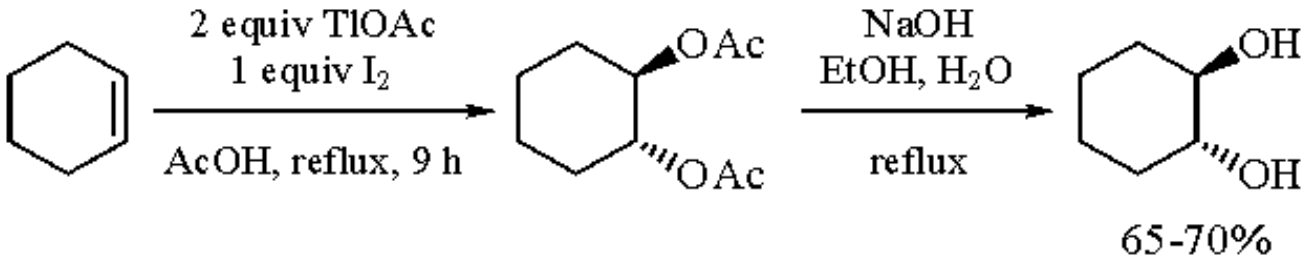

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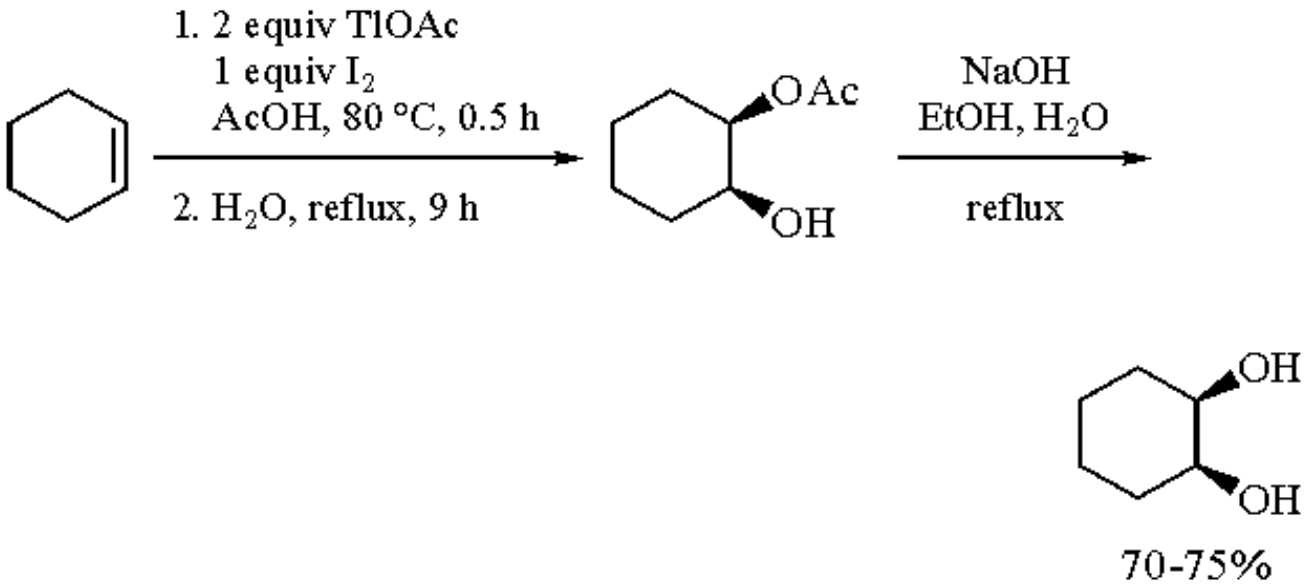

(4)

Intramolecular iodocarboxylation of unsaturated carboxylic acids in the presence of a stoichiometric amount of TlOAc in CH_2Cl_2 leads to iodolactones in high yields (eq 5).[3] The kinetically controlled product is formed under neutral and nonaqueous conditions.

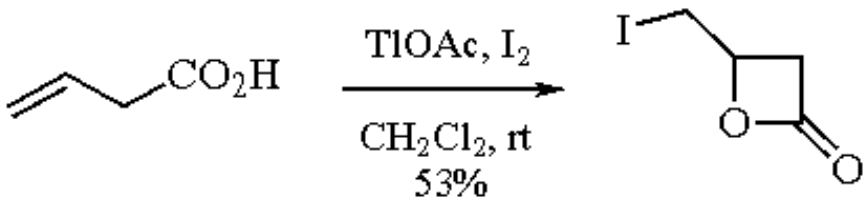

(5)

As a Catalyst or an Additive.

TlOAc catalyzes the formation of isothiocyanates from isocyanides and disulfides (eq 6).[11] Various isocyanides can be used in this reaction, and the best yields are obtained with dibenzoyl disulfide. The reactions are carried out at 61-85 °C in various solvents such as $CHCl_3$, toluene, cyclohexane, EtOH, and dioxane. TlOAc also catalyzes rearrangements of ten-membered-ring allenes to tricyclic compounds in acetic acid at room temperature (eq 7).[12] The double bond at C-5-C-6 is required for the rearrangement to occur.

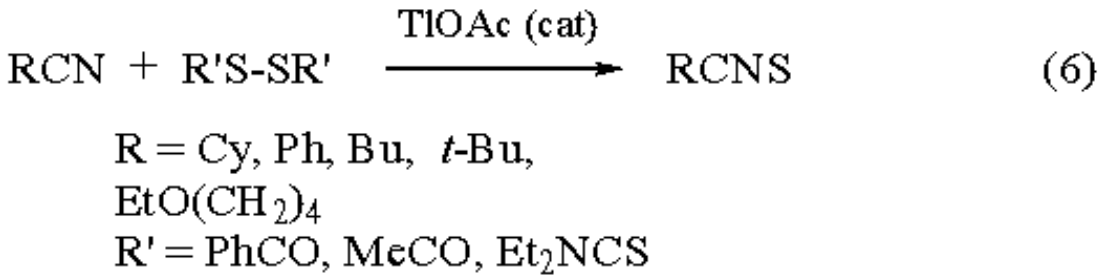

(6)

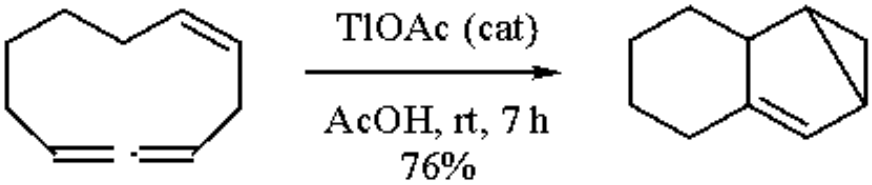

(7)

TlOAc promotes palladium-catalyzed intramolecular cyclization-carbonylation of properly substituted aromatic iodides (eq 8).[13] When ***Triethylamine*** is used as the base instead of TlOAc, a low yield of cyclization-carbonylation product is obtained, which is accompanied by the product derived from the direct carbonylation process. Besides the above examples, bromination of benzene or toluene and selective *ortho*-iodination of phenols mediated by TlOAc were reported.[14,7]

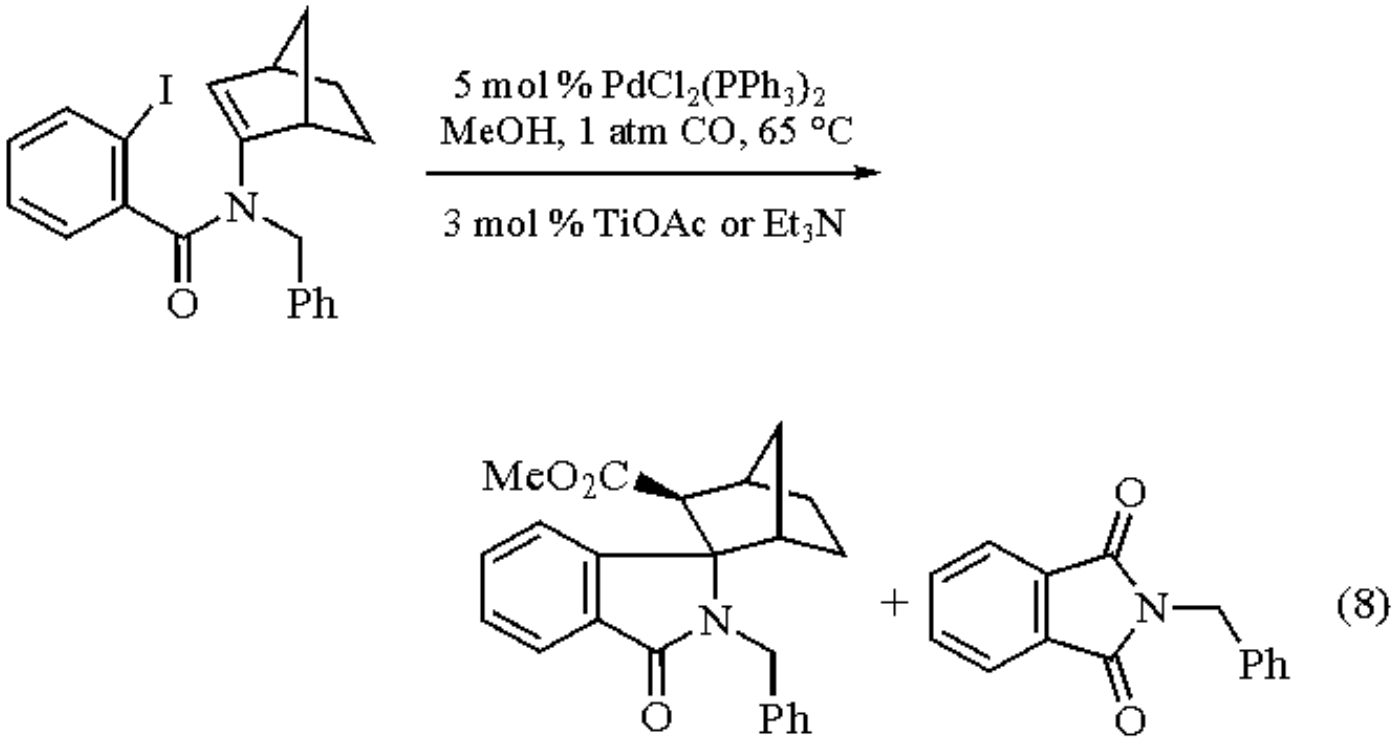

TlOAc	86%	-
Et_3N	13.6%	1.4%

1. Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *CC* **1973**, 359.
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Thallium(III) Acetate

$Tl(OAc)_3$

[2570-63-0] · $C_6H_9O_6Tl$ · Thallium(III) Acetate · (MW 381.53)

(oxidation of alkenes[4] and alkynes;[5] oxidation of conjugated dienes;[7] hydroxylation of double bonds;[11] cleavage of cyclopropane rings;[15] oxidation of enamines;[18] oxidative rearrangements;[20,21,23] bromination of aromatic compounds;[24] oxidation of thiols[25] and *p*-toluenesulfonylhydrazones;[26] formation of acyloxy carboxylic acids;[27] oxidative cyclizations[28])

Physical Data: mp 195 °C.

Solubility: sol hot acetic acid, alcohols, H_2O.

Form Supplied in: white solid; commercially available (98.6%). *Drying:* dry over P_2O_5.

Preparative Methods: was first described by Meyer and Goldschmidt[1] in 1903. It can also be prepared[2] by dissolving thallium(III) oxide in acetic acid and acetic anhydride and stirring at 80-90 °C. The solution is filtered, cooled and the product obtained is recrystallized.

Purification: use after crystallization from acetic acid for best results.

Handling, Storage, and Precautions: remains stable for long periods if kept in a well-sealed desiccator and away from light. It is extremely poisonous. Use in a fume hood.

Oxidation of Alkenes and Alkynes.

It was expressed by Kabbe[3] that thallium(III) acetate as an oxidizing agent occupies an important place between ***Lead(IV) Acetate*** and ***Mercury(II) Acetate***. Oxidation[4] of cyclohexene (**1**) with thallium(III) acetate in acetic acid at rt (several days) yields *cis*/*trans* diacetates (**2**) and (**3**) (40-50%), ring contracted diacetate (**4**) and aldehyde (**5**) (50-60%), and allylic oxidation product (**6**) (2-3%) (eq 1). In dry solvent the *trans*-diacetate (**2**) is obtained in major yield (88%), whereas in moist solvent the *cis*-diacetate (**3**) (81%) predominates. It has been observed that similar oxidation with lead(IV) acetate yields the same five products but the yield of allylic acetate (**6**) is increased by 37% whereas the oxidation carried out with mercury(II) acetate affords exclusively the allylic acetate (**6**). It has been observed[5] that terminal alkynes (**7**) react with thallium(III) acetate in acetic acid or chloroform at 0-20 °C to give a new type of oxythallation adduct (**8**), which on being heated with one equivalent of thallium(III) acetate can be converted to methyl ketone (**9**) (eq 2). Although this procedure for the preparation of ketones was reported[6] previously, the intermediates were not isolated at that time.

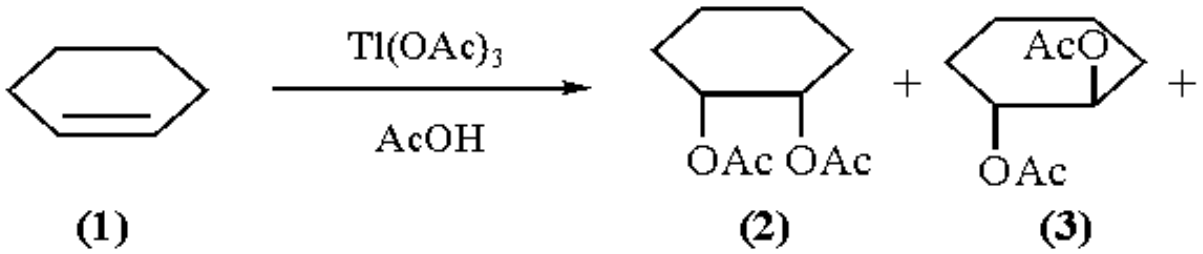

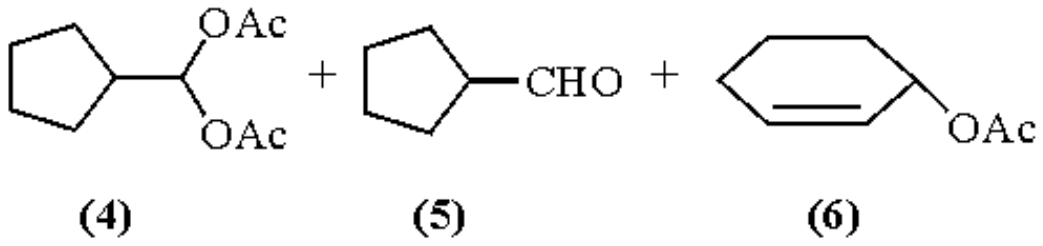

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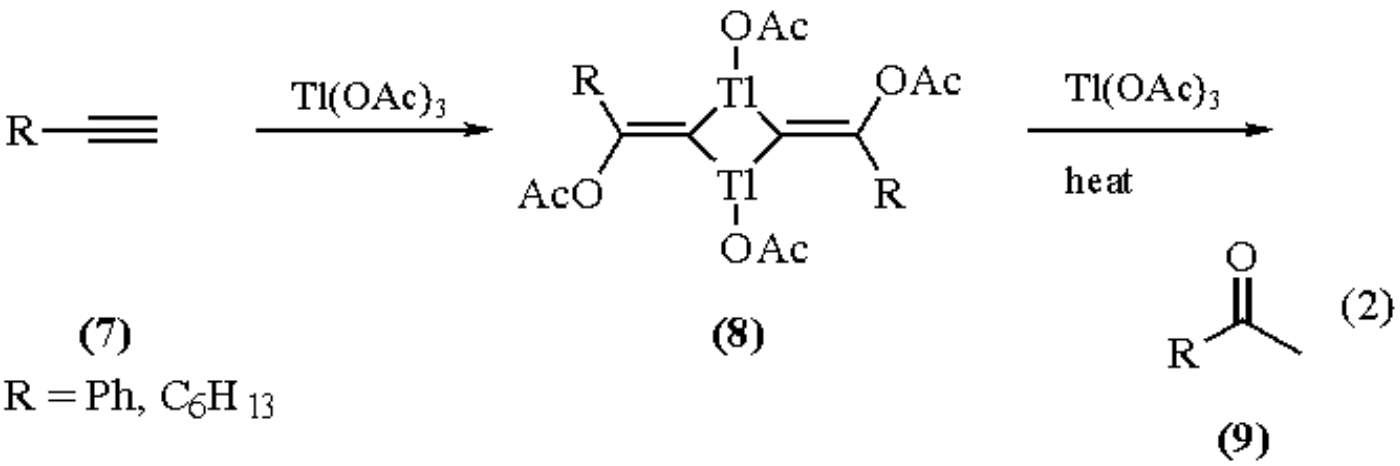

(2)

Oxidation of Conjugated Dienes.

Conjugated dienes (isoprene, 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, etc.) react with thallium(III) acetate in acetic acid at 10-65 °C (0.5-15 h) to give an isomeric mixture (1,2 and 1,4) of the corresponding diacetoxyalkenes in 10-72% yield.[7] All the dienes studied except 1,3-cyclopentadiene afford the 1,2-addition adduct predominantly. The reaction of 2,3-dimethyl-1,3-butadiene (**10**) with thallium(III) acetate has been reported to give the 1,2-addition product (**11**) in good yield and the 1,4-addition product (**12**) in inferior yield (eq 3). In the oxymercuration of dienes with mercury(II) acetate the formation of 1,4-addition products has not been reported.[8] The reaction of diene (**13**) with thallium(III) acetate has been described (eq 4).[9] The resulting product on alkaline hydrolysis has been found to yield alcohols (**14**), (**15**), (**16**), (**17**), and (**18**). The alcohols (**15**) and (**16**) have been utilized for the synthesis of drimane sesquiterpenes. It is worthwhile to mention that the conjugated dienes also undergo *cis* addition[10] with ***Thallium(III) Trifluoroacetate***.

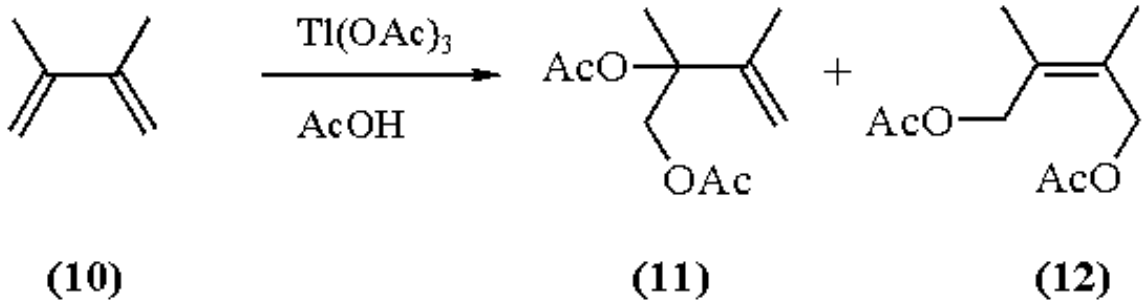

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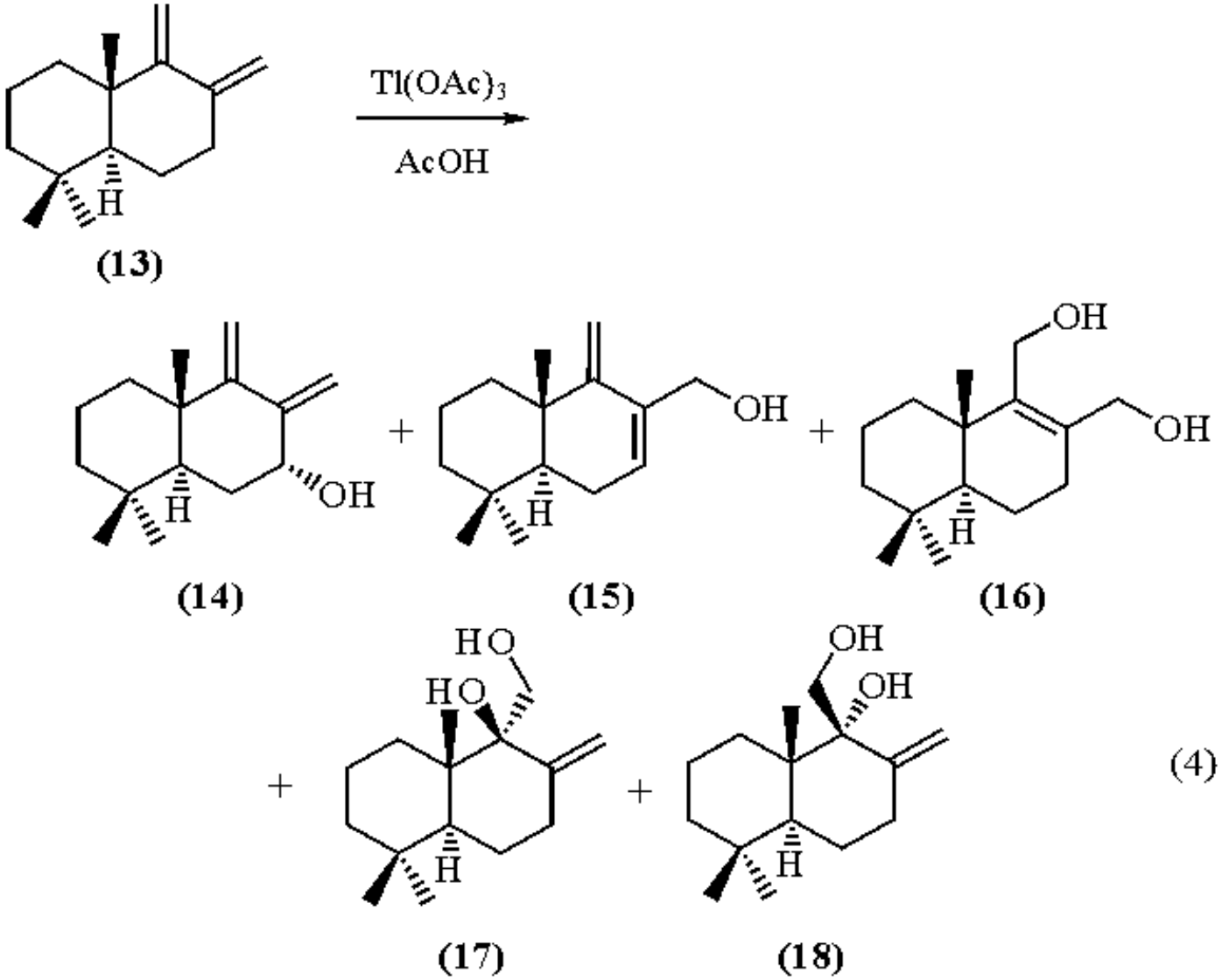

Hydroxylation of Double Bonds.

The stereoselective *cis* hydroxylation of unsaturated steroids such as (**19**) has been effected[11] with thallium(III) acetate in acetic acid. In addition to the *cis*-glycol monoacetates (**20**) and (**21**) (76%), small amounts of *cis*-diacetate (**22**) (7%) and *trans*-glycol monoacetates are obtained (eq 5). The alkaline hydrolysis of monoacetates (**20**) and (**21**) affords the triol (**23**). A number of steroidal alkenes have been hydroxylated with this reagent. This constitutes a convenient procedure for the *cis* hydroxylation of double bonds which have been effected with other procedures.[12-14]

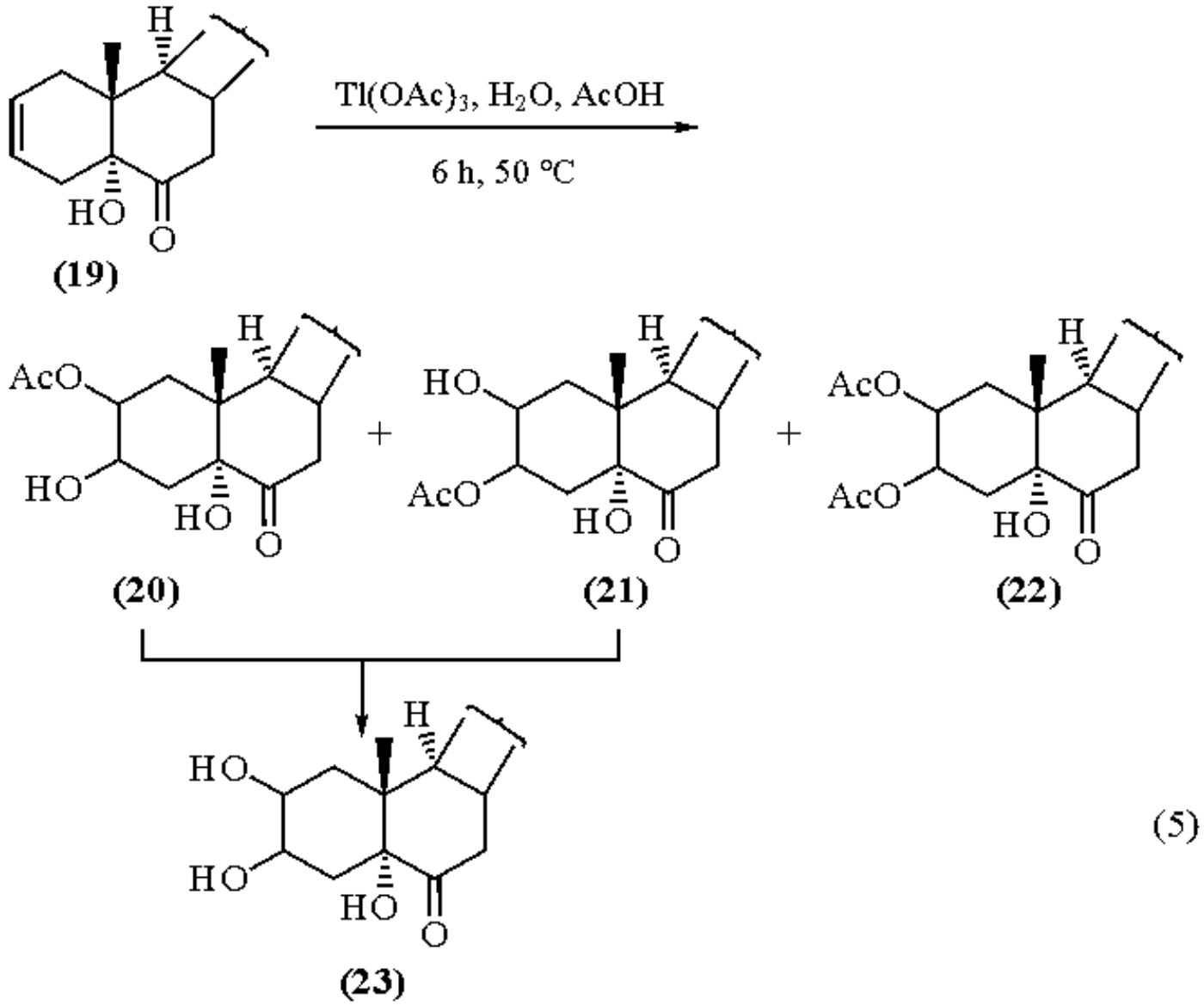

(5)

Cleavage of Cyclopropanes.

The phenylcyclopropane (**24**) undergoes cleavage[15] with thallium(III) acetate in acetic acid, yielding mainly diacetoxypropane (**25**) (92%) and a small amount of *trans*-cinnamyl acetate (**26**) (8%) (eq 6). The reaction can also be effected with thallium(III) oxide because under the reaction conditions it is converted to thallium(III) acetate and thus the use of the moisture sensitive thallium(III) acetate can be avoided. The same cleavage reaction when effected with lead(IV) acetate[16] yields the same products (**25**) (63%) and (**26**) (5%) along with another diacetate (**27**) (32%).

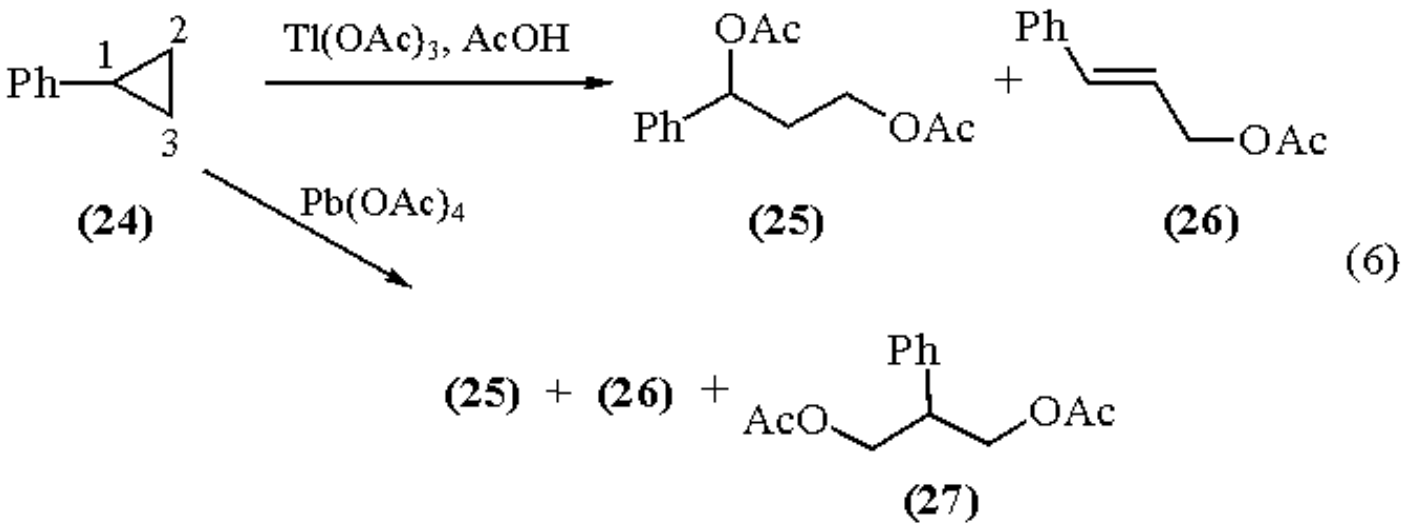

(6)

The formation of the products (**25**) and (**26**) can be accounted for as a result of the cleavage of C-1-C-2, whereas the cleavage of bond C-2-

C-3 yields the diacetate (**27**). It is important to note that the cleavage of cyclopropane with thallium(III) acetate, which requires 120 h at 75 °C for completion, can be effected with lead(IV) acetate in 10 h.

The cyclopropane ring of methyl *ent*-trachyloban-19-oate (**28**) undergoes an interesting cleavage[17] with thallium(III) acetate in acetic acid, affording four products (**29**), (**30**), (**31**), and (**32**) (eq 7).

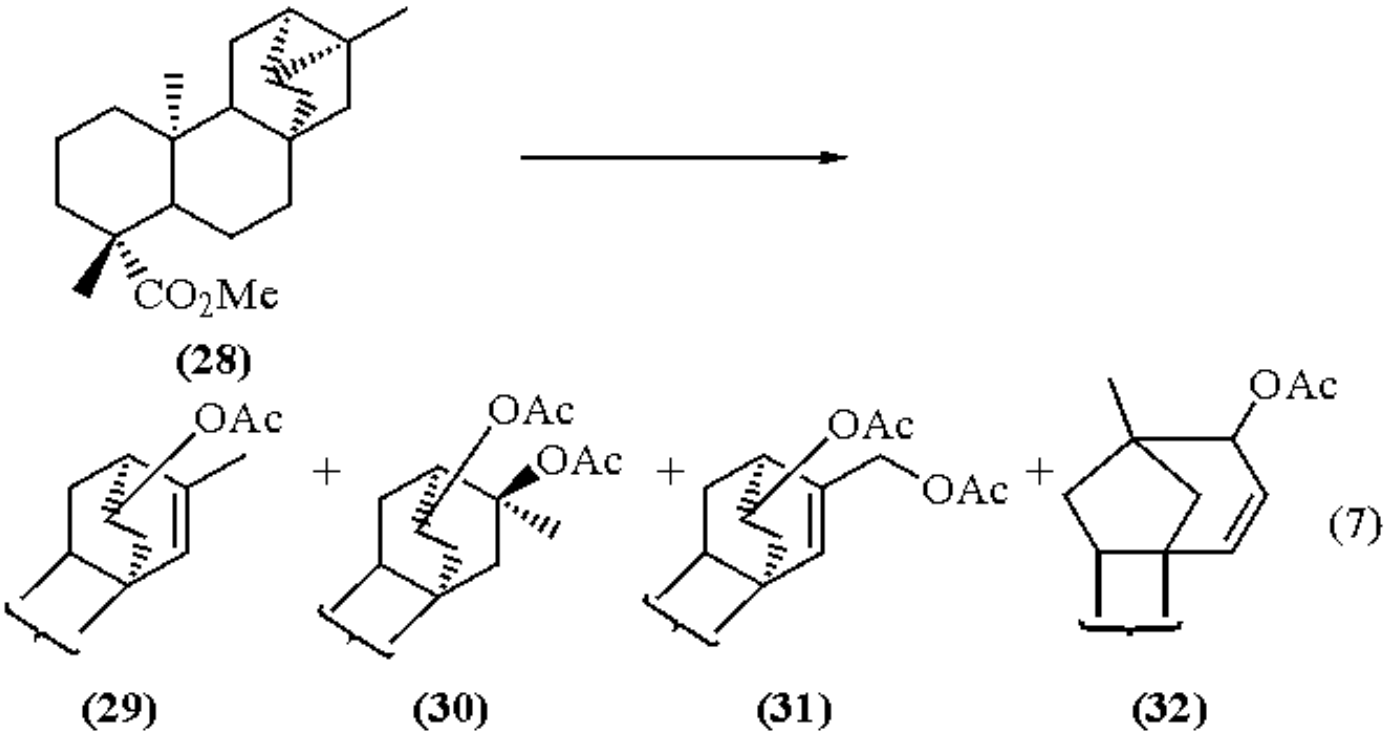

(7)

Oxidation of Enamines.

The oxidation of various enamines with thallium(III) acetate at rt in glacial acetic acid or chloroform followed by hydrolysis gives α-acetoxy derivatives of the parent ketone.[18] Thus morpholinocyclohexene (**33**) was converted to 2-acetoxycyclohexanone (**34**) in 70% yield (eq 8). The same reaction can also be carried out on a combination of cyclohexene and morpholine (in situ generation of enamine) and this gives a superior yield (77%). The yield was lower when the pyrrolidine enamine, instead of morpholine enamine, was used. The yield of α-acetoxy ketone is superior to that obtained by direct oxidation of ketones with thallium(III) acetate or lead(IV) acetate. This particular reaction is of preparative value. It has received application in the synthesis of antitumor alkaloids of the vinblastine group.[19] It is necessary to point out that the synthetic utility of this oxidation reaction depends on the use of the equivalent amount of the reaction components.

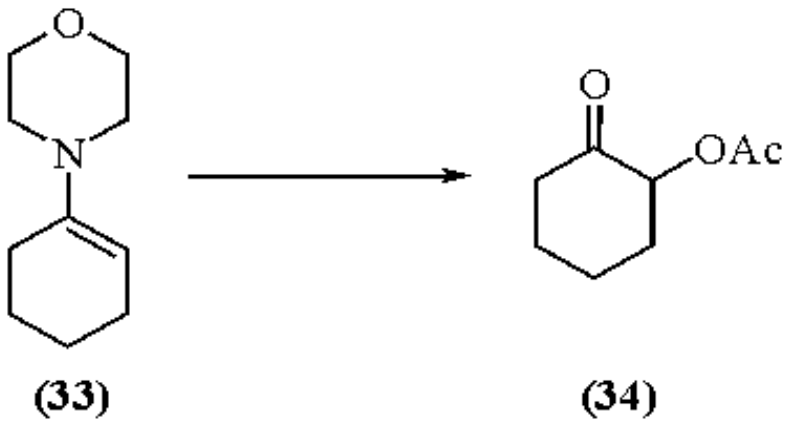

(8)

Oxidation of Ketones.

A number of cyclic ketones, specially steroidal ketones, have been subjected to oxidation by thallium(III) acetate in acetic acid. Three types of reactions have been noted during the oxythallation of ketones,[20] namely acetoxylation, dehydrogenation, and ring contraction. The ketone (**35**) on treatment with thallium(III) acetate in acetic acid yields the dienone (**36**) and acetoxy derivative (**37**) in 23% and 30% yields, respectively (eq 9). Both products presumably arise from the same thallium adduct (A). The ketone (**38**) on similar treatment affords the ketone (**39**) and the ring contracted acid (**40**) (eq 10). The ketone (**39**) probably arises from a thallium enolate (B).

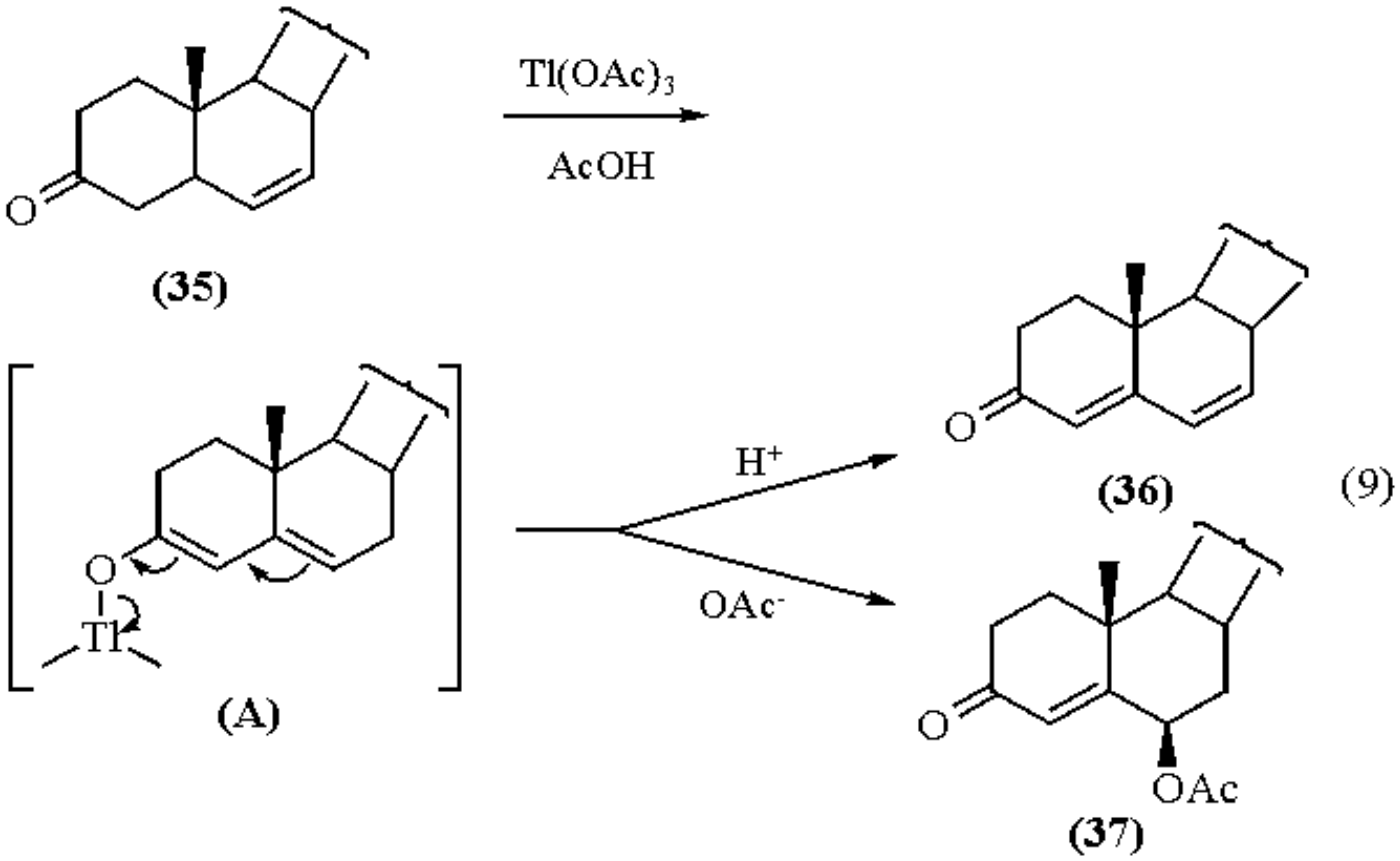

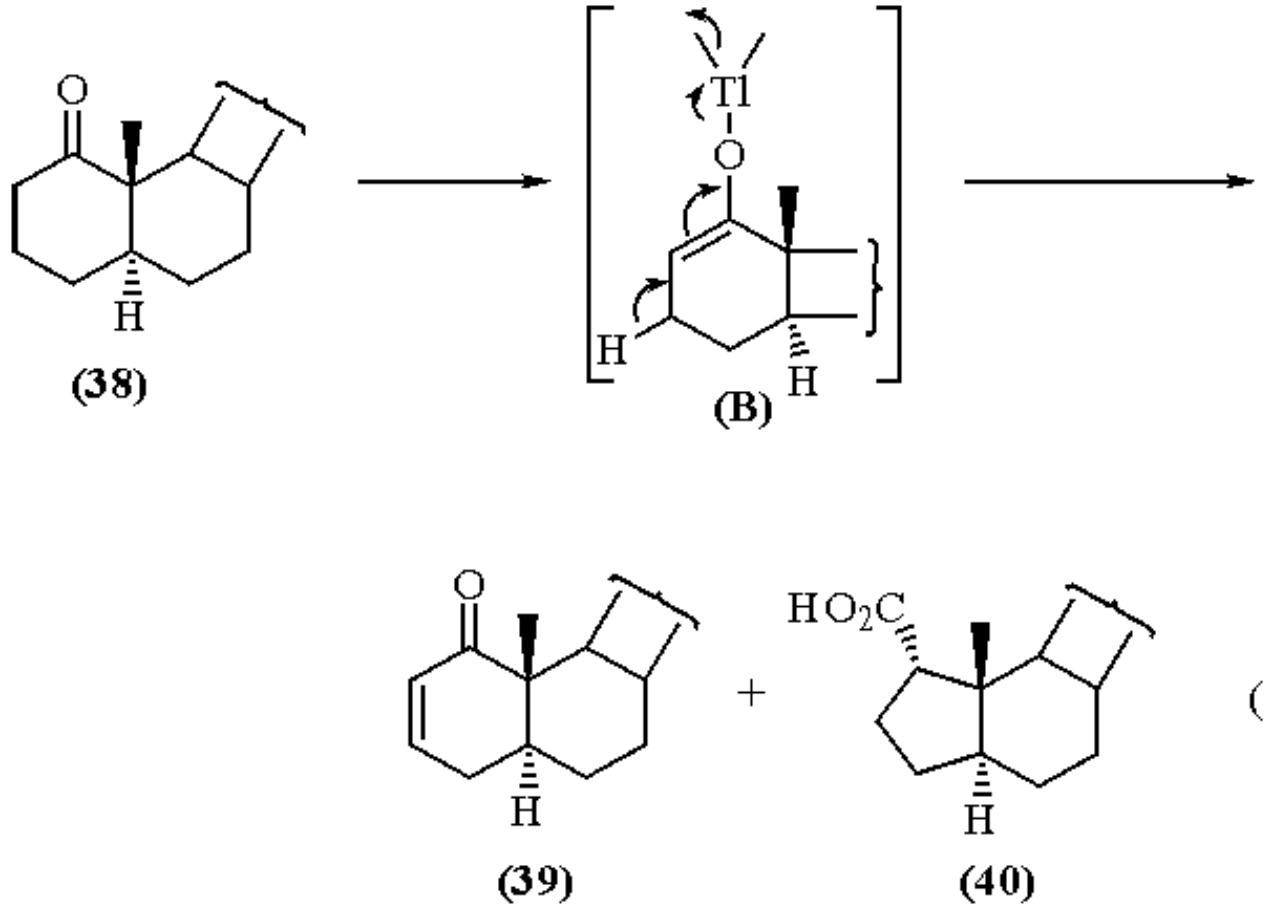

The oxidation of α,β-unsaturated ketones (**41**), (**42**), and (**43**) with thallium(III) acetate in acetic acid yields only the dienones (**44**), (**45**), and (**46**), respectively (eqs 11-13).[21] The formation of other products, as in the case of steroidal ketones, is not observed. The oxidation of these ketones with ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** (DDQ) gives better yields of the dienone, whereas little improvement in the yield of the dienones is observed when the oxidation reaction is repeated with benzeneseleninic anhydride (BSA) (see ***Benzeneseleninic Acid***). These experiments indicate that the potential of thallium(III) acetate is similar to that of DDQ or BSA.

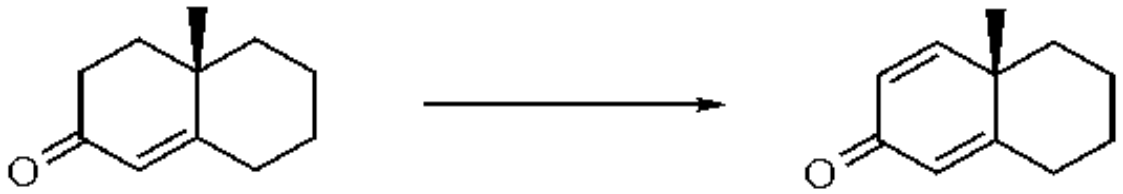

(41) (44) (11)

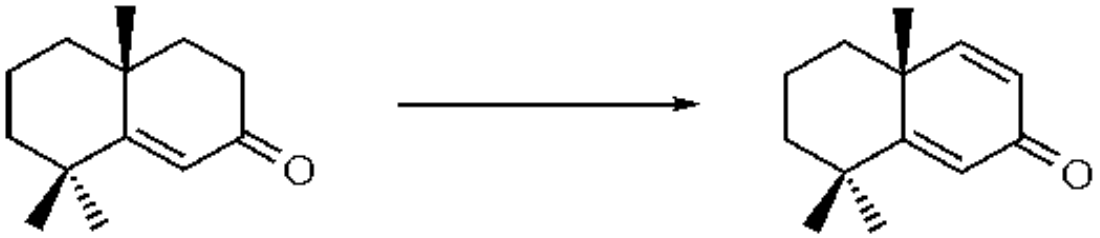

(42) (45) (12)

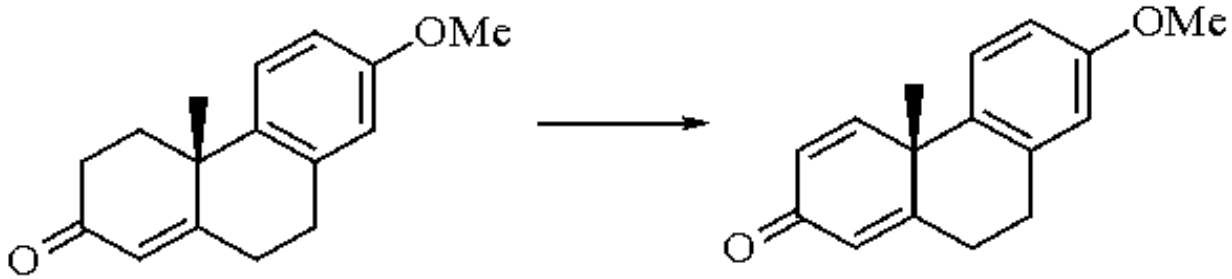

(43) (46) (13)

Oxidative Rearrangements.

Molecular rearrangement has also been observed during oxidation reactions with thallium(III) acetate in acetic acid or methanol. The 3β-acetoxypregn-5-en-20-one (**47**) undergoes Wagner-Meerwein rearrangement with thallium(III) acetate in acetic acid yielding the product (**48**)[20] as a result of attack on the more stable $\Delta^{17,20}$-enol (eq 14). This is in contrast to the kinetically controlled acetoxylation at C-21 in reaction with lead(IV) acetate.[22] The chalcone (**49**) on treatment with thallium(III) acetate in boiling methanol yields the isoflavone (**50**) (eq 15).[23] This finding proves that thallic acid induced rearrangement involves exclusively 1,2-aryl migration and thus demonstrates the direct utilization of chalcones rather than flavanones in isoflavone biosynthesis.

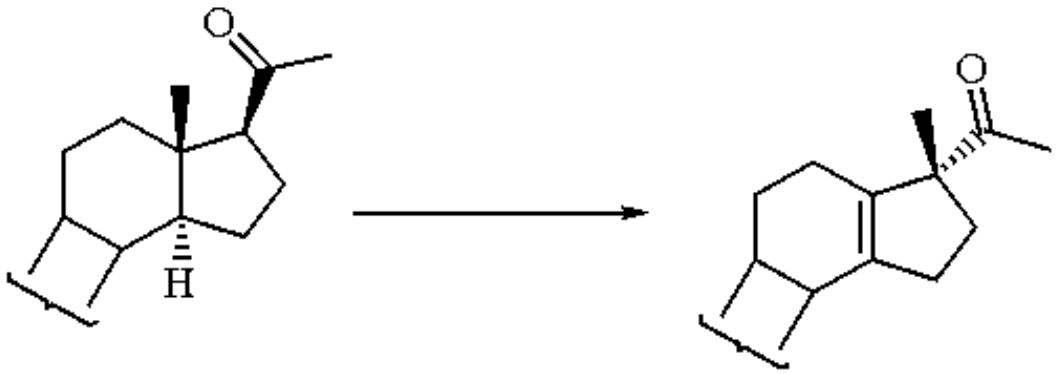

(47) (48) (14)

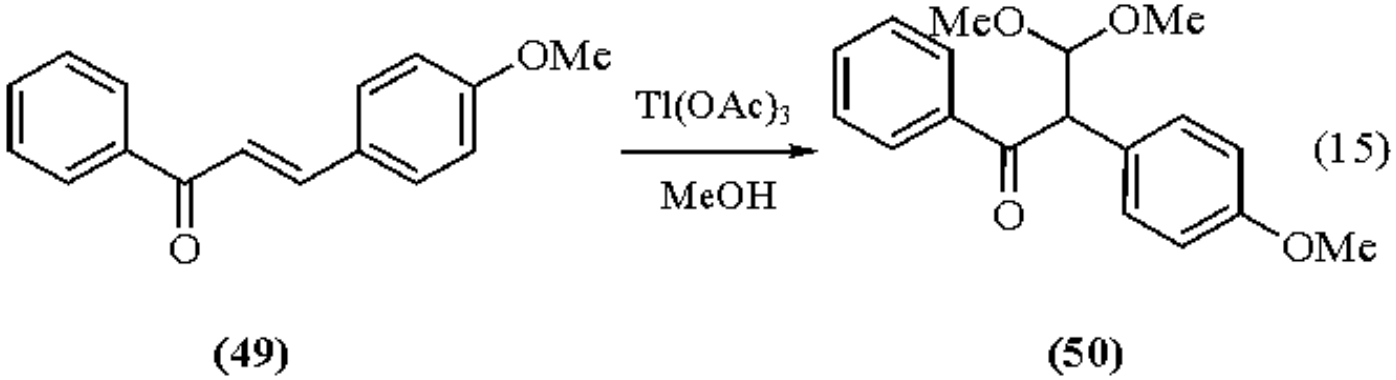

A very interesting rearrangement of the ketone (**51**) was observed with thallium(III) acetate in acetic acid.[21] Instead of the expected dienone (**52**), the catechol derivative (**53**) was obtained (eq 16). This transformation probably involves three processes: (i) acetylation, (ii) dehydrogenation, and (iii) aromatization. A combination of two effects, steric and inductive, is probably responsible for the angular methyl migration and aromatization sequence. The presence of the C-4 methyl group plays an important role in this rearrangement. A similar rearrangement does not occur in the absence of the C-4 methyl group.

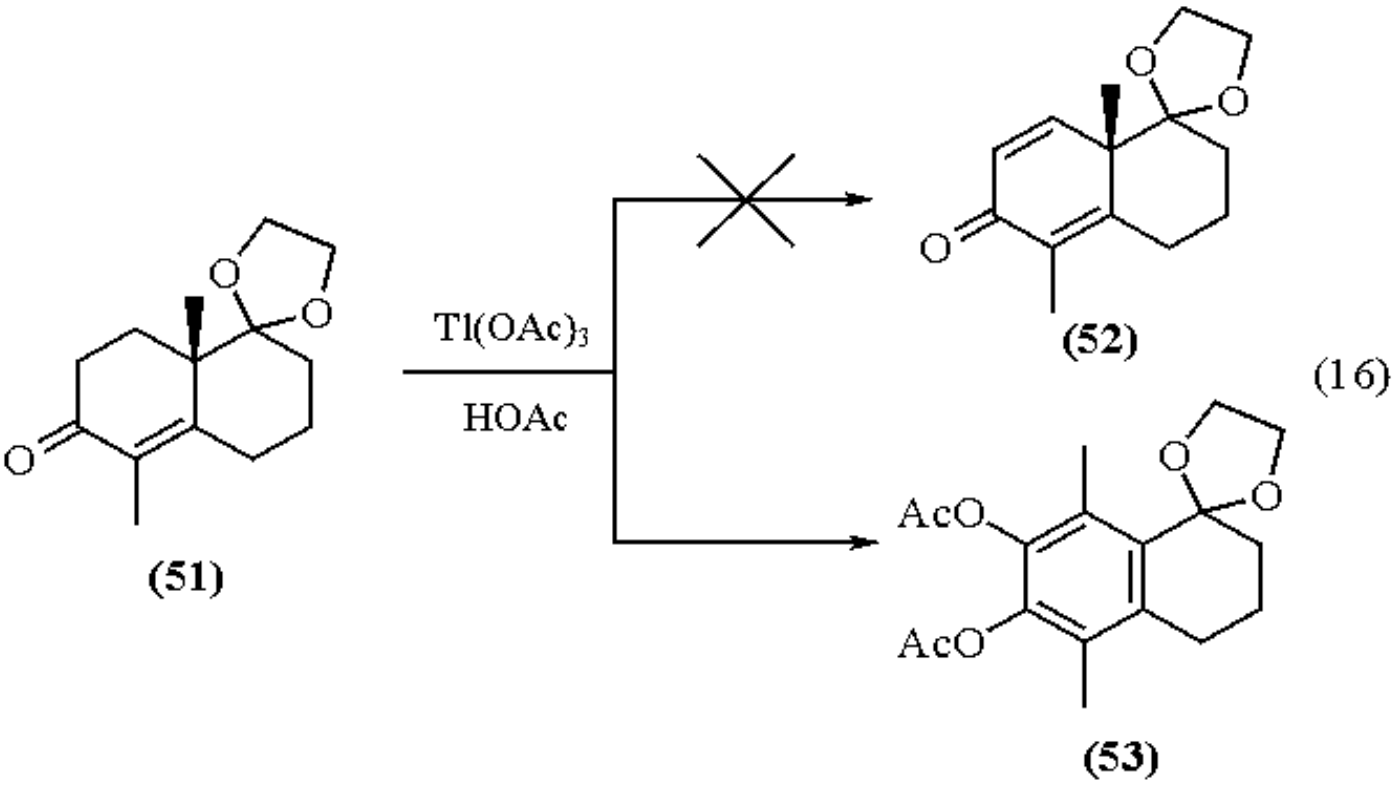

Preparation of Aromatic Bromides.

A mixture of thallium(III) acetate and ***Bromine*** in CCl_4 is a mild and effective reagent for the bromination of aromatic compounds.[24] In addition to experimental simplicity, the reaction is remarkable in that a single pure monobromo isomer is generally obtained and this is the special advantage that the reaction possesses over the vast majority of electrophilic halogenation reactions. Exclusive *p*-substitution is observed with almost all monosubstituted benzenes. It should be noted that electron-withdrawing groups inhibit the bromination of monosubstituted benzenes. The present method is particularly useful for the preparation of bromides for sensitive substrates such as 9-bromoanthracene (**55**) (eq 17), 2-bromobiphenylene (**57**) (eq 18), and 2-bromofluorene (**59**) (eq 19) from anthracene (**54**), biphenylene (**56**), and fluorene (**58**), respectively. It is concluded from experimental results that the reaction involves bromination by molecular bromine catalyzed by either thallium(III) bromide or thallium(III) acetate.

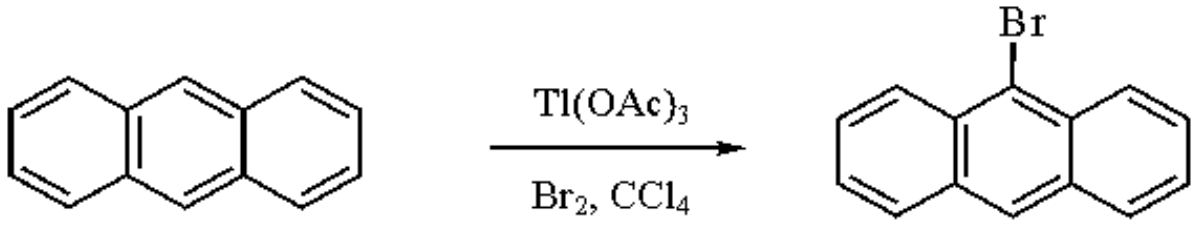

(17)

(54) (55)

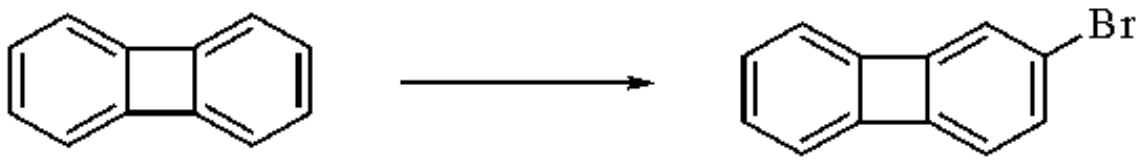

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(56) (57)

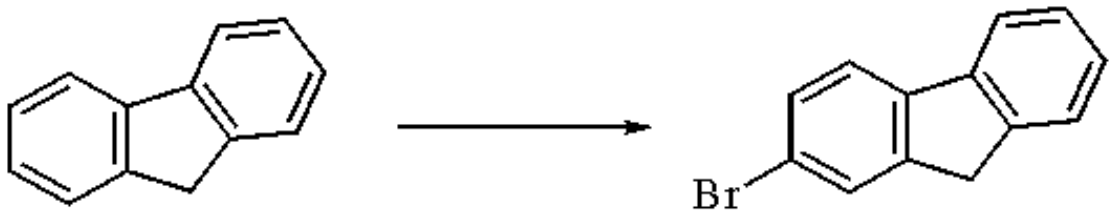

(19)

(58) (59)

Thiols to Disulfides.

A number of thiols undergo oxidation by thallium(III) acetate in chloroform.[25] As an oxidizing agent, thallium(III) acetate is more effective than lead(IV) acetate or mercury(II) acetate. The conversion of thiols (**60**) and (**61**) to disulfides. (**62**) and (**63**), respectively, are the typical examples of this oxidation (eqs 20, 21).

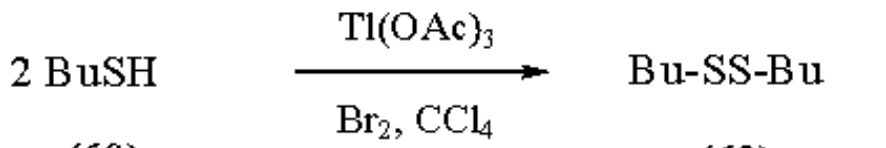

(20)

(60) (62)

(21)

(61) (63)

Oxidation of *p*-Toluenesulfonylhydrazones.

Thallium(III) acetate in acetic acid is useful for the regeneration of both aldehydes and ketones from tosylhydrazones.[26] The cleavage can be effected at room temperature in the case of aldehydes, but reflux temperature is required for ketones. The reagent can also be used for the regeneration of ketones from semicarbazones. The reaction requires reflux temperature and acetoxylation is a side reaction. The reactivity of thallium(III) acetate has been compared with lead(IV) acetate and mercury(II) acetate.[26]

α-Acyloxy Carboxylic Acids.

Thallium(III) acetate has been found to react with a number of aliphatic carboxylic acids, yielding α-acyloxy carboxylic acids.[27] Thus acetic acid (**64**) gives acetoxyacetic acid (**65**) (eq 22). α-Acyloxy carboxylic acids can be hydrolyzed to α-hydroxy acids.

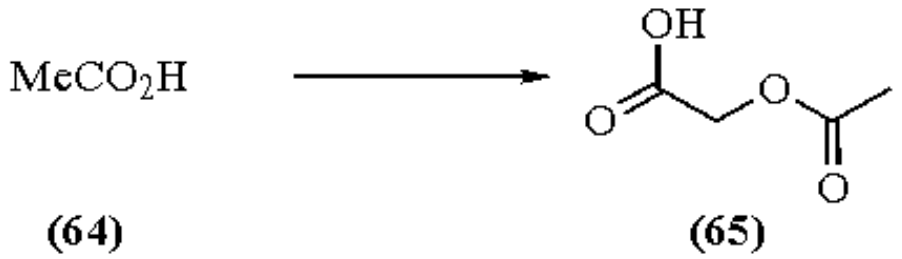

(22)

Oxidative Cyclization.

Thallium(III) acetate has played an important role in oxidative cyclizations of *o*-hydroxyphenyl or *o*-methoxyphenyl ketones, yielding benzofuran compounds.[28] Thus the ketones (**66**) and (**68**) are converted to benzofurans (**67**) and (**69**), respectively, on heating at 75-85 °C with thallium(III) acetate (3 equiv) in acetic acid (eqs 23, 24). Ketones monosubstituted at the α-carbon give good yields (65-84%), while the unsubstituted and disubstituted ketones give lower yields.

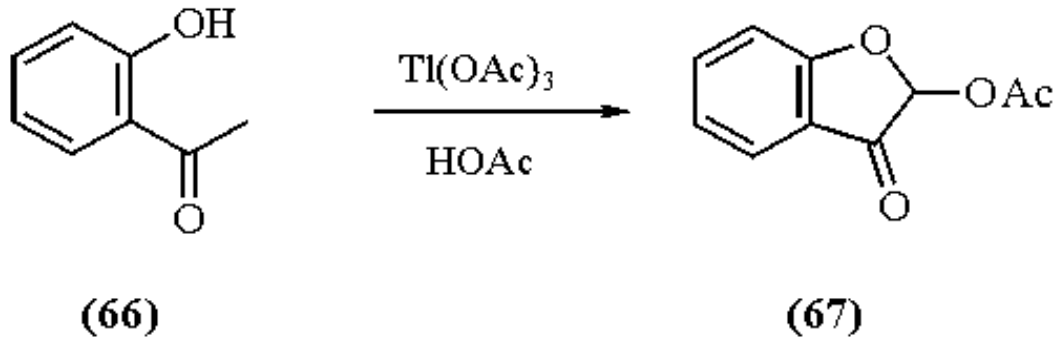

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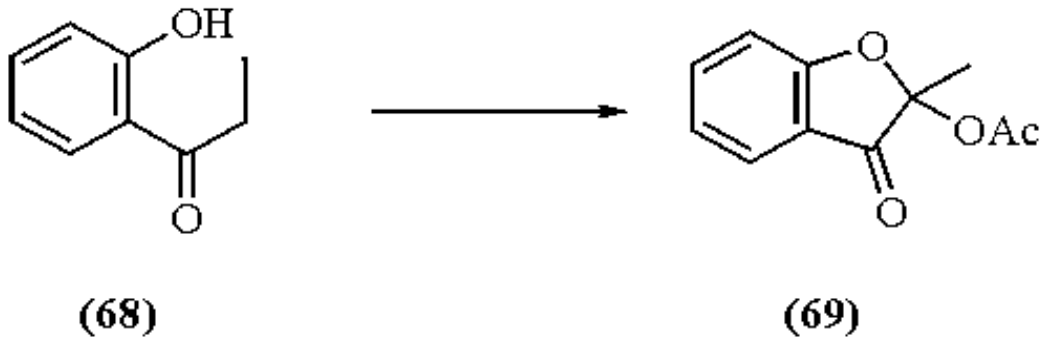

(24)

Homoallylic alcohols undergo cyclization, resulting in the formation of tetrahydrofurans.[29] Thus the alcohol (**70**) is converted to tetrahydrofuran (**71**) by stirring with thallium(III) acetate at rt (eq 25). It was reported[30] that various substituted 4-alkenols undergo electrophilic cyclization with thallium(III) acetate, affording a convenient procedure for the synthesis of *trans*-disubstituted furans. Thus the alkenol (**72**) produces disubstituted furan (**73**) in 60-80% yield (eq 26) with only traces of *cis*-isomer or a tetrahydropyranyl regioisomer. The same reaction using lead(IV) acetate gives (**73**) in only 31% yield.

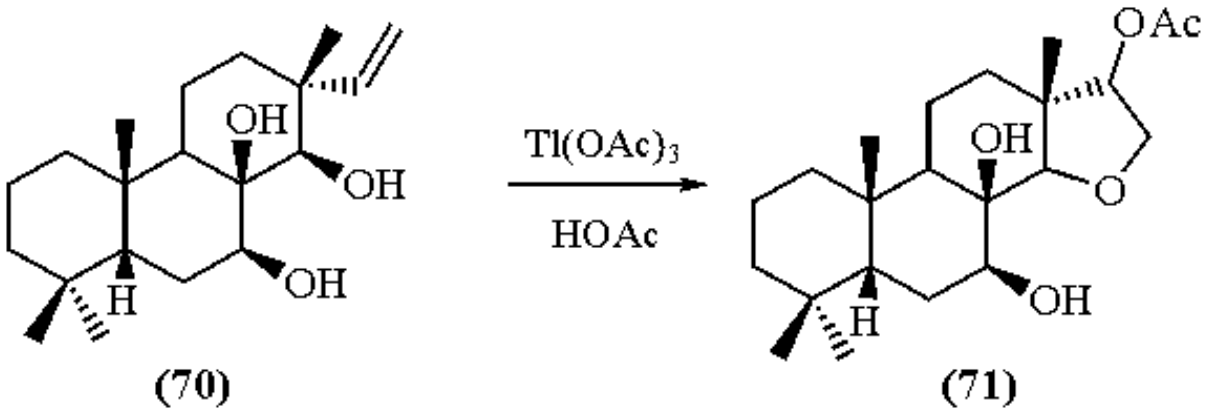

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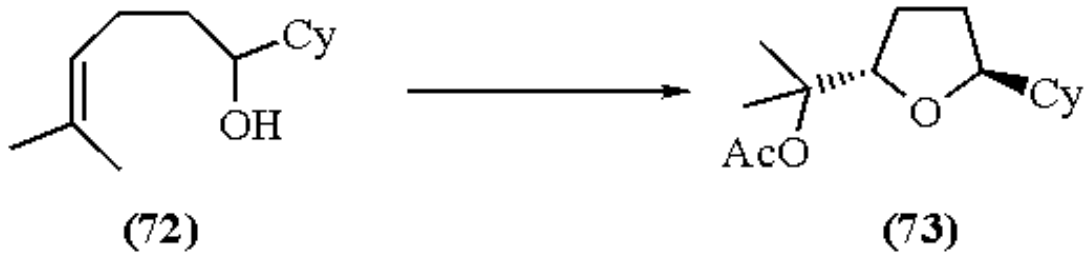

(26)

(72) (73)

Several years ago it was reported[31] that ethylene reacts with acetylacetone in acetic acid containing thallium(III) acetate and perchloric acid to yield the furan derivative (**74**) (eq 27). Similarly, styrene also gives furan derivatives.

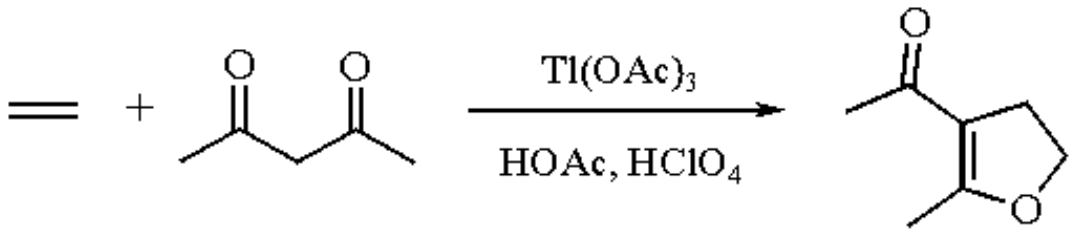

(27)

(74)

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Thallium(III) Acetate-Bromine[1]

$Tl(OAc)_3$-Br_2

[2570-63-0] · $C_6H_9O_6Tl$ · Thallium(III) Acetate-Bromine · (MW 381.53)

[7726-95-6] · Br_2 · Thallium(III) Acetate-Bromine · (MW 159.80)

(brominating agent)

Physical Data: see entries ***Thallium(III) Acetate*** and ***Bromine***.

Form Supplied in: generated in situ by simple admixture of the two commercially available components.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

A mixture of thallium(III) acetate and bromine has been shown to be a superior reagent for the bromination of aromatic compounds (eq 1, Table 1).[2] When care is taken to control the rate of addition of the bromine solution, use of this system results in good selectivity, giving the monobrominated product in very good yields. It has also been shown to be especially useful for the preparation of 9-bromoanthracene, 2-bromobiphenylene, and 2-bromofluorene, compounds otherwise difficult to obtain using conventional bromination methods. Although this methodology has been used successfully on a wide variety of aromatic substrates, it is not suitable for those with strongly deactivating groups on the aromatic ring; if a readily oxidized group is present (e.g. benzyl alcohol or benzaldehyde), oxidation at this site competes with the substitution reaction (see, however, entry 5 in Table 1). Earlier researchers postulated that the reason for the good regioselectivity was the formation of a Tl^{III}-bromine-arene complex whose steric demands regulated the position of the bromine. However, further work[3] demonstrated that excellent regioselectivity results even in the presence of competing steric requirements (eq 2). Thus it was concluded that this reaction provides a demonstration of remarkable electronic control, not steric governance.

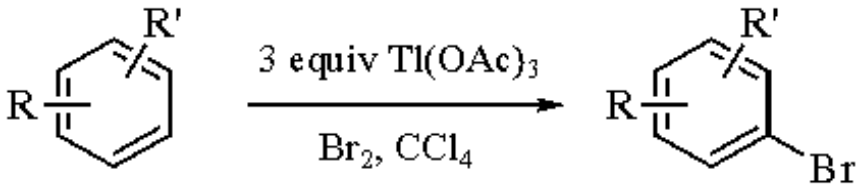

(1)

Table 1 Bromination of Aromatic Substrates With $Tl(OAc)_3/Br_2$

Entry	R	R¢	Product	Yield (%)
1	H	H	Bromobenzene	83
2	Ph	H	4-Bromobiphenyl	93
3	MeNH	H	*p*-$CH_3NHC_6H_4Br$	62
4	Br	H	*p*-Dibromobenzene	73
5	CHO	4-MeO	3-Bromo-4-methoxybenzaldehyde	66
6	Thiophene		2-Bromothiophene	82
7	Fluorene		2-Bromofluorene	80

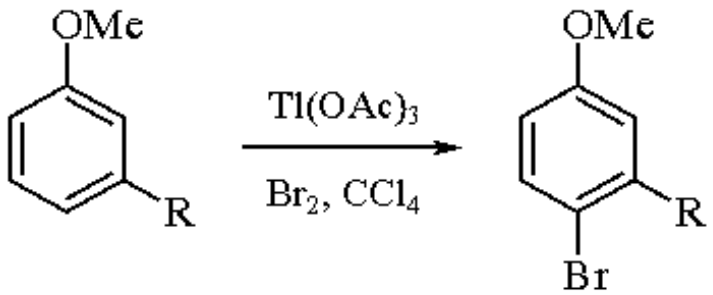

(2)

R = Me, 96%; Et, 93%; *i*-Pr, 88%; *t*-Bu, 40%

Other thallium reagents have also been used synthetically in conjunction with elemental bromine. For example, there have been several examples of the use of thallium(I) reagents with bromine to affect a Hunsdieker reaction (eq 3).[4] The transformation begins with the conversion of the carboxylic acid to the thallium salt, which is then treated with a solution of bromine in carbon tetrachloride to accomplish the bromodecarboxylation. The reaction is successful only for primary carboxylic acids. It is interesting to note that a thallium(III) species is involved in the reaction; it has been determined[5] that 1.1 equiv of bromine is used to convert the thallium carboxylate to a Tl^{III} carboxylate dibromide, which is then converted to the alkyl bromide product upon treatment with an additional 0.5 mol bromine.

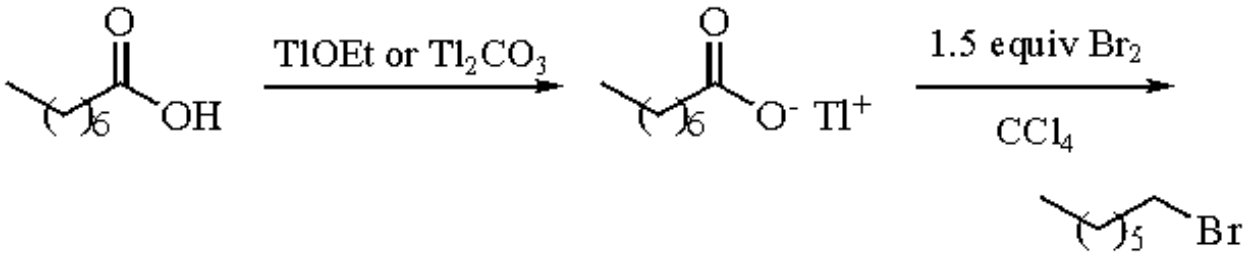

(3)

Related Reagents.

Bromine; ***Thallium(III) Acetate***; ***Thallium(I) Bromide***; ***Thallium(I) Carbonate***.

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2. (a) McKillop, A.; Bromley, D.; Taylor, E. C. *TL* **1969**, 1623. (b) McKillop, A.; Bromley, D.; Taylor, E. C. *JOC* **1972**, *37*, 88.
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Thallium(I) Acetate-Iodine

TlOAc-I_2

[563-68-8] · $C_2H_3O_2Tl$ · Thallium(I) Acetate-Iodine · (MW 263.43)

[7553-56-2] · I_2 · Thallium(I) Acetate-Iodine · (MW 253.80)

(preparation of *vic*-iodoacetates for Prevost (dry) and Woodward-Prevost (wet) conversion of alkenes into *trans*- and *cis*-diols;[1] for iodolactonizations,[2] iodination of phenols,[3] formation of α-iodo ketones[4])

Physical Data: TlOAc: mp 131 °C; *d* 3.76 g cm^{-3}. I_2: mp 113.5 °C; bp 184.35 °C; *d* 4.93 g cm^{-3}.

Solubility: TlOAc: v sol cold H_2O, EtOH, $CHCl_3$; insol acetone. I_2: sparingly sol hot H_2O (0.078 g/100 mL); sol ether (20.6 g/100 mL), EtOH (20.5 g/100 mL).

Preparative Methods: prepared in situ by heating ***Thallium(I) Acetate*** (2 equiv) with dry acetic acid under reflux for 1 h, and then treating the cooled mixture with the alkene (1 equiv) and ***Iodine*** (1 equiv). The resulting suspension is stirred and heated at reflux, filtered from yellow thallium(I) iodide, and worked up[1] to give the *vic*-diol ester. Alternatively, a dichloromethane solution of iodine (1 equiv) is added dropwise to a stirred suspension of thallium(I) acetate (1 equiv) in dichloromethane containing the alkene (1 equiv) and the mixture worked up to give the *vic*-iodocarboxylate.

Handling, Storage, and Precautions: thallium salts are extremely toxic and thus great care must be taken in their use and disposal. All operations should be carried out in an efficient fume hood, and rubber gloves should be worn. Dispose of thallium wastes carefully.[5-8]

α-Iodocarboxylations.

The reaction of an alkene with iodine and thallium(I) acetate in the ratio 1:1:1.2 in acetic acid at room temperature gives the *trans*-α-iodoacetate, generally in yields of 85-89% (eq 1). Thallium(I) benzoate in benzene can also be used.[1,2]

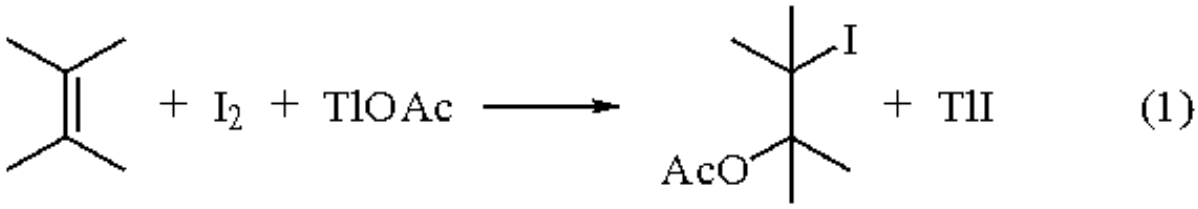

(1)

Since the iodocarboxylates can be transformed into appropriate derivatives of either *syn*- or *anti*-diols by suitable choice of conditions for solvolysis, the reaction provides an inexpensive alternative to the Prevost reaction,[9] which uses silver(I) carboxylates. Thus solvolysis of a *trans*-iodoacetate in wet acetic acid gives the corresponding *cis*-hydroxyacetate; *trans*-diacetates are obtained by solvolysis in dry acetic acid with added sodium acetate. Unlike silver(I) carboxylates, thallium(I) carboxylates are readily prepared in high yield as crystalline solids and they do not induce solvolysis at room temperature.[2,10] With the exception of 3-phenylpropene, reactions with unsymmetrical alicyclic alkenes are regioselective, addition occurring in the Markovnikov orientation (eq 2).

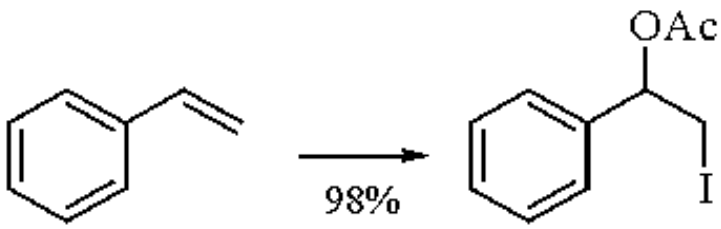

(2)

Marked differences exist between the modes of reaction of thallium(I) carboxylates and silver(I) carboxylates. No reaction occurs between the thallium(I) carboxylate, iodine, and an alkene unless all three are present, in contrast to the silver(I)-mediated systems where prior formation of the Simonini complex between the acyl hypoiodite, the silver carboxylate, and iodine is the case. Thus it has been suggested that an iodonium ion is formed from the interaction of a thallium(I) species and an alkene-iodine π-complex (eq 3), which gives the iodocarboxylate that then reacts by a normal Woodward or Woodward-Prevost mechanism.[1]

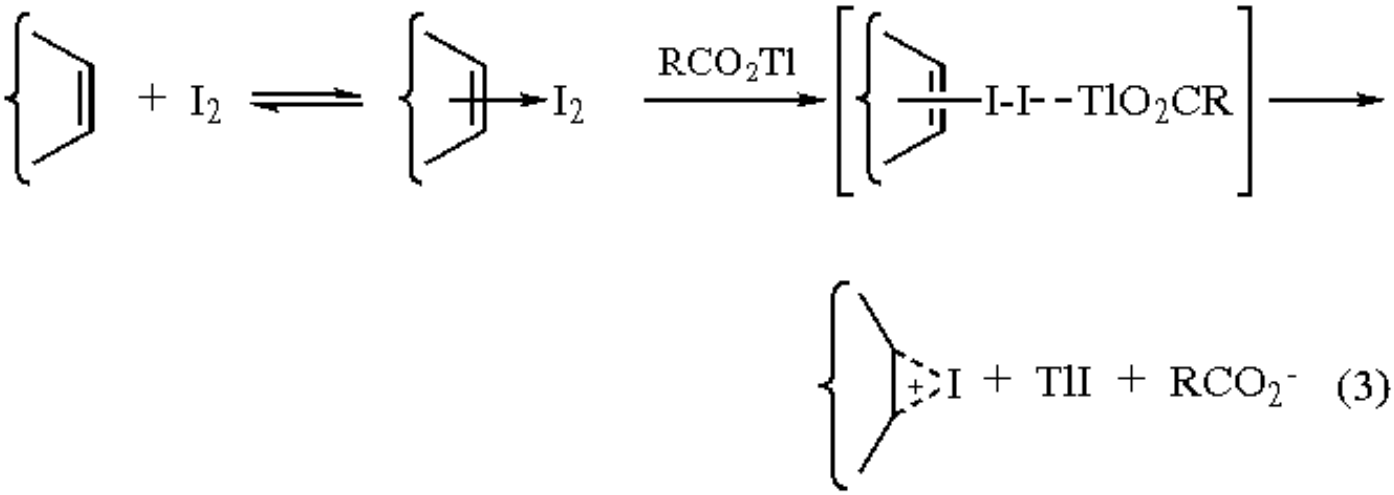

Reaction of thallium(I) acetate-iodine with 1-methylcyclohexene in wet acetic acid at 20 °C gives a *trans*-iodoacetate as the major product, but also affords a significant amount of regioisomer (eq 4), indicating that the high regioselectivity observed for acyclic compounds does not apply to substituted carbocycles.[11] Likewise, 3-*t*-butylcyclohexene gives a mixture (ca. 3:1) of stereoisomeric iodoacetates (eq 5).[12]

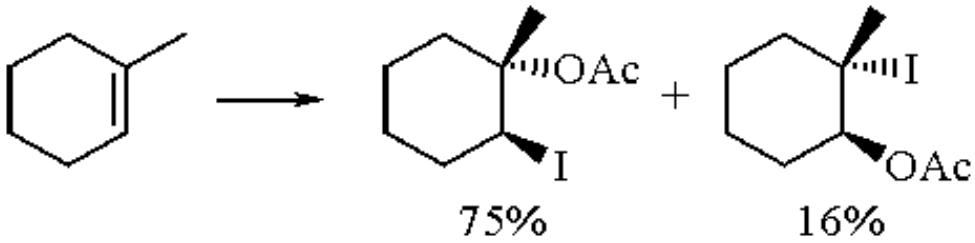

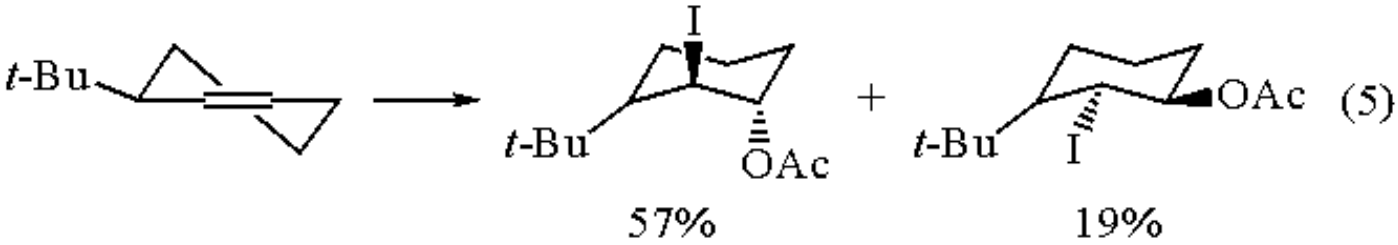

These results can be explained based on the assumption that two stereoisomeric iodonium ions are formed in a reversible pre-equilibrium, which then react at rates dependent on steric and conformational factors.

Substituted cyclopropanes (e.g. phenylcyclopropane) react with thallium(I) acetate-iodine less readily than alkenes, but give ring opened 1,3-disubstituted propanes as the major products, and in some cases products from solvolysis of intermediate iodoacetates (eq 6).[13]

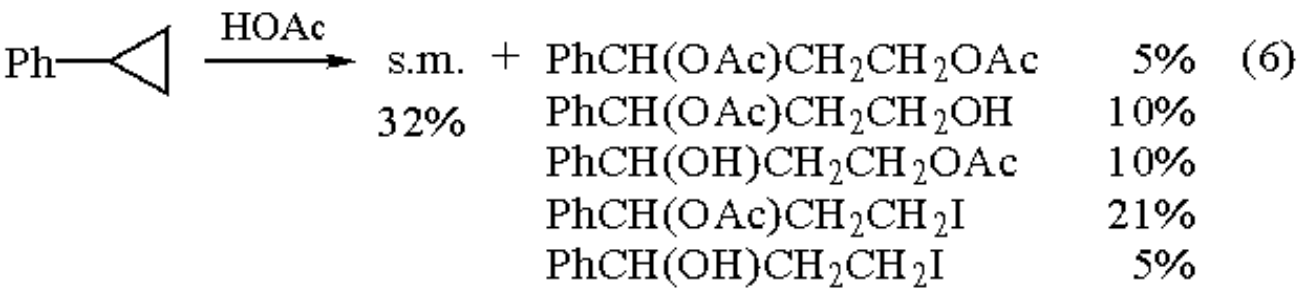

Neighboring groups influence the course of reactions by taking part in rearrangements which typically involve carbocationic intermediates.[14]

The *trans vic*-iodoesters formed from alkenes are readily converted into *cis*-hydroxyesters by oxidative displacement with ***m-Chloroperbenzoic Acid*** (eq 7).[15]

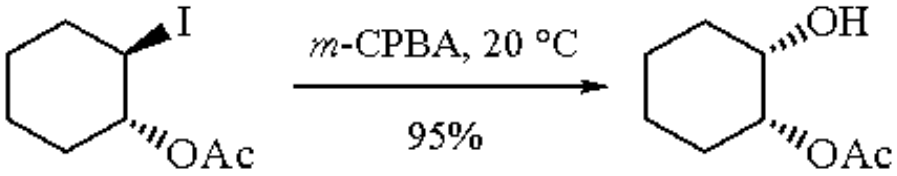

(7)

Unlike iodine(I) acetate (prepared from iodine(I) chloride and ***Silver(I) Acetate***) which oxidatively cleaves *vic*-diols rapidly and in high yield at 20 °C, thallium(I) acetate and iodine(I) chloride has no effect.[16]

Iodolactonizations.

Addition of iodine in ether to a suspension of an unsaturated thallium(I) carboxylate in ether at room temperature using a stoichiometric ratio of 1:1 gives high yields of iodolactones.[17] Addition to β,γ-unsaturated acids can in appropriate cases give β-lactones as the products of reaction under kinetic control. Rearrangement then gives the isomeric γ-lactone (eq 8). Using thallium(I) acetate and iodine in a nonpolar solvent at 0 °C gives even better yields of the lactones (eq 8).[18] This reaction has been extended to bromolactonization using ***Thallium(I) Carbonate*** and bromine.[19]

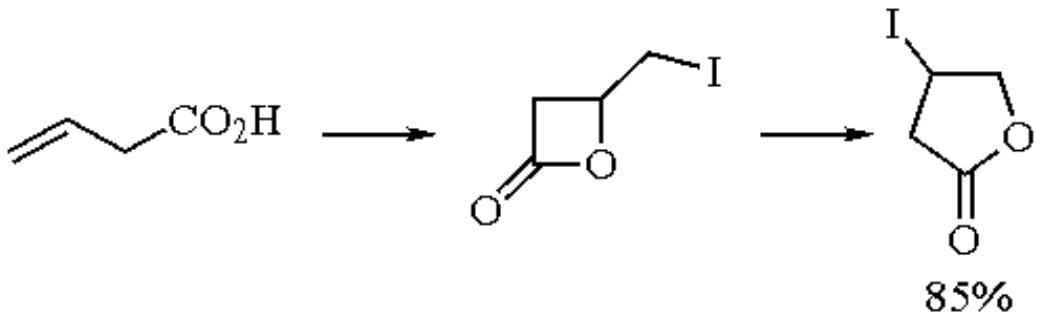

(8)

Iodination of Phenols.

Iodination of activated phenols with thallium(I) acetate-iodine using a ratio of 1:1:1.2 gives selective *ortho*-iodination (eq 9).[3] Use of dichloromethane as the solvent rather than acetic acid results in increased solubility of the iodine and facilitates workup since neutralization of the acetic acid is no longer necessary.

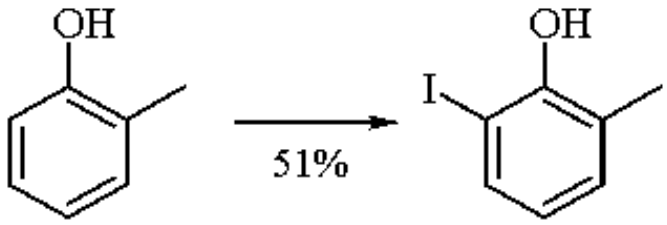

(9)

Formation of α-iodo Ketones.

Treatment of enol acetates with thallium(I) acetate-iodine affords high yields of α-iodo ketones (eq 10).[4] The α-iodo ketones are probably formed via an acetoxyiodonium ion by a pathway similar to that for iodocarboxylations of alkenes.

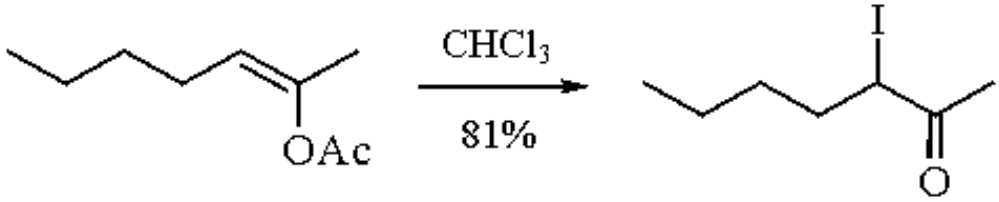

(10)

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14. Cambie, R. C.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *JCS(P1)* **1976**, 845.
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Richard C. Cambie, Peter S. Rutledge & Paul D. Woodgate

University of Auckland, New Zealand

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Thallium(I) Bromide[1]

TlBr

[7789-40-4] · BrTl · Thallium(I) Bromide · (MW 284.28)

(Lewis acid; reagent for coupling and bromination)

Physical Data: mp 480 °C.

Solubility: sol 2360 parts water.

Form Supplied in: pale yellow crystalline powder; commercially available.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

The primary utility of thallium(I) bromide is in Ullmann-like coupling reactions of aryl and alkyl Grignard reagents. A very practical method for the synthesis of biaryls from aryl Grignards using TlBr as a reagent has been developed (eq 1).[2] These reactions are operationally simple and proceed in good to high yields, thus providing a good alternative to similar coupling reactions mediated by other metals. The optimal ratio of thallium bromide to aryl Grignard reagent was found to be 1:1.5. Thallium bromide is regenerated during the coupling reaction. Coupling of two different aryl Grignards with thallium bromide provides all three possible biphenyls. The unsymmetrical biphenyl is generally the major product but the formation of multiple products makes this process of marginal utility. The coupling reaction of 3- and 4-substituted aryl Grignards provide the corresponding biphenyls in good yields. The only drawback to the reaction is that *ortho*-substituted aryl Grignards give no coupling products.

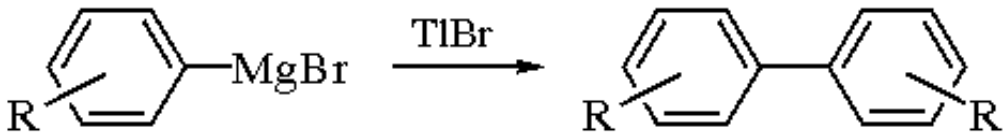

(1)

R = H, 85%; 4-Me, 83%; 4-OMe, 99%
4-Cl, 73%; 4-F, 73%; 3-Me, 85%

This reaction has been extended to secondary aliphatic bromides.[3] The reactions proceed only in moderate yields (eq 2). Similar reactions with primary aliphatic Grignards give only traces of the coupled products.

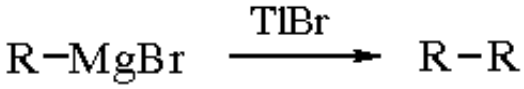

(2)

R = cyclohexyl, 58%; cyclopentyl, 56%; 2-pentyl, 50%

Thallium(I) bromide serves as a catalyst for nuclear bromination of aromatic compounds (eq 3).[4] For example, benzene can be converted to bromobenzene in moderate yields. Similarly, toluene reacts to produce a mixture of *o*- and *p*-bromotoluene, and the product resulting from benzylic bromination was not observed. These brominations proceed more effectively with Tl^{III} salts as compared to Tl^{I} salts.

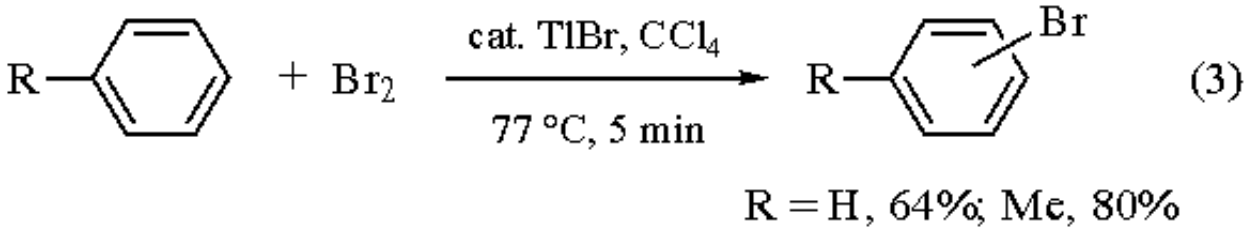

Triorganothallium derivatives are useful reagents in organic synthesis. The utility of this reagent in ketone synthesis has been reported.[5] Thallium(I) bromide serves as a precursor for the preparation of triorganothallium reagents. Two methods for the preparation of this reagent are illustrated in eqs 4 and 5.[5,6]

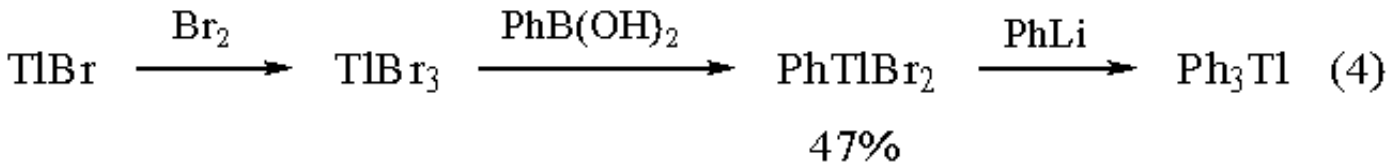

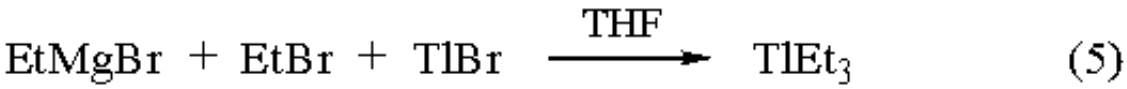

Related Reagents.

Thallium(III) Acetate-Bromine.

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1. (a) McKillop, A. *PAC* **1975**, *43*, 463. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465.
2. (a) McKillop, A.; Elsom, L. F.; Taylor, E. C. *T* **1970**, *26*, 4041. (b) Elsom, L. F.; McKillop, A.; Taylor, E. C. *OS* **1976**, *55*, 48.
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Thallium(I) Carbonate[1]

Tl_2CO_3

[6533-73-9] · CO_3Tl_2 · Thallium(I) Carbonate · (MW 468.77)

(base; promoter of coupling reactions)

Physical Data: mp 272 °C; *d* 7.110 g cm^{-3}.

Solubility: sol 24 parts water; 3.7 parts boiling water; sol typical organic solvents; insol alcohol.

Form Supplied in: white solid; commercially available. *Drying:* decomposes on heating.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium carbonate exhibits a variety of interesting applications. The most important of these is the use of thallium carbonate in the Suzuki palladium-catalyzed cross-coupling reaction of alkylboronic esters.[2] As shown in eq 1, the coupling reaction occurs in high yield to give the hydrocarbon product. ***Thallium(I) Hydroxide*** can also be used as the base for this valuable transformation, but thallium carbonate offers the advantage of nonaqueous conditions.

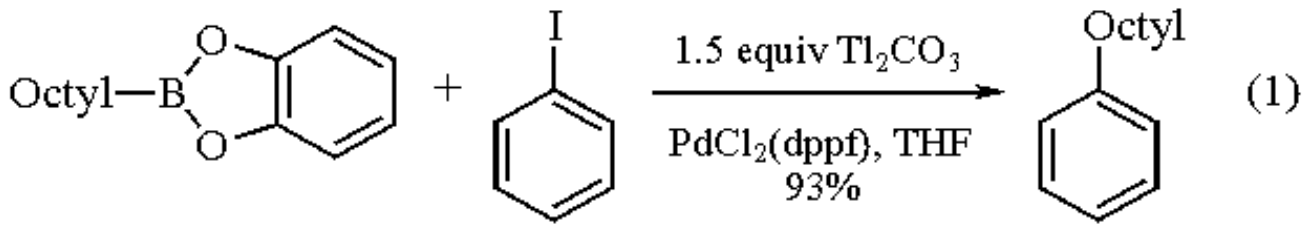

Thallium carbonate has also been used to generate thallium carboxylates, which are then transformed to the alkyl bromide in a thallium version of the Hunsdieker reaction (eq 2).[3] These researchers found that the carbonate was a better reagent than thallium ethoxide for preparing the thallium carboxylates, due to its increased stability.

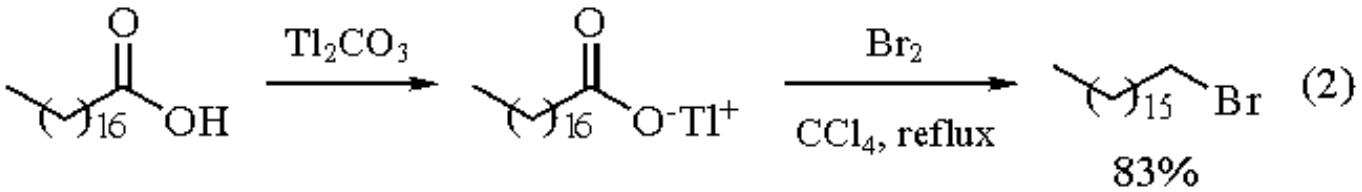

Both thallium carbonate and ***Thallium(III) Nitrate*** have been examined as additives for promotion of a palladium-catalyzed tandem cyclization-anion capture protocol (eq 3).[4] The presence of this particular additive affects the ratio of the cyclized product (**2**) to the direct capture product (**1**).

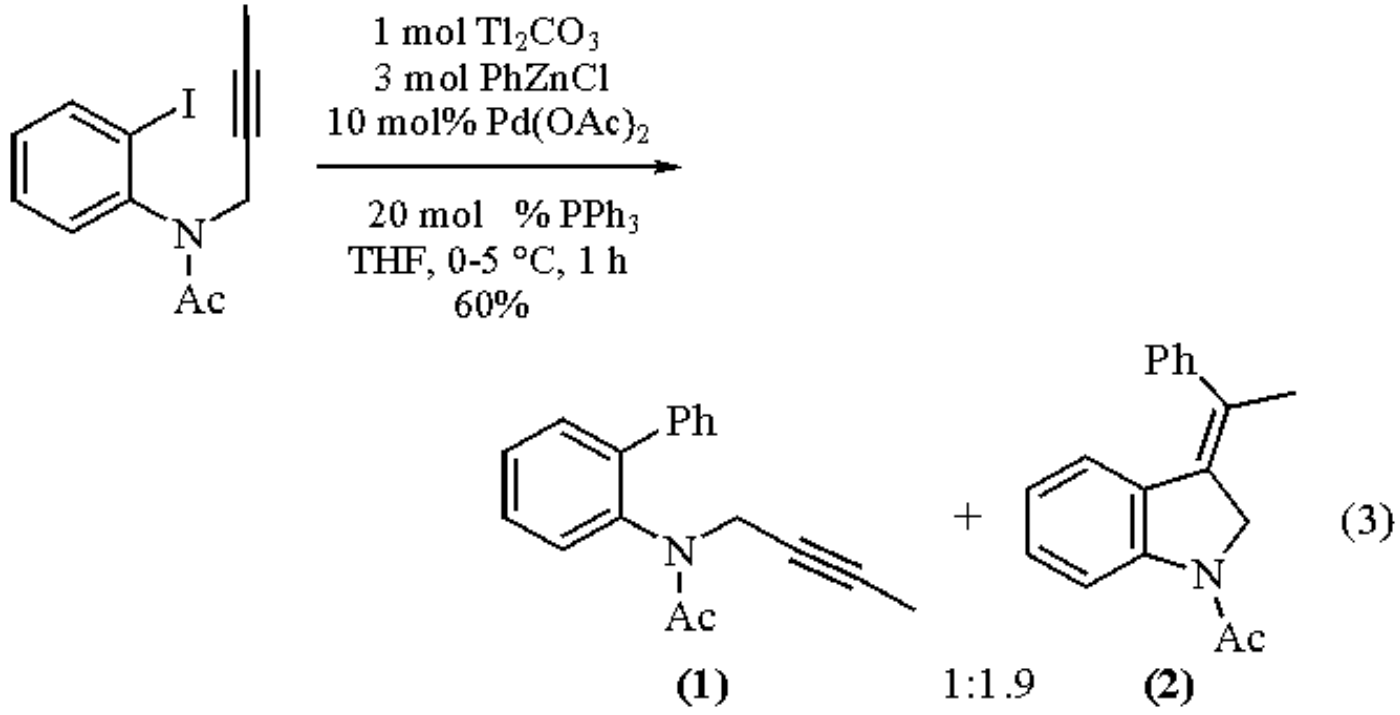

The use of thallium carbonate to generate macrocyclic lactones has been investigated,[5] as shown in eq 4. While the thallium salt did effectively promote the ring closure, it was found that ***Cesium Carbonate*** was a superior reagent in this regard.

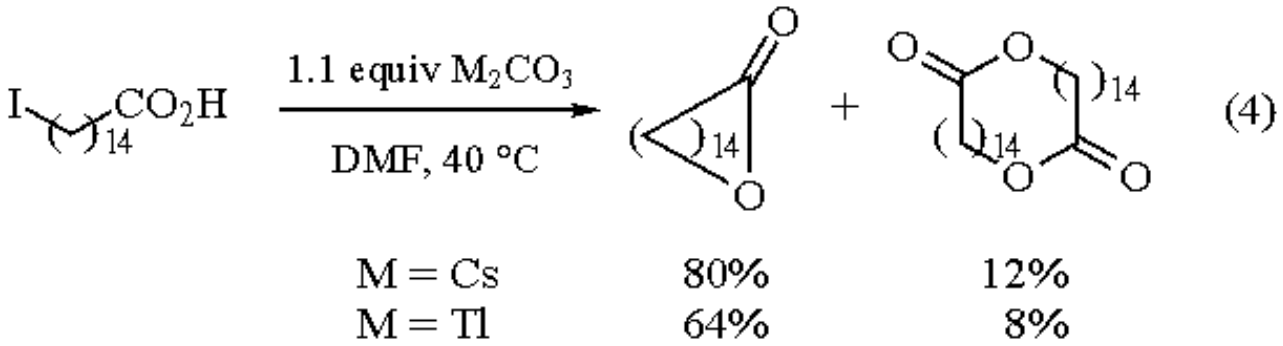

Thallium carbonate has been utilized in transesterifications with the sensitive epoxy alcohol 2,3-epoxypropanol (eq 5).[6] It was found that thallium salts could mediate the transesterification without accompanying decomposition of the epoxypropanol. A very wide range of thallium salts (both Tl^{I} and Tl^{III}) was examined. There was no significant difference in the outcome of the reaction among the various salts.

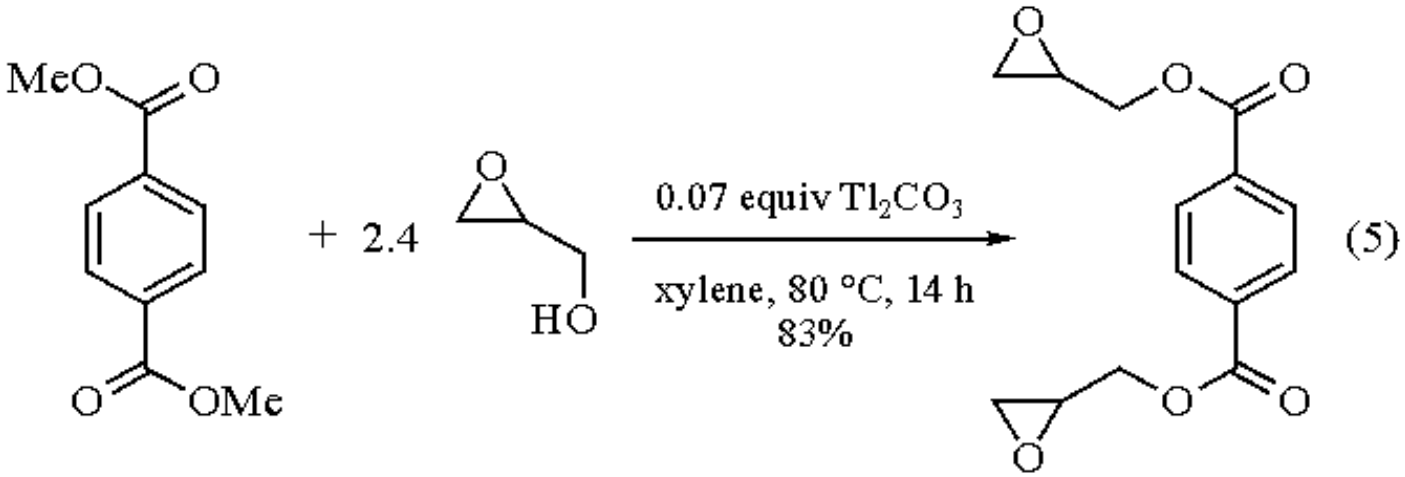

Thallium carbonate is also used in the preparation of thallium zeolite, an insoluble promoter for *O*-glycosylation reactions.[7] The zeolite is prepared by stirring 4&AAring; molecular sieves with thallium carbonate in water, followed by washing with water, then acetone, and drying at 190 °C. The glycosylation reaction, using a fourfold excess of the zeolite, proceeds smoothly in 30-90% yields, with the thallium zeolite behaving similarly to Ag, Co, and Cd zeolites.

1. (a) McKillop, A. *PAC* **1975**, *43*, 463. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465.
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4. Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *TL* **1990**, *31*, 6573.
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Thallium(I) Cyclopentadienide[1]

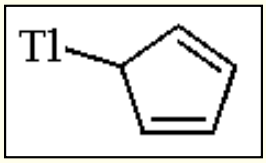

[34822-90-9] · C_5H_5Tl · Thallium(I) Cyclopentadienide · (MW 269.48)

(cyclopentadienyl ligand)

Physical Data: mp >300 °C.

Solubility: sol organic solvents.

Form Supplied in: light yellow solid readily prepared from thallium hydroxide and dicyclopentadiene;[2] commercially available. *Drying:* purified by sublimation.

Handling, Storage, and Precautions: stable for several months if stored under nitrogen in a Schlenk flask kept in the dark. All thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium(I) cyclopentadienide is a versatile reagent for the introduction of the cyclopentadienyl ligand into metal complexes.[3] For example, a novel iridium sandwich complex was prepared in 37% yield starting from TlCp (eq 1).[4]

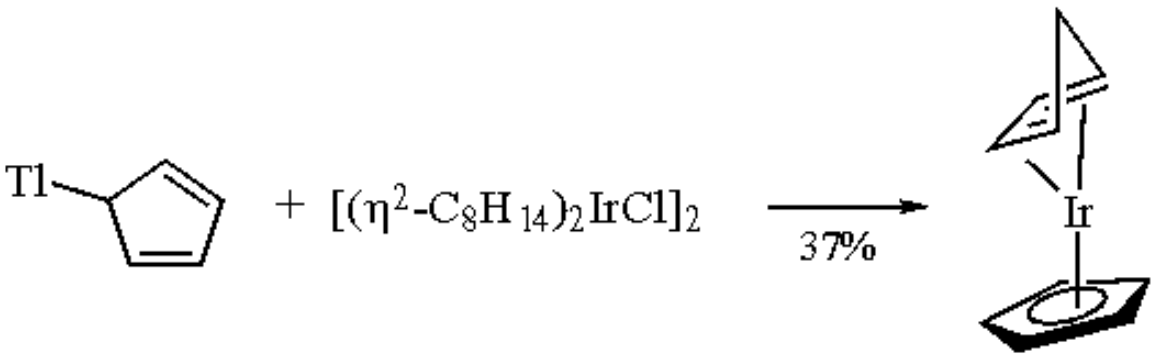

(1)

Monosubstituted cyclopentadienes can be readily prepared from the reaction of TlCp and alkylating agents. This reagent is superior compared to lithium or sodium cyclopentadienide, since isomerization of the resultant monosubstituted cyclopentadiene is minimal. Additionally, product isolation is very simple since the thallium halide byproduct is very insoluble in organic solvents. In a synthesis of prostaglandins, monosubstituted cyclopentadienes were prepared using thallium cyclopentadienide (eq 2).[5] The same strategy has been used by others to prepare several 5-substituted 1,3-cyclopentadienes cleanly.[6]

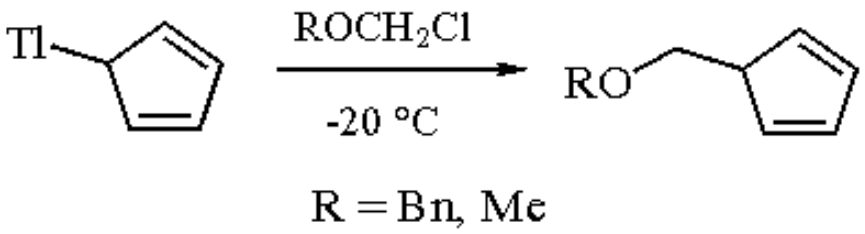

(2)

TlCp is also a convenient precursor for the preparation of 5-halo-1,3-cyclopentadiene (eq 3)[7] and 5-heteroatom-substituted 1,3-cyclopentadiene (eq 4).[8]

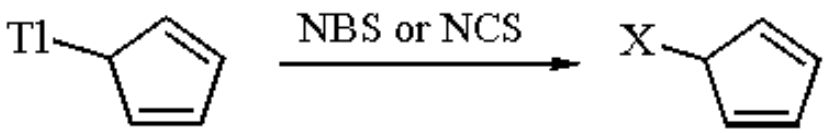

(3)

X = Br, Cl

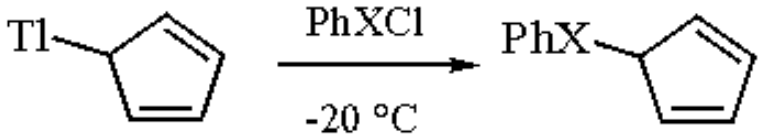

(4)

X = S, Se

TlCp reacts with acyl iodides to provide 1-acyl-1,3-cyclopentadienes in good yields (eq 5).[9] The product dienes were used in an ensuing Diels-Alder reaction without isolation. The corresponding reaction with acid chlorides was too slow to be of practical utility.

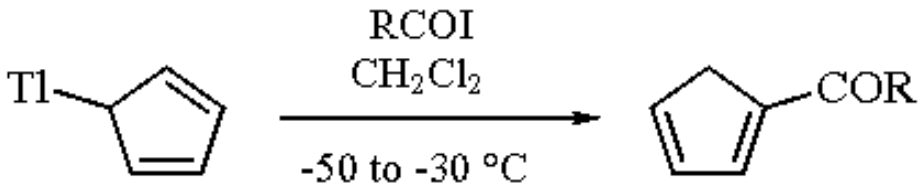

(5)

R = Me, C_7H_{15}, *i*-Pr, *t*-Bu

TlCp reacts with electron-deficient alkenes such as ***Tetracyanoethylene*** by an addition-elimination pathway to produce an ionic thallium(I) salt (eq 6).[10]

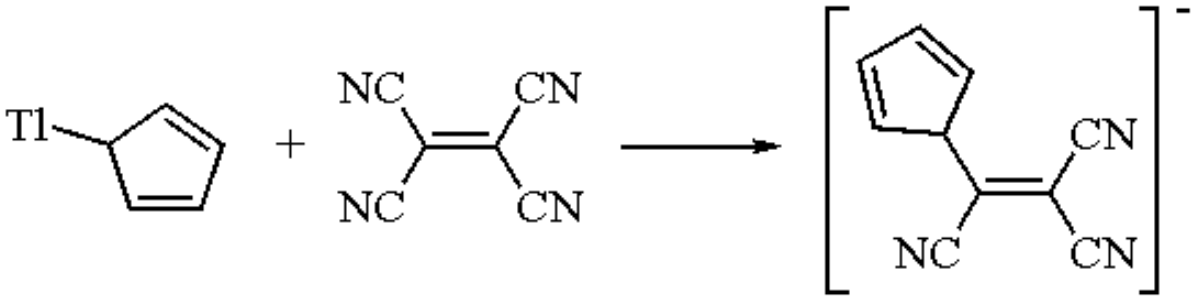

(6)

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1. (a) McKillop, A. *PAC* **1975**, *43*, 463. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465.
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3. Szajeck, L. P.; Shapley, J. R. *OM* **1991**, *10*, 2512.
4. The actual bonding situation in TlCp is a matter of debate. The η^1 structure is drawn here for convenience.
5. Corey, E. J.; Koelliker, U.; Neuffer, J. *JACS* **1971**, *93*, 1489.
6. (a) Battiste, M. A.; Timberlake, J. F. *JOC* **1977**, *42*, 176. (b) Madhavan, G. V. B.; Martin, J. C. *JOC* **1986**, *51*, 1287. (c) Ranganathan, S.; Ranganathan, D.; Iyengar, R. *T* **1976**, *32*, 961.
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9. Grundke, G.; Hoffmann, H. M. R. *JOC* **1981**, *46*, 5428.
10. Freeman, M. B.; Sneddon, L. G. *IC* **1980**, *19*, 1125.

Thallium(I) Hydroxide[1]

TlOH

[4310-83-4] · HOTl · Thallium(I) Hydroxide · (MW 221.39) (.H_2O)

[12026-06-1]

(base; additive for cross-coupling reactions)

Physical Data: mp 139 °C (dec).

Solubility: sol water, ethanol.

Form Supplied in: yellow needles; commercially available. *Drying:* decomposes on heating.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium hydroxide has been found to be an especially useful base for the enhancement of the Suzuki cross-coupling of alkyl boronic acids and esters with vinyl and aryl halides.[2] This thallium hydroxide-mediated transmetalation has been used for the preparation of a key diene in the synthesis of palytoxin (eq 1).[3] The use of TlOH instead of ***Potassium Hydroxide*** resulted in a dramatic 1000-fold rate enhancement.

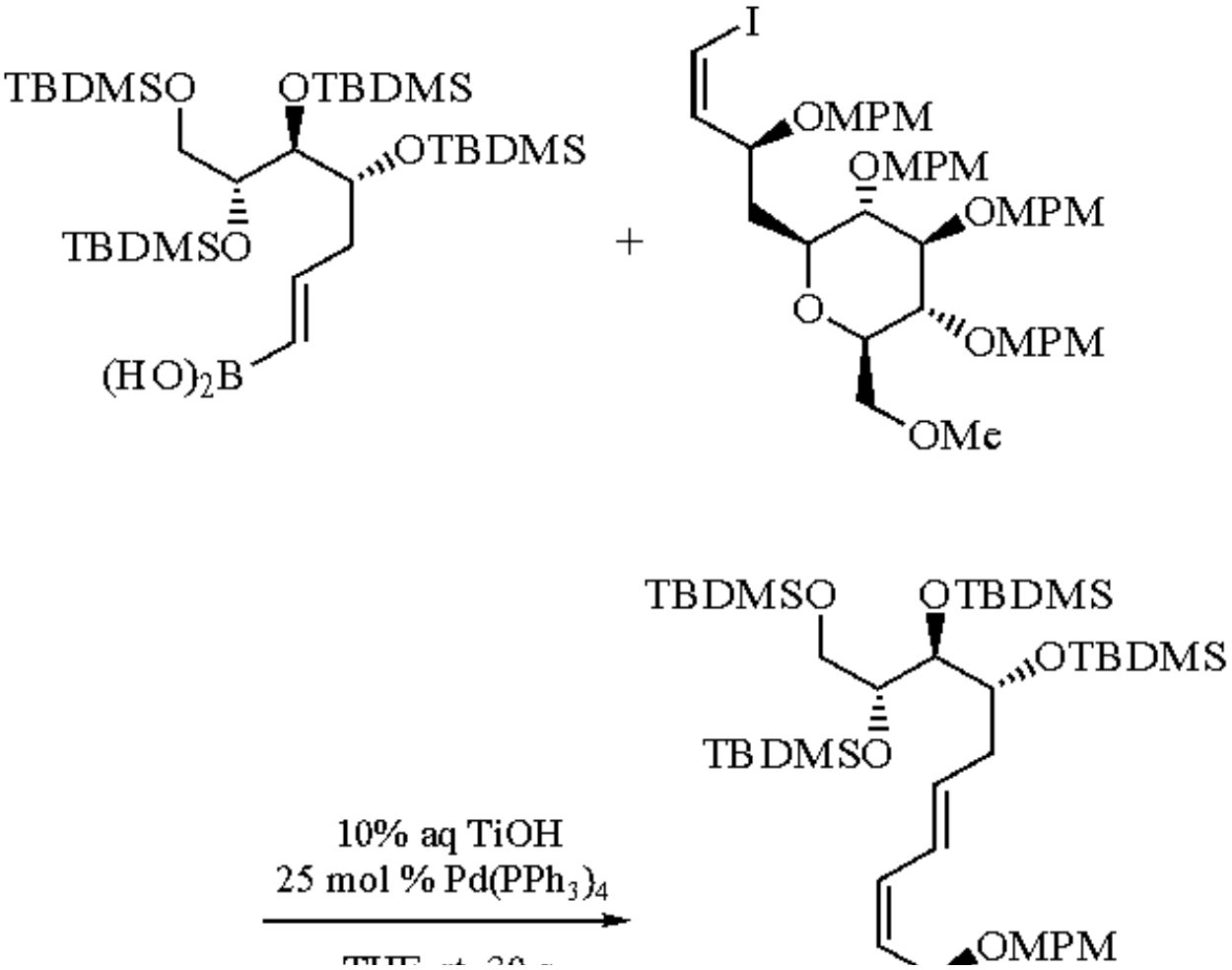

(1)

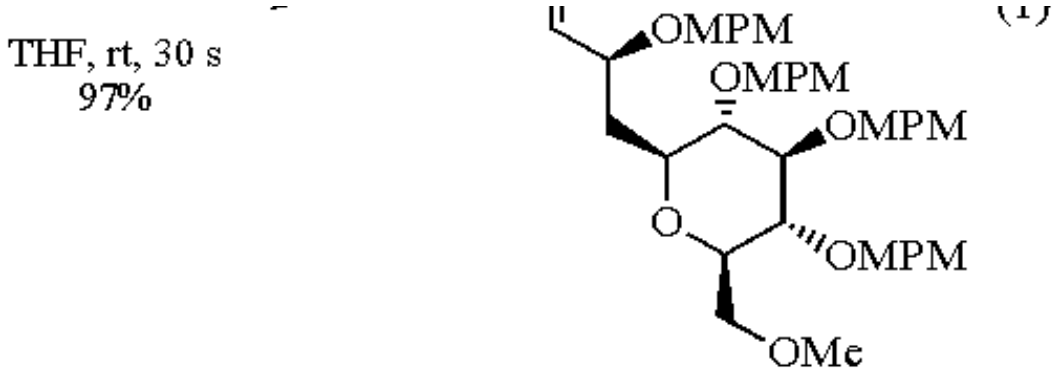

This method was also successfully used as a diene preparation in an approach to the bottom half of chlorothricolide (eq 2).[4] The yield of this transformation was considerably improved by the use of thallium hydroxide (cf. 55% for ***Sodium Hydroxide***). It is interesting to note that the boronic acid ester was used in this transformation. Like Suzuki,[2] these researchers found the ester gave better results. However, in subsequent work[4b] it was determined that the boronic acid gave optimal results, presumably due to ease in purification of the acid derivatives.

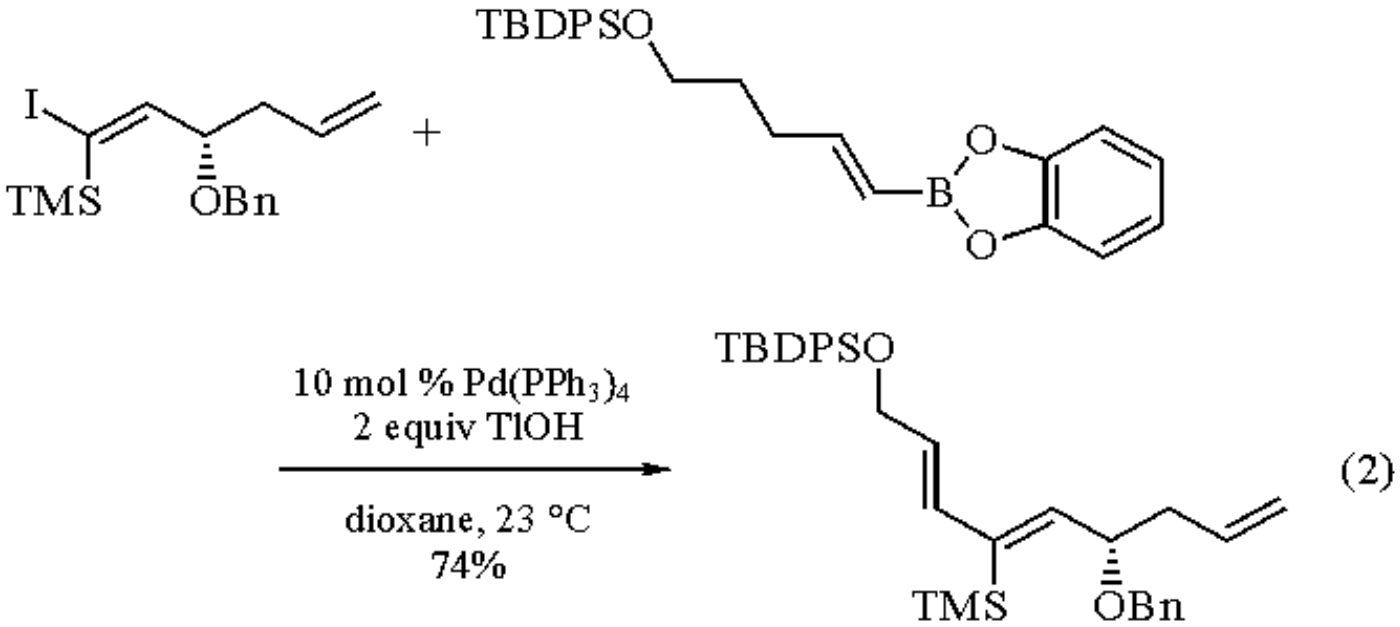

(2)

Thallium hydroxide has been used in the preparation of thallium(I) salts of β-keto esters.[5] These thallium salts are subsequently condensed with various electrophiles to obtain useful adducts (eq 3).

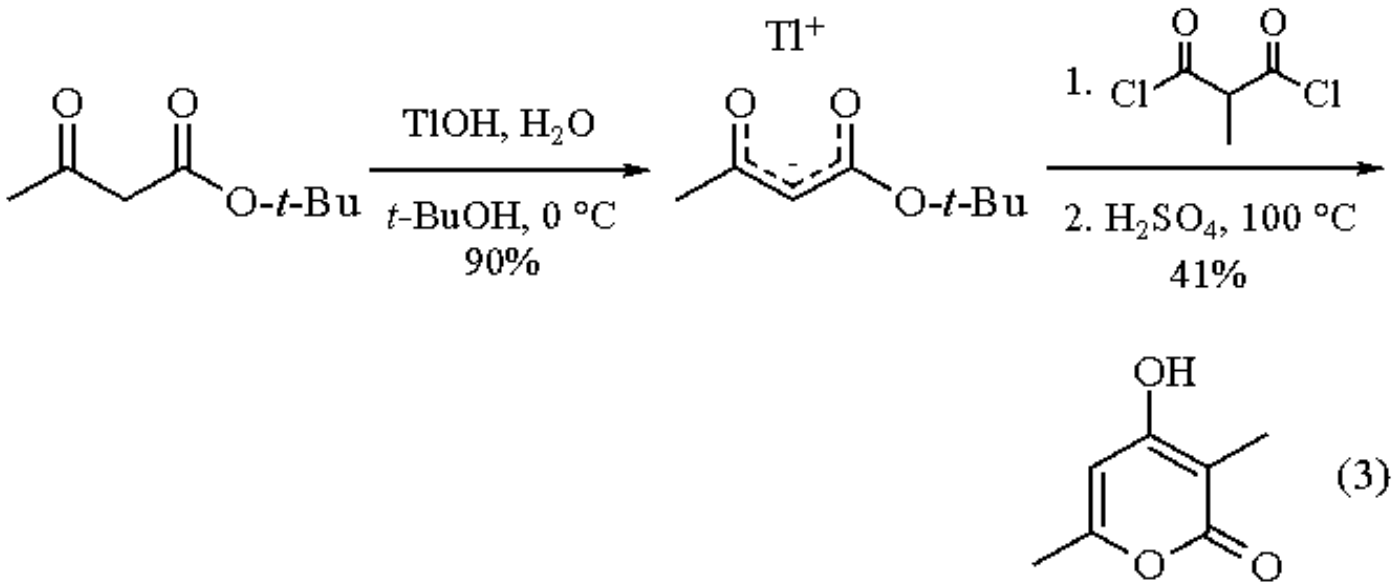

(3)

Thallium hydroxide has also been studied in the condensation of ***Formaldehyde*** with α-hydroxy ketones, and found to be better than calcium hydroxide in terms of solubility and catalytic action.[6]

1. (a) McKillop, A. *PAC* **1975**, *43*, 463. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465. (c) Taylor, E. C.; McKillop, A. *ACR* **1970**, *3*, 338.
2. Sato, M.; Miyaura, N.; Suzuki, A. *CL* **1989**, 1405.
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6. Guillot, G.; Sadet, J.; Rumpf, P. *BSF(2)* **1972**, *6*, 2393.

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Thallium(I) 2-Methyl-2-propanethiolate

t-BuSTl

[56393-79-4] · C_4H_9STl · Thallium(I) 2-Methyl-2-propanethiolate · (MW 293.58)

(nucleophile; reagent for preparation of thiol esters)

Physical Data: mp 170-175 °C (dec).

Solubility: sol organic solvents.

Form Supplied in: bright yellow solid. *Drying:* can be dried under vacuum.

Preparative Methods: can be readily prepared starting from *t*-butyl thiol and thallium(I) ethoxide.[1]

Handling, Storage, and Precautions: the compound should be stored in a dark bottle under argon. All thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium 2-methyl-2-propanethiolate is a convenient nucleophile for the preparation of thiol esters.[2] The thiol esters can be prepared starting from either acid chlorides (eq 1) or diethyl phosphates (eqs 2 and 3) and *t*-BuSTl.[3] The reaction conditions are simple, proceed in good yields, and the workup procedure is straightforward.

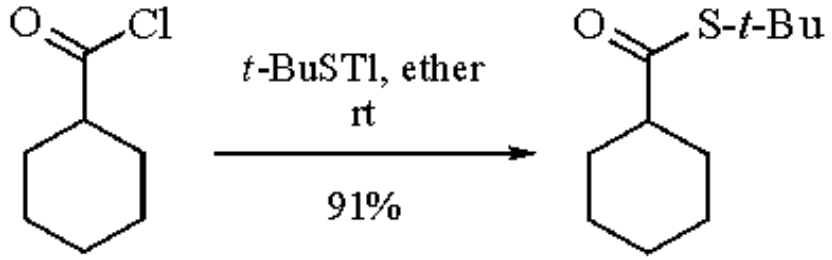

(1)

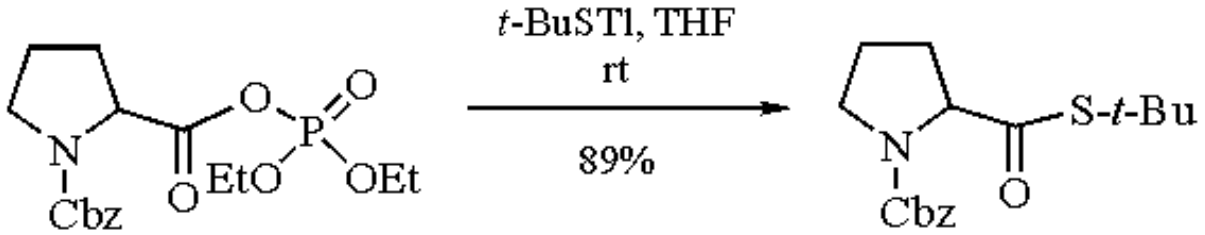

(2)

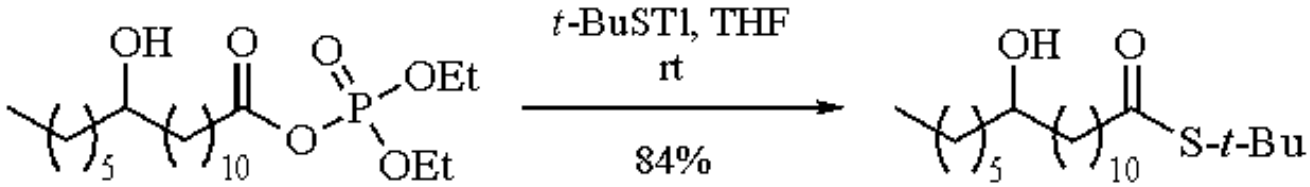

(3)

Due to the thermal instability of the diethyl phosphates, the preparation of thiol esters from this starting material is most efficient with thallium thiolates. Reactions with sodium and potassium thiolates in place of thallium give unsatisfactory results. The superiority of

thallium thiolates can be attributed to their ease of preparation and solubility in aprotic solvents.

Thallium 2-methyl-2-propanethiolate can also be used for the formation of metal-sulfur bonds.[1b,4] An example of this type of transformation in the formation of a tungsten-sulfur bond is shown in eq 4.

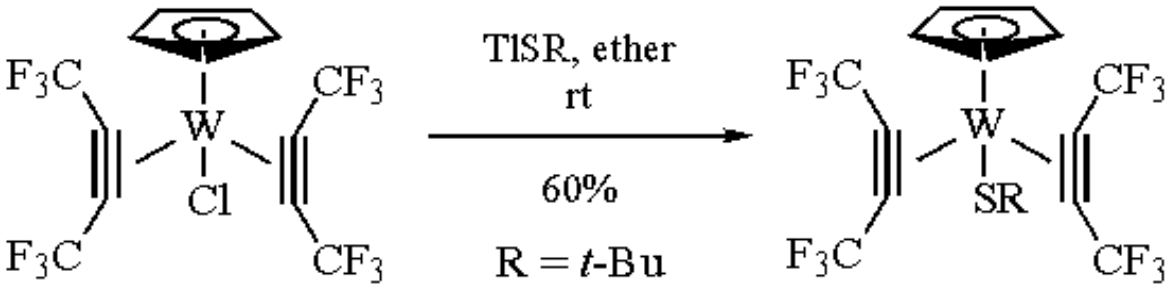

(4)

Related Reagents.

Thallium(I) 1-Propanethiolate.

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1. (a) Spessard, G. O.; Chan, W. T.; Masamune, S. *OS* **1983**, *61*, 134. (b) Carlton, L.; Davidson, J. L. *JCS(D)* **1987**, 895.
2. For alternative methods of thiol ester synthesis, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; p 263.
3. (a) Spessard, G. O.; Chan, W. T.; Masamune, S. *OS* **1983**, *61*, 134. (b) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *CJC* **1975**, *53*, 3693. (c) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *JACS* **1975**, *97*, 3513. (d) Masamune, S.; Kamata, S.; Schilling, W. *JACS* **1975**, *97*, 3515.
4. Davidson, J. L.; Sence, F. *JOM* **1991**, *409*, 219.

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Thallium(III) Nitrate Trihydrate[1]

$Tl(NO_3)_3.3H_2O$

[13453-38-8] · N_3O_9Tl · Thallium(III) Nitrate · (MW 444.47)

(oxidizing agent; Lewis acid for alkene cyclization)

Alternate Name: TTN.

Physical Data: mp 102-105 °C.

Solubility: sol water, organic solvents.

Form Supplied in: moist white crystals, hygroscopic; widely available. *Drying:* compound decomposes on heating.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

Oxidations.

Thallium trinitrate is a powerful oxidant. A variety of substituted phenols undergo oxidation using TTN to provide quinones.[2] For example, hydroquinones are oxidized to quinones in good yields. *p*-Alkoxyphenols are oxidized to *p*-quinone acetals in good yields by TTN in methanol (eq 1). Similarly, naphthols are oxidized to naphthoquinones using TTN. This oxidation proceeds in higher yields if TTN on ***Celite*** is used as the oxidant.[3]

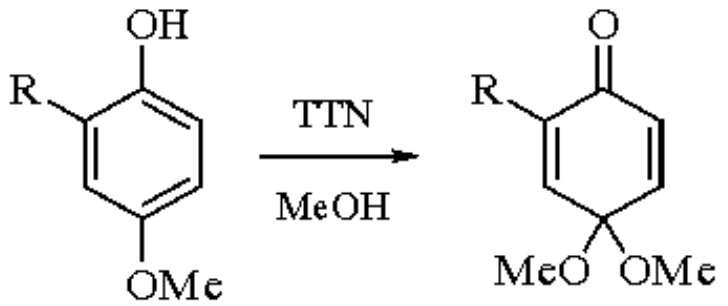

(1)

R = H, 97%; Cl, 97%; Br, 91%; Me, 87%

Chalcones are oxidized under acidic conditions to 1,2-diketones using three equivalents of TTN (eq 2).[4]

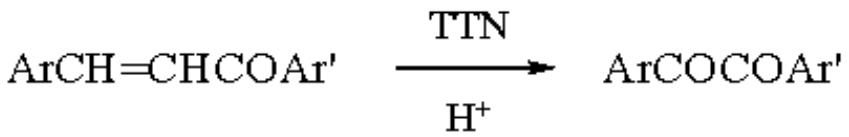

(2)

Ar = Ar' = Ph, 61%
Ar = 4-BrC_6H_4, Ar' = Ph, 55%
Ar = Ph, Ar' = 4'-BrC_6H_4, 70%
Ar = Ph, Ar' = 4'-MeC_6H_4, 49%
Ar = Ph, Ar' = 4'-$MeOC_6H_4$, 49%

TTN is a trihydrate and generally reactions with it are carried out under fairly acidic conditions. TTN oxidations in methanol as a solvent are also strongly acidic, since nitric acid is produced as a byproduct. Reactions that fail or proceed poorly with TTN (TTN in methanol or acetic acid), or where the substrates are acid sensitive, can be promoted by using a 1:1 mixture of methanol and trimethyl orthoformate (TMOF) (see ***Triethyl Orthoformate***) or neat TMOF as solvent. Oxidation of cinnamaldehyde with TTN in methanol proceeds very slowly and produces seven products. On the other hand, cinnamaldehydes are rearranged to aryl malondialdehyde tetramethyl acetals in good yields on treatment with TTN in 1:1 MeOH-TMOF (eq 3).[5]

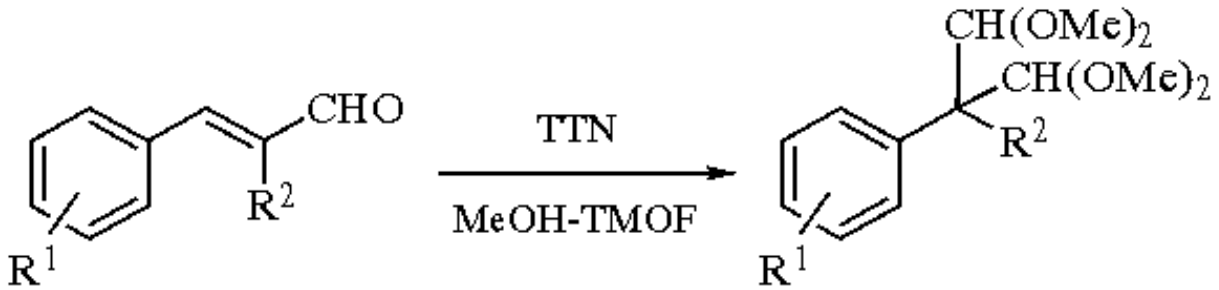

(3)

$R^1 = R^2 = H$, 79%
$R^1 = 4\text{-MeO}$, $R^2 = H$, 84%
$R^1 = 4\text{-}NO_2$, $R^2 = H$, 63%
$R^1 = H$, $R^2 = Me$, 83%
$R^1 = 3\text{-}NO_2$, $R^2 = Me$, 50%

TTN adsorbed on ***Montmorillonite K10*** is an effective reagent for the conversion of ketones to rearranged esters. For example, acetophenone is readily converted to phenylacetate on treatment with TTN/K-10 reagent (eq 4).[6] Supported TTN reagents are practical, since product isolation from the insoluble inorganic byproducts is simple.

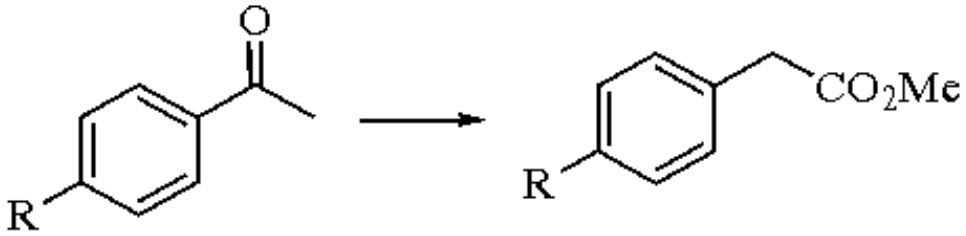

(4)

R	TTN, MeOH, $HClO_4$	TTN/K-10
H	84%	86%
F	44%	88%
Me	86%	84%
Br	35%	89%

Alkene Oxidation.

Simple alkenes are converted to aldehydes or ketones in good yields using TTN. These reactions proceed with migration of the higher migratory aptitude substituent.[7] The preparation of arylacetaldehyde dimethyl acetals by oxidative rearrangement of substituted styrenes using TTN proceeds in good yields (eq 5). The reaction proceeds through the exclusive migration of the aryl substituent and the yields are higher if TTN supported on K-10 is used as the oxidant.[1b,6b]

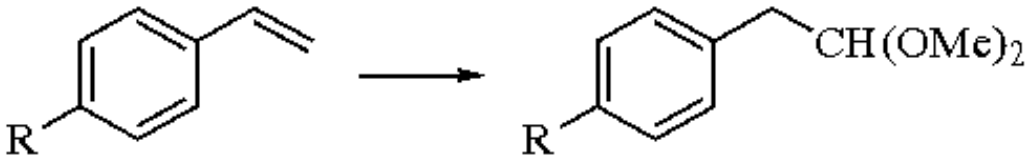

(5)

R	TTN, MeOH	TTN/K-10
H	85%	92%
F	27%	79%
OMe	64%	81%
Br	30%	76%

Cycloalkenes provide ring contracted aldehydes on oxidation with TTN under acidic conditions. Corey and Ravindranathan have used this methodology to prepare a key prostaglandin intermediate (eq 6).[8] Similarly, enol ethers also undergo oxidative ring contraction on treatment with TTN (eq 7).[9] If methanol is used as the solvent, the corresponding acetals are formed as the products.[10] In contrast to the ring contractive oxidation of monocycloalkenes, bicyclic alkenes furnish nitrate esters on treatment with TTN.[11] Exocyclic alkenes furnish ring enlarged ketones on oxidation with TTN (see ***Thallium(III) Perchlorate*** for similar reactions).[12]

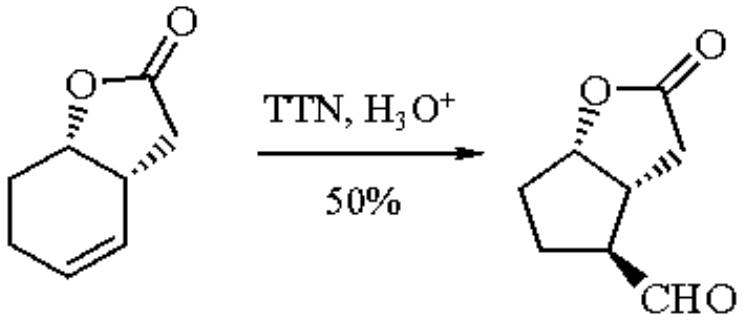

(6)

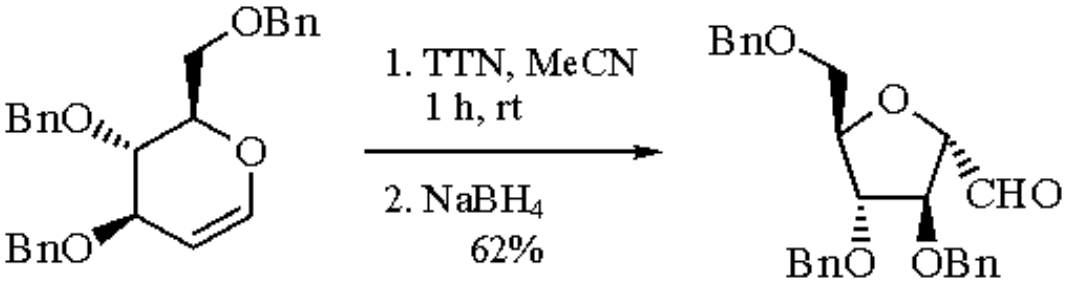

(7)

Diarylalkynes are converted to 1,2-diketones using two equivalents of TTN (eq 8) and terminal alkynes are oxidized to carboxylic acids (eq 9).[13]

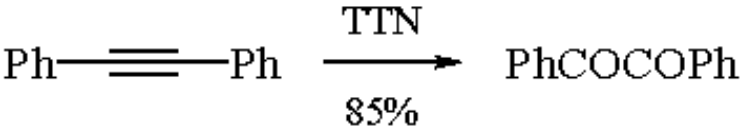

(8)

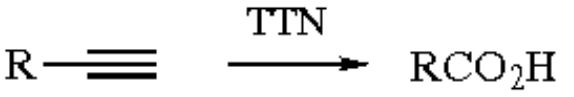

(9)

$R = C_6H_{13}$, 80%; C_5H_{11}, 55%

TTN can be used for electrophilic cyclizations of polyalkenes.[14] The oxythallative cyclization of elemol acetate using TTN in acetic acid produces a guaiene diol after ***Lithium Aluminum Hydride*** reduction (eq 10).[15] In contrast, ***Mercury(II) Acetate*** mediated cyclization of elemol produces the unrearranged cryptomeridiol.

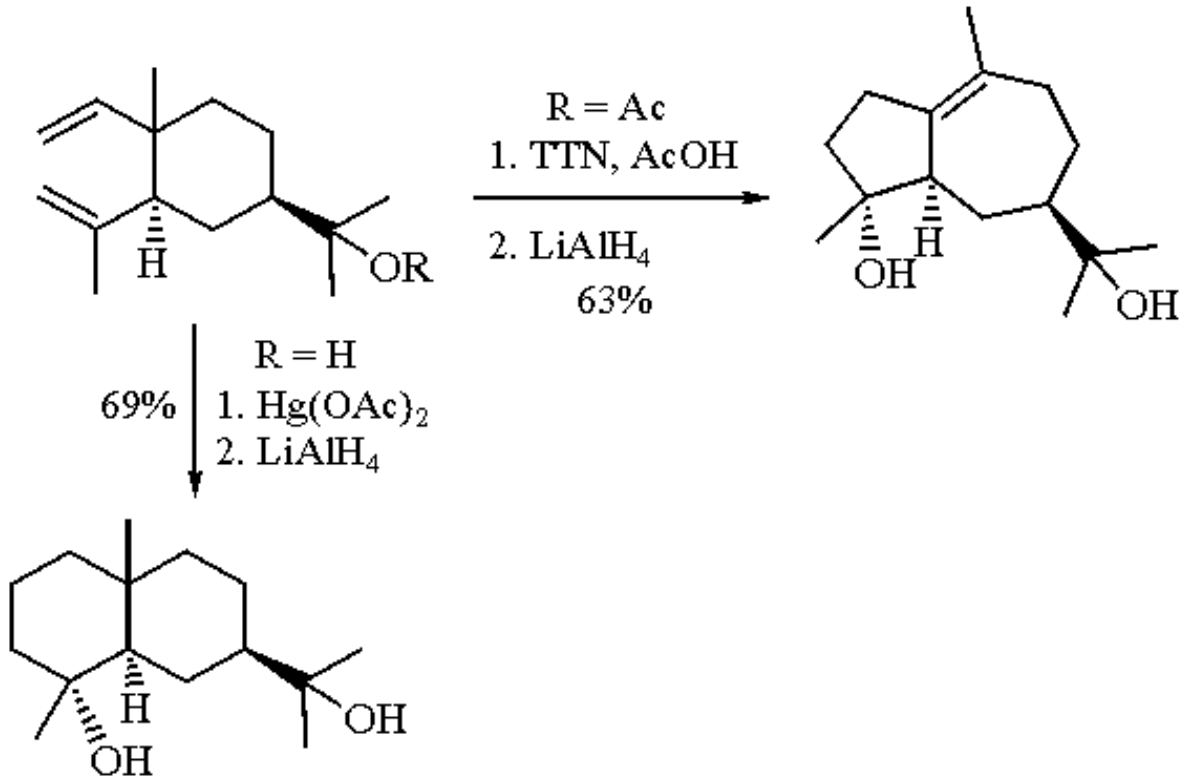

(10)

Allylations Using Allysilanes and TTN.

Aromatic compounds are allylated using allylsilanes and TTN, but in poor yield.[16] Allylsilanes are converted to allylic ethers (eq 11),[17] *N*-allylic amides (eq 12),[18] and allylic nitrates[19] on treatment with TTN and the appropriate nucleophile.

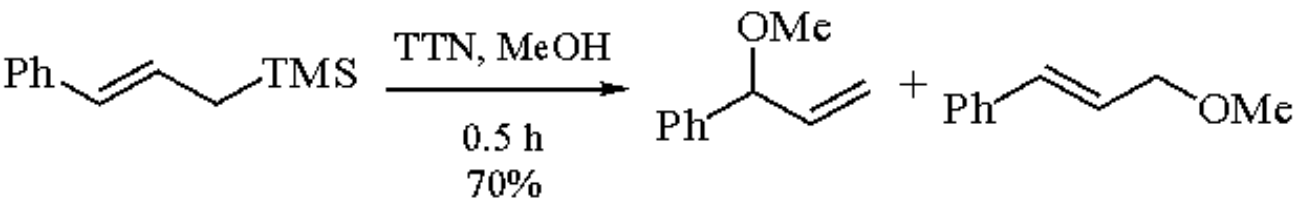

(11)

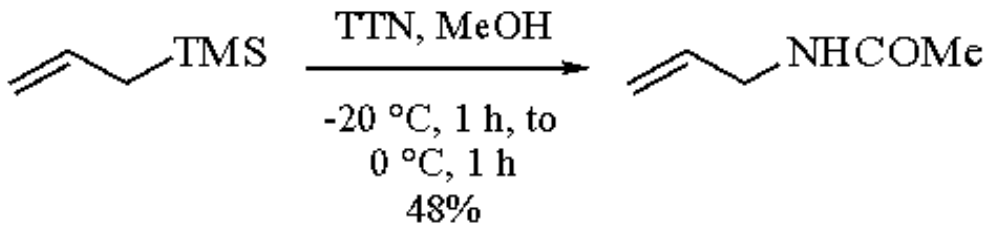

(12)

Functional Group Interconversions.

TTN finds utility in a variety of functional group interconversions. Phenols are readily converted to anilines using TTN.[20] Sulfides and selenides are converted to sulfoxides (eq 13) and selenoxides, respectively, on oxidation with TTN.[21] Other transformations include the preparation of allene esters from α-alkyl-β-keto esters (eq 14),[22] carbamates from isocyanides (eq 15),[23] and lactones from γ,δ-unsaturated acids.[24]

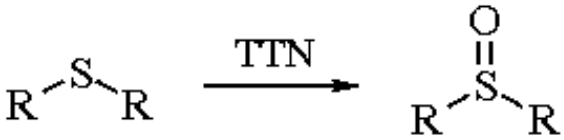

(13)

R = Et, 85%; Pr, 92%; Bu, 94%; Ph, 82%

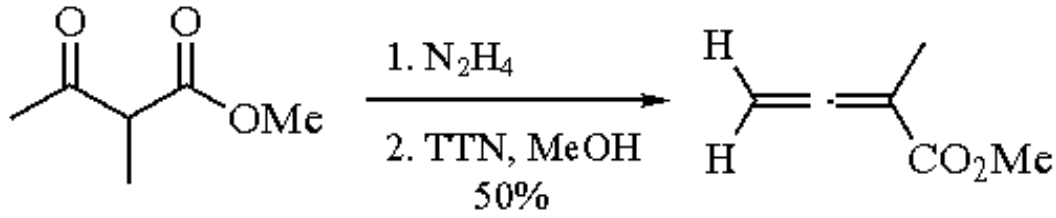

(14)

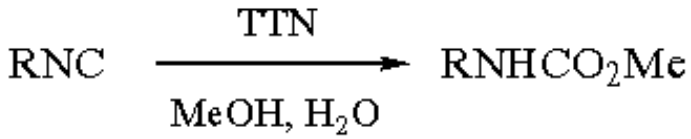

(15)

R = $EtOCOCH_2$, 84%; Cy, 90%; *t*-Bu, 35%; Ph, 93%; 4-MeC_6H_4, 85%

TTN has been used to selectively deprotect bisthioacetals to give monothioacetals (eq 16).[25] Simple thioacetals can also be deprotected using TTN. Oximes are converted to aldehydes or ketones in high yields on treatment with TTN in methanol at rt (eq 17).[26]

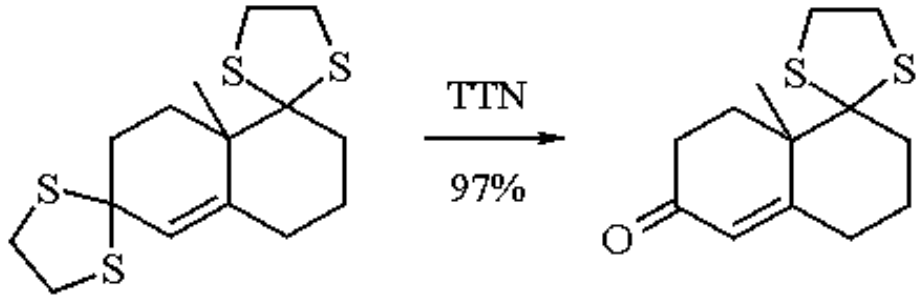

(16)

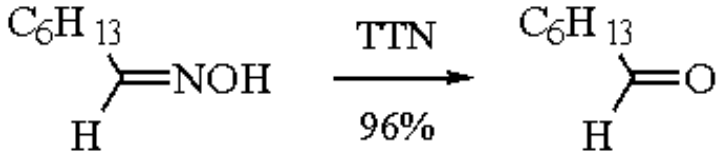

(17)

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25. (a) Smith, R. A. J.; Hannah, D. J. *SC* **1979**, *9*, 301. (b) Fujita, E.; Nagao, Y.; Kaneko, K. *CPB* **1978**, *26*, 3743.
26. McKillop, A.; Hunt, J. D.; Naylor, R. D.; Taylor, E. C. *JACS* **1971**, *93*, 4918.

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Thallium(III) Perchlorate Hexahydrate

$Tl(ClO_4)_3.6H_2O$

[15596-83-5] · $Cl_3O_{12}Tl$ · Thallium(III) Perchlorate · (MW 610.85)

(oxidizing agent; mild Lewis acid for alkene cyclization)

Physical Data: melts with decomposition.

Solubility: sol water.

Form Supplied in: colorless hygroscopic crystals; widely available. *Drying:* compound decomposes on heating.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. All perchlorates are potentially explosive and appropriate care should be exercised. Use in a fume hood.

Oxidations.

Thallium perchlorate is an efficient oxidizing agent. It converts *p*-alkylphenols to the corresponding *p*-quinols in high yields.[1] Oxidation of 5-hydroxyindan to 6-hydroxybicyclo[4.3.0]nona-1,4-dien-3-one can be achieved in 80% yield by a biphasic reaction using methylene chloride and aqueous thallium perchlorate solution at low temperatures (eq 1).

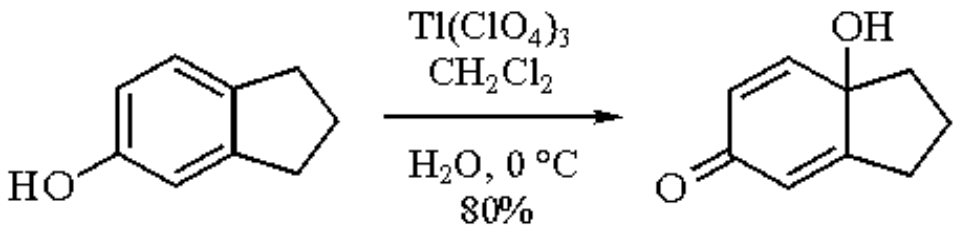

(1)

Alternatively, oxidation of *p*-alkylphenols using higher concentrations of perchloric acid at rt provides 2-substituted hydroquinones by a dienone-phenol rearrangement. The hydroquinones are further oxidized to substituted benzoquinones (eq 2).[2]

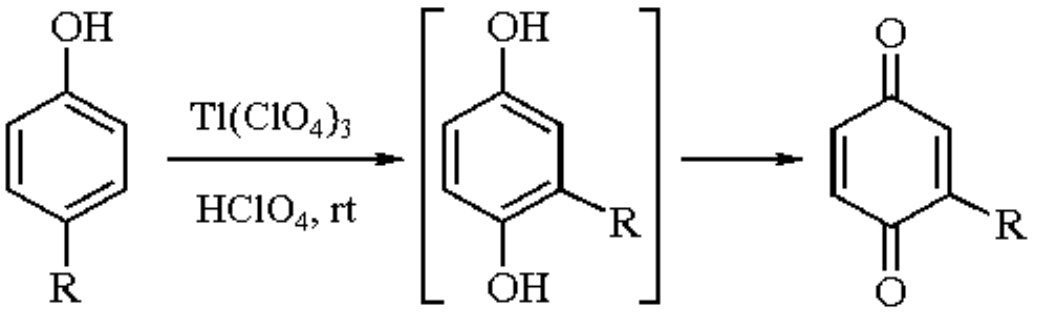

(2)

R = Me, 70%; CH_2CH_2OAc, 66%

A selective and remote oxidation of estrone using thallium perchlorate has been reported (eq 3).[3] Oxidation of estrone provides the 11-keto-*p*-quinol (**1**) as the major product, along with lesser amounts of (**2**). This is in contrast to oxidation with ***Thallium(III) Trifluoroacetate***, where (**2**) is formed as the sole product.[4]

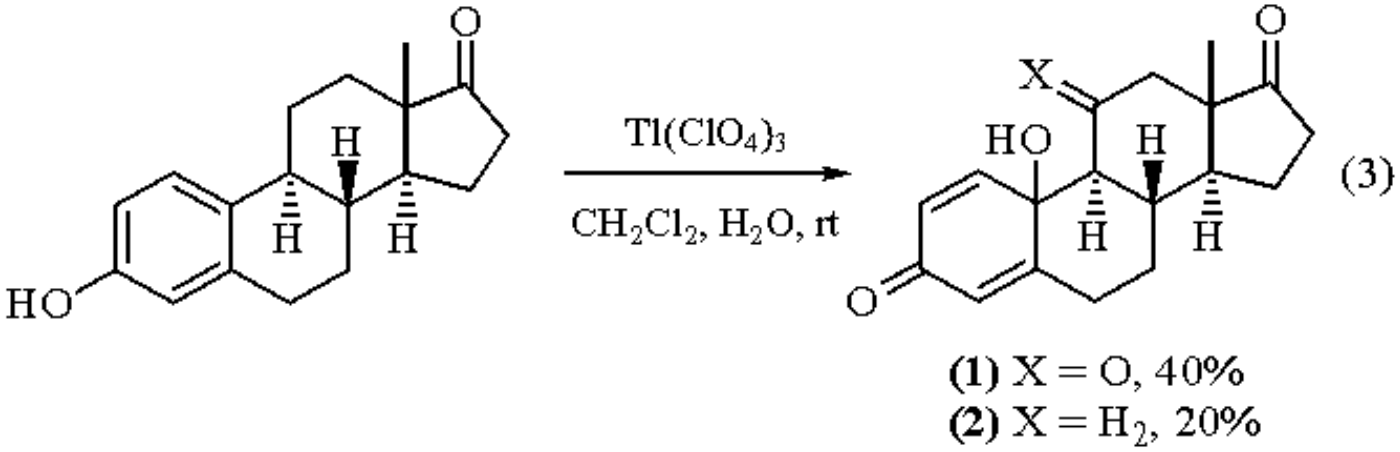

Enol ethers of alkyl aryl ketones are oxidized very selectively to 2-aryl alkanoates using thallium perchlorate (eq 4).[5] Similar oxidations can also be achieved using other thallium(III) salts such as ***Thallium(III) Nitrate***, ***Thallium(III) Sulfate***, and ***Thallium(III) Acetate***.

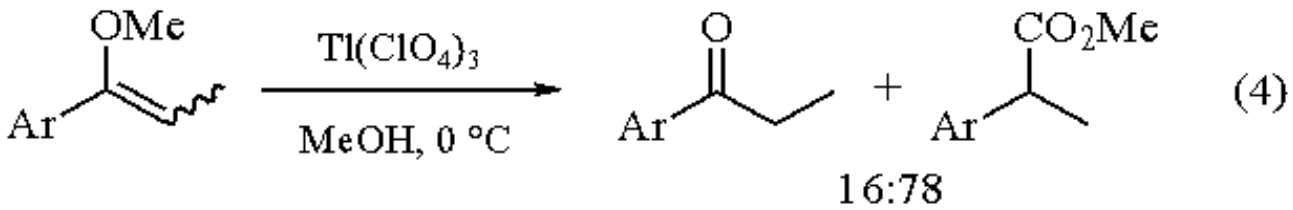

Reactions with Alkenes.

Thallium perchlorate has been effectively used for ring-expansion of cyclic ketones.[6] The sequence involves the formation of exocyclic alkenes from the ketone by a Wittig reaction, followed by oxidation using thallium perchlorate (eq 5). The ring expansion is most effective when the double bond is exocyclic to four- or five-membered rings.

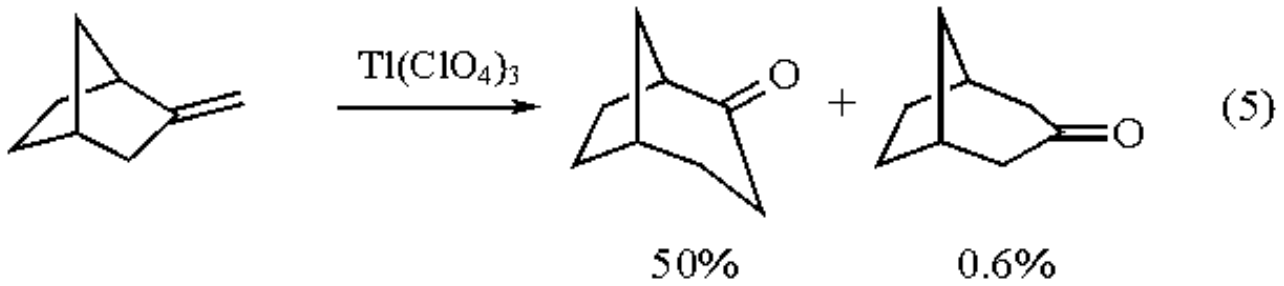

Polyalkenes can cyclize on treatment with thallium perchlorate. For example, geraniol reacts with thallium perchlorate to provide three carbocyclic products (eq 6).[7] The reaction is noteworthy since cyclization yields the five-membered carbocycle predominantly.

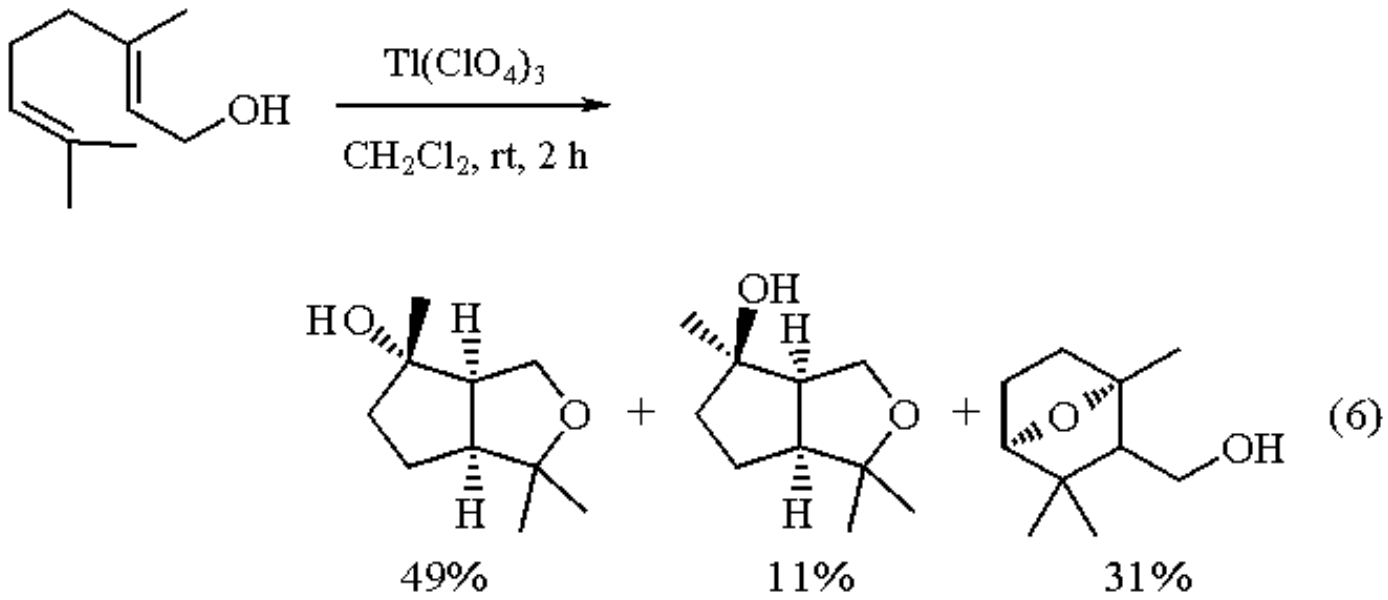

In contrast to its geometrical isomer geraniol, nerol reacts with thallium perchlorate to furnish two isomeric oxabicyclo[3.2.1]octanes and four diastereomeric dioxabicyclo[3.3.1]nonanes (eq 7).[8]

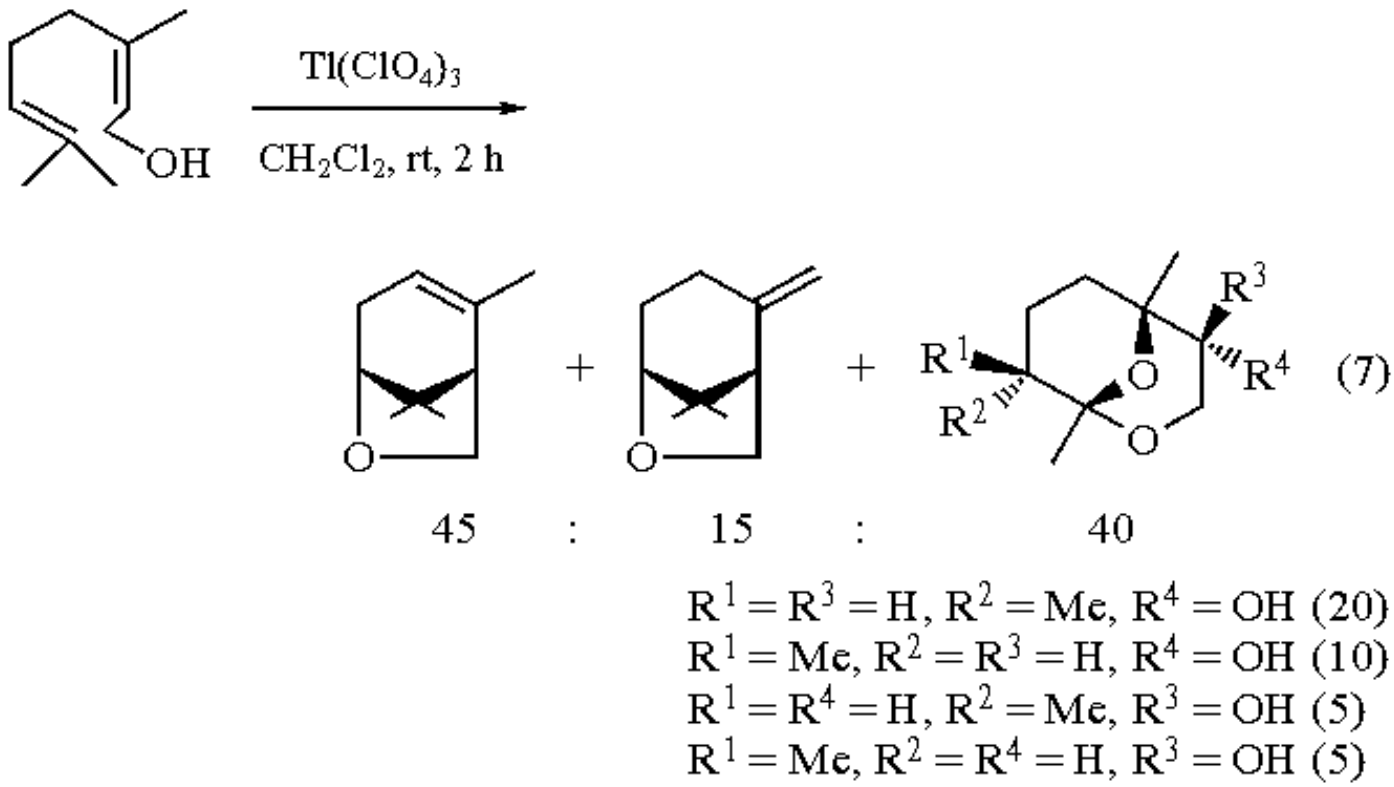

Citral also undergoes a similar cyclization on treatment with thallium perchlorate, yielding diastereomeric dioxabicyclo[3.2.1]octanes (eq 8).[9]

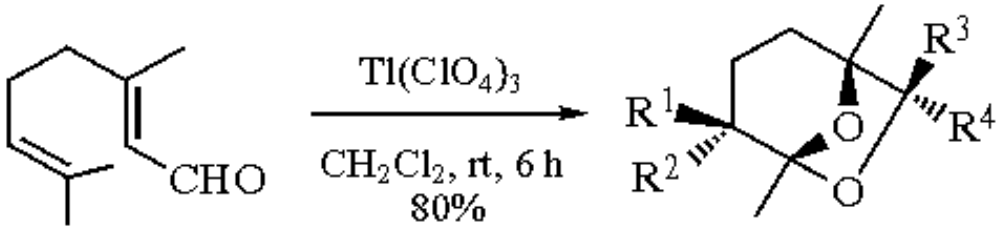

(8)

$R^1 = R^4 = H$, $R^2 = Me$, $R^3 = CHO$ (12)
$R^1 = Me$, $R^2 = R^4 = H$, $R^3 = CHO$ (11)
$R^1 = R^3 = H$, $R^2 = Me$, $R^4 = CHO$ (37)
$R^1 = Me$, $R^2 = R^3 = H$, $R^4 = CHO$ (20)

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1. Yamada, Y.; Hosaka, K.; Sanjoh, H.; Suzuki, M. *CC* **1974**, 661.
2. Yamada, Y.; Hosaka, K. *S* **1977**, 53.
3. Yamada, Y.; Hosaka, K.; Sawahata, T.; Watanabe, Y.; Iguchi, K. *TL* **1977**, 2675.
4. Coombs, M. M.; Jones, M. B. *CI(L)* **1972**, 169.
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8. Yamada, Y.; Sanjoh, H.; Iguchi, K. *TL* **1979**, 1323.
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Thallium(I) 1-Propanethiolate

***n*-PrSTl**

[58587-01-2] · C_3H_7STl · Thallium(I) 1-Propanethiolate · (MW 279.55)

(nucleophile; reagent for preparation of thiol esters)

Solubility: sol in organic solvents.

Form Supplied in: can be readily prepared in situ. *Drying:* can be dried under vacuum.

Preparative Methods: can be readily prepared starting from 1-propanethiol and thallium(I) ethoxide.[1]

Handling, Storage, and Precautions: the compound should be stored in a dark bottle under argon. All thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium-1-propanethiolate is a convenient nucleophile for the preparation of thiol esters (see also ***Thallium(I) 2-Methyl-2-propanethiolate***).[2] The thiol esters can be prepared starting from diethyl phosphates and thallium 1-propanethiolate (eqs 1-3).[3] The reaction conditions are simple, proceed in good yields, and the workup procedure is straightforward.

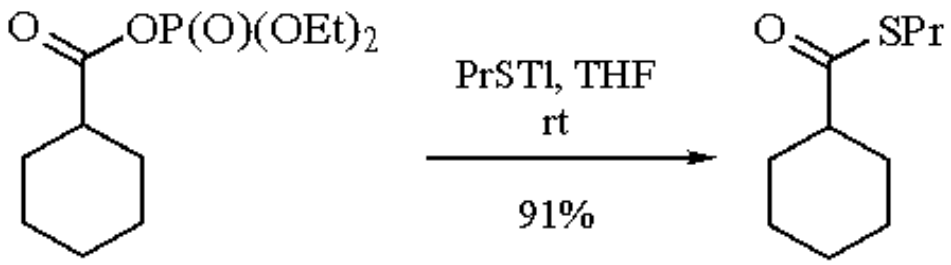

(1)

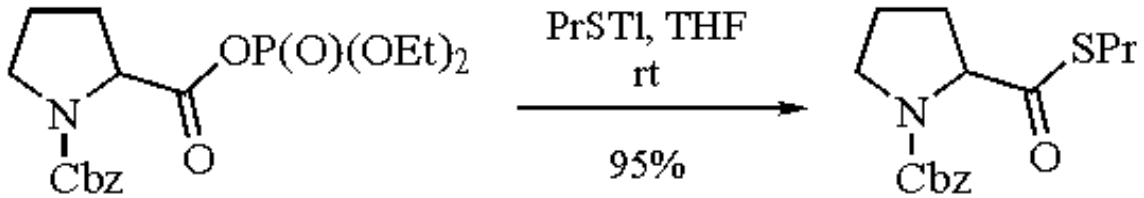

(2)

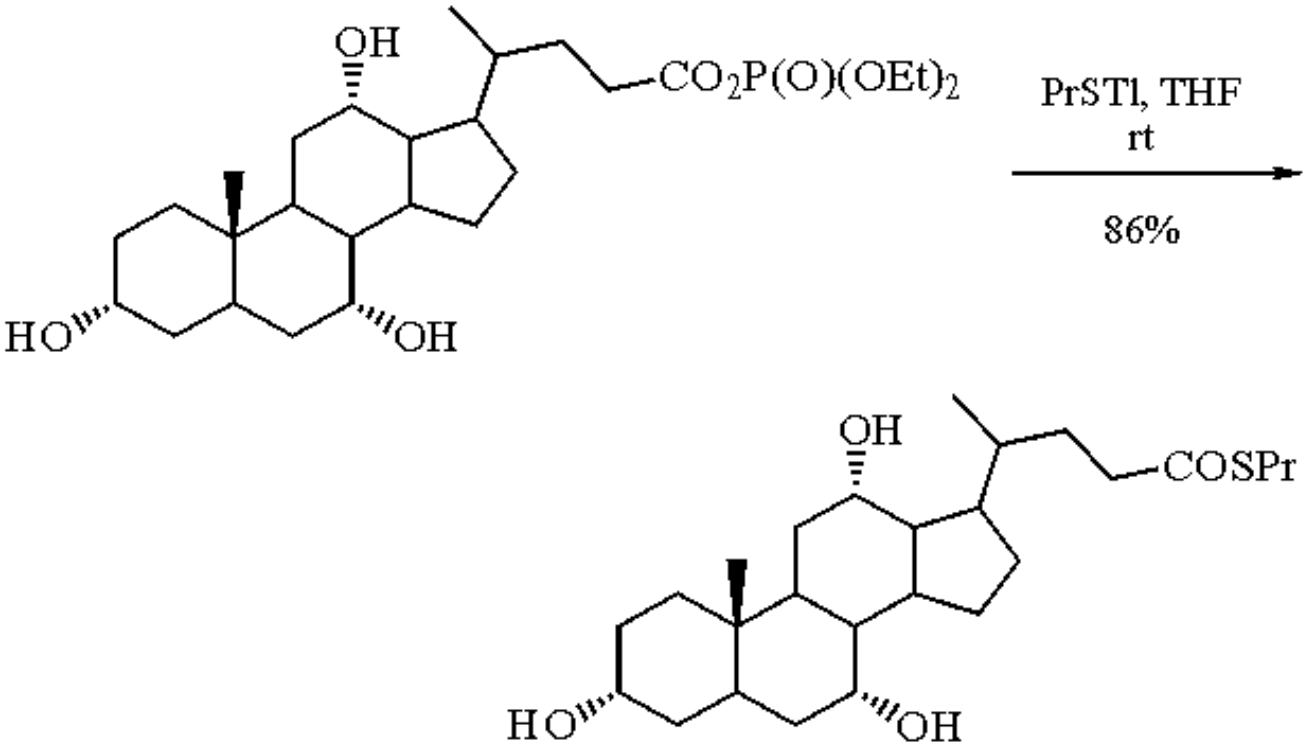

(3)

As indicated in the case of *t*-BuSTl, the preparation of thiol esters from diethyl phosphates and thallium 1-propanethiolate is the most efficient. Reactions with sodium and potassium thiolates in place of thallium can give unsatisfactory results. The superiority of thallium 1-propanethiolate can be attributed to the ease of preparation and solubility in aprotic solvents.

Thallium 1-propanethiolate can also be used for the formation of metal-sulfur bonds.[1,4] An example of this type of transformation in the formation of molybdenum-sulfur bond is shown in eq 4.

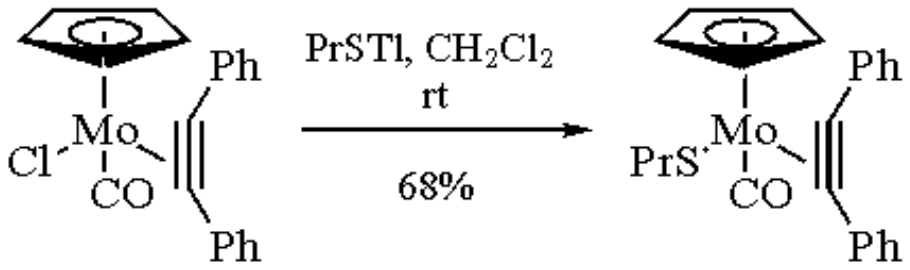

(4)

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Thallium(III) Sulfate[1]

$Tl_2(SO_4)_3$

[16222-66-5] · $O_{12}S_3Tl_2$ · Thallium(III) Sulfate · (MW 696.97)

(oxidizing agent)

Physical Data: mp 102-105 °C.

Solubility: sol water, organic solvents.

Form Supplied in: generally prepared in situ; commercially available.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium(III) sulfate is a versatile oxidant, although most reports have been in kinetic and mechanistic studies of thallium(III) salts in general. The reagent is usually formed in situ by dissolving another thallium compound (e.g. ***Thallium(I) Hydroxide*** or Tl_2O_3) in sulfuric acid. Thus formed, thallium(III) sulfate has been used to oxidize both alkenes and aliphatic ketones. In the latter case, α-hydroxy ketones result.[2] The oxidation of alkenes can result in either vicinal diols or carbonyl compounds. Oxidation of ethylene by thallium(III) sulfate has been investigated[3] from a mechanistic viewpoint. In a kinetic study,[4] the oxidation of methylpentenes with this reagent was reported (eq 1). Good yields of a mixture of the carbonyl product and the vicinal diol were obtained.

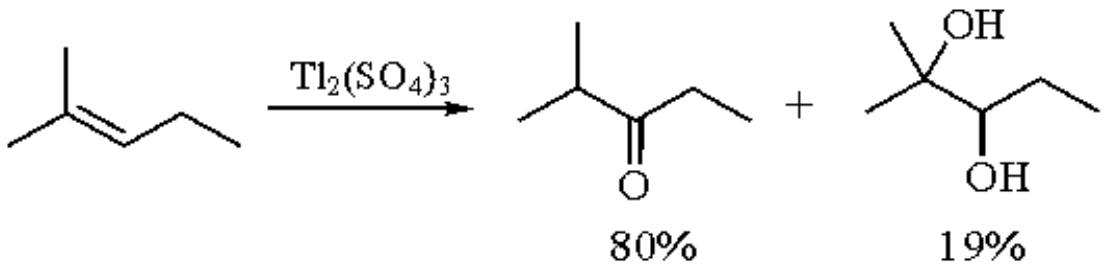

(1)

The oxidation of cyclohexenes with thallium sulfate has also been studied.[5] Thus thallium(III) sulfate oxidation of *t*-butylcyclohexene provides primarily the *trans*-diol (**1**) with lesser amounts of the isomeric byproducts shown (eq 2).

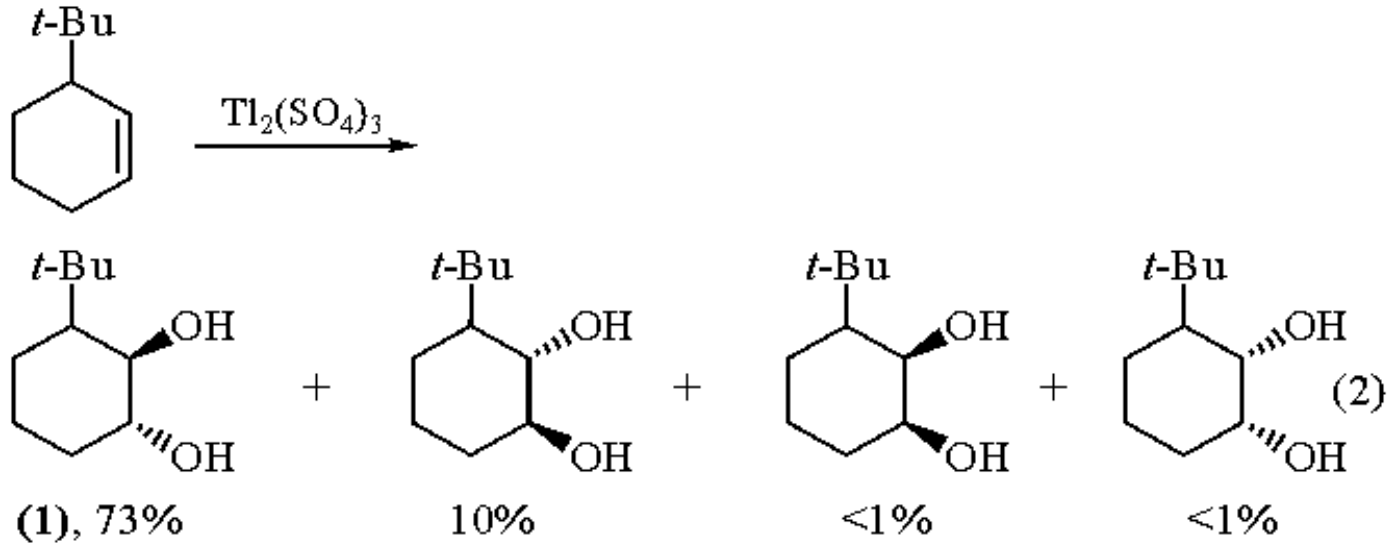

An interesting variation of alkene oxidation by thallium(III) sulfate has been demonstrated in a preparation of 3-chromanols (eq 3).[6] The alkylthallium salt postulated as an intermediate in the oxidation is susceptible to intramolecular attack by the aromatic ring, thus forming the ether. In the case of R = NO_2, the aromatic ring was sufficiently deactivated by the nitro group to prevent cyclization, resulting in a mixture of the methyl ketone (**2**) and the diol (**3**) (eq 4).

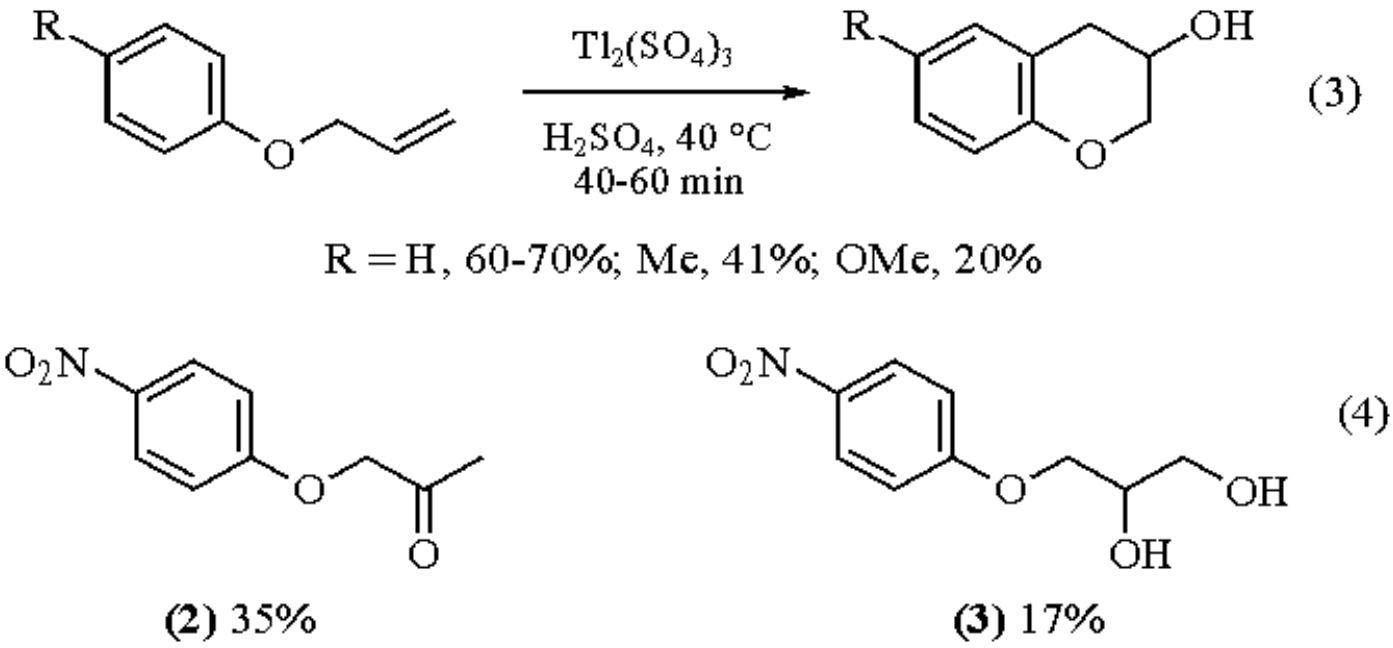

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1. (a) McKillop, A. *PAC* **1975**, *43*, 463. (b) McKillop, A.; Taylor, E. C. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 7, p 465.
2. Pechál, M.; Strasák, M. *CCC* **1983**, *48*, 2819.
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Thallium(III) Trifluoroacetate[1]

$Tl(OCOCF_3)_3$

[23586-53-0] · $C_6F_9O_6Tl$ · Thallium(III) Trifluoroacetate · (MW 543.44)

(oxidizing agent; thallating agent; Lewis acid; reagent for dethioacetalization)

Alternate Name: TTFA.

Physical Data: mp 100 °C (dec).

Solubility: sol water, organic solvents.

Form Supplied in: moist white crystals, hygroscopic; widely available. *Drying:* decomposes on heating.

Preparative Method: readily prepared by refluxing a suspension of thallium(III) oxide with ***Trifluoroacetic Acid*** (TFA).[2]

Handling, Storage, and Precautions: water sensitive solid. All thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

Thallation.

Thallium trifluoroacetate is the most versatile of all the thallium reagents. It has seen extensive utility in a variety of organic transformations.[1] The solution of TTFA in TFA is a potent thallating reagent. Aromatic compounds react with TTFA to provide thallated aromatics (eq 1). As is the case with other electrophilic aromatic substitution reactions, thallation is most efficient with electron-rich aromatics. Other methods are now available for the preparation of thallated aromatics using TTFA.[3] Generally, the thallated intermediates are not isolated, but are transformed to a variety of compounds in a subsequent reaction with nucleophiles.

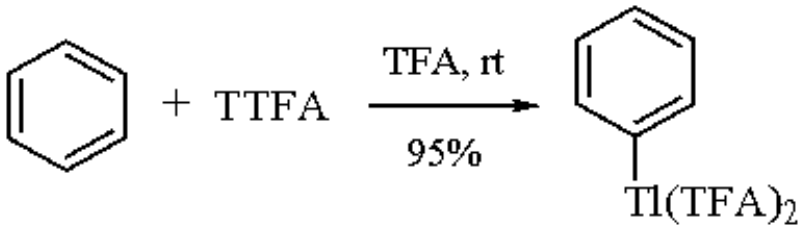

(1)

Thallation of substituted aromatics with TTFA is highly regioselective, depending on the nature of the substituent and reaction conditions. The reaction is reversible, requires a moderately large activation energy, and has large steric constraints. The electrophilic character of TTFA can be increased by the addition of Lewis acids such as ***Boron Trifluoride*** or ***Antimony(V) Fluoride***.[4] Thallation of substituted aromatics (nonheteroatom substituents) under kinetic control (short reaction times) yields the *para*-thallated product, illustrating the steric requirements of the reaction. The *meta*-thallated product can be obtained by conducting the reaction in refluxing TFA (eq 2).[5]

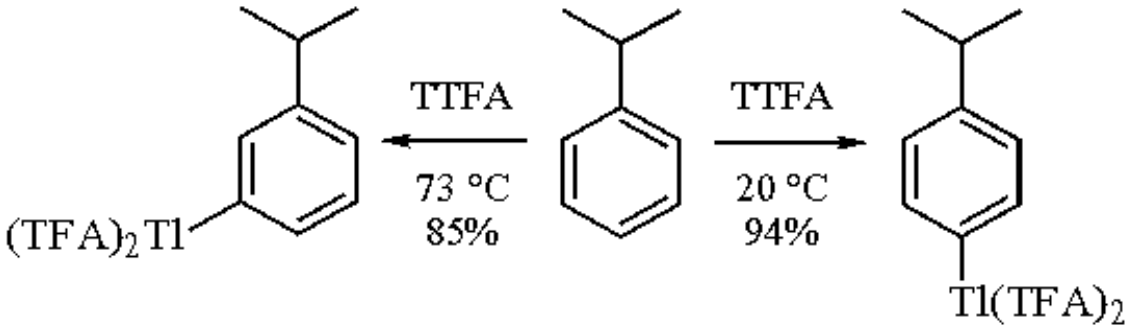

(2)

Thallation of aromatics possessing heteroatom-containing substituents (CO_2R, CO_2H, OR, CH_2OH, etc.) shows a different type of regioselectivity, providing the *ortho*-thallated product (eq 3).[6] This selectivity has been rationalized as intramolecular delivery of the thallium electrophile. The monothallated species generally deactivates the ring toward further thallation.

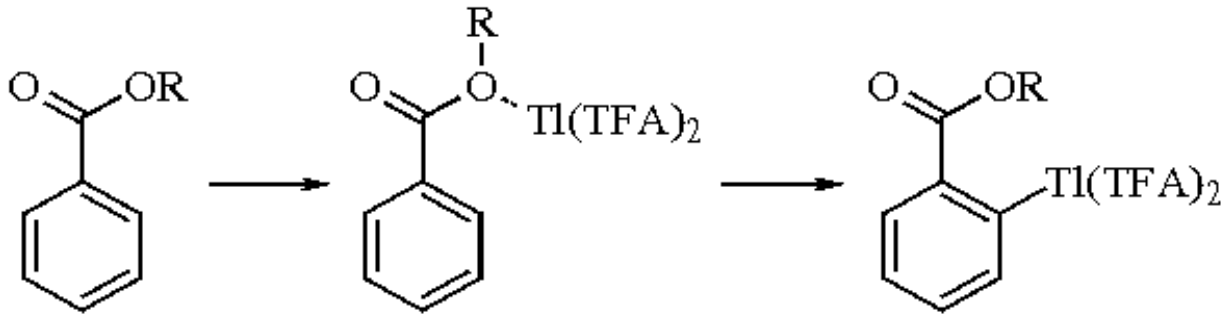

(3)

Anisole can be polythallated using excess TTFA in TFA (eq 4).[7] The thallated intermediate can be converted to the corresponding iodo compound on treatment with ***Sodium Iodide***.

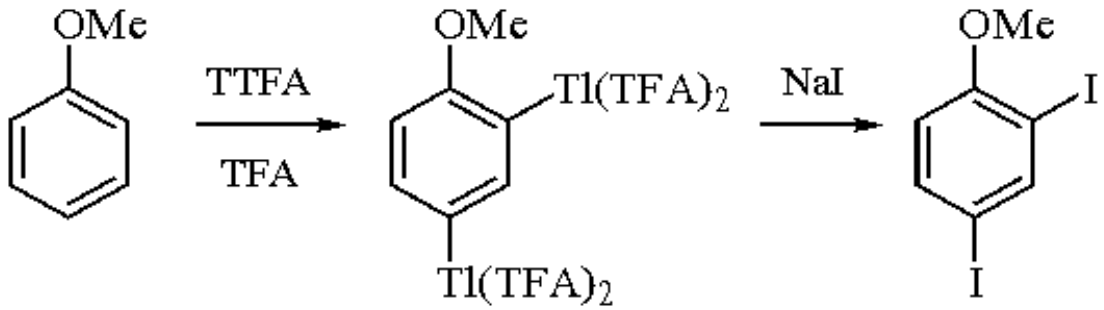

(4)

Electrophilic thallations are not restricted to aromatic compounds. Heterocyclic compounds, such as thiophenes, furans, and indoles, undergo thallations cleanly.[8] These thallated intermediates can also be treated with nucleophiles to provide substituted heterocycles.

ipso-Displacements.

The thallated aromatics are useful in the preparation of a variety of substituted compounds. The reaction involves treatment of the thallated intermediates with nucleophiles, alkenes, arenes, and cations.[1] The introduction of the nucleophile takes place with very high selectivity: the nucleophile occupies the same position as the thallium (*ipso* substitution) (eq 5) (see ***Phenylthallium Bis(trifluoroacetate)*** for examples).

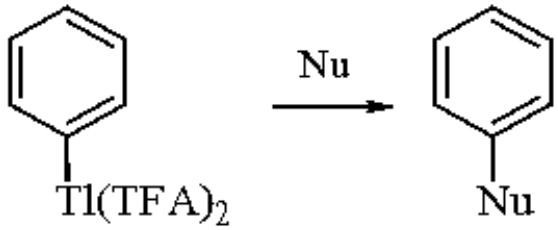

(5)

Nu = OH, F, Cl, Br, I, SCN, CN, SeCN, NO_2, Alkyl, SH, etc

Preparation of aryl fluorides from thallated aromatics has been attempted by several researchers with mixed results.[9] Only Taylor et al.[9b] have been successful, using the three-step method (including the preparation of the arylthallium bis(trifluoroacetate)) shown in eq 6. While

Taylor's method is less complicated than the Balz-Schiemann method of preparing fluoride compounds, it is limited to those aromatic substrates that do not contain electron-withdrawing groups, or oxygen or nitrogen functionality.

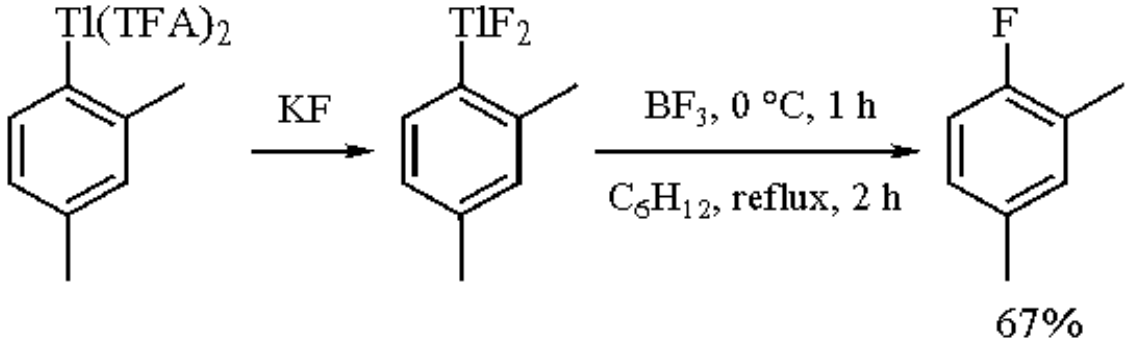

(6)

Phenols are also readily accessed via this methodology. Arylthallium bis(trifluoroacetate) salts can be oxidized in a single step to phenols, as shown in eq 7.[10] An interesting alternative which combines both boron and thallium chemistry has been developed whereby the arylthallium compound is treated with diborane to provide the arylboronic acid.[11] Oxidation of the boronic acid under standard conditions (eq 8) yields the phenol.

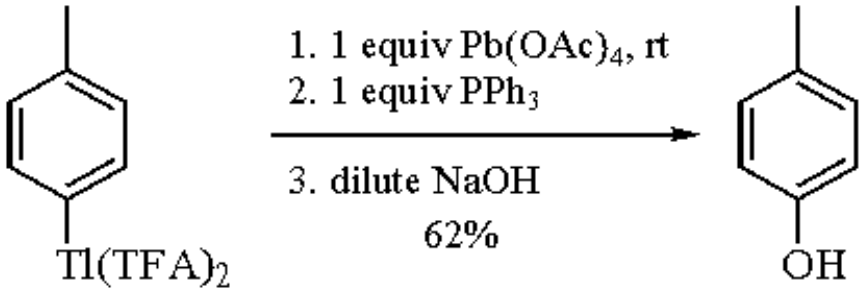

(7)

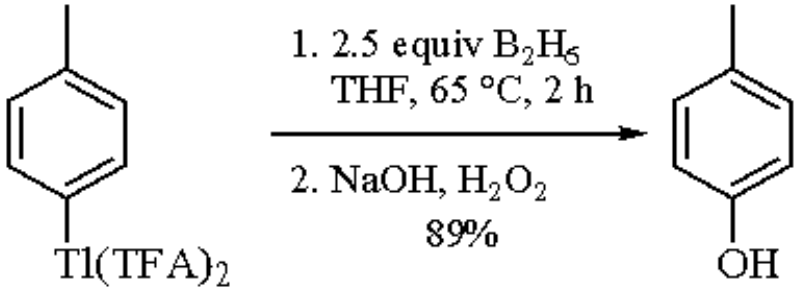

(8)

Thallation of substituted arenes provides entry into indoles under notably mild conditions (eqs 9 and 10).[12,13]

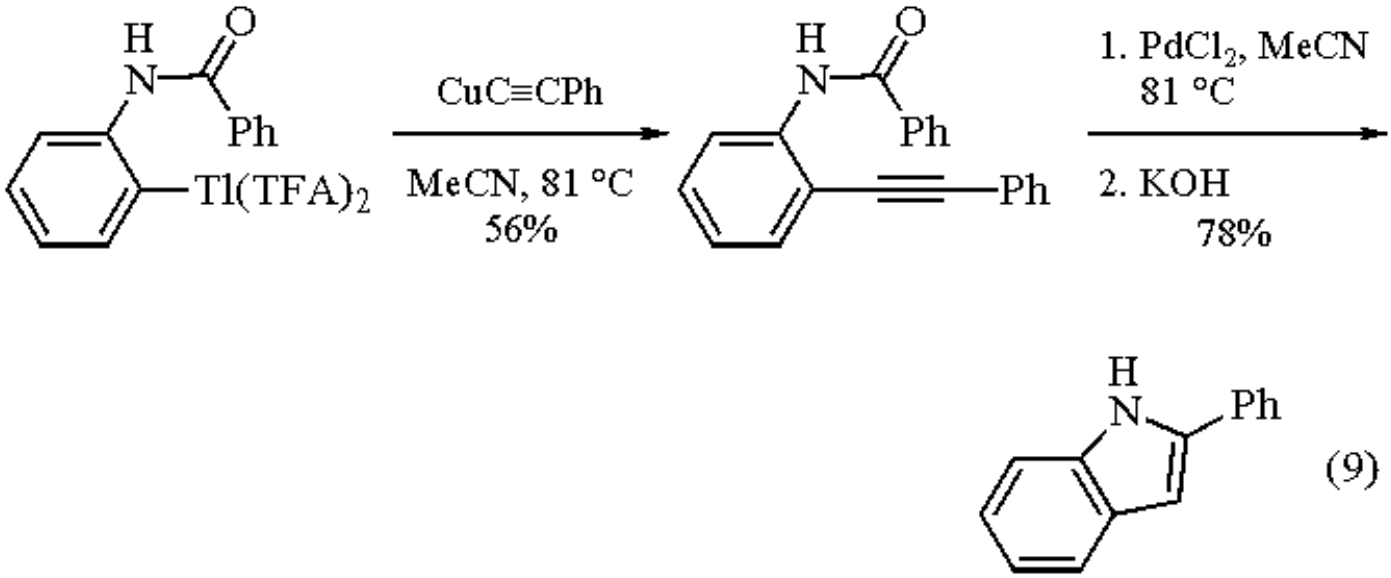

(9)

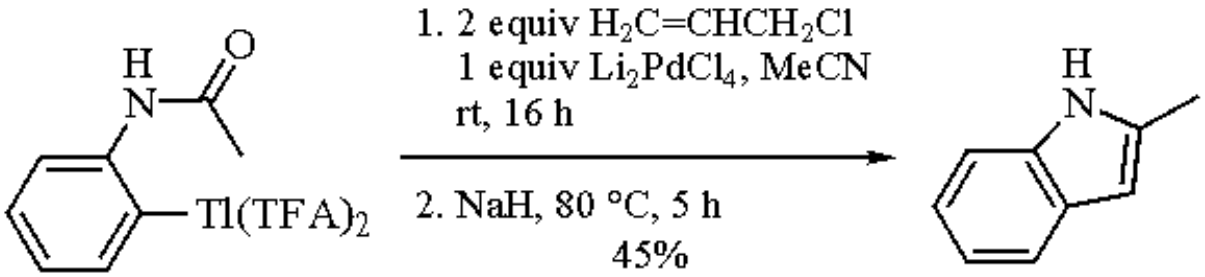

(10)

Silyl enol ethers have been treated with tolylthallium bis(trifluoroacetate) to generate the novel α-metallo ketones shown in eq 11.[14] These compounds are enolate equivalents in titanium-mediated aldol condensations.

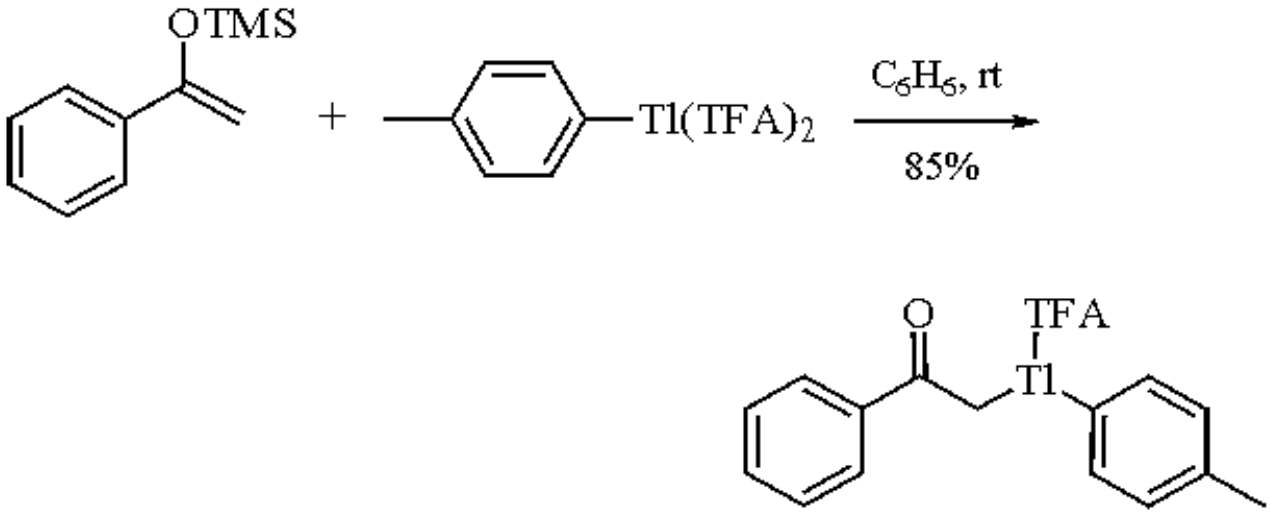

(11)

Oxidations.

TTFA is a very useful oxidant. Simple alkenes undergo oxidation when treated with thallium(III) salts. The reaction proceeds by an initial oxythallation of the alkene followed by dethallation to give the oxidation product and thallium(I). The intermediate thallium(III) salts are not generally isolated. The oxidation products are glycols, their mono- and diesters, aldehydes, ketones, and epoxides, and the reaction generally involves the migration of a substituent. The product distribution is dependent on reaction conditions and the nature of the thallium(III) salt. An illustration of the use of TTFA in alkene oxidation is shown in eq 12.[15] The reagent of choice for alkene oxidations is, however, ***Thallium(III) Nitrate***.

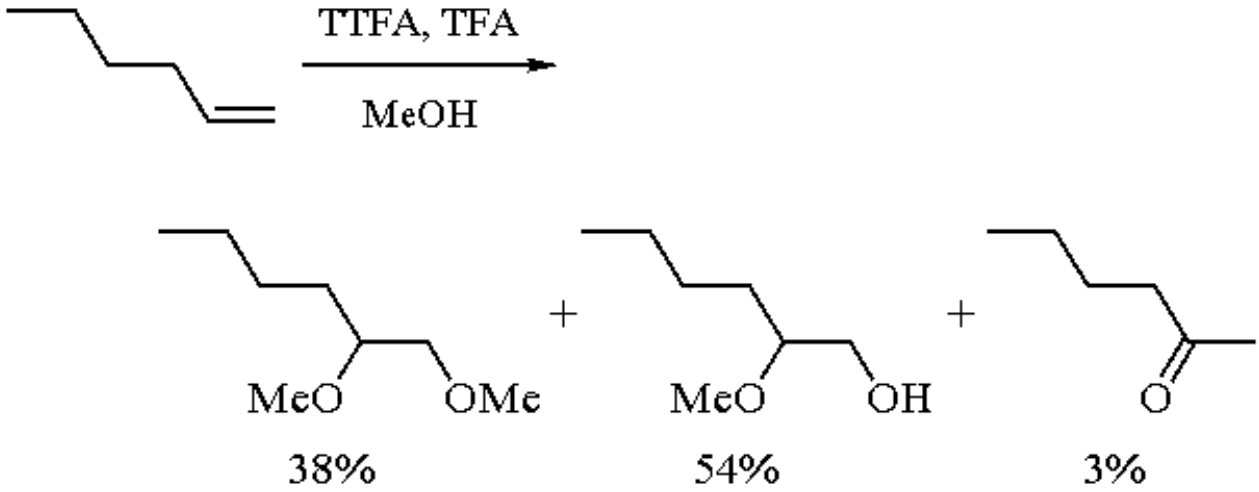

(12)

Acyclic conjugated dienes react with TTFA to provide 1,2-diacetoxyalkenes in low yields.[16] This is in contrast to ***Thallium(III) Acetate***, which provides both 1,2- and 1,4-addition products.[17] On the other hand, reaction of cyclic dienes with TTFA provides both the 1,2- and 1,4-addition products with *cis* stereochemistry (eq 13). Oxidation of nonconjugated dienes with TTFA is also possible. An example of this methodology in the transannular cyclization of 1,5-cyclooctadiene is shown in eq 14.[18]

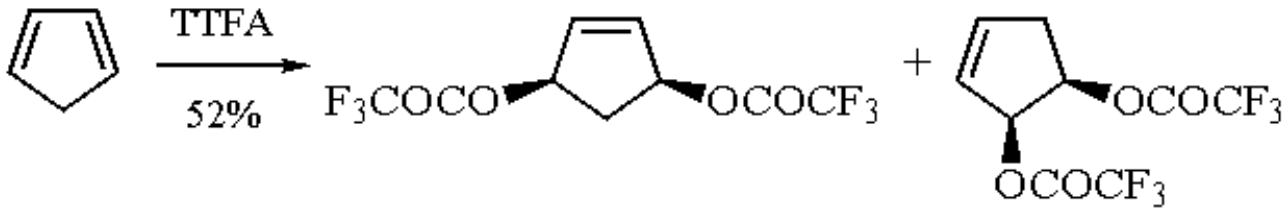

(13)

59:41

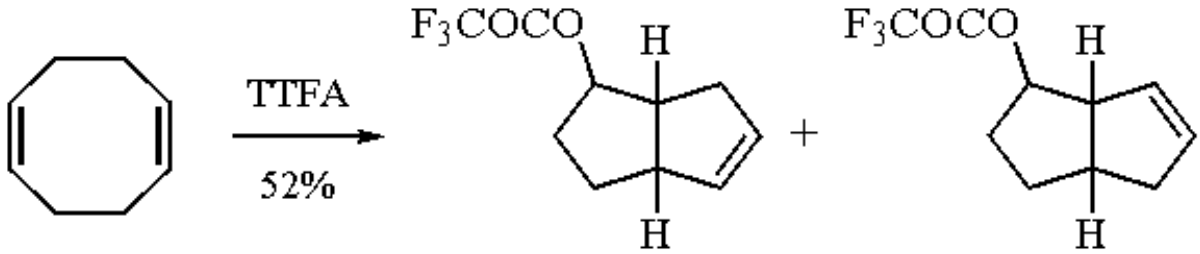

(14)

3:2

Efficient routes have been developed for the preparation of *p*-quinones from a variety of aromatic substrates.[19] For example, substituted 4-*t*-butylphenols can be converted to quinones in good yields (eq 15). Similarly, hydroquinones, 4-aminophenols, and 4-halophenols can be converted to *p*-quinones in good yields (eq 16).

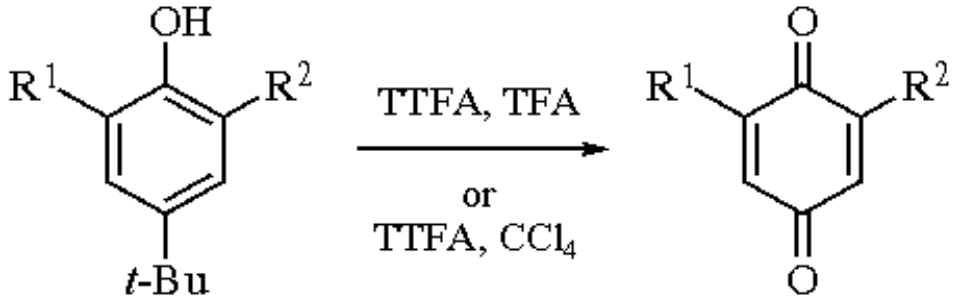

(15)

$R^1 = Br, R^2 = H$; 57%
$R^1 = Br, R^2 = Me$; 89%
$R^1 = I, R^2 = t\text{-}Bu$; 87%
$R^1 = Me, R^2 = Me$; 88%

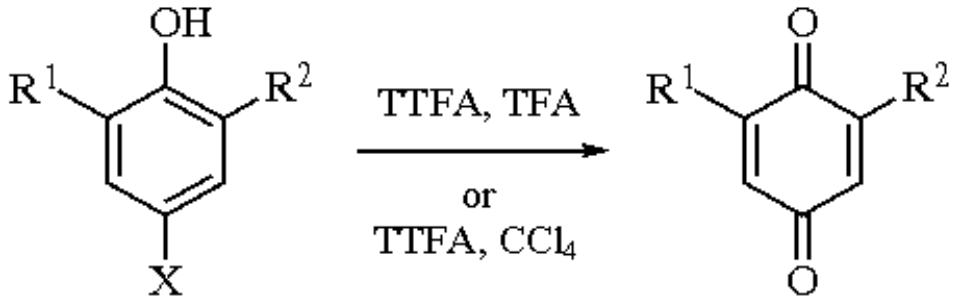

(16)

$R^1 = R^2 = H, X = OH$; 68%
$R^1 = Me, R^2 = H, X = OH$; 77%
$R^1 = Ph, R^2 = H, X = OH$; 73%
$R^1 = R^2 = H, X = NH_2$; 88%
$R^1 = R^2 = Br, X = NH_2$; 81%
$R^1 = R^2 = X = Br$; 77%

Thallated aromatics also undergo oxidation with ***Trifluoroperacetic Acid*** to provide quinones (eq 17). The reaction proceeds with the migration of an R group or by elimination of hydrogen halide (R^1 = halogen).[20]

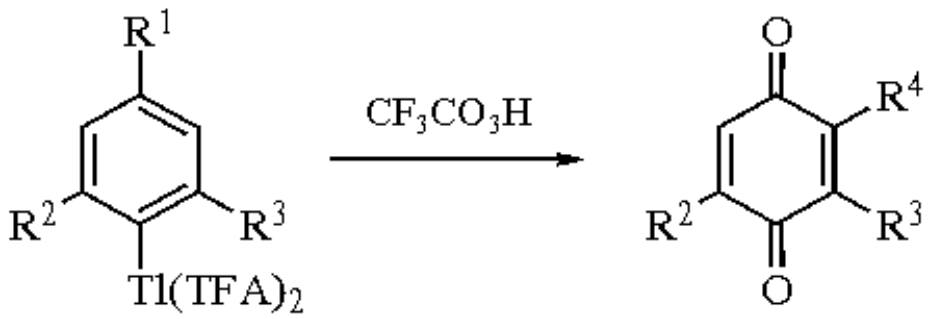

(17)

$R^1 = R^2 = R^3 = R^4 = H$; 65%
$R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Me$; 68%
$R^1 = Cl$, $R^2 = R^3 = R^4 = H$; 42%
$R^1 = OMe$, $R^2 = R^3 = R^4 = H$; 61%

Methoxy-substituted phenylpropanoic acids undergo oxidation with 2 equiv TTFA to provide *p*-quinones (eq 18).[21] The reaction involves a one-electron oxidation to form a radical cation, followed by trapping of the intermediate with the carboxyl group and subsequent oxidation to the quinone by the second equivalent of TTFA.

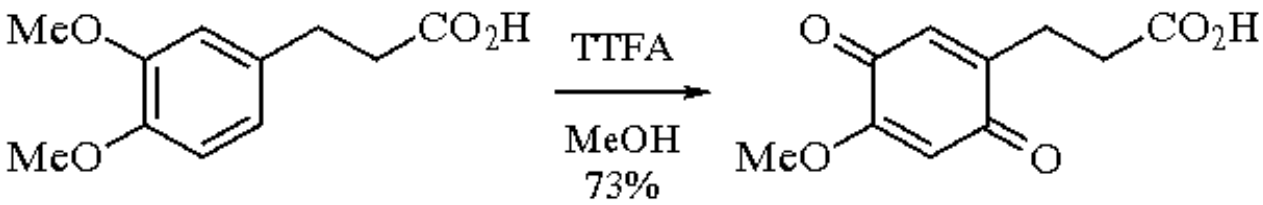

(18)

TTFA has found extensive utility in intramolecular oxidative phenolic coupling reactions and has been elegantly used in the synthesis of many natural products. This coupling strategy, which mimics the biosynthesis of these natural products, provides a laboratory analog of this important reaction. In these reactions, TTFA functions as a two-electron oxidant. The *ortho-para* coupling strategy in the synthesis of a precursor for racemic oxocrinine is shown in eq 19.[22]

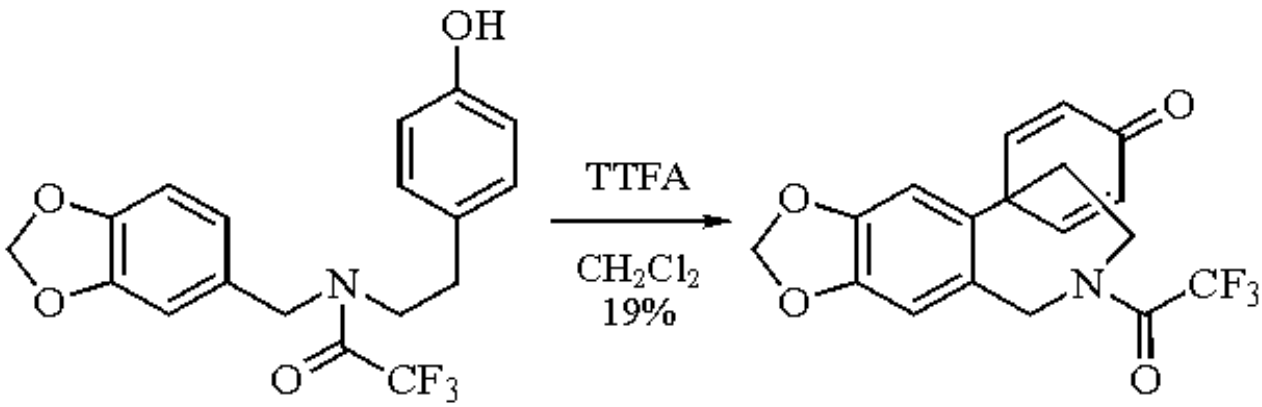

(19)

The major problems associated with this type of coupling reaction are regioselectivity, oxidation of other functional groups, and low yields. A solution to the above problems has been presented in the synthesis of narwedine by the use of a palladacycle to direct the mode of cyclization and to protect the oxidizable functional groups (eq 20).[23] The reaction furnishes a 51% yield of narwedine.

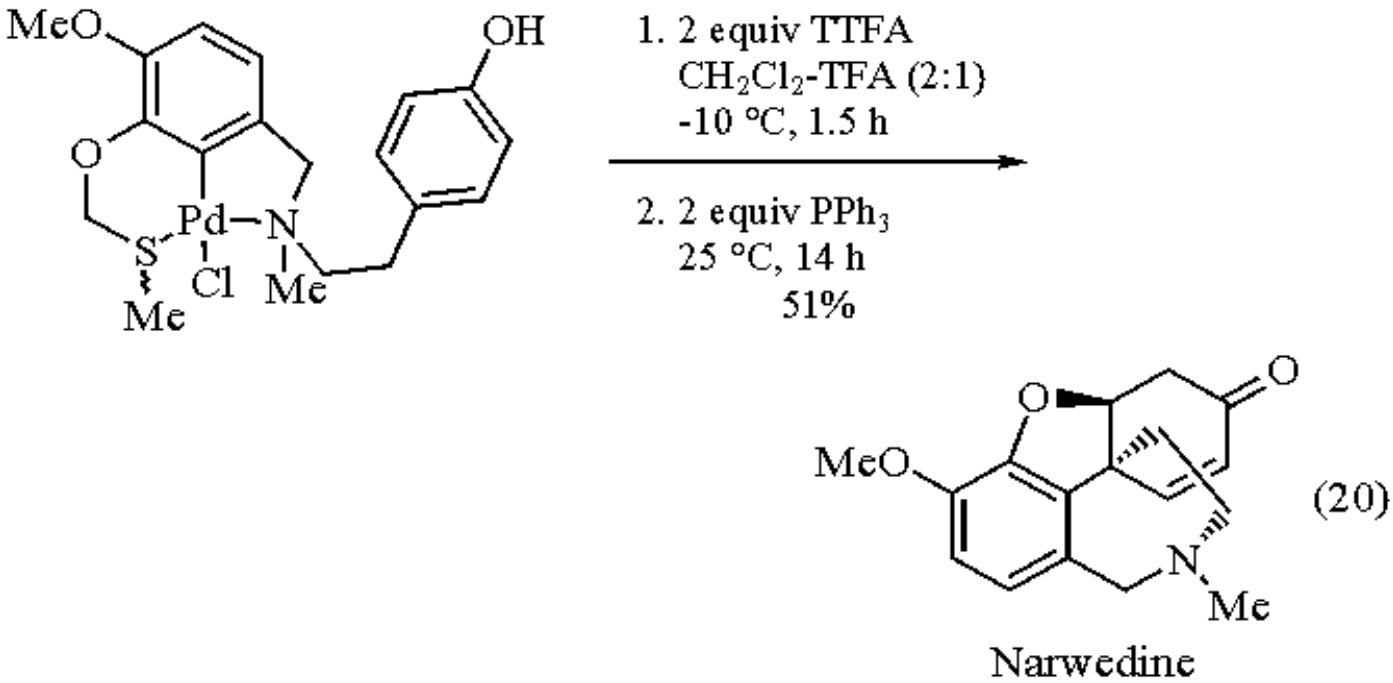

Oxidative dimerization reactions of cinnamic acids have been explored. The reaction proceeds in the presence of ***Boron Trifluoride Etherate*** to provide fused bislactones (eq 21).[24]

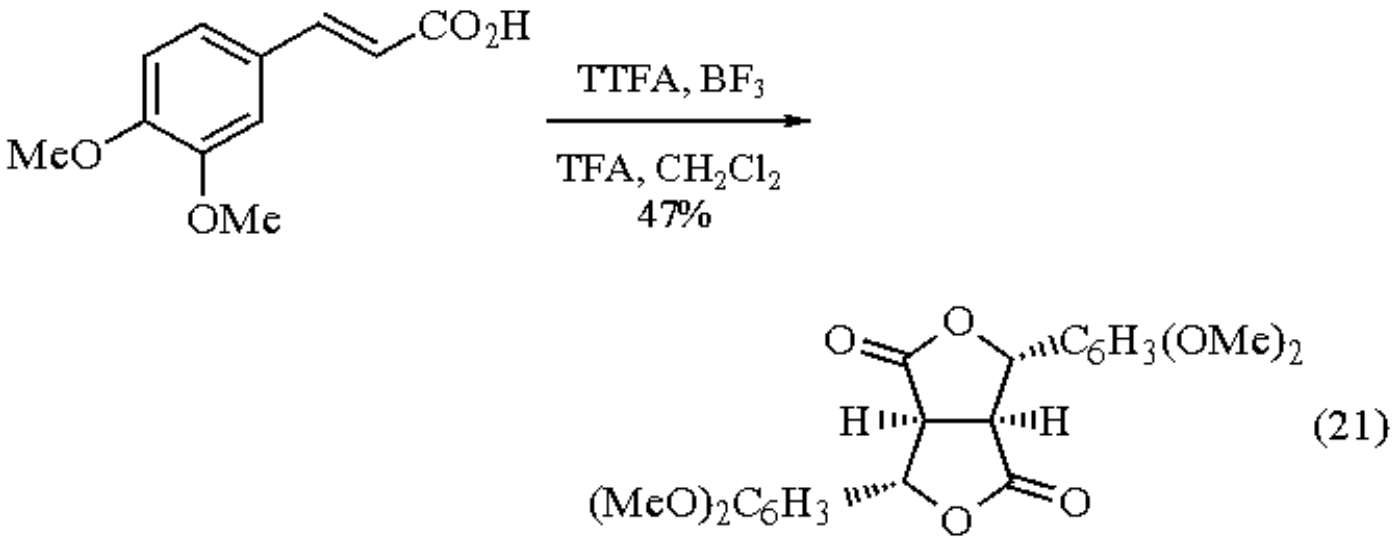

TTFA can be effectively used for both inter- and intramolecular biaryl coupling reactions (Ullmann-type couplings). An example of an intermolecular coupling reaction is illustrated in eq 22.[25] (for similar biaryl coupling reactions with TTFA and palladium catalysis, see ***Thallium(III) Trifluoroacetate--Palladium(II) Acetate***). The details of the various reaction conditions for this coupling reaction have been determined.[25] The coupling reactions work well with moderately electron-rich aryls and poorly with electron-poor aryls. Modification of the reaction conditions for coupling of highly electron-rich aryls has also been reported.[26]

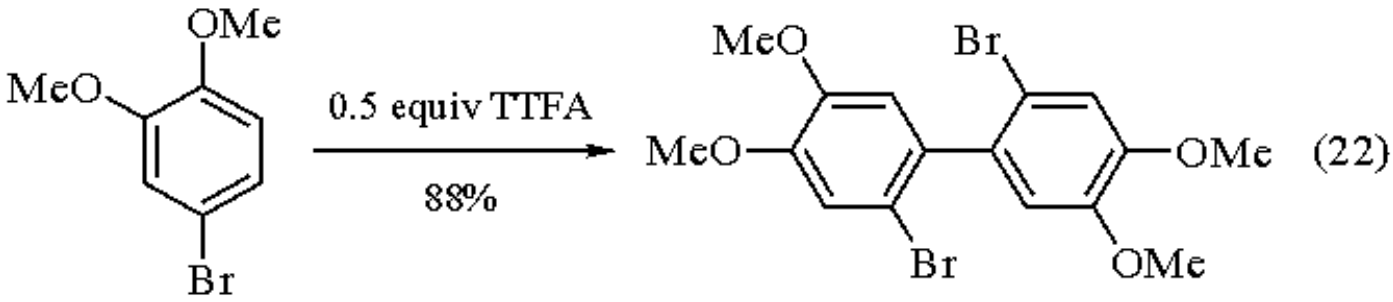

Intramolecular biaryl coupling reactions using TTFA also proceed in a facile fashion. An example of this methodology in the synthesis of the aporphine alkaloid ocoteine is shown in eq 23.[27] TTFA is a superior reagent to ***Vanadyl Trifluoride*** in this type of coupling, since the latter reagent generally gives *O*-demethylated compounds.

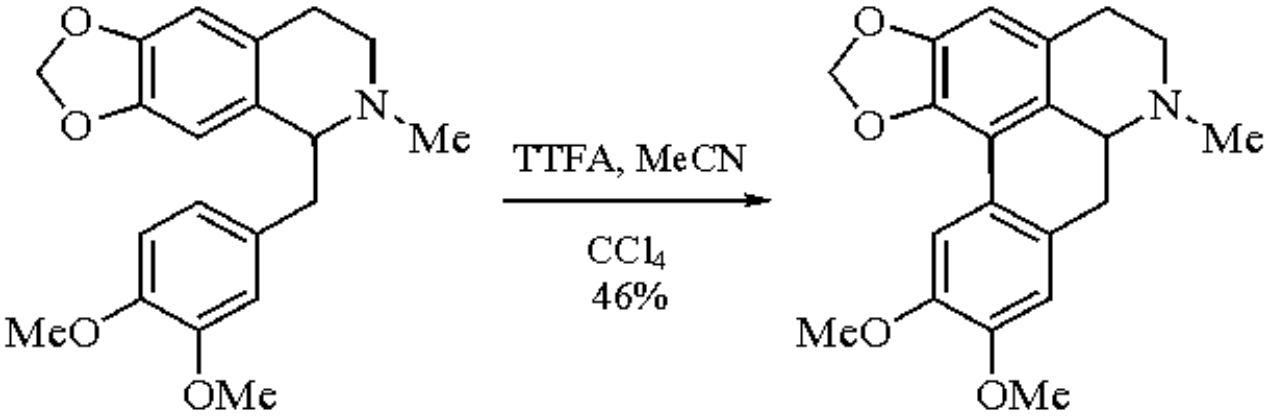

(23)

An interesting example of the biaryl coupling reaction in the synthesis of macrocyclic lactones has been reported (eq 24).[28] Other examples of oxidative biaryl coupling reactions include the synthesis of lignan natural products.[29]

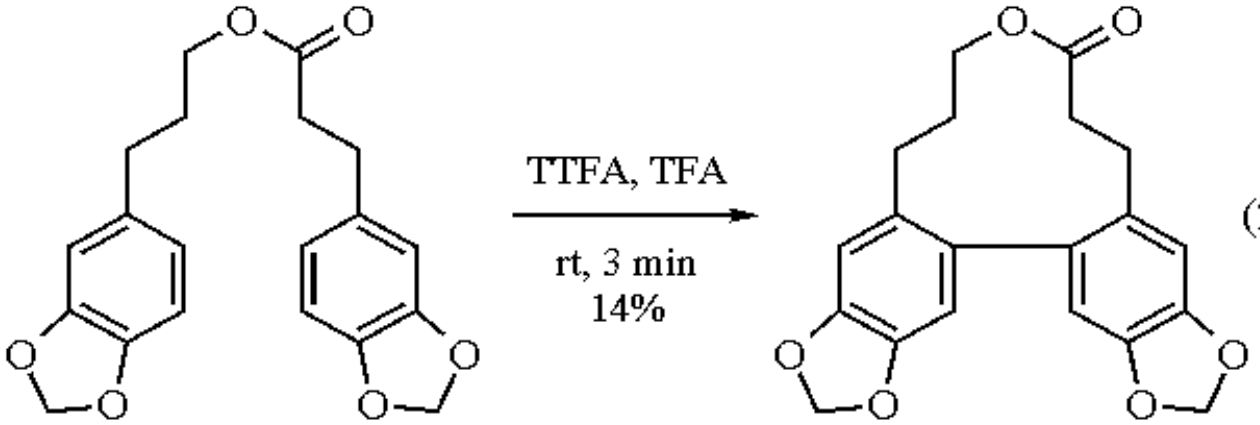

(24)

Miscellaneous.

Aromatic compounds are allylated using allylsilanes and TTFA.[30] Allylsilanes are converted to allyl ethers,[31] *N*-allyl amides,[32] and allyl nitrates[33] on treatment with TTFA and the appropriate nucleophile. The soft Lewis acid properties of TTFA can be effectively applied in the deprotection reactions of sulfur-containing compounds. Thioacetals can be deprotected to form the corresponding carbonyl compounds in high yields (eq 25).[34]

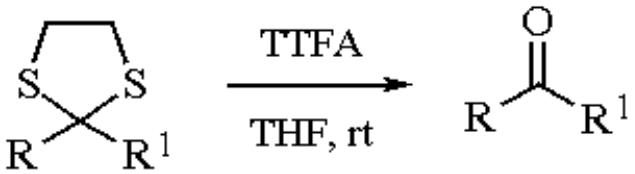

(25)

R = Ph, R^1 = Me; 84%
R = R^1 = Ph; 95%
R = Ph, R^1 = H; 83%

TTFA has also been used for the deprotection of sulfur protecting groups in cysteines and subsequently as an oxidant to yield cystines (eq 26).[35] The reaction has been extended to intramolecular disulfide bond formation in cystine-containing peptides. The reaction employs very mild conditions and proceeds in high yields without the problems associated with other oxidants such as iodine.

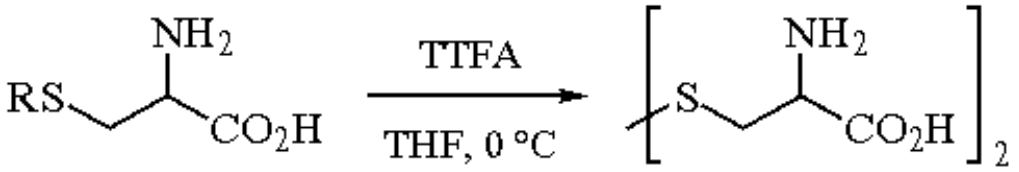

(26)

R = adamantyl, 80%; Bn, 0%; *t*-Bu, 80%; trityl, 87%

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Thallium(III) Trifluoroacetate--Palladium(II) Acetate[1]

$Tl(OCOCF_3)_3$-$Pd(OAc)_2$

[23586-53-0] · $C_6F_9O_6Tl$ · Thallium(III) Trifluoroacetate--Palladium(II) Acetate · (MW 543.44)

[3375-31-3] · $C_4H_6O_4Pd$ · Thallium(III) Trifluoroacetate--Palladium(II) Acetate · (MW 224.52)

(catalyst for aryl couping, carbonylation, and alkenation)

Physical Data: see entries ***Thallium(III) Trifluoroacetate*** and ***Palladium(II) Acetate***.

Solubility: sol common organic solvents; limited sol hexane.

Form Supplied in: white solid ($Tl(OCOCF_3)_3$); orange-brown solid ($Pd(OAc)_2$); commercially available.

Handling, Storage, and Precautions: all thallium compounds are extremely toxic to inhalation, skin contact, and ingestion. Toxicity is cumulative. Extreme caution should be used when handling these materials. Use in a fume hood.

General Discussion.

Thallium(III) salts are efficient reagents for the conversion of aryls to biaryls under mild conditions.[2] The major drawback of these reactions is the requirement of at least one electron-donating substituent on the aromatic ring. A practical alternative for the preparation of biaryls containing both electron-donating and mild electron-withdrawing groups has been developed.[3] The reaction involves the coupling of arylthallium bis(trifluoroacetates) in the presence of catalytic palladium(II) acetate (eq 1).

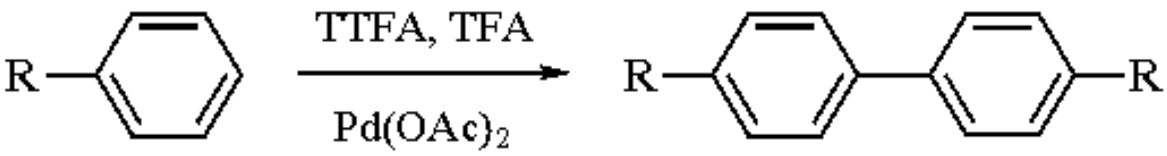

(1)

R	Temp. (°C)	Yield (%)
H	65	64
Me	105	93
OMe	50	79
Cl	105	66
F	70	86

The reaction proceeds in good to high yields, with thallium(III) functioning as a reoxidant for palladium. These reactions are homogeneous and product isolation is simple. Lithium tetrachloropalladate has been used as the catalyst in similar coupling

reactions to produce good yields of biaryls (eq 2).[4] It is interesting to note that the palladium(II) acetate-catalyzed reaction with chlorobenzene gives a higher yield of the biphenyl as compared to the reaction with lithium tetrachloropalladate (66% vs. 20%).

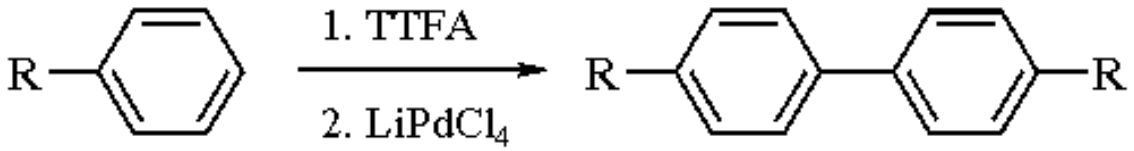

(2)

R = H, 88%; Me, 97%; OMe, 89%; Cl, 20%; *t*-Bu, 72%

A tandem thallation-carbonylation process has been developed for arenes en route to aromatic esters, phthalides, anhydrides, imides, and 3,4-dihydroisocoumarins.[5] The reaction involves the carbonylation of arylthallium bis(trifluoroacetates) in the presence of catalytic ***Palladium(II) Chloride***, ***Carbon Monoxide***, and ***Lithium Chloride*** at room temperature and atmospheric pressure. The preparation of a variety of esters and phthalides are shown in eqs 3 and 4, respectively.

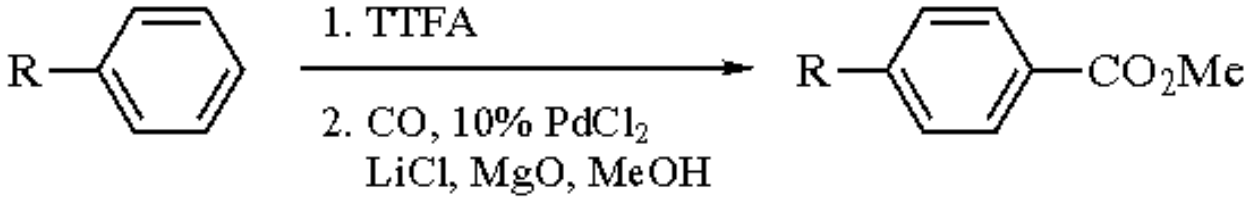

(3)

R = H, 55%; F, 42%; OMe, 62%; *t*-Bu, 80%

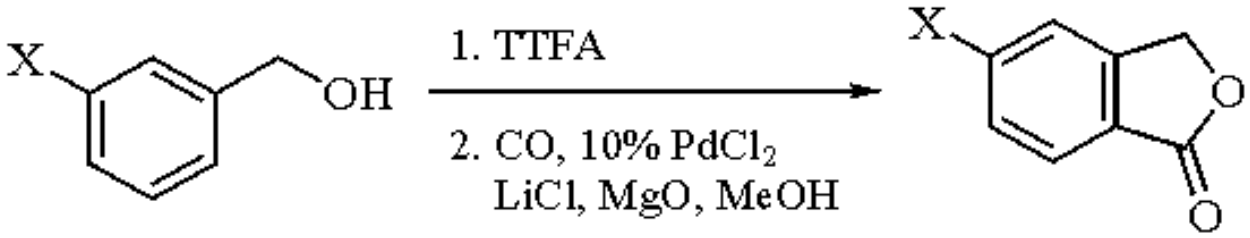

(4)

X = H, 18%; OMe, 47%; OH, 95%; Cl, 45%

Palladium(II)-catalyzed alkenation of arylthallium bis(trifluoroacetates) has been explored by several groups.[6] An interesting Heck-type alkenation of arylthallium bis(trifluoroacetate) with ***Methyl Vinyl Ketone*** has been reported.[7] This reaction uses lithium tetrachloropalladate as the catalyst and proceeds under mild reaction conditions (eq 5).

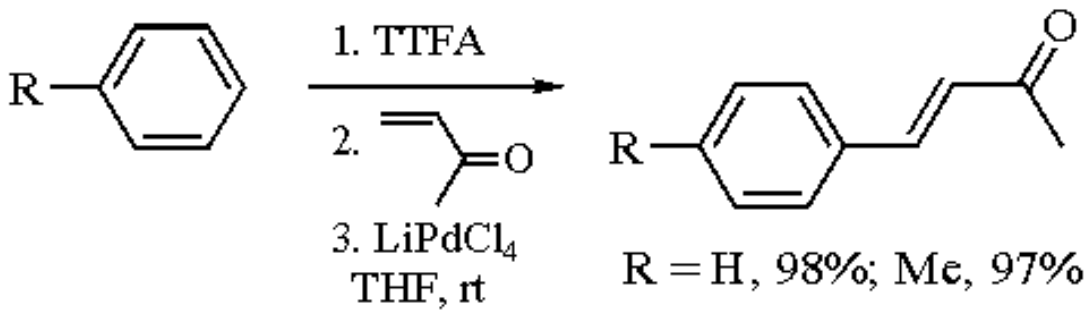

(5)

R = H, 98%; Me, 97%

Related Reagents.

Palladium(II) Acetate; ***Phenylthallium Bis(trifluoroacetate)***; ***Thallium(III) Trifluoroacetate***.

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Thexylborane[1]

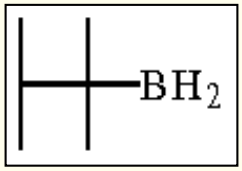

[3688-24-2] · $C_6H_{15}B$ · Thexylborane · (MW 98.02)

(readily available monoalkylborane useful for regioselective hydroboration of alkenes and dienes; thexylalkylboranes and thexyldialkylboranes are useful intermediates for the synthesis of unsymmetrical ketones, cyclic ketones, *trans* disubstituted alkenes, conjugated dienes, and diols[1])

Alternate Name: (1,1,2-trimethylpropyl)borane.

Physical Data: generally prepared in situ; dimeric in THF. It can be isolated as a liquid, mp -34.7 to -32.3 °C.[2]

Solubility: sol ether, hydrocarbon, and halocarbon solvents; THF is generally the solvent of choice; reacts rapidly with protic solvents.[1a]

Form Supplied in: not commercially available.

Analysis of Reagent Purity: analyzed by NMR and IR spectroscopy and by hydrogen evolution upon reaction with methanol.[1a,3]

Preparative Method: most conveniently prepared from ***Borane-Tetrahydrofuran*** and 2,3-dimethyl-2-butene in THF (eq 1).[1a,2]

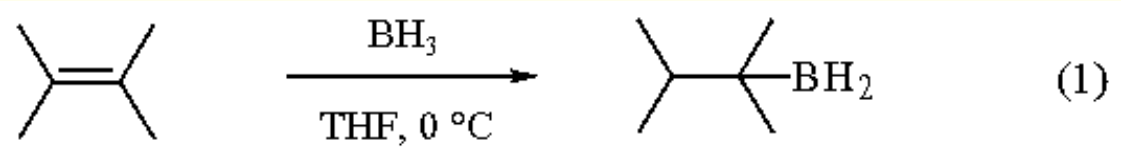

Handling, Storage, and Precautions: very reactive with oxygen and moisture; must be handled using standard techniques for handling air-sensitive materials.[3] The reagent is reported to be stable for at least a week when stored at 0 °C in THF solution under N_2.[1a] However, at rt the boron atom slowly migrates from the tertiary position to the primary (3% in 8 days).[4] Use in a fume hood.

Hydroboration of Alkenes.

Reactions of alkenes with thexylborane have been extensively studied and several reviews have appeared.[1] Thexylborane ($ThxBH_2$) in THF reacts with 2 equiv of relatively unhindered alkenes to form thexyldialkylboranes. The regioselectivity in the hydroboration of alkenes with thexylborane is similar to that of borane in THF. For example, hydroboration of 2 equiv of 1-hexene with thexylborane followed by oxidation produces a 95:5 mixture of 1-hexanol and 2-hexanol. Hydroboration of a terminal monosubstituted alkene with thexylborane in a 1:1 ratio gives a mixture of both the thexylmonoalkylborane and thexyldialkylborane. (Preparation of thexylmonoalkylboranes from monosubstituted alkenes can be accomplished using ***Chloro(thexyl)borane-Dimethyl Sulfide***). With most disubstituted and some trisubstituted alkenes, it is possible to prepare the corresponding thexylmonoalkylborane by treating 1 equiv of the alkene with thexylborane at -20 to -25 °C.[5] Thexylmonoalkylboranes can hydroborate relatively unhindered alkenes to form thexyldialkylboranes containing two different alkyl groups (eq 2).[6]

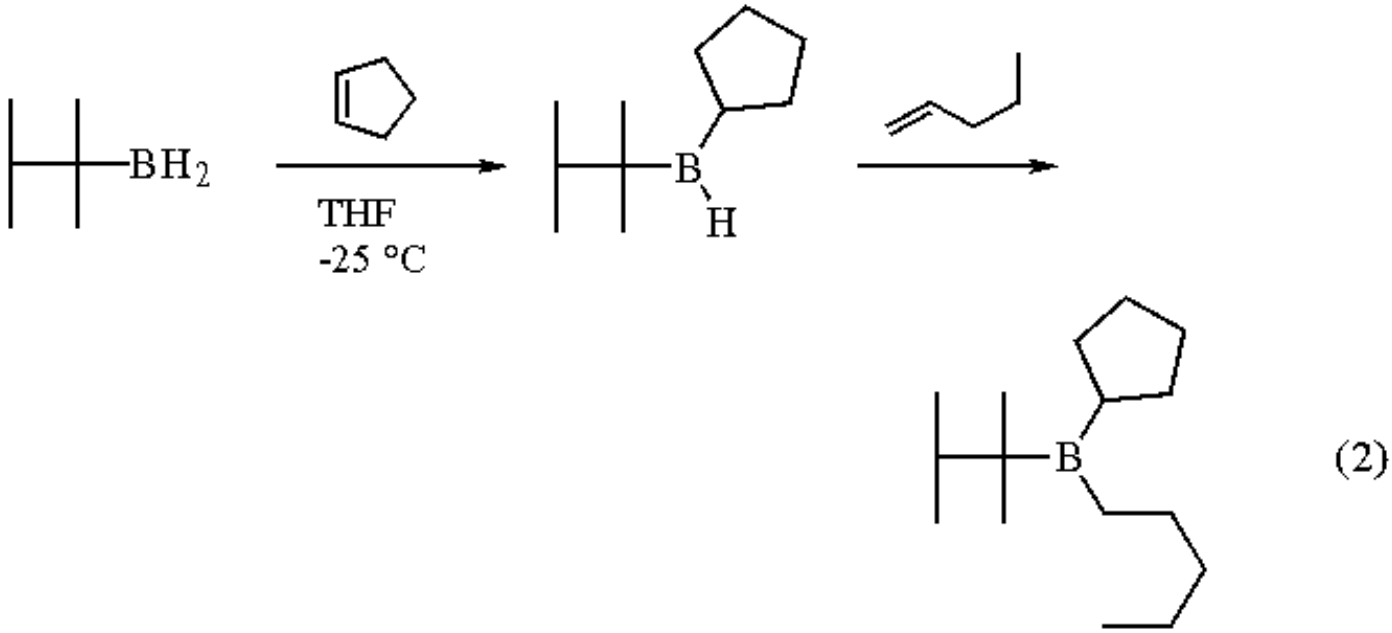

(2)

Hydroboration of a hindered alkene with either thexylborane or thexylmonoalkylborane is slow and is accompanied by dehydroboration of the thexylmonoalkylborane, producing a monoalkylborane and 2,3-dimethyl-2-butene. Lower reaction temperatures and the presence of excess 2,3-dimethyl-2-butene in the reaction may reduce the amount of dehydroboration.[6] Sterically hindered alkenes can be hydroborated under high pressure (6000 atm) to produce highly hindered trialkylboranes, such as trithexylborane,[7] but this procedure does not appear to be practical for synthetic purposes.

Mixed thexyldialkylboranes have also been prepared by treating thexylborane consecutively with different halomagnesium or lithium dialkylcuprates.[8] This procedure offers the advantage of being able to introduce methyl or aryl groups onto the boron atom.

The hydroboration of either terminal or internal alkynes with thexylborane in a 2:1 ratio gives good yields of the expected thexyldialkenylboranes, but the reaction of thexylborane with 1 equiv of a terminal alkyne is reported to give at most 20% of the thexylalkenylborane.[1a,4]

Complete dehydroboration of the thexyl group in thexylmonoalkylboranes can be achieved by treating thexylmonoalkylboranes with a fourfold excess of ***Triethylamine***.[5] This reaction provides a general method for the synthesis of monoalkylboranes as the triethylamine complexes. More recently, it has been found that thexylborane-triethylamine or thexylborane-***N,N,N´,N´-Tetramethylethylenediamine*** adducts can be used to hydroborate hindered alkenes directly (with concomitant loss of the thexyl group as 2,3-dimethyl-2-butene) to give the monoalkylborane-amine adducts.[9] ***Monoisopinocampheylborane***, a useful chiral hydroborating reagent, can be prepared by this reaction.[10]

Thexylborane is the reagent of choice for the hydroboration of dienes to form *B*-thexylboracyclanes (eq 3)[11] since the reaction of borane with dienes tends to give polymeric products.[12] Stereoselective cyclic hydroboration of dienes by thexylborane has been employed to prepare acyclic diols with 1,3-, 1,4-, and 1,5-asymmetric induction (eq 4).[13] In the cyclic hydroboration of appropriately substituted 1,5-dienes to yield 1,5-diols, 1,2-asymmetric induction was employed as a key step (eq 5) in the synthesis of the Prelog-Djerassi lactone.[14]

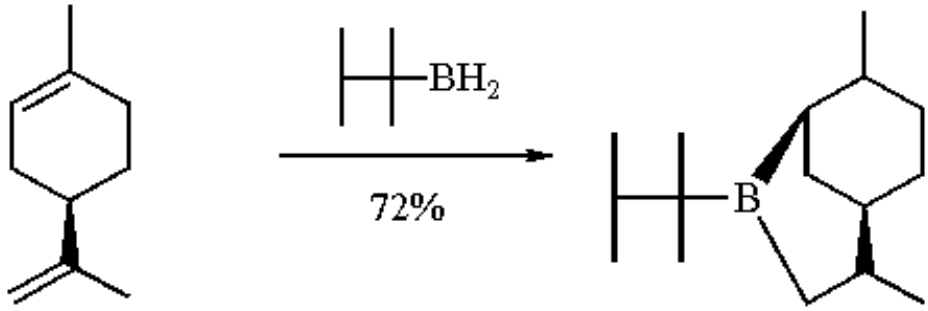

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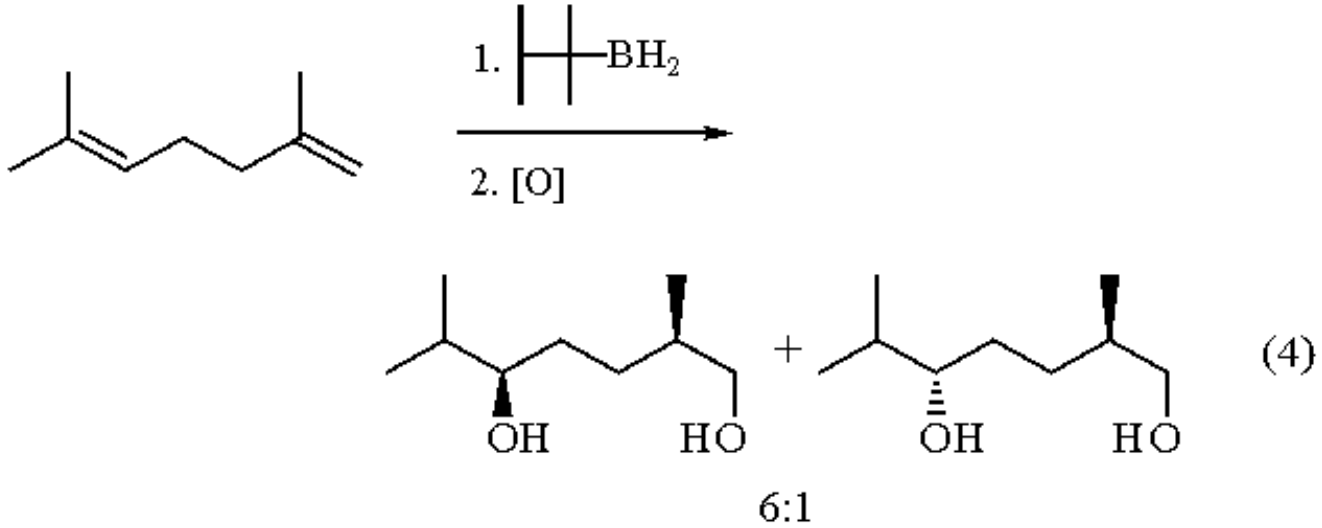

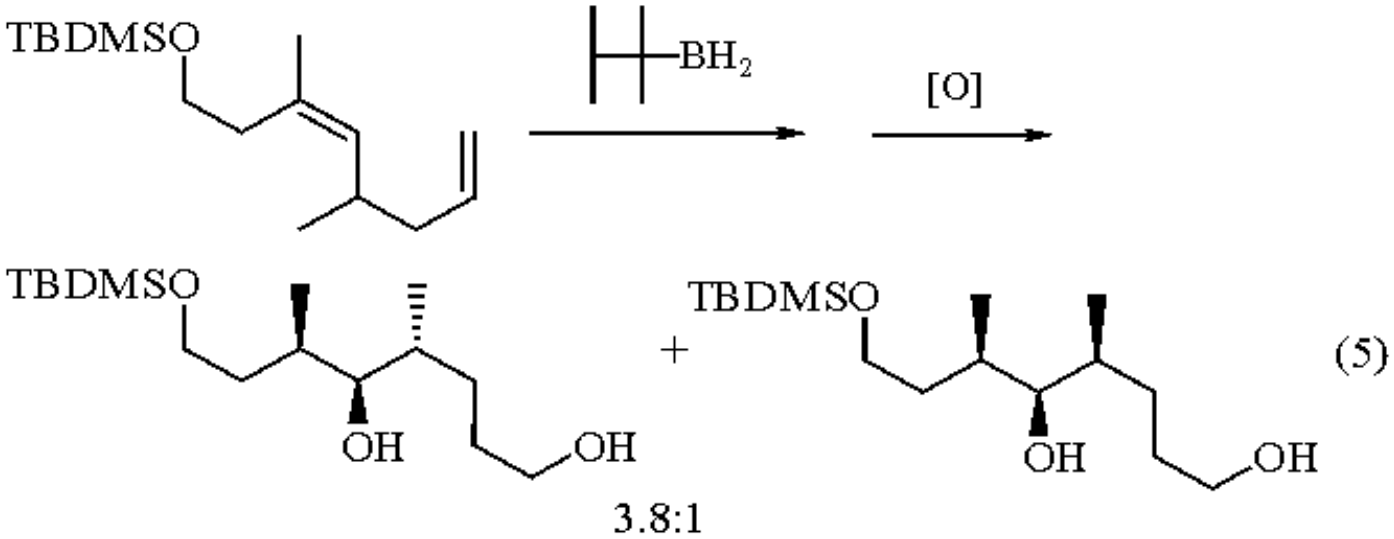

Cyclic hydroboration of allyl vinyl ethers provides a highly stereoselective synthesis of 1,3-diols with *syn* stereochemistry (eq 6).[15] The *syn* stereoselectivity observed in the cyclic hydroboration of allyl vinyl ethers is opposite to the stereoselectivity observed in the acyclic hydroboration of allylic alcohols (see eq 9).[18] Remote stereocontrol in the hydroboration-reduction of enones with thexylborane has also been reported (eq 7).[16] This reaction is proposed to occur by a rapid hydroboration of the carbon-carbon double bond followed by an intramolecular reduction of the carbonyl group by the intermediate dialkylborane.

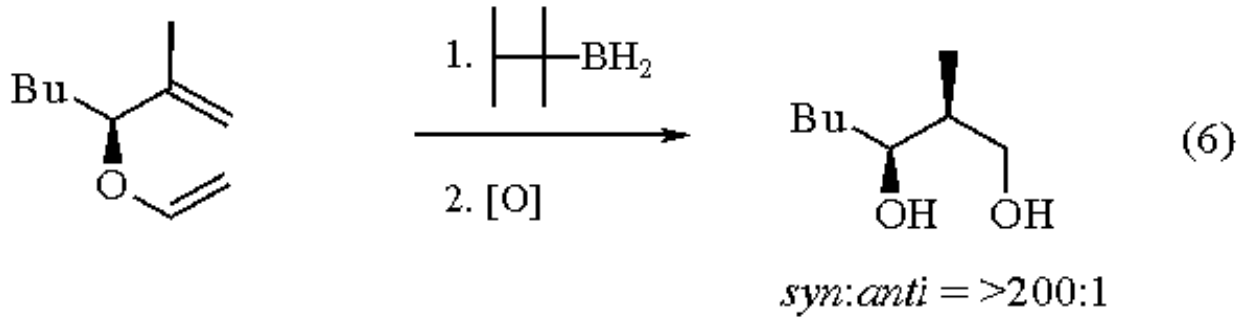

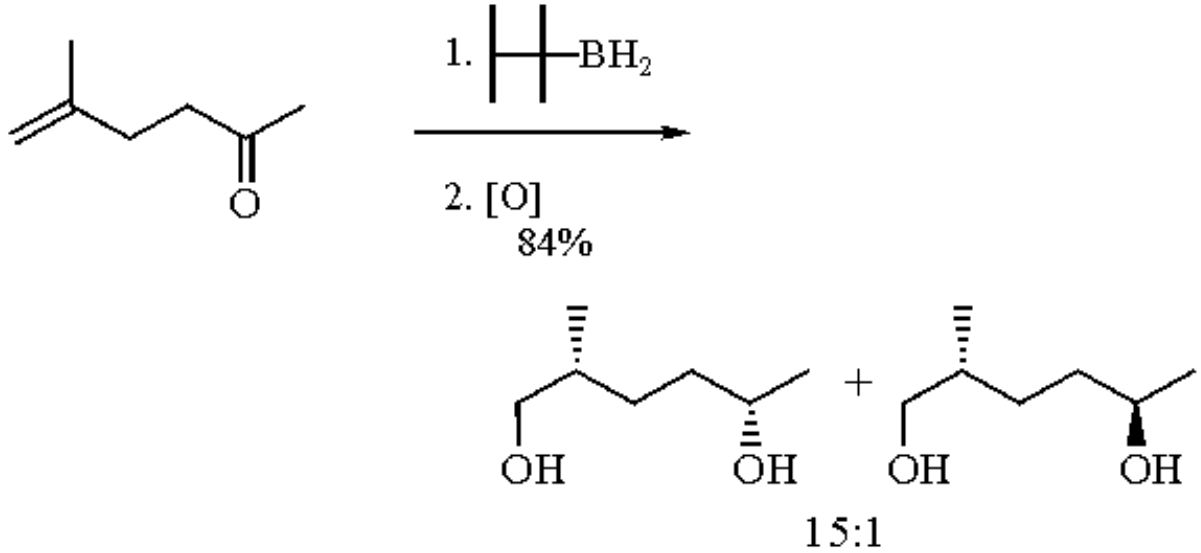

(7)

Acyclic diastereoselection in the hydroboration of alkenes has been reported by several groups. Evans and co-workers[17] observed high levels of 1,3-asymmetric induction in the hydroboration of a number of terminal alkenes bearing substituents at the 2-position of the alkene and a proximal chiral center, as illustrated in eq 8. These workers concluded that the diastereoselection is directed primarily by the nearest chiral center in each of the substrates, and they proposed a transition state model to account for the observed diastereoselectivity. The hydroboration of acyclic secondary allylic alcohols with thexylborane, yielding 1,3-diols with high *anti* (or *threo*) diastereoselection, has also been reported (eq 9).[18] The diastereoselection observed in this reaction does not require the use of a protecting group on the allylic alcohol. Thexylborane proves to be the hydroboration reagent of choice for reaction with trisubstituted alkenes, but terminal alkenes give higher diastereoselection with the more sterically demanding reagents ***9-Borabicyclo[3.3.1]nonane*** or ***Dicyclohexylborane***.

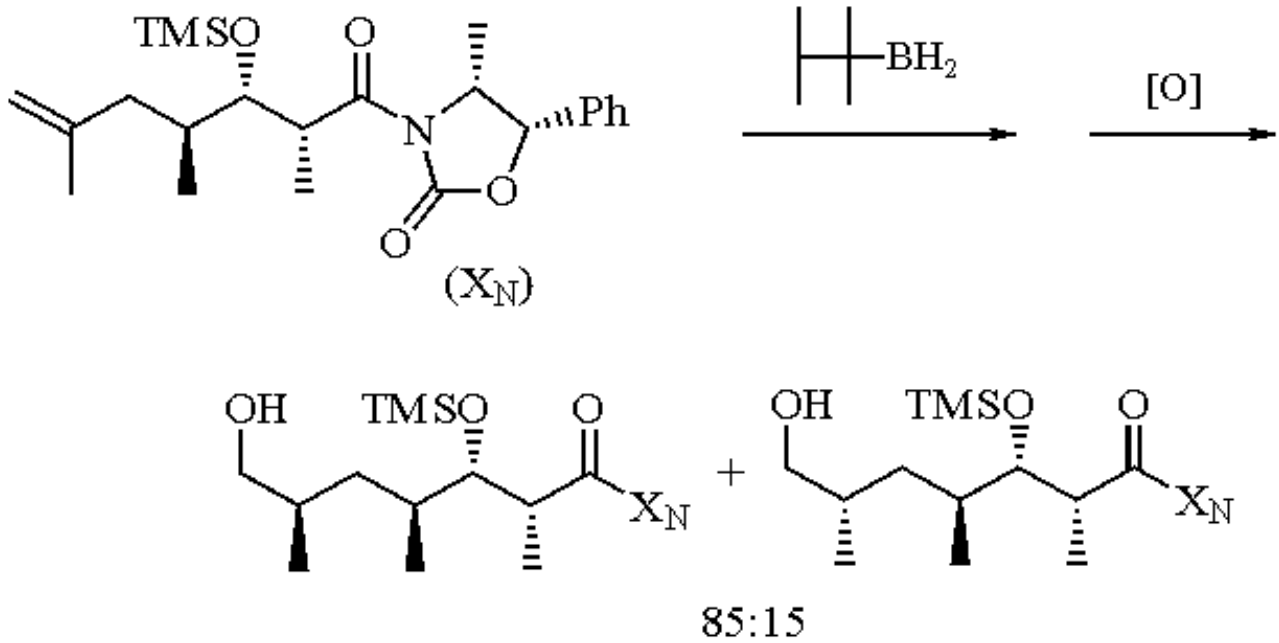

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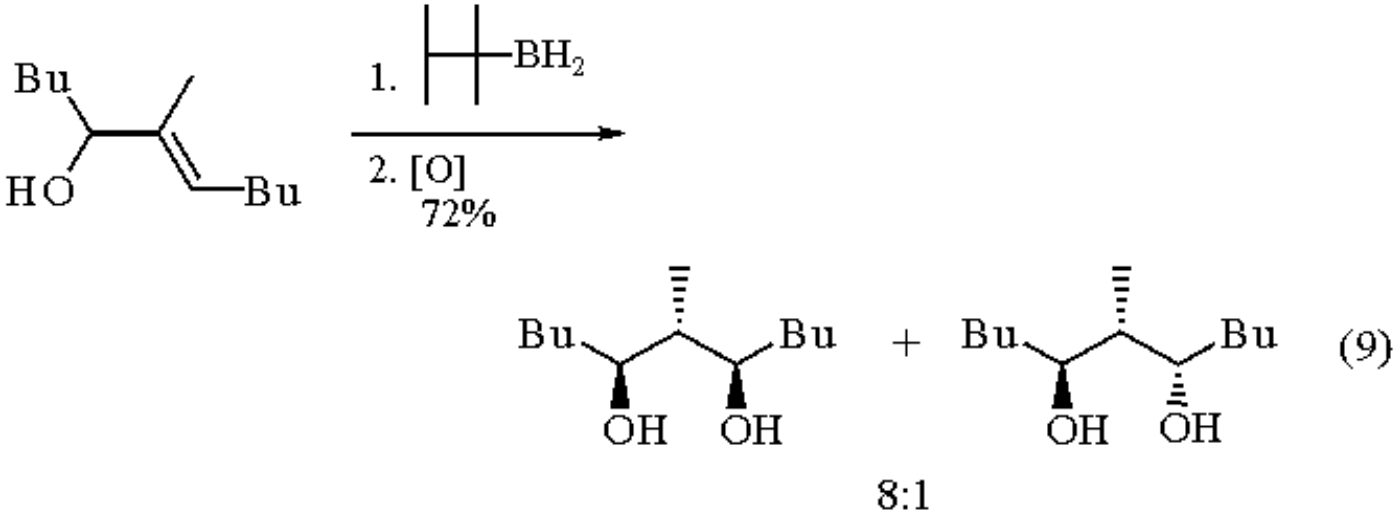

Selective Functional Group Reductions.

The selective reduction of functional groups by thexylborane has been reported,[19a] and the relative reactivity of thexylborane with common functional groups has been compared to that of other borane reagents (***Diborane***, ***Disiamylborane***, and thexylchloroborane-dimethyl sulfide).[19] Acidic hydrogens in -OH, -CO_2H, and -SO_3H groups react at moderate to rapid rates with thexylborane with the evolution of hydrogen. Aldehydes generally react rapidly with thexylborane yielding alcohols after hydrolysis. However, ketones and most other carbonyl groups react only slowly with thexylborane. Carboxylic acids can be reduced to aldehydes by 2.5 equiv of thexylborane, but ***Chloro(thexyl)borane-Dimethyl Sulfide*** is the borane reagent of choice for this transformation. Nitriles, oximes, epoxides, and aromatic nitro compounds are reduced only slowly, and alkyl nitro compounds, disulfides, sulfones, and tosylates do not react with thexylborane.

Use of Thexyldialkylboranes in Synthesis.

Thexyldialkylboranes are particularly useful in synthetic reaction sequences due to the availability of a variety of these compounds and the low migratory aptitude of the tertiary thexyl group in most rearrangement reactions. Several reviews of the role of boron in synthesis have appeared.[1,2,20]

Synthesis of Ketones.

Reaction of thexyldialkylboranes with ***Carbon Monoxide*** in the presence of water followed by oxidation provides a novel route to the synthesis of ketones (eq 10).[21] Yields in this reaction are generally in the 50-80% range. The observed migratory aptitude for the alkyl groups is: primary > secondary >> tertiary. Cyclic ketones can be prepared from dienes by cyclic hydroboration with thexylborane followed by carbonylation and oxidation (eq 11).[22] This annulation procedure stereoselectively provides the *trans*-ring fusion in both the indanone and decalone systems. This methodology has been successfully employed in the stereospecific annulation of 1,5-diene substrates to form the *trans*-hydroazulene nucleus.[23]

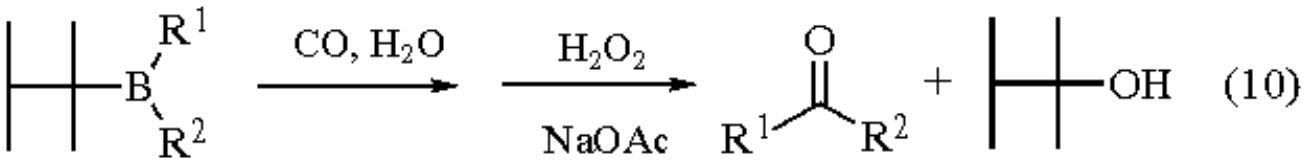

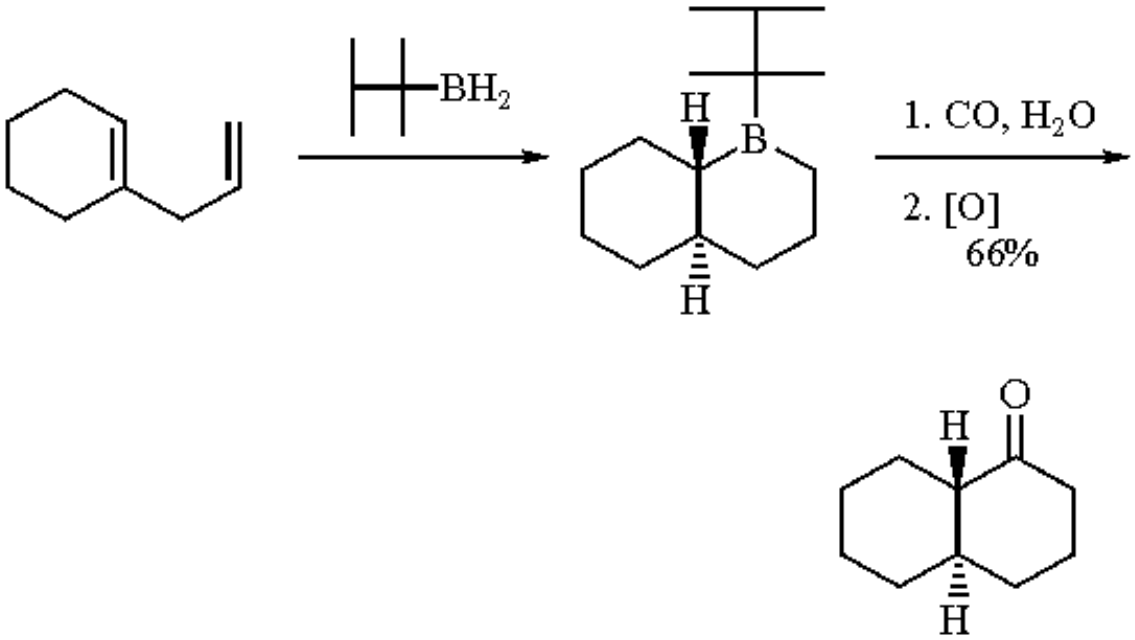

(11)

An alternate procedure to convert thexyldialkylboranes into ketones via an intermediate cyanoborate has been reported (eq 12)[24] which avoids the use of carbon monoxide under high pressure. Yields are quite good, generally >75%, and no special equipment is required for the reaction. This procedure has been employed in the synthesis of the heterocyclic ring system of δ-coniceine (**1**) (eq 13).[25]

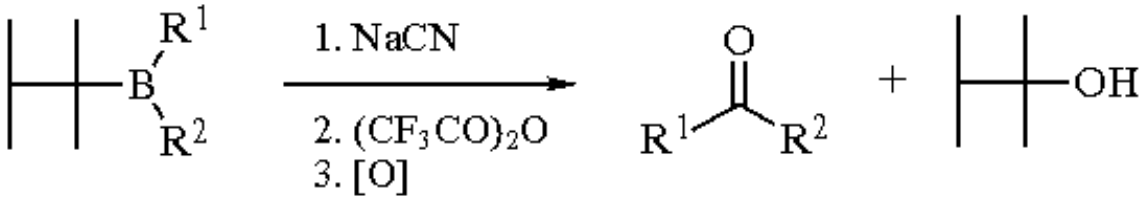

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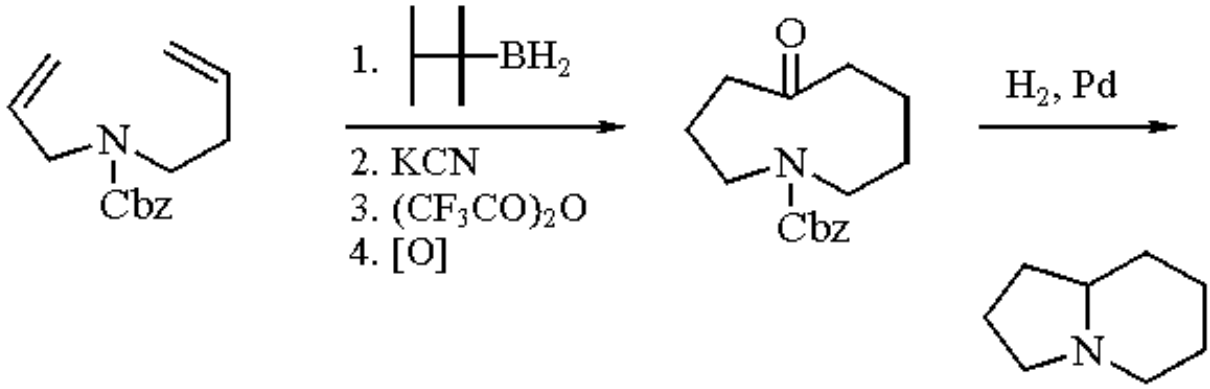

(13)

(1)

Synthesis of Alkenes.

The stereoselective synthesis of (*E*)-disubstituted alkenes[26] can be carried out by treating a thexylmonoalkylborane (**2**) with a 1-bromo-1-alkyne to yield the intermediate thexylalkyl(1-bromo-1-alkenyl)borane (**3**), which is then treated with ***Sodium Methoxide*** to induce a stereospecific rearrangement of the alkyl group (R^1) from boron to carbon. Stereospecific protonolysis of the resulting intermediate (**4**) provides the (*E*)-alkene in high isomeric purity and good to excellent yield (eq 14).

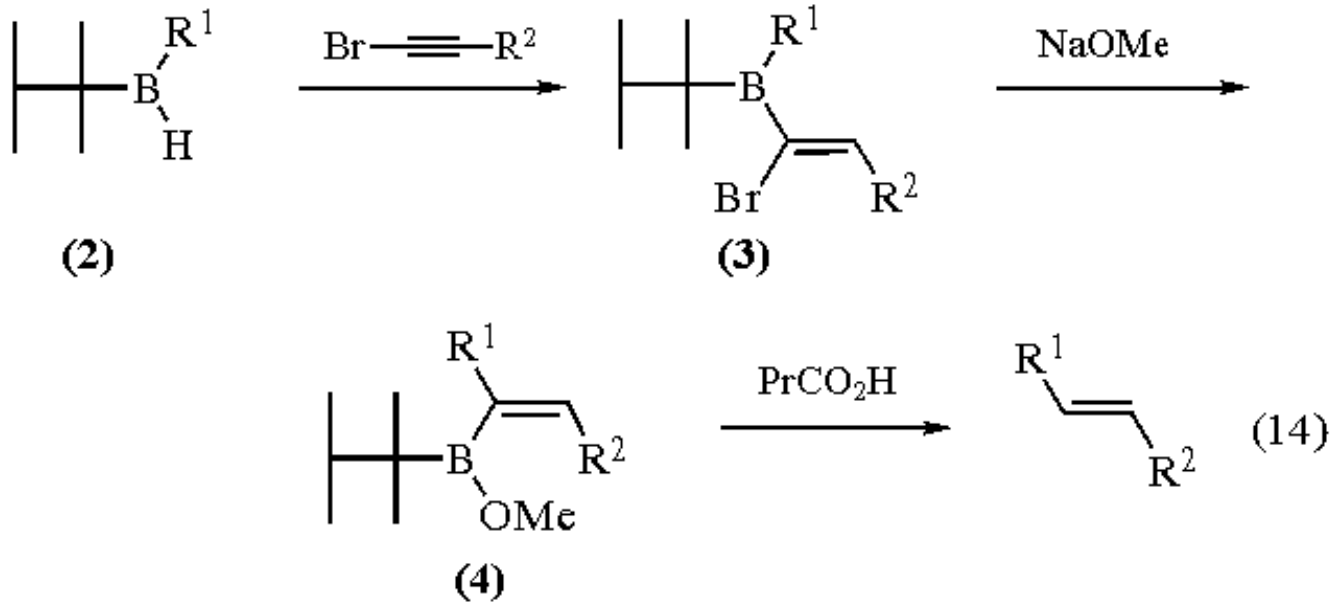

Trisubstituted alkenes can be synthesized[27] by first treating a thexyldialkylborane (**5**) with an alkynyllithium to yield a thexyldialkylalkynylborate (**6**), which is then alkylated with migration of an alkyl group from boron to carbon to give the thexylalkylvinylboranes (**7** and **8**) (eq 15). After acid hydrolysis, the trisubstituted alkenes (**9** and **10**) are obtained in >70% yield in a ratio of about 9:1. The major product (**9**) in all cases is the isomer in which the migrating group (R^1) and the group introduced by alkylation (R^3) are *cis* to each other. Various alkylating agents are effective in this reaction including primary alkyl iodides, benzyl and allyl bromides, ***Dimethyl Sulfate***, and ***Triethyloxonium Tetrafluoroborate***.

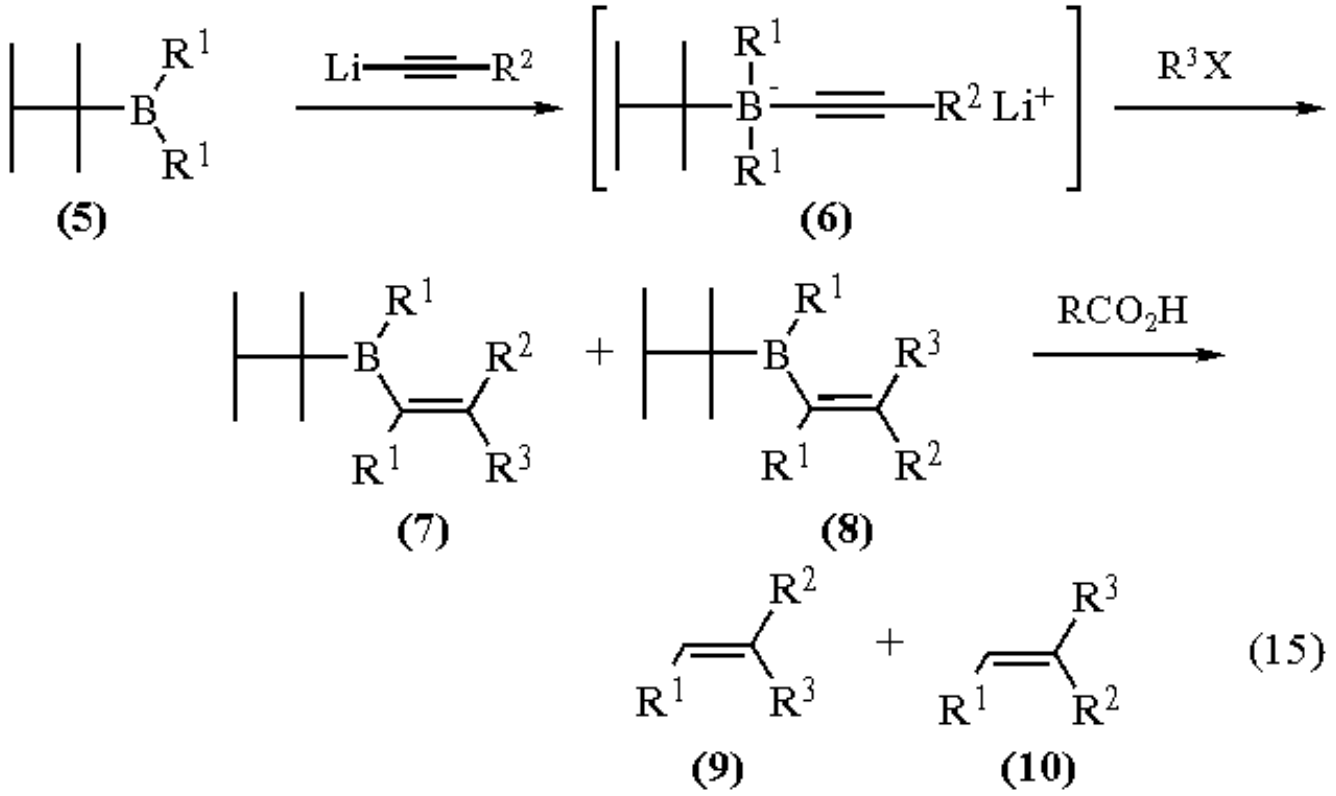

Synthesis of Dienes.

Thexylborane reacts with 2 equiv of 1-alkyne to give the corresponding thexyldialkenylborane (**11**) in good yield (eq 16).[4] However, when (**11**) is treated with ***Sodium Hydroxide*** and ***Iodine*** to induce rearrangement, an almost equal mixture of the desired (*E*,*Z*)-diene (**12**) and alkene (**13**) results where either the alkenyl group or the thexyl group migrates with approximately equal facility.[28] This problem can be surmounted by selectively oxidizing the thexyl group in the thexyldialkenylborane (**11**) with ***Trimethylamine N-Oxide*** before the reaction with iodine and sodium methoxide.[28] This procedure appears to be useful only for the synthesis of symmetrical (*E*,*Z*)-dienes (**12**) due to the difficulty in preparing unsymmetrical thexyldialkenylboranes in a stepwise hydroboration sequence from two different 1-alkynes.

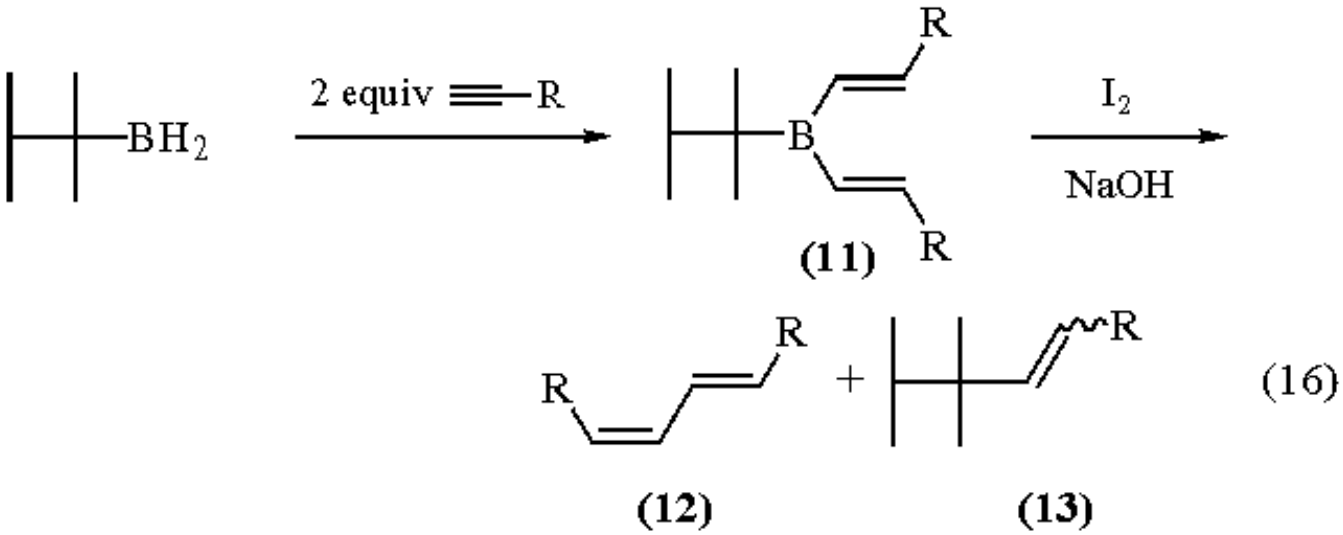

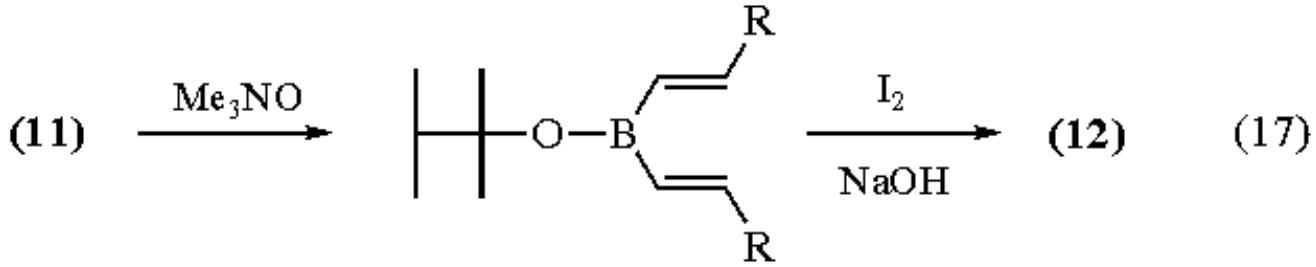

However, thexylborane will react with 1-chloro-1-alkynes and 1-bromo-1-alkynes (but not with 1-iodo-1-alkynes) to give thexyl(1-haloalkenyl)boranes (**14**) in high yield (eq 18).[29] This observation enabled the development of a general and highly stereospecific synthesis of conjugated (*E*,*E*)-dienes. The borane (**14**) reacts stereoselectively with a 1-alkyne to give the thexyldialkenylborane (**15**), which is then treated with sodium methoxide to produce (**16**). Compound (**16**) is protonolyzed with refluxing isobutyric acid to give the (*E*,*E*)-diene (**17**) in 53-63% yield and >98% isomeric purity.[29] The intermediate (**16**) is also transformed into the (*E*)-enone (**18**) in 50% yield by oxidation with ***Hydrogen Peroxide*** and NaOAc (eq 19).[29]

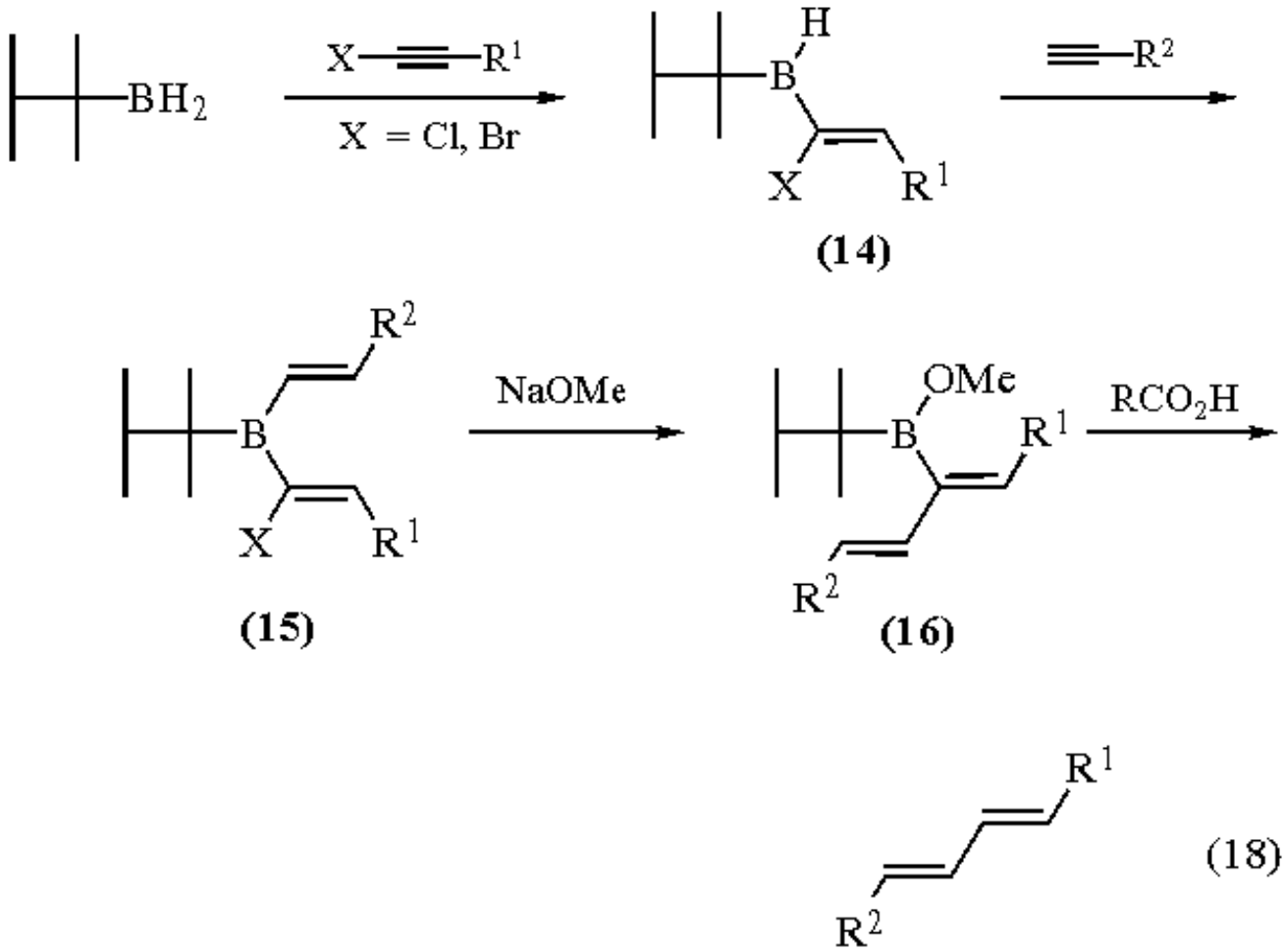

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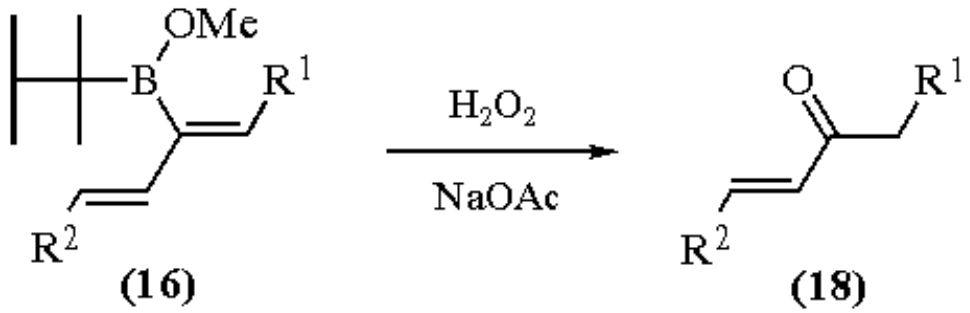

(19)

A stereoselective synthesis of 1,2,3-butatrienes was also developed based on the reaction of thexylborane with 1-halo-1-alkynes. In this synthesis, 2 equiv of a 1-iodo-1-alkyne react with thexylborane to give the thexyldialkenylborane (**19**) that rearranges to the 1,2,3-butatriene (**21**) upon treatment with 2 equiv of sodium methoxide (eq 20).[29b,30] Although the yields of (**21**) are only moderate (47%, R = butyl; 29%, R = cyclohexyl), the products are of high isomeric purity.

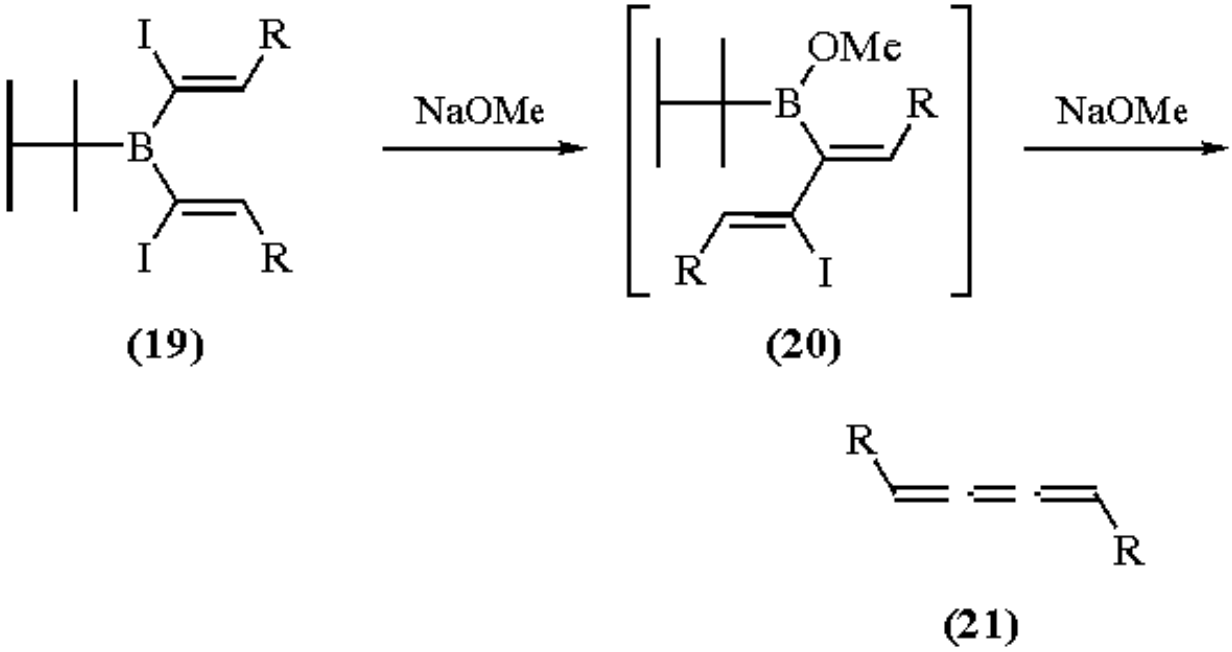

(20)

Synthesis of Carboxylic Acids.

A convenient procedure for the direct oxidation of organoboranes from terminal alkenes to carboxylic acids has been reported.[31] The oxidation gives high yields with a number of different organoboranes derived from a variety of borane reagents including thexylborane. Several different oxidizing agents (***Pyridinium Dichromate***, ***Sodium Dichromate*** in aqueous H_2SO_4, and ***Chromium(VI) Oxide*** in 90% aqueous acetic acid) are effective for the reaction. For example, 2-methyl-1-pentene is converted to 2-methylpentanoic acid in 86% yield (eq 21).

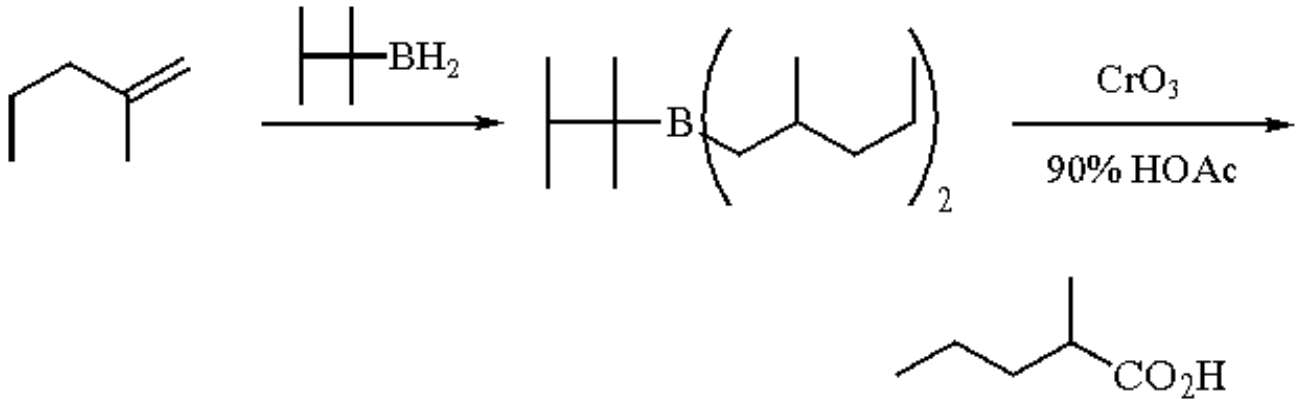

(21)

Related Reagents.

9-Borabicyclo[3.3.1]nonane; ***Borane-Tetrahydrofuran***; ***Chloro(thexyl)borane-Dimethyl Sulfide***; ***Dicyclohexylborane***; ***Disiamylborane***.

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1,3-Thiazolidine-2-thione[1]

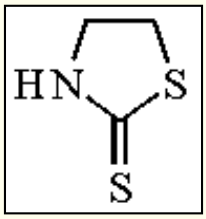

[96-53-7] · $C_3H_5NS_2$ · 1,3-Thiazolidine-2-thione · (MW 119.23)

(activating group for carboxylic acids;[1] 3-acyl derivatives can be reduced to aldehydes,[2,3] used in peptide synthesis,[4] or selectively aminolyzed[1,5,6])

Physical Data: mp 106-107 °C.

Solubility: sol acetone, ethanol, water; moderately sol benzene.

Preparative Method: readily synthesized from ***Carbon Disulfide*** and aminoethyl hydrogen sulfate.[7]

Handling, Storage, and Precautions: the solid is quite stable and fairly resistant to hydrolysis. Thiazolidinethione derivatives show a wide variety of biological activity, and should be treated with due caution.

3-Acylthiazolidine-2-thiones.

The reaction between 1,3-thiazolidine-2-thione and either carboxylic acids or acyl halides produces a useful amide intermediate (eq 1) which can subsequently be transformed into a variety of compounds. The amide linkage in 3-acylthiazolidone-2-thiones (ATTs) is more reactive than usual, and is susceptible to attack by a variety of nucleophiles. The yellow colour of the 3-acyl intermediate also allows easy monitoring of the progress of subsequent transformations. Synthesis of ATTs in useful yields (70-80%) can be achieved by the condensation of a carboxylic acid and 1,3-thiazolidine-2-thione in the presence of either ***1,3-Dicyclohexylcarbodiimide*** or ***2-Chloro-1-methylpyridinium Iodide***.[2,3] Higher yields (80-97%) are obtained by using an acyl chloride with ***Triethylamine***, or by employing the thallium salt of 1,3-thiazolidine-2-thione.[3]

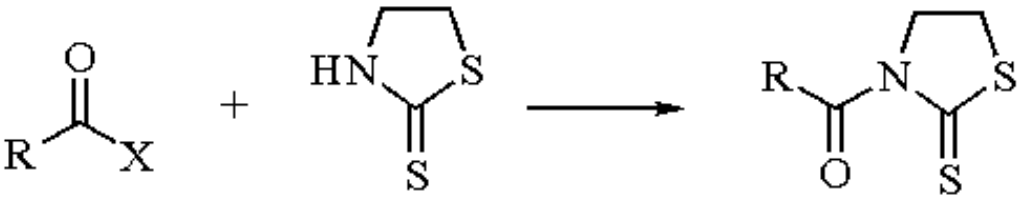

(1)

Aldehydes are generated by the action of ***Diisobutylaluminum Hydride*** on ATTs in moderate to good yield (54-93%).[2,3] One advantage of this route is that the intermediate reduced complex (unlike in many similar reductions) is stable towards excess DIBAL, and so over-reduction is not a problem. Similarly, treatment with ***Sodium Borohydride*** results in the formation of alcohols in high yield, even in the presence of another amide or ester functionality. Amides are produced from the reaction between amines and ATTs under mild conditions (25 °C, THF or CH_2Cl_2), often in almost quantitative yield.[1,5,6] The reaction is quite sensitive to the electronic and steric environment of the amine, allowing useful selectivities to be achieved when there is possible competition for amide formation. Hydroxy and thio functionality does not interfere in this reaction. The order of reactivity of various amines is: aliphatic > aromatic; RCH_2NH_2 > R_2CHNH_2 >> R_3CNH_2; RNH_2 &egt; R_2NH. This selectivity is used in the synthesis of maytenine (eq 2).[5] Macrolactams with ring sizes up to 50 atoms have also been constructed using this method.[6] The reaction can also be extended to include peptide synthesis using Cbz- or Boc-protected amino acids.[4] The yellow color of the ATT intermediate means that the extent of the reaction can be followed easily. No racemization of the amino acids is detected in the final peptides and overall yields are in the range 50-75%; the poorest step is the initial formation of the ATT-amino acid intermediate.

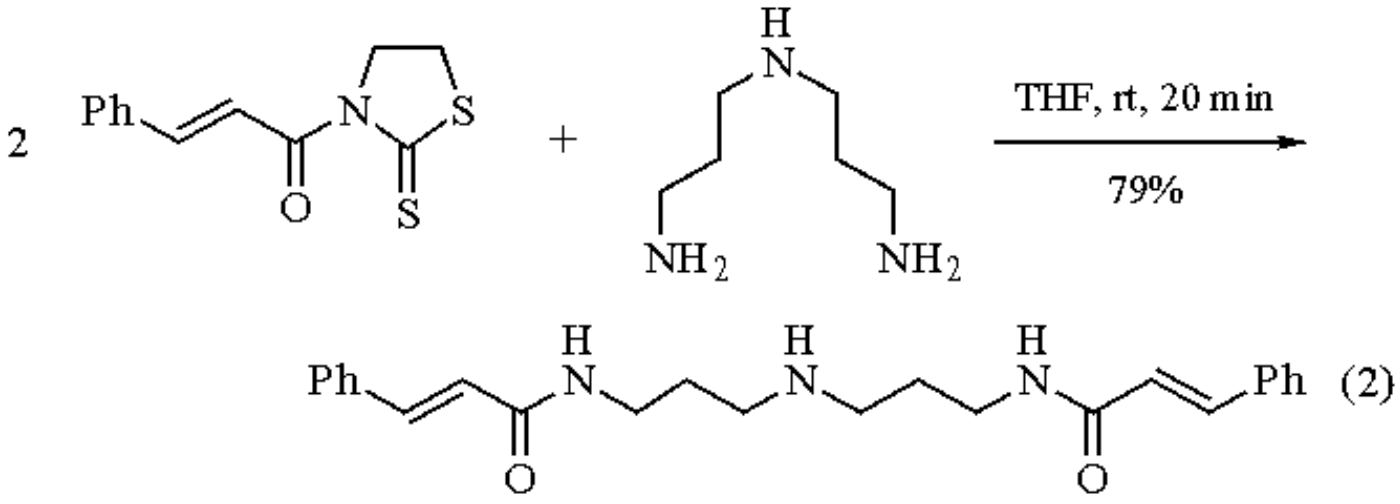

Chiral analogs of 1,3-thiazolidine-2-thione have been used to control asymmetric induction in a variety of reactions, including aldol condensations.[8]

---

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Thioanisole

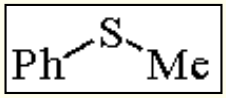

[100-68-5] · C_7H_8S · Thioanisole · (MW 124.22)

(preparation of phenylthiomethyllithium[1-3] and (2-lithiophenylthio)methyllithium;[2] deprotection of aromatic methyl ethers;[9] deprotection of *N*-benzyloxycarbonyl groups;[10] cleavage of epoxides;[11] oxidation of diols to hydroxy ketones[12])

Physical Data: bp 188 °C.

Form Supplied in: colorless liquid; commercially available.

Handling, Storage, and Precautions: stench; handle in a fume hood.

Phenylthiomethyllithium.

Thioanisole (**1**) can be efficiently monometalated by treatment with ***Phenyllithium***,[1] ***n-Butyllithium*** and DABCO,[1] *n*-butyllithium and TMEDA,[2] or ***t-Butyllithium*** and HMPA[3] to afford phenylthiomethyllithium (**2**) which reacts smoothly with primary and secondary alkyl halides, leading to alkylaryl sulfides (eq 1).[1,2]

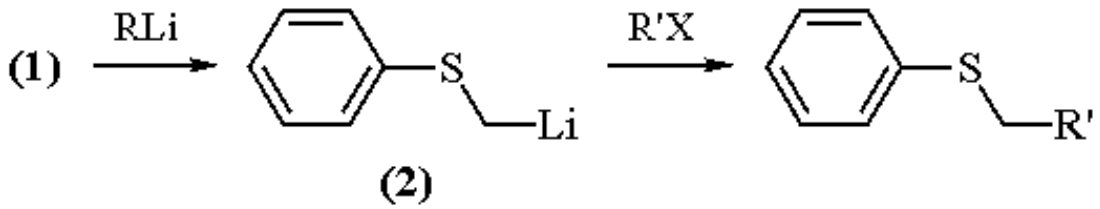

Treatment of phenylthiomethyllithium (**2**) with ketones produces (phenylthiomethyl)carbinols (eq 2), which can be dehydrated to vinyl sulfides[1] or converted to alkenes, either directly[4] or via the corresponding benzoate esters.[5]

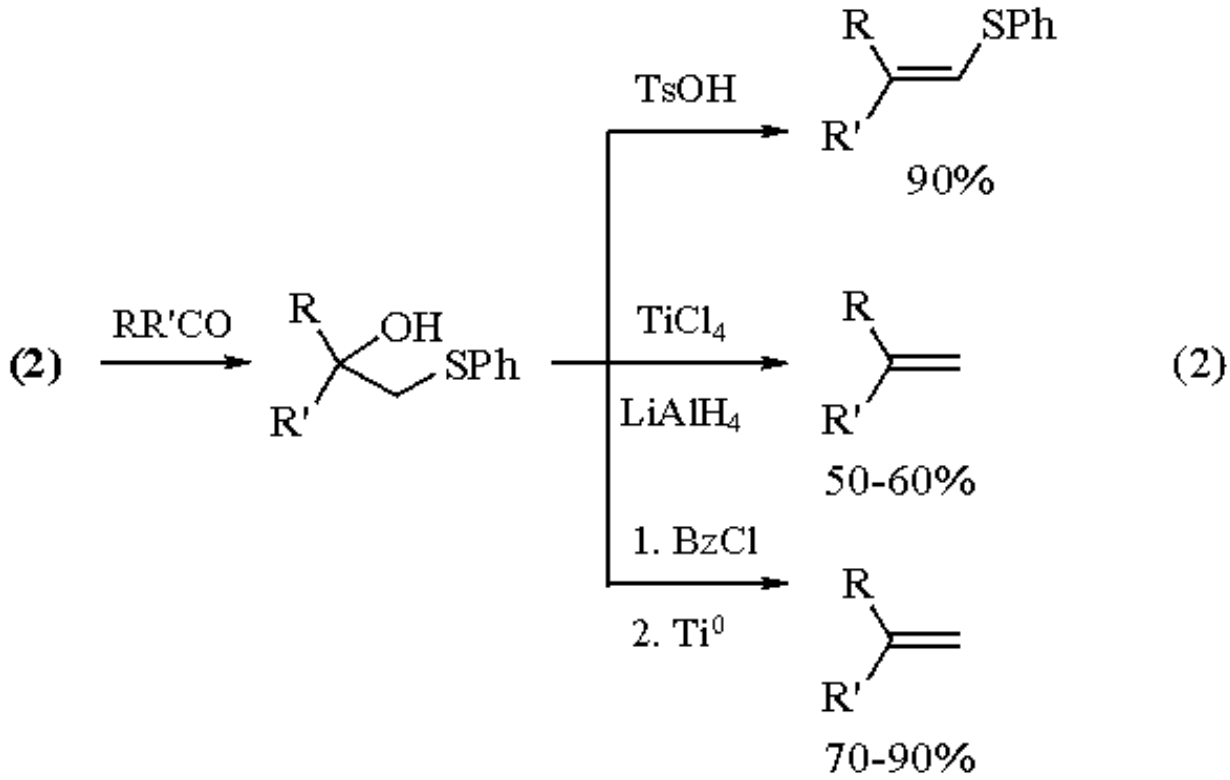

(2)

In the case of cyclic α,β-unsaturated ketones, exclusive 1,2-addition of phenylthiomethyllithium (**2**) occurs to provide tertiary allylic alcohols which can undergo oxidative allylic transposition to afford 3-(phenylthio)methyl α,β-unsaturated ketones (eq 3).[6]

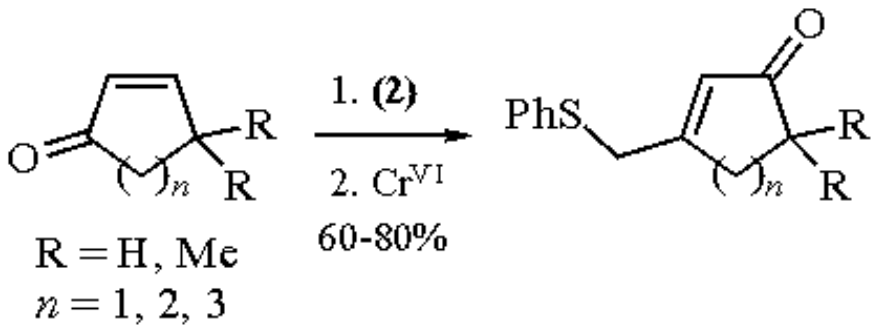

(3)

A one-pot synthesis of substituted cyclopent-2-en-1-ones relies on the addition of phenylthiomethyllithium (**2**) to ethyl 2-chloro-2,3-dialkylbut-3-enoate esters, followed by sulfur-assisted S_N2' displacement of chloride ion and [1,2]-sigmatropic rearrangement of the resultant ylide (eq 4).[7] This procedure has been applied to the synthesis of *cis*-jasmone and dihydrojasmone.[7]

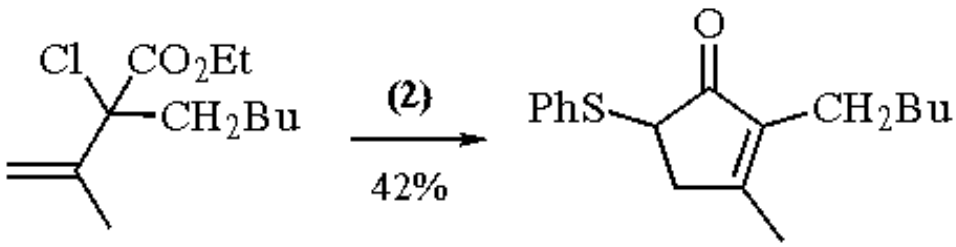

(4)

(2-Lithiophenylthio)methyllithium.

When thioanisole (**1**) is treated with 2.2 equiv of *n*-butyllithium and TMEDA, dimetalation occurs to give (2-lithiophenylthio)methyllithium.[2,8] The latter compound can be dialkylated, diacylated, dicarboxylated, or disilylated (eq 5).[2] Monoacylation of (2-lithiophenylthio)methyllithium is followed by intramolecular cyclization, leading to benzothiophenes after dehydration (eq 6).[8]

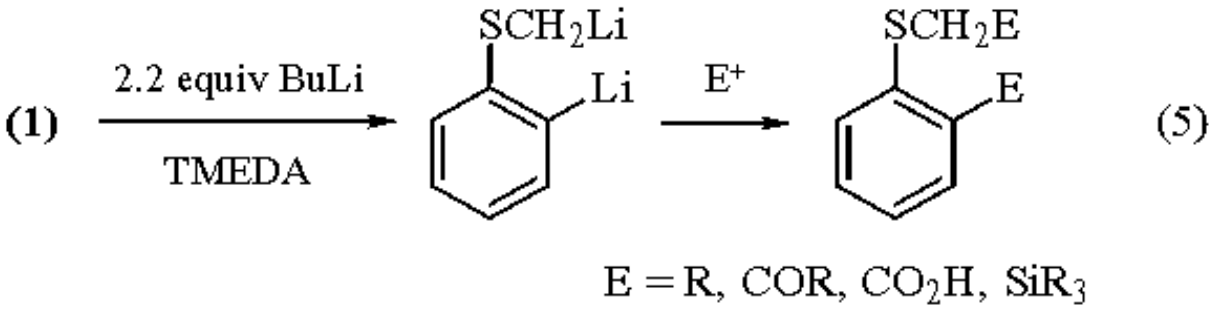

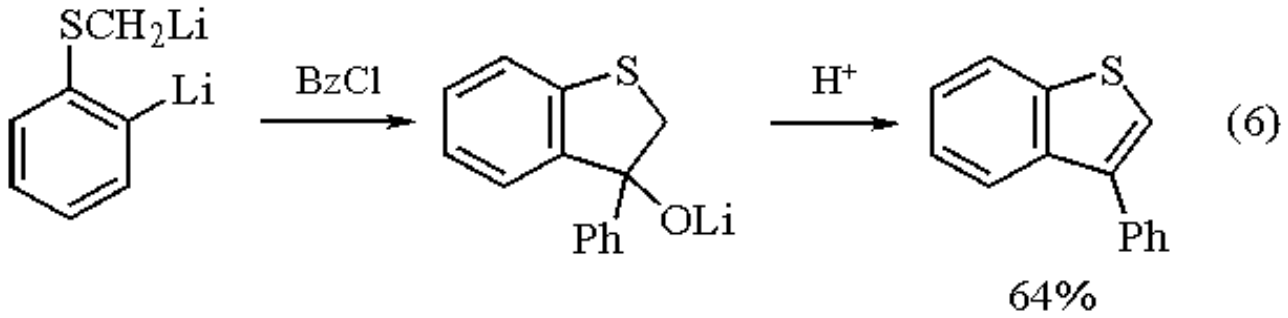

Deprotection of Aromatic Methyl Ethers and *N*-Benzyloxycarbonyl Groups.

In combination with ***Trifluoromethanesulfonic Acid***, thioanisole (**1**) effects the demethylation of *O*-methyltyrosine (eq 7).[9] Similarly, ***Trifluoroacetic Acid*** and thioanisole (**1**) remove the *N*-benzyloxycarbonyl (*N*-Cbz) group from the amino terminus of peptides (eq 8).[10]

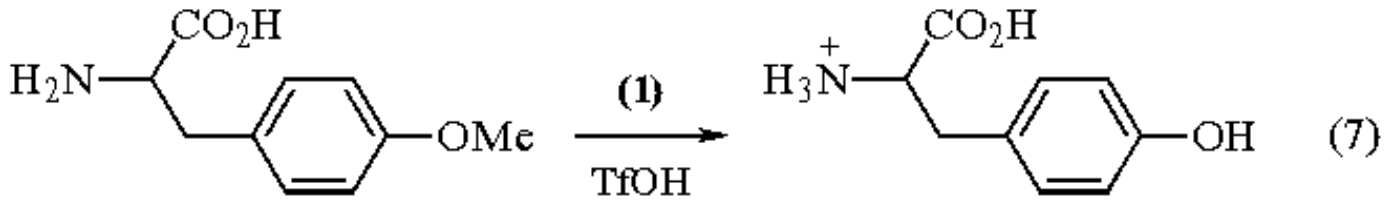

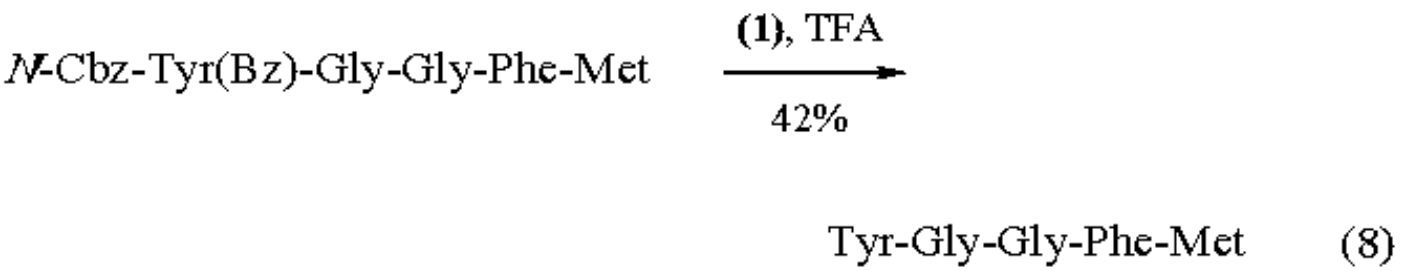

Epoxide Cleavage and Oxidation of Diols.

The chlorosulfonium salt, formed when thioanisole (**1**) is reacted with ***Chlorine***, causes ring opening of epoxides to give α-chloro sulfoxonium salts which can be converted to α-chloro alcohols or α-chloro ketones (eq 9).[11] When 1,2-diols are treated with the thioanisole (**1**)-chlorine complex, oxidation to α-hydroxy ketones takes place (eq 10).[12]

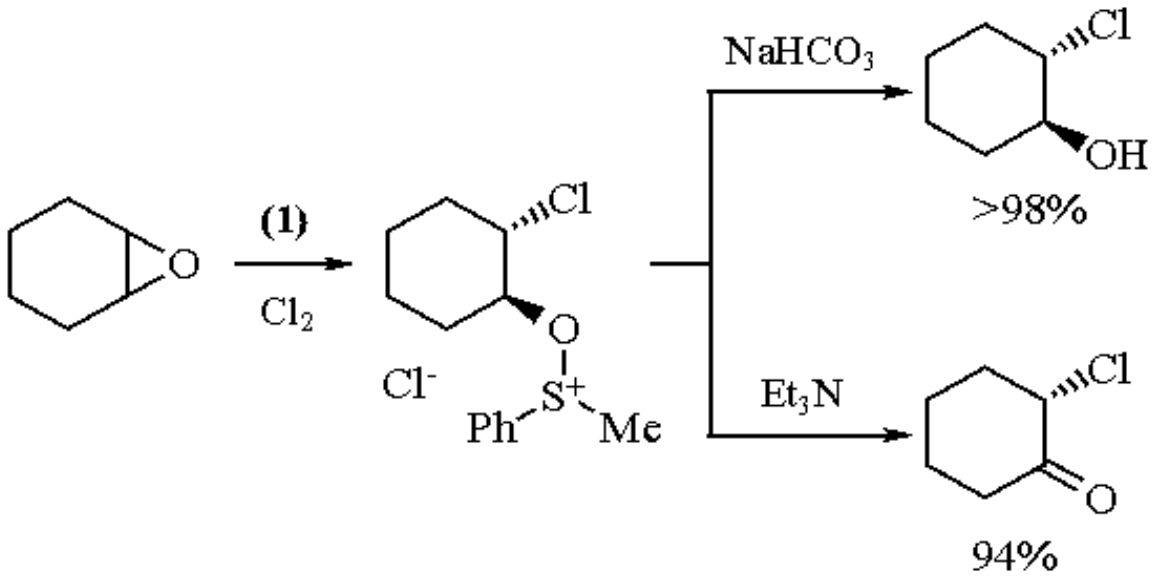

(9)

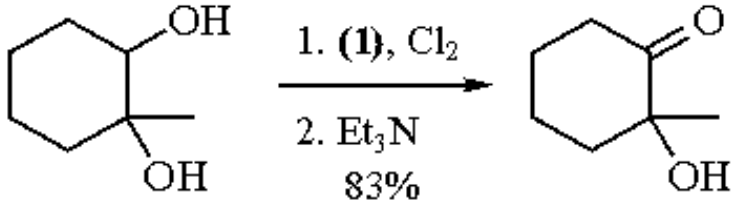

(10)

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2. Cabiddu, S; Fattuoni, C; Floris, C; Gelli, G; Melis, S; Sotgiu, F. *T* **1990**, *46*, 861.
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11. Nakai, H; Kurono, M. *CL* **1977**, 995.
12. Corey, E. J; Kim, C. U. *TL* **1974**, 297.

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1,1´-Thiocarbonyldiimidazole[1]

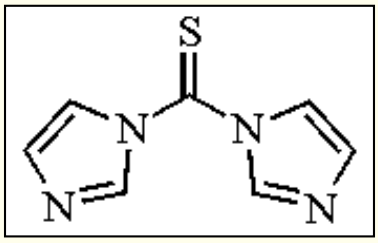

[6160-65-2] · $C_7H_6N_4S$ · 1,1´-Thiocarbonyldiimidazole · (MW 178.24)

(conversion of vicinal diols to alkenes;[1] deoxygenation of alcohols;[13] thiocarbonyl transfer agent[29])

Alternate Name: TCDI.

Physical Data: mp 101-103 °C.

Solubility: sol many organic solvents including THF, CH_2Cl_2, toluene.

Form Supplied in: yellow solid; 90% pure or >97% pure.

Preparative Methods: prepared by the reaction of ***Thiophosgene*** with 2 equiv of ***Imidazole***.

Purification: can be recrystallized from THF to give yellow crystals; can also be sublimed.

Handling, Storage, and Precautions: very hygroscopic; should be reacted and stored in a dry atmosphere.

Alkene Synthesis.

The Corey-Winter alkene synthesis is an effective method for the deoxygenation of vicinal diols.[1,2] The method involves formation of a 1,3-dioxolane-2-thione [cyclic thionocarbonate (or thiocarbonate)] by treatment of a vicinal diol with TCDI. Decomposition of the thionocarbonate, usually with a phosphorus compound, affords the alkene (eq 1).[3] The breakdown of the thionocarbonate occurs in a stereospecific sense; details of investigations into the mechanism have been summarized.[1]

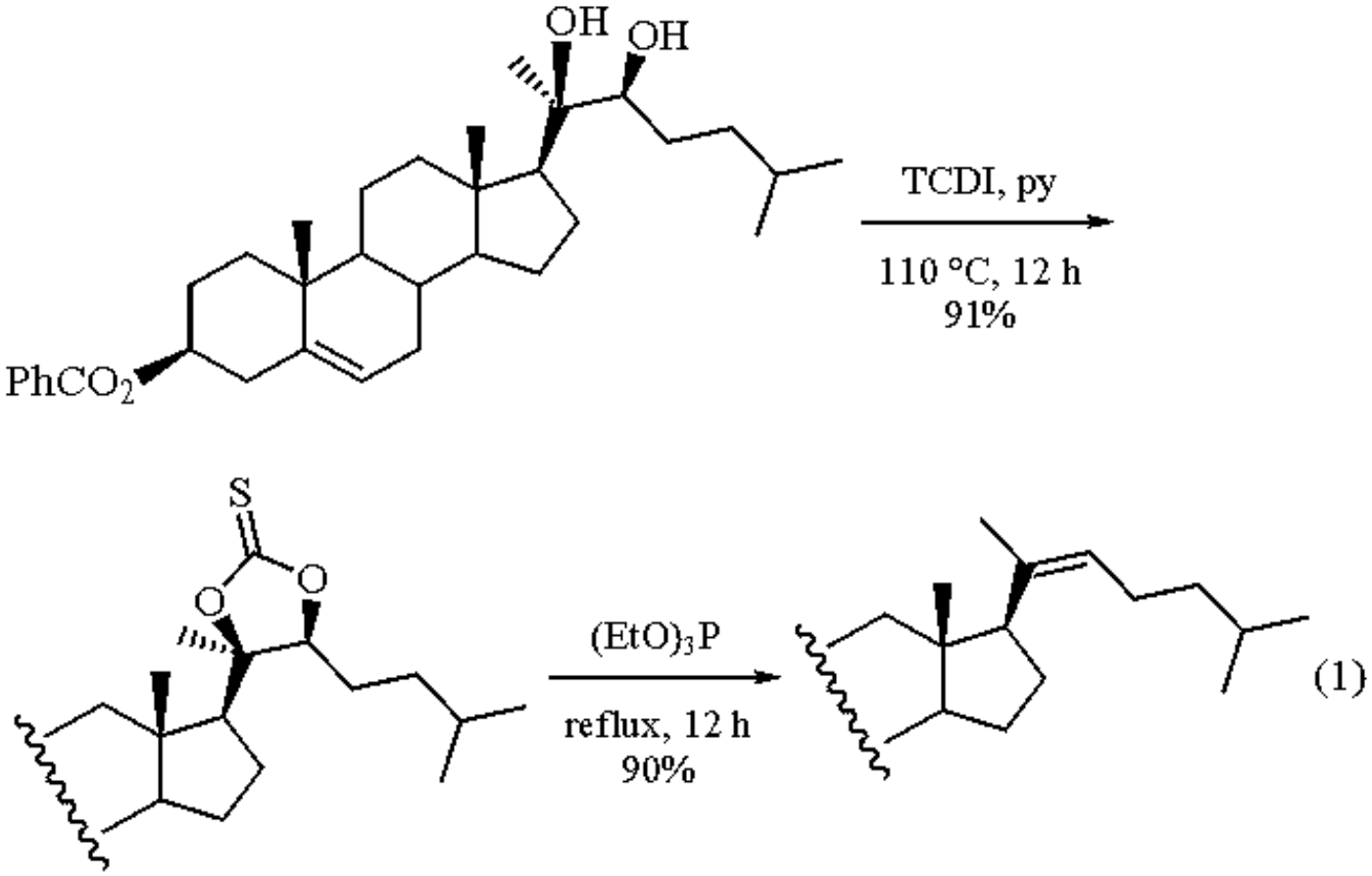

The conditions required for the introduction of the thiocarbonyl group vary greatly, depending on the structure of the diol.[1,4] The thionocarbonate may also be prepared without TCDI. The reaction of vicinal diols with thiophosgene/DMAP/CH_2Cl_2/0 °C,[5] with base/CS_2/MeI/heat,[1] or with 1,1´-thiocarbonyl-2,2´-pyridone/toluene/110 °C[6] also provides thionocarbonates. Along with phosphines and phosphites, other reagents can decompose the thionocarbonates, but not always in a stereospecific manner. The Corey-Hopkins reagent 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine,[5] along with ***Raney Nickel***[7] and ***Bis(1,5-cyclooctadiene)nickel(0)***,[8] affords products of stereospecific *cis*-elimination, while the alkyl iodide/***Zinc*** combination[9] and ***Pentacarbonyliron***[10] yield products of nonstereospecific elimination or unknown stereochemistry.

The Corey-Winter synthesis has proved useful for the generation of a large number of structurally interesting alkenes,[1] including some unstable alkenes that must be captured in situ (eq 2).[4]

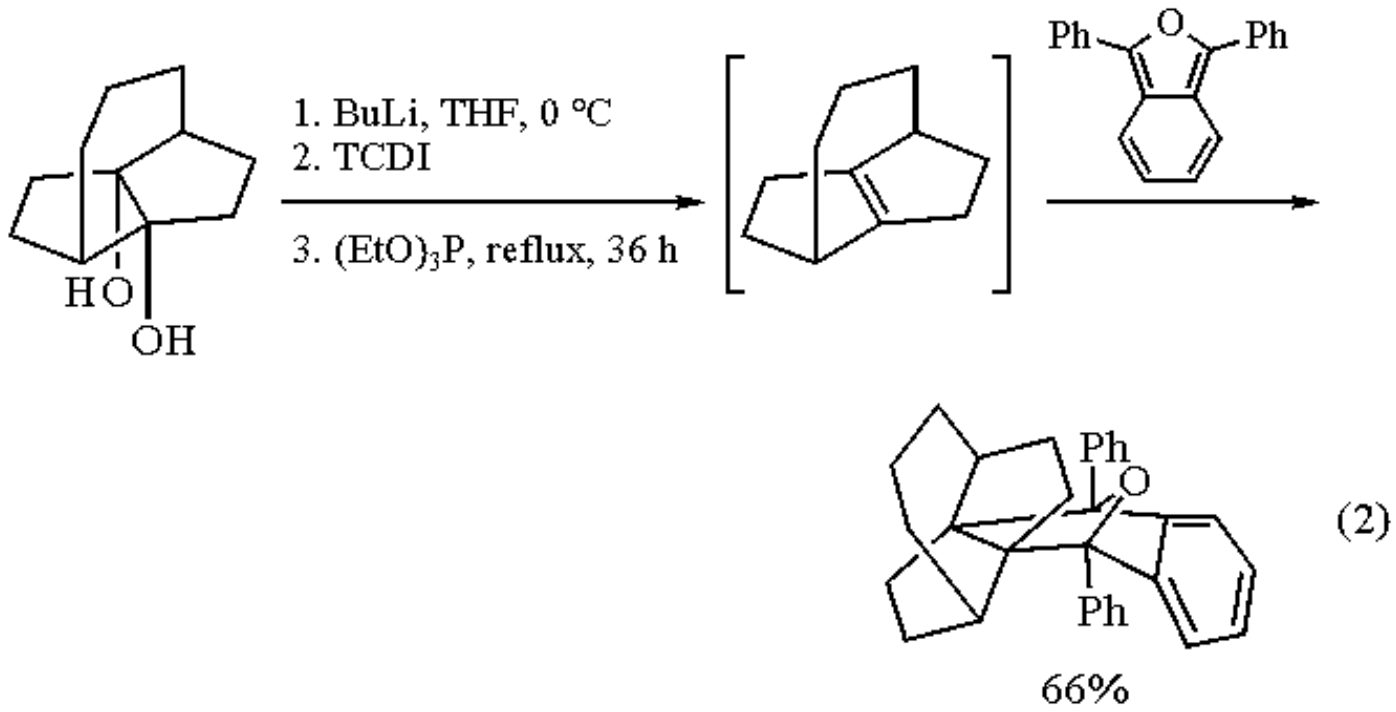

The method has found its niche in the chemistry of sugars. Their polyhydroxylated nature make them excellent substrates provided the by-standing hydroxyls are protected (eq 3).[11] The 2´- and 3´-oxygens of nucleosides are readily are removed under the Corey-Winter conditions.[12]

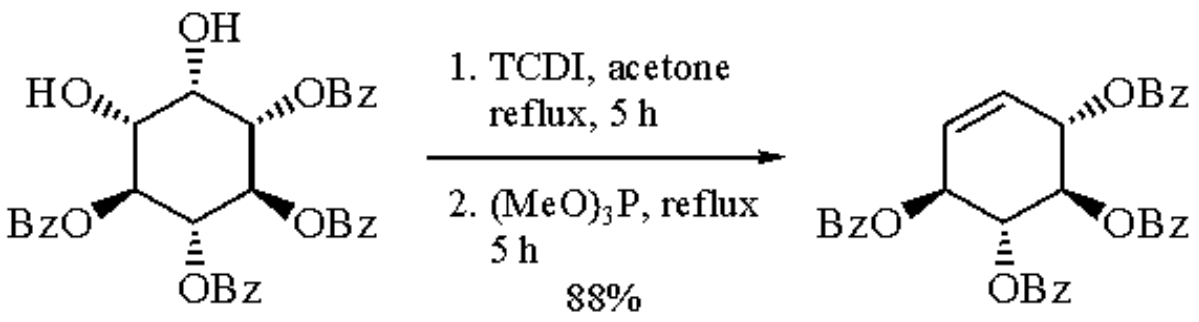

(3)

Radical Chemistry.

Treatment of secondary alcohols with 1 equiv of TCDI affords an imidazole-1-thiocarbonyl derivative (imidazolide), which can be reduced to a CH_2 unit under ***Tri-n-butylstannane*** (TBTH) radical chain reaction conditions.[13,14] The deoxygenation of secondary alcohols by way of an imidazolide or other thiocarbonyl derivative is called the Barton-McCombie reaction (eq 4).[6,14] Since imidazolide formation (TCDI, reflux, 65 °C) and the subsequent radical chemistry are done under neutral or near-neutral conditions, the overall reduction is tolerant of the presence of many sorts of functional groups. Furthermore, the low solvation requirements of radical species permits deoxygenation in sterically congested environments (eq 5).[15]

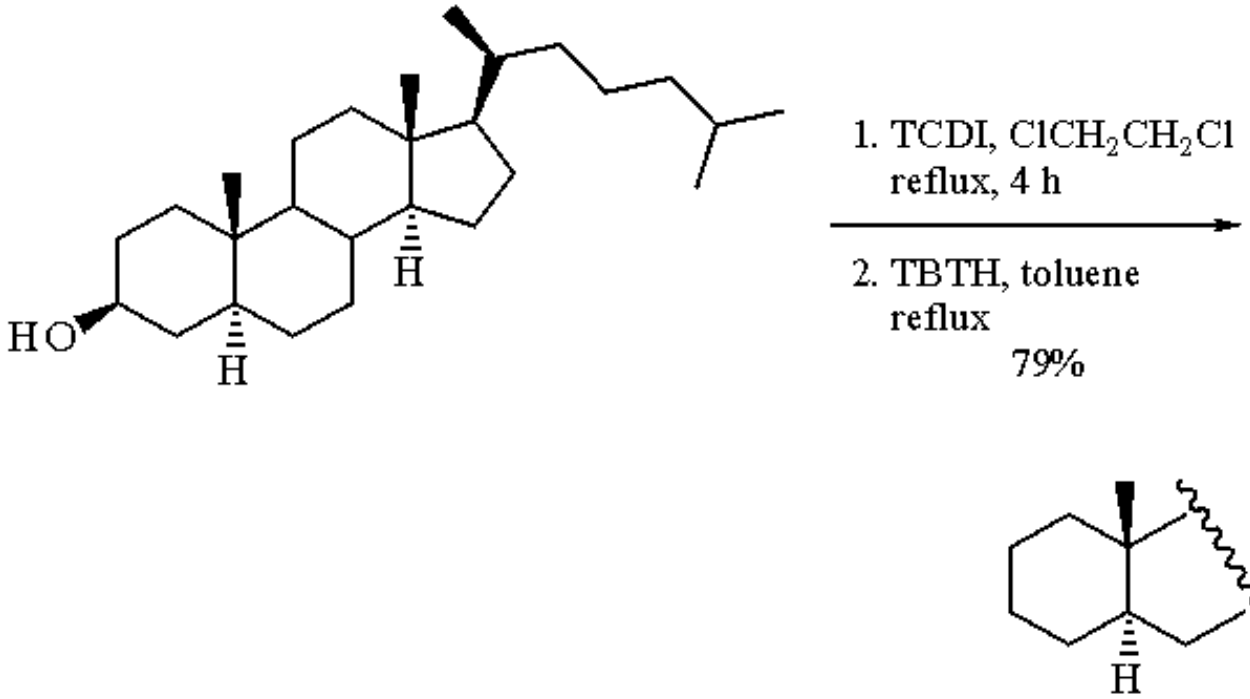

(4)

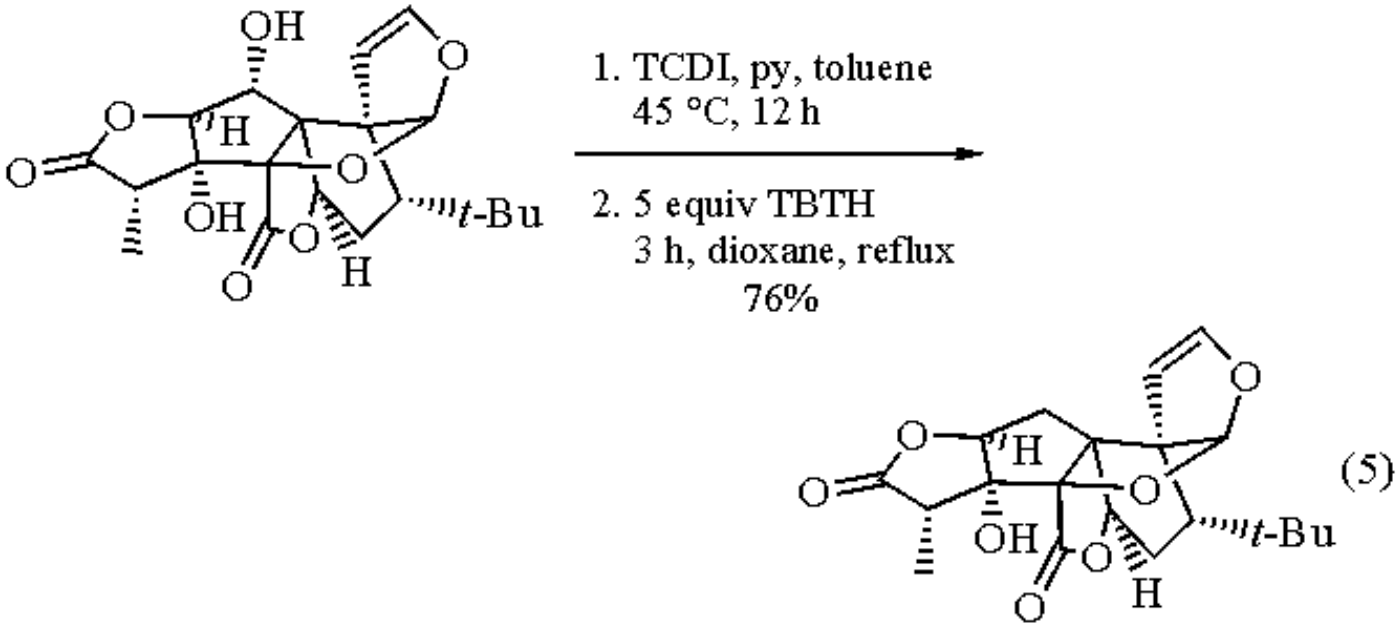

The mechanism of the radical attack at the thiocarbonyl group and the ensuing breakdown has been outlined elsewhere.[13,14] Some groups have studied the comparative chemistries of the possible thiocarbonyl derivatives, with no particularly obvious trends arising.[13,16,17] There are numerous reports of the deoxygenation of carbohydrates[13,16,18] and related polyhydroxylated species.[14,17,19,20] In one instance of amino glycoside deoxygenation, the C(3´)-OH group can be selectively functionalized with TCDI, while the C(5)-OH group is unaffected and the radical reduction proceeds without protection of the C(5)-OH group (eq 6).[20]

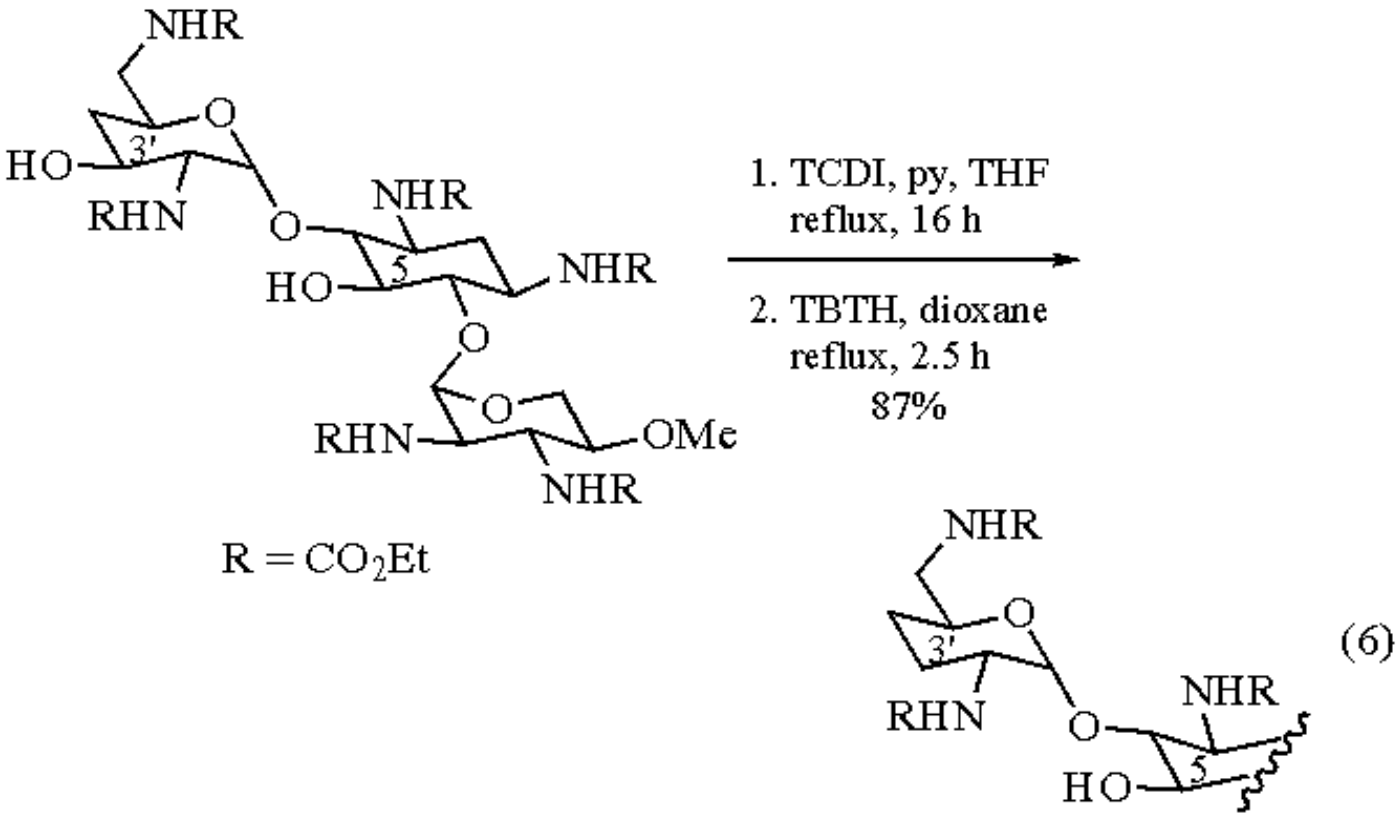

Reduction of tertiary alcohols is not recommended due to the instability of the tertiary imidazolide, although, as an alternative, a thioformaldehyde version has been developed.[21] Imidazolides from primary alcohols do not respond well to the same conditions as the secondary systems, but performing the radical chemistry at 130-150 °C can lead to deoxygenation.[22] As an alternative to the high-temperature radical chemistry, the imidazolide can be converted by methanolysis to a thiocarbonate which can be reduced at room temperature (Et_3B, TBTH, benzene).[23] Tin hydride treatment of thionocarbonates derived from primary/secondary diols affords, after base exposure, the product of selective reduction of the secondary site, leaving the primary hydroxyl (eq 7).[14,24] The approach has also been successfully applied to 1,3-diols.[24,25]

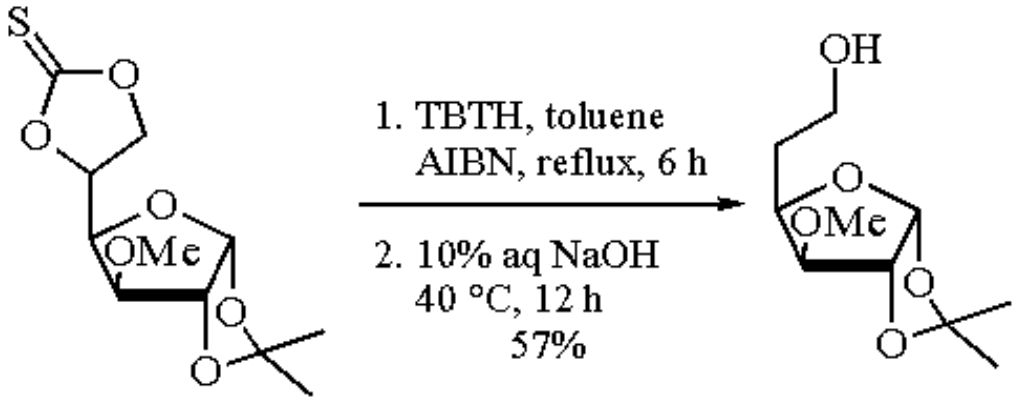

(7)

Since the reduction method proceeds via radical chemistry, the intermediate radicals are prone to bimolecular chemistry and unimolecular reactions such as rearrangements or β-scission, if suitable functionality is proximal.[14] Indeed, the imidazolides have been employed as radical precursors when rearrangement is the desired result.[14]

Thiocarbonyl Transfer.

While virtually all uses of TCDI involve a thiocarbonyl transfer reaction, this section covers those uses of the thiocarbonyl transfer that do not lead to radical chemistry or alkene syntheses. TCDI has been used for the simple placement of a thiocarbonyl group between two nucleophilic atoms of one[26] or two molecules.[27] An alcohol which has been converted to an imidazolide is a reactive functionality for coupling reactions,[28] for sigmatropic rearrangements,[29] and for elimination (eq 8).[30] The TCDI alternative 1,1´-thiocarbonyl-2,2´-pyridone[6] seems to be an excellent thiocarbonyl transfer agent.

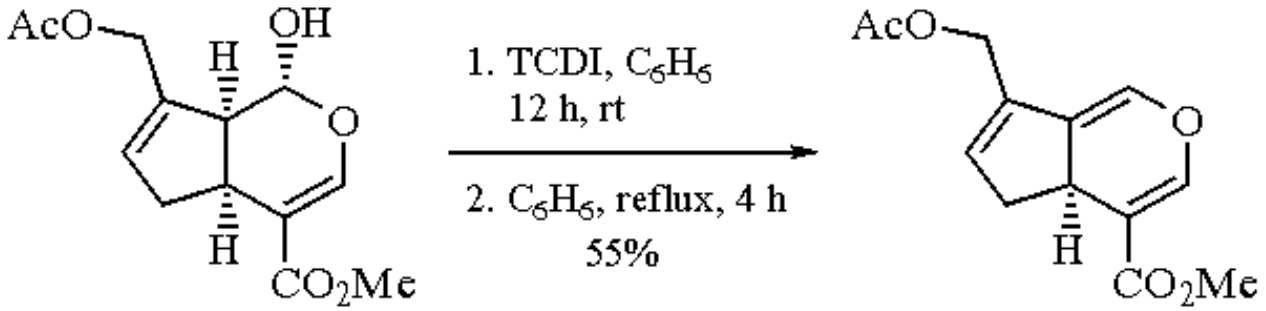

(8)

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Thiocyanogen[1]

$(SCN)_2$

[505-14-6] · $C_2N_2S_2$ · Thiocyanogen · (MW 116.18)

(mono- or dithiocyanation of organic compounds by electrophilic or radical chemistry[1])

Physical Data: mp -3 to -2 °C.

Solubility: sol alcohol, CS_2, benzene, ether, acetic acid, halogenated solvents.

Preparative Methods: prepared for reaction in various solvents by treating dry $Pb(SCN)_2$ with ***Bromine*** at rt, sometimes followed by filtration in an inert atmosphere. It can also be obtained by reacting ***Potassium Thiocyanate*** and Br_2 at -70 °C or by the electrolysis of alkali or ammonium thiocyanates.

Handling, Storage, and Precautions: the neat material is explosive at >20 °C. Stable in acetic acid/anhydride as 0.1 M solution over 8 days. Use of polar protic solvents, including the stabilizing EtOH in $CHCl_3$, may give erratic results and lower yields. Electrophilic reactions should be carried out in the dark or under diffuse light conditions. Use under N_2 or Ar.

Substitution.

The electrophilic reactivity of the pseudohalogen thiocyanogen lies between those of ***Bromine*** and ***Iodine***. Therefore, in reactions with aromatic compounds, anilines and phenols readily undergo *para* thiocyanation, but less activated aryl rings require a Friedel-Crafts catalyst.[1] Polyaromatic species such as anthracene react readily with thiocyanogen, and the reaction may give a dithiocyanato derivative.[1] Electron-rich heteroaromatic species such as pyrroles undergo thiocyanation readily (eq 1),[1,2] but thiocyanation of thiophene requires a catalyst. Numerous other heterocycles react with thiocyanogen.[1] *Ipso* substitution of silylated aromatics is also possible (eq 2).[3] The polarization of thiocyanogen and the electrophilic nature of the mechanism prevent formation of any isothiocyanato compounds, products which may arise from nucleophilic substitution reactions with a metal thiocyanate.[1]

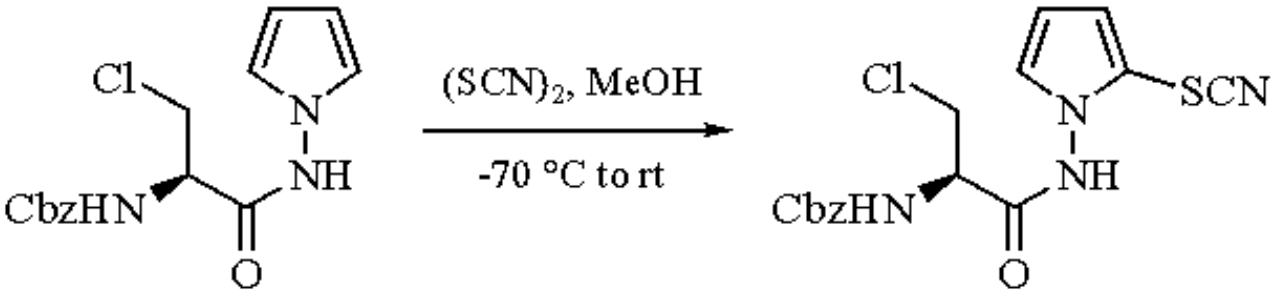

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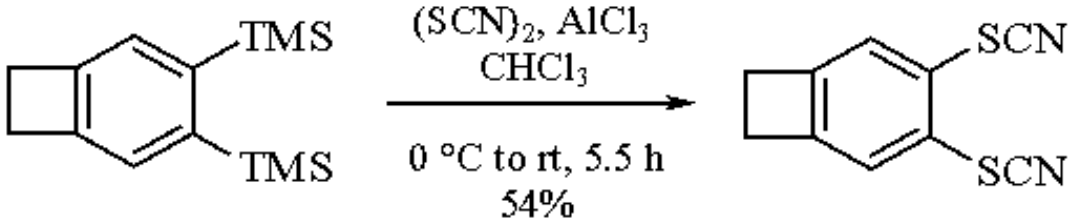

(2)

Other nucleophiles also attack thiocyanogen to effect substitution. Thiocyanation occurs at the nitrogen of primary and secondary amines,[4] at the sulfur of divalent sulfur compounds[1] and sulfinate anions,[5] and at the carbon of enols,[1] some enamines,[6] and related nucleophiles.[1] Organomercury compounds undergo thiocyanation at their metalated site.[1] Grignard reagents do not tend to react well,[1] but the reaction of organolithiums with $Zn(SCN)_2$ and then ***N-Chlorosuccinimide*** affords the corresponding thiocyanate.[7] Radical chain substitution proceeds well with primary and secondary benzylic hydrogens of phenyl alkanes. The reaction of tertiary benzylic hydrogens affords significant

isothiocyanate.[8]

Electrophilic Addition.

Thiocyanogen may add across the π-bond of alkenes or alkynes by an electrophilic or radical mechanism. The electrophilic mechanism is similar to the electrophilic halogenation of alkenes: an initially formed cyanosulfonium ion (**1**) is attacked by thiocyanate or solvent to complete the addition process. Hence additions to simple alkenes occur with *trans* stereospecificity and no regiospecificity. On the other hand, with aryl alkenes the intermediate is not cyclic (**2**) and the overall addition occurs with regiospecificity but not stereospecificity.[1]

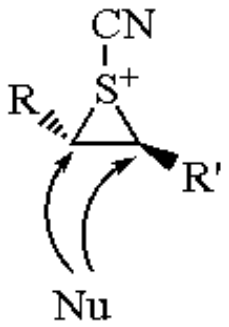

(1)

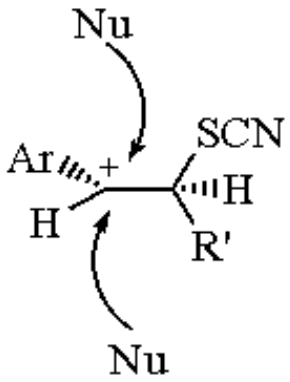

(2)

The interference of radical species is troublesome in the addition reaction. Other problems may occur through the formation of isothiocyanato thiocyanates which originate from nucleophilic attack on the intermediate cation by the nitrogen of the thiocyanate ion. The best yields of α,β-dithiocyanates are obtained when the reactions are performed (i) in the dark or with a radical inhibitor present (up to 15 mol %),[9] (ii) with a metal or metal salt present,[9,10] (iii) with a filtered thiocyanogen solution,[9,10] and (iv) in polar or dipolar aprotic solvent[9] (eq 3).[10] A radical chain mechanism is also suitable for the synthesis of α,β-dithiocyanates from simple alkenes.[1,11] The addition of thiocyanogen across alkynes should be done under radical conditions; the *trans*-isomer usually predominates.[12] In all addition reactions of thiocyanogen with alkenes or alkynes, prolonged stirring may lead to the thermodynamically more stable isothiocyanate isomers.[1,12]

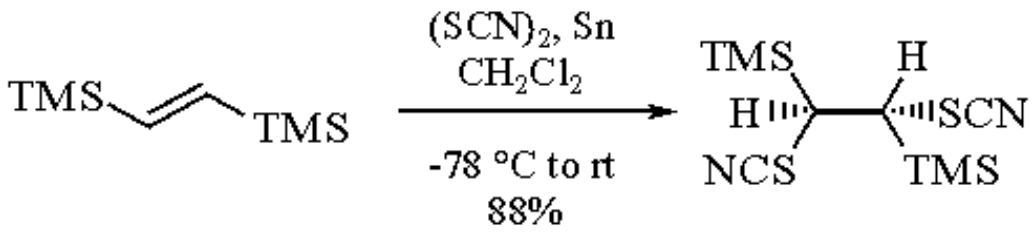

(3)

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Thiolacetic Acid

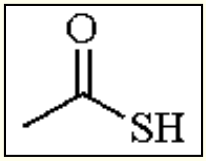

[507-09-5] · C_2H_4OS · Thiolacetic Acid · (MW 76.13)

(addition to α,β-unsaturated carbonyl compounds; radical additions to alkenes and alkynes; chiral dithioacetal formation; selective acylating agent; S_N2 substitutions to make thiolesters)

Physical Data: bp 88-91.5 °C; *d* 1.065 g cm^{-3}.

Solubility: sol hot H_2O, alcohol.

Form Supplied in: light yellow liquid (impurity: acetic acid).

Purification: fractional distillation.

Handling, Storage, and Precautions: use only in fume hood. Wear protective clothing such as safety goggles and chemical-resistant gloves. Harmful if swallowed, inhaled, or absorbed through the skin. Corrosive. Lachrymator. Flammable. Stench. May develop pressure. Refrigerate. Forms explosive mixtures in air. Vapor may travel considerable distance to source of ignition and flash back. Incompatible with oxidizing agents and strong bases.

Conjugate Addition to α,β-Unsaturated Carbonyl Compounds.

The addition of thiolacetic acid to α,β-unsaturated aldehydes, ketones, and carboxylic acids and their derivatives occurs at the β-position, regardless of whether the mechanism is radical or ionic in nature.[1] Stereoselective addition to the less hindered face of the double bond is observed in cases in which there is an inherent facial preference. A representative example is the addition of thiolacetic acid to a $\Delta^{1,2}$-3-oxo steroid (**1**) to give the product in which the acylthio substituent is in the α-configuration (eq 1).[2]

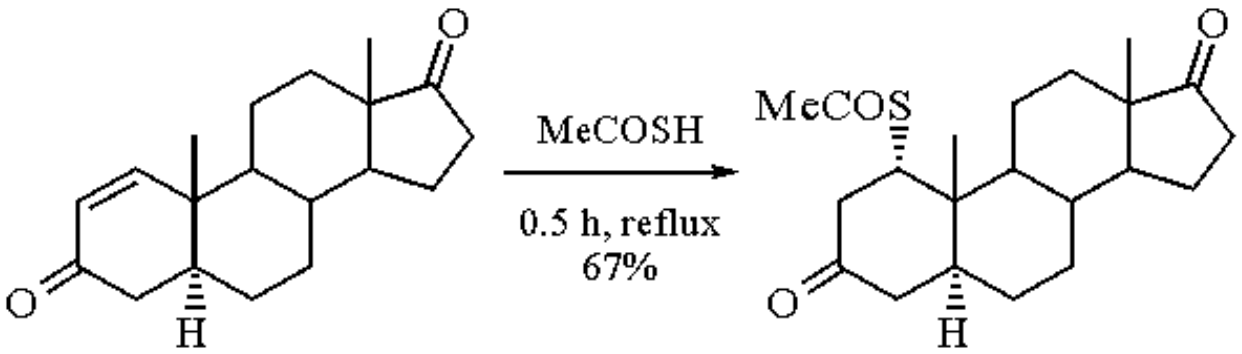

(1)

(1)

A more recent example by Bartmann[3] is the addition of thiolacetic acid to the unsaturated lactone (**2**) to give exclusively the (*R*) configuration at the newly formed stereogenic center (eq 2). The enoate double bond undergoes reaction preferentially to the conjugated diene portion of the molecule, but with longer reaction times and an excess of reagent (25 °C, 2 days, 1.7 equiv MeCOSH, 0.2 equiv Et_3N), the 1,4-addition products (**3**) and (**4**) are also obtained.

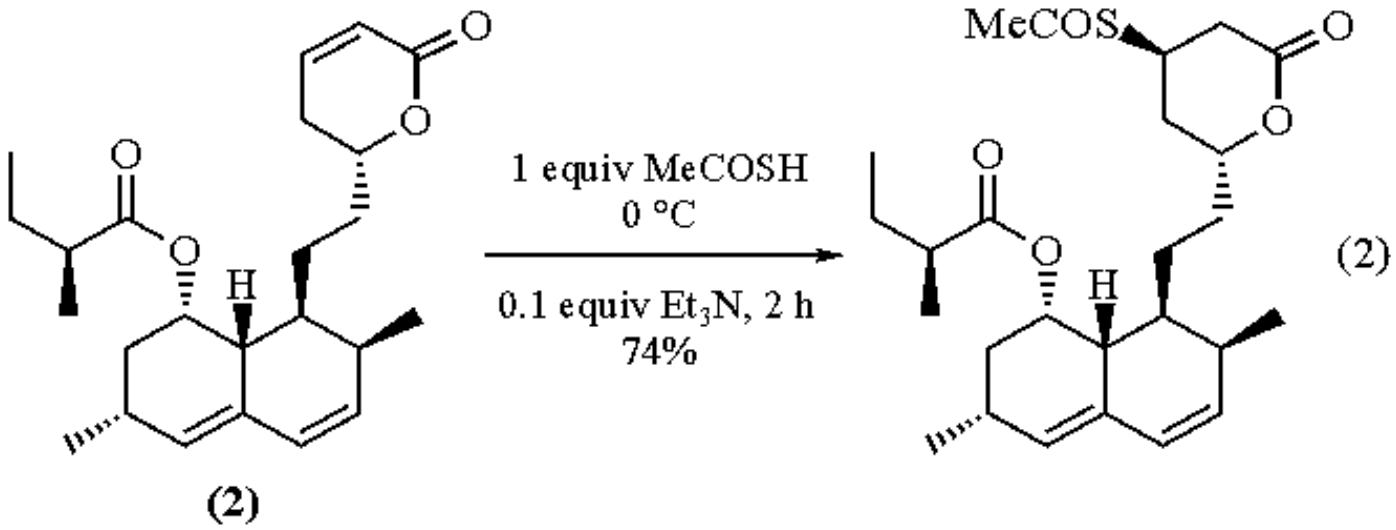

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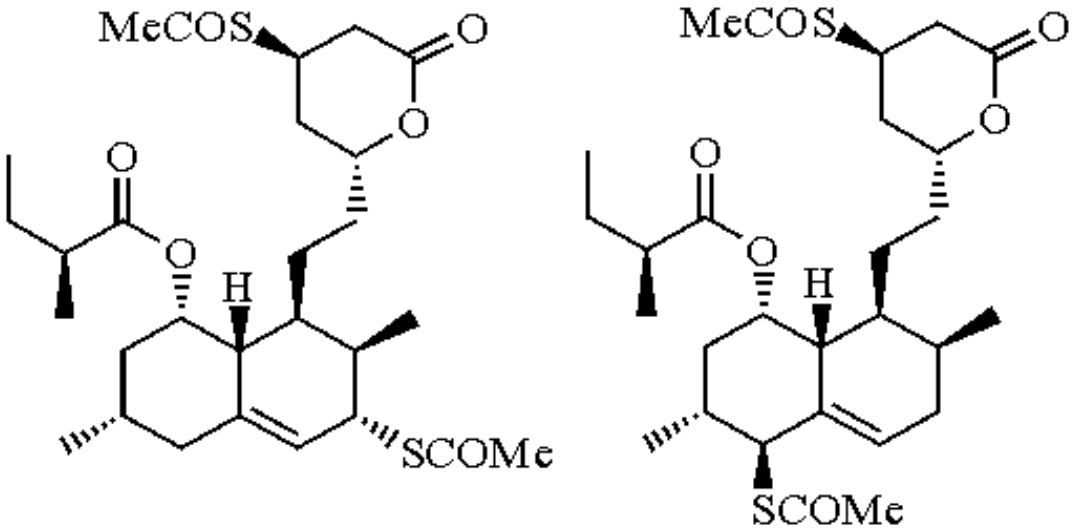

(3) (4)

Asymmetric induction in the addition of thiolacetic acid to cyclic and acyclic enones and to α,β-unsaturated mono- and diesters has been investigated by Gawronski and co-workers.[4] Of the catalysts studied, the cinchona alkaloids are the most effective. The enantiomeric excess in the reaction of thiolacetic acid with cyclohexenone increases from the 50% to the 60% range with variations of catalyst structure and concentration (eq 3).[4a,4c] It was also found that under standard conditions (1 mol % cinchonine), alteration of the thiolacid structure improves enantiomeric excesses, with cyclohexanethiolcarboxylic acid and *t*-butyl thiolcarboxylic acid giving the highest ee's (68% and 64%, respectively).

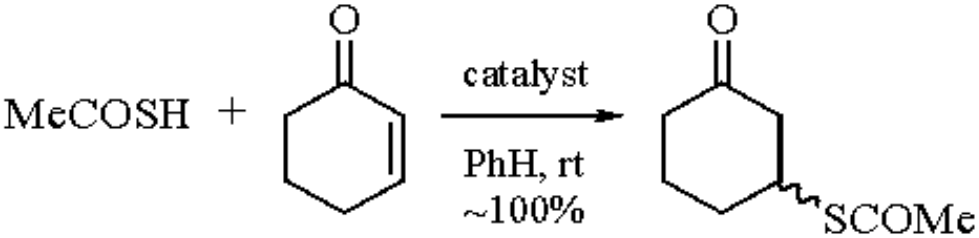

(3)

catalyst	mol %	% ee
11-thiobenzyl cinchonine	1.0	61 *(S)*
11-thiobenzyl quinidine	1.0	59.5 *(S)*
cinchonine	2.0	58 *(S)*
cinchonine	5.0	61 *(S)*

Acyclic enals and enones which differ in conformation due to steric demands of the ketone alkyl group give products with different absolute configurations at the newly formed stereogenic center.[4d] Thus cinnamaldehyde (**5a**), which exists predominantly in the *s-trans* conformation, gives the (*S*)-product due to *si*-face attack on the alkene, while benzylideneacetophenone (**5b**) in the *s-cis* conformation gives the (*R*)-product of *re*-face attack (eqs 4 and 5).

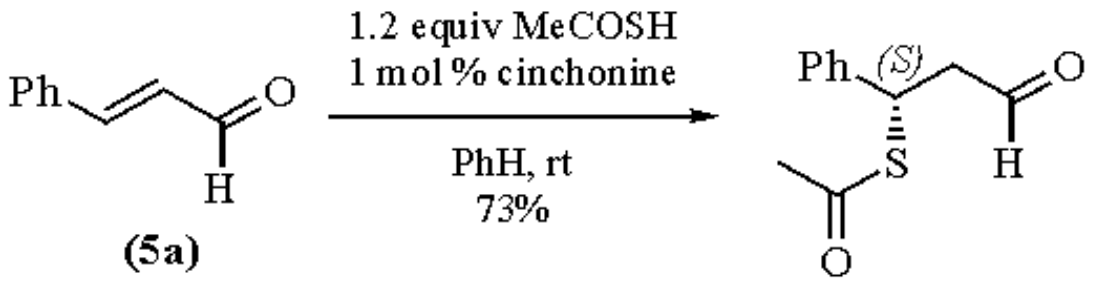

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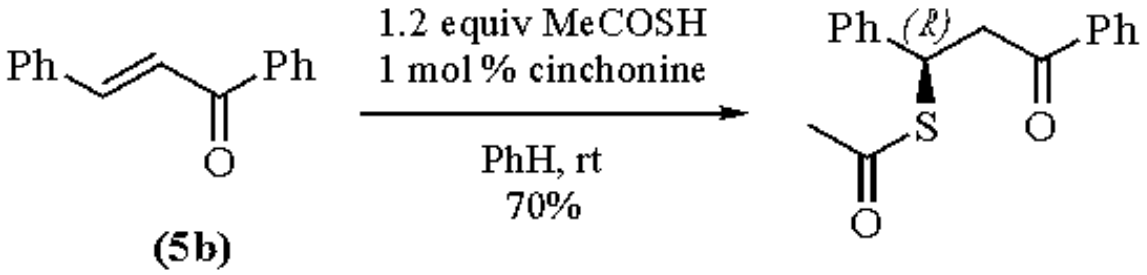

(5)

Although absolute configurations can be assigned using circular dichroism, enantiomeric excesses cannot be determined due to product degradation during acetal formation (for a description of this method of determining ee's, see Wynberg.[22]) The stereochemical outcome of these reactions is rationalized by the transition state complex of enone, thiolacetic acid, and cinchonine in which the cinchonine is in the preferred *gauche* conformation and is hydrogen-bonded to the enone carbonyl group. Thiolacetate and protonated quinuclidine base form an ion pair, and the *si*- and *re*-face attacks of *s-trans* and *s-cis* enones, respectively, can be visualized (eq 6).

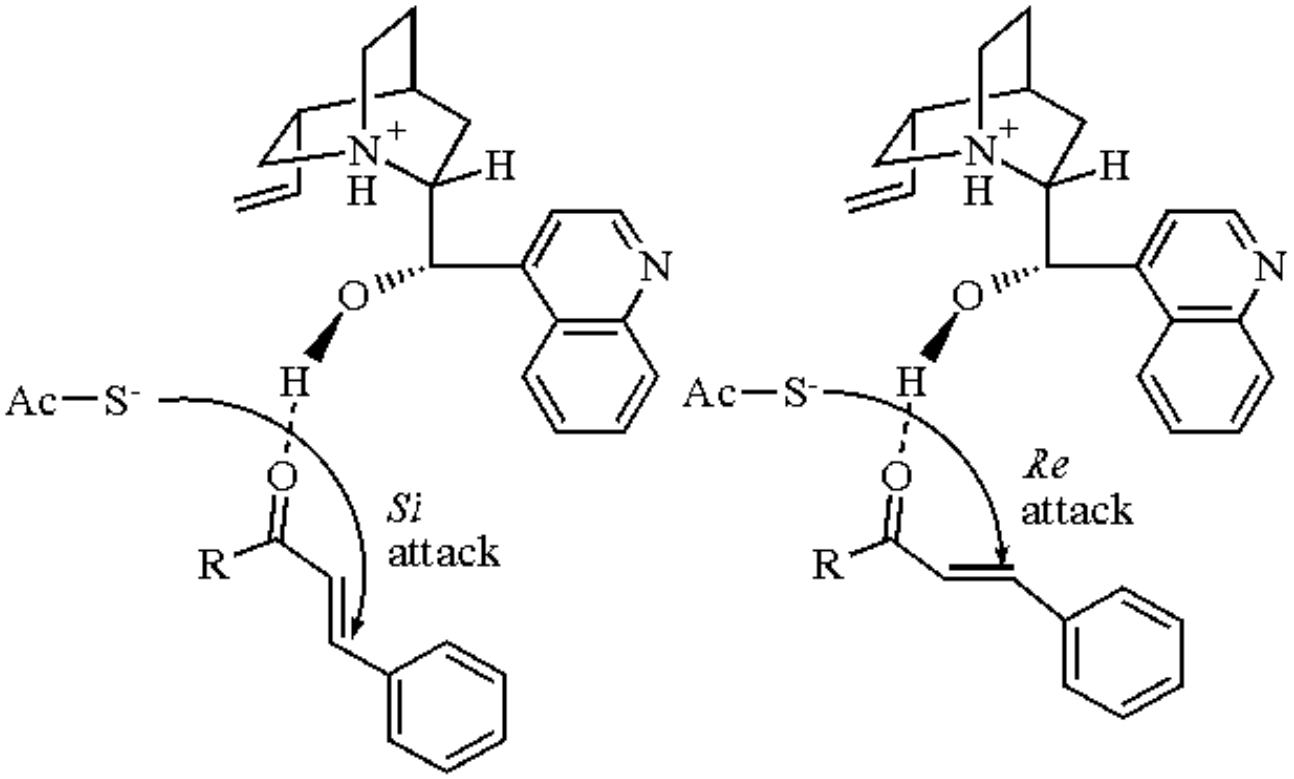

(6)

α,β-Unsaturated mono- and diesters are also subject to asymmetric addition of thiolacetic acid in the presence of cinchona catalysts, but to a lesser degree.[4b] Derivatives of 2-methylpropenoic acid are used in the monoester cases, and best results are obtained with *S*-alkyl thiolesters, which give only a 27% enantiomeric excess (eq 7). In the diester cases, the degree of asymmetric induction is difficult to ascertain due to *cis*/*trans* isomerization of the substrates. Qualitatively, however, these results indicate that *cis*-butenedioates enhance the ee's of products and that small alkoxy substituents (such as OEt) result in higher diastereoselectivity of the addition to the *cis*/*trans* isomers. It should be noted that asymmetric induction of chirally derivatized α,β-unsaturated mono- and diesters has been attempted by Yoshihara et al.,[5] but gives poor results in comparison to Gawronski's work. Using (-)-menthol as a chiral auxiliary, enantiomeric excesses of 15-18% for monoesters and 12% for diesters are obtained in the best cases.

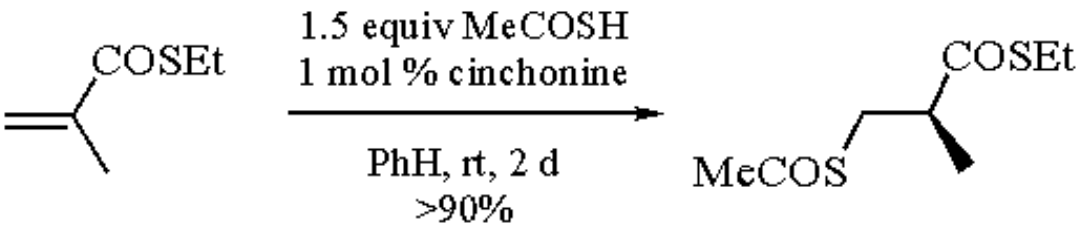

(7)

Thiolacetic acid has also been utilized as an enone protecting group.[6] Although few addition products in this study are formed in good yields, an interesting example is the protection of the dienone macrolide (**6**) (eq 8), which does give a good yield of the (11*S*)-11-acetylthio derivative (**7**), along with 3% of the (11*R*) derivative and 16% of recovered (**6**). It is interesting to note that in no instance is addition to the terminal position of the dienone observed. Deprotection of (**7**) with ***Tetra-n-butylammonium Fluoride*** to regenerate the dienone presumably occurs smoothly, although no yield is given.

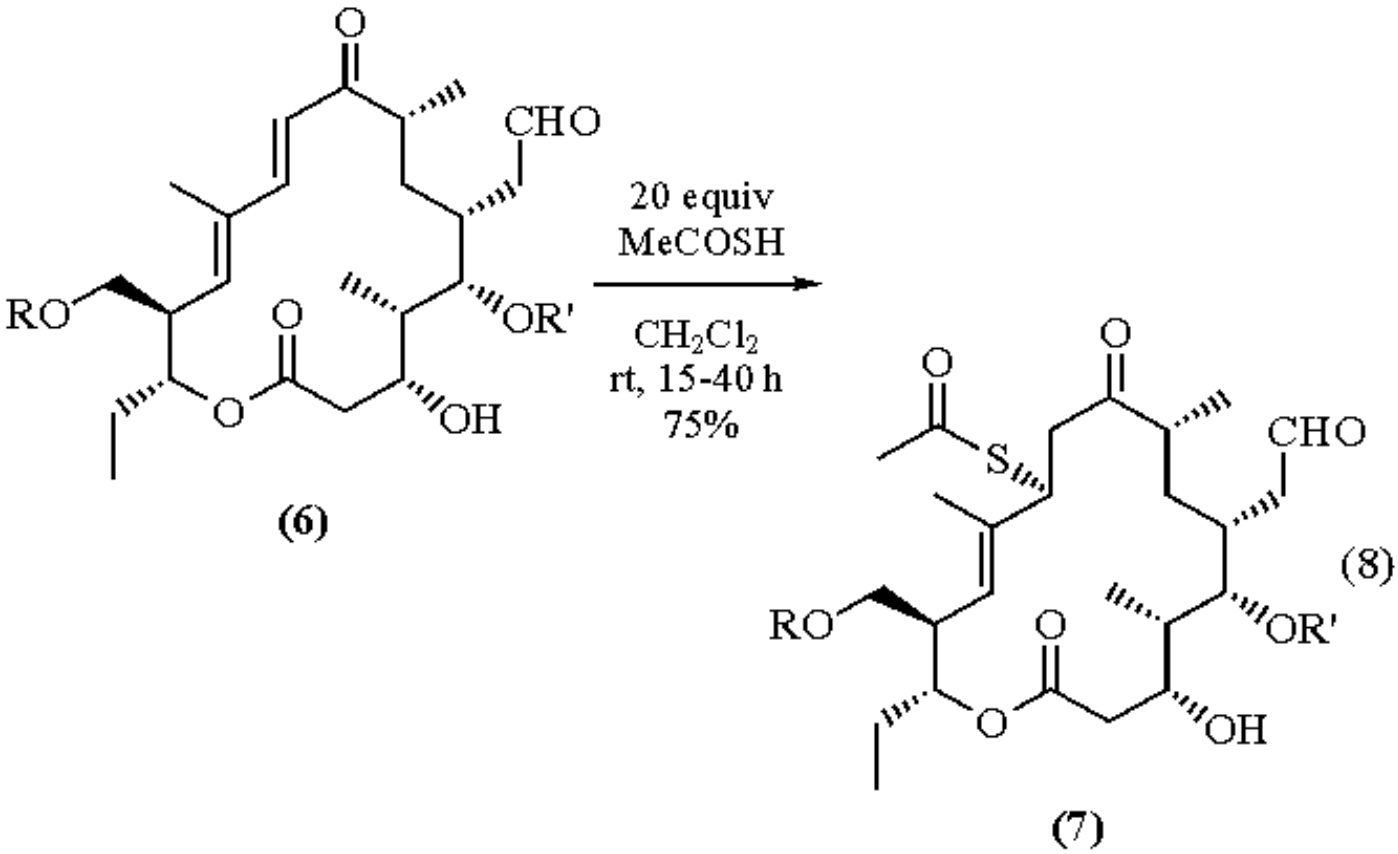

(8)

Radical Additions to Alkenes and Alkynes.

Thiolacetic acid typically adds to unsymmetrical alkenes in an anti-Markovnikov sense,[7] although exceptions have been noted in cases in which the anti-Markovnikov intermediate C-radical is less stable than the Markovnikov C-radical.[8] The addition of thiolacetic acid to cyclic alkenes is stereoselective,[7] with *trans* addition to obtain the *cis* product preferred over *cis* addition to obtain the *trans* product in additions to both cyclohexenes and cyclopentenes (eq 9).[9]

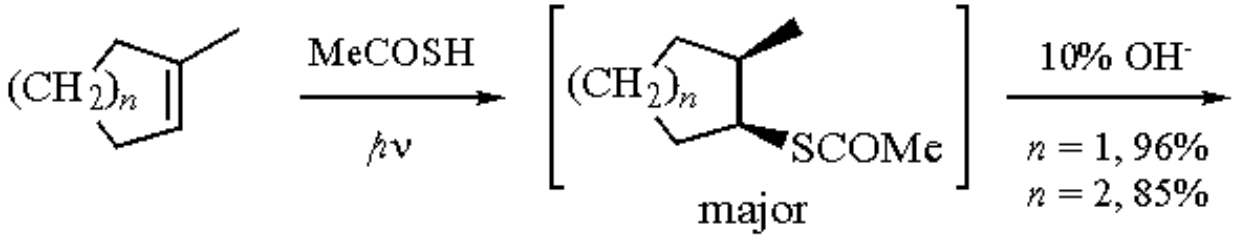

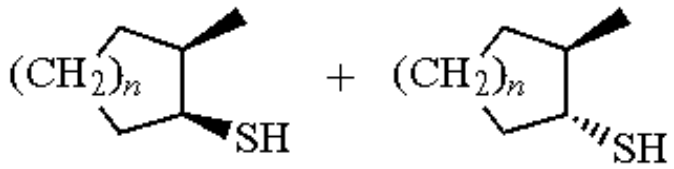

(9)

$n = 1$	71% *cis*	29% *trans*
$n = 2$	83% *cis*	17% *trans*

The addition of thiolacetic acid to acyclic alkenes is generally nonstereoselective, but attempts have been made to induce asymmetry through the use of chiral additives.[10] In the presence of (-)-menthol or deoxycholic acid (DCA) and ***Azobisisobutyronitrile*** (AIBN), 2-octene gives addition products (**8**) and (**9**) (eq 10) with ee's of 28% with (-)-menthol and 7% with DCA for compound (**8**). Although the absolute configuration of (**8**) was determined to be (*S*), no such determination was made for (**9**), and no ee's for (**9**) were reported.

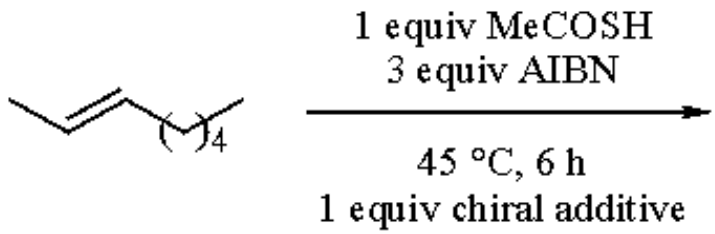

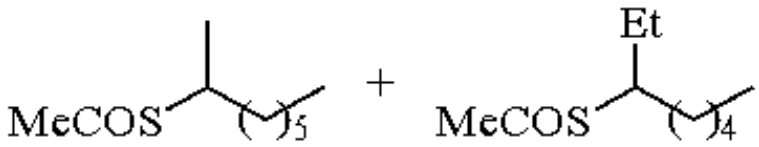

(10)

(8) **(9)**

chiral additive	**(8)**	**(9)**
(-)-menthol	45% (28% ee)	40%
DCA	40% (7% ee)	38%

Radical addition of thiolacetic acid to alkenes is the key step in a preparation of alkanesulfonic acids developed by Swern and co-workers (eq 11).[11] This method is nonideal for complex or sensitive substrates, however, and a much milder method has been reported by Musicki (eq 12)[12] which employs α-lithio sulfonates. Subsequent hydrolysis of the sulfonate ester (**10**) gives the sulfonate (**11**), which can then be coupled with other ribose units.

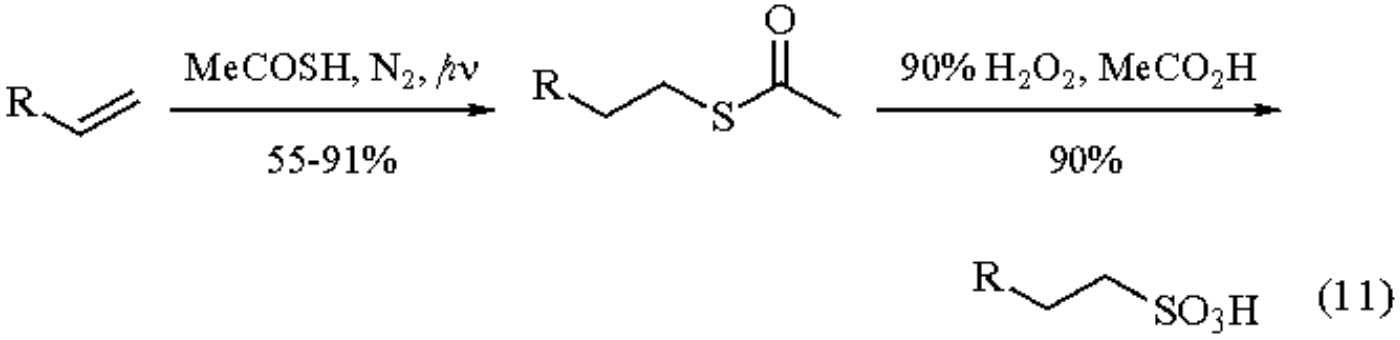

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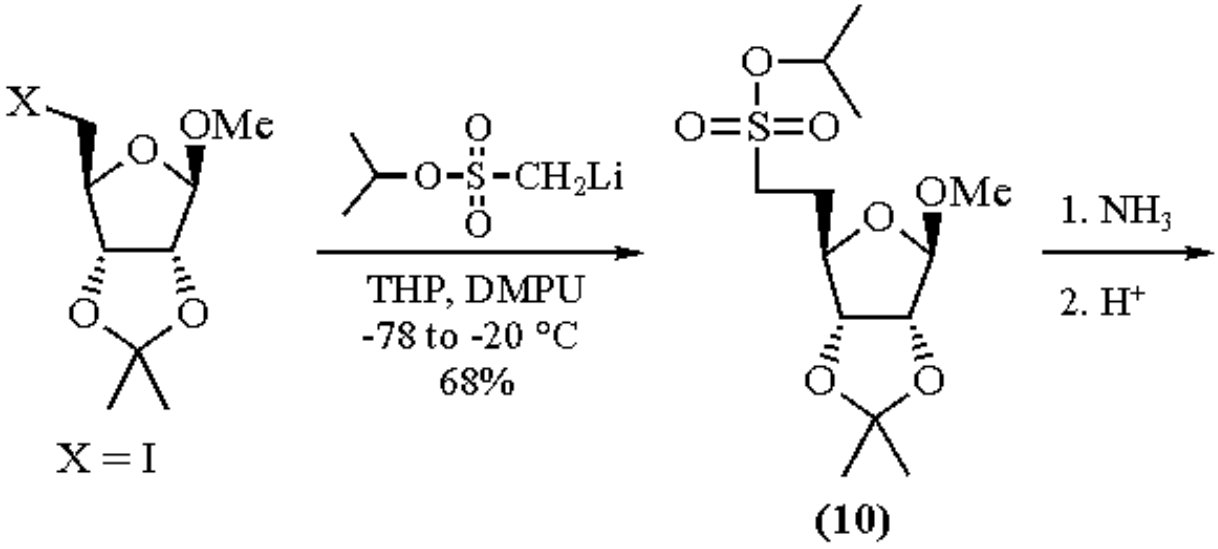

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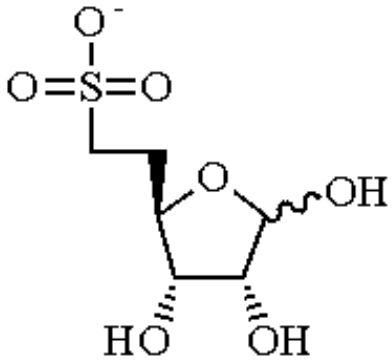

(12)

(11)

Thiolacetic acid adds readily to alkynes to give mono- and bis-adducts. If the alkyne is monosubstituted, anti-Markovnikov regioselectivity is observed in the monoadduct. Varying yields of both the mono- and bis-products are obtained, depending on the structure of the alkynyl substrate and the amount of thiolacetic acid added, and yields are often improved by the addition of initiators, such as peroxide.[13,1b] Monoadducts can be further transformed into aldehyde equivalents such as semicarbazones (**12**) (eq 13), which are synthetically useful intermediates.

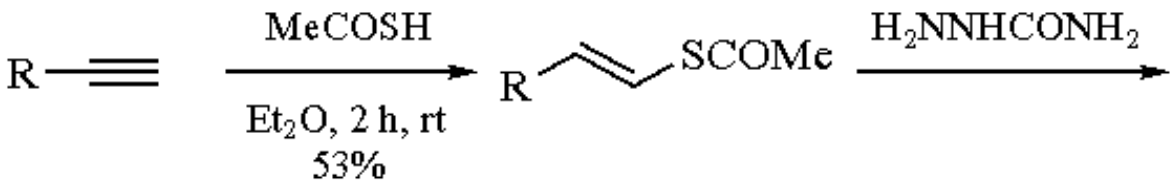

(13)

(12) 57%

A more recent method that is much milder and potentially more useful is the conversion of ethynyl carbinols into α,β-unsaturated aldehydes via a two-step Meyer-Schuster rearrangement (eq 14).[14] This method employs ***Thiophenol*** rather than thiolacetic acid. The (*E*/*Z*) ratio of the α,β-unsaturated aldehyde products range from 94/6 to 66/34, depending on the reaction conditions.

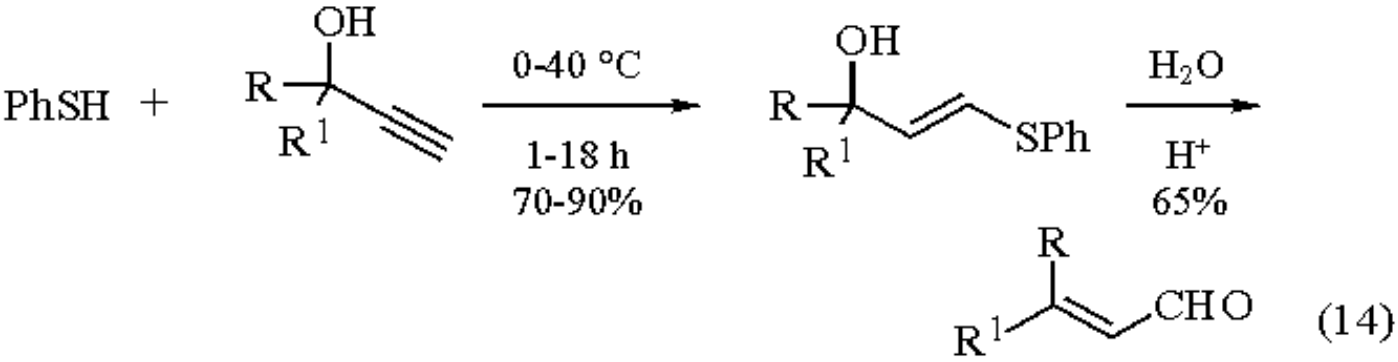

Use in the Formation of Chiral Dithioacetals.

Mixed acyl dithioacetals (**13**) have been prepared in good yield by the reaction of an aldehyde, a thiol, and thiolacetic acid in the presence of an acid catalyst (eq 15).[15a] These compounds can then be hydrolyzed and alkylated to give chiral dithioacetals (**14**), which are key functional groups in a series of potent and specific leukotriene D_4 antagonists developed by Gauthier et al.[15] Highest yields of the acyldithioacetals (**13**) are obtained with ***Zinc Iodide*** as the catalyst in refluxing dichloromethane for 2 h (86-91%). Deacylation with ***Potassium Carbonate***, ***Sodium Methoxide***, or ***Methyllithium***, followed by alkylation at low temperature (-10 to -80 °C), gives chiral dithioacetals (**14**) in good yield (86-97%). As an extension of this method, optically active dithioacetals can be prepared by use of a chiral thiolacid which renders the intermediate acyl dithioacetals diastereomeric and, thus, separable. Each diastereomer can then be further reacted to yield an optically active dithioacetal (**14**) with no loss of configurational purity.[15b,c]

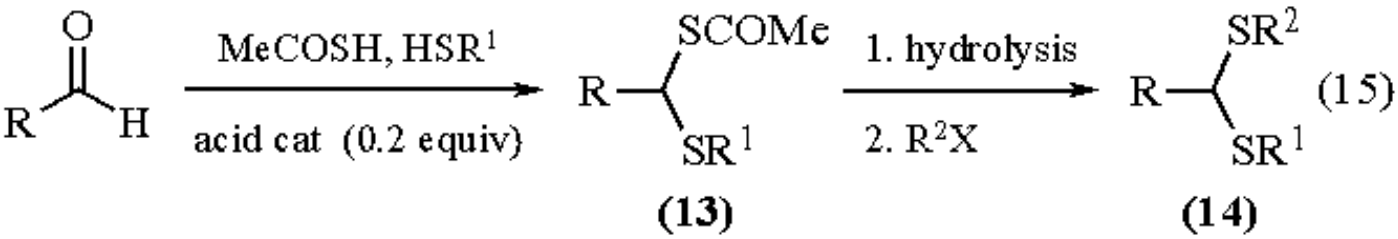

As an Acylating Agent.

Thiolacetic acid is not generally used as an acylating agent. It has been employed to acylate aromatic amines[16] and thiols,[17a,b] but in these cases there is no distinct advantage of thiolacetic acid over more commonly used acylating agents such as acid chlorides and anhydrides. Thiolacetic acid has the capability, however, of selectively acylating certain functional groups in the presence of others. For example, van Montagu et al.[18] selectively acylated the primary amino group of a cytidine moiety in the presence of a primary alcohol (eq 16). Acylation of alcohols will occur but typically requires forcing conditions. This is a common side reaction when thiolacetic acid is employed in 1,4-addition to enones containing alcohol groups.[2,5] Chemoselective reductive acylation of azides has also been observed with thiolacetic acid (eq 17).[19]

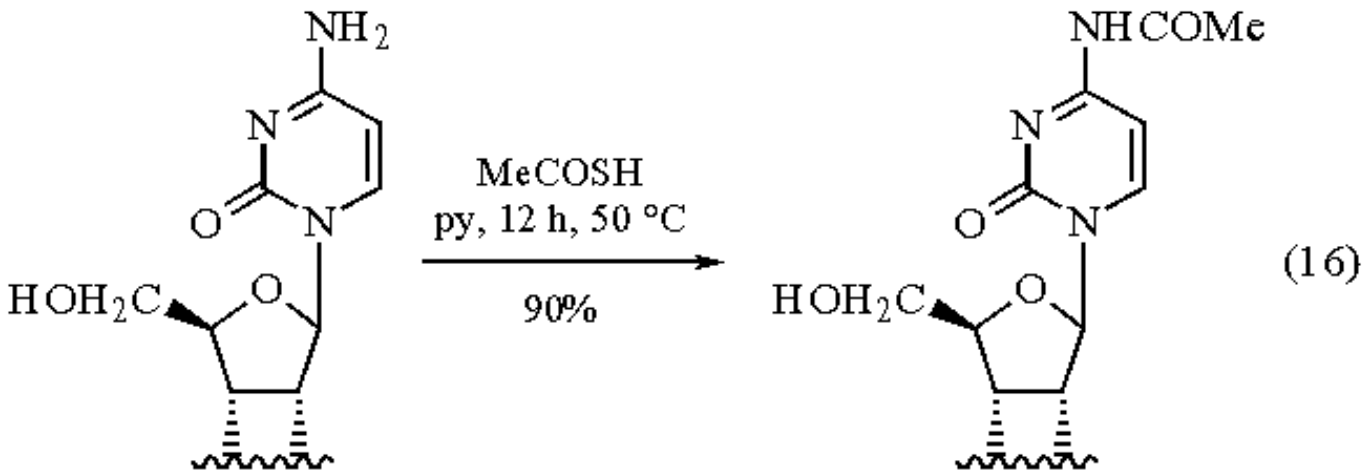

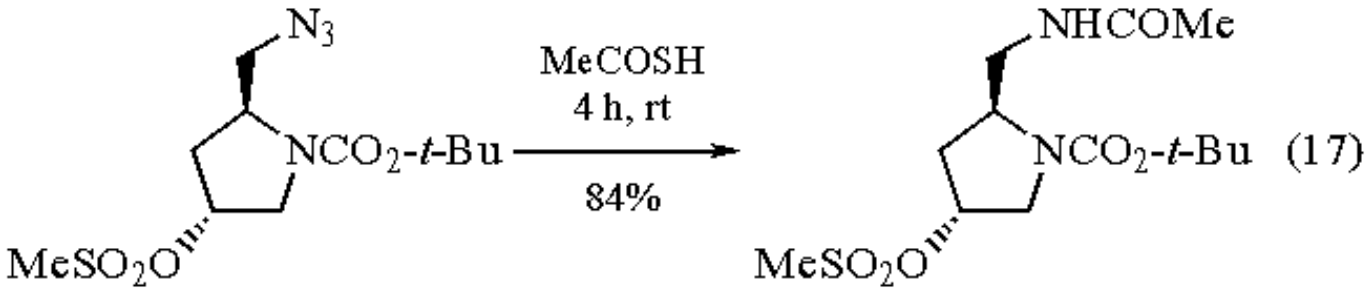

(17)

S_N2 Substitutions of Halides and Activated Alcohols.

Just as in the case of carboxylic acids, thiolacetic acid can be successfully used to effect Mitsunobu-type substitutions of secondary alcohols to give thioesters with inversion of configuration at the carbinol center (eq 18).[20] S_N2 substitution by thiolacetic acid of α-glycosides, activated at the anomeric position, has been observed by several groups (eqs 19 and 20).[21] In all cases, the β-thioglycoside product predominates.

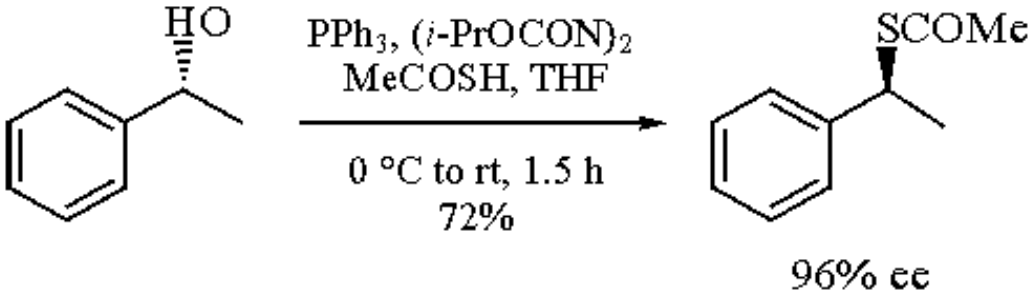

(18)

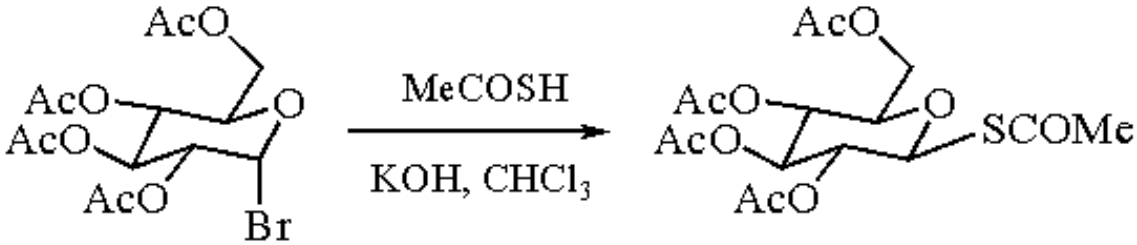

(19)

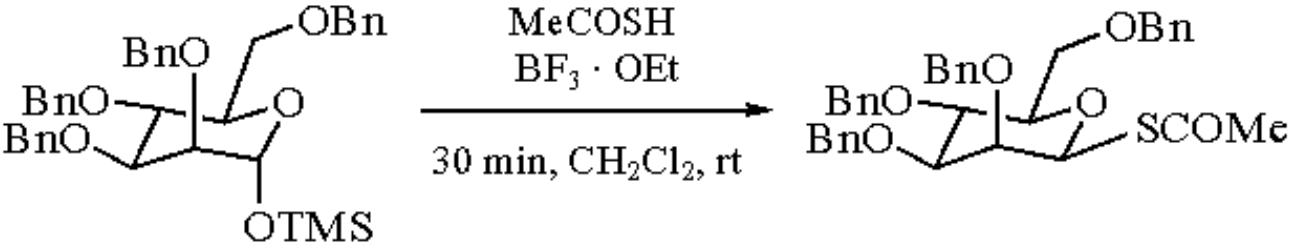

(20)

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Thionocarbonates[1]

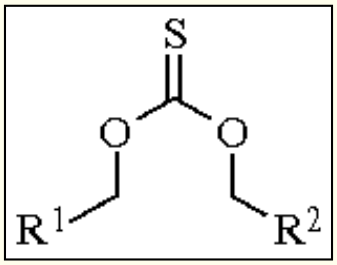

(method used for the deoxygenation of alcohols;[6] conversion of vicinal diols to alkenes;[3] undergo cyclizations,[3g] radical allylation,[6e] rearrangements[12])

Solubility: sol methanol, ethanol, most organic solvents.

Preparative Methods: see text.

Purification: chromatography or distillation where appropriate.

Definition.

Thionocarbonates are a class of chemical compounds having the general structure shown. There are two further classifications of this general structure: *cyclic*, where the two carbons are connected directly or via a carbon or heteroatom chain; and *acyclic*, where the two carbons are not connected. These compounds exhibit a wide range of activity, allowing the chemist to deoxygenate alcohols or to convert vicinal diols to alkenes (Corey-Winter reaction). In addition, thionocarbonates undergo cyclizations, rearrangements, and radical allylations.

Synthesis.

There are a wide variety of methods for preparing thionocarbonates. They are usually catered to fit the specific substrate and can vary widely with regard to pH, solvent, and temperature constraints. Cyclic thionocarbonates can be prepared by one of three general methods:

- 1)Vicinal diols can be reacted with ***1,1´-Thiocarbonyldiimidazole*** (TCDI) in a suitable solvent such as methylene chloride, acetone, or xylene. Temperatures vary from ambient to reflux. In one case, pyridine was added to facilitate formation of the thionocarbonate. Yields vary widely but in general are good.[2] This method is especially useful with acid sensitive substrates. Unfortunately, this method is unsatisfactory for large scale preparations due to the high cost of TCDI.[3]
- 2)***Thiophosgene*** reacts with diols in the presence of a base such as ***4-Dimethylaminopyridine*** (DMAP) to give thionocarbonates. The solvent is usually dichloromethane but can vary, depending on the substrate. Reaction temperatures vary also (0 °C to room temperature), as do yields (ca. 80%). Care must be taken in handling thiophosgene as it is highly toxic.[4]
- 3)Cyclic thionocarbonates have also been prepared by reaction of the diol with a base (***n-Butyllithium***, ***Sodium Hydride***, etc.) followed by quenching with ***Carbon Disulfide*** then ***Iodomethane***. Reaction temperatures and solvents vary according to the substrate. Reported yields are generally poor (<40%).[5]

Acyclic thionocarbonates are prepared by reaction of an alcohol with an aryl chlorothioformate (aryl = Ph, 4-FC_6H_4, C_6F_5, 2,4,6-$Cl_3C_6H_2$). Solvents that are used include acetonitrile, methylene chloride, THF, pyridine, and acetone. A base is also added (pyridine, DMAP, *n*-BuLi). Temperatures vary widely, as do yields (40-100%).[6]

Alkene Synthesis.

The conversion of vicinal diols to alkenes via the thionocarbonates is commonly known as the Corey-Winter reaction.[3c] As originally reported, cyclic thionocarbonates are treated with a trialkyl phosphite to give the alkene via *cis* elimination (eq 1). It was originally postulated that the reaction proceeds through a concerted cycloelimination mechanism,[3a] but evidence has also been presented supporting a carbene intermediate which decomposes to give CO_2 and the alkene.[7] Yields are generally high (>90% in some cases). A wide variety of substrates have been synthesized using this protocol, but it appears especially useful in the synthesis of highly strained alkenes.

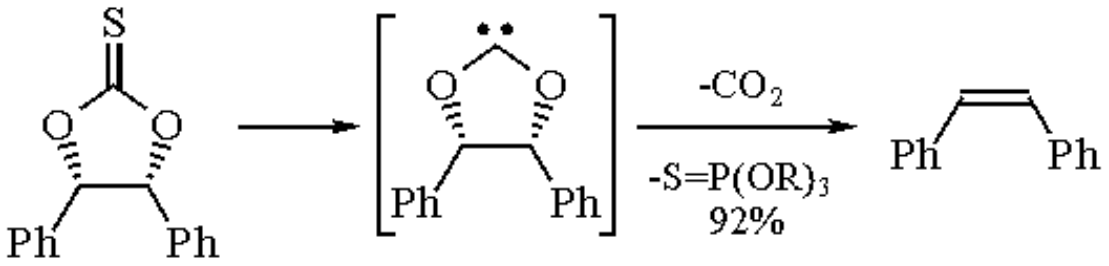

(1)

Other procedures have been identified to effect the elimination of the thionocarbonate to give an alkene. ***Pentacarbonyliron***,[8] ***Bis(1,5-cyclooctadiene)nickel(0)***,[9] and diazaphosphonolides (**1**)[4c] have been used in lieu of trialkyl phosphites. This procedure has been utilized by Paquette in the synthesis of cyclobutenes[3b,d] and $(CH)_{12}$ hydrocarbons,[4d] Ireland in the lasolocid A synthesis,[3e] and Barton in a synthesis of conduritol-B peracetate.[4b]

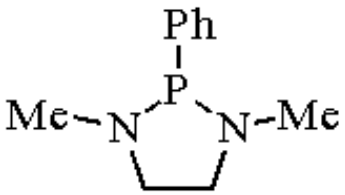

(1)

Vedejs and Wu reported manipulation problems with (**1**). This led to the development of a less direct conversion involving treatment with an alkyl halide (R = Me, *i*-Pr) followed by reductive elimination when treated with ***Magnesium Amalgam*** (eq 2).[2]

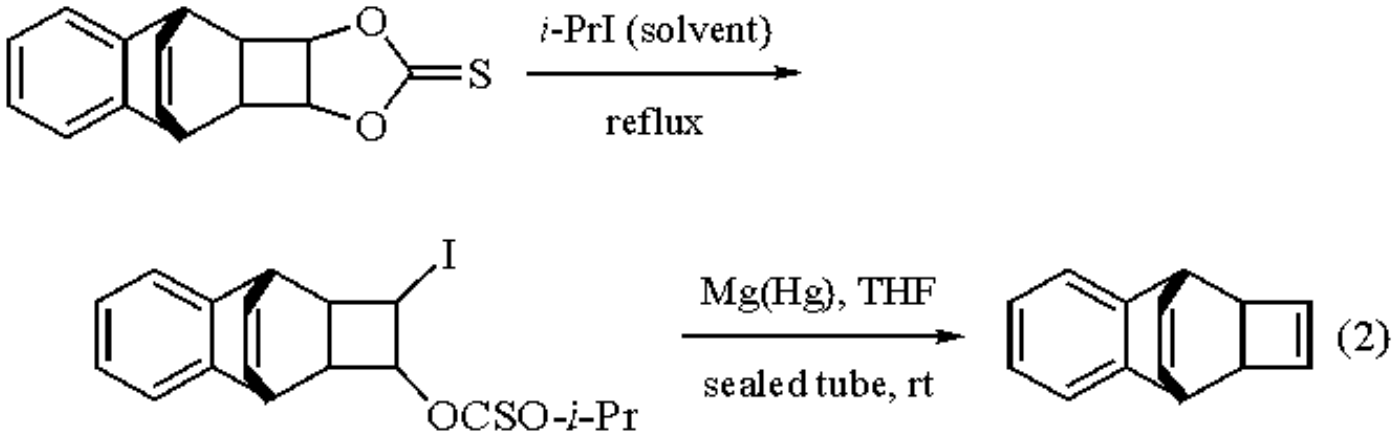

(2)

Alkenes have been introduced into monohydroxy alcohols using acyclic thionocarbonates. Eq 3 shows how a double bond is introduced by refluxing the phenylthioformate in xylene. This provides a key intermediate in the synthesis of pyrrolo[1,4]benzodiazepine antibiotics.[6i] Similar transformations have been accomplished with different conditions such as thermolysis[6h] or radical elimination[6g] of an acyclic thionocarbonate.

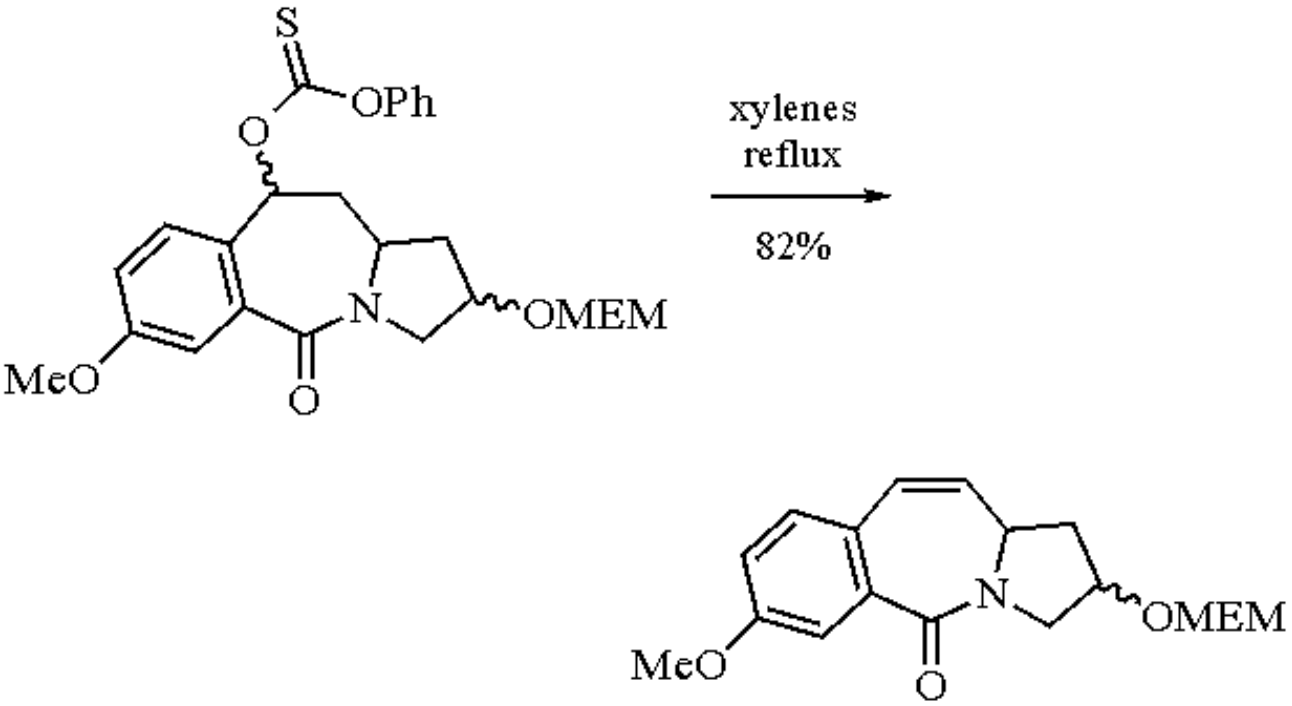

(3)

Deoxygenation.

Thionocarbonates provide a useful avenue for removal of hydroxyl groups from certain substrates. Typically, the thionocarbonate is treated with R_3SnH in the presence of a radical initiator (***Azobisisobutyronitrile*** or ***Dibenzoyl Peroxide***). Other hydrogen donors have been utilized including Ph_2SiH_2 and ***Tris(trimethylsilyl)silane***.[10] The reactions are run in refluxing toluene or xylene. Sugars are easily deoxygenated via this protocol[6a,b,d,j,k] and Martin et al. used this method in the preparation of difluoroalkylphosphonates.[11] One interesting observation was made during the deoxygenation of vicinal bromo thionocarbonates. In this case, treatment with Bu_3SnH/AIBN/toluene (reflux) gives the alkene (eq 4).[6a]

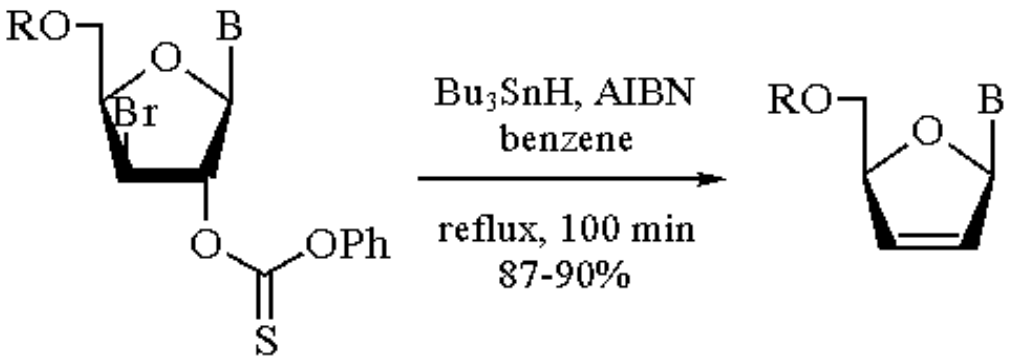

(4)

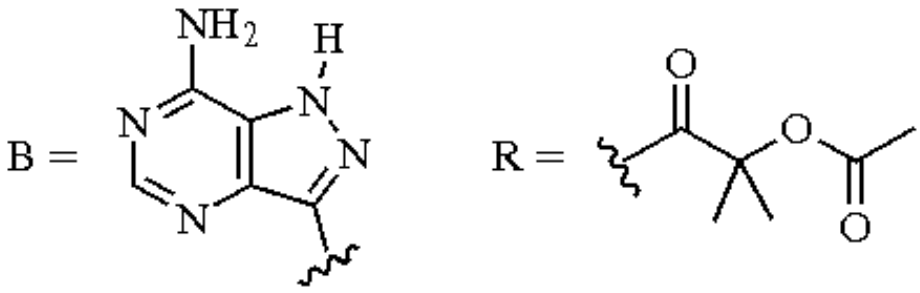

Other Reactions.

Medium-ring cyclic thionocarbonates undergo [3,3]-sigmatropic rearrangements to give cyclic thiolcarbonates on treatment with base (eq 5) (70-80%).[12] A similar rearrangement allows the conversion of an alcohol to a thiol (eq 6).[3f]

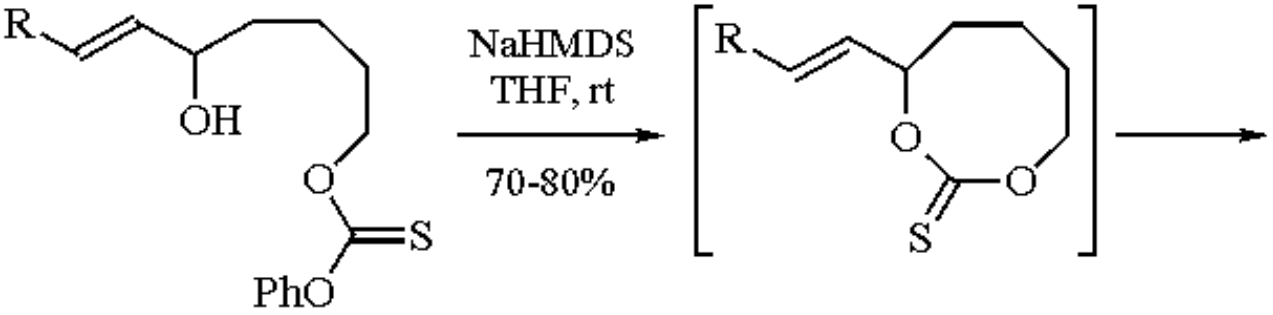

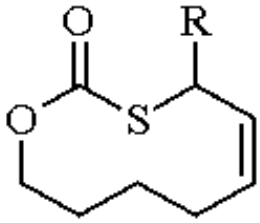

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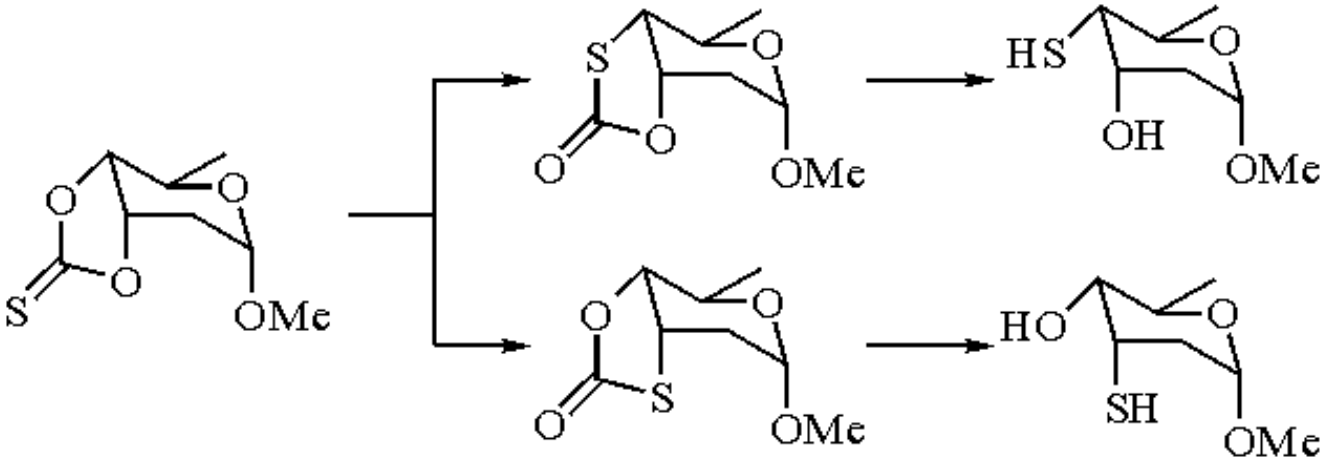

(6)

Radical cyclizations have been observed when thionocarbonates have been treated with ***Tri-n-butylstannane*** (eq 7 AIBN/toluene; 60%).[3g] Allyl groups have been introduced via the Keck procedure (***Allyltributylstannane***/AIBN/toluene). This is particularly useful in the synthesis of nucleosides (eq 8) (50-74%).[6e]

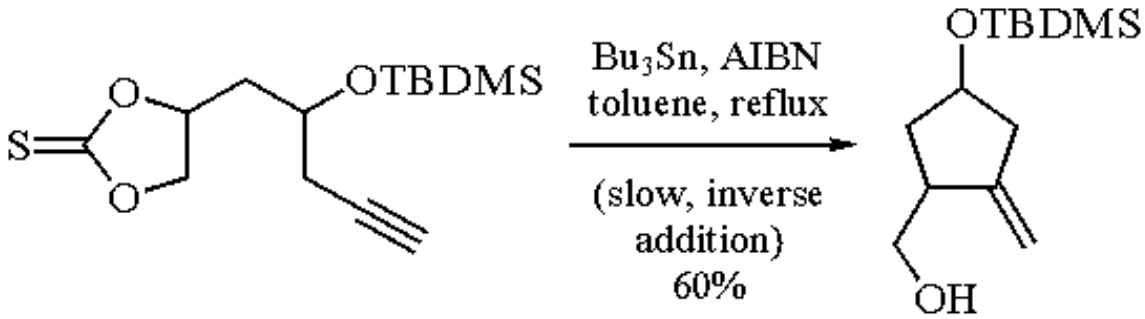

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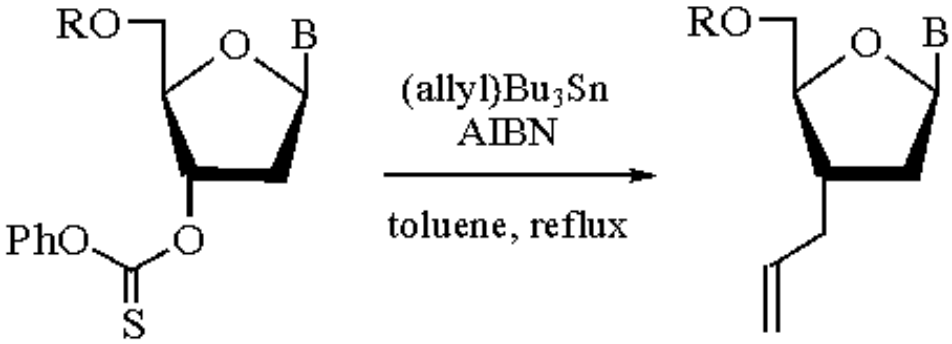

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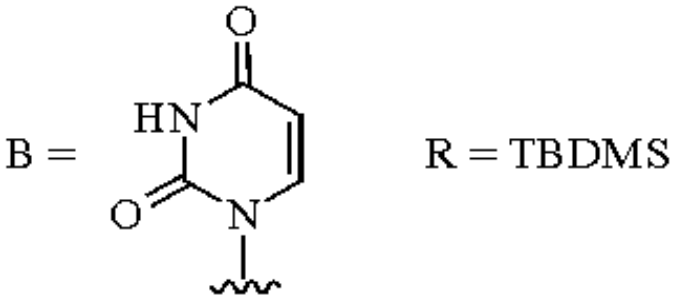

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2-Thiono-1,3-dioxol-4-ene

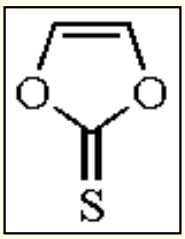

[37635-87-3] · $C_3H_2O_2S$ · 2-Thiono-1,3-dioxol-4-ene · (MW 102.12)

(dienophile in Diels-Alder reactions;[1] acetylene equivalent in cycloaddition reactions;[2] source of ketene;[3] forms dication dichalcogenides with strong Lewis acids[4])

Alternate Name: vinylene thionocarbonate.

Physical Data: mp 48 °C; bp 60-70 °C/0.2 mmHg.

Solubility: sol acetonitrile, benzene, carbon tetrachloride, dichloromethane, toluene; insol hexane.

Form Supplied in: not commercially available.

Preparative Method: prepared by reaction of ***Phosphorus(V) Sulfide*** with ***Vinylene Carbonate***.[1]

Purification: recrystallization from benzene-hexane gives white crystals; sublimation at 120 °C generates long white needles.

Handling, Storage, and Precautions: material is apparently stable.

Cyclization with Dienes.

The reaction of 2-thiono-1,3-dioxol-4-ene with anthracene at elevated temperatures leads to the production of the bicyclic adduct (**1**) (eq 1).[1,2] No other dienes have been reported to cyclize with this reagent. Diels-Alder adducts could be treated with phosphines to effect a Corey-Winter alkenation, which would render the reagent an acetylene equivalent.

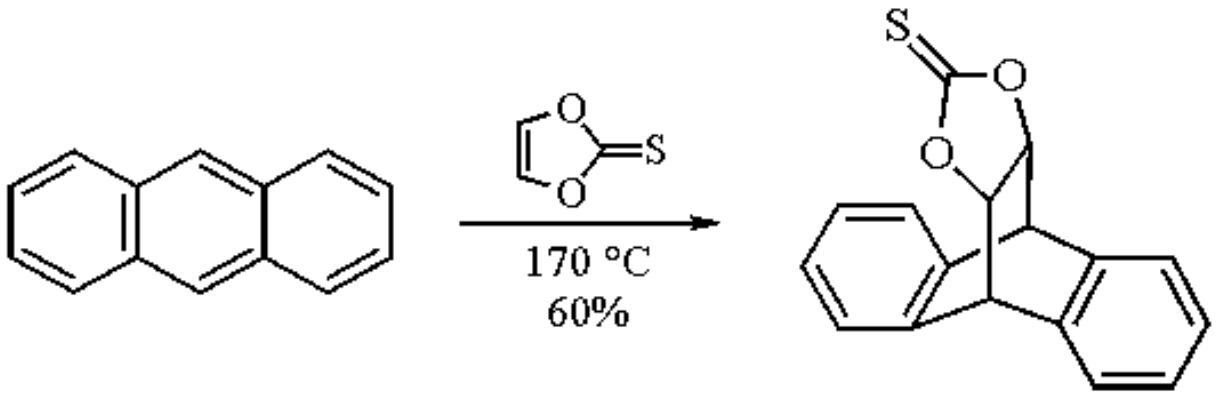

(1)

(1)

Synthesis of Ketene.

Photolysis (270 nm) of 2-thiono-1,3-dioxol-4-ene results in the quantitative formation of ketene via Wolff rearrangement of the corresponding α-ketocarbenes (eq 2).[3] Substituted dioxolenes can also be used in this fashion to generate substituted ketenes (eq 3). This serves as a convenient alternative to the use of α-diazo ketones in the generation of ketenes.

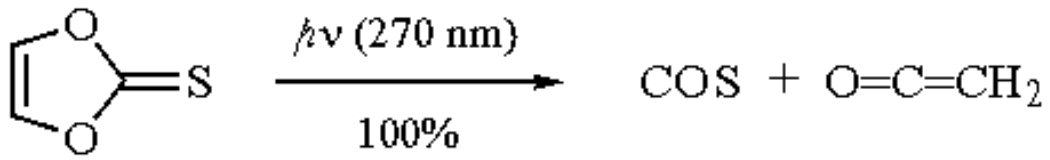

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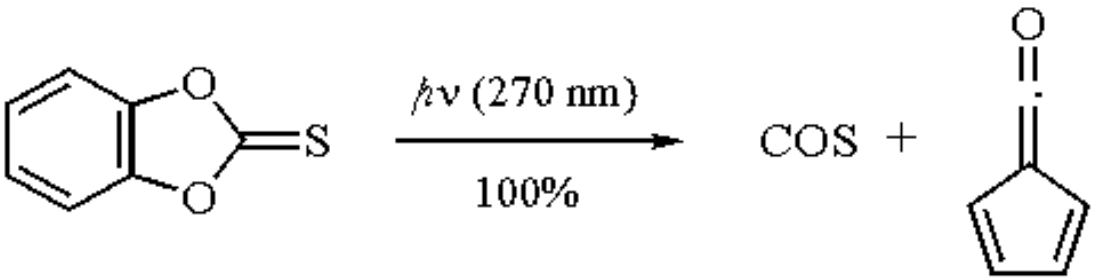

(3)

Preparation of Dication Dichalcogenides.

Treatment of 2-thiono-1,3-dioxol-4-ene with ***Trifluoromethanesulfonic Anhydride*** leads to the formation of the corresponding dimeric dication (eq 4).[4] Hydrolysis of this stable dication with aqueous base generates equimolar amounts of both vinylene carbonate and vinylene thionocarbonate.[4]

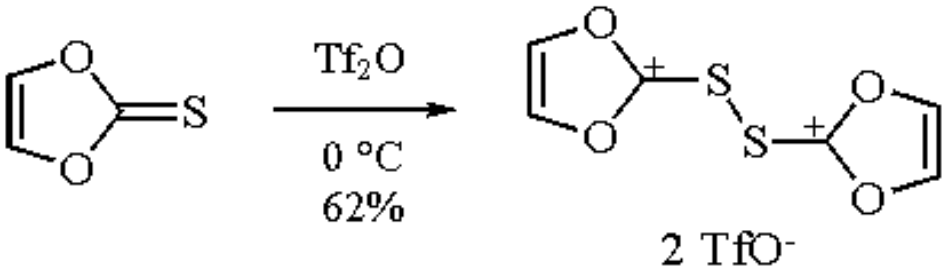

(4)

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Thionyl Bromide[1]

$SOBr_2$

[507-16-4] · Br_2OS · Thionyl Bromide · (MW 207.87)

(brominating agent for alcohols, carboxylic acids, alkenes, and ketones)

Physical Data: mp -52 °C; bp 68 °C/40 mmHg; *d* 2.688 g cm^{-3}.

Solubility: sol benzene, chloroform, carbon tetrachloride.

Form Supplied in: commercially available.

Handling, Storage, and Precautions: less stable than thionyl chloride and will slowly decompose, even in a stoppered container. Stable if kept dry, but reacts violently with water. Extremely destructive to tissue of mucous membranes, upper respiratory tract, eyes, and skin. Reacts vigorously with acetone to form a lachrymator. Should be handled in a fume hood.

Thionyl bromide is considerably more reactive than ***Thionyl Chloride*** and is more difficult to use.[2] Unlike thionyl chloride, whose reactions are often carried out in pyridine, thionyl bromide undergoes a reaction with this solvent to form a nonreactive salt (eq 1).[3]

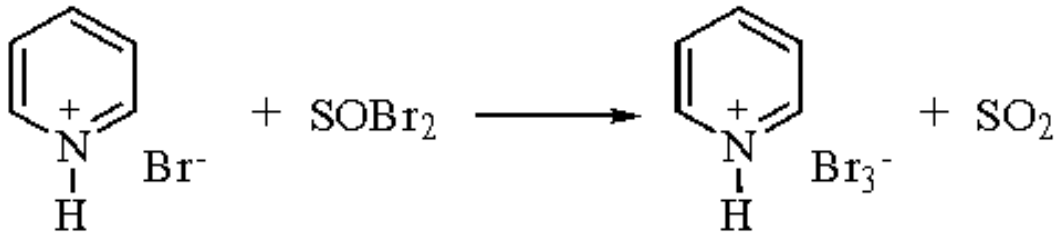

(1)

Preparation of Acid Bromides from Carboxylic Acids.

Although not often used, thionyl bromide can convert a simple organic acid to the acid bromide.[4] When the acid is an α,β-unsaturated acid, addition of bromine across the double bond occurs, generally in quantitative yield (eqs 2 and 3).

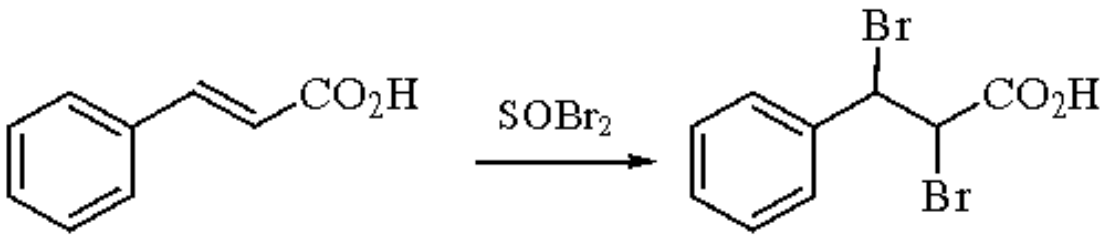

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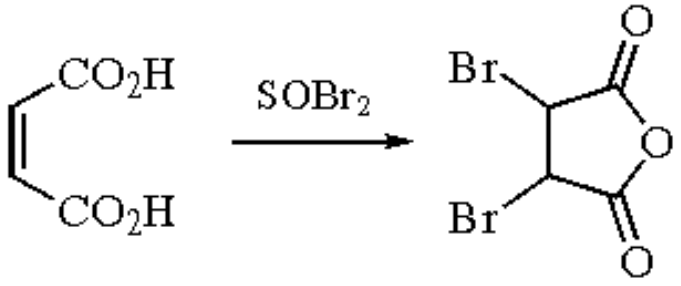

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For simple aliphatic acids, formation of the acid bromide is a high yield reaction (eq 4). Simple aromatic carboxylic acids also form the acid bromides in good yield.

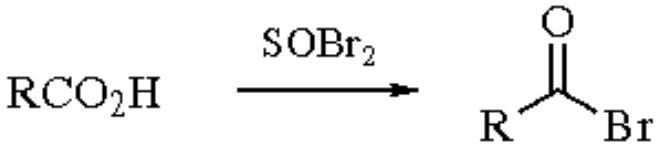

(4)

R = Me, 85%; Et, 90%; Pr, 92%; Bu, 90%

Thionyl bromide can function as a dehydrating agent for suitably positioned dicarboxylic acids (eq 5).

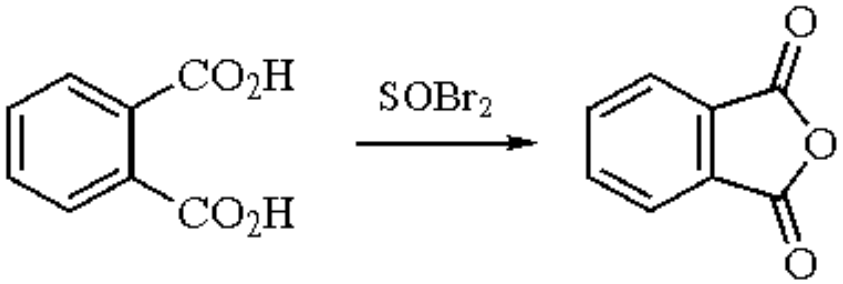

(5)

Preparation of Bromides from Alcohols.

In the ribonucleotide series, specific OH replacement has been noted (eq 6).[5] Other examples of the transformation of OH to Br are illustrated in eqs 7 and 8.[6,7] Conversion of an alcohol to a dibromo derivative has been reported (eq 9).[8]

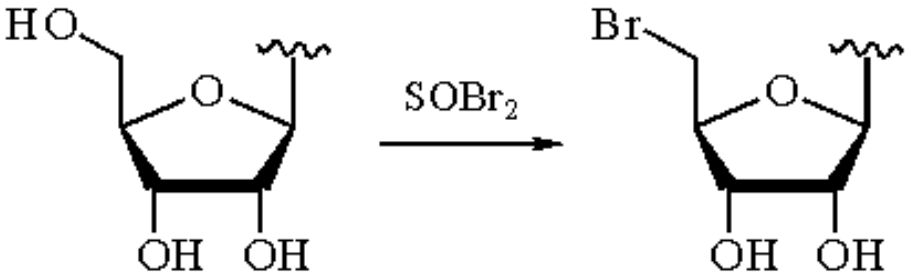

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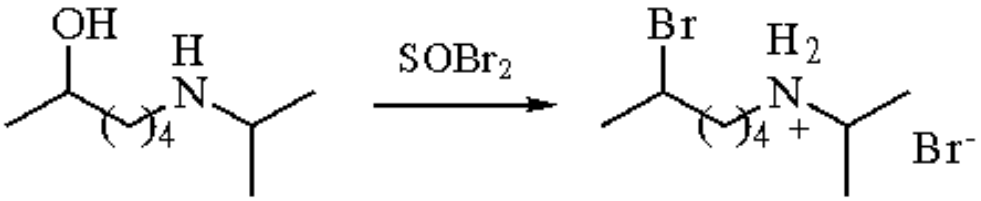

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62 g 82 g

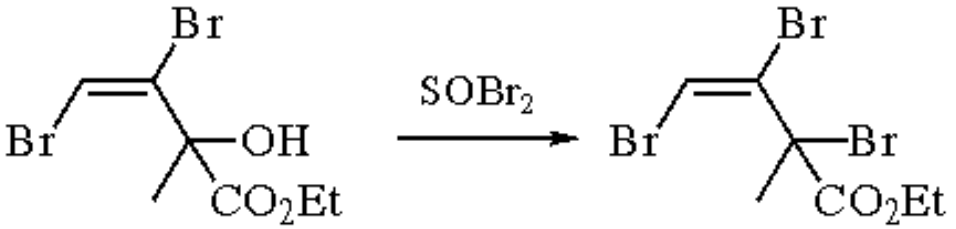

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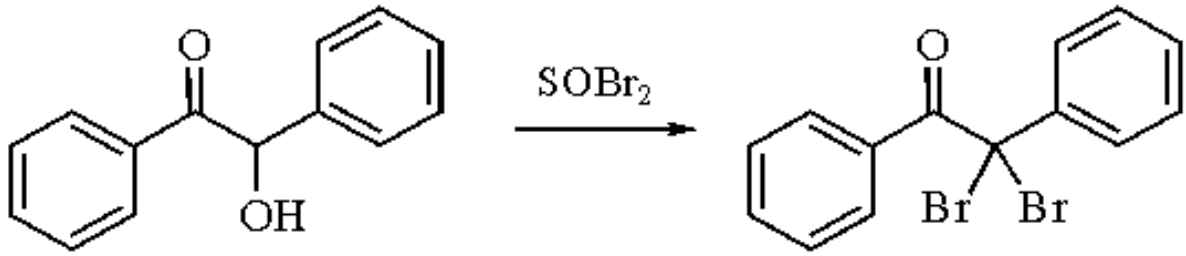

(9)

Bromination α to a Carbonyl Group.

Aromatic ketones with active methylene protons can be brominated with thionyl bromide. There is an example of dibromination of a methyl ketone (eq 10).[8] Propiophenone gives a mixture of α-bromopropiophenone and α-bromo-α-methylpropiophenone. The reaction with unsaturated ketones gives addition to the double bond (eq 11).[9]

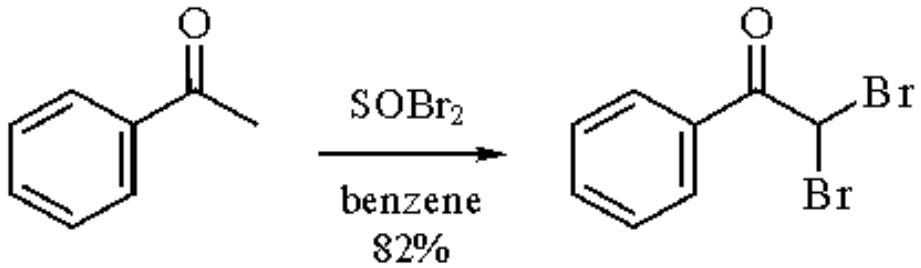

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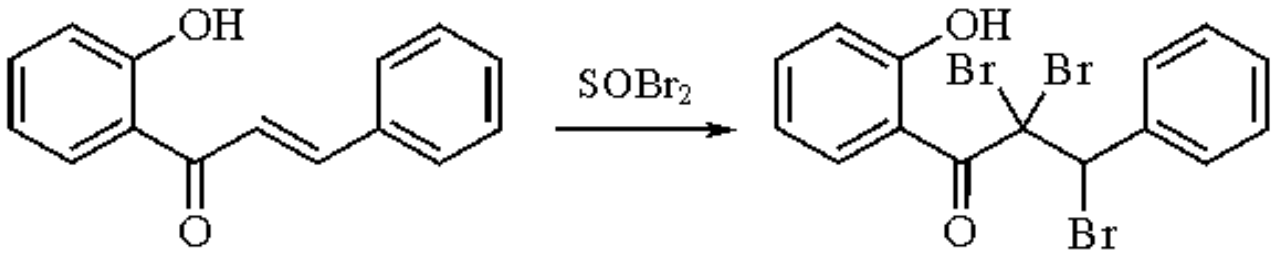

(11)

Preparation of *N*-(1-Bromoalkyl)heteroarylium Salts.

A general reaction is given in eq 12.[10]

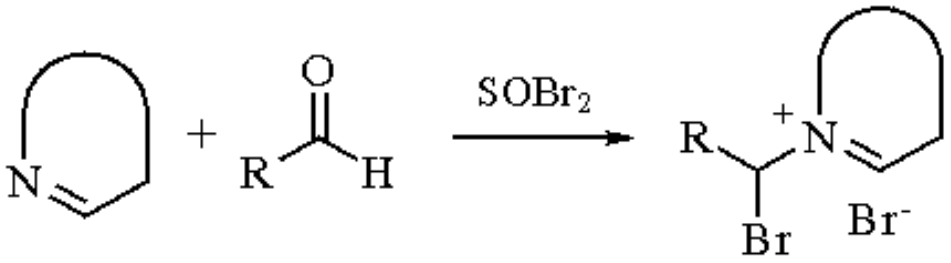

(12)

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Thionyl Chloride[1]

$SOCl_2$

[7719-09-7] · Cl_2OS · Thionyl Chloride · (MW 118.97)

(chlorination of alcohols,[2] carboxylic acids,[3] and sulfonic acids;[4] dehydration of amides;[5] formation of imidoyl chlorides,[6] sulfur-containing heterocycles,[7] and the Vilsmeier reagent)

Physical Data: [8] bp 76 °C; *d* 1.631 g cm^{-3}.

Solubility: sol ethers, hydrocarbons, halogenated hydrocarbons; reacts with water, protic solvents, DMF, DMSO.

Form Supplied in: colorless to yellow liquid.

Purification: impurities cause formation of yellow or red colors. Iron contamination can cause a black color. Fractional distillation, either directly[9] or from triphenyl phosphite[10] or quinoline and linseed oil,[11] has been recommended.

Handling, Storage, and Precautions: very corrosive and reactive; the vapor and liquid are irritating to the eyes, mucous membranes, and skin. Protective gloves should be worn when handling to avoid skin contact. Thionyl chloride should be stored in glass containers at ambient temperature and protected from moisture. It reacts with water to liberate the toxic gases HCl and SO_2. Since most reactions using $SOCl_2$ evolve these gases, they should be performed only in well-ventilated hoods. Above 140 °C, $SOCl_2$ decomposes to Cl_2, SO_2, and S_2Cl_2. Iron and/or zinc contamination may cause catastrophic decomposition.[12]

Chlorides from Alcohols.

Thionyl chloride reacts with primary, secondary, and tertiary alcohols to form chlorosulfite esters (eq 1) which can be isolated.[13] The fate of these esters depends on the reaction conditions, especially the stoichiometry, solvent, and base. If 2 equiv of alcohol and pyridine are used relative to thionyl chloride, dialkyl sulfites may be isolated (eq 2).[14]

$$ROH + SOCl_2 \longrightarrow ROSOCl + HCl \qquad (1)$$

$$2\,BuOH + SOCl_2 \xrightarrow[77\text{-}84\%]{py} BuOSO_2Bu \qquad (2)$$

When thionyl chloride is in excess, or when alkyl chlorosulfites are treated with thionyl chloride,[15] alkyl chlorides are produced and the byproducts are HCl and SO_2. The mechanism of this reaction may be S_N1, S_N2, S_Ni, or S_N2' (with allylic or propargylic alcohols). In the absence of base the S_Ni mechanism operates; retention of configuration is observed in the alkyl chloride (eq 3).[16] Considerable ionic character may be involved in this process and small amounts of elimination or rearrangement are common as side reactions.[17]

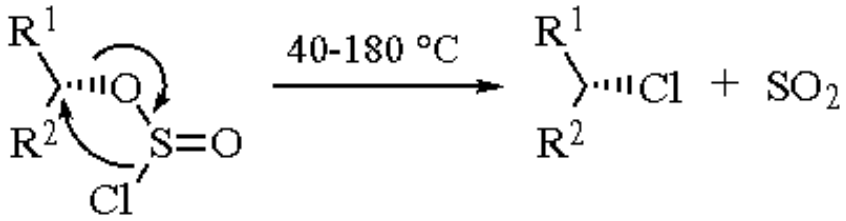

(3)

Thus, simple heating of the alcohol with thionyl chloride alone is often the preferred method for retaining the configuration of the alcohol

in the chloride. Alternatively, use of amine bases, most commonly ***Pyridine***,[18] results in a shift in the mechanism to S_N2 (eq 4) and consequently overall inversion. Excess pyridine may cause dehydrochlorination or alkylation of the base. If inversion of the substrate is desired or the stereochemical outcome need not be controlled, the use of pyridine or other amine base is recommended since the resulting high chloride concentrations minimize rearrangements and eliminations.[19,17a] Alternatively, catalysis of the chlorination by ***Hexamethylphosphoric Triamide*** results in inversion.[20] With allylic substrates, rearranged products generally predominate, especially in nonpolar solvents.[21] Use of ***Tri-n-butylamine*** as the base can result in unrearranged allylic products.[22]

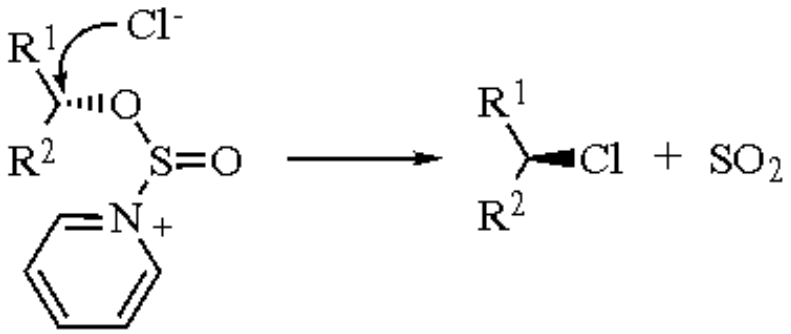

(4)

Representative procedures are available for the chlorination of tetrahydrofurfuryl alcohol,[23] benzoin,[24] and ethyl mandelate.[25] The use of thionyl chloride for this transformation usually gives less rearrangement and elimination than conc HCl, PCl_3, or PCl_5. For compounds which are acid-sensitive, ***Triphenylphosphine-Carbon Tetrachloride*** may be used.

Carboxylic Acid Chlorides from Acids.

Thionyl chloride has been the most widely used reagent for the preparation of acid chlorides. Carboxylic anhydrides also react with $SOCl_2$, giving 2 equiv of the acid chloride.[26] The procedure normally involves heating the carboxylic acid with a slight to large excess of $SOCl_2$ in an inert solvent or with $SOCl_2$ itself as the solvent. Operation at the boiling point of the solvent speeds removal of the byproducts, HCl and SO_2. The ease of removal of the byproducts is the chief advantage of $SOCl_2$ over PCl_5 and PCl_3. This simple procedure gives good yields of the acid chlorides of butyric,[27] cinnamic,[28] and adipic acid.[29] The reactions are first order in each reactant and electron-withdrawing groups on the acid decrease the rate.[30] Several agents have been developed for the catalysis of this reaction. Pyridine was historically the most common; its presumed mode of action is to ensure the presence of soluble chloride (as ***Pyridinium Chloride***) which reacts with the intermediate as shown in eq 5. Catalytic pyridine ensures that the chlorination of certain diacids such as succinic acid proceeds completely to the diacid chloride rather than stopping at the anhydride.[31] The preparation of aromatic acid chlorides also commonly uses pyridine as a catalyst (eq 6).[32] Trichloroacetic acid, which is unreactive toward thionyl chloride alone, is chlorinated by the use of pyridine catalyst.[33]

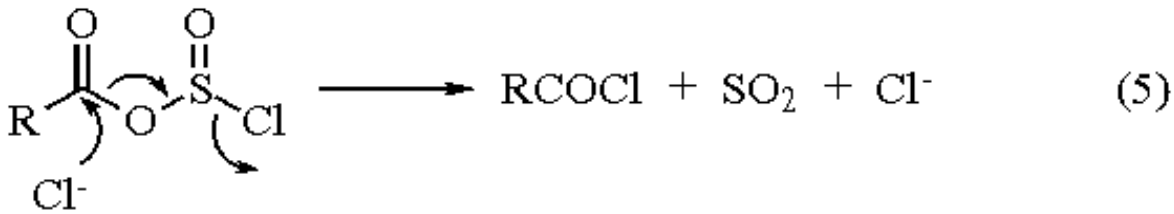

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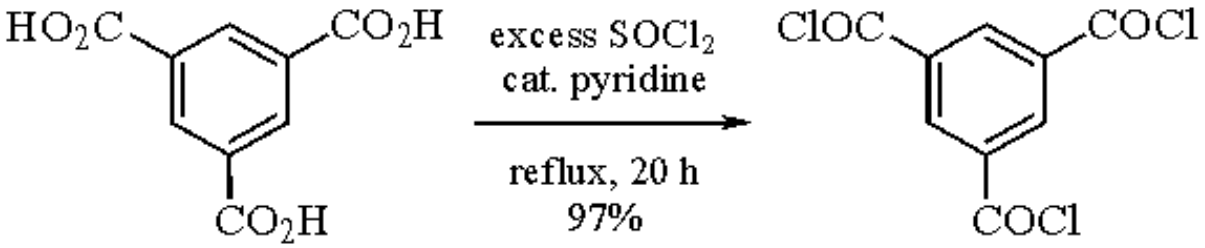

(6)

N,N-Dimethylformamide is a particularly effective catalyst for the formation of acid chlorides with $SOCl_2$ and is now commonly the catalyst of choice.[34] The chloromethyleneiminium chloride intermediate is the active chlorinating species (see ***Dimethylchloromethyleneammonium Chloride***).

Esters of amino acids may be produced directly from the amino acid, alcohol, and thionyl chloride. One procedure involves the sequential addition of thionyl chloride and then the acid to chilled methanol.[35] Alternatively, benzyl esters have been prepared by the slow addition of $SOCl_2$ to a suspension of the amino acid in benzyl alcohol at 5 °C.[36]

For the formation of acid chlorides, the competing reactions of concern are α-oxidation and acid-catalyzed degradation. The use of solid

Sodium Carbonate in the reaction mixture can minimize the latter for some compounds.[37] As shown in eq 7, even simple carboxylic acids with enolizable hydrogens α to the carboxylic functionality are subject to oxidation under standard chlorinating conditions.[38] Since the unoxidized acid chloride is the precursor to the sulfenyl chloride, careful attention to stoichiometry and reaction time can effectively minimize this problem.

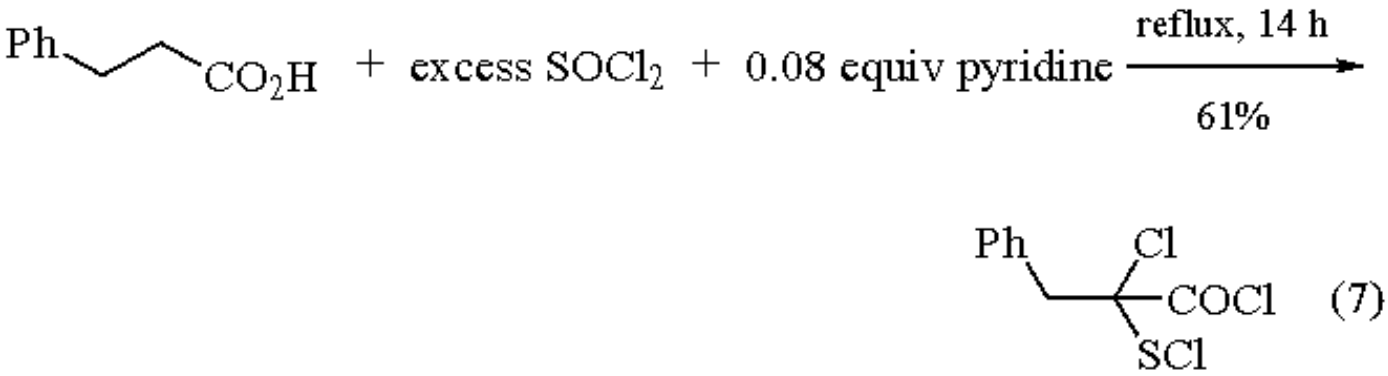

Sulfonyl and Sulfinyl Chlorides from Sulfonic and Sulfinic Acids.

Alkyl or arylsulfonyl chlorides are prepared by heating the acid with thionyl chloride; DMF catalyzes this reaction. (+)-Camphorsulfonyl chloride is produced in 99% yield without a catalyst.[39] Use of the salts of sulfinic acids minimizes their oxidation; *p*-toluenesulfinyl chloride is produced in about 70% yield from sodium *p*-toluenesulfinate dihydrate with excess thionyl chloride.[40] ***Phosphorus(V) Chloride*** is more commonly used for this transformation.

Nitriles and Isocyanides via Amide Dehydration.

Thionyl chloride dehydrates primary amides to form nitriles (eq 8); for example, 2-ethylhexanonitrile is produced in about 90% yield by heating with $SOCl_2$ in benzene.[41] Substituted benzonitriles are readily produced from benzamides.[42] These reactions may also be catalyzed by DMF.[43] *N*-Alkylformamides may be dehydrated to isocyanides.[44]

Reactions with Secondary Amides.

Treatment of *N*-alkyl or *N*-aryl secondary amides with thionyl chloride in an inert solvent such as methylene chloride results in the formation of imidoyl chlorides (eq 9).[45] Upon heating, the imidoyl chlorides from *N*-alkylamides undergo scission to generate nitriles and alkyl chlorides via the von Braun degradation (eq 10).[46]

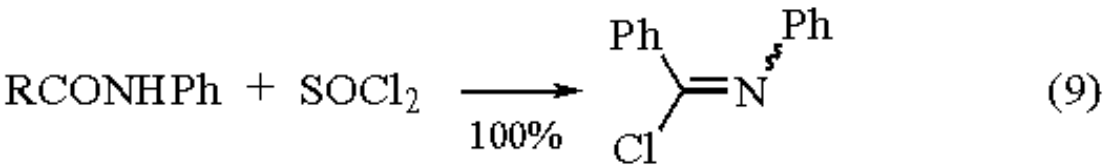

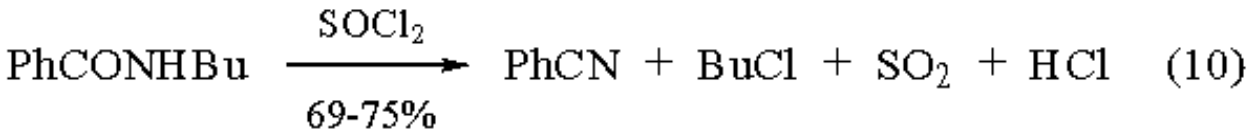

Reactions with Aldehydes and Ketones.

Aromatic or α,β-unsaturated aldehydes or their bisulfite addition compounds are converted to *gem*-dichlorides by treatment with $SOCl_2$, either neat or in an inert solvent such as nitromethane (eq 11).[47] This process is readily catalyzed by HMPA.[48] Thionyl chloride may be preferred over the more commonly used PCl_5 if removal of byproducts is problematic with the latter reagent.

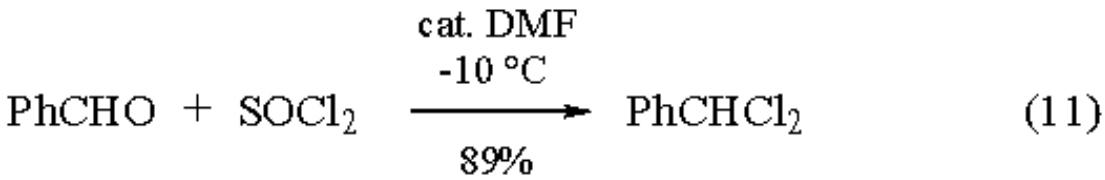

Carbonyl compounds or nitriles[49] with α-hydrogens may be oxidized at this position by thionyl chloride. This reaction appears more often as a troublesome side reaction than a useful synthetic procedure. Nitriles with one α-hydrogen produce α-cyanosulfinyl chlorides (eq 12) while those with two α-hydrogens give moderate yields of α-chloro-α-cyanosulfinyl chlorides.[50]

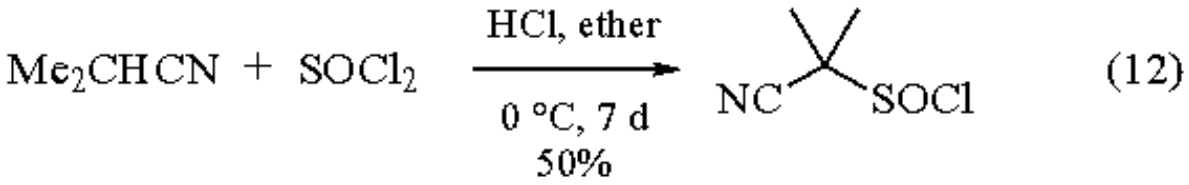

Oxidation of Activated C-H Bonds.

As shown in eq 13, extensive oxidation adjacent to carbonyl groups is possible with $SOCl_2$ under relatively mild conditions.[51] The process often stops after formation of the α-chlorosulfenyl chloride. Remarkably, these may be easily hydrolyzed back to the carbonyl compounds from which they were derived.[52] Alternatively, they may be treated with a secondary amine such as morpholine followed by hydrolysis to yield the α-dicarbonyl compound. Similar oxidation of acid derivatives during acid chloride formation is possible (see above).

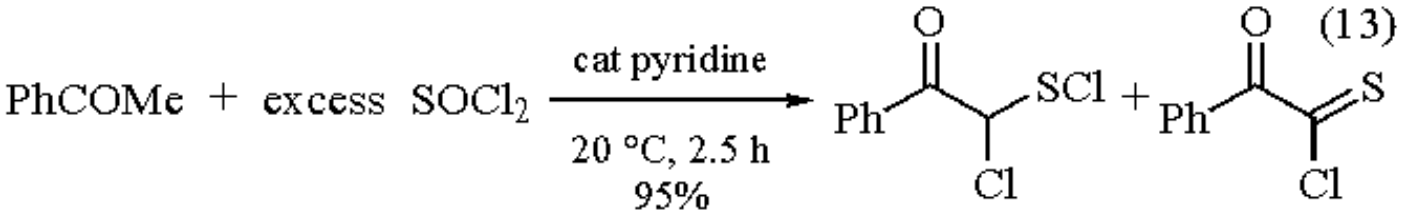

Methyl groups attached to benzenoid rings may be oxidized by $SOCl_2$ without added catalysts. The range of reactivity is large and not well understood; the products may be monochlorinated or further oxidation to the trichloromethyl aromatic system is possible.[53] 2-Methylpyrroles are similarly oxidized.[54] In systems with vicinal methyl and carboxylic acid groups, both oxidation of the methyl group and cyclization to a γ-thiolactone can occur.[55] In conjunction with radical initiators, $SOCl_2$ can chlorinate alkanes.[56] Aryl methyl ethers can be oxidized on the aromatic ring to give arylsulfenyl chlorides which may undergo further reactions.[57] This latter process, which presumably occurs via electrophilic aromatic substitution, is another potential serious side reaction for active substrates.

Rearrangement Reactions.

Thionyl chloride can act as the dehydrating agent in the Beckman[58] and Lossen rearrangements[59] and promotes the Pummerer rearrangement.[60]

Synthesis of Heterocyclic Compounds.

Thionyl chloride and pyridine at elevated temperatures convert diarylalkenes, styrenes, and cinnamic acids to benzo[*b*]thiophenes[61] and adipic acid to 2,5-bis(chlorocarbonyl)thiophene.[62] Additional heterocycles which have been prepared include thiazolo[3,2-*a*]indol-3(2*H*)-ones,[63] oxazolo[5,4-*d*]pyrimidines,[64] and 1,2,3-thiadiazoles.[65] Treatment of 1,2-diamino aromatic compounds with thionyl chloride gives good yields of fused 1,2,5-thiadiazoles.[66]

Other Applications.

Thionyl chloride has been used to convert epoxides to vicinal dichlorides[67] and for the preparation of dialkyl sulfides from Grignard reagents.[68] Phenols react with $SOCl_2$ to produce aryl chlorosulfites and diaryl sulfites[69] or nuclear substitution products. As shown in eq 14, ***Aluminum Chloride*** catalysis yields symmetric sulfoxides, while in the absence of Lewis acids, aromatic thiosulfonates are the principal products.[70] Primary amines, especially aromatic ones, react with $SOCl_2$ to produce *N*-sulfinylamines, which are potent enophiles and useful precursors to some heterocyclic compounds.[71]

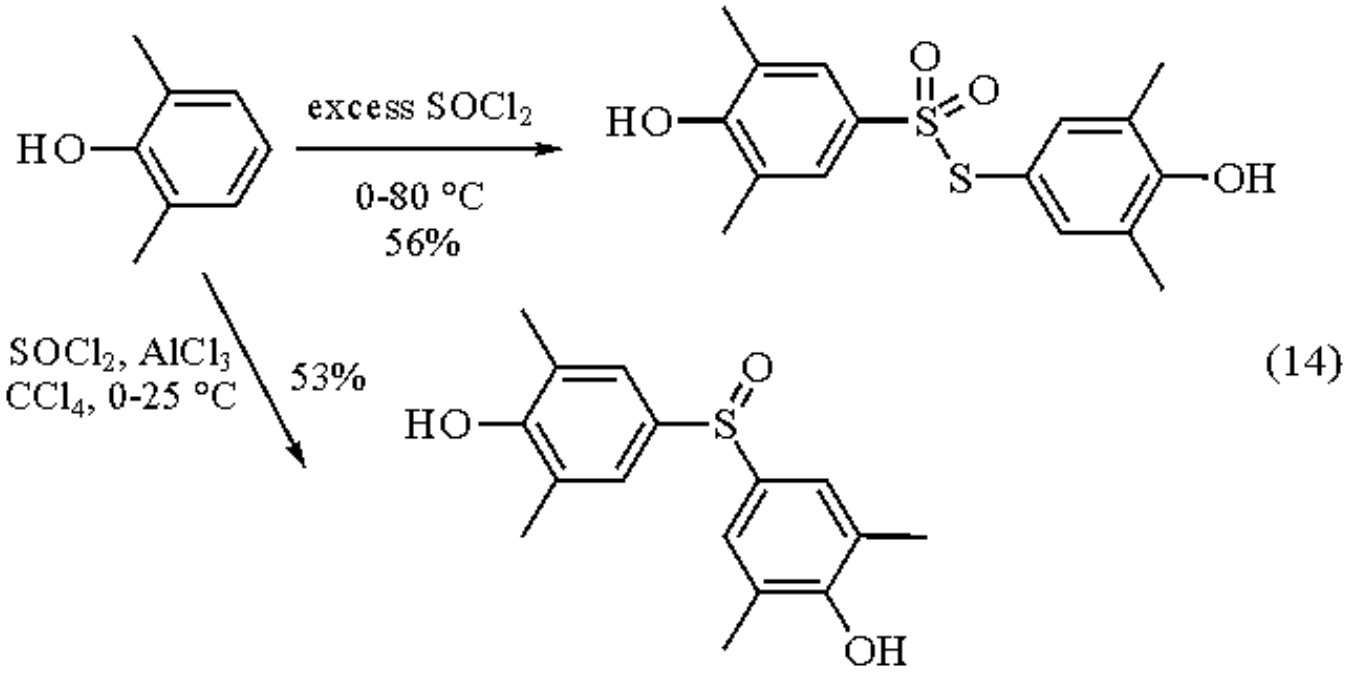

Related Reagents.

Dimethylchloromethyleneammonium Chloride; ***Hexamethylphosphoric Triamide-Thionyl Chloride***; ***Hydrogen Chloride***; ***Oxalyl Chloride***; ***Phosgene***; ***Phosphorus(III) Chloride***; ***Phosphorus(V) Chloride***; ***Phosphorus Oxychloride***; ***Phosphorus(V) Oxide***; ***Triphenylphosphine-Carbon Tetrachloride***; ***Triphenylphosphine Dichloride***.

---

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1,1´-Thionylimidazole[1]

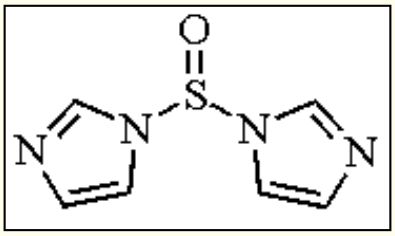

[3005-50-3] · $C_6H_6N_4OS$ · 1,1´-Thionylimidazole · (MW 182.23)

(forms *N*-acylimidazolides[1] used to synthesize amides, peptides,[2] esters,[3] and ketones;[4] synthesis of symmetrical sulfoxides,[5] inorganic esters,[6] and *N*-alkylimidazoles[7])

Alternate Names: N,N´-thionylimidazole; *N,N´*-thionyldiimidazole; TDI.

Physical Data: mp 78-79 °C.

Solubility: sol THF, CH_2Cl_2, toluene.

Form Supplied in: not commercially available; usually used in THF solution.

Analysis of Reagent Purity: usual preparations are used immediately without analysis.

Preparative Method: the reagent is prepared by reacting ***Thionyl Chloride*** with 4 equiv of ***Imidazole*** in anhydrous THF at 0 °C. The precipitated imidazole hydrochloride is filtered and the solution is pure enough to use.[8]

Purification: filter to remove imidazole hydrochloride. Analytically pure samples have been prepared by reaction of thionyl chloride and ***N-(Trimethylsilyl)imidazole***.[9]

Handling, Storage, and Precautions: extremely hygroscopic; reacts exothermically with water and alcohols. Store as a solution in THF or CH_2Cl_2 under dry N_2.[8b] Use in a fume hood.

N-Acylimidazolides.

N,N´-Thionylimidazole reacts with carboxylic acids to form *N*-acylimidazolides (eq 1) that readily acylate amines, amino acids, or alcohols.[1] The products are readily purified since the byproducts, imidazole and SO_2, are easily removed. ***N,N´-Carbonyldiimidazole*** (CDI) is another useful reagent for formation of *N*-acylimidazolides. TDI is used less frequently for formation of *N*-acylimidazolides because of its high reactivity; also, CDI is commercially available and easier to handle. Most reported transformations from *N*-acylimidazolides involve CDI; however, TDI should give similar results.

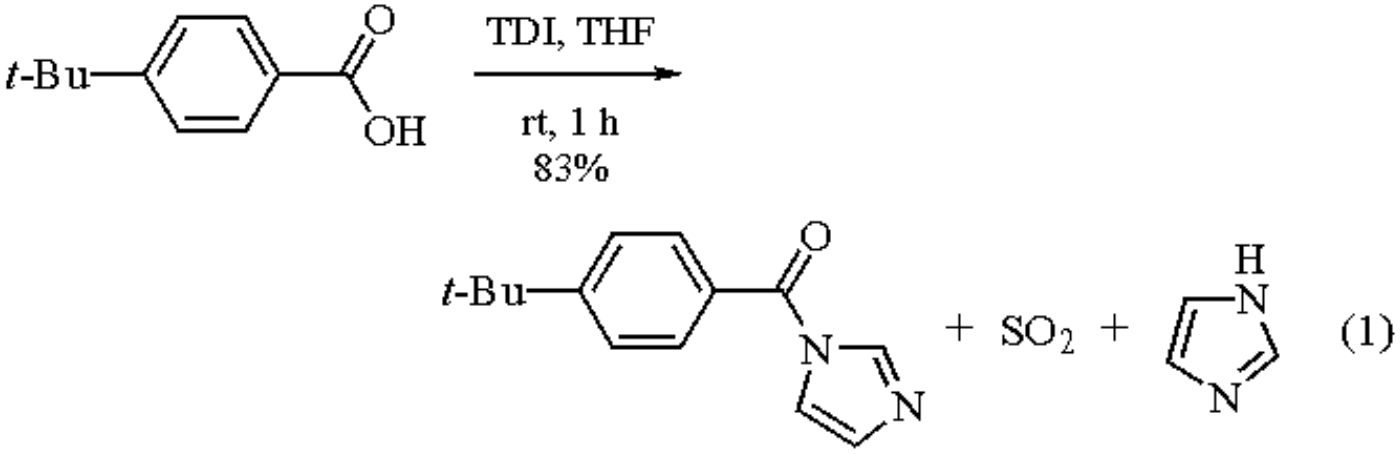

Peptide Coupling Reagent.

N-Acylimidazolides are useful acylating intermediates in peptide synthesis (eq 2).[2] These are direct couplings where the amine and acid components are premixed in solution. There are only a few examples of peptides being synthesized with this reagent. Therefore it is not known what limitations exist, such as extent of racemization, ease of handling, etc. Comparisons with many of the well-known peptide coupling reagents (e.g. ***1,3-Dicyclohexylcarbodiimide***) have not been published. CDI is used more frequently if the imidazolide intermediate is desired because of its ease of handling.

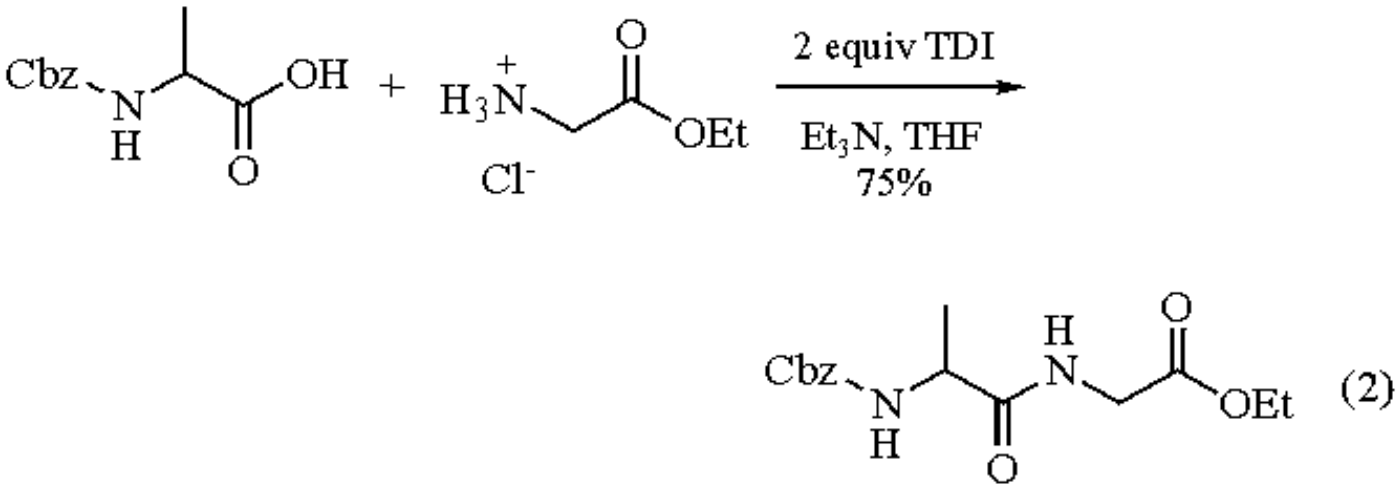

Ester Formation.

N-acylimidazolides react with alcohols very fast in the presence of catalytic amounts of the alkoxide (eq 3).[3] With this method the methyl ester of vitamin A has been obtained in 91% yield.[3]

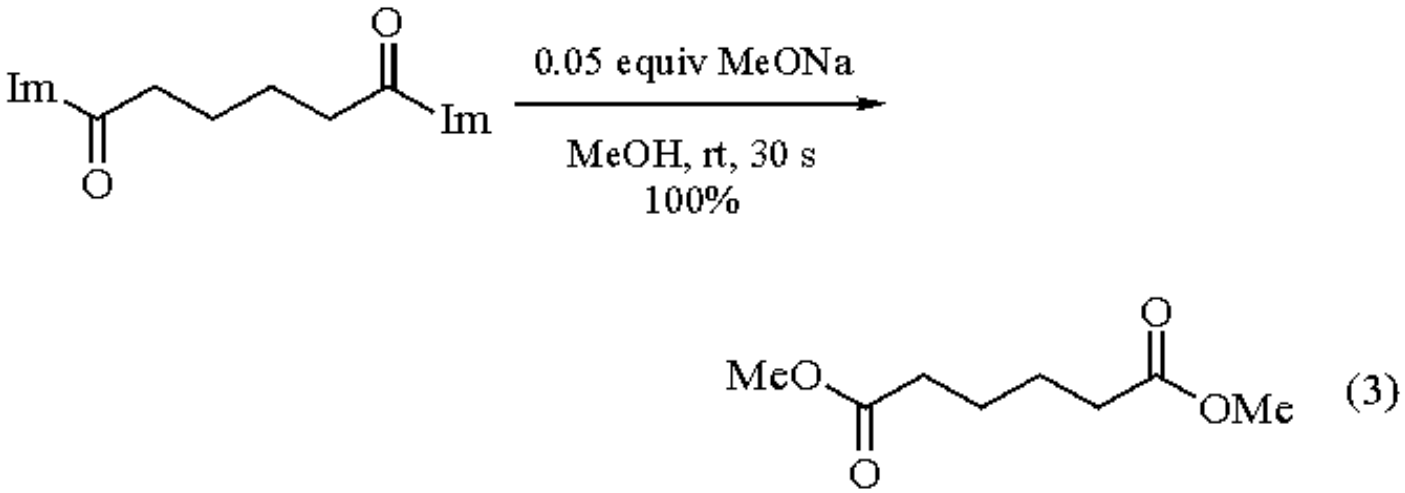

Ketones.

N-Acylimidazolides react with Grignard reagents to give ketones in good yields.[4] A comparison of *N*-acylimidazolides and mixed acid anhydrides in Grignard reactions indicates that the imidazolides result in higher yields (eq 4).[10] There are many procedures for reacting Grignard reagents with activated carboxylic acids to give ketones. Other reagents used with varying degrees of success are acid chlorides (e.g. ***Ethyl Chloroformate***), nitriles, and 2-pyridylthiol esters (e.g. ***2-Thiopyridyl Chloroformate***).[11]

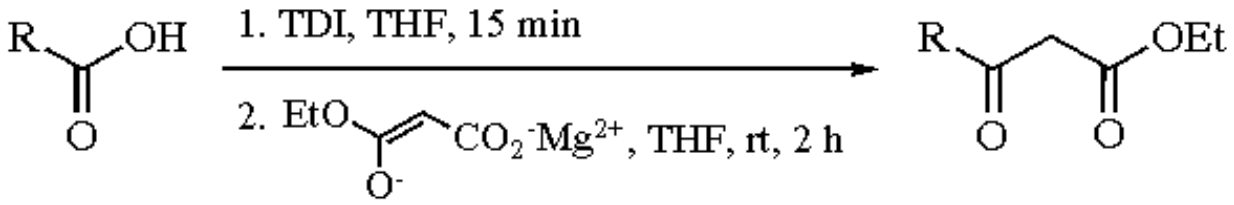

(4)

R	Anhydride	Imidazolide
Et	57	68
Pr	57	74
C_6H_{13}	62	74
Ph	0	79

Symmetrical Sulfoxides.

Thionylimidazole reacts directly with Grignard reagents resulting in symmetrical sulfoxides in reasonable yields (eq 5).[5] This method offers an easy workup and purification since the main byproduct is imidazole.

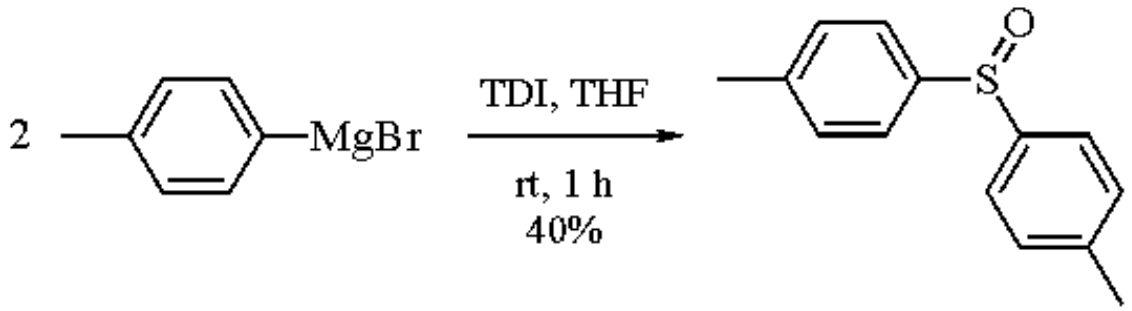

(5)

Inorganic Ester Formation.

Phenols and alcohols react exothermically with TDI to give sulfonic acid diesters in high yield (eq 6).[6]

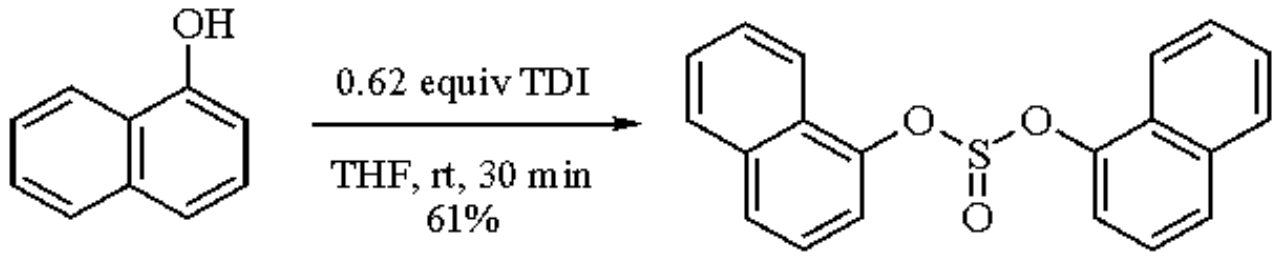

(6)

N-Alkylimidazoles.

Thionylimidazole has found great utility in the synthesis of *N*-alkylimidazoles.[7] Tertiary alcohols react with TDI to form monosulfonic ester imidazolides that rearrange to transfer the imidazole to the tertiary carbon (eq 7).[12] The products are also obtained by treatment of the trityl chloride with imidazole; however, comparison of the two procedures is not possible as yields were not reported.[12]

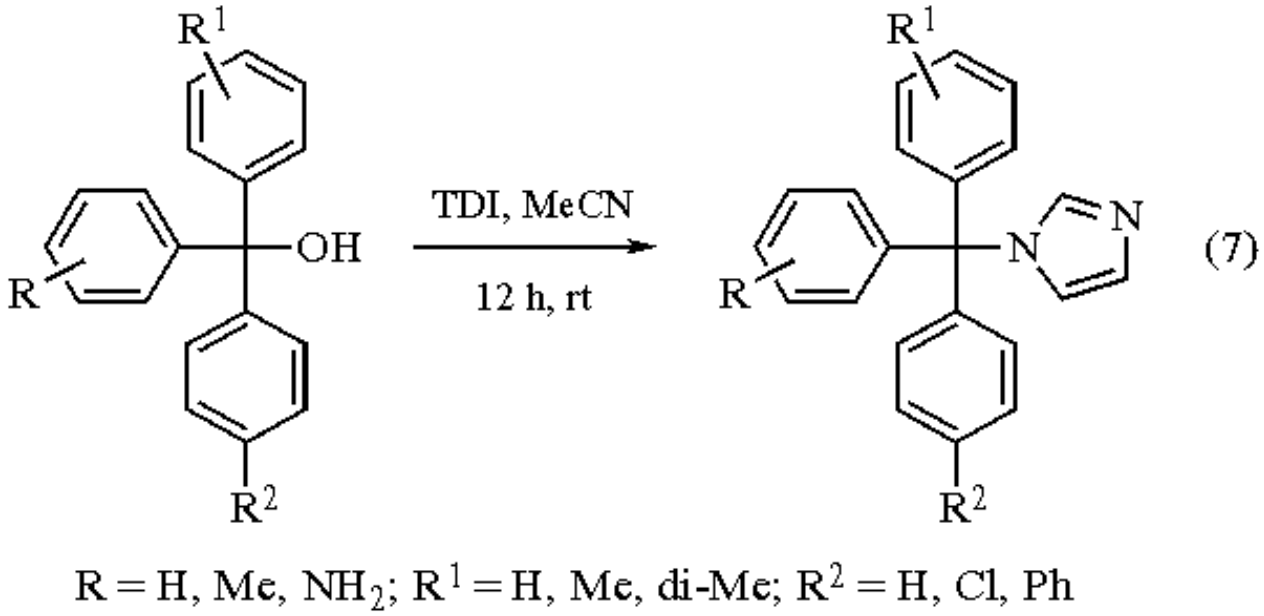

This imidazole transfer reaction occurs readily with *o*-hydroxybenzyl alcohols, giving the imidazole from a primary or secondary alcohol (eq 8).[7] It is thought that the *o*-hydroxy group contributes to the facile transfer of the imidazole. Similarly, *o*-amines promote the transfer of the imidazole. Carbonyl diimidazole also works in this imidazole transfer reaction, but it usually gives lower yields of the desired product.[7]

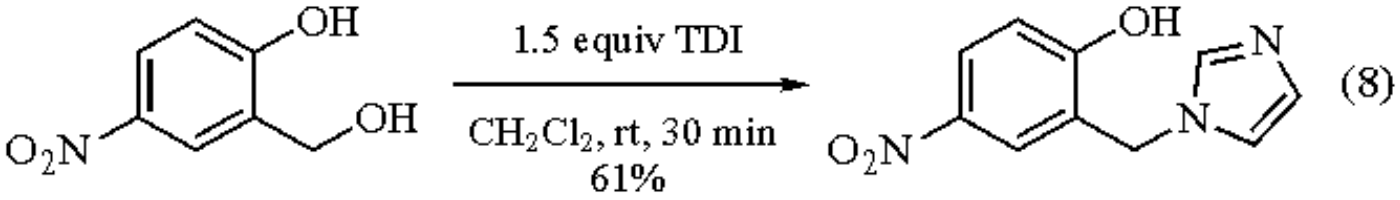

This imidazole transfer reaction works with ketones as well; however, in this case two products, the mono- and diimidazoles, are obtained (eq 9).[13] Increasing the temperature does not change the product ratio or yield. Some examples contain hydrogen-bonding groups on the ring, but this does not modify the product ratio or yield either. CDI gives similar results in most cases. This imidazole transfer reaction does not work with aldehydes under these conditions.[13]

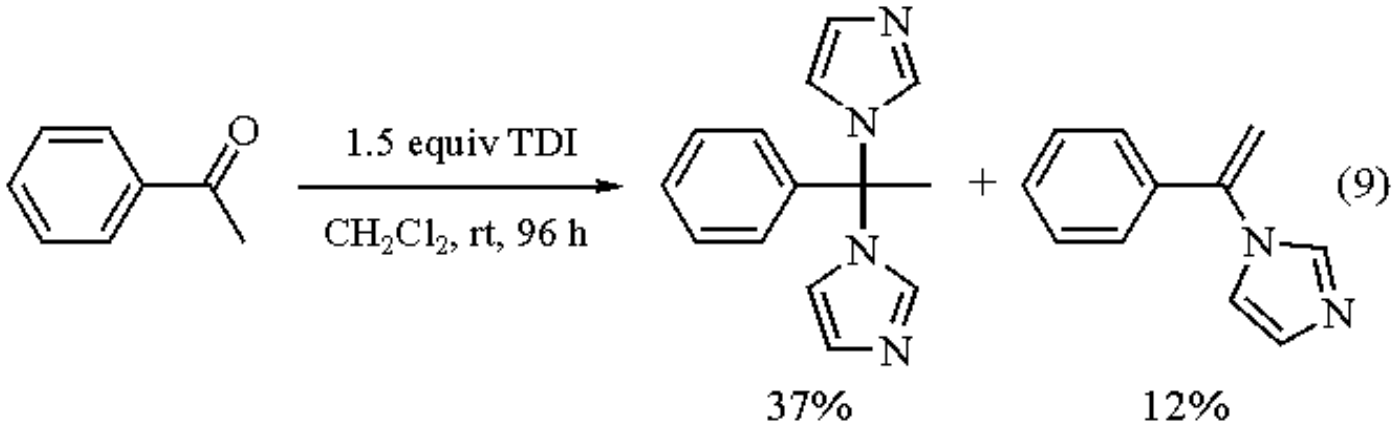

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Thiophenol

PhSH

[109-98-5] · C_6H_6S · Thiophenol · (MW 110.19)

(precursor of the thiophenoxy radical, which adds to alkenes and alkynes, initiating cyclizations; *cis*/*trans* alkene isomerization; synthesis of vinyl sulfides, alkyllithiums, pyridines; transacetalization; Michael addition)

Physical Data: mp -15 °C; bp 169 °C, 46.4 °C/4 mmHg; n^{20} 1.5893; d^{20} 1.0766 g cm^{-3}.

Solubility: sol alcohol, ether, benzene, methylene chloride.

Form Supplied in: liquid; commercially available.

Handling, Storage, and Precautions: handle under an inert atmosphere as oxygen causes oxidation to the disulfide. This may accelerated in the presence of base. Stench reminiscent of garlic. Very toxic. Handle only in an efficient fume hood.

Radical Reactions.

Thiophenol is best known as a hydrogen atom source or radical initiator in radical reactions. Vinylcyclopropanes can undergo a radical-induced rearrangement (eq 1).[1] In this example, addition of the thiophenoxy radical to the alkenic terminus is followed by opening of the cyclopropane ring; this radical may then add to another alkene to give a radical primed to undergo a 5-*exo-trig* closure onto the remaining alkene. The dienylic cyclopropane can undergo a similar reaction but instead the radical can also undergo cyclization without an added alkene (eq 2).[2] As in most radical cyclizations, formation of five-membered carbocyclic rings is generally favored.

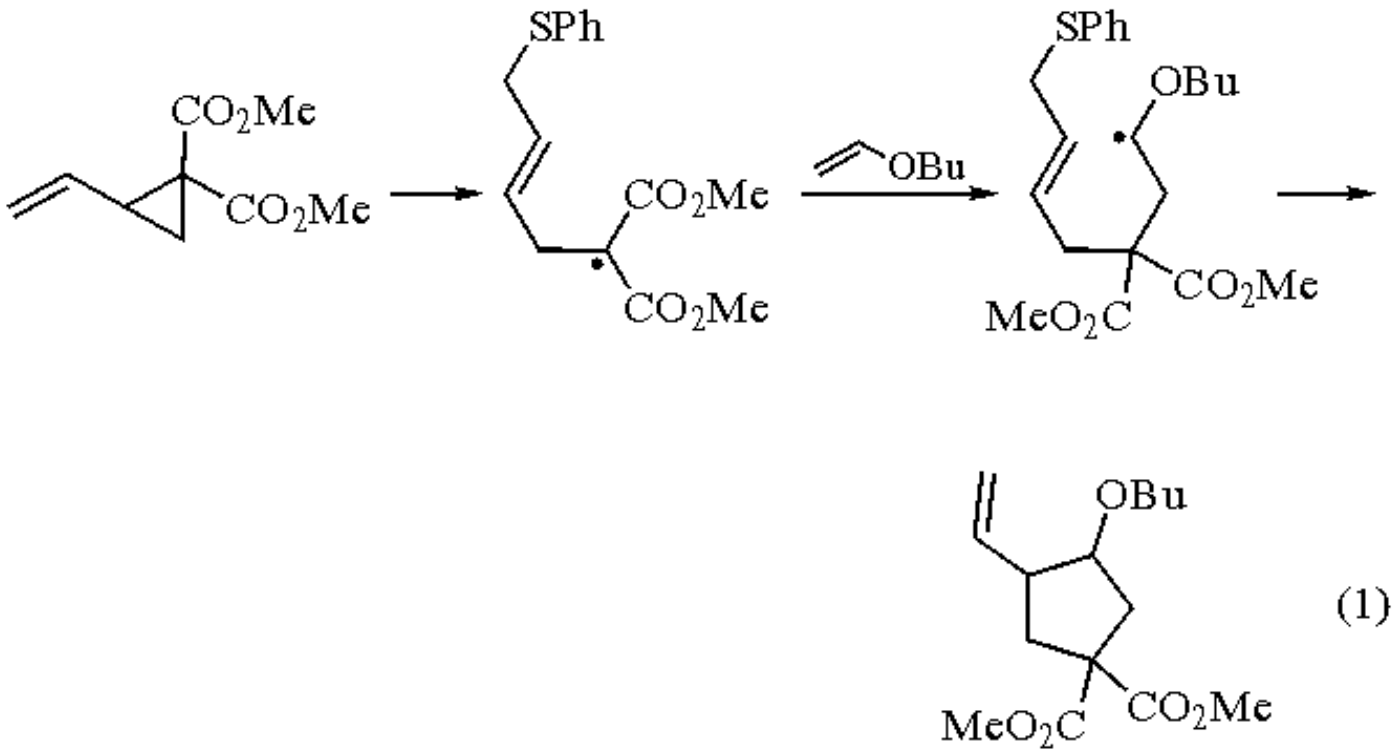

(1)

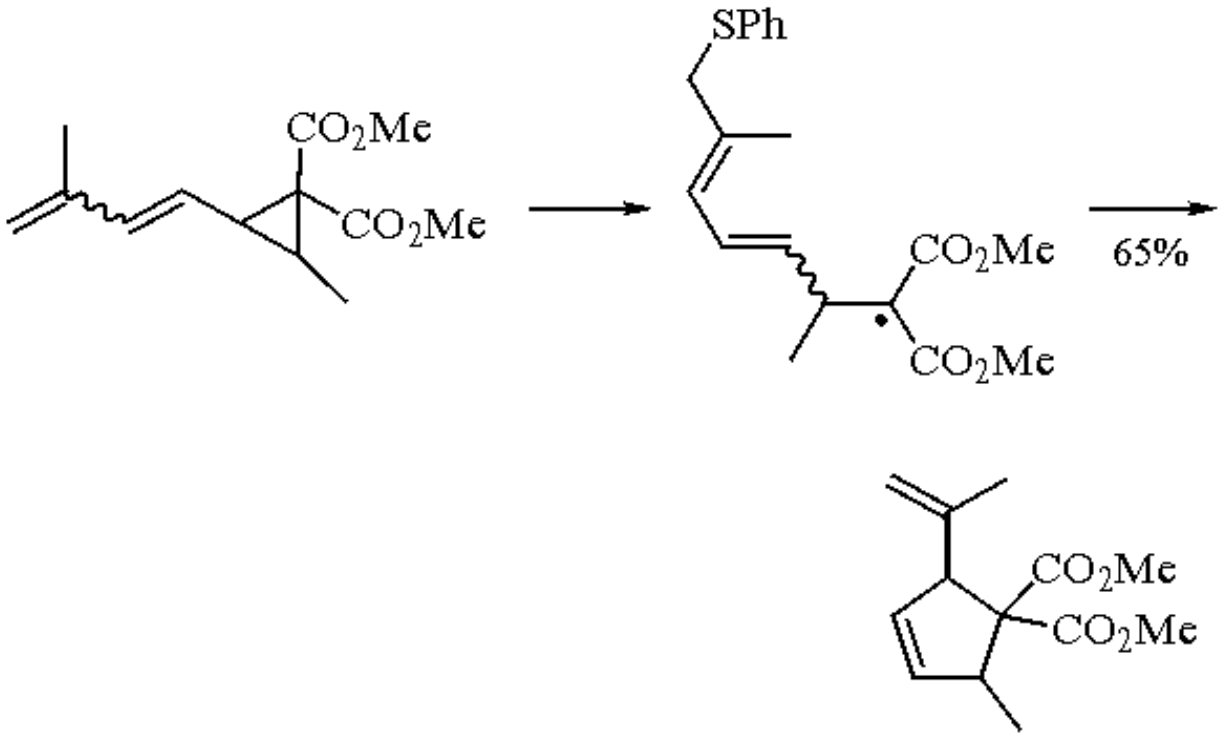

(2)

Alkynes separated from an alkene by a three-carbon tether are similarly prone to cyclize on treatment with thiophenol.[3] This reaction is initiated by addition of the thiyl radical to the alkyne to form a vinyl radical which then closes (eq 3). The cyclization in this case must compete with hydrogen atom abstraction, resulting in low yields. The alkyne addition to form a vinyl sulfide without the cyclization is also known, wherein thiophenol adds across the triple bond of an alkyne in the presence of ***Triethylborane*** as radical initiator to form a vinyl sulfide (eq 4) (see below for other routes to vinyl sulfides and for another application of this reaction).[4]

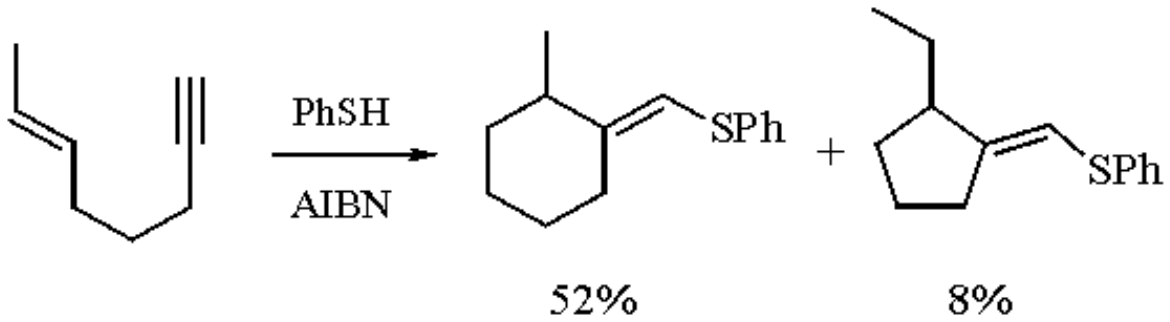

(3)

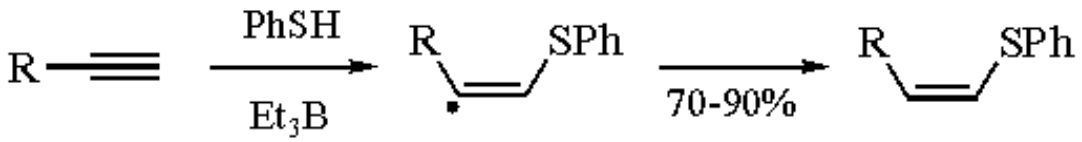

(4)

Another very common usage of thiophenol is to change the *cis*/*trans* isomer ratio of alkenes to favor the *trans* configuration (eq 5).[5]

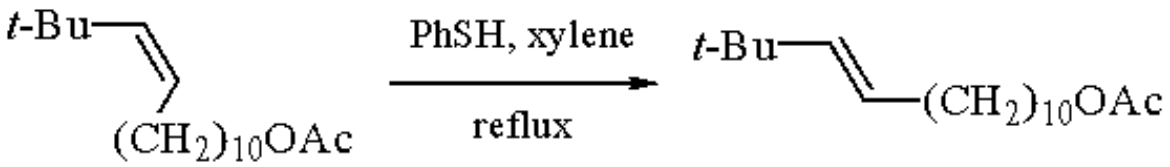

(5)

Vinyl Sulfides.

A useful application of thiophenol is as an in situ source of ***Benzenesulfenyl Chloride*** (generated from thiophenol and ***N-Chlorosuccinimide*** or ***Sulfuryl Chloride***).[6] This can add electrophilically across alkenes to generate vicinal chloro sulfides (eq 6). Subsequent elimination of HCl using ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** or ***Sodium Carbonate*** provides vinyl sulfides which are useful as precursors to sulfones (by oxidation) and to vinyllithiums (see below), or as synthetic equivalents to enols.[7] An alternative route towards cyclic vinyl sulfides involves ***Montmorillonite K10*** catalysis (eq 7) and cyclic ketones.

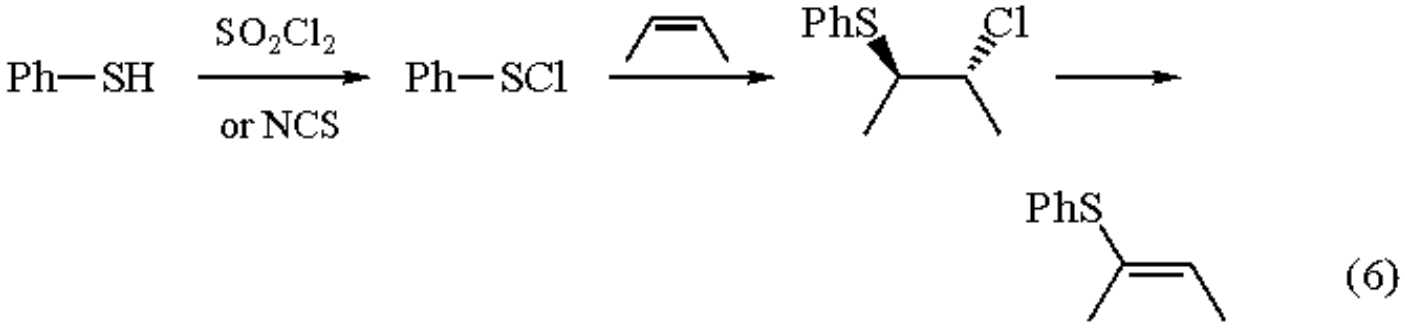

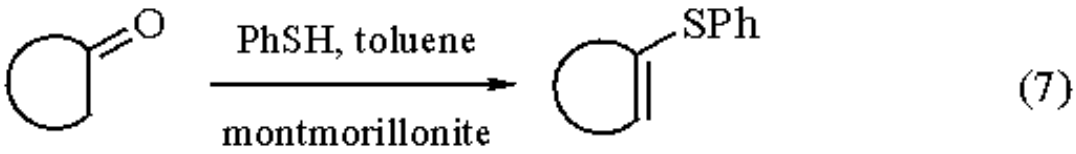

Alkylation; Alkyllithiums.

Thiophenol is also the precursor of choice to make alkyl phenyl sulfides by nucleophilic substitution of an alkyl halide. These have recently become popular precursors to complex alkyllithiums via reductive lithiation of phenyl sulfides (eq 8). These reactions are generally done in THF, utilizing ***Lithium Naphthalenide***,[8] ***Lithium 1-(Dimethylamino)naphthalenide***,[9] or ***Lithium 4,4´-Di-t-butylbiphenylide***.[10]

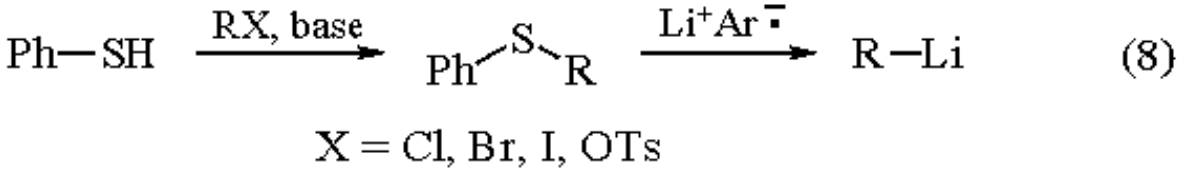

Conjugate Additions.

The nucleophilic properties of thiophenoxide are also apparent in Michael reactions. Thiophenoxide is easily formed in the presence of ***Triethylamine*** (eq 9) and adds to α,β-unsaturated enones and enoates[11] with equal ease and in high yield. It has been used as a key reagent in the synthesis of butenolides from γ-hydroxy α,β-unsaturated enoates[12] (eq 10).

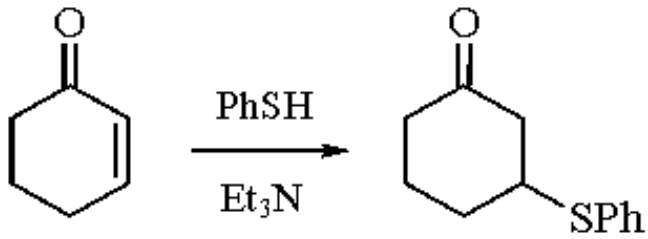

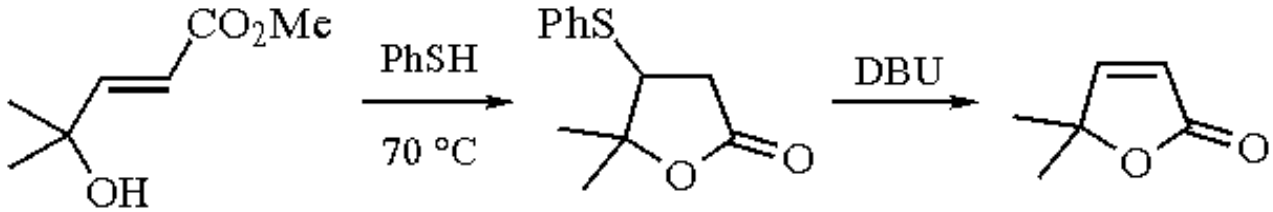

Michael addition to activated acetylene derivatives, such as propiolate esters, may also be carried out with subsequent trapping by electrophiles such as benzaldehyde (eq 11).[13]

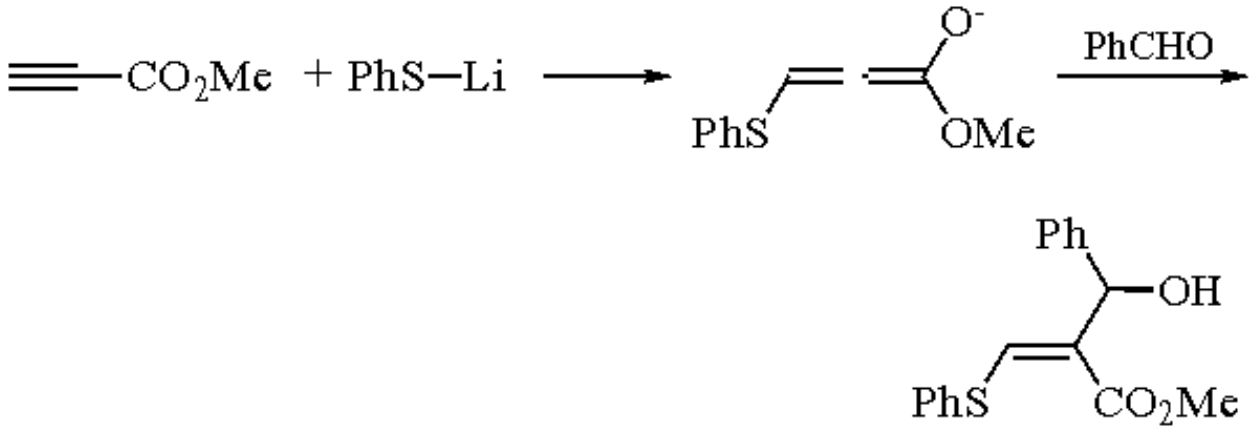

(11)

Pyridine Synthesis.

Thiophenol also shows some utility in the synthesis of a wide variety of substituted pyridines from acyclic precursors (eq 12) in overall yields of 45-60%. In this example, treatment of thiophenol with ***Methyl Vinyl Ketone*** to obtain the Michael adduct, followed by condensation with a ketone enolate (made with ***Lithium Diisopropylamide***) and dehydration with ***Thionyl Chloride***, provides the 4-(phenylthio) enone. Oxidation to the sulfoxide, Pummerer rearrangement, and treatment with ***Ammonia*** provide the pyridine.[14]

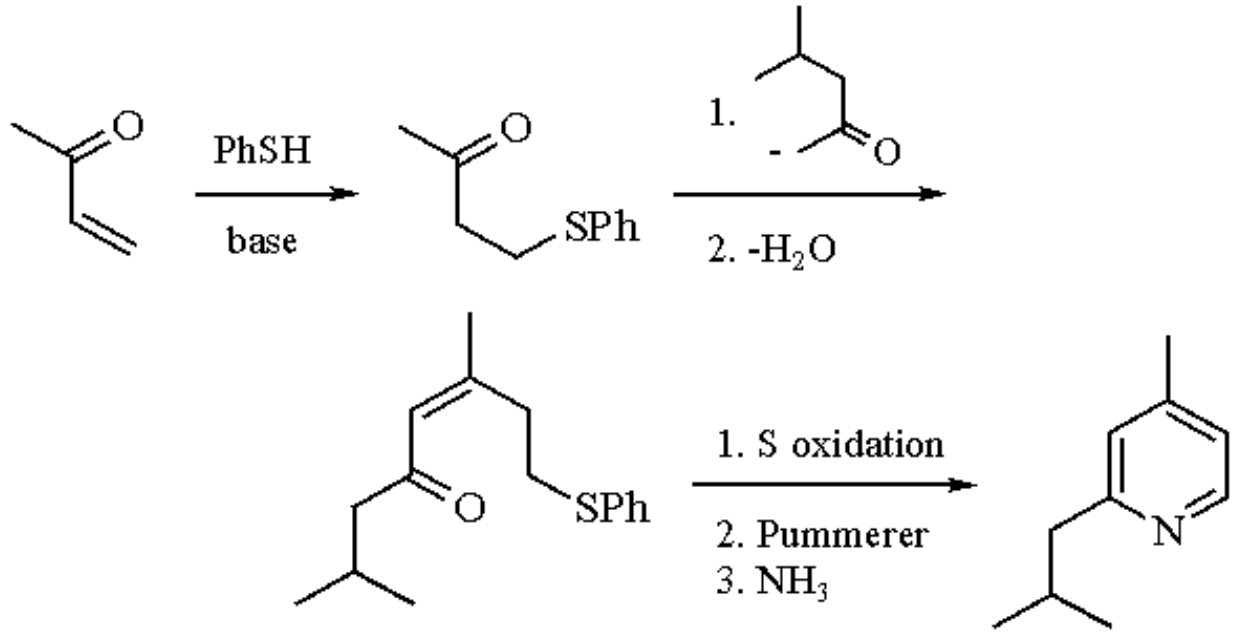

(12)

Thioacetals and Glycosides.

It is also possible to take advantage of the nucleophilicity of thiophenol to carry out transacetalizations. These are done in the presence of a Lewis acid. In examples such as MOM ethers this provides a net deprotection, as shown recently in the final step of Corey's synthesis of gingkolide A (eq 13).[15] The resulting coproduct is a useful reagent in its own right, shown by Livinghouse to be a formyl anion equivalent.[16] Thiophenol's main use in this area, however, is in the synthesis of thioglycosides. Acid-catalyzed transacetalization of either the acetyl glycoside[17] or the hemiacetal can provide the required 2-thiopyran ring (eq 14). Lewis acid-catalyzed synthesis must have an oxygen acceptor in the system to work, an example being ***Zinc Chloride*** with ***Phosphorus Oxychloride***[18] or ***Trimethylsilyl Trifluoromethanesulfonate***.[19]

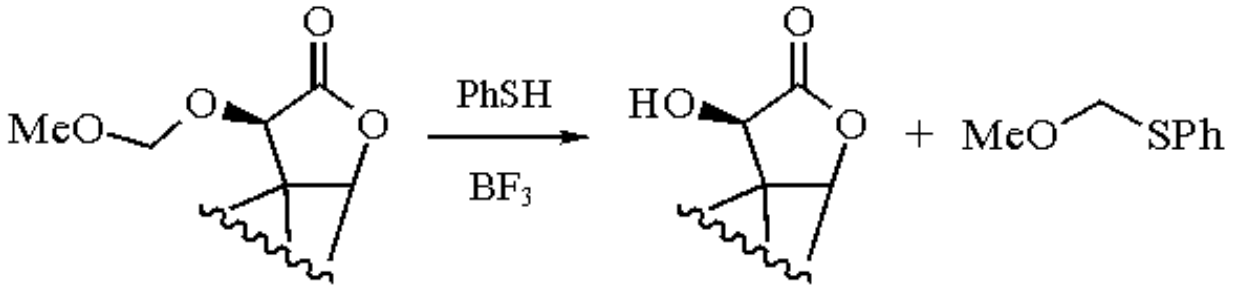

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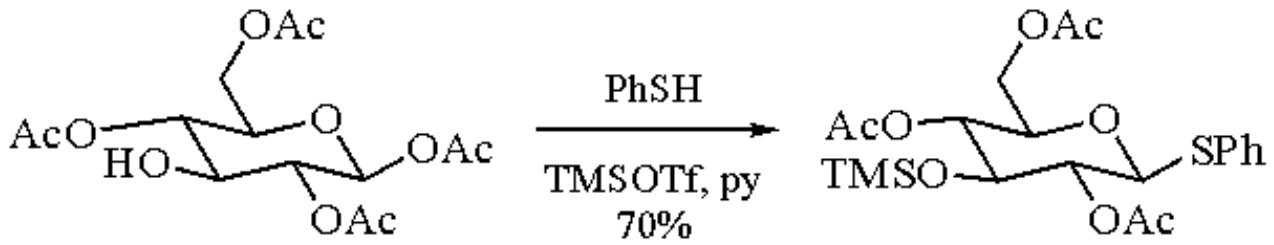

(14)

Other Applications.

Thiophenol can also be utilized in the transformation of acetylenic alcohols to unsaturated aldehydes with allylic transposition (eq 15).[20] The reaction begins with treatment of an acetylenic alcohol with thiophenol to obtain a vinyl sulfide in a radical-induced reaction (see above). Acid-catalyzed hydrolysis then provides a homologated α,β-unsaturated aldehyde.

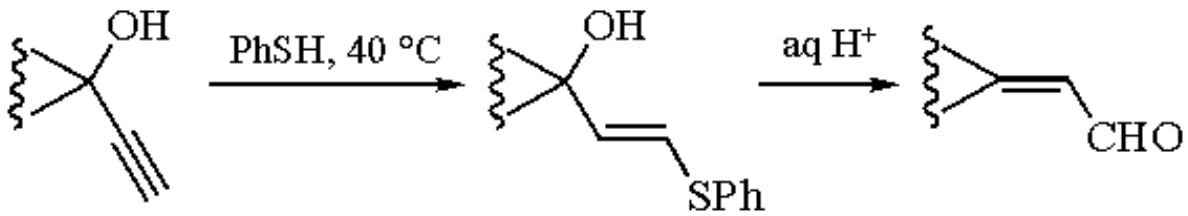

(15)

An interesting photochemical application of thiophenol is in the cleavage of β-phenylthio alcohols (available from reaction of epoxides with thiophenol). Irradiation of these alcohols at 350 nm using benzophenone as sensitizer causes cleavage of the central bond and formation of the ketone in good yield (eq 16).[21]

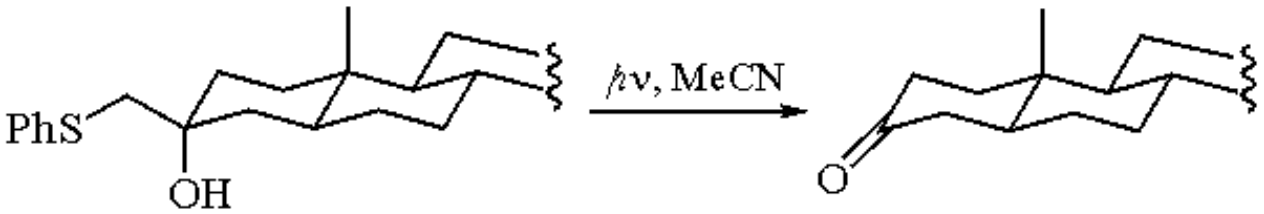

(16)

Related Reagents.

Thiophenol-Azobisisobutyronitrile.

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Thiophenol-Azobisisobutyronitrile

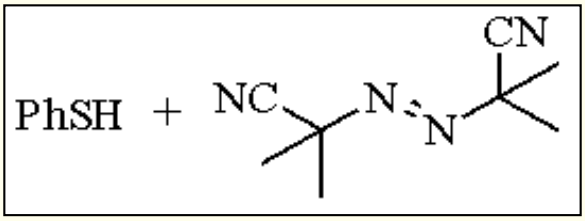

(PhSH)

[108-98-5] · C_6H_6S · Thiophenol-Azobisisobutyronitrile · (MW 110.19) (AIBN)

[78-67-1] · $C_8H_{12}N_4$ · Thiophenol-Azobisisobutyronitrile · (MW 136.22)

(preparation of benzenethiyl radicals with subsequent use in radical addition reactions of thiophenol to alkenes and alkynes;[1-4] alkene isomerizations[5])

Preparative Methods: prepared from ***Thiophenol*** and ***Azobisisobutyronitrile***, both of which are commercially available.

Synthesis of Sulfide Derivatives from Alkenes.

Thermally induced decomposition of AIBN to cyanopropyl radicals initiates hydrogen abstraction from thiophenol in the title reagent system to give benzenethiyl radicals. Kinetic studies involving the addition of the thiol radical to 1,4-divinylbenzene (eq 1), using a catalytic amount of AIBN, demonstrate that the sulfide-containing styrene monomer can be prepared in high yield by carrying out the reaction at 60 °C with an equimolar ratio of thiophenol and the alkene.[1] More vigorous reaction conditions (170 °C) are necessary, however, in the thio radical addition to triethoxyvinylsilane (eq 2), since no reaction takes place even on prolonged heating at 100-110 °C.[2]

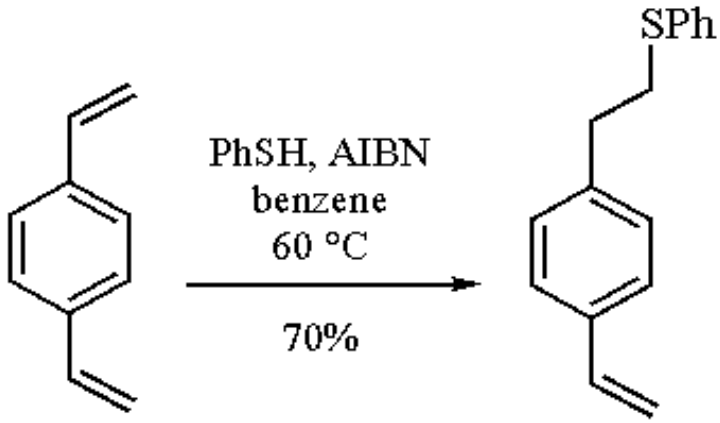

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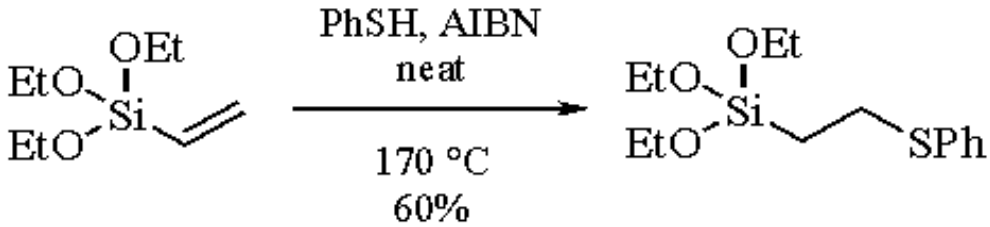

(2)

Synthesis of Vinyl Sulfides from Alkynes.

The AIBN radical-initiated addition reaction of thiophenol to the terminal alkyne of a ynoic acid (eq 3) derivative provides the corresponding vinyl sulfide intermediate used in the synthesis of cyclohexanone derivatives.[3] This process has also been used in the synthesis of a chiral diene (eq 4) from an enyne precursor, a key intermediate in the enantiospecific total synthesis of (+)-compactin.[4]

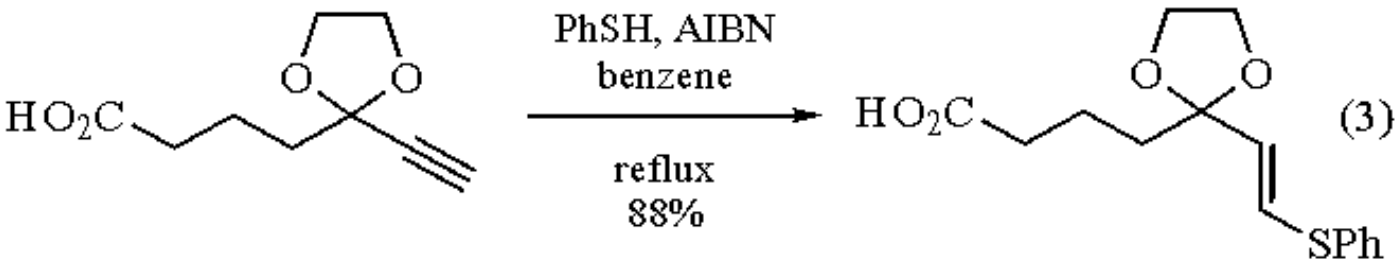

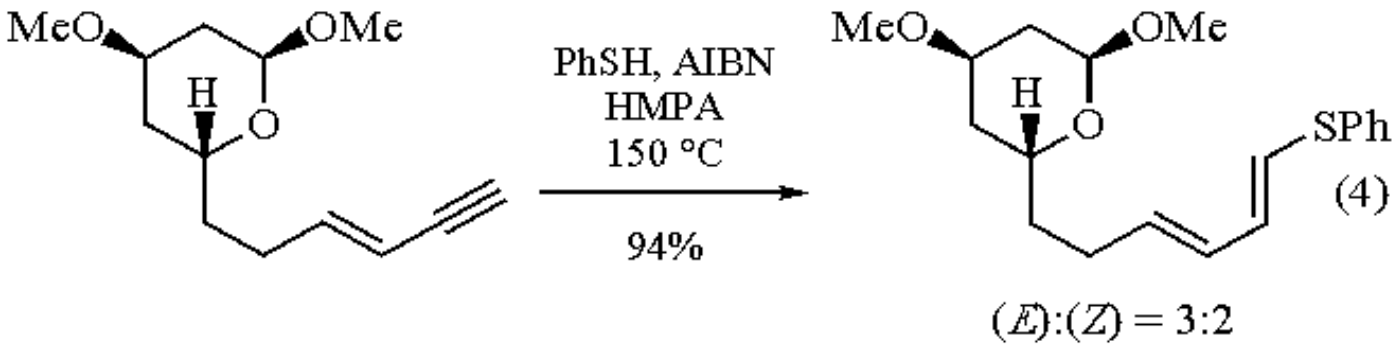

Thiophenol-Mediated Alkene Inversion.

trans-Substituted alkenes containing a quarternary carbon center adjacent to the double bond are difficult to prepare by standard techniques, such as the Wittig reaction or by chemical reduction of the corresponding alkyne. However, they have been prepared by isomerizing the readily available *cis*-alkene using thiophenol-AIBN (eq 5).[5]

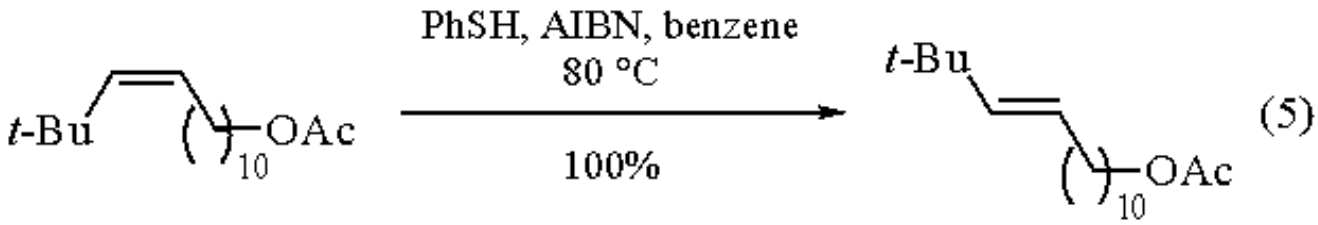

Heterocyclic Synthesis.

The reaction of 1,2,3-benzothiadiazole with PhSH/AIBN in refluxing EtOAc provides a mixture of products including dibenzo[*c*,*e*]-*o*-dithiin (**1**), thianthrene (**2**), and 2-(phenylthio)diphenyl disulfide (**3**).[6]

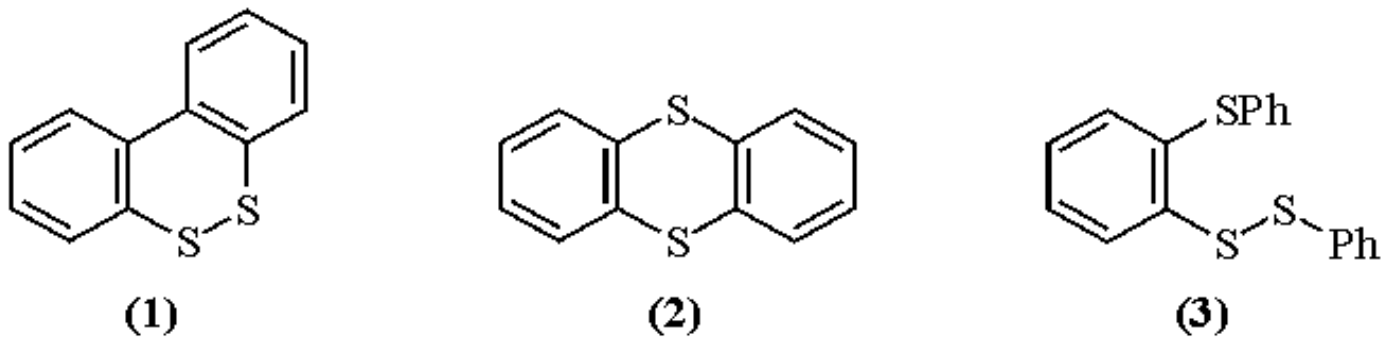

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Thiophosgene[1]

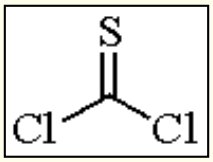

[463-71-8] · CCl_2S · Thiophosgene · (MW 114.98)

(very electrophilic reagent capable of forming isothiocyanates with amines;[1] used in forming various heterocycles;[12] in combination with phosphorus reagents, capable of forming *cis*- and *trans*-alkenes from cyclic thiocarbonates (Corey-Winter alkenation);[22] dienophile in Diels-Alder reactions[25])

Physical Data: bp 73 °C; *d* 1.508 g cm^{-3}.

Solubility: sol most organic solvents; decomposes in H_2O and alcoholic solvents.

Form Supplied in: red-orange liquid; widely available.

Handling, Storage, and Precautions: wear appropriate safety equipment. Use only in a chemical fume hood; keep container tightly closed; unpleasant odor. Moisture sensitive; store under nitrogen; refrigerate. Highly toxic; may be fatal if inhaled, swallowed, or absorbed through skin; corrosive; lachrymator.

Reactions with Nitrogen Nucleophiles.

Thiophosgene has most commonly been used to convert primary aliphatic and aromatic amines (eq 1) into isothiocyanates[2,3] and thioureas (eq 2).[4,5] Secondary amines have been converted to aminothiocarbonyl chlorides,[6] *N*,*N*-disubstituted thiocarbamates,[7] and thioureas (eq 3).[8] Tertiary amines can be transformed to thiocarbamoyl chlorides[9] and isothiocyanato acid chlorides.[10]

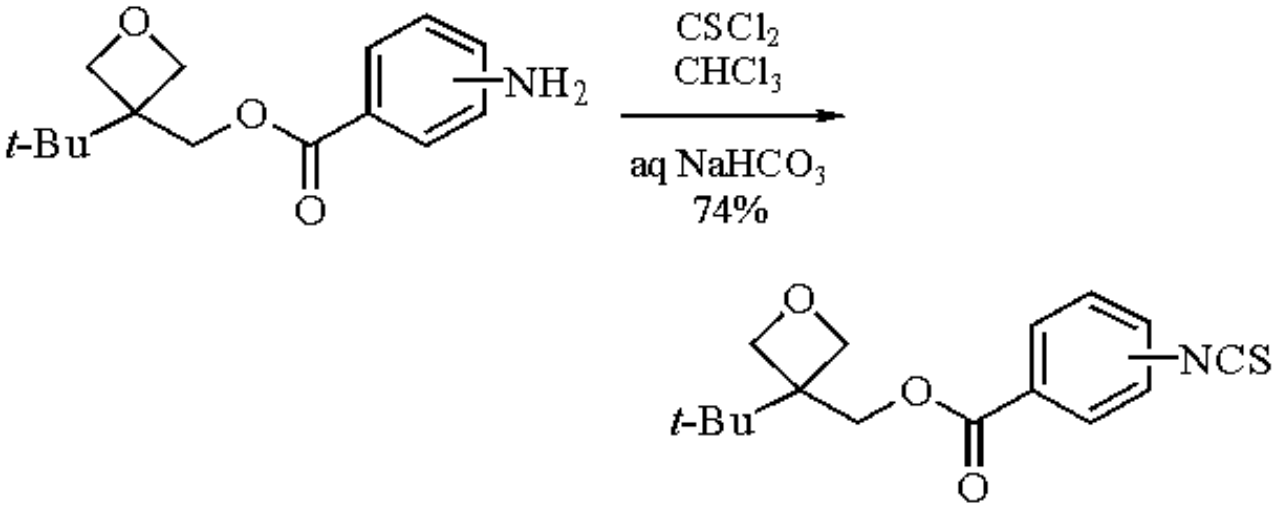

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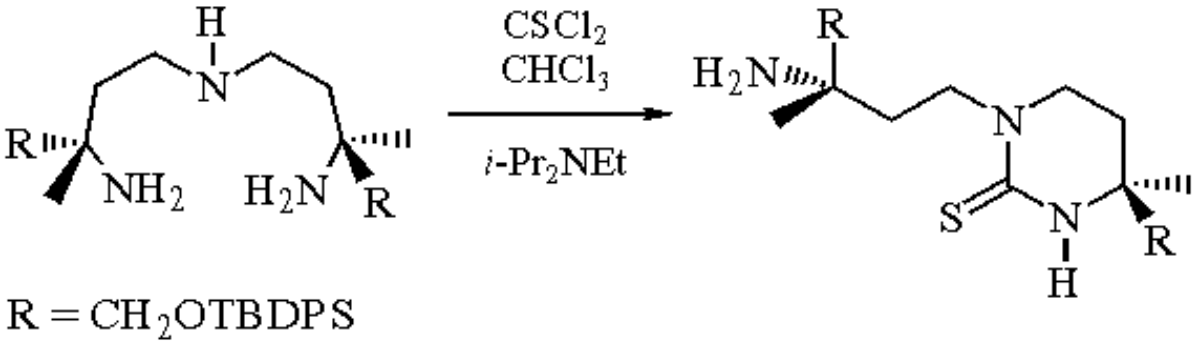

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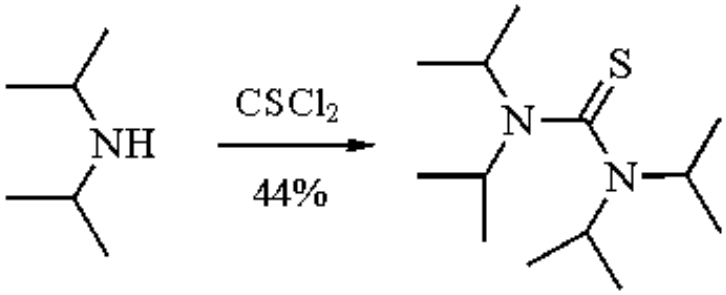

(3)

Primary amines react selectively with thiophosgene in the presence of other reactive functional groups (OH, NH, CO_2H, CONH, SO_3H, or SH), situated far from the reacting amine, to form isothiocyanates (eq 4).[11] However, reactive functional groups present in the vicinity of the reactive amino group interact with the thiophosgene or the isothiocyanate generated in situ to afford a wide variety of heterocycles.[4,11a,12] Examples include formation of heterocyclic thiones (eq 5)[13] and benzoxazines (eq 6).[14]

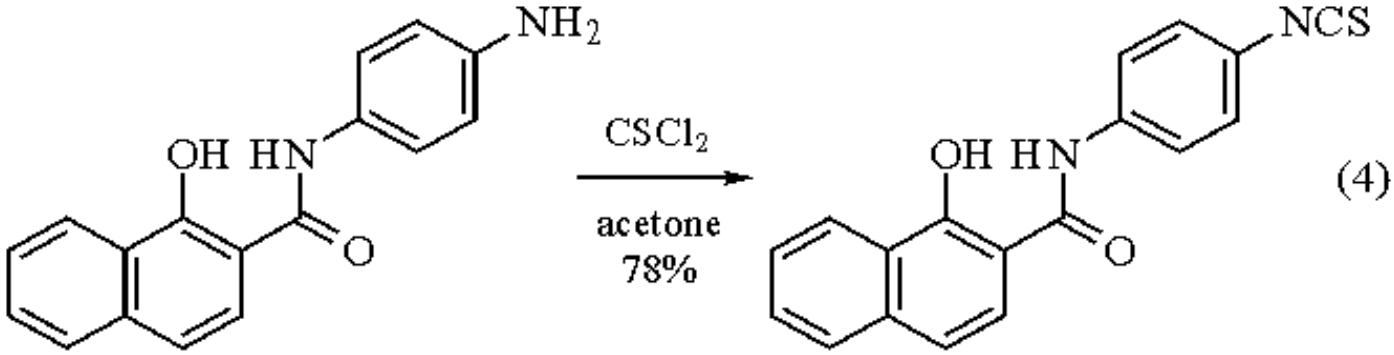

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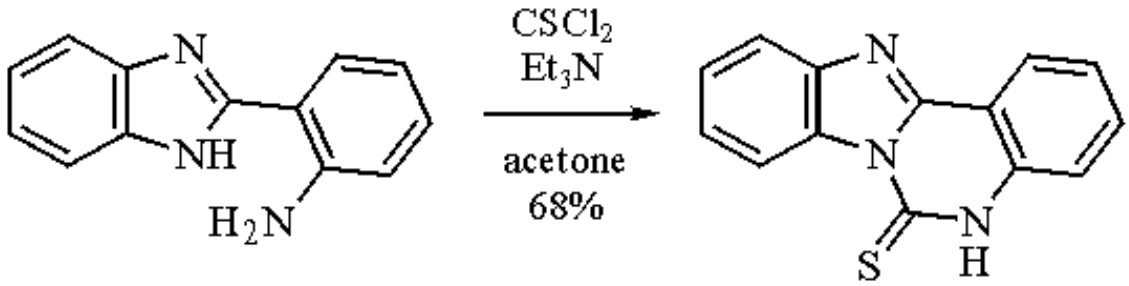

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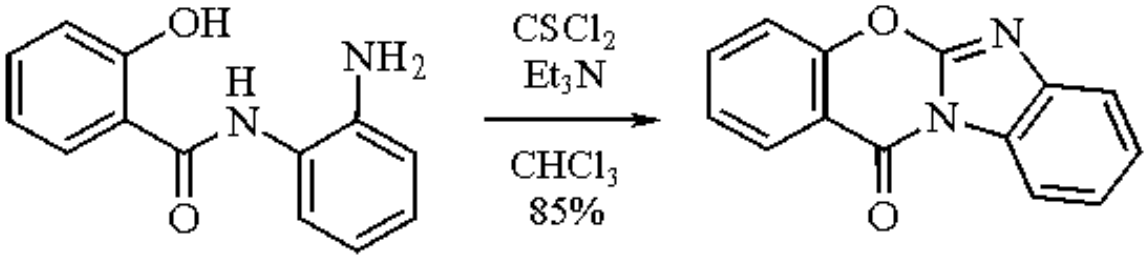

(6)

The reaction of primary amides with thiophosgene may yield the corresponding isothiocyanate[15] or a nitrile and a thione, depending on the reaction conditions.[16] Also, subjecting thioureas and thioamides to thiophosgene followed by hydrolysis is a useful way to prepare the corresponding ureas and amides.[17] Ketimines which do not have a β-hydrogen atom react with thiophosgene to give α-chloroalkyl isothiocyanates, while those carrying a β-hydrogen give α-alkenyl isothiocyanates.[18] A number of fused 2*H*-1,3-oxazine-2-thiones have

been prepared by reacting 1,2-hydroximines with thiophosgene.[19] *N*-Isothiocyanato amines are prepared by reacting hydrazines with thiophosgene.[20]

Reactions with Oxygen Nucleophiles.

In the presence of thiophosgene, alcohols and phenols have been converted into chlorothioformates[21] which can be useful precursors of thiocarbonates, thiocarbamates, and dithiocarbonates.[1] Diols have been shown to form cyclic thiocarbonates. Specifically, 1,2-diols have been transformed into cyclic thiocarbonates which can be further transformed stereospecifically to *cis*- or *trans*-alkenes (eq 7).[22]

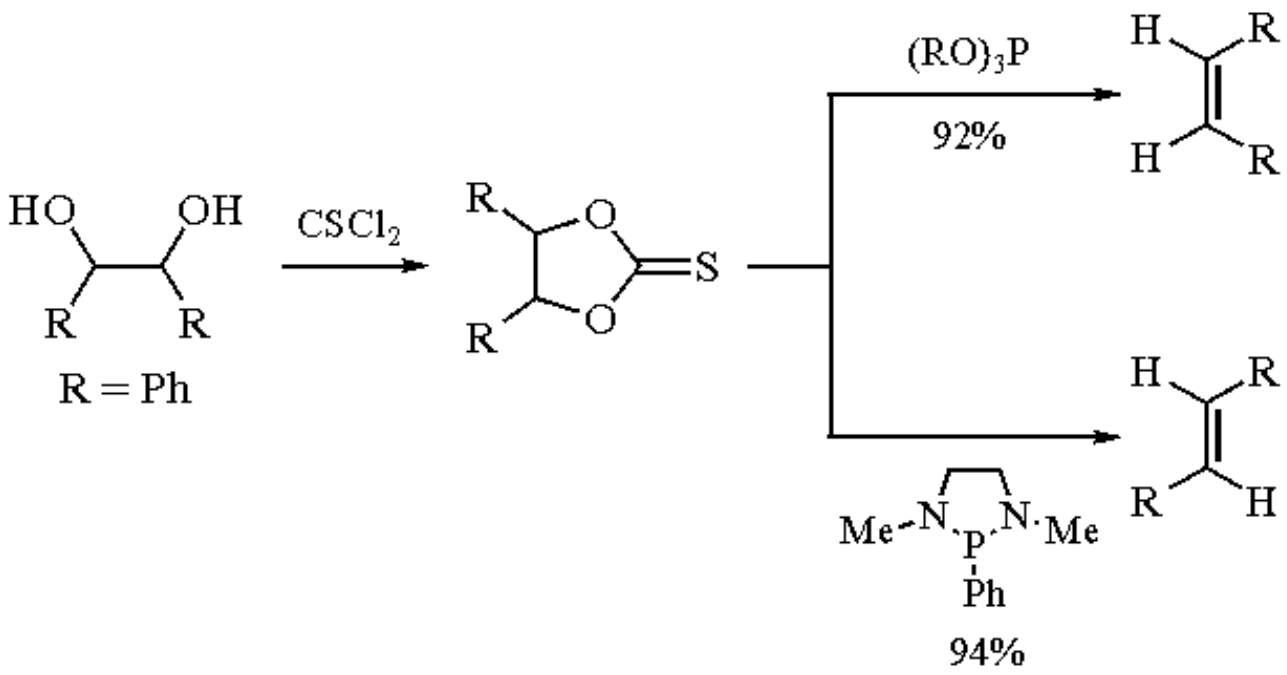

(7)

Reactions with Sulfur Nucleophiles.

Thiols have been converted to chlorodithioformates (eq 8),[23] trithiocarbonates,[24] and cyclic thiones[12] in the presence of thiophosgene, depending on the reaction conditions.

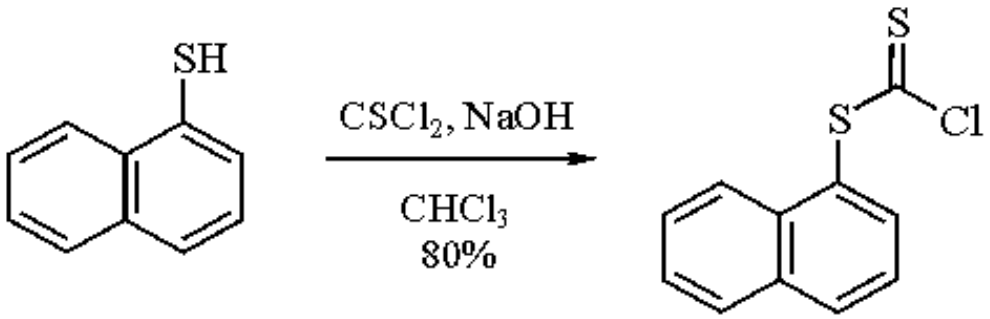

(8)

Miscellaneous Reactions.

Thiophosgene has been used as a dienophile in the Diels-Alder reaction.[25] Examples include the synthesis of thiopyranones (eq 9)[26] and bicyclic systems (eq 10).[27] [2 + 2] Cycloaddition reactions have also been achieved with thiophosgene.[28] Thiiranes have been prepared from diazo compounds,[29] and thioketenylidenetriphenylphosphorane from methylenetriphenylphosphorane,[30] when combined with thiophosgene.

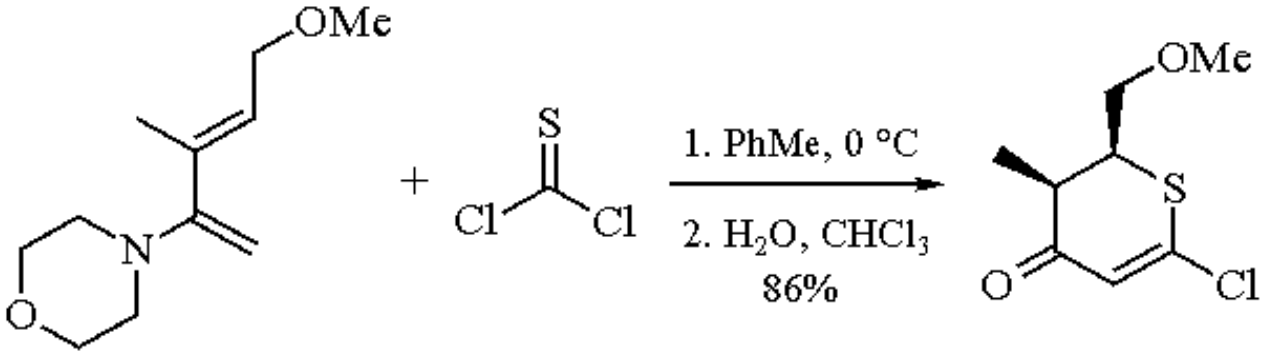

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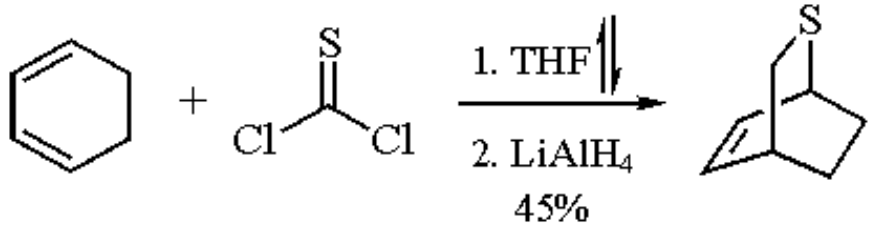

(10)

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Thiophosphoryl Chloride

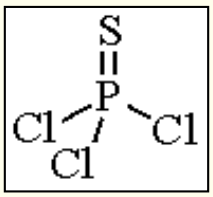

[3982-91-0] · Cl_3PS · Thiophosphoryl Chloride · (MW 169.39)

(thionation of amides; thiophosphorylating agent for alcohols, amines, diols, amino alcohols, diamines, etc.)

Physical Data: mp -35 °C; bp 125 °C; n_D 1.550; *d* 1.668 g cm^{-3}.

Solubility: sol benzene; CCl_4, $CHCl_3$, CS_2; reacts with alcohols and amines.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^{31}P NMR.

Purification: distillation.[1]

Handling, Storage, and Precautions: highly toxic; corrosive, undergoes slow hydrolysis when exposed to moisture. Must handled in a fume hood and reactions performed under a dry, inert atmosphere.

Thionation of Tertiary Amides.[2]

Thiophosphoryl chloride and its *N,N*-dimethylamide derivatives (eq 1)[3] react with amides at elevated temperature to give thioamides in good yield. The reaction is run in an excess of the thiophosphorus compounds. The most efficient of the thionating agents examined is *N,N,N´,N´*-tetramethylamidophosphonothioic chloride.

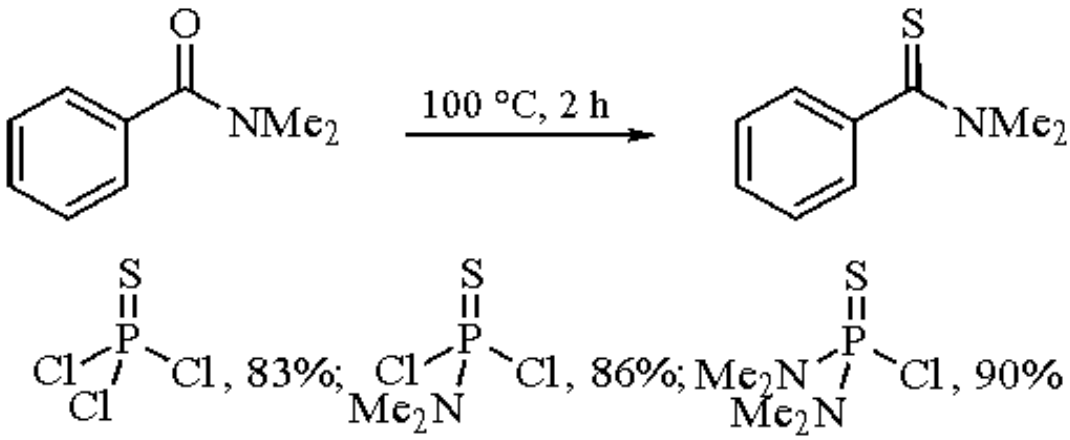

(1)

Thiophosphorylation.

Thiophosphoryl chloride will thiophosphorylate amines,[3] alcohols,[4] amino alcohols,[5] diols,[6] and diamines.[7] The rate of reaction decreases as each chlorine atom in replaced; thus it is possible to replace each chlorine atom with a different substituent under controlled reaction conditions. Thiophosphoryl derivatives of chiral amino alcohols have been studied extensively as stereochemical probes for the stepwise hydrolyses and alcoholysis of thiophosphates (eq 2), which can lead to the formation of nonracemic chiral thiophosphates.[8] They have also been used as chiral derivatizing agents for the NMR analysis of chiral alcohols and amines.[9]

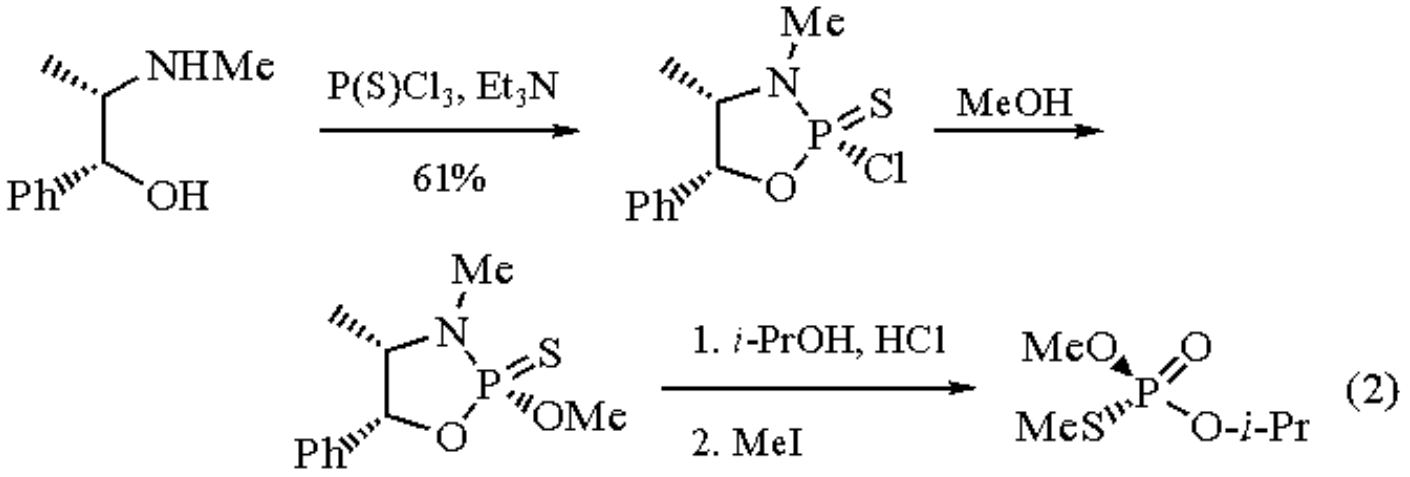

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2-Thiopyridyl Chloroformate[1]

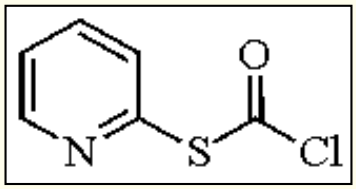

[73371-99-0] · C_6H_4ClNOS · 2-Thiopyridyl Chloroformate · (MW 173.63)

(convenient preparation of 2-pyridylthiol esters;[2] subsequent transformation into lactones,[3] peptides,[4] and ketones[5])

Physical Data: ^1H NMR ($CDCl_3$) δ 8.64 m (1H), 7.75 m (2H), 7.38 m (1H).

Solubility: sol CH_2Cl_2, ether.

Form Supplied in: colorless oil; main impurity is bis(thiopyridyl) carbonate; not commercially available.

Analysis of Reagent Purity: IR (CH_2Cl_2) 1765 cm^{-1} (C=O); main impurity: IR (CH_2Cl_2) 1715 cm^{-1} (C=O).

Preparative Method: ***Phosgene*** (5 equiv) in toluene and CH_2Cl_2 is cooled to 0 °C. Dropwise addition (5 min) of a CH_2Cl_2 solution of ***Triethylamine*** (slight excess) and ***2-Pyridinethiol*** is followed by stirring for 10 min. After removal of excess phosgene and CH_2Cl_2 in vacuo, hexane is added and the resulting precipitate is filtered. After concentration of the combined filtrates, the colorless oil (96%) is dissolved in CH_2Cl_2 and stored at -25 °C.

Handling, Storage, and Precautions: very unstable to water and silica gel; however, it can be handled in air. It is stable for one month if stored at -25 °C. Since phosgene is used in preparing this reagent, preparation should be in a working fume hood and extreme caution is required.

Preparation of 2-Pyridylthiol Esters.

2-Pyridylthiol esters are formed by treating a carboxylic acid with 2-thiopyridyl chloroformate under extremely mild conditions (eq 1).[2] The $Et_3N.HCl$ is removed by filtration or by washing with cold aqueous acid and base. After thorough drying, the thiol esters are generally pure enough to use in many synthetic applications.

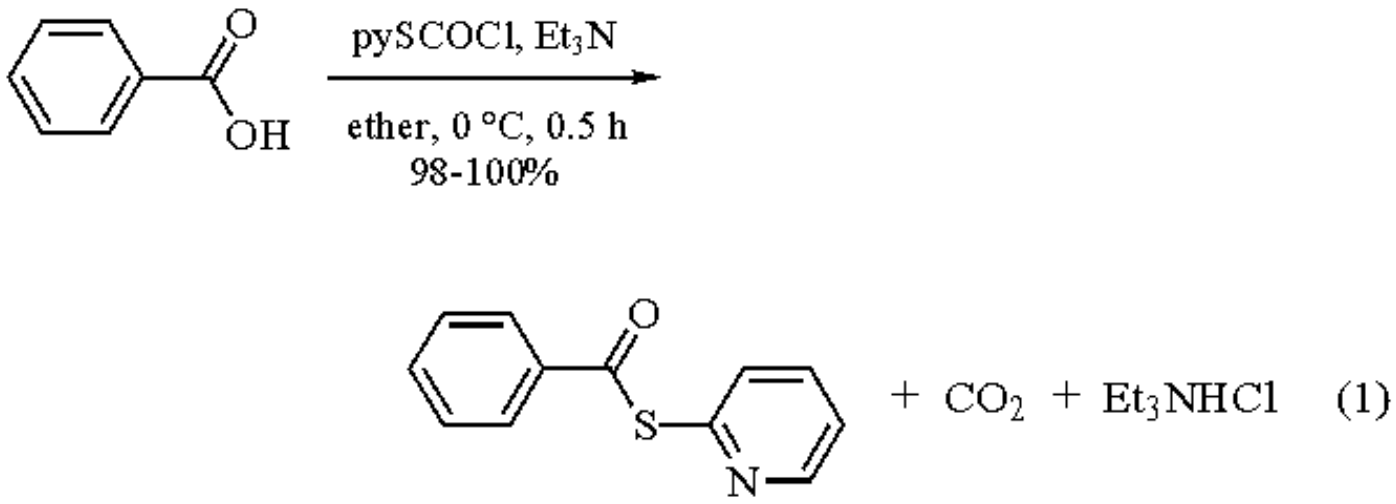

There are several other reagents for preparing 2-pyridylthiol esters. ***1,3-Dicyclohexylcarbodiimide***[4] generally gives lower yields of the thiol ester and removal of the dicyclohexylurea can be difficult. Treating an acid chloride with thallium(I) 2-pyridinethiolate[6] has been

used, but thallium salts are toxic. The method used most frequently before the introduction of 2-thiopyridyl chloroformate involves reacting a carboxylic acid with ***Triphenylphosphine*** and ***2,2´-Dipyridyl Disulfide***.[7] This procedure suffers from the necessity of removing 2-pyridinethiol and triphenylphosphine oxide by chromatography, which precludes preparing large batches of the thiol esters since there can be a loss of product by reaction with the silica gel. 2-Thiopyridyl chloroformate provides access to many reported synthetic transformations. In some of these reports, the thiol ester has been prepared by other methods. However, use of 2-thiopyridyl chloroformate should make these transformations even more accessible.

Lactone Formation.

There are several examples of the synthesis of lactones with 2-pyridylthiol esters.[3] Since this is a facile reaction, reasonable yields of complex macrocycles are obtained (eq 2).[8] The pyridine nitrogen may provide anchimeric assistance for the approaching nucleophile, thus facilitating the acylation.[3]

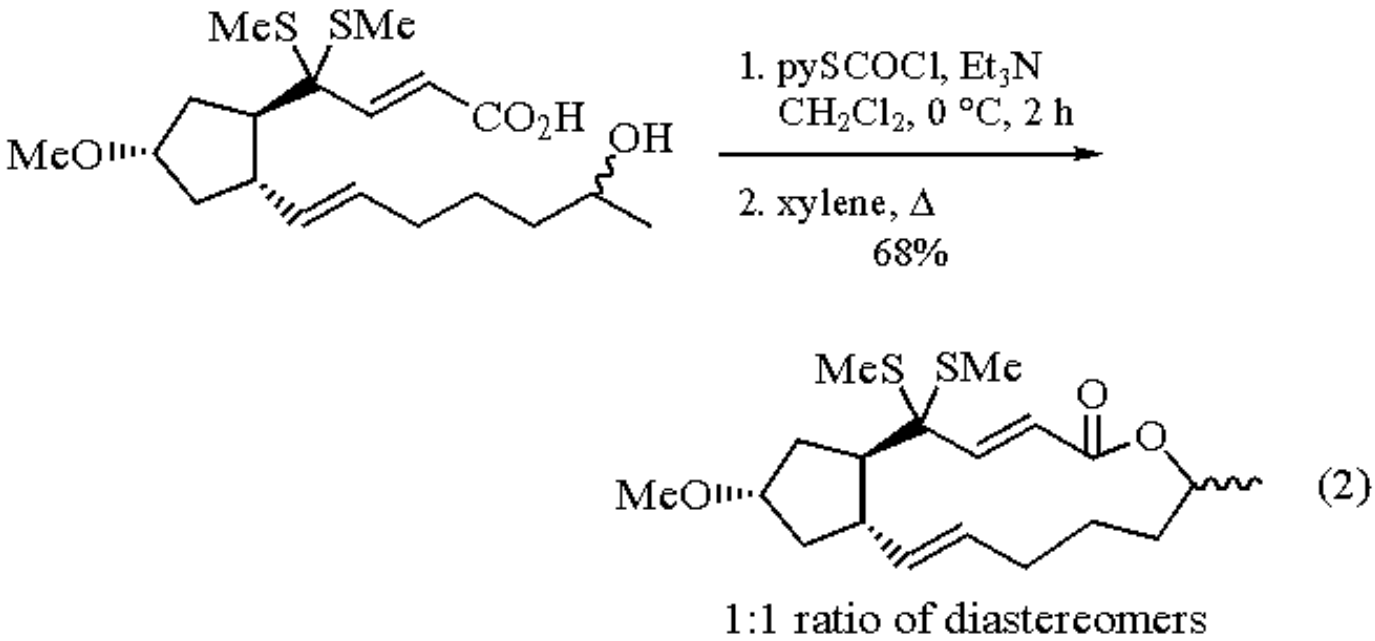

Ester Formation.

2-Pyridylthiol esters acylate lysophosphatidylcholines rapidly when catalyzed by silver ion, giving mixed-chain phosphatidylcholines in high yields and isomeric purity (eq 3).[9] The main advantages of this procedure over the usual ***4-Dimethylaminopyridine*** catalyzed acylation with acid anhydrides[10] are that less acylating reagent is required to give high yields and rearrangement of the fatty acids is minimized. The main disadvantage is the sensitivity of the 2-pyridylthiol ester to water.

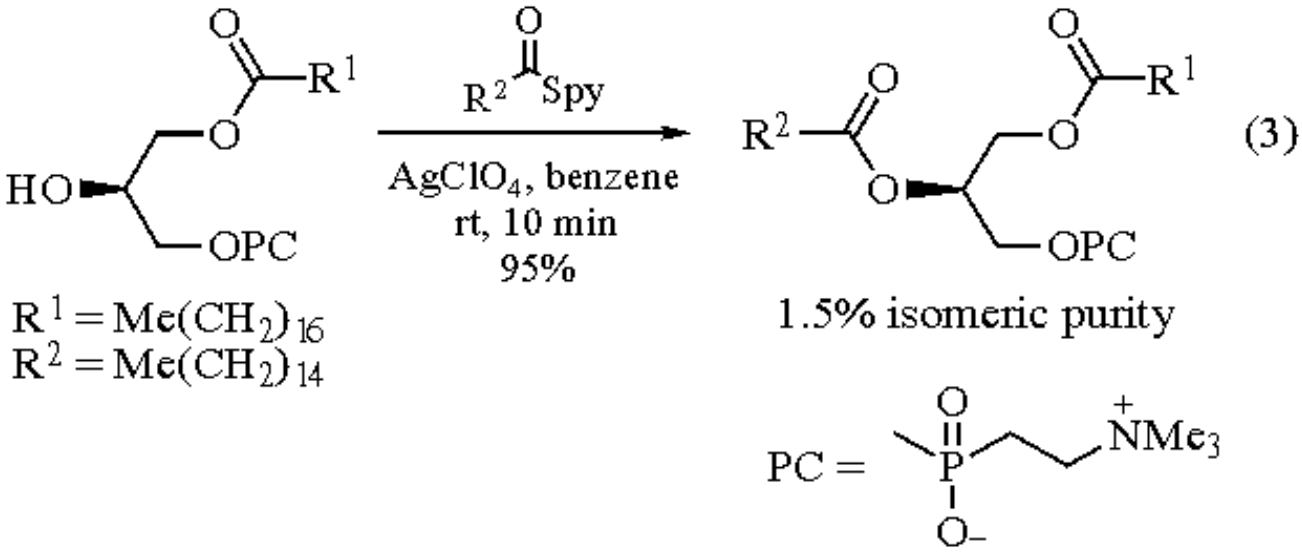

Peptide Coupling.

These thiol esters have been used in the synthesis of several dipeptides. Many of the examples involve highly sterically hindered amino acids and result in very good yields and high optical purity (eq 4).[4] There are many useful active esters for peptide coupling, such as ***Pentafluorophenol***, ***p-Nitrophenol***, and ***N-Hydroxysuccinimide***. However, these do not work as well with the hindered amino acids shown in eq 4. Additionally, there are many direct coupling procedures; therefore the 2-pyridylthiol esters have not been used frequently.

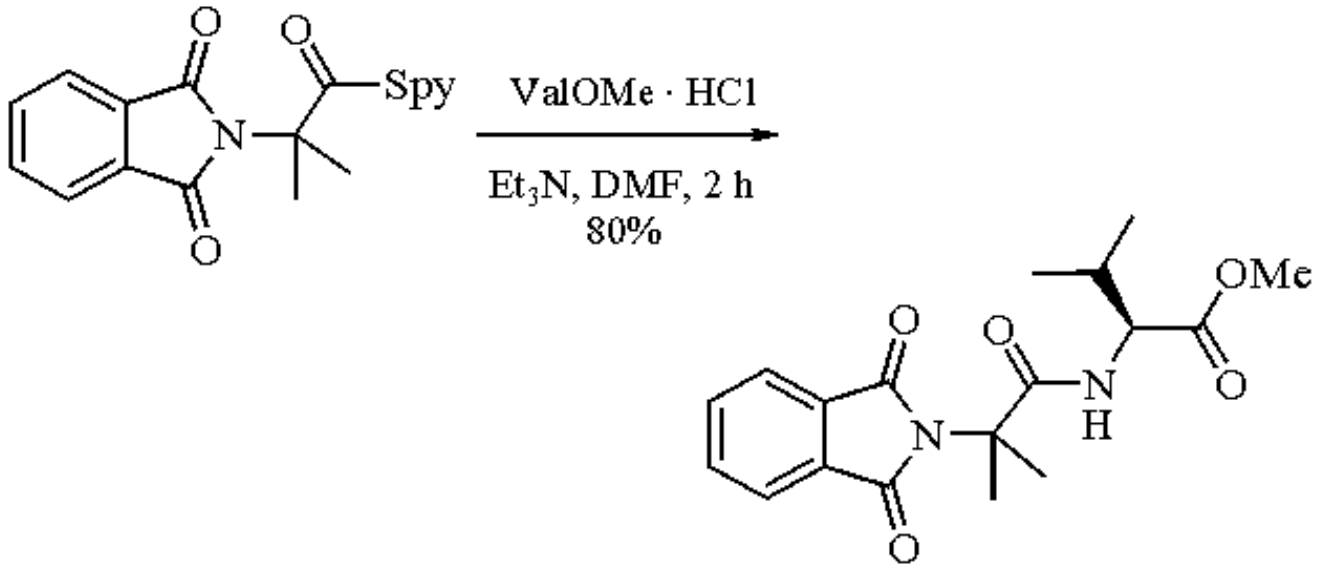

(4)

Ketones.

Reaction of 2-pyridylthiol esters with Grignard reagents occurs rapidly to give ketones in almost quantitative yields (eq 5).[5] In all studies, less than 1% of the tertiary alcohol is observed. This procedure works reasonably well with a suitably protected amino acid to give the ketone (eq 6).[11] Phthaloyl protection of the amine is required since esters with amide NH groups decompose when treated with Grignard reagents.[11]

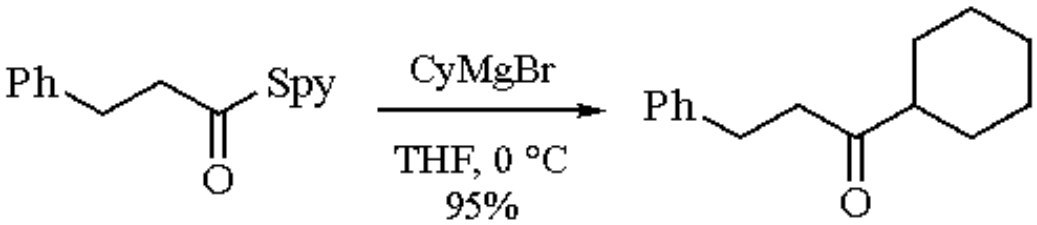

(5)

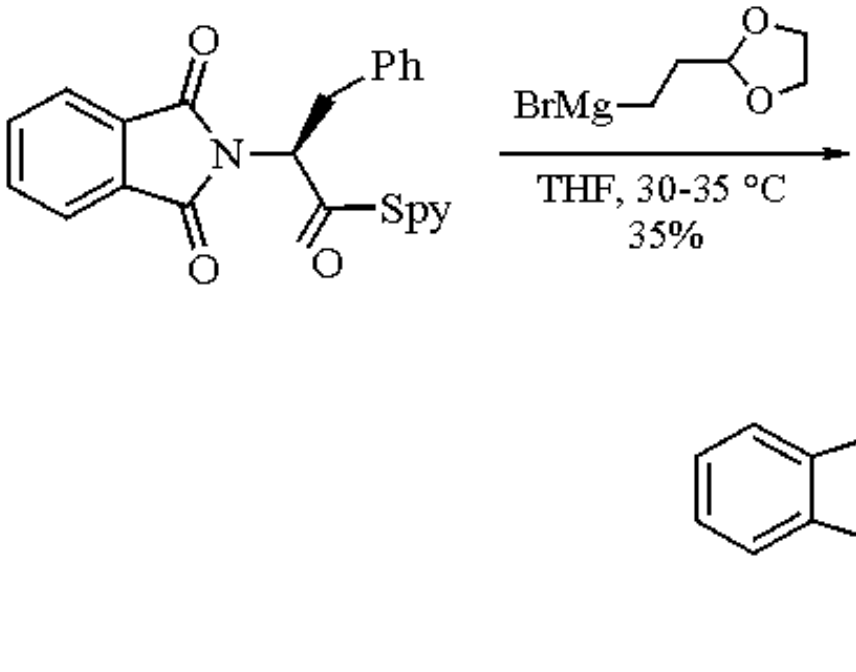

(6)

Preparation of thiol esters of highly elaborated phosphoranes with thiopyridyl chloroformate has been reported. Treatment of the thiol ester with an aryl Grignard reagent gives the corresponding ketone without epimerization of the chiral centers (eq 7).[12] There are many

procedures for reacting Grignard reagents with activated carboxylic acids to give ketones. Other reagents used with varying degrees of success include acid chlorides, nitriles, acid anhydrides, and *N*-acylimidazolides (e.g. ***N,N´-Carbonyldiimidazole***, ***1,1´-Thionylimidazole***).[13] Many of these give higher yields of the tertiary alcohol. However, treating acid chlorides with Grignard reagents at -78 °C gives better results,[14] so this may be an alternative to the thiol esters.

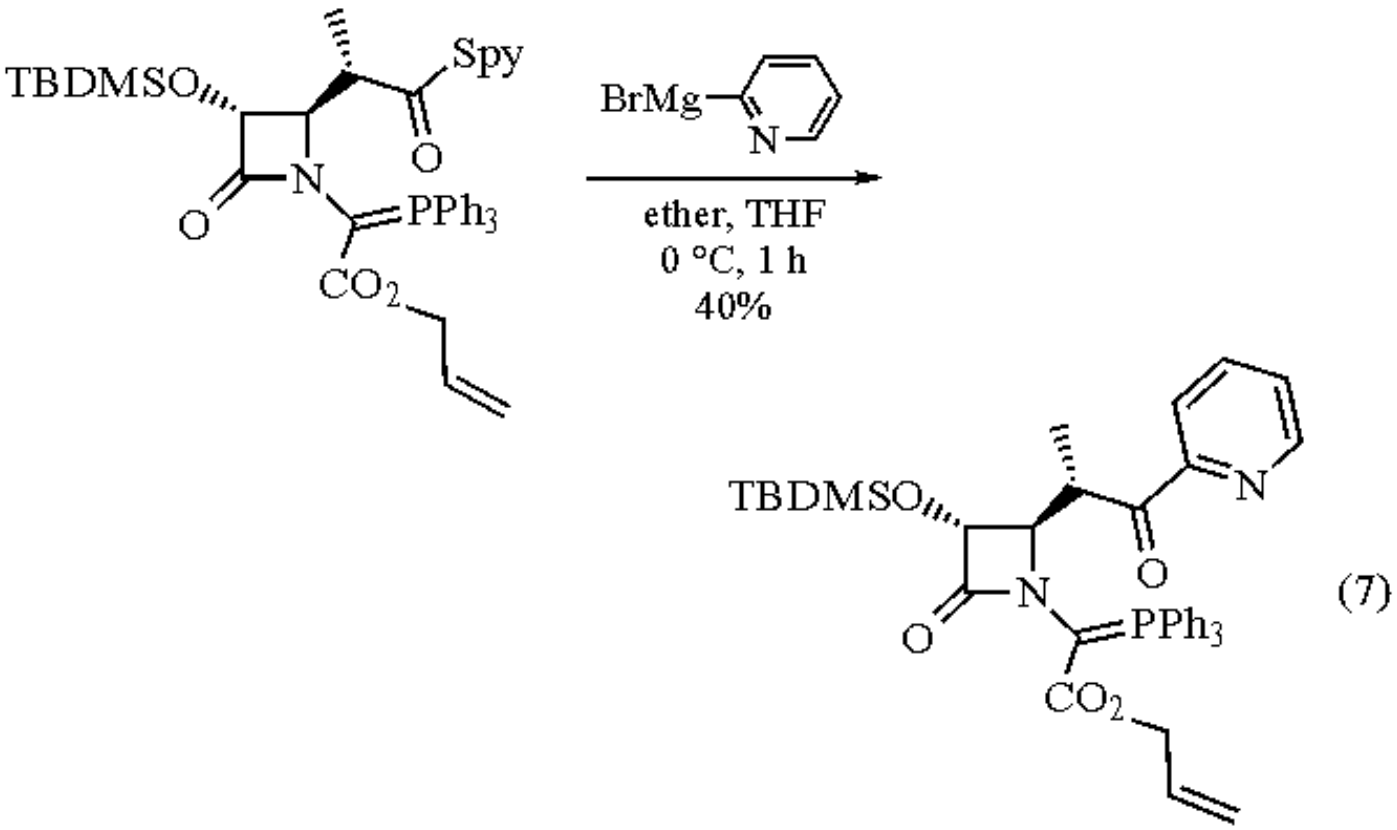

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Thiourea

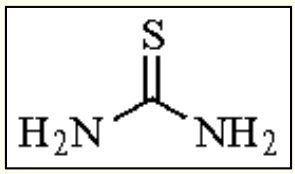

[62-56-6] · CH_4N_2S · Thiourea · (MW 76.14)

(reduction of endoperoxides and ozonides; nucleophilic H_2S equivalents; aminothiazole, pyrimidine, and episulfide synthesis; precursor of formamidinesulfinic acid)

Physical Data: mp 182 °C; *d* 1.405 g cm^{-3}.

Solubility: sol water, alcohol.

Form Supplied in: solid; commercially available.

Handling, Storage, and Precautions: liable to hydrolysis with generation of hydrogen sulfide. Powder is therefore toxic as well as malodorous. Should be used only with adequate ventilation. Use in a fume hood.

Reduction of Peroxides.

One of the more common uses of thiourea is in the reduction of peroxides to the alcohols. Examples include the reduction of cyclopentadiene endoperoxide[1] to form the corresponding diol (eq 1) and the reduction of ozonides[2] to the corresponding carbonyl compounds (eq 2) with a minimum of expense or odor.

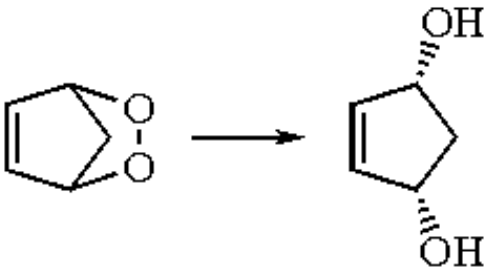

(1)

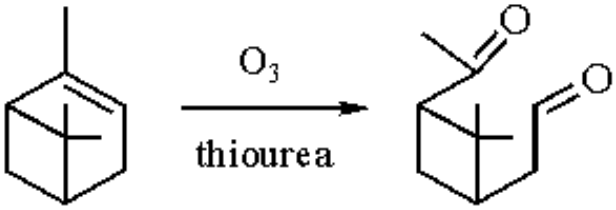

(2)

Isothiuronium Salts.

Another use of thiourea is related to its synthetic equivalence to ***Hydrogen Sulfide***. Reaction with an alkyl halide or sulfonate via the sulfur of thiourea provides the isothiuronium salt (eq 3). This alternative provides an advantage over the use of hydrogen sulfide in that it avoids formation of dialkyl sulfides. Alkaline hydrolysis of the isothiuronium salt provides the thiol;[3] aqueous chlorination can provide the sulfonyl chloride.[4] Alternatively, the sulfur fragment may be easily displaced with an amine in a synthesis of substituted guanidines (eq 4).[5]

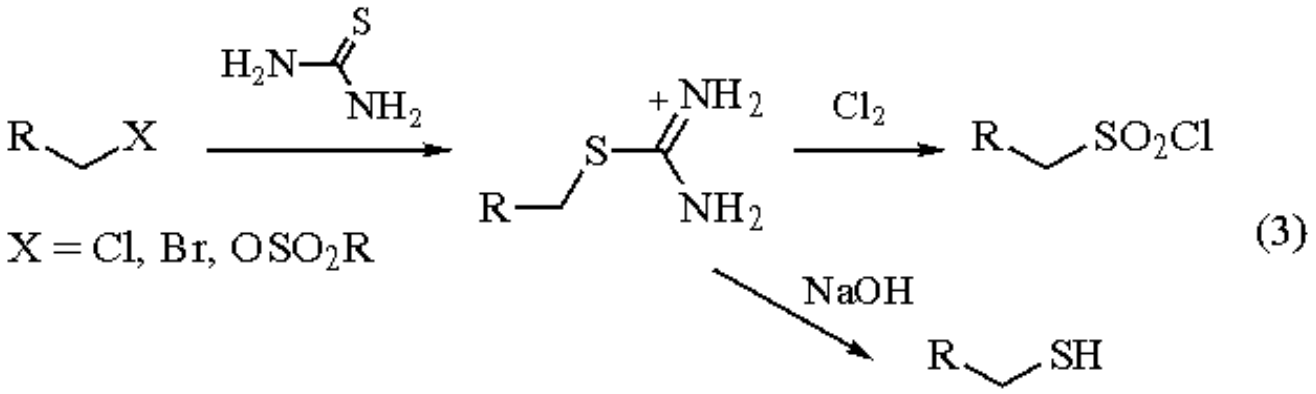

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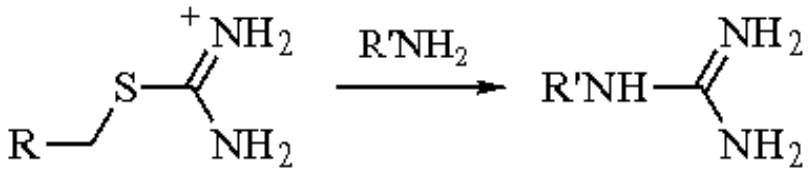

(4)

Heterocycle Synthesis.

A major use of thiourea is in the construction of heterocycles. Aminothiazoles can be synthesized by the Hantzsch synthesis wherein an α-halo carbonyl compound is treated with thiourea.[6a,b] The reaction of the carbonyl with one of the thiourea nitrogens to form the imine is the first step of the synthesis. Upon further heating, the sulfur displaces the halide with cyclization (eq 5). Pyrimidines are made by reaction of thiourea with β-dicarbonyl compounds[7a,b] via an initial attack by a thiourea nitrogen on a carbonyl, followed by cyclization and tautomerization (eq 6). Thiourea is the key reagent for the synthesis of episulfides[8a,b] from the corresponding epoxides, in one step and in synthetically useful yield (eq 7).

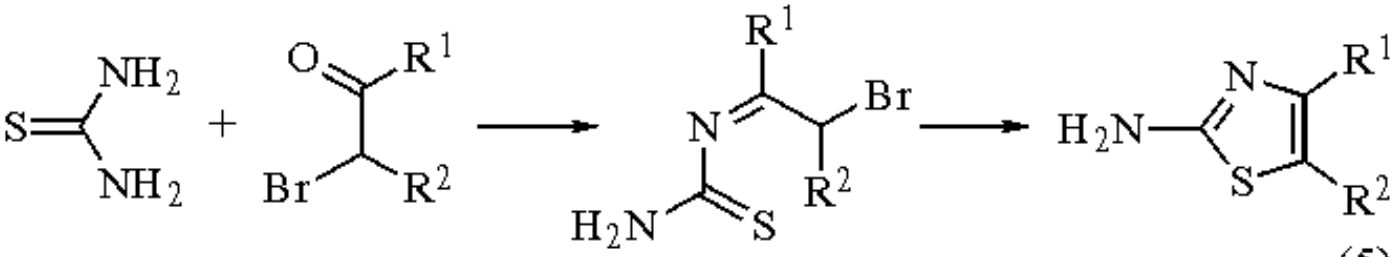

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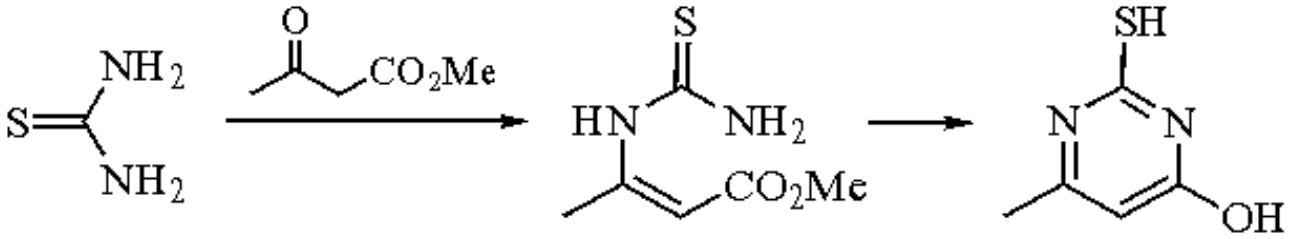

(6)

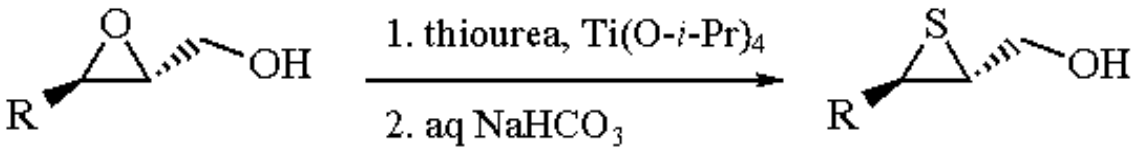

(7)

Lastly, thiourea and ***Hydrogen Peroxide*** are the starting materials for synthesis of ***Thiourea Dioxide*** (eq 8)[9] a mild reducing agent commonly used in the reduction of ketones to secondary alcohols.[10]

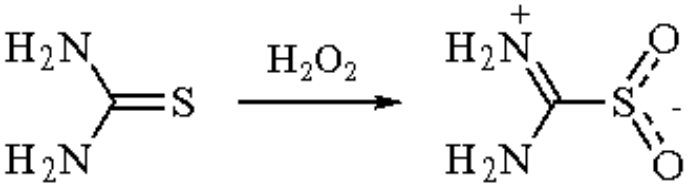

(8)

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Onorato Campopiano

DuPont Agricultural Products, Wilmington, DE, USA

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Thiourea Dioxide[1]

$NH_2C(=NH)SO_2H$

[1758-73-2] · $CH_4N_2O_2S$ · Thiourea Dioxide · (MW 108.14)

(convenient and economical reducing agent for obtaining secondary alcohols from aliphatic,[2] alicyclic,[2] aromatic,[2] heterocyclic,[2] and steroidal ketones;[3] efficient reducing agent for the conversion of disulfides to thiols,[4] of *N*-tosylsulfilimines to sulfides,[4] of sulfoxides to sulfides,[5] and of halides and oxides of organotellurium and organoselenium to tellurides and selenides;[6] synthesis of substituted imidazoles[7])

Alternate Names: TUD; formamidinesulfinic acid; aminoiminomethanesulfinic acid.

Physical Data: mp 144 °C (dec).

Solubility: partially sol cold water; insol in organic solvents.

Preparative Method: prepared by oxidation of ***Thiourea*** with ***Hydrogen Peroxide***.[8]

Handling, Storage, and Precautions: moisture sensitive.

Reduction of Ketones to Secondary Alcohols.[2]

A variety of ketones are reduced by TUD, in an aqueous ethanolic solution in the presence of NaOH, to the corresponding secondary alcohol in good yield. Generally, reduction of ketones requires 1-3 equiv of TUD and 2-6 equiv of NaOH; for example, dipropyl ketone gives heptan-4-ol (74%), benzophenone gives benzhydrol (100%), and 3-pyridyl phenyl ketone gives 3-pyridylphenylmethanol (100%). From the reaction mixture, almost theoretical amounts of the byproducts, sodium bisulfite and urea, are obtained.

Steroidal Ketones.[3]

Using TUD, in the presence of an alkoxide in alcohol, steroidal ketones are reduced to the corresponding secondary alcohols. The reduction proceeds satisfactorily in the case of 3- and 6-keto steroids.[3] Steroidal diketones having a 20-oxo group do not undergo reduction with TUD. The results obtained from TUD, metal-alcohol (Bouveault-Blanc), and ***Lithium Aluminum Hydride*** reductions are compared in Table 1. With all three reducing agents, 5α-cholestan-3-one gives the equatorial isomer as the major product. With 3β-hydroxy-5α-cholestan-3-one, TUD favors α-attack to produce predominantly the axial isomer.

Table 1 Comparison between TUD, Metal Alcohol and $LiAlH_4$ Reductions

Substrate	Products	Yield (%)		
		TUD	Na ROH	$LiAlH_4$
5a-Cholestan-3-one	3a-ol	10		10
	3b-ol	90	100	90
3b-Hydroxy-5a-cholestan-6-one	3b,6a-diol	16	95	33
	3b,6b-diol	84	5	67

Reduction of Disulfides and of *N*-Tosylsulfilimines.[4]

Disulfides and *N*-tosylsulfilimines are transformed into the corresponding thiols and sulfides (eq 1), respectively. For example, dibutyl disulfide is reduced to butanethiol (90%) and diphenyl disulfide to thiophenol (77%). The reactions are carried out under phase transfer conditions in the presence of a catalyst such as ***Tri-n-butylhexadecylphosphonium Bromide***.

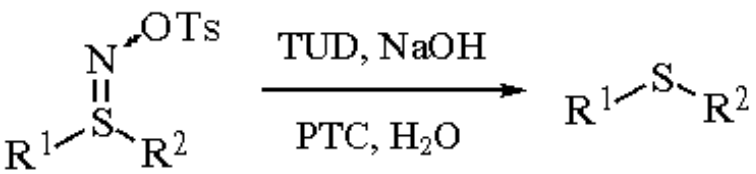

(1)

R^1	R^2	Yield (%)
Ph	Me	93
Bn	Me	68
Bn	Ph	83
Bn	Bn	67

Reduction of Sulfoxides.[5]

Sulfoxides are reduced to the corresponding sulfides by TUD in the presence of ***Iodine***; for example, dibutyl sulfoxide gives dibutyl sulfide (89%) and diphenyl sulfoxide gives diphenyl sulfide (95%). The reaction is generally carried out by adding sulfoxides and iodine to a suspension of TUD in acetonitrile and then refluxing the mixture for a short time.

Reduction of Organoselenium and -tellurium Halides and Oxides.[6]

TUD reduces aryltellurium trihalides to diaryl ditellurides (eq 2) and diorganyltellurium dihalides and telluroxides to diorganyl tellurides (eq 3) in high yield. The corresponding selenium compounds are reduced similarly. Some examples are given in Table 2. The reduction is performed by premixing the substrate and 2 N NaOH at room temperature for 15 min prior to the addition of TUD in petroleum ether.

$$ArMX_3 \xrightarrow[25\ °C]{NaOH,\ H_2O} [ArMO_2^-] \xrightarrow{TUD} (ArM)_2 \qquad (2)$$

M = Te, Se

$$R_2MX_2 \xrightarrow[25\ °C]{NaOH,\ H_2O} [RM(O)R] \xrightarrow{TUD} RMR \qquad (3)$$

M = Te, Se

Table 2 Reduction of Organotellurium and Organoselenium Halides and Oxides by TUD

Starting material	Product	Yield (%)
$PhTeCl_3$	$(PhTe)_2$	92
$(C_{12}H_{25})_2TeCl_2$	$(C_{12}H_{25})_2Te$	86
PhTe(O)Bu	PhTeBu	77
$PhSeBr_3$	$(PhSe)_2$	93
Ph_2SeCl_2	PhSePh	92
Ph_2SeO	PhSePh	90

Reaction of Acylvinylphosphonium Halides with TUD.[7]

Triphenyl-β-acetylvinylphosphonium halides (X = Cl, Br) react with TUD (in DMSO) in the presence of base (***Sodium Hydride***) to give the imidazolylphosphonium salts in high yield (eq 4). These imidazolyl halides can be readily converted to multifunctional imidazoles with quantitative recovery of PPh_3; for example, 4-methyl-(5-methylimidazolyl)triphenylphosphonium halide, on treatment with NaOMe in MeOH, affords 5-methyl-4-methoxymethylimidazole.

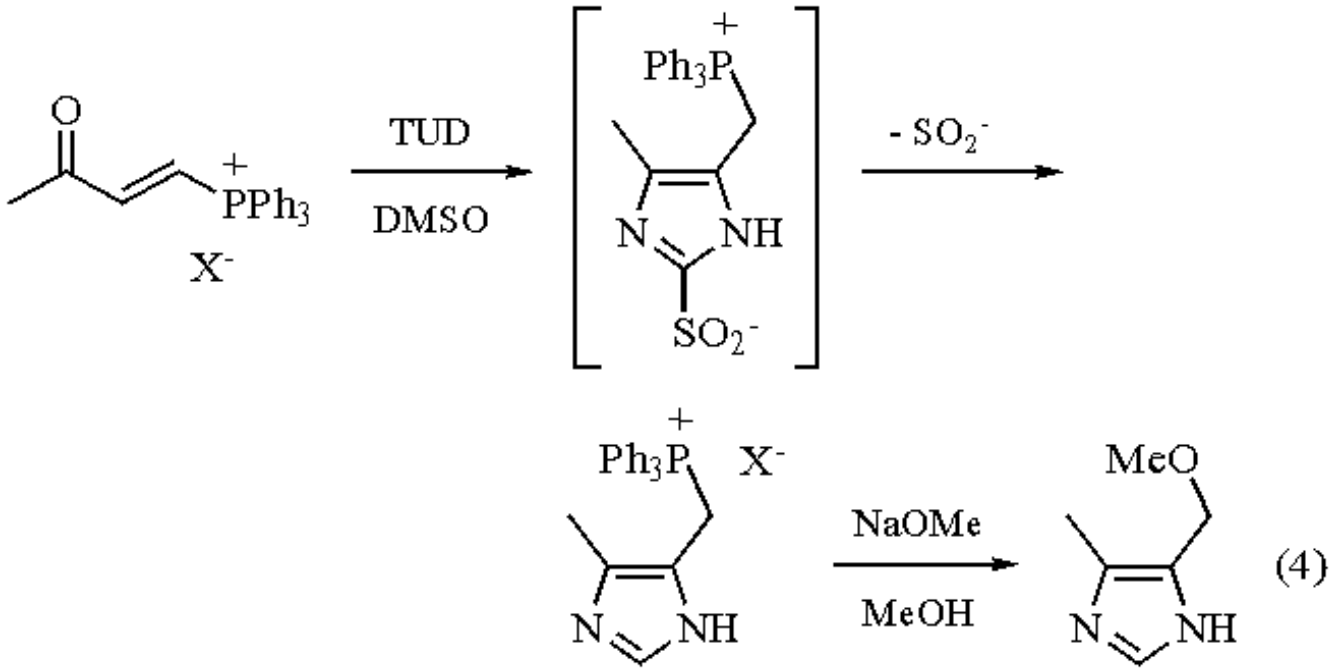

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Tin[1]

Sn

[7440-31-5] · Sn · Tin · (MW 118.71)

(with HCl, reduces a variety of functional groups;[2] stereoselective allylation of carbonyl compounds;[3] in situ generation of tin enolates for directed aldol reactions[4])

Physical Data: mp 232 °C; bp ~2270 °C; *d* 7.31 g cm^{-3}.

Solubility: insol water, organic solvents; reacts with mineral acids.

Form Supplied in: foil, moss, powder, granules, shot, and wire.

Preparative Methods: activated form is prepared from ***Tin(II) Chloride*** in THF by reduction with ***Lithium Aluminum Hydride***[5] or ***Potassium*** metal;[6] tin amalgam is prepared from ***Mercury(II) Chloride*** and 30-mesh Sn in water;[7] tin-copper couple is prepared from ***Copper(II) Acetate*** and 30-mesh tin in acetic acid.[8]

Handling, Storage, and Precautions: incompatible with strong acids and strong oxidizing agents; powdered form is air and moisture sensitive and should not be inhaled or contacted with the eyes or skin; amalgam is stored under water; tin-copper couple is stored under ether.

Functional Group Reductions.

The use of tin and ***Hydrochloric Acid*** is a classical method for the reduction of a variety of functional groups.[2] However this procedure has decreased in importance since the development of catalytic hydrogenation and of metal hydride reducing agents, and the harsh reaction conditions (strong acids and high temperatures) are often incompatible with other functional groups. Many reductions effected by tin are more conveniently carried out with ***Tin(II) Chloride***, which is soluble in some organic solvents. Nevertheless, the method is still used, most notably for the reduction of aromatic nitro compounds to amines, for which metal hydrides are less effective (see ***Lithium Aluminum Hydride***). Representative examples of standard procedures which utilize Sn/HCl include the reductions of 2,6-dibromo-4-nitrophenol to the aminophenol,[9] 2,4,6-trinitrobenzoic acid to the triamine (eq 1),[10] and nitrobarbituric acid to the amine (uramil).[11] Aromatic nitro group reductions with tin and hydrochloric acid have been employed in the preparation of functionalized paracyclophanes[12] and hemispherands.[13] 8-Nitroquinolines have been reduced to the corresponding amines with a combination of tin and tin(II) chloride.[14] In some cases the generated amines undergo further reactions (eq 2).[15]

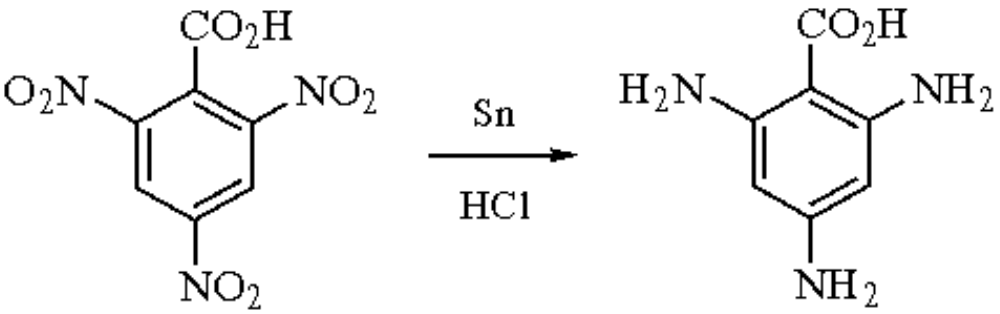

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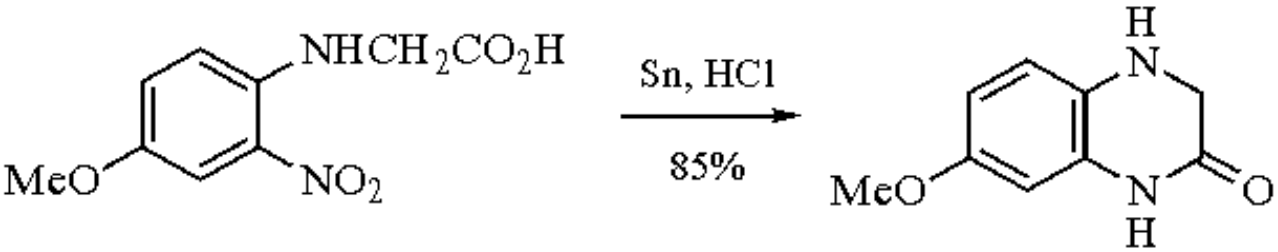

(2)

Sterically hindered aliphatic vicinal diamines have recently been prepared by Sn/HCl reductions of the corresponding 1,2-dinitro compounds (eq 3).[16] Under the same conditions, a geminal dinitro compound is reported to give the corresponding oxime (eq 4).[16] *N*-Nitrosamines are reduced by tin and HCl to the denitrosated amines (eq 5),[17] whereas the corresponding ***Zinc*** reduction produces the hydrazines.

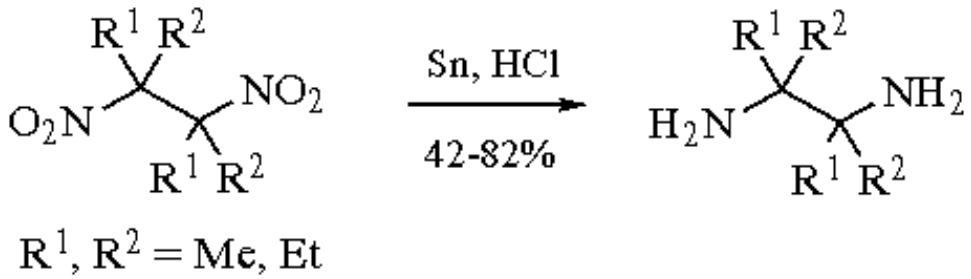

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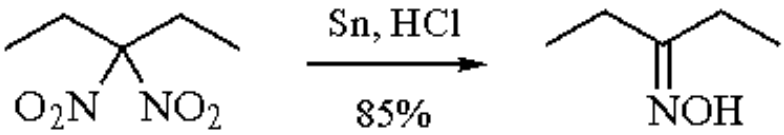

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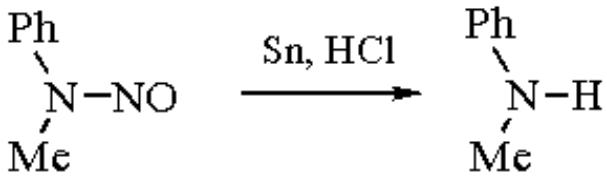

(5)

Examples of reductions of other functional groups by tin and HCl include the reduction of isoquinoline methiodides,[18] of tetrahydrocarbazole to hexahydrocarbazole,[19] and of 5-(chloromethyl)uracil to thymine (eq 6),[20] the selective debromination of 1,6-dibromo-2-naphthol (eq 7),[21] and the reduction of anisoin to deoxyanisoin,[22] of anthraquinone to anthrone (eq 8),[23] and of benzaldehydes to stilbenes.[24]

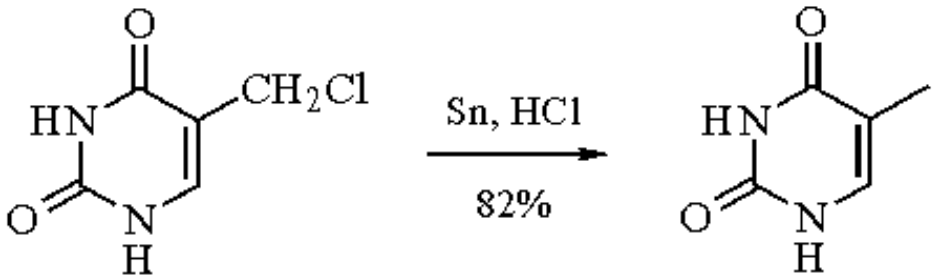

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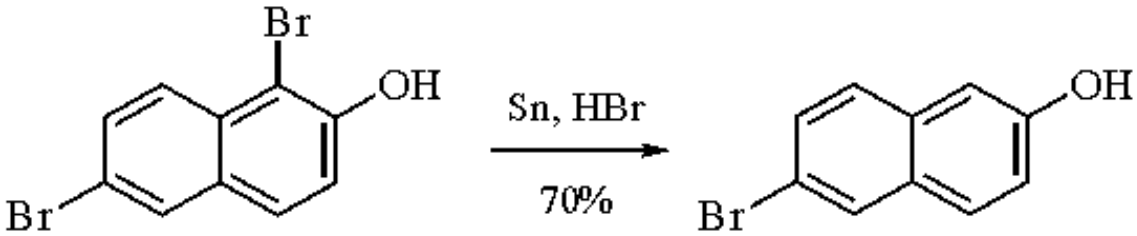

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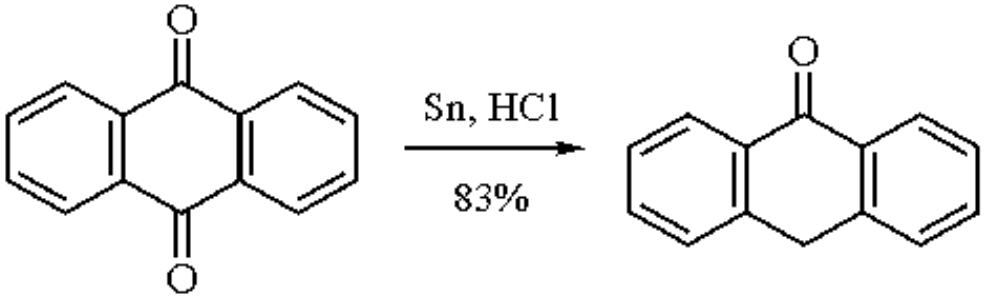

(8)

Tin amalgam and hydrochloric acid is useful for the selective reduction of the double bond of conjugated enediones in high yield (eq 9)[7] and for the controlled reduction of benzils to either benzoins or deoxybenzoins.[25] Tin amalgam in ***Acetic Acid*** also reduces benzoquinones to hydroquinones.[7,26]

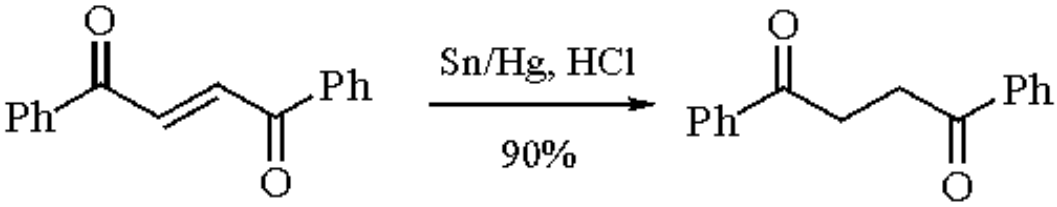

(9)

Tin reductions have also been used for the conversion of arylsulfonyl chlorides to the corresponding thiols[27] and for the preparation of ***Thiophosgene*** from thiocarbonyl perchloride.[28] Metallic tin has recently been used for the in situ generation of low-valent bismuth and titanium species that catalyze cyclizations to 3-hydroxycephems (eq 10).[29] A tin-copper couple has been used for the selective debromination of activated dibromides (eq 11),[8] in cases where the more commonly employed ***Zinc/Copper Couple*** leads to overreduction.

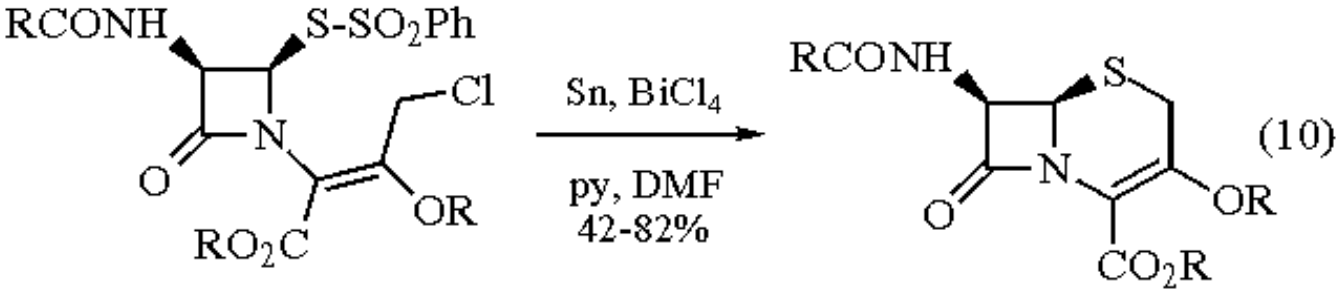

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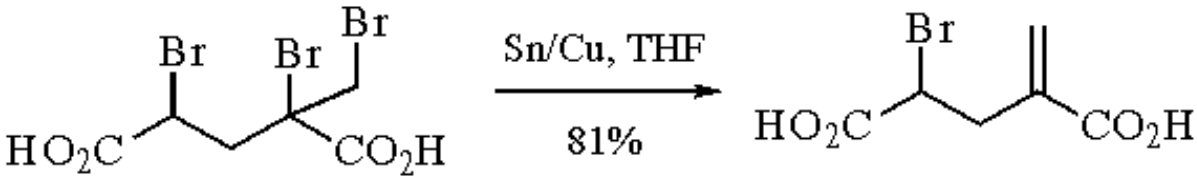

(11)

Barbier-Type Allylations and Related Reactions.

The reaction of carbonyl compounds with allylmetal reagents to give homoallylic alcohols is an extremely important reaction in organic synthesis.[3,30] Metallic tin can be used for the in situ generation of diallyltin dihalides for subsequent reaction with aldehydes or ketones in good yield (eq 12).[31] The procedure is considerably more convenient than that involving isolation of allyltin intermediates and can be carried out in the presence of water.[32] Moderate asymmetric induction is observed when the reaction is carried out in the presence of monosodium (+)-diethyl tartrate.[33] The yields are improved by sonication[34] and this procedure has recently been applied to chain extensions of carbohydrates.[35] The reaction can be made catalytic by electrochemical regeneration of the tin reagent.[36]

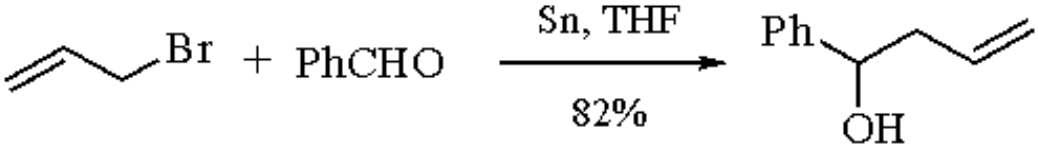

(12)

A further improvement involves performing the reaction in the presence of ***Aluminum*** powder in a THF-water mixture.[32] Under these conditions, allyl chloride also reacts[37] and yields are improved for reactions of substituted allyl halides. In such cases the

diastereoselectivity is dependent on the specific reactants and reaction conditions. For example the Sn/Al reaction of benzaldehyde with crotyl bromide gives the *syn* diastereoisomer as the major product (eq 13),[32] whereas reaction with cinnamyl chloride occurs with exclusive *anti* selectivity (eq 14).[38] Under the same conditions cinnamyl chloride reacts with enals by exclusive 1,2-regioselective addition and complete *anti* diastereoselectivity and with 2-phenylpropanal with moderate Cram selectivity (eq 15).[38] These reactions are compatible with a variety of other functional groups,[32,39,40] although in some cases these may induce further reactions (eq 16).[40] A mechanistic study of the tin-promoted reactions of allylic iodides with benzaldehydes has recently been reported.[41] It has also recently been shown that allylic alcohols undergo similar reactions with metallic tin in the presence of ***Chlorotrimethylsilane*** and ***Sodium Iodide***.[42] Under these conditions, substituted allylic alcohols undergo carbon-carbon bond formation to the less substituted allylic carbon.[42]

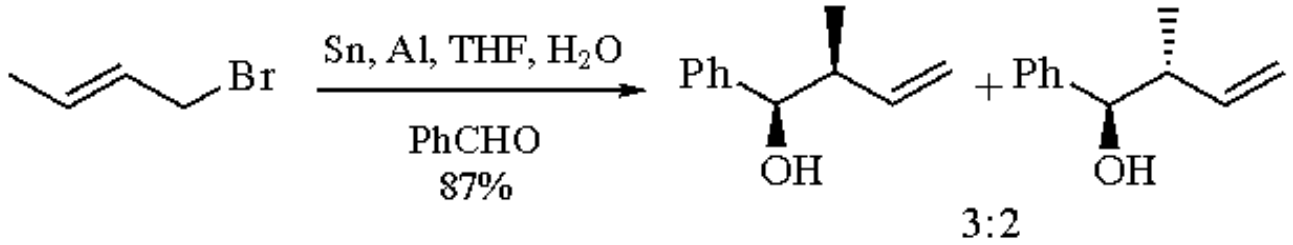

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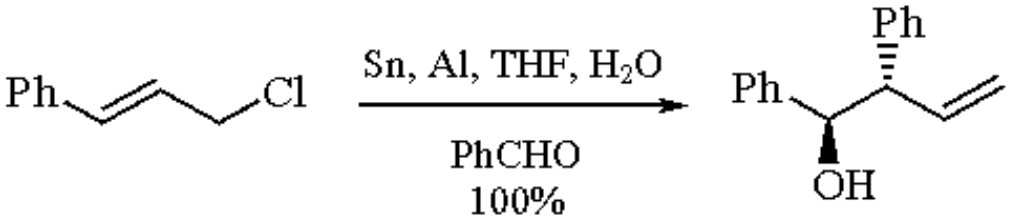

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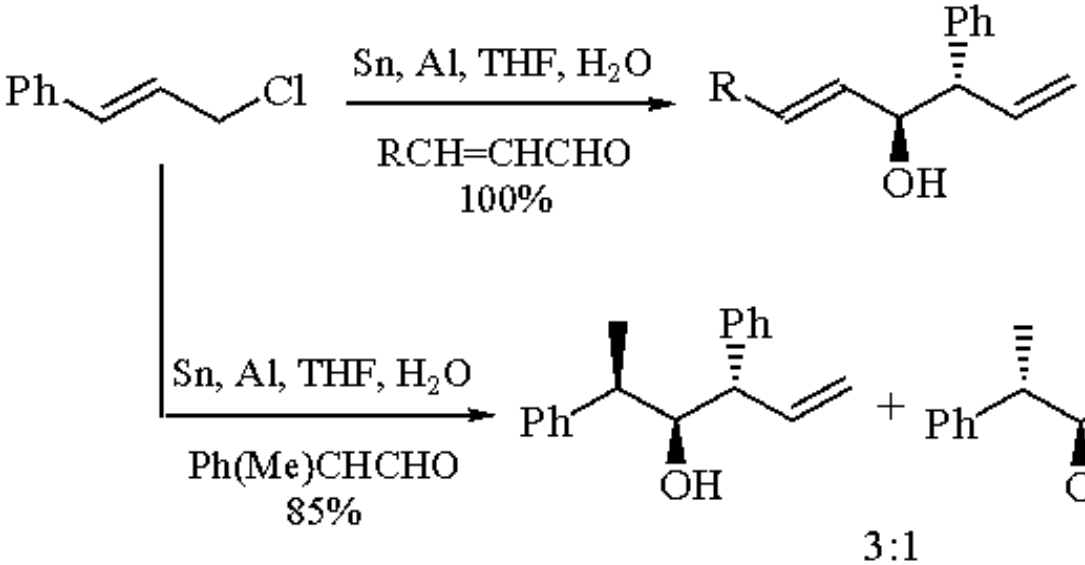

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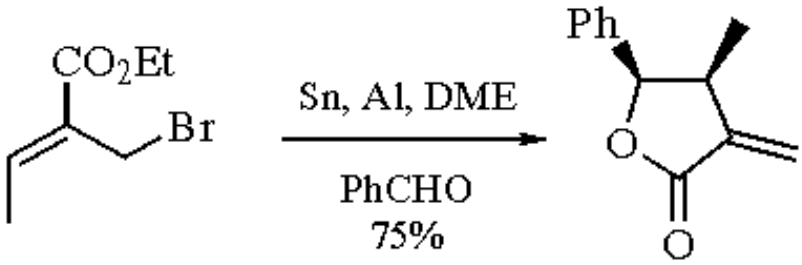

(16)

The Sn/Al procedure has been further extended to the reactions of propargylic halides and such reactions can give both alkynic and allenic products, depending on the reaction conditions (eq 17).[43] The direct reaction of metallic tin with simple alkyl halides to give dialkyltin dihalides is an industrially important reaction and is usually restricted to the reactions of alkyl iodides.[44] More recently, a phase-transfer catalyzed procedure has been developed that facilitates reactions of alkyl bromides and chlorides.[45]

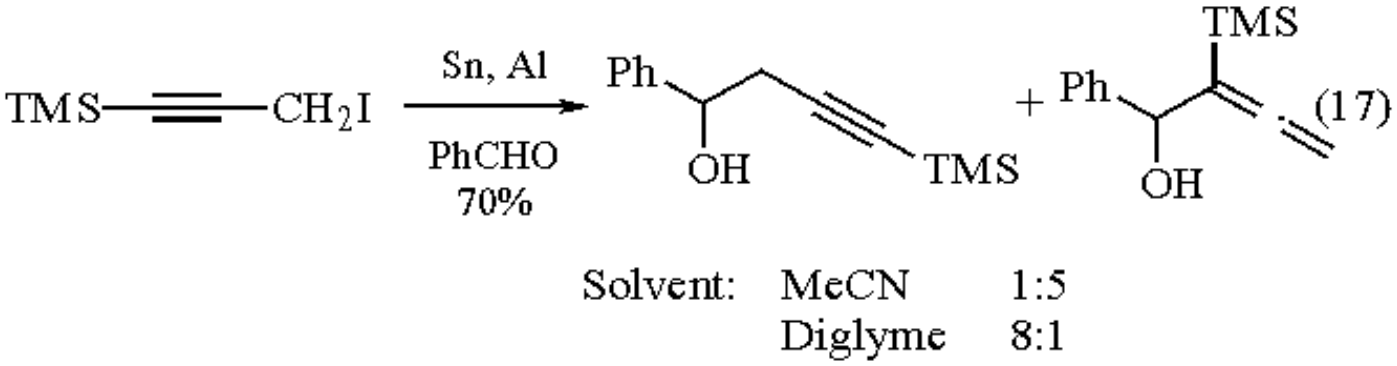

Tin Enolates.

Tin enolates are useful intermediates for use in directed aldol reactions.[4,46] Tin(II) enolates are usually prepared[47] by reaction of enolizable ketones with ***Tin(II) Trifluoromethanesulfonate***, but can also be prepared from reactions of α-bromocarbonyl compounds with activated metallic tin. Such enolates react with aldehydes and ketones under mild conditions to give aldols, generally in high yield (eq 18).[48] With α-substituted enolates high *syn* selectivity is observed (eq 19);[48] this is the opposite selectivity to that found with tin(IV) enolates. It has recently been shown that such reactions can be carried out in aqueous media with unactivated tin powder, but that under these conditions the metal enolate is probably not involved; a single-electron-transfer mechanism has been suggested.[49] In a related reaction, metallic tin has been used to generate a highly functionalized tin(II) enolate for alkylation of an azetidinone as part of a carbapenam synthesis (eq 20).[50]

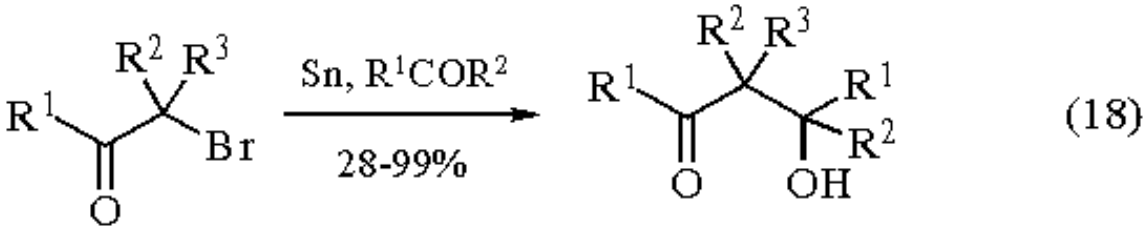

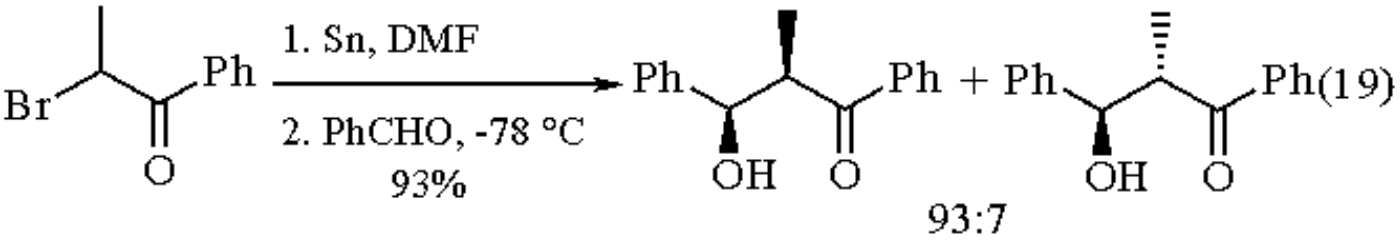

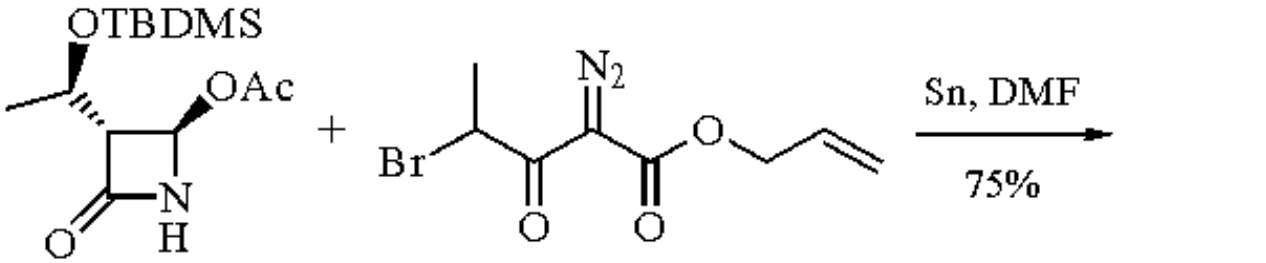

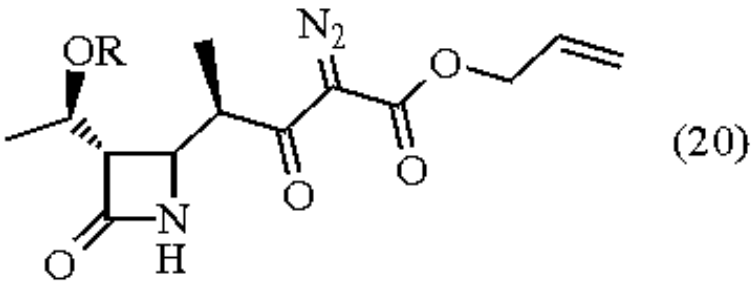

β:α = 3:1

Tin(II) ester enolates can also be prepared by reaction of α-bromo carboxylic acid esters for Reformatsky-type reactions under very mild conditions (eq 21).[5] Reaction of an α-diketone or α-keto aldehyde with activated metallic tin produces a tin(II) enediolate that reacts with aldehydes to produce α,β-dihydroxy ketones in high yield (eq 22).[51] The diastereoselectivity of this reaction can is controlled by the addition of hexafluorobenzene.

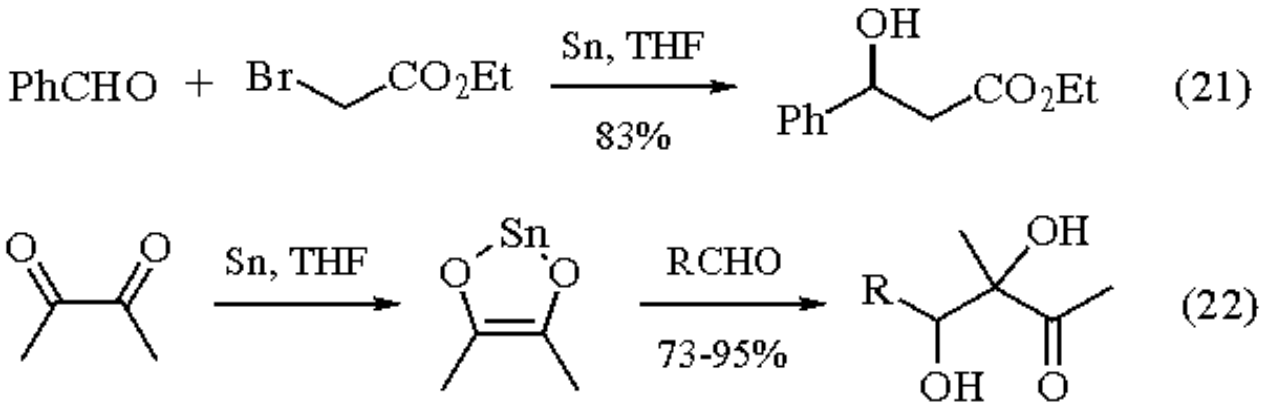

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Tin(II) Bromide

$SnBr_2$

[10031-24-0] · Br_2Sn · Tin(II) Bromide · (MW 278.51)

(mild Lewis acid used in halogenative allylation and Friedel-Crafts allylation; synthesis of α-nucleosides; α-methylation of ketones; reduction of acetals and aromatic nitro compounds; reductive dimerization of imines)

Alternate Name: stannous bromide.

Physical Data: mp 215.5 °C; bp 620 °C; *d* 5.1 g cm^{-3}.

Solubility: sol water (85.2 g/100 mL at 0 °C, 222.5 g/100 mL at 100 °C), alcohol, ether, acetone.

Form Supplied in: pale yellow rhombic crystals; commercially available.

Handling, Storage, and Precautions: corrosive and moisture sensitive; should be stored in a tightly closed container protected from light.

Allylations.

Oriyama[1] has shown that aromatic acetals can be converted in 63-87% yield to α-allylbenzyl bromides utilizing ***Allyltrimethylsilane*** and a catalytic amount of $SnBr_2$ in combination with excess ***Acetyl Bromide*** (eq 1). This reaction works equally well with $SnCl_2$ and ***Acetyl Chloride*** to yield the corresponding α-allylbenzyl chlorides. The Friedel-Crafts allylation of anisole with allylic bromides catalyzed by $SnBr_2$ has also been reported (eq 2).[2]

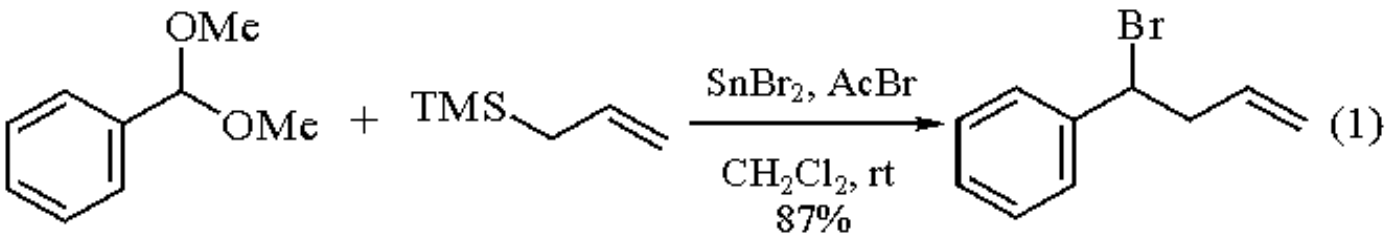

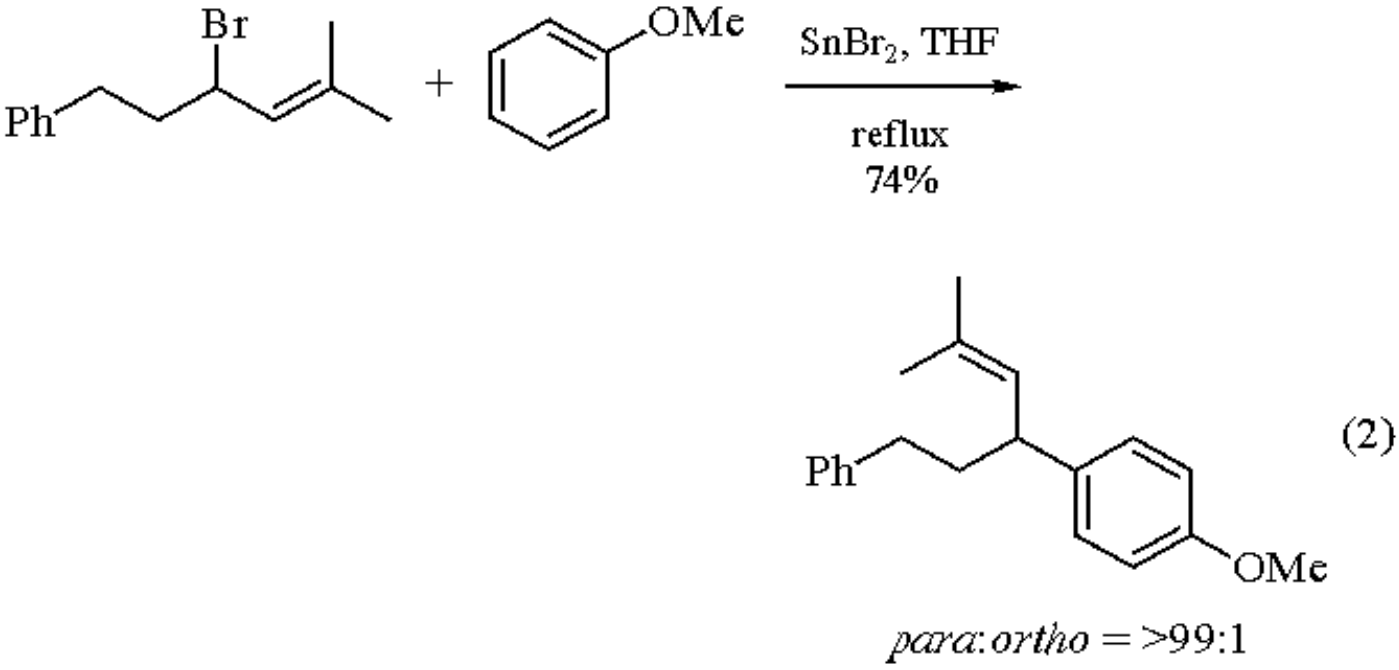

α-Methylene Ketones.

Silyl enol ethers react with ***Bromomethyl Methyl Ether*** in the presence of a catalytic amount of $SnBr_2$ to yield α-bromomethyl ketones. The α-bromomethyl ketones can be isolated or converted in a one-pot procedure to α-methylene ketones by treatment with ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (eq 3).[3] Other tin halides such as ***Tin(II) Fluoride*** and ***Tin(II) Chloride*** can be used successfully in the reaction. This one-pot procedure is a convenient method for the introduction of α-methylene groups to ketones. Other methods such as the introduction of dialkylaminomethyl[4] or arylthiomethyl[5] groups α to a ketone, followed by activation and elimination, are two-step procedures. This methodology has been used in the synthesis of the antitumor antibiotic sarkomycin (**1**) (eq 4).

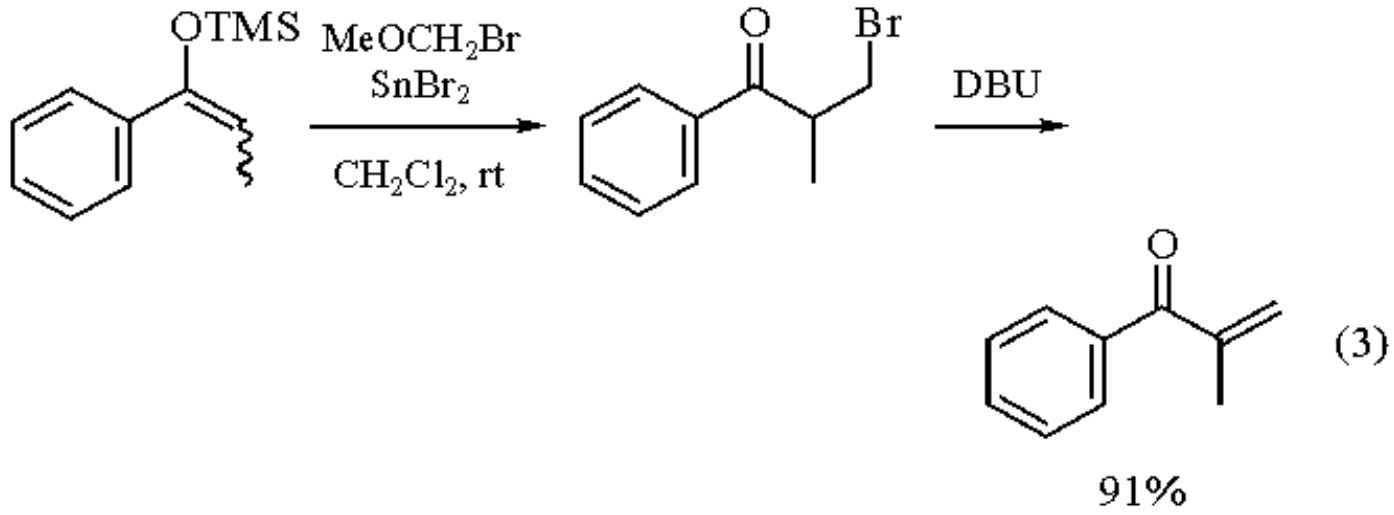

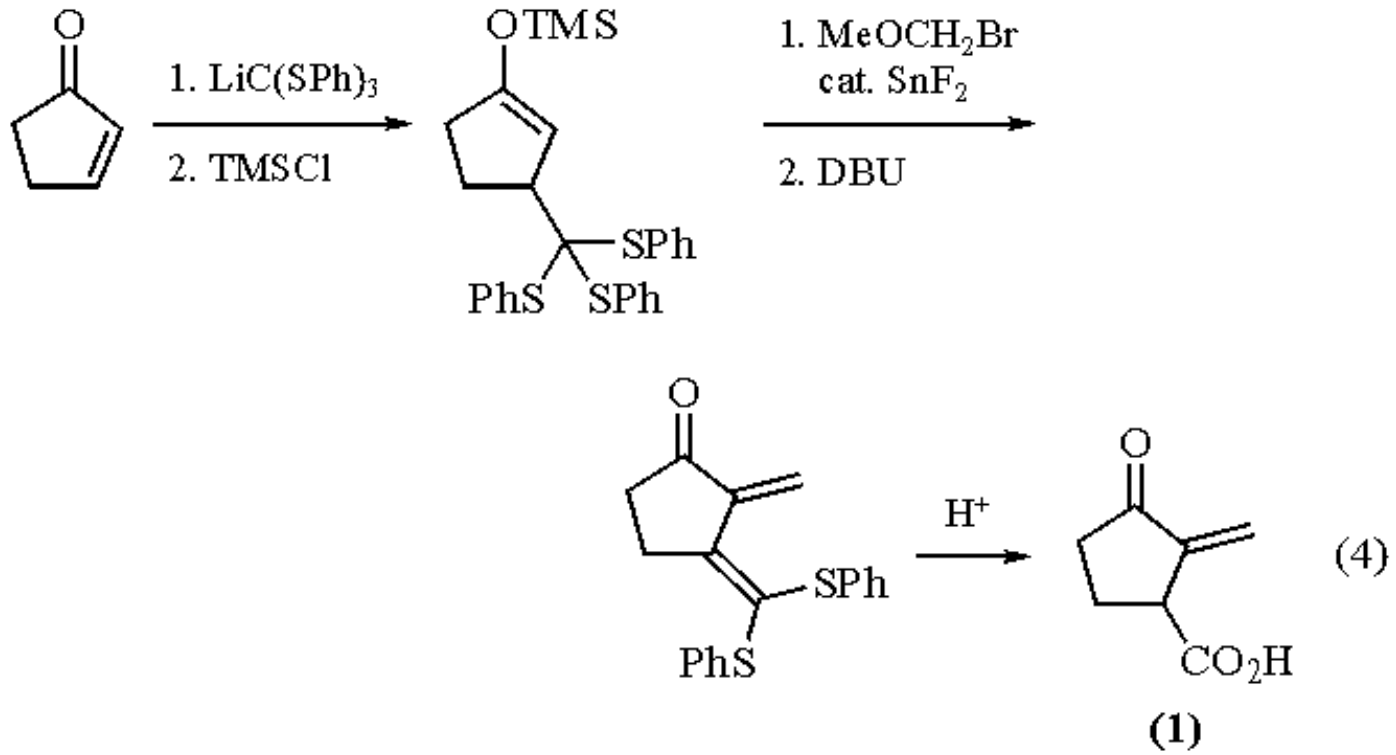

Reductive Dimerization of Imines.

The reductive dimerization of *N*-alkyl imines to vicinal diamines can be effected in 62-90% yields with ***Aluminum*** and a catalytic amount of a Sn^{II} or Pb^{II} salt in the presence of ***Trifluoroacetic Acid*** or ***Aluminum Bromide*** (eq 5).[6] The $PbBr_2$/Al bimetal redox system is the best combination although $SnBr_2$/Al is also effective. The reaction works best on both substituted and unsubstituted aromatic imines; however, aliphatic and aromatic ketimines will undergo reductive dimerization under refluxing conditions. This method produces slightly better yields than two other recently developed methods for the preparation of vicinal diamines, namely the niobium(IV) promoted dimerization of *N*-trimethylsilylimines[7] and the reductive dimerization of *N*-alkylbenzylimines with titanium(0).[8]

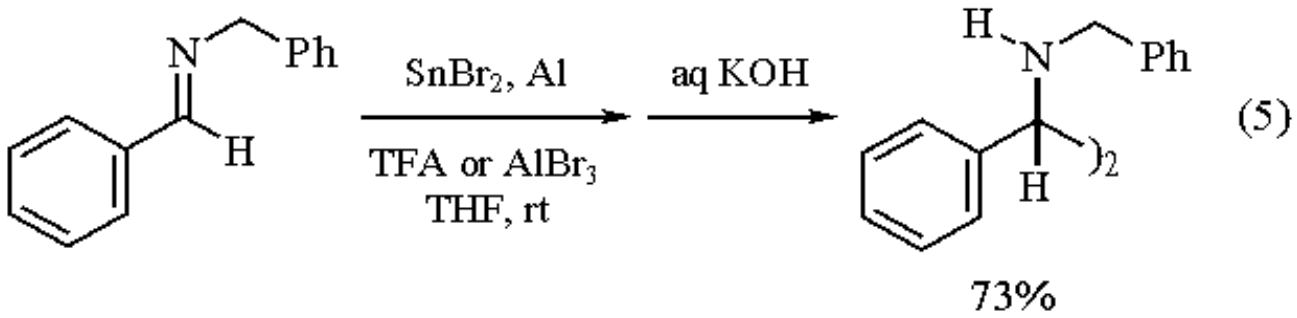

Nucleosides from Acyclic Epoxy Aldehydes.

Acyclic epoxy aldehydes undergo an addition-cyclization process with the tin(II) salts of nucleoside bases in the presence of $SnBr_2$ to yield nucleosides having predominately the α configuration (eq 6).[9] This methodology can be used to prepare stereoselectively 2´-deoxyribonucleosides that are difficult to prepare by other means.

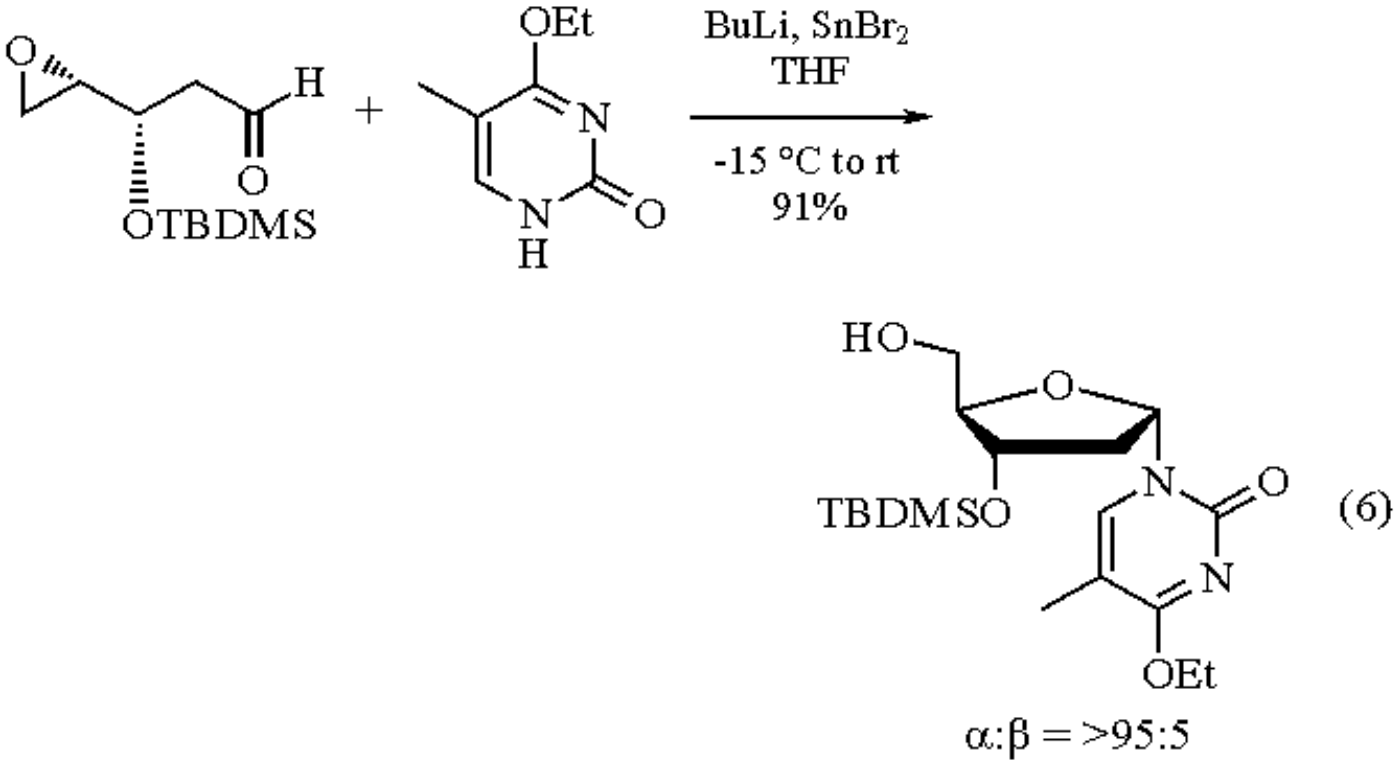

(6)

Reductions.

Aromatic acetals can be reductively halogenated in high yield to give benzylic bromides[1] by employing a catalytic amount of $SnBr_2$ in the presence of ***Triethylsilane*** and excess acetyl bromide. The intermediate bromides can be further reduced with ***Lithium Aluminum Hydride*** or ***Tri-n-butylstannane*** to the corresponding hydrocarbon (eq 7).[10] This methodology has been extended to the reduction of aliphatic and aromatic ketone acetals; however, the product may be contaminated with small amounts of alkene as a byproduct (eq 8). This three-step conversion of ketones and aldehydes to the corresponding alkanes represents a mild and convenient alternative to the Wolff-Kishner and Clemmensen reductions.

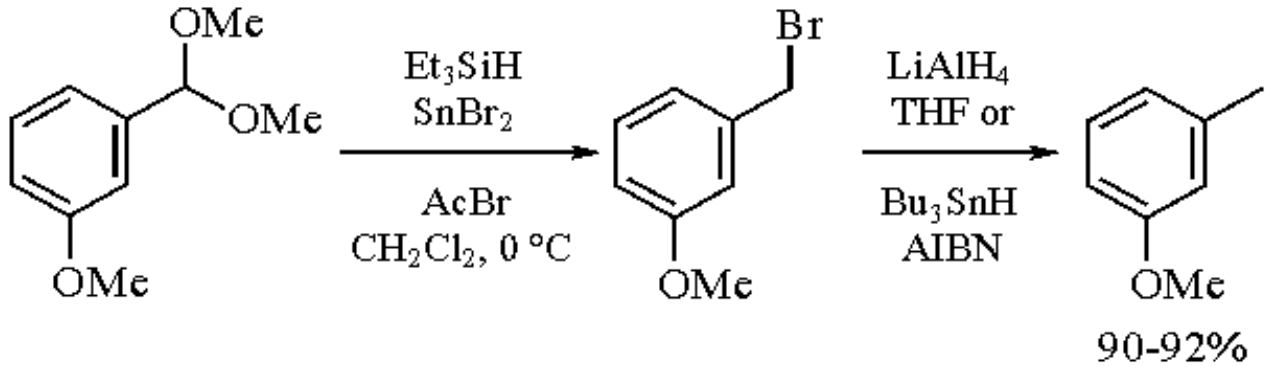

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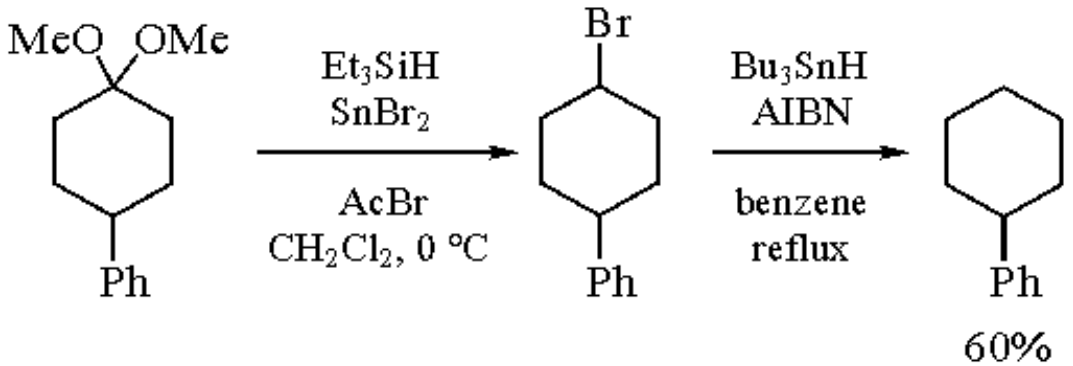

(8)

It has been reported that *m*-bromobenzaldehyde can be prepared by reduction of *m*-nitrobenzaldehyde with $SnBr_2$/HCl, followed by diazotization of the resulting aminoaldehyde with ***Sodium Nitrite***, and treatment of the diazonium ion solution with ***Copper(I) Bromide***/HBr (eq 9).[11] The use of $SnBr_2$ is important in the reduction step because substitution of $SnCl_2$ leads to a product mixture containing up to 20% of *m*-chlorobenzaldehyde.

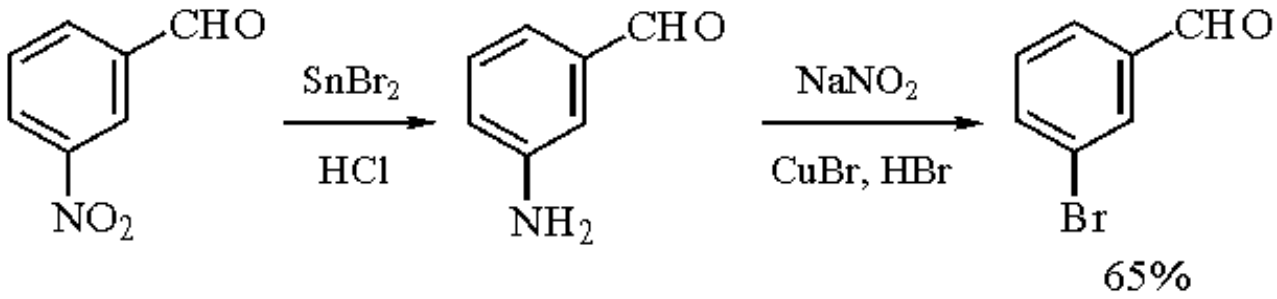

(9)

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Tin(II) Chloride

$SnCl_2$

[7772-99-8] · Cl_2Sn · Tin(II) Chloride · (MW 189.61)

(reducing agent for many functional groups; carbonyl allylation; Lewis acid catalyst in C-C bond-forming reactions; catalyst with $AgClO_4$ for the synthesis of α-glycosides; synthesis of alkenes, dienes, *cis*-vinyloxiranes, and allylic selenides; deoxygenation of 1,4-endoperoxides; protection of carboxylic acids as 1,3-dithianes; selective *p*-methoxybenzyl ether cleavage reagent; additive in hydroformylation and carbonylation reactions[1])

Alternate Name: stannous chloride.

Physical Data: mp 246.8 °C; bp 623 °C; *d* 3.95 g cm^{-3}.

Solubility: insol xylenes; sol water, ethanol, acetone, diethyl ether, methyl acrylate, methyl ethyl ketone, isobutyl alcohol.

Form Supplied in: white crystalline solid; widely available.

Preparative Methods: analytical reagent grade tin(II) chloride is prepared by adding the dihydrate to a vigorously stirred solution of acetic anhydride (120 g salt per 100 g anhydride). After ca. one hour, the anhydrous $SnCl_2$ is filtered on a dry sintered glass or Buchner funnel, washed free from acetic acid with dry Et_2O, and dried in vacuo. It is best stored in a sealed container.[2]

Functional Group Reductions.

$SnCl_2$ is an effective reducing agent under acidic conditions.[3] $SnCl_2$ selectively reduces aromatic nitro compounds under nonacidic and nonaqueous conditions. Nearly quantitative yields of arylamines are obtained by using $SnCl_2.2H_2O$ in ethanol or ethyl acetate, or anhydrous $SnCl_2$ in alcohol at 70 °C. Under these conditions, other reducible or acid sensitive groups such as ketones, esters, nitriles, halogen, oximes, and alkenes are unaffected (eq 1).[4]

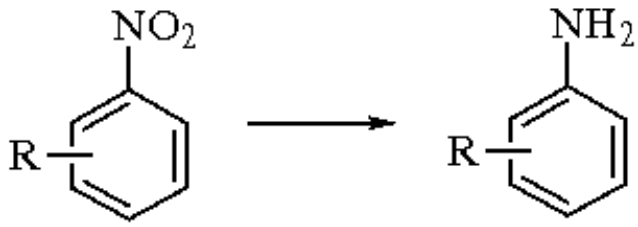

(1)

R = H, Cl, OH, CO_2H, CHO, OMe, CO_2R, OAc

$SnCl_2$ is used in the reduction of nitriles to aldehydes.[5] For example, treatment of the nitrile (**1**) with hydrochloric acid generates the intermediate (**2**). This is reduced with anhydrous $SnCl_2$ to (**3**), which precipitates as a complex with $SnCl_4$ and is then hydrolyzed to the aldehyde (**4**) (eq 2).[2] This protocol, known as the Stephen reaction, is most successful with aromatic nitriles, but it has been reported for aliphatic nitriles with up to six carbons. An alternative procedure in which (**2**) is obtained from the *N*-phenylamide, ArCONHPh, by treatment with ***Phosphorus(V) Chloride*** is known as the Sonn-Müller method.[6] Carboxylic acids can be prepared by reduction of cyanosilyl ethers (**5**) with $SnCl_2$ in AcOH and HCl (eq 3).[7]

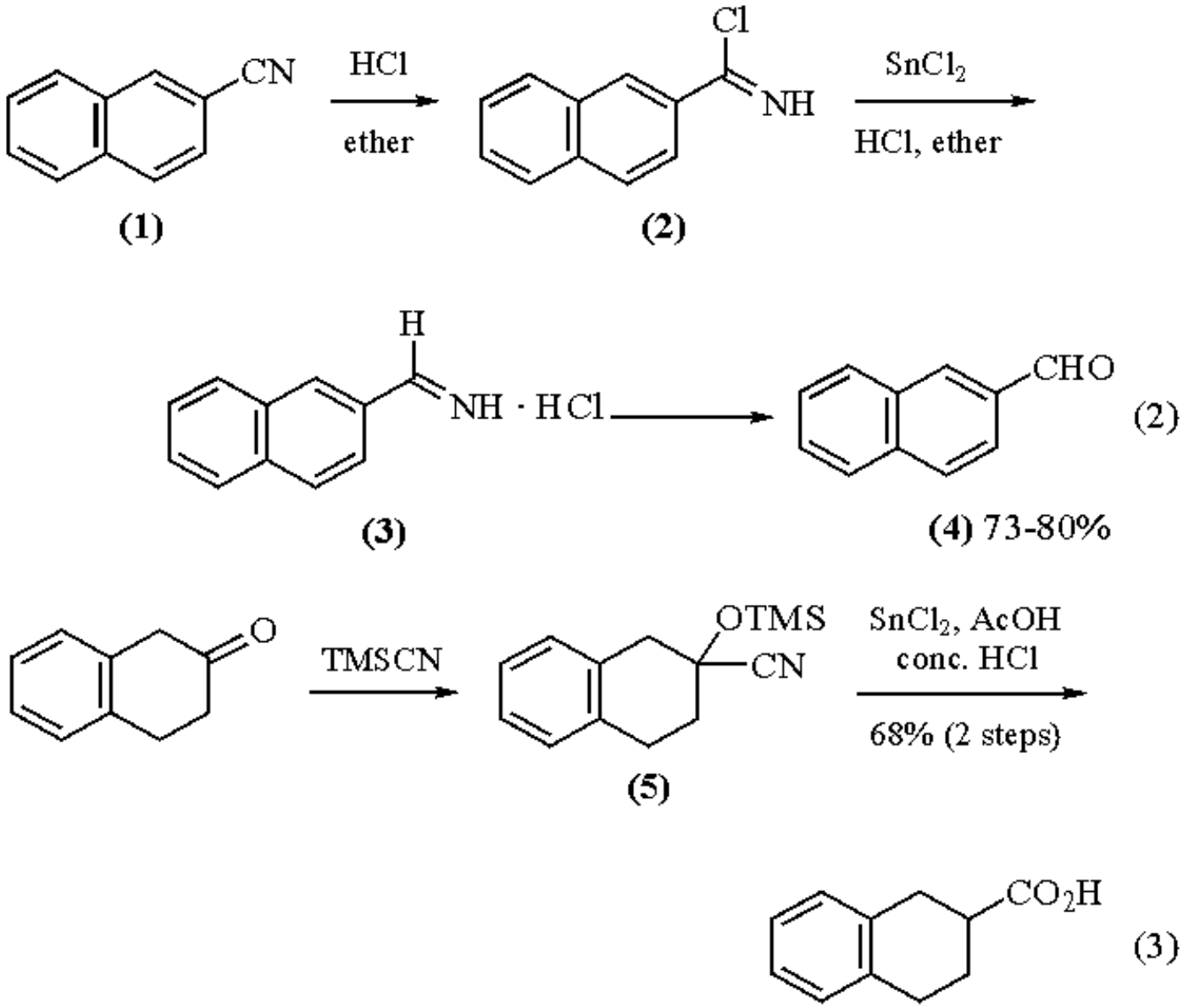

Organic azides are reduced by $SnCl_2$ in methanol to the corresponding amines in 85-98% yield.[8] For less reactive azides, it is necessary to initiate the reaction by adding catalytic amounts of ***Aluminum Chloride***

α-Halo ketones are hydrodehalogenated to the corresponding ketones in good yield using $SnCl_2$ in combination with a variety of additives, e.g. sodium halides (chloride, bromide, iodide) and pseudohalides (thiocyanate, cyanate, chloride),[9] sulfur compounds (NaSH, Na_2S, $NaHSO_3$, Na_2SO_3), and aromatic compounds (benzene, pyridine, aniline) (eq 4).[10] $SnCl_2$ is more effective than other metal halides, such as $SnCl_4$, $FeCl_2$, $AlCl_3$, and $CrCl_3$.

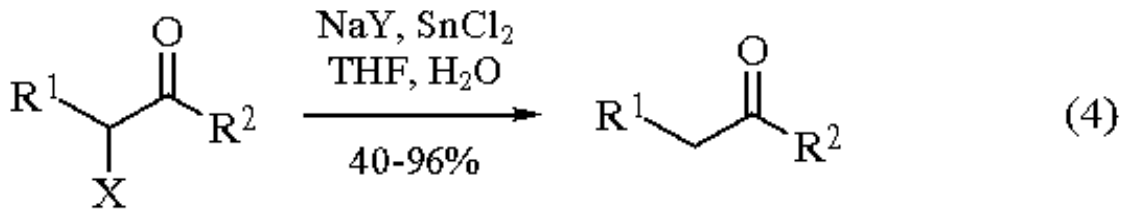

(4)

X = Cl, Br; Y = Cl, Br, I, SCN, OCN, ClO_2, HS, HSO_3, NO_2

Treatment of an α-bromo carbonyl compound with $SnCl_2$ and ***Diethylaluminum Chloride*** effects dehydrohalogenation with formation of an aluminum enolate, which can react with an aldehyde or ketone to give the β-hydroxy carbonyl compound in 61-95% yield, in a modification of the Reformatsky reaction (eq 5).[11] Catalytic quantities of ***Tetrakis(triphenylphosphine)palladium(0)*** promote the reduction and improve the yield of the desired aldol adducts.

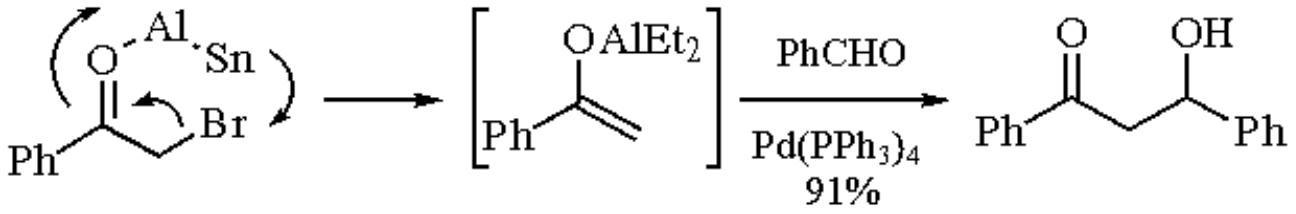

(5)

The reagent prepared from ***Sodium Cyanoborohydride*** and $SnCl_2$ in a 2:1 ratio will reduce tertiary, allyl, and benzyl halides in good yields and is thus comparable to $NaBH_3CN$-$ZnCl_2$. However, other functional groups such as aldehydes, ketones, and acid chlorides are reduced to alcohols. Esters and amides are unaffected.[12]

Carbonyl Reduction.

Asymmetric reduction of prochiral ketones,[13] α-, β-, and γ-keto esters,[14] and prochiral hydroxy ketones[15] can be achieved with a reagent prepared from $SnCl_2$ and ***Diisobutylaluminum Hydride***, in the presence of a chiral diamine derived from (*S*)-proline (eq 6).

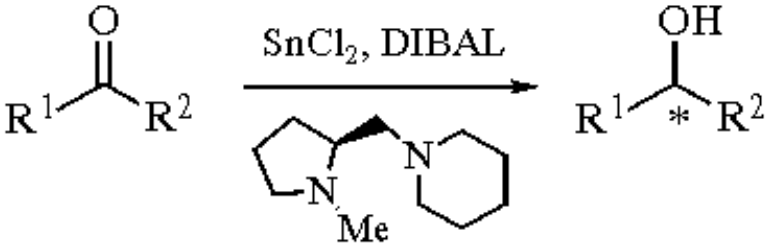

(6)

R^1	R^2	Yield (%)	ee (%)
Bn	Me	71	78
Ph	Me	80	76
Ph	Et	74	74
Ph	CH_2OMEM	81	91
Ph	CO_2MEM	82	89
Me	CO_2MOM	60	48

β-Diketo Ester Synthesis.

Aldehydes are efficiently converted to β-diketo esters in 50-90% yield by addition of ***Ethyl Diazoacetate*** in the presence of $SnCl_2$ (eq 7). Although the reaction can be effected by a variety of Lewis acids, $SnCl_2$, BF_3, and $GeCl_2$ are the most effective.[16]

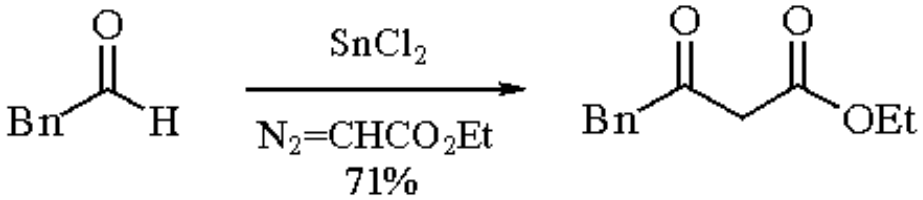

(7)

Treatment of a number of trisubstituted alkenes with ***Ozone*** followed by the addition of $SnCl_2$ and ethyl diazoacetate affords the β-diketo esters in 47-90% yield (eq 8). For monosubstituted alkenes to be successful, they must first be treated with ozone in the presence of methanol to generate methoxy hydroperoxides, which can subsequently be reduced to the β-diketo esters in 47-74% yield.[17] 1,3-Diketones can be prepared in 42-90% yield by $SnCl_2$-catalyzed reaction of α-diazo ketones with aldehydes (eq 9).[18]

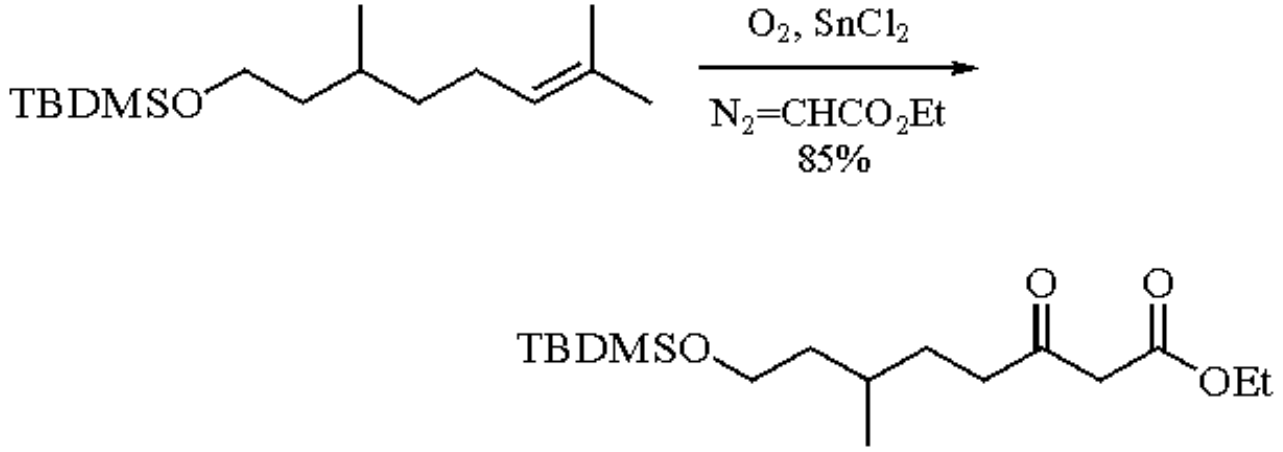

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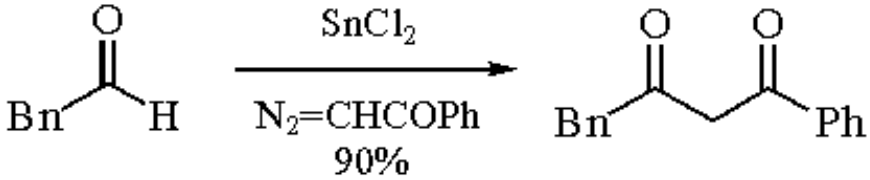

(9)

Diastereoselective Carbonyl Allylation.

High regio- and diastereoselectivity can be achieved in the reaction of cinnamyl chloride with aldehydes using $SnCl_2$ and ***Aluminum***.[19] The reaction proceeds through zerovalent tin and affords the *anti*-adducts with high selectivity (eq 10). Under the same conditions, enals provide 1,2-adducts.

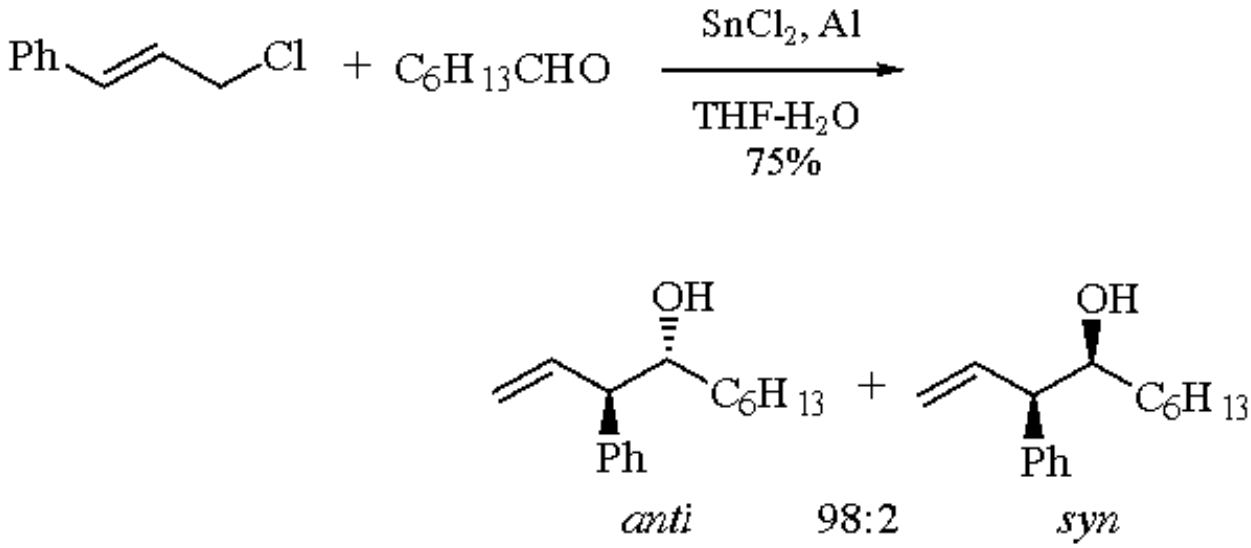

(10)

$SnCl_2$ acts as a reducing agent in the allylation of carbonyl compounds using allylic alcohols and Pd^0; this reaction proceeds through a π-allylpalladium complex (eq 11). The order of reactivity of allylating agents is allylic carbonate > allylic alcohol > allylic acetate, and that of carbonyl compounds is aldehyde > ketone. High regioselectivity is obtained in polar solvents such as DMF, DMI (1,3-dimethyl-2-imidazolidone), and DMSO, where the carbonyl compound attacks the more substituted allylic position of the π-allylpalladium complex.

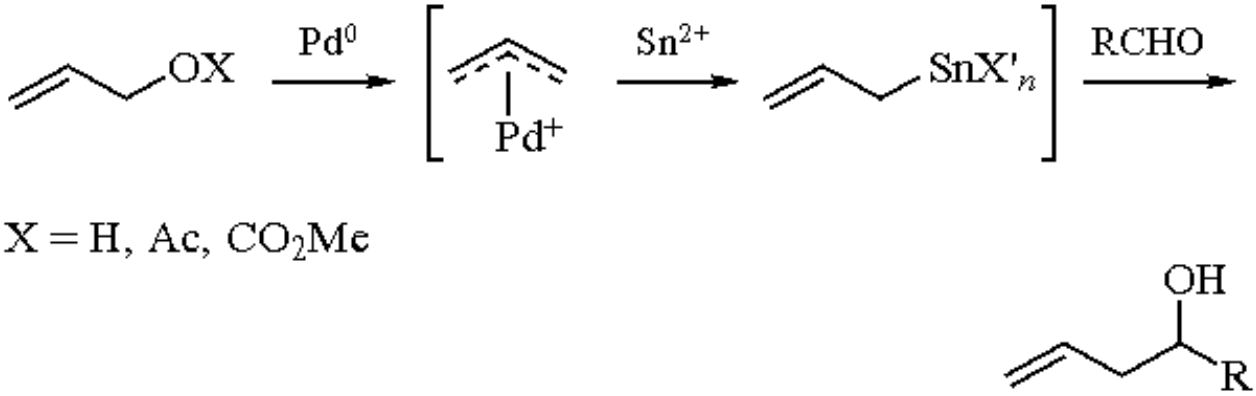

(11)

Diastereocontrol in the Pd-catalyzed carbonyl allylation of allylic alcohols with $SnCl_2$ is dependent on the nature of the solvent. Use of DMSO at 25 °C affords the *syn*-adduct, while *anti* selection is found in THF, DMF, and DMI. The addition of water in any solvent accelerates the rate of the reaction and enhances both regioselectivity and diastereoselectivity (eq 12). For reactions in DMSO-H_2O, the ratio of *syn*:*anti* products can be controlled by the amount of water added to the reaction.[20] SnF_2 and $Sn(OAc)_2$ cannot replace $SnCl_2$ in this allylation reaction.

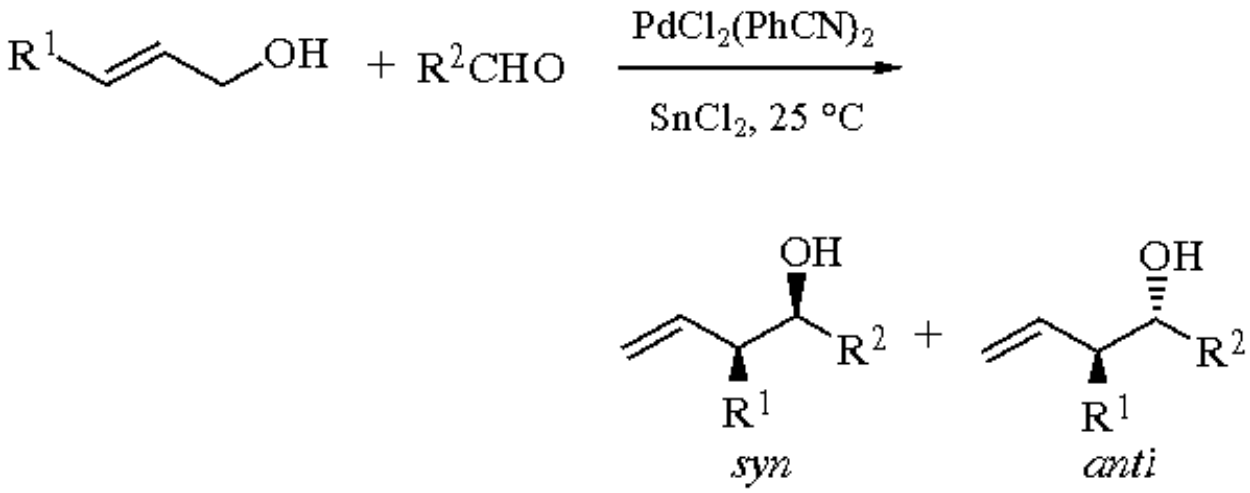

(12)

R^1	R^2	Solvent	Yield (%)	*syn*:*anti*
Me	*p*-$MeO_2CC_6H_4$	DMSO-H_2O	90	77:23
Me	*p*-$MeO_2CC_6H_4$	DMF	99	22:78
Pr	Ph	THF-H_2O	82	20:80
Pr	Ph	DMSO-H_2O	83	70:30
Me	Ph	THF	81	9:91
Me	Ph	DMSO	34	65:35

This reaction has been extended to the synthesis of α-methylene-γ-hydroxy lactones by allylation of carbonyl compounds with ethyl α-(hydroxymethyl)acrylate in DMI/H_2O (eq 13).[21] When the hydroxymethyl group bears an alkyl substituent, the product is obtained with high *syn* selectivity (eq 14).

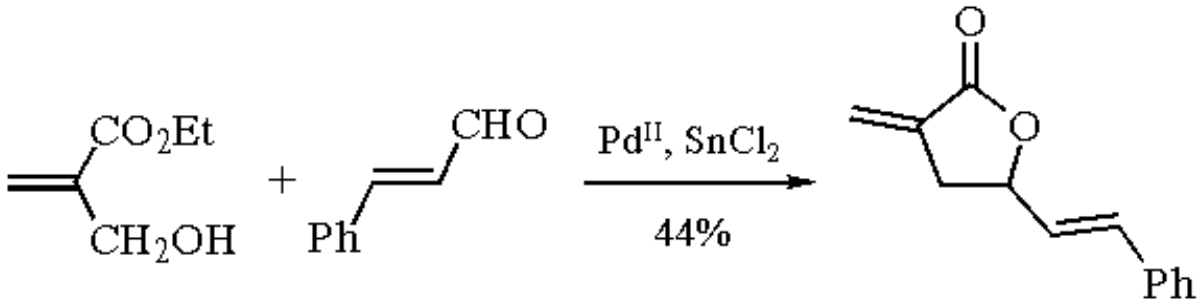

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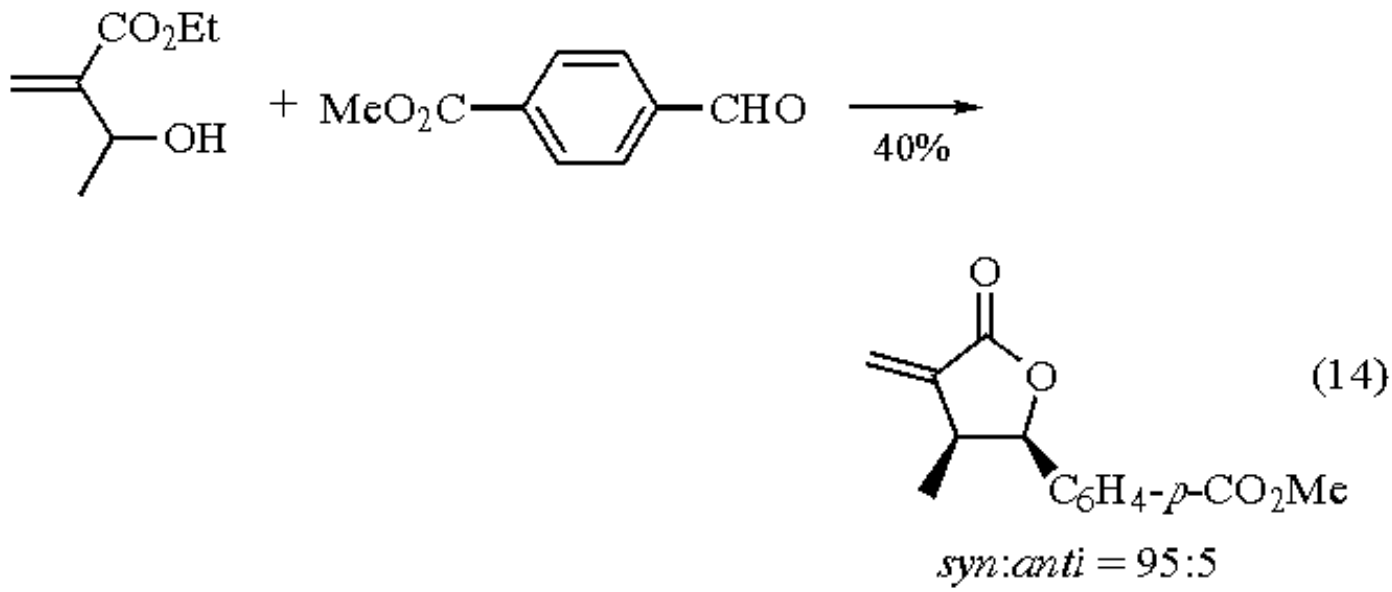

(14)

C-C Bond Formation.

Acetals, aldehydes, orthoesters, and α,β-unsaturated ketones are sufficiently activated by a combination of $SnCl_2$ and ***Chlorotrimethylsilane***[22] or $SnCl_2$ and trityl chloride[23] to react with silyl enol ethers to give the corresponding addition products in 70-97% yield (eq 15). These reagents are also effective in facilitating the reaction of activated alkenes, such as 3,4-dihydro-2*H*-pyran, vinyl ethers, and styrene, with acetals to afford the corresponding adducts in 55-85% yield under extremely mild conditions.[24] $SnCl_2$ facilitates the workup in the ***Titanium(IV) Chloride***-catalyzed reaction of aldehydes with silyl enol ethers by inhibiting β-elimination and formation of polymers (eq 16).[25]

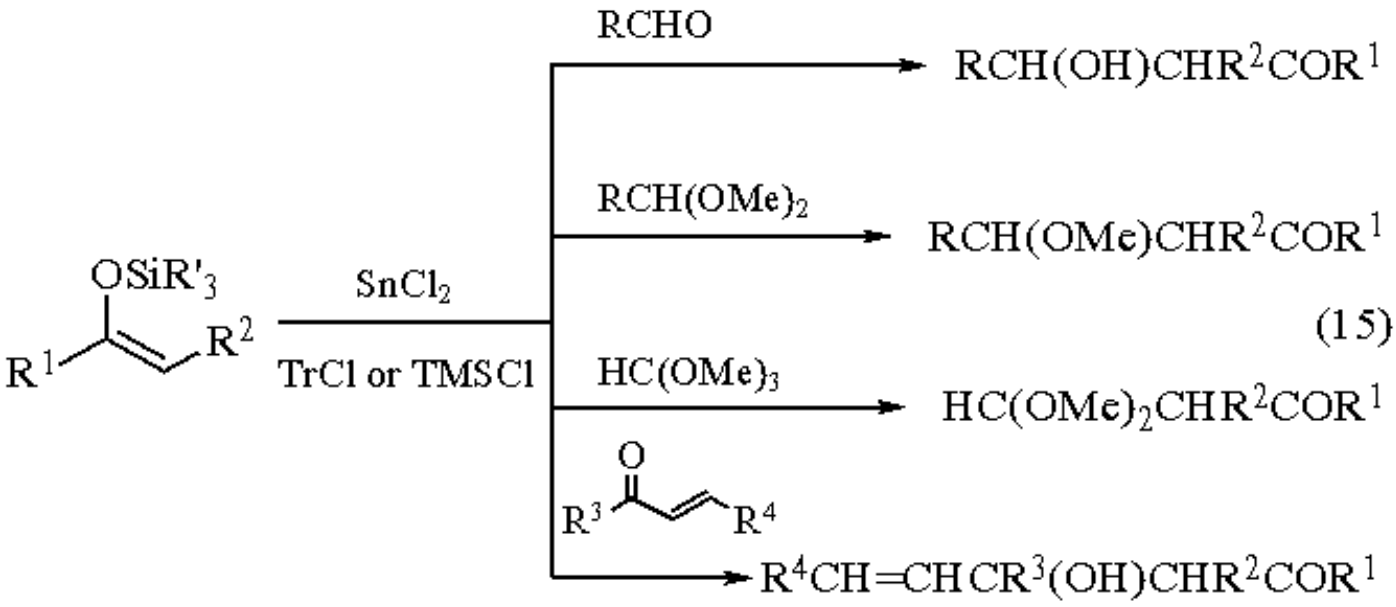

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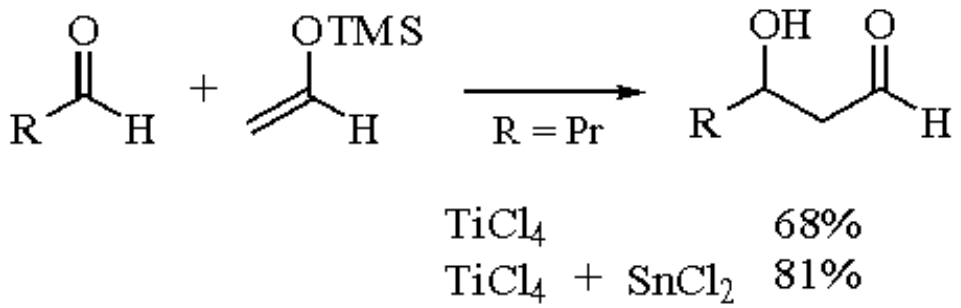

(16)

α-Glycosidation.[26]

α-Glycosides are formed predominantly by reaction of an alcohol with 2,3,4,6-tetra-*O*-benzyl-β-glucosyl fluoride in the presence of ***Tin(II) Chloride-Silver(I) Perchlorate*** (eq 17).

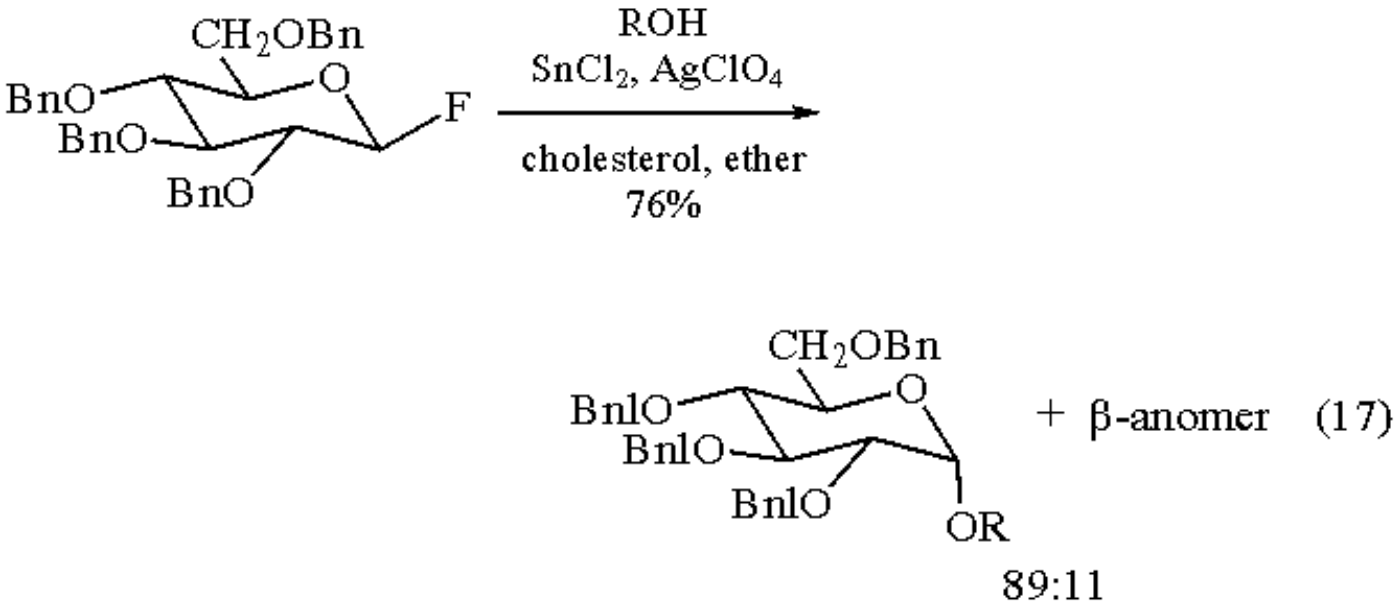

Alkenes and (*E*)-1,3-Dienes.

vic-Dinitro compounds can be denitrated to yield alkenes using either anhydrous $SnCl_2$ or the dihydrate. This method fails for aliphatic *vic*-dinitro compounds.[27] Alkenes can also be obtained in good yield from the *vic*-dibromo compounds using $SnCl_2$ and DIBAL (eq 18).[16]

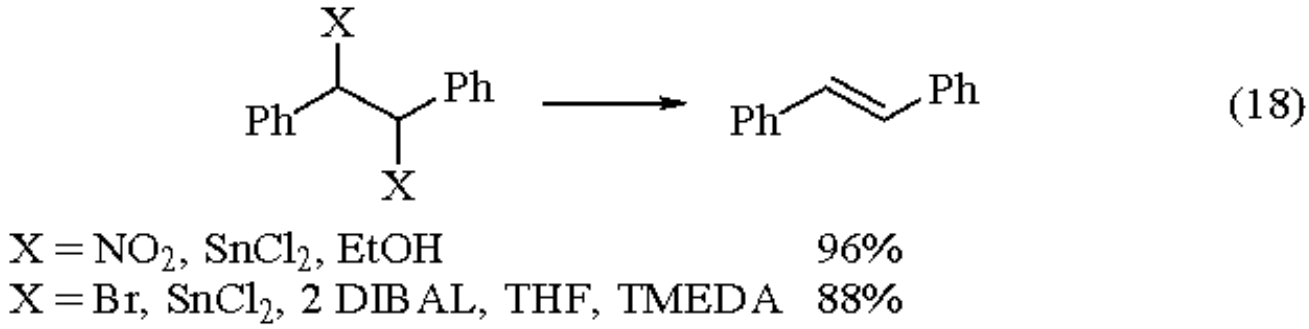

Reaction of a variety of aldehydes with 1-bromo-3-iodopropene in the presence of 2 equiv of $SnCl_2$ yields the corresponding (*E*)-1,3-dienes in 40-70% yield (eq 19).[28] When an enal is employed a terminal conjugated triene is obtained. Treatment of 1-chloro-3-iodopropene with 1 equiv of $SnCl_2$ in DMF, and reaction with an aldehyde followed by NaOMe yieldes *cis*-vinyloxiranes in 51-53% yield (eq 20).[29]

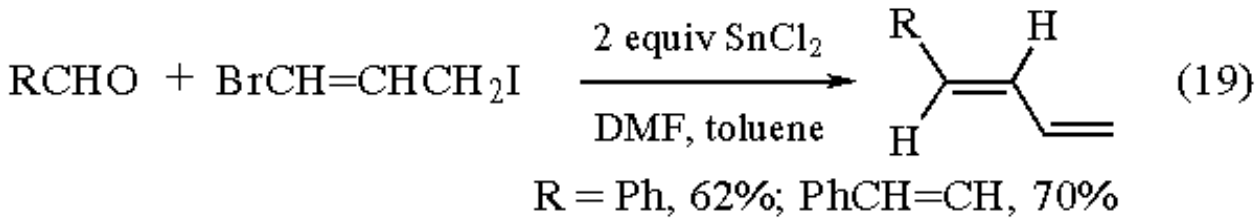

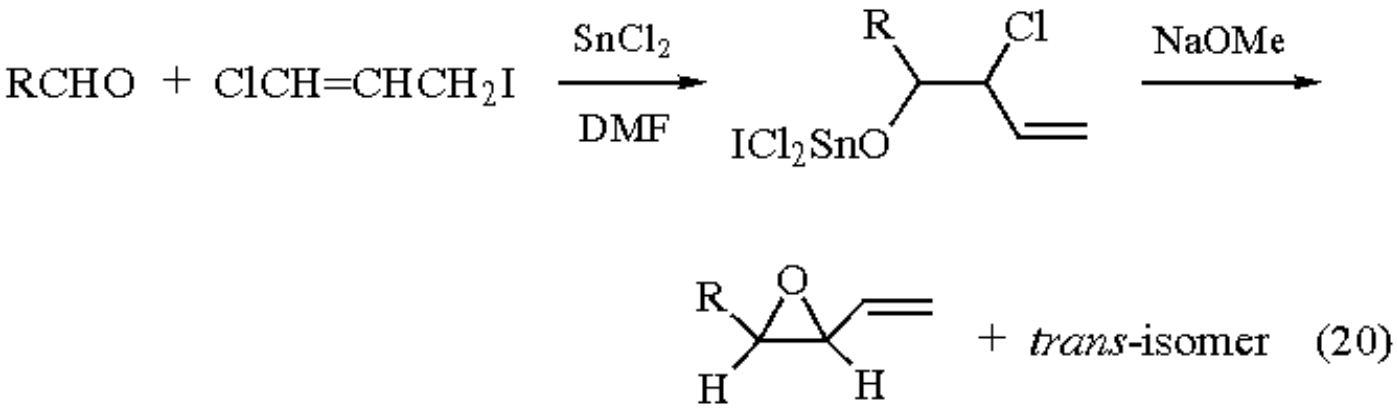

Propargylic iodides form an adduct with $SnCl_2$, which can react with aldehydes to form a mixture of α-hydroxy allenes and β-hydroxy alkynes, in which the former usually predominates. DMI is the preferred solvent (eq 21).[30]

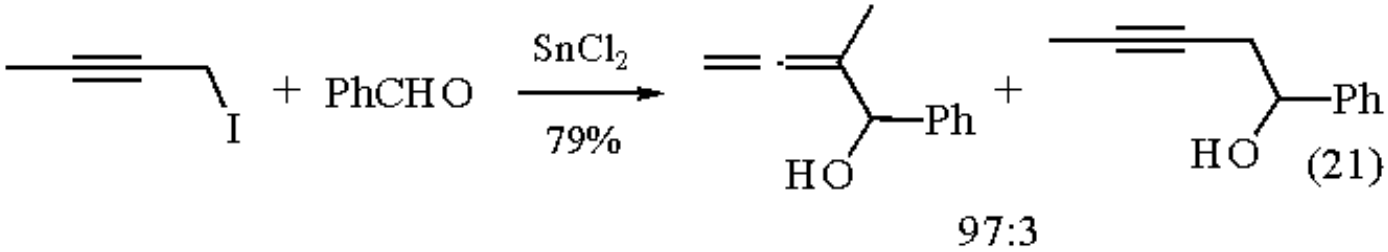

Deoxygenation of 1,4-Endoperoxides of 1,3-Dienes.[31]

1,4-Endoperoxides are converted to the corresponding 1,3-dienes in 15-70% yield using $SnCl_2$ (eq 22).

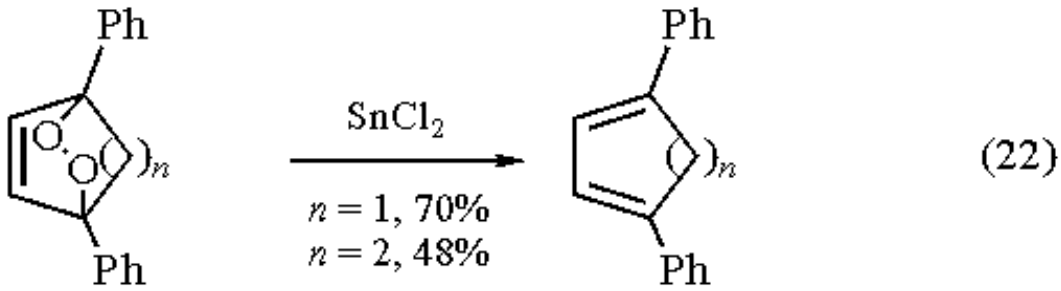

Rearrangements of 2-Hydroxy-3-trimethylsilylpropyl Selenides.[32]

Addition of ***Trimethylsilylmethyllithium*** to α-phenylseleno aldehydes generates 2-hydroxy-3-trimethylsilylpropyl selenides which rearrange in the presence of $SnCl_2$ to allylic selenides (eq 23).

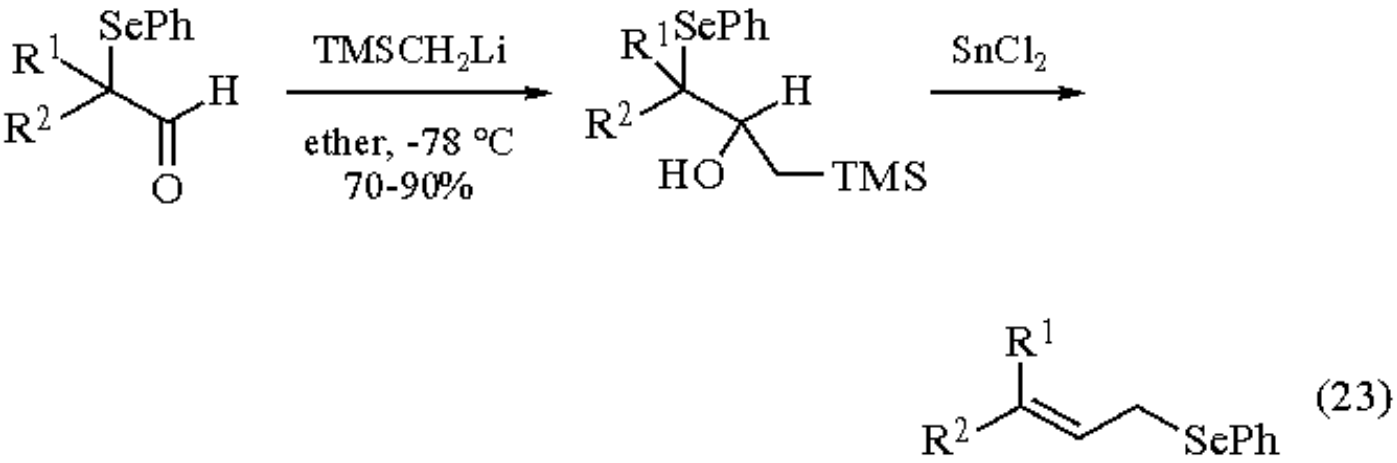

Direct Conversion of Carboxylic Acids into 1,3-Dithianes.[33]

Reactions of carboxylic acids with 1,3,2-dithiaborinane-dimethyl sulfide in the presence of $SnCl_2$ in THF affords the corresponding 1,3-dithianes in high yields. This method is also sufficient to distinguish between carboxylic acids and isolated double bonds (eq 24).

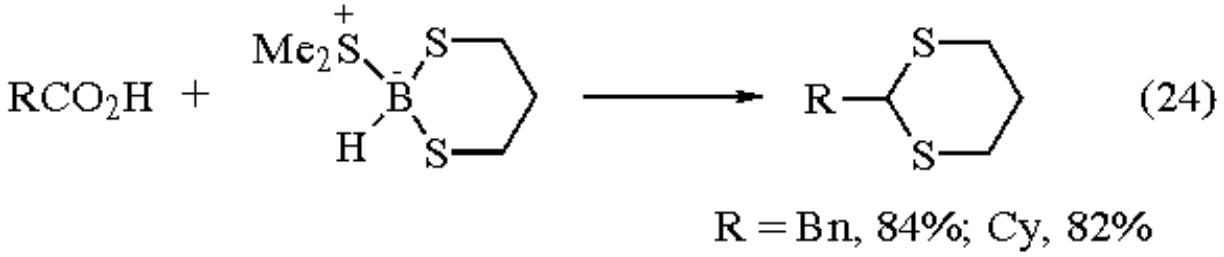

Deprotection.[34]

p-Methoxybenzyl (PMB) ethers can be cleaved selectively in the presence of benzyl ethers by employing TMSCl/anisole and a catalytic amount of $SnCl_2$ (eq 25).

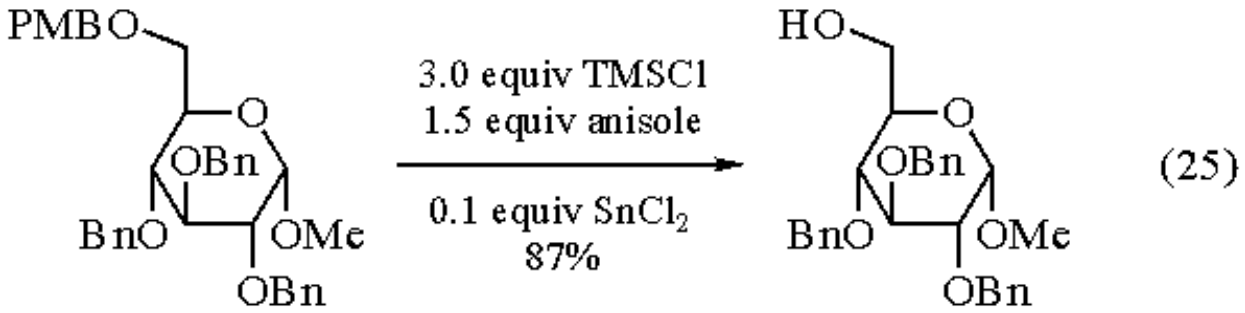

Related Reagents.

Cerium(III) Chloride-Tin(II) Chloride; ***Dichlorobis(triphenylphosphine)platinum(II)-Tin(II) Chloride***.

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Margaret M. Faul

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Tin(IV) Chloride

$SnCl_4$

[7646-78-8] · Cl_4Sn · Tin(IV) Chloride · (MW 260.51)

(strong Lewis acid used to promote nucleophilic additions, pericyclic reactions, and cationic rearrangements; chlorination reagent)

Alternate Name: stannic chloride.

Physical Data: colorless liquid; mp -33 °C; bp 114.1 °C; *d* 2.226 g cm^{-3}.

Solubility: reacts violently with water; sol cold H_2O; dec hot H_2O; sol alcohol, Et_2O, CCl_4, benzene, toluene, acetone.

Form Supplied in: colorless liquid; 1 M soln in CH_2Cl_2 or heptane; widely available.

Purification: reflux with mercury or P_2O_5 for several hours, then distill under reduced nitrogen pressure into receiver with P_2O_5. Redistill. Typical impurities: hydrates.

Handling, Storage, and Precautions: hygroscopic; should be stored in a glove box or over P_2O_5 to minimize exposure to moisture. Containers should be flushed with N_2 or Ar and tightly sealed. Perform all manipulations under N_2 or Ar. Solvating with H_2O liberates much heat. Use in a fume hood.

Introduction.

$SnCl_4$ is used extensively in organic synthesis as a Lewis acid for enhancing a variety of reactions. $SnCl_4$ is classified as a strong Lewis acid according to HSAB theory, and therefore interacts preferentially with hard oxygen and nitrogen bases. Six-coordinate 1:2 species and 1:1 chelates are the most stable coordination complexes, although 1:1 five-coordinate species are also possible.[1] $SnCl_4$ can be used in stoichiometric amounts, in which case it is considered a promoter, or in substoichiometric amounts as a catalyst, depending upon the nature of the reaction. $SnCl_4$ is an attractive alternative to boron, aluminum, and titanium Lewis acids because it is monomeric, highly soluble in organic solvents, and relatively easy to handle. $SnCl_4$ and $TiCl_4$ are among the most common Lewis acids employed in chelation control strategies for asymmetric induction. However, $SnCl_4$ is not often the Lewis acid of choice for optimum selectivities and yields.

$SnCl_4$ is also the principal source for alkyltin chlorides, R_nSnCl_{4-n}.[2] Allyltrialkyltin reagents react with $SnCl_4$ to produce allyltrichlorotin species through an S_E2' pathway (eq 1).[3] Silyl enol ethers react with $SnCl_4$ to give α-trichlorotin ketones (eq 2).[4] Transmetalation or metathesis reactions of this type are competing pathways to nucleophilic addition reactions where $SnCl_4$ is present as an external Lewis acid. As a consequence, four important experimental variables must be considered when using $SnCl_4$ as a promoter: (1) the stoichiometry between the substrate and the Lewis acid; (2) the reaction temperature; (3) the nature of the Lewis base site(s) in the substrate; and (4) the order of addition. These variables influence the reaction pathway and product distribution.[5]

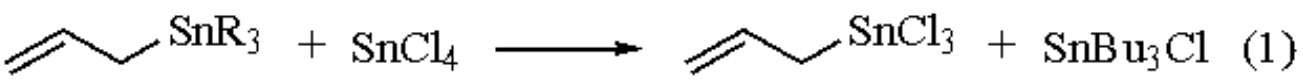

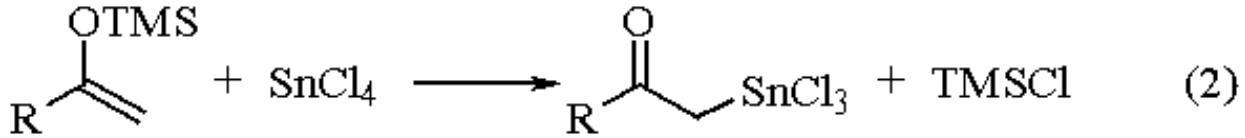

Nucleophilic Additions to Aldehydes.

$SnCl_4$ is effective in promoting the addition of nucleophiles to simple aldehydes. Among the most synthetically useful additions are allylstannane and -silane additions. The product distribution in the stannane reactions can be influenced by the order of addition, stoichiometry, and reaction temperature. The *anti* geometry of the tin-aldehyde complex is favored due to steric interactions. Furthermore, the six-coordinate 2:1 complex is most likely the reactive intermediate in these systems. The use of crotylstannanes provides evidence for competing transmetalation reaction pathways (eq 3).[6] Superior selectivities are provided by ***Titanium(IV) Chloride***.

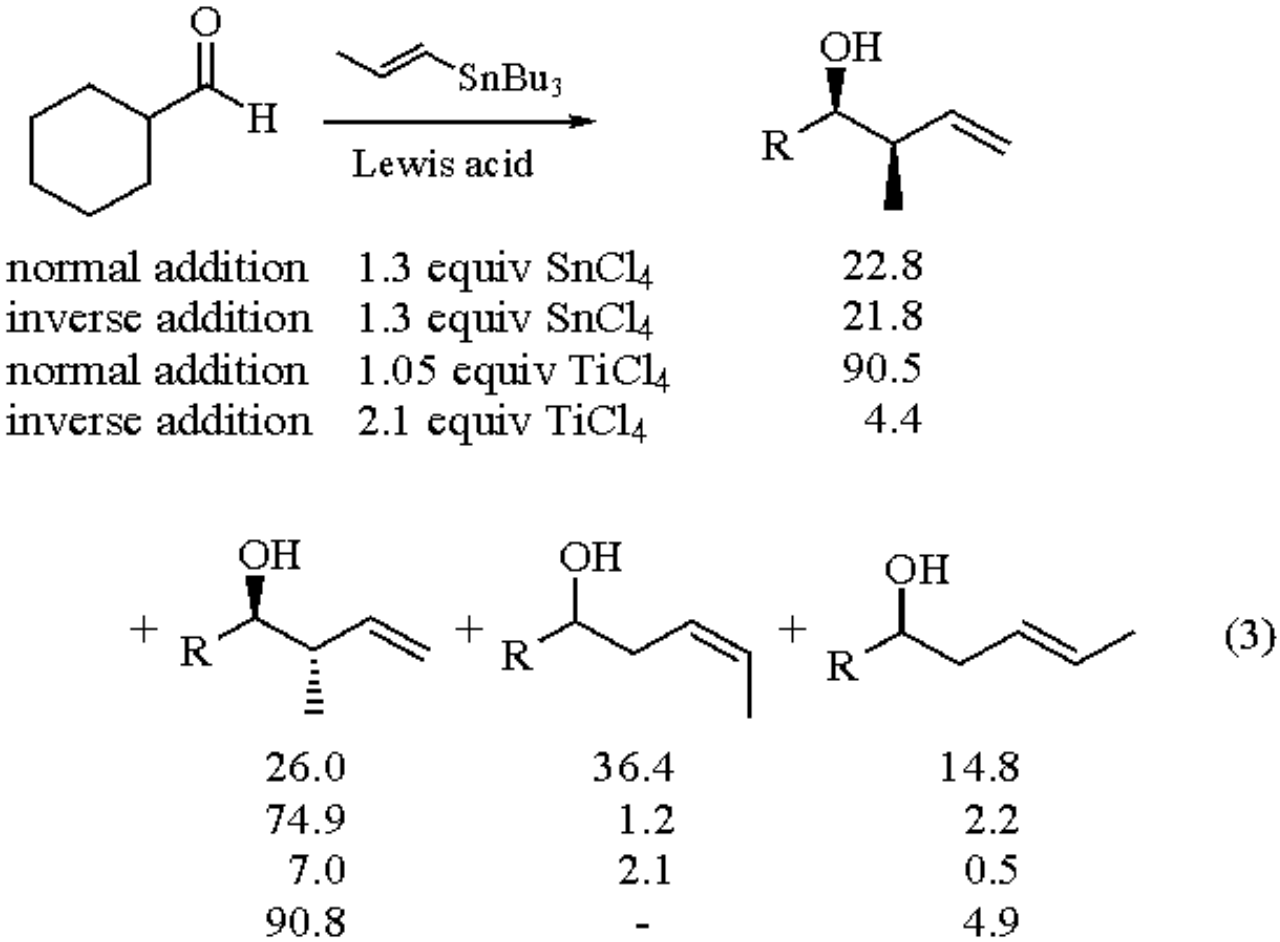

The presence of additional Lewis base sites within the molecule can result in the formation of chelates with $SnCl_4$ or $TiCl_4$, which can lead to 1,2- or 1,3-asymmetric induction with the appropriate substitution at the C-2 or C-3 centers. NMR studies have provided a basis for explaining the levels of diastereofacial selectivity observed in nucleophilic additions to Lewis acid chelates of β-alkoxy aldehydes with substitution at the C-2 or C-3 positions.[7] These studies reveal that $SnCl_4$ chelates are dynamically unstable when substrates are sterically crowded at the alkoxy center, thus enhancing the formation of 2:1 complexes and/or competing metathesis pathways. Furthermore, for β-siloxy aldehydes, the 2:1 $SnCl_4$ complex is formed preferentially over the corresponding chelate.[8]

Mukaiyama Aldol Additions.

Lewis acid-promoted additions of a chiral aldehyde to a silyl enol ether or silyl ketene acetal (the Mukaiyama[9] aldol addition) occurs with good diastereofacial selectivity.[10] The reaction has been investigated with nonheterosubstituted aldehydes, α- and β-alkoxy aldehydes,[11] α- and β-amino aldehydes,[12] and thio-substituted aldehydes.[13] High diastereoselectivity is observed in the $SnCl_4$- or $TiCl_4$-promoted aldol addition of silyl enol ethers to α- and β-alkoxy aldehydes. Prior chelation of the aldehyde before addition of the enol silane is important because certain enol silanes interact with $SnCl_4$ to produce α-trichlorostannyl ketones, which provide lower selectivity.[14] Simple diastereoselectivity is independent of the geometry of the enol silane, and the reaction does not proceed through prior Si-Ti or Si-Sn exchange. Good *anti* selectivities (up to 98:2) are obtained in the $SnCl_4$-promoted reactions of chiral α-thio-substituted aldehydes only with α-phenylthio-substituted aldehydes (eq 4). Stereorandom results are obtained with $SnCl_4$ when other alkylthio-substituted aldehydes, such as α-isopropylthio-substituted aldehydes, are used. ***Boron Trifluoride Etherate*** catalysis gives better *anti* selectivities than $SnCl_4$ for aldehydes with smaller alkylthio substituents. Excellent *syn* selectivities are obtained for α-thio-substituted aldehydes with $TiCl_4$.

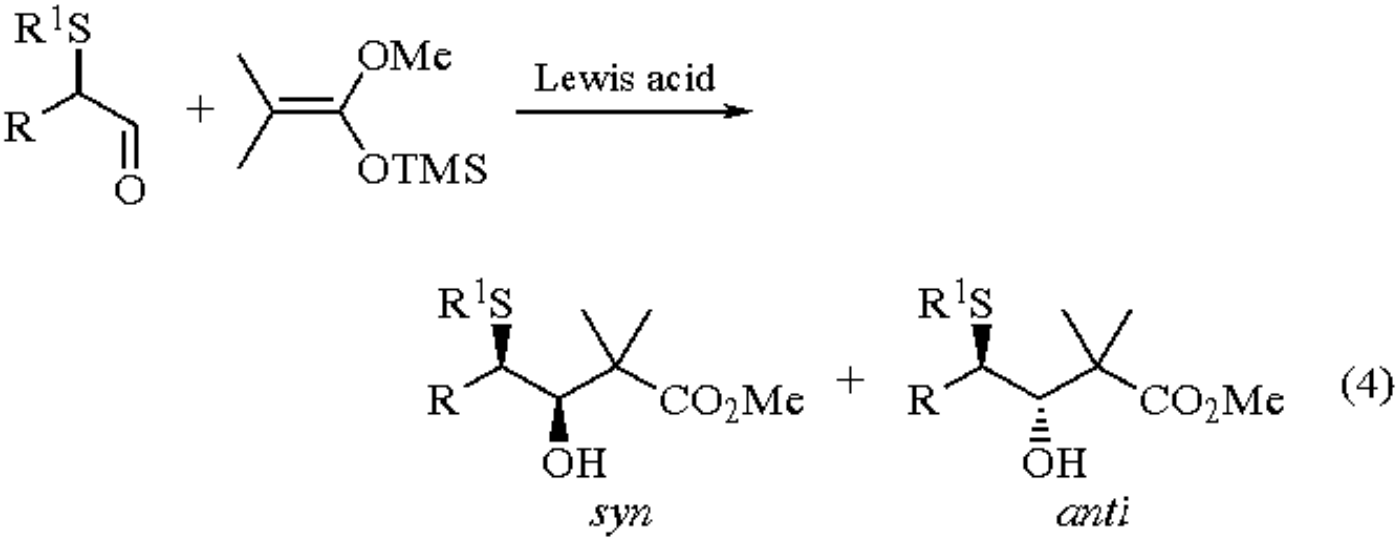

Additions to Nitriles.

$SnCl_4$-promoted addition of malonates and bromomalonates to simple nitriles (not electron deficient) gives α,β-dehydro-β-amino acid derivatives (eq 5).[15] $SnCl_4$ is the Lewis acid of choice for the condensation of aroyl chlorides with sodium isocyanate, affording aroyl isocyanates in 70-85% yields.[16] Nonaromatic acyl chlorides react under more variable reaction conditions.

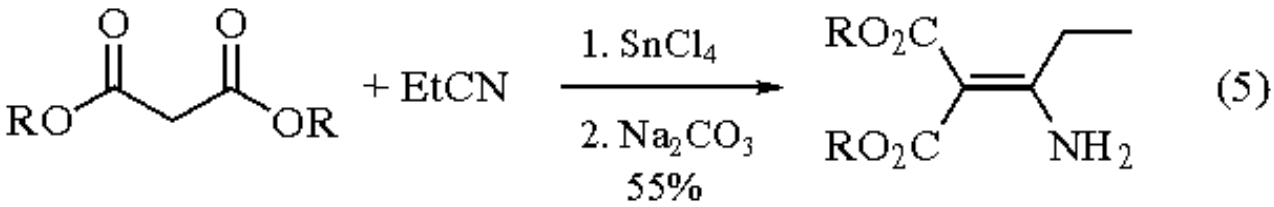

Hydrochlorination of Allenic Ketones.

$SnCl_4$ is also a source for generating chloride anions which form new carbon-chlorine bonds. This occurs through a ligand exchange pathway which has been exploited in the formation of β-chloro enones from conjugated allenic ketones (eq 6).[17] Yields range from 36-82% with complete selectivity for the *trans* geometry. A variety of substituents (R^1, R^2) can be tolerated including aryl, rings, and alkoxymethyl groups (R^1).

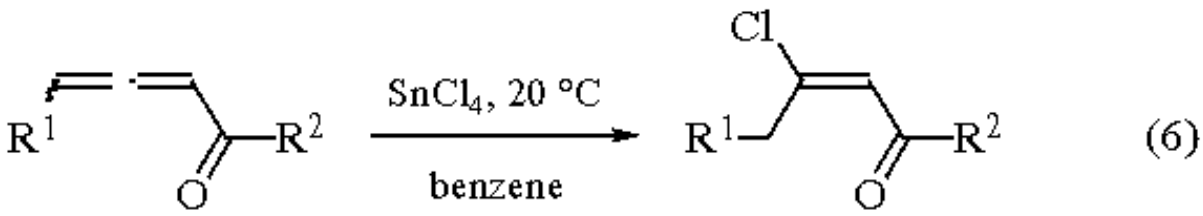

Glycosylations.

The reaction of glycofuranosides having a free hydroxyl group at C-2 with functionalized organosilanes, in the presence of $SnCl_4$, provides *C*-glycosyl compounds in high stereoselectivity (eq 7).[18] Organosilanes such as 4-(chlorodimethylsilyl)toluene, chlorodimethylvinylsilane, ***Allyltrimethylsilane***, and allylchlorodimethylsilane are effective reagents. The presence of a leaving group on the silane is essential for good selectivity since the reaction proceeds intramolecularly through a 2-*O*-organosilyl glycoside. The availability of furanosides in the ribo, xylo, and arabino series make this reaction valuable for the stereoselective synthesis of *C*-furanosides. Regioselective glycosylation of nitrogen-containing heterocycles is also effectively promoted by $SnCl_4$, and has been used in the synthesis of pentostatin-like nucleosides, such as (**1**).[19]

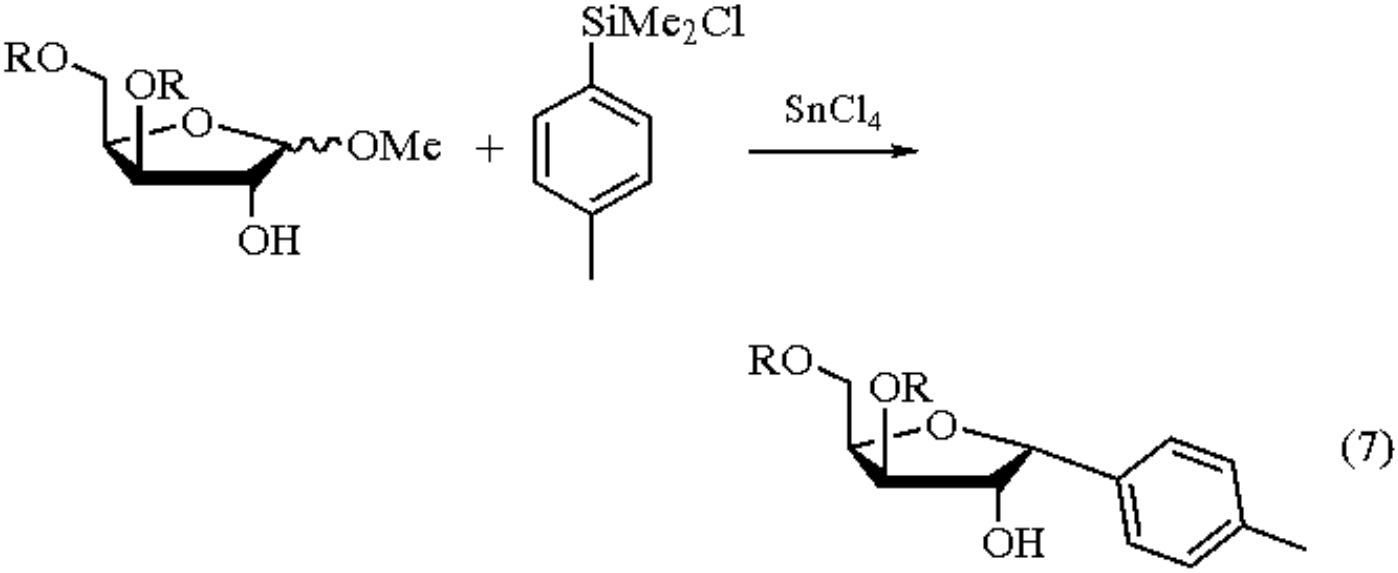

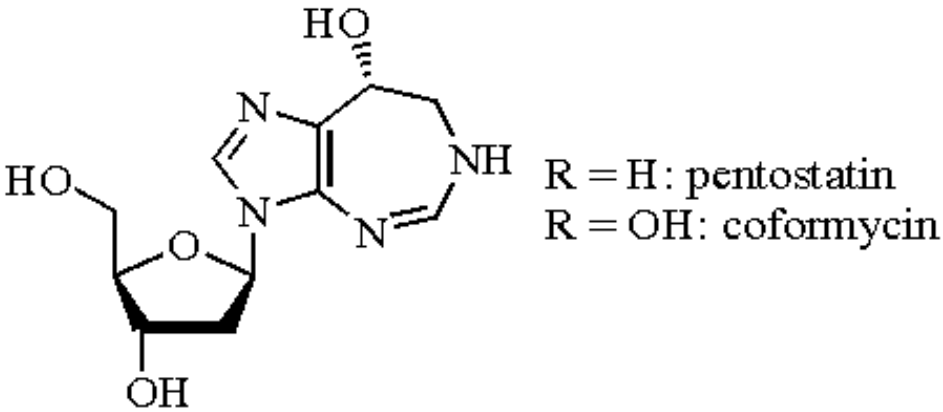

(1)

Selective De-*O*-benzylation.

Regioselective de-*O*-benzylation of polyols and perbenzylated sugars is achieved with organotin reagents or other Lewis acids.[20,21] The equatorial *O*-benzyl group of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose is selectively cleaved by $SnCl_4$ or $TiCl_4$ (eq 8).[2] The equatorial *O*-benzyl group is also selectively cleaved when one of the axial *O*-benzyl groups is replaced by an *O*-methyl group. The 2-*O*-benzyl group of 1,2,3-tris(benzyloxy)propane is selectively cleaved (eq 9), but no debenzylation is observed with 1,2-bis(benzyloxy)ethane.

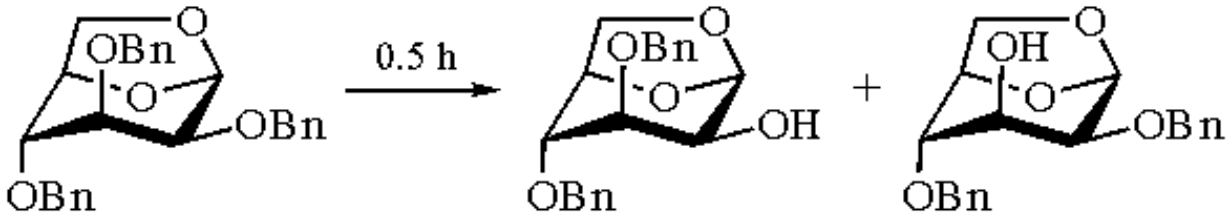

$SnCl_4$	92%	5%
$TiCl_4$	77%	19%

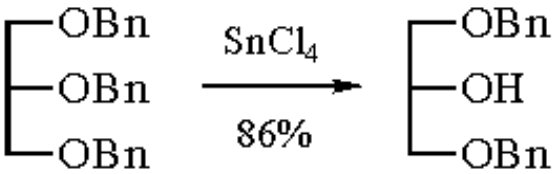

(9)

Rearrangement of Allylic Acetals.

Lewis acid-promoted ($SnCl_4$ or ***Diethylaluminum Chloride***) rearrangements of allylic acetals provide substituted tetrahydrofurans.[22] Upon addition of Lewis acid, (**2**) rearranges to the *all-cis* furan (**3**) (eq 10). No racemization is observed with optically active allylic acetals; however, addition of KOH completely epimerizes the furan-carbonyl bond, as does quenching at room temperature. Acetals successfully undergo similar rearrangement provided the alkene is substituted. Completely substituted tetrahydrofurans are synthesized stereoselectively (>97% ee) by the rearrangement of disubstituted allyl acetals (eq 11). This reaction is related to the acid-catalyzed rearrangements of 5-methyl-5-vinyloxazolidines to 3-acetylpyrrolidines, which involves an aza-Cope rearrangement and Mannich cyclization.[23]

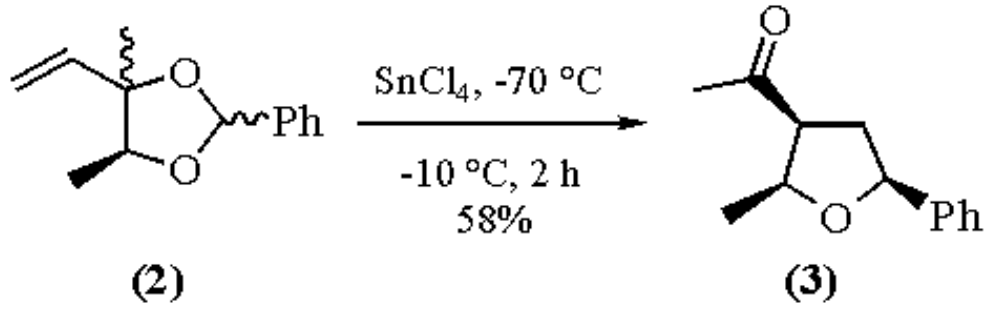

(10)

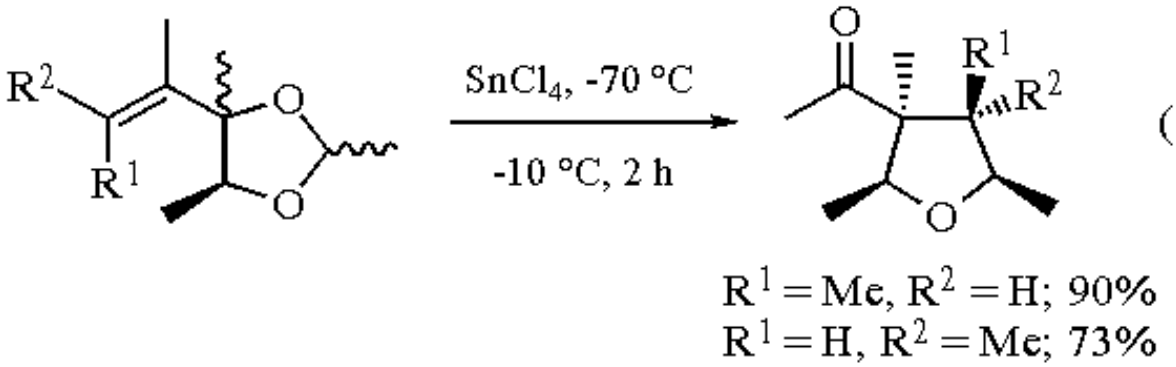

(11)

The rearrangement is also useful for furan annulations, through enlargement of the starting carbocycle.[24] Thus addition of $SnCl_4$ to either diastereomer of the allylic acetal (**4**) produces the *cis*-fused cycloheptatetrahydrofuran (**5**) in 48-76% yield (eq 12). Acetals derived from *trans*-diols rearrange to the same *cis*-fused bicyclics in higher yield. The stereochemistry of a terminal alkene is transmitted to the C-3 carbon of the bicyclic products (eq 13). Rearrangements of acetals require substitution at the internal alkene carbon.

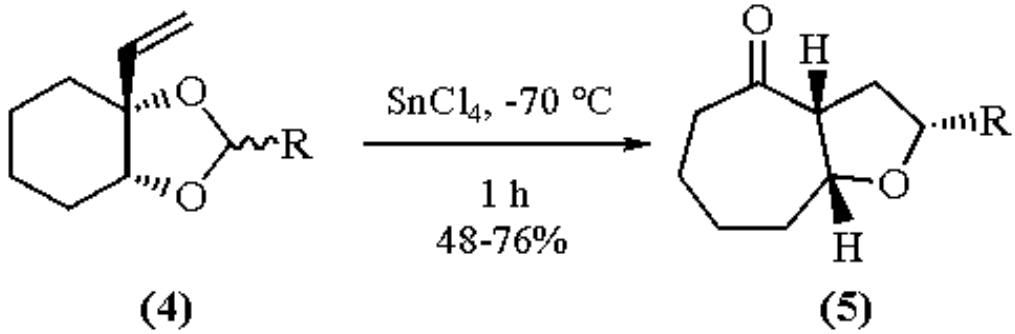

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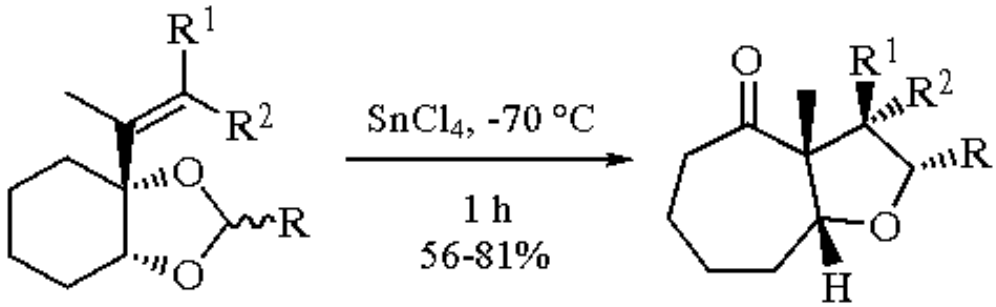

(13)

α-*t*-Alkylations.

$SnCl_4$-promoted α-*t*-alkylations of alkenyl β-dicarbonyl compounds is a particularly useful cyclization reaction.[25] Cyclization occurs through initial formation of a stannyl enol ether, followed by protonation of the alkene to form a carbocation which undergoes subsequent closure (eq 14). The analogous α-*s*-alkylation reactions are best catalyzed by other Lewis acids.

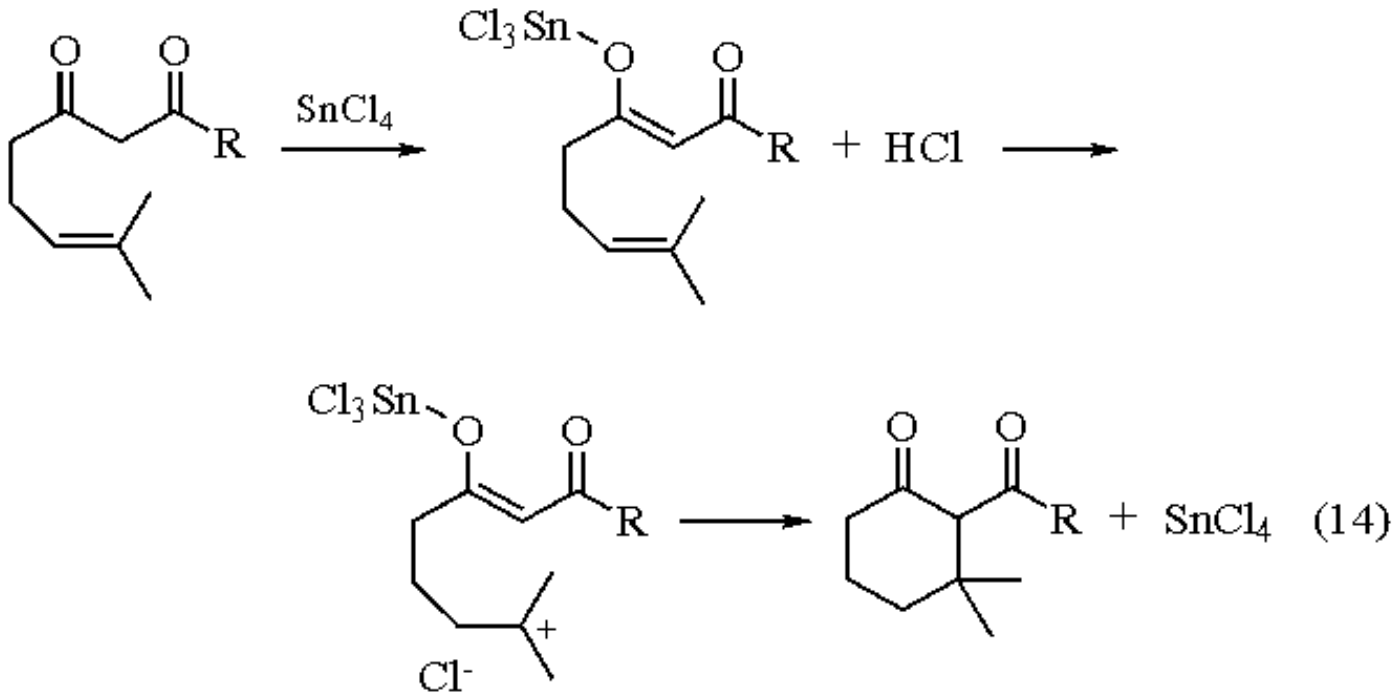

This reaction is useful for cyclizations involving 6-*endo*-trigonal (eq 14) and allowed 7-*endo* trigonal processes (eq 15), but not for those involving 5-*endo* trigonal processes (eq 16). These observations are consistent with the Baldwin rules.

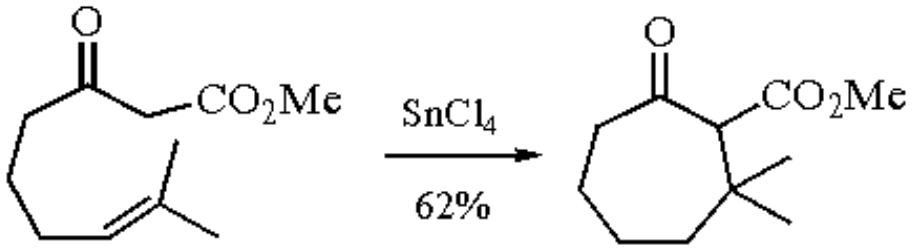

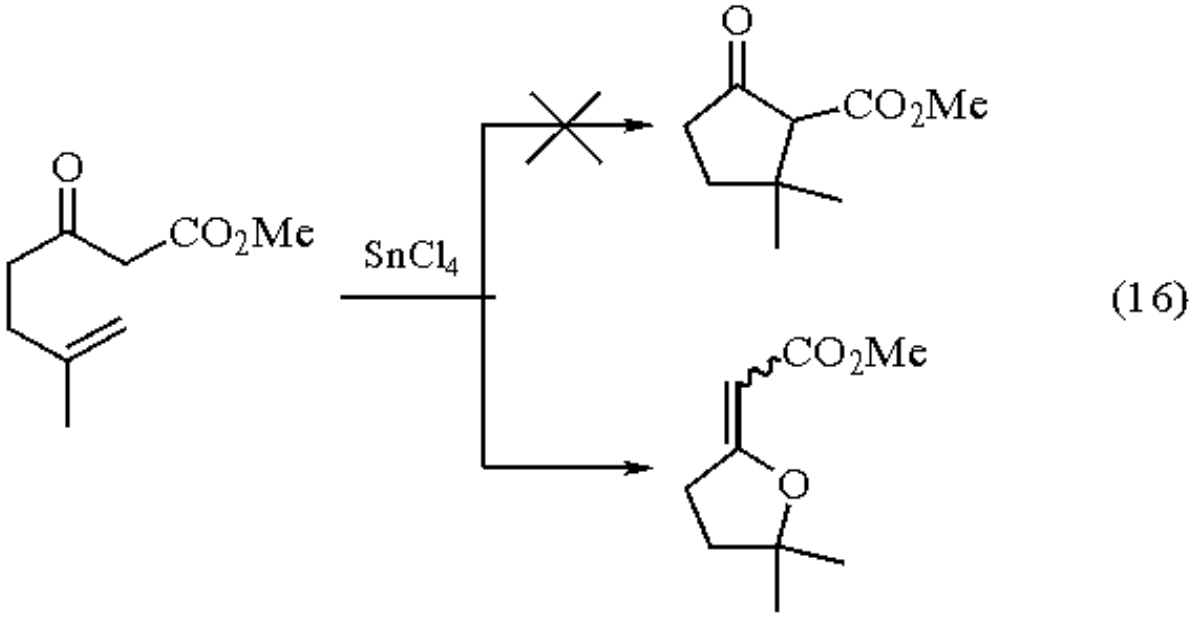

Reactions involving 4- and 6-*exo* trigonal cyclizations result in poor yields or undesired products, while those involving 5-*exo* trigonal cyclizations produce higher yields (eq 17). This synthetic strategy can also be used to form bicyclic and spiro compounds (eqs 18 and 19).

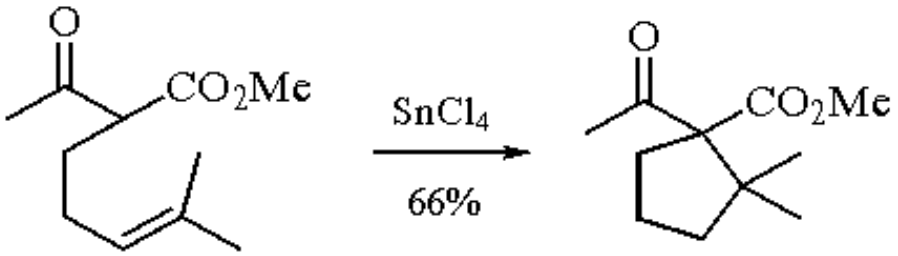

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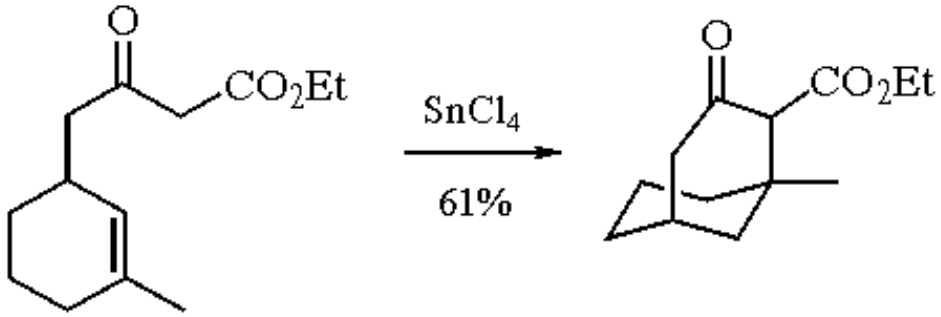

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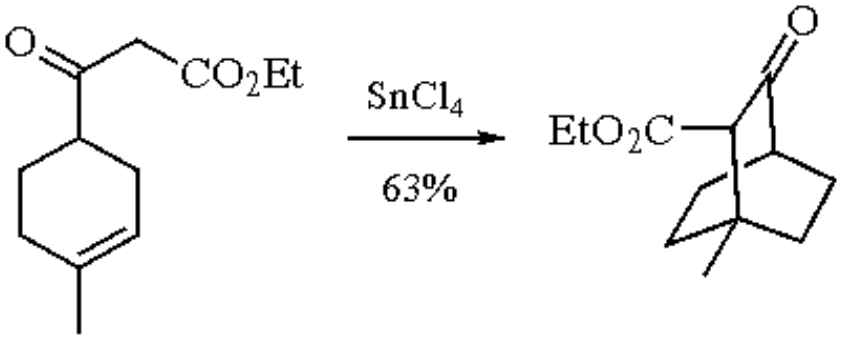

(19)

Alkene Cyclizations.

Cationic cyclizations of polyenes, containing initiating groups such as cyclic acetals, are promoted by $SnCl_4$ and have been utilized in the synthesis of *cis*- and *trans*-decalins, *cis*- and *trans*-octalins, and tri- and tetracyclic terpenoids and steroids.[26] In most instances, *all-trans*-alkenes yield products with *trans,anti,trans* stereochemistry (eq 20), while *cis*-alkenes lead to *syn* stereochemistry at the newly formed ring junctions. The stereoselectivity of polyene cyclizations are often greatly diminished when the terminating alkene is a vinyl group rather than an isopropenyl group. Acyclic compounds which contain terminal acyclic acetals and alkenes or vinylsilanes can be cyclized in a similar fashion to yield eight- and nine-membered cyclic ethers (eq 21).[27]

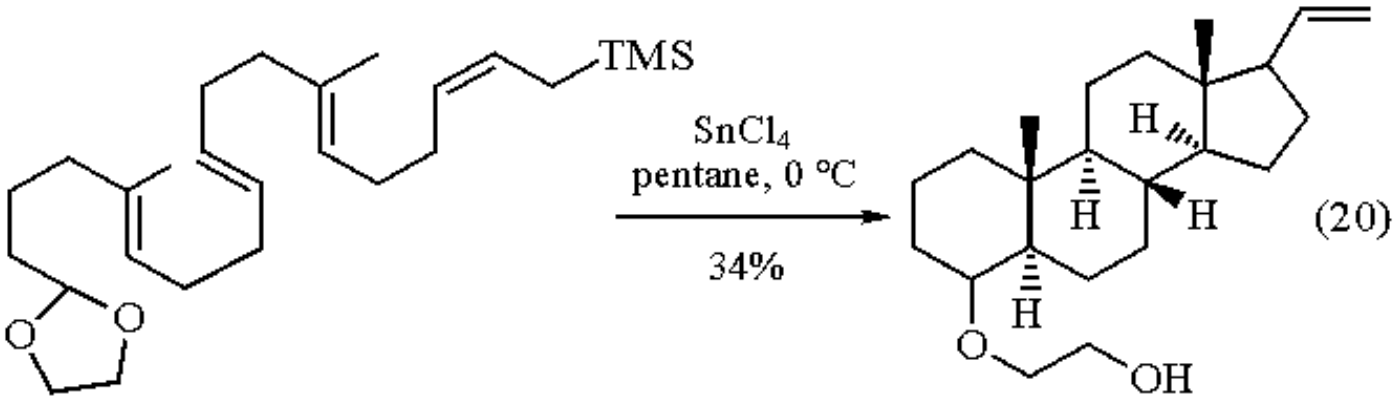

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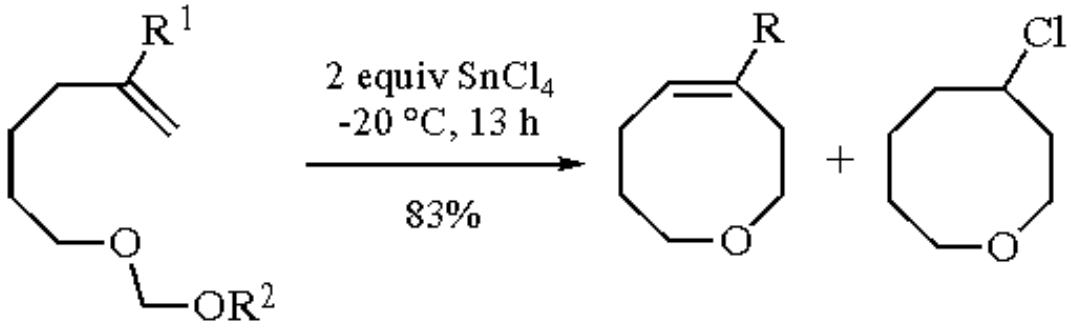

(21)

$R^1 = H$, TMS; $R^2 = (CH_2)_2OMe$

The analogous cyclization of chiral imines occurs in high yields (75-85%) with good asymmetric induction (36-65% ee).[28] For example, the cyclization of aldimine (**6**), derived from methyl citronellal, using $SnCl_4$ affords only the *trans*-substituted aminocyclohexane (**7**) in high yield (eq 22). *Exo* products are formed exclusively or preferentially over the thermodynamically favored *endo* products.

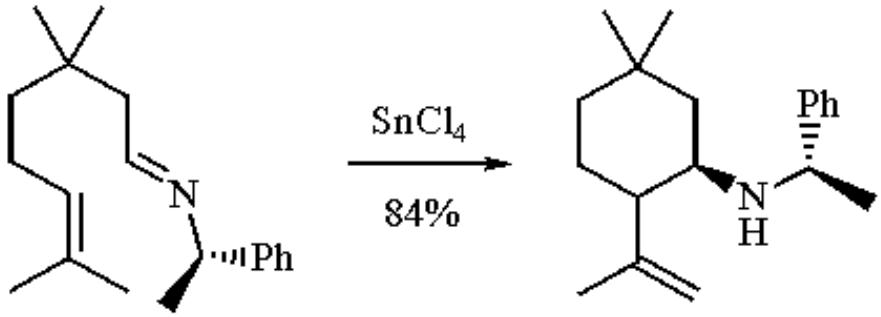

(22)

(6) **(7)**

$SnCl_4$-induced cyclizations between alkenes and enol acetates result in cycloalkanes or bicycloalkanes in high yield (eq 23). It is interesting to note that the TMSOTf-catalyzed reaction can yield fused products rather than bicyclo products. Alkenic carboxylic esters, allylic alcohols, sulfones, and sulfonate esters are also cyclized in the presence of $SnCl_4$; however, alkenic oxiranes often cyclize in poor yield.[26a]

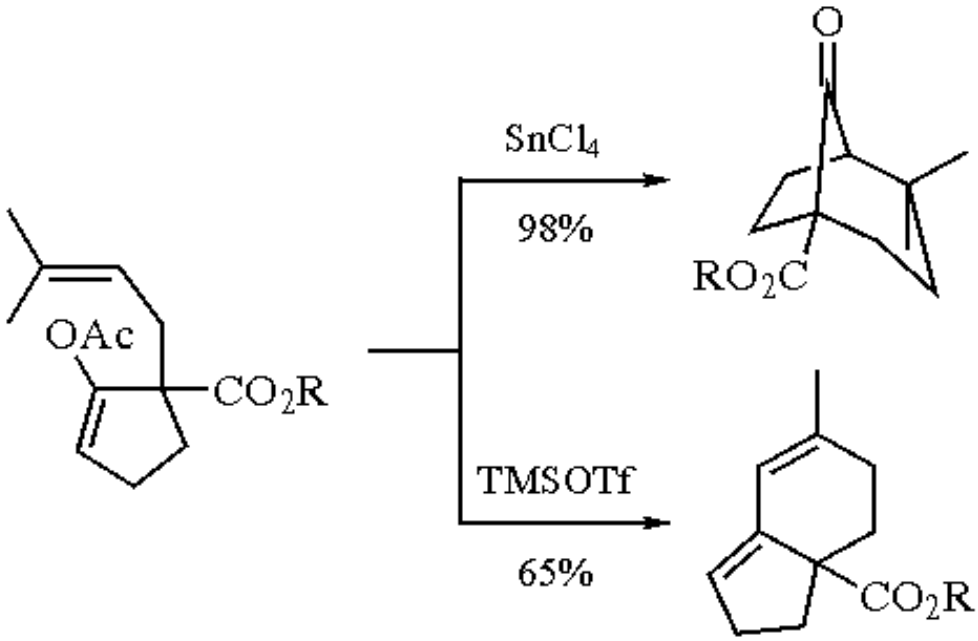

(23)

$SnCl_4$ is also effective in the opening of cyclopropane rings to produce cationic intermediates useful in cyclization reactions. For example, the cyclization of aryl cyclopropyl ketones to form aryl tetralones, precursors of aryl lignan lactones and aryl naphthalene lignans, is mediated by $SnCl_4$ (eq 24).[29] The reaction is successful in nitromethane, but not in benzene or methylene chloride. Analogous cyclizations with epoxides result in very low yields (2-5%).

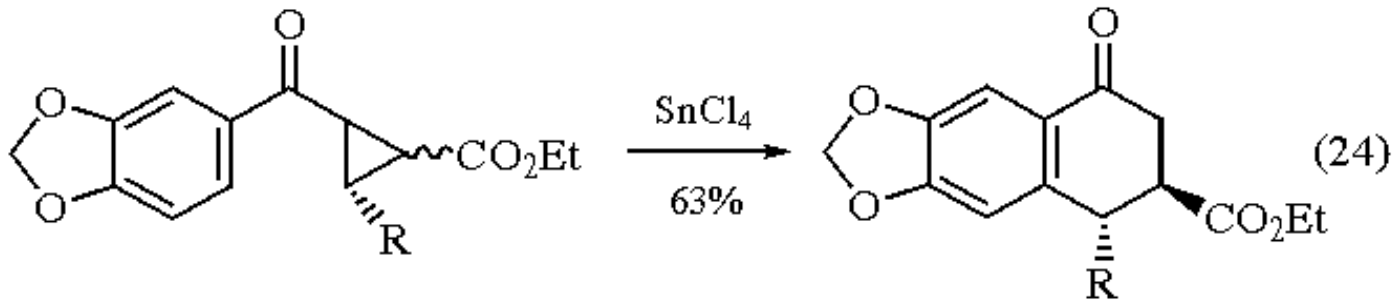

Polymerization.

Cationic polymerizations are catalyzed by $SnCl_4$ and other Lewis acids (eq 25). Propagation is based upon the formation of a cationic species upon complexation with $SnCl_4$.[30] Radical pathways are also possible for polymer propagation.[31]

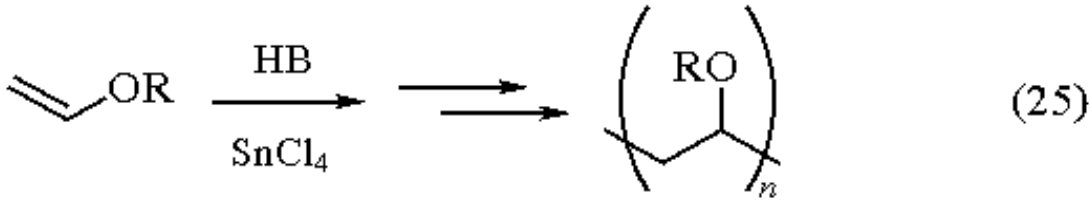

Diels-Alder Reactions.

Diels-Alder reactions are enhanced through the complexation of dienophiles or dienes by Lewis acids.[32] Furthermore, Lewis acids have been successfully employed in asymmetric Diels-Alder additions.[33] Although $SnCl_4$ is a useful Lewis acid in Diels-Alder reactions, in most instances titanium or aluminum Lewis acids provide higher yields and/or selectivities. The stereoselectivity in Lewis acid-promoted Diels-Alder reactions between chiral α,β-unsaturated *N*-acyloxazolidinones shows unexpected selectivities as a function of the Lewis acid (eq 26).[34] Optimum selectivity is expected for chelated intermediates, yet both $SnCl_4$ and $TiCl_4$ perform poorly relative to Et_2AlCl (1.4 equiv). The formation of the $SnCl_4$-*N*-acyloxazolidinone chelate has been confirmed by solution NMR studies.[35] These data suggest that other factors such as the steric bulk associated with complexes may contribute to stereoselectivity.

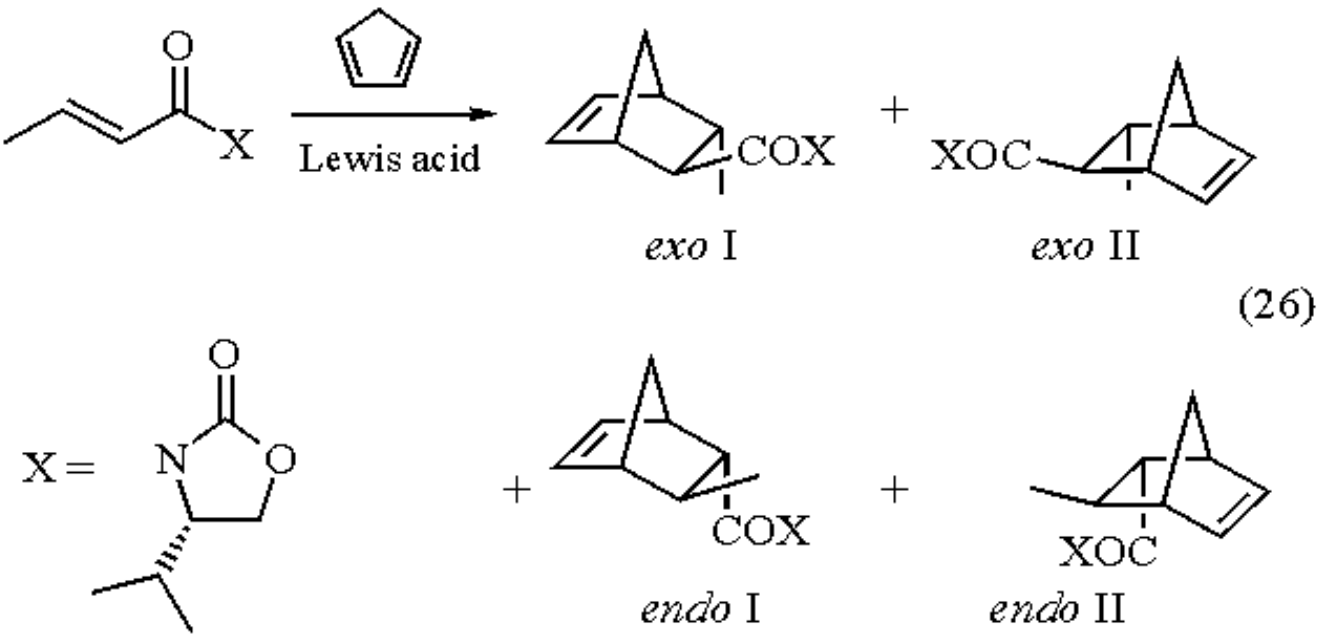

Lewis acid	conv %	Σ*endo*:Σ*exo*	*endo* I:*endo* II
1.1 equiv $SnCl_4$	70	14.9	3.1
1.1 equiv $TiCl_4$	100	9.9	2.7
1.4 equiv Et_2AlCl	100	50.0	17

In Lewis acid-promoted Diels-Alder reactions of cyclopentadiene with the acrylate of (*S*)-ethyl lactate, good diastereofacial and *endo*/*exo* selectivity are obtained with $SnCl_4$ (84:16; *endo*/*exo* = 18:1) and $TiCl_4$ (85:15; *endo*/*exo* = 16:1).[36] It is interesting to note that boron, aluminum, and zirconium Lewis acids give the opposite diastereofacial selectivity (33:67 to 48:52). Competing polymerization of the diene is observed in methylene chloride, particularly with $TiCl_4$, but not in solvent mixtures containing *n*-hexane.

Cycloalkenones generally perform poorly as dienophiles in Diels-Alder reactions but their reactivity can be enhanced by Lewis acids.[37] $SnCl_4$ is effective in promoting the Diels-Alder reaction between simple 1,3-butadienes, such as isoprene and piperylene, and cyclopentenone esters. For example, the $SnCl_4$-promoted cycloaddition between (**8**) and isoprene is completely regioselective, providing the substituted indene in 86% yield (eq 27).[38] However, cycloaddition does not occur in the presence of $SnCl_4$ when the diene contains an oxygen-bearing substituent such as an alkoxy or siloxy group. In these cases, as is generally true for the Diels-Alder reactions of cycloalkenones, other Lewis acids are more effective. For example, $SnCl_4$-promotion of the cycloaddition between (**8**) and 3-methyl-2-(*t*-butyldimethylsiloxy)butadiene yields 37% of the desired product, while ***Zinc Chloride*** provides a 90% yield. When furan or 2-methyl-1-alkylsiloxybutadiene are utilized as dienes, only decomposition of the starting material is observed with $SnCl_4$.

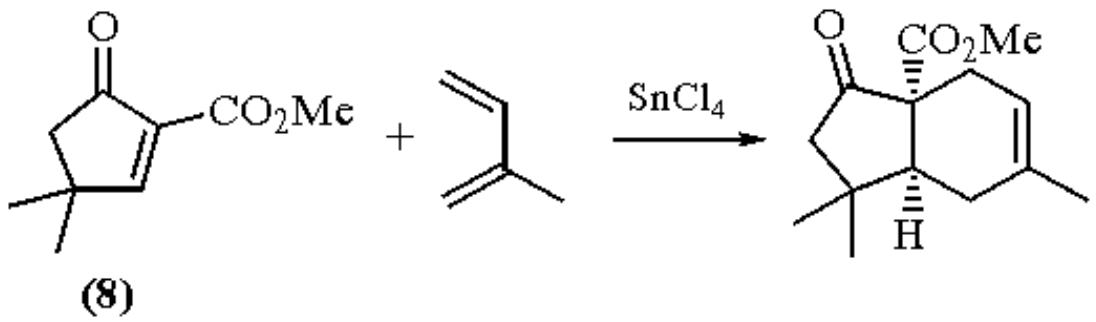

(27)

The Lewis acid-promoted Diels-Alder reaction has been employed in the assembly of steroid skeletons.[39] The cycloaddition reaction between a substituted bicyclic diene and 2,6-dimethylbenzoquinone produces two stereoisomers in a 1:5 ratio with a yield of 83% when $SnCl_4$ is used in acetonitrile. $TiCl_4$ provides slightly higher selectivities (1:8) but lower yield (70%) (eq 28).

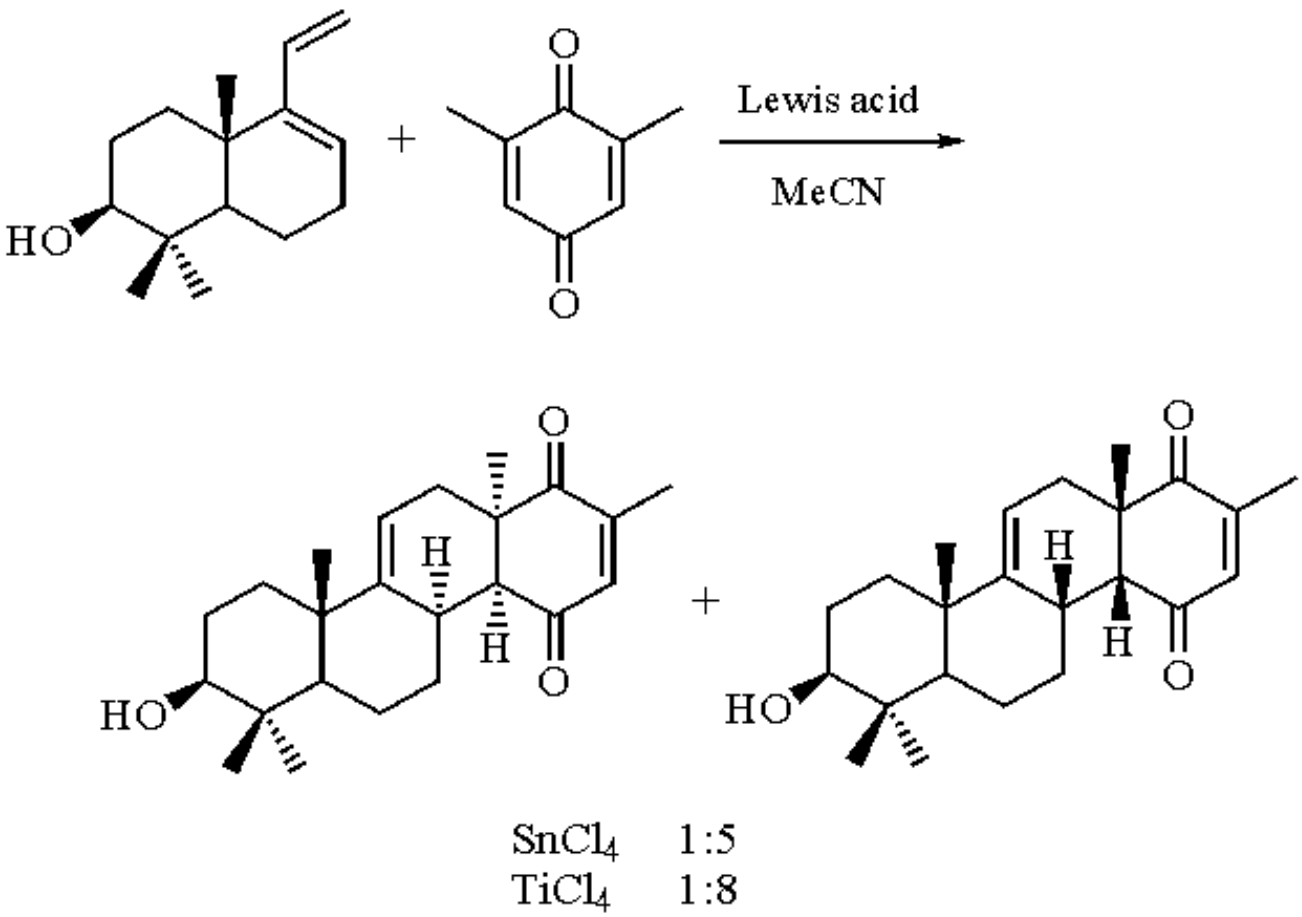

(28)

When the dienophile *N*-α-methylbenzylmaleimide (**9**) is reacted with 2-*t*-butyl-1,3-butadiene in the presence of Lewis acids, cycloadducts (**10**) and (**11**) are formed (eq 29).[40] While $SnCl_4$ provides (**10**) and (**11**) in a 5:1 ratio, $TiCl_4$ and $EtAlCl_2$ both provide a 15:1 ratio. Polymerization of the diene competes with adduct formation under all conditions.

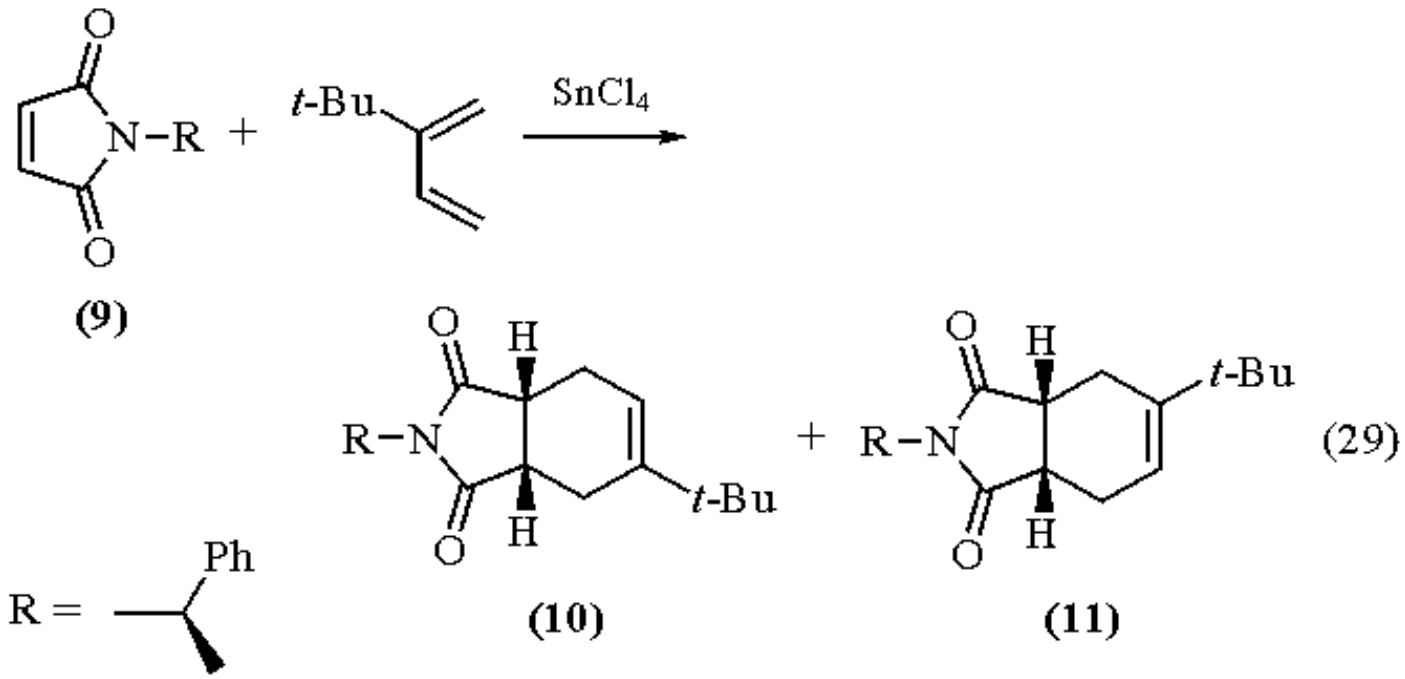

(29)

[4 + 3] Cycloadditions.

Oxyallyl cations,[41] which react as C_3 rather than C_2 components in cyclization reactions, are generated by the addition of $SnCl_4$ to substrates which contain silyl enol ethers which are conjugated with a carbonyl moiety. Thus 2-(trimethylsiloxy)propenal undergoes cyclization with cyclopentadiene or furan (eq 30).[42] Substituted 1,1-dimethoxyacetones also form these intermediates and undergo subsequent cyclizations (eq 31).[43] This method complements the usual synthesis of oxyallyl cations involving reductive elimination of halogens from halogenated ketones or electronically equivalent structures.[44]

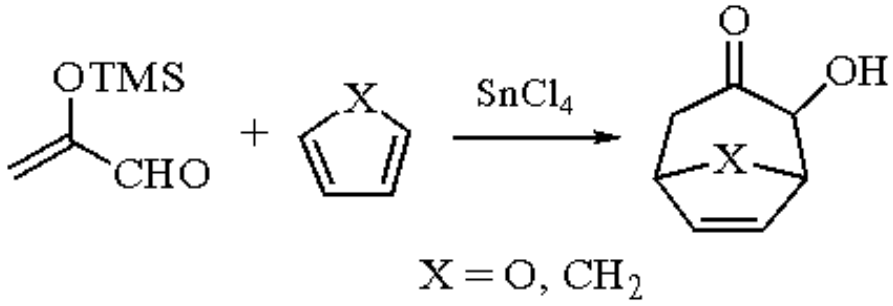

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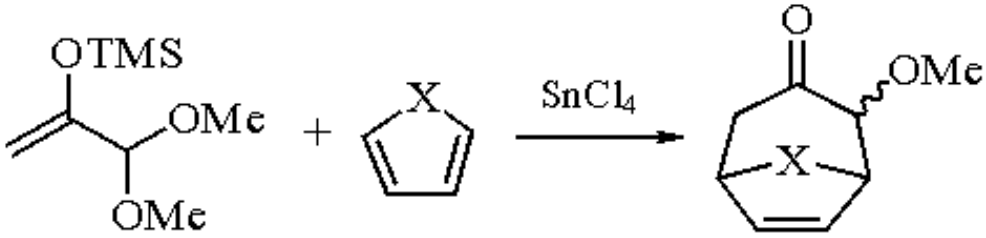

(31)

[3 + 2] Cycloadditions.

Lewis acid-mediated [3 + 2] cycloadditions of oxazoles and aldehydes or diethyl ketomalonate have been observed using organoaluminum and Sn^{IV} Lewis acids.[45] The reactions are highly regioselective, with stereoselectivity extremely dependent upon Lewis acid (eq 32). For example, the (BINOL)AlMe-promoted reaction between benzaldehyde and the oxazole (**12**) provides the oxazoline with a *cis*/*trans* ratio of 98:2. The selectivity is reversed with $SnCl_4$ which provides a *cis*/*trans* ratio of 15:85. *trans*-5-Substituted 4-alkoxycarbonyl-2-oxazolines are synthesized under thermodynamic conditions in the aldol reaction of isocyanoacetates with aldehydes.[46]

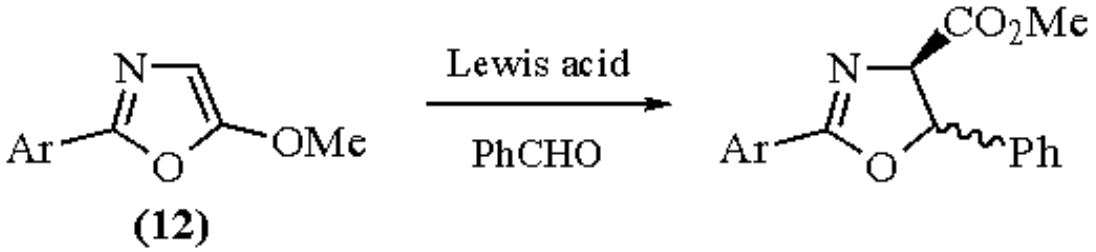

(32)

[2 + 2] Cycloadditions.

The regioselectivity in the cycloaddition reactions of 2-alkoxy-5-allyl-1,4-benzoquinones with styrenes is controlled by the choice of Ti^{IV} or $SnCl_4$ Lewis acids (eq 33).[47] The use of an excess of $TiCl_4$ or mixtures of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ produces cyclobutane (**13**) as the major or exclusive product, while $SnCl_4$ promotion with one equivalent of Lewis acid results in the formation of (**14**) only. These reactions represent a classic example of the mechanistic variability often associated with seemingly modest changes in Lewis acid.

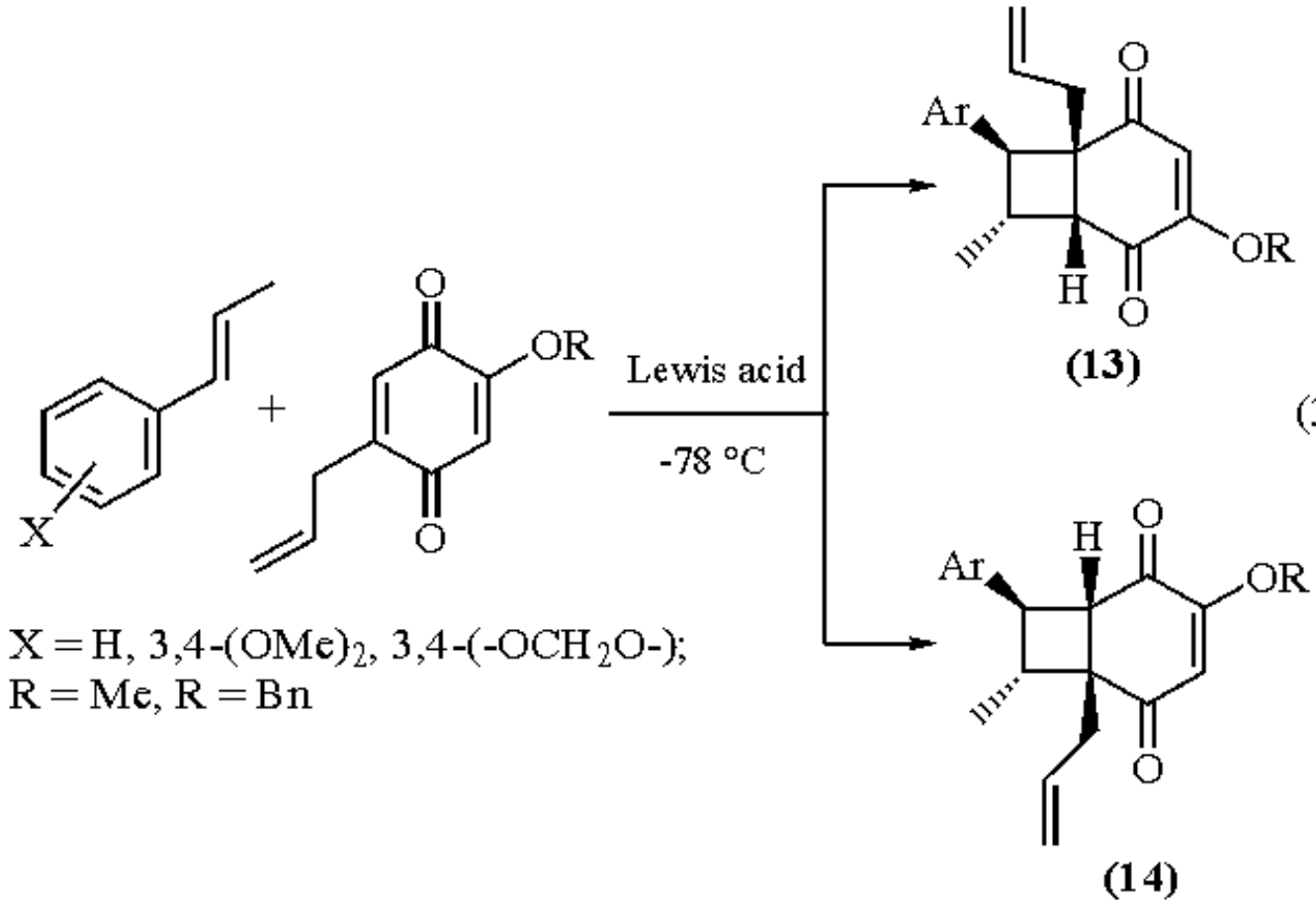

(33)

Ene Reactions.

The Lewis acid-catalyzed ene reaction is synthetically useful methodology for forming new carbon-carbon bonds.[48] Ene reactions utilizing reactive enophiles such as formaldehyde and chloral can be promoted by $SnCl_4$. $SnCl_4$ also enhances intramolecular ene reactions, such as the cyclization of (**15**) which produces the α-hydroxy δ-lactone in 85% yield (eq 34).[49] The ene cyclization of citronellal to give isopulegol has also been reported.[50] Proton scavenging aluminum Lewis acids such as $RAlCl_2$ are most often used in ene reactions to eliminate proton-induced side reactions.

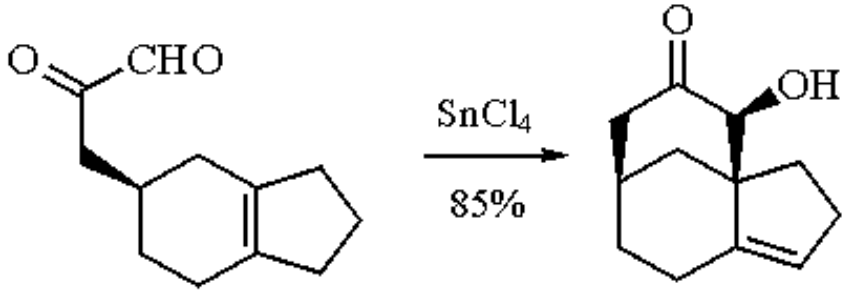

(34)

(15)

Related Reagents.

Tin(IV) Chloride-Zinc Chloride.

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Tin(II) Chloride-Silver(I) Perchlorate[1]

$SnCl_2$-$AgClO_4$

($SnCl_2$)

[7772-99-8] · Cl_2Sn · Tin(II) Chloride-Silver(I) Perchlorate · (MW 189.61) ($AgClO_4$)

[14242-05-8] · $AgClO_4$ · Tin(II) Chloride-Silver(I) Perchlorate · (MW 207.32)

(glycosylation promoter;[2] activates glycosyl fluoride[2])

Physical Data: $SnCl_2$: bp 247 °C; *d* 3.95 g cm^{-3}. $AgClO_4$: dec 486 °C; *d* 2.806 g cm^{-3} (25 °C).

Solubility: $SnCl_2$: sol H_2O, ethanol, acetone, ether. $AgClO_4$: sol water.

Form Supplied in: $SnCl_2$ (anhydrous): white solid; widely available. $AgClO_4$: widely available as a hydrated form.
Drying: anhydrous $SnCl_2$ is dried for 1 h at 100 °C under reduced pressure (ca. 0.5 mmHg). Commercially available $AgClO_4.H_2O$ is dissolved in benzene and the solution is refluxed for 6 h using Dean-Stark equipment (water is separated as the benzene azeotrope). After cooling and filtration, crude anhydrous $AgClO_4$ is recrystallized from benzene and dried at room temperature for 24 h.

Preparative Methods: the ***Tin(II) Chloride-Silver(I) Perchlorate*** reagent is usually prepared in situ by mixing an equimolar amount of $SnCl_2$ and $AgClO_4$ in an appropriate solvent such as Et_2O.

Handling, Storage, and Precautions: anhydrous $SnCl_2$ and $AgClO_4$ are handled and stored under an argon atmosphere. Anhydrous $AgClO_4$ explodes readily when struck or heated.

Promoter for Stereoselective Glycosylations.

Combined use of tin(II) chloride ($SnCl_2$) and silver perchlorate ($AgClO_4$) effectively promotes the stereoselective glycosylation reaction of glucosyl fluorides with hydroxy compounds. α-Glucopyranosides are predominantly prepared by the reaction of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl fluoride (**1**) with various hydroxy compounds, including sterically hindered ones (eq 1).[2,3]

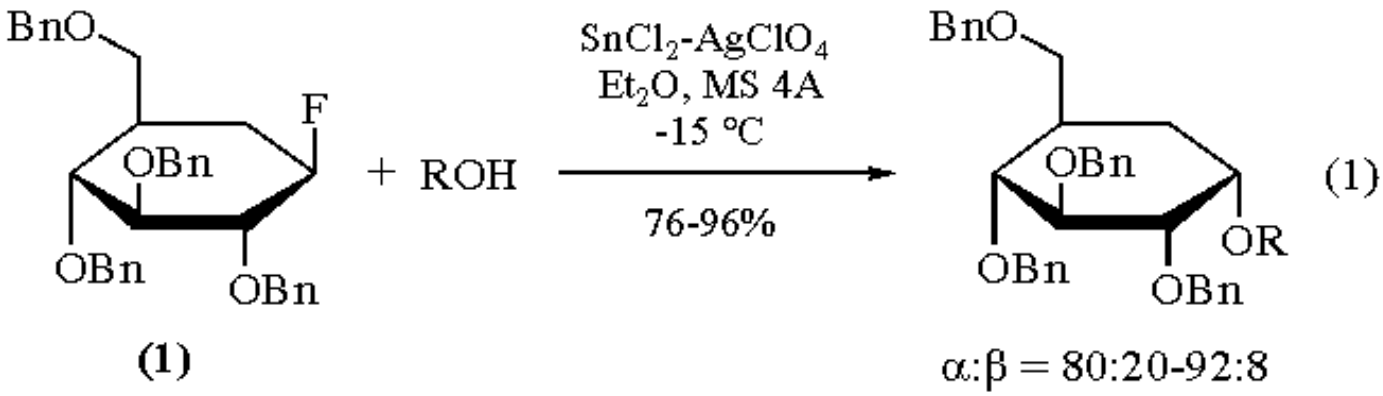

Under the same reaction conditions, a β-ribofuranoside is obtained as a major product from 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride (**2**). α-Ribofuranosides are prepared when $SnCl_2$ is combined with ***Triphenylmethyl Perchlorate*** ($TrClO_4$) instead of $AgClO_4$ (eq 2).[4]

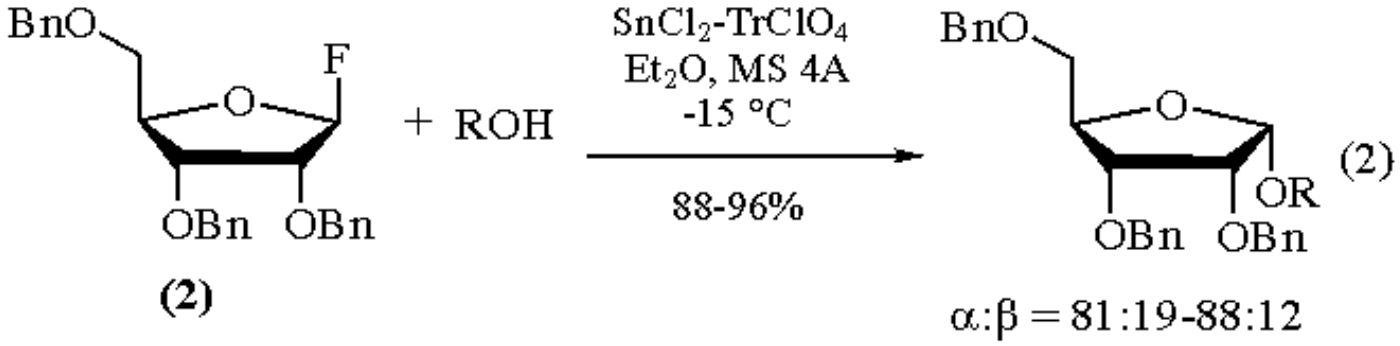

Although the precise structure of an active species generated from $SnCl_2$ and $AgClO_4$ is not clear, formation of $SnCl(ClO_4)$ or $Sn(ClO_4)_2$ is postulated. On the other hand, combination of ***Dichlorobis(cyclopentadienyl)hafnium*** and 2 equiv $AgClO_4$ is reported to form $Cp_2Hf(ClO_4)_2$, which is effective in the β-selective glycosylation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl fluoride (**3**) (eq 3).[5] In this case, use of 2 equiv of $AgClO_4$ gives better results than those obtained by use of 1 equiv.[5d] Some other examples of stereoselective glycosylations of glycosyl fluorides using other activators such as SiF_4,[6] TMSOTf,[7] $BF_3.OEt_2$,[8,9] TiF_4,[10] Tf_2O,[11] and Me_2GaCl[12] have also been reported.

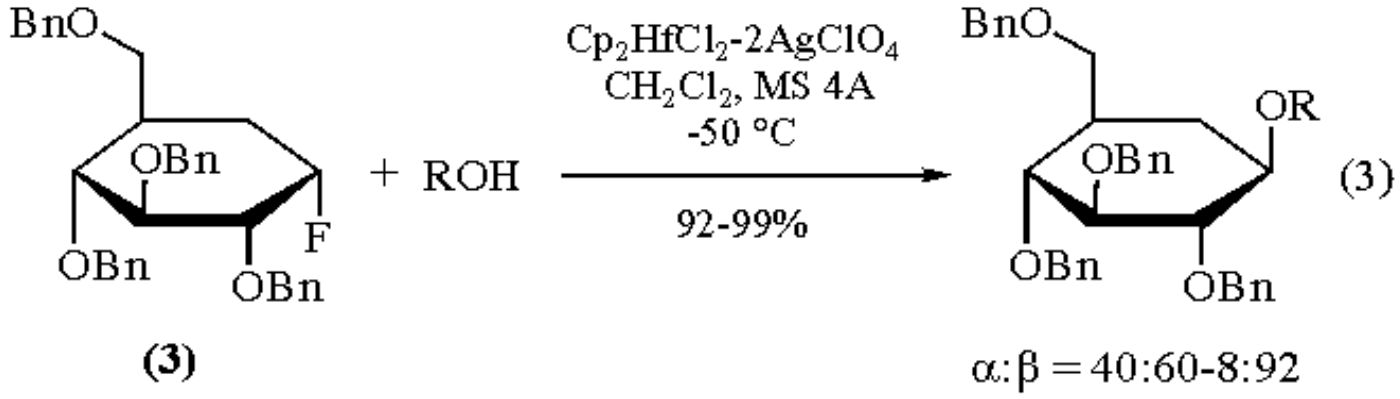

While more than stoichiometric amounts of promoters are required in the above examples, catalytic reactions are realized by using ***Tin(IV) Chloride***-$AgClO_4$. In the presence of a catalytic amount of $SnCl_4$-$AgClO_4$, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**4**) reacts with alcohol trimethylsilyl ethers to afford the corresponding α-glucopyranosides in high yields (eq 4).[13] Other examples of the preparation of β-glucosides[14] and α-[15] and β-2-amino-2-deoxyglycosides[16] have also been reported.

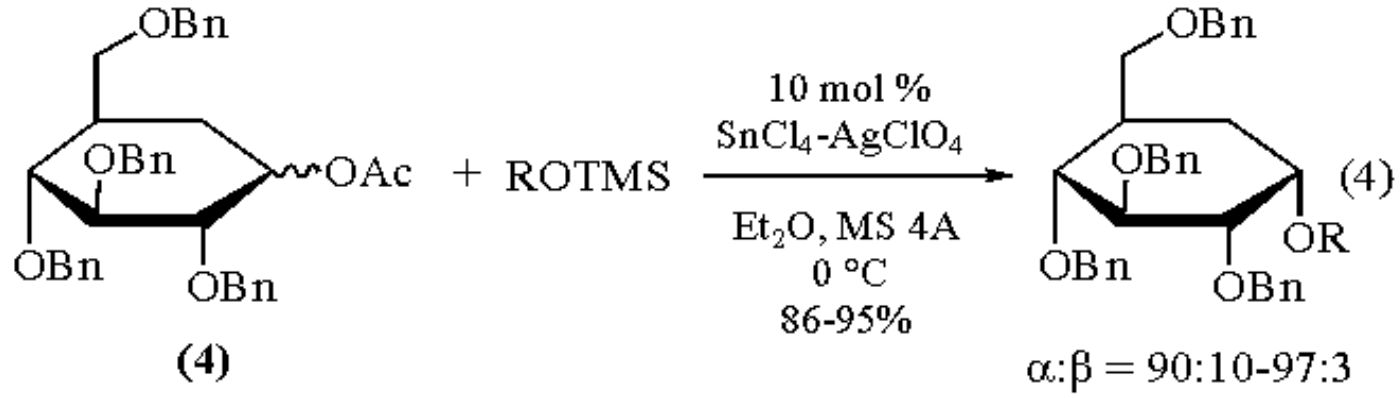

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Tin(IV) Chloride-Zinc Chloride[1]

$SnCl_4$-$ZnCl_2$

($SnCl_4$)

[7646-78-8] · Cl_4Sn · Tin(IV) Chloride-Zinc Chloride · (MW 260.51) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Tin(IV) Chloride-Zinc Chloride · (MW 136.29)

(catalyst for bond formation between silyl nucleophiles and carbonyl groups or enones[1])

Physical Data: $SnCl_4$: mp -33 °C; bp 114.1 °C; *d* 2.226 g cm^{-3}; $ZnCl_2$: mp ca. 290 °C; bp 732 °C.

Solubility: both reagents react violently with water. $SnCl_4$: sol cold H_2O; dec hot H_2O; sol alcohol, ether, CCl_4, benzene, toluene, acetone. $ZnCl_2$: sol H_2O (432 g/100 g at 25 °C, 614 g/100 g at 100 °C); 2% HCl (4 g/1 mL); alcohol (1 g/1.3 mL); glycerol (1 g/2 mL); freely sol acetone.

Form Supplied in: blend not commercially available. Anhydrous $SnCl_4$: colorless liquid; 1 M soln CH_2Cl_2 or heptane; widely available. Anhydrous $ZnCl_2$: white, odorless granules, lumps, or rods; 1 M soln in Et_2O, 0.5 M soln in THF; widely available.

Purification: $SnCl_4$: heat to reflux with mercury or P_2O_5 for several hours, then distil under reduced nitrogen pressure into receiver with P_2O_5. Redistil. Typical impurities: hydrates. $ZnCl_2$: heat to reflux in dioxane (100 g/800 mL) with zinc dust (10 g), filter hot, and cool to precipitate $ZnCl_2$. Crystallize from dioxane. Impurities: H_2O, zinc oxychloride.

Handling, Storage, and Precautions: both reagents are hygroscopic and should be stored in a glove box or over P_2O_5 to minimize exposure to moisture. Containers should be flushed with N_2 or Ar and tightly sealed. Perform all manipulations under N_2 or Ar. Solvating $SnCl_4$ with H_2O is highly exothermic. Use in a fume hood.

Introduction.

The ***Tin(IV) Chloride-Zinc Chloride*** blend[1] is one of many Lewis acid blends, such as $Sn(OTf)_2$-Bu_3SnF,[2] $SnCl_4$-$Sn(OTf)_2$,[3] $SbCl_5$-$Sn(OTf)_2$,[4] TMSCl-$SnCl_2$,[5] TrCl-$SnCl_2$ (Tr = trityl),[6] SnO-TMSOTf,[7] and $GaCl_3$-$AgClO_4$,[8] which are effective catalysts in carbon-carbon bond forming reactions. The active catalyst is believed to be ^+ZnCl-$SnCl_5^-$ which is formed prior to the addition of organic reactants. Single Lewis acids ($SnCl_4$, $TiCl_4$, etc.) promote these reactions, but do not catalyze them.[9]

Ethynylation of Acetals and Aldehydes.[1]

The $SnCl_4$-$ZnCl_2$ blend is the most useful catalyst (10 mol %) for the preparation of secondary propargylic ethers from 1-trimethylsilyl-1-alkynes and acetals (eq 1).[1] Conventional promoters such as TrCl-$SnCl_2$ and TMSCl-$SnCl_2$ are not effective, and Sn^{II}-Sn^{IV}, Sn^{II}-Ti^{IV}, and Zn^{II}-Ti^{IV} blends provide lower yields. Moderate yields (29-53%) are obtained for acetals with large alkoxy groups (R^2); however, cyclic acetals, such as 1,3-dioxolane, do not react. Aromatic and conjugated dimethyl acetals provide dipropargyl derivatives as side products. Ethynylation of aldehydes is accomplished by forming intermediate hemiacetal-like compounds from aldehydes and alkoxytrimethylsilanes in the presence of the Lewis acid blend. These intermediates then undergo reaction with 1-trimethylsilyl-1-alkynes to form the desired secondary propargylic ethers (eq 2).

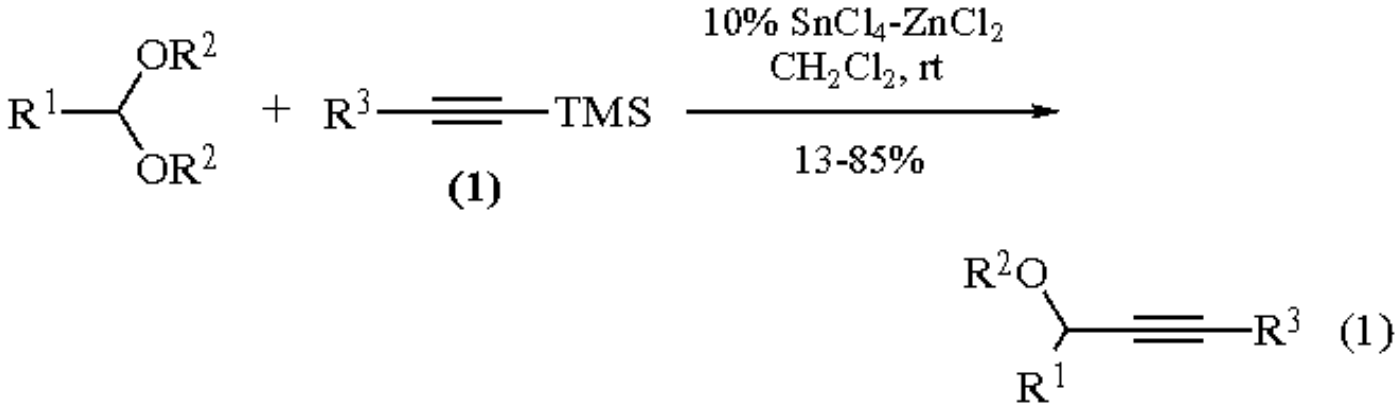

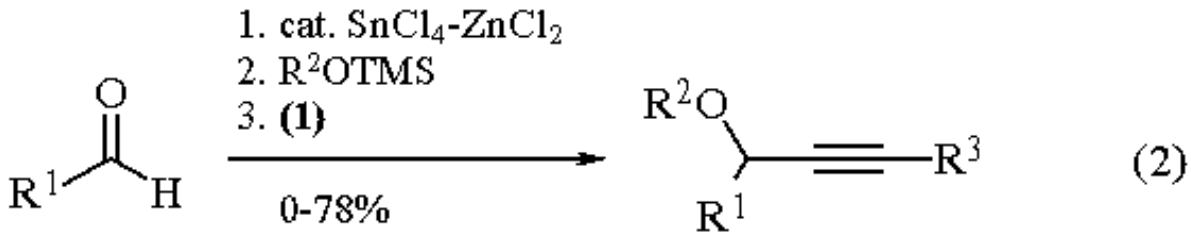

Allylation of Secondary Propargylic Ethers and Aldehydes.[1]

Propargylic ethers are allylated by ***Allyltrimethylsilane*** in the presence of the $SnCl_4$-$ZnCl_2$ blend (eq 3). Thus acetals can be transformed to 1,5-enynes in one pot with sequential nucleophilic additions. The blend also catalyzes the allylation of aldehydes by allyltrimethylsilane, yielding homoallylic alcohols in good yields (61-74%).

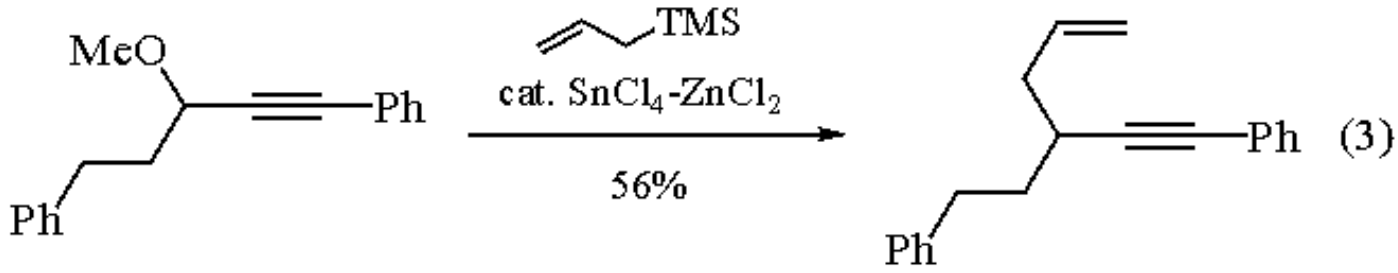

Aldol and Michael Reactions.[1]

The $SnCl_4$-$ZnCl_2$ blend is an effective catalyst in the aldol reaction of silyl enol ethers with aldehydes (eq 4), acetals (eq 5), or ketones. The product *anti*/*syn* ratios are variable (32:69 to 89:11). The blend also catalyzes the Michael addition of silyl enol ethers with α,β-unsaturated ketones (eq 6), yielding alkylation products (84-100%) with *anti* selectivity (*anti*/*syn* = 55:45 to 87:23)

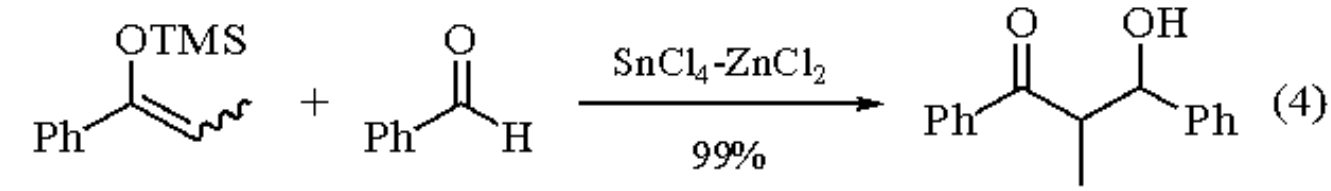

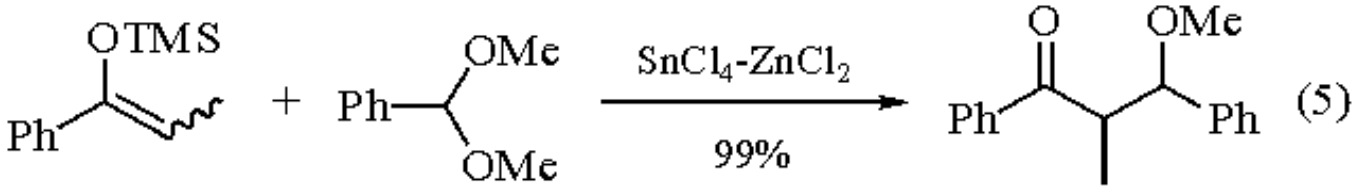

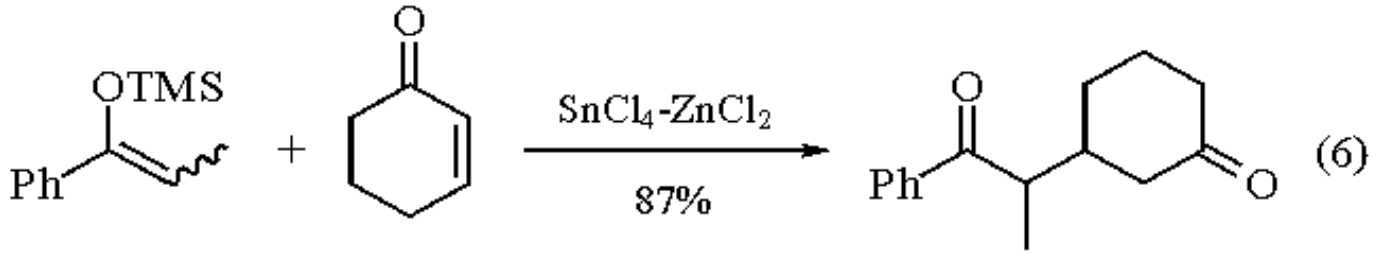

Related Reagents.

Tin(IV) Chloride; ***Zinc Chloride***.

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Tin(II) Fluoride[1]

SnF_2

[7783-47-3] · F_2Sn · Tin(II) Fluoride · (MW 156.71)

(Knoevenagel[2] and aldol-type[3] catalyst; oxidative addition to carbon-halogen bonds;[4,5] stereocontrolled [3 + *n*] (*n* = 3, 4, or 5) annulations;[6,8,9] conversion of allylic phosphonates to allyltin intermediates[7])

Alternate Name: stannous fluoride.

Physical Data: mp 213 °C, 219.5 °C; bp 850 °C; *d* 4.570 g cm^{-3}.

Solubility: v sol water (>30% w/w); sol aq potassium hydroxide, fluoride solutions, mineral acids. Readily dissolves in donor solvents such as acetone, ethyl acetate, or pyridine, forming presumed pyramidal (&PPsi;-tetrahedral) complexes.

Form Supplied in: white, monoclinic crystals; widely available.

Handling, Storage, and Precautions: slowly hydrolyzes in water to SnO. Converts to $SnOF_2$ upon exposure to air. Stable in aq mineral acids. Aq solutions are readily oxidized (catalyzed by light). Fluoride solutions react with SnF_2, providing SnF_3^- (p*K* = 10) which absorbs oxygen but does not oxidize. Containers of SnF_2 should be stored under a dry, inert atmosphere. LD_{50} 128.4 mg/kg (mouse), 188.2 mg/kg (rat).

Knoevenagel Condensations.

Among 14 metallic fluorides, Lelean[2] has shown that tin(II) fluoride is a superior catalyst in the Knoevenagel condensation of a tetrahydropyrimidine with 2-thiophenecarbaldehyde in methylcyclohexane at reflux (eq 1). Complete conversion (based upon the amount of water formed) is observed with only 9.3 mol % of catalyst.

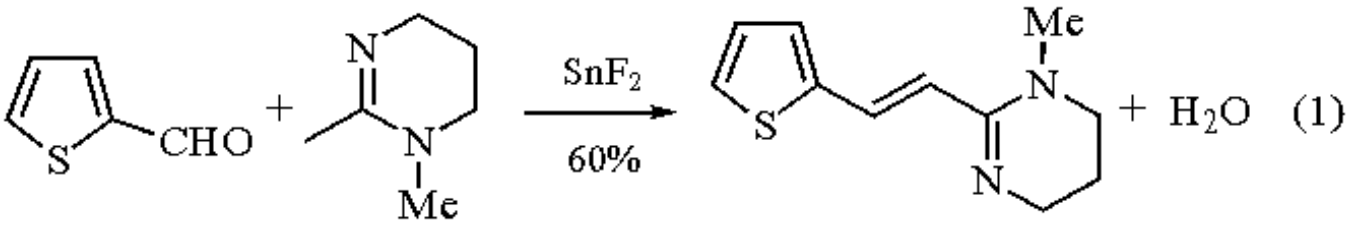

Oxidative Addition to Carbon-Halogen Bonds.

Tin(II) fluoride undergoes oxidative insertion with α,α-dibromoacetophenone derivatives (eq 2) (R^1 = Me, Et), affording the tin enolate which undergoes addition to aliphatic and aromatic aldehydes (R^2 = $PhCH_2CH_2$, Ph, *n*-C_8H_{17}, *p*-ClC_6H_4) at -45 °C. Treatment of the aldol intermediate with ***Cesium Fluoride*** (or ***Triethylamine***) promotes closure to the α,β-epoxy ketone in 52-81% yields.[3]

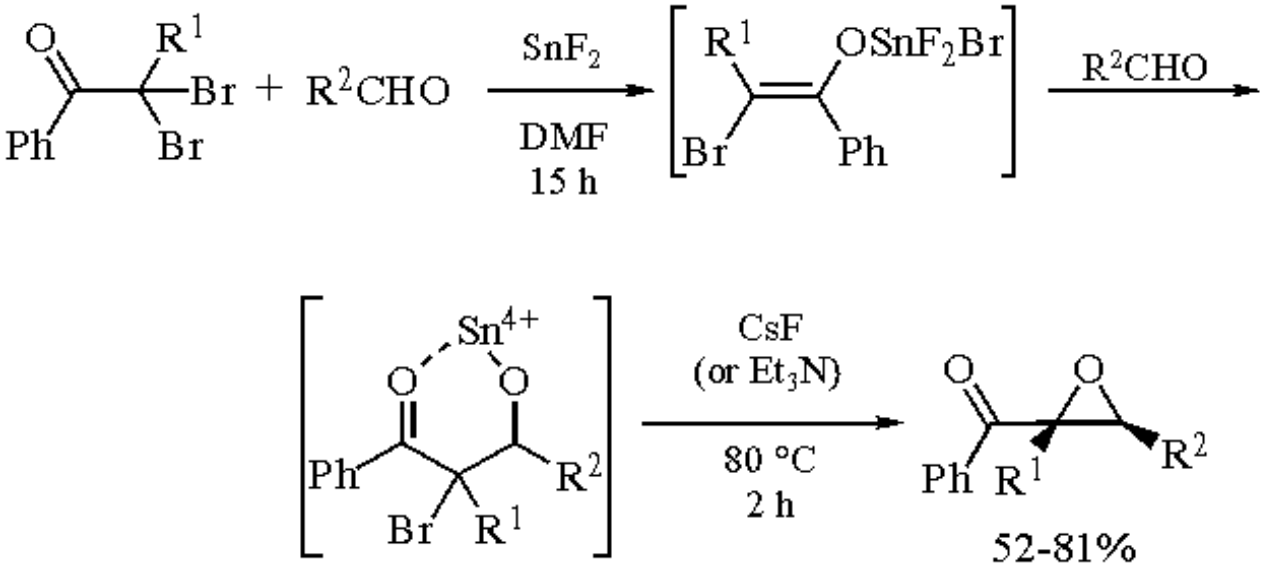

(2)

Mukaiyama[4] has shown that ***Allyl Iodide*** reacts with SnF_2 to give an allyltin species (eq 3) which adds to aldehydes (R^1 = $PhCH_2CH_2$, PhCH=CH, Ph) to give an intermediate which, in turn, can be trapped with acid chlorides (R^2 = Me, $PhCH_2CH_2$), affording esters of homoallylic alcohols.

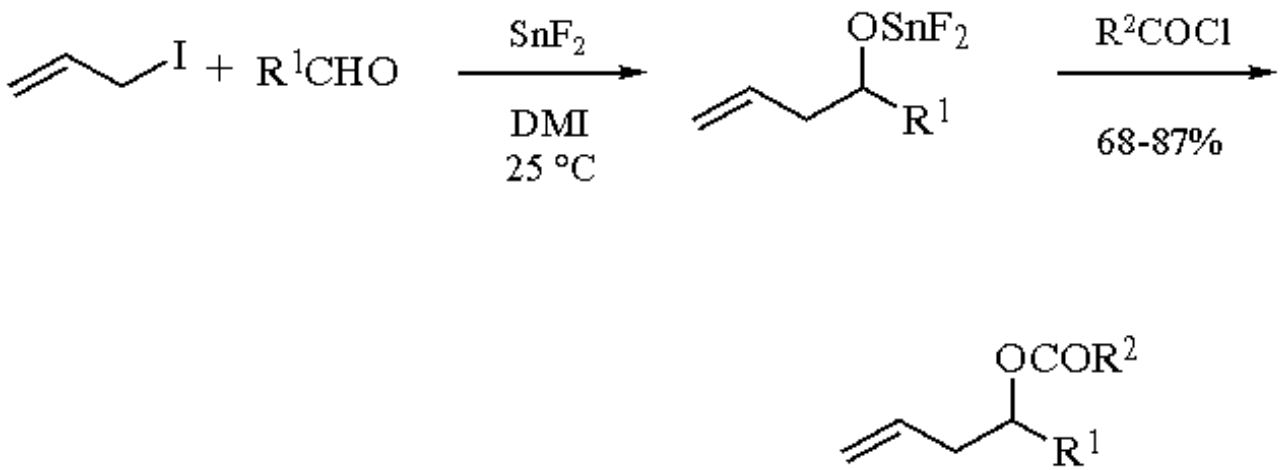

(3)

This methodology has been applied to a four-pot synthesis of 2-deoxy-D-ribose (eq 4).[4] Allylation/trapping of 1,2-*O*-isopropylidene-D-glyceraldehyde with phenoxyacetyl chloride gives a 78% yield of the *erythro*-homoallylic alcohol (admixed with 19% of the *threo*-isomer). Cleavage of the phenoxyacetyl group with ***Ammonia*** affords the acetonide in 71% yield. Hydrolysis then gives the triol in 95% yield, and this affords 2-deoxy-D-ribose in 75% yield after ozonolysis with a reductive workup.

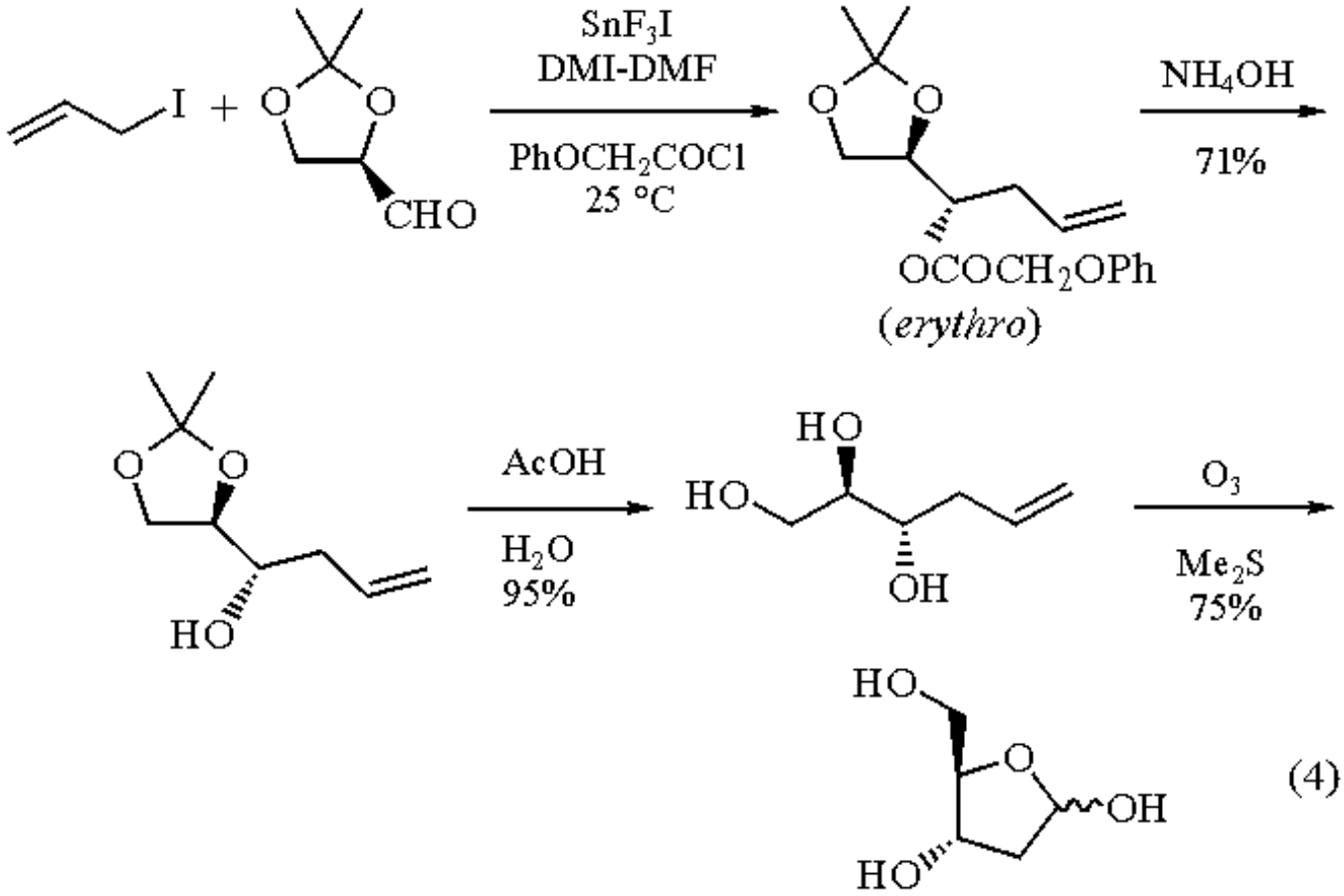

(4)

In a similar manner, reaction of ***Carbon Tetrabromide*** with SnF_2 in DMSO at 25 °C gives an intermediate which adds to aldehydes (R = Ph, 1-furyl, $PhCH_2CH_2$, *n*-C_8H_{17}, PhCH=CH, PhCO, PhCH(Me)), affording the corresponding tribromoethanols in 46-80% yields (eq 5).

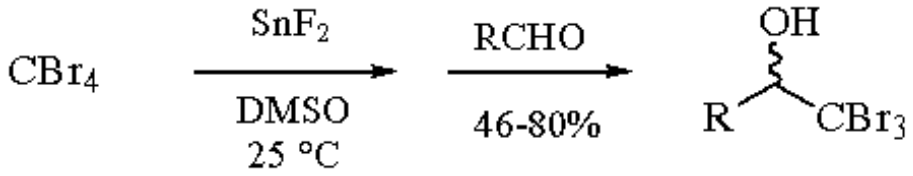

(5)

Tribromoethanols are useful precursors of α-hydroxy carboxylic acids and have been employed in the synthesis of 2,3-diacetyl-D-erythronolactone[5] from 1,2-*O*-isopropylidene-D-glyceraldehyde (eq 6).

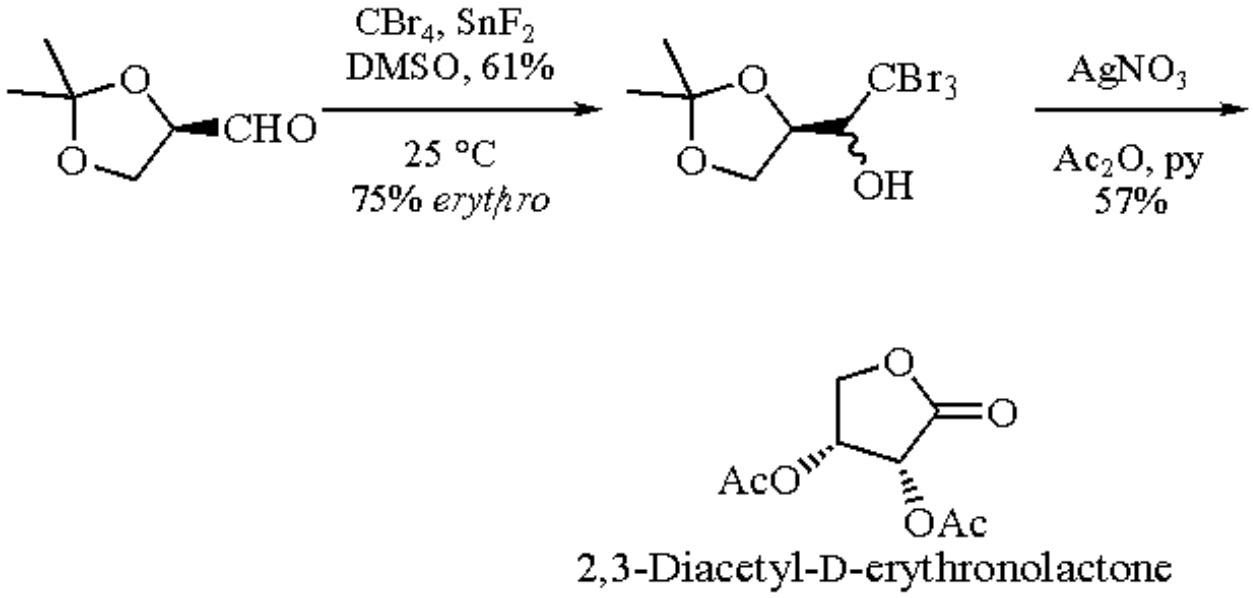

(6)

Stereocontrolled [3 + *n*] (*n* = 3, 4, or 5) Annulations.[6,8,9]

Molander reports the stereocontrolled synthesis of cyclopentanoids[6] (eq 7) using a 1,2-dicarbonyl component and a 1,3-dianion synthon derived from the treatment of 3-halo-2-[(trimethylsilyl)methyl]propenes (X = I, Br) with SnF_2 in THF at 25 °C. Several 1,2-diketones (R, R^1 = Me, Et, Ph, *n*-Pr, $Cl(CH_2)_4$, $-(CH_2)_4-$; 0% for R = R^1 = Ph) afford the *cis*-diols.

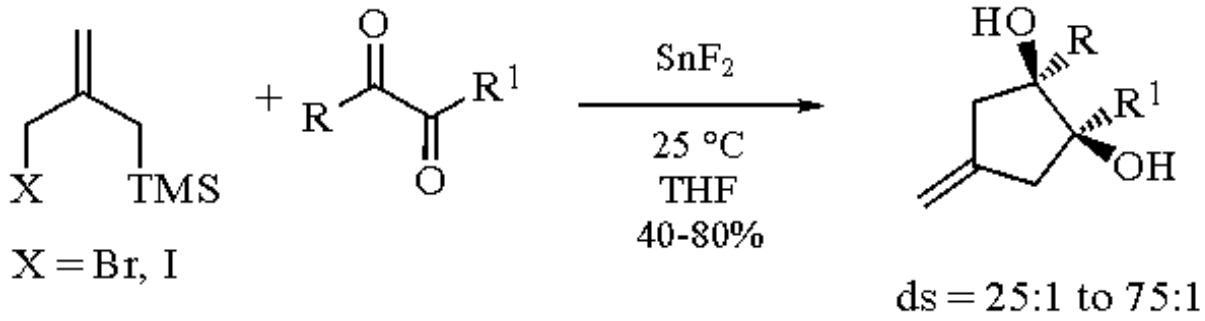

(7)

SnF_2 appears unique for this annulation. After generation of the allylstannane, the Sn^{4+} serves as a Lewis acid catalyst and provides internal chelation. The fluoride counterion is an ideal nucleophile for the activation of the allylsilane. The high stereoselectivity (25:1 to 75:1) is attributed to chelation (eq 8).[6]

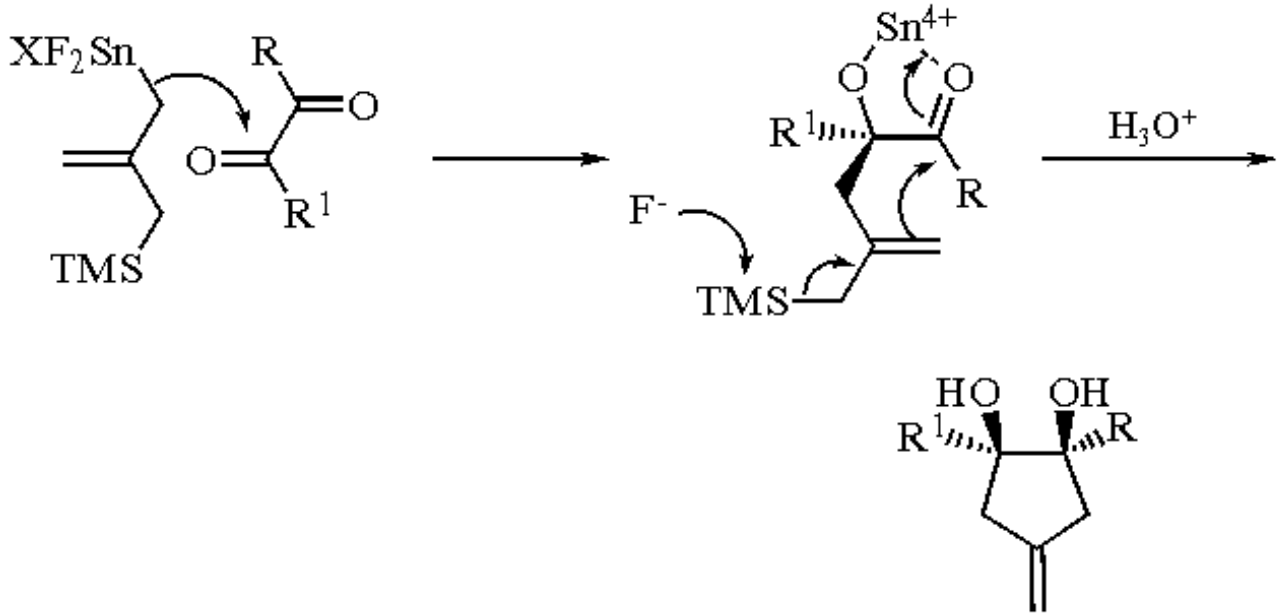

(8)

Reaction of an asymmetrically substituted 1,2-dione with the allylstannane as described above gives predominantly the diastereomer predicted by the Felkin-Ahn model (eq 9).[6]

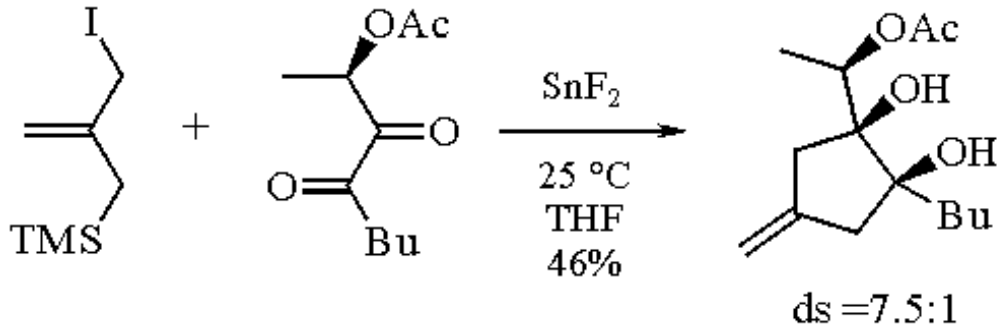

(9)

Cyclohexanediols are prepared in approximately 20-60% yields (diastereomeric ratios from 4:1 to 50:1) by a [3 + 3] annulation using α,β-epoxy aldehydes (R = alkyl, H) as the dielectrophilic partner (eq 10).[8] The high degree of stereoselectivity and the lack of appreciable [3 + 2] annulation is attributed to internal chelation and an internal *trans*-diaxial epoxide opening (eq 11).[8]

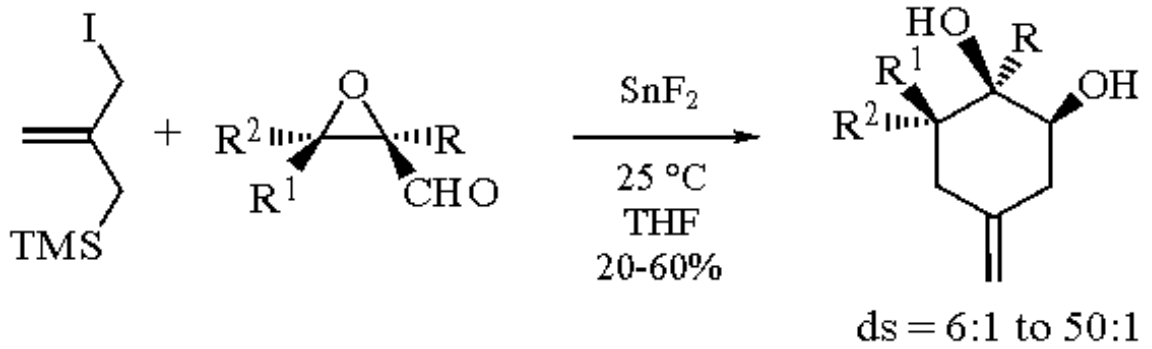

(10)

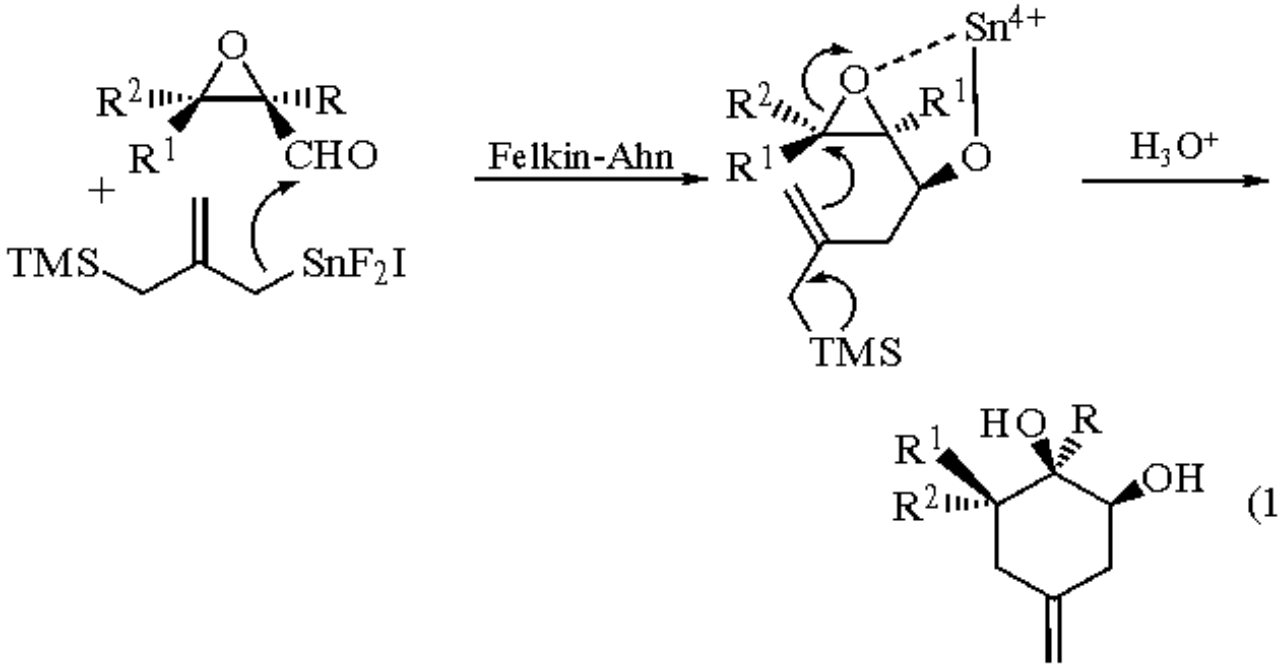

(11)

Annulations with 1,4-dicarbonyl or 1,5-dicarbonyl substrates (R = aryl, aliphatic) give seven- and eight-membered ethers in high yields (eqs 12 and 13).[9] The ethers are obtained since the initial adduct may form an internal acetal (eq 14).[9]

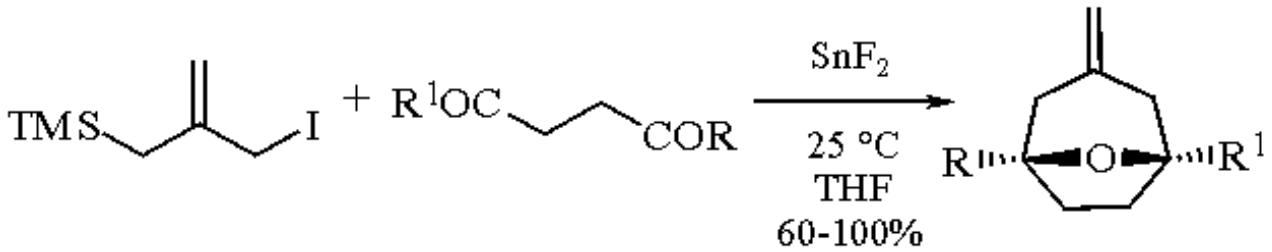

(12)

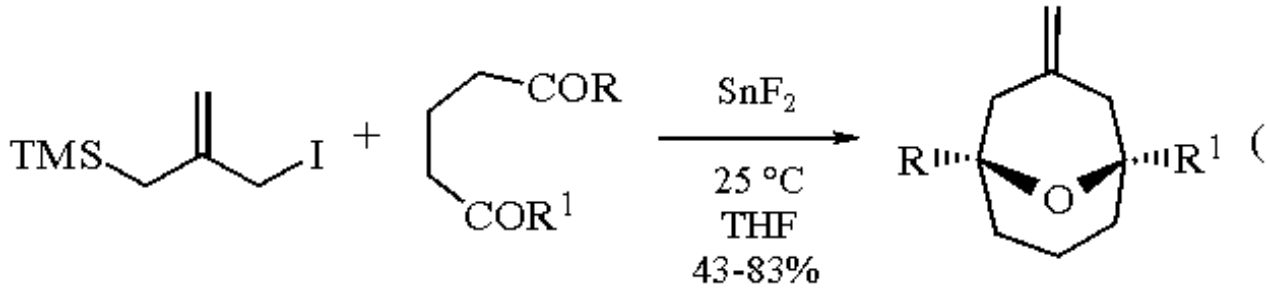

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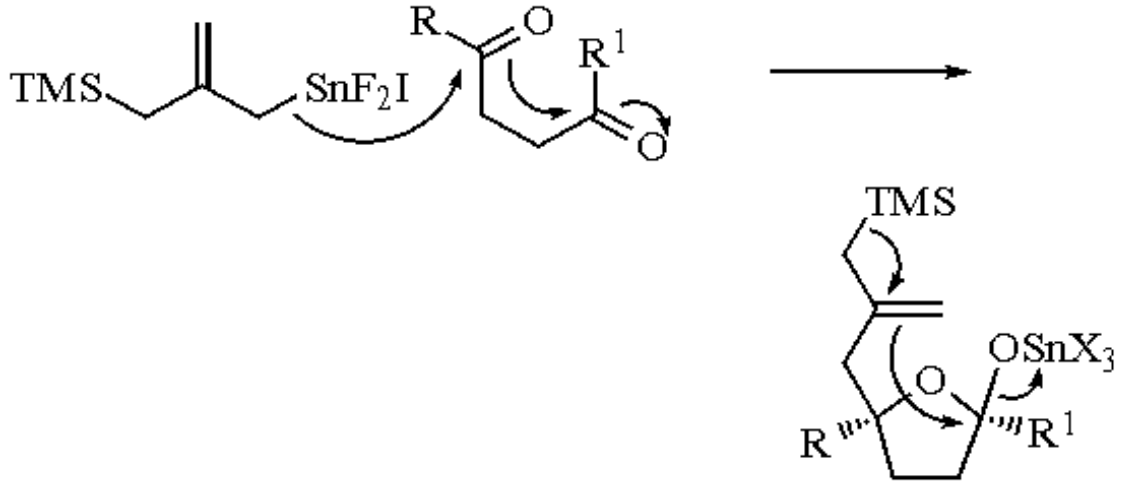

(14)

Allylations of Aldehydes with Allylic Phosphonates.

Allylic phosphonates (R = H or Me) react with $Et_2AlSnClF_3$ (formed in situ with SnF_2 and ***Diethylaluminum Chloride*** with a catalytic amount of ***Tetrakis(triphenylphosphine)palladium(0)***), giving an allyltin reagent which adds to benzaldehyde or hexanal in high yields (eq 15).[7] The *syn*/*anti* selectivities of the homoallylic alcohols range from 25/75 to 55/45.

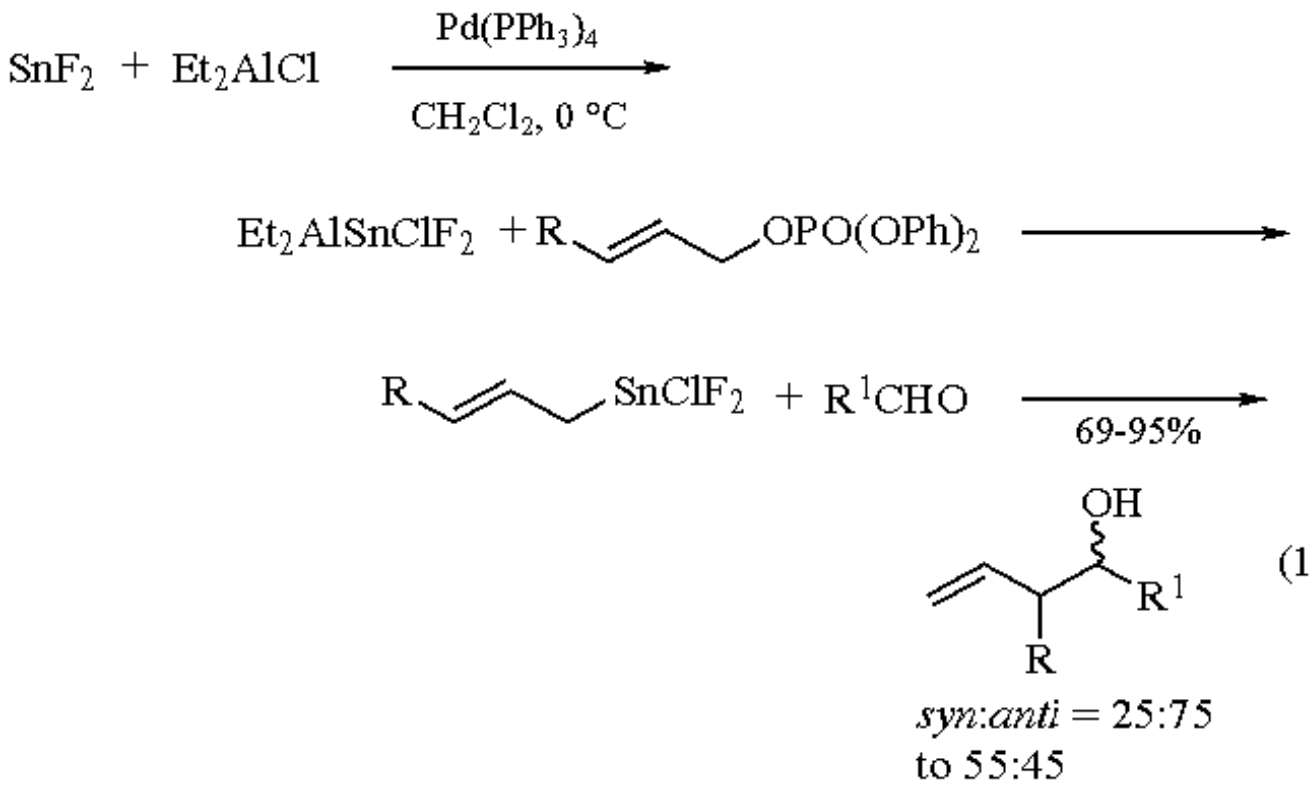

(15)

Related Reagents.

Tin(II) Bromide; ***Tin(II) Chloride***.

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1. *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 1983; Vol. 23, pp 42-77.
2. Lelean, P. M.; Morris, J. A. *CC* **1968**, 239.
3. Shoda, S.; Mukaiyama, T. *CL* **1981**, 723.
4. Harada, T.; Mukaiyama, T. *CL* **1981**, 1109.
5. Mukaiyama, T.; Yamaguchi, M.; Kato, J. *SL* **1981**, 1505.
6. Molander, G. A.; Shubert, D. C. *JACS* **1986**, *108*, 4683.
7. Matsubara, S.; Wakamatsu, K.; Morizawa, Y.; Tsuboniwa, N.; Oshima, K.; Nozaki, H. *BCJ* **1985**, *58*, 1196.
8. Molander, G. A.; Shubert, D. C. *JACS* **1987**, *109*, 576.
9. Molander, G. A.; Shubert, D. C. *JACS* **1987**, *109*, 6877.

Tin(II) Trifluoromethanesulfonate

$Sn(OTf)_2$

[62086-04-8] · $C_2F_6O_6S_2Sn$ · Tin(II) Trifluoromethanesulfonate · (MW 416.87)

(mild Lewis acid used primarily for the generation of tin(II) enolates for stereoselective aldol and Michael reactions;[1] [2,3]-Wittig and Ireland-Claisen rearrangements;[2] addition of tin(II) acetylides to aldehydes;[3] asymmetric allylation of aldehydes[4])

Physical Data: mp >300 °C.

Form Supplied in: fine white powder.[5]

Purification: can be purified by washing with diethyl ether.[6]

Handling, Storage, and Precautions: moisture and air sensitive; all handling and storage should be done under nitrogen.

Aldol Reaction.

Mukaiyama has developed the use of tin(II) triflate in diastereoselective and enantioselective aldol-type reactions.[1,7] Initially, the stereoselective aldol reactions were demonstrated using a stoichiometric amount of tin(II) triflate.[8] The reaction between 3-acylthiazolidine-2-thione and 3-phenylpropionaldehyde is a representative example of a diastereoselective *syn*-aldol synthesis (eq 1).

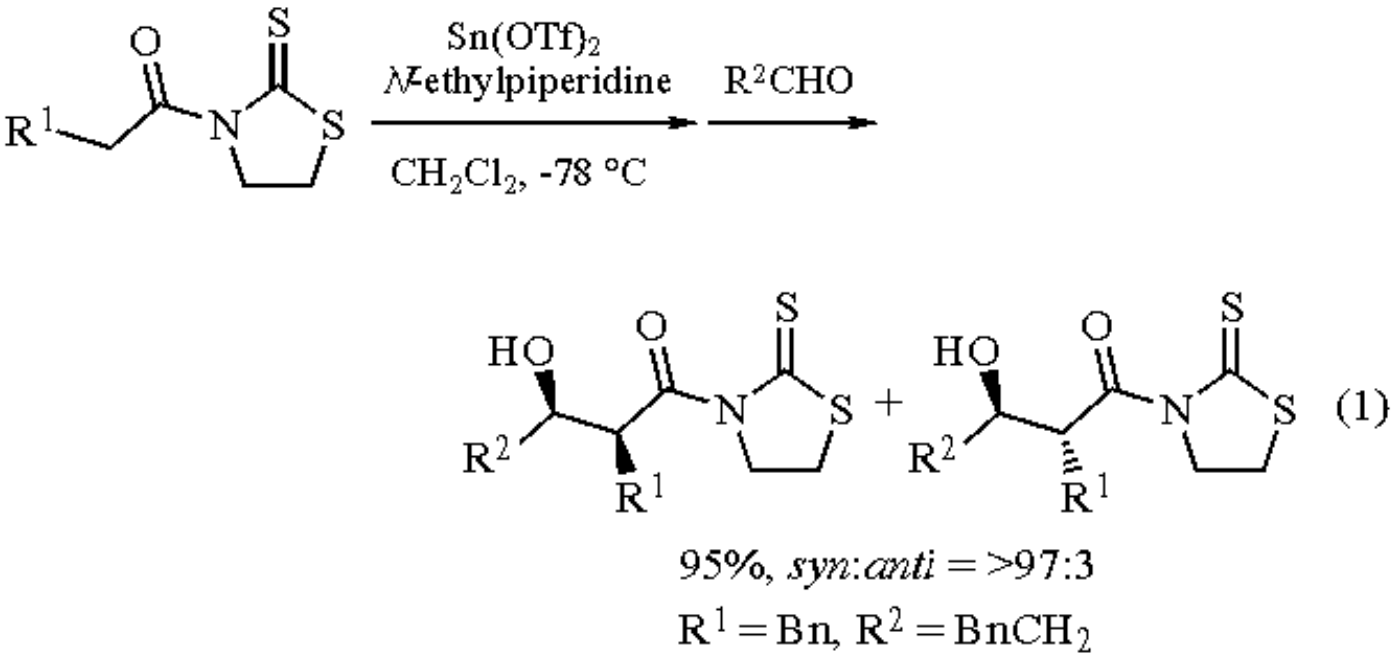

Enantioselective aldol-type reactions have been achieved by addition of a chiral diamine to the reaction mixture.[9] Specifically, addition of (*S*)-1-methyl-2-[(piperidin-1-ylmethyl]pyrrolidine to the reaction of 3-acetylthiazolidine-2-thione and 3-phenylpropionaldehyde provides the *syn*-aldol with greater than 90% ee (eq 2).

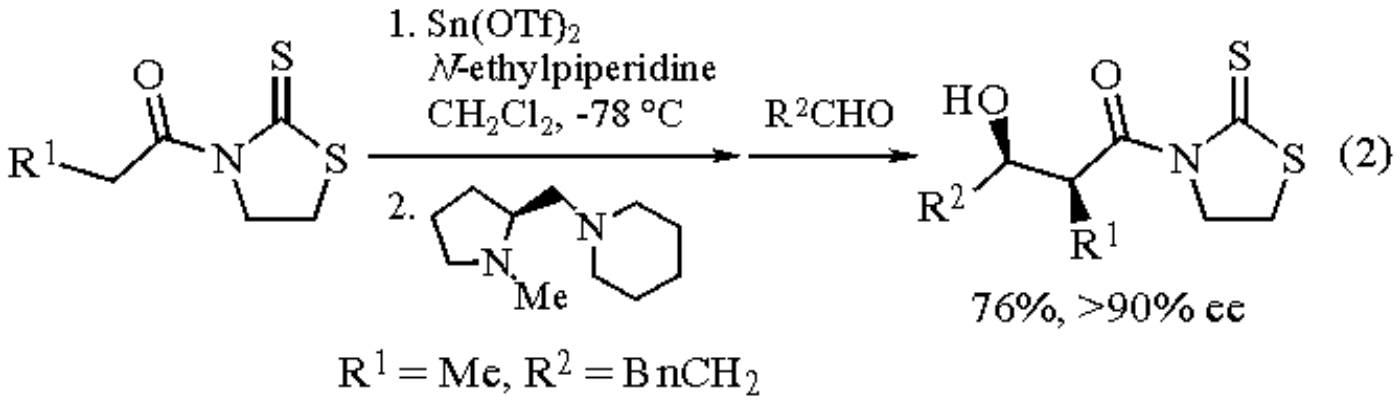

Reactions of ketene silyl acetals with various aldehydes in the presence of a stoichiometric amount of a tin(II) triflate-tin(IV) additive-chiral diamine complex have also been performed with excellent enantioselectivity (eq 3).[10]

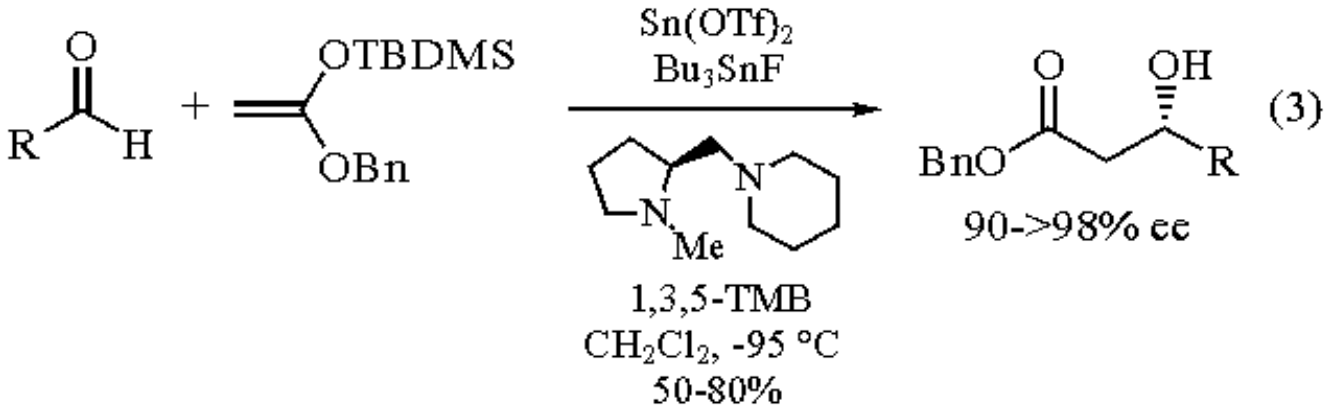

Stereoselective aldol reactions using a catalytic amount of tin(II) triflate have been developed. The diastereoselective reaction between ***Methyl Vinyl Ketone*** and benzaldehyde first demonstrated the usefulness of tin(II) triflate as a catalyst (eq 4).[1]

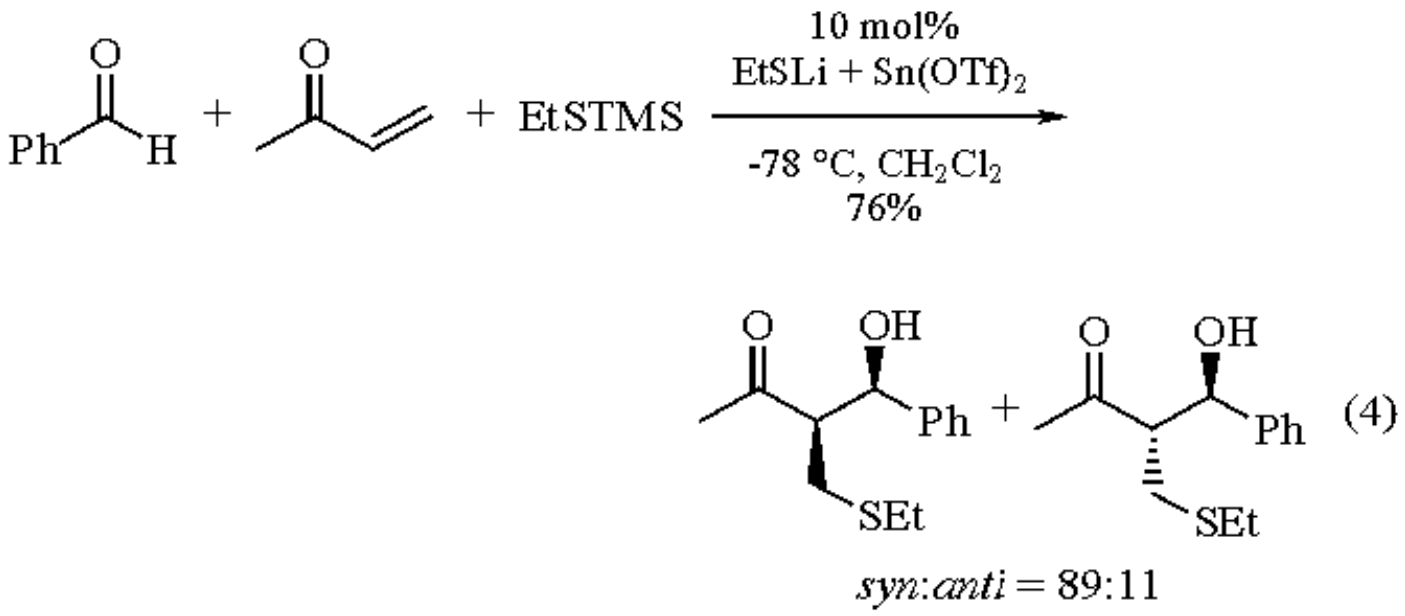

The development of catalytic enantioselective reactions of silyl enol ethers with aliphatic, aromatic, alkynic, and α,β-unsaturated aldehydes has broadened the scope of this catalytic process (eqs 5-7).[7a,b]

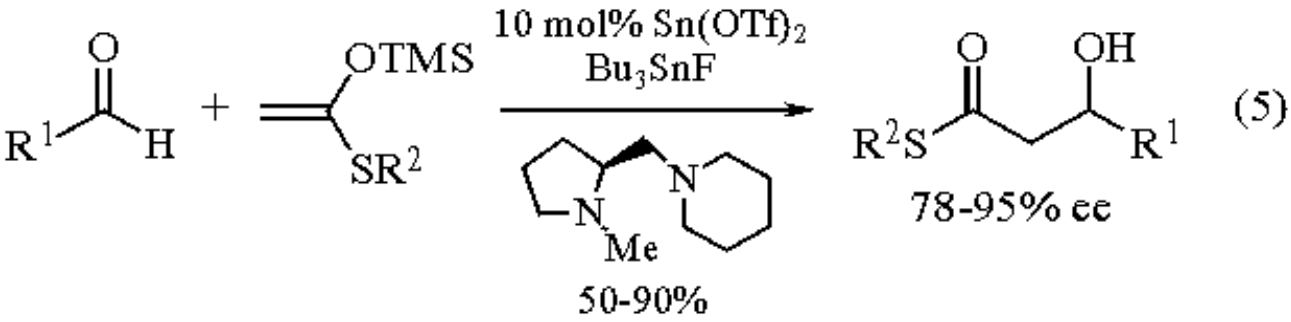

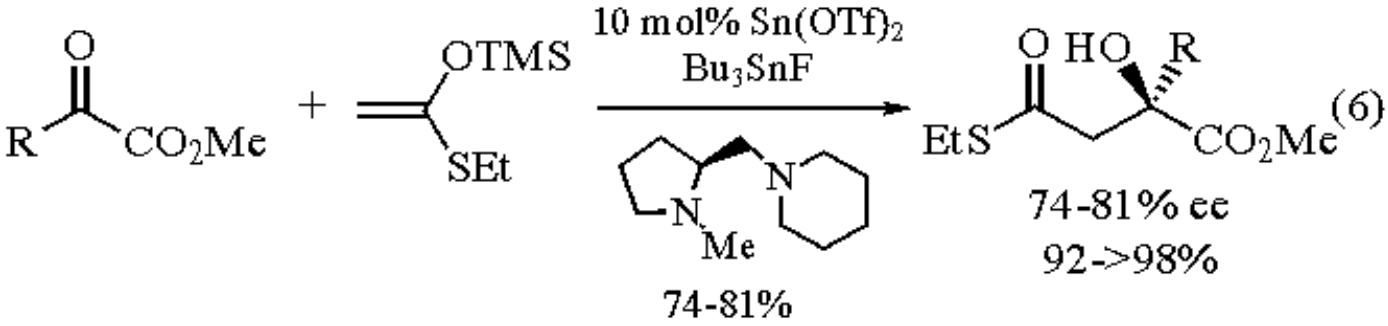

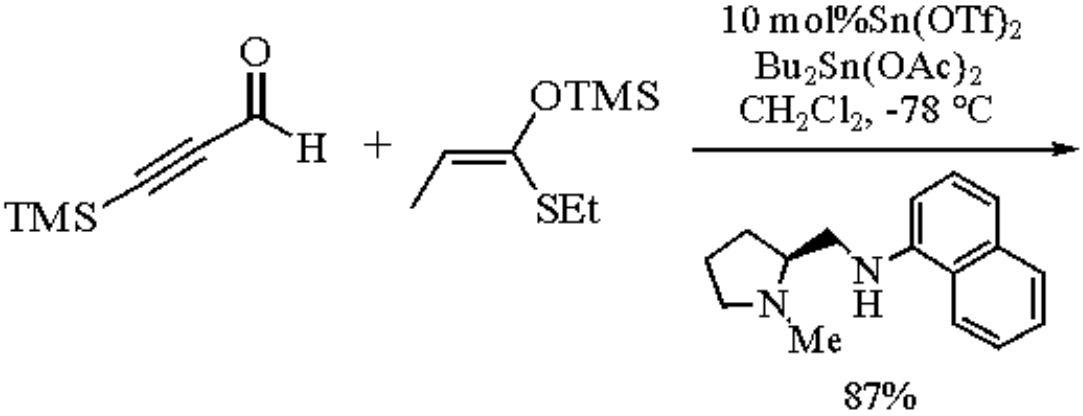

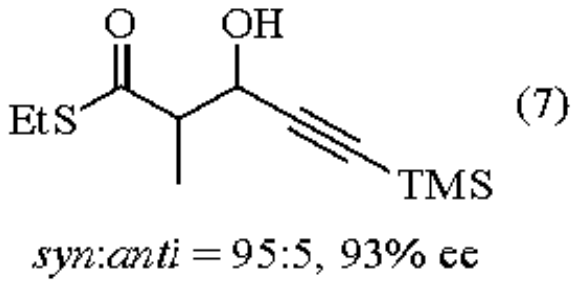

In addition, Mukaiyama has shown that the stereochemistry of these reactions is controlled by the tin(II) triflate-tin(IV) additive-chiral diamine complex and is therefore independent of the chirality of the aldehyde (eqs 8 and 9).[7b,11]

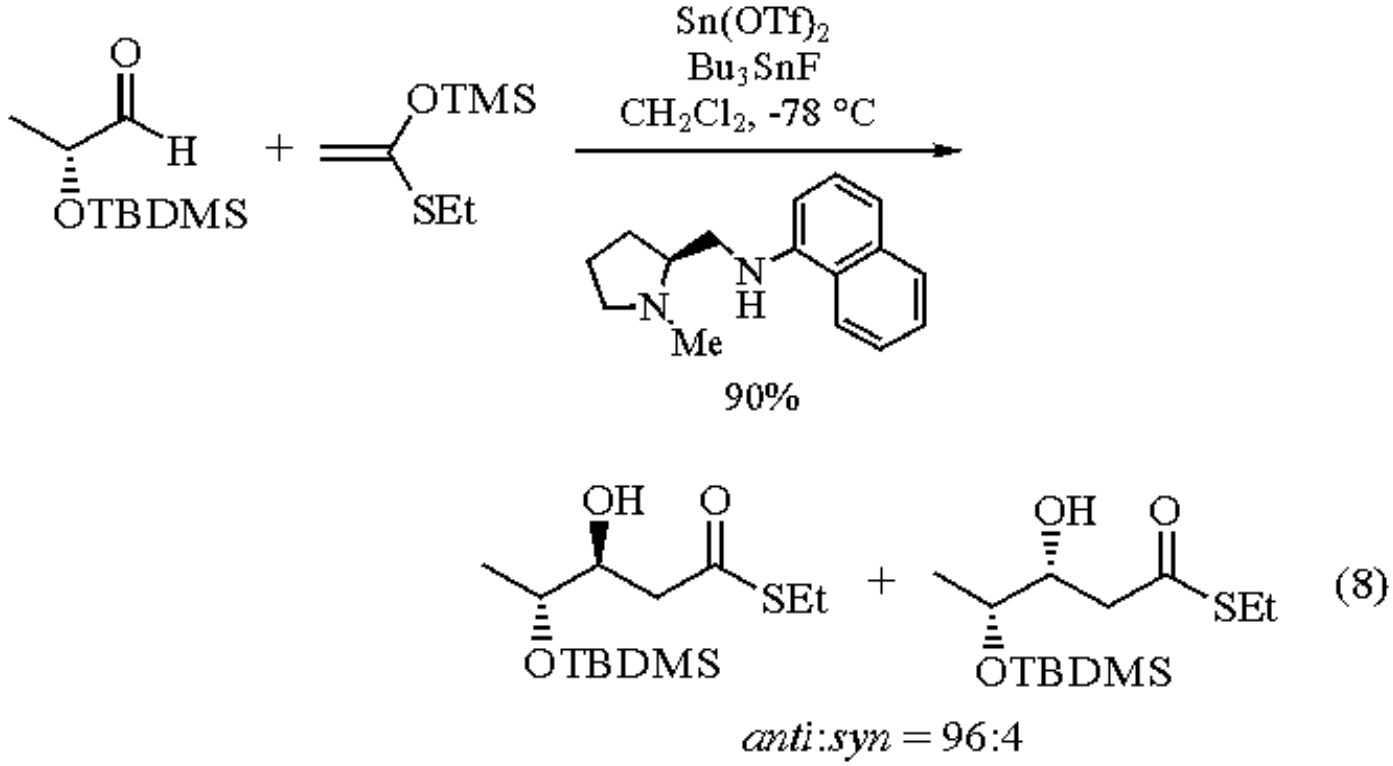

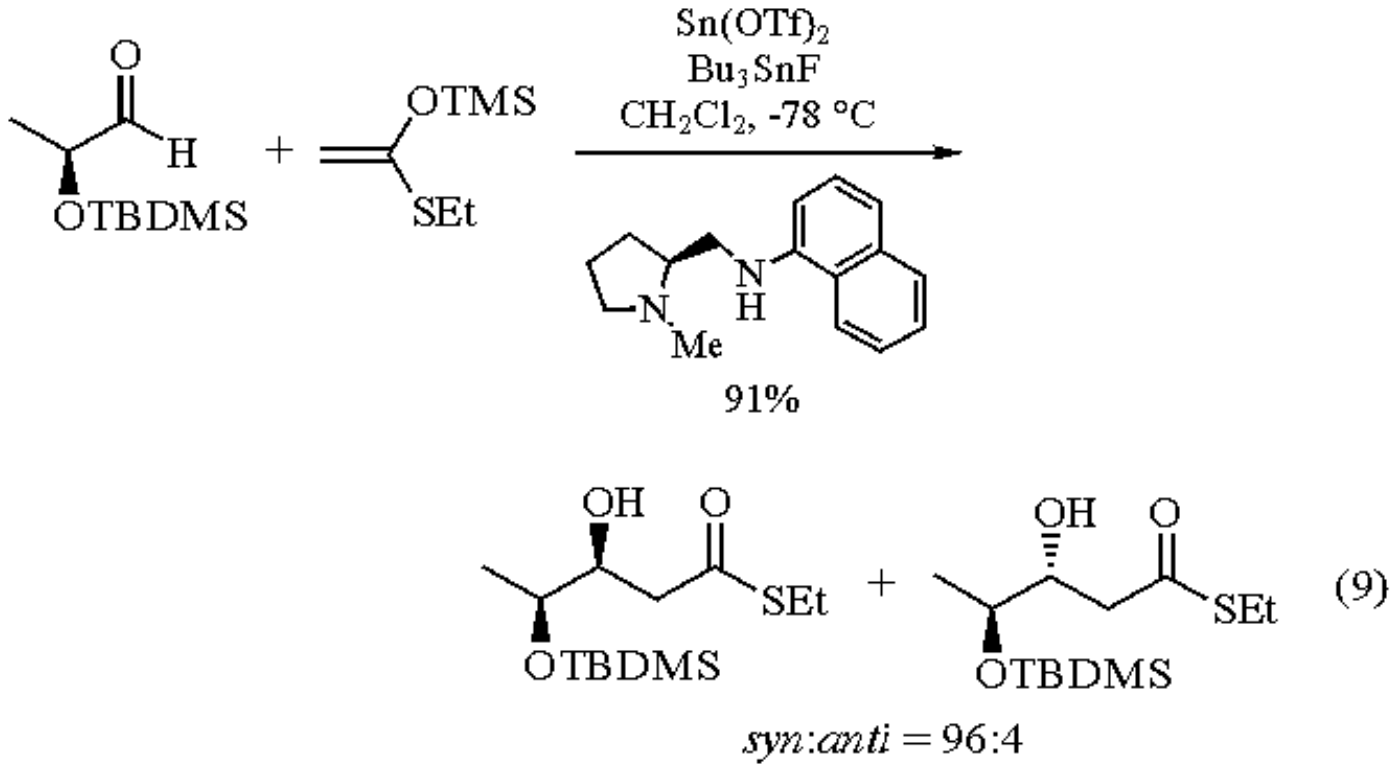

Michael Reaction.

The development of catalytic aldol-type reactions led to the discovery of a tin(II) triflate-catalyzed asymmetric Michael reaction.[1] Specifically, tin(II) enolates, prepared in situ from silyl enethiolates with catalytic amounts of tin(II) triflate and a chiral diamine, react with various α,β-unsaturated ketones to give chiral Michael adducts with 40-70% ee (eq 10).[12] Previously, asymmetric Michael reactions of tin(II) enolates with enones had been demonstrated in stoichiometric systems (eq 11).[13]

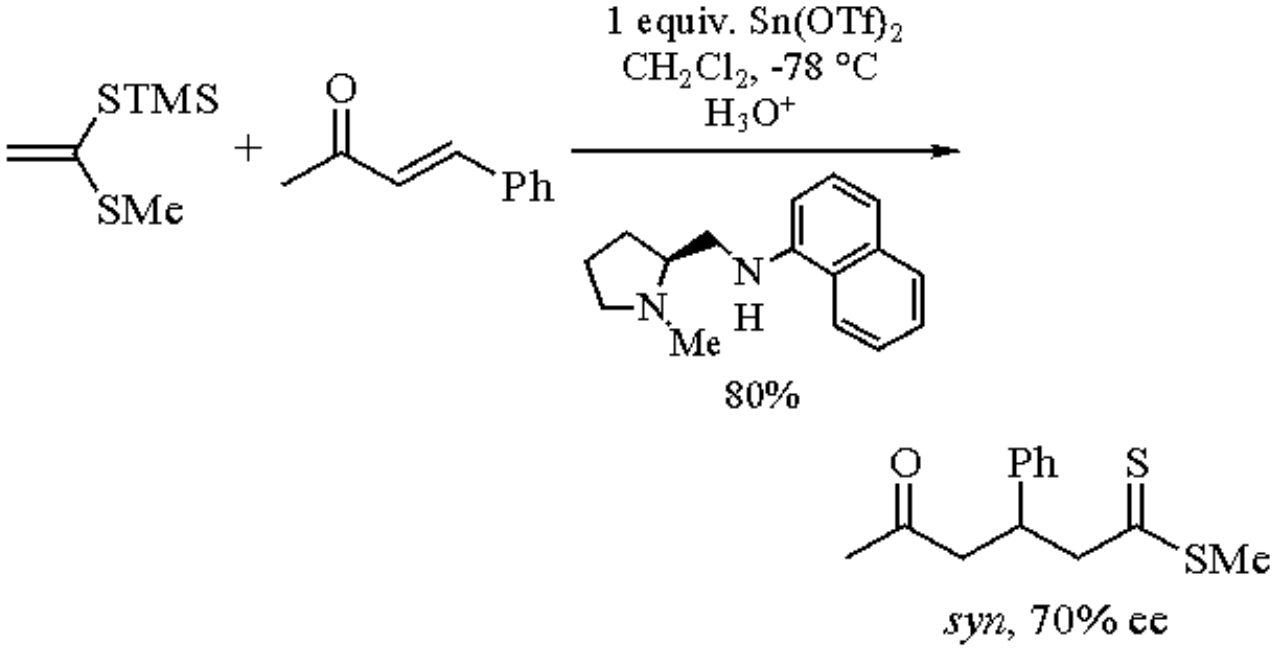

(10)

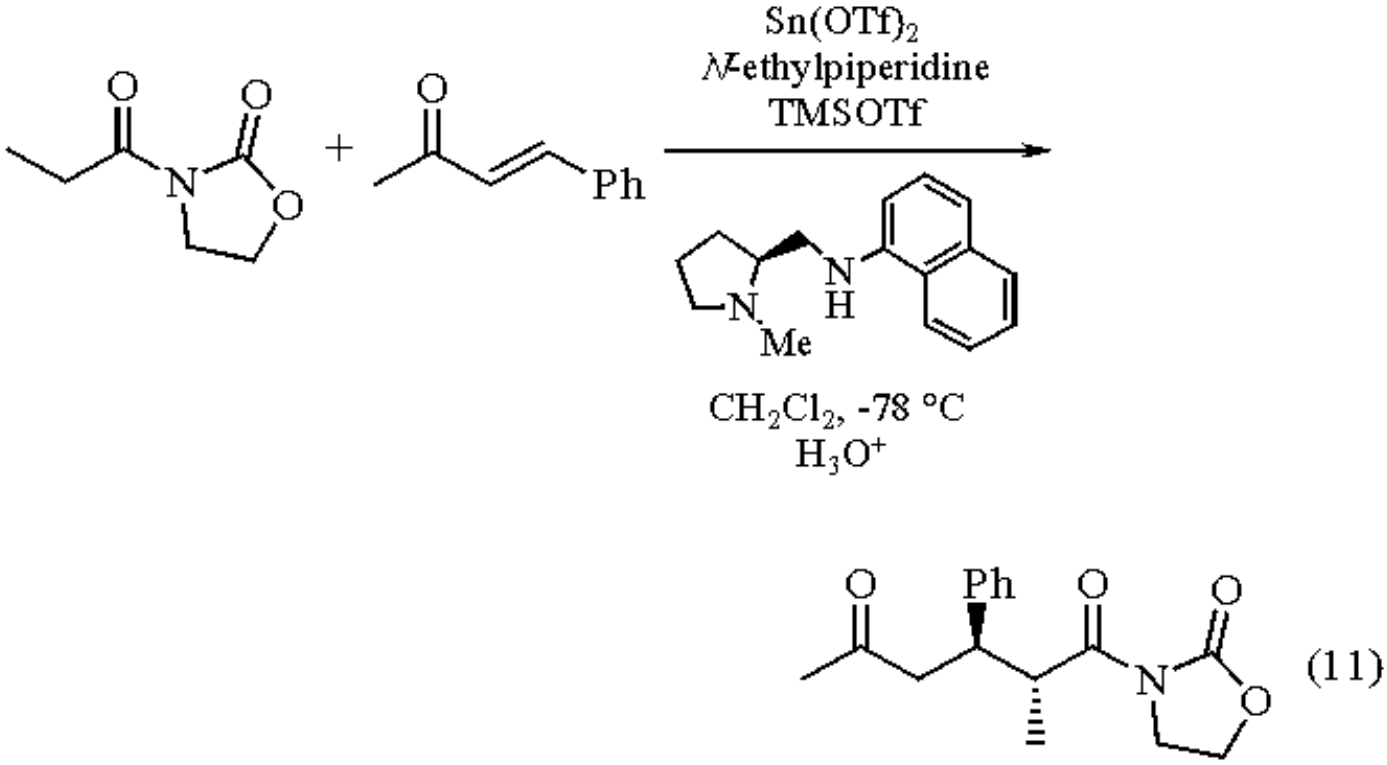

(11)

[2,3]-Wittig Rearrangements.

Tin(II) enolates, generated from allylic glycolate esters and tin(II) triflate in the presence of ***Diisopropylethylamine***, undergo [2,3]-Wittig rearrangements upon warming to room temperature (eq 12).[2a] The corresponding boron enolates of the esters rearrange in a similar manner but with less stereoselectivity.

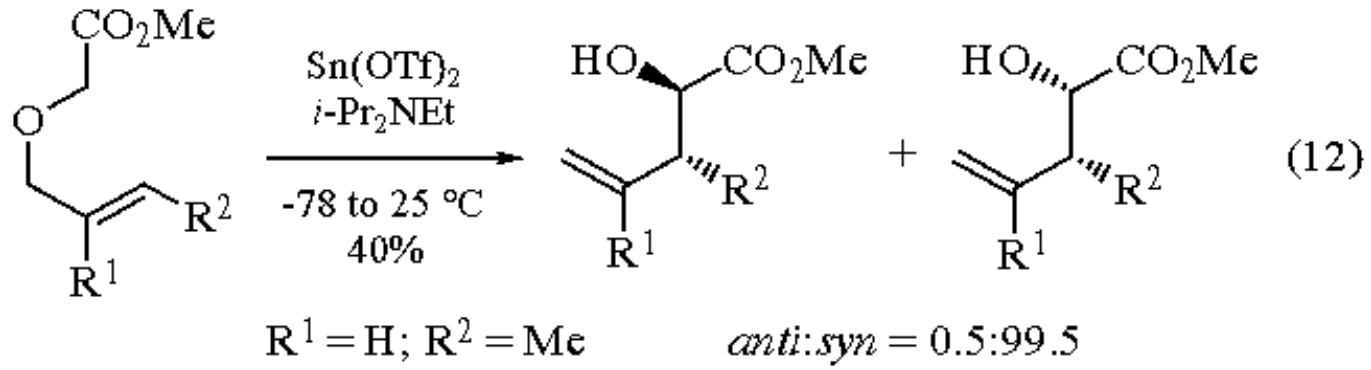

Ireland-Claisen Rearrangement.

An isolated case of an α-alkoxy ester rearranging via a tin(II) enolate has been reported (eq 13).[2b]

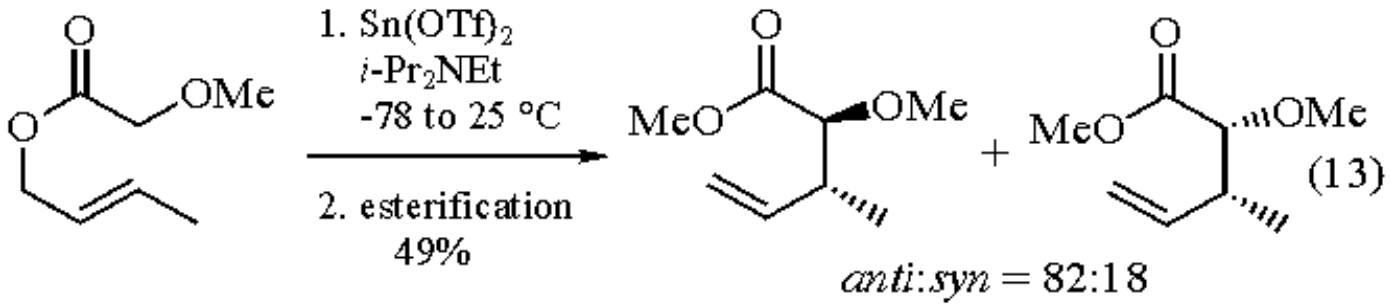

Addition of 1-Alkynes to Aldehydes.

In the presence of a stoichiometric amount of tin(II) triflate, 1-alkynes react with aldehydes and ketones to give alkynic alcohols in 57-91% yield (eq 14).[3] The mechanism of this reaction is, at present, unclear. It has been proposed that the tin(II) triflate reacts with the alkyne to form a tin acetylide which adds to the aldehyde.

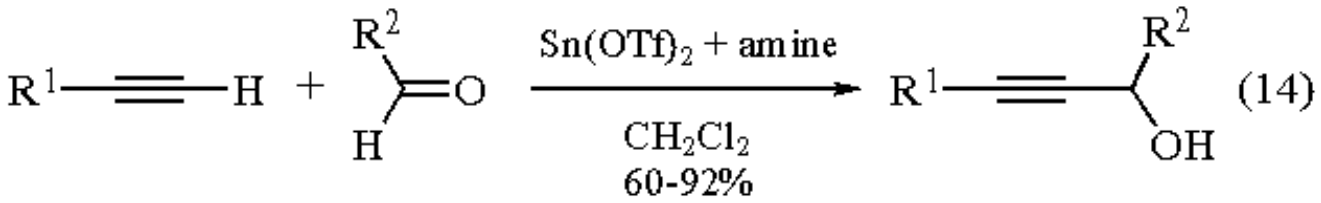

Asymmetric Allylation.

Mukaiyama has designed a chiral allylating agent consisting of an allyldialkylaluminum and a chiral diamine chelated to tin(II) triflate. The reaction of this agent with various aldehydes gives corresponding homoallylic alcohols with good to excellent enantioselectivity (eq 15).[4] Other tin(II) compounds ($SnCl_2$, $SnBr_2$, SnF_2, $Sn(OAc)_2$) react in this system to give the homoallylic alcohols in good yield but with virtually no enantioselectivity.

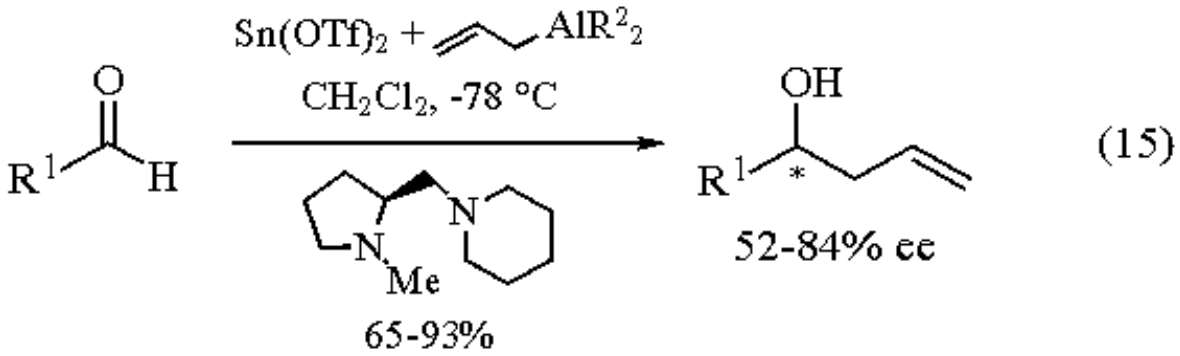

1. Iwasawa, N.; Yura, T.; Mukaiyama, T. *T* **1989**, *45*, 1197.
2. (a) Oh, T.; Wrobel, Z.; Devine, P. *SL* **1992**, 81. (b) Oh, T.; Wrobel, Z.; Rubenstein, S. M. *TL* **1991**, *32*, 4647.
3. Yamaguchi, M.; Hayashi, A.; Minami, T. *JOC* **1991**, *56*, 4091.
4. Mukaiyama, T.; Minowa, N. *BCJ* **1987**, *60*, 3697.
5. Tin(II) triflate is commercially available in >97% purity.
6. Evans, D.; Weber, A. *JACS* **1986**, *108*, 6757.
7. (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *TA* **1991**, *2*, 635. (b) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *CL* **1991**, 989. (c) Kobayashi, S.; Ohtsubo, A.; Mukaiyama, T. *CL* **1991**, 831.
8. Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *T* **1984**, *40*, 1381.
9. (a) Mukaiyama, T.; Asanuma, H.; Hachiya, I.; Harada, T.; Kobayashi, S. *CL* **1991**, 1209. (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *JACS* **1991**, *113*, 4247.
10. Mukaiyama, T.; Kobayashi, S.; Sano, T. *T* **1990**, *46*, 4653.
11. For more details on the tin(II) triflate-tin(IV) additive-chiral diamine complex see: Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *CL* **1989**, 1757.
12. Roush, W. *Chemtracts-Org. Chem.* **1988**, 439.
13. Yura, T.; Iwasawa, N.; Mukaiyama, T. *CL* **1988**, 1021.

Samantha Janisse

Eli Lilly and Company, Indianapolis, IN, USA

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Titanium[1]

Ti

[7440-32-6] · Ti · Titanium · (MW 47.88)

(low-valent titanium, i.e. Ti^0/Ti^I, can be generated from a variety of sources and is used for the inter- and intramolecular reductive coupling of carbonyl and dicarbonyl compounds, imines, and iminium species, and for reductive elimination reactions and reductions)

Physical Data: mp 1677 °C; *d* (α-form) 4.506 g cm^{-3}.

Solubility: unknown but presumably low in most organic solvents. THF and DME appear to be the favored solvents for reactions involving low-valent titanium.

Form Supplied in: a 4:1 ball-milled mixture of $TiCl_3$ and $LiAlH_4$ is available commercially and serves as a precursor to the McMurry reagent (see ***Titanium(III) Chloride-Lithium Aluminum Hydride***). Low-valent titanium can be generated in situ from a variety of other sources as discussed below.

Preparative Methods: low-valent titanium reagents, including Ti^0, can be generated by in situ reduction of Ti^I-Ti^{IV} chlorides. At least a dozen commonly used procedures have been reported including those involving $TiCl_3$/Zn,[2] $TiCl_3$/Mg,[3] $TiCl_3/LiAlH_4$,[4] $TiCl_3$/K,[5] $TiCl_3$/Li,[6] $TiCl_3$/Zn(Cu),[5] $TiCl_3/C_8K$,[7] $CpTiCl_3/LiAlH_4$,[8] $TiCl_4$/Zn,[9] $TiCl_4/Al/AlCl_3$,[8] and $TiCl_4$/Mg(Hg).[8,10] Whether a Ti^0 or a Ti^I species is generated is dependent upon various factors, including the particular reagent combination used and the titanium chloride to reductant ratio employed.

Handling, Storage, and Precautions: most commonly, low-valent titanium species are prepared under an inert atmosphere (nitrogen or argon) immediately prior to use. Presumably, the reagent is pyrophoric although this property may be due to the residual reducing agent used in the preparation process and may not be an inherent property of Ti^0/Ti^I itself. The reagent is moisture sensitive.

Inter- and Intramolecular Coupling of Carbonyl and Dicarbonyl Compounds.

The capacity of low-valent titanium species to effect reductive couplings was reported in 1973-1974 by several independent groups,[1,3,9] but McMurry and his co-workers have exploited such processes most extensively. A number of excellent reviews[1] are available on this and related topics. McMurry has now developed[11] an optimized procedure involving a combination of the $TiCl_3$/dimethoxyethane solvate $TiCl_3(DME)_{1.5}$ and ***Zinc/Copper Couple***. Thus coupling of diisopropyl ketone with the $TiCl_3(DME)_{1.5}$/Zn(Cu) reagent gives an 87% yield of the expected alkene (eq 1). A 4:1 ratio of $TiCl_3(DME)_{1.5}$ to carbonyl compound appears to give the best results. When the same conversion is effected using $TiCl_3/LiAlH_4$ and $TiCl_3$/Zn(Cu), yields of 12% and 37%, respectively, are obtained. Cross coupling of different carbonyl compounds to produce unsymmetrical alkenes can be effected in acceptable yield if one of the components, often acetone, is used in excess.[10] The coupling conditions have proven to be compatible with a variety of other potentially reducible functional groups including carboxylate and sulfonate esters,[12] as well as halides.[13]

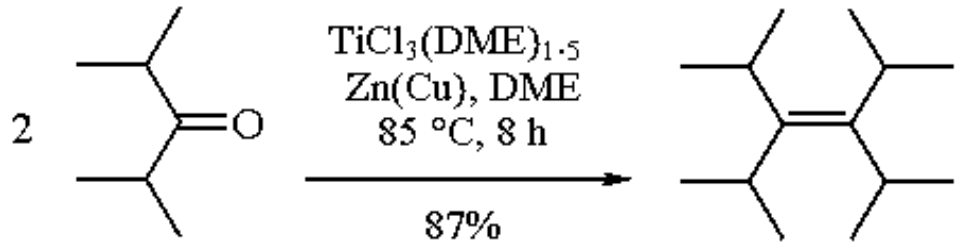

(1)

Intramolecular couplings of dicarbonyl compounds (including diketones, dialdehydes and keto esters) can be effected very efficiently with low-valent titanium (eq 2) and such processes have been exploited extensively in the synthesis of a number of natural products[1] and various novel hydrocarbons[1] (see ***Titanium(III) Chloride-Zinc/Copper Couple*** for examples).

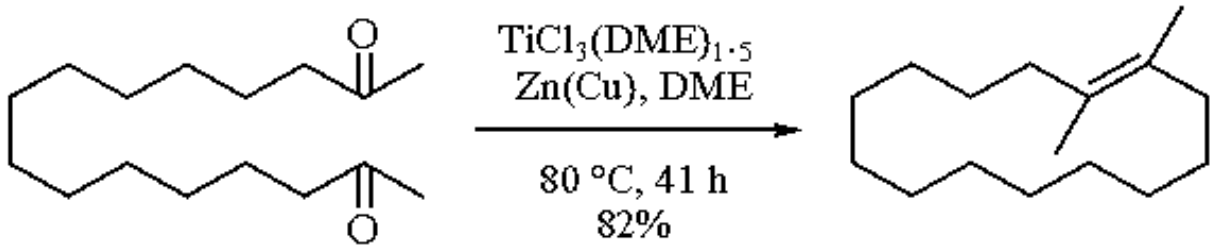

(2)

The geometry (*E* or *Z*) about the alkene double bond being formed in these so-called McMurry reactions is apparently controlled by thermodynamic factors. When the energy difference between the (*E*)- and (*Z*)-alkenes exceeds 4-5 kcal mol^{-1} the former isomer is formed preferentially.[14] However, coupling of alkyl aryl ketones affords the (*Z*)-alkene preferentially, perhaps because of π-complexation between the phenyl rings and Ti^0.[15] The mechanism proposed (eq 3)[1,16] to account for these conversions involves initial pinacolic-type coupling followed by successive elimination of 2 equiv of Ti=O to produce the observed products. When short reaction times and low temperatures are used, pinacols can be isolated. If such species are resubjected to the normal coupling conditions, deoxygenation occurs and the expected alkene results. Interestingly, when stereochemically pure pinacols are subjected to reaction with low-valent titanium reagents, then mixtures of (*E*)- and (*Z*)-alkenes are produced although some stereochemistry is preserved.[1a]

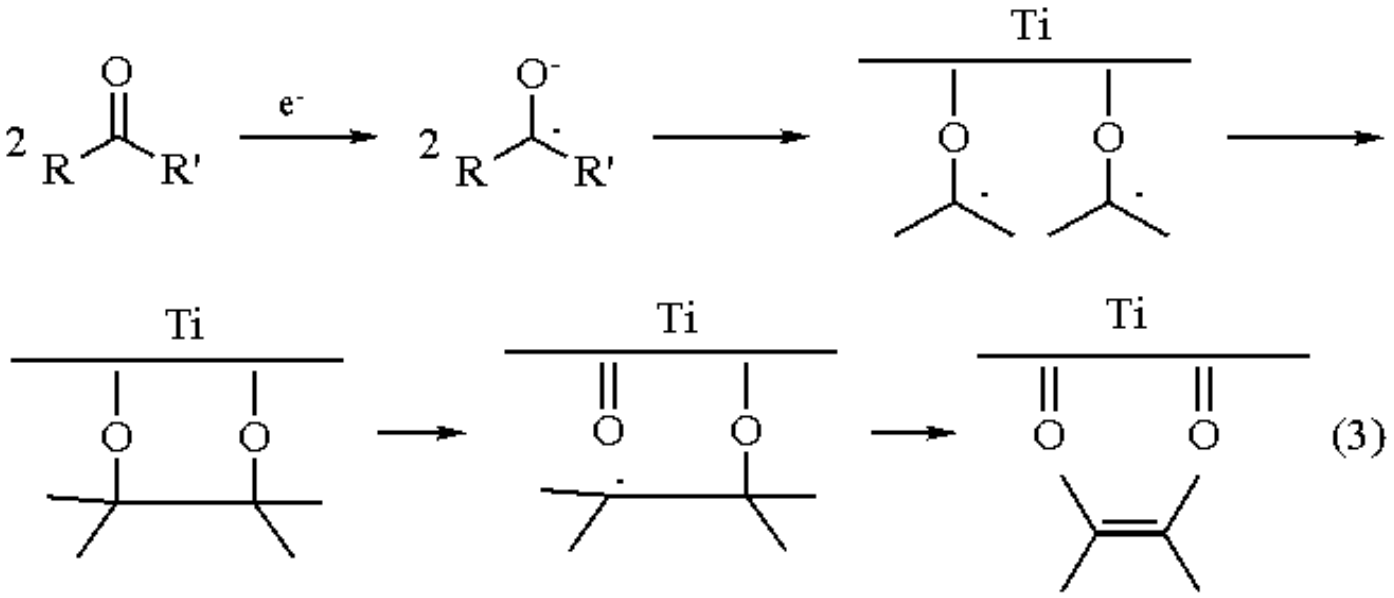

(3)

The reductive coupling of imines and related iminium species to give *vic*-diamines can be effected by low-valent titanium species.[17-19] In those cases where it is relevant, low to modest diastereoselectivities are observed (eq 4). Allylic alcohols, benzylic alcohols, and benzylic halides all undergo reductive coupling in the presence of certain low-valent titanium reagents (see ***Titanium(III) Chloride-Lithium Aluminum Hydride***).

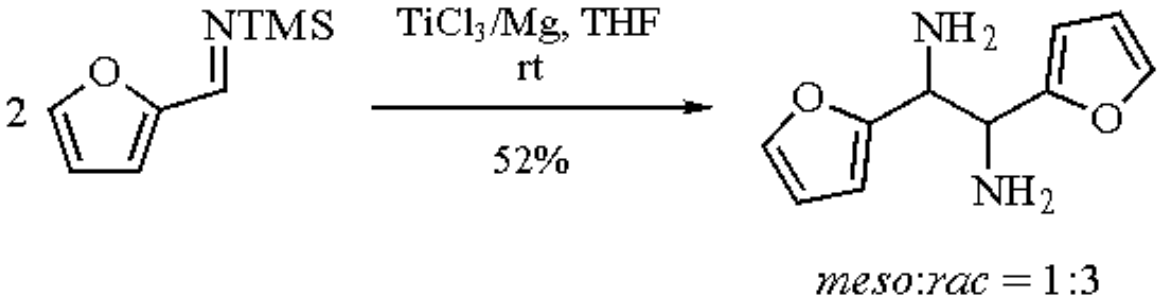

(4)

Reductive Eliminations.

vic-Dibromides,[20,21] bromohydrins,[22,23] epoxides,[22,24-27] hydroxy sulfides,[28-30] and allylic diols,[31-34] as well as 1,2-diols (pinacols), undergo reductive elimination on exposure to various low-valent titanium species, resulting in the formation of the corresponding alkene or 1,3-alkadiene. The dithioacetals of various acyloins also suffer reductive elimination upon treatment with Ti^0, thereby affording vinyl

sulfides.[35]

Reductions.

Various reductions can be effected with Ti^0/Ti^I species. Thus enol phosphates are converted into the corresponding alkenes[36] while analogous reduction of aryl phosphates[37] provides a useful protocol for the deoxygenation of phenols. Acyl, vinyl, and alkyl halides, as well as dithioacetals, can all be converted into the corresponding hydrocarbon on exposure to various sources of low-valent titanium,[38-41] while both nitriles[42] and isocyanides[43] suffer reductive removal of the -CN and -NC groups, respectively. Reduction (net addition of the elements of H_2) of both isolated[44-46] and conjugated[47,48] double bonds can also be accomplished with low-valent titanium.

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Titanium(IV) Chloride

[7550-45-0] · Cl_4Ti · Titanium(IV) Chloride · (MW 189.68)

(Lewis acid catalyst;[52] affects stereochemical course in cycloaddition[38,39] and aldol reactions;[4-17] electrophilic substitutions;[55] powerful dehydrating agent; when reduced to low-valent state, effects C-C bond formation by reductive coupling;[7-9] reduction of functional groups[81])

Physical Data: mp -24 °C, bp 136.4 °C, *d* 1.726 g cm^{-3}.

Solubility: sol THF, toluene, CH_2Cl_2.

Form Supplied in: neat as colorless liquid; solution in CH_2Cl_2; solution in toluene; $TiCl_4$.2THF *[31011-57-1]*.

Preparative Methods: see Perrin et al.[1]

Purification: reflux with mercury or a small amount of pure copper turnings and distill under N_2 in an all-glass system. Organic material can be removed by adding aluminum chloride hexahydrate as a slurry with an equal amount of water (ca. 2% weight of the amount of $TiCl_4$), refluxing the mixture for 2-6 h while bubbling in Cl_2 which is subsequently removed by a stream of dry air, before the $TiCl_4$ is distilled, refluxed with copper, and distilled again. Volatile impurities can be removed using a technique of freezing, pumping, and melting.[2]

Handling, Storage, and Precautions: moisture sensitive; reacts violently, almost explosively, with water; highly flammable; toxic if inhaled or swallowed; causes burns on contact with skin; use in a fume hood.

General Discussion.

$TiCl_4$ is a strong Lewis acid and is used as such in organic reactions. It has high affinity for oxygenated organic molecules and possesses a powerful dehydrating ability. Low-valent titanium, from the reduction of $TiCl_4$ by metal or metal hydrides, is used for reductive coupling reactions and for reduction of functional groups.

Carbon-carbon bond formation by reductive coupling of ketones by low-valent titanium leads to vicinal diols and alkenes, as does coupling using low-valent reagents from ***Titanium(III) Chloride***. Reviews are available on the preparation and reactions of low-valent titanium.[3-6] The reagent from ***Titanium(IV) Chloride-Zinc*** in THF or dioxane in the presence of pyridine transforms ketones into tetrasubstituted alkenes. Unsymmetrical ketones yield (*E*)/(*Z*)-isomer mixtures (eq 1). Strongly hindered ketones react slowly and may preferentially be reduced to alcohols.[7] Reductive coupling of diketo sulfides yields 2,5-dihydrothiophenes (eq 2).[8] The macrocyclic porphycene has been obtained, albeit in low yield, by McMurry coupling of diformylbipyrrole (eq 3).[9] Aldimines are reductively coupled in a reaction analogous to the reaction of carbonyl compounds. The product is a 1:1 mixture of *meso*- and (±)-isomers (eq 4).[10]

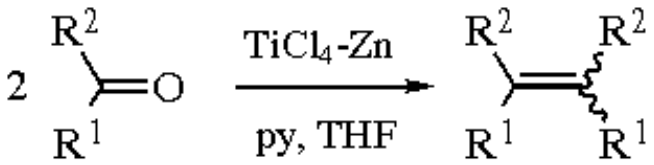

(1)

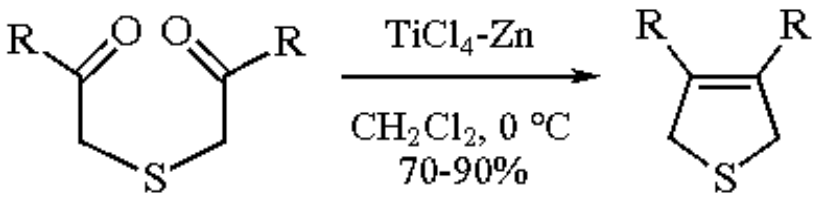

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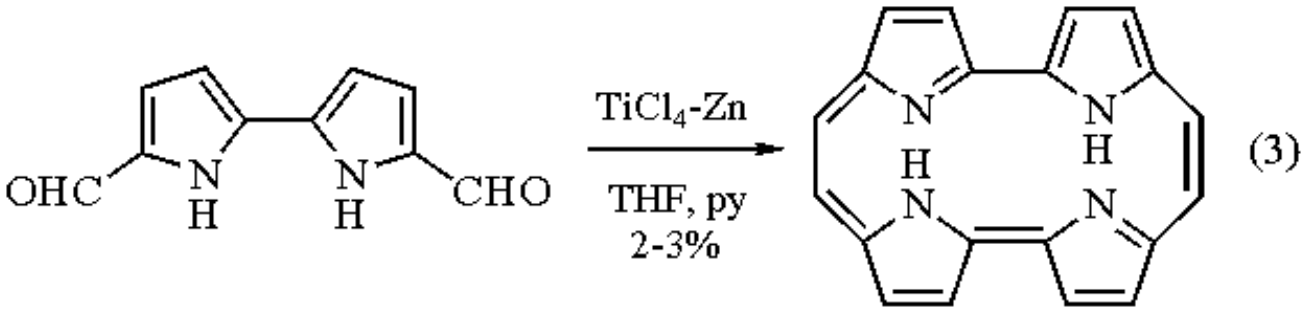

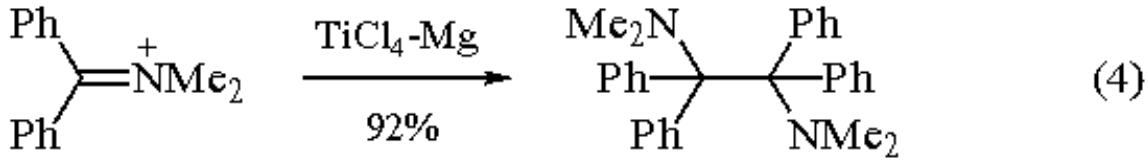

Methylenation of aldehydes and ketones results from reactions with the complex from $TiCl_4$-Zn and ***Diiodomethane*** or ***Dibromomethane*** (eq 5). The reagent can be used for methylenation of enolizable oxo compounds.[6] Recommended modifications to the reagent have been reported.[11] In keto aldehydes, selective methenylation of the keto group results when the aldehyde is precomplexed with ***Titanium Tetrakis(diethylamide)***. Chemoselective methenylation of the aldehyde function is possible by direct use of CH_2I_2/Zn/***Titanium Tetraisopropoxide*** (eq 6).[12] Cyclopropanation to *gem*-dihalocyclopropanes uses ***Lithium Aluminum Hydride-Titanium(IV) Chloride***. The exclusion of a strong base, as frequently used in alternative procedures, is an advantage (eq 7).[13] Allylation of imines has been effected by low-valent titanium species generated from $TiCl_4$ and ***Aluminum*** foil (eq 8).[14]

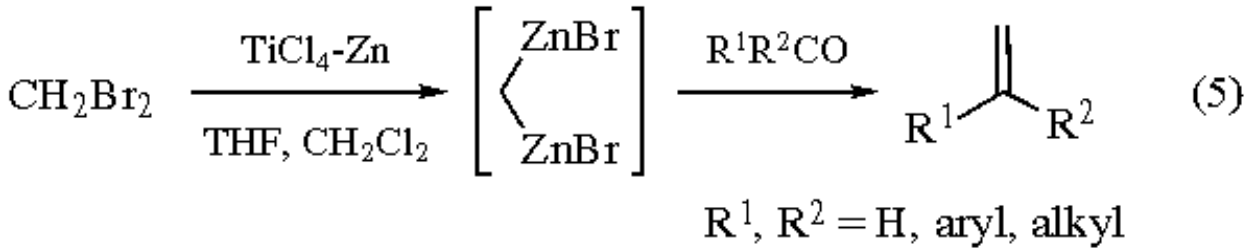

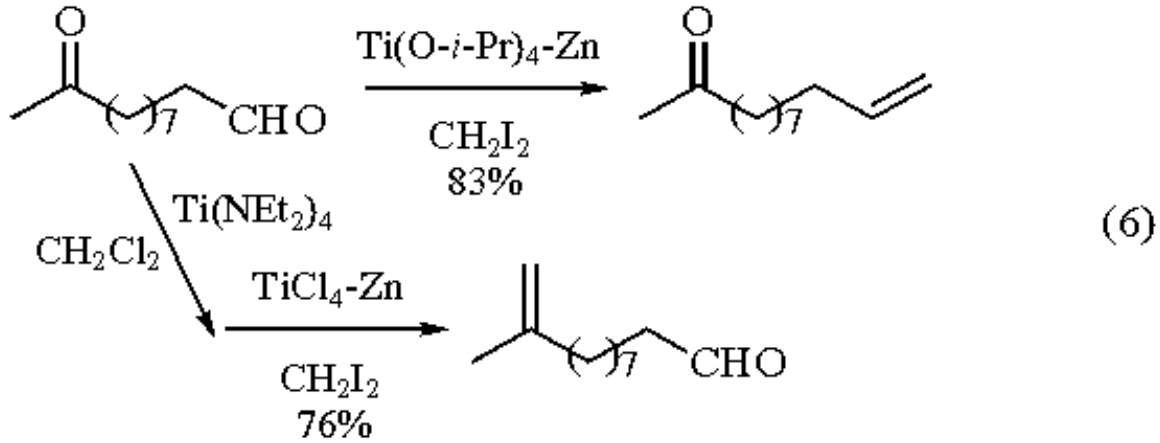

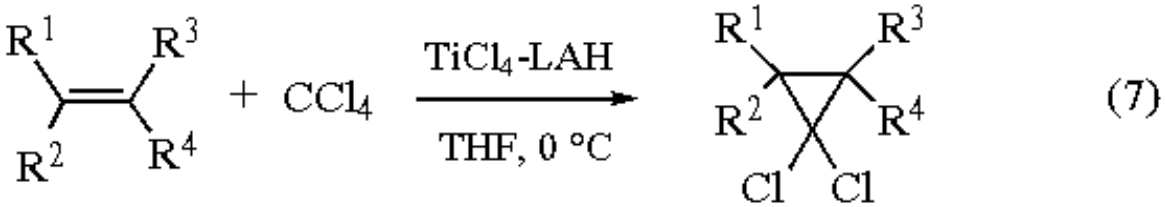

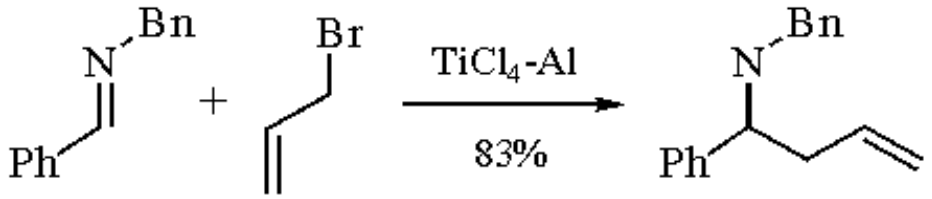

(8)

$TiCl_4$ is a powerful activator of carbonyl groups and promotes nucleophilic attack by a silyl enol ether. The product is a titanium salt of an aldol which, on hydrolysis, yields a β-hydroxy ketone. $TiCl_4$ is generally the best catalyst for this reaction. The temperature range for reactions with ketones is normally 0-20 °C; aldehydes react even at -78 °C, which allows for chemoselectivity (eq 9).[15] In α- or β-alkoxy aldehydes, the aldol reaction can proceed with high 1,2- or 1,3-asymmetric induction. With the nonchelating Lewis acid ***Boron Trifluoride Etherate***, the diastereoselectivity may be opposite to that obtained for the chelating $TiCl_4$ or ***Tin(IV) Chloride*** (eq 10).[16]

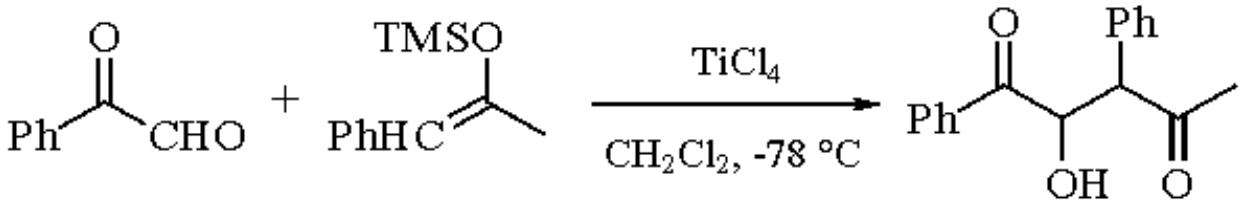

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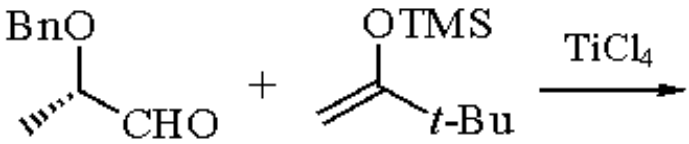

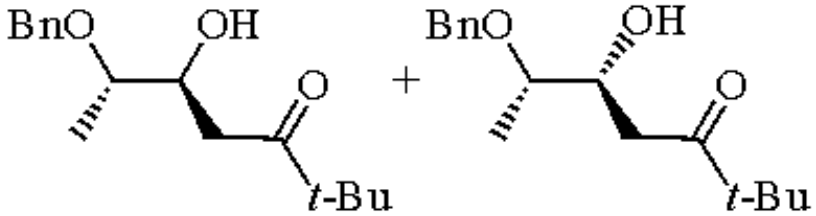

(10)

$TiCl_4$,	85%	>95:5
BF_3		10:90

Titanium enolates are generally prepared by transmetalation of alkali-metal enolates but may also arise as structural parts of intermediates in $TiCl_4$-promoted reactions. This is illustrated in a stereoselective alkylation using an oxazolidinone as a chiral auxiliary (eq 11). The enolate, or its ate complex, may be the intermediate in the reaction.[17]

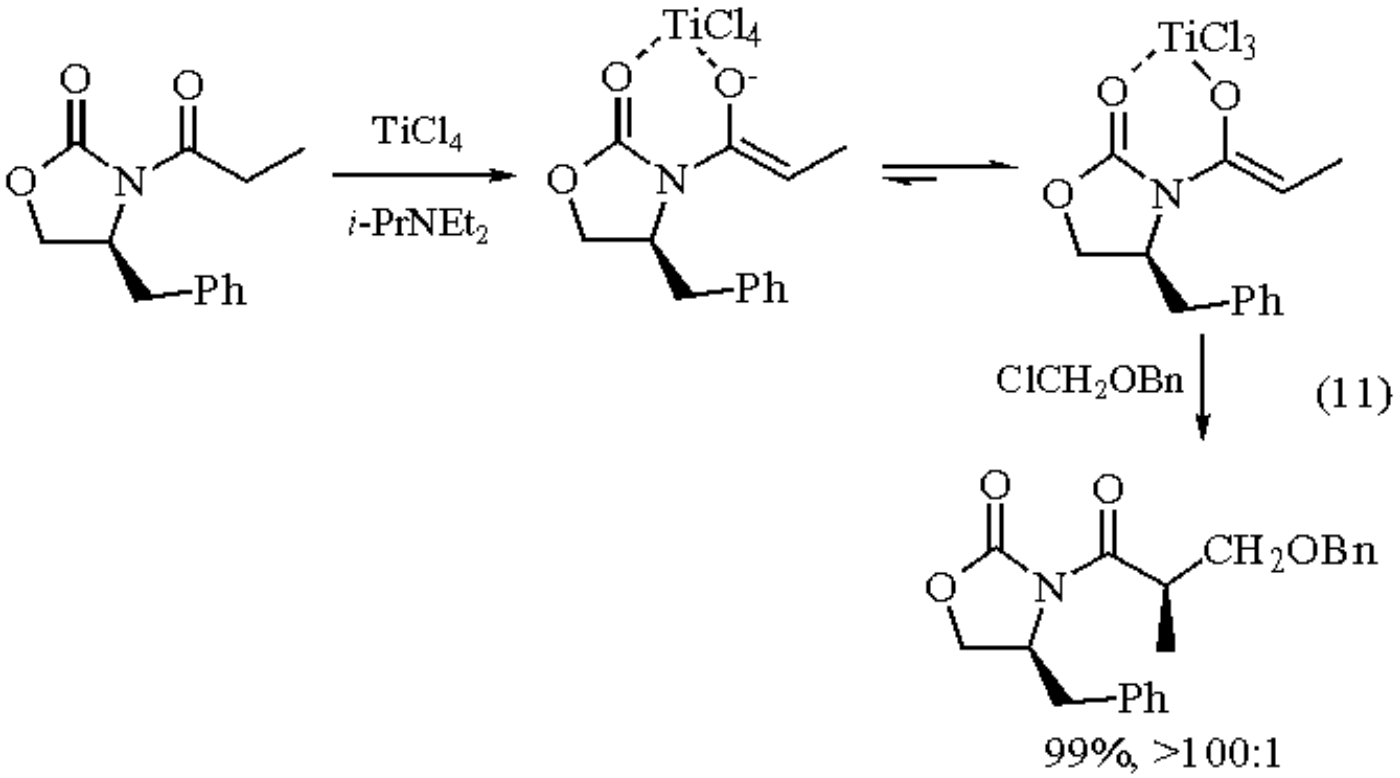

(11)

The stereoselectivity in $TiCl_4$-promoted reaction of silyl ketene acetals with aldehydes may be improved by addition of ***Triphenylphosphine*** (eq 12).[18] Enol ethers, as well as enol acetates, can be the nucleophile (eqs 13 and 14).[19] 2-Acetoxyfuran, in analogy to vinyl acetates, reacts with aldehydes to furnish 4-substituted butenolides under the influence of $TiCl_4$ (eq 15).[20]

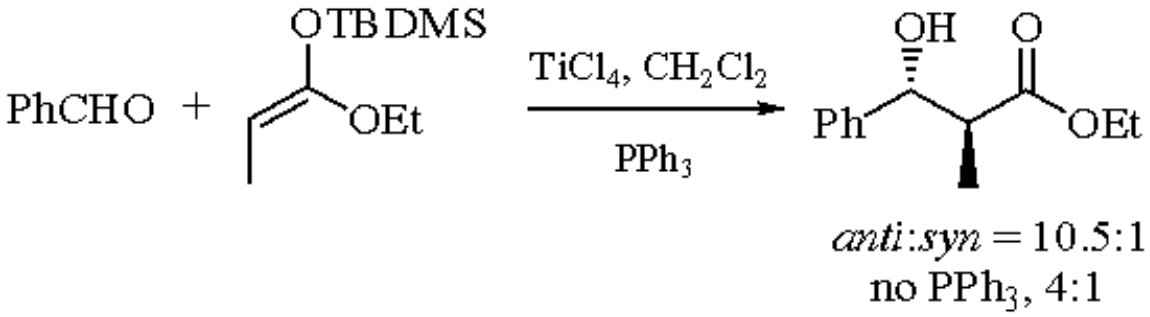

(12)

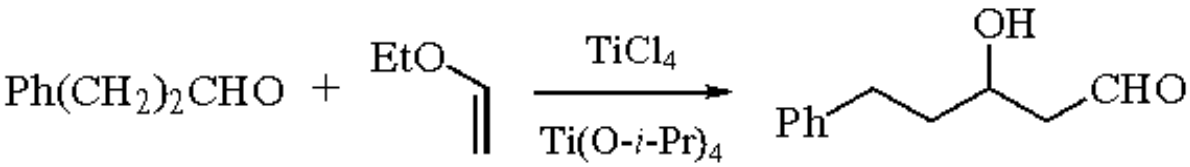

(13)

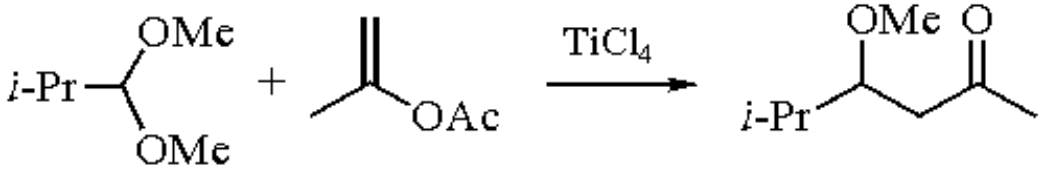

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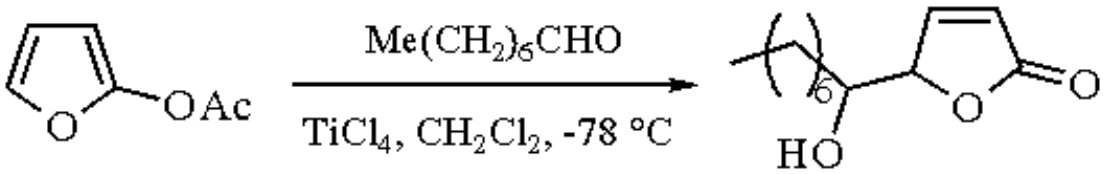

(15)

Silyl enol ethers react with acetals at -78 °C to form β-alkoxy ketones.[21] In intramolecular reactions, six-, seven-, and eight-membered rings are formed.[22] With 1,3-dioxolanes (acetals), 1-2 equiv of $TiCl_4$ leads to pyranone formation (eq 16), whereas no cyclization products are obtained with $SnCl_4$ or $ZnCl_2$.[23]

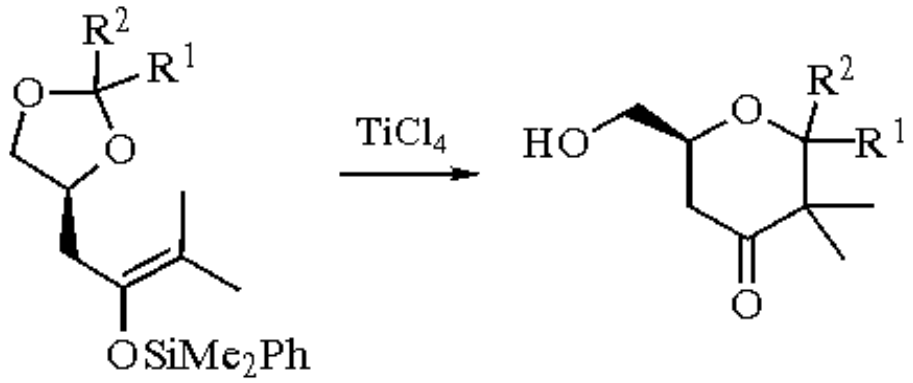

(16)

Alkynyltributyltin compounds react with steroidal aldehydes. In the presence of $TiCl_4$ the reaction gives 9:1 diastereoselectivity (eq 17). Reactions of alkynylmetals with chiral aldehydes generally show only slight diastereoselectivity.[24] With silyloxyacetylenes and aldehydes, α,β-unsaturated carboxylic acid esters are formed with high (*E*) selectivity (eq 18).[25]

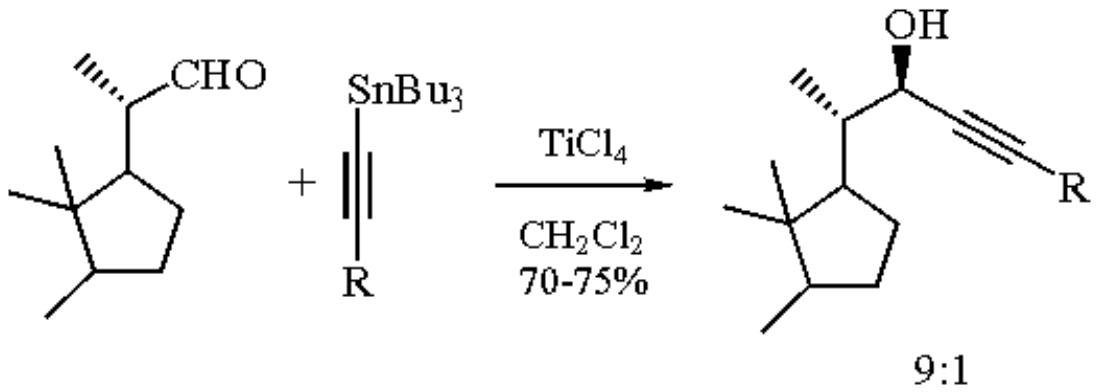

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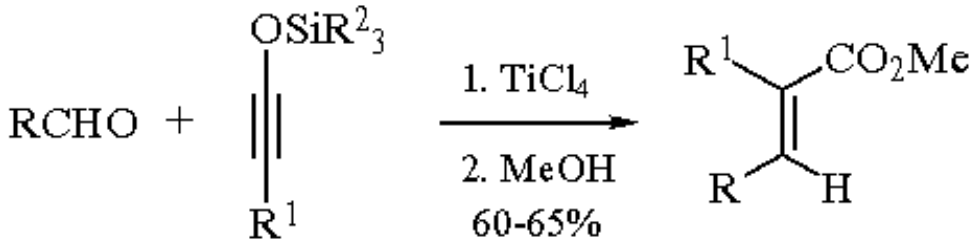

(18)

Allylsilanes are regiospecific in their Lewis acid-catalyzed reactions, the electrophile bonding to the terminus of the allyl unit remote from the silyl group (eq 19).[26,27] Allylstannanes are less reliable in this respect.[26,28] The example in eq 19 illustrates regioselectivity.[29] On extended conjugation the reaction takes place at the terminus of the extended system (eq 20).[30]

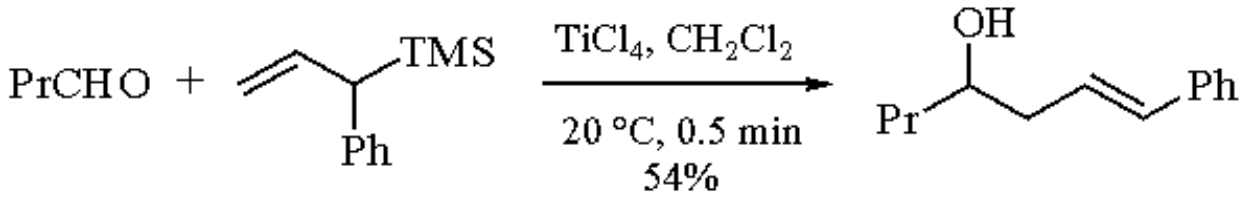

(19)

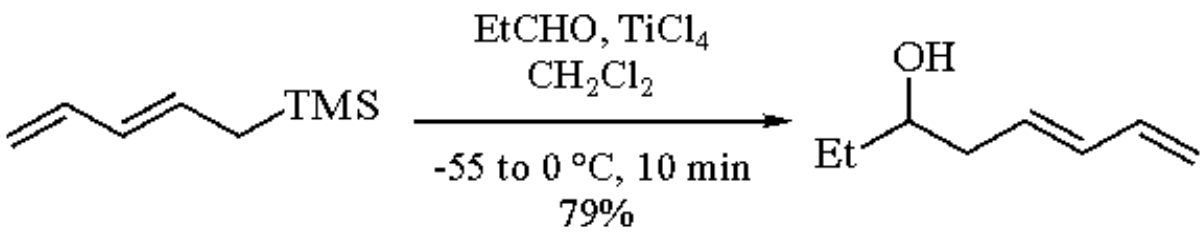

(20)

Intramolecular reactions work well, both for allylstannanes and allylsilanes. An epoxide can be the electrophile. Opening of the epoxide with allylic attack gives the cyclic product (eq 21). $TiCl_4$ is superior to $Ti(O\text{-}i\text{-}Pr)_4$, $SnCl_4$, and ***Aluminum Chloride***, the other Lewis acids tested in the cyclization reaction. The reaction is stereospecific.[31]

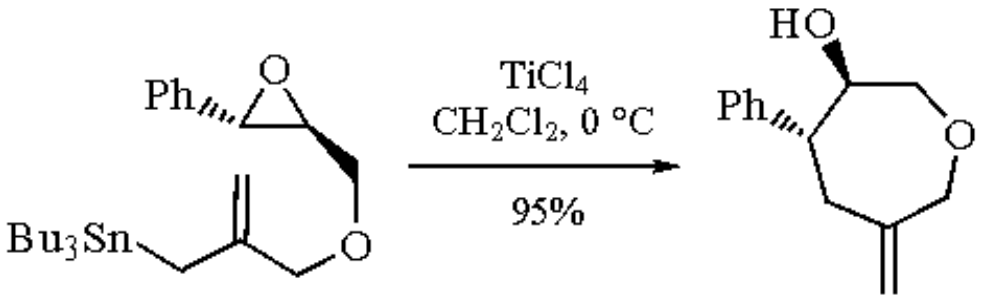

(21)

Stereochemical aspects in these $TiCl_4$-promoted reactions have been covered in reviews.[26,27] Acetals are very good electrophiles for allylsilanes, and may be better than the parent oxo compounds because the products are less prone to further reaction; intramolecular reactions are facile.[26,32] In the unsymmetrical acetal in eq 22, the methoxyethoxy group departs selectively because of chelation to the Lewis acid.[33]

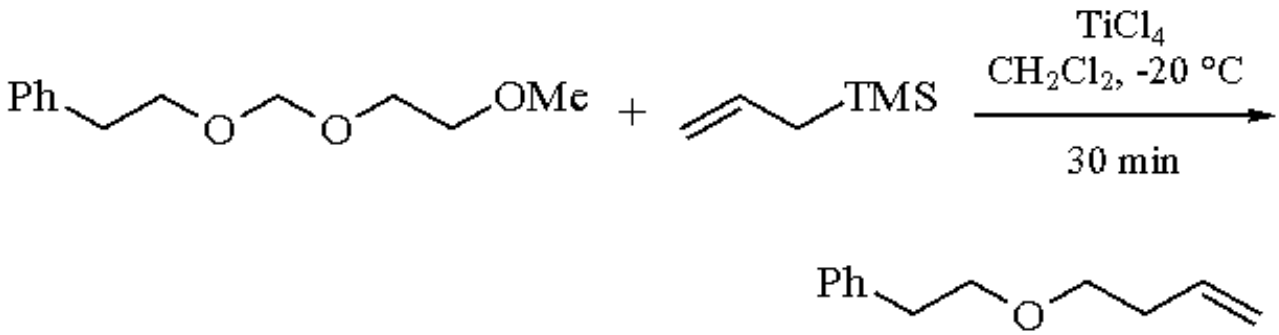

(22)

The $TiCl_4$-mediated addition of allenylsilanes to aldehydes and ketones provides a general, regiocontrolled route to a wide variety of substituted homopropargylic alcohols. With acetals, corresponding ethers are formed (eq 23).[34] Allenylation of acetals results from the reaction of propargylsilanes with acetals. The products are α-allenyl ethers (eq 24).[35]

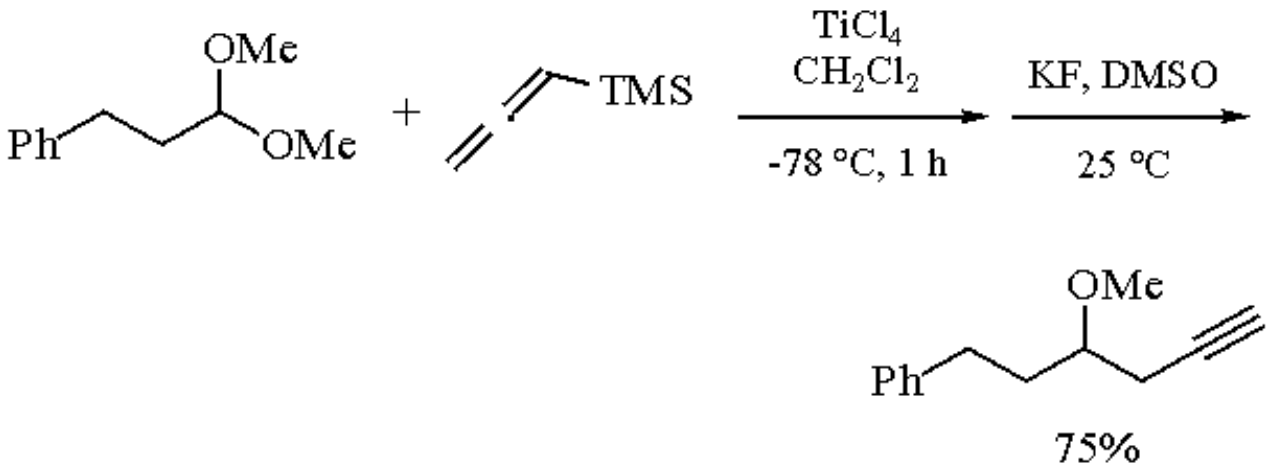

(23)

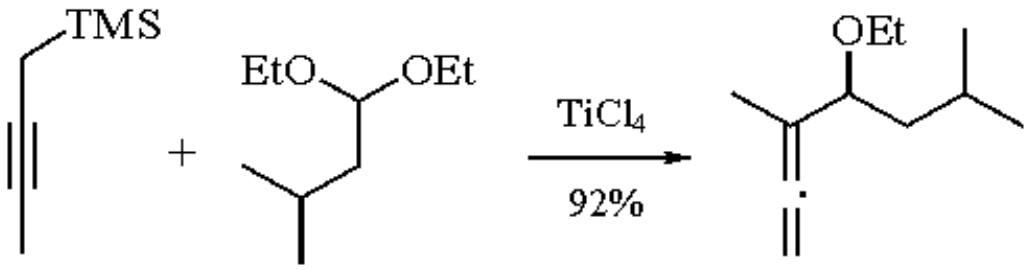

(24)

Homoallylamines are formed in $TiCl_4$- or $BF_3.OEt_2$-mediated reactions between allylstannanes and aldimines. Crotyltributyltin gives mainly *syn*-β-methyl homoallylamines under optimal conditions (eq 25).[36]

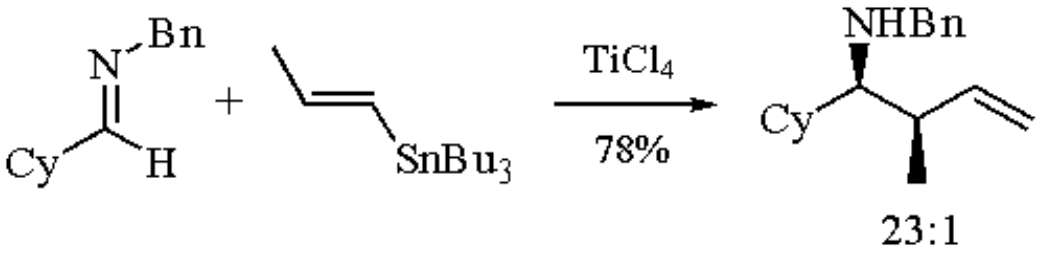

(25)

Diastereoselective Mannich reactions may result with $TiCl_4$ as adjuvant (eq 26); transmetalation of the initial lithium alkoxide adduct and displacement by a lithium enolate gives a diastereoselectivity of 78%.[37]

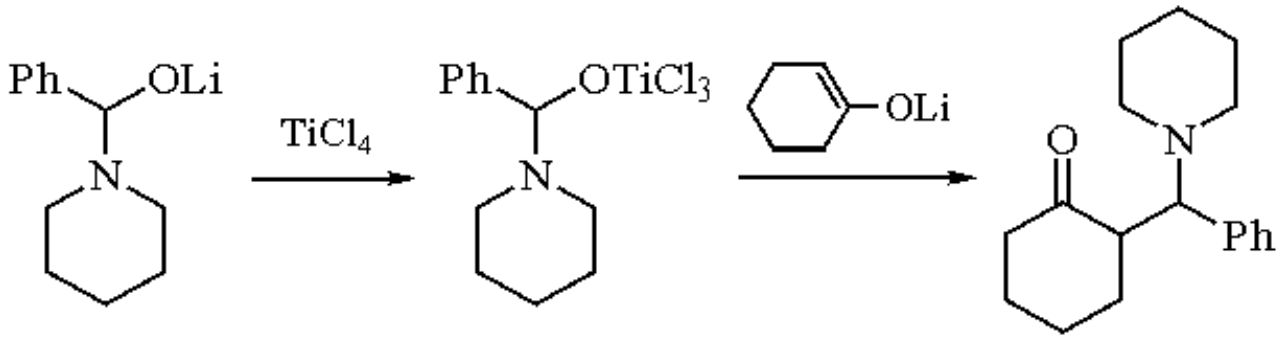

(26)

Lewis acid catalysis increases the reactivity of dienophiles in Diels-Alder reactions by complexing to basic sites on the dienophile. In aldehydes, complexation takes place via the lone pair on the carbonyl oxygen. The stereochemistry is strongly influenced by the Lewis acids.[38] Under chelating conditions, when α-alkoxy aldehydes are used, the prevalent products from $TiCl_4$ catalysis have *cis* configuration (eqs 27 and 28). Stereochemical aspects of pericyclic pathways or passage through aldol type intermediates have been summarized and discussed.[38,39]

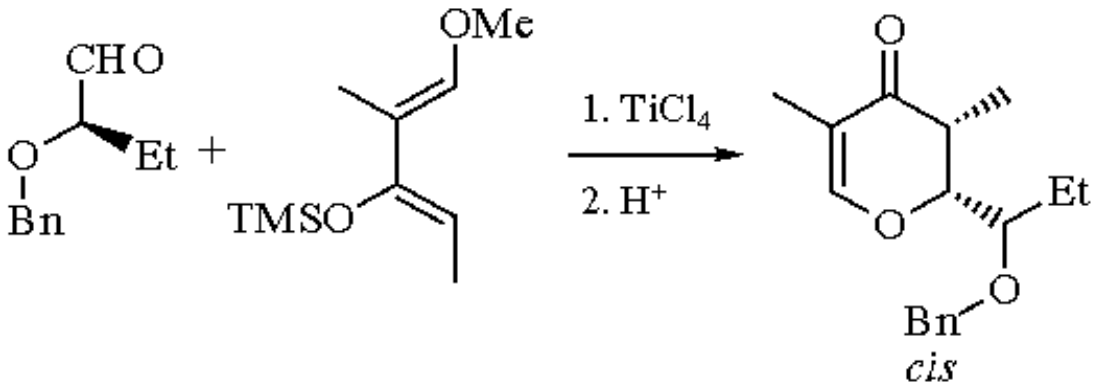

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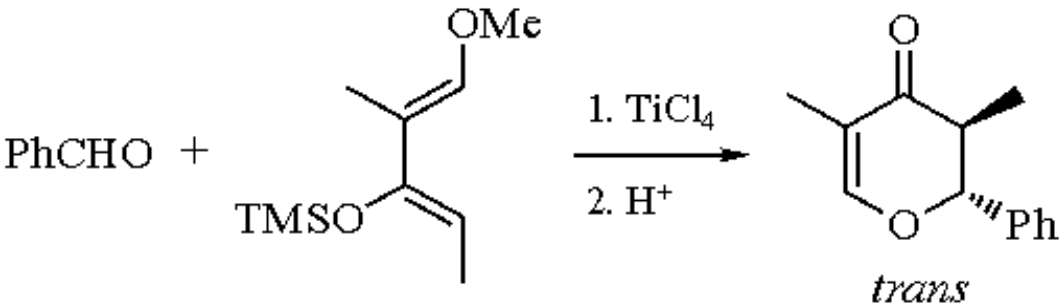

(28)

Ketene silyl acetals can be dimerized to succinates on treatment with $TiCl_4$ in CH_2Cl_2 (eq 29). No reaction occurs with $TiCl_3$, nor are other metal salts efficient.[40] β-Amino esters are formed in the presence of Schiff bases (eq 30).[41]

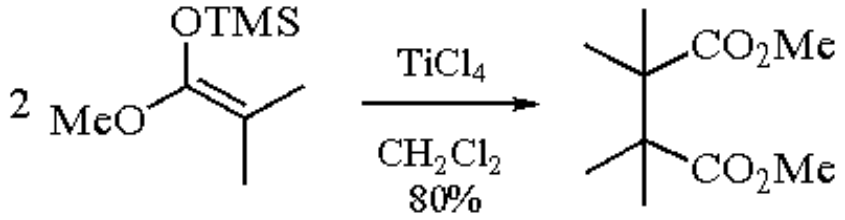

(29)

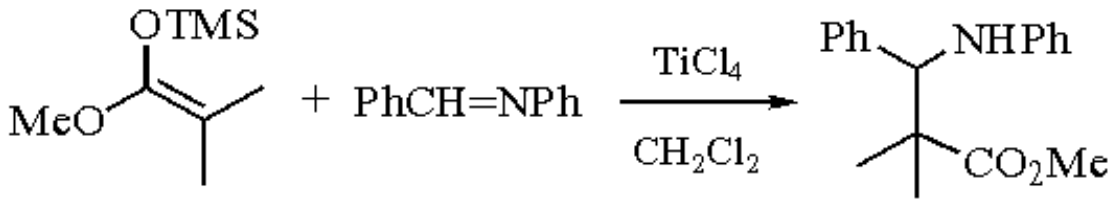

(30)

Cycloaddition of alkenes to quinones is effected by Ti^{IV} derivatives. The composition of the Ti^{IV} adjuvant largely controls the type of cycloadduct. $TiCl_4$ favors [3 + 2] cycloaddition; [2 + 2] cycloaddition requires a mixed $TiCl_4$-Ti(O-*i*-Pr)$_4$ catalyst (eq 31).[42]

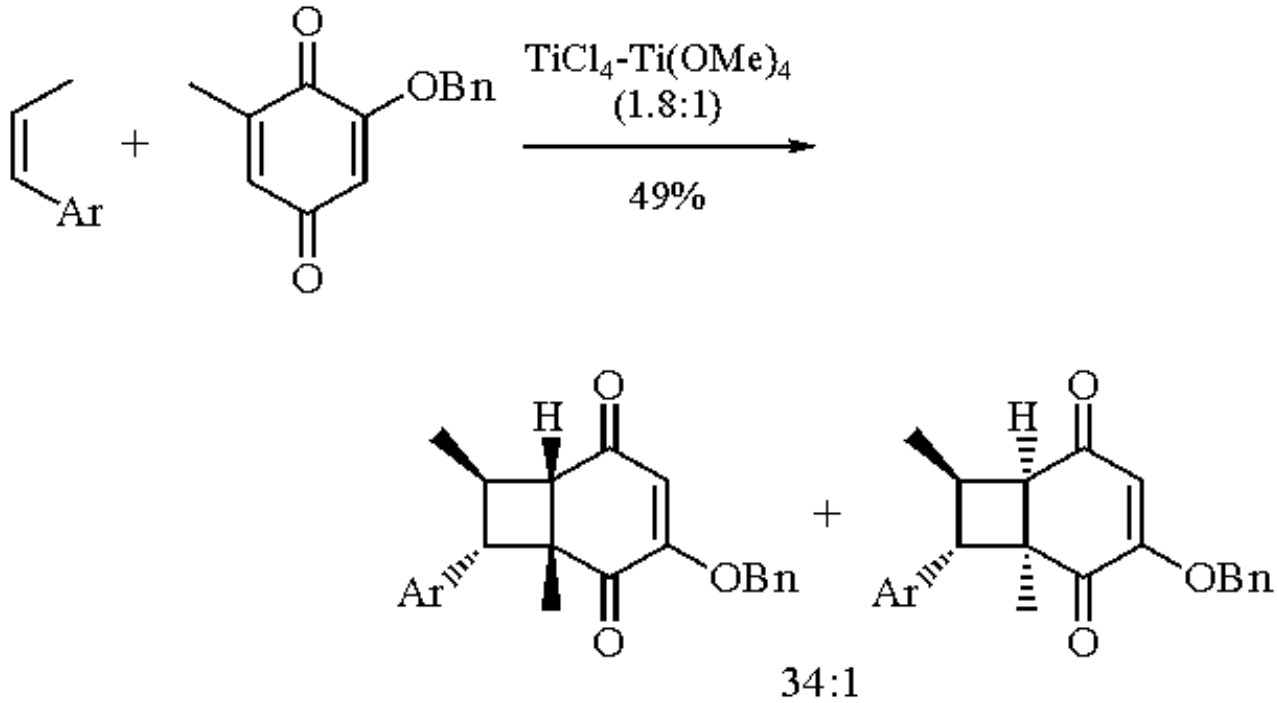

(31)

The $TiCl_4$-promoted Michael reaction proceeds under very mild conditions (-78 °C); this suppresses side-reactions and 1,5-dicarbonyl compounds are formed in good yields.[3] For $TiCl_4$-sensitive compounds, a mixture of $TiCl_4$ and Ti(O-*i*-Pr)$_4$ is used. From silyl enol ethers and α,β-unsaturated ketones, 1,5-dicarbonyl compounds are formed (eq 32).[3] The reaction also proceeds for α,β-unsaturated acetals.[43] Silylketene acetals react with α,β-unsaturated ketones or their acetals to form δ-oxo esters (eq 33).[44]

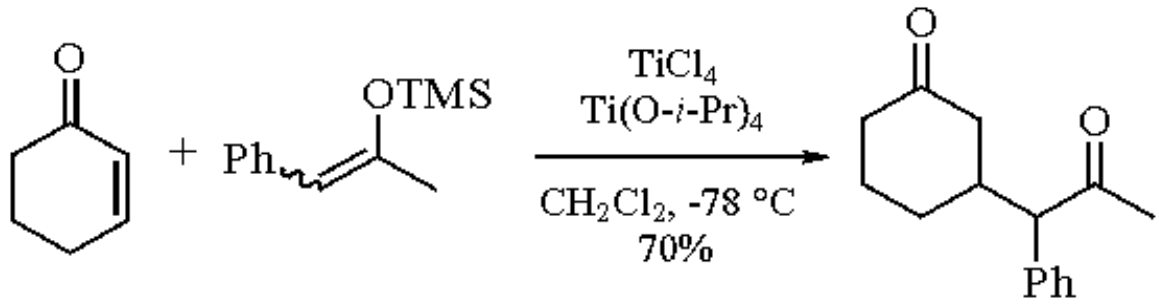

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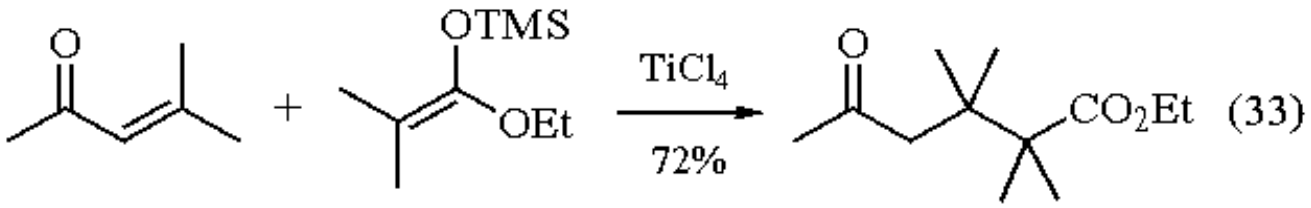

Conjugate addition of allylsilanes to enones results in regiospecific introduction of the allyl group (eq 34).[45] The reaction can be intramolecular (eq 35).[46] $TiCl_4$ or $SnCl_4$ activates nitro alkenes for Michael addition with silyl enol ethers or ketene silyl acetals. The silyl nitronate product is hydrolyzed to a 1,4-diketone or γ-keto ester (eq 36).[47]

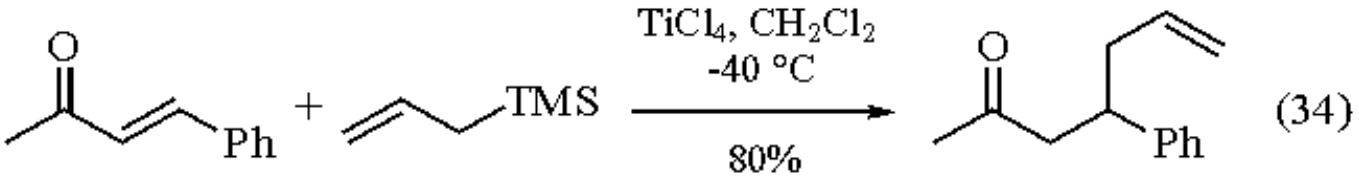

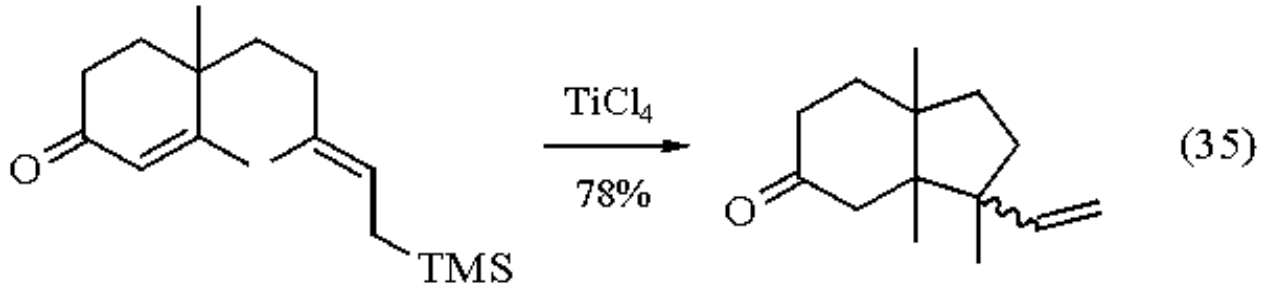

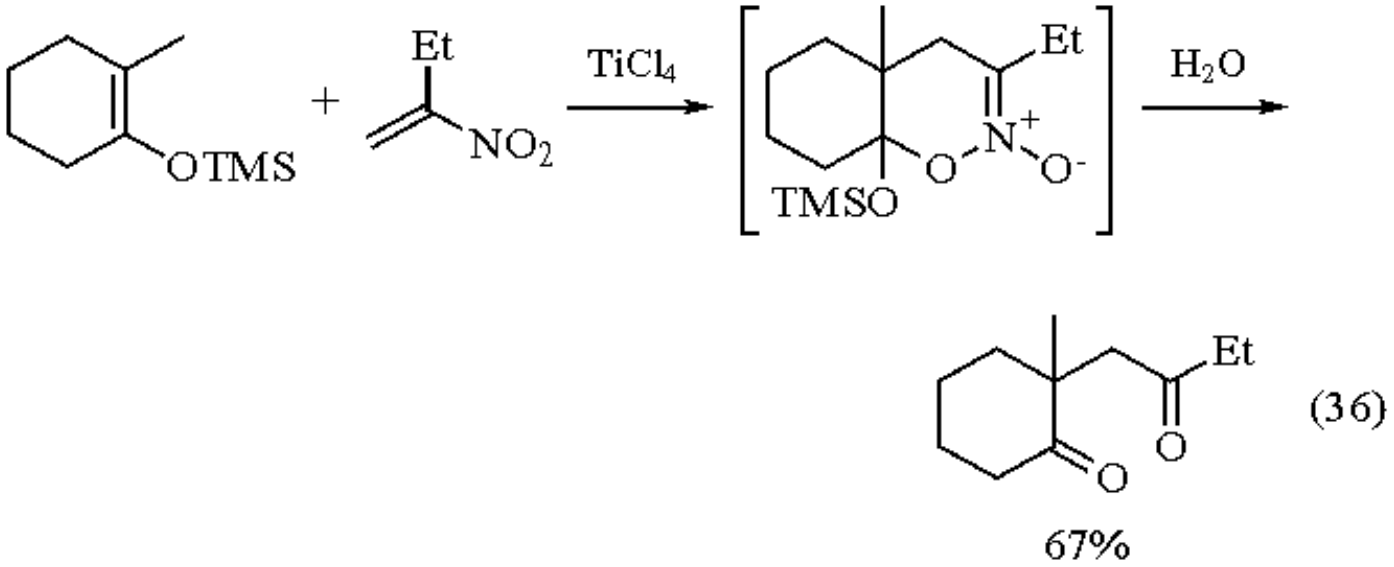

Conjugate propynylation of enones results from $TiCl_4$-mediated addition of allenylstannanes. Other Lewis acids are ineffective in this reaction (eq 37).[48]

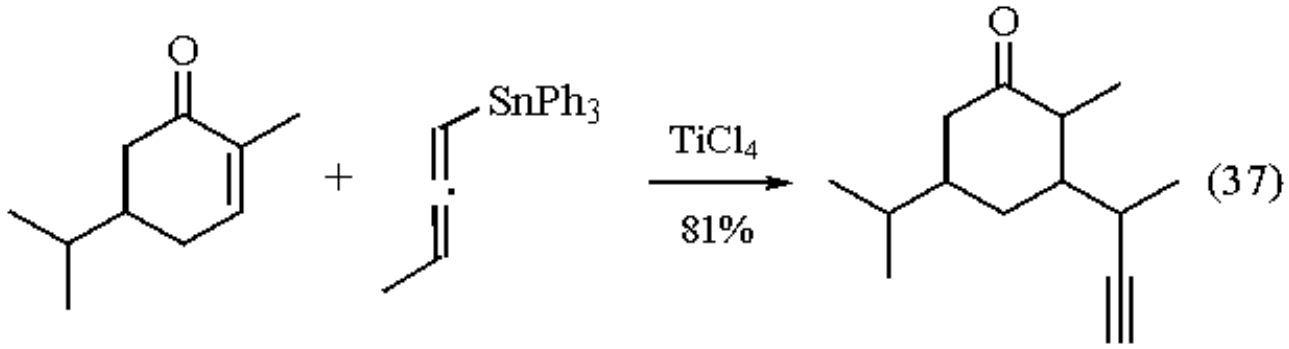

The 3,4-dichloro derivative of squaric acid, on $TiCl_4$-catalysis, reacts with silyl enol ethers or allylsilanes to form 1,2- or 1,4-adducts depending on the substitution. The 3,4-diethoxy derivative, however, adds silyl enol ethers in a 1,4-fashion; the adduct subsequently eliminates the ethoxy group (eq 38).[49]

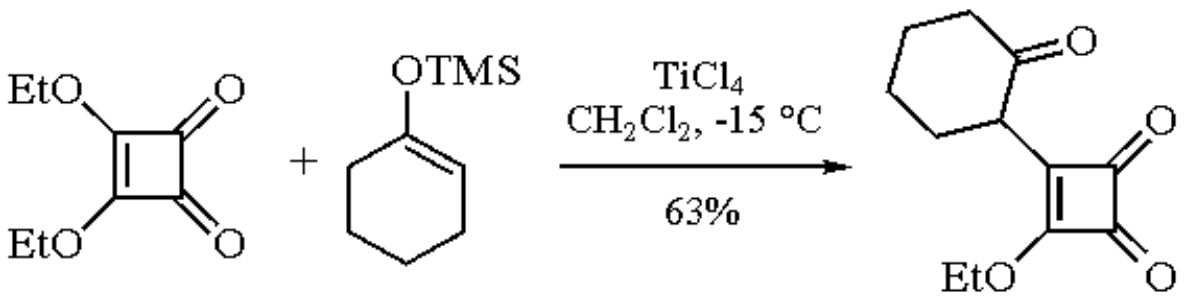

(38)

The Knoevenagel reaction with $TiCl_4$ and a tertiary base (eq 39) is recommended over methods which rely on strongly basic conditions.[50] The $TiCl_4$-procedure at low temperature is suitable for base-sensitive substrates.[51]

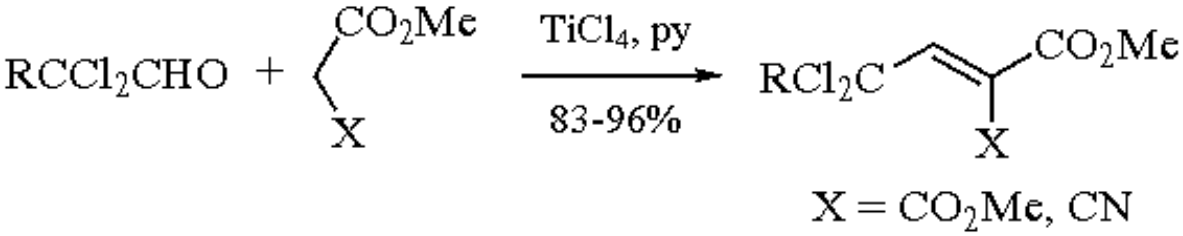

(39)

$TiCl_4$, as a Lewis acid, is used as a catalyst in Friedel-Crafts reactions. $AlCl_3$, $SnCl_4$, and $BF_3.OEt_2$ are more commonly used Friedel-Crafts catalysts for reactions with arenes.[52] Use of $TiCl_4$ as catalyst in the preparation of aromatic aldehydes is shown in eq 40.[53]

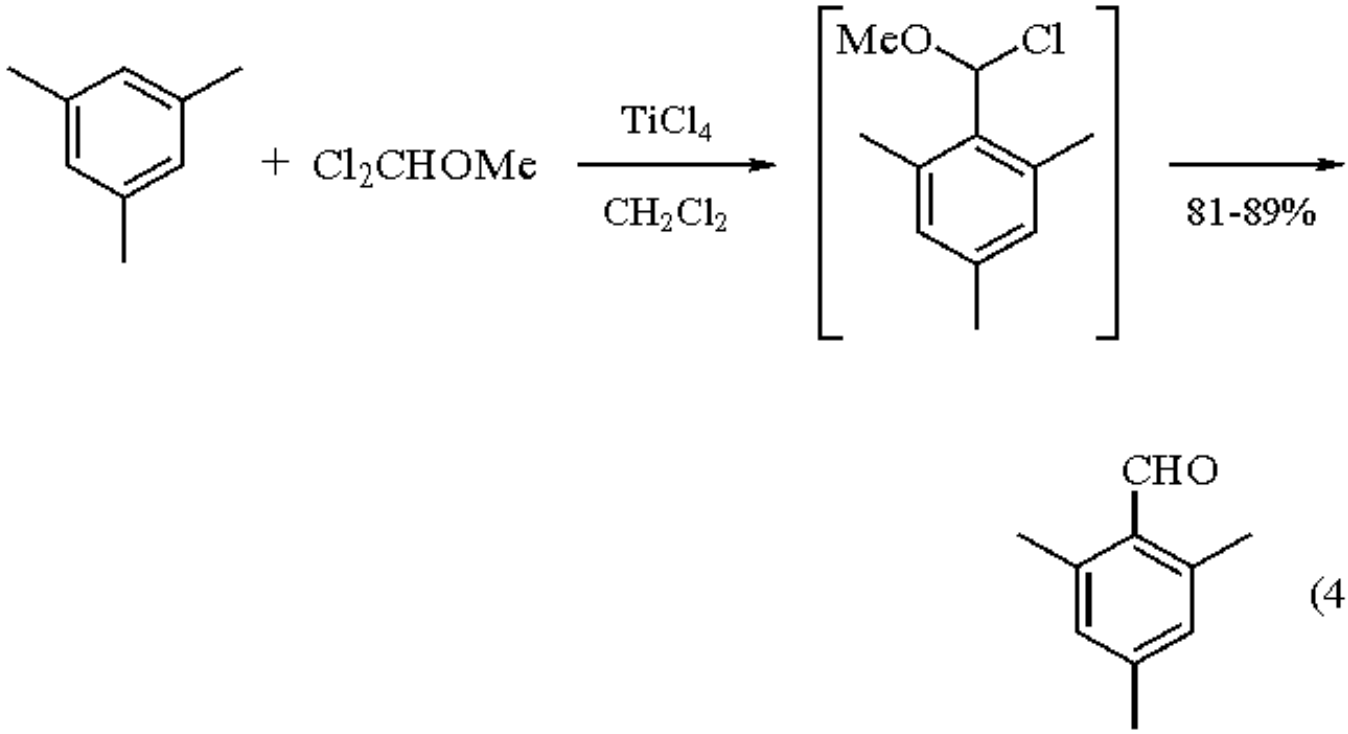

(40)

The formylation reaction can be used to prepare (*E*)-α,β-unsaturated aldehydes from vinylsilanes by *ipso* substitution (eq 41).[54] Regioselectivity in alkylation reactions may depend on the Lewis catalyst. In a fluorene, regioselective 1,8-chloromethylation results with $TiCl_4$ (eq 42).[55] $TiCl_4$ activates nitroalkenes for electrophilic substitution into arenes. The intermediate is hydrolyzed to the oxoalkylated product (eq 43).[56]

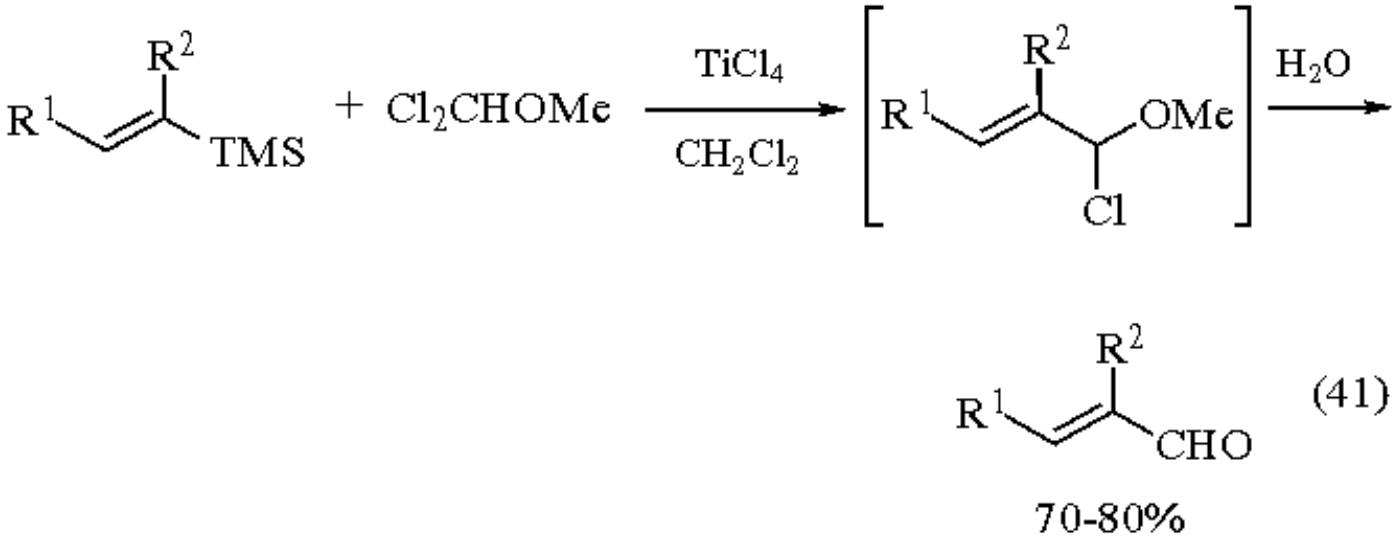

(41)

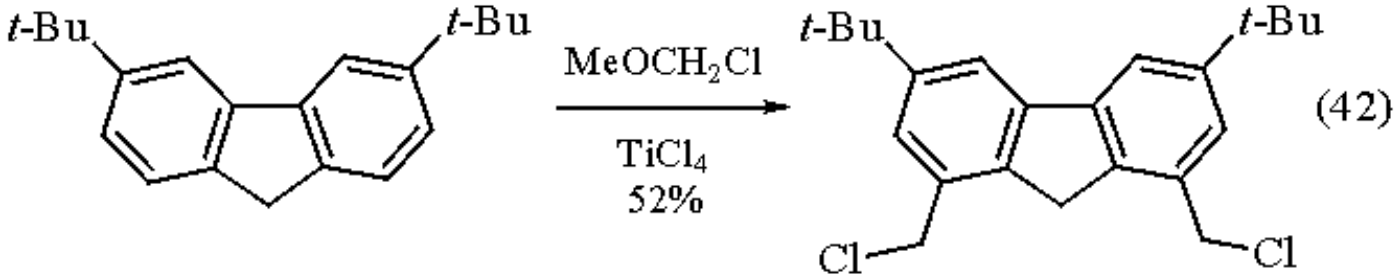

(42)

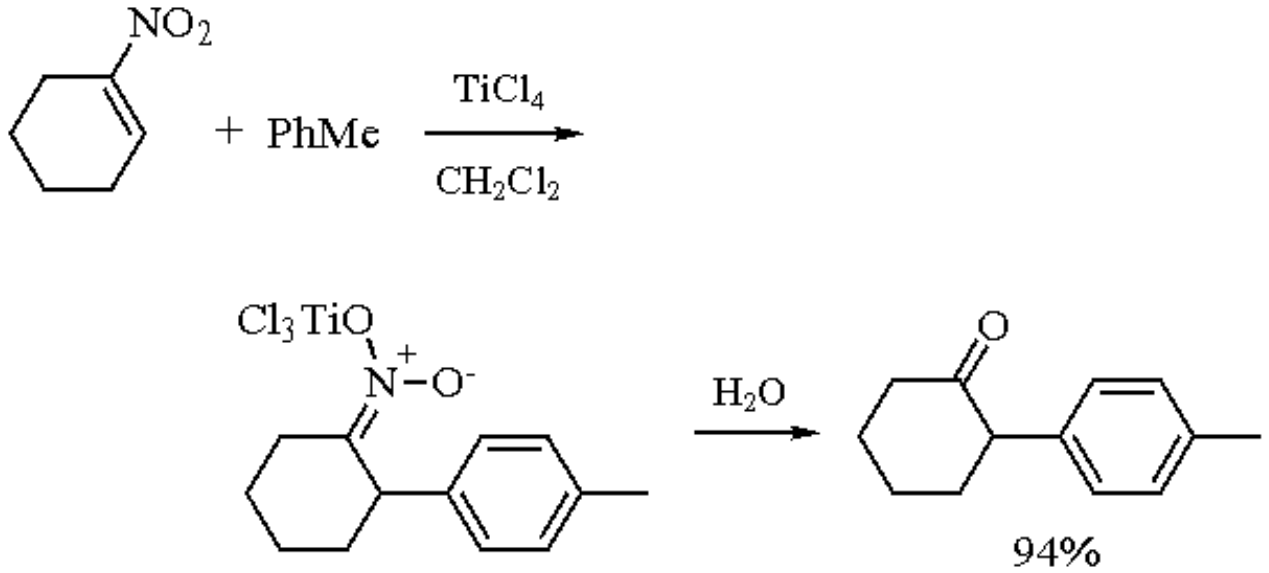

(43)

$TiCl_4$ is generally a good catalyst for Friedel-Crafts acylation of activated alkenes. In the acylation of pyrrolidine-2,4-diones, particularly with unsaturated acyl substrates, $TiCl_4$ is superior to $SnCl_4$ and $BF_3.OEt_2$ (eq 44).[57]

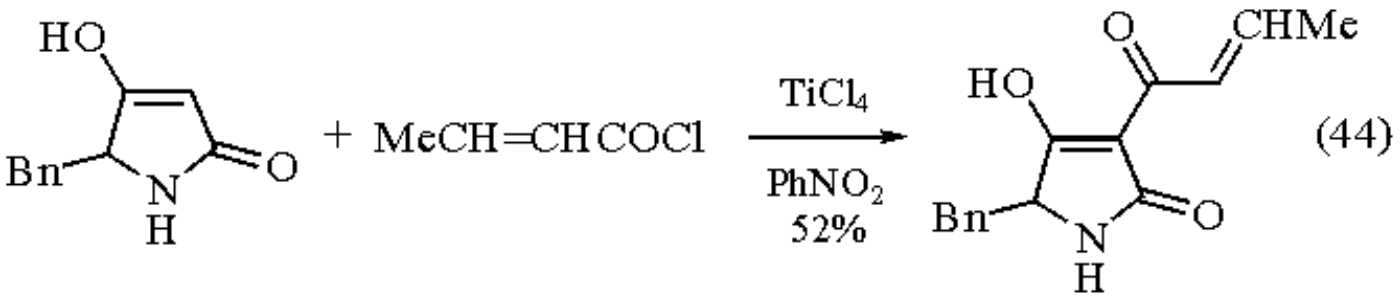

(44)

The ready *ipso* substitution of a silyl group favors substitution rather than addition of electrophiles in alkenylsilanes.[58] Direct acylation of isobutene is not satisfactory, but the acylation is successful on silyl derivatives (eq 45).[59] Intramolecular acylation of alkenylsilanes leads to cyclic products. Even (*E*)-silylalkenes have been cyclized to enones (eq 46).[60]

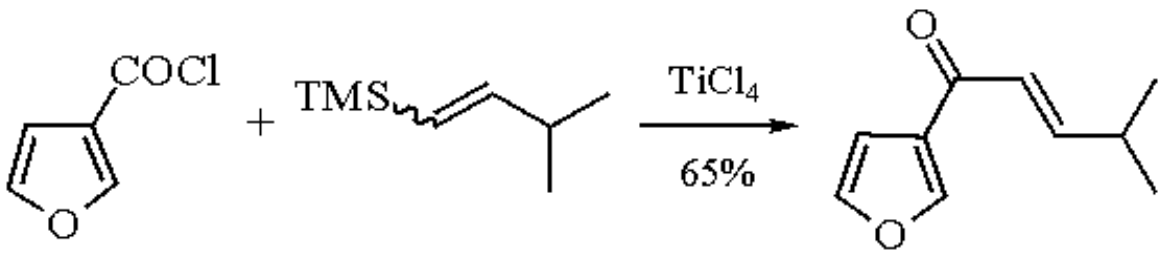

(45)

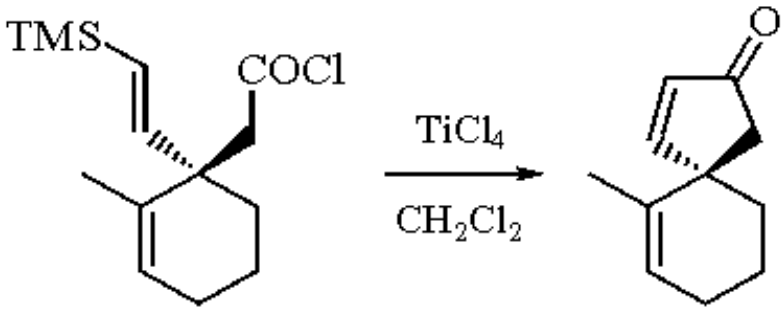

(46)

In analogy to the acylation reactions, vinylsilanes can be alkylated by *ipso* substitution. In the example in eq 47, the MEM group is activated as leaving group by metal complexation[61] The silyl group in allylsilanes directs the incoming electrophile to the allylic γ-carbon (eq 48). $TiCl_4$ is one of several Lewis acids used for catalysis in acylations.[58] The same reaction is seen in allylsilanes with extended conjugation.[62] Eq 49 shows the $TiCl_4$-catalyzed alkylation of an allylsilane.[63]

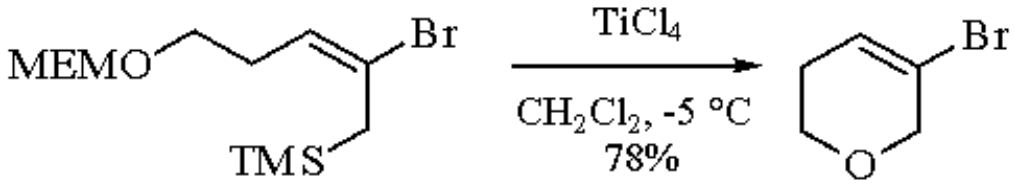

(47)

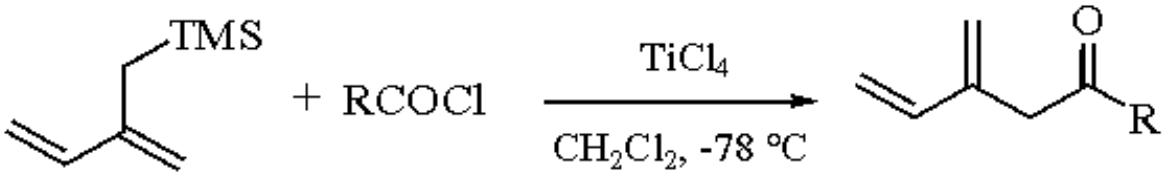

(48)

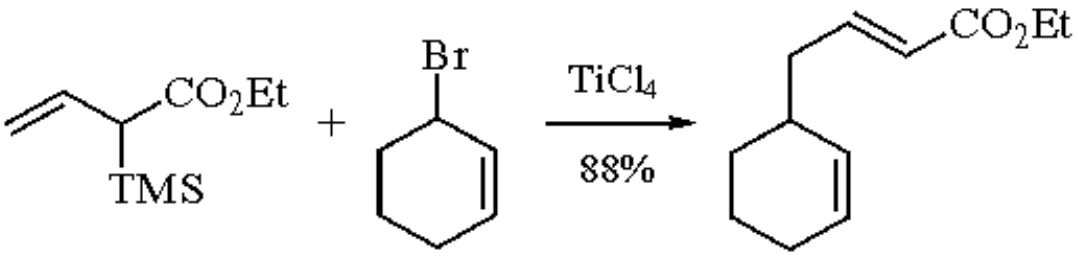

(49)

$TiCl_4$ is a useful catalyst for the Fries rearrangement of phenol esters to *o*- or *p*-hydroxy ketones (eq 50). $TiCl_4$ is a cleaner catalyst than the more frequently used $AlCl_3$, which may cause alkyl migrations.[64]

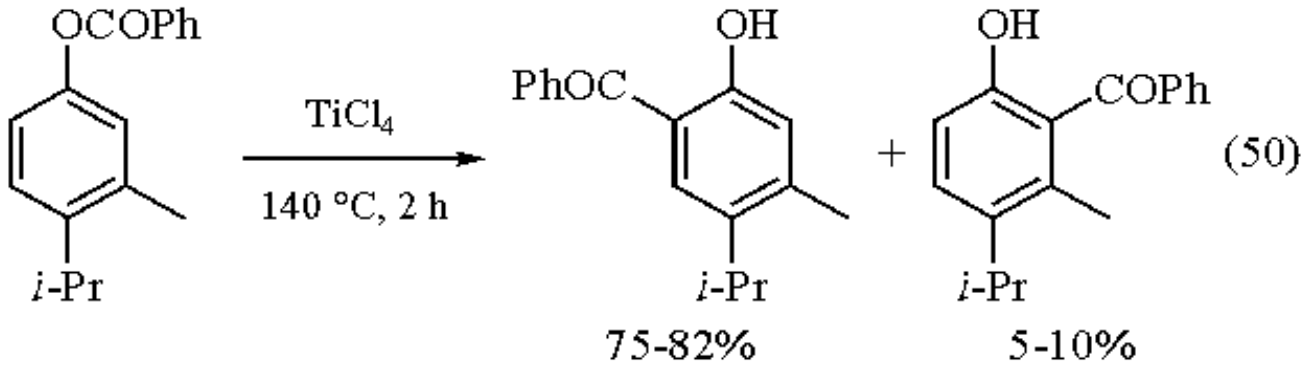

$TiCl_4$ is both a strong Lewis acid and a powerful dehydrating agent, and hence useful as a water scavenger in the synthesis of enamines. It is particularly useful for the preparation of enamines of acyclic ketones. It is recommended that $TiCl_4$ is complexed with the amine before addition of the ketone.[65] Highly sterically hindered enamines are available by this method (eq 51).[66] Primary amines generally react very slowly with aromatic ketones to form imines. $TiCl_4$ is a good catalyst (eq 52).[67]

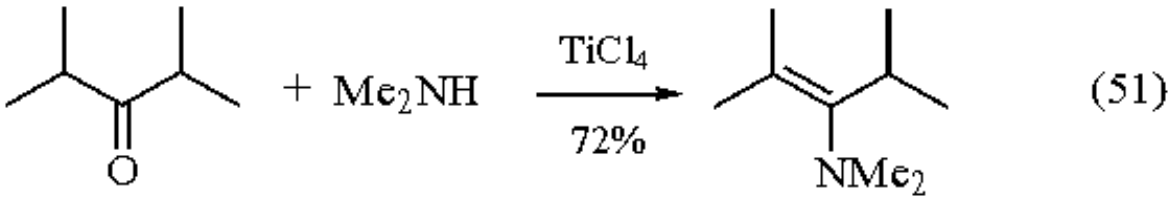

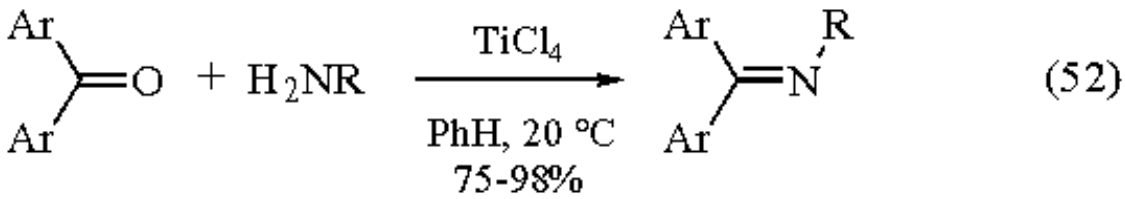

$TiCl_4$ with a tertiary base provides mild conditions for dehydration of both aldoximes and primary acid amides to form nitriles.[68] Vinyl sulfides are formed from oxo compounds using $TiCl_4$ and a tertiary amine.[3] $TiCl_4$ activates carbon-carbon double bonds for thiol addition (eq 53).[3]

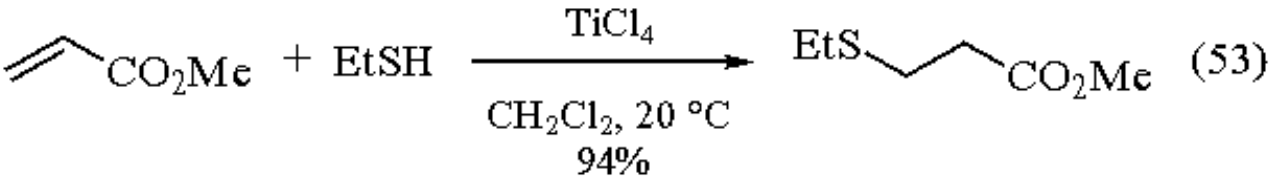

$TiCl_4$ mediates thioacetalization of aldehydes and ketones with alkanethiols or alkanedithiols in yields >90%. The reaction is satisfactory also for readily enolizable oxo compounds.[69] γ-Lactols, which are generally more stable than acyclic analogs, are amenable to dithiol cleavage (eq 54).[70]

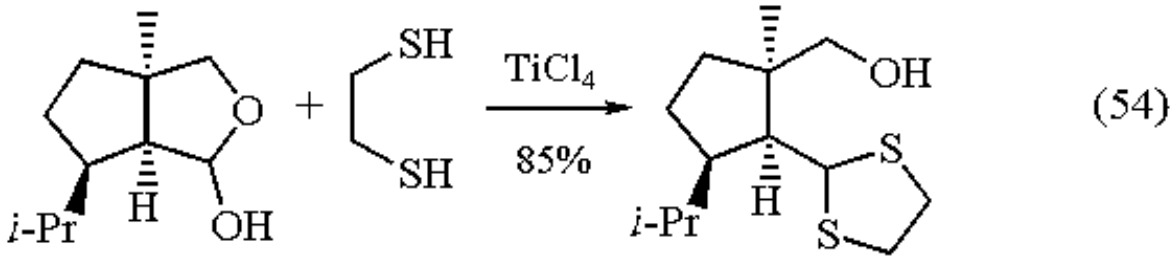

α-Hydroxy amides are formed in a reaction involving an isocyanide, $TiCl_4$, and an aldehyde or a ketone (eq 55).[71] Vinyl chlorides undergo ready hydrolysis on combined use of $TiCl_4$ and MeOH-H_2O (eq 56).[72] $TiCl_4$-mediated hydrolysis of vinyl sulfides is a good preparative route to ketones.[3,73]

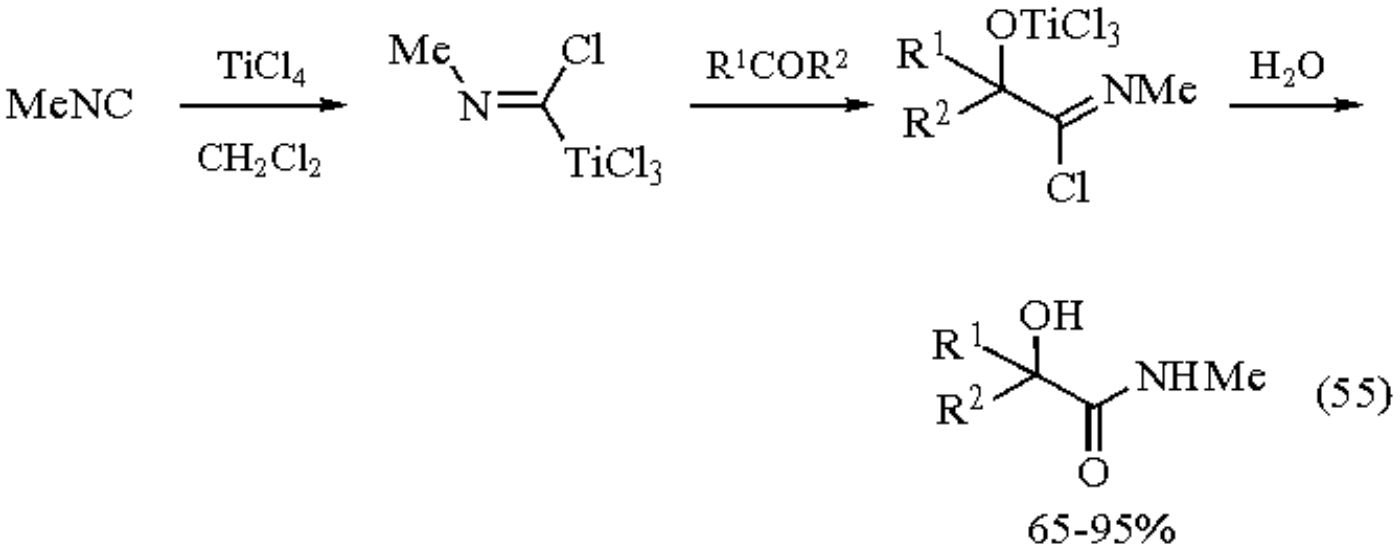

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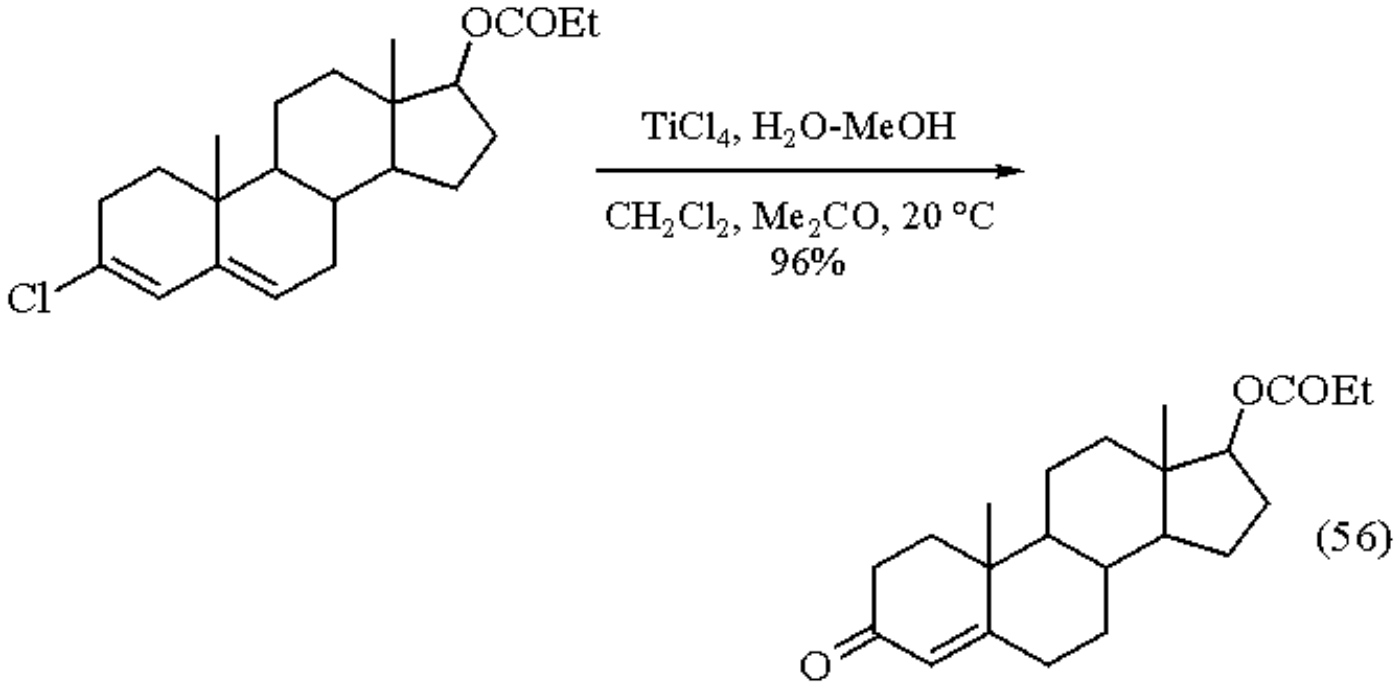

(56)

Low-valent titanium can be used to reduce sulfides and haloarenes to the corresponding hydrocarbons (eq 57).[3,74] Low-valent titanium, prepared from $TiCl_4$ and ***Magnesium Amalgam***, will reduce nitroarenes to amines in THF/*t*-BuOH at 0 °C without affecting halo, cyano, and ester groups.[75] $SnCl_2.2H_2O$ is an alternative reagent for nitro group reduction.[76]

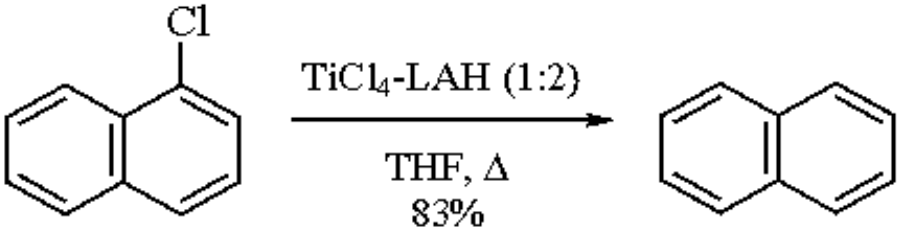

(57)

Deoxygenation of sulfoxides is a rapid reaction using $[TiCl_2]$ formed in situ by reduction of $TiCl_4$ with Zn dust in CH_2Cl_2 or Et_2O at rt, with yields in the range 85-90%.[77] For deoxygenation of *N*-oxides of pyridine-based heterocycles, a reagent prepared from $TiCl_4$-$NaBH_4$ (1:2) in DME has been described.[78] Carboxylic acids can be reduced to primary alcohols by $TiCl_4$-$NaBH_4$ (ratio 1:3). For reduction of amides and lactams the optimum molar ratio is 1:2.[79]

Several low-valent metal species have been found active in reductive elimination of vicinal dibromides to the corresponding alkenes. In most cases, e.g. with $TiCl_4$-LAH and $TiCl_4$-Zn, the reactions proceed through predominant *anti* elimination to yield alkenes with high isomeric purity.[80] The low-valent titanium reagent obtained from $TiCl_4$-LAH (ca. 2:1) will saturate the double bond of enedicarboxylates in the presence of triethylamine (eq 58).[81]

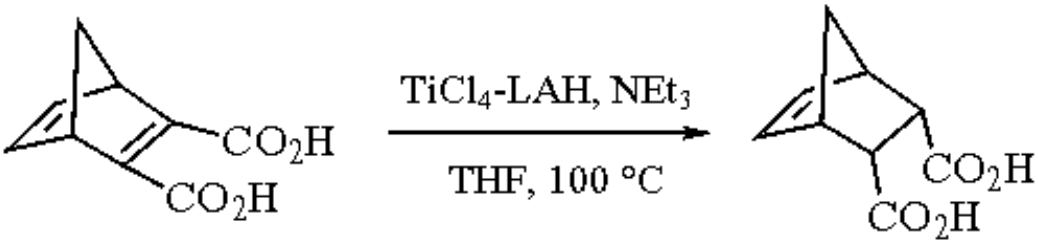

(58)

Related Reagents.

Dibromomethane-Zinc-Titanium(IV) Chloride; ***Diiodomethane-Zinc-Titanium(IV) Chloride***; ***(4R,5R)-2,2-Dimethyl-4,5-bis(hydroxydiphenylmethyl)-1,3-dioxolane-Titanium(IV) Chloride***; ***Lithium Aluminum Hydride-Titanium(IV) Chloride***; ***Titanium(IV) Chloride-Diazabicyclo[5.4.0]undec-7-ene***; ***Titanium(IV) Chloride-2,2,6,6-Tetramethylpiperidine***; ***Titanium(IV) Chloride-Triethylaluminum***; ***Titanium(IV) Chloride-Zinc***.

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Titanium(III) Chloride

[7705-07-9] · Cl_3Ti · Titanium(III) Chloride · (MW 154.23)

(aqueous functional group reducing agent; after reducing to low-valent species, reductive coupling reagent of carbonyls to vicinal diols and alkenes)

Physical Data: mp 440 °C (dec); *d* 2.640 g cm^{-3}.

Solubility: sol water, alcohol; insol diethyl ether, $CHCl_3$, CCl_4, CS_2, benzene.

Form Supplied in: dark red-violet solid; dimethoxyethane complex, $TiCl_3$.1.5DME *[18557-31-8]*, solution in CH_2Cl_2/THF, solution in hydrochloric acid.

Purification: sublimation of solid at 1 mmHg.[1b]

Analysis of Reagent Purity: aqueous solutions of $TiCl_3$ can be titrated against 0.1 N cerium(IV) sulfate.[2]

Handling, Storage, and Precautions: dry powder is pyrophoric in air; moisture sensitive; reacts violently with water, and causes skin burns. Heating in vacuo over ca. 450 °C gives $TiCl_2$ and $TiCl_4$. Use in a fume hood and in a dry box under inert atmosphere. $TiCl_3.(DME)_{1.5}$ is air sensitive, but can be stored indefinitely under Ar at room temp. Reactions involving low-valent titanium should be run under argon.[1]

Introduction.

The low-valent titanium species (Ti^0/Ti^I) generated from $TiCl_3$ are very useful for reductive coupling of aldehydes and ketones to give vicinal diols and further to alkenes. Aqueous $TiCl_3$ is used for the reduction of various functional groups (-SO, $-NO_2$, -NHOR, -X).

Reductive Coupling.[3-8]

The reagent composition of the low-valent species (Ti^0/Ti^I) to be used in the coupling reaction depends on the reducing conditions for its generation. $TiCl_3$ and ***Lithium Aluminum Hydride*** in a 1:0.6 molar ratio produces a Ti^0 species, and the molar ratio 1:0.5 a Ti^I species.[4] Other reducing agents such as ***Lithium***,[9,10] ***Sodium***,[9] ***Potassium-Graphite*** (C_8K),[11] ***Magnesium***,[9,12,13] ***Zinc/Copper Couple***[12] and Rieke titanium have been applied to $TiCl_3$.[14] Low-valent titanium species can also be obtained from ***Titanium(IV) Chloride*** by similar reductive procedures.[4] THF is usually the preferred solvent in the reductive coupling reactions, although other solvents such as dioxane or dimethoxyethane have also been used. The reaction should be performed under argon. The reagents and solvents must be pure and absolutely dry, since traces of oxidation or hydrolysis products can interfere. Variable yields in closely related reactions, and reactions difficult to reproduce, have been ascribed to aged and ineffective batches of $TiCl_3$. The variable nature of $TiCl_3$ samples is overcome by prior conversion of $TiCl_3$ into a dimethoxyethane complex, $TiCl_3.(DME)_{1.5}$. The complex is readily purified by crystallization.[7] According to McMurry et al., the optimized titanium reagent for the reductive carbonyl coupling is prepared by the Zn/Cu couple reduction of $TiCl_3.(DME)_{1.5}$.[7]

Mechanism of Carbonyl Coupling.

The reducing metal adds an electron to the oxo group and the anion radical dimerizes in a pinacol reaction (eq 1). The intermediate pinacols can be isolated at low temperature (0 °C), and are dehydroxylated at higher temperature (60 °C) to alkenes on the surface of zero-valent titanium particles.[7] For the reductive pinacol formation, ***Samarium(II) Iodide*** is an alternative.[15]

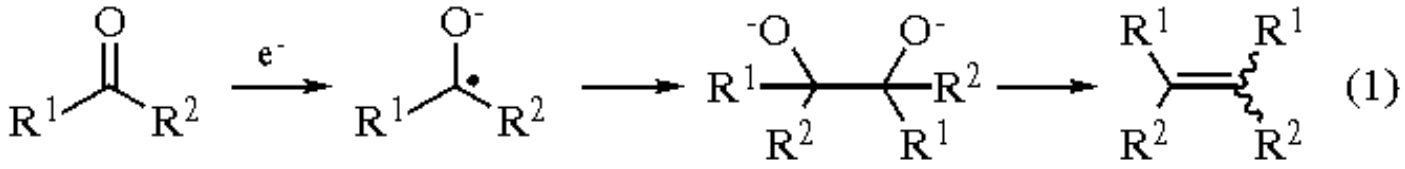

Intermolecular Coupling.

The reaction is most suitable for the preparation of symmetrical alkenes by joining two of the same carbonyl compounds, and is an excellent method for coupling of aliphatic carbonyl compounds (eq 2).[8] It is also an effective method for the synthesis of highly strained alkenes (eqs 3 and 4).[16]

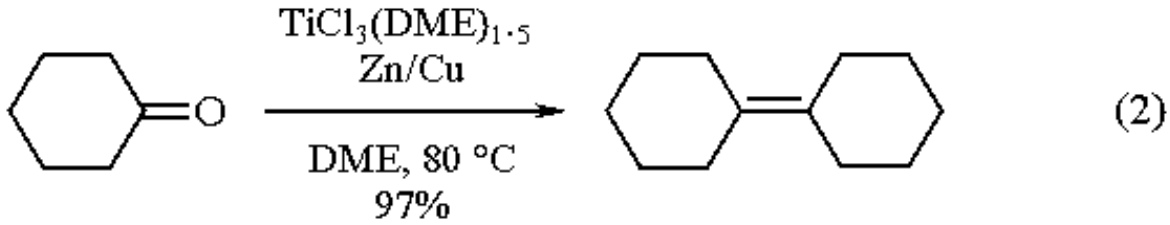

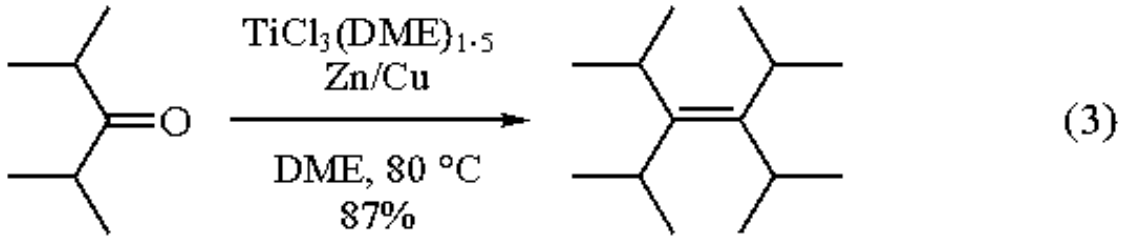

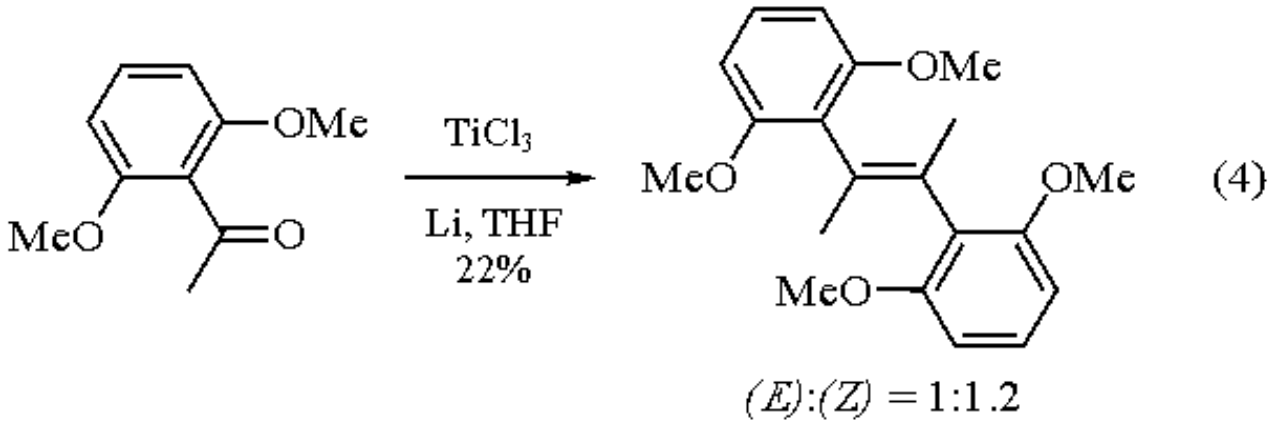

Mixed Coupling.

A mixture of two different carbonyl compounds will generally react to afford a nearly statistical mixture of alkenes. However, by applying an excess of one carbonyl compound, mixed couplings can be synthetically useful (eq 5).[17]

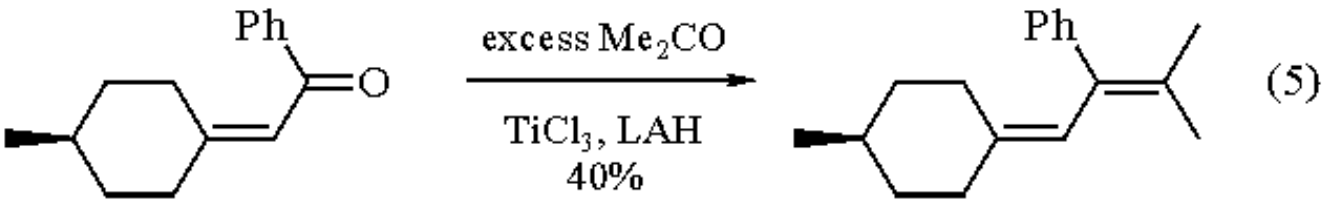

Intramolecular Coupling.

Coupling of α,o-dicarbonyl compounds gives cycloalkenes (eq 6).[7] Difficult intramolecular couplings leading to medium- and large-ring cycloalkenes require a lengthy addition time to achieve high dilution, and the use of 4 or more equiv of titanium per carbonyl group.

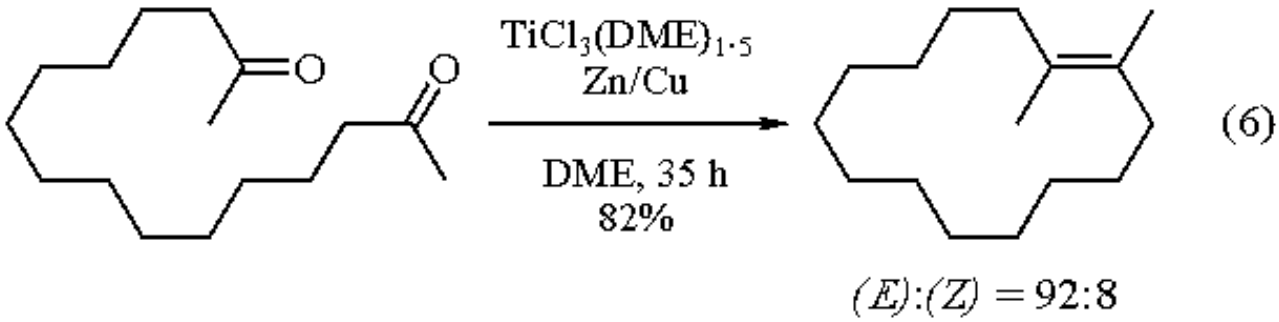

Keto-ester couplings work well for five- to seven-membered ring formation. The product is the corresponding ketone.[18] Functional group compatibility includes acetal, alcohol, alkene, alkylsilane, amine, ether, halide, sulfide, and vinylsilane; incompatible are allylic alcohol, 1,2-diol, epoxide, halohydrin, α-halo ketone, nitro group, oxime, and sulfoxide.[3]

Reductions.[6]

Aqueous $TiCl_3$ is a very useful reagent for the reduction of oximes to imines. The imines are rapidly hydrolyzed to carbonyl derivatives at low pH, and the overall reaction is a mild, rapid, and efficient deoximation procedure.[19] Cr^{II} [20] and V^{II} [21] reagents have also been used for this purpose. The usefulness is exemplified by a synthesis of a vicinal tricarbonyl system via an oxime which is readily available by nitrosation of the 1,3-dioxo derivative (eq 7).[22]

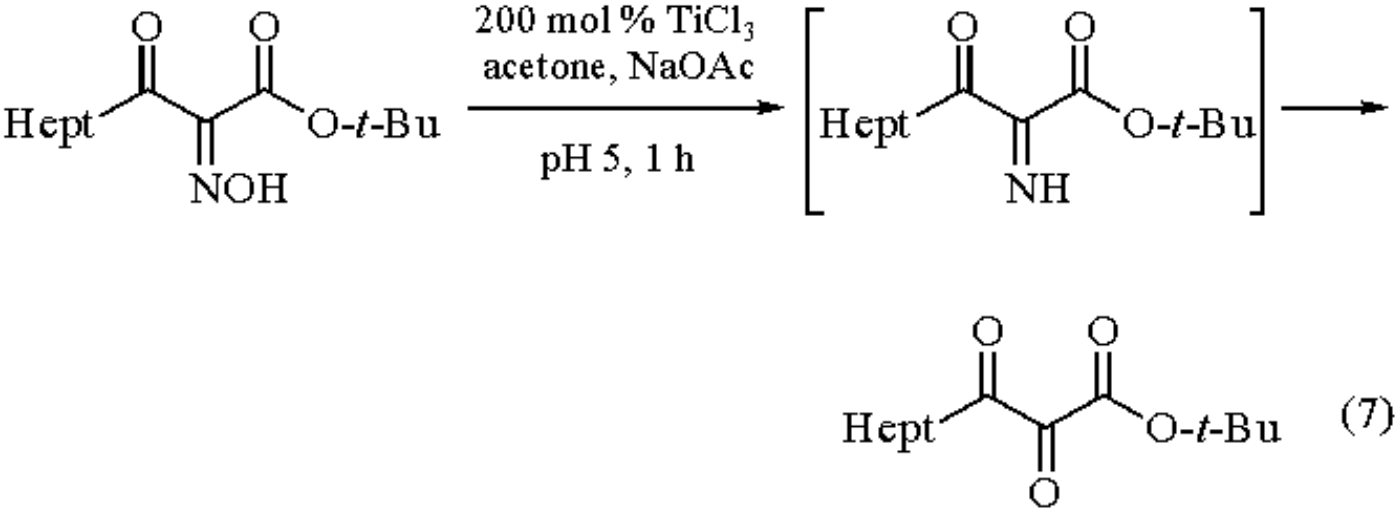

The reaction with α-hydroxyimino-β-keto esters may also lead to pyrazine formation.[23] With added ***Sodium Borohydride***, amine formation has been used in the synthesis of α-amino acids.[24] By analogy to the oxime reduction, aliphatic nitro compounds are transformed into carbonyl derivatives. Reduction of the nitro group gives the corresponding nitroso derivative, with subsequent tautomerism to the oxime which reacts further as above (eq 8).[25]

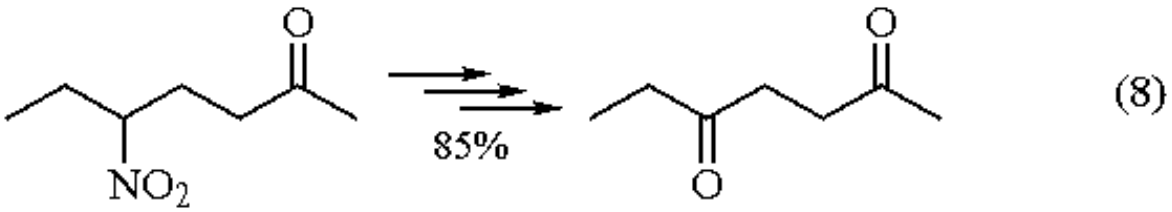

Aromatic and heteroaromatic nitro compounds are also reduced to amines under mild conditions.[26] Buffered aqueous $TiCl_3$ can also be used to reduce hydroxamic acids, cyclic or acyclic (eq 9).[27] The ready cleavage of N-O bonds is attributed in part to titanium's high affinity for oxygen. Accordingly, sulfoxides are also deoxygenated cleanly and in high yields to the corresponding sulfides.[28]

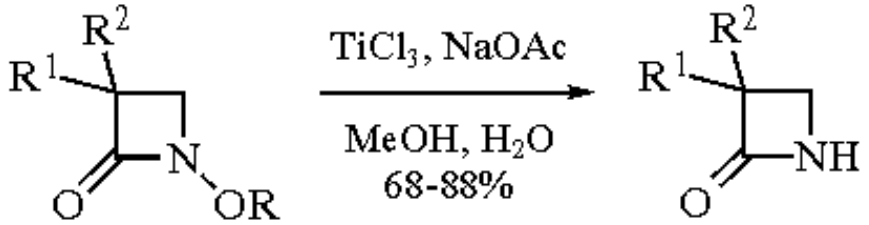

(9)

α-Halo ketones are dehalogenated by $TiCl_3$.[29] A number of reductive transition metal complexes,[30] as well as SmI_2,[31] possess this ability. $TiCl_3$ is commercially available and therefore a convenient reagent. Halogen atoms in aromatics can also be removed by aqueous $TiCl_3$. Both halo- and cyanopyridines are reduced to pyridines with aqueous $TiCl_3$,[32] which should find wide application in heterocyclic chemistry (eq 10).

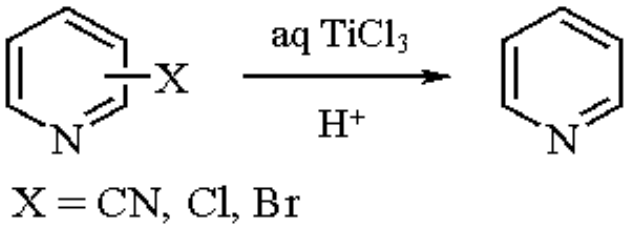

(10)

Highly electrophilic and polarized carbon-carbon double bonds can also be reduced with aqueous $TiCl_3$ (eq 11).[33]

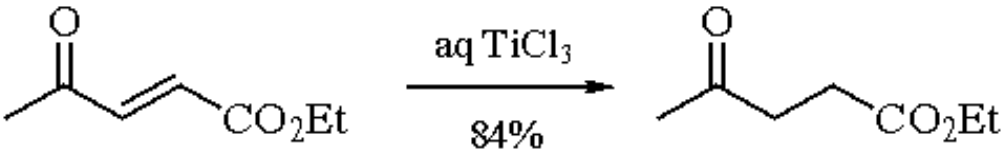

(11)

Related Reagents.

Niobium(V) Chloride-Zinc; ***Samarium(II) Iodide***; ***Titanium(III) Chloride-Potassium***; ***Titanium(III) Chloride-Lithium Aluminum Hydride***; ***Titanium(III) Chloride-Zinc/Copper Couple***.

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Titanium(IV) Chloride-Diazabicyclo[5.4.0]undec-7-ene

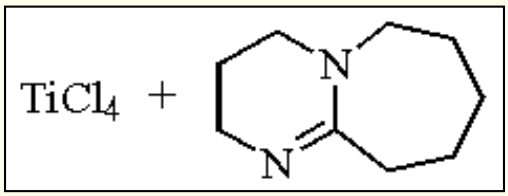

($TiCl_4$)

[7550-45-0] · Cl_4Ti · Titanium(IV) Chloride-Diazabicyclo[5.4.0]undec-7-ene · (MW 189.68) (DBU)

[6674-22-2] · $C_9H_{16}N_2$ · Titanium(IV) Chloride-Diazabicyclo[5.4.0]undec-7-ene · (MW 152.27)

(combination of reagents which allows the opening of epoxides to give chlorohydrins in the presence of acid labile groups[1])

Physical Data: see ***Titanium(IV) Chloride*** and ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.

Solubility: $TiCl_4$: sol aromatic hydrocarbons, ether, THF, dioxane, chlorohydrocarbons. DBU: sol ethers, chlorohydrocarbons, aromatic solvents.

Form Supplied in: $TiCl_4$: colorless liquid, or as a crystalline complex with THF. DBU: colorless liquid.

Preparative Methods: DBU (2 equiv) is added to a solution of the epoxide in dichloromethane. The mixture is cooled to -78 °C. $TiCl_4$ (1 equiv) is then added and the mixture allowed to warm to rt.

Handling, Storage, and Precautions: $TiCl_4$ is corrosive and moisture sensitive. DBU is a flammable liquid. The combination reagent is moisture sensitive and reactions are best performed under a dry inert atmosphere. Solvents should be dried before use.

Preparation of Chlorohydrins.

Epoxides are treated with the reagent to give chlorohydrins.[1] Mono- and disubstituted epoxides are converted in excellent yields (eq 1). Trisubstituted epoxides give moderate yields. The regiochemical outcome is such that the chlorine is added to the more stabilized carbocation center and the stereochemistry is that of a *trans* opening of the epoxide. The chlorohydrin (**2**) obtained from (-)-dihydrogeraniol epoxide (**1**) could be converted back to the epoxide without loss of optical activity (eq 2).[1] The presence of DBU is essential for the survival of acid-sensitive groups such as acetals. ***4-Dimethylaminopyridine*** has been used as an alternative to DBU but the yields are lower.

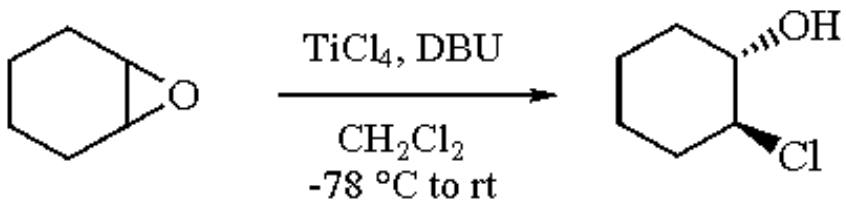

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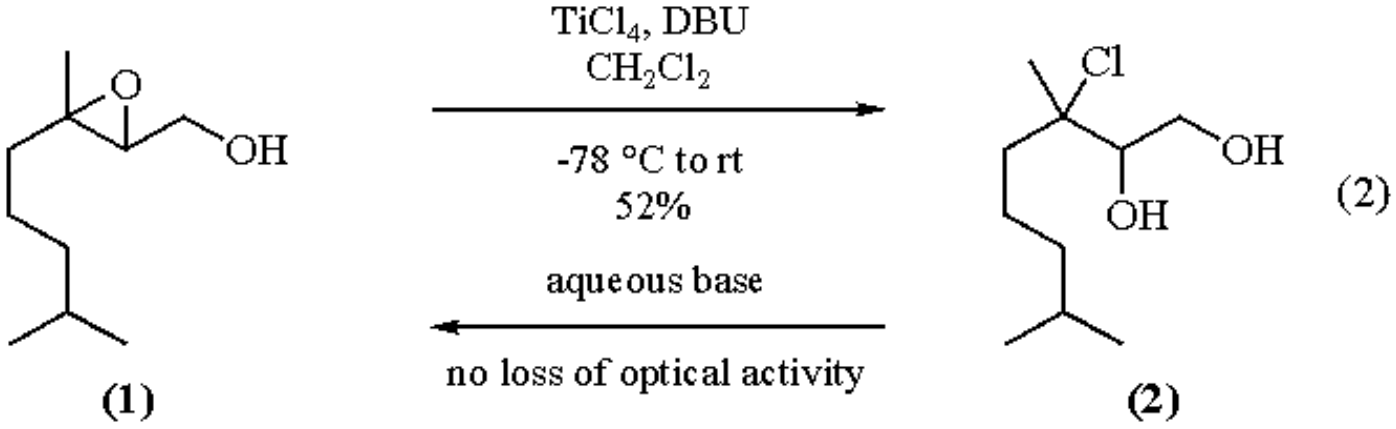

Related Reagents.

Dichlorotitanium Diisopropoxide; ***Tin(II) Chloride***; ***Titanium(IV) Chloride***.

---

1. Spawn, C. L.; Drtina, G. J.; Wiemer, D. F. *S* **1986**, 315.

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Titanium(III) Chloride-Potassium[1]

$TiCl_3$-K

($TiCl_3$)

[7705-07-9] · Cl_3Ti · Titanium(III) Chloride-Potassium · (MW 154.23) (K)

[7440-09-7] · K · Titanium(III) Chloride-Potassium · (MW 39.10)

(combination of reagents used for the in situ generation of highly oxophilic low-valent titanium species[2] which are used to effect the reductive coupling of carbonyl groups[2] (McMurry coupling) and reductive deoxygenations[3])

Physical Data: see ***Titanium(III) Chloride*** and ***Potassium***.

Solubility: $TiCl_3$: sol alcohol, hydrochloric acid; v. slightly sol DME, THF. K: insol DME, THF.

Form Supplied in: $TiCl_3$: violet, air-sensitive solid. K: metal under paraffin.

Preparative Methods: potassium metal (3.2 equiv) is washed with hexane and added to a slurry of titanium(III) chloride (1 equiv) in THF at rt under an inert atmosphere. The mixture is heated under reflux for 1 h, during which time the reaction mixture turns black. The mixture is cooled to rt and is then ready for the addition of the reaction substrates.

Handling, Storage, and Precautions: care is required when handling potassium because it reacts violently with water and protic solvents, liberating highly flammable gases which are readily ignited. Titanium(III) chloride should be stored and used under argon, preferably in a glove bag or box. The low-valent titanium reagent is sensitive to air and moisture; therefore to obtain good yields, it must be freshly prepared. All reactions should be performed under argon. If excess reagent is used, it should be quenched prior to workup by the cautious addition of methanol. Alternatively, if the use of methanol is incompatible with the products, the reaction mixture may be filtered carefully through a pad of Celite; care must be taken as the residues collected may be pyrophoric. All solvents must be dried and preferably deoxygenated or degassed before use.

Coupling of Aldehydes and Ketones.

Reduction of $TiCl_3$ with 3 equiv of potassium gives a Ti^0 species which is used in the reductive coupling (McMurry coupling) of carbonyl compounds (eq 1). Other less hazardous methods exist for the generation of Ti^0, e.g. ***Titanium(III) Chloride-Zinc/Copper Couple*** or $TiCl_3$/Li, but the reagent generated from potassium gives the most consistent results and the highest yields when coupling aliphatic aldehydes and ketones.[4] When aldehydes or nonsymmetrical ketones are coupled, the (*E*)-alkene product predominates. Even with the highly hindered 1-methyl-2-adamantanone, coupling could be achieved in 52% yield (eq 2).[5] The recently reported generation of Ti^0 from the $TiCl_3(DME)_{1.5}$ solvate and ***Zinc/Copper Couple***[6] is likely to be the reagent of choice in future. It gives good to excellent yields, while avoiding the hazards associated with the use of potassium.

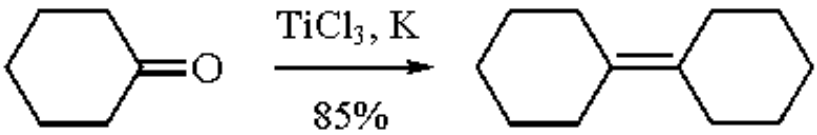

(1)

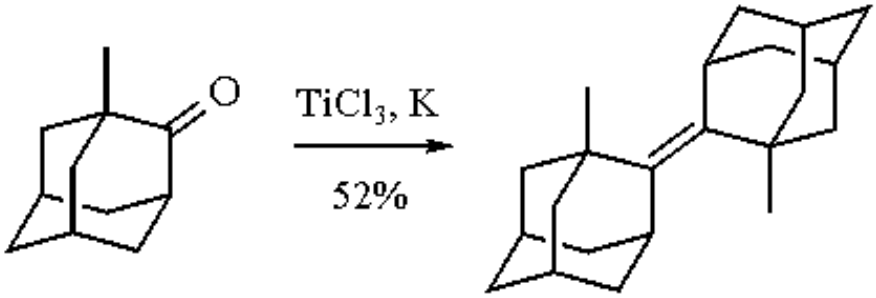

(2)

The mechanism of the McMurry coupling has been studied.[7] The reaction proceeds via a pinacol coupling and subsequent deoxygenation. Using the title reagent, it is only possible to isolate good yields of the pinacol product when the formation of the alkene is disfavored, e.g. in compound (**1**),[8] where the double bond would have to be formed at a strained bridgehead (eq 3). A wide range of functionality is compatible with carbonyl coupling,[1a] although allylic alcohols, epoxides, oximes, sulfoxides, and nitro groups are not.

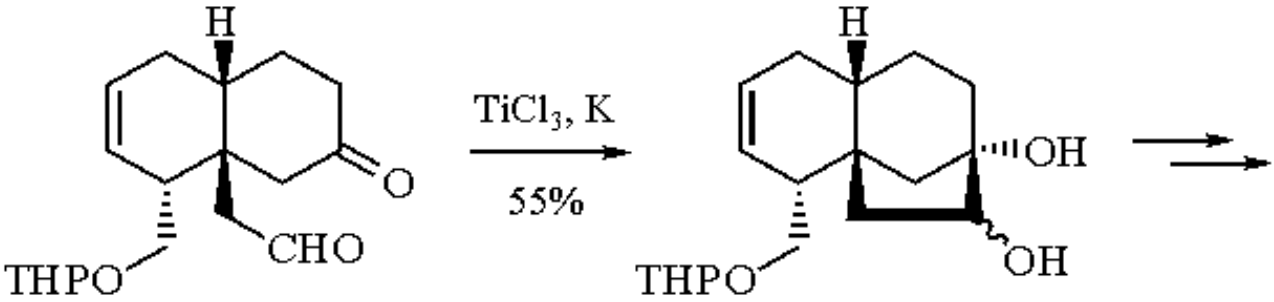

(1)

Gibberellic acid (3)

The reagent has been modified by the use of ***Potassium-Graphite*** as the reducing partner,[9,10] with the Ti^0 being formed on the surface of the graphite. Again, 3 equiv of potassium are generally used, although the cyclization of (**2**) to (**3**) was optimized using 2 equiv of potassium (eq 4).[11] Formally, this requires a Ti^I species for the coupling. The reaction was highly specific: no epimerization was noted at C-8a, nor was there any loss of the acetal.

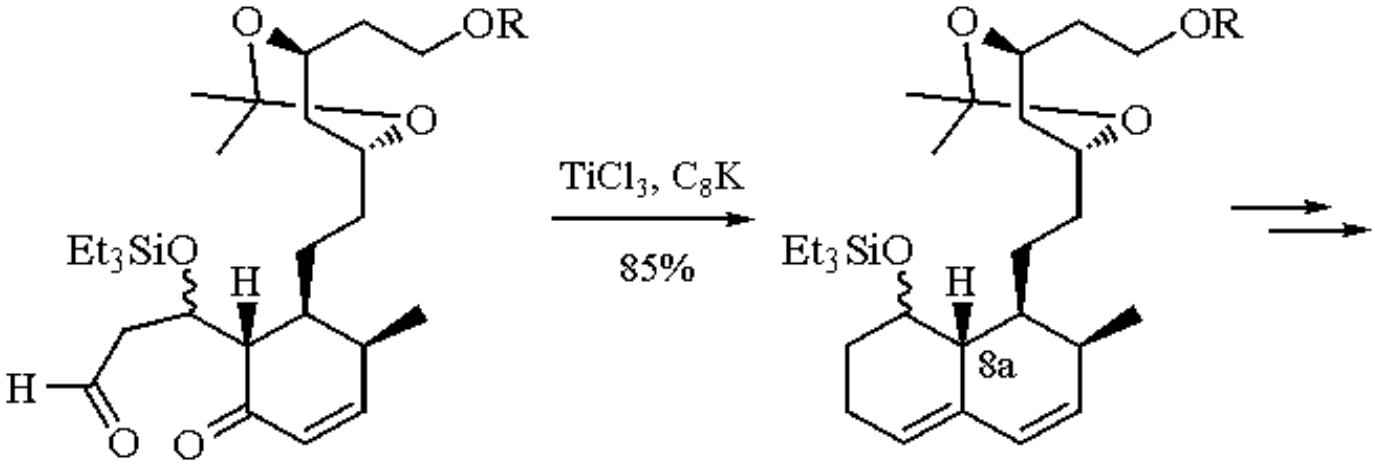

(2) **(3)**

Compactin (4)

Coupling of Esters and Amides.

The Ti^0 on graphite reagent facilitates the intramolecular coupling of ketones to esters,[10] yielding enol ethers which subsequently hydrolyze to ketones (eq 5). This type of reaction has also found use in the synthesis of furans and benzofurans by the coupling of *O*-benzoyl derivatives of 1,3-dicarbonyl compounds (eq 6);[12] yields are improved by further aromatic substituents. Indoles may be prepared by analogous methods (eq 7).[12]

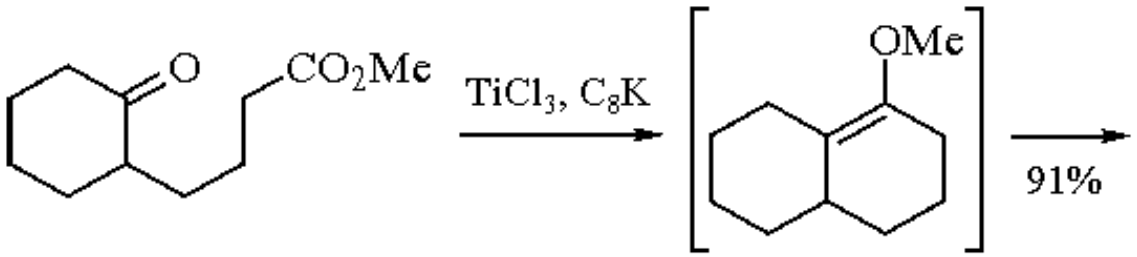

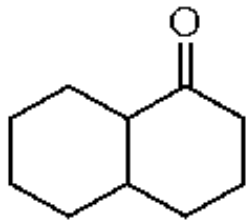

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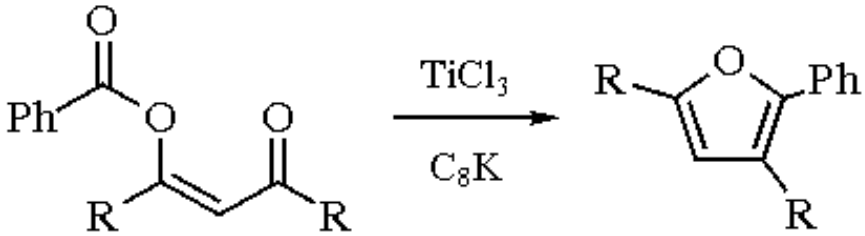

(6)

R = Ph, 92%; Me, 58%

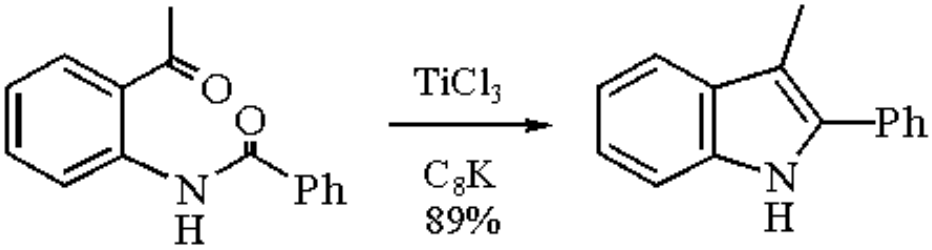

(7)

Deoxygenations.

As the McMurry coupling proceeds via the pinacol, it is not surprising that Ti^0 is capable of converting 1,2-diols to alkenes in good to excellent yields. In addition to diols, $TiCl_3$/K also converts 1-phenylthio-2-benzoyloxyethanes to alkenes (eq 8).[13] Deoxygenation of phenols and enolizable ketones is achieved via the *O*-phosphate derivative (eqs 9 and 10).[3]

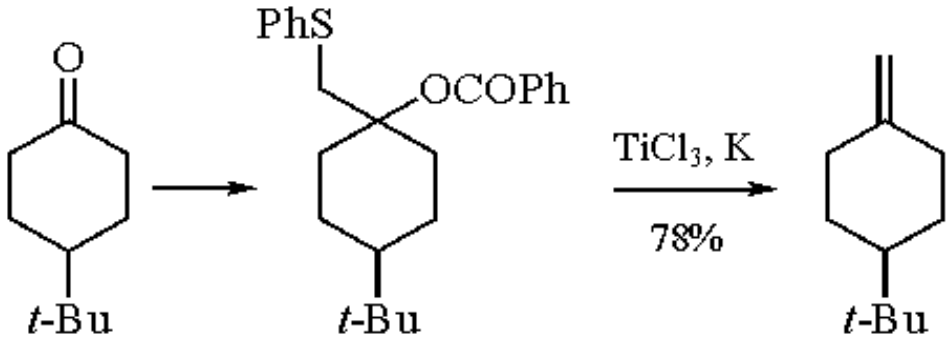

(8)

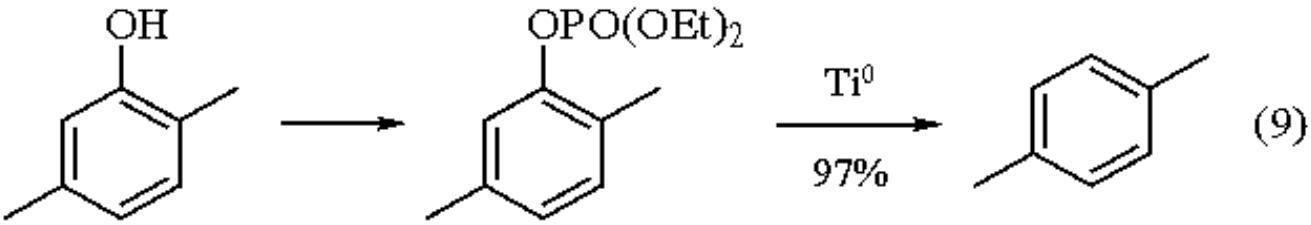

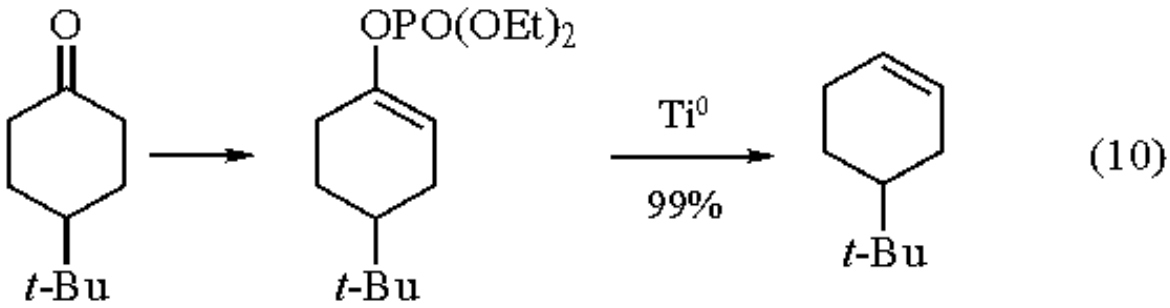

Miscellaneous Reductions.

The Ti^0 produced by the title reagents can be expected to perform the transformations achieved by Ti^0 generated from other reagents, e.g. coupling of thiocarbonyls to alkenes or allylic alcohols to 1,5-dienes. However, in these cases the use of potassium is not justified.

---

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13. Welch, S. C.; Loh, J.-P. *JOC* **1981**, *46*, 4073.

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Titanium(IV) Chloride-2,2,6,6-Tetramethylpiperidine

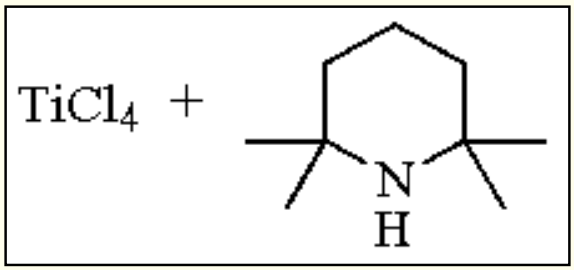

($TiCl_4$)

[7550-45-0] · Cl_4Ti · Titanium(IV) Chloride-2,2,6,6-Tetramethylpiperidine · (MW 189.68) (TMP)

[768-66-1] · $C_9H_{19}N$ · Titanium(IV) Chloride-2,2,6,6-Tetramethylpiperidine · (MW 141.29)

(oxophilic Lewis acid for the intramolecular cyclization of unsaturated (*Z*)-allylic alcohols[1])

Physical Data: see ***Titanium(IV) Chloride*** and ***2,2,6,6-Tetramethylpiperidine***.

Solubility: $TiCl_4$: sol aromatic hydrocarbons, ether, THF, dioxane, chlorohydrocarbons. TMP: sol acid, ethers, chlorohydrocarbons, aromatic solvents.

Form Supplied in: $TiCl_4$: colorless liquid, or as a crystalline complex with THF. TMP: colorless liquid.

Preparative Methods: TMP (1.5 equiv) is added to a solution of $TiCl_4$ (1.5 equiv) in dichloromethane at 0 °C. It is assumed that a complex, analogous to the $TiCl_4$-*N*-methylaniline complex,[1,2] is formed. The mixture is then cooled to -23 °C and the (*Z*)-allylic alcohol added.

Handling, Storage, and Precautions: $TiCl_4$ is corrosive and moisture-sensitive. TMP is a flammable liquid which should be stored in colored glass. The reagent will be moisture sensitive so the reactions are best performed under a dry inert atmosphere. Solvents should be dried before use.

Cyclization of Unsaturated (*Z*)-Allylic Alcohols.

Nerol has been cyclized using $TiCl_4$-TMP to give the chloroisopropylcyclohexene shown (eq 1).[1] Use of $TiCl_4$ alone gave a complex mixture. The use of *N*-methylaniline in place of TMP gave (**1**) in 67%; this latter reagent has been much more widely used. By analogy, (*E*)-allylic alcohols could be expected to give the allylic halide, as could (*Z*)-allylic alcohols lacking further suitably disposed alkenic bonds.

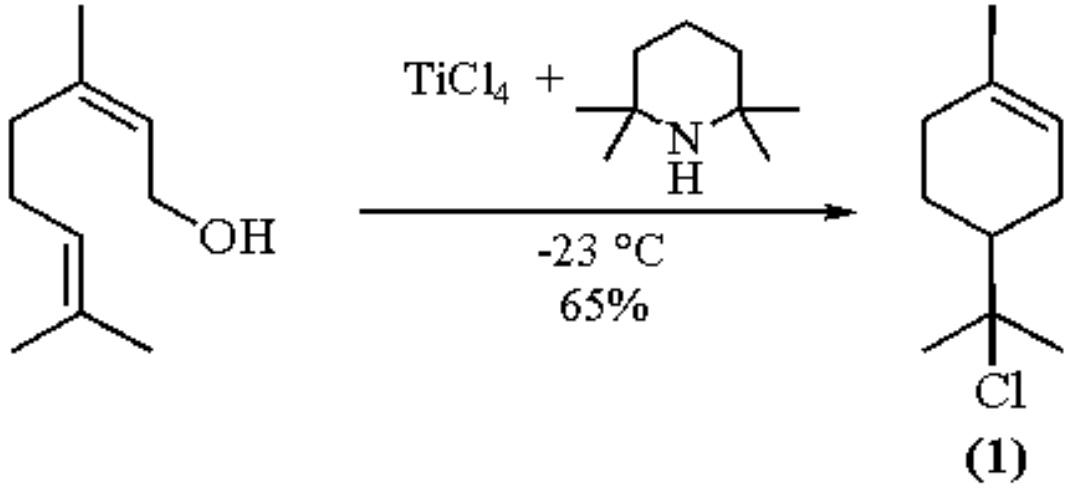

(1)

Related Reagents.

Titanium(IV) Chloride.

---

1. Saito, T.; Itoh, A.; Oshima, K.; Nozaki, H. *TL* **1979**, 3519.
2. See also Burger, V. H.; Nesse, H. J. *Z. Anorg. Allg. Chem.* **1969**, *365*, 243.

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Titanium(IV) Chloride-Triethylaluminum[1]

$TiCl_4$-$AlEt_3$

($TiCl_4$)

[7550-45-0] · Cl_4Ti · Titanium(IV) Chloride-Triethylaluminum · (MW 189.68) ($AlEt_3$)

[97-93-8] · $C_6H_{15}Al$ · Titanium(IV) Chloride-Triethylaluminum · (MW 114.19)

(alkene polymerization and/or oligomerization catalyst;[1] alkyne polymerization, oligomerization, and/or trimerization catalyst;[2] cationic polymerization catalyst for aldehydes, epoxides; alkylation of alkenes[3])

Physical Data: see ***Titanium(IV) Chloride*** and ***Triethylaluminum***.

Form Supplied in: $TiCl_4$: colorless (occasionally pale yellow) liquid; 1.0 M solution in dichloromethane or toluene; widely available. $AlEt_3$: colorless liquid; 1.0 M hexane solution; 25 wt % toluene solution; widely available.

Purification: reflux $TiCl_4$ with mercury or a small amount of pure copper turnings to remove the last traces of light color (due to $FeCl_3$ and VCl_4), then distil under nitrogen in an all-glass system, taking precautions to exclude moisture.[4] Distil $AlEt_3$ under vacuum in a column containing a heated nichrome spiral.[5]

Handling, Storage, and Precautions: $TiCl_4$ is moisture sensitive; fumes in air; an irritant to eyes and respiratory tract. $AlEt_3$ is flammable in air; should be kept away from water, and stored under an inert atmosphere. Use in a fume hood.

Polymerization of Ethylene, Propylene or Other α-Alkenes.

The Ziegler-Natta catalyst[6] is one of the most widely used organometallic catalysts. This type of catalyst has made it possible to obtain linear polyethylene and isotactic polypropylene under mild reaction conditions (eq 1).

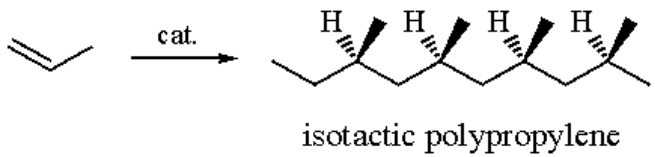

(1)

The recent development of $MgCl_2$-supported catalysts has been a major breakthrough in the production of polyalkenes.[7] By the addition of other components (Lewis bases as internal and external electron donors), high isotacticity as well as high activity can be achieved.[8] $TiCl_4/AlEt_3$ without the Lewis base may be used for polyethylene synthesis or the polymerization of other monomers, but not for the preparation of isotactic polypropylene because of their low stereospecificity. When stereospecific poly(α-alkene) is the desired product, the following five components are basically used as catalyst: (1) transition metal compounds, typically $TiCl_4$; (2) a solid support ($MgCl_2$ is the most commonly reported); (3) an internal Lewis base, typically aromatic esters such as ethyl benzoate and dialkyl phthalate; (4) organoaluminum compounds (so-called cocatalyst), typically $AlEt_3$; and (5) an external Lewis base, such as aromatic esters, phenylalkoxysilanes, and ***2,2,6,6-Tetramethylpiperidine***. Although many variations are possible for this catalyst system, this article will describe only some typical examples.

Practical procedures for the preparation of a solid catalyst ($MgCl_2$-supported $TiCl_4$ with an internal Lewis base) can be found in a number of patents and in the literature. An outline of a typical procedure is as follows. Anhydrous $MgCl_2$ is mechanically co-milled with ethyl benzoate for 10-100 h and rinsed out of the mill with heptane. The solid support is suspended in a heptane solution of $TiCl_4$ and stirred for several hours at 80-100 °C. The solid is filtered and washed with hydrocarbons to remove unreacted $TiCl_4$ and dried. The content of Ti in the solid catalyst is ca. 2-5 wt %.

Polymerization is often carried out under atmospheric pressure in propylene-saturated heptane at 40-60 °C. After an external Lewis base is added, polymerization is started by adding organoaluminum compounds such as $AlEt_3$. The solvent and inert gas should be purified carefully since contamination by a slight amount of oxygen or water may affect not only the activity of the catalyst, but also the microstructure of polymers obtained. A variety of supports and their preparation methods have also been investigated. Some examples of the polymerization of propylene are shown in Table 1. Extensive investigations have also been performed for the polymerization of higher α-alkenes.[9]

Table 1 Polymerization of Propylene Catalyzed by $TiCl_4/AlEt_3$

Support	Internal Lewis base	External Lewis base	Al/Ti	Polymn. temp. (°C)	Activity[a]	I.I[b] (%)
$MgCl_2$	Ethyl benzoate[10]	Ethyl benzoate	20	rt	2.7	94
$MgCl_2$	Dibutyl phthalate[11]	$Ph_2C(OMe)_2$	140	70	4.5 6[c]	97 98
$MgCl_2$	Diisobutyl phthalate[12]	$Ph_2Si(OMe)_2$	200	60	7.0	98.5
$MgCl_2$	Dioctyl phthalate[13]	TMP[d]	50	50	10	96
$MgCl_2$	Ethyl benzoate, *p*-cresol[14]	Methyl *p*-toluate	167	50	4.0	96
$MgCl_2$[e]	Dioctyl/dibutyl phthalate[14]	$PhSi(OEt)_3$	167	50	16.1	98.6
$Mg(OEt)_2$	Ethyl benzoate[15]	$PhSi(OEt)_3$		70	31	90
$SiO_2/MgCl_2$	Dibutyl phthalate[16]	$Ph_2Si(OMe)_2$	40 50	70	13	99

[a] Grams of polypropylene per gram of Ti per hour. [b] Isotactic index: insoluble part of polymers in heptane which gives an index of isotacticity of obtained polymers. [c] Productivity (grams of polypropylene per gram of Ti). [d] TMP = 2,2,6,6-tetramethylpiperidine. [e] Prepared from homogeneous solution.

γ-$TiCl_3/AlEt_2Cl$, as well as $TiCl_4/AlEt_3$, is also known as a stereospecific catalyst. In the case of $TiCl_3$, a less stereoregular polymer is obtained with $AlEt_3$.[17] Many other metals, such as vanadium,[18] chromium,[19] etc., are also used as catalysts. A comparison of the Ti catalyst with Cr and V is shown in Table 2.

Table 2 Polymerization of Propylene with Various Metal Catalysts[20]

Catalyst				Polymerization			
Type	Amount of metal[a] (mmol)	Amount of $AlEt_3$ (mmol)	Monomer (mol L^{-1})	Temp. (°C)	Time (min)	Yield (g)	Activity[e]
$MgCl_2/TiCl_4$	2.46	0.51	0.27	50	20	1.89	48.3
UC-Cr[b]	142	0	0.22	60	60	3.28	0.45
P-Cr[c]	86	0	20 psi[d]	50	60	1.51	0.34
VCl_3	136	2.2	0.39	50	10	2.54	2.2

[a] Metal = T, Cr, V. [b] Chromocene supported on silica. [c] Phillips CrO_3 supported on silica/alumina. [d] Gas-phase polymerization at 20 psi pressure. [e] kg of polymer per gram of metal per hour.

In the copolymerization of ethylene and α-alkenes, the distribution and sequence of each unit in the polymer chain should be considered. It is known that the presence of an α-alkene enhances the activity of the catalyst for ethylene polymerization.[21] Some examples of copolymerization are summarized in Table 3. It is commonly believed that the oxidation state of Ti at the active site is Ti^{III}. It is important for copolymerization because Ti^{III} is effective for polymerization both of ethylene and other α-alkenes, while Ti^{II} can polymerize only ethylene.[22] The existence of Ti^{II} in the catalyst system causes a mixture of copolymer and ethylene homopolymer to be formed.

Table 3 Copolymerization of a-Alkenes

Support	Internal Lewis base	External Lewis base	Monomers M_1 M_2	Polymn. temp. (°C)	Activity[a]	r_1, r_2
$MgCl_2$	Ethyl benzoate		Ethylene propylene[23]	50	58	$r_1 = 11.9$, $r_2 = 0.18$
$MgCl_2$	Dioctyl phthalate	$PhSi(OEt)_3$	Ethylene propylene[24]	60	1.7	$r_1 \cdot r_2 = 2.5$
No support			Ethylene 1-butene[25]	80		$r_1 \cdot r_2 = 0.6$ 1.1
MgH_2			Ethylene 1-hexene[26]			$r_1 = 29$ 62, $r_2 = 0.008$ 0.02
$SiO_2/EtMgCl$			Ethylene 1-hexene[27]	50	3.6 8.4	$r_1 = 26$ 53
$MgCl_2$	Diisobutyl phthalate	TMP[b] or $PhSi(OMe)_3$	Propylene 1-butene[28]	15	20 30[c]	$r_1 \cdot r_2 = 1.2$ 1.5

[a] kg of polymer per gram of Ti per hour. [b] TMP = 2,2,6,6-tetramethylpiperidine. [c] Grams of polymer per gram of catalyst.

Polymerization of Conjugated Dienes.

$TiCl_4/AlEt_3$ with a nickel catalyst is effective for the preparation of *cis*-1,4-polybutadiene.[29] *trans*-1,4-Polybutadiene can be obtained with the $TiCl_4/VCl_4/AlEt_3$ system (eq 2).[30]

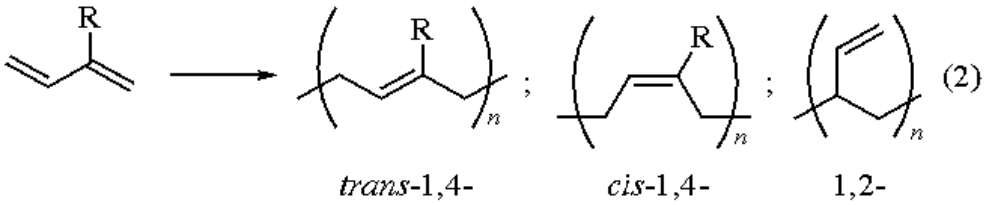

Various transition metal catalysts other than titanium catalysts can also be used. A cobalt catalyst with $AlEt_3$ and $AlEt_2Cl$ gives 1,2-polybutadiene and *cis*-1,4-polybutadiene, respectively.[31] For the polymerization of isoprene, the combination $TiCl_4/AlEt_3$ gives *cis*-1,4-polymer,[32] while ***Vanadium(IV) Chloride***/$AlEt_3$[33] and $V(acac)_3/AlEt_3$[34] give *trans*-1,4-polymer and 3,4-polymer, respectively. Other substituted[35] or cyclic[36] dienes can also be polymerized with Ziegler-Natta catalysts. The $TiCl_4/AlEt_3$/phosgene system affords a random copolymer of butadiene and propylene.[37] Copolymerization of ethylene-butadiene with titanium has also been investigated.[38]

Polymerization of Other Vinyl Compounds.

Titanium-catalyzed polymerization of other vinyl compounds, such as internal alkenes,[39] cyclic alkenes, allenes,[40] and those with functional groups, have been investigated. Three modes of polymerization are known for norbornenes[41] and its derivatives:[42] a vinyl polymerization and two types of ring-opening polymerization providing polymers with *trans* and *cis* double bonds (eq 3).

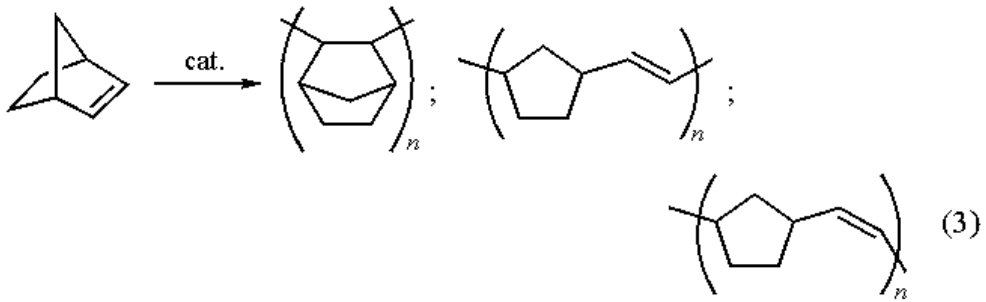

Cycloalkenes show a similar behavior in their polymerization.[43] The mechanism of ring-opening polymerization is explained by metathesis at the catalyst metal.[44] Some examples have been reported on vinyl monomers with functional groups such as alkyl acrylates,[45] vinyl chloride,[46] vinylidene fluoride,[47] vinyl acetate,[48] etc.

Polymerization and Oligomerization of Alkynes.[2,49]

Although a variety of methods for the preparation of conjugated polyacetylene is known, Ziegler-Natta catalysts are the most suitable for obtaining polyacetylene film (eq 4).

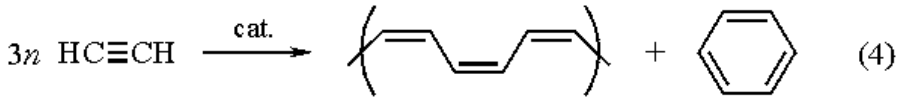

$Ti(OBu)_4/AlEt_3$ provides a good film of polyacetylene on the surface of a catalyst solution.[50] In this method, a concentrated solution of $AlEt_3$ is needed. Since it can ignite easily in air, the concentrated solution should be handled carefully under an inert atmosphere. Acetylene gas is also potentially explosive. Trimerization of acetylene often competes with polymerization to give benzene (eq 4).[51] A combination of titanium compounds and ***n-Butyllithium*** is also a good catalyst system for the formation of polyene.[52] It is known that the polymerization of mono- and disubstituted acetylene is catalyzed by Group 5 or 6 metal systems[53] rather than titanium. Some substituted alkynes, such as phenylacetylene,[54] phenoxyacetylene,[55] trimethylsilylacetylene,[56] and dihaloacetylene,[57] can be polymerized or oligomerized by Ti catalysts.

Polymerization and Oligomerization of Other Compounds.

Various other kinds of compounds can be polymerized or oligomerized by the $TiCl_4/AlEt_3$ catalyst system. Ring-opening polymerization of cyclopropanes proceeds in the presence of $TiCl_4$ as well as ***Tungsten(VI) Chloride*** or ***Tin(IV) Chloride***.[58] Cyclic ethers such as trioxane[59] and propylene oxide[60] also undergo ring-opening polymerization to afford polyethers. Some bifunctional compounds, such as *o*-phthalaldehyde,[61] malealdehyde,[62] and succinonitrile[63] afford cyclopolymerization products.

Miscellaneous Reactions Yielding Small Molecules.

Some synthetic reactions which give small molecules are known. Cyclotrimerization of butadiene gives 1,5,9-cyclodecatriene.[64] Cross-cyclodimerization of ethylene and butadiene proceeds catalytically to afford vinylcyclobutane (eq 5).[65]

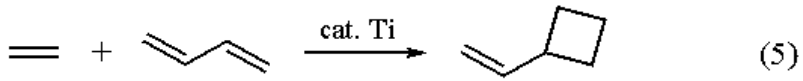

(5)

Alkylation of alkenes with organoaluminum reagents is catalyzed by titanium salts to give organoaluminum compounds.[3,66] $AlEt_2Cl$ rather than $AlEt_3$ usually gives better results (eq 6).

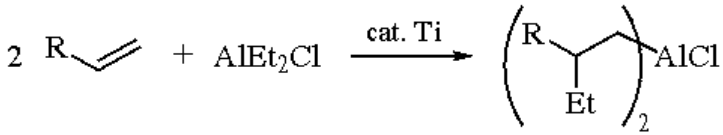

(6)

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Titanium(IV) Chloride-Zinc

$TiCl_4$-Zn

($TiCl_4$)

[7550-45-0] · Cl_4Ti · Titanium(IV) Chloride-Zinc · (MW 189.68) (Zn)

[7440-66-6] · Zn · Titanium(IV) Chloride-Zinc · (MW 65.39)

(combination of reagents which generates a divalent titanium chloride species: an oxophilic reducing agent used for carbonyl couplings[1] and reduction of sulfoxides,[2] etc.)

Physical Data: see ***Titanium(IV) Chloride*** and ***Zinc***.

Solubility: $TiCl_4$: sol aromatic hydrocarbons, ether, THF, dioxane, chlorohydrocarbons. Zinc: insol organic solvents.

Form Supplied in: $TiCl_4$: colorless liquid, or as a crystalline complex with THF; also supplied as solutions in toluene or dichloromethane. Zinc: metallic grey powder.

Preparative Methods: zinc powder (3 equiv) is added slowly to a mixture of the reagent(s) and $TiCl_4$ (1.5 equiv) in THF at -10 °C under argon. The mixture is then heated to the required temperature for an appropriate time.

Handling, Storage, and Precautions: $TiCl_4$ is corrosive and moisture sensitive. Zinc powder will react with water, liberating flammable gases and may spontaneously ignite in air. $TiCl_2$ is moisture and oxygen-sensitive and all reagents and reaction mixtures should therefore be handled under a dry inert atmosphere. Solvents should be dried before use.

Coupling of Aldehydes and Ketones.

Mukaiyama et al. reported that the reagent can be used to effect pinacol couplings (THF, rt, 2 h) or, under more forcing conditions, to give alkenes (THF or dioxane, reflux, >4 h; McMurry coupling).[1] When aldehydes or nonsymmetrical ketones are coupled, the stereochemistry about the new double bond is predominantly (*E*) (eq 1).

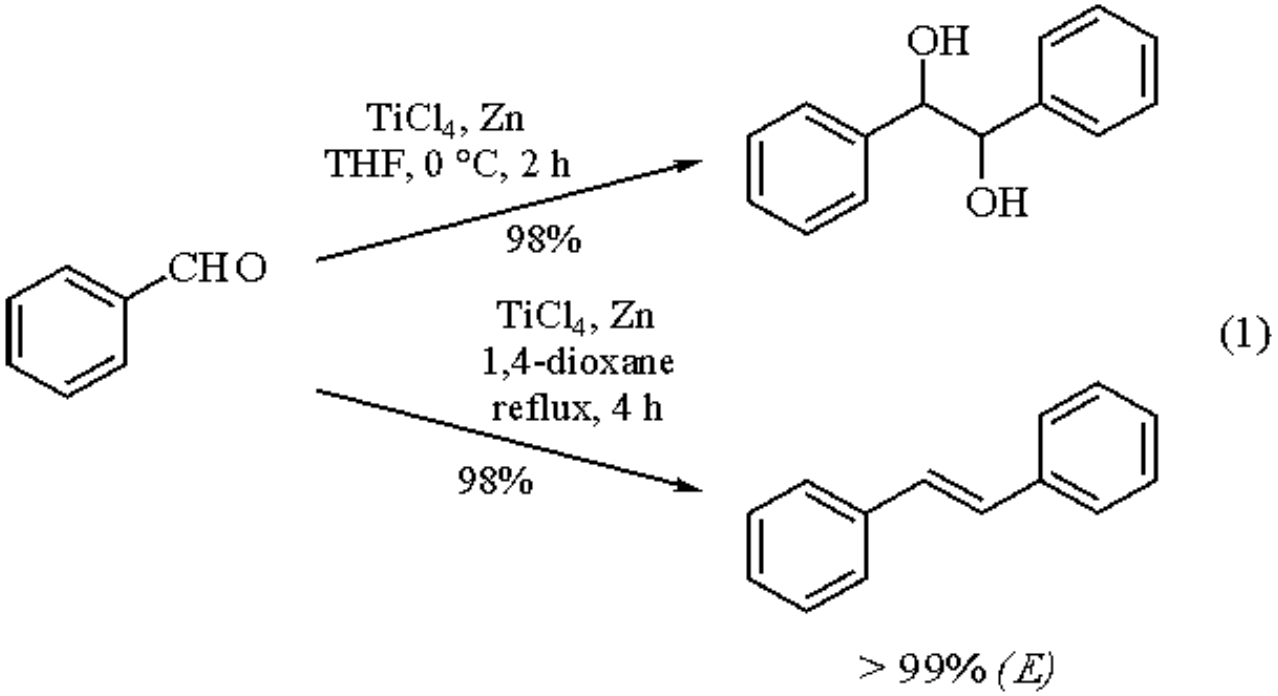

(1)

Alicyclic ketones are also coupled in high yields, although longer reaction times are required (eq 2).[3]

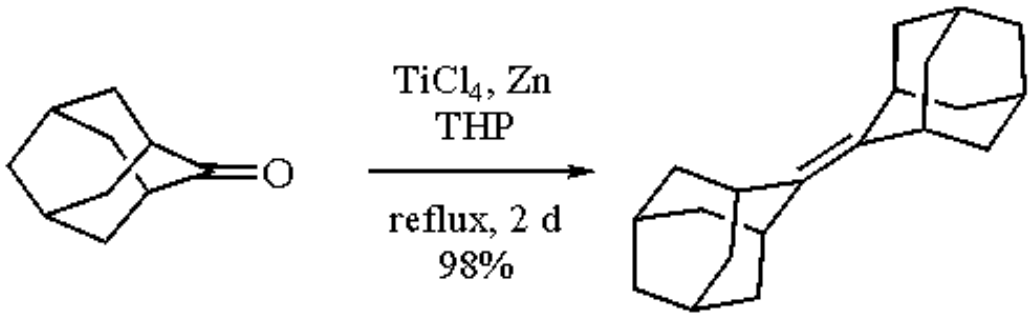

(2)

Intramolecular couplings have been used to prepare cembrane-type diterpenes,[4,5] e.g. isosarcophytol A (eq 3), thiophenes,[6] and 2,5-dihydrothiophenes (eq 4).[7]

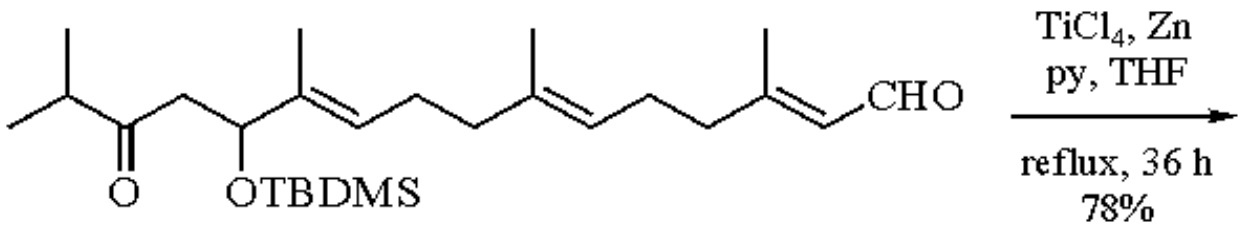

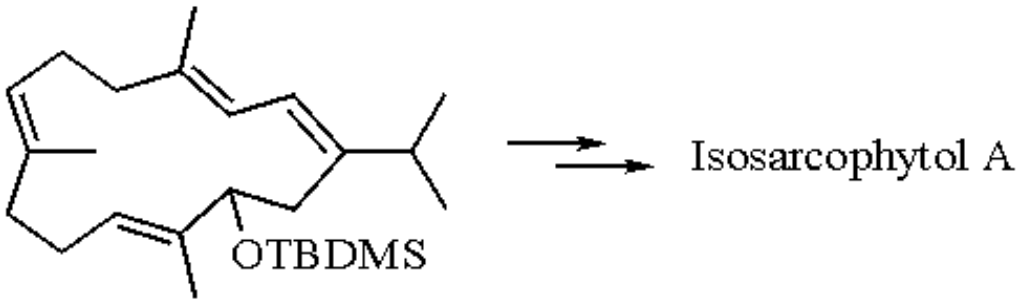

(3)

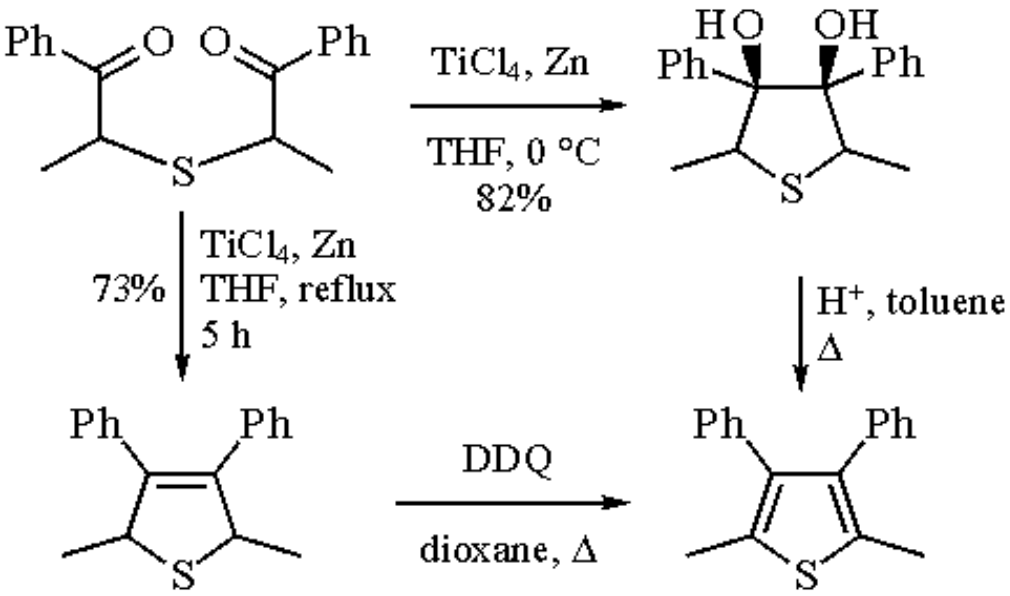

(4)

Other Reductive Coupling Reactions.

Ketones have been shown to couple intramolecularly with esters,[8] imines,[9] and nitro groups.[9] Aryl ketones give moderate yields of benzofurans (eq 5); aryl substituents in the 2-position of the furan are advantageous. Coupling with imines is analogous to the pinacol coupling, giving 2-aminoethanols (eq 6). The reaction with nitro groups affords cyclic imines and has been used to effect a reasonable synthesis of some diarylpyrrolines (eq 7).

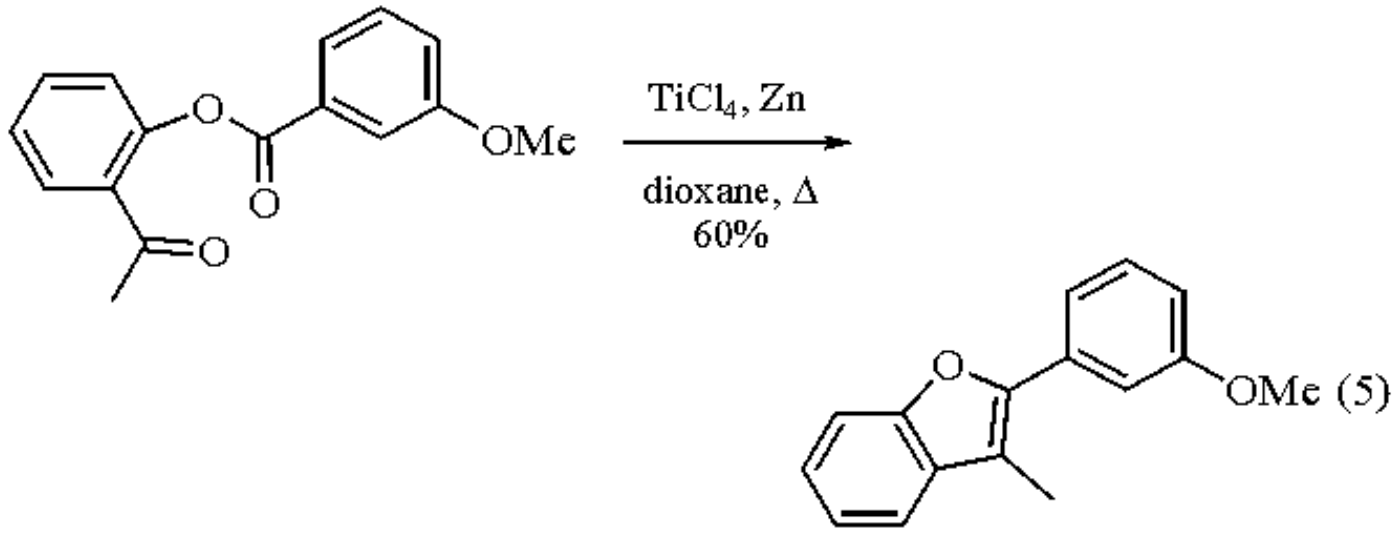
TiCl4, Zn
dioxane, Δ
60%
OMe
(5)

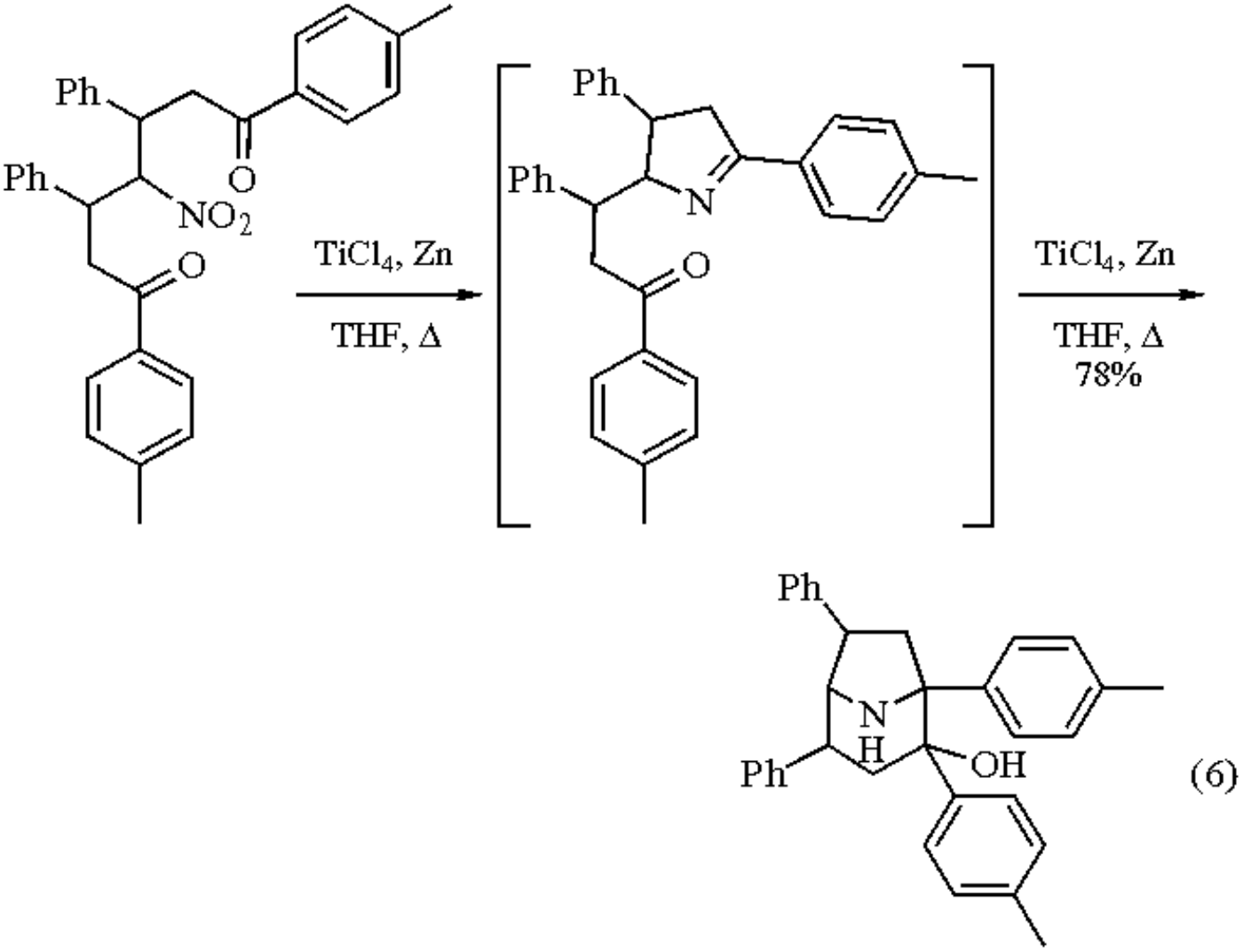
Ph
Ph
NO2
TiCl4, Zn
THF, Δ
TiCl4, Zn
THF, Δ
78%
N
H
OH
(6)

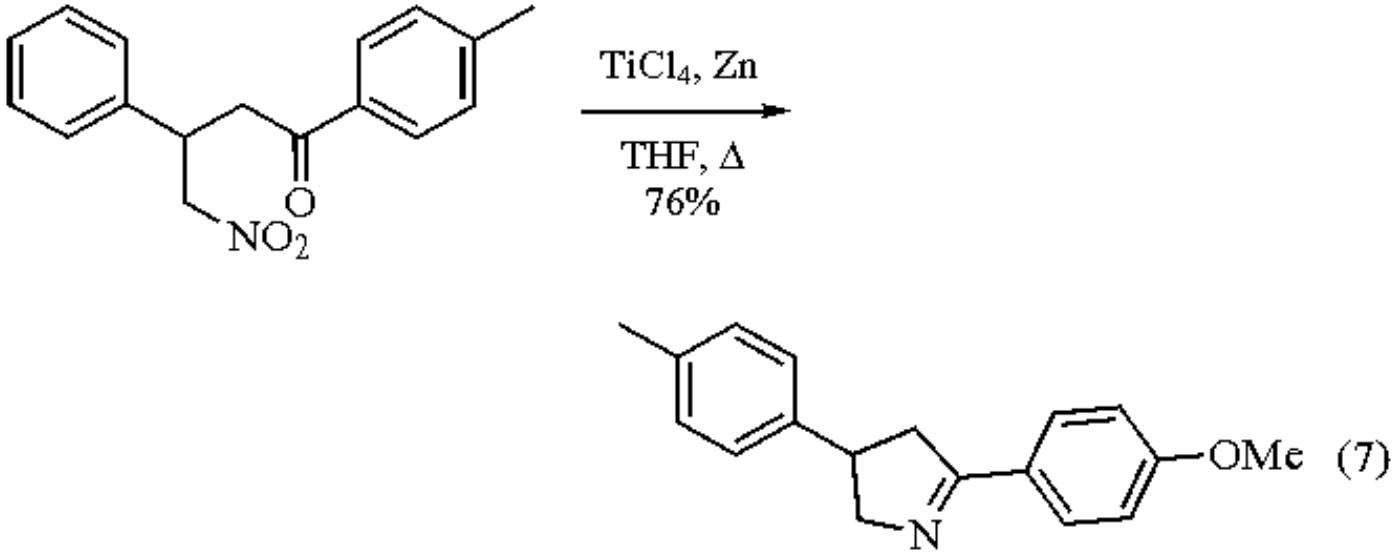

Benzonitriles are coupled to give 1,2-diarylethanones in moderate yield,[10] while alicyclic dinitriles separated by 3-5 atoms gives pyrazolines in modest yield (eq 8).[11] Aryl aldoximes and ketoximes give 1,2-diamino compounds in low yields.[12]

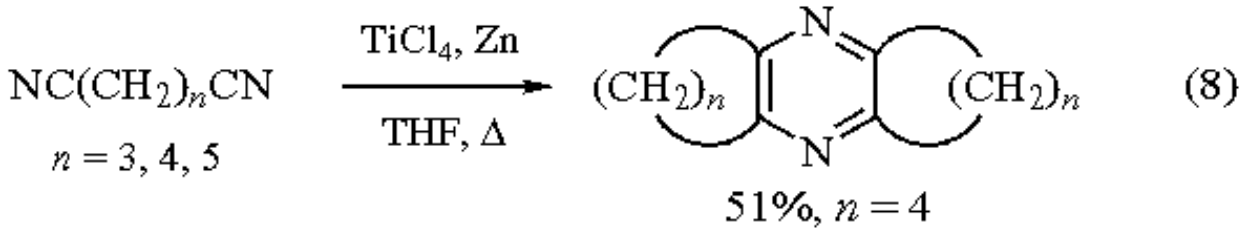

Alkene Synthesis.

The action of $TiCl_4$/Zn/dihaloalkanes is discussed in ***Titanium(IV) Chloride***. As well as converting 1,2-diols to alkenes (see above), β-hydroxy phenyl sulfides (eq 9),[13,14] β-hydroxy pyridyl sulfides (eq 10),[14] and β-benzoyloxy sulfides (eq 11)[15] undergo reductive elimination to give alkenes. To achieve good yields, either pyridine is used as solvent or an amine is added to the reaction mixture. In the latter case, good yields of *exo*-methylene compounds can be obtained. However, more direct methods, e.g. Wittig or Tebbe, are preferred.

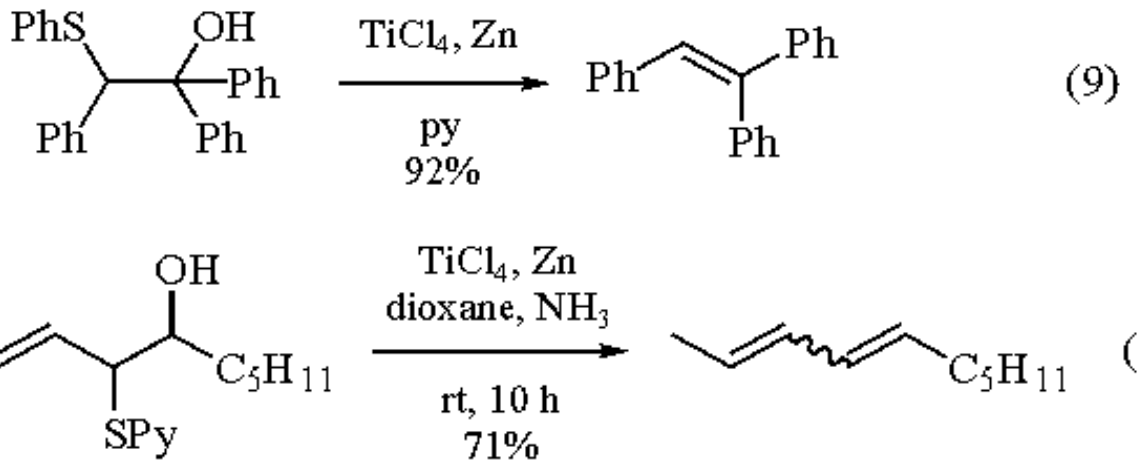

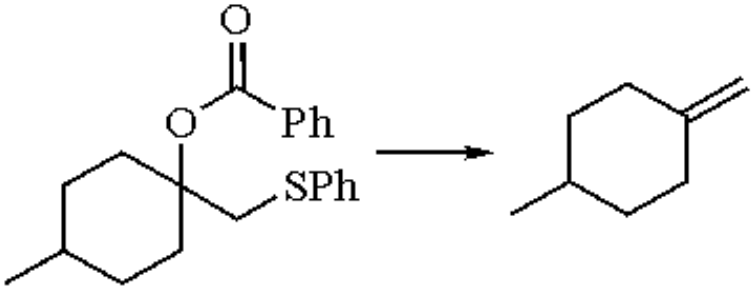

(11)

Phenyl vinyl sulfides may be obtained from β-hydroxy thioacetals[14] or from α-halo-β-hydroxy sulfoxides,[16] while α,α-dichloro sulfoxides give the chloroalkene (eq 12).[16]

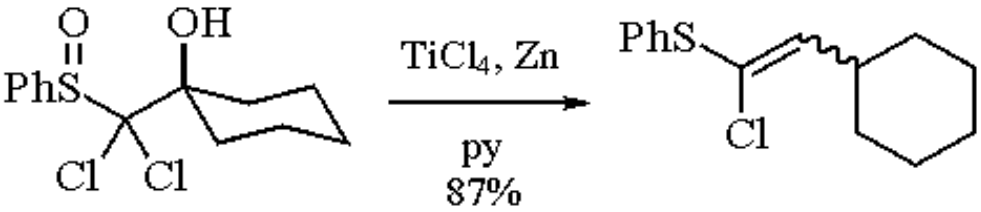

(12)

Excellent yields of alkenes are obtained from 1,2-dibromo compounds when treated with zinc and catalytic amounts of $TiCl_4$[17] via a *trans*-stereoselective reductive elimination (eqs 13 and 14).

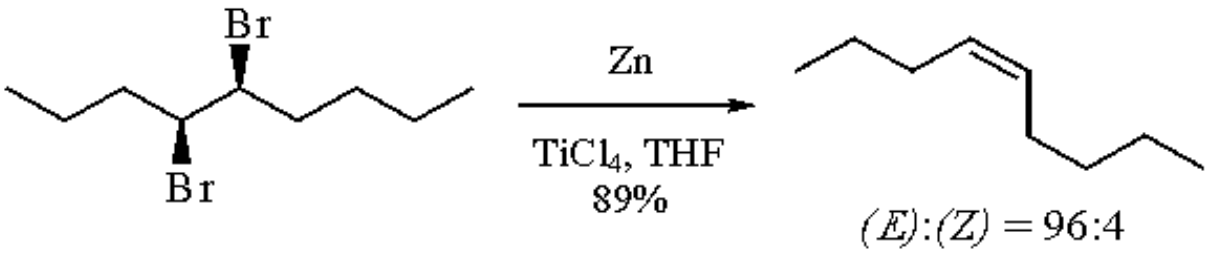

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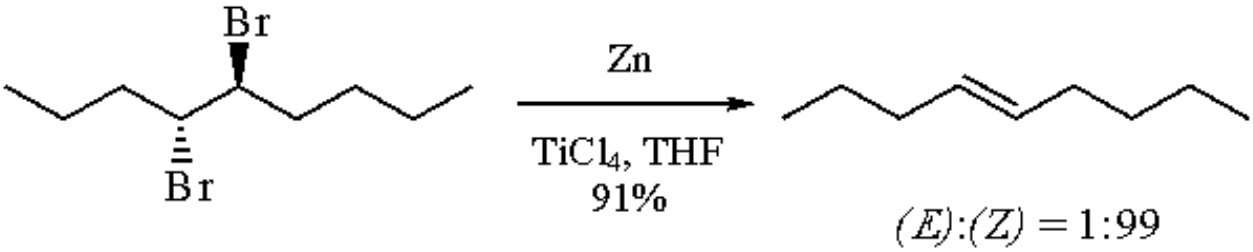

(14)

Deoxygenations.

Heteroaromatic amine oxides are reduced to the corresponding nitrogen-containing heteroaromatic system,[18] sulfoxides to sulfides (eq 15),[2] and triphenylarsine oxide to triphenylarsine,[19] all in good to excellent yields. The reduction of sulfoxides proceeds more rapidly and under less extreme conditions than those for ***Titanium(III) Chloride***.

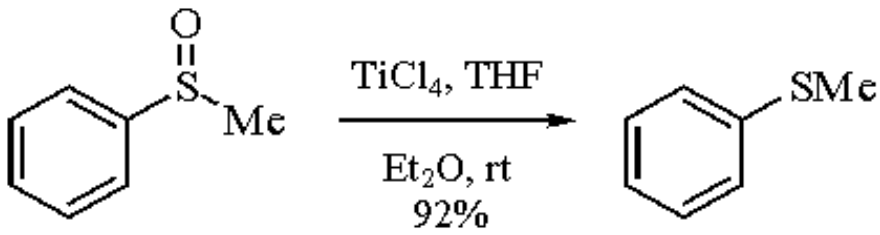

(15)

Difluoromethylaldol Condensations.

Zinc and catalytic quantities of $TiCl_4$ react with chlorodifluoromethyl ketones and ketones or aldehydes to give the aldol products (eq 16).[20] Yields are moderate to good, but poor when the electrophile is an enone, enal, or aromatic carbonyl.

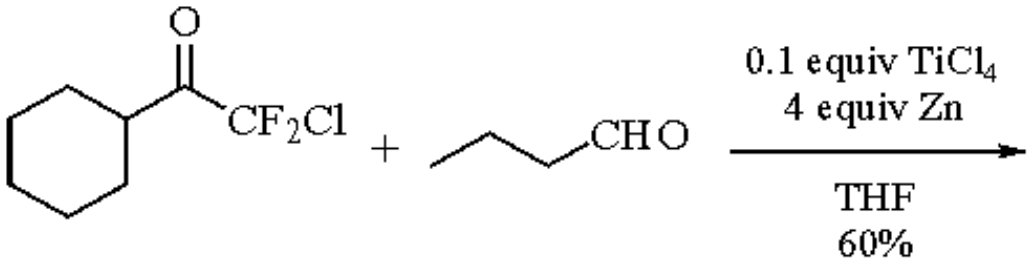

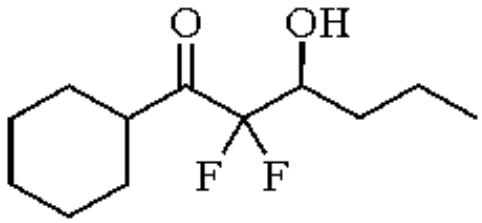

(16)

Simple α-chloro ketones undergo *erythro*-selective aldol reactions,[20] but the yields and selectivities do not reach the levels expected for controlled aldol condensations.

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Ian C. Richards

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Titanium Tetraisopropoxide[1]

Ti(O-*i*-Pr)$_4$

[546-68-9] · $C_{12}H_{28}O_4Ti$ · Titanium Tetraisopropoxide · (MW 284.28)

(mild Lewis acid used as a catalyst in transesterification reactions, nucleophilic cleavages of 2,3-epoxy alcohols and isomerization reactions; additive in the Sharpless epoxidation reaction and in various reactions involving nucleophilic additions to carbonyl and α,β-unsaturated carbonyl compounds)

Physical Data: mp 18-20 °C; bp 218 °C/10 mmHg; *d* 0.955 g cm^{-3}.

Solubility: sol a wide range of solvents including ethers, organohalides, alcohols, benzene.

Form Supplied in: low-melting solid; widely available.

Handling, Storage, and Precautions: flammable and moisture sensitive; acts as an irritant.

Transesterification and Lactamization Reactions.[2-5]

Ti(O-*i*-Pr)$_4$, as well as other titanium(IV) alkoxides, has been recommended as an exceptionally mild and efficient transesterification catalyst which can be used with many acid-sensitive substrates (eq 1).[2,3] Thus the acetonide as well as C=O, OH, OTBDMS, and lactam functional groups (eq 2) are unaffected by these conditions, although acetates are hydrolyzed to the parent alcohol. The alcohol solvent employed in such processes need not be anhydrous, nor need it be identical with the OR group in the titanate, because exchange of these moieties is generally slow compared to the transesterification reaction.

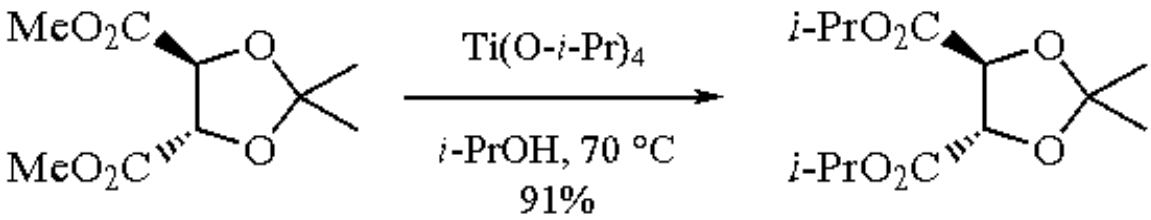

(1)

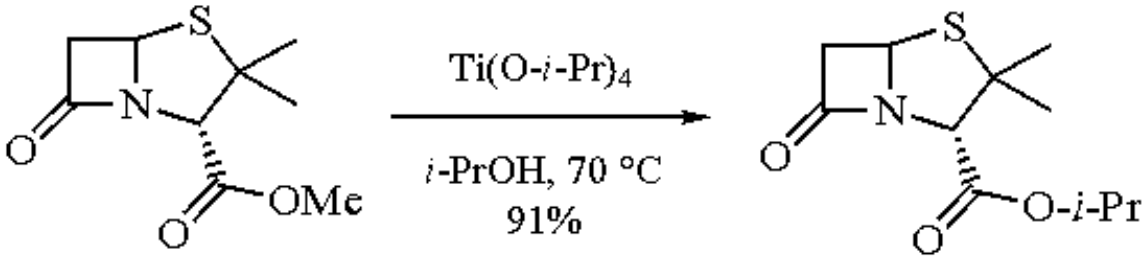

(2)

N-Protected esters of dipeptides can be transesterified using Ti(O-*i*-Pr)$_4$ in the presence of 4 Å molecular sieves and this procedure provides a good way of converting methyl esters into their benzyl counterparts. Such reactions (eq 3) proceed without racemization in 70-85% yield.[4] In a related process,[5] β-, γ-, and δ-amino acids undergo lactamization on treatment with Ti(O-*i*-Pr)$_4$ in refluxing 1,2-dichloroethane (eq 4).

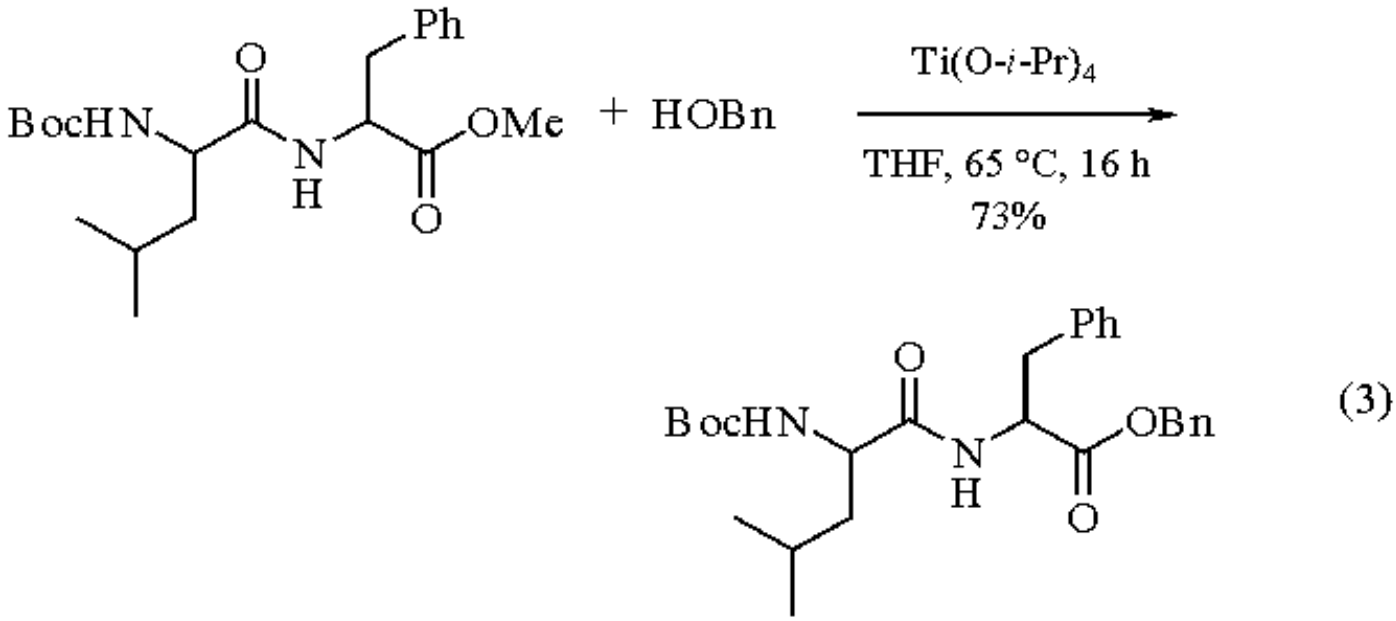

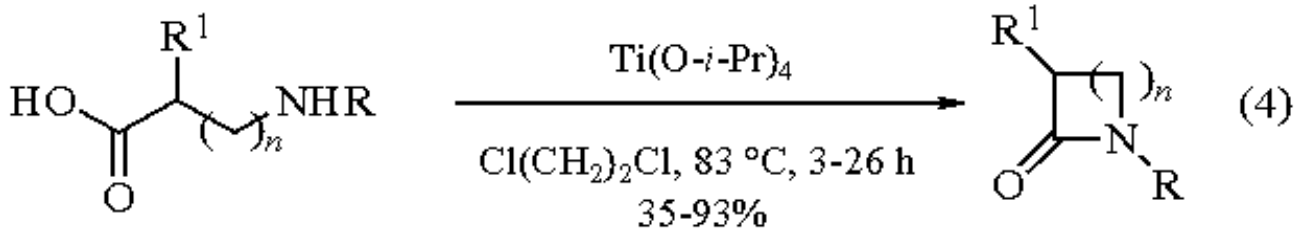

R, R^1 = H, Me

n = 1-3

Nucleophilic Cleavage of 2,3-Epoxy Alcohols and Related Compounds.[6-10]

Titanium alkoxides are weak Lewis acids which generally have no effect on simple epoxides. However, reaction of 2,3-epoxy alcohols (available, for example, from the Sharpless-type epoxidation of allylic alcohols) with nucleophiles in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ results in highly regioselective ring-cleavage reactions involving preferential nucleophilic attack at C-3 (eq 5).[6] In the absence of the titanium alkoxide, no reaction is observed under otherwise identical conditions, except in the case of PhSNa.

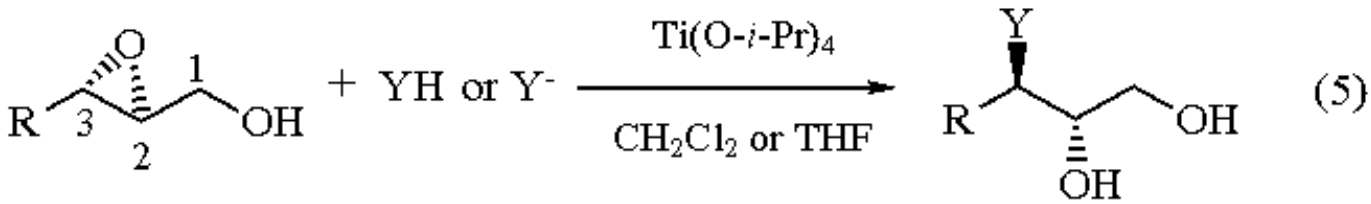

R = $Me(CH_2)_2$; YH = $CH_2{=}CHCH_2OH$	90%; C-3:C-2 > 100:1
R = $Me(CH_2)_2$; YH = Et_2NH	90%; C-3:C-2 = 20:1
R = $Me(CH_2)_2$; YH = $PhCO_2H$	74%; C-3:C-2 > 100:1
R = $Me(CH_2)_2$; YH = TsOH (with 2,6-lutidine)	64%; C-3:C-2 > 100:1
R = $Me(CH_2)_2$; YH = PhSH	95%; C-3:C-2 = 6.4:1
R = $Me(CH_2)_6$; YH = AcSH	91%; C-3:C-2 > 100:1
R = $Me(CH_2)_6$; $Y^- = NO_3^-$	86%; C-3:C-2 > 100:1

These types of conversion can be extended[7] to 2,3-epoxy carboxylic acids (glycidic acids) and the related amides. The former compounds are readily available through ***Ruthenium(VIII) Oxide***-mediated oxidation of the appropriate 2,3-epoxy alcohols (eq 6).

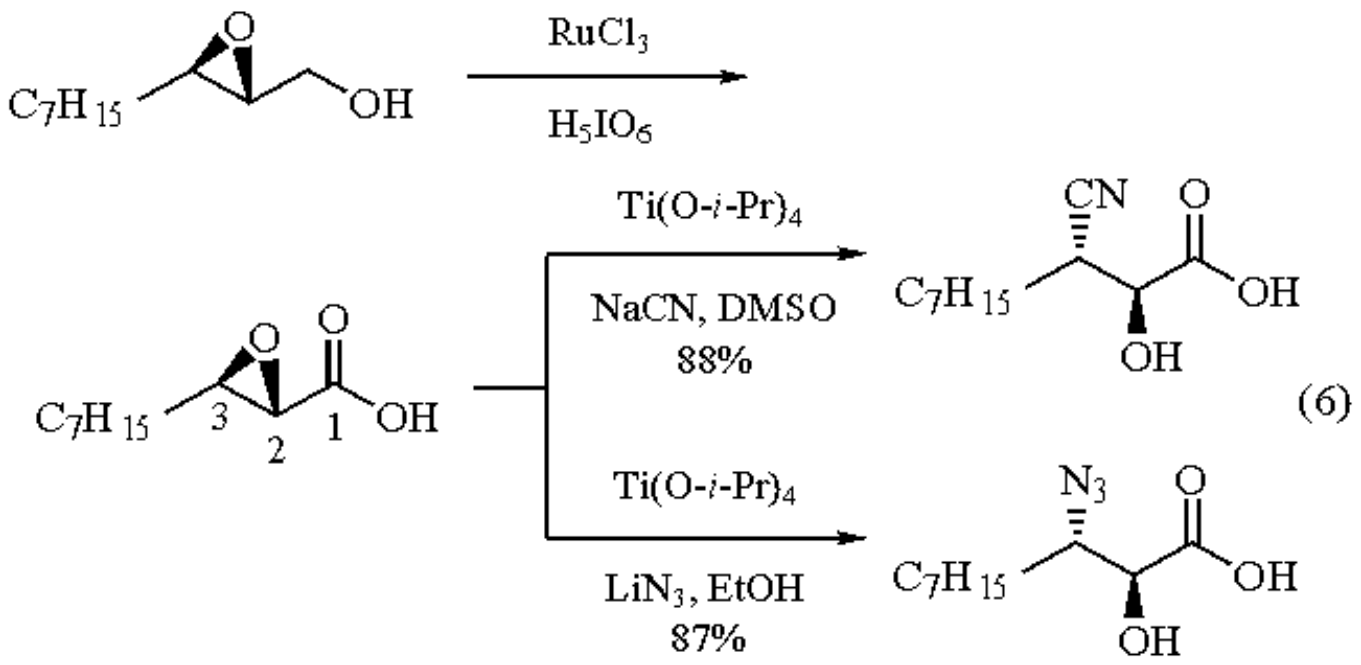

(6)

The C-3:C-2 selectivity is, in the cases shown above, greater than 100:1, although lower selectivities (e.g. 20:1) are observed with other nucleophiles such as Et_2NH and PhSH. It should be noted that glycidic acids and amides react preferentially with dialkylamines at C-2, but one equivalent or greater of $Ti(O\text{-}i\text{-}Pr)_4$ ensures reaction occurs with high selectivity at C-3. Combining this type of protocol with the Sharpless asymmetric epoxidation reaction has permitted the development of stereoselective syntheses (eqs 7 and 8)[6,7] of all four stereoisomers of the unusual *N*-terminal amino acid of amastatin, a tripeptide competitive inhibitor of aminopeptidases.[8]

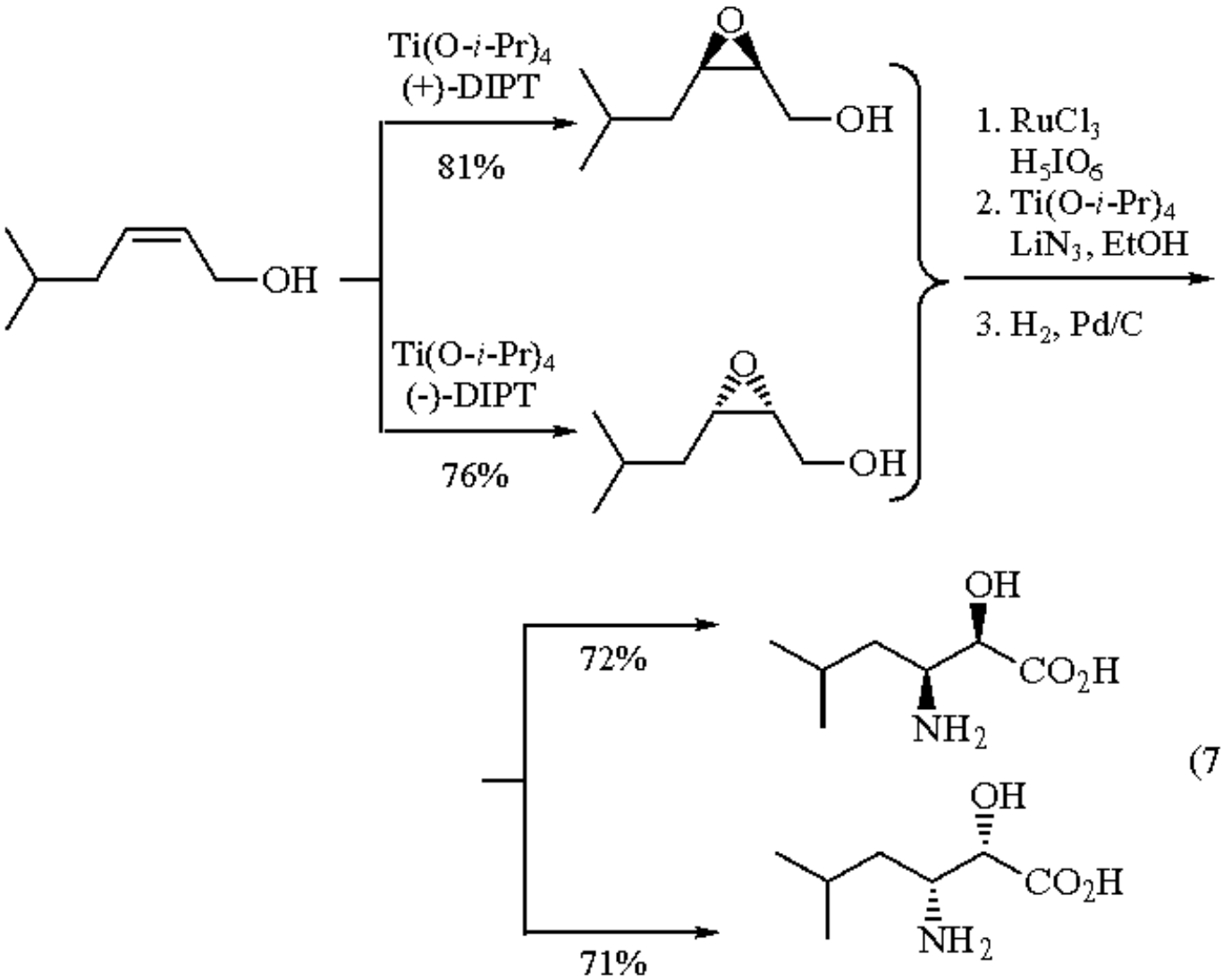

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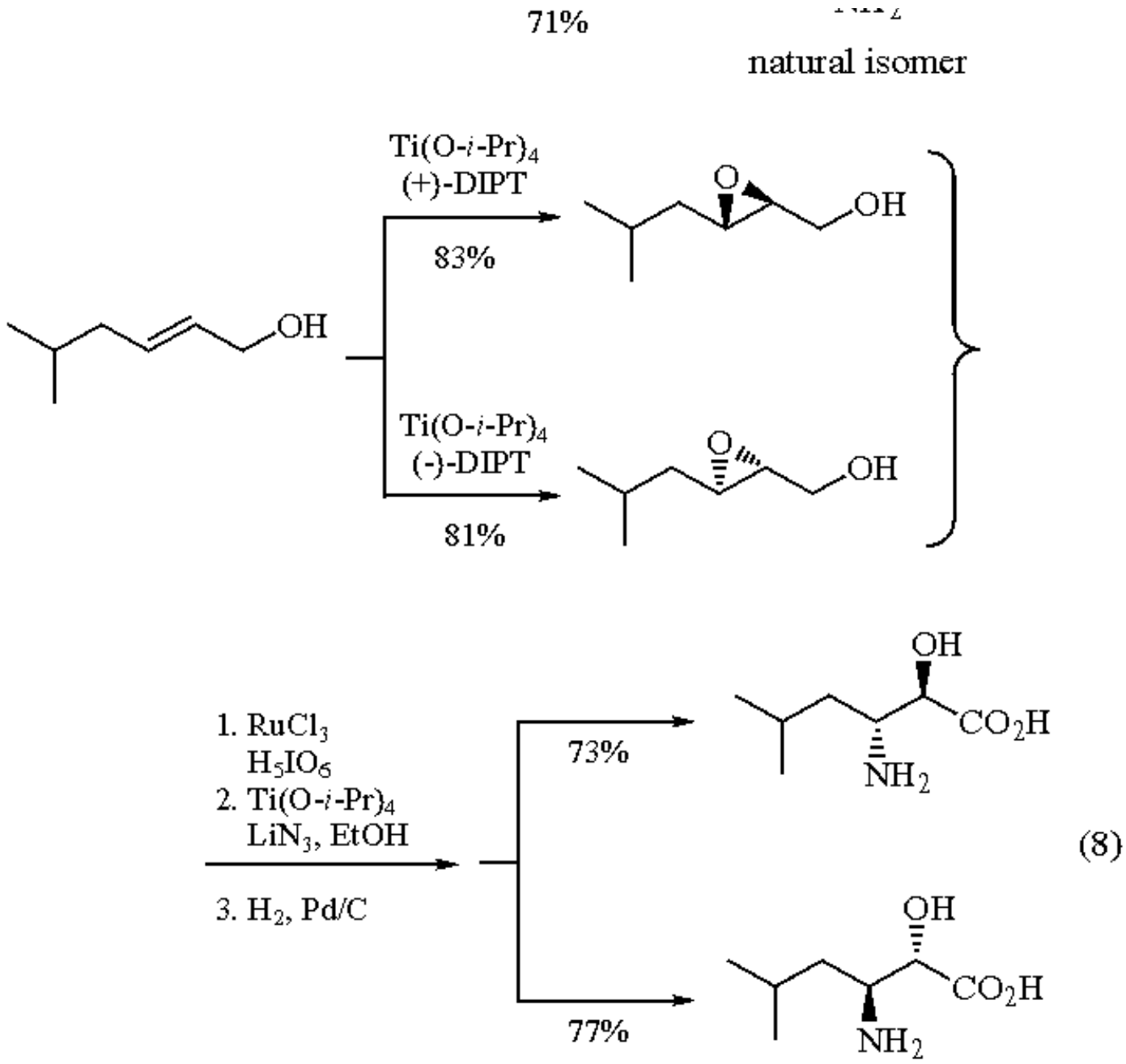

(8)

The reaction of both open-chain and cyclic 2,3-epoxy alcohols with molecular ***Bromine*** or ***Iodine*** in the presence of Ti(O-*i*-Pr)$_4$ at 0 °C leads to the regioselective formation of halo diols (eq 9).[9a] Interestingly, if these reactions are conducted at 25 °C a 1:1 mixture of the C-2 and C-3 cleavage products is obtained, and the same outcome is observed, even at 0 °C, when the acetate derivative of the 2,3-epoxy alcohol is involved as substrate. Dialkylamine hydrochlorides can be used as sources of halide nucleophiles in these types of epoxide ring-cleavage reactions.[9b]

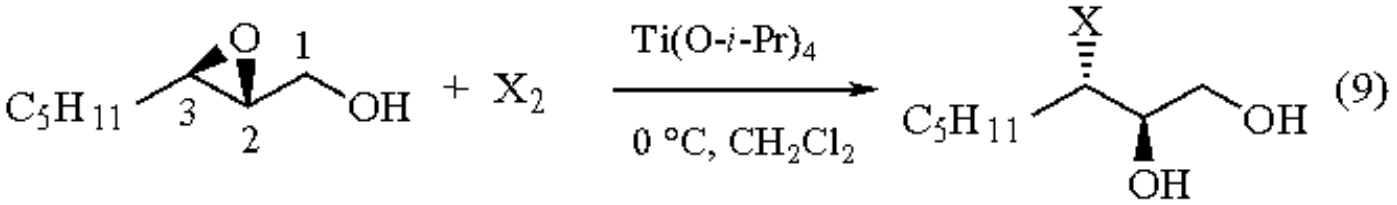

(9)

87% (X = I); C-3:C-2 = 7:1
78% (X = Br); C-3:C-2 = 15:1

2,3-Epithio alcohols have been obtained by reacting 2,3-epoxy alcohols with ***Thiourea*** at room temperature or 0 °C in the presence of Ti(O-*i*-Pr)$_4$ and using THF as solvent (eq 10).[10] The reactions proceed with high regio- and stereoselectivity, *trans*-substituted 2,3-epoxy alcohols giving only *trans*-2,3-epithio alcohols with complete inversion of configuration at both stereogenic centers. However, when *cis*-2,3-epoxy

alcohols are used as starting materials the yields of epithio alcohols were low and thiodiols were also formed. Epithiocinnamyl alcohols could also be prepared from the corresponding epoxycinnamyl alcohols at 0 °C. However, these products were found to decompose to cinnamyl alcohol and sulfur on standing. Without Ti(O-*i*-Pr)$_4$, thiourea was insoluble in THF and the reaction did not proceed. One equivalent of Ti(O-*i*-Pr)$_4$ was required to achieve complete reaction, and THF was the best solvent (no reaction was observed in ether, CH_2Cl_2, or benzene under similar conditions).

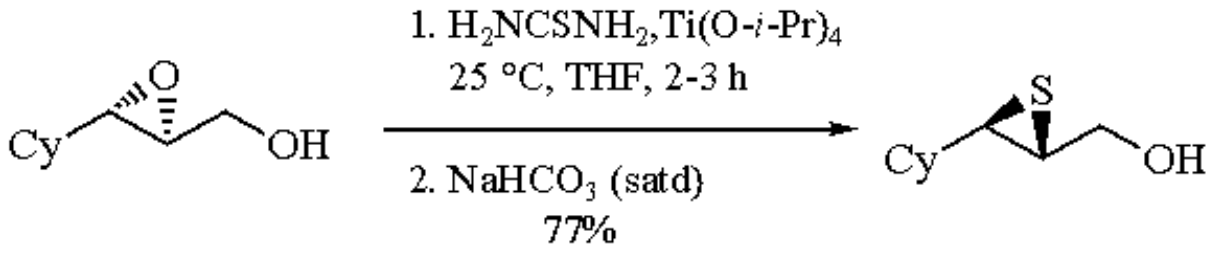

(10)

Isomerization Reactions.[11-14]

The reaction of certain 2,3-epoxy alcohols with Ti(O-*i*-Pr)$_4$ can result in isomerization. For example (eq 11), reaction of the illustrated substrate in CH_2Cl_2 results in rearrangement to the isomeric enediol, and this conversion represents a key step in a synthesis of the marine natural product pleraplysillin.[11]

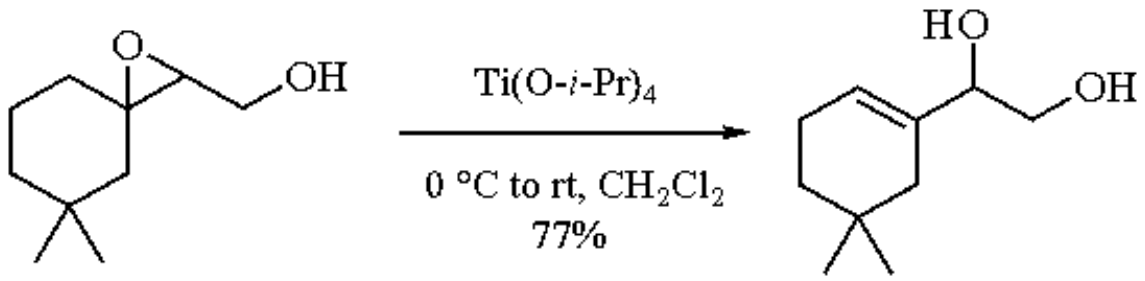

(11)

Under similar conditions, the pendant double bond attached to a 2,3-epoxy alcohol acts as an internal nucleophile attacking at C-3, resulting, after proton loss, in a mixture of cyclized products (eq 12).[12] The cyclopropane-containing products are believed to arise via a retro-homo Prins reaction. Pendant triple bonds can also participate in related cyclization reactions and cyclic allenes result (eq 13).[12] The observation that the *threo* isomer of the substrate shown in eq 12 is stable to Ti(O-*i*-Pr)$_4$ has led to the suggestion that an intramolecular metal alkoxide is the active catalyst in successful cyclization reactions.

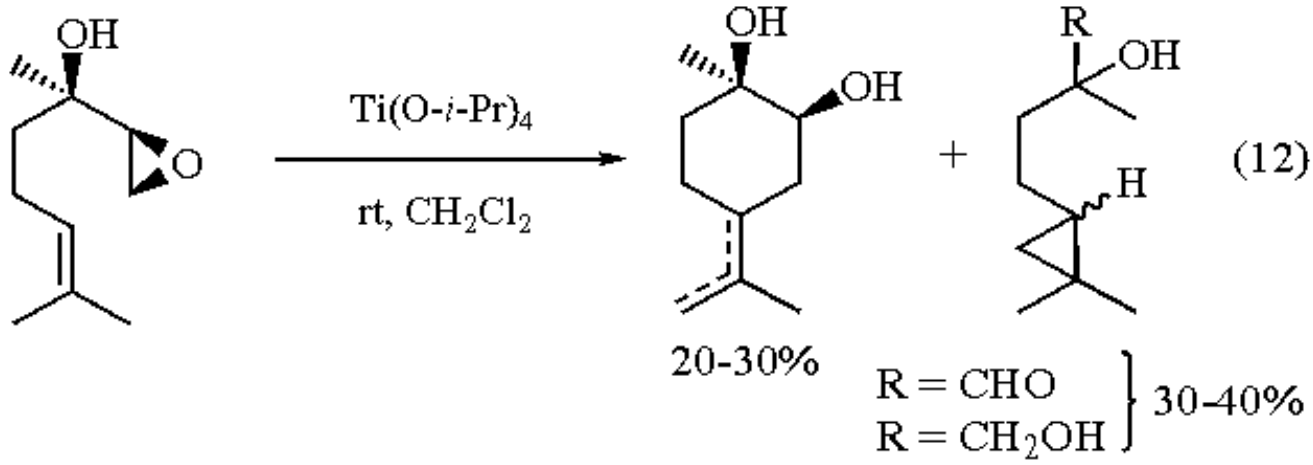

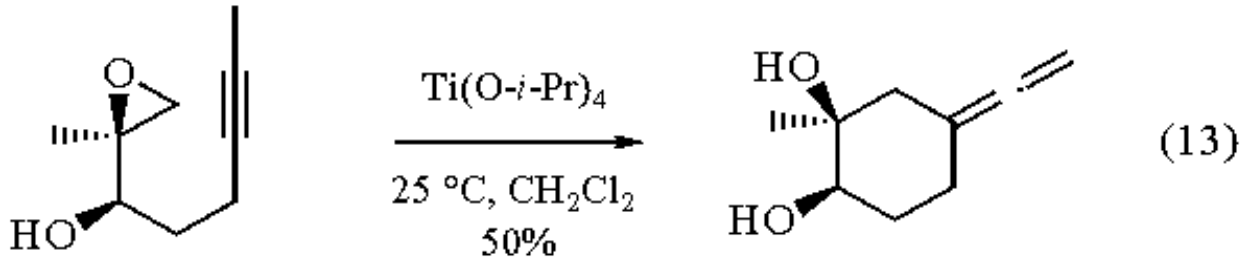

Ti(O-*i*-Pr)$_4$ has also played a key role in the synthesis of taxanes (eq 14).[12b,c]

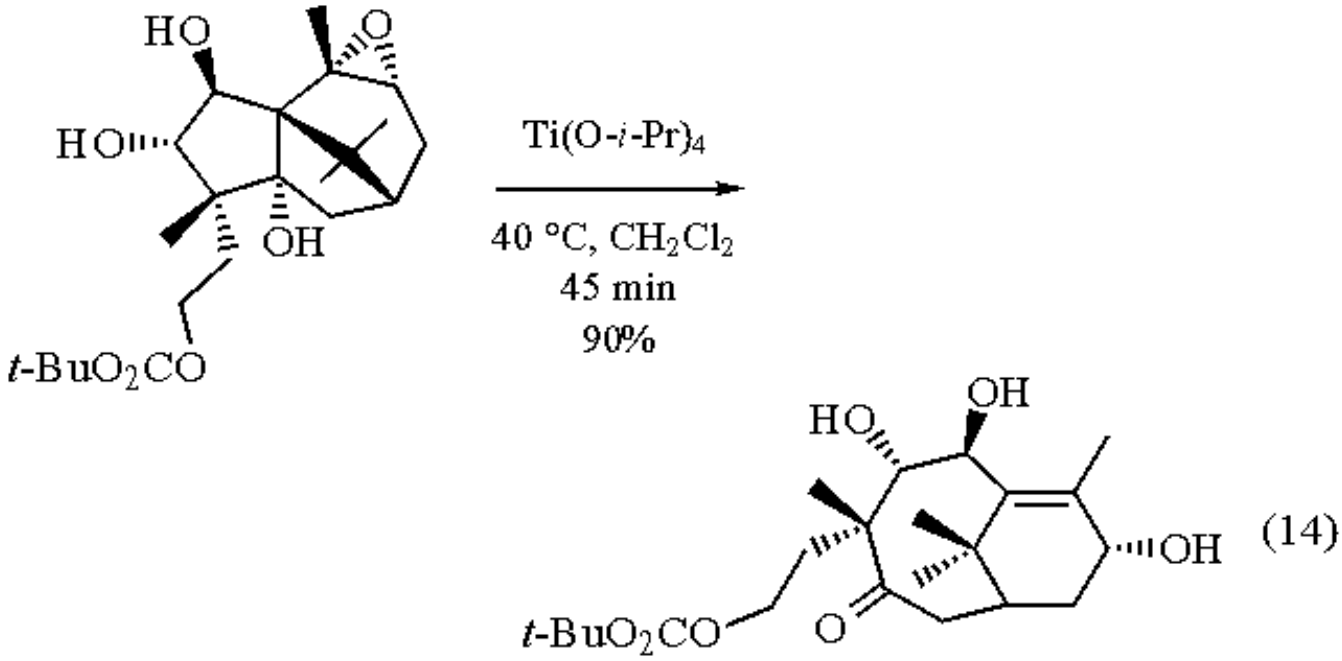

Allylic hydroperoxides, which are readily obtained by reaction of the corresponding alkene with ***Singlet Oxygen***, have been shown to isomerize to the corresponding 2,3-epoxy alcohol when treated with catalytic amounts of Ti(O-*i*-Pr)$_4$ (eq 15).[13] The title reagent is the one of choice when converting di-, tri-, and tetrasubstituted alkenes (both cyclic and acyclic) into the corresponding 2,3-epoxy alcohols by this protocol. The reactions are generally highly stereoselective and deoxygenation of the allylic hydroperoxide (to give the corresponding allylic alcohol) is not normally a process which competes significantly with the isomerization reaction.

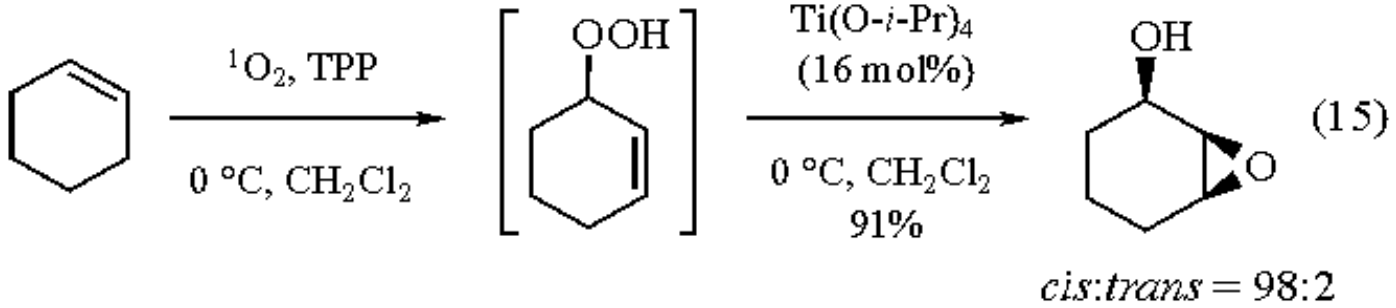

This type of chemistry has been extended to the preparation of epoxy diols from chiral allylic alcohols (eq 16).[13,14] The methodology is impressive in that three successive chiral centers are constructed with predictable configuration. Furthermore, the rapid rate of the isomerization process is remarkable, given that α,β-unsaturated diols are generally poor substrates for titanium metal-mediated epoxidations. This rate enhancement is attributed to the tridentate nature of the intermediate hydroperoxides.

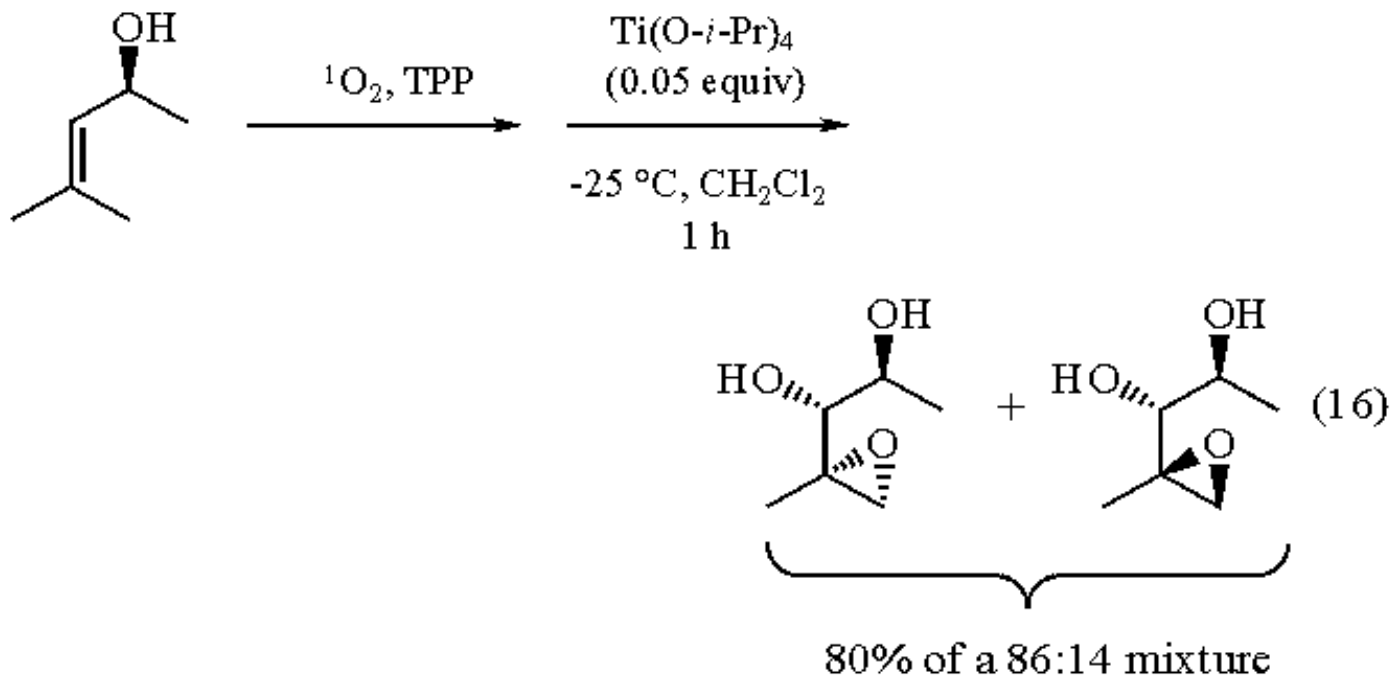

Asymmetric Epoxidation Reactions.[15]

While Ti(O-*i*-Pr)$_4$ clearly has the capacity to bring about the nucleophilic ring-cleavage of 2,3-epoxy alcohols (see above), it remains the preferred species for the preparation of the titanium tartrate complex central to the Sharpless asymmetric epoxidation process (see, for example, eq 7). Since *t*-butoxide-mediated ring-opening of 2-substituted 2,3-epoxy alcohols (a subclass of epoxy alcohols particularly sensitive to nucleophilic ring-cleavage) is much slower than by isopropoxide, the use of Ti(O-*t*-Bu)$_4$ is sometimes recommended in place of Ti(O-*i*-Pr)$_4$. However, with the reduced amount of catalyst that is now needed for all asymmetric epoxidations, this precaution appears unnecessary in most instances.

Nucleophilic Additions to Carbonyl Compounds.[16-28]

A wide range of organometallic compounds react with Ti(O-*i*-Pr)$_4$ to produce organotitanium/titanium-ate species which may exhibit reactivities that differ significantly from those of their precursor.[1] Thus Ti(O-*i*-Pr)$_4$ forms -ate complexes with, amongst others, Grignard reagents and the resulting species show useful selectivities in their reaction with carbonyl compounds. For example, the complex with allylmagnesium chloride is highly selective in its reaction with aldehydes in the presence of ketones, or ketones in the presence of esters (eq 17).[16] Interestingly, the corresponding amino titanium-ate complexes react selectively with ketones in the presence of aldehydes.

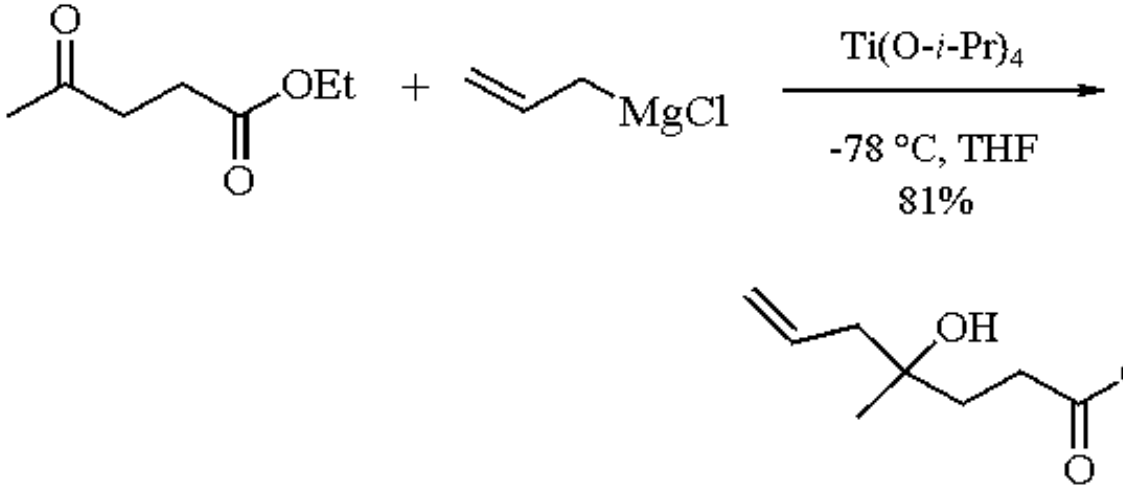

(17)

Reaction of certain sulfur-substituted allylic anions with Ti(O-*i*-Pr)$_4$ produces a 3-(alkylthio)allyltitanium reagent that condenses, through its α-terminus, with aldehydes to give *anti*-β-hydroxy sulfides in a highly stereo- and regioselective manner (eq 18). These latter compounds can be transformed, stereoselectively, into *trans*-vinyloxiranes or 1,3-dienes.[17]

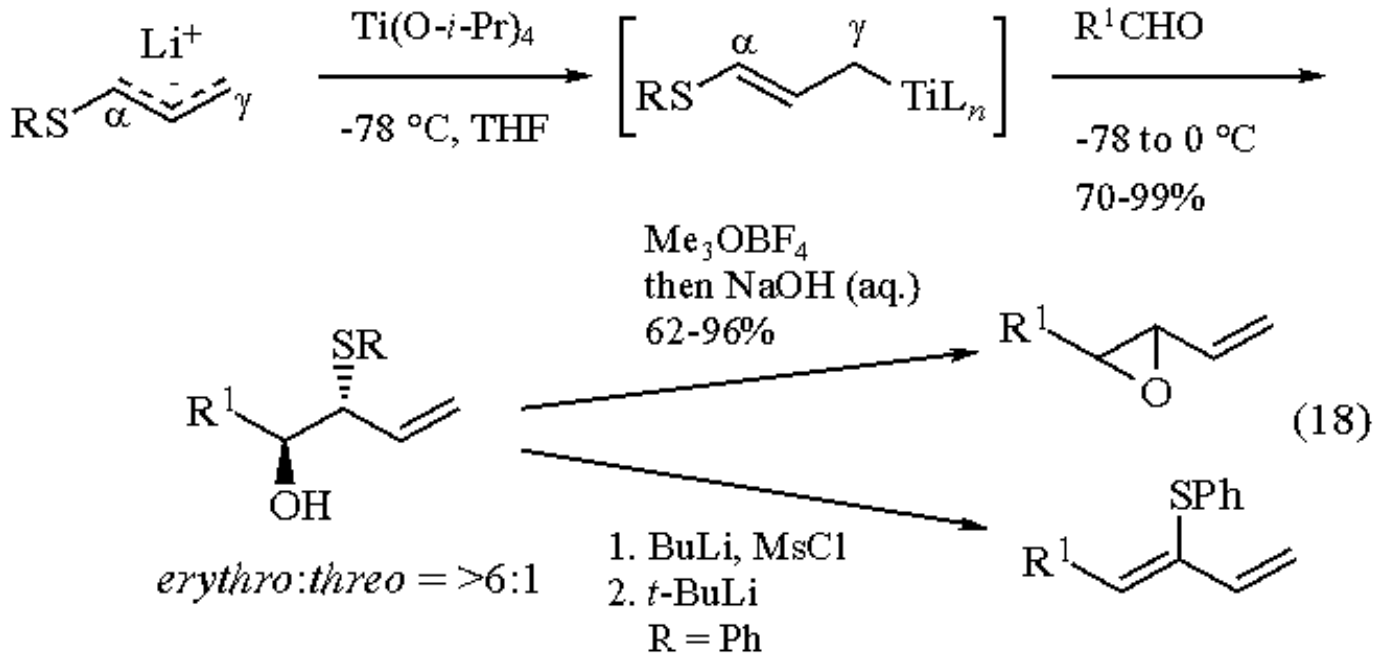

(18)

The titanium species derived from sequential treatment of α-alkoxy-substituted allylsilanes with ***s-Butyllithium*** then Ti(O-*i*-Pr)$_4$ engages in a Peterson alkenation reaction with aldehydes to give, via electrophilic attack at the α-terminus of the allyl anion, 2-oxygenated 1,3-butadienes which can be hydrolyzed to the corresponding vinyl ketone (eq 19).[18a]

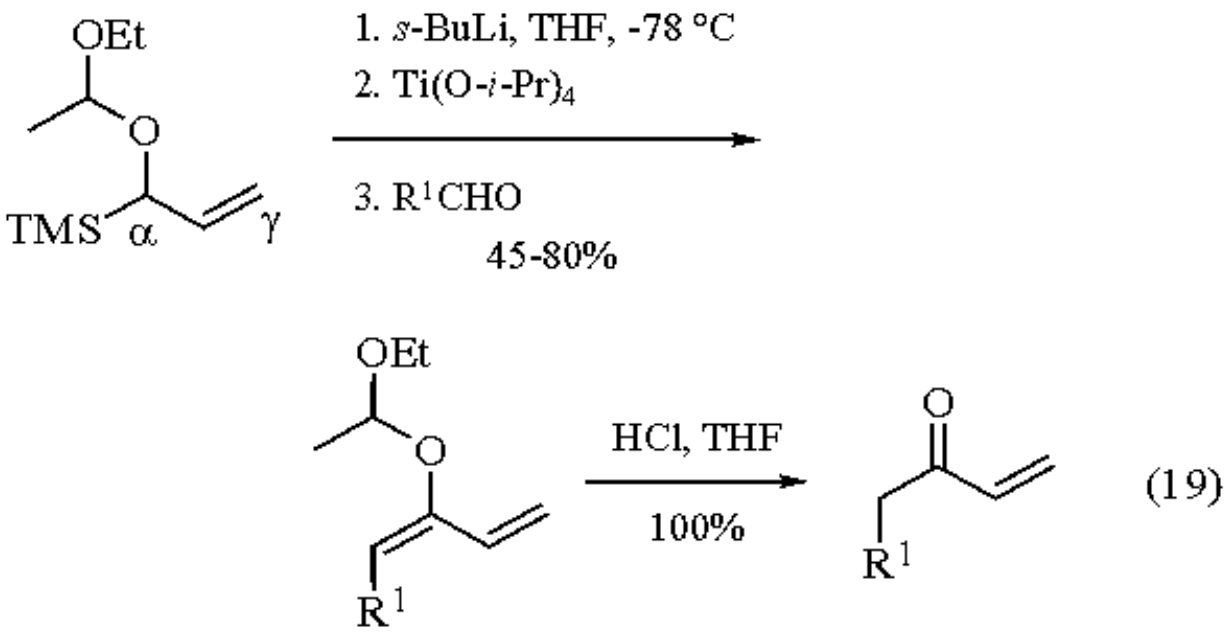

(19)

The titanium-ate complexes of α-methoxy allylic phosphine oxides, generated in situ by reaction of the corresponding lithium anion and Ti(O-*i*-Pr)$_4$, condense with aldehydes exclusively at the α-position to produce homoallylic alcohols in a diastereoselective fashion.[18b] The overall result is the three-carbon homologation of the original aldehyde, and this protocol has been used in a synthesis of (-)-aplysin-20 from nerolidol.[19] The titanium-ate complex produced by reaction of the chiral lithium anion of an (*E*)-crotyl carbamate with Ti(O-*i*-Pr)$_4$ affords γ-condensation products (homoaldols) on reaction with aldehydes.[18c,d] Allyl anions produced by the reductive metalation of allyl phenyl sulfides condense with α,β-unsaturated aldehydes in a 1,2-manner at the more substituted (α) allyl terminus in the presence of Ti(O-*i*-Pr)$_4$.[20] 1,2-Addition of dialkylzincs to α,β-unsaturated aldehydes can be achieved with useful levels of enantiocontrol when the reaction is conducted using a chiral titanium(IV) catalyst in the presence of Ti(O-*i*-Pr)$_4$ (eq 20).[21] Higher ee values are observed when an α-substituent (e.g. bromine) is attached to the substrate aldehyde, but a β-substituent *cis*-related to the carbonyl group has the opposite effect.

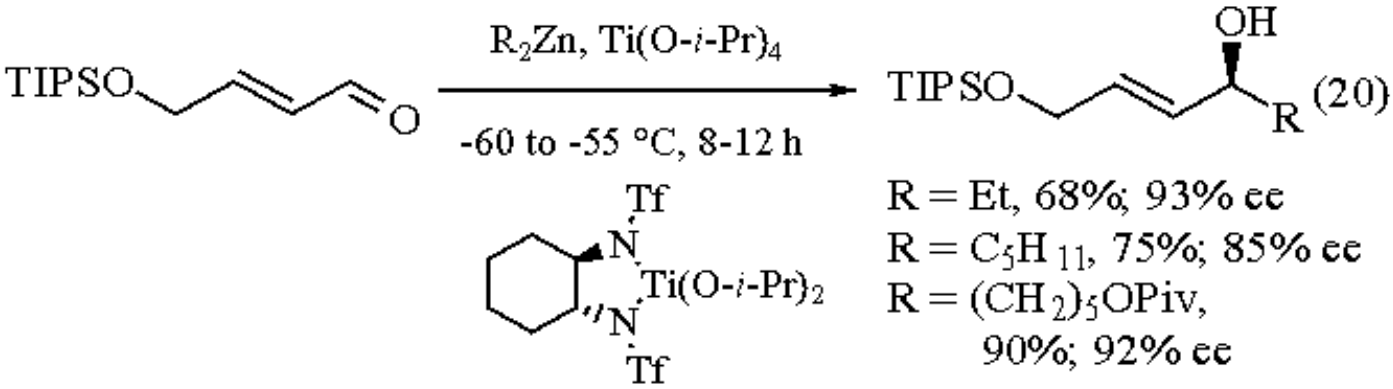

(20)

Highly enantioselective trimethylsilylcyanation of various aldehydes can be achieved by using ***Cyanotrimethylsilane*** in the presence of a modified Sharpless catalyst consisting of Ti(O-*i*-Pr)$_4$ and chiral diisopropyl tartrate.[22] Best results are obtained using dichloromethane as solvent and isopropanol as additive and running the reaction at 0 °C. The same type of catalyst system also effects the asymmetric ring-opening of symmetrical cycloalkene oxides with ***Azidotrimethylsilane***. *trans*-2-Azidocycloalkanols are obtained in up to 63% optical yield.[22] The titanium amide complexes derived from the reaction of lithium dialkylamides with Ti(O-*i*-Pr)$_4$ condense with alkyl and aryl aldehydes and the resulting aminal derivatives undergo C-O bond displacement by benzylmagnesium chloride, thereby generating α-substituted β-phenethylamines (eq 21).[23]

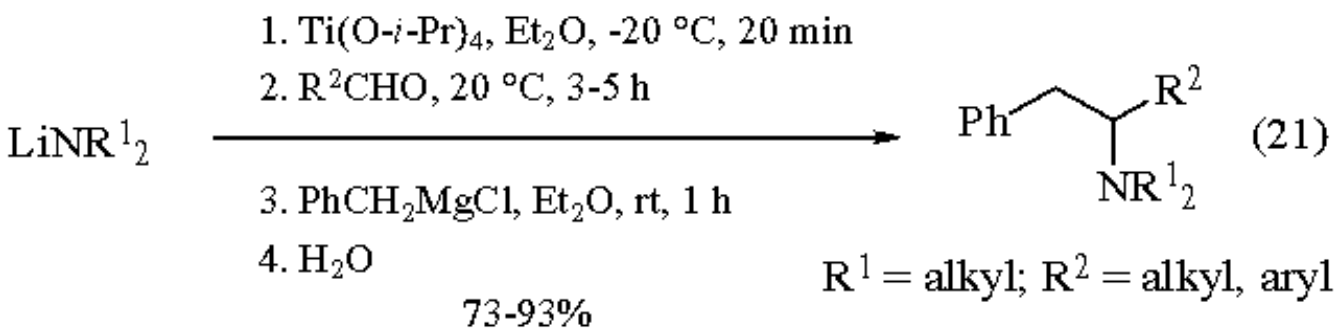

(21)

The aldol-type condensation of aldehydes and ketones with ketenimines[24] and ketones[25] can be catalyzed by titanium alkoxides and, in appropriate cases, useful levels of stereocontrol can be achieved (eq 22).

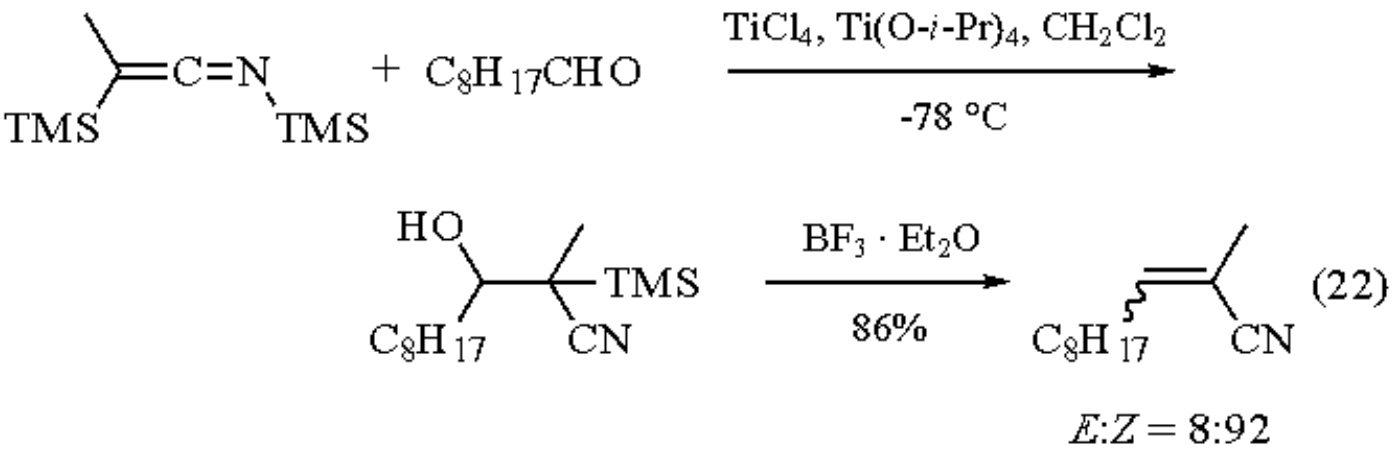

(22)

A variety of useful reducing agents have been generated by combining hydrides with Ti(O-*i*-Pr)$_4$.[26-28] For example, the combination of 5 mol % Ti(O-*i*-Pr)$_4$ with 2.5-3.0 equiv of ***Triethoxysilane*** cleanly hydrosilylates esters to silyl ethers at 40-55 °C, and these latter compounds can be converted into the corresponding primary alcohols via aqueous alkaline hydrolysis (eq 23).[26] The actual reducing agent is presumed to be a titanium hydride species which is produced by a σ-bond metathesis process involving Ti(O-*i*-Pr)$_4$ and the silane. The procedure has considerable merit in that no added solvent is required and the active reagent can be generated and used in air. Halides, epoxides, alcohols, and an alkyne all survive the reduction process. ***Lithium Borohydride*** reduction of 2,3-epoxy alcohols yields 1,2-diols highly regioselectively when used in the presence of Ti(O-*i*-Pr)$_4$,[27] while the combination of the reagent with ***Sodium Cyanoborohydride*** is reported[28] to offer superior results in reductive amination processes with difficult carbonyls and those sensitive to acidic conditions.

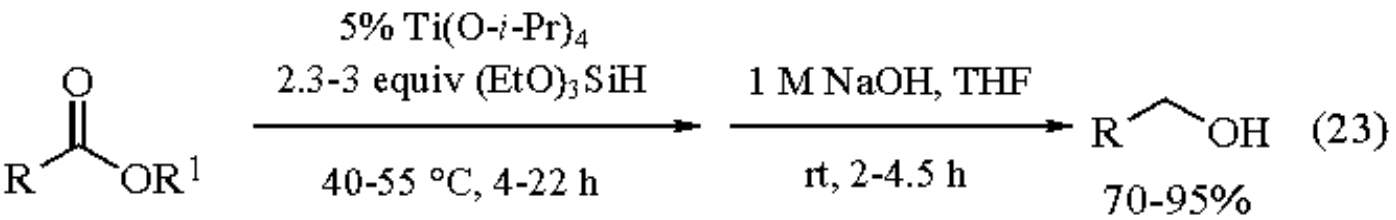

(23)

Miscellaneous Applications.[29-31]

The chemoselective oxidation of alcohols and diols using Ti(O-*i*-Pr)$_4$/***t-Butyl Hydroperoxide*** has been reported.[29] The title reagent has also been employed as a catalyst in Diels-Alder reactions[30] and as an additive in the palladium-catalyzed reaction of aryl-substituted allylic alcohols with zinc enolates of β-dicarbonyl compounds (eq 24).[31] The latter reaction is presumed to generate *C*-allylated β-dicarbonyl compounds as the primary products of reaction, but these compounds suffer deacylation in the presence of Ti(O-*i*-Pr)$_4$.

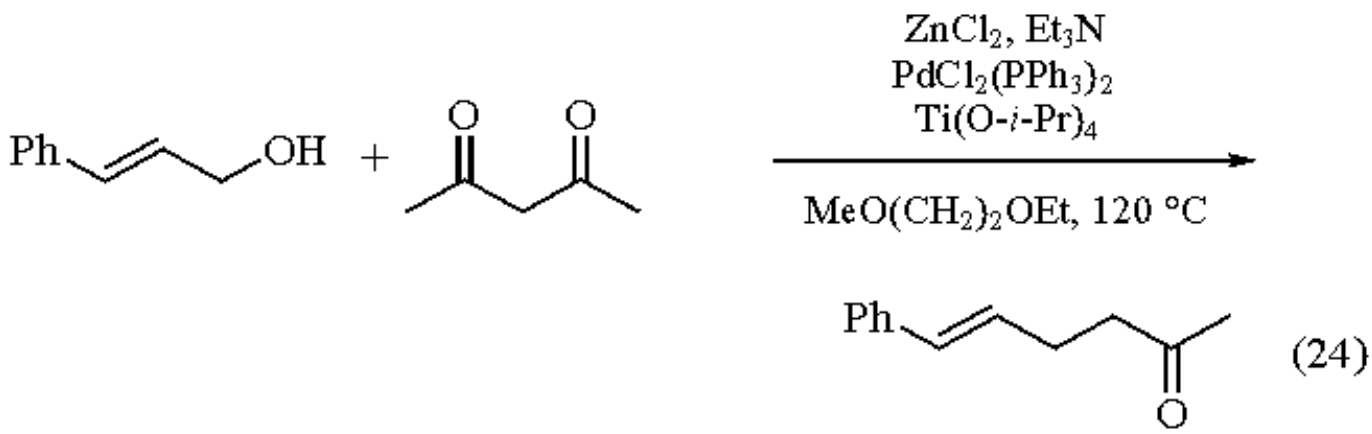

(24)

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Titanium Tetrakis(diethylamide)[1]

$Ti(NEt_2)_4$

[4419-47-0] · $C_{16}H_{40}N_4Ti$ · Titanium Tetrakis(diethylamide) · (MW 336.48)

(for the in situ protection of aldehydes and ketones,[2] for the formation of enamines from ketones;[3] for conjugate diethylamino addition to α,β-unsaturated ketones and esters;[4] and for diethylamino transfer to carboxylic[5] and phosphonic acid esters[6])

Physical Data: bp 112 °C/0.3 mmHg; *d*204 0.931 g cm^{-3}; ^{13}C NMR (benzene-d_6): δ = 45.5, 15.7 ppm.

Solubility: sol THF, ether, CH_2Cl_2.

Form Supplied in: not commercially available.

Preparative Methods: a number of syntheses of $Ti(NEt_2)_4$ have been described,[7] the following affording a very pure product (eq 1).[8]

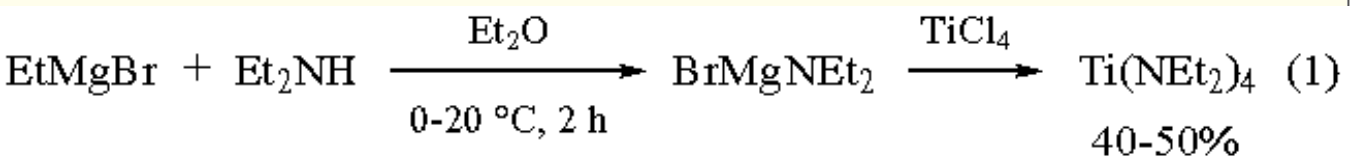

It is likely that the parent compound $Ti(NMe_2)_4$ is accessible via the analogous route, although this has not been demonstrated. $Ti(NMe_2)_4$ is best synthesized by reacting $LiNMe_2$, prepared from $HNMe_2$ and *n*-butyllithium, with $TiCl_4$.[7]

Handling, Storage, and Precautions: is moisture sensitive and should be handled and stored under an inert gas atmosphere (e.g. N_2); nonprotic solvents need to be used; syringe techniques are adequate. Use in a fume hood.

In Situ Protection of Aldehydes and Ketones.

Classical reagents such as alkyllithium reagents and Li enolates derived from esters generally do not react chemoselectively with dicarbonyl compounds or other polyfunctional substrates. In many cases, titanation of such reactive reagents using ***Titanium(IV) Chloride***, ***Chlorotitanium Triisopropoxide***, or ***Titanium Tetraisopropoxide*** solves such problems, as in aldehyde-selective addition reactions of keto aldehydes.[1] However, if the *less* reactive site is required to undergo C-C bond formation, a three-step sequence involving protection, reaction, and deprotection is necessary. Since the introduction of protective groups is not always completely regioselective, difficulties arise. In such cases the in situ protection of carbonyl functionalities using $Ti(NR_2)_4$ (R = Me, Et) may solve the problem.[2] Aldehydes readily react with $Ti(NEt_2)_4$ at -78 °C to form amide adducts which are stable in solution (eq 2), whereas ketones require temperatures above -30 °C at which the corresponding adducts begin to fragment. The less bulky reagent $Ti(NMe_2)_4$ forms stable adducts with aldehydes and ketones at low temperatures.[2]

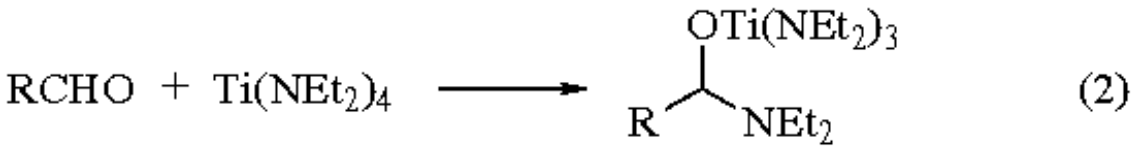

Consequently, complete chemoselective in situ protection of the aldehyde function of keto aldehydes is possible. Addition of a reactive carbon nucleophile such as $CH_2{=}CHCH_2MgCl$, $PhSO_2CH_2Li$, or $CH_2{=}CH(OEt)OLi$ then occurs at the less reactive ketone site. Since deprotection at the aldehyde function occurs quantitatively during aqueous workup, the one-pot procedure constitutes a simple way to enforce ketone selectivity (eq 3).[2]

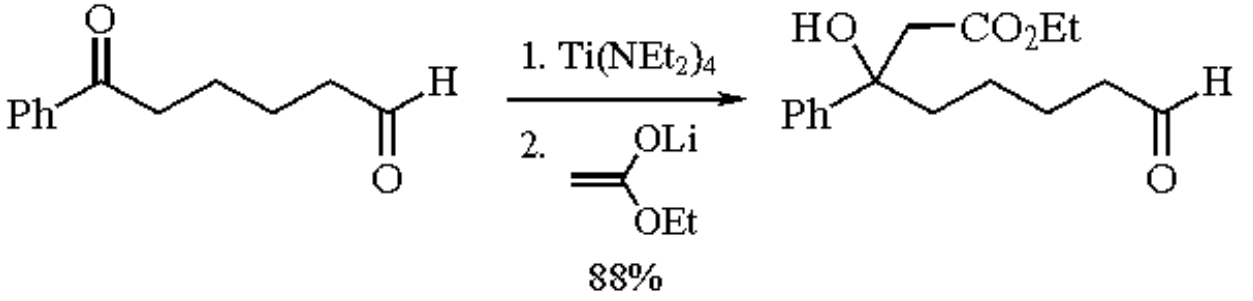

This protocol for in situ protection has been applied in the regioselective alkenation of keto aldehydes (eq 4).[9]

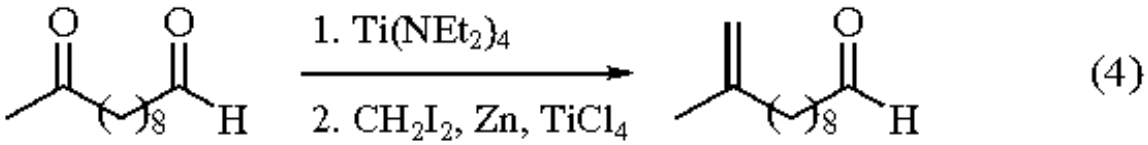

Site selectivity in diketones is also possible, in such cases the parent compound $Ti(NMe_2)_4$ being the reagent of choice. Here again, the direction of chemoselectivity is reversed with respect to the reaction of organotitanium reagents in the absence of $Ti(NR_2)_4$. In situ protection allows for reactions at the sterically more hindered site, e.g. (eq 5).[2]

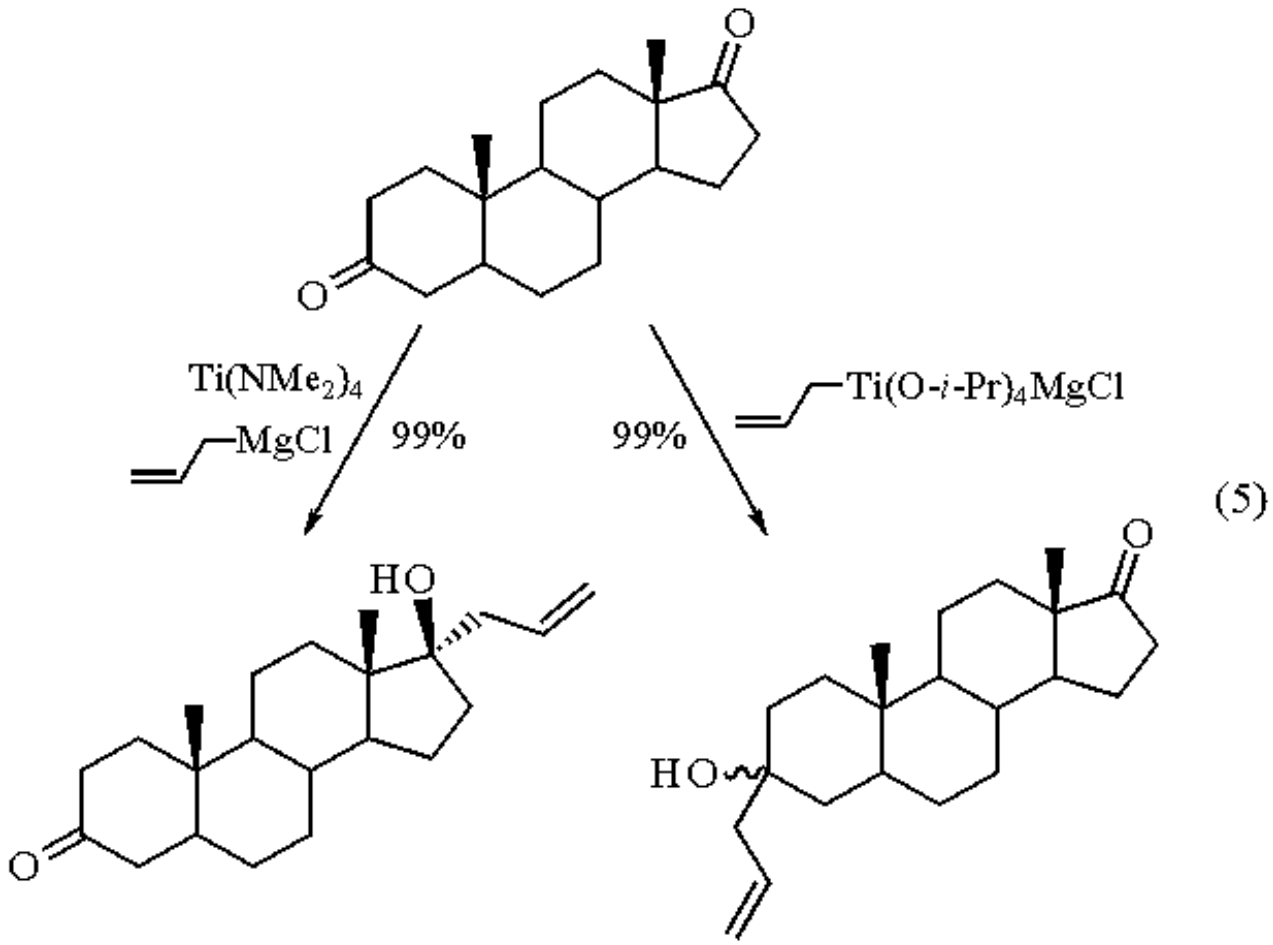

The above in situ methodology has limitations in that very reactive carbon nucleophiles need to be employed following the protection step, i.e. rapid reactions below -30 °C need to be carried out at which temperature the protected forms maintain stability. Indeed, refluxing ketones with $Ti(NEt_2)_4$ is a method of enamine formation.[3] A related protocol based on the in situ protection of aldehydes by $TiCl_4/PPh_3$ is also easy to perform, but its synthetic scope remains to be established.[10] Lithium morpholide likewise adds to aldehydes in situ (mainly aromatic aldehydes), but the basic nature of the reagent causes undesired enolization in the case of ketones.[11]

Michael Additions to α,β-Unsaturated Carbonyl Compounds.

Titanium amides such as $Ti(NEt_2)_4$ readily add to α,β-unsaturated esters and ketones in a Michael fashion.[4] The intermediate tris(amino)titanium enolates can be intercepted with aldehydes, the overall process being a tandem conjugate addition-aldol reaction

sequence.[4] α,β-Unsaturated aldehydes were not tested, but an earlier publication reports the reaction of cinnamaldehyde with $Ti(NMe_2)_4$, leading to the corresponding aminal via 1,2-addition.[5]

Dialkylamino Group Transfer to Carboxylic and Phosphonic Acid Esters.

Carboxylic acid esters react with $Ti(NMe_2)_4$ to form the corresponding amides.[5] Similar exchange reactions have been used extensively in phosphorus chemistry, as in the selective diethylamino group transfer to phosphoryl centers (eq 6).[6]

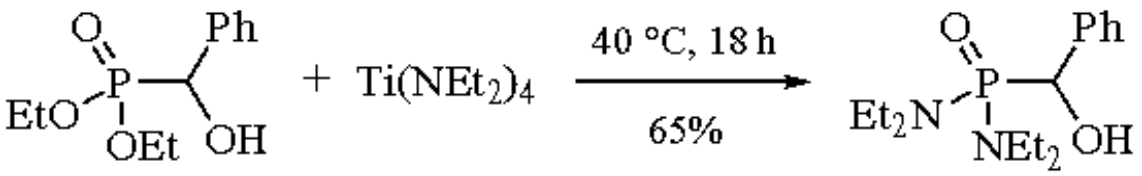

(6)

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Titanium(III) Chloride-Lithium Aluminum Hydride[1]

$TiCl_3$-$LiAlH_4$

($TiCl_3$)

[7705-07-9] · Cl_3Ti · Titanium(III) Chloride-Lithium Aluminum Hydride · (MW 154.23) ($LiAlH_4$)

[16853-85-3] · AlH_4Li · Titanium(III) Chloride-Lithium Aluminum Hydride · (MW 37.96)

(reagent combination for the production of low-valent titanium which is used for the inter- and intramolecular reductive coupling of carbonyl and dicarbonyl compounds, as well as reductive elimination reactions)

Physical Data: see ***Titanium(III) Chloride*** and ***Lithium Aluminum Hydride***.

Solubility: THF and DME are the favored solvents for reactions involving low-valent titanium.

Form Supplied in: a 4:1 ball-milled mixture of $TiCl_3$ and $LiAlH_4$ is available, which serves as a precursor to the McMurry reagent.

Handling, Storage, and Precautions: most commonly, low-valent titanium species are prepared, under an inert atmosphere (nitrogen or argon), immediately prior to use. Presumably the reagent is pyrophoric, although this property may be due to the residual reducing agent used in the preparation process rather than an inherent property of Ti^0/Ti^I itself. The reagent is moisture sensitive.

Reductive Coupling Reactions.[2-14]

The combination of $TiCl_3$ and $LiAlH_4$ produces the McMurry reagent which has been one of the most popular of the low-valent titanium reagents (see ***Titanium***) employed for reductive coupling of carbonyls to alkenes. Depending on the molar ratio of $TiCl_3$ to $LiAlH_4$ used, either Ti^I or Ti^0 is produced. It has been suggested that the optimum ratio of $TiCl_3$ to $LiAlH_4$ for coupling is 2:1.[3] Crossed intermolecular reductive couplings of two different carbonyl compounds are readily effected by this reagent if one of the components, often acetone, is used in excess (eq 1).[4]

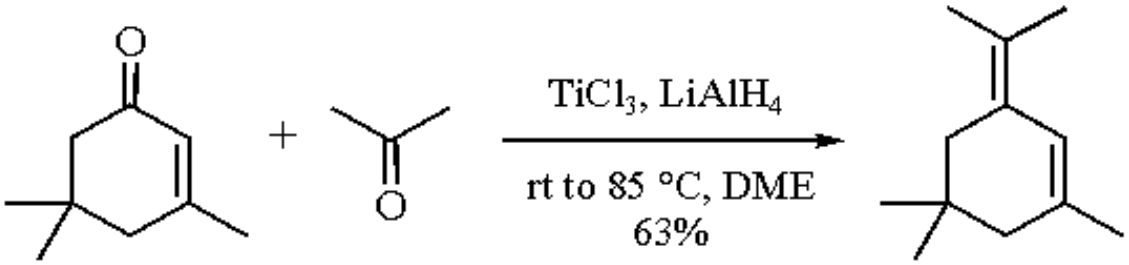

(1)

The McMurry coupling reaction has provided a means for the synthesis of a range of novel hydrocarbons,[1] including strained alkenes,[5] and torsionally distorted systems (eq 2).[6] When the illustrated reaction is carried out in a chiral solvent, the (±)-isomer is produced preferentially.

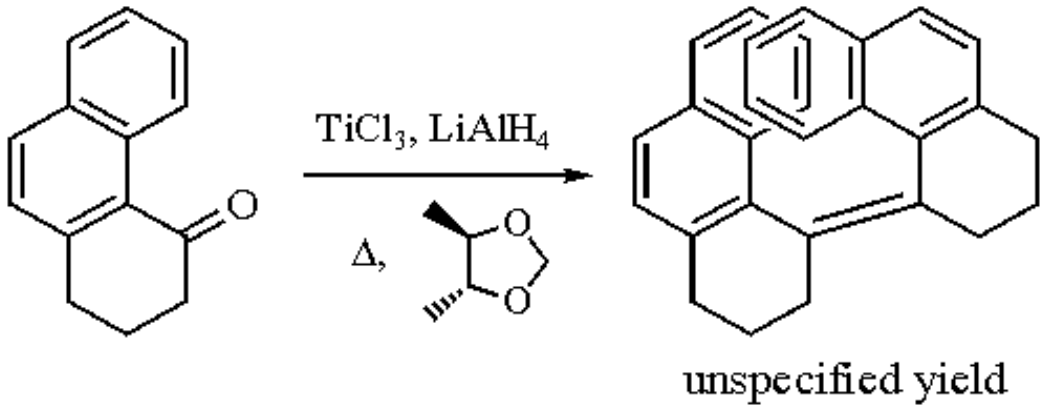

(2)

Intramolecular couplings of a wide range of α,o-diketones are readily effected by $TiCl_3/LiAlH_4$ and even highly strained cyclopropenes can be prepared (eq 3).[7] However, it is generally found that the ***Titanium(III) Chloride-Zinc/Copper Couple*** reagent is more effective for such intramolecular processes.

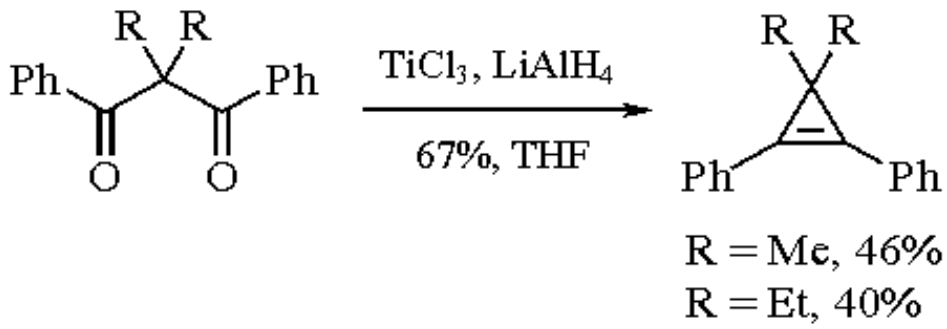

(3)

These cyclocoupling processes have been extended to keto esters and keto acids,[8] with the resulting formation of cycloalkanones. Such a conversion has been employed as the key step in the synthesis of a ring-fused cyclononanone (eq 4), a precursor to the natural product isocaryophyllene.[9] Interestingly, accompanying the cyclization process is the (*E*) -> (*Z*) isomerization about the double bond. Such cyclizations presumably proceed through the intermediate enol ether which hydrolyzes to the product cycloalkanone on acidic workup. Such intramolecular keto ester couplings work particularly well for the formation of five- to seven-membered rings, but higher homologs are formed in lower yield. Often, a considerable amount of work is needed to optimize the yields in such reactions. The best results are obtained with a low-valent titanium reagent prepared by the reduction of $TiCl_3$ with $LiAlH_4$ in the presence of ***Triethylamine***. For reasons not fully understood, neither the $TiCl_3$/Zn(Cu) nor the $TiCl_3(DME)_{1.5}$/Zn(Cu) reagent works as well.

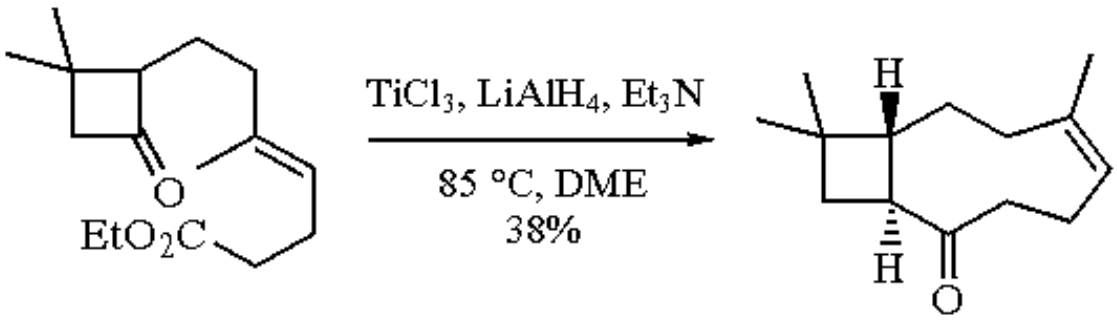

(4)

The reagent produced from a 3:1 mixture of $TiCl_3$ and $LiAlH_4$ effects reductive couplings of allylic and benzylic alcohols (eq 5);[10] Ti^{II} alkoxides may be involved.[11] In some cases (e.g. with farnesol), couplings lead to mixtures of regioisomeric products. Reduction of benzyl alcohols affords the corresponding 1,2-diphenylethane.[10] Benzyl halides behave in a similar fashion, while α,α-dihalotoluenes react with the McMurry reagent to give stilbenes (eq 6).[12]

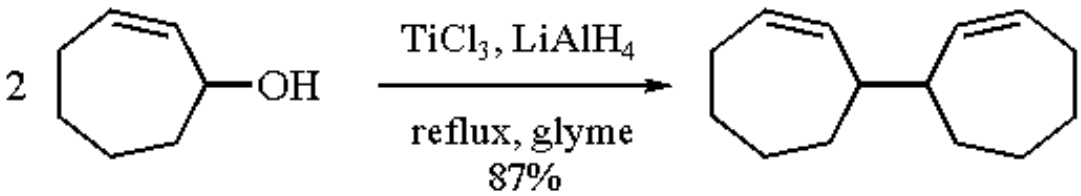

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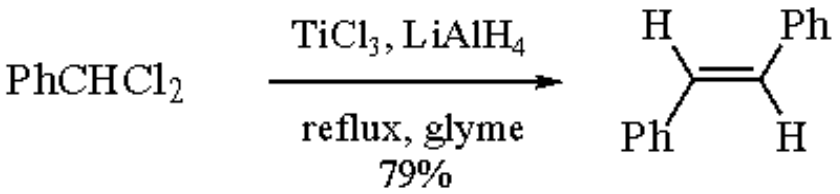

(6)

Intramolecular variants of such processes are also known. Thus reductive cyclization of certain 1,3-diols affords cyclopropanes (eq 7).[13] In the example given, inversion of configuration is observed at one of the cyclization centers; this has been taken as evidence that an anionic intermediate is involved which cyclizes in the illustrated manner.

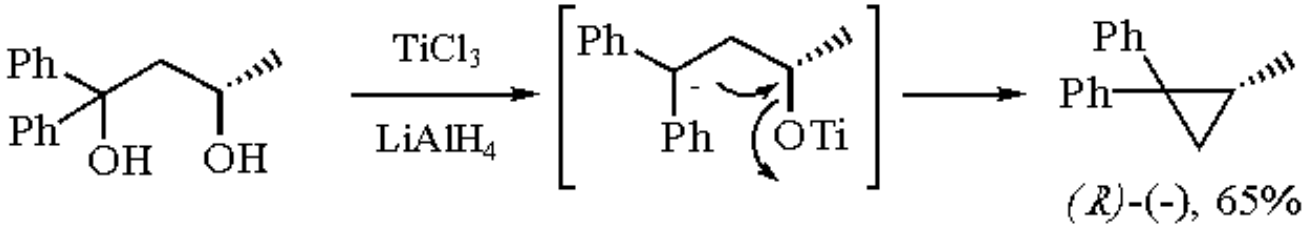

(7)

The bis-*O*-methyl ether derivative of the diol shown in eq 7 also cyclizes to give the same product, this time in 60% yield. In a presumably related process (eq 8), the reagent derived from a 4:1 mixture of $TiCl_3$ and $LiAlH_4$ effects the conversion of α,α´-bis(trimethylsiloxy) sulfides into the corresponding alkenes. The reaction probably proceeds via an intermediate episulfide.[14]

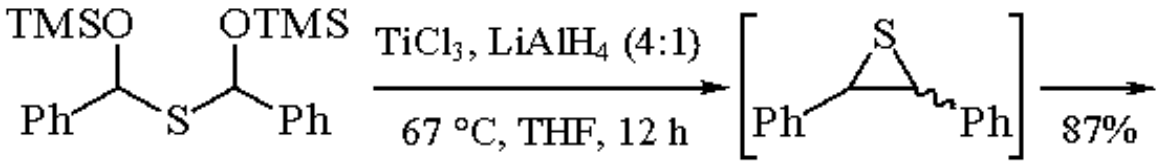

PhCH=CHPh (8)

>80% (*E*)

Reductive Elimination Reactions.[12,15-18]

The conversion of β-ionone into vitamin A involves, in the later stages, reaction of the low-valent titanium species produced from a 2:1 mixture of $TiCl_3$ and $LiAlH_4$ with an allylic diol (either the (*E*)- or (*Z*)-isomer) (eq 9). The result is the formation of an (*E*,*E*)-diene.[15]

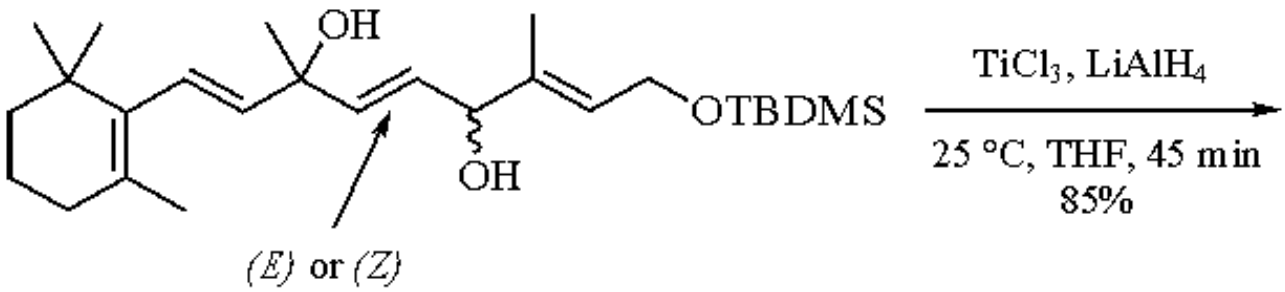

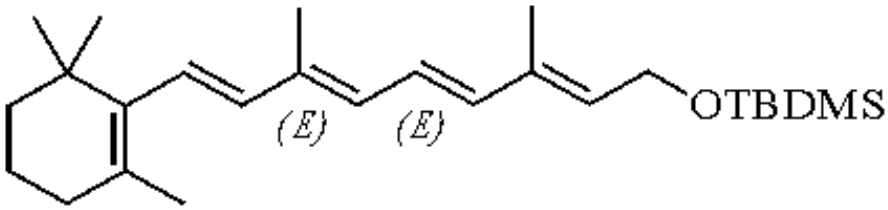

(9)

Analogous reduction of the primary acetate (as opposed to the primary silyl ether shown) gave a mixture of the (*E*,*E*)- and (*E*,*Z*)-dienes.[15] A similar reduction process has been employed in a synthesis of 13-*cis*-retinoic acid.[16] The McMurry reagent has also been used to prepare

alkenes from the corresponding bromohydrin,[17] epoxide,[18] and *vic*-dibromide.[12] In the latter two cases, at least, the reaction is not stereospecific. For example, reduction of either pure (*Z*)- or pure (*E*)-5-decene epoxide gives a 4:1 mixture of (*E*)- and (*Z*)-5-decene.[18]

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Titanium(III) Chloride-Zinc/Copper Couple[1]

$TiCl_3$-Zn(Cu)

($TiCl_3$)

[7705-07-9] · Cl_3Ti · Titanium(III) Chloride-Zinc/Copper Couple · (MW 154.23) (Zn)

[7440-66-6] · Zn · Titanium(III) Chloride-Zinc/Copper Couple · (MW 65.39)

(reagent combination for the production of low-valent titanium which is used for the inter- and intramolecular reductive coupling of carbonyl and dicarbonyl compounds)

Physical Data: see ***Titanium(III) Chloride*** and ***Zinc/Copper Couple***.

Solubility: unknown but presumably low in most organic solvents. THF and DME are the favored solvents for reactions involving this reagent combination.

Handling, Storage, and Precautions: the low-valent titanium species produced by reacting $TiCl_3$ with zinc/copper couple is generally made under an argon atmosphere immediately prior to use. The reagent may be pyrophoric and is certainly moisture sensitive.

Reductive Coupling Reactions.[1-12]

Among the numerous sources of low-valent ***Titanium*** used for the reductive couplings of carbonyl compounds, the Ti^0 reagent produced by reacting $TiCl_3$ with freshly prepared zinc/copper couple[2] is considered the most effective for many intramolecular coupling reactions of dicarbonyls (see, however, ***Titanium(III) Chloride-Lithium Aluminum Hydride***). Up to 22-membered cycloalkenes have been formed by coupling the appropriate open-chain dicarbonyl precursor with this reagent. The reagent has been employed by its originator, McMurry,[2] in the key steps of a number of natural product syntheses. For example, such reductive cyclizations have been used in the preparation of humulene (eq 1),[3] as well as a 45:55 mixture of helminthogermacrene and β-elemene (eq 2).[4] The reagent has also been exploited in the preparation of compactin and mevinolin analogs,[5] flexibilene,[3a,c] some zizaene sesquiterpenes including (±)-isokhusimone,[6] as well as verticillene.[7]

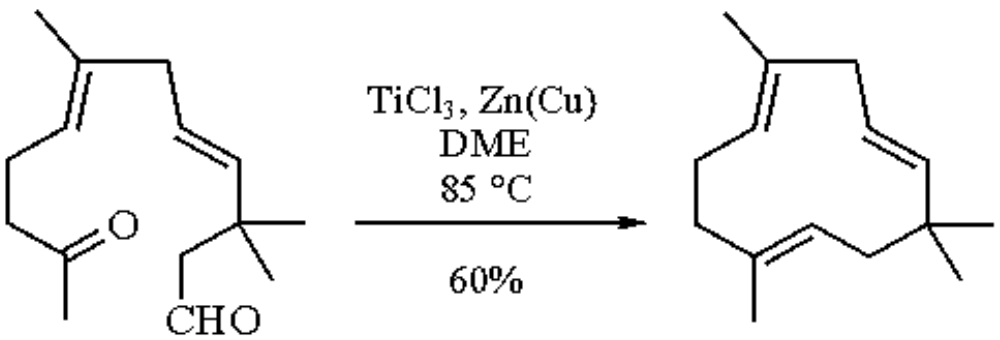

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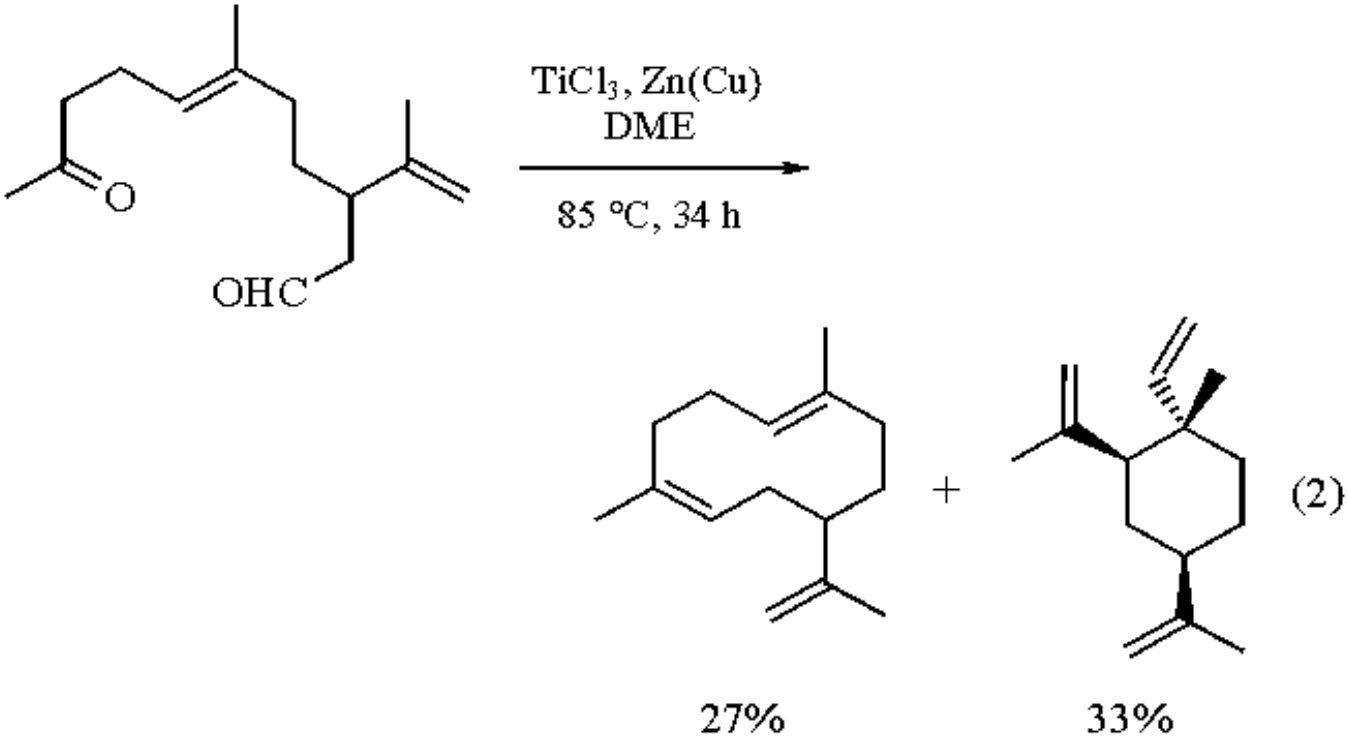

Under thermally mild conditions (<=25 °C), α,o-dials react with a 1:9 mixture of $TiCl_3$:Zn(Cu) in DME to give 6- to 14-membered cyclic pinacols. *cis*-Pinacols are the major products when 6- to 8-membered rings are produced while *trans*-pinacols predominate in rings of 10 or more members.[8] This type of cyclization has been employed in the synthesis of the 14-membered ring associated with sarcophytol B (eq 3).[8b]

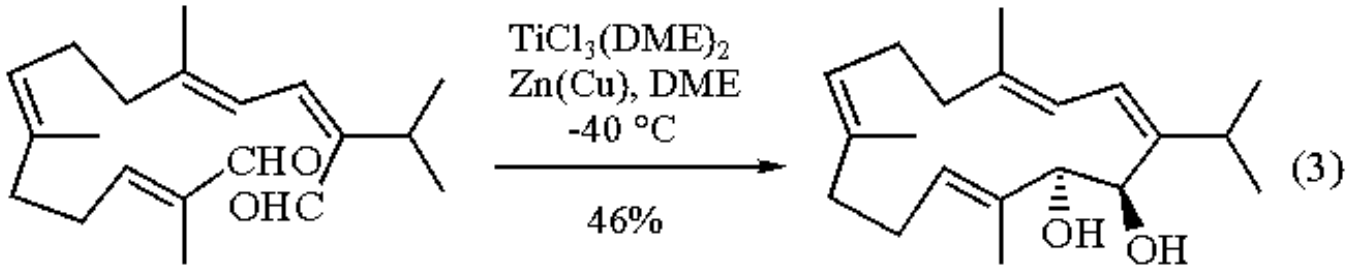

A range of structurally novel hydrocarbons[1] have been prepared using the title reagent, including optically active doubly bridged allenes,[9] betweenanenes,[10] in-out bicycloalkanes,[11] and intracyclic π-systems (eq 4),[12] some of which are capable of forming stable metal complexes.

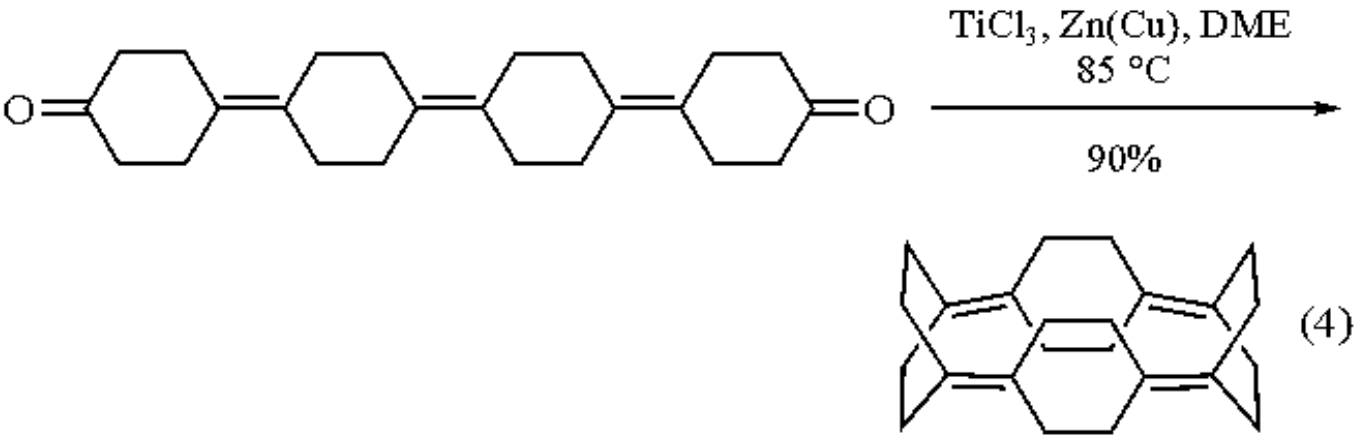

The intermolecular coupling of two molecules of retinal to yield β-carotene (94%) has been effected with the title reagent and, by virtue of the product's use as a yellow food-coloring agent and a source of vitamin A, this efficient titanium-based synthesis is now licensed for use in commercial production.[13] Aromatic aldehydes and ketones possessing other potentially reducible groups (such as the acyloxy, methoxy carbonyl, and tosyloxy moieties) give Ti^0-induced carbonyl reductive coupling products in high yields when the $TiCl_3$/Zn(Cu) reagent is employed.[14]

McMurry has now developed[15] an optimized procedure for the reductive coupling of dicarbonyls which employs a combination of the solvate

$TiCl_3(DME)_{1.5}$ and a Zn(Cu) couple to form the low-valent titanium reagent.

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Titanocenemethylene-Zinc Halide Complex[1]

$Cp_2Ti{=}CH_2.ZnX_2$

(methylenation reagent of unsaturated carbonyl groups[1])

Solubility: sol THF, toluene.

Preparative Methods: the reaction of ***Diiodomethane*** with ***Zinc*** dust in THF at 45 °C produces $CH_2(ZnI)_2$ in ca. 45% yield. Its reaction with ***Dichlorobis(cyclopentadienyl)titanium*** (25 °C, 30-60 min) affords a deep red solution of the titanocenemethylene-zinc halide complex (ca. 45-55% yield).[2]

Handling, Storage, and Precautions: should be handled and stored under an inert atmosphere.

Methylenation of Unsaturated Carbon Centers.

The titanocenemethylene-zinc halide complex reacts rapidly with ketones in good yields (eq 1).[2] The alkenation of an α,β-unsaturated ketone gives the corresponding diene (eq 2).[2] Whereas no clean reaction is observed with acid chlorides, the addition of the titanocenemethylene complex to a nitrile provides, after a workup with D_2O, an α-deuterated ketone (eq 3).[2] The reaction with alkynes is less straightforward and moderate regio- and chemoselectivity is observed (eq 4).[2]

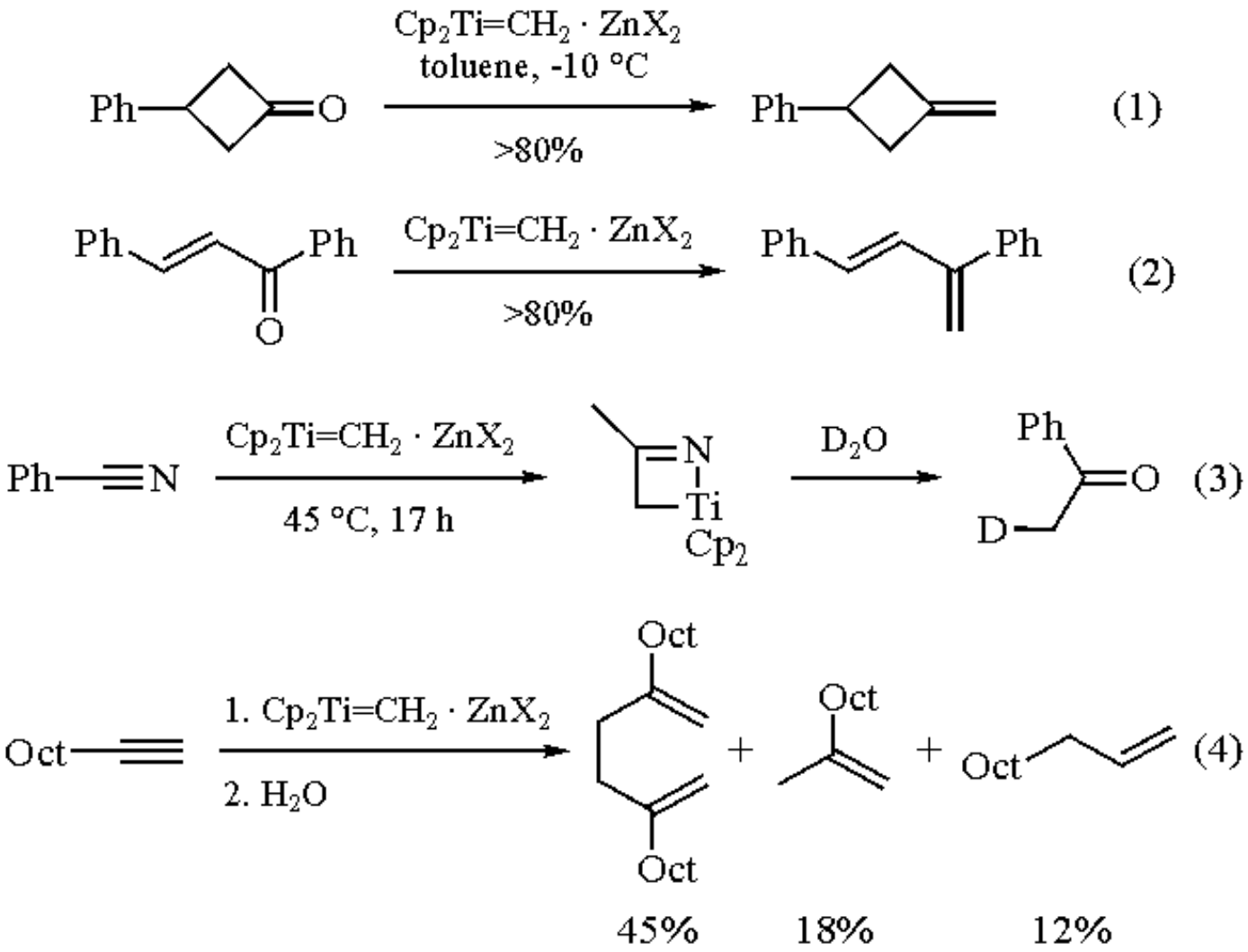

Alternative titanium-based reagents can be used and have found more applications than the titanocenemethylene-zinc halide complex.[1] The Tebbe reagent μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***, although involving the use of pyrophoric ***Trimethylaluminum***, has found broader application in synthesis.[1,3] A related reagent prepared from zinc, a dihalomethane, and ***Titanium(IV) Chloride*** (Takai reagent)[4] proved also to be a useful methylenation reagent of aldehydes and ketones. After a modification, this reagent is also able to perform a methylenation (and alkylidenation) of various carboxylic acid derivatives (eq 5).[5] The preparation modification reported by Lombardo provides a mild, nonbasic method for the methylenation of ketones. The Lombardo reagent is compatible with a wide variety of functional groups. Compared to the original procedure of Takai, the modification of Lombardo involves the preformation of the reagent, which was found to be stable at low temperature (eq 6).[6] Finally, Nysted reported the preparation of the alkenation reagent [$XZnCH_2ZnCH_2ZnX.THF$] which, in the absence of titanium salts, proved to be highly efficient for the methylenation of steroids (eq 7).[7]

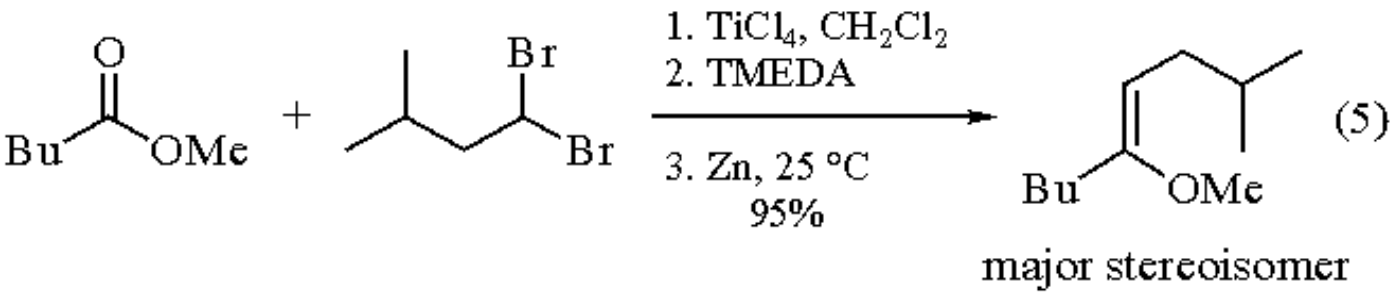

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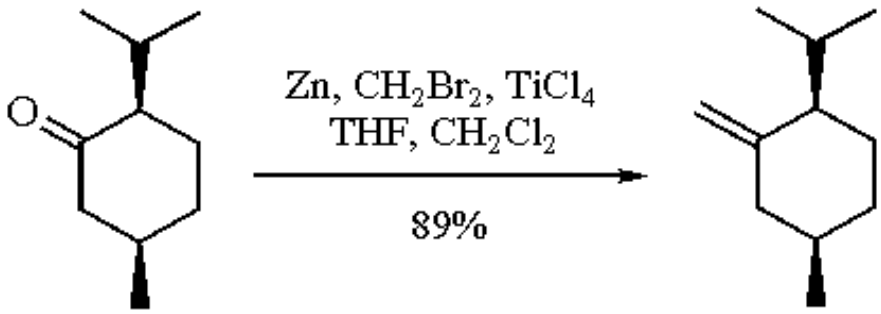

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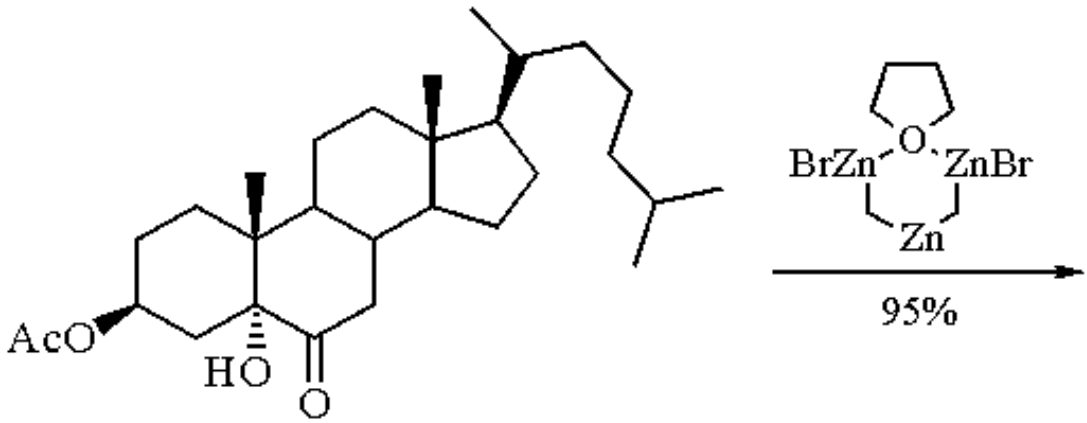

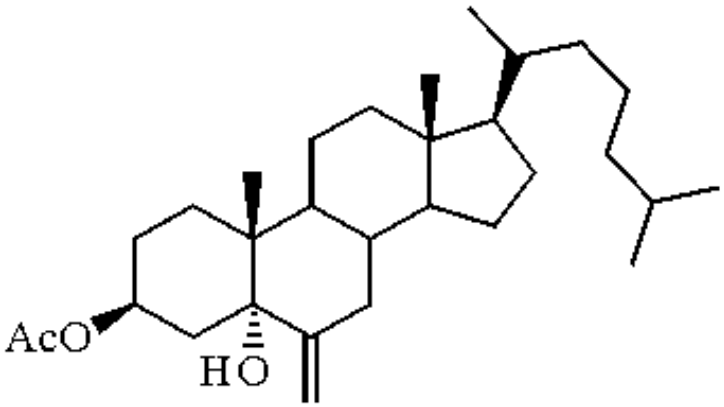

(7)

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p-Toluenesulfinic Acid

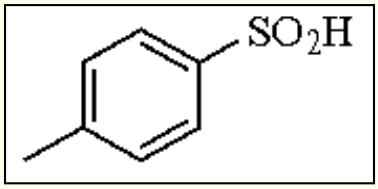

[536-57-2] · $C_7H_8O_2S$ · *p*-Toluenesulfinic Acid · (MW 156.22) (Na salt.H_2O)

[824-79-3] · $C_7H_9O_3NaS$ · *p*-Toluenesulfinic Acid · (MW 196.22)

(preparation of alkyl, vinyl, and allyl sulfones; starting material for the preparation of chiral sulfoxides; mild acid catalyst)

Physical Data: mp 85 °C; pK_a 1.66. The sodium salt hydrate has mp >300 °C.[1]

Solubility: sol ethanol, ether; sparingly sol water, hot benzene.

Form Supplied in: commercially available as the sodium salt hydrate; the lithium salt *[16844-27-2]* is also available.

Preparative Methods: isolation of the free acid via acidification of an aqueous solution of the sodium salt has been described;[1b] partial conversion to ***p-Toluenesulfonic Acid*** frequently accompanies drying of the free acid.

Purification: recrystallizes in water in long rhombic needles or plates.

Handling, Storage, and Precautions: should be stored in a cool, dry place away from strong oxidizing agents.

Synthesis of Sulfones.

p-Toluenesulfinic acid is a frequently used reagent for the synthesis of organic sulfones. The sulfone group has played an extensive role in recent synthetic organic chemistry; some of its common applications are described below, following preparation of representative sulfones from the title reagent. Unless otherwise noted, the reactions described use the sodium salt rather than the free acid.

Alkylation of arenesulfinate salts is a very general reaction for the preparation of alkyl sulfones.[2] Reaction conditions utilizing alcoholic or dipolar aprotic solvents are typical, but phase-transfer conditions have been described.[3] Reaction with reactive halides is generally facile (eq 1);[4] triflates have likewise been displaced with ease by *p*-toluenesulfinate.[5]

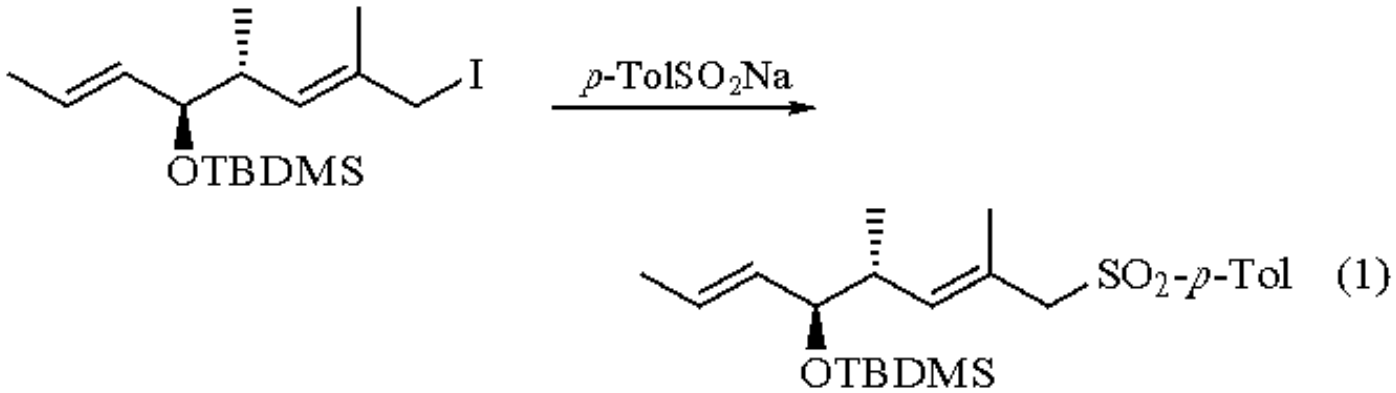

(1)

The sulfones so obtained are useful in a variety of organic transformations. Alkyl sulfones are readily deprotonated with bases, and the resulting carbanions are good nucleophiles. Sulfones thus function as activating groups which can subsequently be removed under mild conditions.[6] Alkylation of alkyl sulfones by alkyl halides, followed by reductive cleavage with ***Lithium*** metal or ***Sodium Amalgam***, provides a method of coupling alkyl halides which has been useful in the synthesis of 1,4-dienes.[7] Sodium *p*-toluenesulfinate also

undergoes conjugate addition reactions[8] and has been used as a nucleophile in palladium-catalyzed substitution reactions of allylic substrates.[9]

The addition of sulfone-substituted anions to carbonyl compounds yields β-hydroxy sulfones. These are useful intermediates for the synthesis of unsaturated compounds via elimination processes.[10-13] β-Hydroxy sulfones may also be prepared via the regioselective ring opening of epoxides by sodium *p*-toluenesulfinate.[14]

The radical addition of sulfinates to unsaturated compounds via the iodosulfonylation-dehydroiodination[15] reaction sequence constitutes a general method for the preparation of vinyl sulfones; the latter may be rearranged to allylic sulfones by treatment with base.[16] The radical addition may be carried out on α,β-unsaturated carbonyl compounds as well as alkenes.[17] In the case of unsaturated carbonyl compounds the elimination process can be quite stereoselective, (*E*)-alkenes being normally formed. For the addition to nonconjugated alkenes, conditions have been described for the preparation of either (*E*)- or (*Z*)-alkenes.[16]

Cleavage of Vinylsilanes.

p-Toluenesulfinic acid has been used for the protodesilylation of vinylsilanes to provide alkenes.[18] This method is milder than the usual strong acids used for this purpose. The cleavage is not stereospecific.

Synthesis of Chiral Sulfoxides.

Chiral sulfoxides have been used extensively in asymmetric synthesis.[19] An extremely common method for the preparation of these compounds involves the reaction of resolved diastereomeric sulfinate esters with Grignard reagents and organolithium species.[20] Menthol has classically been used to form diastereomeric esters of *p*-toluenesulfinic acid; an improved method using sulfinate esters of *trans*-2-phenylcyclohexanol has recently been reported.[21]

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p-Toluenesulfonic Acid

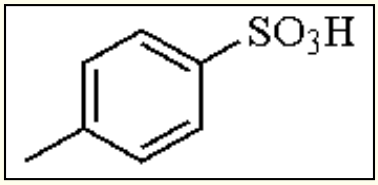

[104-15-4] · $C_7H_8O_3S$ · *p*-Toluenesulfonic Acid · (MW 172.22) (monohydrate)

[6192-52-5] · $C_7H_{10}O_4S$ · *p*-Toluenesulfonic Acid · (MW 190.24) (Na salt)

[657-84-1] · $C_7H_7NaO_3S$ · Sodium *p*-Toluenesulfonate · (MW 194.20)

(acid catalyst frequently used in nonpolar media; effective in carbonyl protection-deprotection; selectively cleaves *N*-Boc, other amine protecting groups; superior for enol ether, acetate preparation; used in esterifications, dehydrations, isomerizations, rearrangements)

Alternate Name: tosic acid.

Physical Data: the anhydrous acid exists as monoclinic leaflets or prisms, mp 106-107 °C; pK_a -6.62 (H_2SO_4).[1] There is also a metastable form, mp 38 °C. The monohydrate is a white crystalline powder, mp 103-106 °C.

Solubility: sol water (67 g/100 mL), ethanol, ethyl ether. The sodium salt is very sol water.

Form Supplied in: widely available as the monohydrate, which is commonly used. Various metal salts are also commercially available.

Analysis of Reagent Purity: by acid-base titrimetry.[46]

Purification: precipitated or crystallized from HCl soln, aq EtOH; the free acid has been crystallized from several organic solvents.[47]

Handling, Storage, and Precautions: highly toxic, oxidizing agent. Extremely irritating to the skin and mucous membranes. Use of gloves and protective clothing is recommended.[2] Use in a fume hood.

Acid Catalyst.

Tosic acid is one of the most widely used organic acid catalysts, particularly in nonpolar solvents. It is utilized frequently in many of the common acid-catalyzed reactions and transformations in organic chemistry, including esterification, formation of acetals, dehydration processes, preparation of enol ethers and acetates, and rearrangement and isomerization processes. A comprehensive literature review of even its recent uses is beyond the scope of this publication; representative examples of each of the above-mentioned classes are presented.

Formation and Cleavage of Acetals.

Tosic acid is perhaps the most common acid catalyst for the protection of ketones as acetals. The reaction is conventionally carried out in refluxing toluene or benzene with removal of water by a Dean-Stark trap (eq 1).[3] Although ***Boron Trifluoride Etherate*** is the customary catalyst for the condensation of ketones with alkyldithiols, tosic acid is a milder reagent and has been used for this purpose (eq 2).[4] *p*-Toluenesulfonic acid may also be used in lieu of $BF_3.Et_2O$ in the tetrahydropyranylation and methoxytetrahydropyranylation of alcohols (3 examples).[5]

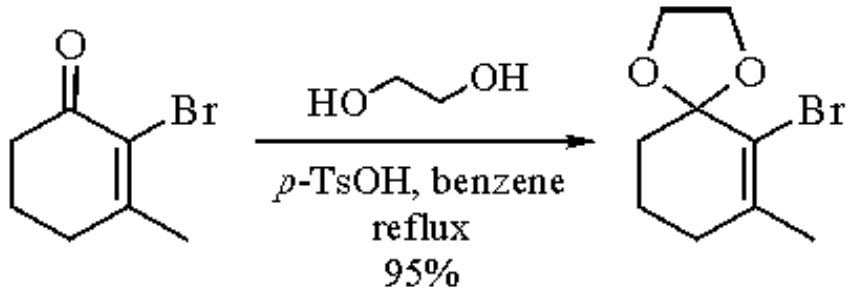

(1)

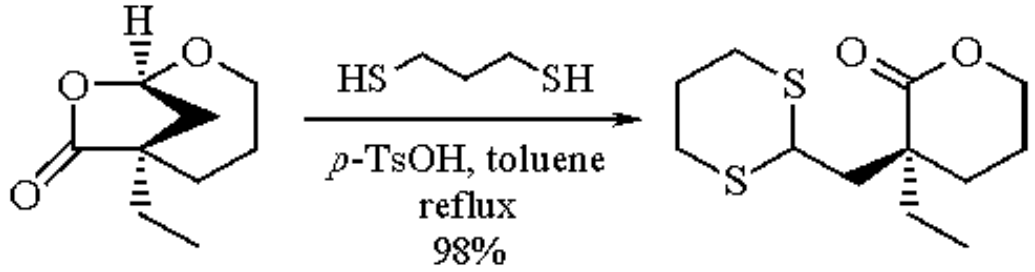

(2)

Treatment of acetals (eqs 3 and 4)[6,7] with aqueous tosic acid effects cleavage to the carbonyl compounds.

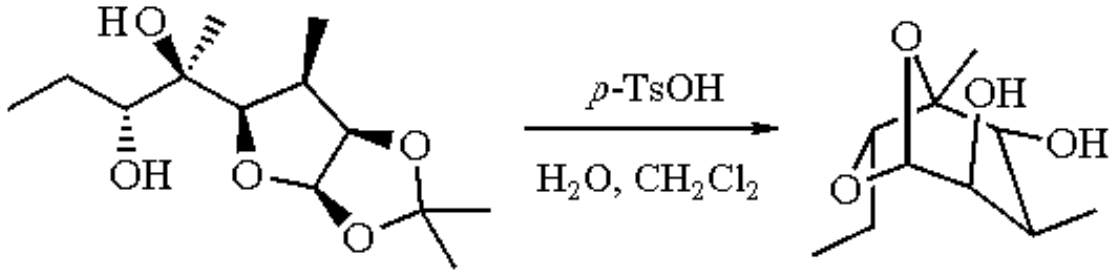

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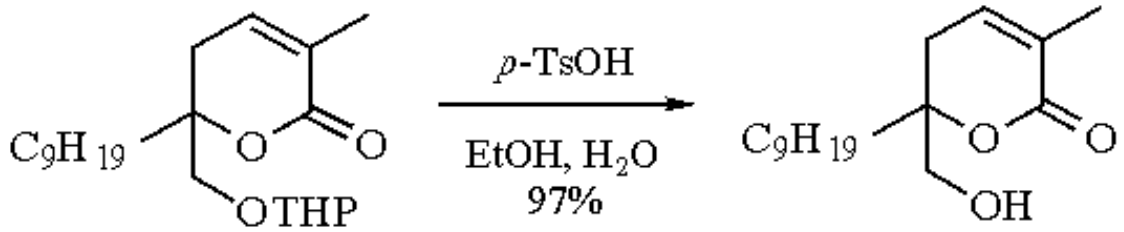

(4)

In a recently described synthesis of (+)-phyllanthocin,[8] spiroacetalization of (**1**) to form key intermediate (**2**) was studied (eq 5). Acid-catalyzed cyclization by tosic acid was found to be superior to ***10-Camphorsulfonic Acid***- or base-catalyzed cyclization using ***1,8-Diazabicyclo[5.4.0]undec-7-ene***.

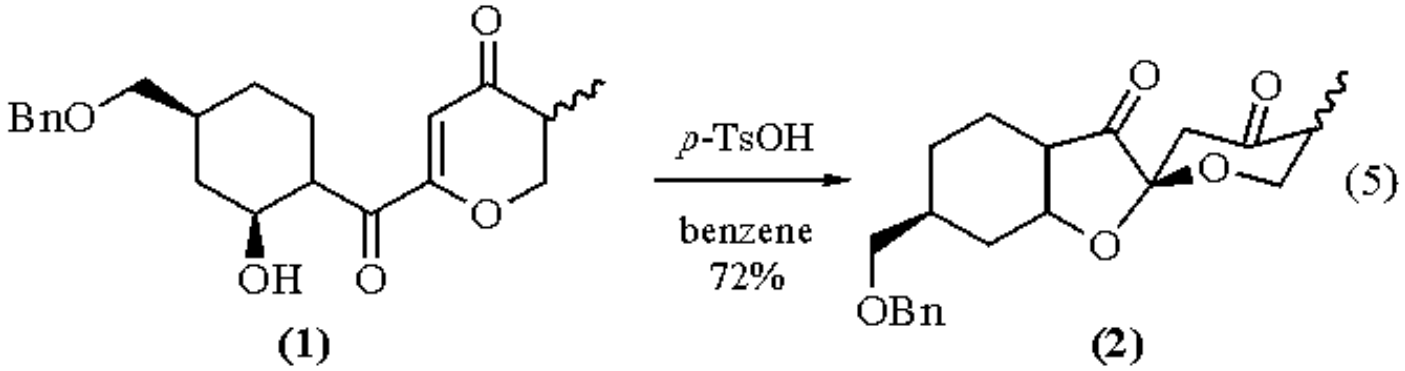

(5)

Esterification and Lactone Formation.

Tosic acid has been used in lieu of mineral acid in Fischer esterifications of carboxylic acids (eq 6).[9] Hydroxy acids (eq 7)[10,11] and aldehyde carboxylic acids (eq 8)[10] may be cyclized to lactones and enol lactones, respectively, by treatment with tosic acid in organic solvent.

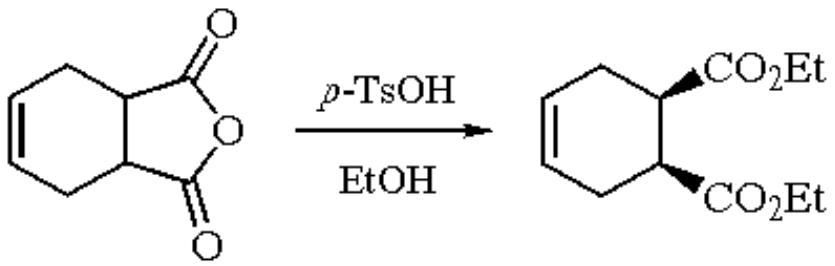

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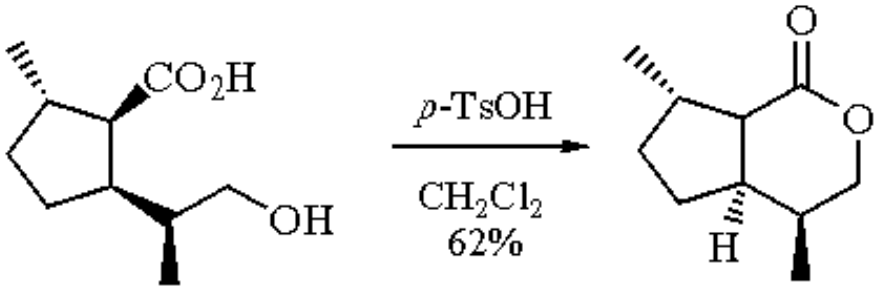

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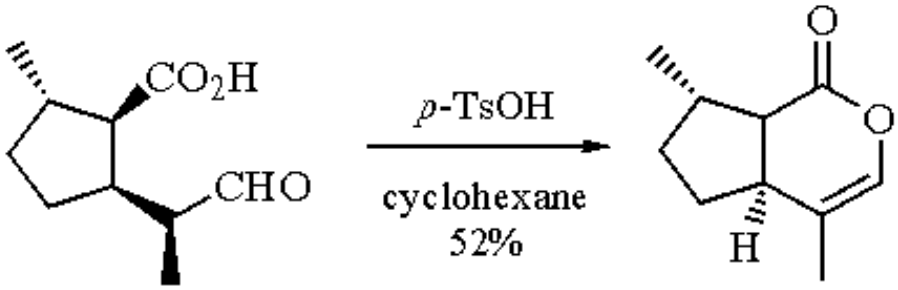

(8)

Tosic acid has also been used to catalyze internal translactonization processes (eq 9).[12]

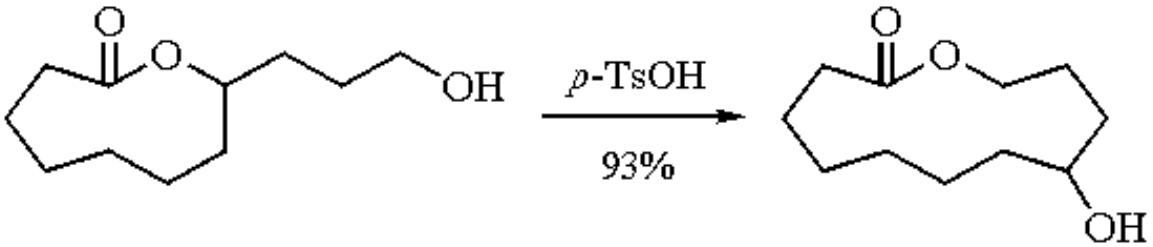

(9)

Dehydration Processes.

Dehydration of ketols to α,β-unsaturated compounds is effectively catalyzed by tosic acid;[13] addition of calcium chloride to the reaction mixture has been noted to give superior results in some instances.[14,15] Other acid-catalyzed processes can occur concomitantly, such as cleavage of silyl ethers.[16] Tosic acid adsorbed on silica gel was found to be an effective catalyst for the dehydration of secondary and tertiary alcohols (16 examples),[17] including a number of steroid alcohols which are resistant to most methods of catalyzed dehydration (eq 10).

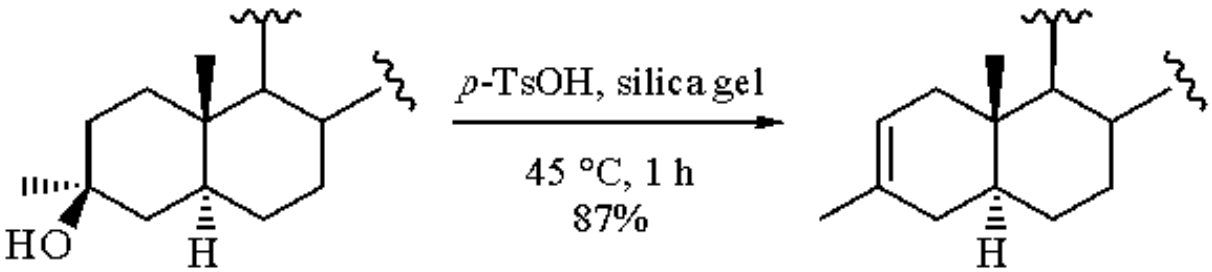

(10)

p-Toluenesulfonic acid has been used to catalyze the formation of enamines; water is removed via azeotropic distillation.[18] The dehydration of primary nitro compounds by tosic acid provides access to nitrile oxides, which can subsequently engage in 1,3-dipolar

cycloaddition reactions.[19] Oximes may be dehydrated to nitriles by heating with tosic acid in DMF.[20] Reaction of cyclohexanone oximes with ketene in the presence of tosic acid results in aromatization to aryl amines.[21] This constitutes a milder method for Semmler-Wolff aromatization than those previously reported.

Cationic Rearrangements and Isomerizations.

In a study of Wagner-Meerwein rearrangements of tricyclo[4.3.2.0]undecanones catalyzed by tosic acid,[22] (**3**) was converted to (**4**) in refluxing benzene in 82% yield (eq 11). A similar rearrangement has been utilized in the synthesis of cyclopentanoid sesquiterpenes (eq 12).[23] Similar processes in which the migrating atom is sulfur have been reported;[24] sulfur-containing bicyclo[10.5.0]alkenes and related compounds have been obtained via tosic acid-catalyzed ring expansions of sulfoxides (eq 13).[25]

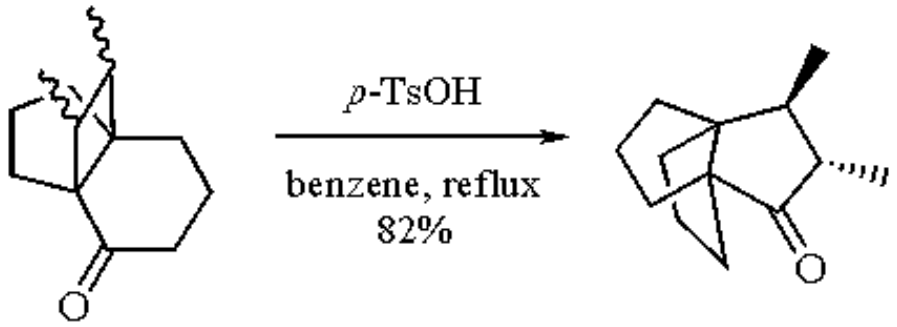

(3) (4) (11)

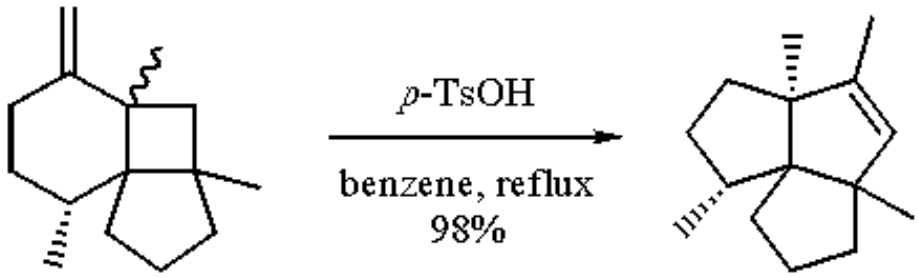

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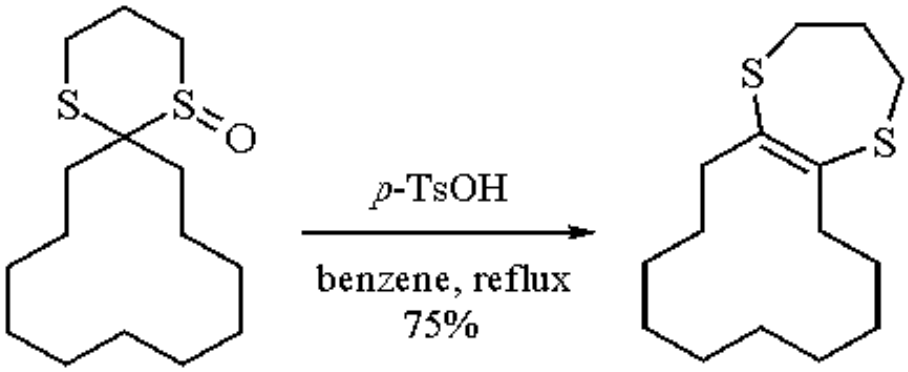

(13)

Treatment of tertiary vinyl alcohols with tosic acid in a mixture of ***Acetic Acid*** and ***Acetic Anhydride*** effects their conversion to allylic acetates (eq 14).[26] Treatment of β-hydroxyalkyl phenyl sulfides with tosic acid in refluxing benzene results in migration of the phenylthio group to generate allylic sulfides.[27]

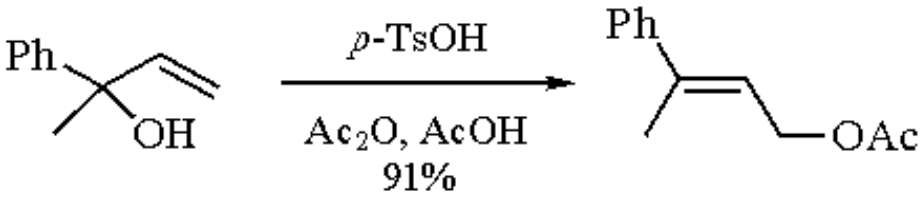

(14)

Synthesis of Enol Ethers and Acetates.

Tosic acid is, in general, superior to other common catalysts (***Sulfuric Acid***, ***Phosphoric Acid***, potassium acetate) for enolization in the conversion of ketones to their enol acetates using acetic anhydride.[28,29] This methodology has been used extensively in steroid synthesis.[30-33] Isopropenyl acetate may also be used with removal of acetone by slow distillation (eq 15).[34] Enol ethers may similarly be obtained by treatment with tosic acid and alcohol in refluxing benzene or toluene followed by azeotropic removal of water.[35]

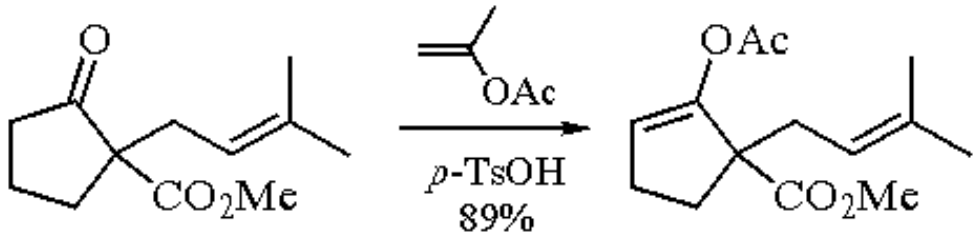

(15)

Synthesis of Steroid Acetates.

Tosic acid has been used to good effect in the acetylation of steroid substrates, replacing the commonly used ***Pyridine*** catalyst. Treatment of cholestane-3β,5α,6β-triol with pyridine and acetic anhydride afforded the 3,6-diacetate; heating the triol with tosic acid in acetic anhydride provided the desired triacetate.[36] Acetylation of the 17α-hydroxyl group of progesterone has been accomplished by this method.[37,38]

Addition of Alcohols to Nitriles (Ritter Reaction).

Esters may be prepared by the acid-catalyzed addition of alcohols to nitriles. Tosic acid is the preferred catalyst for this reaction.[39]

Cleavage of Amine Protecting Groups.

t-Butyloxycarbonyl (Boc) groups may be cleaved from protected amines in the presence of *t*-butyl- and *p*-methoxybenzyl esters by the action of tosic acid in a mixture of ethanol and ether (eq 16) (seven examples).[40] *p*-Methoxybenzyloxycarbonyl groups may be removed with tosic acid in acetonitrile.[41]

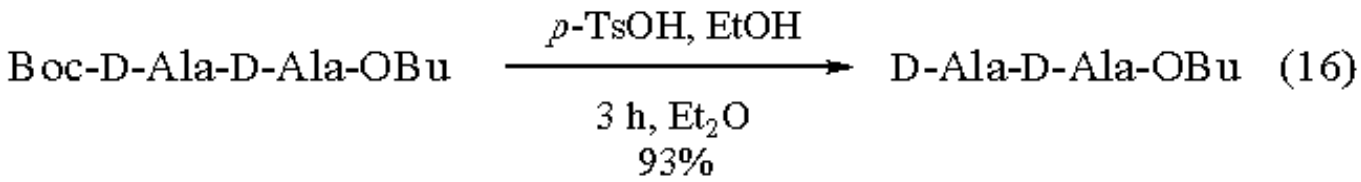

(16)

Synthesis of Substituted Methylbenzenes.

Tosic acid is lithiated at the 2-position with 2 equiv of ***n-Butyllithium***; the resulting anion may be reacted with various electrophiles. Desulfonylation of the substituted product constitutes a synthesis of *meta*-substituted toluenes.[42]

Synthesis of Sulfones.

Alkyl *p*-tolyl sulfones may be prepared by reaction of the ***p-Toluenesulfonyl Chloride*** with Grignard reagents. *p*-Tolyl aryl sulfones can be synthesized by the condensation of tosic acid with aromatic compounds in ***Polyphosphoric Acid***;[43] alternatively, the sulfonyl chloride may be reacted with aromatic substrates under Friedel-Crafts conditions.[43] Milder conditions using ***Phosphorus(V) Oxide-Methanesulfonic Acid*** have been reported.[44]

Amine Salts.

Amines are frequently converted to their tosylate salts for characterization.[45]

Related Reagents.

Hydrochloric Acid; ***Methanesulfonic Acid***; ***Sulfuric Acid***; ***Trifluoroacetic Acid***; ***Trifluoromethanesulfonic Anhydride***.

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p-Toluenesulfonyl Chloride[1]

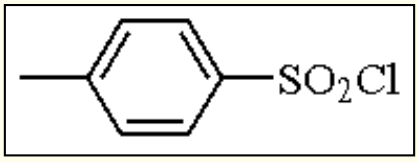

[98-59-9] · $C_7H_7ClO_2S$ · *p*-Toluenesulfonyl Chloride · (MW 190.66)

(sulfonyl transfer reagent; *O*-sulfonylation of alcohols[2] for conversion to chlorides[3] or intermolecular[4] and intramolecular[5] displacements, vicinal diols for epoxidation,[6] 1,3-diols for oxetane formation,[7] carboxylic acids for esterification[8] or decarboxylation,[9] oximes for Beckmann rearrangements[10] or fragmentations[11] and Neber rearrangements,[12] hydroxamic acids for Lossen rearrangements,[13] nitrones for rearrangements,[14] conversion of *N*-cyclopropylhydroxylamines to β-lactams;[15] *N*-sulfonylation of aliphatic amines[16] for subsequent deamination[17] or displacement,[18] aromatic amines for protection;[19] *C*-sulfonylation of alkenes[20] and silylalkynes;[21] dehydration of ureas,[22] formamides,[23] and amides[24])

Alternate Names: tosyl chloride.

Physical Data: mp 67-69 °C; bp 146 °C/15 mmHg.

Solubility: insol H_2O; freely sol ethanol, benzene, chloroform, ether.

Form Supplied in: white solid, widely available.

Purification: upon prolonged standing the material develops impurities of *p*-toluenesulfonic acid and HCl. Tosyl chloride is purified by dissolving 10 g in a minimum volume of $CHCl_3$ (ca. 25 mL), filtering, and diluting with five volumes (ca. 125 mL) of petroleum ether (bp 30-60 °C) to precipitate impurities (mostly tosic acid, mp 101-104 °C). The solution is filtered, clarified with charcoal, and concentrated to ca. 40 mL by evaporation. Further evaporation to a very small volume gives 7 g of pure white crystals (mp 67.5-68.5 °C).[25]

Tosyl chloride may also be recrystallized from petroleum ether, from benzene, or from toluene/petroleum ether (bp 40-60 °C) in the cold. Tosyl chloride in diethyl ether can be washed with aqueous 10% NaOH until colorless, then dried with Na_2SO_4 and crystallized by cooling in powdered dry ice. It can also be purified by dissolving in benzene, washing with aqueous 5% NaOH, drying with K_2CO_3 or $MgSO_4$, and distilling under reduced pressure.[26]

Handling, Storage, and Precautions: freshly purified tosyl chloride should be used for best results. Tosyl chloride is a moisture-sensitive, corrosive lachrymator.

General Discussion.

The tosylation of alcohols is one of the most prevalent reactions in organic chemistry.[1] Optimized conditions for this reaction include the use of a 1:1.5:2 ratio of alcohol/tosyl chloride/pyridine in chloroform (eq 1).[2a] This procedure avoids formation of unwanted pyridinium salts inherent to reactions where higher relative quantities of pyridine have been employed.[2b]

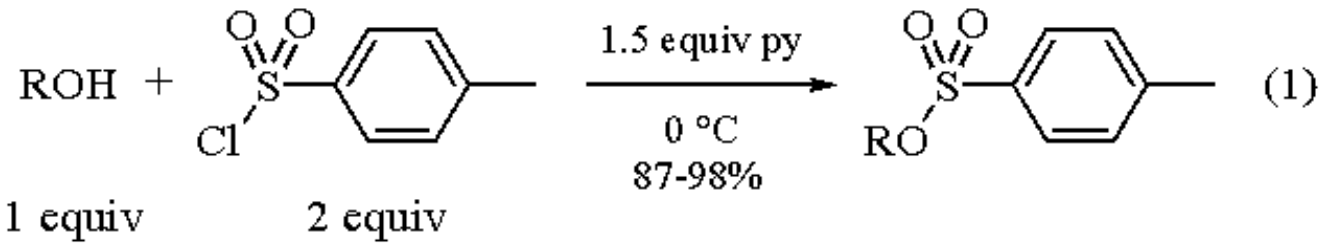

Good yields (81-88%) for tosylation have also been observed under biphasic conditions where ***Benzyltriethylammonium Chloride*** is employed as a phase-transfer catalyst between benzene and aqueous sodium hydroxide solution.[2c]

It has long been known that it is possible to selectively tosylate primary over secondary alcohols (eq 2).[2d]

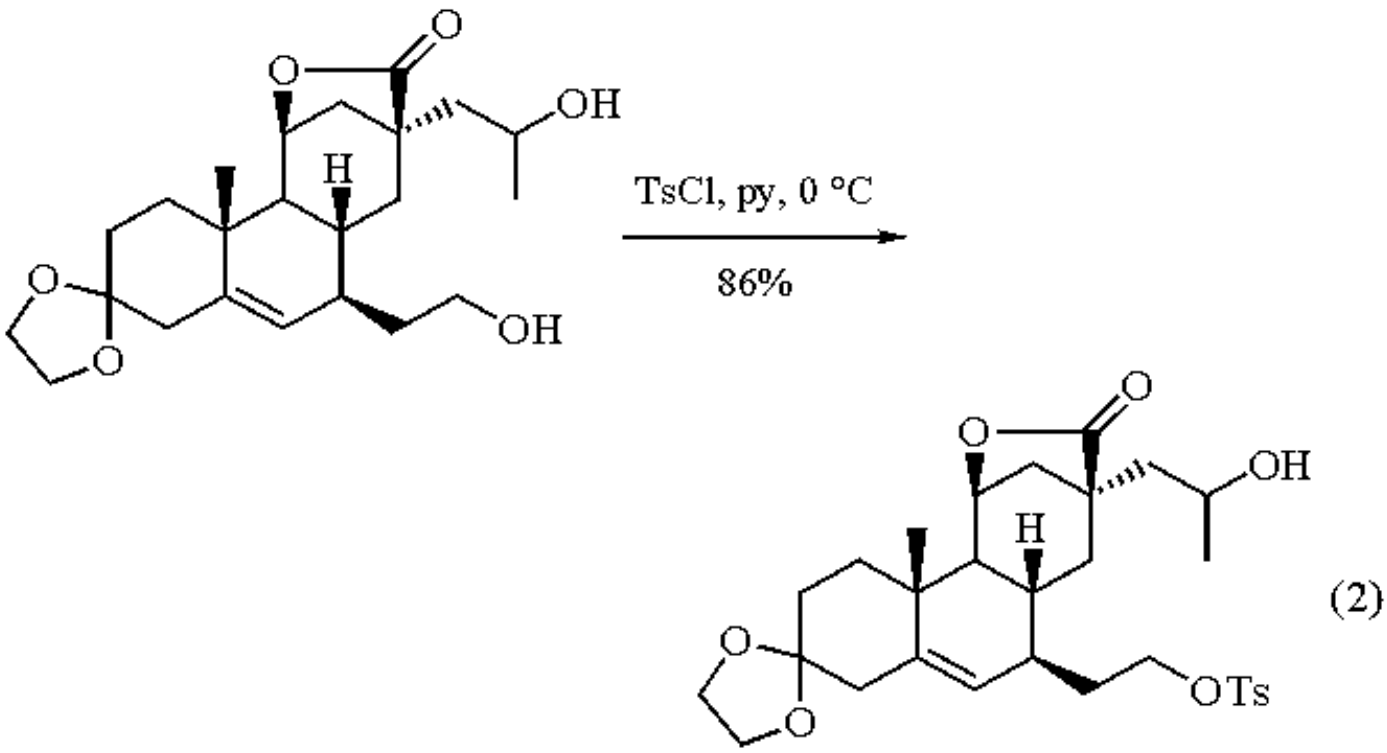

It is also possible to regioselectively mono-*O*-tosylate various nonprotected hydroxyl functionalities, as illustrated in Scheme 1.[2e] This method employs a preliminary activation of a glycopyranoside with ***Di-n-butyltin Oxide*** and usually requires the use of a basic catalyst such as ***4-Dimethylaminopyridine*** (DMAP) in conjunction with tosyl chloride. Regioselectivity differs markedly from acylation reactions and is thought to be a function of changes in the kinetics of the reactions with the various tin intermediates which are in equilibrium.

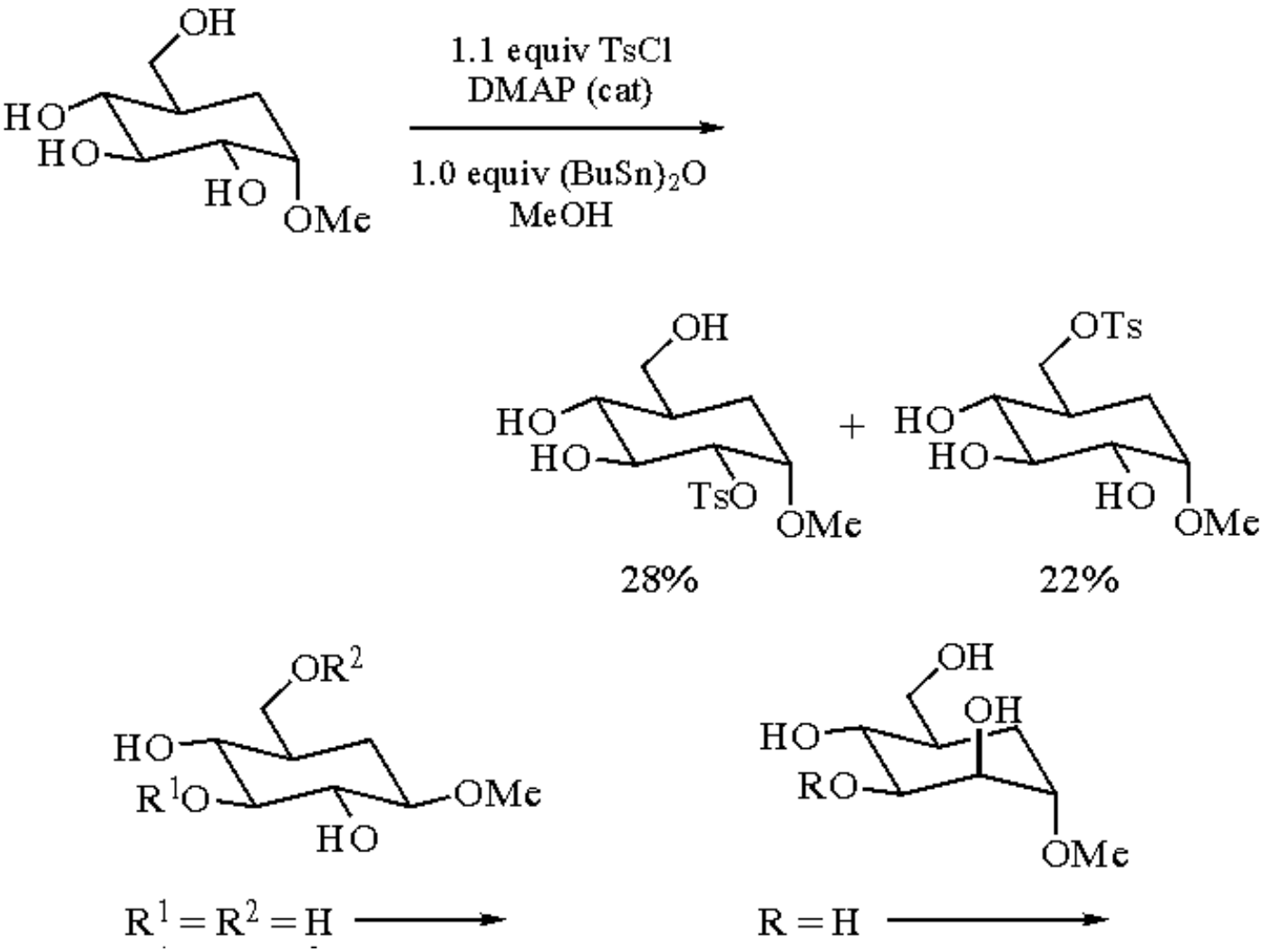

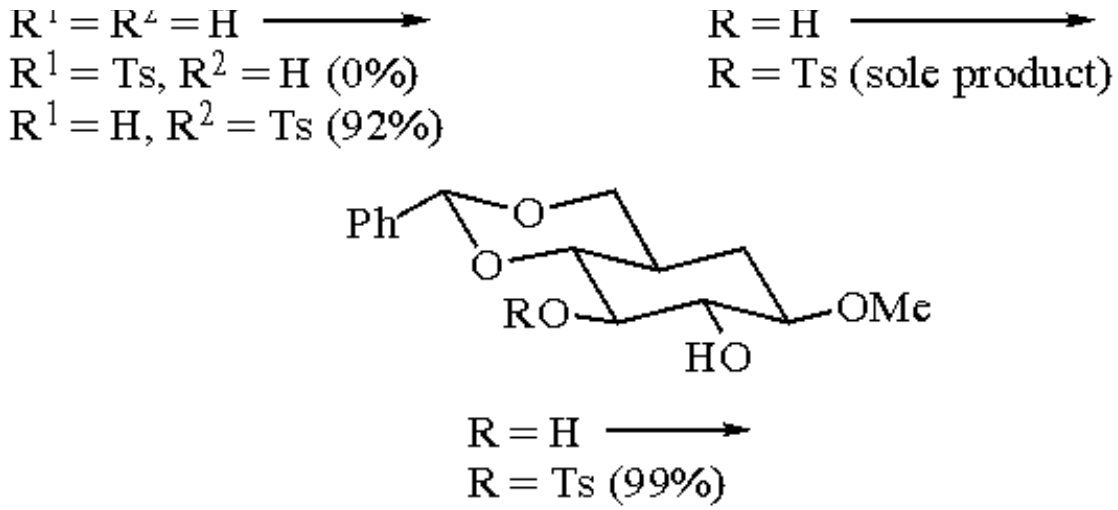

Scheme 1

Regioselective mono- and ditosylation of aldonolactones has also been reported.[2f] A few of these products are shown in Scheme 2. In no instances was the β-hydroxy function tosylated.

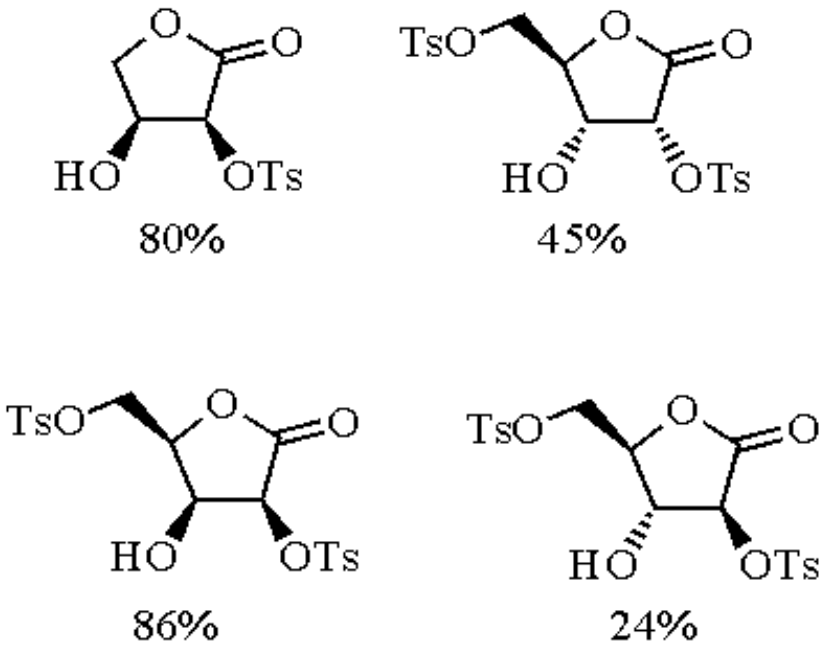

Scheme 2

The regioselective tosylation of various cyclodextrins has been reported. The two major products resulting from the tosylation of β-cyclodextrin are heptakis(6-*O*-(*p*-tosyl))-β-cyclodextrin (**1**) and heptakis(6-*O*-(*p*-tosyl))-2-*O*-(*p*-tosyl))-β-cyclodextrin (**2**).[2g,h] Yamamura has also prepared hexakis(6-*O*-(*p*-tosyl))-α-cyclodextrins[2i] as well as polytosylated γ-cyclodextrins.[2j]

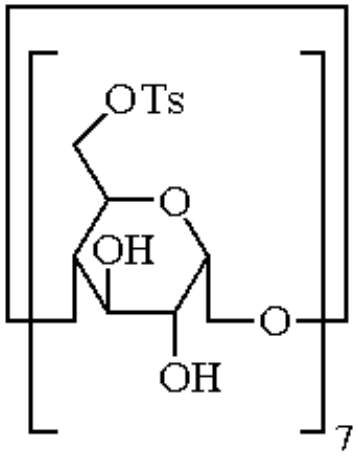

(1) 24%

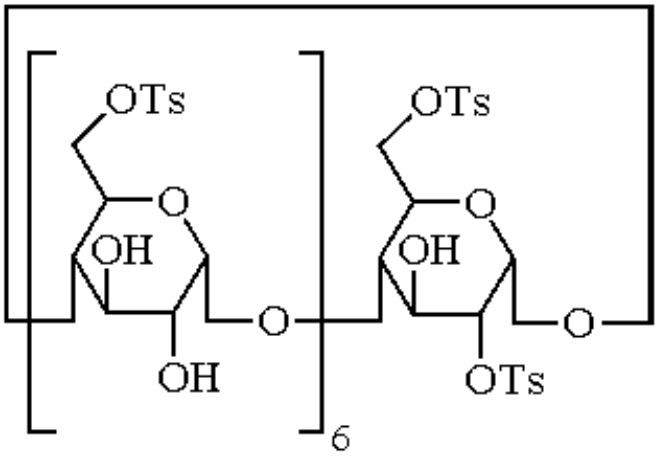

(2) 15%

By proper choice of base it is possible to selectively *O*-tosylate in the presence of a free amine or *N*-tosylate in the presence of a free hydroxyl, with yields in excess of 94% (eq 3). The probable explanation for selective *O*-tosylation in the presence of the stronger base is formation of an adequate amount of phenoxide to allow the anion to act as the nucleophile.[2k]

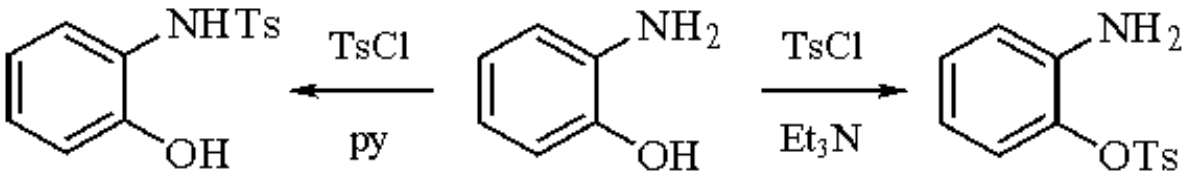

(3)

Tosyl chloride has been used in the preparation of allylic chlorides from their respective alcohols, leaving in place sensitive groups and with no rearrangement of the allylic substrate (eq 4).[21]

(4)

Studies on reactions of various types of alcohols with the related tosyl chloride/dimethylaminopyridine (TsCl/DMAP) system have led to the following conclusions: allylic, propargylic, and glycosidic hydroxyls quickly react to form the corresponding chlorides, 2,3-epoxy and selected primary alcohols yield chlorides but at a slower rate, and reactions of aliphatic secondary alcohols stop at the tosylate stage. Example reactions are illustrated in eqs 5-10.[3a]

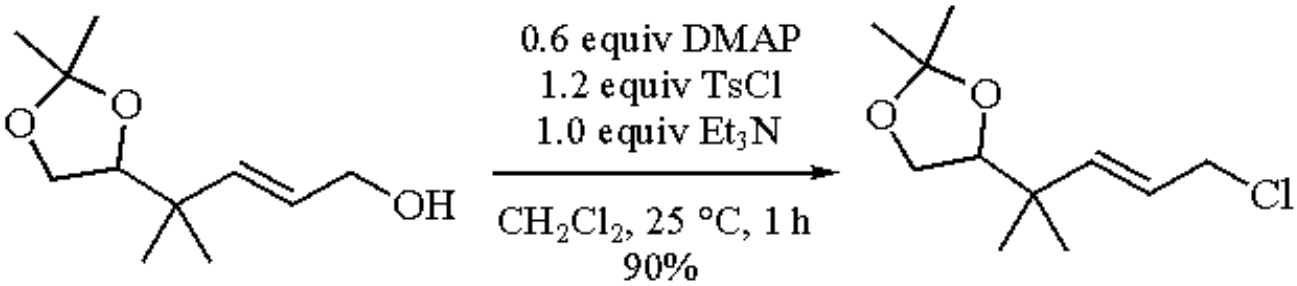

(5)

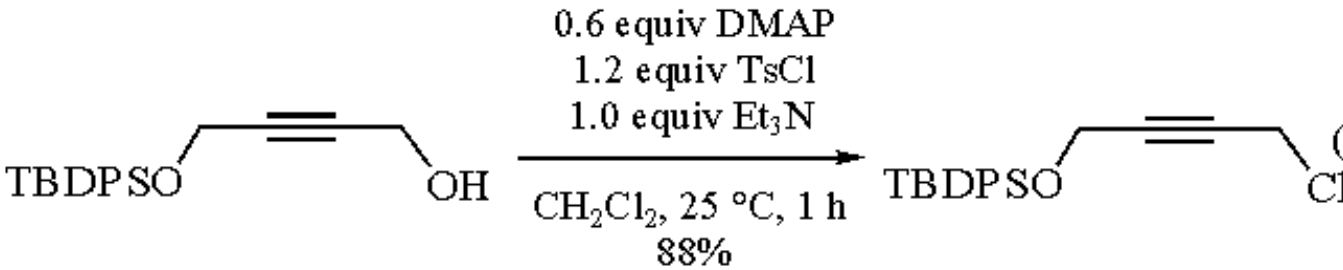

(6)

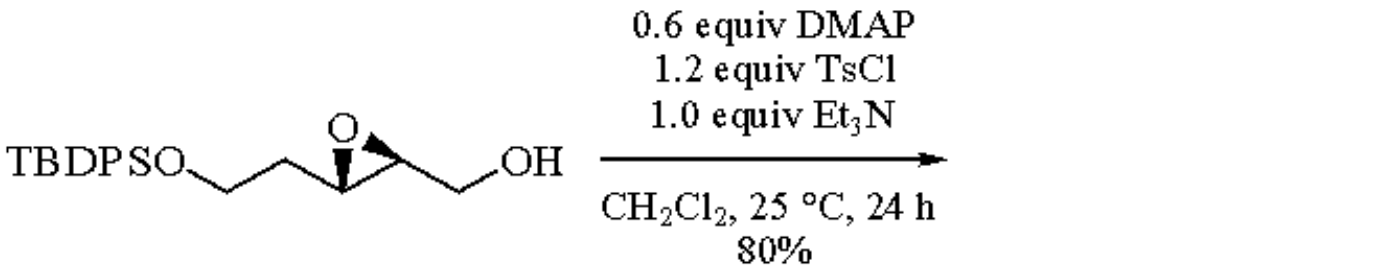

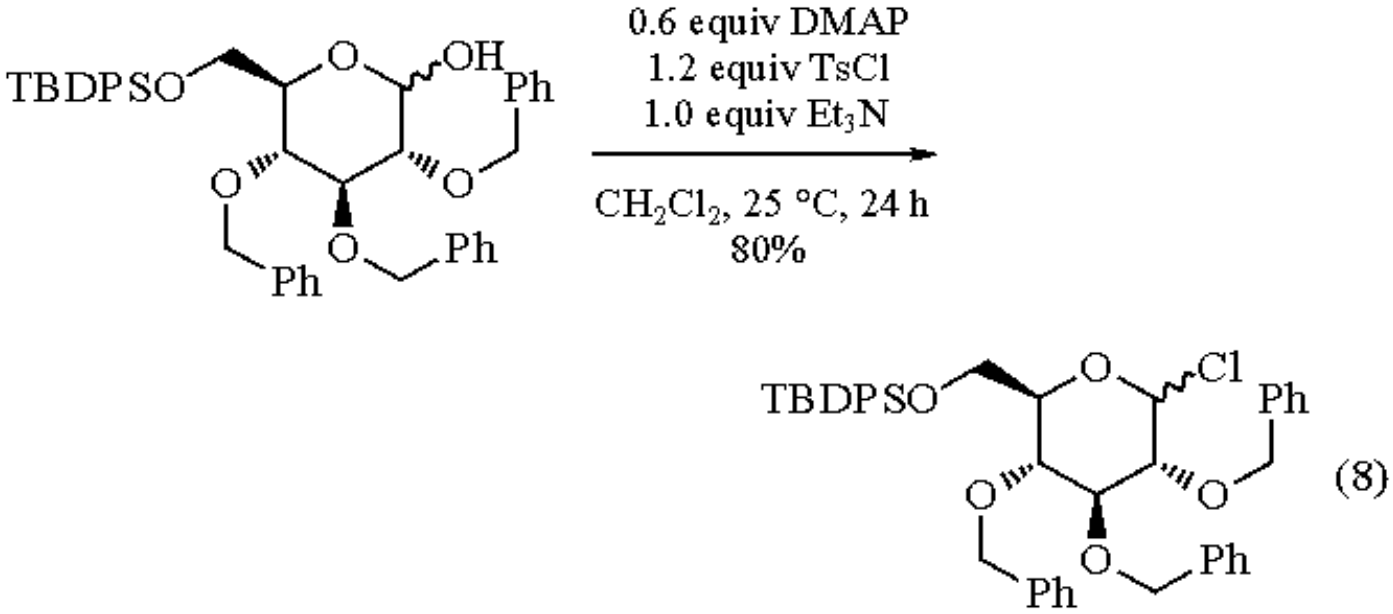

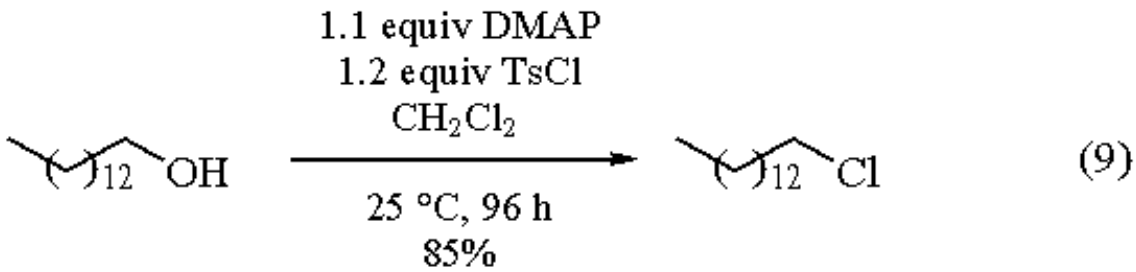

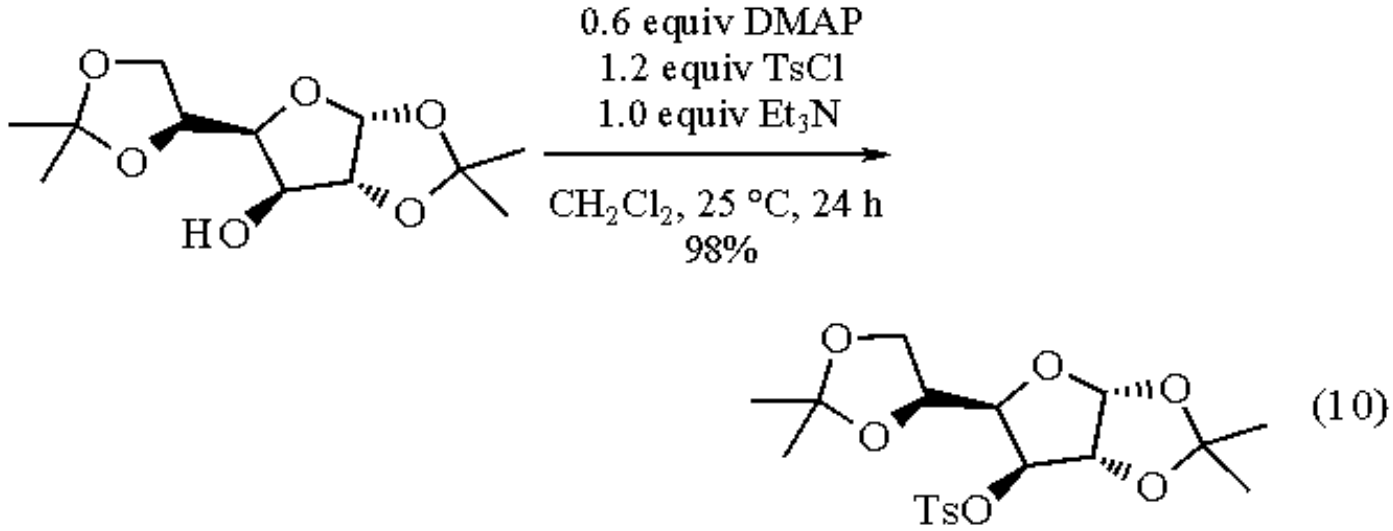

Attempted tosylation of 3β-methoxy-21-hydroxy-5α-pregnan-20-one afforded its α-chloro derivative.[3b] This reinforces the rule that as

hybridization α to the alcohol increases in s character, displacement of the intermediate tosylate is facilitated (eq 11).

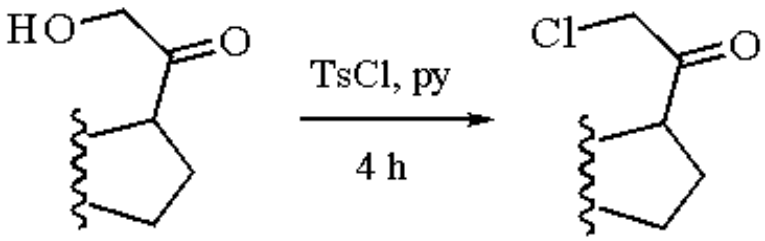

(11)

The α-chlorination of sulfoxides can also be achieved using tosyl chloride and pyridine, albeit in poor yield (32%), as shown in eq 12.[3c]

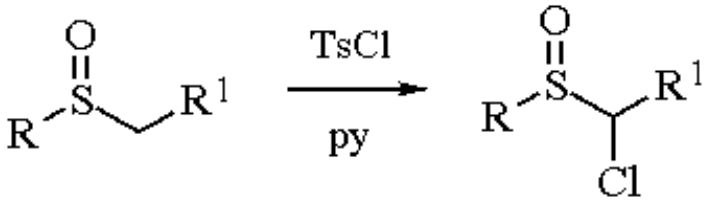

(12)

Alcohols treated with tosyl chloride are transformed into their corresponding sulfonate esters without manipulation of existing stereochemistry in the substrate. The *p*-toluenesulfonyloxy moiety subsequently serves as a good leaving group in intermolecular nucleophilic substitution or elimination reactions.[4] Treatment of multifunctional alcohols with tosyl chloride can result in the formation of intermediate *O*-sulfonylated species, which can undergo intramolecular displacement of the tosylate group. For example, treatment of *trans*-2-hydroxycyclohexaneacetamide with tosyl chloride in pyridine is the key step in the conversion of the lactone of *trans*-2-hydroxycyclohexaneacetic acid to its *cis* isomer (eq 13).[5a]

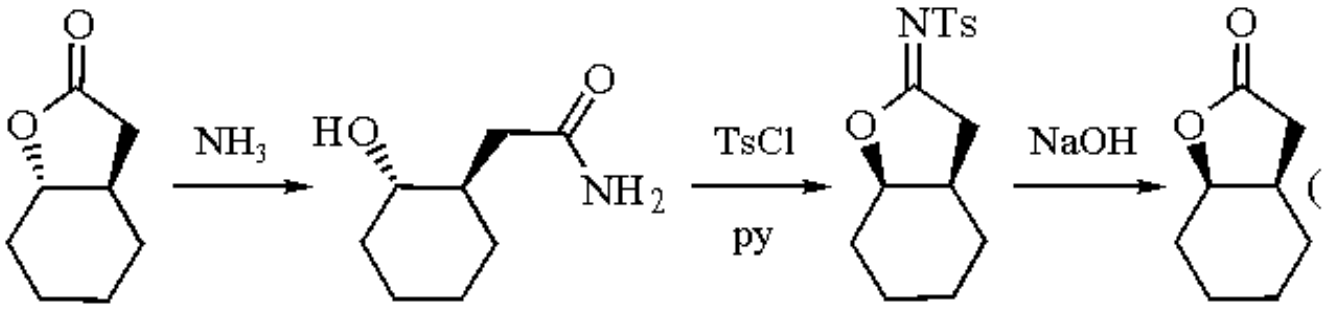

(13)

Alcohols treated with tosyl chloride can also serve as alkylating agents for thioamides to make thiazolines (eq 14).[5b]

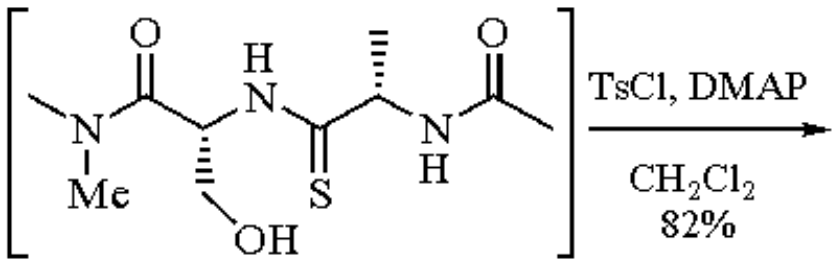

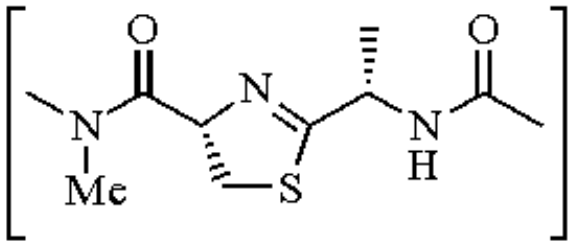

(14)

Several useful one-pot procedures employing the reaction of tosyl chloride with vicinal diols have been used to form epoxides. Treatment of variously substituted diols with 1 equiv of tosyl chloride and sodium hydroxide in monoglyme provides access to a variety of 1-alkynyloxiranes (R^1 and/or R^3 being terminal or substituted alkynes) in moderate to good yield (eq 15).[6a]

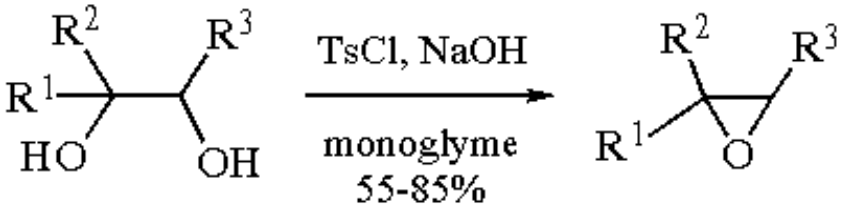

(15)

Another method entails treatment of the diol in THF with 2.2 equiv of ***Sodium Hydride*** followed by reaction with a slight molar excess of tosyl chloride. This fast reaction, illustrated in eq 16, can be used to prepare enantiopure epoxides in good to excellent yields.[6b]

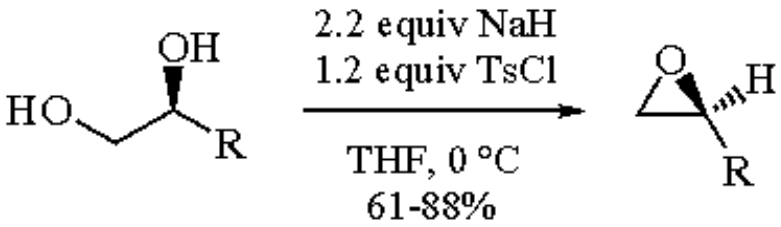

(16)

Phase-transfer catalysis has also been successfully employed to achieve epoxidation. A variety of cyclic *trans*-substituted diols in dichloromethane were treated with a 50% aqueous solution of sodium hydroxide in the presence of the phase-transfer catalyst benzyltriethylammonium bromide. Consistently good yields were achieved for these as well as glycosidic and acyclic substrates (eq 17).[6c]

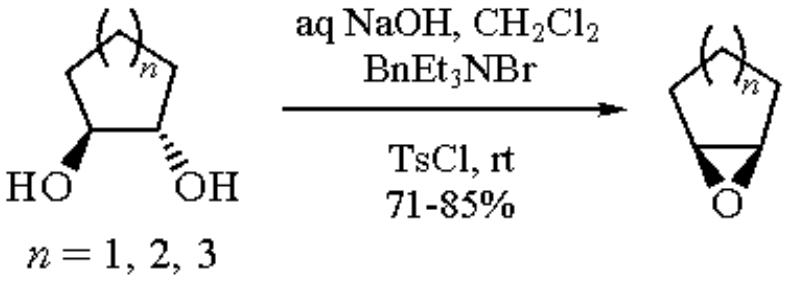

(17)

A one-pot conversion of a variety of 1,3-diols to oxetanes has also been reported.[7] The procedure entailed alcohol deprotonation with one equivalent of ***n-Butyllithium*** followed by treatment with tosyl chloride and then a second equivalent of base (eq 18).

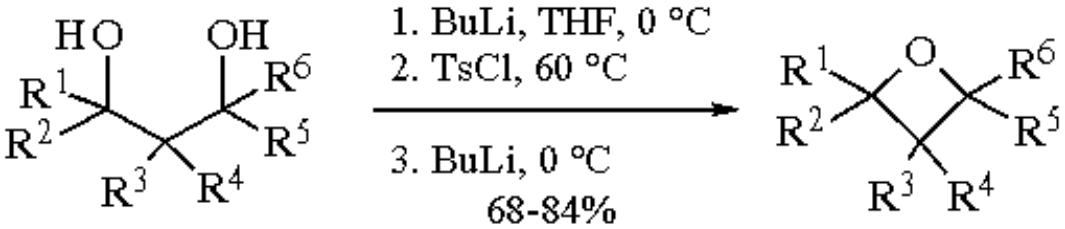

(18)

When a solution of a carboxylic acid and an alcohol in pyridine is treated with tosyl chloride, an ester is formed rapidly in excellent yield. This procedure is useful especially in the esterification of tertiary alcohols. The combination of a carboxylic acid and tosyl chloride serves as a convenient method of in situ preparation of symmetrical acid anhydrides for further formation of esters and amides (eq 19). The novelty of this protocol is that the acid can be recycled through the anhydride stage in the presence of the alcohol, thereby resulting in complete conversion to the ester (eq 20).[8a] Reactivity is determined by the strength of the acid: strong acids facilitate the esterifications.[8b]

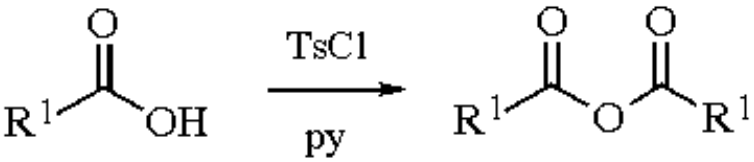

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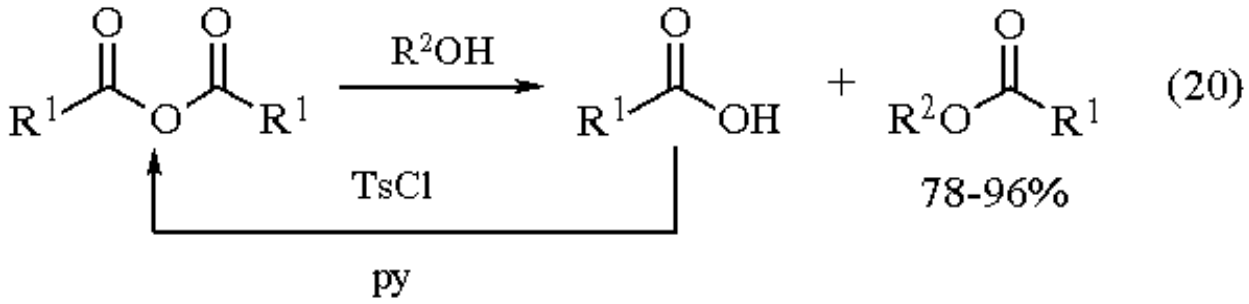

Similarly, a two-step procedure employing treatment of a mixture of tosic acid and various amino acids with alcoholic tosyl chloride results in the isolation of the esters of the amino acids as their *p*-toluenesulfonate salts in excellent yield. The tosic acid used in the esterification is added to make the amino acids more soluble and to prevent *N*-tosylation (eq 21).[8c]

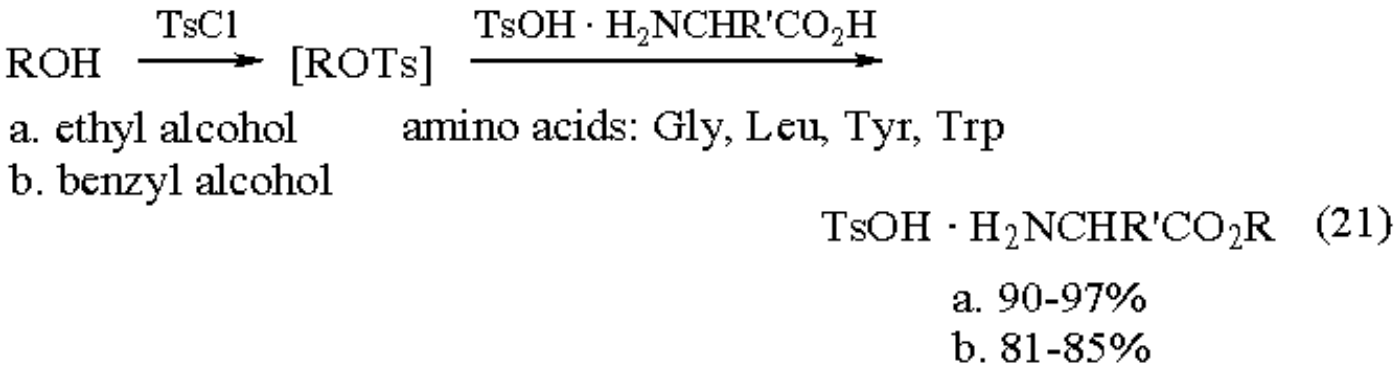

A novel formal decarboxylation of the amino acid α-anilino-α,α-diphenylacetic acid has been observed upon treatment with tosyl chloride in pyridine.[9] It has been proposed that a mixed anhydride of *p*-toluenesulfonic acid has undergone an elimination via *N*-deprotonation and synchronous extrusion of carbon monoxide in this reaction. Interestingly, no *N*-tosylation occurs (eq 22).

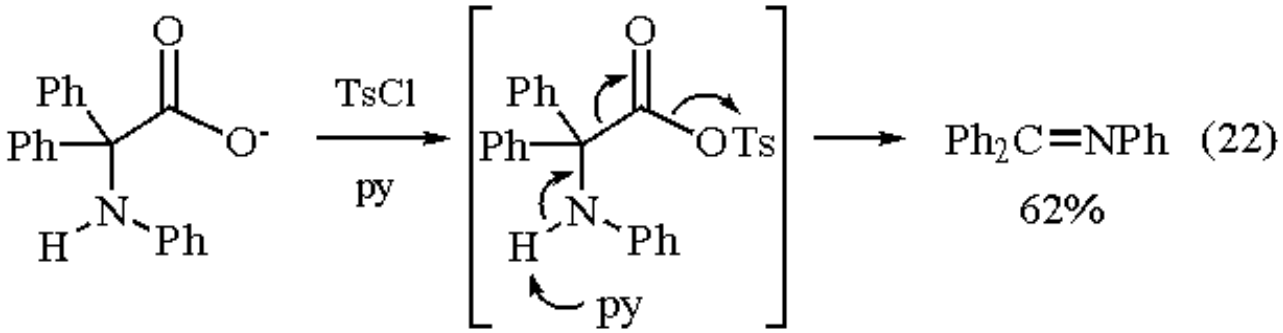

Spontaneous Beckmann rearrangement has been observed upon *O*-tosylation of oximes. Lactams can therefore be conveniently prepared from cyclic oximes, as shown in eq 23.[10a] The rearrangement has long been known to proceed with retention of configuration of the migrating group.[10b,c] This is complementary to the reaction of oximes with ***Sulfuric Acid*** (eq 24).[10b]

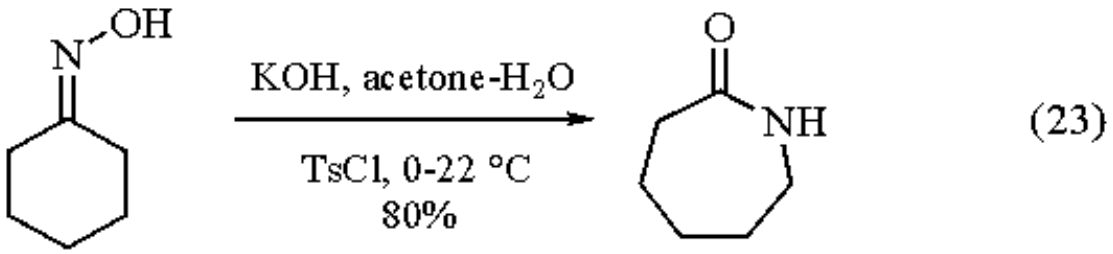

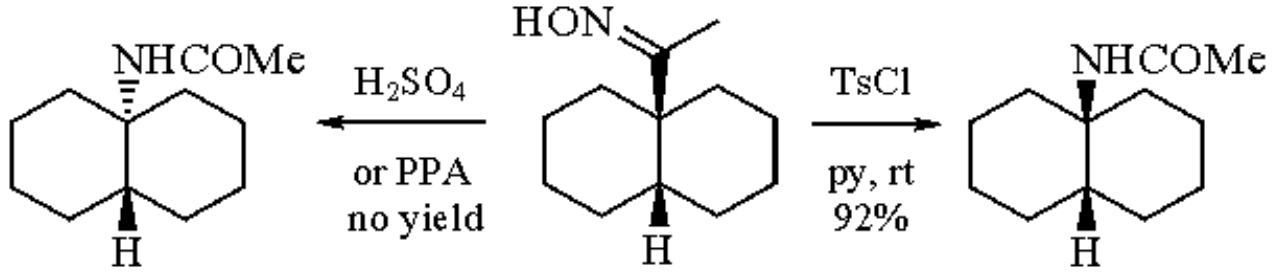

(24)

A Beckmann fragmentation of oximes using tosyl chloride in a basic ethanol-water system has also been observed.[11] Formation of the cyclic product shown in eq 25 was consistent with a base-induced opening of an intermediate lactone followed by rearrangement and incipient extrusion of benzoic acid.

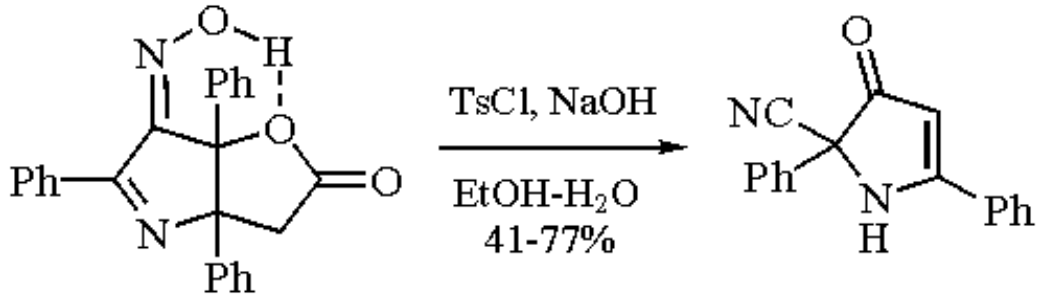

(25)

Oximes which are treated with tosyl chloride can also be used as substrates in the Neber rearrangement to α-amino ketones.[12a] The mixture shown in eq 26 was further subjected to reductive amination to yield 14% of the CNS-active *cis-N,N*-dimethylated α-amino alcohol.[12b]

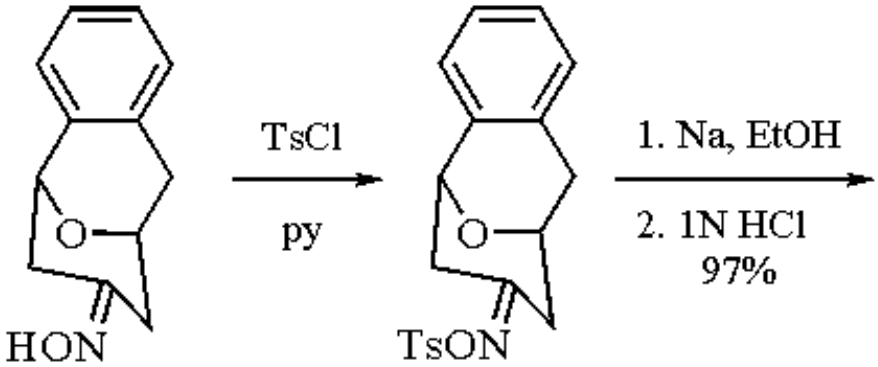

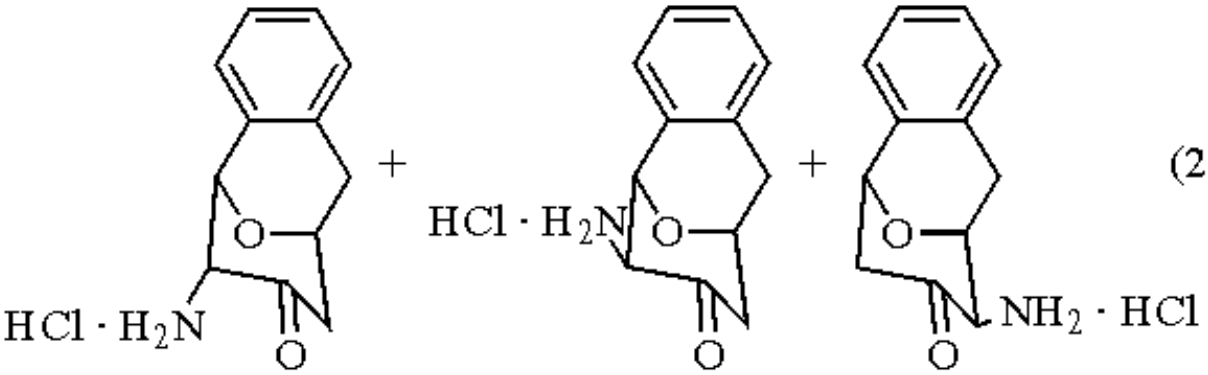

(26)

2:1:1 inseperable mixture,

Rearrangements of hydroxamic acids using sulfonyl chlorides have been accomplished, albeit without reported yields, the net result being a unique variation of the Lossen rearrangement (eq 27).[13]

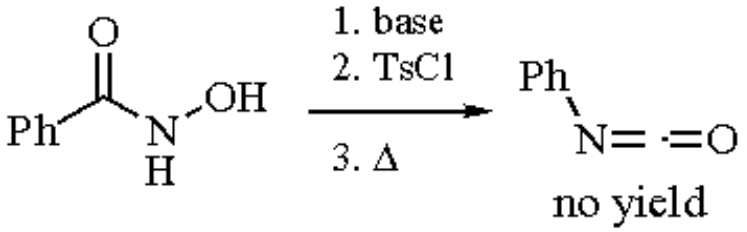

(27)

As an alternative to the Beckmann rearrangement, ketonic nitrones can be treated with tosyl chloride in pyridine in the presence of water, as illustrated in eq 28.[14]

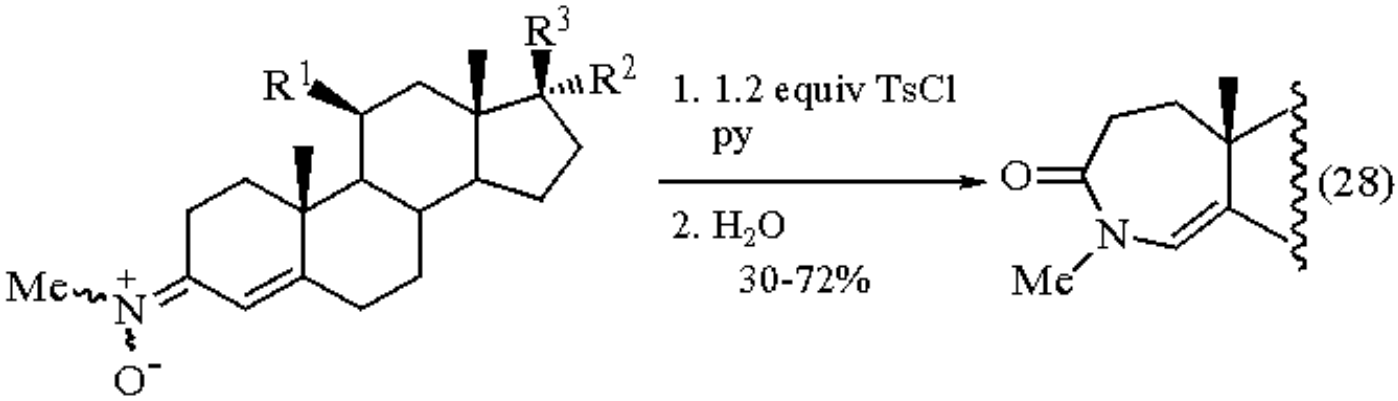

(28)

Rearrangement reactions which utilize tosyl chloride seem to progress in a two-step process: the displacement of chlorine from the sulfonyl halide resulting in the formation of an oxygen-sulfur bond, followed by the migration, elimination, or intramolecular displacement of the sulfonylate anion.[8a] When the series of carbinolamines depicted in eq 29 were treated with tosyl chloride, they decomposed into the corresponding electron-deficient nitrogen species, which subsequently triggered ring enlargement to the β-lactams in moderate yields.[15]

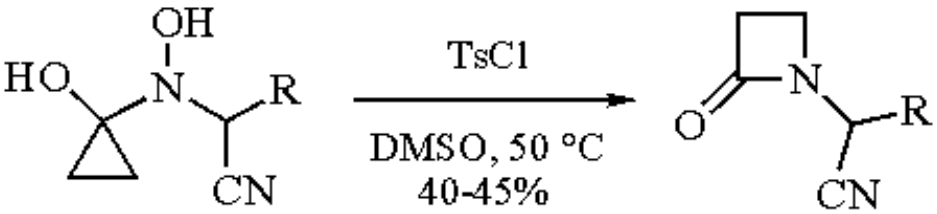

(29)

R = various alkyl groups

N-Tosylation is a facile procedure. For inexpensive amines a useful procedure entails treating 2 equiv of the amine with tosyl chloride. This is the first step in the convenient preparation of Diazald (***N-Methyl-N-nitroso-p-toluenesulfonamide***), a ***Diazomethane*** precursor (eq 30).[16a]

(30)

Protection of 3-amino-3-pyrazoline sulfate, a key intermediate in the preparation of 3(5)-aminopyrazole, was achieved in the presence of an excess of sodium bicarbonate in good yields (eq 31).[16b]

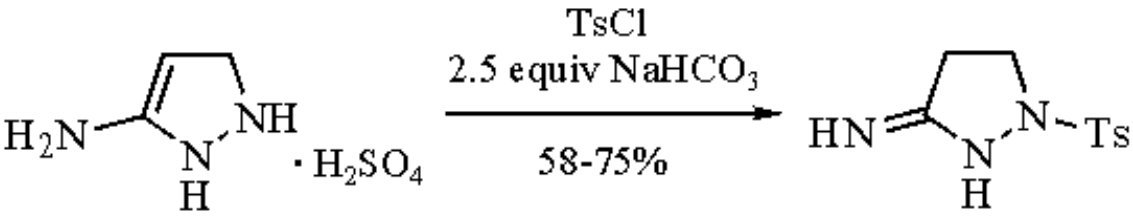

(31)

Sodium Carbonate can also be used as the base in the tosylation of amines, as shown in the reaction of anthranilic acid with tosyl chloride. There was no competing nucleophilic attack at sulfur by the resonance-stabilized carboxylate group (eq 32).[16c]

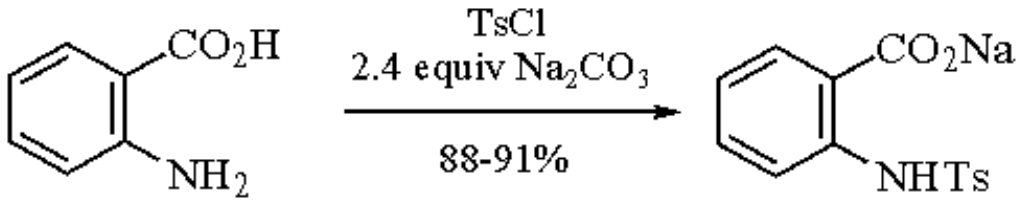

(32)

Primary, benzyl, and unhindered secondary amines can be ditosylated and deaminated in good to excellent yields, using ***Sodium Borohydride*** as the nucleophile, to afford the corresponding alkanes; only highly congested substrates experience competing attack at nitrogen.[17] Similarly, primary aliphatic amines, when ditosylated and treated with iodide ion in DMF at 90-120 °C yielded, as their major products, the corresponding alkyl iodides, with some competition arising from elimination reactions (eqs 33 and 34).[18]

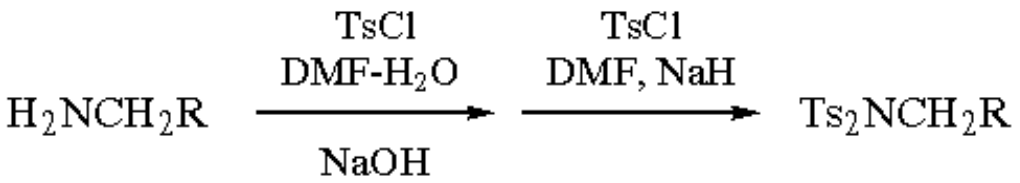

(33)

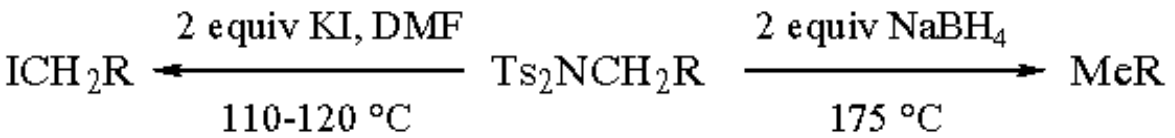

(34)

Tosyl chloride has been used in the protection of the imidazole residue of N^{α}-acylhistidine peptides[19a,b] and the guanidino residue of arginine peptides.[19c] The resulting nitrogen-protecting group is stable to most conditions but is easily removable in anhydrous hydrogen fluoride at 0 °C.

The tosylation of carbon can be accomplished using electron transfer conditions. Treatment of styrene[20a] and analogs[20b] with ***Copper(II) Chloride*** and tosyl chloride or ***Benzenesulfonyl Chloride*** results in a formal replacement of the vinyl proton by the sulfonyl moiety (eq 35). The intermediacy of a *trans*-β-chloro sulfone has been demonstrated by ^{1}H NMR. Treatment with base induced the elimination of HCl. A variety of other sulfonyl transfer reagents can be employed in the synthesis of isolated β-chloro sulfones, with good results (60-97% yield) for a variety of alkenes (ethylene, 1-butene, 2-butene, 1-octene, acrylonitrile, methyl acrylate, and 1,3-butadiene).[20a]

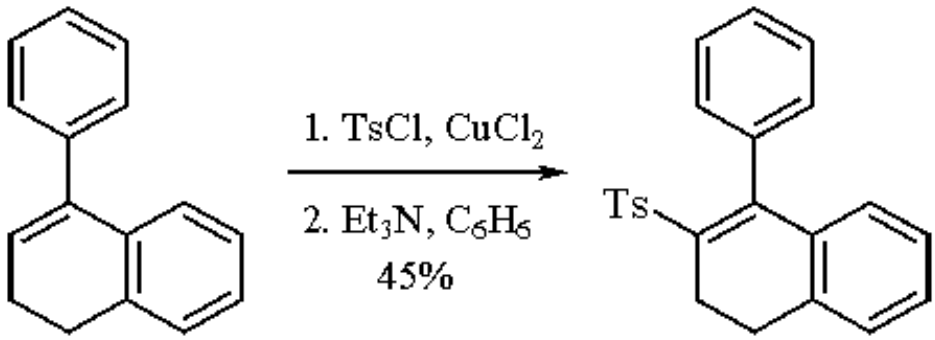

(35)

Although it was found that tosyl chloride does not react with 3-sulfolene at temperatures below 110 °C, upon further warming to 140 °C addition to the diene afforded 1-chloro-4-tosyl-2-butene in a convenient procedure that did not require the use of a sealed tube or bomb (eq 36).[20c] Cycloheptatriene, 1,4-norbornadiene, and phenylacetylene are a few examples of a variety of compounds which are reactive substrates in this protocol.

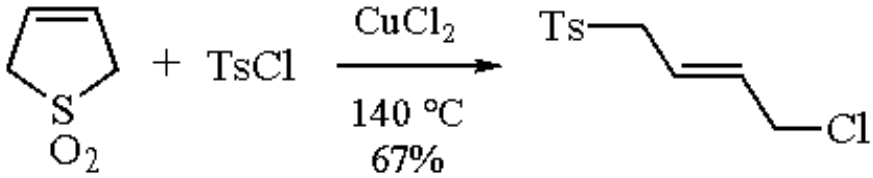

(36)

Radical addition of tosyl chloride to norbornene and aldrin without skeletal rearrangement can be achieved using ***Dibenzoyl Peroxide*** as an

initiator (eq 37).[20a,d] Reaction with 1,4-norbornadiene gives rise to a rearranged addition product.

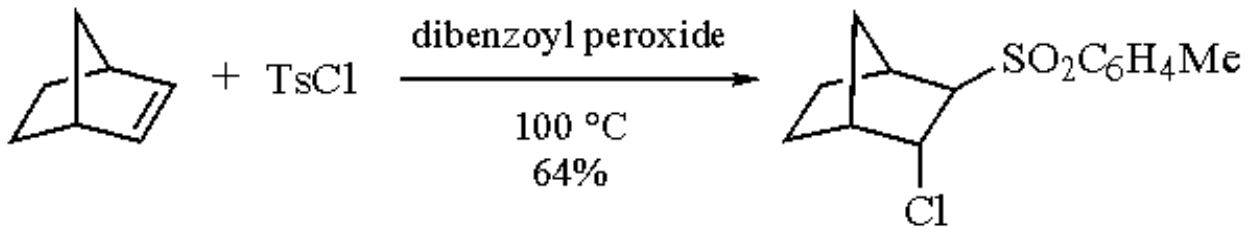

(37)

Treatment of bis(trimethylsilyl)acetylene with tosyl chloride and a slight excess of anydrous ***Aluminum Chloride*** affords *p*-tolyl (trimethylsilyl)ethynyl sulfone, a precursor to the reactive Michael acceptor ethynyl *p*-tolyl sulfone (eq 38).[21]

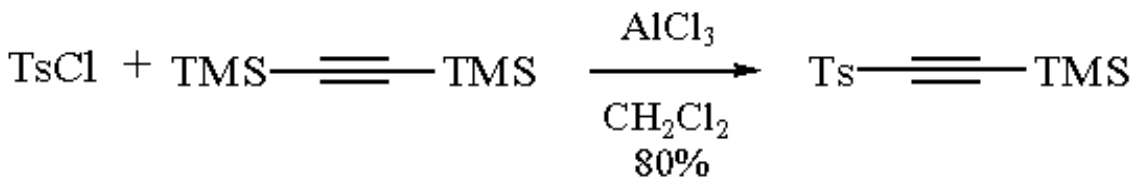

(38)

The dehydration of ureas employing tosyl chloride provides access to substituted carbodiimides, as depicted in eq 39. The urea made from treatment of ethyl isocyanate with *N*,*N*-dimethyl-1,3-propanediamine was treated in situ with 1.1 equiv of tosyl chloride and a large excess of ***Triethylamine*** to afford the corresponding carbodiimide in high yield.[22a,b]

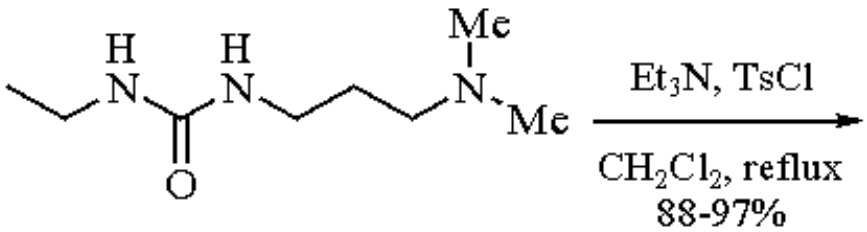

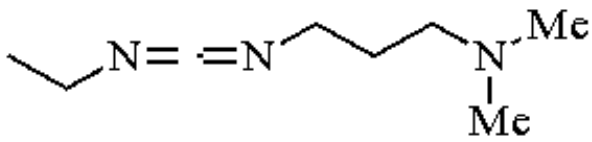

(39)

Various ureas upon treatment with tosyl or benzenesulfonyl chloride in the presence of a phase transfer catalyst, benzyltriethylammonium chloride, results in moderate to excellent yields of carbodiimides (eq 40).[22c] The polymeric carbodiimide in eq 41 offers the advantages of cleaner workup and recyclability if used to prepare aldehydes under Moffatt oxidation conditions.[22d]

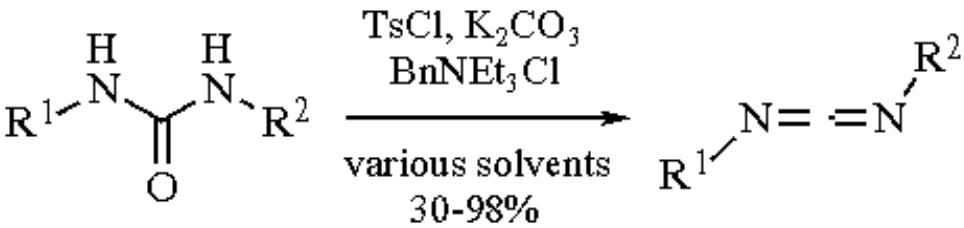

(40)

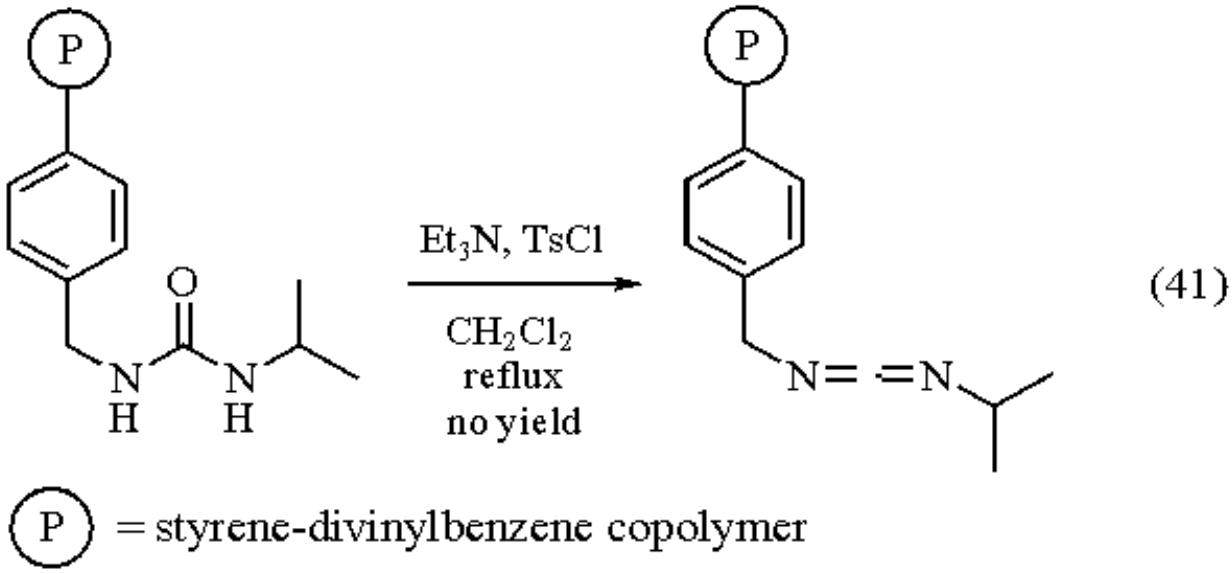

Isocyanides can be made from treatment of formamides with tosyl chloride in pyridine, as illustrated in eq 42.[23a,b] Similarly, nitriles can be synthesized in moderate to good yields by dehydration of primary amides using tosyl chloride in pyridine[23a,b] or quinoline (eq 43).[23c]

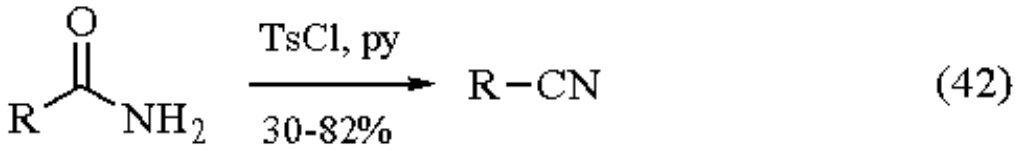

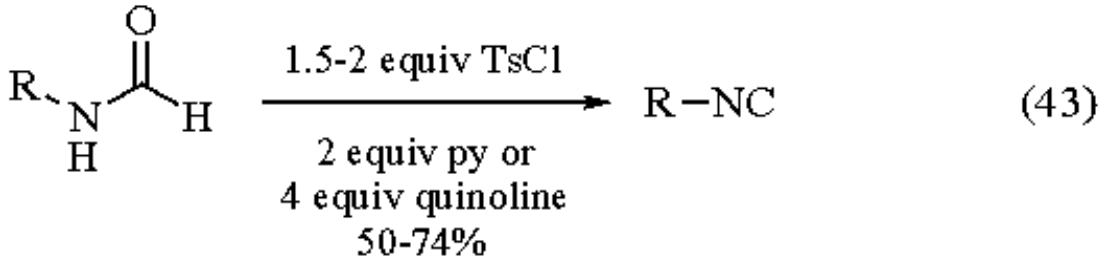

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1. *FF* **1967**, *1*, 1179; *FF* **1972**, *3*, 292; *FF* **1974**, *4*, 510; *FF* **1975**, *5*, 676; *FF* **1977**, *6*, 598; *FF* **1980**, *8*, 489; *FF* **1981**, *9*, 472; *FF* **1984**, *11*, 536; *FF* **1988**, *13*, 313.
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p-Toluenesulfonyl Cyanide

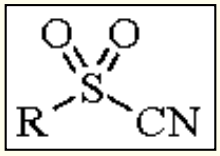

(R = *p*-tolyl)

[19158-51-1] · $C_8H_7NO_2S$ · *p*-Toluenesulfonyl Cyanide · (MW 181.23) (R = methyl)

[24225-08-9] · $C_2H_3NO_2S$ · Methanesulfonyl Cyanide · (MW 105.13) (R = phenyl)

[24224-99-5] · $C_7H_5NO_2S$ · Benzenesulfonyl Cyanide · (MW 167.20)

(nitrile group as dienophile in [4 + 2] cycloadditions; nitrile group as source of $^+$CN and &bdot;CN)

Alternate Name: tosyl cyanide

Physical Data: R = *p*-tolyl, mp 49-50 °C. R = methyl, bp 68-69 °C/15 mmHg. R = phenyl, bp 73 °C/0.1 mmHg.

Form Supplied in: tosyl cyanide is available as an off-white solid.

Preparative Methods: sulfonyl cyanides are best prepared by the reaction of cyanogen chloride with the sodium salt of a sulfinic acid. Procedures for tosyl cyanide[1] and methanesulfonyl cyanide[2] have been published.

Handling, Storage, and Precautions: tosyl cyanide has been reported to undergo occasionally violent decomposition on drying.[1] Methanesulfonyl cyanide can be stored in a well-stoppered bottle, at or below 0 °C, over a prolonged period without loss of purity and can be distilled without decomposition.[2] Use in a fume hood.

Cycloadditions.

In contrast to the situation with most nitriles, the cyano group of sulfonyl cyanides can function as a dienophile in [4 + 2] cycloadditions under relatively mild conditions. Reaction of cyclopentadiene with either tosyl[1] or methanesulfonyl[3] cyanide leads, after hydrolysis of the intermediate formed, to 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) (eq 1), a useful intermediate for the preparation of carbanucleosides.

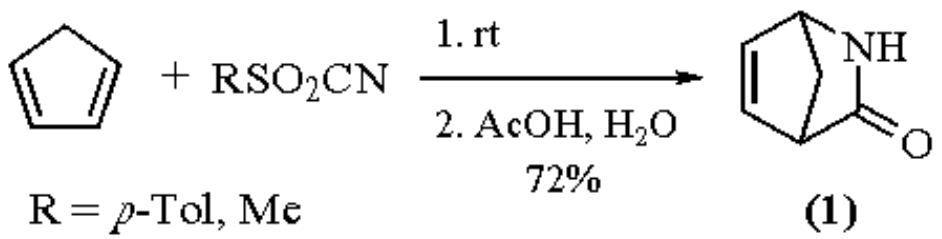

(1)

The reaction of tosyl cyanide with 2-aza-1,3-dienes has been used to prepare pyrimidines (eq 2);[4] ***Trichloroacetonitrile*** showed comparable reactivity in this reaction. The regioselective cycloaddition of tosyl cyanide with 1-alkoxy-1,3-dienes has been used for the preparation of 2-arylsulfonylpyridines.[5]

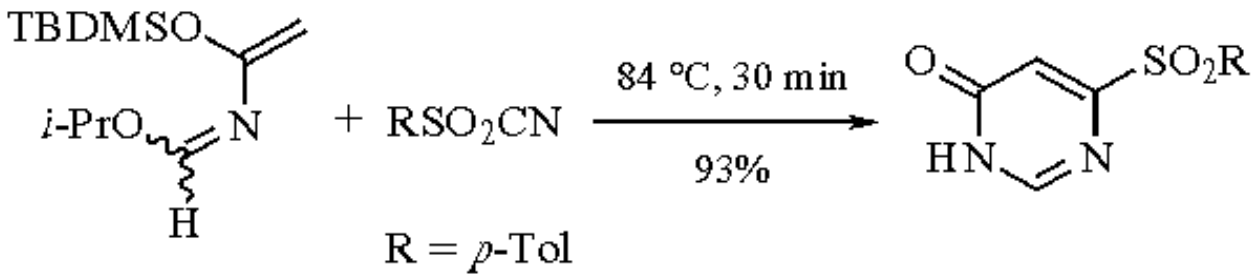

(2)

Cycloadditions with 1,3-dipoles are also known: tosyl cyanide reacts with diazomethane to give 4-tosyl-1,2,3-triazole (68% yield) and with benzonitrile *N*-oxide to give 3-phenyl-5-tosyl-1,2,4-oxadiazole (78% yield).[6]

Reactions with Nucleophiles.

Tosyl cyanide acts as an electrophilic cyanating agent in reactions with many nucleophiles including phenoxides, Grignard reagents, amines, and thiols.[7] Tosyl cyanide proved to be a much more effective reagent for the cyanations of ketone enolates than either ***Cyanogen Bromide*** or phenyl cyanate, although the yields were low with methyl ketones.[8] Reaction of vinylcuprates with tosyl cyanide provided a stereospecific synthesis of 2-alkenenitriles (yields >90%), although cyanogen chloride could also be used.[9] A convenient synthesis of 2-cyanoimidazoles using either tosyl cyanide or phenyl cyanate has been reported (eq 3).[10]

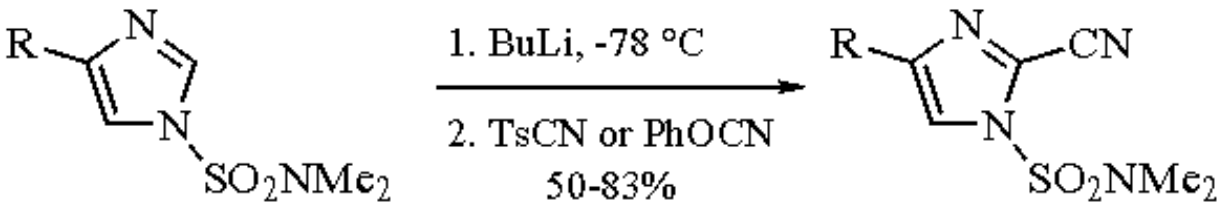

(3)

A magnesium complex of the cyanobisoxazoline (**2**), prepared in high yield (>70%) using $PhSO_2CN$ (eq 4), was useful as a catalyst for the enantioselective conversion of aldehydes to cyanohydrins using ***Cyanotrimethylsilane***.[11]

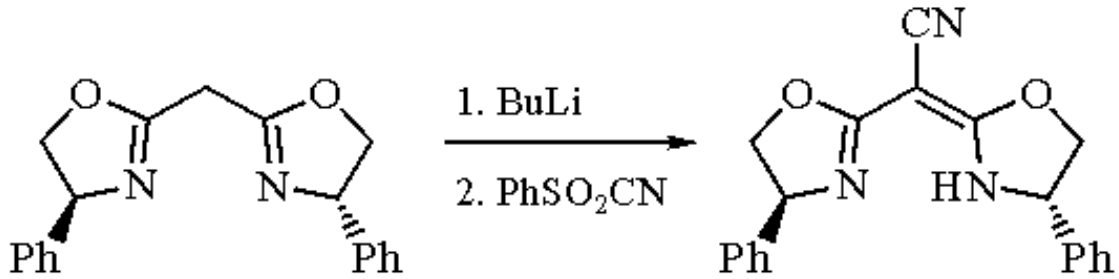

(4)

(2)

Both tosyl and methanesulfonyl cyanide react with alcohols in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** or ***1,4-Diazabicyclo[2.2.2]octane*** at or below rt to give sulfinate esters. A mechanism involving the intermediacy of sulfinyl cyanates was proposed (eq 5).[12]

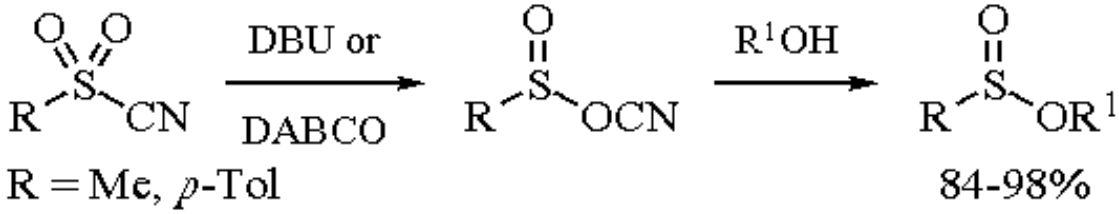

(5)

Isolable adducts can be obtained from the reaction of sulfonyl cyanides with α-nucleophiles. Reaction of tosyl cyanide with phenylhydrazine gave (**3**), which was reacted further with ***Triethyl Orthoformate*** to the triazole (**4**) (eq 6).[13] Similarly, hydroxylamine reacts with arylsulfonyl cyanides to give isolable arylsulfonyl formamidoximes (63-87%), which were converted to 5-amino-3-arylsulfonyl-1,2,4-oxadiazoles.[14]

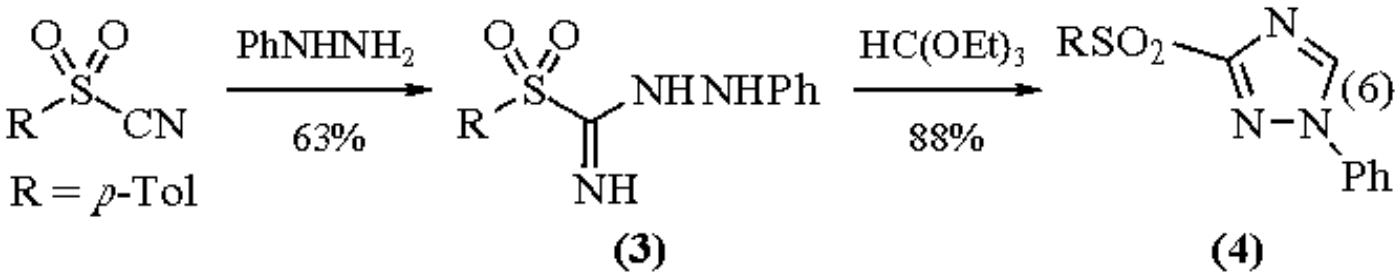

Radical Reactions.

The photochemical (UV irradiation)[15] and thermal (***Azobisisobutyronitrile*** catalyzed)[16] addition of sulfonyl cyanides to alkenes has been described (eq 7). The photochemical reaction was reported not to function with alkynes; however, AIBN-catalyzed thermal addition of tosyl cyanide to 1-hexyne gave (**5**) as a mixture of geometrical isomers (eq 8).[16] The AIBN-catalyzed reaction of sulfonyl cyanides with 1,3-dienes gave products of 1,4-addition.[16]

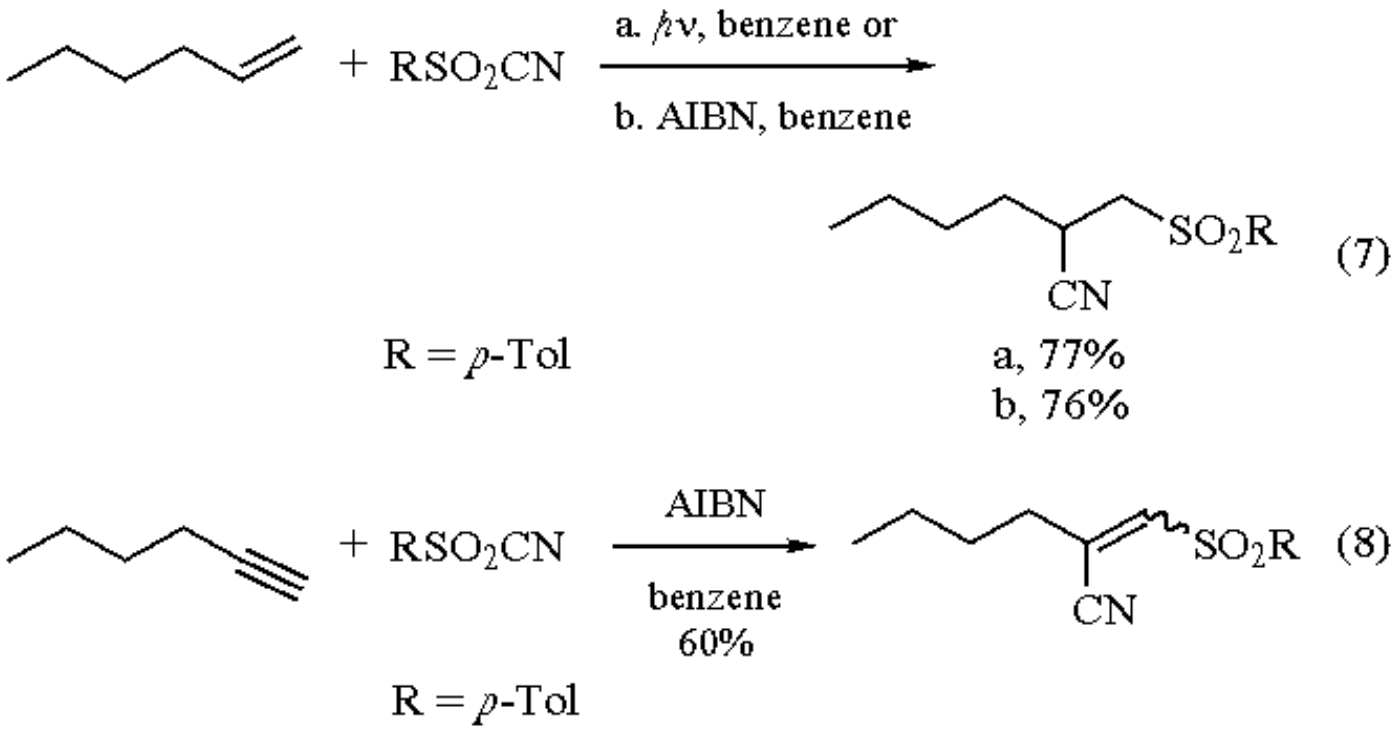

The reaction of sulfonyl cyanides with carbon radicals generated by visible irradiation of (**6**) gave nitriles in good yields (eq 9).[17]

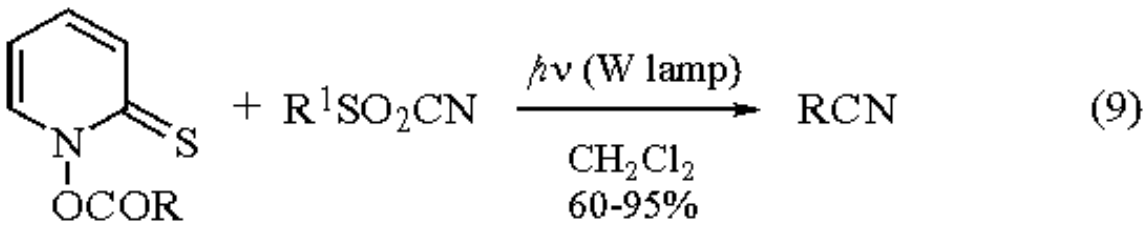

Related Reagents.

Chlorosulfonyl Isocyanate; ***Cyanogen Bromide***; ***Trichloroacetonitrile***.

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p-Toluenesulfonylhydrazide[1]

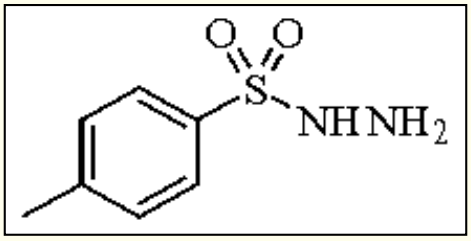

[1576-35-8] · $C_7H_{10}N_2O_2S$ · *p*-Toluenesulfonylhydrazide · (MW 186.26)

(used as a source of diazene;[2] condensed with ketones and aldehydes to form hydrazones that can be converted into reactive intermediates such as diazoalkanes, carbenes, carbenium ions, alkyllithiums, or umpolung synthons;[7] used in 1,3-dipolar cycloaddition reactions to form N-heterocycles; used to make propargyl aldehydes and ketones via the Eschenmoser fragmentation;[44] ketone hydrazones are deoxygenated with mild reagents in a modified Wolff-Kishner reduction[50])

Alternate Name: tosyl hydrazide.

Physical Data: mp 108-110 °C (dec).

Solubility: sol virtually all organic solvents except hydrocarbons; insol water.

Form Supplied in: solid; widely available.

Handling, Storage, and Precautions: is thermally labile at elevated temperatures, but can be stored at or below room temperature. It is a toxic, potentially flammable solid which should be handled with gloves under inert atmosphere.

Alkene Reduction/Allylic Diazene Rearrangement.

p-Toluenesulfonylhydrazide may be thermolyzed in solution to generate diazene (diimide) for alkene reduction.[2] It is the least reactive member of the common arenesulfonylhydrazides, with ***Mesitylenesulfonylhydrazide*** being 24 times more reactive and ***2,4,6-Triisopropylbenzenesulfonylhydrazide*** being 380 times more reactive under base-catalyzed decomposition conditions. The latter has largely supplanted tosyl hydrazide as a source of diazene because of the low-temperature convenience.[3,4]

Sigmatropic rearrangement of allylic and propargylic diazene intermediates is well established and is a reliable means of alkene synthesis.[5] Several options are available to generate these intermediates, such as hydride reduction of tosylhydrazones (refer to eqs 14 and 15), elimination of *p*-toluenesulfinic acid from an allylic hydrazine (eqs 1 and 2), Wolff-Kishner reduction of an α,β-unsaturated ketone, or oxidation of alkylhydrazines.[5]

p-Tolyl sulfones have been prepared in excellent yield by halide displacement with toluenesulfinate ion.[6]

Nucleophilic Addition to Hydrazones.

The bulk of tosyl hydrazide's synthetic utility comes from its condensation products with ketones and aldehydes.[7,8] Synthetically useful addition reactions typically only succeed with nonenolizable ketone hydrazones.[9,10] The treatment of enolizable ketone tosyl hydrazones with alkyllithium nucleophiles invariably results in the formation of a dianion rather than addition to the azomethine bond. In contrast, aldehyde tosylhydrazones do not form dianions but instead undergo addition with both alkyllithiums and cuprate reagents to give reductive alkylation products.[11,12] A versatile extension of this methodology involves either vinyllithium addition to *N*-*t*-butyldimethylsilyl tosylhydrazones or the complementary 1,2-addition of alkyllithium to α,β-unsaturated *N*-*t*-butyldimethylsilyl tosylhydrazones. Reductive addition in either case produces an *N*-TBDMS allylic diazene intermediate which undergoes protodesilylation and subsequent 1,5-sigmatropic rearrangement. (*E*)-Alkenes are prepared with high stereoselectivity due to $A_{1,3}$-strain in the transition state (eqs 1 and 2), and epimerization of adjacent stereocenters is not observed.[5]

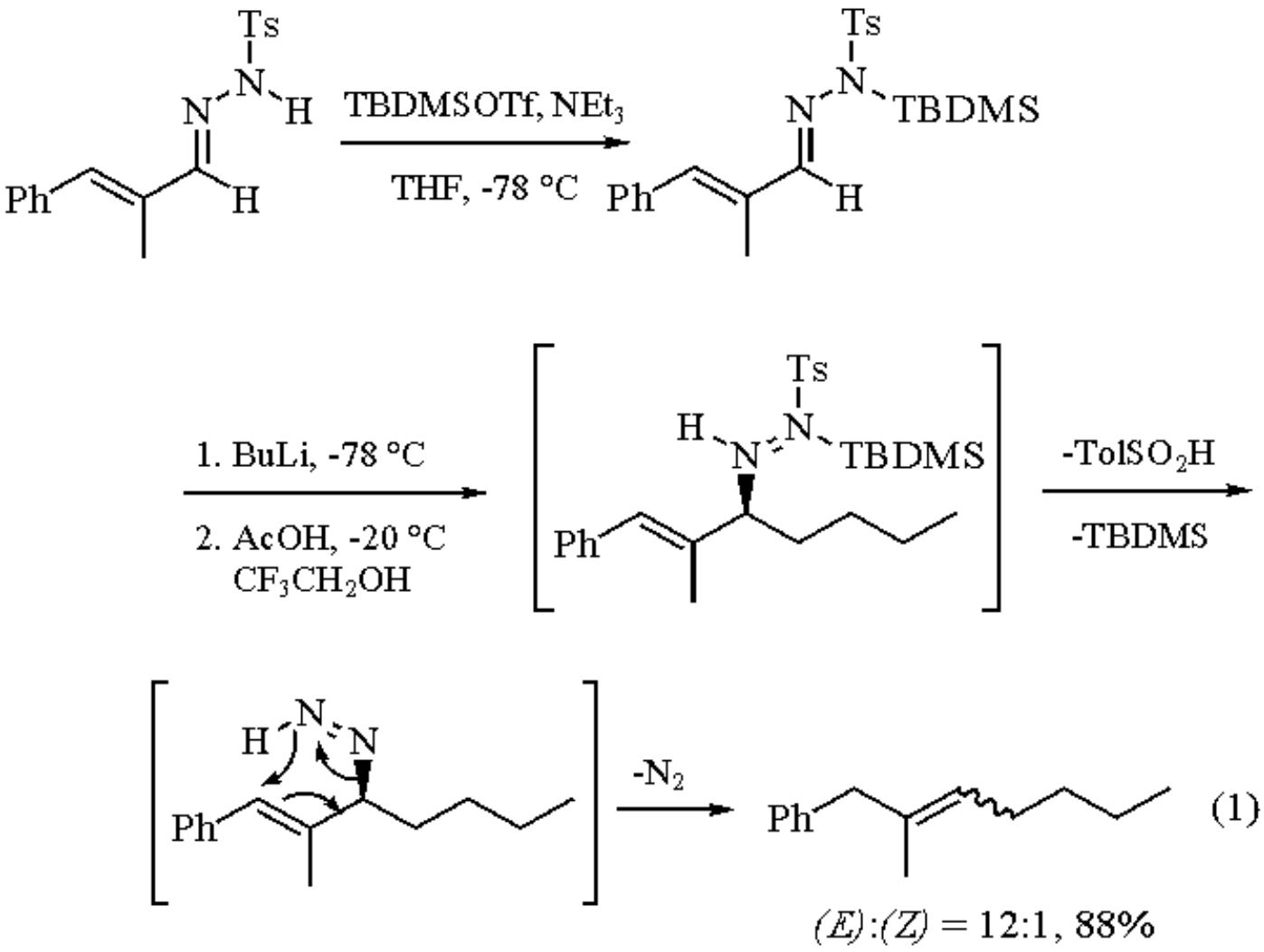

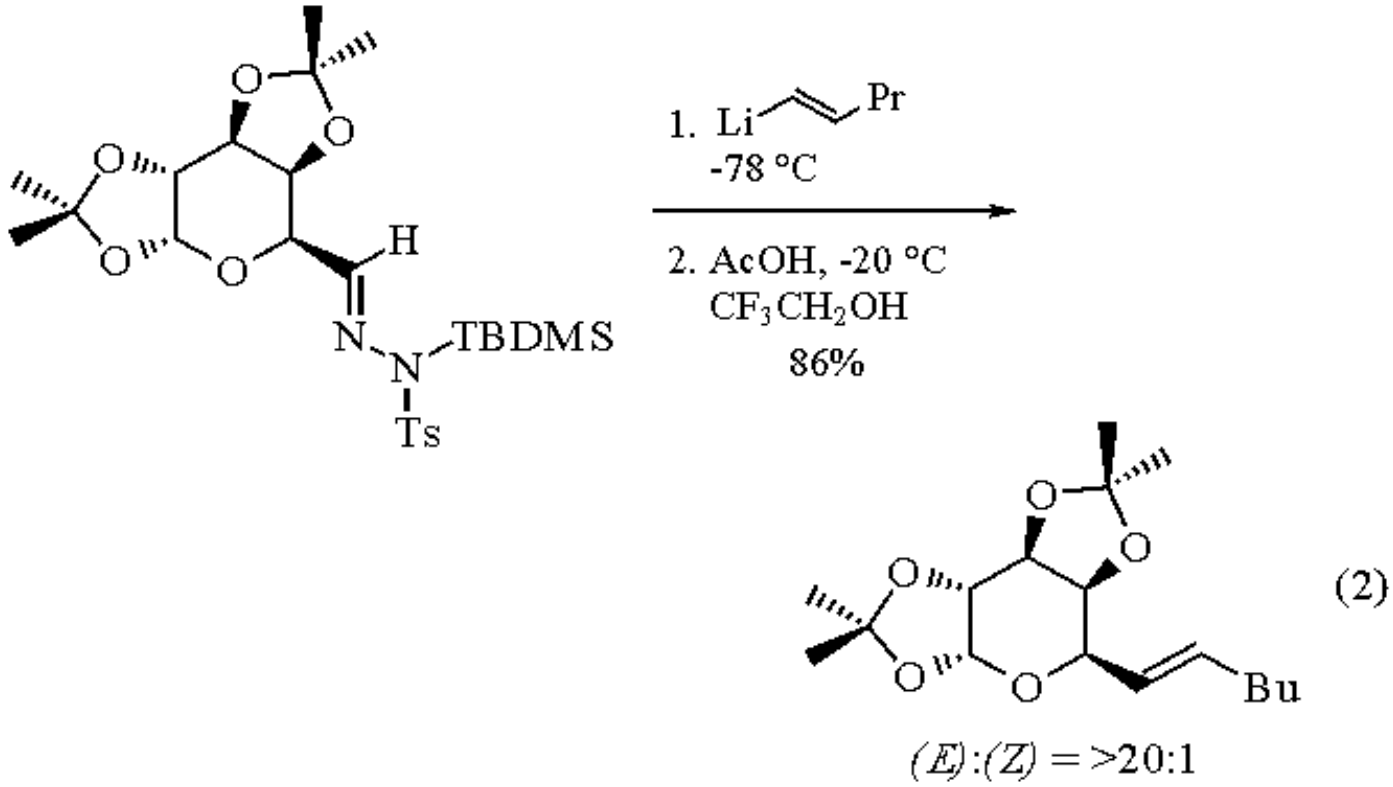

Other nucleophiles, such as cyanide ion, similarly add to aldehyde and ketone tosylhydrazones, which constitutes a useful one-carbon homologation.[13] ***Diphenylphosphine Oxide*** or dimethyl phosphite addition followed by decomposition of the intermediate with base or ***Sodium Borohydride*** gives alkyldiphenylphosphine oxides and *s*-alkanephosphonates, respectively.[14]

Formation of tosylhydrazones from α-halo ketones, followed by vinylogous halide elimination using mild base, gives *p*-

toluenesulfonylazoalkenes, which undergo S_N2'-type addition of strong nucleophiles (eq 3).[15] This sequence constitutes a synthetically useful carbonyl umpolung synthon for introducing nucleophiles in the α-position of ketones. Examples of simple alkyllithium and 1,3-diketone enolate nucleophilic addition are also known.[16]

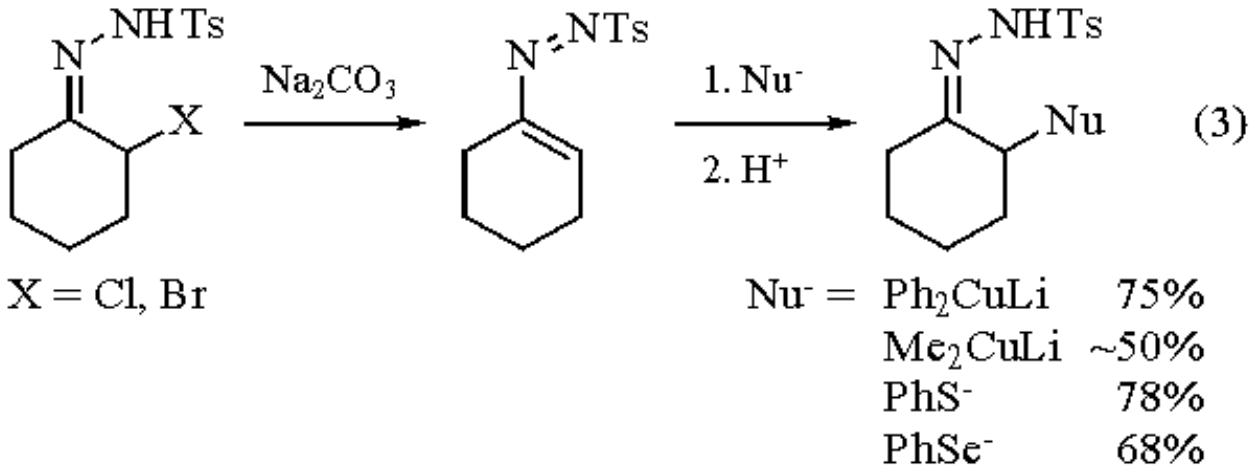

In another example, thermolysis of the tosylhydrazone of an α-hydroxy steroid in ethylene glycol without base resulted in reductive dehydroxylation, presumably through rearrangement of an intermediate epoxydiazene.[17]

Electrophilic Addition to Hydrazone Anions.

α-Deprotonation of tosylhydrazones with 2 equiv of strong base give highly nucleophilic azaenolates that react with a variety of electrophiles.[18] Trisyl hydrazones have also received considerable attention for this transformation[19] (see ***2,4,6-Triisopropylbenzenesulfonylhydrazide***. However, some cyclohexanones, such as 4-*t*-butylcyclohexanone, require tosyl hydrazones for successful alkylation since the corresponding trisyl hydrazones undergo significant Shapiro elimination (see below) even at -78 °C.[18c]

The regioselectivity of deprotonation for unsymmetrical tosylhydrazones often is high, and is dictated by three factors. In many cases the configuration of the C=N double bond plays an important role since the sulfonamide anion induces *syn* deprotonation in ethereal solvents.[20] Thus the ratio of α vs. α´ anions reflects the C=N isomeric ratio, which is typically 85:15 (*E*):(*Z*) or greater in unsymmetrical ketones.[21,22] The *syn*-directing effect is inoperative in TMEDA solvent, allowing excellent regioselectivity of deprotonation, independent of the hydrazone geometrical isomer population.[23] Electron-stabilizing groups in the α-position direct deprotonation, and finally, the acidity of α-hydrogens follows the generalization that methyl > methylene > methine with only a few exceptions.

Bamford-Stevens and Shapiro Reactions.

Tosylhydrazones may be converted into a variety of reactive intermediates depending upon the specific reaction conditions employed. The protic Bamford-Stevens reaction conditions (ethylene glycol; NaOR; heat) give diazoalkane intermediates that, on occasion, can be isolated but more often undergo in situ protonation followed by loss of dinitrogen to give cationic intermediates. These intermediates tend to give the more substituted double bond, but predicting regioselectivity is dubious, and cationic rearrangements are common (eq 4).[24]

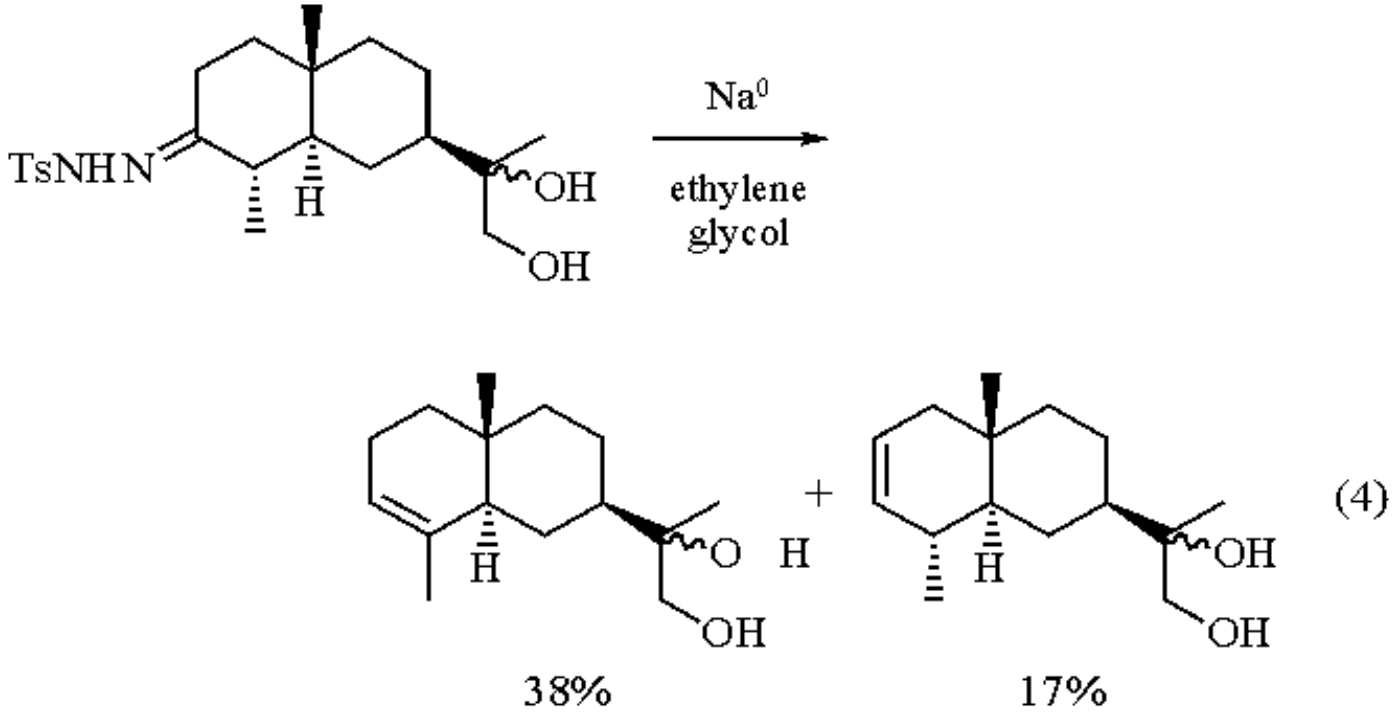

Triisopropylbenzenesulfonyl and mesitylenesulfonyl hydrazones are far superior to tosyl hydrazones if isolation of the diazo compound is desired, primarily because much lower temperatures are required to induce the sulfinate elimination.[25]

The aprotic Bamford-Stevens reaction involves deprotonation of the acidic sulfonamide hydrogen in an aprotic solvent (e.g. glyme) to form a salt (Li, Na, and K are common) which is pyrolyzed or photolyzed to generate carbenes (eq 5).[26]

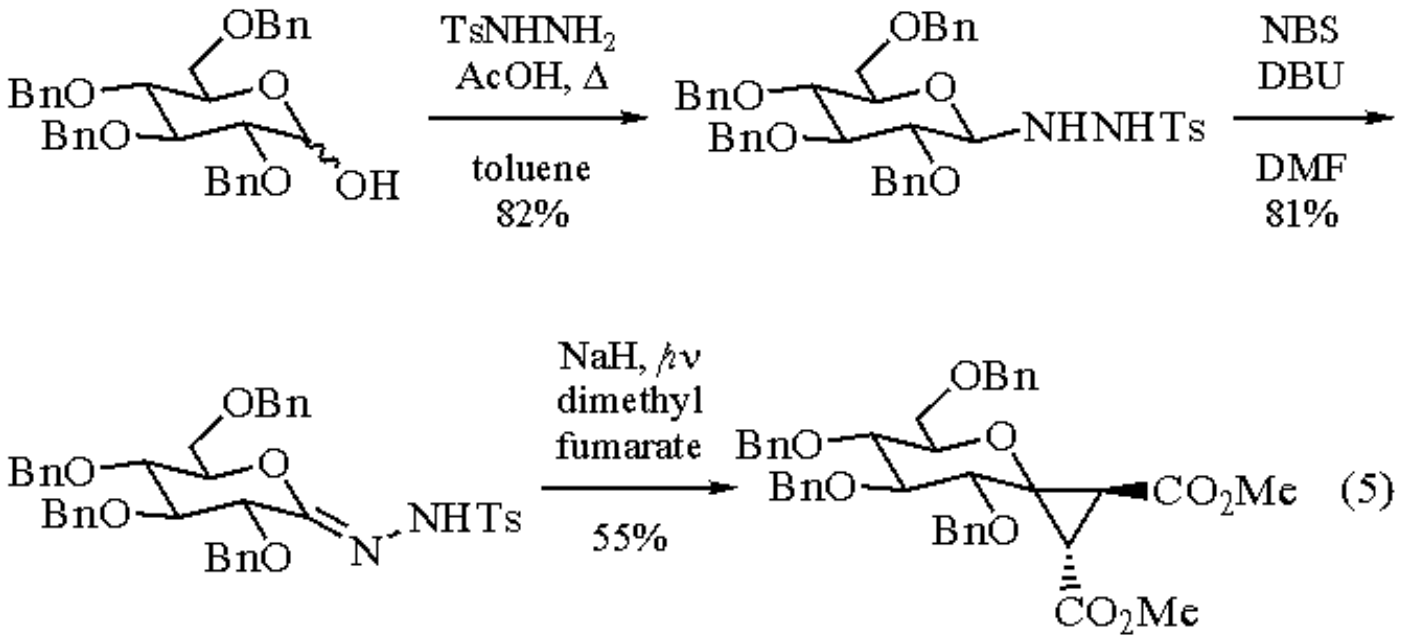

Five- and six-membered ring ketones usually undergo 1,2-hydride migration to preferentially give the more substituted alkene.[27,12,4] Regioselectivity is usually modest but high selectivity is found in some instances, such as the synthesis of furanose glycals,[28] Δ^2 unsaturation in *trans*-A/B steroids, and Δ^3 unsaturation in *cis*-A/B steroids.[29] Nevertheless, examples of competitive cyclopropanation[30] and C-H bond insertion in medium-sized rings[31] abound.

The Shapiro reaction is extremely useful for the regioselective conversion of ketones into alkenes.[1] The anions of tosylhydrazones eliminate *p*-toluenesulfinate and dinitrogen between 0 °C and room temperature over the course of several hours to give the corresponding least-substituted alkene. Acyclic azaenolates have a strong preference for E_{CC} geometry and react equally well to yield (*Z*)-alkenes stereoselectively unless α-branching causes too much allylic strain in the transition state.[1a,3,8,32] This method has been used extensively in the synthesis of natural products such as alkaloids,[33] prostaglandins,[34] and especially terpenes (eq 6).[24a,35]

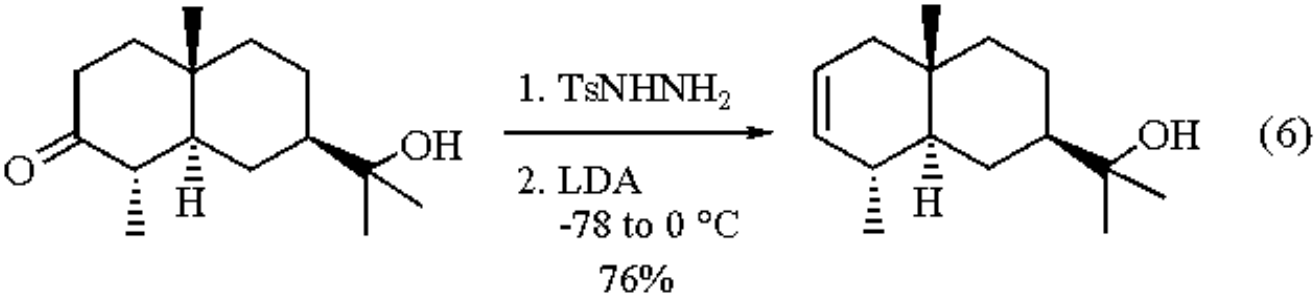

The intermediate in this reaction is an alkenyllithium, which can be trapped under certain conditions with electrophiles,[21,36] providing general access to allylic alcohols, α,β-unsaturated aldehydes and acids,[37] vinyl halides, vinyl sulfides,[38] and vinylsilanes.[39] Use of trisylhydrazones typically gives superior results because the intermediate alkenyllithium is formed at lower temperature and does not require excess base to circumvent quenching of the intermediate by orthometalation.[40,21] Tandem one-pot electrophilic addition/Shapiro elimination sequences reliably provide alkenes with highly variable substitution patterns (eq 7), including tetrasubstitution.[18c]

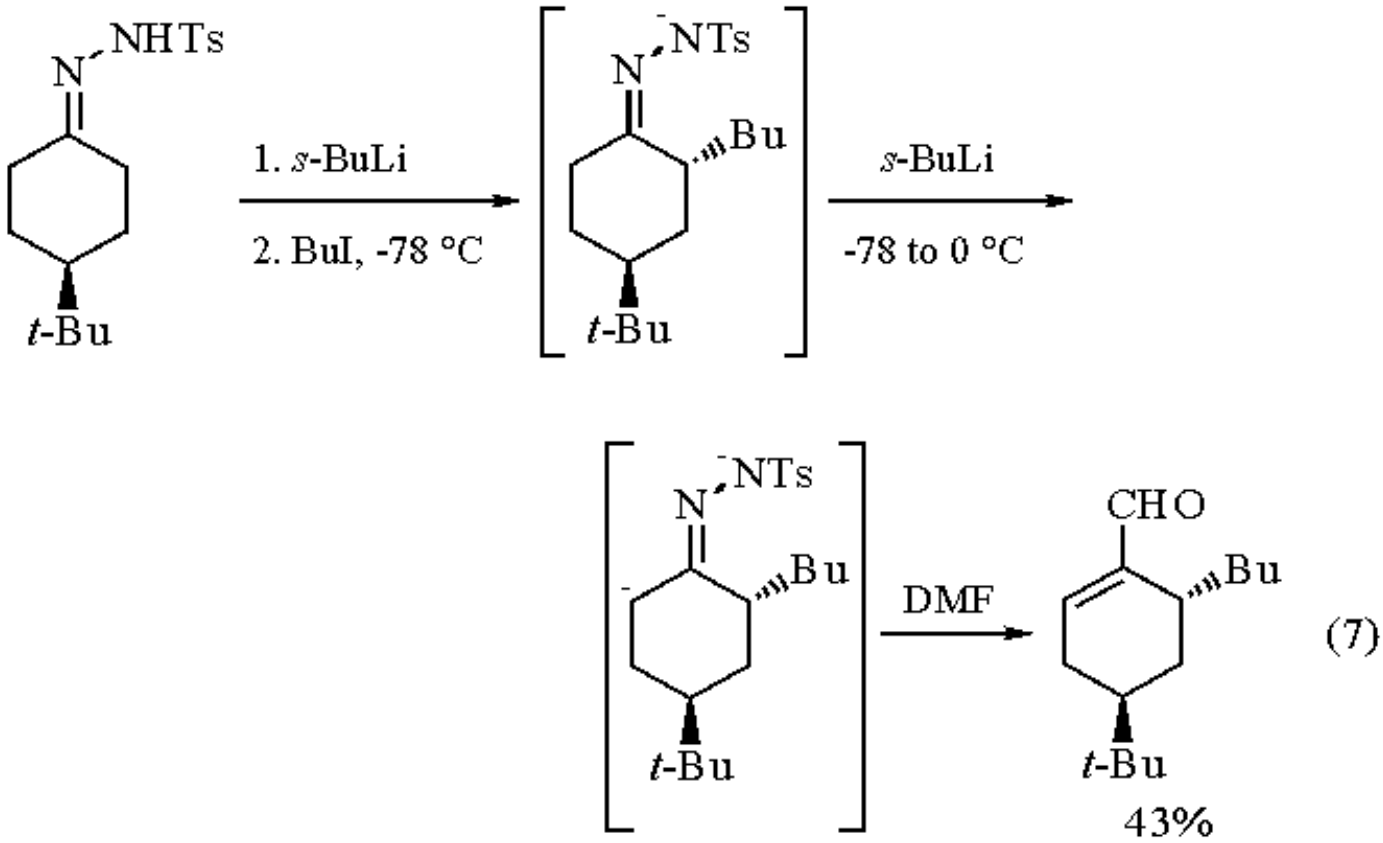

Tosylhydrazones of α,β-unsaturated ketones likewise participate in the Shapiro elimination to give 2-lithioalkadiene intermediates which may be protonated to give the corresponding dienes, or be trapped with electrophiles.[41] Regioselectivity cannot be predicted with certainty, but in general an α´-proton is removed (giving the cross-conjugated azaenolate) in preference to a γ-proton, once again analogous to the kinetic deprotonation of α,β-unsaturated ketones.[42] Tosylhydrazones of β-keto esters are deprotonated to give trianions that decompose to give β,γ-unsaturated esters in fair yield.[22,8] Cyclic 1,3-diketone monotosylhydrazones analogously give enones when treated with ***Potassium Carbonate***.[43]

Eschenmoser Fragmentation and Related Eliminations.

Preparation of macrocyclic cycloalkynones by fragmentation of α,β-epoxy ketones is also possible with this reagent (eq 8).[44]

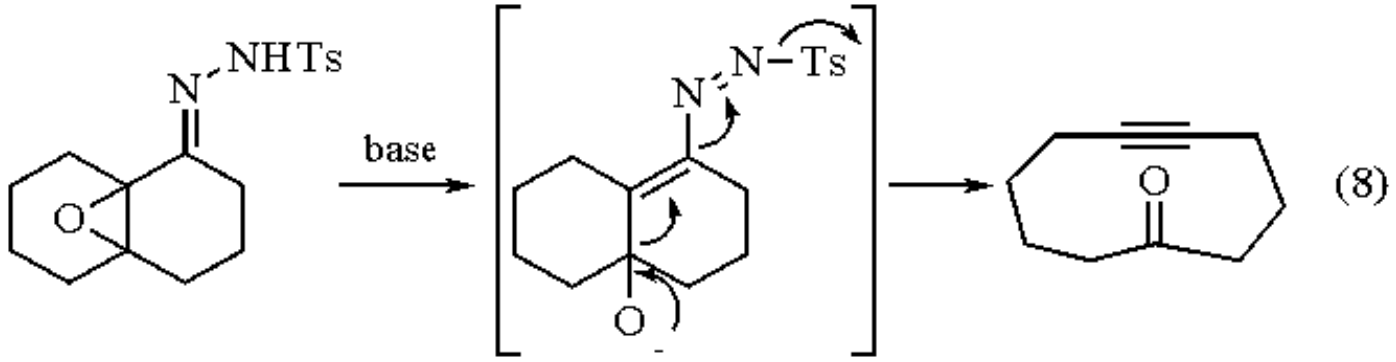

These fragmentation reaction conditions are too harsh to give the corresponding propargylic aldehydes in good yield.[45] More recently, other reagents have proved more efficacious for this transformation (see ***2,4-Dinitrobenzenesulfonylhydrazide*** and ***Mesitylenesulfonylhydrazide***).

Arenesulfonylhydrazones with leaving groups in the α-position proceed through well-documented intermediates or related fragmentation reactions. For instance, treatment of α-bromotosylhydrazones with mild base triggers vinylogous halide elimination to give tosylazoalkenes (eq 9, and also refer to eq 3 and related text). Addition of strong base to these compounds provides 2-lithioalkadienes[46] and is a complementary route to the enone method described above.

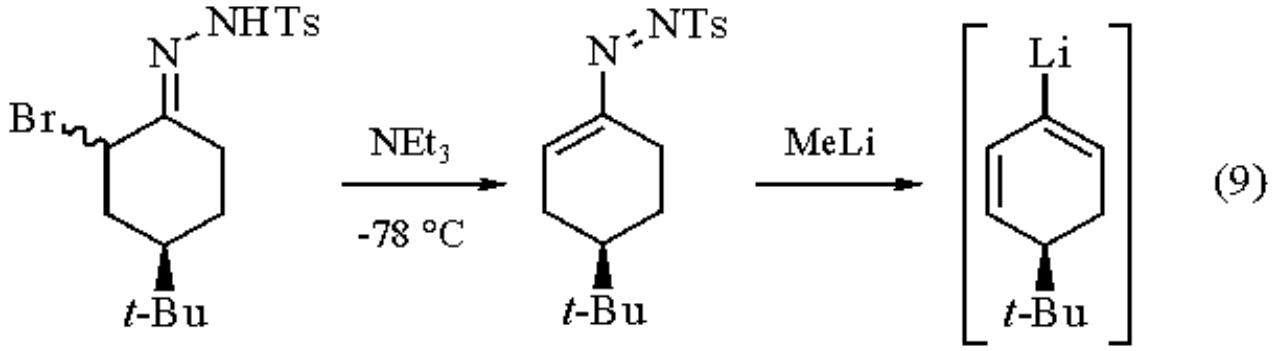

In acyclic cases the same intermediates seem to eliminate differently to give alkynes (eq 10).[47] Eq 11 illustrates a Shapiro elimination in which the resultant vinyllithium intermediate fragments by displacing alkoxide to give the unanticipated hydroxyalkyne in high yield.[48] If deprotonation occurs on the α-carbon not occupied by the leaving group, the alkenyllithium intermediate fragments to a hydroxyallene in fair yield (eq 12).[49]

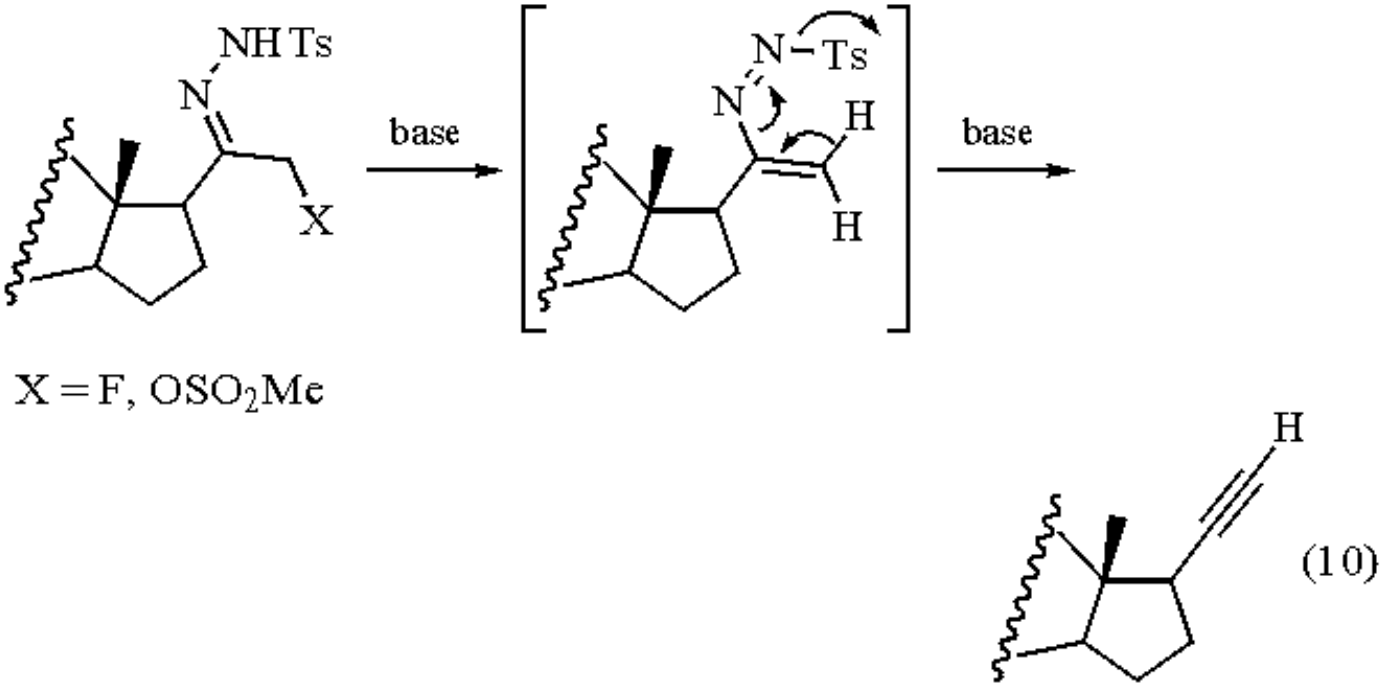

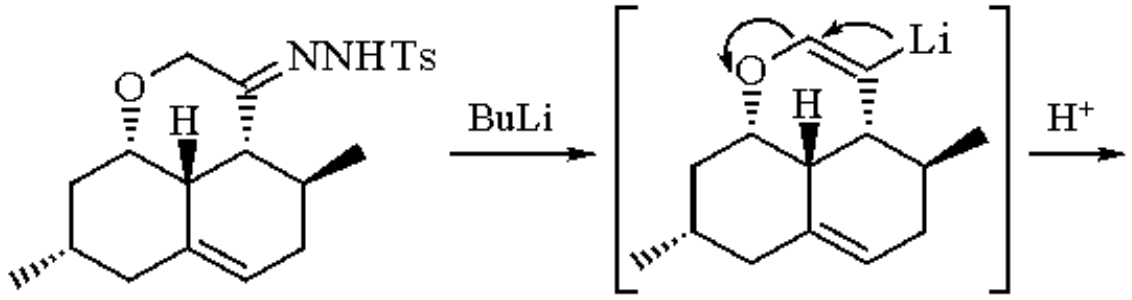

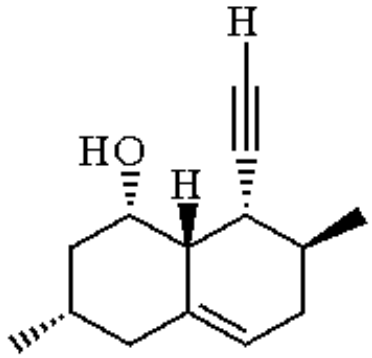

(11)

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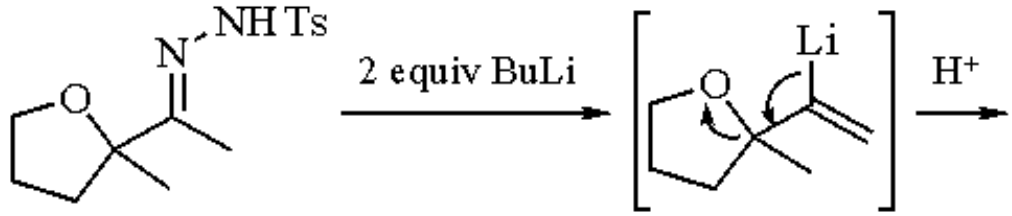

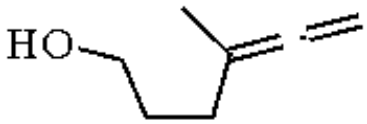

(12)

Reductions of Tosylhydrazones.[50]

Reduction of aldehyde and ketone tosylhydrazones in a Wolff-Kishner-type reaction was first described using ***Lithium Aluminum Hydride*** which was effective in several cases, but proved to be basic enough to produce Shapiro elimination side products.[51,52] More recently, milder reductions such as ***Sodium Borohydride***, ***Sodium Trimethoxyborohydride***, ***Sodium Triacetoxyborohydride***, ***Sodium Cyanoborohydride***, and ***Catecholborane*** have greatly expanded the scope and utility of these reductions well beyond the classic Wolff-Kishner and Clemmenson reductions, to become one of the mildest deoxygenation procedures known.

$NaBH_4$ is an effective tosylhydrazone reducing agent when used in methanolic dioxane ($NaBH(OMe)_3$ is most likely the active reducing species), acetic acid ($NaBH(OAc)_3$ is most likely the active reducing species), and less commonly in isopropanol and DMF (eq 13).[53]

Selective formation of hydrazones (using a stoichiometric amount of tosyl hydrazide) in the presence of relatively hindered or deactivated ketones is easily achieved in high yield and, in the case of eq 13, the ketones are not reduced under the reaction conditions.[54] Reductions occur between room temperature and 70 °C for most tosylhydrazones without epimerization of α-stereocenters.[55] The reaction proceeds by reductive elimination of *p*-toluenesulfinate and extrusion of dinitrogen to form an alkyllithium, which is quenched by solvent. Use of $NaBD_4$ in AcOH or AcOD allows for mono- and dideuterio incorporation.[53c] Catecholborane is an equally effective reducing agent.[56]

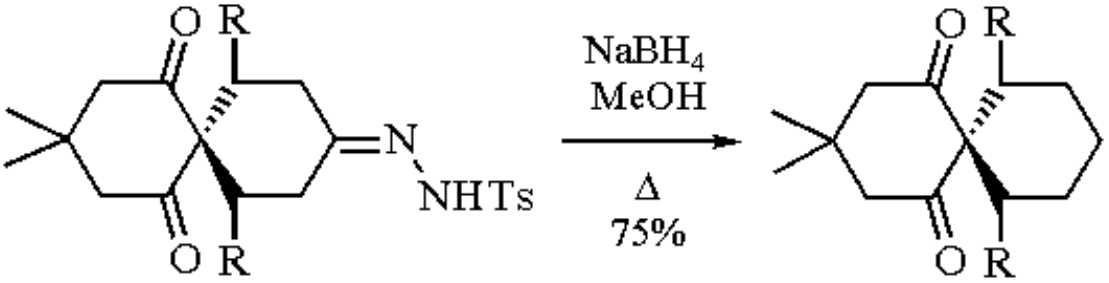

(13)

$NaBH_3CN$ has proved particularly serviceable for reducing tosylhydrazones that can be generated in situ, since iminium ions reduce much faster than carbonyl groups with this reagent.[57] The reactions are usually carried out in acidic 1:1 DMF--sulfolane at 100 °C, but even milder conditions have been used,[50b,58] providing products in fair to good yield.[59]

Reduction of α,β-unsaturated tosylhydrazones with the boron reagents gives 1,2-hydride delivery followed by extrusion of toluenesulfinic acid to give an allylic diazene. Note that this process gives a similar intermediate to that obtained by alkyl- and alkenyllithium addition to *N*-TBDMS tosylhydrazones (eqs 1 and 2). Thus, reduction of these systems gives allylic migration of the double bond independent of thermodynamic preference, and is an excellent means of deconjugating double bonds with an intervening methylene (eqs 14 and 15).[60]

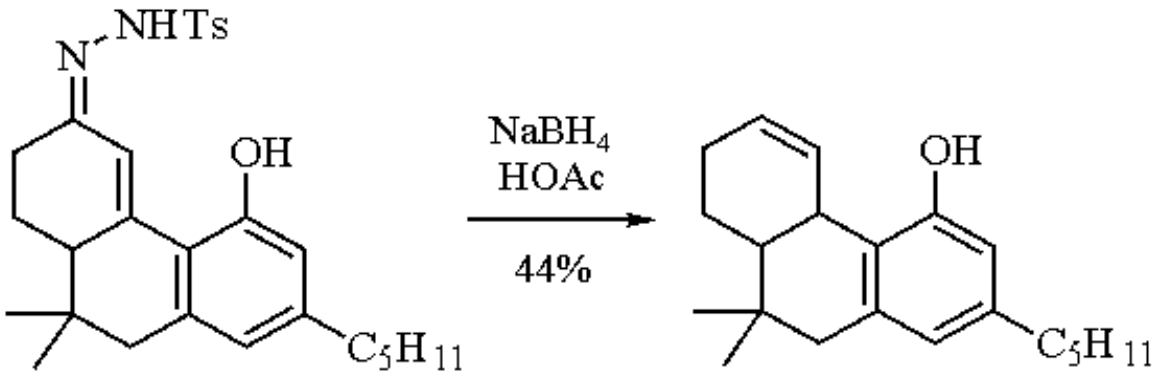

(14)

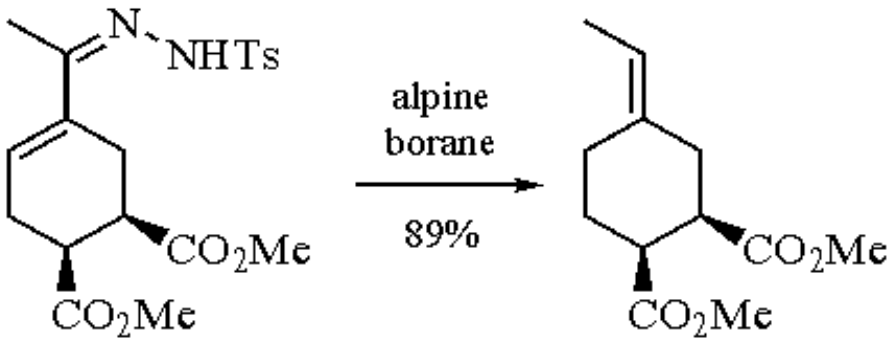

(15)

The $NaBH_4$/MeOH conditions do not give good yields in this process due to predominating Bamford-Stevens-type reactions.[61] $NaBH_4$ and $NaBH_3CN$ work equally well in AcOH but catecholborane is the best reagent for this transformation because 1,4-addition of hydride is minimal. Catecholborane adds axially to bridgehead enones and undergoes 1,5-sigmatropic reduction on the convex face to give *cis*-decalin systems with good selectivity.[62]

Miscellaneous.

Intramolecular 1,3-dipolar cycloadditions of intermediate diazoalkanes derived from tosylhydrazones have been conducted under ***Boron Trifluoride Etherate*** or aprotic Bamford-Stevens reaction conditions to give pyrazolines and related compounds.[63,30a] [4 + 2] Cycloadditions of α,β-unsaturated aldehyde tosylhydrazones gave low yields of dihydropyridines.[64] 1,2-Enone transpositions have been described using vinylsilanes and vinyl sulfides.[65] Tosylhydrazones may also be converted into alkyl hydroperoxides via a two-step procedure.[66]

Related Reagents.

2,4-Dinitrobenzenesulfonylhydrazide; ***Mesitylenesulfonylhydrazide***; ***2,4,6-Triisopropylbenzenesulfonylhydrazide***.

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[*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane

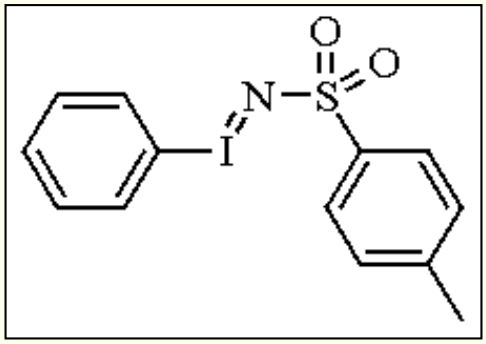

[55962-05-5] · $C_{13}H_{12}INO_2S$ · [*N*-(*p*-Toluenesulfonyl)imino]phenyliodinane · (MW 373.23)

(nitrogen atom source; reacts with heteroatom lone pairs to form ylides; capable of C-H bond insertion or alkene aziridination in the presence of transition metal catalysts)

Physical Data: mp 102-104 °C (dec).[1]

Solubility: v sl sol nonpolar solvents; sol DMSO (decomposes slowly); reacts with THF, MeOH.

Form Supplied in: light yellow solid, commercially available.

Analysis of Reagent Purity: ^{1}H NMR spectra can be obtained in DMSO-d_6, although the reagent slowly reacts with the solvent. Other assays include iodometric analysis[1] and reaction with triphenylphosphine to form the phosphinimine.[2]

Preparative Methods: prepared by the reaction of $PhI(OAc)_2$ with $TsNH_2$ and KOH in MeOH, from which the product precipitates upon addition of water (eq 1).[1] Another preparation employs the reaction of $TsNH_2$ with $PhI(OMe)_2$ in MeOH or in CH_2Cl_2 (eq 2).[2]

$$PhI(OAc)_2 \xrightarrow[\text{MeOH}]{\text{KOH, TsNH}_2} \text{PhI=NTs} \qquad (1)$$

$$\text{PhIO} \xrightarrow[\text{3 mol. sieves}]{\text{MeOH}} \text{PhI(OMe)}_2 \xrightarrow[\text{MeOH or CH}_2\text{Cl}_2]{\text{TsNH}_2} \text{PhI=NTs} \qquad (2)$$

Handling, Storage, and Precautions: store at -20 °C; should be used within 6 months. The reagent can be weighed out in air. No known toxicity. Use in a fume hood.

Nitrogen Atom Transfer to Heteroatoms.

PhI=NTs reacts with heteroatom lone pairs to generate ylides.[1] Reaction with ***Triphenylphosphine*** at 100 °C affords 69% of the phosphinimine (**1**) (eq 3). Likewise, PhI=NTs reacts with ***Thioanisole*** to generate the iminosulfurane (**2**) in 49% yield (eq 4) and with ***Dimethyl Sulfoxide*** to quantitatively produce the sulfoximine (**3**) (eq 5).

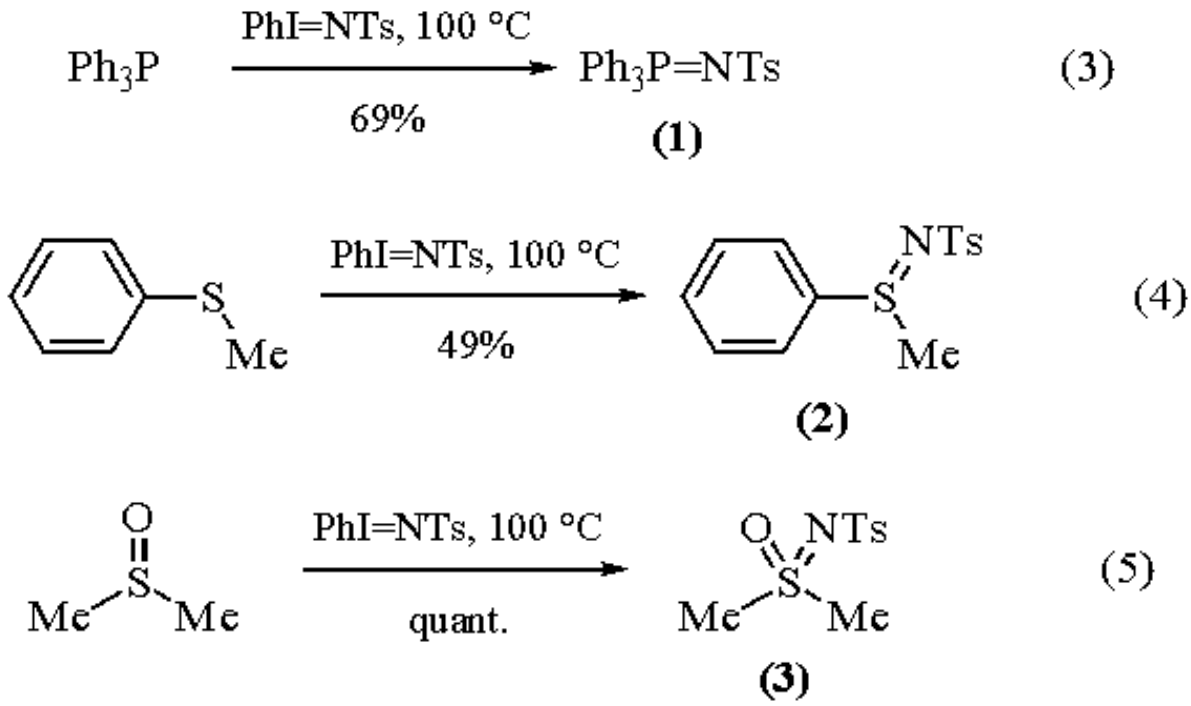

Amination of Alkanes and Alkenes.

PhI=NTs can be employed as a nitrogen source in the transition metal-catalyzed amination of alkanes and the allylic amination of alkenes. Manganese porphyrin complexes catalyze the amination of cyclohexane to generate *N*-tosylcyclohexylamine in 15% yield, while adamantane is aminated in 56% yield (eqs 6 and 7).[3] Manganese porphyrins also catalyze the amination of alkenes to generate allylic amine derivatives.[4] In this manner, *N*-tosyl-2-cyclohexeneamine was synthesized in 70% yield based on oxidant (eq 8). The amination of open-chain alkenes is hampered by attenuated reactivity and poor regioselectivity.

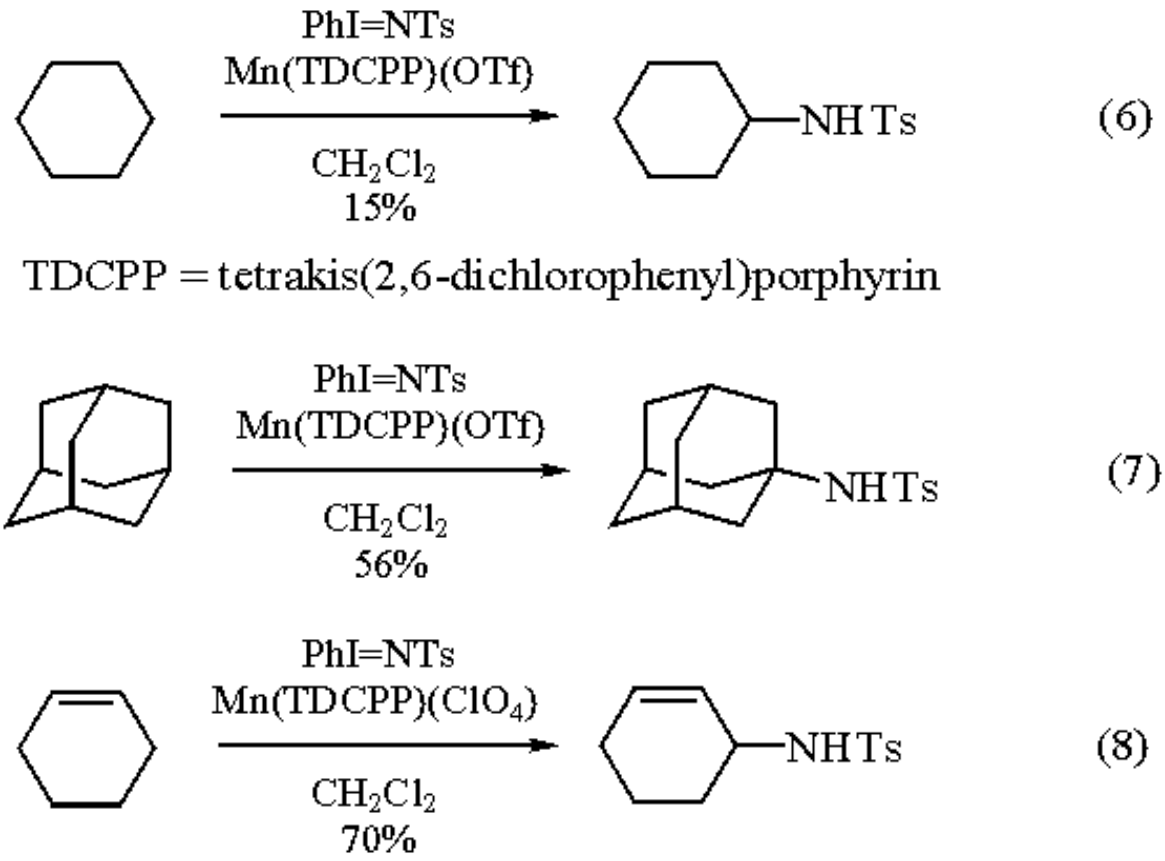

A complex generated in situ by the addition of ***Iron(II) Chloride*** to ***Chloramine-T*** effects similar aminations of hydrocarbons.[5] When adamantane is introduced to a solution of this complex, *N*-tosyladamantan-1-amine is isolated in 63% yield (eq 9). Extension of the reaction to other substrates is complicated by the generation of chlorine-containing products.

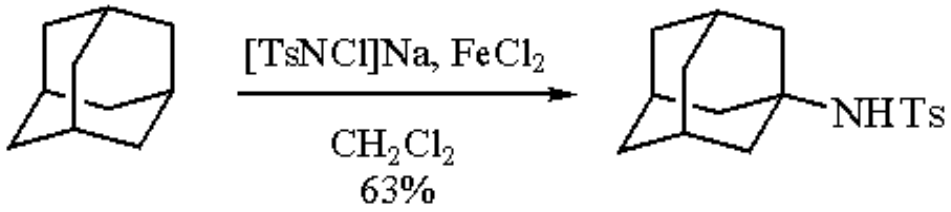

(9)

The insertion of nitrenes, generated via the photolysis or thermolysis of azides, into C-H bonds is well known, although the yields are generally poor.[6,7] However, when ***Ethyl Azidoformate*** is thermolyzed in the presence of 1-chlorocyclohexene, the allylic insertion product is formed in 49% yield (eq 10).[8] In this case it is not clear if the product is formed through direct insertion or by the ring opening of an aziridine intermediate.

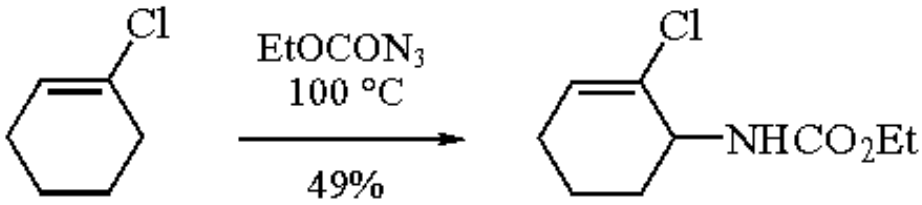

(10)

Aziridination of Alkenes.

Iron- and manganese-porphyrin complexes catalyze the reaction of PhI=NTs with alkenes to form the corresponding *N*-tosylaziridines.[9] Mn(TPP)Cl is generally a better catalyst than the analogous iron complex, affording 80% of the aziridine from the reaction with styrene (eq 11). Good yields are also obtained in the manganese-catalyzed reactions with 1,1- and 1,2-diphenylethylenes.[10] Yields of aziridines derived from aliphatic alkenes remain low and are complicated by the formation of allylic amines.

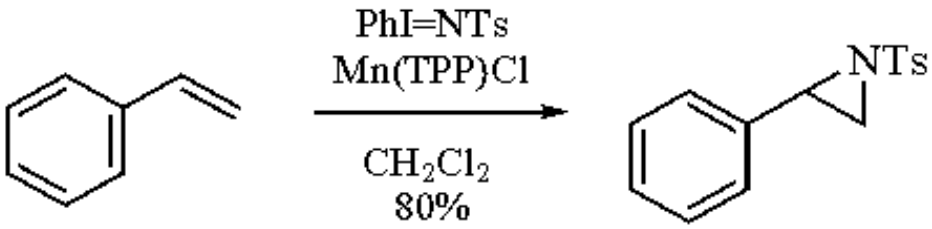

(11)

TPP = tetraphenylporphyrin

Copper-based complexes have been found to be excellent catalysts for the aziridination of alkenes employing PhI=NTs as the nitrene precursor (eq 12).[11] Both Cu^{I} and Cu^{II} efficiently catalyze the reaction, and the best results are usually obtained with the cationic complexes ***Tetrakis(acetonitrile)copper(I) Perchlorate*** and ***Copper(II) Trifluoromethanesulfonate***. Good yields are obtained with a variety of substrates, including aliphatic alkenes and enolsilanes (eq 13), the latter delivering α-amino ketones upon hydrolysis of the intervening silyloxyaziridine.

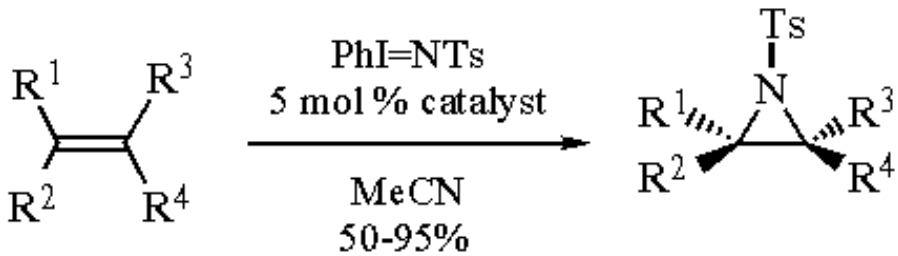

(12)

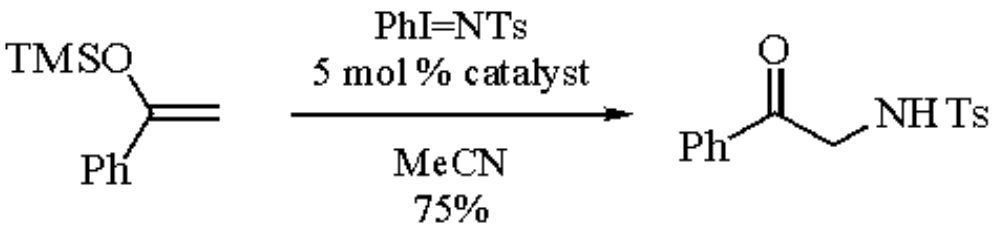

(13)

Other nitrene precursors have been employed in the aziridination of alkenes. Azides have been shown to form aziridines when photolyzed or thermolyzed in the presence of alkenes, though these reactions usually exhibit low yields.[12,13] However, the possibility of a transition metal-catalyzed process remains. In 1968, it was reported that heating ***Benzenesulfonyl Azide*** with cyclohexene in the presence of ***Copper*** powder produces the corresponding aziridine, albeit in low yield (15%).[14] Pd^0 catalyzes the aziridination of allylic ethers with methyl azidoformate.[15]

Asymmetric Aziridination of Alkenes.

The copper-catalyzed aziridination reaction can be rendered enantioselective by the addition of chiral ligands. The first example of an enantioselective aziridination of an alkene employed the bis(oxazoline) ligand (**4**) (R = *t*-Bu) and ***Copper(I) Trifluoromethanesulfonate*** as the metal catalyst (eq 14).[16] This catalyst system affords the aziridine in 97% yield and 61% ee. Other reports have appeared subsequently regarding the extended scope of this reaction.[17-21] Important contributions to this area include the copper/bis(oxazoline)-catalyzed aziridination of aryl acrylate esters (eq 15)[20] and the copper/bis(imine)-catalyzed aziridination of cyclic *cis*-alkenes with the bis(imine) ligand (**5**) (eqs 16 and 17).[19]

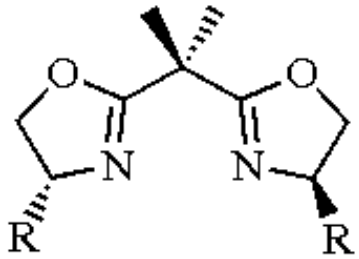

(4) R = Ph, *t*-Bu

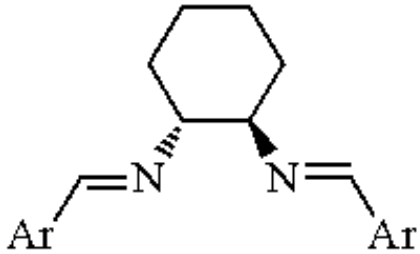

(5) Ar = 2,6-$Cl_2C_6H_3$

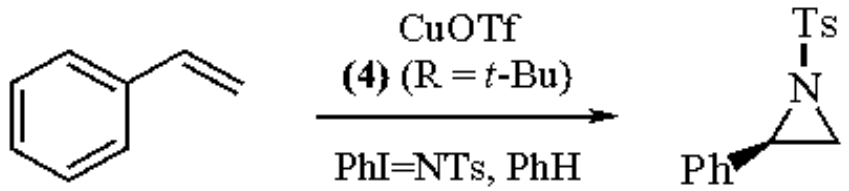

61% ee

(14)

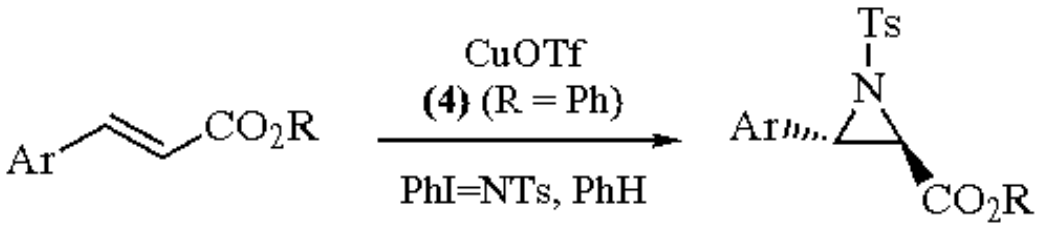

94-96% ee

(15)

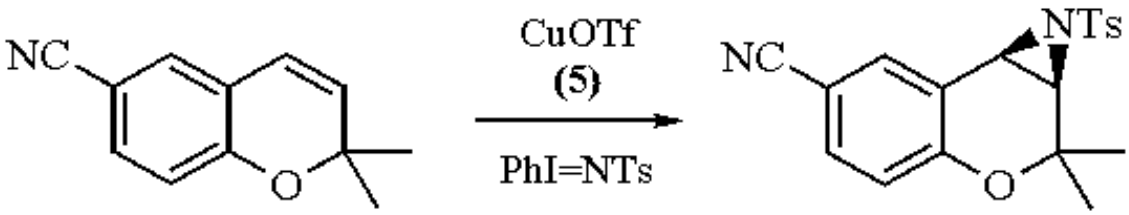

>98% ee

(16)

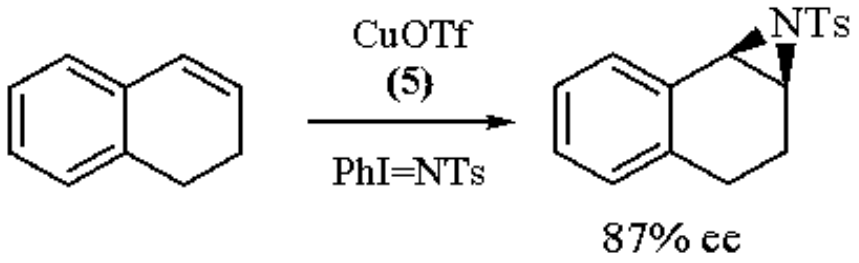

(17)

Formation of Isocyanates.

The Pd-catalyzed reaction of PhI=NSO_2Ar in the presence of CO generates the isocyanates $ArSO_2NCO$.[22] Thus ***Bis(benzonitrile)dichloropalladium(II)*** catalyzes the formation of the isocyanate TsNCO (which can be isolated as the urea (**6**) in 60% yield after reaction with 2-chloroaniline) with PhI=NTs (eq 18). This reaction has been reported for several arylsulfonylimino iodinanes. Similar results can be achieved, however, by employing the less expensive chloramine-T and its derivatives as reagents.[23]

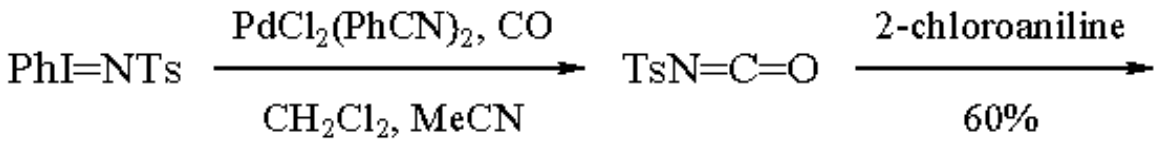

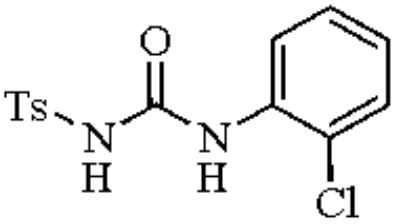

(18)

(6)

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p-Toluenesulfonyl Isocyanate[1]

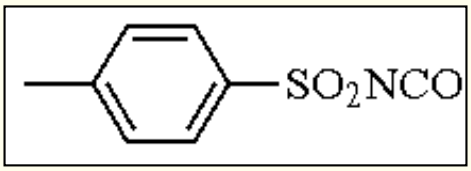

[4083-64-1] · $C_8H_7NO_3S$ · *p*-Toluenesulfonyl Isocyanate · (MW 197.23)

(converts oxiranes to 2-oxazolinones;[2] undergoes many [2 + *x*] cycloadditions; useful for (thio)carbonyl to imine functional group interchange; introduces the Tac protecting group to amino acids[3])

Alternate Name: tosyl isocyanate.

Physical Data: bp 144 °C/10 mmHg; *d* 1.295 g cm^{-3}.

Solubility: sol chlorinated, aromatic, and ethereal solvents; reacts violently with H_2O and basic and protic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: lachrymator; corrosive; use only in a fume hood. Wear protective gloves and, preferably, a NIOSH-approved respirator. All transfers and reactions should be carried out under anhydrous conditions. Store in a cool dry place, taking care to avoid contamination with protic, basic, or organometallic materials, as these may induce polymerization. See Karol[4a] and Henderson[4b] for toxicity data of isocyanates.

Conversion of Oxiranes to 2-Oxazolinones.

Tosyl isocyanate can be considered either as a heteroatom ring-expanding reagent, or as an NH_3 synthetic equivalent. A prime example might be its Lewis or π-acid catalyzed reaction with epoxides to give *N*-tosylated 2-oxazolinones directly,[2,5] or 1,2-amino alcohols after hydrolysis. An elegant and powerful variation utilizing chiral, nonracemic Pd-phosphine complexes, which exploits the greater reactivity of sulfonylated isocyanates, has also been developed, giving access to optically active cyclic 1,2-amino alcohols (eq 1).[6] In a related sequence, allylic amines are converted to *N*,*N*′-cyclic ureas with I_2 catalysis.[7]

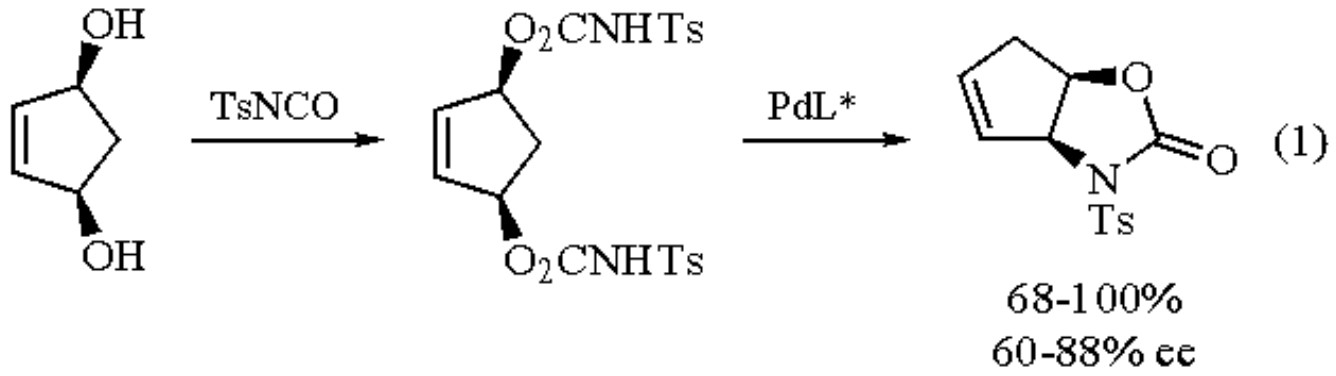

[2 + *x*] Cycloadditions.

Highly reactive tosyl isocyanate readily undergoes a wide variety of [2 + 2] cycloadditions.[8] Much effort has been expended upon the preparation of *N*-tosylated β-lactams. Despite the difficulty of removal of the sulfonyl group without cleaving the β-lactam,[9] novel variations continue to appear (eq 2).[10]

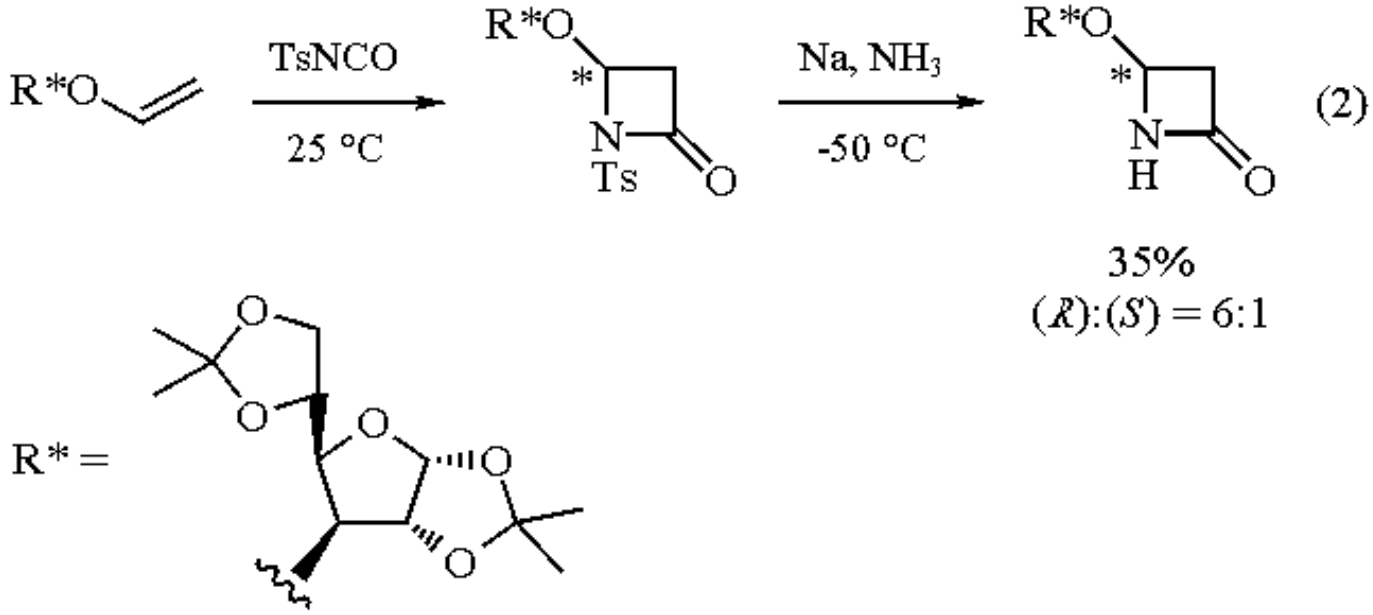

Other [2 + 2] cycloadditions have been reported with hydrazones,[11] and imino ethers.[12] [2 + 3] Cycloadditions that afford pyrrolidinone derivatives from transition metal complexes have recently been reported (eq 3).[13] Higher-order cycloadditions also appear in the literature.[14]

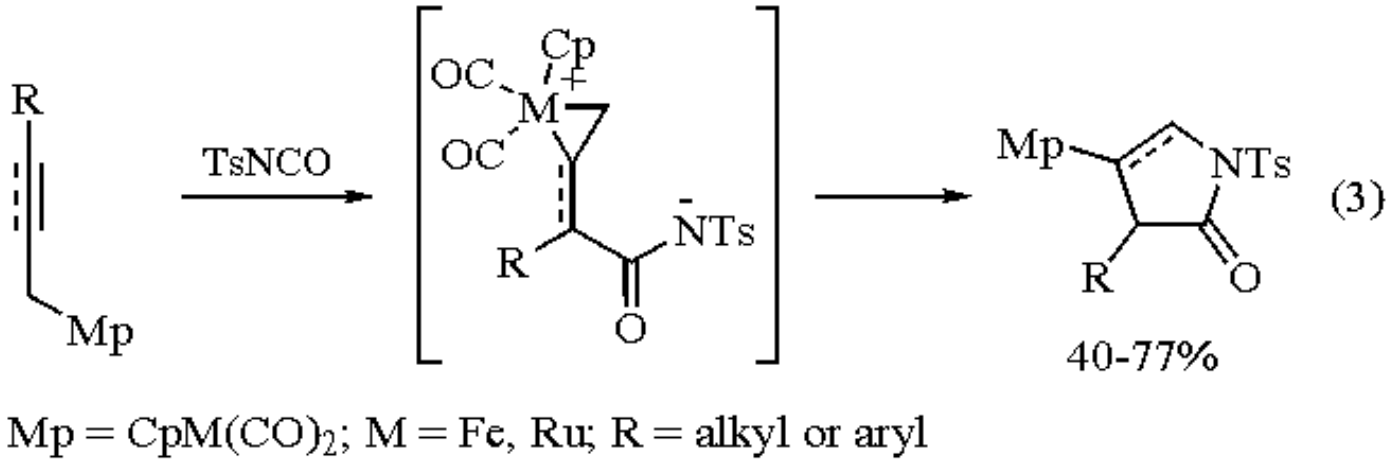

(Thio)carbonyl to Imide Reactions.

Desulfur- and deoxygenations of (thio)lactams, glyoxaldehydes, and phosphine oxides induced by tosyl isocyanate liberate CO_2 or COS. The product *N*-sulfonyl amidines, which give novel stereochemistry in aldol reactions,[15] glyoximines, which may be used directly in aza-Diels-Alder reactions,[16] and phosphinimines[17] are obtained in high yields.

Miscellaneous Reactions.

Reaction (20-80%) with amino acids introduces the *N*-Tac group, which, while stable to cold TFA, dilute base, HBr/acetic acid, and catalytic hydrogenation, may be removed by hot primary alcohols.[3] Tosyl isocyanate is an efficient dehydrating agent for tertiary (especially allylic) alcohols.[18] The *N*-tosyl group is a pharmacophore.[19] Novel ring expansions of medium- and large-ring keto esters triggered by tosyl isocyanate afford macrolactams.[20]

Related Reagents.

Benzenesulfonyl Isocyanate; ***Chlorosulfonyl Isocyanate***.

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p-Toluenesulfonyl Azide[1]

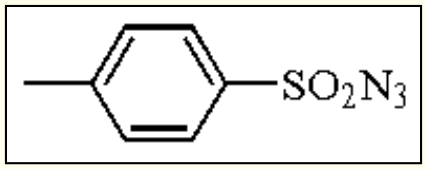

[941-55-9] · $C_7H_7N_3O_2S$ · *p*-Toluenesulfonyl Azide · (MW 197.24)

(introduction of azide and diazo groups into organic compounds;[2] serves as a source of nitrene and 1,3-azide dipoles for [3 + 2] cycloadditions;[3] used for the synthesis of *N*-tosylphosphinimines,[4] -sulfimines, and -sulfoximines[5])

Alternate Names: tosyl azide.

Physical Data: mp 21-22 °C; bp 110-115 °C/0.001 mmHg;[6] d^{25} 1.286 g cm^{-3}; *n*25589 1.55010.

Solubility: sol chloroform, diethyl ether, acetone.

Form Supplied in: oily colorless liquid.

Analysis of Reagent Purity: IR (neat) ν = 2130 (strong, N=N=N), 1380 and 1180 (strong, SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.47 (s, CH_3), 7.40 (d, *J* = 8 Hz, *m*-$SO_2C_6H_4$), 7.84 (d, *J* = 8 Hz, *o*-$SO_2C_6H_4$).[7]

Preparative Methods: the simplest synthetic method for tosyl azide is the reaction of ***p-Toluenesulfonyl Chloride*** with ***Sodium Azide***. Tosyl azide prepared in ethanol may contain 7-20% of ethyl *p*-toluenesulfonate;[8] the formation of this byproduct can be avoided by working in aqueous acetone instead of ethanol.[9,10] The ^1H NMR spectrum of tosyl azide prepared (99% yield) according to Curphey exhibits signals for traces of dichloromethane (<1%);[10] the compound is pure by TLC, while HPLC reveals traces (>1.5%) of an impurity. Polymer-bound tosyl chloride can be transformed to polymer-bound tosyl azide.[11] A polymer-bound phase-transfer catalyst may also be employed (94% yield).[12] Further methods for the preparation of tosyl azide are the oxidation of ***p-Toluenesulfonylhydrazide*** by ***Iron(III) Nitrate-K10 Montmorillonite Clay*** (83% yield),[13] by ***Nitrogen Dioxide*** in CCl_4 (95% yield),[14] or by ***Nitrosonium Tetrafluoroborate*** (85% yield). [15]

Handling, Storage, and Precautions: crystallizes to a white solid at -20 °C and can be stored indefinitely at this temperature. Particular care is required for all reactions in which tosyl azide is heated at or above 100 °C. The initial temperature of the explosive decomposition is about 120 °C.[16] Severe explosions during the attempted distillation of tosyl azide have been reported.[6,17] Polymer-bound tosyl azide can be stored indefinitely at room temperature and, in contrast to tosyl azide itself, is not sensitive to mechanical shock. Use in a fume hood.

Synthesis of Azides.

Tosyl azide acts as a transfer reagent to introduce the azide group to anions of C-H acidic compounds such as malonate derivatives (eq 1);[18] aryl azides are obtained from the reactions of aryl Grignard reagents with tosyl azide after cleavage of the primarily formed triazene salt intermediates with sodium pyrophosphate (eq 2);[19] azidothiophenes and -bithiophenes[20] or azidotetrazolium salts[21] can be prepared similarly (using organolithium compounds). The anions of primary amines, generated from the latter by treatment with Grignard reagents[22] or preferably with ***Sodium Hydride*** in THF,[23] also react with tosyl azide to furnish azides (diazo group transfer to primary amines, eq 3). α-Azido sulfones are formed in one step by reactions of aliphatic nitro compounds with ***Potassium Hydride*** in THF and subsequent treatment with tosyl azide (eq 4).[24]

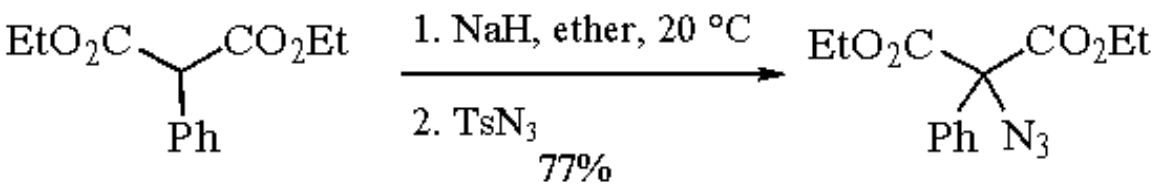

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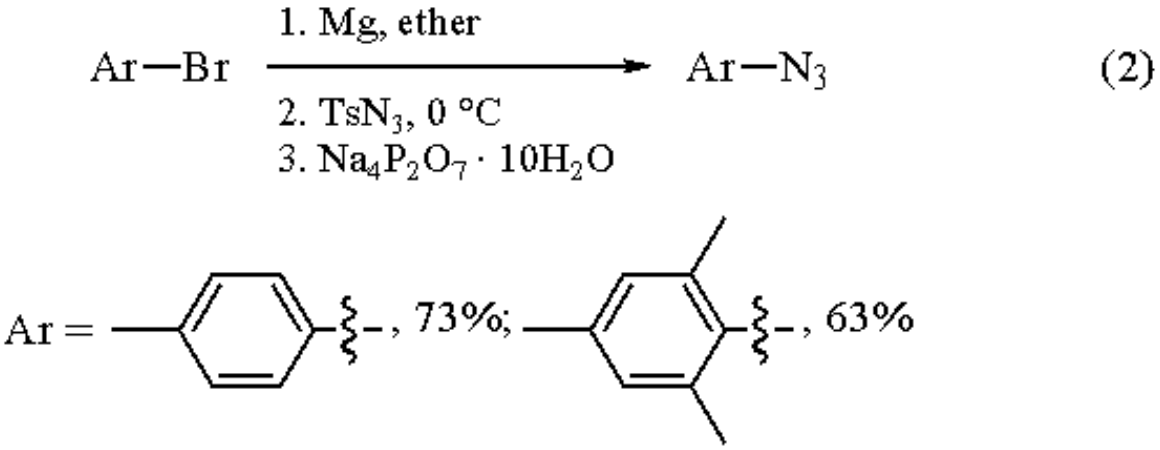

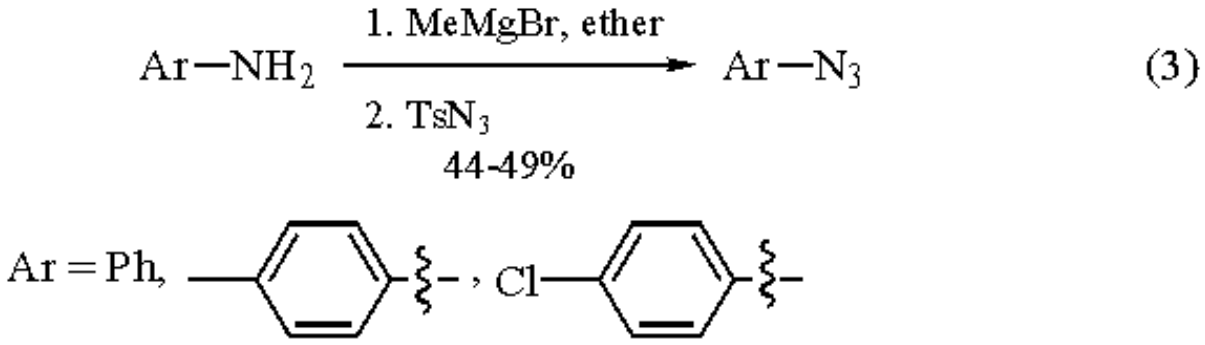

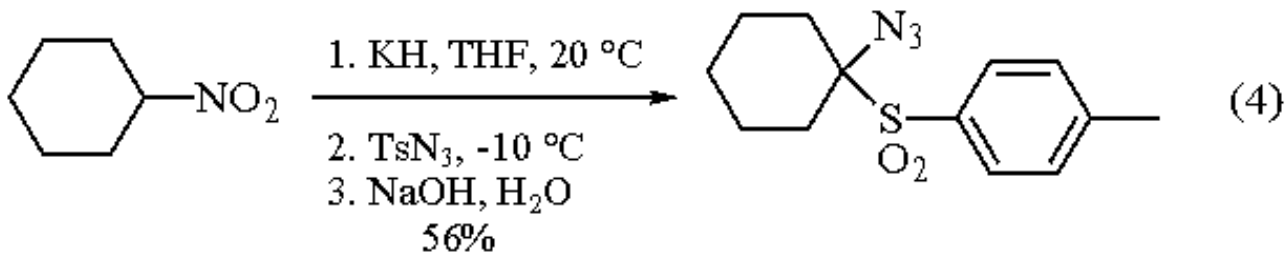

Synthesis of Diazo Compounds.[2]

The synthesis of diazo compounds from a carbon nucleophile and an arenesulfonyl azide, preferably tosyl azide (eq 5), is known as diazo group transfer.[25] The actual reaction in a somewhat different form has been known for a long time;[26] it was first employed for the synthesis of diazocyclopentadiene from the cyclopentadienide anion and tosyl azide[27] and has since been developed intensively.

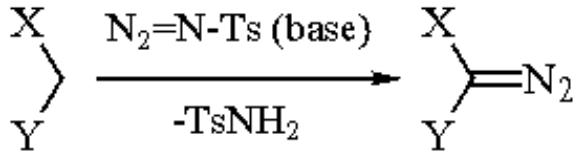

X, Y = CO_2R, CHO, COR, $CONR_2$, CN, NO_2, SOR, POR_2, $PO(OR)_2$, Ar

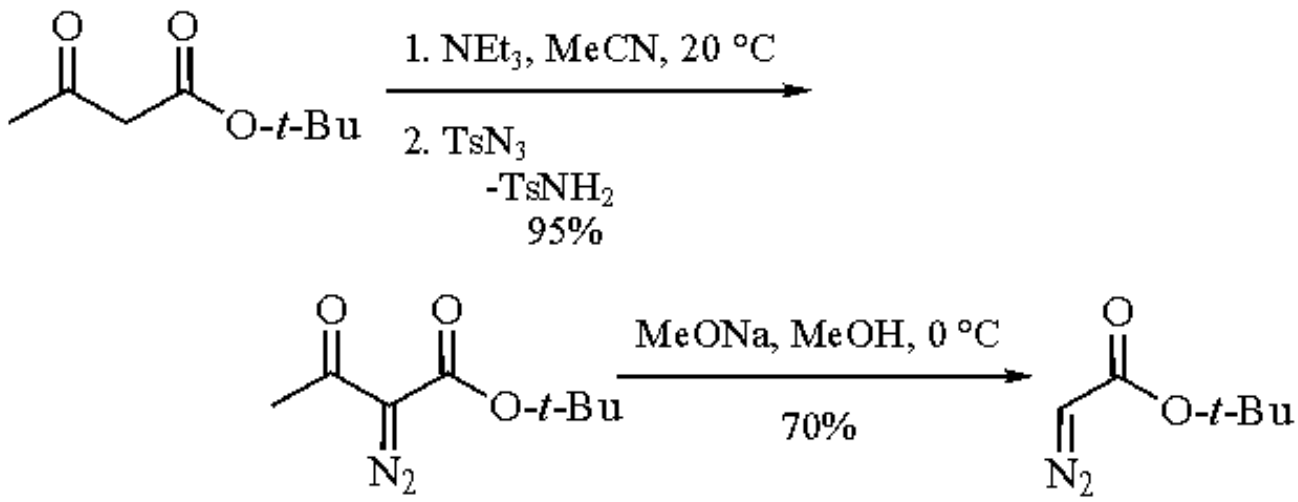

(5)

When X and Y are suitable electron-attracting groups such as CO_2R, COR, NO_2, SO_2R, Ar, etc., the required carbanion can be generated by treatment of the corresponding methylene compound with an appropriate base (NEt_3, pyridine/piperidine, NaOEt, *t*-BuOK). The synthesis of *t*-butyl diazoacetate is an explicit example.[8] The use of a phase-transfer catalyst is sometimes advantageous for the generation of the carbanion.[28] When only one electron-attracting, activating group is present in the substrate, diazo group transfer can be effected by an indirect route in which, for example, a ketone is transformed to an α-formyl ketone which is, in turn, converted by treatment with tosyl azide in the presence of a base to the desired diazo compound by cleavage of *N*-formyltosyl amide (deformylating diazo group transfer, eq 6).[29]

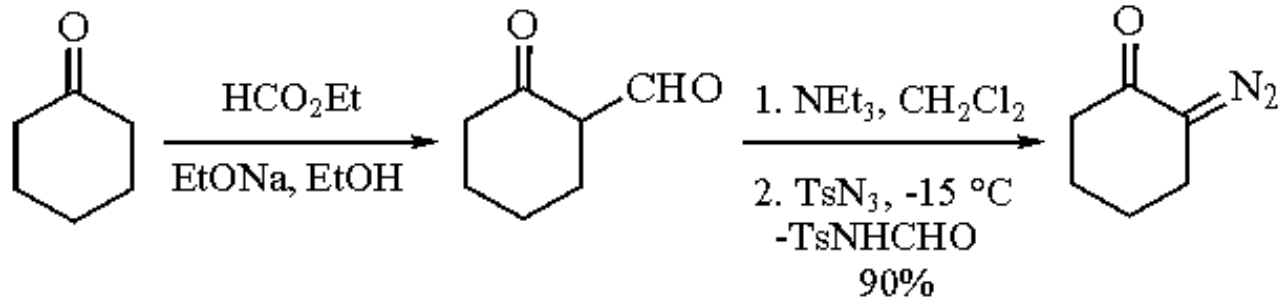

(6)

Tosyl azide is the reagent employed most frequently. However, ***p-Dodecylbenzenesulfonyl Azide***,[16] *p*-carboxybenzenesulfonyl azide,[30] polymer-bound tosyl azide,[11] trifluoromethanesulfonyl azide (triflyl azide),[31] (azidochloromethylene)dimethylammonium chloride,[32] ***2,4,6-Triisopropylbenzenesulfonyl Azide*** (trisyl azide),[33] and others[34] have also been used. 2-Azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate and 2-azido-1-ethylpyridinium tetrafluoroborate[35] have proven to be useful as diazo group transfer reagents since they can also be employed in weakly acidic media with base-sensitive methylene compounds. In addition to the requirement for a less hazardous reagent than tosyl azide, the separation of the inevitably formed amine from the desired diazo compound represents the main stimulant for the continued search for novel diazo group transfer reagents.

Supplementary to the classic diazo group transfer to activated methylene compounds described briefly above, the reactions of tosyl azide with enamines, enol ethers, ynamines, ynethers, activated alkenes and alkynes, cyclopropenes, and methylenephosphoranes may also be included in this reaction type in its widest sense, when the respective reactions give rise to diazo compounds (see the examples in eqs 7 and 8);[36] see also cycloaddition reactions (below) as an alternative.

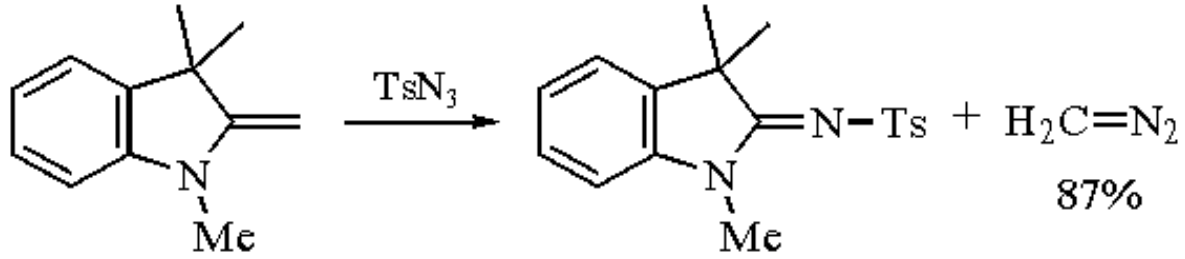

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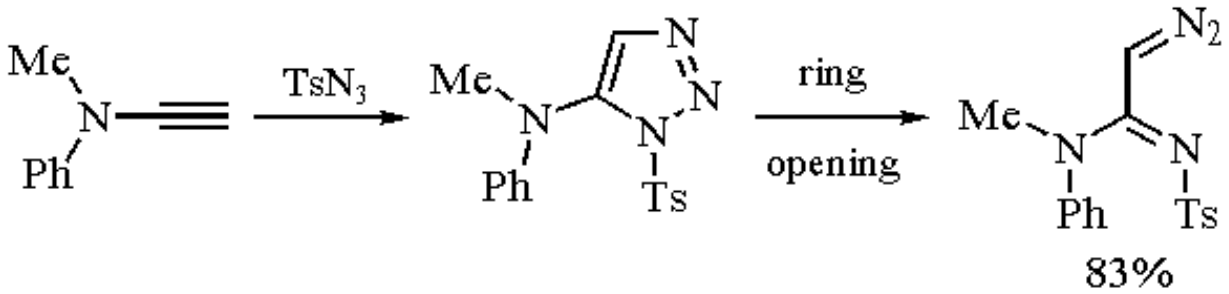

(8)

Cycloaddition Reactions.

The 1,3-dipolar cycloadditions of tosyl azide to alkenes primarily furnish the 4,5-dihydrotriazoles which can seldom be isolated.[37] Generally, subsequent reactions such as the [3 + 2] cycloreversion to *N*-tosylimines and diazo compounds (diazo group transfer), the cleavage of nitrogen in *N*-tosylaziridines, or the concomitant 1,2-shift of a substituent in *N*-tosylimines with rearranged molecular skeletons (eq 9) predominate.[38] All processes can occur in parallel; however, there is a pronounced reaction selectivity in dependence on the group X (the electron donating substituent).

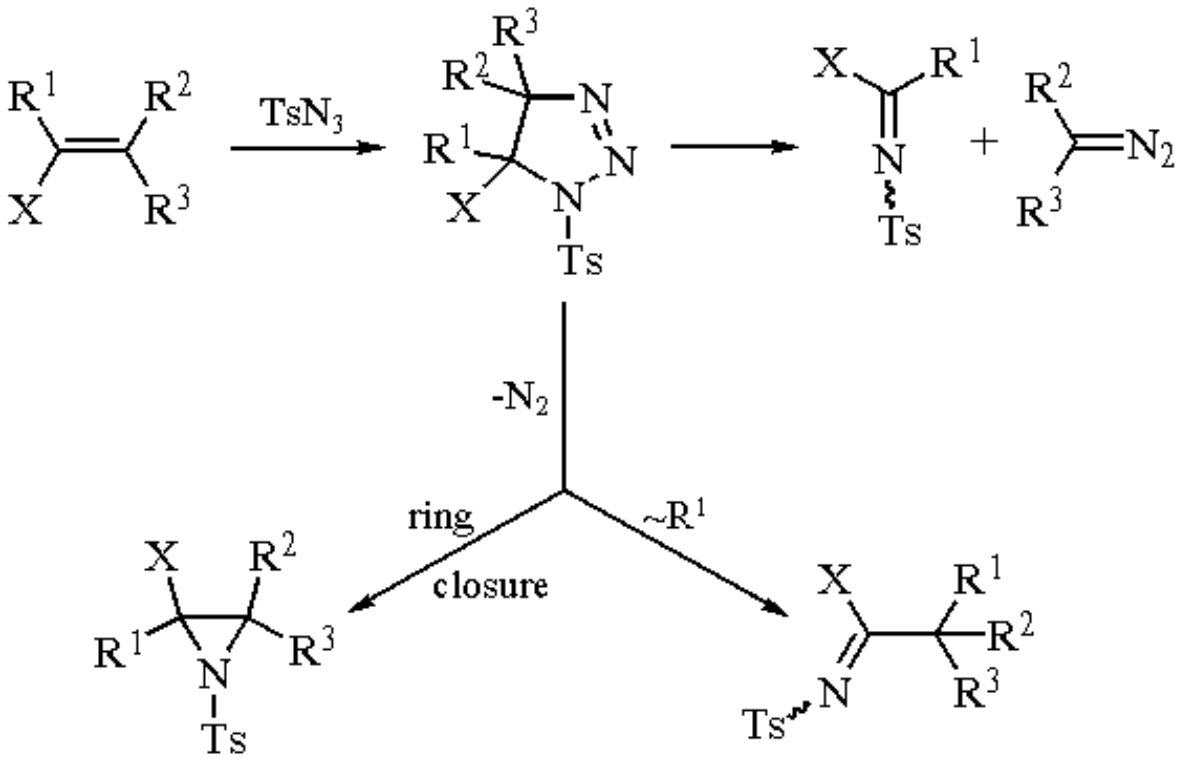

(9)

From the plethora of synthetic applications of tosyl azide, its examples of the reactions with nonstrained cycloalkenes leading to *N*-tosylimines (eq 10),[39] with cyclic enamines which give amidines (eq 11),[40] with indoles to furnish 2-tosyliminoindoles (eq 12),[41] and with enol ethers giving rise to imidates in quantitative yield (eq 13)[42] are mentioned as examples. When the alkene carries a further substituent capable of elimination, the cycloadditions give rise to 1,2,3-triazoles directly (eq 14).[43] The *N*-tosyl group can be readily removed by hydrolysis to liberate the corresponding NH compound. Thus in this sense, tosyl azide can be considered as a synthetic equivalent of the difficult to handle hydrogen azide (***Hydrazoic Acid***, HN_3).

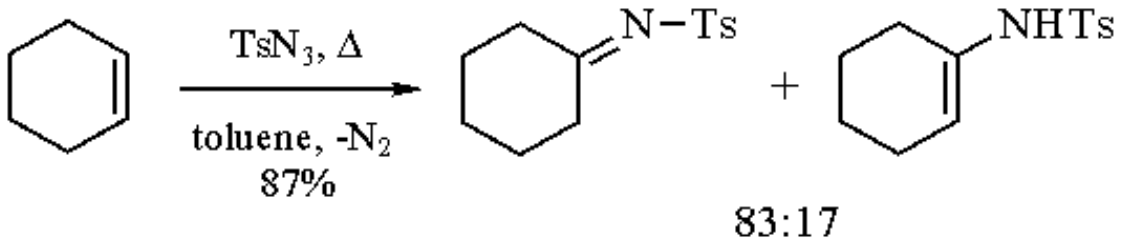

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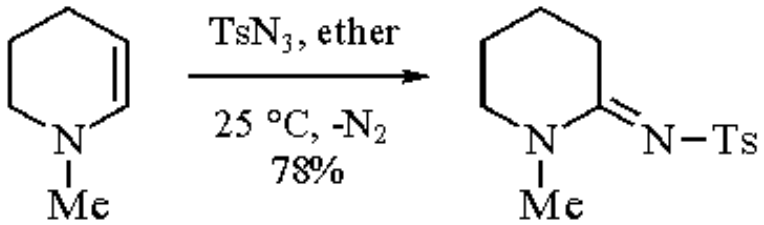

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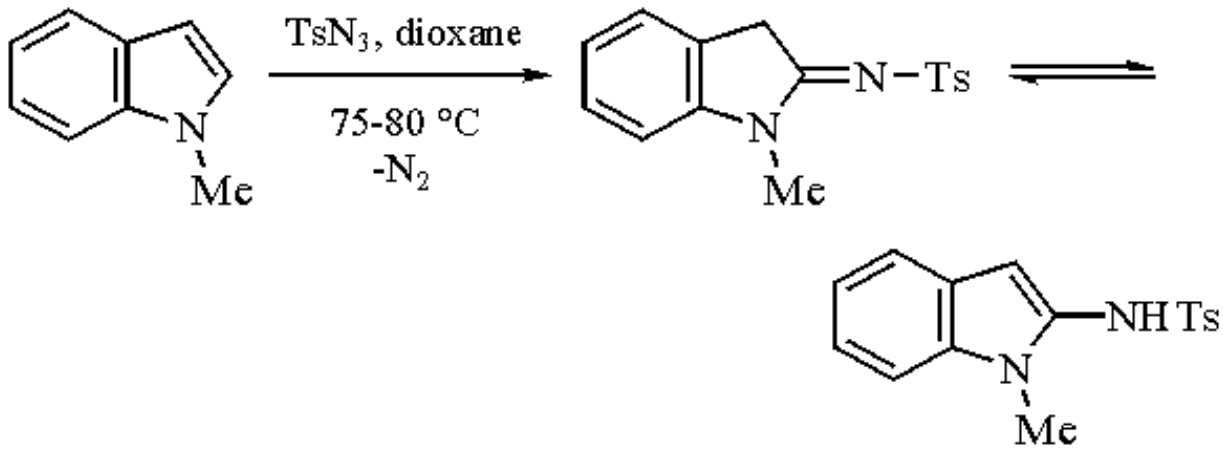

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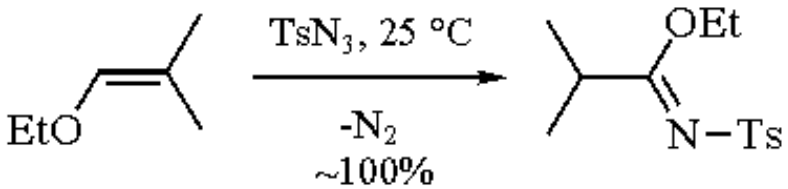

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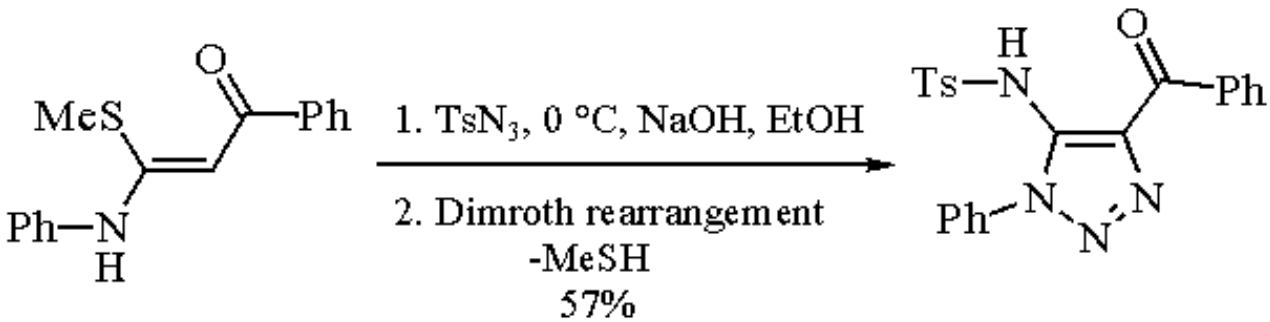

(14)

Miscellaneous.

The reactions of aryl and heteroaryl hydrazides with tosyl azide in the presence of NaOH under phase-transfer conditions give rise to the corresponding aromatic and heteroaromatic compounds (eq 15).[44] After oxidative workup, reactions with trialkylboranes yield alkyl aryl sulfides (eq 16).[45]

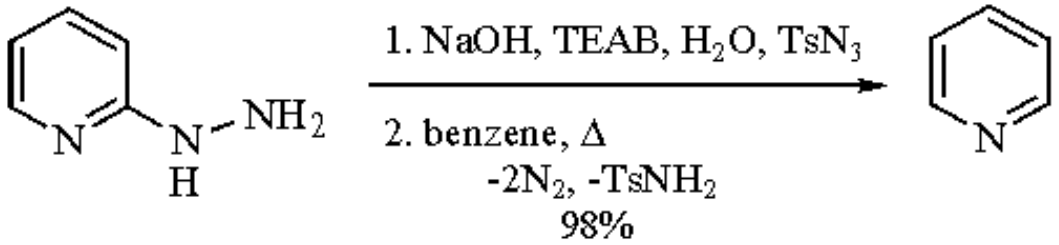

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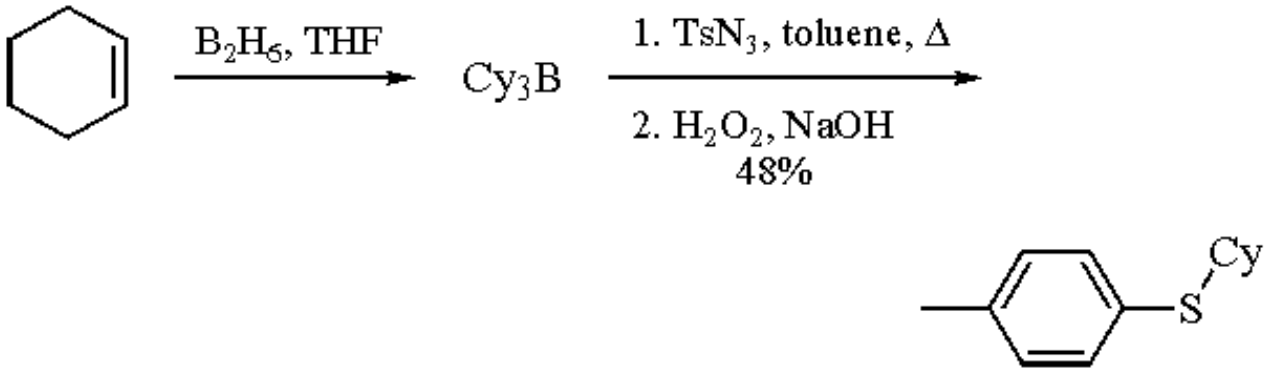

(16)

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N-(*p*-Toluenesulfonyloxy)phthalimide

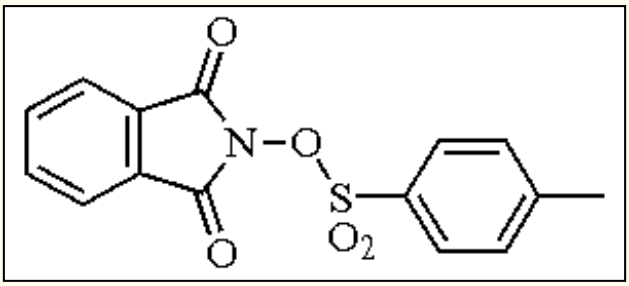

[56530-39-3] · $C_{15}H_{11}NO_5S$ · *N*-(*p*-Toluenesulfonyloxy)phthalimide · (MW 317.34)

(transformation of aryllithiums and enolates into 3,3-disubstituted quinoline-2,4-diones[1])

Alternate Name: *N*-tosyloxyphthalimide.

Physical Data: mp 161-162 °C.

Solubility: sol ether, THF; slightly sol alcohol.

Preparative Methods: prepared[2] by reaction of *N*-hydroxyphthalimide[3] with diethylamine and ***p-Toluenesulfonyl Chloride*** in dry benzene.

Amination.

For carbanion amination, various *O*-sulfonylhydroxylamines have been used,[4] and Grignard reagents, organolithiums, and enolates have been converted into primary and tertiary amines (eq 1).

$$R_2NOSO_2R^1 + R^2M \longrightarrow R_2NR^2 + MOSO_2R^1 \qquad (1)$$

$$M = Li, MgX; \quad R = Me, Et$$

However, the reactions of aryl carbanions and enolates with *N*-tosyloxyphthalimide gives 3,3-disubstituted quinoline-2,4-diones (eq 2) in moderate to good yields (eqs 3 and 4).[1]

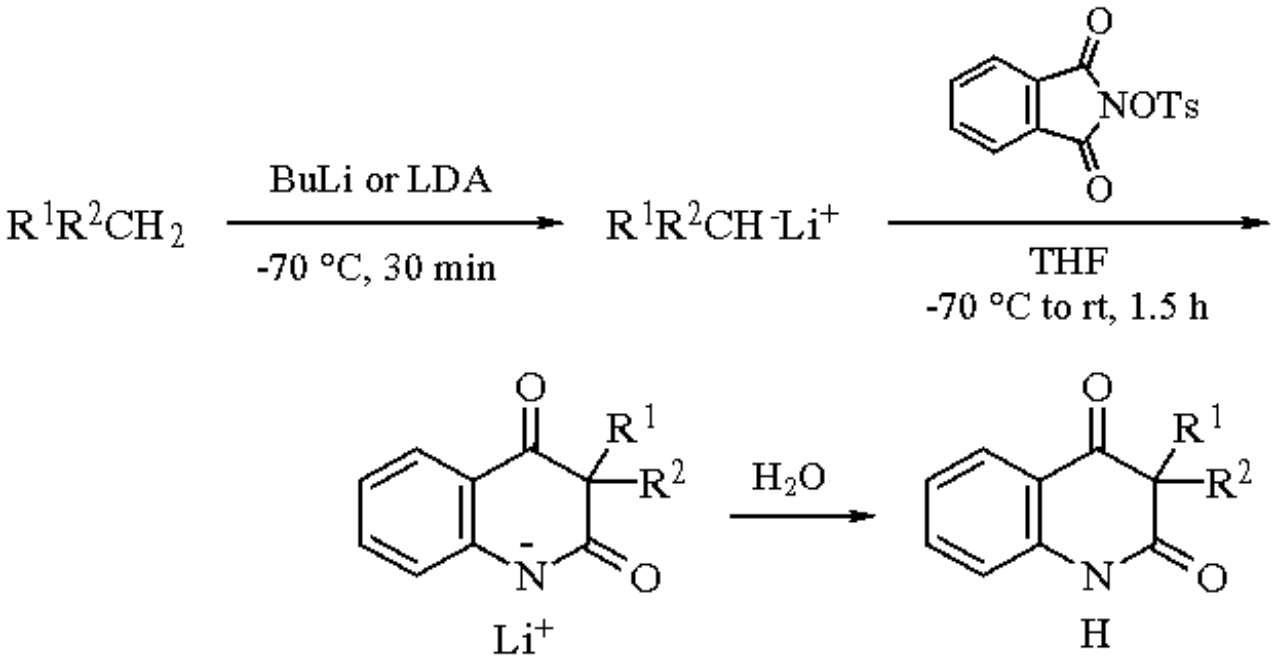

(2)

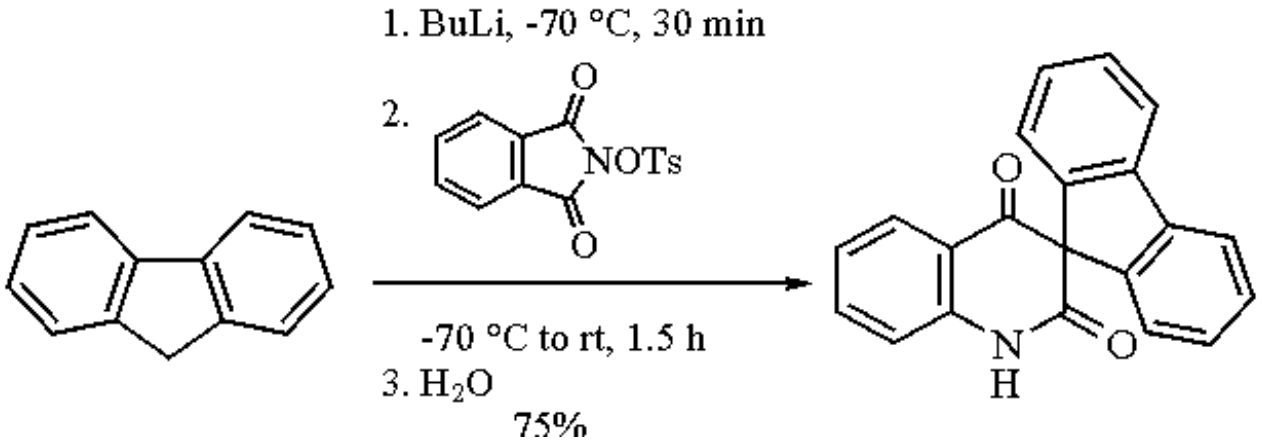

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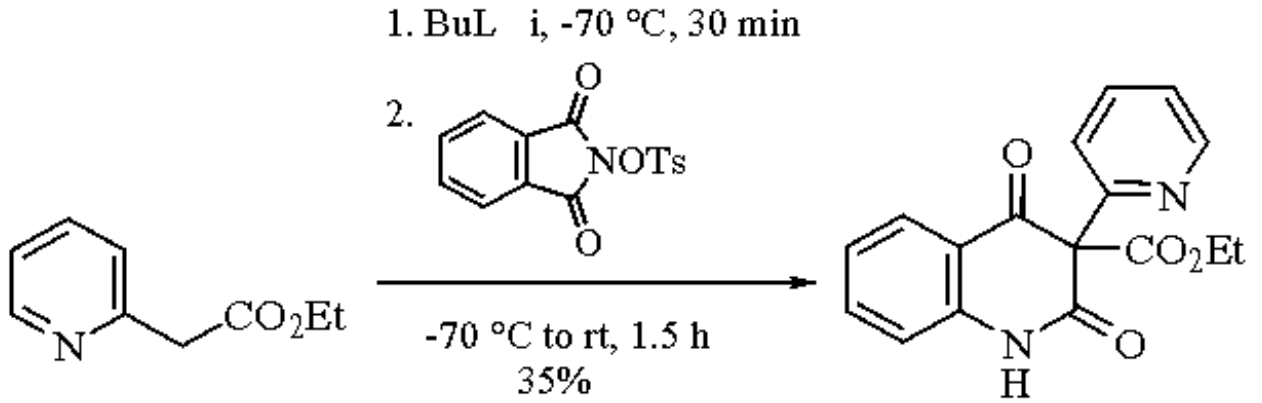

(4)

The reaction is carried out as follows. Aryllithium or enolate is prepared by using ***n-Butyllithium*** at -70 °C in THF and a solution of *N*-tosyloxyphthalimide (0.5 equiv) is added with stirring. Stirring is continued until the temperature reaches 15 °C, when the solution is poured into aqueous acid. After extraction with dichloromethane and evaporation, the residue is crystallized.

The proposed mechanism involves the possible intermediate isocyanato ketone, which is attacked by the carbanion to form another carbanion which then undergoes intramolecular attack at the carbonyl group, leading to cyclization to form the dione (eq 5).

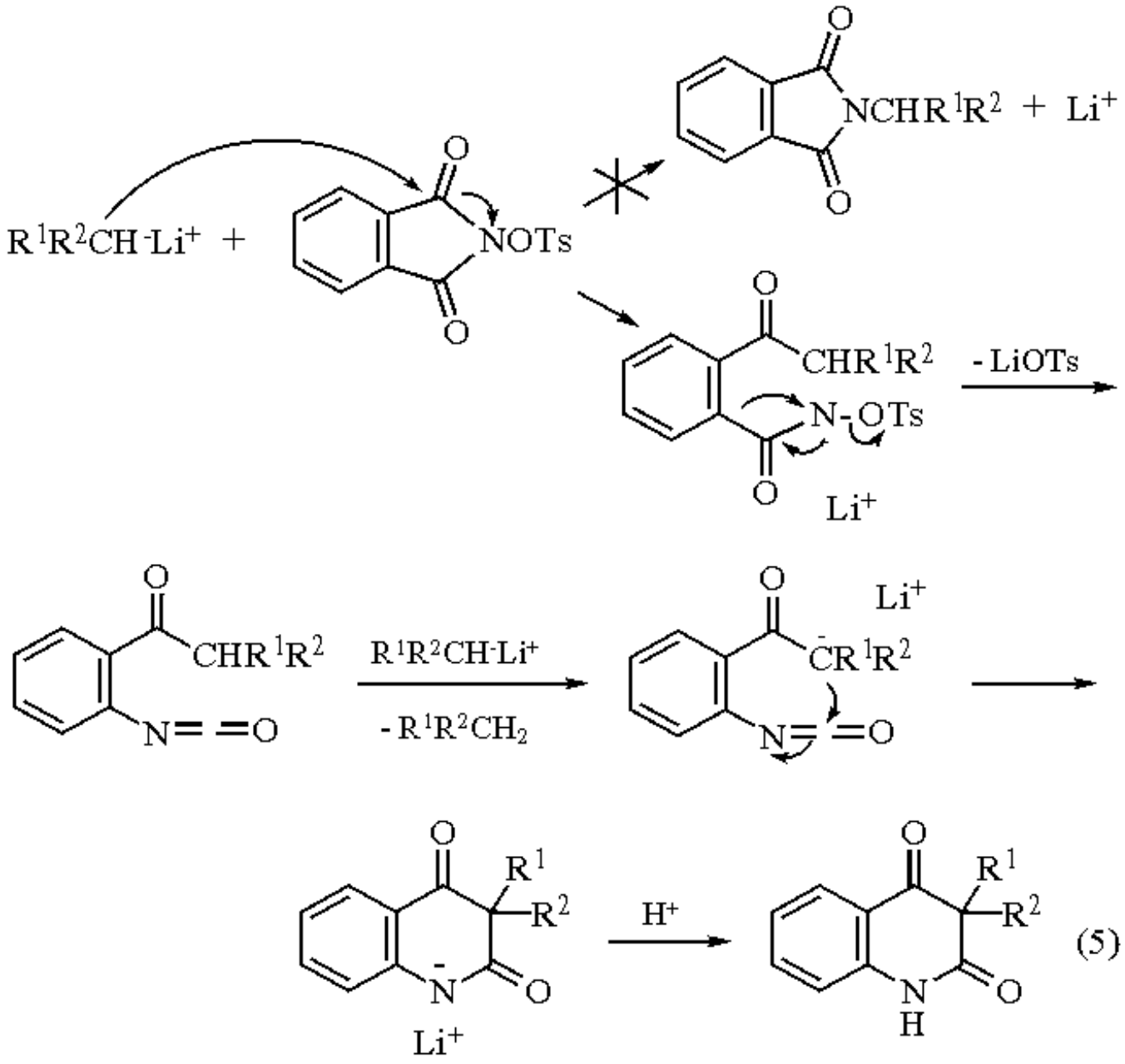

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O-p-Tolyl Chlorothioformate

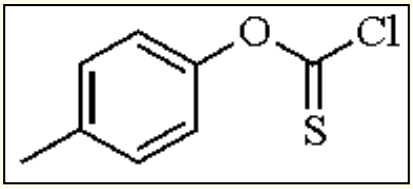

[937-63-3] · C_8H_7ClOS · *O-p*-Tolyl Chlorothioformate · (MW 186.67)

(synthesis of alkenes from hindered alcohols;[1] deoxygenation of alcohols[7])

Physical Data: bp 52-53 °C; *d* 1.21 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: commercially available as liquid (97% pure).

Analysis of Reagent Purity: GC.

Handling, Storage, and Precautions: moisture sensitive; keep cold; corrosive; toxic; use in a fume hood.

Synthesis of Alkenes.

Formation of thiocarbonate *O*-esters from sterically hindered alcohols, followed by pyrolysis, provides an alternative to the Chugaev reaction in the synthesis of alkenes. In the examples shown in eqs 1 and 2, pyrolysis of the corresponding xanthates gives lower yields.[1,2]

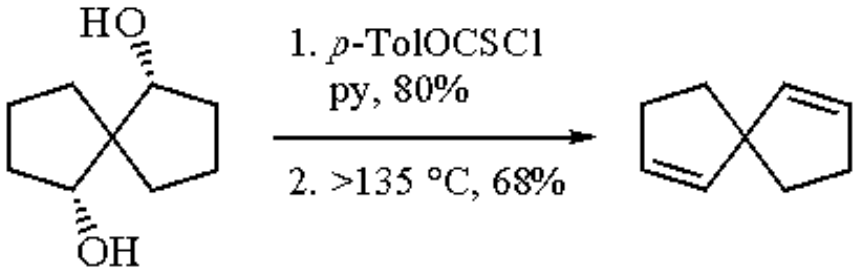

(1)

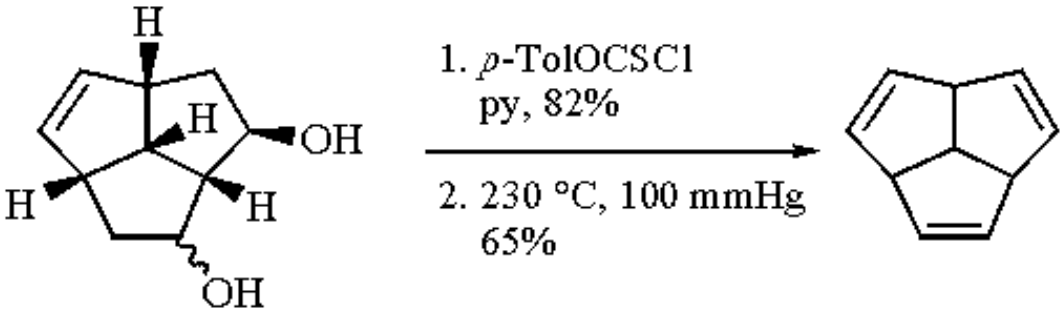

(2)

The pyrolysis of thiocarbonate *O*-esters has been utilized in the synthesis of several natural products. In an approach to the synthesis of (-)-acorenone (eq 3), pyrolysis of the xanthate gives consistently low yields.[3] The favored pathway appears to be conversion to the dithiol carbonate. Alternatively, conversion to the thiocarbonate *O*-ester and subsequent pyrolysis gives the desired alkene in 68% yield. This methodology has also been successfully used in a total synthesis of (±)-silphenene (eq 4).[4] Ordinary dehydration conditions lead to retroaldolization, while pyrolysis of the thiocarbonate *O*-ester gives the desired enone in 84% yield. An intermediate in the total synthesis of (-)-hibaene has been prepared by pyrolysis of the respective monothiocarbonate *O*-esters of both epimeric diols (eq 5).[5]

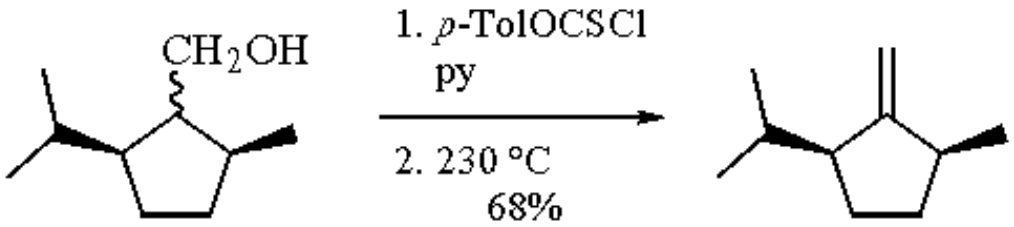

(3)

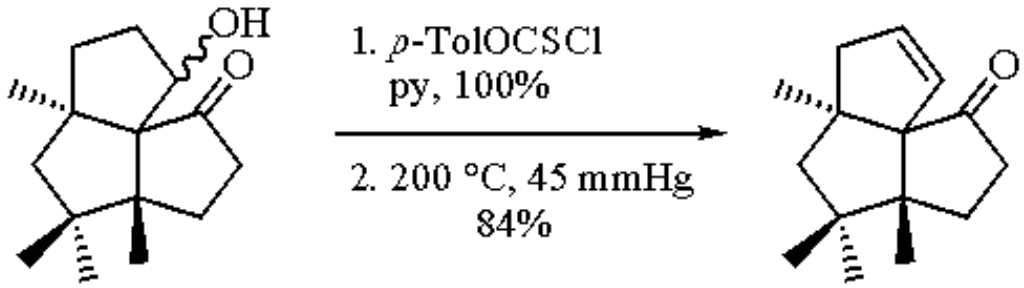

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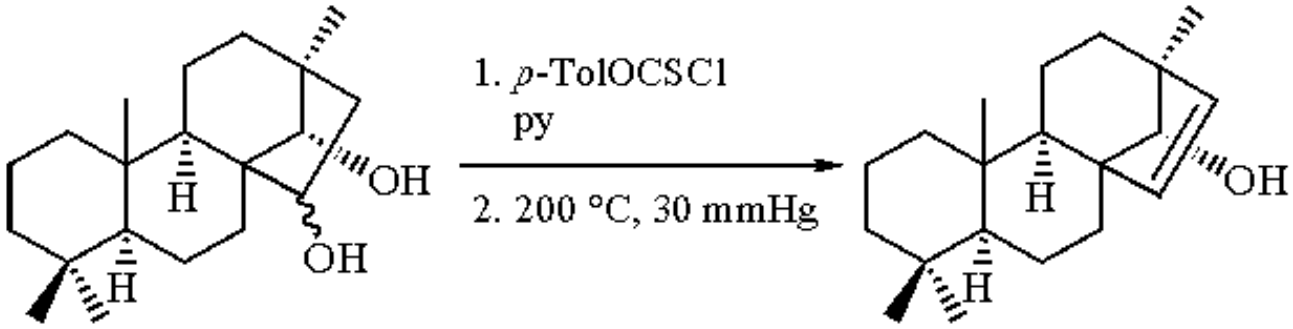

(5)

Deoxygenation of Alcohols.

Thiocarbonate esters of alcohols can be deoxygenated using the Barton-McCombie procedure.[6] Several examples of this deoxygenation methodology in the synthesis of deoxyribose nucleosides have been cited (eq 6).[7-9]

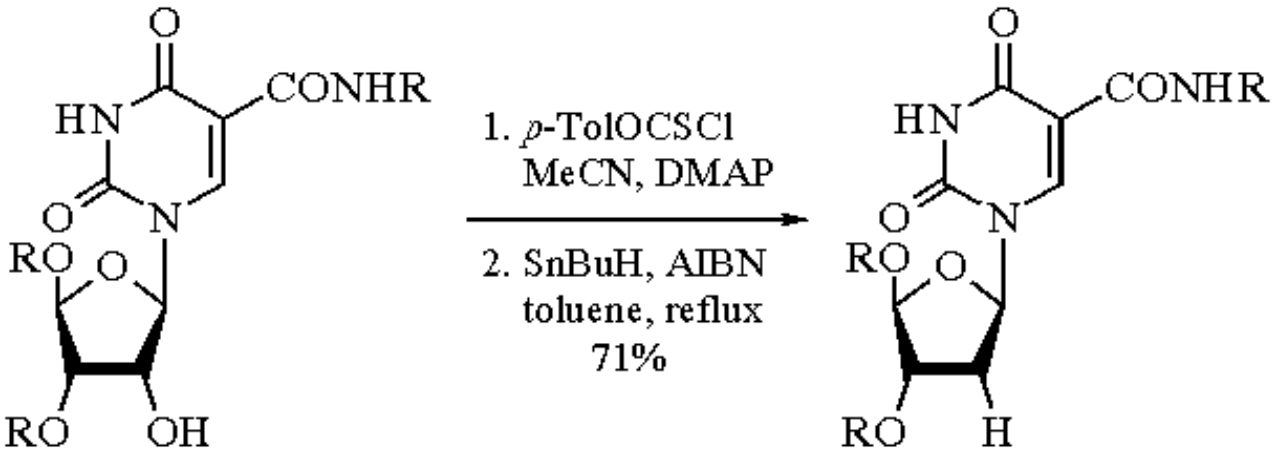

(6)

[Heteroaryl(hydroxy)methyl]phosphonates are readily converted to *O*,*O*-thiocarbonates on treatment with *O*-*p*-tolyl chlorothioformate in MeCN/DMAP, while the reaction in pyridine/CH_2Cl_2 affords the isomeric *O*,*S*-thiocarbonates (eq 7).[10] Homolytic cleavage with ***Tri-n-butylstannane***/***Azobisisobutyronitrile*** provides a convenient approach to dialkyl heteroarylmethylphosphonates.

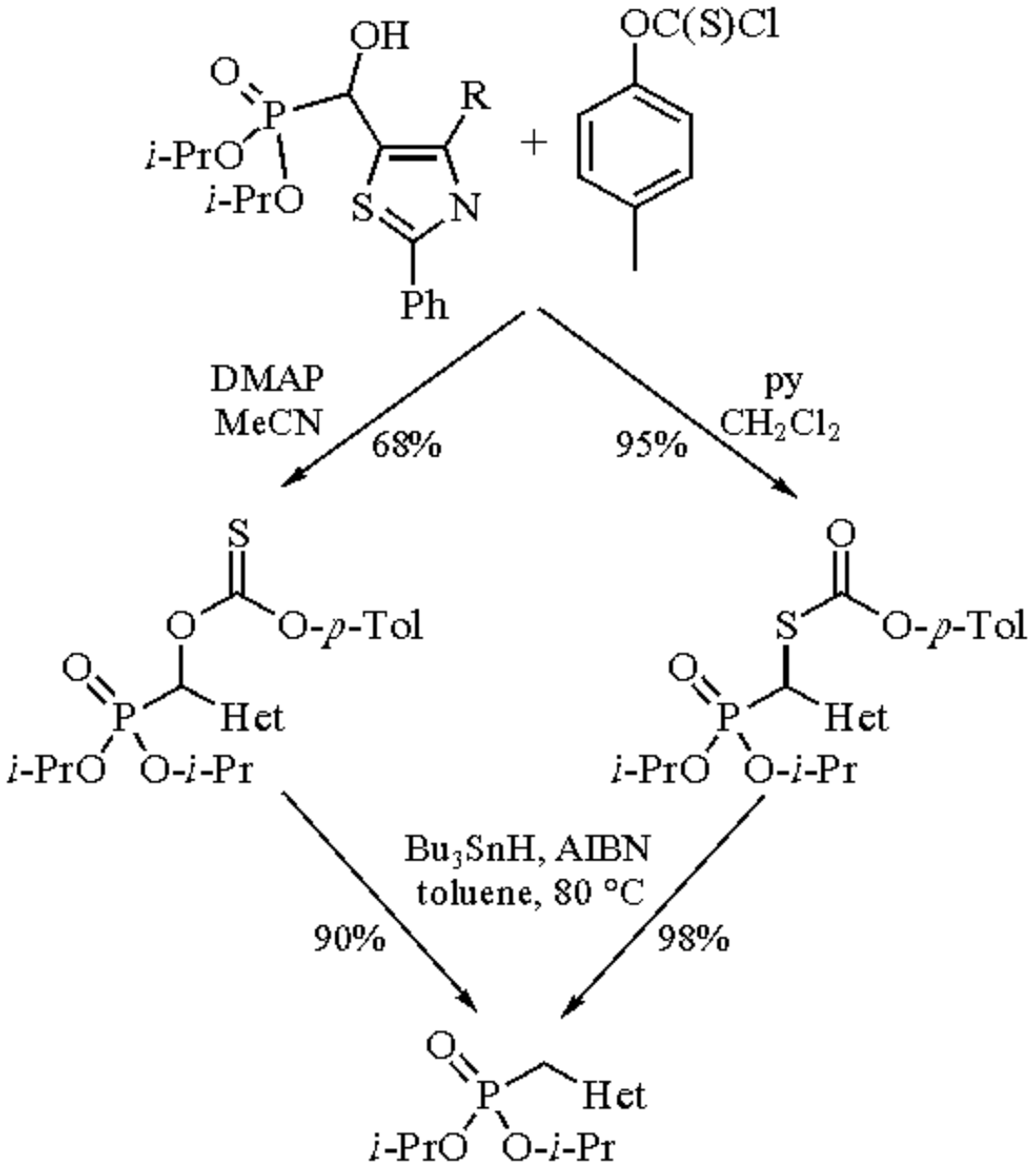

(7)

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o-Tolyl Isocyanide[1,2]

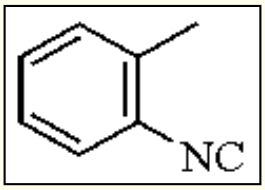

[10468-64-1] · C_8H_7N · *o*-Tolyl Isocyanide · (MW 117.16)

(synthesis of N-heterocycles and azomethines)

Physical Data: bp 75 °C/16 mmHg; *d* 0.97 g cm^{-3}.

Solubility: sol most organic solvents, e.g. methanol, ethanol, ether, toluene, dichloromethane.

Analysis of Reagent Purity: by gas chromatography.

Preparative Method: see Ugi and Meyr.[3]

Handling, Storage, and Precautions: should be freshly distilled before use. Foul smelling liquid; store and use in a fume hood. Contaminated equipment should be washed with 5% methanolic sulfuric acid.

Introduction.

o-Tolyl isocyanide can be used to synthesize a great variety of compounds.[1,2] The aromatic *o*-methyl group can be lithiated to create a bifunctional isocyanide reagent (eq 1).[4]

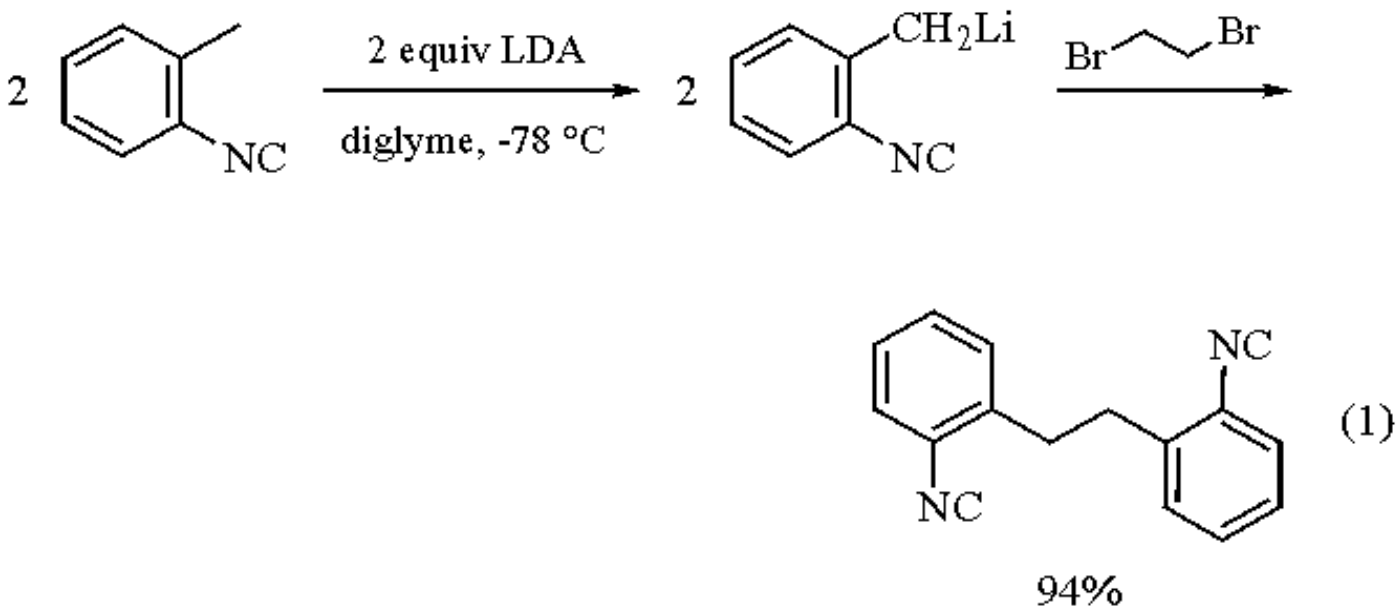

(1)

Indole Synthesis.

Reaction of *o*-tolyl isocyanide with ***Lithium Diisopropylamide*** followed by alkylation[5,6] or acylation[7-9] and then cyclization gives 3-substituted indoles (eqs 2-4).

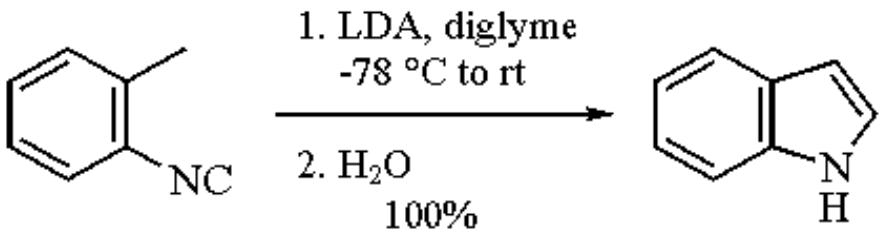

(2)

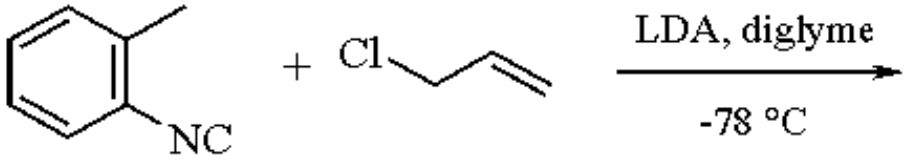

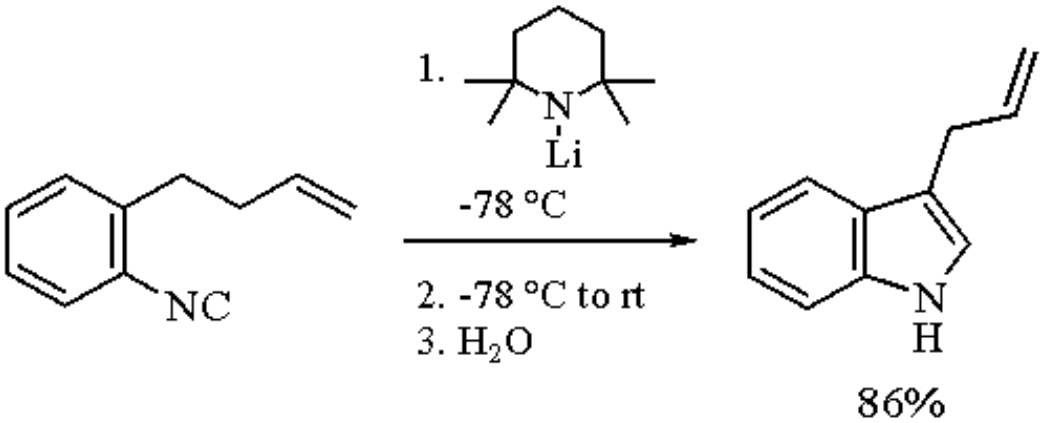

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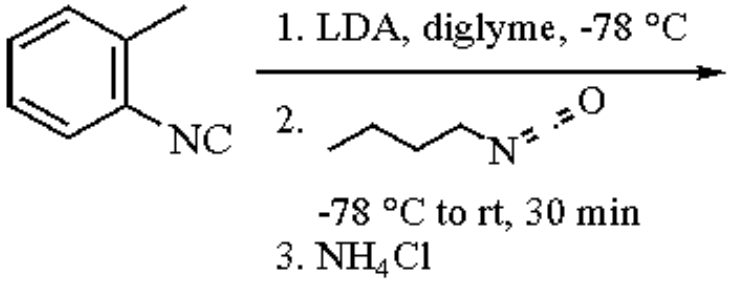

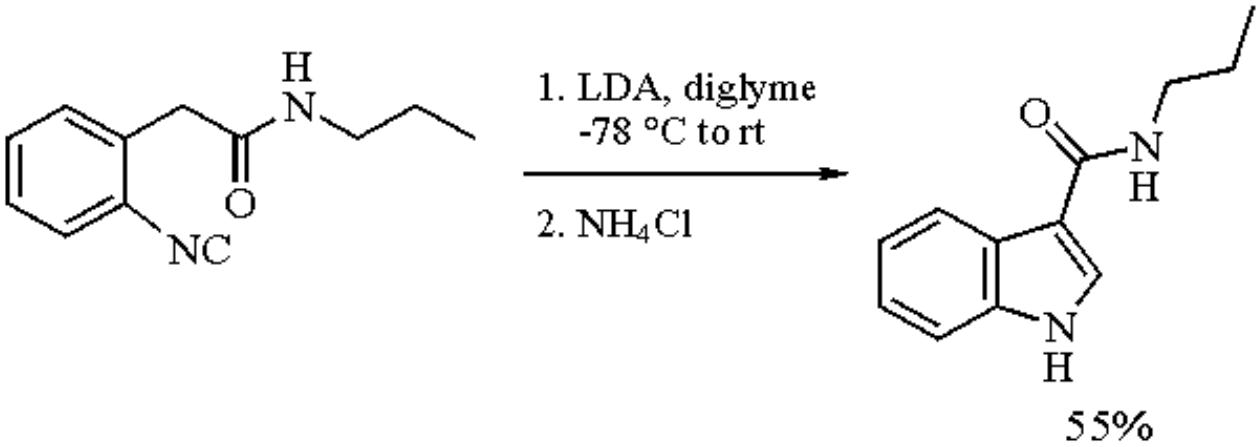

(4)

Synthesis of Other Heterocycles.

β,γ-Butenolide imines can be made in reasonable yields by Lewis acid-catalyzed [4 + 1] cycloaddition (eq 5).[10] The azetidine ring system, otherwise very difficult to obtain, results in reasonable yield in a one-step [2 + 2 + 2] cycloaddition using *o*-tolyl isocyanide (eq 6).[11]

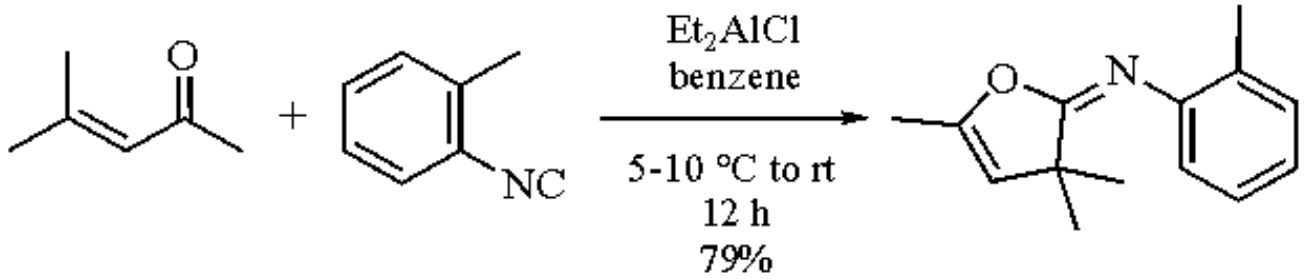

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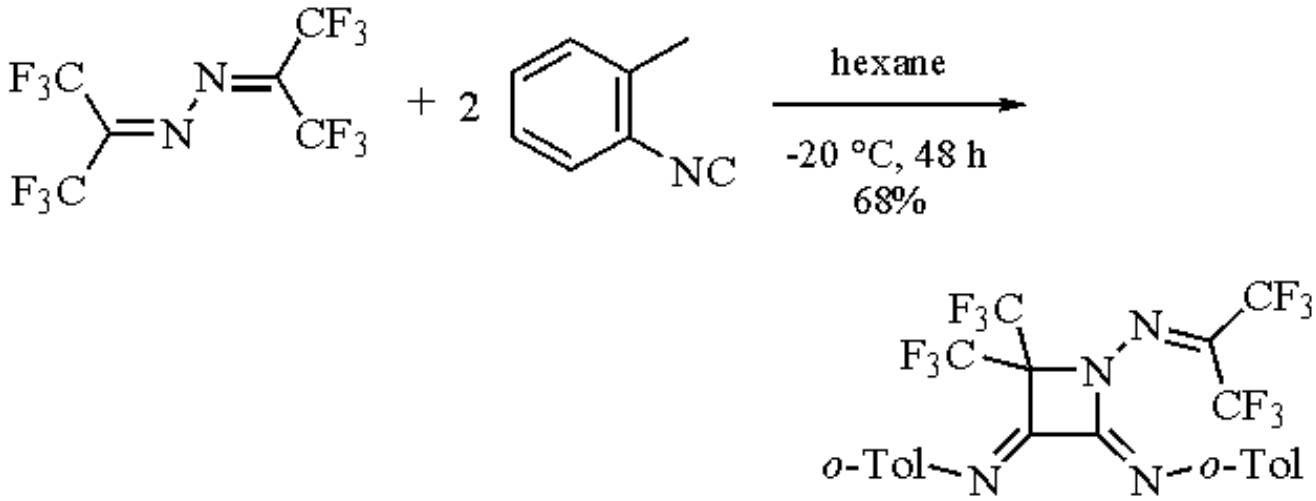

(6)

Azomethines.

Nucleophilic attack of organozinc compounds on the isocyanide carbon leads to the corresponding Schiff bases (eq 7).[12] Similarly, Pd^0 catalysis effects insertion of *o*-tolyl isocyanide into the Si-Si bond of bis-silyl compounds (eq 8).[13]

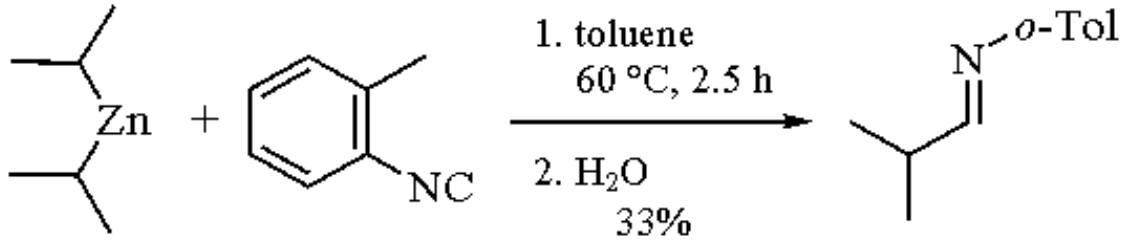

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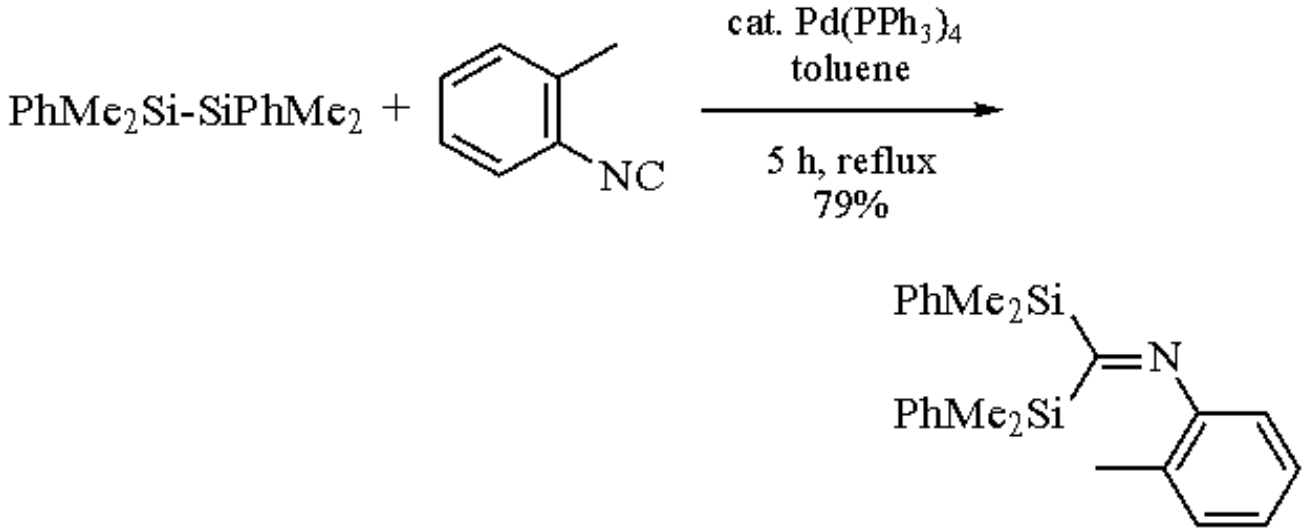

(8)

Related Reagents.

t-Butyl Isocyanide; ***Cyclohexyl Isocyanide***; ***Ethyl Isocyanoacetate***; ***Isocyanomethyllithium***; ***Methyl Isocyanide***; ***Phenyl Isocyanide***;

1,1,3,3-Tetramethylbutyl Isocyanide.

---

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(*R*)-(+)-*p*-Tolylsulfinylacetic Acid

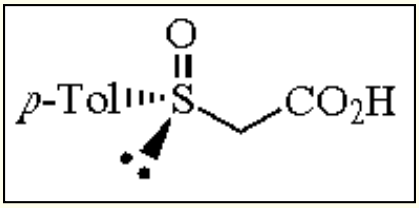

[88981-65-1] · $C_9H_{10}O_3S$ · (*R*)-(+)-*p*-Tolylsulfinylacetic Acid · (MW 198.26)

(optical resolution of amines[1,3,4])

Physical Data: $[\alpha]_D$ = +143.5° (acetone, *c* = 33.0). The absolute configuration of this reagent (and other arylsulfinyl acetic acids) is characterized by two CD Cotton effects which are observed in the presence of the metal cluster $[Mo_2(OAc)_4]$ in DMSO solution above 300 nm.[2]

Preparative Method: prepared by carboxylation of ***(R)-(+)-Methyl p-Tolyl Sulfoxide*** carbanion generated with ***Lithium Diisopropylamide*** (eq 1).[1]

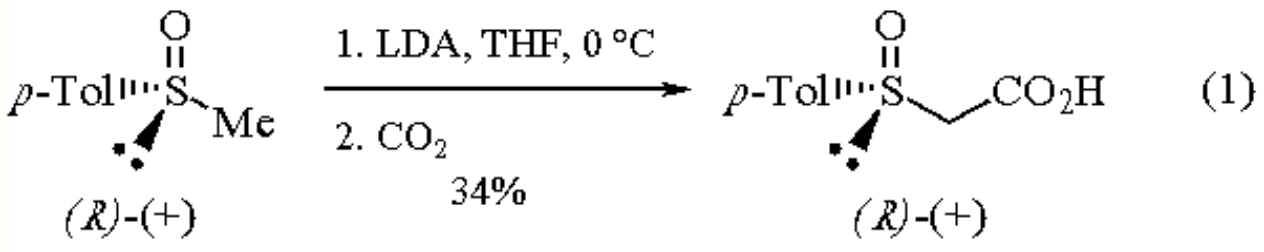

Optical Resolution of Indole Alkaloid Precursors.

This reagent has been used for optical resolutions of tetracyclic alkaloids such as 10,22-dioxokopsane (**1**)[1] and kopsinine (**2**).[3]

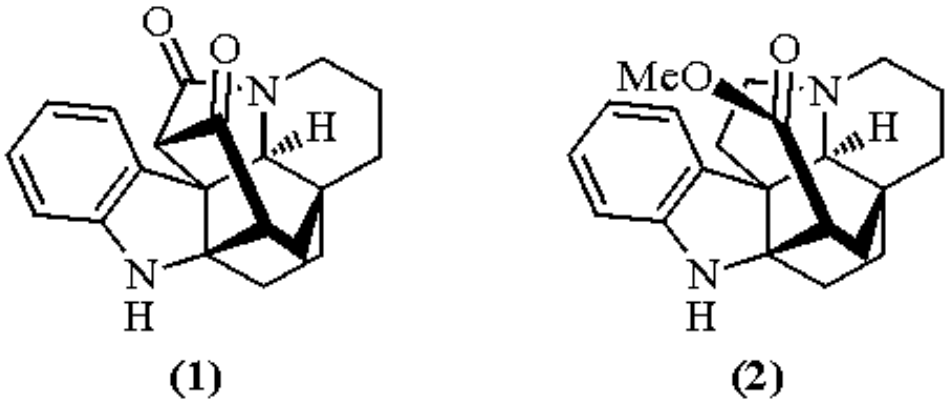

The racemic tetracyclic amine (**3**) can be coupled to (*R*)-(+)-*p*-tolylsulfinylacetic acid using the modified carbodiimide reagent ***1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide Metho-p-toluenesulfonate*** to give the diastereomeric sulfinyl amides (**4**) and (**5**) (eq 2), which are readily separated by HPLC.[1,3]

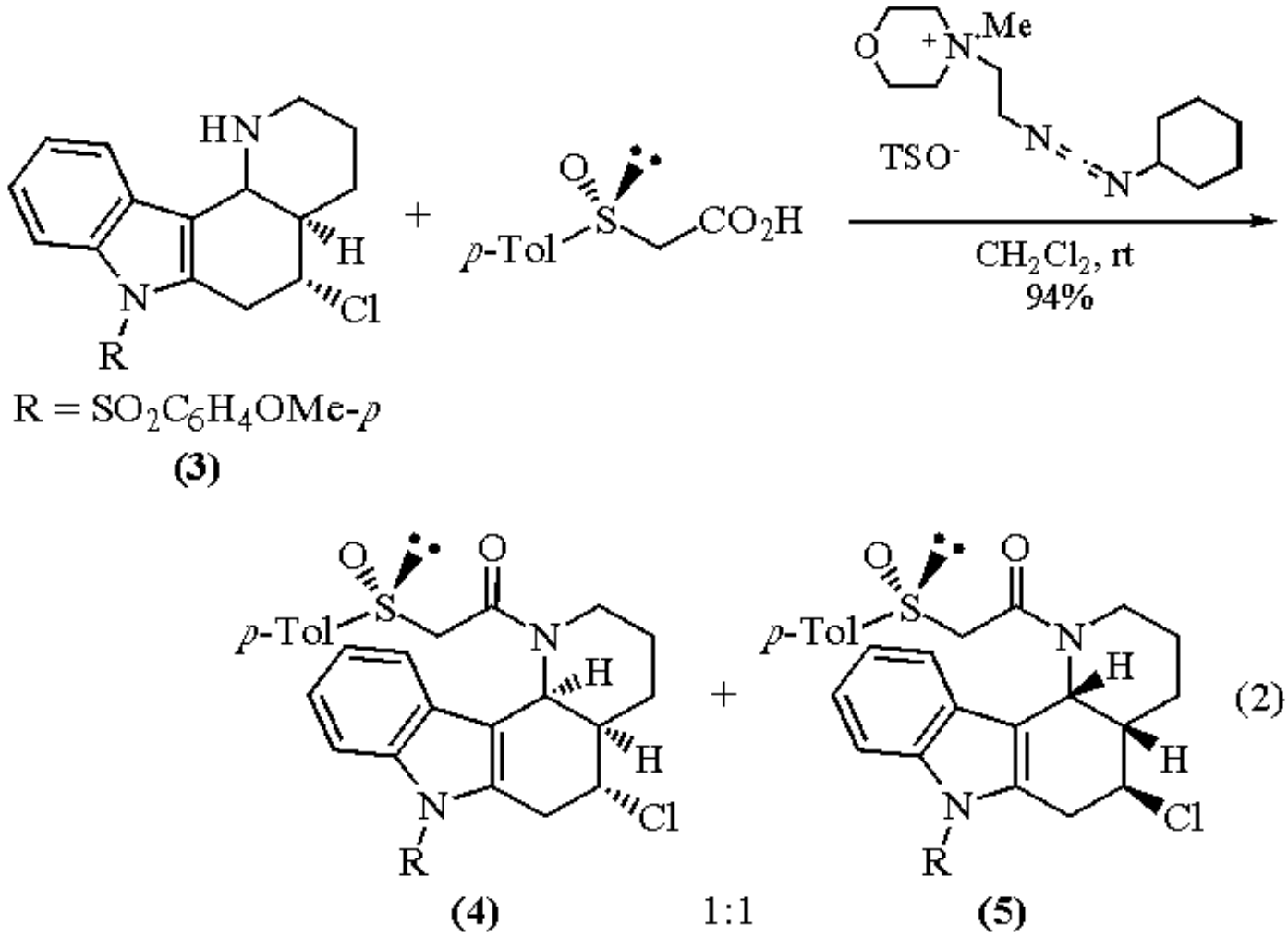

Similarly, in a total synthesis of strychnine, the optical resolution was carried out by separation of the sulfinyl lactam diastereomers (**7**) and (**8**), which were obtained from the heptacyclic indole alkaloid precursor (**6**); this was first transformed with (*R*)-(+)-*p*-tolylsulfinylacetic acid into the corresponding sulfinyl amide and then converted to the diastereomeric lactams (**7**) and (**8**) by an intramolecular conjugate addition (eq 3).[4]

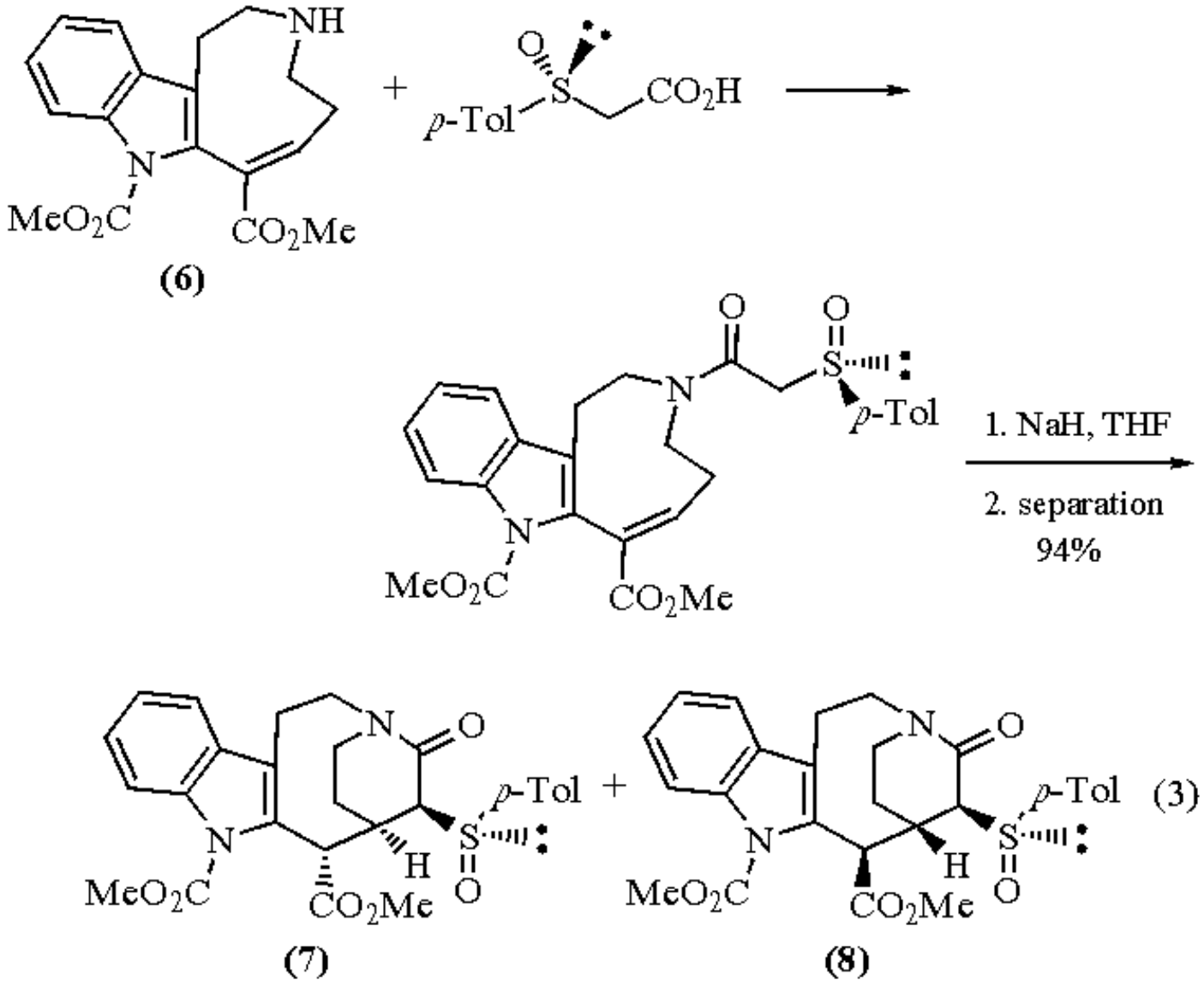

1. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *JACS* **1984**, *106*, 2105.
2. Drabowicz, J.; Mikolajczyk, M. *Croat. Chem. Acta* **1989**, *62*, 423.
3. Magnus, P.; Brown, P. *CC* **1985**, 184.
4. Magnus, P.; Melvyn, G.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *JACS* **1992**, *114*, 4403.

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(*R*)-(+)-α-(*p*-Tolylsulfinyl)-*N,N*-dimethylacetamide

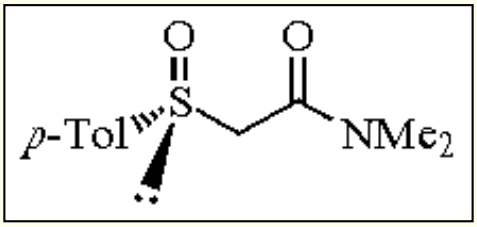

[72298-22-7] · $C_{11}H_{15}NO_2S$ · (*R*)-(+)-α-(*p*-Tolylsulfinyl)-*N,N*-dimethylacetamide · (MW 225.34)

(asymmetric aldol-type condensation[1,2])

Physical Data: $[\alpha]_D$ = +194.7° ($CHCl_3$, *c* = 1).

Preparative Method: prepared[1,2] by reaction of ***Lithio-N,N-dimethylacetamide*** with (*S*)-(-)-menthyl *p*-toluenesulfinate (see ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***) (eq 1).

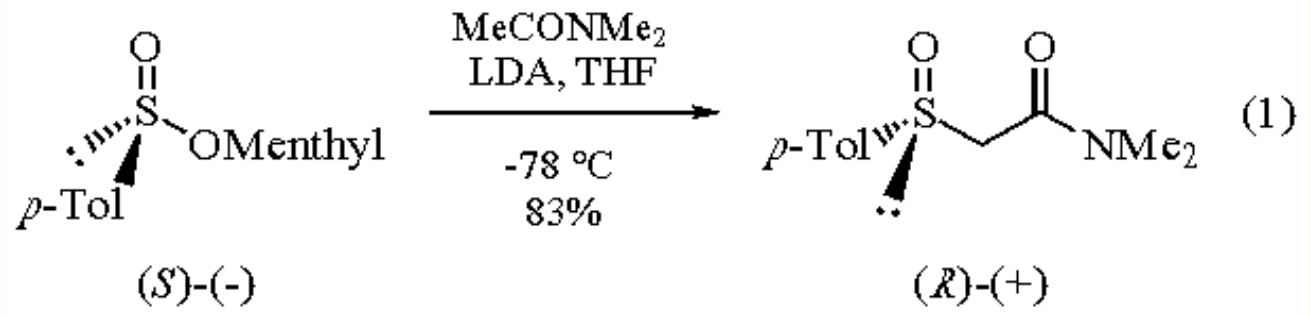

The Pummerer reaction of optically active (*R*)-(+)-α-(*p*-tolylsulfinyl)-*N,N*-dimethylacetamide with ***Acetic Anhydride*** in the presence of ***1,3-Dicyclohexylcarbodiimide*** is highly stereoselective, affording the corresponding α-acetoxy sulfide in moderate yield but with nearly 70% ee (eq 2).[3,4] The recovered starting sulfoxide is obtained in 63% yield.

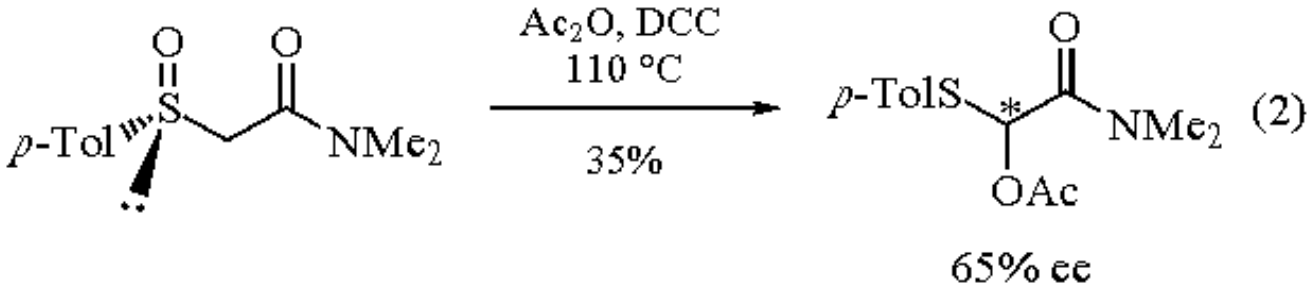

Good asymmetric induction is also observed during the aldol-type condensation of the magnesium enolate of (*R*)-(+)-α-(*p*-tolylsulfinyl)-*N,N*-dimethylacetamide with aldehydes (eq 3).[1,2]

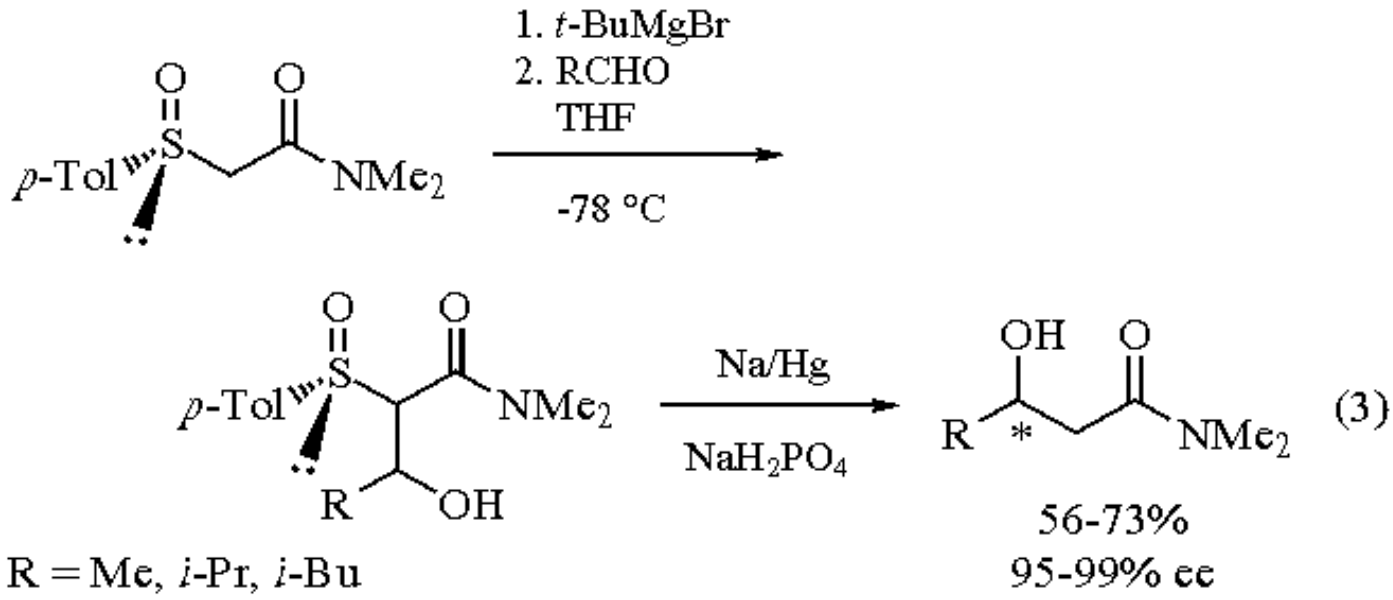

A model (**1**), similar to that proposed for aldol-type condensation of α-sulfinyl esters,[5] has been proposed to predict the chirality of the resulting β-hydroxy amides.

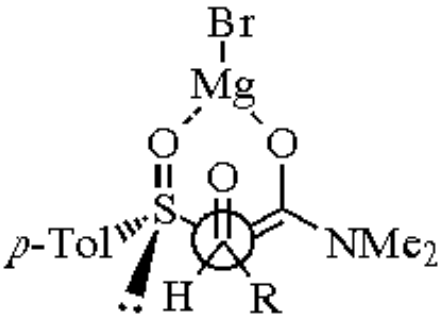

(1)

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1. Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A. *CC* **1983**, 1138.
2. Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A. *T* **1984**, *40*, 3815.
3. Numata, T.; Itoh, O.; Oae, S. *TL* **1979**, *21*, 1869.
4. Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *BCJ* **1983**, *56*, 257.
5. Mioskowski, C.; Solladié, G. *T* **1980**, *36*, 227.

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(3*R*)-(*p*-Tolylsulfinyl)-*N*-methoxyacetimidic Acid Ethyl Ester

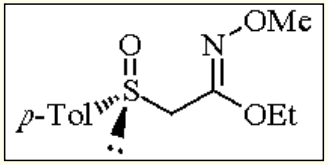

[95614-76-9] · $C_{12}H_{17}NO_3S$ · (3*R*)-(*p*-Tolylsulfinyl)-*N*-methoxyacetimidic Acid Ethyl Ester · (MW 255.37)

(asymmetric aldol-type condensation[1])

Alternate Name: ethyl (*p*-tolylsulfinyl)-*N*-methoxyacetimidate.

Physical Data: $[\alpha]_D$ = +28° (*c* = 1, $CHCl_3$).

Preparative Method: prepared in 89% yield by reacting the lithium enolate of ethyl *N*-methoxyacetimidate with (-)-(*S*)-menthyl *p*-toluenesulfinate (see ***(-)-(1R,2S,5R)-Menthyl (S)-p-Toluenesulfinate***) (eq 1).[1]

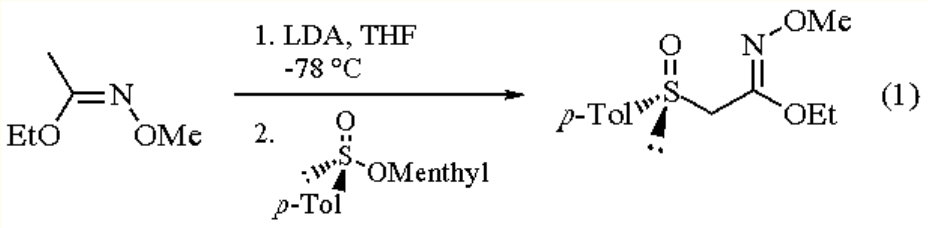

Aldol-Type Condensation.

Aldol-type condensation of the lithium enolate of ethyl (*R*)-(*p*-tolylsulfinyl)-*N*-methoxyacetimidate (prepared with ***n-Butyllithium***) with aldehydes affords, after desulfurization with ***Raney Nickel***, β-hydroxy esters with high enantioselectivity (eq 2).[1]

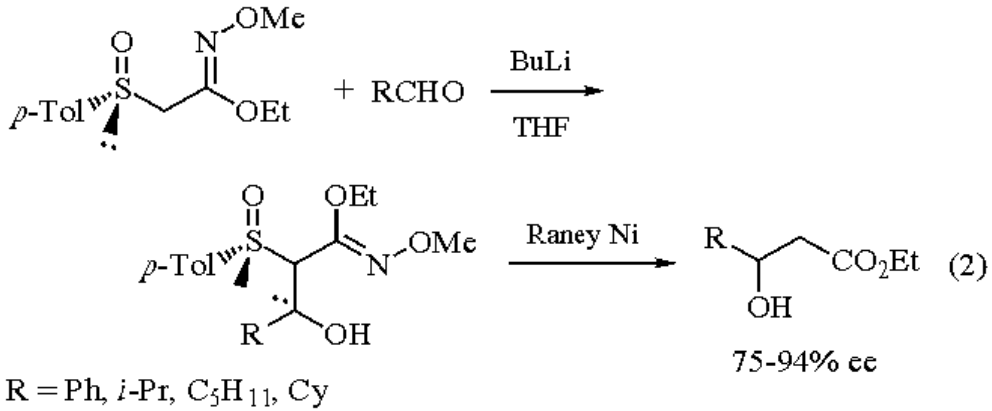

Anti diastereoselectivity gives the optically active (*S*)-β-hydroxy ester while *syn* diastereoselectivity leads to the (*R*)-β-hydroxy ester, via a chelated six-membered transition state (eq 3). Since the *anti* intermediate is more stable, the (*S*)-β-hydroxy ester predominates under thermodynamic conditions (Table 1, entry 1). Higher diastereoselectivity is achieved by changing the counterion from lithium to a more chelating one such as zinc (Table 1, entry 2). On the other hand, in order to obtain diastereoselection under kinetic control, zirconium enolates (prepared by treating the lithium enolate with ***Dichlorobis(cyclopentadienyl)zirconium***) are used, leading to the (*R*)-β-hydroxy ester (Table 1, entry 3) in high yield.

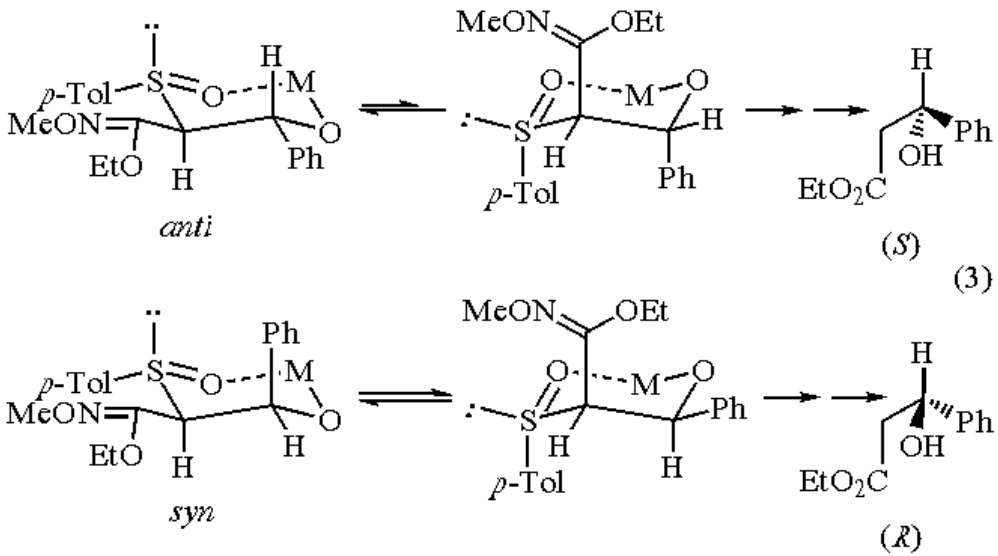

Table 1 Diastereoselection in the Aldol-Type Reaction

Entry	Aldehyde	Metalation conditions	Condensation conditions	Abs. conf.	ee
1	R = Ph	BuLi, - 78 °C, 15 min	- 78 °C to 0 °C, 4 h	(*S*)	75%
2	R = Ph	BuLi, - 78 °C, 15 min 1 equiv. $ZnCl_2$, - 78 °C, 30 min	- 78 °C to 0 °C, 4 h 20 °C, 30 min	(*S*)	86%
3	R = Ph	BuLi, - 78 °C, 15 min 2 equiv. Cp_2ZrCl_2, - 78 °C, 30 min	- 78 °C, 2.5 h	(*R*)	88%

1. Bernardi, A.; Colombo, L.; Gennari, C.; Prati, L. *T* **1984**, *40*, 3769.

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p-Tolylsulfinylmethyllithium[1]

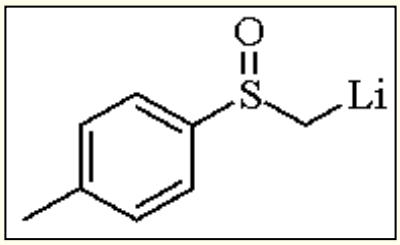

[1519-39-7] · C_8H_9LiOS · *p*-Tolylsulfinylmethyllithium · (MW 160.18)

(asymmetric synthesis; adds diastereoselectively to carbonyl compounds,[1] esters,[1] imines,[1b,f] nitrones,[2] and nitrile oxides[3])

Physical Data: stable in THF even above 0 °C.

Solubility: sol THF.

Form Supplied in: generated in situ from precursors, ***(R)-(+)-Methyl p-Tolyl Sulfoxide***, mp 73-75 °C, $[\alpha]^{20}$ +145° (*c* = 2, acetone), and (*S*)-(-)-methyl *p*-tolyl sulfoxide, mp 75-77 °C, $[\alpha]^{20}$ -147° (*c* = 2, acetone), both of which are commercially available and can also be prepared by a number of methods.[1,4]

Preparative Method: prepared in situ by the reaction of enantiomers of methyl *p*-tolyl sulfoxide with ***Lithium Diethylamide*** or ***Lithium Diisopropylamide*** in THF at 0 to -78 °C.[1]

Handling, Storage, and Precautions: highly sensitive to air and moisture. Its generation and handling must be carried out under an inert atmosphere of nitrogen or argon. Normally, preparation is carried out immediately prior to use.

Introduction.

Most of the synthetic applications are carried out with (*R*)-(+)-*p*-tolylsulfinylmethyllithium. The carbanion undergoes copper-promoted oxidative dimerization to the optically pure 1,2-bis-sulfoxide (eq 1).[5]

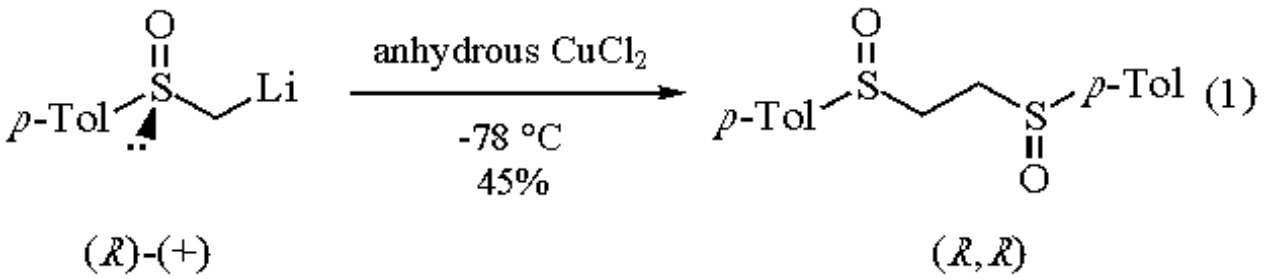

Addition to Carbonyl Compounds.

The addition of *p*-tolylsulfinylmethyllithium to carbonyl compounds gives the β-hydroxy-α-*p*-tolylsulfinyl adducts in poor diastereoselectivity; normally, an approximately 1:1 diastereomeric mixture is obtained.[6] The diastereoselection with benzaldehyde is improved to about 80% with the addition of ***Zinc Chloride***.[7] Although proceeding with a poor diastereoselectivity, the reaction can be applied to the asymmetric synthesis of optically active alcohols. The two diastereomeric adducts can be separated by chromatography. Desulfinylation of each diastereomer gives the corresponding optically active alcohol (eq 2).[6] Optically active alcohols can also be prepared from epoxides (eq 3).[6]

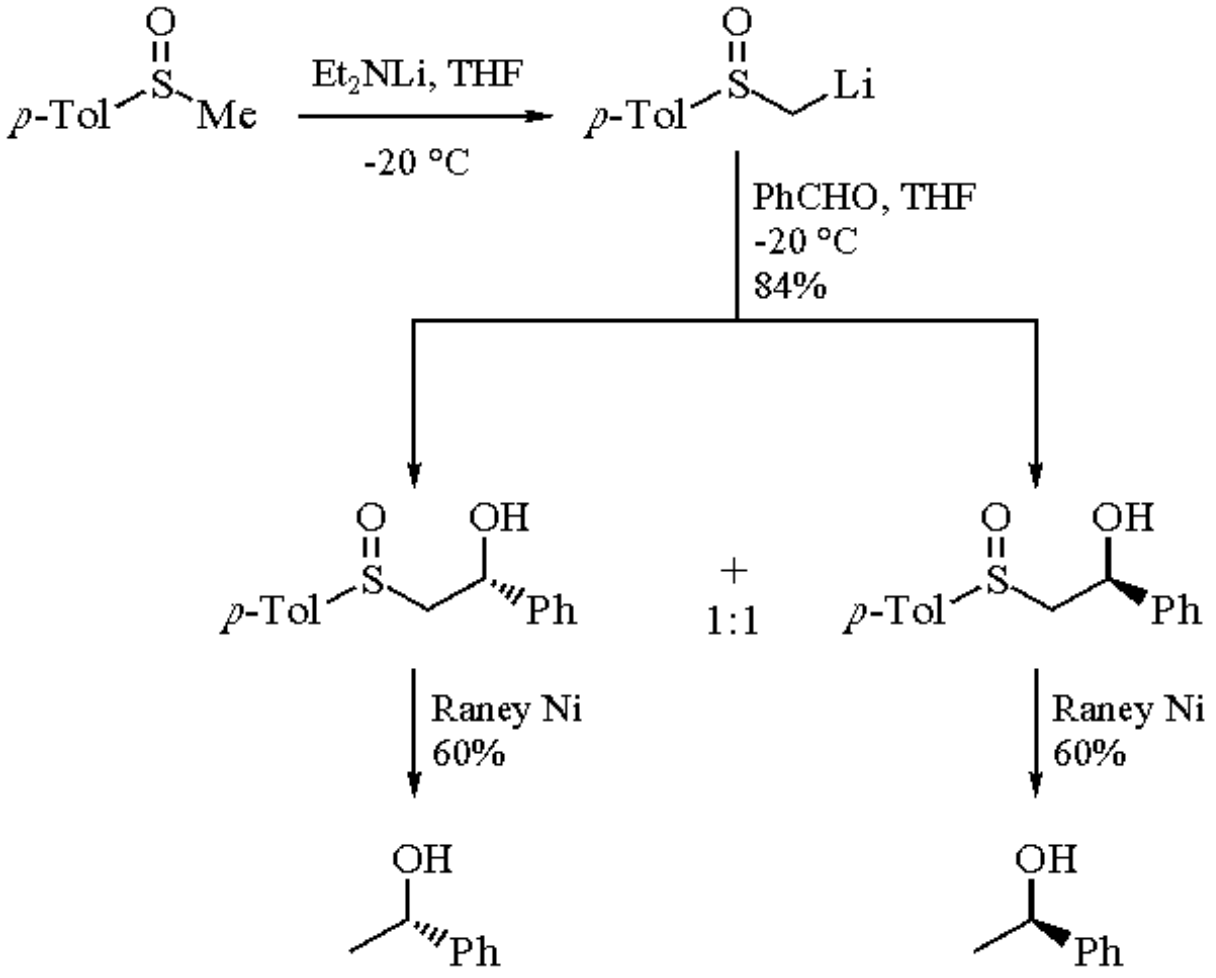
p-Tol
Me
Et2NLi, THF
-20 °C
Li
PhCHO, THF
-20 °C
84%
OH
Ph
+
1:1
Raney Ni
60%

(2)

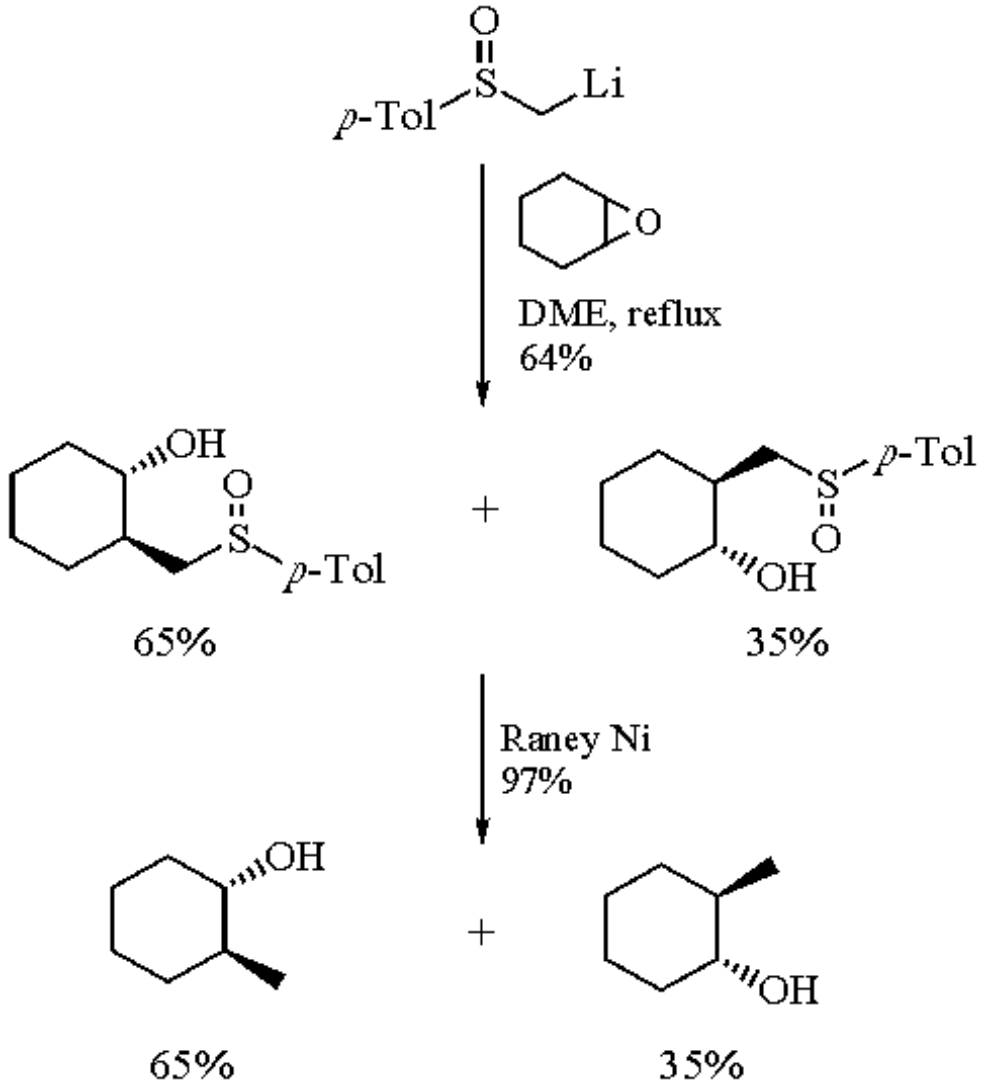
p-Tol
Li
O
DME, reflux
64%
OH
+
65%
35%
Raney Ni
97%

(3)

(*R*)-(+)-*trans*-β-Styryl *p*-tolyl sulfoxide, produced by the reaction of the benzaldehyde adduct with excess ***Sodium Hydride*** and ***Iodomethane***, undergoes selective Michael reaction with diethyl sodiomalonate to give the (R_C,R_S) product as the major isomer, which can be obtained in pure form by fractional crystallization. The product can be transformed into optically active (-)-3-phenylbutyric acid (eq 4).[8]

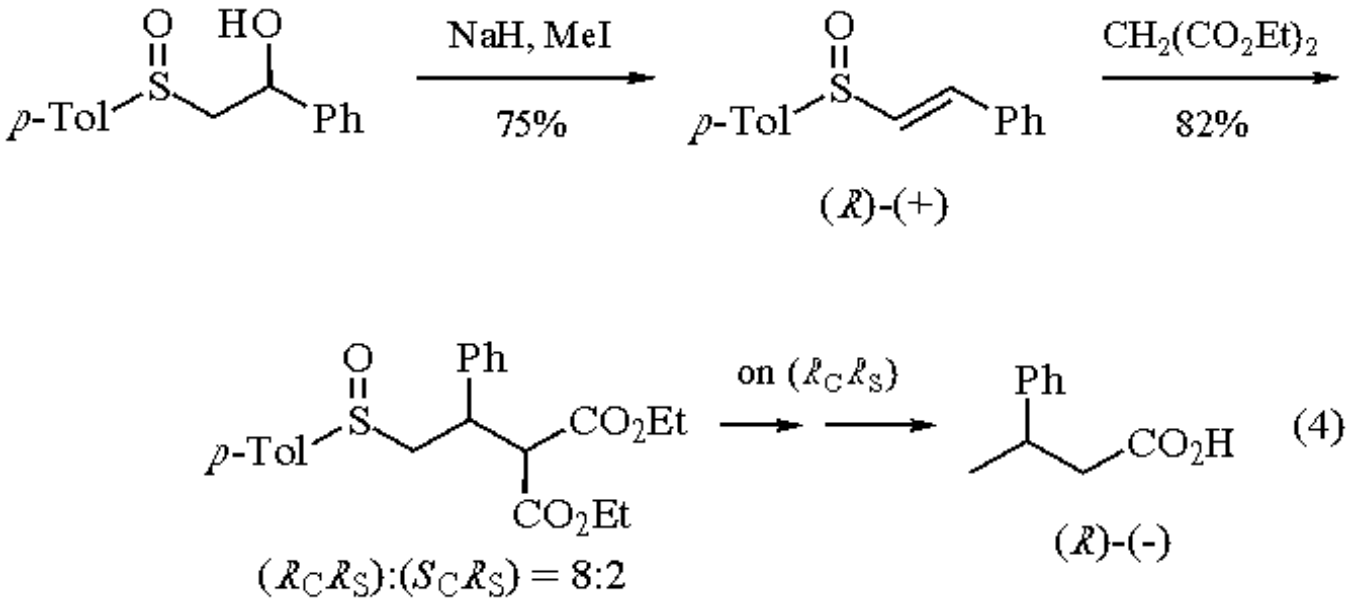

(4)

The dianion of (*R*)-3-(*p*-tolylsulfinyl)propionic acid, prepared from the alkylation product of *p*-tolylsulfinylmethyllithium with lithium bromoacetate, adds to aldehydes to give diastereomeric lactones which can be separated by chromatography; their pyrolyses give optically pure 5-substituted furan-2(5*H*)-ones (eq 5).[9]

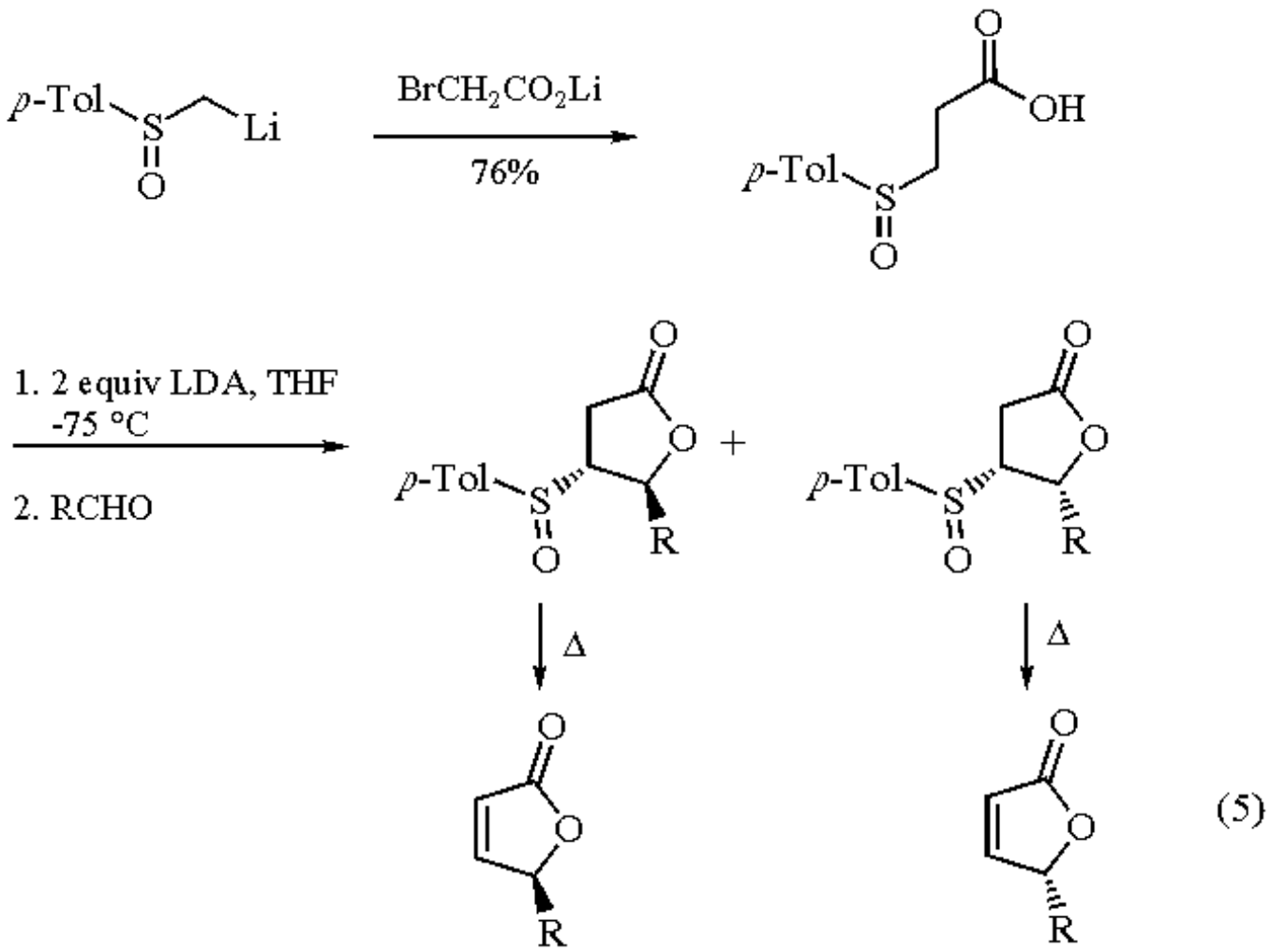

(5)

Addition to Esters.

Racemic *p*-tolylsulfinylmethyllithium reacts with (*R*)-(-)-menthyl benzoate in enantiodifferentiating fashion to give the corresponding optically active β-keto sulfoxide together with optically active methyl *p*-tolyl sulfoxide which has the opposite configuration.[10] A similar result is obtained in the reaction of ethyl carboxylates in the presence of (-)-sparteine (eq 6).[11] The optically active β-keto sulfoxides, which are very important chiral synthons for the synthesis of optically active materials, are normally prepared by the reaction of (*R*)-*p*-tolylsulfinylmethyllithium with carboxylic acid esters.[1a] *p*-Tolylsulfinylmethyl phenyl ketone reacts with ***Diethylaluminum Cyanide*** in toluene diastereoselectively to give one diastereomer of the corresponding cyanohydrin which can be transformed into the optically active alcohol (eq 7).[12]

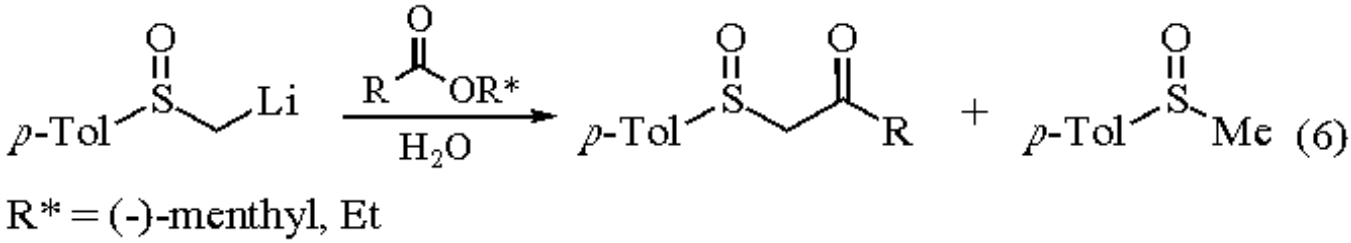

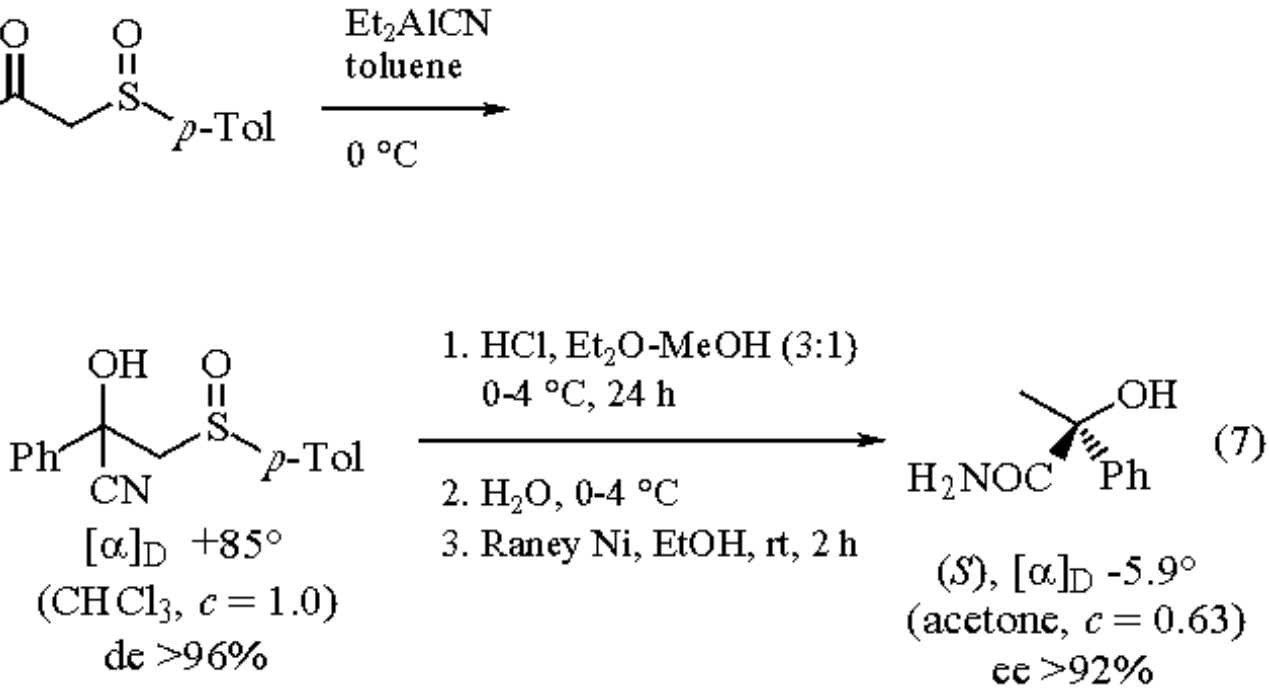

β-Hydroxy sulfoxides of opposite stereochemistry can be prepared in very high diastereomeric excesses (90-95%) by the reduction of β-keto sulfoxides with ***Lithium Aluminum Hydride***, ***Diisobutylaluminum Hydride***, or DIBAL/$ZnCl_2$.[13] The optically pure diastereomers of the β-hydroxy sulfoxides can be transformed into optically active epoxides (eq 8),[14] alcohols (eq 9),[15] and 4-substituted butenolides (eq 10).[16]

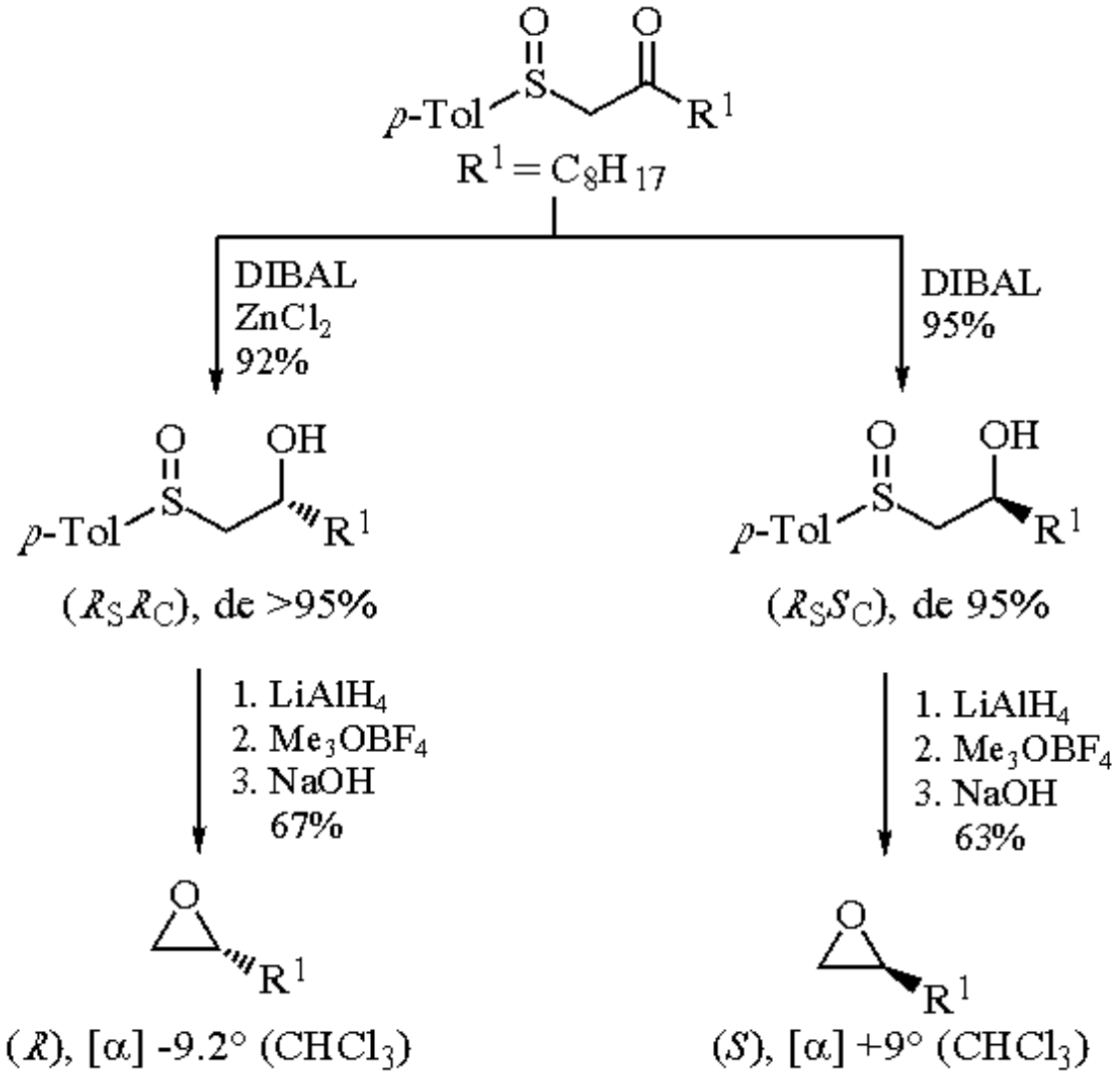
p-Tol
R1 = C8H17
DIBAL
ZnCl2
92%
DIBAL
95%
(RSRC), de >95%
(RSSC), de 95%
1. LiAlH4
2. Me3OBF4
3. NaOH
67%
1. LiAlH4
2. Me3OBF4
3. NaOH
63%
(R), [α] -9.2° (CHCl3)
(S), [α] +9° (CHCl3)

(8)

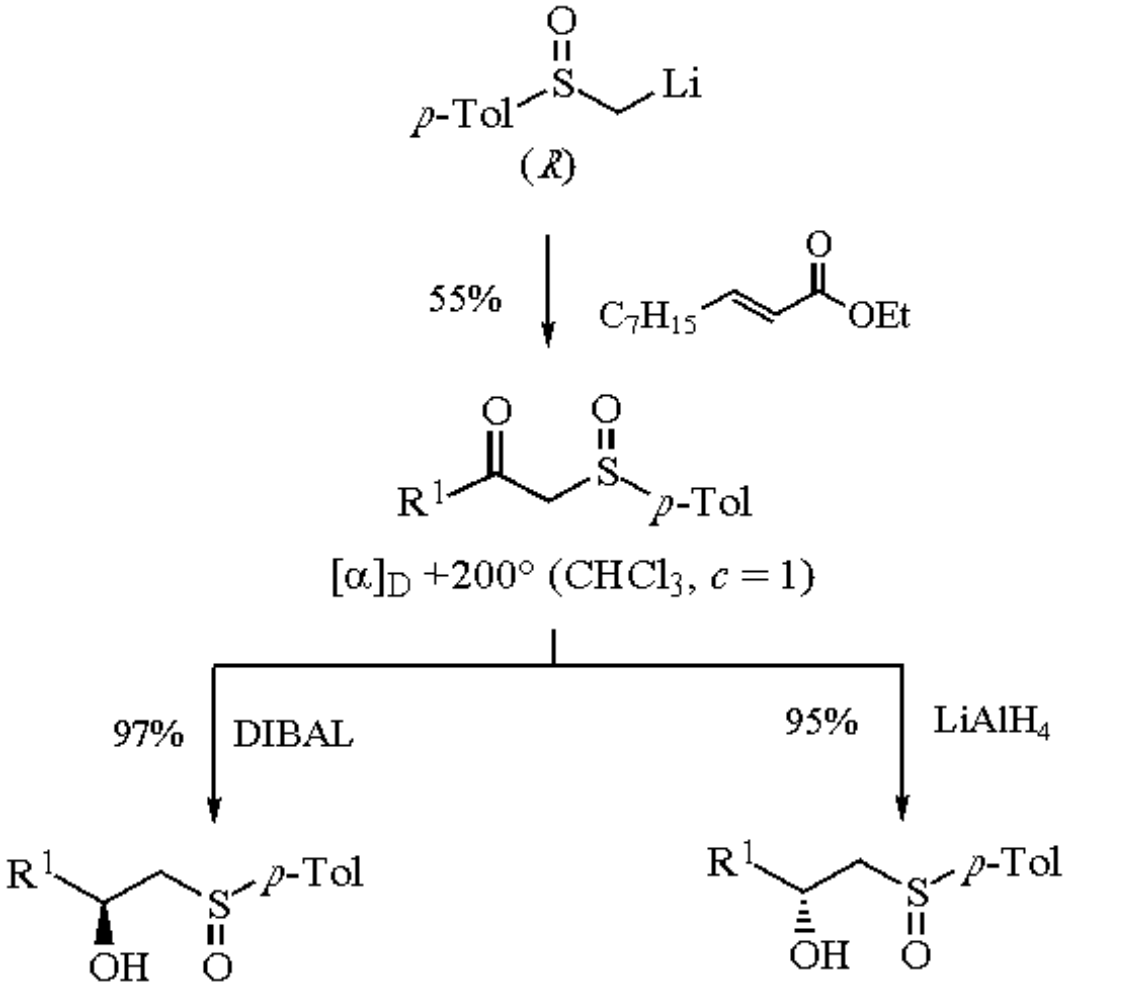
p-Tol
Li
(R)
55%
C7H15
OEt
[α]D +200° (CHCl3, c = 1)
97%
DIBAL
95%
LiAlH4

(9)

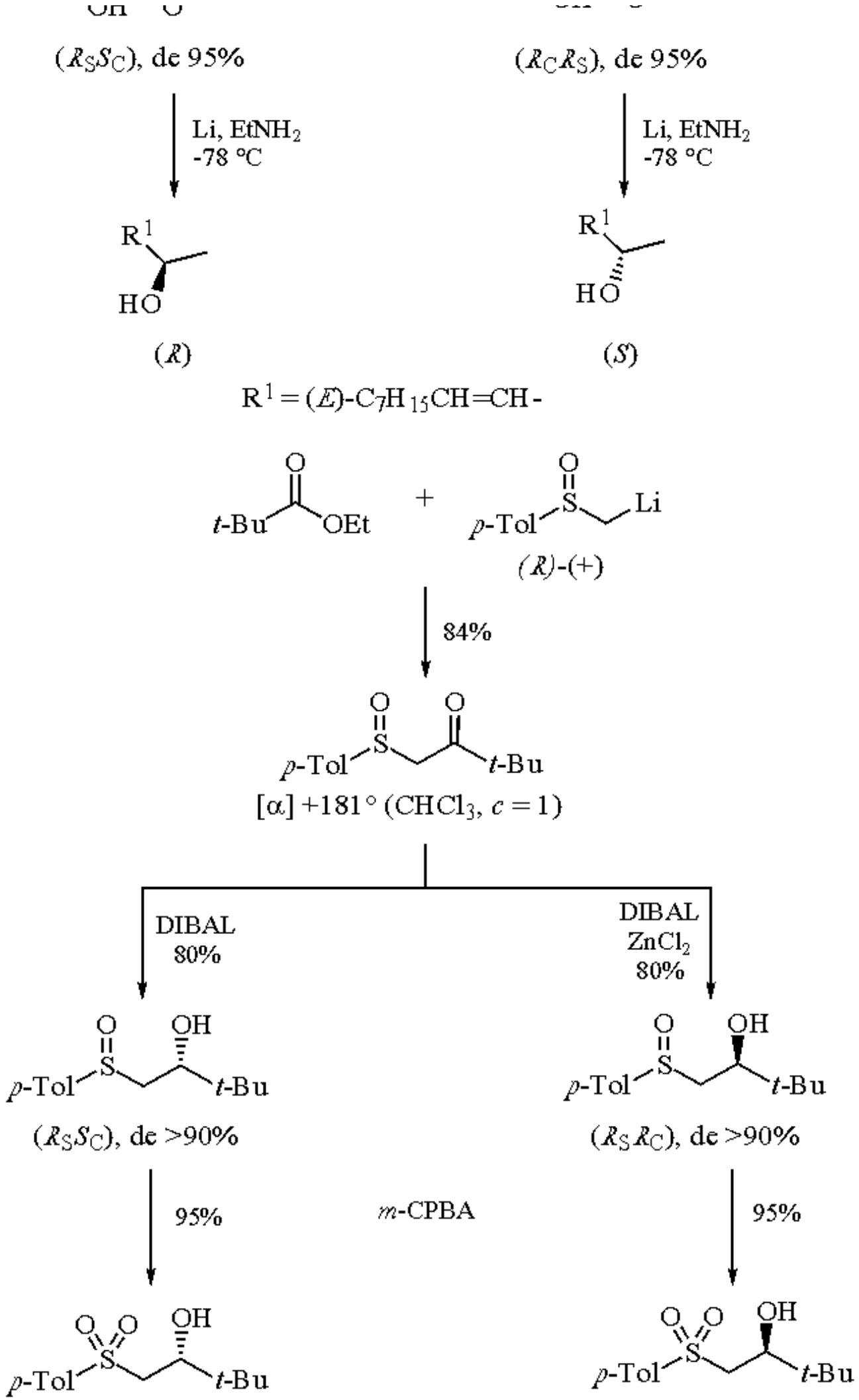
($R_S S_C$), de 95%
($R_C R_S$), de 95%
Li, EtNH2
-78 °C
Li, EtNH2
-78 °C
R1
HO
(R)
(S)
R1 = (E)-C7H15CH=CH-
t-Bu
OEt
p-Tol
S
Li
(R)-(+)
84%
[α] +181° (CHCl3, c = 1)
DIBAL
80%
DIBAL
ZnCl2
80%
OH
($R_S S_C$), de >90%
($R_S R_C$), de >90%
95%
m-CPBA
95%

Addition to Arenesulfinic Esters.

The reaction of (*R*)-(+)-*p*-tolylsulfinylmethyllithium with (-)-menthyl (*S*)-*p*-toluenesulfinate gives (*S*,*S*)-bis(*p*-tolylsulfinyl)methane. (*S*)-(-)-*p*-Tolylsulfinylmethyllithium reacts similarly with (-)-menthyl (*S*)-*p*-toluenesulfinate, producing (*R*,*S*)-bis(*p*-tolylsulfinyl)methane (eq 11).[4c] In contrast to the poor diastereoselection in the reaction of (*R*)-(+)-*p*-tolylsulfinylmethyllithium with carbonyl compounds, (*S*,*S*)-(+)-bis(*p*-tolylsulfinyl)methyllithium reacts with aromatic aldehydes with high diastereoselectivity. Its reaction with α,β-unsaturated aldehydes yields 4-substituted (*E*,*E*)-(*S*,*S*)-1,1-bis(*p*-tolylsulfinyl)-1,3-butadiene (eq 12).[17]

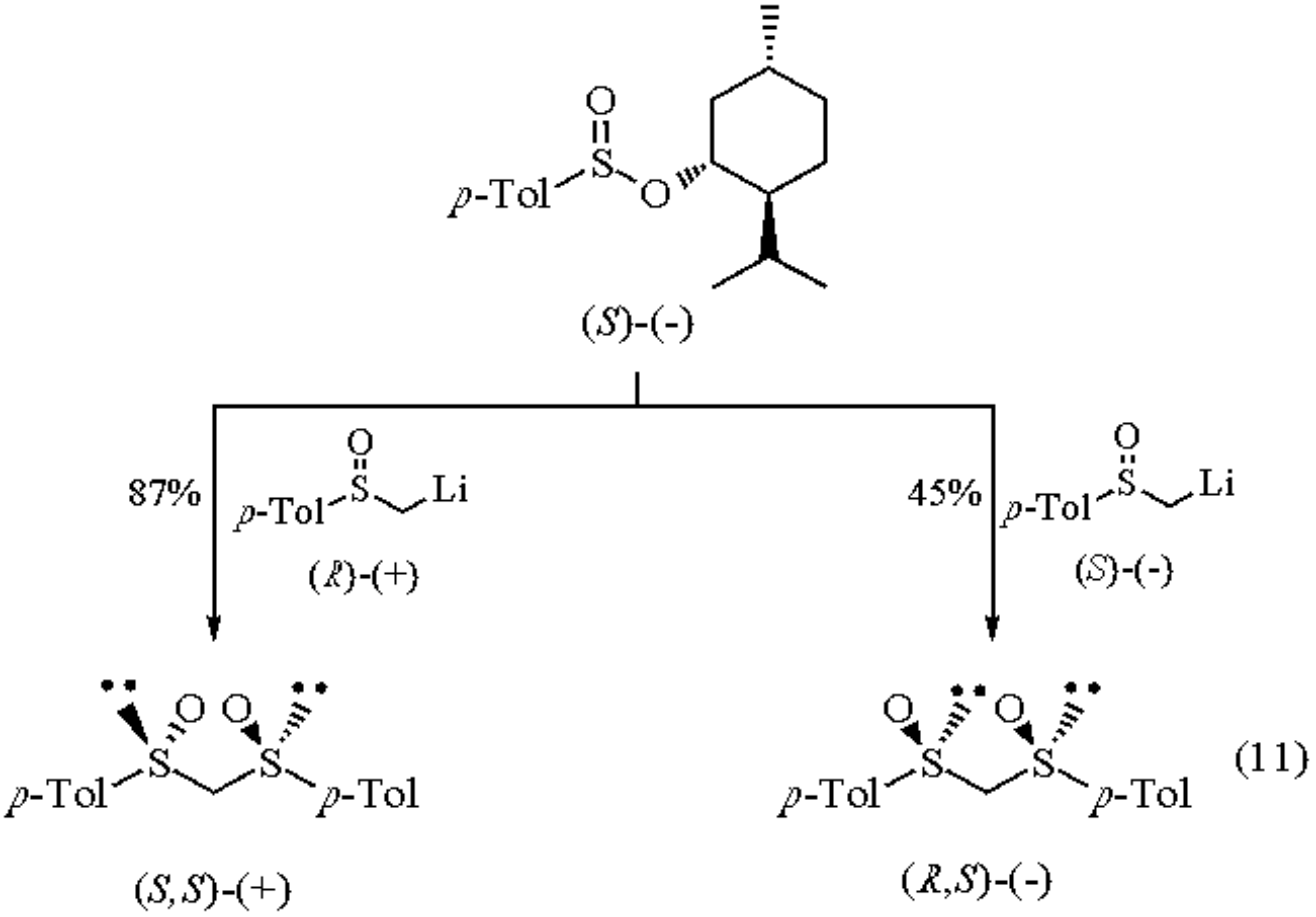

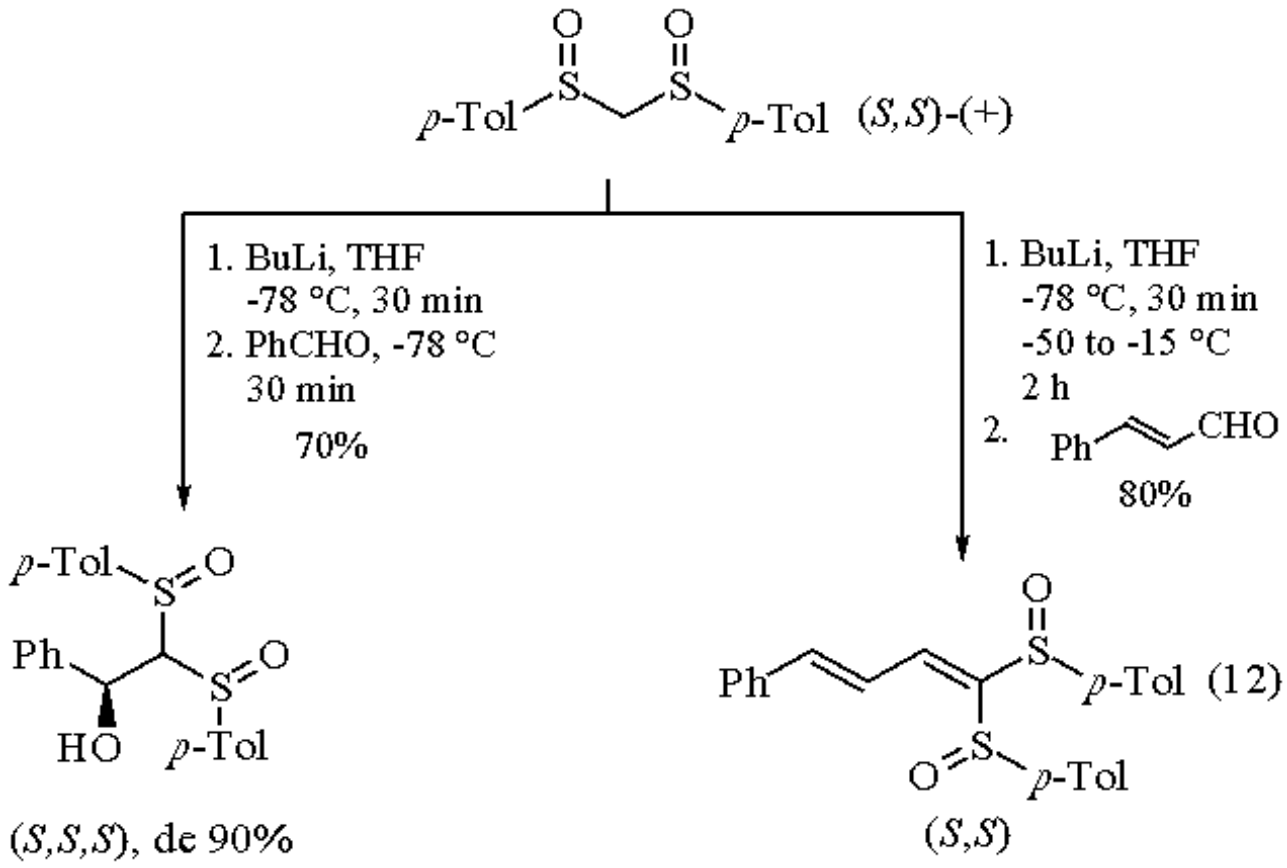

Addition to Imines.

The addition of (*R*)-(+)-*p*-tolylsulfinylmethyllithium to benzylideneaniline produces (R_SR_S)-(+)-*N*-phenyl-2-amino-2-phenylethyl *p*-tolyl sulfoxide in high diastereoselectivity (eq 13).[18] Acyclic and cyclic imines react similarly. The chair transition state can account for the diastereoselective process. Detailed investigations reveal that diastereoselectivity depends on several factors, i.e. the temperature used for deprotonation of methyl *p*-tolyl sulfoxide (optimum conditions: LDA, THF, 0 °C)[18c] and kinetically and thermodynamically controlled reaction conditions. Equilibrium between the diastereomeric adducts is thought to occur over the timescale of the addition reaction. Diastereoselectivity is better under kinetic control than under the thermodynamic control.[18b] This methodology has been applied to the syntheses of (*R*)-(+)-carnegine and (*R*)-(+)-tetrahydropalmatine (eq 14).[19]

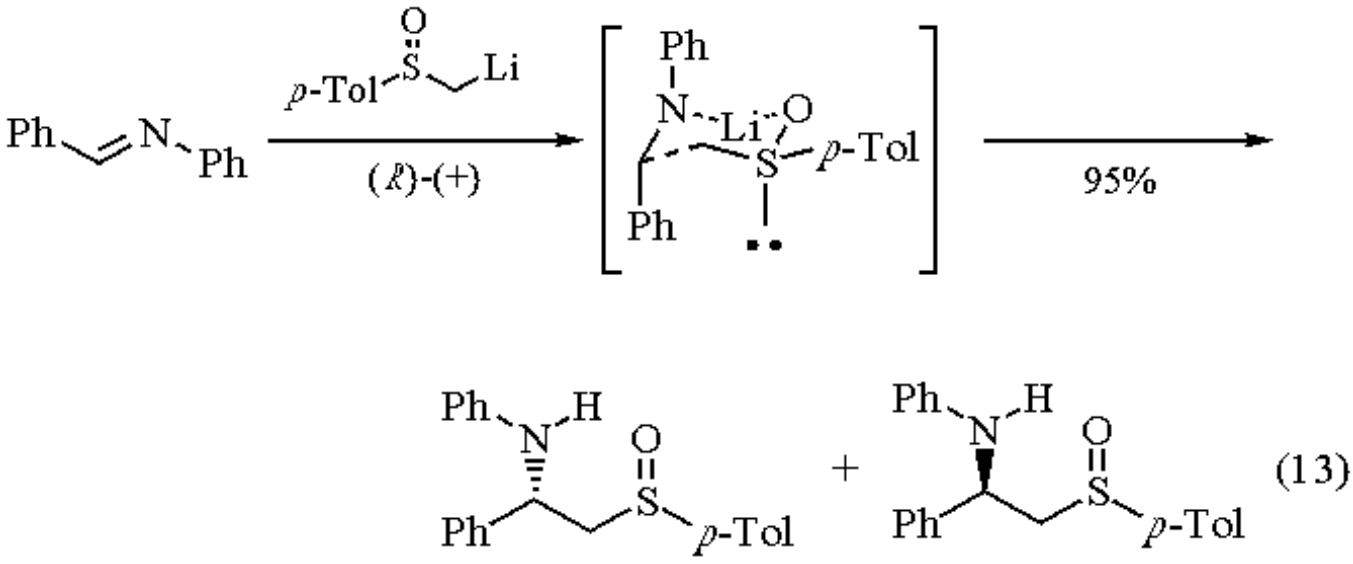

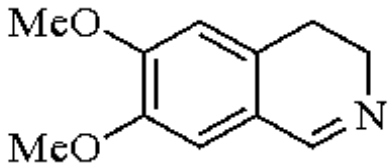

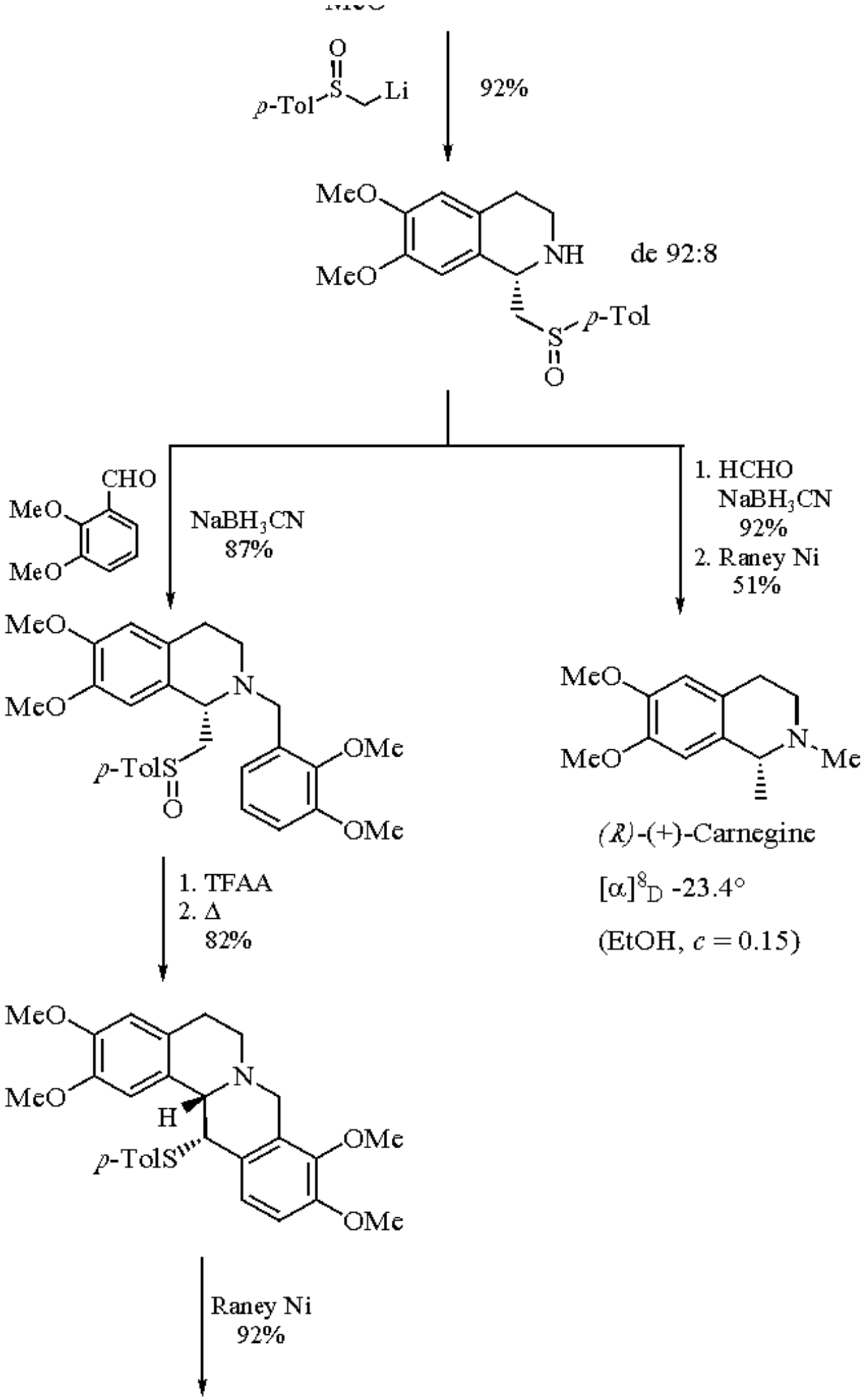
p-Tol
Li
92%
MeO
MeO
NH
de 92:8
p-Tol
CHO
MeO
MeO
NaBH3CN
87%
1. HCHO
NaBH3CN
92%
2. Raney Ni
51%
N
OMe
OMe
p-TolS
1. TFAA
2. Δ
82%
(R)-(+)-Carnegine
[α]8D -23.4°
(EtOH, c = 0.15)
H
Raney Ni
92%

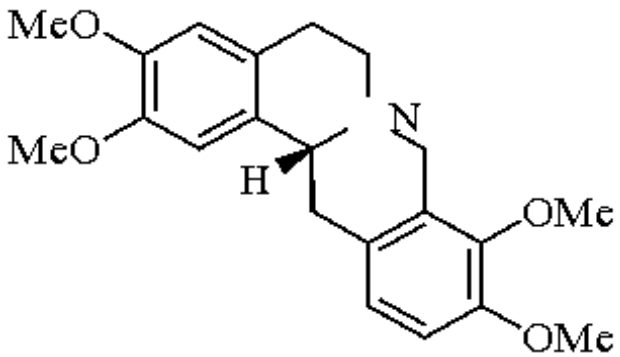

(14)

(*R*)-(+)-Tetrahydropalmatine

$[\alpha]^{20}_{D}$ +288.5° (EtOH, $c = 2.0$)

(*R*)-(+)-p-Tolylsulfinylmethylmagnesium bromide reacts with 4-bromobutanenitrile to provide (*R*)-(+)-4,5-dihydro-2-(*p*-tolylsulfinylmethyl)-3*H*-pyrrole in low yield (eq 15).[20] This pyrrole derivative, which can be prepared in 92% yield by reaction of α-lithiated 3,4-dihydro-5-methyl-2*H*-pyrrole with (*S*)-(-)-menthyl *p*-toluenesulfinate, is utilized in the syntheses of (+)-elaeokanine A and (-)-elaeokanine B (eq 16).[20b] A similar approach has been utilized in the synthesis of yohimban alkaloids (eq 17).[20c]

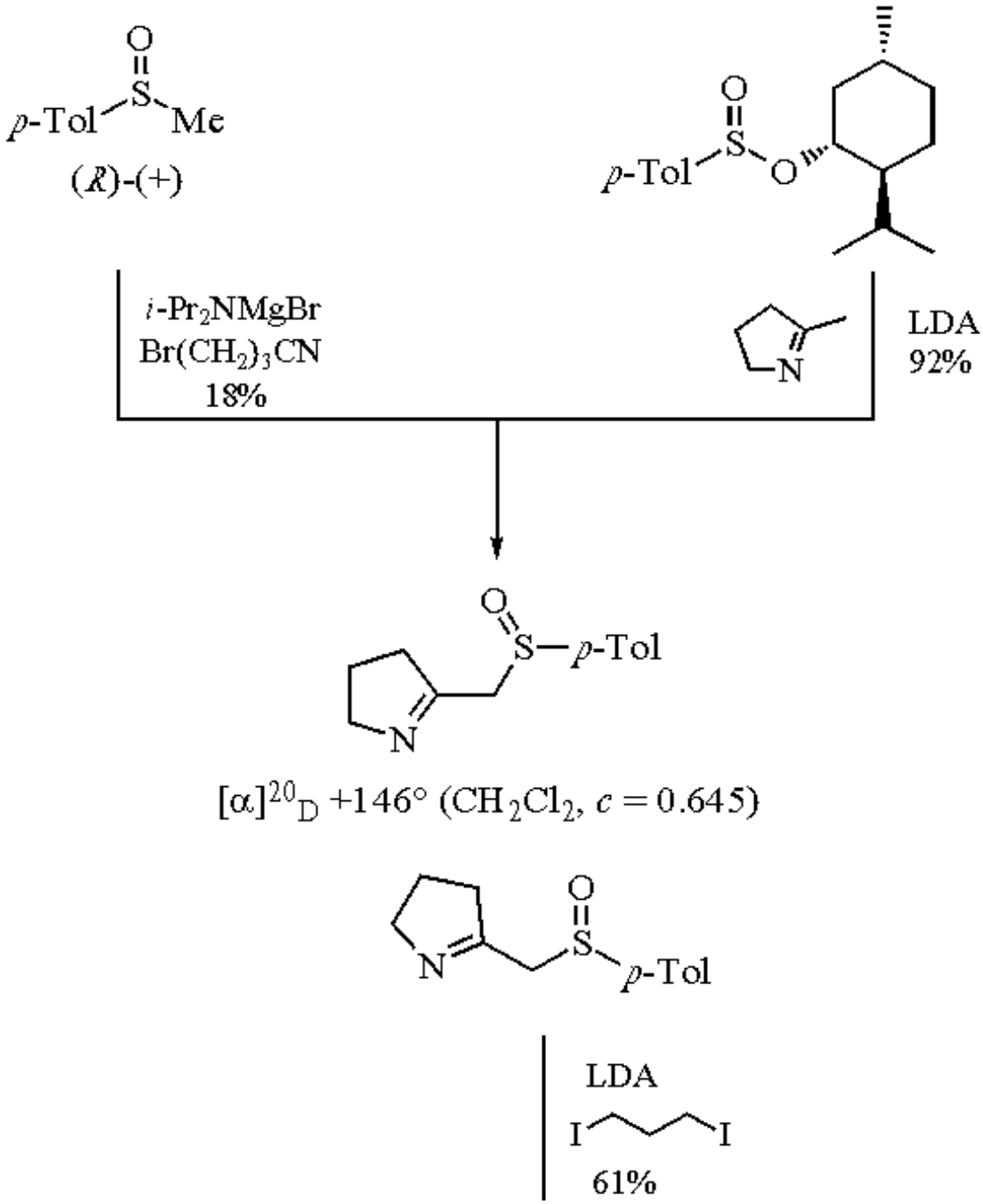

(15)

$[\alpha]^{20}_{D}$ +146° (CH_2Cl_2, $c = 0.645$)

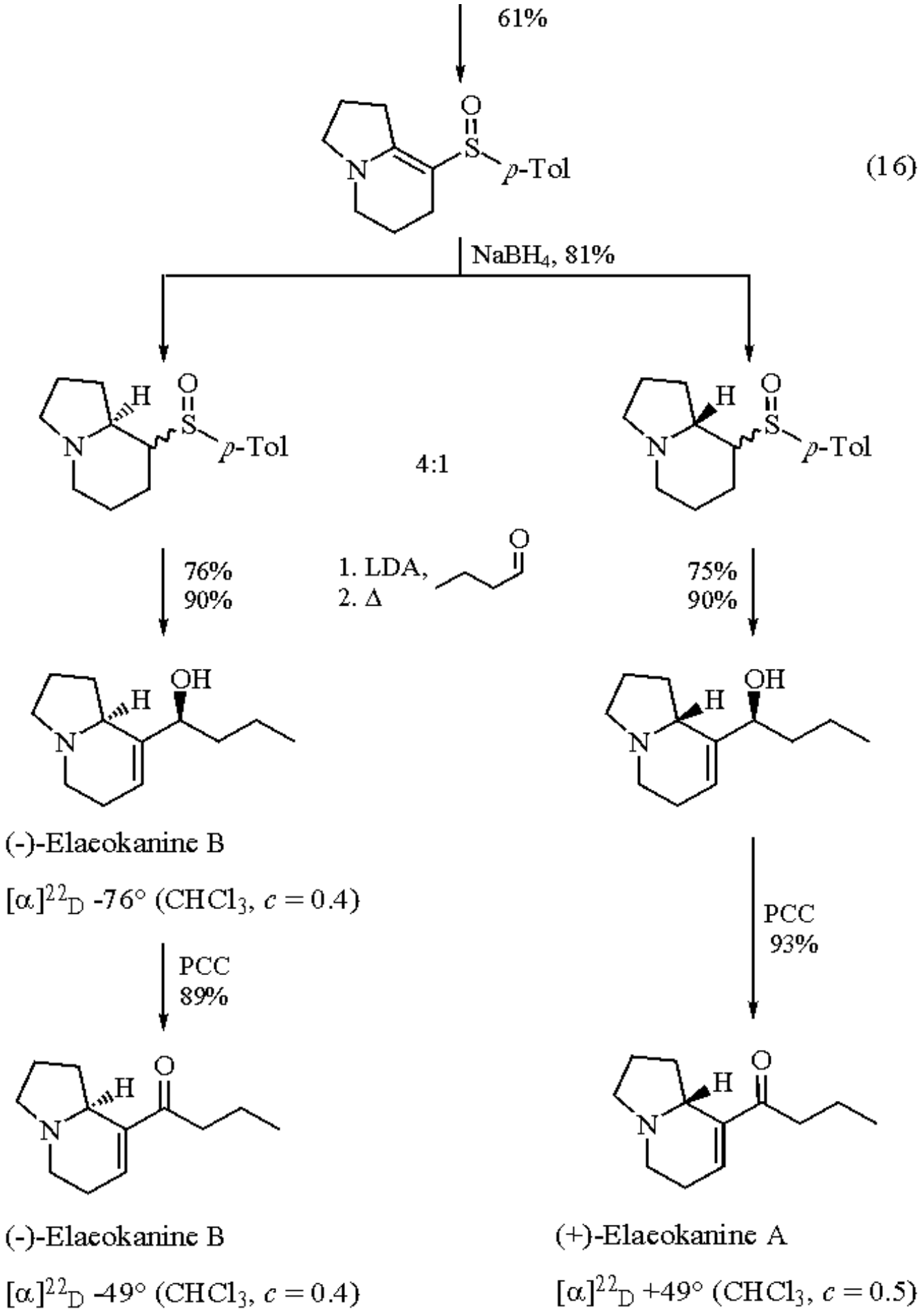
61%
p-Tol
(16)
NaBH4, 81%
4:1
76%
90%
1. LDA,
2. Δ
75%
90%
(-)-Elaeokanine B
[α]22D -76° (CHCl3, c = 0.4)
PCC
89%
PCC
93%
(-)-Elaeokanine B
[α]22D -49° (CHCl3, c = 0.4)
(+)-Elaeokanine A
[α]22D +49° (CHCl3, c = 0.5)

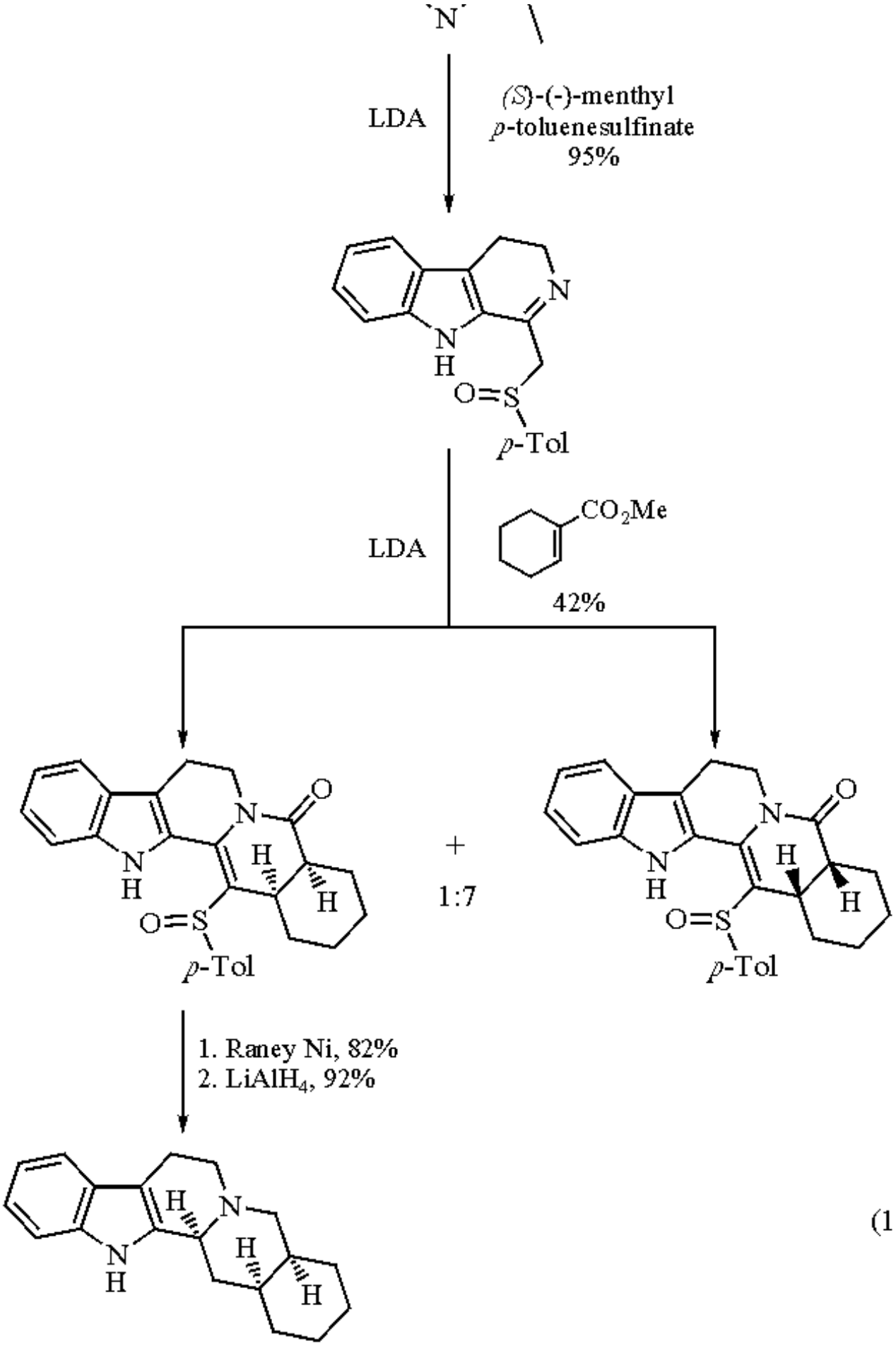

(17)

(-)-Alloyohimban

$[\alpha]^{22}_{D}$ -166° (py, $c = 0.4$)

Addition to Nitrones and Nitrile Oxides.

The reaction with 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide in the presence of quinidine is a highly diastereoselective process. The *N*-hydroxytetrahydroisoquinoline adduct can be desulfurized to (*R*)-(+)-salsolidine (eq 18).[2b] The addition of (*R*)-(+)-*p*-tolylsulfinylmethyllithium to arylnitrile oxides gives β-oximino sulfoxides with high optical purity (eq 19).[3]

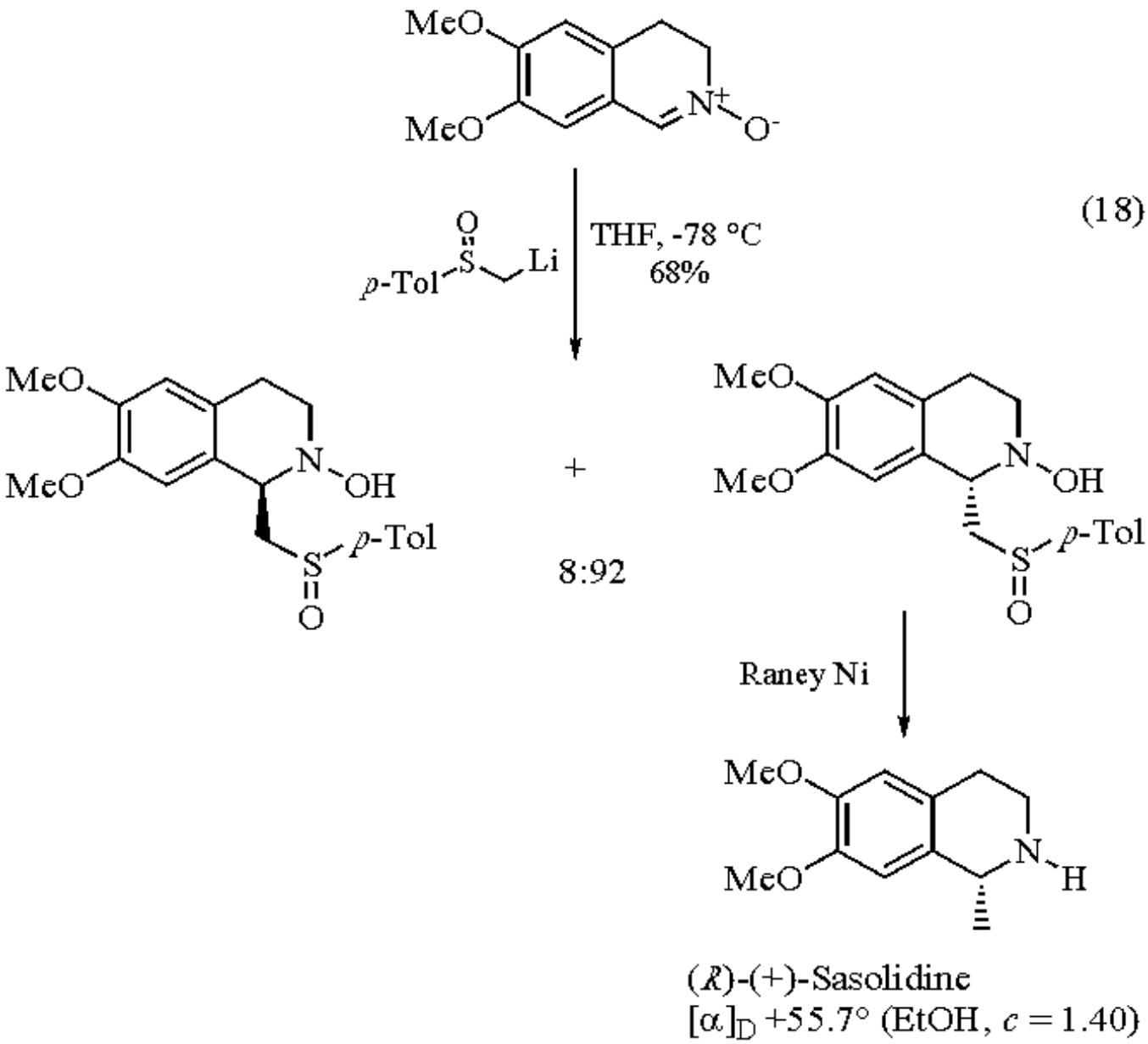

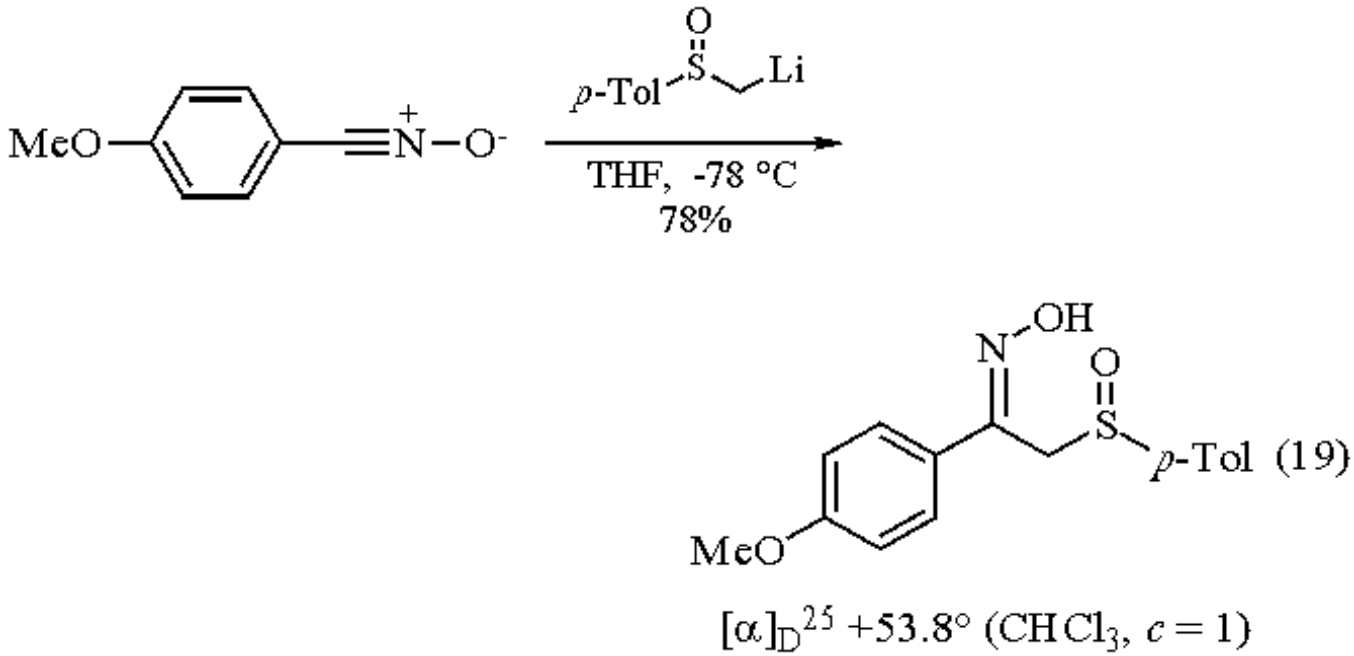

Related Reagents.

Methyl Phenyl Sulfone; ***Phenylthiomethyllithium***.

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(*R*)-(+)-3-(*p*-Tolylsulfinyl)propionic Acid

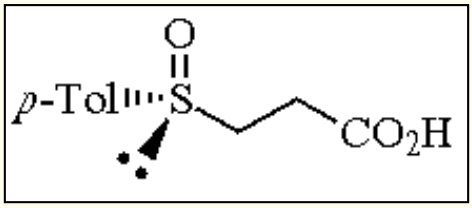

[90334-31-9] · $C_{10}H_{12}O_3S$ · (*R*)-(+)-3-(*p*-Tolylsulfinyl)propionic Acid · (MW 212.29)

(asymmetric aldol-type condensation[2])

Physical Data: $[\alpha]_D$ = +180° ($CHCl_3$, *c* = 0.7), $[\alpha]_D$ = +188° (MeOH, *c* = 0.7).

Preparative Method: conveniently prepared in 76% yield by addition of a suspension of lithium bromoacetate to a solution of the anion of ***(R)-(+)-Methyl p-Tolyl Sulfoxide*** (eq 1).[1,2]

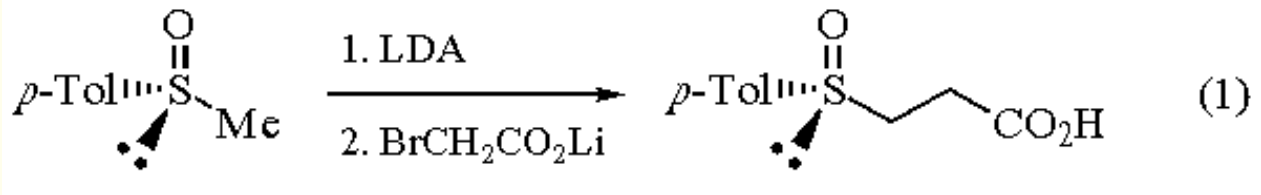

Aldol-Type Condensation.

Dimetalation of (*R*)-(+)-3-(*p*-tolylsulfinyl)propionic acid with ***Lithium Diisopropylamide*** produces a chiral homoenolate dianion equivalent which reacts with carbonyl compounds to afford β-sulfinyl-γ-hydroxy acids; these spontaneously cyclize to give the corresponding β-sulfinyl γ-lactones (eq 2).[1,2]

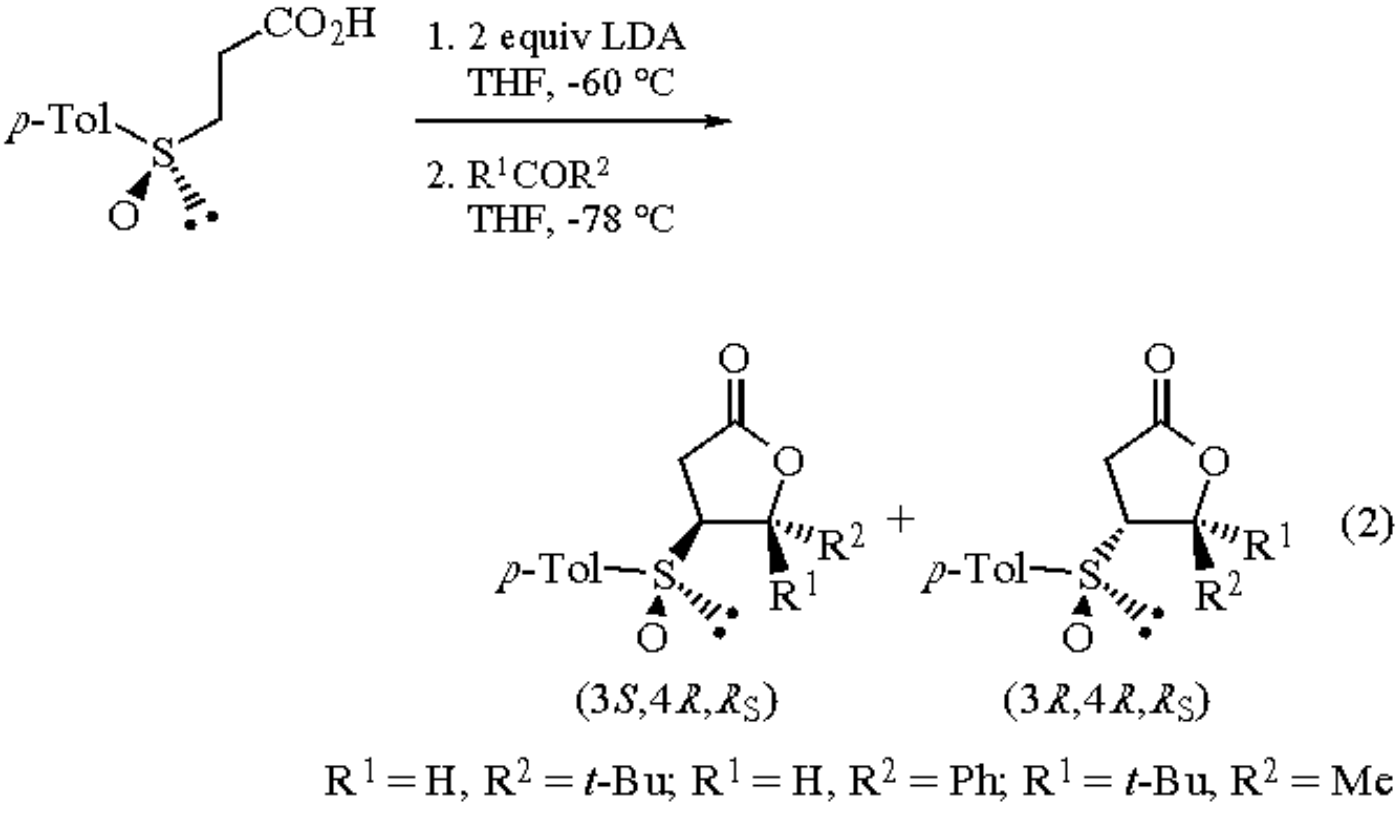

Two new chiral carbon atoms are formed in the condensation and four diastereoisomeric β-sulfinyl γ-lactones can therefore in principle be obtained. However, only two diastereoisomers, (3*S*,4*R*,R_S) and (3*R*,4*S*,R_S), are isolated when the carbanion is condensed with pivalic aldehyde, benzaldehyde, or pinacolone (yield 65-70% for aldehydes, ratio 53:47; yield 47% for pinacolone, ratio 81:19). The diastereoselectivity decreases when the two substituents of the carbonyl group are sterically similar. However, single diastereoisomers can easily be separated through chromatography and transformed in high yield into both enantiomers of optically pure saturated (by desulfurization) and α,β-unsaturated γ-lactones (by pyrolytic sulfoxide elimination) (eq 3). The relative and absolute stereochemistry of all the products have been determined by circular dichroism, nuclear Overhauser effects, and X-ray analyses.

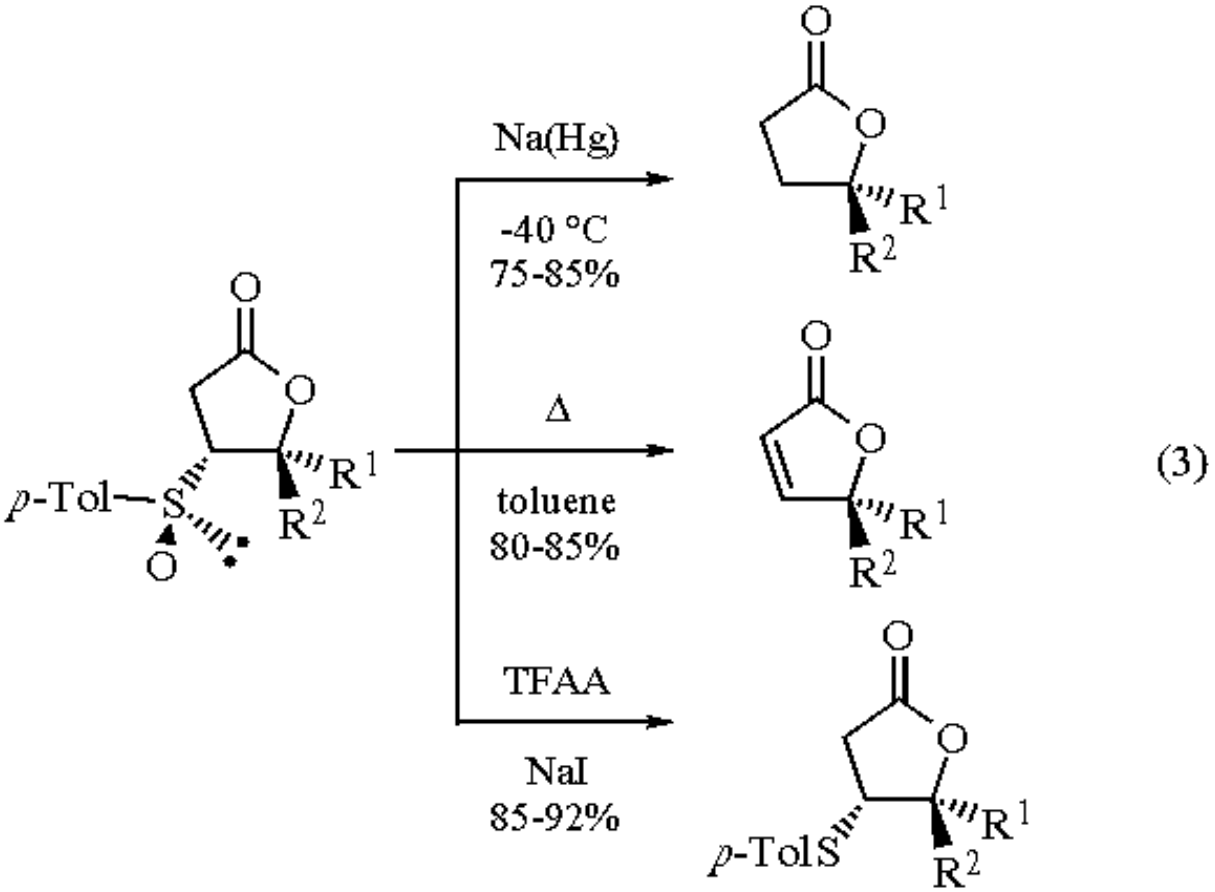

The condensation of the dilithio derivative of (*R*)-(+)-3-(*p*-tolylsulfinyl)propionic acid with protected glycoaldehydes (*O*-*t*-butyl and *O*-

benzyl) gives 5-alkoxy-4-hydroxy-3-(*p*-tolylsulfinyl)pentanoic acids, which spontaneously cyclize to the corresponding 3-sulfinyl-4-alkoxymethyl butanolides (eq 4).[3] Pure diastereomers can be separated by flash chromatography and are obtained in comparable amounts. The corresponding optically pure butenolides are obtained by pyrolytic elimination of the sulfoxides and then transformed into natural (+)-(*R*)-umbelactone (eq 5).

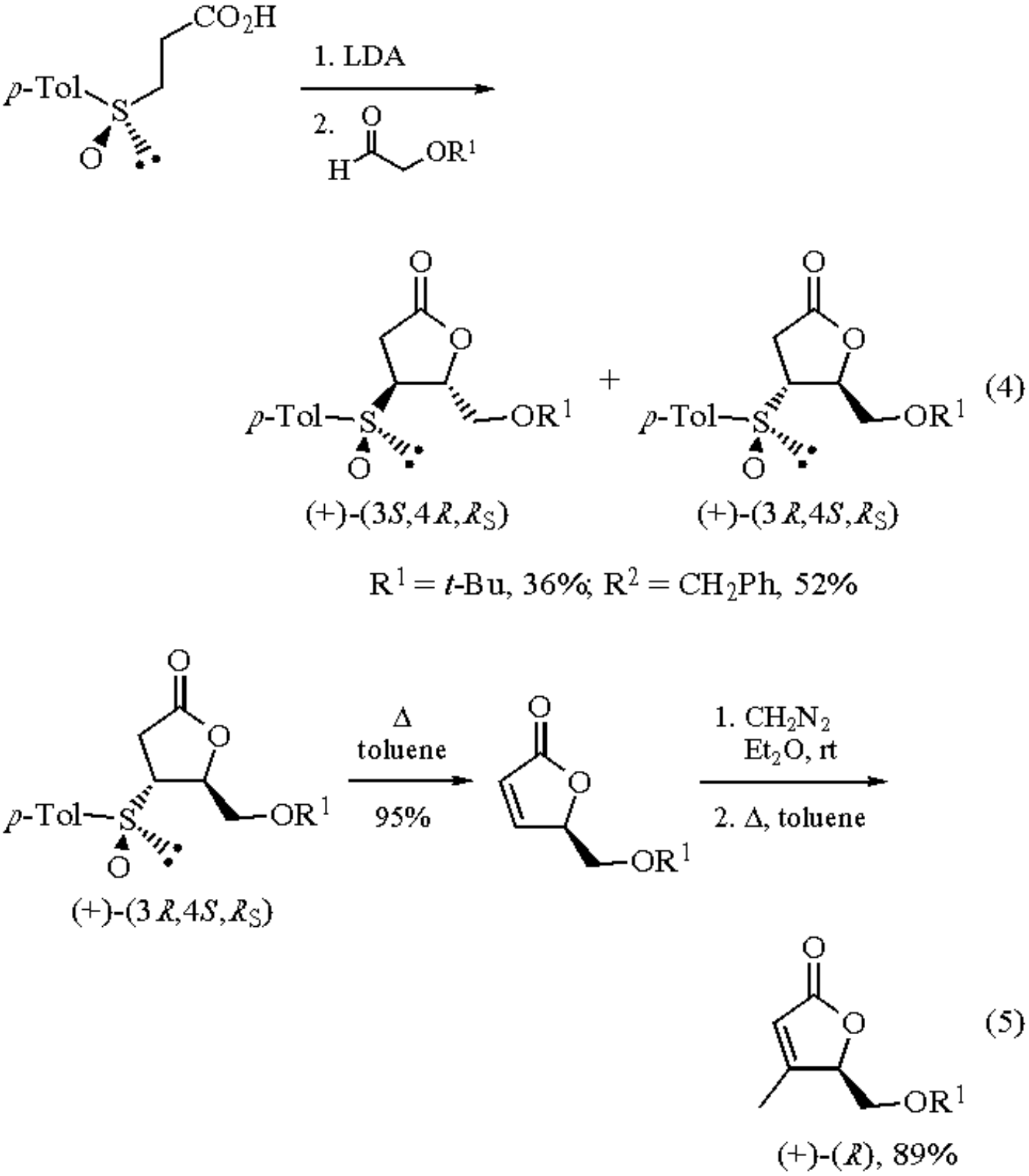

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Guy Solladié & Françoise Colobert

p-Tolylthiomethyl Isocyanide

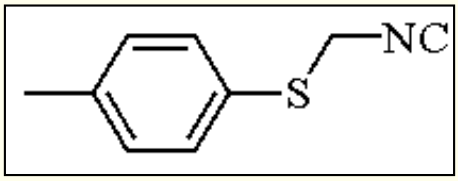

[41514-80-1] · C_9H_9NS · *p*-Tolylthiomethyl Isocyanide · (MW 163.26)

(synthesis of imidazoles from cyanides;[1] conversion of aldehydes and ketones to ketene *N*,*S*-acetals[2])

Physical Data: bp 60 °C/0.001 mmHg.

Form Supplied in: ill-smelling colorless liquid, which solidifies at -10 °C; turns yellow on standing.

Analysis of Reagent Purity: IR (neat) 2150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4 (s, CH_2).

Preparative Method: prepared by dehydration of *N*-(*p*-tolylthiomethyl)formamide in 89% yield.[2]

Handling, Storage, and Precautions: should be stored at -20 °C. Use in a fume hood.

Introduction.

p-Tolylthiomethyl isocyanide (**1**) is one of the (hetero) substituted derivatives of methyl isocyanide, and thus belongs to a class of reagents which includes ***p-Tolylsulfonylmethyl Isocyanide*** (TosMIC), ***Diethyl Isocyanomethylphosphonate***, ***Methyl N-(p-Tolylsulfonylmethyl)thiobenzimidate*** (a TosMIC derivative), and ***Ethyl Isocyanoacetate***. TosMIC is a multipurpose synthesis reagent which, for example, forms imidazoles in a base-induced cycloaddition of its C-N-C unit across the C=N bond of imines.[3] *p*-Tolylthiomethyl isocyanide (**1**) has been developed as an alternative for TosMIC on the assumption that the anion of (**1**) is a stronger nucleophile than the anion of TosMIC.[4] Indeed, (**1**) is able to convert cyanides into imidazoles with greater efficiency than TosMIC (eqs 1-3).[1,4] Several analogs of (**1**) have been prepared, among which are (2-naphthylthio)methyl isocyanide (**2**) (mp 76-78 °C) and (*p*-chlorophenylthio)methyl isocyanide (**3**) (mp 76-77 °C).[2] Reagent (**2**) should replace (**1**) in future applications, because: (1) it does not have the characteristic (bad) smell of isocyanides; and (2) being a solid, it is more stable and can be stored for long periods at room temperature.[2]

Synthesis of Imidazoles and Oxazoles.

Imidazoles are formed in one operation by a base-induced cycloaddition of (**1**) to the triple bond of cyanides (eqs 1-3).[1,4] The *p*-tolylthio group remains part of the product, unlike imidazoles prepared from imines and TosMIC where the tosyl group is eliminated.[3] The formation of oxazoles from (**1**) and ***Acetic Anhydride***[5] or ***Methyl Formate***[6] has also been reported.

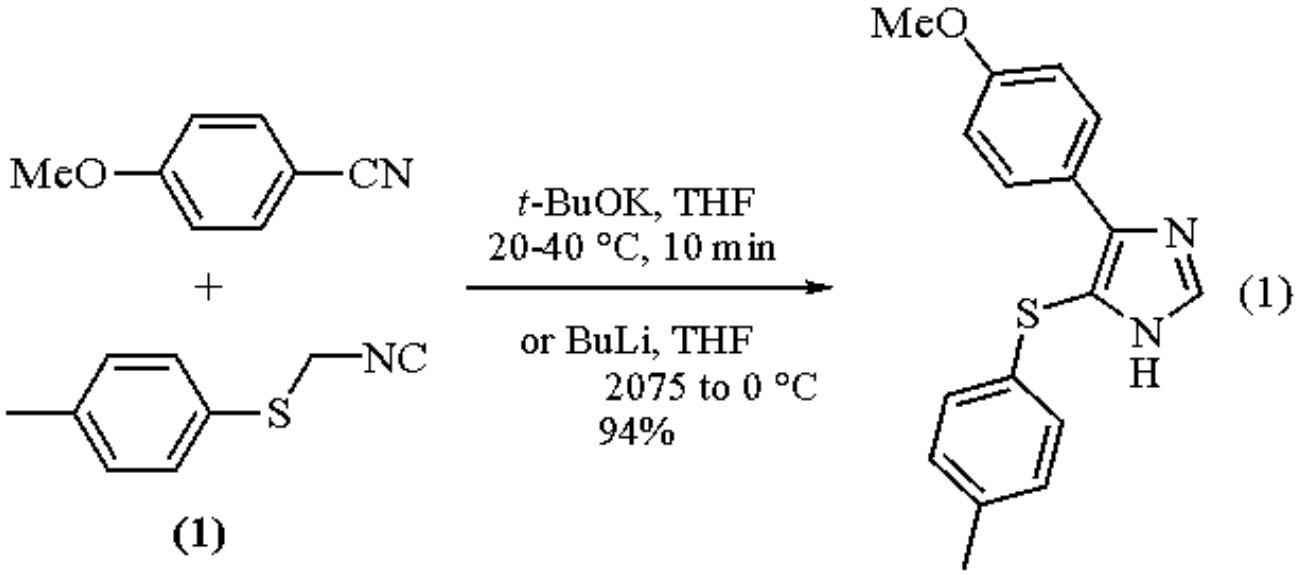

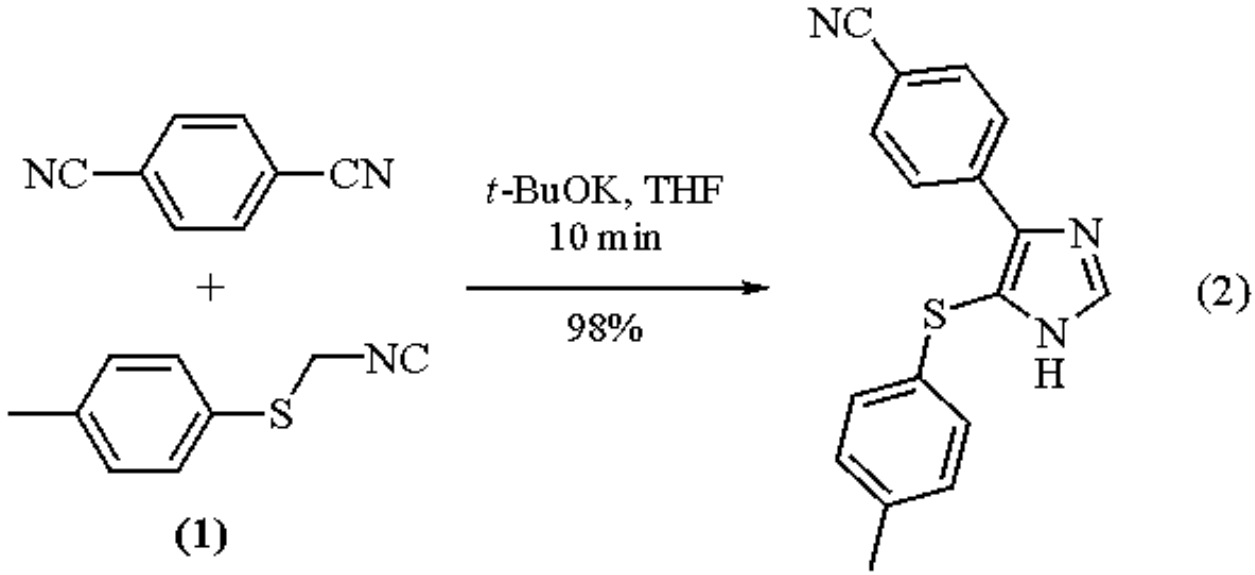

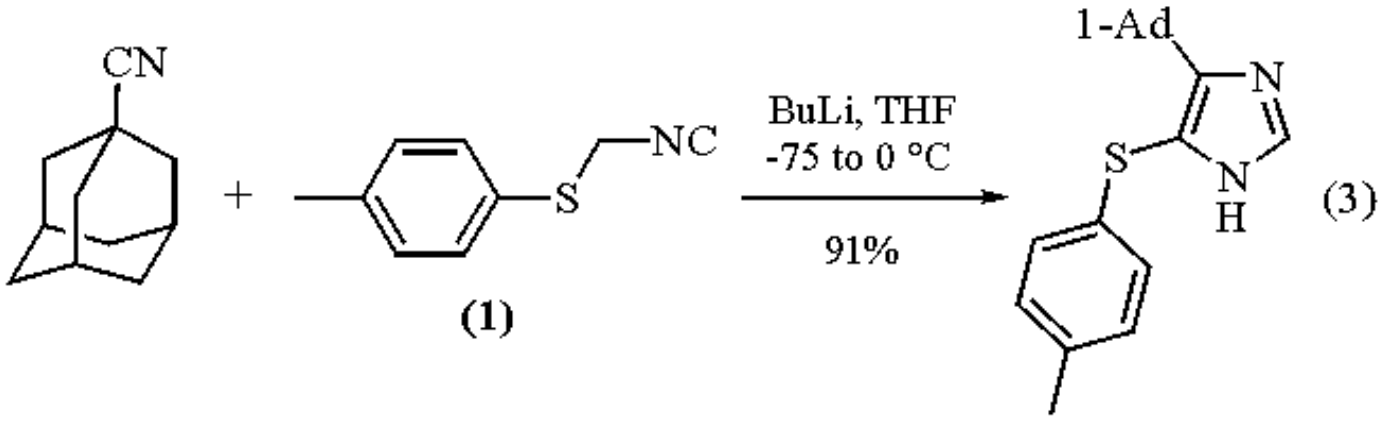

Synthesis of Ketene *N,S*-Acetals.

The Peterson alkenation of (**2**) with ketones and aldehydes provides 1-(2-naphthylthio)alkenyl isocyanides, which form a new class of ketene *N,S*-acetals (eqs 4 and 5).[2] The trimethylsilyl derivative of (**2**) is formed in situ.

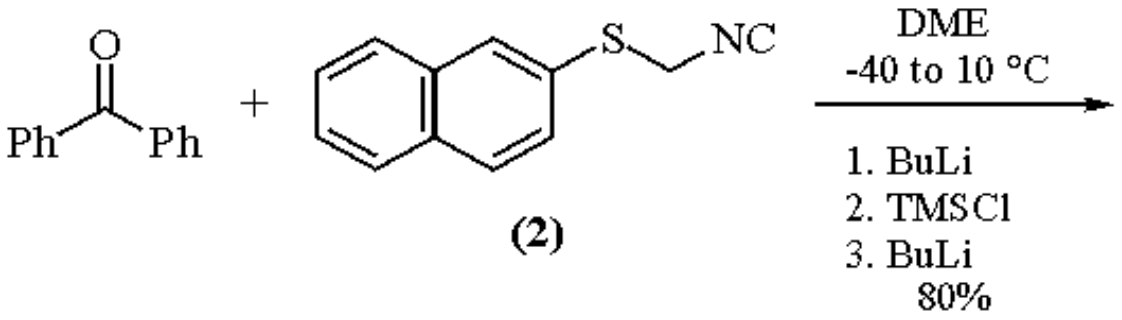

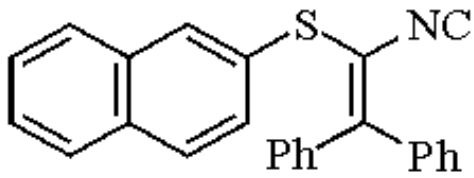

(4)

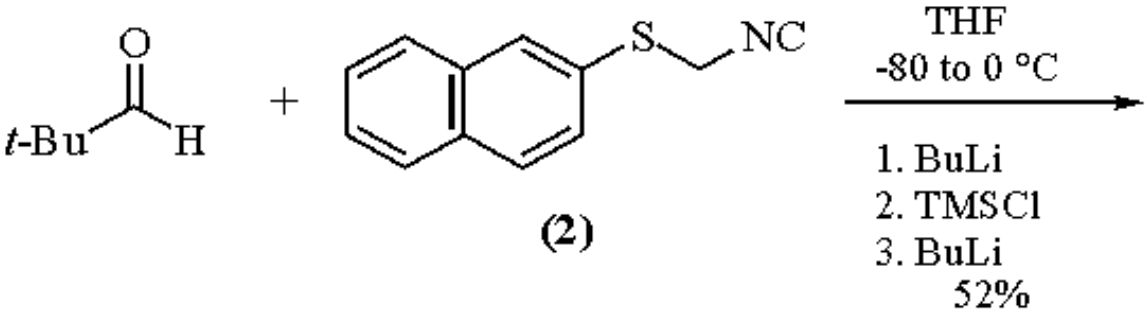

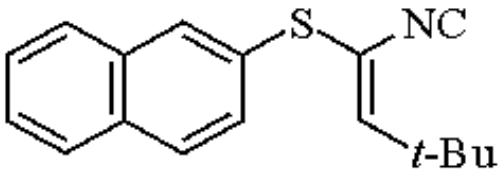

(5)

(*E*):(*Z*) = 9:1

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4. Compare: van Nispen, S. P. J. M.; Mensink, C.; van Leusen, A. M. *TL* **1980**, *21*, 3723.
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p-Tolyl Vinyl Sulfoxide[1]

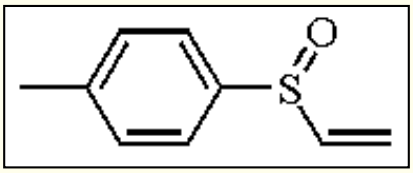

[36832-47-0] · $C_9H_{10}OS$ · *p*-Tolyl Vinyl Sulfoxide · (MW 166.26)

(a vinyl sulfoxide,[2] typically used in enantiomerically pure form in conjugate additions,[3] cycloadditions,[4] and Pummerer-type reactions,[5] and to prepare vinyl anions[6])

Physical Data: bp 110 °C/1.0 mmHg; 79-80 °C/0.04 mmHg; (*R*)-(+)-enantiomer: [α]26D +421° (*c* 0.15, EtOH).

Solubility: sol most moderately polar to polar solvents.

Preparative Method: (*R*)-(+)-*p*-tolyl vinyl sulfoxide is usually prepared via Andersen sulfinylation,[7] beginning with (1*R*,2*S*,5*R*,S_S)-(-)-menthyl *p*-toluenesulfinate, which is prepared as follows.[8] A two-neck round-bottom flask, equipped with N_2 inlet and magnetic stirring bar, is purged with N_2 and then charged with 2.75 equiv of ***Thionyl Chloride***. Under a N_2 atmosphere, anhydrous sodium *p*-toluenesulfinate (see ***Sodium Benzenesulfinate***) is added in portions over 1 h, with the addition of dry benzene as needed to facilitate stirring. After stirring for an additional 1.75 h, additional benzene is added and the mixture transferred to a one-neck round-bottom flask. The volatiles are removed by rotary evaporation, with occasional addition of benzene to ensure that all excess $SOCl_2$ has been removed. The flask, containing crude *p*-toluenesulfinyl chloride, is equipped with a magnetic stirring bar and constant pressure addition funnel. Ether is added and the resultant suspension is cooled to 0 °C. 1.0 Equiv of (1*R*,2*S*,5*R*)-(-)-menthol in excess pyridine is added over a few minutes, and the reaction is stirred overnight. The product is isolated by addition of ice, extraction, washing of the ether layer with 20% aq HCl, and drying (Na_2SO_4 + K_2CO_3). Filtration and concentration by rotary evaporation, followed by crystallization from acetone at -20 °C, affords the ester, mp 105-106 °C, $[\alpha]_D^{25}$ -199.4° (*c* 1.5, acetone).

The ester is converted into (*R*)-(+)-*p*-tolyl vinyl sulfoxide in the following manner.[9] A two-neck round-bottom flask equipped with constant pressure addition funnel, N_2 inlet, and magnetic stirring bar is charged with a suspension of 1.3 equiv of (1*R*,2*S*,5*R*,S_S)-(-)-menthyl *p*-toluenesulfinate in dry THF under N_2. Cooling to -78 °C is followed by dropwise addition of 1.0 equiv of ***Vinylmagnesium Bromide*** in THF and slow warming to room temperature. Satd aq NH_4Cl is added; separation is followed by drying ($MgSO_4$) and concentration by rotary evaporation. Distillation under reduced pressure affords the sulfoxide. The corresponding (*S*)-(+)-*p*-tolyl vinyl sulfoxide may be prepared from (1*S*,2*R*,5*S*,R_S)-(+)-menthyl *p*-toluenesulfinate. Alternative preparations via TBAF-mediated desilylation of (*R*)-(+)-*p*-tolyl α-trimethylsilylvinyl sulfone[10] and hydrogenation of (*R*)-(+)-ethynyl *p*-tolyl sulfoxide[2] are possible. Although rarely used, (*RS*)-*p*-tolyl vinyl sulfoxide should be available in a manner analogous to the preparation of (*RS*)-phenyl vinyl sulfoxide, by oxidation of the sulfide.[11]

Handling, Storage, and Precautions: sulfoxides are known to undergo thermal racemization.[12]

Conjugate Additions.

Compared to α,β-unsaturated ketones, vinylic sulfoxides are sluggish substrates for conjugate additions. Nonetheless, excellent chemical yields are obtained with heteroatom nucleophiles, including amines, thiols, and alcohols.[9a,9c,13] Michael additions of active methylene compounds,[13b,14] such as ***Diethyl Malonate*** or ***Ethyl Acetoacetate***,[15] are less satisfactory. Alkylmetal conjugate donor reagents, such as cuprate reagents, are rarely successful;[16] α-metalation of the vinyl moiety usually competes or predominates.[17] It is not uncommon to enhance reactivity by introducing an α-carbonyl substituent[6] using an α-acylation strategy that exploits an intermediate conjugate addition (e.g. eq 1).[18]

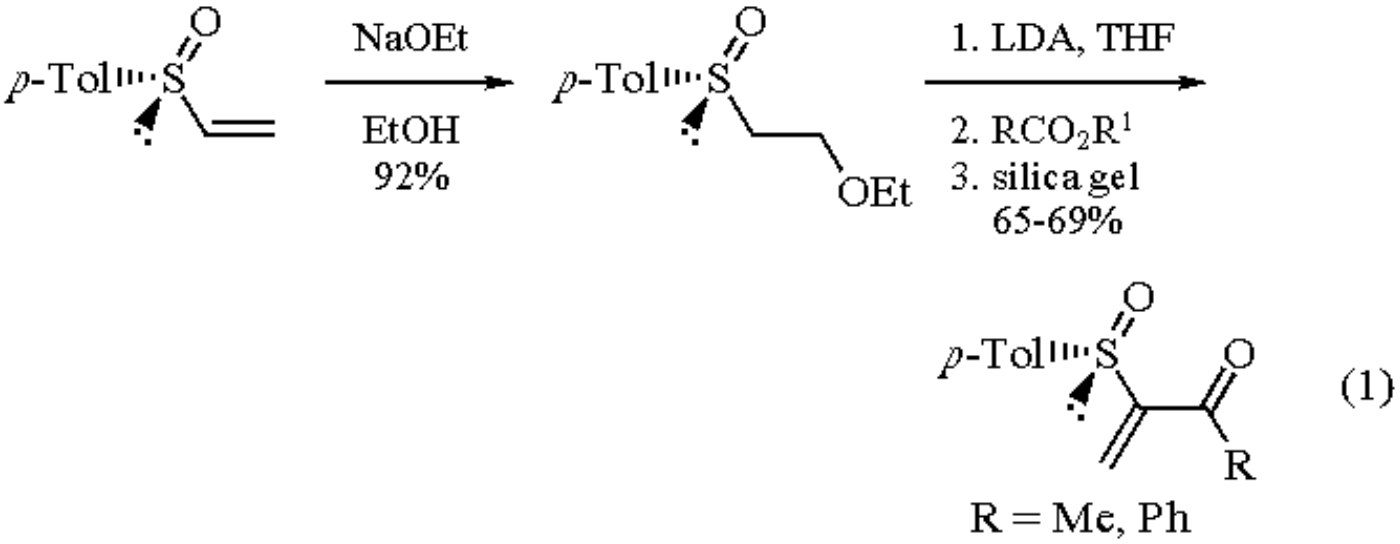

Cycloadditions.

Aryl vinyl sulfoxides are useful, moderately reactive, dienophiles in [4 + 2] cycloadditions;[11a] they function, for example, as synthons for ***Acetylene***,[19] ***Ethylene***,[20] vinylsilanes,[21] and ketene.[22] Enantiomerically pure aryl vinyl sulfoxides can be used to induce asymmetry in Diels-Alder reactions.[4,13a,18,23] In an application to 1,3-dipolar cycloaddition, (*R*)-(+)-*p*-tolyl vinyl sulfoxide reacts with the *N*-phenyl nitrone of benzaldehyde to produce a 95:5 mixture of (3*R*,4*R*,*RS*$_S$)-3-phenyl-4-(*p*-tolylsulfinyl)isoxazolidines in 57% yield (eq 2); the asymmetric induction at C-3 exceeds 90%.[23a]

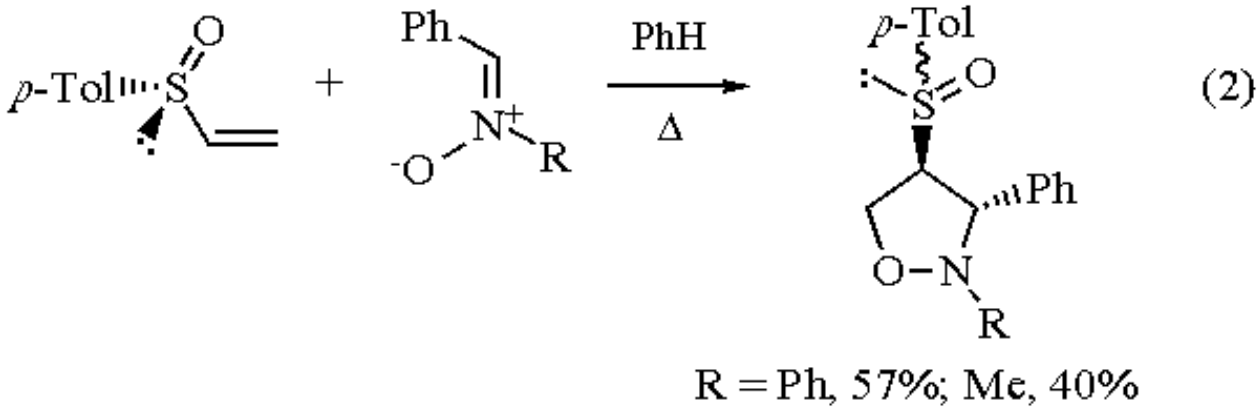

Pummerer-Type Reactions.

An alternative to activating aryl vinyl sulfoxides to nucleophilic addition by α-acylation is to employ an additive Pummerer-type reaction,[24] which is initiated by attack of an electrophile on the sulfoxide oxygen and results in α,β-disubstituted alkyl aryl sulfides. *p*-Tolyl vinyl sulfoxide undergoes vicinal Pummerer diallylation with excess ***Allylmagnesium Bromide*** (eq 3);[23b] similarly, enantiomerically pure aryl vinyl sulfoxides have been used in highly efficient asymmetric syntheses of quaternary carbon centers[25] and γ-butyrolactones.[26] Although aryl vinyl sulfoxides are unreactive under classical Pummerer reaction conditions, an anomalous Pummerer reaction between ***Isopropenyl Acetate*** and phenyl vinyl sulfoxides provides a route to β-keto sulfides.[27]

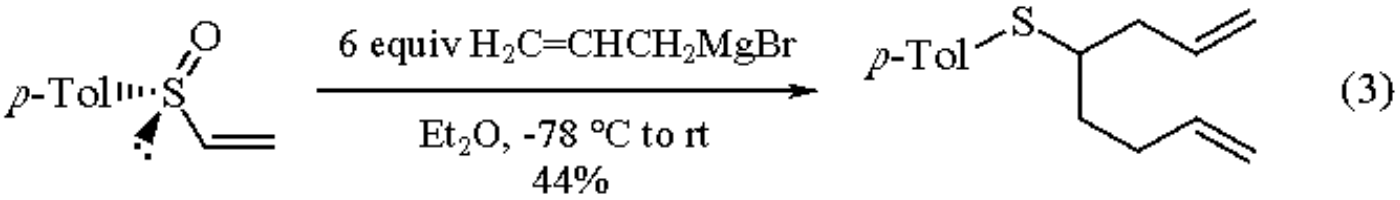

Other Reactions.

Electrophilic addition of ***Bromine*** to (*R*)-(+)-*p*-tolyl vinyl sulfoxide is chemically efficient, but proceeds with low asymmetric induction.[9c,28] ***Triphenylstannane***, on the other hand, fails to undergo addition.[29] Homopolymerization of (*R*)-(+)-*p*-tolyl vinyl sulfoxide fails when any of a number of radical initiators are used, but copolymerization with styrene in bulk using ***Azobisisobutyronitrile*** as initiator

produces an optically active polymer.[9a] Finally, aryl vinyl sulfoxides can be converted to their corresponding sulfoximides using *N*-aminophthalimide and ***Lead(IV) Acetate***; the configuration of the sulfur center apparently is retained.[13c,30]

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p-Tolylsulfonylmethyl Isocyanide[1]

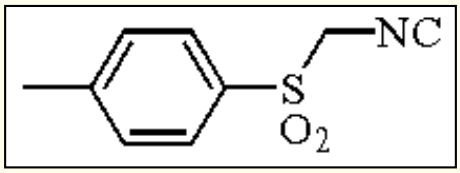

[36635-61-7] · $C_9H_9NO_2S$ · *p*-Tolylsulfonylmethyl Isocyanide · (MW 195.26)

(reductive cyanation of ketones[2a] and aldehydes;[2b] synthesis of azoles (pyrroles, oxazoles, imidazoles, thiazoles, etc.) by delivering a C-N-C fragment to polarized double bonds;[3] connective reagent for coupling of alkyl halides (or carbonyl compounds) by a CO[4a] or a CH_2 bridge;[4b] preparation of (formal) Knoevenagel condensation products from aldehydes and ketones[5])

Alternate Name: tosylmethyl isocyanide; TosMIC.

Physical Data: mp 116-117 °C (dec).

Solubility: sol THF, CH_2Cl_2, $CHCl_3$, DME, AcOEt, benzene; slightly sol Et_2O, EtOH, MeOH.

Form Supplied in: white to near-white, odorless, commercially available solid.

Analysis of Reagent Purity: IR (Nujol) 2150 (N=C), 1320, 1155 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.5 (s, CH_3), 4.6 (s, CH_2); ^{13}C NMR ($CDCl_3$) δ 61.1 (CH_2), 165.7 (N=C).

Preparative Method: by dehydration of *N*-(*p*-tolylsulfonylmethyl)formamide.[6]

Handling, Storage, and Precautions: shelf stable.

Introduction.

p-Tolylsulfonylmethyl isocyanide is the best known compound of a series of (hetero-)substituted derivatives of methyl isocyanide, which includes ***Diethyl Isocyanomethylphosphonate***, ***p-Tolylthiomethyl Isocyanide***, ***Methyl N-(p-Tolylsulfonylmethyl)thiobenzimidate*** (a TosMIC derivative), and ***Ethyl Isocyanoacetate***. TosMIC is a multipurpose synthesis reagent, and by far the most versatile and most widely applicable reagent of the above series.

Typical Applications.

One characteristic example of each category of TosMIC applications will be given first (to be followed by further illustrative examples below).

Reductive Cyanations.

Most ketones are converted with TosMIC in one operation into cyanides (introduction of a one-carbon unit) using ***Potassium t-Butoxide*** (1-7 equiv) in nonprotic solvents (e.g. DME, DMSO) (eq 1).[2a] The reductive cyanation of aldehydes is carried out at lower temperatures and needs addition of MeOH in the final stage of the process (eq 2).[2b,7] In eqs 1 and 2, the carbonyl oxygen is removed (unlike the well known addition of HCN); hence the name of this process: reductive cyanation.

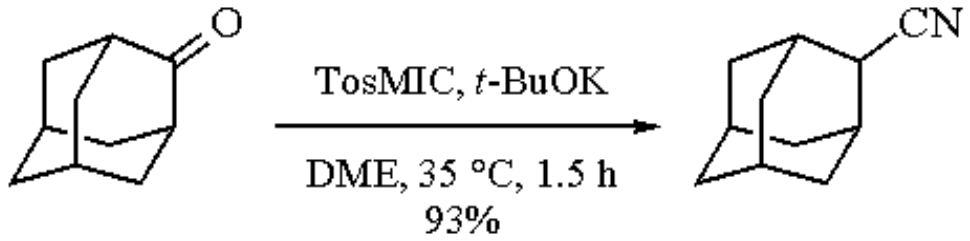

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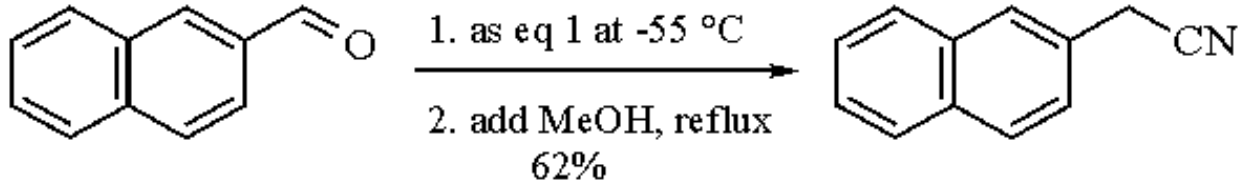

(2)

Synthesis of Azoles.

Reaction of TosMIC with aldehydes in protic solvents, e.g. MeOH at 20 °C, leads to oxazolines (eq 3),[8a] whereas oxazoles are formed in refluxing MeOH by elimination of *p*-toluenesulfinic acid (salt) (eq 4).[5c,8a] Reaction of TosMIC with acid chlorides, anhydrides, or esters leads to oxazoles in which the tosyl group is retained.[8]

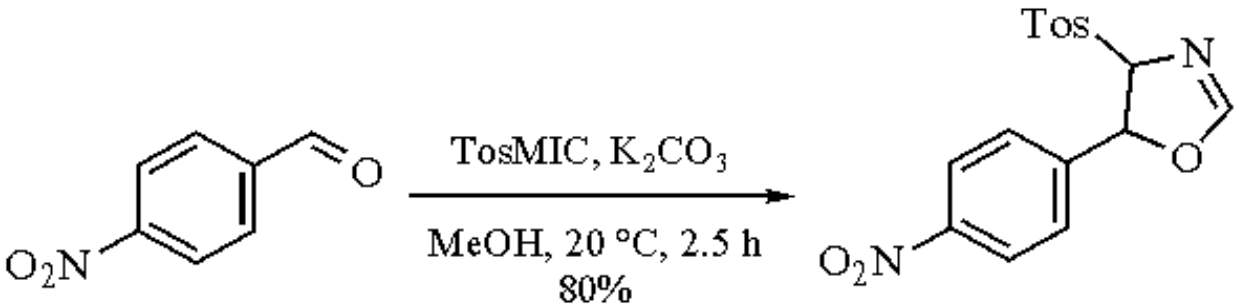

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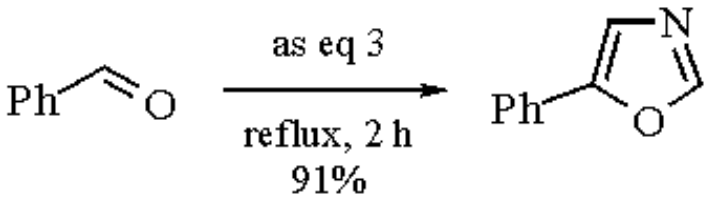

(4)

Imidazoles are obtained analogously from imines,[3b] thiazoles from dithioesters or CS_2,[9] and 1,2,4-triazoles from diazonium salts.[10] More widely applied, however, is the synthesis of pyrroles from TosMIC and Michael acceptors (eq 5).[11] The pyrroles are formed in one operation; dihydropyrrole derivatives (compare eqs 3 and 4) are not usually observed. The pyrrole ring positions 1, 2, and 5 remain intrinsically unsubstituted, which is one of the virtues of this method, since such pyrroles otherwise have to be prepared by temporarily using protective groups at these positions.[11]

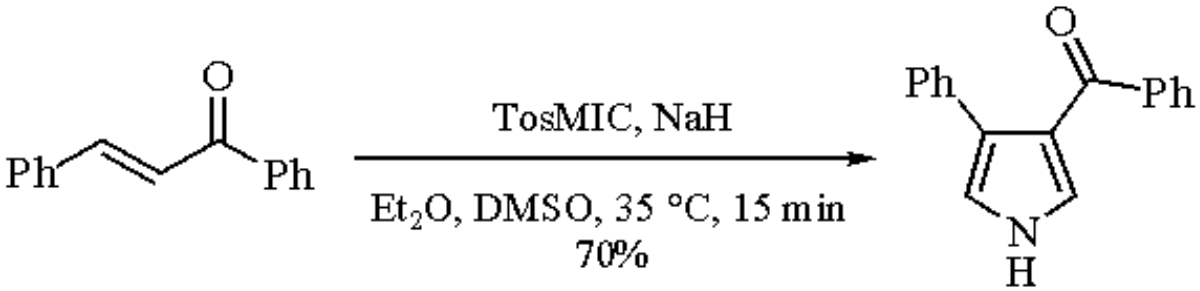

(5)

Connective Reagent.

The two methylene hydrogens of TosMIC have been replaced consecutively by base-induced alkylations (eqs 6 and 7).[12] Reactions as in eq 6 are carried out under phase-transfer catalysis (PTC) conditions to prevent twofold alkylation. In the product of eq 7, two alkyl halides (MeI and octyl iodide) are connected by the TosMIC methylene group; hence the name: connective reagent. This application of TosMIC is

complementary to other reagents with activated methylenes, such as ***1,3-Dithiane***[13] and ***Methylthiomethyl p-Tolyl Sulfone***. Acid hydrolysis of the geminal Tos and N=C groups produces ketones (i.e. a CO bridge, eq 7), whereas reduction with ***Lithium*** in liquid ammonia provides a methylene bridge (eq 8).[4b] Monosubstituted TosMIC derivatives, as obtained by eq 6, may replace TosMIC in eqs 3-5 to provide azoles with an additional substituent, e.g. an additional Me at position 2 of the pyrrole ring in eq 5.[3c]

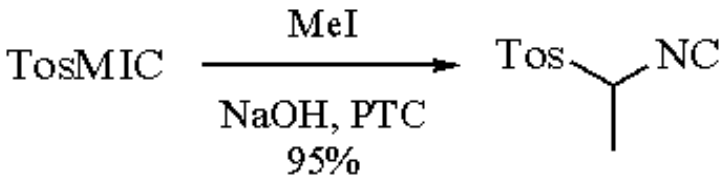

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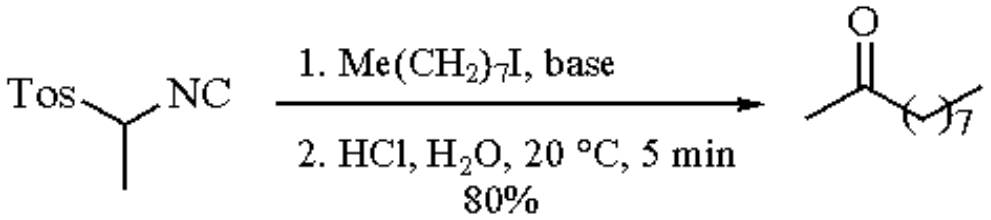

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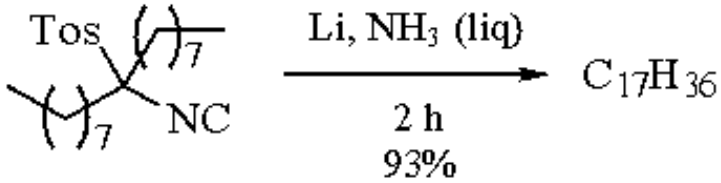

(8)

Knoevenagel Condensation Products.

Reactions of TosMIC with aldehydes or ketones have been directed such that formal Knoevenagel condensation products are formed by overall elimination of H_2O (as contrasted to the reductive cyanation in eqs 1 and 2). In fact, this process requires two steps (eqs 9 and 10).[5b,d] Knoevenagel products have also been obtained by applying Peterson alkenation conditions to TosMIC (eq 11).[14]

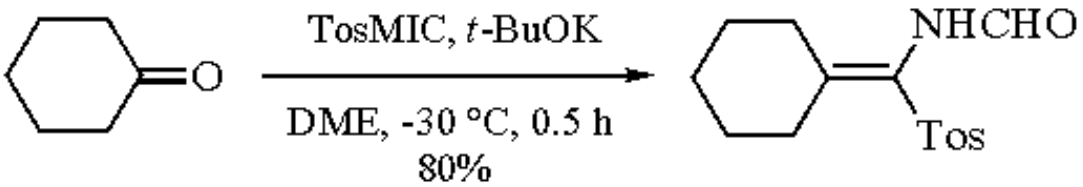

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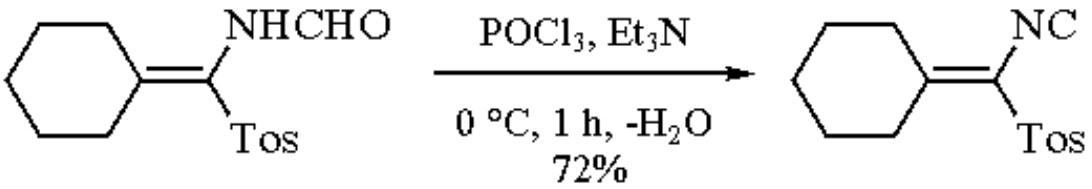

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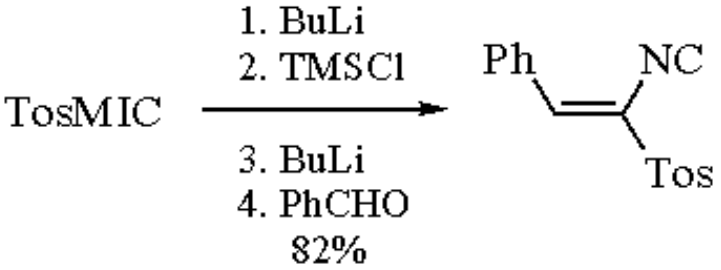

(11)

The isocyano carbon of TosMIC is directly involved in the initial stages of the reductive cyanations, the azole syntheses, and the (formal) Knoevenagel condensations, but not in the application of TosMIC as a connective reagent. In fact, the first three types of reaction are based on a common reaction scheme;[2a,15] different products are obtained by using different reaction conditions. To emphasize this point, eq 12 describes the three different products that have been obtained separately from TosMIC and benzaldehyde.[2b,5d,8a]

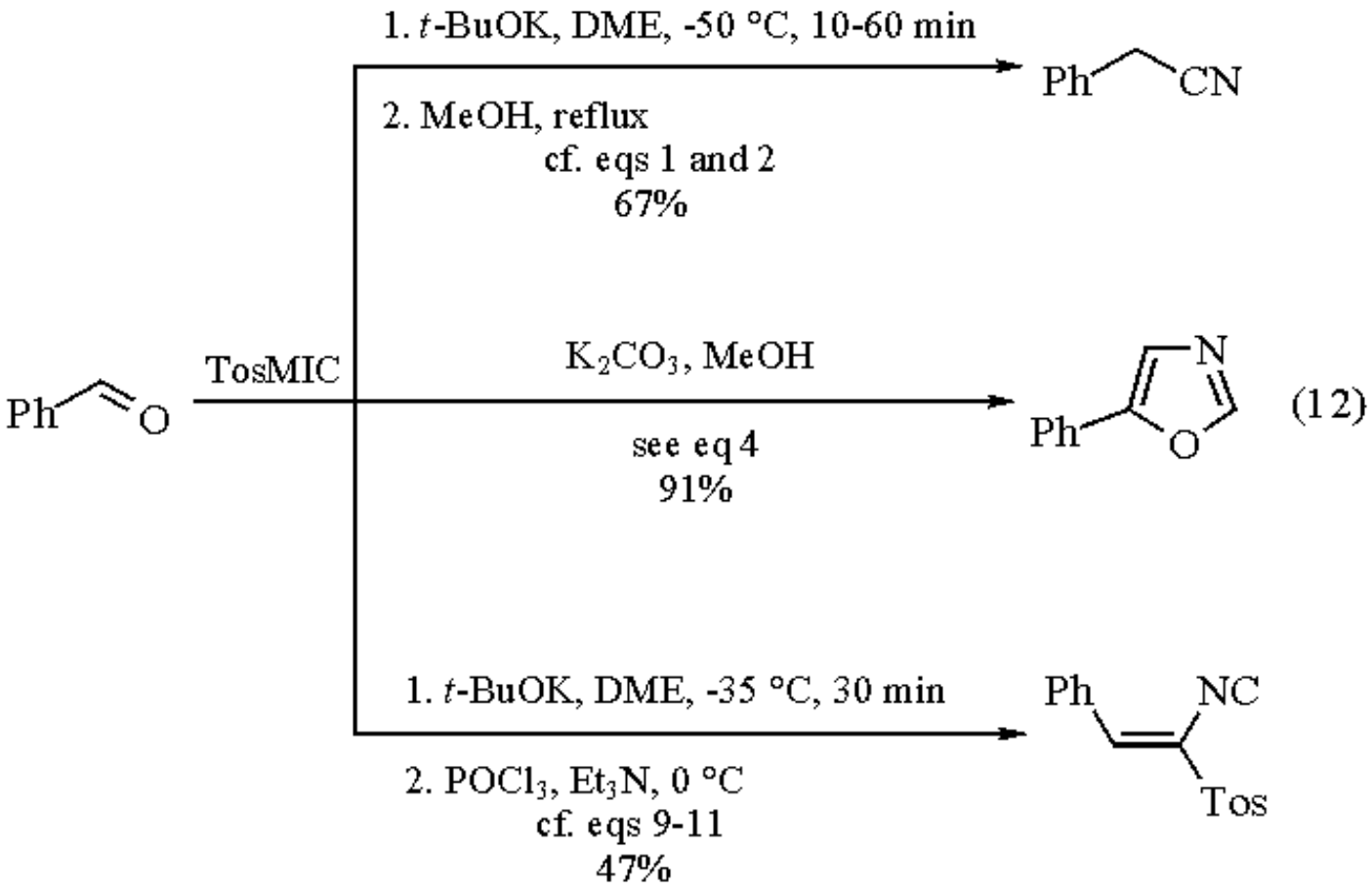

Fundamental Aspects of TosMIC Chemistry.

In this section, the interrelation of TosMIC reactions is discussed briefly. TosMIC is prepared in two steps: a Mannich reaction of ***p-Toluenesulfinic Acid*** (TosH), formaldehyde, and formamide gives *N*-(*p*-tolylsulfonylmethyl)formamide (TosMIC precursor), which is dehydrated ($POCl_3/Et_3N$ or *i*-Pr_2NH) to TosMIC.[6] The Mannich reaction is reversible, but after dehydration to TosMIC the reverse reaction (of the TosMIC precursor) is blocked. Both TosMIC and the TosMIC precursor are *N*,*S*-acetals of formaldehyde. The methylene group of TosMIC is highly activated (estimated $pK_a = 14$) by the two electron-withdrawing substituents. Deprotonation of TosMIC has been achieved with an array of bases, ranging from ***Potassium Carbonate*** in MeOH to ***n-Butyllithium*** in THF. Even dilithio-TosMIC has been reported.[8b] Thus TosMIC is a formaldehyde derivative of reversed polarity (umpolung);[13] eqs 6-8 are based on this principle. Acid-catalyzed hydration of dialkylated TosMIC derivatives provides formamides, which upon hydrolysis (reversed Mannich) lead to the product ketones (eqs 7 and 35-38). In other applications of TosMIC, attack of the TosMIC anion on a carbonyl carbon is followed (or accompanied) by ring closure of the carbonyl oxygen to the electrophilic isocyano carbon to form an oxazoline (eq 3). Base-induced ring opening of these oxazolines gives α,β-unsaturated tosylformamides (eq 9), which have been dehydrated subsequently (eqs 10 and 12). Base-induced elimination of TosH from these unsaturated tosyl formamides gives *N*-formylketenimines ($R_2C{=}C{=}NCH{=}O$; not identified), which through nucleophilic removal of the formyl group eventually produce cyanides (eqs 1, 2, and 13-16). Details of these reactions have been described.[2a,15]

Reductive Cyanation.

Few examples have been described of the reaction of TosMIC with aldehydes. Examples are given in eqs 2 and 13.[2b,16] The reaction with ketones, however, is very general (eqs 1 and 14-16).[2a,15,16] Only severely sterically hindered ketones (e.g. di-*t*-butyl ketone) and readily enolizable ketones (e.g. benzyl phenyl ketone) will not undergo the reductive cyanation reaction.[2a]

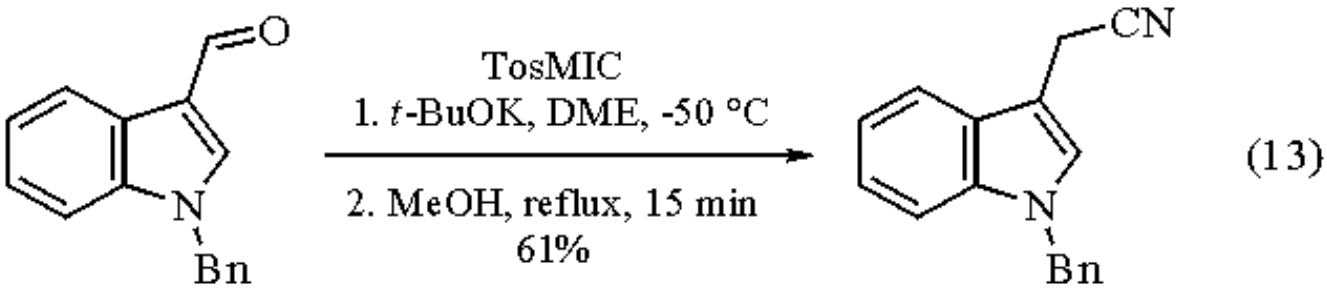

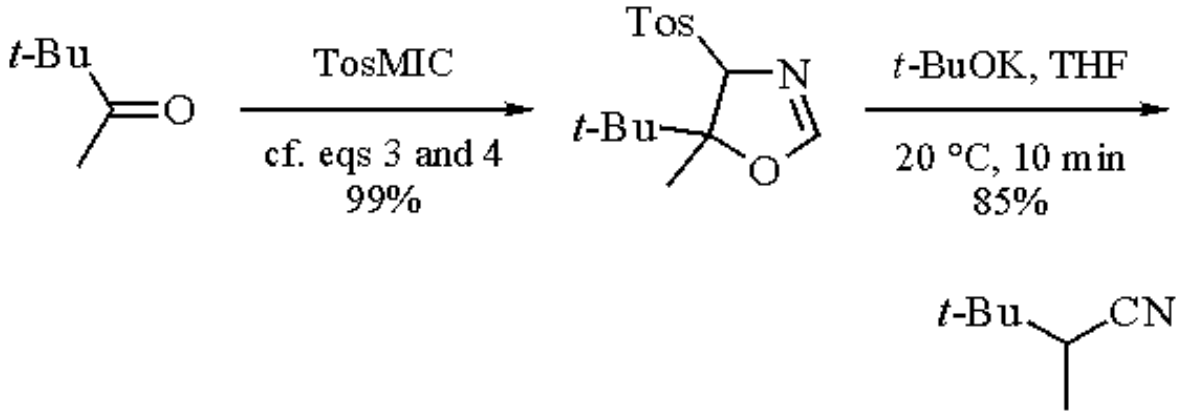

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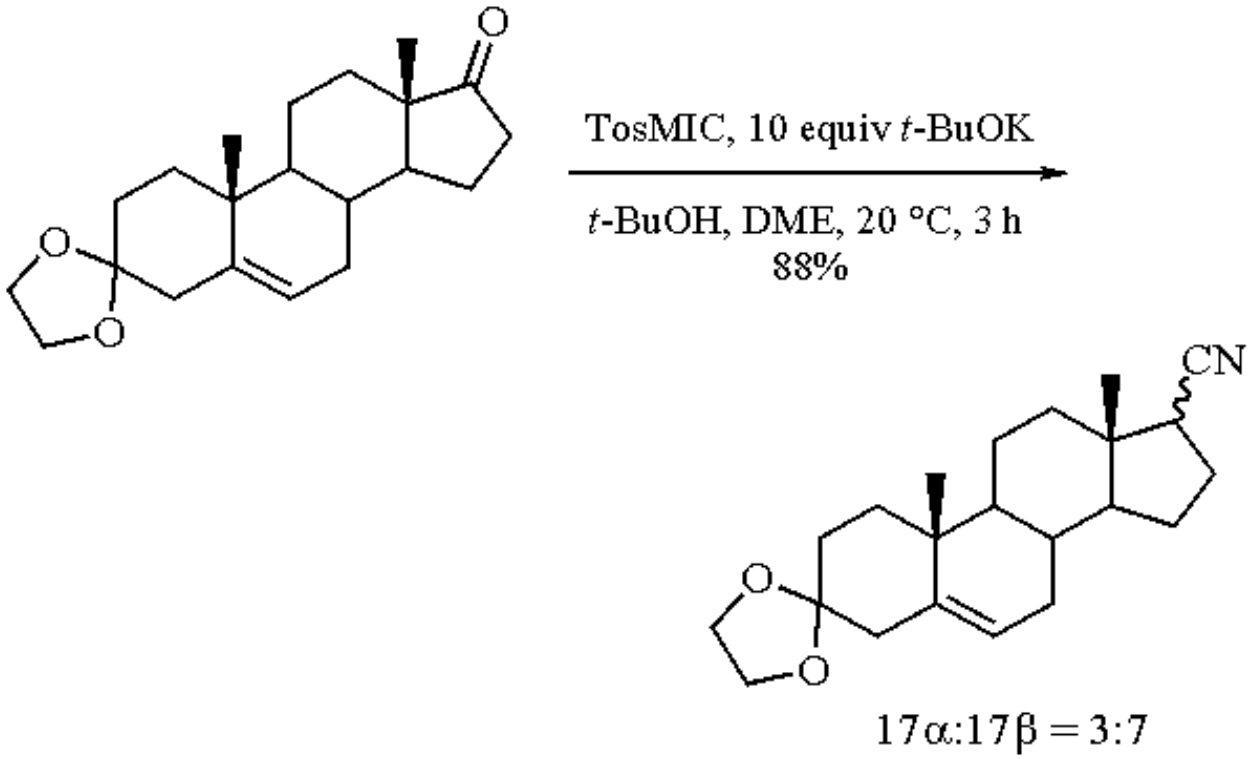

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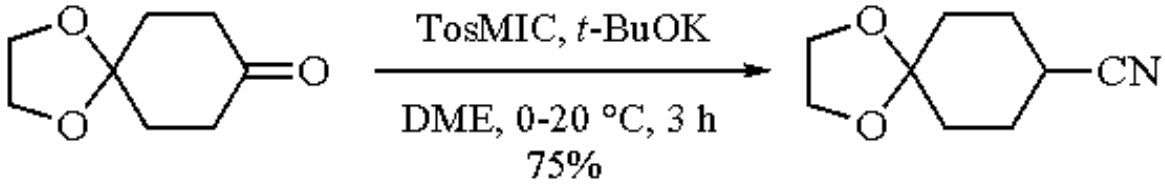

(16)

Synthesis of Azoles (Pyrroles in Particular).

The reaction of TosMIC, or monosubstituted TosMIC derivatives (see eq 6), with Michael acceptors has been used frequently for the synthesis of 1,2,5-unsubstituted pyrroles and 1,5-unsubstituted pyrroles, respectively (eqs 5 and 21-24; compare eqs 25-29, 31, and 32). Over 50 papers and patents refer to this type of application of TosMIC.[17] Fewer papers deal with the use of TosMIC in the synthesis of other azoles, such as oxazoles from aldehydes (eq 4), imidazoles from imines (eq 17),[3b] thiazoles from dithioesters or CS_2 (eq 18),[9] and 1,2,4-triazoles from diazonium salts (eq 19).[10] Eqs 20 and 21 show that monosubstituted TosMIC molecules react similarly to give azoles with an additional substituent.[3c]

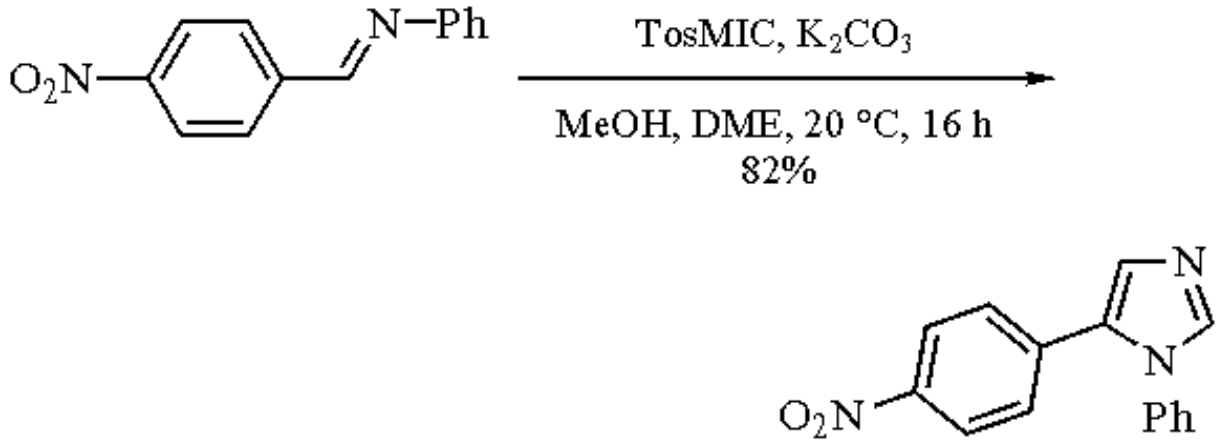

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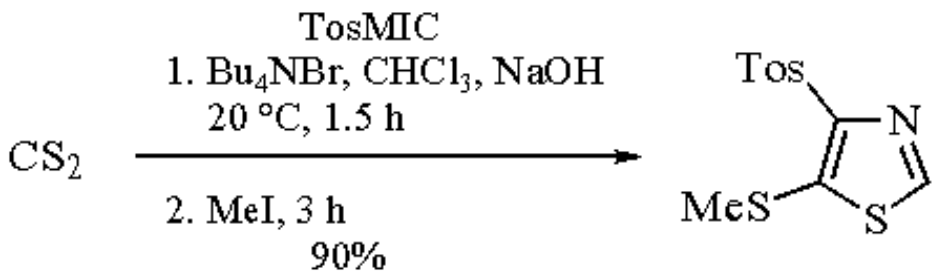

(18)

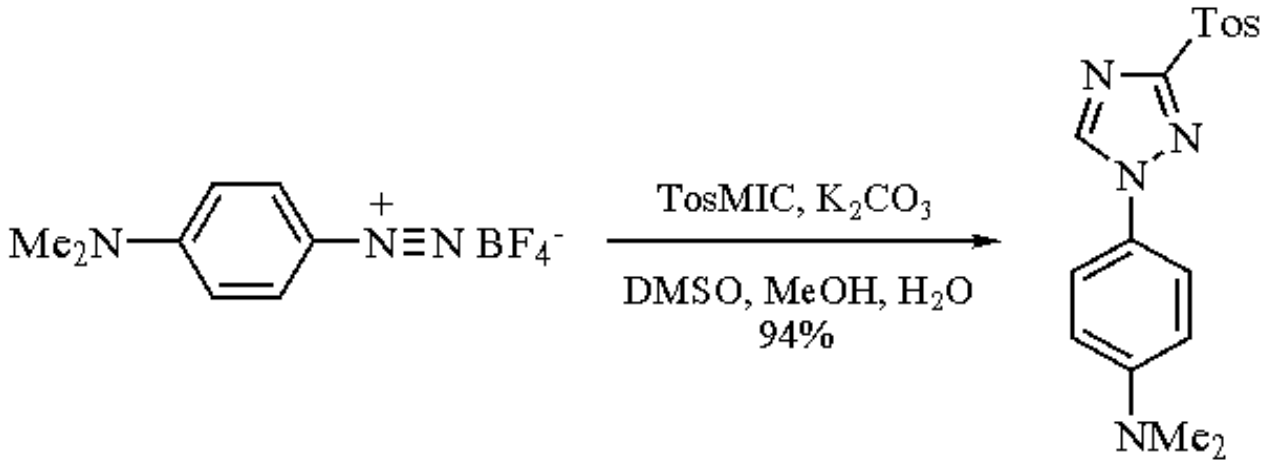

(19)

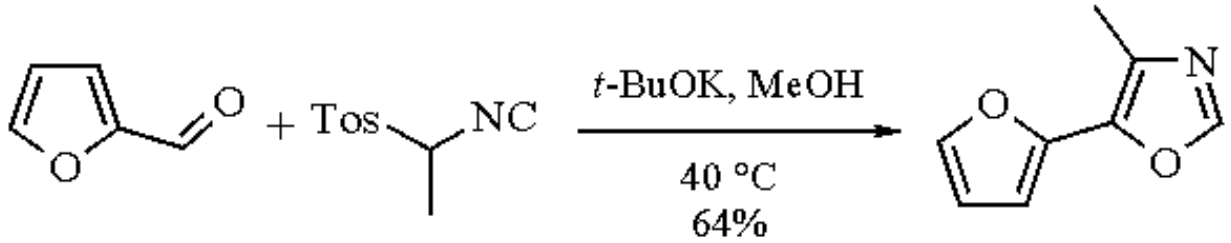

(20)

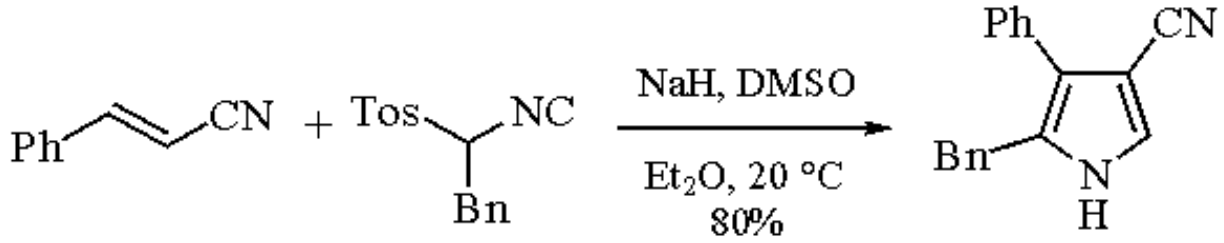

(21)

The usual electron-withdrawing groups (EWG) in Michael acceptors are operative in the TosMIC based pyrrole synthesis (COR, CO_2R, CN, NO_2; eqs 5, 21-25, 27, and 28). Only for EWG = CHO, will the TosMIC anion react preferentially with the aldehyde group to form oxazoles,[5c,11] as is also the case with aromatic aldehydes (cf. eqs 4 and 20). Several base/solvent systems have been used in the TosMIC pyrrole syntheses; the trend is to use an excess of base (up to 3 equiv) when less reactive Michael acceptors are used, whereas lower temperatures (to -70 °C) are recommended for the more reactive Michael acceptors. TosMIC has been used for the synthesis of antibiotically active pyrroles such as verrucarine E (eq 22)[18a] and 3-cyano-4-(2,3-dichlorophenyl)pyrrole (Fenpiclonil®) (see eq 31). Three

separate reactions have been reported between TosMIC and methyl sorbate (a dienyl Michael acceptor): depending on the conditions of the reaction, one of the two monopyrroles or an oxazole is formed (eq 23).[8b] A bipyrrole has been synthesized from ethyl sorbate using 2 equiv of TosMIC. However, this process requires three steps. After the introduction of the first pyrrole ring, the remaining α,β-double bond needs to be activated (by *N*-sulfonylation of the first-formed pyrrole ring) before the second pyrrole ring can be realized (eq 24).[19a] Recently, a heptapyrrole has been developed along related lines.[19b] Other pyrrole syntheses based on TosMIC will be discussed in the next section.

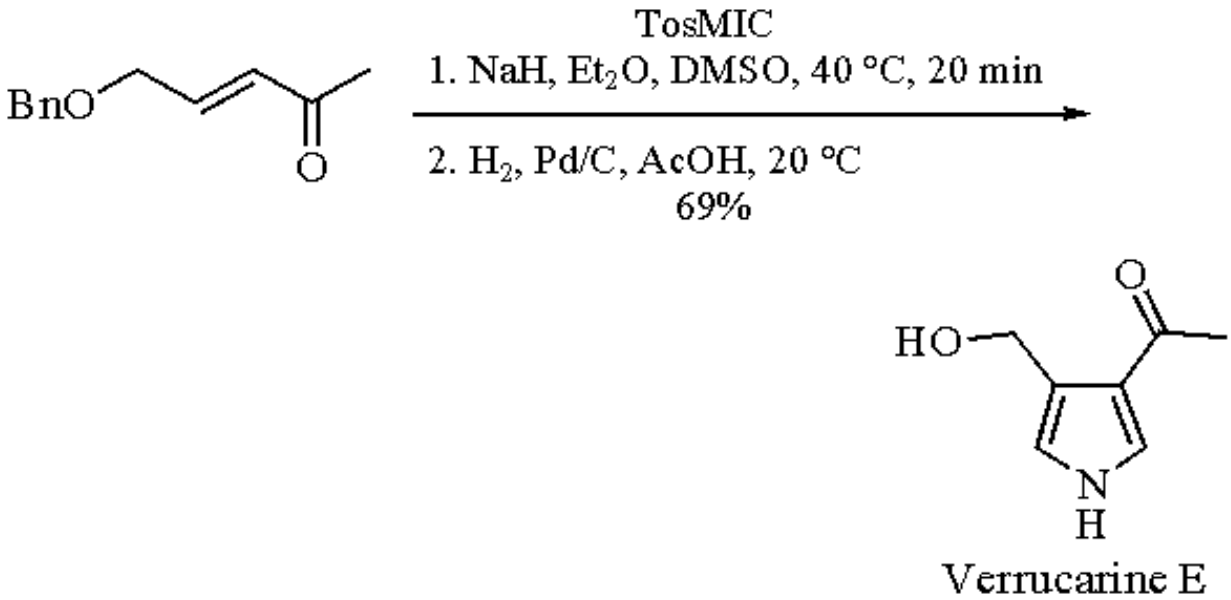

(22)

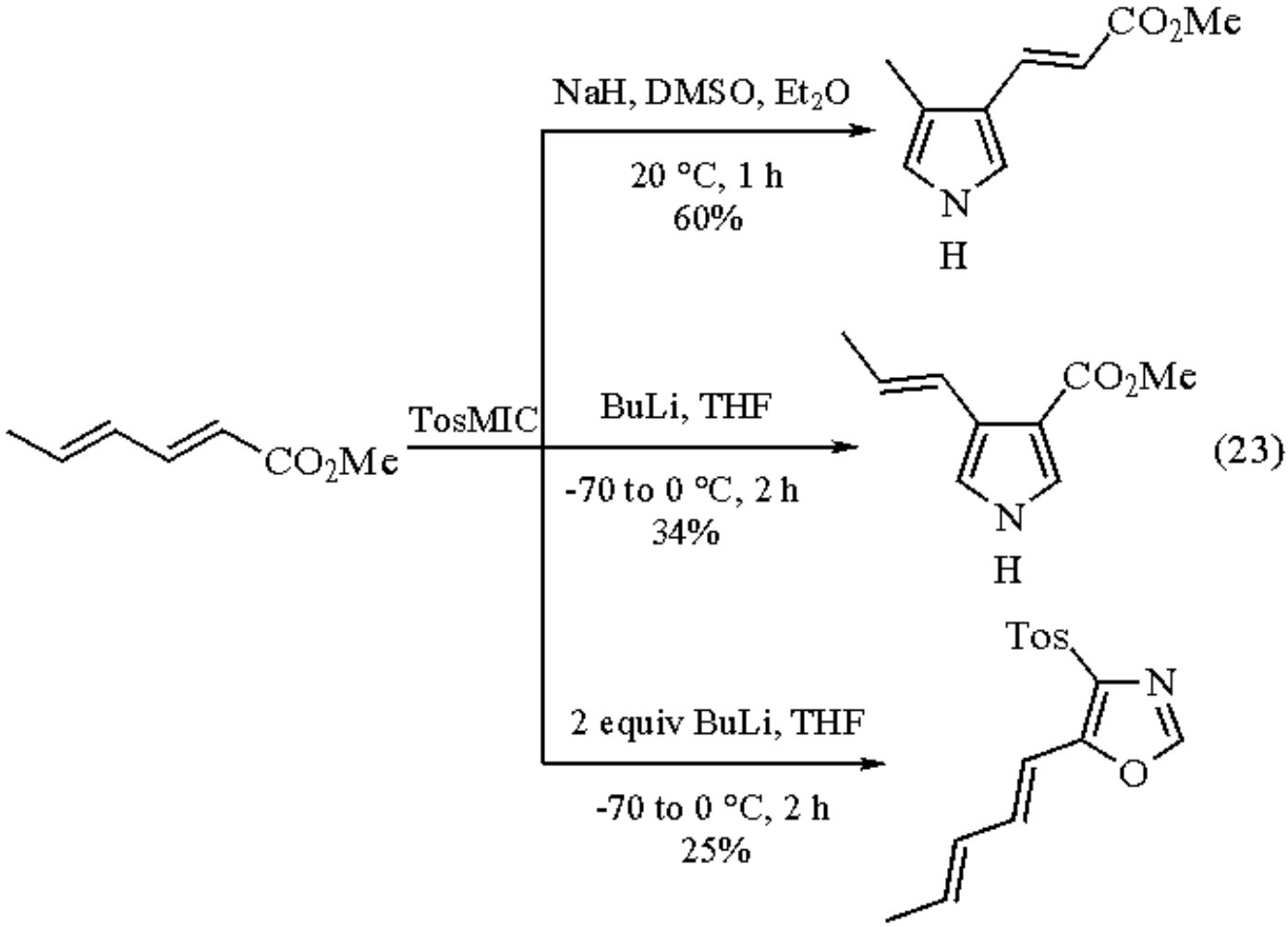

(23)

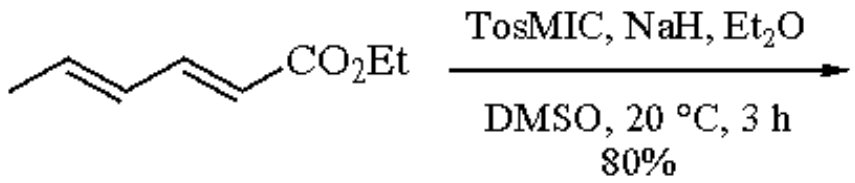

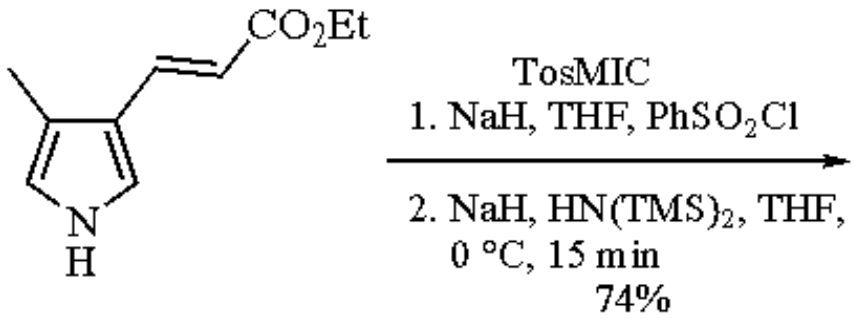

(24)

Knoevenagel-Type Condensation Products; Synthesis of (Di)Vinylpyrroles, Indoles, 3-Nitropyrroles, 3-Cyanopyrroles, and 3,4-Dialkylpyrroles.

Two different types of reactions are possible with the (formal) Knoevenagel condensation products (eqs 9-12) of TosMIC. They can act as Michael acceptors (eqs 29-32) or as monosubstituted TosMIC derivatives. Eqs 25-28 provide examples of the latter type of reaction. γ-Deprotonation of the condensation product of TosMIC and cyclopentanone (eq 25)[5b] produces an allylic anion, which reacts exclusively via its α-carbon with Michael acceptors to form pyrroles, in much the same way as in eq 21. The difference, clearly, is that in eq 25 a 2-(alk-1-enyl)pyrrole is formed. These 2-vinylpyrroles are efficient precursors for an alternate synthesis of indoles, provided that they bear a second vinyl substituent at position 3. Thermal or photochemical electrocyclic ring closure of the 6π-electron system, followed by dehydrogenation, leads to indoles (eqs 26-28). When the 3-vinyl substituent is part of an aromatic ring, electrocyclization is achieved photochemically (eq 26) but not thermally.[5b] Thermal ring closure is effective with normal 3-vinyl substituents, obtained via dienic and trienic Michael acceptors (eqs 27 and 28, respectively).[5b,20] The main product of eq 28 is formed by an intramolecular Diels-Alder reaction of the initially formed dihydroindole (not shown).[20]

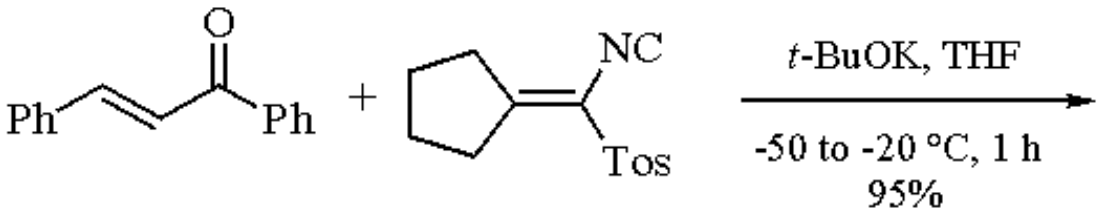

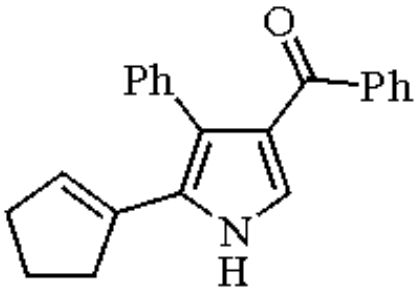

(25)

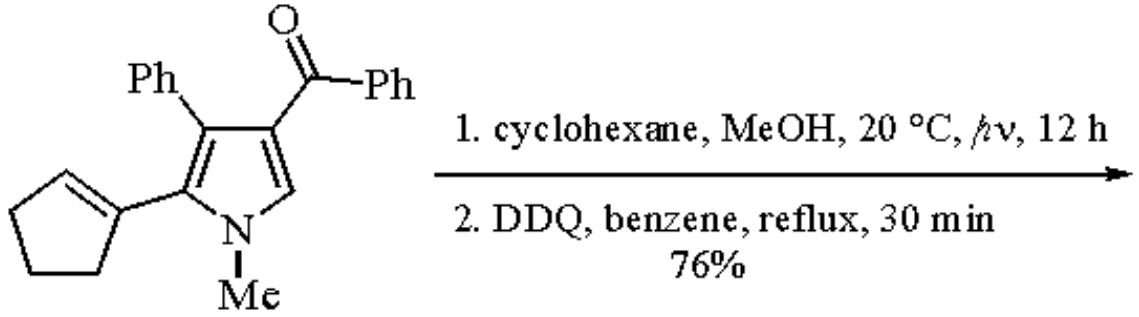
Ph
O
Ph
N
Me
1. cyclohexane, MeOH, 20 °C, hν, 12 h
2. DDQ, benzene, reflux, 30 min
76%

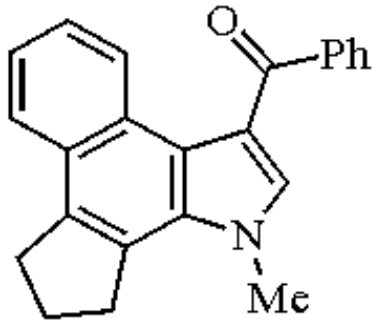
O
Ph
N
Me

(26)

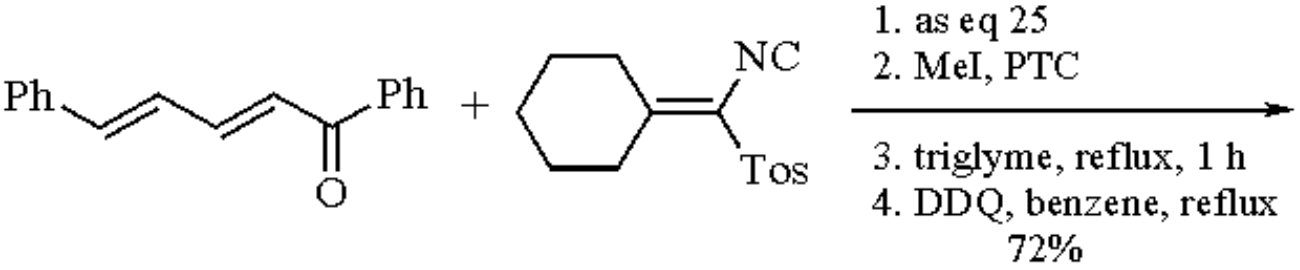
Ph
Ph
O
+
NC
Tos
1. as eq 25
2. MeI, PTC
3. triglyme, reflux, 1 h
4. DDQ, benzene, reflux
72%

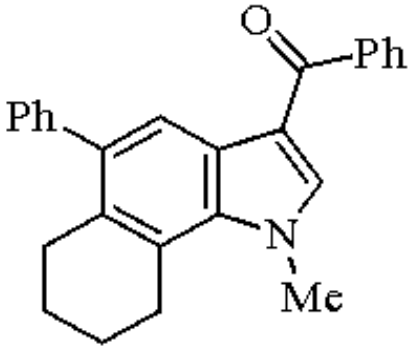
O
Ph
Ph
N
Me

(27)

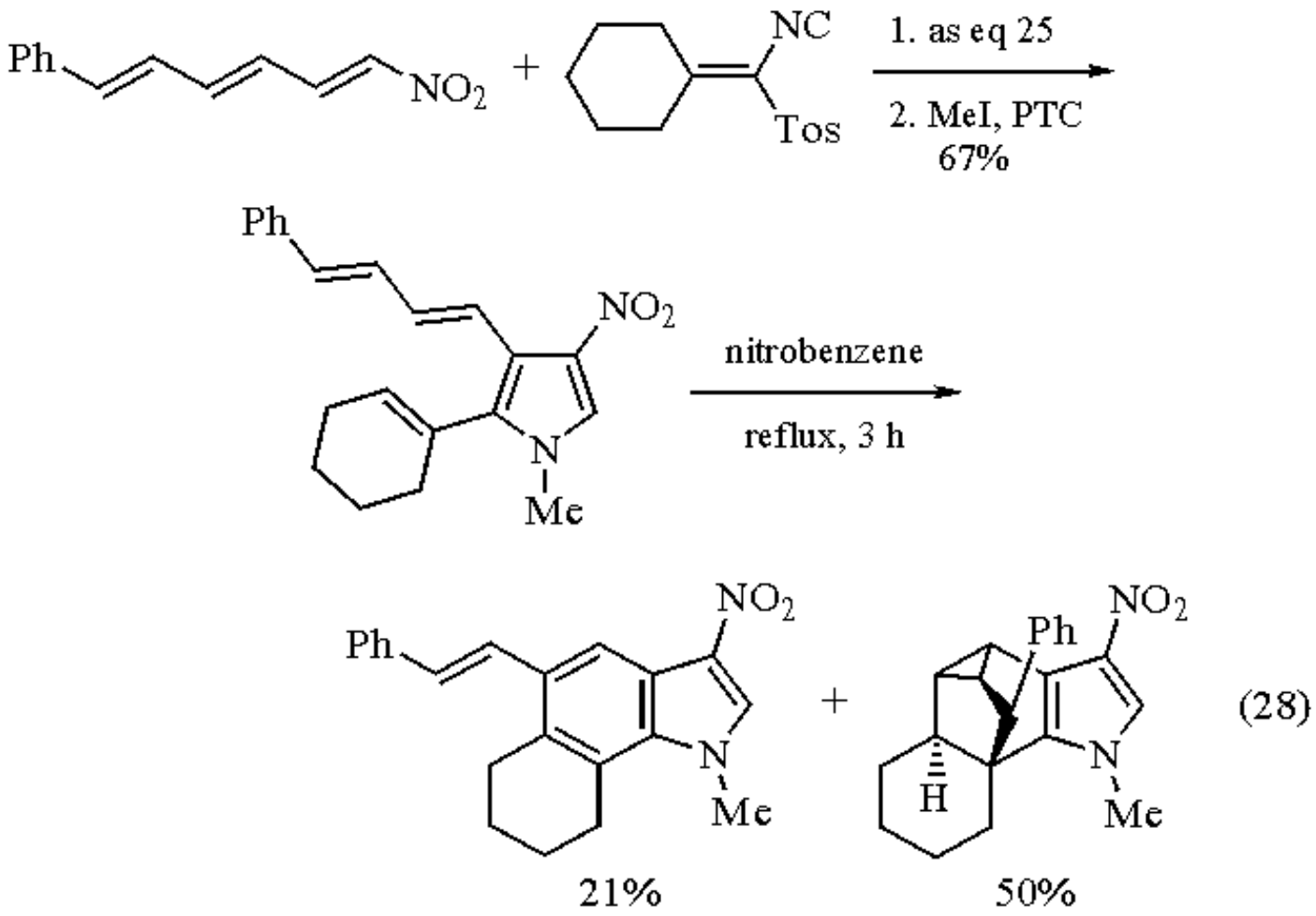

In yet another synthesis of pyrroles, the Knoevenagel condensation products of TosMIC and aldehydes (eqs 11 and 12) are used as Michael acceptors (eqs 29-32). Eq 29 shows a highly efficient, one-step synthesis of 3-nitropyrroles (difficult to access otherwise),[21b] in which the ***Nitromethane*** carbon links the isocyano- and β-carbons of the Michael acceptor into a pyrrole ring.[21a] The same product of eq 29 has been obtained in the reaction of TosMIC and β-nitrostyrene in only 27% yield.[22] No reaction takes place when the nitromethane in eq 29 is replaced by acetonitrile. 3-Cyanopyrroles, however, are obtained effectively when cyanoacetate is used instead. Eq 31[3a] gives an example in the form of an alternate synthesis of a commercially employed seed-protecting agent, which is produced from TosMIC and ethyl α-cyano-2,3-dichlorocinnamate.[21c] This approach even applies to the synthesis of 3,4-dialkylpyrroles (eq 32),[3a] which obviously cannot be prepared from TosMIC and alkenes (compare eq 5).

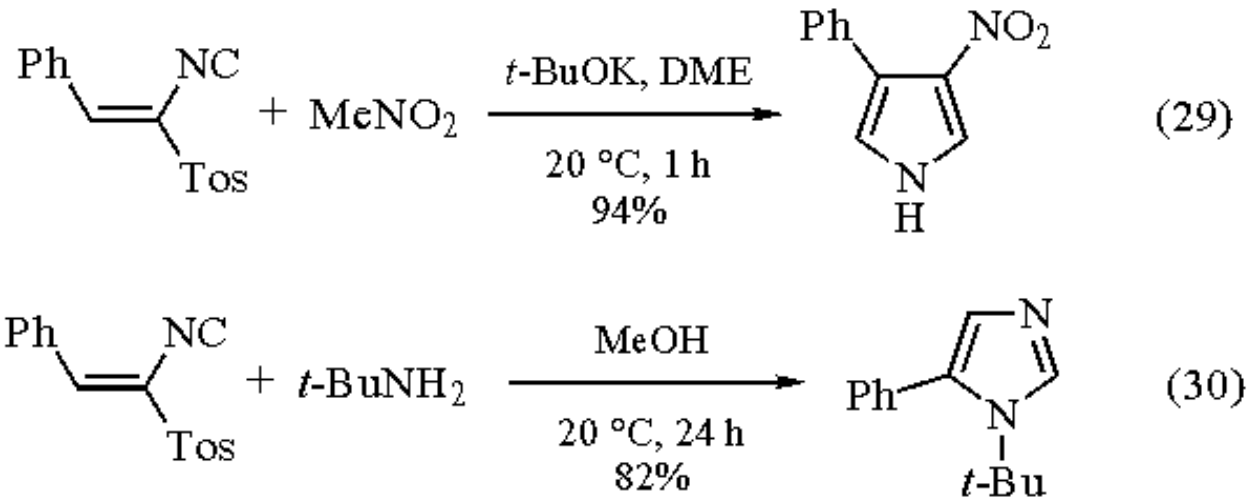

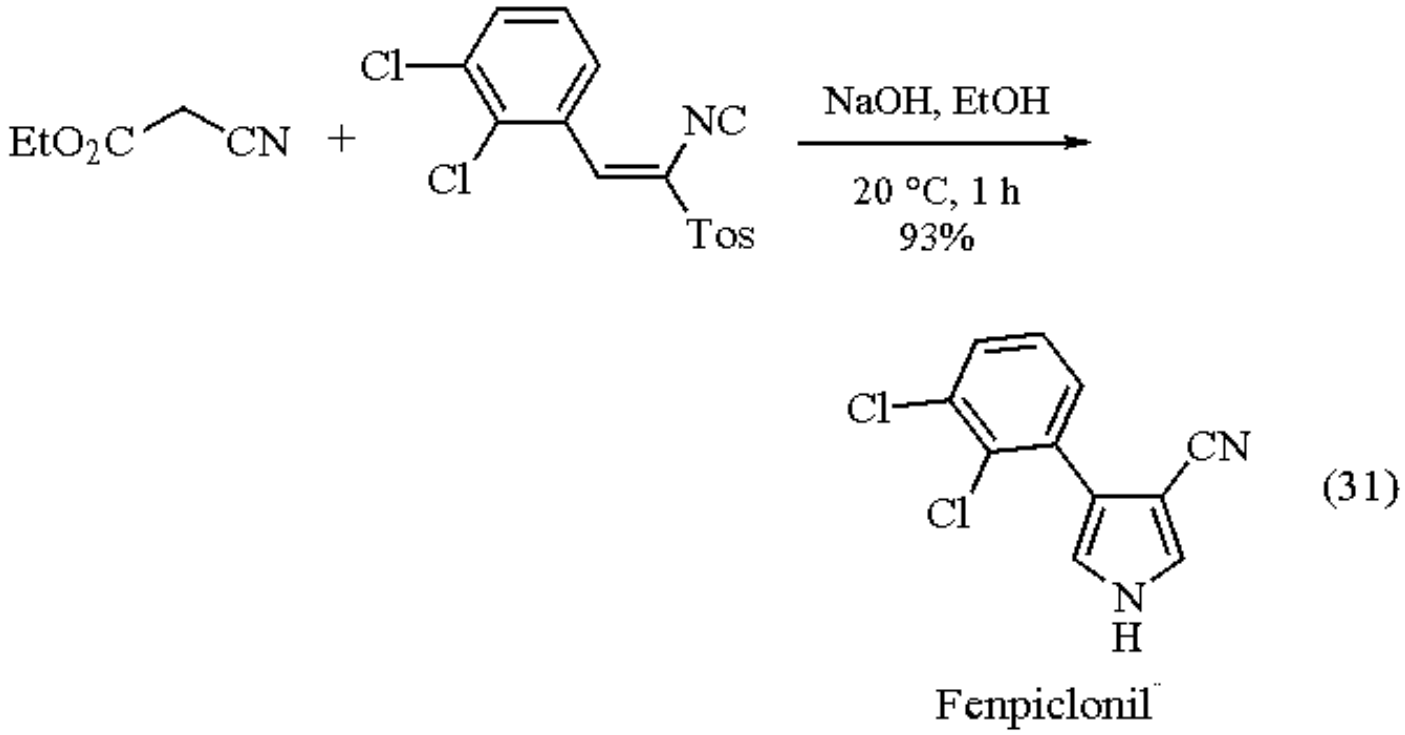

(31)

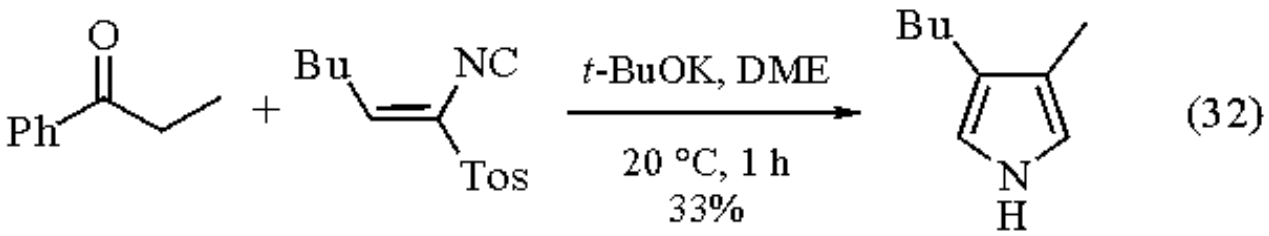

(32)

TosMIC as a Connective Reagent.

The principle of using TosMIC as a connective reagent to form CO or CH_2 bridges has been exploited in several different ways (eqs 6-8 and 33-38). Eq 33 describes the synthesis of muscalure, a pheromone of the common house fly.[4b] The isocyano group is retained at the bridging carbon when electroreduction is applied (eq 34).[23] A practical synthesis of cyclobutanone is based on the use of TosMIC as an intramolecular connective reagent (eq 35),[24a] a method which has been extended to the (first) synthesis of (*R*)- and (*S*)-2-methylcyclobutanone from *rac*-1,3-dibromobutane and a chiral analog of TosMIC, (+)-neomenthylsulfonylmethyl isocyanide.[24b] Eq 36 gives another recent example of the synthesis of cyclic ketones.[24c] Several symmetrical and unsymmetrical acyclic diketones have been prepared by using TosMIC twice (eq 37).[4a] TosMIC has been used extensively in the construction of hydroxyacetyl side chains of corticosteroids and acetyl side chains as in progesterone (eq 38),[5e] starting from 17-oxo steroids.

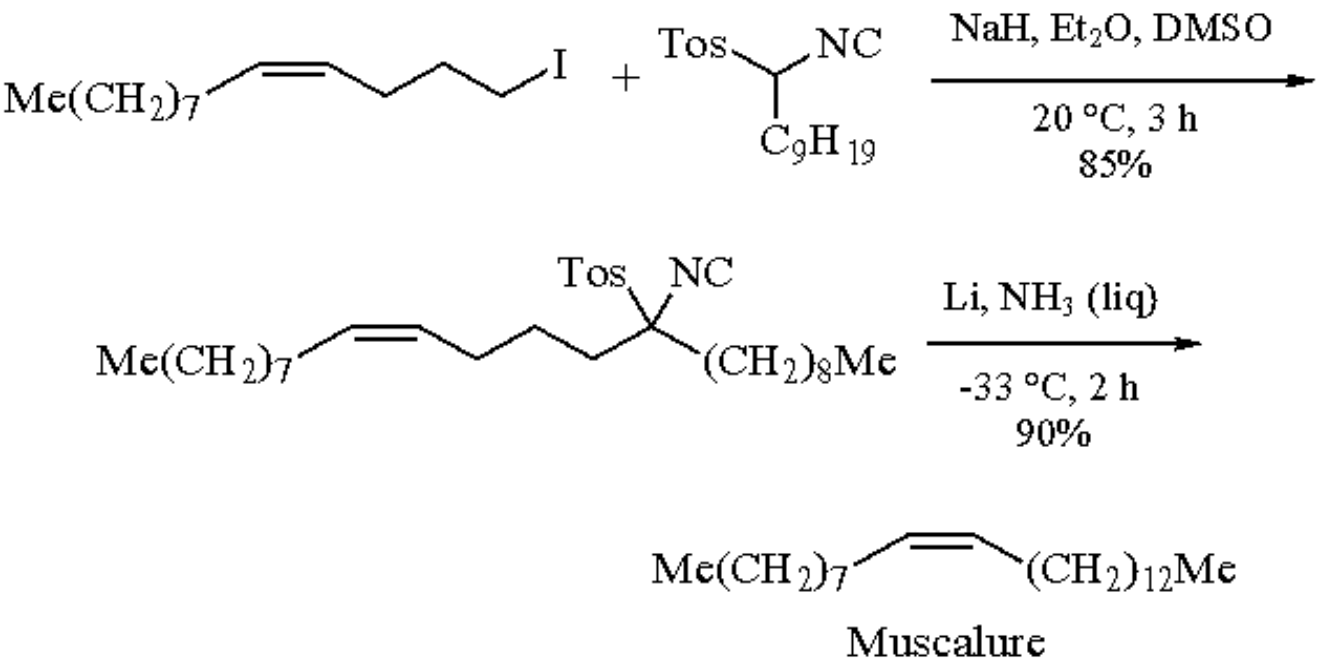
Me(CH2)7
I
Tos
NC
C9H19
NaH, Et2O, DMSO
20 °C, 3 h
85%
Tos
NC
Me(CH2)7
(CH2)8Me
Li, NH3 (liq)
-33 °C, 2 h
90%
Me(CH2)7
(CH2)12Me
Muscalure

(33)

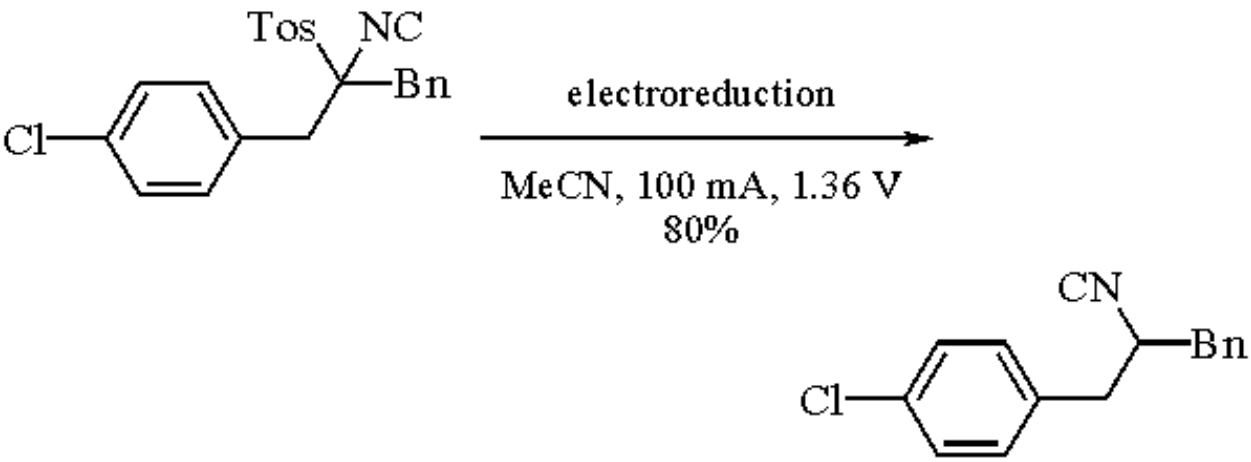
Tos
NC
Bn
Cl
electroreduction
MeCN, 100 mA, 1.36 V
80%
CN
Bn
Cl

(34)

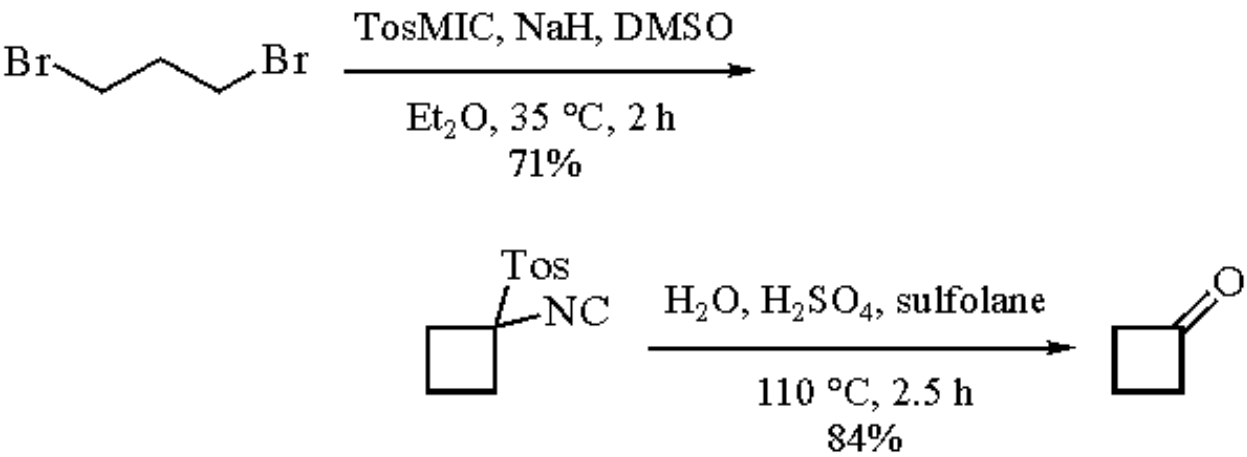
Br
Br
TosMIC, NaH, DMSO
Et2O, 35 °C, 2 h
71%
Tos
NC
H2O, H2SO4, sulfolane
110 °C, 2.5 h
84%
O

(35)

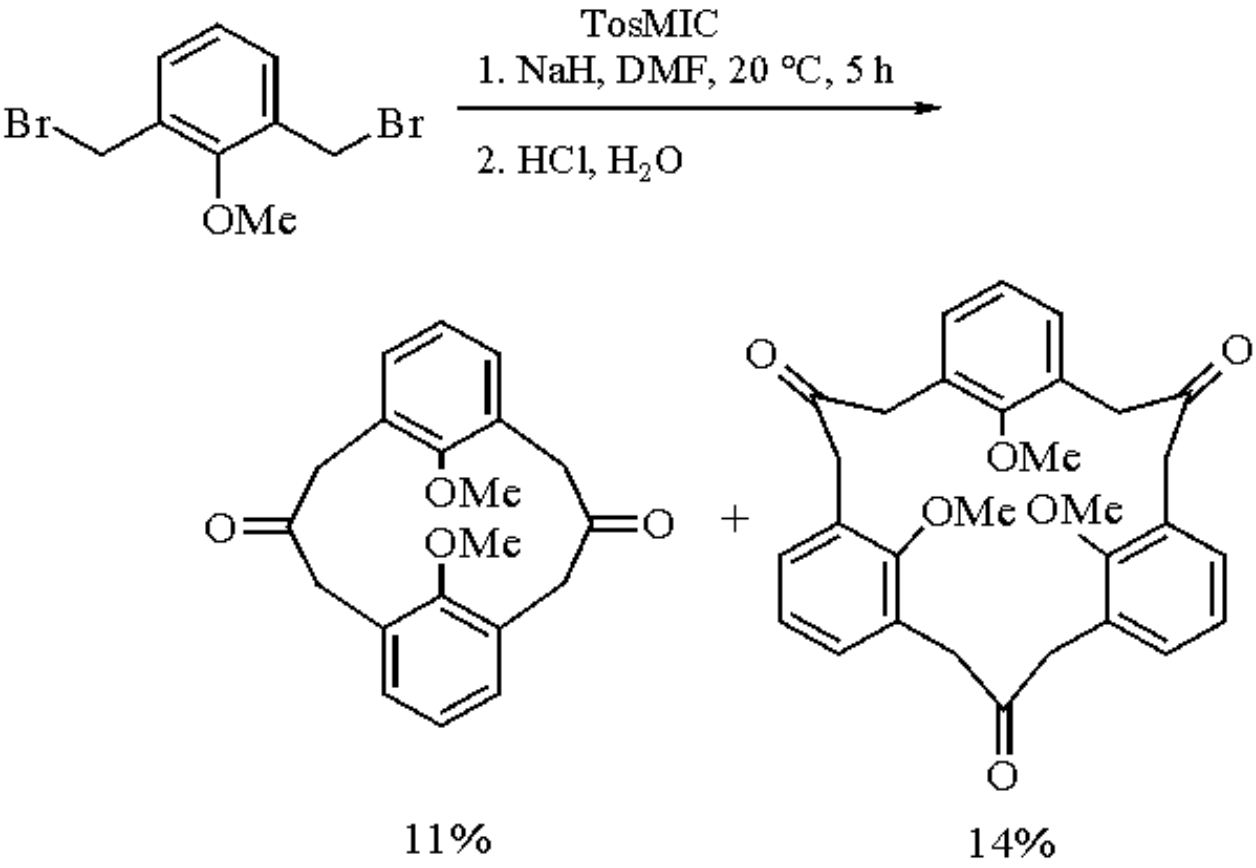
TosMIC
1. NaH, DMF, 20 °C, 5 h
2. HCl, H2O
Br
Br
OMe
OMe
OMe
O
O
+
OMe
OMe OMe
O
O
O
11%
14%

(36)

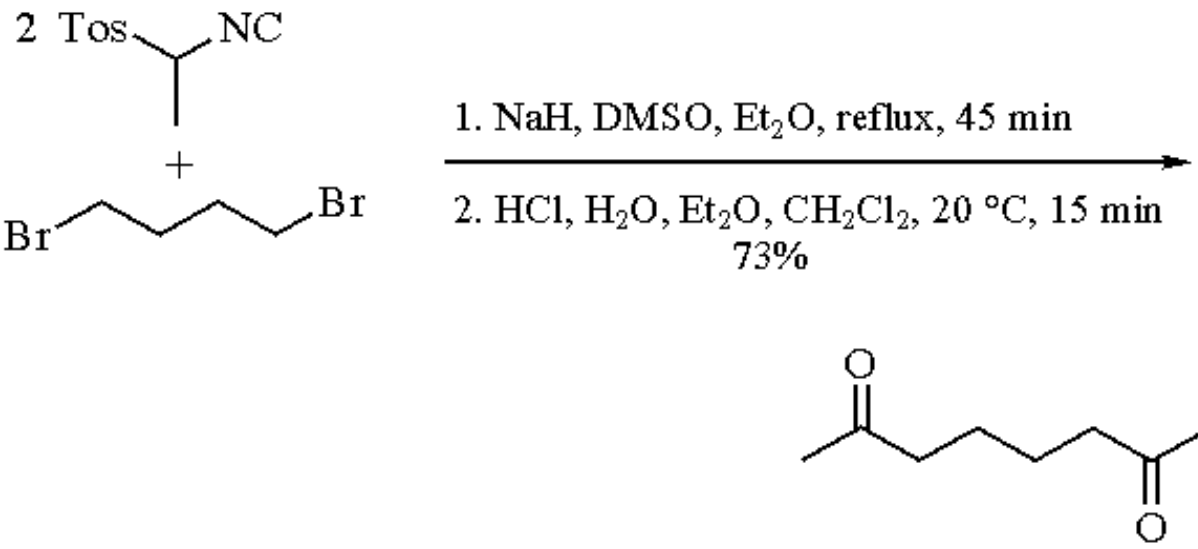
2 Tos
NC
+
Br
Br
1. NaH, DMSO, Et2O, reflux, 45 min
2. HCl, H2O, Et2O, CH2Cl2, 20 °C, 15 min
73%
O
O

(37)

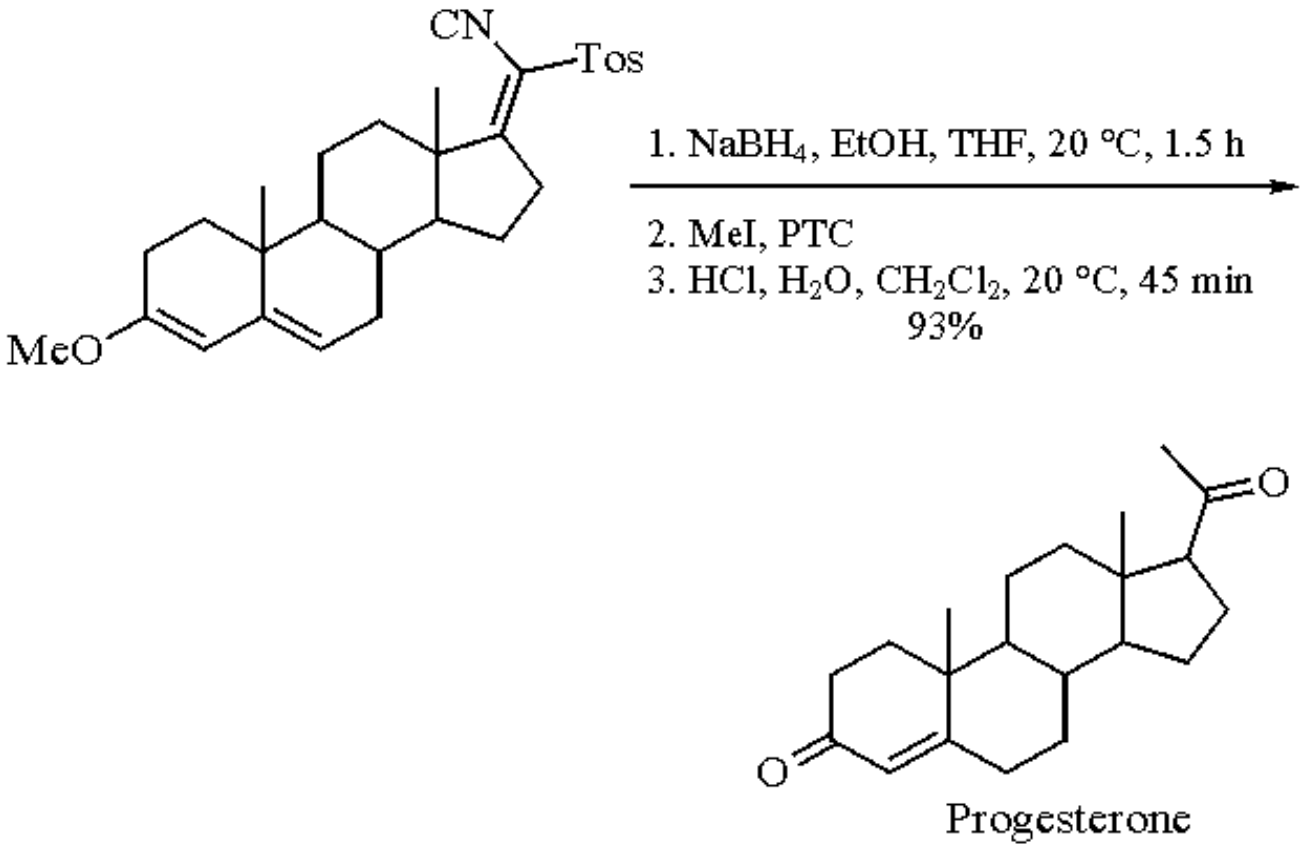

(38)

TosMIC Analogs and Derivatives.

Three labeled TosMIC compounds have been reported: Tos^{14}CH$_2$N=C,[2a] TosCH$_2$N=^{13}C,[18a] and TosCH$_2$^{15}N=C.[18b] Derivatives of TosMIC, of which one or both methylene hydrogens are replaced by alkyl, aryl, silyl, or alkylidene groups, have been included in the above discussion. Furthermore, the *p*-tolyl group of TosMIC has been replaced by various other aryl or alkyl groups,[1a,b] among which are several chiral groups.[24b,25a] The TosMIC sulfur has been made a stereogenic center by replacing one oxygen for a TosN= group.[25b] Also, both oxygens of the sulfonyl group have been formally removed, providing the reagent ***p-Tolylthiomethyl Isocyanide***. Finally, the isocyano carbon of TosMIC has been equipped with two substituents, for example Ph and MeS groups,[26a] two MeO groups,[26a] or a Ph$_3$C-N= group.[26b] All analogs and derivatives of TosMIC show TosMIC-like ch emistry, but they have been applied much less frequently than TosMIC itself.

Related Reagents.

N,N-Diethylaminoacetonitrile; ***Diethyl Isocyanomethylphosphonate***; ***Ethyl Isocyanoacetate***; ***Isocyanomethyllithium***; ***2-Lithio-1,3-dithiane***; ***Methoxyacetonitrile***; ***Methyl Isocyanide***; ***Methylthiomethyl p-Tolyl Sulfone***; ***Methyl N-(p-Tolylsulfonylmethyl)thiobenzimidate***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***p-Tolylthiomethyl Isocyanide***.

---

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4. (a) van Leusen, A. M.; Oosterwijk, R.; van Echten, E.; van Leusen, D. *RTC* **1985**, *104*, 50. (b) Yadav, J. S.; Reddy, P. S.; Joshi, B. V. *T* **1988**, *44*, 7243.
5. (a) van Leusen, D.; van Echten, E.; van Leusen, A. M. *RTC* **1992**, *111*, 469. (b) Moskal, J.; van Leusen, A. M. *JOC* **1986**, *51*, 4131. (c) Moskal, J.; van Stralen, R.; Postma, D.; van Leusen, A. M. *TL* **1986**, *27*, 2173. (d) van Leusen, A. M.; Schaart, F. J.; van Leusen, D. *RTC* **1979**, *98*, 258. (e) van Leusen, D.; van Leusen, A. M. *S* **1991**, 531.
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20. Leusink, F. R.; ten Have, R.; van den Berg, K. J.; van Leusen, A. M. *CC* **1992**, 1401.
21. (a) van Leusen, D.; Flentge, E.; van Leusen, A. M. *T* **1991**, *47*, 4639. (b) Barton, D. H. R.; Kervagoret, J.; Zard, S. Z. *T* **1990**, *46*, 7587. (c) See footnotes 8 and 9 in Ref. 3a.
22. Ref. 21a; meanwhile the yield of that reaction has been improved to 70% by using NaH in DME at -40 °C at lower concentrations (ten Have, R., unpublished results).
23. Hesz, U.; Brosig, H.; Fehlhammer, W. P. *TL* **1991**, *32*, 5539.
24. (a) van Leusen, D.; van Leusen, A. M. *S* **1980**, 325. (b) van Leusen, D.; Rouwette, P. H. F. M.; van Leusen, A. M. *JOC* **1981**, *46*, 5159 ((*R*)- and (*S*)-2-methylcyclobutanone were not obtained enantiomerically pure). (c) Breitenbach, J.; Vögtle, F. *S* **1992**, 41.
25. (a) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *T* **1987**, *43*, 5073. (b) van Leusen, D.; van Leusen, A. M. *RTC* **1984**, *103*, 41.
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1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[1]

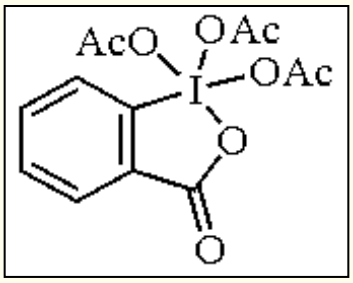

[87413-09-0] · $C_{13}H_{13}IO_8$ · 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one · (MW 424.16)

(selective oxidation of primary,[1] secondary,[1] allylic,[2] allenic,[3] propargylic,[4] benzylic,[5] and α-fluorinated alcohols;[6] monoprotected 1,2- and 1,3-diols and amino alcohols;[7-10] α- and β-hydroxy ketones,[11,12] α- and β-hydroxy esters,[13,14] β-hydroxy amides,[15] β-hydroxy sulfones;[16] nucleosides;[17] carbohydrates;[18] compatible with a variety of protecting groups,[19,20] unsaturation,[21,22] basic nitrogen,[23] divalent sulfur[24] and selenium,[25] and halogen[26])

Alternate Names: Dess-Martin periodinane; TAPI.

Physical Data: mp 124-126 °C (dec).

Solubility: appreciably sol CH_2Cl_2, $CHCl_3$, MeCN, THF; effectively insol aromatic and aliphatic hydrocarbons, ether.

Form Supplied in: white free-flowing moisture- and light-sensitive solid; not currently commerically available due to the potential explosion hazard (see below).

Analysis of Reagent Purity: recommended methods include ^{1}H NMR,[1] and standardization by oxidation of benzyl alcohol;[27] however, a typical iodimetric titration used for the standardization of peracids and other oxidants can likely also be employed. NMR data for the reagent: ^{1}H NMR (300 MHz in $CDCl_3$): δ 8.29 (d, *J* = 8.1 Hz, 2H), 8.09 (t, *J* = 8.1 Hz, 1H), 7.91 (t, *J* = 7.4 Hz, 1H), 2.32 (s, 3H), 1.99 (s, 6H); minor impurity peaks are observed at δ 8.39 (d), 8.21 (d), 8.00 (d), 7.27 (s), and 2.08 (s); ^{13}C NMR (75 MHz in $CDCl_3$): δ 175.7, 174.0, 166.1, 142.2, 135.8, 133.8, 131.7, 126.5, 125.9, 20.4, 20.2.

Preparative Method: prepared from commercially available 2-iodobenzoic acid (recrystallized) by oxidation with ***Potassium Bromate*** in aqueous sulfuric acid at 65 °C for 3.6 h to afford the highly insoluble and sensitive (explosion hazard) hydroxyiodinane oxide (**2**) which is washed free of residual $KBrO_3$ by sequential washing with water, ethanol, and then water again; vacuum filtration then affords the oxide as a moist solid (thorough drying is not recommended due to explosion hazard). This moist oxide is directly transformed to the reagent by treatment with excess ***Acetic Anhydride*** and ***Acetic Acid*** at 62 -> 96 °C for ~35 min (or until conversion is complete by analysis of an aliquot of the reaction mixture by NMR) followed by cooling for 12 h at room temperature. The solid reagent is collected by vacuum filtration under an inert atmosphere (glove bag/box or Schlenk techniques should be employed), and dried on the filter bed for 0.5 h; this affords the reagent (**1**) in 68-75% yield over the two steps (eqs 1 and 2).[1,27] A recent modification by Ireland recommends the use of ***p-Toluenesulfonic Acid*** as a catalyst in the conversion of the oxide (**2**) to (**1**).[28]

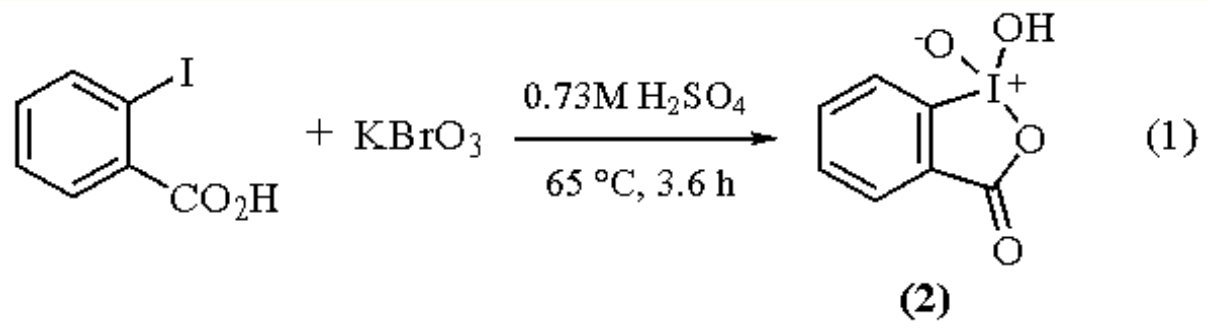

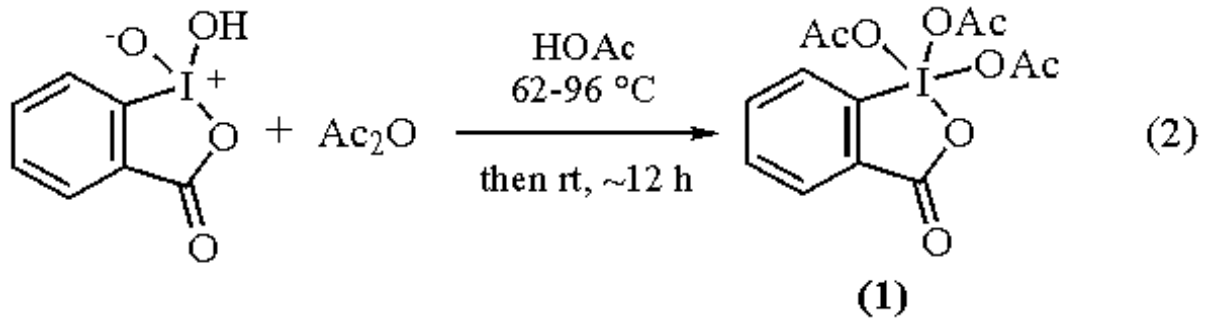

Difficulties have sometimes attended the preparation of (**1**) for a variety of reasons, including but not limited to: (1) incomplete removal of $KBrO_3$ and possibly Br_2 during preparation of the hydroxyiodinane oxide (**2**); (2) incomplete or lack of removal of traces of ethanol used in washing the oxide intermediate (an obligatory process to avoid a potential explosion hazard); (3) incomplete acetylation of the oxide (**2**), as the presence of the monoacetoxy periodinane oxide has been implicated in the impact sensitivity shown by some but apparently not all samples of the reagent; and (4) partial or complete hydrolysis of the reagent during isolation by excessive exposure to atmospheric moisture (partial hydrolysis affords the aforementioned monoacetoxyiodinane oxide, and complete hydrolysis produces iodoxybenzoic acid, known to be explosive, which may contribute to the impact sensitivity observed).[1]

Purification: the reagent, when prepared properly, is sufficiently pure for use after standardization if desired. No purification method has been described.

Handling, Storage, and Precautions: the reagent is a moisture- and light-sensitive material.[1] While it can be handled briefly in the air, extensive exposure to moisture should be avoided. Transfers of solutions should be conducted using syringe techniques, and transfers of the solid are best done in a glove bag or box to avoid deterioration of the reagent. The pure solid reagent is stable indefinitely at room temperature when precautions are taken to avoid exposure to moisture and light.[1] Storage should be in an amber bottle under an inert atmosphere or other means of protection from atmospheric moisture. Safety evaluations show that the precursor oxide is impact sensitive, and explosively decomposes when heated (>150 °C), with the onset varying with the sample. Handling the material as a moist solid appears to significantly reduce, but not completely remove, this explosion hazard. The pure periodinane has been stated to not exhibit impact sensitivity and to thermally decompose without explosion.[1] An independent evaluation of typical samples prepared as above shows that, although the reagent is less sensitive than the precursor oxide, it has the potential to decompose violently when heated (>200 °C) and shows impact sensitivity, although less than the oxide precursor. Thus, prudence requires that the preparation, handling, and use of this reagent and its precursor be conducted with due care and precaution against potential explosion (use of appropriate explosion shields, etc.), particularly on a substantial scale. Nevertheless, as the following discussion will attest, the reagent has been prepared and utilized widely with only one report of an explosion,[29] so that there is good cause to believe that, with appropriate precautions, the reagent can be prepared and handled safely on a normal laboratory scale.

Introduction.

In the short time since its original description in the literature in 1983, the Dess-Martin periodinane (**1**) has enjoyed remarkably widespread use as a reagent for the oxidation of complex, sensitive, multifunctional alcohols of a startling array of structural types. The periodinane (**1**) is a member of the 12-I-5 group of hypervalent iodine species. A number of related structures, which also function as oxidizing agents for alcohols, have been described.[1] Among the advantages of the periodinane (**1**) over the myriad of other oxidizing agents which are available are: (1) functional groups lacking a hydroxylic function are exchanged into the ligand sphere of (**1**) slowly. Alcohols, particularly primary alcohols, undergo rapid and near-quantitative ligand exchange which is largely insensitive to the steric environment of the OH group. This ligand exchange is the obligatory first step in oxidation, which provides an inherent functional group selectivity in the oxidation reactions of (**1**). (2) The reagent is exceptionally versatile, having probably the broadest scope of any of the oxidizing agents commonly employed to convert alcohols to carbonyl derivatives, and generally provides exceptionally clean reactions and excellent yields. (3) When pyridine or di-*t*-butylpyridine is employed to buffer the reaction mixture and sodium thiosulfate/sodium bicarbonate is employed for workup, the entire oxidation/workup procedure can be conducted under near-neutral conditions compatible with even the most sensitive functionality. (4) The workup procedure is very simple, and the byproducts from the oxidation are readily removed by precipitation or chromatography, even without use of an aqueous workup. (5) The reagent is a shelf-stable solid, possessing adequate stability to moisture to permit ready metering and handling, even on very small scale, as is typically required in synthetic sequences leading to complex multifunctional molecules. The rates of oxidation of allylic and benzylic alcohols are highest, but oxidation of electron deficient carbinols such as α-fluorinated alcohols still occurs in good yields.

Typical Oxidation and Workup Procedures.

The oxidation of alcohols is conducted at temperatures ranging from -20 to 35 °C (with ambient temperature being most common), typically in CH_2Cl_2 and occasionally in $CHCl_3$, acetonitrile, or THF, by admixing the reagent (typically 1-3 equiv per OH group), either as the solid or as a solution in the reaction solvent, with a solution of the alcohol. For very acid-sensitive substrates or products, the reaction mixture is buffered by the prior addition of 3-10 equiv of pyridine or 2,6-di-*t*-butylpyridine. The reaction mixture is then held at the appropriate temperature for as little as 5 min to as long as 120 h (most commonly 0.5-1.5 h) before dilution with ether (precipitation of periodinane byproducts occurs), addition of

either aqueous NaOH solution or, for base-sensitive products, a mixture of aqueous $Na_2S_2O_3$ and $NaHCO_3$, stirring until the phases are homogeneous (~15 min), and isolation of the products by extraction. It is possible to avoid the use of aqueous workup conditions altogether by introduction of the reaction mixture, after dilution with ether, directly onto a chromatographic column for separation of the organic oxidation product(s).

Oxidation of Primary Alcohols to Aldehydes.

Since many oxidants will satisfactorily accomplish this transformation, this discussion will focus on cases where (**1**) has been of particular value. The strength of the periodinane (**1**) is its ability to effect oxidation under neutral conditions, thus avoiding side reactions in sensitive substrates possessing multiple functional groups such as the enediyne (**3**) (eq 3),[30] or a variety of protecting groups, as in the azadirachtin intermediate (**4**) (eq 4).[31] Side reactions, such as β-elimination of oxygen and nitrogen functions, are seen with other oxidants for (**5**) (eq 5),[32,33] as are epimerization of α-stereogenic centers or exchange of label in labeled substrates,[34,35] and conjugation of β,γ-unsaturation.[36]

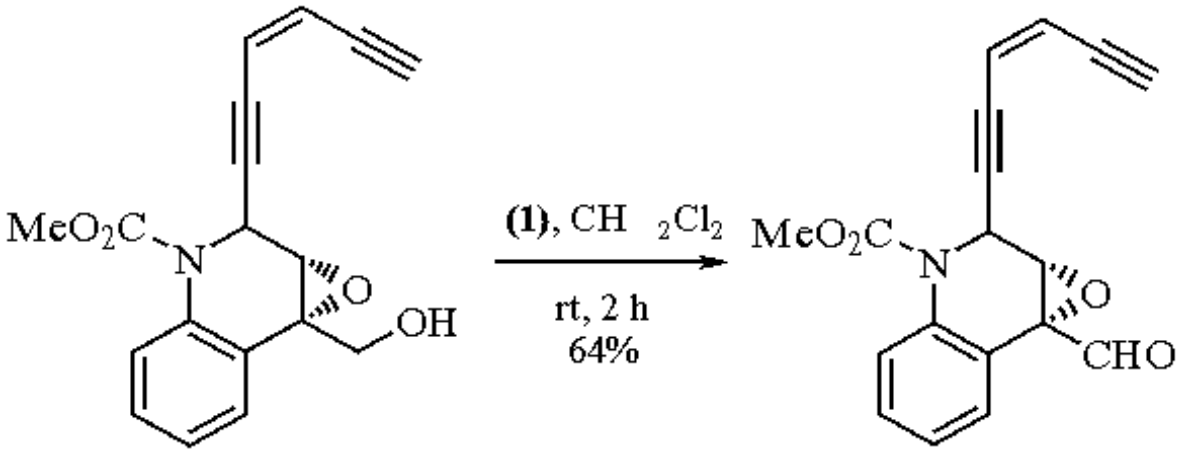

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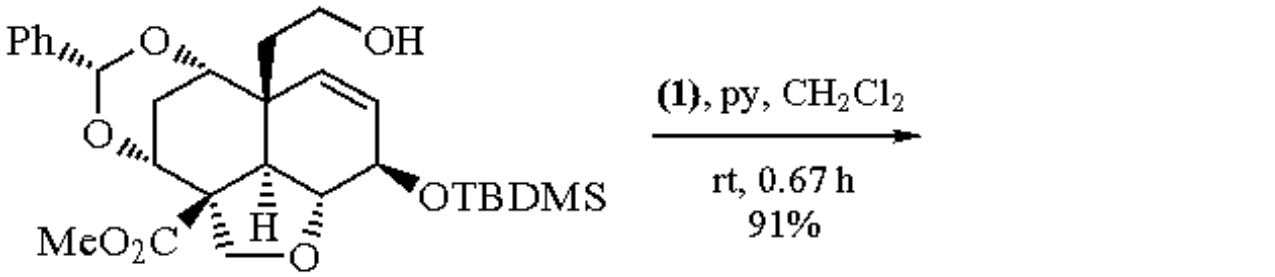

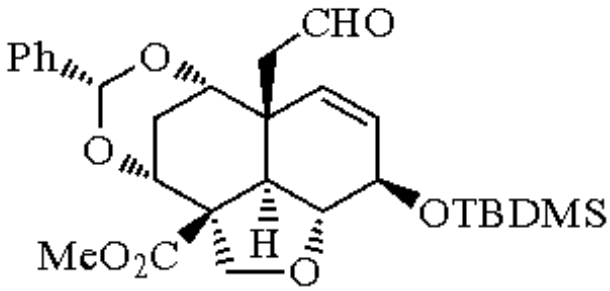

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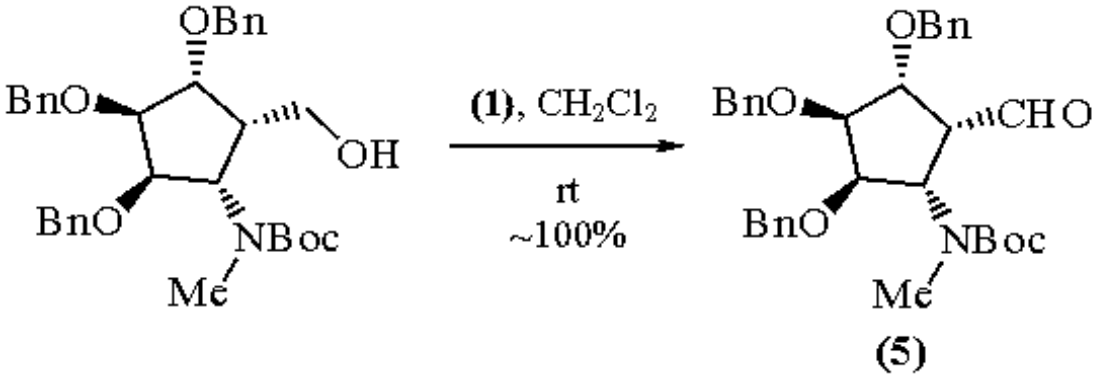

(5)

Disubstituted malondialdehydes (**6**) (eq 6) and malonaldehyde esters have been prepared without the intervention of oxidative cleavage.[37,38] Relative reactivity data based on steric environment is sparse; however, a notable case of selectivity for a primary over a hindered secondary alcohol in the preparation of the spiroacetal aldehyde (**7**) (eq 7) has been recorded.[39] Very few failures have been documented, and often no other oxidation reagent proved satisfactory in these cases.[40]

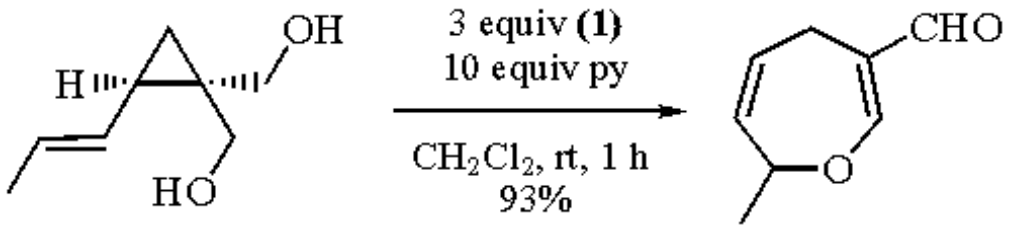

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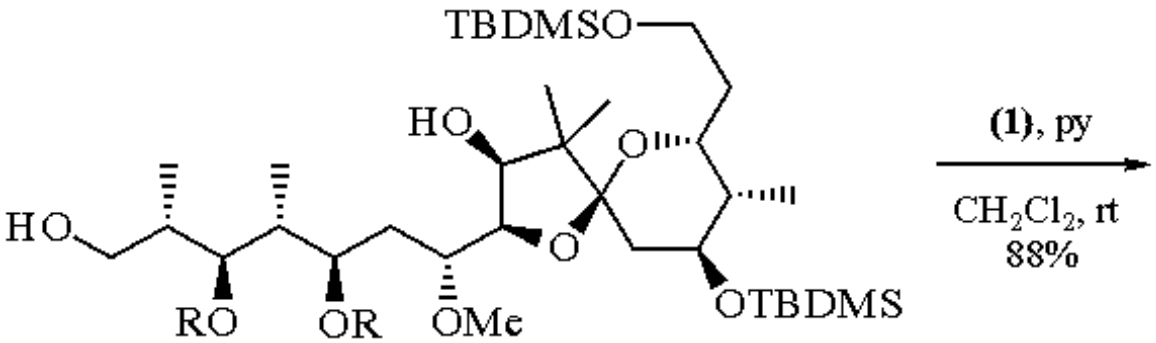

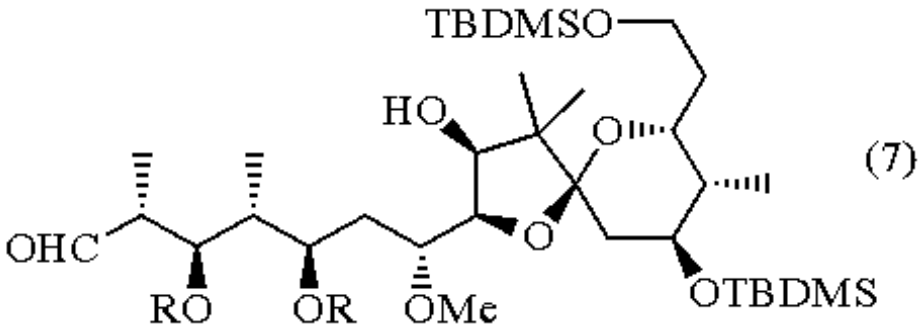

(7) R = TBDMS

Oxidation of Secondary Alcohols to Ketones.

In the case of secondary alcohols, (**1**) has also proven valuable in avoiding epimerization of α-stereogenic centers,[41,42] loss of β-acyloxy, β-alkoxy, and protected nitrogen functions during oxidations such as of β-acyloxy ketone (**8**) (eq 8), and undesired conjugation of β,γ-unsaturation as in the case of the alkaloid intermediate (**9**) (eq 9).[43-45] Overoxidation at activated methylene groups, such as benzylic centers or susceptible aromatic systems, is not normally a problem.[46,47]

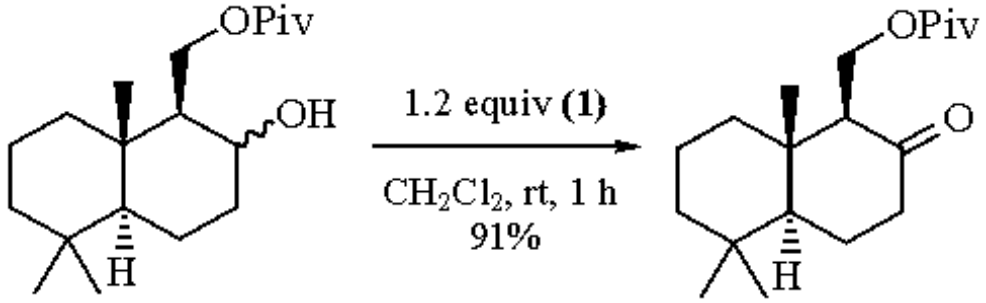

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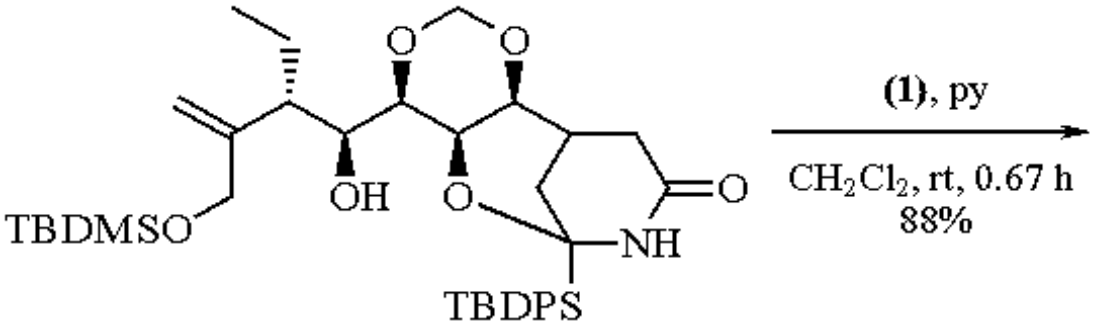

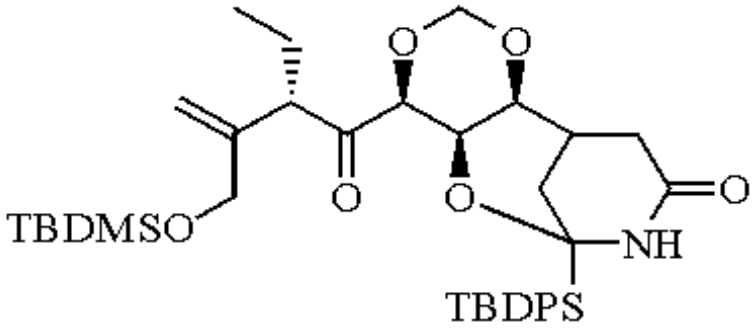

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Appropriately protected α-heteroatom-substituted systems are smoothly oxidized without epimerization or isomerization of the β,γ-double bond, as in the ketone (**10**) (eq 10).[48] Oxidation of secondary alcohols in suitably protected nucleosides and carbohydrates has also been documented, even in cases where the substrates are exceedingly acid-sensitive such as the trisaccharide (**11**) (eq 11).[49,50] Even sterically-congested secondary alcohols undergo smooth oxidation, most often in excellent yield as in the case of ketone (**12**) (eq 12).[51-53]

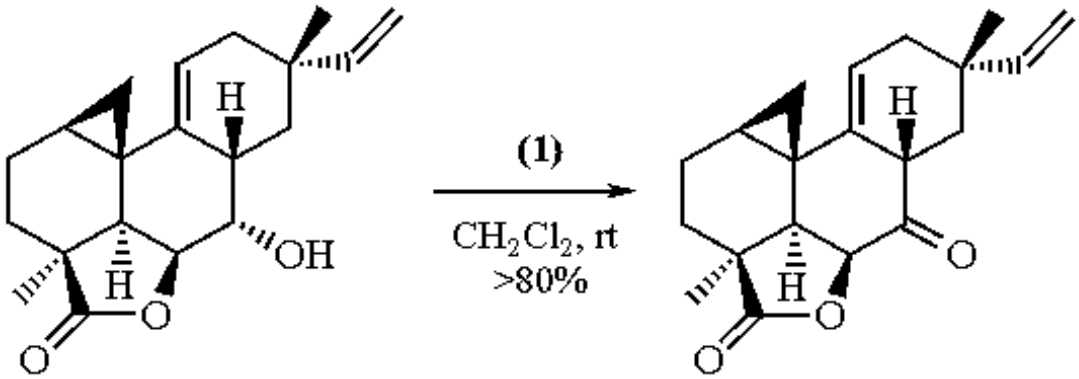

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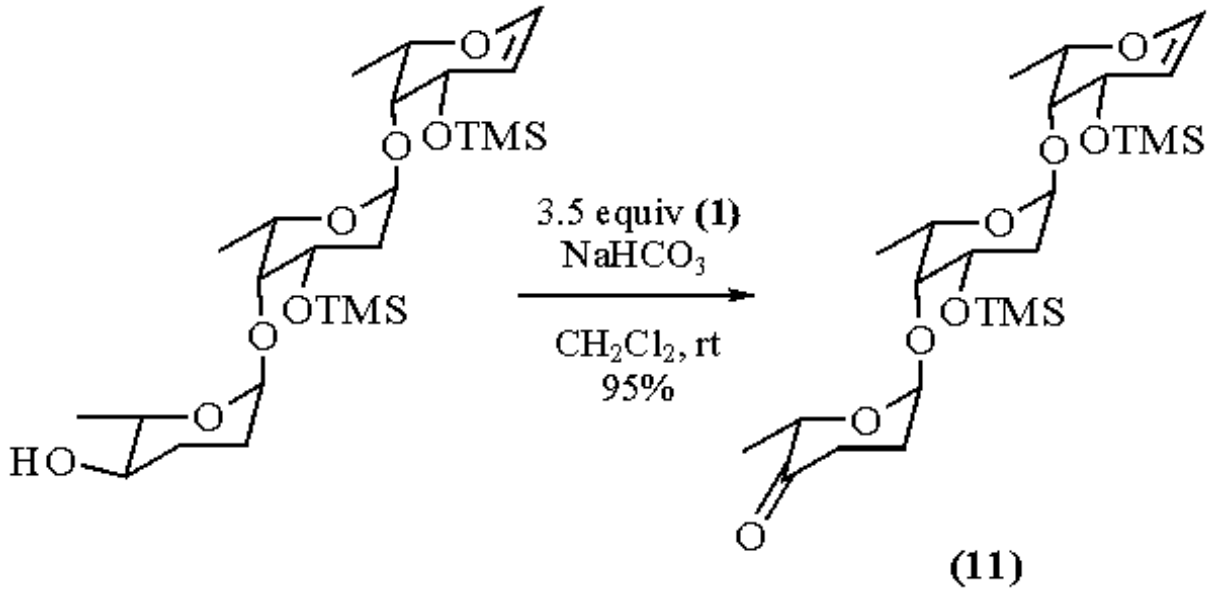

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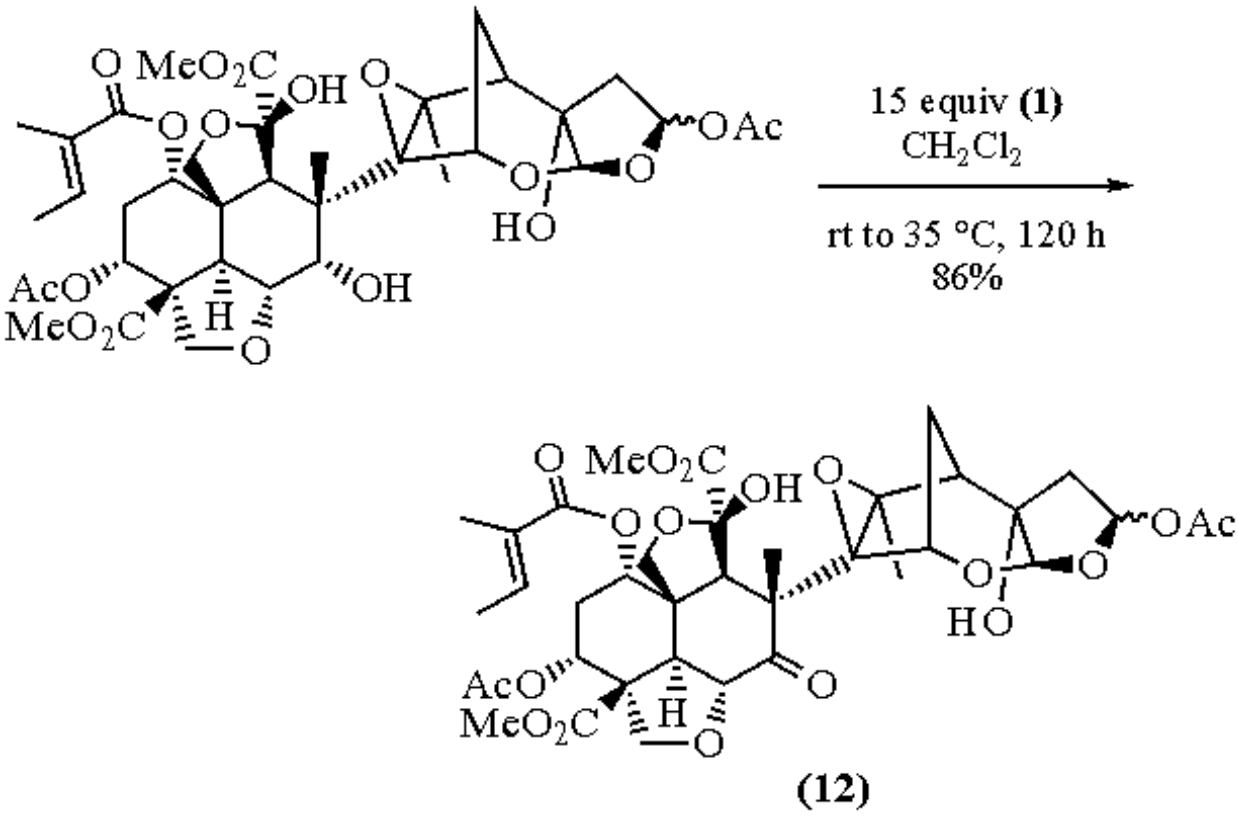

(12)

Secondary α- and β-hydroxy ketones and esters, and β-hydroxy amides and sulfones, are also smoothly oxidized to the corresponding α- and β-diketones, α- and β-keto esters, β-keto amides, and β-keto sulfones, such as the β-keto ester (**13**) (eq 13).[54] Remarkably, even substrates containing divalent sulfur and selenium, as well as bromine, have been smoothly oxidized to the corresponding ketones, such as the β-lactam (**14**) (eq 14).[55,56] Furthermore, substrates containing secondary basic nitrogen centers have been smoothly oxidized without concomitant oxidation at nitrogen, for example ketone (**15**) (eq 15).[57] Even electron-deficient, weakly nucleophilic substrates such as α-trifluoromethyl and α,α-difluoroalkyl alcohols also undergo smooth transformation to the corresponding ketones.[58,59]

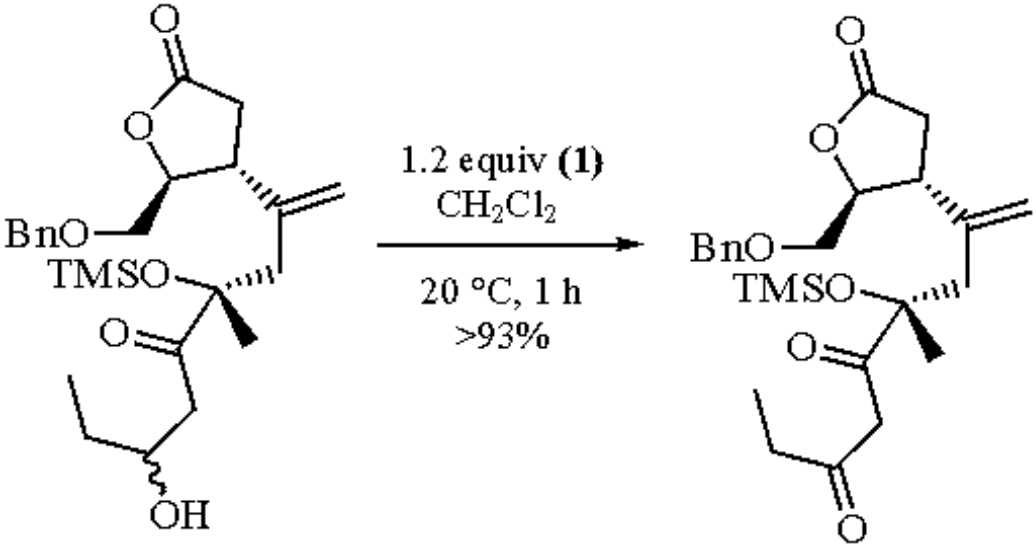

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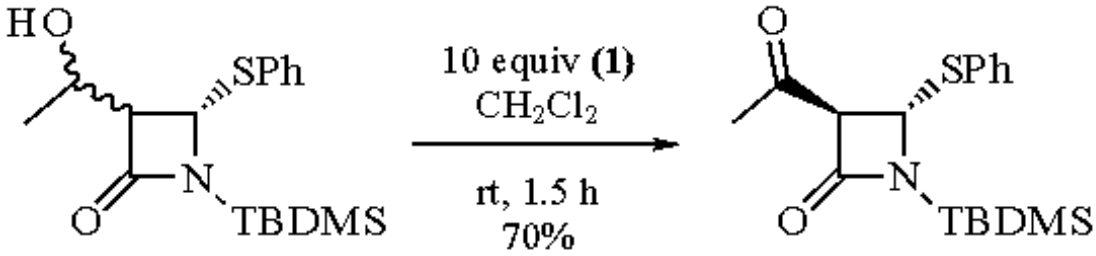

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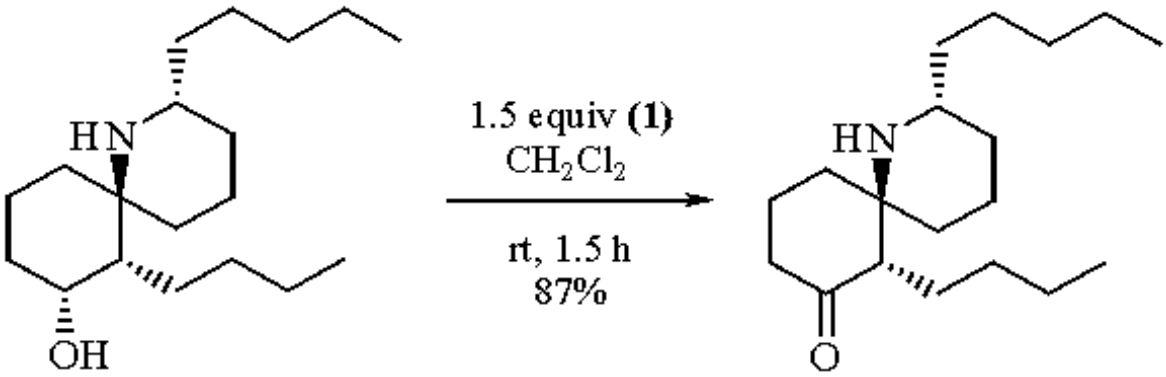

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In some cases, unprotected 1,2-diols undergo fragmentation to carbonyl compounds in a manner similar to their reactions with related periodates and periodic acid.[1,60] However, an example of the selective oxidation of a complex 2,3-dihydroxypyran to the related α-hydroxy δ-lactone (**16**) in excellent yield has been described (eq 16).[61] Of course, oxidation of remote primary-primary and secondary-secondary diols to the dicarbonyl compounds proceeds uneventually when sufficient periodinane (**1**) is employed, but statistical mixtures usually result from attempts at selective oxidation, except in cases where the hydroxyl groups differ markedly in steric environment.[39,69]

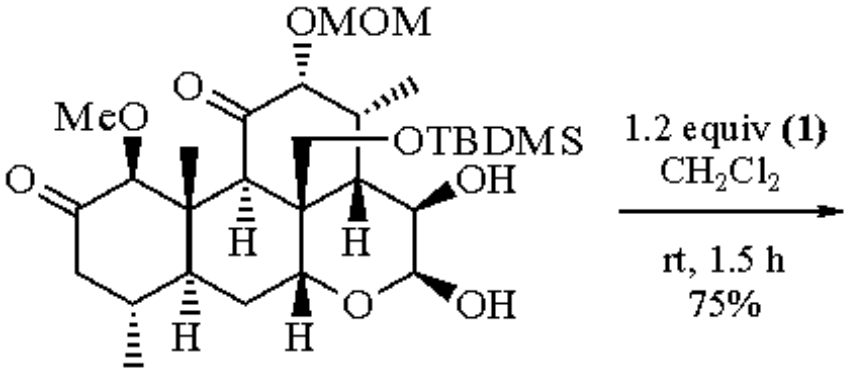

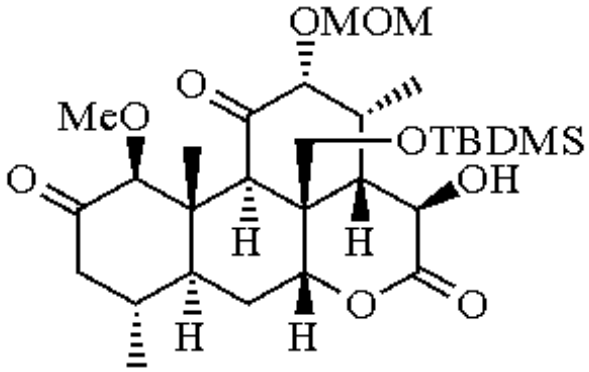

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Oxidation of Primary and Secondary Allylic, Benzylic, Propargylic, and Allenyl Alcohols.

The oxidation of allylic and benzylic alcohols by the periodinane (**1**) has been demonstrated to be significantly faster (&egt;~5×) than that of the corresponding saturated alcohols in competition experiments.[1] This selectivity is exemplified by the oxidation of the precursor secondary allylic-secondary diol to the ketol (**17**) (eq 17).[62]

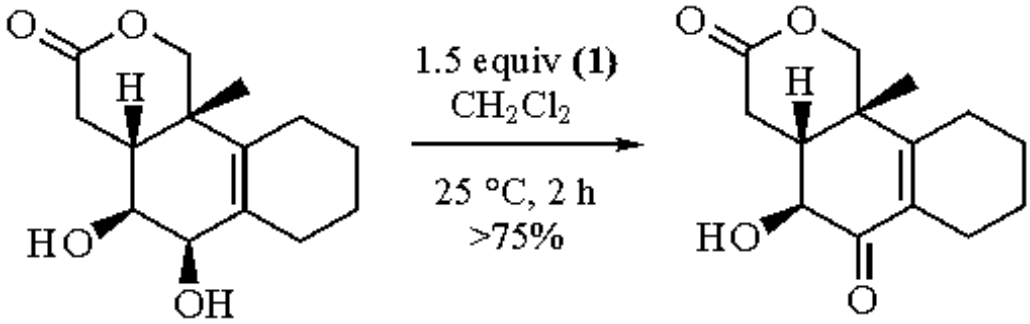

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However, in some instances, oxidative cleavage occurs in preference to simple oxidation (see below). It is in the oxidation of this general class of allylic, benzylic, and related unsaturated and acetylenic alcohols that the periodinane (**1**) has proven consistently superior to other oxidants for complex acid and base-sensitive substrates. As shown below, the range of complex substrates is truly impressive. For example, acid- and oxidation-sensitive benzyl and pyridyl alcohols are smoothly oxidized to the corresponding carbonyl compounds (**18**) and (**19**) (eqs 18 and 19).[63,64] In the latter case, the aldehyde (**19**) is obtainable in acceptable yields only by use of the periodinane (**1**). In the case of 6α-epipretazzetine (**20**) (eq 20), no overoxidation and isomerization to tazzetine is observed.[65] Furthermore, no concomitant oxidation of susceptible aromatic systems or nitrogen is detected.

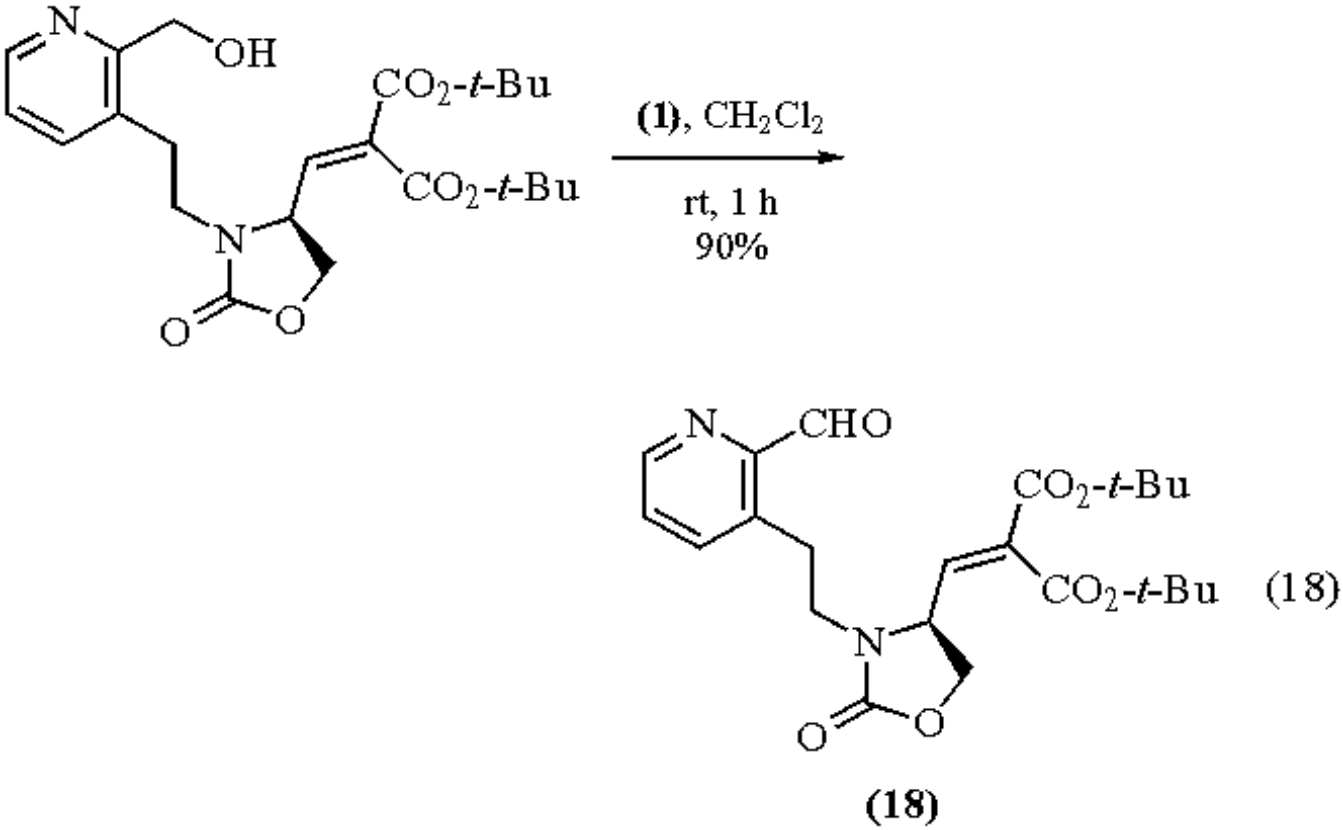

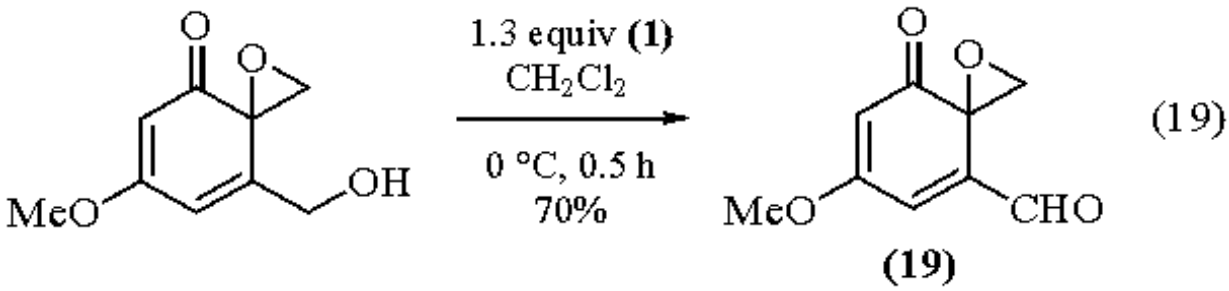

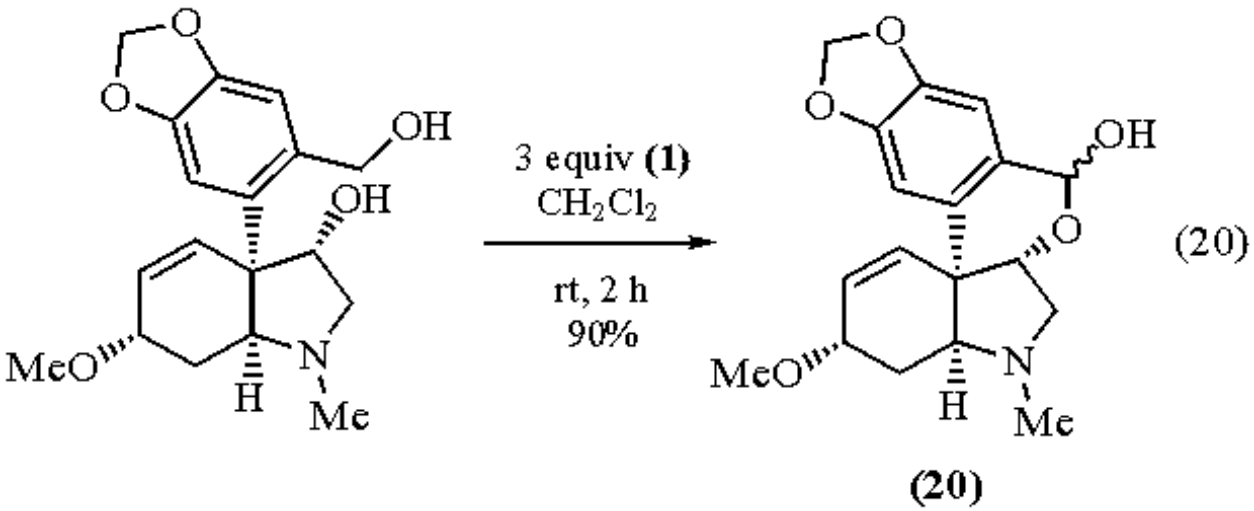

In the case of allylic alcohols, including α-methylenecycloalkanols and cyclopentenols, the periodinane (**1**) has afforded exceedingly acid-, base-, thermal-, and/or oxidation-sensitive enones, e.g. (**21**) and (**22**), in excellent yields (eqs 21 and 22).[66,67] Most impressively, (*Z*)-allylic alcohols afford the corresponding aldehydes and ketones with minimal or no loss of the geometric integrity of the alkene, as seen in the oxidations affording (**23**) and (**24**) (eqs 23 and 24).[68,69]

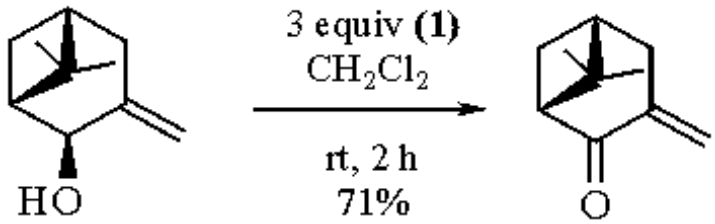

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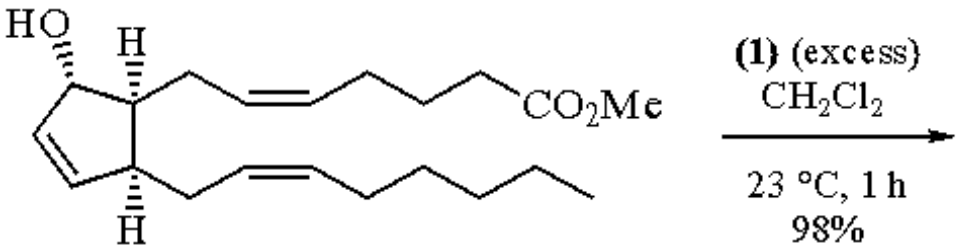

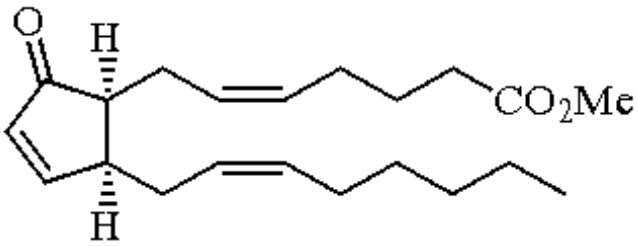

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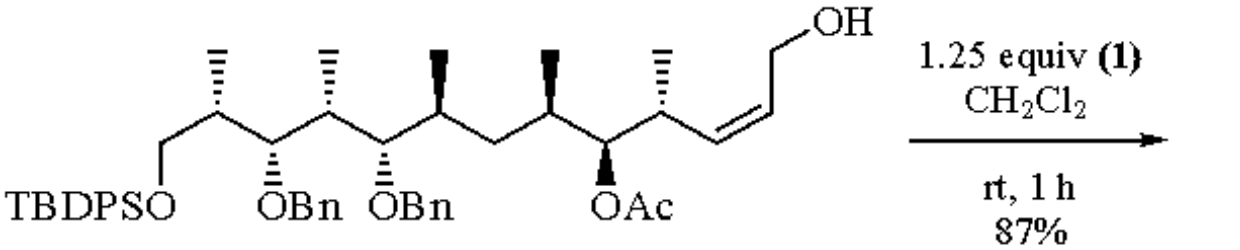

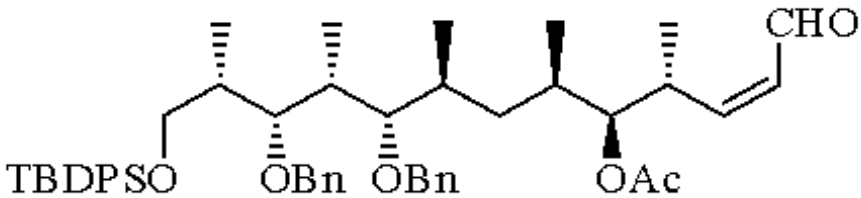

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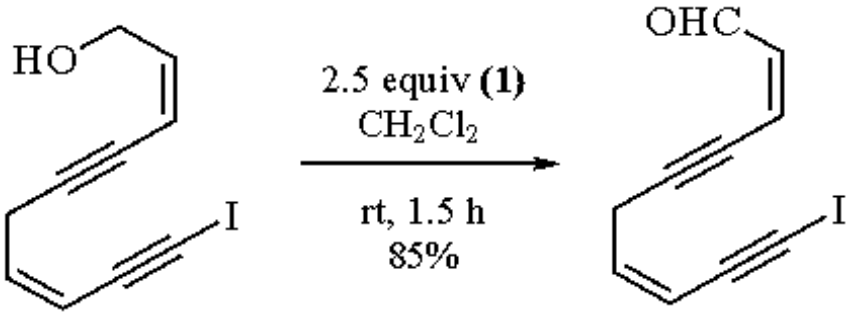

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Allylic and propargylic alcohols possessing α´- or δ-stereogenic centers can be oxidized without compromising the integrity of the stereogenic centers, even in demanding situations such as the cases of the ketone (**25**) (eq 25) and the diynone (**26**) (eq 26).[70,71] Primary and secondary allenic alcohols also afford the corresponding carbonyl derivatives smoothly upon oxidation with (**1**).[72,73] Even allylic benzylic systems afford the corresponding aryl vinyl ketones largely or completely without oxygen transposition, even in the remarkably hindered ketone (**27**) (eq 27).[74,75] Note that the ketone (**27**) has an internal barrier to rotation about the aryl-carbonyl single bond of in excess of 20 kcal mol^{-1}.

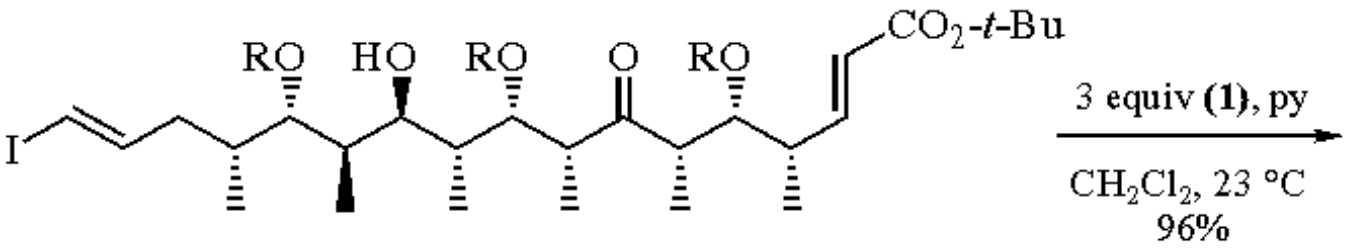

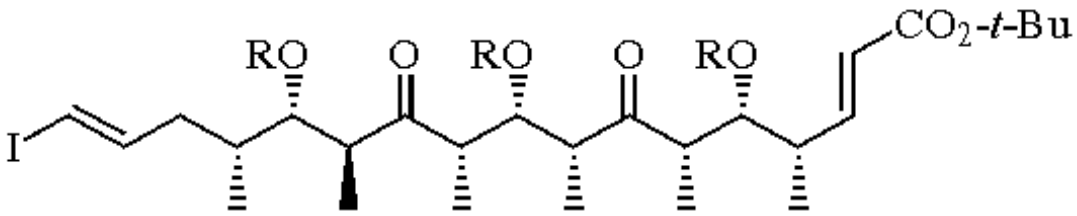

(25)

(25) R = TBDMS

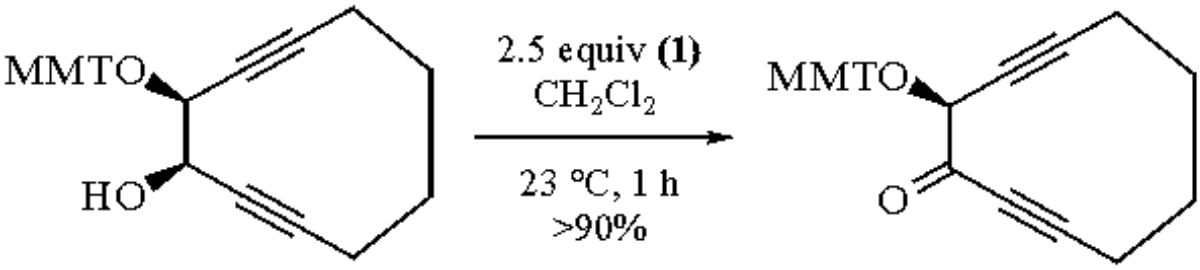

(26)

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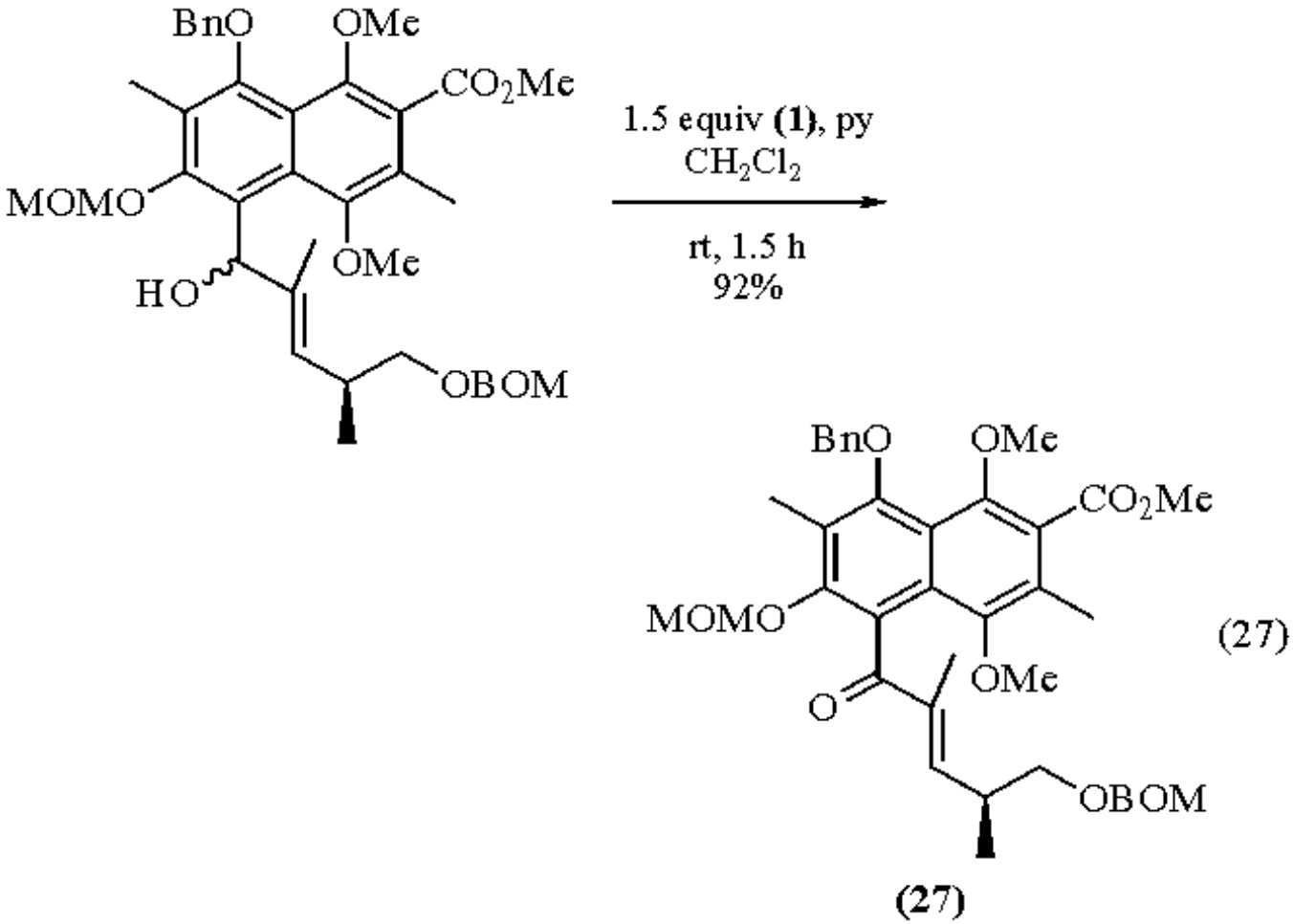

Examples have also been reported of oxidation of allylic or benzylic alcohols by (**1**) in the presence of divalent sulfur and basic nitrogen without concomitant oxidation at these heteroatoms.[76,77]

Oxidation at Methine and Methylene Groups.

Relatively recently, as a result of the interest in the synthesis of derivatives of the immunosuppressive agent FK-506, which possesses the relatively rare 2,3-dioxo amide unit, it has been recognized that the periodinane (**1**), when employed in excess, is capable of oxidizing α-thioaryl β-keto amides to the related 2,3-dioxo amides, accompanied by the derived enol(s) and the hydrate of the 2-oxo function. This oxidation, whose mechanism has not been established as yet, may proceed via the enol or via the corresponding sulfoxide by way of a Pummerer-type rearrangement.[78] Subsequently, the direct oxidation of β-keto esters and amides by the periodinane (**1**) to 2,3-dioxo esters and amides has been reported.[79]

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1,3,5-Triazine[1]

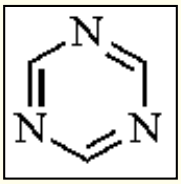

[290-87-9] · $C_3H_3N_3$ · 1,3,5-Triazine · (MW 81.09)

(C_1 electrophile; formylating agent;[2] methylenating and aminomethylenating agent;[3] in combination with cyclic amines, dehydro-Mannich bases[4,5] are formed)

Alternate Name: *s*-triazine.

Physical Data: mp 80-82 °C (very pure: 85-86 °C); bp 114 °C; *d* 1.38 g cm^{-3}.

Solubility: sol alcohol, ether, most organic solvents; 1 g dissolves freely in 10 mL methanol.

Form Supplied in: white solid; widely available.

Handling, Storage, and Precautions: very volatile; hygroscopic and very sensible to solvolysis in water, alcohols, and solvents with OH groups. Distillation over sodium for purification has to be done cautiously to avoid overheating at the end, otherwise triazine-sodium compounds are formed which can lead to explosive decomposition of triazine.[1]

Formylating Agent.

In Gattermann's aldehyde synthesis, ***Hydrogen Cyanide*** can be replaced by 1,3,5-triazine. Under the action of ***Hydrogen Chloride***, the triazine undergoes an electrophilic attack on aromatic compounds. The intermediate aldimine hydrochlorides are hydrolyzed to the aldehydes (eq 1).[2] Nucleophilic arenes such as furans, pyrroles and polyhydroxybenzenes need no catalyst,[2a,b] while phenols and alkylbenzenes require ***Aluminum Chloride***.[2b,c] Formylation of 2-hydroxydeoxybenzoins and cyclocondensation with ***Boron Trifluoride Etherate*** affords isoflavones.[6]

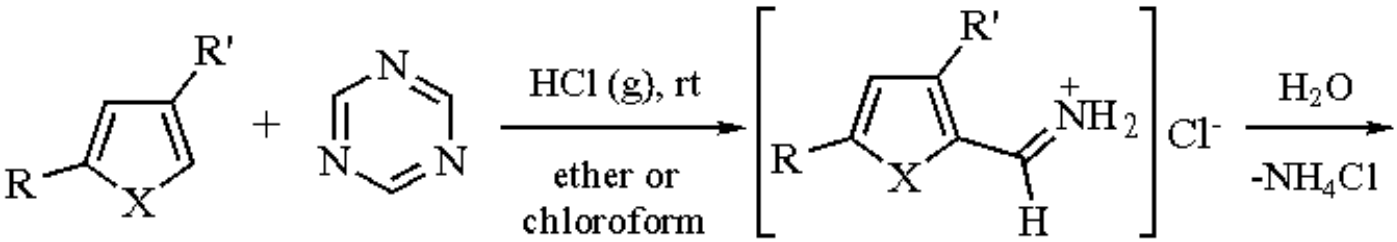

X = O, NH, NMe, NBu; R, R' = H, Me

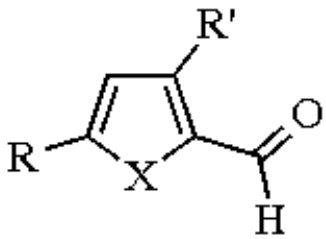

31-86% (1)

Methynylating Agent.

Although the triazine ring is aromatic, it is nonetheless very susceptible to nucleophilic attack. Two molecules of a primary amine H_2NR can add to each carbon atom, leading to ring cleavage, release of ammonia, and 3 equiv of a disubstituted formamidine, RHN-CH=NR. 1,3,5-Triazine is a synthetic equivalent for ***Formic Acid***, formamide, or trialkyl orthoformates. As the only byproduct is gaseous ammonia, contamination of the main product is avoided; yields are good and the products pure. The starting materials can also be mixed and melted for reaction. Reaction of aliphatic or aromatic diamines with triazine leads to heterocyclic compounds (eq 2); 2-aminophenols and thiophenols may also be used.[7]

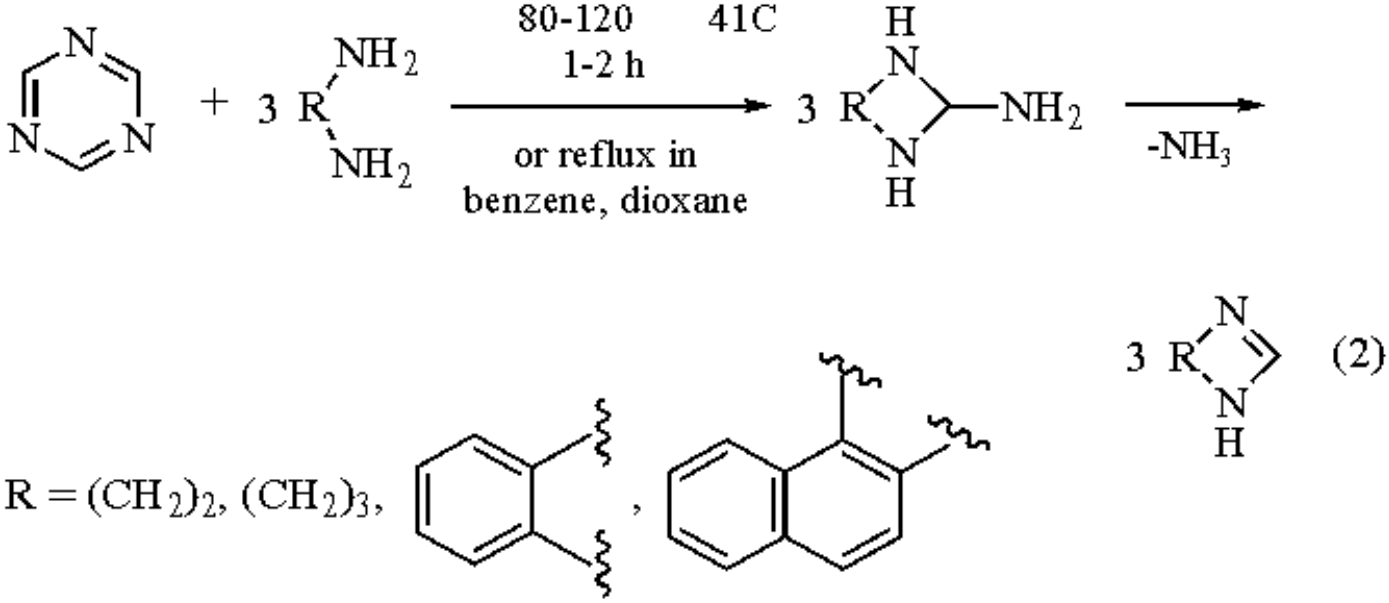

Acidic α-methylene compounds such as malonic acid derivatives can also be used. The electron-rich nitrogen atom of the triazine can abstract a proton and the resulting carbanion can add to the triazine carbon. The intermediate aminomethylene compound may recyclize to produce 4,5-disubstituted pyrimidines (eq 3).[8]

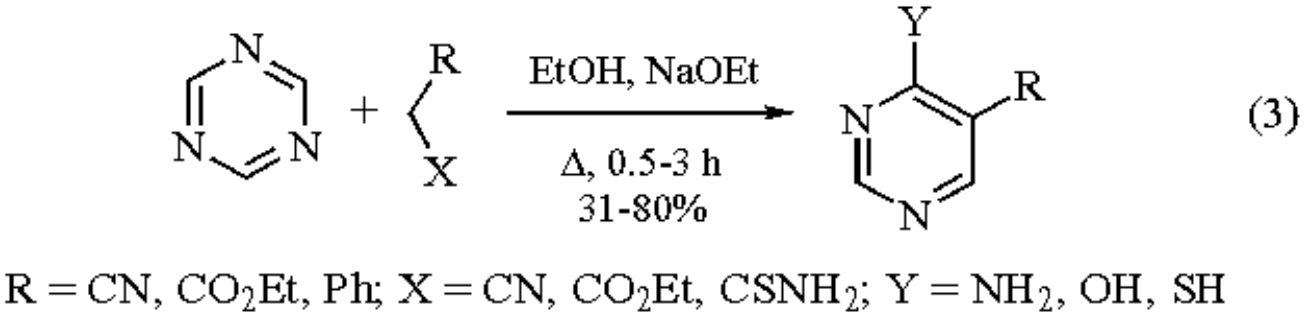

1,3,5-Triazine can aminomethylenate aromatic or heterocyclic amines, thus introducing a =CH-NH_2 group. The formamidine may react further (eq 4),[3] e.g. to 4-aminoquinazolines. Other compounds which have CH acidic protons that can be aminomethylenated include derivatives of malonic acid[9] or barbituric acid[10] and cyclopentadiene (gives pentafulvenes).[11] Pyrazolinones can also condense to the bispyrazolinones.[12]

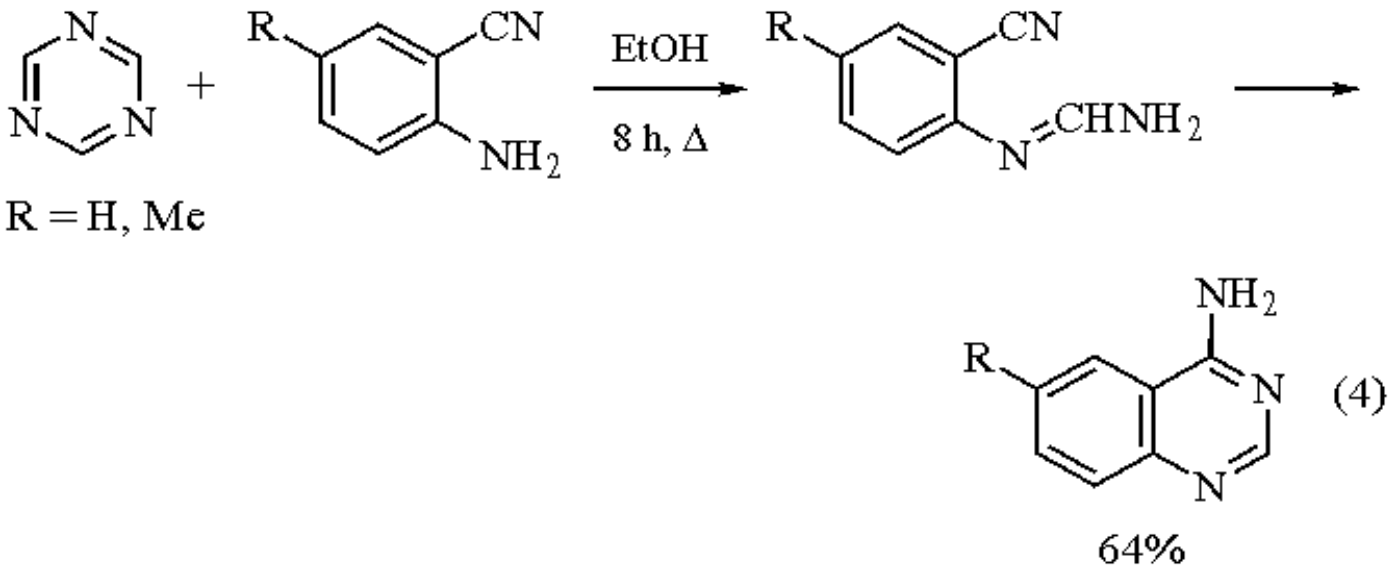

When the auxiliary base required for the aminomethylenation (a cyclic amine) is used as the solvent, a three-component reaction takes place, which can be considered as a Mannich-type condensation. Dehydro-*N*-Mannich bases are obtained from ***Cyanamide***[4a,b] or heterocyclic amines[4c,d] (eq 5). Carbon acidic components yield dehydro-*C*-Mannich bases.[5] 1,3,5-Triazines react regioselectively with dienophiles in cycloaddition reactions.[13a] Pyrimidine annulation occurs with pyrrolidine enamines in an inverse electron demand Diels-Alder reaction.[13b]

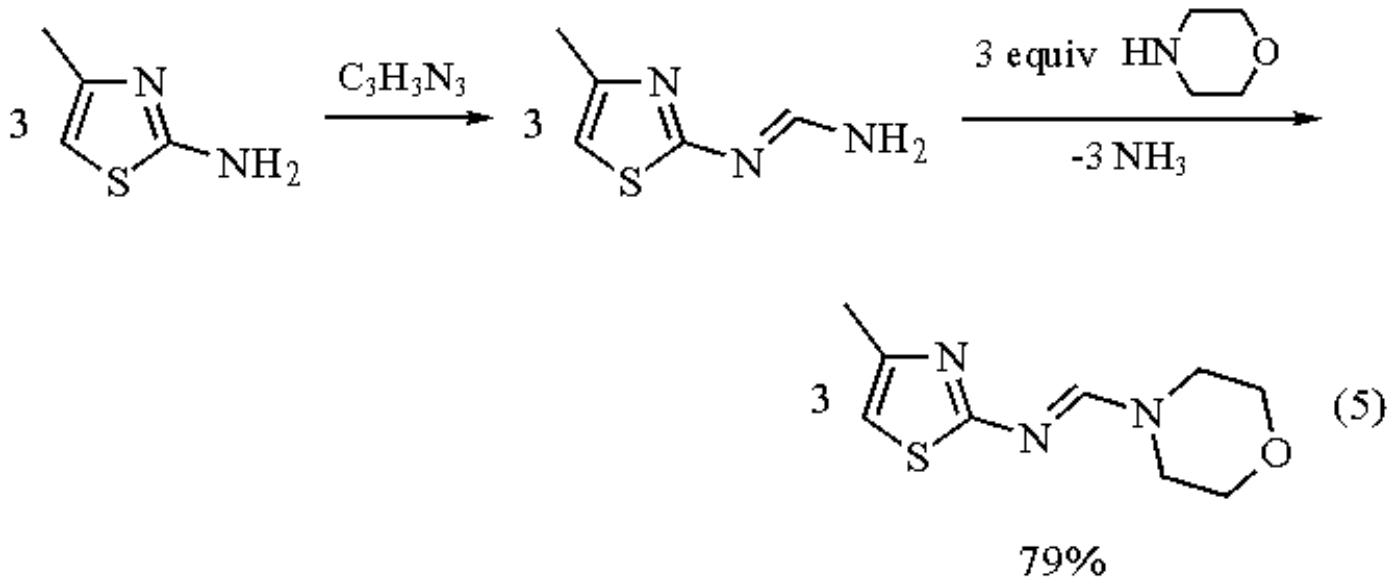

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1,2,4-Triazine[1]

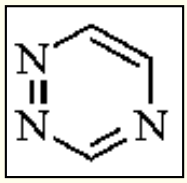

[290-38-0] · $C_3H_3N_3$ · 1,2,4-Triazine · (MW 81.09)

(electron-deficient heteroaromatic azadiene capable of participation in inverse electron demand Diels-Alder reactions with electron-rich dienophiles[1])

Alternate Names: as-triazine; α-triazine; isotriazine.

Physical Data: mp 16-17.5 °C; bp 158 °C; *n*25D 1.5150.

Solubility: sol $CHCl_3$, THF, dioxane, DMSO.

Form Supplied in: pale yellow oil.

Preparative Methods: [2] a cooled (-75 °C) solution of monomeric ***Glyoxal*** (90.0 mmol) in absolute MeOH (200 mL) is added to a solution of formamidrazone hydrochloride (40 mmol) in absolute MeOH (300 mL) at -50 °C. Et_3N (200 mmol) is added and the resulting reaction mixture is allowed to stand at 25 °C for 24 h. The MeOH is removed in vacuo at 20 °C and the residue extracted with Et_2O (peroxide free, 5×). Vacuum distillation of the residue after evaporation of the Et_2O affords 1,2,4-triazine (bp 25-28 °C/0.5 mmHg). Alternative preparations of 1,2,4-triazine have been detailed.[2]

Handling, Storage, and Precautions: best stored at 0 °C or below. It is stable to acid, less stable to base, and is hygroscopic; should be stored under anhydrous conditions since it reacts slowly with water and protic solvents.

Cycloaddition Reactions.

1,2,4-Triazine (**1**) is the parent agent representative of a class of synthetically accessible, substituted, electron-deficient 1,2,4-triazines capable of diene 4π participation in inverse electron demand Diels-Alder reactions with electron-rich dienophiles.[1] Cycloaddition reactions between 1,2,4-triazine and enamines have been shown to be general and regioselective, and occur with [4 + 2] addition exclusively across C-3/C-6 of the 1,2,4-triazine nucleus with the more nucleophilic carbon of the dienophile attaching to C-3. This cycloaddition reaction is followed by in situ retro-Diels-Alder reaction with loss of N_2 and in situ elimination of pyrrolidine to afford 3,4-disubstituted pyridines (eq 1).[3] A general pyridine annulation based on a catalytic Diels-Alder reaction has been developed (eq 2),[4] and its application in the synthesis of rigid norbornylogous spacers for long-range electron transfer studies has been described (eq 3).[5]
[4 + 2] Cycloaddition reactions of 1,2,4-triazine with *N*,*O*-ketene acetals (eq 4)[6] and ynamines (eq 5)[7] have also been detailed. However, the cycloaddition reaction of (**1**) with ynamines generally proceeds through a C-5/N-2 cycloaddition process with subsequent loss of a nitrile to afford substituted pyrimidines (eq 5).[1,7]

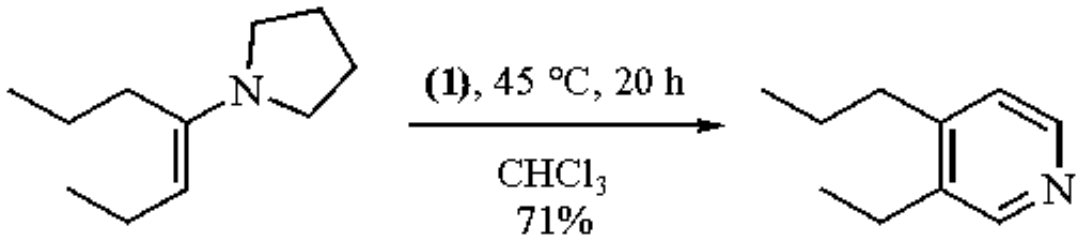

(1)

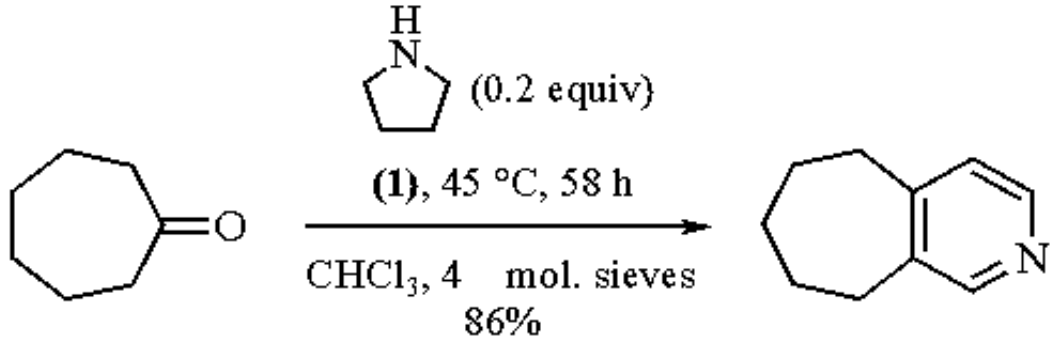

(2)

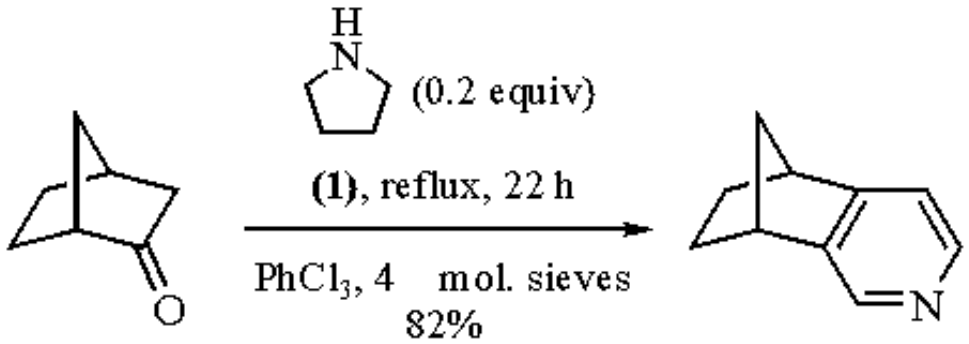

(3)

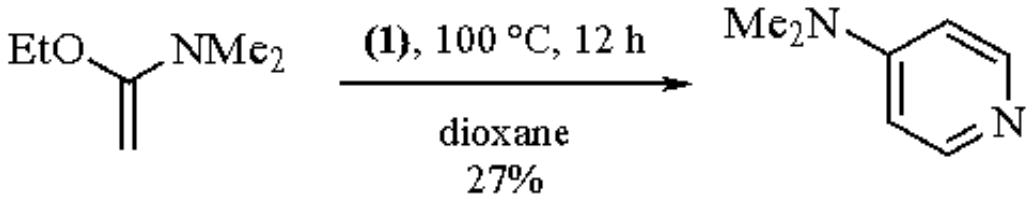

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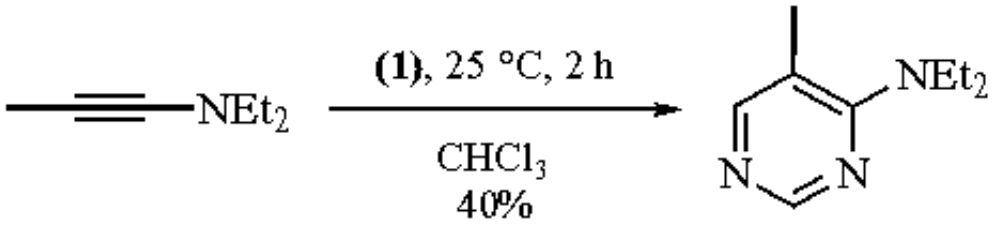

(5)

Less nucleophilic alkenes, including β-enamino ketones, β-alkoxy enones, trimethylsilyl enol ethers, and tri-*n*-butylstannyl enol ethers, are not sufficiently reactive to participate in a Diels-Alder reaction with the parent 1,2,4-triazine.[3] Complementary addition of electron-withdrawing substituents to the 1,2,4-triazine nucleus increases its rate of participation in inverse electron demand Diels-Alder reactions (eqs 6-9),[8,9] influences the mode of [4 + 2] cycloaddition,[1] and controls the observed regioselectivity (eqs 6, 8, and 9)[8] (see also ***Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate***).

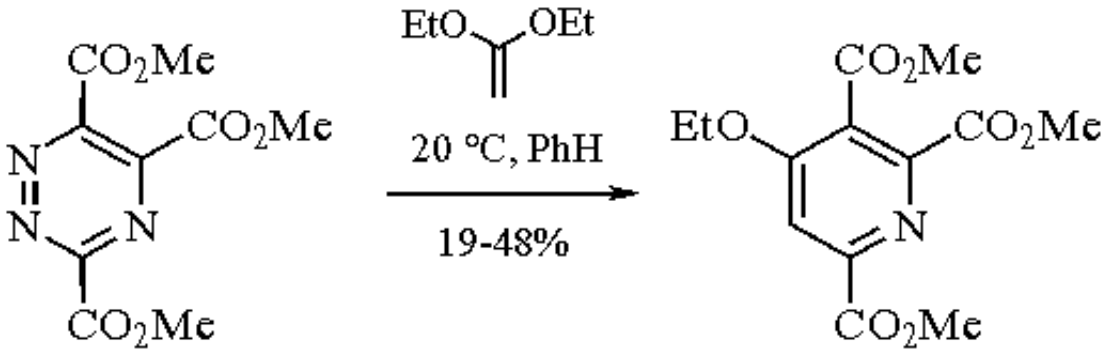

(6)

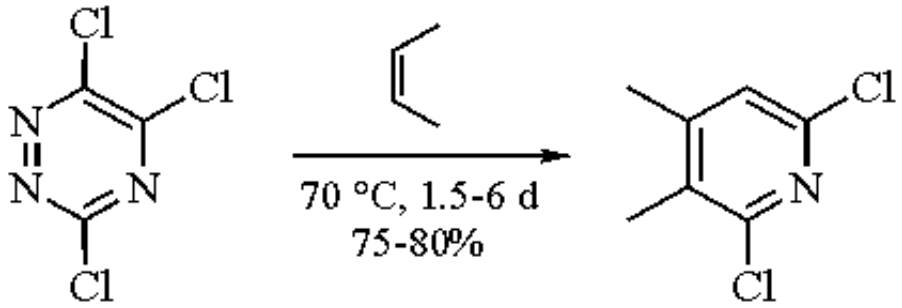

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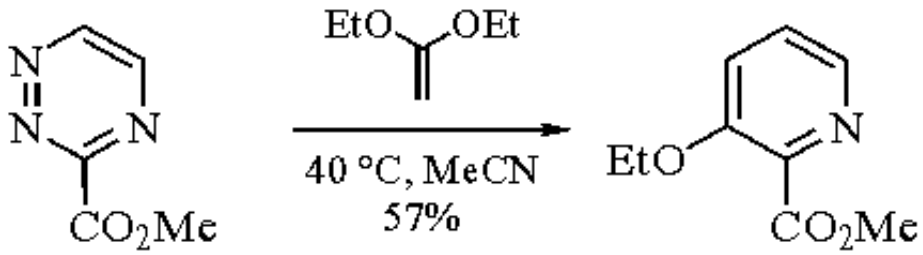

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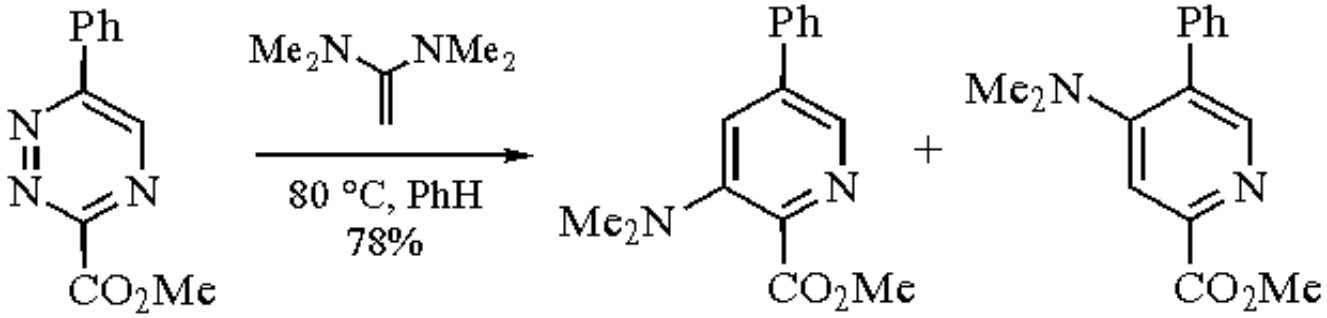

(9)

55:45

Related Reagents.

3,6-Diphenyl-1,2,4,5-tetrazine; ***1,3,5-Triazine***; ***Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate***.

---

1. (a) Boger, D. L. *T* **1983**, *39*, 2869. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 385-456. (c) Boger, D. L. *CRV* **1986**, *86*, 781. (d) Boger, D. L. *BSB* **1990**, *99*, 599. (e) Boger, D. L., Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987.
2. (a) Neunhoeffer, H.; Hennig, H. *CB* **1968**, *101*, 3592. For an alternative, though indirect preparation, see: (b) Krass, D.; Paudler, W. W. *S* **1974**, 351. (c) Paudler, W. W.; Chen, T.-K. *JHC* **1970**, *7*, 767. (d) Paudler, W. W.; Barton, J. M. *JOC* **1966**, *31*, 1720.
3. Boger, D. L.; Panek, J. S. *JOC* **1981**, *46*, 2179.
4. Boger, D. L.; Panek, J. S.; Meier, M. M. *JOC* **1982**, *47*, 895.
5. Golka, A.; Keyte, P. J.; Paddon-Row, M. N. *T* **1992**, *48*, 7663.
6. Neunhoeffer, H.; Frühauf, H.-W. *LA* **1972**, *758*, 120.
7. Neunhoeffer, H.; Frühauf, H.-W. *LA* **1972**, *758*, 125.
8. Burg, B.; Dittmar, W.; Reim, H.; Steigel, A.; Sauer, J. *TL* **1975**, 2897.
9. Barlow, M. G.; Haszeldine, R. N.; Simpkin, D. J. *CC* **1979**, 658.

Dale L. Boger & Minsheng Zhang

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1,2,4-Triazole

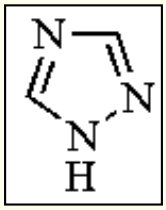

[288-88-0] · $C_2H_3N_3$ · 1,2,4-Triazole · (MW 69.08)

(transacylating agent used for ester and amide synthesis, especially in peptide synthesis; cyclization reactions; oligonucleotide synthesis)

Physical Data: mp 120-121 °C; bp 260 °C (dec above 187 °C); fp 140 °C.

Solubility: sol water, alcohol.

Form Supplied in: white powder.

Acylating Reagent.

The great ability of triazole to accept and transfer acyl groups has made it a catalyst for the synthesis of esters and amides. In particular, triazole has been used in peptide synthesis, for the formation of peptide links as well as for the introduction of amino-protecting groups. It acts as a bifunctional catalyst, accelerating the aminolysis of *p*-nitrophenyl esters[1] and *p*-thiocresyl esters.[2] The catalytic effect is both by a general base mechanism (eq 1) and a specific mechanism (eq 2).

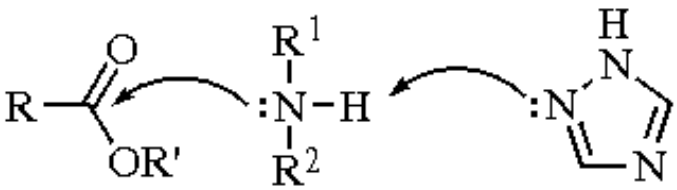

(1)

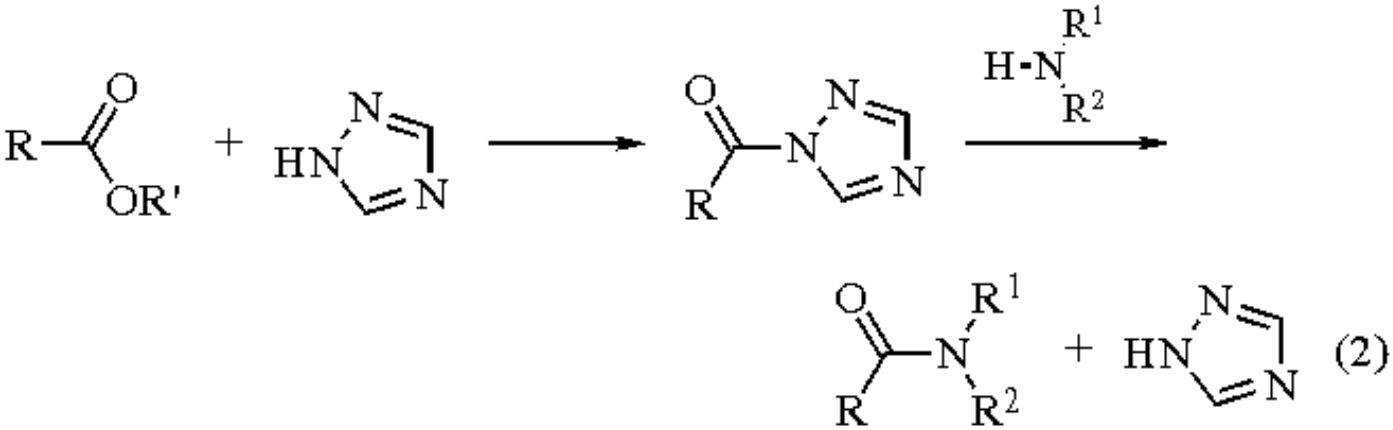

(2)

It has been used to introduce the Boc group onto an amino acid from *t*-butyl carbonates (eq 3), and it allows the coupling of an *N*-protected amino acid with a fully unprotected amino acid (eq 4). Interestingly, racemization is not observed during coupling of amino acids in the presence of 1,2,4-triazole.[1] Nevertheless, its coupling efficiency depends on the reaction medium and in solvents like DMF, which increase the rate of aminolysis, its usefulness is limited. 1,2,4-Triazole is now seldom used in peptide synthesis, whereas other catalytic additives like ***1-Hydroxybenzotriazole*** are widely used as activated esters as well as in conjunction with coupling reagents like ***1,3-Dicyclohexylcarbodiimide***.

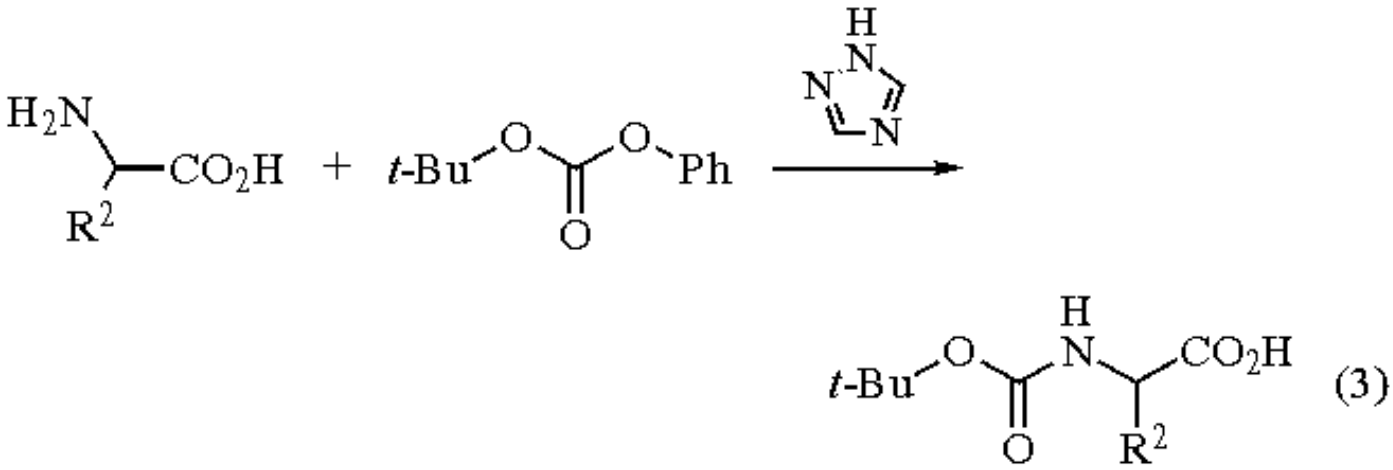

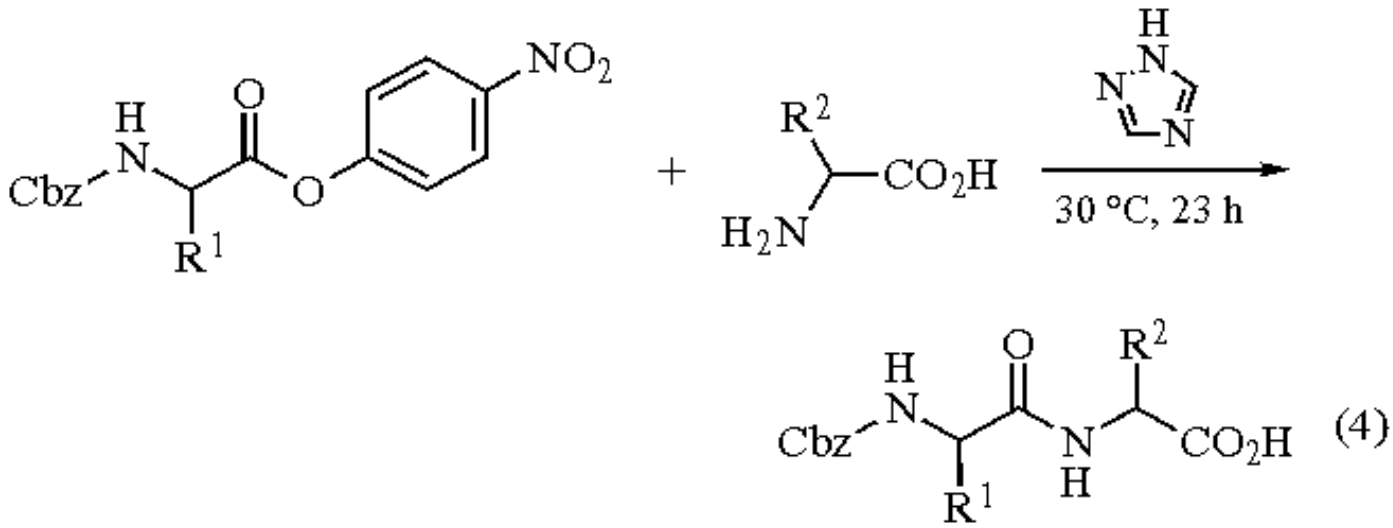

Catalysis of Ring Formation.

1,2,4-Triazole can induce the formation of isoxazole rings from conjugated ketones and hydroxylamine (eq 5).[3]

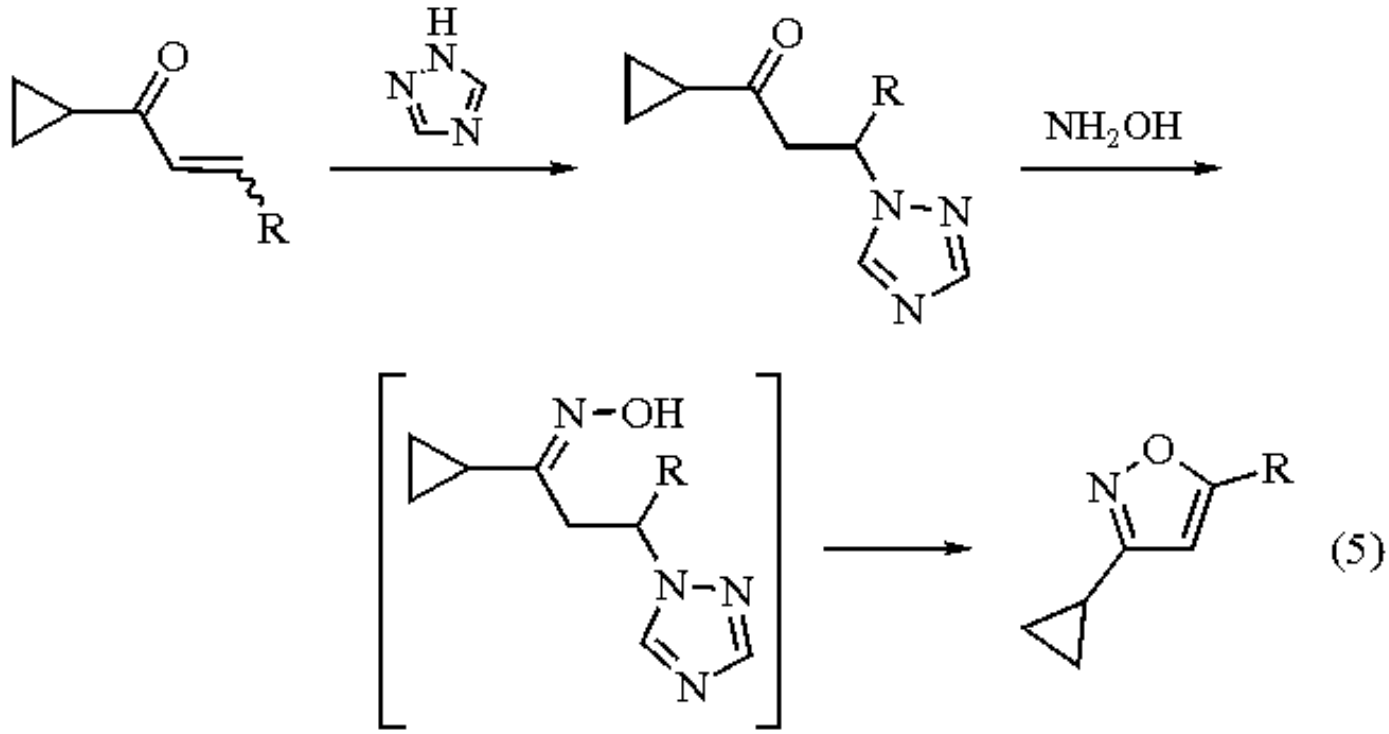

Oligonucleotide Synthesis.

Sulfonyl derivatives of 1,2,4-triazole, e.g. (**1**), are used as efficient coupling reagents in oligonucleotide synthesis by the phosphotriester method.[4] A nitro derivative (**2**) allows esterification of amino acids onto hydroxymethyl polymers.[5]

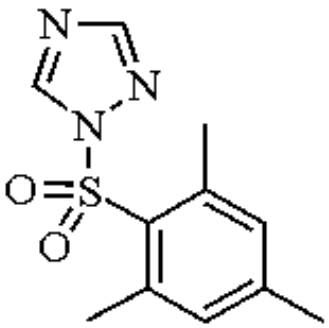

(1)

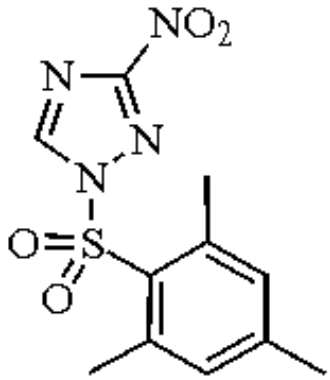

(2)

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1. Beyerman, H. C.; Massen van den Brink, W.; Weygand, F.; Prox, A.; König, W.; Scmidhammer, L.; Nintz, E. *RTC* **1965**, *84*, 213.
2. Wieland, T.; Kahle, W. *LA* **1966**, *691*, 212.
3. Rentzea, C. N. *AG(E)* **1981**, *20*, 885.
4. Reese, C. B.; Titmas, R. C.; Yau, L. *TL* **1978**, 2727.
5. Blankemeyer-Menge, B.; Nintz, M.; Frank, R. *TL* **1990**, *31*, 1701.

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Tribenzylchlorosilane

$(PhCH_2)_3SiCl$

[18740-59-5] · $C_{21}H_{21}ClSi$ · Tribenzylchlorosilane · (MW 336.96)

(reagent for alcohol protection[5])

Physical Data: mp 141-142 °C;[1,2] a somewhat higher value (143-145 °C) is cited in the Aldrich catalog.

Solubility: sparingly sol cold petroleum ether; moderately sol hot petroleum ether; sol ether.

Form Supplied in: white crystalline solid; commercially available.

Preparative Methods: prepared by reaction of benzylmagnesium chloride with $SiCl_4$ in ether;[3] separation from mono- and dibenzylated chlorosilane byproducts is then accomplished by fractional distillation (boiling range 300-360 °C/100 mmHg). Other preparations involve the chlorination of tribenzylsilane using Cl_2[1] or an acyl chloride.[1,3] No yields are reported for any of the above preparative procedures.

Purification: can be recrystallized from petroleum ether.[2]

Handling, Storage, and Precautions: corrosive; should be handled with caution. It does not fume perceptibly in air,[2] but it is moisture sensitive and is slowly decomposed by water over several hours to give the corresponding silanol.[3]

Protection of Alcohols.

Tribenzylchlorosilane is highly reactive towards nucleophilic displacement of chloride ion,[4] but it has found only limited application as a bulky silyl protecting group for alcohols. The protection of the allylic alcohol (**1**) as the tribenzylsilyl ether (**2**) (eq 1) allowed for high π-facial selectivity in a subsequent epoxidation reaction at the 10,11-double bond.[5] The tribenzylsilyl ether group can be efficiently deprotected to the free alcohol using AcOH/THF/H_2O (3:1:1) at room temperature.[5]

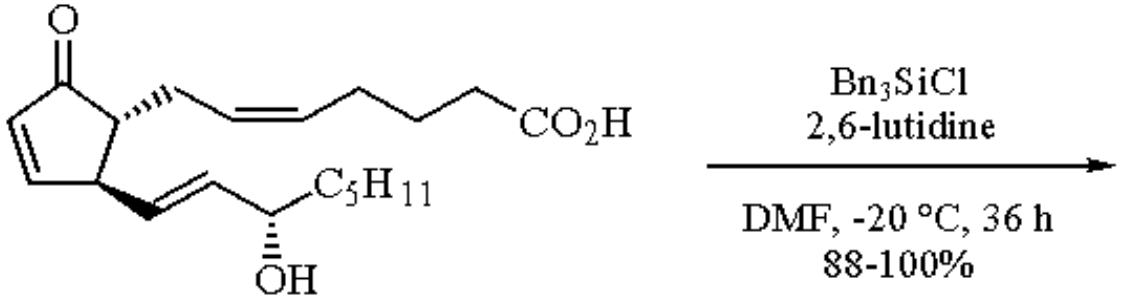

(1)

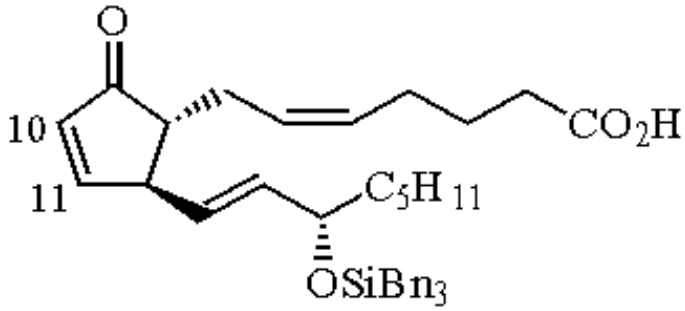

(2) (1)

Silylation of Azomethine Anions.

The only other synthetically useful reaction reported for tribenzylchlorosilane involves the *C*-silylation of azomethine anions. Deprotonation of the parent imine (***n-Butyllithium***) followed by *C*-trapping of the resulting azomethine anion affords the α´-silylimine in moderate yield (eq 2).[6]

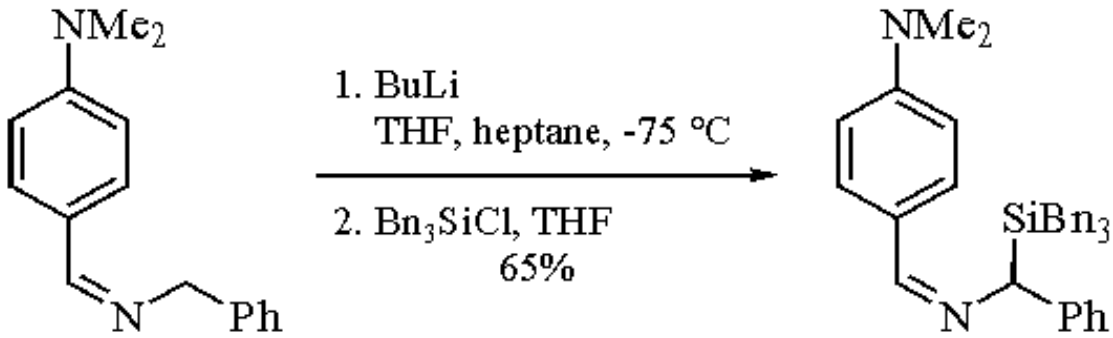

(2)

Related Reagents.

t-Butyldimethylchlorosilane; ***t-Butyldimethylsilyl Trifluoromethanesulfonate***; ***Chlorotriethylsilane***.

---

1. Jenkins, J. W.; Post, H. W. *JOC* **1950**, *15*, 556.
2. Robison, R.; Kipping, F. S. *JCS* **1908**, 439.
3. Martin, G.; Kipping, S. F. *JCS* **1909**, 302.
4. Grant, M. W.; Prince, R. H. *JCS(C)* **1969**, 1138.
5. Corey, E. J.; Ensley, H. E. *JOC* **1973**, *38*, 3187.
6. Popowski, E.; Konzempel, K.; Schott, G. *ZC* **1974**, *14*, 289.

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Tribromoacetyl Bromide

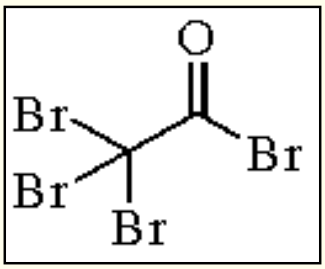

[10588-31-5] · C_2Br_4O · Tribromoacetyl Bromide · (MW 359.64)

(tribromoacetylating agent for amines and alcohols;[1] precursor for the synthesis of dibromoketene[2])

Physical Data: bp 86 °C/11 mmHg; *d* 2.810 g cm^{-3}.

Solubility: sol ether, benzene, toluene.

Form Supplied in: not commercially available.

Preparative Method: prepared by the action of ***Phosphorus(III) Bromide*** on tribromoacetic acid.[1,2]

Purification: can be purified by vacuum distillation.

Handling, Storage, and Precautions: moderately stable at room temperature; should be freshly distilled prior to use. Light-sensitive; should be used and stored with the rigorous exclusion of light.

Tribromoacetylation of Amines and Alcohols.

Tribromoacetamides have been prepared by the reaction of tribromoacetyl bromide with the requisite amine (eq 1).[1] The tribromoacetamides so produced are light sensitive and must be used immediately. Photoirradiation of these amides promotes homolytic cleavage and can generate the corresponding dibromo primary radical.[3] Alcohols can also be acylated with tribromoacetyl bromide (eq 2).[1] However, unless use of the tribromide is absolutely necessary, commercially available ***Trichloroacetyl Chloride*** is superior and the corresponding trichloroacetylated products can usually be used in subsequent reactions in the same manner as the tribromoacetylated materials.

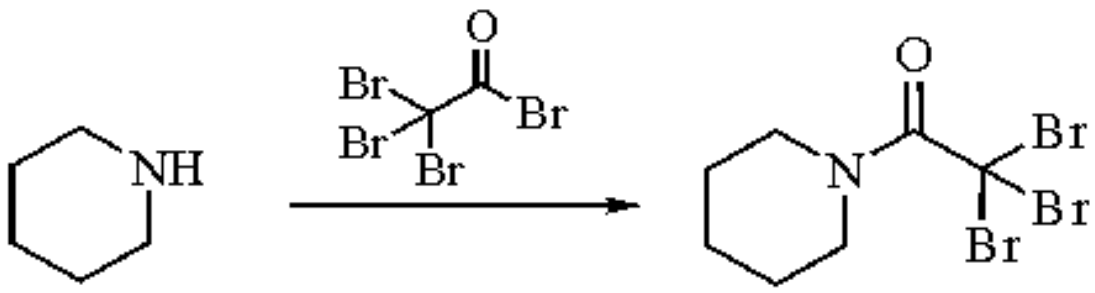

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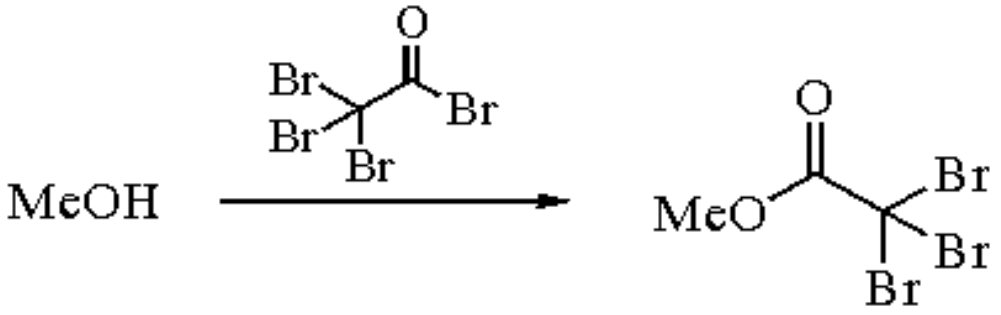

(2)

Generation of Dibromoketene.

Tribromoacetyl bromide can be debrominated with ***Zinc*** that has been activated with copper to afford a solution of dibromoketene in ether (eq 3).[2] The dibromoketene generated in this manner readily undergoes [2 + 2] cyclization with ***Cyclopentadiene*** to give the corresponding cyclobutanone (eq 4).[2] Dibromoketene has been used effectively in the synthesis of prostaglandins and other natural products.[4,5] Dibromoketene has also been prepared by the elimination of HCl from dibromoacetyl chloride and by reaction of trimethylsilyl tribromoacetate with ***Triphenylphosphine***.[6,7] In fact, this latter method is superior for the preparation of dibromoketene as a synthetic precursor, as the subsequent cyclization can be performed in a single reaction vessel (eq 5).[7] High yields of the cyclized material are obtained in this manner.

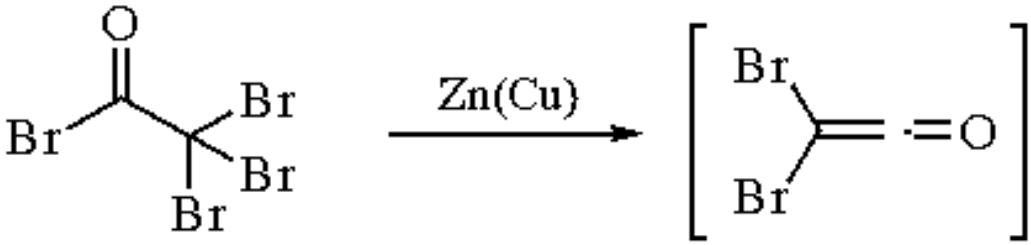

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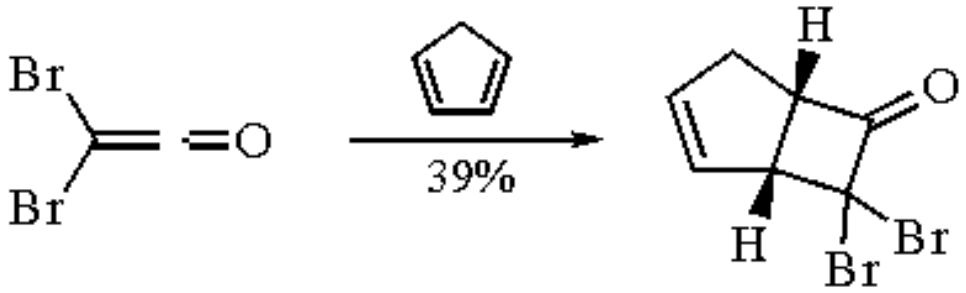

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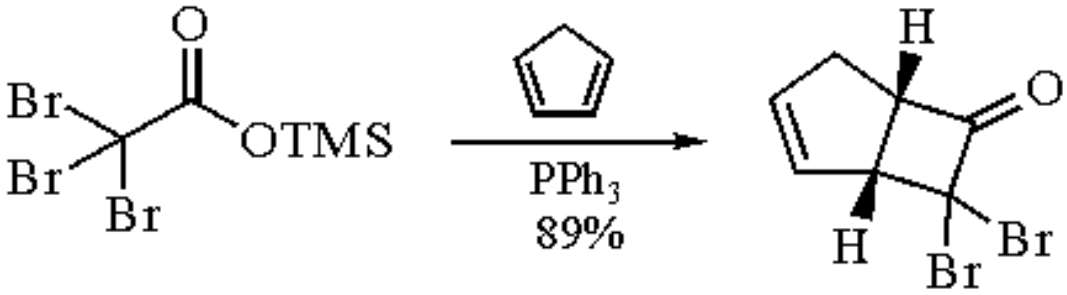

(5)

Related Reagents.

Dichloroketene; ***Trichloroacetyl Chloride***.

1. Parrot, J.; Hervieu, J.; Ursy, Y.; Paty, M. *BSF* **1964**, 1063.
2. Brady, W. T. *JOC* **1966**, *31*, 2676.
3. Imanishi, Y.; Tanaka, M.; Bamford, C. H. *Int. J. Biol. Macromol.* **1985**, *7*, 89.
4. Nakamura, N.; Sakai, K. *TL* **1978**, 1549.
5. Boland, W.; Jaenicke, L. *CB* **1978**, *111*, 3262.
6. Brady, W. T.; Vaughn, W. L.; Hoff, E. F. *JOC* **1969**, *34*, 843.
7. Okada, T.; Okawara, R. *TL* **1971**, *30*, 2801.

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2,2,2-Tribromoethyl Chloroformate

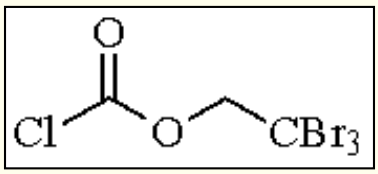

[17182-43-3] · $C_3H_2Br_3ClO_2$ · 2,2,2-Tribromoethyl Chloroformate · (MW 345.20)

(protecting agent for alcohols[1,2] and carboxylic acids[3])

Physical Data: bp 47-50 °C/0.05 mmHg, 103 °C/10 mmHg.

Form Supplied in: no longer commercially available.

Preparative Method: prepared[1] by the reaction of 2,2,2-tribromoethanol with ***Phosgene*** in benzene under pyridine catalysis.

Handling, Storage, and Precautions: although no details are available, the high toxicity and the lachrymatory and corrosive nature of the closely related ***2,2,2-Trichloroethyl Chloroformate*** suggest that 2,2,2-tribromoethyl chloroformate should be handled with caution.

Protection of Alcohols.

2,2,2-Tribromoethyl chloroformate has found application in the protection of primary and secondary alcohols. The attraction of the resulting tribromoethoxycarbonyl protecting group includes its stability to the acidic conditions (e.g. 80% acetic acid at 100 °C for 35 min, or at rt for 6 h) used for the removal of many other *O*-protecting groups (e.g. the trityl group).[1] In addition, it is readily removed via β-elimination using a ***Zinc/Copper Couple***, preferably in acetic acid but also (albeit more slowly) in ethanol or DMF, under conditions where many common protecting groups (e.g. *O*-acetyl, *N*-benzoyl, and *O*-trityl)[1] survive. Deprotection of tribromoethyl carbonates using a Zn/Cu couple in acetic acid (complete in 20 min at rt) proceeds an order of magnitude faster than cleavage of the more widely used trichloroethyl (troc) carbonates (see ***2,2,2-Trichloroethyl Chloroformate***) suggesting that it has potential (as yet untapped) as a complementary protecting group to the troc group. Selective protection of primary over secondary alcohols can be accomplished, albeit in only modest yield, using tribromoethyl chloroformate in the presence of either *N*,*N*-diethylaniline or 2,6-lutidine as base (eq 1).[2]

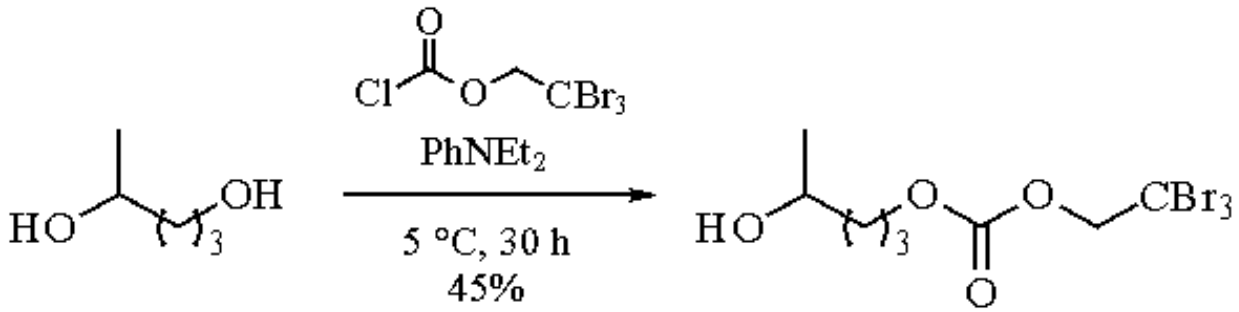

(1)

Tribromoethyl chloroformate is useful for the protection of primary and secondary hydroxyl groups in nucleosides and their derivatives;[1] reactions are generally complete in 0.5-2.0 h at 0 °C in anhydrous pyridine/DMF and typically proceed in good to excellent yield. Since tribromoethyl chloroformate reacts vigorously with DMF at rt and reacts slowly even at 0 °C, DMF solutions must be prepared at 0 °C and then immediately be added to the nucleoside in pyridine in order to avoid significant chloroformate decomposition. Selective 5´-protection of 2´-deoxynucleosides is possible (eq 2). Attempts to protect 2´,3´-dihydroxynucleosides lead to the formation of a 2´,3´-cyclic carbonate in addition to the desired 2´,3´-bis(tribromoethyl) carbonate (eq 3). Prior *N*-protection of nucleosides containing amino-substituted bases is necessary; nucleosides containing free amino groups give complex mixtures of products.

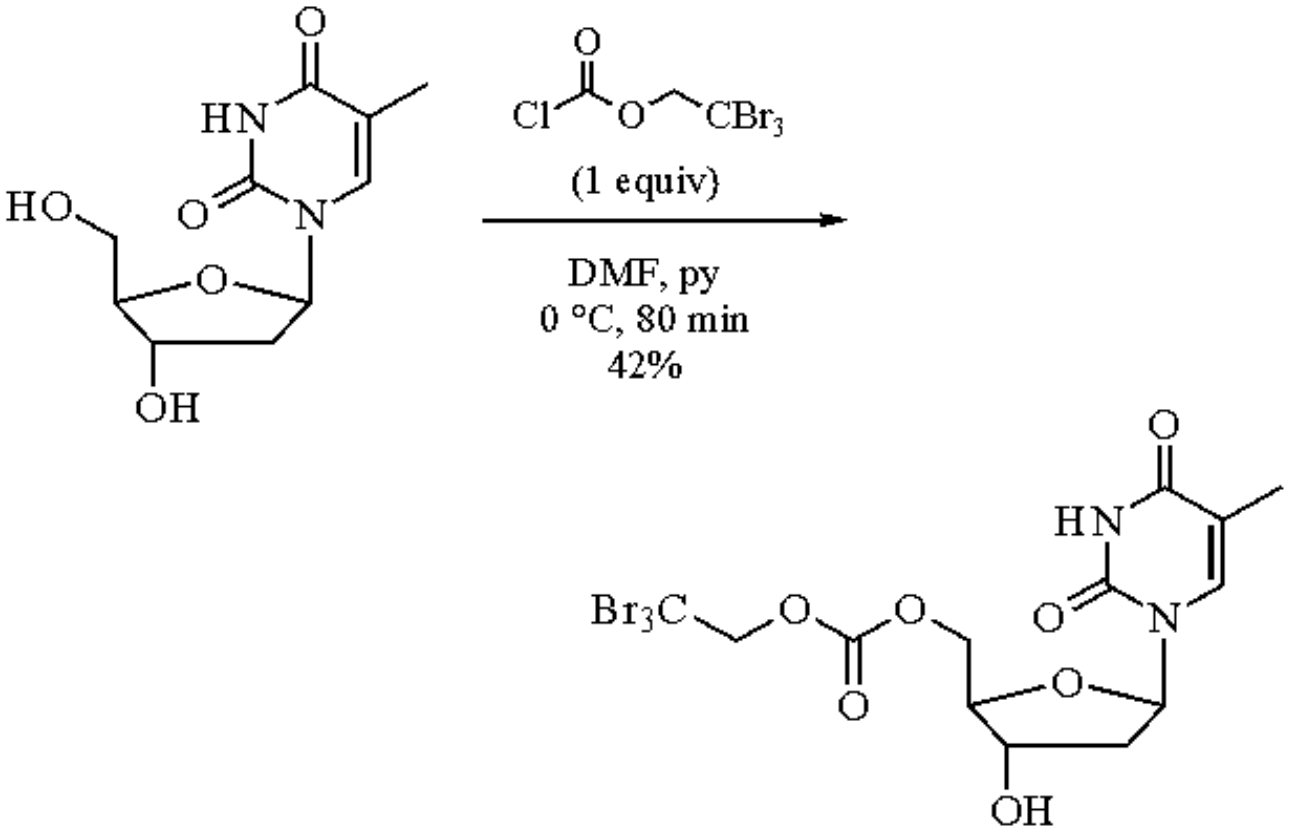

(2)

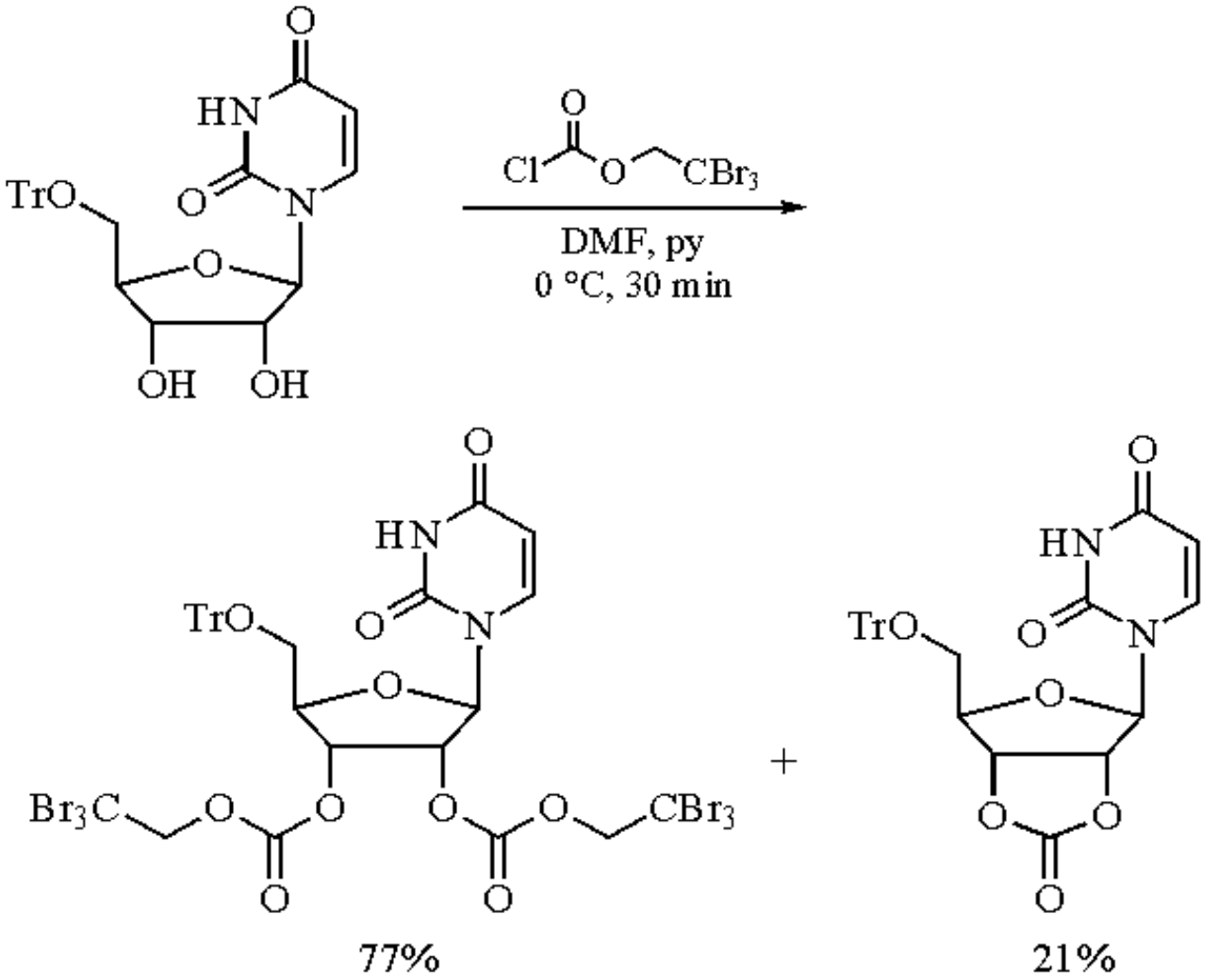

(3)

Protection of Carboxylic Acids.

Tribromoethyl chloroformate has been used for the protection of benzoic acid as its tribromoethyl ester.[3] An attractive feature of the

tribromoethyl ester protecting group is its facile cleavage by electrolytic reduction (-0.70 V, 85% yield). In contrast, cleavage of the related trichloroethyl ester requires much higher voltages (-1.65 V) and often results in the formation of small amounts of dichloroethyl ester byproduct (see ***2,2,2-Trichloroethyl Chloroformate***).[3]

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Tribromomethyllithium

$LiCBr_3$

[16644-71-6] · CBr_3Li · Tribromomethyllithium · (MW 258.65)

(nucleophilic tribromomethylation[1])

Physical Data: low temperature ^{13}C and ^{6}Li NMR data are available,[2] as are matrix IR data.[3]

Preparative Methods: solutions of the title compound can be obtained by treatment of ***Carbon Tetrabromide*** with ***n-Butyllithium*** or ***Phenyllithium*** in THF/ether/hexane (4:4:1) at -110 °C for ca. 1 hour,[4] by deprotonation of ***Bromoform*** with ***Dichloromethyllithium*** in THF at -100 °C,[5] and by deprotonation of $CHBr_3$ with lithium dimethylamide in THF/HMPA at -105 °C.[6]

Handling, Storage, and Precautions: there is considerable decomposition of the reagent at -100 °C over several hours,[4] increasing in rate with increasing temperature. Comparison of ether and THF as solvents for reagents of this type suggests that the latter both accelerates the formation of α-halo organolithiums at low temperature and increases their thermal stability.[7]

General Considerations.

Alkyllithiums bearing halogens on the α-carbon are frequently referred to as carbenoids reflecting a major mode of reactivity. Good general reviews of such species are available.[1] At very low temperatures, however, this reagent reacts like a typical alkyllithium. It should be noted that $LiCBr_3$ has been studied much less than the analogous ***Trichloromethyllithium***, perhaps due to the greater thermal stability of the latter. However, the reagents are not analogous in all of their reactions.

Nucleophilic Tribromomethylation/Carbonyl Homologation.

The reagent can be used in the displacement of iodides and bromides to produce terminal tribromoalkanes (**1**) (eq 1).[8] Such compounds serve as intermediates in a homologation process.[9] The tribromoalkane can be metalated to (**2**) and added to an aldehyde to provide an intermediate lithioalkoxide (eq 2). This can be treated with *n*-BuLi to provide the dilithium reagent (**3**), which undergoes Fritsch-Buttenberg-Wiechell rearrangement to either (**4**) or (**5**) depending on the identity of R´. Quenching of the mixture gives rise to (**6**) and/or (**7**) in 50-100% yield. The aldehyde is usually formed as a minor product when benzaldehydes or alkenals are used as substrates. Cyclic ketones undergo ring expansion in the same process as shown in eq 3.

$$R{-}X + LiCBr_3 \xrightarrow[\text{-110 °C}]{\text{THF, HMPA}} \underset{\textbf{(1)}}{R{-}CBr_3} \qquad (1)$$

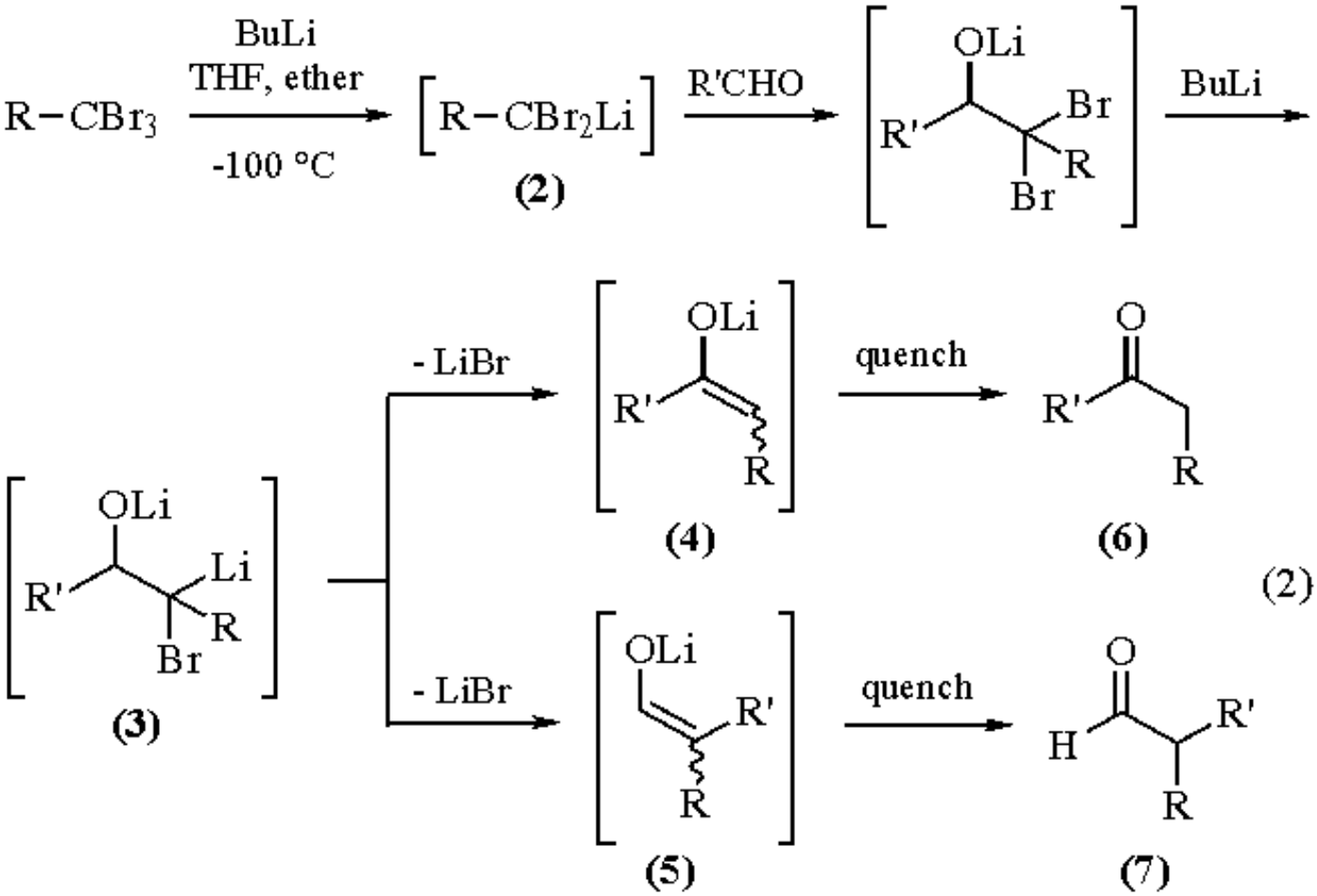

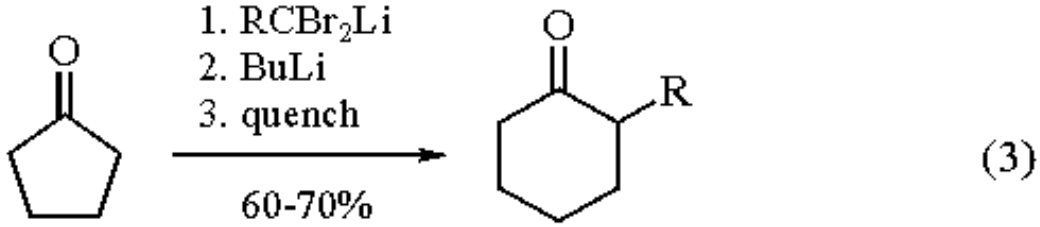

The adducts of $LiCBr_3$ with cyclohexanone and other ketones have been prepared by Yamamoto in a general synthesis of polyhalomethylcarbinols.[10] Addition of ***Lithium Dicyclohexylamide*** to a solution of cyclohexanone and $CHBr_3$ in THF results in deprotonation of the $CHBr_3$ and carbonyl addition giving the adduct (eq 4).

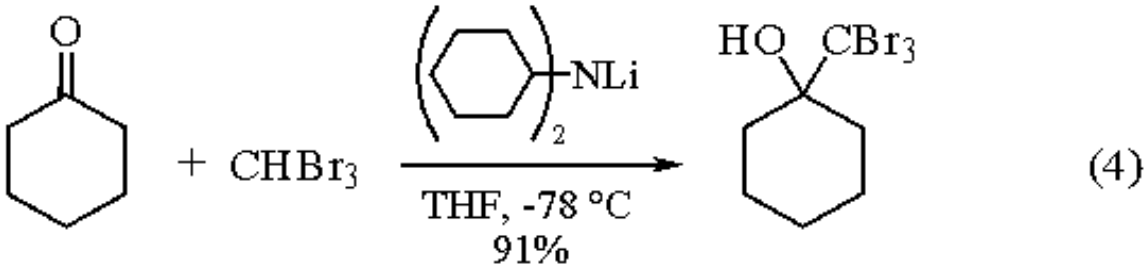

Dibromomethylenation.

The reagent can also be used to convert aldehydes to 1,1-dibromoalkenes.[11] Addition of $LiCBr_3$ to aldehydes and *O*-alkylation with ***Iodomethane***, ***Chlorotrimethylsilane***, or ***Acetyl Chloride*** gives the alkoxy (or acyloxy) tribromoalkane (**8**) (eq 5). Treatment of (**8**) with slightly more than 1 equiv of *n*-BuLi in THF/ether at -60 °C results in formation of the dibromoalkene (**10**) by loss of ROLi from the presumed intermediate (**9**). Yields are moderate.

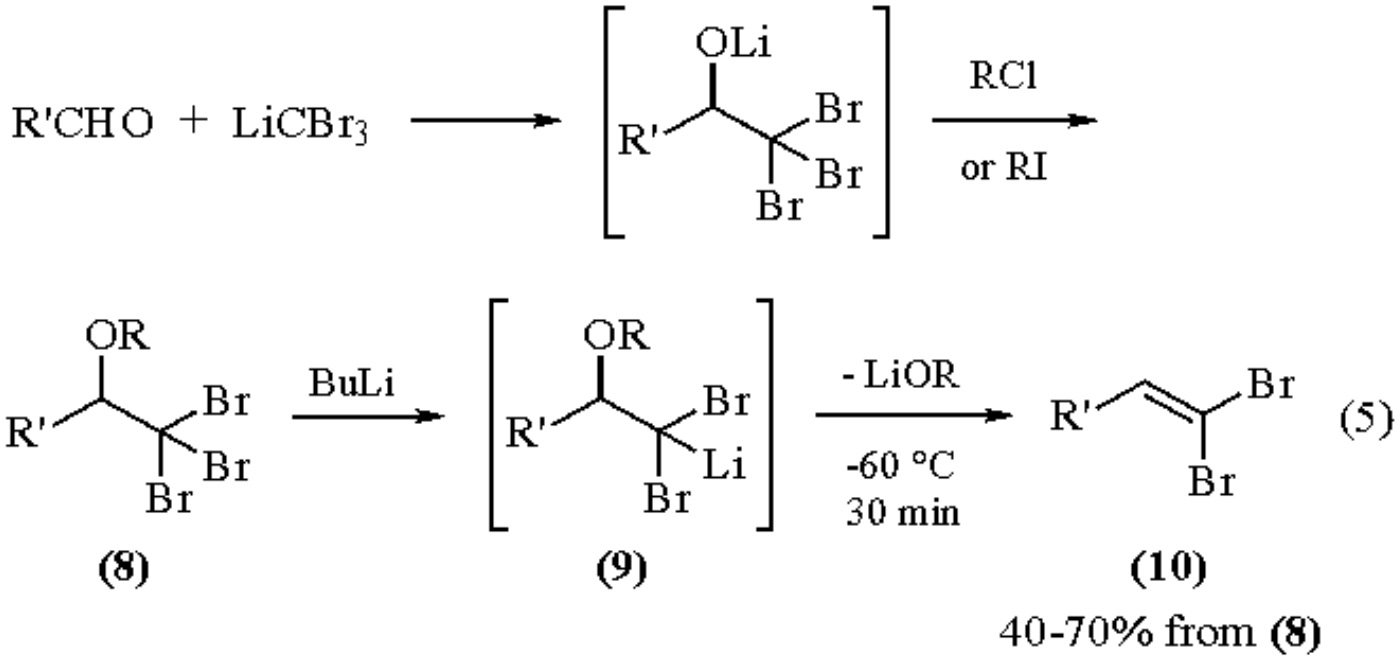

Cyclopropanation/C-H Insertion.

Cory has developed a clever in situ procedure for the construction of bridged ring systems incorporating a cyclopropane.[12] Treatment of CBr_4 with ***Methyllithium*** at -75 °C followed by an alkene results in the formation of a dibromocyclopropane via decomposition of $LiCBr_3$ to dibromocarbene. Treatment with a second equivalent of MeLi transmetalates a halogen and promotes carbene formation via α-elimination of LiBr. The carbene can insert into a proximate C-H bond, resulting in a large increase in molecular complexity in a single operation. Thus (**11**) is converted to (**12**) and (**13**) in good yield (eq 6), while the more complex (**14**) is converted to (**15**) in 26% yield (eq 7).

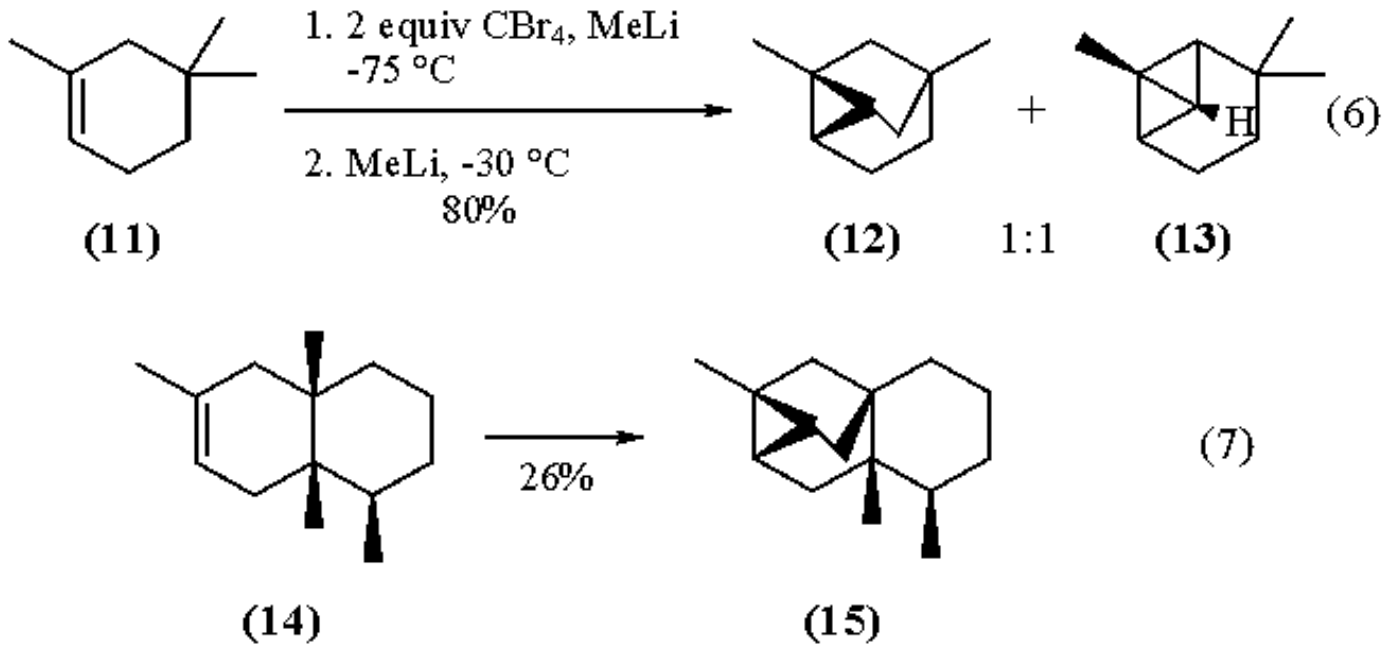

Counterions Other than Li.

The analogous reagents $NaCBr_3$ and $KCBr_3$ have also been prepared by deprotonation of $CHBr_3$ using the requisite metal hexamethyldisilazide.[13] No significant chemical reactivity was reported.

Related Reagents.

Dibromomethyllithium; ***Dichloromethyllithium***; ***Trichloromethyllithium***.

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Tri-*n*-butylamine

***n*-Bu$_3$N**

[102-82-9] · $C_{12}H_{27}N$ · Tri-*n*-butylamine · (MW 185.40)

(high boiling tertiary amine, used as a base in intramolecular Diels-Alder reactions,[1] metal-catalyzed couplings and reductions, ketene generation, and hydrogenations)

Physical Data: bp 216 °C; mp -70 °C; *d* 0.778 g cm^{-3}.

Solubility: sparingly sol H_2O; very sol alcohols and ethers; sol acetone, benzene.

Form Supplied in: liquid; commercially available.

Handling, Storage, and Precautions: a corrosive and toxic liquid. Bottles of tri-*n*-butylamine should be flushed with nitrogen or argon to prevent exposure to carbon dioxide. The vapors are harmful and care should be taken to avoid absorption through the skin. Use in a fume hood.

Intramolecular Diels-Alder Reactions.

The addition of tri-*n*-butylamine to high-temperature intramolecular Diels-Alder reactions[1] tends to reduce unwanted acid-catalyzed side reactions involving the reaction substrates and/or the Diels-Alder adducts. For example, heating the trienol (**1**) at 185 °C in chlorobenzene containing a catalytic amount of tri-*n*-butylamine leads to the four possible isomeric Diels-Alder products (**2**) in nearly quantitative yield (eq 1).[2] Omitting the tri-*n*-butylamine results in only a 14% yield of the desired adducts. A major byproduct is the tetraene (**3**), the product of an acid-promoted dehydration.

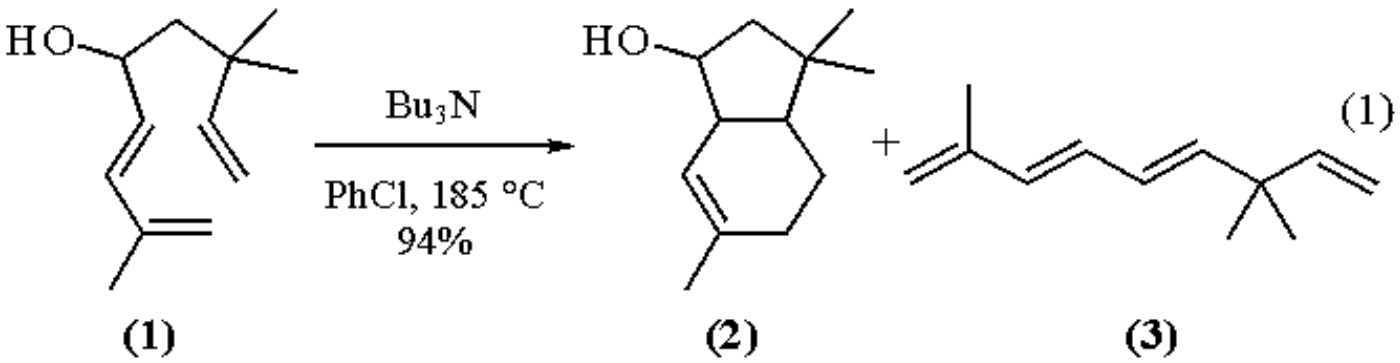

Similarly, heating the mixture of the substituted 1,3-cyclopentadienes (**4**) in tri-*n*-butylamine at 190 °C for 10 h leads to the norbornadiene (**5**) in a distilled yield of 78% (eq 2).[3] In contrast, use of HMPA as solvent at 220 °C generates the double bond isomer (**6**), the product of either an allene/alkyne equilibration of (**4**) prior to the intramolecular Diels-Alder reaction or an acid-catalyzed rearrangement of the Diels-Alder product (**5**). An acid-catalyzed isomerization of (**5**) to (**6**) has been observed using dilute sulfuric acid at room temperature.[3]

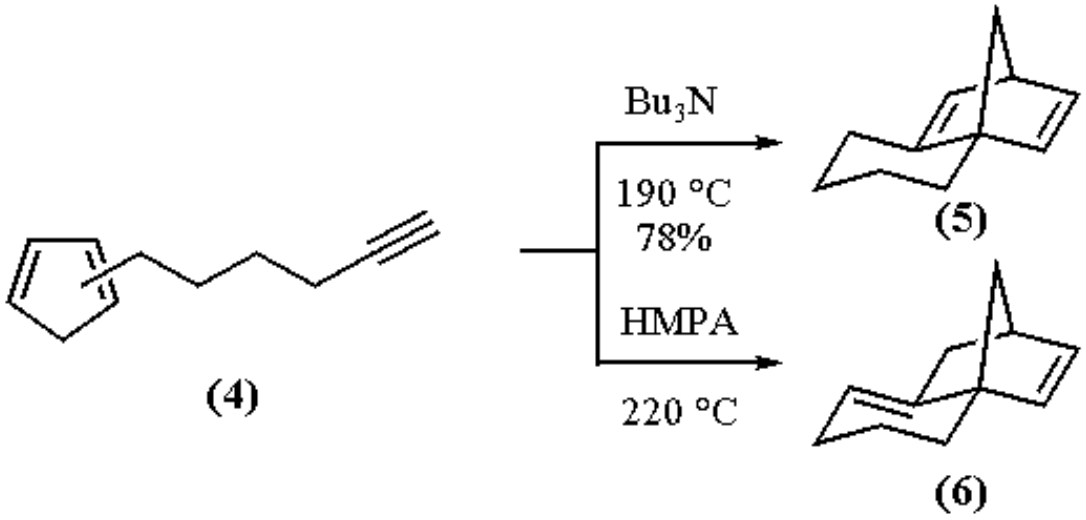

(2)

Metal-Catalyzed Reactions.

o-Bromoacetanilides and related substrates undergo palladium-catalyzed carbonylations using palladium catalysts and gaseous CO in tri-*n*-butylamine and water to generate anthranilic acid derivatives (eq 3).[4] The method finds use in the carbonylative cyclization of substituted aminopyridines to prepare pyrido[2,1-*b*]quinazolines (eq 4).[5]

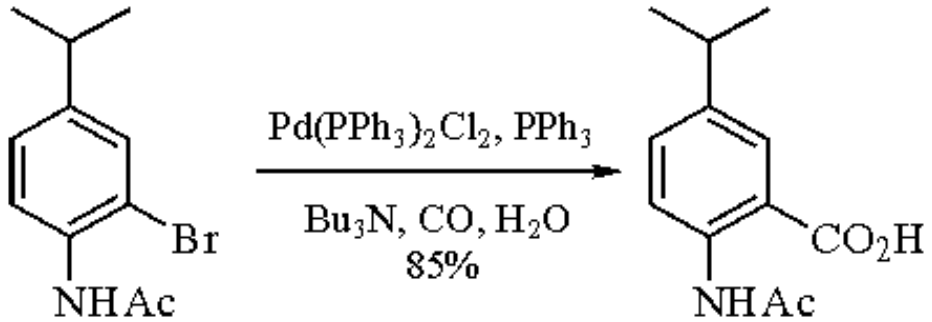

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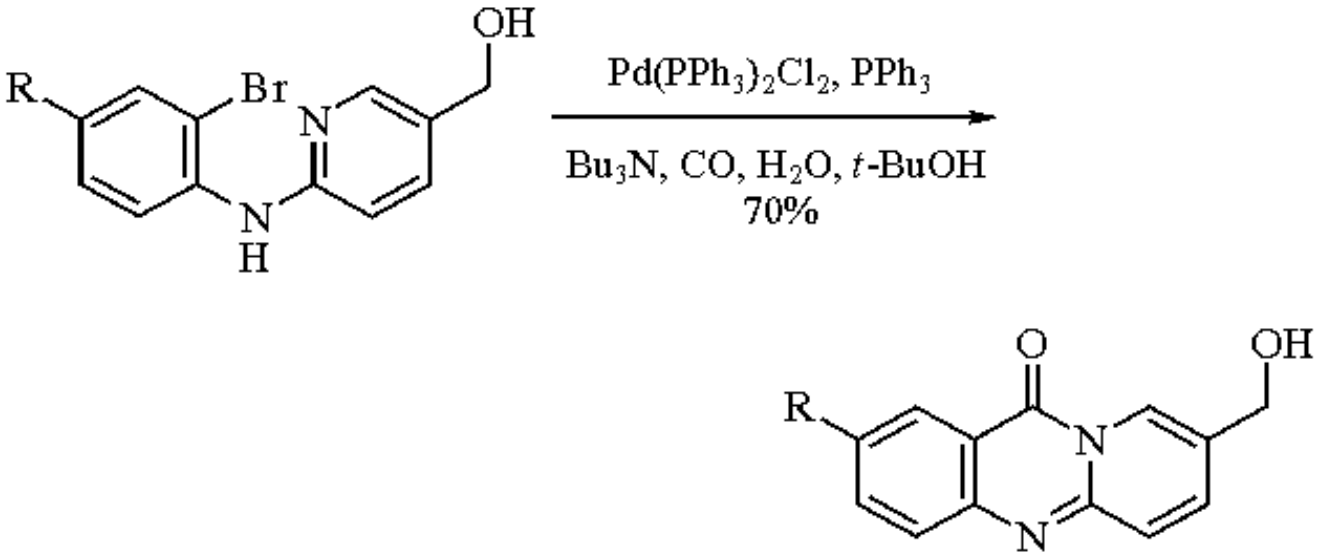

(4)

Enol trifluoromethanesulfonates (triflates) and aryl triflates undergo efficient Pd-catalyzed couplings with olefinic substrates to afford dienes,[6] carbonylations with CO to afford carboxylic acids,[7] and reductions with trialkylammonium formates to afford alkenes.[8] β-Hydroxy enol triflates undergo a carbonylative cyclization with ***Tetrakis(triphenylphosphine)palladium(0)*** and tri-*n*-butylamine under a CO atmosphere to generate α,β-butenolides in good yields (eq 5).[9] Likewise, treatment of the enol triflate (**7**) with tri-*n*-butylamine, ***Palladium(II) Acetate***, and ***1,1´-Bis(diphenylphosphino)ferrocene*** (dppf) under a CO atmosphere in aqueous DMF leads to the diacid (**8**) in 42% isolated yield (eq 6).[10]

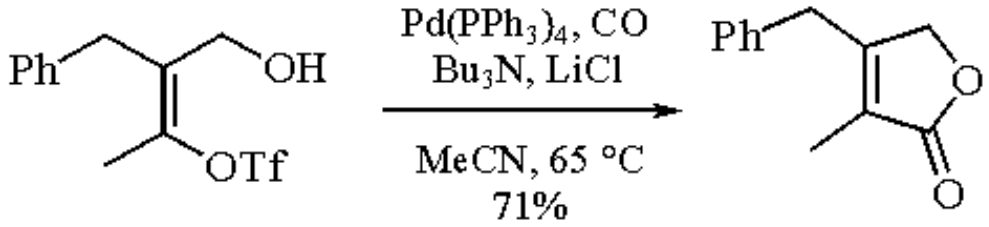

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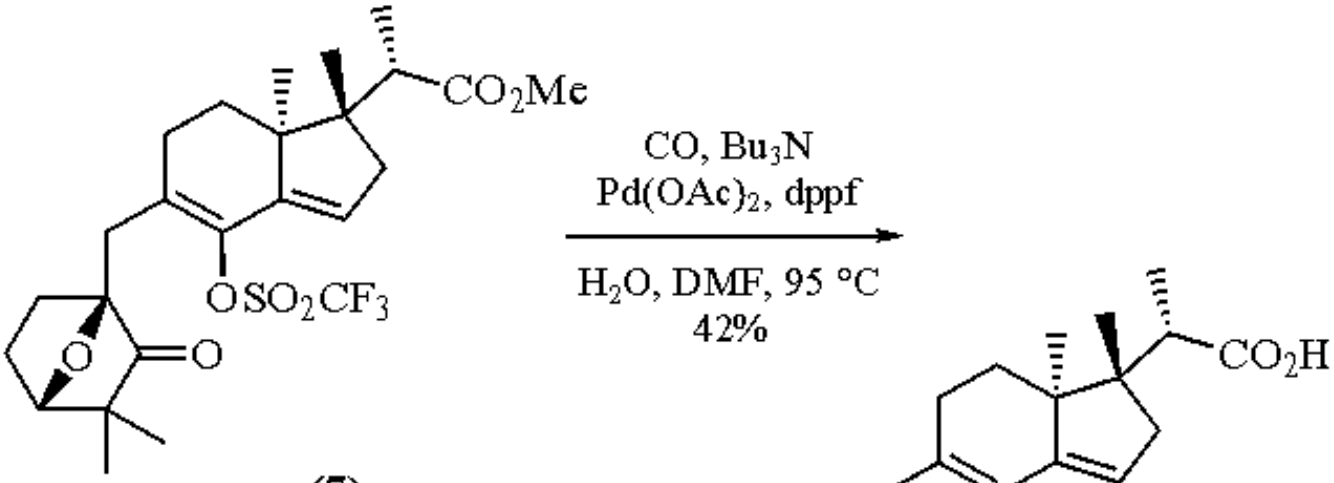

(7) (6) (8)

Enol triflates, as well as aryl triflates and aryl fluoroalkanesulfonates,[11] are selectively deoxygenated to the corresponding alkenes and arenes using the combination of ***Formic Acid*** and tri-*n*-butylamine in the presence of a catalytic amount of ***Bis(triphenylphosphine)palladium(II) Acetate*** in DMF (eq 7).[8,12] In the case of highly hindered aryl triflates, use of ***1,3-Bis(diphenylphosphino)propane*** (dppp) as a ligand tends to increase the yields of the desired arenes (eq 8).[13]

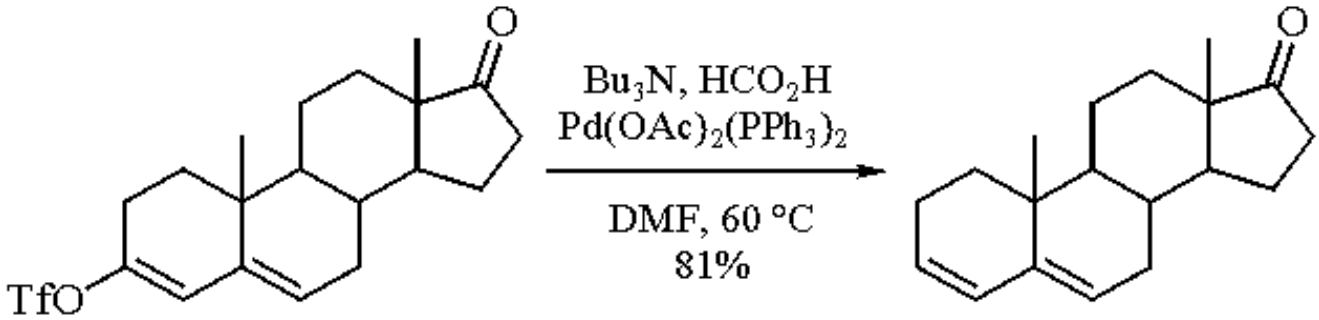

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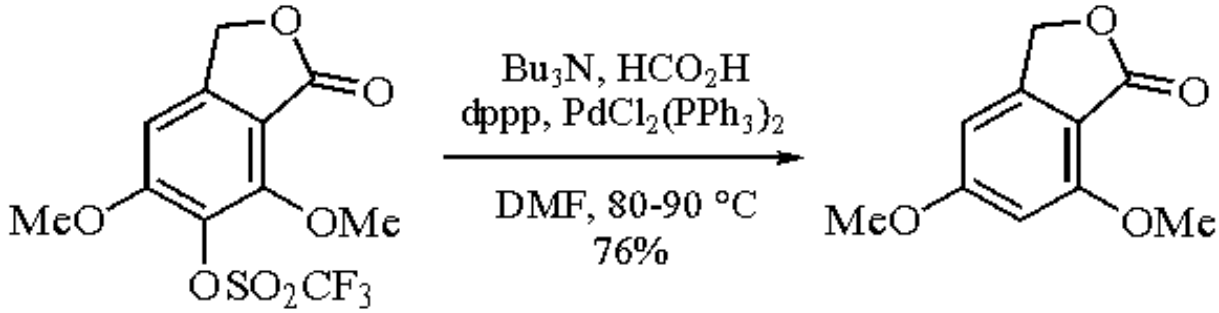

(8)

Aryl iodides react with 4-hydroxy-2-alkynoates in the presence of formic acid, tri-*n*-butylamine, and a palladium(II) catalyst in DMF to generate highly substituted α,β-butenolides via a one-pot hydroarylation/cyclization sequence (eq 9).[14] The regioselectivity is controlled

by steric constraints and metal-coordination factors involved during the Pd-C bond forming step. 4-Hydroxy-2-alkynoates undergo a reductive cyclization under similar conditions to afford butenolides in high yields (eq 10). Use of a large excess of formic acid leads to fully saturated lactones.

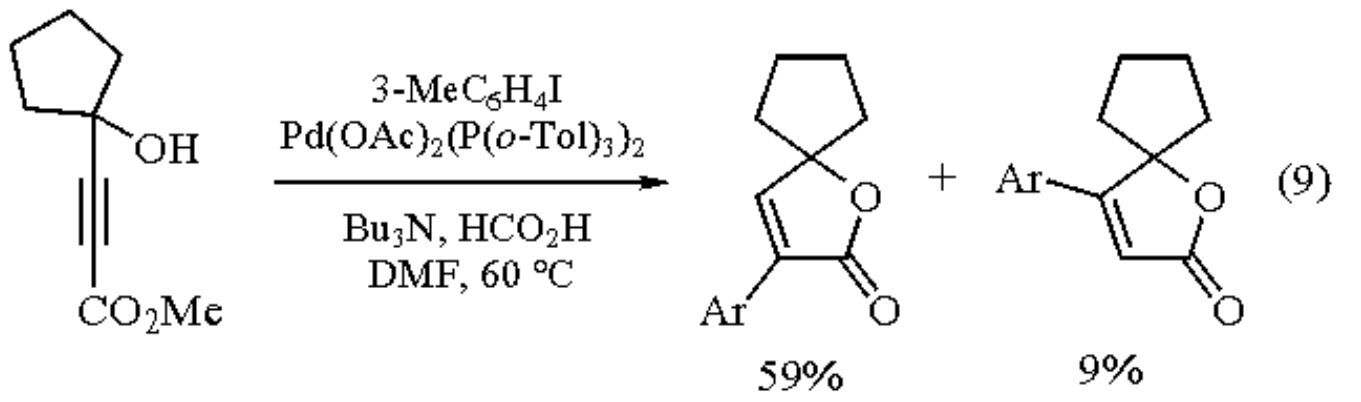

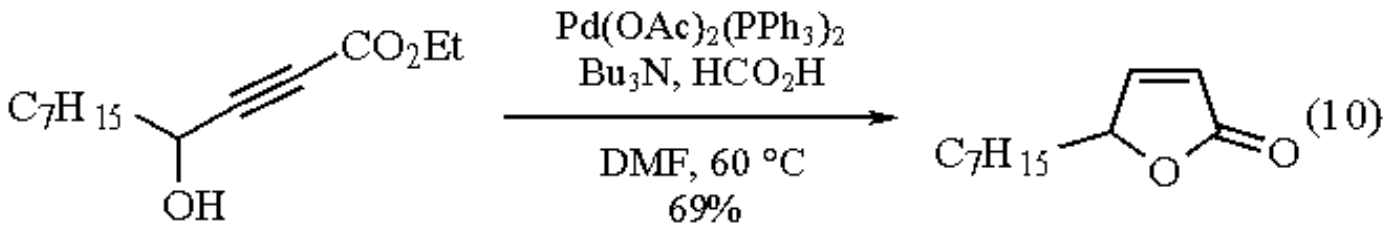

Heck-type reactions,[15] involving the coupling of aryl halides and substituted alkenes to produce arylated alkene derivatives, can be accomplished using tri-*n*-butylamine as a base and a variety of palladium catalysts. The arylation of conjugated alkenes is catalyzed efficiently using the clay-anchored catalyst montmorillonite-ethylsilyldiphenylphosphinepalladium(II) chloride, in tri-*n*-butylamine at 100 °C to produce the *trans*-alkenic products selectively in excellent yields (eq 11).[16] The cross coupling between aryl iodides and vinyl acetates to generate *trans*-stilbene derivatives is made possible with the use of the clay-anchored catalyst and tri-*n*-butylamine (eq 12).[17]

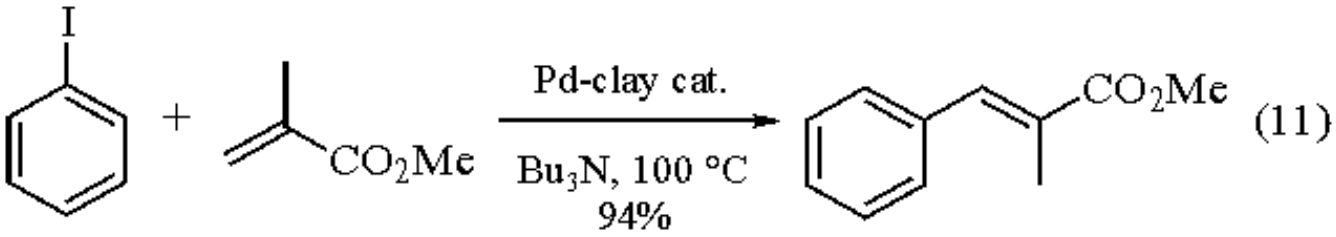

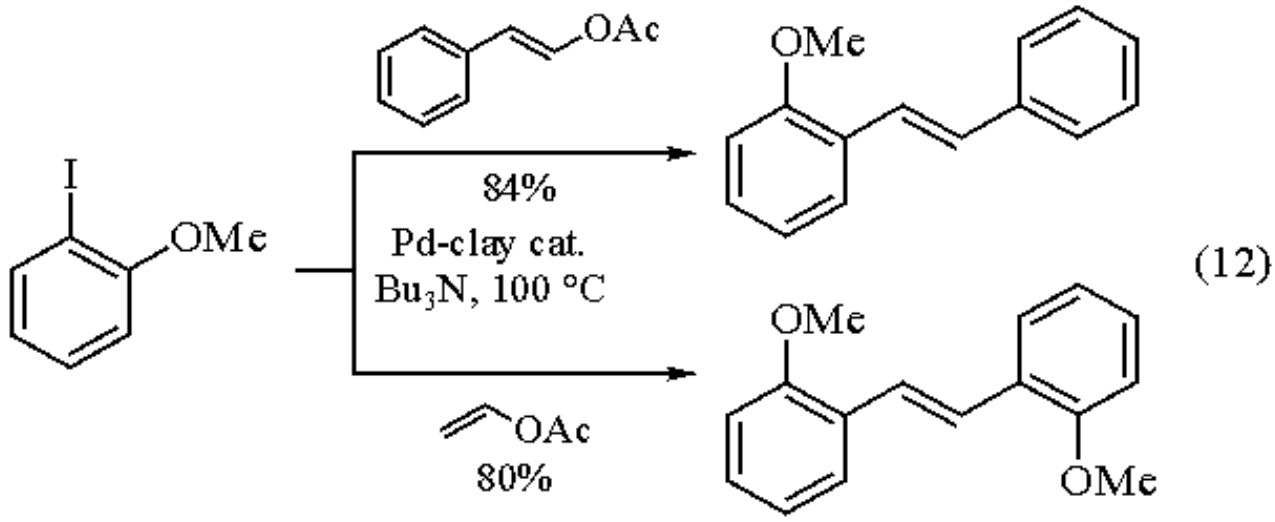

C-Glycosides are assembled using a palladium-mediated glycal-aglycon coupling sequence.[18] Reaction of furanoid glycals with aryl halides in the presence of a catalytic amount of palladium acetate and tri-*n*-butylamine in DMF at room temperature results in high yields of *C*-furanosyl products, usually with a high degree of regio- and stereocontrol (eq 13).[19] Good regio- and stereocontrol is found with 3-deoxypyranoid glycals under similar reaction conditions.[20]

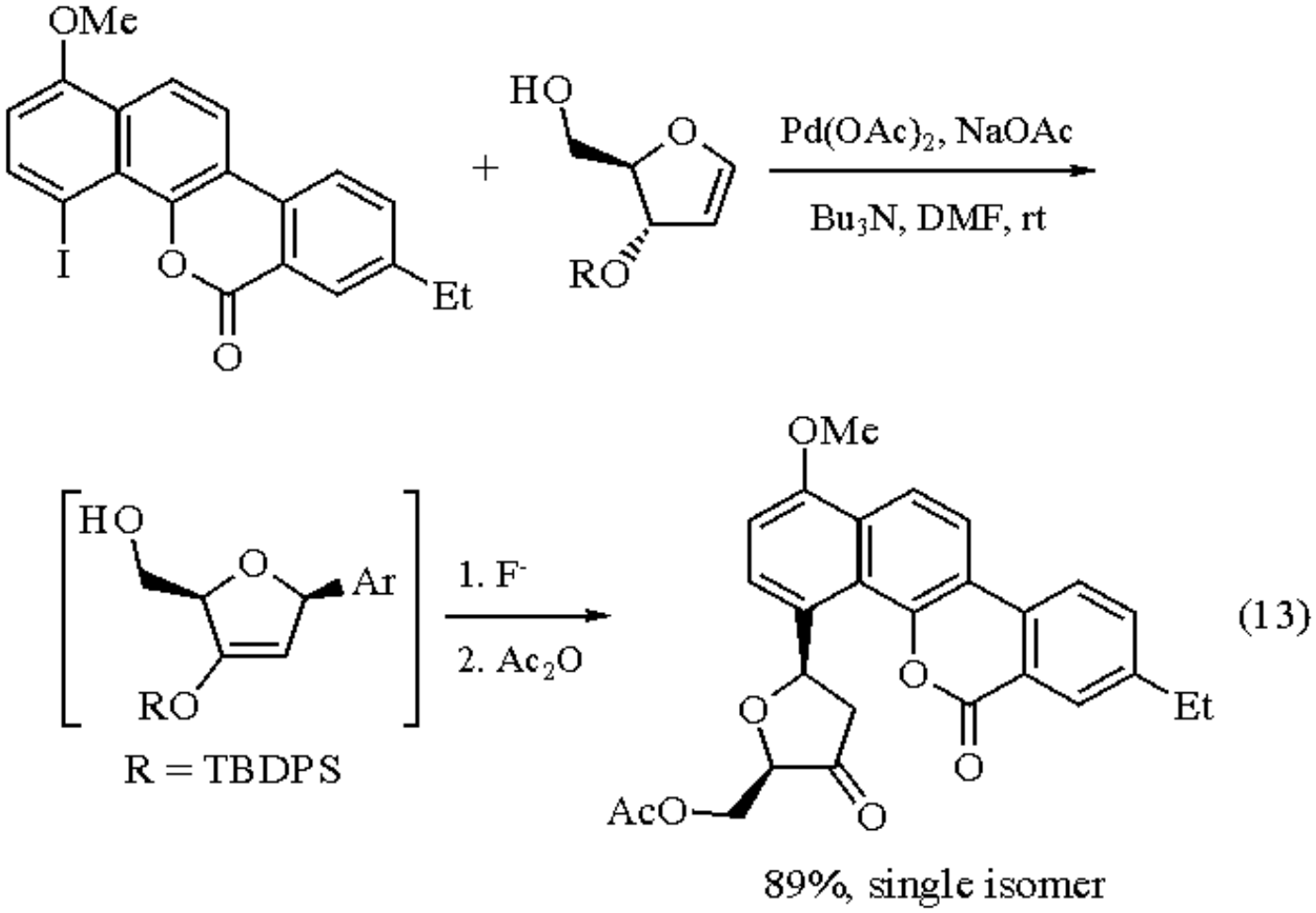

The reduction of enantiomerically enriched phosphine oxides is accomplished using an excess of ***Trichlorosilane*** to afford phosphines with retention of configuration. However, the use of strong organic amine bases (pK_b < ca. 5), such as ***Triethylamine***, leads to phosphines with inversion of configuration, while the use of weak amine bases (pK_b > ca. 7) results in retention of configuration.[21] Treatment of enantiomerically enriched bisphosphine oxides with trichlorosilane and tri-*n*-butylamine[22] (or triethylamine)[23] in acetonitrile at 70 °C affords enantiopure phosphines in high yields (eq 14).[21] The combination of tri-*n*-butylamine and acetonitrile ensures a homogeneous reaction mixture and prevents incomplete reduction and the production of *meso*-bisphosphines.

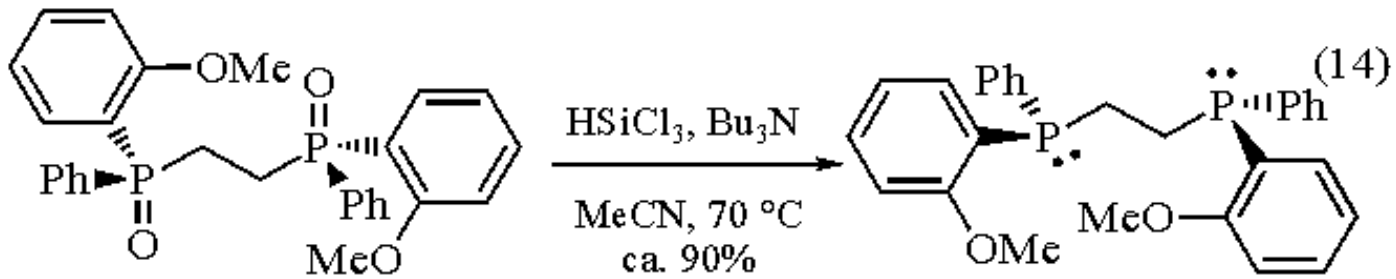

The high boiling point of tri-*n*-butylamine makes it an attractive base in reactions requiring high temperatures. For example, intramolecular ketene-alkene [2 + 2] cycloaddition is accomplished by slowly adding the acid chloride (**9**) to an excess of tri-*n*-butylamine in refluxing toluene to afford the tricyclic ketone (**10**) in 71-87% yield (eq 15).[24] The elimination of the anomeric methoxy group is catalyzed by the tri-*n*-butylammonium chloride produced in the reaction.

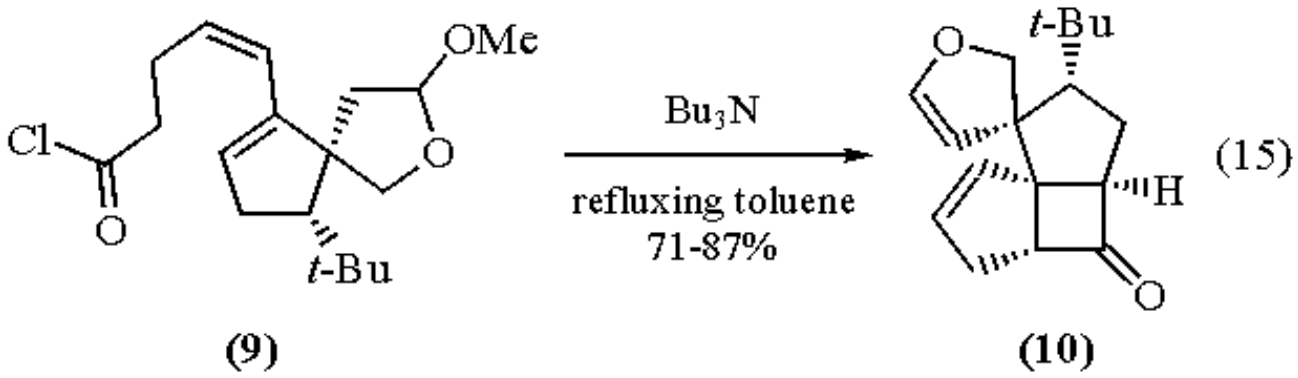

Thermolysis of ethyl alkynyl ethers in the presence of 10 equiv of tri-*n*-butylamine in refluxing xylenes (137-144 °C) leads to good yields of macrocyclic lactones. The tri-*n*-butylamine facilitates the cyclization step involving the ketene intermediate produced by a retro-ene reaction (eq 16).[25]

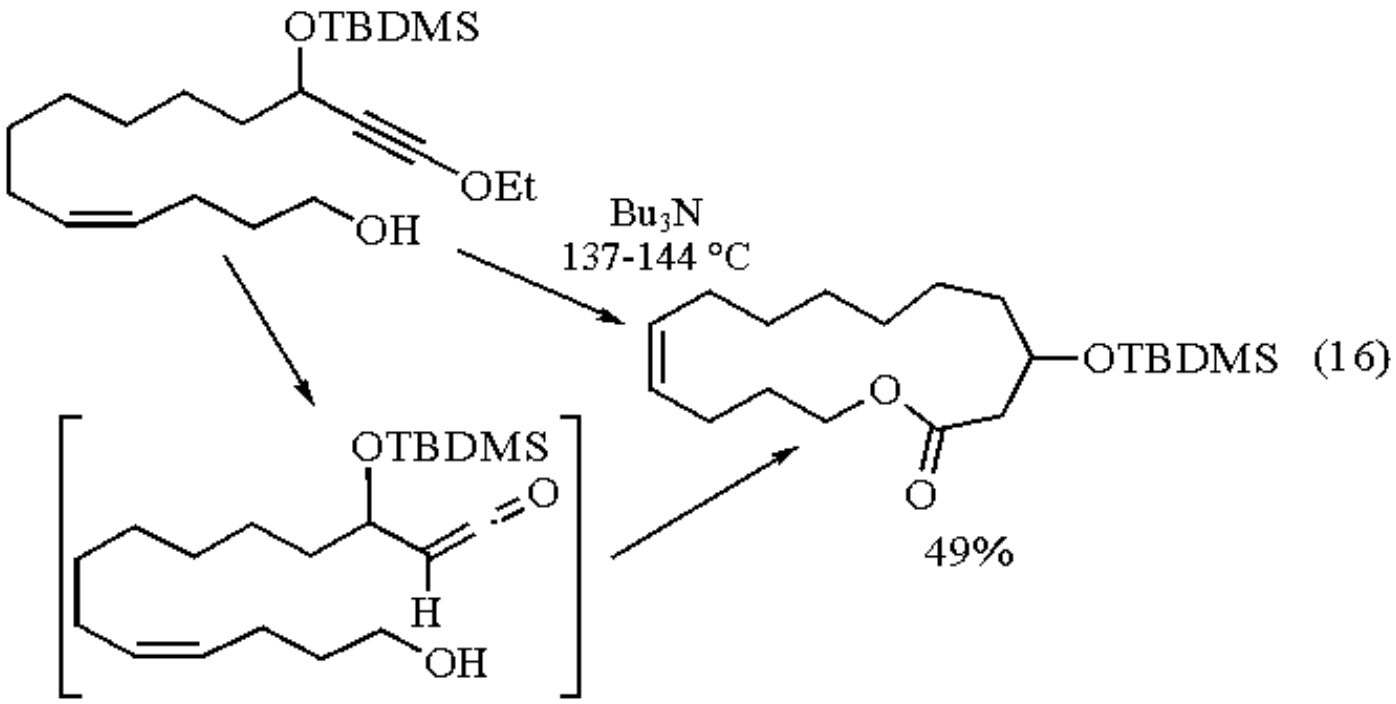

Hydrogenations.

The enantioselective hydrodechlorination of L-5,5-dichloro-1-(chlorocarbonyl)proline esters (**11**) to afford L-proline in 78% yield is achieved using a 10% ***Palladium on Carbon*** catalyst and 180 bar of H_2 pressure in tri-*n*-butylamine at 50 °C. The tri-*n*-butylammonium chloride produced in the reaction remains in solution and the catalyst retains its full activity (eq 17).[26] When other tertiary amine bases such as triethylamine are used, the trialkylammonium salt produced tends to precipitate onto the catalyst surface. As a result, the catalyst becomes deactivated and the overall yield is reduced.

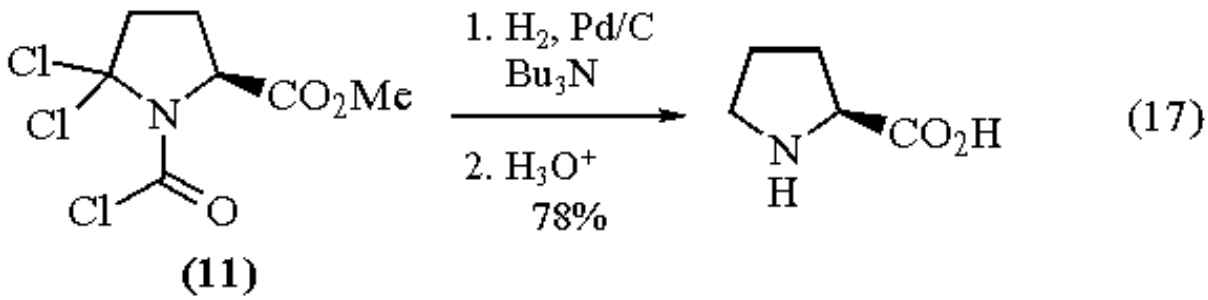

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Tri-*n*-butylborane

***n*-Bu$_3$B**

[122-56-5] · $C_{12}H_{27}B$ · Tri-*n*-butylborane · (MW 182.20)

(good chelating reagent;[1,2] radical initiator;[3] starting material for the synthesis of Bu_2BOTf[4] and Bu_2BSR[5])

Physical Data: bp 108-110 °C/20 mmHg, 90-91 °C/9 mmHg; *d* 0.747 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: colorless liquid; commercially available.

Purification: distillation from CaH_2.

Handling, Storage, and Precautions: moisture sensitive. Use in a fume hood.

Stereoselective Reduction of β-Hydroxy Ketones.

Highly stereoselective reduction of β-hydroxy ketones is realized via boron chelates.[1] Dibutylboronates of β-hydroxy ketones are formed in situ from β-hydroxy ketones and tributylborane with the catalytic action of air in THF. Treatment of the mixture with ***Sodium Borohydride*** at -78 °C then affords *syn*-1,3-diols stereoselectively (eq 1). The selectivity is better when the reduction is carried out at a lower (-100 °C) temperature. In some instances, triisobutylborane gives a better selectivity than tributylborane, but the reduction proceeds more slowly.

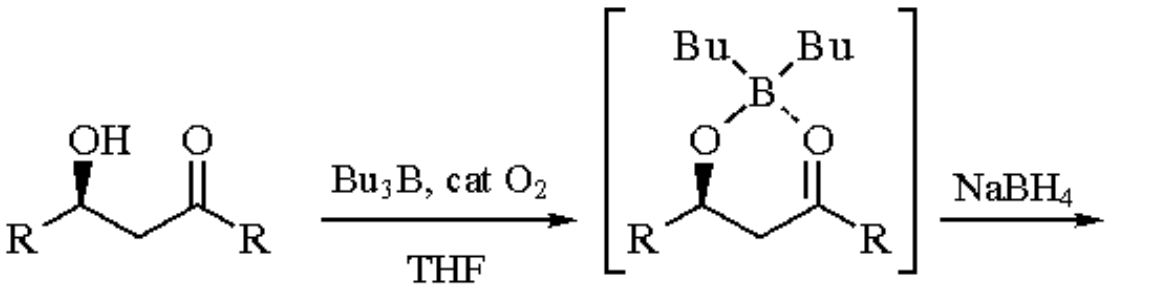

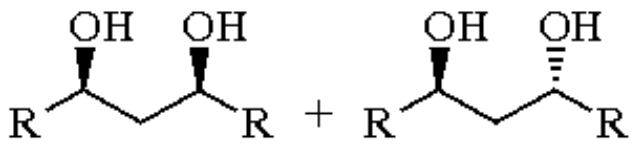

(1)

R	
Ph	98:2
Bu	96:4

For example, this stereoselective reduction is utilized in the synthesis of a β-hydroxy-δ-lactone HMG-CoA reductase inhibitor (eq 2).[6] This procedure is also applicable to the stereoselective reduction of *syn*-α-substituted β-hydroxy ketones.[1] The reduction gives 1,3-diols with *syn,syn* stereochemistry exclusively (eq 3). However, the stereoselectivity of reduction of *anti*-α-substituted β-hydroxy ketones depends on the alkyl substituents, R^1 and R^2 (eq 4).

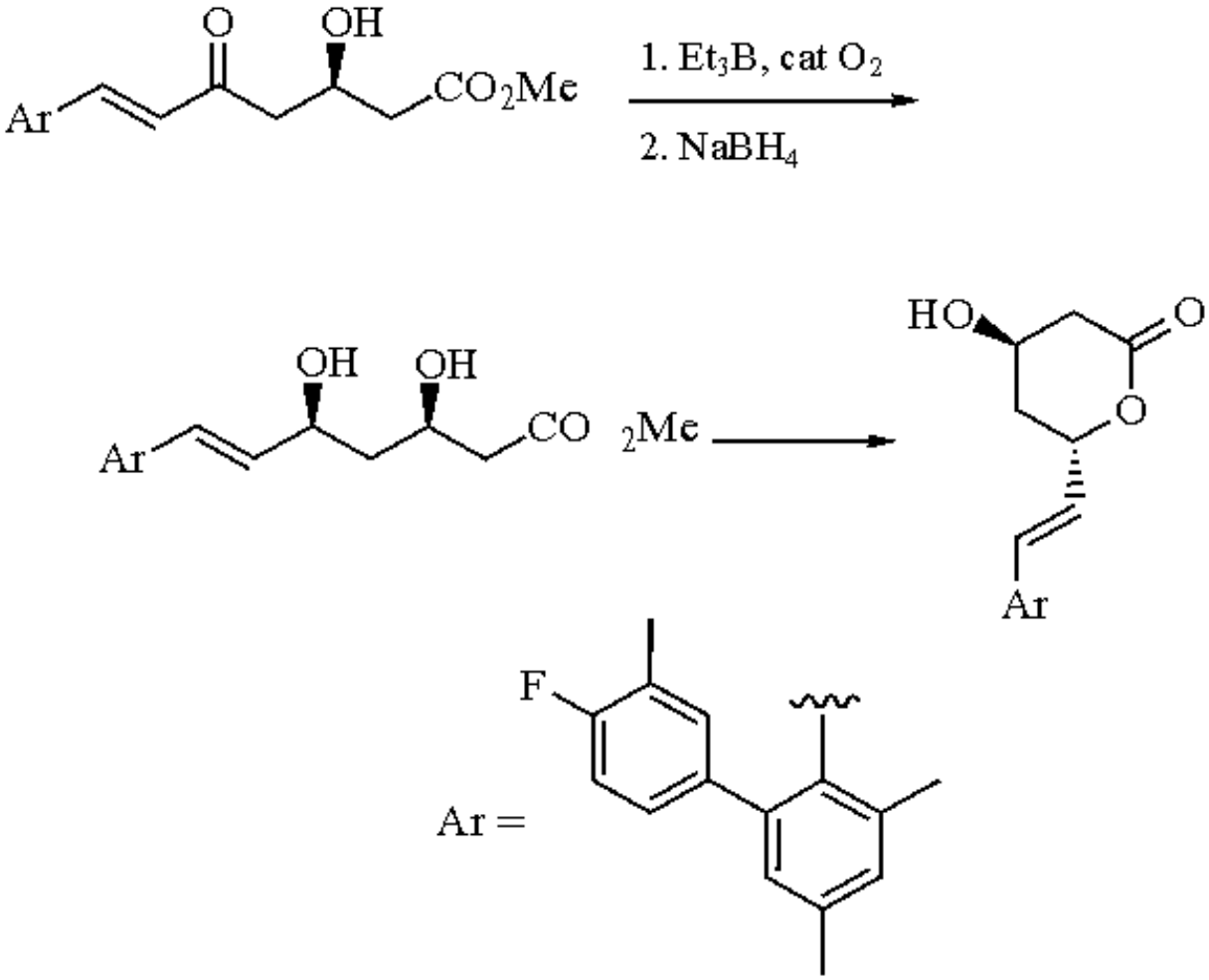

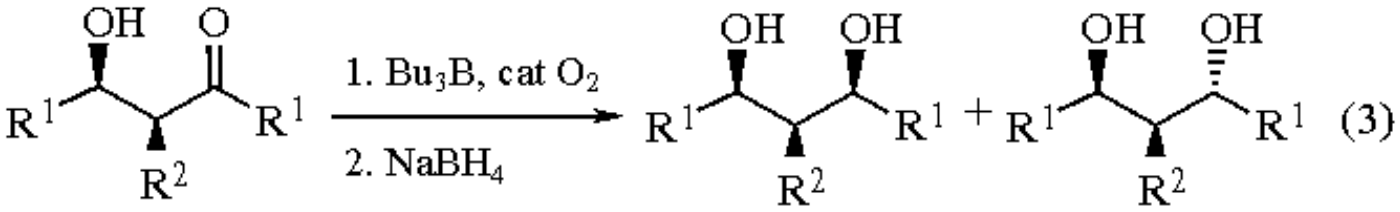

R^1	R^2	
i-Pr	Me	100:0
Ph	Bu	100:0

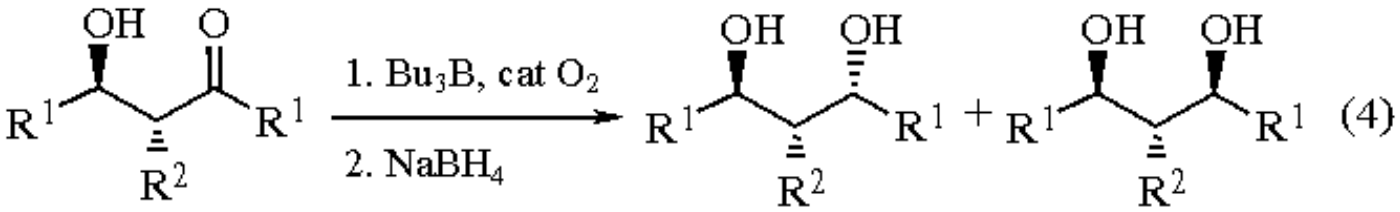

R^1	R^2	
i-Pr	Me	27:73
Ph	Bu	87:13

Stereoselective Reaction of Allylic Boronates.[2]

In the presence of an equimolar amount of tributylborane (***Triethylborane*** is also effective), but-2-enyllithium reacts with aldehydes to give

the *anti*-homoallyl alcohols predominantly. For example, in the reaction with benzaldehyde the *anti*-isomer is obtained in 74% yield, along with the *syn*-isomer in 15% yield (eq 5).

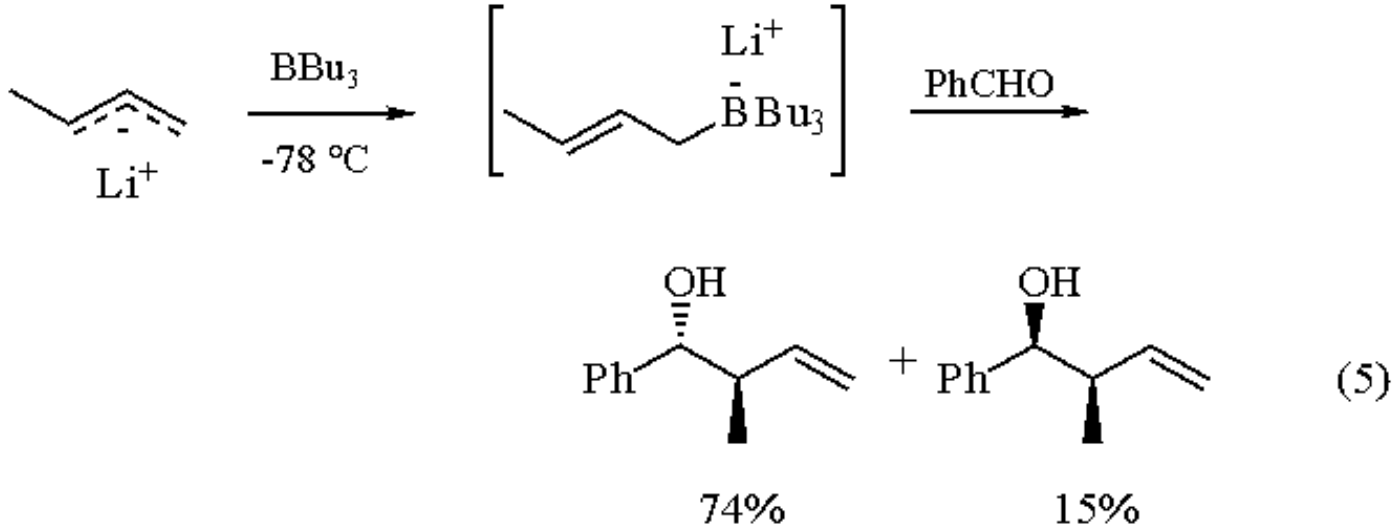

Bu_3B-Induced Chlorination of Alkanes.[3]

The chlorination of alkanes with ***Chlorine***, ***t-Butyl Hypochlorite***, or ***N-Chlorosuccinimide*** proceeds at 20 °C in carbon tetrachloride, in the presence of a catalytic amount of tributylborane, even in the dark, giving monochloroalkanes. For the chlorination of 2,3-dimethylbutane, 3-methylpentane, and *n*-heptane, the regioselectivity is dependent on the chlorinating reagents, as shown in eq 6. Trihexylborane and tricyclohexylborane are also effective initiators.

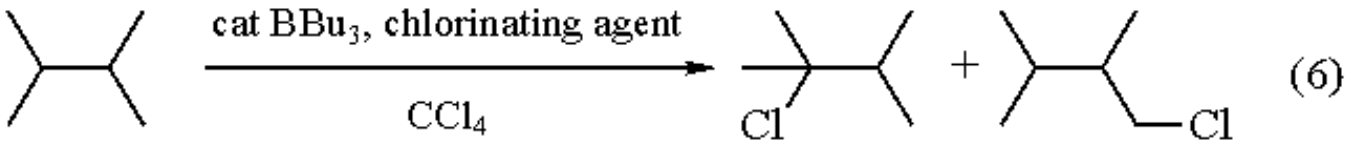

Cl_2	35%	47%
t-BuOCl	80%	9%
NCS	63%	0.6%

Dibutylboryl trifluoromethanesulfonate.

Di-n-butylboryl Trifluoromethanesulfonate, which is useful for cross-aldol reactions of ketones with aldehydes (eq 8), is prepared from equimolar amounts of tributylborane and ***Trifluoromethanesulfonic Acid*** (eq 7).[4]

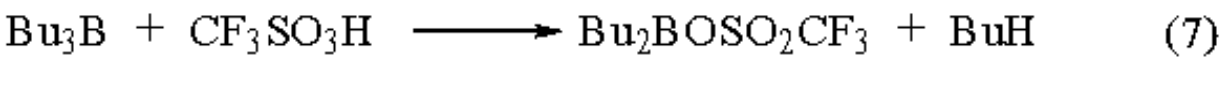

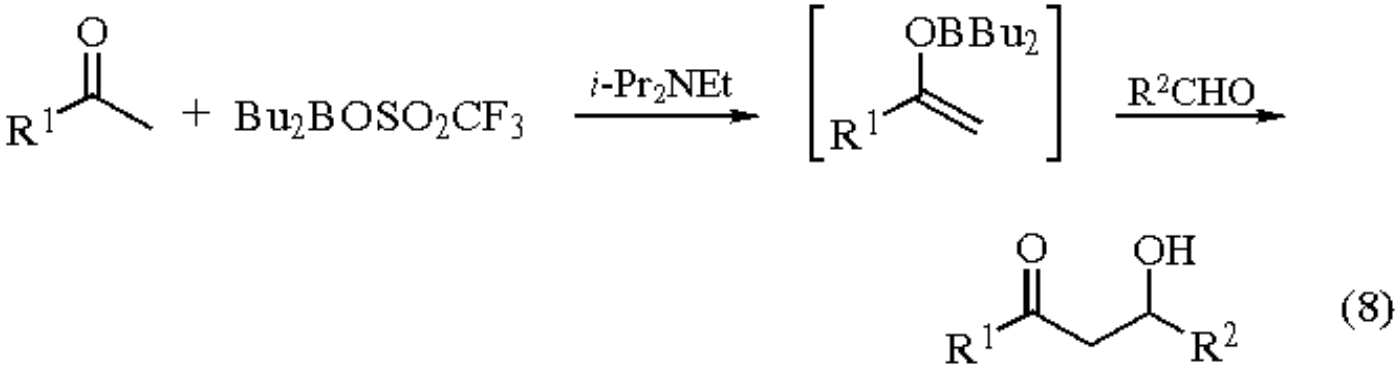

Alkylthiodibutylboranes.

Alkylthiodibutylboranes are easily prepared from tributylborane and thiols (eq 9).[5] The reaction of these boranes with ketene generates vinyloxyborane intermediates, which react with ketones, aldehydes, or nitriles to afford β-hydroxy or β-imino thioesters (eq 10).[7]

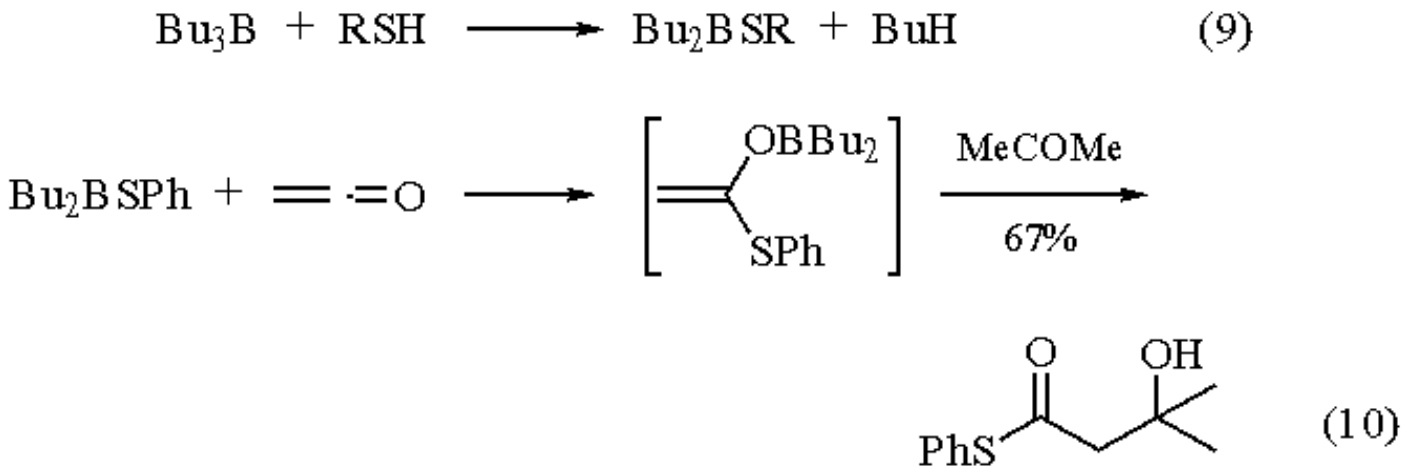

Alkylthiodibutylboranes also react with α,β-unsaturated ketones to generate vinyloxyborane intermediates, which react with aldehydes to afford β-hydroxy ketone derivatives (eq 11).[7]

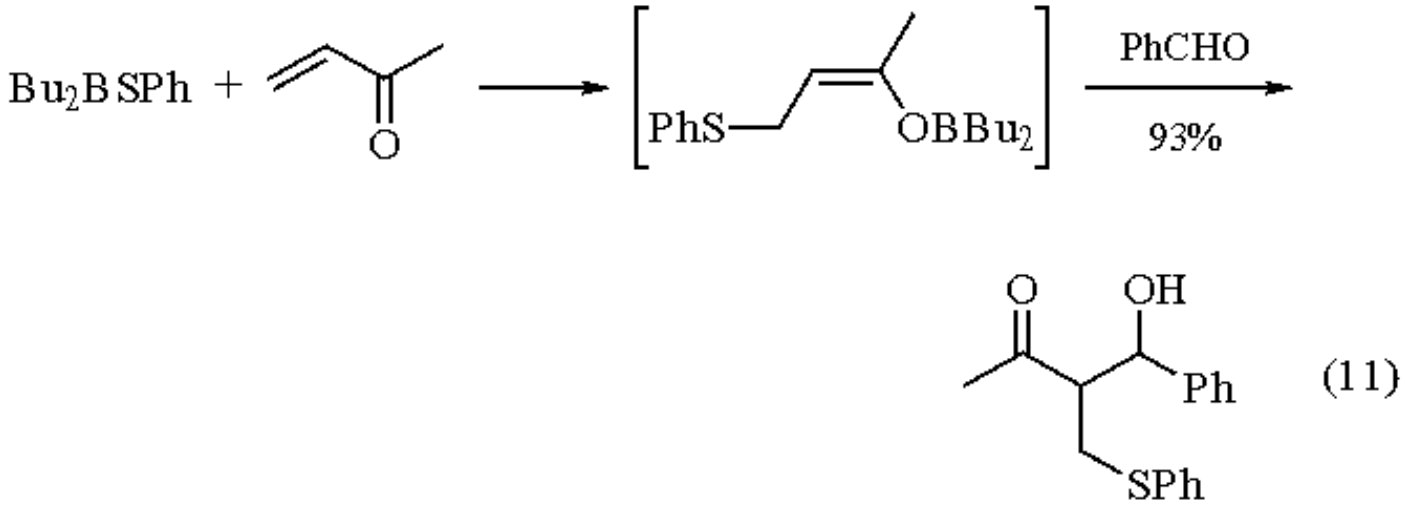

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Tri-*n*-butylfluorostannane

Bu_3SnF

[1983-10-4] · $C_{12}H_{27}FSn$ · Tri-*n*-butylfluorostannane · (MW 309.10)

(selective silyl/stannyl exchange of enol silyl ethers;[1] fluoride source[2])

Alternate Name: fluorotributyltin.

Form Supplied in: white solid; commercially available. *Drying:* this chemical seems not to be hygroscopic. Drying may be done in vacuo (ca. 0.1 mmHg) for 6 h at 100 °C (bath temperature).[1,2]

Handling, Storage, and Precautions: this reagent is toxic (acute oral LD_{50} (rats): 200 mg kg^{-1})[3] and should be handled with care. Use in a fume hood.

Arylation, Alkenylation, and Aldol Reactions of Enol Silyl Ethers via Tin Enolates and/or α-Stannyl Ketones.

This reagent reacts with enol silyl ethers of methyl ketones to generate tin enolates and/or α-stannyl ketones in the presence of a palladium catalyst (eq 1).[1] The palladium may work as a mild Lewis acid to activate the enol silyl ether. The resulting stannyl enolate derivatives can be trapped in situ with aryl or alkenyl bromides in the presence of the palladium catalyst to give α-aryl or α-alkenyl ketones in a regioselective manner, as shown in eqs 2 and 3.[1,4] The reaction with aldehydes affords aldols (eq 4).[5] The latter example demonstrates site selectivity for silyl/stannyl exchange at the less hindered silyl enol ether.

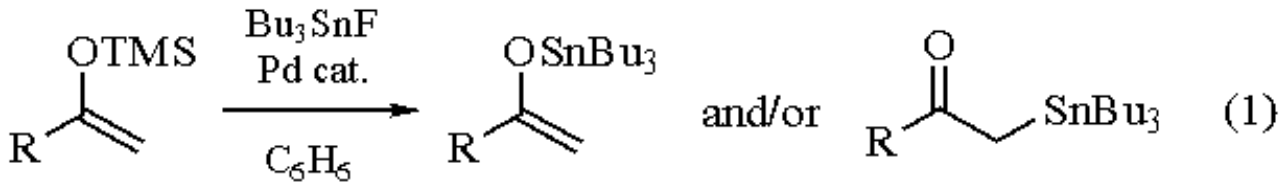

Pd cat = $Pd[(o\text{-}MeC_6H_4)_3P]_2Cl_2$

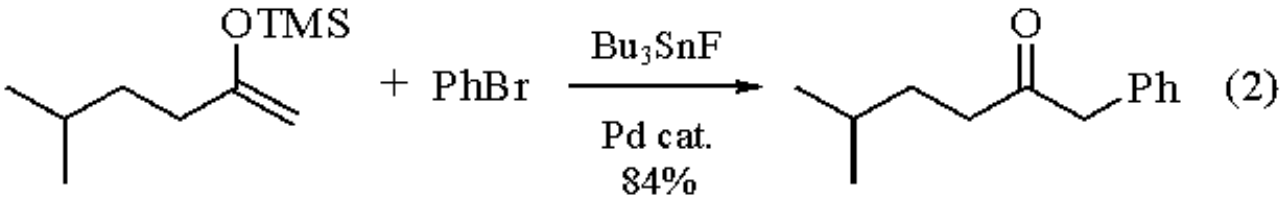

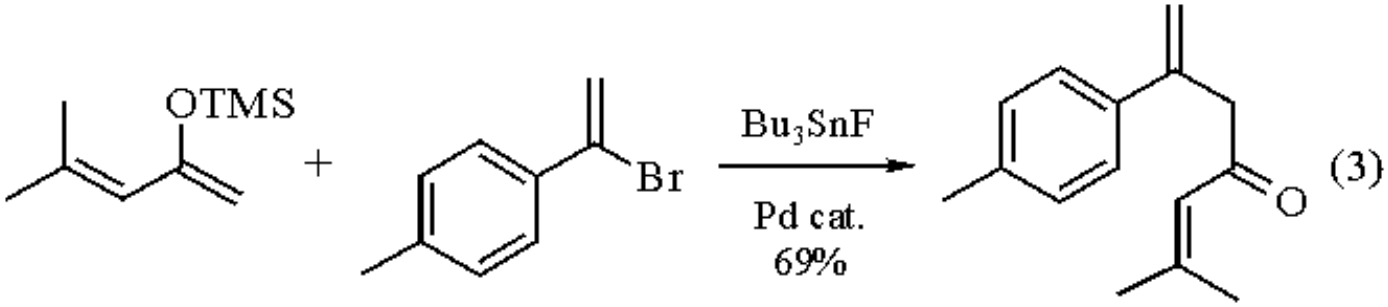

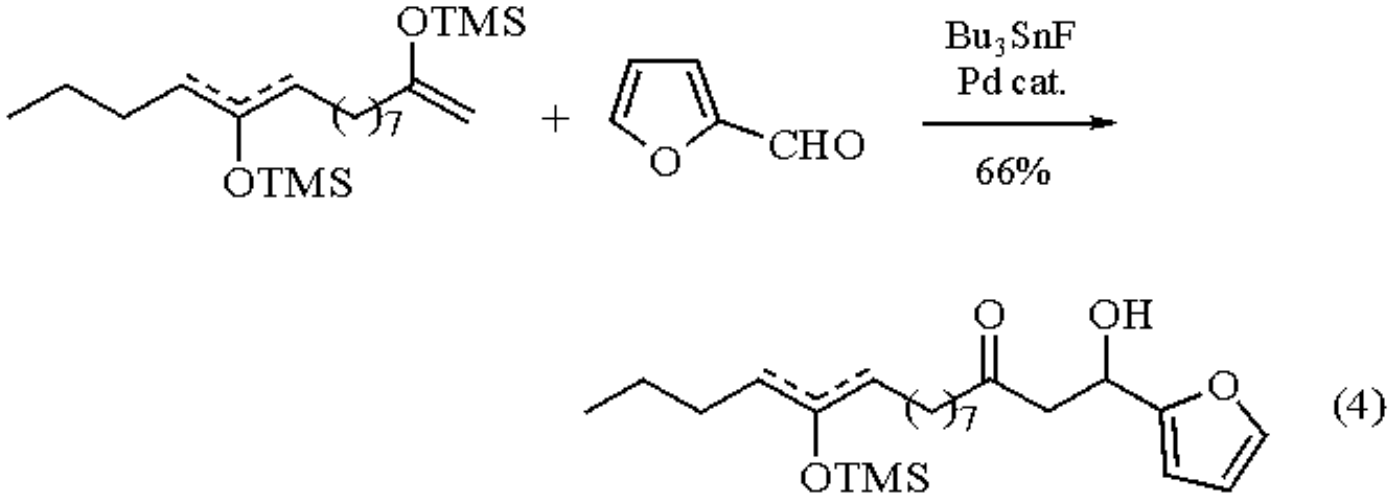

Selective Desilylation of Bis-silyl Enol Ethers.

As described above, the silyl/stannyl exchange with Bu_3SnF/Pd catalyst is greatly influenced by the steric hindrance around the enol silyl ether moiety. Thus the highly selective desilylation of bis-silyl enol ether derivatives of diketones is also possible, (probably via intermediacy of a tin derivative) (eqs 5 and 6).[6,7] This method for the differentiation of two ketone groups should complement existing methods for selective monosilylation of diketones.

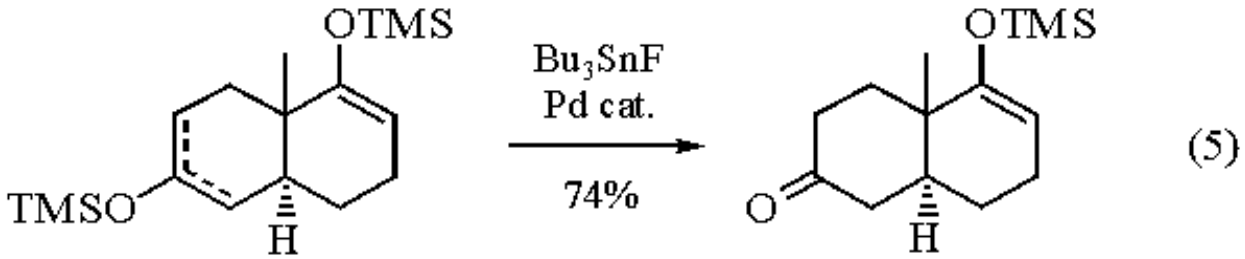

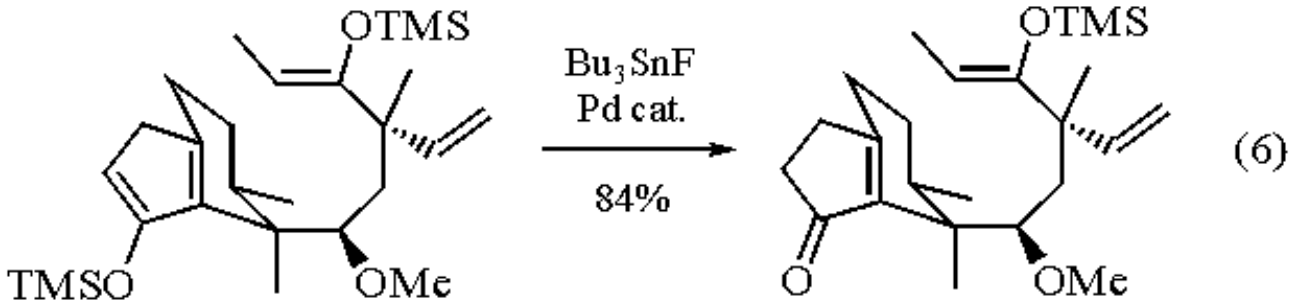

Additive to Facilitate Reactions.

Some other uses of Bu_3SnF (and also Me_3SnF or Ph_3SnF) to promote reactions have been documented and are illustrated in eqs 7 and 8.[2,8,9] In the latter case, it is proposed that Bu_3SnF serves as a mild source of fluoride ion.

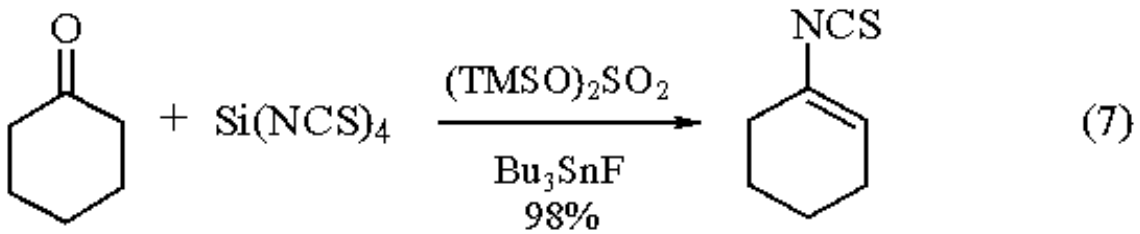

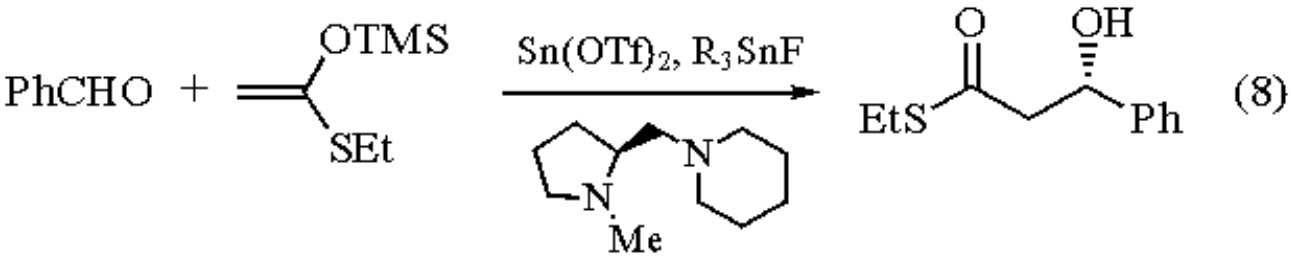

R_3SnF	Yield (%)	ee (%)
Bu_3SnF	78	82
Me_3SnF	64	76
Ph_3SnF	74	12

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Tri-*n*-butylhexadecylphosphonium Bromide[1]

$C_{16}H_{33}{+}PBu_3Br^-$

[14937-45-2] · $C_{28}H_{60}BrP$ · Tri-*n*-butylhexadecylphosphonium Bromide · (MW 507.75)

(phase-transfer catalyst[2,3])

Alternate Name: HDBP.

Physical Data: mp 56-58 °C.

Solubility: insol H_2O.

Form Supplied in: white solid; widely available.

Preparative Method: by heating equimolar amounts of 1-bromohexadecane and ***Tri-n-butylphosphine*** at 65 °C for 3 days (yield 68%).[4,5]

Introduction.

Tributylhexadecylphosphonium bromide is used as a typical phase-transfer catalyst in two-phase reactions carried out without or with a base. HDBP is thermally stable,[6] but is much less stable under basic conditions than corresponding quaternary ammonium salts.[7] Because of its high lipophilicity, HDBP cannot be readily removed from nonpolar solvents. A method of removal of HDBP from the crude products consists in stirring of the reaction mixture with an ion exchange resin (H-form) at room temperature.[8] It appears that HDBP does not offer any advantages over typical phase-transfer catalysts, i.e. tetraalkylammonium salts, being much more expensive; nevertheless, it has been applied in many reactions.

Reductions with Aqueous $NaBH_4$.

Haloalkanes and sulfonate esters are reduced by ***Sodium Borohydride*** to hydrocarbons (eq 1);[9] CO_2R, $CONR_2$, NO_2, and CN groups are not affected. By using $NaBD_4$ in D_2O, deuterio derivatives can be obtained. The reactions can also be catalyzed by tetraoctylammonium chloride. Alkyl-, aryl-, and arylsulfonyl azides are reduced to the corresponding amines or sulfonamides (eq 2).[10] Using this reaction, alkyl bromides can be converted into amines in a one-pot phase-transfer reaction. The halide first reacts with ***Sodium Azide***/H_2O in the presence of HDBP; the aqueous phase is then replaced by an aqueous solution of $NaBH_4$.[10]

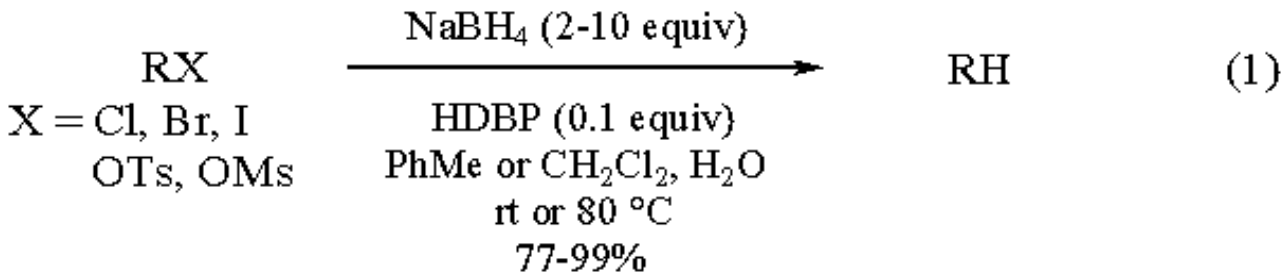

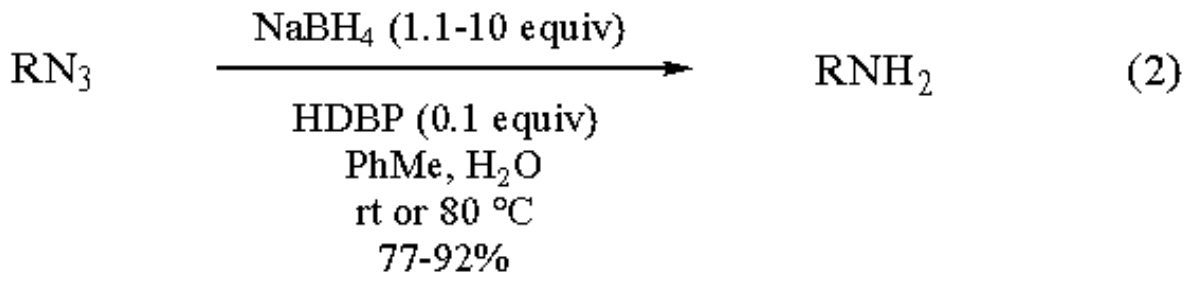

Other Reactions.

HDBP has been used in the reduction of disulfides and *N*-tosylsulfilimines to thiols and sulfides, respectively, by aminoiminomethanesulfinic acid (eq 3),[11] and in the debromination of *vic*-dibromoalkanes by ***Sodium Iodide*** and an excess of ***Sodium Thiosulfate***[12] or ***Sodium Sulfide***[13] (eq 4); the latter process is also catalyzed by quaternary ammonium salts.[14]

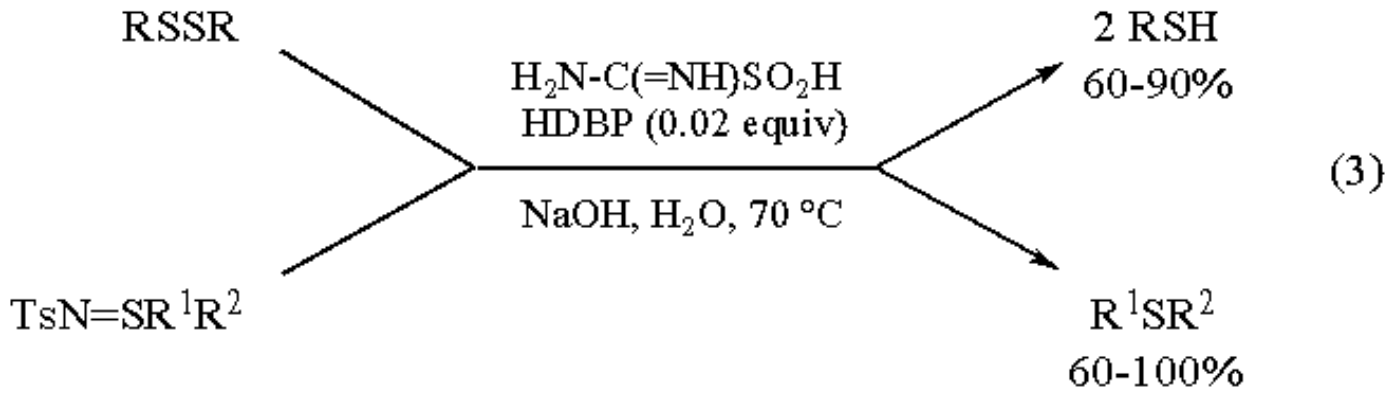

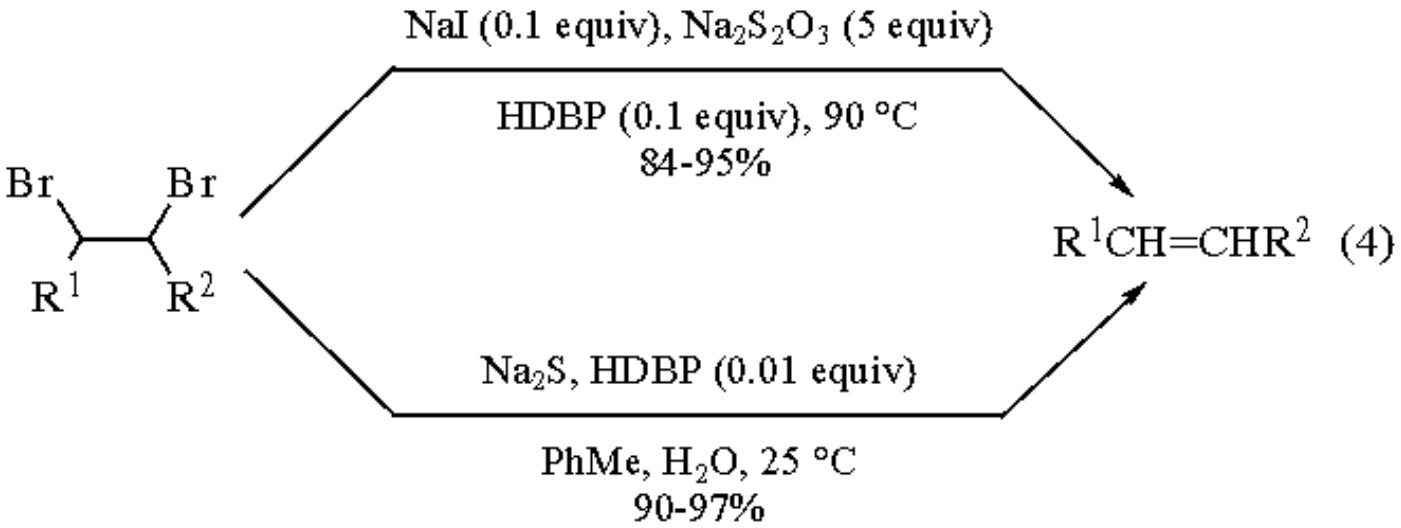

N-Alkylation of potassium phthalimide with alkyl halides or methanesulfonates has been achieved in a solid-liquid two-phase reaction (eq 5).[15] ***18-Crown-6*** is an equally efficient catalyst.[16] HDBP catalyzes the addition of hydrohalic acids to alkenes (eq 6),[17] and the conversion of water-insoluble *n*-alkanols into alkyl chlorides with aq HCl (eq 7);[18] other catalysts can also be used.[19]

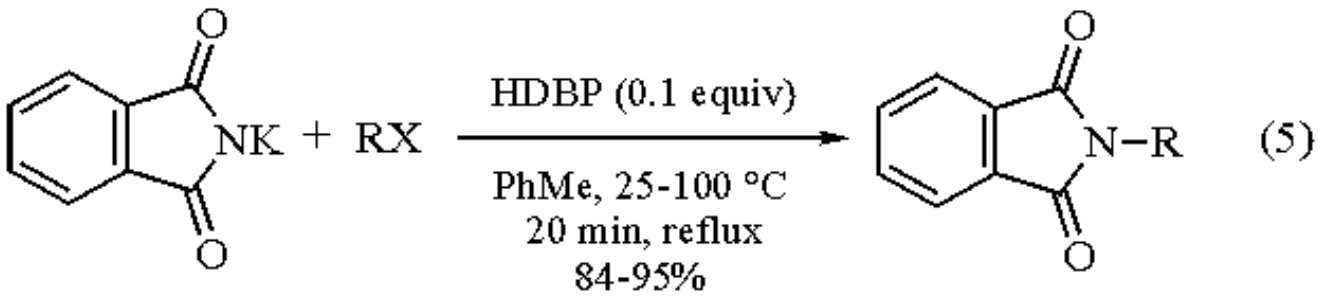

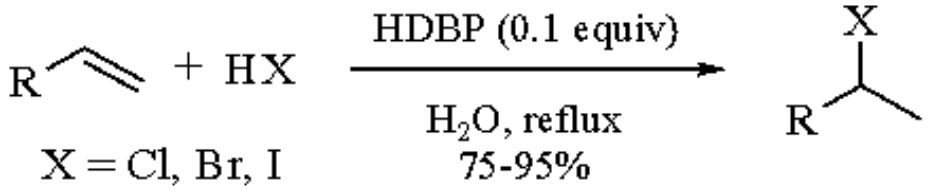

(6)

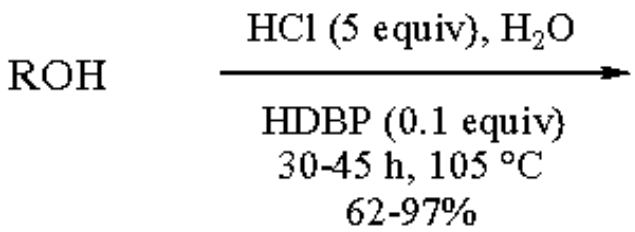

(7)

The cleavage of dialkyl and aryl alkyl ethers with concd. HBr is accelerated by HDBP.[20] Dialkyl ethers are converted into alkyl bromides (eq 8), whereas alkyl aryl ethers form phenols and alkyl bromides. Other catalysts have also been used.

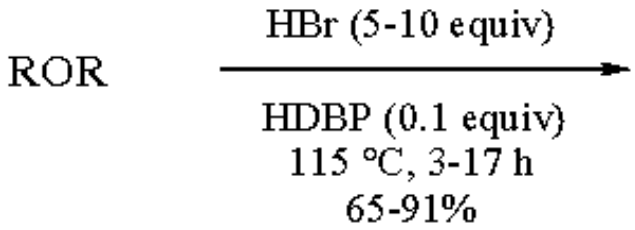

(8)

The addition of ***Chloramine-T*** to sulfides produces sulfilimines (eq 9);[20] other catalysts have also been used.[21] The selective oxidation of sulfides to sulfoxides by ***Sodium Periodate*** (eq 10)[22] has been achieved using HDBP. HDBP has been used in the conversion of alkyl halides or methanesulfonates into alkyl fluorides with aq ***Potassium Fluoride*** (eq 11).[23] Secondary alkyl halides undergo β-elimination in competition with substitution.

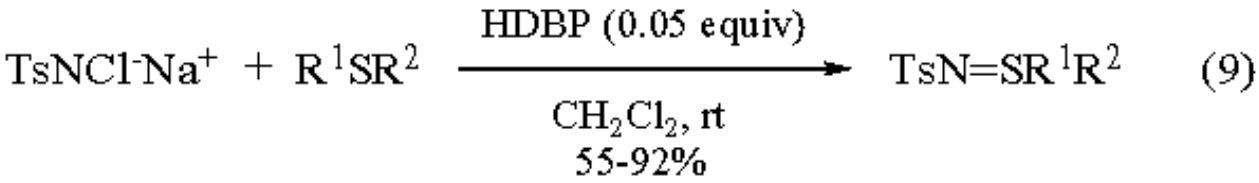

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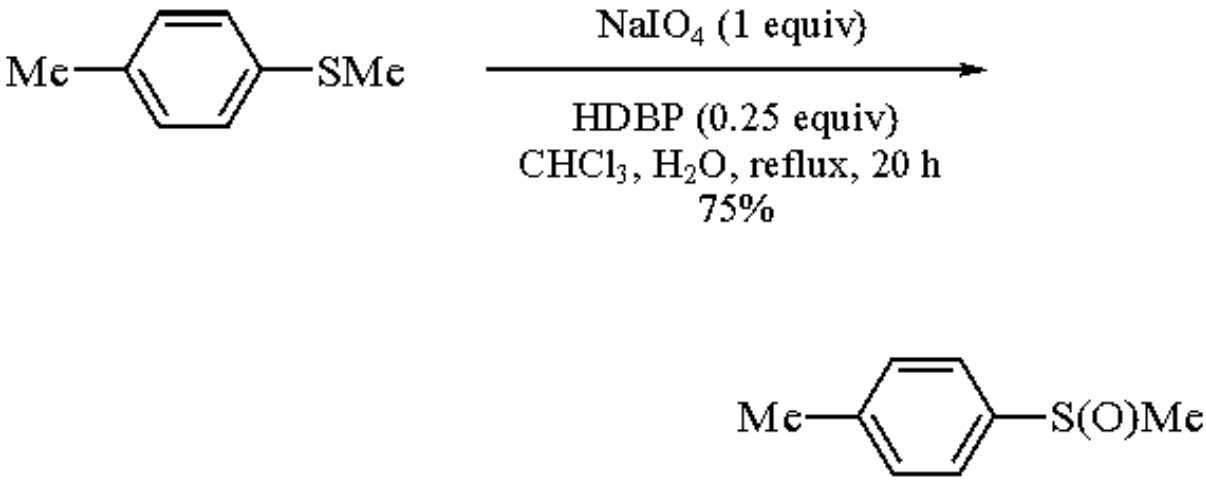

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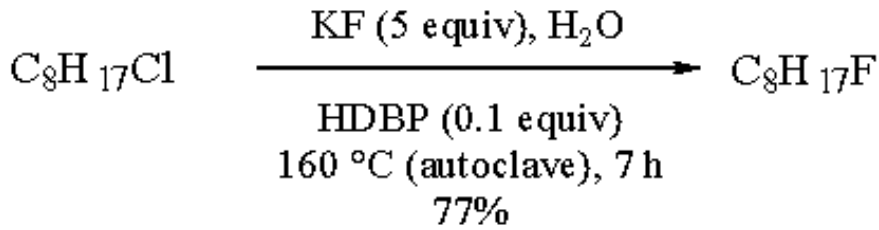

(11)

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Tri-*n*-butyl(iodoacetoxy)stannane[1]

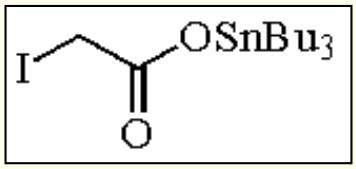

[73927-91-0] · $C_{14}H_{29}IO_2Sn$ · Tri-*n*-butyl(iodoacetoxy)stannane · (MW 475.04)

(γ-lactone preparation;[2] annulation)

Alternate Names: tributylstannyl iodoacetate; tributyl(iodoacetoxy)tin.

Physical Data: mp 94.4 °C.

Solubility: insol cold H_2O; sol THF, CH_2Cl_2, acetone, alcohol.

Preparative Method: [3] two equiv of iodoacetic acid and one equiv of ***Bis(tri-n-butyltin) Oxide*** are heated to 130 °C for 30 min. The cooled mixture is extracted with hot hexanes. The hexanes are removed in vacuo to afford tributyl(iodoacetoxy)tin. This preparation generates a product sufficiently pure for use in the reactions described below.

Handling, Storage, and Precautions: best results are obtained if the reagent is used within one week of the date of preparation. Use in a fume hood.

General Discussion.

Tributyl(iodoacetoxy)tin is readily prepared by the reaction of bis(tri-*n*-butyltin) oxide and iodoacetic acid.[3] This reaction has general applicability for the preparation of other halo esters and of higher homologs. By using this reagent in the presence of ***Azobisisobutyronitrile***, many alkenes can be converted into γ-lactones in a single step (eq 1). The reaction of tributyl(iodoacetoxy)tin with alkenes proceeds by way of a radical mechanism.[4] As illustrated in eq 2, the mechanism involves a radical chain reaction beginning with homolytic cleavage of the carbon-iodine bond followed by radical addition to the alkene. The reaction of the resulting radical with a molecule of tributyl(iodoacetoxy)tin followed by a rapid cyclization with concurrent loss of tributyliodotin completes the mechanism. Because of the electrophilic nature of the radical, this reaction proceeds well with electron-rich alkenes. Electron-deficient alkenes do not react.

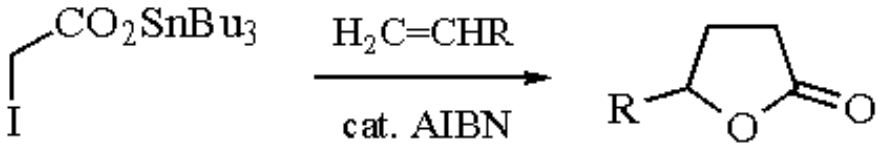

(1)

R = Bu, CH_2TMS, OEt, CH_2OH

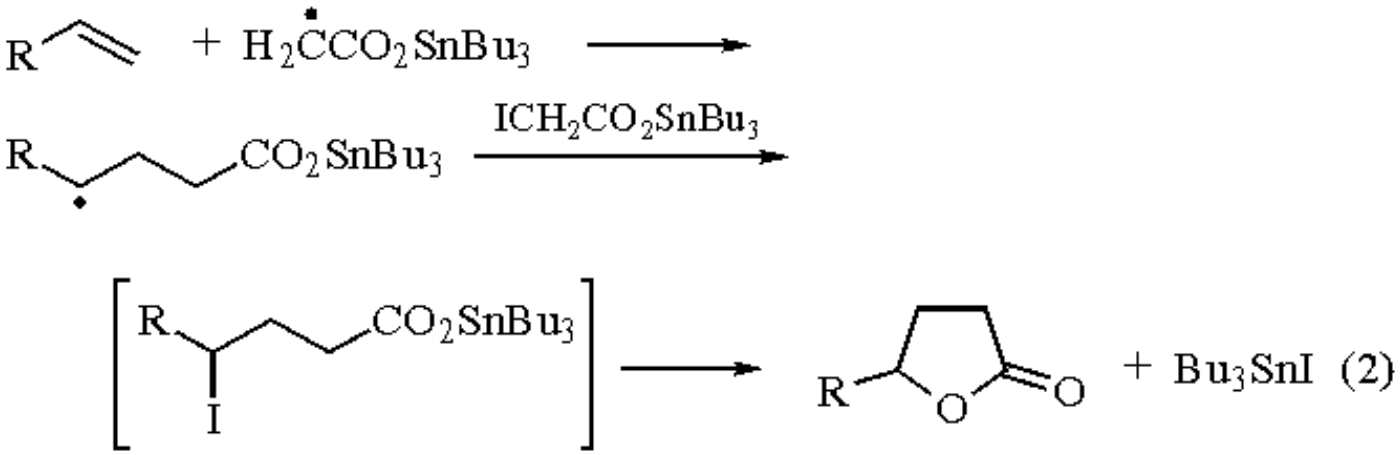

This reaction has been used for the preparation of a bicyclic furo[2,3-*b*]furan subunit (eq 3) in the synthesis of clerodane terpenes.[5] The intramolecular variant of this reaction has also been reported.[1] In this case a strained bicyclic lactone is formed in 40% yield (eq 4).

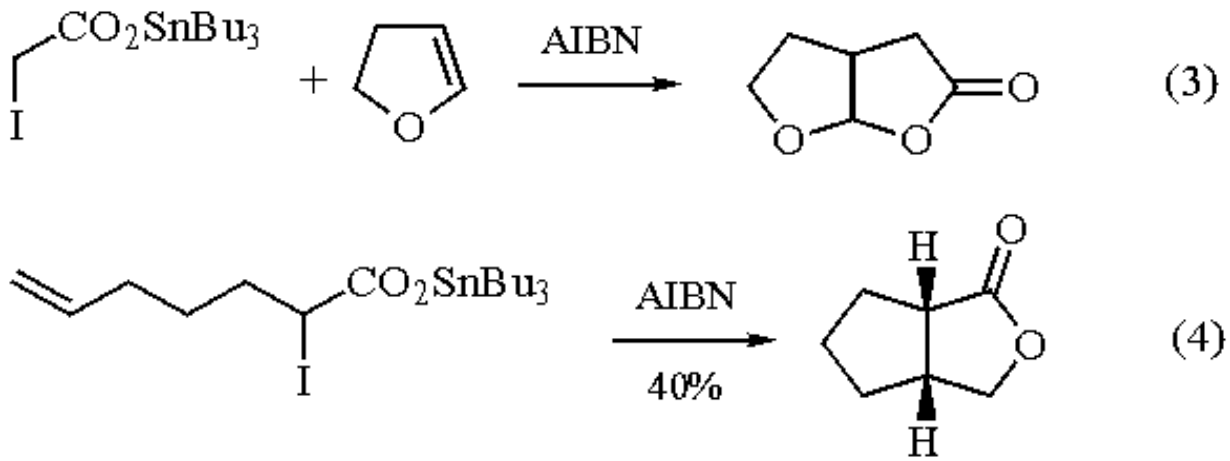

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Tri-*n*-butyl(iodomethyl)stannane

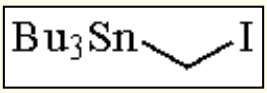

[66222-29-5] · $C_{13}H_{29}ISn$ · Tri-*n*-butyl(iodomethyl)stannane · (MW 431.03)

(preparation of (α-heteroalkyl)stannanes for subsequent tin-lithium exchange[1] or [2,3]-Wittig rearrangement;[2] preparation of (tri-*n*-butylstannyl)methyllithium[3])

Alternate Name: tributyl(iodomethyl)tin.

Physical Data: colorless liquid; bp 100-110 °C/0.01 mmHg.

Preparative Methods: prepared by treatment of ***Iodomethylzinc Iodide*** with ***Tri-n-butylchlorostannane***,[4] or by reaction of tri-*n*-butyl(chloromethyl)tin with NaI.[5]

Handling, Storage, and Precautions: potentially toxic; should be handled in a well ventilated hood.

General Discussion.

Tri-*n*-butyl(iodomethyl)tin (**1**) has been used extensively as an electrophile in the preparation of α-heteroalkylstannanes such as tri-*n*-butylstannylmethyl ethers,[2] *N*-acylated α-aminostannanes,[1] and *S*-stannylmethyl phosphinothioates.[6] Tri-*n*-butylstannylmethyl ethers of allylic alcohols undergo tin-lithium exchange and [2,3]-sigmatropic rearrangement upon treatment with ***n-Butyllithium***. For example, the stannylated ether (**2**) provides the homoallylic alcohol (**3**) with nearly exclusively the (*Z*) configuration (eq 1).[2]

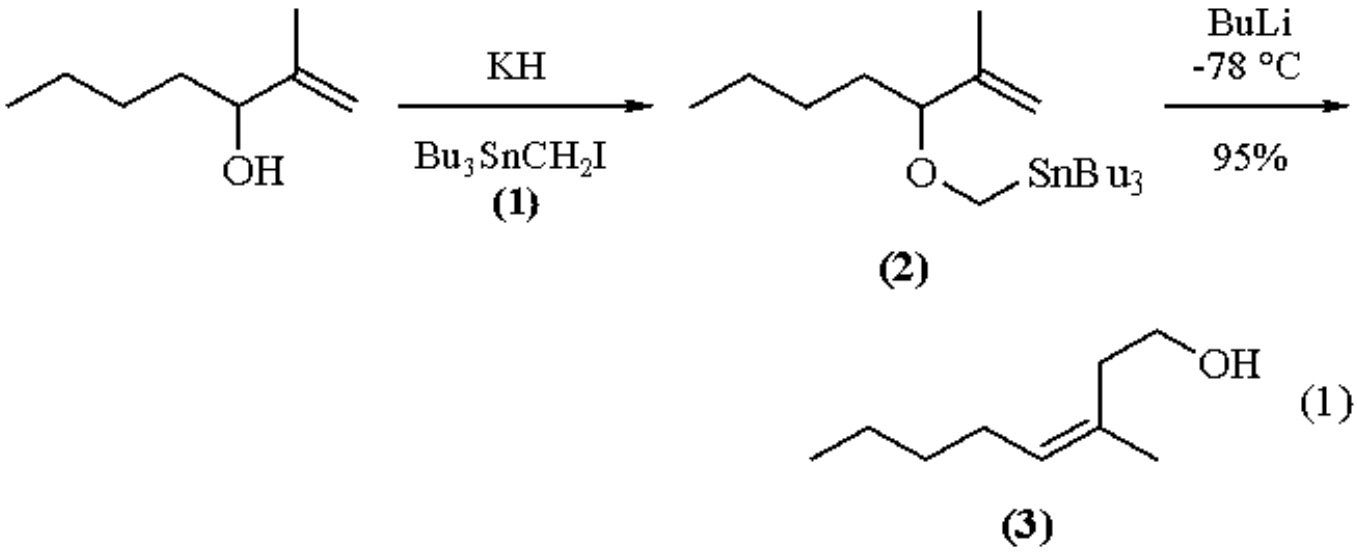

(1)

Diastereoselective [2,3]-Wittig rearrangements of this type have been reported.[7] This reaction sequence has been applied to the synthesis of alkene dipeptide isosteres,[8] as well as a number of natural products including (-)-punctatin A (eq 2).[9] The homoallylic (tri-*n*-butylstannyl)methyl ether (**4**) undergoes stereoselective anionic cyclization to the *cis*-2,4-disubstituted tetrahydrofuran (**5**) upon transmetalation with *n*-BuLi (eq 3).[10] Tin-lithium exchange of the oxazolidinone-derived α-aminostannane (**6**) generates nitrogen-substituted organolithium compounds which react with a variety of electrophiles (eq 4).[1]

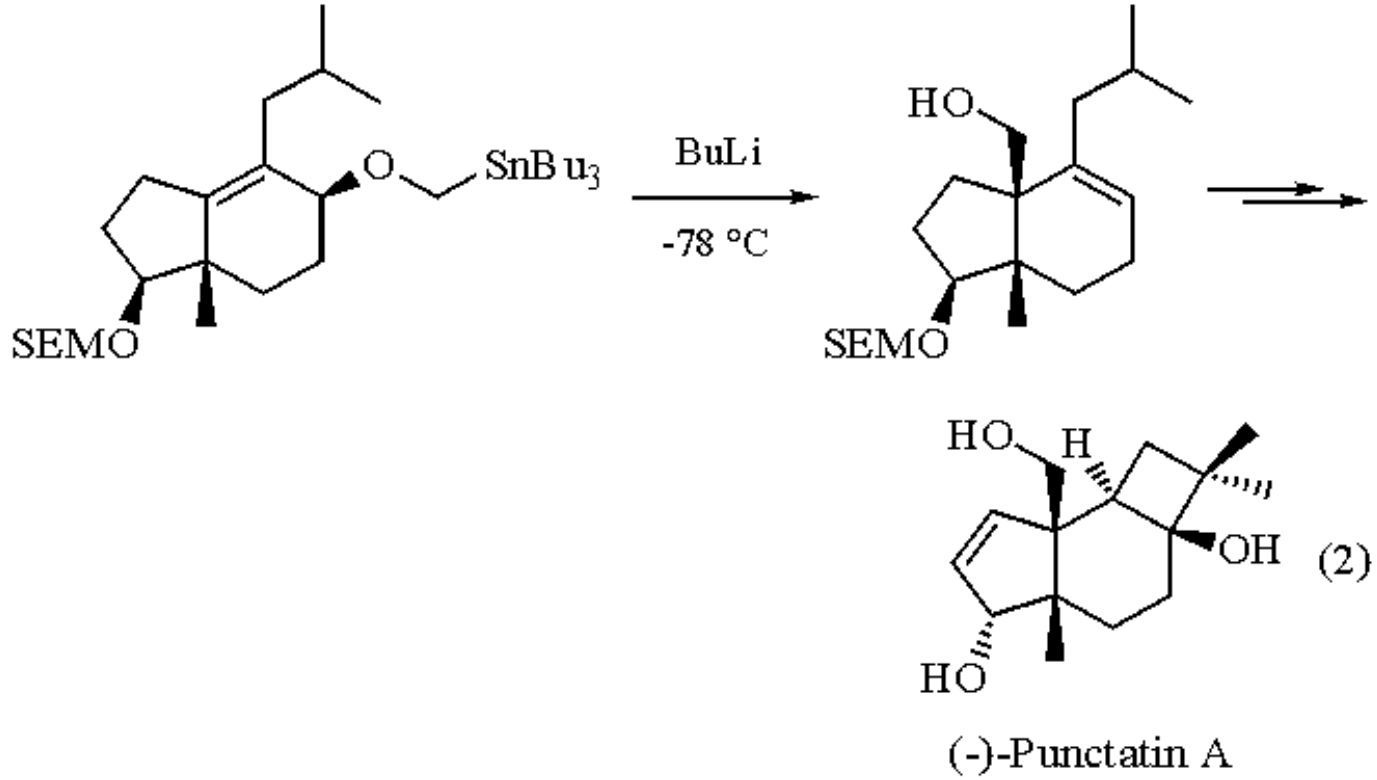

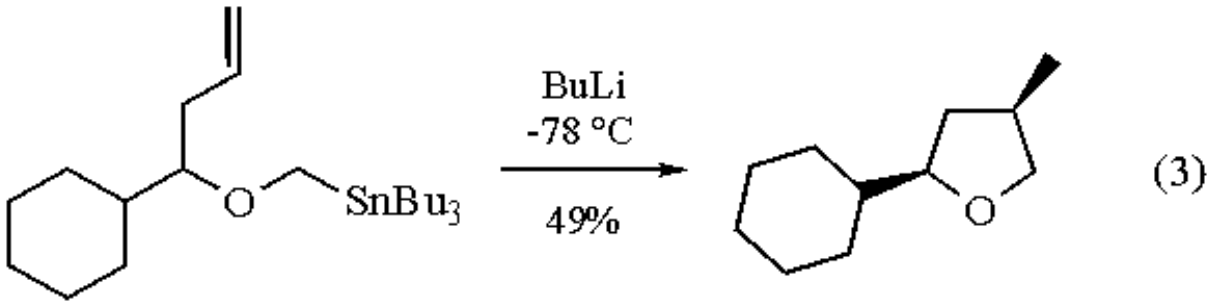

(4) **(5)**

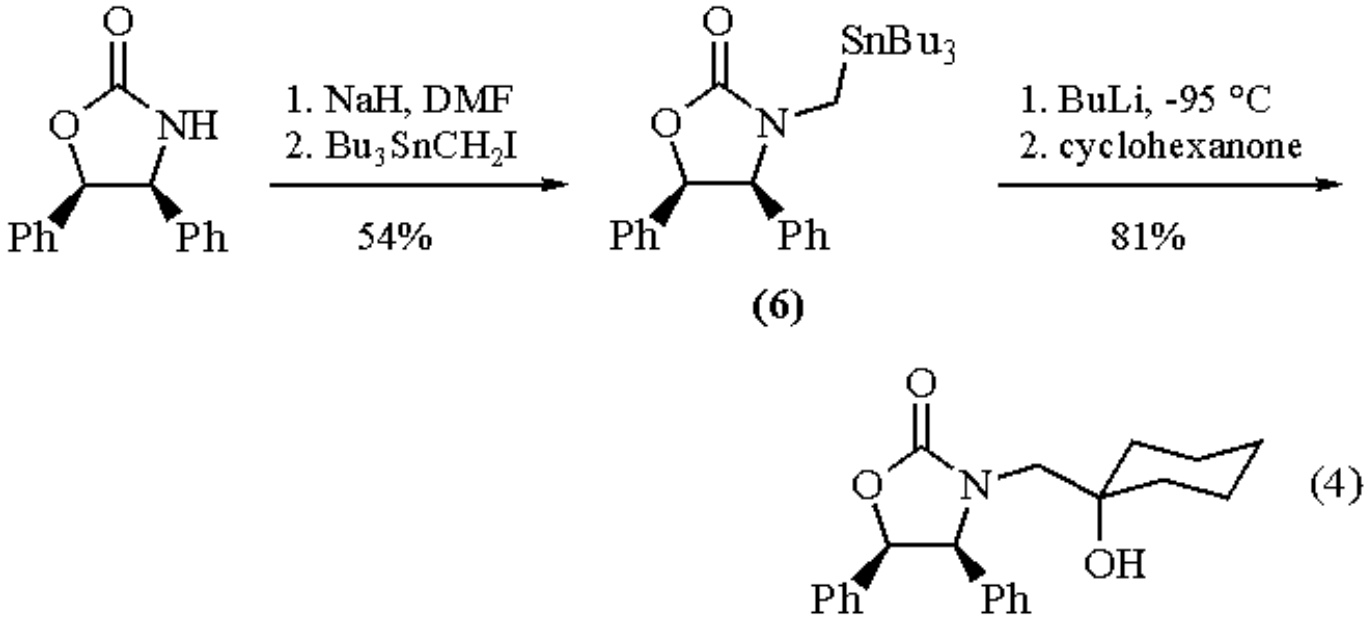

(6)

Tri-*n*-butyl(iodomethyl)tin is a useful reagent for the preparation of alkenes from sulfides,[11] sulfones,[12] and nitriles.[13] The moderately hindered sulfone (**7**) is converted to the corresponding exocyclic alkene by fluoride-induced desulfonylstannylation of (**8**) (eq 5).[14] Tri-*n*-butyl(iodomethyl)tin has also been used to prepare (tri-*n*-butylstannyl)methyllithium (**9**), which reacts with electrophiles as a methylene double anion equivalent.[15] For example, transmetalation of (**1**) using *n*-BuLi followed by addition of an ester generates the corresponding ketone enolate which may participate in aldol reactions (eq 6).

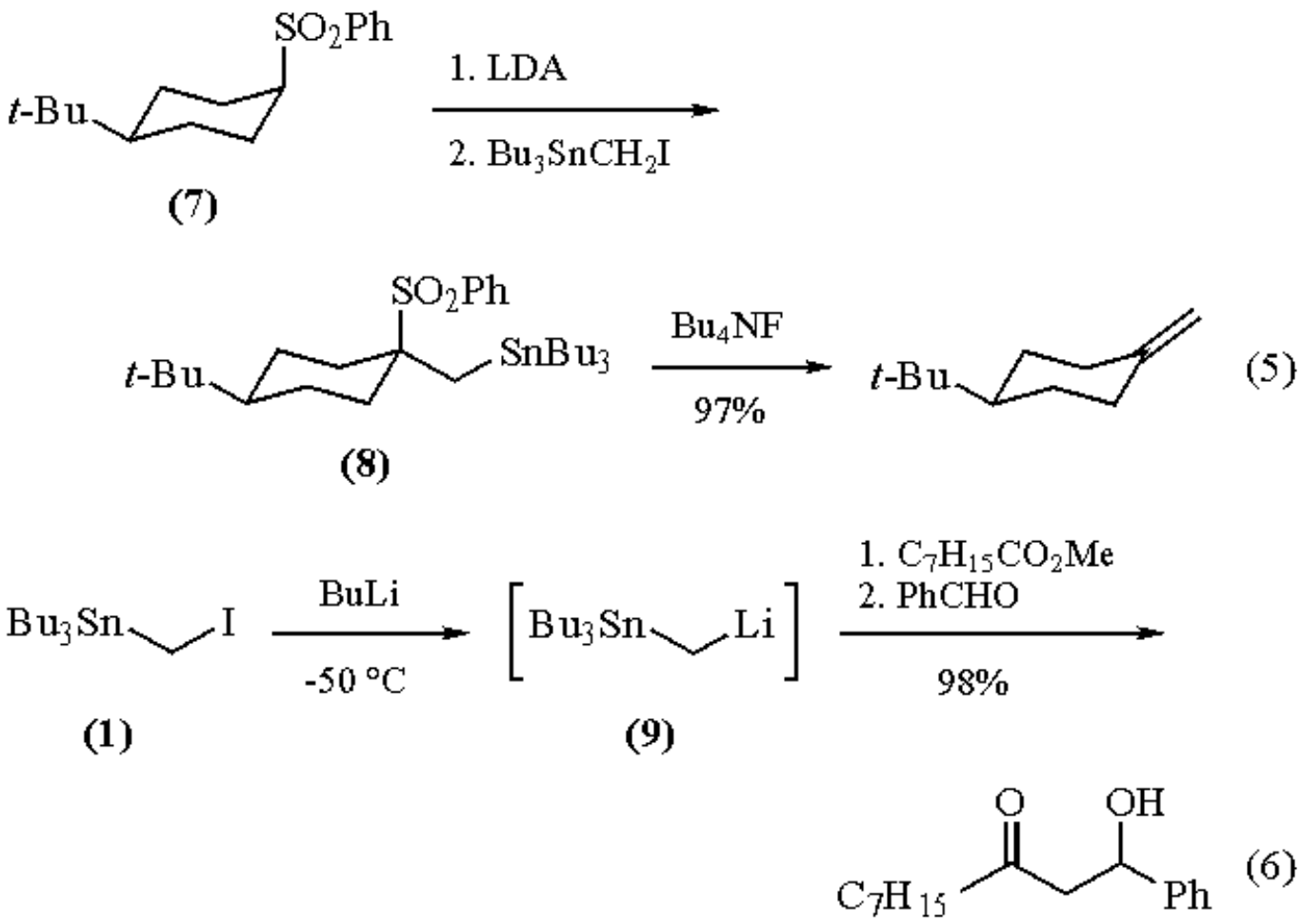

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Tri-*n*-butyl(1-methoxymethoxy-2-butenyl)stannane

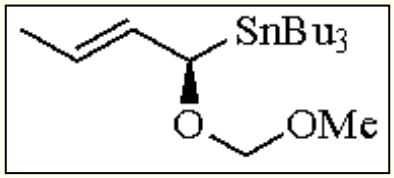

[84510-37-2] · $C_{18}H_{38}O_2Sn$ · Tri-*n*-butyl(1-methoxymethoxy-2-butenyl)stannane · (MW 405.27)

(allylation of aldehydes[1])

Alternate Names: α-methoxymethoxycrotylstannane; tributyl(1-methoxymethoxy-2-butenyl)tin.

Physical Data: colorless, odorless oil.

Solubility: sol CH_2Cl_2, THF, ether; insol H_2O.

Form Supplied in: not commercially available.

Preparative Methods: racemic forms can be prepared from ***Crotonaldehyde*** via addition of ***Tri-n-butylstannyllithium***, followed by protection of the resulting hydroxystannane with ***Chloromethyl Methyl Ether*** (MOM-Cl) and ***Diisopropylethylamine*** (eq 1).[1] Tributyl(1-benzyloxymethoxy-2-butenyl)tin can be similarly prepared.

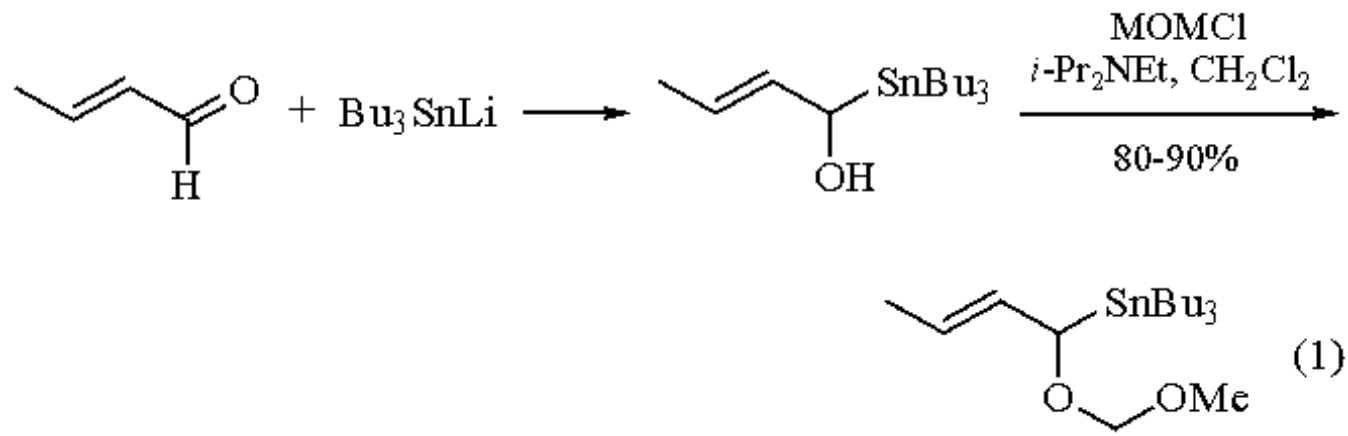

(1)

Optically enriched tributyl(1-methoxymethoxy-2-butenyl)tin can be prepared by asymmetric reduction of the corresponding acyltin, which is obtained by oxidation of the racemic hydroxystannane with ***1,1´-(Azodicarbonyl)dipiperidine*** (ADD) or DIAD (diisopropyl azodicarboxylate), (eq 2).[1,2] The reduction of acylstannanes by (*R*)-BINAL-H produces hydroxystannanes in the (*S*)-configuration in greater than 95% ee. The results of asymmetric induction for acylstannanes are different from those of normal ketones, i.e. the reduction of normal prochiral ketones by (*R*)-BINAL-H usually produces (*R*)-alcohols. This fact was explained by Marshall with the assumption of a pentacoordinated tin complex (**1**).[1] α-Ethoxy analogs can be prepared from diethoxymethyltributyltin via treatment with acetyl chloride, followed by a vinyl Grignard reagent (eq 3).[3]

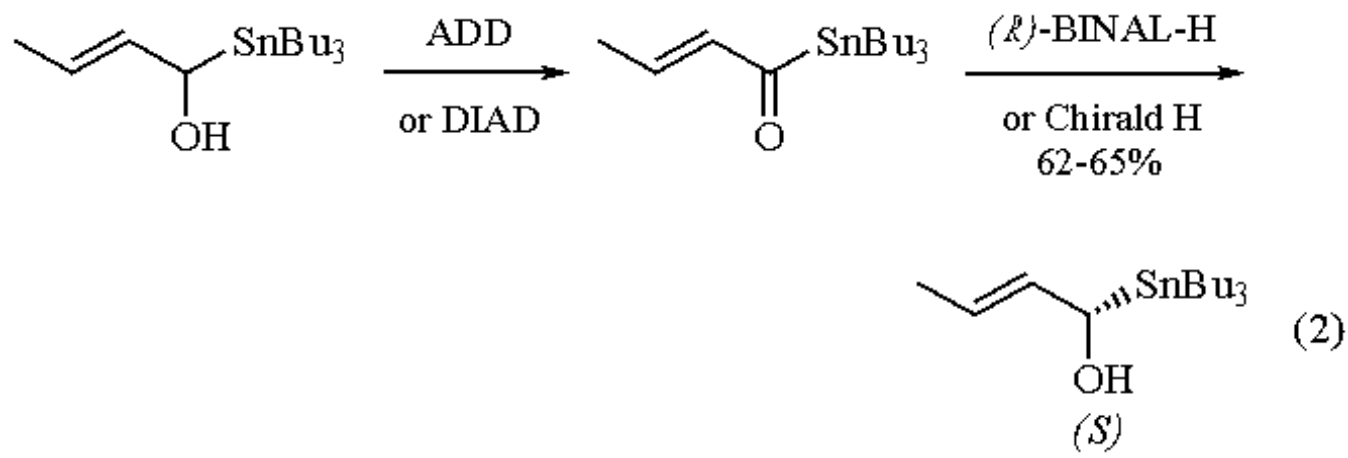

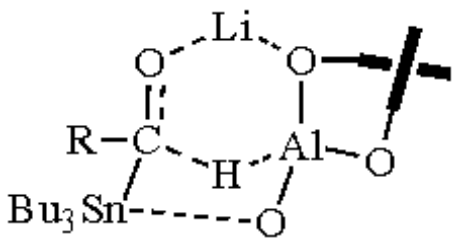

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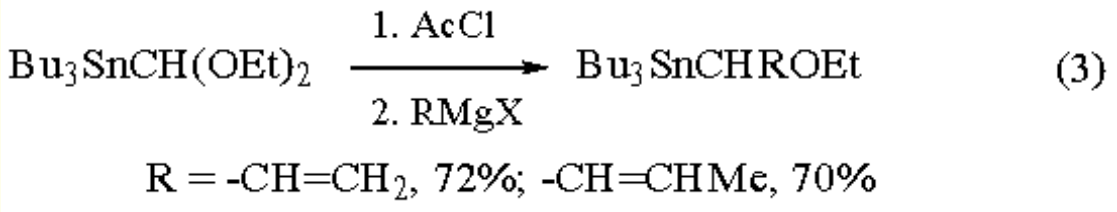

Handling, Storage, and Precautions: stable over a period of several months if stored in a refrigerator. However, decomposition occurs slowly if exposed to air at rt. It is recommended that tributyl(1-methoxymethoxy-2-butenyl)tins are freshly prepared before use.

Allylation of Aldehydes.

In the presence of ***Boron Trifluoride Etherate***, tributyl(1-methoxymethoxy-2-butenyl)tin undergoes facile addition to aldehydes via an SE´ mechanism (eqs 4 and 5).[1] The major product is the *syn*-(*E*)-isomer for aliphatic aldehydes. Comparable results can be achieved using tributyl(1-benzyloxymethoxy-2-heptenyl)tin (eq 6).

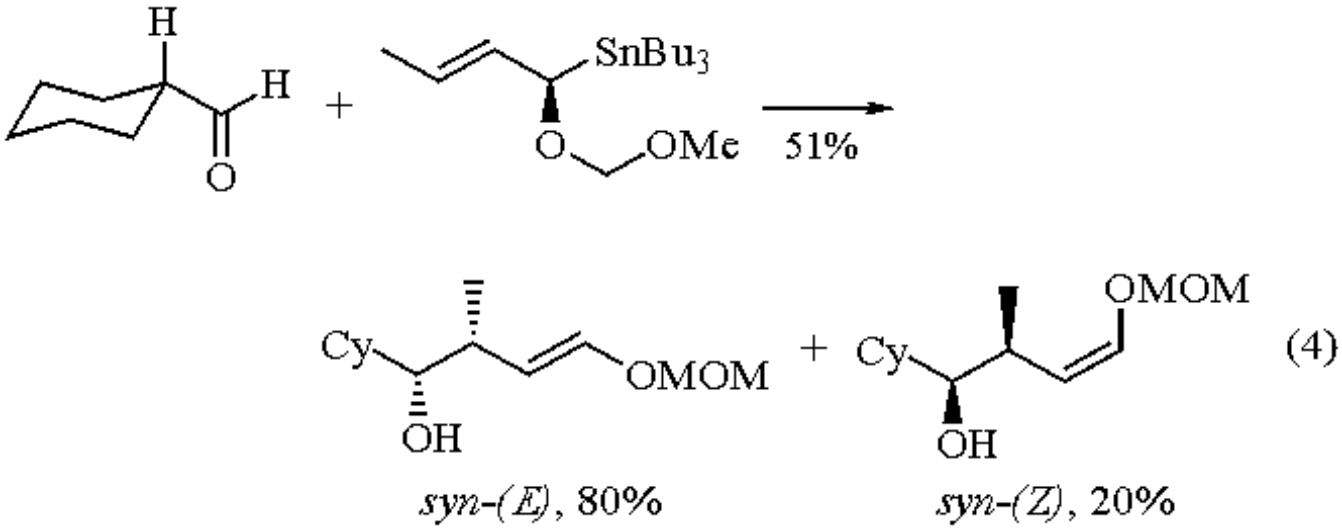

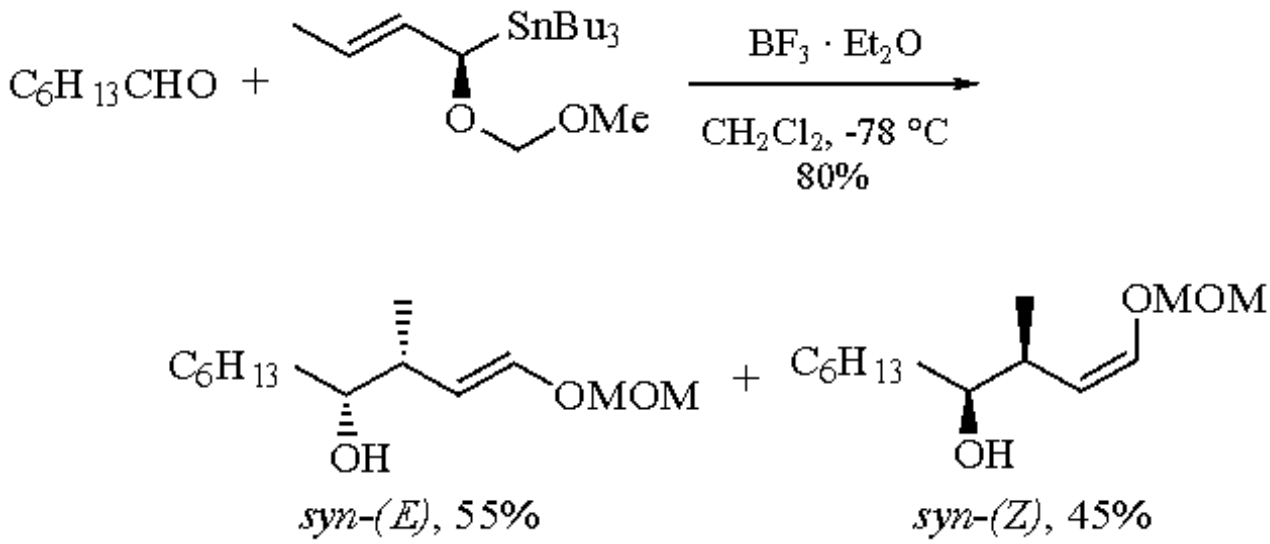

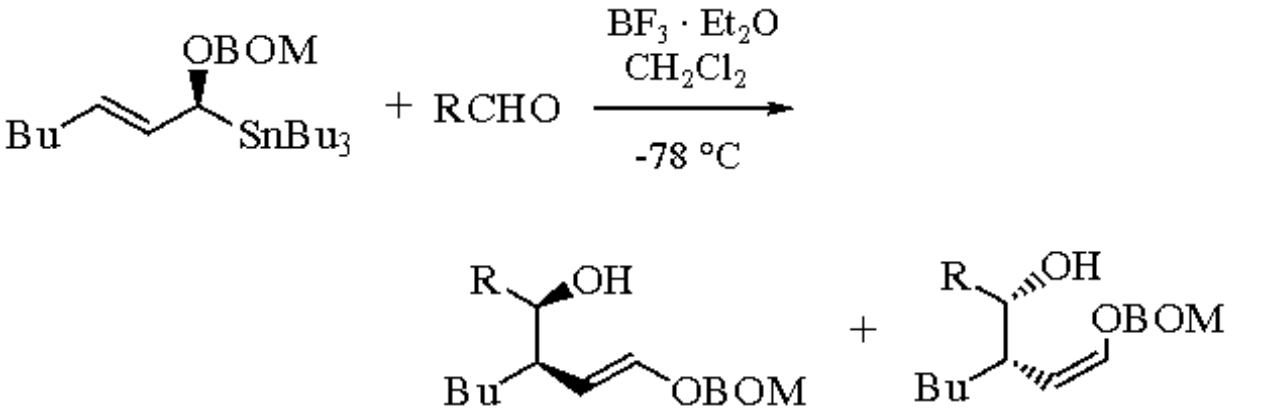

R	*syn-(E)*	*syn-(Z)*
C_6H_{13}	70	27
(E)-BuCH=CH	80	17
BuC≡C	51	25

In contrast, additions to aromatic aldehydes give products with almost exclusively *syn*-(*Z*) stereochemistry (eq 7).[4] The reactions occur through an SE´ mechanism with respect to the α-alkoxyallylstannanes. The aldehydes, when complexed to $BF_3.Et_2O$, are sufficiently electrophilic to attack the double bond of the allyltributyltin.

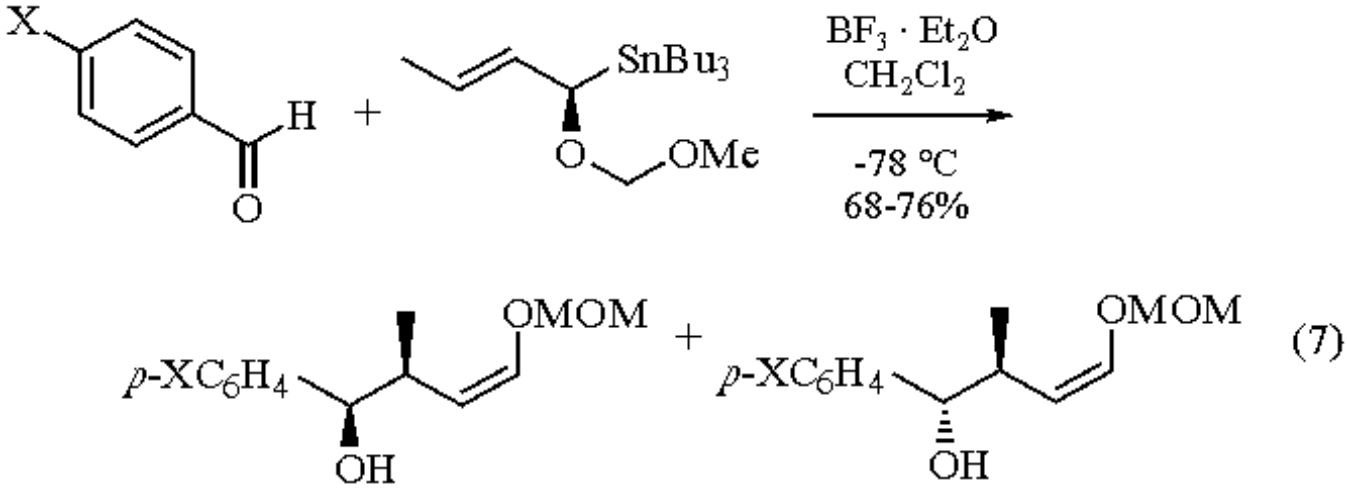

X	*syn-(E)*	*anti-(Z)*
H	>95%	<5%
Cl	>95%	<5%
NO_2	>95%	<5%

An important feature of the Lewis acid-catalyzed reaction is that the C-C bond formation occurs stereospecifically *anti* to the Bu_3Sn group of the allylic stannanes. This is consistent with steric and stereoelectronic principles.[5] Possible transition states producing the different results for aliphatic and aromatic aldehydes have been suggested (eqs 8 and 9).[4] Of the two favorable staggered transition states, aliphatic aldehydes slightly prefer the antiperiplanar arrangement in order to avoid gauche interactions between the methyl group and the R^1 group. In contrast, aromatic aldehydes prefer the synclinal arrangement due to their strong *anti* complexation with the Lewis acid.[6] In the antiperiplanar transition state, a *syn*-pentane interaction exists between the methyl group and the BF_3. While the loose complexation of aliphatic aldehydes with BF_3 tolerates this unfavorable interaction, the tight complexation of aromatic aldehydes with BF_3 prefers the synclinal arrangement. The synclinal arrangement allows the inside alkoxy alignment of the methoxymethoxy group. This conformation has been suggested to be favored in electrophilic additions to the allylic system.[7]

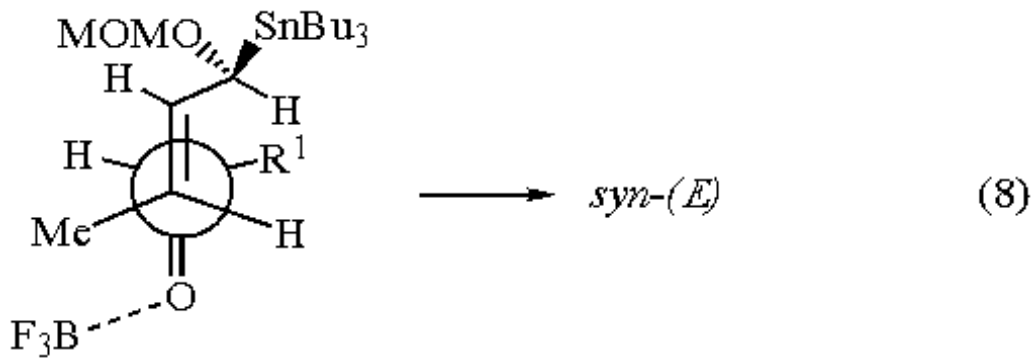

Antiperiplanar

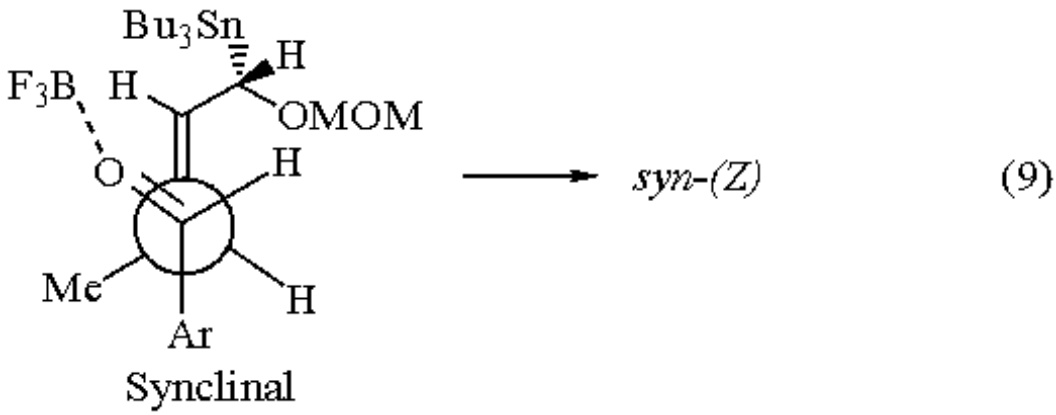

Synclinal

In the absence of a Lewis acid, high temperature is required to complete the reaction of an aldehyde with tributyl(1-methoxymethoxy-2-

butenyl)tin.[8] Based on the stereochemistry of the product, a cyclic transition state has been suggested for the thermal reactions (eq 10).

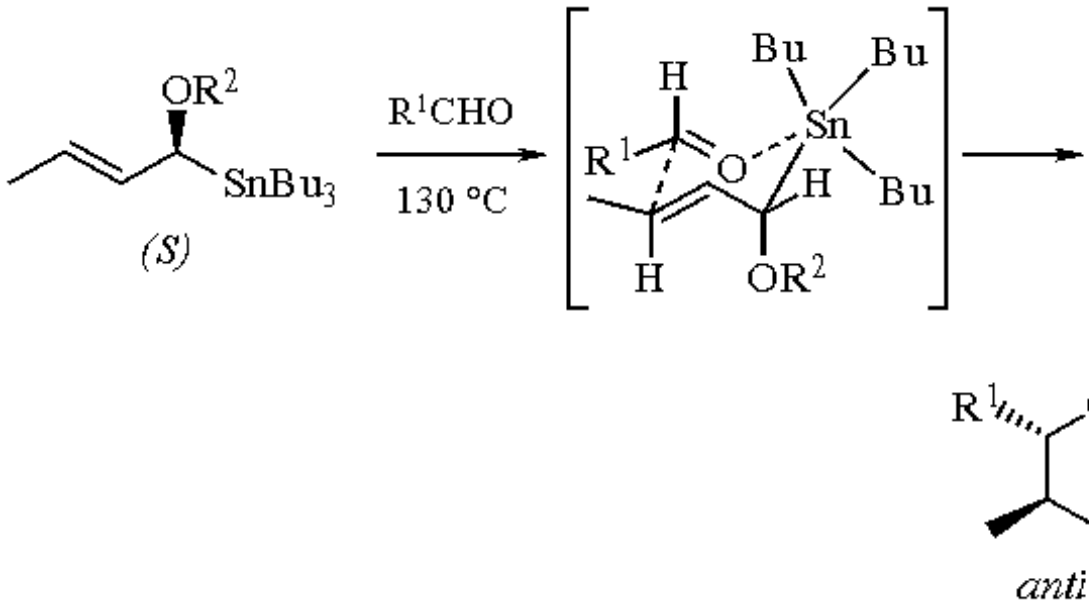

(10)

Intramolecular Allylations via α-Alkoxyallyltributyltins.

Because of the relative stability of α-alkoxyallyltributyltins towards the aldehyde function at room temperature, the intramolecular version of the allylation reactions has been applied to form macrocycles (eq 11).[2,9] These experiments are carried out under highly dilute conditions (ca. 0.001 M). A solution of the substrate (an α-alkoxyallyltributyltin aldehyde) is added dropwise to a solution of $BF_3.Et_2O$ in CH_2Cl_2 over several hours. Usually, the reaction is completed when the addition is finished. Consistent high yields are obtained with the substrate shown in eq 11. Several members of the cembranolide family of natural products have been synthesized using this strategy.[2]

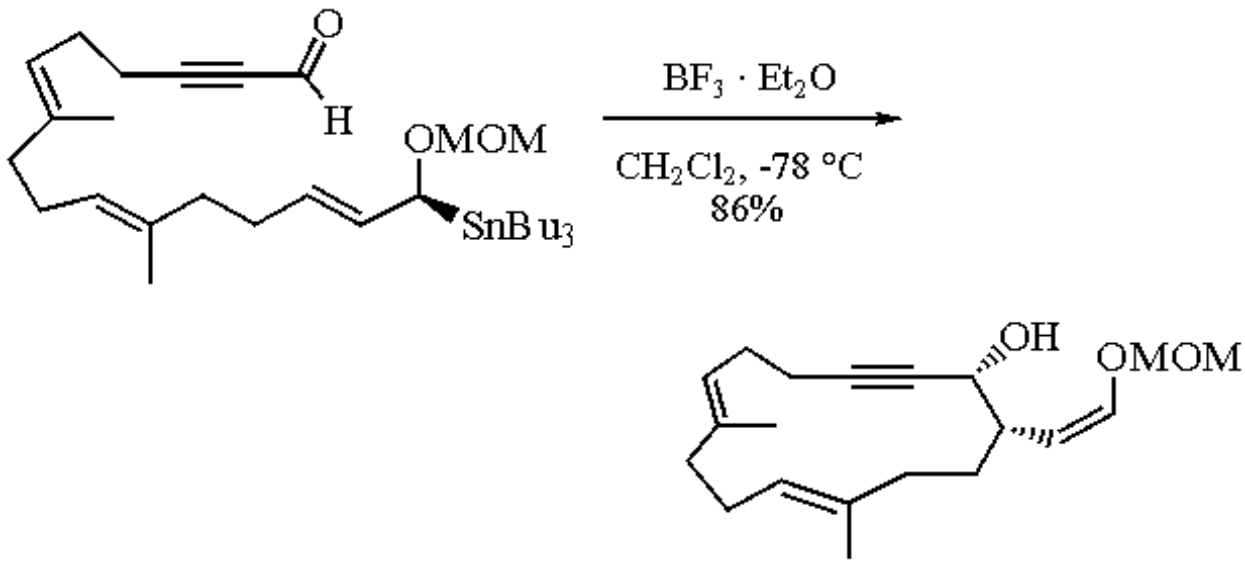

(11)

Isomerization of Tributyl(1-methoxymethoxy-2-butenyl)tins.[11]

Treatment of (*S*)-tributyl(1-methoxymethoxy-2-butenyl)tin with $BF_3.Et_2O$ at -78 °C leads to a facile 1,3-stereospecific isomerization to produce (*S*)-(γ-methoxymethoxyallyl)tin (eq 12). Mechanistic studies of the rearrangement have shown that the 1,3-tin migration is intermolecular.[10,11] The product of the 1,3-isomerization is a useful reagent for the enantioselective synthesis of carbohydrates.[12]

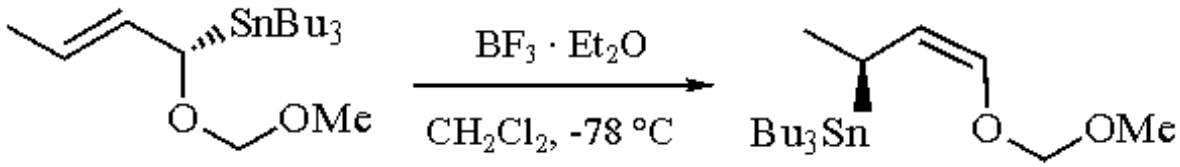

(12)

Double Diastereofacial Differentiation.

Although the π-facial selectivity of the allylation by tributyl(1-methoxymethoxy-2-butenyl)tin is only moderate on aliphatic aldehydes (eqs 4 and 5), much greater selectivity can be achieved by using α-chiral aldehydes. Excellent π-facial selectivity is obtained when matched pairs of α-chiral aldehydes and (1-methoxymethoxy-2-butenyl)stannanes are allowed to react (eq 13).[13] On the other hand, poor selectivity is observed when mismatched pairs are the reacting partners (eq 14).

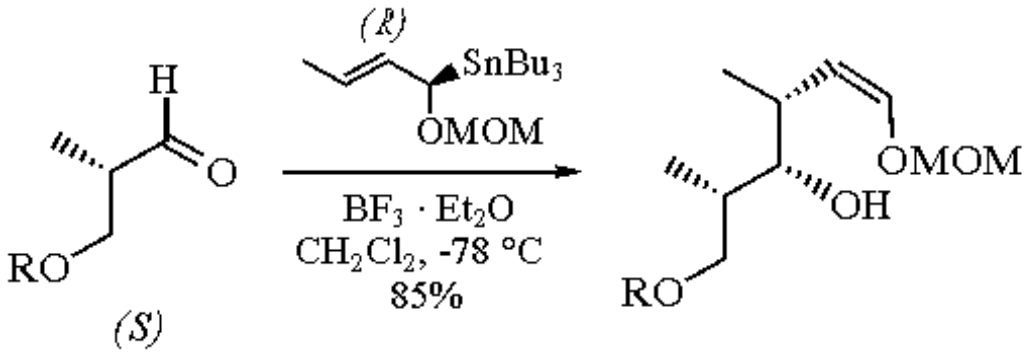

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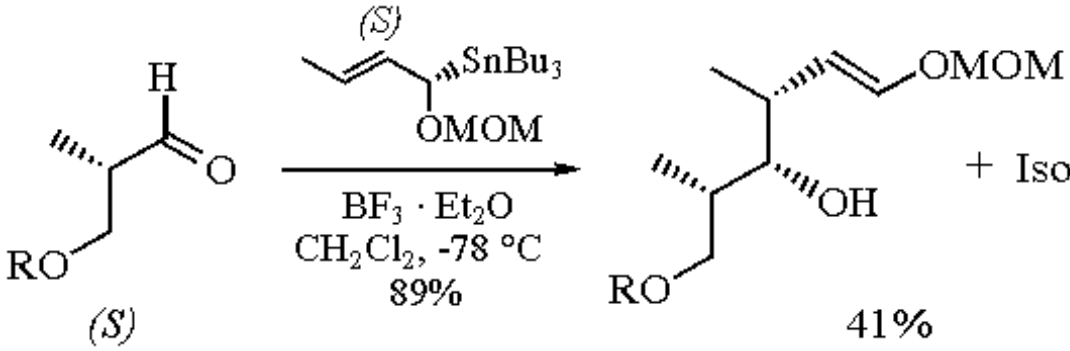

(14)

+ Isomeric adducts 48%

Kinetic Resolution.

When a racemic mixture of tributyl(methoxymethoxy-2-butenyl)tin is allowed to react with an optically pure α-chiral aldehyde, a single adduct can be isolated along with the recovery of enantiomerically enriched (γ-methoxymethoxyallyl)tin (eq 15).[13] The (*S*)-enantiomer of the allylstannane reacts much faster than the (*R*)-enantiomer with the α-chiral aldehyde to produce the adduct. The (*R*)-enantiomer rearranges to give the (*R*)-(γ-methoxymethoxyallyl)tin (eq 16).

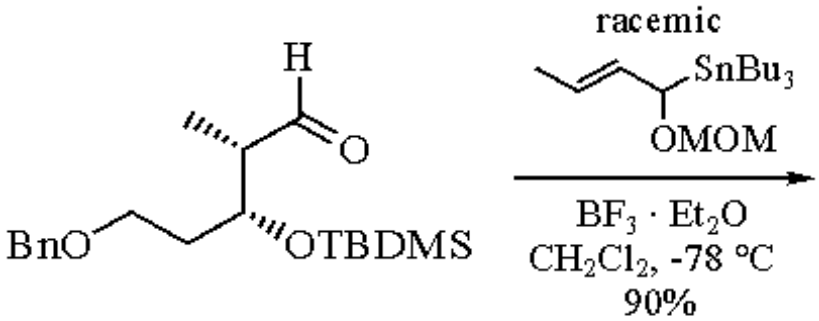

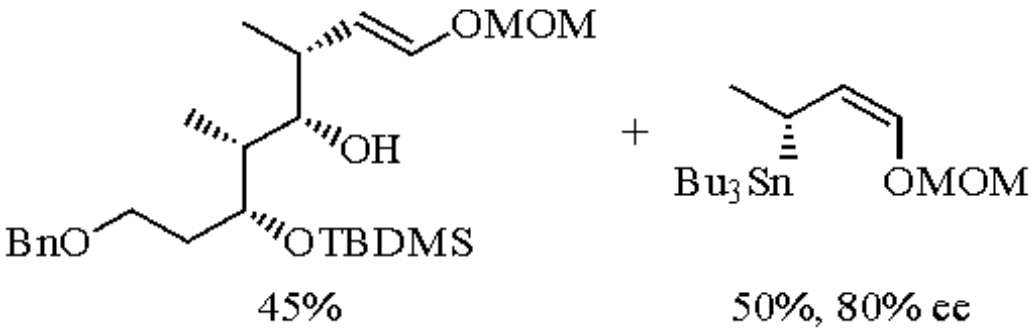

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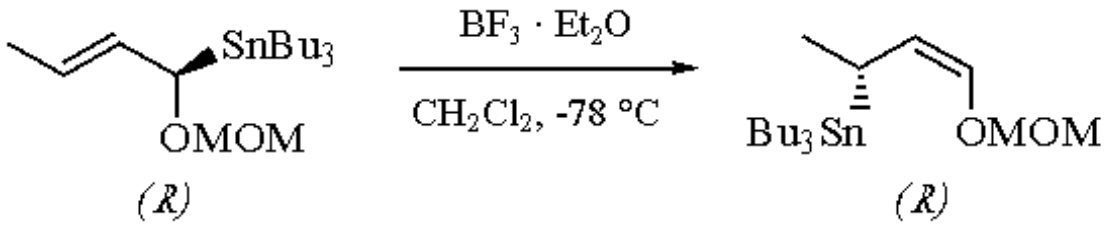

(16)

Summary.

The allylation of aldehydes using tributyl(1-methoxymethoxy-2-butenyl)tin leads to adducts with two new stereocenters. These reactions proceed under mild conditions and in high yields. The stereochemistry of the products can be predicted by controlling the reaction conditions and substrate structures. BF_3-catalyzed additions are highly *syn* selective. In contrast to many other allylic metallic reagents, (1-alkoxyallyl)stannanes are stable and isolable intermediates, making the intramolecular version of the allylation reaction practical.

---

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Tri-*n*-butyl[(methoxymethoxy)methyl]stannane

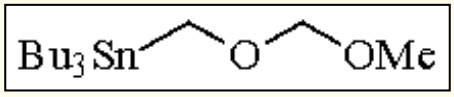

[100045-83-8] · $C_{15}H_{34}O_2Sn$ · Tri-*n*-butyl[(methoxymethoxy)methyl]stannane · (MW 365.20)

(hydroxymethyl anion equivalent[1])

Physical Data: bp 117 °C/0.34 mmHg.

Solubility: sol THF.

Analysis of Reagent Purity: by gas chromatographic analysis on a 0.25 mm × 30 m DB-1701 fused silica capillary column, 12 psi column pressure, 120-250 °C at 10 °C/min, then 250 °C; retention time: 13.1 min. ^{1}H NMR (300 MHz CD-Cl_3): δ 0.8-1.1 (m, 15H), 1.2-1.7 (m, 13H), 4.02 (d, 2 H, *J* = 4.5 Hz).

Preparative Methods: the most convenient preparation involves the two-step procedure outlined in eq 1.[2] The first step involves the addition of ***Tri-n-butylstannyllithium*** to ***Paraformaldehyde*** as described by Still.[2,8] In the second step, methoxymethylation is achieved via acetal exchange with ***Dimethoxymethane***, promoted by ***Boron Trifluoride Etherate*** and ***Molecular Sieves***.[2,6] This procedure provides the desired reagent in higher yields compared to an alternative procedure which uses ***Phosphorus(V) Oxide*** to promote the acetal exchange step.[9] This method is also superior to an alternative approach which involves alkylation of (tributylstannyl)methanol with ***Chloromethyl Methyl Ether***.[10]

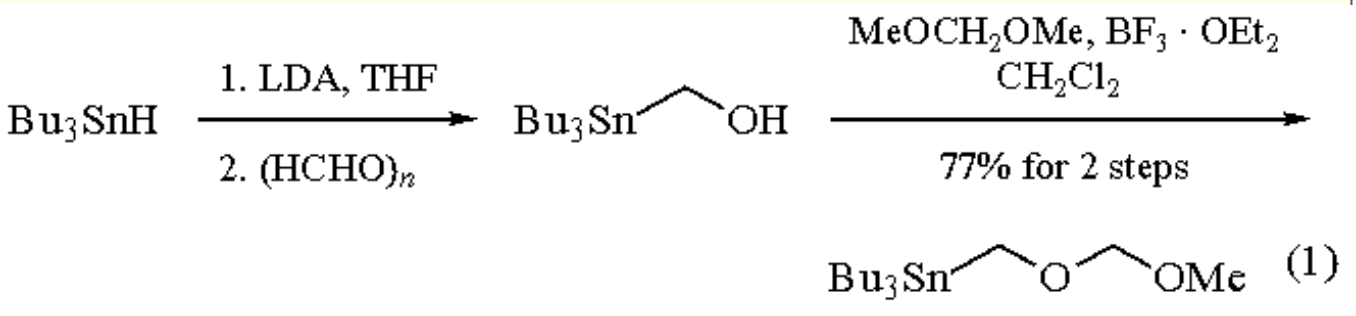

Purification: by filtration through alumina followed by distillation.[2]

Handling, Storage, and Precautions: as with all organostannanes, precautions should be taken to avoid all contact with tributyl[(methoxymethoxy)methyl]stannane. The reagent should be handled in a fume hood. The reagent can be stored neat in a freezer under nitrogen for several months.

Addition to Carbonyl Compounds.

Tributyl[(methoxymethoxy)methyl]stannane undergoes tin-lithium exchange with ***n-Butyllithium*** to generate the organolithium intermediate (**1**), a hydroxymethyl anion equivalent. (**1**) adds to ketones to form monoprotected 1,2-diols in very good yield (eq 2), and the acetal protective group can be removed under mild acidic conditions (eq 3).[1] This stannane reagent complements the (isopropoxydimethylsilyl)methyl group as a hydroxymethyl anion equivalent, since the latter group is converted to alcohol using oxidative basic conditions.[3]

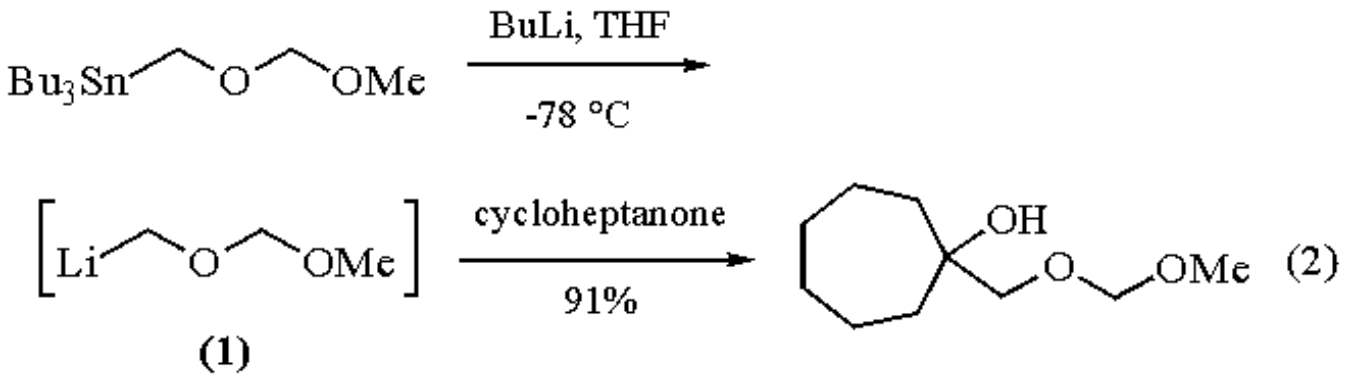

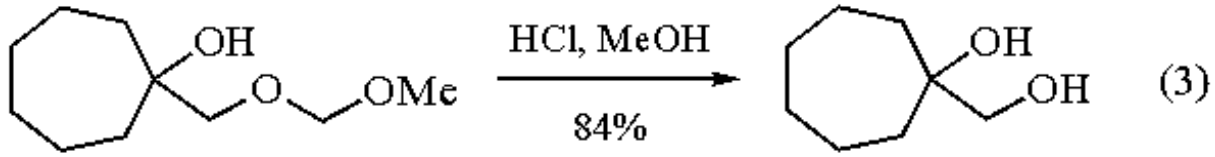

The stannane reagent has been added to a variety of carbonyl compounds. Aldehydes[4] and lactones[5] react with (**1**) in a manner analogous to the ketone example above. Other substrates include β-alkoxy enones (eq 4)[6] and α,β-unsaturated carbonyl compounds.[7] In the latter case, the intermediate tertiary alcohol formed by 1,2-addition of (**1**) is converted by oxidation to a 3-substituted α,β-unsaturated enone (eq 5).

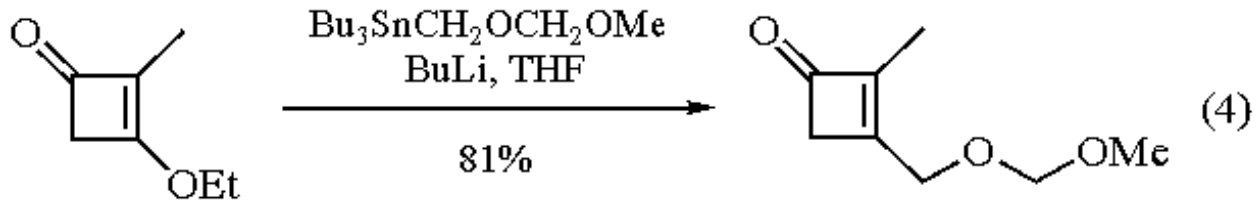

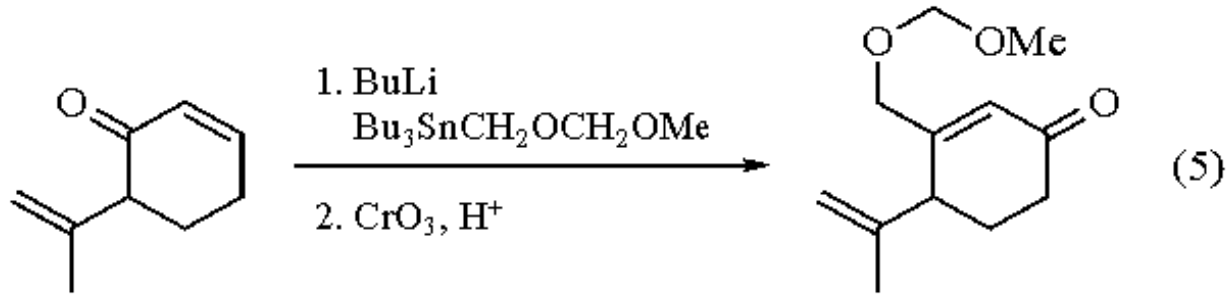

In synthetic work, tributyl[(methoxymethoxy)methyl]stannane is preferred over the closely related (ethoxyethylmethyl)tributylstannane developed earlier by Still.[8] Since the MOM ether reagent does not contain a chiral center, the formation of diastereomeric intermediates is avoided.

Related Reagents.

t-Butoxymethyllithium.

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1. Johnson, C. R.; Medich, J. R.; Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. K. *OS* **1992**, *71*, 140.
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Tri-*n*-butyl(methoxy)stannane[1]

***n*-Bu_3SnOMe**

[1067-52-3] · $C_{13}H_{30}OSn$ · Tri-*n*-butyl(methoxy)stannane · (MW 321.14)

(mild methoxide source with strong nucleophilic properties but with reduced basicity, making it less likely to induce elimination reactions; precursor to other alkoxytributylstannanes)

Alternate Names: tributyltin methoxide; methoxytributylstannane.

Physical Data: bp 90 °C/0.1 mmHg; *d* 1.129 g cm^{-3}; ^1H NMR ($CDCl_3$) 3.54 ppm (OMe); ^{119}Sn NMR 83 ppm.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: toxic, as are most organotin reagents; should be manipulated in a fume hood and handled with gloves. Readily hydrolyzable, it must be stored in the absence of moisture and CO_2. Exposure to moist air leads to hexabutyldistannoxane and tributylstannyl carbonate.

Introduction.

This reagent can be used in substitution, oxidation, or addition reactions. It is also employed as a catalyst for urethane, polylactone, polylactide, and polycarbonate synthesis.

Substitution Reactions.

Methoxytributylstannane and related compounds react with acyl chlorides or anhydrides to give esters under very mild conditions (eq 1).[2] This smooth reaction is particularly useful in carbohydrate chemistry.[1d]

$$Bu_3SnOMe + RCOX \xrightarrow{-Bu_3SnX} RCO_2Me \qquad (1)$$

$$X = Cl, OCOR$$

Methoxytributylstannane is also useful for the preparation of peresters, as reactive stannyl peroxide intermediates are quantitatively obtained from the corresponding hydroperoxides.[3] Methoxytriethylstannane can be used under palladium catalysis to give aryl esters from aryl iodides and carbon monoxide (eq 2).[4]

$$ArI + CO + Et_3SnOMe \xrightarrow[-Et_3SnI]{PhPdI(PPh_3)_2} ArCO_2Me \qquad (2)$$

These esterifications have been generalized to organosulfur and organophosphorus chemistry. With sulfenyl chlorides,[5] Bu_3SnOMe gives access to sulfenates in better yields than does ***Sodium Methoxide*** (eq 3). *O*-Alkyl *S*,*S*-diaryl phosphorodithioates are converted to *O*,*O*-dialkyl *S*-aryl phosphorothioates (eq 4)[6] and dinucleoside *S*-aryl phosphorothioates give dinucleoside *O*-methyl phosphates (eq 5).[7]

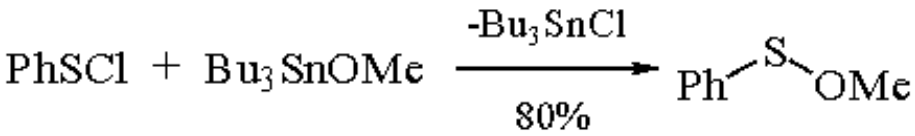

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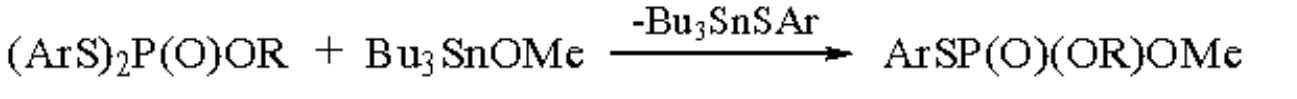

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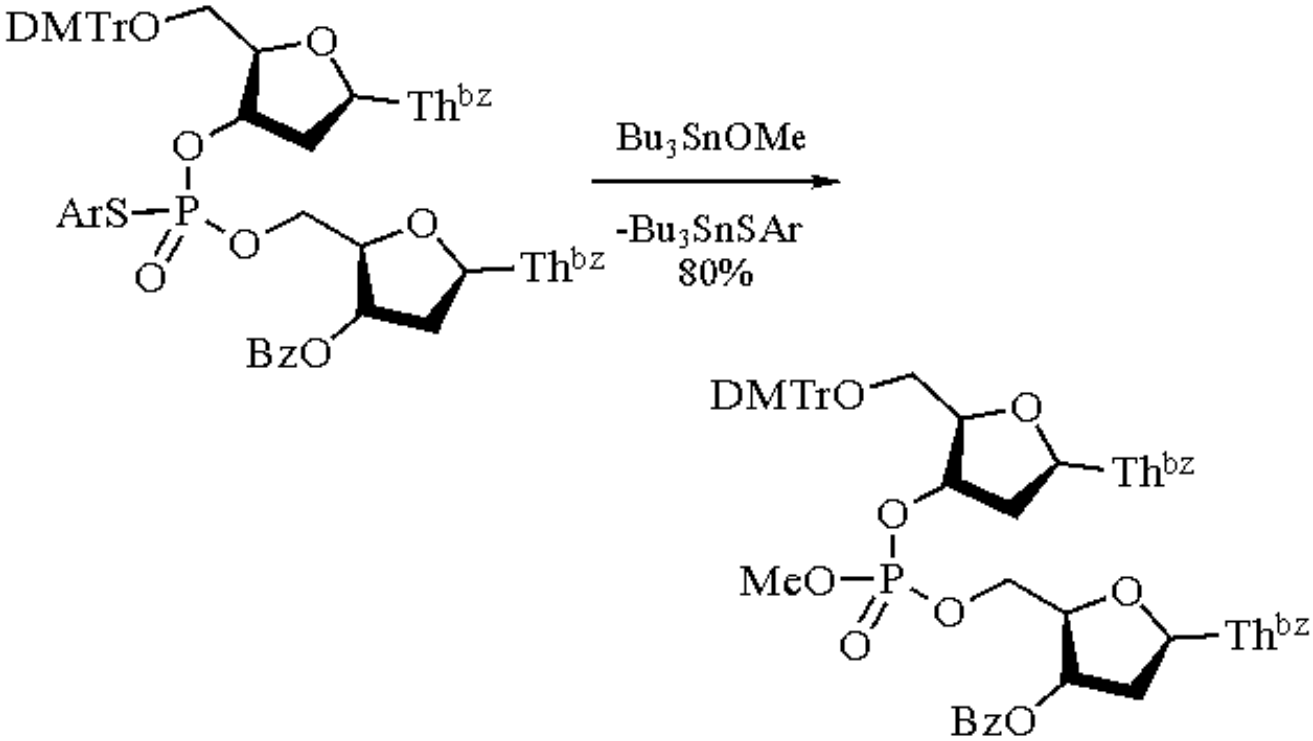

(5)

In the presence of ***Lithium Chloride*** as an activating agent, methoxytributylstannane promotes mild, chemoselective debenzoylations. Thus debenzoylation of 7,13-diacetylbaccatin III (a precursor of taxol) occurs only at C-2 (eq 6). In a highly polar solvent, NMP, none of the four other acyl groups is affected to any appreciable extent.[8] *O*-Deacetylation of sugars is readily accomplished with methoxytributylstannane. Anomeric acetates are more reactive than primary or secondary acetates, thereby enabling selective removal.[9]

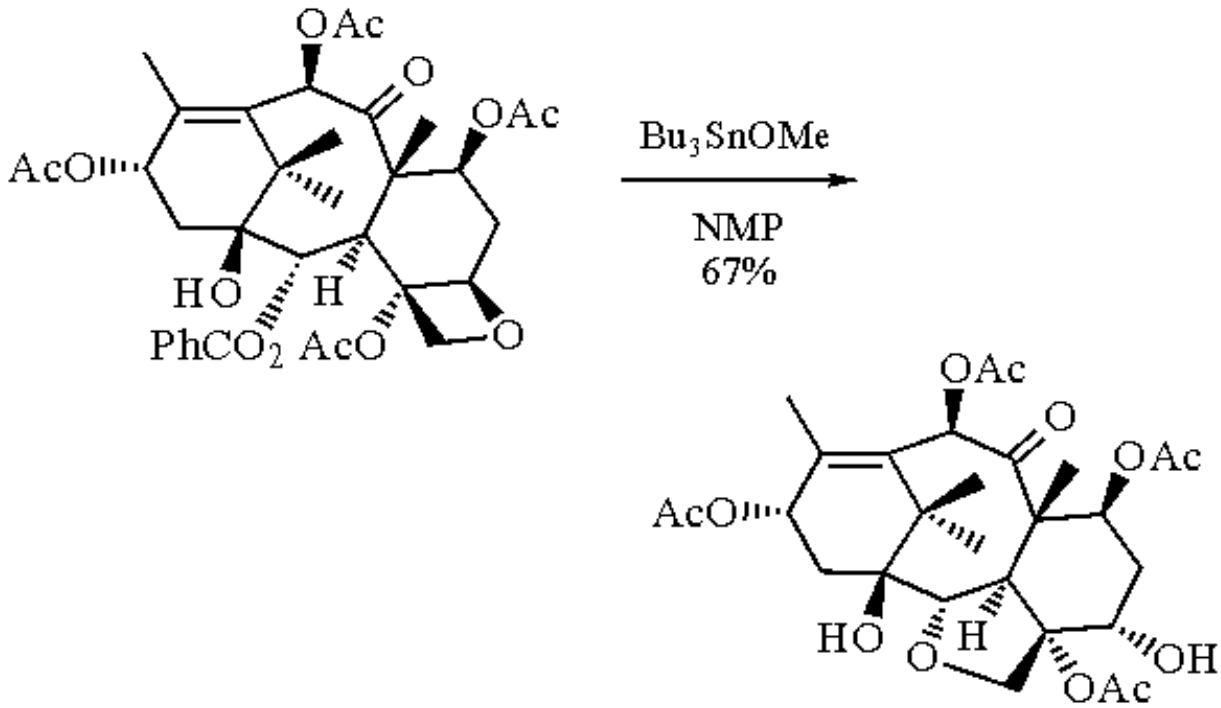

(6)

Dioxybis(tributylstannane), prepared from methoxytributylstannane and ***Hydrogen Peroxide***, allows the preparation of primary, secondary, and tertiary dialkyl peroxides from the corresponding triflates in good yields.[10]

The modulation of the nucleophilicity of an alkoxy group by the tin atom is particularly useful in methoxylation reactions,[11] where the absence of base even allows the use of base sensitive halides (eq 7).

$$Bu_3SnOMe + RX \longrightarrow ROMe + Bu_3SnX \qquad (7)$$

Alkyl glycosides can be prepared by using alkoxytributylstannanes. Per-*O*-acetyl-α-D-glucopyranosyl bromide reacts with methoxytributylstannane in the presence of catalytic amounts of ***Tin(IV) Chloride*** to give methyl per-*O*-acetyl-β-D-glycoside (eq 8). Replacement of tin(IV) chloride by 0.5 equiv of triethylammonium bromide completely changes the course of the reaction; epimerization to the more reactive β-anomeric configuration occurs during the reaction, affording an *exo*-orthoester (eq 9).[12]

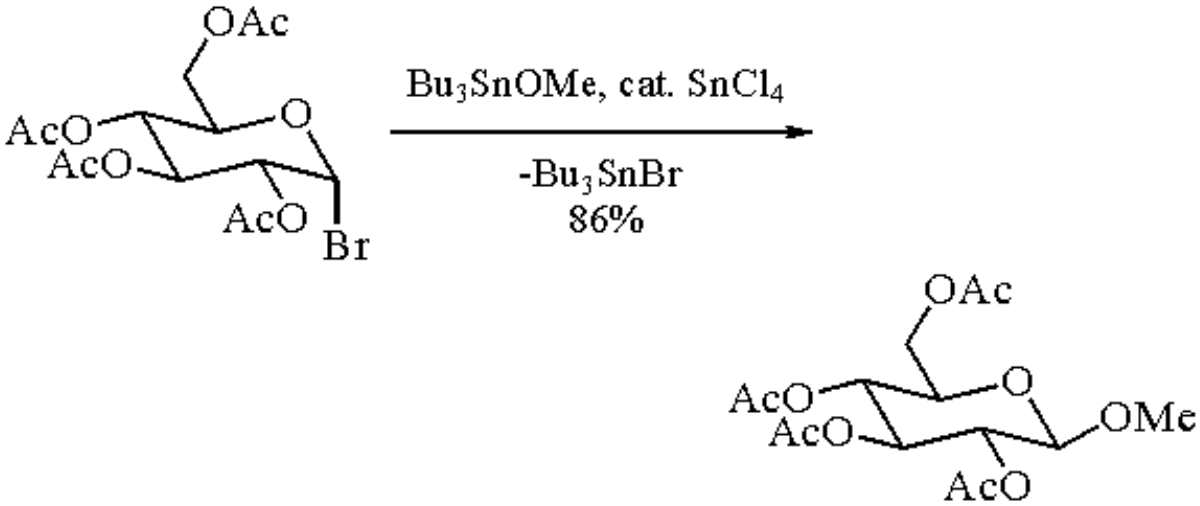

(8)

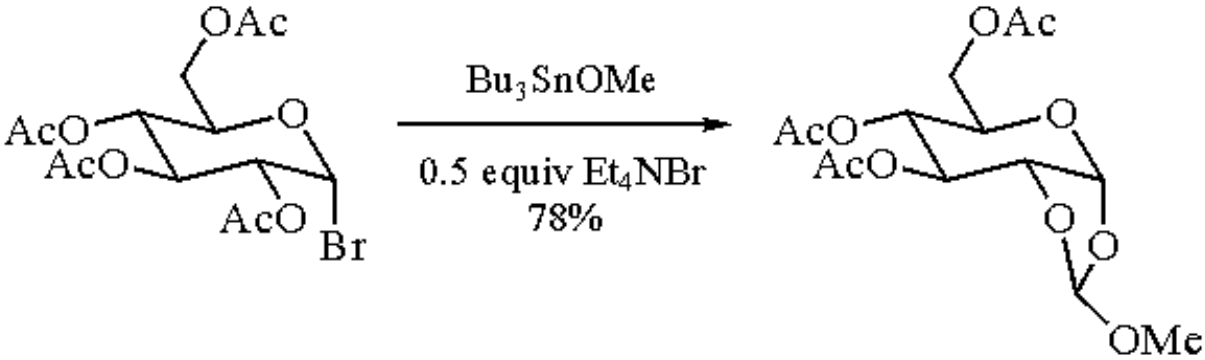

(9)

When 2-, 3-, 4-, or 5-halogenated alcohols are used, methoxytributylstannane first reacts with the hydroxyl in an exchange reaction. Then the alkoxide intermediates undergo intramolecular alkoxylation to give oxiranes, oxetanes, tetrahydrofurans, or tetrahydropyrans, respectively (eq 10).[13] The displacement is stereospecific, as *erythro*-3-bromo-2-butanol leads mainly to (*E*)-butene oxide and *threo*-3-bromo-2-butanol to the (*Z*)-isomer (*n* = 1).

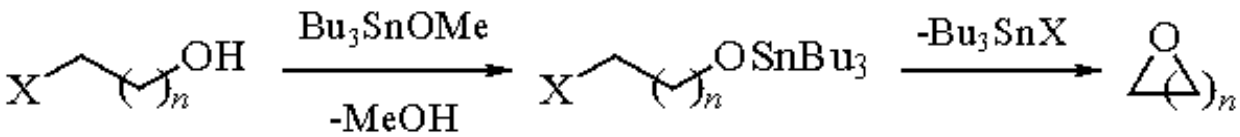

(10)

Methoxylation with methoxytributylstannane is not limited to halogenated derivatives. Under palladium catalysis, allyl acetates are transformed into allyl methyl ethers. This chemoselective approach to allyl etherification is often stereoselective and tolerates other electrophilic functional groups such as primary halides. It has been applied to carbohydrate chemistry (eq 11).[14]

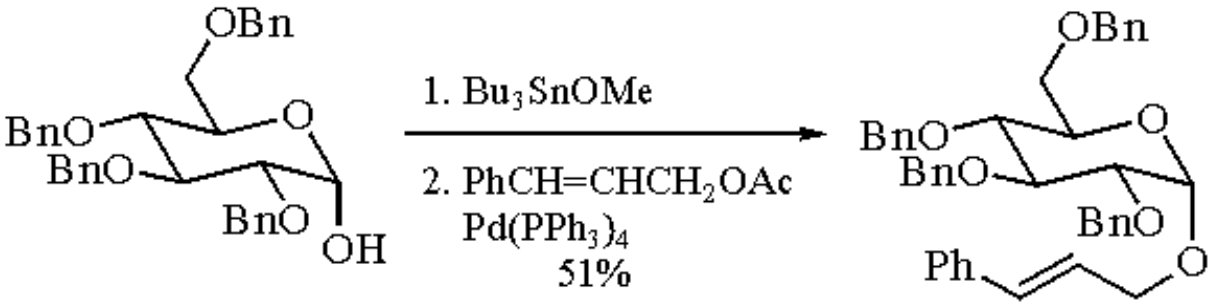

(11)

β-Lactams are stereospecifically methoxylated at the 4-position by methoxytributylstannane when a phenylsulfinyl group is used as leaving group (eq 12). Thus 3-substituted or unsubstituted 4-phenylsulfinyl-2-azetidinones lead to the corresponding 4-methoxy-2-azetidinones in the presence of catalytic amounts of ***Trimethylsilyl Trifluoromethanesulfonate*** at rt.[15]

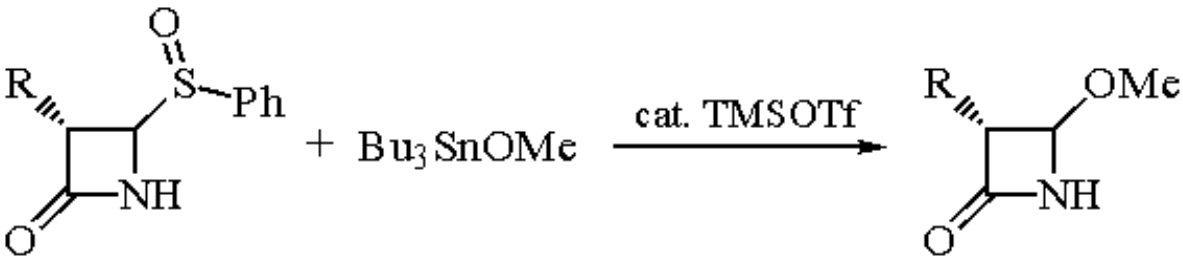

(12)

Enoxytributylstannanes (tin enolates) can be regiospecifically prepared by transesterification of enol acetates derived from aldehydes[16] or ketones[17] with methoxytributylstannane. The formation of new carbon-carbon bonds can be accomplished with primary alkyl halides, allyl halides, or functional halides. This coupling is regiospecific (eqs 13 and 14).

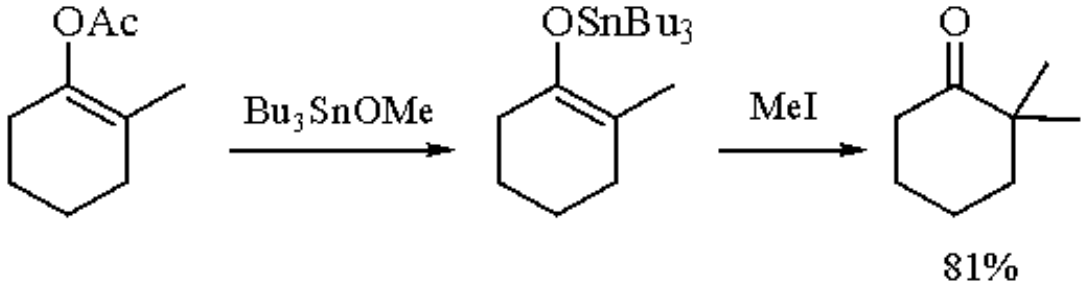

(13)

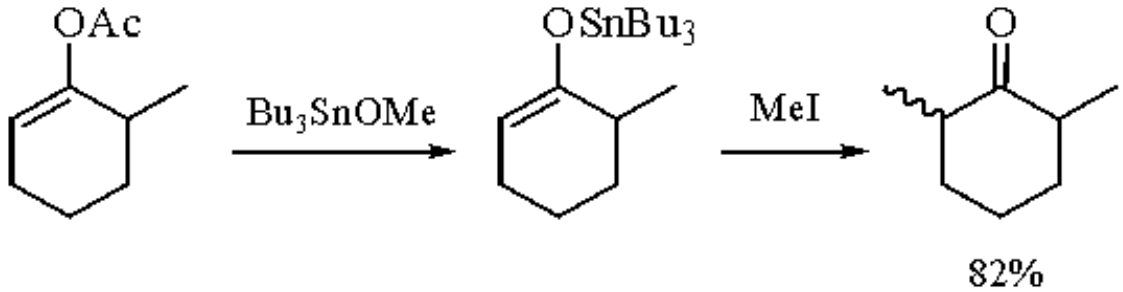

(14)

Under palladium catalysis, aryl[18], vinyl,[19] or heteroaryl[20] halides, or allyl acetates[21] may be used instead of allyl or alkyl halides (eqs 15 and 16). This reaction is also regiospecific.[22] It allows arylation of chroman-4-ones into isoflavanones.[23] In contrast, a different reaction takes place in acetonitrile, which leads to α-enones. This process has been applied to the synthesis of α,β-unsaturated large-ring ketones from enol esters (eq 17).[24]

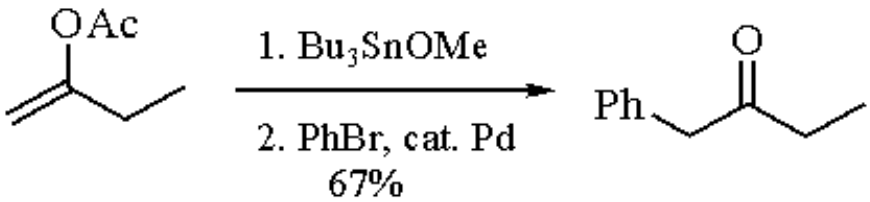

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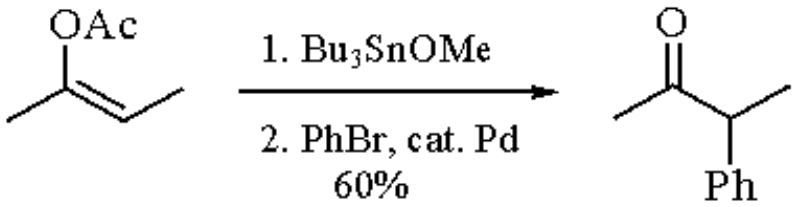

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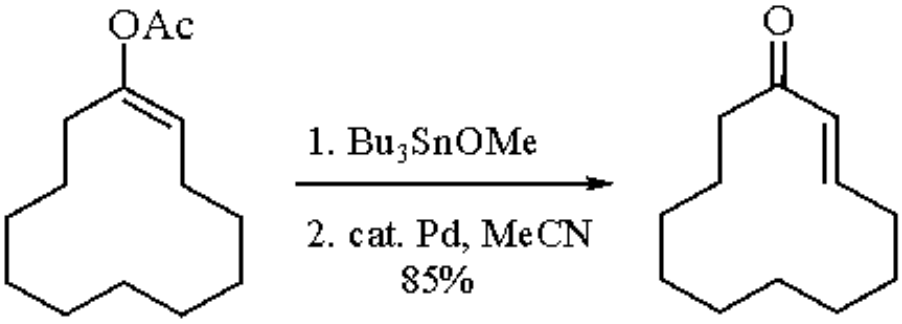

(17)

Metalation of alkynes by methoxytributylstannane gives alkynyltributylstannanes, which are able to undergo further reactions with acyl chlorides, leading to alkynyl ketones (eq 18).[25] With 1,3-dienes, [4 + 2] cycloadditions give cyclic vinylic organotins which are easily transformed into functional cyclohexadienes (eq 19) through vinyllithium intermediates.[26]

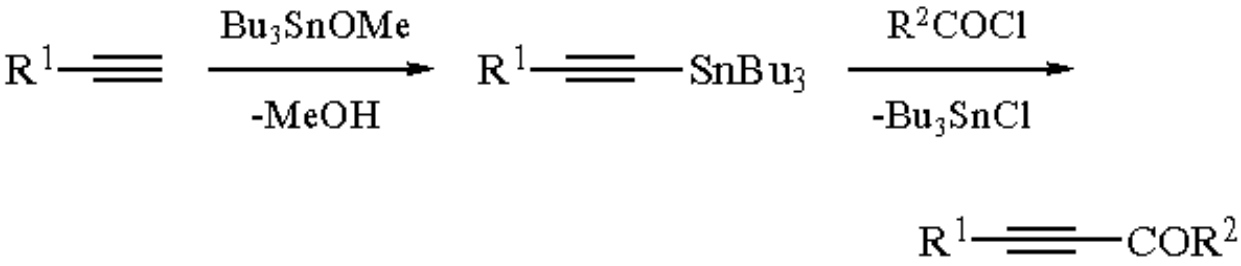

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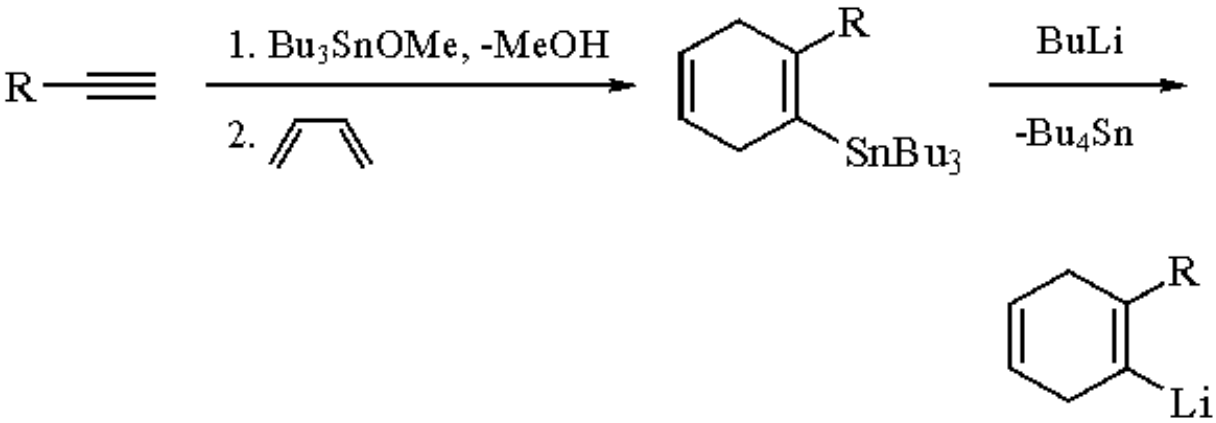

(19)

Oxidation Reactions.

Alkoxystannanes, conveniently prepared from methoxytributylstannane and alcohols, are oxidized under very mild conditions by bromotrichloromethane,[27] ***1,1-Di-t-butyl Peroxide***,[28] ***Bromine***,[29] ***N-Bromosuccinimide***,[30] or ***Nitronium Tetrafluoroborate*** (eq 20).[31] Secondary alcohols are selectively transformed into ketones, even in the presence of primary alcohols.[32]

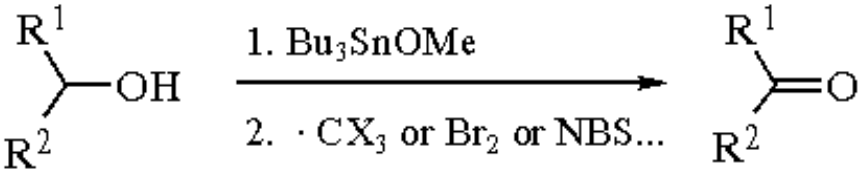

(20)

Disulfides are obtained when thiols are treated with methoxytributylstannane and anhydrous ***Iron(III) Chloride***, through an oxidation reaction involving thiostannane intermediates (eq 21). Tertiary, as well as primary, secondary, or aryl thiols may also be employed. Various functionalities, such as hydroxy, amino, amido, or ester groups, remain intact under the reaction conditions.[33]

$$RSH + Bu_3SnOMe \xrightarrow{FeCl_3} 1/2\ RSSR + Bu_3SnCl \qquad (21)$$

Addition Reactions.

Enoxytributylstannanes, prepared from methoxytributylstannane, add to aldehydes[34] to give predominately the *anti*-aldols at low temperature, whereas *syn* selectivity is observed at higher temperature (eq 22).[35]

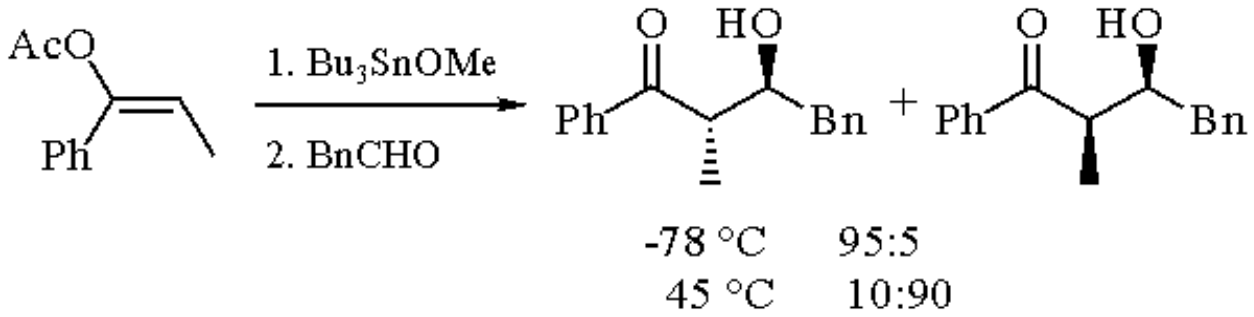

(22)

Intramolecular opening of oxiranes by tin alkoxides leads to cyclic ethers. After treatment by methoxytributylstannane, substituted 3-epoxybutanols stereospecifically give either oxetanemethanols (eq 23) or 3-oxolanols (eq 24) on heating, depending on the substituents.[36]

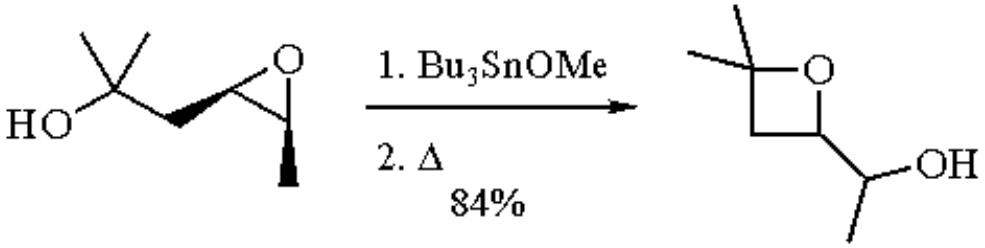

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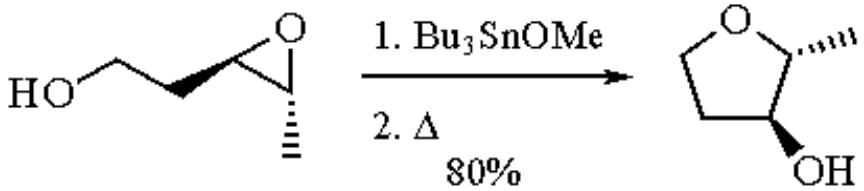

(24)

Nucleophilic additions of methoxytributylstannane to isocyanates or ketenes lead to reactive intermediates giving heterocycles after further condensations. Mixed isocyanurates are obtained when different isocyanates are involved in the reaction (eq 25).[37]

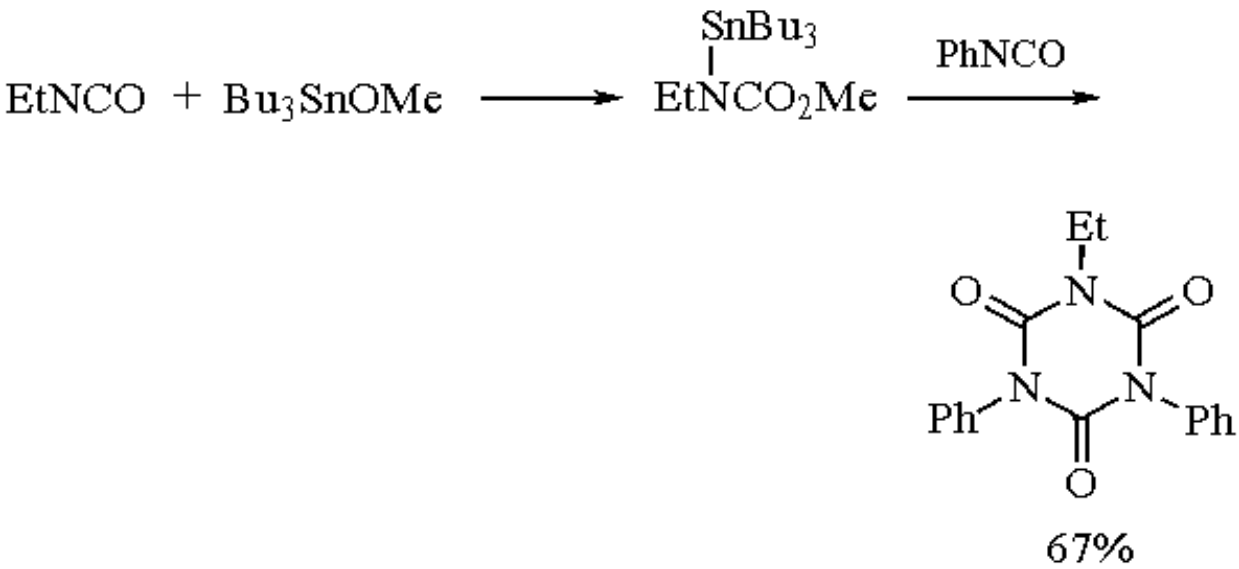

(25)

Alkoxides resulting from the opening of halogenated lactones by methoxytributylstannane add to isocyanates to give 2-oxazolidones (eq 26),[38] or 2-oxazinones,[39] depending on the ring size of the starting lactones. Other heterocumulenes, such as diimides, isocyanates or carbon dioxide, react equally well (eq 27).

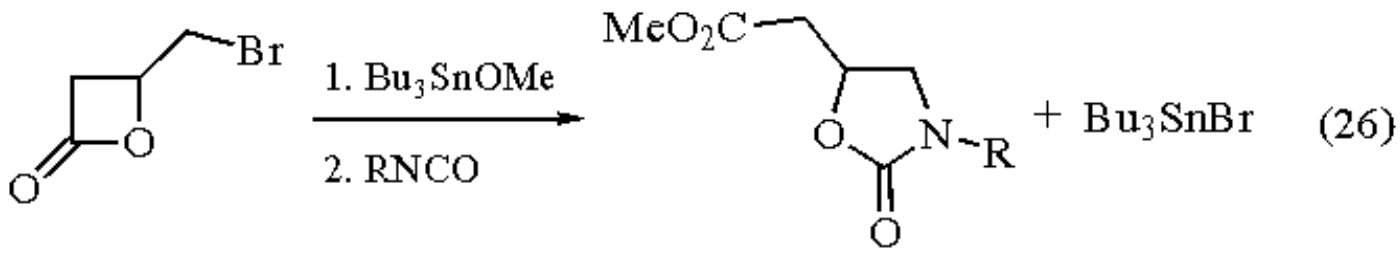

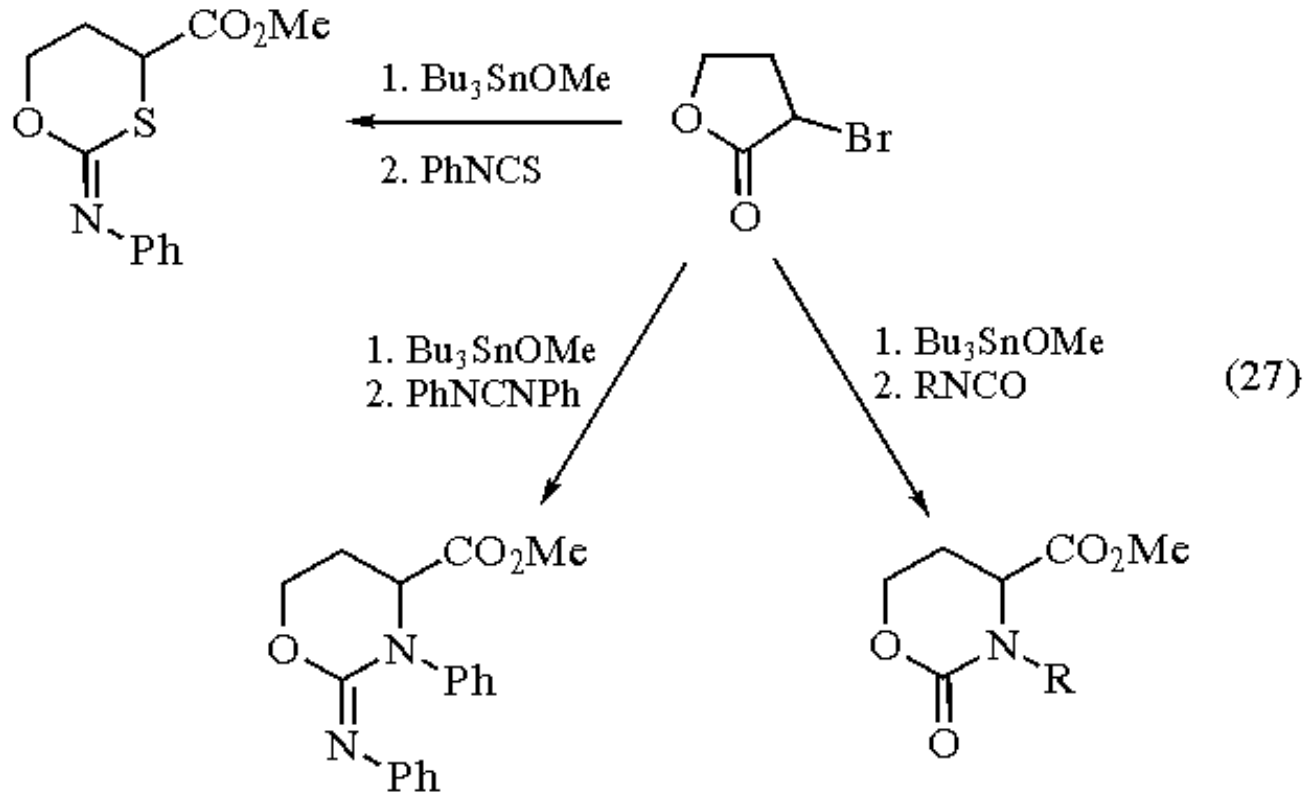

A Darzens reaction can be performed under mild, neutral conditions with the stannyl carbamate resulting from the addition of methoxytributylstannane to ethyl isocyanate (eq 28). This adduct selectively generates organotin enolates from α-halo ketones even when enolizable α´-hydrogens are present in the halo ketone.[40]

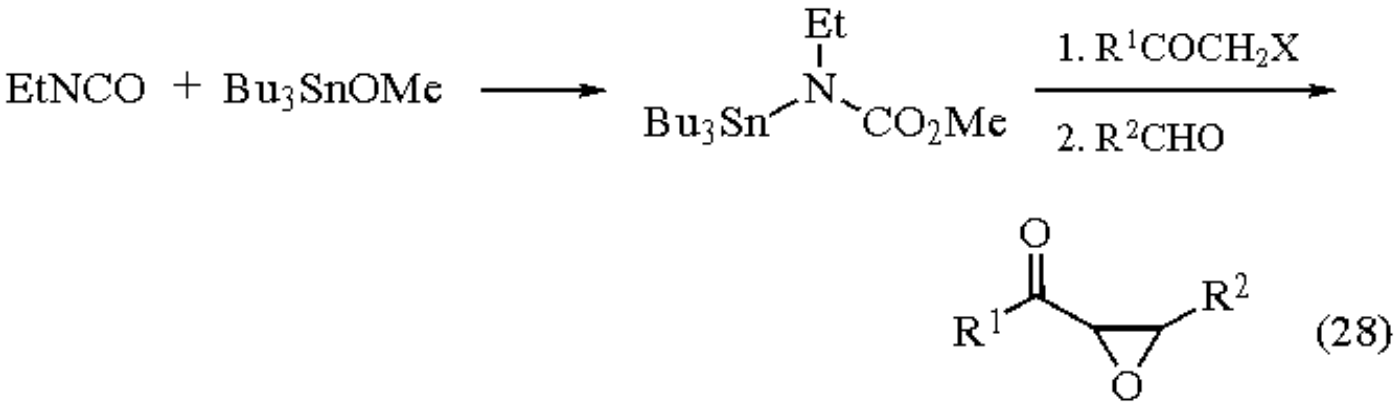

Methoxytributylstannane adds to silylketenes under very mild conditions (eq 29). Condensation of the adduct with aldehydes in the presence of titanium tetrachloride gives β-hydroxy-α-silyl esters with very high *syn* selectivity. A stereocontrolled elimination in these esters subsequently leads to (*E*)- or (*Z*)-α,β-unsaturated esters, depending on the conditions used.[41]

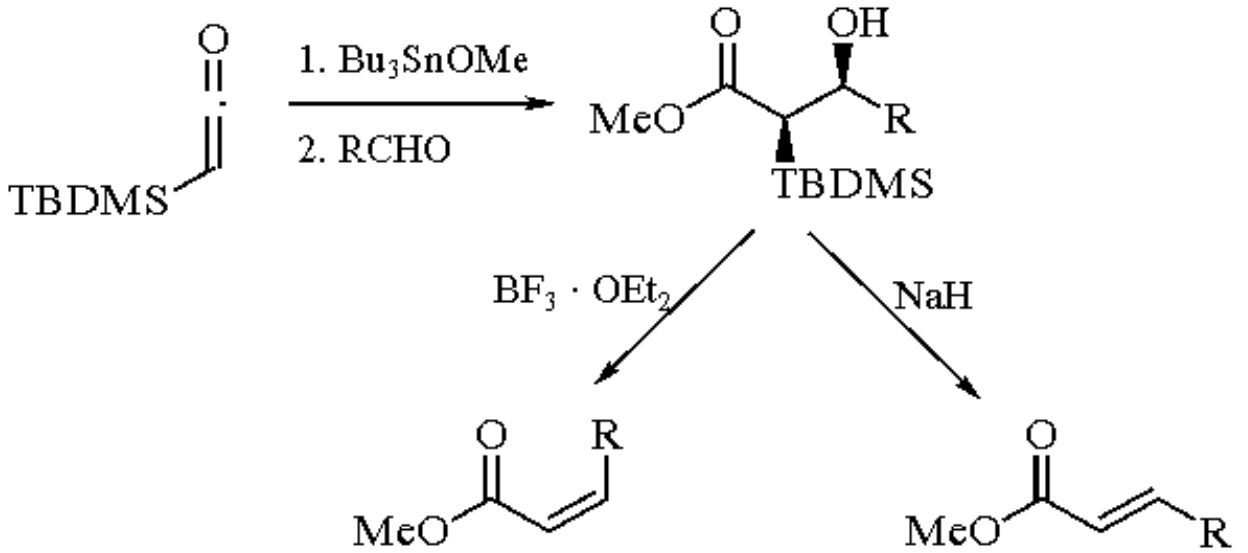

(29)

Stannyl quinones are formed by the thermal isomerization of 4-stannyloxy-4-alkynylcyclobutenones (eq 30) via a ketene intermediate. Once this intramolecular rearrangement is accomplished, the stannyl group can be substituted under palladium catalysis by various organic halides to give substituted quinones.[42]

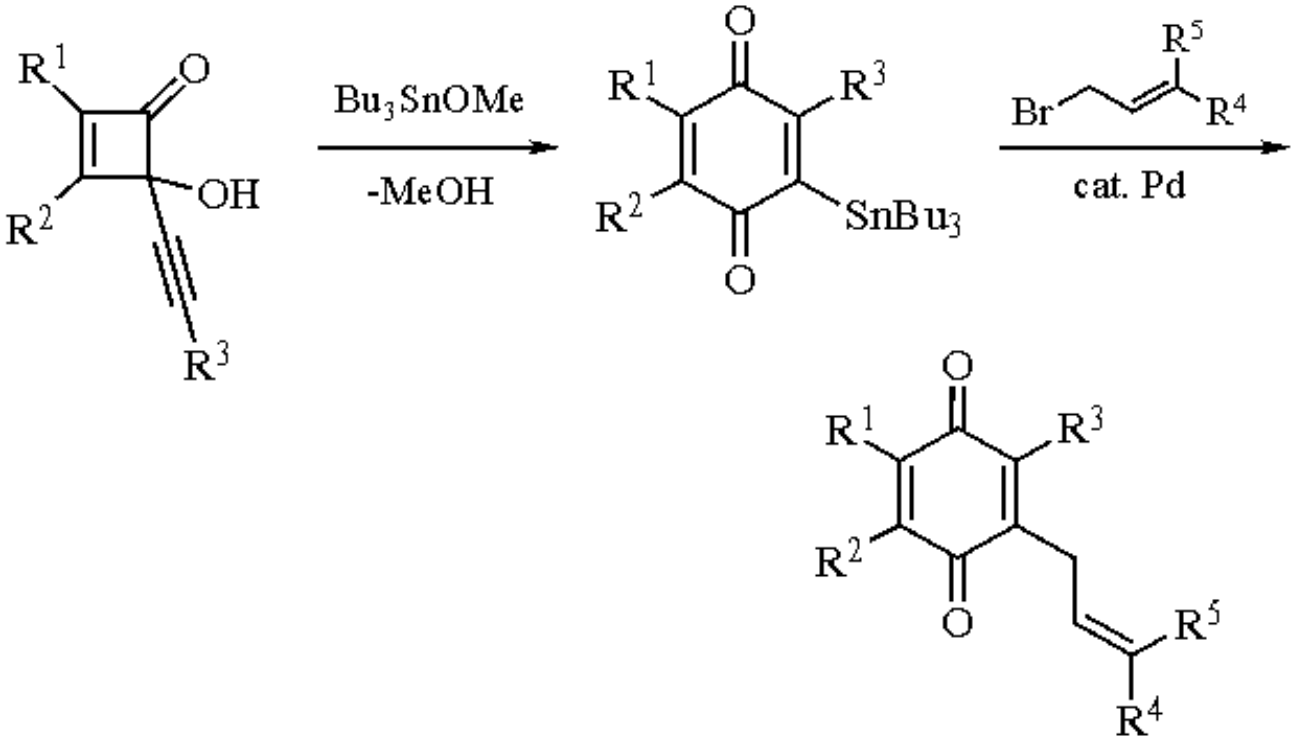

(30)

Iminocarbonylation of aryl bromides, involving the palladium-catalyzed condensation of *t*-butyl isocyanide, methoxytributylstannane, and an aryl bromide, leads to imidates (eq 31).[43]

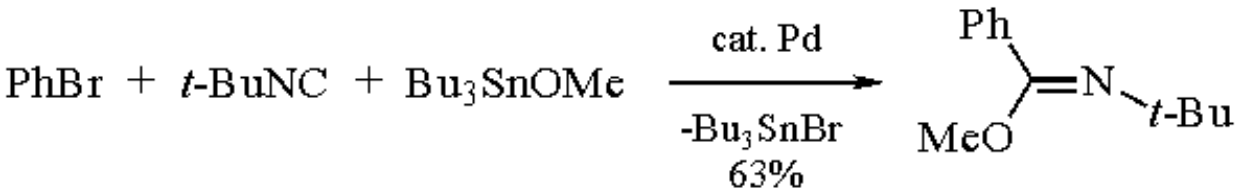

(31)

Catalysis.

Methoxytributylstannane is used as a catalyst for polymerization of lactones,[44] lactides,[45] and 1,3-dioxan-2-one.[46] The reaction is suggested to proceed by a coordinative insertion mechanism involving the cleavage of the acyl-oxygen bond of the monomer, and not by an ionic mechanism.

Related Reagents.

Di-n-butyltin Oxide; ***Sodium Methoxide***.

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Tri-*n*-butylphosphine

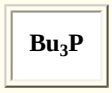

[998-40-3] · $C_{12}H_{27}P$ · Tri-*n*-butylphosphine · (MW 202.36)

(1,4-addition catalyst; used with disulfides for the thioetherification of alcohols; acylation catalyst; used to prepare active esters)

Physical Data: bp 240 °C; bp 130 °C/20 mmHg; *d* 0.812 g cm^{-3}.

Solubility: sol most organic solvents; slightly sol MeCN, H_2O.

Form Supplied in: widely available, neat; usually requires distillation.

Analysis of Reagent Purity: ^{31}P NMR.[1]

Purification: distillation at reduced pressure. Improperly stored bottles of Bu_3P are invariably contaminated with tributylphosphine oxide and butyl dibutylphosphinate.

Handling, Storage, and Precautions: can be stored at room temperature indefinitely under an inert atmosphere. Oxygen should be rigorously excluded to avoid free radical chain oxidation. Tributylphosphine is pyrophoric and has an unpleasant odor. Toxicity: LD_{50} (rat) 750 mg kg^{-1}.[2]

Introduction.

Of the commonly used tertiary phosphines, tributylphosphine[3] is exceptionally nucleophilic. It is a relatively weak base (pK_a 8.70 in $MeNO_2$, 5.60 in MeOH)[4] and rather stable to atmospheric oxidation, surviving for days in nondegassed solvents under nitrogen. Exposure to O_2 results in radical oxidation, giving mixtures of $Bu_2P(O)OBu$ and Bu_3PO in variable ratios, depending on the solvent.[5]

Thioetherification.

Tributylphosphine reacts with disulfides and alcohols to give the corresponding thioethers and Bu_3PO. This mild procedure was first used to prepare nucleoside thioethers (eq 1).[6] The activation step is similar to that used in the synthesis of peptides with ***Triphenylphosphine/2,2´-Dipyridyl Disulfide***,[7] and is conceptually related to the Mitsunobu activation method. This protocol has been used effectively in the synthesis of complex small molecules.[8] In some synthetic applications, thioetherification is followed by oxidation (***m-Chloroperbenzoic Acid***) and elimination (0 °C) to obtain the alkene.[9]

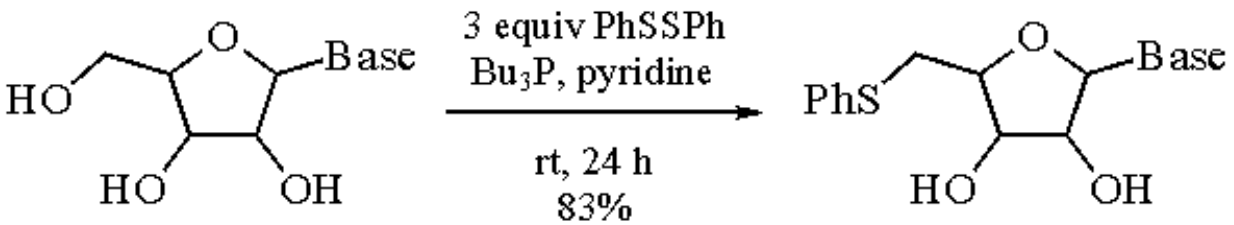

(1)

The thioetherification of diols occurs with remarkable chemoselectivity: ***Diphenyl Disulfide***/Bu_3P (Hata reagent) can distinguish between primary and secondary neopentyl alcohols.[10] Activation of allylic alcohols by the Hata reagent results in partial allylic transposition, giving ca. 2:1 mixtures of isomers (eq 2).[11] Thiophenylsuccinimides have also been employed in the preparation of phenyl thioethers.[12]

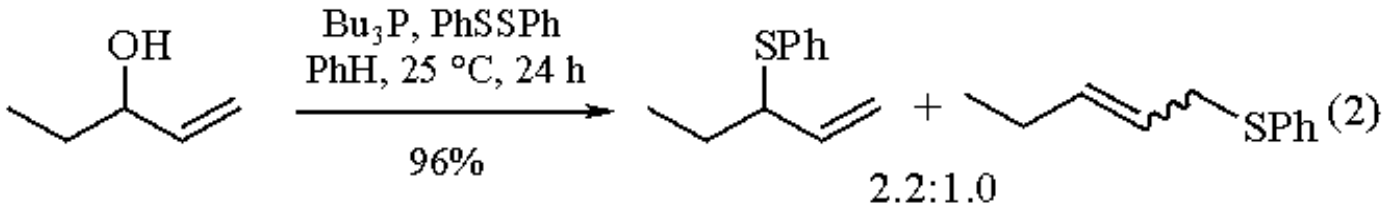

Thio- and selenoetherification is believed to proceed with inversion of configuration at the reacting center. In accord with this presumption, chiral secondary alcohols react with phenyl selenocyanates and Bu_3P, undergoing 93-96% inversion to the phenyl selenoethers.[13] The fidelity of the inversion may be subject to the same electronic factors which affect the Mitsunobu activation of ionization-prone alcohols.[14]

Activated Esters.

Aryl thio- and selenocyanates react with freshly distilled Bu_3P and carboxylic acids to give thiol- and selenolesters,[15] which can be isolated, or reacted in situ with amines (eq 3). The resulting amides are obtained in high yields with the Grieco reagent, although the method fails for the preparation of large ring lactams.[16] Analogously, carboxylic acids react with ***Diphenyl Diselenide***/Bu_3P to give activated selenolesters, which are used in the synthesis of peptides.[17]

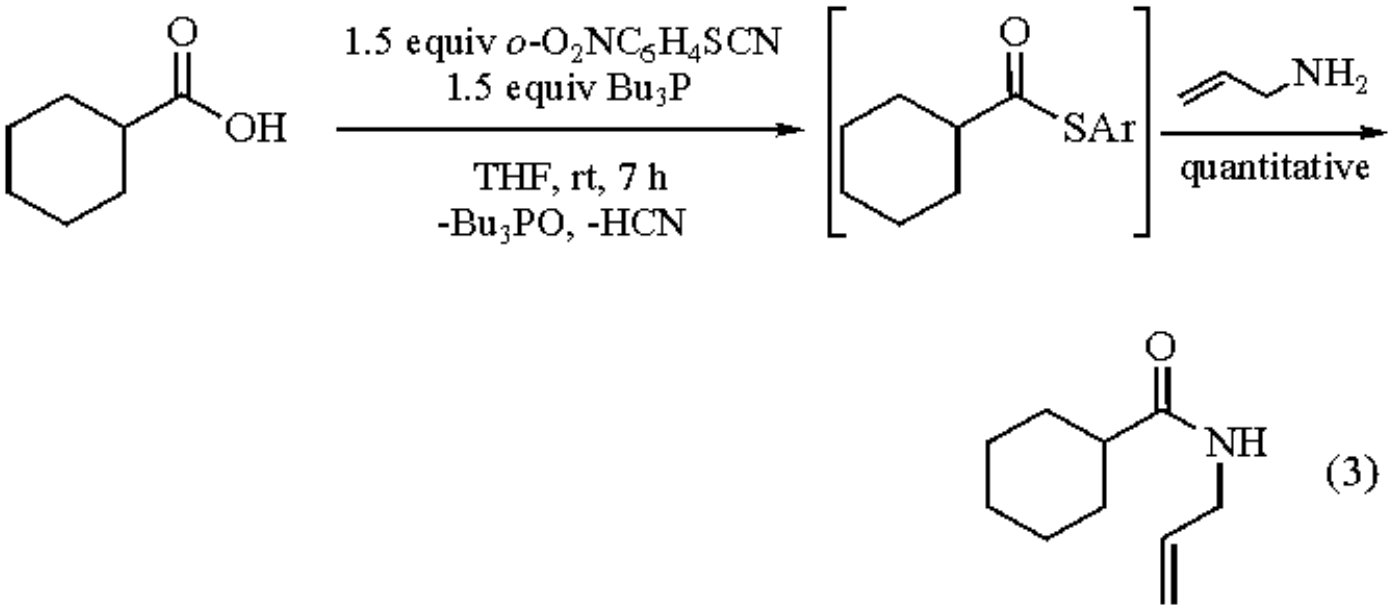

Acylation Catalyst.

Tributylphosphine has been used as a nucleophilic acylation catalyst.[18] Acetylation and benzoylation of hindered secondary and tertiary alcohols with ***Acetic Anhydride*** and ***Benzoic Anhydride*** in the presence of 0.1 equiv of Bu_3P occurs in high yield with or without added base. In some applications, catalytic rate accelerations match those of ***4-Dimethylaminopyridine*** (DMAP). The Bu_3P/Ac_2O reagent may prove to be a nonbasic alternative to DMAP and might be utilized in situations where DMAP fails or gives significant side reactions. The use of Bu_3P as a nucleophilic catalyst has been extended to a wide variety of substrates.[19]

1,4-Addition Catalyst.

Tributylphosphine has been most widely used as a 1,4-addition catalyst.[20] Although arylalkylphosphines and triphenylphosphine have been used in this application, Bu_3P is markedly superior due to its pronounced nucleophilicity (eq 4).[21] Amines fail to catalyze the reaction, and because phosphines are less basic (thus unable to deprotonate the nitroalkane), nucleophilic catalysis has been inferred. The yields correlate with phosphine nucleophilicity. The problem of monoalkylation of gramine-derived 3-methyleneindoline species with nitroalkanes has been solved using Bu_3P.[22] The authors observe no reaction in the absence of Bu_3P and speculate that the intermediacy of P^V may account for the selectivity observed. Recently, this method has been applied in the synthesis of (+)-paraherquamide (eq 5).[23] Interestingly, demethoxycarbonylation of the carbamate also occurs.

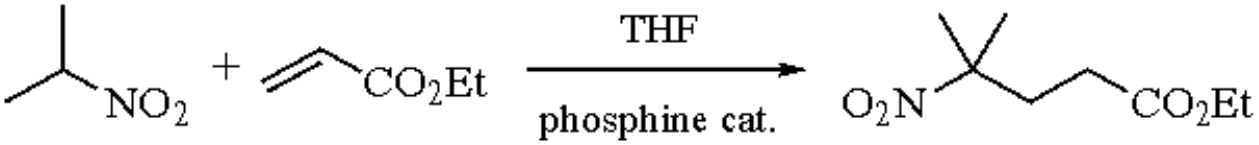

(4)

Catalyst	Equiv.	Yield (%)	Time (h)
Bu_3P	0.5	82	1.5
Ph_3P	10.0	36	160.0

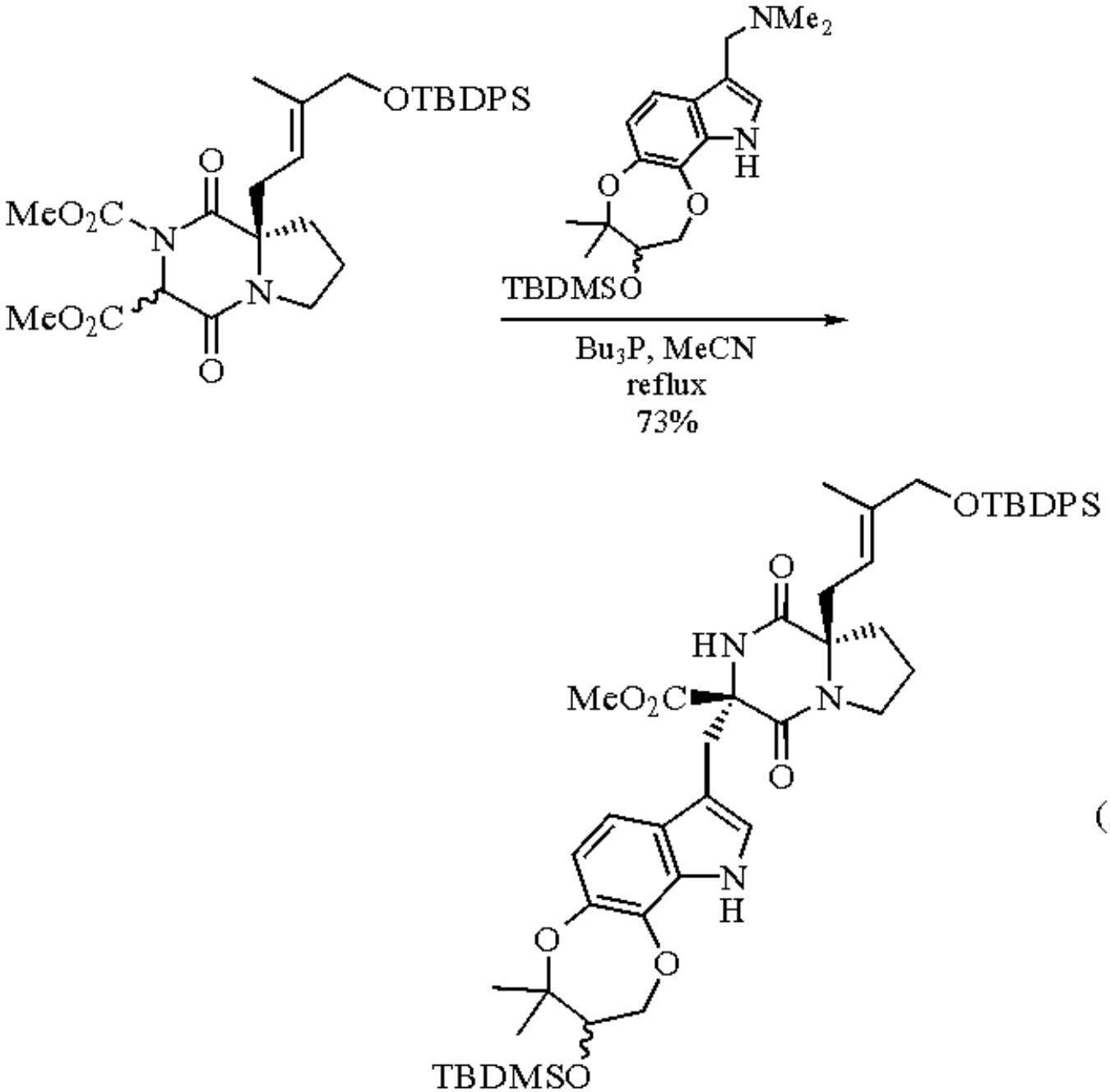

(5)

The Bu_3P-catalyzed 1,4-addition of alcohols to ynoates has recently been reported.[24] In addition to short reaction times (10 min vs. 8 h with Ph_3P), tributylphosphine gives enhanced (*E*)/(*Z*) ratios (99:1 vs 5:1 with Ph_3P) in the resulting 3-benzyloxy enoates. Tributylphosphine also catalyzes the ring opening of cyclobutenones.[25] Presumably, initial 1,4-addition is followed by electrocyclic ring opening. The crystalline tricyclohexylphosphine has been used to initiate (by 1,4-addition) an Ireland ester enolate Claisen rearrangement,[26] and ***Triphenylphosphine*** (or Bu_3P) isomerizes alkynones to the all-*trans* dienones.[27] Tributylphosphine has been utilized in aqueous systems (pK_a 8.43 in H_2O).[28]

Tributylphosphine can intercept π-allyl palladium complexes to yield allylic phosphonium salts, which have been deprotonated and used in

Wittig alkenation of aldehydes.[29] The use of Bu_3P shows improved (*E*) selectivities over Ph_3P, and does not isomerize the alkene geometry of the allylic starting material. In these examples, the role of tributylphosphine extends well beyond that of ancillary ligand.[30]

Mitsunobu Reaction.[31]

Different selectivities have been obtained using Bu_3P rather than Ph_3P in the Mitsunobu reaction.[32] In one case, Bu_3P gives retention of configuration whereas Ph_3P shows (normal)[31] inversion of alcohol configuration.[33] Although a complete mechanistic picture is as yet unclear, recent studies suggest a more reactive Bu_3P/***Diethyl Azodicarboxylate*** (DEAD) reagent. ^{31}P NMR monitoring of the Bu_3P/DEAD/ROH reaction shows the presence of an alkoxyphosphonium species instead of the derived phosphorane which is observed with Ph_3P.[34] Furthermore, the Bu_3P-derived betaine reacts faster with nucleophiles than the Ph_3P-derived betaine, which has synthetic implications for the order of addition of reagents (e.g. Bu_3P, DEAD, ROH, then $R'CO_2H$).[28] Premature addition of the carboxylic acid component results in symmetrical anhydride formation, which may explain some of the poor yields reported using Bu_3P. A more reactive Mitsunobu reagent, comprised of Bu_3P and ***1,1´-(Azodicarbonyl)dipiperidine***, has been described.[35]

Miscellaneous.

The synthesis of *O*-silyl cyanohydrins by the 1,2-addition of ***Cyanotrimethylsilane*** to aldehydes benefits from tributylphosphine catalysis.[36] In the reaction of TMSCN with hydrocinnamaldehyde, Bu_3P gives the best yield (eq 6). In a hindered intramolecular example of the aza-Wittig reaction, Ph_3P fails to give any product but Bu_3P gives moderate yields of the desired 1,4-benzodiazepin-5-ones.[37]

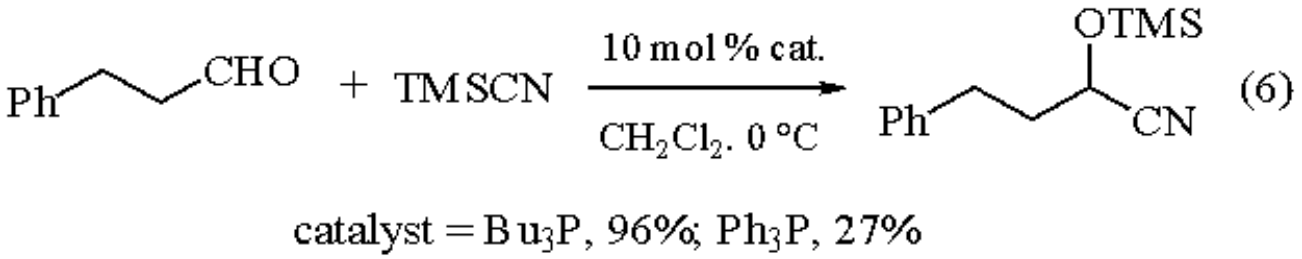

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Tri-*n*-butylstannylacetylene[1]

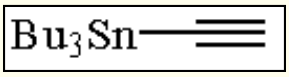

[994-89-8] · $C_{14}H_{28}Sn$ · Tri-*n*-butylstannylacetylene · (MW 315.13)

(addition of organometallic reagents affords alkenic stannanes; palladium-catalyzed coupling yields enynes; 1,3-dipolarophile)

Physical Data: bp 70 °C/0.2 mmHg; *d* 1.089 g cm^{-3}.

Solubility: sol common hydrocarbon and ethereal solvents.

Form Supplied in: available from several commercial sources.

Preparative Method: prepared by the reaction of ***Lithium Acetylide*** with ***Tri-n-butylchlorostannane***.[2]

Purification: distillation.

Handling, Storage, and Precautions: organostannane reagents are potentially toxic.[3] Therefore their preparation and use must be conducted wearing appropriate protective clothing and in a well ventilated fume hood.

Addition Reactions.

Addition of ***Tri-n-butylstannane*** to tributylstannylacetylene (**1**) affords the synthetically useful reagent *trans*-1,2-bis(tributylstannyl)ethylene.[2] Stannylcupration of (**1**) with the higher order cuprate $(Me_3Sn)_2Cu(CN)Li_2$, followed by protonation of the intermediate vinyl cuprate, yields *trans*-1-(tributylstannyl)-2-(trimethylstannyl)ethylene in excellent yield.[4] Hydrozirconation of (**1**) with ***Chlorobis(cyclopentadienyl)hydridozirconium*** and protonation of the intermediate vinylzirconate proceeds smoothly to afford ***Vinyltributylstannane***.[5] Addition of ***Triethylborane*** to (**1**) stereospecifically affords (*E*)-2-(diethylboryl)-1-(tributylstannyl)-1-butene, through an alkynylborate intermediate.[6]

Cross-Coupling Reactions.

Stille et al. pioneered the palladium-catalyzed cross-coupling reaction of organostannanes with a variety of electrophilic partners. These reactions proceed under mild conditions which are often compatible with typically sensitive functional groups.[1] Tributylstannylacetylene (**1**) couples smoothly with vinyl halides to afford the corresponding enyne in high yield (eq 1).[7a] The alkene geometry of the starting halide is retained in the product.[7] Aryl halides and triflates also couple with (**1**) to afford the corresponding arylacetylenes.[8]

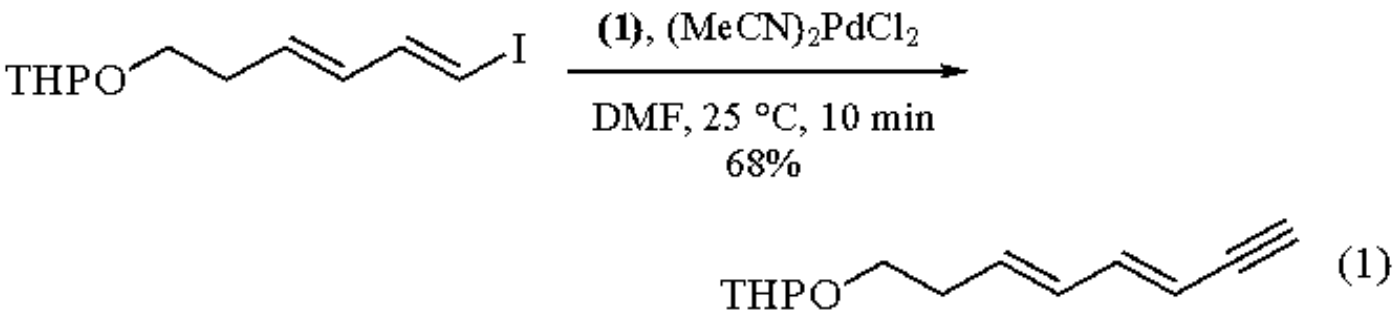

(1)

Cycloaddition Reactions.

Tributylstannylacetylene is an effective 1,3-dipolarophile, reacting with nitrile oxides to afford 5-tributylstannylisoxazoles (eq 2).[9] The synthetic utility of this latent 1,3-dicarbonyl equivalent is demonstrated by its straightforward conversion to chromones,[9a,b] 4(1*H*)-

quinolones, and indoles.[9a] Tributylstannylpyrazoles are prepared by reaction of (**1**) with diazoalkanes.[10]

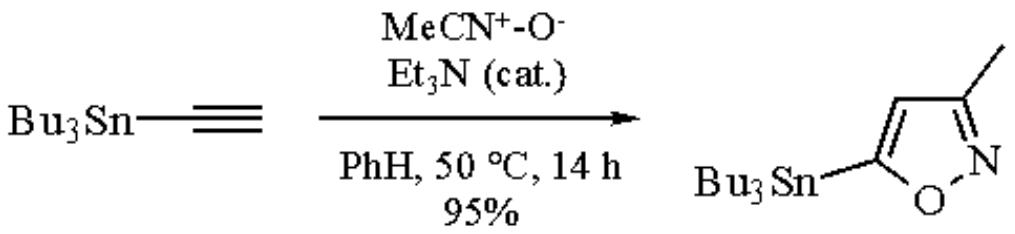

(2)

Tributylstannylacetylene is an effective dienophilic partner in the inverse electron demand Diels-Alder reaction. Stannyl-substituted pyrazines are prepared in moderate yield by reaction with 1,2,4,5-tetrazines.[11] Stannyl-substituted pyridines are formed in moderate to poor yields by reaction with (6*H*)-1,3-oxazin-6-ones (eq 3).[12] These compounds are best prepared from the corresponding halo-substituted heterocycles.[13]

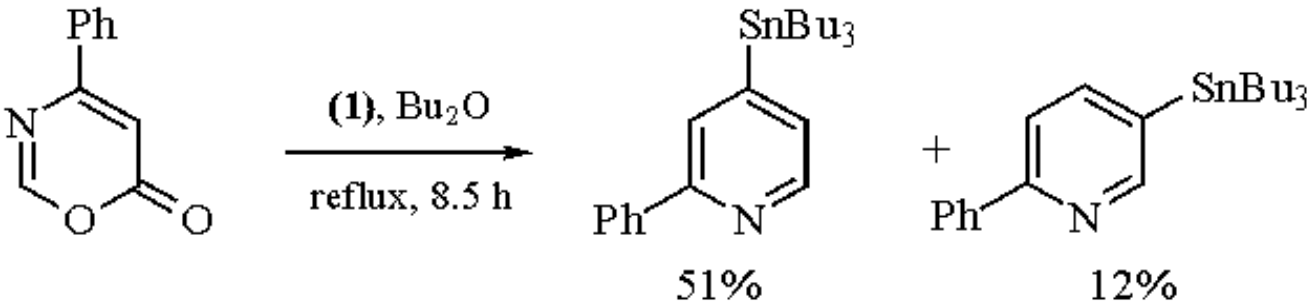

(3)

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Tri-*n*-butylstannylcopper

Bu_3SnCu

[82097-93-6] · $C_{12}H_{27}CuSn$ · Tri-*n*-butylstannylcopper · (MW 353.65)

(incorporation of tributyltin via reaction with electrophilic substrates[1-6])

Physical Data: prepared in situ; its THF solution is dark red.

Solubility: sol THF.

Preparative Methods: Bu_3SnCu (**1**) is prepared by reaction of ***Tri-n-butylstannyllithium*** with 1 equiv of ***Copper(I) Iodide*** (eq 1).[1,2,5,8] A closely related reagent, $Bu_3SnCu.Me_2S$ (see ***Trimethylstannylcopper-Dimethyl Sulfide***), is readily obtained by treatment of Bu_3SnLi with an equimolar quantity of $CuBr.Me_2S$ (**2**) (see ***Copper(I) Bromide***) (eq 2).[3,4,9-13]

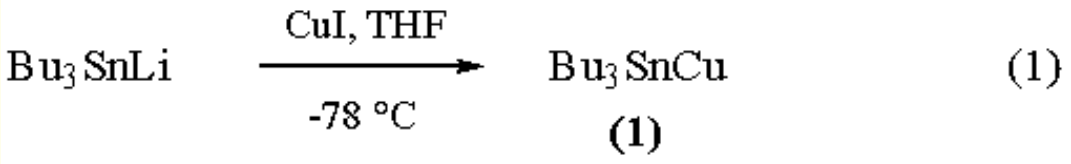

(1)

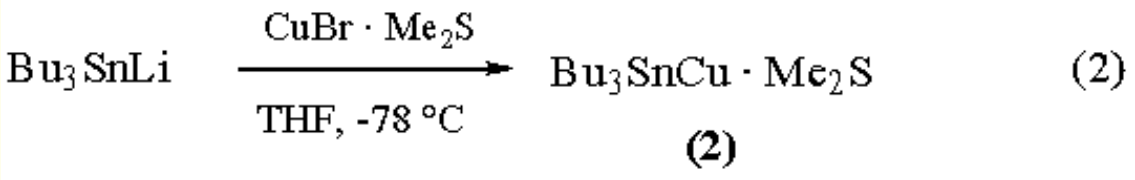

(2)

Handling, Storage, and Precautions: should be prepared in dry solvent and used under an inert atmosphere. Organotin compounds are toxic;[7] therefore, reaction workup should be carried out in a fume hood.

Substitution Reactions.

Bu_3SnCu (**1**) reacts with methyl 3-chloro- and 3-iodoacrylates to produce the corresponding 3-tributylstannylacrylates. These reactions, which presumably proceed via a conjugate addition-elimination mechanism, occur under mild conditions and, importantly, are stereospecific (eqs 3 and 4).[1] In similar fashion, treatment of ethyl (*Z*)-3-(*p*-tolylsulfonyloxy)acrylate with (**1**) provides, stereoselectively, ethyl (*Z*)-3-tributylstannylacrylate (eq 5).[1]

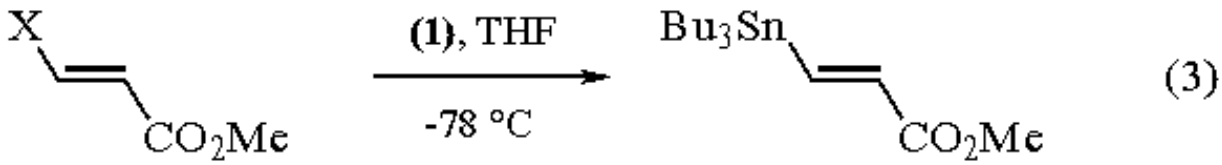

(3)

X = Cl, 58%; I, 62%

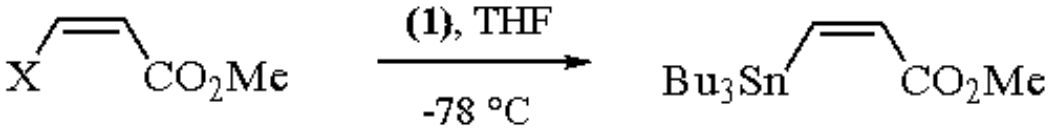

(4)

X = Cl, 62%; I, 47%

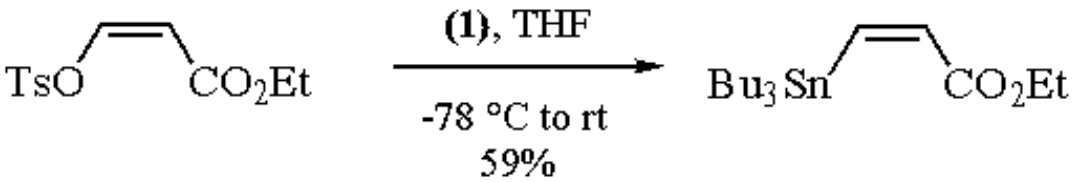

(5)

In a related process, reagent (**1**) reacts with (*E*)-2-chloro-1-(phenylsulfonyl)ethylene to provide the corresponding tributylstannane (eq 6),[2] a useful intermediate for the synthesis of 1-tributylstannyl-1-alken-3-ols.[2]

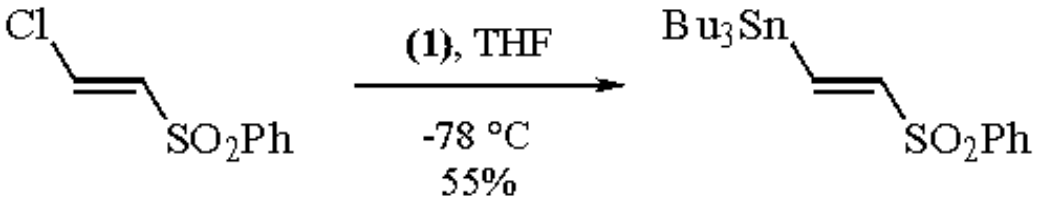

(6)

Tributylstannylcopper replaces the 4-iodo group of the functionalized pyrimidines (**3**) and (**4**) (eq 7).[5] The stannylated products (**5**) and (**6**) are valuable for the preparation of substituted pyrimidine derivatives.[5]

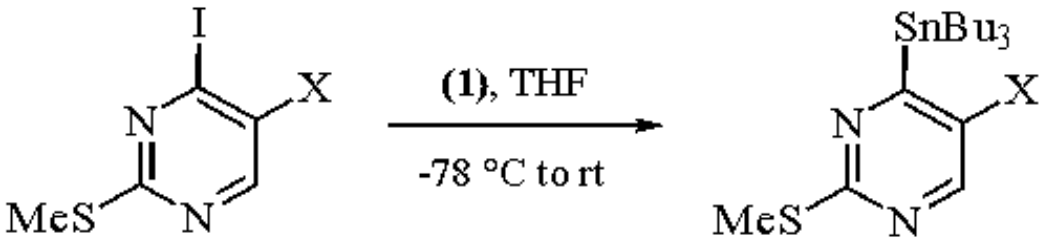

(7)

(3) X = H
(4) X = Cl

(5) X = H, 41%
(6) X = Cl, 52%

Reactions with Alkynic Substrates.

Reagent (**2**) is very useful for effecting the highly stereocontrolled conversion of α,β-alkynic esters into alkyl (*E*)-3-tributylstannyl-2-alkenoates.[3,9,11-13] Examples are given in eqs 8 and 9.[11,12] The (*E*)-3-tributylstannyl-2-alkenoates are valuable synthetic intermediates that have been employed as precursors to radical cyclization substrates,[9,11,12] to configurationally defined alkenyllithium reagents,[3,13] and in natural product synthesis.[3,9,13] For instance, compounds (**7**) (eq 8) and (**8**) (eq 9) have been transformed into the intermediates (**9**) and (**10**), respectively. Radical-mediated cyclization of (**9**) provides primarily the highly functionalized heterocycle (**11**) (eq 10),[11] while treatment of (**10**) with bis(cyclopentadienyl)titanium(III) chloride gives the ester alcohol (**12**) with high stereoselectivity (eq 11).[12] Additionally, (**13**), derived by reaction of ethyl 2-pentynoate with (**2**),[3] is readily converted into (**14**). The latter substance is a convenient precursor to (*Z*)-3-lithio-2-pentene (**15**), which played an important role in a total synthesis of the unusual natural product triophamine (**16**).[3]

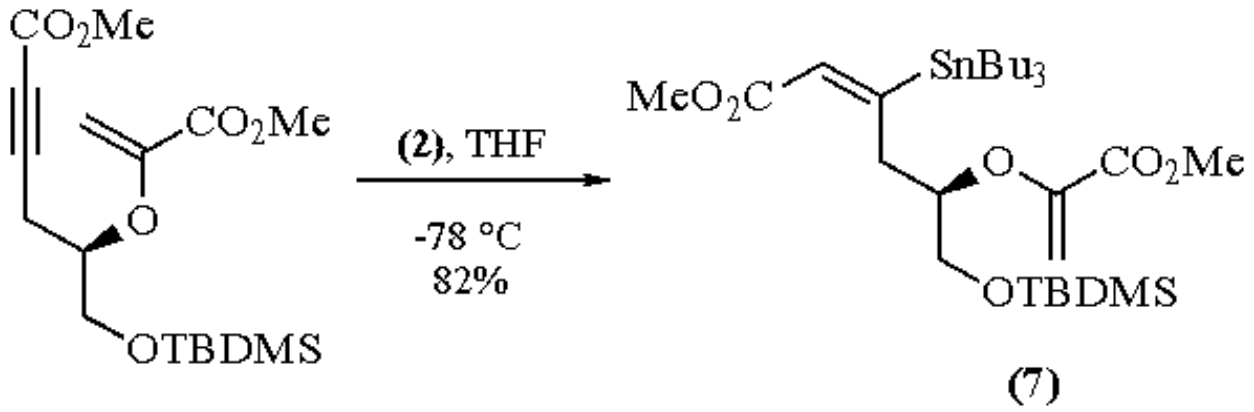
CO2Me
CO2Me
O
OTBDMS
(2), THF
-78 °C
82%
MeO2C
SnBu3
O
CO2Me
OTBDMS
(7)

(8)

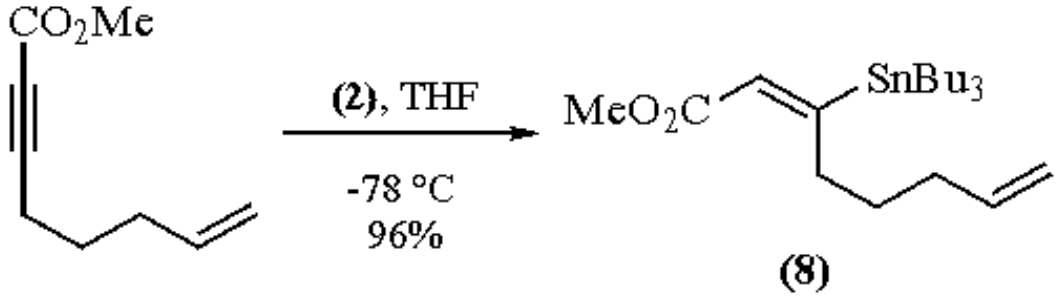
CO2Me
(2), THF
-78 °C
96%
MeO2C
SnBu3
(8)

(9)

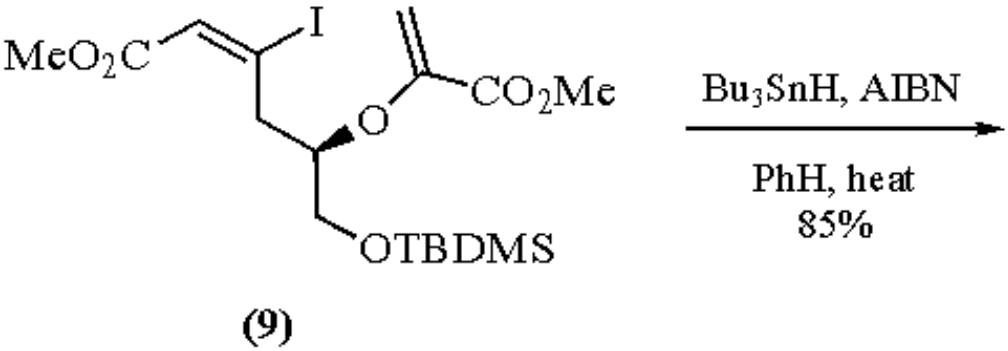
MeO2C
I
O
CO2Me
OTBDMS
(9)
Bu3SnH, AIBN
PhH, heat
85%

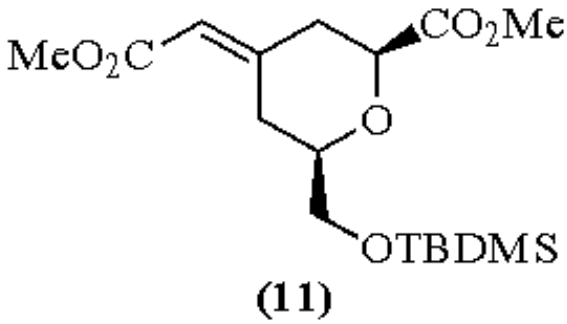
MeO2C
CO2Me
O
OTBDMS
(11)

(10)

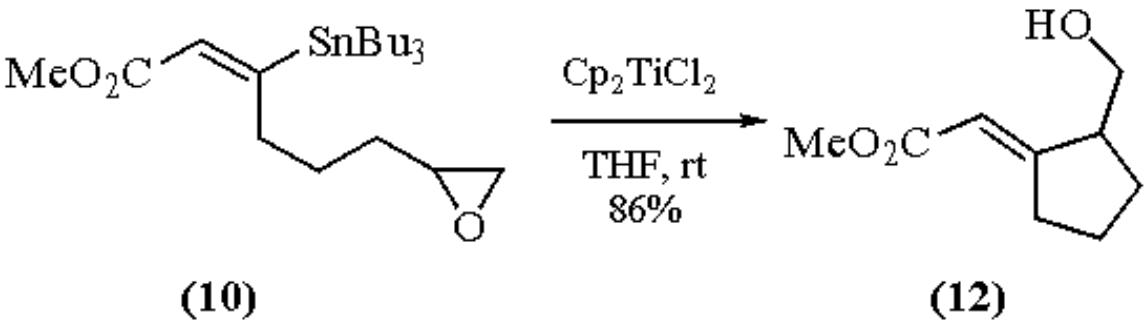
MeO2C
SnBu3
O
(10)
Cp2TiCl2
THF, rt
86%
HO
MeO2C
(12)

(11)

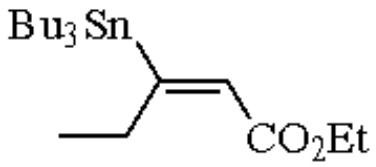

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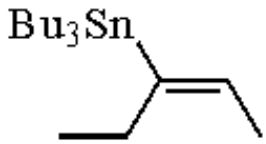

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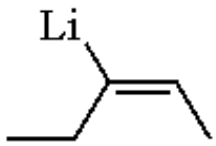

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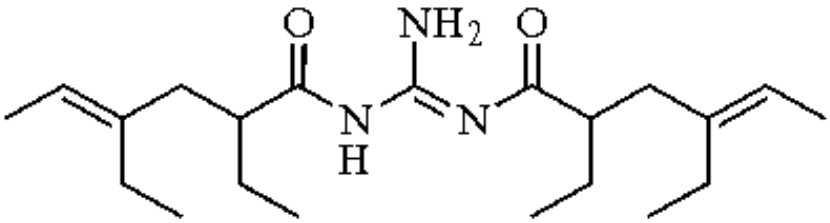

(16)

Reagent (**2**) can also be employed to achieve the stereoselective *cis*-addition of the elements of Bu_3Sn-H across the triple bond of propargylic alcohols. Examples are given in eqs 12 and 13.[4,6,10] Substance (**17**) has been used in the synthesis of novel compounds structurally related to the enediyne antibiotic dynemycin A.[6] The diol stannane (**18**) has served as an excellent precursor for the preparation of 3-lithiofuran[4] and 2-tributylstannyl-1,3-butadiene.[14] Diels-Alder reactions of the latter material have been investigated.[10,14]

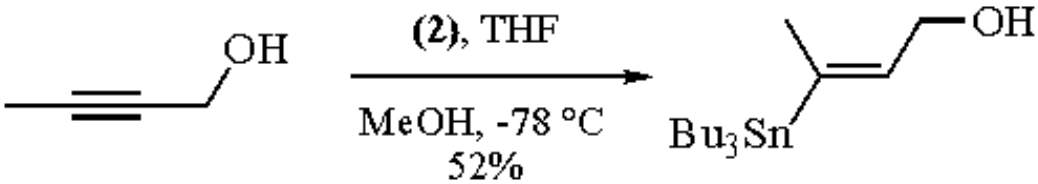

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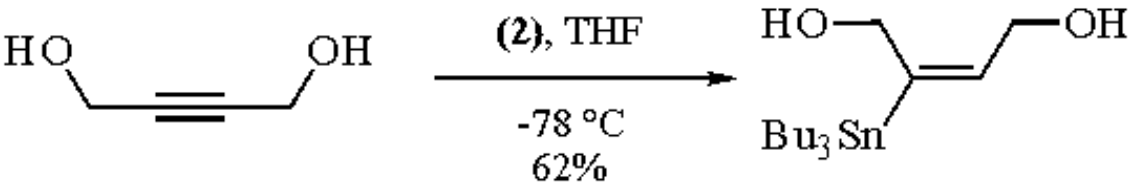

(13)

(18)

Related Reagents.

Bis(methylthio)(trimethylstannyl)methane; ***2,3-Bis(trimethylstannyl)-1,3-butadiene***; ***4-Chloro-2-trimethylstannyl-1-butene***; ***(E)-1-Lithio-2-tributylstannylethylene***; ***Lithium Phenylthio(trimethylstannyl)cuprate***; ***Methyl Tributylstannyl Sulfide***; ***trans-1,2-Bis(tributylstannyl)ethylene***; ***Tri-n-butylstannylacetylene***; ***Tri-n-butylstannyllithium***; ***Trimethylstannylcopper-Dimethyl Sulfide***; ***2-Trimethylstannylmethyl-1,3-butadiene***; ***Trimethylstannyllithium***; ***(Triphenylstannylmethyl)lithium***.

---

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N-[(Tri-*n*-butylstannyl)methyl]benzaldimine

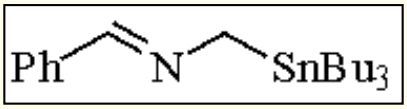

[116360-40-8] · $C_{20}H_{35}NSn$ · *N*-[(Tri-*n*-butylstannyl)methyl]benzaldimine · (MW 408.27)

(synthesis of 2-phenylpyrrolidines by [3 + 2] cycloaddition of the derived 2-azaallyl anion with alkenes;[1,2] related compounds allow synthesis of other 2-substituted, 2,2-disubstituted, 2,5-disubstituted, or 2,2,5-trisubstituted pyrrolidines or pyrrolines[1-3])

Physical Data: bp 145-155 °C/0.1 mmHg (Kugelrohr air bath).

Solubility: freely sol common organic solvents.

Form Supplied in: clear, colorless oil; not available commercially.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: prepared by Staudinger reaction between benzaldehyde, ***Triphenylphosphine***, and (azidomethyl)tributylstannane [prepared from (iodomethyl)tributylstannane and ***Sodium Azide***].[2] A more convenient procedure for the preparation of similar stannanes by condensation of an aldehyde or ketone with (aminomethyl)tributylstannane has been developed.[3] Related 2-azaallylstannanes such as 1-alkyl-, 1,1-dialkyl-, 1,3-dialkyl-, and 1,1,3-trialkyl-2-azaallylstannanes may also be prepared, particularly using the latter method.

Handling, Storage, and Precautions: since tetraalkylstannanes in general are considered toxic,[4] handling in a fume hood is recommended. The reagent is stable in a freezer for extended periods, but is easily hydrolyzed by aqueous acids, and is partially hydrolyzed by silica gel chromatography.

Synthesis of 2-Phenylpyrrolidines.

Treatment of *N*-[(tributylstannyl)methyl]benzaldimine with ***n-Butyllithium*** in the presence of stilbene produces 2,3,4-triphenylpyrrolidine in good yield (eq 1).[1,2] The reaction proceeds by transmetalation to produce a 2-azaallyl anion, which undergoes a [$_\pi4_s$ + $_\pi2_s$] cycloaddition with stilbene, generating an *N*-lithiopyrrolidine. Quenching the reaction with water or other electrophiles allows the introduction of a variety of *N*-substitutents. The anionophile must be present during the transmetalation, since the 2-azaallyl anions have a limited lifetime under these conditions. The best anionophiles are those that are relatively stable to butyllithium at low temperature, and are relatively reactive due to the presence of substituents which may stabilize negative charge build up. Successful examples include stilbene, styrene, α-methylstyrene, diphenylacetylene, phenyl vinyl sulfide, phenyl vinyl selenide, and various vinylsilanes.[1,2] More electron-deficient anionophiles such as acrylates are unsuccessful. Examples are shown in eq 2.[2]

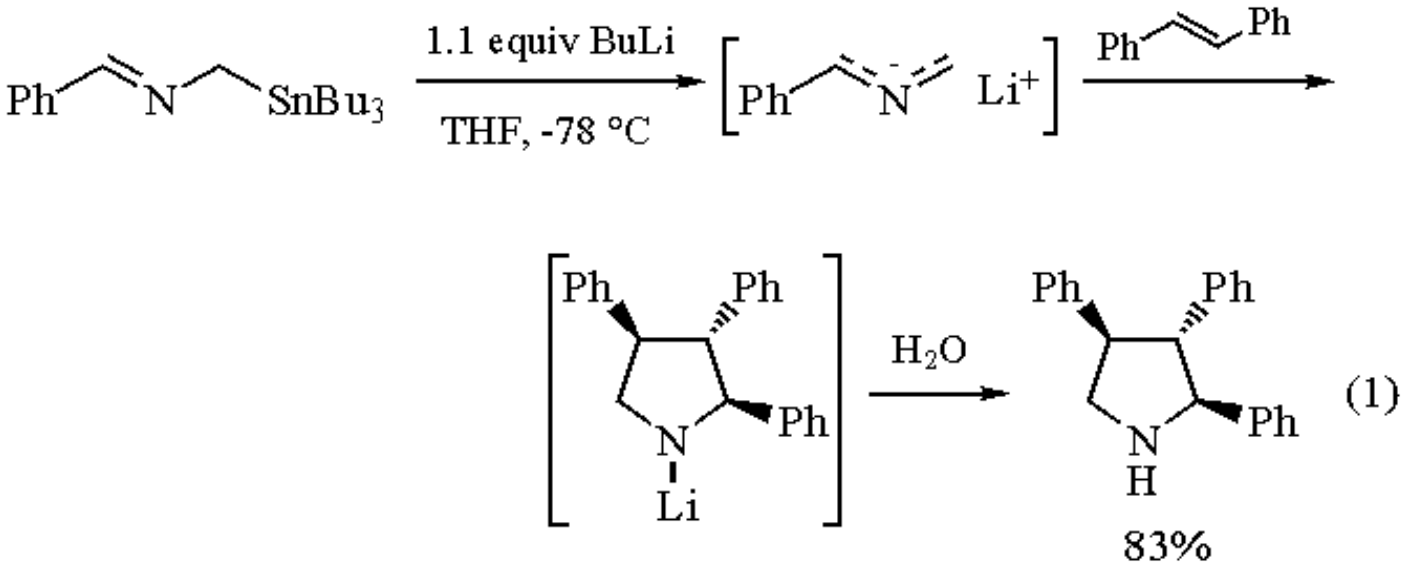

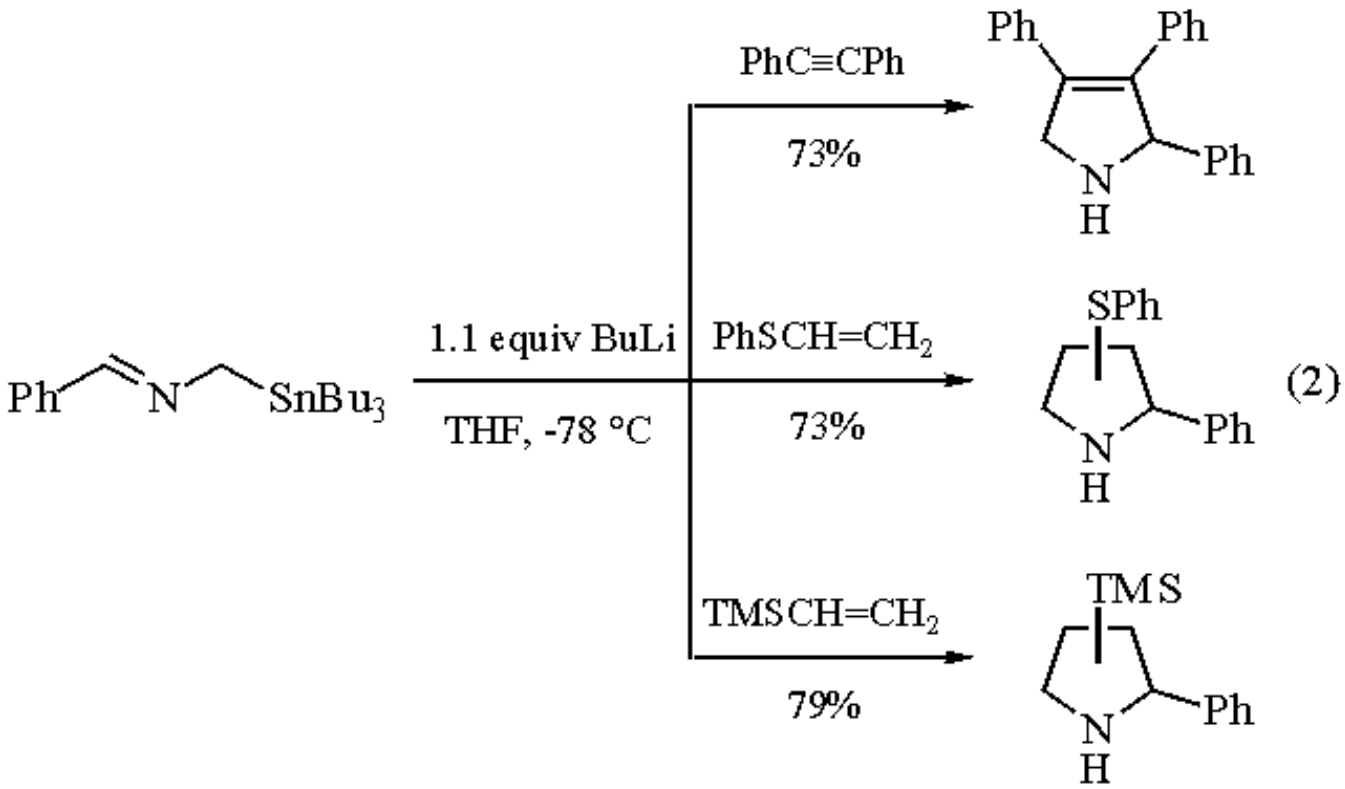

Related Pyrrolidine Syntheses using 2-Azaallyl Anion Cycloadditions.

In addition to the synthesis of 2-arylpyrrolidines as shown above, the 2-azaallyl anion method is useful for the preparation of a variety of 2-alkylpyrrolidines.[1,2] Similar restrictions regarding the anionophile apply. For example, vinyl selenides are excellent reaction partners (eq 3).[2] The phenylseleno group may be reductively or oxidatively removed, producing simple pyrrolidines or pyrrolines (eq 4).[2] Intramolecular examples are also known (eq 5).[1,2] More recently, 2-azallyl anions bearing two or three alkyl groups have been generated and used in cycloadditions, leading to 2,2-disubstituted, 2,5-disubstituted, and 2,2,5-trisubstituted pyrrolidines.[3] Example are shown in eqs 6 and 7. Note that 1,3-dialkyl-2-azaallyl anions produce pyrrolidines with a 2,5-*cis*-relationship, presumably due to the preferential formation of the W form of the anion (eq 7).

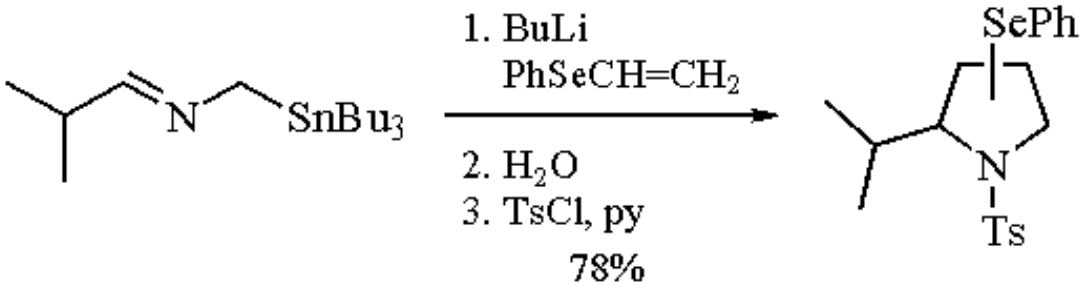

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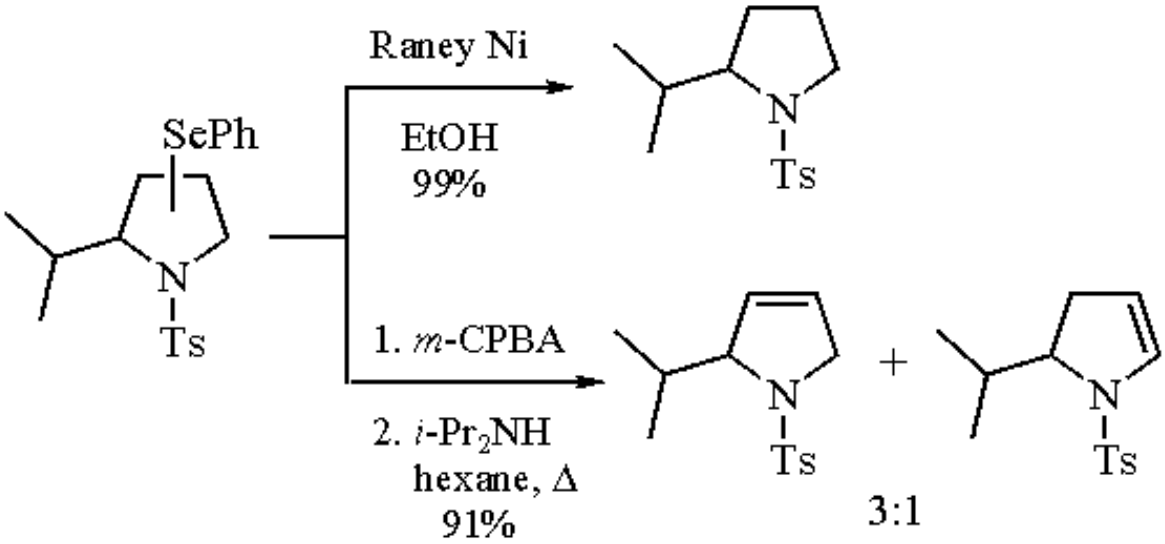

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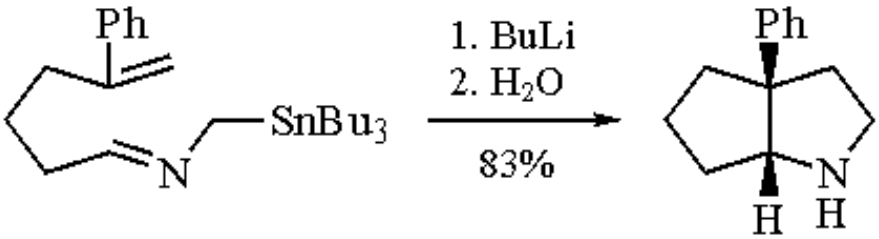

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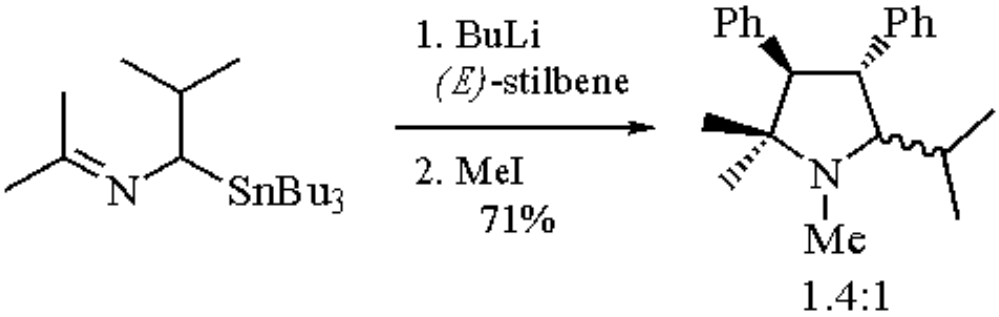

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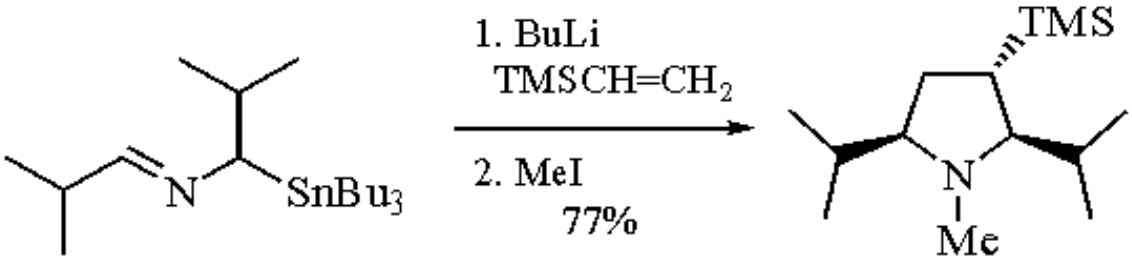

(7)

Related Methods for Pyrrolidine Synthesis.

Kaufmann has studied the formation and cycloaddition of 2-azaallyl anions derived from the deprotonation of imines such as *N*-benzylidenebenzylamine with amide bases.[5] Only anions bearing two or more aryl groups may be used, unless the cycloaddition is intramolecular, where one aryl group on the anion is necessary.[6] The generation of aryl-substituted 2-azaallyl anions by the desilylation of

N-(trimethysilyl)methanimines has been reported.[7,8] A variety of 2-azaallyl anions bearing strong electron-withdrawing groups have been generated and used in cycloaddition reactions.[9] The lower reactivity of these anions necessitates the use of more reactive anionophiles such as acrylates. Azomethine ylides are closely related to 2-azaallyl anions, and have also been used to synthesize pyrrolidines by dipolar cycloadditions with alkenes.[10] A review which compares the two methods has appeared.[11]

Related Reagents.

N-Benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine.

---

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University of Michigan, Ann Arbor, MI, USA

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(*E*)-3-Tri-*n*-butylstannyl-2-propenyl 2-Tetrahydropyranyl Ether[1]

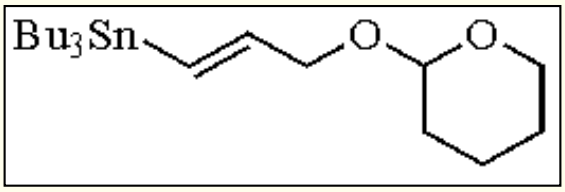

[55723-10-9] · $C_{20}H_{40}O_2Sn$ · (*E*)-3-Tri-*n*-butylstannyl-2-propenyl 2-Tetrahydropyranyl Ether · (MW 431.31)

(efficiently transmetalated by alkyllithium reagents;[2] palladium-catalyzed coupling affords substituted allylic alcohols)

Physical Data: bp 140-142 °C/0.1 mmHg;[2] ^{1}H NMR data have been reported.[4]

Solubility: sol THF, DMF.

Preparative Method: hydrostannation of propargyl tetrahydropyranyl ether affords the (*Z*)-isomer *[87830-21-5]*, which isomerizes at temperatures above 80 °C.[2,3]

Purification: can be purified by distillation.[2,3]

Handling, Storage, and Precautions: organostannane reagents are potentially toxic. Therefore their preparation and use must be conducted wearing appropriate protective clothing and in a well-ventilated hood. The reagent should be stored under an inert atmosphere and protected from light.

Transmetalation.

Alkyllithium reagents efficiently transmetalate (*E*)-3-tributylstannyl-2-propenyl 2-tetrahydropyranyl ether (**1**) to afford (*E*)-3-lithiopropenyl 2-tetrahydropyranyl ether, which exhibits reactivity typical of vinyllithium reagents.[2]

Cross-Coupling Reactions.

Stille et al. pioneered the palladium-catalyzed cross-coupling reaction of organostannanes with a variety of electrophilic partners. These reactions proceed under mild conditions, which are often compatible with typically sensitive functional groups.[1] Palladium-catalyzed couplings of (**1**) with vinyl halides (eq 1)[5] and heteroaryl halides (eq 2)[6] have been reported. Coupling of (**1**) (7:1 *E*/*Z* ratio) with aromatic triflates affords a 3:1 mixture of alkenic products (eq 3).[7a] Isomerically pure allylic alcohols can be obtained directly from the palladium-catalyzed coupling of (*E*)- and (*Z*)-1-(tributylstannyl)-1-propen-3-ol with aromatic triflates.[7a]

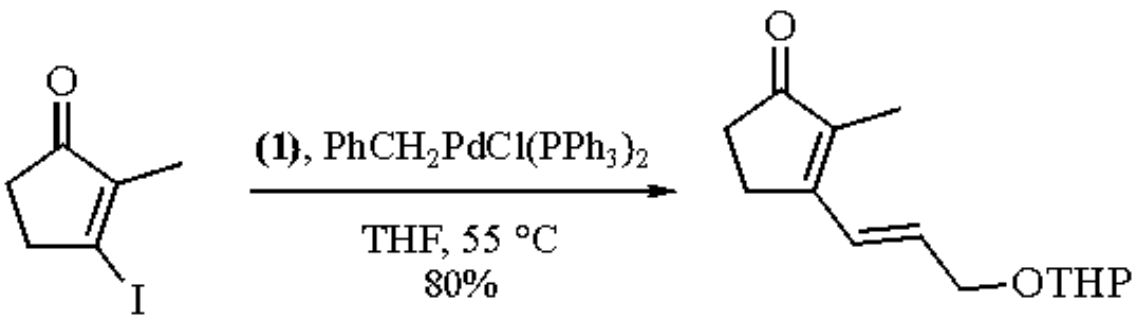

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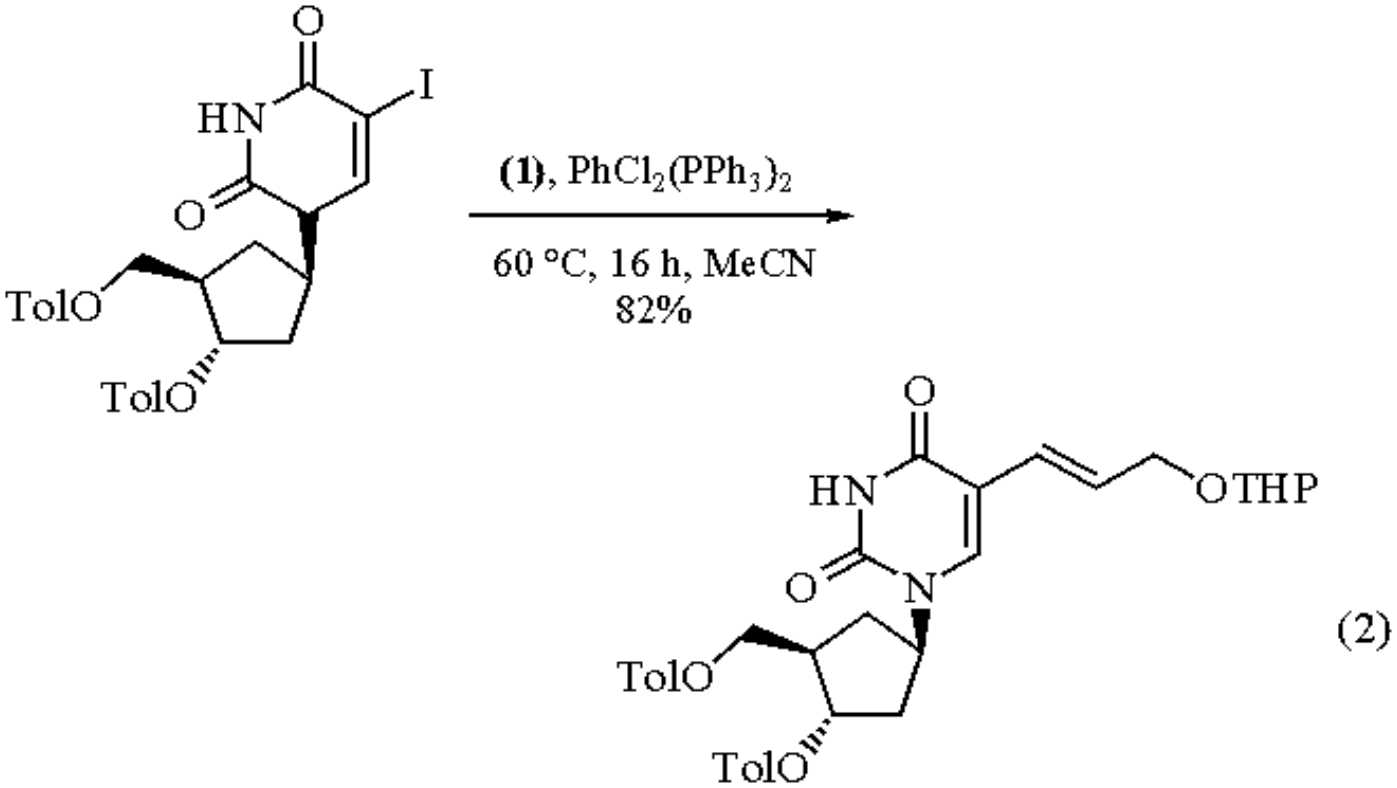

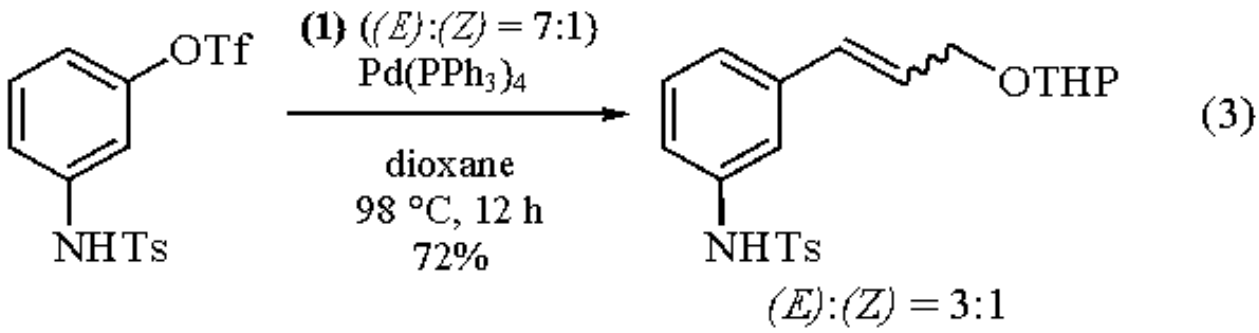

Aromatic triflates[7b] and allylic halides[8] couple with (**1**) in the presence of carbon monoxide to afford the corresponding α,β-unsaturated ketones (eq 4).[7b]

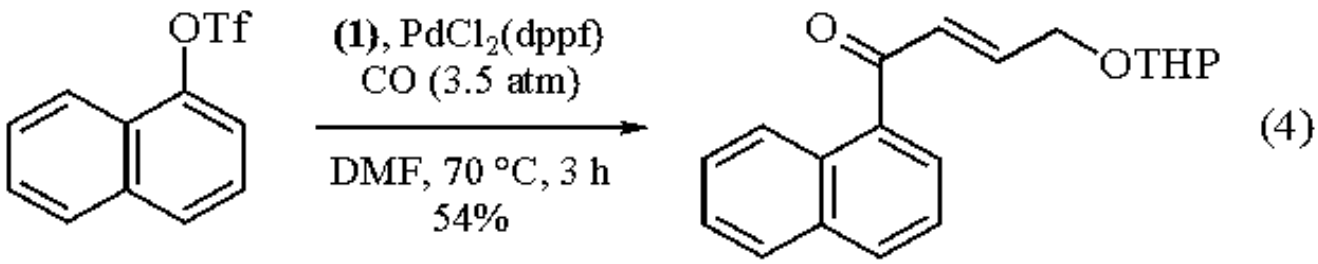

Coupling of (**1**) (1:1 *E*/*Z* ratio) with sulfonyl chlorides affords the corresponding isomerically pure (*E*)-allylic sulfone in good yield (eq 5).[9] Presumably, a mixture of allylic sulfones is formed initially which subsequently isomerizes under the reaction conditions to provide the thermodynamically more stable (*E*)-isomer. Similar isomerizations are observed in the palladium-catalyzed coupling of acid chlorides with (*Z*)-vinylstannanes.[10]

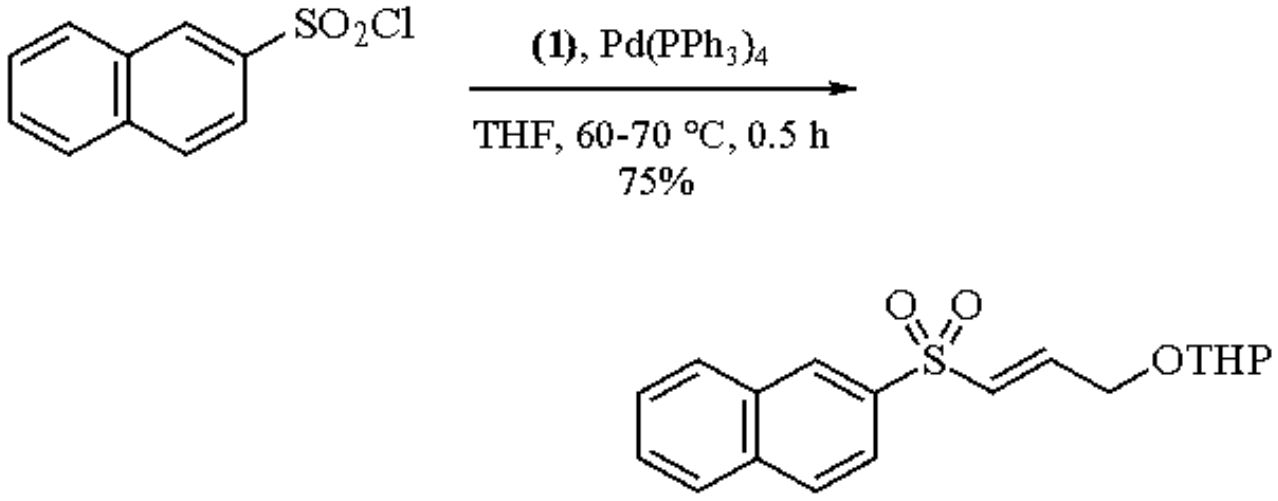

(5)

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(*E*)-1-Tri-*n*-butylstannyl-2-trimethylsilylethylene[1,2]

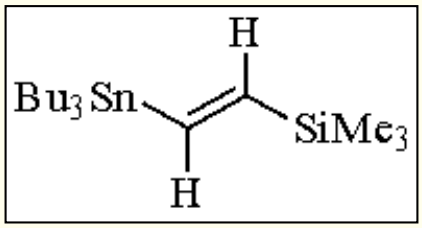

[58207-97-9] · $C_{17}H_{38}SiSn$ · (*E*)-1-Tri-*n*-butylstannyl-2-trimethylsilylethylene · (MW 389.35)

(used in the Pd^0-catalyzed cross coupling of vinyl and aryl halides or triflates;[1,2] a source of β-trimethylsilylvinyllithium[3])

Physical Data: bp 96-102 °C/0.5 mmHg.

Analysis of Reagent Purity: IR 1538 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, CH_2Cl_2) δ 0.12 (9H, s), 0.95 (9H, t, *J* = 7 Hz), 1.41 (18H, m), 6.65 and 7.08 (2H, AB pattern, *J* = 23 Hz).

Solubility: sol ethers, DMF, hydrocarbon, aromatic solvents.

Preparative Method: bis(tri-*n*-butylstannyl)ethylene is treated successively with molar equivalents of ***n-Butyllithium*** and ***Chlorotrimethylsilane*** to give (*E*)-1-tri-*n*-butylstannyl-2-trimethylsilylethylene.[5]

Handling, Storage, and Precautions: most tin compounds are toxic and are readily absorbed through the skin.[4] Their preparation and use should be carried out at all times in a well-ventilated fume hood.

Pd^0-Catalyzed Cross Couplings.

In general, (*E*)-1-tri-*n*-butylstannyl-2-trimethylsilylethylene undergoes the same types of Pd^0-catalyzed cross-coupling reactions as other substituted vinylstannanes. It readily couples with vinyl halides in the presence of catalytic amounts of Pd^0, giving 1,3-dienes in high yields (eq 1).[6] Vinyl and aryl triflates can undergo the cross-coupling reactions with the organostannane reagent, yielding 1,3-dienes provided ***Lithium Chloride*** is also present (eq 2).[7,8]

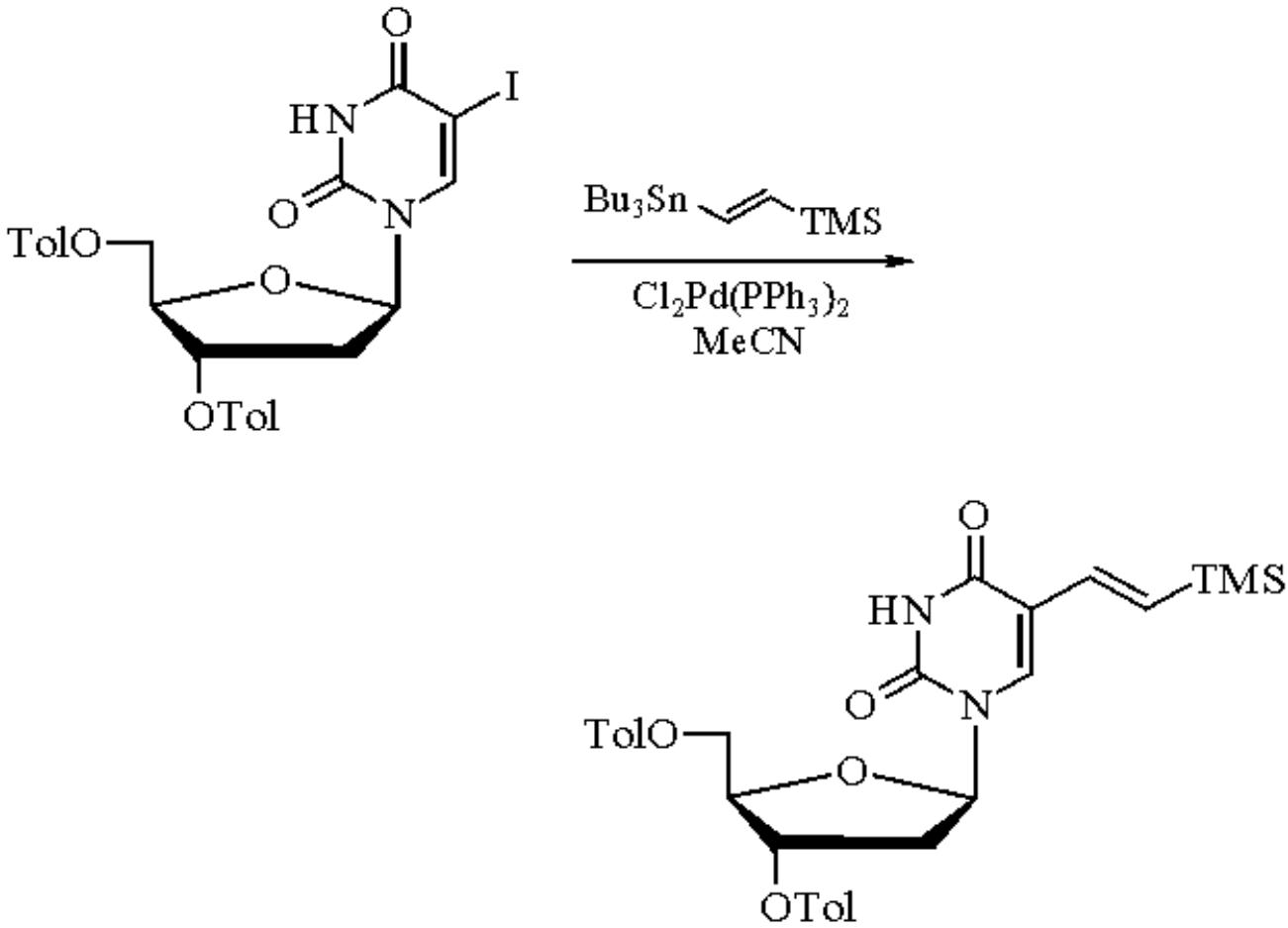

(1)

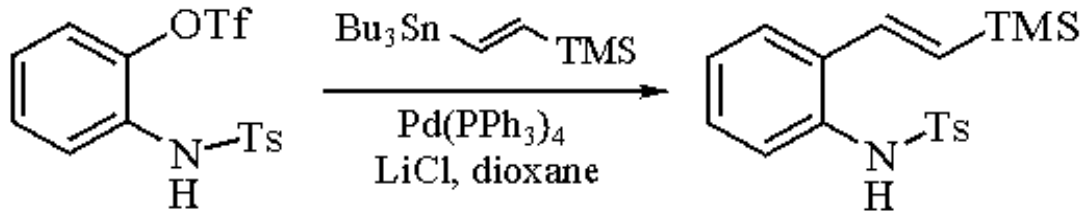

(2)

When the coupling reactions of vinyl and aryl triflates are carried out in the presence of ***Carbon Monoxide*** and LiCl, good yields of the cross-coupled ketones are obtained (eqs 3 and 4).[9] This is a particularly attractive route to divinyl ketones which are important substrates in the Nazarov cyclization.

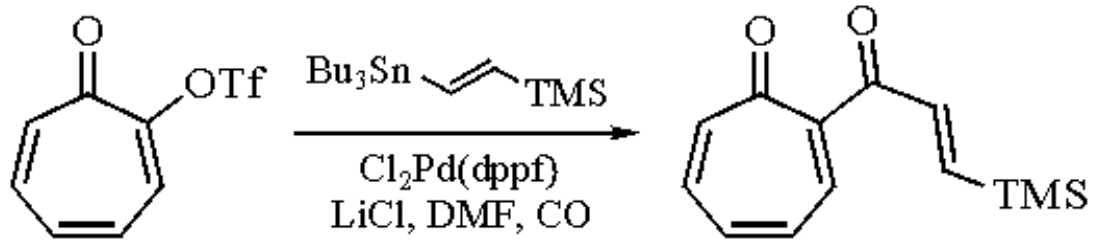

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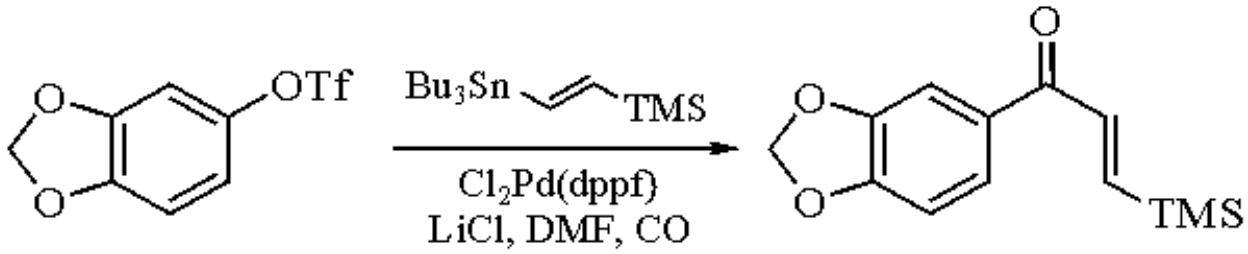

(4)

The reagent also couples predominantly 1,4 to acyclic vinyl epoxides to give allylic alcohols. The regioselectivity is controlled by the substitution pattern of the vinyloxirane. The 1,4 versus 1,2 selectivity could be further enhanced by the addition of water (10 equiv based on the vinyl epoxide) (eq 5).[10,11]

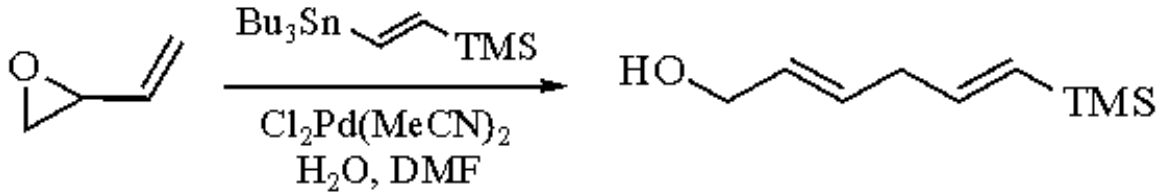

(5)

For additional discussion about palladium-catalyzed coupling reactions, see also those entries dealing with organopalladium catalysis (e.g. ***Tetrakis(triphenylphosphine)palladium(0)***, ***Tris(dibenzylideneacetone)dipalladium***, and ***(E)-1-Trimethylsilyl-2-trimethylstannylethylene***.

Transmetalation Reactions.

Transmetalation of trimethylsilyl-2-trimethylstannylethylene at low temperature with BuLi affords *trans*-β-trimethylsilyllithium in high yield, as evidenced by derivatization of 2-methyldimedone isobutyl ether (eq 6).[3,12-14]

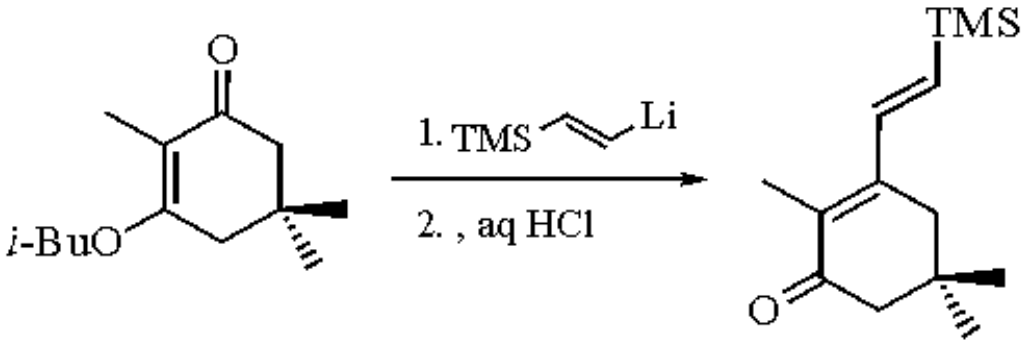

(6)

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Tri-*n*-butylstibine[1]

***n*-Bu_3Sb**

[2155-73-9] · $C_{12}H_{27}Sb$ · Tri-*n*-butylstibine · (MW 293.14)

(agent for making carbon-carbon bonds between α-halogeno carboxylic derivatives[2] (or α-halo ketones)[3] and carbonyl compounds in neutral conditions; can promote the cyclopropanation reaction between electron-deficient alkenes with dibromomalonate and its analogs;[4] formation of quaternary stibonium salt)

Physical Data: bp 131 °C/12 mmHg; *d* 1.197 g cm^{-3}.

Solubility: insol H_2O, ethanol; sol ether, petroleum ether, THF etc.

Preparative Method: prepared from ***Antimony(III) Chloride*** and 3 equiv of *n*-butylmagnesium bromide in absolute ether.[5]

Handling, Storage, and Precautions: pyrophoric; store and handle under nitrogen. Use in a fume hood.

General Discussion.

Phenyl-substituted stibonium salts are difficult to form by reaction of triphenylstibine with halides. Ylides with strong α electron-withdrawing groups in the alkylidene moiety can be prepared by reaction with diazo compounds, but they are unreactive to carbonyl compounds.[6] In contrast, trialkylstibines react readily with halides, especially with α-halo carboxylic derivatives, to form quaternary stibonium salts which react with carbonyl compounds to form alkenation products (eq 1).[1]

$$Bu_3Sb + XCHRE + R^1R^2CO \xrightarrow{60\text{-}130\ ^\circ C} R^1R^2C{=}CRE + Bu_3SbX(OH) \quad (1)$$

$$R = H, Me, Et;\ R^1, R^2 = alkyl, H;\ X = Cl, Br, BPh_4$$
$$E = CO_2Et, CONEt_2, COMe, CN$$

When R = H, R^1 = alkyl, R^2 = H, and E = CO_2Et (or $CONEt_2$, COMe), the products are highly stereoselective; when R = H, R^1 = alkyl, R^2 = H, and E = CN, the (*E*):(*Z*) ratio of products is ca. 3:2.[2]

β-Hydroxy ketones can be synthesized in excellent yield by the reaction of α-bromo ketones with various aldehydes mediated by Bu_3Sb in the presence of a catalytic amount of ***Iodine*** (2-4%).[7]

The reaction of ***Diethyl Dibromomalonate*** and its analogs with electron-deficient alkenes mediated by Bu_3Sb takes places easily under mild conditions and gives cyclopropane derivatives in high yields (eqs 2 and 3).[4]

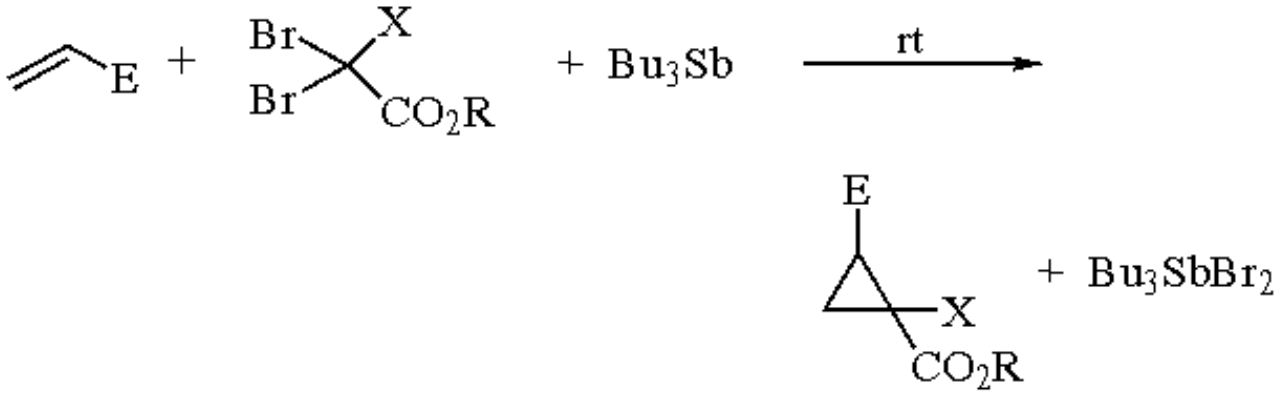

(2)

E = CHO, CN, COMe, CO_2Et; X = CO_2R, CN, Ph; R = Me, Et

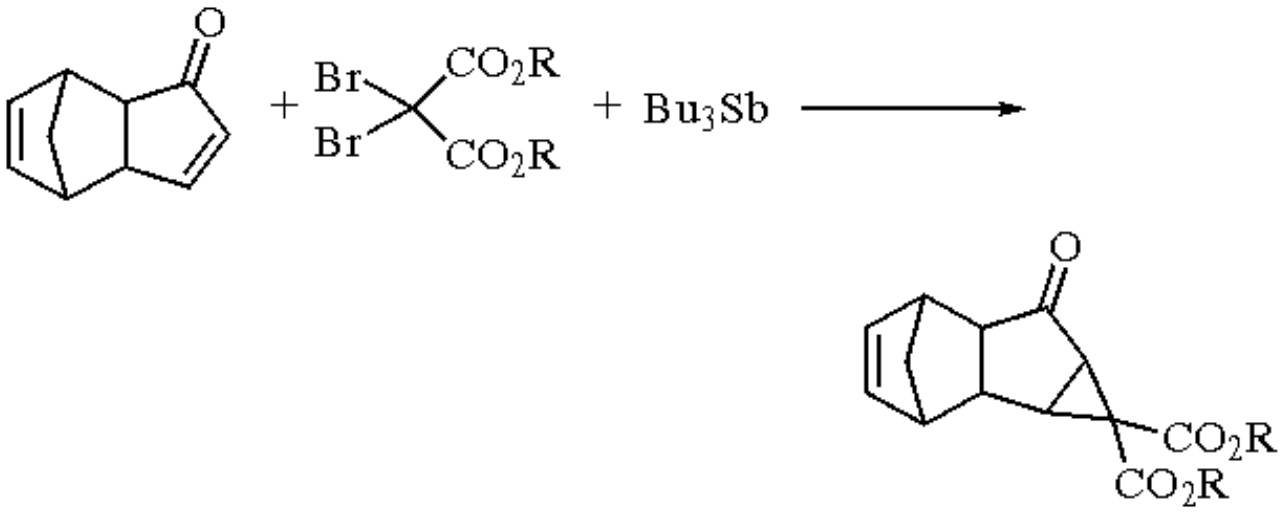

(3)

A Barbier-type reaction by means of Bu_3Sb has been reported (eq 4).[8] The *erythro*/*threo* ratio is approximately 2:1 to 3:1.

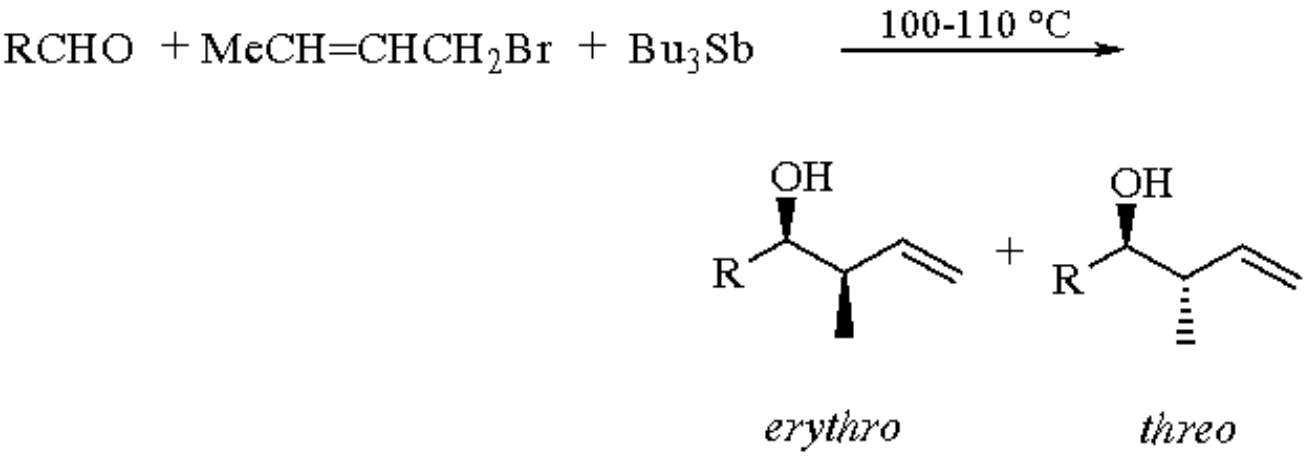

(4)

Since Sb has a greater tendency to form pentaalkyl derivatives than do P and As, treatment of quaternary stibonium with a strong nucleophilic base R´M affords pentaorganyl stiboranes (λ^5-stibanes).[9] These react with aldehydes to give secondary alcohols (eq 5).[10] In the presence of ***Aluminum Chloride***, pentaorganylstiboranes react with ketones to give tertiary alcohols.[11]

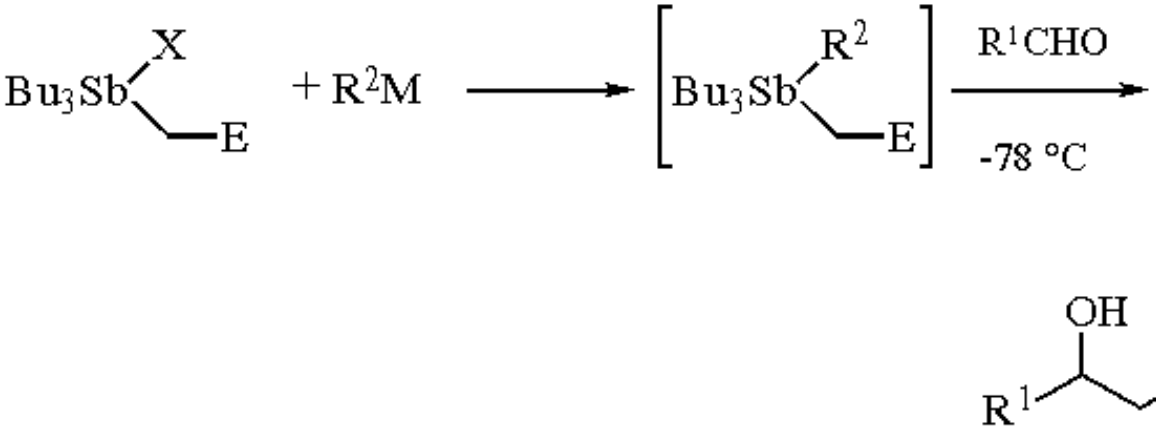

(5)

E = Ph, CH=CH$_2$, CH=CHCO$_2$Et, CN; X = Br, I, BPh$_4$; R^2 = Bu, *t*-Bu, Ph; M = Li, MgBr

The reaction of Bu_3Sb with propargyl bromide (see ***Propargyl Chloride***), bromo-2-butyne, and trimethylsilylpropargyl bromide gave allenic and alkynic stibonium salts. The pentaorganylstiboranes formed by reaction with BuM react with aldehydes to give alkynic or allenic alcohols as major products (eqs 6-8).[12]

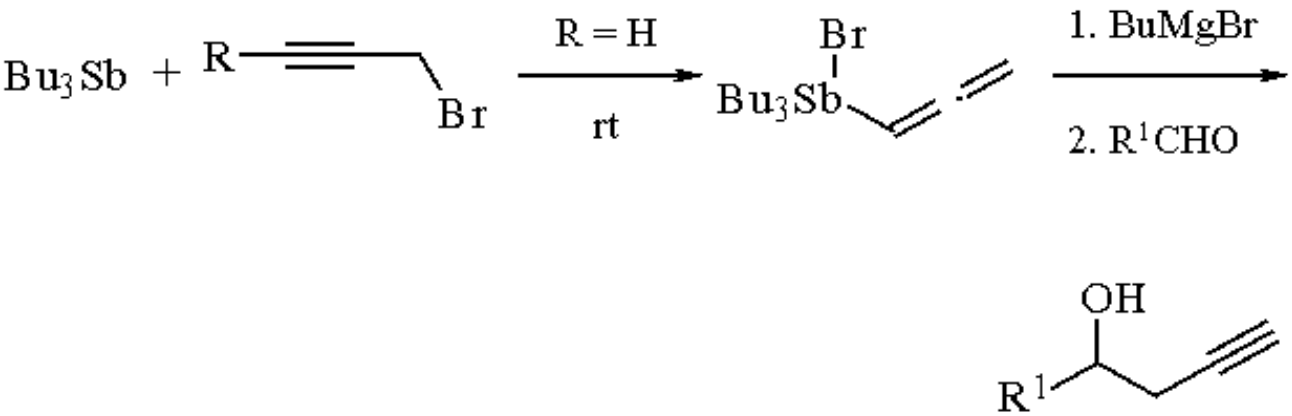

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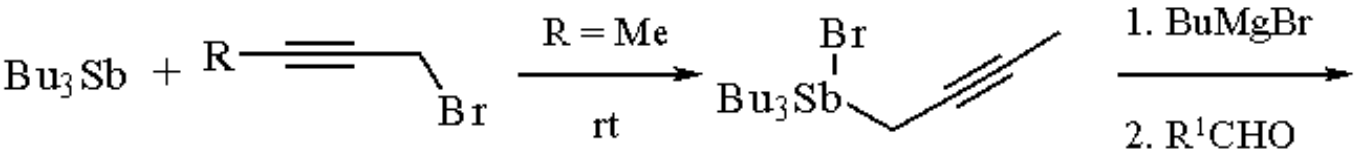

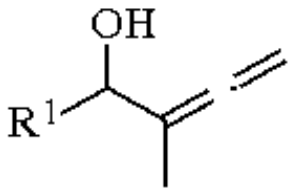

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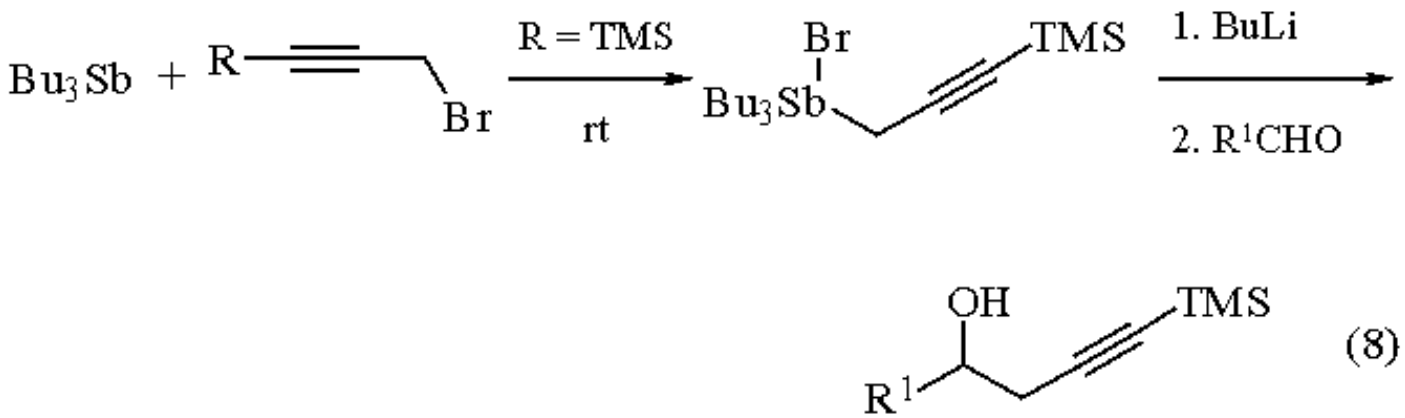

(8)

With less nucleophilic bases such as ***Lithium Diisopropylamide*** or ***Potassium t-Butoxide***, the quaternary stibonium salts give stibonium ylides. These react with carbonyl compounds to give alkenes (eq 9).[13]

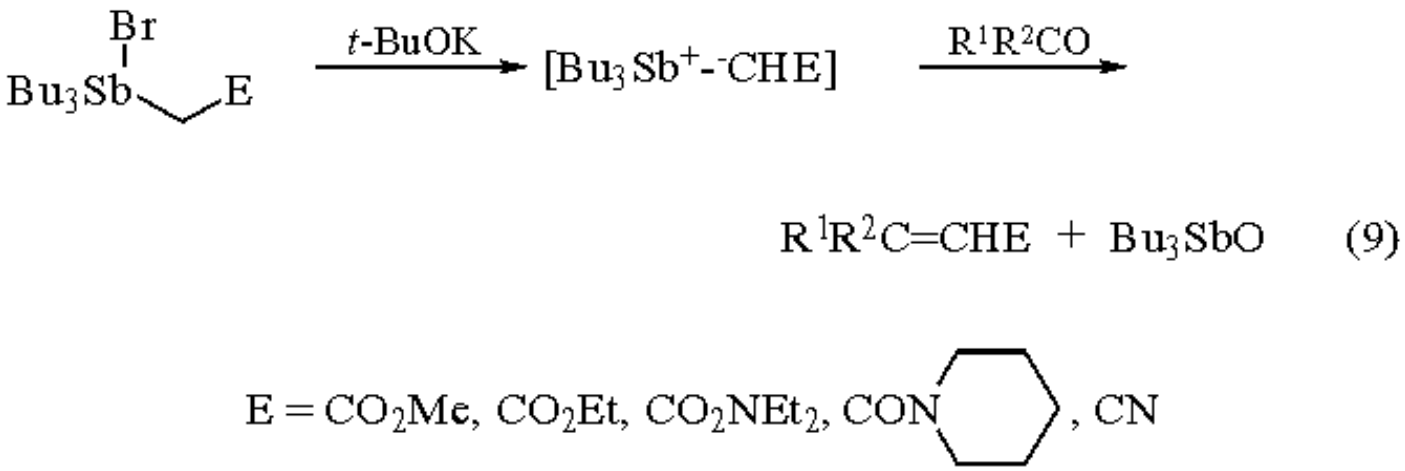

(9)

A novel alkenation of diazo compounds with carbonyl compounds mediated by Bu_3Sb and a catalytic amount of copper(I) halide has been reported (eq 10).[14] Stibonium ylides have been suggested as possible intermediates in these reactions.[15]

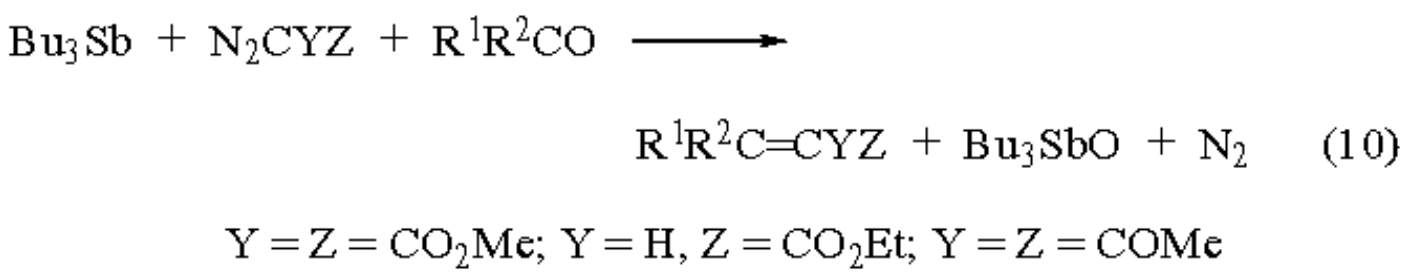

(10)

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Tri-*n*-butyltin Azide[1]

***n*-Bu$_3$SnN$_3$**

[17846-68-3] · $C_{12}H_{27}N_3Sn$ · Tri-*n*-butyltin Azide · (MW 332.13)

(nucleophilic azide equivalent; useful for the preparation of tetrazoles and triazoles via 1,3-dipolar cycloaddition reactions;[2] cleaves oxiranes to give 1,2-azido alcohols;[3] reacts with anhydrides and acid chlorides to give isocyanates[4])

Alternate Name: azidotributylstannane.

Physical Data: bp 118-120 °C/0.18 mmHg.[4,5]

Solubility: sol most nonprotic organic solvents (i.e. toluene, hexane, acetonitrile, THF, etc.).

Preparative Method: prepared in 91% yield by the reaction of ***Tri-n-butylchlorostannane*** with aqueous ***Sodium Azide*** at 0 °C.[4,5]

Purification: distillation.[4,5]

Handling, Storage, and Precautions: organotin derivatives are known to be toxic.[6] Avoid inhalation and contact with skin. Organotin azides are claimed to be thermally very stable.[2a] However, extreme caution should be exercised when heating an azide solution due to the possibility of explosion. Use in a fume hood.

Preparation of Tetrazoles.

The reaction of tributyltin azide with nitriles serves as one of the most convenient and versatile methods for the preparation of tetrazoles.[2a] The reaction proceeds via a 1,3-dipolar cycloaddition to give directly a 5-tributyltin-substituted tetrazole (eq 1). The Sn-N bond is readily cleaved by treatment with ***Hydrochloric Acid*** to give the free tetrazole and Bu$_3$SnCl. In general, reactions are carried out under inert atmosphere either neat or in solvents such as acetonitrile, 1,2-dimethoxyethane, THF, benzene, toluene, and xylene. Reaction temperature and duration are largely dependent on steric and electronic factors associated with the nitrile substrate.[2a]

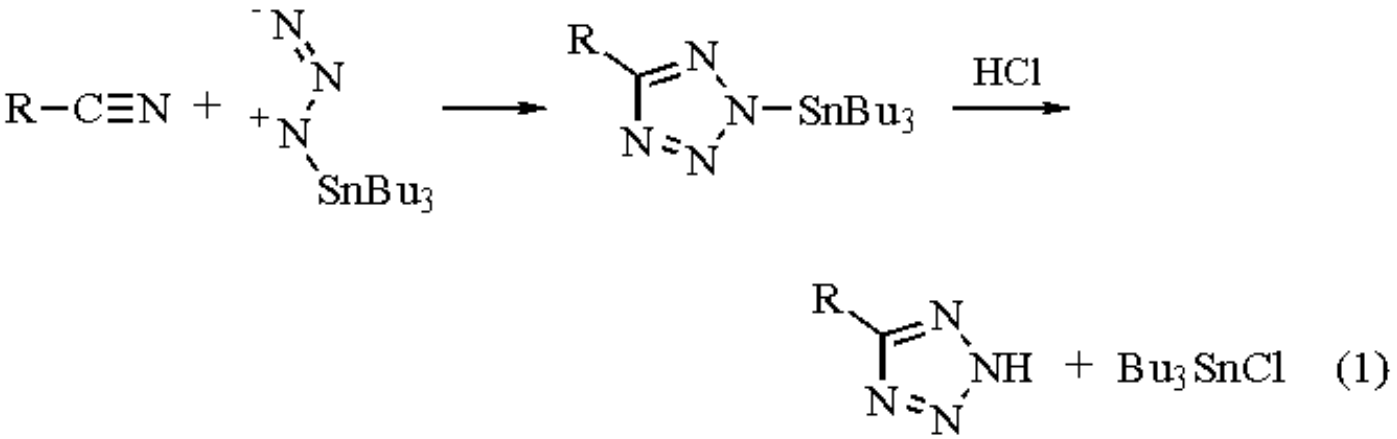

Tributyltin azide has been used in the synthesis of many complex molecules of pharmaceutical interest where a tetrazole is desired as a carboxylic acid bioisostere. Examples that illustrate the use of this reagent include application to the synthesis of an HMG-CoA reductase inhibitor (eq 2),[7] NMDA antagonist (eq 3),[8] leukotriene receptor antagonist (eq 4),[9] and a peptide inhibitor of vitamin K dependent carboxylation (eq 5).[10]

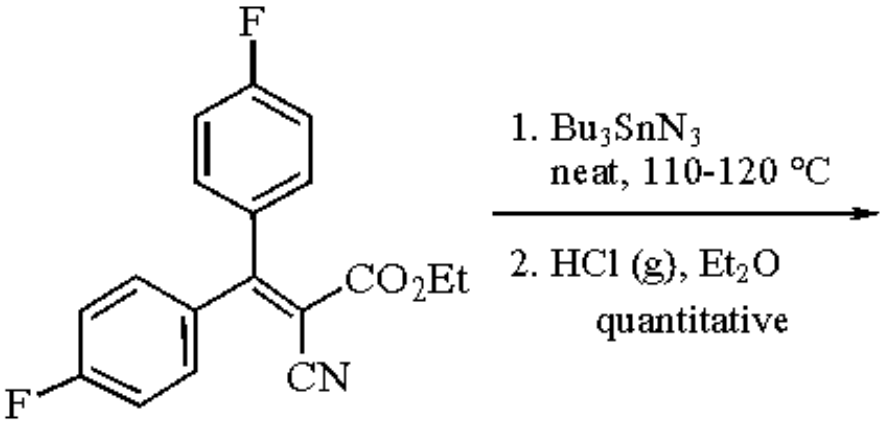
F
CO2Et
CN
F
1. Bu3SnN3
neat, 110-120 °C
2. HCl (g), Et2O
quantitative

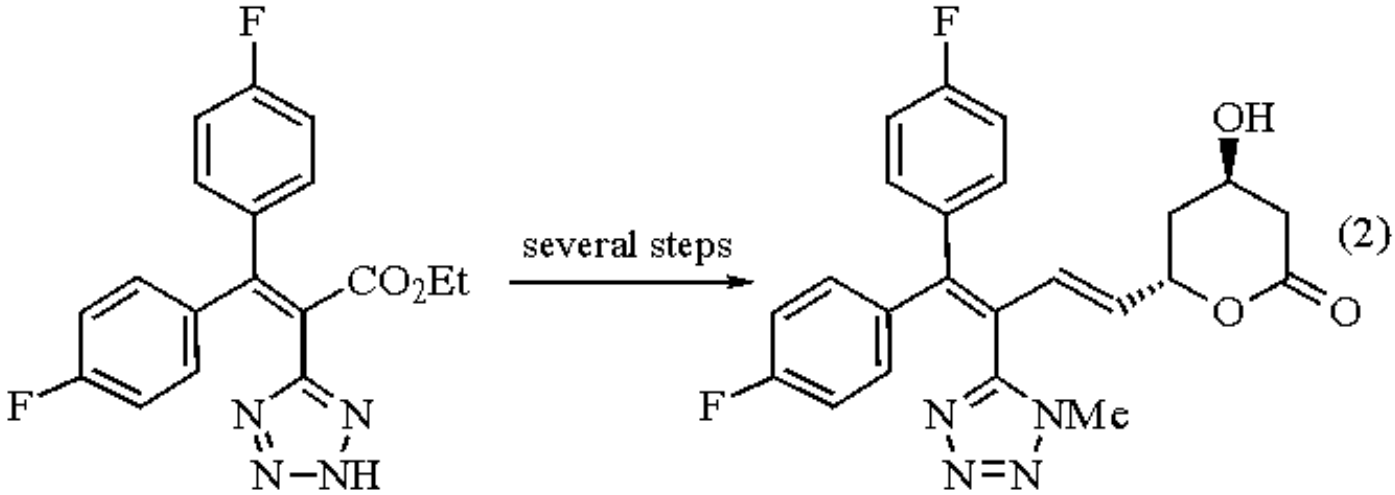
F
CO2Et
F
N
N
N–NH
several steps
F
OH
O
O
F
N
NMe
N=N

(2)

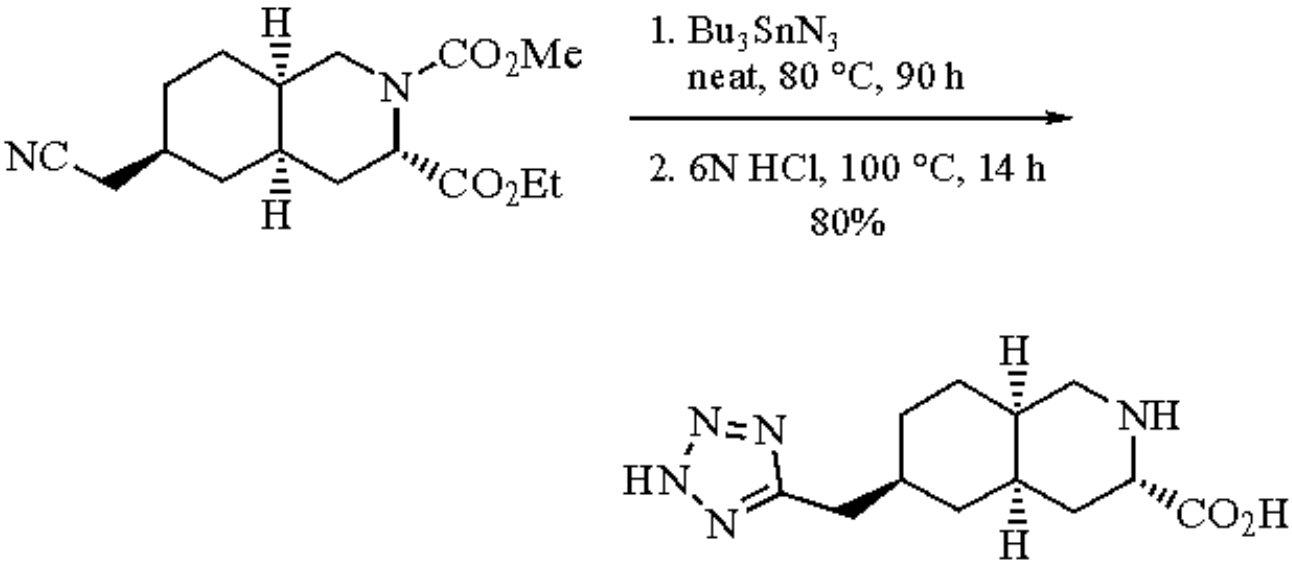
H
CO2Me
N
NC
CO2Et
H
1. Bu3SnN3
neat, 80 °C, 90 h
2. 6N HCl, 100 °C, 14 h
80%
H
N=N
HN
N
NH
CO2H
H

(3)

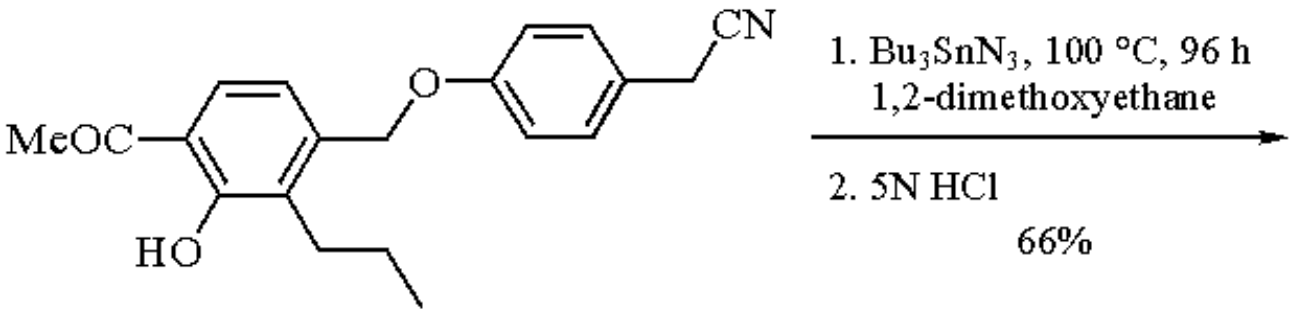

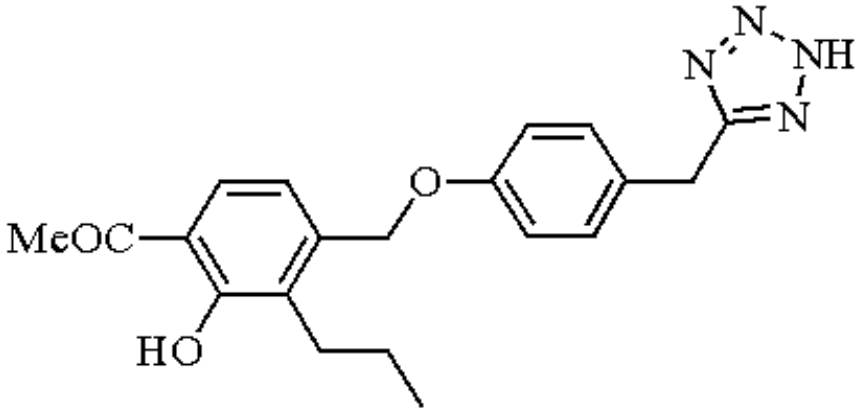

(4)

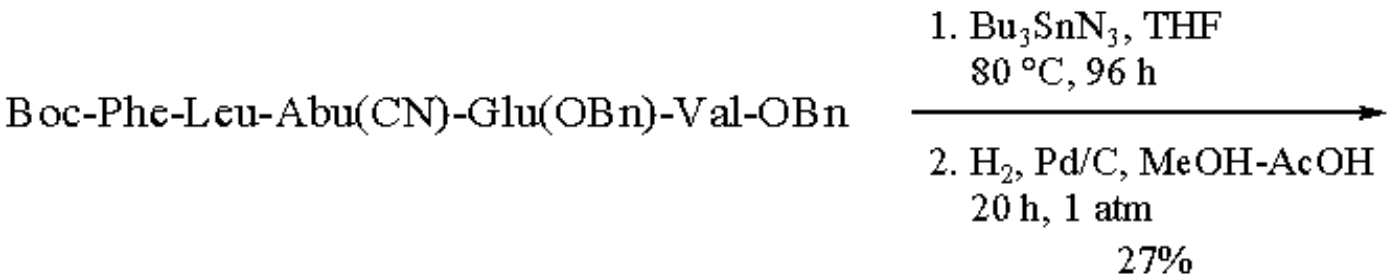

Phe-Leu-Abu(tetrazole)-Glu-Val (5)

Additionally, tributyltin azide has been used in the preparation of a key biphenyltetrazole intermediate employed in the synthesis of angiotensin II receptor antagonists (eq 6).[11,12] It was found that treatment of the tin adduct with ***Sodium Hydroxide*** followed by trityl chloride led directly to the highly crystalline trityl-protected tetrazole.[12] This modification facilitates isolation of the tetrazole that is generally made difficult by the presence of organic soluble tin residues.

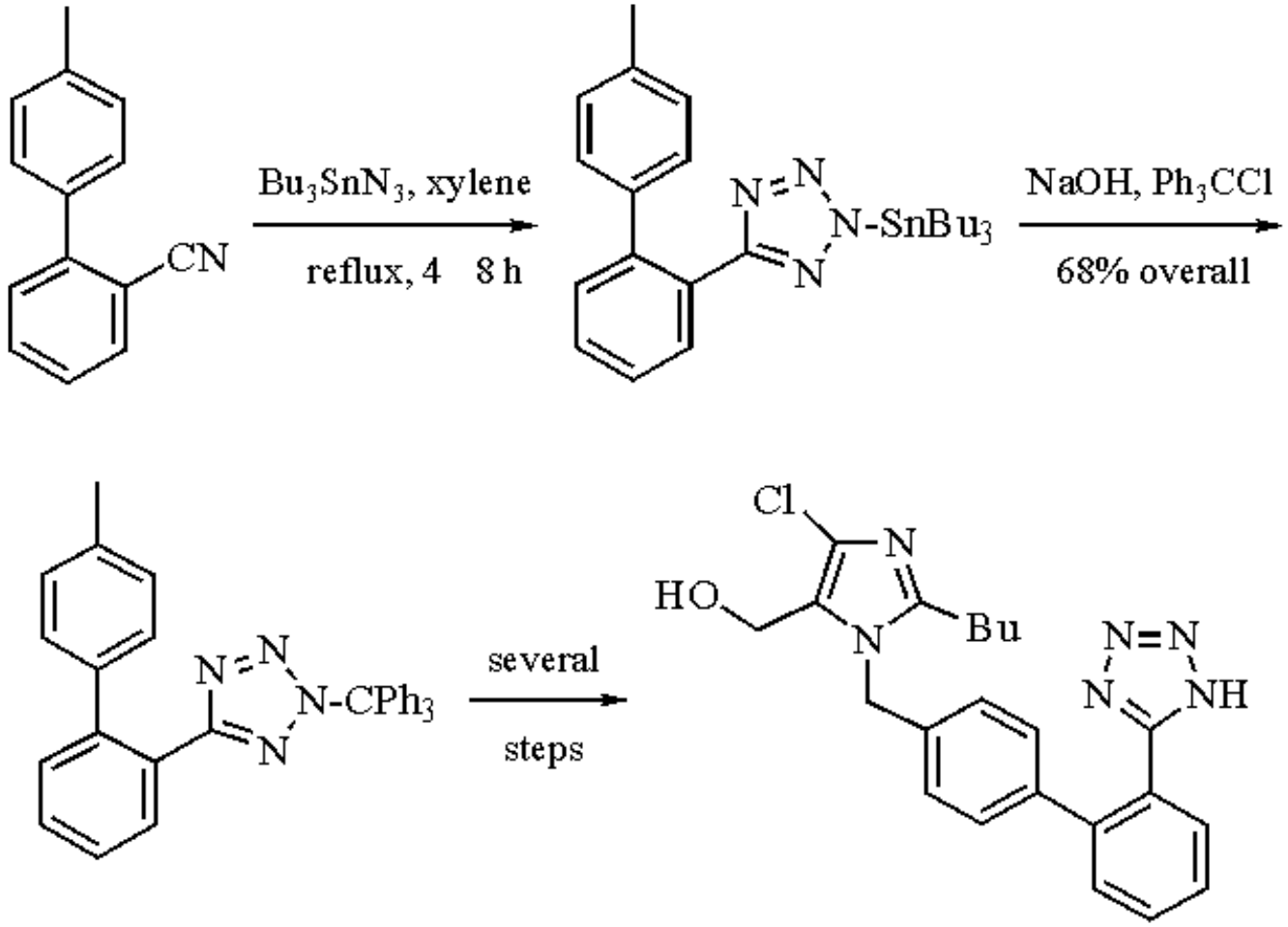

(6)

In a similar manner to that described for nitriles, tributyltin azide reacts with isothiocyanates to yield thiotetrazoles upon acidic workup (eq 7).[2d,e] A comparison of tributyltin azide with other methods for tetrazole synthesis has been published.[12]

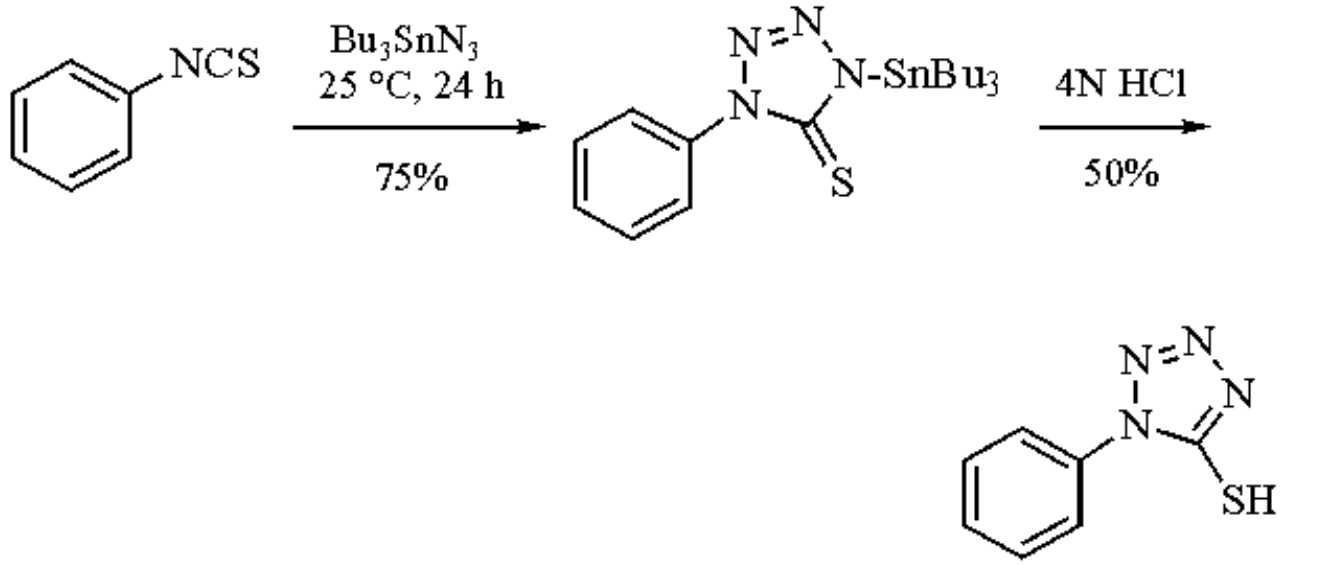

(7)

Preparation of 1,2,3-Triazoles.

Tributyltin azide reacts with mono- and disubstituted alkynes via a 1,3-dipolar cycloaddition reaction to yield tributyltin-substituted 1,2,3-triazoles (eqs 8 and 9).[2b,c] As with tetrazoles, the Sn-N bond is readily cleaved by treatment with HCl to give the triazole N-H derivative.

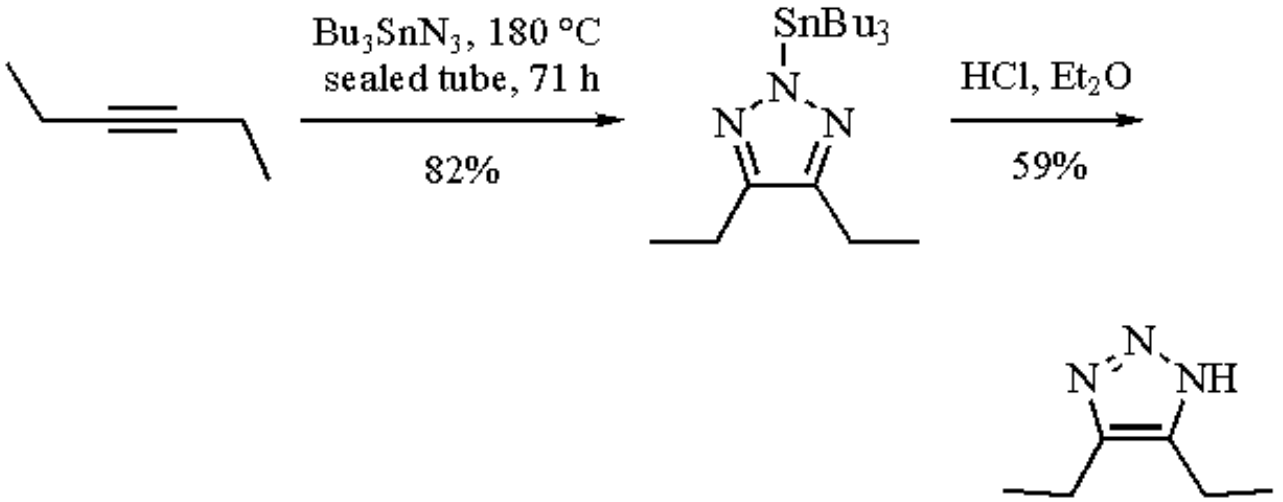

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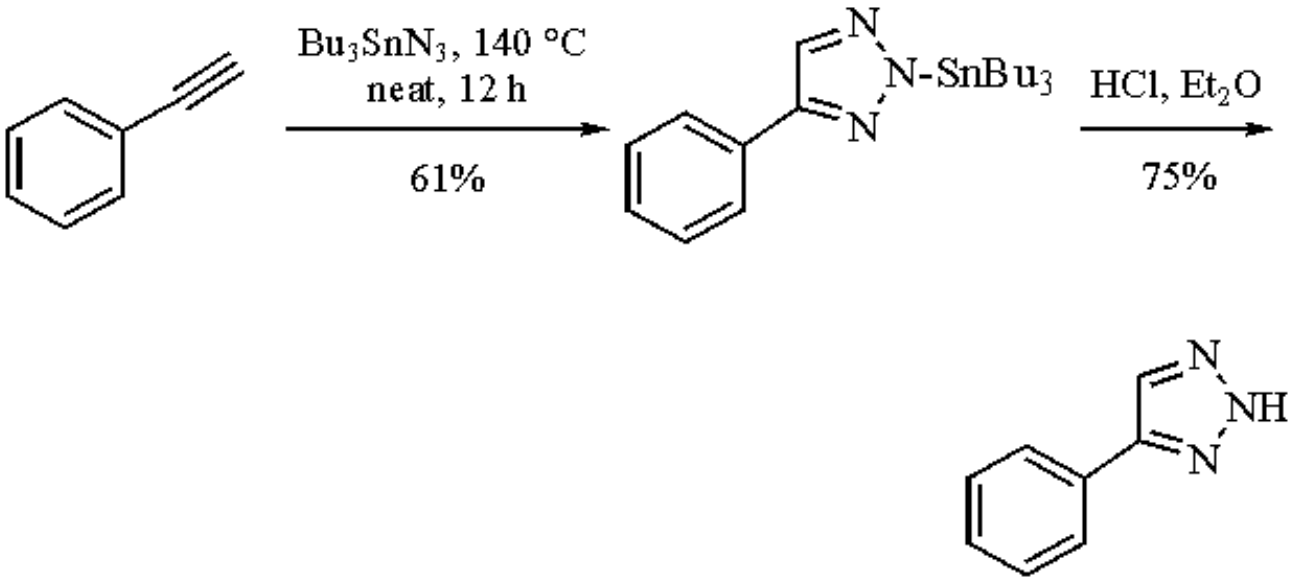

(9)

Preparation of Isocyanates, Carbamates, and Ureas.

Tributyltin azide reacts with acid chlorides under mild conditions to give isocyanates.[4] In a one-pot procedure, the isocyanate can be treated with an amine or alcohol to yield a urea (eq 10) or carbamate (eq 11), respectively. Anhydrides can be used in place of acid chlorides. This method serves as an alternative to using ***Azidotrimethylsilane***.[13]

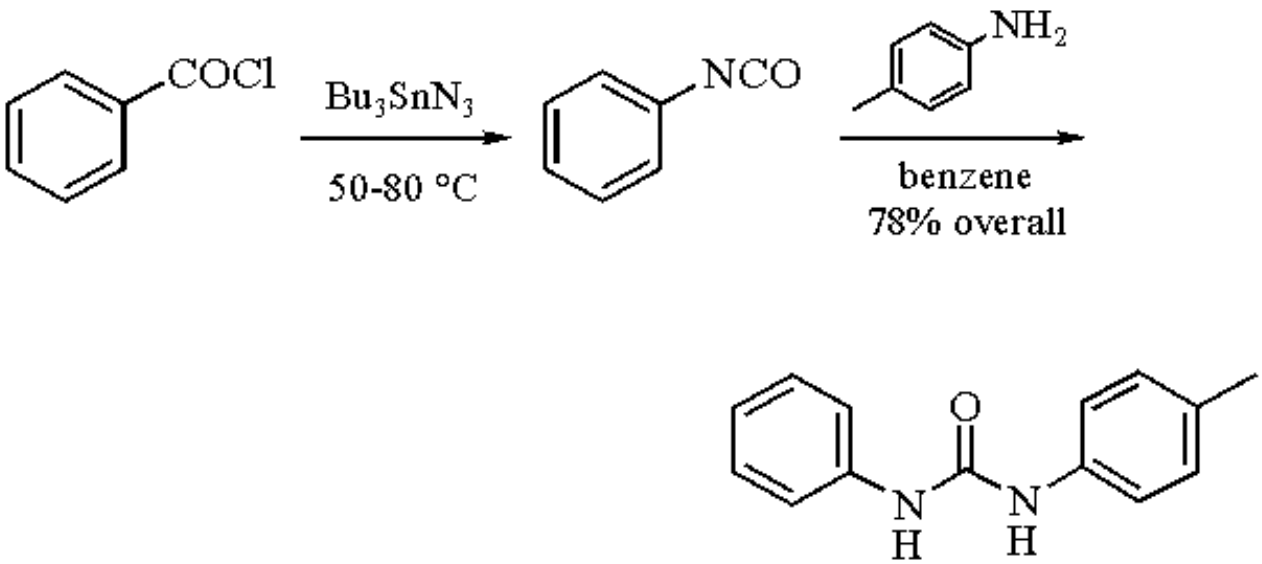

(10)

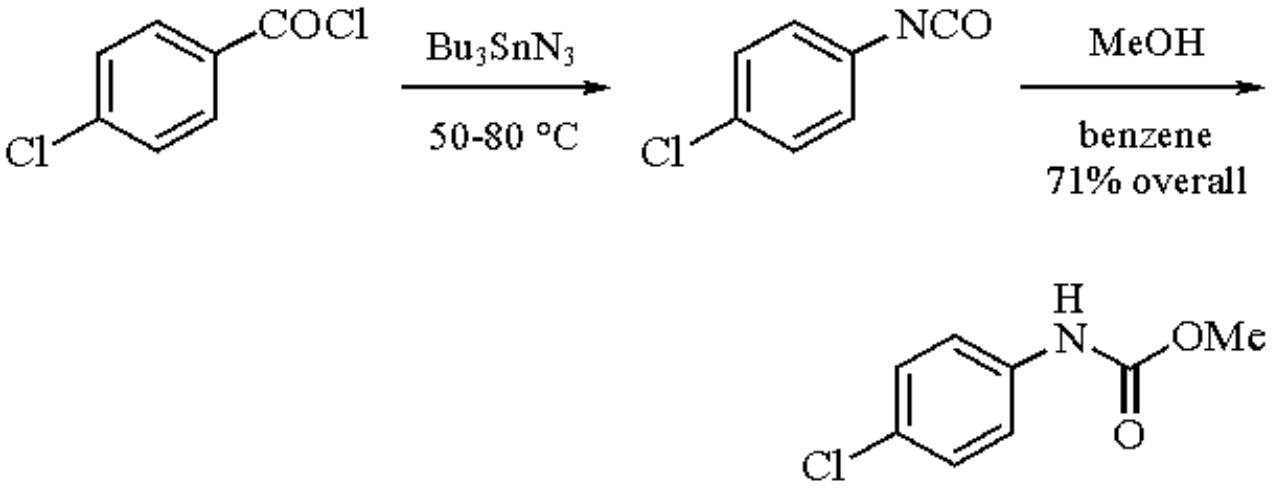

(11)

Preparation of 1,2-Azido Alcohols.

In contrast to trimethylsilyl azide, tributyltin azide is very reactive toward nucleophilic ring cleavage of oxiranes leading to 1,2-azido alcohols.[3] Reactions are typically carried out neat at 60 °C. The rate of reaction is highly dependent on the structure of the oxirane. Simple, nonsterically hindered oxiranes react rapidly (eq 12), while those with neighboring alkoxy groups (eq 13) or ester functions (eq 14) require longer reaction times. This difference in reactivity is attributed to modulation of the Lewis acidity of the tin species by the neighboring oxygen functionality.

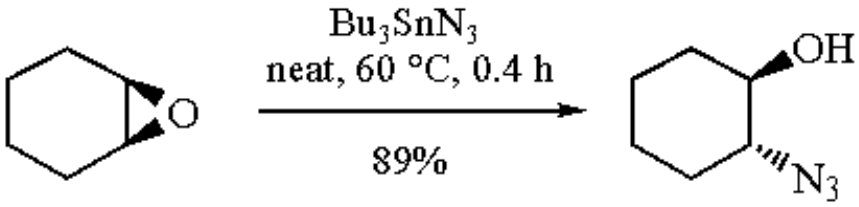

(12)

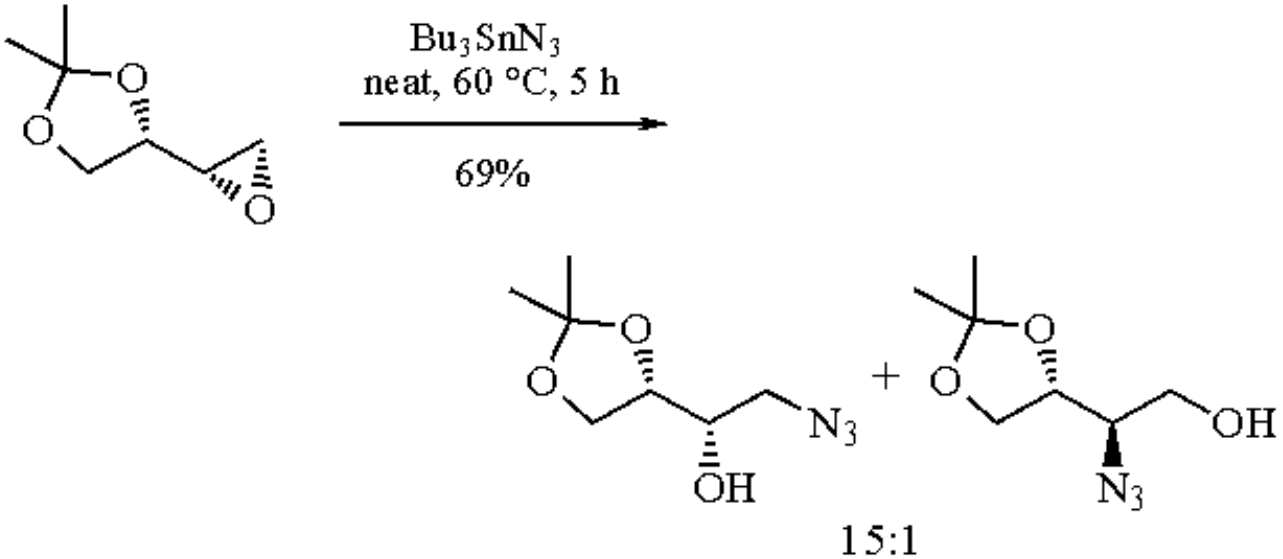

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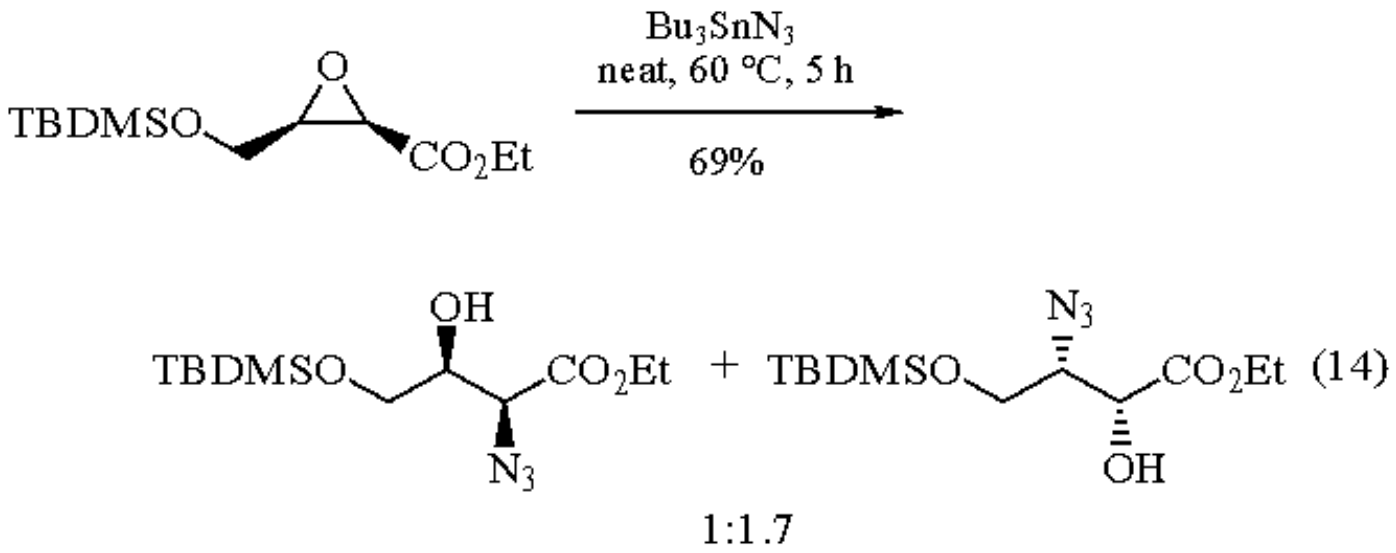

One limitation of this method is the difficulty of removing organotin residues from the reaction products. This has partially been addressed by studying a catalytic system using 10 mol % tributyltin azide and trimethylsilyl azide.[3a] Additionally, the use of dibutyltin diazide in place of tributyltin azide in nucleophilic cleavage of oxiranes has been reported to circumvent some of the problems associated with product isolation, as well as displaying enhanced reactivity.[3b]

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Tri-*n*-butylchlorostannane

***n*-Bu_3SnCl**

[1461-22-9] · $C_{12}H_{27}ClSn$ · Tri-*n*-butylchlorostannane · (MW 325.55)

(precursor of other organotributyltin reagents;[1] allylic tributyltins for the diastereoselective synthesis of homoallyl alcohols;[2] tributyltin enolates for alkylation[3] and regioselective C-C bond formation[4])

Alternate Name: tributyltin chloride.

Physical Data: bp 171-173 °C/25 mmHg; *n*20D 1.400; *d* 1.200 g cm^{-3}; fp >110 °C.

Form Supplied in: colorless liquid; widely available.

Solubility: sol ether, THF, hexane, CH_2Cl_2, MeOH.

Handling, Storage, and Precautions: in general, tributyltin compounds are highly toxic. The LD_{50} value for oral administration of Bu_3SnCl to rats is 122-349 µg g^{-1}. This reagent is absorbed through the skin to induce temporary skin burns. It must be handled with gloves in a well-ventilated hood. The reagent is air-stable, but slowly decomposes in presence of moisture.

Precursor to other Tributyltin Reagents.

Since the chlorine atom can be readily replaced by a variety of nucleophiles, tributyltin chloride is widely used for the preparation of other synthetically useful organotin compounds[1] such as ***Tri-n-butylstannane***,[5] ***Tri-n-butyl(methoxy)stannane***,[6] diethylaminotributyltin,[7] ***Cyanotributylstannane***,[8] ***Tri-n-butyltin Azide***,[9] ***Hexabutyldistannane***,[10] and ***Bis(tri-n-butyltin) Oxide*** (eq 1).[11]

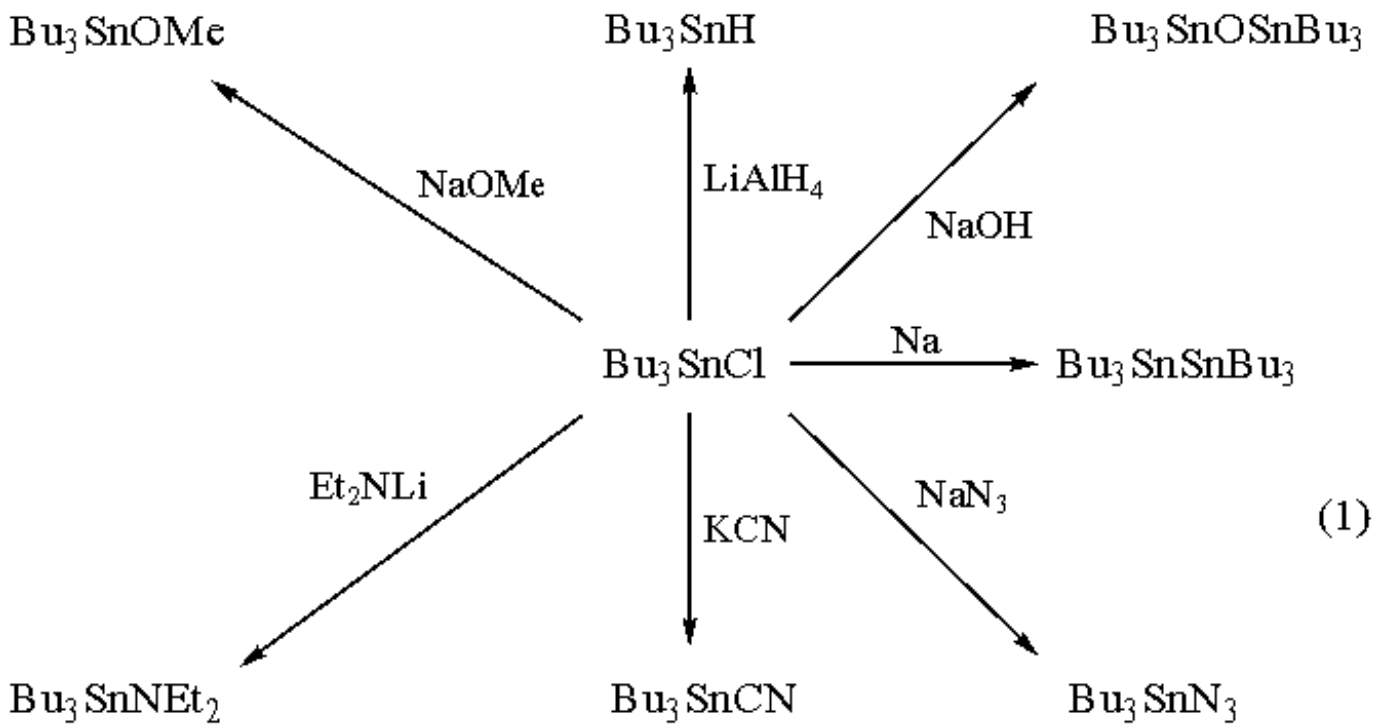

(1)

Tri-n-butylstannyllithium is readily prepared by the treatment of tributyltin chloride with ***Lithium*** metal[12] and is a valuable reagent for the preparation of organotin compounds.[1a] The stannyllithium is also prepared from *n*-Bu_3SnH and ***Lithium Diisopropylamide***, or from $Bu_3SnSnBu_3$ and ***n-Butyllithium***. Among these preparative methods, the procedure using *n*-Bu_3SnH provides the highest yield of *n*-Bu_3SnLi.[10a] The reaction of the stannyllithium reagent with aldehydes followed by alcohol protection affords α-alkoxystannanes, which are

treated with *n*-butyllithium to yield α-alkoxyllithium derivatives (eq 2).[14] ***Tri-n-butylstannylcopper*** (or cuprate) reagents are prepared from the stannyllithium and copper salts.[15] These reagents are employed for the preparation of β-stannyl-α,β-unsaturated carbonyl compounds (eq 3).[16]

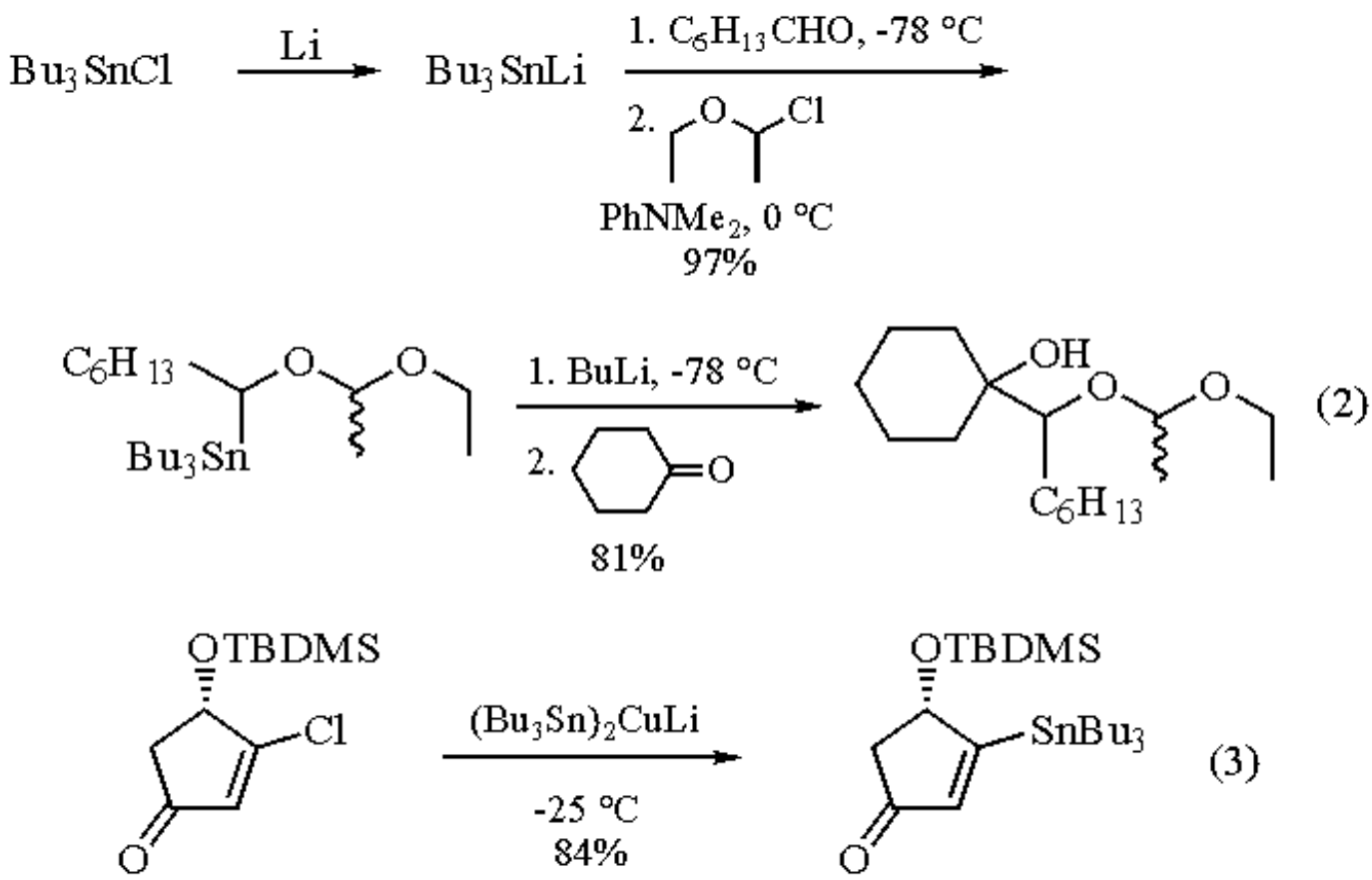

Allyl-, Alkenyl-, and Alkynyltin Reagents.

Simple allyltins are prepared by the reaction of Grignard reagents with tributyltin chloride.[17] γ-Alkoxyallyltins are obtained by trapping the allyl anions generated from allyl ethers.[2a] In this case, tributyltin chloride attacks the γ-position of the allyl anions to produce the (*Z*)-allyltins, owing to the strong coordination ability of the oxygen atom toward the lithium atom. γ-Methoxyallyltin reacts with aldehydes in the presence of Lewis acids to give *syn*-1,2-diol derivatives with high diastereoselectivity (eq 4).[2] An intramolecular allylic tin-aldehyde condensation has been applied to the synthesis of medium-ring cyclic ethers (eq 5).[18]

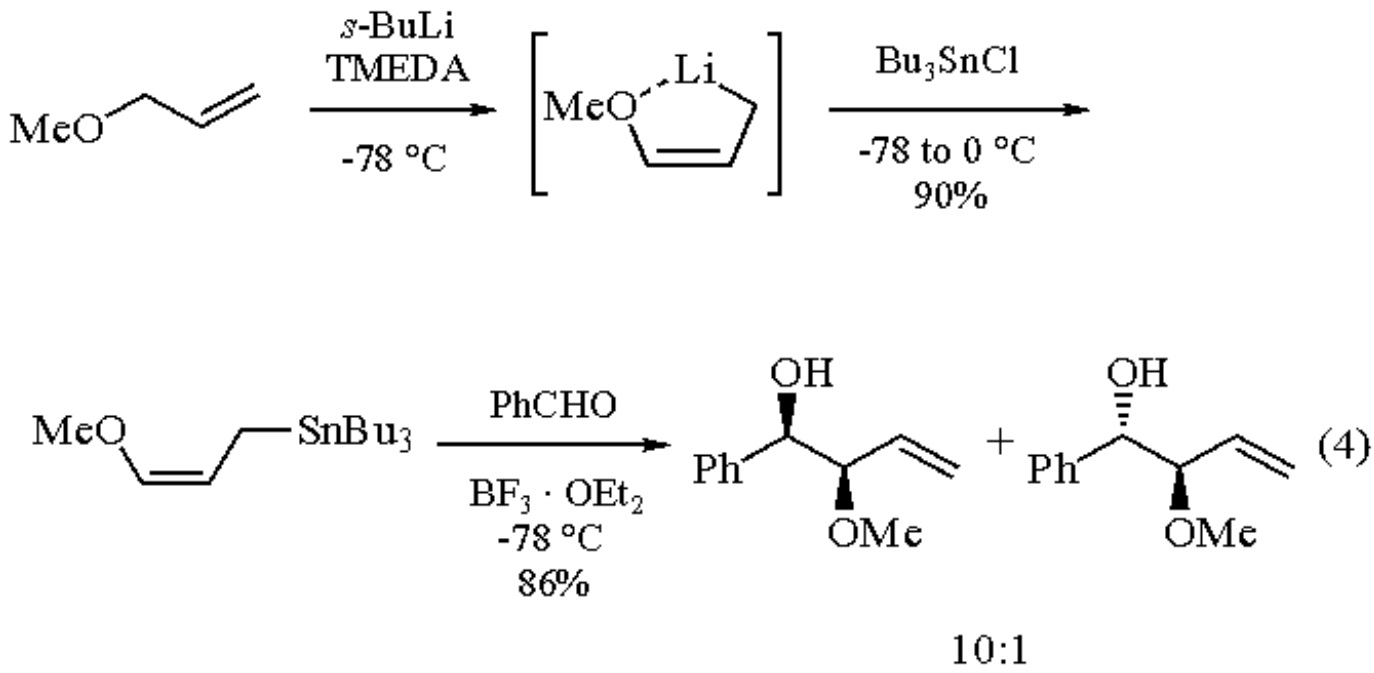

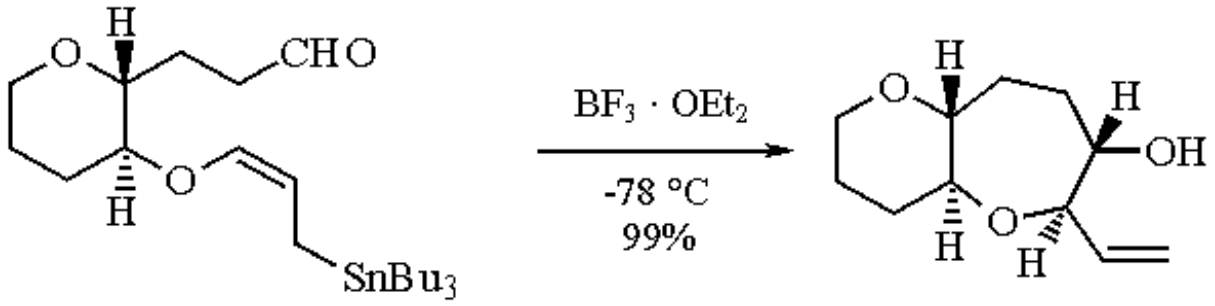

(5)

Tributyltin chloride reacts with alkenylcopper reagents, generated by the reaction of alkylcoppers and terminal alkynes, to give (*Z*)-alkenyltin derivatives (eq 6).[19] In contrast, the reaction of the alkenylaluminum obtained by hydroalumination affords the (*E*)-isomer (eq 7).[20] Dienyltin derivatives are prepared via the hydrozirconation of 1-en-3-yne.[21] Terminal alkynes react with *n*-$Bu_3SnAlEt_2$, prepared in situ from *n*-Bu_3SnLi and ***Diethylaluminum Chloride***, in the presence of Cu^I or Pd^0 catalysts, to give 1,2-dimetallo-1-alkenes with high regio- and stereoselectivity. These intermediates can be selectively functionalized at the vinyl-aluminum bond to provide alkenyltins (eq 8).[13]

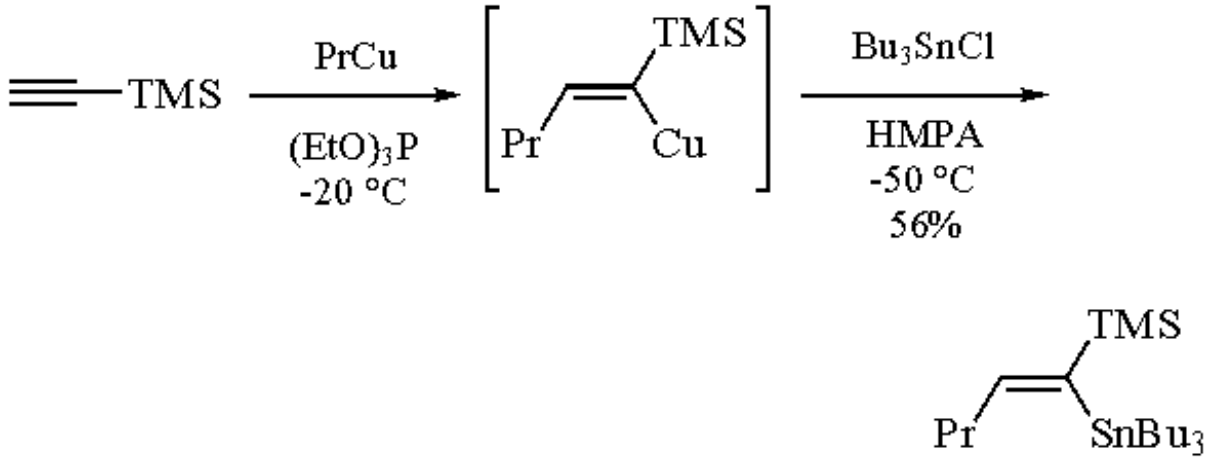

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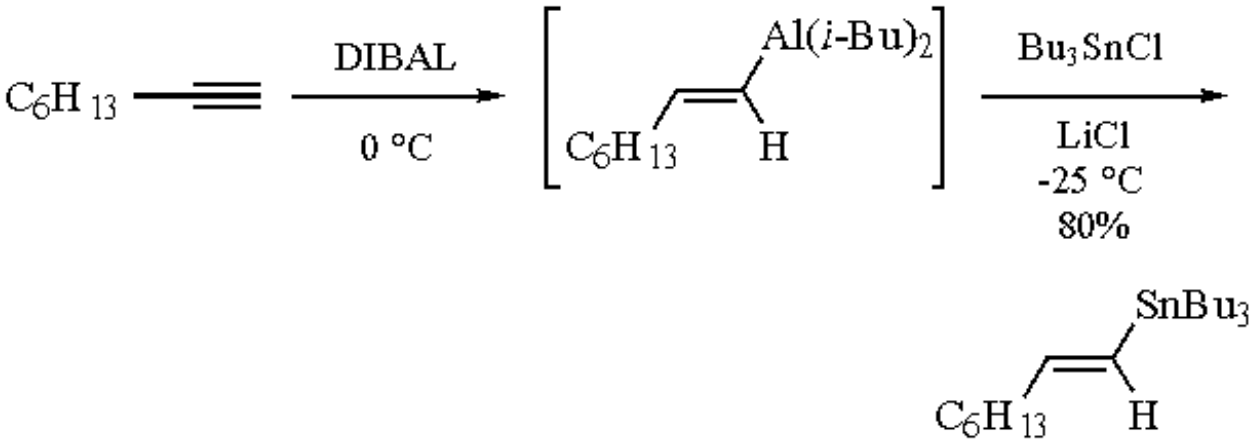

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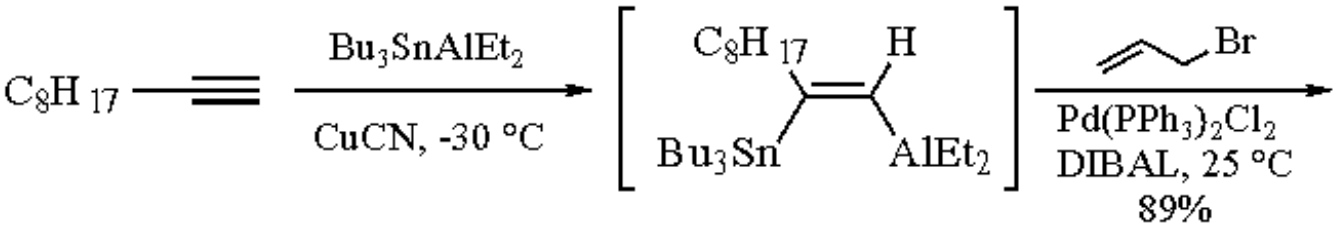

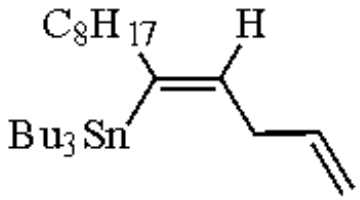

(8)

Alkynyltins are easily made by the reaction of lithium or sodium acetylides with tributyltin chloride.[22] These compounds undergo coupling with vinyl iodides in the presence of a palladium catalyst to give conjugated enynes (eq 9).

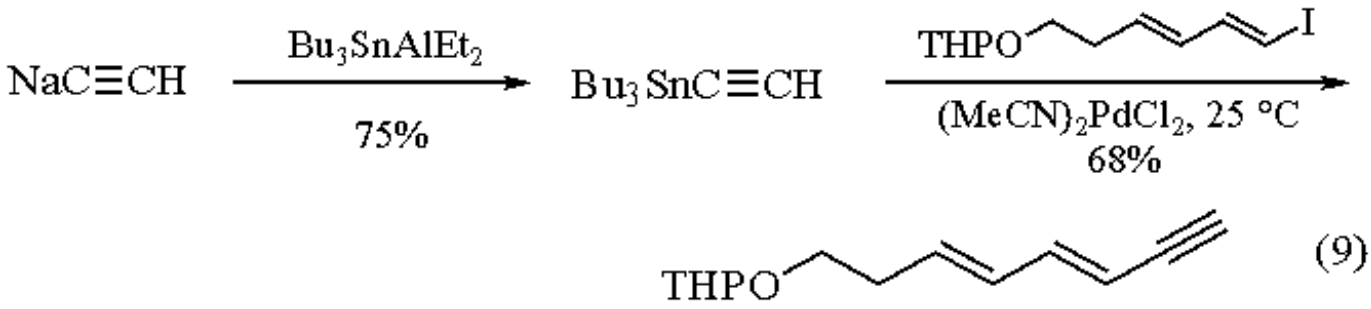

Tin Enolates.

Tin enolates prepared by transmetalation of lithium enolates with tributyltin chloride undergo rapid aldol condensations with aldehydes (eq 10).[23] This approach has been used to enhance the yield of the alkylation of the enolate generated by the conjugate addition of lithium enolate to cyclopentenone (eq 11).[3] A complicated mixture is obtained in the absence of the tin reagent.

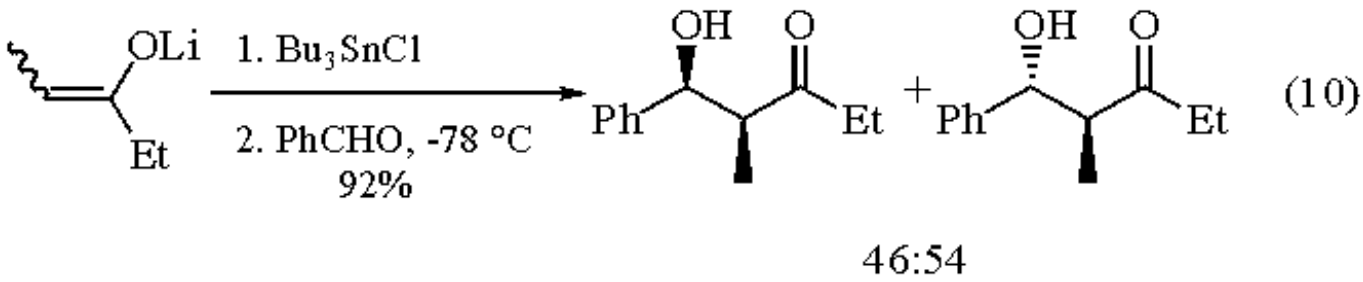

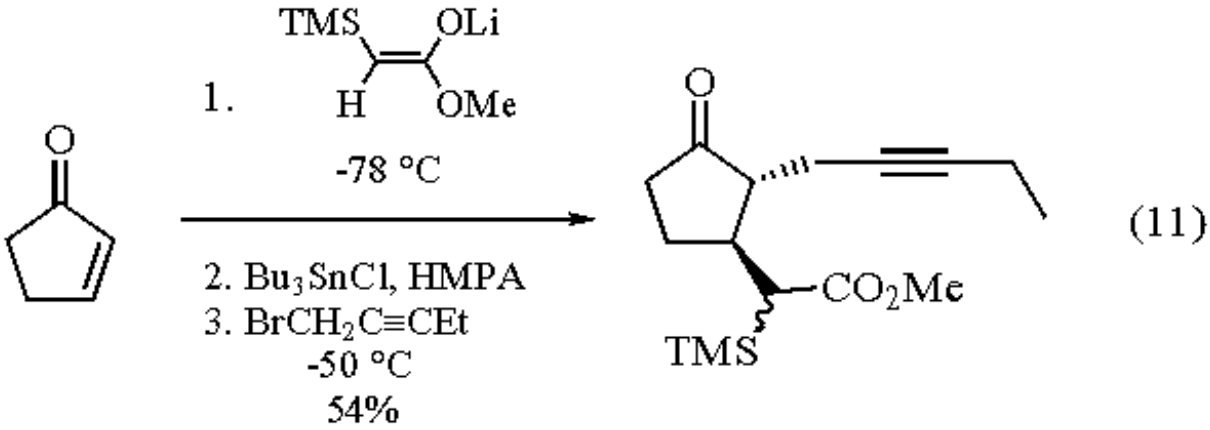

The reaction of lithium dienolates with tributyltin chloride gives γ-stannylated α,β-unsaturated esters, which are stable enough to be isolated by distillation (eq 12).[4] The aldol-type condensation of the tin-masked dienolates proceeds at the α-position of the dienolates with high regio- and stereoselectivity in the presence of Lewis acid.[4a,b] On the other hand, the palladium-catalyzed coupling reaction with organic halides takes place at the position directly bonded to tin.[4a,c]

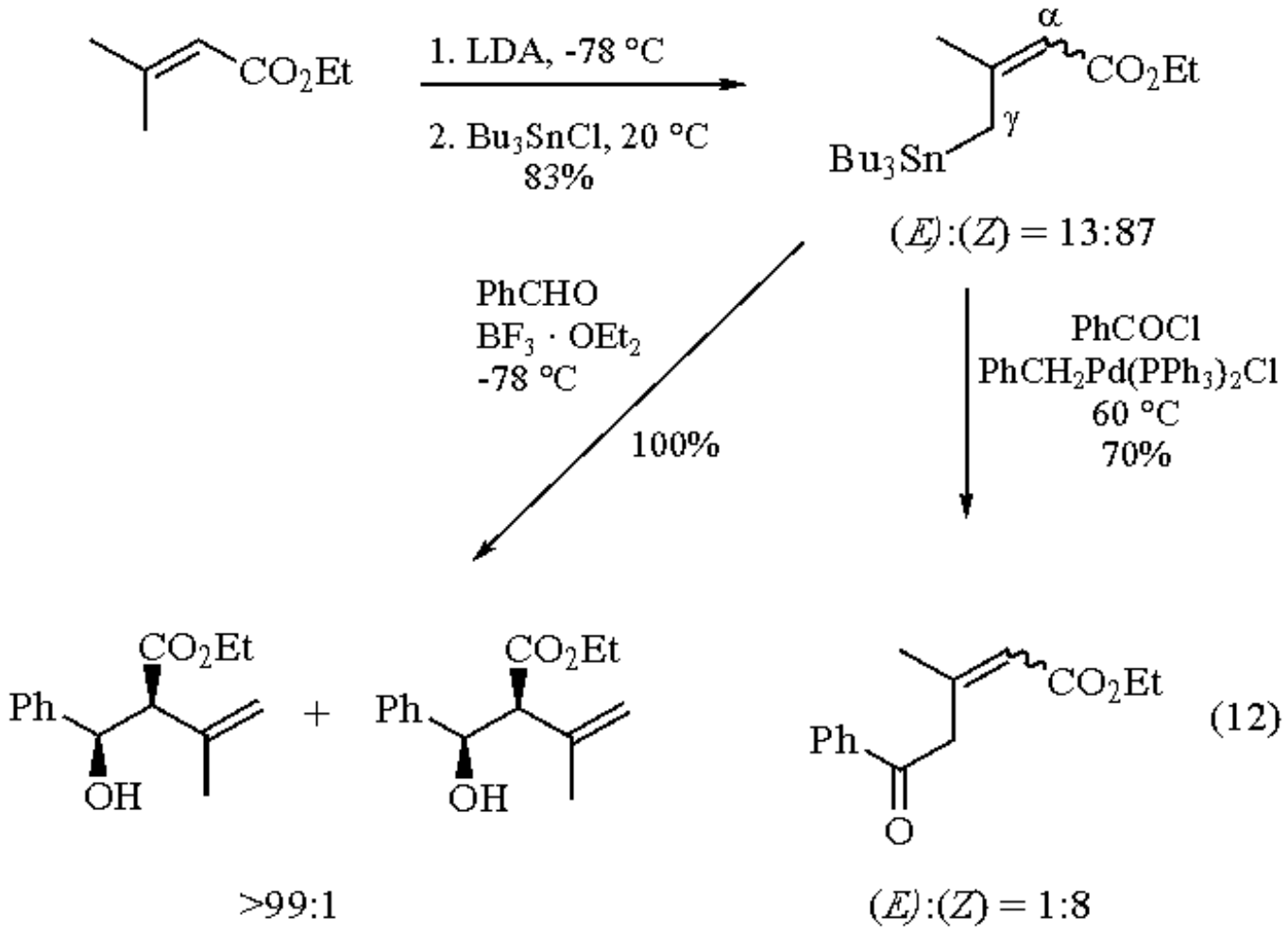

Related Reagents.

Tributyltin chloride is used more frequently than ***Chlorotrimethylstannane***, perhaps owing to its lower toxicity. The latter reagent is useful in reactions which require a sterically compact trialkylstannyl substituent. See also ***Chlorotriphenylstannane***.

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Tri-*n*-butylstannane[1]

***n*-Bu_3SnH**

[688-73-3] · $C_{12}H_{28}Sn$ · Tri-*n*-butylstannane · (MW 291.11)

(source of Bu_3Sn&bdot; radical which produces carbon radicals by (a) abstraction of X from C-X derivatives[1,2] and (b) addition to alkenes, alkynes,[3,4] and carbonyl compounds; hydrogen donor (with concomitant generation of the chain carrier, Bu_3Sn&bdot;) for radicals;[2] hydrostannylation of alkenes, alkynes,[5,6] and carbonyl compounds;[7] desulfurative stannylation of propargylic or allylic sulfides;[8] catalyst for S_H2' reactions of allylic stannanes;[9] radical ring expansion;[10,11] selective reduction of acid chlorides to aldehydes;[12] oxygenation[13] and carbonylation[14] of radicals; source of tributyltin anion[15])

Alternate Name: tributyltin hydride; TBTH.

Physical Data: bp 80 °C/0.4 mmHg; *d* 1.082 g cm^{-3}.

Solubility: freely sol organic solvents.

Form Supplied in: clear colorless liquid; 97% pure.

Analysis of Reagent Purity: major impurity is oxidation product $(Bu_3Sn)_2O$; purity ascertained by gas volumetric methods using dichloroacetic acid or by IR spectroscopy.[1e]

Handling, Storage, and Precautions: irritant. Even though this reagent appears to be relatively innocuous,[1a] tin compounds in general are toxic[16] and should be handled with care in a fume hood. It should be kept in brown bottles away from light and air. Some pressure may develop upon long term storage. Workup procedures for the isolation of tin-free organic products from reactions involving TBTH have been published.[1e,77b]

Introduction.

Tributyltin hydride is the most commonly used source of Bu_3Sn&bdot; which initiates a variety of radical chain reactions.[1,2] Bu_3Sn&bdot; may be generated either thermally or photochemically. ***Azobisisobutyronitrile*** (AIBN) is the most commonly used radical initiator. Three important classes of reactions have been recognized for R_3Sn&bdot;: (a) atom or group abstraction, (b) addition to multiple bonds, and (c) homolytic substitution reactions. The primary products of (a) and (b) are themselves radicals and they undergo a variety of useful transformations such as atom abstraction reactions, rearrangements, fragmentation reactions, and intra- and intermolecular additions to carbon-carbon and other multiple bonds. Tributyltin hydride acts as a hydrogen atom source to trap the radical products, with concomitant generation of the radical chain carrier Bu_3Sn&bdot;. These primary steps are illustrated for prototypical radical reactions in eqs 1-6.

$$RX + Bu_3Sn\bullet \longrightarrow R\bullet + Bu_3SnX \qquad (1)$$

$$R\bullet \longrightarrow \left[\begin{array}{c}\text{rearrangement}\\ \text{fragmentation}\\ \text{addition to C=X}\end{array}\right] \longrightarrow R'\bullet \qquad (2)$$

$$R\bullet + Bu_3SnH \longrightarrow RH + Bu_3Sn\bullet \qquad (3)$$

$$R'\bullet + Bu_3SnH \longrightarrow R'H + Bu_3Sn\bullet \qquad (4)$$

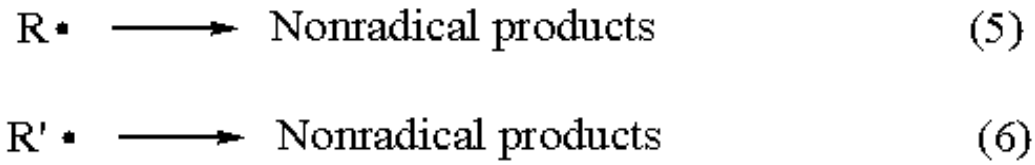

The lifetimes of the radicals R&bdot; and R´&bdot;, are determined by the chain transfer steps 3 and 4 and side reactions of steps 5 and 6. For the efficient formation of preparatively useful radical intermediates R and R´&bdot;, the kinetics of each step must cooperate. For example, only reactions that are faster than the chain transfer step 3 can be executed in step 2. It should be understood that the overall rates of the chain transfer steps can be controlled to some extent by the concentration of the Bu_3SnH reagent. Likewise, the rates of step 2 can be altered by electronic and steric characteristics of R&bdot; and of any reaction partners involved. Fortunately kinetics, thermodynamics,[17] and substituent effects for the individual steps have been studied in some detail and it is possible to design useful synthetic strategies.[18]

Reactions Initiated by Bu_3Sn Radical.

C-X Homolysis followed by H abstraction.

Dehalogenation.

Chemoselective replacement of halogens (except fluorine) with hydrogen is one of the major uses of TBTH in synthesis.[1h] The examples below show the versatility of the method and the range of substrates that can be used in this reaction. Replacement of bridgehead halogen (eq 7)[19] and selective removal of one of the halogens from a geminal dihalocyclopropane (eq 8)[20] are particularly noteworthy. TBTH can be generated catalytically for the dehalogenation reaction (eq 9).[21]

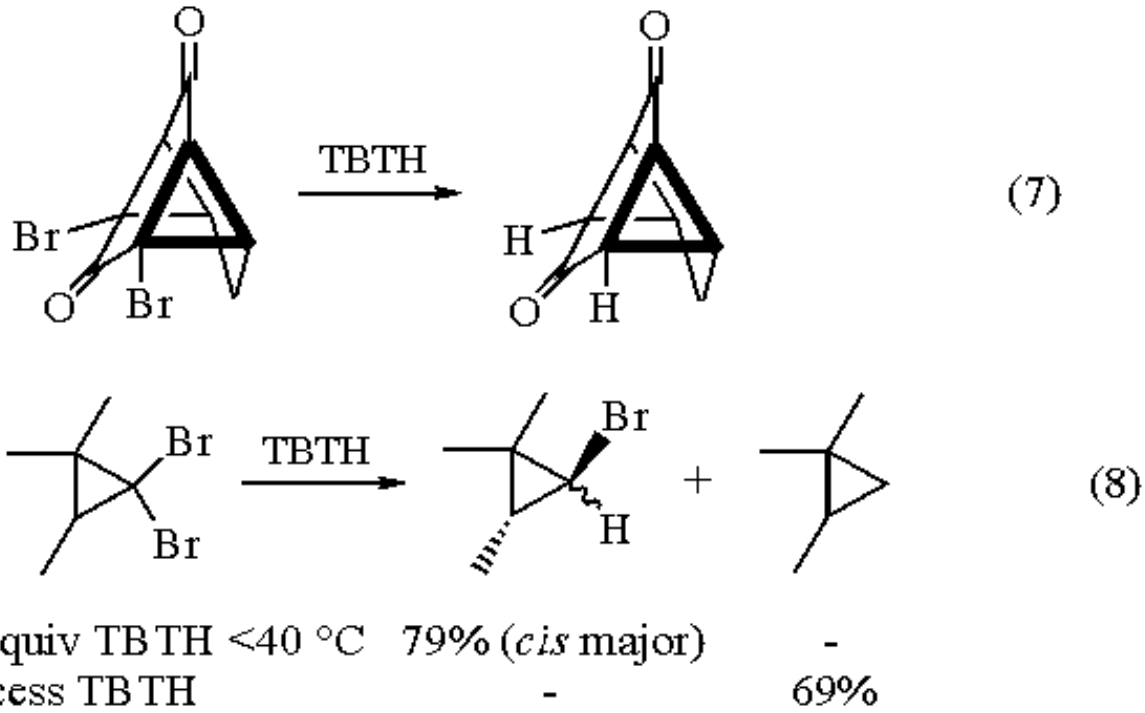

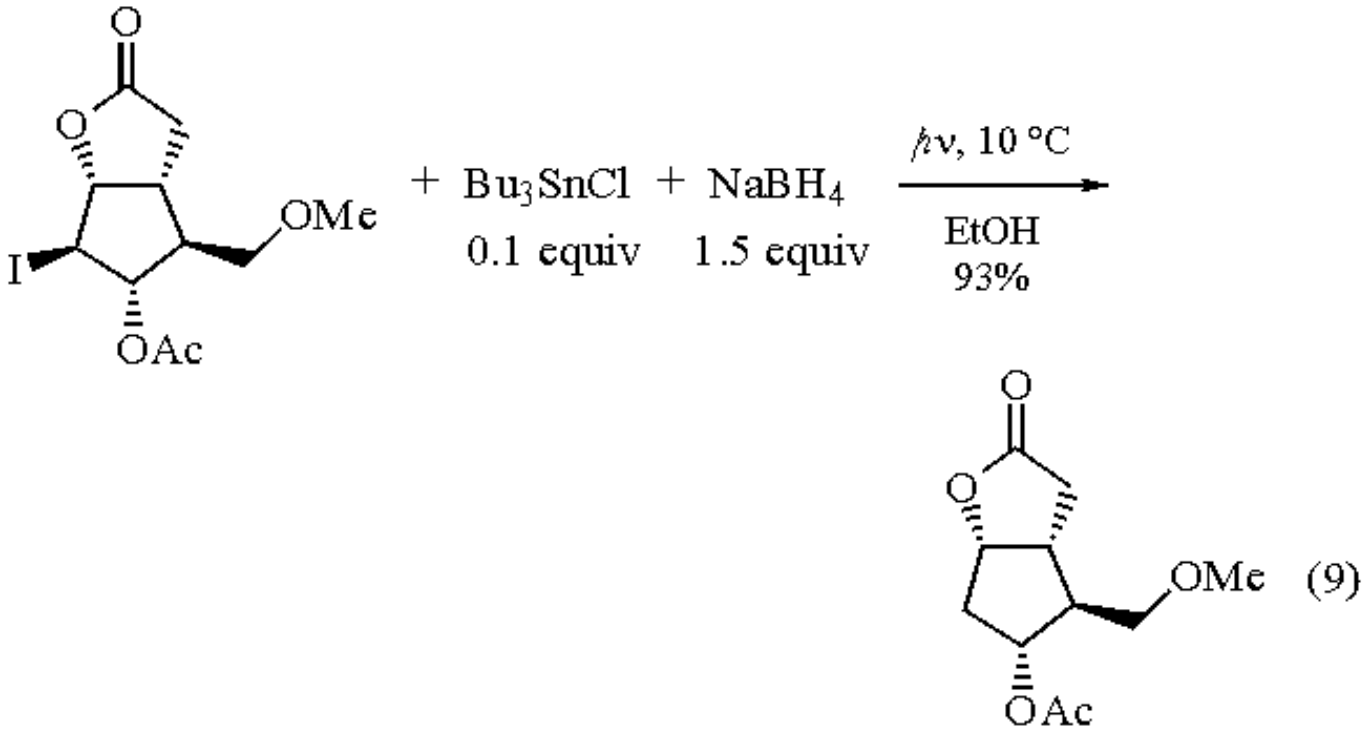

Applications in the β-lactam[22] and carbohydrate (eqs 10 and 11)[23,24] areas illustrate the compatibility of the radical intermediates with a wide range of functional groups and reaction conditions. It should be noted that unlike reactions involving polar intermediates, hydroxyl and amino groups need not be protected under conditions where radicals are generated. Bu_3SnT is the reagent of choice for the regiochemical introduction of tritium into the steroid molecule (eq 12).[25] Debromination with TBTH was a crucial step in a model study directed towards the synthesis of a highly labile thromboxane A_2 analog (eq 13).[26]

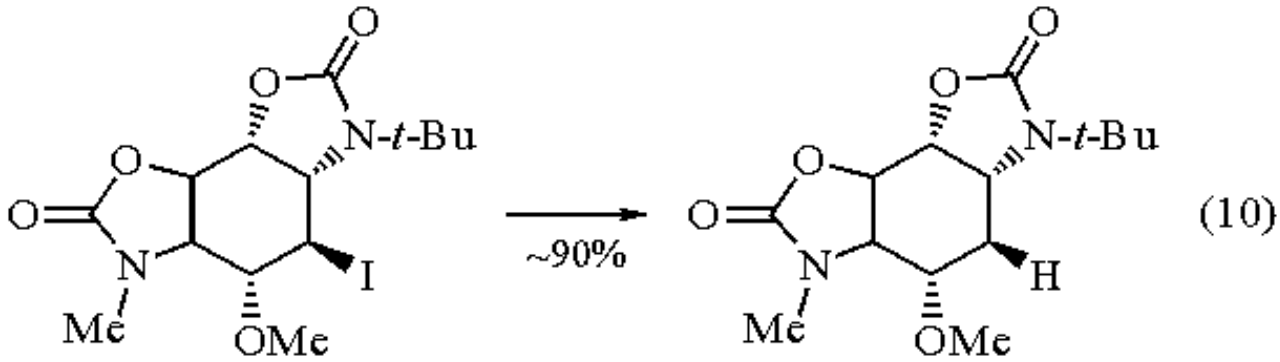

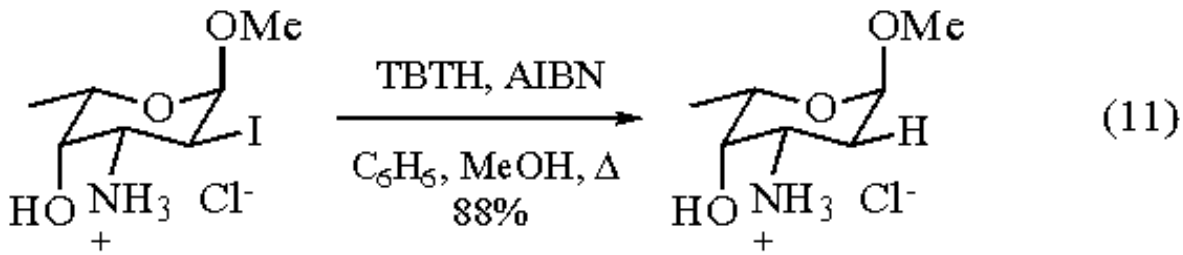

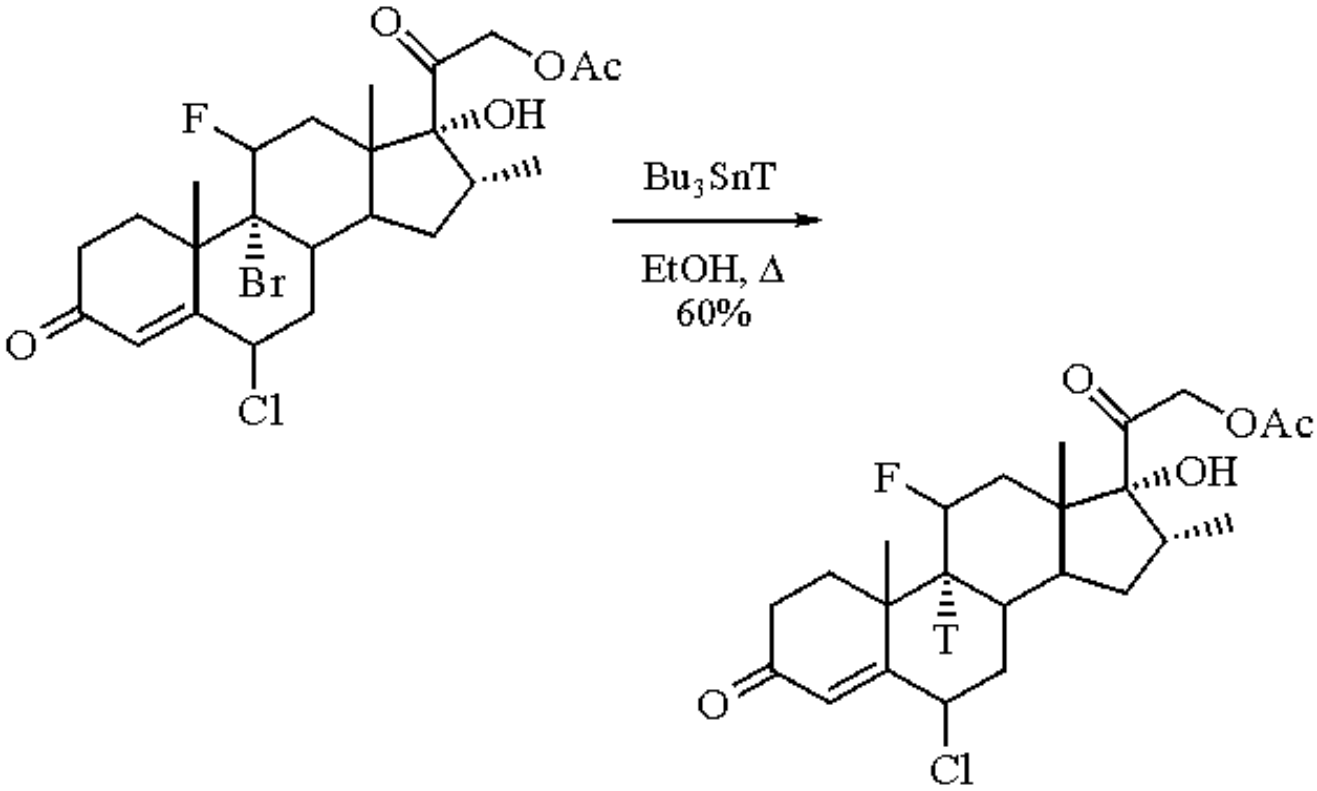

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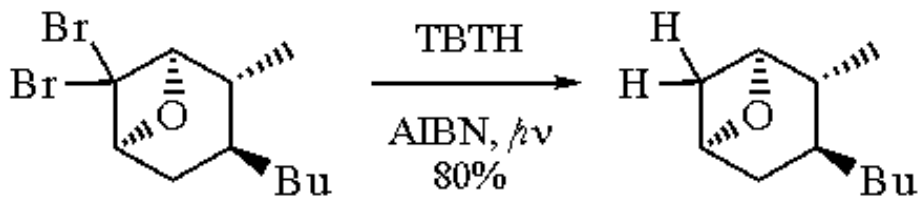

(13)

Deoxygenation.

Deoxygenation of secondary alcohols is best carried out by treatment of the corresponding thiocarbonyl derivatives with TBTH (eq 14).[27,28] Many common functional groups such as amine, alcohol, amido, carbonyl, epoxide, and tosylate are stable to the reaction conditions.

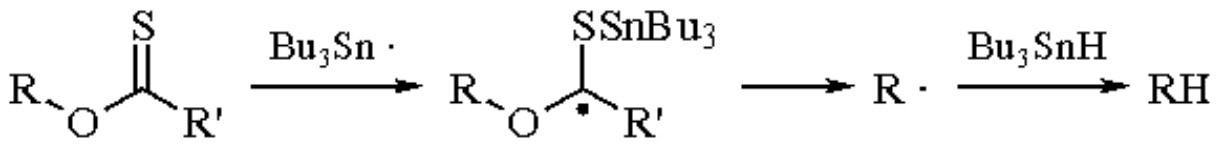

(14)

Typical thiocarbonyl derivatives are xanthates (eq 15),[29] thiocarbonyl imidazolides (R´ = imidazolyl in eq 14), and phenoxythionocarbonate (eq 16).[30] Thioimidazolides, which are prepared under essentially neutral conditions from alcohols and ***1,1´-Thiocarbonyldiimidazole***, are best suited for acid- or base-sensitive substrates (eq 17).[31] Pentafluoro- or trichlorophenyl thionocarbonate is used for the deoxygenation of a primary alcohol under similar conditions.[32] A new procedure for the deoxygenation of tertiary alcohols[33] has also been reported.

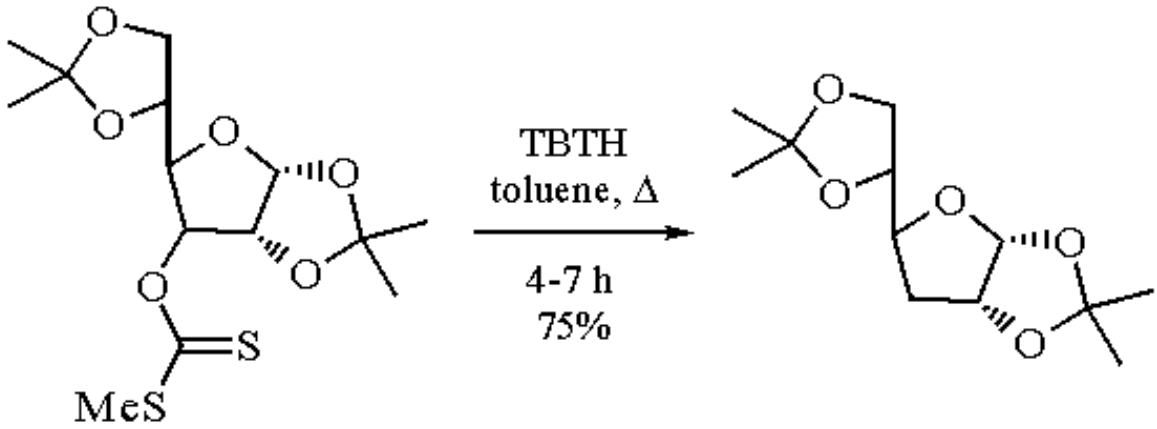

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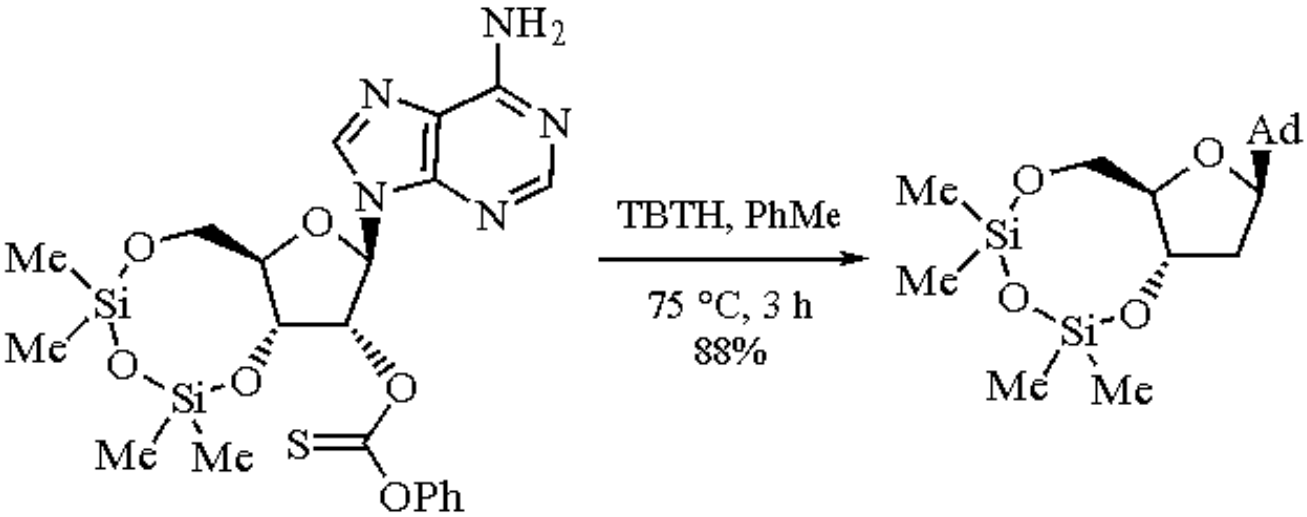

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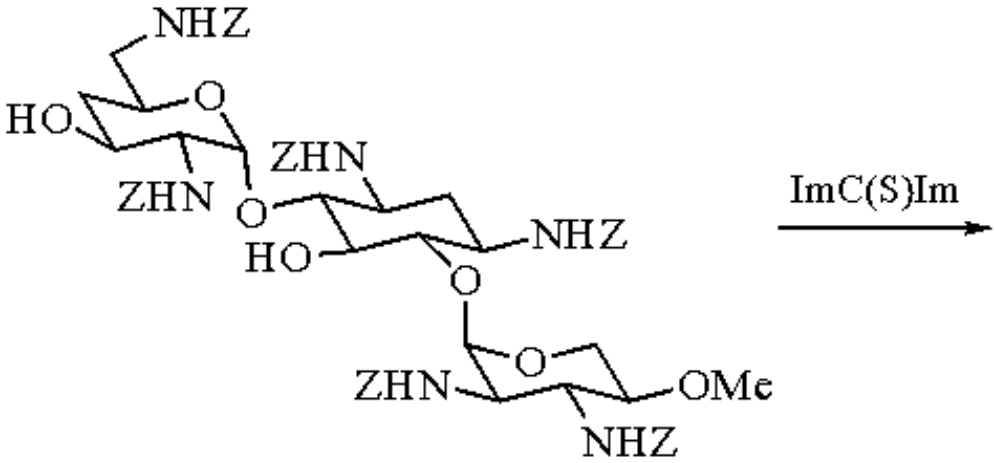

$Z = CO_2Et$

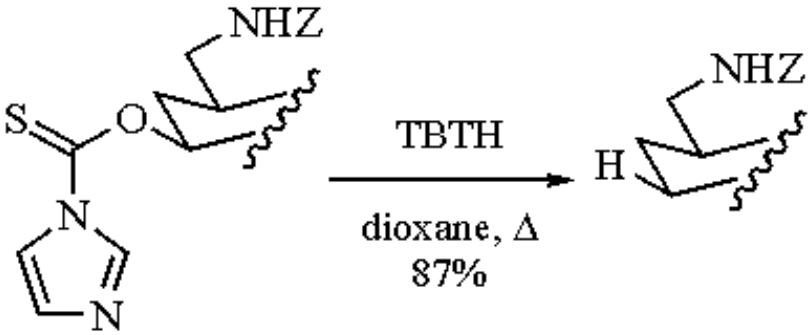

(17)

Decarboxylation.

Photolysis or thermolysis of acyl derivatives of *N*-hydroxy-2-thiopyridone in the presence of TBTH (or, better, *t*-butyl thiol) gives the norhydrocarbon derived from the acyl moiety (eq 18). This method is applicable to a wide variety of aliphatic carboxylic acids (eq 19).[34]

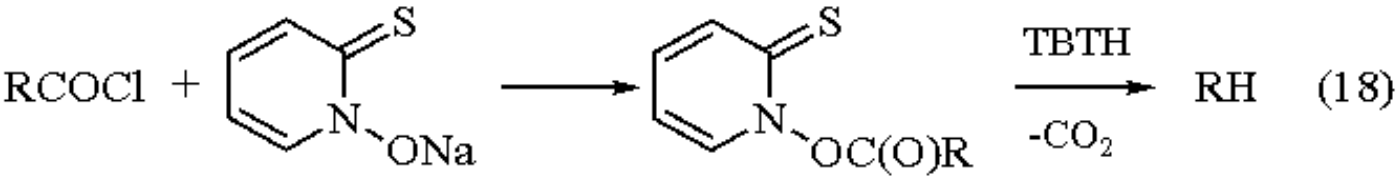

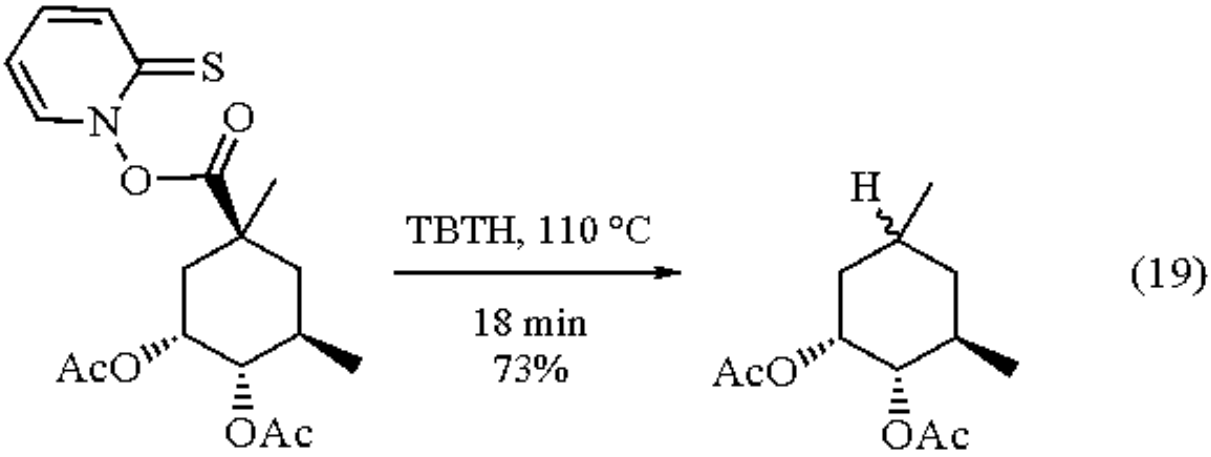

Homolysis of C-N Bonds.

Isocyanides,[35] isothiocyanates, and nitro compounds[36] undergo homolysis of the C-N bond upon treatment with TBTH. Primary amino groups are converted into isocyanides via dehydration of the corresponding formamides. A highly selective reaction of 6β-isocyano-β-lactam (eq 20)[37] proceeds in 63% yield; as expected, the convex α-face of the bicyclic skeleton is more accessible to the hydride reagent.[38]

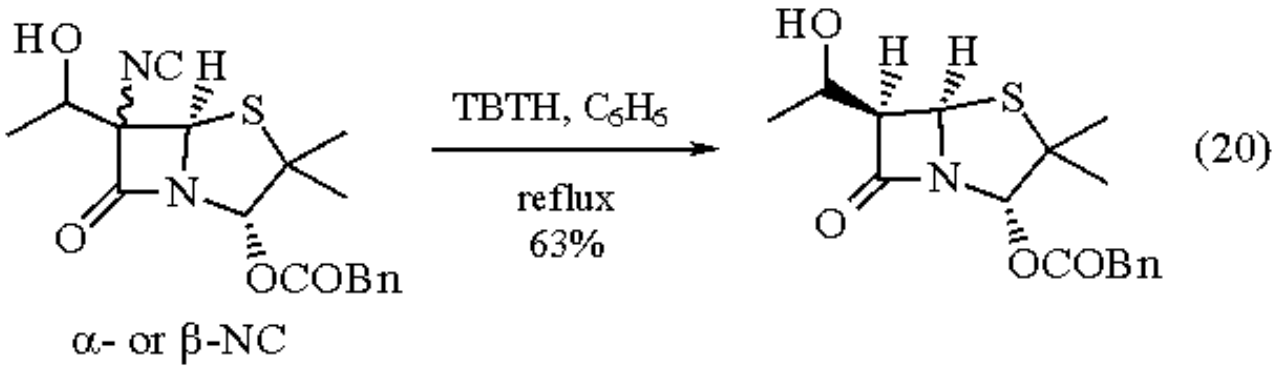

Homolysis of C-S, C-Se, and C-Te Bonds.

TBTH, in the presence of AIBN, reduces primary and secondary thiols,[39] sulfides with at least one radical stabilizing group (for example, α-carbonyl, α-thio, benzyl, *t*-Bu), and thiones to the corresponding hydrocarbons.[40] Se-[41] and Te-C[42] bonds are also cleaved by tin hydrides. Since the Ph-S or Ph-Se bond is almost never cleaved, thiophenyl and selenophenyl derivatives are among the most widely used radical precursors for C-C bond forming reactions (see below). Selenophenyl esters provide aldehydes (80 °C or *hν*, rt) or the norhydrocarbon (164 °C), depending on the reaction conditions.[41]

Radical Rearrangements.

An alternative to the classical Wharton reaction uses the thioimidazolide intermediate for the radical generation and subsequent epoxide opening (eq 21).[43]

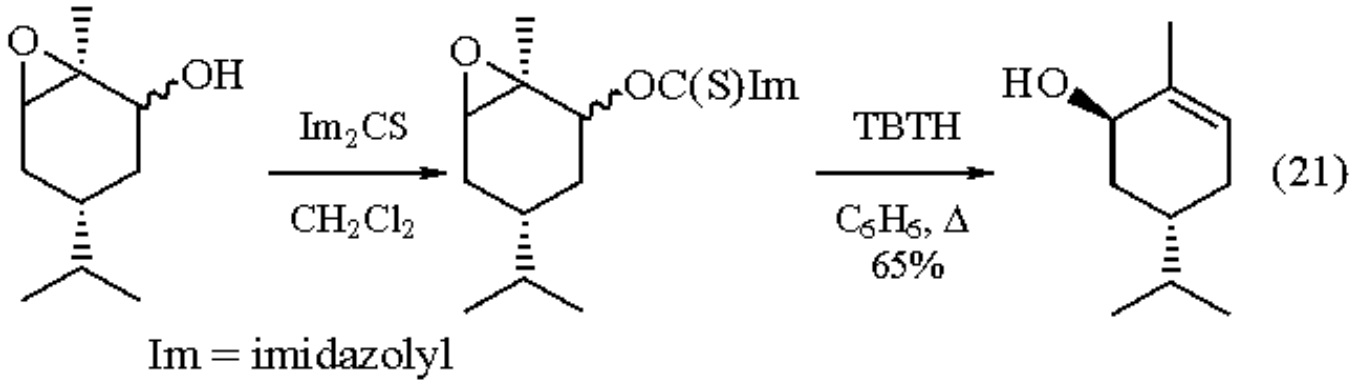

Ring opening of the cyclopropylmethyl radical is one of the most studied radical reactions, though synthetic applications in this area involving TBTH are limited.[44,45] A recent example is shown in eq 22.[46] Opening of *N*-acylaziridines by TBTH has also been described.[47]

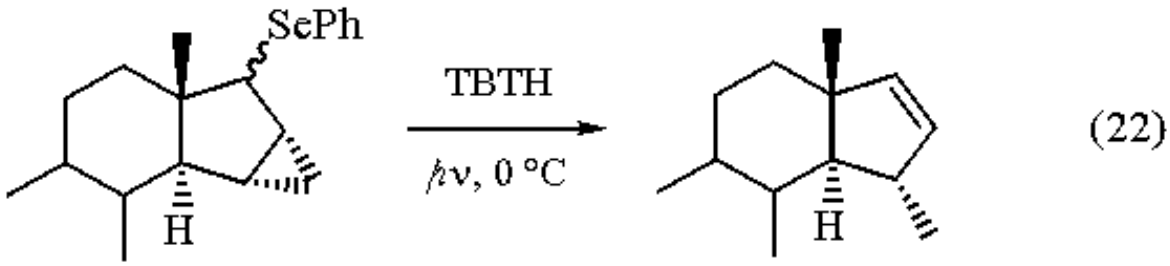

1,2-Migrations to a radical center are rare and take place only at low TBTH concentrations.[48] The example shown in eq 23[49] is particularly noteworthy since it provides a ready access to 2-deoxy sugar derivatives.

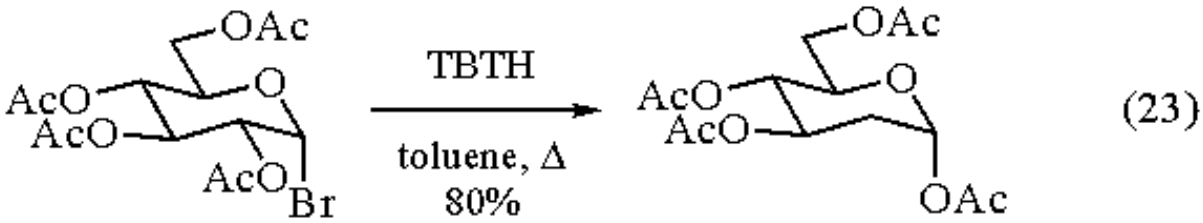

An interesting protocol for the ring expansion of ketones relies on the ability of carbonyl groups to act as acceptors for radicals. The subsequent fragmentation of the resultant oxy radicals is controlled by strategically placed stabilizing groups (eq 24)[10,11] or leaving groups.[50]

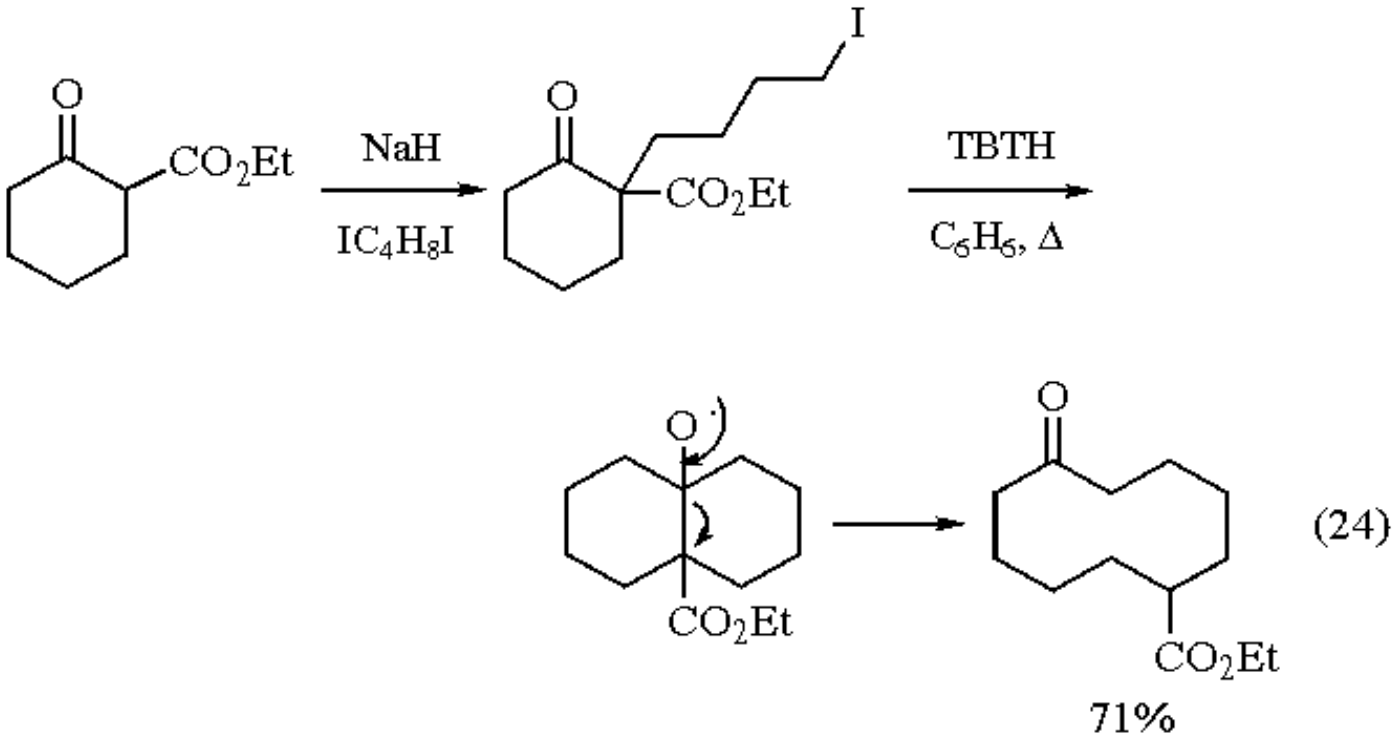

(24)

Intramolecular Additions to Unsaturated Centers.

The hex-5-enyl radical cyclization is one of the most useful radical reactions and this subject has been extensively reviewed.[2,51,57] The examples shown (eqs 25-29)[52-56] illustrate the range of tolerance to various functional groups and the choice of radical precursors possible for this versatile reaction. The stereochemistry of hex-5-enyl radical cyclization has been the subject of a recent review.[57]

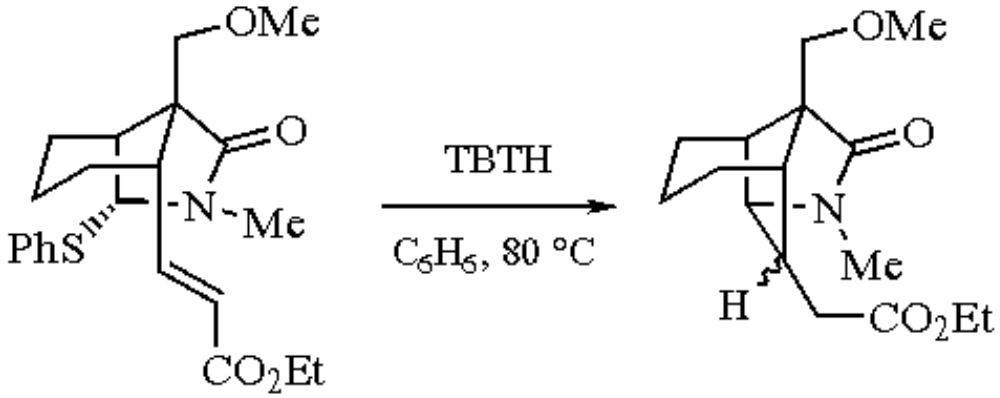

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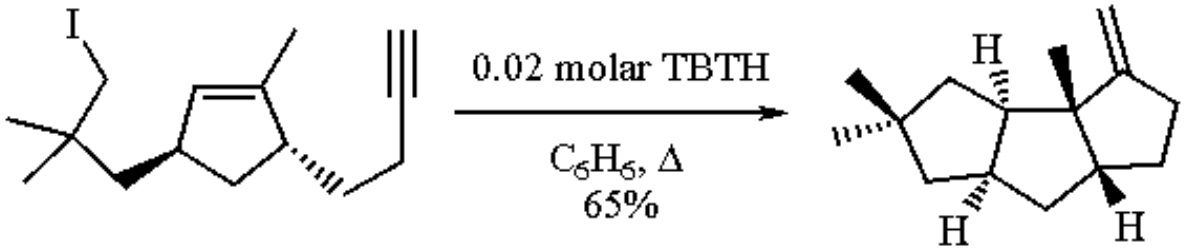

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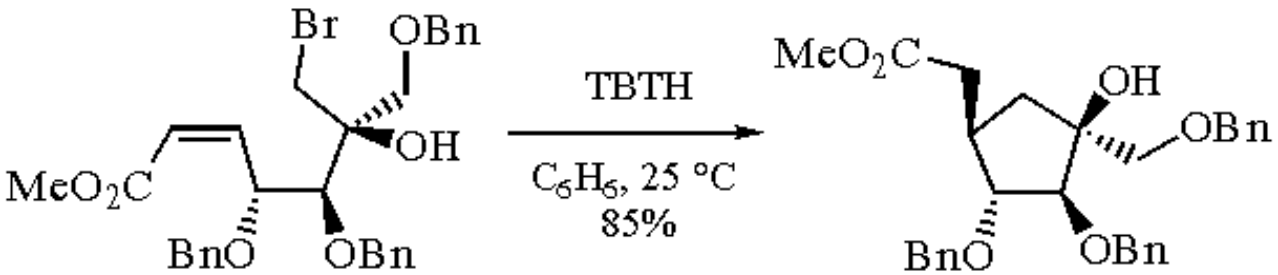

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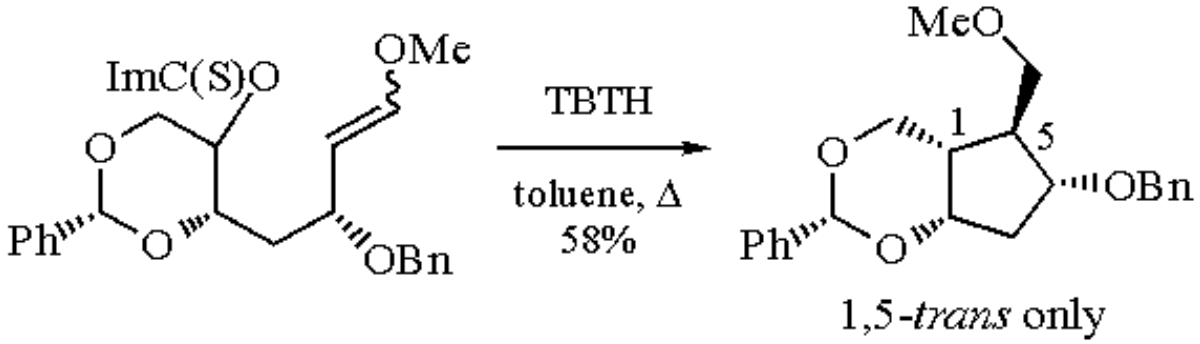

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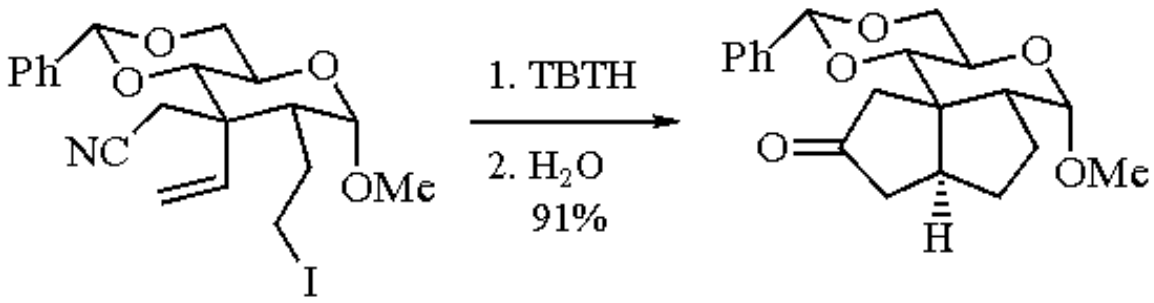

(29)

Appropriately placed haloalkyl side chains, which are readily prepared from allylic or propargylic alcohols, can be used for the stereocontrolled introduction of the hydroxymethyl group (eq 30)[58,60] or lactone annulation.[59] The silacyclopentane in eq 30 produces a 1,3-diol upon Tamao oxidation with ***Hydrogen Peroxide*** and ***Potassium Fluoride***[60] or it can be completely desilylated by treatment with ***Potassium t-Butoxide*** in DMSO.[61]

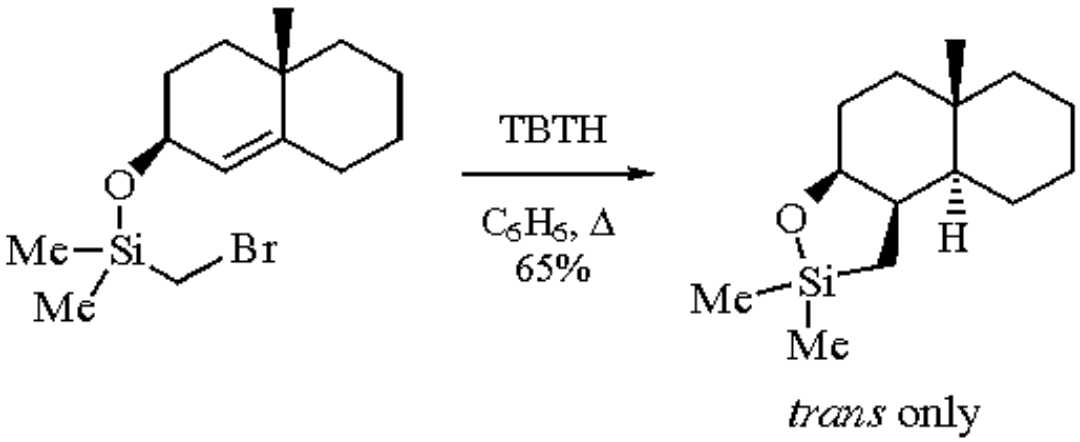

(30)

Several examples of the use of vinyl[2d,3,63,64] and allyl (eq 31)[65] radicals in synthesis have been described. Curran has described the use of a catalytic amount of TBTH for atom transfer reactions.[66]

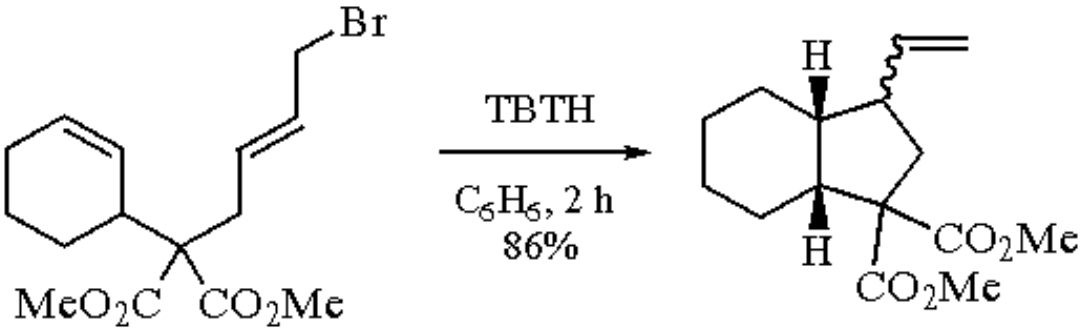

(31)

Exo-hept-6-enyl radical cyclization is about 30 times slower than the corresponding hex-5-enyl cyclization. Nonetheless, by increasing the rate of cyclization (for example, in eq 32[59] with an electron-withdrawing group on the alkene), synthetically useful reactions to make six-membered rings can be accomplished.[67-69]

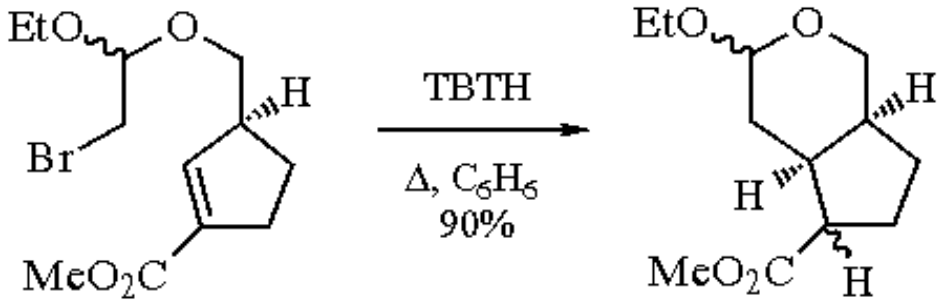

(32)

Acyl radicals generated from selenoesters undergo facile cyclization or intermolecular addition to electron-deficient alkenes faster than H-atom abstraction to give five- and six-membered ketones.[69]

TBTH is useful for the formation of macrolides via radical cyclization from iodoacrylates, if the concentration of both the reagent and substrate are kept low (eq 33). This method is not applicable for medium sized rings, but proceeds well for compounds with 11 or more atoms in the ring. *Endo* cyclization mode is favored when n = 16 or higher.[70]

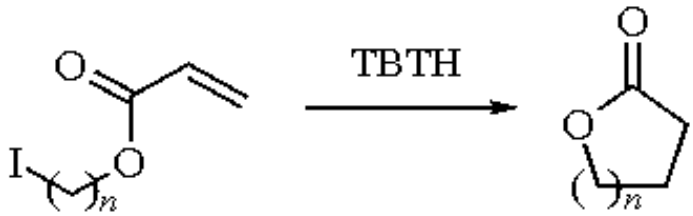

(33)

$n = 8$, 27%; 12, 67%

Intermolecular Additions.

With reactive acceptors in high concentrations, intermolecular addition of radicals proceed with considerable ease and several synthetically useful reactions have been discovered (eqs 34 and 35).[71,72] The example of the *C*-glycoside synthesis (eq 35) is particularly noteworthy; only the α-glycoside is obtained. Stereochemical control in these reactions has been the subject of a recent review.[73] A recent example illustrates the power of this method for rapid assembly of prostaglandin analogs (eq 36).[74]

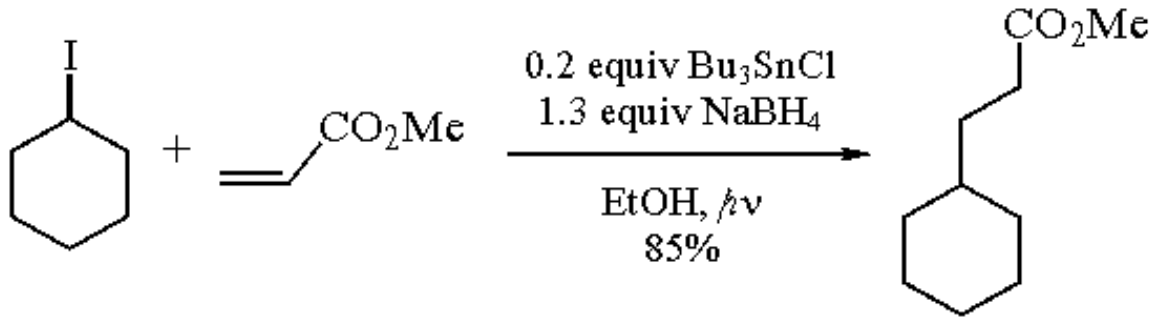

(34)

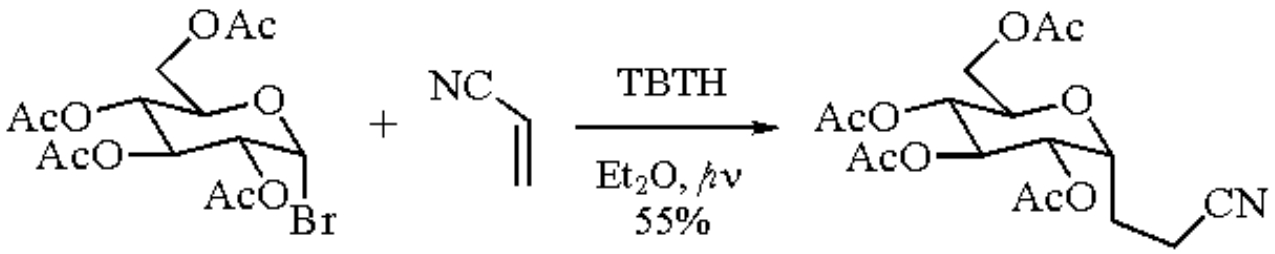

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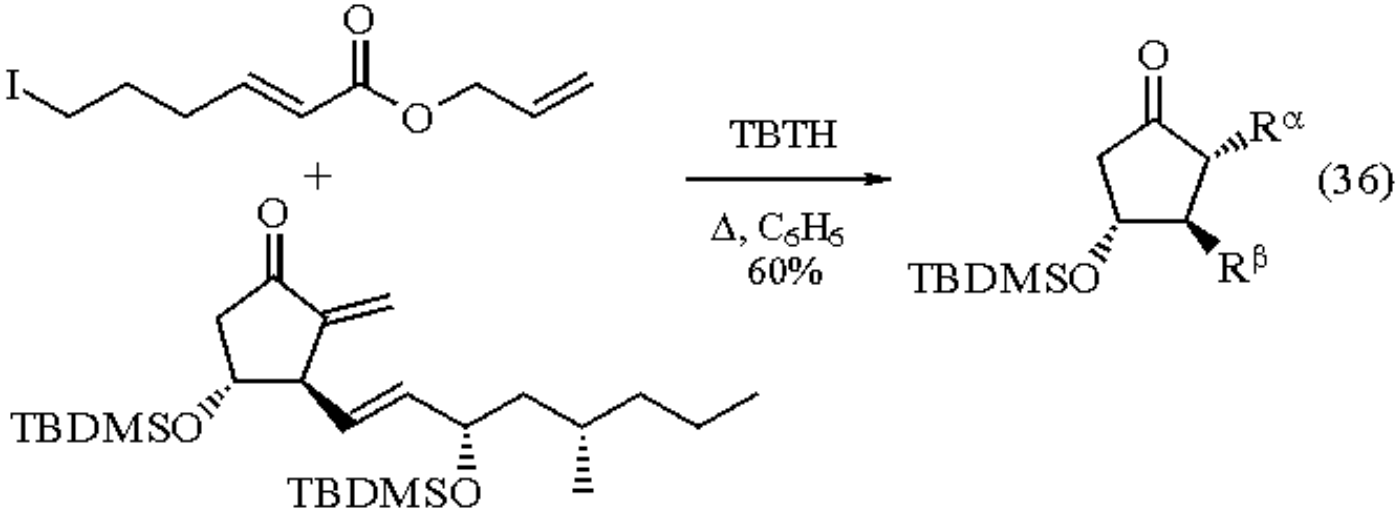

Radicals generated at the end of an intramolecular cyclization can be trapped if the acceptors are sufficiently reactive (eq 37).[62] Such radicals have also been trapped by ***t-Butyl Isocyanide*** to provide the corresponding nitrile.[75] One-carbon elongation can also be achieved by addition of an electrophilic radical to an enamine (eq 38).[76] Clever use of available kinetic and thermodynamic data can lead to the development of new annulation reactions, as shown in eq 39.[77]

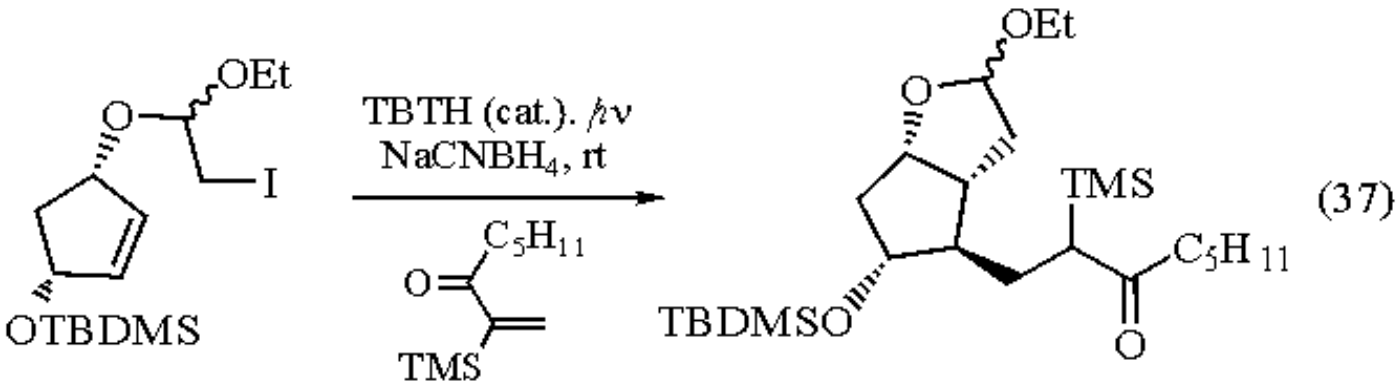

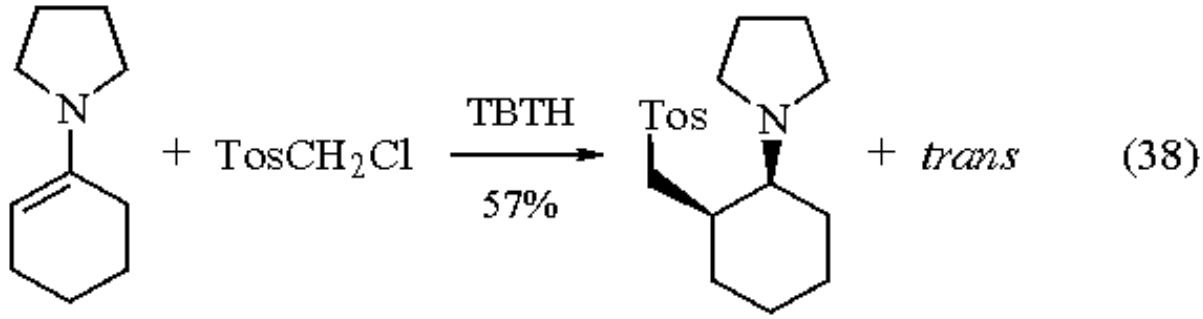

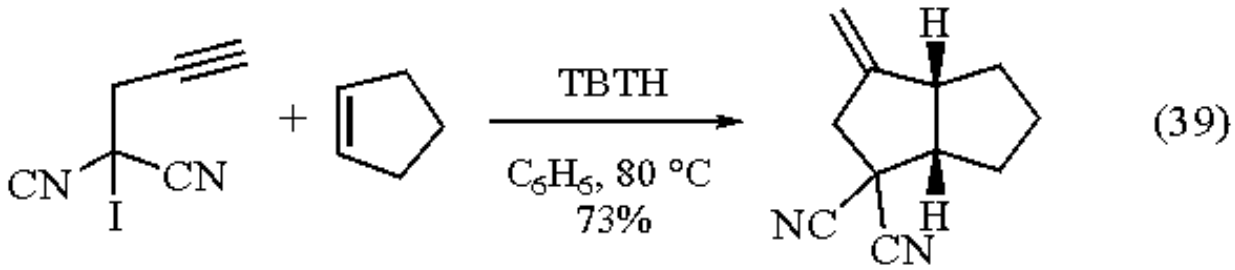

Fragmentation and Homolytic Substitution Reactions.

Allyltributyltin derivatives,[78,79] which have found wide applicability, may be synthesized by intermolecular S_H2 reaction of an appropriately substituted allylic compound (eq 40).[8,80] Intramolecular[9,81] S_H2' reactions have been used for cyclizations.

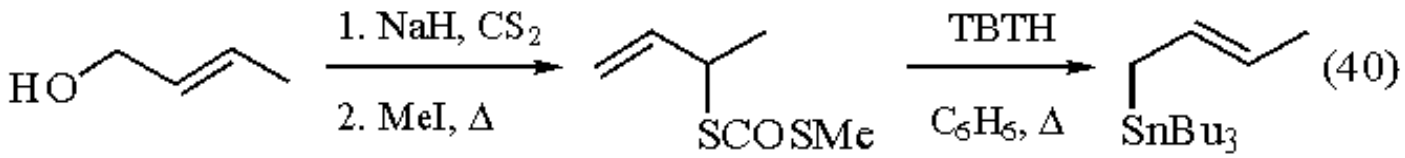

Tributyltin hydride has ben used in catalytic amounts to effect carbocyclic ring expansions of β-stannyl ketones.[50] As shown in eq 41, the fragmentation reaction can be coupled to a radical cyclization reaction to produce ring expanded products from relatively simple substrates.

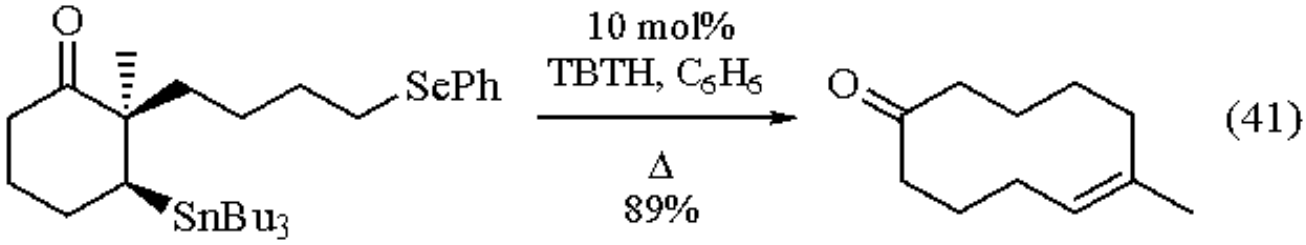

Hydrostannylation of Alkenes, Alkynes, and Carbonyl Compounds.

Hydrostannylation of alkynes and alkenes is a well known reaction[1,6] which may be carried out under either thermal (eqs 42 and 43)[21,4] or sonochemical[82] initiation conditions. The intermediate radical formed upon the addition of R_3Sn&bdot; to alkynes and alkenes can be trapped by an appropriately placed double bond to give carbocyclic compounds.[63,64,83] TBTH adds to the strained single bond of [1.1.1]propellane (eq 44).[84]

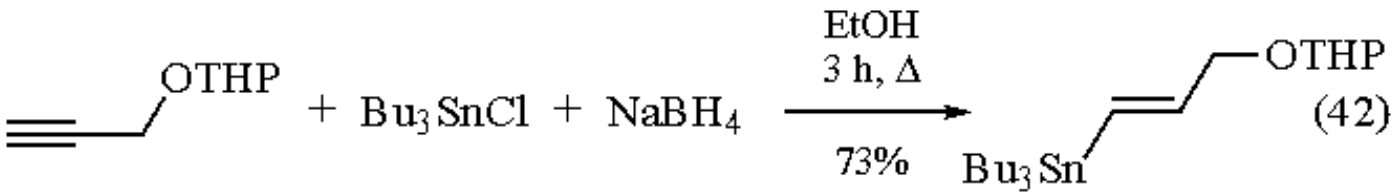

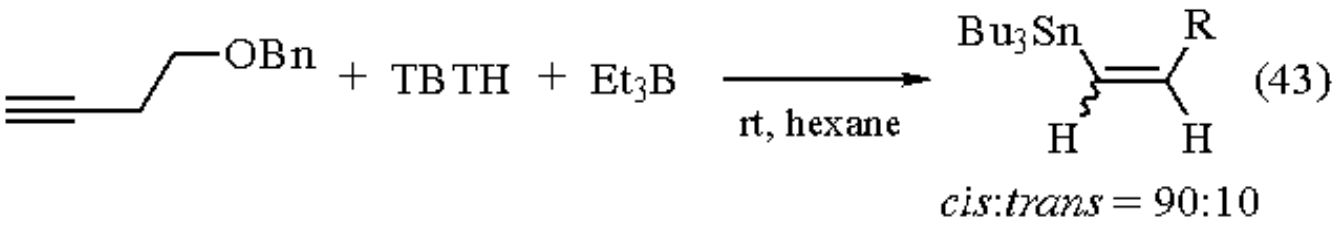

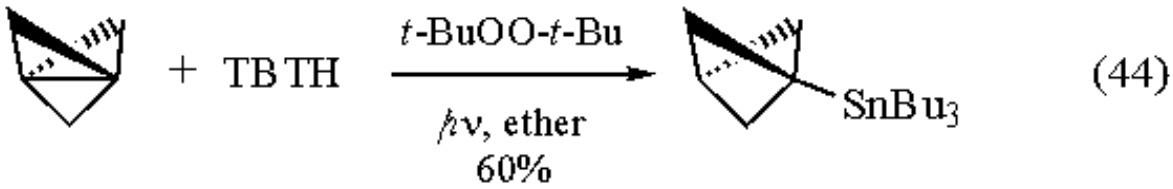

Addition of TBTH to carbonyl compounds requires catalysis by Pd^0 and a promoter Lewis acid (eq 45),[7] or a proton source.[85] Mechanistic studies suggest that TBTH is a hydride donor. Even though the radical additions to simple ketones are slow, α,β-enones readily generate *O*-stannyl ketyls which participate in hex-5-enyl radical cyclization reactions.[86]

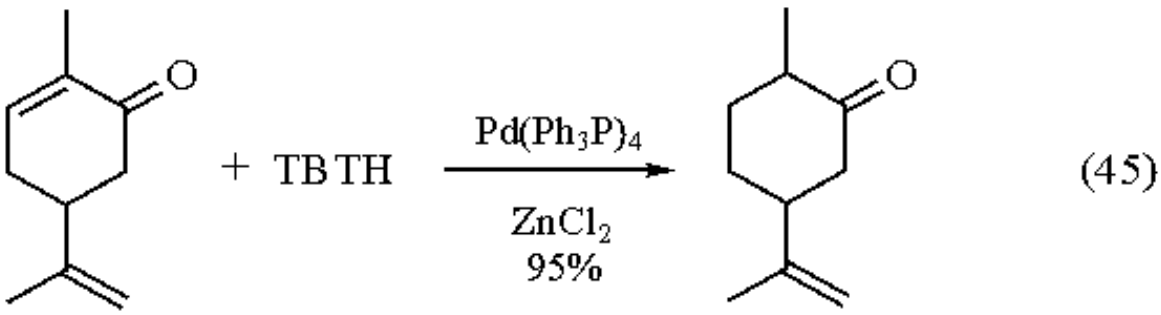

Applications in Organometallic Methodology.

Highly selective reduction of acid chlorides (eq 46)[87] and vinyl triflates[6] may be achieved by the use of Bu_3SnH under Pd catalysis. TBTH/Pd^0 is also an effective system for the reduction of allylic substrates under mild conditions. This reaction is remarkably tolerant of other common functional groups like hydroxy, epoxide, aldehyde, nitrile, and lactone. Radical scavengers improve the yield of the reaction.[88] Pd^0 catalyzes carbonylation of aliphatic, vinyl, and aromatic halides under ***Carbon Monoxide*** in the presence of TBTH.[6] A synthesis of alkyl hydroperoxide uses the homolytic cleavage of an Hg-C bond by tin hydride.[89] Tributyltin hydride has been used to generate a low-valent niobium reagent which is useful for coupling of imines and aldehydes (eq 47).[90]

$$\mathrm{RCOCl} + \mathrm{Bu_3SnH} \xrightarrow[\text{TBTH, } C_6H_6,\ \sim 80\%]{1\ \text{mol\%}\ Pd(Ph_3P)_4} \mathrm{RCHO} \qquad (46)$$

$$\mathrm{NbCl_5} + 2\ \mathrm{Bu_3SnH} \xrightarrow[-\mathrm{Bu_3SnCl}]{\text{DME, -78 °C}} \mathrm{NbCl_3(DME)} + \mathrm{H_2} \quad (47)$$

92%

Carbonylation and Oxygenation of Radicals.

TBTH mediates the oxygenation (eq 48)[13] and carbonylation (eq 49)[14] of radicals.

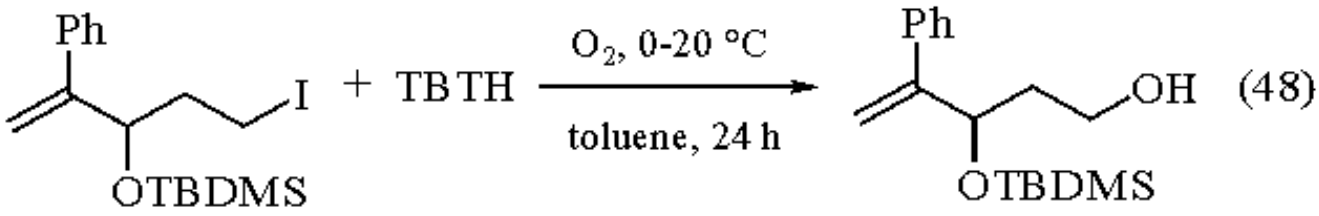

$$C_8H_{17}Br + \mathrm{TBTH} \xrightarrow[\text{AIBN, 80 °C}]{\text{CO (80 atm)}, C_6H_6} C_8H_{17}CHO \qquad (49)$$

61%

TBTH as a Source of Bu_3Sn Anion.

Tributyltin hydride is the best source of tributyltin Grignard or the corresponding lithium reagent, both of which have been used extensively in synthesis.[91] Eqs 50 and 51 are illustrative.[15,92,93]

$$i\text{-PrMgCl} + \mathrm{TBTH} \xrightarrow[\text{reflux, 2 h}]{\text{ether}} \mathrm{Bu_3SnMgCl} \xrightarrow{CH_2O} \mathrm{Bu_3SnCH_2OH} \qquad (50)$$

56%

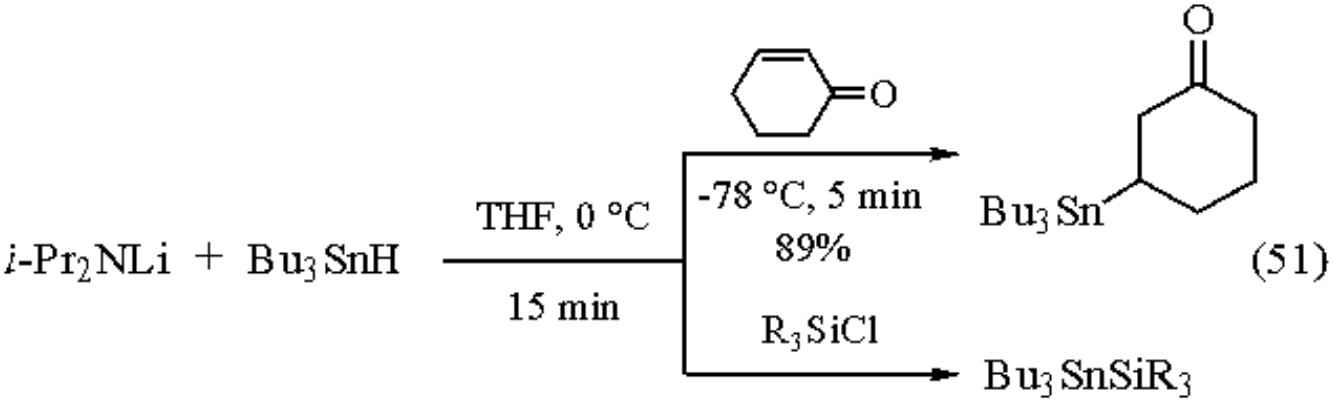

Related Reagents.

See also ***Trimethylstannane***, ***Triphenylstannane***, polymer-supported organotin hydride,[94] ***Tris(trimethylsilyl)silane***.[95]

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1. (a) Neumann, W. P. *The Organic Chemistry of Tin*; Wiley: New York, 1970. (b) Kuivila, H. G. *S* **1970**, 499. (c) Walling, C. *T* **1985**, *41*, 3887. (d) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987. (e) Neumann, W. P. *S* **1987**, 665. (f) Harrison, P. G. *Chemistry of Tin*; Chapman and Hall: New York, 1989. (g) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986. (h) Metzger, J. O. *MOC* **1989**, *19a*.
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Tri-*n*-butylstannyllithium

***n*-Bu$_3$SnLi**

[4226-01-1] · $C_{12}H_{27}LiSn$ · Tri-*n*-butylstannyllithium · (MW 297.04)

(reagent for the synthesis of α-alkoxystannanes,[1] β-stannyl ketones,[1] allenylstannanes,[2] allylstannanes,[3] acylstannanes,[4] and vinylstannanes[5])

Alternate Name: tributyltinlithium.

Preparative Methods: by the reaction of ***Hexabutyldistannane*** and ***n-Butyllithium***, or by the deprotonation of ***Tri-n-butylstannane***.

Handling, Storage, and Precautions: should be used soon after preparation; however, storage of a THF solution for short periods of time (<12 h) at 0 °C is possible. For some applications the purity of the starting material used for generation of the tributyltinlithium reagent is critical. Tributyltin hydride should be distilled prior to deprotonation. Sensitive to air and moisture. Volatile tetraalkylstannanes are toxic and should be handled in a well-ventilated fume hood. Contact with the eyes and skin should be avoided.

General Discussion.

Tributyltinlithium can be prepared from hexabutylditin by reaction with butyllithium[6] or with ***Lithium*** metal,[7] or from ***Tri-n-butylchlorostannane*** and lithium metal.[7b] A more convenient method which eliminates the need to separate the tetraalkyltin byproducts involves the deprotonation of tributyltin hydride by ***Lithium Diisopropylamide***.[1] One of the most extensive uses of tributyltinlithium is in the synthesis of α-alkoxystannanes. Condensation of tributyltinlithium and aldehydes or ketones leads to unstable α-hydroxystannanes which can be protected by a variety of α-chloro ethers (eq 1).[1,8]

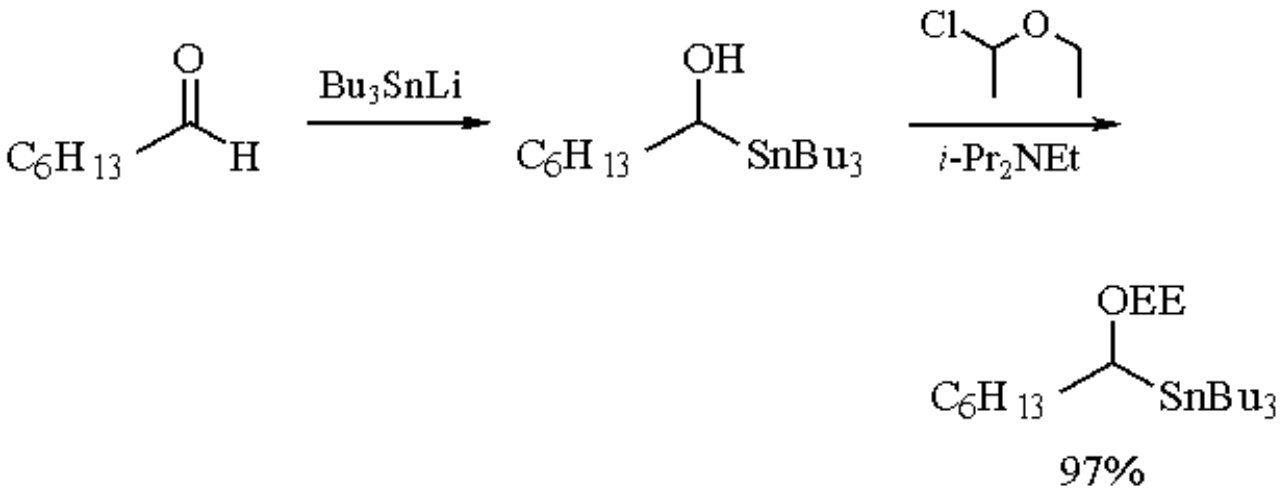

(1)

In reactions with α-substituted aldehydes, the addition of tributyltinlithium resulted in the same selectivity as unhindered Grignard reagents, while β-oxygenated aldehydes gave a higher degree of stereocontrol due to a cyclic chelate mechanism. The α-alkoxystannane can be transmetalated by reaction with butyllithium to provide an α-alkoxy organolithium reagent (eq 2).[6] The relative order of stabilities of α-alkoxyorganolithio reagents obtained from transmetalation of the corresponding α-alkoxystannanes has been defined.[8b] The lithio reagent appears to be stable at low temperatures and can be employed in a variety of subsequent reactions, including alkylation, addition to carbonyls, and transmetalation to organocuprate derivatives.[9] A synthesis of dendrolasin was accomplished using the α-alkoxystannane methodology,[1] offering several advantages over alternative approaches which involved a nonregioselective allyl anion addition (eq 3).

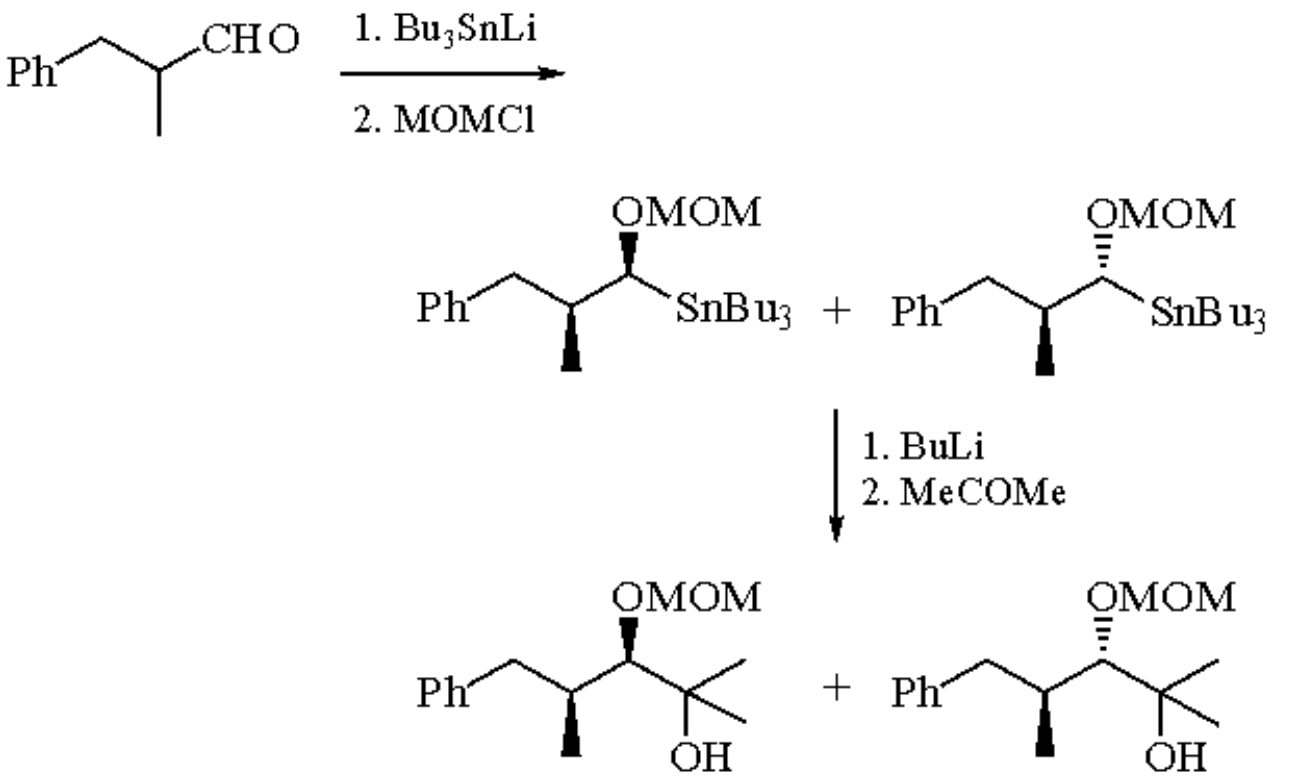

(2)

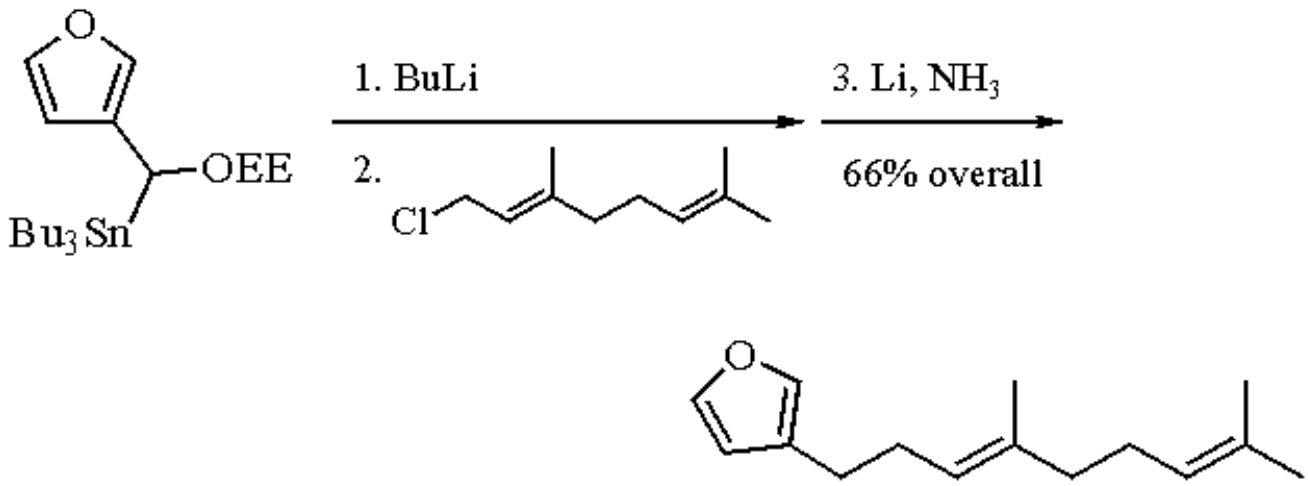

(3)

Conjugate addition of α-alkoxyorganocuprates to cyclic enones followed by an intramolecular Mukaiyama aldol reaction provided a ring annulated tetrahydrofuran (eq 4).[10] The overall procedure is equivalent to regiocontrolled cycloaddition of an unstabilized carbonyl ylide. α-Alkoxyorganostannanes are also precursors for the stereoselective synthesis of enol ethers by a retro Diels-Alder reaction[11] or by transmetalation induced β-elimination.[12]

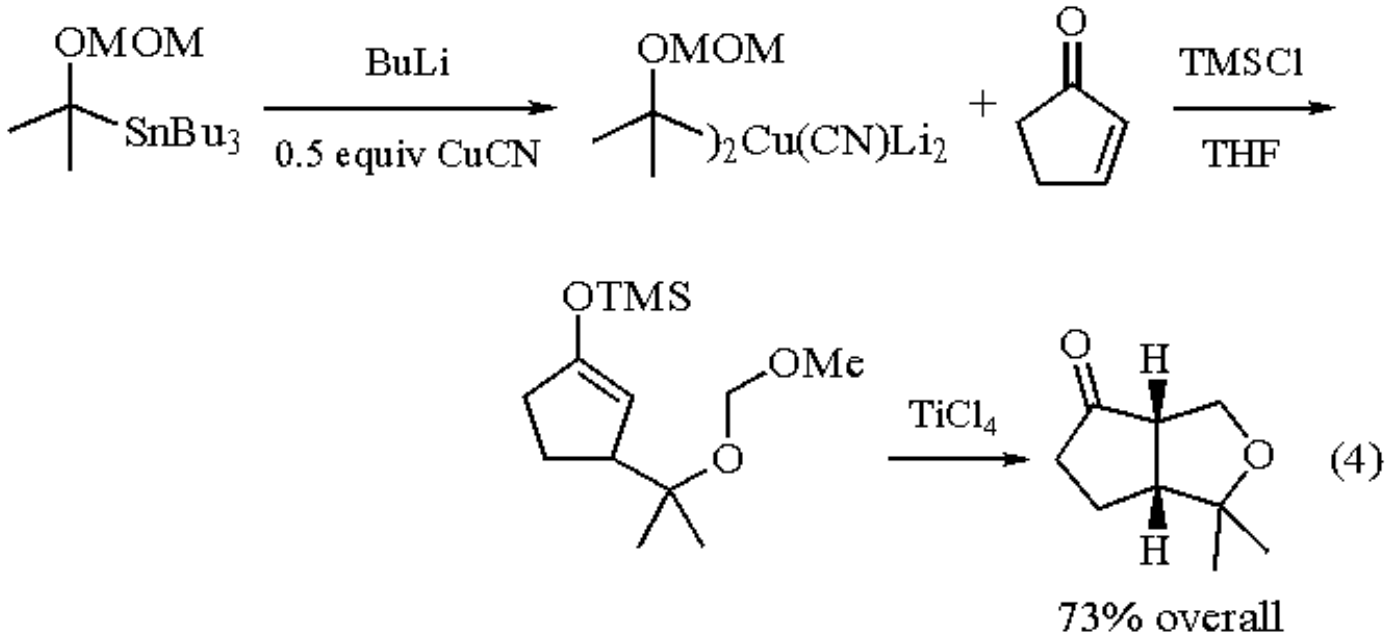

(4)

Addition of tributyltinlithium to 4-*t*-butylcyclohexanone was shown to be a reversible process.[8] Under thermodynamic conditions, axial addition of the tin anion predominated (93:7), while under kinetic conditions (addition at -100 °C) the equatorial stannane predominated (25:75). Both the axial and equatorial stannane underwent transmetalation and alkylation with retention of configuration. The tin anion addition/transmetalation/alkylation sequence provided access to axially substituted cyclohexanols, in contrast to the equatorially substituted products obtained by simple organometallic addition reactions (eq 5).

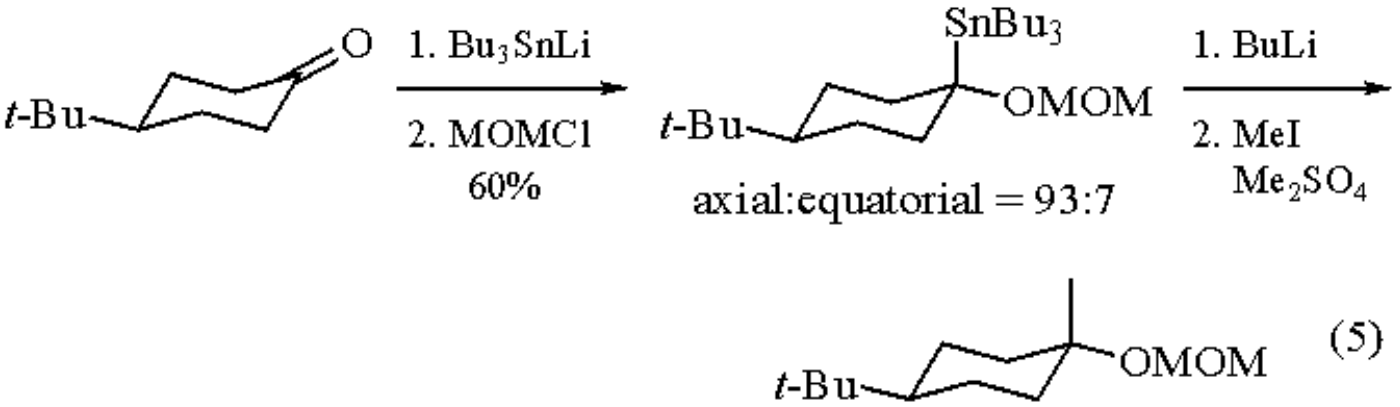

(5)

α-Alkoxyallylstannanes are also obtained by the direct addition of tributyltinlithium to unsaturated aldehydes.[3] The α-alkoxyallylstannanes undergo Lewis acid-catalyzed rearrangement to provide γ-alkoxyallylstannanes.[13] Lewis acid-catalyzed alkylation of ketene silyl acetals with acetal-protected α-alkoxystannanes followed by transmetalation and ring closure of the derived amide resulted in a novel synthesis of furanones (eq 6).[14]

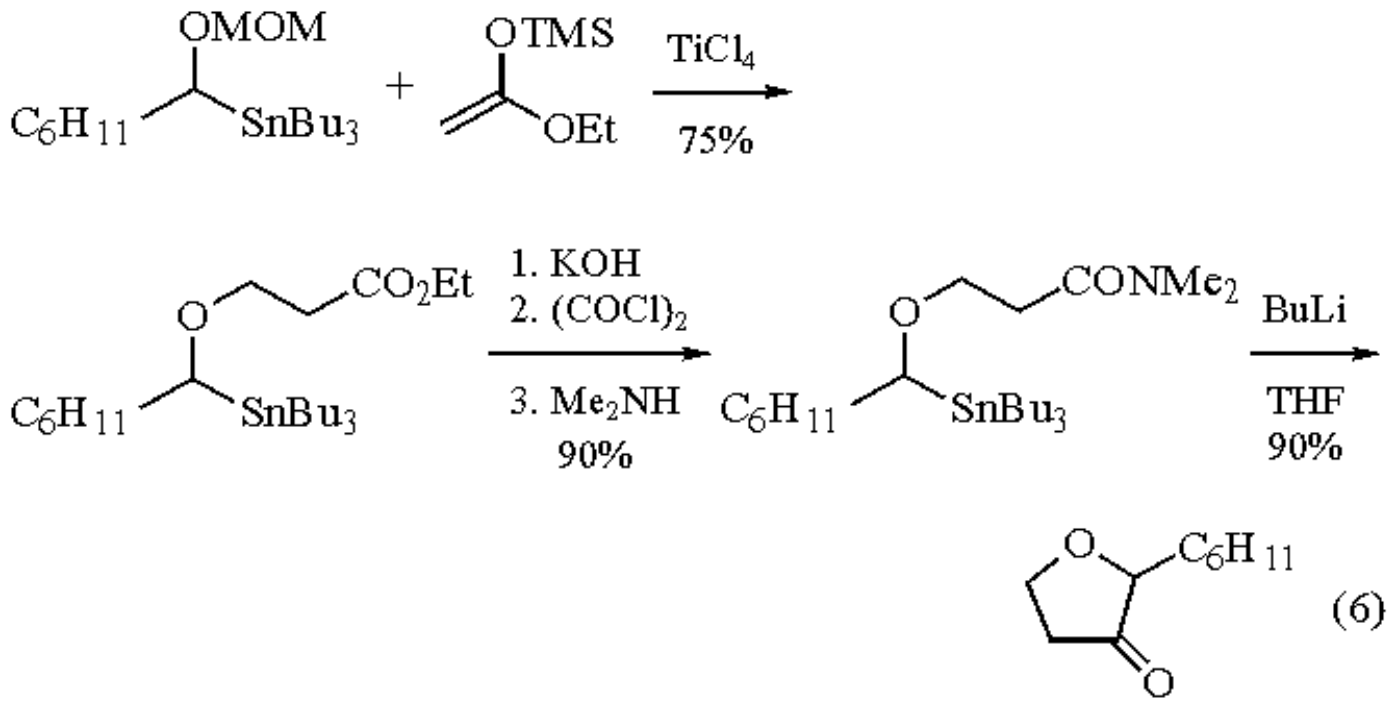

Enantiopure α-alkoxystannanes obtained by the asymmetric reduction of acylstannanes[15] have been employed in the synthesis of optically pure α-alkoxy carboxylic acids,[16] as well as transformed into the corresponding α-alkoxyorganocuprate reagents via the intermediate α-alkoxy lithio species.[17] Transmetalation of enantiopure α-alkoxyorganostannanes and the subsequent alkylation reaction was shown to occur with complete retention of configuration.[18] Access to enantiopure α-alkoxyallylstannanes has also been realized by the asymmetric reduction of unsaturated acylstannanes.[19] An alternative route to enantiopure α-alkoxyorganostannanes involves the direct displacement of α-chloroboronate esters.[20] Mitsunobu inversion of enantiopure α-alkoxyorganostannanes with ***Phthalimide*** provides a route to optically active α-aminoalkyl stannanes.[21] An alternative route to nonracemic (α-aminoalkyl)tributylstannanes has been realized by the direct displacement of sulfones (eq 7).[22]

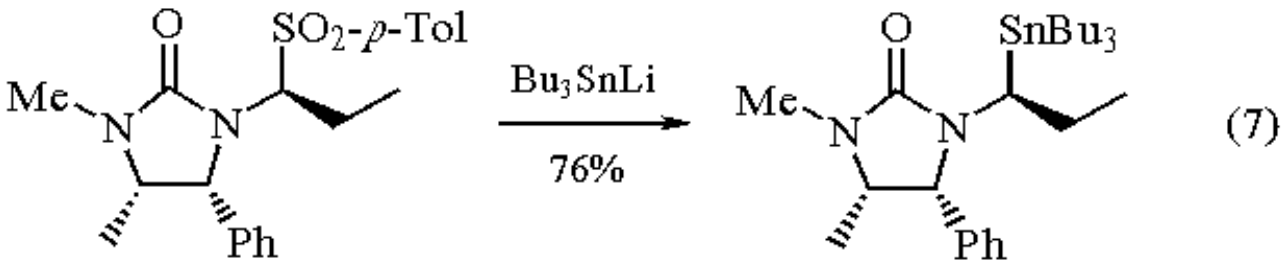

The (α-aminoalkyl)organolithio anions can also be obtained by transmetalation using butyllithium; however, the α-amino lithio species are not as configurationally stable as the α-alkoxy lithio derivatives. Racemic α-aminostannanes are available by the reaction of tributyltinlithium and iminium ions.[23]

Tributyltinlithium also undergoes direct displacement or nucleophilic addition reactions with a variety of other electrophiles. The synthesis of allenylstannanes is accomplished by tributyltinlithium addition to propargylic halides.[2] The direct synthesis of acylstannanes can be accomplished by the reaction of tributyltinlithium and ethyl esters in the presence of ***Boron Trifluoride Etherate***.[4] Addition of tributyltinlithium to thionolactones results in a functionalized stannane that may be transmetalated and alkylated with allyl halides.[24] Addition of tributyltinlithium to epoxides followed by stereospecific elimination of the derived β-acetoxystannane provides a method for the stereospecific transformation of epoxides to alkenes with retention of stereochemistry.[25] A different elimination process results in the conversion of β-stannylvinyl sulfones to γ-hydroxyvinylstannanes.[26] 1,4-Addition of tributyltinlithium to the unsaturated sulfone provides an intermediate enolate which is trapped by reaction with an aldehyde. The alkoxide formed then undergoes an elimination reaction in which the alkoxide assists in the 1,2-elimination of the stannyl and sulfone groups (eq 8).

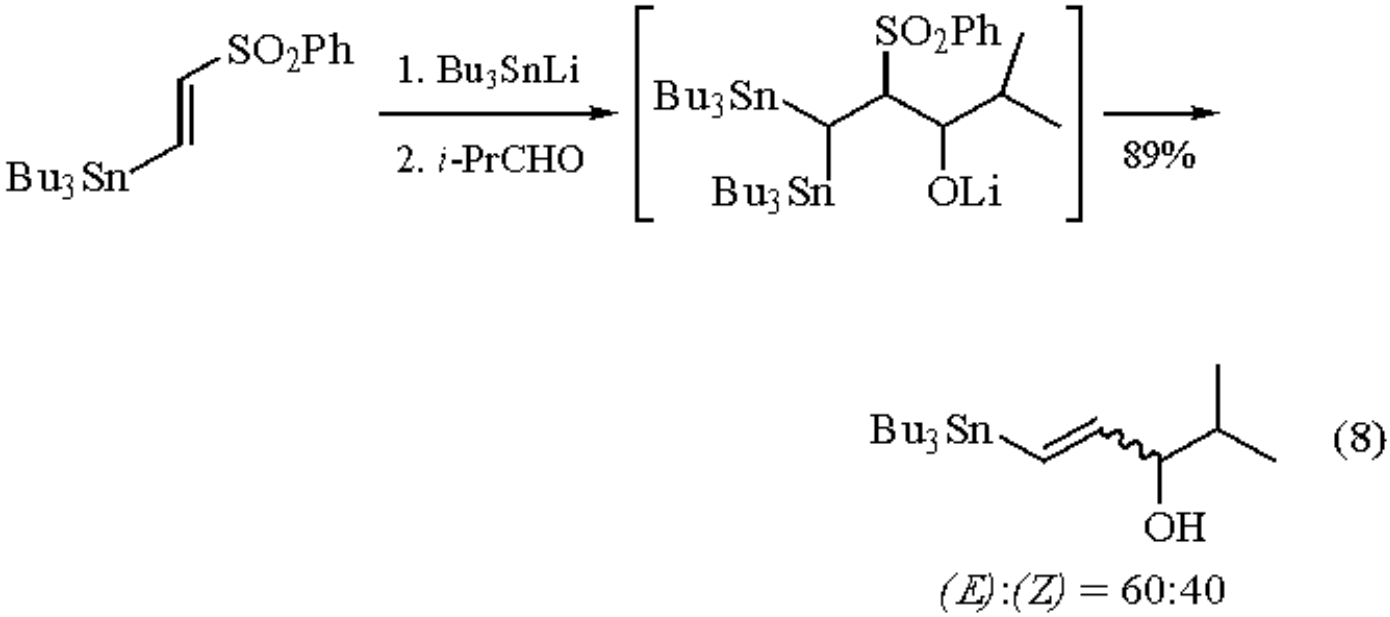

Tributyltinlithium does not always undergo clean displacement or addition reactions. In a synthesis of 1-methoxy-1,3-dienes, tributyltinlithium promotes metal-halogen exchange rather than displacement of an allyl chloride (eq 9).[27] A similar competing metal halogen exchange process was observed in the stannylation of chlorosilanes.[28]

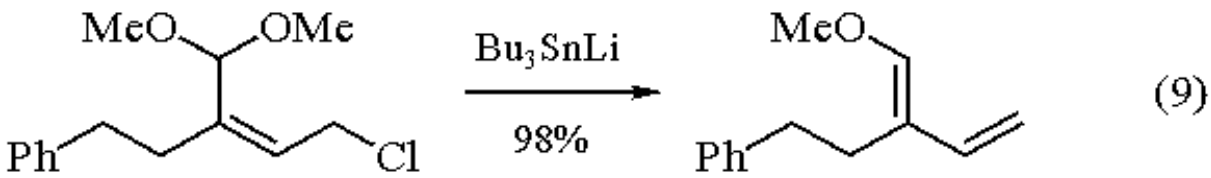

1,4-Addition of tributyltinlithium to enones occurs readily in THF or THF/NH_3. In contrast, ethereal tributyltinlithium adds only in a 1,2-fashion to cyclohexenone.[6] The β-trialkylstannyl ketone can be further transformed by alkyllithium addition to the carbonyl followed by oxidation with excess ***Dipyridine Chromium(VI) Oxide***, resulting in an overall enone transposition. Tributyltinlithium will even add to β,β-disubstituted unsaturated esters (eq 10).[6,29] This relatively unusual reactivity is attributed to the long length of the Sn-C bond (2.2 Å).

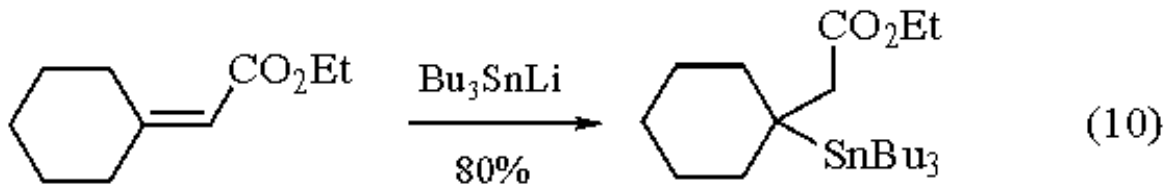

Although the β-stannyl carbonyl moiety is a reactive functional group, many synthetic reactions can be accomplished on the molecule without loss of the tin.[29] The 1,4-addition product obtained from cycloalkenones can also undergo transmetalation and alkylation if the ketone is first protected as an enol ether (eq 11).[30]

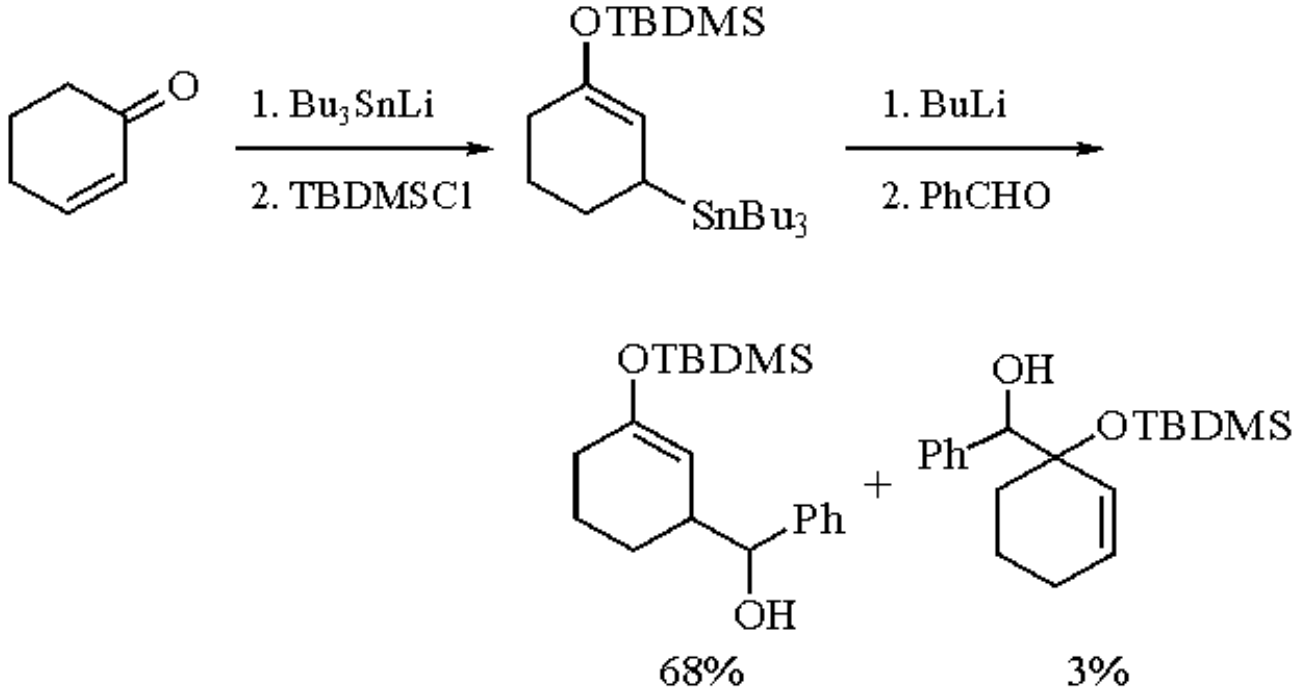

(11)

A similar sequence has been carried out on the morpholine enamine of β-tributylstannylcyclohexanone.[31] 1,4-Addition of tributyltinlithium to 2-phenylselenocyclopentenone with in situ alkylation of the enolate results in a 2-alkyl-2-phenylseleno-3-tributylstannylcyclopentanone. Destannyl-selenylation can be readily accomplished using a variety of Lewis acids or fluoride sources, ultimately to provide a 2-substituted cyclopentenone derivative.[32] The synthesis of a prostaglandin precursor was achieved using this methodology (eq 12).

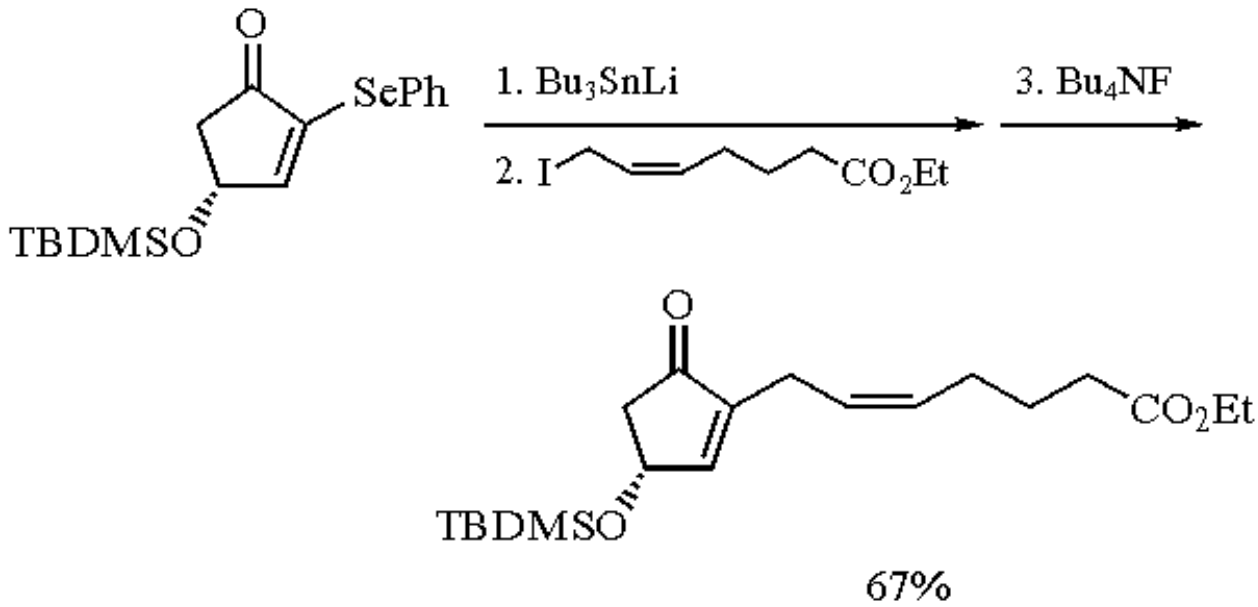

(12)

1,4-Addition products obtained from tributyltinlithium addition to cycloalkenones are also useful precursors for a variety of rearrangement and fragmentation reactions. Lewis acid-catalyzed rearrangement of the alcohol derived from reduction or alkyllithium addition to the carbonyl results in the formation of cyclopropanes.[33] If the ketone is not reduced prior to the addition of a Lewis acid, the cyclopropanol intermediate undergoes fragmentation in situ to provide either the destannylated ketone or the ring contracted product.[34] The cyclopropanol product could be isolated only when the tributyltin bearing carbon was a primary carbon, or when the carbonyl was an aldehyde. The direction of cleavage was consistent with protonation at the less substituted carbon of the cyclopropanol. Treatment of the β-tributylstannyl ketones obtained by 1,4-addition with ***m-Chloroperbenzoic Acid*** resulted in a tin-directed Baeyer-Villager reaction, ultimately providing the alkene ester fragmentation product (eq 13).[35]

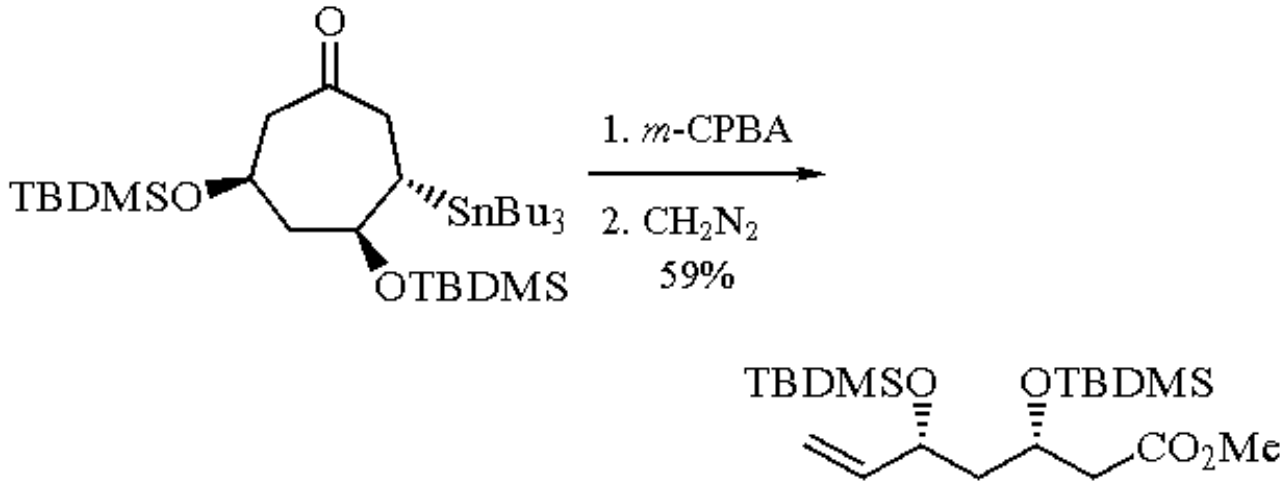

(13)

Migration of the β-tributylalkyl substituent occurred preferentially over *t*-butyl or naphthyl groups; therefore the reaction resulted in a complete reversal of the normal migratory aptitude realized in the Baeyer-Villager reaction. The directing effects of the tin group were also extended to the Beckmann fragmentation of the derived β-tributylstannyl oximes (eq 14).[35]

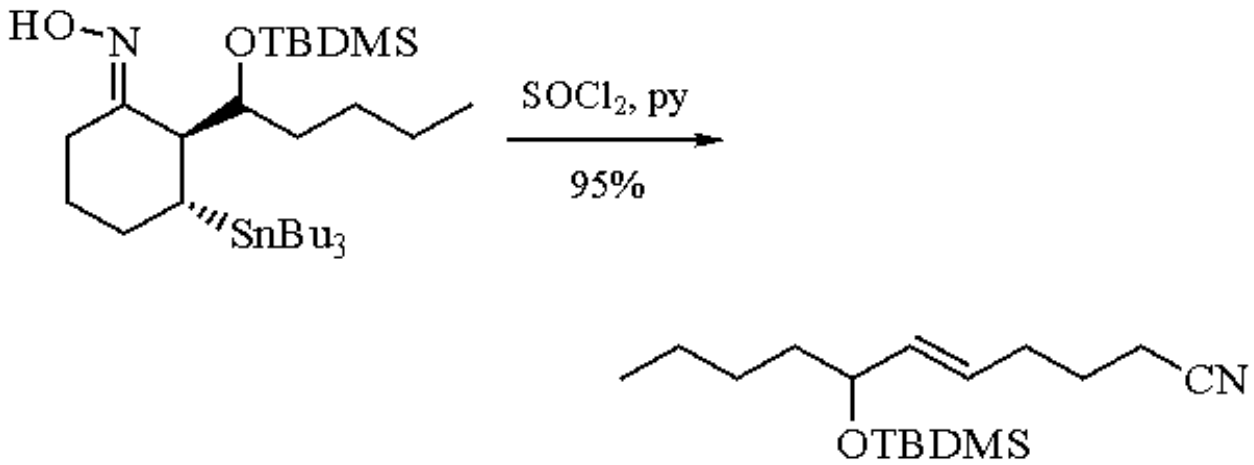

(14)

Oxidative fragmentation of β-tributylstannyl cycloalkanols with iodosobenzene results in the generation of ring-opened keto alkenes.[36] The fragmentation reaction is stereoelectronically controlled and requires an antiperiplanar arrangement of breaking bonds. β-Tributylstannylcyclohexanol derivatives which cannot adopt the correct orientation do not fragment, but rather undergo reaction at a butyl group on tin.[36c] A similar oxidative fragmentation can also be achieved on a cyclic hemiacetal, resulting in formation of a macrocyclic lactone (eq 15).[37]

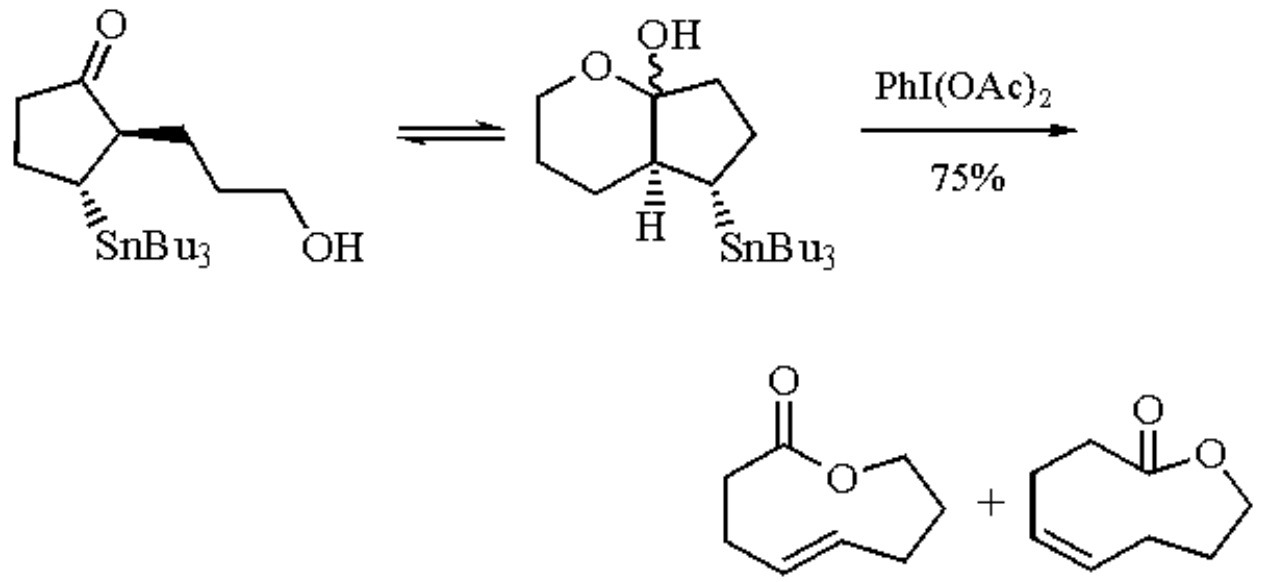

(15)

Oxidative fragmentation can also be induced using ***Lead(IV) Acetate***. An intramolecular dipolar cycloaddition reaction has been accomplished by in situ generation of a nitrile oxide and an alkene by the fragmentation reaction (eq 16).[38]

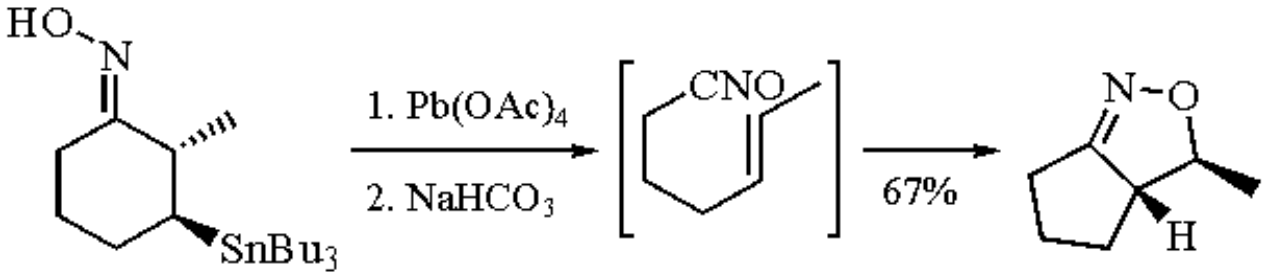

(16)

A one pot four-component annulation procedure has also been developed which is initiated by tributyltinlithium 1,4-addition to an enone.[39] The first intermediate enolate then acts as the nucleophile for a Michael addition reaction to a second enone, followed by a subsequent Michael reaction to an enoate. This sequence results in a cyclic hemiacetal containing a β-tributylstannyl moiety. Lead tetraacetate oxidative fragmentation then results in the generation of a macrocyclic lactone (eq 17).

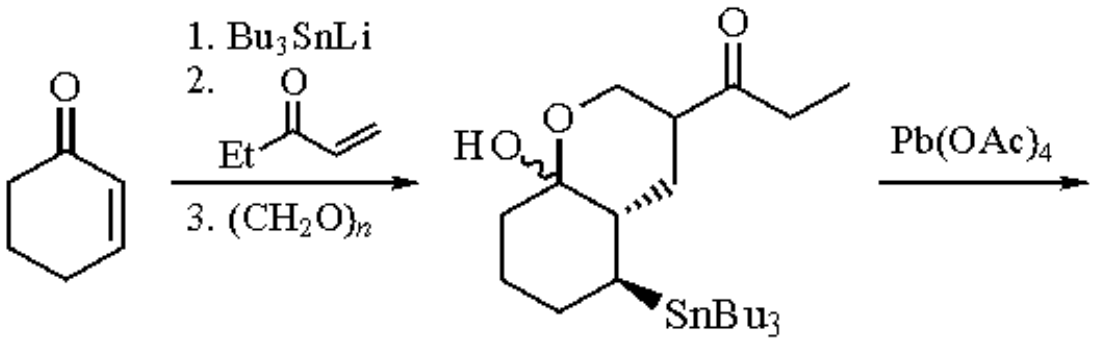

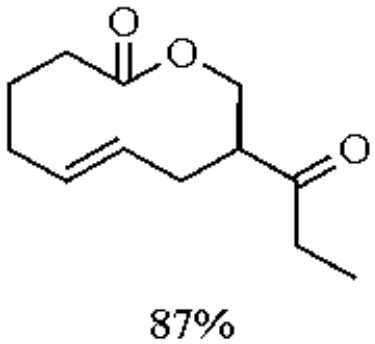

(17)

87%

Transmetalation of tributyltinlithium to a variety of other organometallic reagents has also been accomplished. Organotincuprate reagents undergo 1,4-addition to enones,[40] addition to alkynes,[41] enynes,[42] and addition-elimination reactions to provide β-tributylstannyl unsaturated esters[5] and amides.[43] Tributyltin boron and aluminum reagents have also been prepared.[44]

Related Reagents.

Trimethylstannyllithium.

---

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Tri-*n*-butyltin Trifluoromethanesulfonate[1]

***n*-$Bu_3SnOSO_2CF_3$**

[68725-14-4] · $C_{13}H_{27}F_3O_3SSn$ · Tri-*n*-butyltin Trifluoromethanesulfonate · (MW 439.18)

(powerful stannylating reagent;[1] readily stannylates vinylcuprates and vinylaluminum compounds;[1-3] catalyzes hydrostannation of aldehydes and ketones by tin hydrides[4])

Physical Data: mp 41-43 °C; bp 155-167 °C/0.08 mmHg.

Solubility: freely sol polar and nonpolar organic solvents.

Preparative Methods: by analogy to the preparation of trialkyltin carboxylates,[5] tribuyltin trifluoromethanesulfonate is prepared from ***Bis(tri-n-butyltin) Oxide*** and either ***Trifluoromethanesulfonic Acid*** (with subsequent removal of water) or ***Trifluoromethanesulfonic Anhydride***,[2] as in eq 1.

$$(CF_3SO_2)O + (Bu_3Sn)_2O \xrightarrow[93\%]{} 2\ Bu_3SnOSO_2CF_3 \qquad (1)$$

The following procedure is quite convenient: freshly distilled trifluoromethanesulfonic anhydride[6] is caused to react with an equal molar amount of tributyltin oxide cooled at 20 °C under nitrogen. When the exothermic reaction completely subsides, the flask is set up for a short-path distillation and the resulting red oil is distilled at about 0.1 mmHg. The distillate is collected without cooling to prevent crystallization of the product in the condenser. Alternatively, this reagent can be prepared in situ by the action of trifluoromethanesulfonic acid on ***Tri-n-butylstannane*** in benzene or dichloroethane.[4]

Handling, Storage, and Precautions: this reagent is deliquescent. Therefore it is best handled as a solution in benzene, ether, or hexane, stored at room temperature under nitrogen. Solutions can be dried with 4Å molecular sieves. As with certain other trialkyltin electrophiles, tributyltin trifluoromethanesulfonate is foul smelling. The toxicity of this class of compounds has been described.[7] Use in a fume hood.

Transmetalation Reactions.

The powerful electrophilic property of this reagent makes it particularly attractive for the conversion of vinylcuprates and vinylalanes into vinylstannanes. For example, the reaction of vinyl heterocuprates[8] with this reagent occurs readily to give the corresponding (*Z*)-vinylstannane, even at -78 °C (eq 2). Stannylation of vinylalanes[9] occurs readily to give the corresponding vinylstannane (eq 3). Complementary methods are available for the preparation of both (*Z*)-[2] and (*E*)-vinylstannanes.[1,3] The configuration of the vinylstannane is controlled at the vinylaluminum stage: treatment of ***Propargyl Alcohol*** with ***Lithium Aluminum Hydride*** followed by tributyltin trifluoromethanesulfonate affords the (*Z*)-allyl alcohol, whereas if the addition of $LiAlH_4$ is followed by NaOMe and then the reagent, the (*E*)-allyl alcohol results (eq 4).[1]

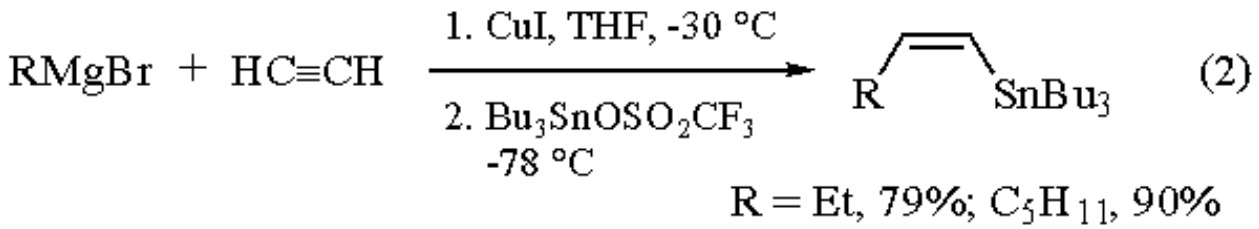

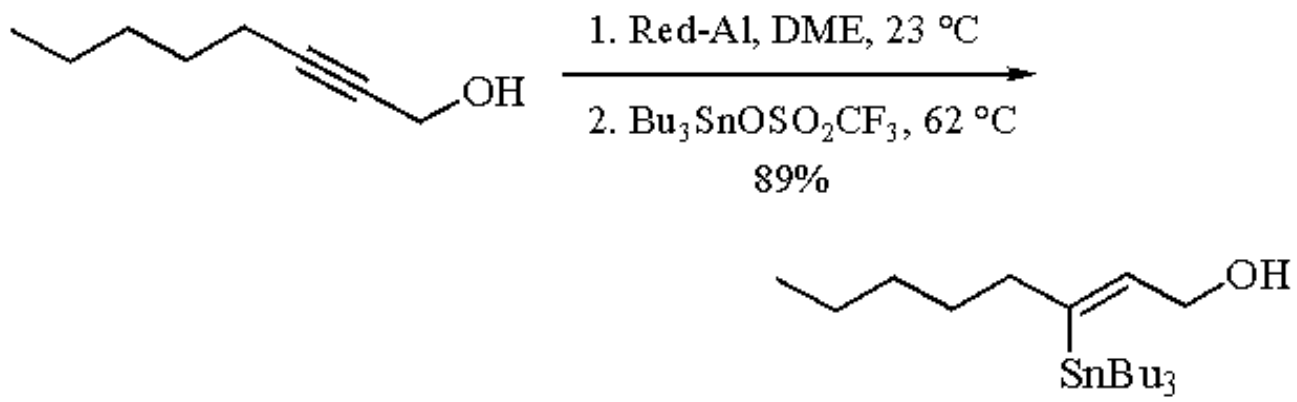

(3)

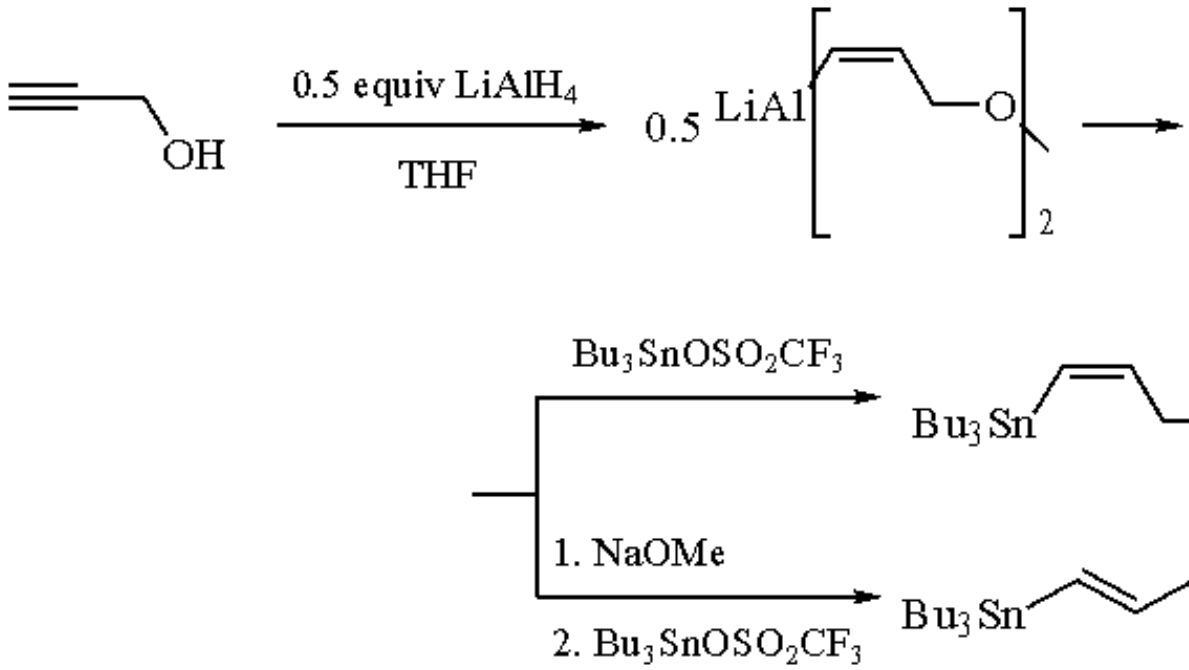

(4)

The (*E*)-vinylstannane also results when the alkyne is treated sequentially with ***Diisobutylaluminum Hydride***, ***Methyllithium***, and then the title reagent.[3] For example, treatment of 1-octyne with DIBAL in hexane followed by MeLi and then the reagent afforded (*E*)-1-tributylstannyl-1-octene in good yield (eq 5).

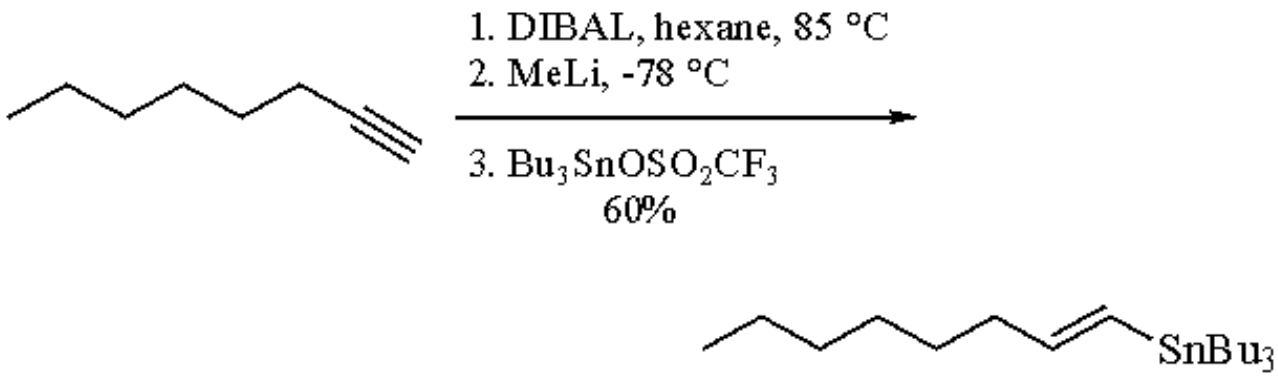

(5)

The title reagent is also suitable for the preparation of allylstannanes from allyllithium reagents,[10] and vinylstannanes from vinyllithium reagents.[11]

Hydrostannation Catalyst.

This triflate is a catalyst in the hydrostannation of aldehydes and ketones by tributyltin hydride.[4] Treatment of aldehydes and ketones with one equiv of Bu_3SnH in benzene or dichloroethane in the presence of 20% of the reagent afforded the corresponding primary or secondary alcohol in high yield. Using this system, aldehydes are preferentially reduced in the presence of methyl ketones (ca. 99:1). In addition, the reagent can be employed as a cocatalyst with $PdCl_2(PPh_3)_2$ in the 1,4-reduction of enone systems (eq 6).

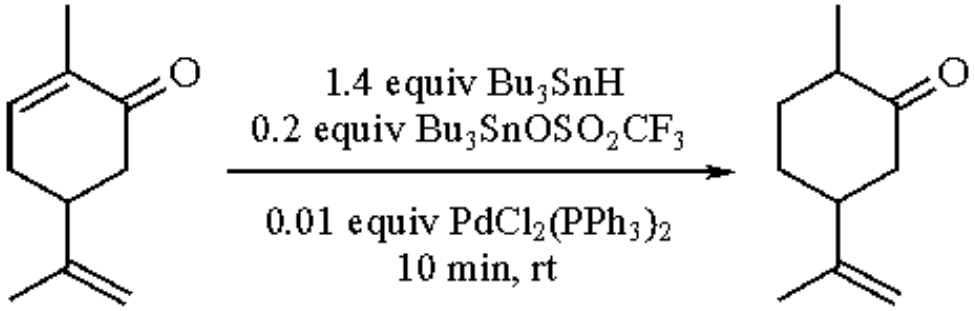

(6)

Stereospecific Arylation of Arylsulfanyl Lactones.

The title reagent catalyzes the rapid and stereospecific cyclization of certain chiral arylsulfanyl lactones to the corresponding optically pure γ-butyrolactones (eq 7).[12]

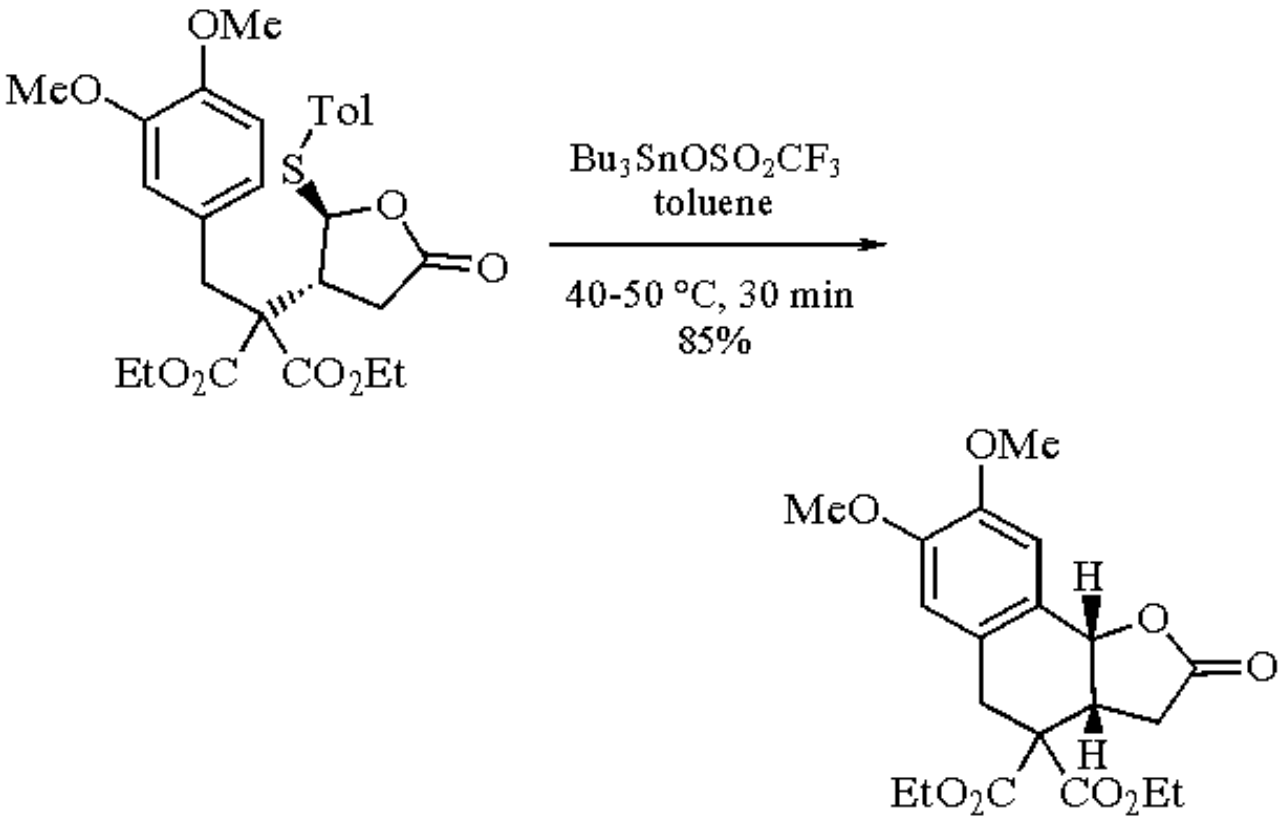

(7)

Related Reagents.

Tri-n-butylchlorostannane.

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Thomas M. Eckrich

Tri-*n*-butyl(trimethylsilylmethyl)stannane

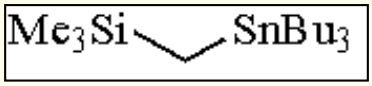

[77425-85-5] · $C_{16}H_{38}SiSn$ · Tri-*n*-butyl(trimethylsilylmethyl)stannane · (MW 377.34)

(precursor to trimethylsilylmethyllithium; methylenation of aldehydes and ketones)

Alternate Name: tributyl(trimethylsilylmethyl)tin.

Physical Data: bp (distillation) 146 °C/2.5 mmHg.

Preparative Methods: is conveniently prepared by the action of ***Tri-n-butylstannyllithium*** on ***(Chloromethyl)trimethylsilane*** in THF/hexane at 0 °C.[1] Alternatively, ***Trimethylsilylmethylmagnesium Chloride*** can be treated with ***Tri-n-butylchlorostannane*** in refluxing ether.[2] Excellent yields (>90%) may be realized by either method.

Handling, Storage, and Precautions: organotin compounds should be considered toxic and should be handled with appropriate care. Use in a fume hood.

Precursor for Trimethylsilylmethyllithium.

Trimethylsilylmethyllithium is a useful reagent for methylenation of aldehydes and ketones (Peterson alkenation),[3] for preparation of α-silyl ketones from carboxylic acids, esters, and acid chlorides,[4] and for further elaboration to synthetically useful organometallic reagents.[5-7] The utility of this versatile organolithium reagent is enhanced by its ready availability from a stable precursor. Peterson reported that tributyl(trimethylsilylmethyl)tin did not undergo transmetalation with ***n-Butyllithium*** in hexane at 25 °C and that addition of ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) resulted in minor improvement. Seitz and Zapata[1] observed a solvent dependency in the transmetalation reaction and were able to define conditions for rapid and complete conversion of tributyl(trimethylsilylmethyl)tin to trimethyl(silylmethyl)lithium (eq 1).

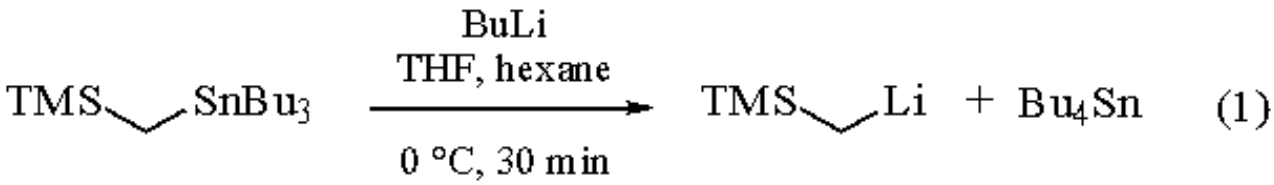

Methylenation of Carbonyl Compounds.

Tributyl(trimethylsilylmethyl)tin was the reagent of choice in Peterson alkenation of a complex and sterically encumbered decalone derivative (eq 2).[8] ***Methylenetriphenylphosphorane*** (the Wittig reagent) is often less effective in the case of hindered ketones.

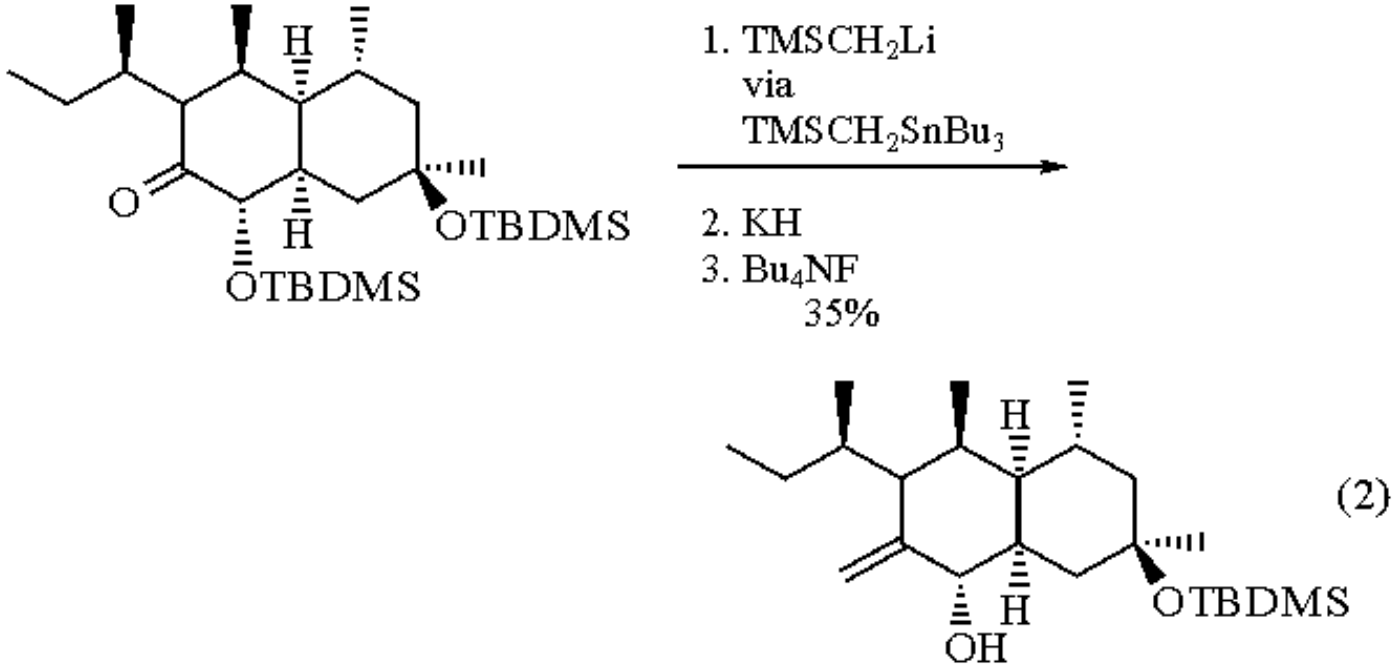

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Tricarbonyl(η^6-chlorobenzene)chromium

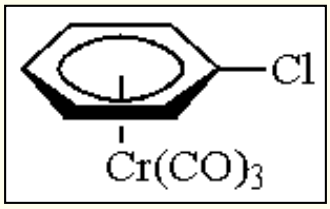

[12082-03-0] · $C_9H_5ClCrO_3$ · Tricarbonyl(η^6-chlorobenzene)chromium · (MW 248.59)

(phenyl cation equivalent[1])

Alternate Name: (chlorobenzene)chromium tricarbonyl

Physical Data: mp 102-103 °C.

Solubility: sol THF, ether, benzene.

Form Supplied in: yellow crystals; not commercially available.

Preparative Method: prepared from the reaction of chlorobenzene with ***Hexacarbonylchromium*** in refluxing dioxane.[2]

Purification: recrystallized from ether/petroleum ether. Can also be purified by column chromatography on silica gel.

Handling, Storage, and Precautions: slightly air sensitive. Use in a fume hood.

Nucleophilic Substitution.

Treatment of tricarbonyl(chlorobenzene)chromium (**1**) with various nucleophiles at 25 °C effects nucleophilic substitution of chlorine.[1,3] Nucleophiles derived from carbon acids having a pK_a > ~20 lead to the arylated products in high yield (eq 1).
Tricarbonyl(fluorobenzene)chromium is recommended for phenylation of less reactive nucleophiles. Nucleophilic addition produces the pentadienylchromium complex (**2**), which converts to the substituted arene complex (**3**). Oxidative removal of the metal with ***Iodine*** produces the free arene (**4**). Kinetically, nucleophiles attack the *ortho* and *meta* positions, and thus nucleophilic addition at low temperature followed by oxidation leads to chlorobenzene derivatives (**5**) and (**6**) (eq 2), in addition to (**4**).[4]

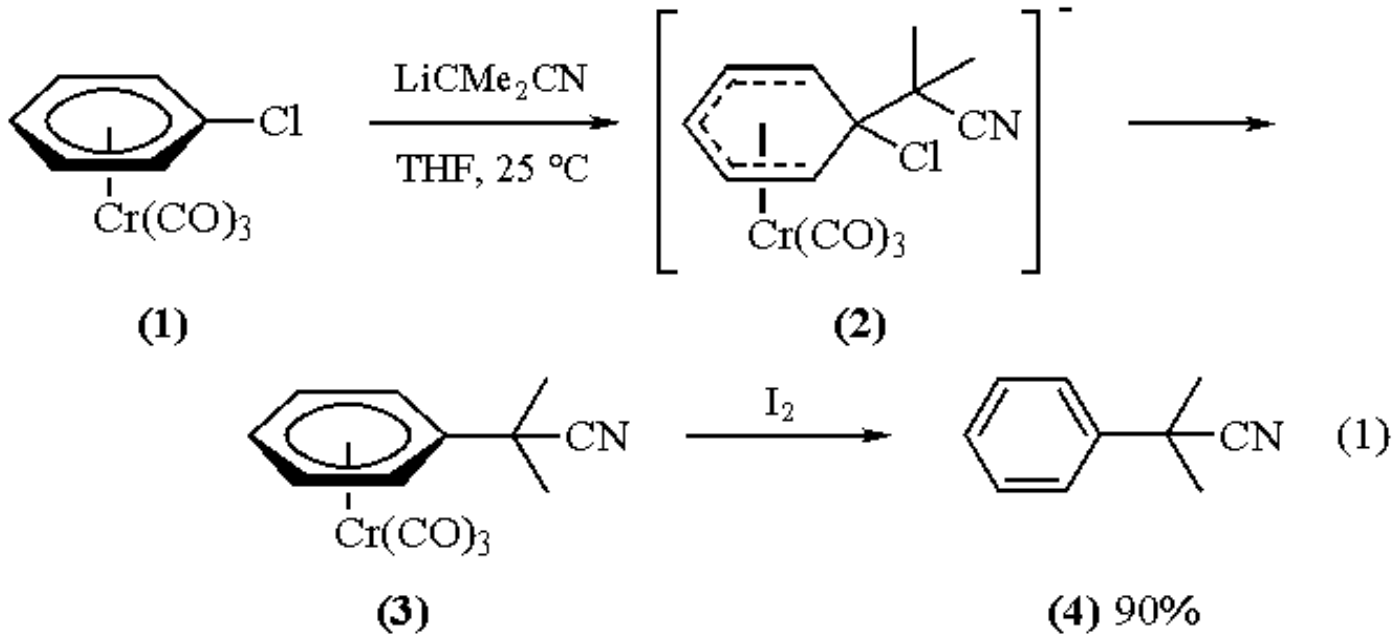

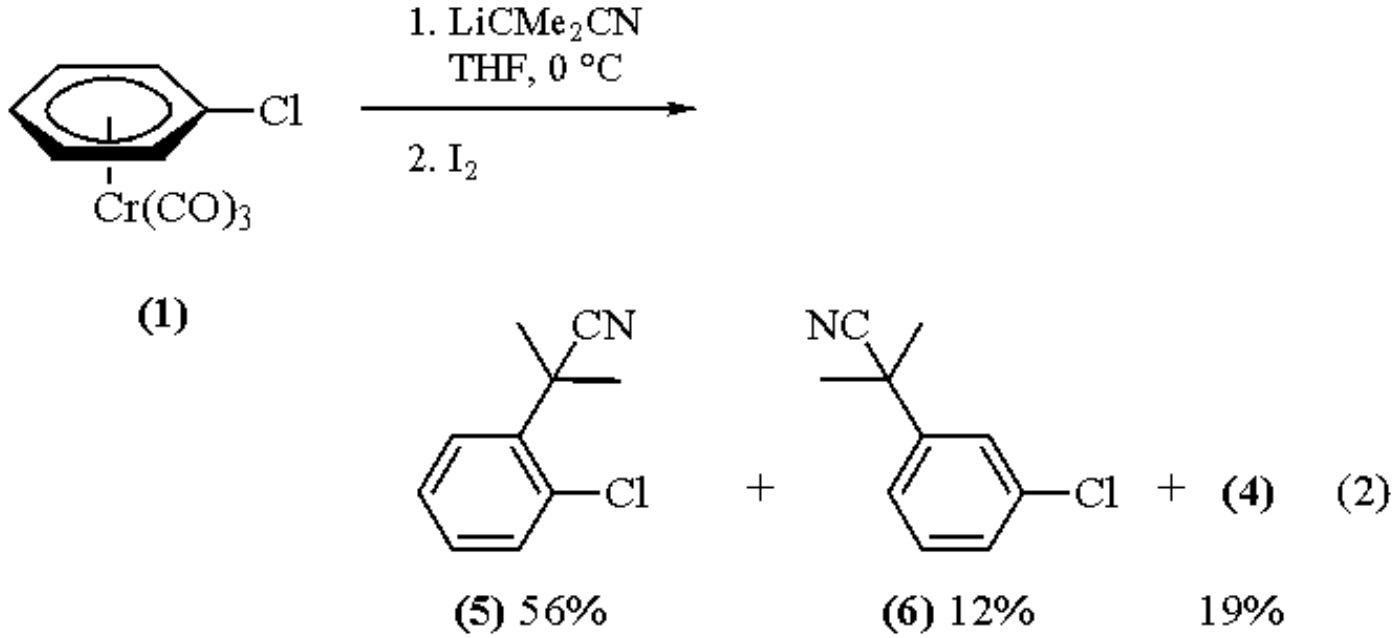

Orthometalation.

Treatment of the title reagent with ***n-Butyllithium*** produces the lithiated arene complex (**7**), which is stable at low temperature. Treatment of complex (**7**) with electrophiles produces the *ortho*-substituted chlorobenzene derivatives (e.g. **8**) (eq 3).[5] At temperatures higher that -78 °C, complex (**7**) undergoes decomposition through a benzyne mechanism.[6]

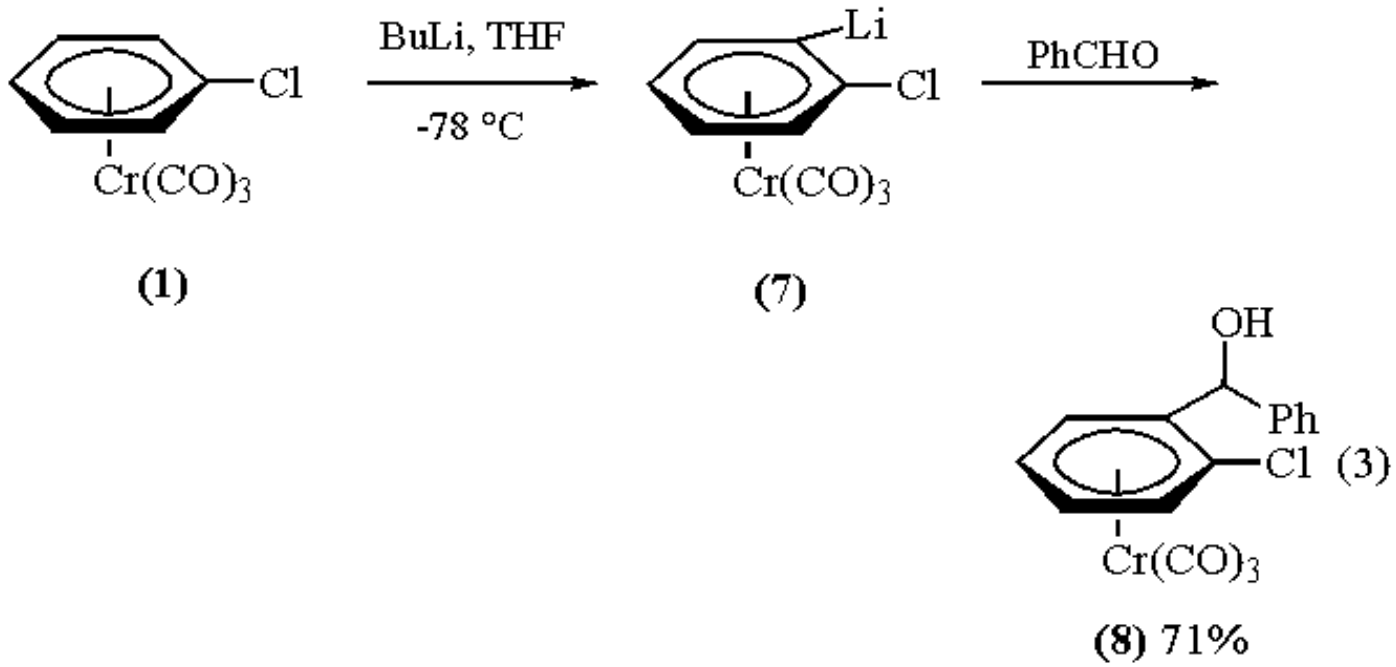

Related Reagents.

(η^6-Benzene)tricarbonylchromium; ***Dibenzenechromium***; ***Hexacarbonylchromium***.

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Tricarbonyl(cyclobutadiene)iron[1]

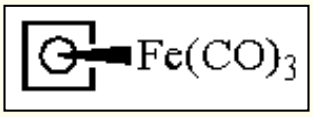

[12078-17-0] · $C_7H_4FeO_3$ · Tricarbonyl(cyclobutadiene)iron · (MW 191.96)

(stable, storeable source of cyclobutadiene)

Physical Data: pale yellow solid, mp 26 °C; bp 68-70 °C/3.0 mmHg; X-ray diffraction.[2]

Solubility: sol polar solvents; sparingly sol in pentane.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: NMR, elemental analysis.

Preparative Methods: may be prepared in good overall yields by the reaction of 3,4-dihalocyclobutene or 1,2,3,4-tetrahalocyclobutane with ***Nonacarbonyldiiron***,[3] or by the photolysis of photo-α-pyrone with ***Pentacarbonyliron*** (eq 1).[4] The reaction of *cis*-3,4-carbonyldioxycyclobutene with $Fe_2(CO)_9$ or ***Disodium Tetracarbonylferrate(-II)*** generates the title reagent (**1**), and while this reaction is stereospecific it is not known if it occurs with inversion or retention of configuration.[5] Thermal reaction of $Fe(CO)_5$ with Ni, Pd, or Pt cyclobutadiene complexes results in π-ligand exchange to give the iron cyclobutadiene complexes in high yield.[6] A variety of simple substituted (cyclobutadiene)$Fe(CO)_3$ complexes may be prepared by these methods. More recently, methodology for the regiospecific preparation of 1,2- or 1,3-differentially disubstituted (cyclobutadiene)$Fe(CO)_3$ complexes from squaric esters has been reported.[7] 1,2-Disubstituted (cyclobutadiene)$Fe(CO)_3$ complexes with two different substituents are chiral, and the two enantiomers may be separated by standard resolution techniques.[8] The optically active cyclobutadiene complexes are stable to racemization at 120 °C for 48 h.

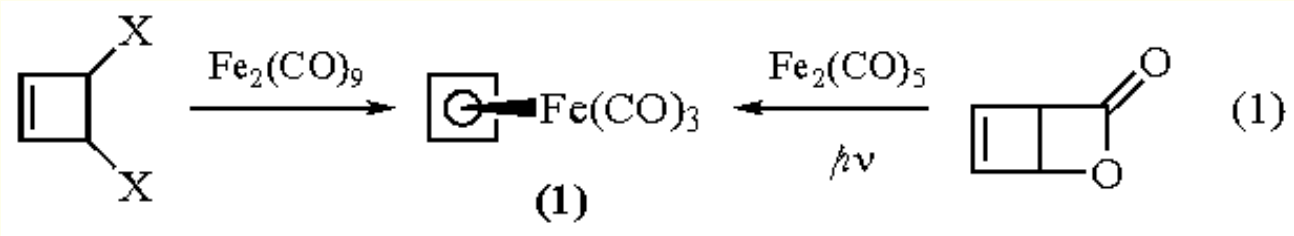

Purification: recrystallization from pentane.

Handling, Storage, and Precautions: may be stored under an inert atmosphere for extended periods.

Reactions of (Cyclobutadiene)$Fe(CO)_3$.

The organic chemistry of (**1**) is much like that of ***Ferrocene***. Acylation, formylation, chloromethylation, aminomethylation, mercuration, sulfonation, and deuteration of (**1**) can be effected by electrophilic substitution (eq 2).[9] Friedel-Crafts alkylation of (**1**) to give simple monoalkyl derivatives is not possible. Acylation of monoalkyl-substituted (cyclobutadiene)$Fe(CO)_3$ complexes generates 1,3-disubstituted (major) and 1,2-disubstituted (minor) derivatives.

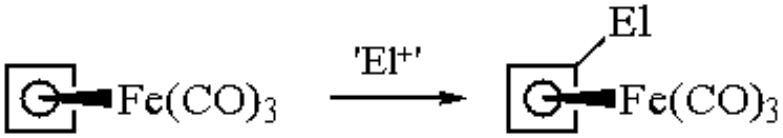

(2)

(1)

El = COMe, CHO, CH_2Cl (**3**), CH_2NMe_2, HgCl (**2**), SO_3H, D

In comparison to ferrocene, direct lithiation of (**1**) by treatment with methyl- or butyllithium is not possible.[1] However, treatment of the chloromercury derivative (**2**) with ***Methyllithium*** or ***Phenyllithium*** at -78 °C effects transmetalation (eq 3). (Lithiocyclobutadiene)$Fe(CO)_3$ can serve as a nucleophile toward triphenylmethyl chloride, ***Chlorotrimethylsilane***, and ketones.[10]

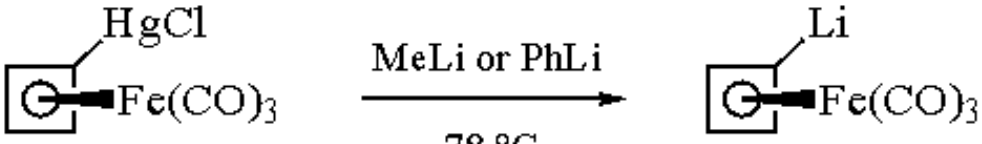

(3)

(2)

Functionalized sidechains attached to (cyclobutadiene)$Fe(CO)_3$ undergo a variety of standard organic transformations without disturbing the organometallic portion of the molecule.[8,9a,11] Solvolysis of (chloromethylcyclobutadiene)$Fe(CO)_3$ (**3**) in 5% aqueous acetone proceeds at a rate 10^8 times faster than that of ***Benzyl Chloride*** (eq 4).[10,12] The rapid rate of this S_N1 solvolysis is attributed to the stability of the α-carbocation. Chemistry of this type has been used to generate the (cyclobutadiene)$Fe(CO)_3$ analog of phenylalanine (**4**) (eq 5).[13]

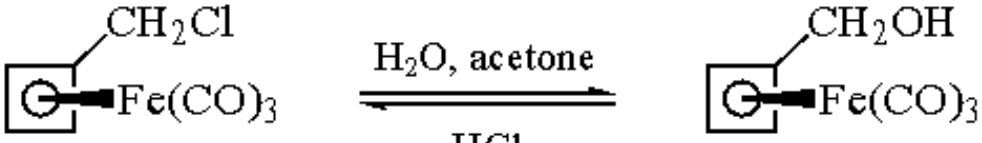

(3)

(4)

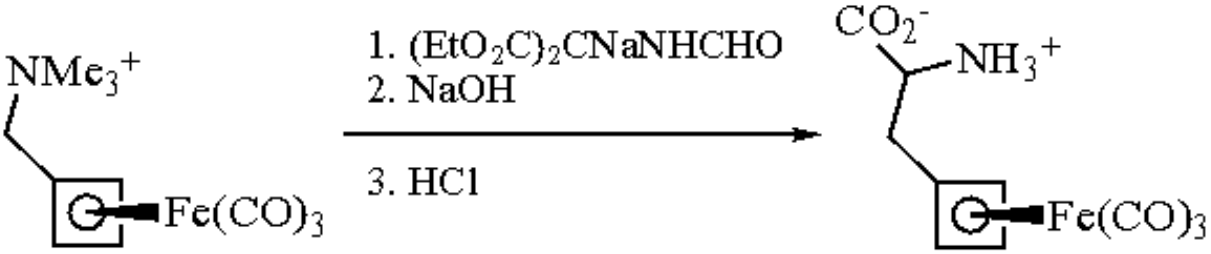

(5)

(4)

Liberation of the Ligand.

The cyclobutadiene ligand may be liberated by oxidation of the complex with ***Cerium(IV) Ammonium Nitrate*** or ***Lead(IV) Acetate***. In the absence of other reactants the cyclobutadiene ligand undergoes dimerization to afford a mixture of *syn*- and *anti*-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene (eq 6).[14]

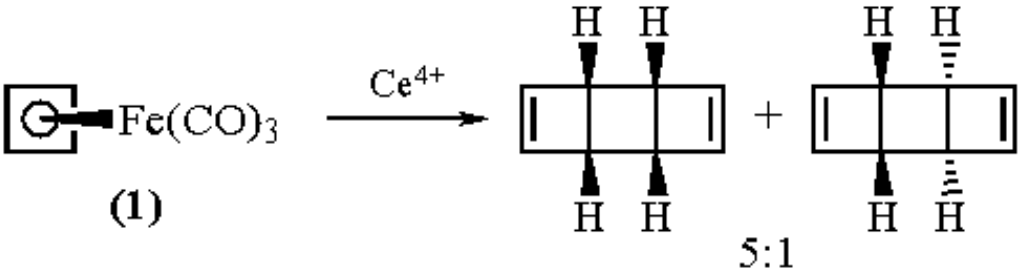

(6)

(1)

In the presence of alkenes, alkynes, or dienes, the liberated cyclobutadiene can act as either a diene or dienophile in Diels-Alder cycloadditions.[15-22] The cyclobutadiene thus generated appears to be a singlet diene. Cycloaddition occurs in a stereospecific fashion with respect to the geometry of the alkene component and with *endo* selectivity. Compound (**1**) has been used as a source of cyclobutadiene for the synthesis of a wide variety of theoretically interesting molecules, including cubane,[16] homocubanone,[17] caged keto sulfides,[18] tricyclo[4.1.0.0^{2,5}]heptanes,[19] tricyclo[4.1.0.0^{2,5}]hept-3-ene,[20] bicyclo[4.2.0]octa-2,4,6-trienes,[21] Dewar benzenes,[22] and Dewar furan.[23] Oxidation of optically active disubstituted (cyclobutadiene)Fe(CO)$_3$ complexes in the presence of a symmetrical alkene generates racemic products (eq 7).[8] Thus the chemical oxidation appears to generate free cyclobutadiene. Additional evidence for the presence of the free ligand was provided by the three-phase test. Transfer of the ligand from a polymer-bound (cyclobutadiene)iron complex by oxidation in the presence of a separately polymer-bound dienophile can only be accounted for by the generation of the free ligand, since there is negligable contact between the functionalized sites of the two different polymeric supports.[24] In contrast, oxidation of the optically enriched complex (**5**) containing a dangling dienophile produced the achiral phthalan and the optically active tricyclic ketone (**6**) (eq 8).[25] The product (**6**) is proposed to arise via initial coordination of the dienophile to the oxidized complex, followed by alkene insertion, carbonyl migration, and reductive elimination.

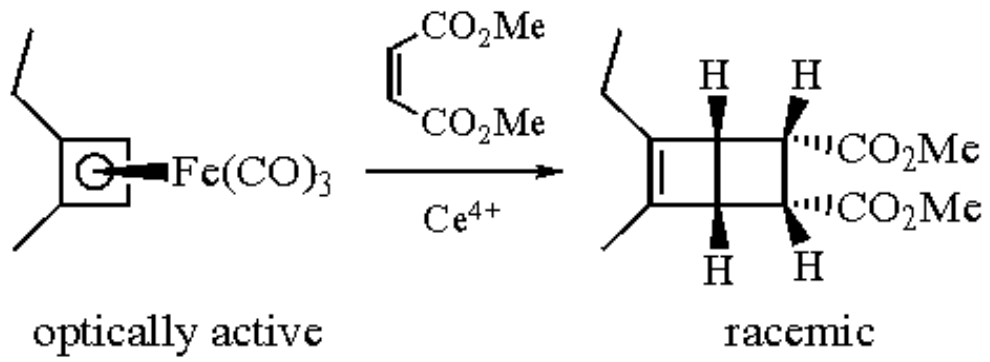

(7)

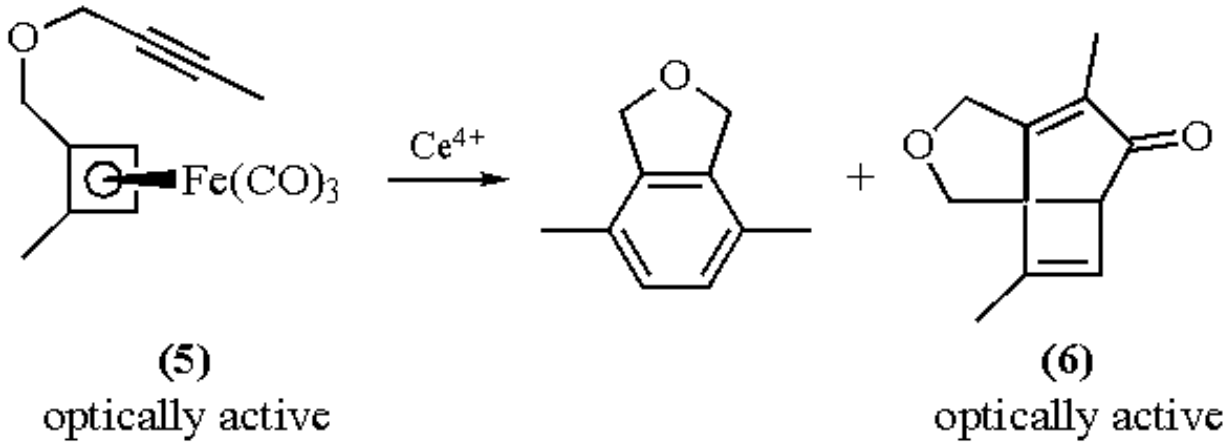

(8)

Photolysis of substituted (cyclobutadiene)Fe(CO)$_3$ complexes in the presence of alkynes affords substituted benzenes as a mixture of regioisomers (eq 9).[26] The distribution of products is not statistical, which suggests that the free cyclobutadiene ligand is not involved. It is proposed that the reaction occurs via initial loss of carbon monoxide and coordination of the alkyne. Insertion of the alkyne generates a bridged species which reductively eliminates to a Dewar benzene. Secondary photolysis of the Dewar benzene gives the aromatic product.

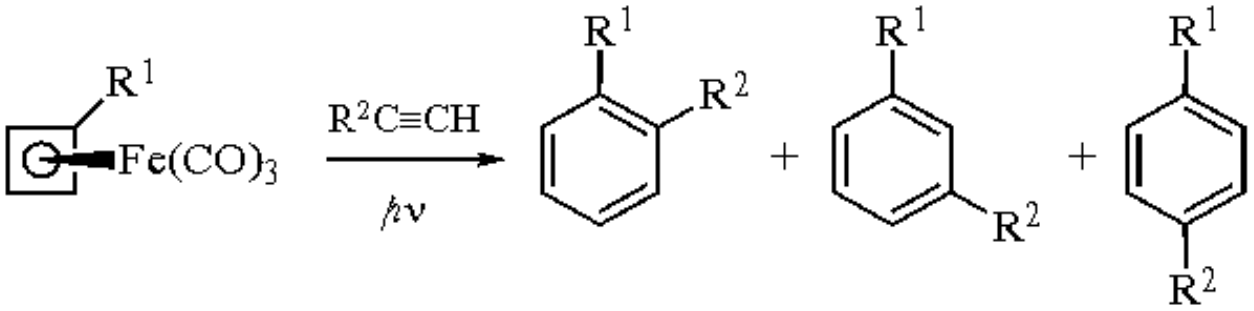

(9)

The photochemical reduction of (benzoylcyclobutadiene)Fe(CO)$_3$ in acetic acid gives 2-cyclobutenyl phenyl ketone as the product (eq 10).[27]

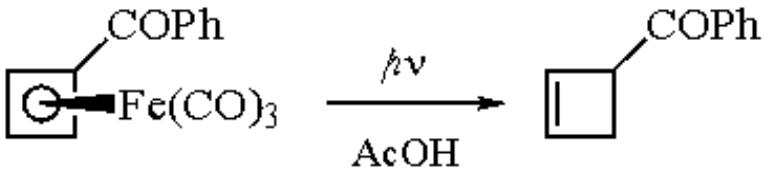

(10)

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Tricarbonyl(cyclohexadienyl)iron Tetrafluoroborate[1]

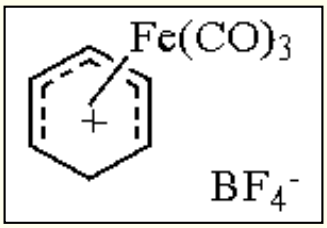

[33678-01-2] · $C_9H_7BF_4FeO_3$ · Tricarbonyl(cyclohexadienyl)iron Tetrafluoroborate · (MW 305.82)

(mild electrophile capable of reacting with a wide range of nucleophiles under mild conditions[1,2])

Physical Data: mp 193 °C (dec).

Solubility: readily sol H_2O, DMSO, DMF, $MeNO_2$; difficult in nonpolar solvents.

Form Supplied in: yellow solid; widely available.

Preparative Methods: readily obtained from tricarbonylcyclohexadieneiron by hydride abstraction with trityl fluoroborate in methylene chloride followed by precipitation of the salt with ether. Salts of this type are invariably yellow microcrystalline involatile solids.

Handling, Storage, and Precautions: this solid is stable to air and moisture.

Introduction.

As might be expected from its cationic nature, the dienyl-$Fe(CO)_3$ complex reacts with nucleophiles to give neutral diene complexes.[1a] The cation possesses sufficient stability towards water to be recrystallized from it and yet, on the other hand, conveniently reacts with nucleophiles stronger than water to afford addition products with attack occurring at carbon to give 5-substituted 1,3-cyclohexadiene-$Fe(CO)_3$ derivatives. The reaction is usually very clean and is regiospecific (terminal C atom) and stereospecific (opposite Fe).[1c]

C-X Bond Formation.

Reaction of the cation with anions RO^- (R = H, Me, CMe_3, $SiMe_3$) gives the corresponding complexes as well as dimeric products in yields depending on RO^- and the reaction conditions.[2c,3] The (5-*exo*-halogenocyclohexa-1,3-diene)$Fe(CO)_3$ can be prepared from reaction of the cation with ***Potassium Fluoride***, KBr, or KCl in the presence of ***18-Crown-6***.[4] In contrast, iodide ion ultimately gives the product from addition at iron and displacement of carbon monoxide.[5]

Addition of a wide variety of anilines and pyridines to the cation forms novel *C*- or *N*-alkylation products, depending on the substituents and conditions (eq 1).[6] Electron-withdrawing substituents (4-NO_2) on the arene favor *N*-alkylation whereas electron-donating substituents (3-OMe, 3-NR_2) favor *C*-alkylation.

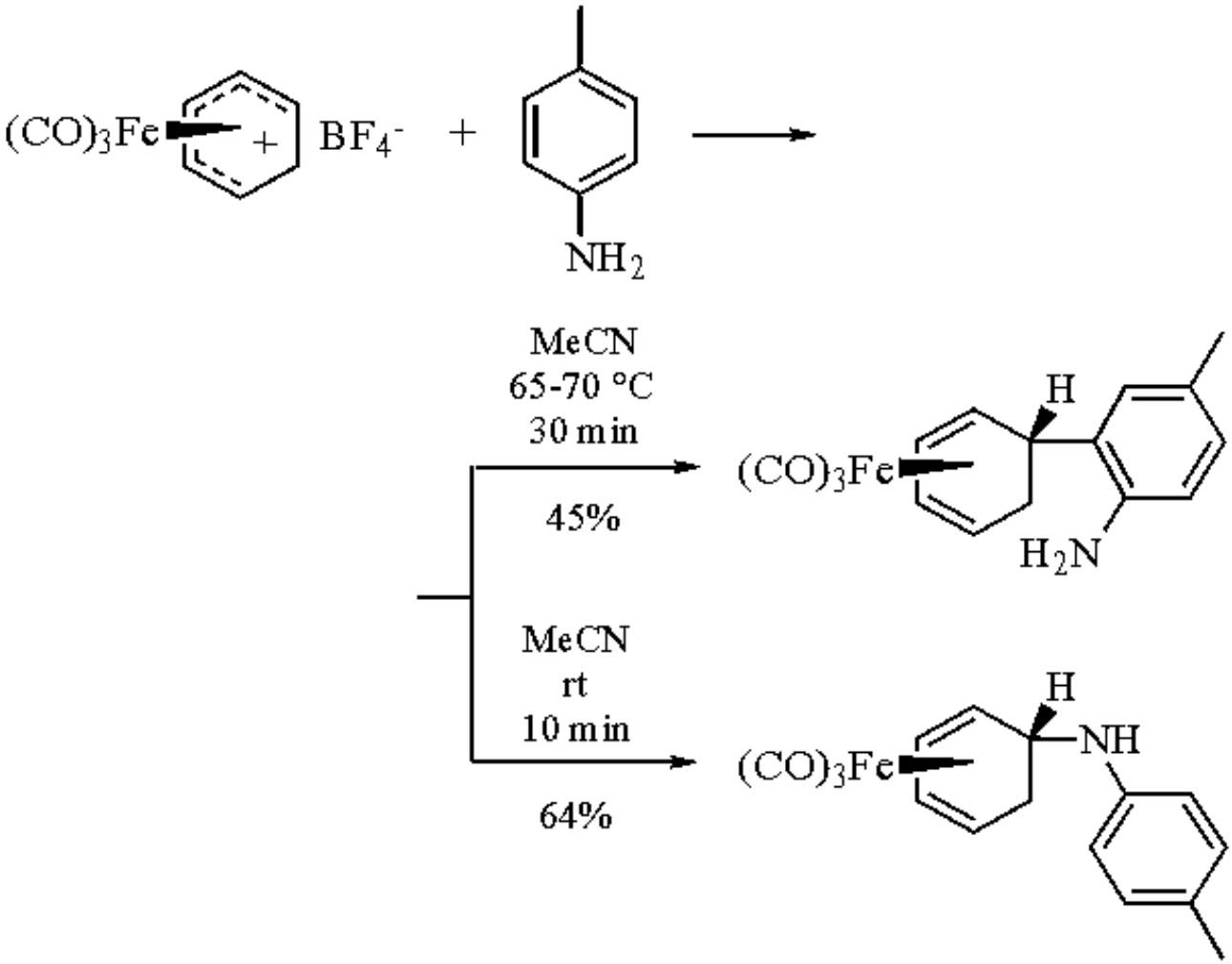

(1)

The *N*-alkylation products may undergo dissociation to the cation upon treatment with acid.[7] Amides[1a,8] form adducts with the cation when the reaction is carried out at higher temperature. Thiourea forms the *S*-linked adducts.[6c,9] Attack of nucleophiles such as nitrosoarenes,[10a] nitrosoalkanes,[10b] phosphorus,[11] ***Acetonitrile***,[12] and thiocyanate[13] also give the corresponding 1,3-diene 5-*exo*-substituted products.

Nucleophilic addition of phosphite and phosphines to the cation has led to a variety of novel phosphorus adducts (eq 2).[14] Reaction of an electron-rich transition metal π-complex could readily give stereo- and regioselective C-C bond formation (eq 3).[15]

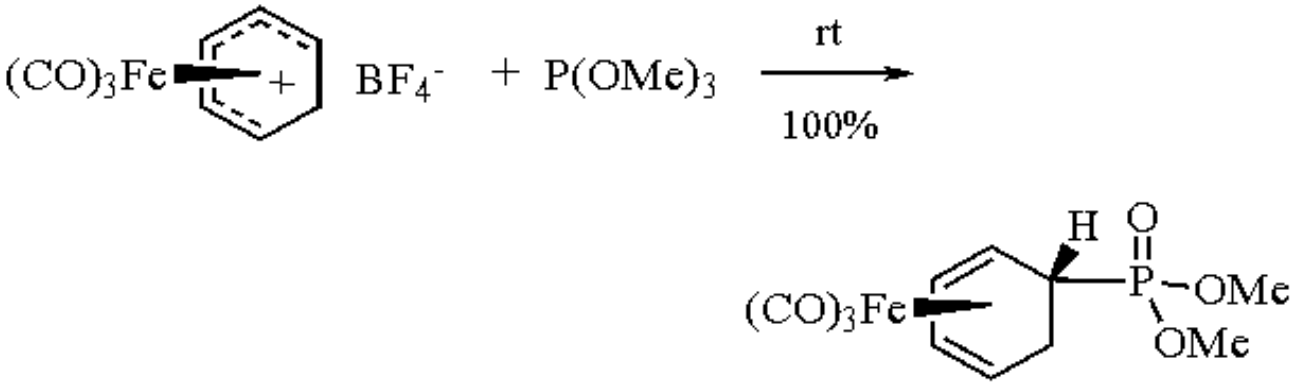

(2)

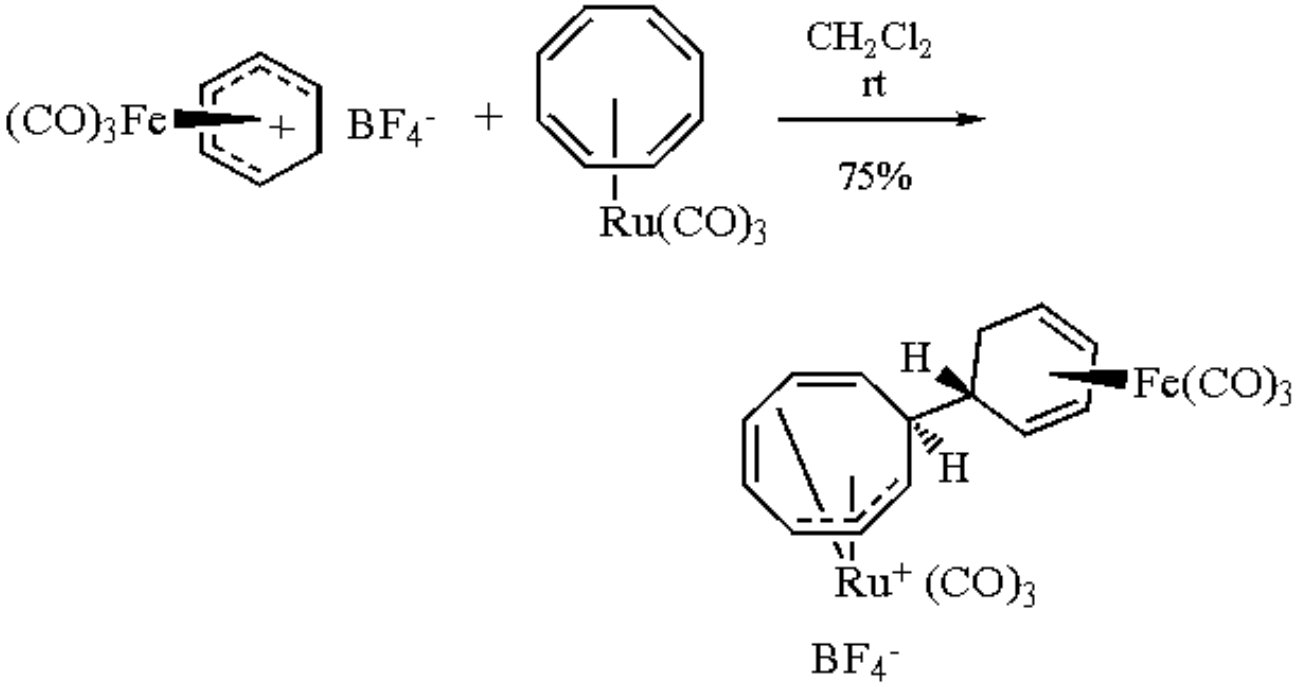

(3)

Addition of metal carbonyl anions [such as $Re(CO)_5^-$, $Mn(CO)_5^-$, $(\eta^5\text{-}(C_5H_5W(CO)_3)^-$] to the cation gives heterobimetallic η^1:η^4-hydrocarbon-bridged complexes, and addition of organometallic nucleophiles [$M(CO)_4^{2-}$ (M = Os, Ru)] leads to the heterotrimetallic η^1:η^4-hydrocarbon-bridged complexes.[16] Hydride reduction of the cation favors simultaneous attack at the ring carbon atom and $Fe(CO)_3$ group.[17] The cation is reduced efficiently by ***Sodium Borohydride***[18] and ***Tri-n-butylstannane***.[14b] Dissolving metal reductions lead to dimerization.[14b]

Alkylating Agent.

Although it is impossible to achieve direct alkylation in good yield with Grignard or alkyllithium reagents,[19] alkylation of the cation can be achieved using organoboron, -zinc, -cadmium, and -copper reagents,[1c,20] enolates,[18,21] allylstannane,[22] enamines,[23] and electron-rich π-systems.[24]

The cation reacts with a wide variety of aromatic compounds.[1a,23,25] Activated arenes, $ArMMe_3$ (M = Si or Sn, Ar = 2-furyl, 2-thienyl, substituted benzene), are more reactive towards the cation than Ar-H compounds.[25] Dimethylaluminum acetylides react with the cation to give the corresponding alkynyl substituted complexes in high yield without competing reduction products (eq 4).[26] Trialkylalkynylborates also react in a stereo- and regiospecific manner to yield novel complexes.[27] Tetraphenylborate serves as a biphenyl anion synthon (eq 5).[28] The reaction of 2-halogenocycloheptadienone enolate with the cation gives 2-substituted tropone (eq 6).[29]

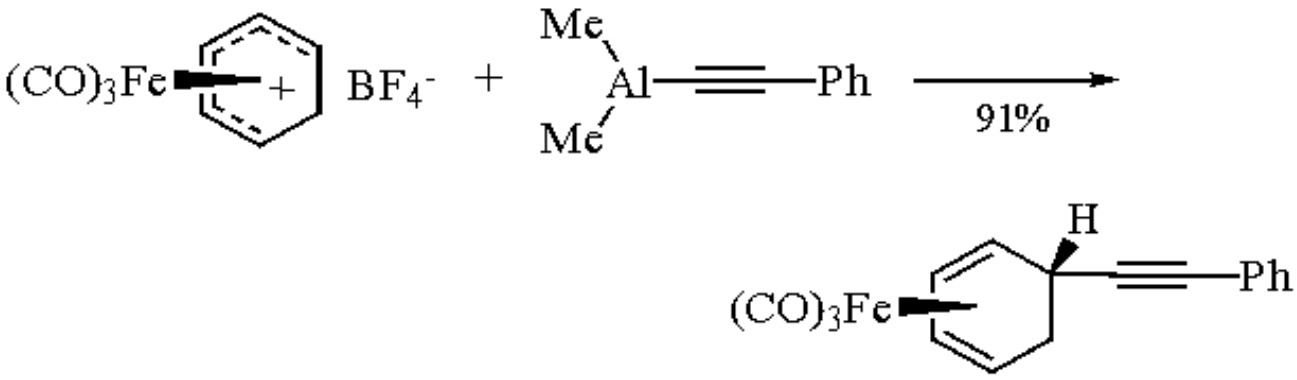

(4)

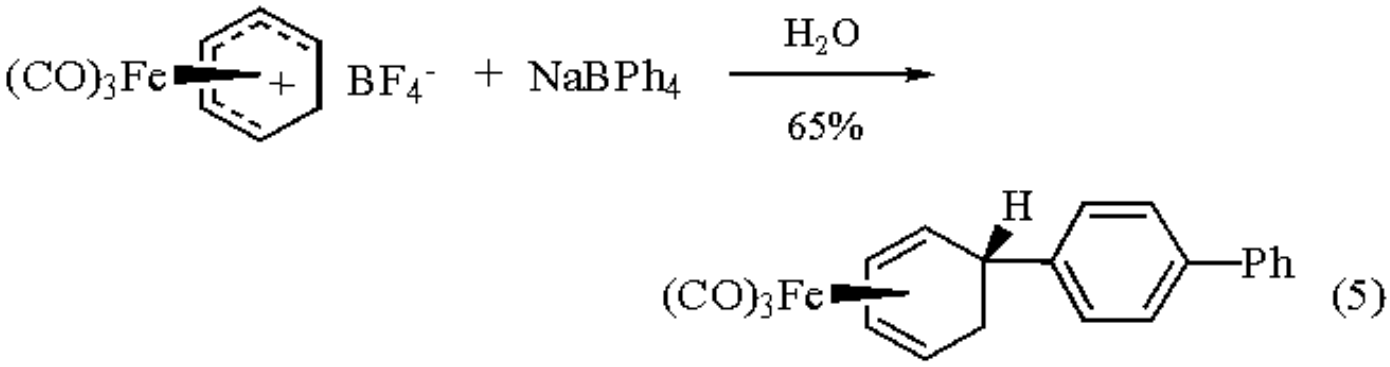

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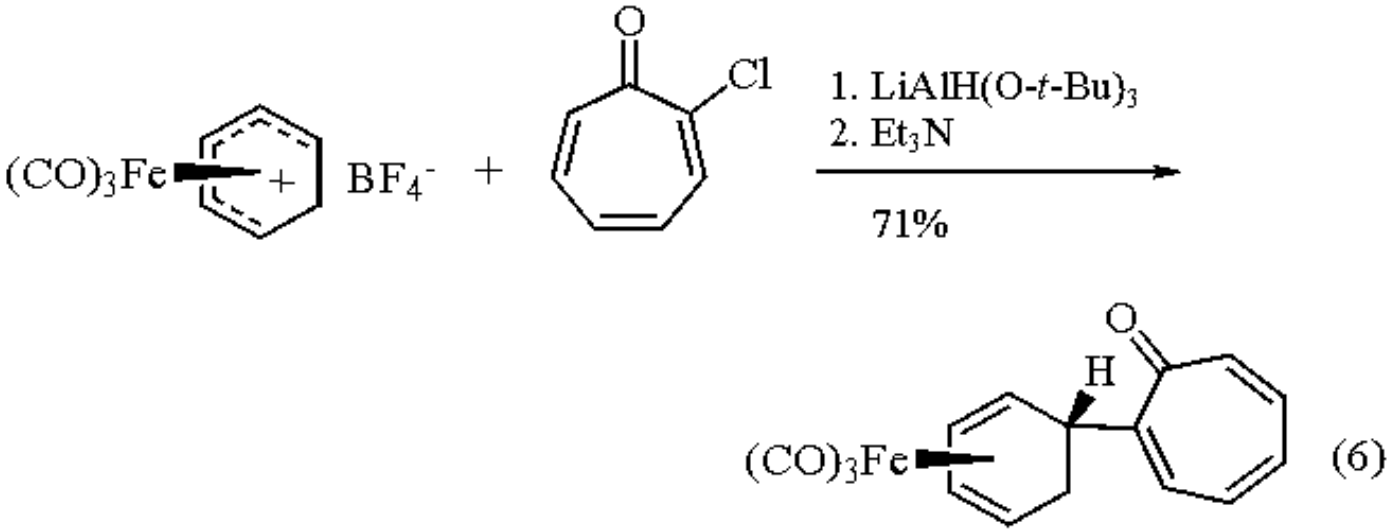

(6)

Aryl Cation Equivalent.

Complexes resulting from nucleophilic addition to the cation can usually be subjected to oxidative reaction conditions which will remove the metal and oxidize the resultant cyclohexadiene to a substituted aromatic compound.[1c] The regio- and stereoselective reactions of the cation with arylamines (eq 7) show excellent potential for application in organic synthesis. A procedure of consecutive iron-induced C-C and C-N bond formation has been developed. The synthesis of various highly substituted dihydrocarbazole and aromatic carbazole derivatives[6c,30] involves electrophilic aromatic substitution of an arylamine, followed by oxidative cyclization to the carbazole derivatives.[30]

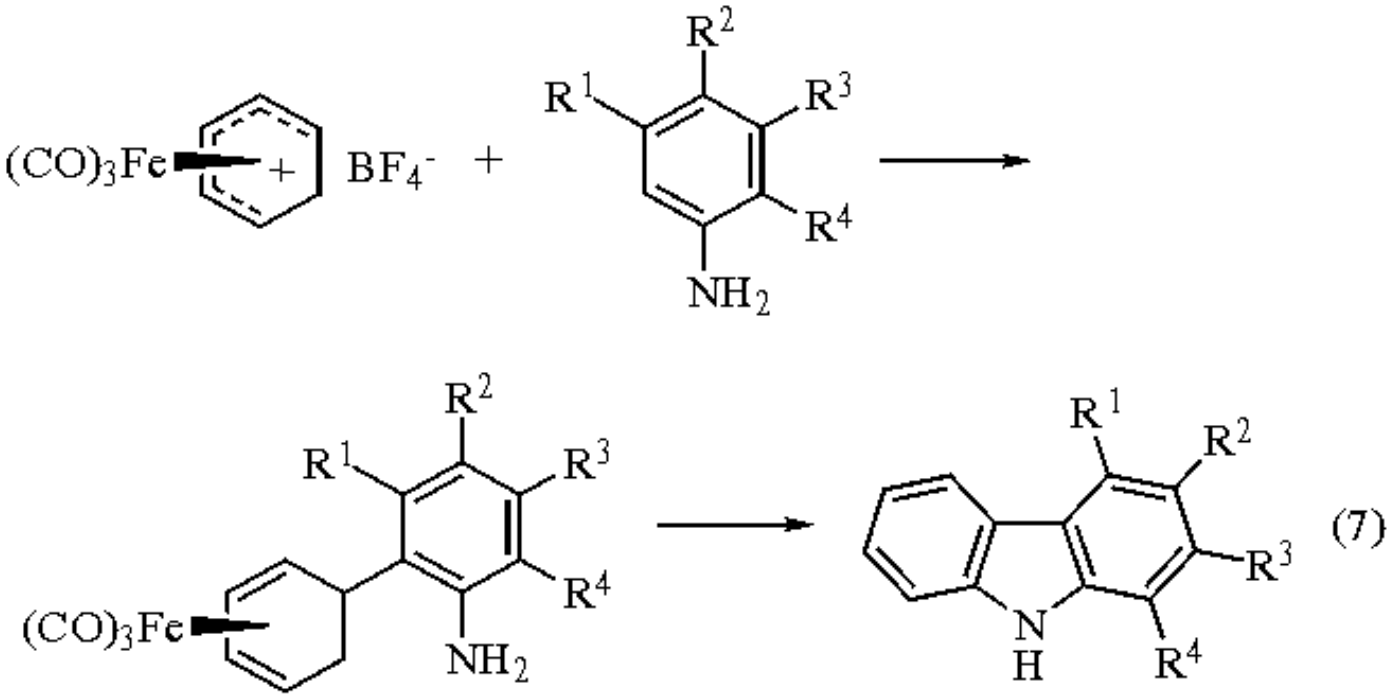

(7)

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Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide

$[Ir(CO)_3Cl]_n$-$HSiEt_2Me$-CO

($[Ir(CO)_3Cl]_n$)

[32594-40-4] · C_3ClIrO_3 · Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide · (MW 311.70) ($HSiEt_2Me$)

[760-32-7] · $C_5H_{14}Si$ · Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide · (MW 102.28) (CO)

[630-08-0] · CO · Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide · (MW 28.01)

(carbonylation of alkenes[1])

Physical Data: $[Ir(CO)_3Cl]_n$: mp 235 °C (dec).

Solubility: $[Ir(CO)_3Cl]_n$: insol common organic solvents.

Form Supplied in: brown solid ($[Ir(CO)_3Cl]_n$); clear liquid ($HSiEt_2Me$); gas (CO).

Purification: $[Ir(CO)_3Cl]_n$: sublimes readily at 150 °C in a stream of CO.

Handling, Storage, and Precautions: $[Ir(CO)_3Cl]_n$: air stable. Use in a fume hood.

Reactions with Alkenes.

The reaction of alkenes with $HSiEt_2Me$ and ***Carbon Monoxide*** (50 atm) in the presence of $[Ir(CO)_3Cl]_n$ at 140 °C gives 1-silyl-1-silyloxyalkenes (eq 1).[1] The reaction is applicable to a wide variety of terminal alkenes bearing a functional group such as silyl, alkoxy, acetal, cyano, and epoxy. The products obtained can be easily hydrolyzed to acylsilanes. ***Triethylsilane*** and ***Dimethyl(phenyl)silane*** can be also used in place of $HSiEt_2Me$. $Ir_4(CO)_{12}$ also exhibited catalytic activity.

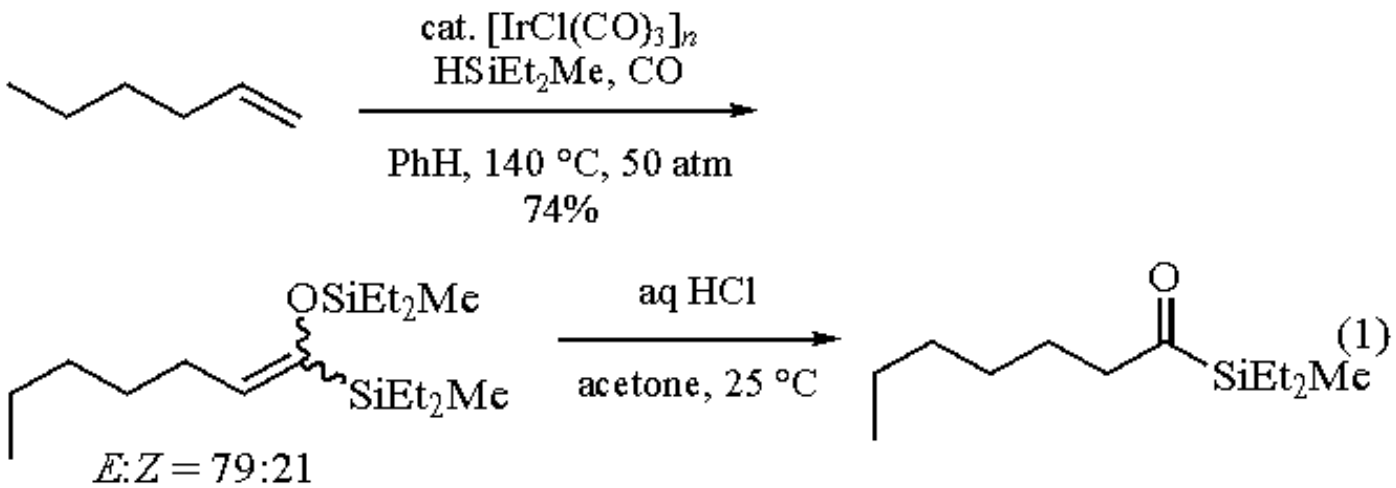

Related Reagents.

Carbon Monoxide; ***Dodecacarbonyltetrarhodium-Dimethyl(phenyl)silane-Carbon Monoxide***; ***Octacarbonyldicobalt-Diethyl(methyl)silane-Carbon Monoxide***.

1. Chatani, N.; Ikeda, S.; Ohe, K.; Murai, S. *JACS* **1992**, *114*, 9710.

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Tricarbonyl(4-methoxy-1-methylcyclohexadienyl)iron Hexafluorophosphate[1]

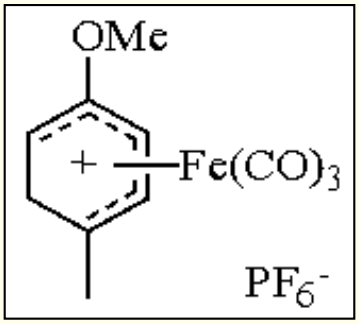

[51508-58-8] · $C_{11}H_{11}F_6FeO_4P$ · Tricarbonyl(4-methoxy-1-methylcyclohexadienyl)iron Hexafluorophosphate · (MW 408.04)

(regiospecifically reacts with a wide range of nucleophiles;[2] serves as a cyclohexenone γ-cation equivalent[1])

Solubility: easily sol MeCN, $MeNO_2$; difficult in nonpolar solvents; partially sol H_2O.

Form Supplied in: yellow powder.

Preparative Methods: easily prepared from 4-methylanisole by Birch reduction, followed by complexation with ***Pentacarbonyliron*** and hydride abstraction.

Handling, Storage, and Precautions: is stable to air and moisture. Potent alkylating agent. Toxicity unknown.

Introduction.

Despite the stability of this iron-bound carbocation, it is highly reactive toward nucleophiles. The cation regiospecifically reacts with a wide range of nucleophiles, including cyanide, malonate, β-diketone enolates, and silyl ketene acetals, to give synthetically useful products. The presence of the iron results in addition almost exclusively at the methyl terminus of the dienyl system (the less electron-rich terminus) on the face of the ligand opposite to the metal to give the substituted diene complexes.[2] Nucleophiles react at C-1 or C-5, but do not attack at C-2, C-3, or C-4.[3]

C-X Bond Formation.

Morpholine and hydroxide ion add at the methylated terminus C-1 of the diene system,[4] in preference to the electronically deactivated terminus C-5 (eq 1), while treatment with ***Sodium Borohydride*** gives addition of H^- at both termini (eq 2).[4] A possible explanation is partial attack on carbonyl to give a formyl complex with transfer of hydride directly to the carbon system.[5]

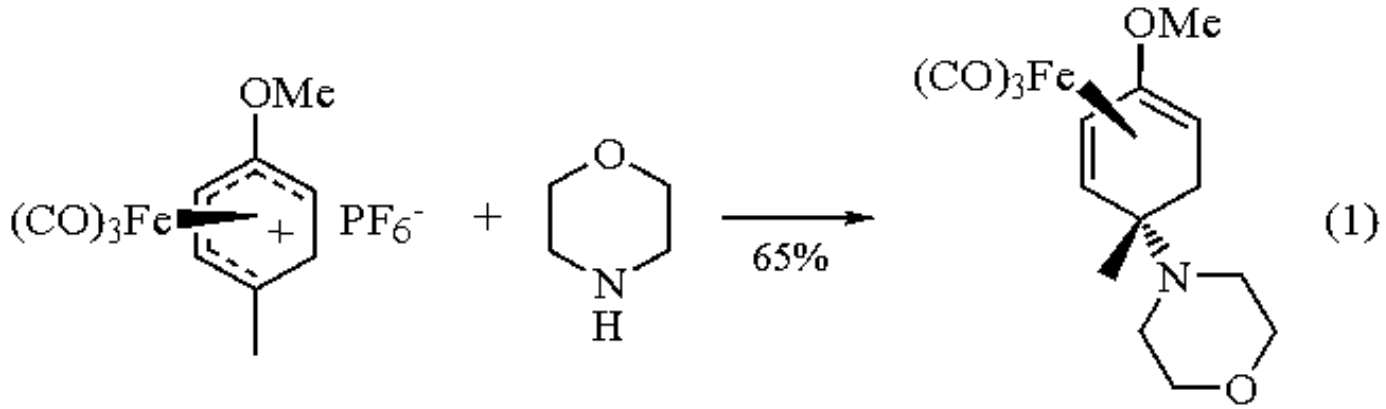

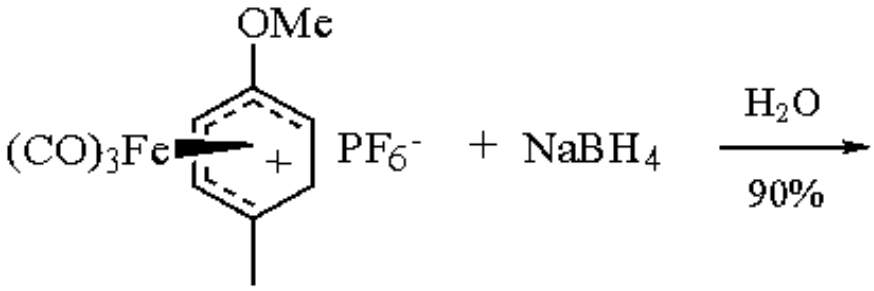

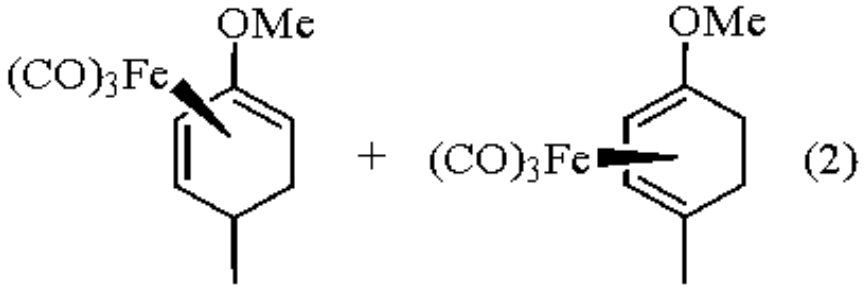

2:3

C-C Bond Formation.

A wide range of carbon nucleophiles react with the cation under mild conditions to give the corresponding C-C bonded product. Nitrile adducts can be obtained with ***Sodium Cyanide***[6] or with ***Cyanotrimethylsilane*** (eq 3).[7,8] The product obtained from reaction of analogs of the complex with sodium malonate can be used for the synthesis of spirocyclic compounds.[9a,10] Reaction of the Reformatsky reagent $BrZnCH_2CO_2Me$ leads to a mixture of alkylation products and triene.[2]

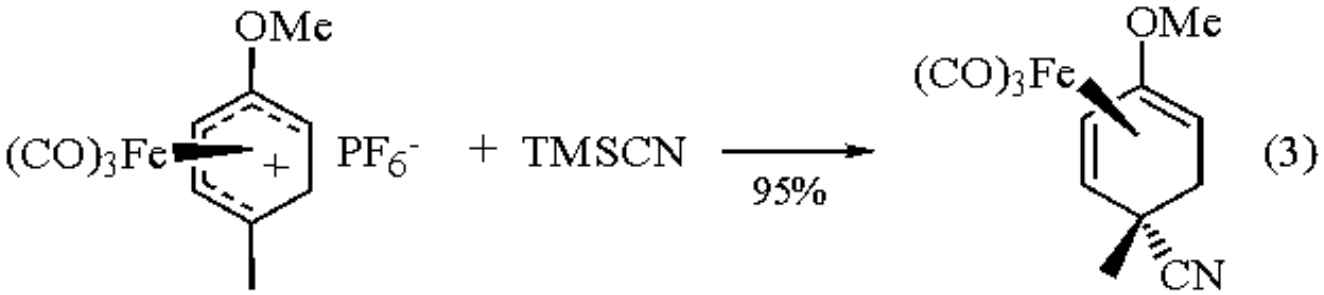

Alkylation with sodium or potassium enolates has potential in organic synthesis.[1,11,12] The reaction intermediates with enolates of keto esters derived from cyclopentanones, cyclohexanones,[13] and tetralones have been used for the synthesis of C-nor-D-homosteroids,[1b,12] D-homosteroids,[12] 12,13-epoxy-14-methoxytrichothecene,[11a] quassinoids,[14] and 6-keto steroids.[13,15] The cation reacts with the potassium enolate of methyl 2-oxocyclopentanecarboxylate to give a quantitative yield of the two diastereoisomers (eq 4) (one of these has been transformed to trichothecane), thus leading to the controlled formation of two contiguous quaternary centers.[11]

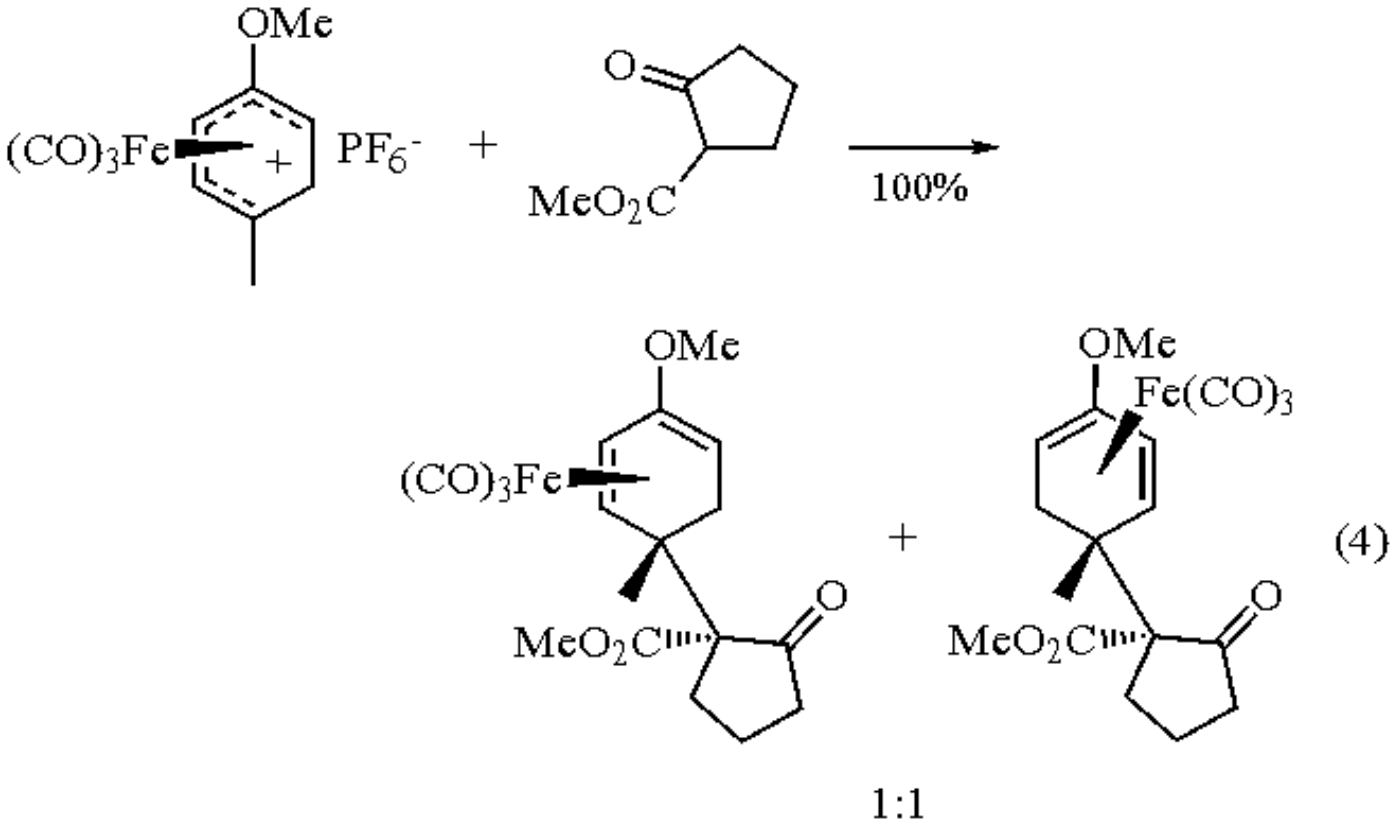

Simple lithium enolates of ketones and esters have proven too basic, causing deprotonation of the cation to give a triene complex instead of the desired addition products. Reaction of the cation with silylketene acetals gives high yields of the desired products (eq 5). Most of the reactions occurred with very high regioselectivity.[16]

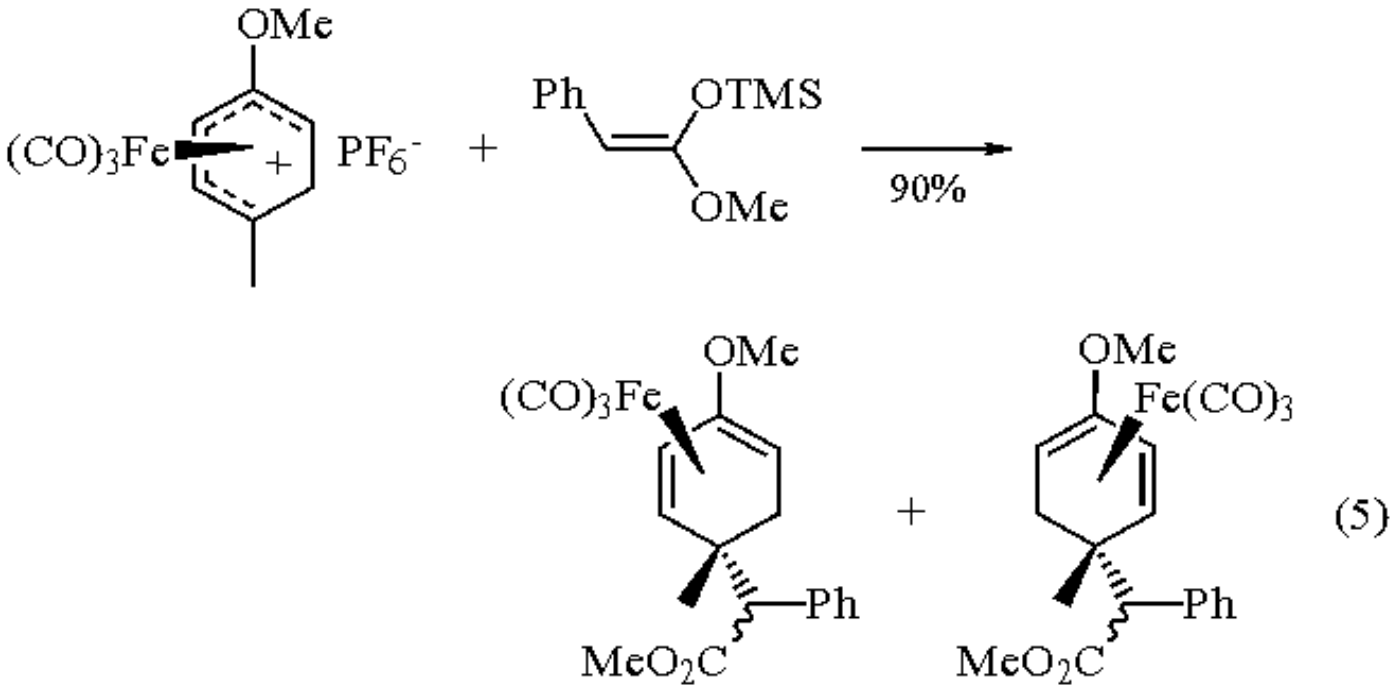

A number of tin enolates react cleanly with the cation in cases where the use of lithium enolate or silyl enol ethers is problematic. This new C-C bond forming reaction allows diastereoselective construction of proximate quaternary centers and provides a key step in a short synthesis of (±)-trichodiene (eq 6),[18] (±)-trichodermol,[19] 3,14-dihydroxytrichothecenes,[20] and (±)-12,13-epoxytrichothec-9-ene.[18]

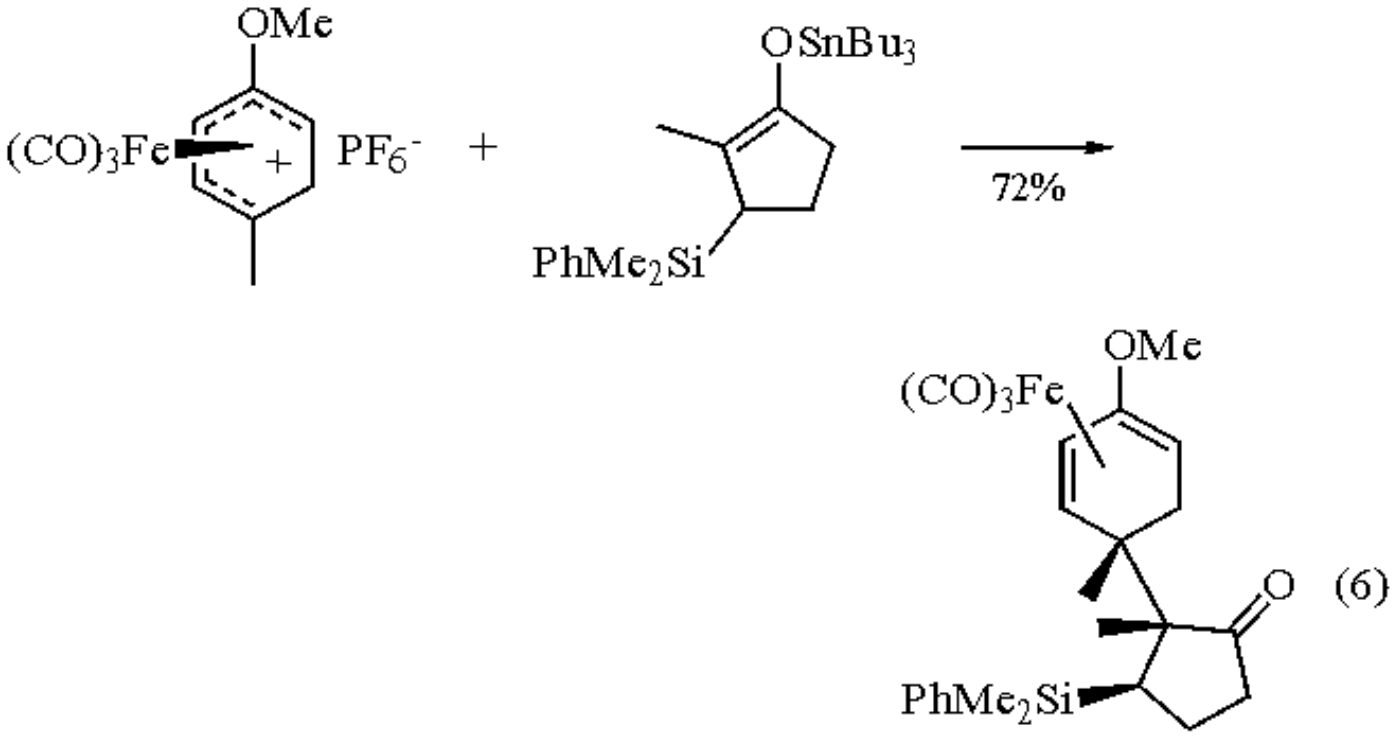

Cyclohexenone γ-Cation Equivalents.

Decomplexation and hydrolysis of the enol ether generates the 4-substituted cyclohexenone, making the starting complex the synthetic equivalent of a cyclohexenone γ-cation.[1] Illustrative of this are syntheses of polycyclic natural compounds, especially terpenes and steroids (eq 7).[1c,16,21,22]

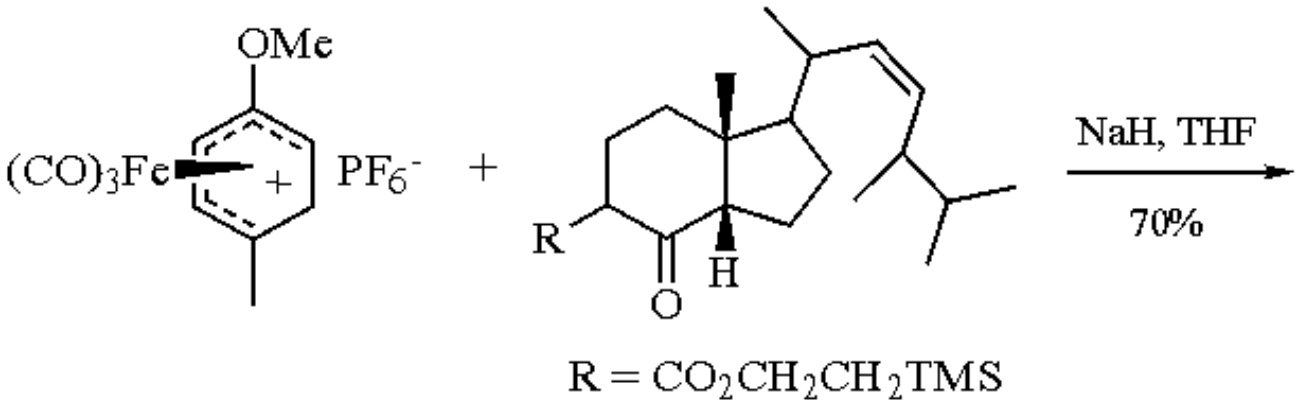

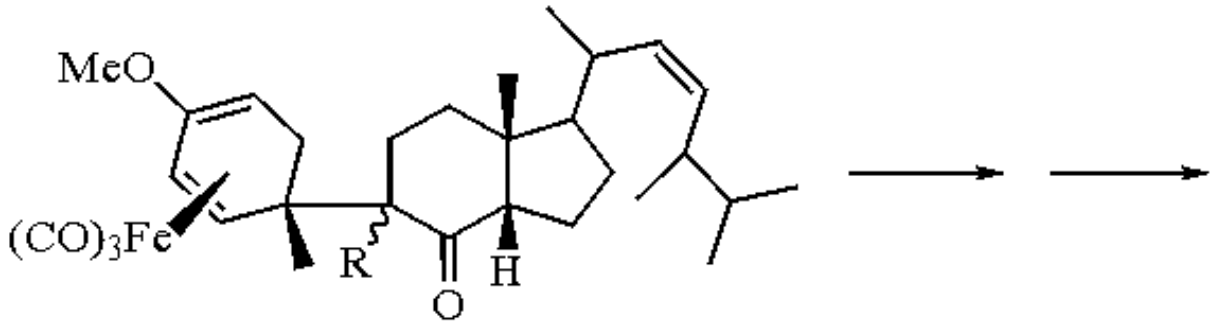

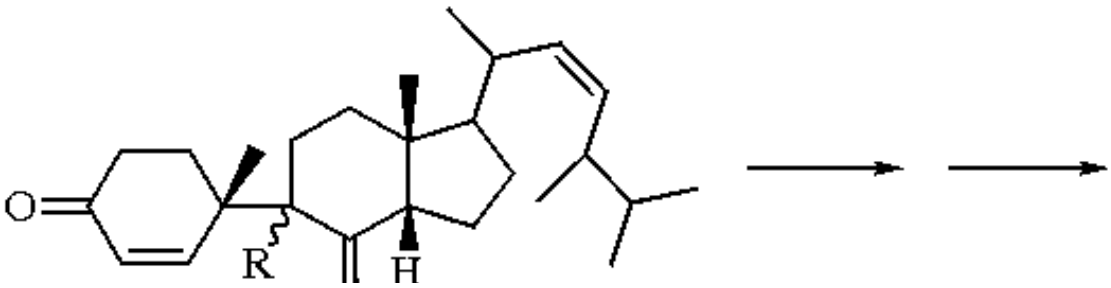

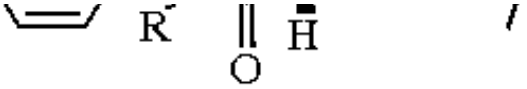

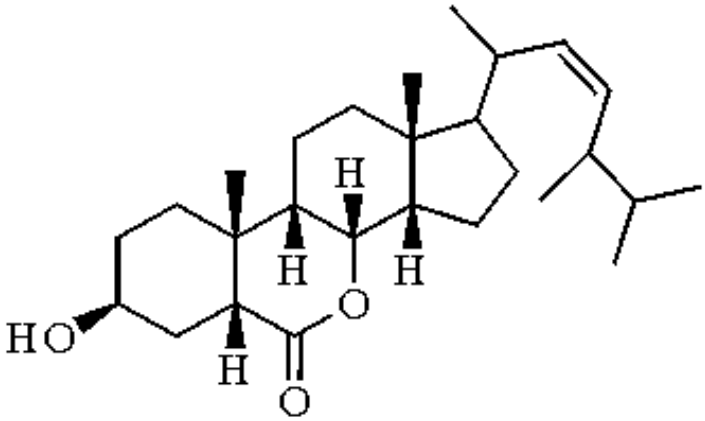

(7)

Chiral Form of the Cation.

Induction[23] of asymmetry during the complexation of 1-methoxy-4-methylcyclohexadiene and reaction[24] of the resulting complex with triphenylmethyl tetrafluoroborate provides a convenient route to partially resolved cation. The complete resolution of the cation by selective crystallization of enantiomers has been achieved.[25]

Reaction of racemic cation with a chiral carbanion occurs enantioselectively.[26,27] The chiral intermediates are converted into optically active natural steroids.[26a]

---

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Tricarbonyl(naphthalene)chromium

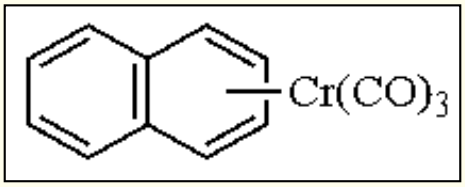

[12110-37-1] · $C_{13}H_8CrO_3$ · Tricarbonyl(naphthalene)chromium · (MW 264.21)

(catalyst for the hydrogenation of alkynes,[2] 1,3-dienes,[3] dienol acetates,[4] and for the isomerization of conjugated dienes,[5] silyloxymethyl-[6] and aminomethylbutadiene[7])

Physical Data: mp 150-160 °C.

Solubility: sol THF, acetone.

Form Supplied in: a red moisture-sensitive crystalline solid.

Preparative Method: prepared in 75-83% yield by treating naphthalene with ***Hexacarbonylchromium*** in dry decalin.[1]

Purification: recrystallized under nitrogen from petroleum ether.

Handling, Storage, and Precautions: should be handled under a nitrogen or argon atmosphere, and a glove box would be ideal. The solid should be stored at low temperature, in the dark, under nitrogen.

Hydrogenation Catalyst.

The title reagent (**1**) is an arene chromium complex which catalyzes the stereoselective hydrogenation of alkynes to the (*Z*)-alkene (in degassed THF) (eq 1).[2]

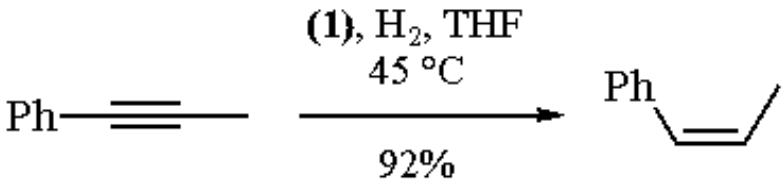

(1)

The title reagent has been reported to catalyze the 1,4-hydrogenation of a carbocyclic 1,3-diene, resulting in the stereospecific formation of an exocyclic (*Z*)-alkene in 95% yield (eq 2).[3]

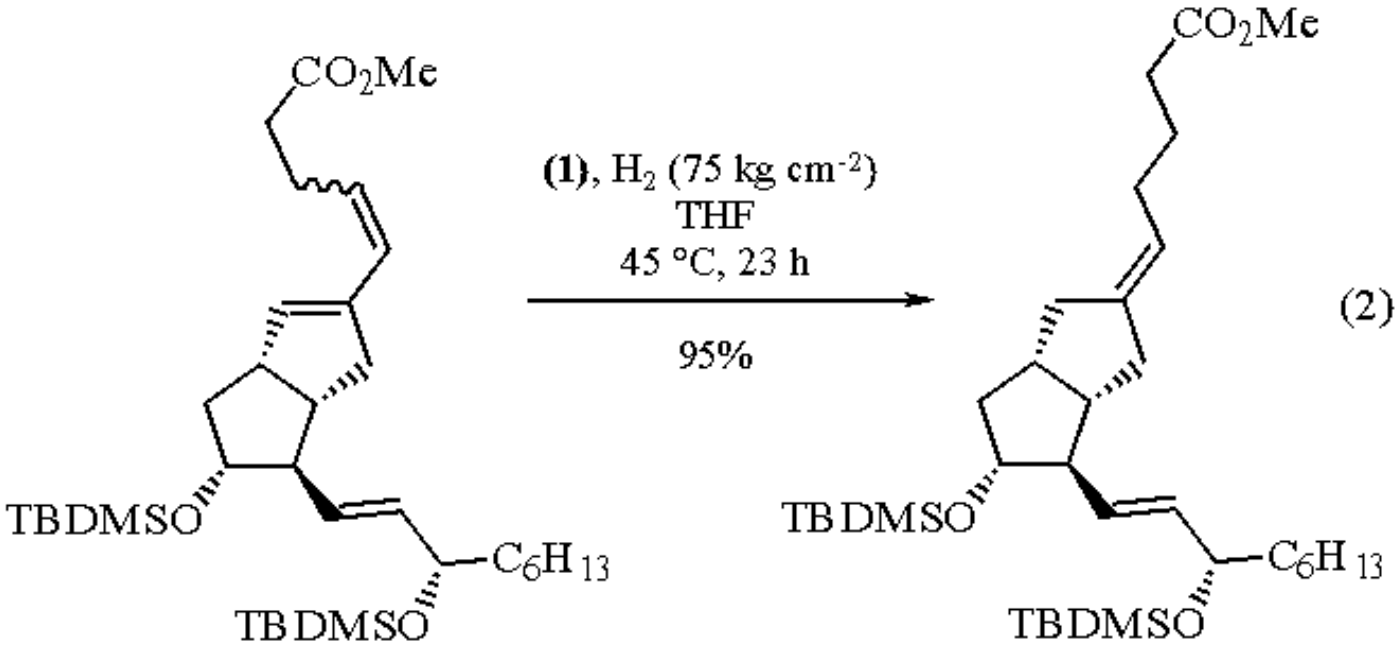

(2)

The resulting exocylic carbocyclic alkene was used in the synthesis of carbacyclin. Use of (**1**) (20 mol %) in the 1,4-hydrogenation of a dienol acetate in the presence of hydrogen (eq 3) resulted in the stereospecific synthesis of a trisubstituted exocyclic (*Z*)-allylic acetate (87% yield).[4] This intermediate was used in the synthesis of anthracycline analogs.

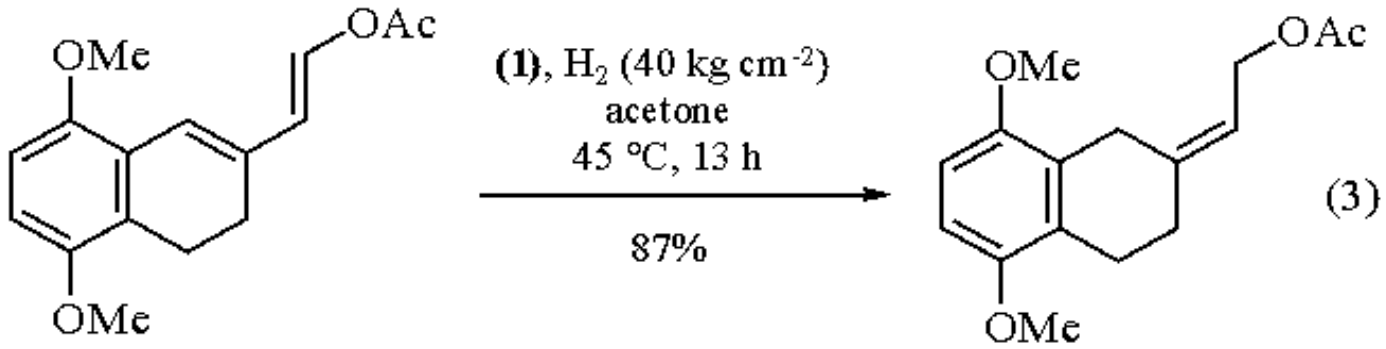

(3)

The use of (**1**) as a hydrogenation catalyst requires the use of polar coordinating solvents (THF or acetone) and degassing of the reaction mixture. Hydrogen or an inert gas is introduced into the reaction flask, depending on the substrate.

Isomerization of Conjugated Dienes.

The title reagent will catalyze the rt isomerization of conjugated dienes, with complete control of the stereochemistry of the resulting alkene in the absence of any molecular hydrogen.[4] The mechanism involves a stereo- and regiocontrolled 1,5-hydrogen shift of the (*Z*)-conjugated diene. Under very mild conditions the stereospecific isomerization of the diene occurs to give an exocylic (*Z*)-diene. Aromatization by means of mild oxidation results in the formation an aryl excocyclic (*Z*)-alkene (eq 4).[5]

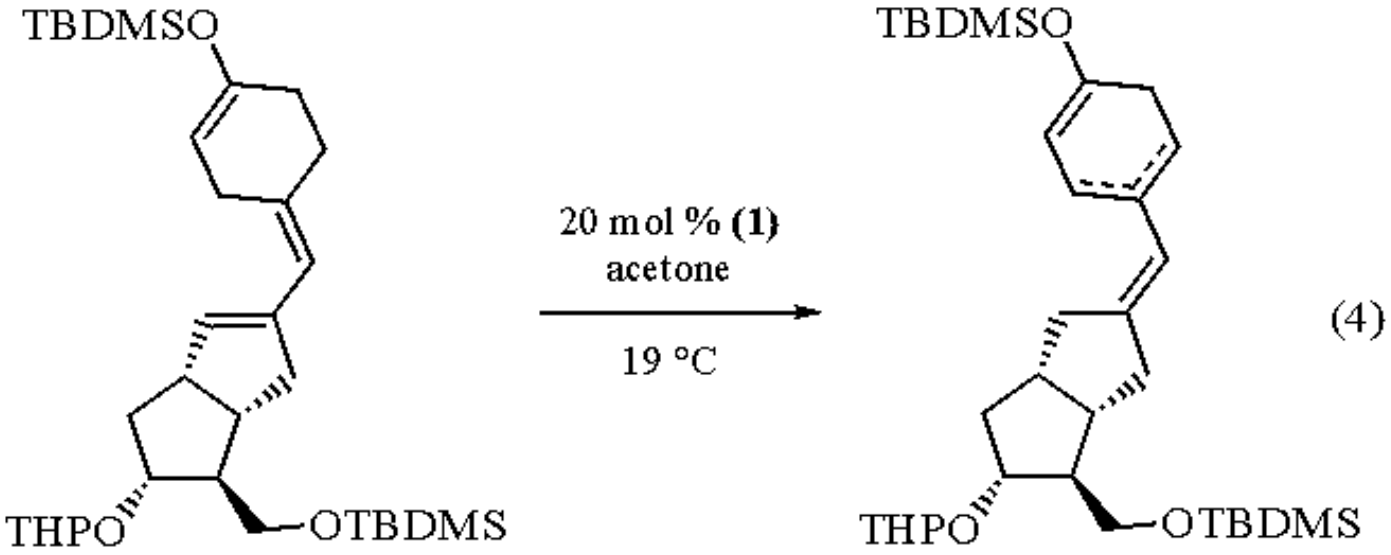

Extension of this methodology to silyloxymethyl- (eq 5)[6] and aminomethylbutadiene derivatives (eq 6)[7] resulted in the stereocontrolled synthesis of (*Z*)-silyl dienol ethers and (*Z*)-dienamines. Yields are good to excellent (57-97%) and the resulting heteroatom-substituted butadienes have been successfully shown to undergo inter- and intramolecular Diels-Alder reactions.[6,7]

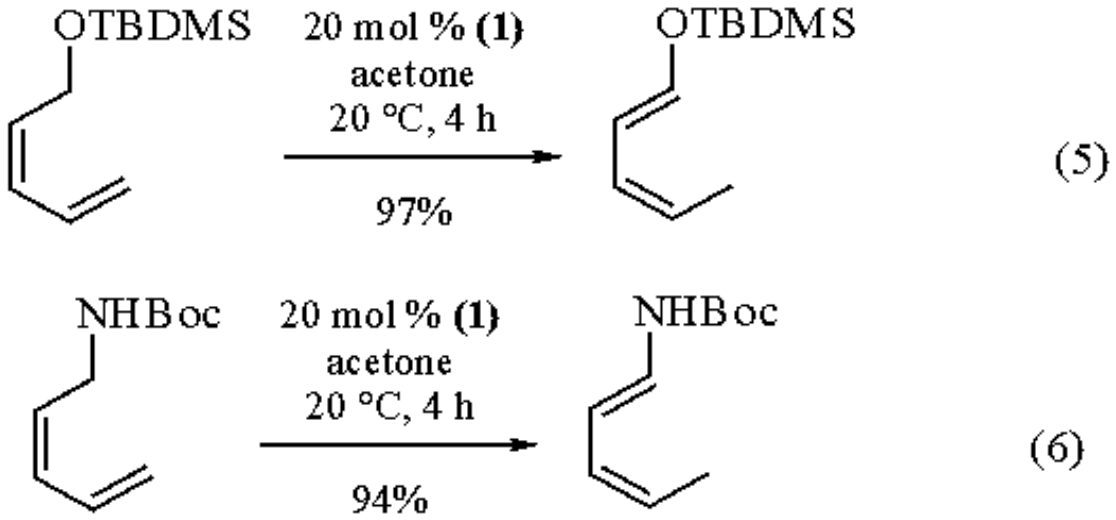

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Tricarbonyl(pentadienyl)iron Tetrafluoroborate

$(C_5H_7)Fe(CO)_3^+BF_4^-$

[12079-72-0] · $C_8H_7BF_4FeO_3$ · Tricarbonyl(pentadienyl)iron Tetrafluoroborate · (MW 293.81)

(organometallic electrophile towards a variety of carbon and heteroatom nucleophiles)

Physical Data: yellow solid, mp 163-165 °C (dec) (PF_6^- salt).

Solubility: sol polar solvents (e.g. $MeNO_2$, Me_2CO); slightly sol $CHCl_3$, CH_2Cl_2; reacts with water, alcohols.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: NMR, elemental analysis.

Preparative Methods: was first prepared by the protonation of tricarbonyl(η^4-pentadienol)iron with ***Tetrafluoroboric Acid*** in the presence of ***Acetic Anhydride*** (eq 1).[1]

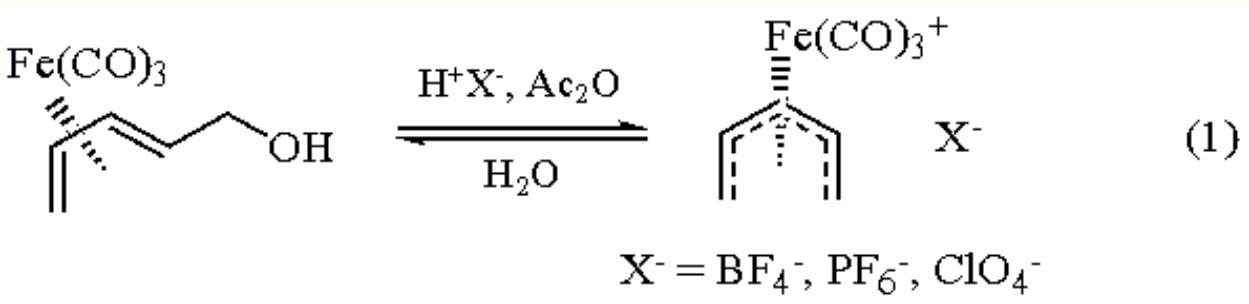

Hexafluorophosphoric acid or perchloric acid may also be used to generate the corresponding PF_6^- and ClO_4^- salts. A wide variety of substituted pentadienyl cations, which may be of greater synthetic interest, have been prepared by protonation of substituted dienol and dienyl ether complexes.[2-17] Bis[(dienyl)$Fe(CO)_3$] dications have been prepared by protonation of bis-dienol complexes.[18] Protonation of tricarbonyl(1,3,5-hexatriene)iron generates the tricarbonyl(1-methylpentadienyl)iron cation.[19] Hydride abstraction from (*cis*-pentadiene)$Fe(CO)_3$ (but not the *trans* isomer) with ***Triphenylcarbenium Tetrafluoroborate*** gives the title cation (eq 2).[1] This methodology has been used to prepare a few substituted cations.[20-22]

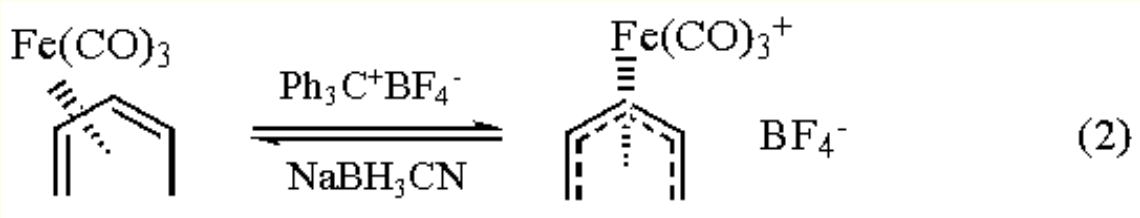

Purification: by reprecipitation from $MeNO_2$/ether.

Handling, Storage, and Precautions: the solid may be stored under inert atmosphere for extended periods. Perchlorate salts of the cation are explosive.

Reaction with Metal Hydrides.

Reaction of the (pentadienyl)$Fe(CO)_3^+$ cation with ***Sodium Cyanoborohydride*** gives (*cis*-pentadiene)$Fe(CO)_3$ (eq 2),[8] while reduction of

the cation with ***Sodium Borohydride*** or ***Lithium Triethylborohydride*** gives mixtures of (*cis*- and (*trans*-pentadiene)$Fe(CO)_3$.[1,8] In general, reaction of substituted (pentadienyl)$Fe(CO)_3^+$ cations with metal hydrides gives mixtures of 1,3-diene complexes, resulting from nucleophilic addition at either the C-1 or C-5 terminus (eq 3);[2,8,13,15,16,22] however, reaction of (1,5-diphenylpentadienyl)$Fe(CO)_3^+$ with $NaBH_3CN$ gives nearly equal proportions of products resulting from attack at the terminal (C-1) and internal (C-2) positions (eq 4).[5]

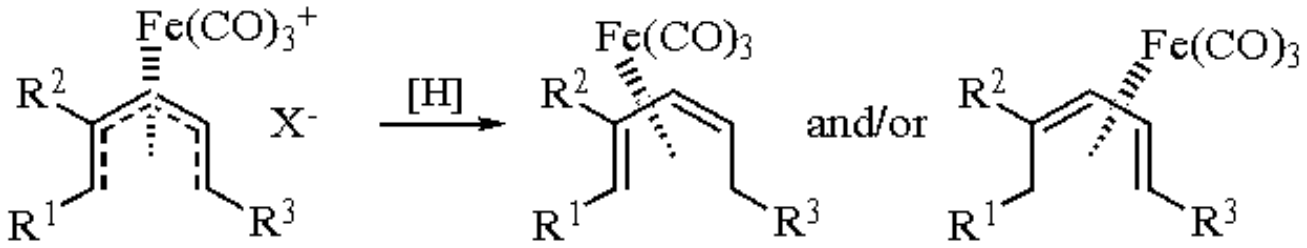

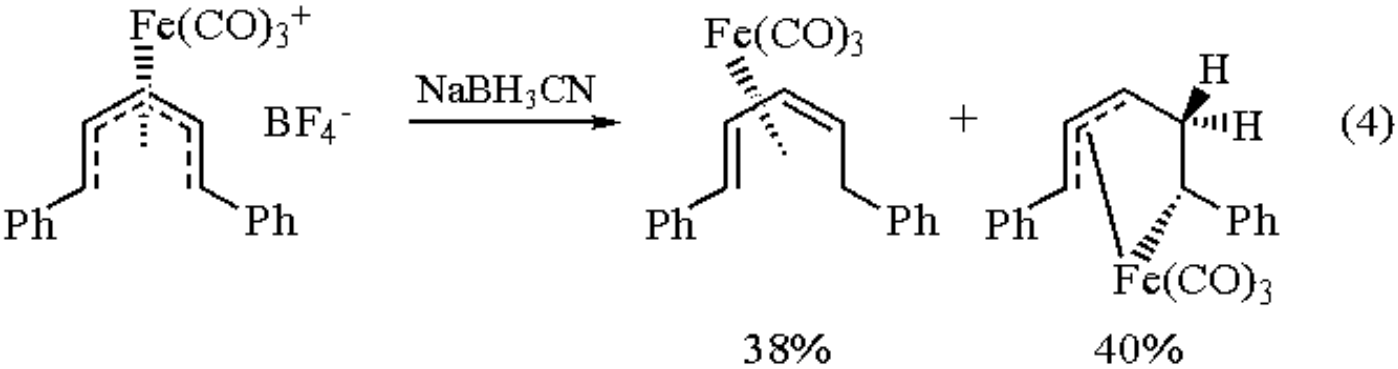

Reaction with Heteroatom Nucleophiles.

Reaction of (pentadienyl)$Fe(CO)_3^+$ cation with water results in formation of (*trans*-pentadienol)$Fe(CO)_3$ (eq 1).[1] In general, reaction of substituted (pentadienyl)$Fe(CO)_3^+$ cations with water or alcohols results in the formation of *trans*-dienol or *trans*-dienyl ether complexes, presumably via nucleophilic attack on the transoid form of the pentadienyl ligand (eq 5).[2,4,7,10,13-17] An exception is the (1-methoxycarbonylpentadienyl)$Fe(CO)_3^+$ cation, which reacts with water to give (5-methoxycarbonyl-(2*Z*,4*E*)-pentadien-1-ol)$Fe(CO)_3$ (eq 6).[11]

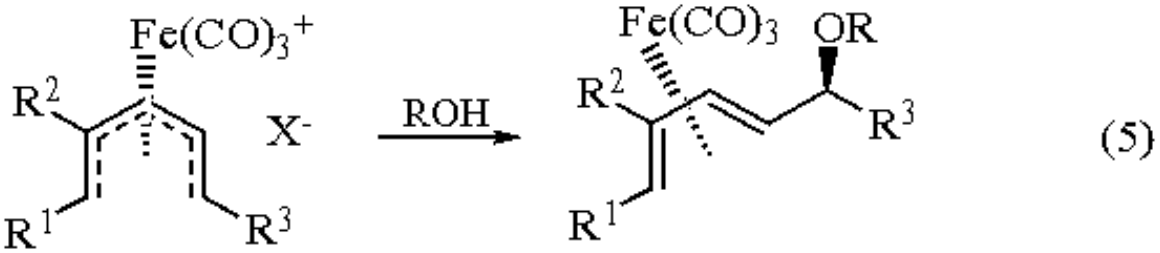

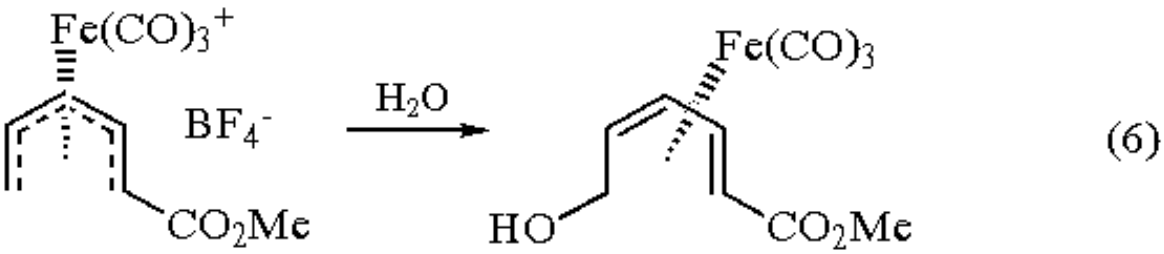

The reaction of (pentadienyl)$Fe(CO)_3^+$ cations with substituted anilines and with benzylamines gives the corresponding dienylamine and bis(dienyl)amine complexes. More basic amine nucleophiles give (*Z*)-dienylamine complexes, while less basic amines give (*E*)-dienyl complexes.[23,24] The reaction of (pentadienyl)$Fe(CO)_3^+$ cations with ***Triphenylphosphine*** gives (*Z*,*E*)-dienylphosphonium salts.[9,13,15-17,24] Upon deprotonation, the ylides isomerize to the corresponding (*E*,*E*)-dienylphosphorane complexes, which can be used in Wittig condensations with aldehydes.[25] Nucleophilic attack by halide ions occurs at iron.[26]

Reaction with Metals.

The reaction of (pentadienyl)$Fe(CO)_3^+$ cations with ***Zinc*** results in reductive dimerization of the ligand to afford a bis-complexed (η^8-1,3,7,9-decatetraene) (eq 7).[2,18,21] The reaction of (pentadienyl)$Fe(CO)_3^+$ with $CpMo(CO)_3^-$ is believed to proceed via rapid, reversible formation of a (*Z*)-diene bimetallic complex at low temperature (-78 °C). Upon warming to rt, only an (*E*)-diene complex is isolated (eq 8).[27] This bimetallic complex eventually decomposes on standing to give the bis-complexed (η^8-1,3,7,9-decatetraene).

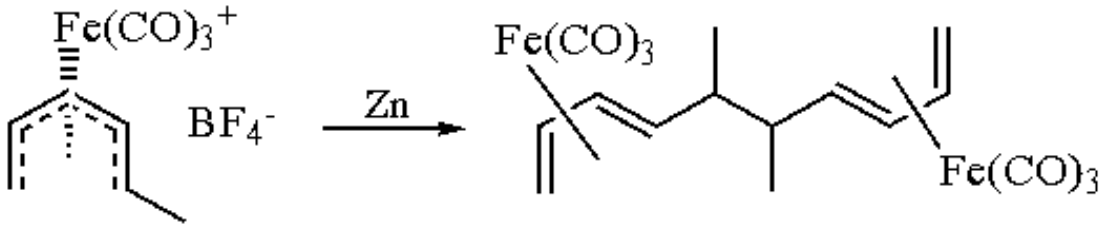

(7)

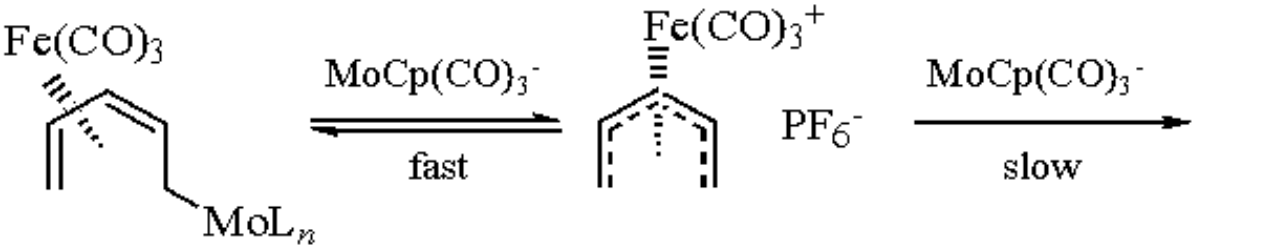

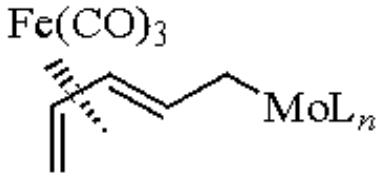

(8)

$MoL_n = MoCp(CO)_3$

Reaction with Carbon Nucleophiles.

The parent (pentadienyl)$Fe(CO)_3^+$ cation reacts with organocadmium reagents[28] and with functionalized organocuprates[29] to afford the corresponding substituted (*Z*)-diene complex (eq 9). Likewise, substituted (pentadienyl)$Fe(CO)_3^+$ cations react with organocuprates by attack at the less hindered terminus.[13,15,30,31] In contrast, reaction of (pentadienyl)$Fe(CO)_3^+$ cations with organolithium reagents or alkynylcerates results in attack at both C-1 and at C-2.[32] In general, attack by malonate anion on (pentadienyl)$Fe(CO)_3^+$ cations gives (*Z*)-diene complexes (eq 10).[10,13-15,20,31,33] For substituted pentadienyl cations the regioselectivity is variable and depends on the substituents present on the pentadienyl ligand. Attack at a substituted pentadienyl terminus occurs in a stereospecific fashion, presumably by approach of the nucleophile on the face of the ligand opposite to iron. A few examples of pentenediyl complexes, formed by nucleophilic attack of malonate at C-2, have been reported.[14,31,33] With weak carbon nucleophiles, such as electron-rich aromatics,[6] and ***Allyltrimethylsilane***,[13,17,34] the acyclic (pentadienyl)$Fe(CO)_3^+$ cation reacts via its less stable transoid isomer (eq 11).

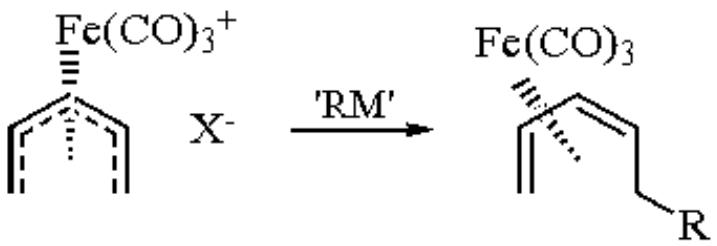

(9)

R = Ph, Bn, allyl, $(CH_2)_nFG$
M = Cd, Cu(CN)ZnI

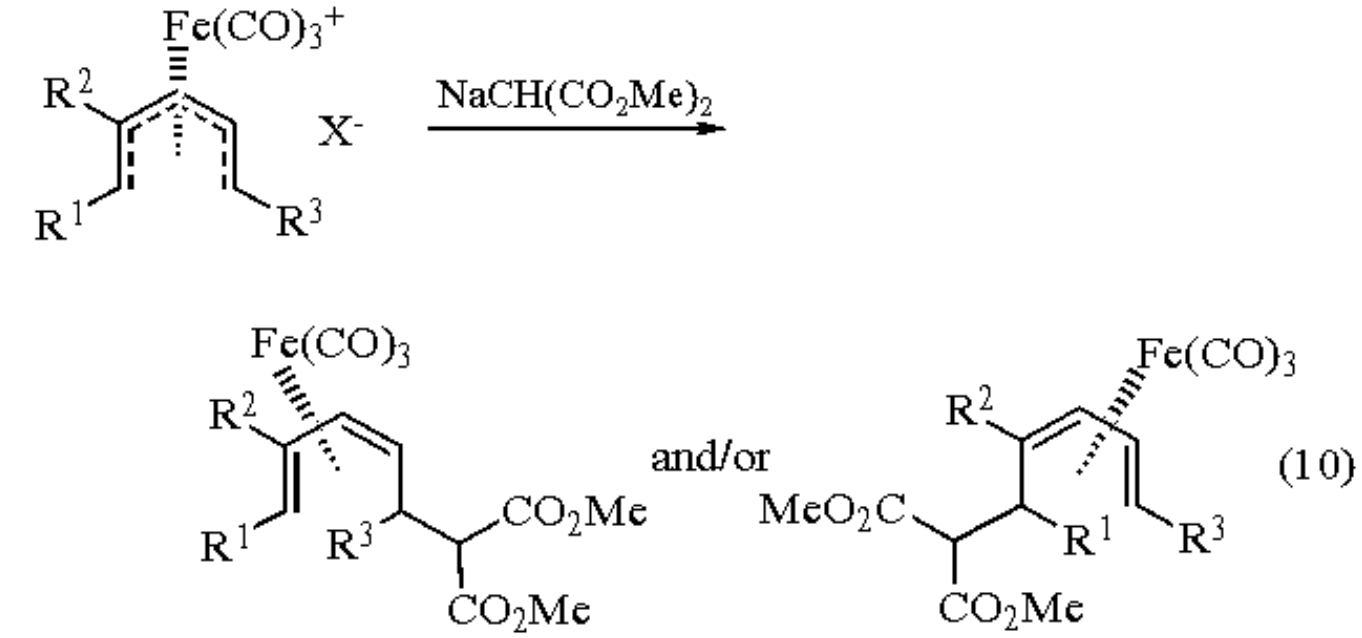

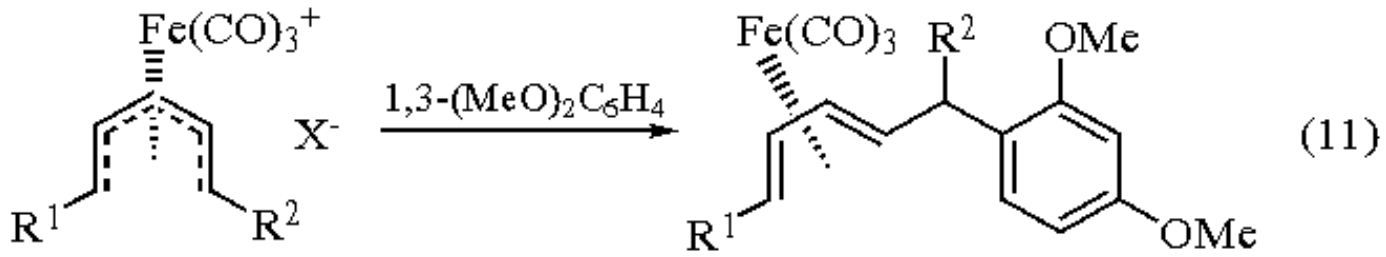

Applications to Natural Product Synthesis.

(Pentadienyl)Fe$(CO)_3^+$ cations react as organometallic electrophiles in the the formation of (diene)iron complexes. In order for these cations to be useful in organic synthesis there must exist methods for excising the metal. The diene ligand may be liberated by oxidation of iron.[1] Photochemical reduction of (diene)Fe$(CO)_3$ complexes in AcOH leads to the corresponding alkene,[35] and nucleophilic attack on neutral (diene)Fe$(CO)_3$ complexes has been reported.[36] Substituted (pentadienyl)Fe$(CO)_3^+$ cations have been used in the synthesis of Δ^3-lepelin,[13] AF toxin IIa,[37] 5-HETE methyl ester,[30c] and lasiol.[31]

---

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Trichloramine

NCl_3

[10025-85-1] · Cl_3N · Trichloramine · (MW 120.36)

(reactive *N*-haloamine for the amination of aromatics,[1] tertiary chlorides,[2] and tertiary hydrocarbons;[3] also for chlorination of alkenes[4] and organoboranes[5])

Alternate Name: nitrogen trichloride.

Physical Data: mp <-40 °C; bp <71 °C; explodes at ca. 95 °C; *d* 1.653 g cm^{-3}.

Solubility: insol cold H_2O; sol toluene, methylene chloride, *o*-dichlorobenzene; decomposes in hot H_2O.

Preparative Methods: not commercially available; prepared from calcium hypochlorite, ammonium chloride, and hydrochloric acid in methylene chloride-water, followed by separation of the organic phase, drying, and storage in solution at 0-5 °C or below.[6,7]

Analysis of Reagent Purity: determination of positive chlorine can be carried out iodometrically.[6,7]

Handling, Storage, and Precautions: toxic and may explode, especially on heating or when concentrated. Dilute, cold solutions of NCl_3 in various organic solvents are stable for several days.[6] Store under inert atmosphere. Use only behind a safety shield in an efficient fume hood.

Amination of Aromatics.

The reaction of benzene and derivatives with NCl_3 and ***Aluminum Chloride*** in organic solvents can be a useful preparation for *meta*-substituted amines. However, yields are only moderate, and mixtures of isomers are often obtained. Arenes include mono-[7-9] and dialkylbenzenes,[9,10] halobenzenes,[11] biphenyl, and naphthalene.[1] With trichloroamine/$AlCl_3$, the conversions of toluene to *m*-toluidine (eq 1) and of 1,3-dimethylbenzene to 3,5-dimethylaniline (eq 2) in moderate yields have been observed.

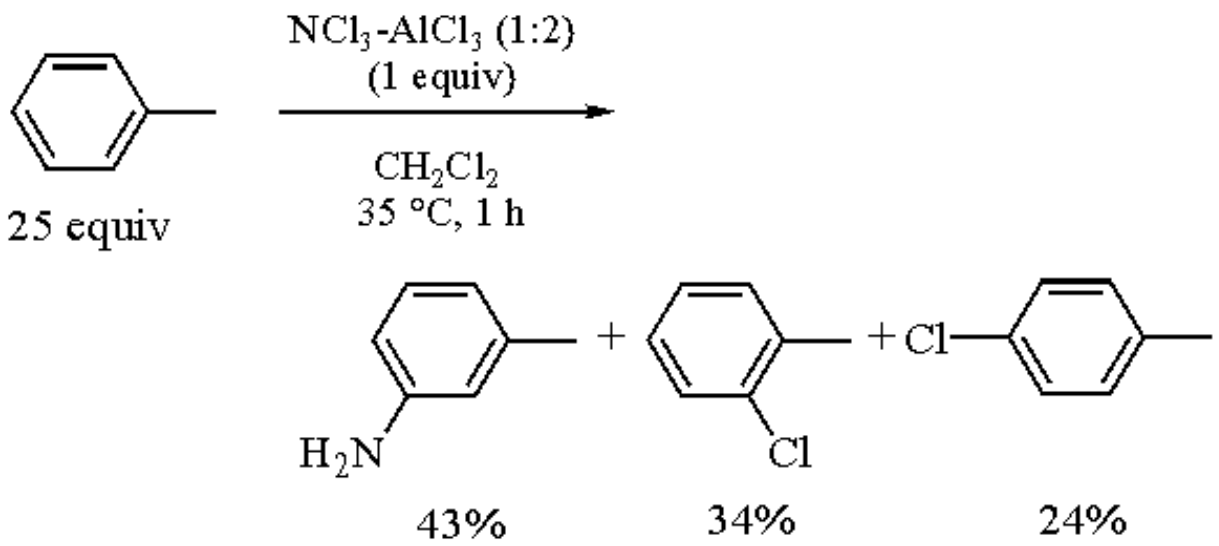

(1)

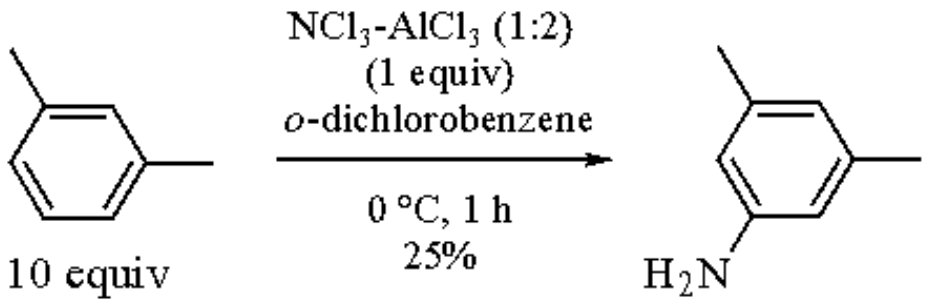

(2)

An addition-elimination mechanism involving a chloroarenium intermediate has been proposed for the amination reactions (eq 3).[10]

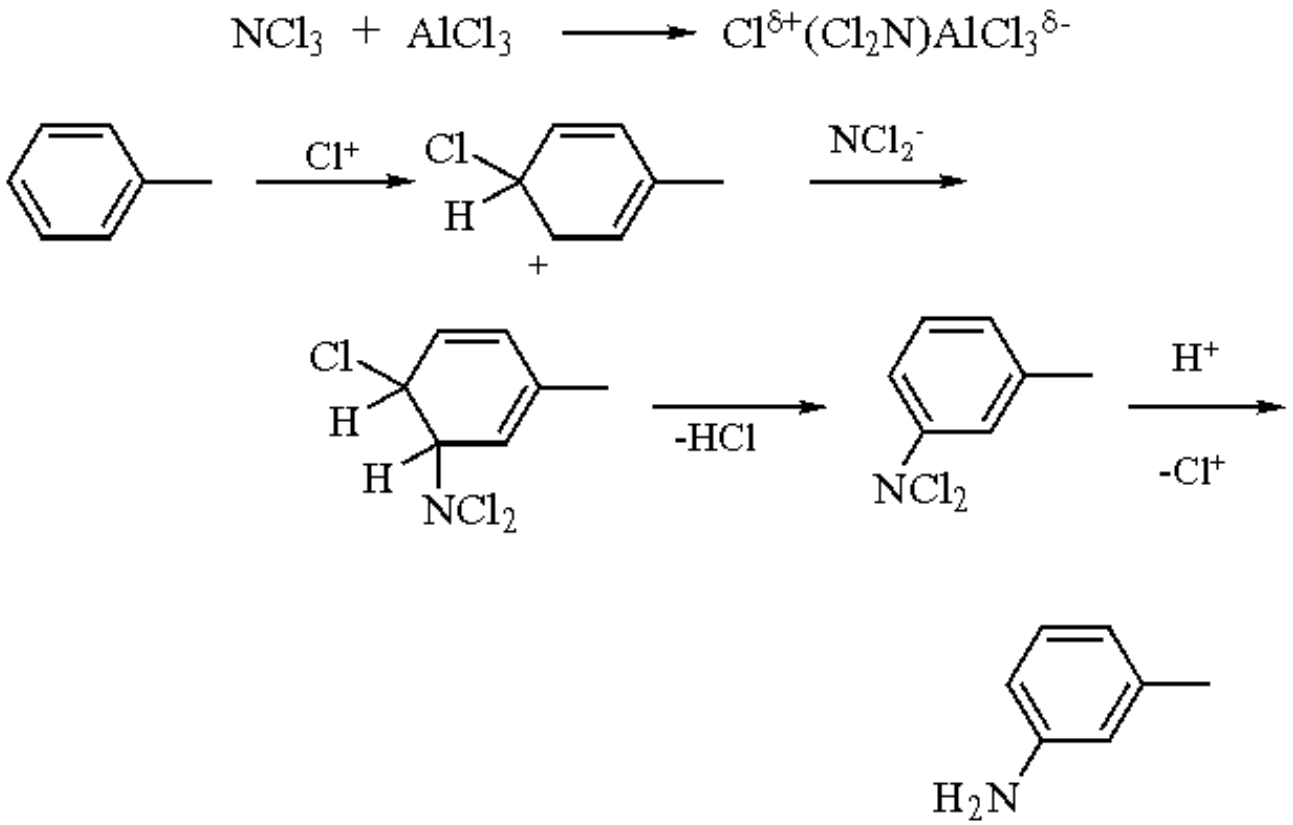

(3)

Amination of halobenzenes and halotoluenes with trichloramine/$AlCl_3$ proceeds by two competing processes in moderate yields.[11] For example, fluorobenzene gives predominantly *m*-fluoroaniline and *p*-chloroaniline (eq 4). It has been proposed that the former is produced by a substitution (addition-elimination) mechanism, while the latter is formed by a pathway involving nucleophilic displacement of halide in a chloroarenium cation by a nitrogen containing nucleophile (eq 5).

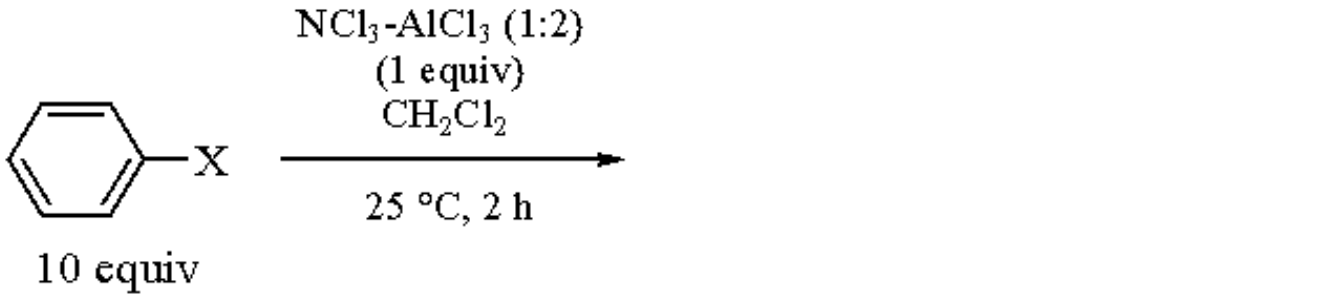

X = F	19%	1%	13%
X = Cl	33%	1%	-

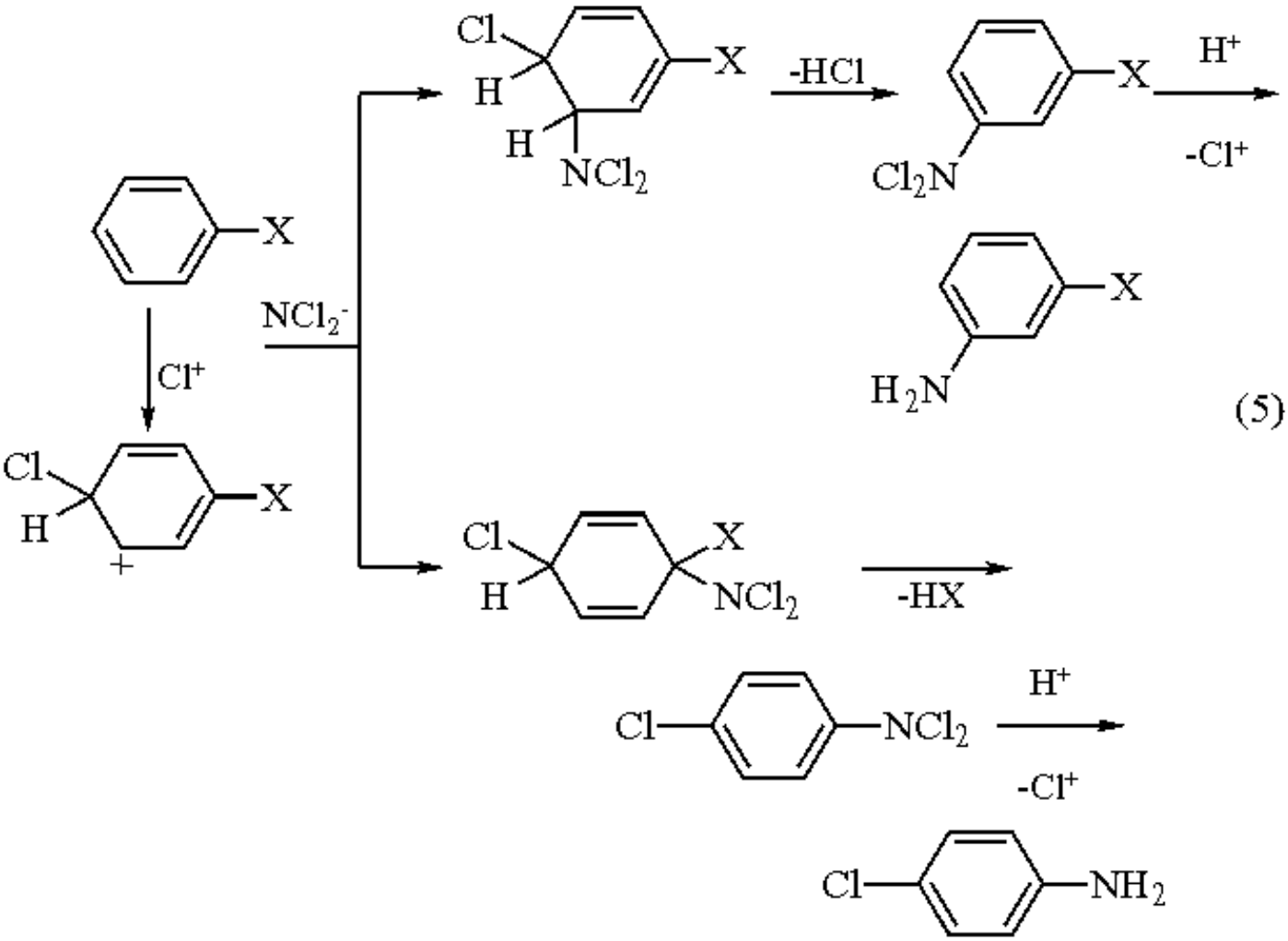

Amination of biphenyl gives 3-aminobiphenyl (eq 6) and amination of naphthalene gives a mixture of 1- and 2-amino derivatives in low yields.[1]

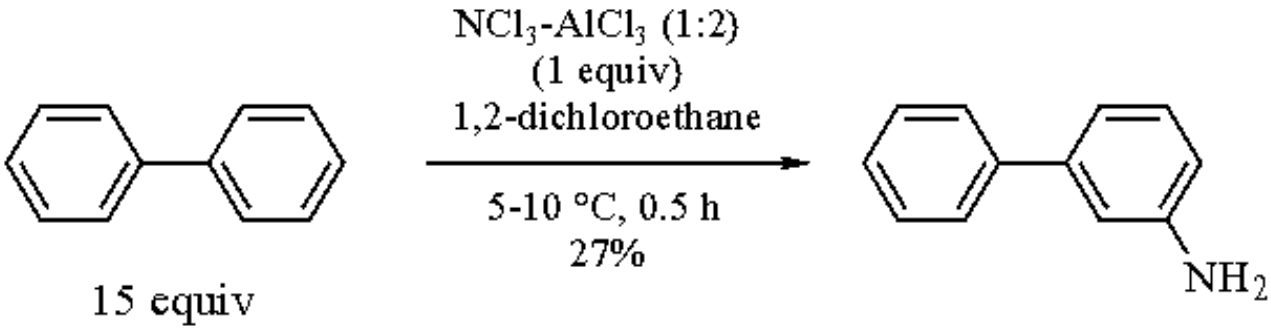

(6)

Amination of Alkanes.

The trichloramine/$AlCl_3$ system has also been used for the amination of monocyclic[12,13] bicyclic,[13,14] and tricyclic[3,15] alkanes. C_5-C_8 cycloalkanes and their mono- and dimethyl derivatives are aminated in good yields.[13] Methylcyclohexane[12,16] and methylcyclopentane[13] are converted to 1-amino-1-methylcycloalkanes on treatment with trichloramine/$AlCl_3$ (eq 7). Treatment of decalin and hydrindane with the trichloroamine/$AlCl_3$ system affords *cis*-9-aminodecalin (eq 8) and *cis*-8-aminohydrindane, respectively, in good yields.[13]

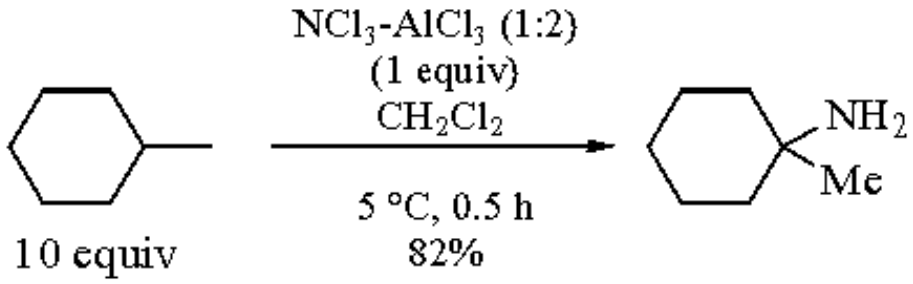

(7)

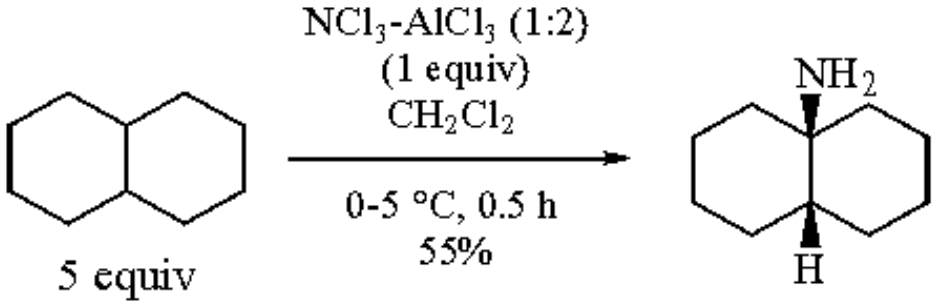

(8)

The trichloroamine/$AlCl_3$ amination route provides a simple one-step method of obtaining aminoadamantanes in high yield (eq 9).[3,15] Diamantane[17] can also be efficiently aminated in this fashion. When hydrocarbons which do not contain a tertiary hydrogen are subjected to reaction with NCl_3/$AlCl_3$, cationic rearrangements and fragmentations are observed.[18]

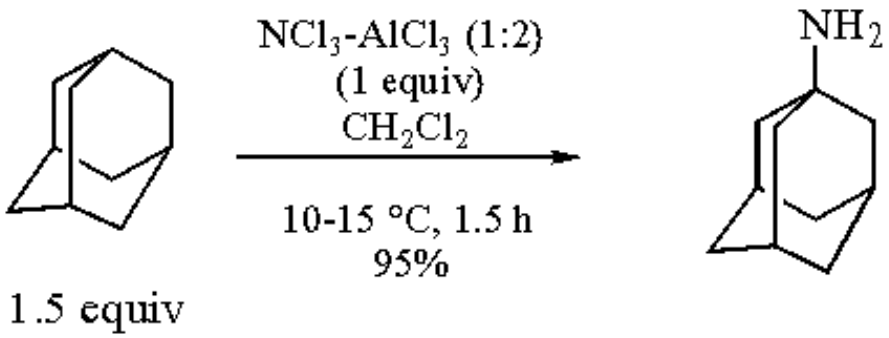

(9)

Amination of Alkyl-Substituted Aromatics.

Various monoalkyl substituted arenes have been aminated on the alkyl side chain to form *t*-benzylamines in the system trichloroamine/$AlCl_3$/*t*-butyl bromide (an efficient additive).[19-21] *p*-Alkyl and *p*-haloisopropylbenzenes give the corresponding aminated products in high yields (eq 10).

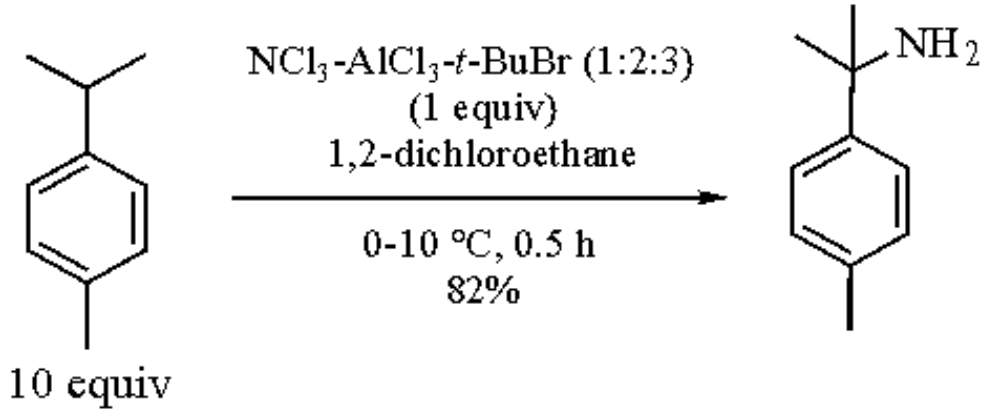

(10)

Tertiary Amines from Chlorides.

When simple tertiary alkyl chlorides are exposed to NCl_3 and $AlCl_3$ in methylene chloride at -10 °C, varying yields of the corresponding amines can be obtained. *t*-Pentyl chloride under these conditions provides *t*-pentylamine in 82% yield (eq 11), while *t*-octylamine is obtained in 35% yield from the corresponding chloride.[2]

$$MeCH_2CMe_2Cl \xrightarrow[\substack{CH_2Cl_2,\ -10\ °C \\ 82\%}]{NCl_3,\ AlCl_3} MeCH_2CMe_2NH_2 \qquad (11)$$

Primary and secondary halides give isomeric amines resulting from skeletal rearrangement, as well as aziridines (eqs 12-14). Mechanistic details of this reaction have been reported.[22]

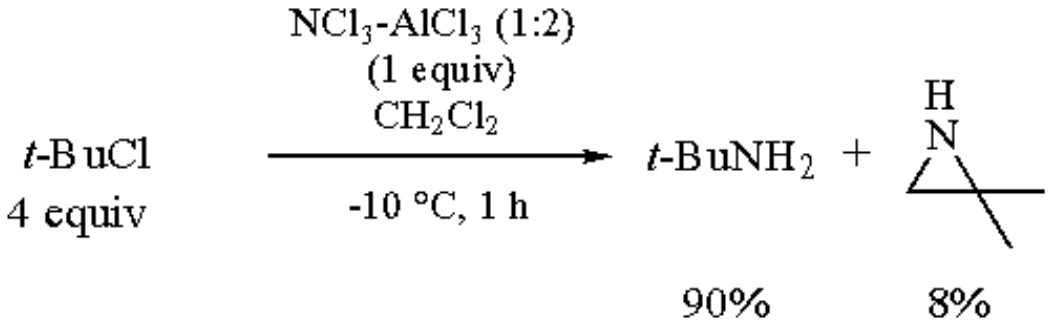

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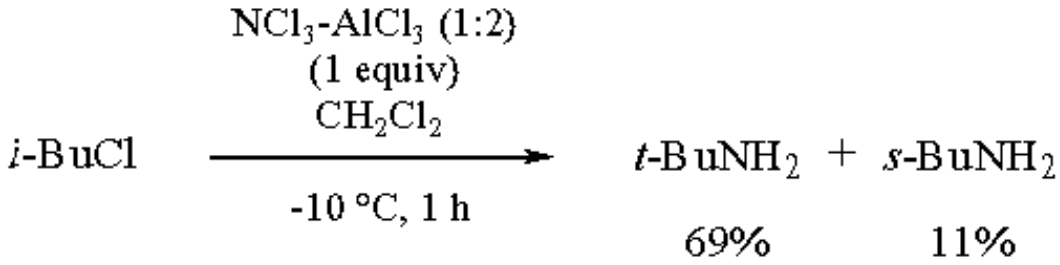

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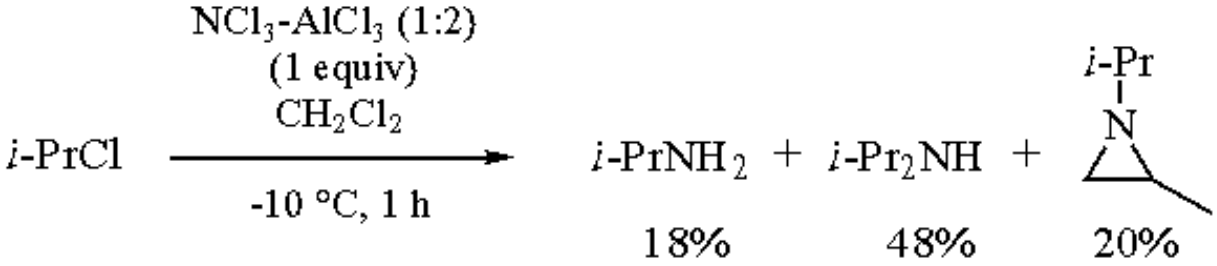

(14)

Vicinal Dichlorides from Alkenes.

The reaction of NCl_3 with a variety of mono- and disubstituted alkenes, both cyclic and acyclic, affords the corresponding 1,2-dichlorides in high yield. For example, cyclopentene with NCl_3 at 0 °C gives *trans*-1,2-dichlorocyclopentane in 89% yield (eq 15).[4]

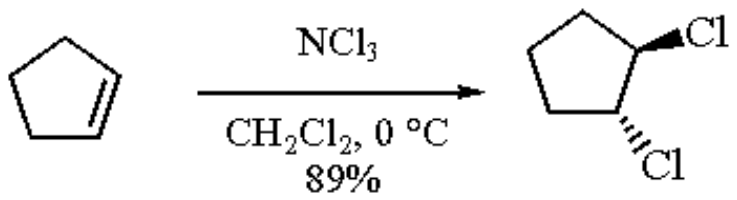

(15)

These transformations tend to be high yielding and the products formed are generally simple to purify. In comparison with other reagents commonly used for chlorination of alkenes (***Sulfuryl Chloride***, ***Chlorine***, ***Phosphorus(V) Chloride***),[4,23] NCl_3 usually gives fewer byproducts such as allylic chlorides. However, this method fails in the case of trisubstituted alkenes, as well as for styrene.

Conversion of Organoboranes to Alkyl Chlorides.

Trialkylboranes can be oxidized to the corresponding alkyl chlorides with NCl_3 in methylene chloride at 0 °C.[5,24] Yields range from 66-94% overall from the alkene (eq 16).

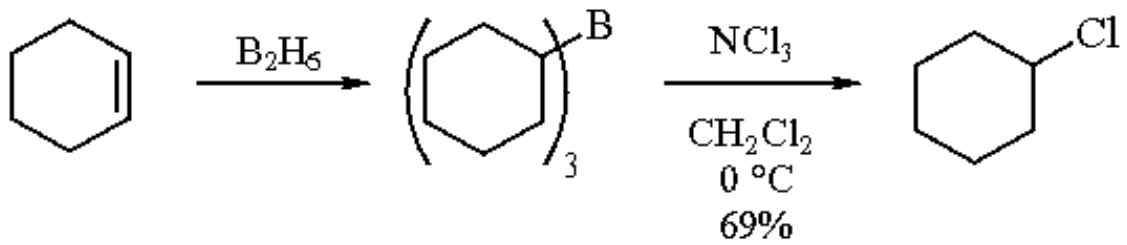

(16)

Other reagents (PCl_5, SO_2Cl_2, ***N,N-Dichlorourethane***) known to chlorinate organoboranes are usually considerably less efficient.

Other Reactions.

Fluorocyclohexane is obtained in 45% yield from cyclohexene in the presence of NCl_3 and ***Boron Trifluoride***.[25]

---

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19. Kovacic, P.; Hopper, R. J. *T* **1967**, *23*, 3965.
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23. (a) Field, K. W.; Kovacic, P. *S* **1969**, 135. (b) Strand, J. W.; Kovacic, P. *SC* **1972**, 129.
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Trichloroacetic Acid

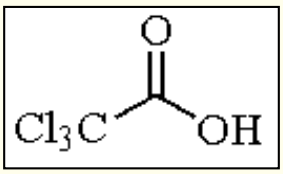

[76-03-9] · $C_2HCl_3O_2$ · Trichloroacetic Acid · (MW 163.38)

(strong acid catalyst used in diazotization reactions and porphyrin syntheses; dichlorocarbene precursor)

Alternate Name: TCA.

Physical Data: mp 57-58 °C; bp 196-197 °C; *d* 1.629 g cm^{-3}.

Solubility: sol alcohol, ether, water.

Form Supplied in: white crystals, widely available.

Handling, Storage, and Precautions: very caustic; should only be handled in a fume hood. Rubber gloves should be worn when handling this reagent. Extremely destructive to mucous membranes and tissues of upper respiratory tract, eyes, skin. Keep away from strong bases.

Diazotization of Amines.[1]

Trichloroacetic acid is used as a catalyst in the diazotization of amines by nitrites (eq 1). In this reaction, strong mineral acids (***Hydrochloric Acid***, ***Sulfuric Acid***) give unsatisfactory results, as does ***Acetic Acid***. Other catalysts used for this reaction are perfluorobutyric acid and ***Trifluoroacetic Acid***.

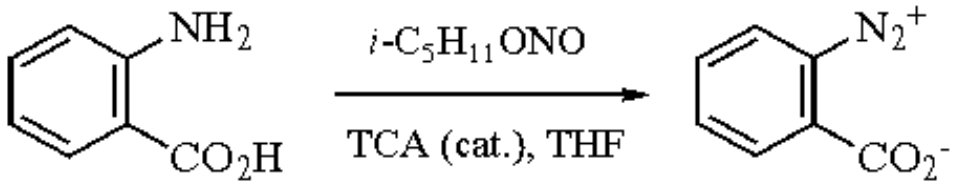

(1)

Synthesis of Porphyrins.[2]

The use of TCA as a catalyst allows the use of aldehydes with acid labile groups, such as acetals, in the synthesis of porphyrins (eq 2). This method is a convenient alternative to other methods available, which may not be as tolerant of other functionalities in the aldehydes.

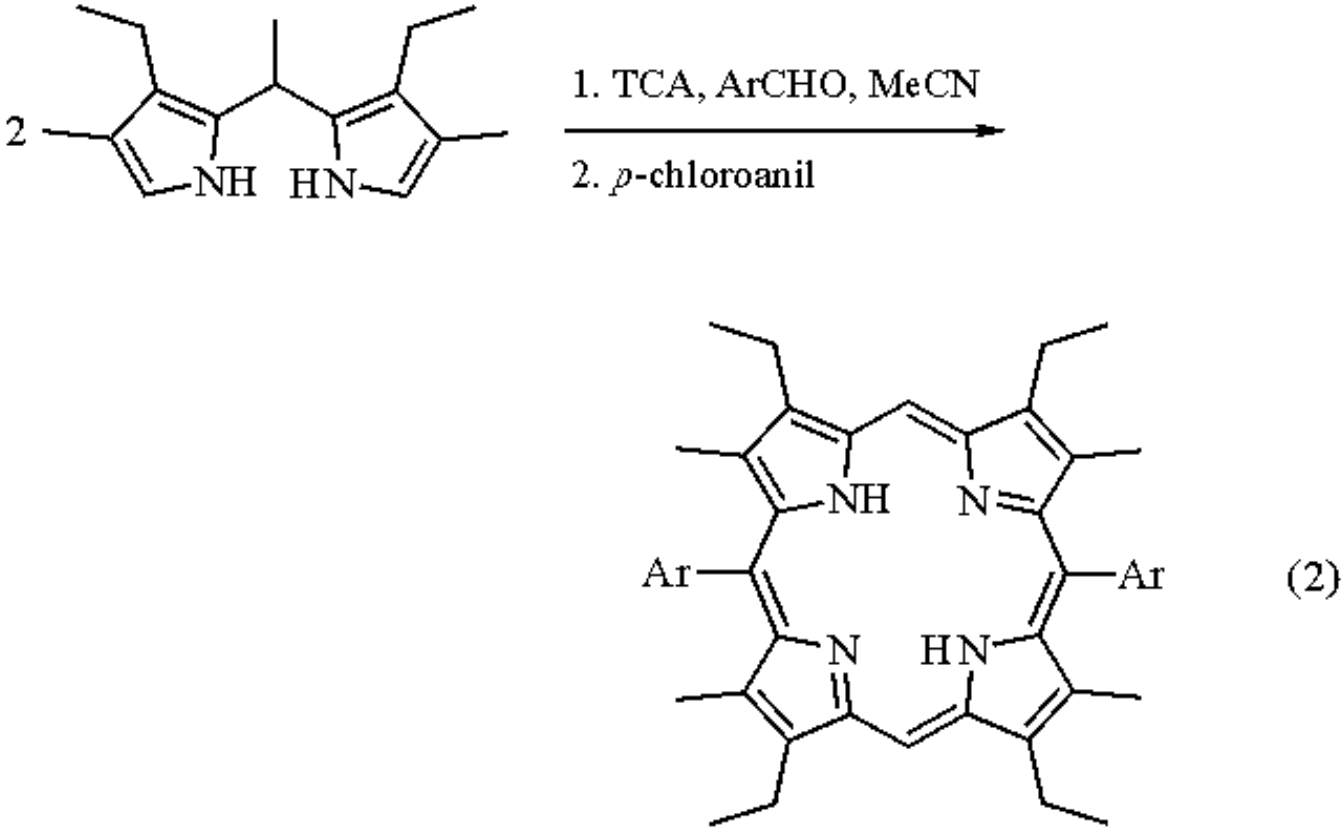

Condensation of Silanols and Alkoxysilanes.[3]

Along with various other acids and bases, TCA catalyzes the condensation of silanols with alkoxysilanes (eq 3). This catalysis is believed to be bifunctional, with the acidic proton of TCA coordinating to the oxygen of the alkoxy silane, while the carbonyl oxygen coordinates to the proton of the silanol.

$$Me(Me_2SiO)_3Me_2SiOH + MeSi(OMe)_3 \xrightarrow[45\%]{TCA,\ rt} Me(Me_2SiO)_3Me_2SiOSi(OMe)_2Me \quad (3)$$

Addition of Chloro-Substituted Carbons into Organic Molecules.

In the presence of strong base, TCA, as well as its esters and salts, reacts with alkenes to give 1,1-dichlorocyclopropanes (eq 4).[4] The reaction of base with TCA eliminates CO_2, leaving a trichloromethyl anion. This anion loses chloride ion to give dichlorocarbene, which subsequently reacts with the alkene to give the substituted cyclopropane. Dihalocarbenes from other sources undergo analogous reactions. The 1,1-dichlorocyclopropanes formed are subject to rearrangement, as shown by the reaction of norbornene with ***Ethyl Trichloroacetate*** (eq 5).[5]

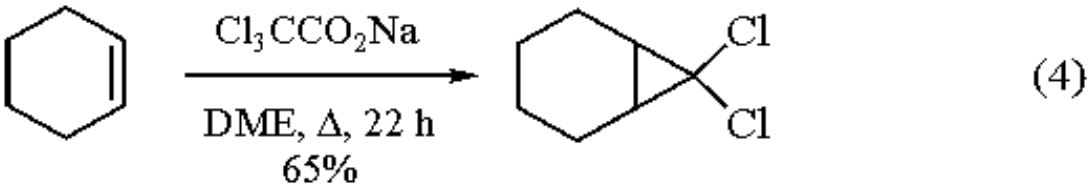

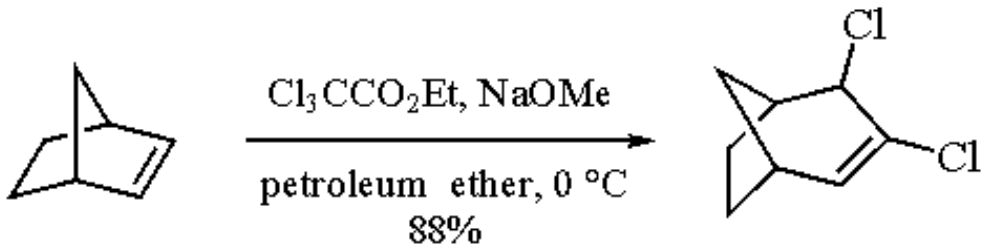

(5)

TCA can be used to effect the Michael addition of trichloromethyl anion into alkenes and aromatic systems with strong electron-withdrawing groups attached, rather than forming 1,1-dichlorocyclopropanes (eqs 6-8).[6] TCA can also react with carbonyls to give 1-(trichloromethyl)-substituted alcohols (eq 9).[7]

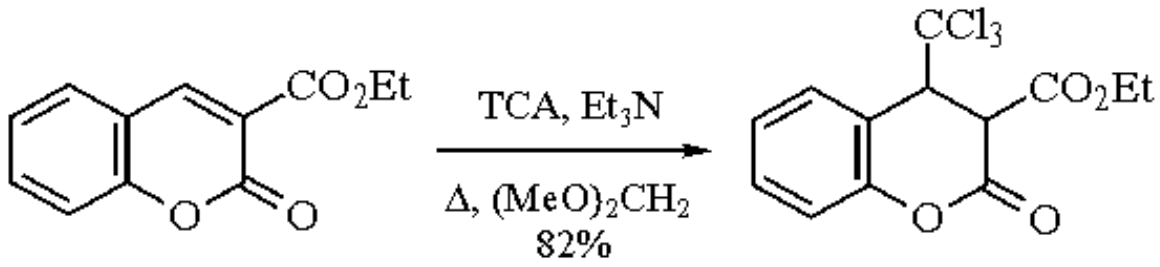

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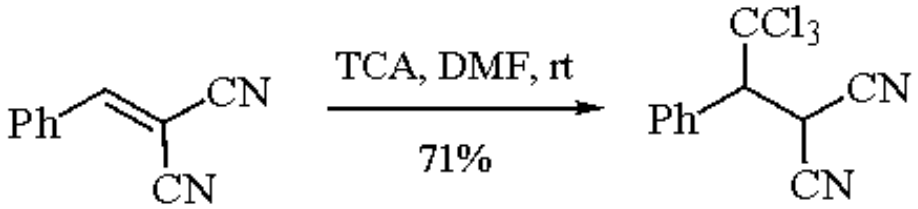

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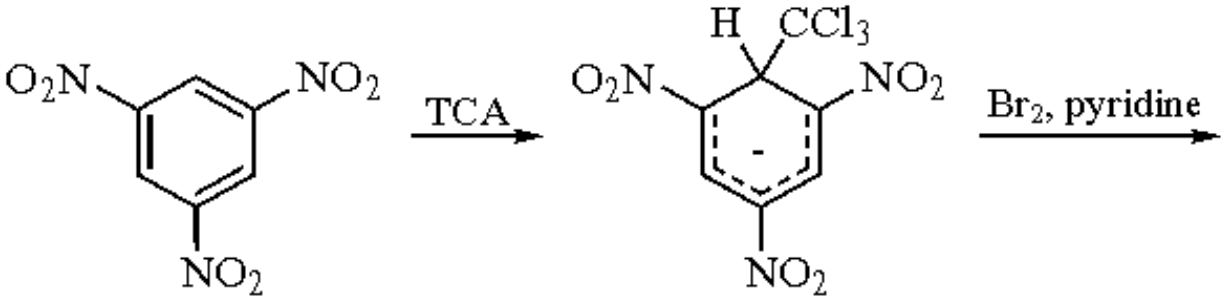

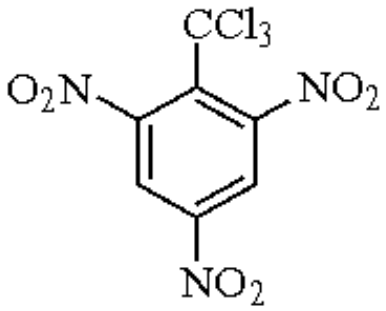

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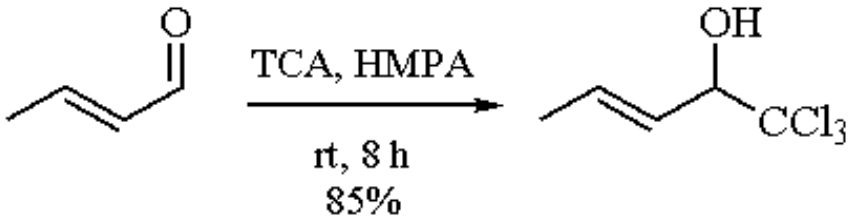

(9)

Enamines react with TCA to give trichloromethyl derivatives, which are somewhat unstable (eq 10).[8] These rearrange to give α-chloroamides, via aziridinium salts. The trichloromethyl derivatives are generated by addition of the trichloromethyl anion to a carbocation formed by protonation of the enamine. Imines undergo a similar reaction.[9]

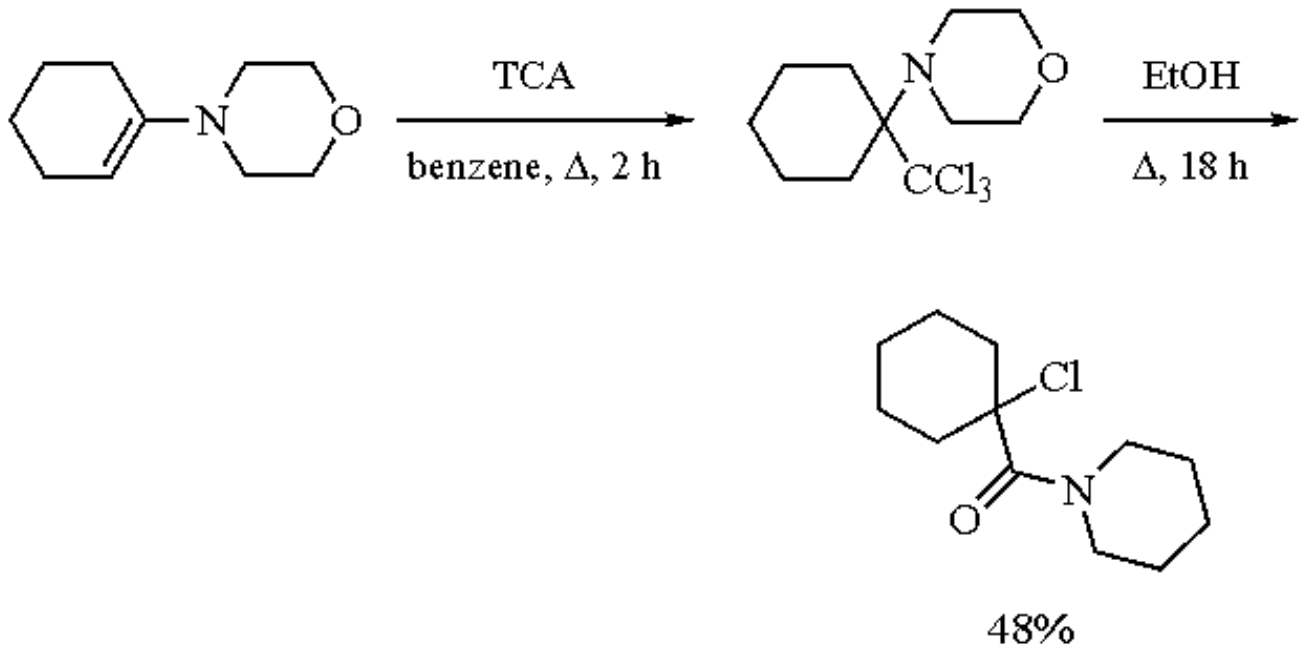

(10)

Primary aryl amines react via a dichlorocarbene formed from the decomposition of ***Sodium Trichloroacetate*** to yield isocyanates (eq 11).[10]

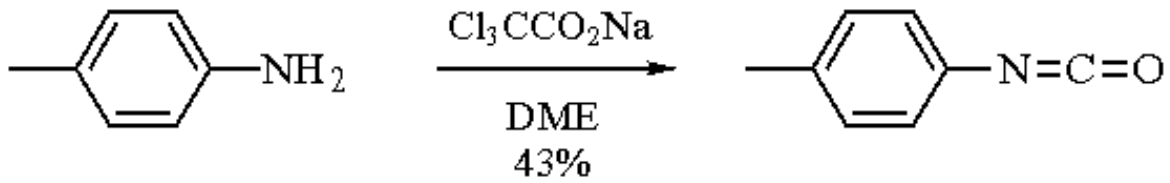

(11)

Interconversion of Optically Active Alcohols.

2-Alkoxybenzothiazolium salts of optically active alcohols, formed in situ by the reaction of 2-fluorobenzothiazolium with the appropriate alcohol, react with TCA to give the corresponding esters of trichloroacetate, which then undergo saponification to give back the optically active alcohols with inverted configuration (eq 12).[11]

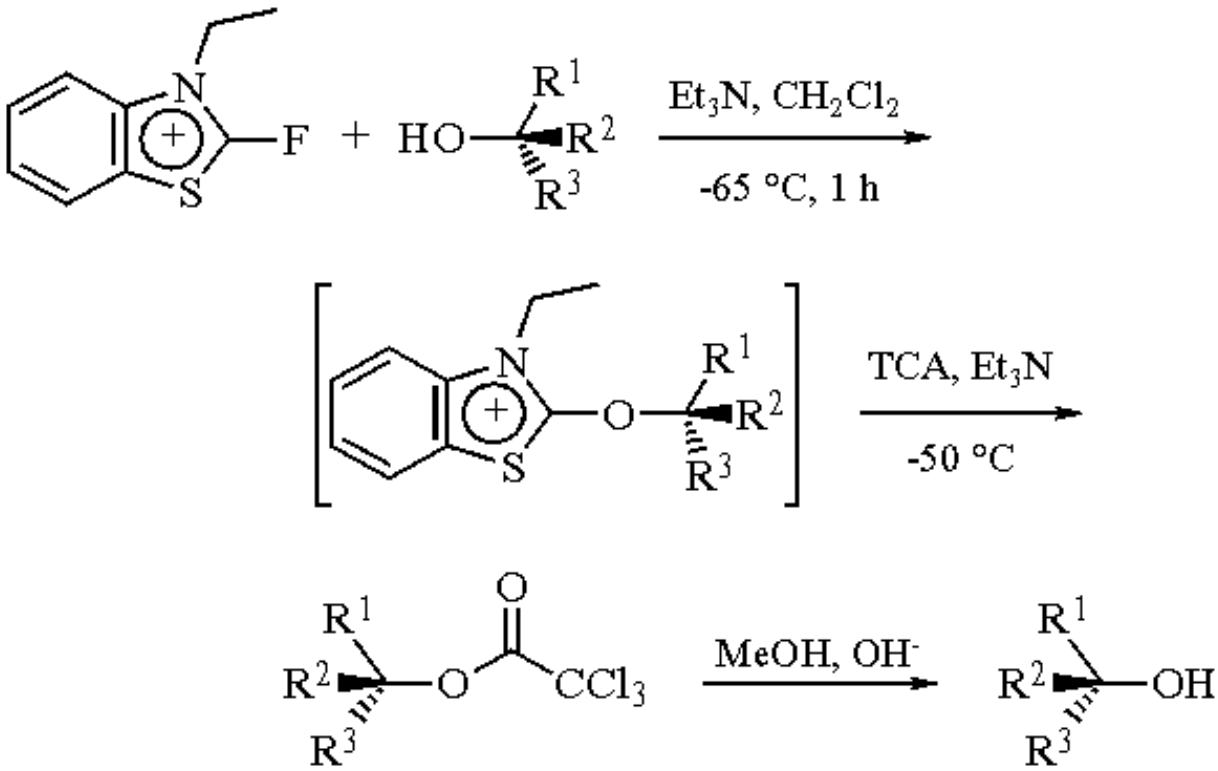

(12)

1. (a) Logullo, F. M.; Seitz, A. H.; Friedman, L. *OS* **1968**, *48*, 12. (b) Logullo, F. M.; Seitz, A. H.; Friedman, L. *OSC* **1973**, *5*, 54.
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Trichloroacetic Anhydride

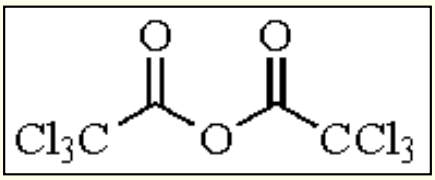

[4124-31-6] · $C_4Cl_6O_3$ · Trichloroacetic Anhydride · (MW 308.74)

(reagent for formation of trichloroacetic esters and amides; formation of trichloromethyl heterocycles;[3] acylation of electron-rich alkenes[5])

Alternate Name: TCAA.

Physical Data: mp -5 °C; bp 139-141 °C/60 mmHg; *d* 1.690 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: clear liquid, widely available.

Purification: distill in vacuo.

Handling, Storage, and Precautions: should be kept under inert gas; very reactive with water; corrosive.

General Reactivity.

The reactivity of trichloroacetic anhydride roughly parallels that of ***Trifluoroacetic Anhydride***. For the formation of trichloroacetic esters and amides, ***Trichloroacetyl Chloride***[1] and hexachloroacetone[2] are generally preferred to react with alcohol and amines, respectively.

Trichloromethyl Heterocycles.

A common use of TCAA has been its condensation with acylhydrazines, oximinoamides, or imidate esters to provide the corresponding five-membered trichloromethyl heterocycles (eq 1).[3] The trichloromethyl group can then be displaced; for example, a 1,2,4-oxadiazole can be reacted with an appropriate nucleophile to provide the 5-amino compound (eq 2). A unique cyclization is the formation of a tetracyclic trichloromethyl amide diacetal (eq 3).[4]

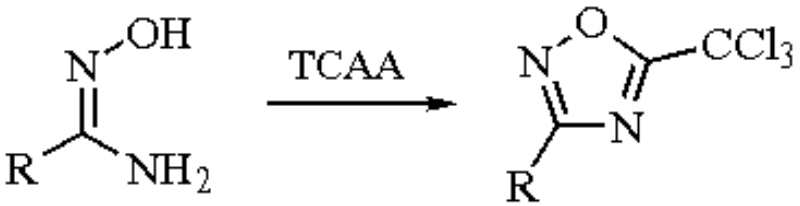

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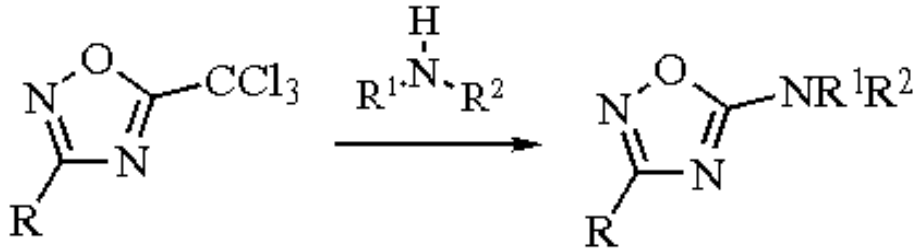

(2)

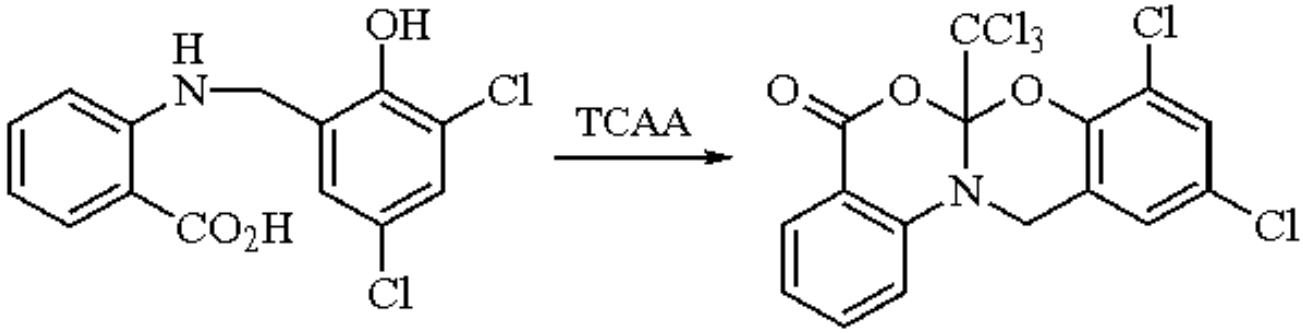

(3)

Formation of 2-Trichloroacyl Vinyl Sulfides.

Reaction of TCAA with trithioorthoacetates produces acylated vinyl sulfides in high yields (eq 4).[5] Later results indicated that the reaction proceeds through a ketene dithioacetal[6] and that the reaction may be extended to vinylketene dithioacetals (eqs 5 and 6)[7] and other functional groups.[8]

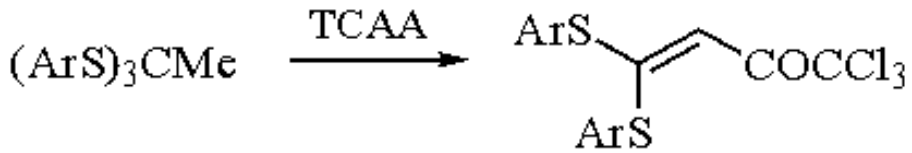

(4)

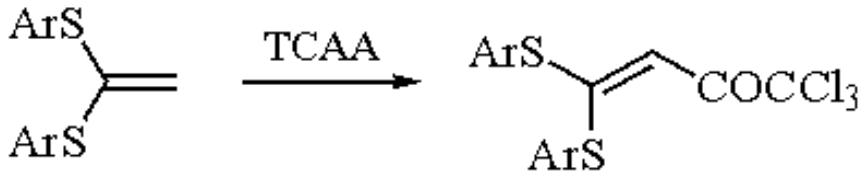

(5)

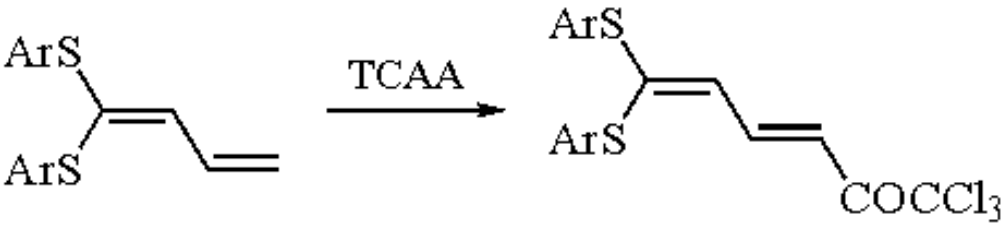

(6)

Schiff Bases and Enamines.

Morimoto and Sekiya discovered that reactions of TCAA with Schiff bases and enamines provided an interesting array of heterocycles and chlorinated products (eqs 7-9).[9]

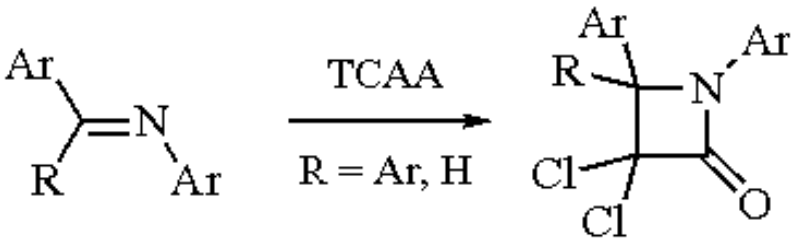

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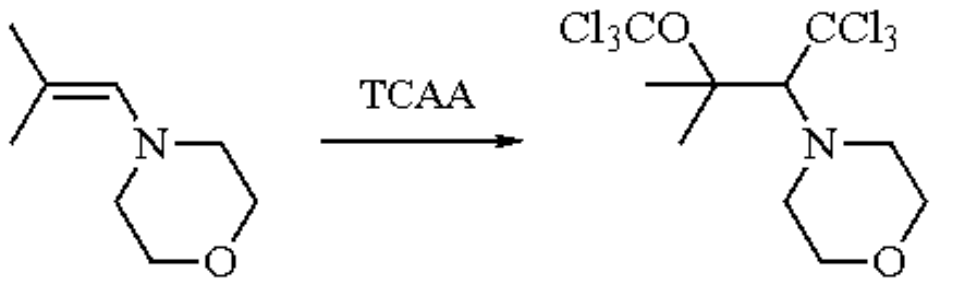

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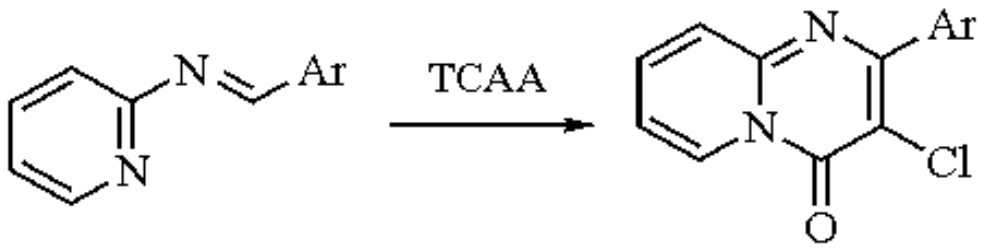

(9)

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2. Sukornick, B. *OSC* **1973**, *V*, 1074.
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9. (a) Morimoto, T.; Sekiya, M. *CPB* **1975**, *23*, 2353. (b) Morimoto, T.; Sekiya, M. *CPB* **1976**, *24*, 1935. (c) Morimoto, T.; Sekiya, M. *CPB* **1977**, *25*, 1230. (d) Morimoto, T.; Sekiya, M. *CPB* **1978**, *26*, 1586. (e) Morimoto, T.; Sekiya, M. *CPB* **1977**, *25*, 1607.

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Trichloroacetonitrile

Cl_3CCN

[545-06-2] · C_2Cl_3N · Trichloroacetonitrile · (MW 144.38)

(makes trichloroacetimidates from alcohols; trichloroacetimidates are used to introduce nitrogen into molecules via rearrangements[1c] and cyclizations; trichloroacetimidates are useful alkylating agents[1d,e])

Physical Data: mp -42 °C; bp 83-84 °C; *d* 1.440 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: neat colorless liquid.

Analysis of Reagent Purity: ^1H NMR, ^{13}C NMR.

Handling, Storage, and Precautions: toxic lachrymator; use only in a fume hood. Reagent can be absorbed through the skin. Always wear gloves when handling this reagent.

Preparation of Trichloroacetimidates.

The imidates derived from the addition of alcohols to trichloroacetonitrile have become important and versatile intermediates in synthetic chemistry.[1] Consequently the principal synthetic use of trichloroacetonitrile has been in the formation of these useful trichloroacetimidate intermediates. The imidates are most often prepared by simple addition of a sodium or potassium alkoxide to the electron-deficient trichloroacetonitrile (eq 1).[1c,d,2] In certain cases, slight modifications of the above procedure are utilized.[2d,3] The product imidates are isolable and, despite their propensity to rearrange,[2b,e,4] can in some instances be purified by distillation[2a,d,e] or chromatography. Typically the addition reaction is sufficiently clean to use the imidates without further purification.[2f]

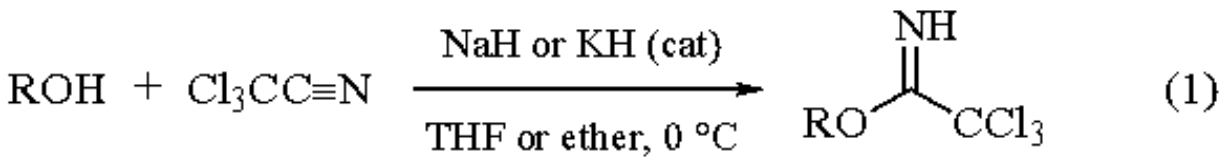

Rearrangement of Trichloroacetimidates.

The thermal rearrangement of imidates has been known for many years.[2b,4] In 1974, Overman[2c] described a useful conversion of allylic alcohols to allylic amines utilizing a [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates (eq 2).[1c,2e] In addition to simple thermolysis it was found that the rearrangement could be catalyzed at room temperature with either Hg^{II} or Pd^{II} salts.[1c,5] As with many sigmatropic rearrangements, the reaction is stereoselective and produces double bonds of defined stereochemistry while efficiently transferring chirality.[1c,5,6]

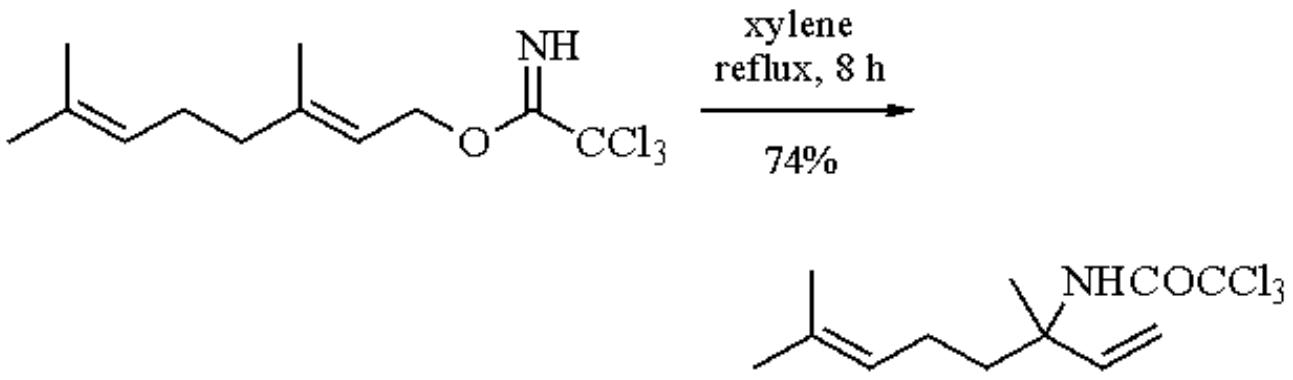

(2)

A comparison of reaction conditions[5b,c,d] has shown that palladium catalysis is particularly effective in achieving complete chiral transfer (eq 3).[5b] Propargylic imidates also rearrange when heated in refluxing xylene.[1c,7] The initially formed allene undergoes a series of tautomerizations so that amino 1,3-dienes are the ultimate products (eq 4).[1c] These dienes have found use in the Diels-Alder reaction.[1c]

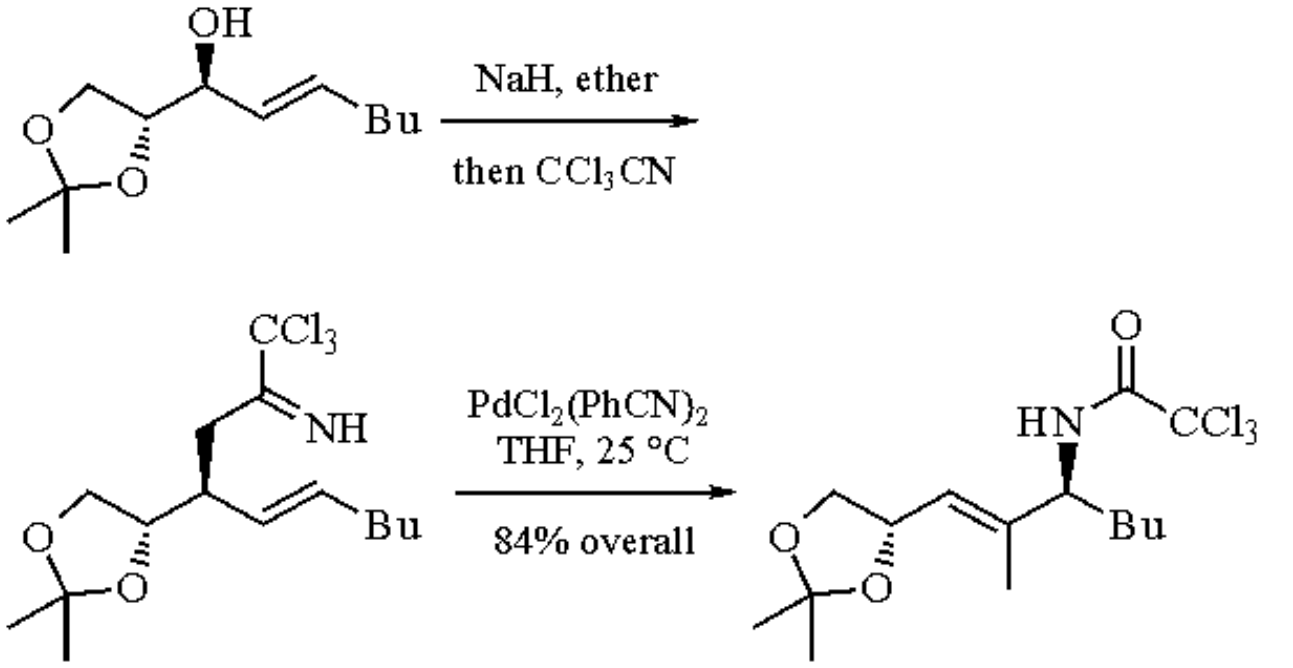

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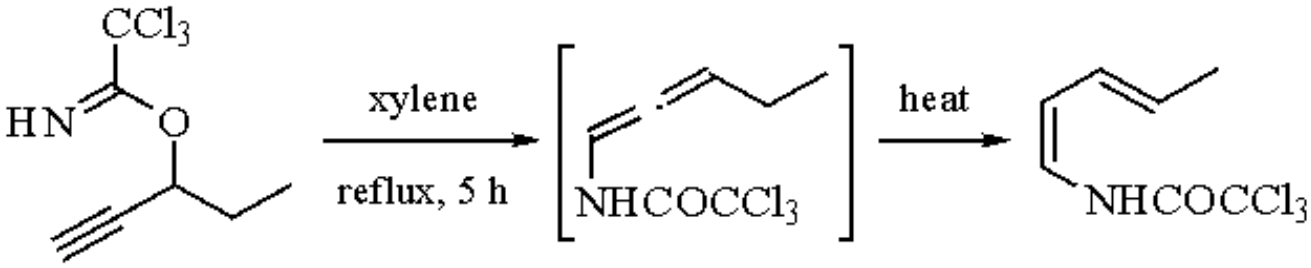

(4)

Electrophilic Cyclization of Trichloroacetimidates.

Trichloroacetimidates derived from allylic[8a,c-f] and homoallylic[8b,c] alcohols undergo electrocyclic ring closure when treated with a source of I^+ (eq 5).[8c] Cyclization can also be triggered via the Lewis acid-mediated opening of epoxides.[9] In at least one case the imidate proved more reactive than related reactions using carbamates.[9c] These are useful methods for the stereoselective introduction of nitrogen into cyclic and acyclic systems.

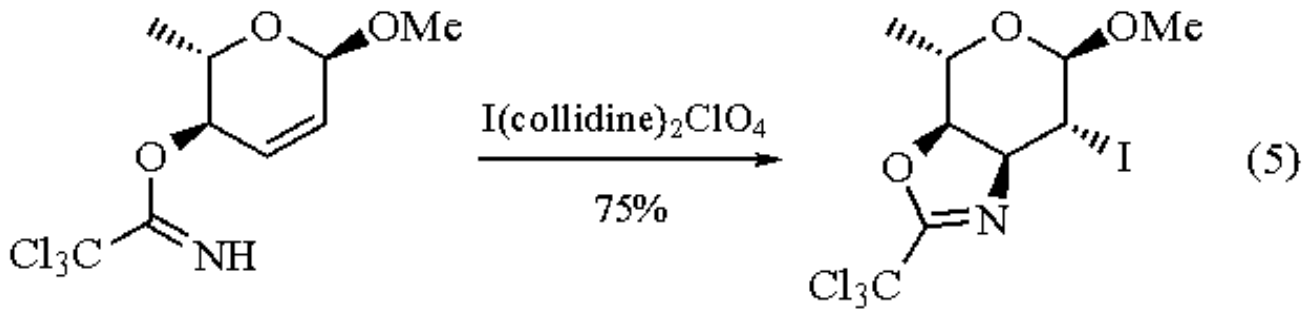

Alkylation using Trichloroacetimidates.

Under mildly acidic conditions, alkyl trichloroacetimidates act as reasonable alkylating agents[2f,10] toward heteroatom nucleophiles, most notably alcohols (eq 6). Alkyl groups which have been transferred include benzyl,[2f,10a,b,d] allyl,[2f] propargyl,[10e] and *t*-butyl.[10c] This methodology has been used to protect alcohols. The use of glycosyl trichloroacetimidates has found widespread use in the synthesis of oligosaccharides and glycoconjugates (eq 7).[1d,e,11] This is a particularly powerful method for controlling stereochemistry at the anomeric position.

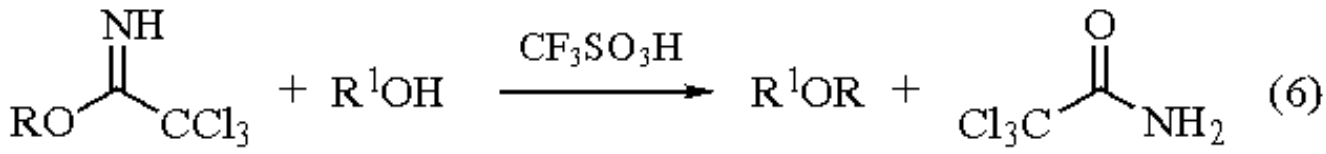

$$R = ArCH_2,\ CH_2{=}CHCH_2,\ MeC{\equiv}CCH_2,\ t\text{-}Bu$$

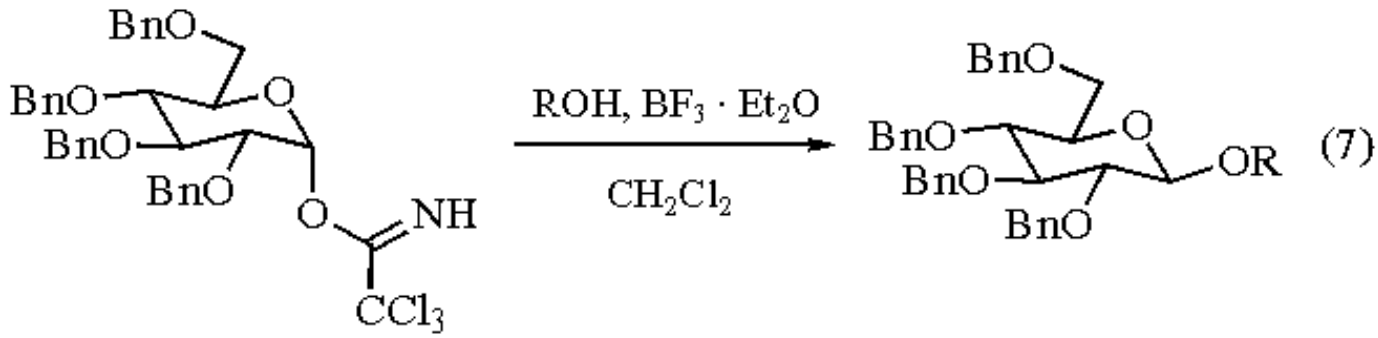

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Trichloroacetyl Chloride

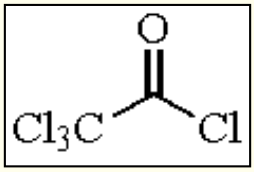

[76-02-8] · C_2Cl_4O · Trichloroacetyl Chloride · (MW 181.82)

(acylation of amines to give trichloroacetamides;[1] undergoes Friedel-Crafts type acylations as an alkyl choroformate equivalent;[2] convenient precursor of dichloroketene;[3] acylates enol ethers;[4] reacts with organozinc reagents to generate trichloromethyl ketones[5])

Physical Data: mp -146 °C; bp 114-116 °C; *d* 1.629 g cm^{-3}

Solubility: sol ether, THF, dichloromethane, benzene, toluene.

Form Supplied in: colorless oil.

Analysis of Reagent Purity: commercial reagent is 99% pure.

Preparative Method: can be generated by action of ***Phosphorus Oxychloride*** on ***Trichloroacetic Acid***.

Purification: distillation with the rigorous exclusion of moisture.

Handling, Storage, and Precautions: reagent is highly toxic and should be handled with gloves.

Formation of Trichloroacetamides.

Amines can be readily converted into the corresponding trichloroacetamides with trichloroacetyl chloride and ***Triethylamine*** (eq 1).[6] Dehydration of amides can be performed in a similar fashion, which allows mild access to the corresponding nitriles (eq 2).[7] Allylic trichloroacetamides can also be used to generate aminochlorohydrins (eq 3).[8]

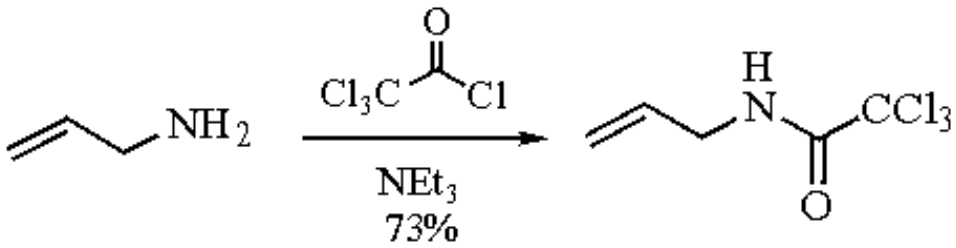

(1)

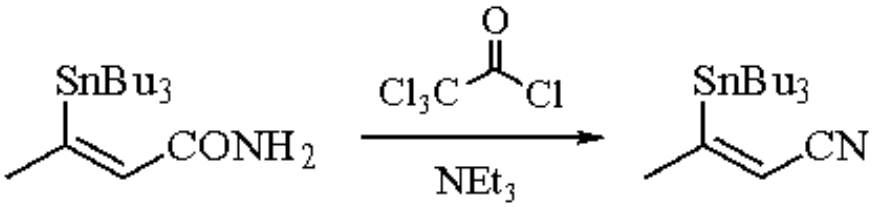

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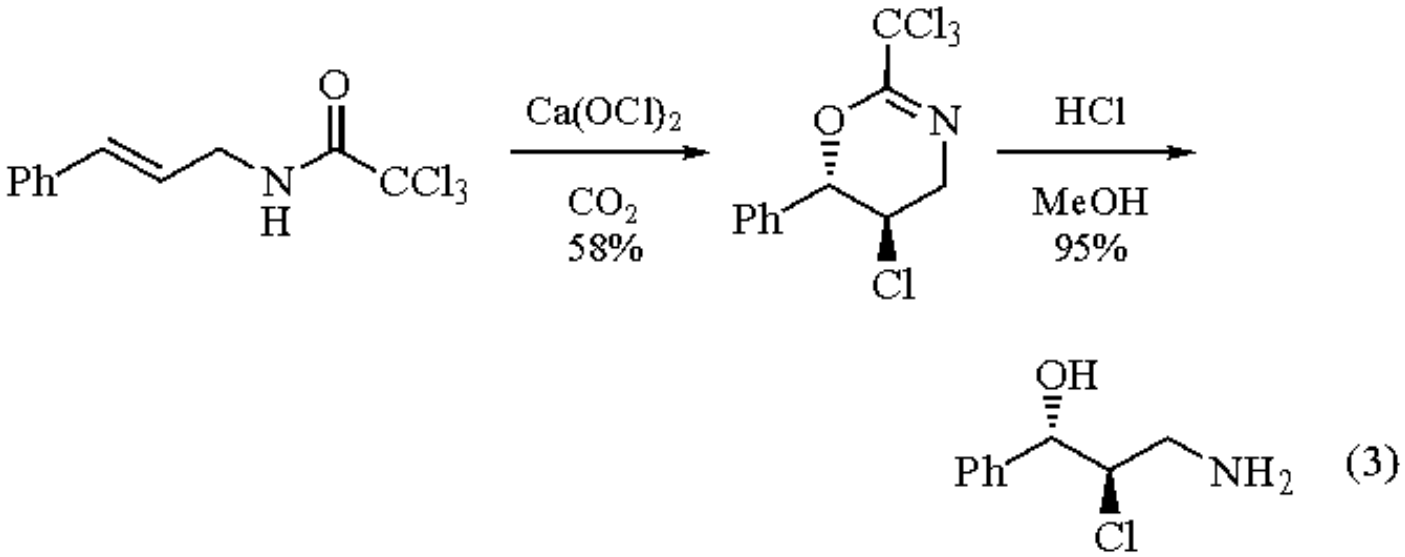

Friedel-Crafts Acylations.

Trichloroacetyl chloride undergoes facile addition to heterocycles in a Friedel-Crafts fashion (eq 4).[9] Given the ability of these products to undergo haloform-type reactions, this allows access to aryl acids, esters, and amides (eq 5).[10,11]

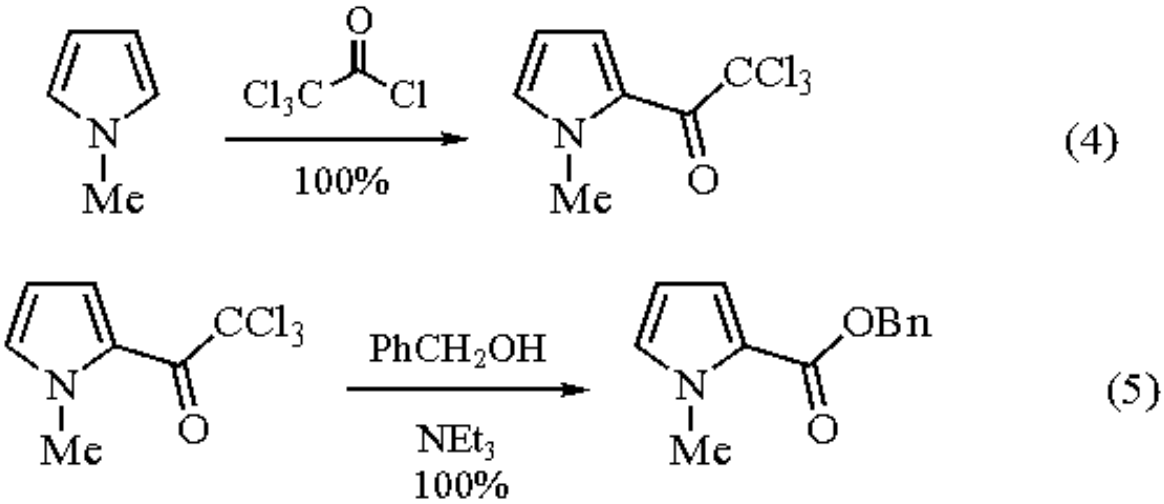

Preparation of Dichloroketene.

Dehalogenation of trichloroacetyl chloride with activated ***Zinc*** yields a solution of dichloroketene (eq 6).[3]

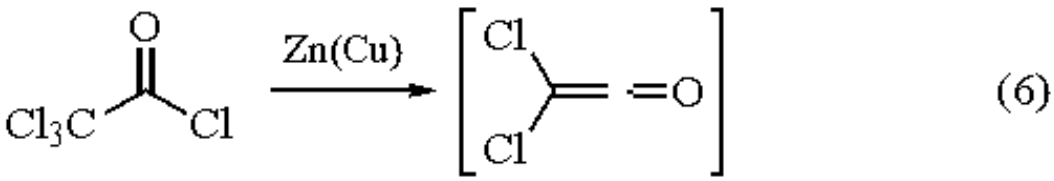

Acylation of Enol Ethers.

Trichloroacetyl chloride adds to enol ethers and thioenol ethers in a regiospecific fashion, and these adducts undergo elimination to generate α,β-unsaturated ketones (eq 7).[12,13]

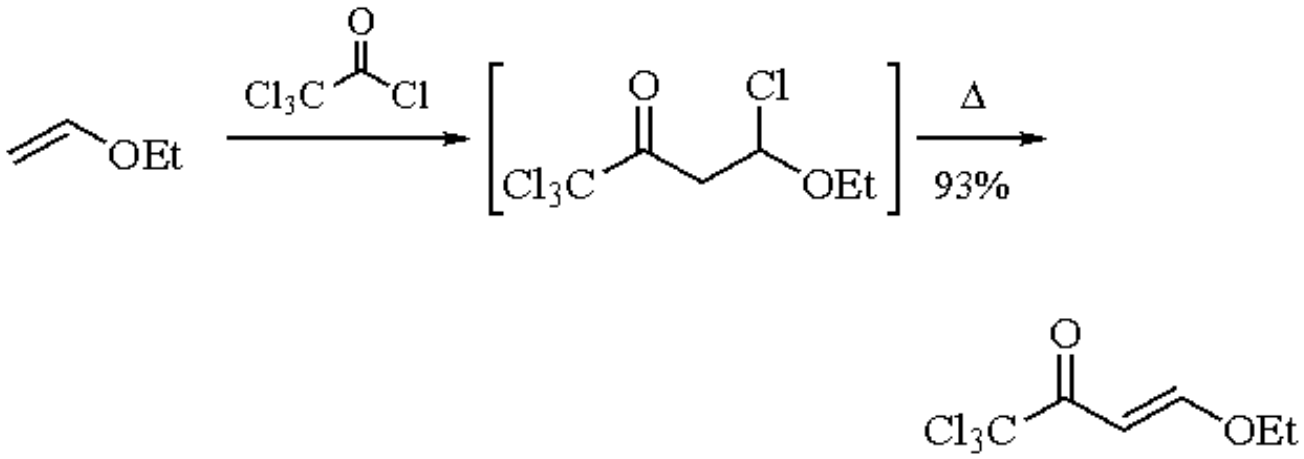

(7)

Generation of Trichloromethyl Ketones.

Addition of trichloroacetyl chloride to an organozinc reagent proceeds without catalyst to give trichloromethyl ketones (eq 8).[5] These can be reduced enantioselectively and therefore serve as a source of asymmetric α-hydroxy and α-amino acids[14]

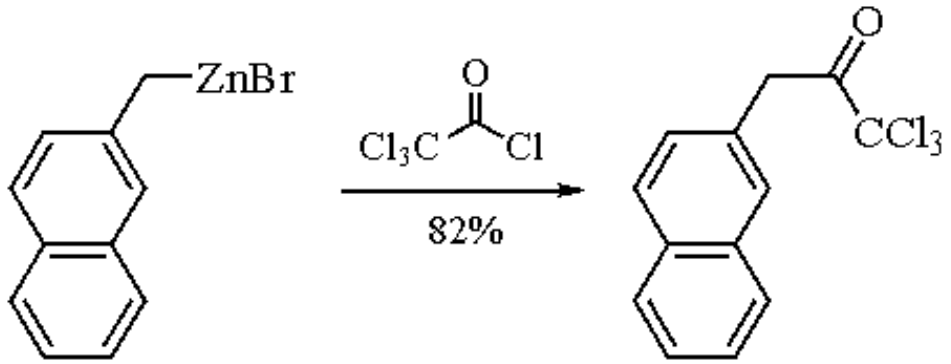

(8)

Related Reagents.

Dichloroketene; ***Tribromoacetyl Bromide***.

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Trichloroacetyl Isocyanate[1]

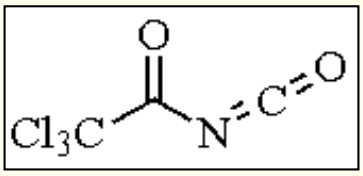

[3019-71-4] · $C_3Cl_3NO_2$ · Trichloroacetyl Isocyanate · (MW 188.39)

(derivatization of alcohols to the trichloroacetyl[2] and unsubstituted[3] carbamates (urethanes); reacts also with phenols, amines, and thiols;[2] [4 + 2] cycloadditions with strained[4] and electron-rich[5] alkenes)

Physical Data: bp 80-85 °C/20 mmHg; *d* 1.581 g cm^{-3}.

Solubility: sol CH_2Cl_2, ether, THF; reacts with H_2O and protic solvents.

Form Supplied in: colorless oil; widely available.

Handling, Storage, and Precautions: should be stored in the absence of moisture and be handled in a fume hood; lachrymator.

Carbamates.

The strong electrophilic properties of this reagent allow ready reaction to occur with alcohols and phenols (*O*-acylation) to form trichloroacetyl carbamates (urethanes),[2,3] with amines to give trichloroacetyl ureas,[2d] and with thiols to give trichloroacetyl thiocarbamates.[2b] These in situ derivatizations are useful for the expeditious classification of alcohols as well as amines and thiols by NMR spectroscopy.[2] However, *C*-acylation sometimes takes place if a pyrrole or furan nucleus is present in the molecule.[6] Selective removal of the trichloroacetyl group is readily achieved by mild hydrolysis under neutral to weakly basic conditions (aq ***Potassium Carbonate***[3a,b,d] or aq $NaHCO_3$[3f] in MeOH or EtOH; ***Ammonia*** in MeOH;[3g] ***Alumina***;[3e] SiO_2 in MeOH[3c]) to give unsubstituted carbamates (eq 1).[3d,7] This procedure has been often used for the synthesis of carbamates in the field of antibiotics.[3c,f,g] This method is complementary to the use of ***Chlorosulfonyl Isocyanate*** to prepare unsubstituted carbamates from alcohols.[7] Carbamates are useful for stereoselective alkene functionalization. Iodonium ion mediates cyclization of allylic and homoallylic carbamates to give cyclic carbonates.[3b] Base-catalyzed intramolecular conjugate addition to activated alkenes afforded oxazolidinones and perhydrooxazinones (eq 1).[7]

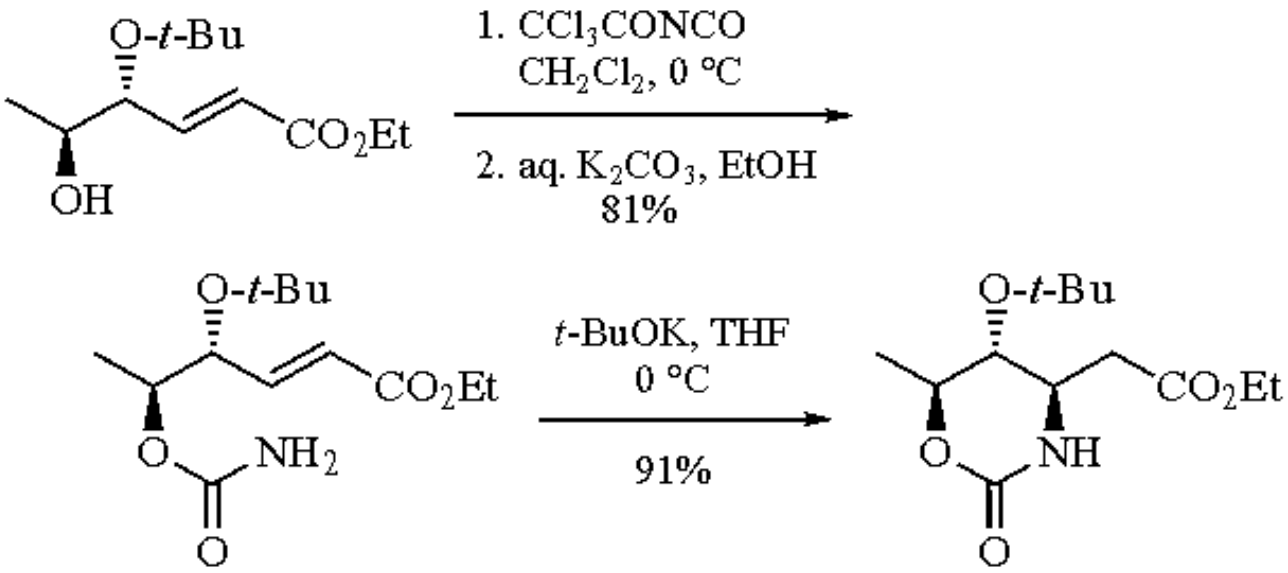

(1)

Trichloroacetyl isocyanate is an effective dehydrating reagent in the preparation of 1,2-benzisoxazoles from salicylaldoximes (eq 2).[8]

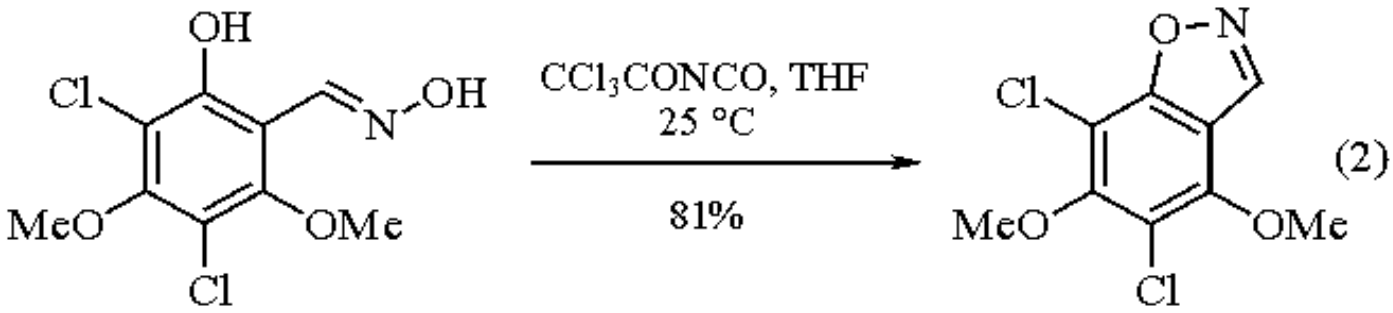

Cycloaddition with Alkenes.

This isocyanate reacts preferably as a 4π component with strained (eq 3)[4b] and electron-rich alkenes (eq 4)[5b] to give [4 + 2] cycloaddition products, in contrast to the [2 + 2] reactions of sulfonyl isocyanates.[4,5] Various other heterocycles have been synthesized similarly via cycloadditions[5,10] and also via *O*-[8] and *N*-acylation.[9]

Oxidation of 4-phenylurazole to triazolinedione is more effectively achieved by use of a DMSO-CCl_3CONCO combination compared with other Pfitzner-Moffatt-type systems.[11]

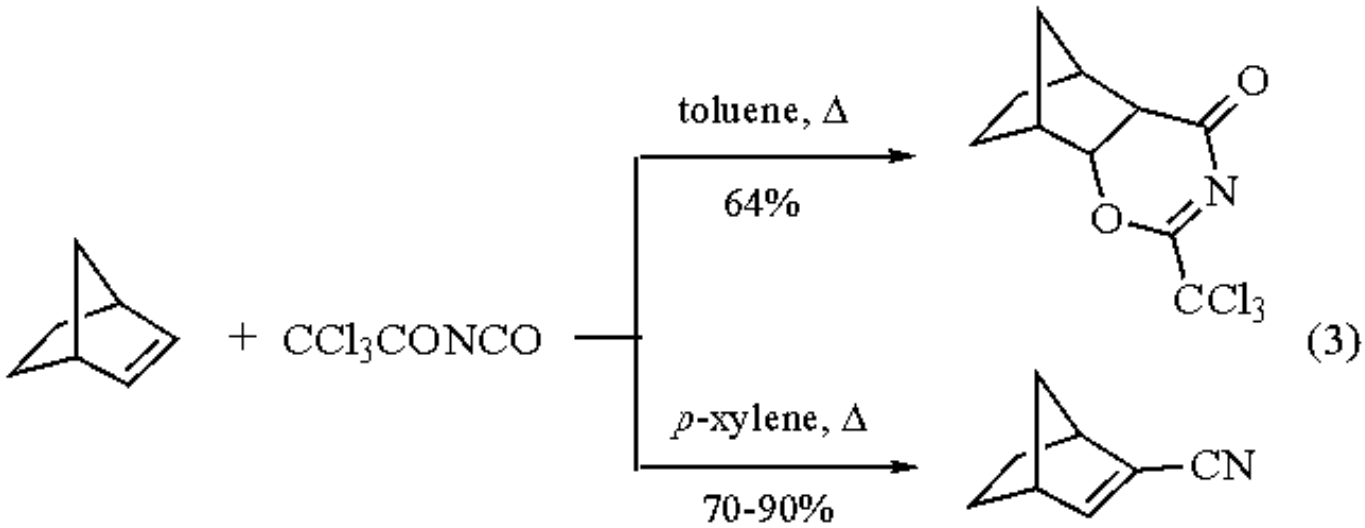

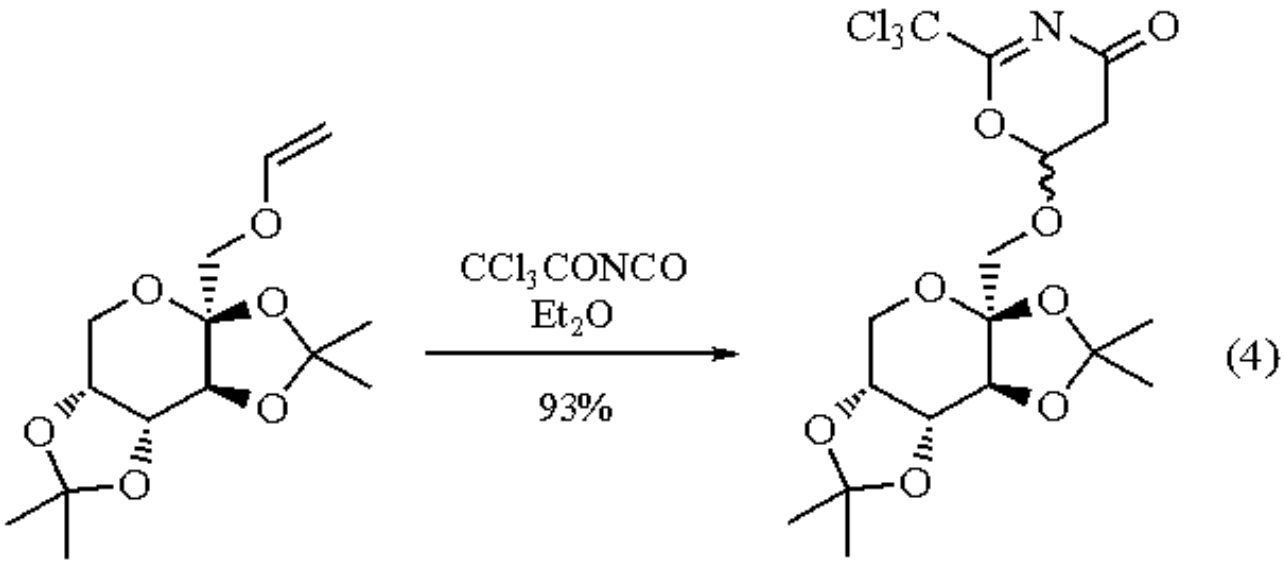

Related Reagents.

Chloroacetyl Isocyanate; ***Chlorosulfonyl Isocyanate***.

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2,4,6-Trichlorobenzoyl Chloride[1]

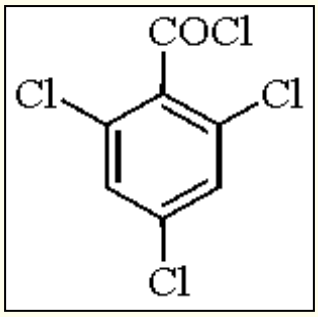

[4136-95-2] · $C_7H_2Cl_4O$ · 2,4,6-Trichlorobenzoyl Chloride · (MW 243.89)

(strong acylating agent; used with DMAP in the formation of esters,[1] thioesters,[2] amides,[3] and, particularly, small- and medium-ring lactones[1,4])

Physical Data: bp 107-108 °C/6 mmHg; *d* 1.561 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: liquid; commercially available.

Purification: redistill under reduced pressure.[5]

Preparative Methods: first prepared by Yamaguchi from 2,4,6-trichloroaniline,[7] but Seebach has reported a simpler synthesis from 1,3,5-trichlorobenzene (**1**) (eq 1).[8]

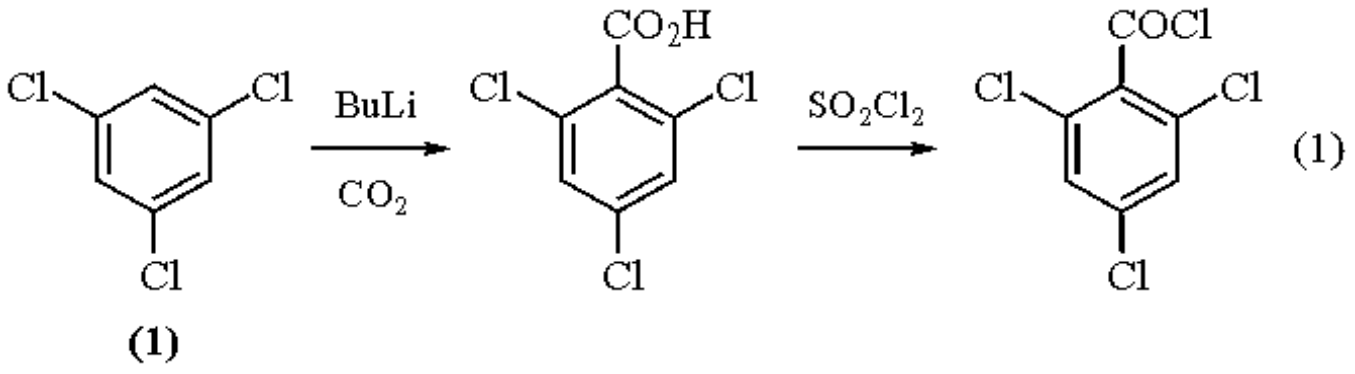

Handling, Storage, and Precautions: irritant and moisture sensitive. Incompatible with strong bases (see Aldrich safety index for ***Benzoyl Chloride***).[6]

Carboxylic Acid Derivatives.

2,4,6-Trichlorobenzoyl chloride was designed to react rapidly with carboxylic acids to form mixed anhydrides (**2**),[9] which would then quickly react with alcohols, amines, and thiols to give esters (**3**), amides (**4**), and thioesters (**5**) in high yields (eq 2).

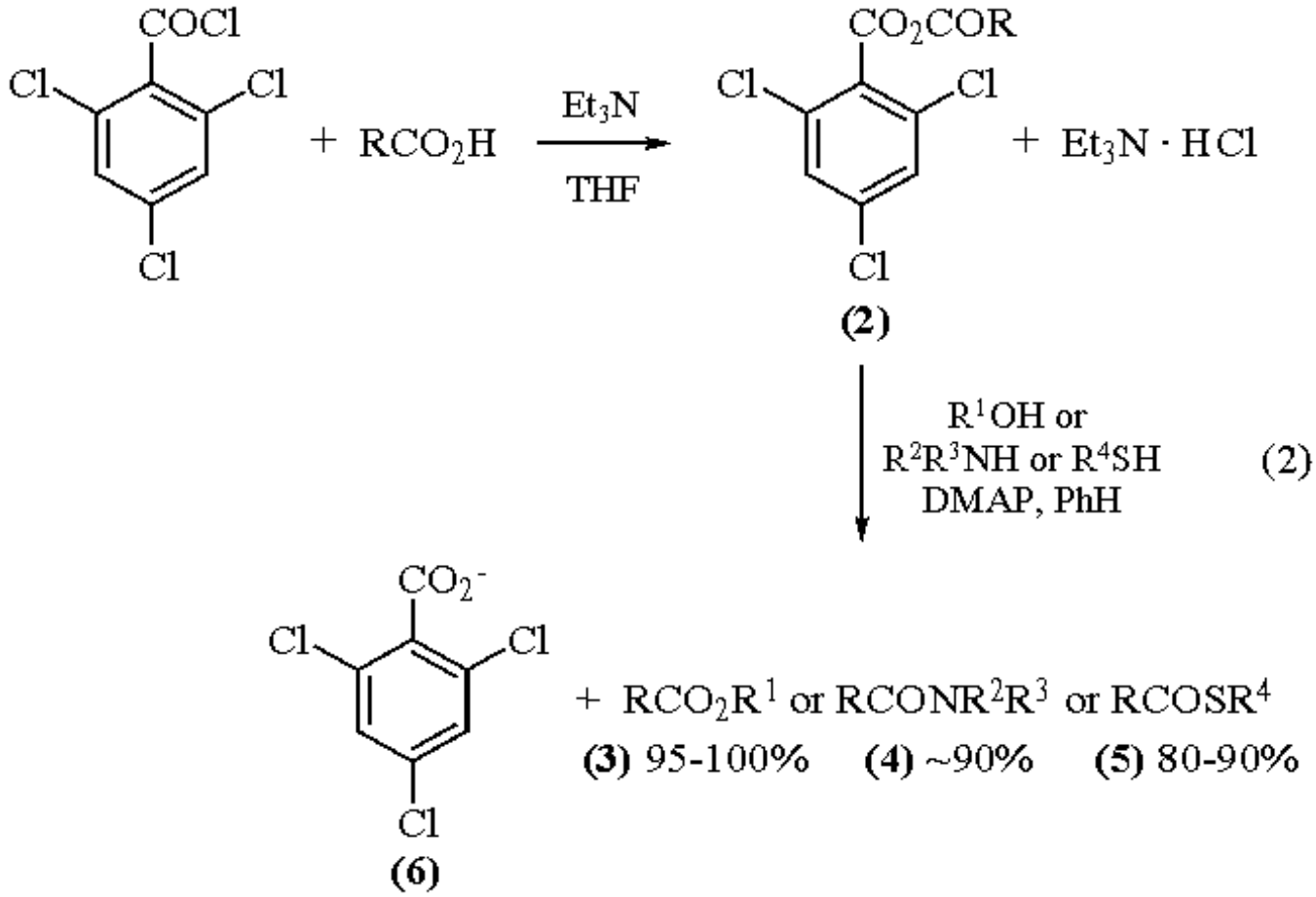

The trichloro-substituted phenyl ring serves two purposes: to prevent any side reaction occurring, due to attack of the alcohol at the carbonyl adjacent to the aromatic ring, and to make the carboxylate anion (**6**) a good leaving group, enhancing the rate of reaction.

Lactone Formation.

Although many methods exist for lactonizing α,o-hydroxy acids,[10] 2,4,6-trichlorobenzoyl chloride remains one of the most powerful and has been widely used in the synthesis of naturally occurring macrolides.[11] Yamaguchi first showed how 9-, 12-, and 13-membered lactones could be synthesized using high dilution techniques (Table 1)[1] and went on to demonstrate the potential of his reagents by using them to synthesize methynolide and (±)-brefeldin A (**7**) (eq 3), 12- and 13-membered lactones, respectively.[7,12]

Table 1 Synthesis of Lactones[1]

Ring size of lactone formed	DMAP (equiv)	Time of addition (h)	Yield of monomer (%)	Yield of dimer (%)
9	3	8	36	23
10[13]	6	20	33	0
12	6	5	48	20
13	6	1.5	67	10

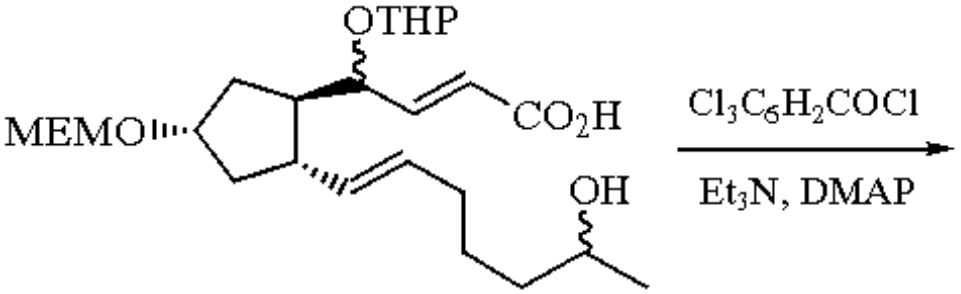

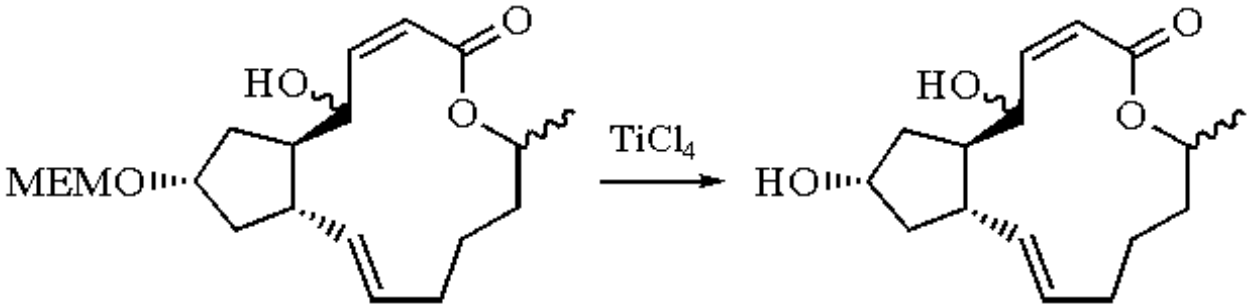

(3)

(7)

Other groups have also used the Yamaguchi lactonization procedure to synthesize natural products, most notably Seebach in the synthesis of (+)-myscovirescine M_2, a 27-membered lactone, in which the seco acid was converted to the lactone in 83% yield.[14] Symmetrical diolides (**8**) have been prepared from unprotected seco acids in fair yields (eq 4)[15] when other lactonization procedures failed.[9] Unsymmetrical diolides require protected seco acids.[16]

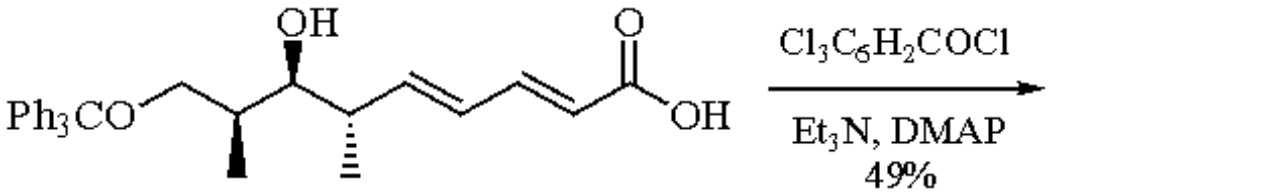

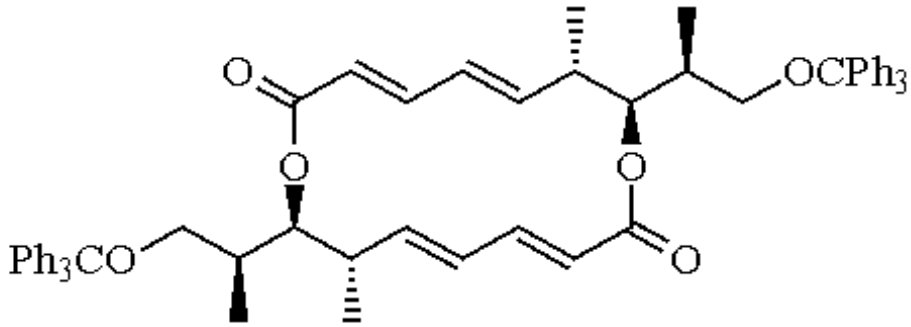

(4)

(8)

More recently, treatment of 3-hydroxybutanoic acid (**9**) under the Yamaguchi lactonization conditions of high dilution gave, in equal proportions, macropentolides, macrohexolides, and macroheptolides in good yields (eq 5).[17]

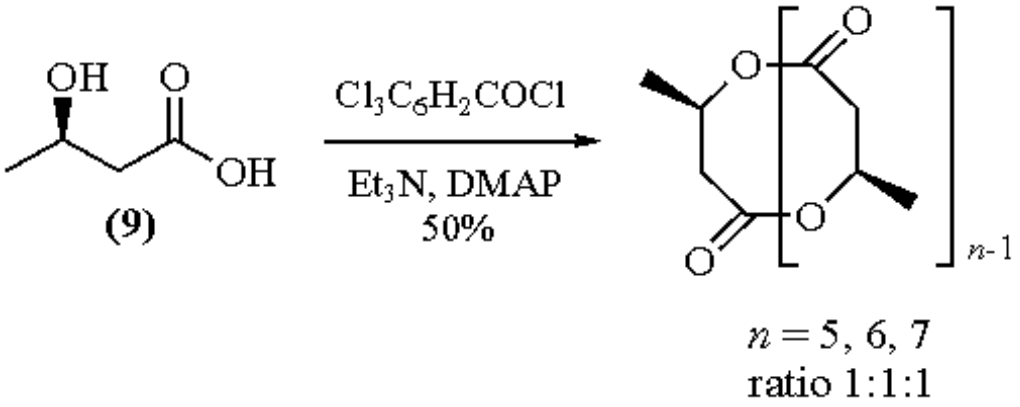

(5)

The Shanzer lactonization method produces a lower overall yield of macrolides, but an increased ratio of the higher homologs.[18]

Effect on Stereochemistry.

The Yamaguchi esterification is also often used in preference to other methods because of its lack of racemization of stereogenic centers. Kunz used it to esterify an *N*-Boc protected aspartate (**10**)[19] when other methods have been known to racemize the chiral center (eq 6).[20]

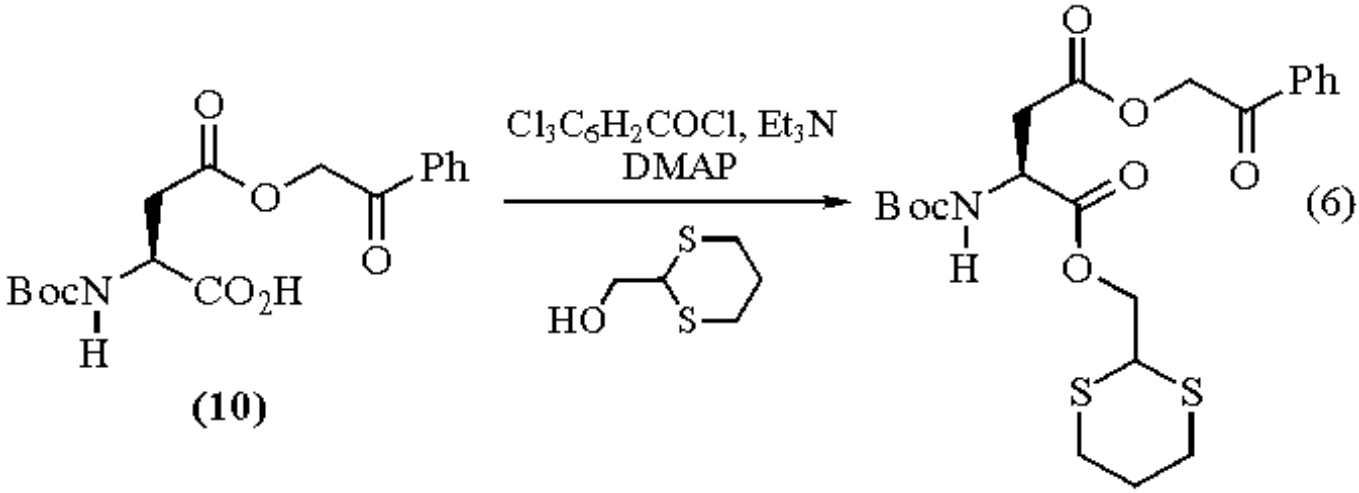

(6)

The Yamaguchi lactonization also leaves intact any stereochemistry at the carbon bearing the hydroxyl group. This is in contrast to the Mitsunobu lactonization, which inverts that stereochemistry (eq 7).[21]

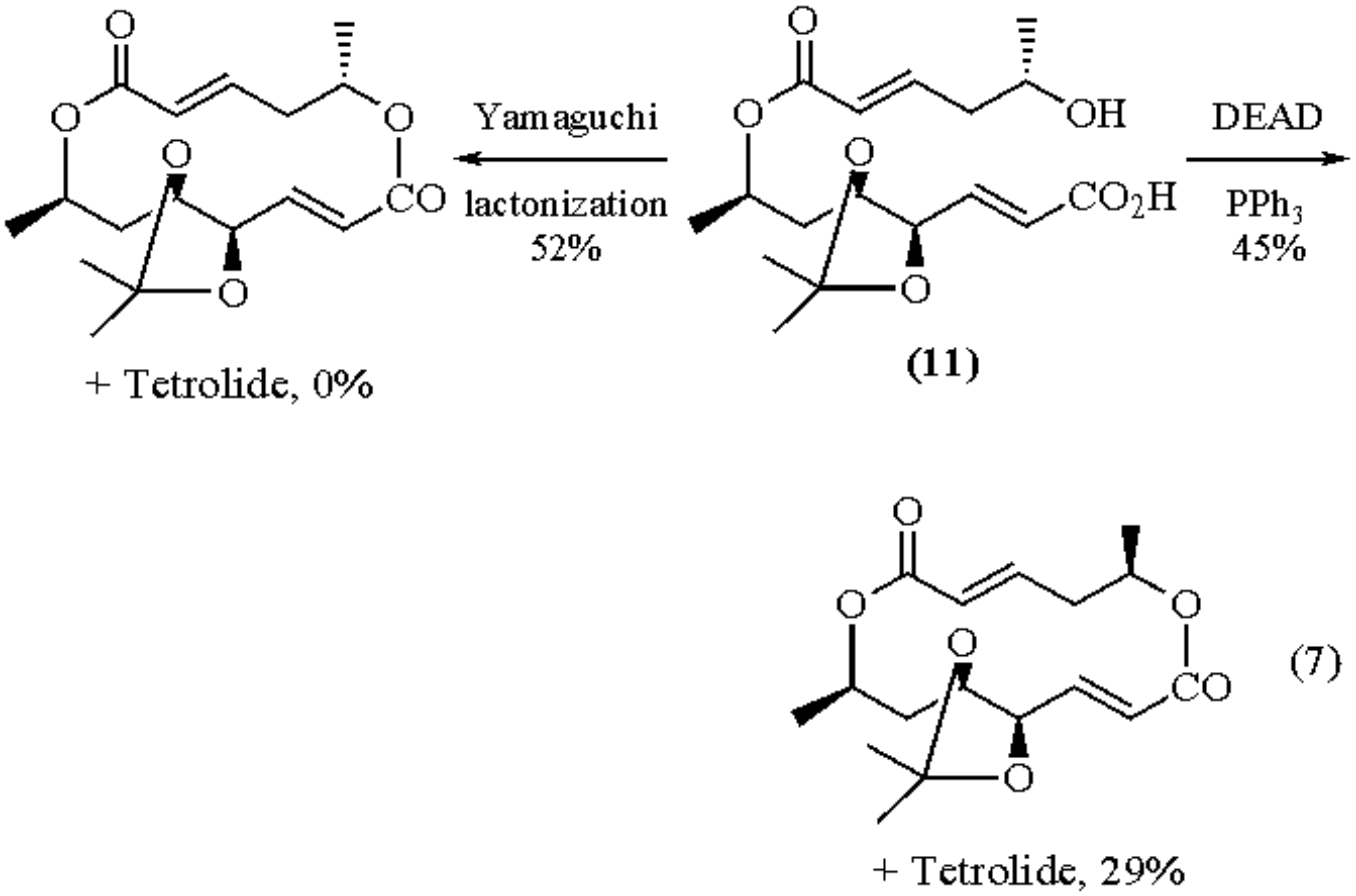

Furthermore, when no base is present during esterification, double bonds are also little affected, as Greene showed when converting a variety of alcohols to angelate esters (**12**) in quantitative yield; standard esterification procedures gave a mixture of angelate and tiglate esters (eq 8).[22]

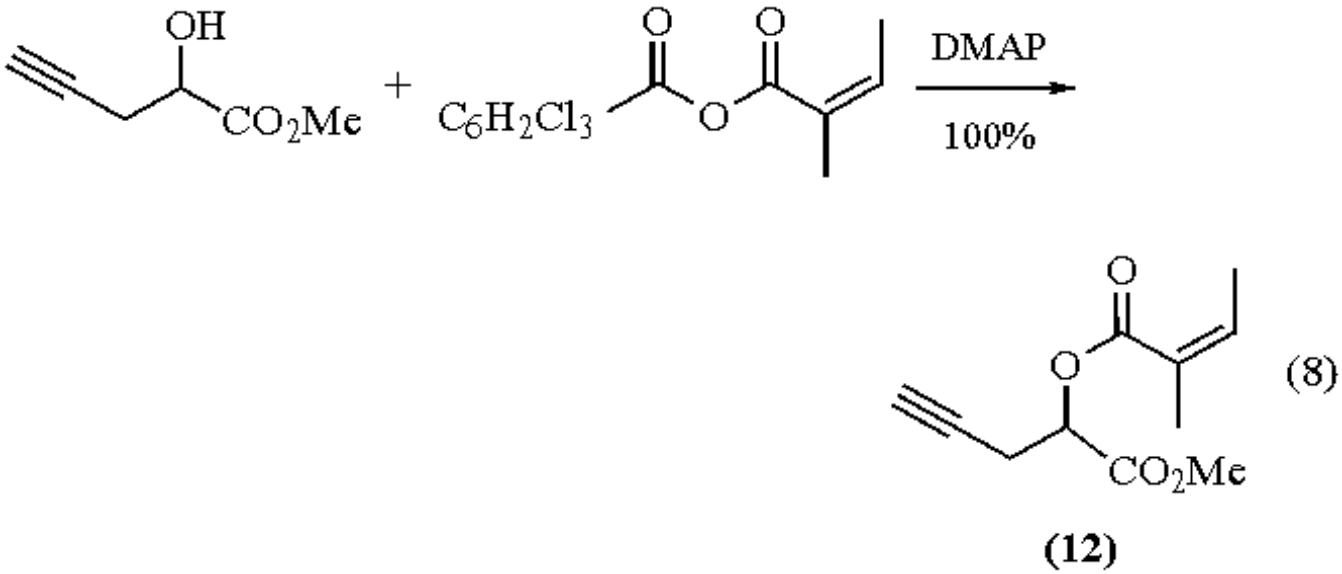

Limitations of the Yamaguchi Lactonization Conditions.

The tendency of the Yamaguchi lactonization conditions to form diolides from some seco acids, as shown by Seebach,[15] can also pose a problem. Steglich has shown that some α,o-hydroxy acids (**13**) tend to dimerize under the Yamaguchi lactonization conditions. However, by using a modified Mitsunobu lactonization, the monolide was obtained in 59% yield (eq 9). All other lactonization procedures also gave varying amounts of diolide, including the standard Mitsunobu lactonization procedure.[23]

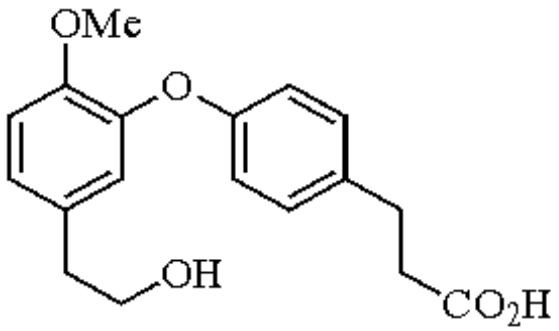

(13)

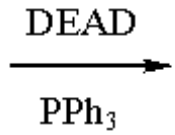

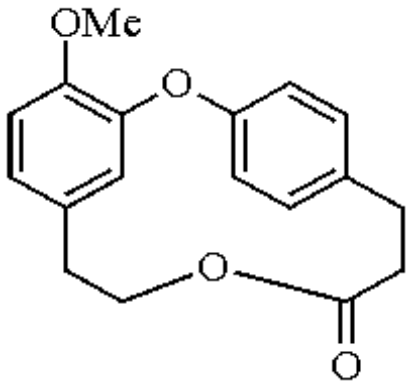

+ Dimer (9)

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2,2,2-Trichloro-*t*-butoxycarbonyl Chloride

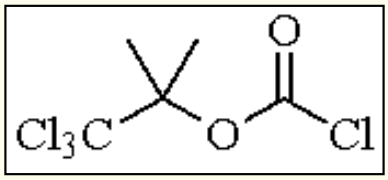

[66270-36-8] · $C_5H_6Cl_4O_2$ · 2,2,2-Trichloro-*t*-butoxycarbonyl Chloride · (MW 239.91)

(easily removable acid- and base-stable protecting group for nitrogen, including amino acids[1] and nucleosides;[2] protecting group for alcohols[3,4])

Alternate Name: TCBOC-Cl.

Physical Data: mp 30-32 °C; bp 77-81 °C/12 mmHg.

Form Supplied in: colorless solid; commercially available.

Preparative Method: from trichloro-*t*-butanol with ***Phosgene***[1] or triphosgene (***Bis(trichloromethyl) Carbonate***) (eq 1).[5]

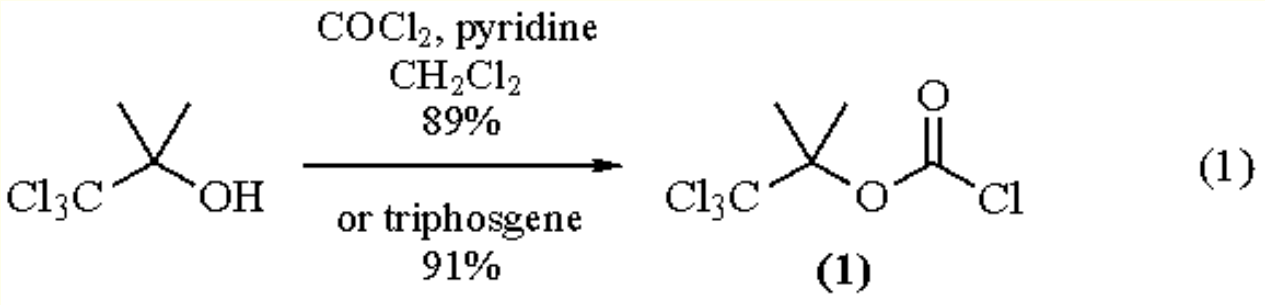

Handling, Storage, and Precautions: moisture sensitive.

General Discussion.

As a protecting group for amines, the TCBOC group is stable to acid and base conditions normally used to remove Boc groups (e.g. TFA) or to hydrolyze methyl esters (NaOH-methanol).[1] The TCBOC group is attached under standard Schotten-Baumann conditions (eq 2). In addition to the reductive conditions[6] originally described for removal of the TCBOC group (eq 3), sodium-2-thiophenetellurolate[7] and zinc-acetylacetone[8] (neutral conditions) also deprotect in high yield. Nucleosides,[2,8] indoles,[7,9] indolines,[7,10] and anilines[7] have been *N*-protected with the TCBOC group.

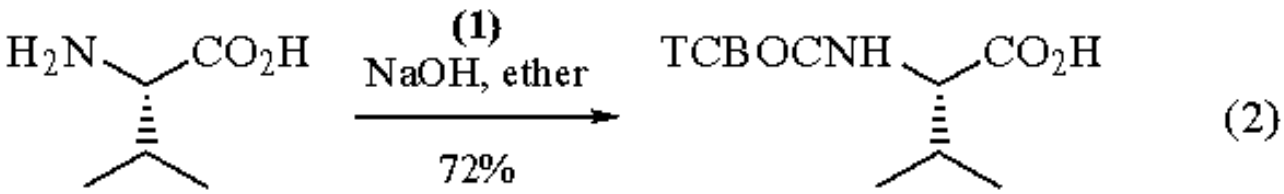

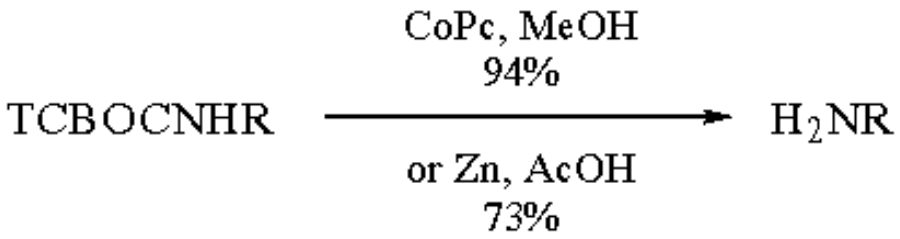

(3)

R = Val-Ala-Phe-O-*t*-Bu; CoPc = lithium cobalt(I) phthalocyanine

The TCBOC group is useful as an alcohol protecting group (eq 4). Horner-Emmons reagent (**3**) is stable below 0 °C and can be used to prepare α-keto esters (eq 5).[3] As an alcohol protecting group the TCBOC group is not stable to aqueous base,[4] in contrast to its use as an amine protecting group.

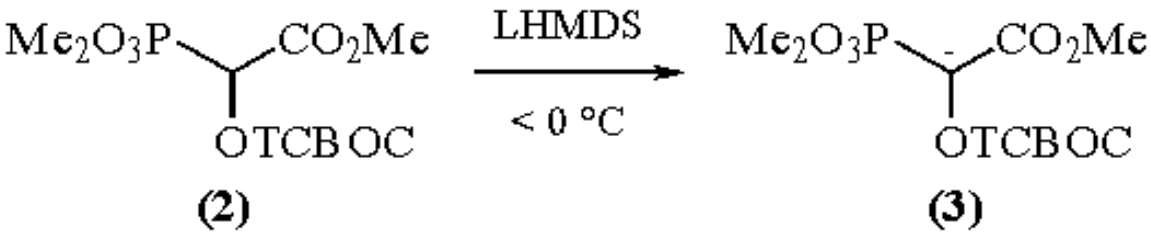

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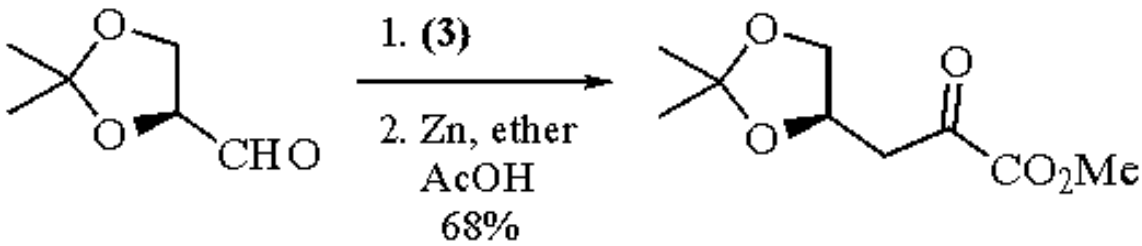

(5)

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Trichloro(cyclopentadienyl)titanium[1]

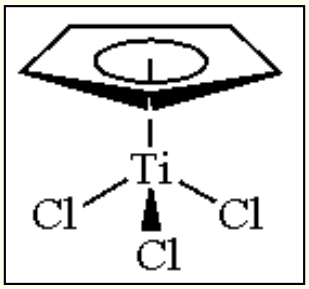

[1270-98-0] · $C_5H_5Cl_3Ti$ · Trichloro(cyclopentadienyl)titanium · (MW 219.33)

(preparation of various cyclopentadienyltitanium(IV) complexes,[1] e.g. enantioselective templates by exchanging two of the chloride ligands with chiral alkoxides;[2] replacement of the third chloride by allyl groups[3] or by ester enolates[4] affords reagents for stereoselective allyltitanation of aldehydes[2b,3] and for aldol reactions,[4] respectively; combination with metal hydrides or with *n*-BuLi results in low-valent species, reagents for various reductions;[5] catalysts for alkene polymerizations are obtained by activation with organoaluminum compounds, methylaluminoxane, or aluminosilicates;[6] Ti-imido complexes derived from primary amines undergo intramolecular cyclizations with triple bonds;[7] the Lewis acidity is used to cleave epoxides and acetals;[8] methyl or ethyl derivatives can be used for the chemoselective alkyltitanation of aldehydes in the presence of ketones[9])

Physical Data: mp 208-211 °C (benzene); crystal structure.[10]

Solubility: sol aromatic hydrocarbons (toluene, dichlorobenzene, xylene), CH_2Cl_2, $CHCl_3$, Et_2O, THF, similar aprotic solvents.

Form Supplied in: yellow-orange powder or crystals.

Analysis of Reagent Purity: ^1H NMR δ ($CDCl_3$): 7.06 ppm (impurity, partial hydrolysis: 6.92 ppm); ^{13}C NMR: 123.4 ppm (impurity: 122.2 ppm).

Preparative Methods: the title reagent $CpTiCl_3$ (**1**) is most conveniently prepared by ligand redistribution between ***Dichlorobis(cyclopentadienyl)titanium*** and ***Titanium(IV) Chloride***,[1,11] or by reaction of 1-trimethylsilyl-2,4-cyclopentadiene with $TiCl_4$.[12] Another method involves chlorination of Cp_2TiCl_2 with ***Sulfuryl Chloride***/***Thionyl Chloride***[13] or titanation of cyclopentadienyl-Tl.[14]

Purification: by recrystallization in the presence of HCl(g)[1,11] followed by sublimation in high vacuum.[10]

Handling, Storage, and Precautions: the crystalline solid must be protected from moisture and prolonged exposure to UV light should be prevented. Reactions should be carried out in dry equipment with absolute solvents in an inert atmosphere (Ar, N_2).

Preparation of Chiral Cyclopentadienyldialkoxytitanium Chlorides.

Cyclopentadienyltitanium complexes can be prepared from $CpTiCl_3$ (**1**) by exchanging one, two, or all three of the chloride ligands.[1] Reaction with alcohols (ROH) results in spontaneous substitution of one chloride with evolution of HCl, affording monoalkoxides (**2**). For the second substitution to the dialkoxides (**3**) the HCl has to be withdrawn from the equilibrium (**2**) &ibond; (**3**) by neutralization with a tertiary amine, e.g. ***Triethylamine***.[3] Preferred solvents for these ligand exchanges are Et_2O and hydrocarbons. In the case of diols leading to favorable cyclic Ti complexes, e.g. (*R*,*R*)-(**4**), the second substitution can also be effected by heating in toluene under a slow stream of Ar or N_2 (eq 1).[2b]

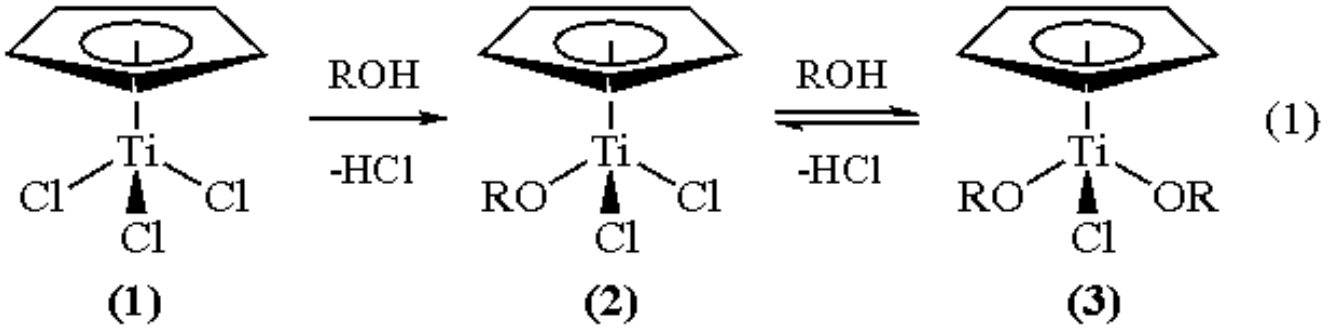

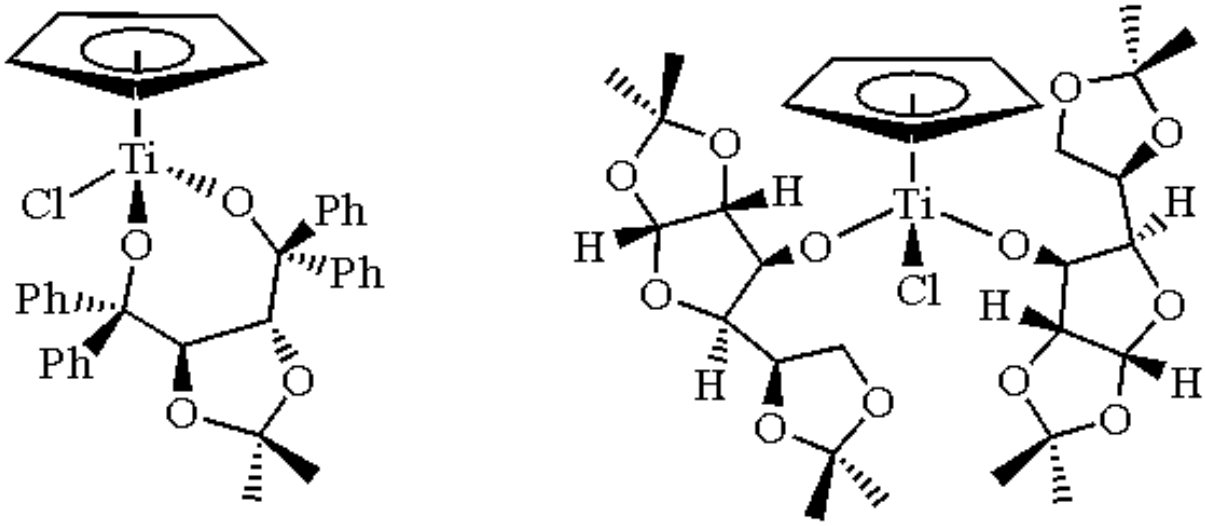

The use of two identical chiral alcohols or a C_2-symmetrical chiral diol leads to chiral Ti complexes without a stereogenic metal center. ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium*** (**5**)[2a,3] and ***Chloro(η^5-cyclopentadienyl)[(4R,trans)-2,2-dimethyl-α,α,α´,α´-tetraphenyl-1,3-dioxolane-4,5-dimethanolato(2-)-O^{α},O$^{α´}$]titanium*** ((*R*,*R*)-**4**)[2b] have been successfully used for the enantio- and diastereoselective additions of nucleophiles to achiral and chiral aldehydes.[2c,d] The cyclic complex (*R*,*R*)-(**4**) and its enantiomer are especially suited for the transfer of allyl and terminally monosubstituted allyl groups, affording homoallyl alcohols of excellent optical purity. The branched *anti*-isomers are obtained in the case of substituted nucleophiles.[2b] While the titanate (**5**) with ligands derived from D-glucose can be used for allyltitanations as well,[3] its optimal use is for highly stereoselective aldol reactions of acetate,[4a] propionate,[4b] and glycine ester enolates.[4c] In this case the enantiomer is not readily available.

Reductions.

Reducing agents can be obtained by the combinations $CpTiCl_3$/***Lithium Aluminum Hydride***,[5a,b,e,f] $CpTiCl_3$/***Sodium Borohydride***,[5d] $CpTiCl_3$/***n-Butyllithium***,[5c,6a] and $CpTiCl_3$/***Sodium Naphthalenide***.[5g] The four-stage conversion of $CpTiCl_3$ (**1**) and $LiAlH_4$ has been studied by calorimetric titration; the titanium is thereby reduced to Ti^{III}.[5a] $CpTiCl_3/LiAlH_4$ has been used for inter- and intramolecular pinacol couplings (eq 2),[5b] deoxygenations of endoxides (eq 3),[5e] and reduction of acetals.[5f]

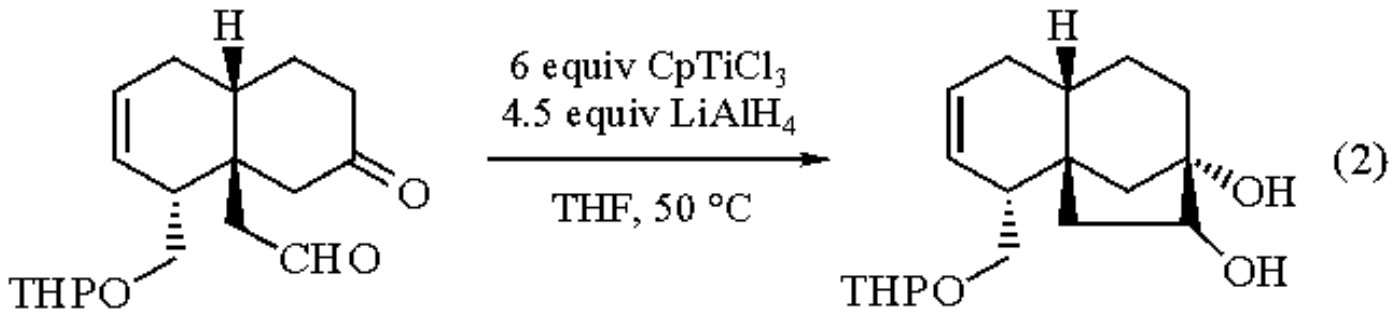

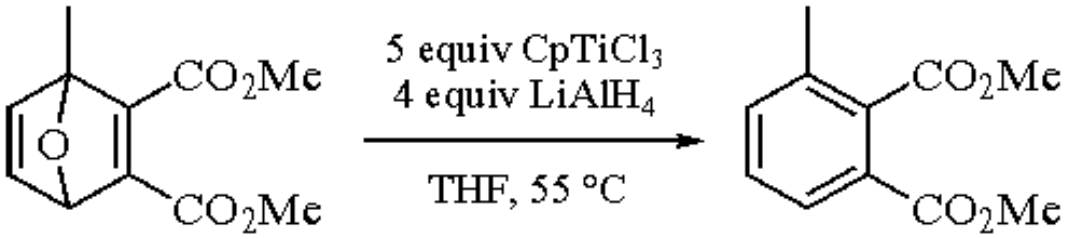

(3)

Reaction of $CpTiCl_3$ (**1**) with BuLi gives a Ti^{II} species, which catalyzes the hydrogenation of simple alkenes.[5c,6a] This catalyst can be immobilized on alumina.[5c] The combination $CpTiCl_3/NaBH_4$ allows the selective reduction of aromatic iodides in the presence of chlorides and bromides.[5d] The reducing power of ***Alumina***-supported (**1**) and Na naphthalenide is sufficient for nitrogen fixation, i.e. the conversion of N_2 to NH_3.[5g] Similar reagents can be obtained from $TiCl_4$, ***Titanium(III) Chloride***, Cp_2TiCl_2, aluminum chlorides, or by using ***Potassium Hydride***, ***Magnesium***, and ***Magnesium Amalgam*** as reducing components.

Alkene Polymerization.

While $CpTiCl_3$ (**1**) is inactive, efficient catalysts for alkene polymerizations are obtained in combination with methylaluminoxane (MAO).[6c,d,e,g] The reaction between (**1**) and MAO has been studied by EPR.[6c] Instead of MAO, ***Diethylaluminum Chloride***[6a] and aluminosilicates[6b,f] have also been used for activation. The prominent features of these catalysts are the stereoregular syndiotactic polymerization of styrene[6c,e] and the *cis*-1,4-polymerization of certain 1,3-dienes.[6e,g] In contrast, a regioirregular polymer is obtained from propene.[6f] Stereoregular Ziegler-Natta-type polymerization catalysts, especially for polypropylene, can also be obtained from *ansa*-bridged titanocenes or zirconocenes with planar chirality.[15]

Lewis Acid Catalysis and Other Applications.

Reaction of $CpTiCl_3$ (**1**) with primary amines gives highly reactive Ti-imido complexes which undergo rapid but reversible cyclodimerization. These imides undergo facile intramolecular [2 + 2] cycloadditions with triple bonds, affording highly strained titanacycles (**6**), which, under catalytic conditions (0.2 equiv. **1**) are further transformed to 1-pyrrolines or 1-piperines,[7a] e.g. (**7**), an elaborated intermediate for the alkaloid monomorine (eq 4).[7b] With stoichiometric amounts of (**1**) the intermediate (**6**) can be trapped by hydrolysis, *C*-acylation with nitriles, or *N*-acylation with acid chlorides (eq 5).[7a]

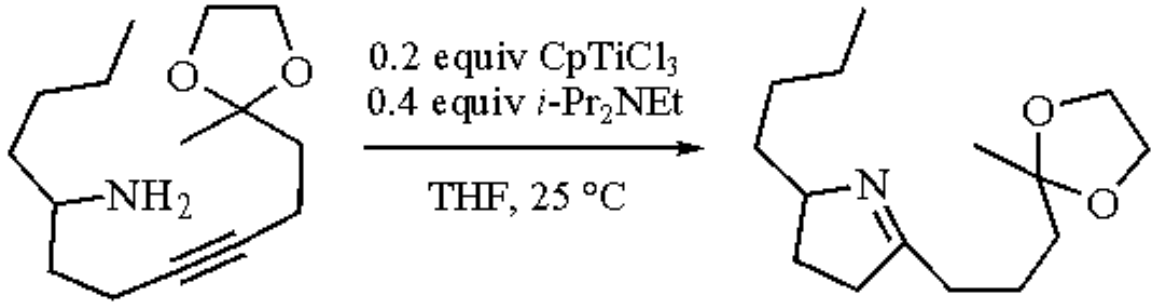

(4)

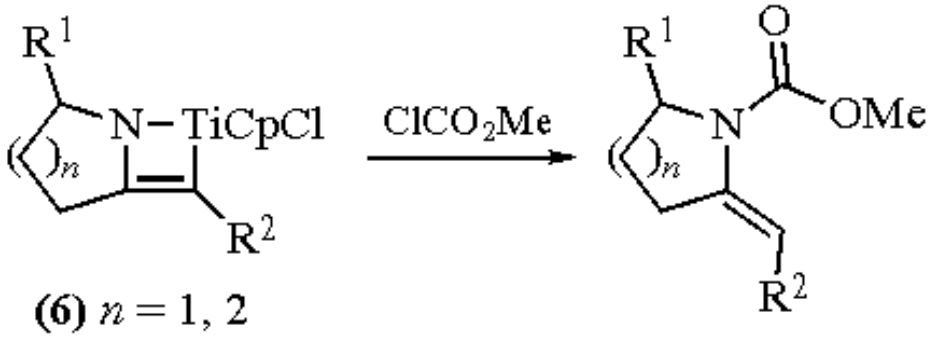

(6) $n = 1, 2$

(5)

Further applications of $CpTiCl_3$ (**1**) include regioselective opening of propylene oxide[8a] and, in combination with ***Sodium Iodide***, the cleavage of cyclohexanone acetals[8b] $CpTiCl_2Me$ can be prepared from (**1**) with Me_2Zn, ***Trimethylaluminum***, ***Methyllithium***, or MeMgCl. In competition experiments it transfers its methyl group to aldehyde and ketone carbonyls (much like ***Methyltitanium Triisopropoxide***), with high preference for aldehydes. However, an advantage over $(i\text{-PrO})_3TiMe$ is its thermal stability, also exhibited by the ethyl analog.[9]

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Trichloro(cyclopentadienyl)zirconium[1]

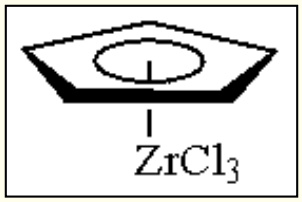

[34767-44-7] · $C_5H_5Cl_3Zr$ · Trichloro(cyclopentadienyl)zirconium · (MW 262.67)

(catalyst for alkene polymerization[2-4])

Physical Data: mp 237-238 °C (dec).

Solubility: insol most noncoordinating solvents; however, it becomes sol in benzene or chloroform in the presence of two equiv of donor agents such as ether, THF, triethylamine, or pyridine.

Form Supplied in: cream solid; readily available as a powder or as the 1,2-dimethoxyethane adduct, $CpZrCl_3$.DME.[4]

Preparative Methods: photoinduced chlorination of ***Dichlorobis(cyclopentadienyl)zirconium***.[1]

Purification: can be purified by vacuum sublimation.

Handling, Storage, and Precautions: solid material is moisture sensitive.

Catalyst for Alkene Polymerization.[2-4]

Trichloro(cyclopentadienyl)zirconium, along with methylaluminoxane (MAO) as co-catalyst, has been mainly used as a catalyst of alkene polymerizations in Ziegler-Natta type processes. Thus 1,5-hexadiene[2] (eq 1) and ethylene[3,4] undergo cyclopolymerization in the presence of $CpZrCl_3$/MAO.

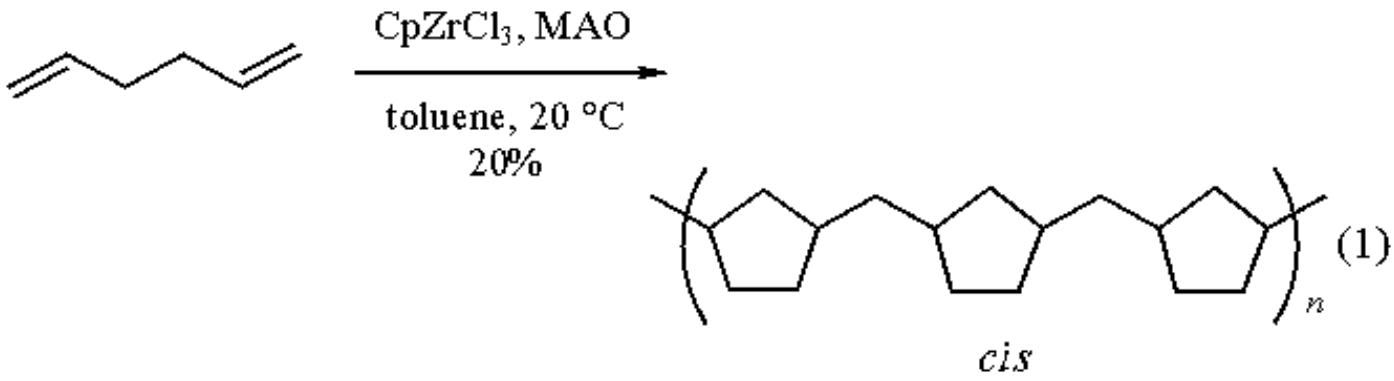

(1)

Precursor for the Synthesis of Other Organometallic Intermediates.

Other Zr-containing organometallic complexes can be synthesized from $CpZrCl_3$. Thus optically active (**1**) was prepared according to eq 2.[5]

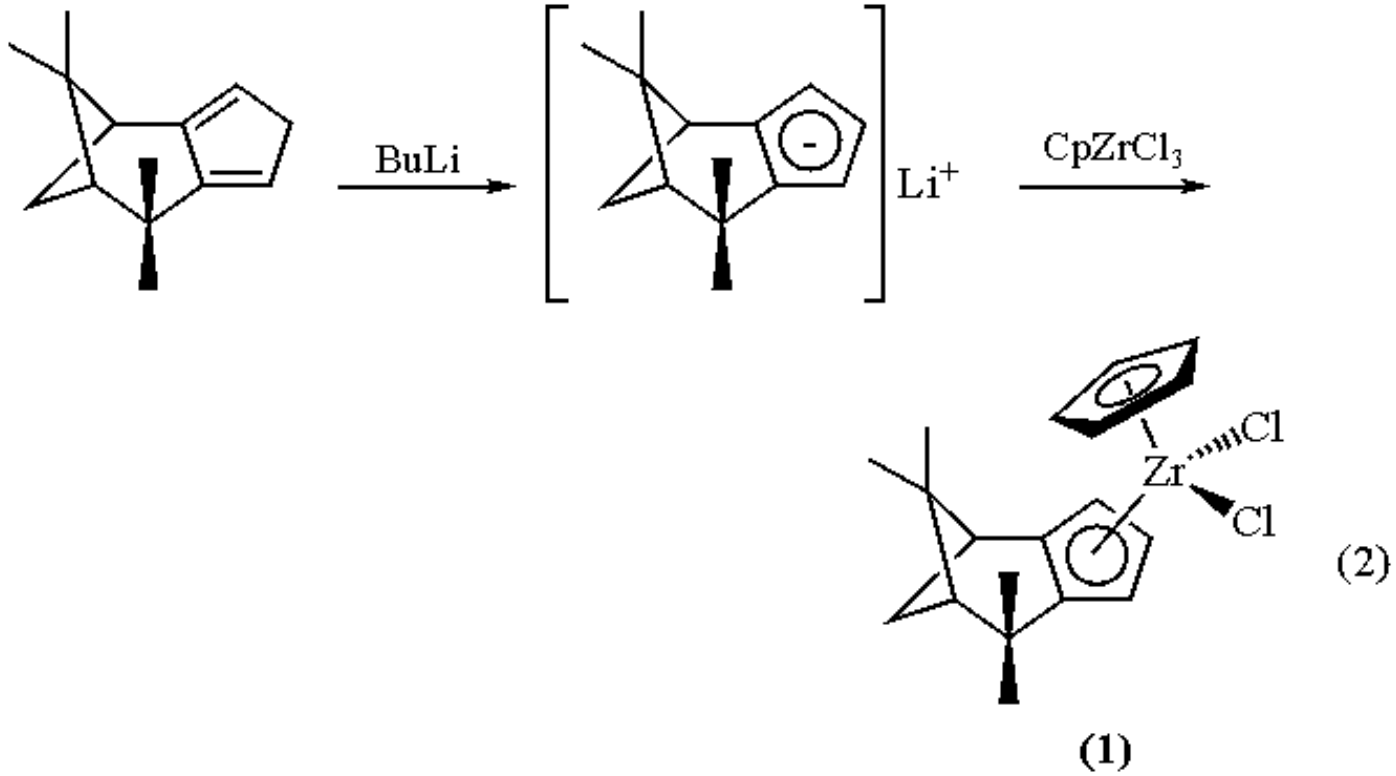

Similarly, an allyl-zirconium complex (**2**) was obtained as shown in eq 3.[6]

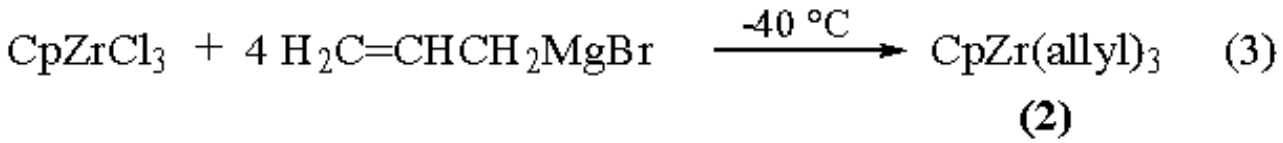

Related Reagents.

Trichloro(cyclopentadienyl)titanium.

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Trichloro(1,2-dimethoxyethane)niobium

$NbCl_3(DME)$

[110615-13-9] · $C_4H_{10}Cl_3NbO_2$ · Trichloro(1,2-dimethoxyethane)niobium · (MW 289.40)

(synthesis of 1,2-amino alcohols,[2] pyrroles,[3] 1,2-diols,[5] *cis*-alkenes, and naphthols[7])

Physical Data: mp 230 °C (dec).

Solubility: sol THF.

Preparative Methods: can be prepared according to the literature procedure,[1] or purchased from commercial sources. The best results are obtained with freshly prepared material.

Handling, Storage, and Precautions: all reactions and manipulations should be performed under nitrogen, either in a dry box or using standard Schlenk techniques. $NbCl_3(DME)$ is stable at room temperature when stored under an inert atmosphere.

Synthesis of 1,2-Amino Alcohols.[2]

Addition of an imine to $NbCl_3(DME)$ results in formation of a metallaaziridine, which is functionally the equivalent of a C,N dianion (eq 1). Subsequent addition of aldehydes or ketones to this intermediate, followed by hydrolysis, gives 1,2-amino alcohols. The yield of this reaction ranges from 33-97%, with *syn*-amino alcohols being obtained as the major diastereomer (Table 1). A wide variety of aldehydes are tolerated; however, nonenolizable imines generally give superior results.

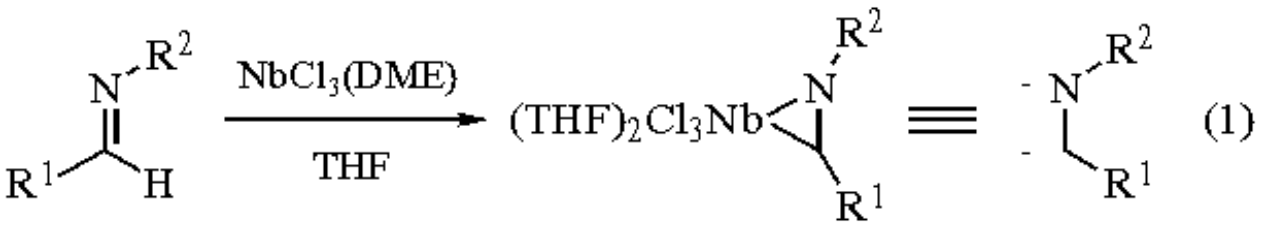

Table 1 Synthesis of 1,2-Amino Alcohols

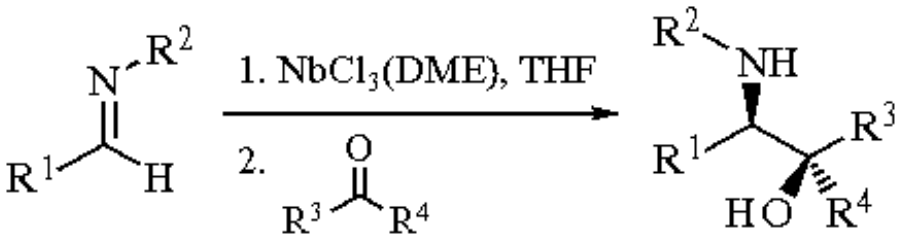

R^1	R^2	R^3	R^4	Yield (%)	ds[a]
Ph	$PhCH_2$	Et	Et	97	-
Ph	$PhCH_2$	*i*-Pr	Me	90	3:1
Ph	$PhCH_2$	CO_2Et	Me	82	3:1
Ph	$PhCH_2$	C_6H_{13}	H	69	4.5:1
Ph	Allyl	*i*-Pr	H	60	3:1
$PhCH_2CH_2$	Allyl	Et	Et	34	-

[a] ds represents *syn*:*anti* ratio.

Synthesis of Pyrroles.[3]

Pyrroles may be directly obtained from the reaction of α,β-unsaturated imines with $NbCl_3$(DME), followed by addition of either a primary ester or ***N,N-Dimethylformamide*** (Table 2). The niobium intermediate behaves like a homoenolate equivalent, condensing with the ester or formamide at the β-position. Following carbon-carbon bond formation, cyclization and dehydration occur to give the pyrrole. Aldehydes and ketones react with α,β-unsaturated imines and $NbCl_3$(DME) to give 2-aminotetrahydrofurans, which hydrolyze to lactols when chromatographed on silica gel.[4]

Table 2 Synthesis of Pyrroles

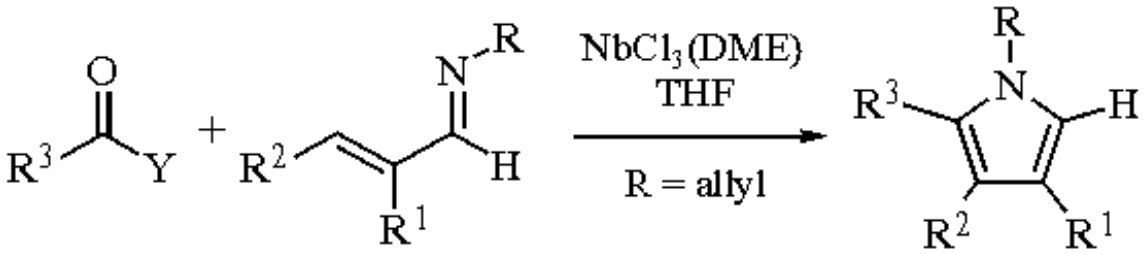

R^1	R^2	R^3	Y	Yield (%)
Me	Ph	Me	OEt	48
Me	Ph	H	NMe_2	58
Me	Ph	PhCH=CH	OMe	63
Me	Ph	CF_3	OMe	60
$-(CH_2)_3-$		H	NMe_2	47

Synthesis of 1,2-Diols.

Aldehydes can be converted to 1,2-diols in the presence of $NbCl_3$(DME), as shown for the coupling of benzaldehyde to (±)-stilbenediol in 78% yield (eq 2).[5] This reaction must be conducted at -10 °C in order to avoid acetalization of the product or reduction of the 1,2-diol to an alkene. Mixtures of products were obtained when unsymmetrical cross couplings of aldehydes were attempted.[6]

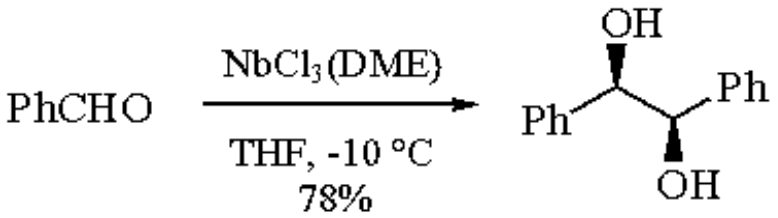

(2)

Synthesis of *cis*-Alkenes and Naphthols.[7]

$NbCl_3$(DME) reacts with internal alkynes to form alkyne complexes, which can be hydrolyzed with aqueous hydroxide to give *cis*-alkenes exclusively (eq 3). In contrast, reaction of $NbCl_3$(DME) with terminal alkynes yields cyclotrimerization products.

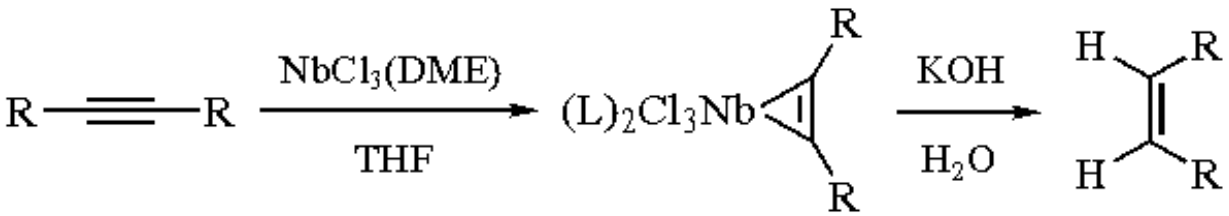

(3)

Niobium alkyne complexes are functionally equivalent to 1,2-dianions of *cis*-alkenes, and further reaction of these intermediates with benzene-1,2-dicarbaldehyde yields 2,3-disubstituted 1-naphthols (Table 3). The regioselectivity of these reactions appears to be influenced predominantly by steric factors. Alkynes substituted with *t*-Bu, TMS, or TBDMS groups, for example, give naphthols with the bulky group at the 3-position.

Table 3 Synthesis of 2,3-Disubstituted 1-Naphthols

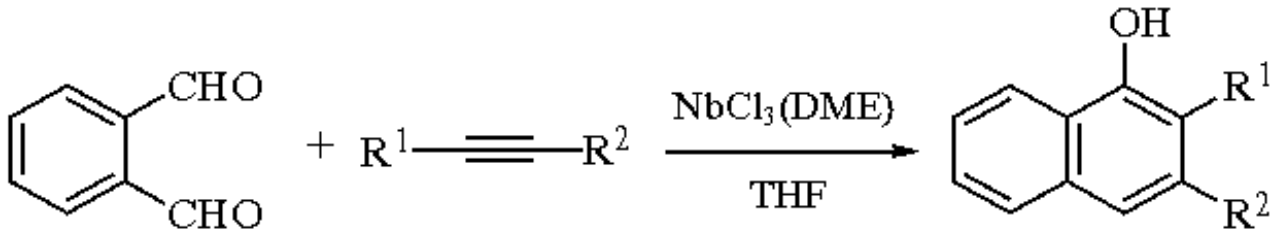

R^1	R^2	Yield (%)	Ratio[a]
Ph	Ph	87	-
Me	*i*-Pr	75	2:1
Me	*t*-Bu	60	>99:1
Me	TMS	70	>99:1
Ph	TBDMS	83	>99:1

[a] Major isomer shown. R^1 and R^2 are reversed in the minor isomer.

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6. Roskamp, E. J.; Pedersen, S. F. Unpublished results.
7. (a) Hartung, Jr., J. B.; Pedersen, S. F. *JACS* **1989**, *111*, 5468. (b) Hartung, Jr., J. B.; Pedersen, S. F. *OM* **1990**, *9*, 1414.

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2,2,2-Trichloroethanol

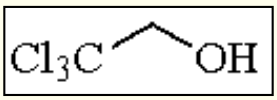

[115-20-8] · $C_2H_3Cl_3O$ · 2,2,2-Trichloroethanol · (MW 149.40)

(formation of 2,2,2-trichloroethyl esters and amides;[2] protection of phosphoryl groups in nucleotide synthesis[5])

Physical Data: mp 17 °C; bp 150 °C; *d* 1.557 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: clear liquid, widely available.

Handling, Storage, and Precautions: poisonous liquid when absorbed by intravenous or intraperitoneal routes. Do not mix with strong alkali solutions.[1]

2,2,2-Trichloroethyl Esters.

The 2,2,2-trichloroethyl moiety is a useful protecting group for acids since it is both formed and cleaved under very mild conditions (eq 1).[2] Woodward exploited the facile removal of this group in his classic synthesis of cephalasporin C (eq 2).[3]

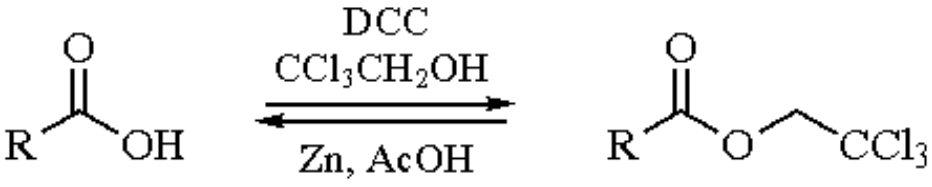

(1)

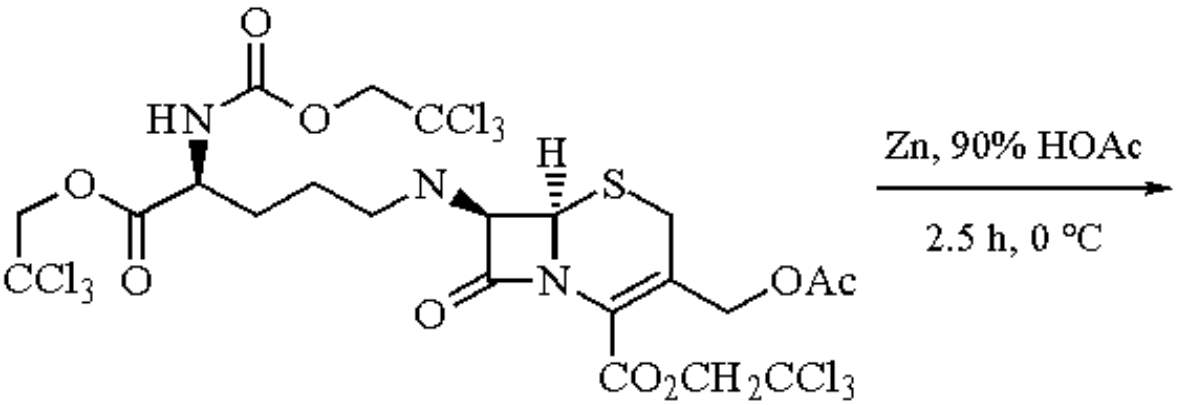

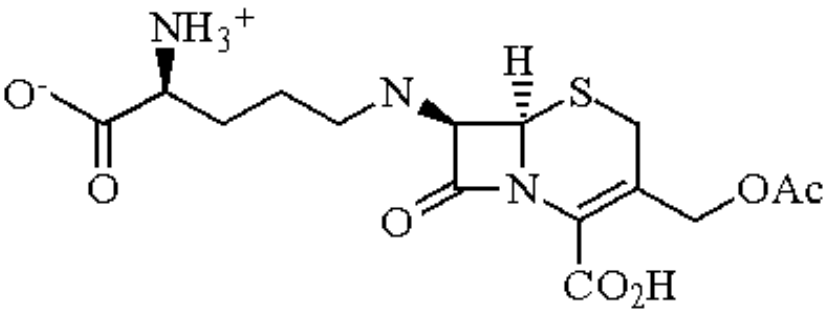

(2)

2,2,2-Trichloroethyl Acetals.

These acetals are most conveniently formed by exchange with dialkyl acetals. They are cleaved under conditions similar to the above esters (eq 3).[4]

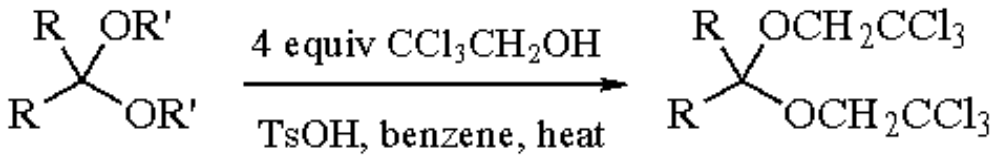

(3)

Nucleotide Synthesis.

In various instances the trichloroethyl group has been utilized in nucleotide chemistry for the protection of phosphoryl groups (eqs 4-6). In this seminal example the mononucleotide of thymidine-3´-*O*-acetate was formed.[5a] Selectively formed phosphotriesters have been converted to diesters under similarly mild conditions.[5] See also ***2,2,2-Trichloroethyl Phosphorodichloridate*** for related chemistry.

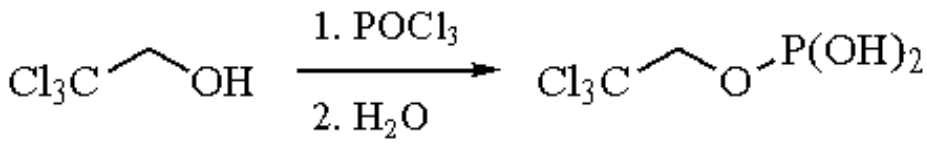

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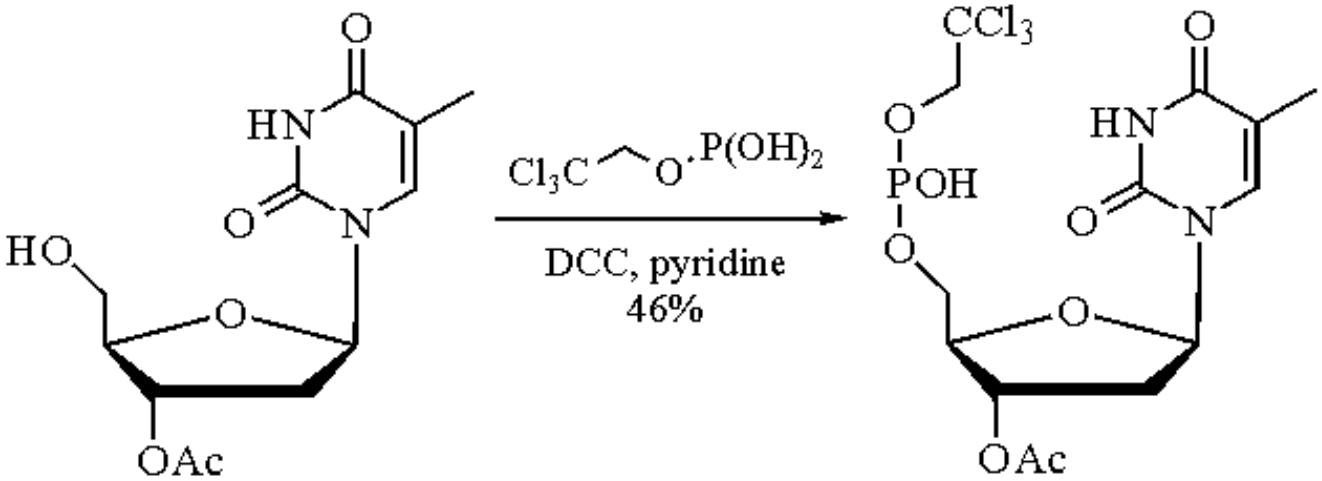

(5)

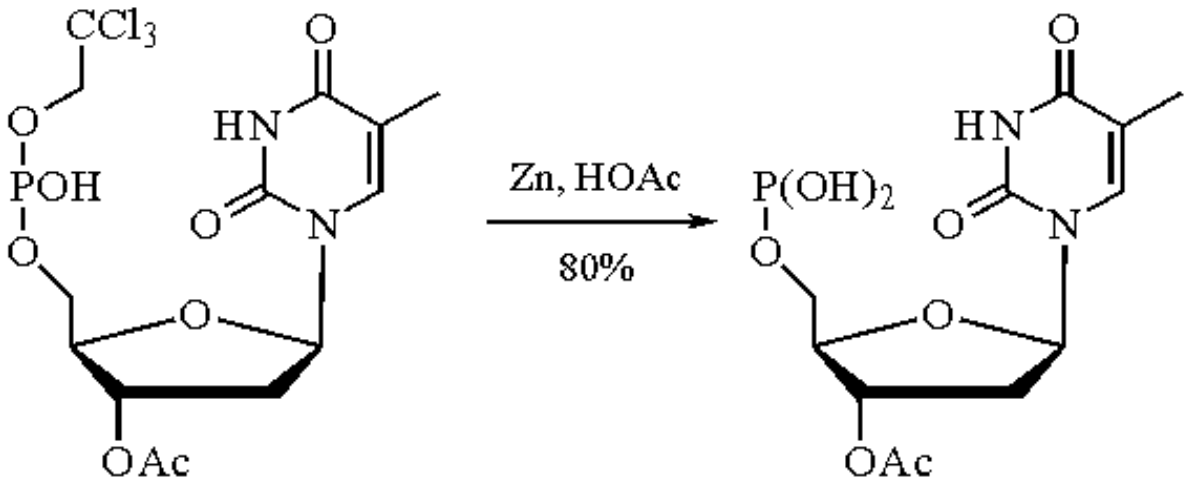

(6)

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2,2,2-Trichloroethyl *trans*-1,3-Butadiene-1-carbamate[1]

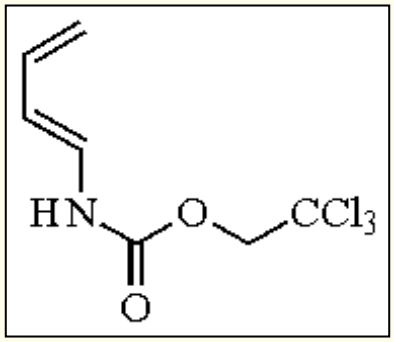

[77627-82-8] · $C_7H_8Cl_3NO_2$ · 2,2,2-Trichloroethyl *trans*-1,3-Butadiene-1-carbamate · (MW 244.51)

(a diene which provides regio- and stereoselective control in Diels-Alder reactions[1])

Physical Data: mp 70-71 °C; IR (KBr): cm^{-1} 3350, 1710, 1660, 1540, 710; ^1H NMR ($CDCl_3$): δ 7.0-5.3 (m), 5.2-4.8 (m), 4.68 (s); ^{13}C NMR: δ 150.7, 132.8, 124.9, 113.3, 112.7, 93.8, 73.5.[2]

Preparative Method: the synthesis of *trans*-1,3-butadienecarbamates utilizes a modified Curtius rearragement.[3,4] In the synthesis of 2,2,2-trichloroethyl *trans*-1,3-butadiene-1-carbamate, ***Malonic Acid*** and ***Acrolein*** were condensed in pyridine to obtain *trans*-2,4-pentadienoic acid in 44-51% yield (eq 1).[5] This compound, which may be stored in a freezer for several months,[4] was treated with ***Ethyl Chloroformate*** and the resulting mixed anhydride transformed into the azide derivative. Due to the explosive nature, the azide was not isolated but immediately added to a refluxing solution of ***2,2,2-Trichloroethanol*** in toluene. Purification by silica gel column chromatography (hexane-ethyl acetate = 9:1) then afforded the title compound.[4]

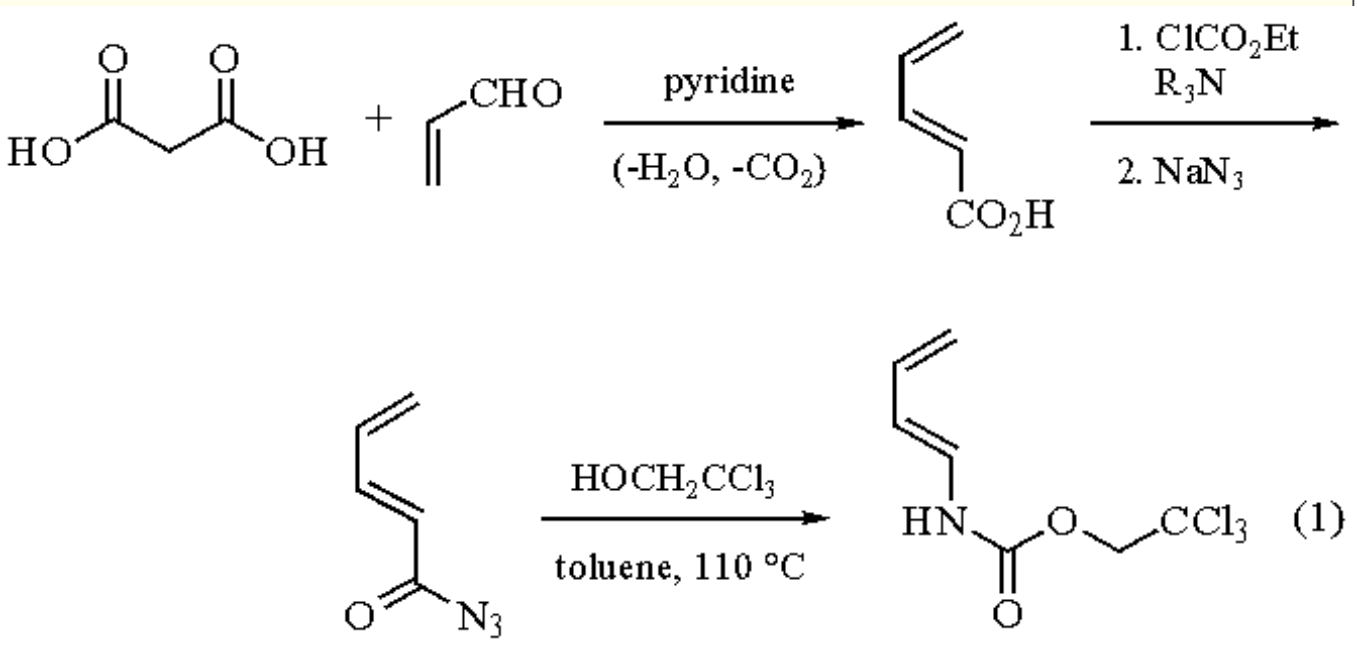

Diels-Alder Reactions.

2,2,2-Trichloroethyl *trans*-1,3-butadiene-1-carbamate, like the related *N*,*N*-dialkyl- and *N*-acyl-*N*-alkyl-1,3-dienes,[6-11] are masked dienamines for Diels-Alder reactions. The advantage of this reagent, however, is that it is thermally more stable than the *N*,*N*-dialkyl-1,3-dienes and, hence, capable of giving higher yields even with poor dienophiles.[1a,12] In addition, the carbamate protecting group is removed under relatively mild conditions (activated ***Zinc-Acetic Acid***, rt, 24 h), providing higher yields of the amine product (eq 2).[2] Like other 1,3-diene-1-carbamates,[13-15] the title compound also gives excellent regio- (*ortho*) and stereo- (*endo*) selectivity in Diels-Alder reactions.[2,12,16] Its reaction with ethyl

atropate, which gives exclusively a product possessing the acylamino and aryl groups in a *cis* orientation,[12] has been exploited in an elegant, stereospecific synthesis of (±)-tilidine (eq 2).[2] Noteworthy is the stereochemical outcome of this Diels-Alder reaction, which was opposite to that provided by the related *N*,*N*-dialkyl-1-amino-1,3-dienes.[1b,17]

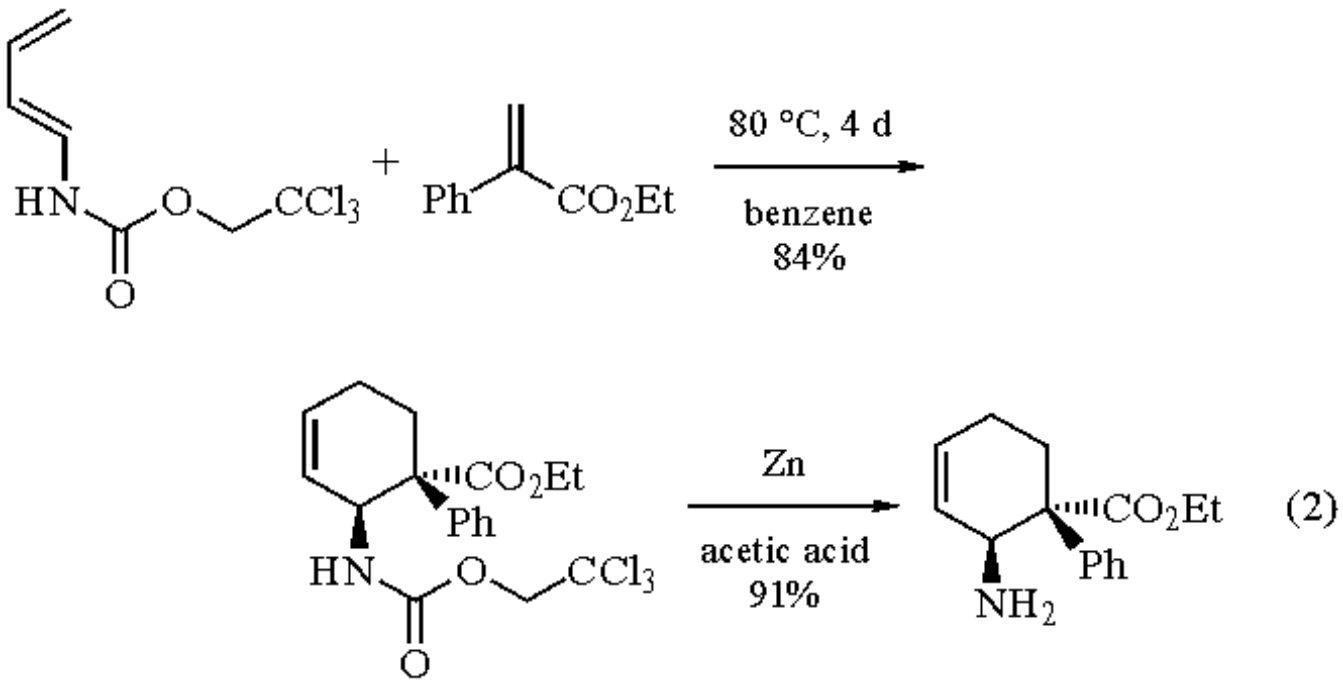

Related Reagents.

Benzyl 1,3-Butadiene-1-carbamate.

---

1. (a) Oppolzer, W. *COS* **1991**, *5*, 315. (b) Hickmott, P. *T* **1984**, *40*, 2989. (c) Overman, L. E. *ACR* **1980**, *13*, 218.
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17. Satzinger, G. *LA* **1969**, *728*, 64.

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2,2,2-Trichloroethyl Chloroformate

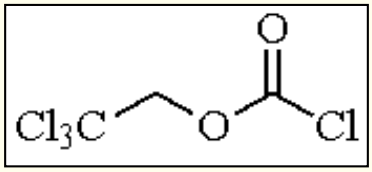

[17341-93-4] · $C_3H_2Cl_4O_2$ · 2,2,2-Trichloroethyl Chloroformate · (MW 211.85)

(protecting agent for many functional groups;[1-5] agent for the net carboxylation of organometallic reagents;[18] achieves the *N*-demethylation and *N*-debenzylation of tertiary amines;[19,20] activates N-heteroaromatic rings toward reaction with organostannanes[25-28])

Alternate Names: troc-Cl; Troc-Cl; TrOC-Cl; Teoc-Cl; TCEC-Cl.

Physical Data: colorless liquid, bp 171-172 °C/760 mmHg, 75-76 °C/60 mmHg; d^{25} 1.539 g cm^{-3}; *n*20D 1.4700.

Preparative Methods: widely available commercially. It can be readily prepared by passing ***Phosgene*** into a solution of ***2,2,2-Trichloroethanol*** in benzene/diethylaniline[1a] or benzene/ether/pyridine.[1b] An alternate two-step approach (93% yield) has been described that employs ***S-Ethyl Chlorothioformate*** instead of phosgene.[2]

Handling, Storage, and Precautions: highly toxic, lachrymatory, and corrosive; it should be handled with caution in a fume hood.

Functional Group Protection.

Alcohols,[1,3] phenols,[1,4] and thiols[5] are readily protected as their trichloroethyl (troc) carbonates/thiocarbonates using 2,2,2-trichloroethyl chlorofomate and ***Pyridine*** or pyridine/***4-Dimethylaminopyridine***. Chemoselective protection of the less crowded of two alcohols is possible (eq 1).[6] Electron-deficient alcohols[7] and thiols[8] (but not phenols)[9] are readily protected. Alkyl- and arylamines are protected as their *N*-troc-carbamate derivatives using troc-Cl/pyridine (eq 2)[1,10] or under Schotten-Baumann conditions.[1] α-Amino acids are typically *N*-troc-protected under Schotten-Baumann conditions (eq 3);[11] however, refluxing a suspension of the α-amino acid in EtOAc containing troc-Cl is reported to be more convenient and high yielding.[12] It should be noted that other reagents are more commonly employed for *N*-α-amino acid protection (see ***Benzyl Chloroformate***, ***t-Butyl Azidoformate***).

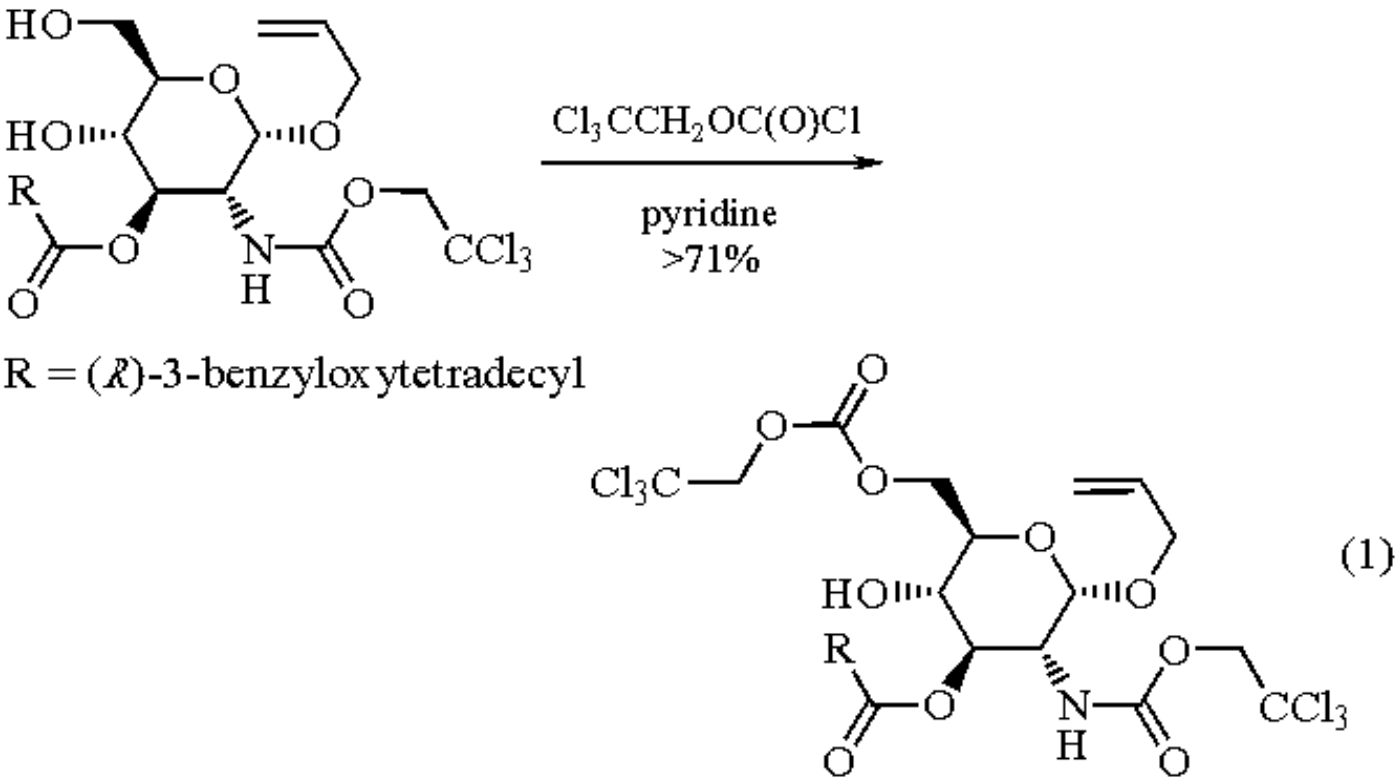

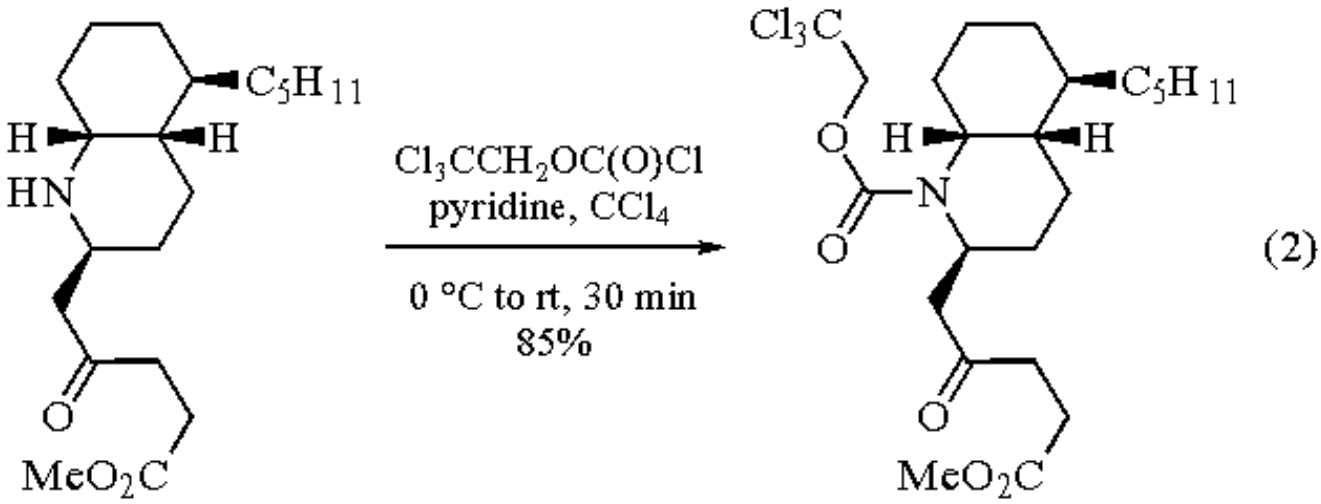

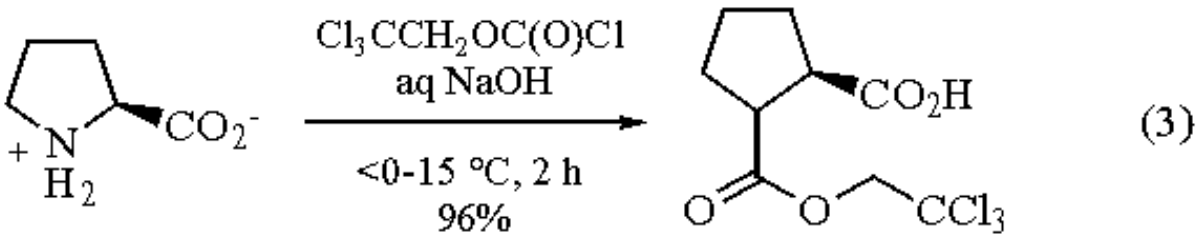

Protection of the usually recalcitrant aryl α-keto acids as their trichloroethyl esters can be achieved using troc-Cl under basic conditions (eq 4).[13] However, the efficiency of such reactions with other carboxylic acids is typically much below those using other chloroformates.[2,14] Both *O*- and *N*-troc-protecting groups are stable under a wide variety of reaction conditions;[1,15] deprotection is usually effected using ***Zinc-Acetic Acid***/rt,[1] or under milder conditions using Zn/MeOH/reflux[1] or Zn/THF-H_2O/pH 4.2/25 °C.[16] Troc-protected alcohols are cleaved ten times more slowly than the corresponding tribromoethyl carbonates (see ***2,2,2-Tribromoethyl Chloroformate***). Troc thiocarbonates can be deprotected to either the thiol or disulfide by electrolysis.[17] 2,2,2-Tribromoethyl esters are cleaved at significantly lower voltages than are needed for electrolytic cleavage of the corresponding trichloroethyl esters.

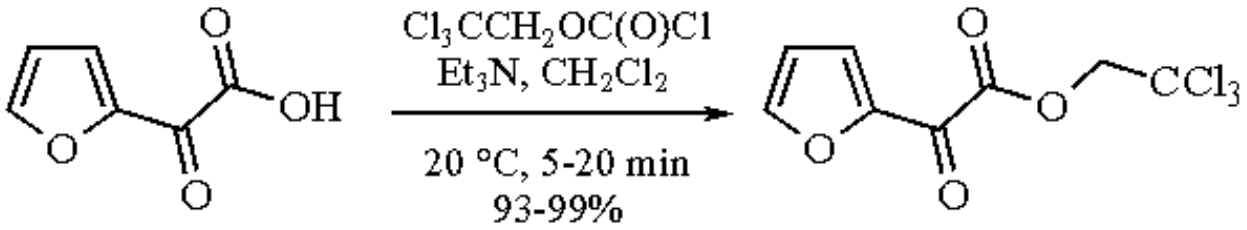

(4)

Carboxylation of Organometallic Reagents.

Troc-Cl has proved useful in the trichloroethoxycarbonylation of alkynyllithium[18] species, although analogous methoxycarbonylation reactions are much more common (see ***Methyl Chloroformate***.) The facile reductive cleavage of the resulting trichloroethyl ester to the corresponding carboxylic acid (see above) makes this an attractive overall *C*-carboxylation protocol.

N-Dealkylation of Tertiary Amines.

Tertiary amines can be readily *N*-demethylated using troc-Cl.[19,20] The common practice of adding mild base appears unnecessary and may actually promote unwanted side reactions.[20] Facile cleavage of the resulting *N*-troc carbamate to the free secondary amine is typically performed using Zn/HOAc,[19] although milder conditions have also proved useful.[16,21] This *N*-demethylation protocol is cleaner and more selective than the classical von Braun reaction (see ***Cyanogen Bromide***), avoids the strongly basic conditions required for the cleavage of carbamates derived from other chloroformates, and is compatible with a variety of sensitive functionalities.[19] The *N*-debenzylation of tertiary benzylamines using troc-Cl appears always to be favored over other *N*-dealkylation pathways (eq 5)[22] and is an attractive alternative to hydrogenolytic *N*-debenzylation. Selective *N*-deallylation is also often preferred over loss of a simple alkyl group,[22b] although steric encumbrance can reverse this trend.[23] The troc-Cl-mediated *N*-dealkylative removal of primary alkyl groups can be unreliable[24] and ***Vinyl Chloroformate*** should be considered for such conversions. In reactions of troc-Cl with tertiary cyclohexylamines bearing only simple *N*-alkyl substituents, deamination to the cyclohexene can compete effectively with *N*-dealkylative removal of a methyl or primary alkyl group.[22b]

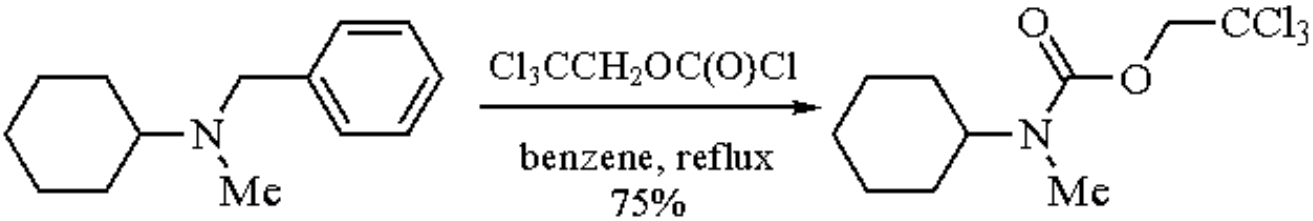

(5)

Activation of N-Heteroaromatic Rings Toward Reaction with Organostannanes.

Troc-Cl strongly activates pyridine toward regioselective 1,4-addition of prenyl[25] and benzylstannanes (eq 6),[26] while regioselective 1,2-addition is observed with ***Allyltributylstannane*** (eq 7).[27]

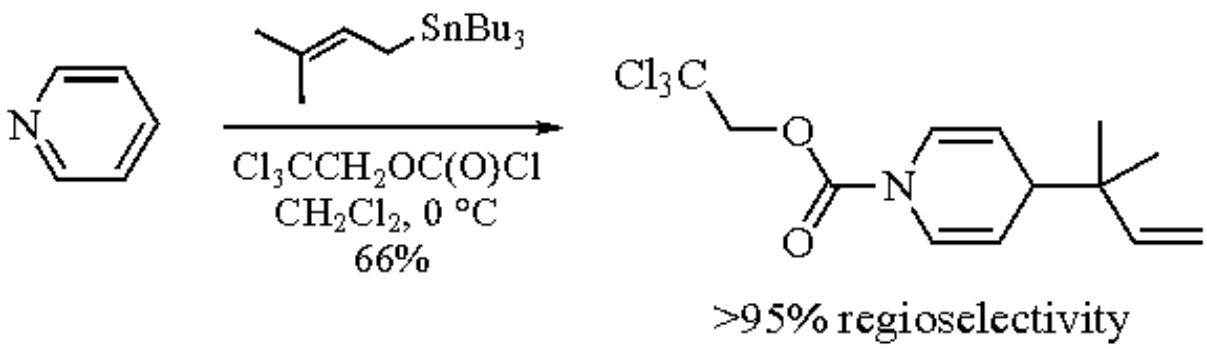

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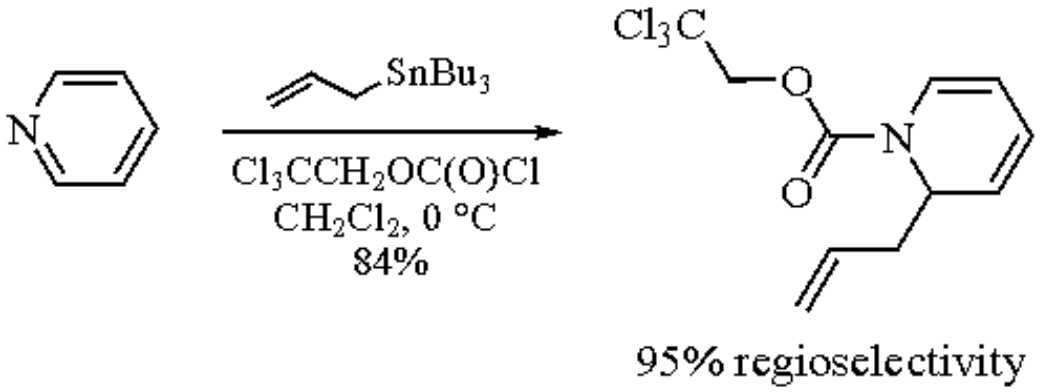

(7)

Quinoline and isoquinoline ring systems undergo selective 1,2-addition reactions with allenylstannanes.[28] Significantly higher yields are obtained when using troc-Cl rather than methyl chloroformate, due to better activation of the aromatic ring toward nucleophilic attack conferred by the strongly electron-withdrawing *N*-troc group.

---

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Trichloroethylene

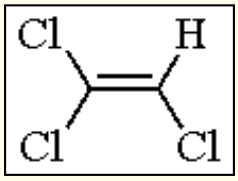

[79-01-6] · C_2HCl_3 · Trichloroethylene · (MW 131.38)

(starting material for the preparation of dichloroacetylene;[1-4] reagent for the preparation of alkynic ethers;[12] reagent for ethynylation and vinylation)

Alternate Name: trichloroethene.

Physical Data: bp 86.9 °C; *d* 1.464 g cm^{-3}.

Solubility: practically insol water; miscible with ether, alcohol, chloroform. *Drying:* can be dried by distillation from phosphorus pentoxide.

Handling, Storage, and Precautions: is slowly decomposed (with formation of HCl) by light in the presence of moisture. Avoid prolonged exposure to excessive heat. Moderate exposures to humans can cause symptoms similar to alcohol inebriation. Higher concentrations can have a narcotic effect. Deaths occurring after heavy exposure have been attributed to ventricular fibrillation. Found to induce hepatocellular carcinomas in mice. Dichloroacetylene (see below) is known to be toxic and, in its pure form, explosive. Use in a fume hood.

Preparation of Dichloroacetylene.

A dichloroacetylene-ether complex is readily prepared from trichloroethylene with ***Lithium Hexamethyldisilazide*** in hexanes at -78 °C[1] or with ***Potassium Hydride*** and catalytic methanol in THF at room temperature.[2] Alternatively, the dichloroacetylene-ether complex can be obtained from a mixture of trichloroethylene and diethyl ether in an aqueous solution of ***Sodium Hydroxide*** in the presence of either a phase transfer catalyst[3] or a catalytic amount of ***Dimethyl Sulfoxide***.[4]

Dichloroacetylene reacts with tertiary ketone or ester enolates to give chloroethynyl adducts in 64-90% yields.[5] The chloroethynyl group can be converted to the ethynyl derivative using ***Copper*** powder in HOAc/THF, or can be directly reduced (H_2/Lindlar catalyst) to the vinyl derivative (eq 1).[5] This method is limited to tertiary enolates.

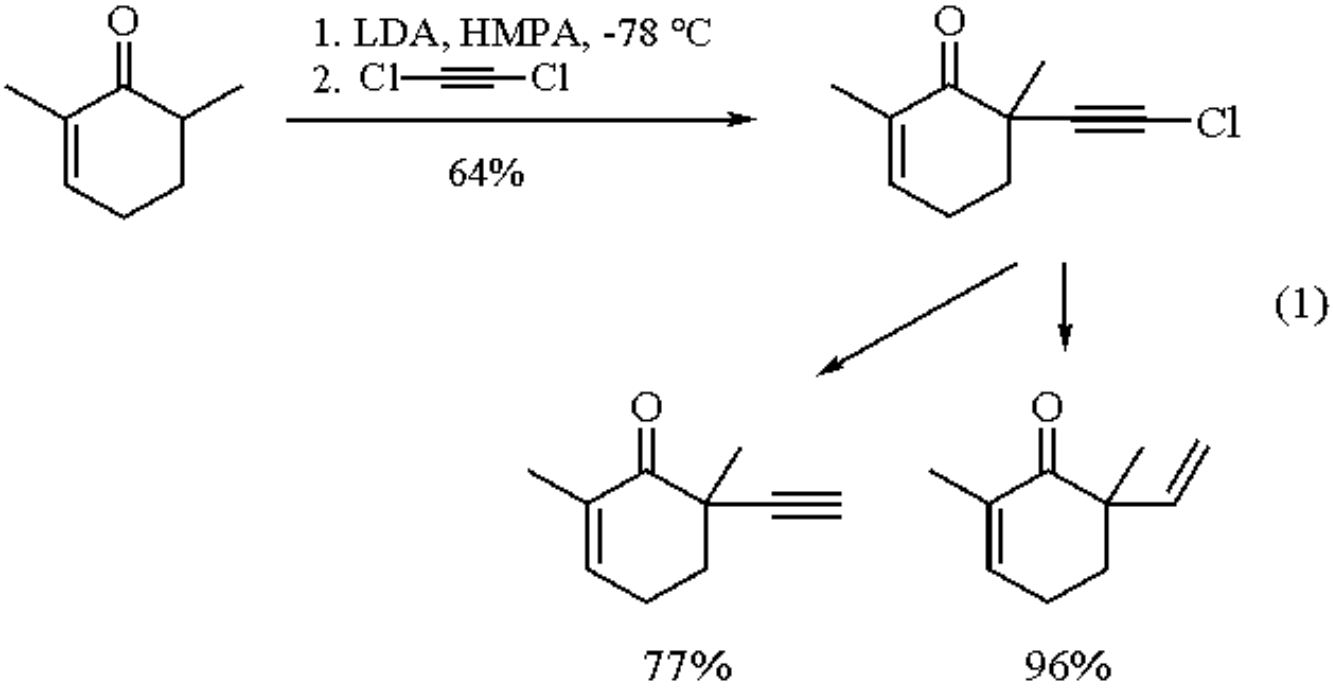

Additional enolate addition/elimination reactions with chloroacetylenes that yield alkynyl derivatives have been reported for ***1-Chloro-2-phenylacetylene***[5] and 1-chloro-2-phenylthioacetylene.[5] Similar alkynylations have been reported for tertiary β-dicarbonyl enolates using alkynyllead triacetates[6] or alkynyliodonium tetrafluoroborates.[7] Direct vinylations have been reported using alkenyllead triacetates,[8] vinyl halides and nickel catalysis,[9] or enol ether iron complexes.[10]

Dichloroacetylene reacts with alkylthiolates under mild conditions to yield bis(alkylthio)acetylenes (eq 2).[11]

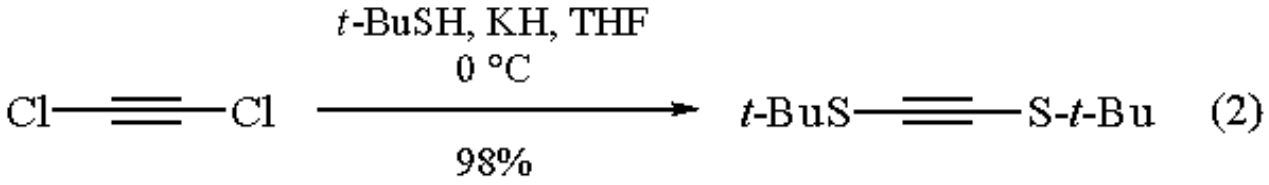

Preparation of Alkynic Ethers.

Secondary alcohols, on treatment in THF with 2 equiv of potassium hydride and trichloroethylene, followed by ***n-Butyllithium*** and a primary iodide (or water), are converted in 66-87% yield to alkynic ethers (eq 3).[12] The potassium alkoxides react with trichloroethylene first to generate and then to add to dichloroacetylene. The resulting dichloro enol ethers on treatment with *n*-butyllithium are converted to the corresponding acetylides, which are then either alkylated or protonated.

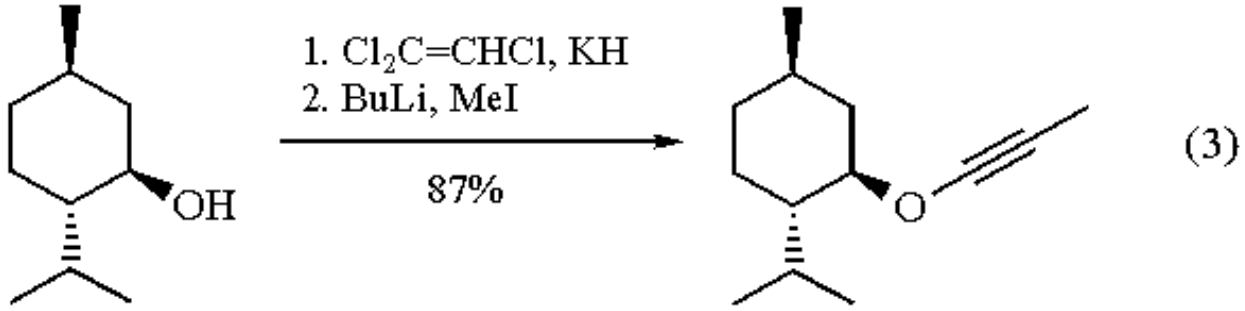

Reaction with Other Nucleophiles.

Trichloroethylene reacts with the enolate of 2,6-dimethylcyclohexenone (***Lithium Diisopropylamide***, HMPA, in THF, -78 °C) to yield the dichlorovinyl adduct (**1**) in 60% yield.[5,13] While the dichlorovinyl adduct may serve as a masked ethynyl group,[13] the reagent of choice is the independently generated dichloroacetylene described above. Under more vigorous conditions (***Sodium Hydride***, HMPA, refluxing THF) the tertiary enolate of diethyl ethylmalonate reacts to give dichlorovinyl adduct (**2**) in 64% yield.[5] These reactions have been demonstrated to proceed through the in situ generation of dichloroacetylene.[14] Comparable reactions have been reported for

CClF=CHCl,[5] CF_2=CHF,[15,16] CF_2=CH_2,[16] and ***Chlorotrifluoroethylene***.[16]

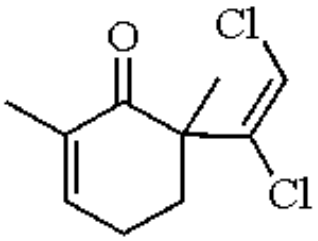

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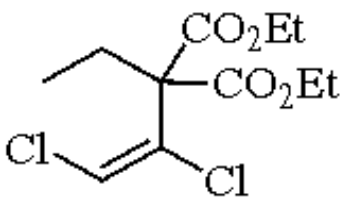

(2)

Trichloroethylene reacts with ***Sodium Amide*** and excess dimethylamine to yield bis(dimethylamino)acetylene (eq 4).[17] With lithium dialkylamides in ether as the base in the presence of excess dialkylamines, the intermediate 1,2-dichloro dialkyl enamines or chloro ketene aminals can be isolated (eq 5).[18] Trichloroethylene also reacts with secondary aliphatic amines in the presence of an aqueous solution of NaOH and a catalytic quantity of ***Benzyltriethylammonium Chloride*** to give glycinamides (eq 6).[19]

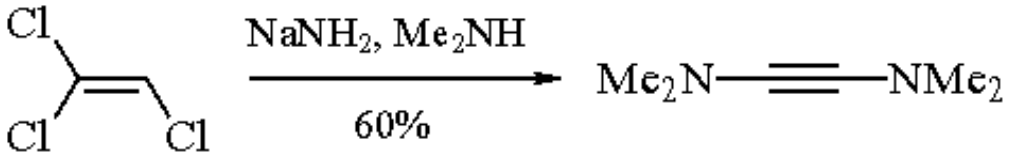

(4)

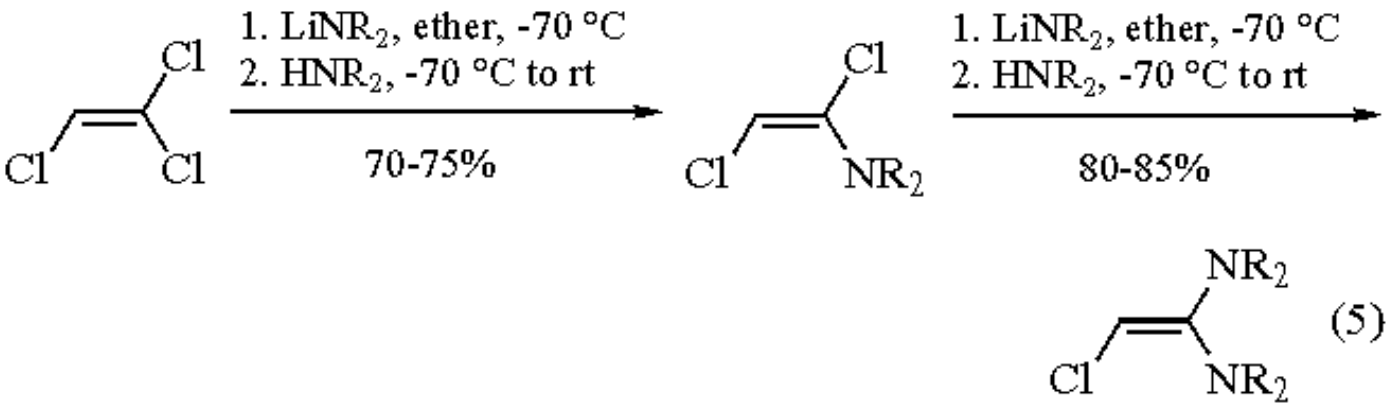

(5)

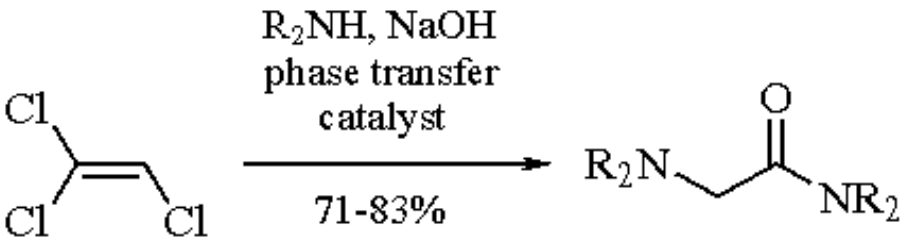

(6)

Trichloroethylene will undergo palladium-catalyzed coupling with arylmagnesium halides to yield (*Z*)-1,2-dichloroethylenes (eq 7).[20] Under alternate conditions with alkylmagnesium halides, 1,1-dichloroalkenes are obtained (eq 8).[21]

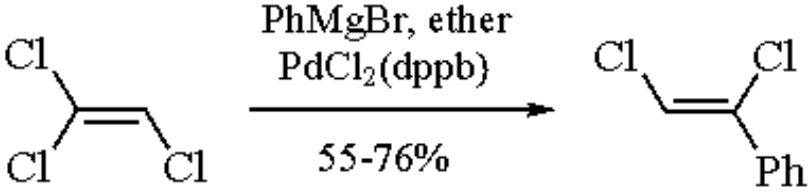

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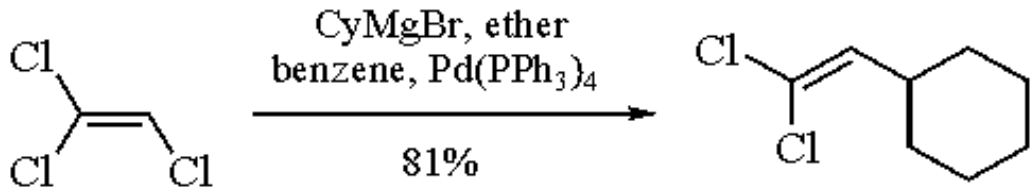

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2,2,2-Trichloroethyl Phosphorodichloridate

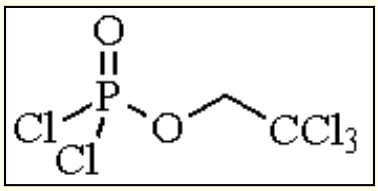

[18868-46-7] · $C_2H_2Cl_5O_2P$ · 2,2,2-Trichloroethyl Phosphorodichloridate · (MW 266.26)

(preparation of phospholipids via phosphotriester intermediates)

Physical Data: mp 28-30 °C.

Form Supplied in: white solid; commercially available.

Preparative Method: a solution of ***2,2,2-Trichloroethanol*** (1 equiv), ***Triethylamine*** (1 equiv) in THF is added to a solution of ***Phosphorus Oxychloride*** (1 equiv) at -70 °C.[1]

Preparation of Phospholipids.

2,2,2-Trichloroethyl phosphorodichloridate (**1**) is a convenient source of phosphate for the synthesis of oligonucleotides. The reaction of (**1**) with amines provides phosphoramidochloridates, which are reacted with glycerols to provide phosphotriesters. The amine and trichloroethanol protecting groups can be efficiently and selectively cleaved, providing phospholipids.

An example of this strategy is the reaction of (**1**) with aniline to provide the phosphoramidochloridate (**2**).[2] Reaction of phosphoramidochloridate (**2**) with 1,2-distearoylglycerol (**3**) afforded phosphotriester (**4**) (eq 1). Both protecting groups were selectively removed in subsequent steps.[3]

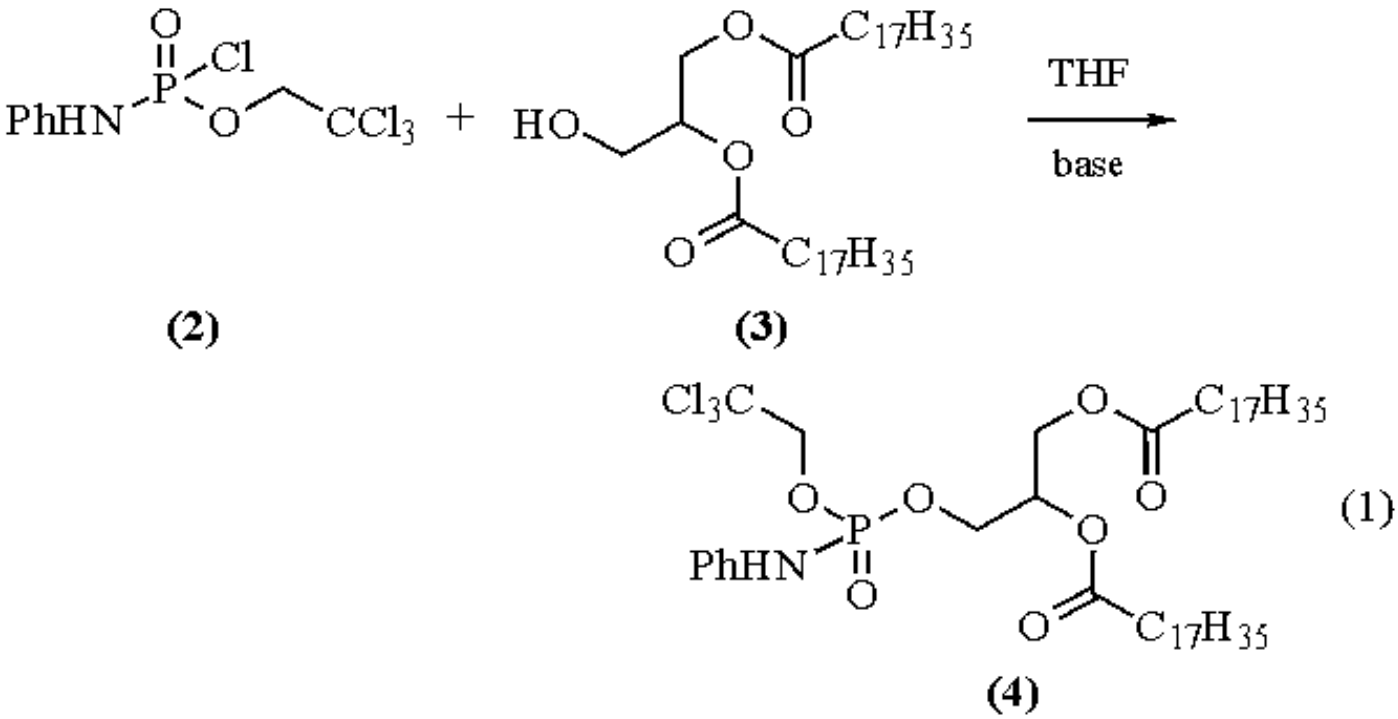

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3. For additional examples, see: (a) Lammers, J. G.; van Boom, J. H. *RTC* **1979**, *98*, 243. (b) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *CJC* **1978**, *56*, 2770. (c) Trigalo, M.; Charon, D.; Szabo, L. *JCS(P1)* **1988**, 2243.

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Trichloroiodosilane

Cl_3SiI

[13465-85-5] · Cl_3ISi · Trichloroiodosilane · (MW 261.34)

(selective ether-cleaving reagent;[1] also cleaves acetals;[1,2] mediates reaction of aromatic aldehydes with nitriles to yield secondary amides;[3] aromatic aldehydes and acrylonitrile give iminoaldehydes[4])

Physical Data: bp 114.5 °C/760 mmHg; mp <-60 °C.

Preparative Methods: prepared through halogen exchange by heating $SiCl_4$ and ***Sodium Iodide*** in methylene chloride-acetonitrile or toluene-acetonitrile.[1] It also has been prepared by the reaction of $SiCl_4$ and ***Hydrogen Iodide***,[5] by heating $SiHCl_3$ with ***Iodine***,[5] and by heating silicon with ICl.[6]

Handling, Storage, and Precautions: Cl_3SiI is a moisture-sensitive material; it could be conveniently used in situ. Use in a fume hood.

Ether Cleavage.

An important application of Cl_3SiI is in regiospecific and selective cleavage of alkyl-alkyl and alkyl-aryl ethers. Primary-secondary alkyl ethers are cleaved to yield primary alkyl iodide and secondary alcohol on workup. This cleavage pattern is opposite to that of boron halides like ***9-Bromo-9-borabicyclo[3.3.1]nonane***[7] and ***Boron Tribromide***,[8] which yield secondary bromide and primary alcohol (eq 1). Compared to ***Iodotrimethylsilane***, Cl_3SiI shows a greater degree of regiospecificity and slightly faster rate of reaction.[1]

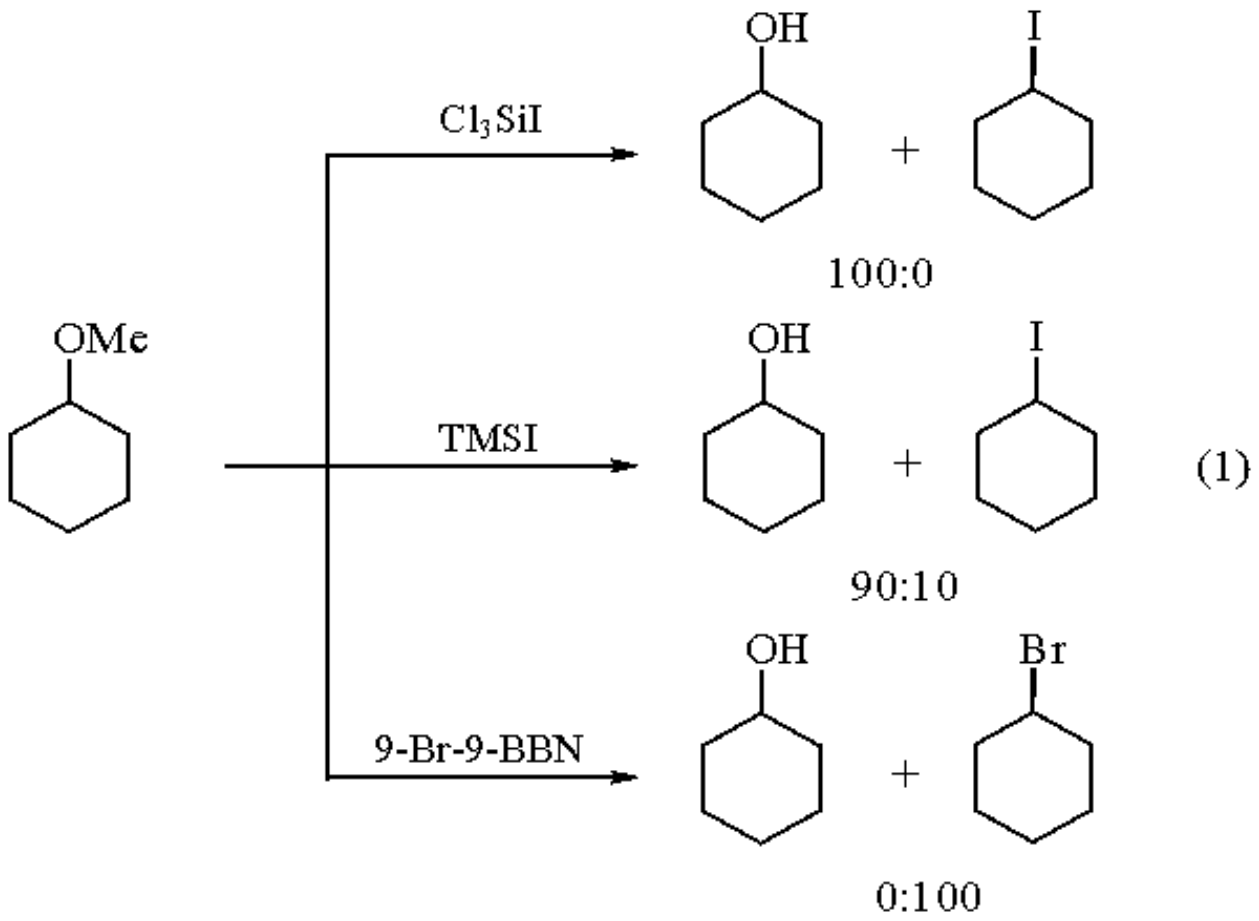

(1)

Selective cleavage of diethers is possible with this reagent (eq 2).

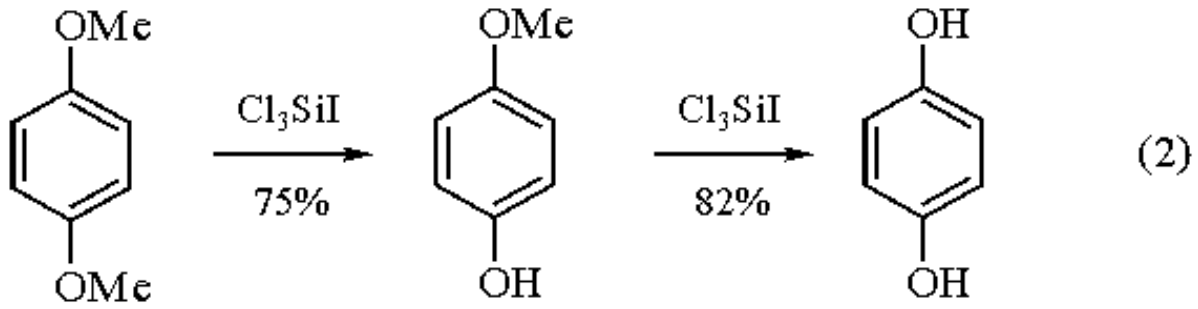

Miscellaneous Transformations.

Aromatic aldehydes and nitriles like ***Acetonitrile*** or benzonitrile are converted by Cl_3SiI to secondary amides, through a redox reaction (eq 3). When ***Acrylonitrile*** is used instead, the product is an imino aldehyde (eq 4).

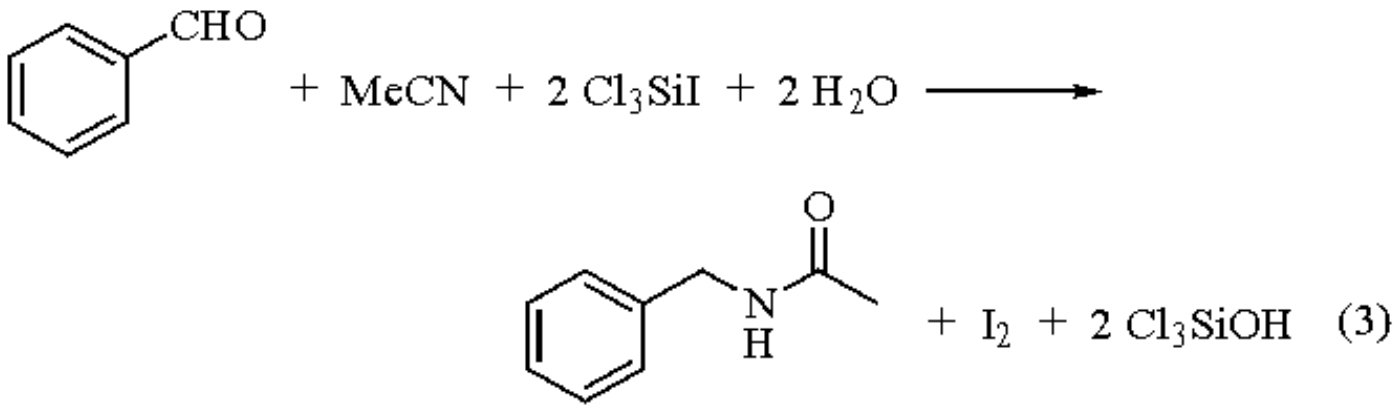

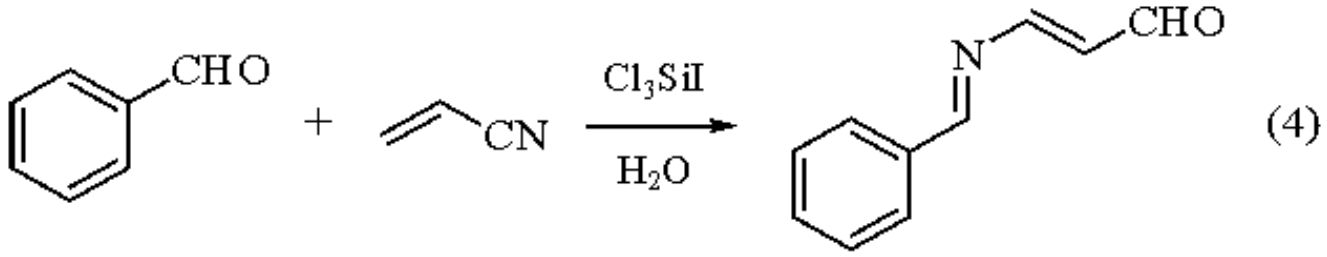

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Trichloroisocyanuric Acid[1]

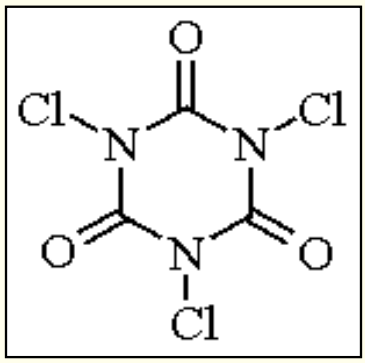

[87-90-1] · $C_3Cl_3N_3O_3$ · Trichloroisocyanuric Acid · (MW 232.41)

(powerful chlorinating agent for sulfides,[3,4] amides and imides,[5] aromatic compounds,[6] ketones,[7] and ethers;[8] oxidizing agent for secondary alcohols,[9] ethers,[10] alkenes,[11] and oximes[12])

Alternate Names: TCICA; 1,3,5-trichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione; trichloro-*s*-triazinetrione; isocyanuric chloride.

Physical Data: mp 249-251 °C.

Solubility: 0.2% in H_2O; very sol acetonitrile; sol acetone, acetic acid, ethyl acetate; sl sol benzene, chloroform, methylene chloride.

Form Supplied in: white granular solid; widely available for swimming pool use; purity 97-99%; available chlorine 88-91% as measured by iodometric titration.[2]

Analysis of Reagent Purity: mp or iodometric titration.

Purification: can be recrystallized from 1,2-dichloroethane or benzene.

Handling, Storage, and Precautions: moisture sensitive, but may be stored under nitrogen at rt for over a year. The dust is extremely destructive to mucous membranes and upper respiratory tract, eyes, and skin. This reagent has been reported to explode after a delay period when in contact with alcohols, amines, or dialkyl sulfoxides, or when contaminated with organic compounds. As with other strong oxidizing agents, it should be added to a solvent.

Chlorination Reactions.

Trichloroisocyanuric acid is an inexpensive, convenient, and effective chlorinating and oxidizing agent. It is more reactive than other *N*-chloro compounds and can often be used in place of chlorine. The cyanuric acid formed as a byproduct is easily removed by filtration.

Allyl phenyl sulfides are converted to 1-(phenylthio)-3-chloro-1-alkenes, which are acrolein synthons (eq 1).[3] Alkyl phenyl sulfides are dichlorinated to 1,1-dichloroalkyl phenyl sulfides.[4] In acetonitrile at rt, amides and imides are chlorinated at nitrogen.[5] Aromatic compounds are chlorinated on the ring or benzylic position.[6] Ketones are converted to α-chloro ketones[7] (see also ***Chlorine***, ***N-Chlorosuccinimide***, and ***Sulfuryl Chloride***). Dry cyclic ethers give 2,3-dichloro cyclic ethers.[8]

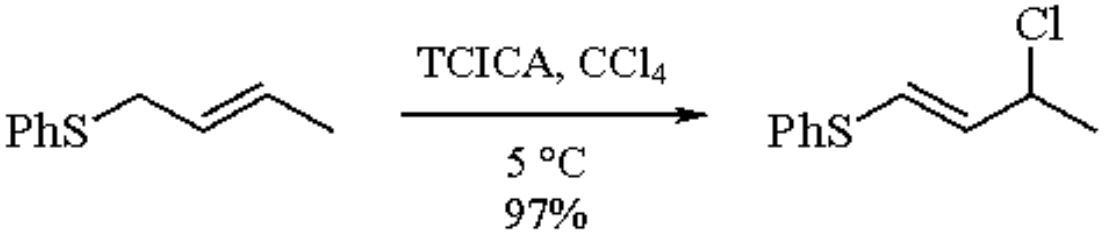

(1)

Oxidation Reactions.

Secondary alcohols are rapidly oxidized to ketones in acetone containing pyridine[9] (see also ***N-Bromosuccinimide***, ***N-Chlorosuccinimide***, ***Potassium Dichromate***, ***Potassium Permanganate***, ***Pyridinium Chlorochromate***, ***Sodium Dichromate***, and ***Sodium Hypochlorite***). Esters are formed by oxidation of ethers in the presence of water.[10] Alkenes react to form chlorohydrins in acetone containing acetic acid and water.[11] Oximes are converted to *gem*-chloronitro compounds (eq 2).[12]

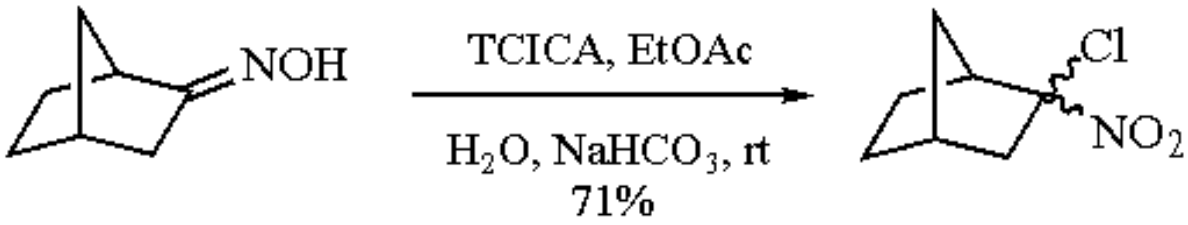

(2)

Other Applications.

N,N´-Disubstituted carbodiimides are produced on treatment of *N,N´*-disubstituted thioureas with trichloroisocyanuric acid in the presence of pyridine or aqueous NaOH.[13] Dithioacetals are converted to ketones by the action of trichloroisocyanuric acid and ***Silver(I) Nitrate*** in aqueous acetonitrile.[14]

---

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Trichloromethyl Chloroformate[1]

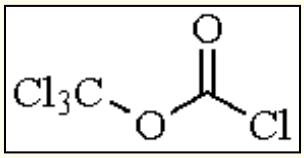

[503-38-8] · $C_2Cl_4O_2$ · Trichloromethyl Chloroformate · (MW 197.82)

(convenient substitute for phosgene; an effective reagent for the synthesis of isocyanates,[2] carbamoyl chlorides,[3] carboxylic acid chlorides,[4] *N*-carboxy-α-amino acid anhydrides,[5] chloroformates,[6] carbonates,[7] isocyanides,[8] nitriles,[9] and various heterocyclic compounds)

Alternate Names: diphosgene; TCF

Physical Data: bp 128 °C, 53-55 °C/53 mmHg; *d* 1.65 g cm^{-3}.

Solubility: sol most organic solvents, but insol water.

Form Supplied in: commercially available as a colorless liquid.

Analysis of Reagent Purity: IR (neat) 1815, 1054, 968, 912, 814, and 764 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 143.9 and 108.4.

Preparative Method: most conveniently prepared by photochlorination of methyl chloroformate.[10]

Purification: distillation at reduced pressure is recommended to avoid possible decomposition to phosgene which occurs at elevated temperatures.[10]

Handling, Storage, and Precautions: although the vapor pressure is low, care should be taken to handle this toxic compound, as in the case of phosgene.[11] It readily decomposes to phosgene in some cases, particularly rapidly on contact with activated charcoal or iron(III) oxide. It is best to store the reagent in a refrigerator to avoid spontaneous decomposition. The reagent should be used in a fume hood.

Carbonylation of Amines to Form Isocyanates.

Both aromatic and aliphatic primary amines (as the free amines or hydrochlorides) give the corresponding isocyanates on treatment with TCF. As in the case of other reactions of TCF, inert solvents such as THF, dioxane, dichloromethane, 1,2-dichloroethane, benzene, and toluene are commonly used. Phenyl isocyanate, for example, is prepared from aniline and 0.5 molar amount of TCF in dioxane (eq 1).[2] In a similar manner, diisocyanates are readily derived from diamines.

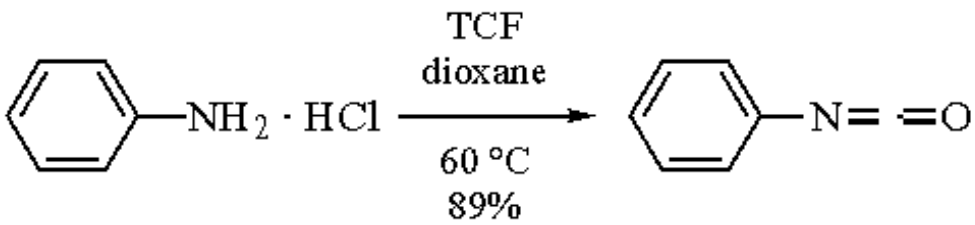

(1)

Various kinds of isocyanates are prepared from esters of α-amino acids by heating with TCF in toluene in the presence of activated charcoal, which promotes the decomposition of TCF to phosgene. Use of amine hydrochlorides may be effective to avoid the formation of 1,3-disubstituted ureas.[12]

Secondary amines give carbamoyl chlorides, as exemplified by the formation of bis(2-chloroethyl)carbamoyl chloride.[3] Monochloroformylation takes place with a urea (eq 2).[13] TCF is also useful for synthesizing various kinds of heterocycles including cyclic ureas,[14] pyrazolooxadiazines,[15] and oxadiazolinones[16] from amine derivatives.

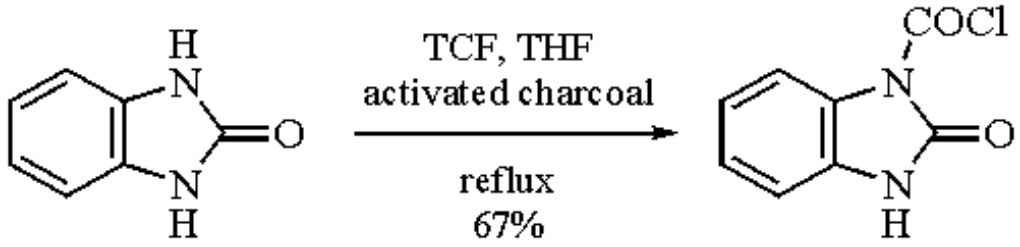

(2)

Synthesis of Acid Chlorides.

Carboxylic acids are easily converted into acid chlorides by the action of TCF. Benzoic acid gives benzoyl chloride when heated with TCF.[4] Treatment of amino acids with TCF results in the formation of isocyanato acid chlorides. 3-Aminopropanoic acid, for example, gives 3-isocyanatopropanoyl chloride (eq 3).[2,10] 2-Isocyanatobenzoyl chloride is prepared similarly from anthranilic acid in 85% yield in the presence of ***Phosphorus(V) Chloride***,[2] although anthranilic acid and the pyridine analogs are cyclized to anhydrides by TCF quantitatively in the absence of PCl_5 (eq 4).[2,17]

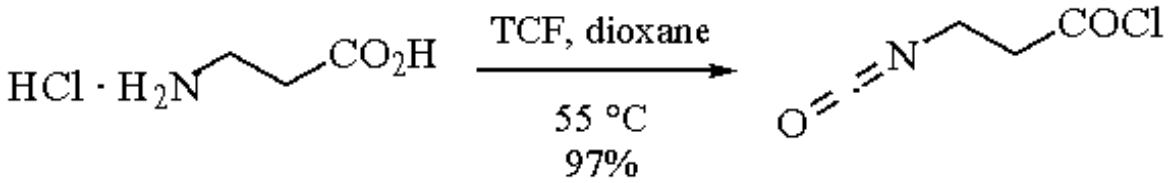

(3)

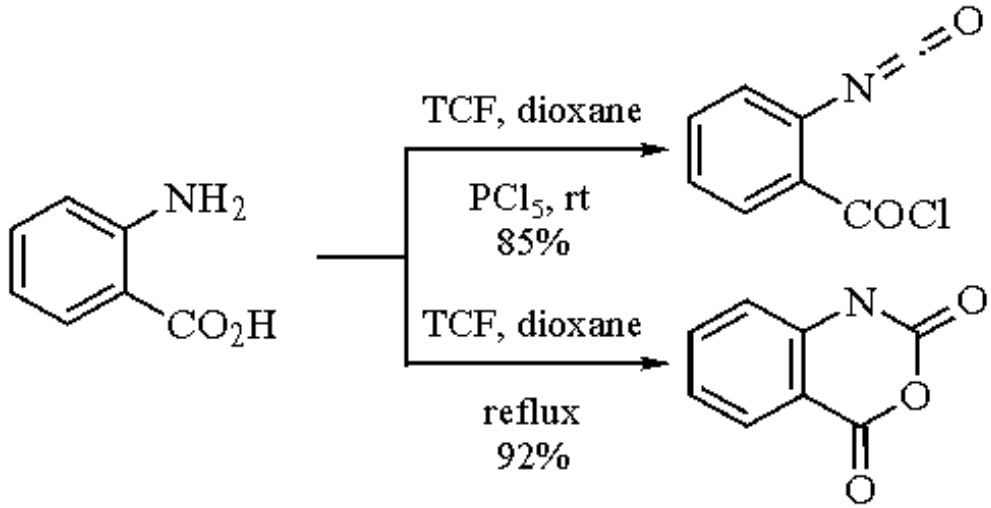

(4)

Synthesis of *N*-Carboxy-α-amino Acid Anhydrides (NCAs) from α-Amino Acids.

Various α-amino acids afford NCAs on treatment with TCF in an appropriate solvent such as THF, and addition of activated charcoal has been suggested to improve the synthesis (eq 5).[5] The reactions, however, proceed smoothly in some cases in the absence of activated charcoal, as evidenced by the quantitative formation of NCAs. Starting from L-glutamic acid, a seven-membered γ-NCA is produced instead of the ordinary five-membered NCAs.[18]

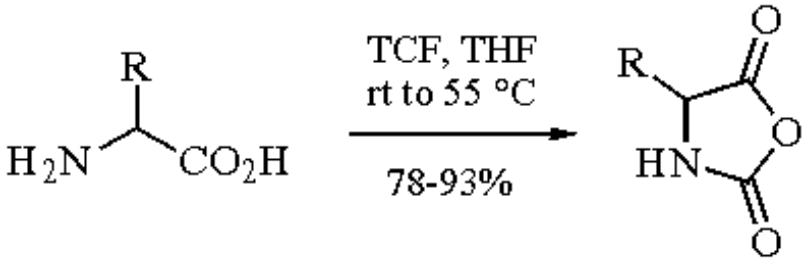

(5)

Synthesis of Chloroformates and Carbonates from Alcohols.

Chloroformates are readily prepared from aromatic or aliphatic alcohols and TCF in high yields.[19] *N*-Hydroxyphthalimide is also converted into the chloroformate quantitatively.[6]

Depending on the reaction conditions (particularly in aqueous alkali solution), however, symmetric carbonates are obtained.[7] When bisphenols in aqueous alkali are treated with TCF in 1,2-dichloroethane in the presence of a phase-transfer catalyst, polycarbonates can be synthesized.[20]

Both 1,2- and 1,3-diols favorably cyclize with TCF to form carbonates. For instance, methyl α-L-rhamnoside gives a five-membered cyclic carbonate almost quantitatively with TCF in pyridine (eq 6).[21] Similarly, 1,3-diols form six-membered cyclic carbonates.[22]

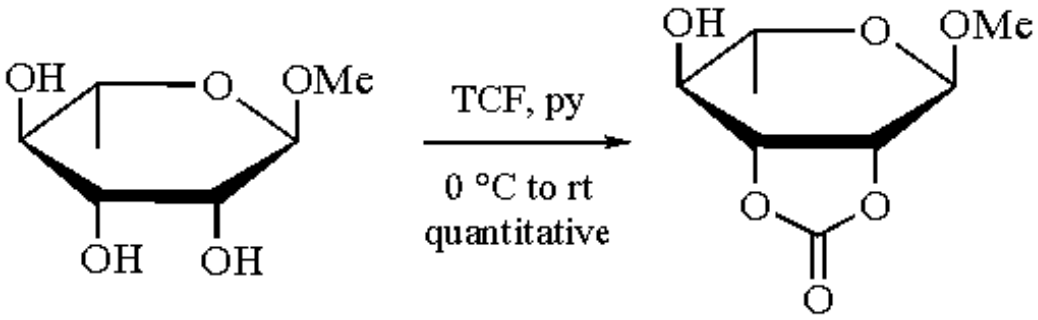

(6)

When 2-aminoethanol and 3-aminopropanol are treated with TCF in dioxane, isocyanato chloroformates are synthesized. In the reaction with 2-aminoethanol at 55 °C, however, a cyclic carbamate, 2-oxazolidinone, is also obtained as a minor product.[2] Amino alcohols, prepared by reducing α-amino acids, are converted into oxazolidinones efficiently at -15 °C (eq 7).[23] 2-Aminobenzyl alcohol gives rise to a six-membered cyclic carbamate in a similar way.[24]

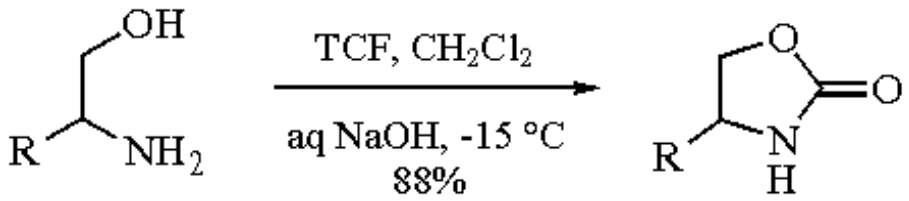

(7)

Dehydration of Formamides and Amides to Isocyanides and Nitriles.

Dehydration of *N*-alkyl- or *N*-arylformamides with TCF or phosgene is an effective way to synthesize isocyanides (eq 8), and the yields are generally higher with TCF than with phosgene, as shown in Table 1.[8]

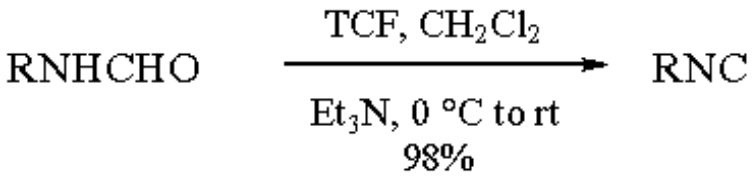

(8)

Table 1 Synthesis of Isocyanides (RNC) from Formamides (RNHCHO)

R	Yield (%) with TCF	Yield (%) with phosgene
t-Bu	97	82
Cy	98	88
Bn	95	82
4-$MeOC_6H_4$	95	64

Aromatic diisocyanides can be synthesized in a similar manner.[25] In the preparation of unstable diisocyanides such as *o*-diisocyanobenzene, however, the reaction should be carried out at low temperatures, and the yield is improved to 92% by starting at -78 °C from 26% at rt.[26]

Both aromatic and aliphatic amides are dehydrated with TCF in ***Trimethyl Phosphate*** to give nitriles in high yields (eq 9).[9] This preparative procedure is superior to the conventional transformation carried out with ***p-Toluenesulfonyl Chloride*** in pyridine.

$$RCONH_2 \xrightarrow[\text{0-60 °C, 97\%}]{\text{TCF, } (MeO)_3PO} RCN \qquad (9)$$

Miscellaneous Reactions.

In the Swern oxidation using the combination ***Dimethyl Sulfoxide-Oxalyl Chloride***, the latter may be replaced by TCF to facilitate the reaction. Various aldehydes and ketones are thus synthesized from primary and secondary alcohols in moderate to high yields.[27]

Direct introduction of a chloroformyl group is possible by heating acid chlorides with TCF at 225 °C. 2-Methylpropanoyl chloride, for example, affords dimethylmalonyl chloride in 70% yield. Cyclohexanecarbonyl chloride gives 1,1-cyclohexanedicarboxylic acid in 81% yield by treating with TCF followed by hydrolysis.[28] Some alcohols, including benzyl and *t*-butyl alcohols, are transformed into the corresponding chlorides by chlorination with TCF.[2,29]

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Trichloromethylisocyanide Dichloride[1]

$Cl_3C\text{-}N{=}CCl_2$

[29164-55-4] · C_2Cl_5N · Trichloromethylisocyanide Dichloride · (MW 215.28)

(strong chlorinating agent; used as a reagent in forming heterocycles and dehydrating amides[1,2])

Physical Data: bp 59-60 °C/12 mmHg; *d* 1.698 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: liquid; must be synthesized.

Preparative Methods: synthesized by chlorinating triethylamine hydrochloride (in low yields)[5] and, in better yields, with *N,N*-dimethylcarbamoyl chloride (**1**) at 250 °C (eq 1).[5,6]

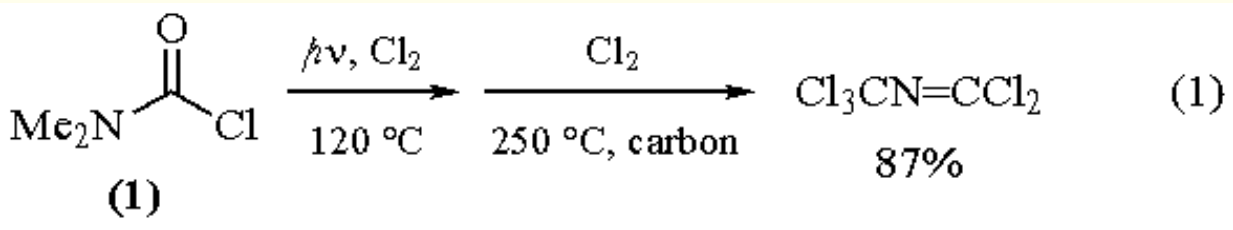

Purification: redistil under reduced pressure.[3]

Handling, Storage, and Precautions: corrosive; moisture and air sensitive. Store under an inert atmosphere (see Aldrich safety index for phosphorus pentachloride[4]).

Chlorination of Functional Groups.

Trichloromethylisocyanide dichloride has been extensively used for the chlorination of functional groups.[1] Alcohols, carboxylic and sulfonic acids, aldehydes, and phosphorus pentasulphide are converted to alkyl chlorides (**2**), acid and sulfonic chlorides (**3**,**4**), alkyl dichlorides (**5**), and phosphorus thiochloride (**6**),[7] respectively (eqs 2-6).

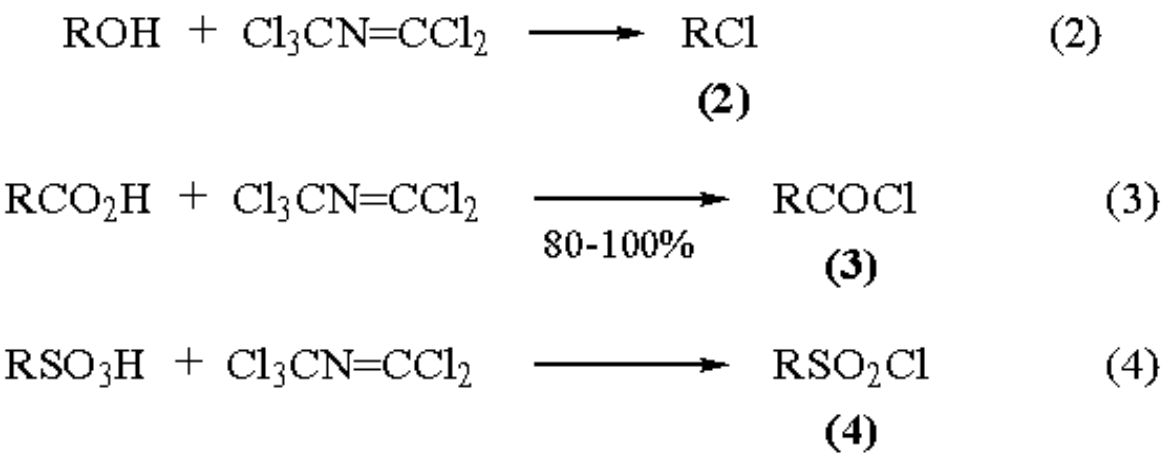

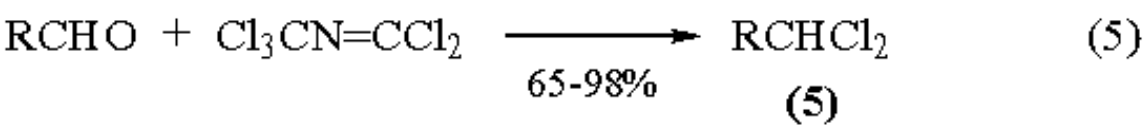

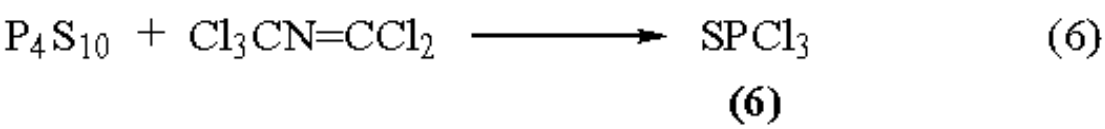

Synthesis of Heterocycles.

Various heterocycles have been synthesized using trichloromethylisocyanide dichloride, normally involving a double nucleophilic attack from various substrates such as nitriles,[8] hydrazines,[9] and aromatic amines[10] (eqs 7-10).

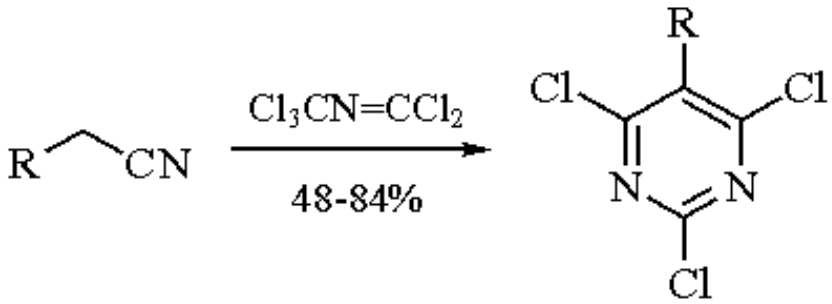

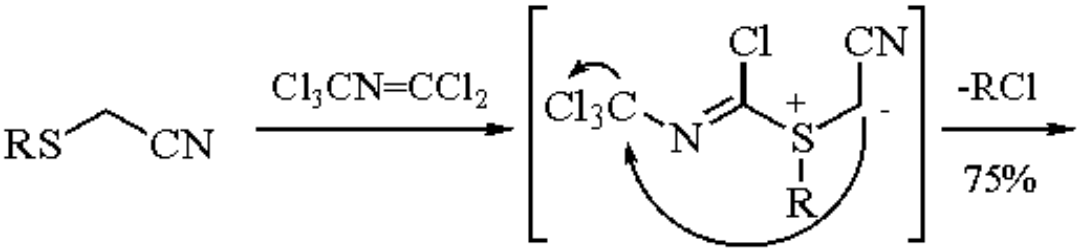

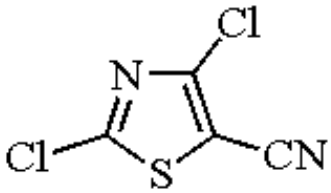

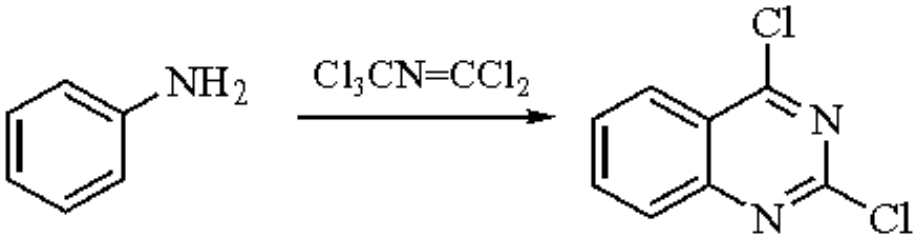

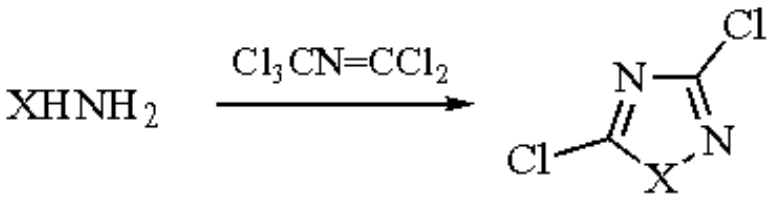

X = NR; O, 90%

Heterocycles have also been formed by activating a carboxylic acid or amide towards cyclization with an amide by using trichloromethylisocyanide dichloride (eq 11).[1]

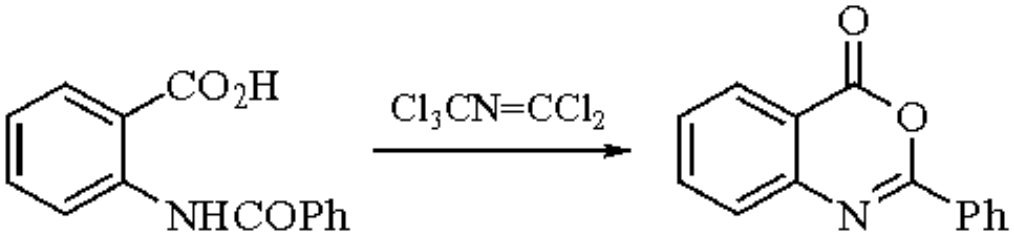

(11)

Dehydration of Amides.

Trichloromethylisocyanide dichloride has also been used to dehydrate amides in good yields (eq 12).[1]

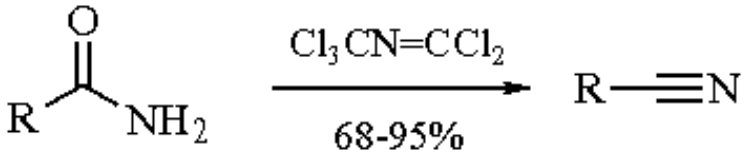

(12)

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Trichloromethyllithium

Li-CCl_3

[2146-66-9] · CCl_3Li · Trichloromethyllithium · (MW 125.30)

(dichlorocyclopropanation and for nucleophilic trichloromethylation)

Physical Data: low-temperature ^{13}C and ^{6}Li NMR data are available,[1] as are matrix IR data.[2]

Preparative Methods: solutions of the title compound can be obtained by treatment of ***Chloroform*** with ***n-Butyllithium*** in THF/ether/pentane (4:1:1) or ether/pentane (1:1) at -110 °C for 20 min.[3] Alternatively, CCl_4 or $BrCCl_3$ may be treated with ***Methyllithium*** or *n*-BuLi in THF/ether/petroleum ether mixtures at -110 °C.[4] The TMEDA complex with $LiCCl_3$ can be prepared by reaction of either $CHCl_3$ or $BrCCl_3$ with the *n*-BuLi.TMEDA complex in isopentane at -108 °C.[5] Deprotonation of $CHCl_3$ with lithium dimethylamide in THF/HMPA at -105 °C does not proceed cleanly.[6]

Handling, Storage, and Precautions: generally stable from -110 °C to about -80 °C, depending on the solvent. There is evidence that carbenoids of this nature show greater thermal stability in THF than in ether.[7] At -70 °C, solutions turn from clear to dark brown with a dark brown-black precipitate. Isolation of the decomposition products reveals what appear to be carbene-derived compounds.[3b] In contrast, the TMEDA complex is stable above -80 °C and decomposes to a brown-black solid material at -60 °C. When the reagent is generated in the presence of LiBr, a rapid exchange to give Li-$CBrCl_2$ occurs.[4b] The reagent is probably best generated from lithium halide-free solutions of alkyllithiums.

General Considerations.

Alkyllithiums bearing halogens on the α-carbon are frequently referred to as carbenoids, reflecting a major mode of reactivity. Good general reviews of such species are available.[8] At very low temperatures, however, the reagent reacts like a typical alkyllithium. The accumulated data suggest that there may be more than one isomeric form of $LiCCl_3$. In solution a C-Li structure is present, as shown by the observation of Li-C *J* coupling in the ^{13}C NMR spectrum.[3a] A calculational study suggests that the reagent may also exist as the rather unusual triply bridged species (**1**).[9] It should be noted that Li-CCl_3 has been studied much more intently than the analogous Li-CBr_3, perhaps due to the greater thermal stability of the former. However, the reagents are not analogous in all of their reactions.

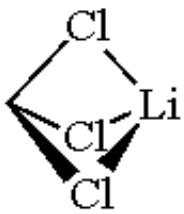

(1)

Cyclopropanations.

Formal loss of LiCl from Li-CCl_3 would provide dichlorocarbene and, indeed, when alkenes are added to solutions of Li-CCl_3 at around -70 °C, rapid reaction occurs resulting in dichlorocyclopropanes.[3c,4b,10,11] Alkene geometry is maintained in these reactions. The situation appears to involve conversion to **:**CCl_2 and subsequent cyclopropanation.[12] The TMEDA.$LiCCl_3$ complex is more stable in the presence of alkenes and gives dichlorocyclopropanes only slowly at -78 °C, requiring extended periods of time (eq 1).[13]

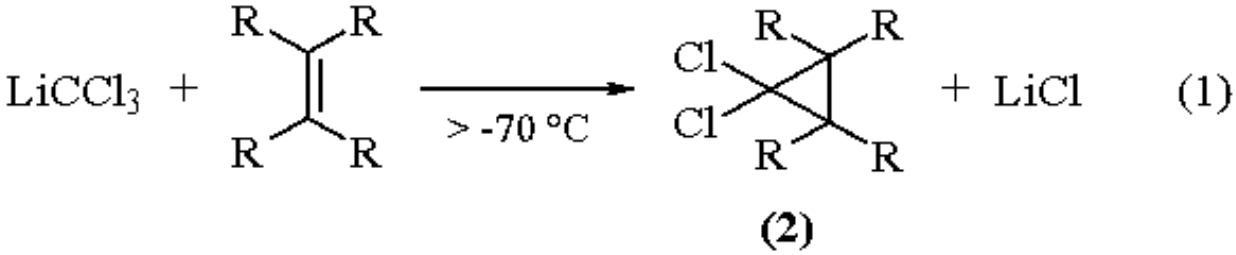

Similarly, reaction of Li-CCl_3 with alkynes provides the dichlorocyclopropenes (**3**), which can be hydrolyzed to cyclopropenones (**4**) in overall yields of about 20% (eq 2).[14]

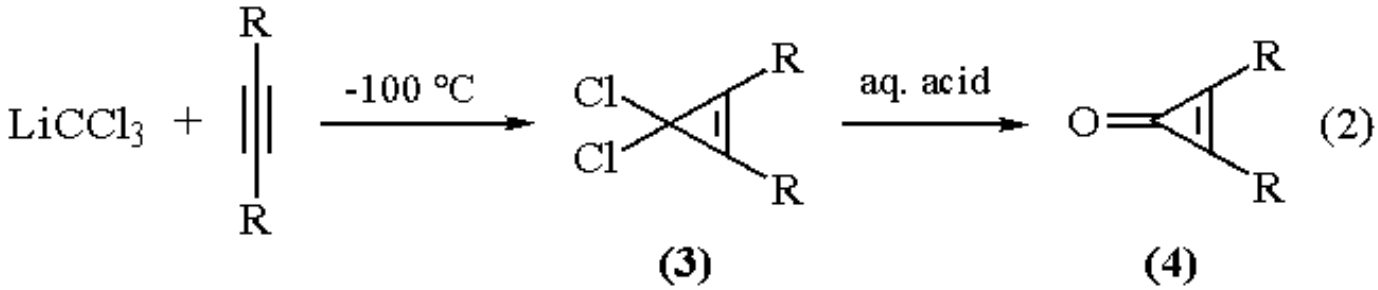

Nucleophilic Trichloromethylation.

Li-CCl_3 reacts as a nucleophile within its temperature limitations. Electrophiles which require reaction temperatures higher than about -70 °C will not react well with the reagent. Yamamoto has partially solved the problem by generating the lithium reagent via deprotonation of $CHCl_3$ with amide base in the presence of carbonyl compounds, resulting in trichlorocarbinols (eq 3).[15] While this appears to be a general reaction between haloalkyllithiums and aldehydes and ketones, reactions of Li-CCl_3 have only been reported with cyclohexanone and cyclopentanone. However, using CCl_4/*n*-BuLi generating conditions, Blumbergs reported the addition of Li-CCl_3 to phenyl cyclobutyl ketone and phenyl isopropyl ketone to provide adducts (**5**) and (**6**) in 44% and 54% yields, respectively.[16] There is a single report of the nonselective addition of Li-CCl_3 to 2-cyclopenten-1-one in low yield.[17]

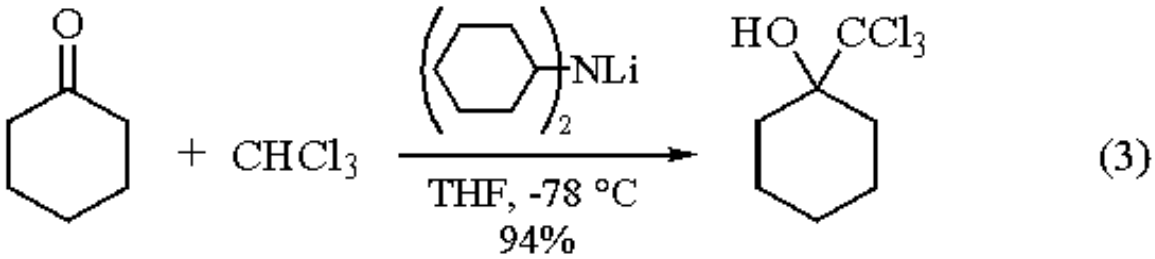

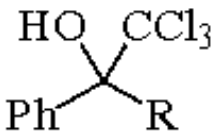

(5) R = cyclobutyl, 44%
(6) R = isopropyl, 54%

Transformations of Trichloromethylcarbinol Adducts.

Trichloromethylcarbinols serve as intermediates in the production of 1,1-dichloroalkenes and alkynes via a β-elimination process, as well as in a homologation process via an α-elimination to produce α-chloro ketones.[18] A trichloromethylcarbinol adduct (**7**) from an aldehyde or ketone can be converted to a methyl or a trimethylsilyl ether (**8**) via *O*-alkylation. This can be treated with *n*-BuLi to provide the lithium reagent (**9**) which undergoes Fritsch-Buttenberg-Wiechell rearrangement to (**11**) or it may undergo loss of RO-Li to give (**10**), depending on the identity of R^1, R^2, and R^3 (eq 4). The reactivity observed appears to be linked to the sizes of the three R groups. Large alkyl groups favor the rearrangement process leading to chloro ketones. When R^1 = H and R^2 is not too large, dichloroalkenes and alkynes result.

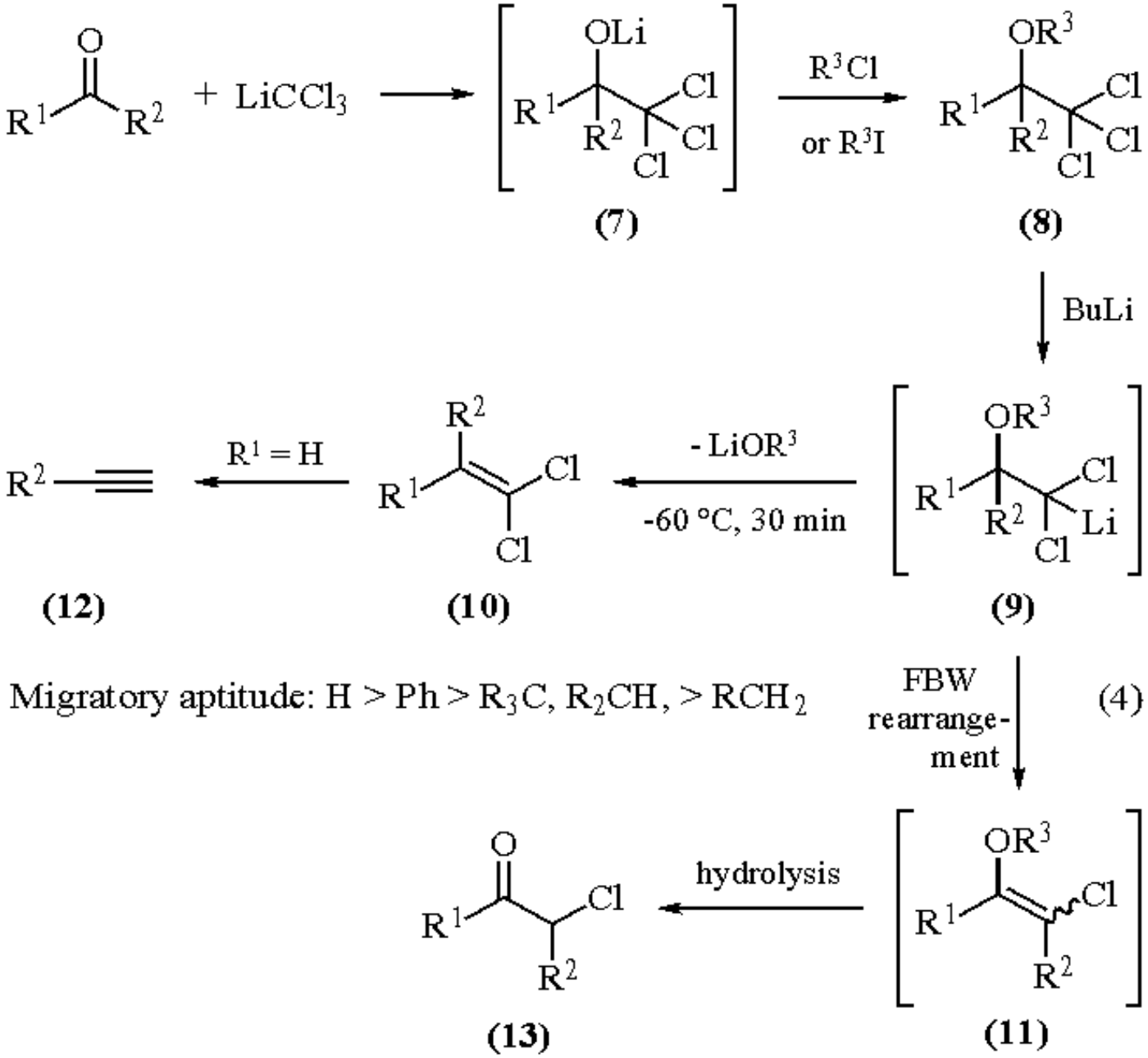

Counterions Other than Li.

The analogous reagents $NaCCl_3$ and $KCCl_3$ have also been prepared by deprotonation of $CHCl_3$ using the requisite metal hexamethyldisilazide.[19] No significant chemical reactivity was reported.

Related Reagents.

Dibromomethyllithium; ***Dichloromethyllithium***; ***Tribromomethyllithium***.

---

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Trichloroperoxyacetamidic Acid

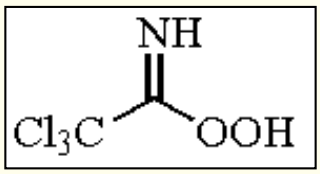

[84694-15-1] · $C_2H_2Cl_3NO_2$ · Trichloroperoxyacetamidic Acid · (MW 178.40)

(oxygen atom transfer reagent that is useful for the epoxidation of alkenes at a neutral pH[8])

Physical Data: not isolated; prepared in situ.

Solubility: sol standard organic solvents such as CH_2Cl_2.

Preparative Methods: ***Trichloroacetonitrile*** (8.5 g, 0.049 mol) and 5-methyl-5-hepten-2-one (3.72 g, 0.029 mol) in 40 mL of methylene chloride were added dropwise to a stirring solution of 5.0 mL of 30% ***Hydrogen Peroxide*** (0.44 mol). The H_2O_2 solution was adjusted to pH 6.8 by the addition of 2.25 g of K_2HPO_4 prior to addition. The biphasic mixture was magnetically stirred at room temperature while the depletion of alkene was monitored by GLC (6 ft column, 10% UCW on Chromosorb W, 130 °C). After 3 h, 25 mL of pentane was added, and the precipitated trichloroacetamide was removed by filtration through a fritted disk and washed with pentane. More complete removal of the trichloroacetamide may be achieved by chilling the reaction mixture prior to filtration. The filtrates were washed with water (20 mL), cold 3% Na_2SO_3 solution (25 mL), and brine (25 mL), and then dried ($MgSO_4$). The solvents were removed by aspiration, and the yellow residue was fractionally distilled to afford 3.35 g (80%) of epoxide, bp 42-42.5 °C/20 mmHg).

Handling, Storage, and Precautions: this reagent is generated in situ and is not stable to storage.

Alkene Epoxidation.

Epoxides are typically prepared from alkenes on a laboratory scale by the action of organic peroxides and metal catalysts or by oxidation with a peroxy acid.[1,2] The more commonly used commercially available oxidants for the epoxidation of simple alkenes include ***Peracetic Acid***, ***m-Chloroperbenzoic Acid*** (*m*-CPBA), and ***Monoperoxyphthalic Acid***, magnesium salt hexahydrate (MMPP). ***Trifluoroperacetic Acid*** is one of the most reactive peroxy acids, but it suffers the disadvantage of having to be prepared in situ by the action of trifluoroacetic anhydride and 90% hydrogen peroxide.[3] The resulting solution is highly acidic and can have a deleterious effect upon the yield of epoxide.

Although hydrogen peroxide is not sufficiently electrophilic to directly epoxidize a nonconjugated carbon-carbon double bond, its reactivity may be enhanced by placing the OOH moiety in conjugation with a multiple bond, as exemplified by a peroxy acid (**1**).[4]

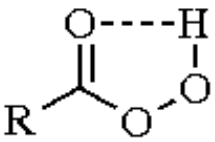

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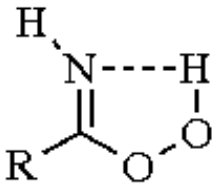

(2)

One of the earliest and most useful adaptations of this concept was accomplished by Payne.[5] He successfully activated the O-O bond by the in situ formation of a peroxyimidic acid (**2**) resulting from the base-catalyzed addition of H_2O_2 to a nitrile. Both aceto- and benzonitrile were employed as coreactants in the epoxidation of a variety of alkenes in methanol solvent. More recently, Rebek[6] and co-workers have developed a number of reactive oxidizing reagents resembling (**1**) and (**2**) and related activated hydroperoxides.

The mechanism of alkene epoxidation involves a bimolecular nucleophilic attack of the alkene (HOMO) on the antibonding σ* orbital of the O-O bond.[7] Consequently, heterolytic cleavage of the peroxide bond is facilitated by electron-withdrawing groups on the multiple

bond. A trichloromethyl substituent increases the reactivity of a peroxy acid and a peroxyimidic acid.[8] Reaction of 30% aqueous H_2O_2 with the electron-deficient nitrile trichloroacetonitrile affords a highly efficient oxygen transfer reagent that can compete with *m*-CPBA on both a cost and reactivity basis (eq 1).

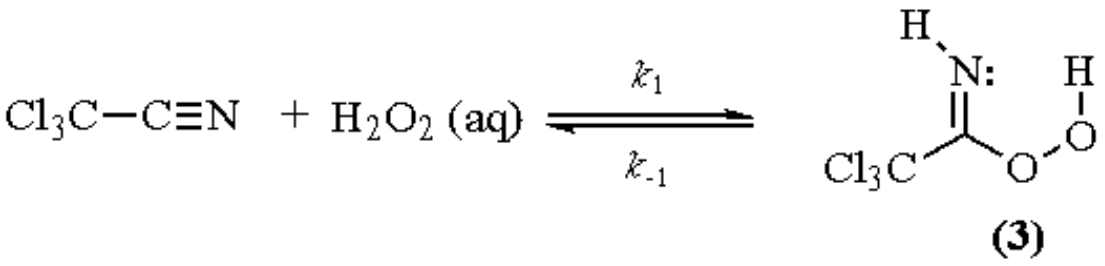

(1)

The rate of epoxidation is faster with more highly substituted and strained alkenes. Trichloroperoxyimidic acid (**3**) is sufficiently reactive to effect epoxidation of the terminal alkene 1-nonene (71%). This reagent will also epoxidize the deactivated double bond of α,β-unsaturated ketones in a highly chemoselective manner without affording products derived from a Baeyer-Villiger oxidation (eq 2).

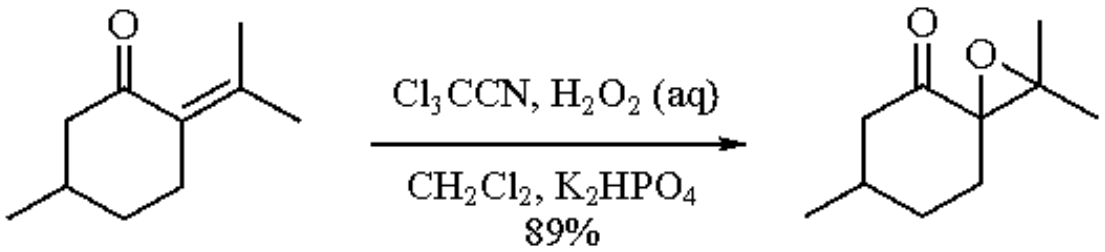

(2)

Another unique feature of the reagent is its ability to epoxidize 1-cyclopenteneacetonitrile without disturbing the nitrile functional group. The oxygen transfer reaction is stereospecific, as evidenced by the formation of only the (*Z*)-epoxide from (*Z*)-stilbene, and the (*E*)-epoxides from (*E*)-cinnamyl alcohol, (*E*)-stilbene, and (*E*)-cyclooctene. The procedure is readily adaptable to the large-scale syntheses of epoxides. For example, 50 g (0.45 mol) of *cis*-cyclooctene on treatment with 1.5 equiv of CCl_3CN and 3 equiv of H_2O_2 (pH 6.8) afforded 48.0 (84%) of *cis*-cyclooctene oxide. On a 2 molar scale the yield of epoxide was 76%.

One potential disadvantage of this procedure from an operational perspective is the fact that it operates in a very narrow pH range. An increase in pH favors the formation of (**3**), but a competing reaction with the anion of H_2O_2 reduces the concentration of active oxygen (eq 3). The formation of dioxygen is pH dependent. Maintaining the optimal pH is best achieved by the use of a pH meter. The mechanism for the addition of H_2O_2 to a nitrile has been studied by Wiberg[9a] in the pH range 7-8 and by McIsaac and his co-workers[9b] at a pH of 9.75. The rate limiting step for oxygen atom transfer is the nucleophilic attack of (**3**) on the carbon-carbon double bond.[9c]

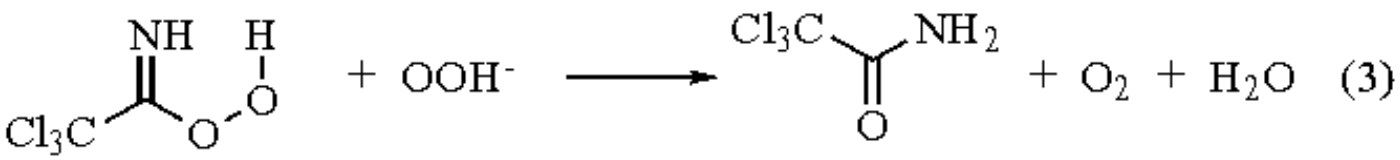

(3)

Related Reagents.

O-Ethylperoxycarbonic Acid; ***Peroxyacetimidic Acid***.

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Trichlorosilane[1]

Cl_3SiH

[10025-78-2] · Cl_3HSi · Trichlorosilane · (MW 135.45)

(reducing agent; hydrosilating agent; precursor of trichlorosilane radical)

Physical Data: mp -126.5 °C; bp 31-32 °C; *d* 1.342 g cm^{-3}.

Solubility: sol benzene, carbon disulfide, chloroform, carbon tetrachloride; dec by water.

Form Supplied in: high quality colorless liquid.

Purification: can be purified by treatment with quinoline to remove hydrogen chloride followed by distillation, first at atmospheric pressure and then under vacuum.

Handling, Storage, and Precautions: this reagent is highly flammable and corrosive; should be stored in the absence of moisture and handled in a fume hood.

Functional Group Reductions.

Trichlorosilane has often been used together with tertiary amines (usually ***Tripropylamine*** or ***Tri-n-butylamine***) to reduce the carbonyl groups of aromatic aldehydes, ketones, acids, amides, acid chlorides, and anhydrides to give the corresponding benzylic trichlorosilanes (eq 1);[1] this is referred to as reductive silylation. The mechanism of this reaction remains unclear; however, studies indicated the possible formation of the trichlorosilyl anion by the action of tertiary amines on trichlorosilane (eq 2).[2] The adduct (**1**) was proposed based on the known propensity of tetracoordinated silicon to form five or six-coordinate complexes.[3] This method provided a new way to form silicon-carbon bonds and, more importantly, the benzylic trichlorosilane products can be cleaved by base treatment to give toluenes. This transformation can be carried out without isolation of the intermediate organosilane (eq 3).[4]

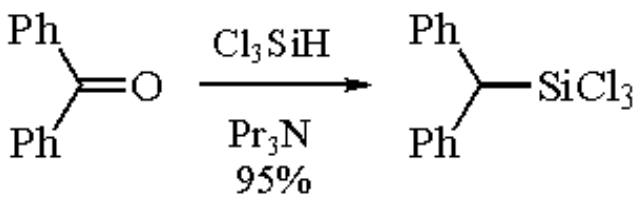

(1)

$$Cl_3SiH + R_3N \rightleftharpoons \underset{\textbf{(1)}}{[R_3N\text{-}SiHCl_3]} \rightleftharpoons R_3NH^+ + {}^-SiCl_3 \qquad (2)$$

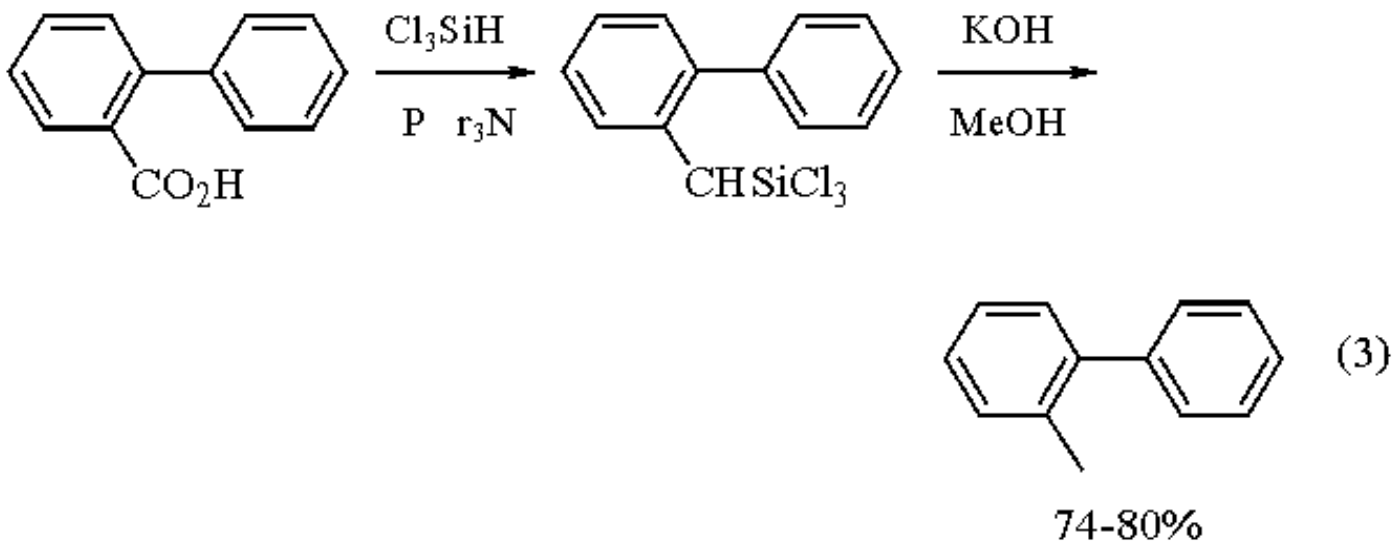

Aromatic esters are unaffected during this reduction; consequently it is possible to effect selective reduction of half-esters (eq 4).[5]

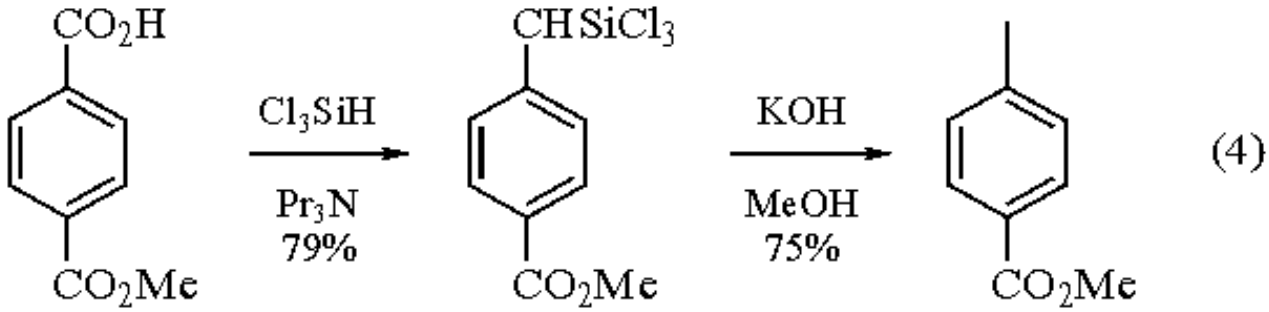

In contrast to the above results, reduction of aldehydes and ketones with premixed trichlorosilane and lithium derivatives of phenols or 1,2-diols gives the corresponding alcohols; pentacoordinate hydridosilicates (such as **2**) are believed to function as the reducing agent (eqs 5 and 6).[6]

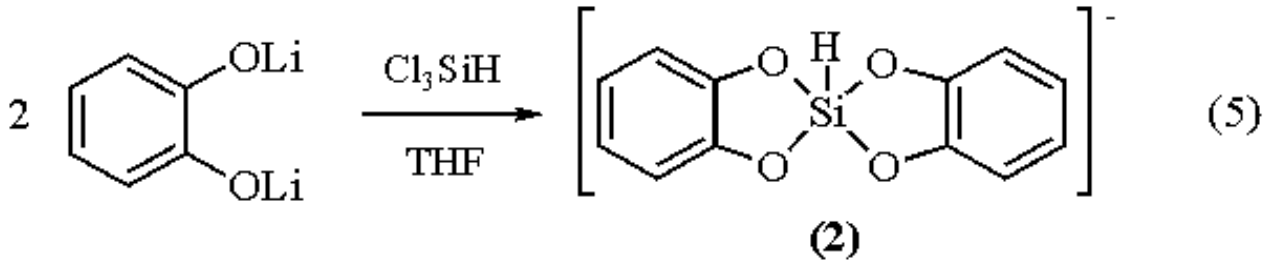

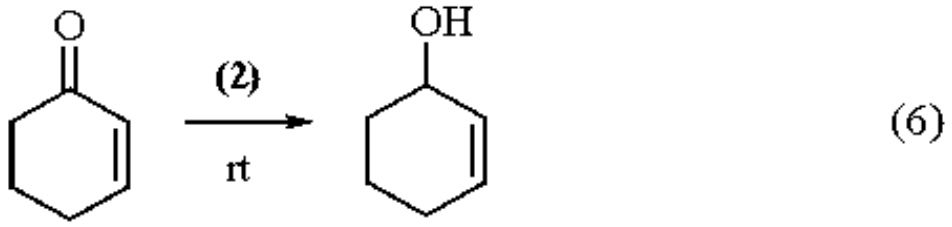

It has also been found that the trichlorosilyl radical is generated in the presence of radical initiators (hν, ***1,1-Di-t-butyl Peroxide***). This radical readily reacts with aliphatic carboxylates (eq 7)[7] and acetals[8] to give dialkyl ethers, and with alkyl halides[9] and acid chlorides[10] to give alkanes. The reaction is believed to proceed by a radical chain mechanism.

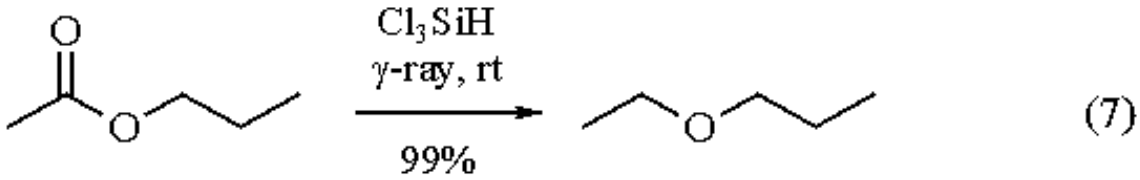

Trichlorosilane also reduces enamines (eq 8)[11] and imines[12] to the corresponding amines; one-step hydroamidation of a Schiff base gives the acetamide (eq 9).[13]

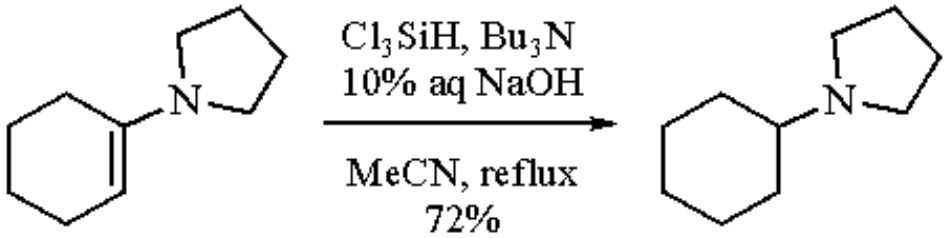

(8)

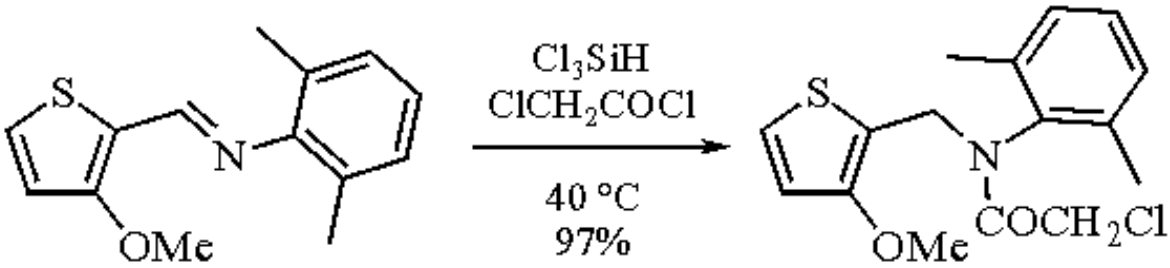

(9)

Reduction of carbamates and isocyanates with trichlorosilane give isocyanides.[13] This provides a relatively simple method for synthesis of vinyl isocyanides from alkenes (eq 10).[14] Due to the mild conditions of the reductions, it has been applied in the resolution of alcohols. Along this line, diastereomeric carbamates obtained by treating racemic alcohols with optically pure isocyanates are separated and reduced to give the desired (*R*)- and/or (*S*)-alcohols (eq 11).[15] This method has been extensively used, such as in the enantioselective syntheses of (+)-sterpurene,[16] NRDC 182,[17] ascofuranone, and ascofuranol.[18]

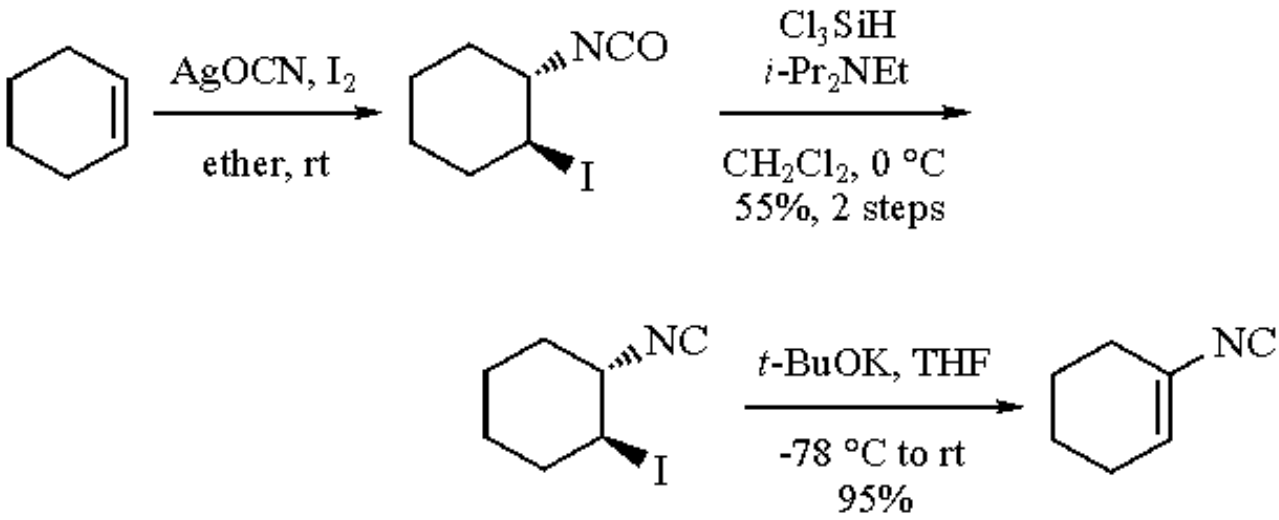

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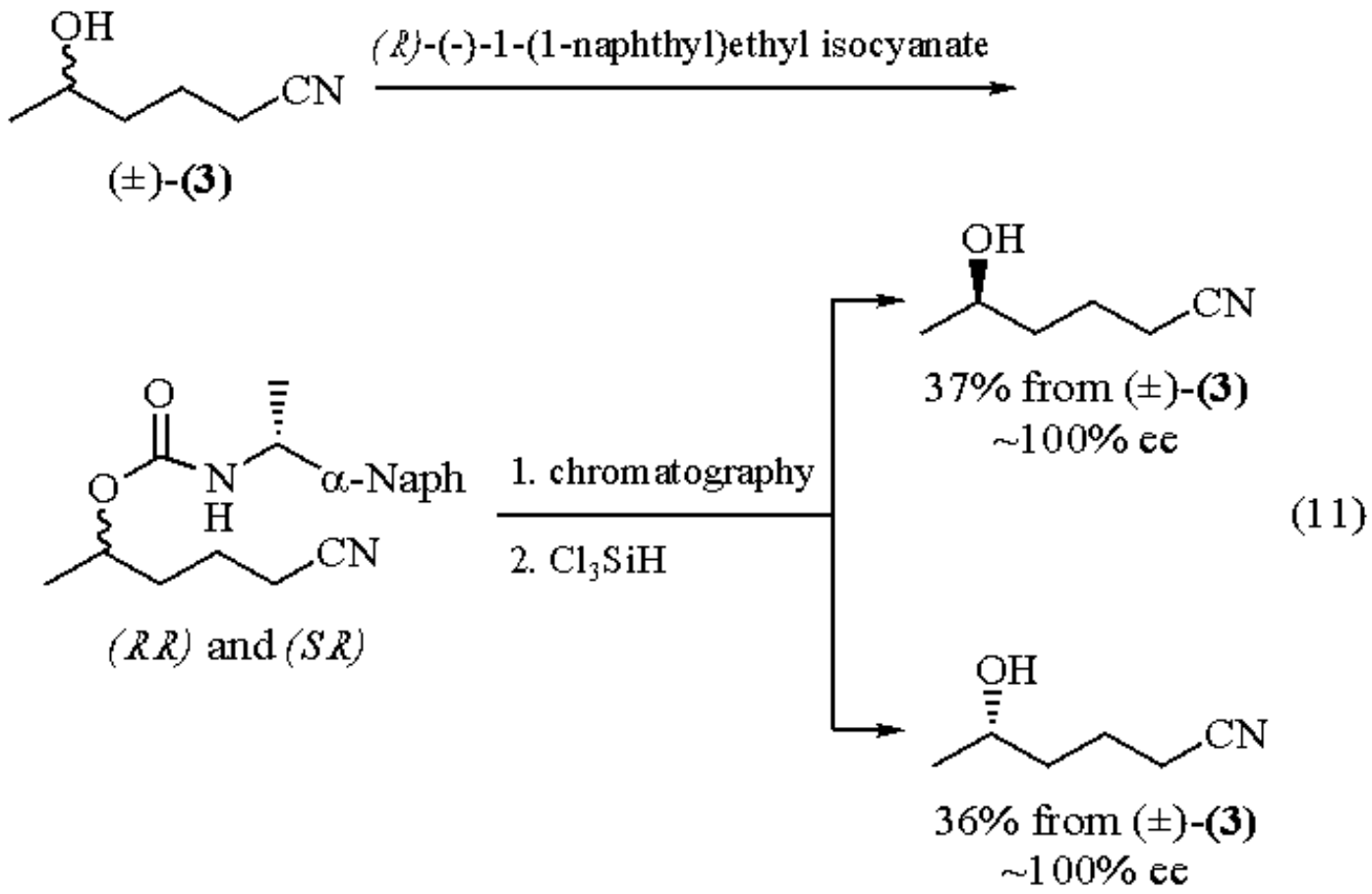

(11)

Hydrosilation.

The additions of trichlorosilane to alkenes and alkynes usually are highly stereoselective[19] and can be effected under a wide variety of conditions. For example, the additions can be brought about thermally,[20] or by using metal complexes (eq 12).[21] In the presence of chiral catalysts, additions proceed enantioselectively.[22] It has been demonstrated that the trichlorosilyl group is a synthetic equivalent for the OH, Cl, and Br groups.[23]

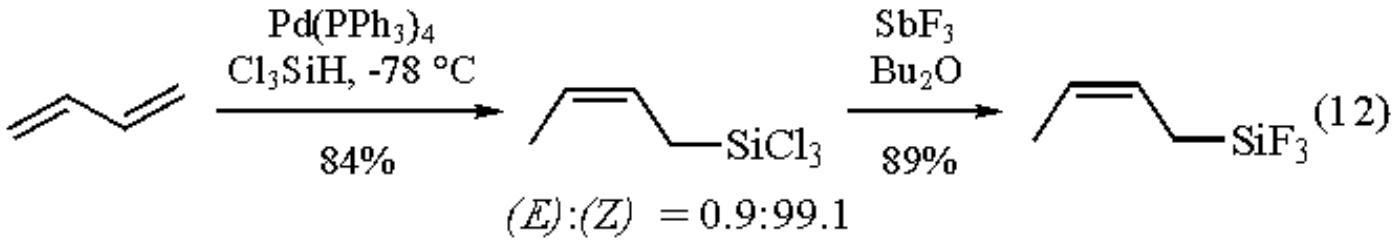

(12)

The addition can also be carried out under radical conditions.[24] The trichlorosilyl radical is more electrophilic than trialkylsilyl radicals, and adds faster to both alkenes and carbonyl groups (eqs 13 and 14).[25]

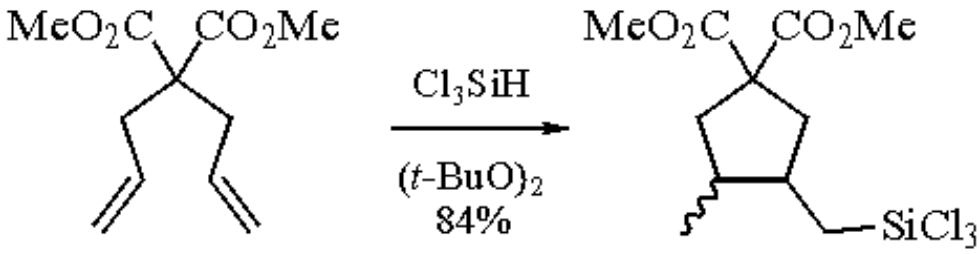

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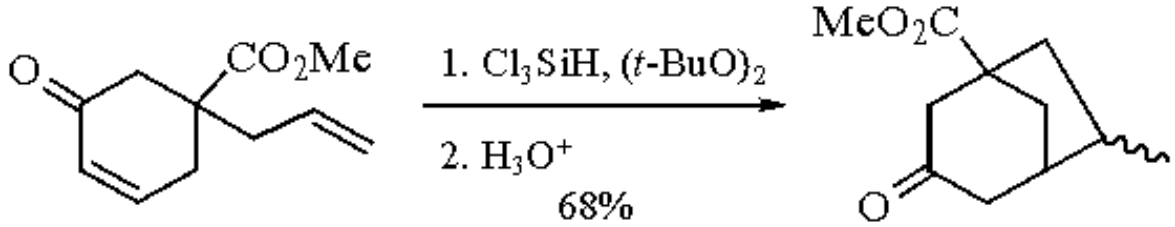

(14)

Reaction with Halides.

Organic halides undergo a variety of transformations in the presence of trichlorosilane, depending upon the reaction conditions. One of the most important applications is the formation of allylsilanes (eqs 15 and 16).[26]

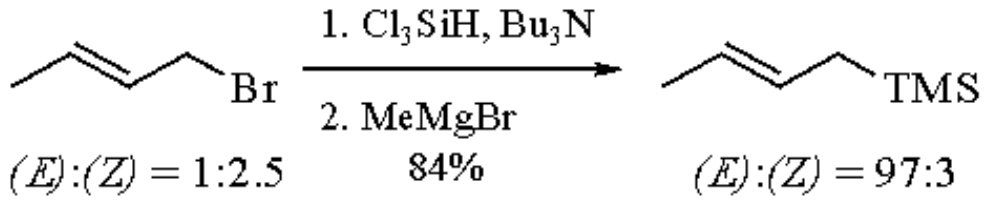

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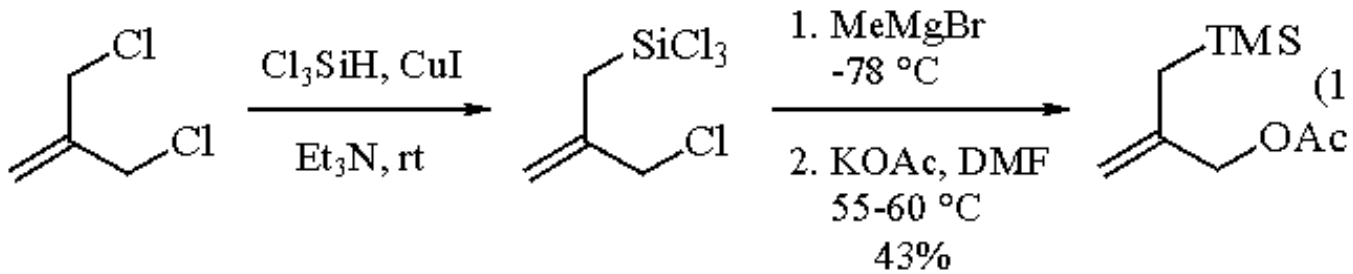

(16)

Reaction with Sulfur and Phosphine Compounds.

Trichlorosilane is also used for the reduction of phosphine oxides to phosphines (eq 17).[27] Sulfenyl, sulfinyl, and sulfonyl chlorides are reduced to symmetrical disulfides.[28]

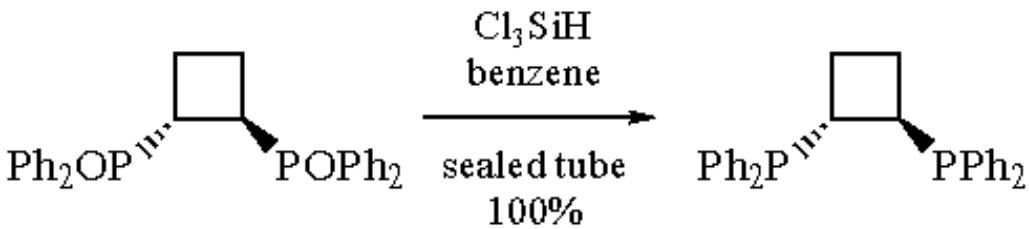

(17)

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Triethoxydiiodophosphorane

$(EtO)_3PI_2$

[59547-92-1] · $C_6H_{15}I_2O_3P$ · Triethoxydiiodophosphorane · (MW 419.98)

(Arbuzov-type intermediate; can be used as a dehydrating or condensing agent[1])

Physical Data: not isolated; prepared in situ.

Solubility: prepared and used in ether, dichloromethane, or acetonitrile.

Preparative Methods: was first prepared[1] as an unstable intermediate during the reaction between ***Phosphorus(III) Iodide*** and ***Triethyl Phosphite***. It was reported as being unstable at room temperature, decomposing to give ethyl iodide and diethyl phosphoriodate.[1] This same report also indicated that the reaction between triethyl phosphite and iodine at -5 °C gave the same two products. A subsequent report[2] described similar reactions with similar results. In 1979, it was reported[3] that the reaction between methyl phosphite and iodine at 0 °C in ether, dichloromethane, or acetonitrile gave a 1:1 adduct with a single ^{31}P NMR absorption which was assigned the triethoxydiiodophosphorane structure. This solution was stable over several days at room temperature.

Handling, Storage, and Precautions: in solution the phosphorane has a half-life of several days.

As Intermediates in the Arbuzov Reaction.[3]

Phosphoranes such as (**2**) are considered to be intermediates in the Arbuzov reaction (eq 1).

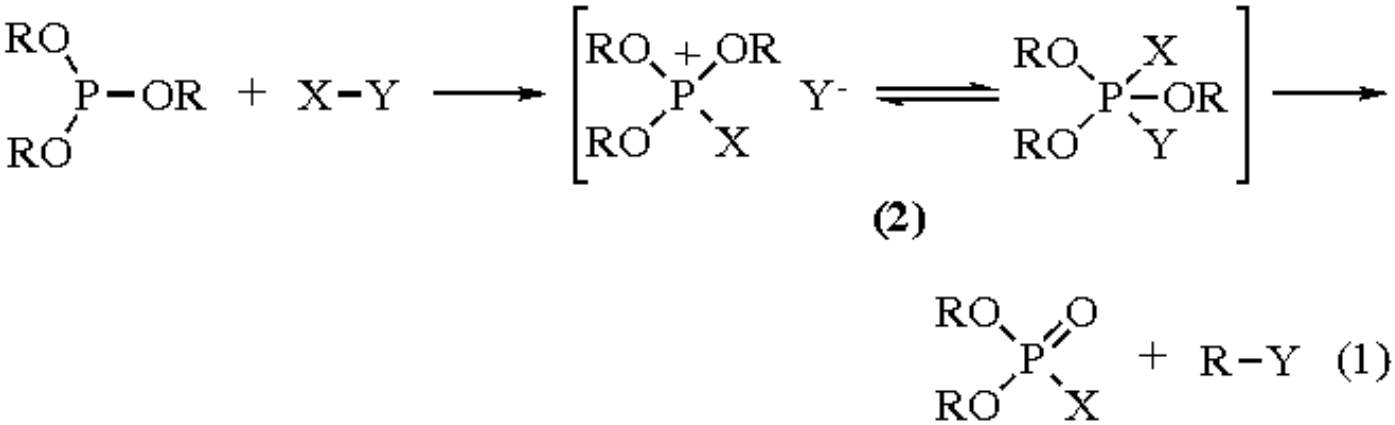

(2)

Only in exceptional cases can they be isolated, but they can be observed by ^{31}P NMR.[4] The relative stability of triethoxydiiodophosphorane allows it to be used as a dehydrating or condensing agent.[3]

Dehydrating Agent.

Benzamide and benzaldoxime have been dehydrated to benzonitrile (eqs 2 and 3) by addition of the amide or oxime to an iodine solution in dichloromethane or acetonitrile at 0 °C followed by 1 equiv of ***Triethyl Phosphite*** and 2 equiv of ***Triethylamine***.[3] Stirring for 2 hours at room temperature leads to dehydration. Ease of workup is aided by the water soluble nature of the byproducts.

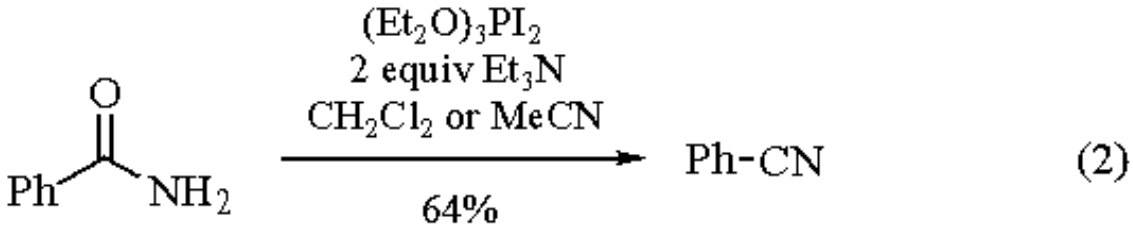

(2)

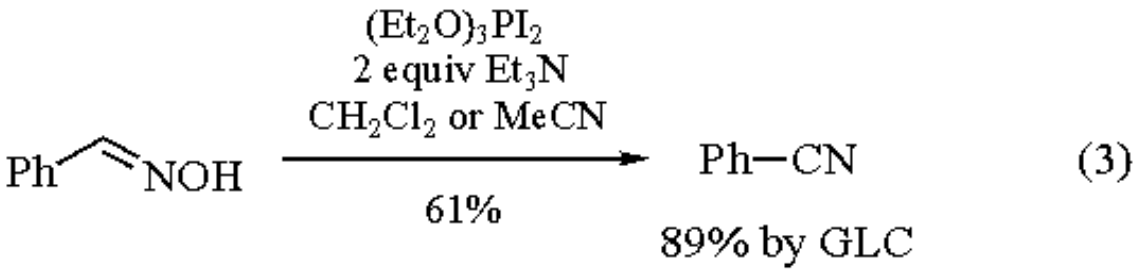

(3)

Condensing Agent.

A solution of triethoxydiiodophosphorane allows the preparation of amides from amines and acids (eq 4).[3]

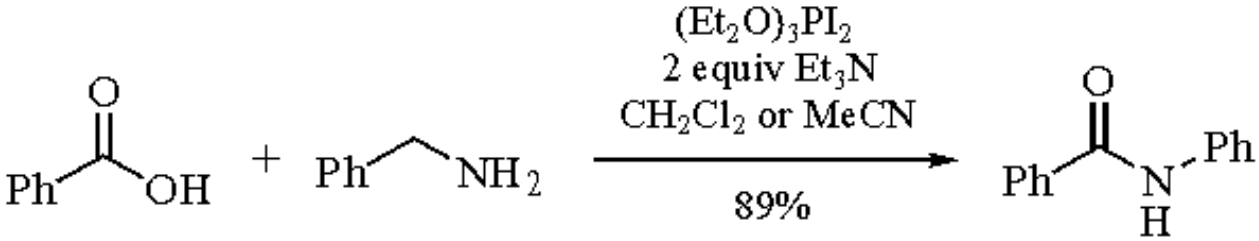

(4)

In the absence of the amine, a slower Arbuzov reaction takes place to give a mixed anhydride via the phosphonium salt (eq 5).[3]

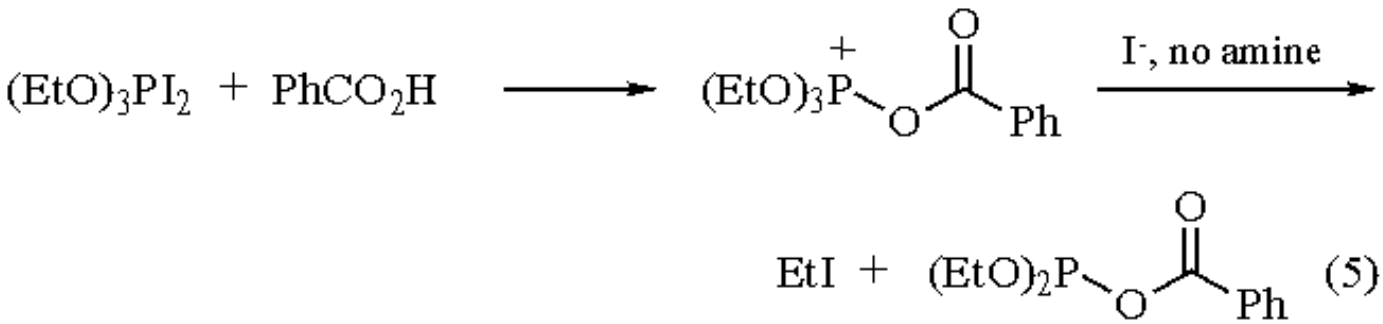

(5)

This reagent has also been used as a condensing agent in the synthesis of a dipeptide from *N*-benzoyl-L-leucine and ethyl glycinate in high yield. The dipeptide obtained was entirely racemic. Addition of ***1-Hydroxybenzotriazole*** to the reaction gave the dipeptide in 83% yield and 39% ee.

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Triethoxysilane

$HSi(OEt)_3$

[998-30-1] · $C_6H_{16}O_3Si$ · Triethoxysilane · (MW 164.31)

(useful reagent for the hydrosilylation of carbon-carbon multiple bonds; reducing agent for carbonyl groups)

Physical Data: bp 134-135 °C; *d* 0.89 g cm^{-3}.

Solubility: sol diethyl ether, THF, alkanes, aromatic and chlorinated solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: is moisture sensitive and should be handled in a well-ventilated hood. Contact with the eyes and skin should be avoided.

Hydrosilylation of Carbon-Carbon Multiple Bonds.

$HSi(OEt)_3$ is an efficient reagent for the hydrosilylation of alkenes, alkynes, and conjugated dienes (eq 1).[1] The reaction is promoted by a variety of transition metal catalysts, including platinum, ruthenium, and rhodium. Chloroplatinic acid hexahydrate, $H_2PtCl_6.6H_2O$ (see ***Hydrogen Hexachloroplatinate(IV)***), is by far the most widely used catalyst and has been shown to be very efficient, particularly in the hydrosilylation of alkenic substrates.[2]

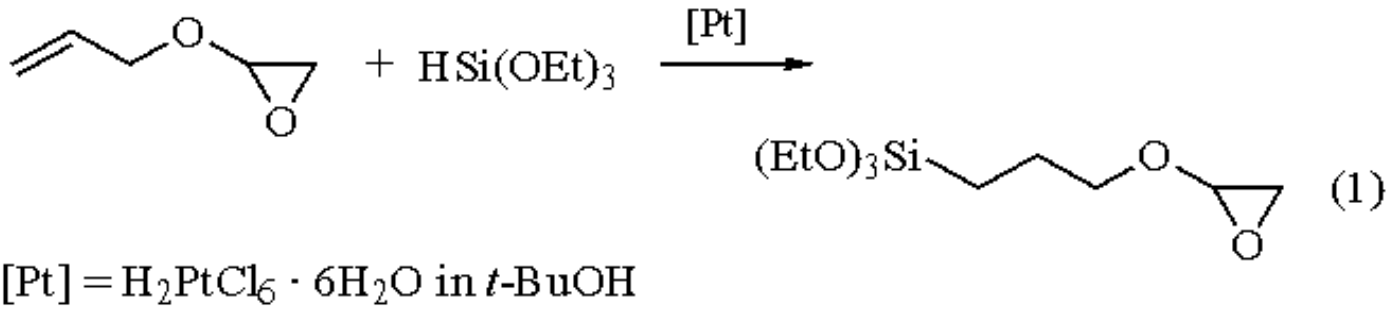

The reaction is especially valuable for the introduction of functionalized groups at silicon,[3] as this cannot be achieved by simple organometallic procedures (eq 1).[4] Furthermore, the reaction may be quite regioselective and stereoselective, as in the case of the hydrosilylation of ocimene (eq 2).[5]

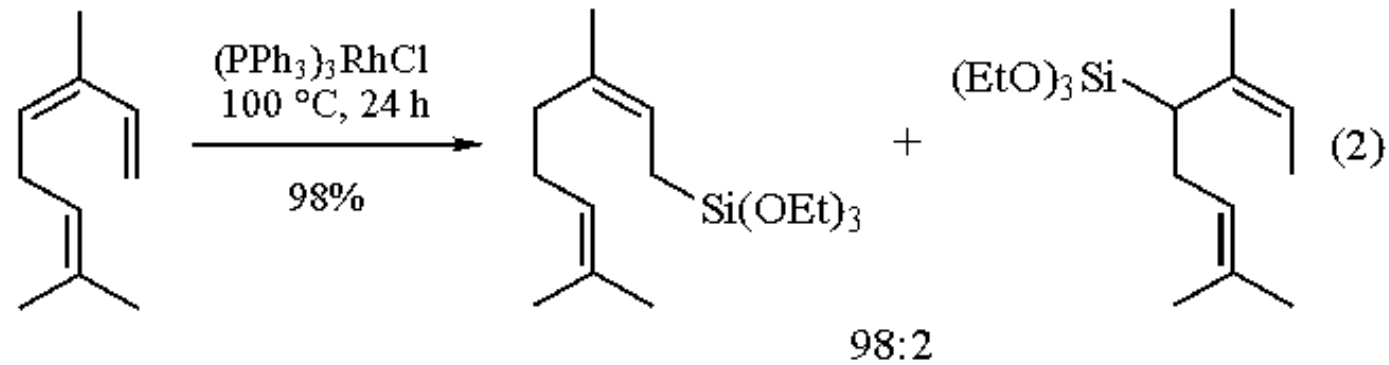

Reduction of Functional Groups Catalyzed by Fluoride or Alkoxide

Salts.[6]

A general and powerful reduction method of carbonyl compounds consists of using $HSi(OEt)_3$ activated by ***Potassium Fluoride*** or ***Cesium Fluoride***.[7] The reaction can proceed without solvent (eq 3)[7a] and is accelerated by polar solvents, e.g. DMSO or DMF.[8] The reduction of aldehydes and ketones is rapid at room temperature; also, esters are smoothly converted to alcohols (eq 4).[7b]

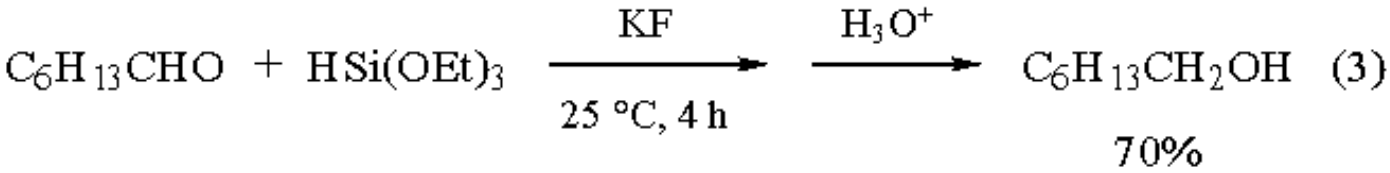

(3)

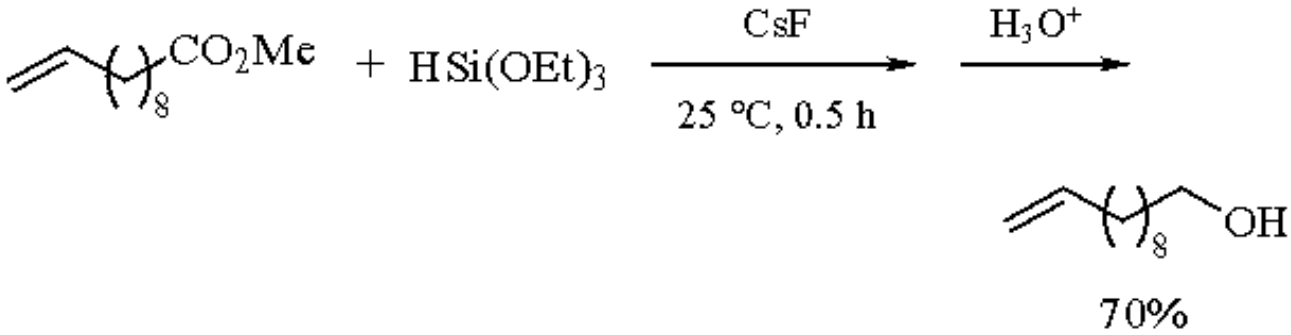

(4)

The reaction is highly chemoselective: aldehydes and ketones possessing functional groups, such as carbon-carbon double bonds, or bromo, nitro, amide, and ester groups, are reduced selectively to the corresponding alcohols (eqs 5 and 6).[7a,9]

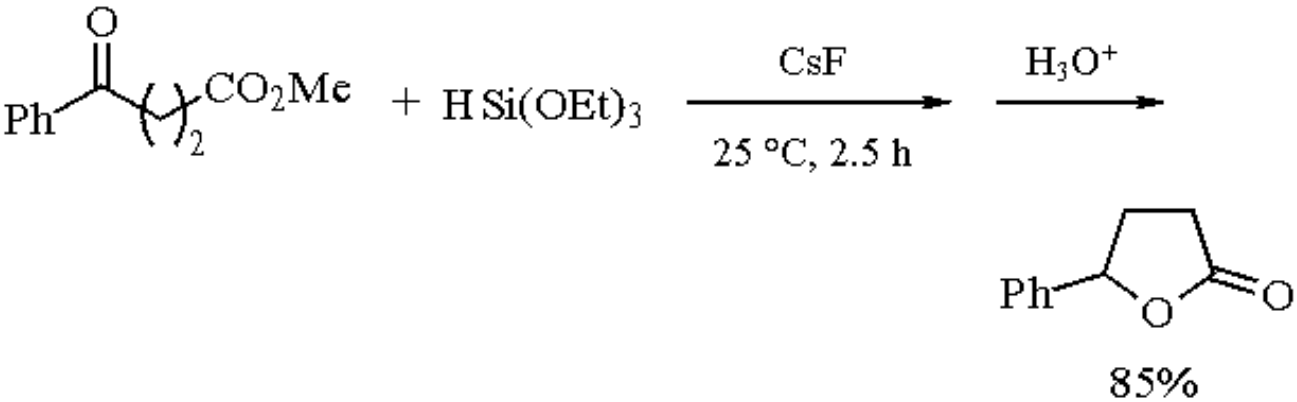

(5)

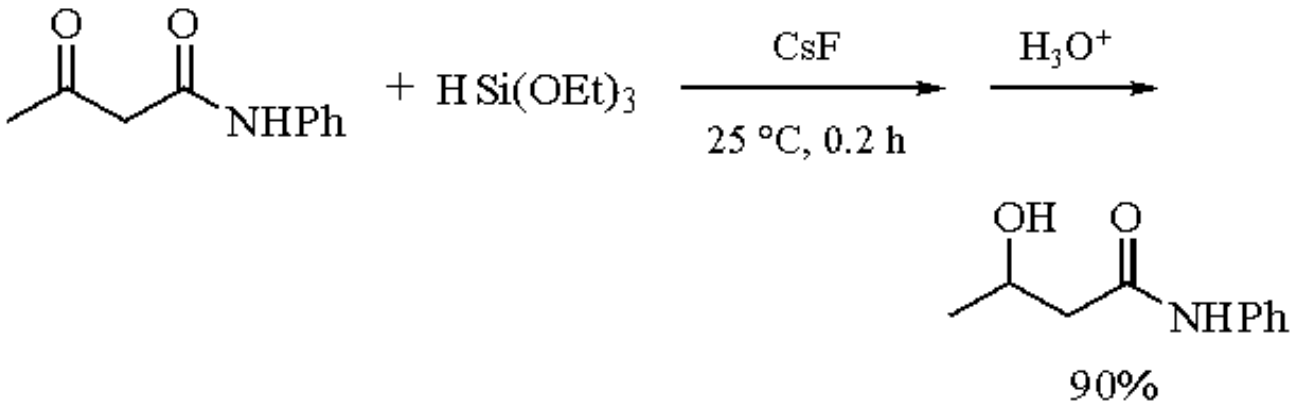

(6)

Alternatively, solutions of $HSi(OEt)_3$ with lithium ethoxide or pinacolate may be used to convert aldehydes and ketones to alcohols.[10] Enantioselective reduction of prochiral ketones is achieved by use of a mixture of $HSi(OEt)_3$ and the dilithium salt of a chiral diol or amino alcohol.[11]

The reaction between carbonyl compounds and $HSi(OEt)_3$ is efficiently catalyzed by inorganic solid bases such as hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, at temperatures ranging from 25 to 90 °C.[12] Enones afford the corresponding 1,2-addition products.

$HSi(OEt)_3$ is easily converted into a more reactive form, namely a pentacoordinate hydridosilicate (eq 7).[13a]

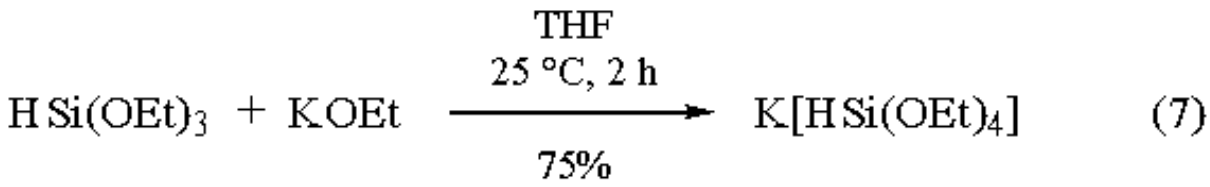

$K[HSi(OEt)_4]$ reduces aldehydes, ketones, and esters in the absence of added catalyst.[13] Treatment of nonenolizable amides yields the corresponding aldehydes. Reaction with 1 equiv of isocyanate in diethyl ether or THF leads quantitatively to the potassium imidate, which can be quenched in situ (eq 8).[13b] Furthermore, use of an excess of aryl isocyanate yields to the corresponding isocyanurate.[13b]

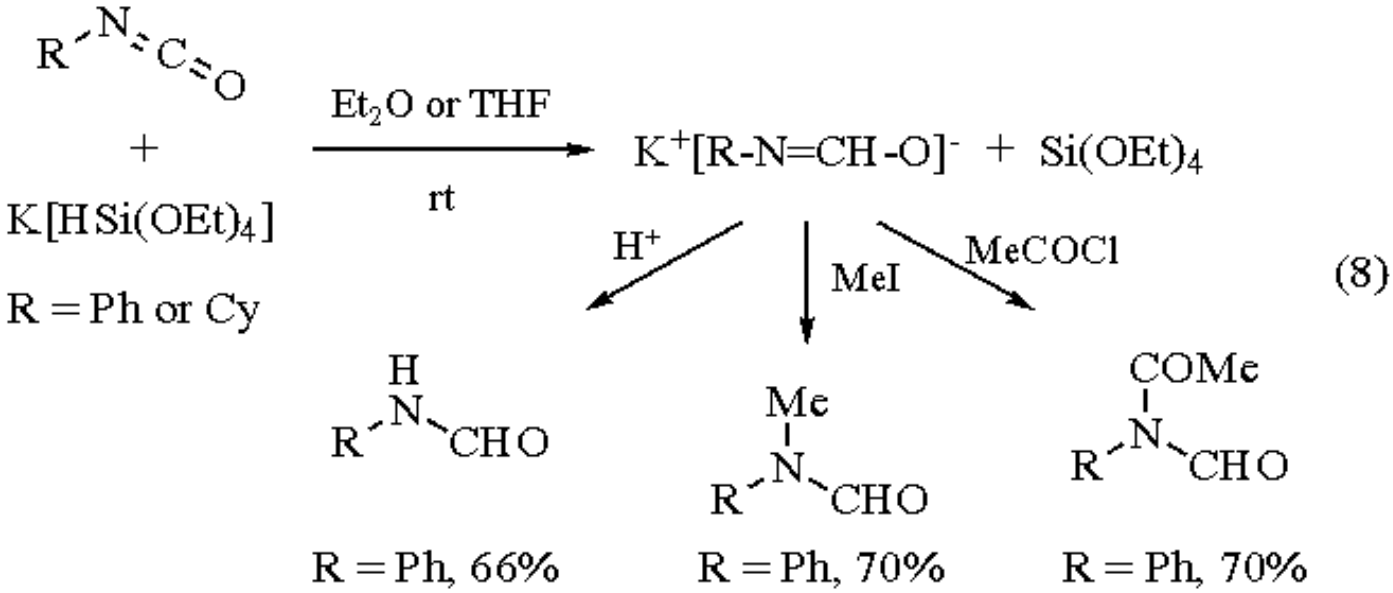

Titanium-Catalyzed Reduction of Esters to Alcohols.

$HSi(OEt)_3$ is used stoichiometrically in conjunction with a titanium-based catalytic system, conveniently prepared by the reaction of 2 equiv of ***n-Butyllithium*** with ***Dichlorobis(cyclopentadienyl)titanium*** (eq 9).[14a]

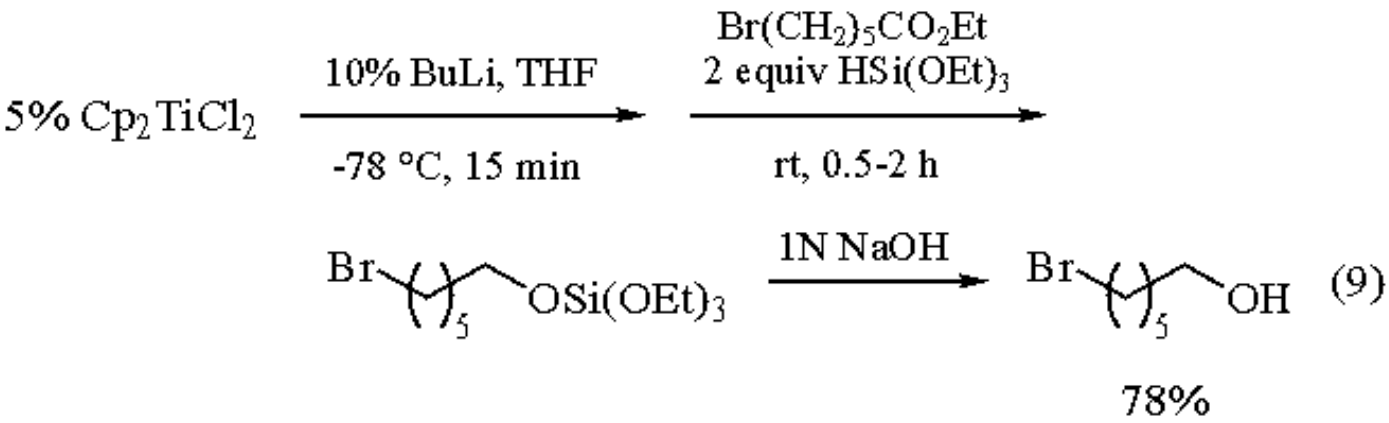

The combination of a catalytic amount of ***Titanium Tetraisopropoxide***, an inexpensive and air-stable liquid, and $HSi(OEt)_3$ also generates an effective and mild system for the conversion of esters into primary alcohols.[14b]

Selective reduction of a great variety of esters has been achieved with these methods. The procedures represent safer and convenient alternatives to those employing reducing agents such as ***Diisobutylaluminum Hydride*** and ***Lithium Aluminum Hydride***.

Related Reagents.

(2-Dimethylaminomethylphenyl)phenylsilane; ***Diphenylsilane-Cesium Fluoride***; ***Phenylsilane-Cesium Fluoride***; ***Triethylsilane***;

Triphenylsilane.

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Triethylaluminum[1]

[97-93-8] · $C_6H_{15}Al$ · Triethylaluminum · (MW 114.19)

(Lewis acid and source of nucleophilic ethyl groups;[2-5] couples with alkenyl halides in the presence of a transition metal catalyst;[8-11] selective hydrocyanation agent in combination with HCN[12])

Physical Data: mp -58 °C; bp 62 °C/0.8 mmHg; *d* 0.835 g cm^{-3} (25 °C).

Solubility: freely miscible with saturated and aromatic hydrocarbons; reacts violently with H_2O and protic solvents.

Form Supplied in: as a neat liquid in a stainless container or as a solution in hydrocarbon solvents (hexane, heptane, toluene).

Analysis of Reagent Purity: brochures from manufacturers, describe an apparatus and method for assay.

Handling, Storage, and Precautions: indefinitely stable under an inert atmosphere. The neat liquid or dense solutions are highly pyrophoric. Solutions more dilute than a certain concentration are not pyrophoric and are safer to handle. The nonpyrophoric limits are 13 wt % in isopentane, 12 wt % in hexane, and 12 wt % in heptane, respectively. Use of halogenated hydrocarbons as solvents should be avoided because of possible explosive reactions sometimes observed for mixtures of CCl_4 and organoaluminums.

Ethylation.

Et_3Al, like other organoaluminums, can act as a Lewis acid to activate Lewis basic functionalities and also as a captor of electrophilic species by ethylation, as illustrated in eq 1.[2] Substitution reactions of glycosyl fluorides (eq 2)[3] and bromides[4] can be effected with Et_3Al. γ-Lactols react with Et_3Al in the presence of ***Boron Trifluoride Etherate*** to deliver 2,5-disubstituted tetrahydrofurans stereoselectively (eq 3).[5]

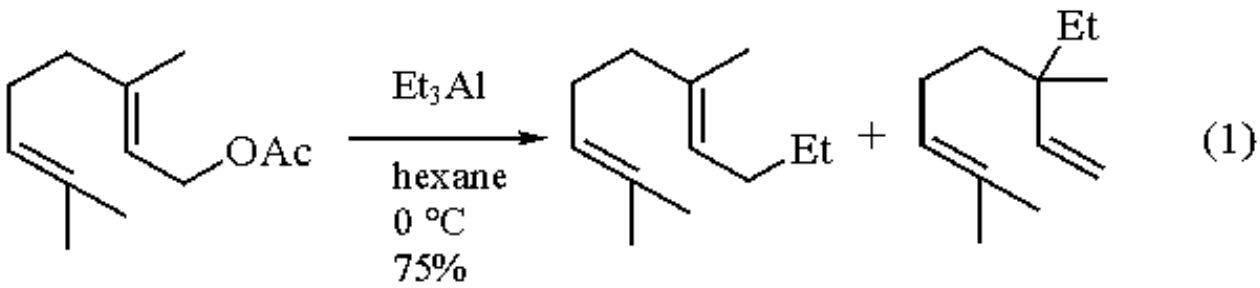

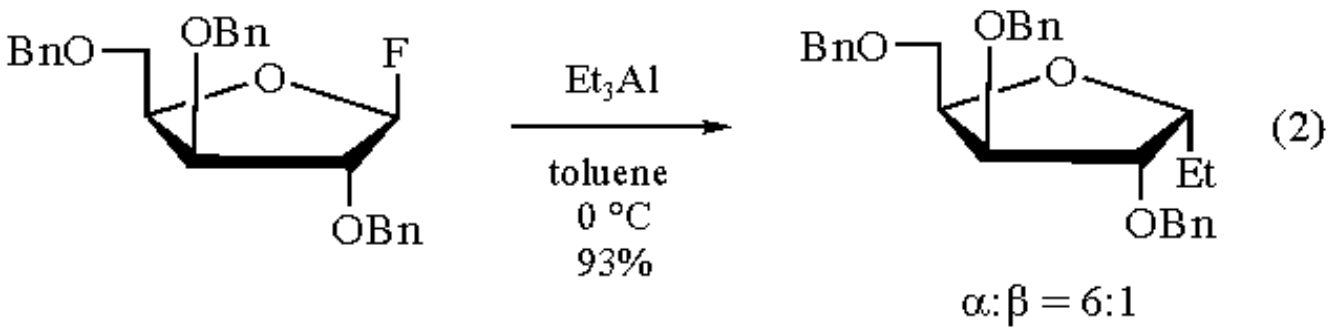

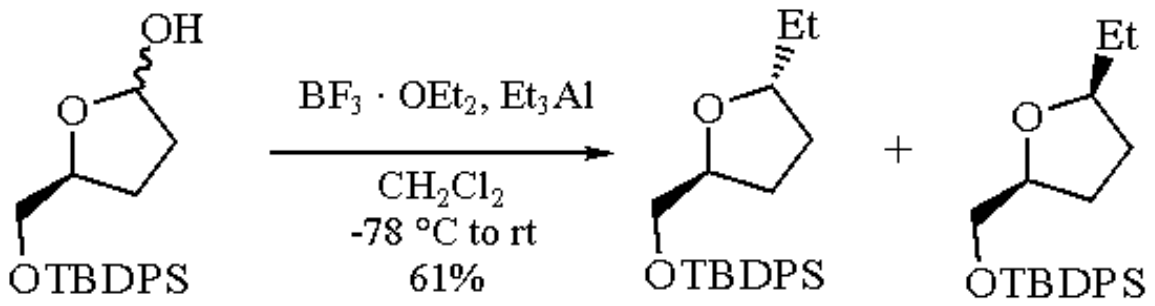

(3)

trans:*cis* = 13:1

Conjugate addition of Et_3Al to 2-nitrofurans provides, after hydrolysis, dihydro-2(3*H*)-furanones (eq 4).[6] Regioselective addition of Et_3Al to unsymmetrical 1,1´-azodicarbonyl compounds has been reported.[7]

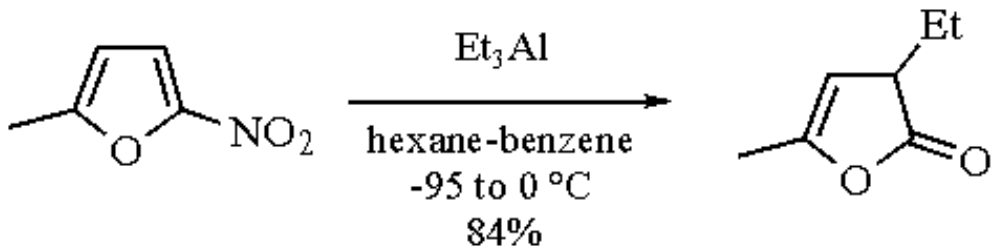

(4)

Cross coupling of Et_3Al with aryl phosphates[8] or alkynyl bromides[9] proceeds with a Ni catalyst to provide alkylated arenes or alkynes (eqs 5 and 6). While Pd or Cu complexes are used as the catalyst for the coupling of Et_3Al with carboxylic acid chlorides or thioesters (eq 7),[10] ***Iron(III) Chloride*** is used for reactions of propargyl acetates to give substituted allenes (eq 8).[11]

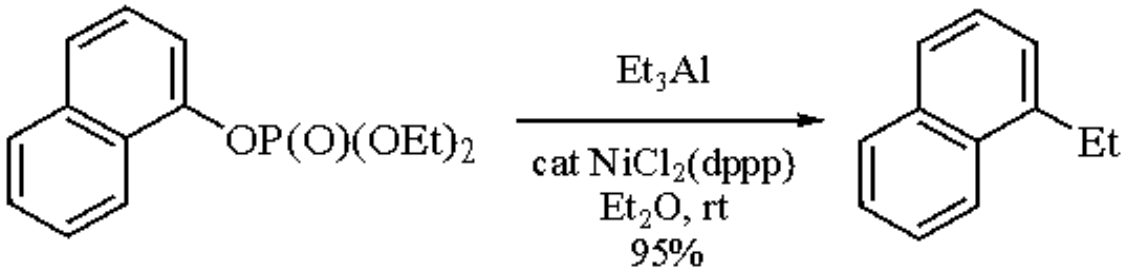

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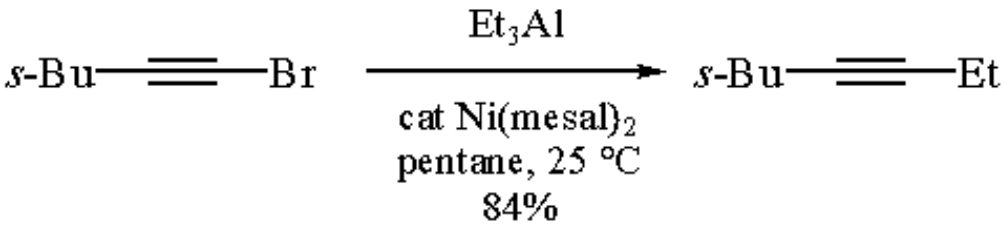

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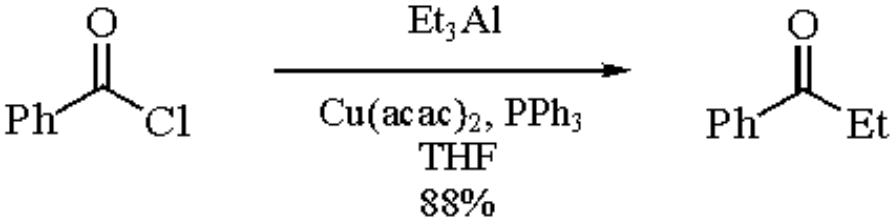

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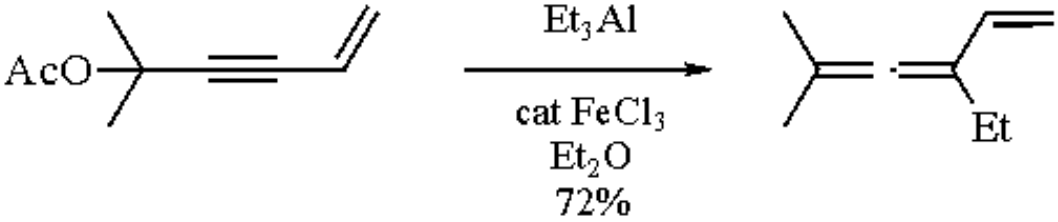

(8)

Lewis Acid.

Et_3Al-***Hydrogen Cyanide*** and ***Diethylaluminum Cyanide*** are two optional reagents for conjugate hydrocyanation of α,β-unsaturated ketones.[12,13] The results from these two reagents often differ. Due to a rather slow reaction rate between Et_3Al and HCN, the former reagent contains a proton source (HCN) which can quench aluminum enolate intermediates. An impressive example is shown in eq 9. Preformed Et_2AlCN gives *cis*-isomer, whereas HCN-Et_3Al leads to *trans*-isomer.[14] A variant involves trapping of the enolates as TMS ethers by use of ***Cyanotrimethylsilane***-Et_3Al (eq 10).[14]

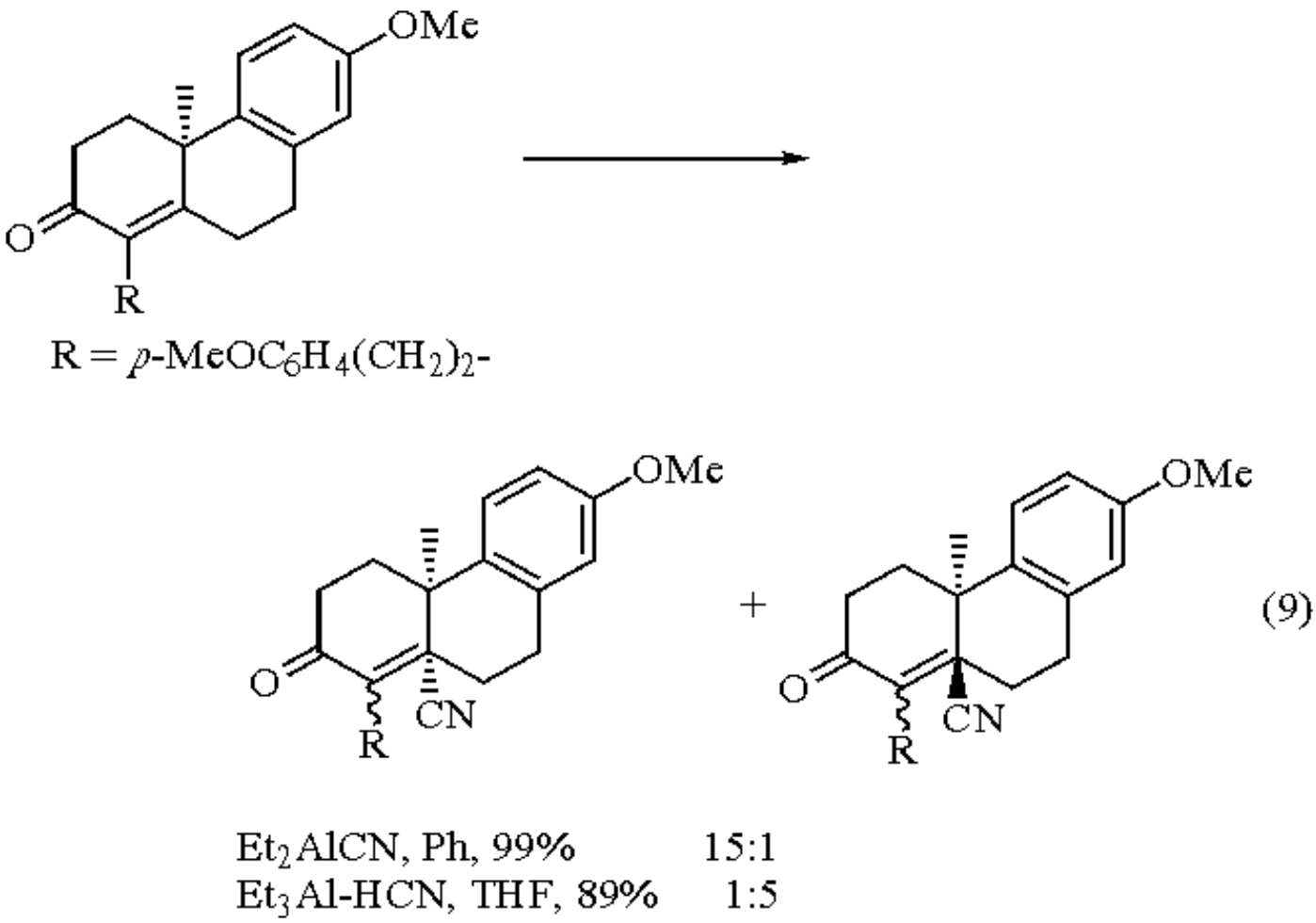

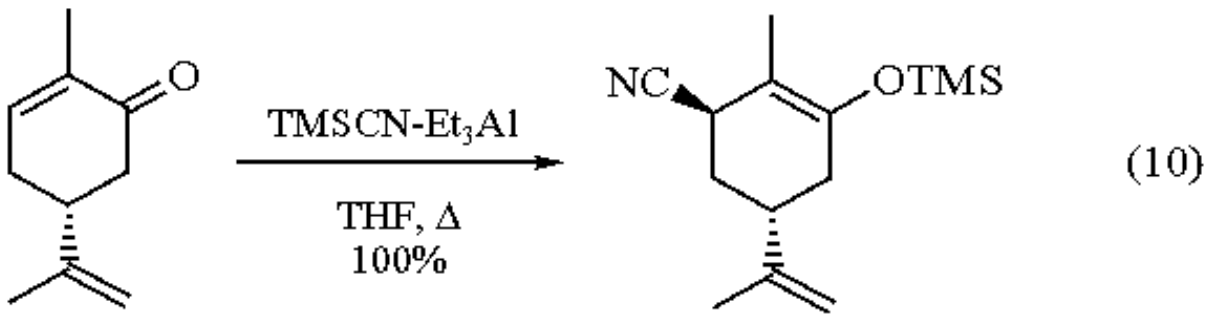

The HCN-Et_3Al system has been used to cleave oxiranes in steroids[15a] or carbohydrates (eq 11) to give β-cyano alcohols.[15b]

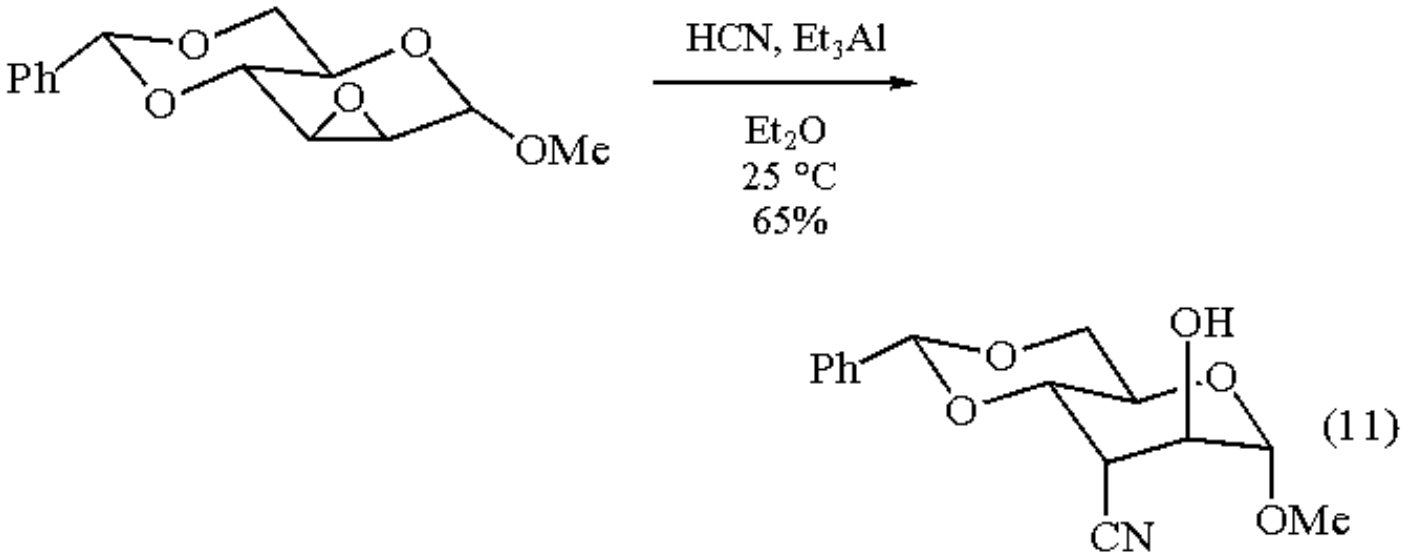

The ate complex, formed on metalation of allyl *i*-propyl ether with ***s-Butyllithium*** followed by addition of Et_3Al, reacts with carbonyl compounds at the α-position in *syn*-selective manner (eq 12).[16]

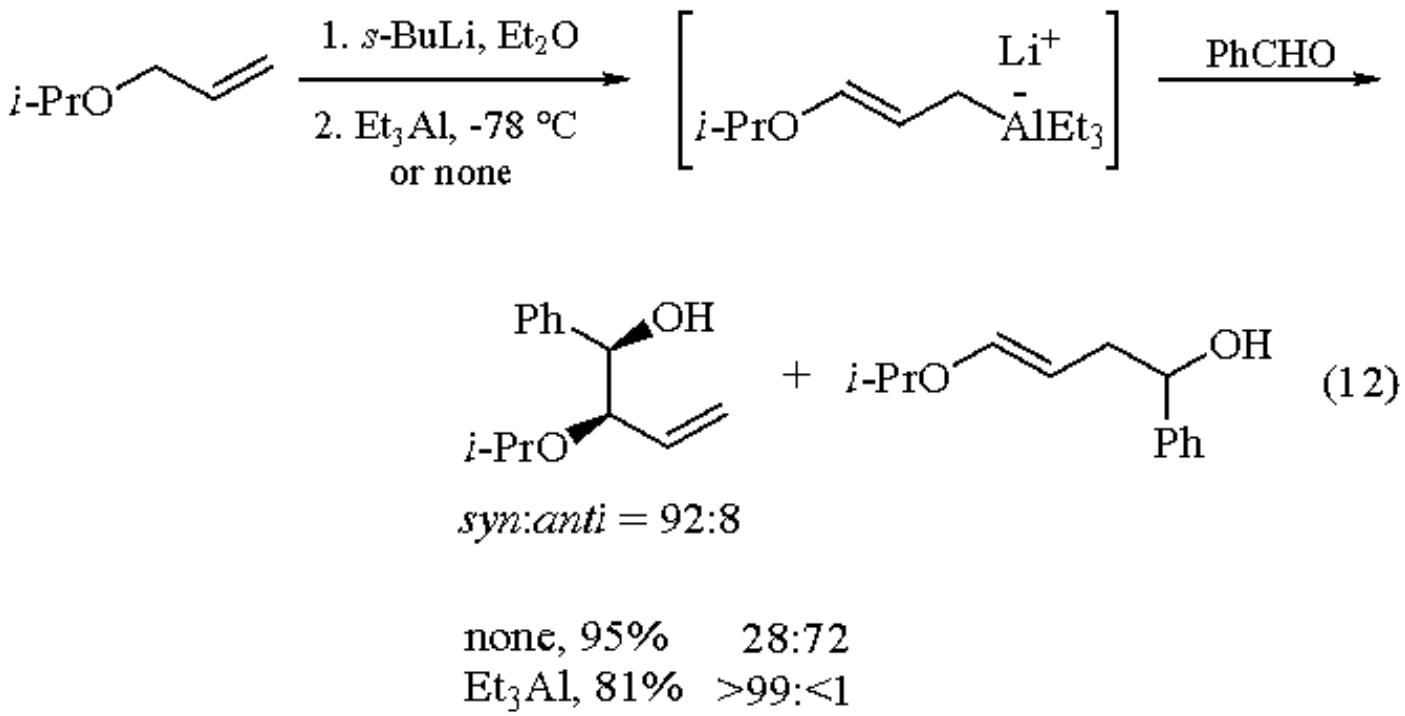

Rearrangements.

Allyl vinyl ethers undergo [3,3]-sigmatropic rearrangements promoted by Et_3Al, which also effects subsequent ethylation of the resulting aldehydes (eq 13). Use of ***Triisobutylaluminum*** leads to primary alcohols by β-hydride reduction.[17]

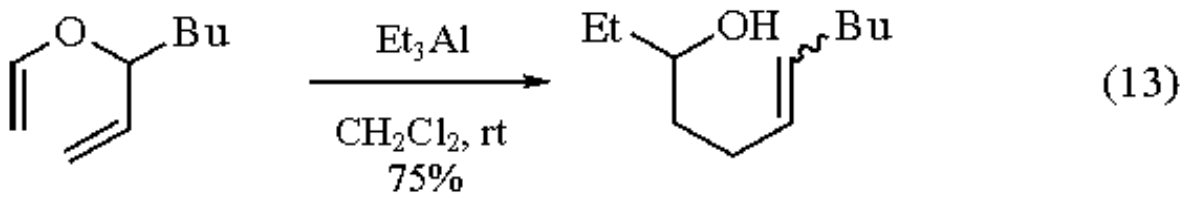

Alkylative Beckmann rearrangements of oxime sulfonates are promoted by trialkylaluminums. The rearrangements give the imines, which are reduced with ***Diisobutylaluminum Hydride*** to the corresponding amines (eq 14).[18] Related alkylative Beckmann fragmentations have also been reported.[19]

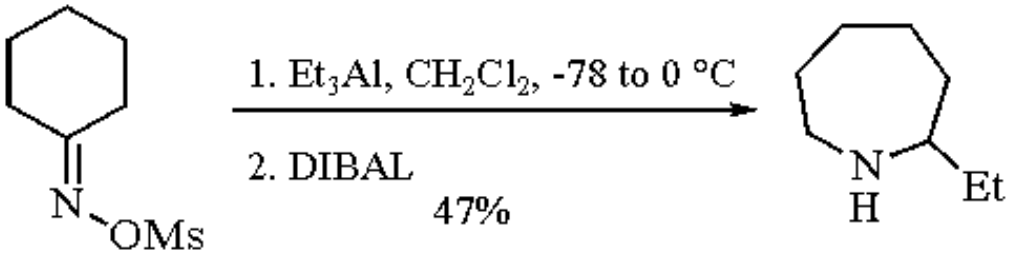

(14)

Et_3Al promotes stereospecific pinacol-type rearrangements of chiral β-methanesulfonyloxy alcohols. Aryl[20a] or alkenyl groups[20b] cleanly take part in the 1,2-migration to provide a range of α-chiral ketones (eq 15). The 1,2-migration of alkyl groups is effected by the more Lewis acidic ***Diethylaluminum Chloride***.[20c] The reagent combination of DIBAL and Et_3Al effects the reductive 1,2-rearrangement of α-mesyloxy ketones (eq 16).[20d,e]

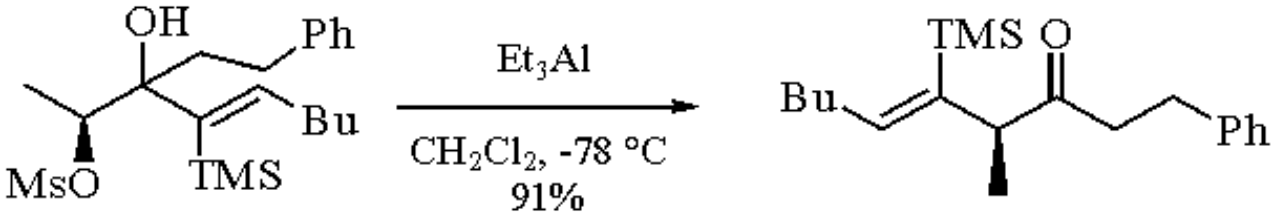

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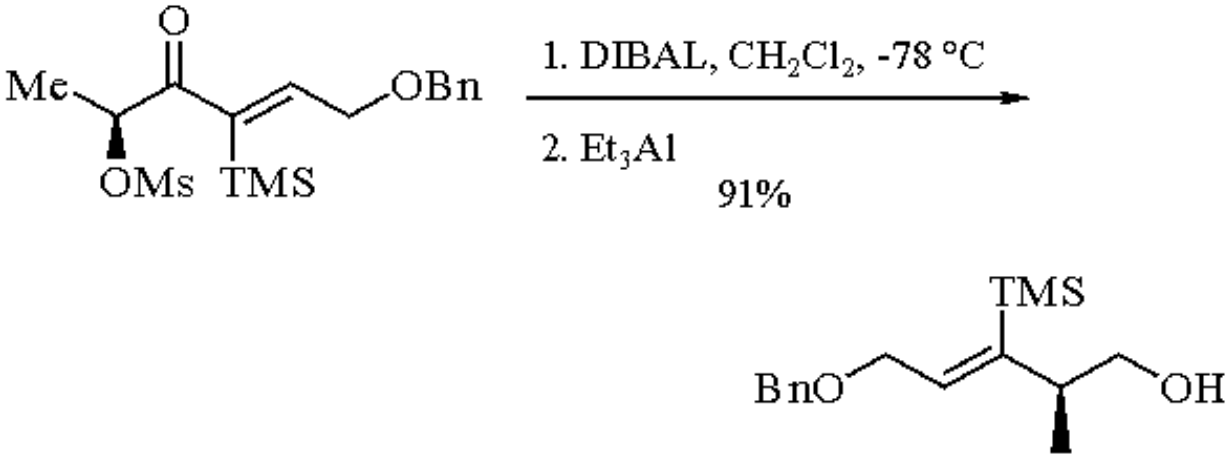

(16)

Cyclopropanation.

The reagent combination of ***Diiodomethane*** and Et_3Al (or other organoaluminums) leads to cyclopropanation of alkenes (eq 17).[21]

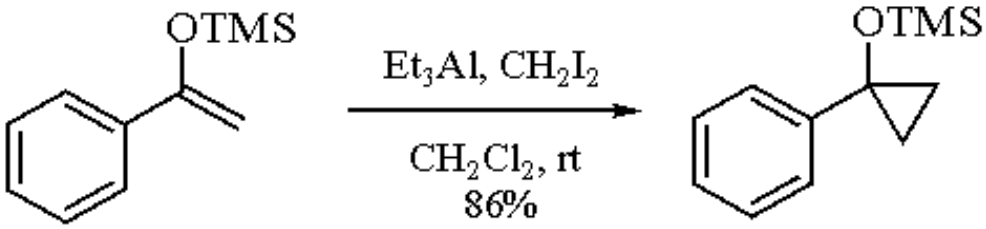

(17)

Related Reagents.

Titanium(IV) Chloride-Triethylaluminum.

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Triethylamine

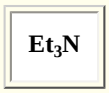

[121-44-8] · $C_6H_{15}N$ · Triethylamine · (MW 101.22)

(tertiary amine base used in oxidation, dehydrohalogenation, and substitution reactions)

Alternate Name: TEA.

Physical Data: bp 88.8 °C; mp -115 °C; *d* 0.726 g cm^{-3}.

Solubility: sol most organic solvents.

Purification: dried over $CaSO_4$, $LiAlH_4$, 4&AAring; sieves, CaH_2, KOH, or K_2CO_3, then distilled from BaO, sodium, P_2O_5 or CaH_2.[1]

Handling, Storage, and Precautions: is a corrosive and flammable liquid. Bottles of triethylamine should be flushed with nitrogen or argon to prevent exposure to carbon dioxide. The vapors are harmful and care should be taken to avoid absorption through the skin. Use in a fume hood.

Introduction.

The most widely used organic amine base in synthetic organic chemistry is probably triethylamine. Its popularity stems from availability and low cost, along with ease of removal by distillation due to a mid-range boiling point (88.8 °C). Also, the hydrochloride and hydrobromide salts are somewhat insoluble in organic solvents, such as diethyl ether, and may be removed by simple filtration. Triethylamine finds wide use in oxidations, reductions, eliminations, substitutions, and addition reactions. There follows a brief compilation of the uses of triethylamine.

Oxidations.

The addition of triethylamine and ***Acetic Anhydride*** during the workup of the ozonolysis of cycloalkenes allows for the selective differentiation of the oxidized termini.[2] Ozonolysis of cycloalkenes in MeOH buffered with $NaHCO_3$ generates the intermediate α-methoxy hydroperoxide aldehyde which dehydrates upon exposure to acetic anhydride and triethylamine to produce aldehyde esters (eq 1). Intermediate peroxy acetals are produced with the addition of ***p-Toluenesulfonic Acid*** to the ozonolysis reaction and similarly dehydrate with triethylamine and acetic anhydride to afford acetal esters. Omitting the acetic anhydride and triethylamine leads to acetal aldehydes under reduction conditions (eq 2).

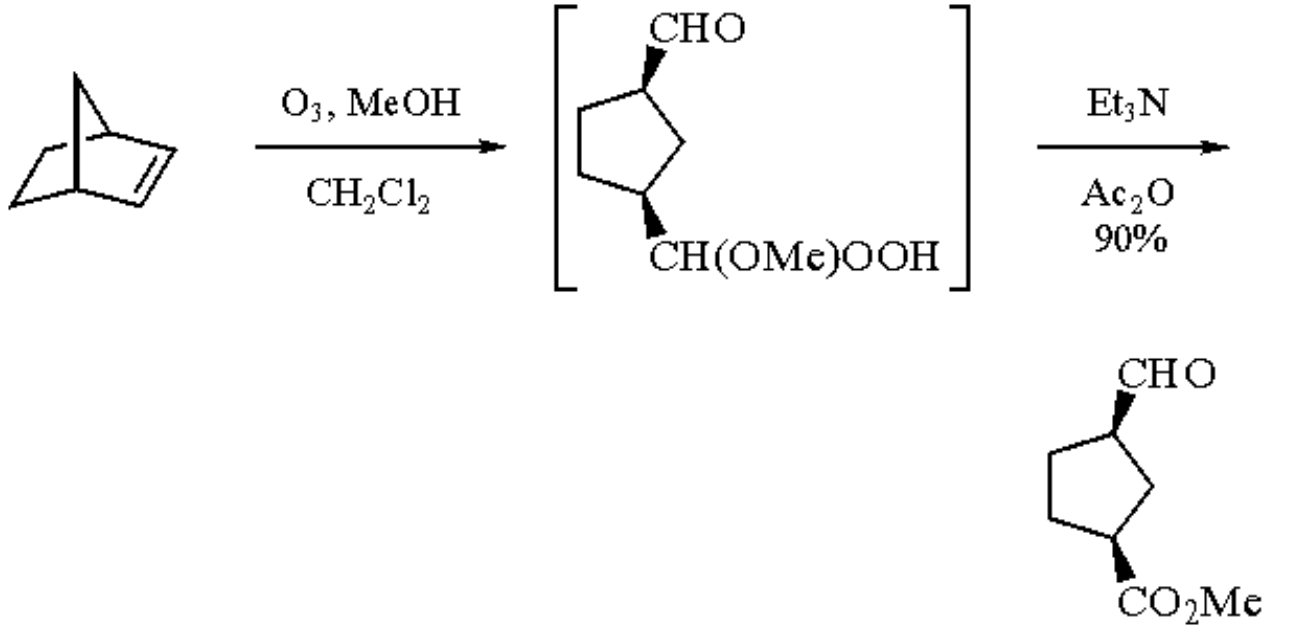

(1)

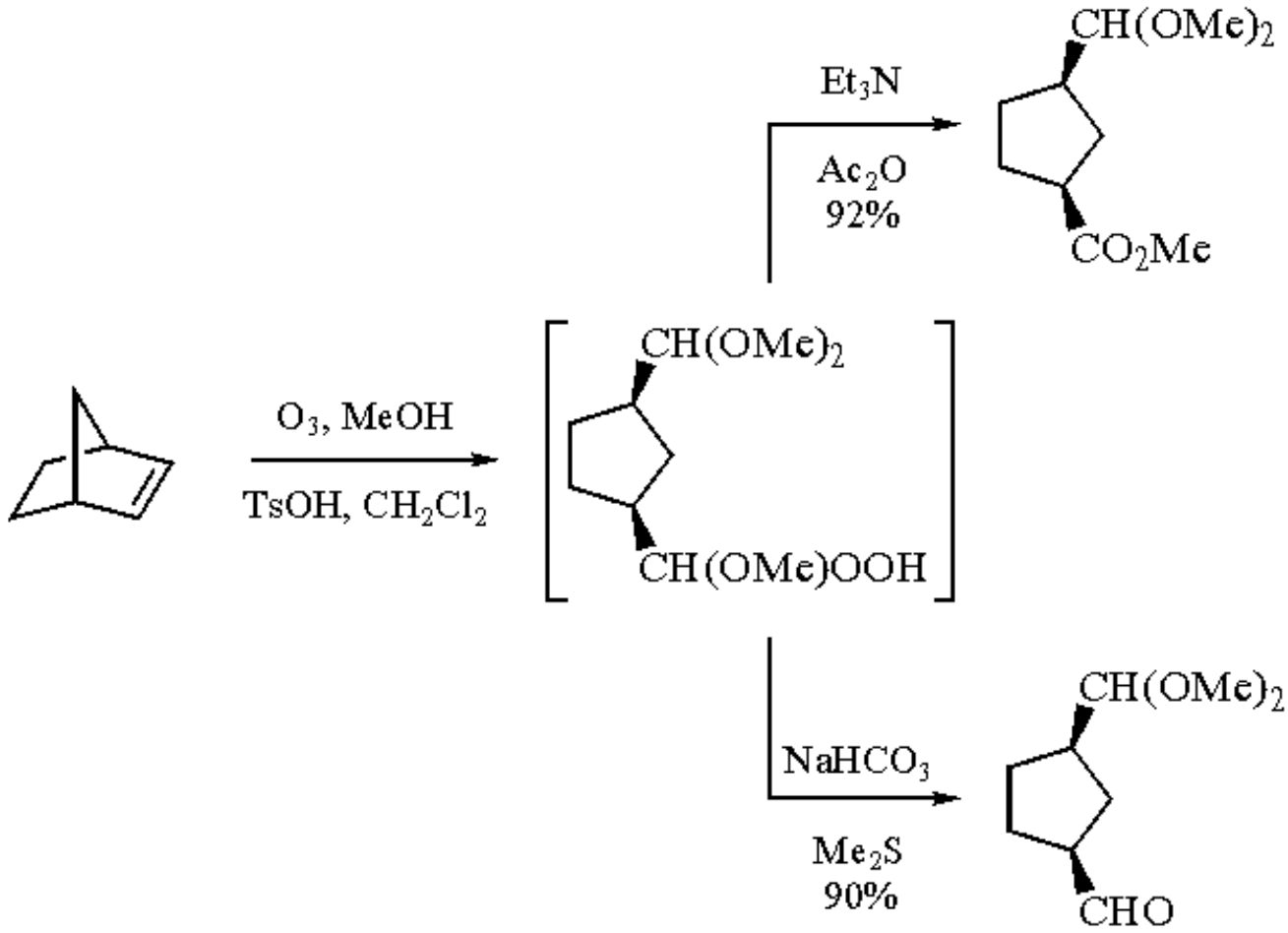

(2)

In the Swern oxidation[3] of alcohols to ketones and aldehydes, employing ***Dimethyl Sulfoxide-Oxalyl Chloride***, triethylamine is usually the amine base utilized in the basification step of the reaction. Mechanistically, the basification step includes deprotonation of the methyl group of the alkoxysulfonium salt intermediate to form an ylide which then yields the carbonyl compound via an intramolecular proton transfer (eq 3).[3b] A similar mechanism is encountered with ***N-Chlorosuccinimide-Dimethyl Sulfide*** and TEA.[4]

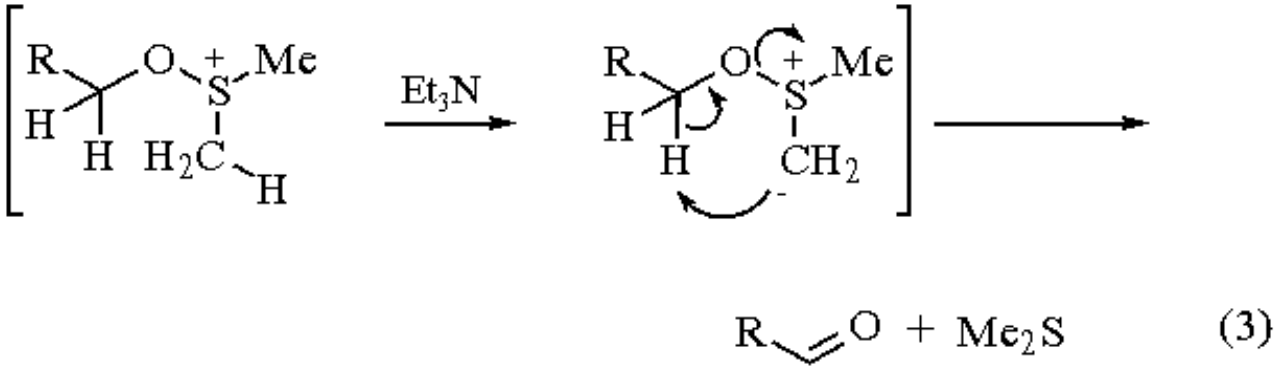

The steric nature of the amine affects the overall performance of the oxidations. In comparative studies involving oxidations with ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***[5] and ***Dimethyl Sulfoxide-Methanesulfonic Anhydride***[6] the sterically hindered ***Diisopropylethylamine*** was found to be superior to TEA (eq 4).[3b]

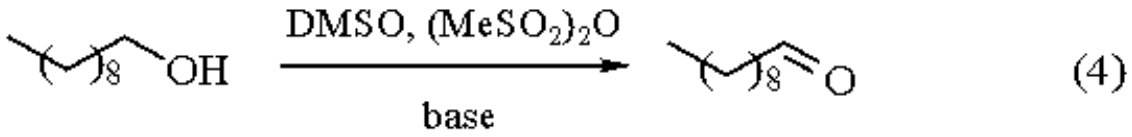

Base	Yield (%)
Et_3N	68
DIPEA	94

The treatment of vicinal diols with an excess of DMSO/trifluoroacetic anhydride followed by basification with TEA results in complete oxidation to α-diketones in good yields (eq 5).[7]

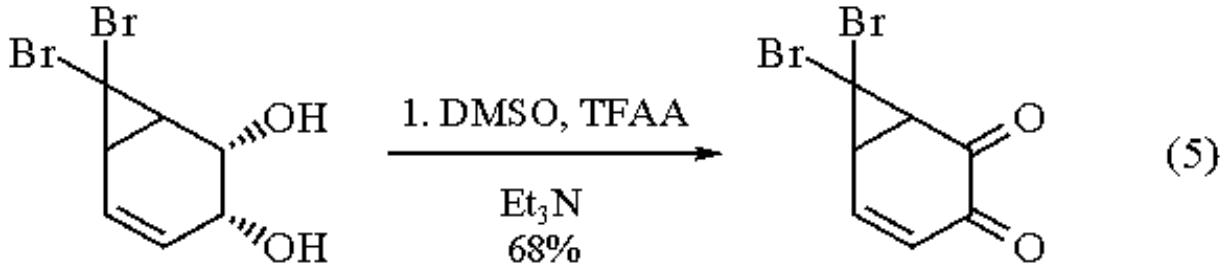

Eliminations.

Dehydrohalogenation of alkyl halides to generate alkenes is normally carried out using alcoholic ***Potassium Hydroxide***; however triethylamine has some utility.[8] For example, bridgehead enones are produced efficiently by treatment of β-bromo ketones with 2 equiv of TEA at 0 °C. The highly reactive enones are not isolated (due to their instability) but can be subsequently trapped with a variety of dienes in a Diels-Alder reaction (eq 6).[9]

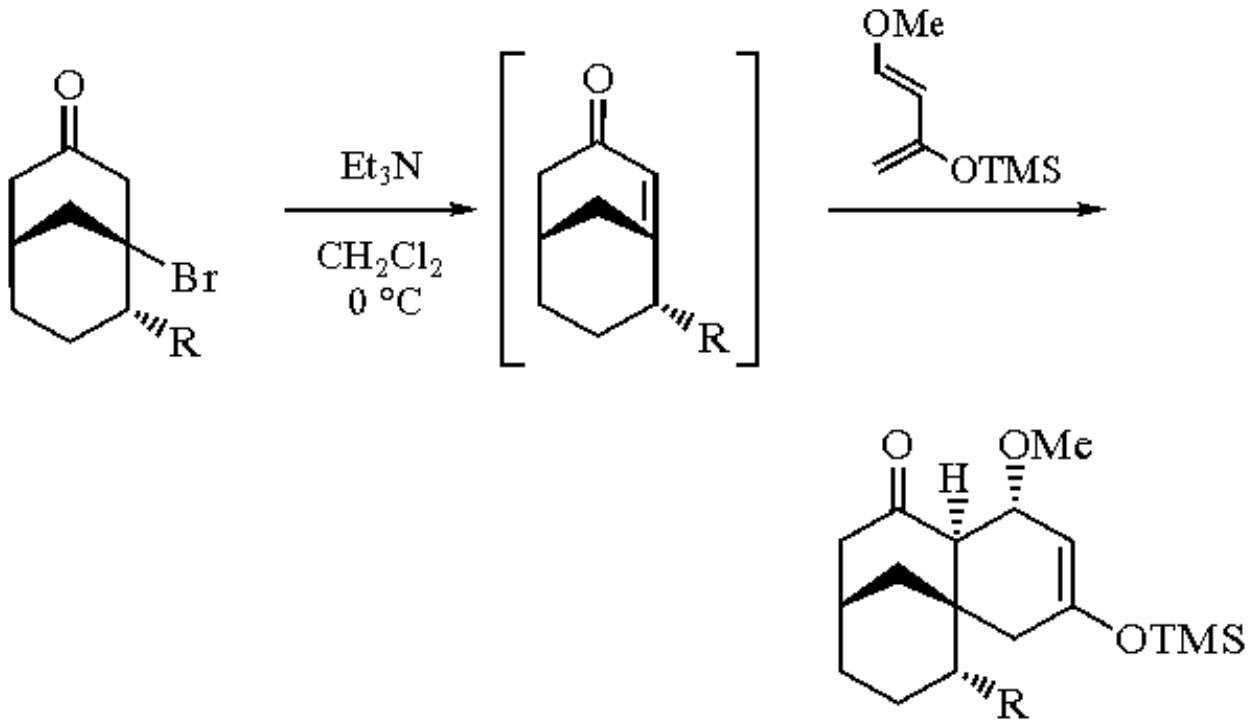

(6)

Triethylamine accomplishes the dehydrobromination of α,α´-dibromo sulfones using TEA in CH_2Cl_2 to afford α,β-unsaturated bromomethyl sulfones in good yields. Further treatment of the sulfones with ***Potassium t-Butoxide*** induces a Ramberg-Bäcklund-like reaction and leads to 1,3-dienes in moderate to good yields (eq 7).[10]

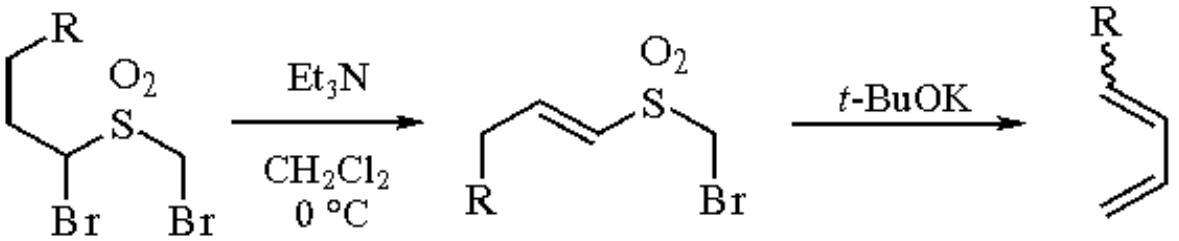

(7)

Chloroalkylidene malonates are converted via a decarboxylation-elimination reaction to alkynic esters by treatment with triethylamine at 90 °C (eq 8).[11] Likewise, triethylamine is the preferred base for the conversion of *erythro*-2,3-dibromobutanoic acid to *cis*-1-bromopropene (eq 9). Pyridine, Na_2CO_3, or $NaHCO_3$ in DMF lead to poor yields of the bromopropene.[12]

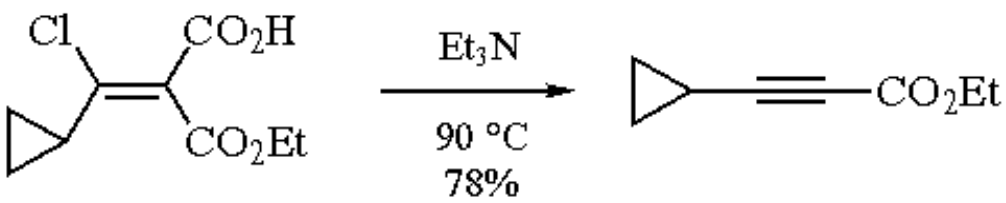

(8)

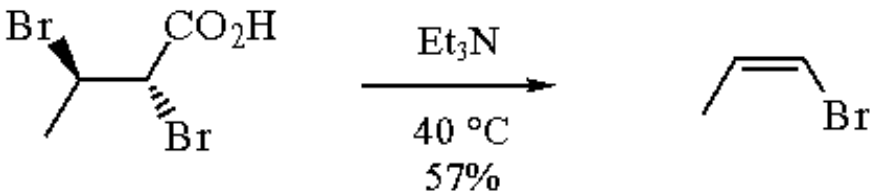

(9)

Exposure of 2,3-dibromo-3,3-difluoropropionyl chloride to ca. 1 equiv of triethylamine in CH_2Cl_2 at 0 °C induces dehydrobromination and leads to 2-bromo-3,3-difluoroacryloyl chloride in 63% yield (eq 10).[13] Under these reaction conditions, the ketene product of dehydrochlorination is not observed.

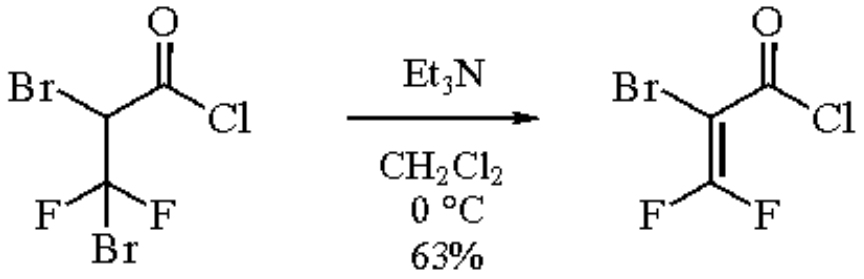

(10)

Dehydrohalogenation of acid chlorides with a tertiary amine is the typical method for the preparation of ketenes,[14] most likely involving an acylammonium intermediate.[15] Other methods are available which involve carboxyl group-activating agents and tertiary amine bases. TEA-generated ketenes find wide application in organic synthesis, in particular in the synthesis of β-lactams[16] using stereo- and enantioselective ketene-imine cycloaddition methodology. For example, the diastereoselective Staudinger [2 + 2] ketene-imine cycloaddition reaction[17] between chiral nonracemic oxazolidinone-*N*-acetyl chlorides and imines[18] generates β-lactams in high yields and with good stereocontrol (eq 11).[19]

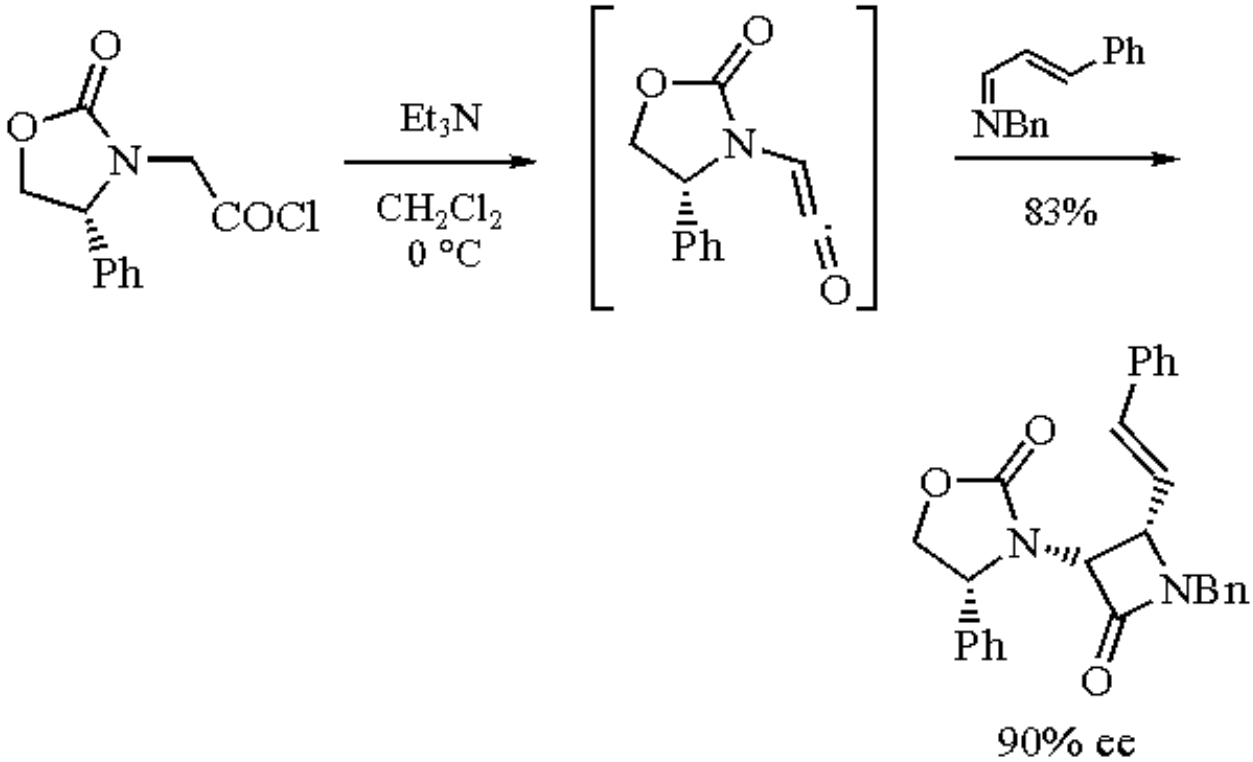

(11)

The dehydration of primary nitroalkanes and the dehydrochlorination of chloroximes allows for the preparation of highly reactive nitrile oxides (eq 12). The nitrile oxides, which are not isolated, undergo facile [3 + 2] cycloaddition reactions[20] with a variety of trapping agents. Subjecting nitroalkanes to 2 equiv of ***Phenyl Isocyanate*** and a catalytic amount of triethylamine[21] effects dehydration to form nitrile oxides (eq 13).[22] Alternatively, treatment of oximes with aqueous ***Sodium Hypochlorite*** and triethylamine in CH_2Cl_2 efficiently produces the nitrile oxides (eq 14).[23]

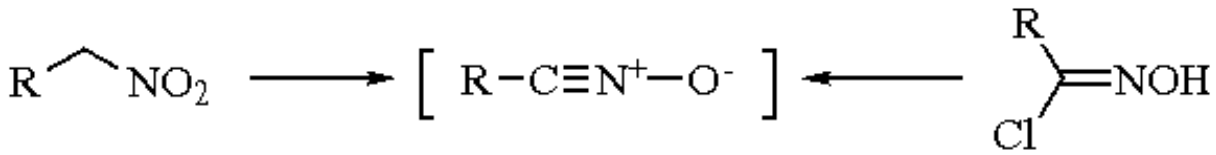

(12)

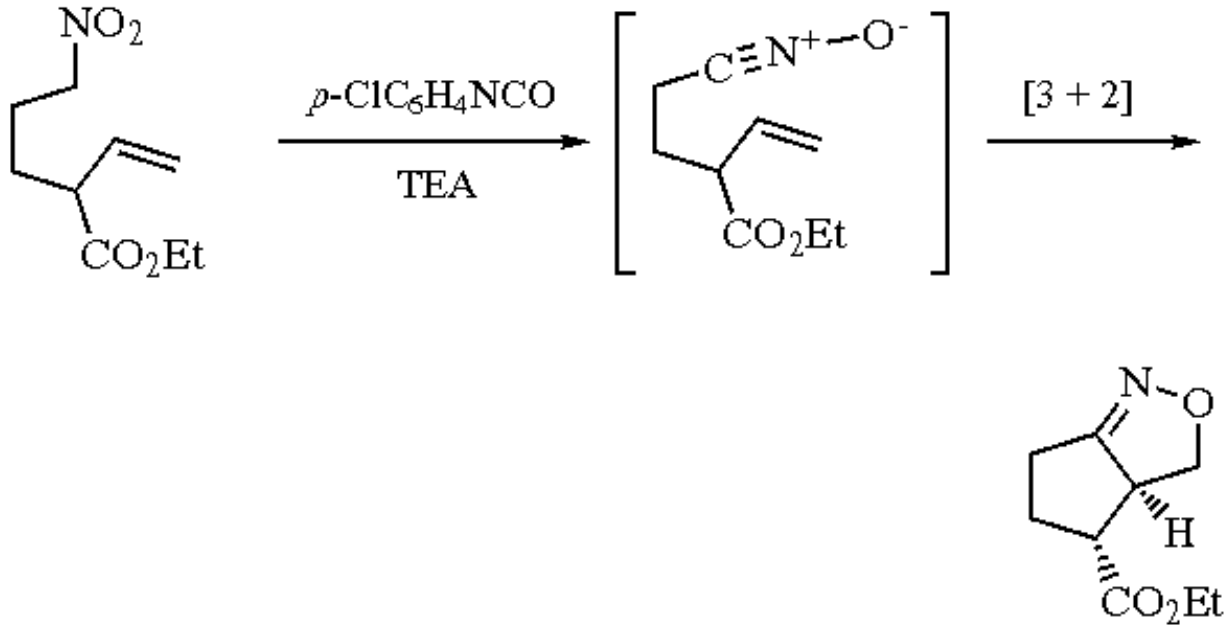

(13)

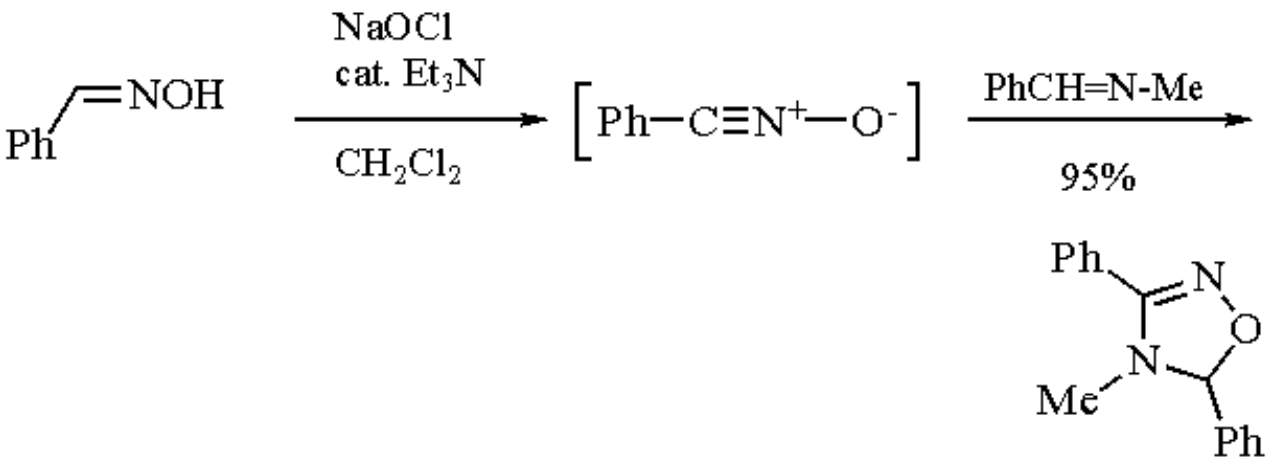

(14)

Substitutions.

Triethylamine finds use as a proton scavenger in palladium-catalyzed coupling reactions involving aryl, alkenyl, allyl, and alkyl derivatives.[24] The palladium-catalyzed coupling of vinyl halides with alkenes (Heck reaction) is an invaluable method for forming carbon-carbon bonds.[25] The elements of an intramolecular Heck reaction and the coupling of allylic alcohols with vinyl halides to afford aldehydes or ketones have been combined to generate moderate to excellent yields of cyclized products (eq 15).[26]

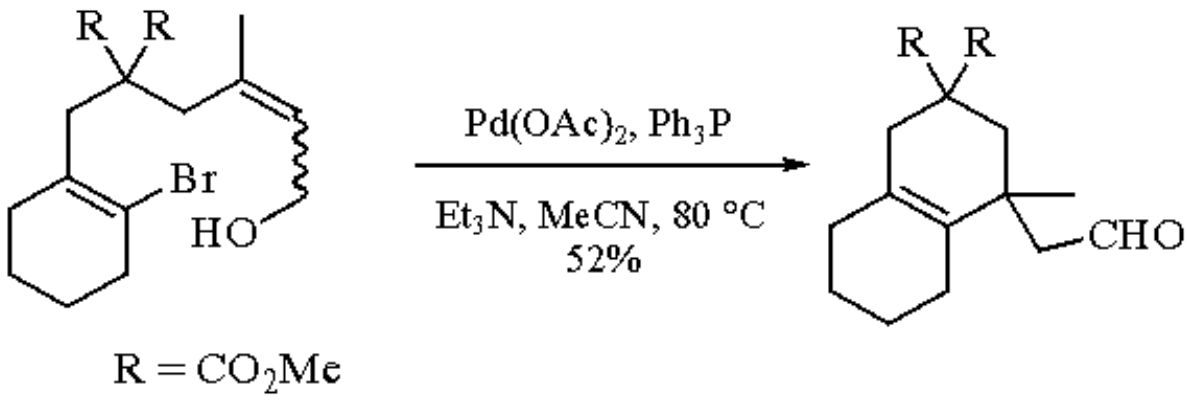

(15)

In an asymmetric variation of the Heck reaction, triethylamine is used in combination with (*R*)-***2,2´-Bis(diphenylphosphino)-1,1´-binaphthyl*** ((*R*)-BINAP) for preparing enantiomerically enriched 2-aryl-2,3-dihydrofurans from aryl triflates.[27] Though TEA resulted in the highest degree of diastereoselectivity, the base ***1,8-Bis(dimethylamino)naphthalene*** (proton sponge) was found to be superior in regards to enantiomeric purity (eq 16).[28,29]

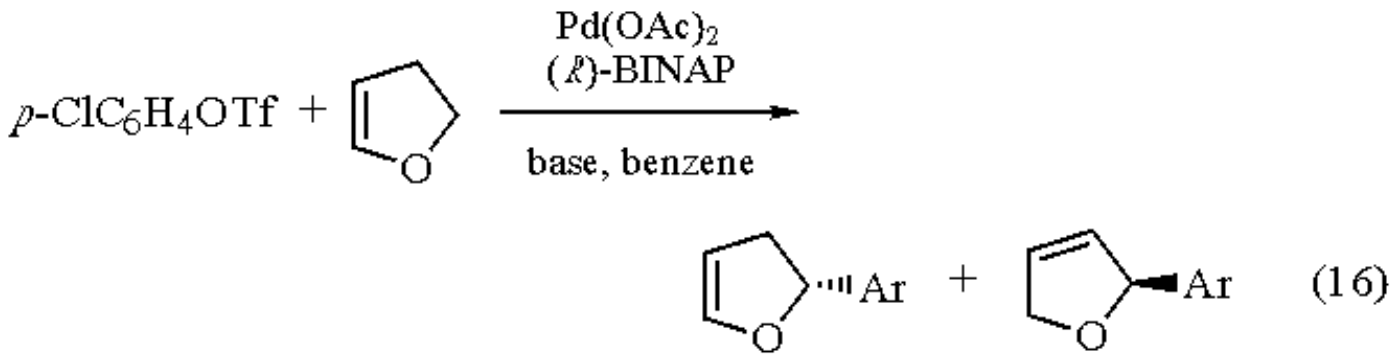

Base	% ee (yield)	% ee (yield)
DIPEA	82 (92)	60 (8)
Et_3N	75 (98)	9 (2)
proton sponge	96 (71)	17 (29)

Triethylamine also finds use in the enolboronation of various carbonyl compounds using dialkylboron halides.[30] These boron enolates are valuable in the stereocontrolled aldol reaction. Proper choice of boron reagent, reaction solvent, reaction temperature, and tertiary amine base influences the enolate geometry of ketones[31] and esters.[32] The use of the sterically demanding dialkylboron halides, such as dicyclohexylboron chloride (Chx_2BCl), with triethylamine favors formation of the (*E*)-enol borinates, while dialkylboron triflates or dialkylboron halides, such as *B*-chloro-9-BBN, with diisopropylethylamine in ether at -78 °C favor the (*Z*)-enol borinates (eq 17).[31a,b] For similar complementary methodologies for generating both the (*E*)- and (*Z*)-boron enolates of esters, see ***Diisopropylethylamine***.

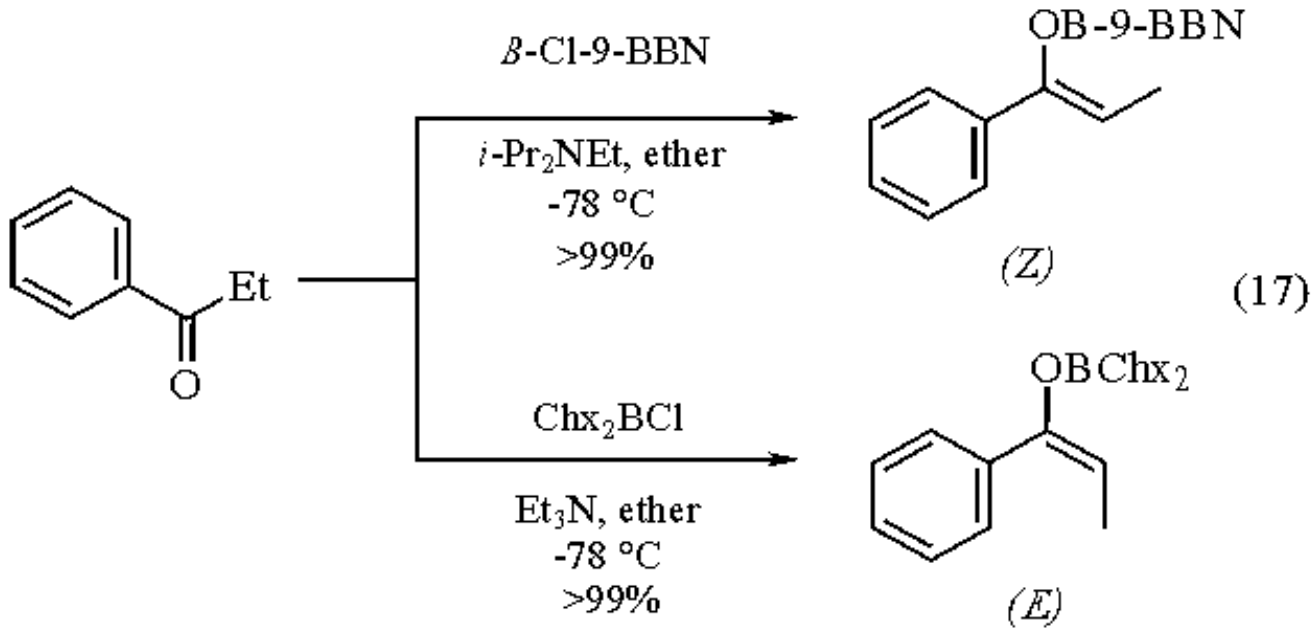

The asymmetric aldol addition involving *N*-acyloxazolidinones and aldehydes can be carried out with high stereoselectivity utilizing ***Tin(II) Trifluoromethanesulfonate*** and triethylamine. Treatment of *N*-(isothiocyanoacetyl)-2-oxazolidinones and aldehydes with tin(II) triflate and TEA at -78 °C in THF leads to high yields of aldol products with high diastereoselectivity (eq 18).[33]

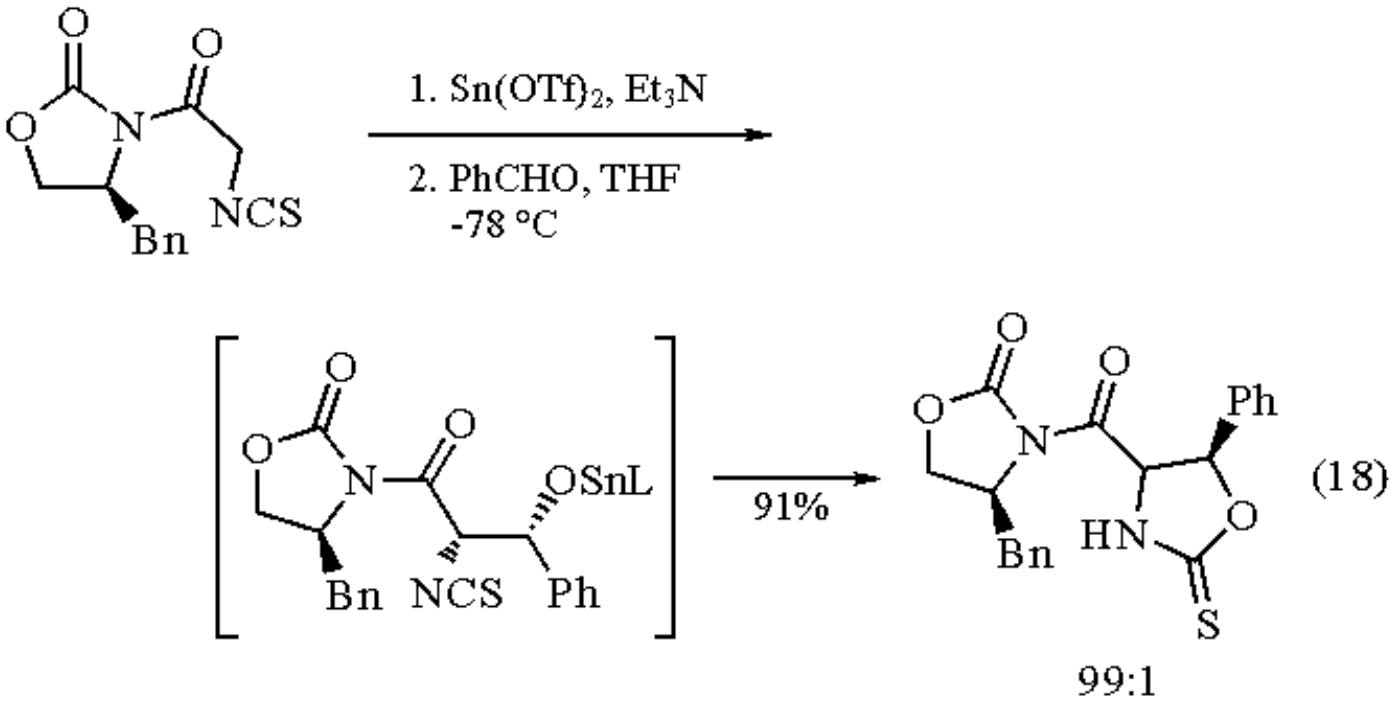

The regioselective synthesis of silyl enol ethers involves the trapping of the enolate anion of ketones and esters under kinetic or thermodynamic conditions.[34] Treatment of the unsymmetrical ketone 2-methylcyclohexanone with TEA and ***Chlorotrimethylsilane*** in DMF affords a 22:78 mixture of the kinetic and thermodynamic trimethylsilyl enol ethers. Using ***Lithium Diisopropylamide*** in DME under kinetic control leads to a >99:1 mixture of the kinetic and thermodynamic silyl enol ethers in 74% yield (eq 19).[35] Likewise, treatment of acetone with chlorotrimethylsilane, TEA, and anhydrous ***Sodium Iodide*** in acetonitrile leads to acetone trimethylsilyl enol ether in good yield.[36]

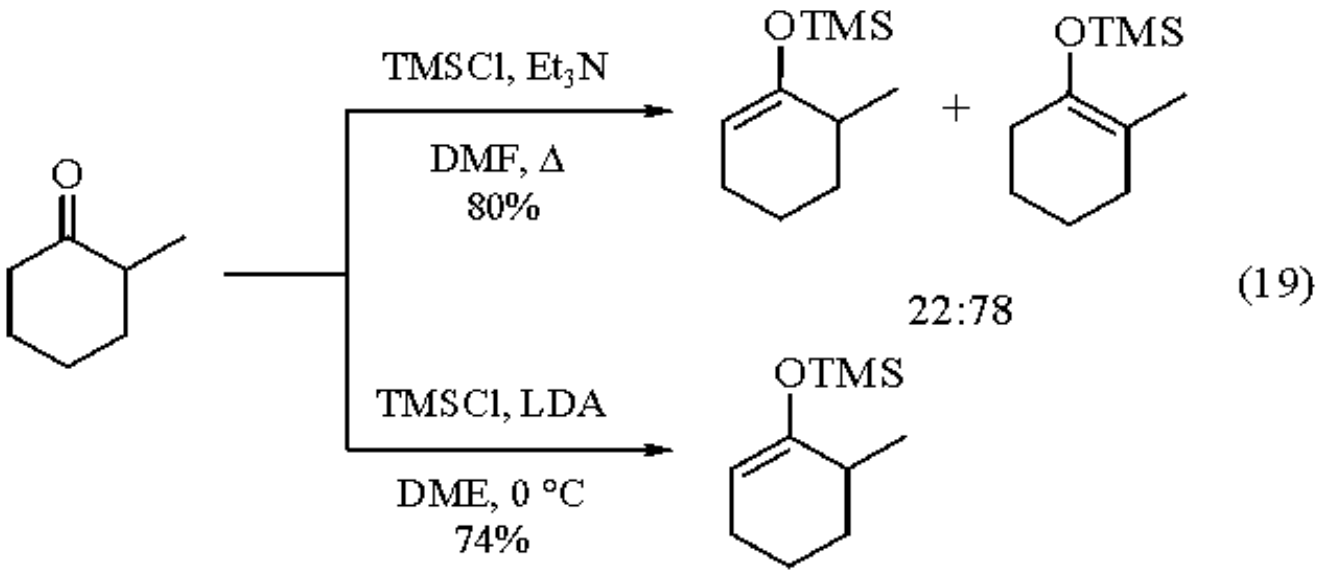

The mixture of TEA and ***Zinc Chloride*** is effective for converting α,β-unsaturated ketones and aldehydes into the corresponding silyl enol ethers. The Danishefsky-Kitahara diene is prepared in 68% yield by treatment of 4-methoxy-3-buten-2-one with an excess of TEA and TMSCl in the presence of a catalytic amount of anhydrous $ZnCl_2$ in benzene (eq 20).[37] Under similar reaction conditions, crotonaldehyde and 3-methylcrotonaldehyde are also converted into their corresponding enol ethers. 3-Methylcrotonaldehyde leads to an 80/20 mixture of (*E*/*Z*) dienes, while crotonaldehyde yields the (*E*)-silyl enol ether exclusively (eq 21).[38]

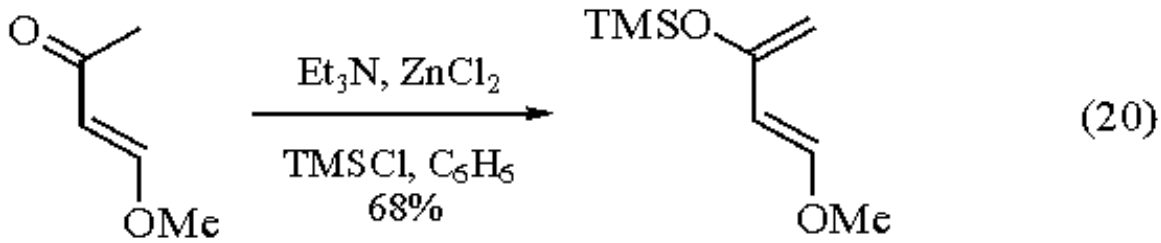

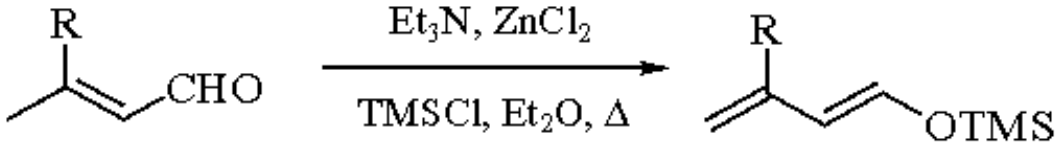

(21)

R = H; *E*:*Z* = 100:0 (62%)
R = Me; *E*:*Z* = 80:20 (74%)

Triethylamine in combination with ***Triethylsilyl Perchlorate*** is somewhat selective in the generation of the (*Z*)-silylketene acetal of isopropyl propionate (eq 22)[39] (see ***2,2,6,6-Tetramethylpiperidine*** for a comparison of other bases). Triethylamine and ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** (TBDMSOTf) are quite effective in preparing silyl enol ethers from sterically hindered ketones and lactones (eq 23).[40]

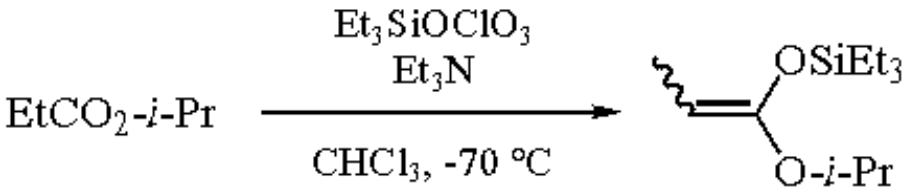

(22)

(*E*):(*Z*) = 37:63

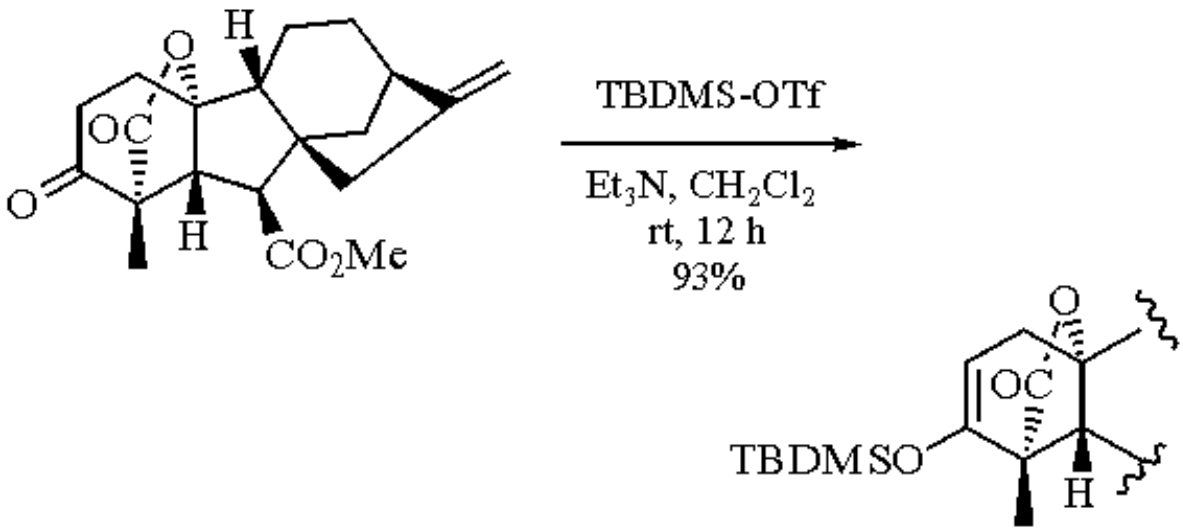

(23)

Triethylamine is the base of choice in neutralizing the acids liberated in preparing (1) diazo ketones from acid chlorides and ***Diazomethane***, (2) mixed anhydrides from carboxylic acids and alkyl haloformates, and (3) esters from carboxylic acids and alkyl halides, such as phenacyl bromide.[41]

Triethylamine is particularly useful as a proton scavenger in the field of protective group chemistry.[42] For just a few examples: alcohols have been protected as substituted methyl ethers with such alkylating agents as ***Chloromethyl Methyl Sulfide***[43] and ***t-Butyl Chloromethyl Ether***[44] using TEA as a base. Primary alcohols can be selectively silylated in the presence of secondary and tertiary alcohols using ***t-Butyldiphenylchlorosilane*** with TEA and a catalytic amount of ***4-Dimethylaminopyridine*** (eq 24).[45] The selective benzoylation of diols can be achieved using 1-(benzoyloxy)benzotriazole (BOBT) and TEA in CH_2Cl_2 at room temperature (eq 25).[46] Diols, in particular 1,2- and 1,3-diols, react with ***Di-t-butyldichlorosilane*** in the presence of TEA and a variety of silyl transfer agents to afford the di-*t*-butylsilylene derivatives in good yields (eq 26).[47]

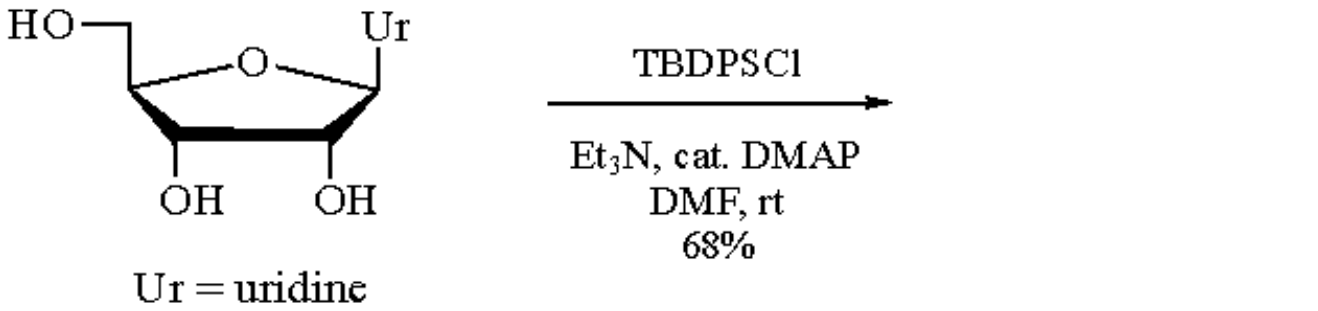

(24)

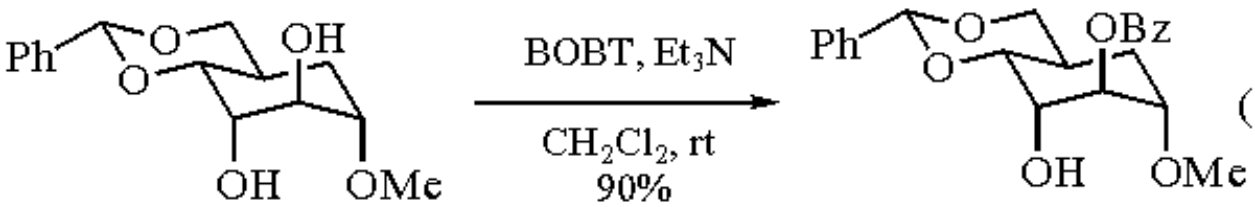

(25)

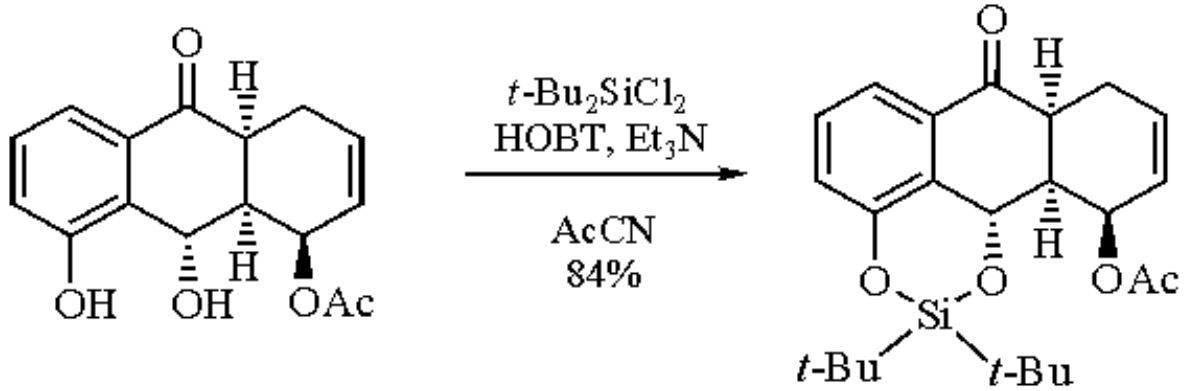

(26)

Carbamates are cleaved easily to alcohols upon exposure to ***Trichlorosilane*** and TEA[48] and carboxylic acids are conveniently esterified using equimolar amounts of alkyl chloroformates with triethylamine and a catalytic amount of ***4-Dimethylaminopyridine***.[49] TEA is an effective base for the alkylation (protection) of carboxylic acids with ***Chloroacetonitrile*** to produce cyanomethyl esters.[50] Primary amines with pK_a values of 10-11 react with 1,1,4,4-tetramethyl-1,4-dichlorodisilethylene in the presence of TEA at rt to afford the disilylazacyclopentane derivatives in high yields (eq 27).[51] Amines with lower pK_a values require ***n-Butyllithium*** as the base or can be protected via a ***Zinc Iodide***-catalyzed trans-silylation with 1,1,4,4-tetramethyl-1,4-bis(*N*,*N*-dimethylamino)disilethylene (eq 28).[52]

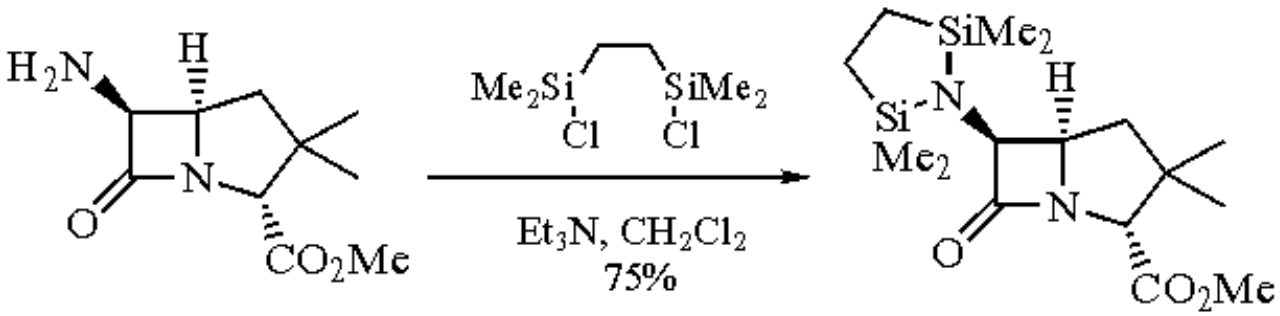

(27)

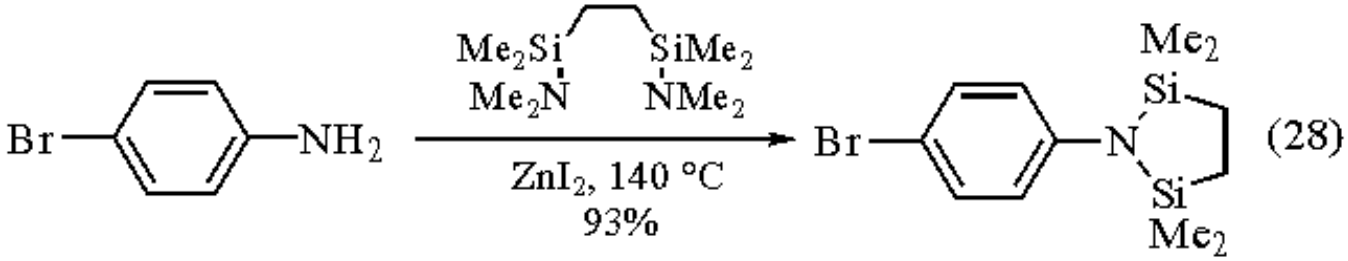

Triethylamine and other tertiary amines find utility in the derivatization of amino acids as well as coupling reactions to prepare peptides.[53] The basicity and steric nature of the tertiary amine utilized during the coupling reaction influences the degree of racemization.[54]

Related Reagents.

Palladium-Triethylamine-Formic Acid.

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Triethylammonium Bis(catecholato)allylsiliconate[1]

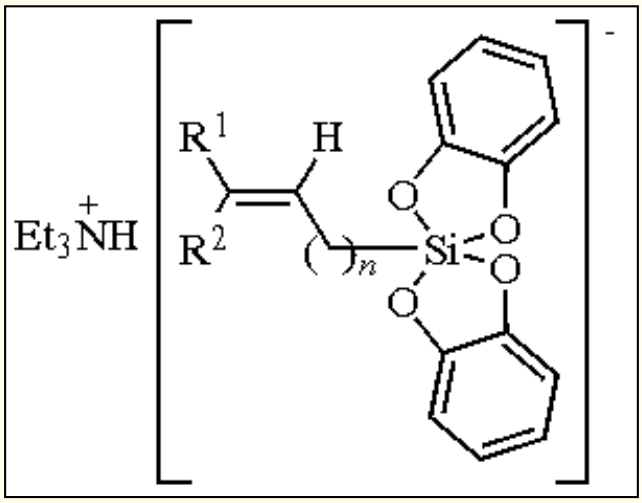

(**1**; $R^1 = R^2 = H$; $n = 1$)

[114612-18-9] · $C_{21}H_{29}NO_4Si$ · Triethylammonium Bis(catecholato)allylsiliconate · (MW 387.60) (**2**; $R^1 = R^2 = Me$; $n = 1$)

[114571-77-6] · $C_{23}H_{33}NO_4Si$ · Triethylammonium Bis(catecholato)prenylsiliconate · (MW 415.66) (*E*)-(**3**; $R^1 = Me$, $R^2 = H$; $n = 1$)

[125715-28-8] · $C_{22}H_{31}NO_4Si$ · Triethylammonium Bis(catecholato)crotylsiliconate · (MW 401.63) (*Z*)-(**3**; $R^1 = Me$, $R^2 = H$; $n = 1$)

[125715-32-4] (**4**; $R^1 = R^2 = H$; $n = 0$)

[123806-99-5] · $C_{20}H_{27}NO_4Si$ · Triethylammonium Bis(catecholato)vinylsiliconate · (MW 373.57) (**5**; $R^1 = Bu$, $R^2 = H$; $n = 0$)

[123723-08-0] · $C_{24}H_{35}NO_4Si$ · Triethylammonium Bis(catecholato)(1-hexenyl)siliconate · (MW 429.69)

(regiospecific and diastereoselective allylation of aldehydes;[2] cross-coupling reaction with organic halides and triflates catalyzed by a palladium complex[3])

Physical Data: (**1**) mp 120 °C (dec); (**2**) mp 94 °C (dec); (**3**) (*E*:*Z* = 90:10), mp 124 °C (dec).

Analysis of Reagent Purity: tetramethylsilane was used as an internal standard for ^1H, ^{13}C, and ^{29}Si NMR: (**1**) ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 9H), 1.69 (d, *J* = 8 Hz, 2H), 3.17 (q, *J* = 7 Hz, 6H), 4.50-4.76 (m, 2H), 5.52-5.91 (m, 1H), 6.67 (m, 8H), 7.69 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 8.72 (q), 24.60 (t), 46.43 (t), 110.69 (d), 111.56 (t), 118.77 (d), 136.91 (d), 149.48 (s); ^{29}Si NMR ($CDCl_3$) δ -78.40. (**4**) ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7 Hz, 9H), 3.17 (q, *J* = 7 Hz, 6H), 5.59-6.24 (m, 3H), 6.67 (m, 8H), 7.48 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 8.75 (q), 28.88 (t), 110.77 (d), 118.84 (d), 132.96 (t), 137.78 (d), 149.40 (s); ^{29}Si NMR ($CDCl_3$) δ -87.45.

Handling, Storage, and Precautions: these reagents should be stored under an inert atmosphere in a dry box.

Allylation of Aldehydes.

Triethylammonium bis(catecholato)allylsiliconates (**1**-**3**) are readily prepared from allyltrimethoxysilanes, two equivalents of ***Catechol***, and

Triethylamine.[4] Synthetic routes to other pentacoordinate allylsiliconates have been described.[5,6] Allylsiliconate (**1**) reacts with aliphatic and aromatic aldehydes without Lewis acid[7] or fluoride ion[8] catalysts to give the corresponding homoallyl alcohols in good yield (eq 1). However, these reagents are not effective for the allylation of ketones. The aldehyde allylation occurs even in the presence of the nitro and cyano groups. The reaction of α,β-unsaturated aldehydes proceeds exclusively by 1,2-addition.

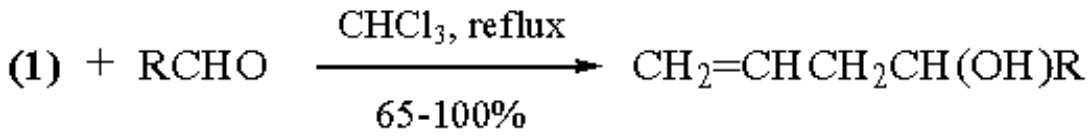

R = Ph, *p*-NCC_6H_4, *p*-$O_2NC_6H_4$, $C_6H_4CH{=}CH$, Pr, etc.

The allylation of aldehydes is completely regiospecific and carbon-carbon bond formation occurs at the γ-position of the allyl group of prenyl- (**2**) and crotylsiliconate (**3**). In addition, high *anti* diastereoselectivity is observed in the reaction of (**3**) (Table 1).

Table 1 Allylation of Aldehydes with Prenyl- or Crotylsiliconate

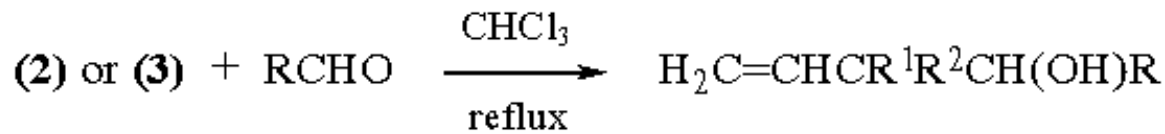

Allylsiliconate	R	Yield (%)	*syn*:*anti*
(2) R^1, R^2 = Me	Ph	72	-
(2) R^1, R^2 = Me	*p*-NCC_6H_4	68	-
(3) R^1 = H, R^2 = Me (*E*:*Z* = 90:10)	Ph	88	10:90
(3) R^1 = H, R^2 = Me (*E*:*Z* = 90:10)	*p*-NCC_6H_4	96	10:90

Allylsiliconates can be generated in situ from trimethoxyallylsilane in the presence of aldehydes (eq 2). Enantioselective allylation of an aldehyde by optically active allyltriethoxysilanes, catechol, and triethylamine reveals that the reaction mechanism involves a cyclic transition state (eq 3), in sharp contrast to the results for the tetracoordinate allylsilane in which the acyclic S_E' pathway has been demonstrated.[9]

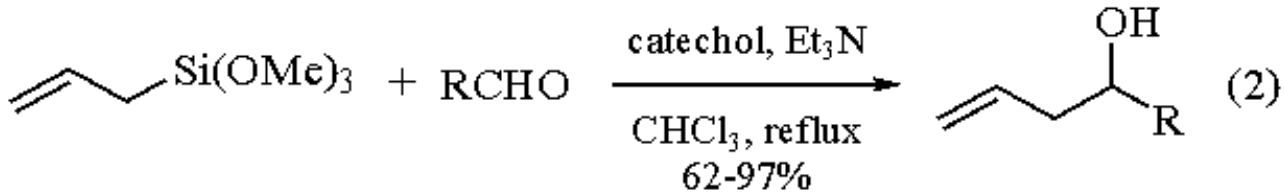

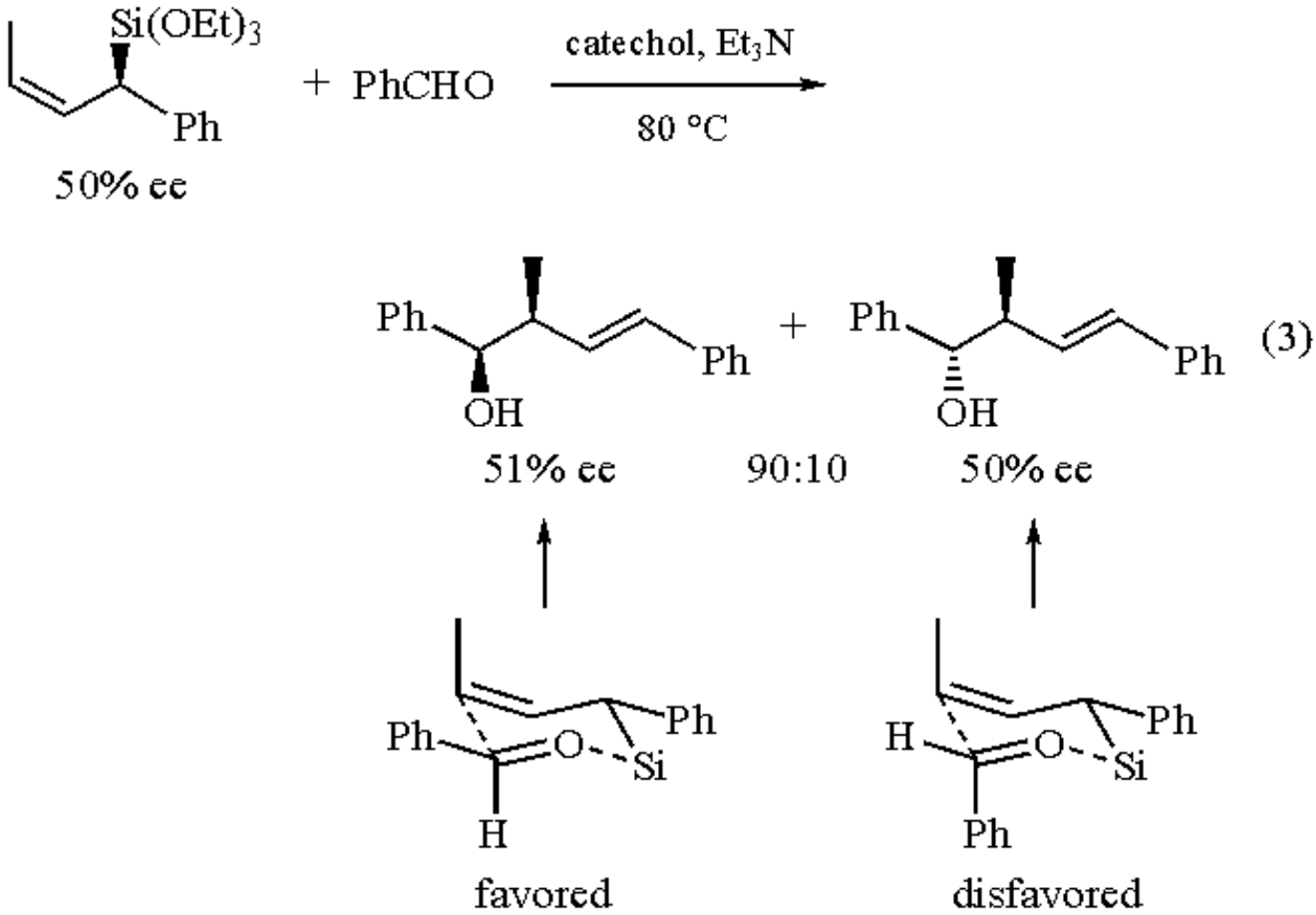

Cross-Coupling Reactions.

Triethylammonium bis(catecholato)vinylsiliconate (**4**), derived from vinyltrimethoxysilane, undergoes palladium-catalyzed cross-coupling reactions with aryl halides or triflates (eq 4). ***Tetrakis(triphenylphosphine)palladium(0)***, ***Bis(benzonitrile)dichloropalladium(II)***, and ***Bis(allyl)di-μ-chlorodipalladium*** are effective catalysts for this reaction, but ***Triethyl Phosphite*** or ***Lithium Chloride*** additives are required. The reaction with (*E*)-1-halo-1-alkenes proceeds with retention of stereochemistry to provide 1,3-dienes (eq 5).

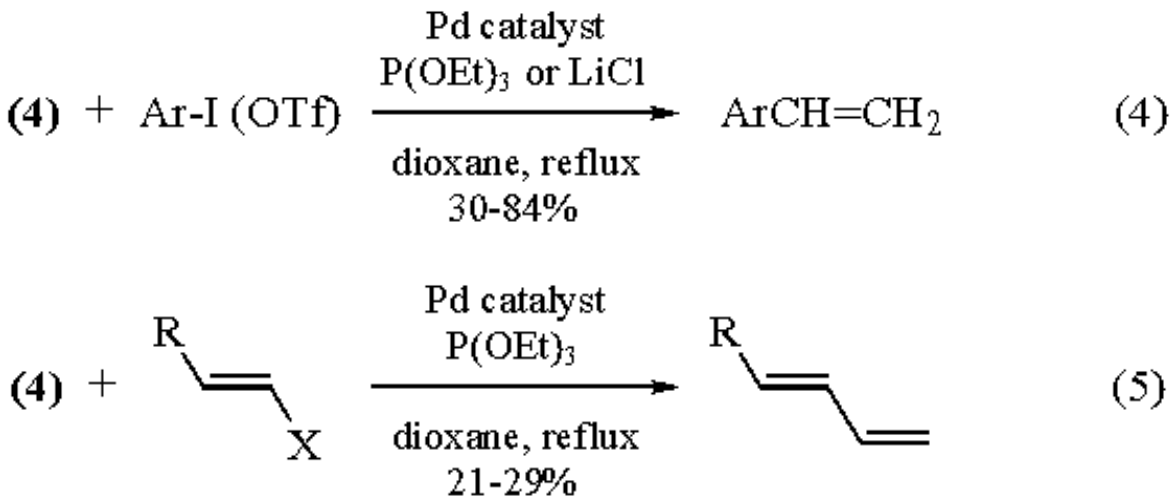

(*E*)-1-Hexenylsiliconate (**5**) can be used for the reaction with aryl halides and triflates, although the products are not 1,2-disubstituted ethylenes, normal coupling products, but 1,1-disubstituted ethylenes (eq 6).[10]

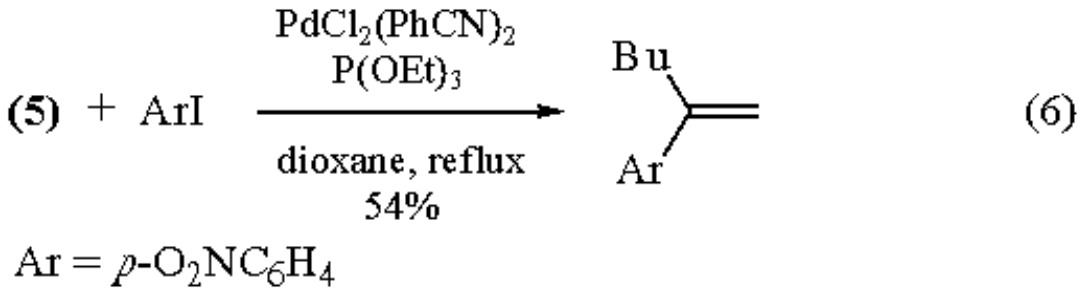

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Triethylborane

Et_3B

[97-94-9] · $C_6H_{15}B$ · Triethylborane · (MW 98.02)

(precursor of triethylborohydride reducing agents;[1] enoxytriethylborates and -diethylboranes for aldol[19,22] and alkylation[17] reactions; regio- and stereoselective reactions of allyltriethylborates;[26,27] alkylating reagents;[1b] stereocontrol of carbanion reactions;[39,41] radical initiator[44])

Physical Data: mp -93 °C; bp 95 °C; *d* 0.677 g cm^{-3}.

Solubility: sol ethanol, acetone, THF, ether, hexane, benzene, $CHCl_3$.

Form Supplied in: colorless liquid; widely available. Since it is highly flammable, triethylborane diluted with hexane or THF (1.0 M solution) is also available.

Handling, Storage, and Precautions: neat triethylborane ignites instantaneously upon contact with air. The reagent should be handled with a syringe under Ar or N_2 atmosphere. It is stable toward moisture and water, and reputed to be toxic. Use in a fume hood.

Reducing Reagents.

Lithium Triethylborohydride, known as Super-Hydride, is prepared in THF by the reaction of lithium hydride with triethylborane (eq 1).[1] Alkali metal trialkylborohydrides are exceptionally powerful nucleophilic reducing agents capable of cleaving cyclic ethers,[2] reducing hindered halides,[3] *p*-toluenesulfonate esters of hindered and cyclic alcohols,[4] epoxides,[5] and activated alkenes[6] rapidly and quantitatively to the desired products. The advantage of $LiEt_3BH$ is especially evident in the reduction of labile bicyclic epoxides (eq 2). Thus benzonorbornadiene oxide, which invariably gives rearranged products with conventional reducing agents, undergoes facile reduction with $LiEt_3BH$ yielding 93% of *exo*-benzonorborneol in >99.9% isomeric purity. The reactivity of the trialkylborohydrides and the stereochemical course of their reactions are strongly influenced by the steric bulk of the alkyl group on boron.[7] The lithium hydride route (eq 1) provides a convenient entry only to the relatively unhindered lithium trialkylborohydrides. However, ***Potassium Hydride*** reacts rapidly and quantitatively with the hindered trialkylboranes, such as tri-*s*-butylborane, yielding the corresponding sterically hindered trialkylborohydride ***Potassium Tri-s-butylborohydride***.[8] A general synthesis of lithium trialkylborohydrides has been developed using lithium trimethoxyaluminohydride (eq 3).[9]

$$LiH + BEt_3 \xrightarrow[25\ °C]{THF} LiEt_3BH \qquad (1)$$

Super-Hydride

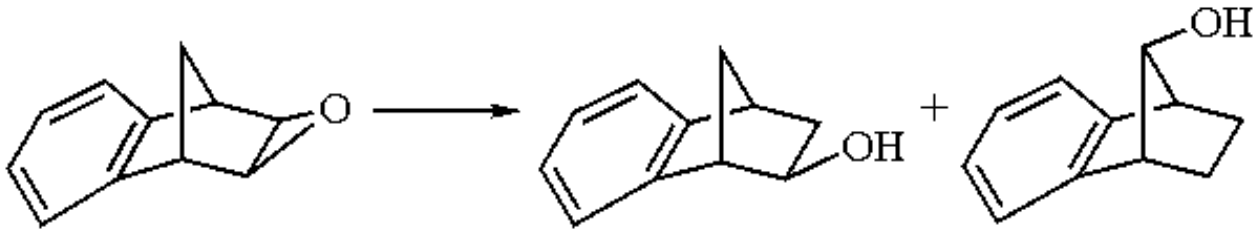

(2)

$LiEt_3BH$, THF, 65 °C, 24 h	93%	<0.1%
$LiAlH_4$, Et_2O, reflux, 24 h	15%	85%
BH_3, THF, reflux, 4 h	54%	23%
Li, ethylenediamine, 50 °C, 24 h	31%	15%

$$R_3B + LiAl(OMe)_3H \xrightarrow[\substack{0.25\ h \\ 100\%}]{THF,\ 25\ °C} LiR_3BH + Al(OMe)_3\downarrow \quad (3)$$

R = Et, Bu, *s*-Bu, *i*-Bu

The combination of ***Lithium Tri-t-butoxyaluminum Hydride*** and triethylborane induces a rapid, essentially quantitative, reductive ring opening of THF to produce 1-butanol upon hydrolysis (eq 4).[10] Cyclohexene oxide and 1-methylcyclohexene oxide are instantaneously and quantitatively cleaved to their corresponding carbinols. Oxetane is readily cleaved to give 1-propanol in 98% yield. The reductive cleavage of both tetrahydropyran and oxepan is very sluggish and incomplete.

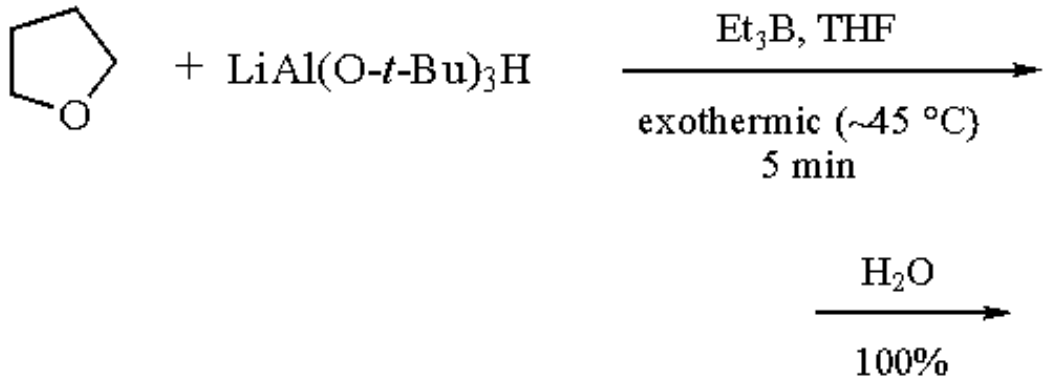

$$+ LiAl(O\text{-}t\text{-}Bu)_3H \xrightarrow[\substack{exothermic\ (\sim 45\ °C) \\ 5\ min}]{Et_3B,\ THF} \xrightarrow[100\%]{H_2O} BuOH \quad (4)$$

Triethyl- or triisopropylborane/***Trifluoromethanesulfonic Acid*** (triflic acid) is a convenient reagent for the selective reduction of hydroxy substituted carboxylic acids, ketones, and aldehydes to yield the corresponding carbonyl compounds (eq 5).[11] Not only tertiary hydroxy but also primary, secondary, and benzylic hydroxy groups are reduced in good to high yields. In general, the triisopropylborane/triflic acid system gives better results than triethylborane/triflic acid.

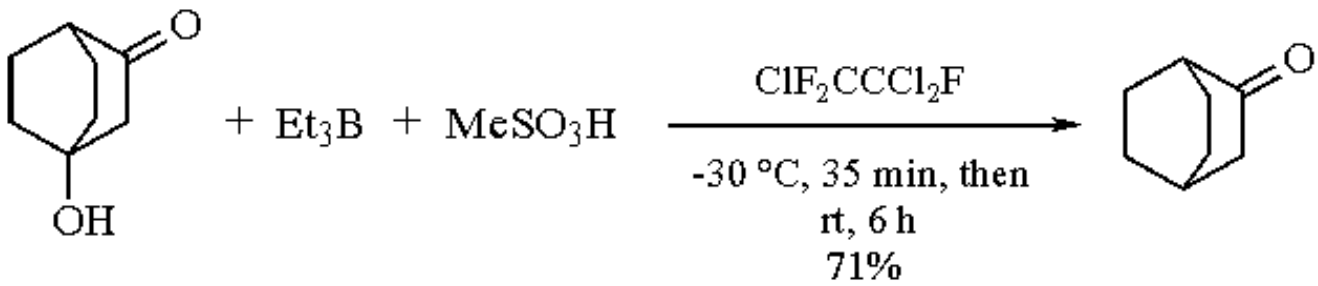

$$+ Et_3B + MeSO_3H \xrightarrow[\substack{-30\ °C,\ 35\ min,\ then \\ rt,\ 6\ h \\ 71\%}]{ClF_2CCCl_2F} \quad (5)$$

Preparation of R_2BOR' is generally carried out by treating alcohols R´OH with trialkylboranes R_3B in the presence of activating reagents like pivalic acid[13] or air.[14] However, Et_2BOMe can be prepared simply by mixing Et_3B with MeOH in THF at room temperature.[12] Using the Et_2BOMe thus generated as a chelating agent, *syn*-1,3-diols are prepared in >98% stereochemical purity by reducing β-hydroxy ketones with ***Sodium Borohydride***.[12]

Enoxytriethylborates and Enoxydiethylboranes.

Potassium enolates of ketones react with an unhindered trialkylborane such as triethylborane to form a potassium enoxytriethylborate, which undergoes selective α-monoalkylation with alkyl halides in high yields (eq 6).[15] In the absence of Et_3B, the potassium enolate itself gives a mixture of 43% mono- and 31% diallylated cyclohexanone along with 28% of recovered cyclohexanone. Monomethylation, -benzylation, and -propargylation of acetophenone also proceed in high yield in the presence of Et_3B. Lithium enolates, such as those obtained from acetophenone and cyclohexanone, do not form the corresponding enoxytriethylborates. Use of ***Potassium Hexamethyldisilazide*** as a base at -78 °C generates the less stable enolate (**1**) with high regioselectivity, while use of potassium hydride at 25 °C generates the most stable enolate (**2**) with &egt;90% regioselectivity (eq 7).[16] The alkylations of these enolates proceed without complication in the presence of Et_3B (eq 7). Comparable regioselectivities are observed in the alkylations of 2-heptanone.

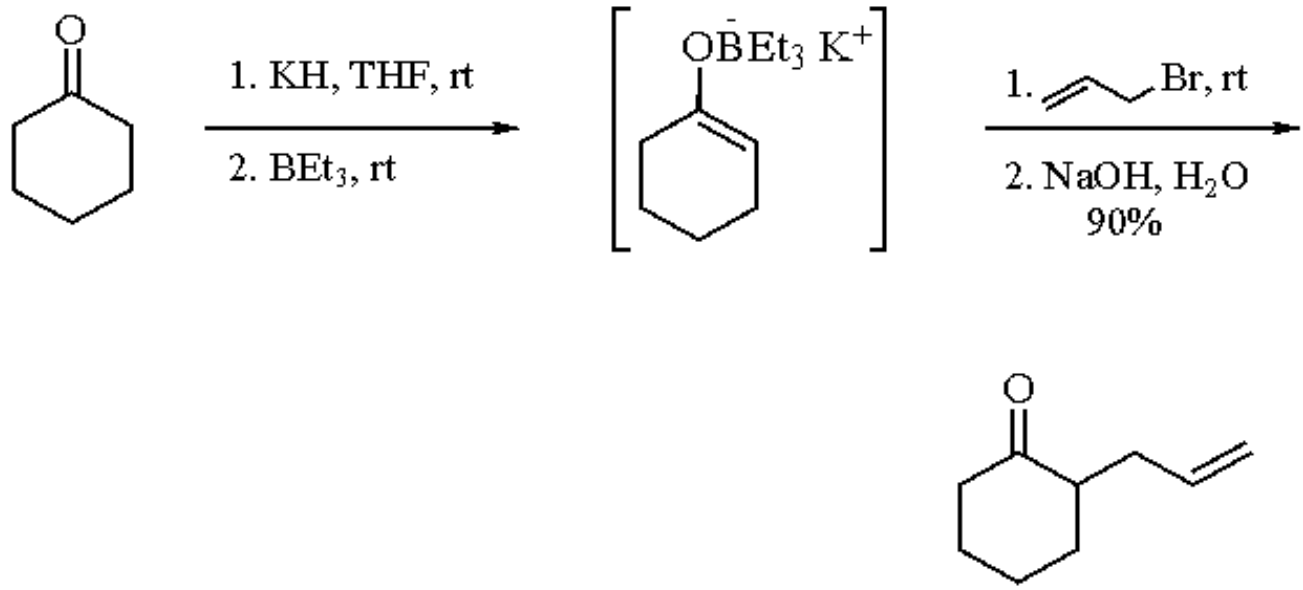

(6)

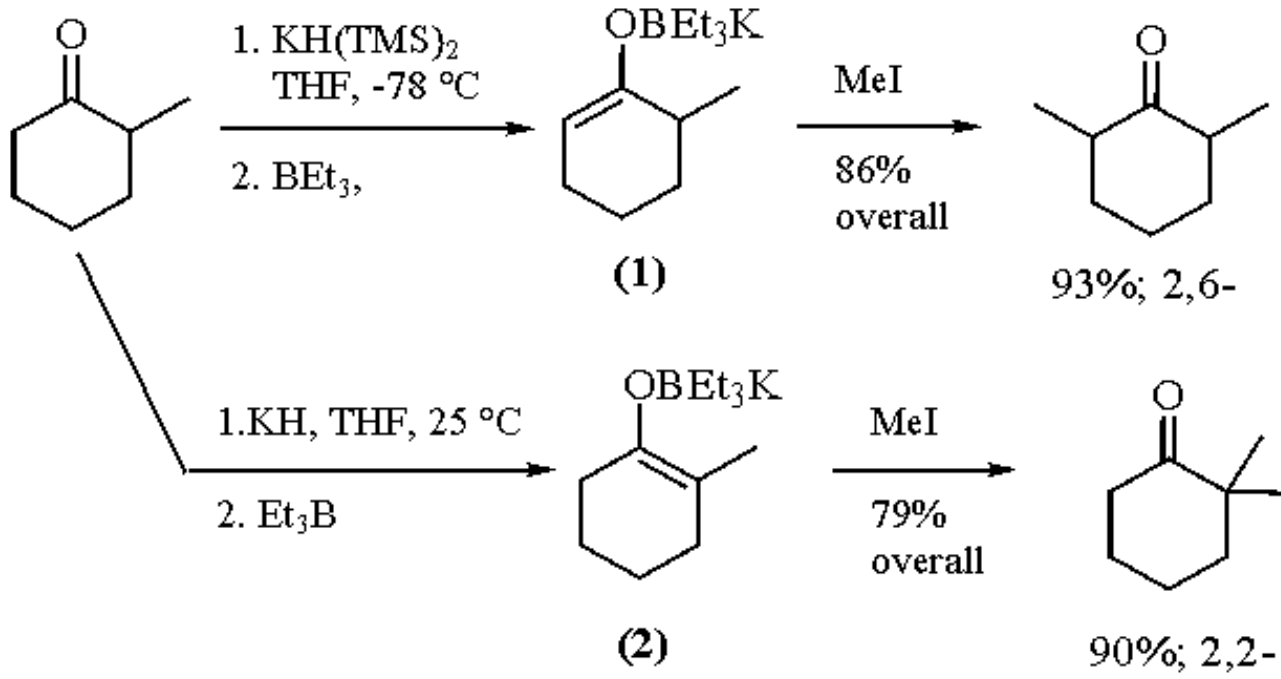

(7)

Allylation of potassium enoxyborates can be catalyzed by ***Tetrakis(triphenylphosphine)palladium(0)***.[17] Zinc enolates, readily obtained by treating lithium enolates with dry ***Zinc Chloride***, also undergo the Pd-catalyzed allylation with high regio- and stereoselectivities. Overall retention is observed with respect to the allylic cation center (eq 8).[17] In the presence of $Pd(PPh_3)_4$ catalyst and 2 equiv of BEt_3, lithium enolates of cyclopentanone and cyclohexanone derivatives react with (*E*)- or (*Z*)-allylic acetate (**3**) to provide (*E*)- or (*Z*)-allylation products with high stereospecificity (eq 9).[18] Both the Pd catalyst and BEt_3 are essential for the stereospecific allylation.

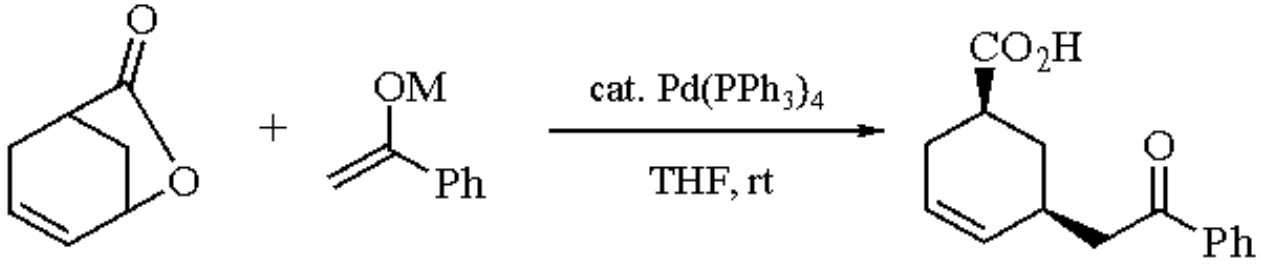

(8)

M = BEt_3K or ZnCl

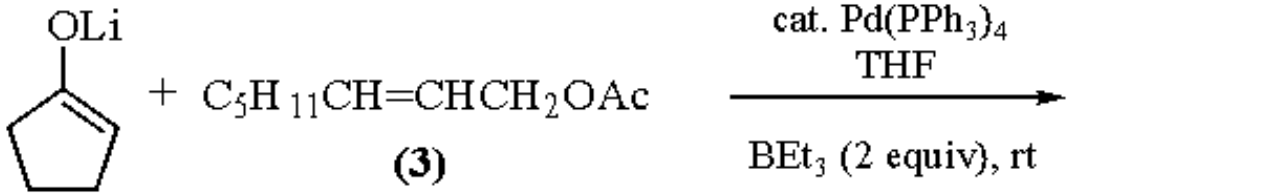

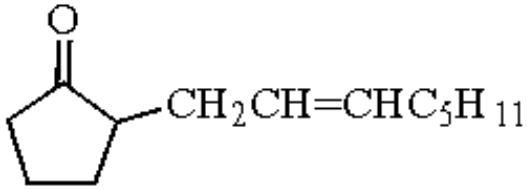

(9)

(*E*)-**(3)**	77%	(*E*):(*Z*) = 98:2
(*Z*)-**(3)**	73%	(*Z*):(*E*) = >97:3

The aldol reaction of preformed lithium enolates with aldehydes in the presence of trialkylboranes, such as BEt_3 and $B(n\text{-}Bu)_3$, leads to product mixtures rich in the more stable *anti*-aldol (eq 10).[19] Use of 3 equiv of BEt_3 gives high *anti* selectivity, while the stereoselectivity is low when 1 equiv of BEt_3 is used (eq 10). When lithium enolates are generated from silyl enol ethers and ***n-Butyllithium*** in THF, use of 1 equiv of BEt_3 is enough to produce high *anti* selectivity. The condensation of the lithio dianion of ethyl 3-hydroxybutyrate with *N*-anisyl cinnamylideneimine in the presence of Et_3B produces excellent 1´,3-*syn*/3,4-*cis* stereoselectivity (eq 11), whereas 1´,3-*syn*/3,4-*trans* selectivity is obtained in the presence of *t*-BuMgCl.[20] Aldol condensation of acetaldehyde and benzaldehyde with the lithium enolate of ethyl *N*,*N*-dimethylglycine in the presence of 1 equiv of Et_3B results in the formation of the corresponding *syn* 3-hydroxy-2-amino acid esters with excellent stereocontrol (>95% de).[21] The stereochemical outcome of these reactions is rationalized via the selective formation of the (*Z*)-enolate of ethyl *N*,*N*-dimethylglycine in the presence of triethylborane.

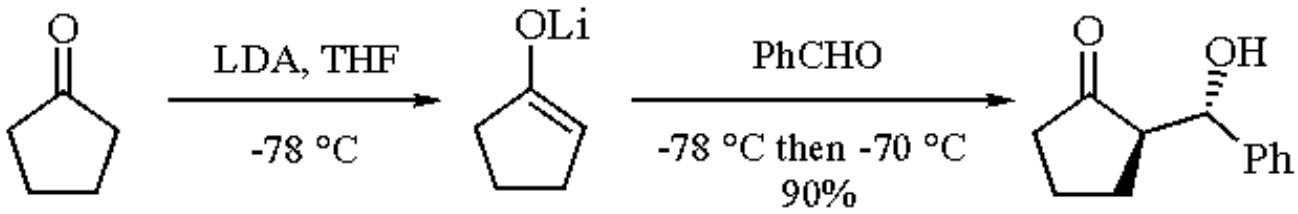

(10)

1 equiv BEt_3, *anti*:*syn* = 1:1
3 equiv BEt_3, *anti*:*syn* = 97:3

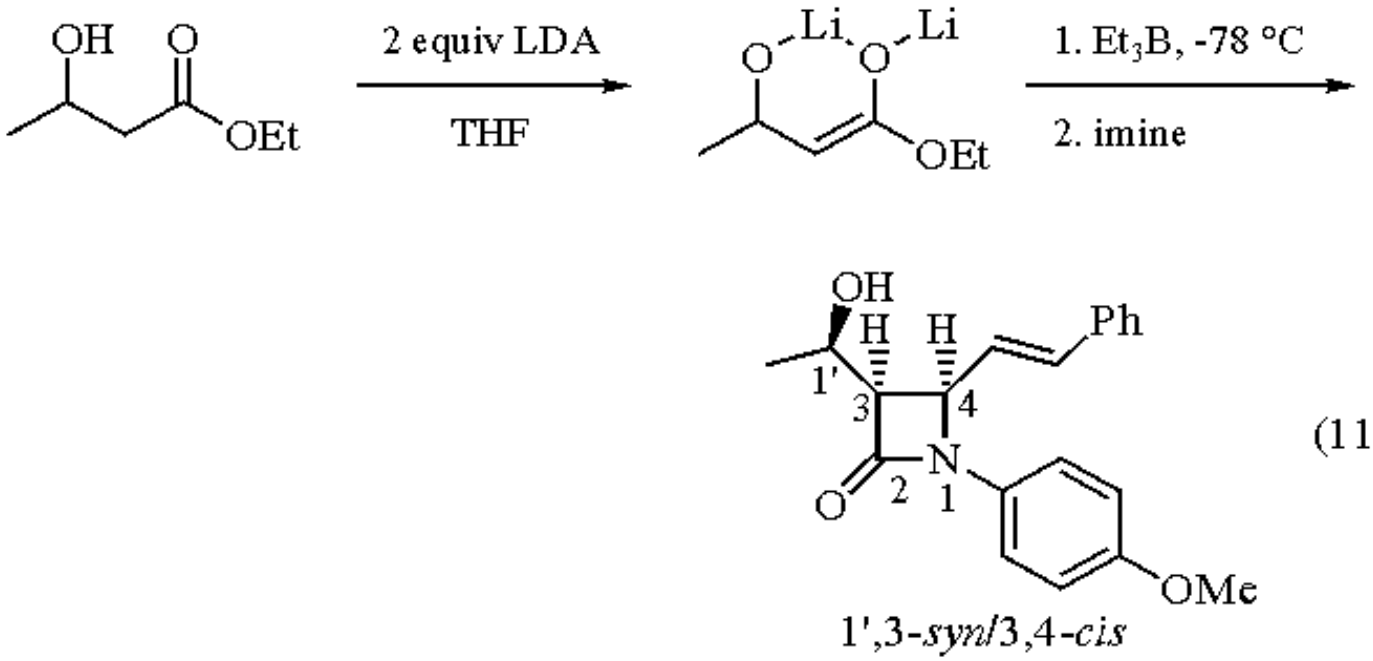

(11)

There are several methods for generation of enoxyboranes (boron enolates).[22] Ketenes react with dialkylthioalkylboranes, $R_2BS(t\text{-Bu})$, to yield alkenyloxyboranes formally derived from thioesters.[22a] A variety of ketones and carboxylic acid derivatives are converted to boron enolates upon treatment with dialkylboryl triflates in the presence of a tertiary amine, and the subsequent aldol condensation of these boron enolates has been studied[22b,c] Trialkylboranes readily react with diazoacetaldehyde to give alkenyloxyboranes.[22d] Trialkylboranes spontaneously transfer an alkyl group to the β-position of β-unsubstituted α,β-unsaturated aldehydes and ketones to give alkenyloxyboranes, which are produced regio- but not stereospecifically.[22e] In the presence of 1-10 mol % of diethylboryl pivalate, Et_3B and ketones $RCOCH_2R'$ react at 85-110 °C to give diethyl(vinyloxy)boranes, $Et_2BOCR{=}CHR'$, in 70-90% yield.[22f] Reaction of α-bromo ketones with ***Triphenylsilane*** in the presence of Et_3B provides boron enolates which react with carbonyl compounds to give β-hydroxy ketones in good yields (eq 12).[23] The Et_3B-induced Reformatsky type reaction of α-iodo ketones with aldehydes or ketones proceeds without Ph_3SnH.[23,24] α-Bromocyclopentanone and -cyclohexanone provide *anti*-adducts with high diastereoselectivity (78-100%), whereas the reaction of 7-bromo-6-dodecanone with benzaldehyde gives a 65:35 mixture of the *syn*- and *anti*-adduct. It is proposed that vinyloxy(diethyl)boranes are involved as intermediates.

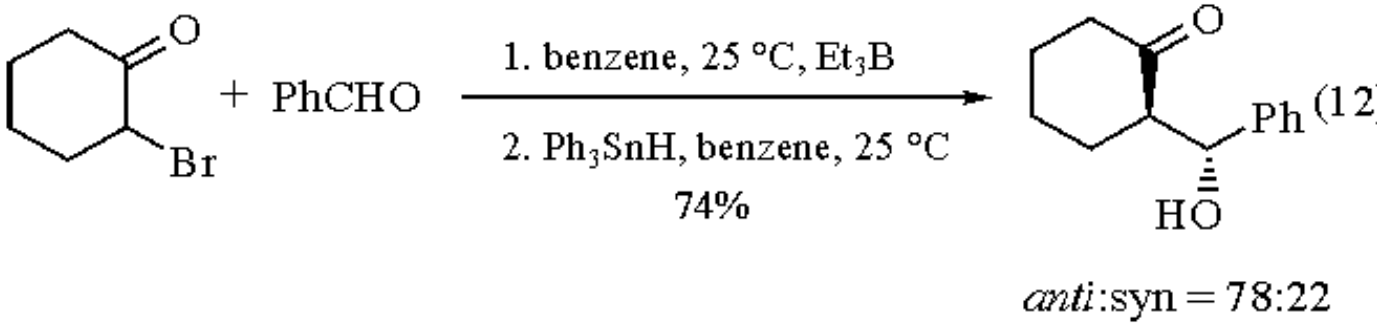

(12)

Allylborates.

2-Butenyllithium reacts with aldehydes to afford the *anti*- and *syn*-β-methylhomoallyl alcohols in nearly equal amounts. However, if trialkylboranes such as Et_3B are present, the *anti*-product predominates (eq 13).[25] The corresponding allylic borate complexes are presumably involved as intermediates. Lithium allylic boronates, prepared by the addition of trialkylboranes (Et_3B, ***Tri-n-butylborane***, or *n*-Bu-9-BBN) to an ether solution of allylic lithium compounds, regioselectively react with allylic halides to produce head-to-tail 1,5-dienes (eq 14).[26] Regio- and stereocontrol via boron ate complexes is applicable to not only simple allylic but also heteroatom substituted allylic anions.[27] The allyloxy carbanions (**4**) generally react with alkyl halides at the α-position, but react with carbonyl compounds at the γ-position. The Et_3B (or ***Triethylaluminum***) ate complexes of (**4**) react with a ldehydes, ketones, and reactive halides at the α-position. The (alkylthio)allyl carbanion (**5**) reacts with alkyl halides at the γ-position, but with carbonyl compounds at the α-position. The Et_3B (or Et_3Al) ate complexes of (**5**) react with aldehydes, ketones, and allylic halides at the α-position. In general, the aluminum ate complex gives higher regioselectivity than the boron ate complex. The regioselectivity of Me_3Si- or pyrrolidine (*N*-atom)-substituted allylic anions is also controlled by the addition of Et_3B (or Et_3Al).[27] Either branched or linear homoallyl alcohols may be prepared by the reaction of (phenylselenyl)allyl carbanion with aldehydes and triethylborane under appropriate reaction conditions (eq 15).[28] The ethyl group of Et_3B in the initially formed ate complex $PhSeCH(\text{-}BEt_3)CH{=}CH_2\ Li^+$ undergoes a facile migration from boron to the α-carbon to give (**6**), which reacts with benzaldehyde to give the linear adduct. The prolonged reaction period at higher temperatures induces the allylic

rearrangement of (**6**) to (**7**), resulting in the formation of the branched adduct.

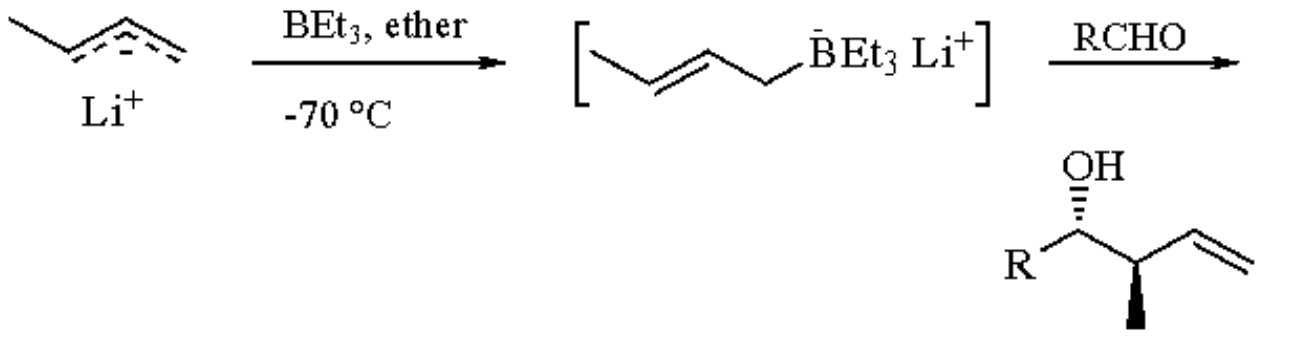

(13)

	anti:*syn*
R = Ph, 90%	82:18
R = Me, 78%	85:15

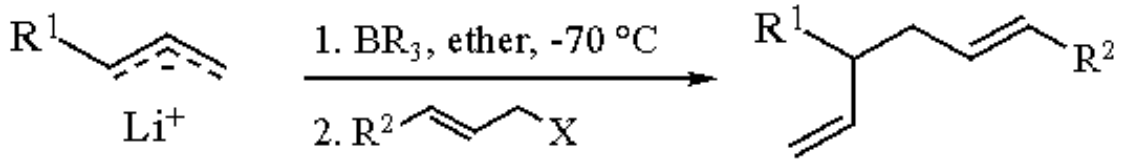

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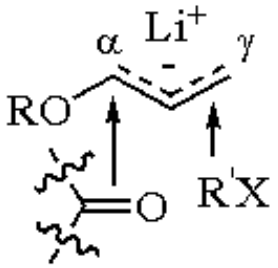

(4a) R = *i*-Pr
(4b) R = $MeOCH_2$

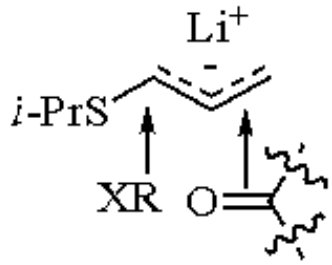

(5)

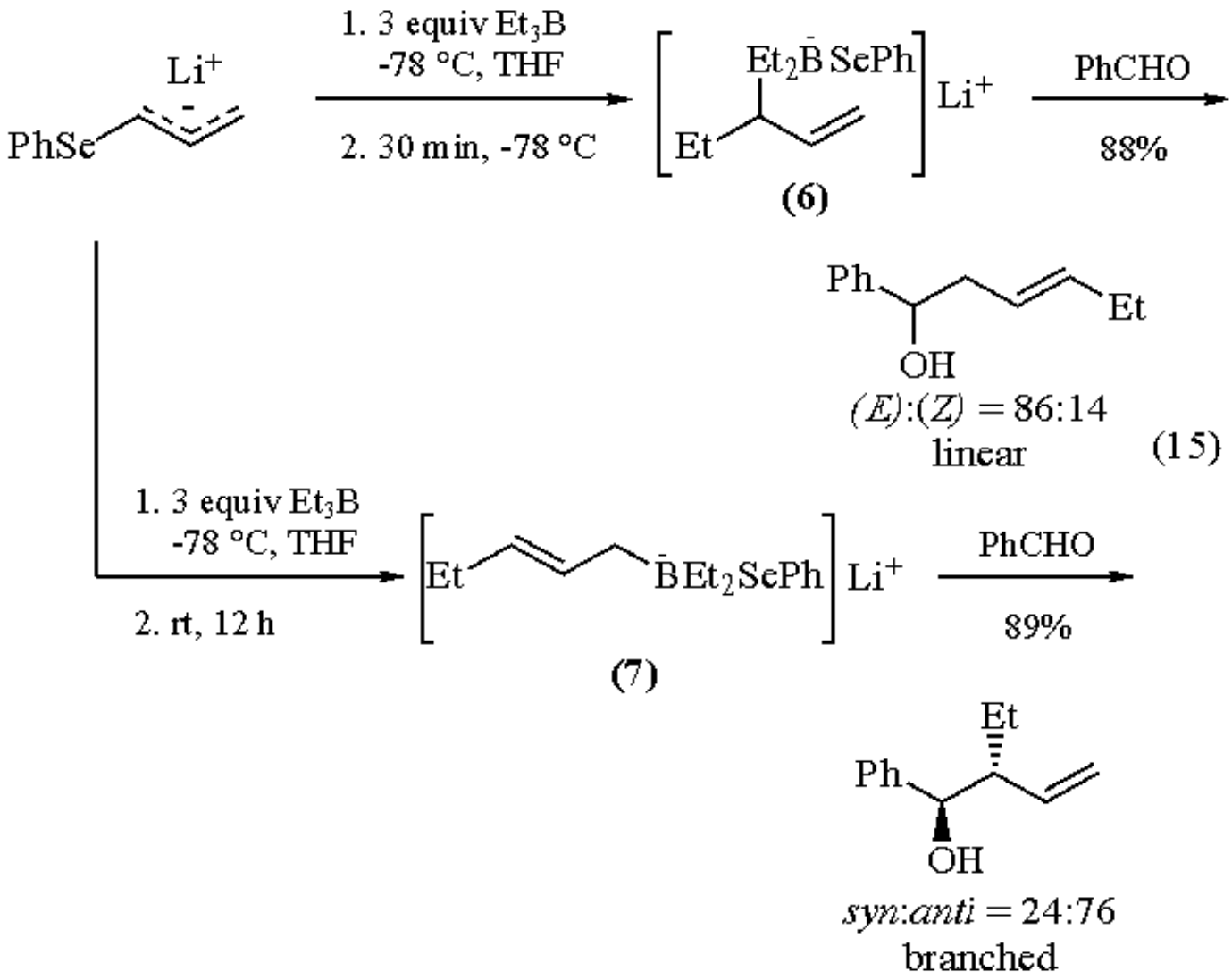

Alkylating Reagents.

Monoalkylation of ketones is accomplished by reaction of trialkylboranes with α-bromo ketones under the influence of ***Potassium t-Butoxide*** in THF.[29] For example, α-bromocyclohexanone reacts with Et_3B to give α-ethylcyclohexanone (eq 16).[29] The reaction involves formation of the anion of the α-bromo ketone, formation of the boron ate complex, and rearrangement of Et from boron to the α-carbon. The use of potassium 2,6-di-*t*-butylphenoxide as a base, instead of *t*-BuOK, provides better results.[30] α-Bromoacetone, chloroacetonitrile, ethyl bromoacetate, and ethyl dibromoacetate are alkylated using this hindered base and R_3B.[30] The reaction of Et_3B with ethyl 4-bromocrotonate in the presence of one equiv of the new base affords ethyl 3-hexenoate (79% *trans*).[31] Monoalkylation of dichloroacetonitrile with Et_3B is achieved in 89% yield, and the dialkylation is carried out by using 2 equiv of base and 2 equiv of Et_3B (97% yield).[32]

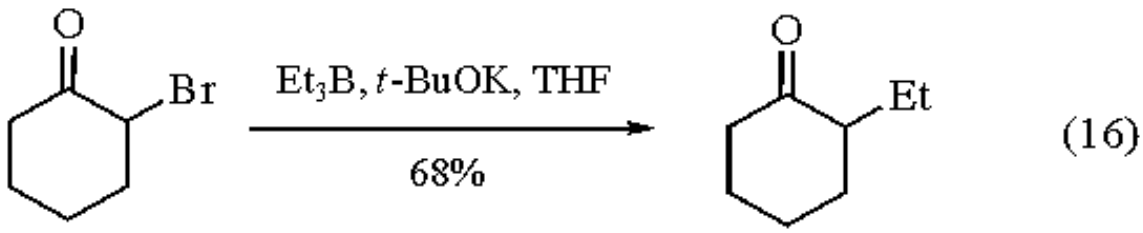

Trialkylcarbinols are prepared by the reaction of trialkylboranes with carbon monoxide in diglyme followed by oxidation with ***Hydrogen Peroxide*** (eq 17).[1b] Alternatively, trialkylcarbinols are obtained by the reaction of trialkylboranes with ***Chlorodifluoromethane*** (or ***Dichloromethyl Methyl Ether***) under the influence of lithium triethylmethoxide,[1b,33] or by the cyanidation reaction of trialkylboranes with ***Sodium Cyanide-Trifluoroacetic Anhydride*** followed by oxidation.[1b,34] Bromination of triethylborane under irradiation in the presence of water followed by oxidation gives 3-methyl-3-pentanol in 88% yield (eq 18).[35] In order to effect successful α-bromination-migration, slow addition of bromine is important to avoid polybromination. The use of ***N-Bromosuccinimide*** in the presence of water increases the yield in eq 18 to 97%.[36] The bromination-migration reaction is applicable to simple trialkylboranes and dialkylborinic acids. The cross-coupling reaction of *B*-alkyl-9-borabicyclo[3.3.1]nonanes (*B*-R-9-BBN) with 1-halo-1-alkenes or haloarenes (R´X) in the presence of a catalytic amount of ***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)*** and bases, such as NaOH and K_2CO_3, gives the corresponding

alkenes or arenes (R-R´).[37] The use of catalytic amounts of $Cl_2Pd[PPh_3]_2$ in combination with ***Bis(acetylacetonato)zinc(II)*** effects carbonylative coupling of trialkylboranes with aryl iodides to give unsymmetrical ketones in 60-80% yields (eq 19).[38]

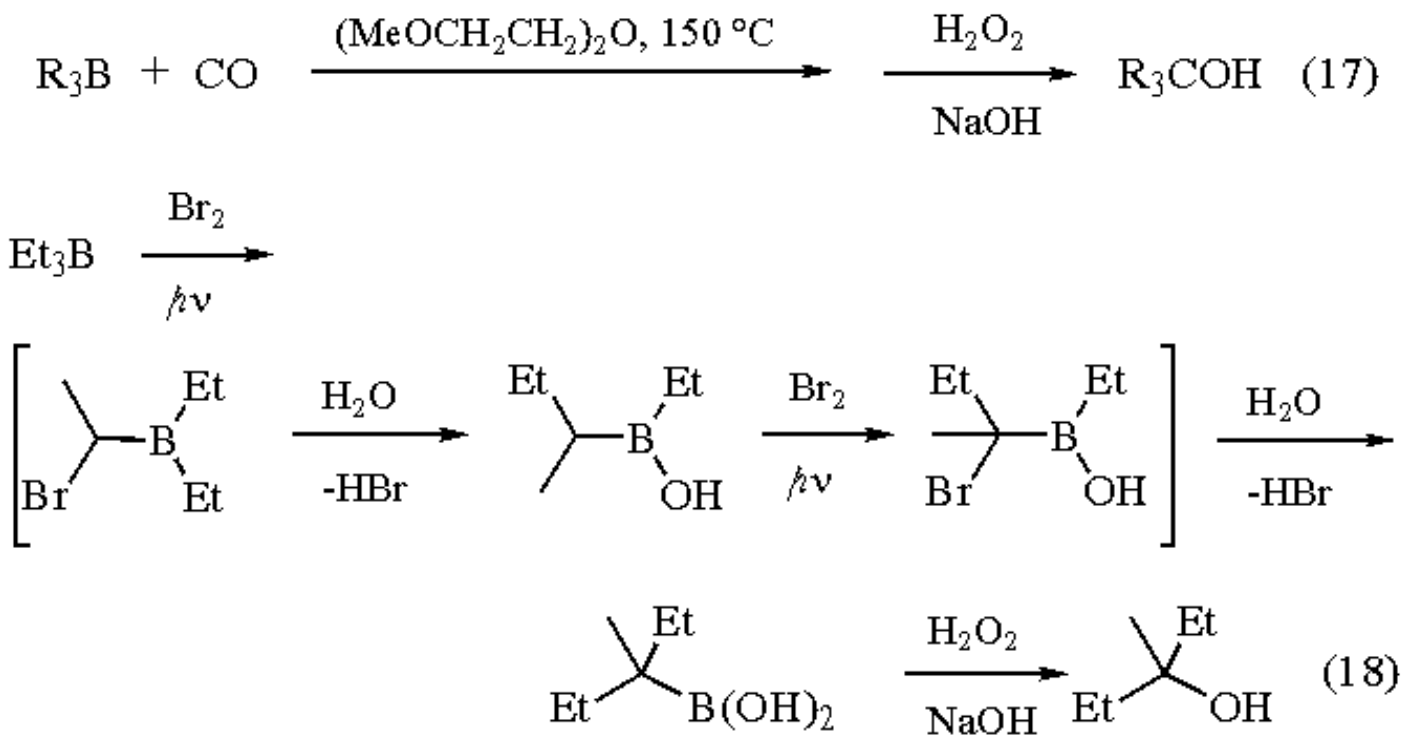

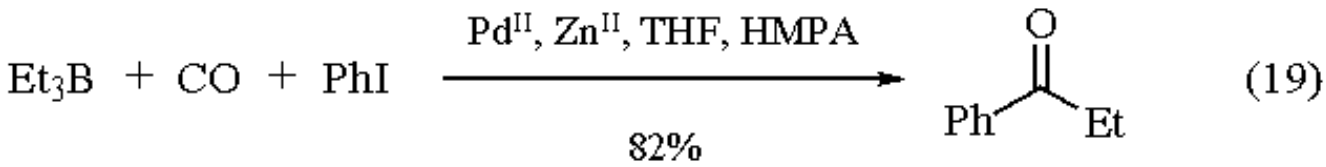

Alkynes are easily synthesized by the reaction of iodine with alkyne ate complexes, readily formed in situ from R_3B and lithium acetylides (eq 20).[1b] Treatment of the alkyne ate complexes with mild electrophiles E^+ results in β-attack on the triple bond and a migration of the organic group R from boron to carbon (eq 20).[1b] The protonation reaction with HX yields a mixture of *cis*- and *trans* alkenes, and mixtures of alkene isomers are also obtained in reactions involving MeI, MeOTs, allyl bromide, and oxirane. However, a single stereoisomer results from the reactions with other electrophiles.

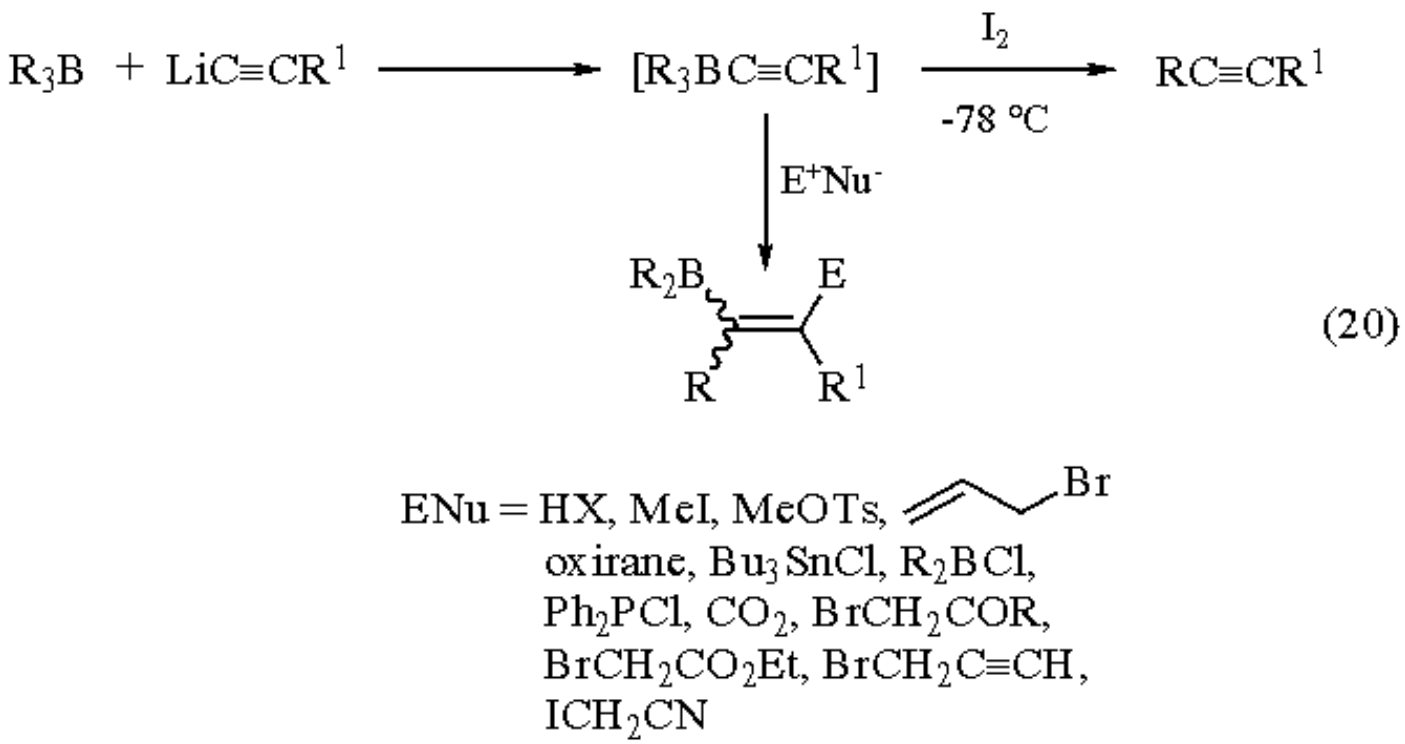

Stereochemical Control Element.

Triethylborane acts as a stereo- and regiocontrol element in certain carbanionic reactions; several examples have been demonstrated in eqs 10, 11, and 13-15. Triethylborane-mediated epimerization of a 1α-methylcarbapenem intermediate proceeds with high stereoselectivity to give the 1β-methyl diastereomer (eq 21).[39] The 1β-methyl derivative is also obtained via alkylation of an 2-azetidinon-4-ylacetic acid derivative by using LDA-Et_3Al-MeI.[39] The deuteration of α-lithiobenzyl methyl sulfoxide in the presence of Et_3Al occurs with inversion, while the reaction in the absence of the additive occurs with retention; the use of Et_3B gives a mixture of the retention and inversion product.[40] The reagent RCu.BEt_3, prepared in situ from RCu and BEt_3 in ether at -70 °C, adds to α,β-alkynic carbonyl compounds with high stereospecificity, which cannot be achieved with conventional reagents such as R_2CuLi (eq 22).[41]

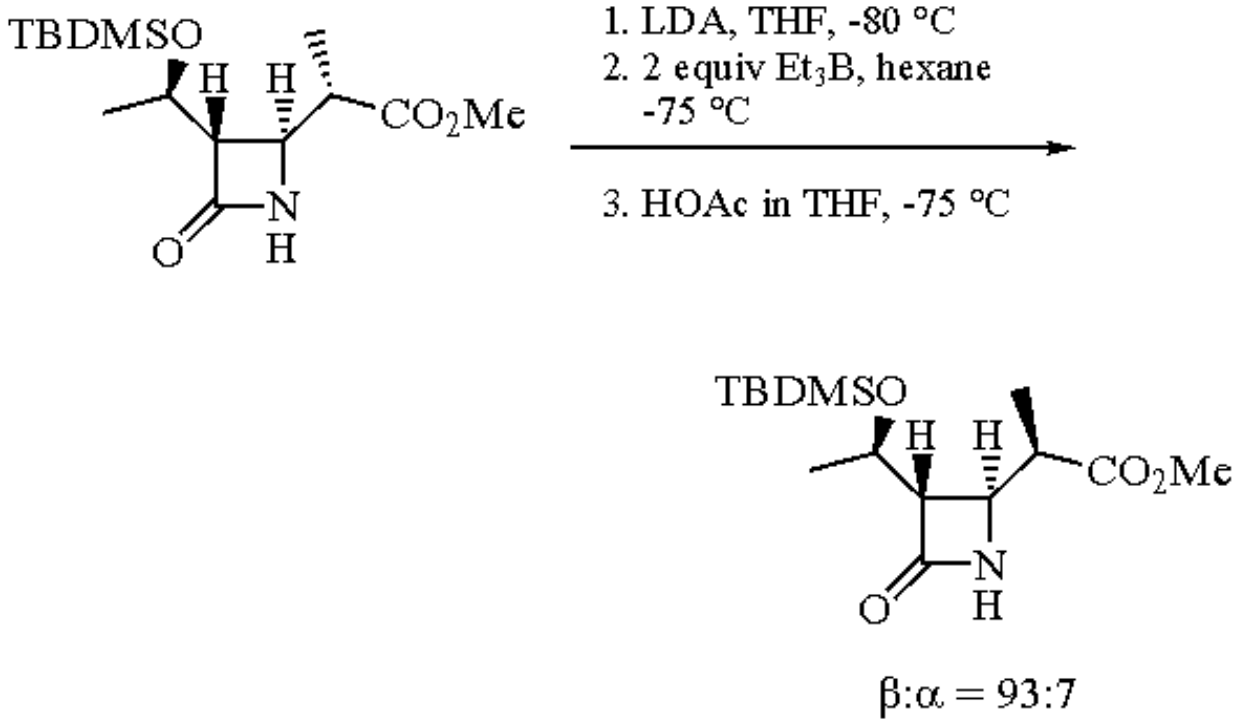

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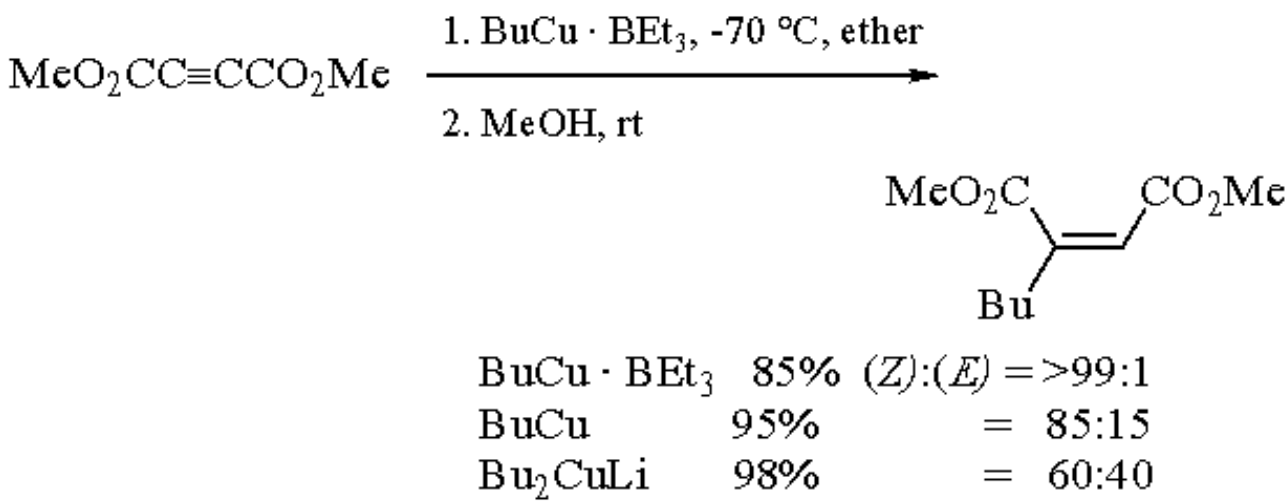

(22)

Lewis Acids and Radical Reactions.

Methylenecyclopropanes react with 2-cyclopentenone in the presence of a Ni^0 catalyst (such as ***Bis(1,5-cyclooctadiene)nickel(0)***), ***Triphenylphosphine***, and triethylborane to afford 6-methylenebicyclo[3.3.0]octan-2-ones (eq 23).[42] Treatment of tantalum-alkyne complexes with dimethylhydrazones and ***Trimethylaluminum*** in a DME, benzene, and THF solvent system at 45 °C gives (*E*)-allylic hydrazines stereoselectively, although the use of Et_3B results in formation of the product in very low yield.[43]

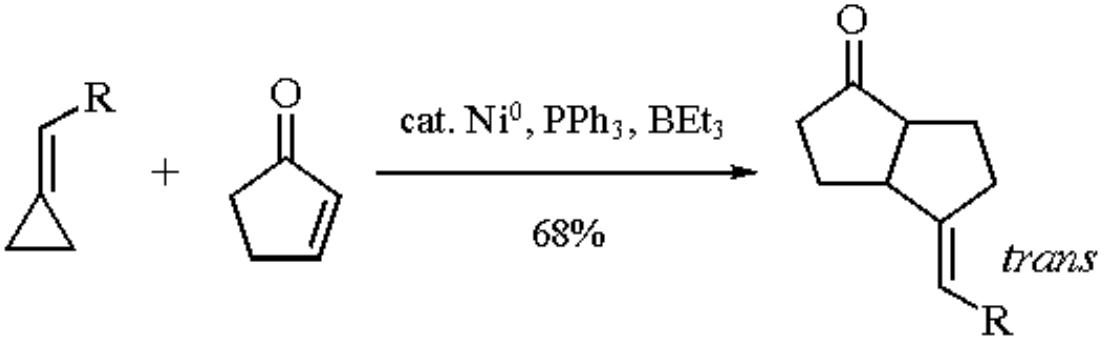

(23)

$R = C_5H_{11}$ *trans*:*cis* = 85:15

Trialkylboranes do not undergo facile addition reactions to carbonyl groups. However, rapid conjugate addition reactions occur with α,β-unsaturated carbonyl compounds, such as ***Acrolein*** and ***Methyl Vinyl Ketone*** (eq 24).[1b] The reaction proceeds through a radical mechanism. Trialkylboranes also participate in facile radical chain reactions with disulfides (e.g. ***Diphenyl Disulfide***), producing the corresponding thioethers (RSPh).[1b] Triphenylgermane adds easily to alkynes (RC&tbond;CH) in the presence of Et_3B to give (*E*)- or (*Z*)-alkenyltriphenylgermanes ($RCH{=}CHGePh_3$) in good yields.[44] The (*Z*)-isomers predominate at -78 °C, whereas the hydrogermylation at 60 °C favors the (*E*)-isomer. Similarly, Et_3B is as efficient as ***Azobisisobutyronitrile*** for initiation of the hydrostannylation of alkynes, resulting in vinyltins.[45] The reaction is sluggish in the absence of oxygen. Triethylborane can also initiate radical cyclization of unsaturated alkynes to vinylstannanes (eq 25).[45] The 1,4-reduction of α,β-unsaturated ketones and aldehydes with ***Triphenylstannane*** or ***Tri-n-butylstannane*** proceeds in the presence of Et_3B to give the corresponding saturated ketones and aldehydes in good yields, whereas the same reaction of α,β-unsaturated esters with Ph_3SnH affords the tin hydride conjugate adduct.[46] Thiols[47a] and perfluoroalkyl iodides[47b] undergo similar addition reactions to alkynes in the presence of catalytic amounts of Et_3B. Treatment of 1-allyloxy-1-phenyl-2-bromo-1-silacyclopentanes with Bu_3SnH in the presence of catalytic amounts of Et_3B provides the cyclization products, which can be converted to 1,4,6-triol derivatives (eq 26).[48] Alkoxymethyl radicals (2-oxahex-5-enyl or 2-oxahept-6-enyl radicals), generated conveniently from phenylseleno precursors upon treatment with AIBN or Et_3B, cyclize to afford substituted tetrahydrofurans and tetrahydropyrans.[49]

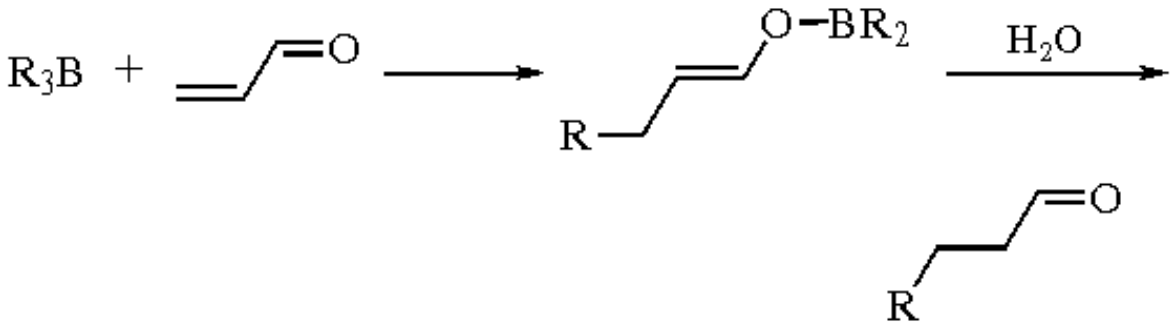

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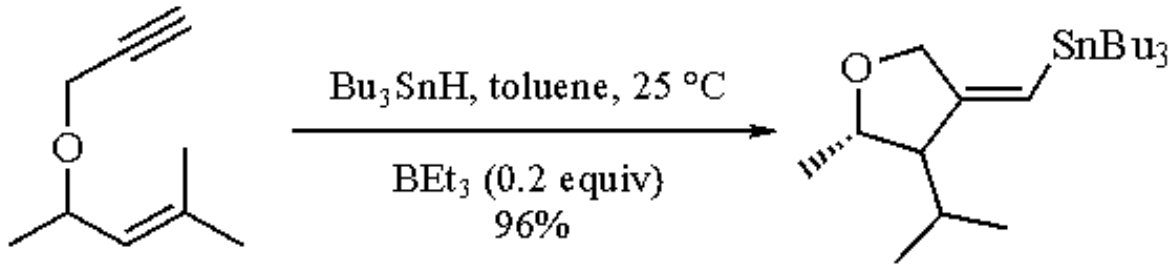

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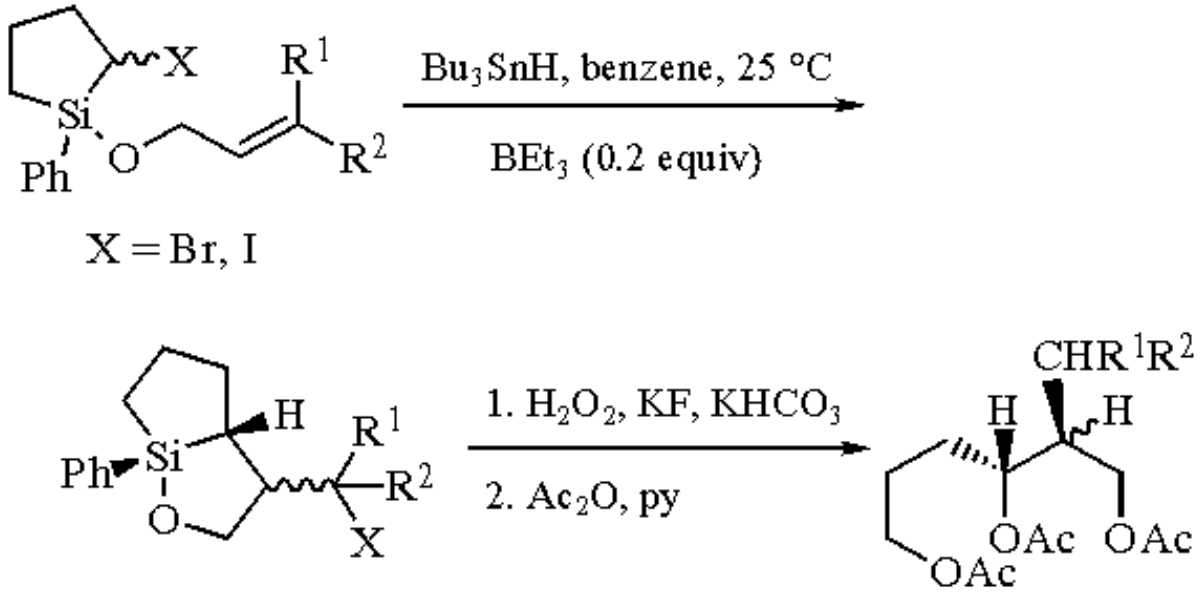

(26)

Related Reagents.

B-Allyl-9-borabicyclo[3.3.1]nonane; ***Crotyldimethoxyborane***; ***Di-n-butylboryl Trifluoromethanesulfonate***; ***Lithium Triethylborohydride***; ***Potassium Tri-s-butylborohydride***.

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Triethyl Methanetricarboxylate[1]

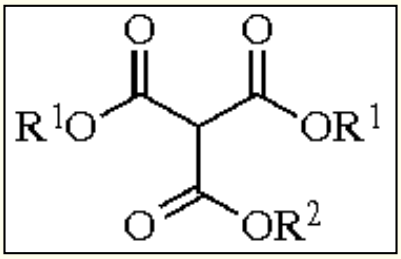

(**1**; $R^1 = R^2 = Me$)

[1186-73-8] · $C_7H_{10}O_6$ · Trimethyl Methanetricarboxylate · (MW 190.17) (**2**; $R^1 = Me$, $R^2 = Et$)

[125563-04-4] · $C_8H_{12}O_6$ · Ethyl Dimethyl Methanetricarboxylate · (MW 204.20) (**3**; $R^1 = Et$, $R^2 = Me$)

[124896-06-6] · $C_9H_{14}O_6$ · Diethyl Methyl Methanetricarboxylate · (MW 218.23) (**4**; $R^1 = R^2 = Et$)

[6279-86-3] · $C_{10}H_{16}O_6$ · Triethyl Methanetricarboxylate · (MW 232.26) (**5**; $R^1 = Et$, $R^2 = t$-Bu)

[71170-90-6] · $C_{12}H_{20}O_6$ · *t*-Butyl Diethyl Methanetricarboxylate · (MW 260.32)

(masked malonate ester equivalent;[2,3] regiospecific radical addition to terminal alkenes;[4] Mn^{III}-induced substitution on electron-rich aromatics[5,6])

Physical Data: (**1**) bp 111-112 °C/4 mmHg; mp 45-46 °C; (**2**) bp 138-139 °C/12 mmHg; (**3**) bp 140-142 °C/12 mmHg; (**4**) bp 135-137 °C/12 mmHg; mp 27-29 °C; *d* 1.100 g cm^{-3}.

Preparative Methods: methanetricarboxylate esters are generally prepared from appropriate malonate esters via formation of a metal salt and addition of an alkyl chloroformate (eq 1). Sodiomalonates work well for most esters (e.g. $R^1 = R^2 = Me$);[7] however, magnesiomalonates generally provide better results for ethyl esters.[8] Acylation of malonate esters has also been accomplished using ***Magnesium Oxide*** as the base,[9] which is advantageous for the preparation of symmetric methanetricarboxylate esters ($R^1 = R^2$) because strictly anhydrous conditions are not required.

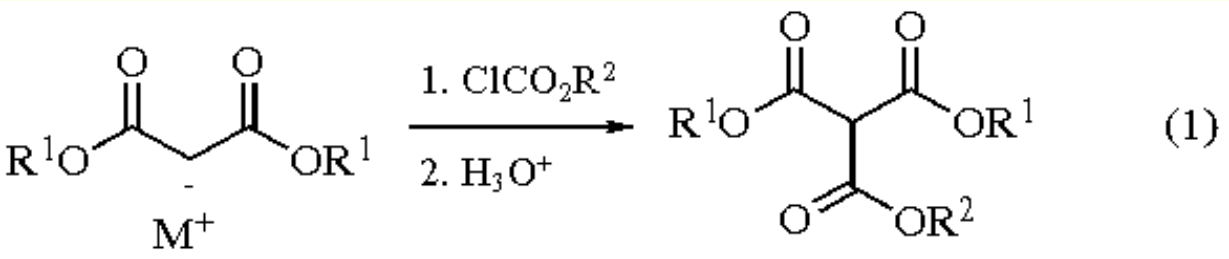

Trialkyl methanetricarboxylates are easily alkylated;[1] facile dealkoxycarbonylation of these triesters has prompted their use as masked malonate esters.[1,2,3] Conjugate addition (eq 2) of triethyl methanetricarboxylate occurs with a variety of Michael acceptors under phase-transfer conditions, providing a convenient two-carbon chain elongation.[10]

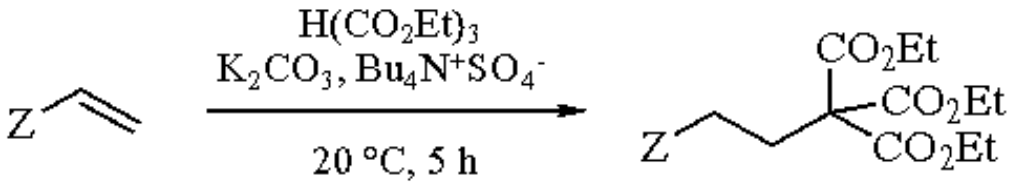

Z = CHO, CO_2Et, CN, COMe, SOPh, SO_2Ph

Trialkyl methanetricarboxylate radicals readily add to terminal alkenes, giving predominately the 1:1 adducts (50-75%).[1,4] Unlike the radical additions of malonate or acetate esters to alkenes, the addition of methanetricarboxylate esters is regiospecific and limited exclusively to α-alkenes.[4] Saponification of the 1:1 adduct, followed by decarboxylation, is a convenient route to *n*-alkylcarboxylic acids and is a two-carbon homologation of the starting alkene. Methanetricarboxylate esters also readily undergo manganese(III)-induced addition to electron-rich aromatic systems;[5] this reactivity is attributed to the very electrophilic nature of the triester radical. This reaction was exploited to give the shortest, most efficient, reported synthesis of the analgesic ketorolac:[6,11] three steps and 64% overall yield from 2-benzoylpyrrole (eq 3).

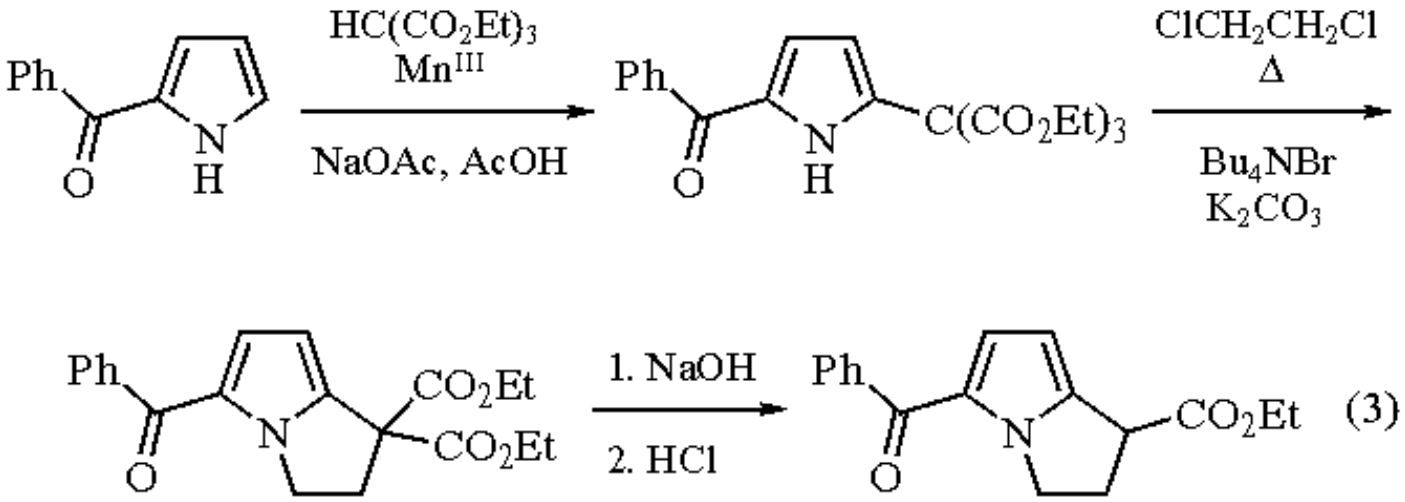

These triesters react with a variety of amines to give a broad range of products.[1] Condensation of the triethyl ester with pyrazoles provided facile access to cross-conjugated mesomeric betaines without the use of chlorocarbonylketenes (eq 4).[12]

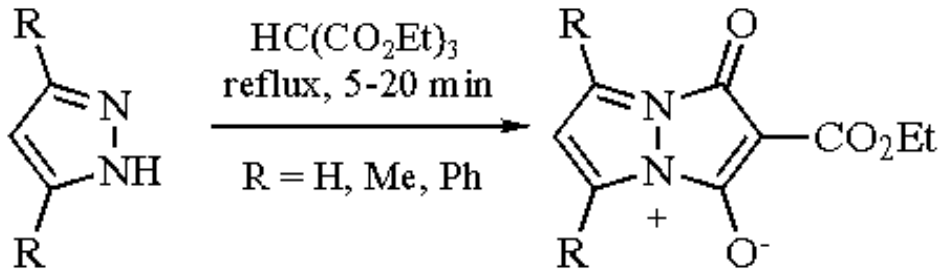

Pyrolysis of *o*-carboranes in the presence of trialkyl methanetricarboxylates produces 9-alkyl-*o*-carboranes in moderate yields, and represents one of the few reliable preparations of these molecules.[13]

Related Reagents.

Diethyl Malonate; ***Ethyl 3,3-Diethoxyacrylate***; ***Diethyl Ethoxymagnesiomalonate***; ***Ethyl Malonate***; ***Ethyl Trimethylsilyl Malonate***; ***Magnesium Ethyl Malonate***; ***Malonic Acid***; ***2,2-Dimethyl-1,3-dioxane-4,6-dione***.

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Triethyl Orthoacetate[1]

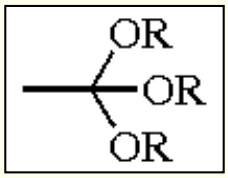

(**1**; R = Et)

[78-39-7] · $C_8H_{18}O_3$ · Triethyl Orthoacetate · (MW 162.26) (**2**; R = Me)

[1445-45-0] · $C_5H_{12}O_3$ · Trimethyl Orthoacetate · (MW 120.17)

(diethyl acetal of ethyl acetate; provides γ,δ-unsaturated ethyl esters from α,β-unsaturated alcohols through the Claisen rearrangement; converts diols to epoxides of the same relative stereochemistry; gives 2-methyl-1,3-heteroatom ring systems)

Physical Data: (**1**) bp 144-146 °C; *d* = 0.8847 g cm^{-3}; (**2**) bp 107-109 °C; *d* = 0.9438 g cm^{-3}.

Orthoester Exchange with Alcohols and Water.

Orthoesters (1,1,1-trialkoxyalkanes, ester acetals) are acid labile, base stable, masked forms of carboxylic acid esters. Mild acid-catalyzed hydrolysis of an orthoester produces an ester and an alcohol, in this instance, ethyl acetate and ethanol. Thus ethyl orthoacetate, and orthoesters in general, can serve to drive the equilibrium in Fischer esterifications of carboxylic acids with ethanol by forming low-boiling ethyl acetate and ethanol from the water generated during the esterification.

Higher molecular weight orthoacetates (orthoesters) of nonallylic alcohols are prepared by acid-catalyzed exchange, with removal of the lower boiling alcohol to shift the equilibrium. When this reaction is conducted with a 1,2-diol such as L(+)-diethyl tartrate in the presence of excess ethyl orthoacetate, two of the ethoxy groups are exchanged to form a 2-ethoxy-2-methyl-1,3-dioxolane (eq 1).

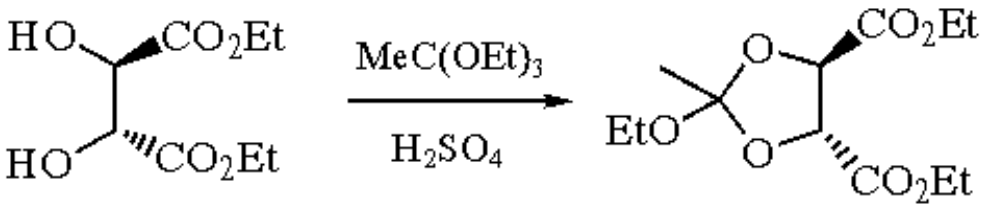

(1)

Interconversion of Orthoesters and Haloesters.

This exchange is an important element in a reaction sequence designed to convert a diol to the corresponding epoxide without loss of stereochemistry. Thus the dioxolane of D(-)-2,3-butanediol, which is formed from methyl orthoacetate, is cleaved with trityl chloride to produce the β-acetoxy chloride, which, upon treatment with KOH, affords D(+)-2,3-epoxybutane (eq 2). The cleavage procedure, which is also effective with 2-ethoxy-2-methyl-1,3-dioxanes (eq 3), occurs through an S_N2 mechanism.[2] Because the formation of methyl trityl ether can complicate isolation, ***Chlorotrimethylsilane***, which gives volatile byproducts, is an effective replacement for trityl chloride in the cleavage of dioxolanes.[3] ***Phosphorus(V) Chloride*** has been found to be effective in the cleavage of a dioxolane derived from ethyl orthoformate (eq 4).[4] These reactions proceed through the formation of a cyclic dioxolenium (eqs 2 and 4) or dioxenium (eq 3) ion, an intermediate that can be accessed in the reverse direction to produce an orthoester. This procedure is typified by the transformation of the tetra-*O*-acetyl glucosyl bromide of eq 5.[5] The remaining ethoxy group of the cyclic orthoester can be exchanged intramolecularly by removing ethanol from the equilibrium even if an unfavorable conformation is required (eq 6).[6]

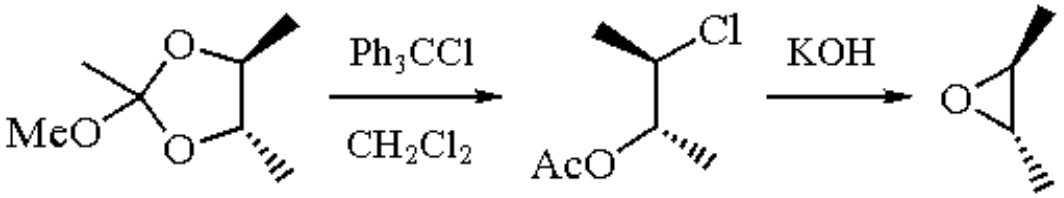

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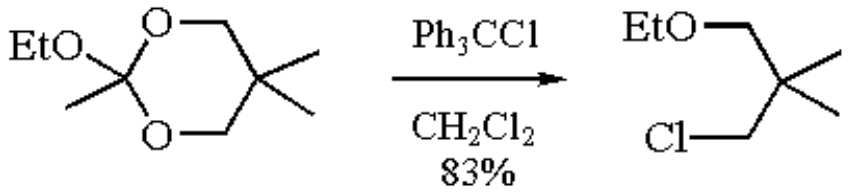

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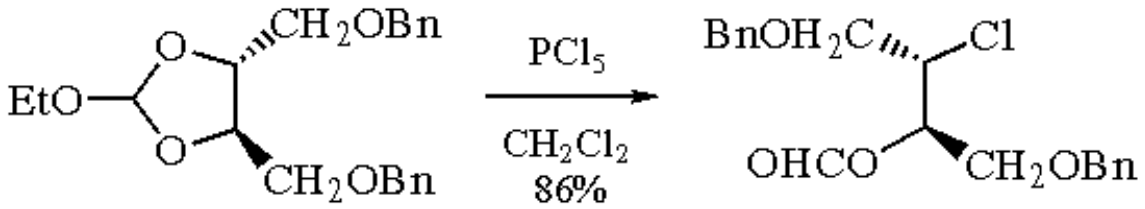

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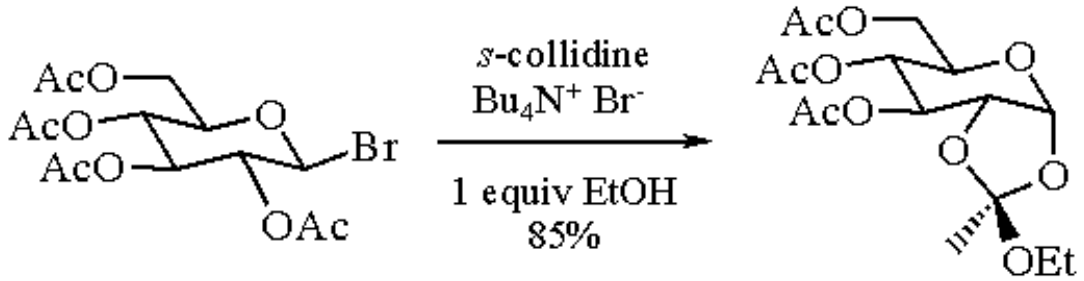

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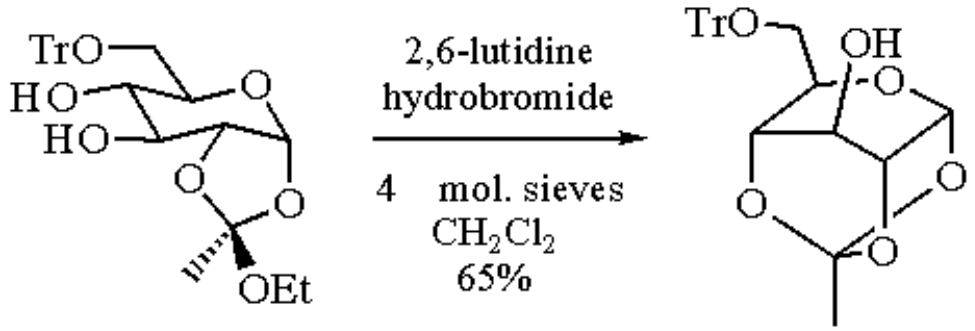

(6)

Orthoester Claisen Rearrangement.

The principal use of triethyl and trimethyl orthoacetate and their more substituted analogs[7] is in the orthoester Claisen rearrangement.[1c] The reagent, which is often used as a solvent, is heated in the presence of an allylic alcohol and a weak acid catalyst with removal of ethanol (or methanol) (eq 7).

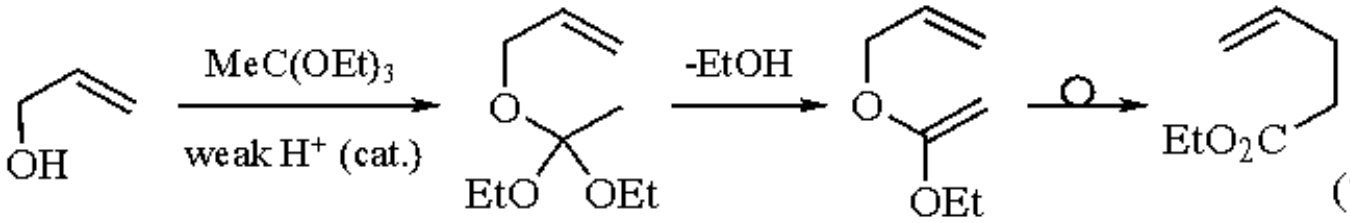

(7)

The reaction was first applied in the synthesis of the triterpene squalene (**1**), using a symmetrical bis-allylic alcohol (eq 8).[8] The trisubstituted (*E*)-alkene is formed in >98% purity in excellent yield. The ester group of the product is converted into a secondary isopropenyl carbinol and it is then subjected to a second orthoacetate rearrangement.

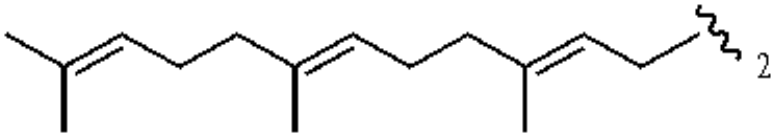

(1)

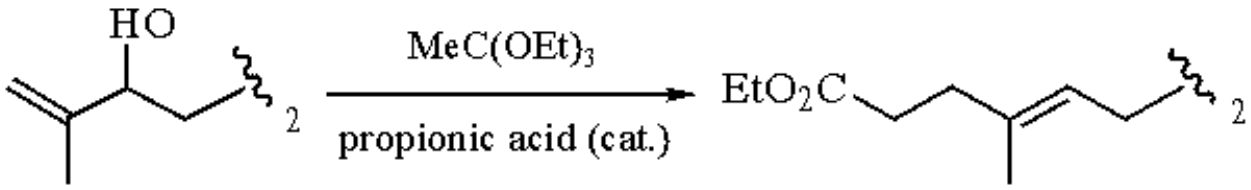

(8)

The (*E*)-alkene selectivity is typical of the rearrangement of secondary allylic carbinols. Enantiomerically pure allylic alcohols (**2**) and (**3**), both of which are accessible from a common source, undergo rearrangement to give the same enantiomerically pure ester (**4**) (eq 9).[9] The results of eqs 8 and 9 demonstrate that propionic acid is capable of forming the dioxenium carbocation from the orthoacetate without isomerizing or racemizing the allylic alcohol and that the rearrangement is suprafacial.

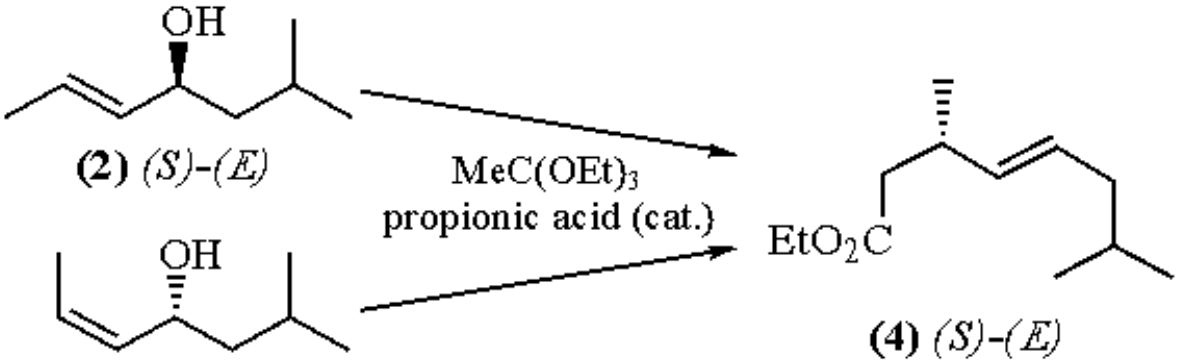

(2) *(S)-(E)*

(3) *(R)-(Z)*

(4) *(S)-(E)*

(9)

The ***Propionic Acid*** catalyst is often consumed in the form of the propionate ester of the allylic alcohol, thereby stopping the rearrangement process (eq 10).

$$EtCO_2H + MeC(OR)_3 \longrightarrow EtCO_2C(Me)(OR)_2 + ROH$$

$$EtCO_2C(Me)(OR)_2 + R'OH \xrightarrow{H^+} EtCO_2R' + MeCO_2R + ROH \qquad (10)$$

Esterification can occur in reactions that are slow because of constraints imposed by the transition state. The second step of eq 10 is repressed by using a hindered carboxylic acid, thereby making the rearrangement competitive with esterification. Thus ***Pivalic Acid*** (5 mol %) as a catalyst leads to a 74% yield of ester (**6**); propionic acid affords lower yields and appreciable quantities of the propionate ester of alcohol (**5**) (eq 11).[10a] Alternatively, 2,4-dinitrophenol can be employed as a catalyst (eq 12).[10b] Rearrangement of allylic alcohol (**7**) at 100 °C is slow because of the low boiling point of methyl orthoacetate (bp 107-9 °C). When propionic acid is employed as the catalyst, the methyl ester is obtained in 50% yield along with esterified allylic alcohol. On occasion, the intermediate ketene acetal can undergo elimination to produce dienes if the rate of rearrangement is slow (eq 13).[11]

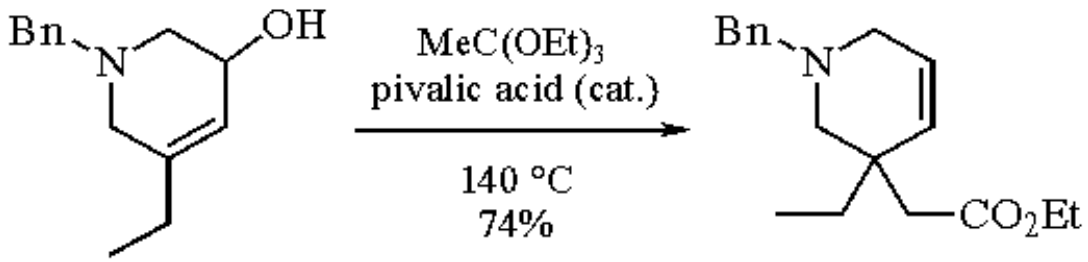

(5) **(6)**

(11)

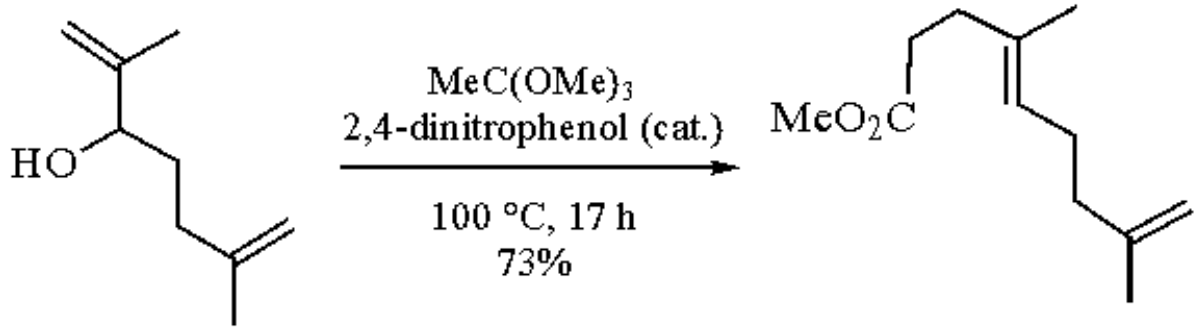

(7) (12)

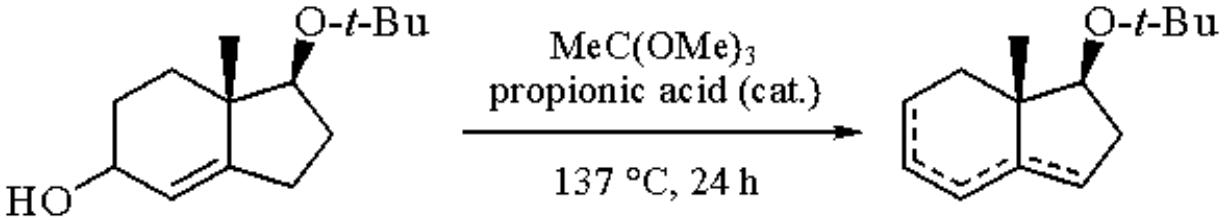

(13)

Carbon-Carbon Bond Formation.

Orthoacetates undergo carbon-carbon bond formation with carbon nucleophiles in the presence of acid catalysts to provide acetals (eqs 14 and 15),[12a,b] enol ethers (eq 16),[13] and azulenes (eq 17).[14] The azulene formation is believed to be an [8 + 2] electrocyclic reaction wherein the ketene acetal from ethyl orthoacetate is functioning as the two-carbon component.

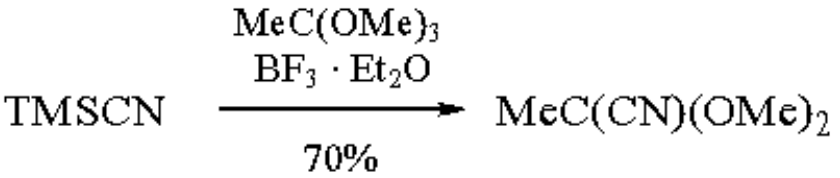

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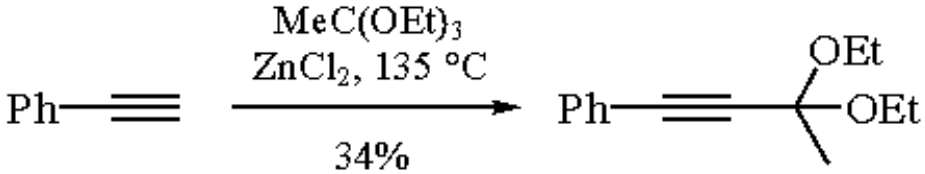

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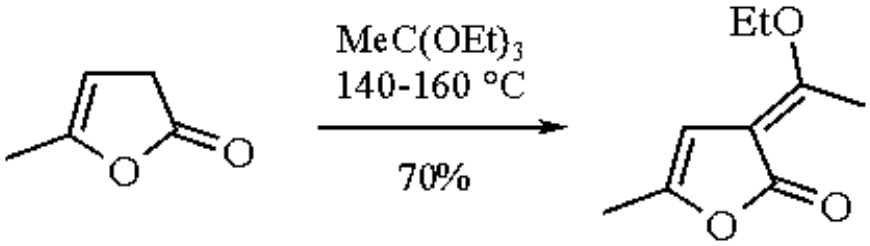

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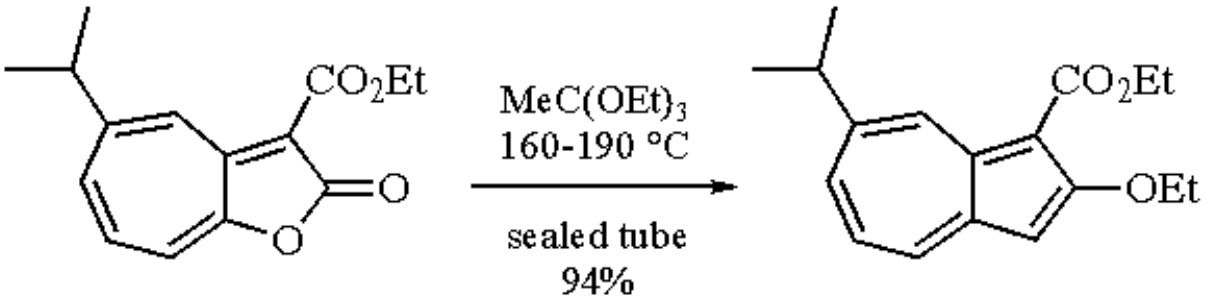

(17)

Exchange with Heteroatoms.

Alkenes are converted into epoxides by 90% ***Hydrogen Peroxide*** in the presence of ethyl orthoacetate. Trisubstituted and 1,2-disubstituted alkenes give yields in excess of 80%. The peroxide is thought to exchange with an ethoxy group to give the diethyl acetal of a peroxy acid as the reactive intermediate.[15] Orthoacetates exchange with one equivalent of a primary amine to give an acetimidate. A second equivalent produces an acetamidine (eq 18).[16]

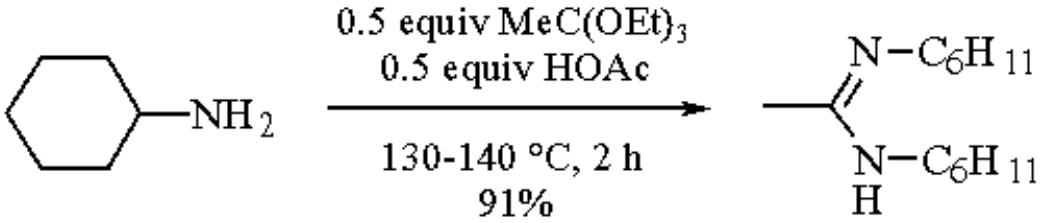

(18)

Formation of Heterocycles.

Intramolecular versions of eq 18 lead to heterocyclic systems through the intermediate acetimidate. By this method, imidazoles (eq 19),[17] oxazoles,[18] benzotriazepinones (eq 20),[19] quinazolinones,[20] dihydroimidazolium,[21] and tetrahydropyrimidinium[21] salts are prepared. In eq 19, the C-2 carbon and the C-2 methyl group of the product are derived from the acetic acid portion of methyl orthoacetate; the *N*-methyl group comes from the methoxy group of the orthoacetate by alkylation of the dioxenium ion. The oxazoline *N*-oxide (eq 21) is a reactive species that can participate in [3 + 2] cycloadditions.[22]

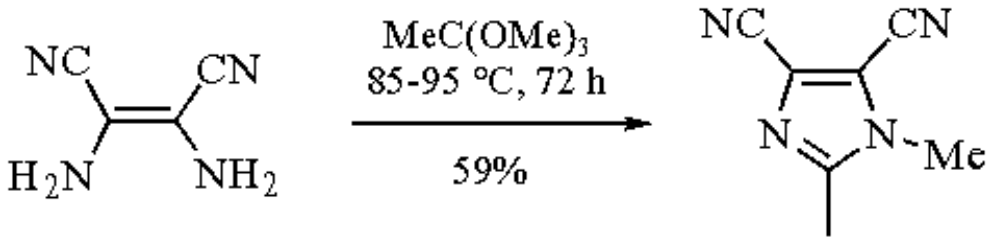

(19)

(8)

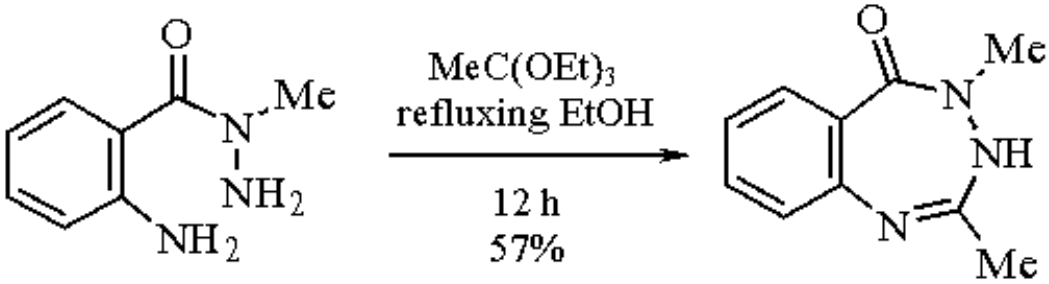

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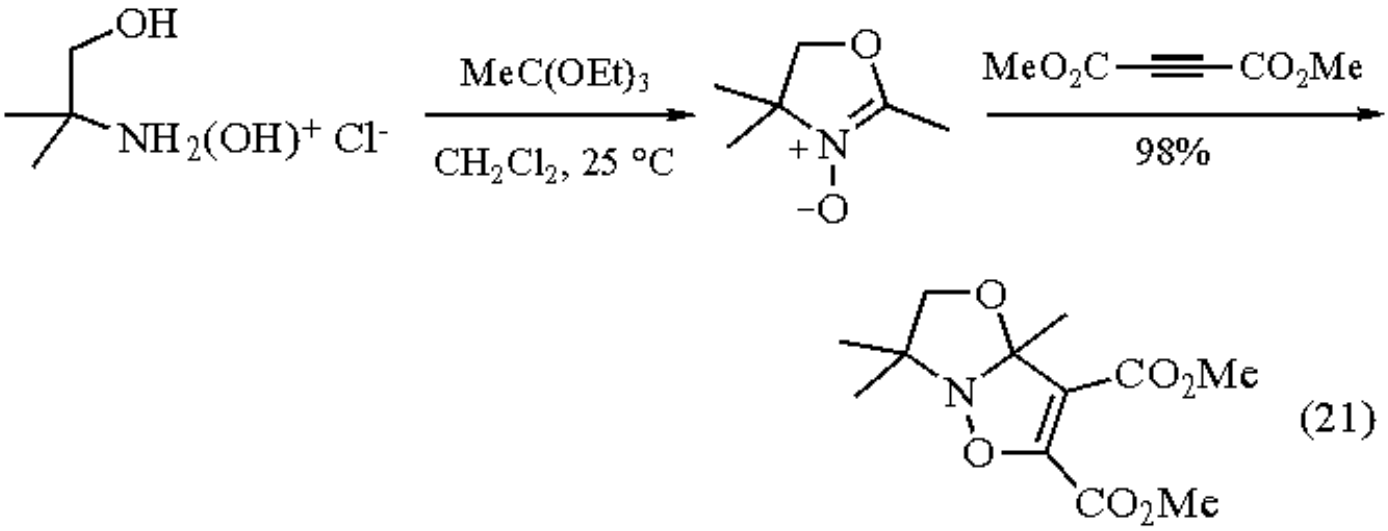

(21)

Reaction of Acetimidate Intermediates with Carbon Nucleophiles.

Compounds with active methylene groups react with acetimidate-like intermediates to form carbon-carbon bonds in addition to heterocyclic rings. The reaction can be conducted in both the inter-[23] (eq 22) and intramolecular sense (eq 23).[24]

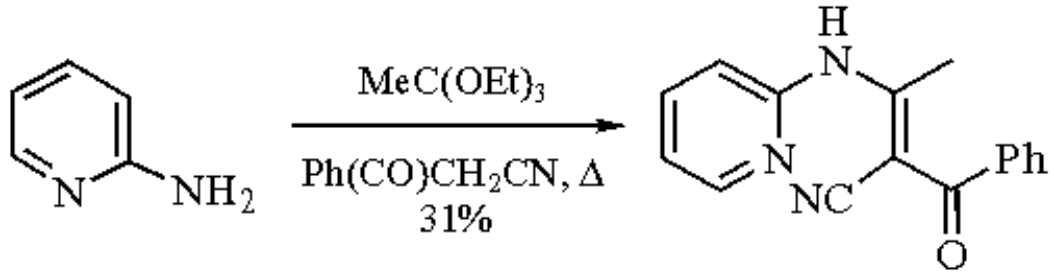

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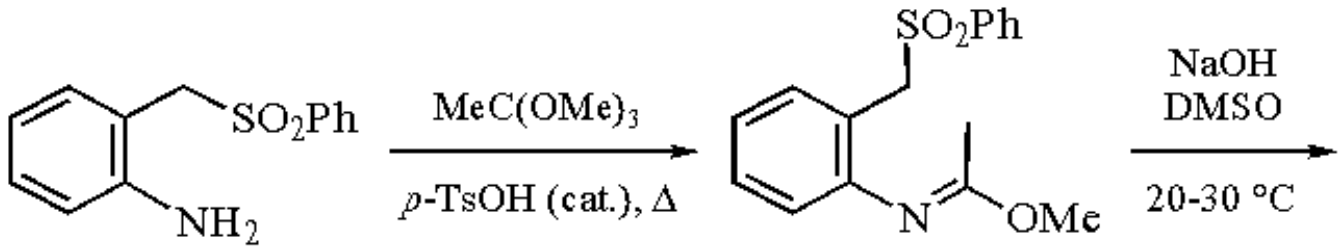

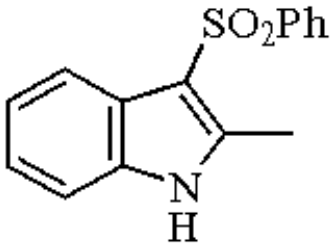

(23)

Related Reagents.

Diethyl Phenyl Orthoformate; ***N,N-Dimethylacetamide Dimethyl Acetal***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Ethoxyacetylene***; ***Ethyl Vinyl Ether***; ***Ketene Bis(trimethylsilyl) Acetal***; ***Ketene t-Butyldimethylsilyl Methyl Acetal***; ***Methylketene Dimethyl Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***Triethyl Orthoformate***.

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Triethyl Orthoformate[1]

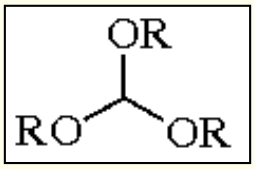

(**1**; R = Et)

[122-51-0] · $C_7H_{16}O_3$ · Triethyl Orthoformate · (MW 148.23) (**2**; R = Me)

[149-73-5] · $C_4H_{10}O_3$ · Trimethyl Orthoformate · (MW 106.14)

(precursor for higher analogs by reaction with alcohols,[1c] including cyclic orthoesters from polyols;[2] for deoxygenation of 1,2-diols, affording alkenes;[3] acetalization of carbonyl compounds;[4] a dehydrating agent[5] for enol ether formation;[6] esterification of acids;[7] formylation of active methylene compounds,[8] heteroatom nucleophiles[9] and organometallic reagents;[10] formylation of electron-rich species; dialkoxycarbenium ion precursor;[11] solvent for thallium trinitrate reactions[12])

Alternate Name: triethoxymethane.

Physical Data: (**1**) bp 146 °C; *d* = 0.891 g cm^{-3}; (**2**) bp 102 °C; *d* = 0.970 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear liquid; widely available.

Purification: distillation.

Handling, Storage, and Precautions: highly moisture sensitive; flammable; irritant with high volatility. Use in a fume hood.

Introduction.

The orthoformates are a remarkably useful group of reagents. They are shelf-stable, yet highly reactive. As alkylating agents, they readily transfer the associated alkyl group, a large variety of which are easily available. As formylation reagents, they are reactive under both acidic and basic conditions. The choice of ester is often arbitrary in this context.

Transesterification.

Higher Orthoformates.

While there are many ways to obtain esters of orthoformic acid,[1c] an easy method takes advantage of the rapid equilibrium among orthoesters (eq 1). By starting with the lowest analog, trimethyl orthoformate, essentially complete conversion to the higher esters is possible by carrying out the reaction at such a temperature as to distill away the evolving methanol. It is important that reactions be carried out under anhydrous conditions to avoid formation of the formate through hydrolysis.

$$HC(OR)_3 + 3\,R'OH \rightleftharpoons HC(OR')_3 + 3\,ROH \qquad (1)$$

Cyclic Orthoformates.[2]

When the above strategy is applied to polyols, cyclic orthoformates can be isolated. Most common are the cyclization of 1,3-diols (eq

2)[2,13] and 1,2-diols,[14] as well as the formation of caged structures from the use of polyols (eq 3).[15,16]

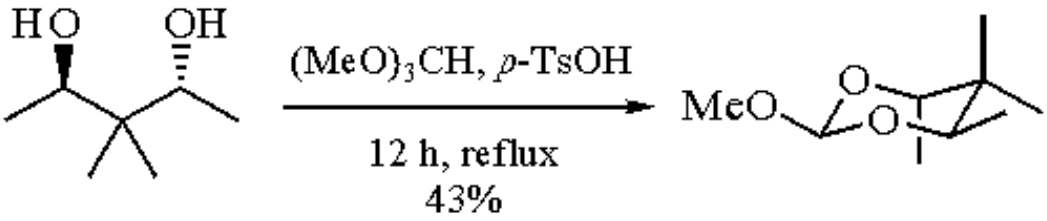

(2)

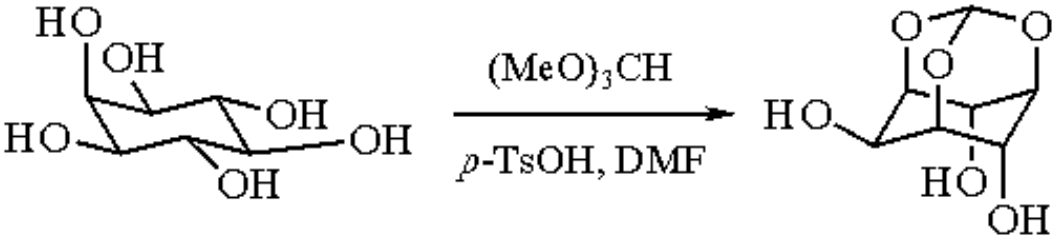

(3)

Those orthoformates obtained from 1,2-diols (eq 4)[3] can undergo cycloelimination upon pyrolysis to afford alkenes in high yield.[17] There are a variety of methods for carrying out this overall process,[18] but the orthoester route is competitive if the alkene is thermally stable.

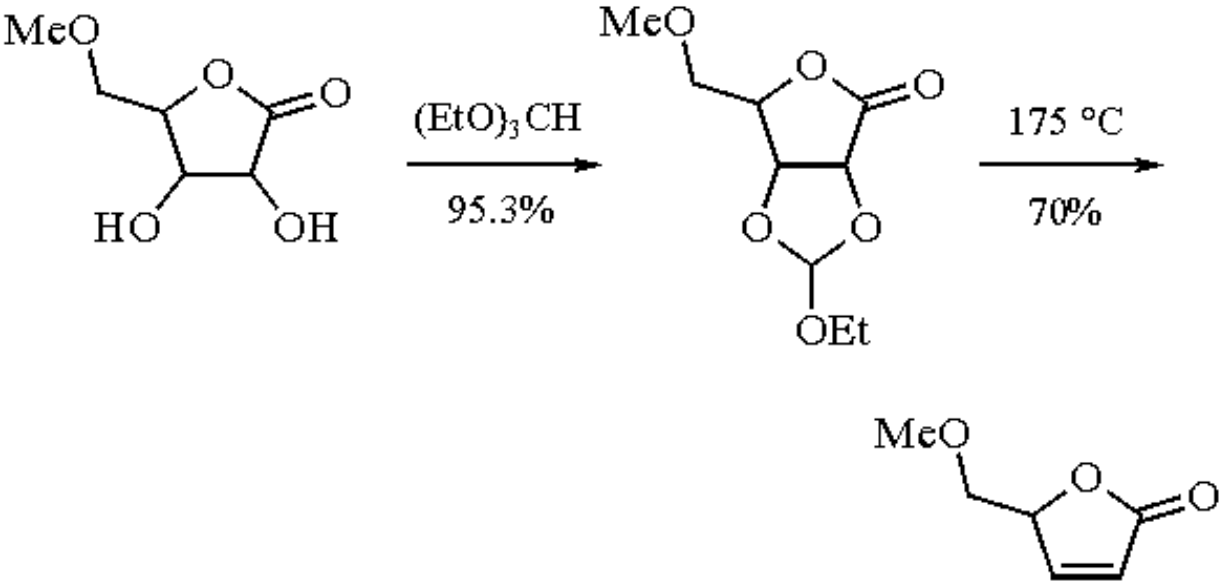

(4)

Acetals and Enol Ethers.

The conversion of the orthoformate to formate is energetically favored. As a result, the acetalization of ketones by orthoformate is a highly favored process and allows the formation of acetals under exceedingly mild conditions. A wide variety of ketones can be converted into dimethyl acetals by the action of trimethyl orthoformate and ***p-Toluenesulfonic Acid***. The methyl formate thus evolved is distilled away.[4]

The process is general and allows isolation of quite sensitive acetals (eq 5).[19] The technique accommodates protection of α,β-unsaturated carbonyl compounds.[20,21,22] While some form of acid catalysis is usually needed, there is great flexibility in the choice of acid, including Amberlyst 15[23] and, in particular, ***Montmorillonite K10***.[24] Cyclic acetals are also accessible (eq 6).[25]

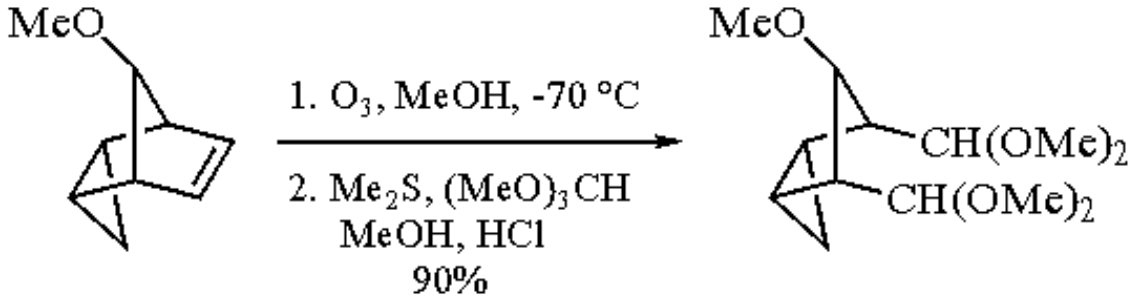

(5)

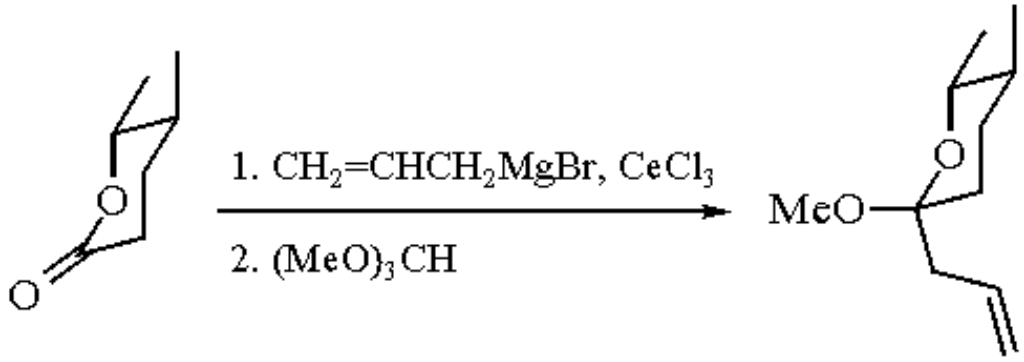

(6)

Upon distillation of some acetals,[26] or upon attempted acetalization of highly conjugated species,[26,27] the enol ether can also be observed. The choice of acid often determines whether the acetal or the enol ether is isolated.

Orthoformates are also useful in promoting the formation of other acetals[5] by functioning as dehydrating agents. This function is useful for β-lactone formation as well (eq 7).[28,29]

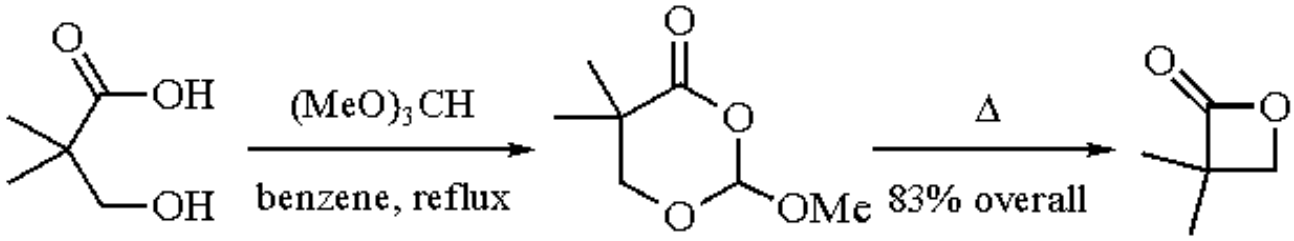

(7)

Esterification.

In a related process, orthoformates are good esterification agents; they operate on carboxylic acids (eq 8),[7] sulfonic acids,[30] and carboxyboranes,[31] often without the need for acid catalysis.

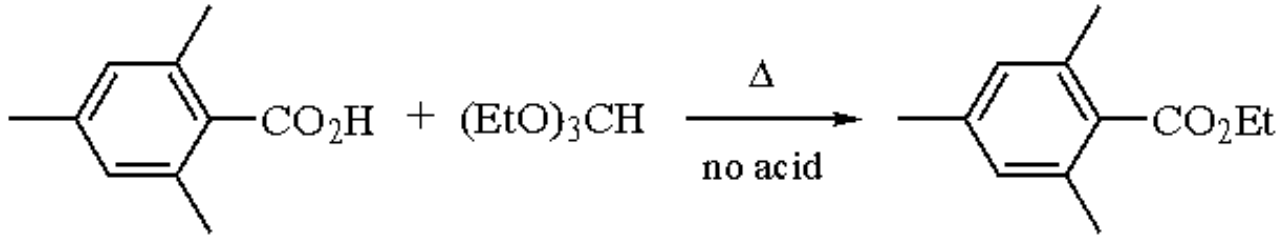

(8)

Formylation.

The orthoformate carbon is highly reactive in a number of bond-forming reactions. It is capable of reaction under both electrophilic and nucleophilic conditions and serves as a formylation reagent.

Active Methylene Compounds.

Triethyl orthoformate can formylate diethyl malonate under slightly acidic conditions.[8] With less activated compounds it can be induced to undergo a Mannich reaction,[32] and can also formylate a cyclohexanone enolate anion (eq 9).[33]

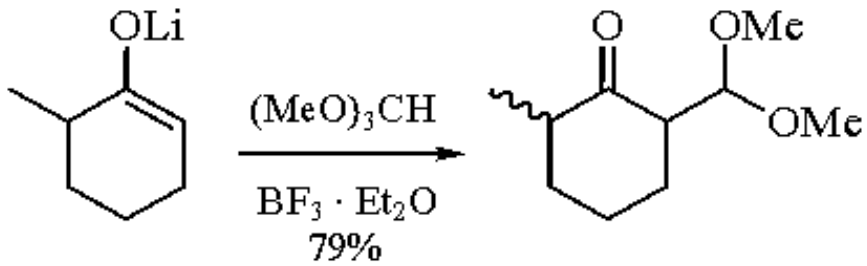

(9)

This reaction is noteworthy in its propensity for *C*-alkylation and the fact that the protected acetal raises the pK_a of the product relative to the unprotected β-dicarbonyl compound.

Heteroatom Nucleophiles.

The formylation of anilines is well known[34] and provides entry to a large array of functional groups.[35] Of greater interest is the ability of the product to be trapped in a subsequent reaction to afford heterocycles (eq 10).[9,36-38] Orthoformates also react readily with phosphorus nucleophiles.[39]

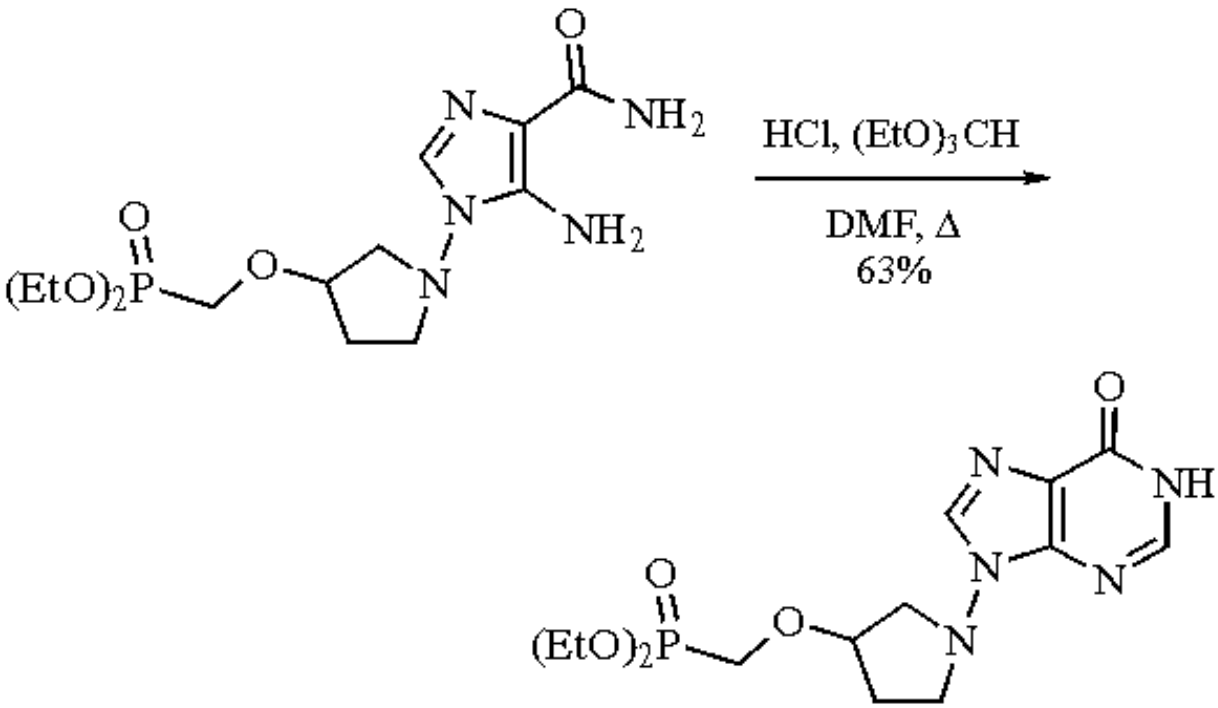

(10)

Organometallic Reactions.

In addition to the enolate reactions described above, orthoformates can also carry out the formal formylation of Grignard reagents.[10]

Electrophilic Formylation.

It has been shown that the dialkoxycarbenium ion can be readily formed by acid treatment of orthoformates. While the reactive ion can be isolated and used directly,[11] the typical practice is to generate it in situ.

While not as universal as the Gatterman-Koch reaction, the cation works well for the formylation of activated aromatic compounds (eq 11).[40,41] Of greater synthetic utility is the effective formylation of alkynes (eq 12)[42] and alkenes (see below).

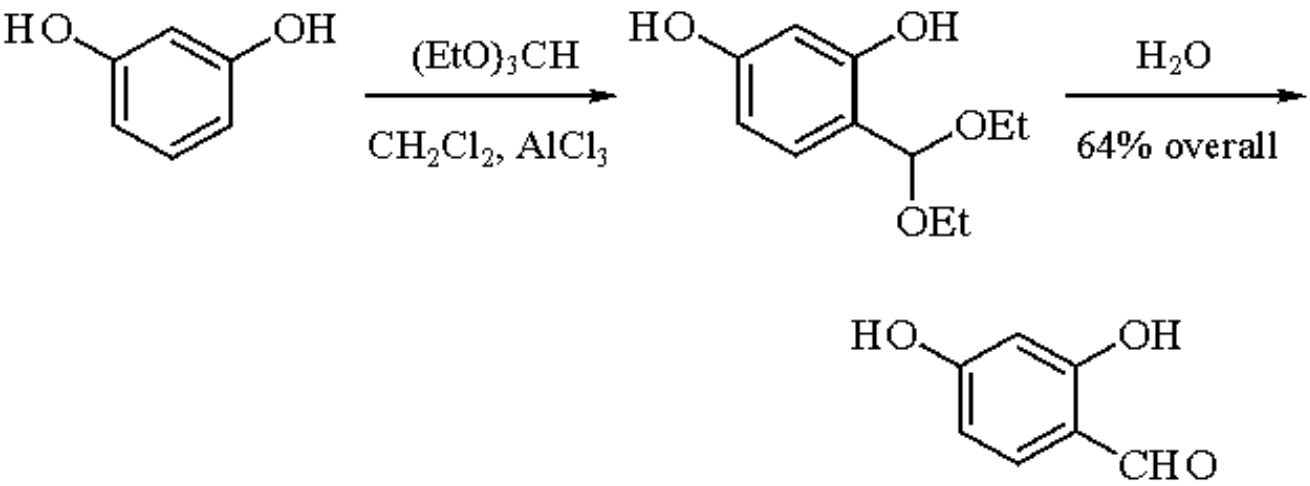

(11)

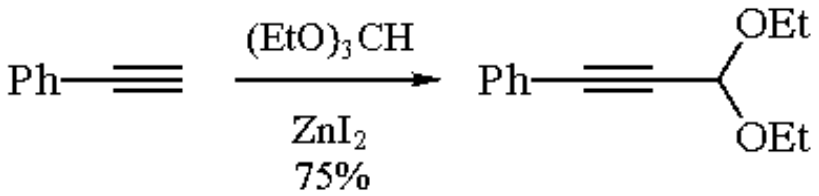

(12)

Reactions of silyl enol ethers with dialkoxycarbenium ions result in α-formyl ketones (eq 13),[43] much like those achieved above through the use of enolate anions. With a dienol silane (eq 14), regioselective γ-formylation is achieved.[44] In extended alkenic systems, cationic cyclization (eq 15) can be realized.[45]

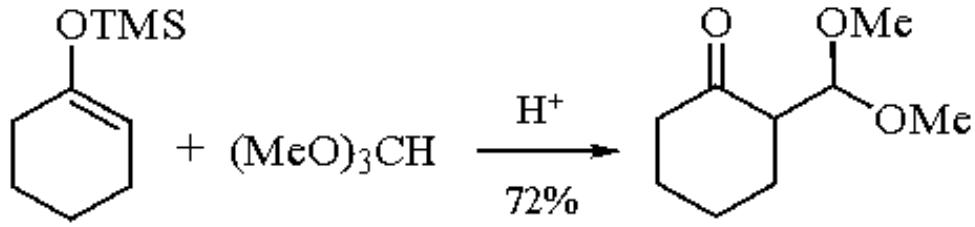

(13)

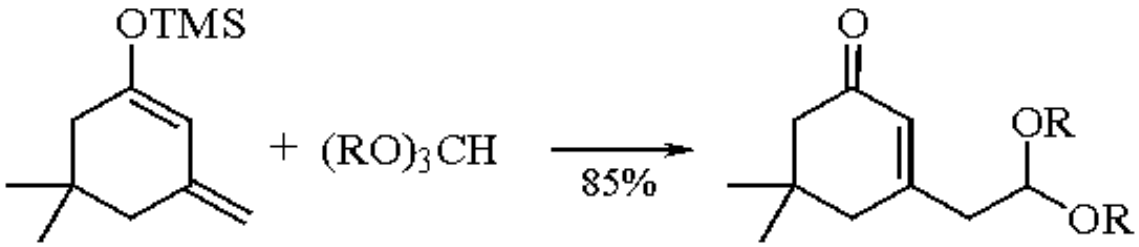

(14)

R = CH_2=$CHCH_2$

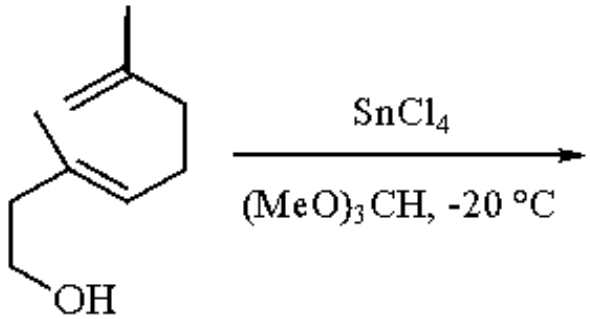

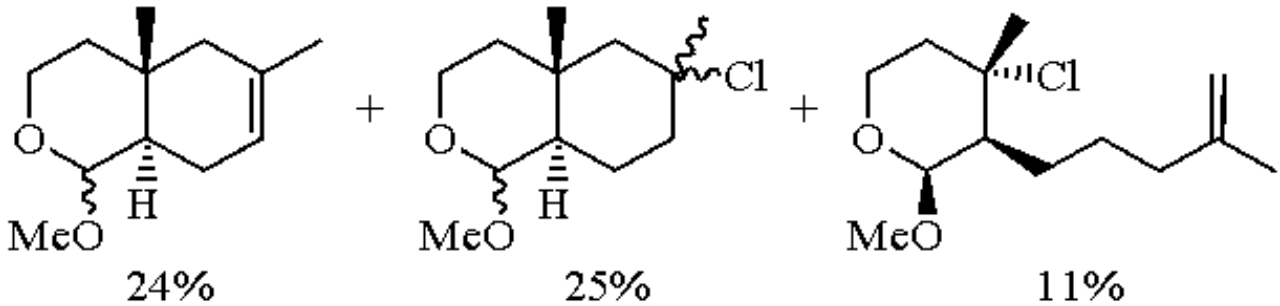

(15)

Solvent for Thallium Trinitrate Oxidations.

While ***Thallium(III) Nitrate*** oxidations of aromatic ketones and chalcones often gives rise to mixtures of products, the use of trimethyl orthoformate as solvent gives substantially cleaner reactions and higher yields (eq 16).[12]

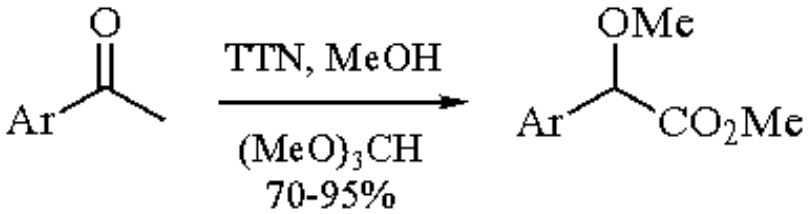

(16)

Related Reagents.

Diethyl Phenyl Orthoformate; ***Dimethoxycarbenium Tetrafluoroborate***; ***Dimethylchloromethyleneammonium Chloride***; ***N,N-Dimethylformamide***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Methyl Formate***.

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Triethyloxonium Tetrafluoroborate[1]

$R_3O^+ X^-$

(**1**; R = Et, X = BF_4)

[368-39-8] · $C_6H_{15}BF_4O$ · Triethyloxonium Tetrafluoroborate · (MW 190.02) (**2**; R = Et, X = PF_6)

[17950-40-2] · $C_6H_{15}F_6OP$ · Triethyloxonium Hexafluorophosphate · (MW 248.18) (**3**; R = Et, X = $SbCl_6$)

[3264-67-3] · $C_6H_{15}Cl_6OSb$ · Triethyloxonium Hexachloroantimonate · (MW 437.66) (**4**; R = Et, X = SbF_6)

[19554-80-4] · $C_6H_{15}F_6OSb$ · Triethyloxonium Hexafluoroantimonate · (MW 338.96) (**5**; R = Me, X = BF_4)

[420-37-1] · $C_3H_9BF_4O$ · Trimethyloxonium Tetrafluoroborate · (MW 147.93) (**6**; R = Me, X = PF_6)

[12116-05-1] · $C_3H_9F_6OP$ · Trimethyloxonium Hexafluorophosphate · (MW 206.09) (**7**; R = Me, X = $SbCl_6$)

[54075-76-2] · $C_3H_9Cl_6OSb$ · Trimethyloxonium Hexachloroantimonate · (MW 395.57) (**8**; R = Me, X = SbF_6)

[29830-67-9] · $C_3H_9F_6OSb$ · Trimethyloxonium Hexafluoroantimonate · (MW 296.87) (**9**; R = Me, X = 2,4,6-trinitrobenzenesulfonate)

[13700-00-0] · $C_9H_{11}N_3O_{10}S$ · Trimethyloxonium 2,4,6-Trinitrobenzenesulfonate · (MW 353.30)

(powerful alkylating agent for the ethylation of sensitive or weakly nucleophilic functional groups;[1] analogous methylations are achieved using trimethyloxonium salts[2])

Alternate Name: Meerwein's salt.

Physical Data: (**1**) mp 92 °C; 116 °C; (**2**) 142-144 °C; (**3**) 130-133 °C; 135-137 °C; (**4**) 139 °C; (**5**) 141-143 °C; 179-180 °C; (**6**) 262 °C; (**7**) 156-158 °C; 159 °C; (**8**) 239-241 °C (**9**) 120-130 °C with effervescence and resolidifying; 181-183 °C.

Solubility: (**1**)-(**8**) sol liquid sulfur dioxide; (**1**) and (**5**) sol dichloromethane, chloroform, nitromethane; insol diethyl ether; (**2**) and (**6**) sol dichloromethane, arsenic trifluoride; (**3**) and (**7**) sol nitromethane; slightly sol dichloromethane, chloroform, tetrachloromethane, 1,2-dichloroethane; (**9**) sol nitromethane. A scale of solvent nucleophilicity has been based on the solvolysis of (**2**).[3]

Form Supplied in: (**2**), (**3**), (**5**), and (**7**) are commercially available as colorless solids; (**1**) is supplied as a 1 M solution in dichloromethane or as a colorless solid stabilized with diethyl ether.

Preparative Methods: there is an established method for (**1**).[4] (**5**) is reported[2] being contaminated by ethyldimethyloxonium salt. Convenient syntheses of pure (**5**) have been published;[5,6] similar methods yield (**2**) and (**6**).[7] Syntheses of (**3**) and (**7**),[1a,8] (**4**) and (**8**),[8] and (**9**)[9] are available.

Handling, Storage, and Precautions: solvent-free (**1**) is hygroscopic; it is conveniently stored in diethyl ether at -20 °C in a tightly stoppered bottle.[10] Contrary to recommendations,[4] the use of a dry box or an inert atmosphere is not required for most applications of (**1**). A sample of the oxonium salt-ether slurry may be transferred to the tared reaction flask, and after removal of the ether on a rotary evaporator the resulting solid may be used without further purification.[10] When alkylation requires the absence of acid, (**1**) should be handled in a dry box and before use it should be washed with anhydrous diethyl ether and dried by a stream of nitrogen.

Solvent-free (**5**) is less hygroscopic[2] than (**1**) and is stored in a tightly sealed bottle at -20 °C. It may be handled in the air for short periods of time. (**9**) is nonhygroscopic, may be stored at rt, but is more laborious to prepare than (**5**).

Trialkyloxonium salts have irritant and corrosive properties and are toxic due to their alkylating ability. In comparison with other alkylating agents, the dangers are minimized by the fact that oxonium salts are water-soluble, nonvolatile, crystalline solids, which are rapidly solvolyzed in aqueous solution. Nevertheless, skin and eyes should strictly be protected from contact with the solid

agents or their solutions. Use in a fume hood.

General Reactivity.

The high alkylating potential of trialkyloxonium salts has been well known since their discovery.[11] When either methylation or ethylation of weakly nucleophilic functional groups is desired, the use of the more reactive Me_3O^+ is preferred to that of Et_3O^+ salts.[2b] Ranking the common methylating agents in a sequence of decreasing methylating ability, $Me_2Cl^+SbF_6^-$ > $(MeO)_2CH^+BF_4^-$ > $Me_3O^+BF_4^-$ ($SbCl_6^-$, PF_6^-) > $MeOSO_2CF_3$ > $MeOSO_2F$ > $(MeO)_2SO_2$ > MeI,[12,13] demonstrates that Me_3O^+ salts possess high, but not the highest, reactivity (see also ***O-Methyldibenzofuranium Tetrafluoroborate***). Since the low solubility of Me_3O^+ salts may be a problem, sometimes the less reactive (and more toxic) $MeOSO_2F$ (magic methyl)[13] may be the reagent of choice for methylations. Trialkyloxonium SbF_6^-, $SbCl_6^-$, and PF_6^- salts are less sensitive to decomposition due to high anion stability than the corresponding tetrafluoroborates.[1e] Nevertheless, the latter are preferentially used depending on convenience and availability.

Alkylation of Anionic Nucleophiles.

The efficient transfer of alkyl groups from Me_3O^+ or Et_3O^+ salts to anionic nucleophiles has been applied to remove halide ions via alkylation and to replace them by suitable complex anions. Thus *N*-cyano- or *N*-acyl-*N*,*N*,*N*-trialkylammonium tetrafluoroborates have been obtained under anhydrous conditions via reaction of the corresponding halides with $Et_3O^+BF_4^-$ (**1**).[14] Since, besides the desired salts, only volatile alkyl halides and the corresponding ethers are formed, the method is superior to the treatment with ***Silver(I) Tetrafluoroborate***, which requires separation from silver halide precipitates. Using $Me_3O^+BF_4^-$ (**5**) the first stable β-phospha- and β-arsatrimethinecyanines (**10**$^+BF_4^-$)[15,16] have been prepared from the appropriate bromophosphane or -arsane precursors (**10**), the solutions of which show only low equilibrium concentrations of cyanine bromides (**10**$^+Br^-$), (eq 1); there are similar applications to transition metal-halogen complexes.[17]

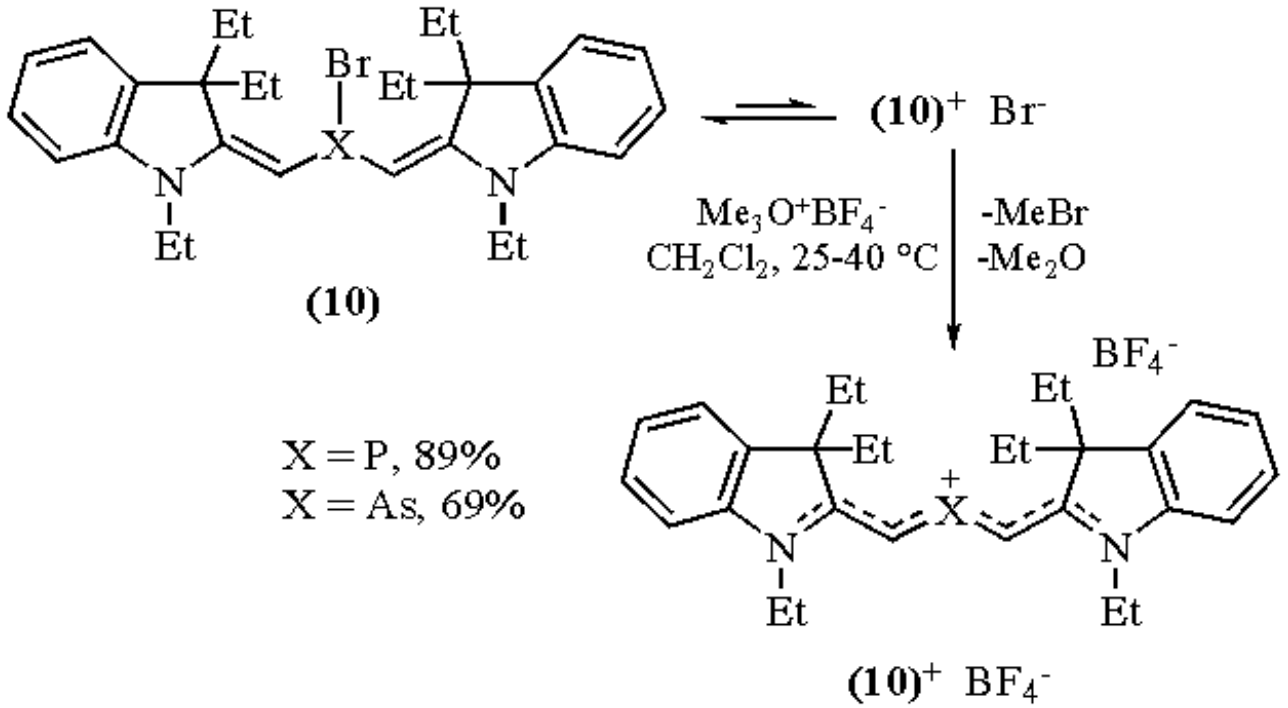

(1)

Of the numerous alkylations of anionic substrates with trialkyloxonium salts,[1c,e] esterification of carboxylate anions is of special preparative interest. Although oxonium salts are readily hydrolyzed in aqueous solution, water may be a suitable solvent, when a high excess of $Et_3O^+BF_4^-$ (**1**) or $Me_3O^+BF_4^-$ (**5**) is used in the presence of $NaHCO_3$ or ***Diisopropylethylamine***.[18,19] Under these conditions, the in situ generated carboxylate anions of *N*-acylamino acids,[18] dipeptides (eq 2),[18] or labile hemins[19] are smoothly *O*-alkylated. ε-Amino, guanidino, carboxamido, and hydroxyl functions of alcohols or phenols may be present, but remain unaltered. Smooth esterifications of even sterically hindered carboxylic acids with equimolar amounts of (**1**) and (**5**) may conveniently be performed in dichloromethane using diisopropylethylamine as base.[10] Similarly, ethyl (*Z*)-2-methyl-4-oxo-2-butenoate is prepared from the corresponding hydroxybutenolide via *O*-ethylation of a carboxylate anion intermediate (eq 3).[20]

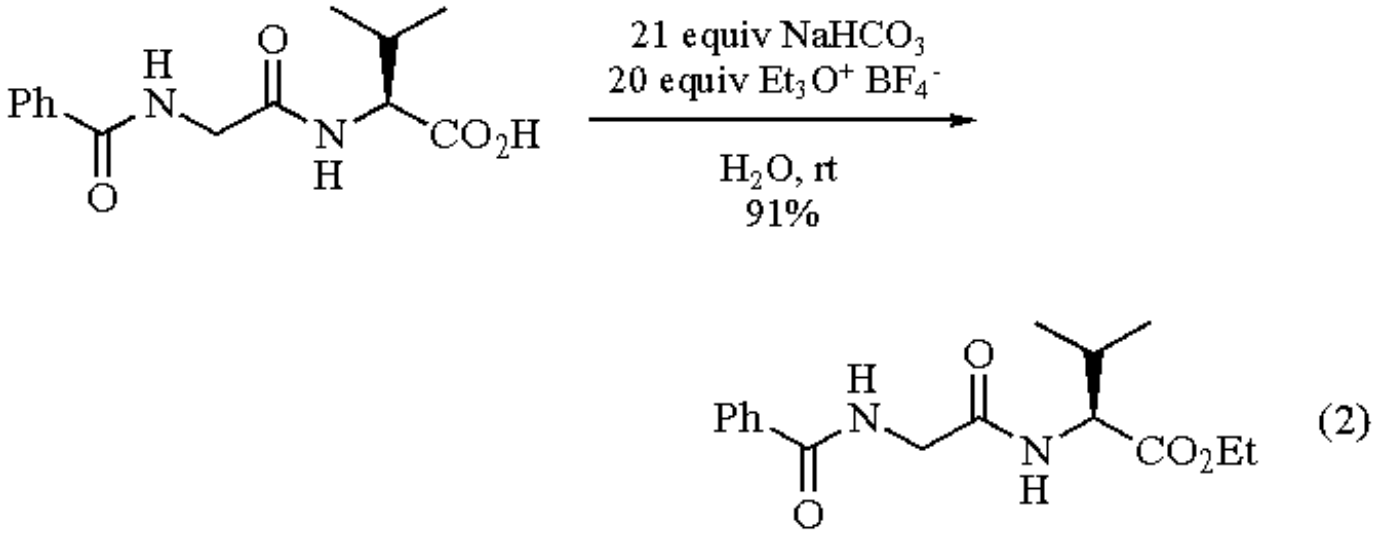

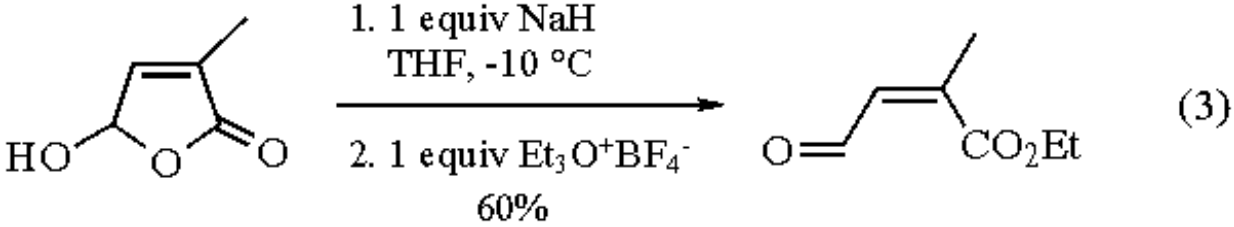

In the absence of a suitable base, no esterification of acetamino acids is achieved using $Me_3O^+BF_4^-$ (**5**), since under these conditions the carboxamide is more reactive than the carboxylic acid. The resulting imino ester salt may readily be converted into the corresponding *N*-ethylamino acid via reduction with $NaBH_4$ (eq 4).[21]

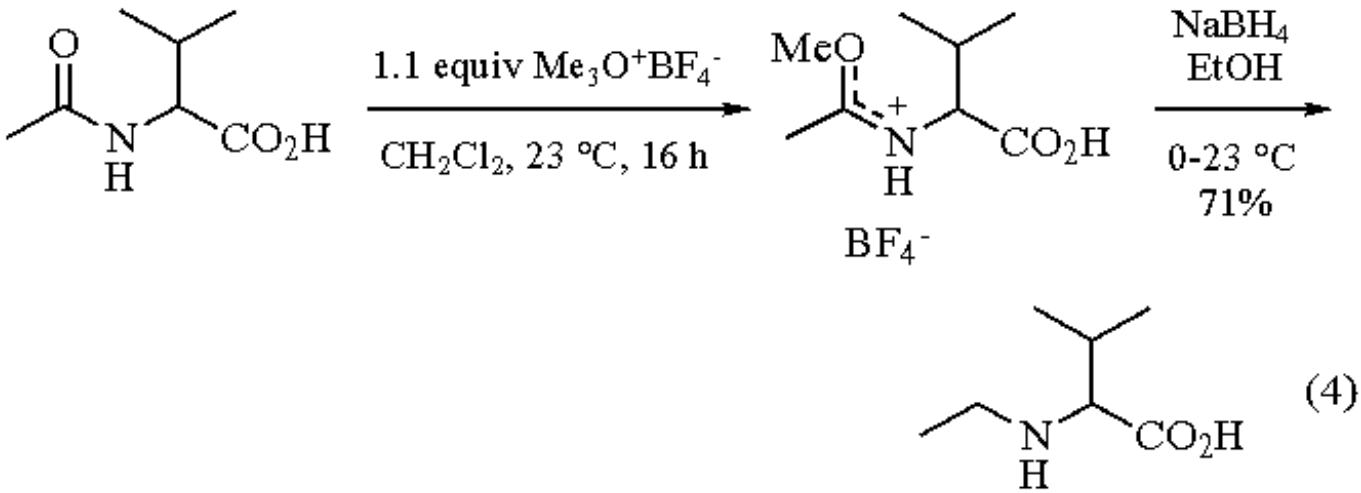

Trialkyloxonium salts, like other strongly electrophilic agents, when treated with ambident anions yield considerable amounts of products derived from alkyl attack at the site of highest electron density.[1d,e,22] Thus, in aprotic polar solvents, enolates of aliphatic ketones give mainly enol ethers via *O*-ethylation with $Et_3O^+BF_4^-$ (**1**),[23] while *C*-alkylation is predominant with the less reactive ethyl iodide (eq 5).[22,23] The ambident anions of imines behave similarly: with (**1**), enamines (via *N*-alkylation) are preferentially formed instead of the usually obtained *C*-alkylation products.[24] A discussion of the factors influencing the competition of *C*- and *heteroatom*-alkylation is available.[22] Exclusive mono- or bis-*O*-alkylations have been reported to occur for the reactions of cyclic β-diketones with equimolar or excess amounts of (**1**) (eq 6).[25]

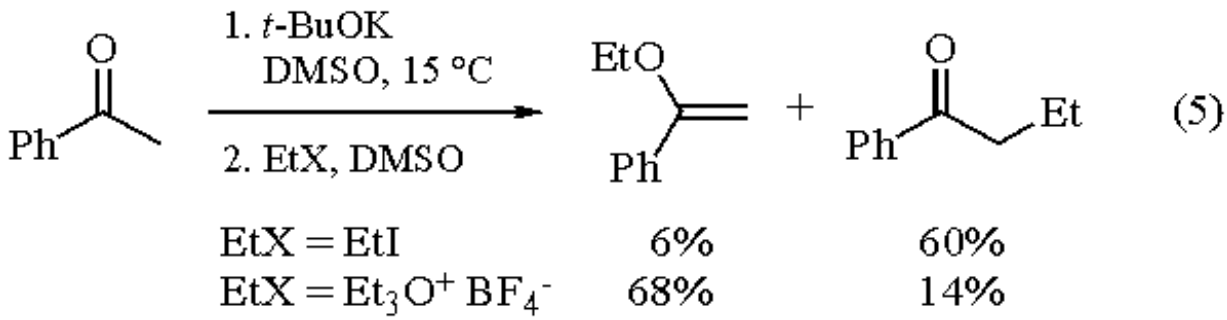

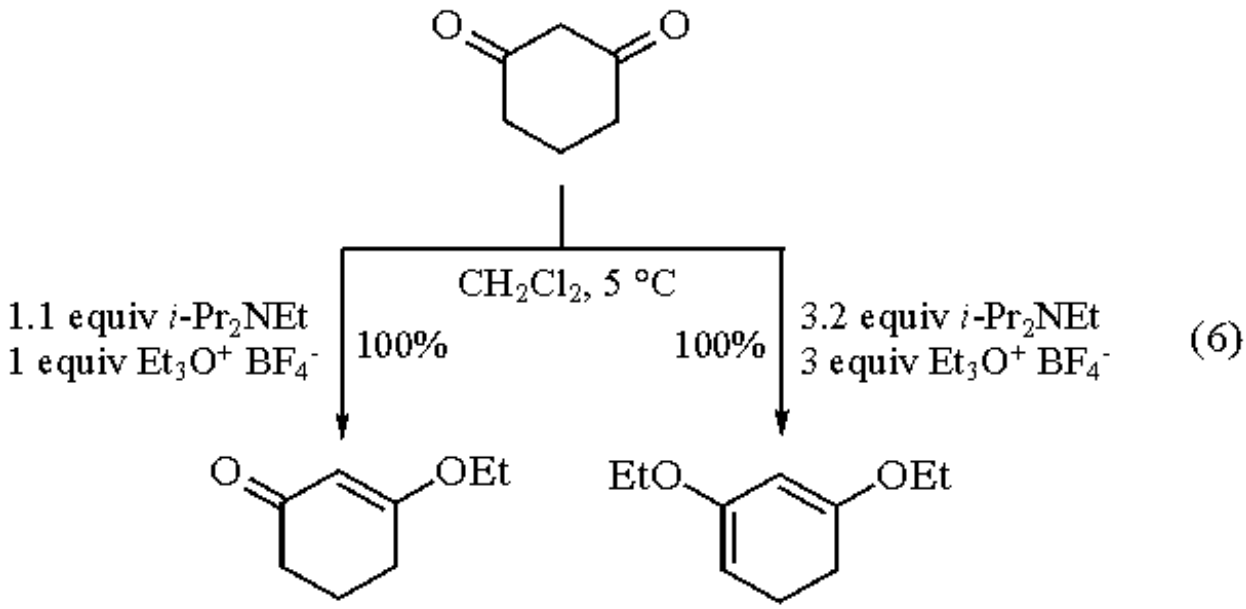

Being formal analogs of enolates, lithium transition metal acylate complexes are readily *O*-alkylated with $Et_3O^+BF_4^-$ (**1**) or $Me_3O^+BF_4^-$ (**5**) to give alkoxycarbene complexes.[26] The metal acylate complexes are conveniently prepared from commercially available metal carbonyl complexes via addition of a suitable nucleophile (e.g. alkyl-, aryl-, alkynyllithium, or lithium dialkylamide). Nucleophilic addition and subsequent alkylation may be performed in a one-pot reaction (eq 7).[26,27] Alkoxycarbene complexes (especially those of chromium or tungsten) are valuable, versatile building blocks for numerous organic syntheses.[28] The unique benzannulation depicted in eq 8 may serve as a representative example;[28a] the starting material of this reaction is available via addition of ***Phenyllithium*** to ***Hexacarbonylchromium*** and sequential methylation with (**5**).[26]

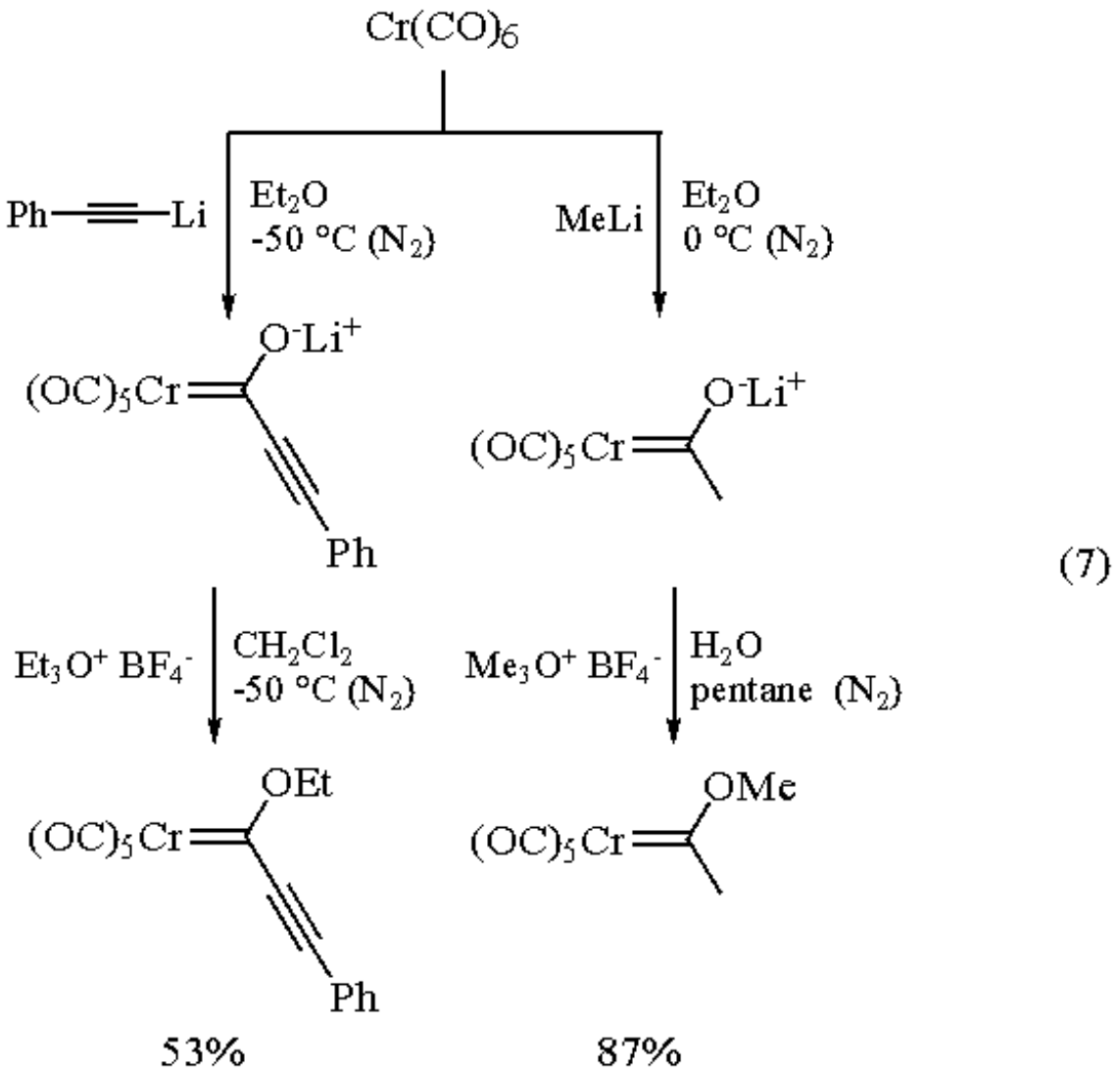

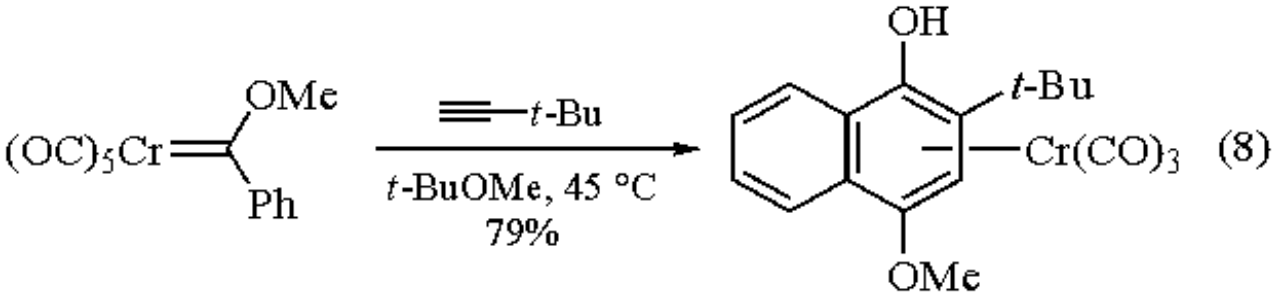

Ethylations of lithium (or sodium) 1-alkynyltrialkylborates with $Et_3O^+BF_4^-$ (**1**) afford (*Z*)/(*E*)-alkenyldialkylboranes via an addition-rearrangement mechanism.[29,30] The boranes may readily be hydrolyzed to the corresponding (*Z*)/(*E*)-alkenes (eq 9).[29a] Oxidation of the alkenyldialkylborane intermediates provides a valuable route to ketones free of complications associated with the production of (*Z*)/(*E*) mixtures (eq 9).[29a] The highly stereoselective formation of a cyclic (*E*)-alkenylborane is favored, when 3-methoxypropynyltriethylborate is alkylated with (**1**) (eq 10).[30]

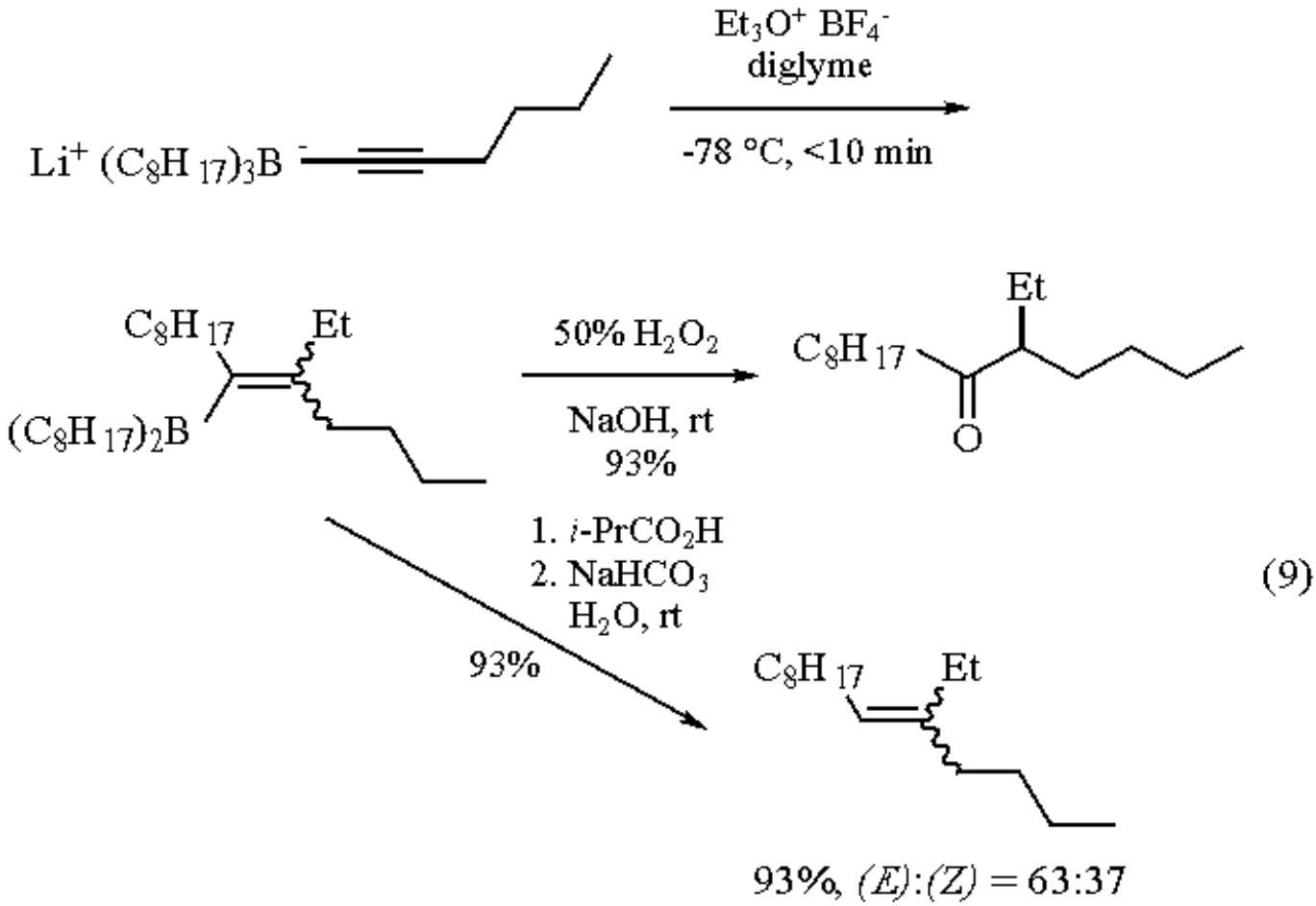

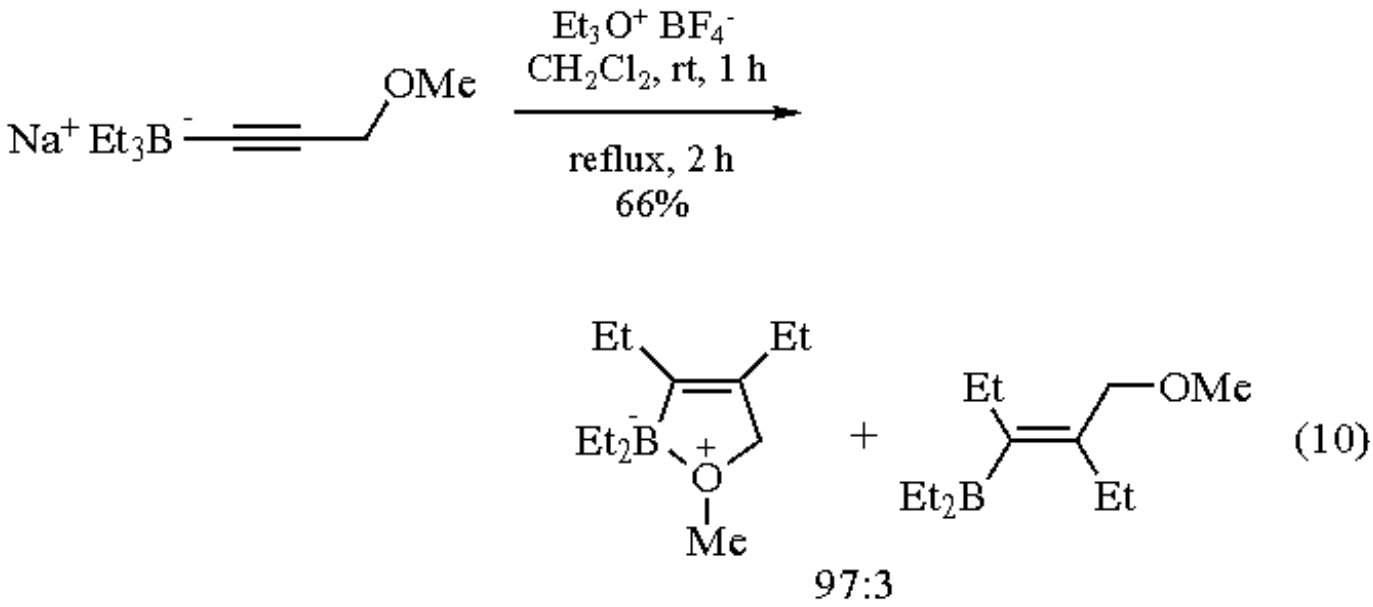

Alkylations of Uncharged Nucleophiles.

Usually Me_3O^+ or Et_3O^+ salts are applied to alkylate uncharged molecules.[1] The resulting cationic intermediates, though frequently subject to subsequent reactions with nucleophiles, have been isolated as stable salts in many cases.[1a,c,e] Thus trialkyloxonium salts are obtained from alicyclic (or acyclic dialkyl) ethers (eq 11)[11b] and alkoxycarbenium salts from dialkyl (or vinyl) ketones.[1a] The structures of some of these salts have been determined by using X-ray diffraction, e.g. the 1-ethoxyhomotropylium cation prepared from cyclooctatrienone according to eq 12 has been shown to be best regarded as a linear ethoxyoctatrienyl cation and not as a homoaromatic system.[31] *O*-Alkyllactonium salts may be generated from lactones (eq 13)[32,33] as well as trialkoxycarbenium salts from dialkyl carbonates.[1a,32a] However, most acyclic esters do not react with Me_3O^+ or Et_3O^+ salts.[1a,c,e,33] A discussion on the basis of equilibrium constants and calculations of methyl affinities has been published.[33] Even *O*-alkylation of *N*-methylenecarbamates leading to 1,1-dialkoxy-2-azapropenylium salts can only be achieved if the *N*-alkylation is sterically unfavorable, otherwise iminium salts are preferentially formed (eq 14).[34]

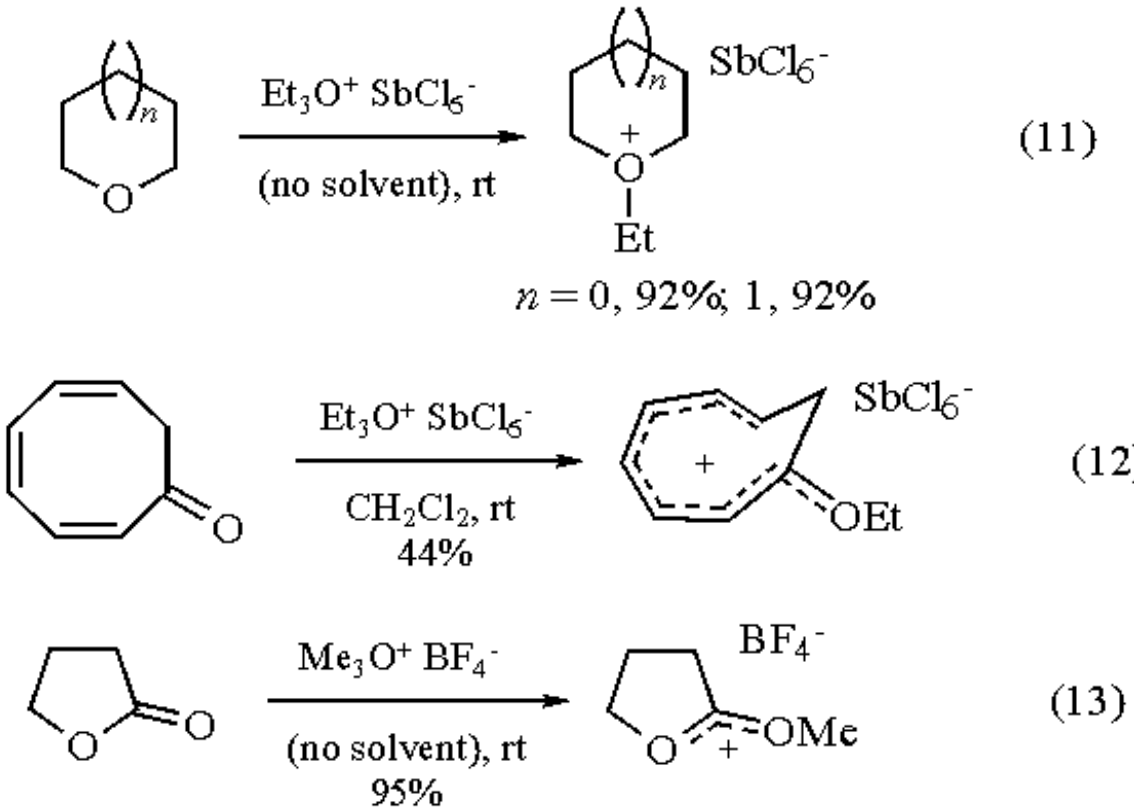

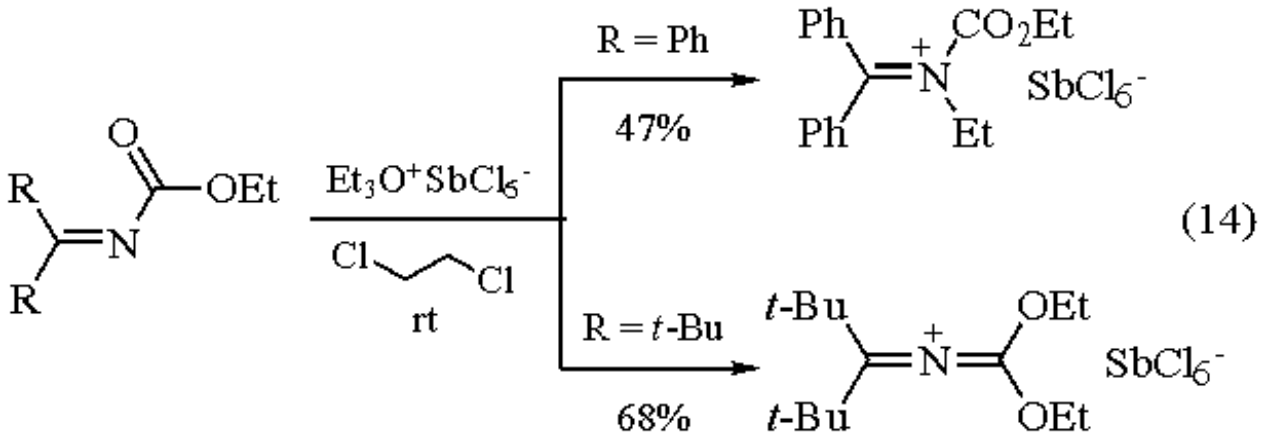

Reactions of Me_3O^+ or Et_3O^+ salts frequently afford isolable salts via elimination of a suitable leaving group from reactive, primary alkylation products, e.g. the alkylation of an alkoxy function generates an unstable trialkyloxonium intermediate, which readily loses a dialkyl ether to yield a stabilized carbocation. The formation of alkoxycarbenium salts from acetals (eq 15)[32a] or that of 1,3-dioxolan-2-ylium salts from 2-alkoxyethyl carboxylates (eq 16)[35] may serve as examples. The latter reaction has also been used to prepare ethylene acetals and hence aldehydes from esters via hydride transfer to 1,3-dioxolan-2-ylium intermediates (eq 17).[36]

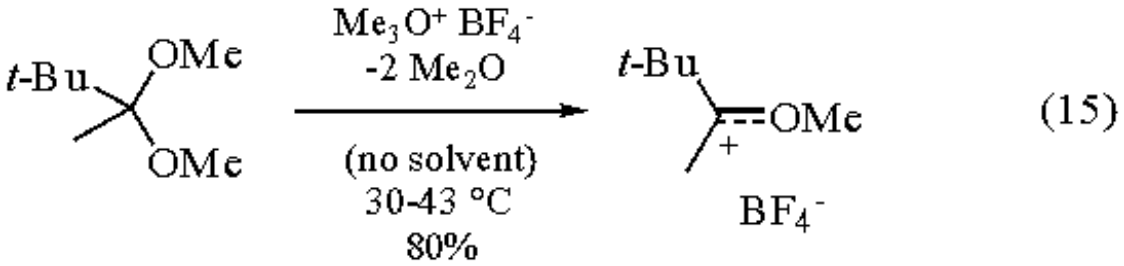

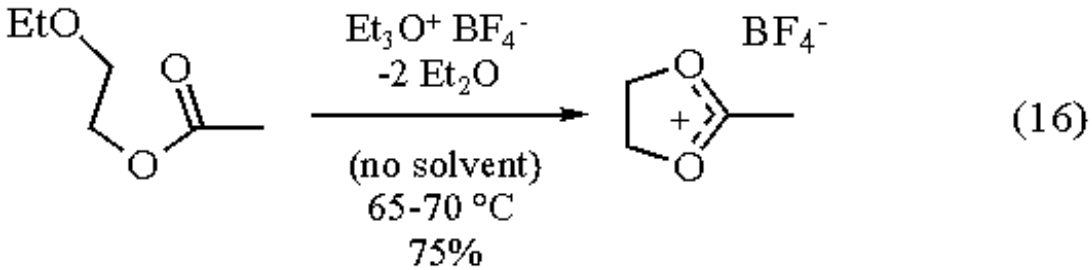

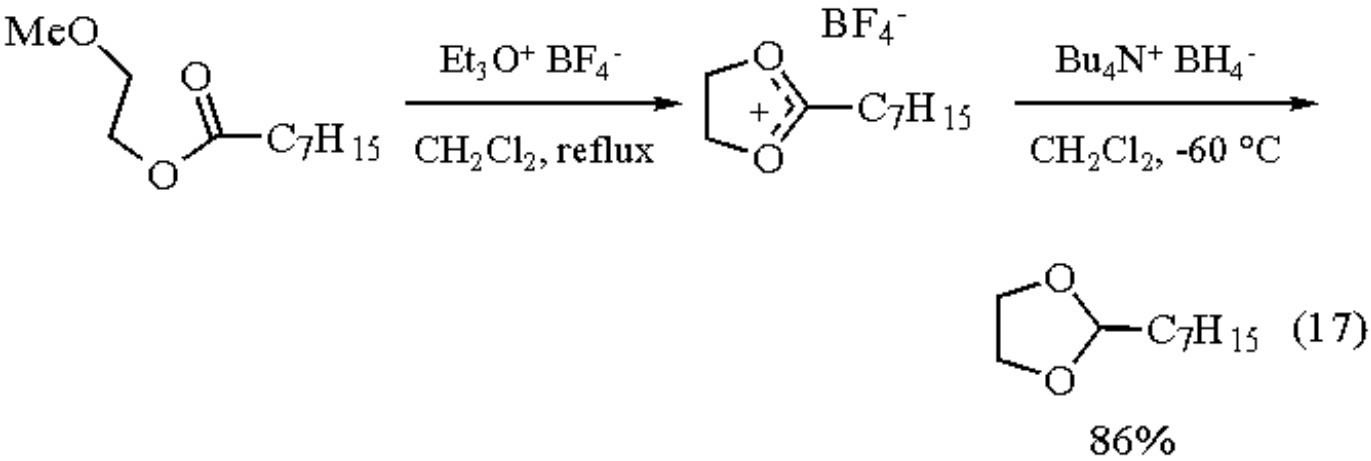

Alkylations with Me_3O^+ or Et_3O^+ salts are usually performed to increase the reactivity of numerous functional groups toward nucleophiles. This is achieved by generating heteroatom-stabilized cations (mostly carbenium ions) from hetero-π-systems or by improving the leaving group ability of saturated *n*-bases via alkylation. For preparative applications, *O*- and *S*-alkylations play the most important role.

Activation via *O*-Alkylation.

With $Et_3O^+BF_4^-$, 2,3-disubstituted cyclopropenones afford 1-ethoxycyclopropenylium salts,[37,38] which readily react with nucleophiles;[38] the

synthesis of cyclic acetals or dithioacetals from 2,3-diphenylcyclopropenone may serve as an example (eq 18).[39] *O*-Alkyllactonium salts, generated according to eq 13, are smoothly converted into cyclic orthoesters with sodium alkanolates[32] or into thionolactones via sulfhydrolysis with sodium hydrosulfide (eq 19).[40] Besides these kinetically controlled additions to the carbenium center, many reactions of lactonium salts with nucleophiles have been reported to occur with ring opening.[1a,c,32a] The highly regio- and stereoselective formation of methyl (*E*)-4,8-alkadienoates via the in situ methylation of γ-alkenyl-γ-butyrolactones in the presence of allylsilanes illustrates this mode of reaction (eq 20).[41]

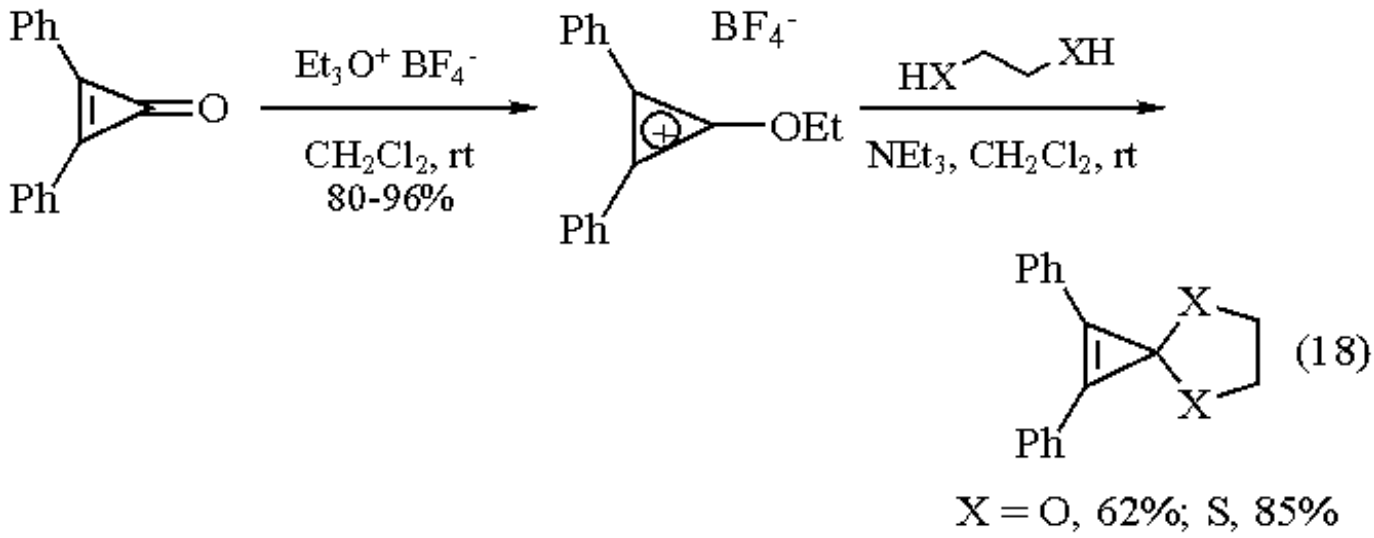

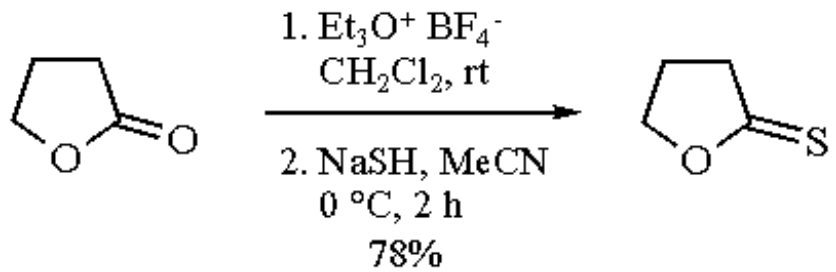

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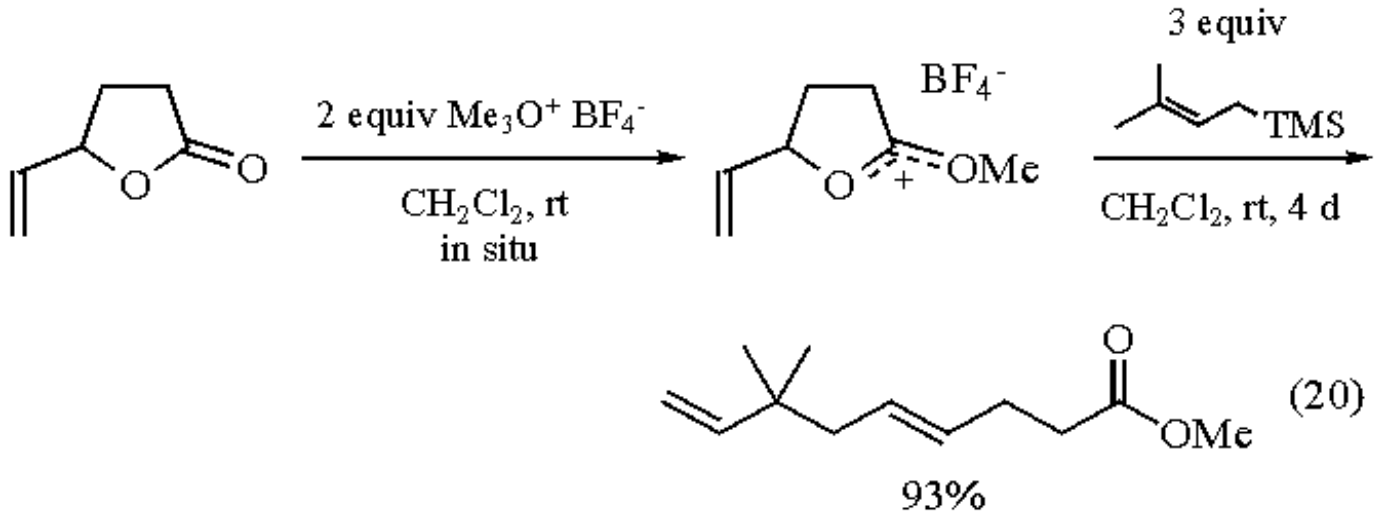

(20)

The rather intractable carboxamide or lactam groups are transformed into highly reactive, versatile intermediates by *O*-alkylations with Me_3O^+ or Et_3O^+ salts.[1c,e,42] Depending on the structure of the substrates and the workup, the resulting alkoxyaminocarbenium salts[1,42,43] (eq 21)[32a] are obtained or their subsequent transformation products: imino esters[1c,44] (eq 22)[44a], amide acetals[1c,42,43] (eq 23),[43a] or ketene *O*,*N*-acetals[43,45] (eq 24)[43a], which are usually submitted to further conversions.[1a,c,e,42-45]

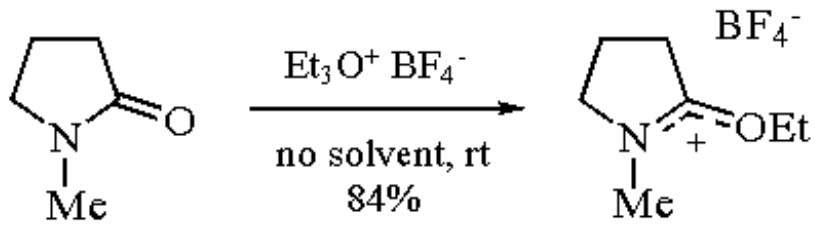

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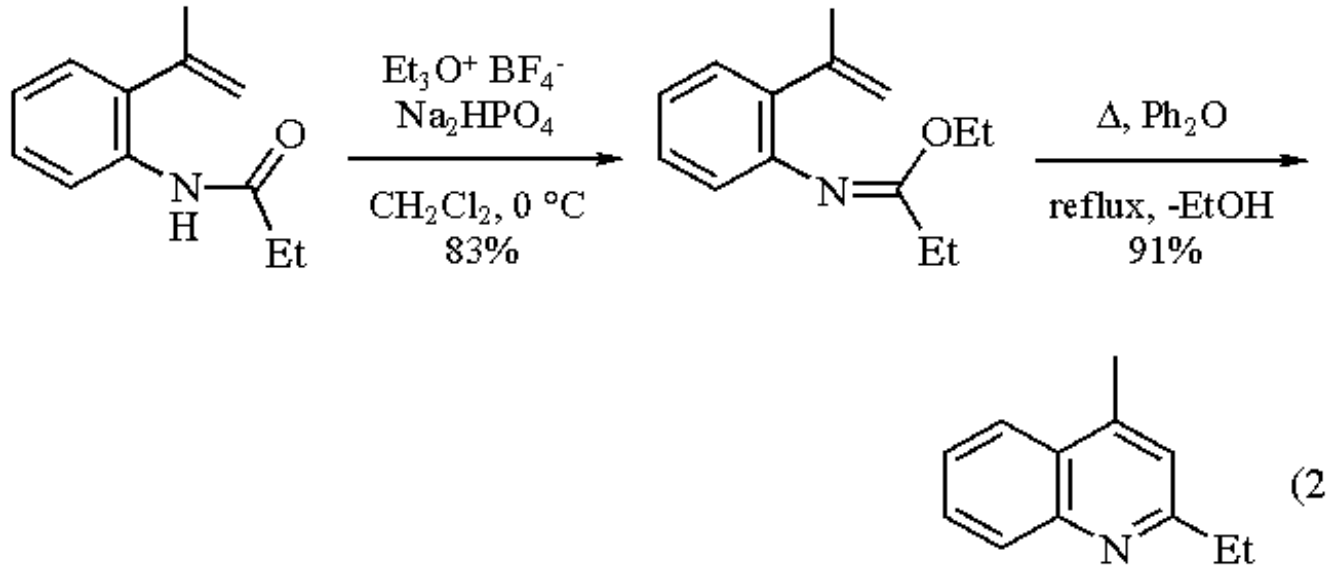

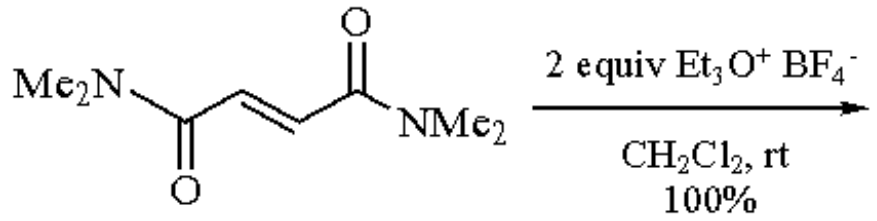

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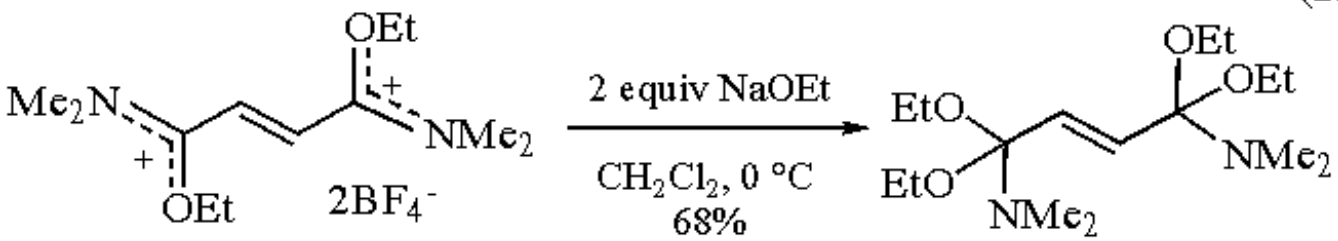

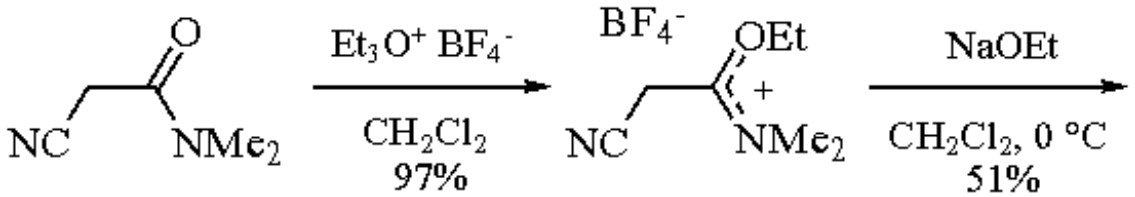

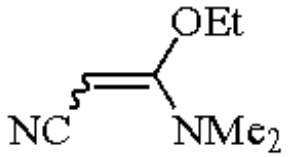

(24)

The important bis-lactim ether method for the enantioselective synthesis of, for example, nonproteinogenic amino acids from the corresponding 2,5-diketopiperazines,[46] is based on the amide *O*-alkylation (eq 25)[46a] as well as the smooth hydrolysis of secondary[1c,21,47] or tertiary[48] carboxamides (eq 26)[48] and lactams.[49]

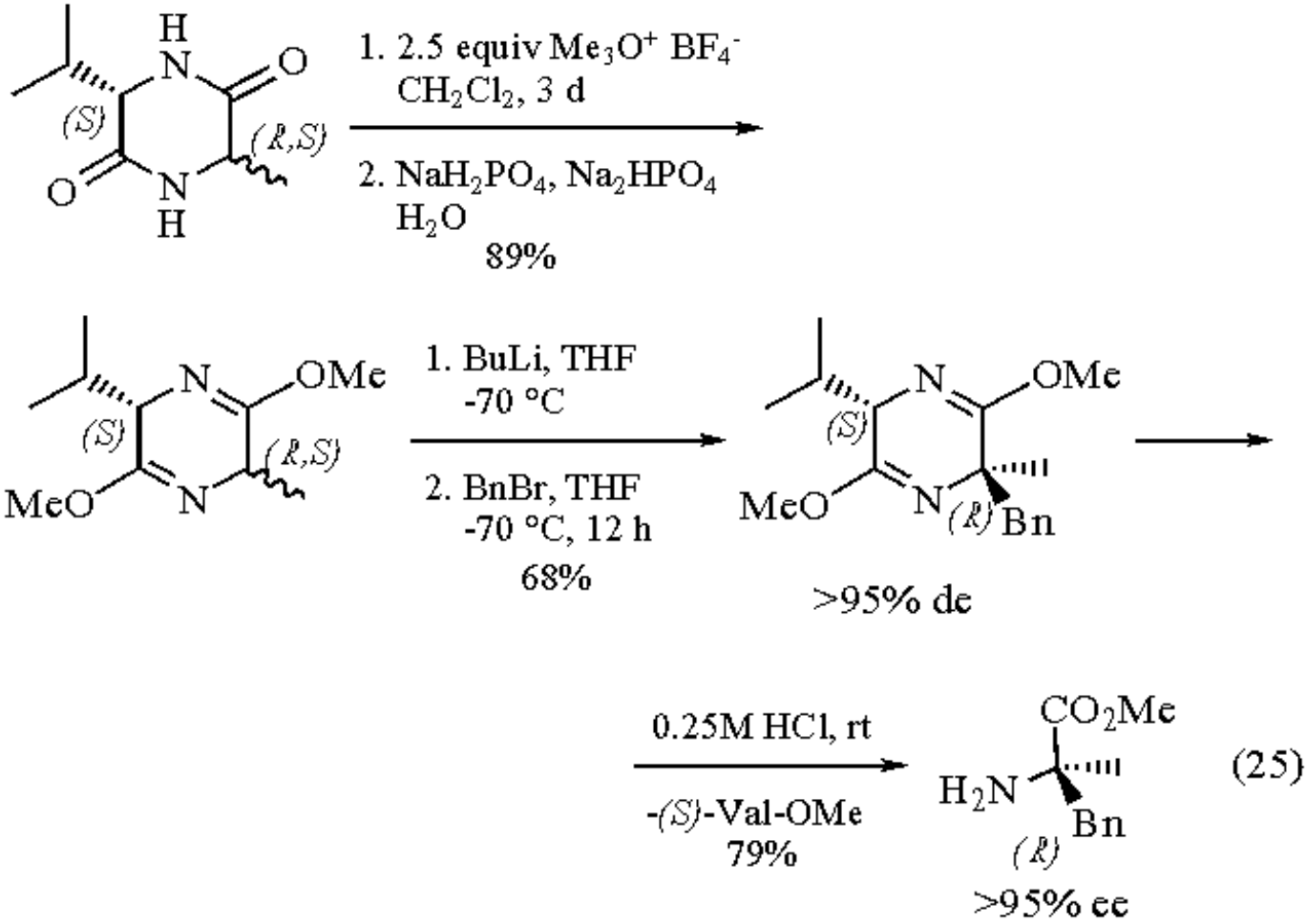

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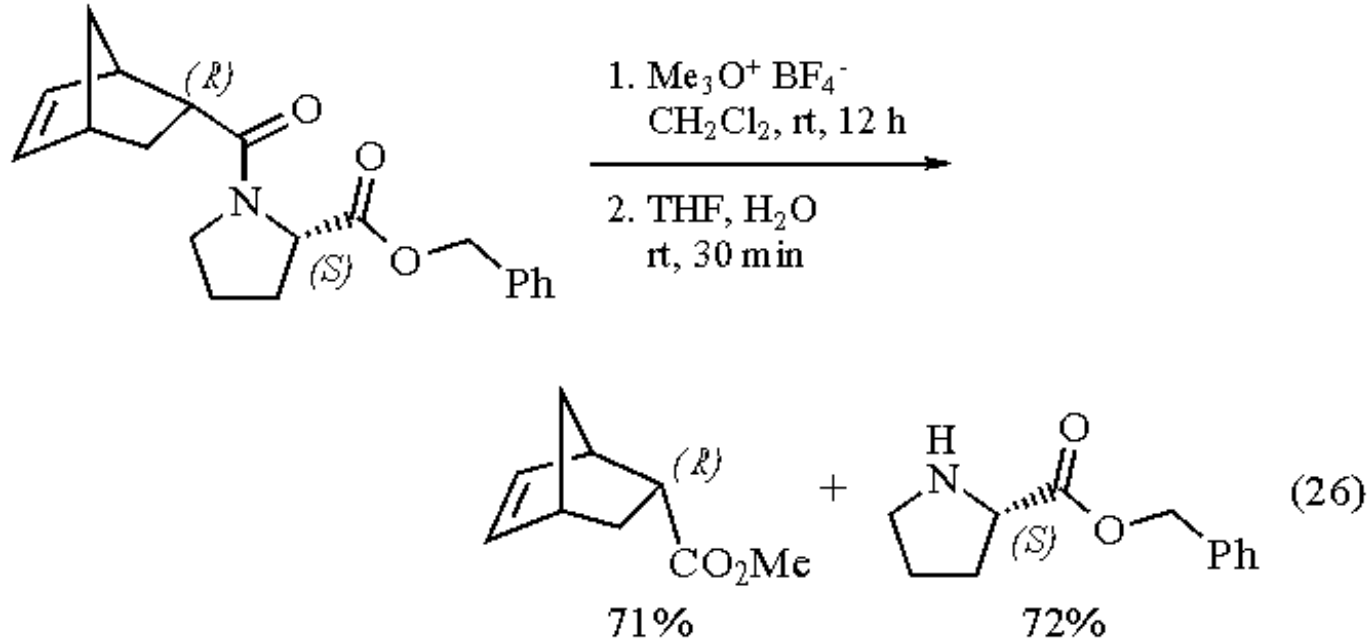

(26)

Activation via *S*-Alkylation.

Although several reagents are available for *S*-alkylations of acyclic or cyclic thioethers, Me_3O^+ or Et_3O^+ salts are frequently preferred since they provide sulfonium salts with nonnucleophilic anions.[1c,e,50] Deprotonation of suitable sulfonium derivatives yields sulfonium ylides as intermediates or isolable species,[51] which are of high preparative value. The stereoselective epoxy-annulation of ketosulfonium salts via sulfonium ylides serves as an example[52] (eq 27).[52a] Sulfonium salts are usually generated to provide leaving groups, e.g. for nucleophilic displacements[53] (eq 28)[53a] or for the formation of reactive iron carbene complexes[54] (eq 29).[54a]

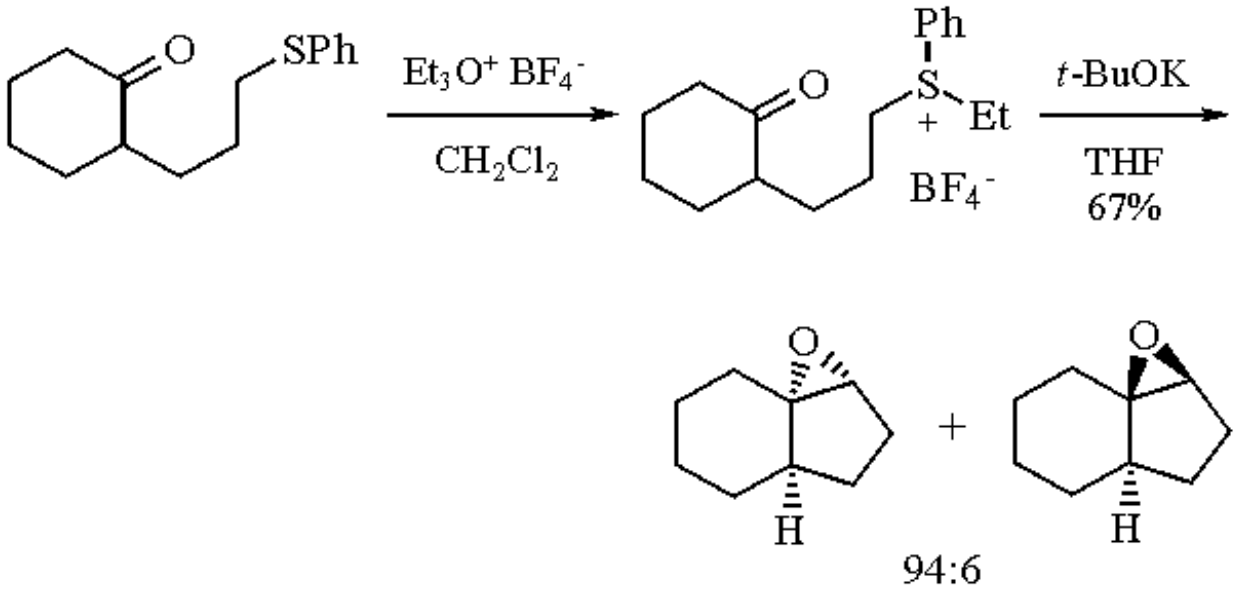

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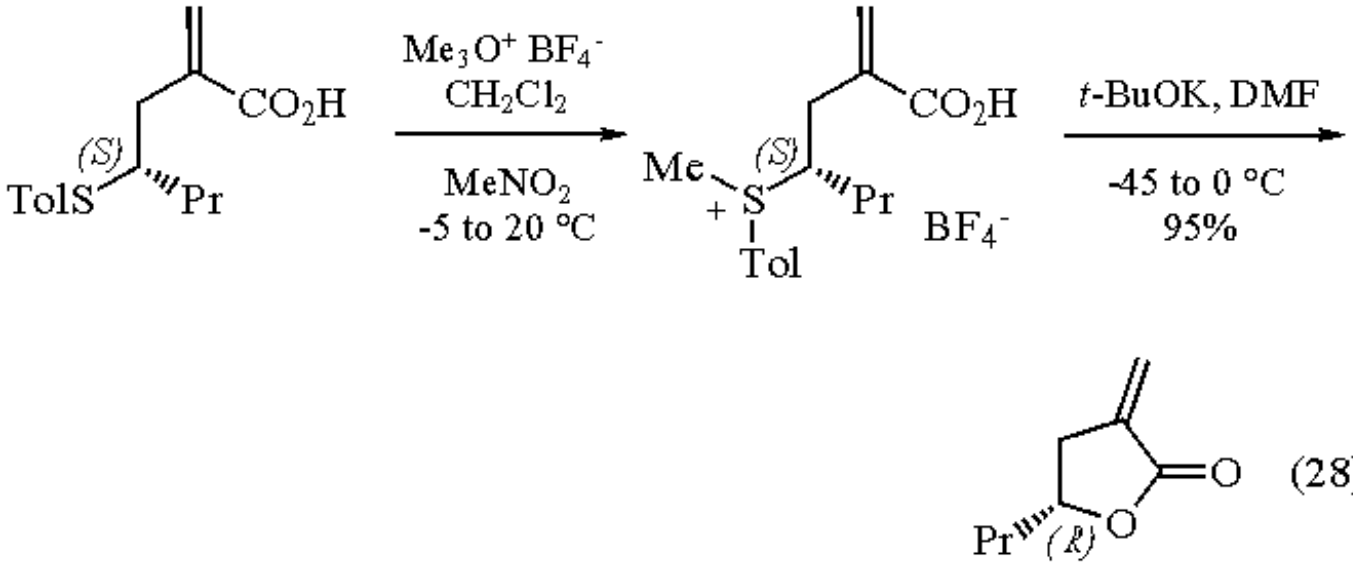

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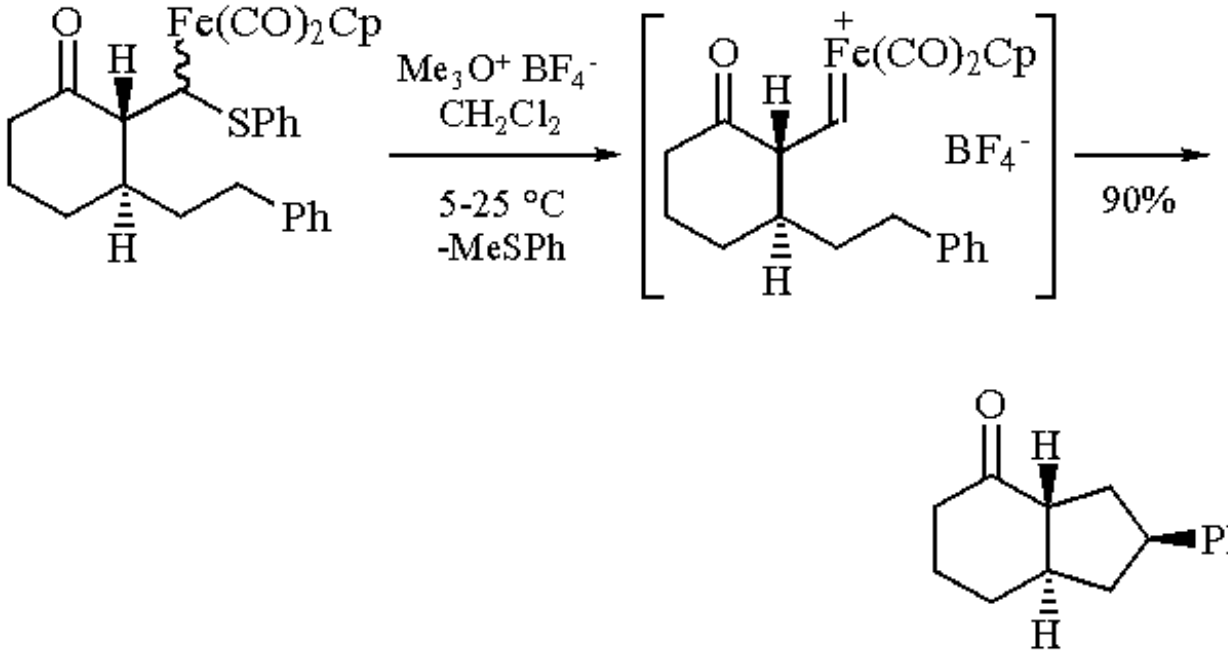

(29)

The rather impracticable hydrolysis of cyclic thioacetals may smoothly be performed via *S*-alkylation[50] with excess $Me_3O^+BF_4^-$ in the presence of water (eq 30).[55] Similarly, a thioamide is easily hydrolyzed after *S*-alkylation with $Et_3O^+BF_4^-$ (eq 31);[56] analogous activations of thiono functions have been reported.[57]

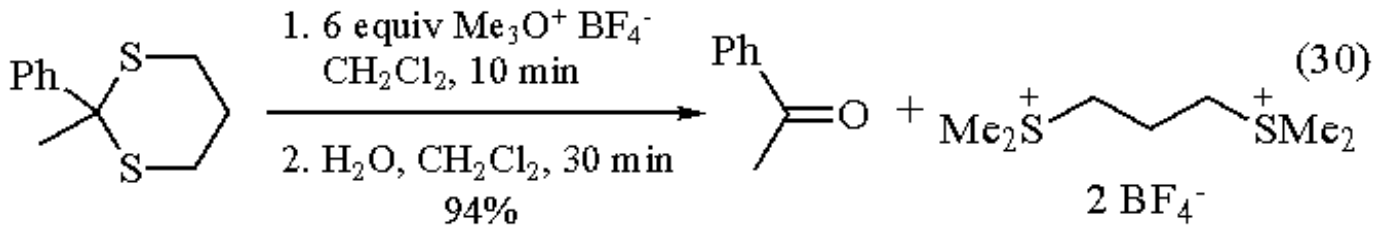

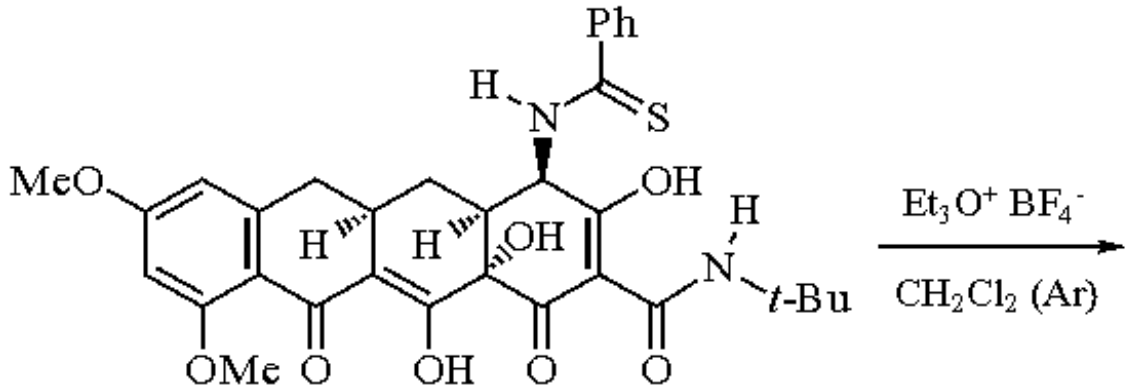

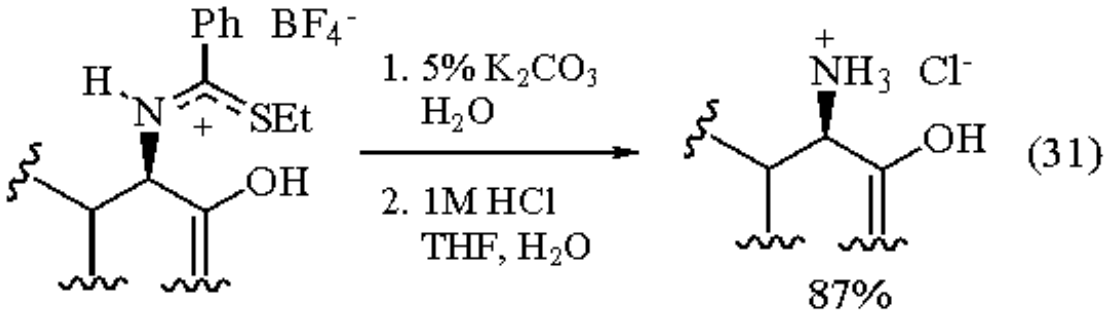

The example depicted in eq 31 shows the striking chemoselectivity of ethylations with $Et_3O^+BF_4^-$ in favor of a thioamide group, which is exclusively attacked at the sulfur atom.[56] The carboxamide function present, which has a similar reactivity,[47b] in this case is sterically shielded.

Activation via *N*-Alkylation.

Alkylations of amines or imines leading to ammonium[58] or iminium salts[59] usually do not require powerful alkylating agents; nevertheless, Me_3O^+ or Et_3O^+ salts have also been applied.[1,58,59] Thus a dibenzo[*b*,*g*][1,5]thiazocine derivative with $Me_3O^+BF_4^-$ is exclusively methylated at the amino group[60] (eq 32).[60a] However, the corresponding sulfoxide yields the *O*-methylated product, in which significant N-S interaction with the hypervalent sulfur atom has been shown to be present[60b] (eq 33).[60a,b]

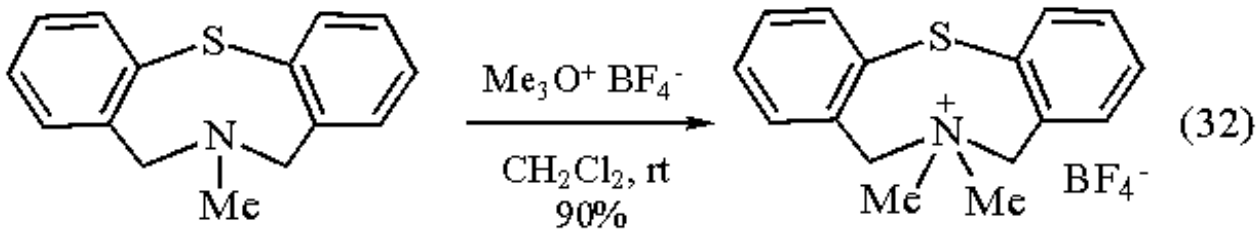

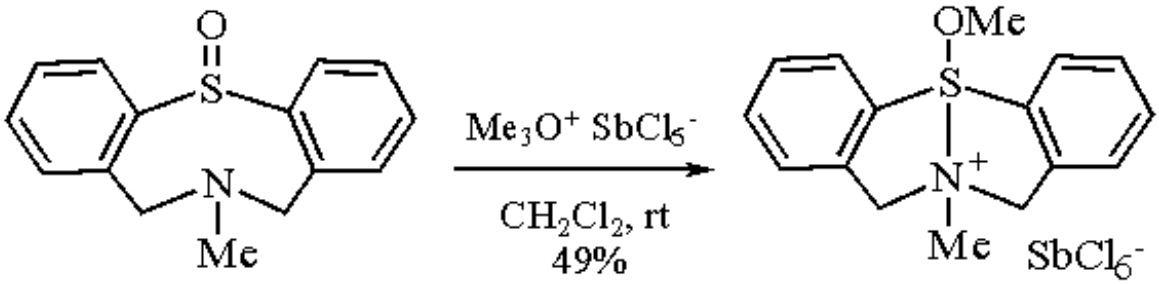

(33)

Besides numerous *N*-alkylations of alicyclic or aromatic five- and six-membered N-heterocycles,[1,61] reactions of preparative interest of Me_3O^+ or Et_3O^+ salts have been carried out with nitriles. The resulting nitrilium salts[1c,62] are versatile and reactive intermediates;[63] (see also ***O-Methyldibenzofuranium Tetrafluoroborate***). Their hydrolysis yields secondary carboxamides, and reactions with alcohols or amines result in the formation of imino esters or amidines.[63]

N-Ethylnitrilium salts are conveniently converted into aldehydes by reduction with trialkylsilanes and sequential hydrolysis of the resulting imines (eq 34).[64] The same salts yield secondary amines via imino esters formed in situ, and subsequent reduction with ***Sodium Borohydride*** (eq 35).[65] Since neither the nitrilium salts nor the intermediates have to be isolated, the transformations are performed as one-pot procedures starting from suitable nitriles.[64,65] *N*-Methylnitrilium salts have also been used for the smooth acylation of pyrrole and indole derivatives (eq 36).[66]

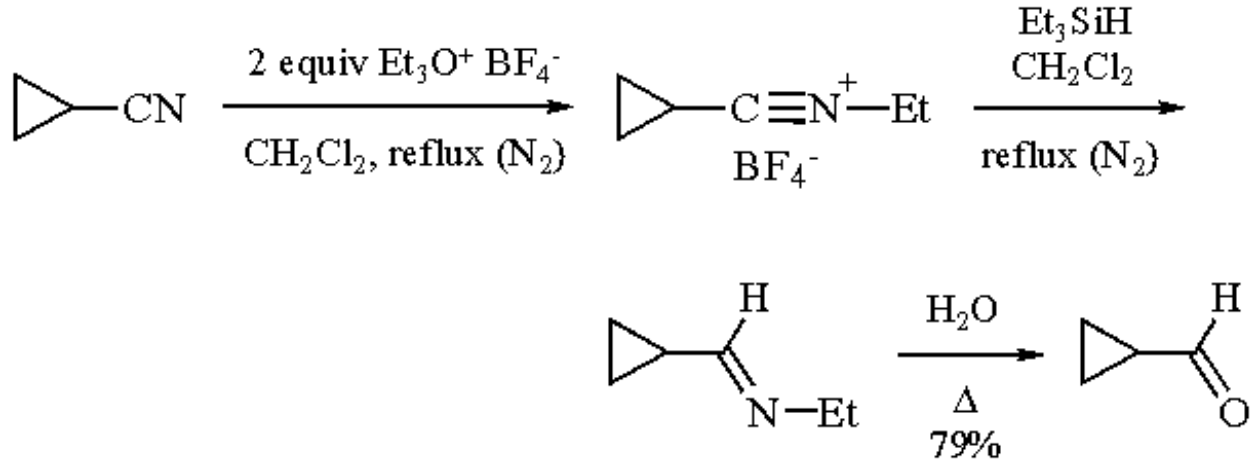

(34)

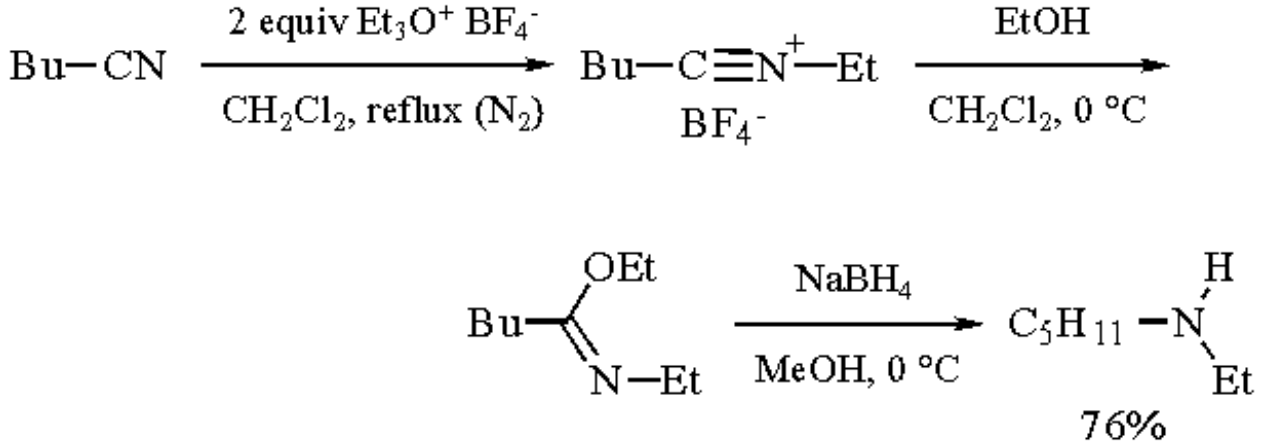

(35)

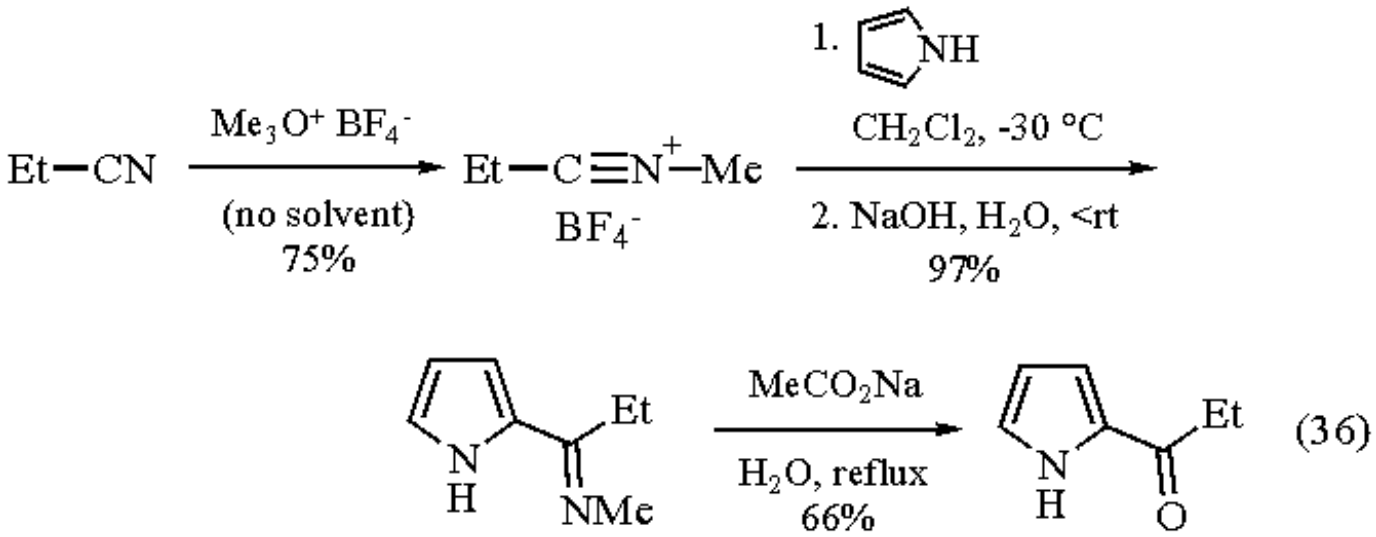

Related Reagents.

Dimethoxycarbenium Tetrafluoroborate; ***Dimethyliodonium Hexafluoroantimonate***; ***O-Methyldibenzofuranium Tetrafluoroborate***; ***Methyl Trifluoromethanesulfonate***.

---

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Triethyl Phosphite[1]

$(EtO)_3P$

[122-52-1] · $C_6H_{15}O_3P$ · Triethyl Phosphite · (MW 166.18)

(can react with electrophiles to form phosphonates or phosphates; can function as a reducing agent for a variety of functional groups; forms a stable complex with copper(I) iodide)

Physical Data: bp 155-157 °C/760 mmHg; *d* 0.958 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear, free flowing liquid in >97% purity.

Handling, Storage, and Precautions: should be stored in a dry place, preferably in a fume hood due to its pungent odor. The reagent is purified[1b] by treating with sodium (to remove water and dialkyl phosphonate), followed by decanting and distillation. The purified material may then be stored over activated molecular sieves.

Transesterification.

Hoffman reported that triethyl phosphite is easily transesterified when heated in the presence of aliphatic alcohols.[2] The uncatalyzed transformation occurs in three distinct steps which proceed at approximately equal rates. Transesterification using trimethanolethane in the presence of triethylamine affords the corresponding crystalline phosphite (eq 1).[3]

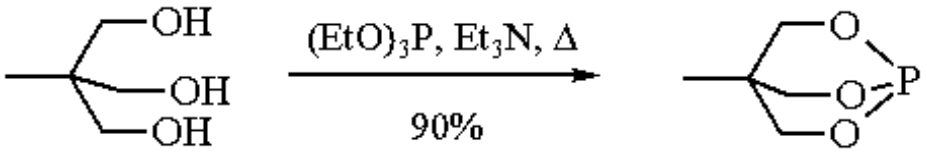

(1)

Organophosphonates.

Triethyl phosphite[4] has been used extensively in the synthesis of phosphonates via the Arbuzov reaction.[5,6] This general protocol works well with a variety of electrophiles and is carried out by simply heating the reactants between 100 °C and 150 °C using phosphite as solvent. Phosphonates bearing electron withdrawing groups β to phosphorus represent a valuable class of reagents which have been creatively applied to the stereoselective synthesis of alkenes (eqs 2-6).[6g-k] Acyl phosphonates, prepared from the corresponding acid halides, have been utilized as intermediates in the overall reduction of acids to aldehydes (eq 7),[7] and as intermediates in the preparation of vinylphosphonates (eq 8).[8]

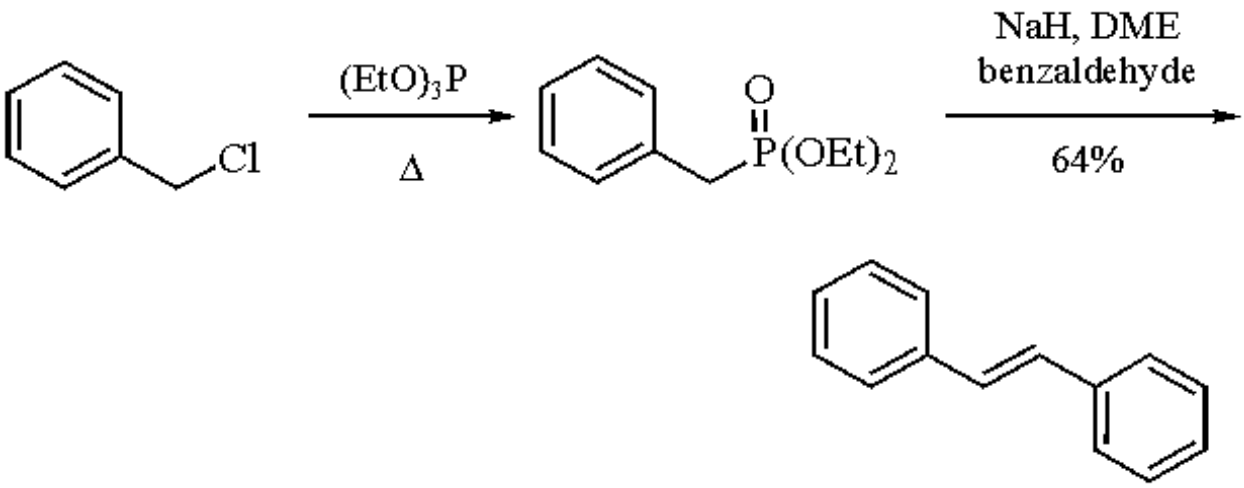

(2)

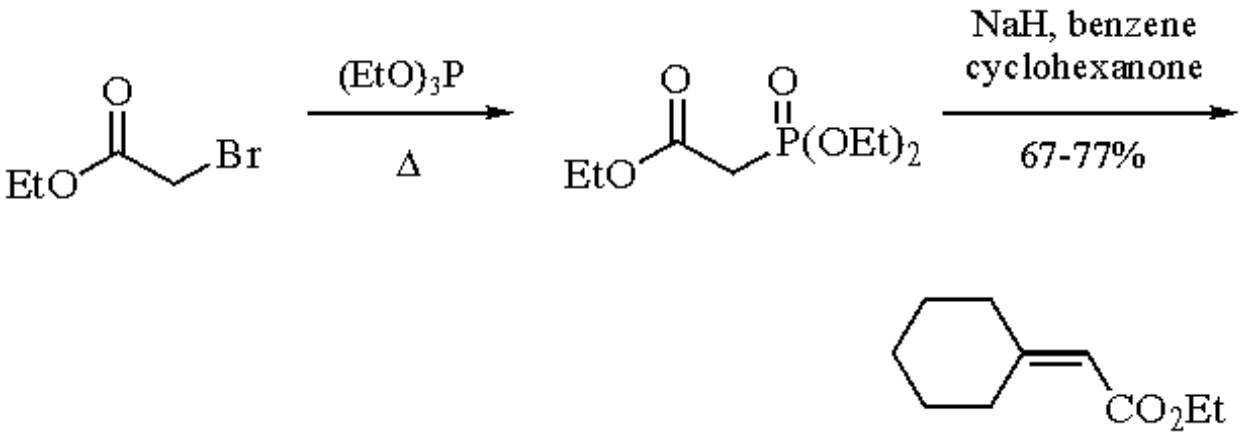
(EtO)3P
Δ
NaH, benzene
cyclohexanone
67-77%
EtO
Br
P(OEt)2
CO2Et

(3)

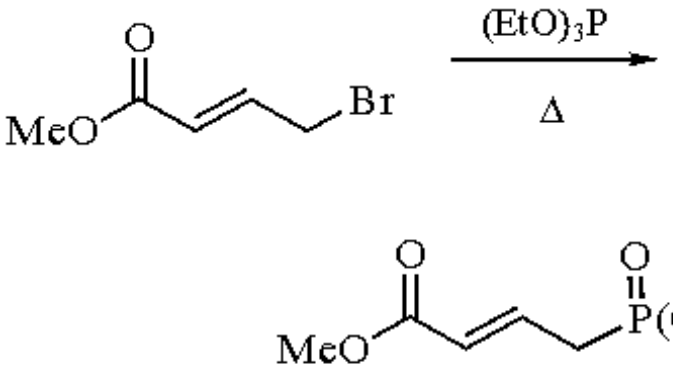
(EtO)3P
Δ
MeO
Br
P(OEt)2
LiHMDS, THF
pivaldehyde
84%
CO2Me

93% (*E*,*E*)

(4)

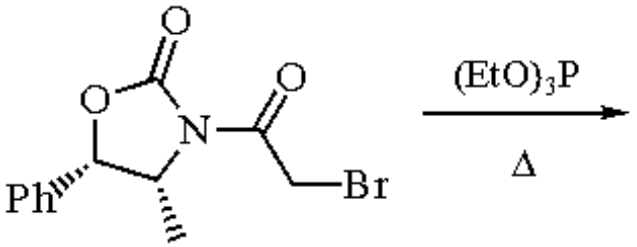
(EtO)3P
Δ
Ph
Br

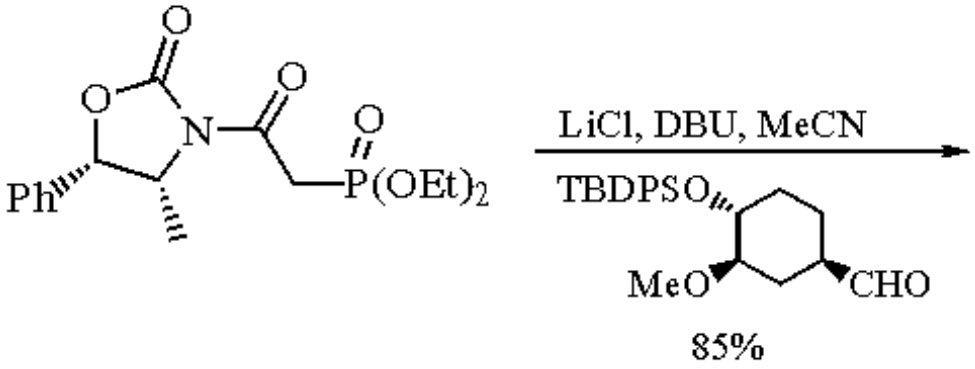
LiCl, DBU, MeCN
TBDPSO
MeO
CHO
85%
P(OEt)2
Ph
TBDPSO
MeO

(5)

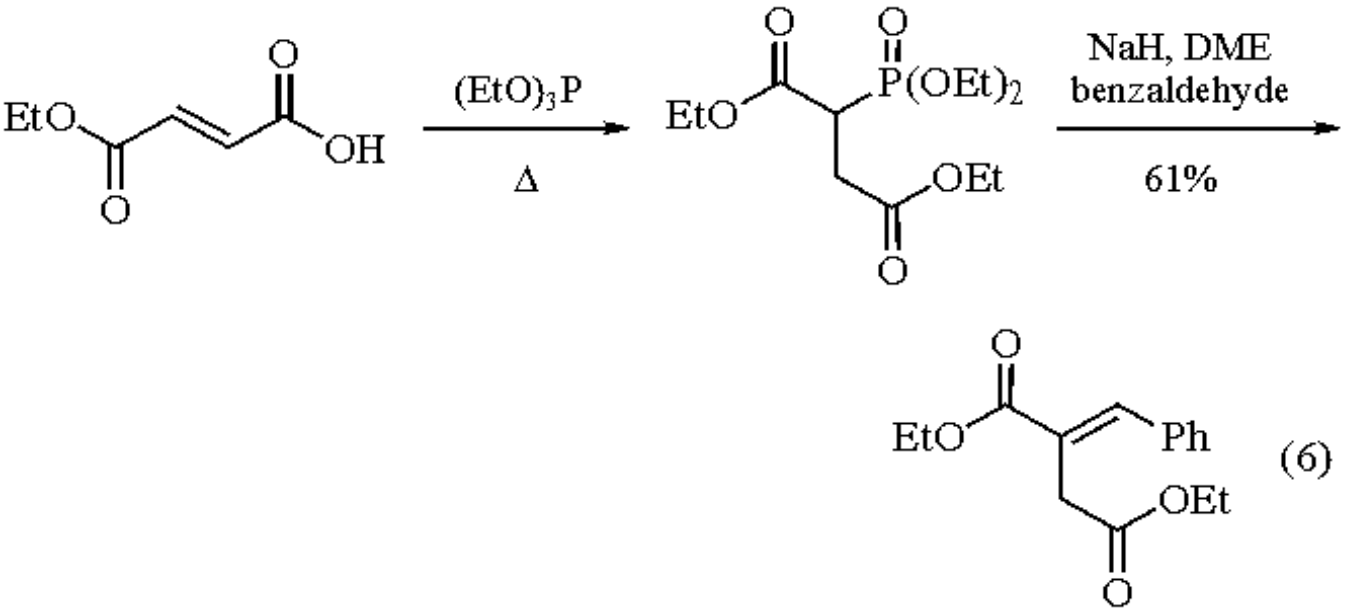
EtO
OH
(EtO)3P
Δ
P(OEt)2
OEt
NaH, DME
benzaldehyde
61%
Ph

(6)

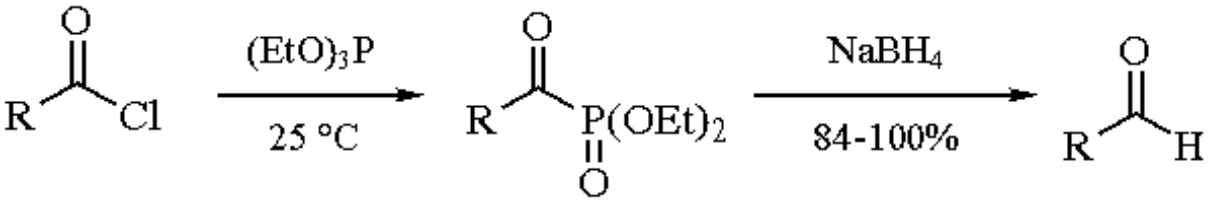
R
Cl
(EtO)3P
25 °C
P(OEt)2
NaBH4
84-100%
H

(7)

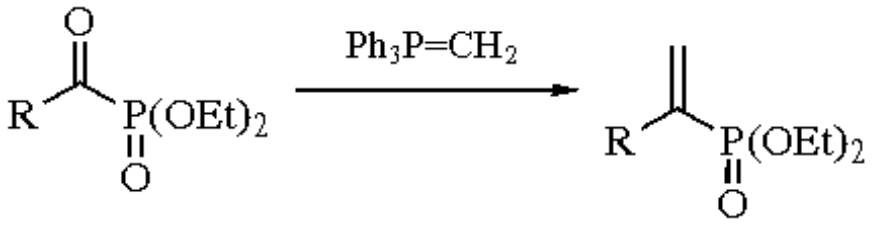

(8)

A nonclassical Arbuzov approach to α-methoxybenzylphosphonates employs the treatment of acetals of aromatic aldehydes with triethyl phosphite in the presence of ***Boron Trifluoride Etherate*** (eq 9).[9] In contrast, direct arene phosphorylation has been achieved through treatment of aromatic substrates with triethyl phosphite and ***Cerium(IV) Ammonium Nitrate***.[10] In this case the active species is believed to be a phosphite radical cation (eq 10).

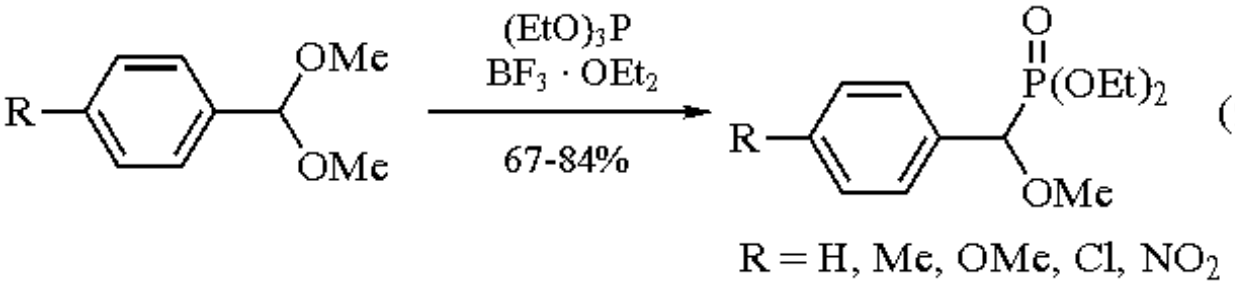

(9)

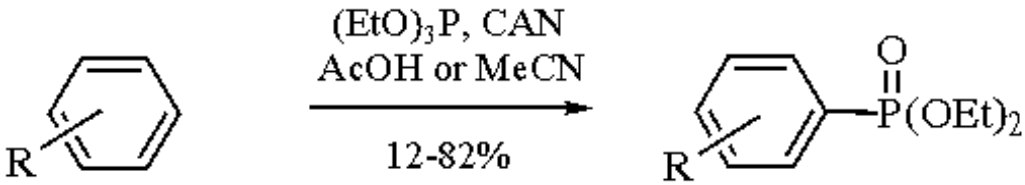

(10)

Vinyl Phosphates.

Perkow[11,12] discovered that α-halo aldehydes and ketones are converted to vinyl phosphates upon treatment with triethyl phosphite (eq 11). These intermediates are easily reduced to alkenes under dissolving metal conditions (eq 12).[13] In cases where the vinyl phosphate is acyclic, treatment with a strong base generally provides good yields of the corresponding alkyne (eq 13).[14]

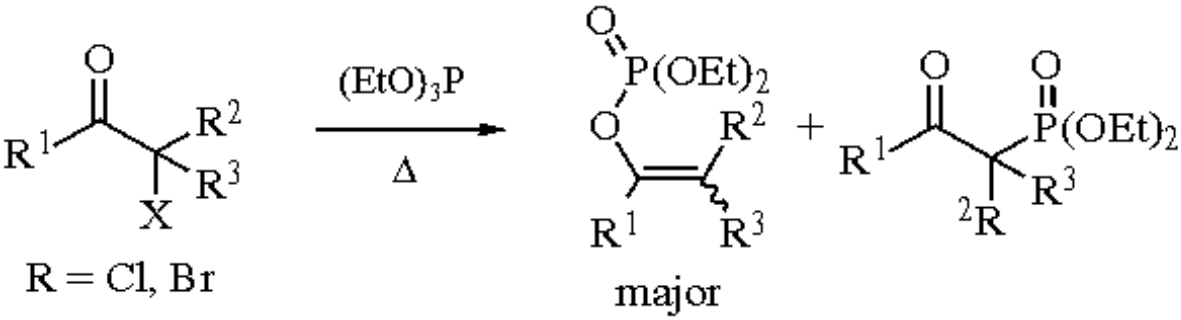

(11)

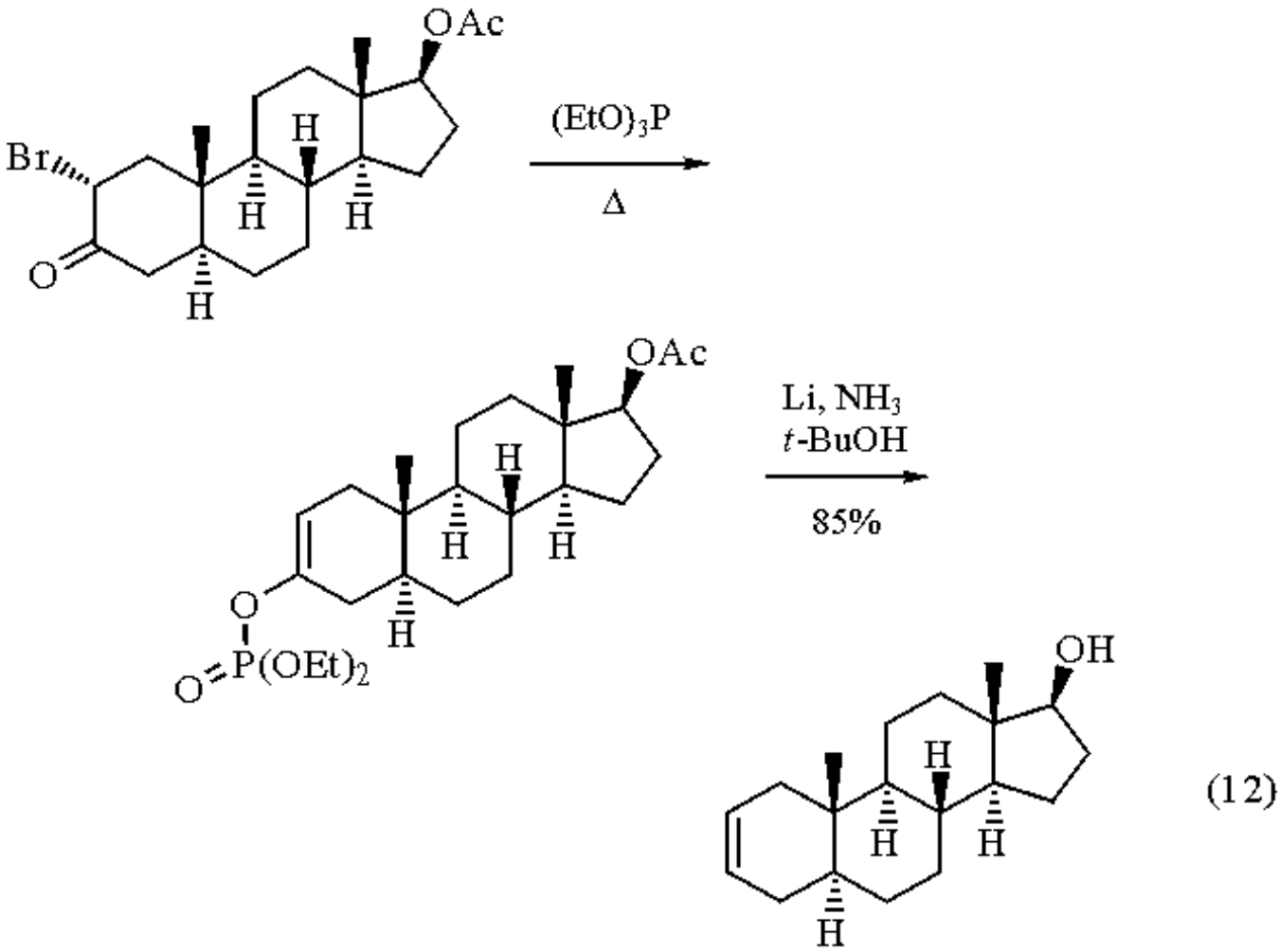

(12)

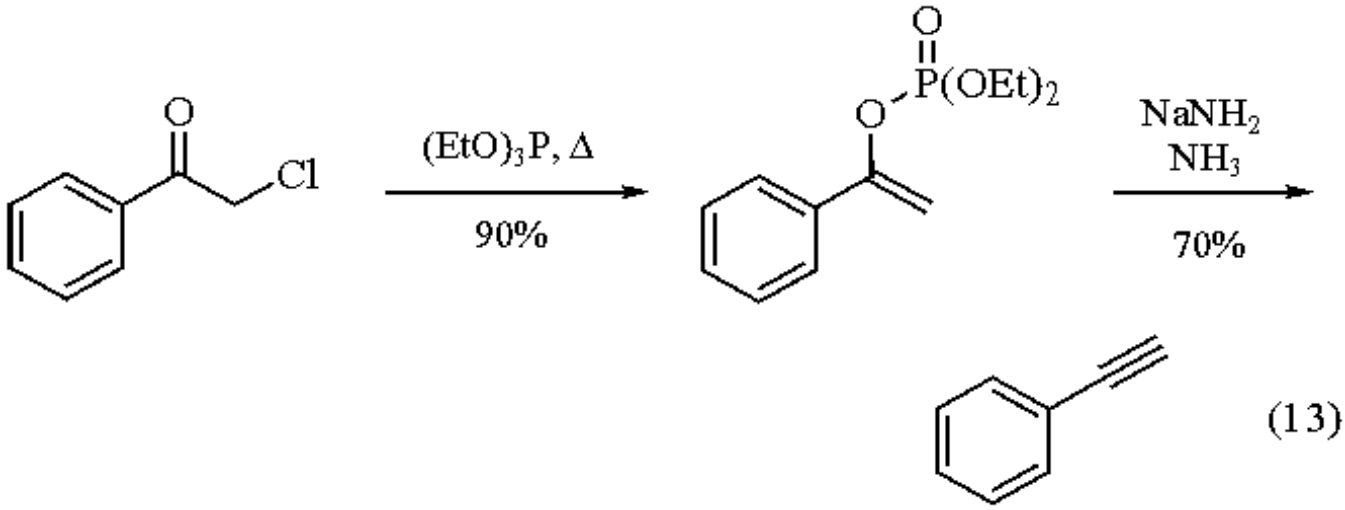

(13)

Deoxygenation.

Triethyl phosphite is capable of deoxygenating a variety of organic substrates. Hydroperoxides, for example, are rapidly converted to alcohols after treatment with one equivalent of the reagent at ambient temperature (eq 14).[15] The reduction of peroxides generated in situ via enolate oxidation is a powerful technique for achieving regio and stereoselective α-hydroxylation (eq 15).[16] In addition to reducing hydroperoxides, triethyl phosphite has been utilized for the deoxygenation of *endo*-peroxides (eq 16),[17] diaroyl peroxides (eq 17)[18] and the reductive coupling of phthalic anhydride (eq 18).[19]

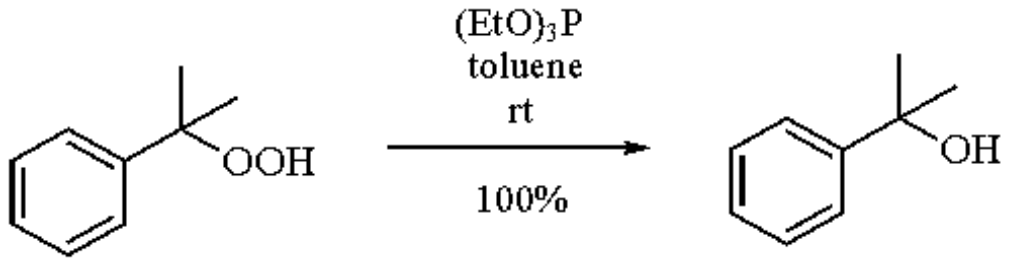

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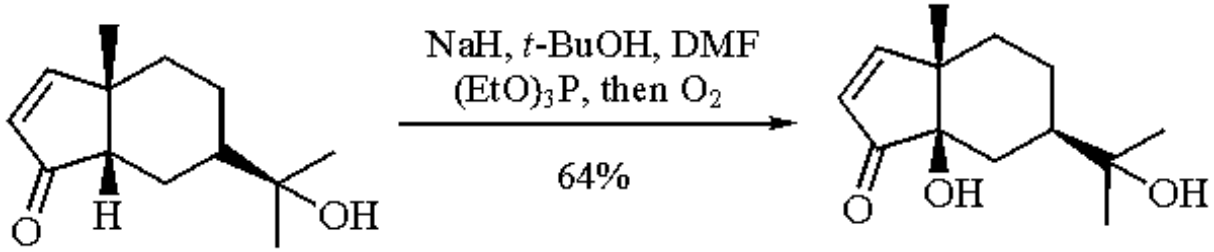

(15)

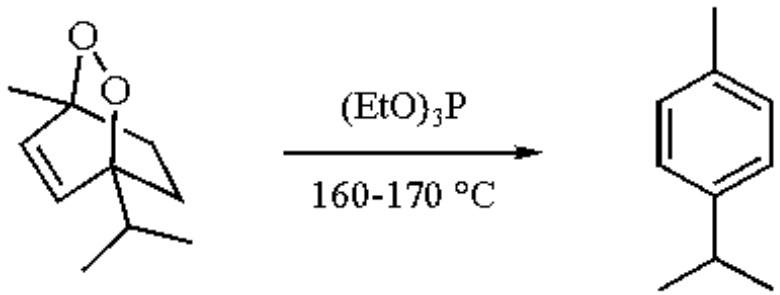

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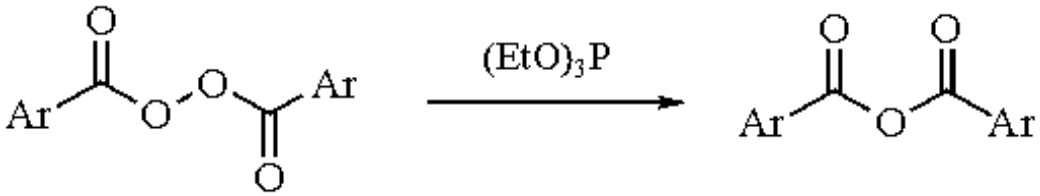

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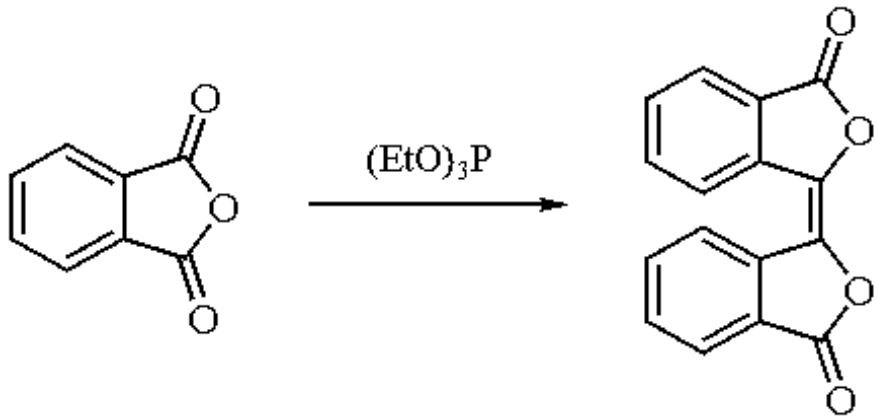

(18)

Scott reported that terminal epoxides can be reduced using forcing conditions while internal epoxides are generally unaffected, even at temperatures approaching 200 °C.[20] In contrast, Saegusa and co-workers discovered that α-keto acids are easily reduced to α-hydroxy acids under mild conditions in good to excellent yields (eq 19).[21]

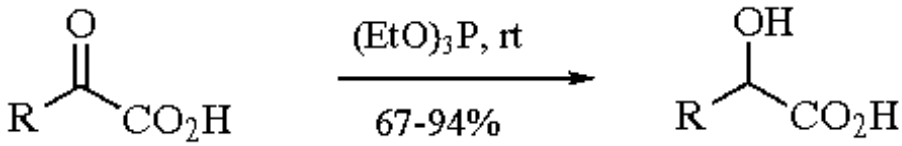

(19)

The deoxygenation of nitrogenous functionalities using triethyl phosphite has also received attention.[22] Reductive cyclization of aromatic nitro-containing compounds has provided entry into a variety of heterocycles (eqs 20 and 21).[23] It has been suggested that a highly reactive nitrene

intermediate is involved in the cyclization process.[24] Aryl nitroso compounds subjected to these conditions experience a similar fate, although the reactive intermediate in this case is believed to be polar in nature (eq 22).[25]

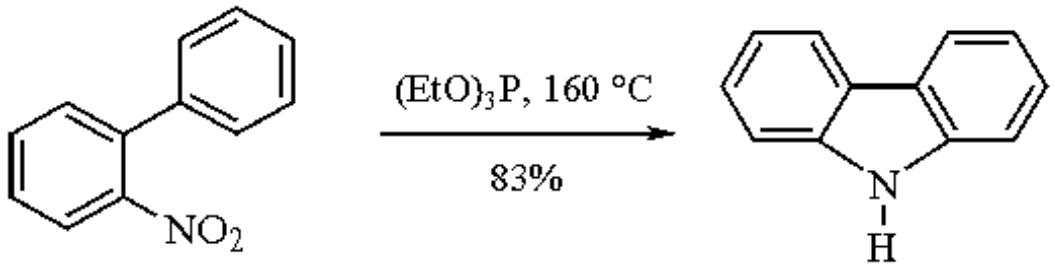

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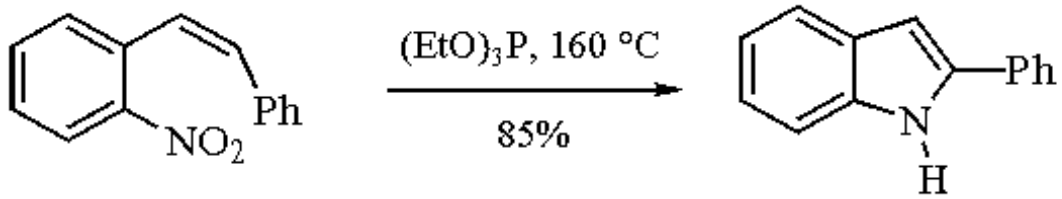

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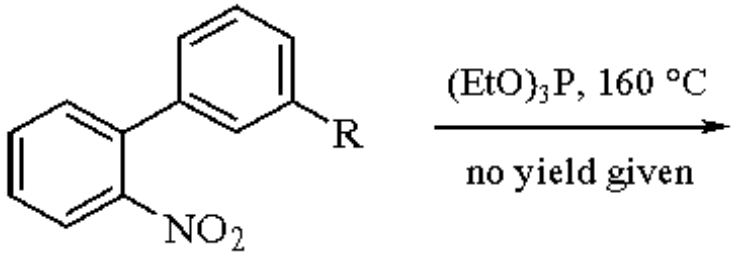

R = Me, OMe

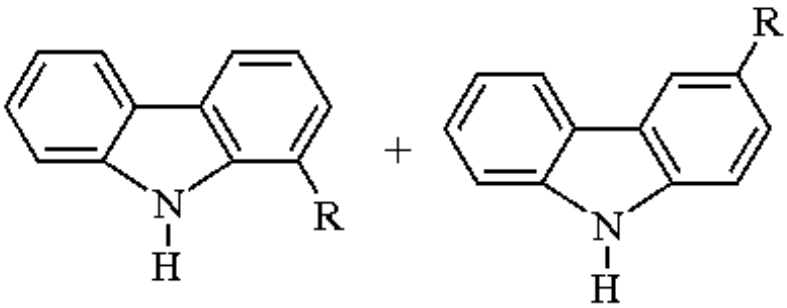

(22)

Azides are also subject to reduction by triethyl phosphite via a modified Staudinger process (eq 23).[26]

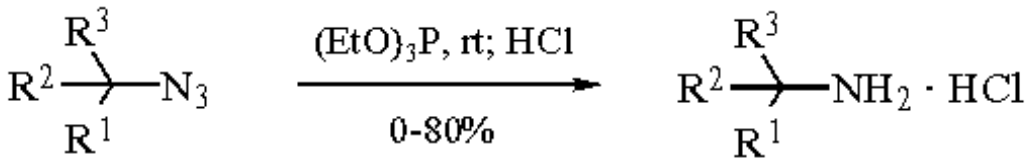

(23)

R^1 = alkyl; $R^1 = R^2 = H$

$R^1 = R^2$ = alkyl; $R^3 = H$

$R^1 = R^2 = R^3$ = alkyl

Desulfurization.

A frequently encountered application of triethyl phosphite is the conversion of cyclic thiocarbonates to the corresponding alkenes (Corey-Winter synthesis).[27] The reaction proceeds stereospecifically via a carbene intermediate and often results in good yields of desired alkene (eqs 24 and 25).[28]

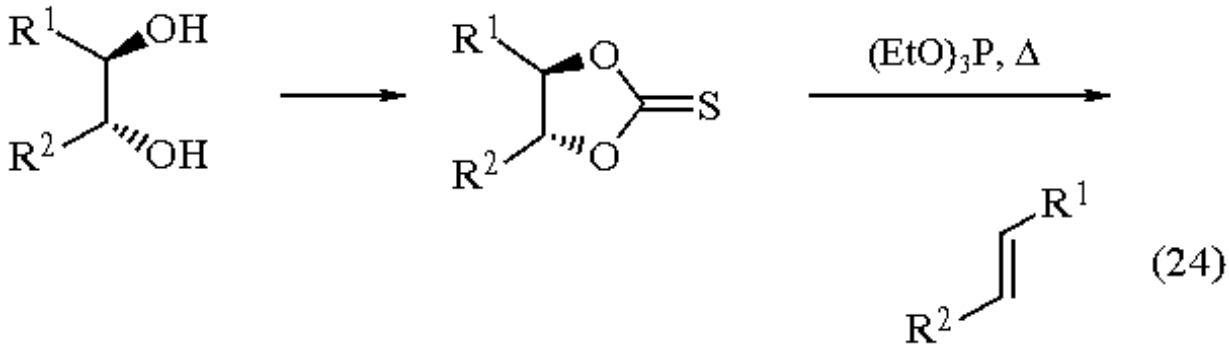

(24)

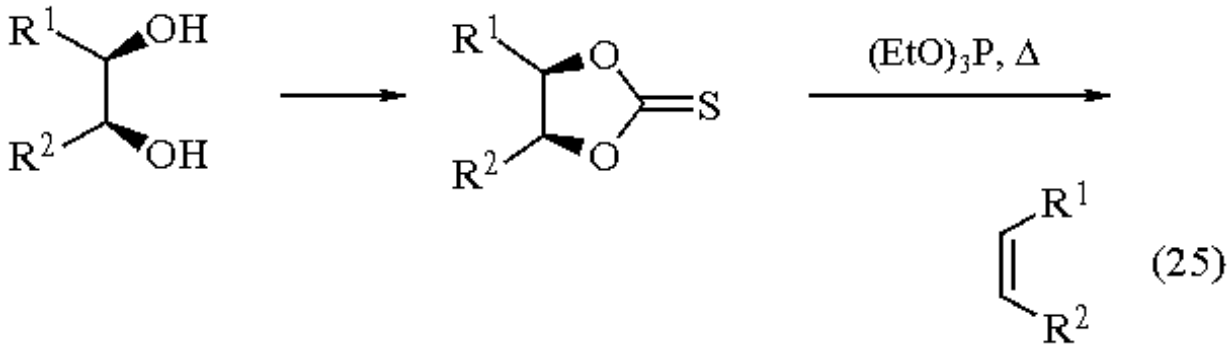

(25)

The conversion of thiiranes to alkenes proceeds readily, in contrast to epoxide reduction.[29] For example, the episulfides of *cis*- and *trans*-2-butene are reduced smoothly and with high stereospecificity. Thiols[30] and disulfides[31] are reduced efficiently as well. In some cases, reductive desulfurization can be coupled with carbon-carbon bond formation. For example, reaction of di-*n*-butyl disulfide with triethyl phosphite in the presence of carbon monoxide gives a nearly quantitative yield of the corresponding homologated thioester (eq 26).[32]

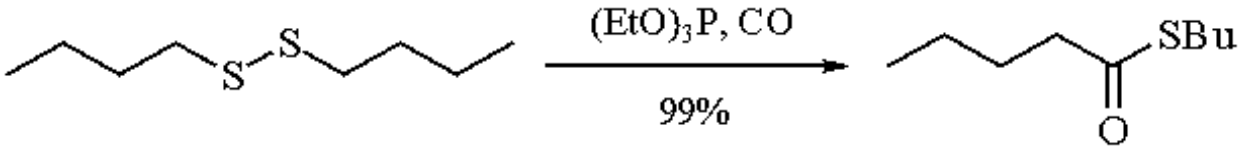

(26)

In a completely unrelated example, [2,2]paracyclophane was synthesized from the corresponding bis-thioether via photochemical extrusion of sulfur mediated by triethyl phosphite (eq 27).[33] The concept of linking proximal carbon atoms with the extrusion of sulfur was used successfully by Eschenmoser in his synthesis of a vitamin B_{12} intermediate (eq 28),[34] while a modification of Barton's method allowed the synthesis of the highly strained diquadricyclanylidene (eq 29).[35]

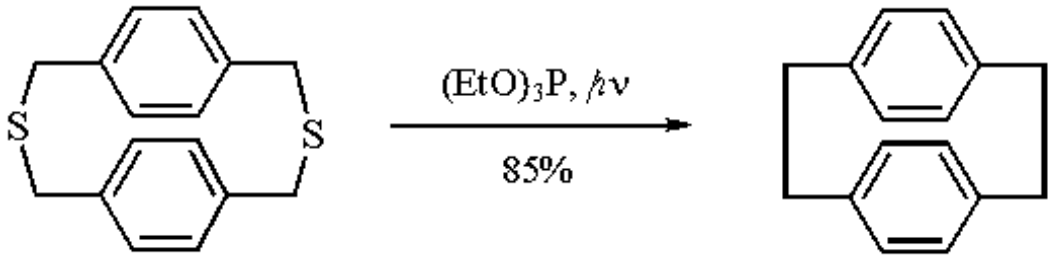

(27)

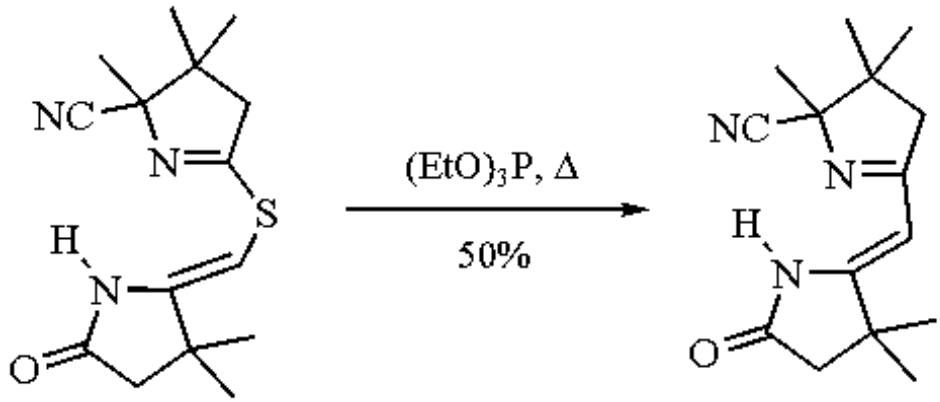

(28)

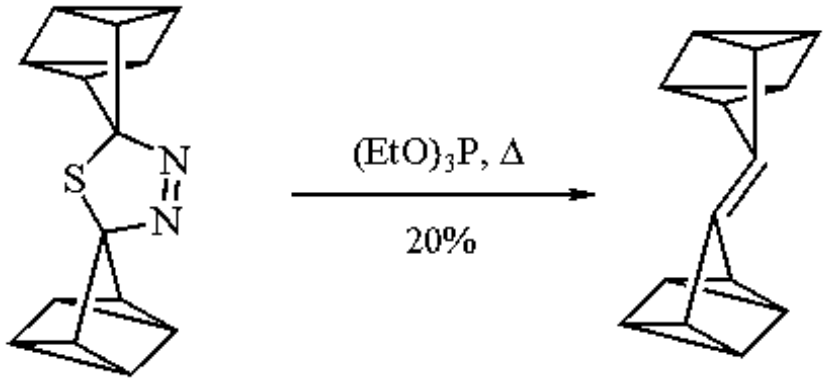

(29)

A bimolecular coupling mediated by triethyl phosphite was applied to the synthesis of an interesting unsymmetrical tetrathiafulvalene, although yields were low due to competing homo coupling (eq 30).[36]

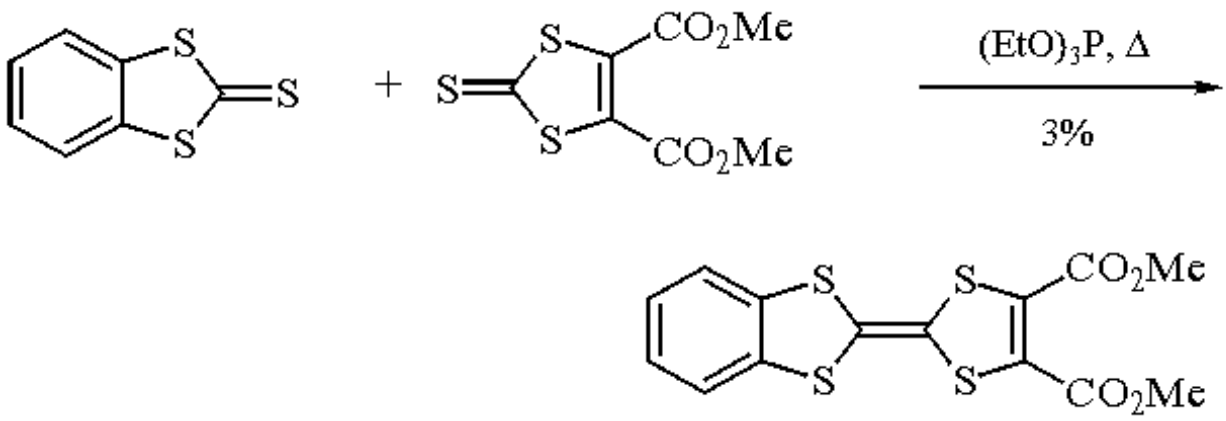

(30)

Carbonyl Adducts.

Triethyl phosphite reacts with α-diketones to form isolable cyclic phosphate esters. Upon additional heating, the corresponding alkynes are obtained (eq 31).[37]

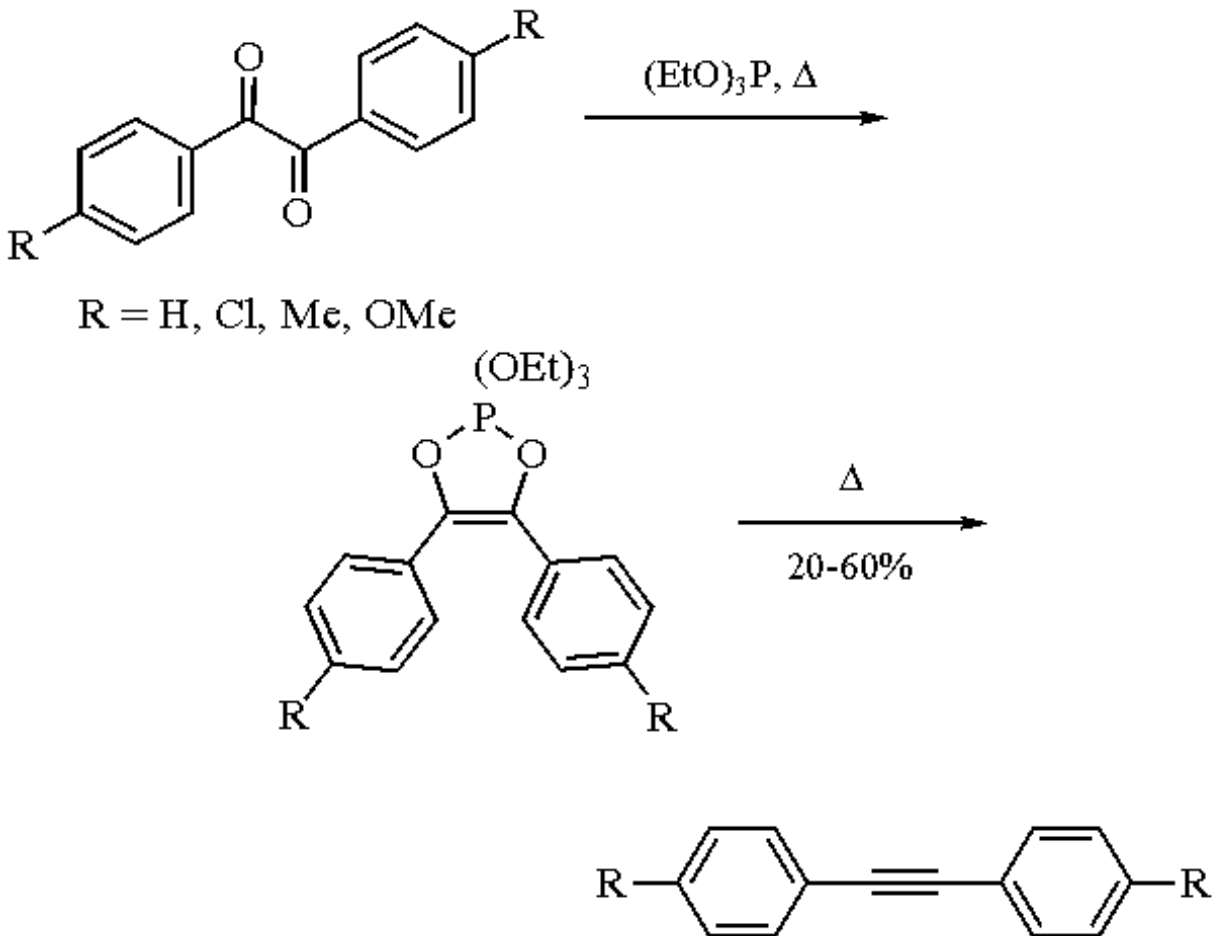

(31)

Use in Cuprate Chemistry.

When added to solutions of *cis*-divinylcuprates, trimethyl phosphite facilitates the transfer of both vinyl groups via stabilization of the vinylcopper intermediate (eq 32).[38]

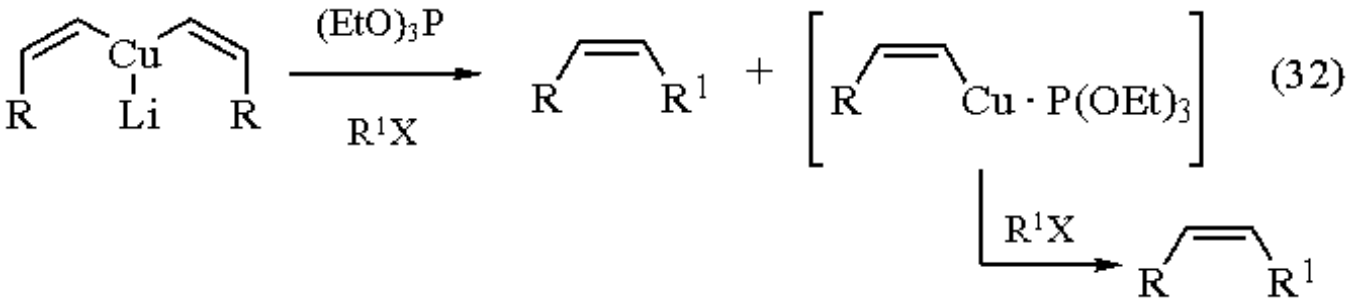

Copper(I) Iodide-Triethyl Phosphite is formed in 89% yield by the reaction of triethyl phosphite and ***Copper(I) Iodide*** in refluxing benzene.[39] The salt has been used to form arylcopper intermediates which participate in a modified Ullmann coupling sequence (eq 33).[40]

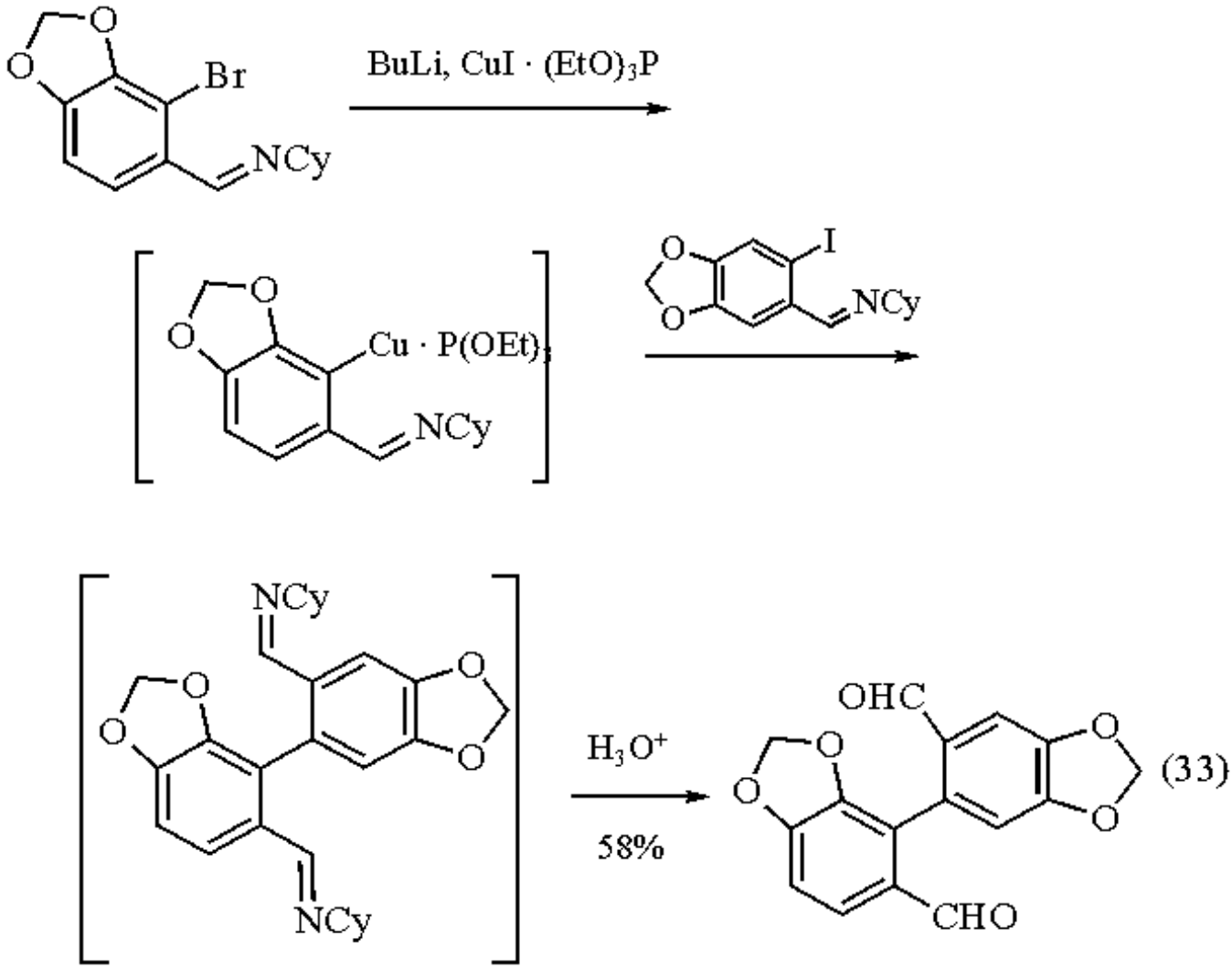

Related Reagents.

Trimethyl Phosphite.

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Triethyl Phosphonoacetate[1]

$(EtO)_2P(O)CH_2CO_2Et$

[867-13-0] · $C_8H_{17}O_5P$ · Triethyl Phosphonoacetate · (MW 224.22)

(treatment with a base gives a phosphoryl-stabilized carbanion that reacts with aldehydes,[1] ketones,[1] nitrones,[2] epoxides,[3] nitroso compounds,[4] ketenes,[5] alkyl halides,[6c] and halogenating agents[6a,b])

Alternate Names: ethyl (diethoxyphosphinyl)acetate; diethyl (ethoxycarbonyl)methylphosphonate.

Physical Data: bp 152-153 °C/20 mmHg; *d* 1.130 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: irritant; store under N_2.

Reactions with Aldehydes and Ketones.

$(EtO)_2P(O)CH_2CO_2Et$ in either DME, THF, DMF, MeCN, dioxane, benzene, or toluene is deprotonated by ***Sodium Hydride***,[7] ***Sodium Amide***,[8] metal alkoxides,[9] and other bases to give a phosphoryl-stabilized carbanion, $[(EtO)_2P(O)\text{-}CHCO_2Et]\ M^+$. Subsequent reaction of the carbanion with an aldehyde or ketone gives an (*E*)-α,β-unsaturated ester as the major product in a Horner-Wadsworth-Emmons (HWE) reaction (eqs 1-4)[1] (see also ***Trimethyl Phosphonoacetate***). The phosphate ester byproduct is water soluble, unlike the Wittig byproduct (Ph_3PO), and is easily removed at the completion of the reaction. Ketones and aliphatic aldehydes often give the (*Z*)-α,β-unsaturated ester in addition to the (*E*)-isomer,[1c,d] the isomer ratio being influenced by the reaction solvent (eq 1).[7a] Some ketones and aldehydes that are unreactive to Wittig alkenation conditions (e.g. 3-keto steriods[9,10] and glucose derivatives[11]) will react with the carbanion of $(EtO)_2P(O)CH_2CO_2Et$. The Peterson alkenation reaction of lithio ethyl trimethylsilylacetate with aldehydes and ketones offers a mild alternative to both the HWE and Wittig approaches to α,β-unsaturated esters.[12] The Peterson reaction often gives the (*Z*)-isomer as the major product.[12b] (*Z*)-Alkenes are also obtained from HWE reactions using bis(2,2,2-trifluoroethyl) phosphonates (see also ***Trimethyl Phosphonoacetate***).[13]

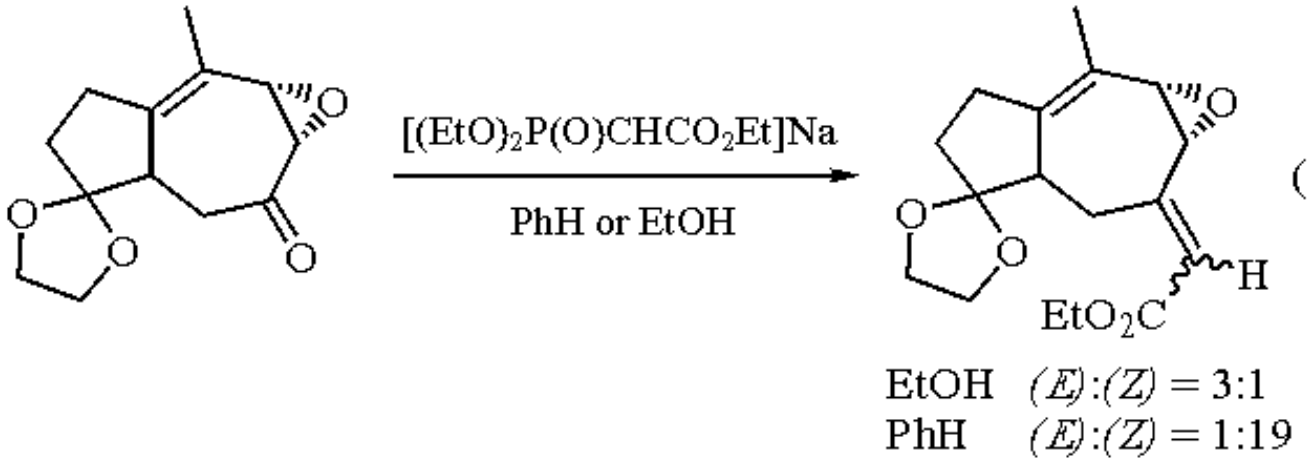

(1)

Milder reaction conditions have been developed to increase yields, accommodate sensitive substrates and minimize undesired side reactions such as double bond migrations, Knoevenagel condensation, Cannizzaro reaction, and Michael addition.[1] HWE reactions of aldehydes and $(EtO)_2P(O)CH_2CO_2Et$ have been carried out in two-phase liquid-liquid conditions (aqueous $NaOH/CH_2Cl_2$) in the presence of a phase transfer catalyst, thus eliminating the need for anhydrous solvents.[14] Superior yields and reduced reaction times were obtained

using aromatic aldehydes and ketones under solid-liquid two-phase conditions (powdered NaOH or KOH/THF) (eq 2).[14b,c]

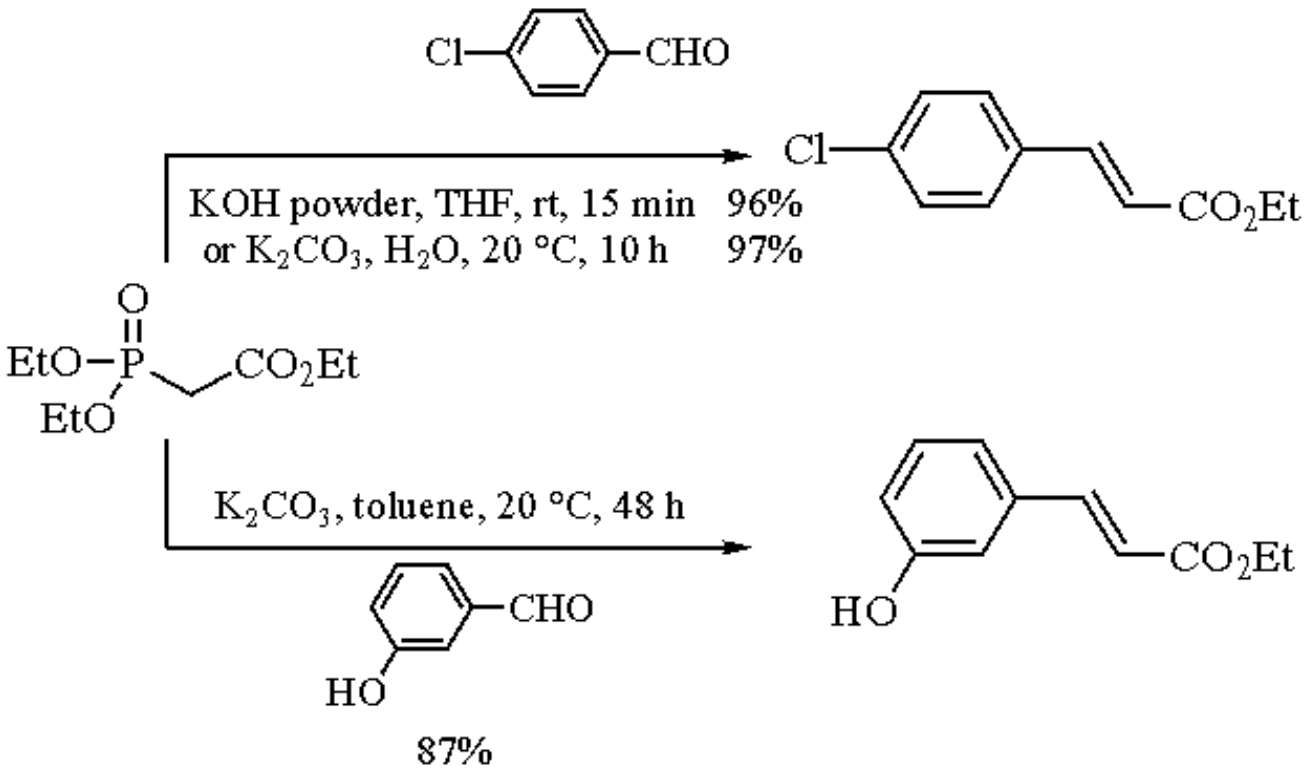

(2)

Aliphatic and particularly aromatic aldehydes give high yields of (*E*)-α,β-unsaturated esters using $(EtO)_2P(O)CH_2CO_2Et$ and K_2CO_3 (eq 2)[15] or Cs_2CO_3[16] under solid-liquid conditions. K_2CO_3 has also been used in highly concentrated (6-10 molar) aqueous solutions under heterogeneous liquid-liquid conditions in the absence of organic solvent (eq 2).[15a,c] The combination of aqueous K_2CO_3 and $(EtO)_2P(O)CH_2CO_2Et$ has been employed elsewhere, e.g. under these conditions glutaraldehyde and succinaldehyde give 1-ethoxycarbonyl-6-cyclohexenol and 1-ethoxycarbonyl-5-cyclopentenol, respectively,[17] and aqueous formaldehyde gives ethyl α-(hydroxymethyl)acrylate[15a] rather than the normal HWE product. The use of D_2O, rather than water, gives a general preparation of α-deuterated α,β-unsaturated esters[18] (%D > 90).

Furfural reacts with $(EtO)_2P(O)CH_2CO_2Et$ and activated ***Barium Hydroxide*** catalyst at 70 °C in dioxane containing a trace of water to give (*E*)-ethyl 3-(2´-furyl)acrylate in quantitative yield.[19] Reaction times are reduced in comparison with other solid-liquid procedures.[19] No secondary reactions were observed, in contrast to aqueous base catalysis, and the method is applicable to hindered aldehydes.[19] A reduction in both the amount of $Ba(OH)_2$ catalyst required and the reaction time is obtained using sonochemical, rather than thermal activation.[20]

The reaction of an aldehyde with $(EtO)_2P(O)CH_2CO_2Et$ and ***Diisopropylethylamine*** (DIPEA)[21,22] or ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU)[21,23] in a stirred suspension of ***Lithium Chloride*** in dry MeCN gives excellent yields of (*E*)-α,β-unsaturated esters (eq 3).[21] The method is widely used with base-sensitive aldehydes.[21-23] Few reports have appeared using a ketone rather than an aldehyde under these conditions.[21,24] The use of DIPEA, rather than DBU, has been reported to give less epimerization of the aldehyde component (eq 4).[22b] An interesting extension of this reaction proceeds by an in situ oxidation and HWE coupling (eq 5).[22c] The combination of $(EtO)_2P(O)CH_2CO_2Et$, TEA, LiCl and an aldehyde also gives high yields of an α,β-unsaturated ester.[25] The use of $(CF_3CH_2O)_2P(O)CH_2CO_2Et$ has extended the scope of this reaction to include ketones.[25,26] Other catalysts of the HWE reaction include ***Alumina***, and ***Potassium Fluoride-Alumina***.[27] Polymer-bound phosphonates have also received some attention.[28]

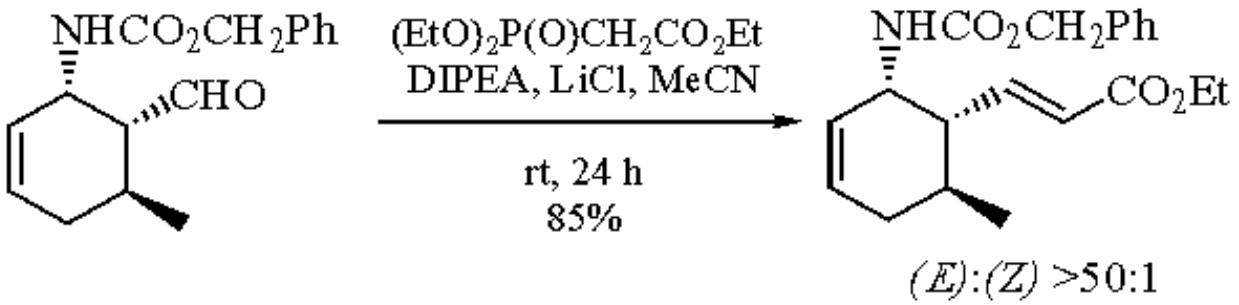

(3)

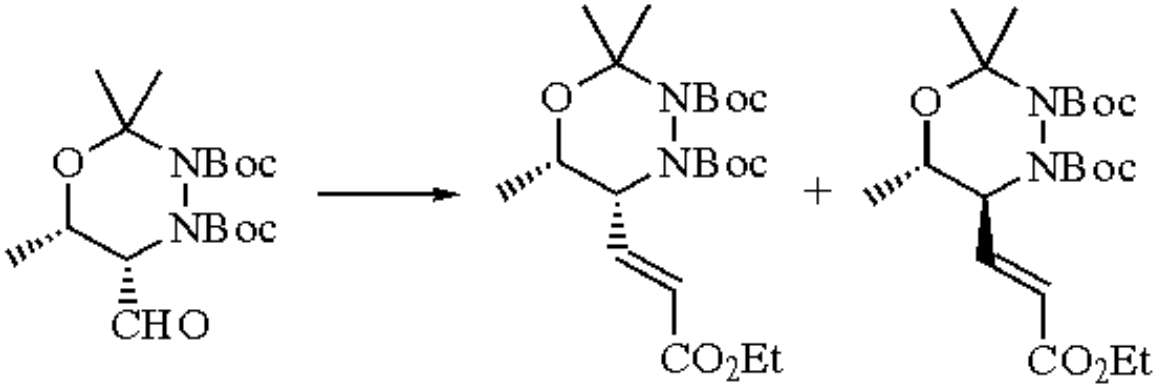

(4)

$(EtO)_2P(O)CH_2CO_2Et$, DIPEA, LiCl, rt	95:5	65%
$(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, rt	22:78	85%
$Ph_3PCH_2CO_2Et$, toluene, reflux	58:42	76%

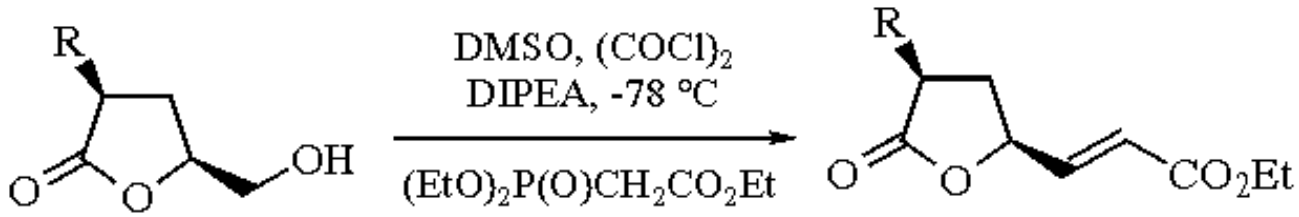

(5)

Diisobutylaluminum Hydride (DIBAL) reduction of saturated esters[29] and lactones[29a] at -78 °C in the presence of the NaH-derived carbanion of $(EtO)_2P(O)CH_2CO_2Et$ gives good yields of the homologous esters with >90% (*E*) stereochemistry and with little or no overreduction of either the starting material or product ester (eq 6).[29a] The reaction of $(EtO)_2P(O)CH_2CO_2Et$ with either glucopyranoses[11b] or hydroxy phthalides in the presence of 1 mol % of tetra-*n*-hexylammonium bromide[30] gives ring-opened alkenes in good yields.

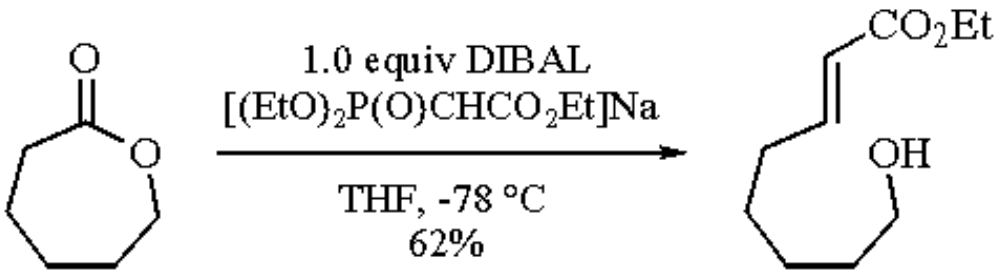

(6)

The addition of an acyl phosphonate [e.g. $(EtO)_2P(O)COPh$] to the NaH-derived phosphoryl carbanion of $(EtO)_2P(O)CH_2CO_2Et$, gives the (*Z*)-alkene as the major product.[31] The analogous Wittig alkenation reaction gives (*E*)-alkenes.[31]

Other Reactions.

Nitrones react with $(EtO)_2P(O)CH_2CO_2Et$ and NaH in DME or alkali metal alkoxides in alcoholic solvents to give aziridines and cyclic enamines (eq 7).[2] Cyclopropanes are prepared by refluxing an epoxide with $(EtO)_2P(O)CH_2CO_2Et$,[3a] or the corresponding sodium phosphoryl carbanion in dioxane or DME[3b] (eq 8).[3c,d]

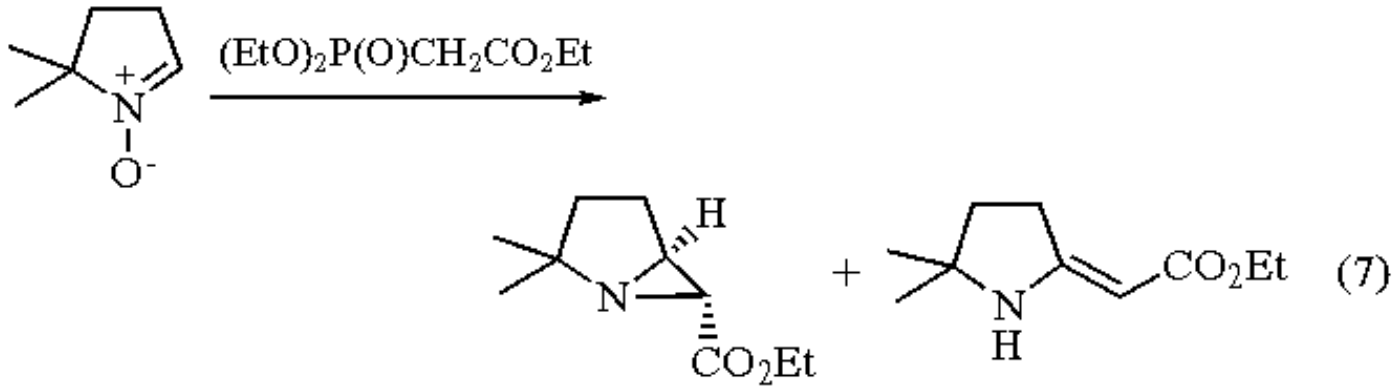

NaH, DME, reflux	35%	-
t-BuONa, *t*-BuOH, reflux	75%	-
MeONa, MeOH, reflux	6%	36%

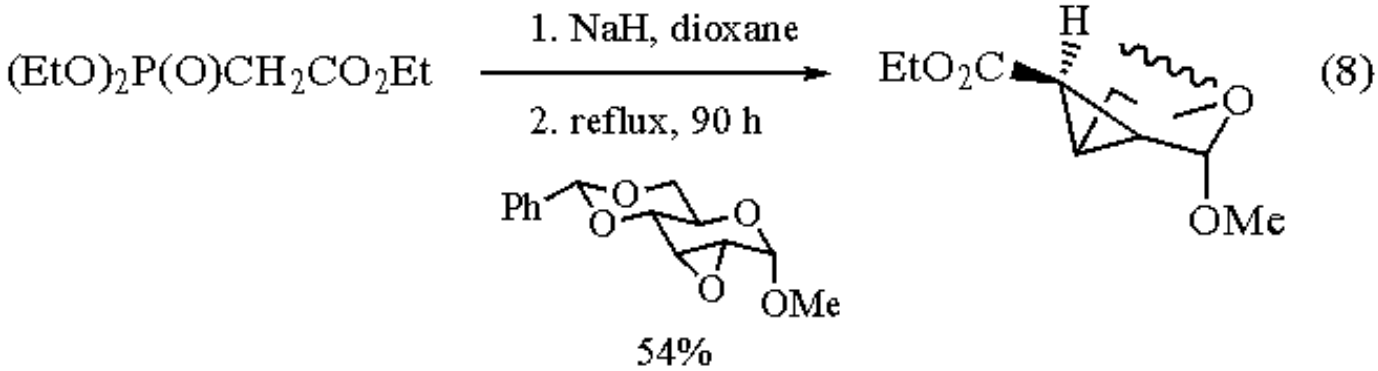

7-Pteridinones are prepared by treating the sodium phosphoryl carbanion of $(EtO)_2P(O)CH_2CO_2Et$ with 4,6-diamino-5-nitrosopyrimidines (eq 9).[4] Ketenes react with the NaH-derived carbanion of $(EtO)_2P(O)CH_2CO_2Et$ in DME at 50 °C to give allenes (eq 10).[5,6a] α-Alkylated and arylated phosphonates are prepared by reacting the carbanion of $(EtO)_2P(O)CH_2CO_2Et$ with an allyl[6c] and benzyl[32] halide, respectively. Triethyl phosphonoacetate is also readily halogenated at the α-position.[6a,b]

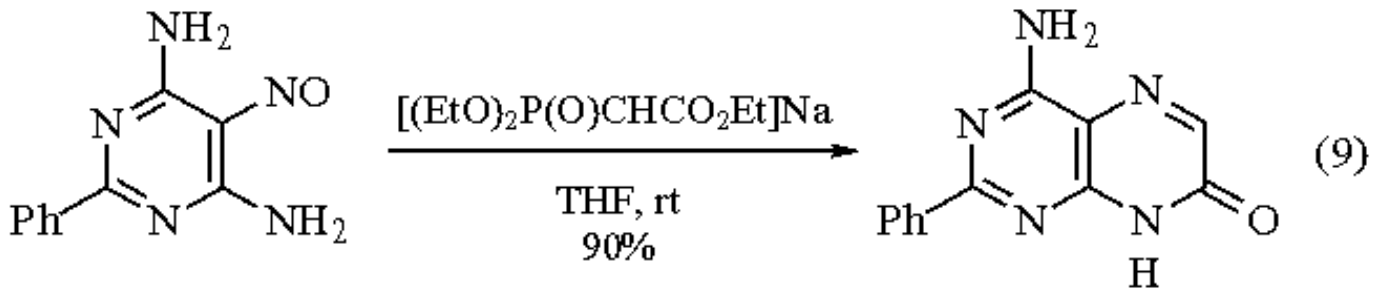

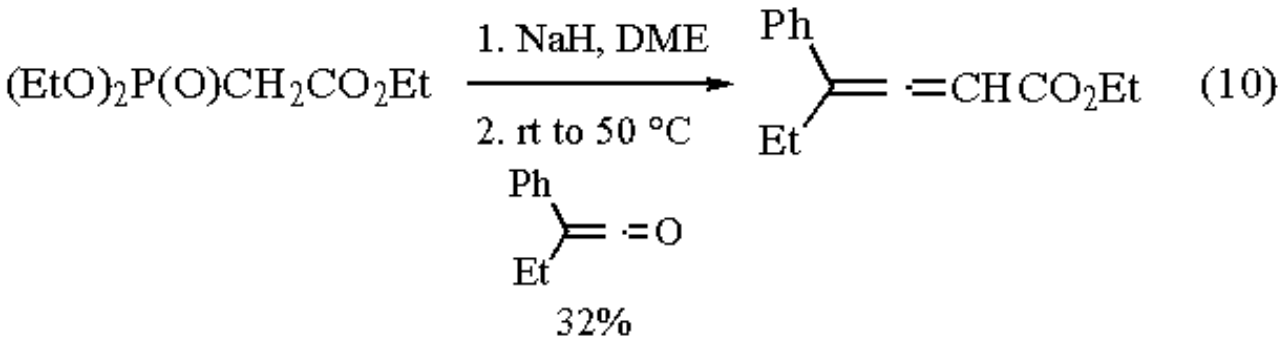

Related Reagents.

Trimethyl Phosphonoacetate.

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Triethylsilane[1]

Et_3SiH

[617-86-7] · $C_6H_{16}Si$ · Triethylsilane · (MW 116.31)

(mild reducing agent for many functional groups)

Physical Data: mp -156.9 °C; bp 107.7 °C; *d* 0.7309 g cm^{-3}.

Solubility: insol H_2O; sol hydrocarbons, halocarbons, ethers.

Form Supplied in: colorless liquid; widely available.

Purification: simple distillation, if needed.

Handling, Storage, and Precautions: triethylsilane is physically very similar to comparable hydrocarbons. It is a flammable, but not pyrophoric, liquid. As with all organosilicon hydrides, it is capable of releasing hydrogen gas upon storage, particularly in the presence of acids, bases, or fluoride-releasing salts. Proper precautions should be taken to vent possible hydrogen buildup when opening vessels in which triethylsilane is stored.

Introduction.

Triethylsilane serves as an exemplar for organosilicon hydride behavior as a mild reducing agent. It is frequently chosen as a synthetic reagent because of its availability, convenient physical properties, and economy relative to other organosilicon hydrides which might otherwise be suitable for effecting specific chemical transformations.

Hydrosilylations.

Addition of triethylsilane across multiple bonds occurs under the influence of a large number of metal catalysts.[2] Terminal alkynes undergo hydrosilylations easily with triethylsilane in the presence of platinum,[3] rhodium,[3a,4] ruthenium,[5] osmium,[6] or iridium[4] catalysts. For example, phenylacetylene can form three possible isomeric hydrosilylation products with triethylsilane; the (*Z*)-β-, the (*E*)-β-, and the α-products (eq 1). The (*Z*)-β-isomer is formed exclusively or preferentially with ruthenium[5] and some rhodium[4] catalysts, whereas the (*E*)-β-isomer is the major product formed with platinum[3] or iridium[4] catalysts. In the presence of a catalyst and carbon monoxide, terminal alkynes undergo silylcarbonylation reactions with triethylsilane to give (*Z*)- and (*E*)-β-silylacrylaldehydes.[7] Phenylacetylene gives an 82% yield of a mixture of the (*Z*)- and (*E*)-isomers in a 10:1 ratio when 0.3 mol % of ***Dirhodium(II) Tetrakis(perfluorobutyrate)*** catalyst is used under atmospheric pressure at 0 °C in dichloromethane (eq 2).[7d] Terminal alkenes react with triethylsilane in the presence of this catalyst to form either normal anti-Markovnikov hydrosilylation products or allyl- or vinylsilanes, depending on whether the alkene is added to the silane or vice versa.[8] A mixture of 1-hexene and triethylsilane in the presence of 2 mol % of an iridium catalyst ($[IrCl(CO)_3]_n$) reacts under 50 atm of carbon monoxide to give a 50% yield of a mixture of the (*Z*)- and (*E*)-enol silyl ether isomers in a 1:2 ratio (eq 3).[9] Hydrolysis yields the derived acylsilane quantitatively.[9]

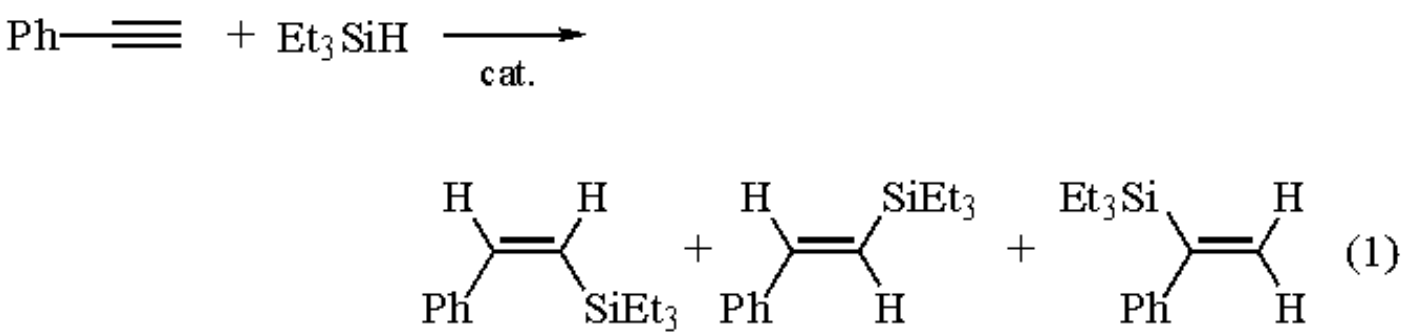

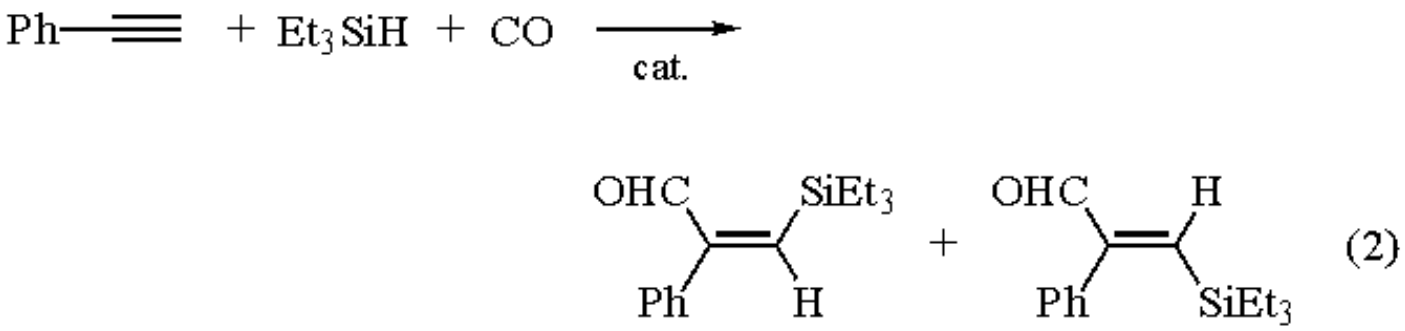

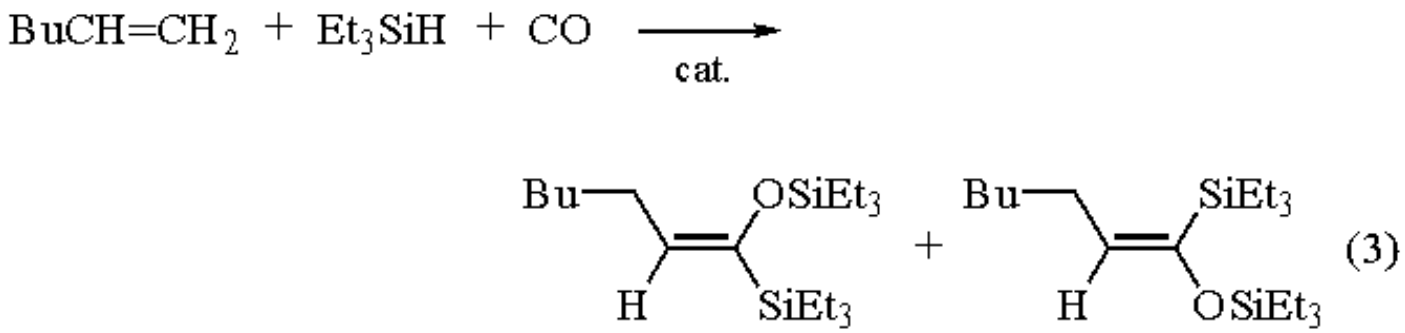

A number of metal complexes catalyze the hydrosilylation of various carbonyl compounds by triethylsilane.[10] Stereoselectivity is observed in the hydrosilylation of ketones[11] as in the reactions of 4-*t*-butylcyclohexanone and triethylsilane catalyzed by ruthenium,[12] chromium,[13] and rhodium[12,14] metal complexes (eq 4). Triethylsilane and ***Chlorotris(triphenylphosphine)rhodium(I)*** catalyst effect the regioselective 1,4-hydrosilylation of α,β-unsaturated ketones and aldehydes.[15,16] Reduction of mesityl oxide in this manner results in a 95% yield of product that consists of 1,4- and 1,2-hydrosilylation isomers in a 99:1 ratio (eq 5). This is an exact complement to the use of phenylsilane, where the ratio of respective isomers is reversed to 1:99.[16]

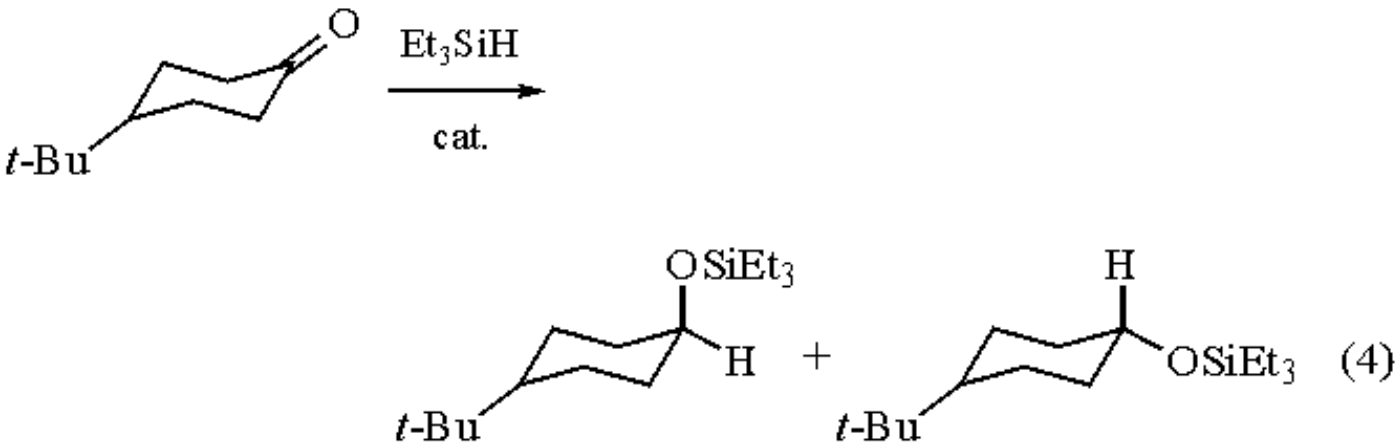

$(Ph_3P)_3RuCl_2$, AgTFA, PhMe, Δ	5:95
Et_4N^+ $[HCr_2(CO)_{10}]^-$, DME, Δ	10:90
$(Ph_3P)_3RhCl$, PhMe, Δ	11:89
$[Rh(\eta^3\text{-}C_3H_5)\{P(OMe)_3\}_3]$, PhH	29:71

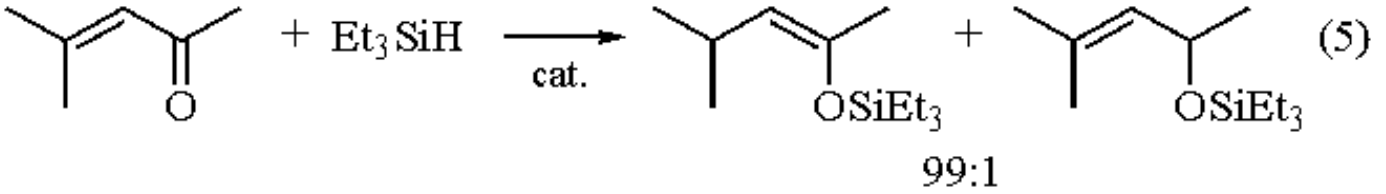

Silane Alcoholysis.

Triethylsilane reacts with alcohols in the presence of metal catalysts to give triethylsilyl ethers.[17] The use of dirhodium(II)

perfluorobutyrate as a catalyst enables regioselective formation of monosilyl ethers from diols (eq 6).[17a]

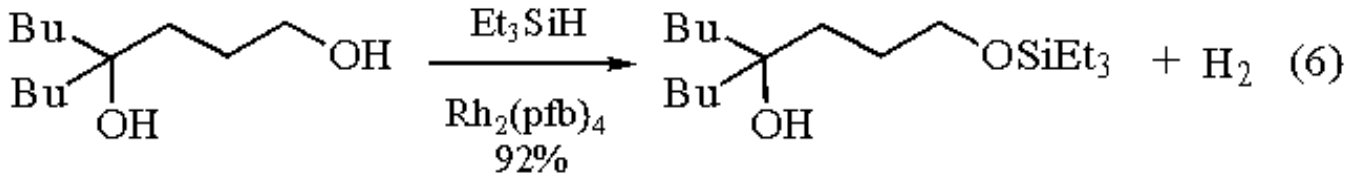

Formation of Singlet Oxygen.

Triethylsilane reacts with ozone at -78 °C in inert solvents to form triethylsilyl hydrotrioxide, which decomposes at slightly elevated temperatures to produce triethylsilanol and ***Singlet Oxygen***. This is a convenient way to generate this species for use in organic synthesis.[18]

Reduction of Acyl Derivatives to Aldehydes.

Aroyl chlorides and bromides give modest yields of aryl aldehydes when refluxed in diethyl ether with triethylsilane and ***Aluminum Chloride***.[19] Better yields of both alkyl and aryl aldehydes are obtained from mixtures of acyl chlorides or bromides and triethylsilane by using a small amount of 10% ***Palladium on Carbon*** catalyst (eq 7).[20] This same combination of triethylsilane and catalyst can effect the reduction of ethyl thiol esters to aldehydes, even in sensitive polyfunctional compounds (eq 8).[21]

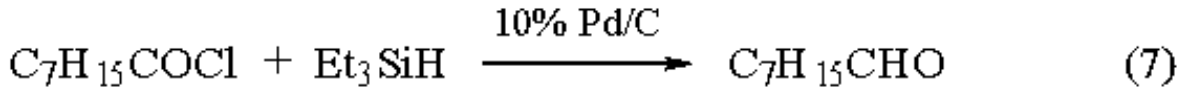

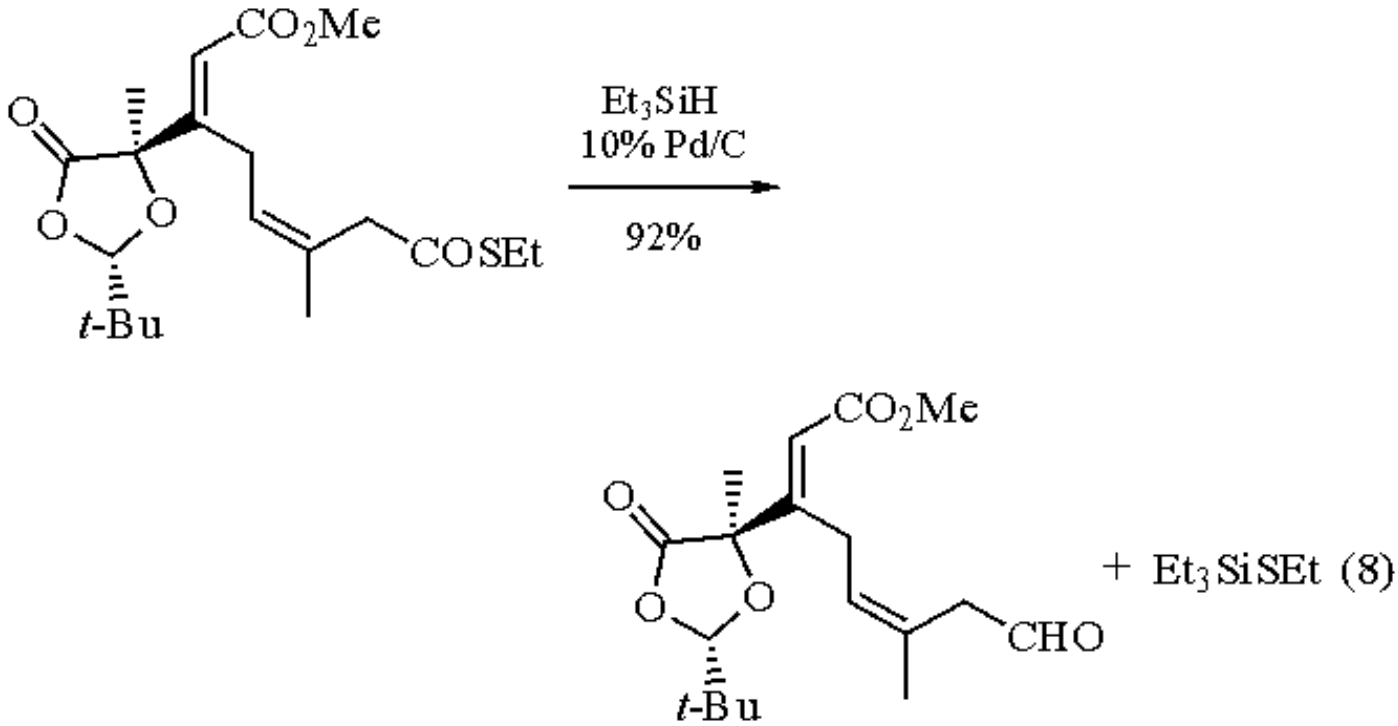

Radical Chain Reductions.

Triethylsilane can replace toxic and difficult to remove organotin reagents for synthetic reductions under radical chain conditions. Although it is not as reactive as ***Tri-n-butylstannane***,[22] careful choice of initiator, solvent, and additives leads to effective reductions of alkyl halides,[23,24] alkyl sulfides,[23] and alcohol derivatives such as *O*-alkyl *S*-methyl dithiocarbonate (xanthate) and thionocarbonate esters.[22,23,25,26] Portionwise addition of 0.6 equiv of ***Dibenzoyl Peroxide*** to a refluxing triethylsilane solution of *O*-cholestan-3β-yl *O*´-(4-fluorophenyl) thionocarbonate gives a 93% yield of cholestane (eq 9).[22] The same method converts bis-xanthates of *vic*-diols into alkenes (eq 10).[22] Addition of a small amount of thiol such as *t*-dodecanethiol to serve as a polarity reversal catalyst[24] with strong radical initiators in nonaromatic solvents also gives good results.[23,25] Treatment of ethyl 4-bromobutanoate with four equiv of triethylsilane, two equiv of dilauroyl peroxide (DLP), and 2 mol % of *t*-dodecanethiol in refluxing cyclohexane for 1 hour yields ethyl butanoate in 97% yield (eq 11).[23]

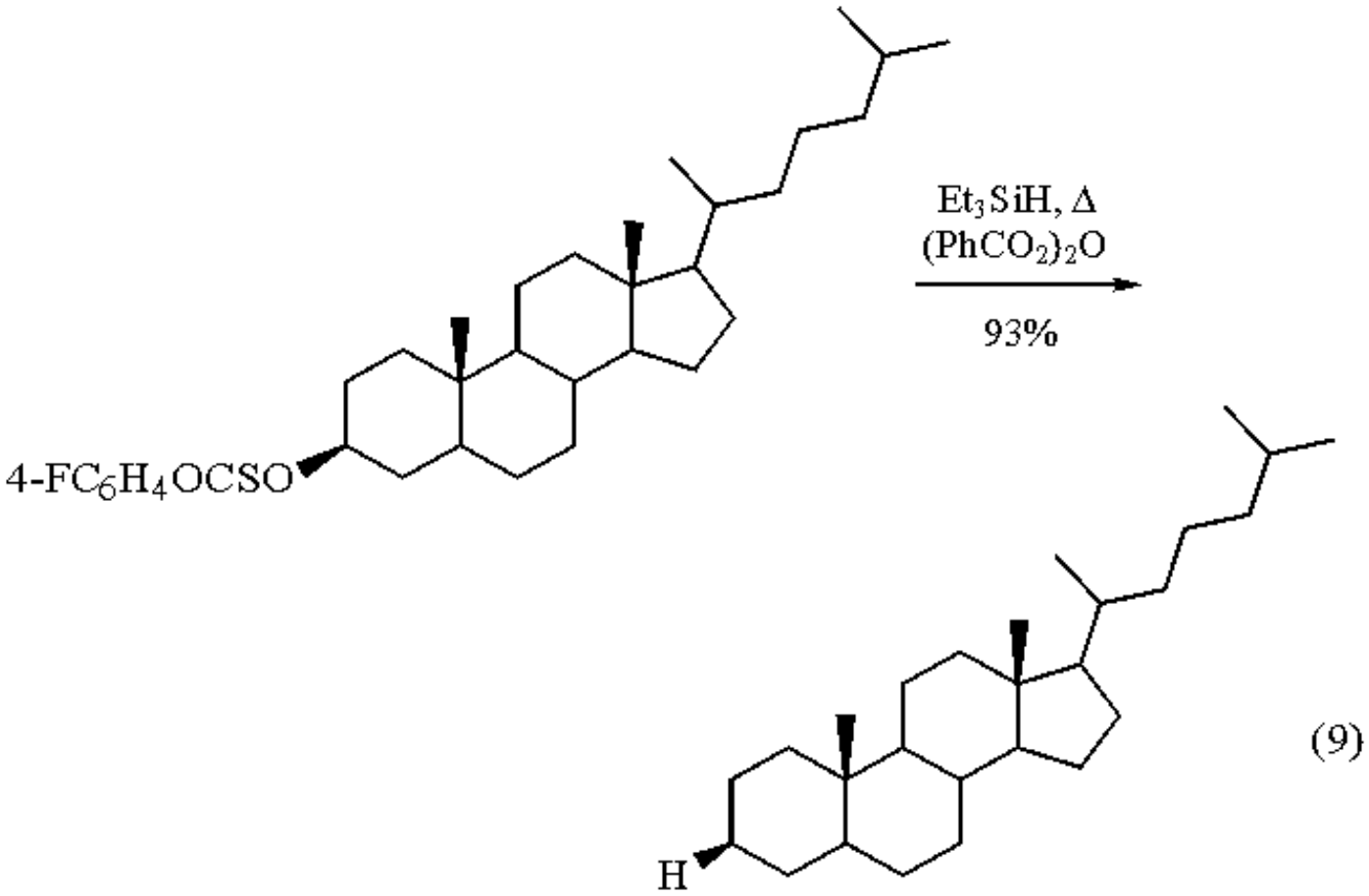

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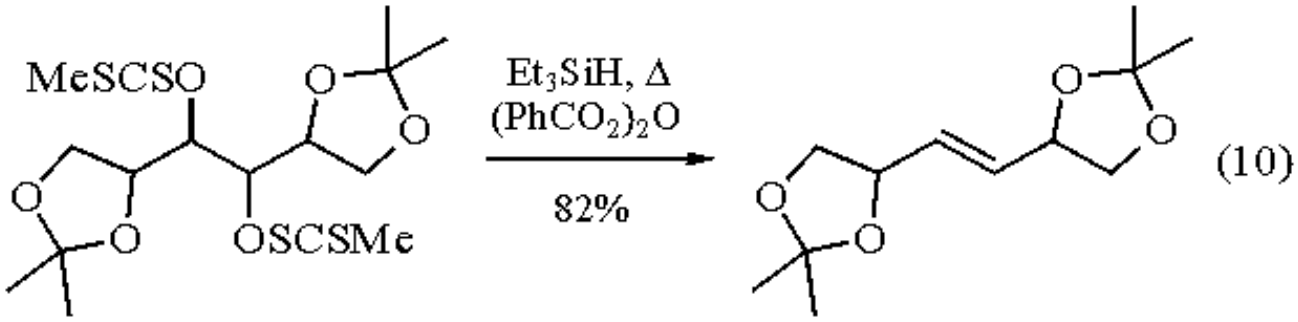

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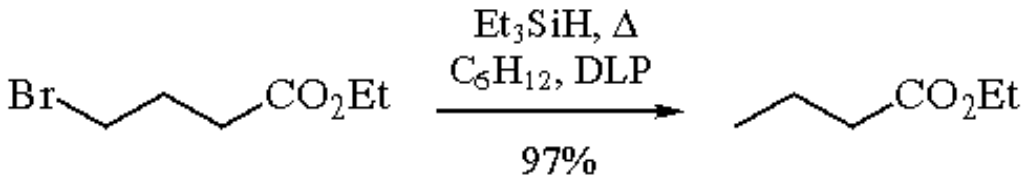

(11)

Ionic Hydrogenations and Reductive Substitutions.

The polar nature of the Si-H bond enables triethylsilane to act as a hydride donor to electron-deficient centers. Combined with Brønsted or Lewis acids this forms the basis for many useful synthetic transformations.[27] Use of ***Trifluoromethanesulfonic Acid*** (triflic acid) at low temperatures enables even simple alkenes to be reduced to alkanes in high yields (eq 12).[28] ***Boron Trifluoride*** monohydrate is effective in promoting the reduction of polycyclic aromatic compounds (eq 13).[29] Combined with thiols, it enables sulfides to be prepared directly from aldehydes and ketones (eq 14).[30] Combinations of triethylsilane with either ***Trifluoroacetic Acid***/ammonium fluoride or ***Pyridinium Poly(hydrogen fluoride)*** (PPHF) are effective for the reductions of alkenes, alcohols, and ketones (eq 15).[31] Immobilized strong acids such as iron- or copper-exchanged ***Montmorillonite K10***[32] or the superacid ***Nafion-H***[33] facilitate reductions of aldehydes and ketones[32] or of acetals[33] by increasing the ease of product separation (eq 16). Boron trifluoride and triethylsilane are an effective combination for the reduction of alcohols, aldehydes, ketones (eq 17),[34] and epoxides.[35] ***Boron Trifluoride Etherate*** sometimes may be substituted for the free gas.[36]

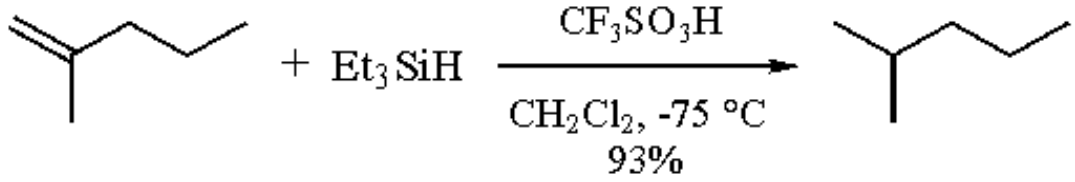

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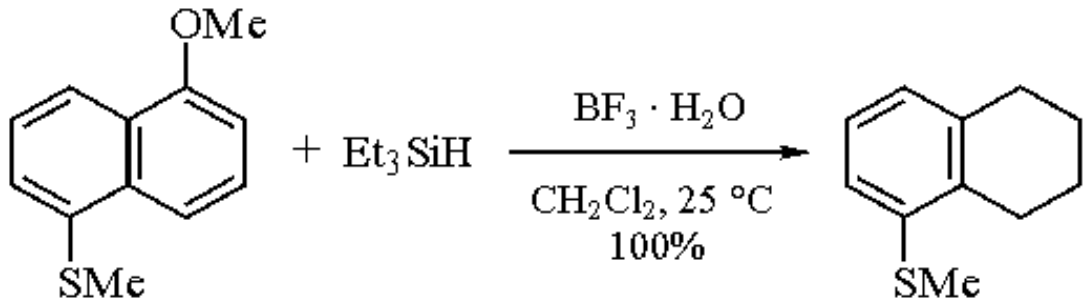

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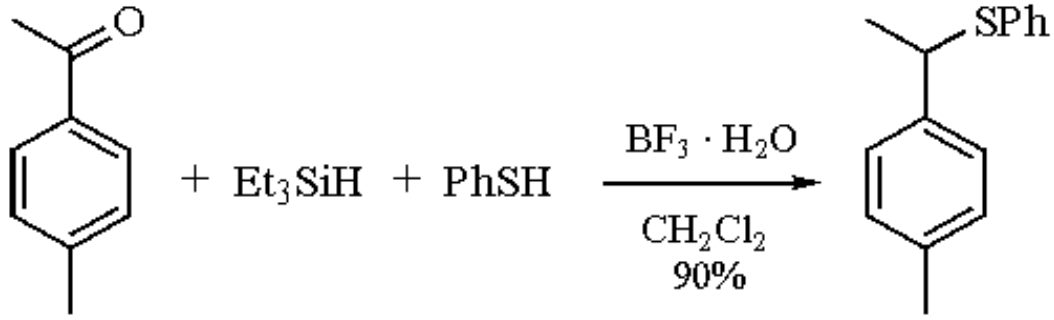

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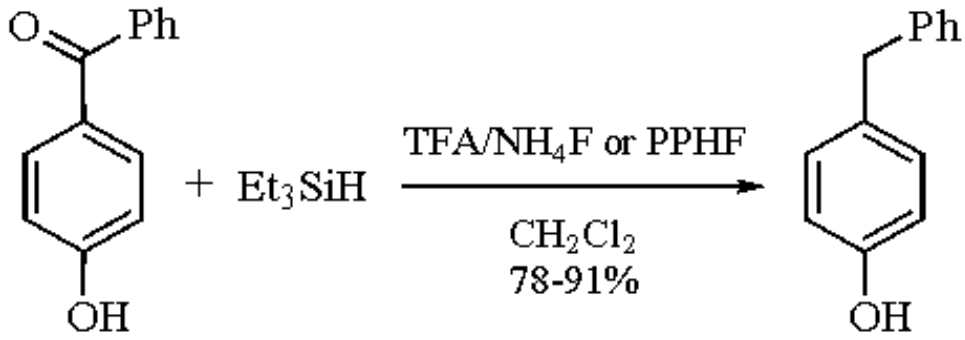

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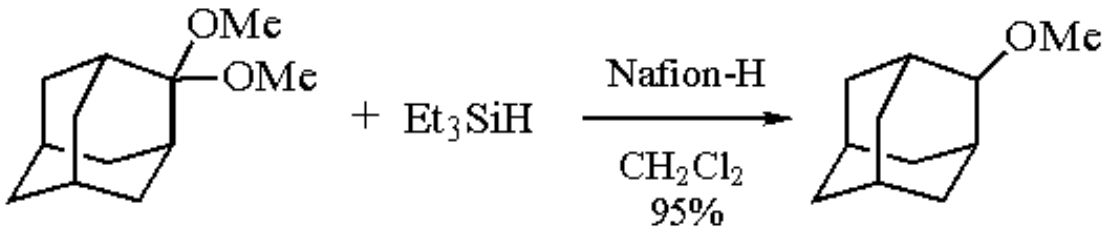

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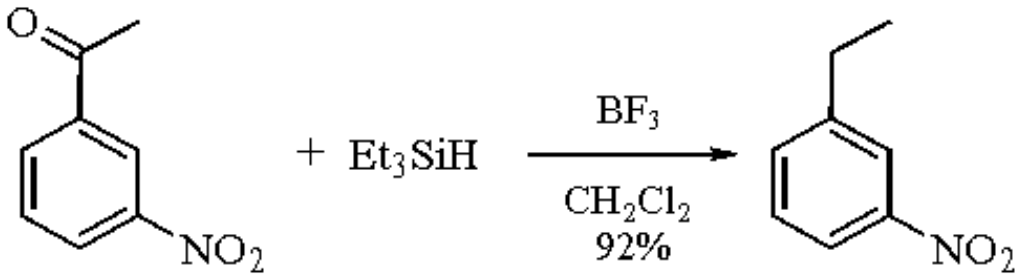

(17)

Triethylsilane in 3M ethereal ***Lithium Perchlorate*** solution effects the reduction of secondary allylic alcohols and acetates (eq 18).[37] The combination of triethylsilane and ***Titanium(IV) Chloride*** is a particularly effective reagent pair for the selective reduction of acetals.[38] Treatment of (±)-frontalin with this pair gives an 82% yield of tetrahydropyran products with a *cis*:*trans* ratio of 99:1 (eq 19).[38b] This exactly complements the 1:99 product ratio of the same products obtained with ***Diisobutylaluminum Hydride***.[38b]

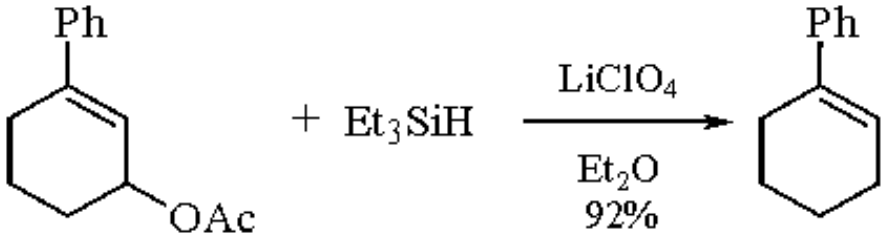

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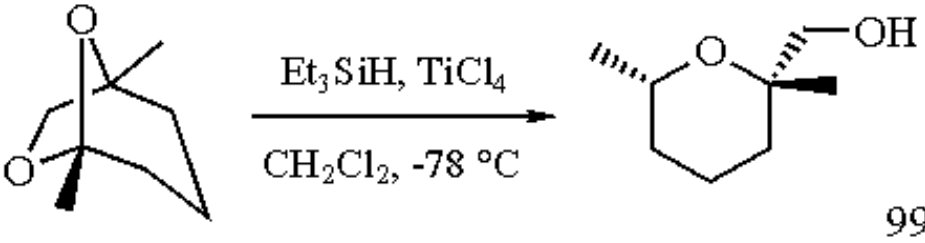

(19)

Triethylsilane and trityl salts[39] or ***Trimethylsilyl Trifluoromethanesulfonate***[40] are effective for the reduction of various ketones and acetals, as are combinations of ***Chlorotrimethylsilane*** and indium(III) chloride[41] and ***Tin(II) Bromide*** and ***Acetyl Bromide***.[42] Isophthaldehyde undergoes reductive polycondensation to a polyether when treated with triethylsilane and ***Triphenylmethyl Perchlorate***.[43]

Triethylsilane reduces nitrilium ions to aldimines,[44] diazonium ions to hydrocarbons,[45] and aids in the deprotection of amino acids.[46] With aluminum halides, it reduces alkyl halides to hydrocarbons.[47]

Related Reagents.

Phenylsilane-Cesium Fluoride; ***Tri-n-butylstannane***; ***Tricarbonylchloroiridium-Diethyl(methyl)silane-Carbon Monoxide***; ***Triethylsilane-Trifluoroacetic Acid***.

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Triethylsilane-Trifluoroacetic Acid[1]

Et_3SiH-CF_3CO_2H

[617-86-7] · $C_6H_{16}Si$ · Triethylsilane-Trifluoroacetic Acid · (MW 116.31)

[599-00-8] · $C_2HF_3O_2$ · Triethylsilane-Trifluoroacetic Acid · (MW 114.03)

(useful reducing agent combination for ionic hydrogenation of many functional groups[1])

Physical Data: see ***Triethylsilane*** and ***Trifluoroacetic Acid***.

Solubility: Et_3SiH: insol H_2O; sol hydrocarbons, chlorocarbons, ethers. CF_3CO_2H: sol H_2O, chlorocarbons, ethers.

Form Supplied in: both are colorless liquids; widely available in pure form.

Purification: simple distillation, if needed.

Handling, Storage, and Precautions: triethylsilane is a flammable, nonpyrophoric liquid, physically similar to comparable hydrocarbons. Proper precautions should be taken to vent possible hydrogen buildup when opening vessels in which triethylsilane is stored. As with all organosilicon hydrides, it is capable of releasing hydrogen gas upon storage, particularly in the presence of acids, bases, or fluoride-releasing salts. Trifluoroacetic acid is a corrosive, toxic acid that produces serious chemical burns upon contact with skin.

Introduction.

The reagent combination of ***Triethylsilane*** as a hydride donor and ***Trifluoroacetic Acid*** (TFA) as a proton donor constitutes a powerful, yet selective, means for the hydrogenation of many functional groups. Many acetals, alcohols, aldehydes, alkenes, cyclopropanes, hemiacetals, ketones, and thiophenes and some alkynes, dihydropyridines, disulfides, enamines, ethers, furans, imidazolones, imines, indoles, *O*-acyl oximes, sulfides, thiopyrans, *p*-quinones, and α,β-unsaturated ketones are reduced by this reagent system. Functionalities which are generally unaffected by these reductive conditions include most amide, arene, carboxylate, ester, ether, halide, nitrile, nitro, sulfonate, and phenolic and primary aliphatic hydroxy groups.

The reactions are sometimes run without solvent, but most often a solvent such as $MeNO_2$, CCl_4, $CHCl_3$, or, preferably, CH_2Cl_2 is used. Reactions are performed at room temperature or below and are worked up by careful addition of a base such as solid, anhydrous ***Potassium Carbonate*** followed by filtration and distillation to separate the product from the solvent and residual reagents and byproducts.[2] Only a slight stoichiometric excess of the silane is normally used, but often several equivalents of acid are used in order to conduct the reductions at reasonable rates.

Specific Functional Group Reductions.

Alcohols capable of producing carbenium ions spanning a range of stabilities of more than 24 pK_{R^+} units are reduced to hydrocarbons when treated with trifluoroacetic acid in the presence of triethylsilane.[2] Cyclopropylcarbinols may be reduced to cyclopropane hydrocarbons without ring opening.[3] Use of deuteriated silane yields deuterium-labeled hydrocarbons (eq 1).[4] Stereospecific reduction of metal-complexed alcohols can be effected without concomitant reduction of isolated terminal C=C bonds (eq 2).[5]

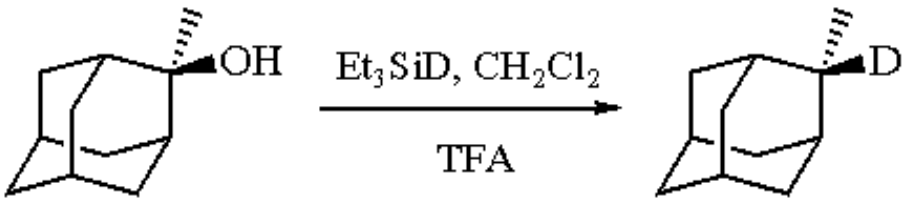

(1)

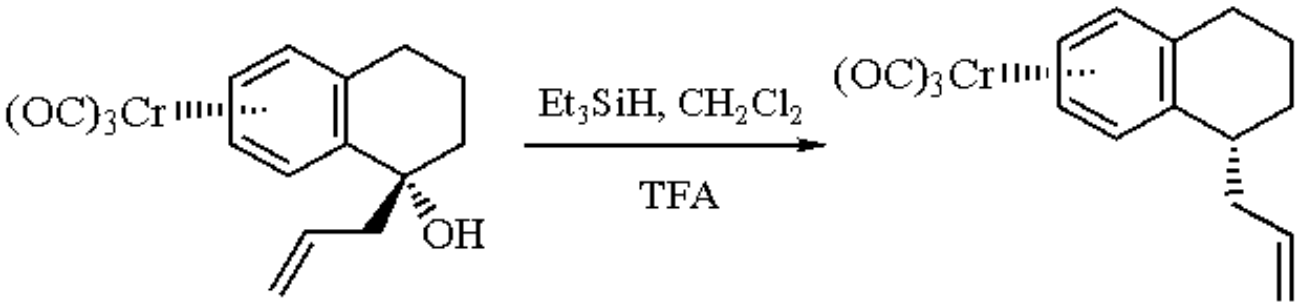

(2)

Sequential treatment of amides, lactams, or ureas with aqueous, basic ***Formaldehyde*** followed by triethylsilane and trifluoroacetic acid causes the intermediate methylols to be reduced to the corresponding *N*-methylated products, generally in very high yields (eq 3).[6] Cyclic hemiacetals may be reduced to cyclic ethers with a high degree of stereoselectivity (eq 4).[7]

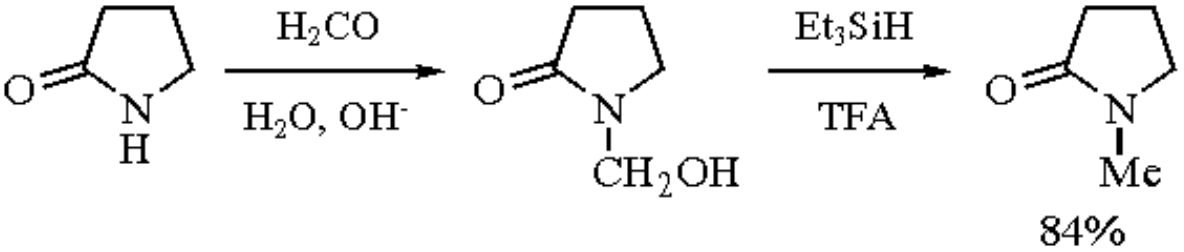

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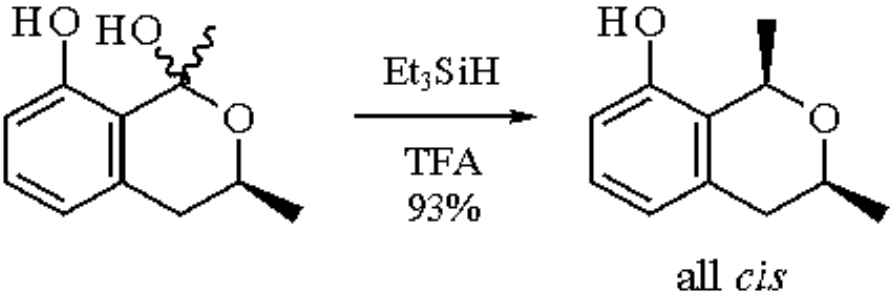

(4)

Alkenes that yield carbenium ions no more stable than secondary alkyl cations upon protonation do not normally undergo reduction by the action of triethylsilane and trifluoroacetic acid: thus isolated terminal -CH=CH_2 groups and simple vicinal 1,2-disubstituted alkenes are normally unaffected, while conjugated or more highly substituted alkene functions are reduced to alkanes.[8] Substituted cyclopropanes undergo reductive ring opening,[9] but alkynes are nearly inert to these conditions.[10] Only the isolated trisubstituted C=C bond is reduced when an unsaturated chroman derivative is treated with a 2-nitropropane solution of triethylsilane and trifluoroacetic acid containing ***Lithium Perchlorate*** (eq 5).[11]

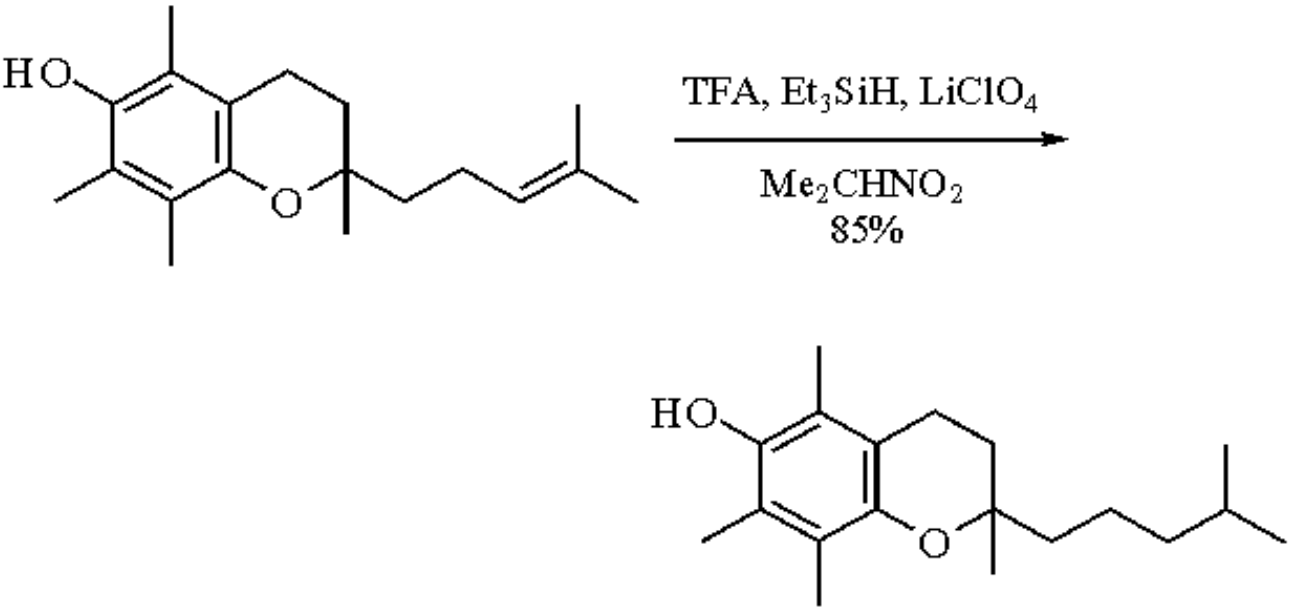

(5)

The reagent combination of triethylsilane and trifluoroacetic acid reduces electron-rich or aromatic aldehydes and ketones to a methyl or

methylene group, respectively.[12] Addition of a catalytic amount of $LiClO_4$ or ***Boron Trifluoride Etherate*** to the reaction mixture permits regioselective reduction of the side chain carbonyl group even in polyfunctional enones (eq 6).[13] Many aldehydes and ketones react to give symmetrical ethers in the absence of external alcohols[14] and unsymmetrical ether products when the reductions are run in the presence of added alcohols (eq 7).[15] Reduction of α,β-unsaturated ketones using a ketone:silane:acid ratio; = 1:1:10 gives products with the C=C bond reduced, whereas changing the ratio to 1:3:10 gives products with both the C=C and C=O bonds reduced (eq 8).[16]

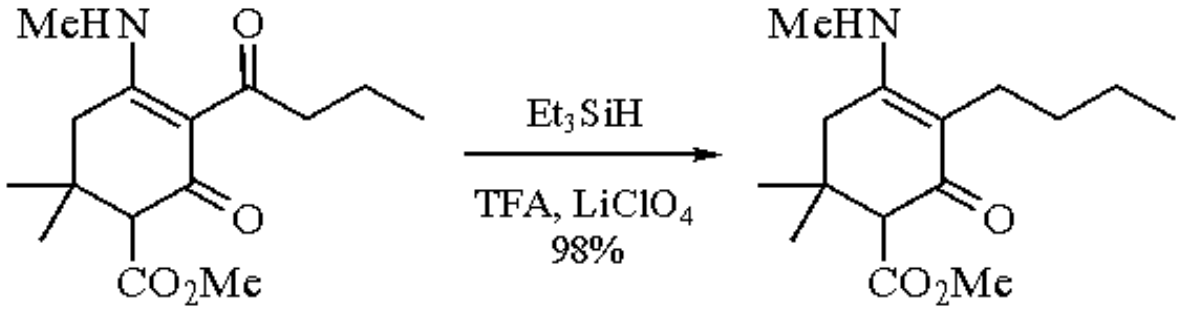

(6)

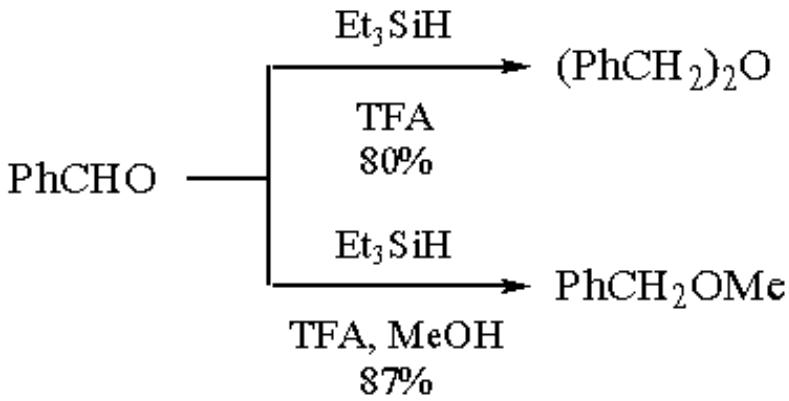

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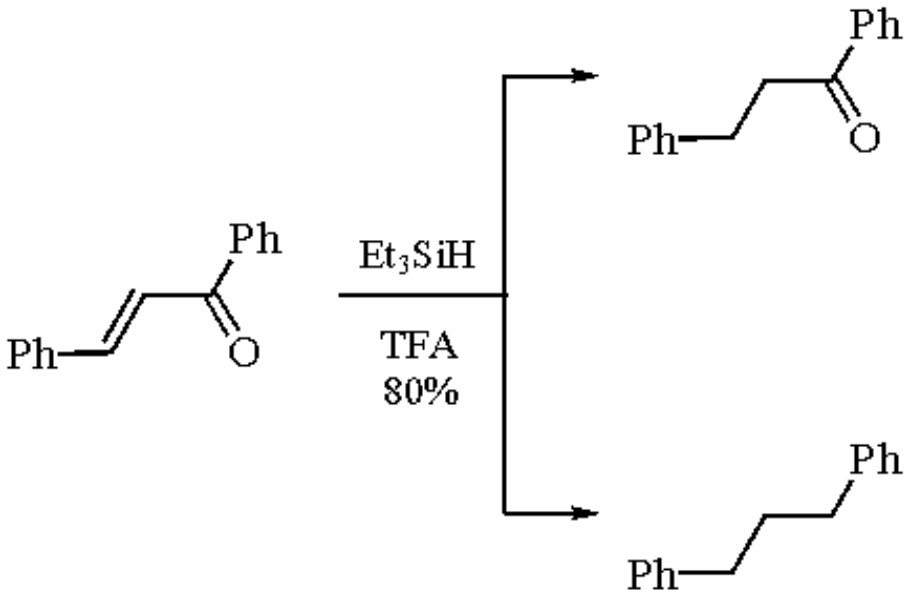

(8)

Reduction of *O*-benzoyl oximes gives *O*-benzoyl amines (eq 9).[17] Tryptophan is reduced and other indoles undergo stereoselective transformations into *cis*-indolines (eq 10).[18]

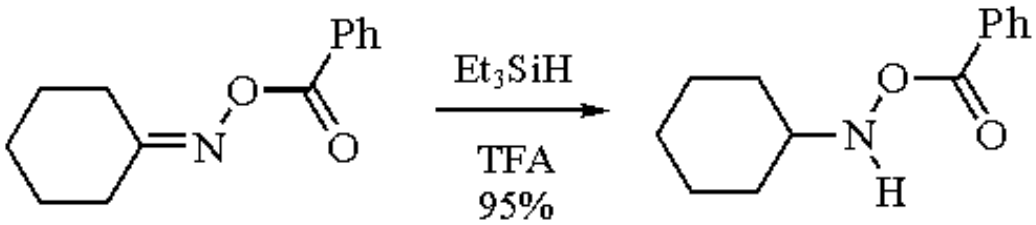

(9)

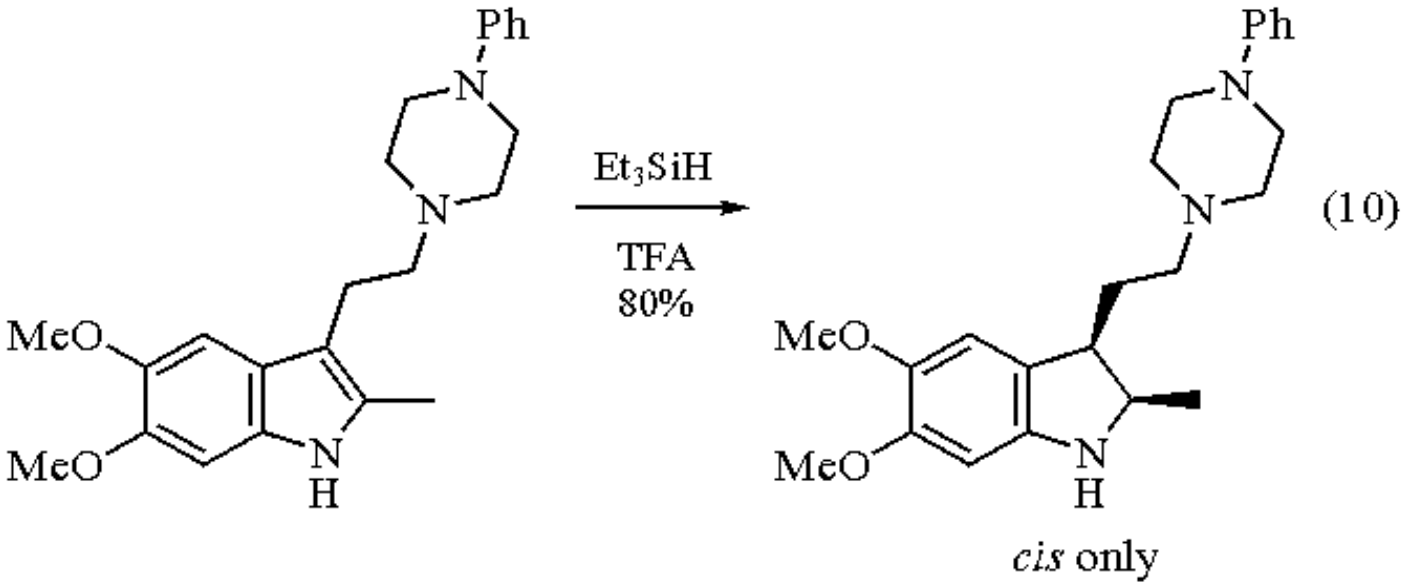

For related discussions, see also the entry on ***Triethylsilane***.

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3-Triethylsilyl-3-buten-2-one

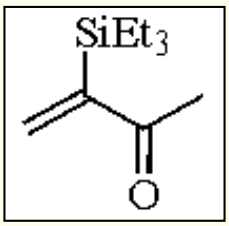

[20533-29-3] · $C_{10}H_{20}OSi$ · 3-Triethylsilyl-3-buten-2-one · (MW 184.39)

(methyl vinyl ketone surrogate[1] useful as Michael acceptor in Robinson annulation reactions[2])

Physical Data: bp 83 °C/7 mmHg.

Analysis of Reagent Purity: ^{1}H NMR spectrum ($CDCl_3$): δ 6.58 (d, *J* = 2 Hz, 1H, C*H*), 6.11 (d, *J* = 2 Hz, 1H, C*H*), 2.15 (s, 3H, CH_3), 0.4-1.2 [m, 15H, $Si(CH_2CH_3)_3$]; IR: 1669 cm^{-1}; mass spectrum: *m/e* 184 (M^+).

Preparative Methods: can be prepared by the reaction of 1-bromo-1-triethylsilylethylene with acetaldehyde.[1] This substance was obtained pure only by preparative gas chromatography. The less pure distilled product can be used in annulations.[2]

Handling, Storage, and Precautions: this material showed no tendency to deteriorate when stored under an argon atmosphere at -20 °C.

Annulation.

One of the most useful synthetic applications of the Michael reaction is the Robinson annulation reaction,[3] which is often utilized in the synthesis of steroids and terpenes. In general, the annulation of cyclohexanone with ***Methyl Vinyl Ketone*** (MVK) and its homologs, especially under aprotic, kinetic enolate conditions, produces rather poor yields of the desired products.[4] This is mainly due to polymerization of the very reactive vinyl ketone under basic conditions, but other factors, including the fact that the intermediate Michael adduct and the original ketone have similar pK_a values and reactivities such that competitive reaction of the product with the vinyl ketone can ensue, may also be involved.

In 1973, Stork and Ganem[2] reported that under aprotic conditions, α-silylated vinyl ketones such as 3-triethylsilyl-3-buten-2-one participate in Michael additions with the lithium enolate of cyclohexanone to give, following cyclization of the product with ***Sodium Methoxide*** in methanol, the desired octalone in 80% overall yield (eq 1) (see also ***3-Trimethylsilyl-3-buten-2-one***). The silyl group is easily removed during the aldol cyclization step; removal occurs by nucleophilic attack on silicon, resulting in displacement of the ketone enolate. The corresponding reaction with methyl vinyl ketone itself gave less than 5% of the Michael addition product.[2]

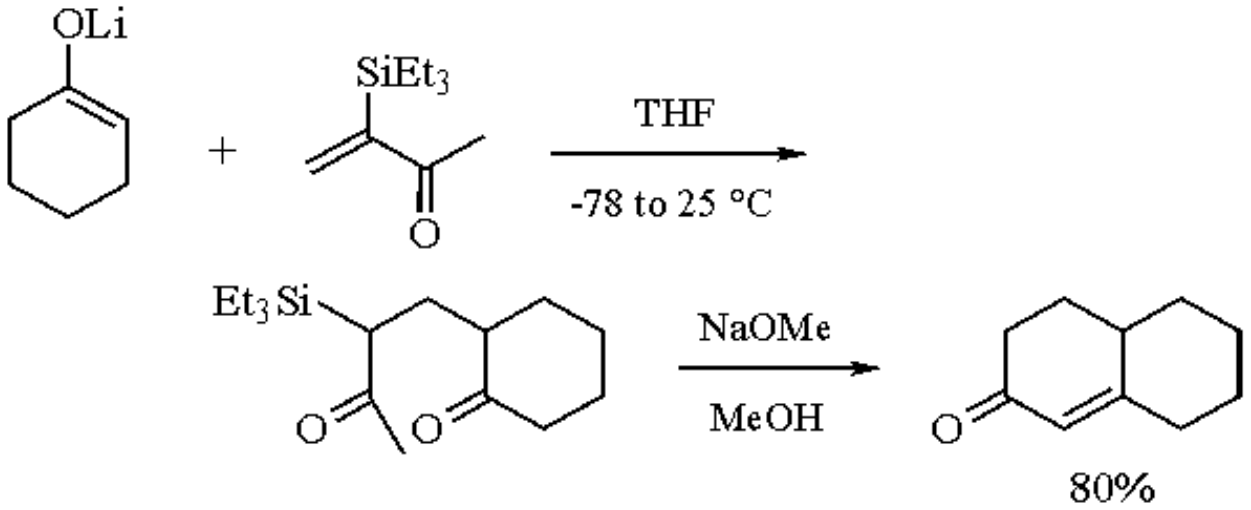

(1)

The annulation of 2-alkylcyclohexanones with methyl vinyl ketone and its homologs has also been examined. While condensation at the less substituted α-carbon can be effected using the corresponding enamines,[5] the basic conditions required for reaction at the more substituted α-carbon generally result in polymerization of the methyl vinyl ketone and low yields. This type of difficulty has been avoided with the use of alkyl halides instead of methyl vinyl ketone, but a number of steps are then required to transform the added alkyl group into the desired 3-ketoalkyl function.[6] Application of the 3-triethylsilyl-3-buten-2-one technology, via reaction with the potassium enolate of 2-methylcyclohexanone in *t*-butanol, produced the desired functionalized octalone in 60% yield following cyclization using a sodium hydroxide-isopropanol solution (eq 2).[2] The steric effect of the large triethylsilyl group may also play a role by preventing further unwanted reactions at the α-carbon of the Michael adduct.

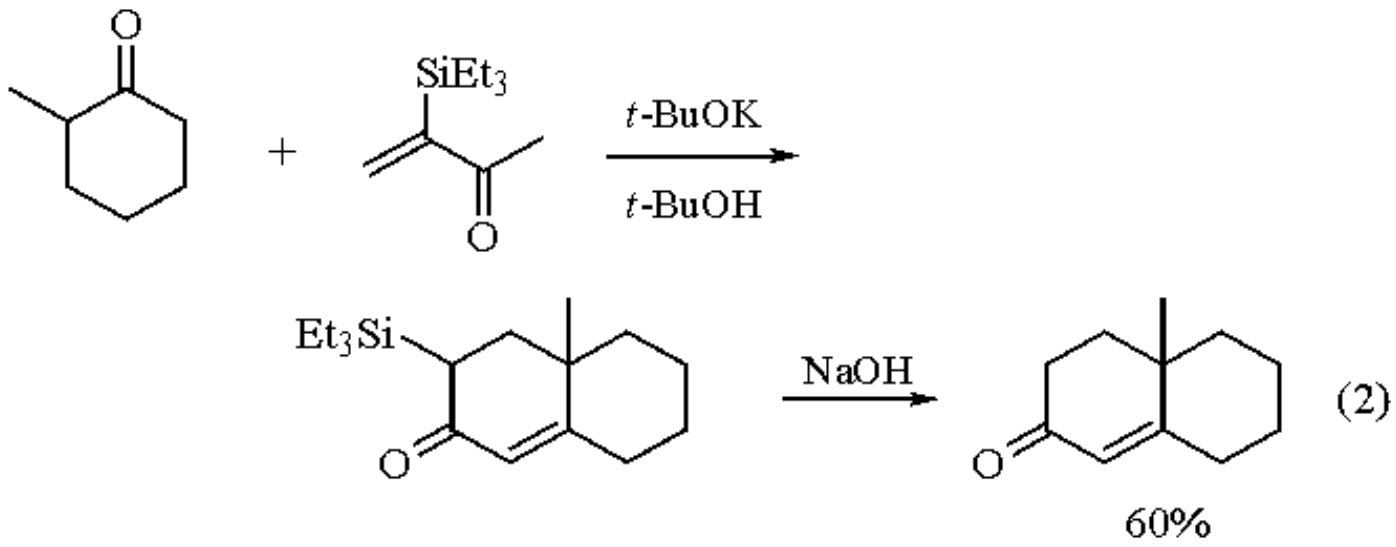

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Triethylsilyl Hydrotrioxide

$Et_3SiOOOH$

[101631-06-5] · $C_6H_{16}O_3Si$ · Triethylsilyl Hydrotrioxide · (MW 164.31)

(alkene oxidation, dioxetane formation[1])

Preparative Methods: addition of ***Triethylsilane*** (2 equiv) to a cold (-78 °C), saturated methylene chloride solution of ***Ozone*** (ca. 0.04 M) results in discharge of the color with formation of triethylsilyl hydrotrioxide within 45 s.[2]

Handling, Storage, and Precautions: is prepared in solution immediately before use. In methylene chloride at -78 °C, the half-life of the reagent has been estimated to be a few minutes.[2] Precautions appropriate for reactions which utilize or generate peroxides should be used.

Alkene Oxidation Reactions.

The reaction of triethylsilane with ozone and use of the intermediate triethylsilyl hydrotrioxide in oxidation reactions have been described. Initial oxidation reactions reported included the formation of the 9,10-endoperoxide from 9,10-dimethylanthracene (eq 1), and an allylic hydroperoxide from 2,3-dimethyl-2-butene (eq 2). Researchers also observed a near-IR emission from triethylsilyl hydrotrioxide as it decomposed at -60 °C, consistent with generation of singlet oxygen.[2] Other workers have characterized triethylsilyl hydrotrioxide by NMR spectroscopy and and measured the kinetics of its decomposition in deuterated acetone.[3]

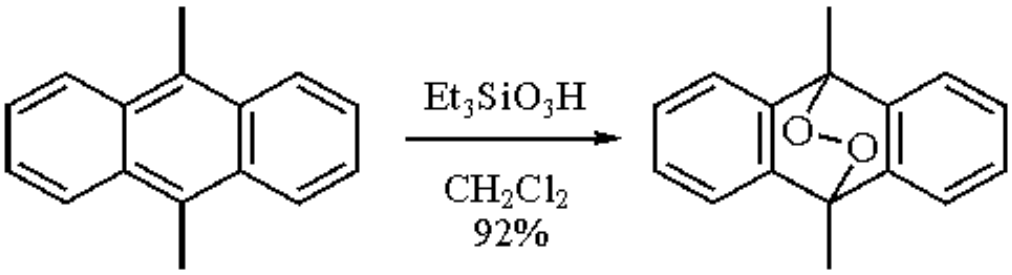

(1)

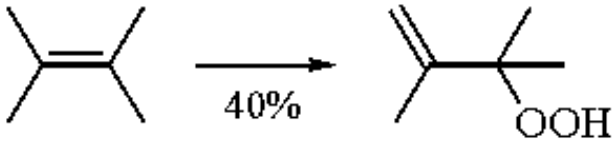

(2)

Subsequent work examined the use of triethylsilyl hydrotrioxide in alkene oxidations and found it to be effective in oxidative cleavage of unactivated terminal and internal alkenes into carbonyl fragments, and in formation of 1,2-dioxetanes from vinyl aromatics and vinyl ethers.[1,4-6] The results of this research indicated that the reaction proceeds via direct interaction of the alkene and triethylsilyl hydrotrioxide without the intermediacy of singlet oxygen. Allylbenzene reacted with triethylsilyl hydrotrioxide followed by ***Lithium Aluminum Hydride*** reduction to give 2-phenylethanol (eq 3). The same sequence of reactions gave 1-nonanol and 1,9-nonanediol in 64% and 74% yield, respectively, from methyl oleate (eq 4).[1] It has been noted in the cleavage of alkenes by triethylsilyl hydrotrioxide that the presence of an ether or ester function in the molecule results in improved yields, even when the oxygen function is remote from the double bond. Addition of diethyl ether or ethyl acetate does not improve the reactions of unsaturated hydrocarbons.[5]

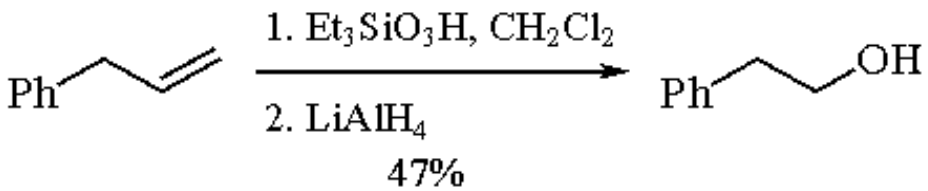

(3)

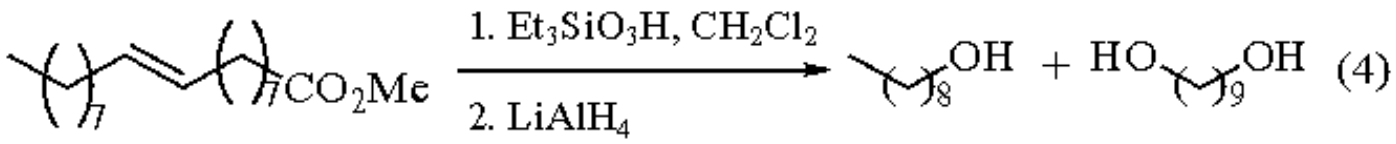

In the case of an enol ether derivative (eq 5), reaction with triethylsilyl hydrotrioxide produced an intermediate dioxetane which was cleaved to give 3-phenylpropionaldehyde upon warming. In contrast, reaction of the same enol ether with photochemically generated singlet oxygen proceeded via an ene pathway. After hydrolysis, this gave an α,β-unsaturated aldehyde in 37% yield.[1]

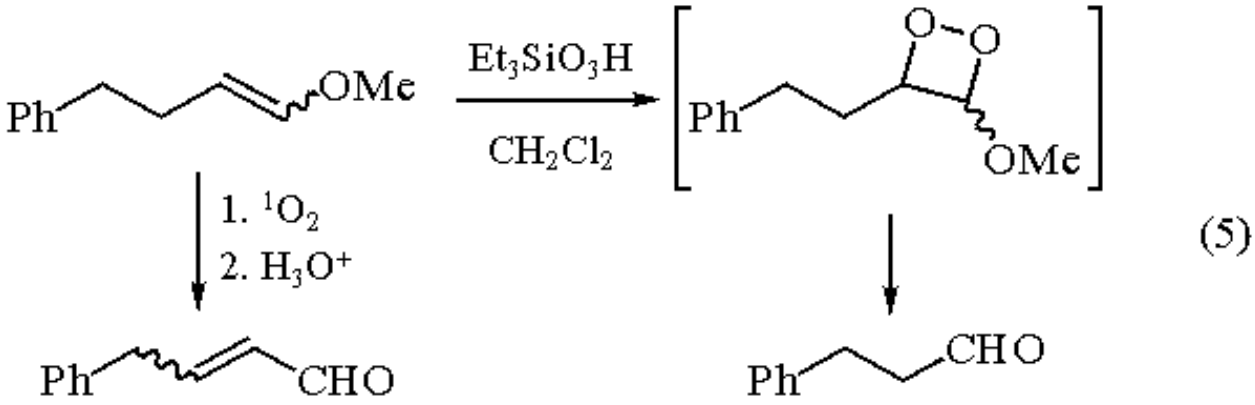

Reaction of triethylsilyl hydrotrioxide with a keto vinyl ether and subsequent rearrangement of the dioxetane intermediate resulted in formation of the 1,2,4-trioxane product in 58% overall yield (eq 6).[5] This model system for the naturally occurring antimalarial artemisin was similarly prepared in 48% yield using singlet oxygen.[7] Both singlet oxygen and triethylsilyl hydrotrioxide have been used in the synthesis of a regiospecifically oxygen-18 labeled model system.[6]

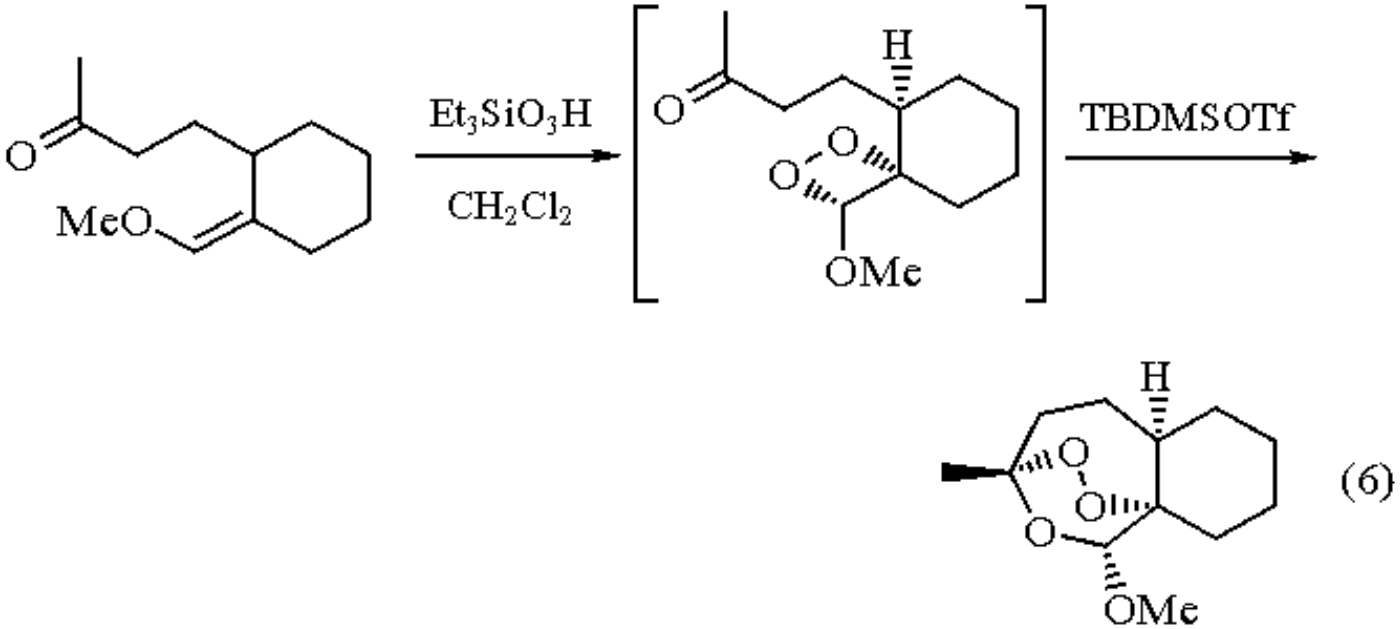

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3-Triethylsilyloxy-1,4-pentadiene

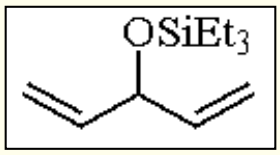

[62418-65-9] · $C_{11}H_{22}OSi$ · 3-Triethylsilyloxy-1,4-pentadiene · (MW 198.42)

(a masked vinyl ketone synthon;[7,8] a precursor for either the diene or dienophile in the intramolecular Diels-Alder reaction[2])

Physical Data: bp 140 °C; *n*20D 1.4390.

Solubility: sol pentane, benzene, THF, ether, CH_2Cl_2.

Analysis of Reagent Purity: NMR, GC (4.56 min on 1 mm 5% OV 225 on Chromosorb W at 108 °C) or TLC: R_f = 0.15 (pentane) or 0.6 (benzene).

Form Supplied in: commercially available.

Preparative Methods: by silylation of 3-hydroxy-1,4-pentadiene with ***Chlorotriethylsilane***.[1,2] Other relatives of the title compound are available by silylation with ***Chlorotrimethylsilane***[2] or ***t-Butyldimethylchlorosilane***.[3] 3-Trimethylsilyloxy-1,4-pentadiene is usually prepared and used in situ. Storage of 3-trimethylsilyl-1,4-pentadiene at -30 °C is recommended.[2] The dianion of the parent 3-hydroxy-1,4-pentadiene can also be prepared.[4]

Handling, Storage, and Precautions: use in a fume hood.

General Discussion.

3-Triethylsilyloxy-1,4-pentadiene may be used to prepare the useful 3-triethylsilyloxypentadienyl anion via metalation with ***s-Butyllithium*** (eq 1).[1,2]

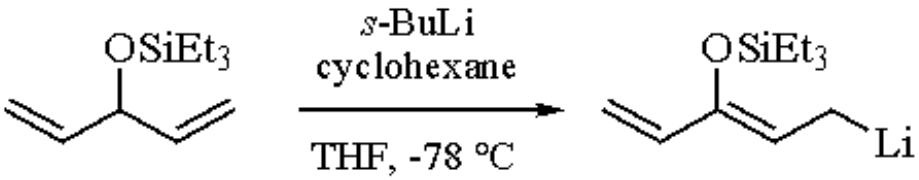

(1)

Reaction of the 3-triethylsilyloxypentadienyl anion with electrophiles is usually regioselective for the γ-adduct (eq 2 and Table 1).[2,5,7] This reaction provides a direct route to substituted dienes, as well as to vinyl ketones after hydrolysis. A representative procedure is as follows: a solution of 3-triethylsiloxy-1,4-pentadiene in THF was cooled to -78 °C and a solution of *s*-butyllithium in cyclohexane (1.1 equiv) was added dropwise over 30 min. The electrophile dissolved in THF was then added dropwise to the often yellow pentadienyl anion solution. The reaction mixture was stirred for 15 min and then quenched with saturated NH_4Cl solution and the product extracted with ether.

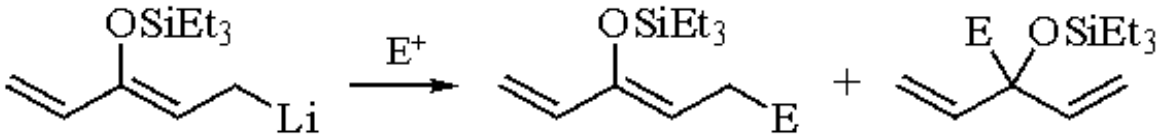

(2)

Table 1 Regioselective Reactions of 3-Triethylsilyloxy-1,4-pentadiene with Typical Electrophiles

Entry	Electrophile (E^+)	Yield (%)	Ratio γ to α product	Ref.
1	H_2O	87	100:0	2
2	TMSCl	89	100:0	2
3	MeCl	85	100:0	2
4	*i*-PrI	85	23:77	2
5	$PhCH_2Cl$	84	49:51	2
6	CH_2O	84	83:17	2
7	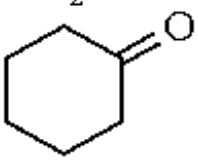	77	96:4	2
8	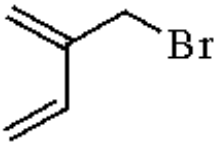	63	4:1	5
9	$PhSiMe_2Cl$	75	100:0	7

A wide variety of electrophiles may be used and the selectivity is based on kinetics. In some cases the products have been thermally interconverted (cf. entry 8, Table 1).[5,6] Because of polarity differences, the isomeric products usually can be separated by silica gel chromatography.

Elaboration of the alkylation products to give vinyl ketones may be accomplished with ***Potassium Fluoride*** in methanol at -10 to 0 °C or in *i*-PrOH at 25 °C (eq 3). For example, preparation of β-hydroxylethyl vinyl ketone synthons has been accomplished using a $PhMe_2Si$ unit as a masked hydroxyl group (eq 3).[7,8]

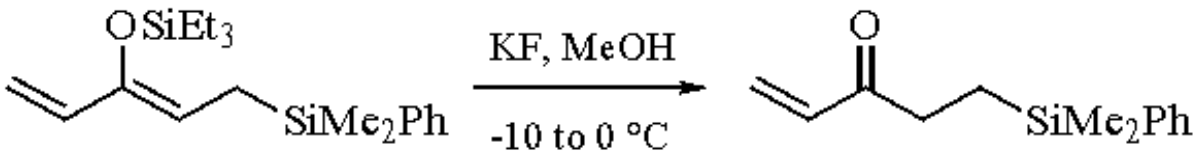

(3)

The method has been used to prepare intermediates for intramolecular Diels-Alder reactions (eqs 4 and 5).[2-6] The title reagent may provide ether the diene for the intramolecular Diels-Alder (eq 4)[4] or, after hydrolysis, the dienophile (eq 5).[3]

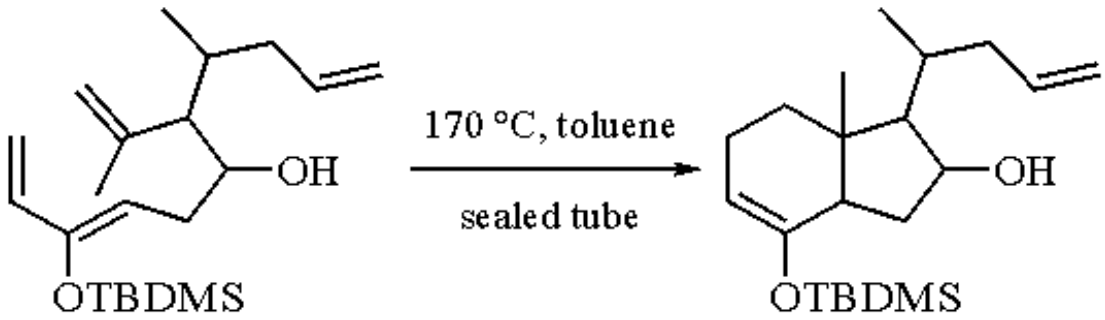

(4)

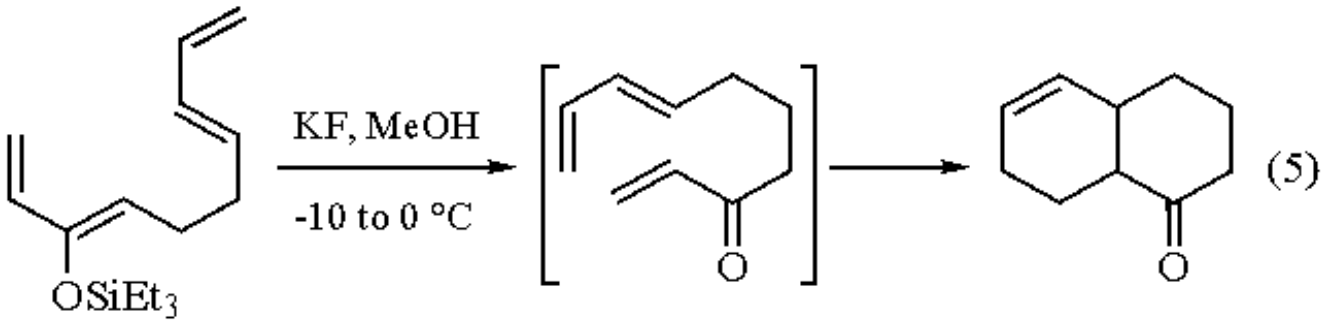

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Triethylsilyl Perchlorate

Et_3SiClO_4

[18244-91-2] · $C_6H_{15}ClO_4Si$ · Triethylsilyl Perchlorate · (MW 214.75)

(potent silylating agent; Lewis acid catalyst)

Physical Data: distillable colorless liquid, bp 45-46 °C/1 mmHg[1] or 43-45 °C/0.5 mmHg.[2]

Solubility: sol most organic solvents; CH_2Cl_2 is most commonly used

Preparative Methods: prepared from ***Chlorotriethylsilane*** using ***Silver(I) Perchlorate***[1] (eq 1) or from ***Triethylsilane*** by treatment with silver perchlorate[3] or ***Triphenylmethyl Perchlorate***[2] (eq 2). Of these methods, the trityl perchlorate procedure may be safer and more cost-effective.

$$Et_3SiCl \xrightarrow{AgClO_4} Et_3SiClO_4 \qquad (1)$$

$$Et_3SiH \xrightarrow[\text{or } AgClO_4]{Ph_3\overset{+}{C}\ \ ClO_4^-} Et_3SiClO_4 \qquad (2)$$

Handling, Storage, and Precautions: reacts rapidly with water and other protic solvents. As for any perchlorate derivative, appropriate precautions should be taken when handling or storing.

General Discussion.

Triethylsilyl perchlorate, a covalent silyl ester of perchloric acid, is a more reactive silylating agent than is chlorotriethylsilane. This is evidenced from the fact that the silyl perchlorate ester is cleaved rapidly and quantitatively by ***Sodium Borohydride***, while the chloride derivative requires the use of ***Lithium Aluminum Hydride*** (eq 3).[4]

$$Et_3SiClO_4 \xrightarrow[\text{dyglyme, rt}\ 100\%]{NaBH_4} Et_3SiH \qquad (3)$$

Wilcox and Babston reported that alkyl esters of aliphatic acids react with Et_3SiClO_4 in the presence of Hünig's base (***Diisopropylethylamine***) or ***2,2,6,6-Tetramethylpiperidine*** to provide (*Z*)-silyl ketene acetals selectively (eq 4).[5] The stereoselectivity of these reactions is dependent on a number of factors, including the nature of the base, the solvent polarity, and workup conditions. This procedure offers higher (*Z*) selectivity than does the usual deprotonation-silylation protocol using ***Lithium Diisopropylamide***/HMPA.

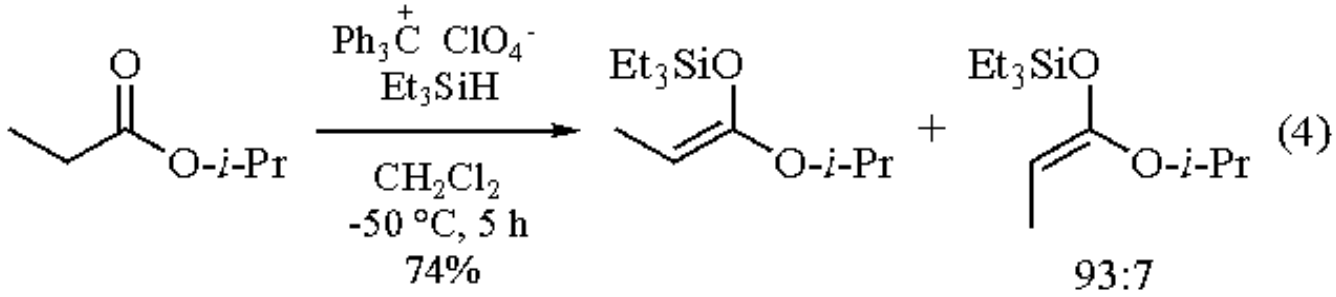

While alkyl esters generally undergo *O*-silylation in reactions with triethylsilyl perchlorate, ethyl diazoacetate was found to give exclusively the *C*-alkylation product (eq 5).[6] This procedure, which presumably involves the intermediacy of a diazonium perchlorate salt, affords higher yields of the α-silyl diazoester relative to other methods.

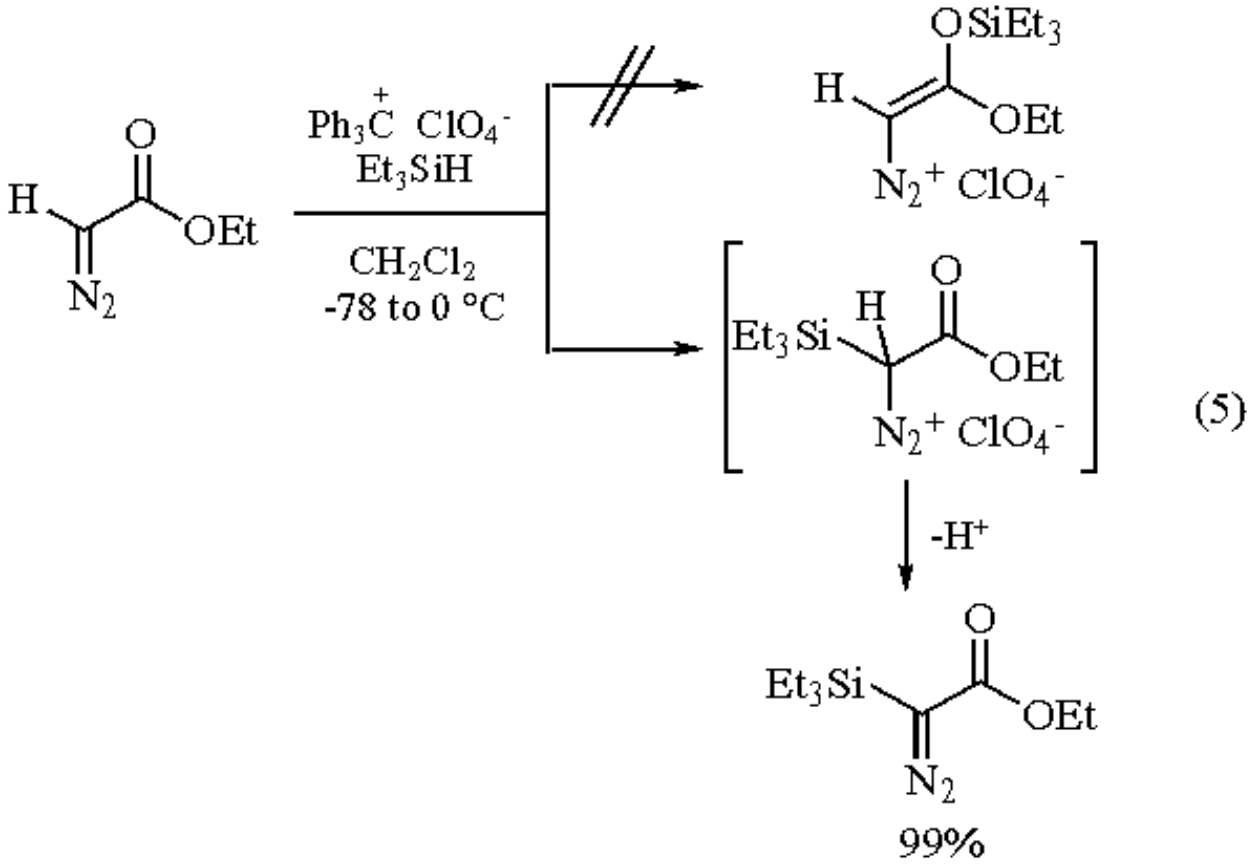

Triethylsilyl perchlorate has been shown to catalyze the Mukaiyama-Michael reaction of silyl ketene acetals with hindered α-enones, enabling 1,5-keto esters having contiguous quaternary centers to be prepared in high yield (eq 6).[7] Upon treatment of an equimolar mixture of unsubstituted and β,β-dimethyl silyl ketene acetals with the enone and a catalytic quantity of Et_3SiClO_4, only the more highly substituted adduct was obtained. To account for this, a mechanism was postulated in which the Lewis acid mediates the transfer of an electron from the silyl ketene acetal to the enone.

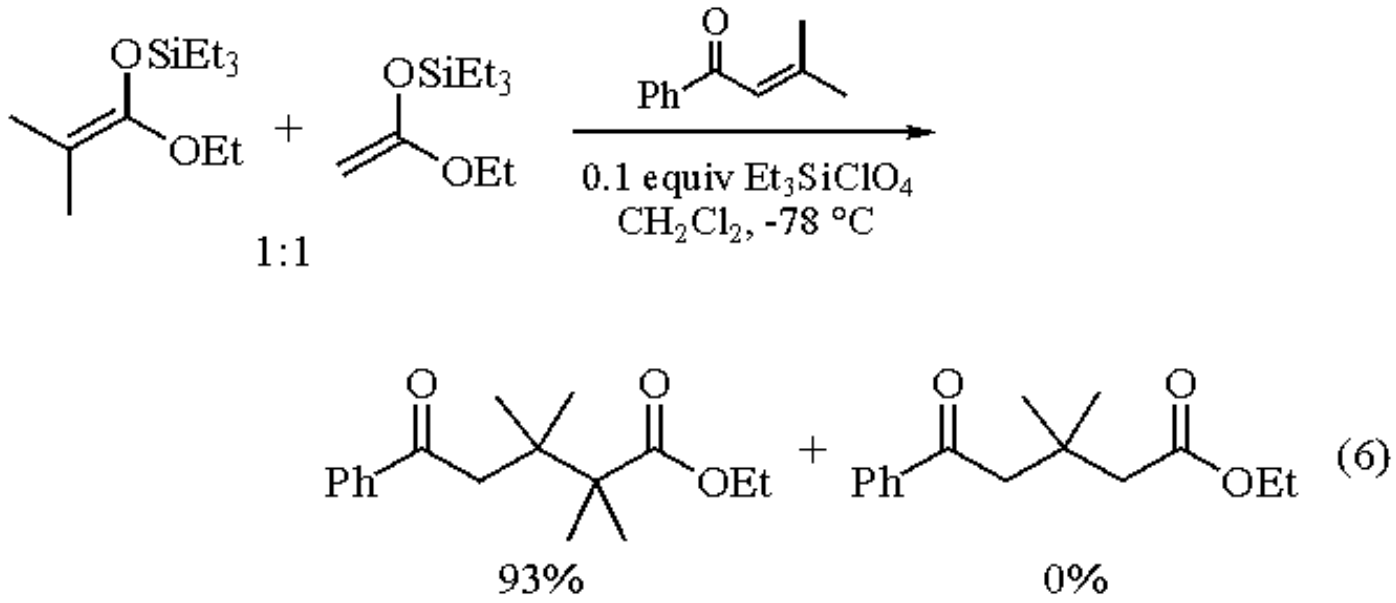

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(α-Triethylsilyl)propionaldehyde Cyclohexylimine

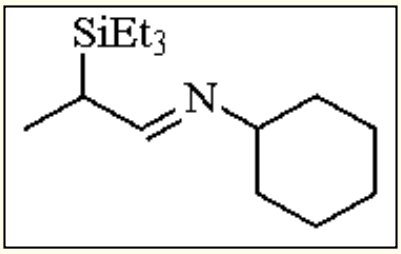

[119711-55-6] · $C_{15}H_{31}NSi$ · (α-Triethylsilyl)propionaldehyde Cyclohexylimine · (MW 253.56)

(reagent used for the selective formation of (*E*)-α-methyl-α,β-unsaturated aldehydes[1])

Physical Data: bp 84-86 °C/0.1 mmHg.

Solubility: sol THF, sol ether.

Analysis of Reagent Purity: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 6.7, 1H); 2.87 (tt, *J* = 10.6 and 4.1 Hz, 1H); 2.03 (pentet, *J* = 7.0 Hz, 1H); 1.82-1.20 (m, 10H); 1.16 (d, *J* = 7.0 Hz, 3H); 0.96 (t, *J* = 7.8 Hz, 9H); 0.60 (q, *J* = 7.9 Hz, 6H).[1]

Preparative Methods: prepared from propionaldehyde *N*-cyclohexylimine[1,2] by treatment with ***Lithium Diisopropylamide*** in THF at -78 °C for 30 min followed by the addition of ***Chlorotriethylsilane*** and gradually warming to 0 °C over a 3-4 h period.[2,3]

Purification: by fractional distillation.[1]

Handling, Storage, and Precautions: use in a well-ventilated fume hood.

Formation of (*E*)-α-Methyl-α,β-unsaturated Aldehydes.

The anions of α-silyl aldimines have been used to prepare unsaturated aldehydes by means of Peterson alkenation reactions.[4,5] The anions of α-trimethylsilyl- or α-triethylsilylpropionaldehyde *t*-butylimine are easily prepared by treatment of the silyl aldimine with LDA or ***s-Butyllithium*** (eq 1).[4]

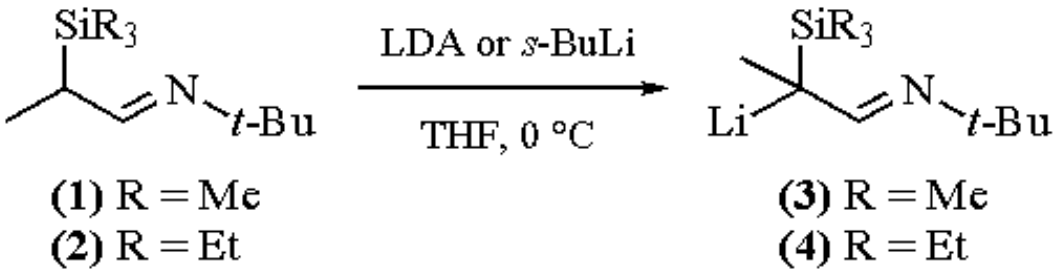

Condensation of the α-lithio species with aldehydes and ketones conveniently yields α,β-unsaturated aldehydes following hydrolysis of the intermediate unsaturated imines (eqs 2 and 3).[3,4]

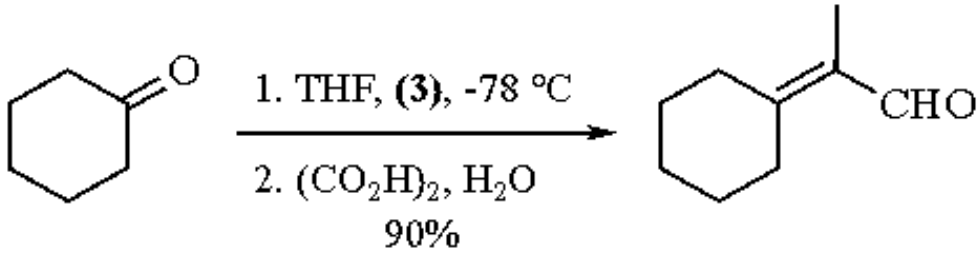

(2)

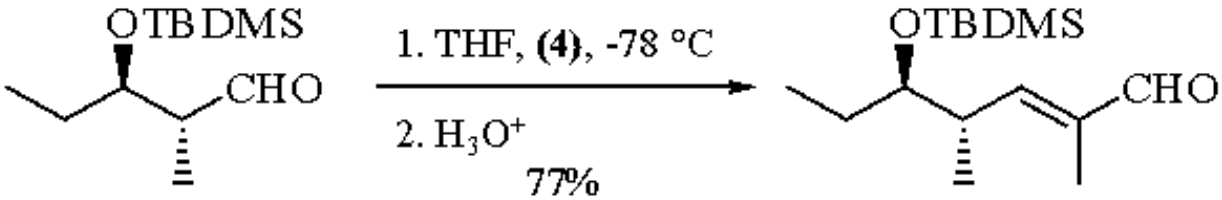

(3)

While the trimethyl and triethylsilyl aldimines (**1**) and (**2**) showed similar behavior in producing α,β-unsaturated aldehydes, the ability to isolate the triethylsilyl reagent (**2**) without contamination by the *N*-silyl enamine isomer makes it the preferred reagent.[3] Additionally, the replacement of the *t*-butylimine with a cyclohexylimine affords a reagent (**5**) which is easily purified by fractional distillation.[1] The anion of α-triethylsilylpropionaldehyde cyclohexylimine (**5**) is formed by the addition of *s*-BuLi in THF at -78 °C (eq 4).[1] This anion condenses with aldehydes to produce α-methyl-α,β-unsaturated aldehydes in good yield after hydrolysis (eq 4).

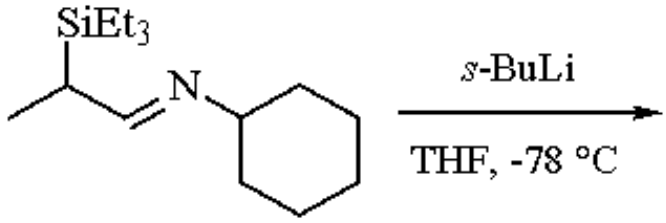

(5)

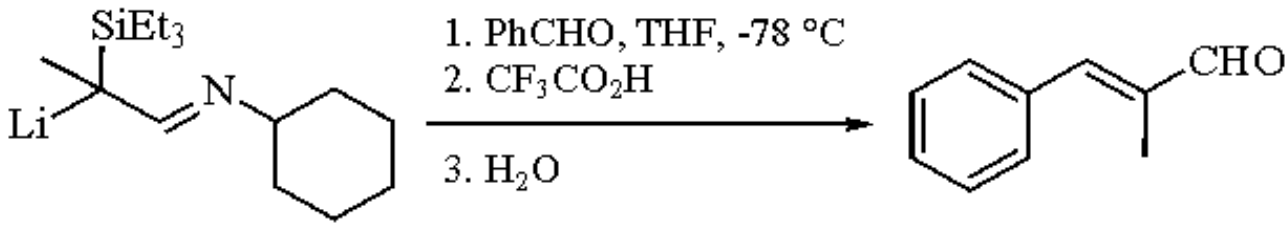

(4)

91%, *(E)*:*(Z)* = 100:1
[*(E)*:*(Z)* = 2:1 with $(CO_2H)_2$ workup]

The ratio of (*E*)- to (*Z*)-alkene products is dependent on the workup conditions. Addition of the α-silylaldimine anion to a carbonyl species gives a mixture of (*E*)- and (*Z*)-α-β-unsaturated imines, which upon hydrolysis with aqueous ***Oxalic Acid*** affords moderately selective formation of (*E*)-α,β-unsaturated aldehydes (eqs 4 and 5). Treatment of the mixture of imines with anhydrous ***Trifluoroacetic Acid*** in THF for a short period of time prior to aqueous hydrolysis serves to isomerize the imines and produce the *trans*-aldehyde with high selectivity (eqs 4 and 5).[1] The anhydrous trifluoroacetic acid workup protocol thus provides a highly selective method for the preparation of (*E*)-α-methyl-α,β-unsaturated aldehydes.[6]

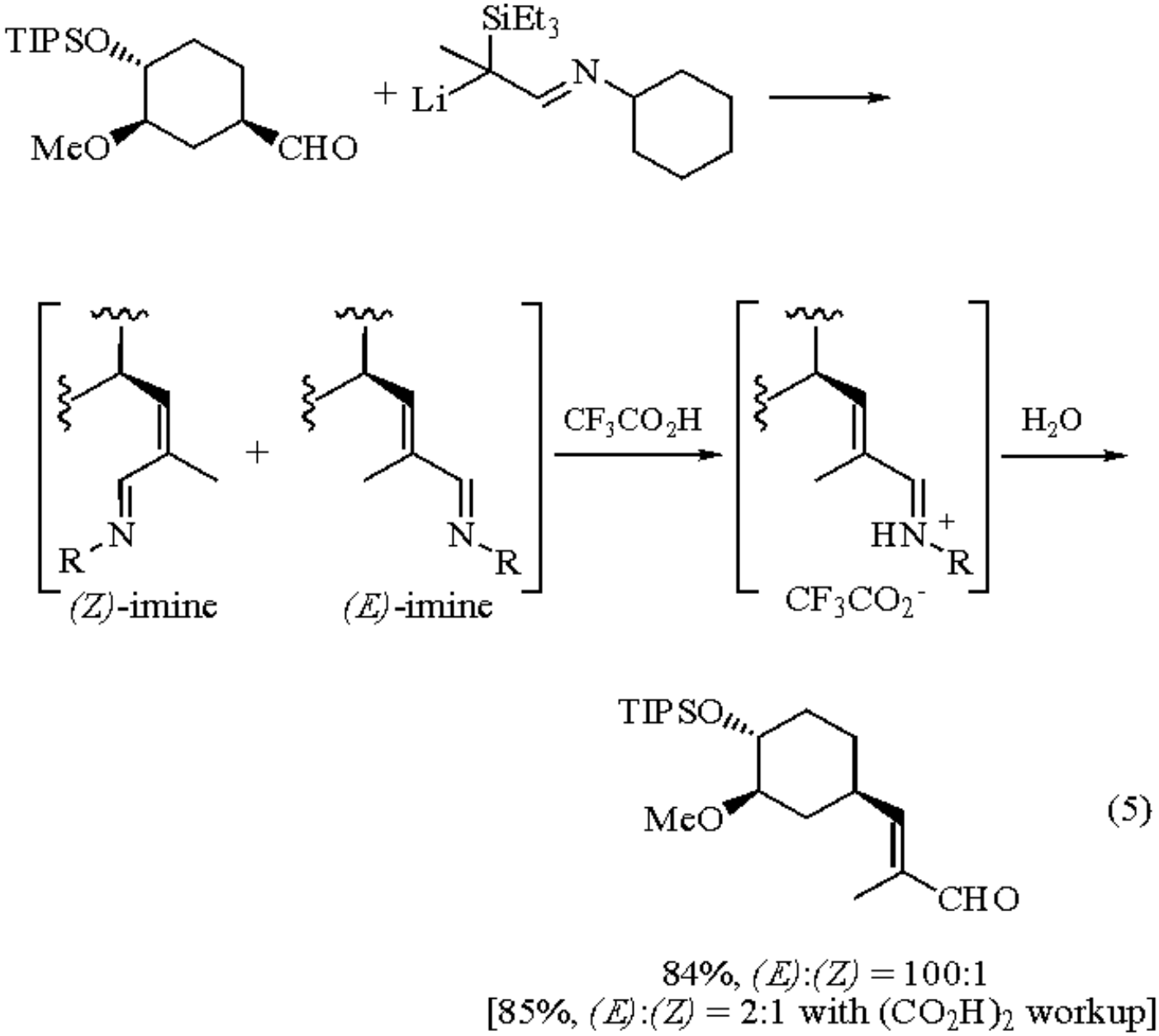

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Triethylsilyl Trifluoromethanesulfonate[1]

$Et_3SiOSO_2CF_3$

[79271-56-0] · $C_7H_{15}F_3O_3SSi$ · Triethylsilyl Trifluoromethanesulfonate · (MW 264.38)

(potent silylating agent;[2-4] Lewis acid catalyst)

Physical Data: 85-86 °C/12 mmHg; *d* 1.169 g cm^{-3}.

Solubility: readily sol hydrocarbons, dialkyl ethers, halogenated solvents. CH_2Cl_2 is employed most commonly. Reactions in 1,2-dichloroethane proceed faster than those in CCl_4 or Et_2O. Protic solvents and THF react with trialkylsilyl triflates and are therefore not suitable.

Form Supplied in: neat colorless liquid.

Preparative Methods: can be prepared by reacting ***Chlorotriethylsilane*** with ***Trifluoromethanesulfonic Acid*** followed by distillation.[1]

Handling, Storage, and Precautions: trialkylsilyl triflates are generally corrosive and moisture sensitive. Appropriate precautions should be taken to ensure that the reagent is handled and stored under rigorously anhydrous conditions.

Reactive Silylating Agent.

Triethylsilyl ethers are generally more stable towards hydrolysis than are trimethylsilyl ethers, and consequently the Et_3Si moiety has gained increasing use as a protecting group for alcohols. However, since it is often difficult to silylate sterically hindered hydroxyl groups using Et_3SiCl, ***Triethylsilyl Perchlorate*** and triethylsilyl triflate (Et_3SiOTf) were introduced to overcome this problem. Although both reagents are much more potent than Et_3SiCl, the triflate is considered to be safer than the perchlorate and is more convenient because it is commercially available.

Secondary and tertiary alcohols can be silylated under mild conditions using Et_3SiOTf and ***2,6-Lutidine*** or a trialkylamine as a proton scavenger (eqs 1 and 2).[2-4]

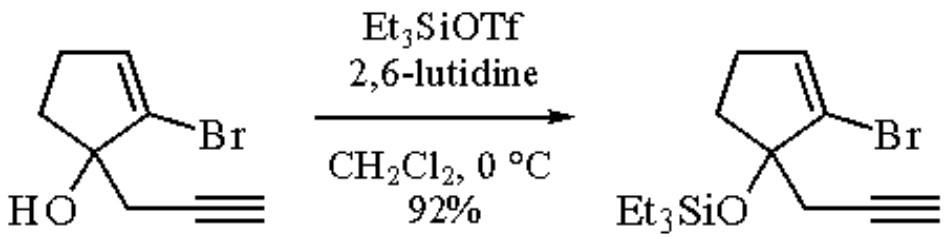

(1)

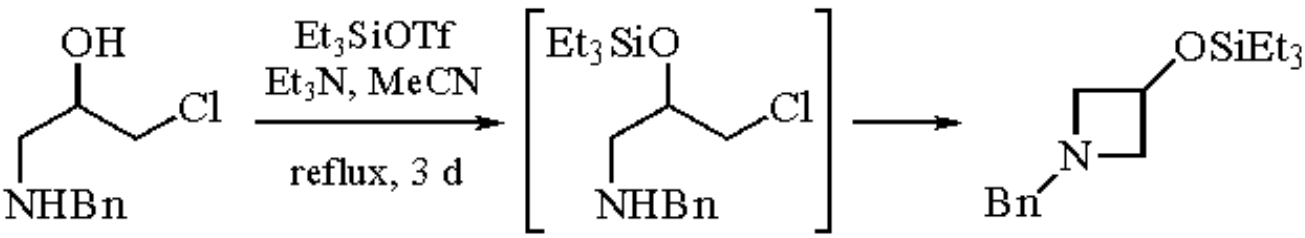

(2)

Silyl enol ethers can be conveniently prepared by treatment of ketones with Et_3SiOTf and ***Triethylamine*** (eq 3).[1,5] Similarly, esters can be converted to silyl ketene acetals; however, large amounts of the *C*-silylated product may also be isolated (eq 4).[1,6,7] Equilibration of *O*- and *C*-silylated products may occur in the presence of catalytic amounts of Et_3SiOTf.[1]

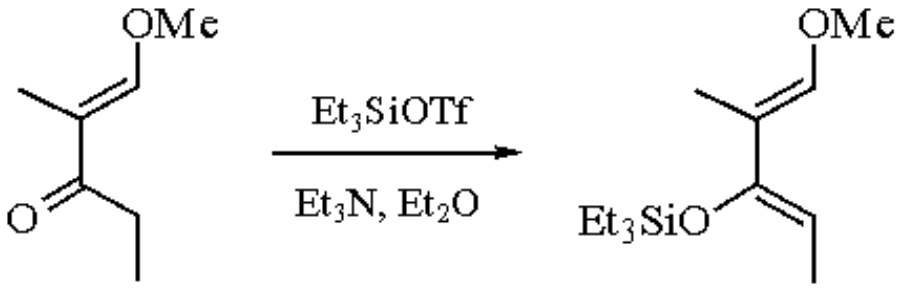

(3)

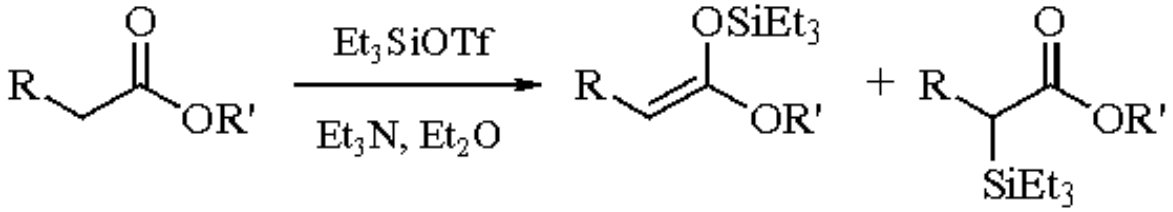

(4)

α-Diazo esters react with Et_3SiOTf and Hünig's base (***Diisopropylethylamine***) to give exclusively α-silyl-α-diazo esters, which can be converted to other silylated compounds by loss of dinitrogen (eq 5).[8]

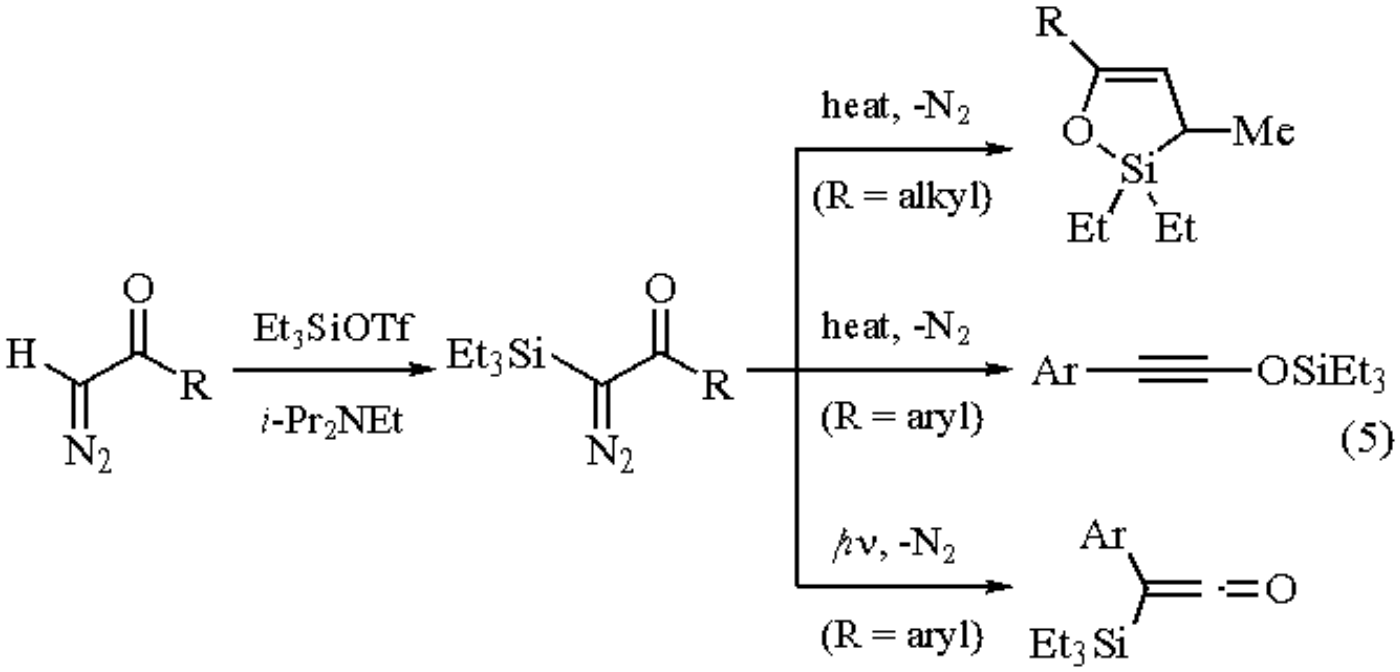

(5)

Nitroalkanes have been shown to give α-siloxy *O*-silyloximes upon reaction with two molar equivalents of the silylating agent (eq 6).[9] The reaction is believed to proceed via a nitrogen-to-carbon 1,3-silyloxy rearrangement.

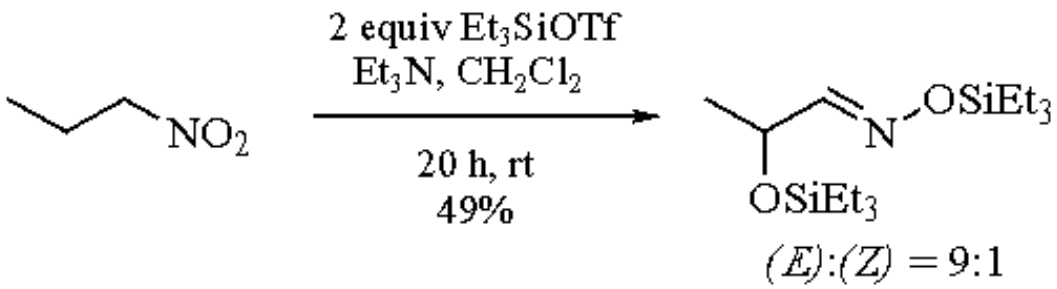

(6)

Linderman and Ghannam have utilized Et_3SiOTf to trap the alkoxide formed from the addition of stannyl anion to aldehydes (eq 7).[10] Upon treatment with excess ***n-Butyllithium***, these adducts undergo a reverse Brook rearrangement to afford α-hydroxysilanes.

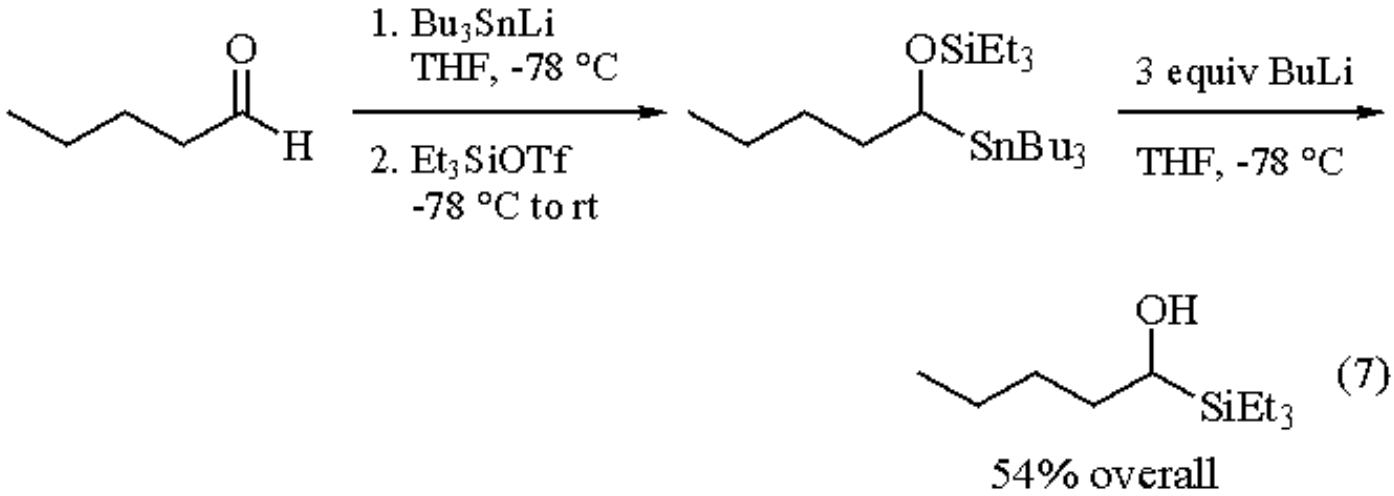

Lewis Acid Catalyst.

Jefford has reported that condensation reactions of 2-trimethylsiloxyfuran with aldehydes can be catalyzed by Et_3SiOTf to give mainly the *threo* addition product (eq 8).[11] Conversely, the *erythro* adduct is favored when fluoride ion is used as the catalyst.

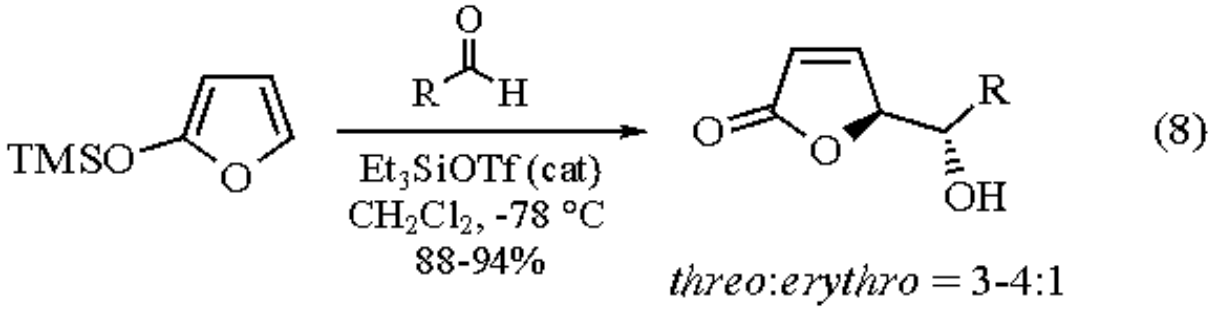

Fraser-Reid has reported that an equimolar mixture of ***N-Iodosuccinimide*** and Et_3SiOTf efficiently promotes the glycosylation of hindered glycoside donors with *n*-pentenyl glycoside acceptors (eq 9).[12]

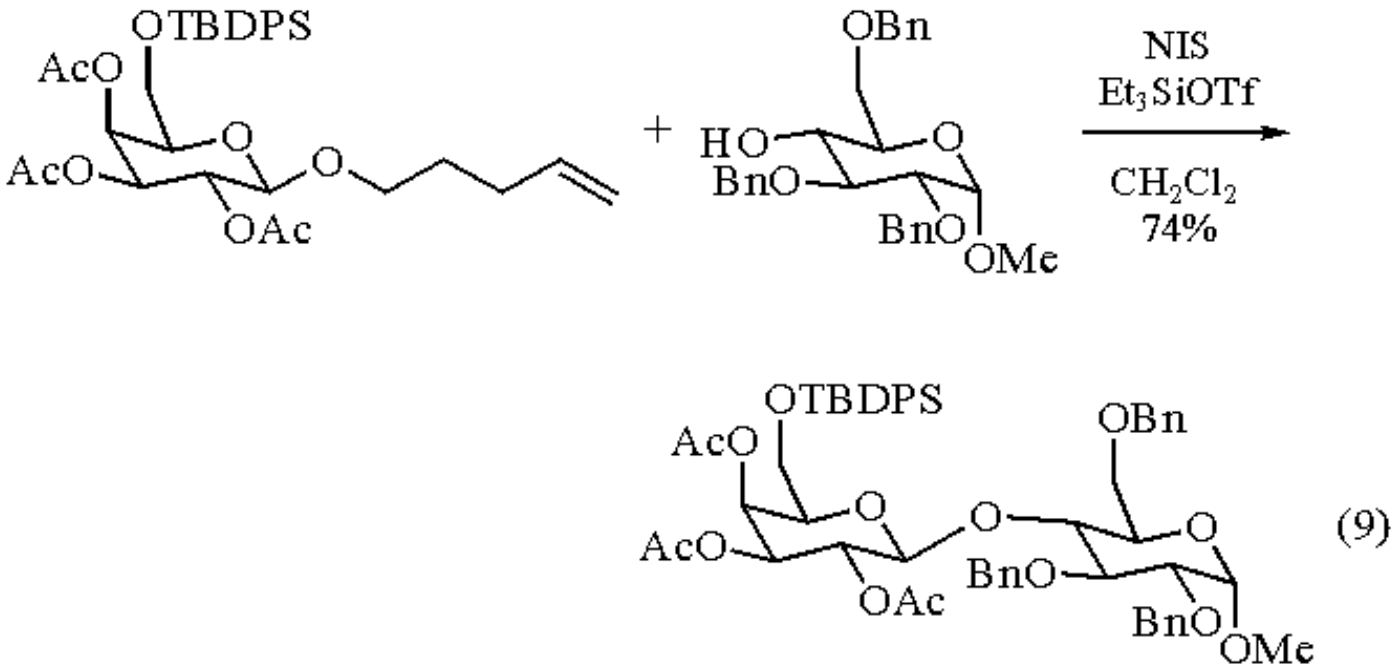

Related Reagents.

Chlorotriethylsilane; ***Triethylsilyl Perchlorate***; ***Trimethylsilyl Trifluoromethanesulfonate***.

1. Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *S* **1982**, 1.
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Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate[1]

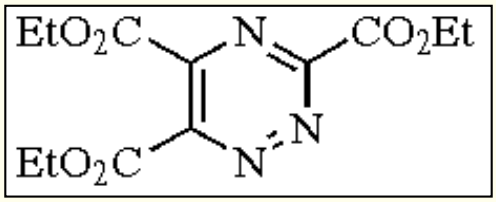

[74476-38-3] · $C_{12}H_{15}N_3O_6$ · Triethyl 1,2,4-Triazine-3,5,6-tricarboxylate · (MW 297.30)

(electron-deficient heteroaromatic azadiene capable of participation in inverse electron demand Diels-Alder reactions employed for the preparation of substituted pyridines)

Physical Data: bp 168-169 °C/1 mmHg, 173 °C/3 mmHg; *n*26D = 1.4949.

Solubility: sol $CHCl_3$, EtOAc, Et_2O; insol H_2O.

Form Supplied in: viscous, yellow oil.

Preparative Methods: a solution of ethyl oxalamidrazonate (88 mmol) in absolute EtOH (350 mL) is added dropwise to a stirring solution of diethyl dioxosuccinate (114 mmol) in absolute EtOH (86 mL) at 25 °C under N_2. After addition is complete, the stirring is allowed to continue at 25 °C for 16 h before the solution is warmed at reflux for 2 h. The reaction mixture is cooled and the solvent is removed under reduced pressure. Chromatography (SiO_2, 10-40% Et_2O-hexane gradient elution) affords the pure reagent.[2]

Handling, Storage, and Precautions: can be stored at 25 °C but is hygroscopic and reacts with protic solvents; should be stored under anhydrous conditions.

Cycloaddition Reactions.

Triethyl 1,2,4-triazine-3,5,6-tricarboxylate (**1**) is a highly electron-deficient heteroaromatic azadiene capable of participation in inverse electron demand Diels-Alder reactions with a variety of electron-rich dienophiles[1] including enamines (eq 1),[3] ketene-*N*,*O*-acetals (eq 2),[4] alkynes (eq 3),[5] benzynes,[6] benzocyclopropenes (eq 4),[7] and indoles (eq 5).[8] The reaction is regioselective with the cycloaddition occurring across C-3/C-6 of the 1,2,4-triazine nucleus with the more nucleophilic carbon of the electron-rich dienophile preferentially attaching to C-3 of 1,2,4-triazine (eqs 1 and 2).[3,4] A decrease or loss of regioselectivity is observed when the reacting sites in the dienophile become electronically and sterically less distinguishable (eqs 3 and 5).[5-8] The reaction is accompanied by a retro Diels-Alder reaction with loss of N_2 and in situ aromatization, constituting a general approach to the preparation of substituted pyridines (eqs 1-5). The methodology has been successfully applied (eq 6) in the total syntheses of streptonigrin (**2**),[9] and lavendamycin (**3**).[10]

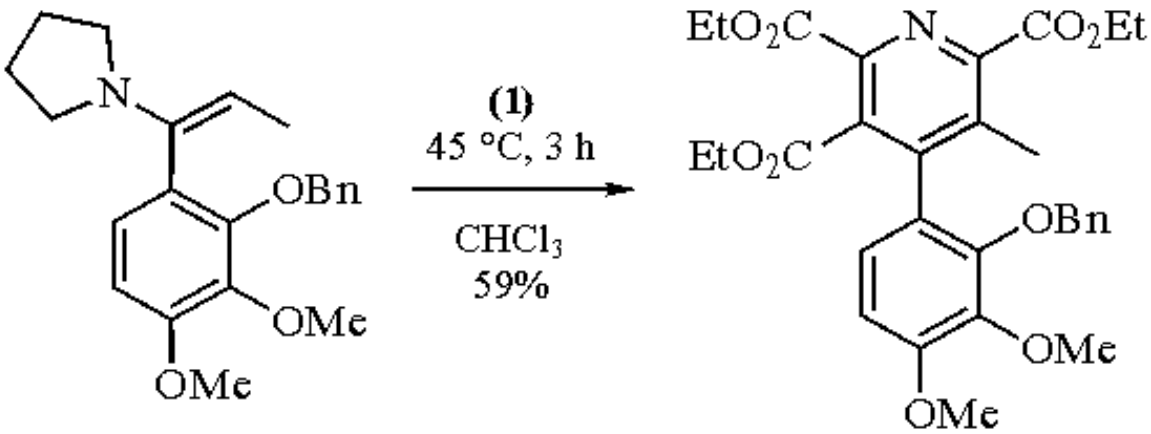

(1)

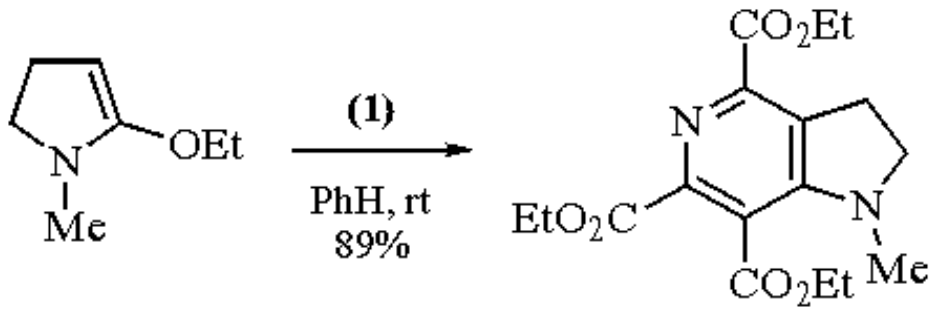
(1)
PhH, rt
89%
OEt
N
Me
CO2Et
EtO2C
CO2Et
N
Me

(2)

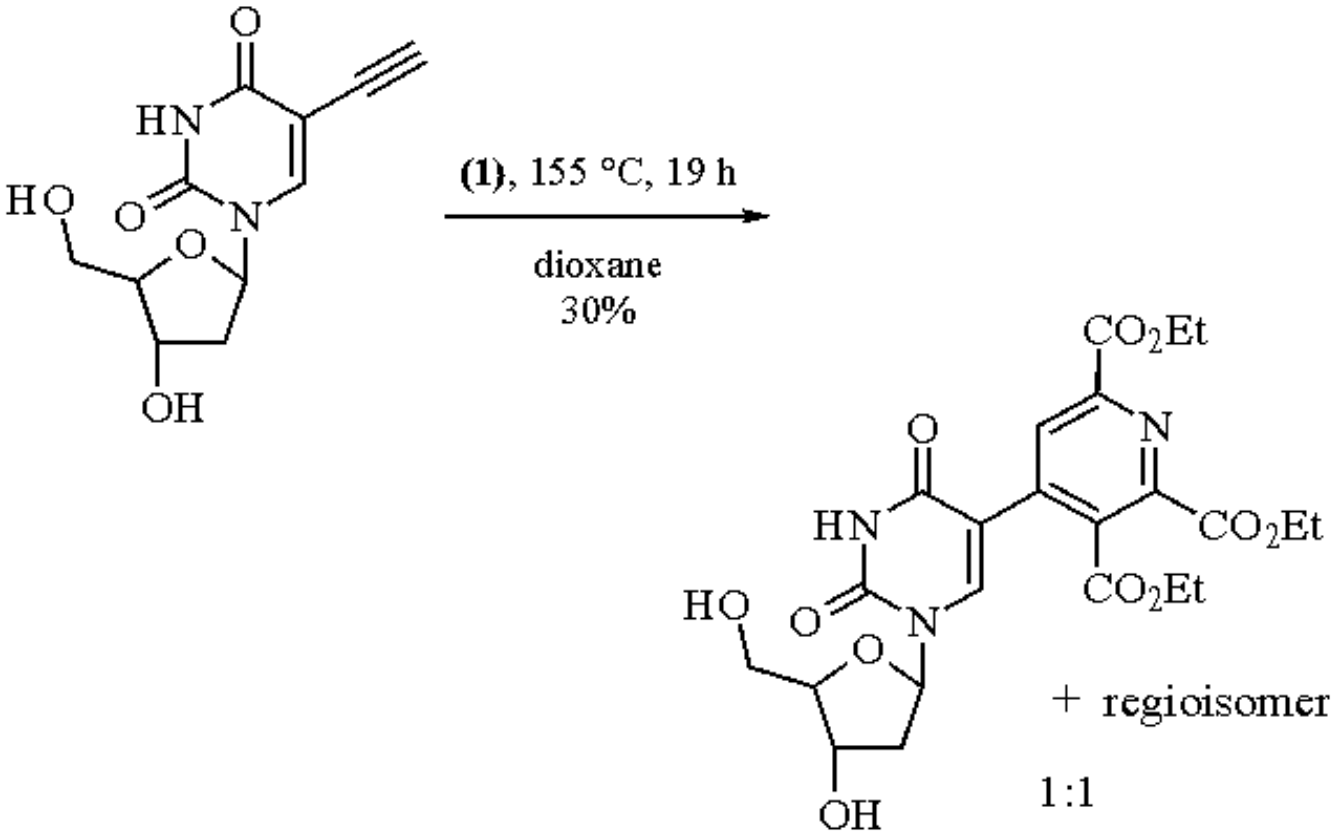
(1), 155 °C, 19 h
dioxane
30%
HN
HO
OH
CO2Et
CO2Et
CO2Et
+ regioisomer
1:1

(3)

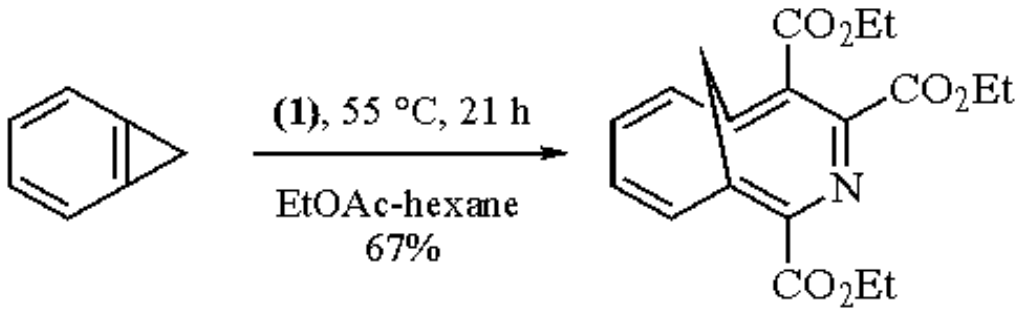
(1), 55 °C, 21 h
EtOAc-hexane
67%
CO2Et
CO2Et
CO2Et

(4)

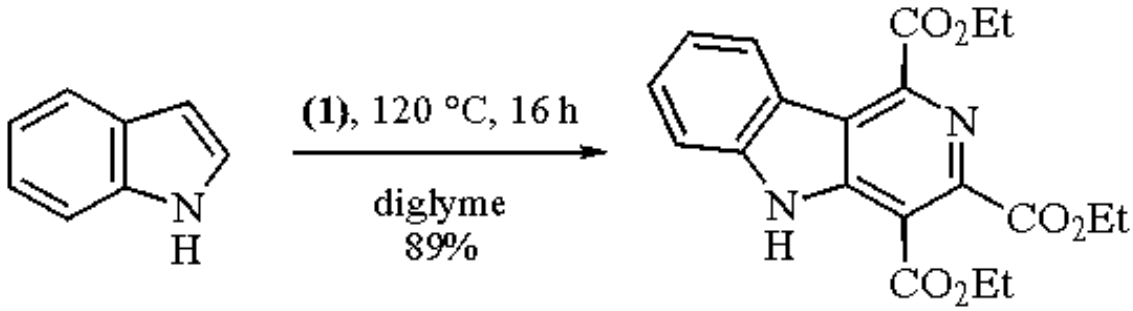
(1), 120 °C, 16 h
diglyme
89%
N
H
CO2Et
CO2Et
CO2Et

(5)

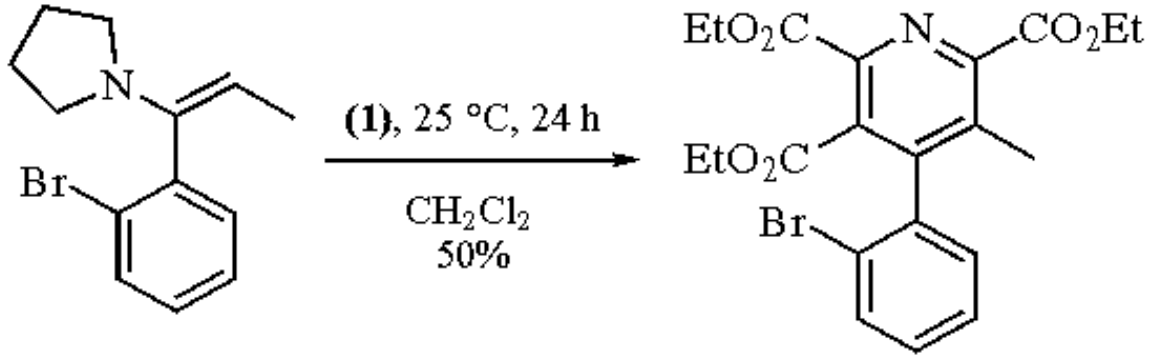

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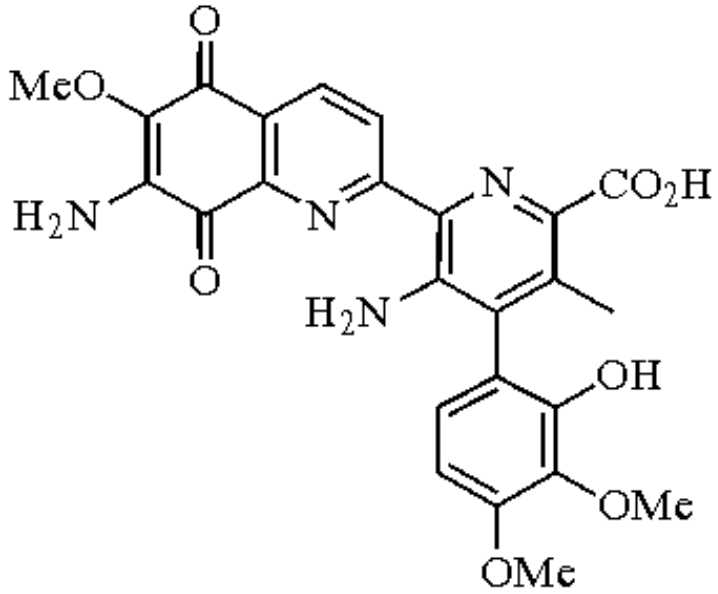

(2) Streptonigrin

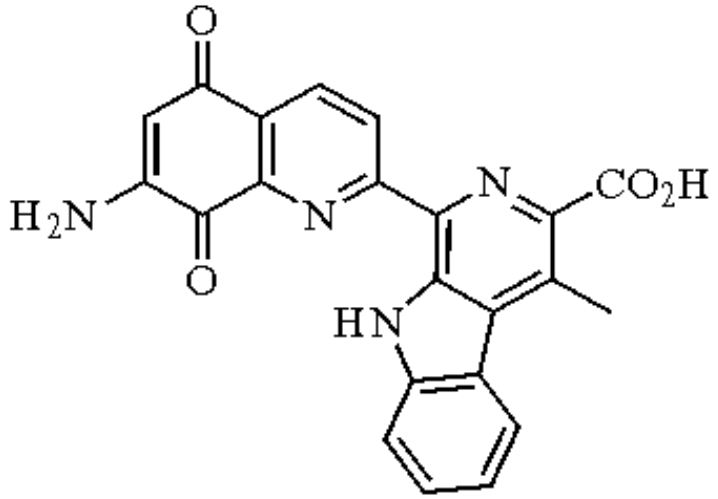

(3) Lavendamycin

Related Reagents.

Dimethyl 1,2,4,5-Tetrazine-3,6-dicarboxylate; ***3,6-Diphenyl-1,2,4,5-tetrazine***; ***1,3,5-Triazine***; ***1,2,4-Triazine***.

---

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Dale L. Boger & Minsheng Zhang

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Trifluoroacetic Acid

CF_3CO_2H

[76-05-1] · $C_2HF_3O_2$ · Trifluoroacetic Acid · (MW 114.03)

(solvent; acid catalyst for diverse organic transformations, including solvolysis,[9] rearrangements,[3] reductions,[17] oxidations,[22] and trifluoromethylation[8,16])

Alternate Name: TFA.

Physical Data: [1] freely flowing clear liquid, mp -15.4 °C, bp 72 °C; pK_a 0.23 (25 °C, H_2O); *d* 1.480 g cm^{-3}. Trifluoroacetic acid and water form an azeotrope, bp 105.5 °C, 20.8% water.

Solubility: miscible with water and most organic solvents, but has limited solubility in alkanes (with more than six carbons) and carbon disulfide.

Form Supplied in: neat liquid; commercially available.

Purification: distilled from traces of $(CF_3CO)_2O$ or P_2O_5; $KMnO_4$ has caused *serious explosions*.[33]

Handling, Storage, and Precautions: [2] is a strong organic acid. It is extremely corrosive and especially destructive to tissue of mucous membranes. Inhalation is a major hazard. Use of a NIOSH/MSHA approved respirator is recommended. Use in a fume hood with gloves and protective clothing to avoid contact. TFA is hygroscopic. Listed incompatibilities include oxidizing and reducing agents; however, literature references report the use of both types of reagents with TFA. TFA should never be mixed with basic solvents or acid-sensitive materials. The acute toxicity of TFA is low.

Acid-Catalyzed Rearrangements.

There are many examples of rearrangements catalyzed by TFA, including acid-catalyzed epoxide ring opening (eq 1),[3] biomimetic cyclizations (eq 2),[4] Cope rearrangements (eq 3),[5] and natural product synthesis (eq 4).[6] The cited references are given as examples; a comprehensive listing is beyond the scope of this publication. Often these reactions are initiated through protonation and dehydration to provide a cationic intermediate for cyclization. TFA is a general catalyst for most acid-catalyzed rearrangements. The physical properties of TFA may provide benefits over alternative acids. The volatility of this catalyst will allow product isolation by simple solvent evaporation. Less volatile alternatives, such as ***Sulfuric Acid*** or ***p-Toluenesulfonic Acid***, may require neutralization or an extractive workup. Owing to the low nucleophilicity of trifluoroacetate anion, TFA has been used as a solvent for basic research into solvolysis mechanisms.[7]

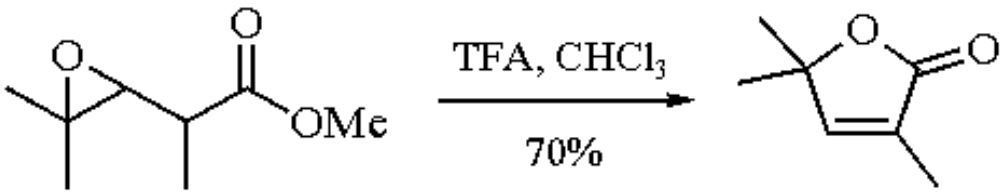

(1)

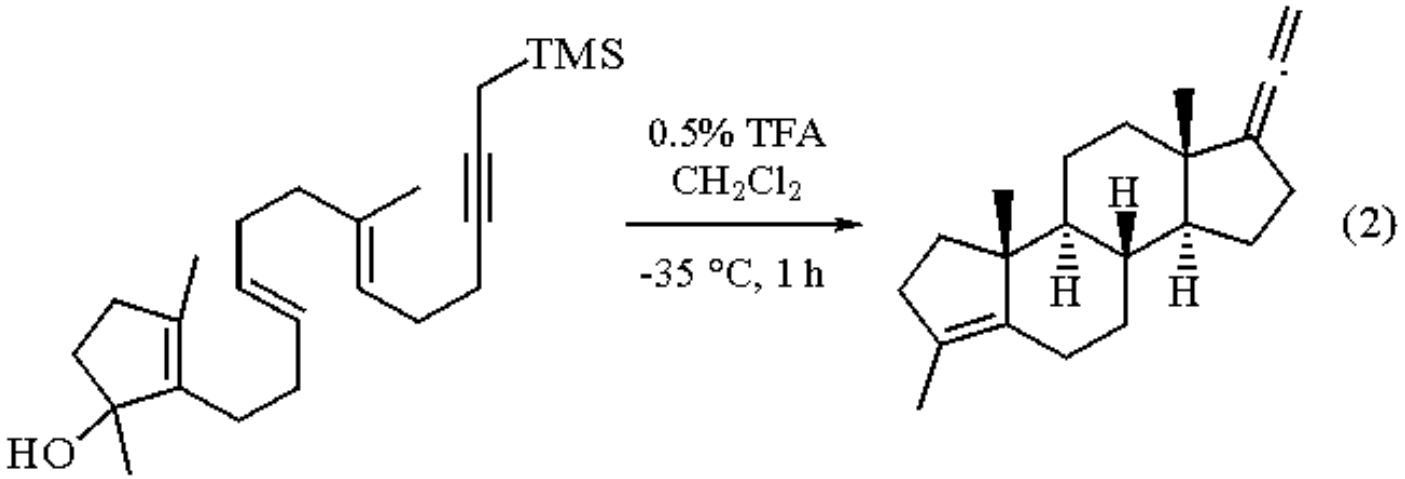

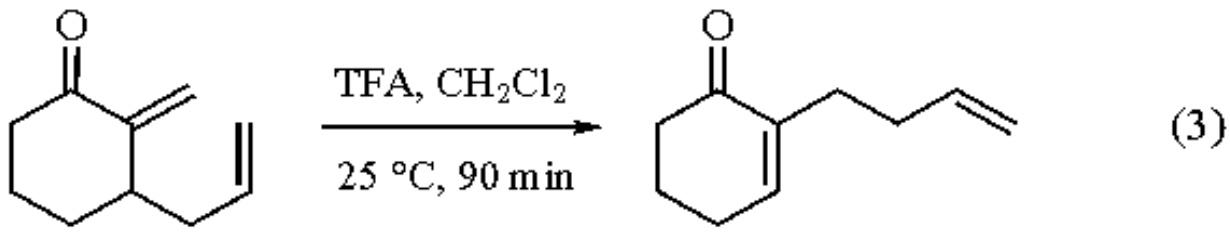

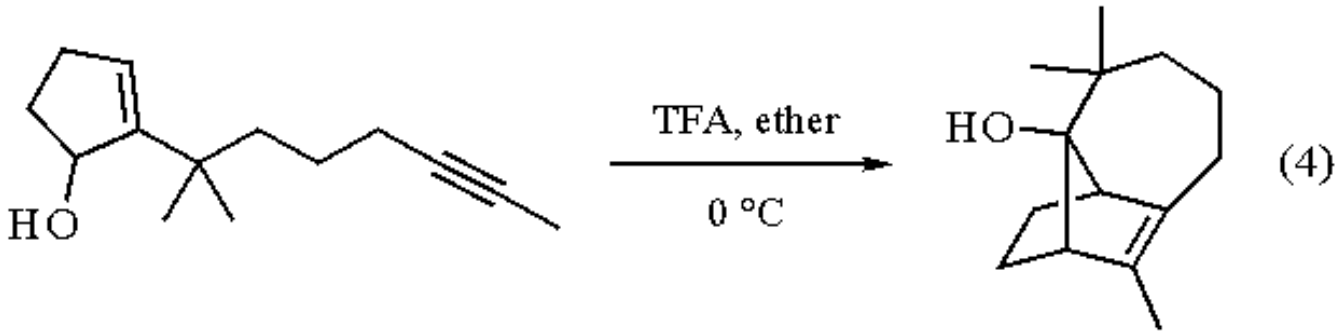

Synthesis of Trifluoromethyl Organic and Organometallic Compounds.

The reaction of TFA with Grignard reagents is general for the formation of trifluoromethyl ketones (eq 5).[8] The reaction is useful only with readily available Grignard reagents, as 1 equiv of organometallic reagent is consumed deprotonating TFA. The best yields are obtained using 2.5-3.0 mol of Grignard reagent per equiv of TFA. Phenyl, alkynyl, and normal alkyl Grignard reagents give superior results. Strongly reducing Grignard reagents, such as ***Isopropylmagnesium Bromide***, tend to produce trifluoromethyl alcohols from reduction of the initially formed ketone.

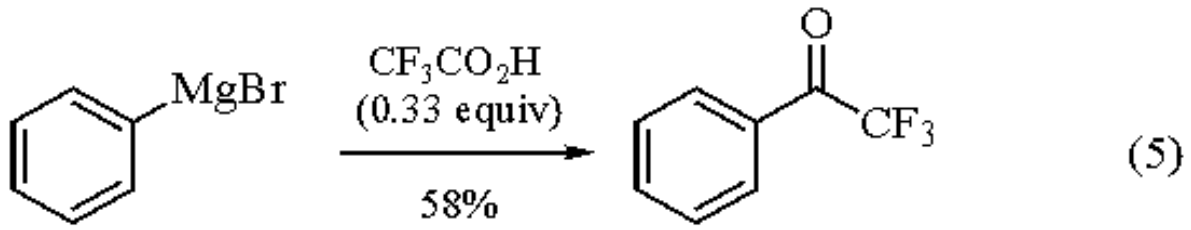

The condensation of ***Mercury(II) Oxide*** with 2 mol of TFA produces ***Mercury(II) Trifluoroacetate***. Thermal decarboxylation in the presence of carbonate followed by sublimation yields bis(trifluoromethyl)mercury.[9] Treatment of bis(trifluoromethyl)mercury with Cu^0 in NMP or DMA produces a stable trifluoromethylcopper reagent.[10] Addition of an aromatic or benzylic halide leads to displacement and incorporation of the trifluoromethyl group (eq 6). Alternatives for the introduction of a trifluoromethyl group as a nucleophile are limited. The trifluoromethyl derivatives of lithium and magnesium are unknown, probably due to fluoride elimination to produce difluorocarbene.[11] Bis(trifluoromethyl)mercury has been used to synthesize trifluoromethyl organometallic derivatives of germanium,[12] tin,[13] zinc,[14] and cadmium.[15]

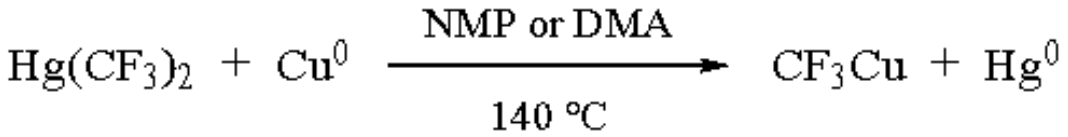

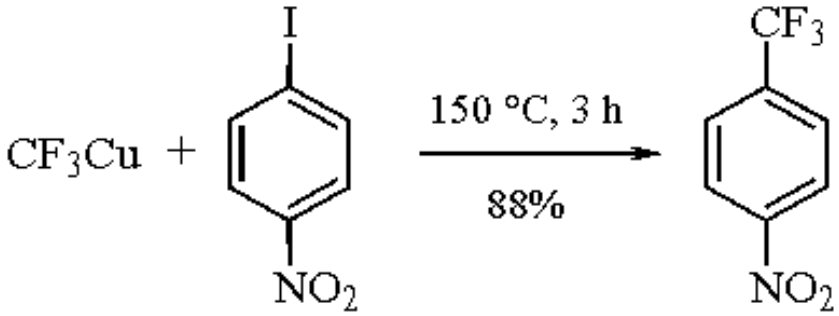

(6)

Direct trifluoromethylation of electron-poor aromatic and heterocyclic systems can be accomplished by treatment with TFA and ***Xenon(II) Fluoride***.[16] The initial reaction is thought to produce $Xe(O_2CCF_3)_2$ which undergoes decomposition to yield carbon dioxide, xenon, and trifluoromethyl radicals. Aromatic and heterocyclic compounds can react with the trifluoromethyl radicals, often with a high degree of selectivity. Yields of trifluoromethylated products vary between good to moderate, but the reaction allows entry into structures that would otherwise be difficult to synthesize. The chemistry has been extended to heterocyclic systems, as demonstrated with an intermediate reaction in the production of 5-(trifluoromethyl)-2´-deoxyuridine, a known antiviral compound (eq 7).[16]

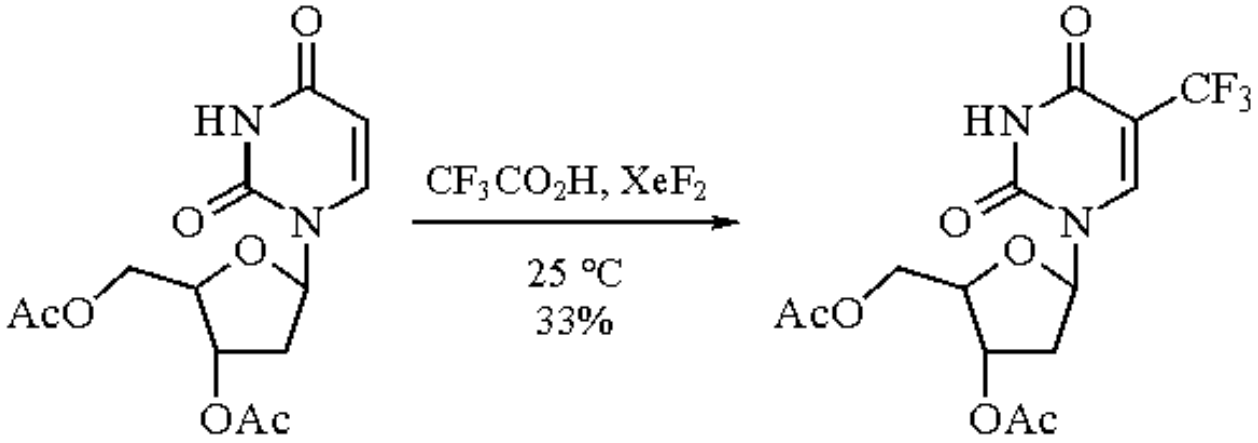

(7)

Reductions with Boron and Silicon Hydrides.

Sodium Borohydride,[17] ***Sodium Cyanoborohydride***,[18] ***Borane-Tetrahydrofuran***,[19] and ***Triethylsilane***[20] have been used in conjunction with TFA to reduce a variety of functional groups. These reactions generally proceed by protonation of a functional group followed by delivery of hydride.

Of special note is the reduction of cobalt-complexed secondary α-alkynic alcohols with sodium borohydride and TFA.[21] Oxidative decomposition of the resulting cobalt complex produces secondary alkynes in good to moderate yields. Production of the identical diastereomer from either epimeric alkynic alcohol is consistent with formation of a common intermediate by protonation and dehydration, followed by stereoselective hydride addition (eq 8).

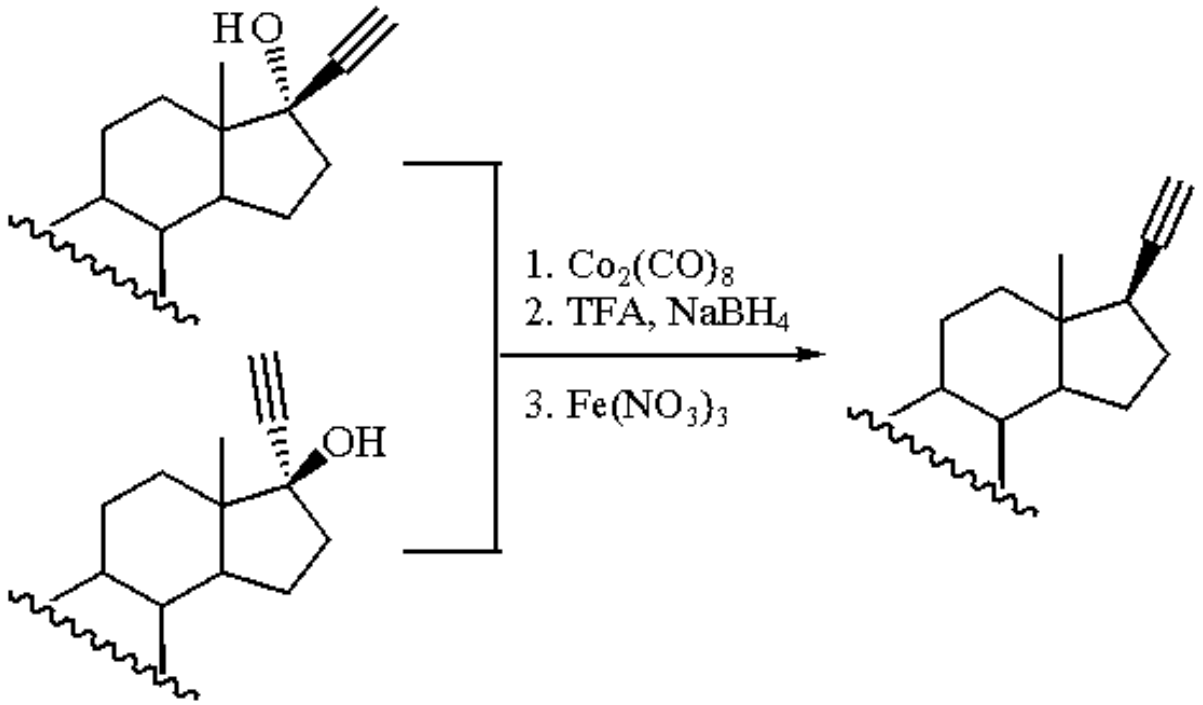

(8)

Baeyer-Villiger Oxidations in TFA.

Trifluoroacetic acid has been reported to catalyze the action of ***m-Chloroperbenzoic Acid*** in the Baeyer-Villiger oxidation of cyclic and acyclic ketones.[22]

Trifluoroperacetic Acid (TFPAA) is remarkably efficient for the oxidation of ketones in the Baeyer-Villiger reaction.[23] This reagent has been prepared from ***Trifluoroacetic Anhydride*** and concentrated ***Hydrogen Peroxide***. Since 90% hydrogen peroxide is no longer available as a commercial reagent, alternatives are needed for classical oxidation procedures. A combination of TFA and sodium percarbonate has been used as a replacement for TFPAA in the Baeyer-Villiger reaction (eq 9).[24] Yields vary between good to excellent. The procedure is not applicable to aliphatic ketones, as TFA esters are produced from transesterification with the solvent.

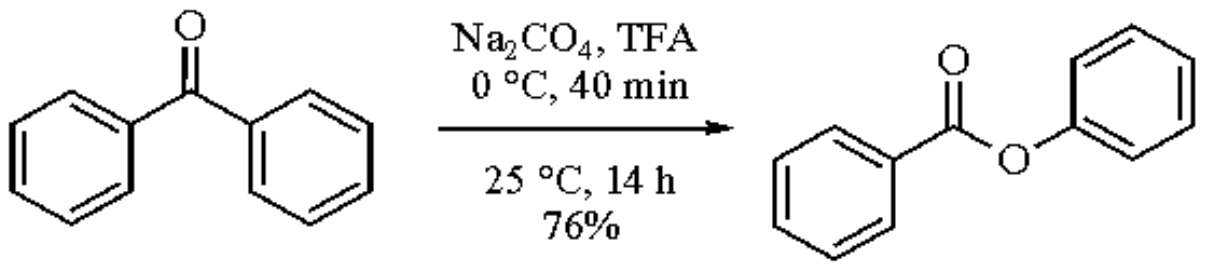

(9)

Cleavage of Nitrogen- and Oxygen-Protecting Groups.

Trifluoroacetic acid has found many applications in the removal of protecting groups. Examples include solvolysis under aqueous and anhydrous conditions. Groups that have been cleaved with TFA include *N*-Boc,[25] *N*-benzyloxymethyl,[26] benzyl ether,[27] *p*-methoxybenzyl ether,[28] *t*-butyl ether,[29] *t*-butyloxymethyl ether,[30] triphenylmethyl ether,[31] and dimethyl acetals.[32]

Related Reagents.

Acetic Acid; ***Fluorosulfuric Acid***; ***Formic Acid***; ***Hydrochloric Acid***; ***Hydrofluoric Acid***; ***Oxalic Acid***; ***Sulfuric Acid***; ***p-Toluenesulfonic Acid***; ***Trichloroacetic Acid***; ***Triethylsilane-Trifluoroacetic Acid***.

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Trifluoroacetic Anhydride[1]

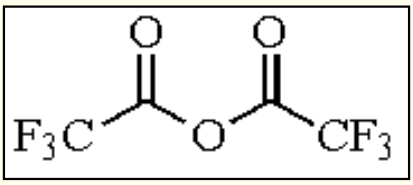

[407-25-0] · $C_4F_6O_3$ · Trifluoroacetic Anhydride · (MW 210.04)

(activating agent; oxidation)

Alternate Name: TFAA.

Physical Data: mp -65 °C; bp 39-40 °C; *d* 1.487 g cm^{-3}.

Solubility: sol C_6H_6, CH_2Cl_2, Et_2O, DMF, THF, MeCN.

Form Supplied in: colorless liquid; commercially available.

Analysis of Reagent Purity: by standard analytical techniques.

Preparative Methods: by distilling ***Trifluoroacetic Acid*** from ***Phosphorus(V) Oxide***.[1]

Handling, Storage, and Precautions: corrosive and moisture sensitive; toxic by inhalation; should be freshly distilled prior to reaction. Use in a fume hood.

Activated Esters.

Mixed anhydrides may be prepared by reaction of carboxylic acids with trifluoroacetic anhydride.[2] The method has been used widely as a means of activating carboxyl groups to nucleophilic attack. The method has also been highly useful in Friedel-Crafts acylation of arenes (eqs 1 and 2).[3,4] Sulfonic acids are also activated to nucleophilic attack; substituted sulfones result. Intramolecular Friedel-Crafts reactions are also facilitated, but only for formation of six-membered rings.[5]

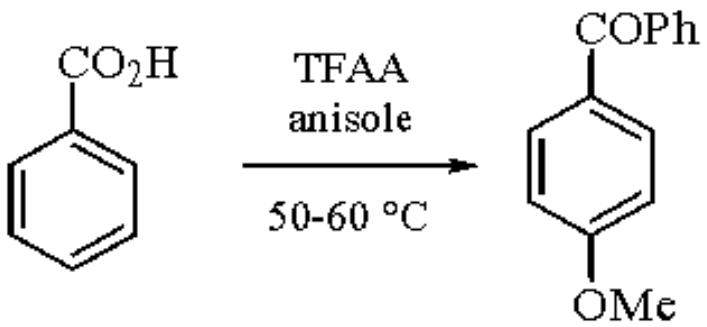

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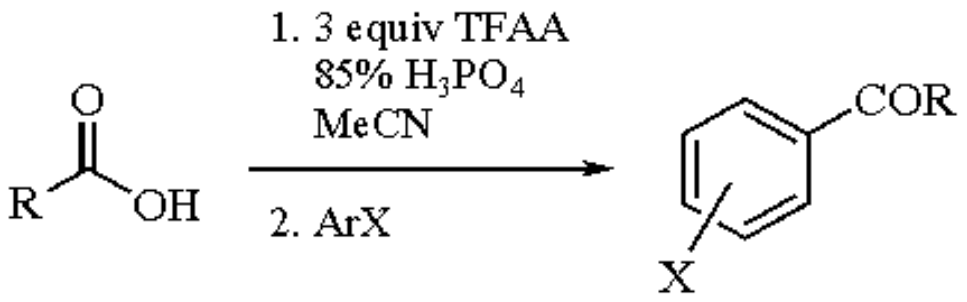

(2)

Anhydrides of diacids are prepared in (about) 90% yield by reaction with TFAA in ether.[6] The method involves formation of the monotrifluoroacetyl mixed anhydride, which may be converted to the cyclic anhydride by heating under vacuum (eq 3).[7]

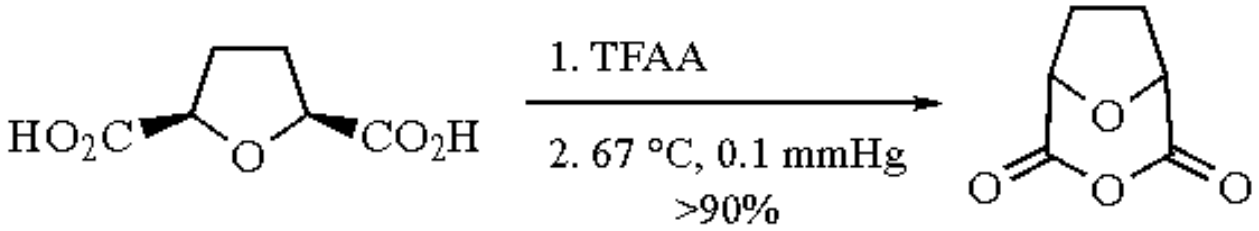

(3)

An inversion of alkene geometry is made possible by the reaction of their derived epoxides with lithium halides and TFAA (eq 4);[8] the products of this reaction are the corresponding halohydrin trifluoroacetates, which undergo a *syn* elimination upon reaction with ***Lithium Iodide***.

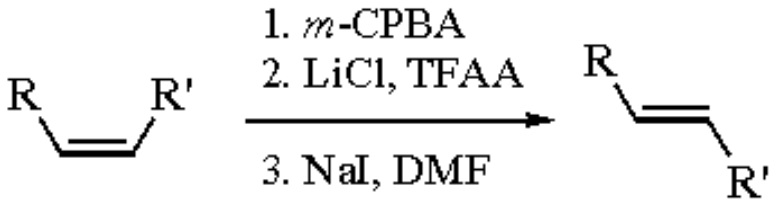

(4)

Primary alkanols and 2-alkenols are converted into the corresponding halides in high yield by a one-pot, two-step reaction via transformation into intermediate trifluoroacetates, followed by nucleophilic substitution with lithium halides (eq 5).[9]

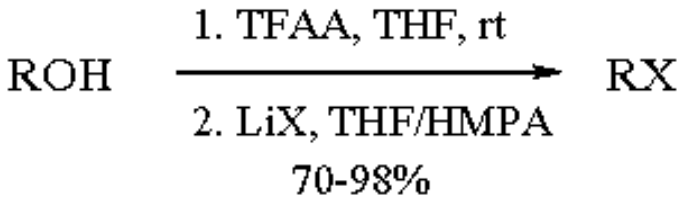

(5)

Sulfoxides are reduced to sulfides under mild conditions with ***Trifluoroacetic Anhydride-Sodium Iodide*** (eq 6).[10]

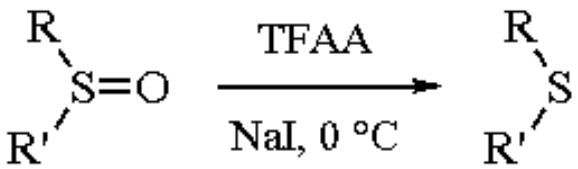

(6)

Primary amides are converted under mild conditions to the corresponding nitriles using TFAA in pyridine (eq 7).[11] Similarly, aldoximes are converted to nitriles by TFAA in pyridine (eq 8).[12]

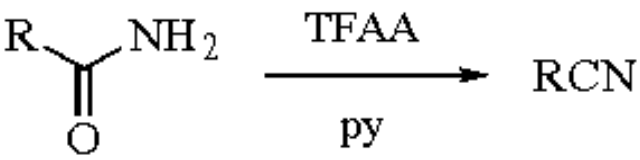

(7)

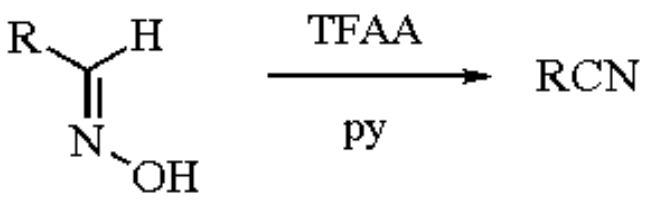

(8)

TFAA in triethylamine can be used for the dehydration of aldols to enones where other methods are less successful (eq 9).[13] When ***Acetic Anhydride*** is employed instead of TFAA, the reaction proceeds slowly.

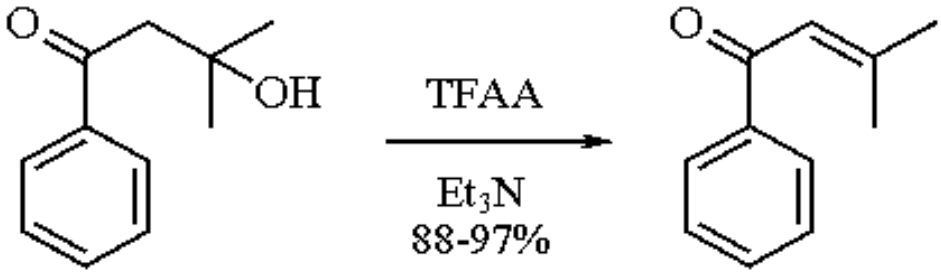

(9)

The Pummerer rearrangement of sulfoxides to α-acyloxy sulfides, induced by TFAA, has been used as a means of converting sulfoxides to aldehydes (eq 10).[14]

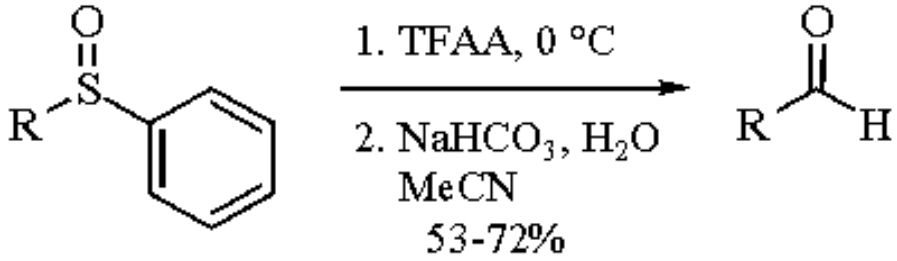

(10)

e.g. R = C_7H_{15}, $PhCH_2OCH_2$

Methyl aryl sulfides are converted in a mild, one-pot, three-step procedure via Pummerer rearrangement of the corresponding sulfoxides, and without purification of intermediates, to provide arylthiols in excellent yields (eq 11).[15]

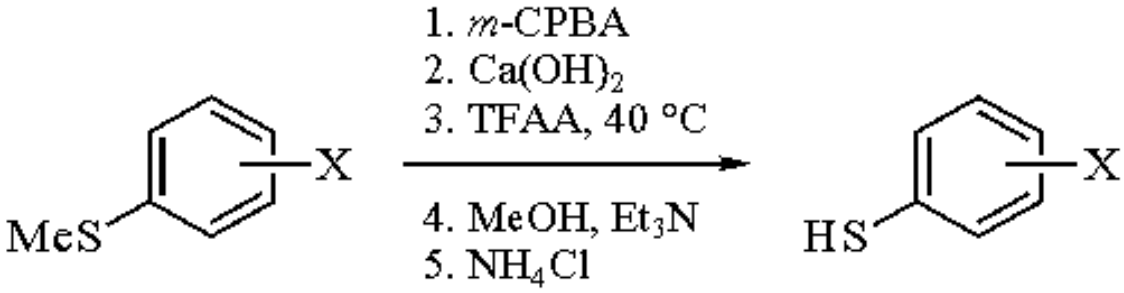

(11)

Oxidation.

Trifluoroacetoxydimethylsulfonium trifluoroacetate is prepared in situ from ***Dimethyl Sulfoxide*** and TFAA below -50 °C and reacts rapidly with alcohols in the presence of ***Triethylamine*** to give the corresponding carbonyl compounds (eq 12).[16]

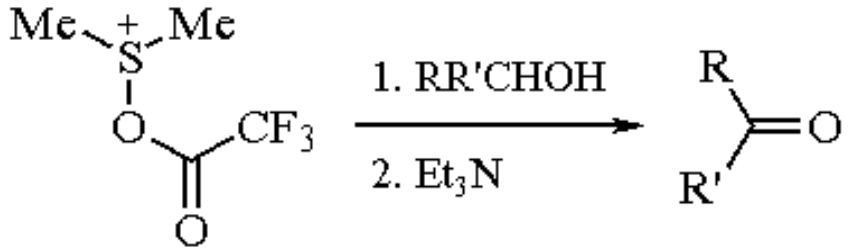

(12)

TFAA/DMSO also efficiently converts vicinal diols to the corresponding α-dicarbonyl compounds or derivatives thereof (eq 13).[17] Unlike the Swern oxidant (***Dimethyl Sulfoxide-Oxalyl Chloride***), this reagent mixture gives good yields for halogenated substrates. The preparation of previously inaccessible compounds (such as σ-homo-*ortho*-benzoquinones) is thus facilitated.

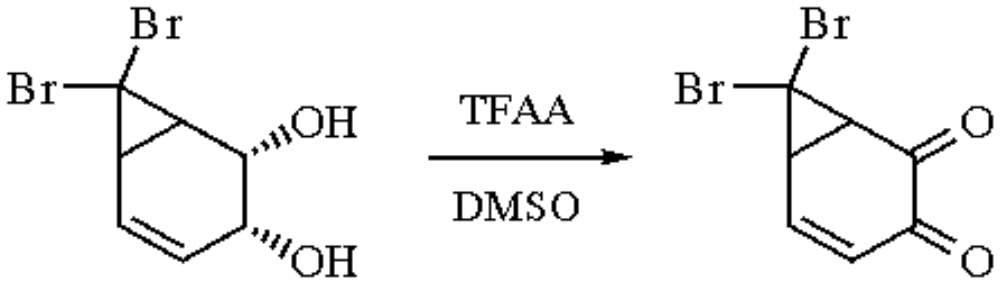

(13)

Undesired electrophilic chlorination as a side-reaction in Swern oxidations is avoided by use of TFAA in place of oxalyl chloride.[18] See also ***Dimethyl Sulfoxide-Trifluoroacetic Anhydride***.

Miscellaneous.

Enamines of α-amino acids react rapidly with TFAA to give pyrrole derivatives (eq 14).[19]

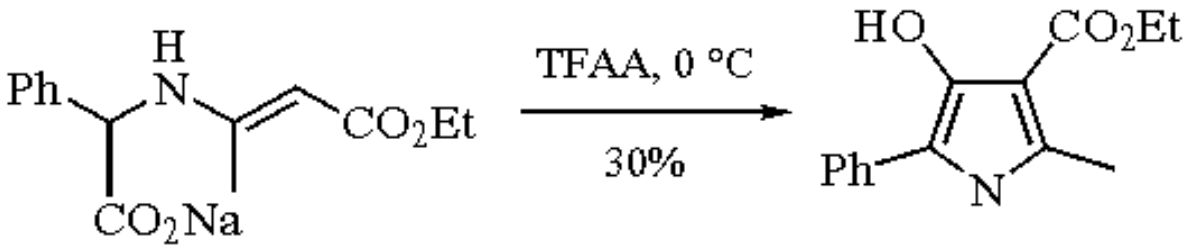

(14)

The reaction of TFAA with triethylamine *N*-oxide leads to formation of the trifluoroacetate salt of *N*,*N*-dimethylformaldimmonium ion. This ion is a superior reagent in the Mannich reaction.[20]

TFAA is used to prepare trifluoroacetamides from amines; these amides may be used in Gabriel-type reactions. The use of TFAA delivers an amide of enhanced acidity and which is easily hydrolyzed in situ, thereby allowing a one-pot alkylation process (eq 15).[21]

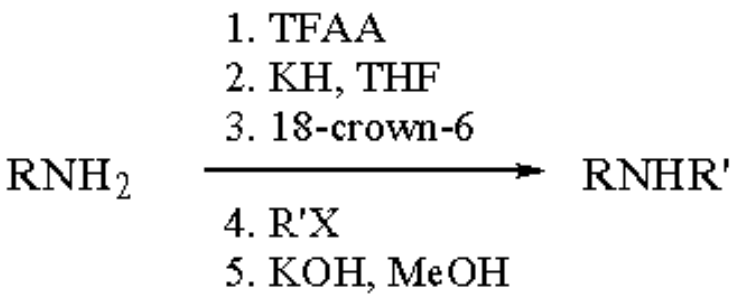

(15)

Reaction of TFAA with ammonium nitrate provides an in situ source of trifluoroacetyl nitrate, which has been used for the nitration of enol acetates[22] and as an *N*-nitrating agent.[23]

TFAA efficiently cleaves *N*-tosyl protecting groups from histidine (eq 16).[24]

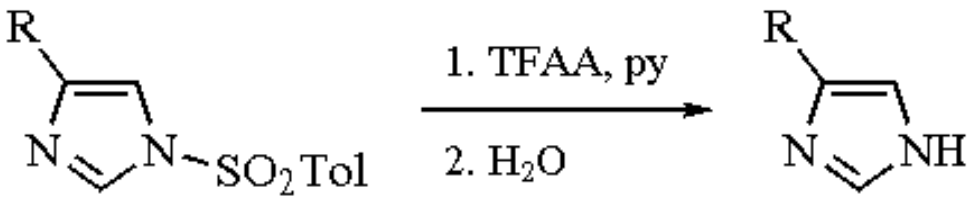

(16)

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Trifluoroacetic Anhydride-Sodium Iodide

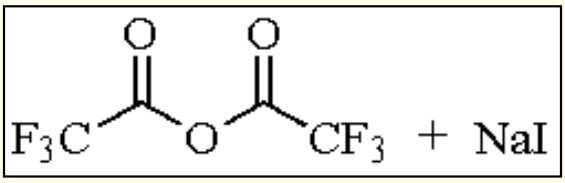

[407-25-0] · $C_4F_6O_3$ · Trifluoroacetic Anhydride-Sodium Iodide · (MW 210.04)

[7681-82-5] · INa · Trifluoroacetic Anhydride-Sodium Iodide · (MW 149.89)

(deoxygenation; converts alcohols to iodides)

Physical Data: see ***Trifluoroacetic Anhydride*** and ***Sodium Iodide***.

Introduction.

The primary use for the combination of trifluoroacetic anhydride and sodium iodide is deoxgenation. It has also been used for the conversion of alcohols to iodides.

Deoxygenation of Sulfoxides.[1]

Sulfoxides are rapidly deoxgenated to sulfides by the use of trifluoroacetic anhydride with sodium iodide. The reaction proceeds instantaneously under cooling at 0 °C when trifluoroacetic anhydride is added to an acetone solution of the sulfoxide and sodium iodide. Dialkyl, alkyl/aryl, and diaryl sulfoxides are all deoxygenated with yields in excess of 90%, with reaction times less than 10 min (eq 1).

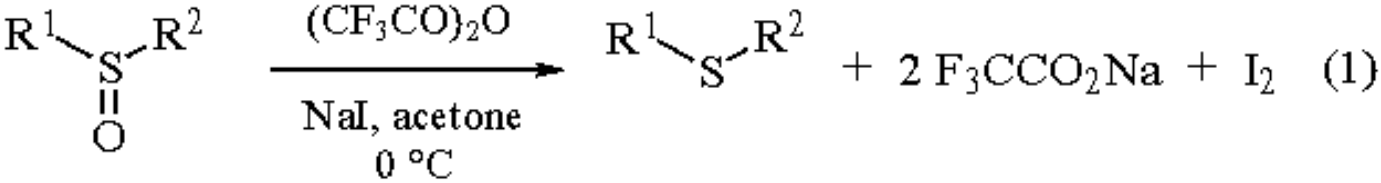

Deoxygenation of Epoxides.[2,3]

Epoxides are deoxygenated with retention of geometry by treatment with trifluoroacetic anhydride (1 equiv) and sodium iodide (4 equiv). Trifluoroacetyl iodide is generated in situ, which reacts with the epoxide in the presence of the excess sodium iodide to give the alkene. The yields are 77-95% after 24 h with a 1:1 mixture of MeCN and THF as solvent (eqs 2 and 3).

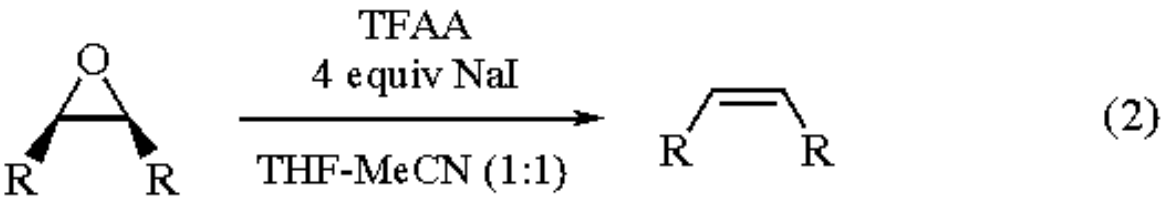

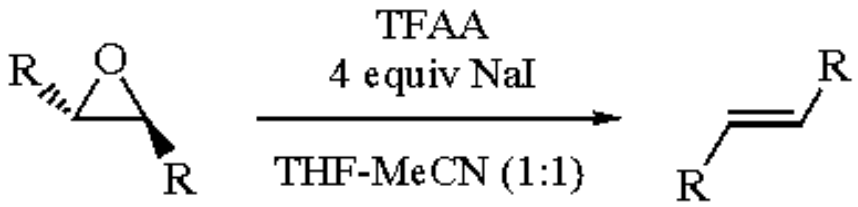

(3)

Conversion of Alcohols to Iodides.[4]

Primary and secondary alcohols are converted to the corresponding iodides in a one-pot two-step reaction. An intermediate trifluoroacetate is formed by reaction of the alcohol with trifluoroacetic anhydride and this is transformed into the halide via nucleophilic substitution with sodium iodide. Substituting sodium iodide with ***Lithium Iodide*** gives higher yields (eq 4). The corresponding chlorides and bromides may be synthesized by use of the appropriate sodium/lithium halide.

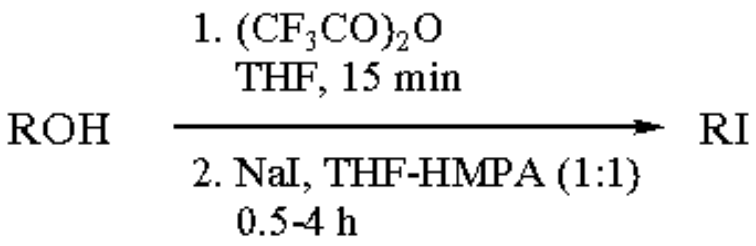

(4)

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2. Sonnett, P. E., *JOC* **1978**, *43*, 1841.
3. Sonnett, P. E., *JOC* **1980**. *45*, 154.
4. Camps, F., Gasol, V., Guernero, A., *S* **1987**, 511.

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Trifluoroacetyl Chloride

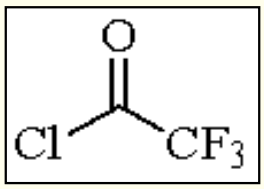

[354-32-5] · C_2ClF_3O · Trifluoroacetyl Chloride · (MW 132.47)

(useful for the preparation of trifluoro ketones[1,2] and for the elimination of epoxides to alkenes[3])

Physical Data: bp -27 °C; mp -146 °C.

Form Supplied in: nonflammable gas supplied in metal cylinders.

Preparative Methods: can be generated in situ from ***Trifluoroacetic Anhydride*** and ***Lithium Chloride***[3] or ***Trifluoroacetic Acid*** and ***Phosphorus(V) Chloride***.[2]

Handling, Storage, and Precautions: highly toxic material; handle accordingly. Use in a fume hood.

General Considerations.

Trifluoroacetyl chloride has limited use in organic synthesis due to its in situ preparation or use of the gas form. The preparation of common trifluoroacetate derivatives is achieved by the action of trifluoroacetic anhydride with the corresponding alcohol or amine.

Trifluoroacetyl chloride has been used to effect the elimination of epoxides to the corresponding alkene. The intermediate chlorohydrin trifluoroacetate must be treated with iodide to achieve elimination (eq 1).

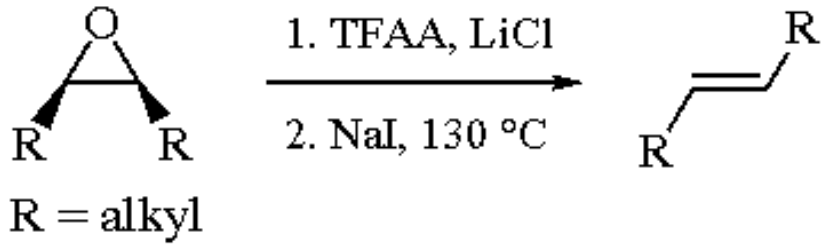

(1)

In practice, the conversion of an alkene from one geometry to the other can be realized via epoxidation and then treatment with trifluoroacetyl chloride followed by ***Sodium Iodide***.

Trifluoroacetophenone[2] is prepared by the action of trifluoroacetyl chloride on benzene in the presence of ***Aluminum Chloride*** (eq 2).

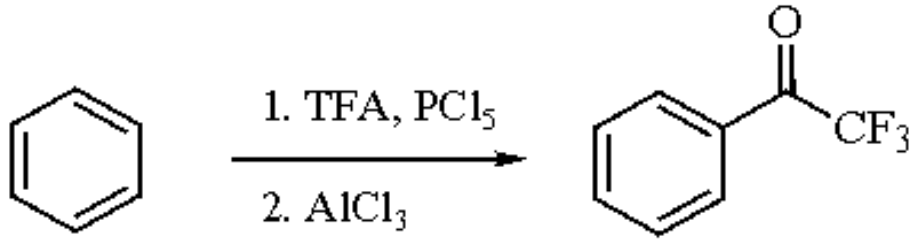

(2)

Trifluoroacetyl chloride reacts with ***N,O-Dimethylhydroxylamine*** hydrochloride in the presence of ***Triethylamine*** to form *N*-methoxy-*N*-methyltrifluoroacetamide (eq 3).[1,4] This interesting reagent reacts with Grignard reagents to form trifluoro ketones (eq 4).

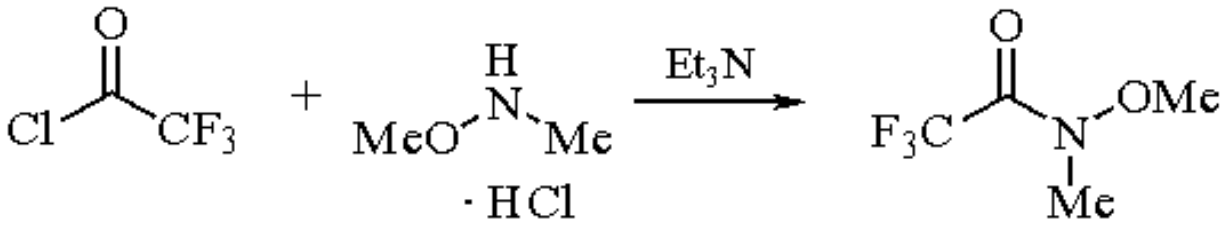

(3)

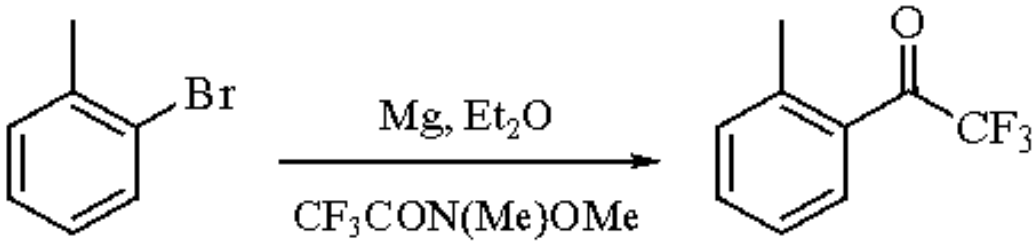

(4)

Trifluoroacetyl chloride is used to acylate an ylide which leads to α,α,α-trifluoro-β-keto esters (eq 5).[5]

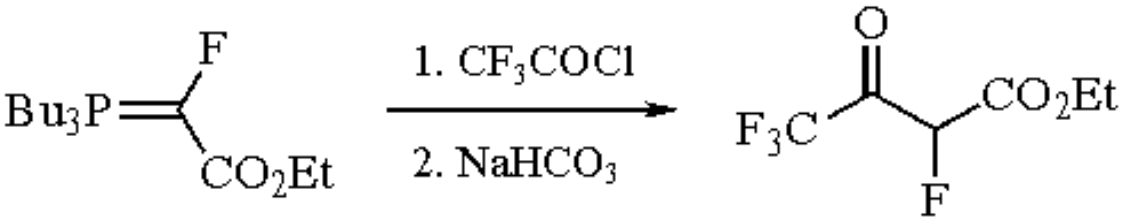

(5)

Related Reagents.

Trifluoroacetic Anhydride.

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Trifluoroacetyl Hypoiodite

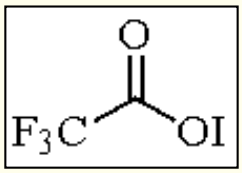

[359-47-7] · $C_2F_3IO_2$ · Trifluoroacetyl Hypoiodite · (MW 239.92)

(source of electrophilic iodine, I^+,[1] in electrophilic aromatic substitution reactions[2] and in addition reactions across double bonds;[3] mild oxidant capable of generating alkoxy radicals[4])

Solubility: sol aromatic solvents, halogenated solvents, ether, acetonitrile, trifluoroacetic acid.

Preparative Methods: is formed in situ from the reaction of equimolar amounts of ***Iodine*** and ***Silver(I) Trifluoroacetate*** or ***Mercury(II) Trifluoroacetate*** in a suitable solvent, typically trifluoroacetic acid (eq 1).[1] Trifluoroacetyl hypobromite can be similarly prepared using bromine instead of iodine.

$$I_2 + AgO_2CCF_3 \underset{rt}{\overset{CF_3CO_2H}{\rightleftharpoons}} CF_3CO_2I + AgI\,(s) \qquad (1)$$

If 2 mol of the silver salt are introduced, then the acyl hypohalite complexes with the additional silver salt to form the complex indicated in eq 2. This preparation is used in addition reactions, whereas the equimolar preparation has been applied in electrophilic substitution reactions.

$$I_2 + 2\,AgO_2CCF_3 \underset{rt}{\overset{CF_3CO_2H}{\rightleftharpoons}} (CF_3CO_2)_2AgI + AgI\,(s) \qquad (2)$$

Trifluoroacetyl hypoiodite may also be formed from equimolar amounts of ***Phenyliodine(III) Bis(trifluoroacetate)*** and iodine (eq 3).[5] This preparation is purported to allow for milder and faster iodination.[6]

$$I_2 + PhI(O_2CCF_3)_2 \underset{rt}{\overset{CCl_4}{\rightleftharpoons}} 2\,CF_3CO_2I + PhI \qquad (3)$$

Handling, Storage, and Precautions: is thermally labile and decomposes to trifluoromethyl iodide and carbon dioxide.[2] Concentrated solutions can decompose by as much as 30% per day; negligible decomposition occurs when the concentration of trifluoroacetyl hypoiodite is kept below 20 mM.[1]

Electrophilic Aromatic Substitution.

Because of the inductive effect of the trifluoromethyl group, trifluoroacetyl hypoiodite is unusually reactive as a positive iodine source for electrophilic aromatic substitution reactions. The relative reactivity order of hypohalites compared to other electrophilic halogen sources has been reported to be Br_2 < ICl &AApprox; CH_3CO_2I &LLt; CF_3CO_2I < CH_3CO_2Br &LLt; CF_3CO_2Br.[1] Product yields from reactions of trifluoroacetyl hypoiodite with aromatics range from 50% to 100% and favor *para* substitution (eq 4).[2,6,7]

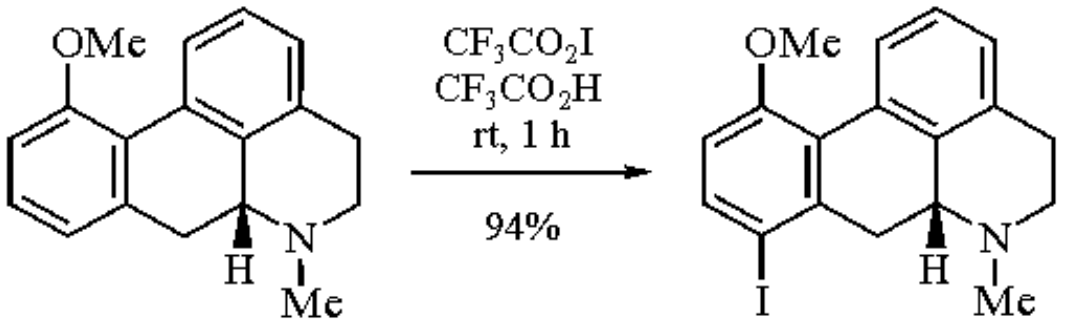

(4)

Addition to Alkenes.

Acyl hypoiodites, complexed by an additional equivalent of silver salt, e.g. $(CF_3CO_2)_2AgI$, add across double bonds to form *vic*-iodocarboxylates. The *vic*-iodocarboxylates are converted in 60-90% yields to *trans*- or *cis*-diols, respectively, under anhydrous and wet conditions[3] (iodine and thallium(I) carboxylates also form *vic*-iodocarboxylates in 60-90% yield).[8] The *vic*-iodotrifluoroacetate derived from the reaction of trifluoroacetyl hypoiodite with an alkene has been used to effect anti-Markovnikov hydration of unsaturated sugars (eq 5).[9]

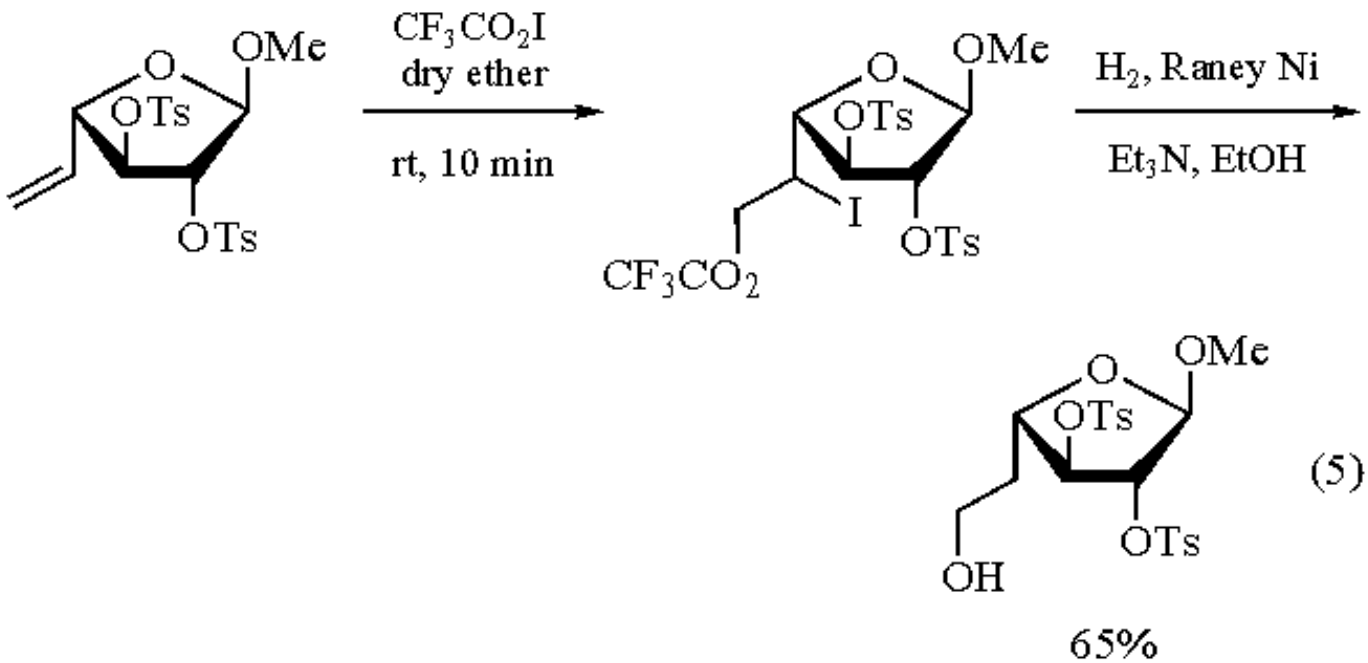

(5)

Other Applications.

When the AgI precipitate is quantitatively removed from the reagent preparation, the trifluoroacetyl hypoiodite, thus prepared, reacts with alcohols to produce alkoxy radicals. The radicals decompose upon irradiation to give aldehydes, ketones, and furans or mixtures thereof in 80-90% yields.[4]

Related Reagents.

Iodine-Potassium Iodate; ***Iodine-Silver Benzoate***.

---

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N-Trifluoroacetylimidazole

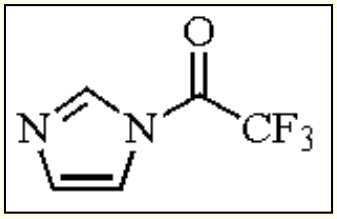

[1546-79-8] · $C_5H_3F_3N_2O$ · *N*-Trifluoroacetylimidazole · (MW 164.10)

(dehydration; protection; acylation)

Physical Data: mp 136-137 °C; bp 45-46 °C/14 mmHg.

Solubility: sol most common solvents, e.g. ether, THF.

Analysis of Reagent Purity: commercial material is 98+% pure.

Preparative Methods: ***N,N´-Carbonyldiimidazole*** (20.5 g) is dissolved in 100 ml of dry THF and treated dropwise with 28.8 g of ***Trifluoroacetic Acid*** in 80 mL of dry THF. The resulting solution is cooled for several hours. Removal of the solvent and distillation of the filtrate gives 14.4 g of material. Alternatively, ***Imidazole*** (25.8 g) in 120 mL of dried THF is treated dropwise, with cooling, with 39.9 g of ***Trifluoroacetic Anhydride*** in 50 mL of dried THF. Filtration, removal of solvent, and distillation gives 24.8 g of product.[1]

Purification: by distillation.

Handling, Storage, and Precautions: store under nitrogen, carefully excluding water. Irritant; moisture sensitive; keep cold; flammable.

Formation of Protected Amino Acids.

The protection of various amino acids has been achieved using this reagent with ***p-Nitrophenol*** to form the *p*-nitrophenyl esters;[2] yields are 50-80%. The method seems less satisfactory than currently available techniques, e.g. the ***1,3-Dicyclohexylcarbodiimide*** method, but may be of use in some specific cases where other methods give low yields, e.g. preparation of *p*-nitrophenyl *N*-benzyloxycarbonyl-β-benzyl-L-aspartate. The formation of simple alkyl and aryl esters by this method proceeds better at higher temperatures. At room temperature, a dramatic increase in yield may be achieved by adding a catalytic amount of alkoxide base. However, neither higher temperature nor alkoxide base increases the yield in the amino acid protection sequence mentioned above.

Synthesis of Carboxylic Acid Anhydrides.

When 1 mol of *N*-trifluoroacetylimidazole is treated with *2* mol of carboxylic acid in THF, a mixed anhydride and the pure anhydride are formed in an equilibrium reaction. The sparingly soluble salt of trifluoroacetylimidazole precipitates out of the solution, driving the reaction to completion (Scheme 1). Thus on standing for 5 h the pure anhydride is obtained in high yield, usually in excess of 80%.[3]

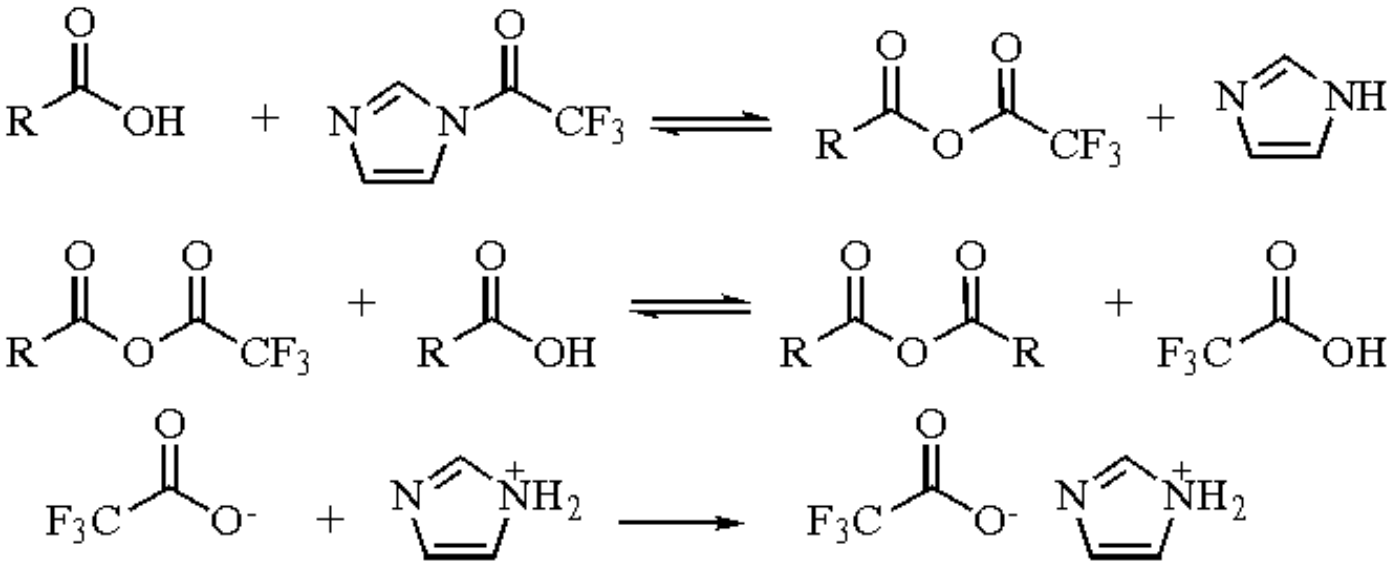

Scheme 1

Synthesis of Trifluoroacetyl Amides.

Reaction of trifluoroacetylimidazole with an equimolar amount of amine in THF or ether, evaporation of solvent followed by washing with water gives the corresponding trifluoroacetamide in good yields (80%).[1]

Synthesis of Nitriles from Aldoximes.

N-Trifluoroacetylimidazole converts aldoximes to nitriles[4] under mild and practically neutral conditions. The reaction is carried out by heating the aldoximes with *N*-trifluoroacetylimidazole in ether or THF under reflux for 2-3.5 h. A wide range of aldoximes are dehydrated, e.g. aliphatic, aromatic, and alkenic. The reaction also tolerates halogen and nitro functional groups. The dehydration of aldoximes is generally considered to be a base-promoted bimolecular mechanism.[5]

Synthesis of Acylated Aromatic Hydrocarbons.

N-Trifluoroacetylimidazole is a powerful acetylating agent for alcohols and amines. If the imidazole is used together with a strong Brønsted acid the nitrogen is protonated to form an imidazolium ion, increasing the electrophilicity of the acyl group. Thus it was found that *N*-trifluoroacetylimidazole in conjuction with trifluoroacetic acid could acylate aromatic hydrocarbons to give ketones[6] in good yield (70-90%).

The use of other acyl imidazoles was also investigated, e.g. PhCO, *p*-$NO_2C_6H_4CO$, and *p*-ClC_6H_4CO imidazoles, and the yields for acyl transfer here too are good (80-95%) except for the *p*-nitrophenyl acyl group which was transferred with a yield of only 16%.

Imidazoles of aliphatic carboxylic or aromatic carboxylic acids containing electron-donating groups gave 2-acylfluorenes in especially high yields. A mechanism is given, as well as a discussion of the Hammett plots for the corresponding reactions.

Synthesis of Volatile Derivatives for GLC.

The reagent is used for the preparation of volatile trifluoroacetyl derivatives of amines, alcohols, etc. for GLC purposes which are sensitive to electron-capture detection.[7]

---

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7. Moss, C. W., Lambert, M. A. *J. Chromatogr*. **1971**, *60*, 134.

2,2,2-Trifluoroethyl *p*-Toluenesulfonate[1]

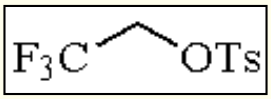

[433-06-7] · $C_9H_9F_3O_3S$ · 2,2,2-Trifluoroethyl *p*-Toluenesulfonate · (MW 254.25)

(trifluoroethylation agent for heteroatom nucleophiles; can function as a nucleophile for synthesis of α-keto acids and 2,2-difluorovinyl compounds)

Alternate Name: 2,2,2-trifluoroethyl tosylate

Physical Data: mp 40-41 °C; bp 102-104 °C/0.8 mmHg; *n*25D 1.4635.

Solubility: sol THF, ether, CH_2Cl_2, toluene.

Form Supplied in: white crystalline solid, commercially available.

Purification: recrystallize from hexane-ether.

Preparative Methods: easily prepared by treating 2,2,2-trifluoroethanol with ***p-Toluenesulfonyl Chloride*** in pyridine[1a] or in aqueous acetone containing NaOH.[1b]

Handling, Storage, and Precautions: quite stable; can be handled without any special technique and stored at room temperature; use in a fume hood.

Trifluoroethylation Agent.

Although this reagent is sluggish in substitution reactions compared to its nonfluorinated counterpart,[2] heteroatom nucleophiles react with the reagent to permit introduction of the 2,2,2-trifluoroethyl group. Thiols,[3,4] thiophenols,[3] and phenols[3b] undergo *S*- and *O*-trifluoroethylation via their sodium salts in good yields (eq 1). For the preparation of alkyl trifluoroethyl ethers, there is an alternative route via the alkylation of trifluoroethanol with alkyl halides.[3b,5] Trifluoroethylation of alkali selenolates[6] and tellurolates[7] is also achieved (eq 2), whereas trifluoroethyl iodide is a better choice in the case of tellurium. *N*-Trifluoroethylation is carried out with amines (eq 3)[8a] and pyrroles[8b] under forcing conditions, while the indole nitrogen is not alkylated but undergoes tosylation instead.[8c] In the trifluoroethylation of less reactive nucleophiles, 2,2,2-trifluoroethyl trifluoromethanesulfonate generally gives better results, especially in case of nitrogen[9a] and carbon nucleophiles.[9b]

$$\mathrm{RSNa} \xrightarrow[\text{DMF, rt}]{\mathrm{CF_3CH_2OTs}} \mathrm{RSCH_2CF_3} \qquad (1)$$

R = Et, 75%; Ph, 73%

$$\mathrm{PhZNa} \xrightarrow[\text{THF-HMPA, }\Delta]{\mathrm{CF_3CH_2OTs}} \mathrm{PhZCH_2CF_3} \qquad (2)$$

Z = Se, 76%; Te, 20%

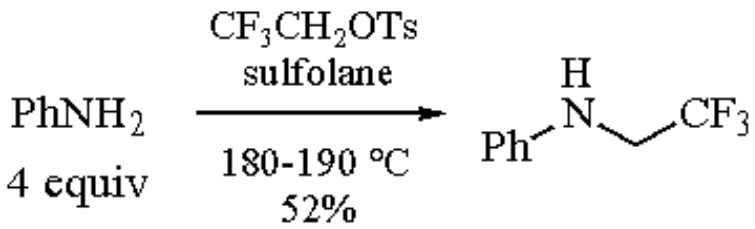

(3)

Synthesis of α-Keto Acids and 2,2-Difluorovinyl Compounds.

The reagent reacts with 2 equiv of ***Lithium Diisopropylamide***[10] or ***n-Butyllithium***[11a] at -78 °C to generate 2,2-difluoro-1-tosyloxyvinyllithium (**1**). This vinyllithium reagent reacts with carbonyl compounds[5,10] to give 3,3-difluoro-2-tosyloxyallyl alcohols (**2**) which undergo ***Sulfuric Acid***-catalyzed hydration to 2-tosyloxyacrylic acids (**3**). Base-catalyzed hydrolysis of (**3**) then affords the two-carbon homologated α-keto acids (eq 4).[10]

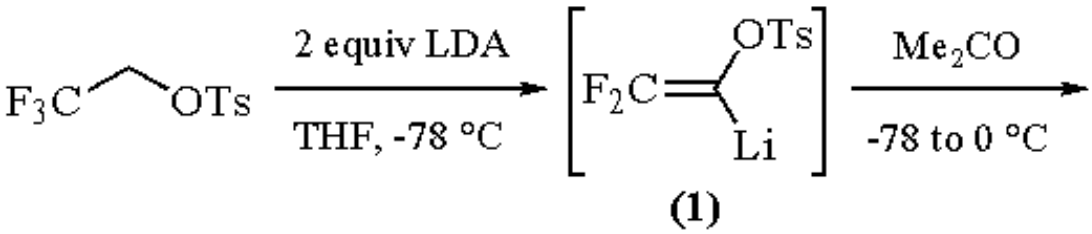

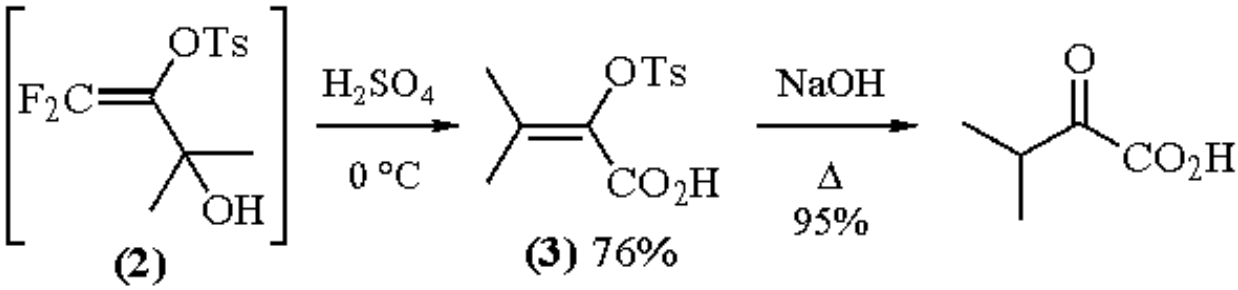

(4)

Vinyllithium (**1**) is also utilized via 2,2-difluorovinylboranes (**4**) (eq 5) to synthesize a wide variety of *gem*-difluorovinyl compounds: 1,1-difluoro-1-alkenes,[11b-e] 1,1-difluoro-1,3-alkadienes,[11f] 1,1-difluoro-1-alken-3-ynes,[11h] 1,1-difluoro-2-iodo-1-alkenes,[11c] β,β-difluoro-α,β-enones,[11a] and 2,2-difluorovinylphosphines,[11g] as well as difluoromethyl ketones[12] (eqs 6-10). In these reactions, the reagent functions as a building block for a difluorovinylidene unit (CF_2=C), to which two different substituents can be successively attached.

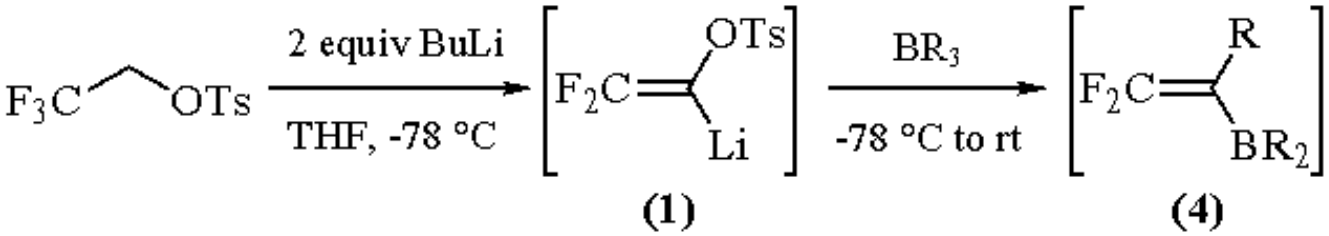

(5)

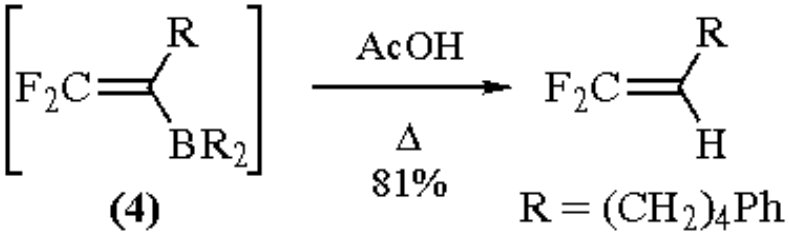

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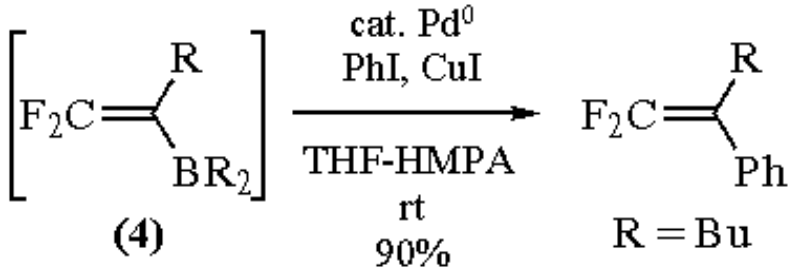

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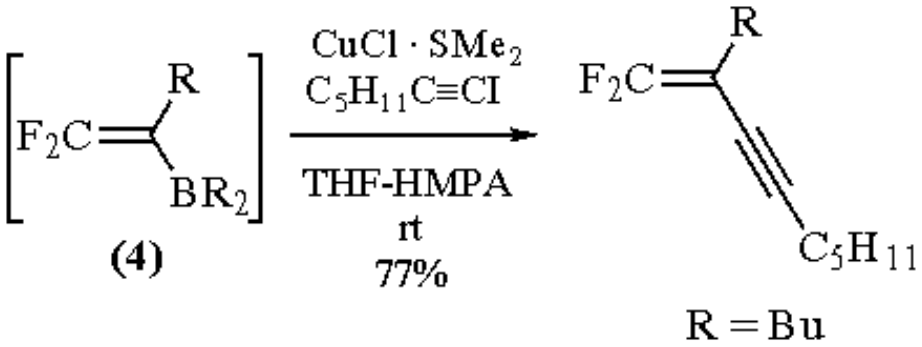

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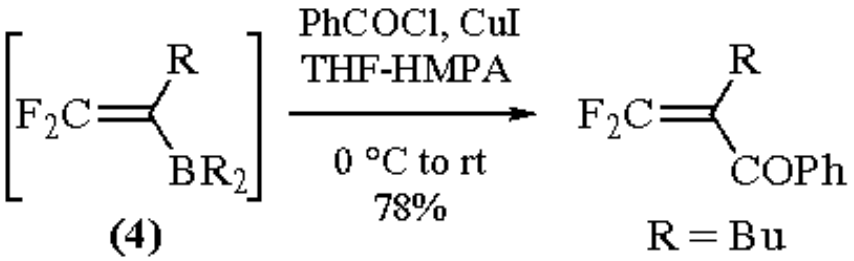

(9)

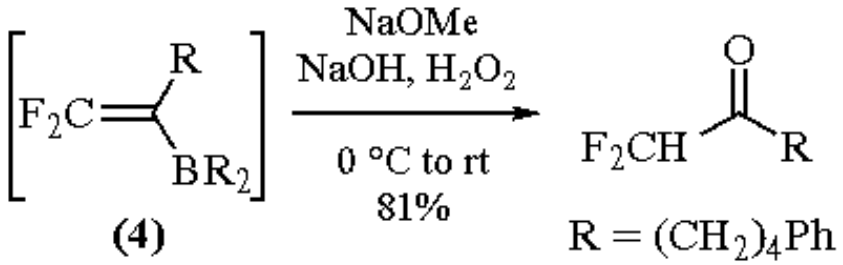

(10)

In addition, trifluoroethyl ethers, thioethers, and selenoethers prepared as above are available for the introduction of an alkyne moiety, leading to alkynic ethers and thioethers (eq 11)[3b] and thio-[3a] and selenoynamines[6a] (eq 12).

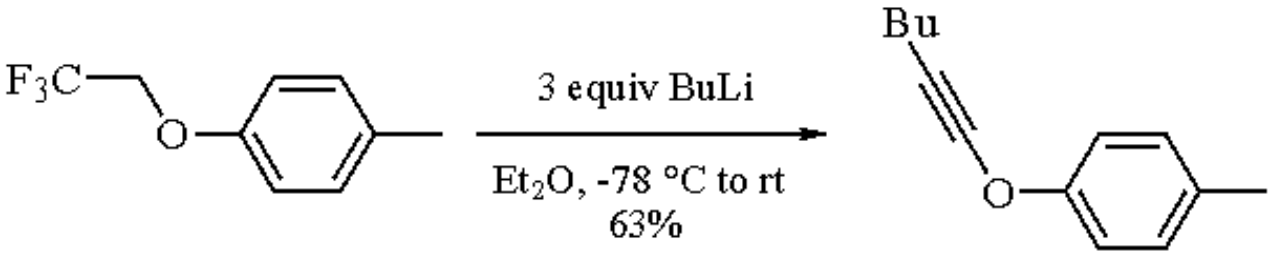

(11)

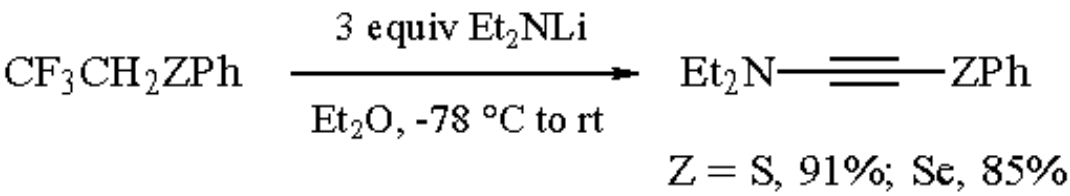

(12)

Related Reagents.

Chlorodifluoromethane; ***Dibromodifluoromethane***; ***1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene***; ***(Diethoxyphosphoryl)difluoromethyllithium***; ***Diethyl Difluoromethylphosphonate***; ***Difluoromethylenetriphenylphosphorane***; ***Ethyl Diethoxyacetate***; ***Glyoxylic Acid***; ***Glyoxylic Acid Diethyl Dithioacetal***; ***Methyl Bis(2,2,2-trifluoroethoxy)phosphinylacetate***; ***2,2,2-Trifluoroethyl Trifluoroacetate***.

---

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2,2,2-Trifluoroethyl Trifluoroacetate

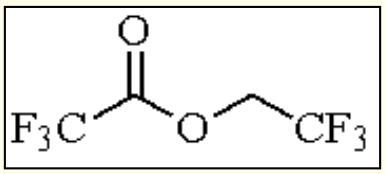

[407-38-5] · $C_4H_2F_6O_2$ · 2,2,2-Trifluoroethyl Trifluoroacetate · (MW 196.06)

(agent for the efficient trifluoroacetylation of ketone enolates; useful in the preparation of α-diazo ketones)

Alternate Name: TFEA.

Physical Data: bp 55 °C; *d* 1.464 g cm^{-3}.

Solubility: sol most commonly used organic solvents.

Form Supplied in: colorless liquid, widely available.

Purification: distillation from calcium hydride at atmospheric pressure.

Handling, Storage, and Precautions: for most applications the reagent can be adequately dried by simple distillation and can be stored under argon over 4Å molecular sieves. It is a flammable liquid and is reported to be corrosive.

General Considerations.

2,2,2-Trifluoroethyl trifluoroacetate has been employed for the in situ activation of a variety of ketone substrates as α-trifluoroacetyl derivatives.[1] In general, activation via trifluoracetylation is superior to older technology, such as Claisen formylation, since kinetically generated ketone enolates react essentially instantaneously with TFEA at -78 °C in high yield. Formylation of ketone substrates with ethyl formate is usually carried out using either ***Sodium Hydride*** or ***Sodium Ethoxide*** as the base and generally requires 12-48 h at room temperature for complete reaction.[2] TFEA is superior to other trifluoroacetylating agents, such as CF_3CO_2Et and ***Trifluoroacetic Anhydride***, in that the desired *C*-acylated products are rapidly formed in high yields.

Synthesis of α-Diazo Ketones via Detrifluoroacetylative Diazo Transfer.

Danheiser and co-workers have employed this strategy in an improved method for the synthesis of α-diazo ketones.[3] The diazo group transfer reaction requires that a stabilized β-diketone enolate be formed in situ for subsequent reaction with a sulfonyl azide reagent. The efficiency of the diazo group transfer reaction is improved, in some cases dramatically, by substituting the trifluoroacetylation of kinetically generated ketone enolates with TFEA for the classic formylation step. The method is particularly advantageous for diazo transfer reactions involving base-sensitive substrates such as certain α,β-enones and heteroaryl ketones. For example, as shown in eq 1, the yield of 1-diazo-4-phenyl-3-buten-2-one is improved from 17% to 85% when trifluoroacetylation with TFEA is substituted for Claisen formylation with ethyl formate. A variety of α-diazo ketones, which are not synthetically accessible via the classic procedures, can be obtained in excellent yields when the kinetic trifluoroacetylation procedure is employed (e.g. eq 2). This method has also been used by Doyle to achieve diazo group transfer to a base-sensitive *N*-acyloxazolidone derivative (eq 3).[4]

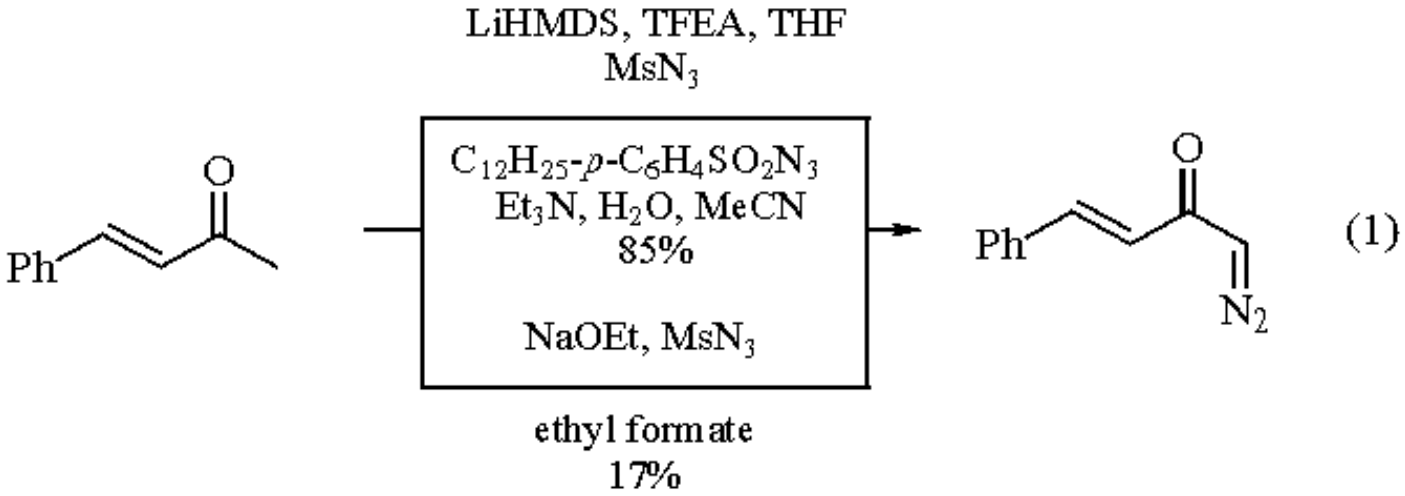

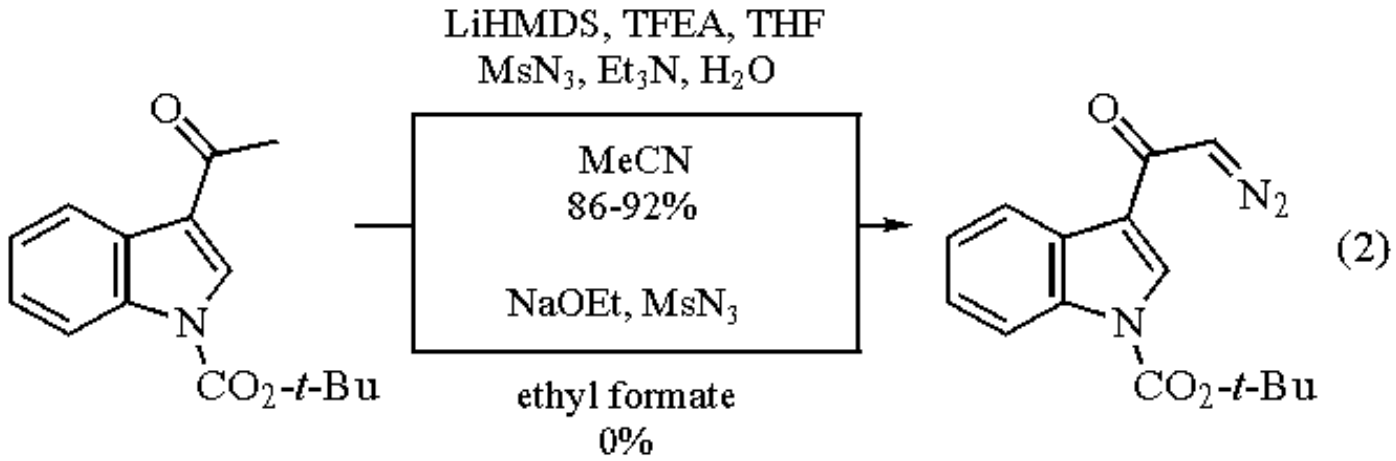

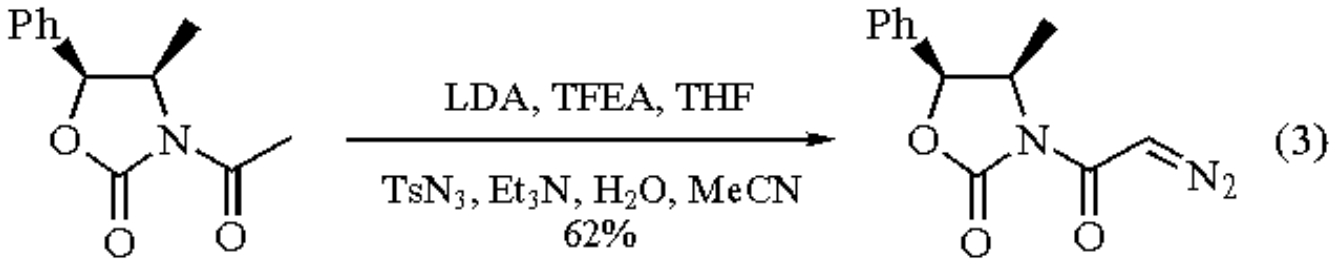

A crucial requirement for the success of the trifluoroacetylation reaction is that TFEA be rapidly added (1-5 s) to a cooled (-78 °C) solution of the ketone enolate (a small amount of white smoke may be noted above the reaction solution). The reaction is allowed to stir for 10 min, and then is quenched by pouring directly into a solution of 5% aq H_2SO_4. If the reagent is added too slowly in a dropwise fashion, varying amounts of starting material are often recovered from the reaction.

---

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Trifluoroiodomethane

CF_3I

[2314-97-8] · CF_3I · Trifluoroiodomethane · (MW 195.91)

(trifluoromethylating reagent)

Alternate Name: trifluoromethyl iodide.

Physical Data: bp -22 °C.[1]

Solubility: sol ether, acetone, alcohol, benzene.

Form Supplied in: gas; commercially available.

Preparative Methods: prepared by the fluorination of CI_4 with IF_5 (eq 1),[2] or by the Hunsdiecker reaction of ***Silver(I) Trifluoroacetate*** with an excess of ***Iodine*** (eq 2),[3] or by the reaction of trifluoroacetyl fluoride with ***Lithium Iodide*** (eq 3).[4] More recently, Chen reported a convenient method for the synthesis of CF_3I by the reaction of XCF_2CO_2Me (X = Br, Cl) with iodine, KF, and CuI (eq 4).[5]

$$CI_4 + IF_5 \xrightarrow[74\%]{} CF_3I \qquad (1)$$

$$CF_3CO_2Ag + I_2 \xrightarrow[90\%]{} CF_3I \qquad (2)$$

$$CF_3C(O)F + LiI \xrightarrow[73\%]{} CF_3I \qquad (3)$$

$$XCF_2CO_2Me + I_2 \xrightarrow[70\%]{KI,\ CuI} CF_3I \qquad (4)$$

$$X = Cl, Br$$

Addition to Alkenes and Alkynes.

Radical addition of CF_3I to alkenes and alkynes is initiated by irradiation,[6] peroxide,[6a] metals,[7] boranes,[8] enzymes,[9] and heating[10] to give the corresponding adducts (eq 5). Enamines react with CF_3I rapidly at room temperature without UV irradiation or initiator to form trifluoromethylated ketones after hydrolysis.[11]

$$CF_3I + H_2C{=}CHR \xrightarrow{\text{initiation}} CF_3CH_2CHIR \qquad (5)$$

Addition to Carbonyl Compounds.

Addition of CF_3I to carbonyl compounds is promoted by metals and metal salts such as ***Zinc***,[12] Zn/MV^{2+} (MV^{2+} = methyl viologen),[13] ***Tin(II) Chloride***,[14] Zn/ultrasound,[15] and ***Magnesium***[16] to form the corresponding trifluoromethylated alcohols (eq 6).

$$CF_3I + RCHO \xrightarrow{\text{metal}} CF_3CH(OH)R \qquad (6)$$

Coupling with Organic Halides.

In the presence of copper metal, CF_3I undergoes coupling with aryl and vinyl iodides to afford the corresponding trifluoromethylated aromatics and alkenes, respectively.[17] Pregenerated CF_3Cu (from the reaction of CF_3I with copper metal in HMPA at 120 °C) reacts with benzyl, allyl, vinyl, acyl, and alkyl bromides to give the corresponding trifluoromethylated products (eq 7).[18]

$$CF_3I + Cu + RX \longrightarrow RCF_3 \qquad (7)$$

$$R = \text{aryl, allyl, vinyl, acyl, alkyl; } X = \text{Br, I}$$

Reaction with Thiolates.

Photoreaction of CF_3I with thiols in liquid NH_3 gives the corresponding trifluoromethyl sulfides (eq 8).[19]

$$CF_3I + RS^- \xrightarrow{h\nu,\ NH_3} CF_3SR \qquad (8)$$

Addition to Aromatic Compounds.

Trifluoromethylation of benzene, thiophene, pyridine, and imidazole has been accomplished via thermolysis or irradiation of CF_3I in the presence of the appropriate aromatic compound (eq 9).[20]

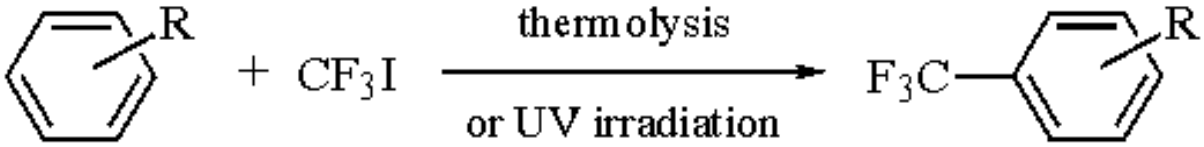

(9)

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Trifluoromethanesulfonic Acid[1]

CF_3SO_2OH

[1493-13-6] · CHF_3O_3S · Trifluoromethanesulfonic Acid · (MW 150.09)

(one of the strongest organic acids; catalyst for oligomerization/polymerization of alkenes and ethers; precursor for triflic anhydride and several metal triflates; acid catalyst in various reactions)

Alternate Name: triflic acid.

Physical Data: bp 162 °C/760 mmHg, 84 °C/43 mmHg, 54 °C/8 mmHg; *d* 1.696 g cm^{-3}.

Solubility: sol water and in many polar organic solvents such as DMF, sulfolane, DMSO, dimethyl sulfone, acetonitrile; sol alcohols, ketones, ethers, and esters, but these generally are not suitable inert solvents (see below).

Analysis of Reagent Purity: IR;[2] ^{19}F NMR.[3]

Preparative Methods: best prepared by basic hydrolysis of CF_3SO_2F followed by acidification.[2]

Purification: distilled with a small amount of Tf_2O.[4]

Handling, Storage, and Precautions: is a stable, hygroscopic liquid which fumes copiously on exposure to moist air. Transfer under dry nitrogen is recommended. Contact with cork, rubber, and plasticized materials will cause rapid discoloration of the acid and deterioration of the materials. Samples are best stored in sealed glass ampules or glass bottles with Kel-F™ or PTFE plastic screw cap linings. Use in a fume hood.

Reaction with P_2O_5.

Trifluoromethanesulfonic acid (TfOH) reacts with an excess of ***Phosphorus(V) Oxide*** to give ***Trifluoromethanesulfonic Anhydride*** (eq 1),[5] while treatment with a smaller amount of P_2O_5 (TfOH:P_2O_5 = 6:1) and slower distillation leads to trifluoromethyl triflate (eq 2).[6]

$$CF_3SO_3H + P_2O_5\ (\text{excess}) \xrightarrow[-H_2O]{\Delta} (CF_3SO_2)_2O \qquad (1)$$

$$6\ CF_3SO_3H + P_2O_5 \xrightarrow[70\%]{\Delta} 3\ CF_3SO_2OCF_3 + 3\ SO_2 + 2\ H_3PO_4 \qquad (2)$$

The synthetic utility of trifluoromethyl triflate as a trifluoromethanesulfonylating agent is severely limited, because the reagent is rapidly destroyed by a fluoride-ion chain reaction in the presence of other nucleophiles.[7]

Dehydration of a 2:1 mixture of CF_3CO_2H and TfOH with P_2O_5 affords trifluoroacetyl triflate (eq 3),[8] which is a very reactive agent for trifluoroacetylations at O, N, C, or halogen centers (eq 3).[8a]

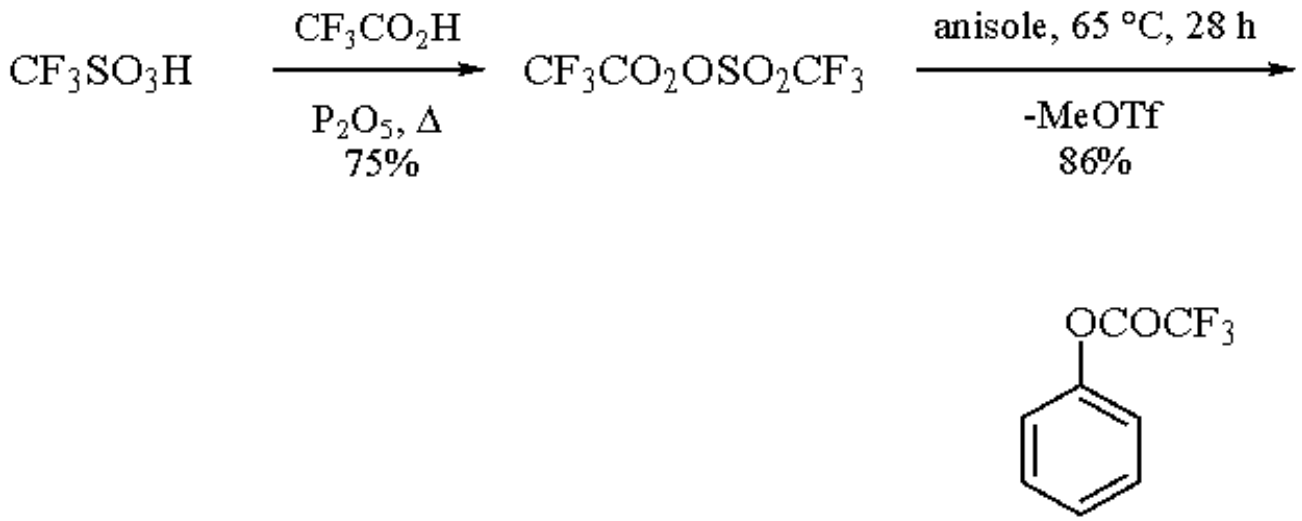

(3)

Protonation and Related Reactions.

TfOH is one of the strongest monoprotic organic acids known. The acid, and its conjugate base ($CF_3SO_3^-$), have extreme thermal stability, are resistant to oxidation and reduction, and are not a source of fluoride ions, even in the presence of strong nucleophiles. They do not lead to sulfonation as do ***Sulfuric Acid***, ***Fluorosulfuric Acid***, and ***Chlorosulfonic Acid*** in some reactions. TfOH is therefore effectively employed in protonation reactions.

The strong protonating property of TfOH is used to generate allyl cations from suitable precursors in low-temperature ionic Diels-Alder reactions. 3,3-Diethoxypropene and 2-vinyl-1,3-dioxolane add to cyclohexa-1,3-diene in the presence of TfOH to give the corresponding Diels-Alder adducts, the latter in high yield (eq 4).[9]

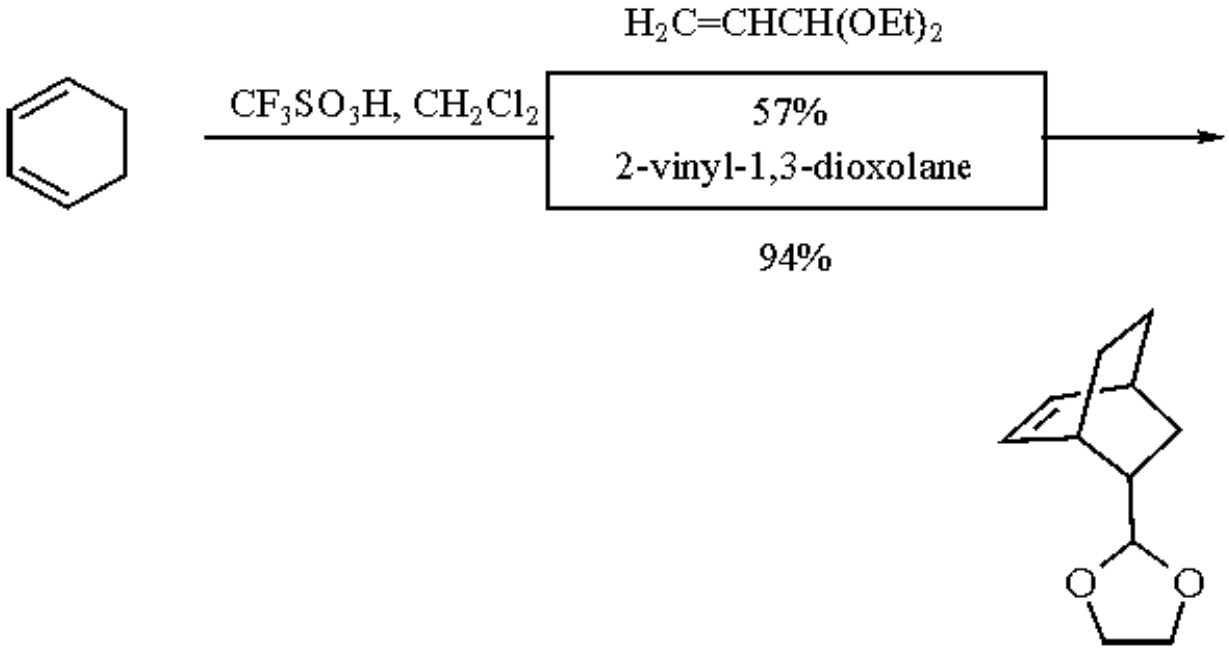

(4)

An intramolecular Diels-Alder reaction with high stereoselectivity occurs involving allyl cations by protonation of allyl alcohols (eq 5).[10]

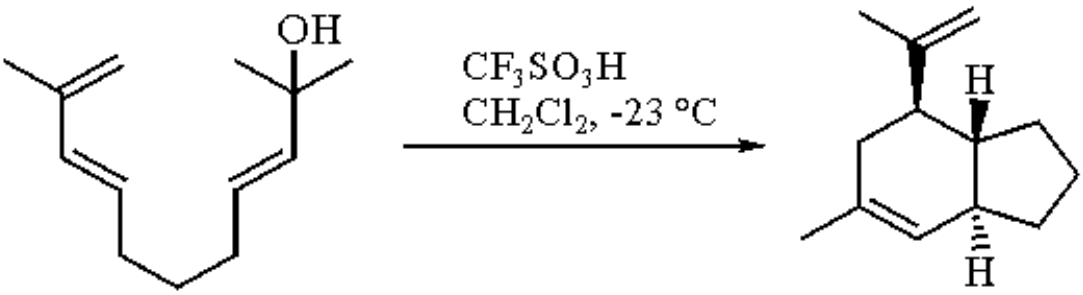

(5)

Alkynes and allenes are protonated with TfOH to give vinyl triflates (eqs 6 and 7),[11] which are precursors to vinyl cations.

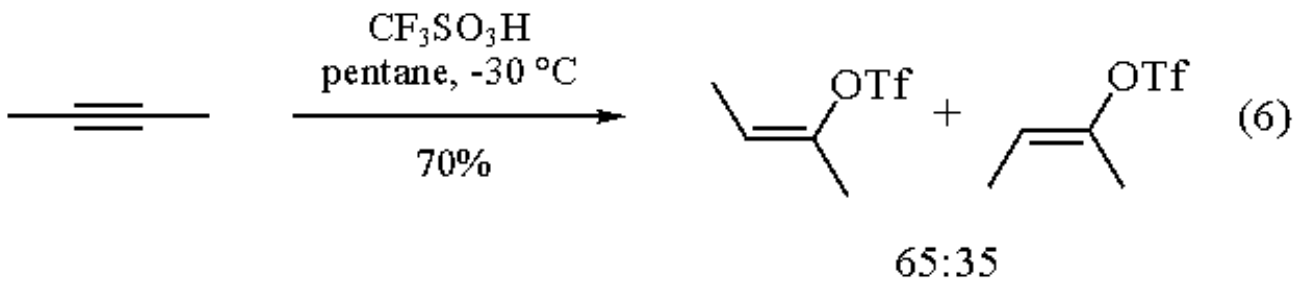

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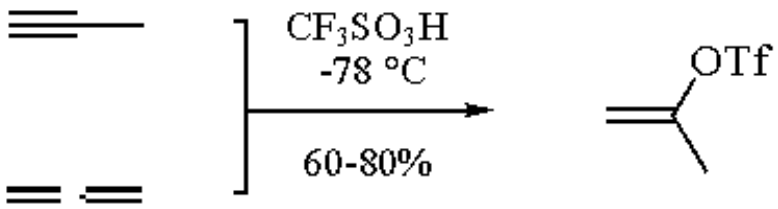

(7)

A convenient synthesis of pyrimidines is developed by protonation of alkynes with TfOH in the presence of nitriles (eq 8).[12]

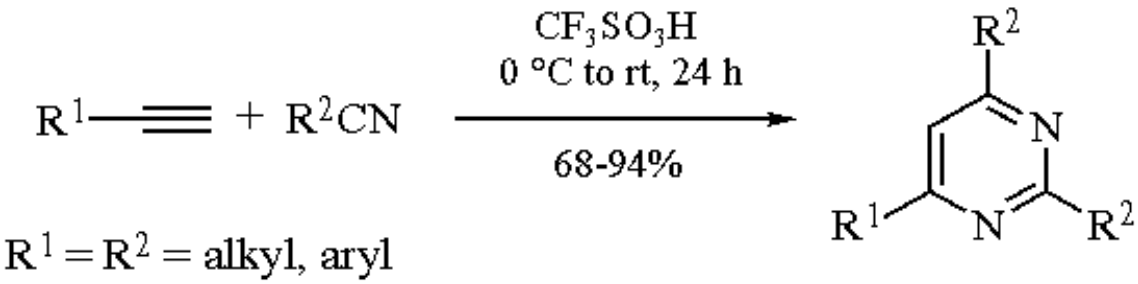

(8)

Triflic acid catalyzes the transformation of α-hydroxy carbonyl compounds to ketones (eq 9).[13]

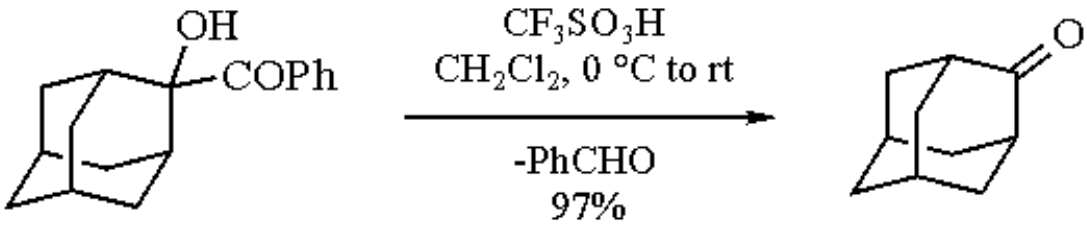

(9)

Oximes undergo Beckmann rearrangement with TfOH in the presence of Bu_4NReO_4 to give amides in high yield (eq 10).[14]

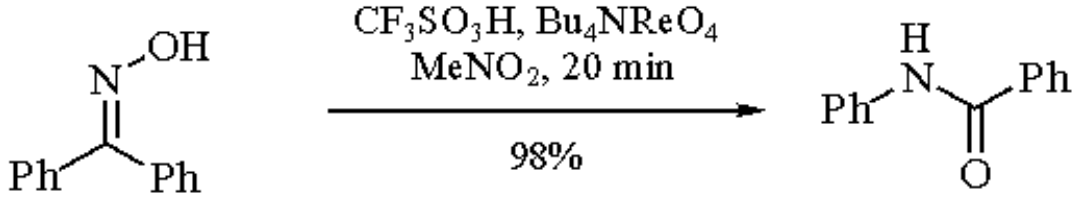

(10)

TfOH protonates nitroalkenes, even nitroethylene, to give *N*,*N*-dihydroxyiminium carbenium ions, which react with arenes to give arylated oximes. This overall process provides a route to α-aryl methyl ketones from 2-nitropropene (eq 11)[15] and constitutes a versatile synthetic method for the preparation of α-arylated ketones, otherwise difficult to synthesize by the conventional Friedel-Crafts reaction.

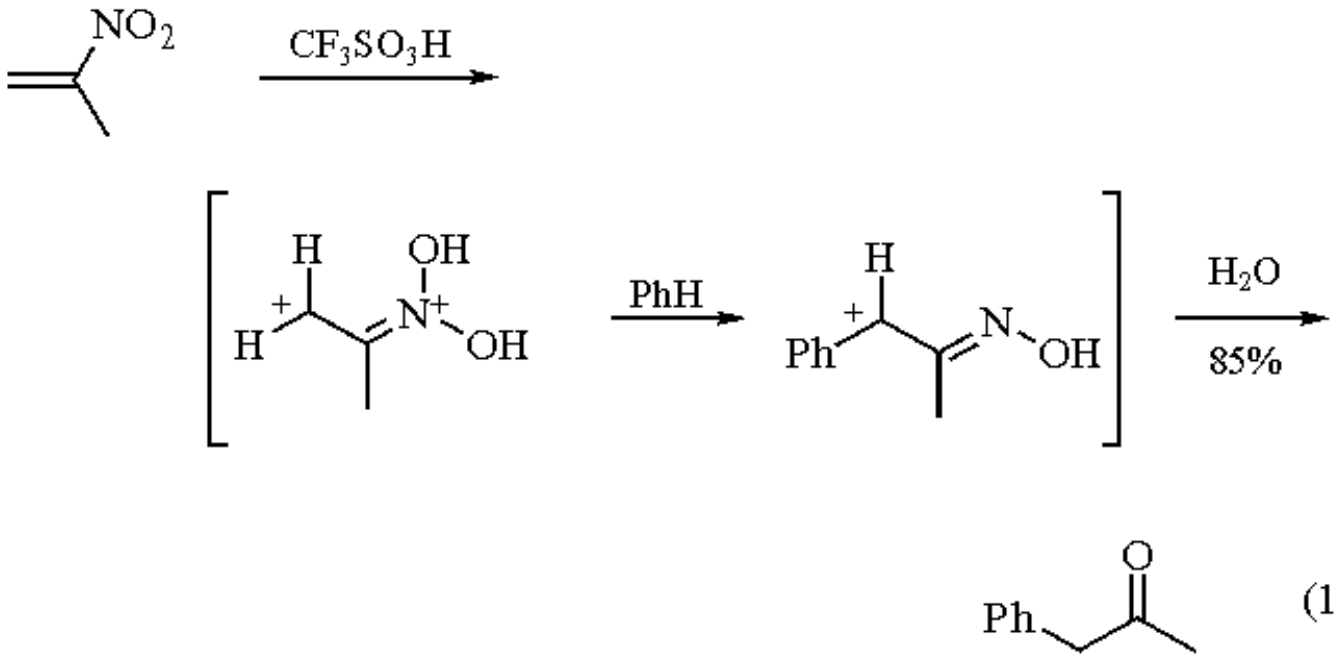

(11)

TfOH catalyzes the removal of *N*-*t*-butyl groups from *N*-substituted *N*-*t*-butylcarbamates to give carbamate-protected primary amines (eq 12).[16]

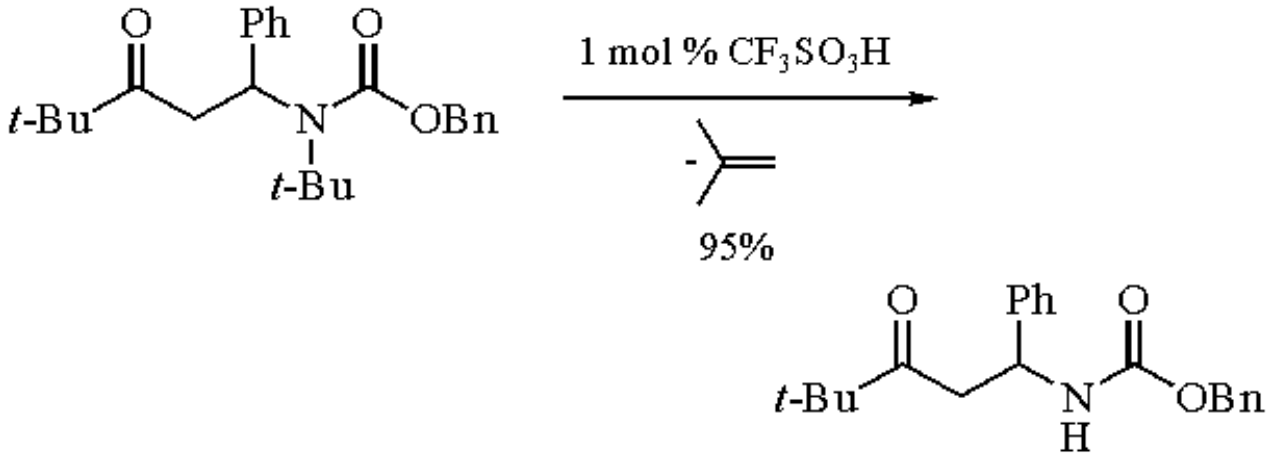

(12)

The methyl group attached to the phenolic oxygen of tyrosine is smoothly cleaved by TfOH in the presence of ***Thioanisole*** (eq 13).[17] This deblocking method was successfully applied to the synthesis of a new potent enkephalin derivative.

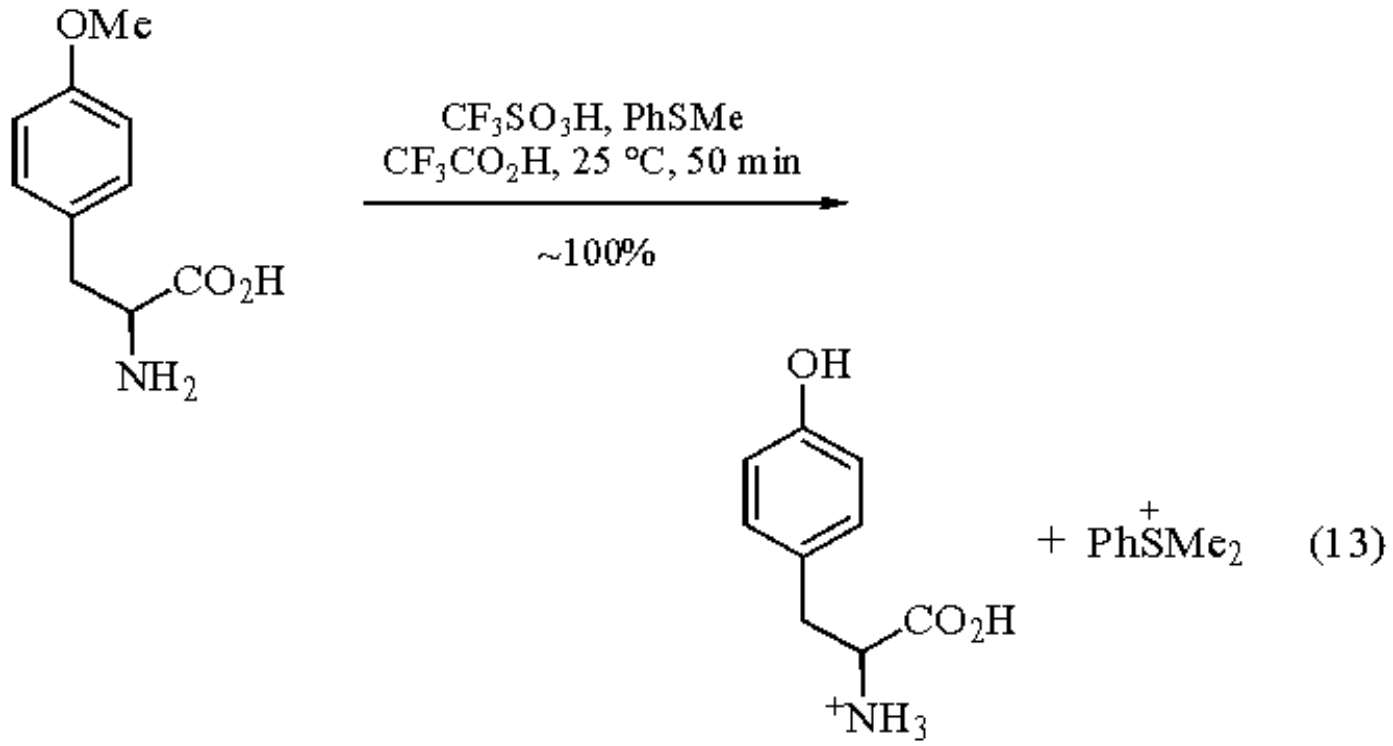

1,3,4-Oxadiazoles are prepared in good yields from silylated diacylhydrazines (formed in situ) by acid-catalyzed cyclization using TfOH (eq 14).[18]

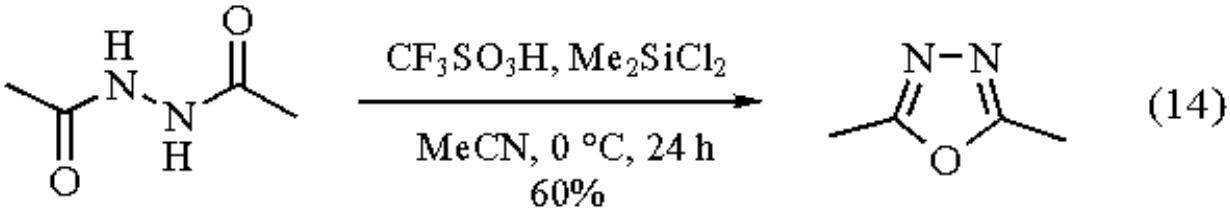

TfOH protonates naphthalene at room temperature to give a complex mixture of products.[19] TfOH promotes aldol reaction of silyl enol ethers with aldehydes and acetals, leading to new C-C bond formation (eq 15).[20] TfOH competes well with other reagents employed for the aldol reaction, while ***Methanesulfonic Acid*** does not afford any product.

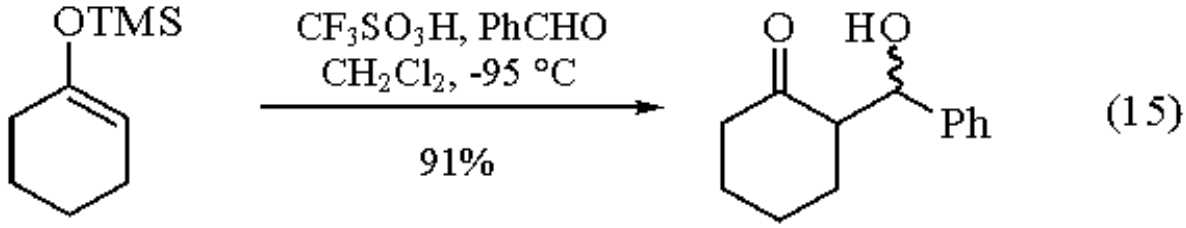

Cyclization of 3- and 4-arylalkanoic acids to bicyclic ketones is effected by TfOH via the corresponding acid chlorides (eq 16).[21]

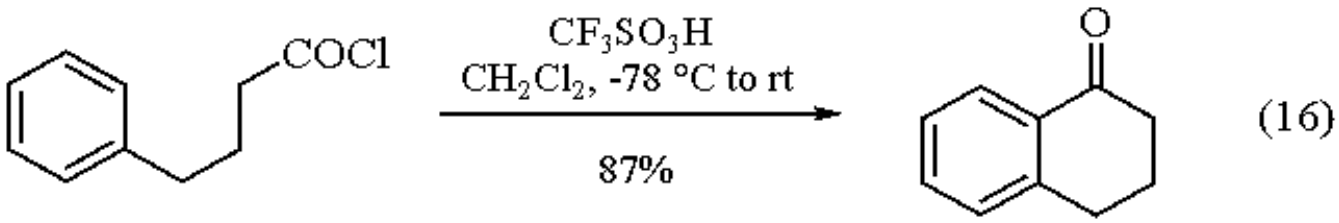

Allylic *O*-methylisoureas are cyclized with TfOH containing ***Benzeneselenenyl Trifluoromethanesulfonate*** to 5,6-dihydro-1,3-oxazines (eq 17).[22]

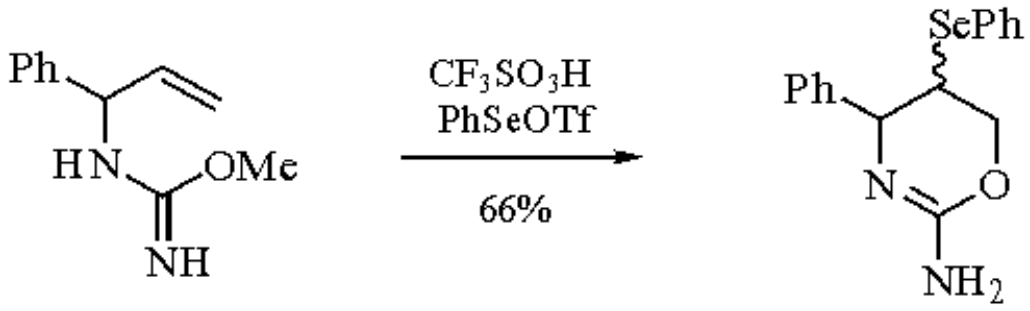

(17)

Tscherniac amidomethylation of aromatics with *N*-hydroxymethylphthalimide in TfOH proceeds smoothly at room temperature to give the corresponding α-amido-methylated products (eq 18).[23]

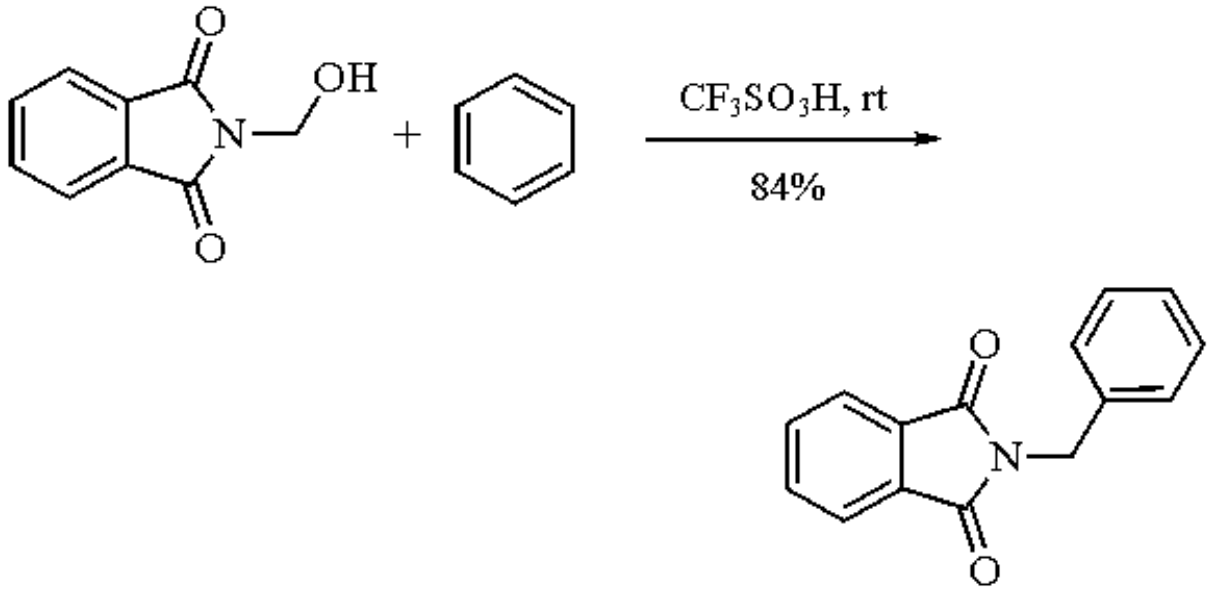

(18)

TfOH catalyzes the amination[24] and phenylamination[25] of aromatics via the corresponding aminodiazonium ion generated from ***Azidotrimethylsilane*** and ***Phenyl Azide*** respectively (eq 19).

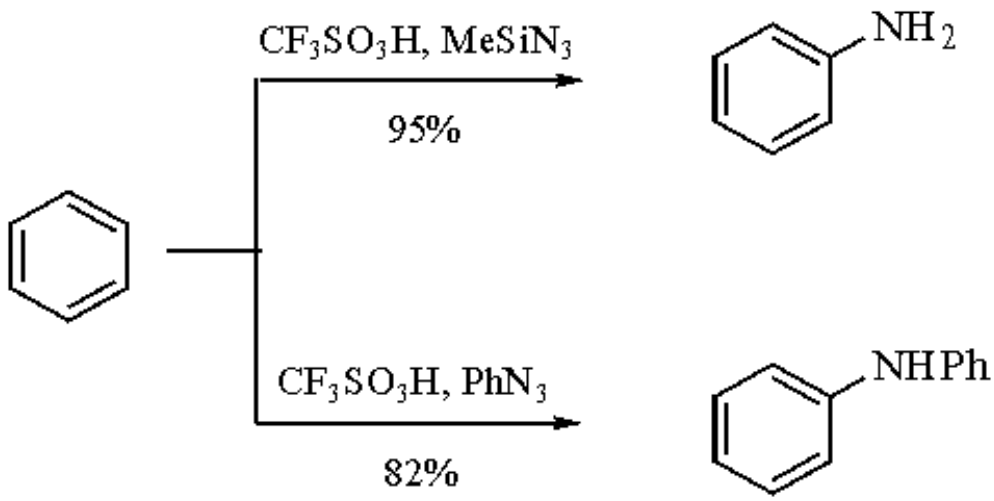

(19)

Electrophilic hydroxylation of aromatics is carried out by protonation of ***Bis(trimethylsilyl) Peroxide*** with TfOH in the presence of the substrate (eq 20).[26]

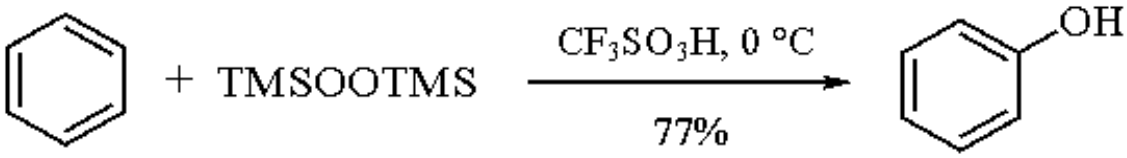

(20)

Phenol and 2,3,5,6-tetramethylphenol are protonated with TfOH under irradiation to afford rearranged products (eqs 21 and 22).[27]

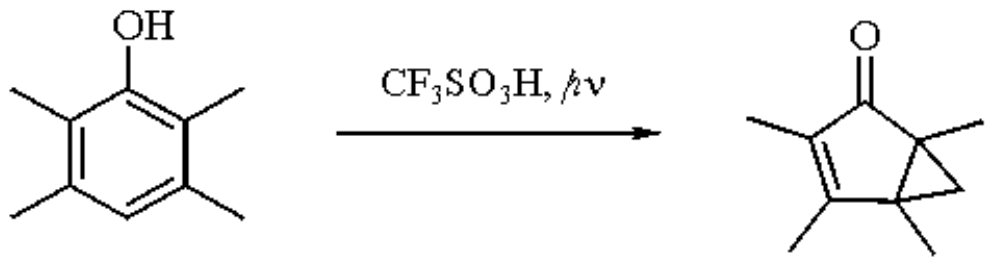

(21)

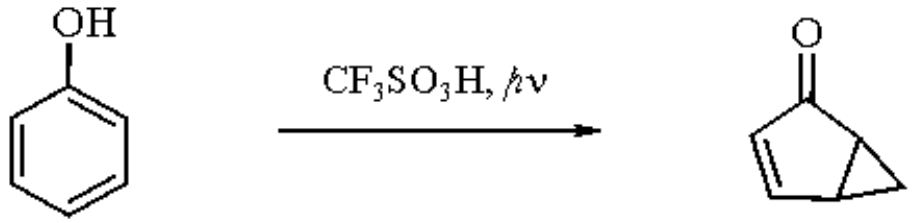

(22)

Other Applications.

TfOH is the starting material for the preparation of the electrophilic reagent ***Trimethylsilyl Trifluoromethanesulfonate***. The latter is prepared by reacting TfOH with ***Chlorotrimethylsilane***[28] or more conveniently with Me_4Si (eq 23).[29]

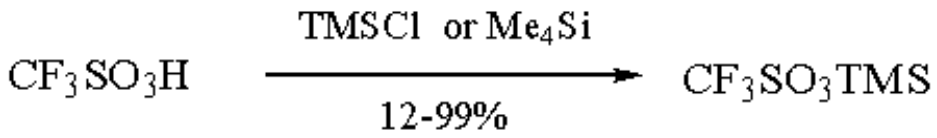

(23)

Functionalized silyl triflates can also be prepared using TfOH (eq 24).[30]

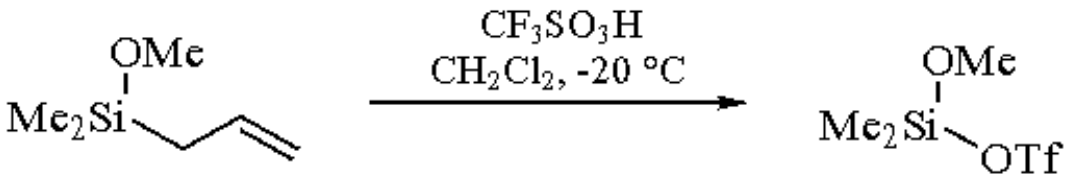

(24)

Reaction of aromatic compounds with ***Bis(pyridine)iodonium(I) Tetrafluoroborate*** in the presence of TfOH is an effective method to form the monoiodo compounds regioselectively (eq 25).[31]

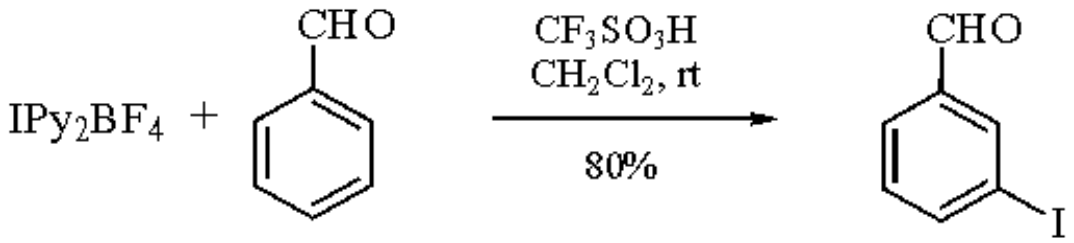

(25)

Ionic hydrogenation of alkenes with trialkylsilanes is possible in the presence of the strong acid TfOH, even at -75 °C (eq 26).[32]

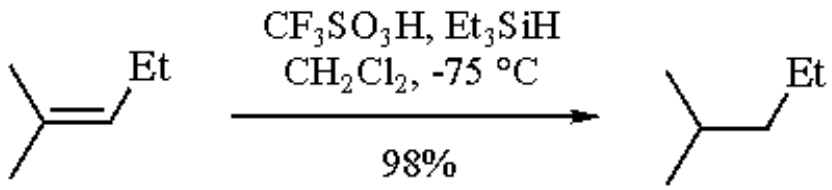

(26)

Hydroxycarbonyl compounds can be selectively reduced to carbonyl compounds by means of TfOH in the presence of trialkylboranes (eq 27).[33]

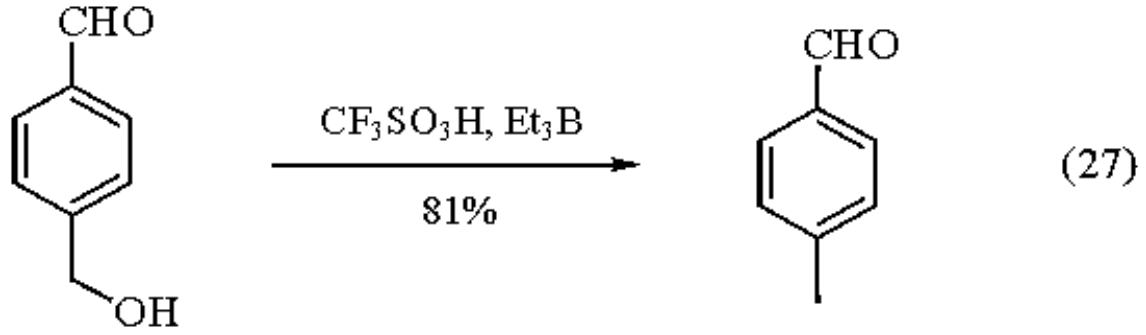

(27)

The triphenylmethyl cation is nitrated with ***Nitronium Tetrafluoroborate*** in the presence of TfOH (eq 28).[34]

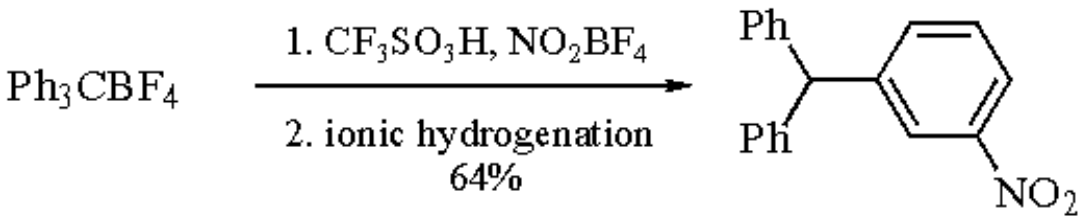

(28)

Sterically hindered azidophenyltriazines decompose in TfOH at 0 °C to give isomeric triflates (eq 29).[35]

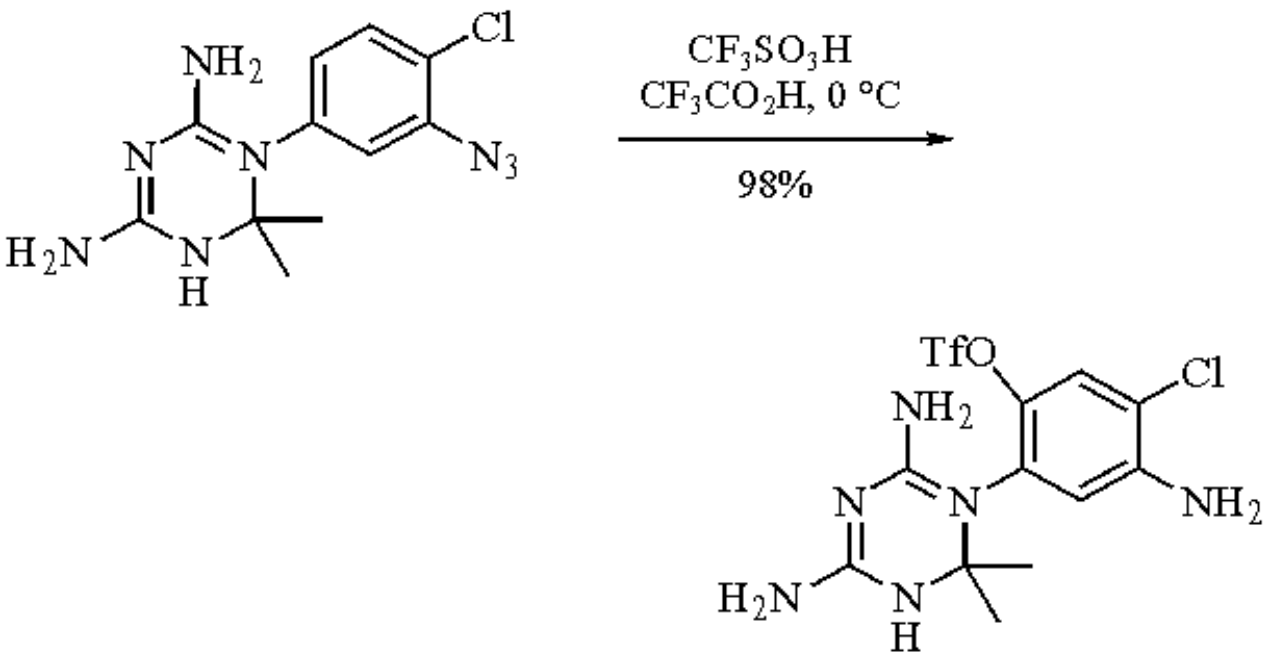

(29)

Benzoyl triflate prepared from TfOH and ***Benzoyl Chloride*** is a mild and effective benzoylating agent for sterically hindered alcohols[36] and acylative ring expansion reactions.[37] The applications of TfOH in Koch-Haaf carboxylation,[38] Fries rearrangement,[39] and sequential chain extension in carbohydrates[40] are also documented. Recent applications of TfOH in cyclization reactions have been published.[41-43]

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Trifluoromethanesulfonic Anhydride[1]

$(CF_3SO_2)_2O$

[358-23-6] · $C_2F_6O_5S_2$ · Trifluoromethanesulfonic Anhydride · (MW 282.16)

(preparation of triflates;[1] mild dehydrating reagent; promoter for coupling reactions in carbohydrates[2])

Alternate Name: triflic anhydride.

Physical Data: bp 81-83 °C/745 mmHg; *d* 1.677 g cm^{-3}; *n*20D 1.3210.

Solubility: sol dichloromethane; insol hydrocarbons.

Form Supplied in: colorless liquid in ampules. Once opened it should be immediately used.

Analysis of Reagent Purity: IR, NMR.

Preparative Methods: by distillation of ***Trifluoromethanesulfonic Acid*** with an excess of ***Phosphorus(V) Oxide***.[1]

Purification: by redistillation with a small amount of P_2O_5. It is advisable to freshly distill the reagent from a small quantity of P_2O_5 before use.

Handling, Storage, and Precautions: the pure reagent is a colorless liquid that does not fume in air and is stable for a long period. It is not soluble in water and hydrolyzes only very slowly to triflic acid over several days at room temperature. Preferably stored under N_2 in a stoppered flask.

Reaction with Alcohols and Phenols.

The reaction of alcohols and phenols with triflic anhydride (Tf_2O) at ~0 °C in the presence of a base (usually ***Pyridine***) in an inert solvent (usually dichloromethane) for 2-24 h affords the corresponding reactive trifluoromethanesulfonate esters (triflates).[1] When triflic anhydride and pyridine are combined, the pyridinium salt forms immediately and normally precipitates out from the reaction mixture. Nevertheless, the salt is an effective esterifying agent, reacting with the added alcohol to give triflates in high yields (eq 1).[3]

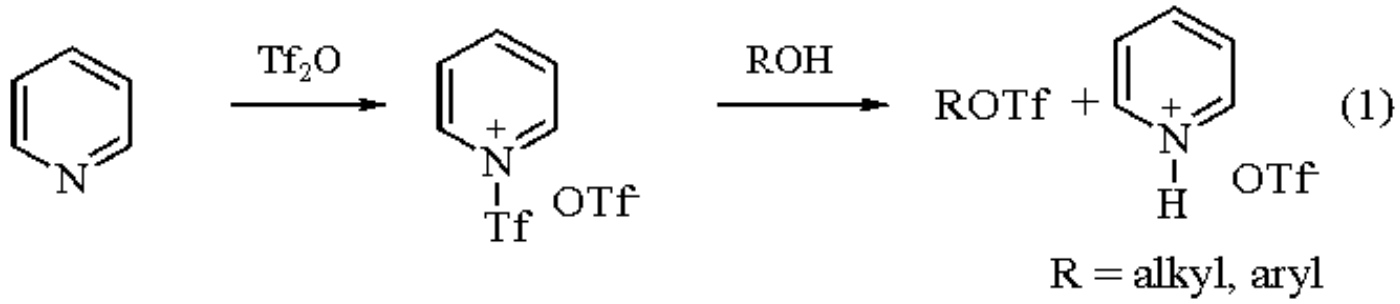

Pyridine can become involved in nucleophilic substitution when very reactive triflates are being synthesized.[2,3] One approach to minimize this disadvantage is to replace it with sterically hindered bases, such as 2,6-di-*t*-butyl-4-methylpyridine,[3,4] 2,4,6-trisubstituted pyrimidines,[5] or nonnucleophilic aliphatic amines (usually *N*,*N*-diisobutyl-2,4-dimethyl-3-pentylamine). No salt formation appears to take place under these conditions. The triflic anhydride seems to be the direct triflating agent and the base only neutralizes the triflic acid formed. Numerous alkyl triflates have been prepared in the literature[1b] by the above method. Some recent examples of triflates prepared from alcohols are illustrated in eqs 2 and 3.[6,7] As an exception, 2,6-dinitrobenzyl alcohol does not react with Tf_2O although similar sulfonyl esters could be prepared.[8]

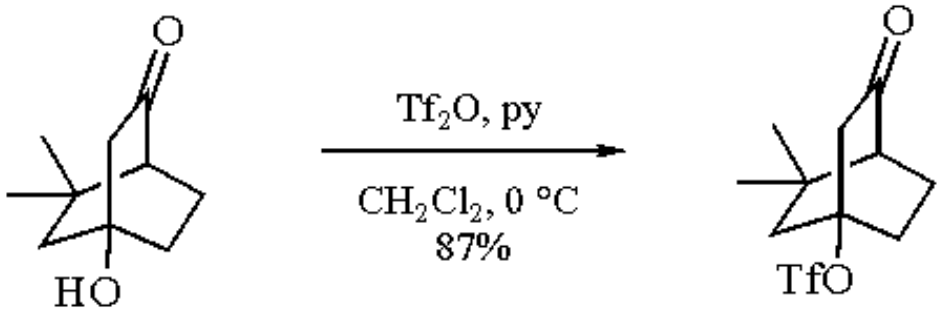

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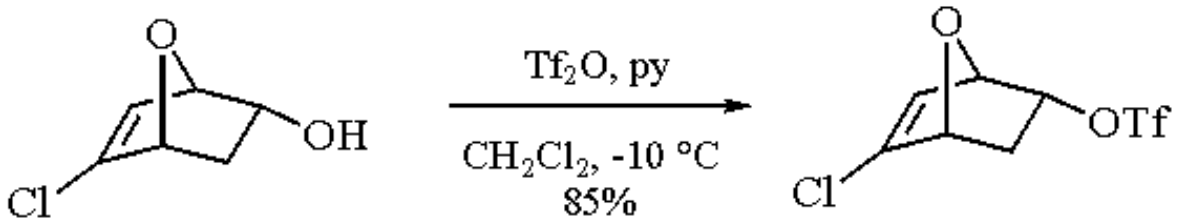

(3)

Alkyl triflates have come to be recognized as useful intermediates for the functionalization of organic substrates by nucleophilic substitution, e.g. in carbohydrate chemistry.[9] Triflate is the best leaving group known[1b] next to the nonaflate and hence a large number of triflates, obtained in good yields by reaction of the corresponding alcohols (or alkoxides) with Tf_2O, have been used to generate unstable or destabilized carbocations under solvolytic conditions.[1b] Some new typical examples are shown in (**1**)-(**4**).[10-13]

(1)

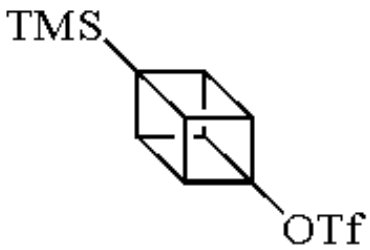

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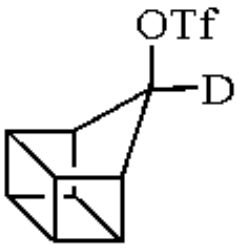

(3)

(4)

Alkyl triflates are known to be powerful reagents for the alkylation of aromatic compounds.[1b,14] However, the reaction of alkyl triflates with heterocycles affords *N*-alkylation products.[15]

In an improved modification of the Ritter reaction, primary and secondary alcohols react with Tf_2O in CH_2Cl_2 in the presence of a 2:1 excess of nitriles to give the corresponding amides in good yields (eq 4).[16]

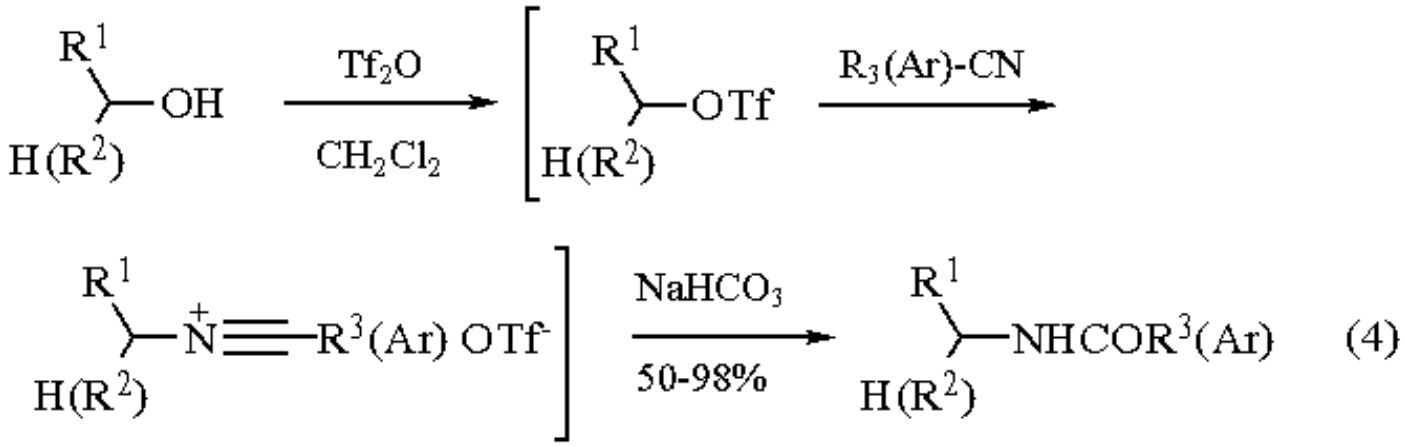

Aryl triflates are prepared from phenols at 0 °C using pyridine as solvent.[1b] Sometimes it is useful to conduct the reaction in CH_2Cl_2 at -77 °C, as in the preparation of 3,5-di-*t*-butyl-4-hydroxyphenyl triflate (eq 5).[17] Aryl triflates are synthetically transformed into several products of interest and applications in organic chemistry, by cross-coupling reactions with organometallics (eqs 5 and 6).[18]

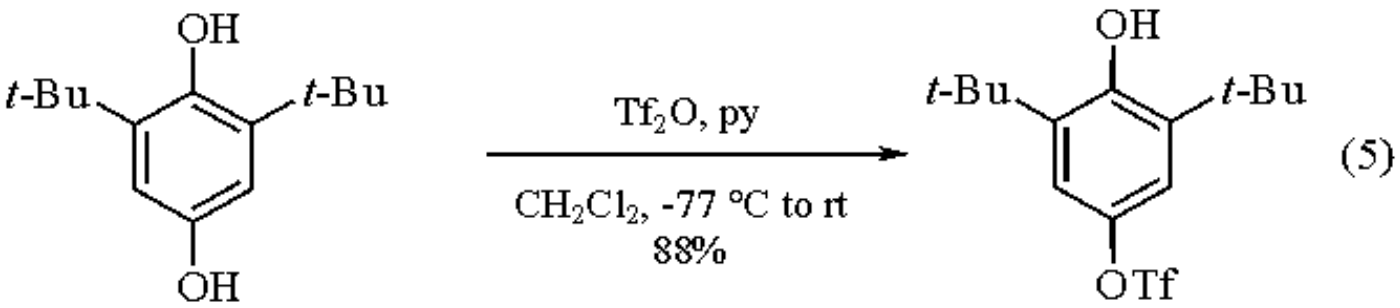

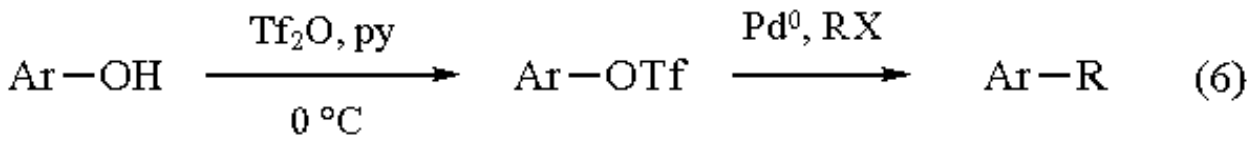

Reaction of Tf_2O with Amines.

The reaction of 1 equiv of Tf_2O in CH_2Cl_2 and Et_3N with amines (or their salts) affords trifluoromethanesulfonamides (triflamides) in good yields.[19,20] If 2 equiv of Tf_2O are used, triflimides are formed. The triflamides are soluble in alkali and readily alkylated to triflimides (eq 7).[19,20]

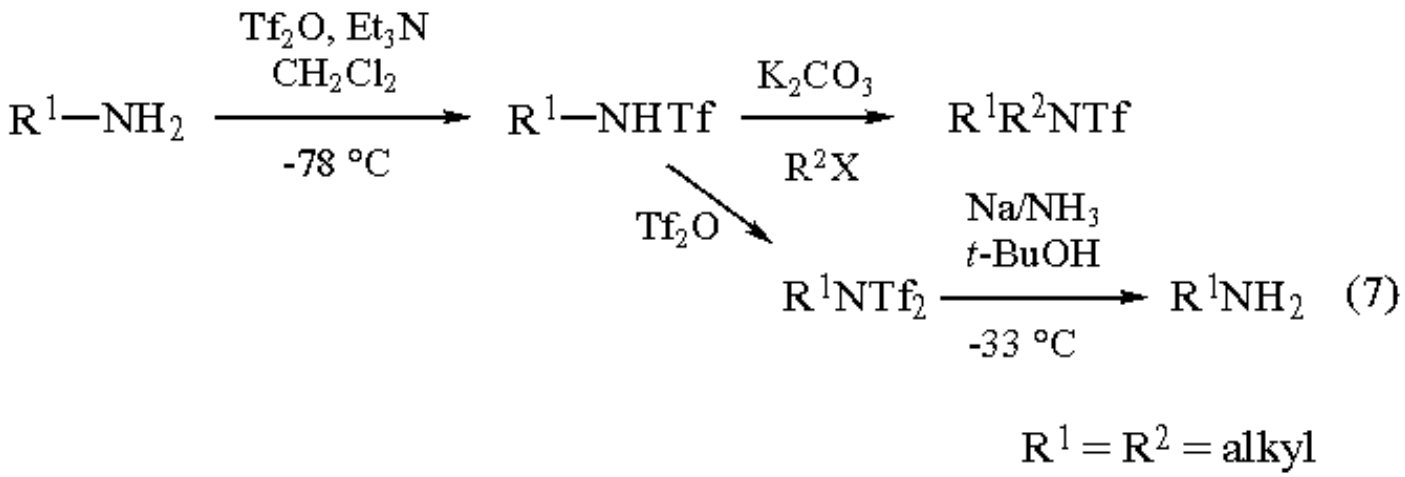

Triflamides can be deprotected reductively (***Sodium-Ammonia***) to yield the corresponding amines.[21] This protocol has been employed in the facile two-step synthesis of aza macrocycles starting from trifluoromethanesulfonyl derivatives of linear tetramines (eq 8).[22]

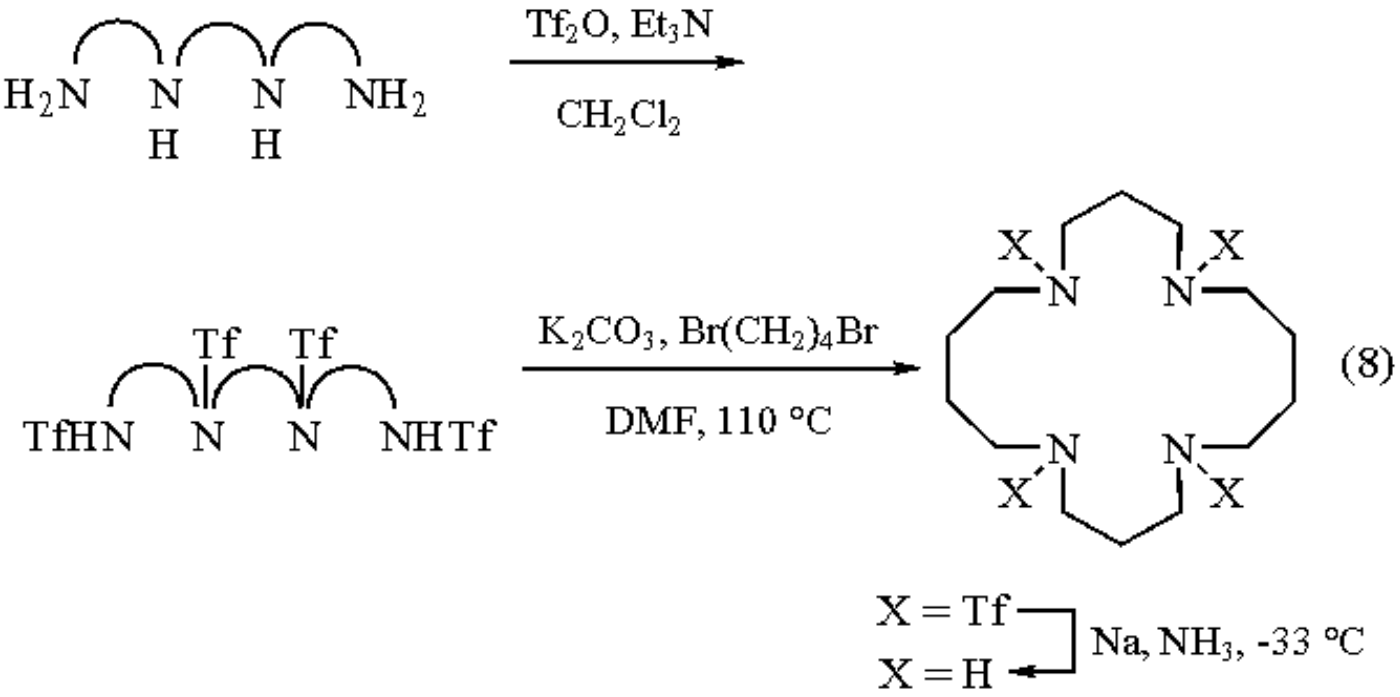

Several triflamides (**5**-**8**)[23] and *O*-triflylammonium salts[24] have been used for the formation of vinyl triflates from regiospecifically generated metalloenolates or for preparing triflates from alcohols.

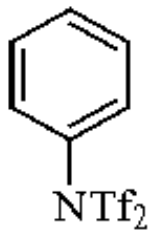

(5)

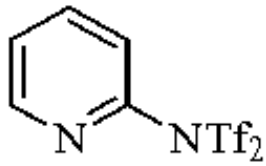

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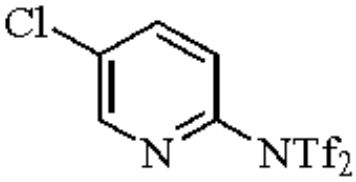

(7)

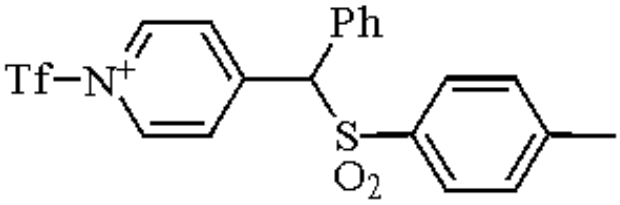

(8)

Reaction of Tf_2O with Carbonyl Compounds.

The reaction of Tf_2O with carbonyl compounds consists of the electrophilic attack of the anhydride on the carboxylic oxygen, resulting in the formation of triflyloxycarbenium ions as intermediates (eq 9). According to the nature of the carbonyl compound, the triflyloxycarbenium cations can eliminate a proton giving a vinyl triflate, undergo a rearrangement, or be trapped by the gegenion yielding *gem*-bistriflates (eq 9).

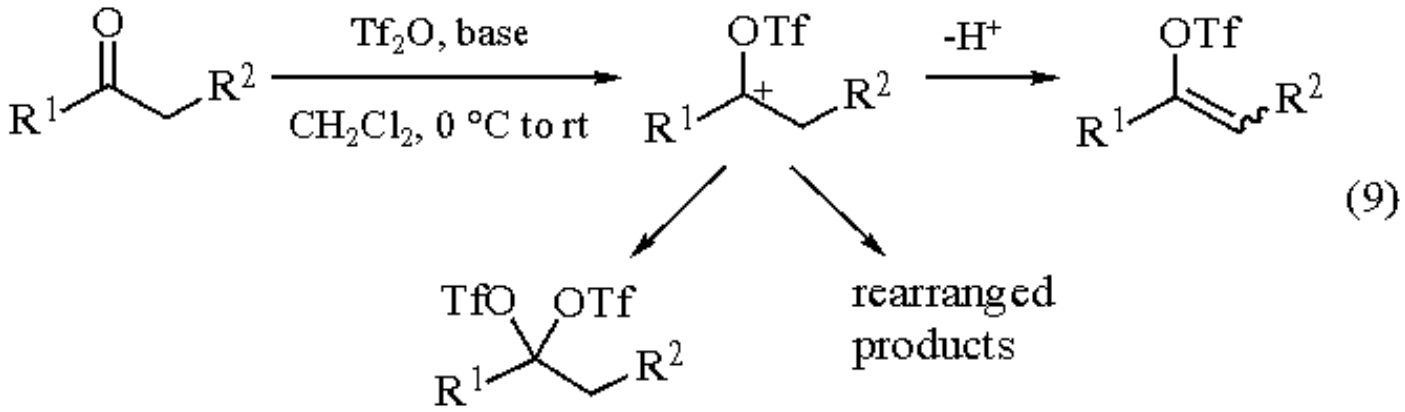

(9)

In the case of acyclic and monocyclic ketones, the reaction with Tf_2O affords vinyl triflates in good yields. Several methods exist to realize this reaction.[1b,25] For example, the reaction is carried out at room temperature in CH_2Cl_2 (or pentane) in the presence of 2,4-di-*t*-butyl-4-methylpyridine (DTBMP) (eq 10).[4]

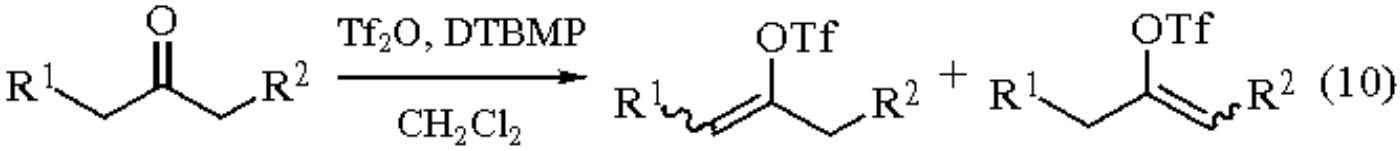

(10)

Other bases such as pyridine,[1b] lutidine,[1b] Et_3N,[1b] polymer-bound 2,6-di-*t*-butyl-4-methylpyridine,[26] and 2,4,6-trialkyl-substituted pyrimidines[27] were also used. The commercially available *N*,*N*-diisobutyl-2,4-dimethyl-3-pentylamine is a very convenient base to prepare the vinyl triflates.[28] In the case of nonfunctionalized ketones, anhydrous Na_2CO_3 has been proved to be very successful.[1b,25]

The reaction of ketones with Tf_2O is governed by Markovnikov's rule and results in the formation of the more substituted triflate as the major product. When the reaction of ketones[27] and α-halo ketones[29] with Tf_2O is carried out in the presence of a nitrile, the intermediate trifloxy cation (eq 9) can be trapped, forming pyrimidines in good yields (eq 11).

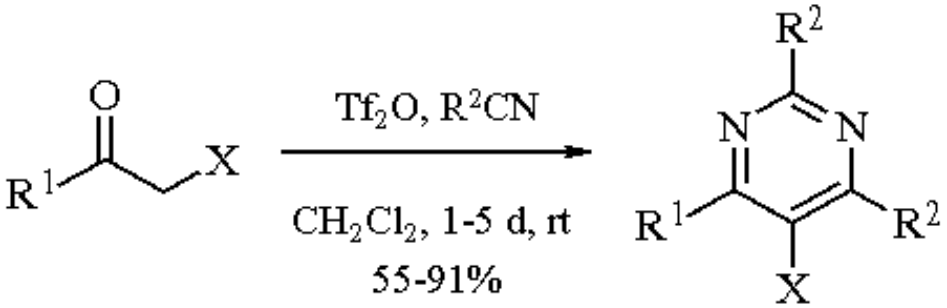

(11)

X = Cl, Br, I

$R^1 = R^2$ = alkyl, aryl

The reaction of Tf_2O with strained bicyclic ketones such as 2-norbornanone and nopinone takes place with Wagner-Meerwein rearrangement of the corresponding triflyloxy cations, forming bridgehead triflates in good yields (eq 12).[30] These triflates are key compounds in the preparation of other bridgehead derivatives by substitution[31] and of substituted cyclopentanes by fragmentation.[32]

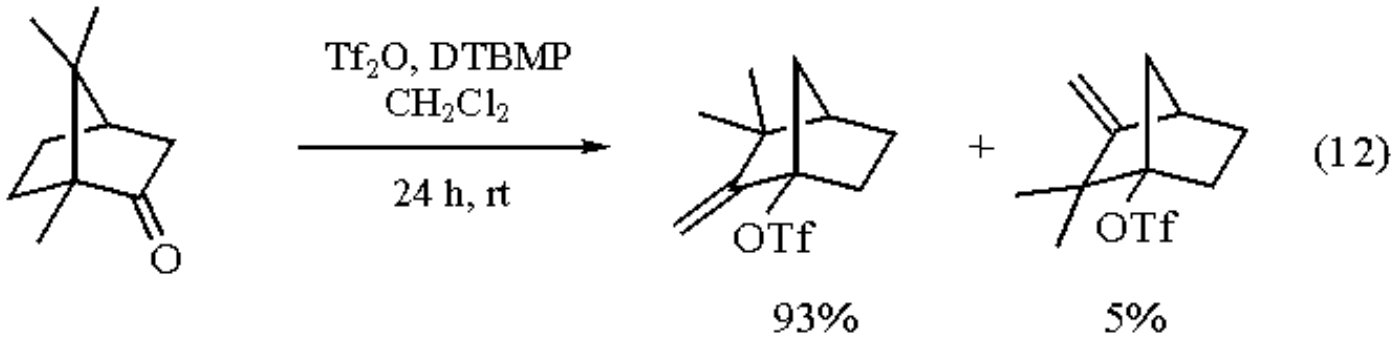

(12)

In the reaction of Tf_2O with norcaranones and spiro[2.5]octan-4-one, the cyclopropane ring undergoes fragmentation to give vinyl triflates (eqs 13 and 14).[33]

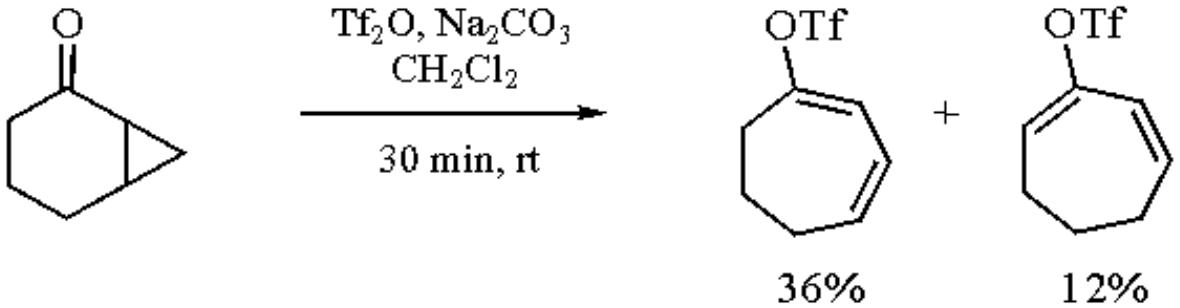

(13)

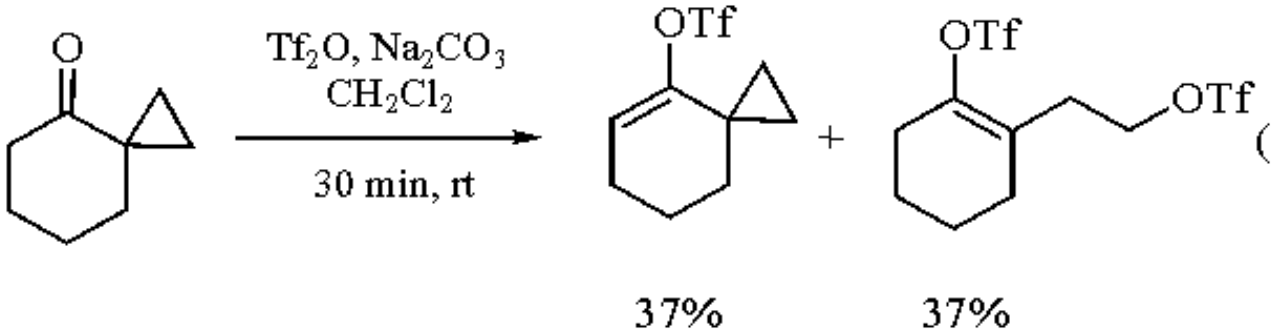

(14)

However, a cyclopropane ring is formed in the reaction of 5-methylnorborn-5-en-2-one with Tf_2O under the same conditions (eq 15).[34]

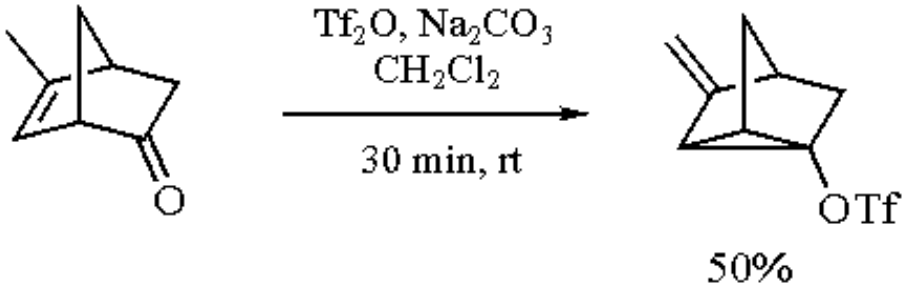

(15)

When the ketone can accomplish neither the stereoelectronic conditions for the elimination of TfOH nor for a rearrangement, the reaction of ketones with Tf_2O results in the formation of a *gem*-bistriflate (eqs 16 and 17).[35]

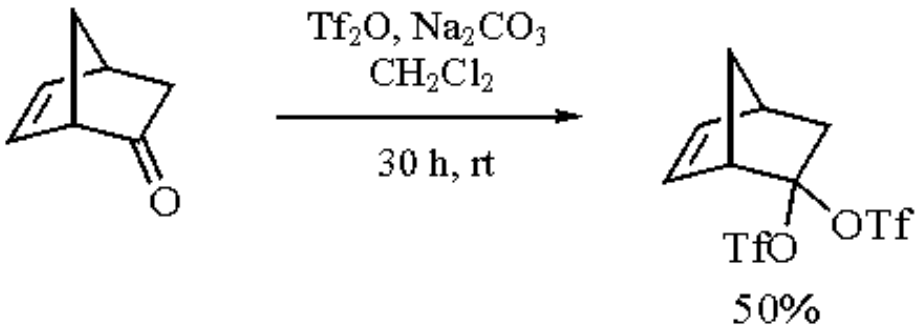

(16)

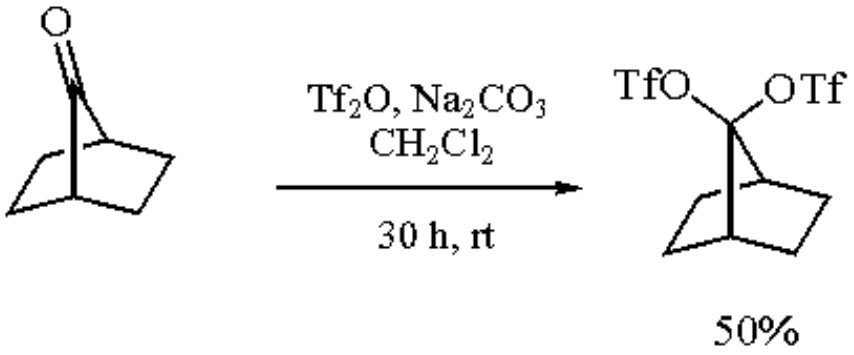

(17)

Sensitive ketones such as 3-pentyn-2-one also afford the corresponding vinyl triflate on treatment with Tf_2O in the presence of a base (eq 18).[36]

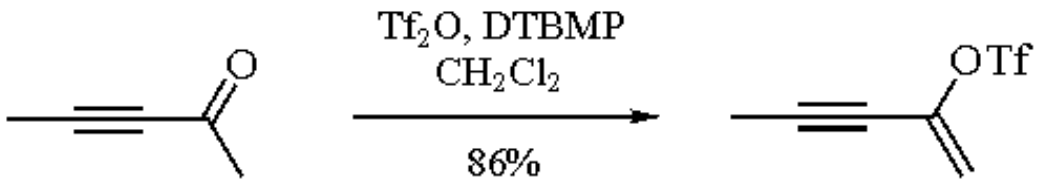

(18)

Substituted cyclopropenones and tropones react with Tf_2O with the formation of the corresponding dication ether salts (eq 19).[37]

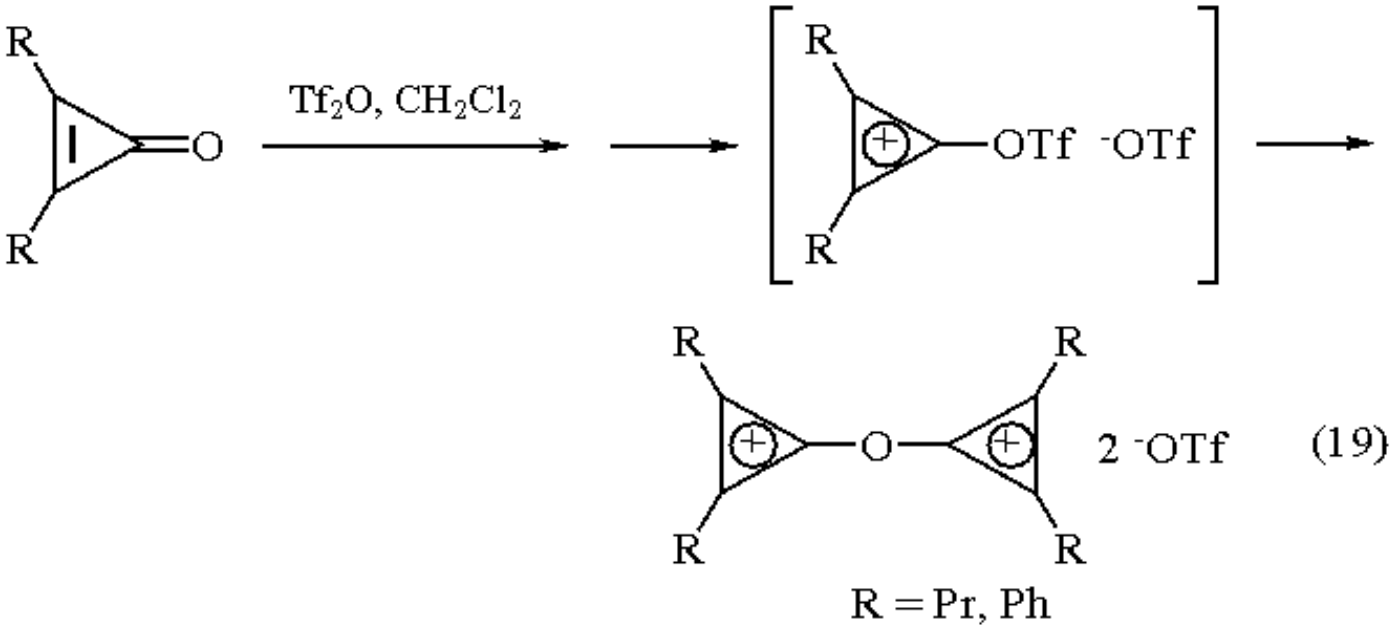

(19)

Treatment of trifluoroacetyl ylides with Tf_2O results in the formation of *gem*-bistriflates (eq 20).[38]

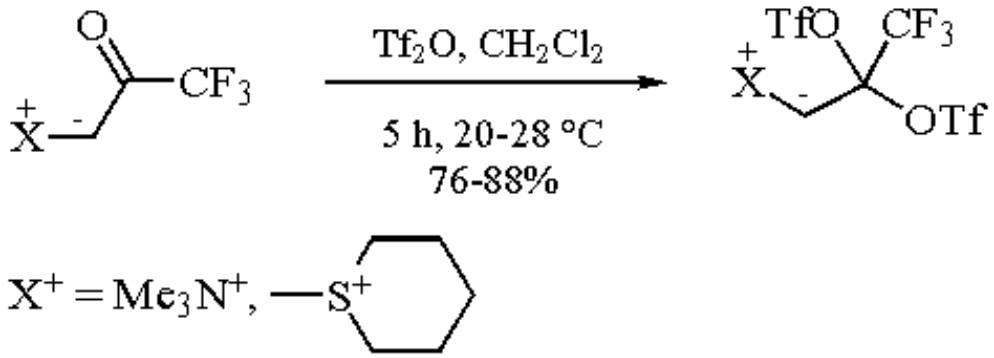

(20)

Reaction of Tf_2O with Aldehydes.

The reaction of aliphatic aldehydes with Tf_2O in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP) in refluxing CH_2Cl_2 or $ClCH_2CH_2Cl$ for 2 h affords the corresponding vinyl triflates as a mixture of (*Z*)- and (*E*)-isomers.[4,39] When the reaction is carried out at 0 °C, *gem*-bistriflates are formed as products (eq 21).[40] The *gem*-bistriflates result due to the trapping of the intermediate triflyloxycarbenium ion by the triflate anion. Primary vinyl triflates have been used extensively in the generation of alkylidene carbenes,[41] and *gem*-bistriflates are interesting precursors for *gem*-dihaloalkanes[42,43] and (*E*)-iodoalkenes.[44]

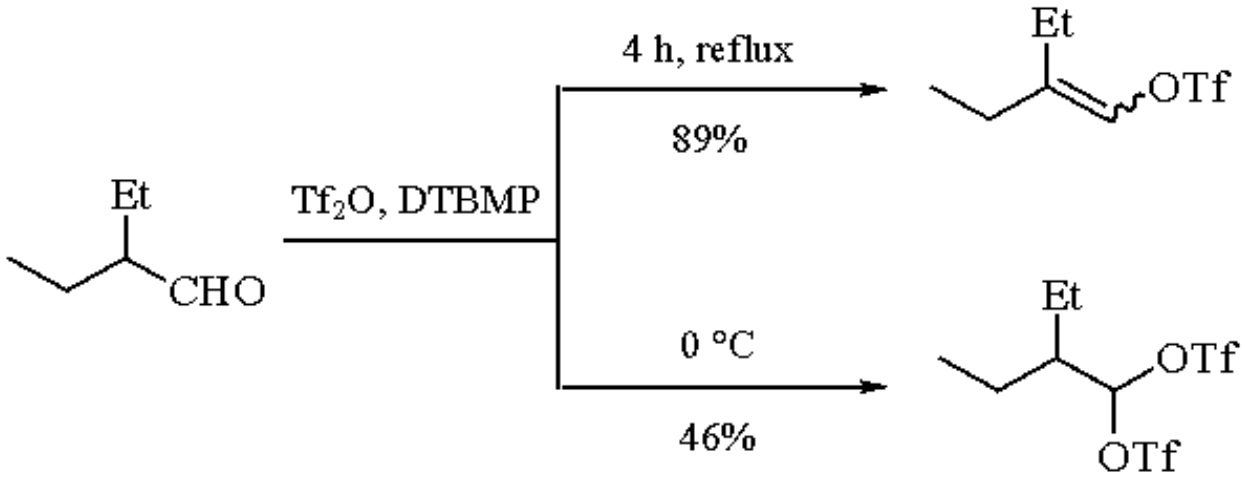

(21)

Reaction with Dicarbonyl Compounds.

1,3-Diketones can be reacted with an equimolar amount of Tf_2O or in excess to furnish the corresponding vinyl triflates or dienyl triflates (eq 22).[45] These triflates are transferred into monoketones, monoalcohols, alkanes, and unsaturated ketones by means of various reducing reagents.[45]

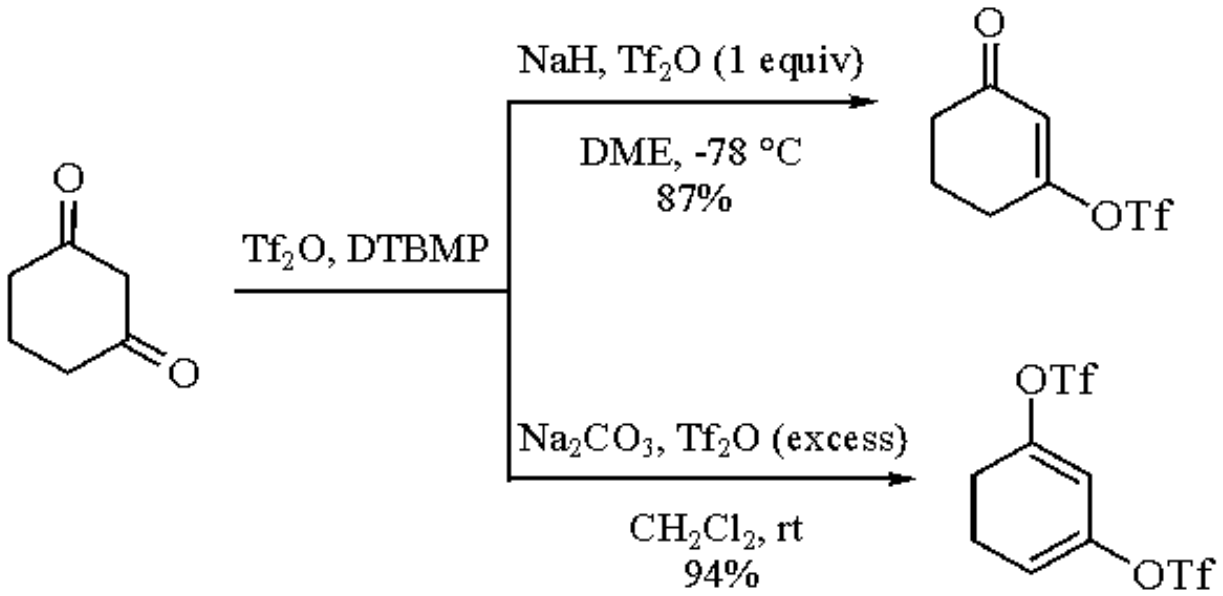

(22)

The reaction of 3-methylcyclopentane-1,2-dione with Tf_2O/Et_3N affords the vinyl triflate in 53% yield (eq 23).[46] The reaction takes place probably through the enol form. The product was coupled with alkenylzinc compounds in the presence of a palladium catalyst.[46]

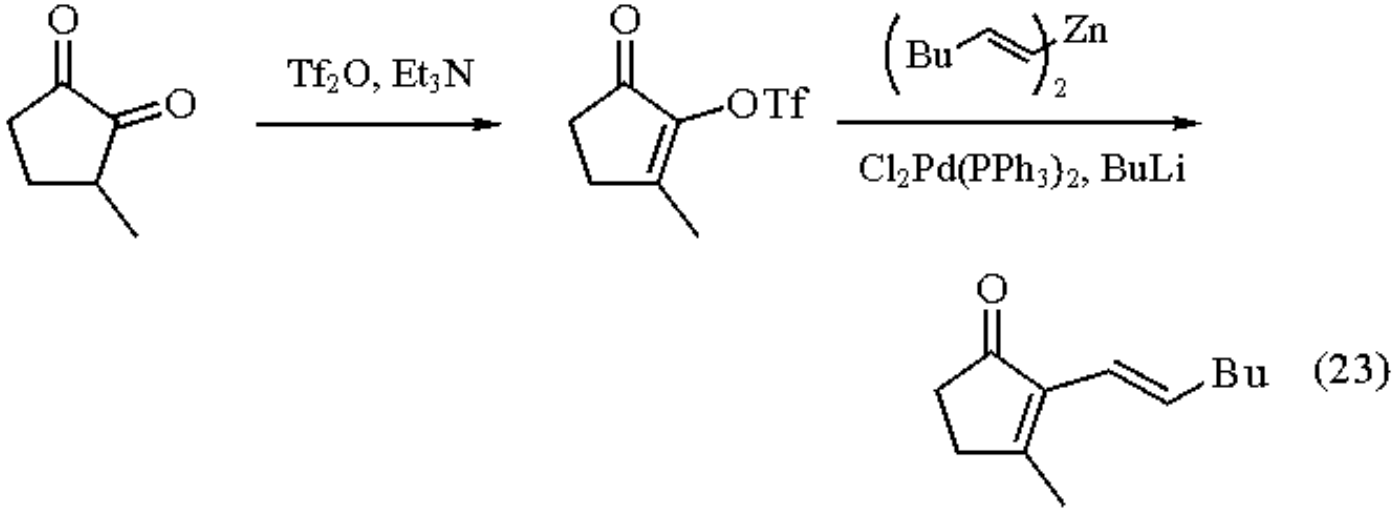

The reaction of β-keto esters[47] with Tf_2O in the presence of a base results in the formation of 2-carboxyvinyl triflates (eq 24). These substrates undergo nucleophilic substitution of the TfO- group (eq 24)[47] and also coupling reactions.[48]

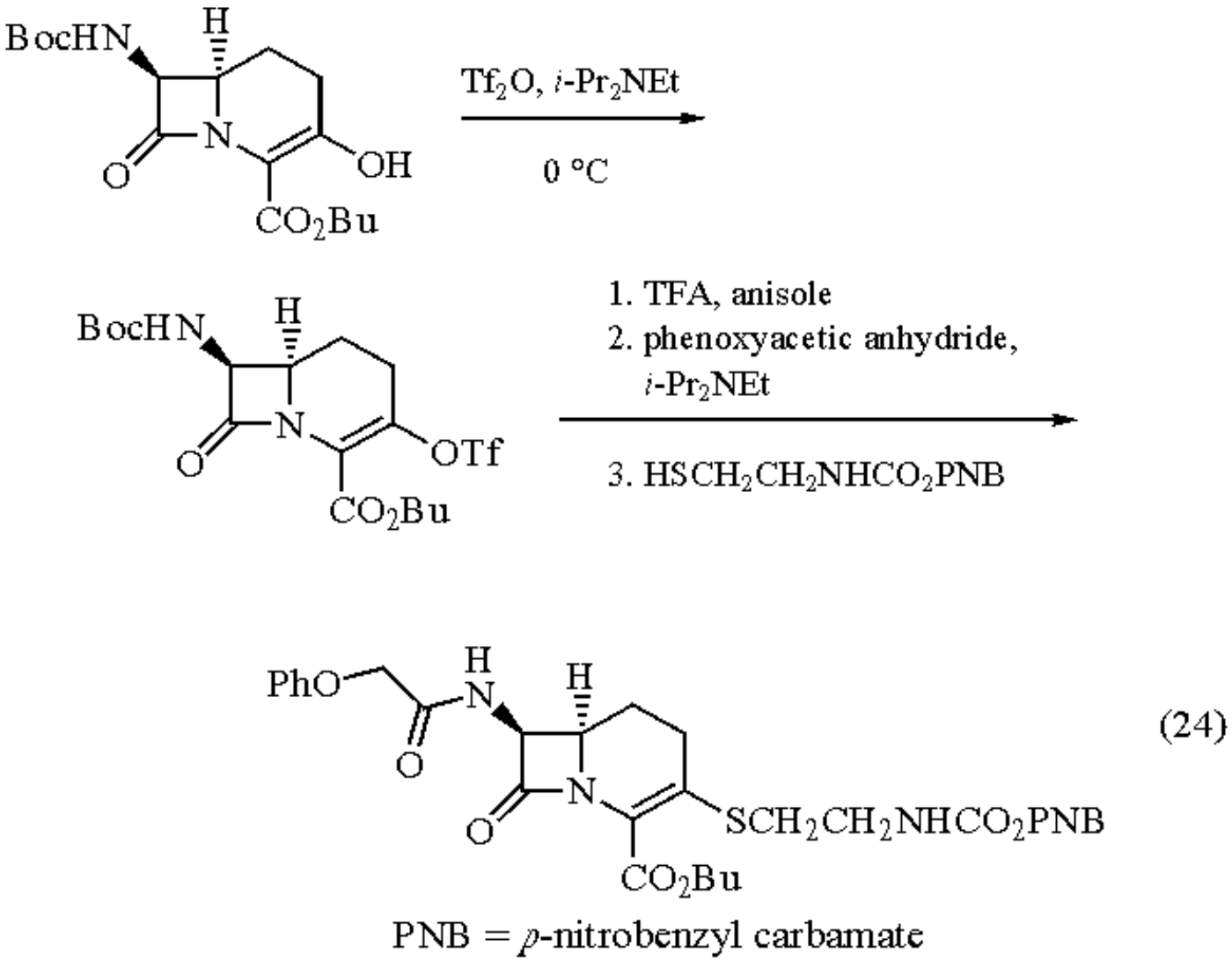

Reaction with Carboxylic Acids and Esters.

The reaction of carboxylic acids and esters with Tf_2O takes place according to the scheme shown in eq 25.[49]

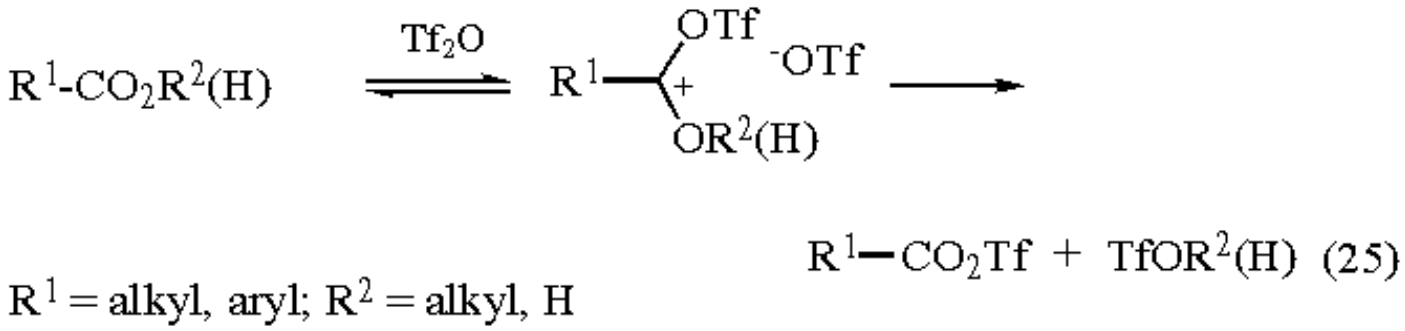

The trifluoromethanesulfonic carboxylic anhydrides are highly effective acylation agents, which react without catalysts even with deactivated aromatics to yield aryl ketones (eq 26).[50]

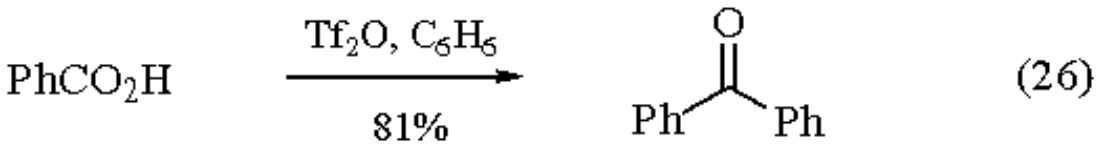

Alkyl arylacetates react with Tf_2O to give a cation which in the presence of a nitrile affords isoquinoline derivatives via cyclization of the intermediate nitrilium cation (eq 27).[50]

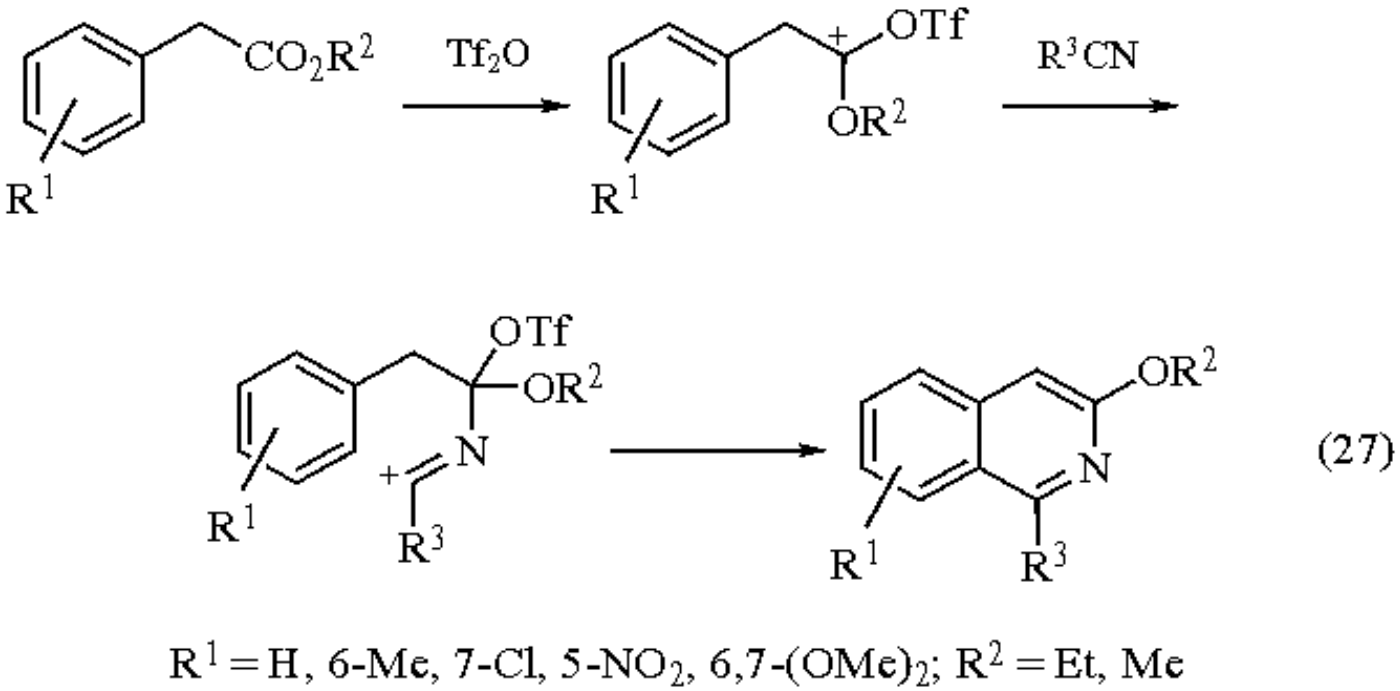

Reaction of Tf_2O with Amides.

The reaction of a 2-oxo-1,2-dihydroquinoline with Tf_2O in the presence of pyridine affords the corresponding 2-quinoline triflate (eq 28).[51]

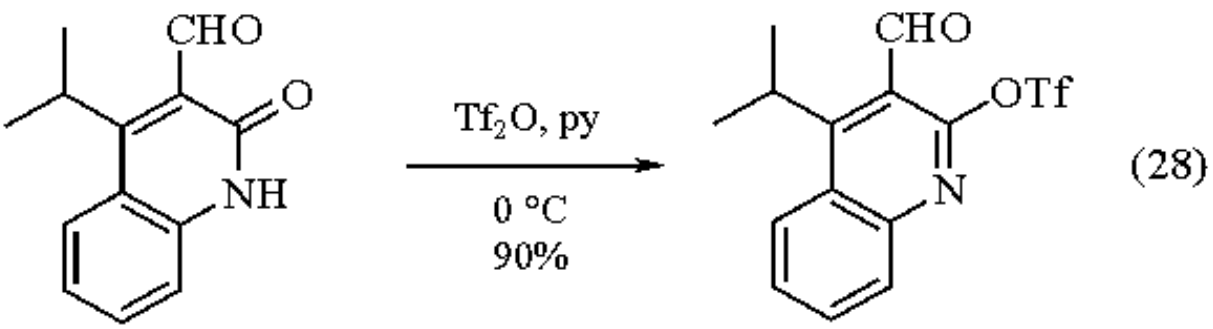

The reaction of tertiary amides with Tf_2O gives a mixture of *O*-sulfonylated (major) and *N*-sulfonylated (minor) products. In the presence

of collidine and an alkene, [2 + 2] cycloadducts are formed which hydrolyze to give cyclobutanones (eq 29).[52]

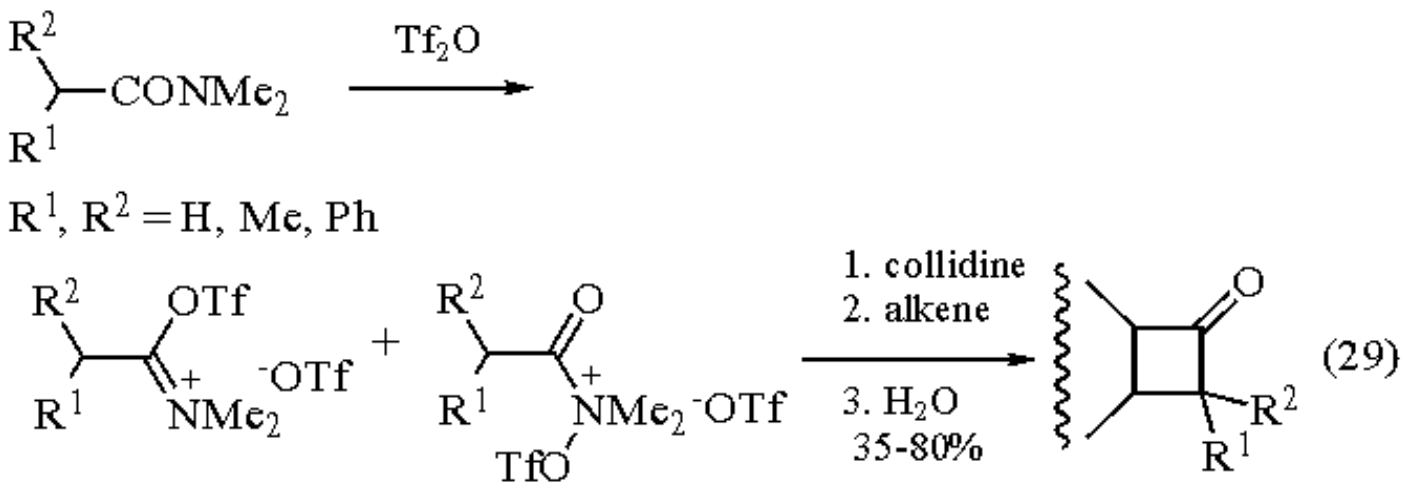

Treatment of DMF with Tf_2O results in the formation of an imminium triflate, which formylates less active aromatics. It is a convenient variation of the Vilsmeier-Haack reaction (eq 30).[53]

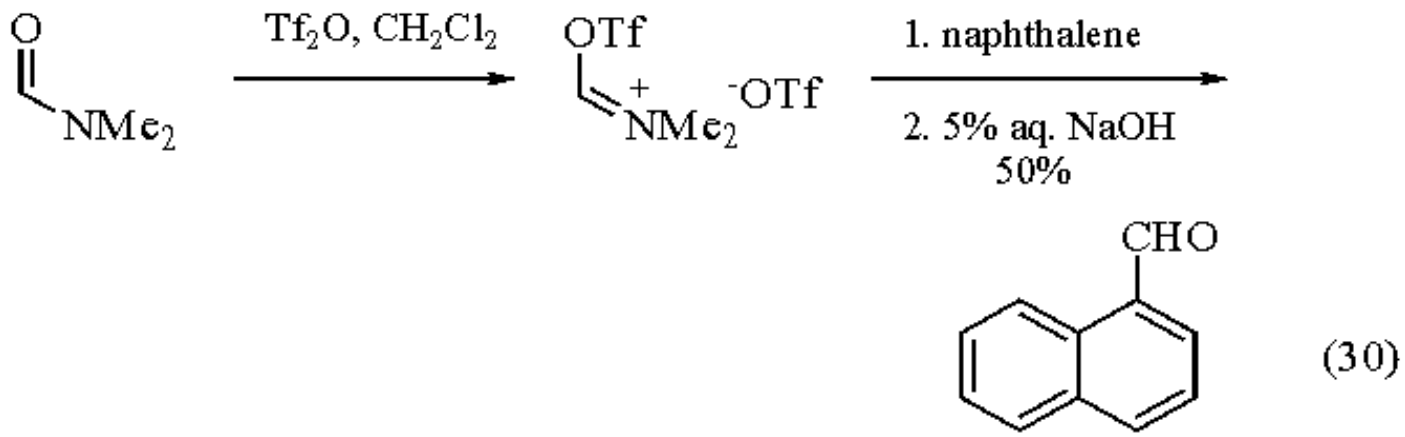

The reaction of *N*-methylpyridone and substituted urea systems with Tf_2O gives heteroatom-stabilized dicarbonium salts (eqs 31 and 32).[37,54]

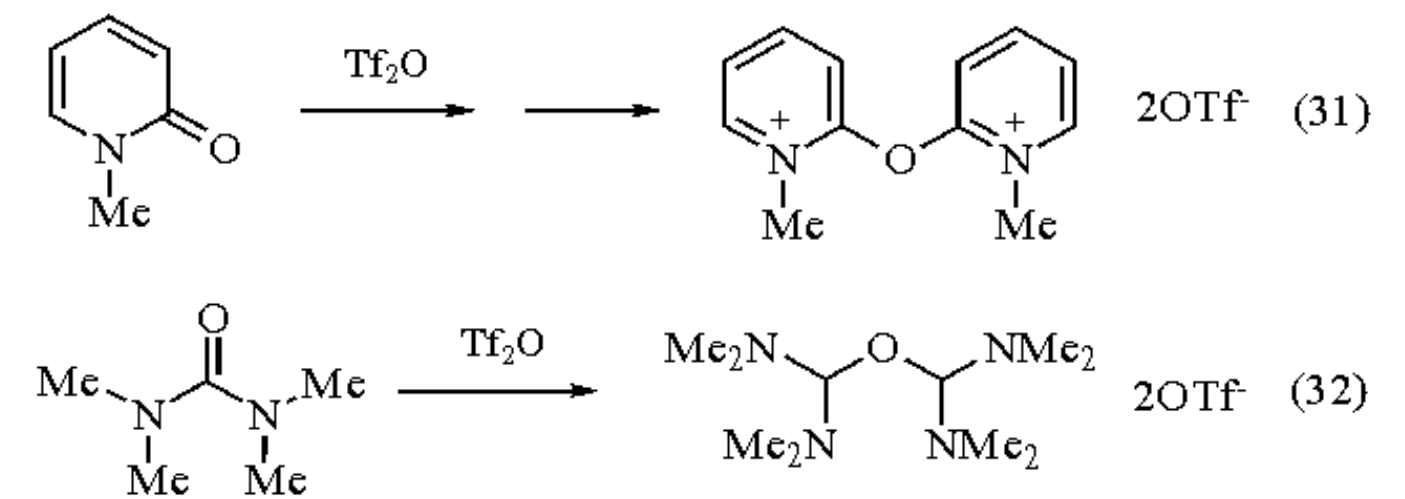

Secondary amides can be converted to tetrazoles with Tf_2O in the presence of ***Sodium Azide*** (eq 33).[55]

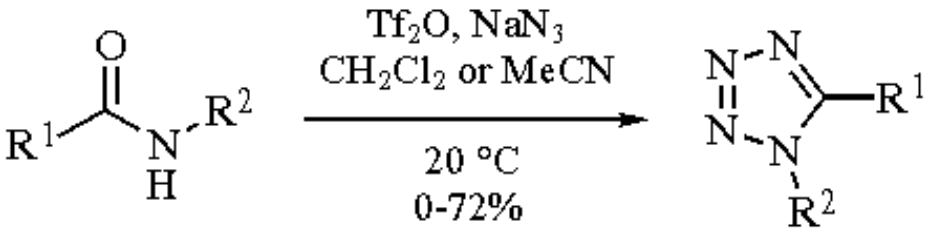

(33)

R^1 = alkyl, Ph; R^2 = alkyl, $(CH_2)_2OAc$, $(CH_2)_2OTBDMS$

Other Applications.

Activated arenes can be converted to aryl triflones by Friedel-Crafts reaction with Tf_2O using ***Aluminum Chloride*** as catalyst (eq 34).[56]

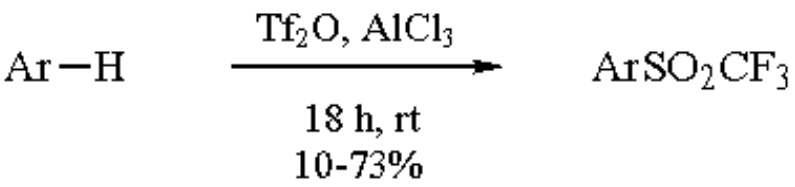

(34)

The reaction of Tf_2O with Ph_3PO in CH_2Cl_2 at 0 °C affords triphenylphosphine ditriflate, which can be used as an oxygen activator, and then to a diphosphonium salt (eq 35).[57]

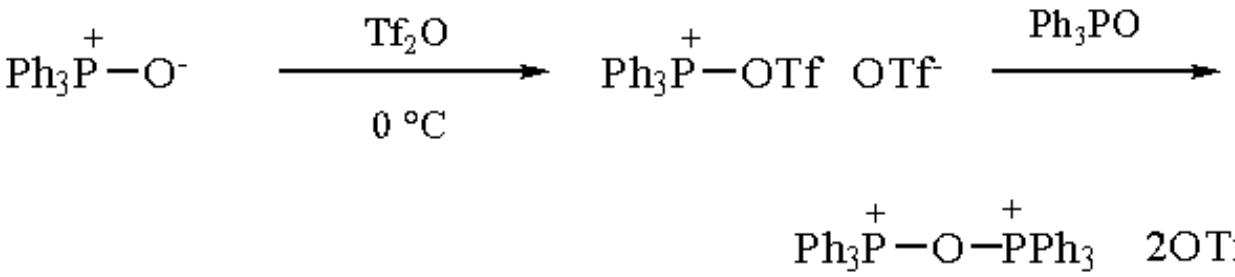

(35)

The less stable dimethyl sulfide ditriflate, obtained from Tf_2O and DMSO, has been used to oxidize alcohols (eq 36).[58]

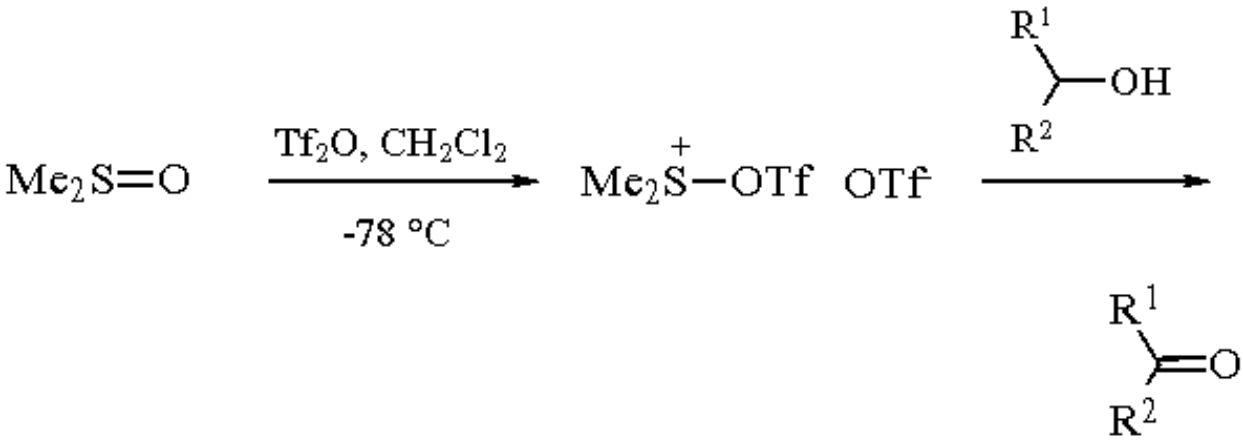

(36)

Tetrahydropyran is not a suitable solvent in reactions involving Tf_2O because it is cleaved, affording 1,5-bistrifloxypentane (eq 37).[59]

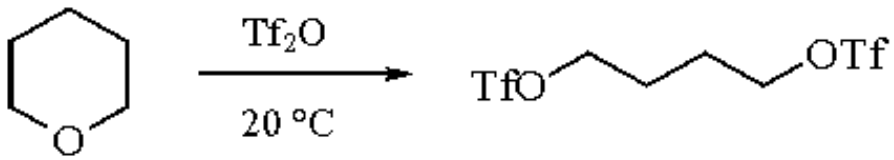

(37)

Diols react with Tf_2O to yield the corresponding ditriflates; however, the reaction of 1,1,2,2-tetraphenyl-1,2-ethanediol with Tf_2O takes

place with rearrangement (eq 38).[59]

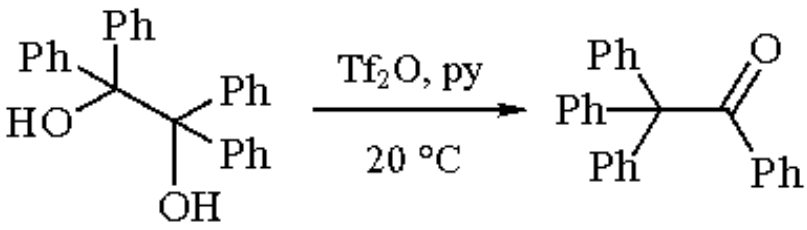

(38)

Vinylene 1,2-bistriflates are formed by the reaction of azobenzils with Tf_2O (eq 39).[60]

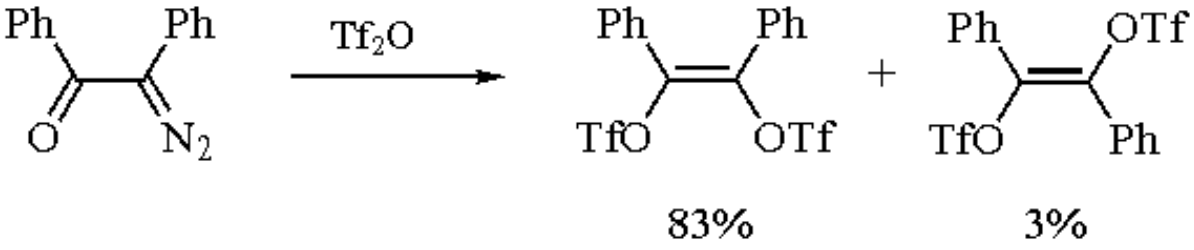

(39)

The reaction of enolates, prepared from silyl enol ethers and ***Methyllithium***, with Tf_2O affords vinyl triflates (eq 40).[61]

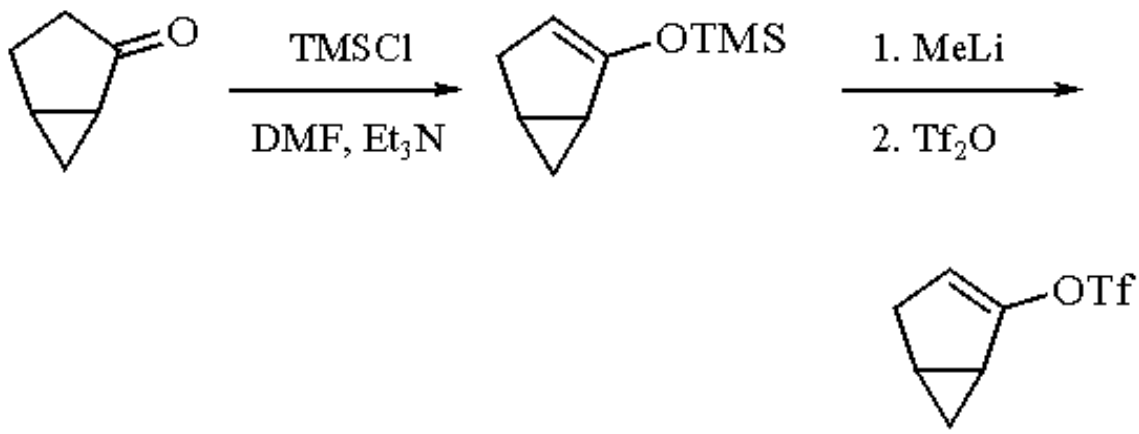

(40)

The combination of equimolecular quantities of ***Iodosylbenzene*** and Tf_2O generates $PhI(OTf)_2$, a compound also formed by treatment of Zefiro's reagent with Tf_2O. As shown in eq 41, this compound can be used to prepare *para*-disubstituted benzene derivatives in good yields.[62]

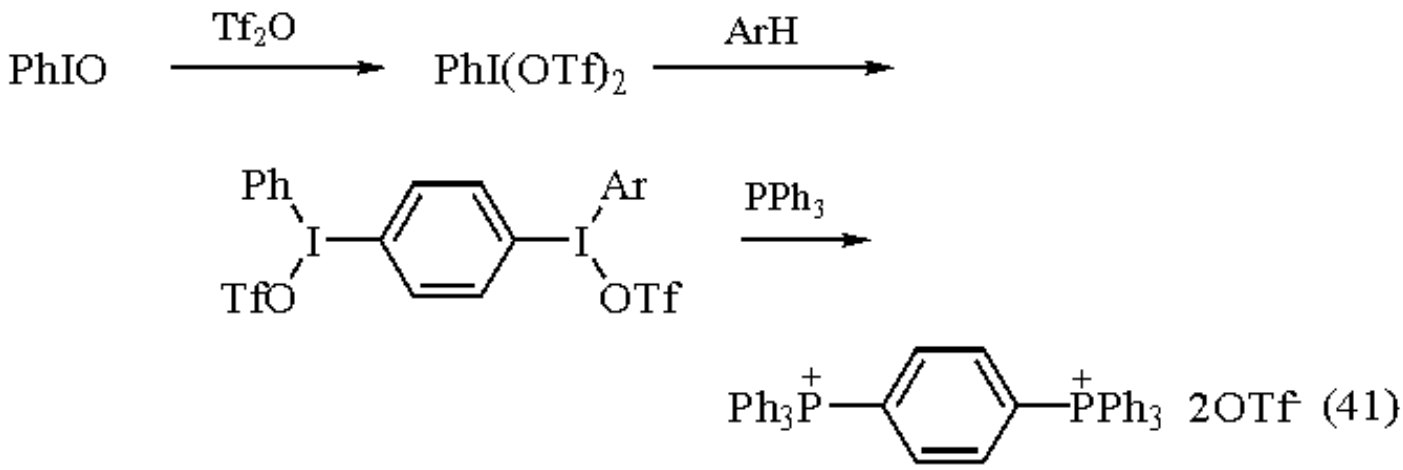

(41)

Tf_2O is a suitable promoter for the stereoselective glucosidation of glycosyl acceptors using sulfoxides as donors.[63]

The reaction of Tf_2O with a catalytic amount of ***Antimony(V) Fluoride*** at 25 °C produces trifluoromethyl triflate in 94% yield (eq 42).[64]

$$(CF_3SO_2)_2O \xrightarrow[80\%]{SbF_5} CF_3OSO_2CF_3 \qquad (42)$$

Useful application of Tf_2O as dehydrating reagent is accounted by the synthesis of isocyanides from formamides and vinylformamides (eq 43).[65]

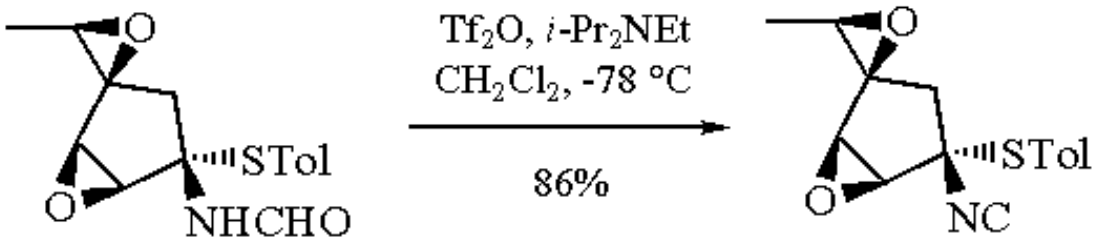

(43)

Reaction of enaminones with Tf_2O in a 1:1 molar ratio affords 3-trifloxypropeniminium triflates by *O*-sulfonylation. From a cyclic enaminone, by using a 2:1 molar ratio, the corresponding bis(3-amino-2-propenylio) bistriflate is obtained (eq 44).[66]

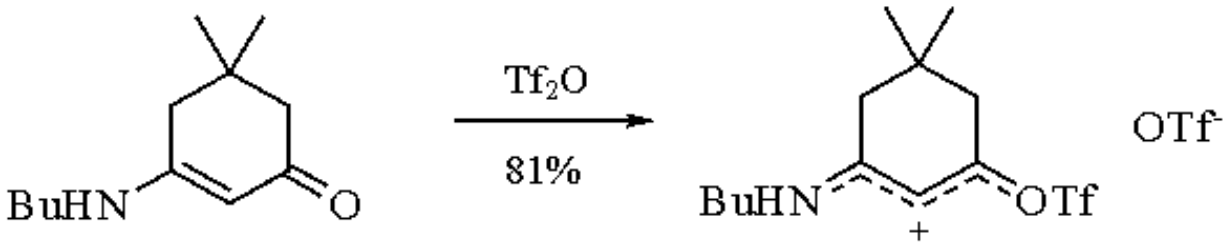

(44)

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Trifluoromethanesulfonyl Chloride[1]

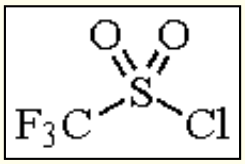

[421-83-0] · $CClF_3O_2S$ · Trifluoromethanesulfonyl Chloride · (MW 168.53)

(trifluoromethylsulfonation agent;[1] chlorinating agent;[2] metal-catalyzed chlorotrifluoromethylation of alkenes[3])

Alternate Name: triflyl chloride.

Physical Data: bp 29-32 °C, *d* 1.583 g cm^{-3}.

Solubility: sol CH_2Cl_2, THF, dioxane.

Form Supplied in: colorless liquid, 99 +%.

Analysis of Reagent Purity: IR: 1424, 1306, 1237, 1115, 771, 611, 565, 532, 404 cm^{-1}.[4]

Preparative Methods: dried ***Zinc Trifluoromethanesulfonate*** is heated with PCl_5.2ZnCl at 260 °C. Fractional distillation of the volatile products gives TfCl (94% yield).[5]

Handling, Storage, and Precautions: moisture sensitive; store under N_2 in the cold. This toxic reagent is corrosive and is a lachrymator. It should only be handled in a fume hood.

Triflate and Triflamide Formation.

Triflyl chloride (TfCl) reacts as an electrophile with oxygen and nitrogen nucleophiles to produce triflate or triflamide derivatives. The trifluoromethanesulfonate group is a highly electron-withdrawing moiety and is a useful leaving group in organic synthesis for nucleophilic displacement, solvolysis, and metal-catalyzed coupling reactions.[1] The sulfonation reaction works well with amines[6] and alcohols, and is especially suitable for phenols.[7] An amine base such as ***Triethylamine*** or ***Diisopropylethylamine*** is usually added as an acid scavenger and to activate the substrates; however, the reactivity of the starting materials can be increased with prior anion formation by a stronger base.[8] Less reactive substrates may be sulfonated using ***Trifluoromethanesulfonic Anhydride*** or other derivatives of triflic acid such as those formulated from imidazole[9] or amides.[10] These are the reagents of choice for the formation of enol triflates from carbonyl compounds having α-hydrogens.[1] Mixed sulfonic anhydrides can be formed by reaction of the silver salt of an alkylsulfonic acid with triflyl chloride.[11]

An enol has been activated toward intramolecular nucleophilic addition with TfCl (eq 1).[12] A pyridine heterocycle reacts in a similar way.[13] In these reactions the triflinate anion ($CF_3SO_2^-$) functions as the leaving group. This sulfinate anion has also been studied as a nucleophile and potassium trifluoromethanesulfinate may be prepared by the reduction of TfCl with ***Potassium Iodide***.[14]

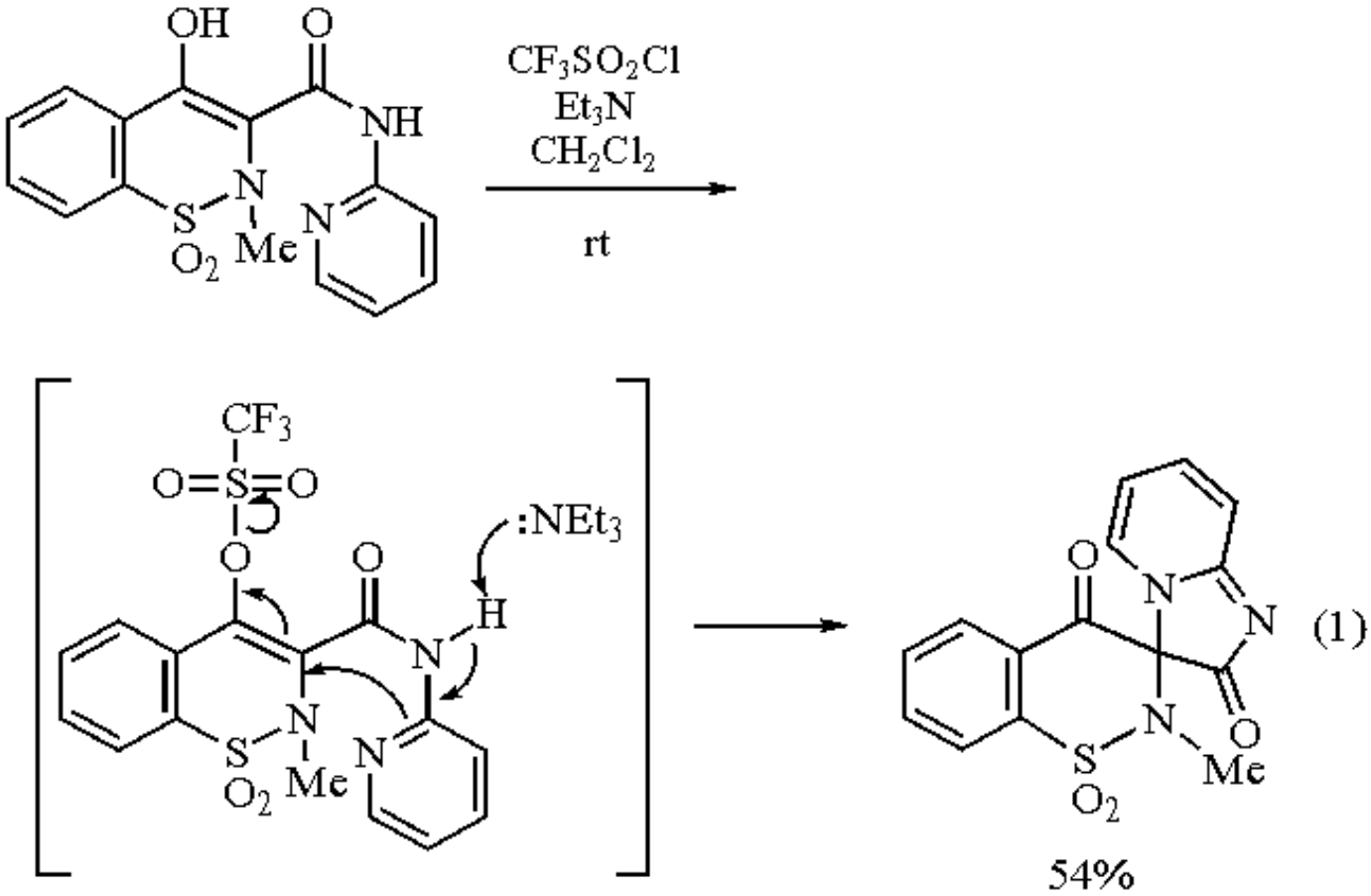

Chlorination of Activated Methylenes.

Triflyl chloride acts as a mild chlorinating reagent with certain carbon acids and nucleophiles.[15] Carbon acids in the pK_a range between diethyl malonate and methyl dichloroacetate react with TfCl in the presence of an amine base such as Et_3N or ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** to replace one or two acidic hydrogens with chlorine. The reaction is highly selective with the rate of chlorination being at least 10^5 greater than the rate of sulfonation. Yields are generally excellent and the reagent is often much more efficient than other chlorinating agents such as ***N-Chlorosuccinimide***. This transformation has been utilized for the synthesis of 2,2-disubstituted tetrahydrofurans, pyrans, and pyrrolidines (eq 2).[16]

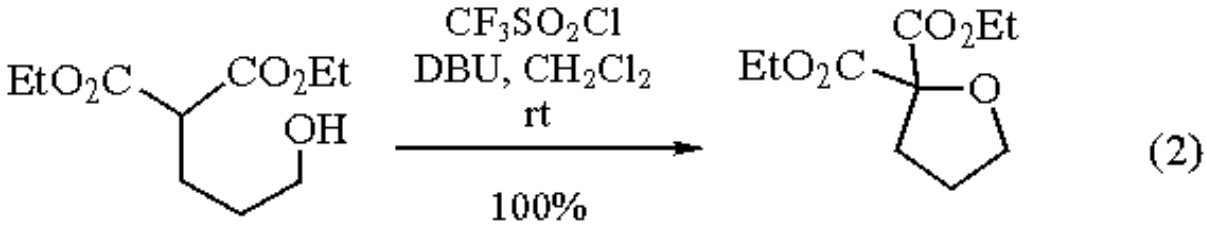

When triflyl chloride and ***Sodium Azide*** are added to carbon acids, a similar reaction is observed and the corresponding azides are obtained in 50-60% yields.[17] The reactive species in this transformation is thought to be $F_3CSO_2N_2$. Similar reactivity has been seen with TfCl and ***Silver(I) Nitrate***. The intermediate $F_3CSO_2NO_2$ reacts with activated methylenes and ***Potassium t-Butoxide*** to give nitro derivatives in fair yields.[18]

Metal-Catalyzed Chlorotrifluoromethylation of Alkenes.

Dichlorotris(triphenylphosphine)ruthenium(II) catalyzes the reaction between triflyl chloride and alkenes to give vicinally chloro/trifluoromethyl-substituted alkanes with the extrusion of sulfur dioxide.[19] The reaction works well for alkenes bearing either electron-withdrawing or electron-donating substituents (eq 3). Terminal alkenes give the best yields but the reaction works with internal double bonds as well. Temperatures &egt;120 °C are required for complete extrusion of sulfur dioxide. Treatment of the products with aqueous ***Potassium Hydroxide*** causes the elimination of HCl to give vinyltrifluoromethane derivatives. The same ruthenium catalyst promotes the reaction between triflyl chloride and arenes to give trifluoromethylated aromatic compounds.[20] Trifluoromethyl iodide, an alternative reagent for the introduction of the trifluoromethane group, is less convenient to work with since it is a gas at rt.[3]

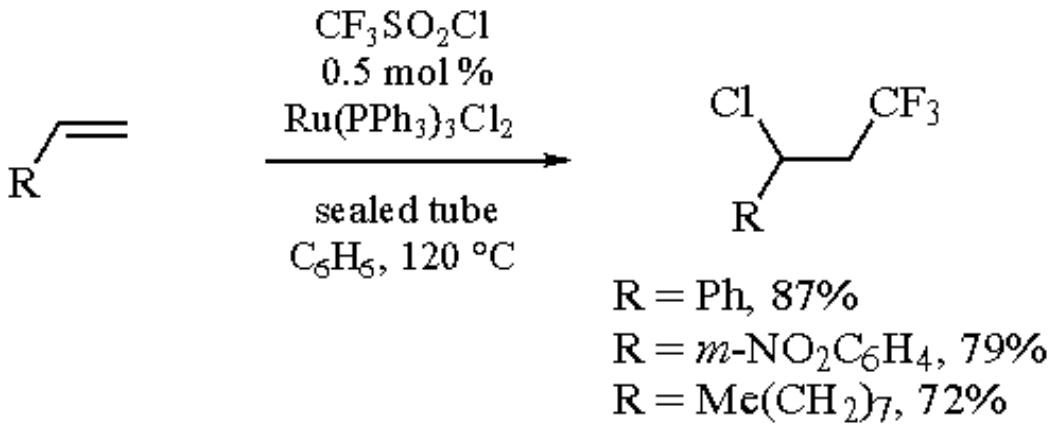

(3)

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Trifluoromethanesulfonylmethyl Methyl Sulfone

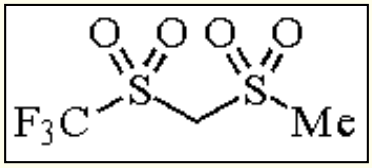

[93916-15-5] · $C_3H_5F_3O_4S_2$ · Trifluoromethanesulfonylmethyl Methyl Sulfone · (MW 226.22)

(equivalent of alkene polyanion[1])

Alternate Name: mesyl triflone.

Physical Data: mp 115-116 °C.

Solubility: insol cold H_2O; sol HCO_3^-, common organic solvents.

Preparative Methods: by triflation of ***Dimethyl Sulfone*** in base (EtMgBr/THF) with trifyl fluoride (CF_3SO_2F)[1] or by analogous sulfonylation of methyl triflone ($CH_3SO_2CF_3$)[2] with ***Methanesulfonic Anhydride***.

Purification: recrystallized from H_2O, dried over P_2O_5 in vacuo.

Handling, Storage, and Precautions: stable solid, no known toxicity.

General Discussion.

The reagent acts as an alkene polyanion equivalent ($^{2-}C{=}C^{2-}$) owing to successive alkylations of its di- or trianion followed by base-catalyzed cheletropic extrusion of SO_2 to form the product alkene (eq 1).[1]

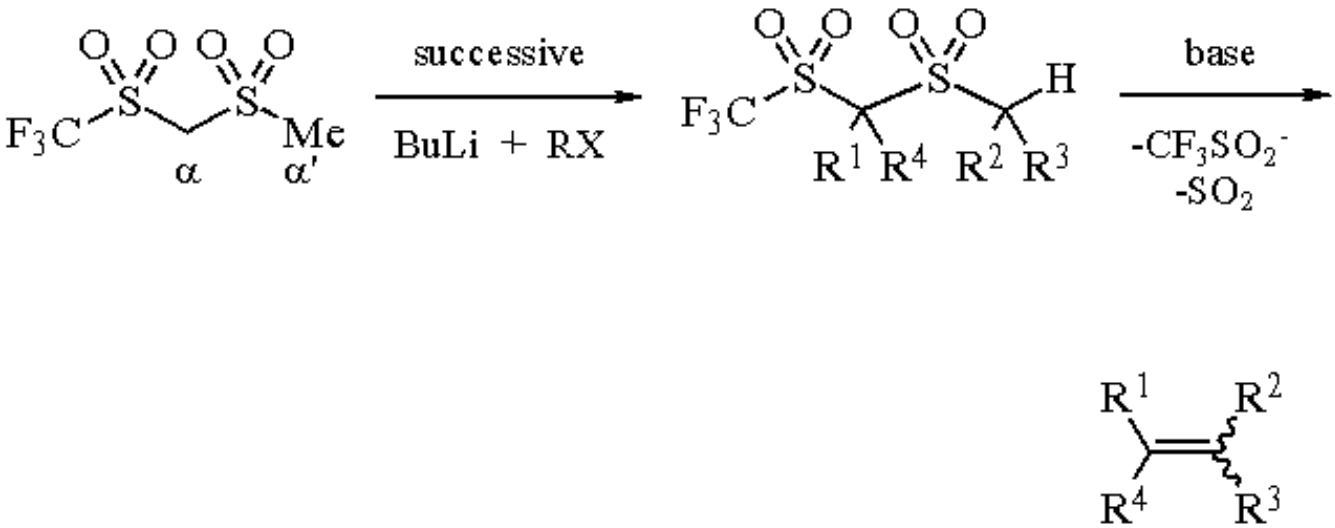

(1)

The successive alkylations, or reactions with other electrophiles, proceed with regiochemical control owing to the very different acidities of the two kinds of C-H bonds at α and α´. The most acidic proton (p*K* 4.3 in H_2O) is at α, and the dianion (2 mol ***n-Butyllithium***/THF at -78 °C) is also fully formed at the α-carbon. Alkylation of this dianion can yield either one or two alkylations at α, the former returning the stable anion of the α-monosubstituted reagent as product; the monoanion at α is very sluggish to alkylation. Successive alkylations, with added base (BuLi) and alkylating agent, proceed cleanly in the order R^1, R^2, R^3, R^4. With stoichiometric control of added base and carbon electrophile, as many as three substitutions may be carried out in one pot without isolation. Only when the α-carbon is fully substituted does treatment with base (*t*-BuO^- was the most effective[1]) afford the Ramberg-Bäcklund extrusion[3] of SO_2; otherwise, the presence of the

stable α-anion precludes it. Although the regiochemistry of substitution is well controlled, the alkene stereochemistry of the product (eq 1) is not controllable.

The final substitution (R^4) requires very active alkylating agents and elevated temperatures unless it is a cyclization. α-Alkylations which provide carbonyl activation, as with α-halo carbonyls, give rise to elimination of triflinate directly (eq 2).[1]

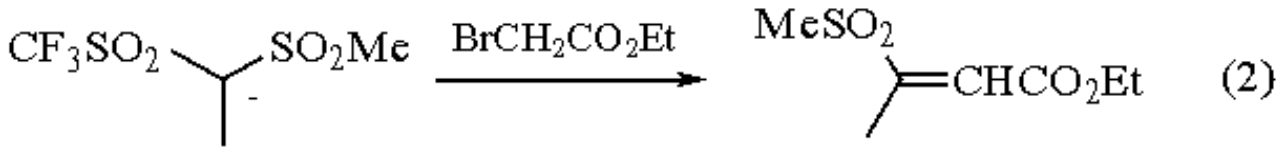

Acylation at α´ is facile (on α,α´-dianions) and requires an extra equivalent of base for the acidic α-acyl sulfone products. Aldehydes and ketones react similarly at α´ to afford β-hydroxy sulfones. Spontaneous cyclization occurred (eq 3) when the allylic alcohol from acrolein was oxidized to the unsaturated ketone (eq 3) and treatment with base completed the conversion to 3-methylcyclopentenone. However, mesylation of the β-hydroxy sulfone gave the four- instead of six-membered cyclization in eq 3 by direct rather than allylic displacement. Other cyclizations are shown in eq 4, the epoxide yielding only the six-membered ring, the dibromo derivative both five- and six-membered rings.

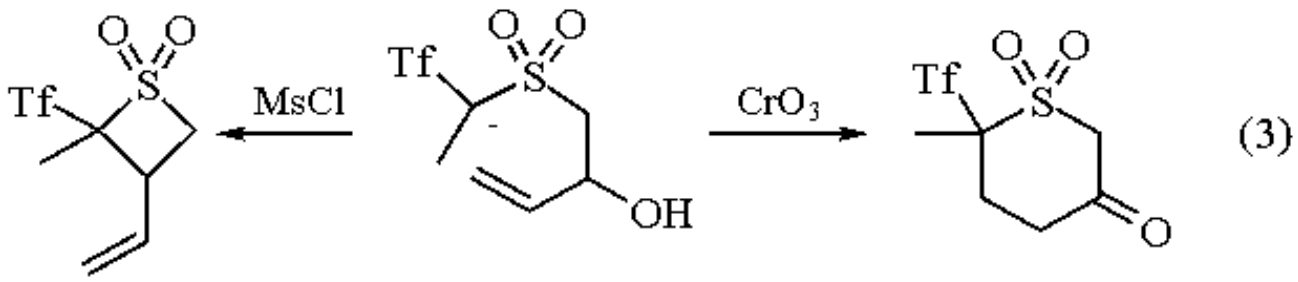

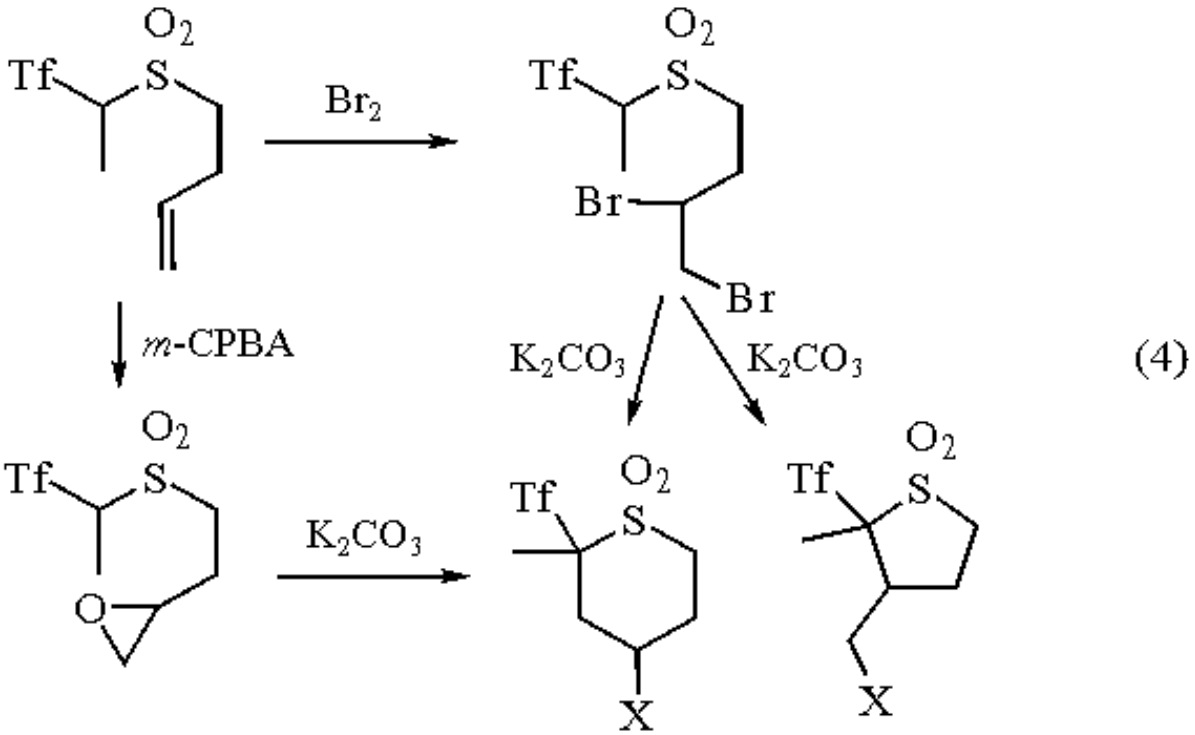

Reaction of the stable α-monoanion with ***Formaldehyde*** quantitatively eliminates triflate ion to create α-methylene sulfones (eq 5).[4] Higher aldehydes did not react with the α-anion, but bromination is facile even at low temperature.

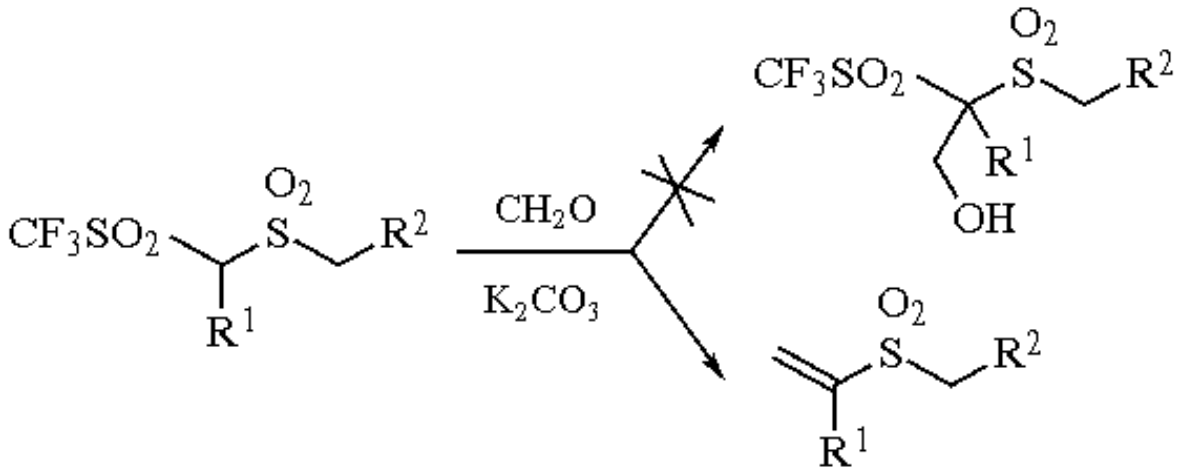

(5)

X-ray structures of several disulfones and their anions have been discussed,[5] and some related ones used in synthesis. The dimesyl analog ($MeSO_2CH_2SO_2Me$) also exhibits its dianion at α and is quite parallel in reactivity toward alkylation.[6] As expected, the α-monoanion is more reactive and more basic (p*K* = 12.5). When fully substituted at α the deprotonation of phenylsulfonyl methyl sulfones at α´ also initiates the Ramberg-Bäcklund rearrangement with loss of phenylsulfinate ion.[7] When no α´-CH is available for deprotonation, treatment with base serves to eliminate triflinate, as in eq 6, and is also used to create cyclic vinyl sulfones when the α-dialkylation is done with α,o-dihalides.[8]

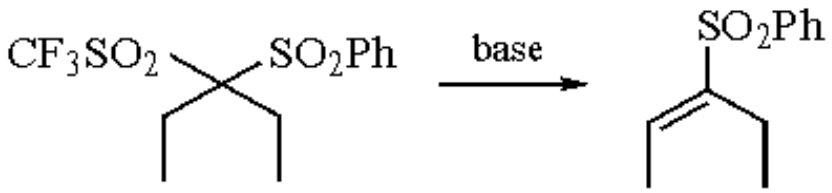

(6)

In summary, the mesyl triflone reagent is useful for preparing 1,1-disubstituted alkenes (eq 1) ($R^2 = R^3 = H$) or cyclopentenones such as dihydrojasmone.[9] However, cyclohexenones were not formed[1] and, while more substituted acyclic alkenes are readily obtained, they arise as *cis-trans* mixtures.

---

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N-Trifluoromethanesulfonyl-*N´*-phenacylhydrazine

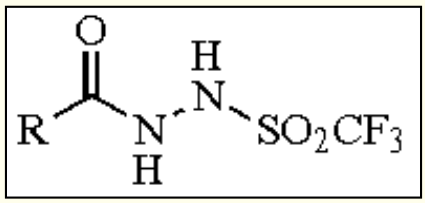

(R = Ph)

[41804-90-4] · $C_8H_7F_3N_2O_3S$ · *N*-Trifluoromethanesulfonyl-*N´*-phenacylhydrazine · (MW 268.24) (R = *t*-BuO)

[56572-25-9] · $C_6H_{11}F_3N_2O_4S$ · *N*-Trifluoromethanesulfonyl-*N´*-*t*-butoxycarbonylhydrazine · (MW 264.26)

(conversion of alkyl halides to hydrazones of aldehydes and ketones)[1]

Alternate Name: N-triflyl-*N´*-phenacylhydrazine.

Physical Data: R = Ph, mp 156-158 °C. R = *t*-BuO, mp 92-94 °C.

Solubility: insol H_2O; sol common organic solvents.

Preparative Methods: triflation of the commercial acylhydrazines with ***Trifluoromethanesulfonic Anhydride*** and ***Triethylamine*** in CH_2Cl_2.

Handling, Storage, and Precautions: both are stable solids with no known toxicity, but the *t*-butyl derivative may decompose on long standing at rt and decomposes on mild heating.

General Discussion.

Designed to afford protected derivatives of sensitive aldehydes or ketones directly from the corresponding alkyl halides, these reagents fulfill this function as shown in eq 1. Owing to the various mild methods available for deprotecting hydrazones,[2] they serve as useful protection derivatives. Triflamide anions are excellent nucleophiles for displacement reactions of primary and activated secondary halides (or sulfonates) in MeCN, and the added base (***Potassium Carbonate***) eliminates triflinate ion to form the hydrazones. The *N´*-acyl group is necessary to activate the elimination, which does not occur in its absence. In the case of the *t*-butoxy derivative, the unsubstituted hydrazone may be recovered with acid as with other *t*-BOC amine derivatives. This also makes possible the synthesis of unsymmetrical azines, $R_2C{=}N{-}N{=}CR'_2$.

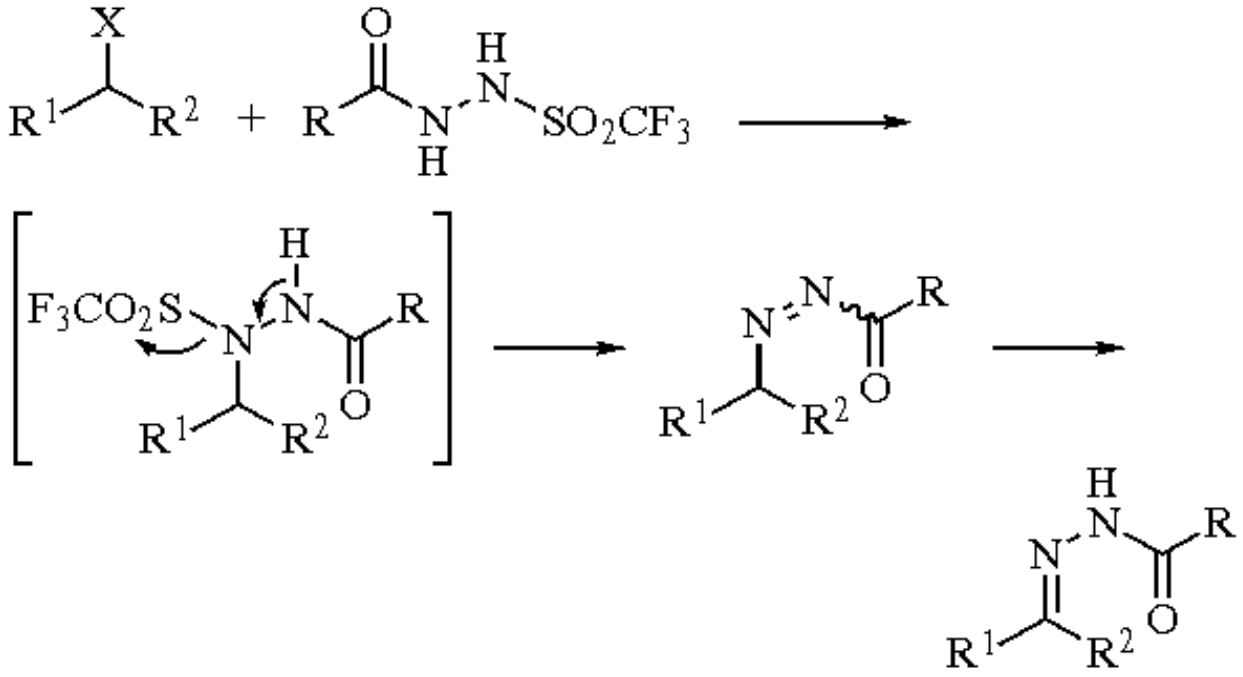

(1)

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N-[4-(Trifluoromethyl)benzyl]cinchoninium Bromide[1]

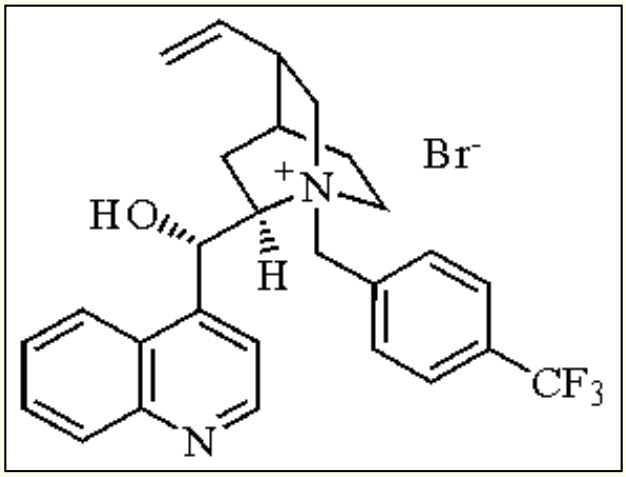

[95088-20-3] · $C_{27}H_{28}BrF_3N_2O$ · *N*-[4-(Trifluoromethyl)benzyl]cinchoninium Bromide · (MW 533.47)

(chiral phase-transfer catalyst for asymmetric alkylations,[2a] amino acid synthesis,[7] hydroxylations,[6] Michael additions,[3] and Robinson annulations[2b])

Physical Data: mp 245 °C (dec).

Solubility: <10^{-5} M in toluene; 20 mM in toluene as dimer.[2a]

Form Supplied in: crystalline salt; commercially available. Can contain anywhere from 0 to 25 mol % of the dihydro analog, usually 15 mol %.

Handling, Storage, and Precautions: do not breath dust; avoid contact with skin and eyes.

Asymmetric Alkylation.[1,2]

N-[4-(Trifluoromethyl)benzyl]cinchoninium bromide (**1**) has been used as chiral phase-transfer catalyst[1,2] in the alkylation of indanones (eq 1).[2a] For the alkylation of α-aryl-substituted carbonyl compounds the diastereomeric *N*-[4-(trifluoromethyl)benzyl]cinchonidinium bromide (**2**) was used to obtain the opposite stereochemistry (eqs 2 and 3).[5] The asymmetric alkylation of oxindoles was used as the key step in an asymmetric synthesis of (-)-physostigmine (eq 4).[4]

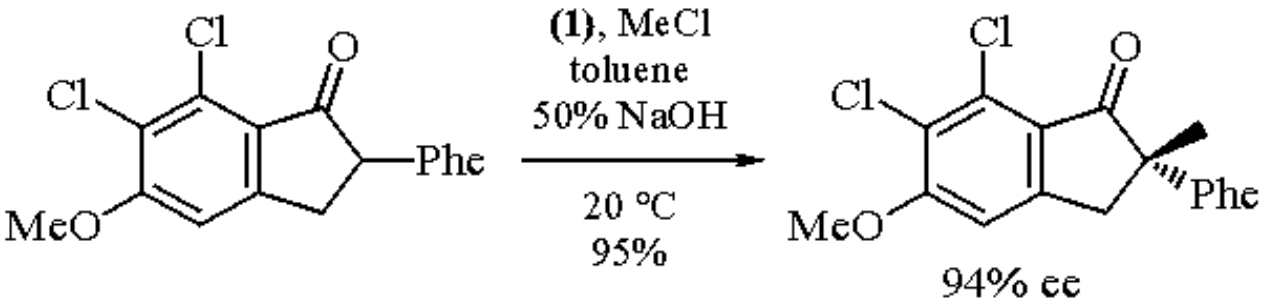

(1)

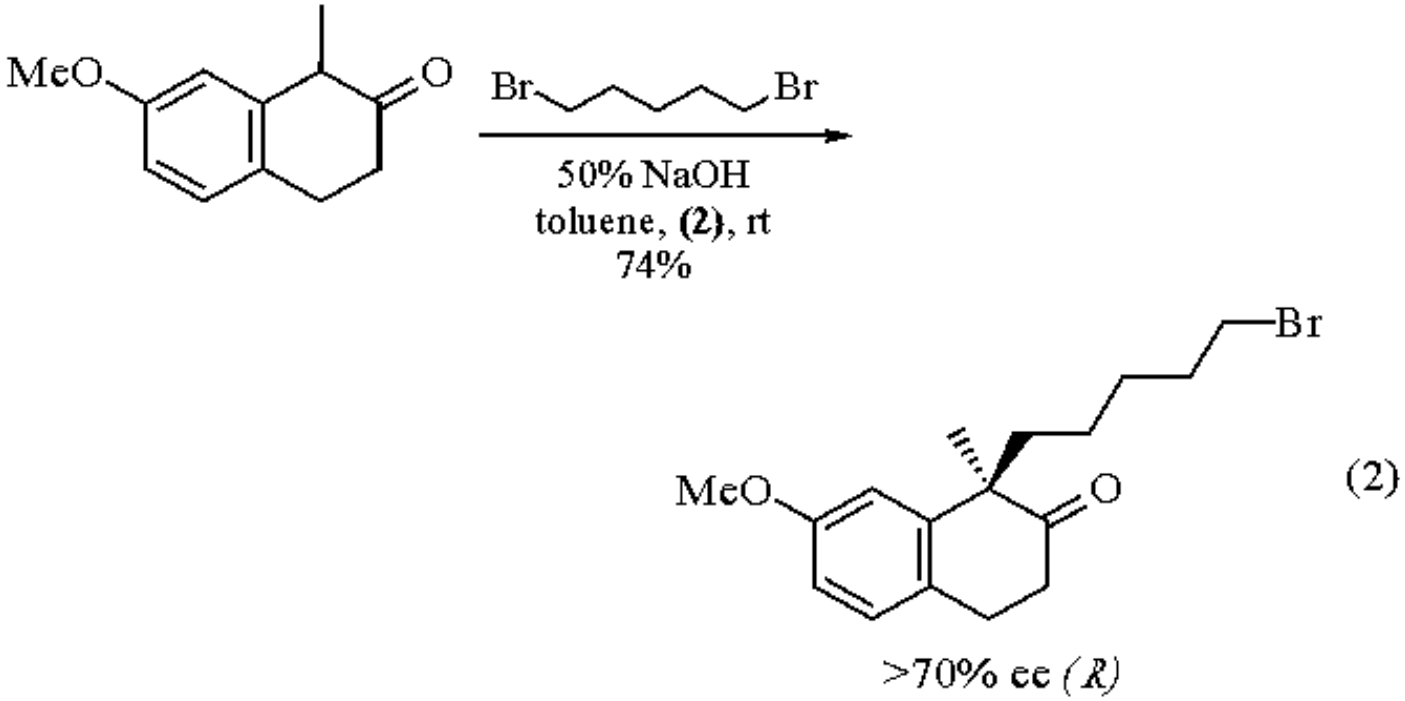

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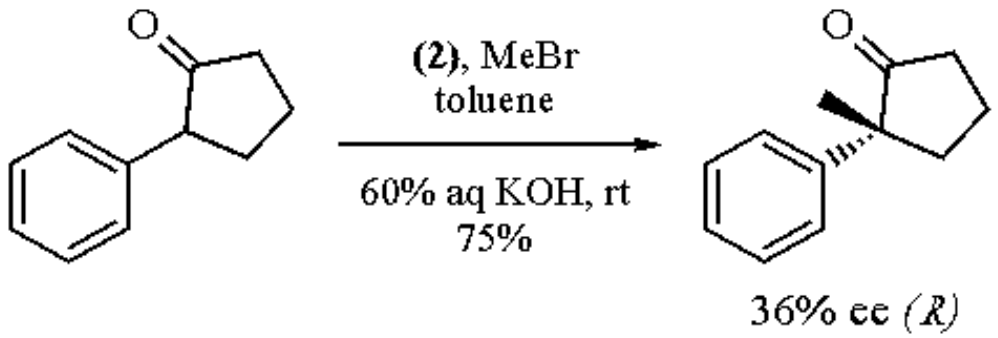

(3)

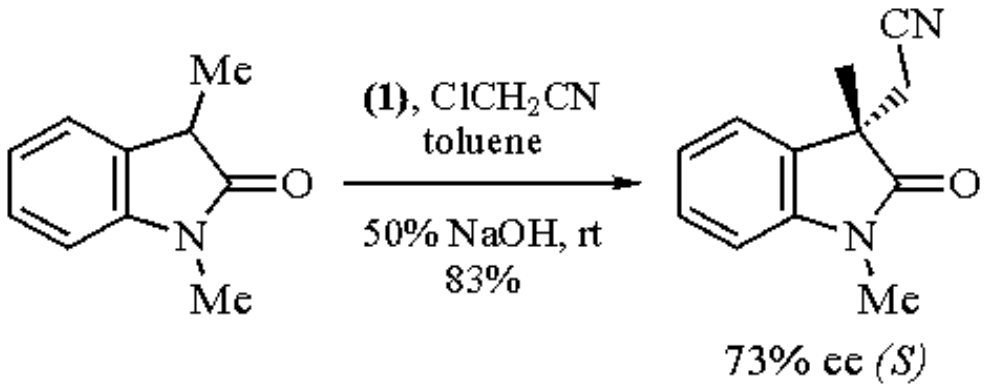

(4)

In all cases it was reported that the trifluoromethyl group enhances the interaction in the prochiral ion pair, resulting in higher ee. The exception appears to be the asymmetric synthesis of α-amino acids via alkylation of the benzophenone Schiff base of glycine alkyl esters with allyl bromide, which produced a 56% ee with the trifluoromethyl-substituted catalyst compared to 66% with the unsubstituted catalysts *N*-benzylcinchoninium chloride (**3**) or *N*-benzylcinchonidinium chloride (**4**) (eq 5).[7]

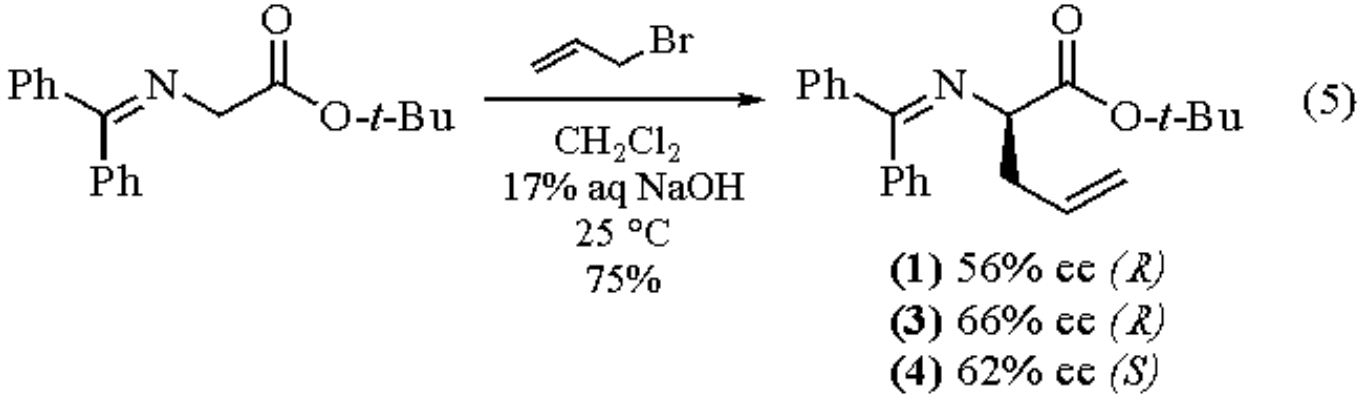

The unsubstituted catalyst (**3**) was also used in an asymmetric Gabriel synthesis of α-amino acids via solid-liquid chiral phase-transfer alkylation of potassium phthalimide with 2-bromocarboxylates.[10]

In general, nonpolar solvents and less reactive alkyl halides (Cl > Br > I) give higher ee values. Aqueous 50% NaOH is the preferred base, as it acts as a dehydrating agent and keeps the organic solvent dry, thus promoting a tight ion pair. During the reaction the catalyst is extracted into the organic layer as a dimer of ammonium bromide and its zwitterionic oxide,[2a] but it reacts as a monomer resulting in an order of 0.5 for the catalyst in the alkylation reaction. The catalyst degrades during the reaction via Hofmann elimination to tertiary amines, which are readily removed by acid extractions during the workup.[2a] Therefore the catalyst usually cannot be recovered. An economical alternative catalyst is *N*-(3,4-dichlorobenzyl)cinchoninium chloride, which may give equivalent results.[2a,3,4a,9] Reduction in catalyst concentration and reaction times may be achieved by addition of a very small amount of a PEG cocatalyst (PEG 400 or PEG *p*-isooctylphenyl ether).[2e,9] The ee will depend on the interaction of the catalyst with the substrate in the ion pair and in certain cases an electron-donating substituent on the benzyl group may provide optimal interaction, as was found for an asymmetric Michael reaction using *N*-methyl-*N*-benzyl ephedrinium bromide as the phase-transfer catalyst.[8]

Asymmetric Michael Addition.

A chiral catalytic addition of methyl vinyl ketone to 2-propylindanone in 93% yield and 80% ee (*S* enantiomer) has been reported (eq 6).[3]

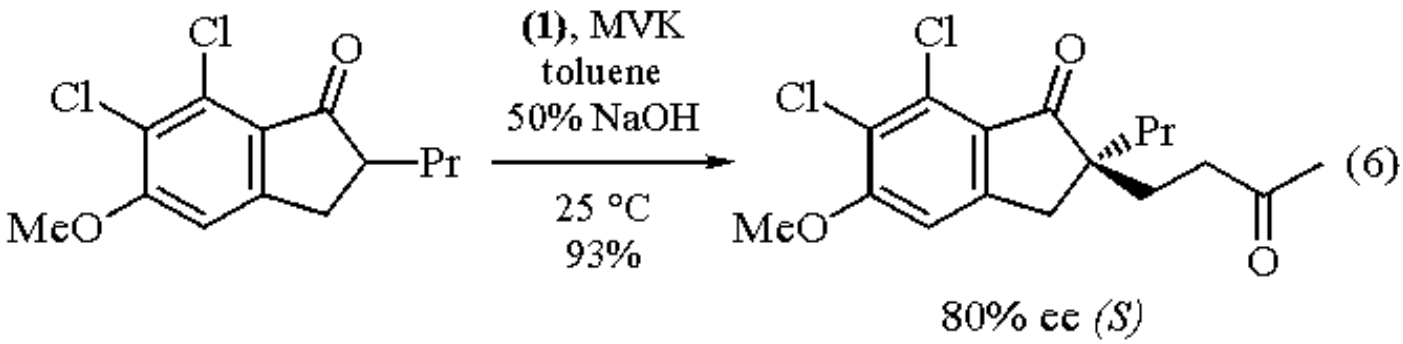

The (*R*) enantiomer was prepared with 40% ee using the cinchonidine catalyst (**2**). When the vinyl group of the catalyst was hydrogenated to the ethyl group (*N*-[4-(trifluoromethyl)benzyl]dihydrocinchonidinium bromide, **5**), the ee improved to 52%. Equally good results were obtained using the basic catalyst dimer[2a] in a homogeneous system which allowed the use of Michael acceptors not compatible with hydroxide bases.

Asymmetric Hydroxylation.

The catalyst has been used for asymmetric α-hydroxylations of indanones and α-tetralones using the standard conditions in combination with oxygen and ***Triethyl Phosphite*** (eq 7).[6] Substituents on the aromatic ring of the substrates will influence the π-π interaction in the ion pair and affect the ee. Similarly, (*E*)-2-ethylidene-1-tetralone was oxidized to the α-hydroxy ketone (eq 8).

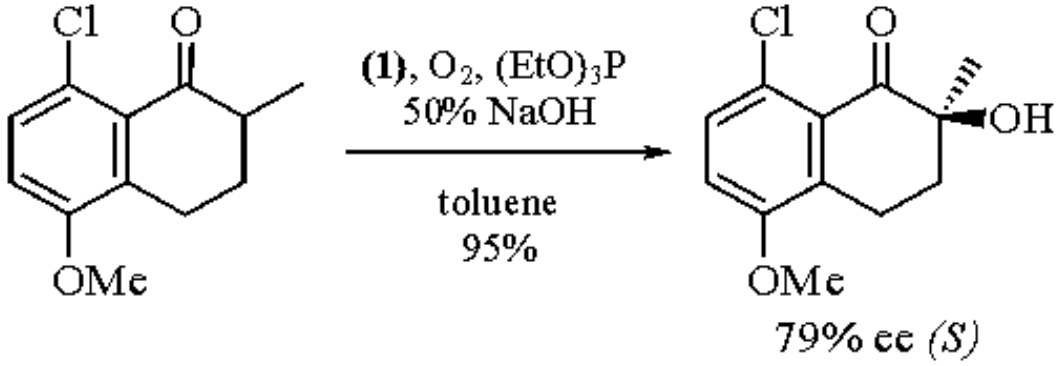

(7)

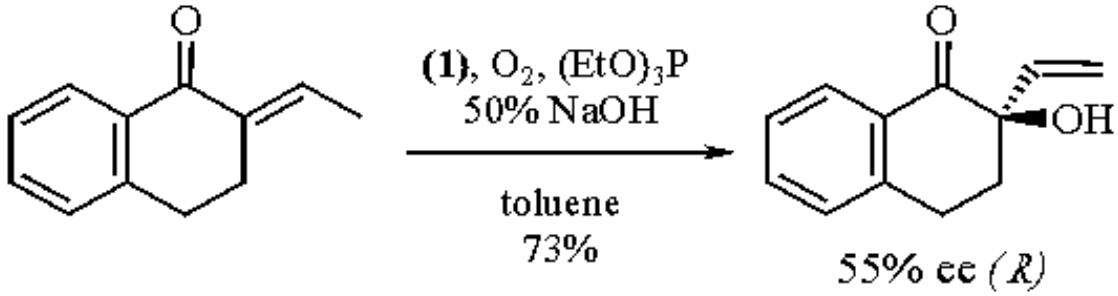

(8)

Asymmetric Robinson Annulation.

2-Propyl-1-indanone undergoes Robinson annulation with the catalyst and methyl vinyl ketone (eq 6).[3] Higher ee values were achieved using 1,3-dichloro-2-butene (Wichterle Reagent) as an MVK surrogate for the Michael addition and overall Robinson annulation (eq 9).[2b,d,e]

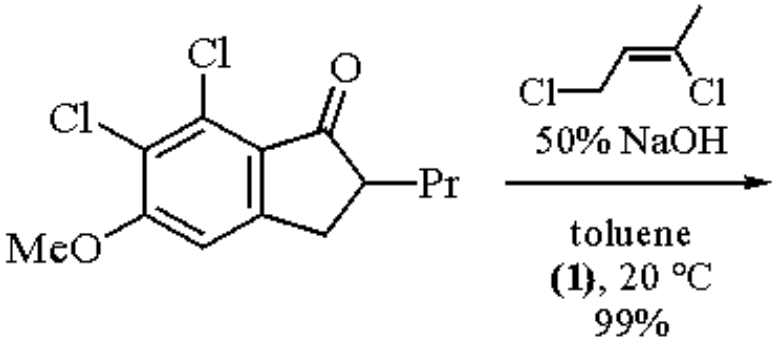

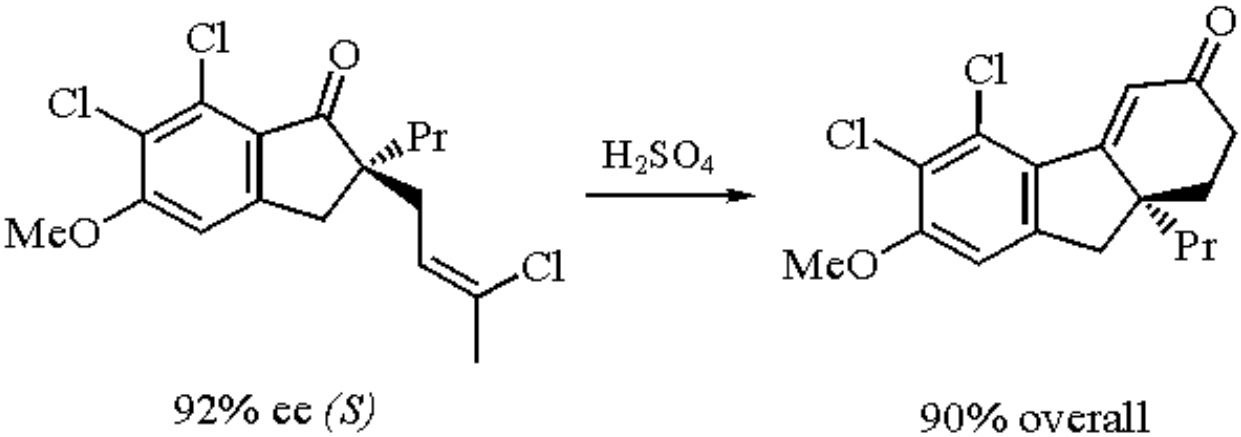

(9)

Using (**2**) as catalyst provided the (*R*) enantiomer in 99% yield, 78% ee. The key introduction of asymmetry during the synthesis of (+)-podocarp-8(14)-en-13-one was the phase-transfer-catalyzed Robinson annulation of 6-methoxy-1-methyl-2-tetralone with ethyl vinyl ketone. The authors carried out a comparative study of the *N*-(4-trifluoromethyl)benzyl derivatives of cinchonine, cinchonidine, dihydrocinchonine, and dihydrocinchonidine and found that (**5**) produced the highest ee of the desired (*S*) enantiomer at -45 °C using toluene and 60% aq KOH (eq 10).[5]

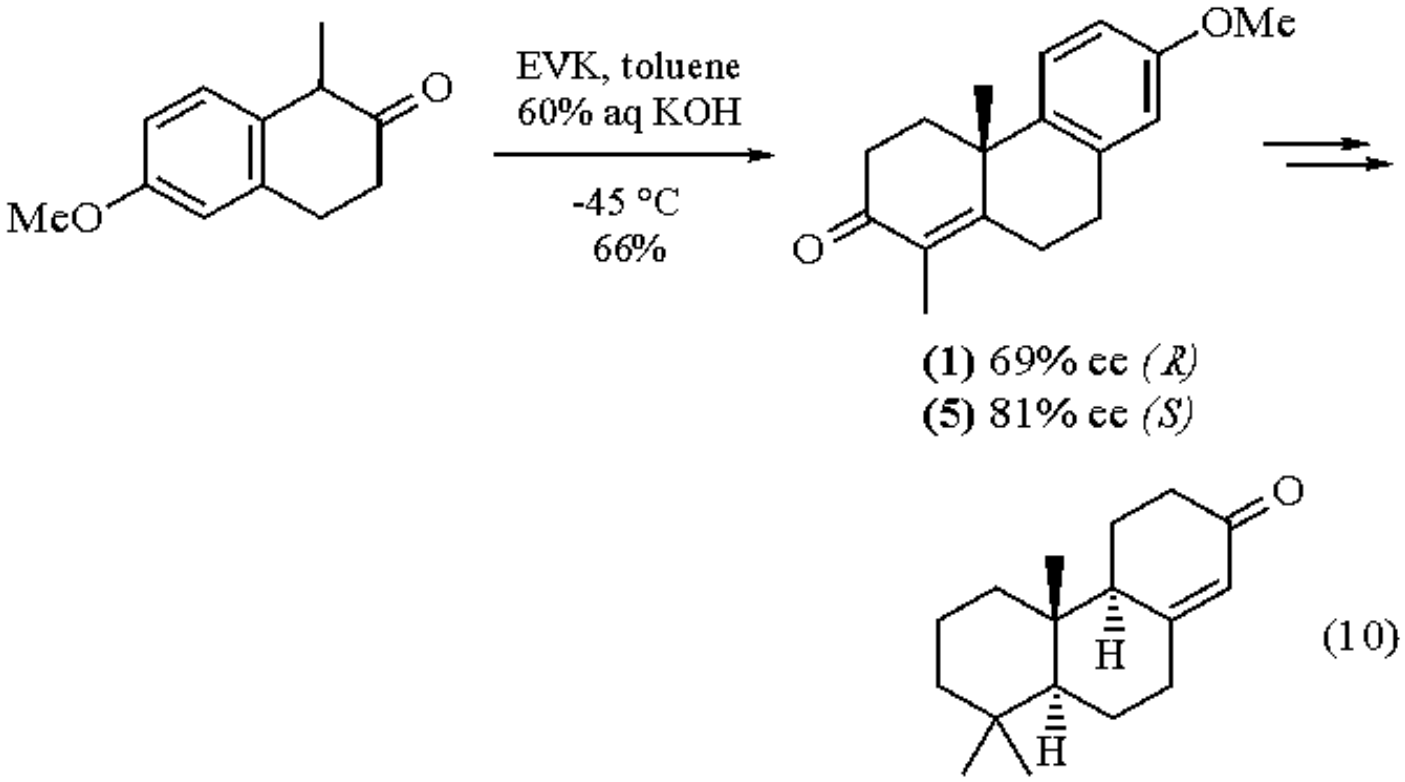

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Ulf-H. Dolling

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Trifluoromethylcopper(I)[1]

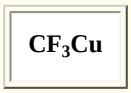

[77152-08-0] · $CCuF_3$ · Trifluoromethylcopper(I) · (MW 132.56)

(trifluoromethylation of aryl, heteroaryl, and allyl halides,[2] propargyl tosylates,[3] and iodonucleosides[4])

Physical Data: obtained only in solution; stabilized by HMPA.[20]

Preparative Methods: by reaction of copper metal and trifluoromethyl halides, or difluorocarbene precursors for in situ reactions; or preformed by metathesis of trifluoromethyl organometallic reagents, with subsequent reaction with electrophiles (see below).

Handling, Storage, and Precautions: sensitive to air and moisture; undergoes chain-extension reactions to form pentafluorocopper in the absence of electrophiles; several precursors of trifluoromethylcopper are toxic; HMPA is carcinogenic. Use in a fume hood.

General Considerations.

Trifluoromethylcopper was initially prepared by Kobayashi and co-workers by the reaction of ***Trifluoroiodomethane*** and ***Copper*** metal in the presence of aryl, allyl, or heteroaryl iodides.[2] Since these initial studies, many reports of the preparation and reaction of trifluoromethylcopper have appeared.[1a,b] Trifluoromethyl-substituted nucleosides have been obtained by reaction of iodonucleosides with CF_3Cu (eq 1).[4]

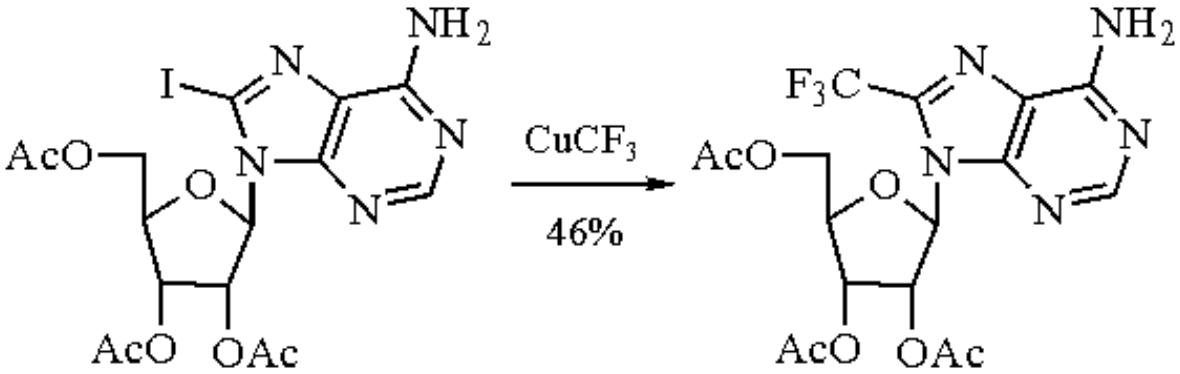

(1)

Trifluoromethyl-substituted allenes have been prepared from primary, secondary, or tertiary propargyl tosylates (eq 2).[3] Reaction of CF_3Cu with 5-iodo-1,3-dioxin-4-ones provides the corresponding trifluoromethyl derivatives which serve as precursors for α-CF_3-β-keto esters (eq 3).[5] Trifluoromethylation reactions are generally carried out using aryl iodides as the substrate. Aryl bromides or chlorides often result in lower yields and lead to the production of larger amounts of perfluoroethyl byproducts.[6] Improved yields of trifluoromethylated aromatics from aryl chlorides have been realized for *ortho*-substituted substrates, and by adding charcoal to the reaction mixture.[7]

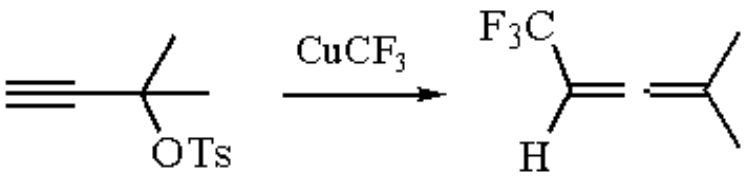

(2)

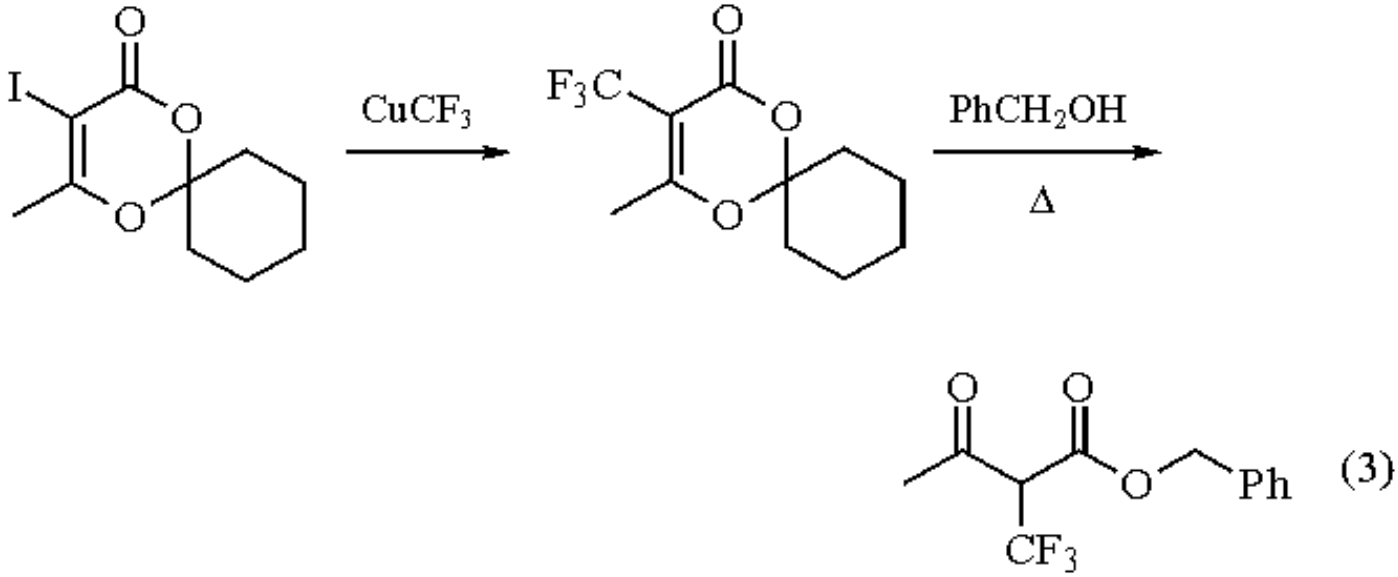

Methods for the preparation of the reagent can be grouped into two general categories: in situ generation from CF_3X and copper metal, by decomposition of metal trifluoroacetates in the presence of ***Copper(I) Iodide***, or from a variety of difluorocarbene precursors in the presence of a fluoride source; and preformation by metathesis reactions. In situ generation is readily accomplished with CF_3I; however, the iodide is expensive and the reaction must be carried out at high temperatures in an autoclave.[2] CF_3Br may also be used, but the yields of trifluoromethylated products are generally not as high as those obtained in reactions using the iodide precursor.[8] CF_3I/Cu in situ generation and reaction of $CuCF_3$ is best accomplished in pyridine or HMPA. ***Trifluoromethanesulfonyl Chloride*** and copper metal also provide in situ generation of CF_3Cu for reaction with aryl iodides.[9] Generation of CF_3Cu from decomposition of metal trifluoroacetates in the presence of copper iodide and an aryl iodide provides the aryl trifluoromethyl derivative in good yield.[10] Sodium trifluoroacetate/copper iodide reactions may be effectively carried out in NMP, HMPA, or DMF. The presence of other functional groups such as nitro, chloro, and methoxy on the aryl iodide do not interfere with the reaction (eqs 4 and 5); however, free hydroxy (phenol) or aryl amino groups are not tolerated.[11]

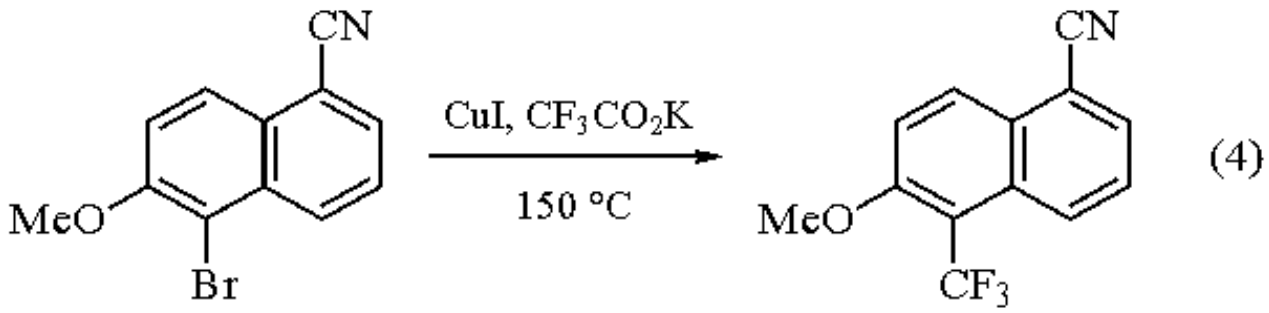

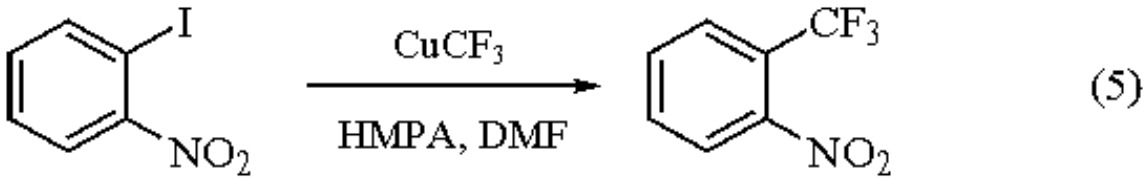

The reaction appears to be a nucleophilic aromatic substitution reaction, as evidenced by the positive ρ value obtained from a Hammett plot of *para*-substituted iodobenzene derivatives.[11] CF_3Cu may also be generated by the reaction of *N*-nitrosotrifluoromethane sulfonamide (TNS-TF) and copper metal.[12] A drawback to this approach is the formation of CF_3NO as well as the instability of TNS-TF. Trifluoromethyltriethylsilane has also been employed as a precursor for in situ generation of CF_3Cu.[13] Aryl and vinyl iodides, as well as allyl and benzyl bromides, undergo trifluoromethylation when admixed with Et_3SiCF_3/CuI (eq 6). No trifluoromethylation is observed in reactions of Et_3SiCF_3 without the addition of copper iodide.

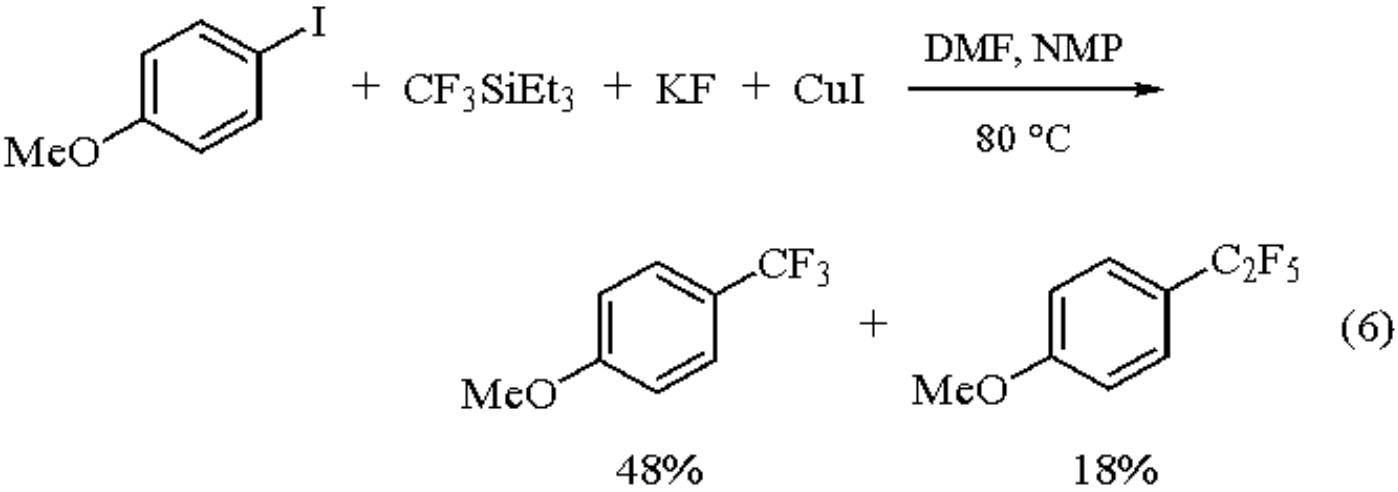

Possibly the most common method for the generation of CF_3Cu involves in situ formation from difluorocarbene precursors. The reagent may be directly prepared by the reaction of CF_2Br_2 with zinc, cadmium,[14] or copper[1a] metal in DMF (Scheme 1).

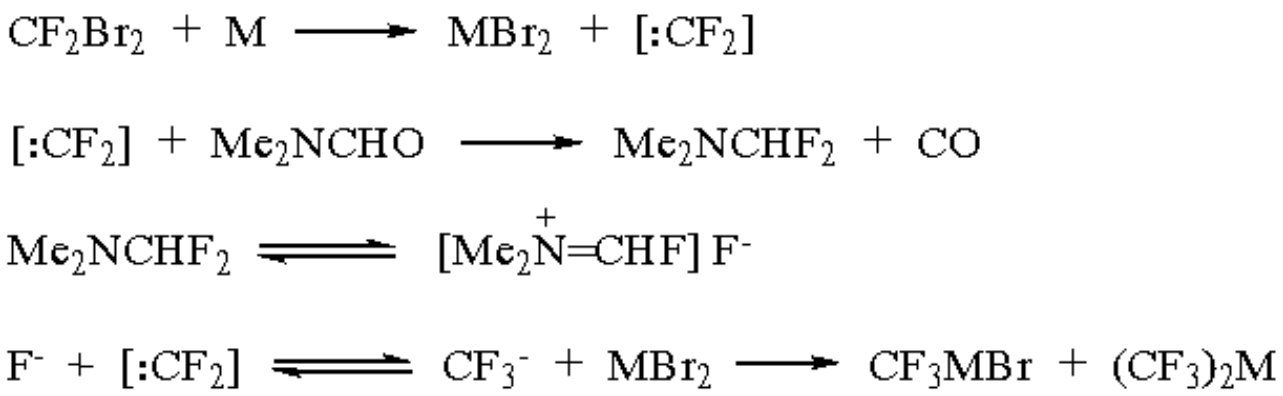

Scheme 1

The mechanism involves generation of difluorocarbene via radical anion formation with subsequent reaction of CF_2**:** and DMF. The fluoride produced then combines with CF_2**:** to generate CF_3^-, which reacts with the in situ formed copper halide to provide CF_3Cu. Without in situ trapping by an electrophile, CF_3Cu will undergo rapid chain extension to C_2F_5Cu. The chain extension reaction can be suppressed by adding excess fluoride anion to the reaction mixture; however, this procedure frequently results in decreased yields of the desired trifluoromethylated product. Fluorosulfonyldifluoromethyl iodide undergoes a single electron transfer (SET) process with copper metal to ultimately provide CF_3Cu via a difluorocarbene intermediate.[15] Methyl fluorosulfonyldifluoroacetate also provides CF_3Cu upon reaction with CuI by means of a difluorocarbene intermediate;[16] the reaction involves initial loss of methyl iodide followed by fragmentation of the copper salt to CO_2, SO_2, Cu^I, difluorocarbene, and fluoride. An advantage of this method is that no perfluoroethyl byproducts are observed in reactions with aryl iodides. A similar process from a less expensive source of difluorocarbene, methyl chlorodifluoroacetate, requires excess ***Potassium Fluoride*** for the generation of CF_3^- anion.[17] Generation of CF_3Cu by the latter method also eliminates the need to prepare FO_2SCF_2COF, the precursor for both fluorosulfonyl intermediates, from tetrafluoroethylene and sulfur trioxide.

Metathesis reactions of trifluoromethyl organometallic compounds to CF_3Cu provide a means to pregenerate the reagent and allow for trifluoromethylation at much lower temperatures than the methods discussed above. The use of preformed CF_3Cu, rather than in situ methods, has also allowed for the multiple trifluoromethylation of thermally unstable polyiodoheteroaryl species (eq 7).[1a]

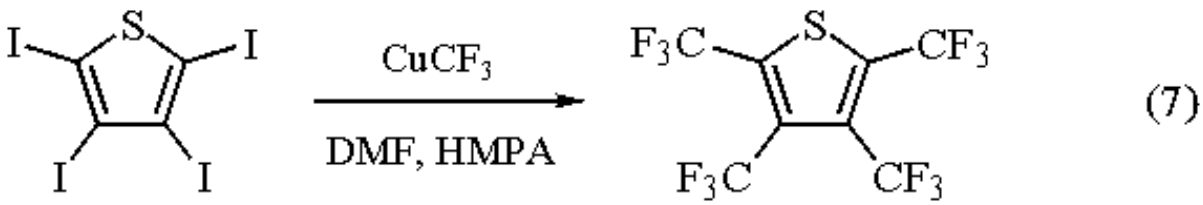

Trifluoromethylmercury, -zinc, and -cadmium species can all undergo metathesis to CF_3Cu. Trifluoromethylmercury has not been generally employed, presumably due to potential toxicity problems.[18] Metathesis of trifluoromethylzinc is prohibitively slow and therefore not synthetically useful; however, metathesis of trifluoromethylcadmium with CuBr in DMF at -50 °C allows for clean formation of the copper reagent.[19] Warming the mixture leads to the formation of two additional trifluoromethylcopper species, observed by ^{19}F NMR, with

the gradual loss of CF_3Cu. Storage at rt produces C_2F_5Cu, with complete consumption of the CF_3Cu after 11 h. The conversion of CF_3 to C_2F_5Cu can be accelerated by heating the mixture to 70 °C. The CF_3Cu reagent may be stabilized by adding HMPA, allowing trifluoromethylation reactions to be carried out in good yield at elevated temperatures.

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S-(Trifluoromethyl)dibenzothiophenium Triflate[1]

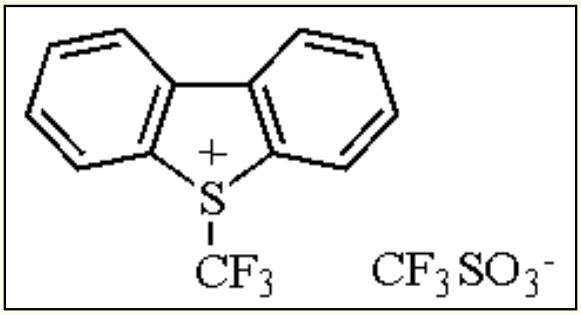

[129946-88-9] · $C_{14}H_8F_6O_3S_2$ · *S*-(Trifluoromethyl)dibenzothiophenium Triflate · (MW 402.36)

(trifluoromethylating agent for many nucleophilic substrates)

Physical Data: mp 155 °C.

Solubility: sol MeCN, DMF, DMSO; slightly sol THF, CH_2Cl_2; insol Et_2O.

Form Supplied in: white crystals; commercially available.

Analysis of Reagent Purity: ^1H and ^{19}F NMR, IR.

Purification: recrystallization from CH_3CN/Et_2O at rt.

Handling, Storage, and Precautions: nonhygroscopic and thermally stable crystals; should be stored in a dry atmosphere protected from light.

Trifluoromethylation.[1,2]

S-(Trifluoromethyl)dibenzothiophenium triflate (**1**) is an electrophilic trifluoromethylating agent. Other related useful trifluoromethylating agents are *S*-(trifluoromethyl)-3,7-dinitrodibenzothiophenium triflate (**2**) and *Se*-(trifluoromethyl)dibenzoselenophenium triflate (**3**). The trifluoromethylating power order of these compounds varies as (**3**) < (**1**) < (**2**). The strongest reagent (**2**) smoothly fluorinates less reactive nucleophiles, while the mildest reagent (**3**) satisfactorily reacts with the more reactive nucleophiles. The title reagent (**1**) trifluoromethylates nucleophiles of intermediate reactivity. Thus (**1**) can trifluoromethylate metal salts of active methylene compounds (eq 1), acetylides (eq 2), enamines, enol silyl ethers (eq 3), reactive aromatics, heteroaromatics (eq 4), arenethiolates, and iodide anions in good yields. Enolate anions are trifluoromethylated in high yields by (**1**) in the presence of an equivalent amount of 2-phenylbenzo-1,3-dioxa-2-borole (eq 5).[3]

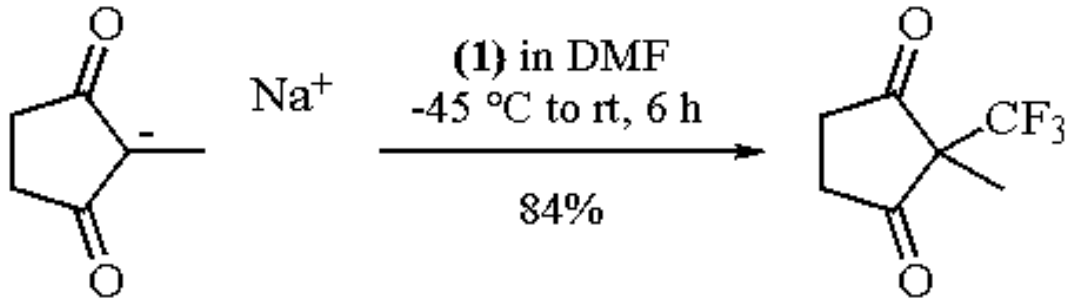

(1)

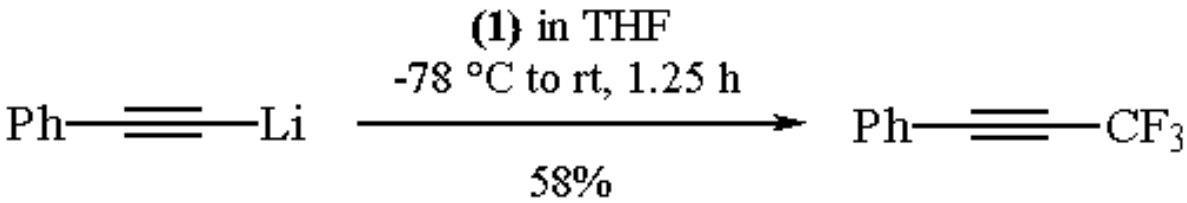

(2)

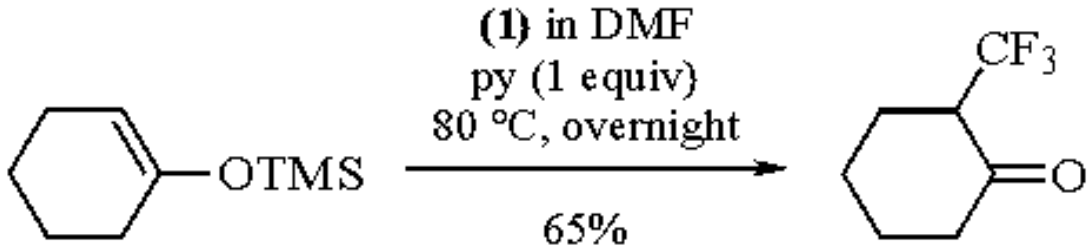

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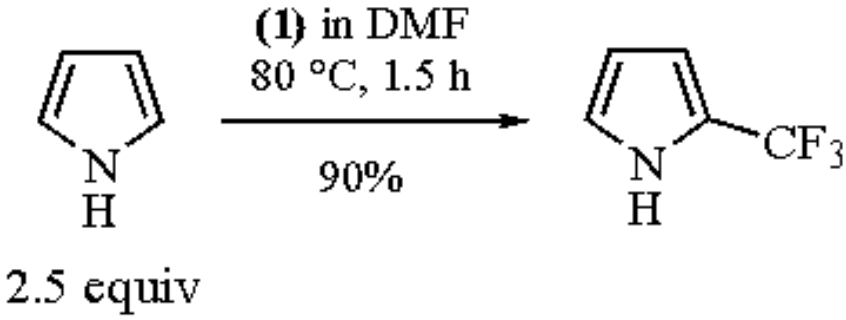

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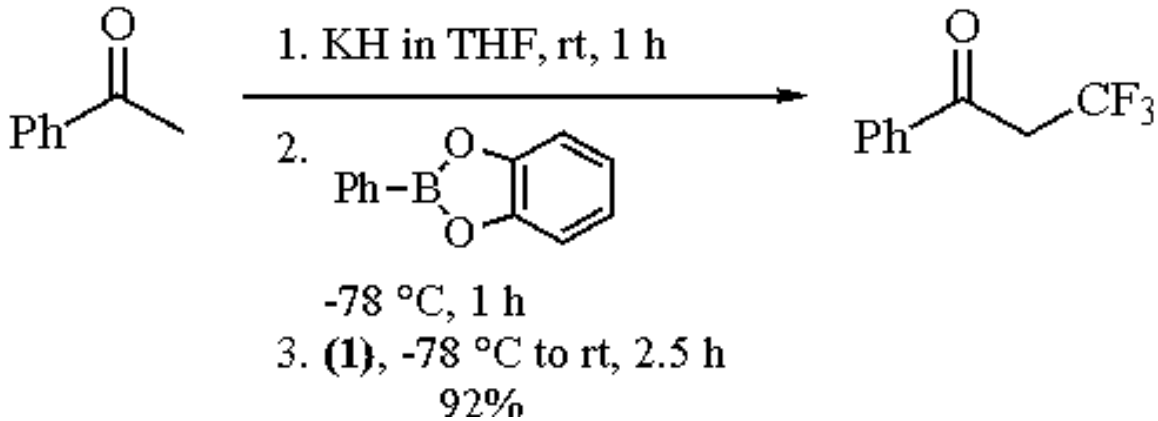

(5)

While (**1**) cannot trifluoromethylate triphenylphosphine, the more powerful reagent (**2**) provides access to (trifluoromethyl)triphenylphosphonium triflate in 78% yield. While (**1**) reacts with an alkanethiolate to give a trifluoromethyl alkyl sulfide in 47% yield along with 30% of a dialkyl disulfide as a byproduct, (**3**) produces a trifluoromethyl alkyl sulfide in 87% yield. The powerful trifluoromethylating agent (**2**) readily reacts with activated aromatics and heteroaromatics to yield trifluoromethylated compounds in good yields. Triflates (**1**)-(**3**) are all commercially available. The corresponding perfluoroalkyl analogs, *S*-(perfluoroethyl)-, -(perfluorobutyl)-, and -(perfluorooctyl)dibenzothiophenium triflates, are also available. Similar perfluoroalkylations are expected.[1] Since (**3**) is much more reactive than (**1**), the stability decreases, and (**3**) should be stored in a refrigerator.

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Trifluoromethyl Hypofluorite[1]

CF_3OF

[373-91-1] · CF_4O · Trifluoromethyl Hypofluorite · (MW 104.01)

(electrophilic fluorinating agent[1b] for the preparation of α-fluoro carbonyl compounds,[10] 2-fluoroaldoses,[13] fluoro dienones,[17] aryl fluorides,[17] 5-fluoropyrimidines (and nucleosides),[22] *N*-fluoroamides,[18] and *N*,*N*-difluoroamines;[27] regioselective replacement of tertiary hydrogen by fluorine[28])

Alternate Name: fluoroxytrifluoromethane

Physical Data: mp <-215 °C; bp -97 °C; *d* 1.9 g cm^{-3} (at -97 °C).

Solubility: slightly sol $CFCl_3$, CF_3CO_2H, CF_3CH_2OH; slightly sol (reacts slowly) $MeCO_2H$, MeCN, $MeNO_2$ (solubility in all solvents increases at low temperature).

Form Supplied in: not presently commercially available; has been available as a compressed gas.

Analysis of Reagent Purity: hypofluorite can be estimated by iodometric titration ($CF_3OF + 2KI + H_2O$ -> $I_2 + CO_2 + 2KF + 2HF$). Comparison of the oxidizing capacity with gas volume and/or acid produced during reduction is a reasonable measure of reagent purity. Reaction with stilbene[2] has been used to assay identity and purity of hypofluorites.[3e]

Preparative Methods: continuous flow fluorination of CO by ***Fluorine*** over supported ***Silver***[3a] or ***Cesium Fluoride***[3b,c] catalyst (latter preferred). Static fluorination of COF_2 by F_2 over CsF.[3d] The aggressive nature of both F_2 and CF_3OF, the extremely exothermic nature of the reactions ($\Delta H_{formation}$ CF_3OF = -775 kJ mol^{-1}), and the variable quality of the catalyst render these preparations rather hazardous. Commercial production (ca. 300 g scale) was plagued by explosions of the liquified product obtained in the first procedures and by rupture of safety discs (200 atm) in the batch process.[4] Fluorination of COF_2 over CsF in an open continuous flow reactor to produce the reagent as needed (without condensation or other accumulation of large amounts of the product) should be considered. A reasonable small-scale alternative may be use of the mixed C_1 and C_2 hypofluorites obtained by the fluorination of CF_3CO_2Na[3e] (a variety of hypofluorites appear to attach a fluorine atom to most substrates in essentially the same way).[5]

Purification: the reagent as prepared often contains COF_2, which may be removed by passing the gas through water.

Handling, Storage, and Precautions: although thermally stable and reported to survive storage for a year in passivated metal cylinders,[3c] CF_3OF is an extremely aggressive oxidant (H_2O is oxidized slowly at neutral pH, quite rapidly at higher pH; unpassivated metal tubing can ignite and burn; explosions have resulted when using PVC tubing). It is recommended that apparatus coming in contact with the reagent be made of glass, passivated metal, or fluorocarbon (e.g. Teflon, Kel-F). Solutions of CF_3OF in $CFCl_3$ are reported to be quite stable;[3e] solutions in most other solvents should be considered metastable and potentially explosive; solutions in oxidizable solvents, particularly ethers, may react spontaneously and explosively. Slow addition of the reagent to the substrate (to minimize accumulation of reagent) is recommended. Reactions should be carried out on a small scale and precautions suited to potentially explosive reactions taken. CF_3OF is highly toxic ($L(ct)_{50}$ ~172 ppm, similar to that of OF_2 and perfluoroisobutene).[4] Daily exposure to 0.1 ppm for 2 h is reported to cause bone damage in rats.[6] Laboratory workers anticipating use of CF_3OF should first familiarize themselves with handling[3c,13a,18] and safety precautions.[3a,c,d,e,22b]

Preparation of α-Fluoro Carbonyl Compounds.

Electrophilic addition of CF_3OF is well illustrated by the fluorination of the vinyl acetate (**1**) to give adducts (**2**) and (**3**) and α-fluoro ketone (**4**) (eq 1).[7]

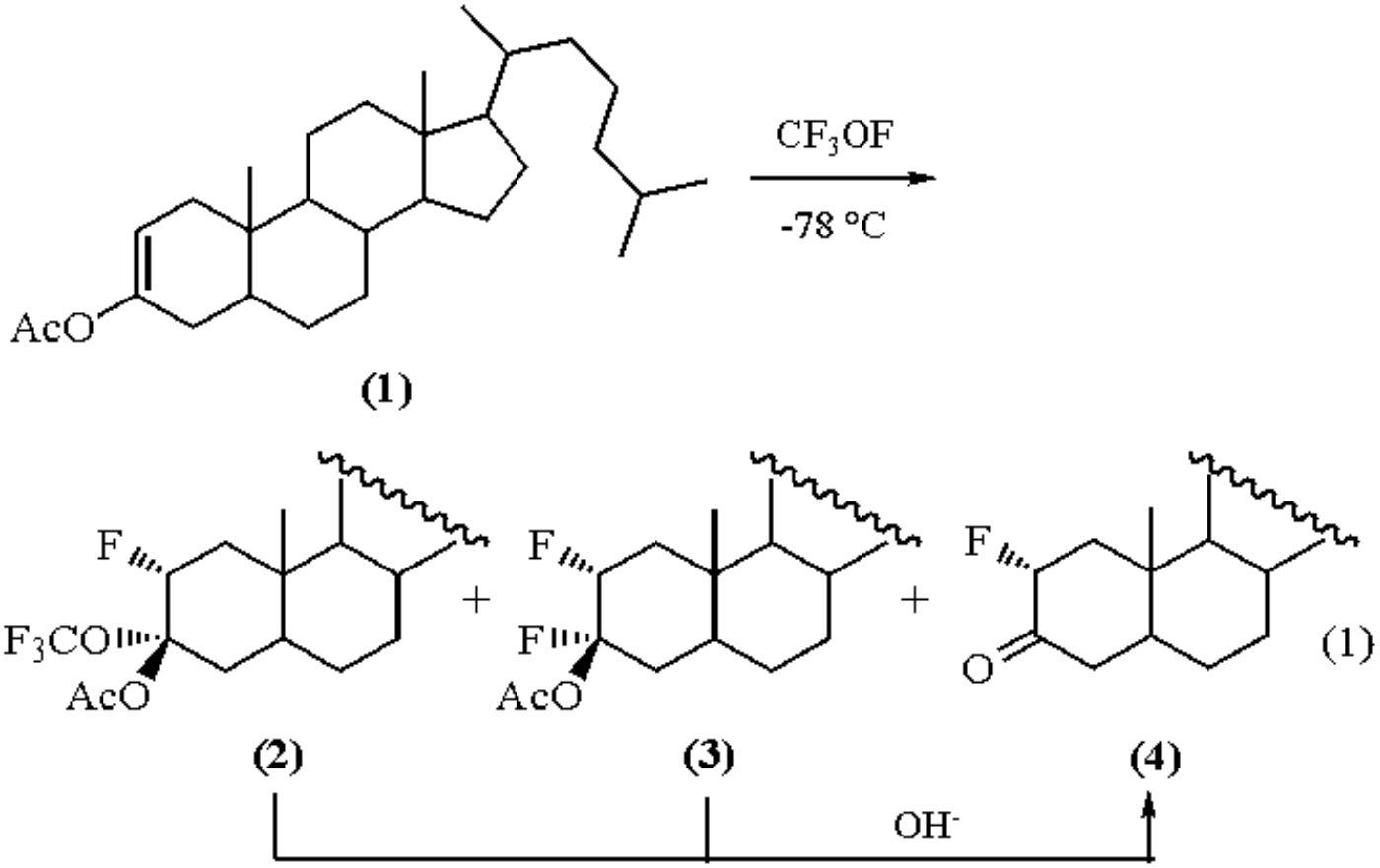

Formation of F_2 adducts such as (**2**) (presumably through decomposition of CF_3O^- into COF_2 and F^-) is characteristic of electrophilic reactions of CF_3OF[1b] (inclusion of a mild, insoluble, inorganic base, for example CaO, MgO, or $NaHCO_3$, protects sensitive substrates). Similar chemistry has been used to prepare 6- and 9-fluorinated steroids.[8,9]

Silyl enol ethers from aldehydes, ketones, esters, and amides react with CF_3OF to provide α-fluoro carbonyl compounds in good yield (eq 2). R can vary widely; note the regioselectivity implicit in formation of (**5**) and (**6**).[10] (A similar fluorination of less complex substrates with F_2 has been reported.[11] Compare also the fluorination of enolate anions with *N*-fluoro-*N*-methyltoluenesulfonamide.) Fluorination of enamides, e.g. (**7**) -> (**8**), provides intermediates for branched chain fluoro sugars (eq 3).[12]

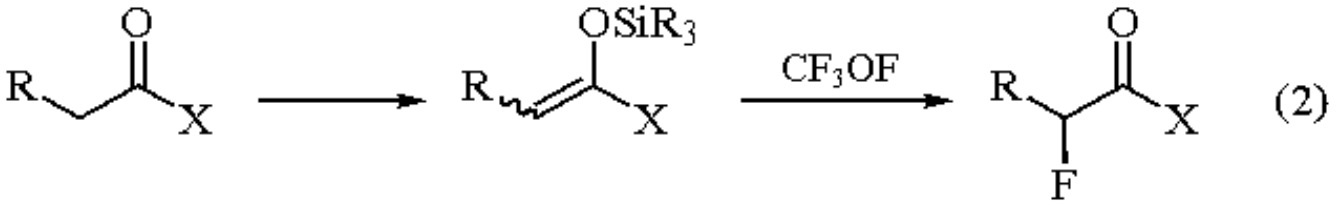

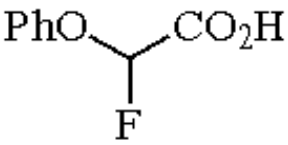

(**5**) 71%

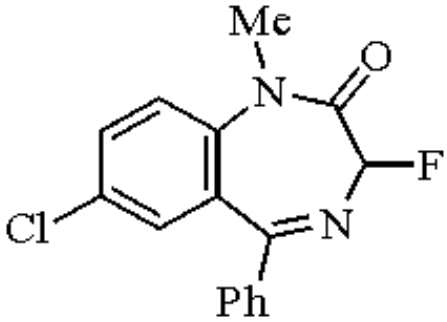

(**6**) 80%

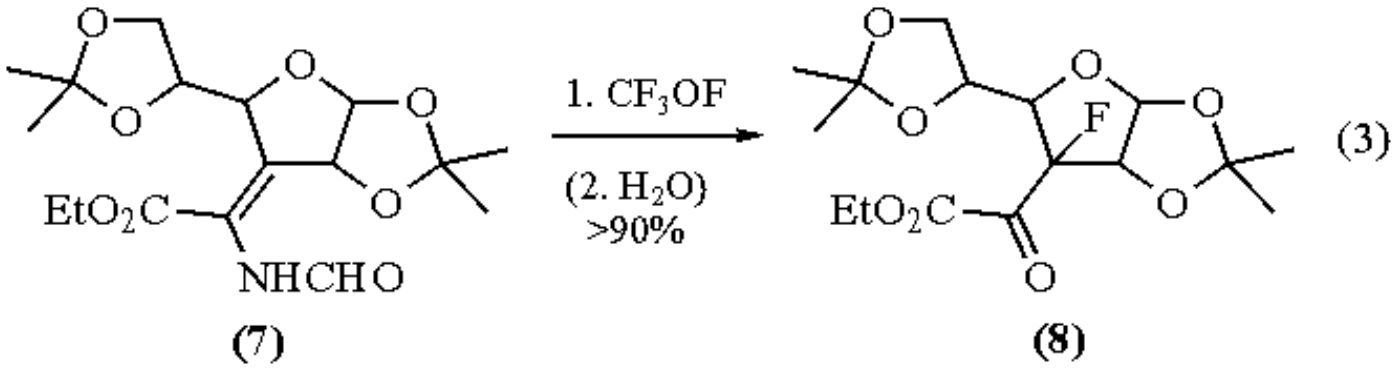

Acetyl D-glucal (**9**) fluorinates smoothly to give the 2-fluoro glucose (**11**) and mannose (**10**) analogs (eq 4).[13a]

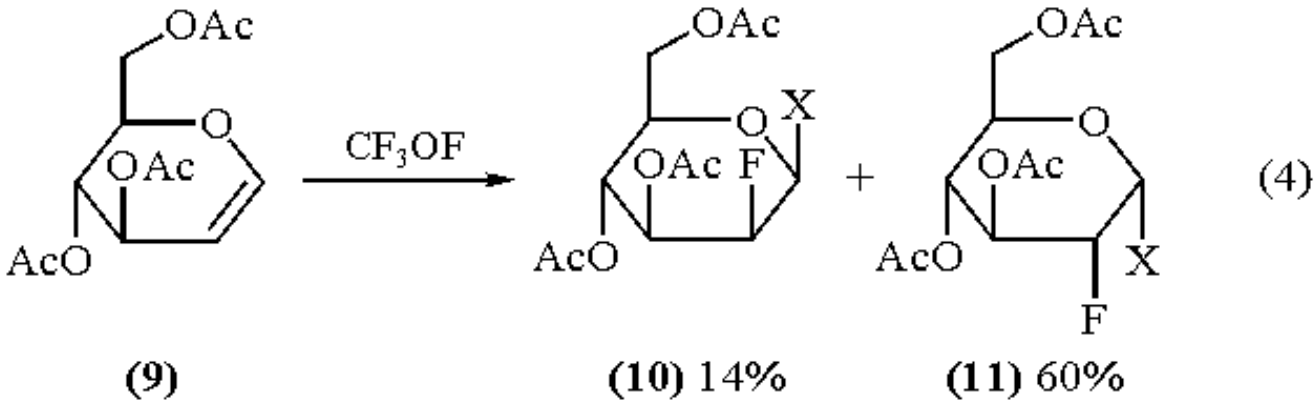

Each of the adducts (X = F or X = OCF_3) can be hydrolyzed to the corresponding pyranose in good yield; this reaction has been used for the synthesis of fluorinated pentoses,[13b] hexoses,[13c] and disaccharides.[13d] The fluorination of acetyl glucal by F_2 (little stereoselectivity[14]) and with ***Acetyl Hypofluorite***[15] (gluco:manno ca. 20:1) has been reported. 8-Fluoroerythronolides A and B have been prepared by a similar fluorination (90%) of an internal enol ether.[16]

Direct Fluorination of Aromatic Rings.

CF_3OF substitutes F for H *ortho* or *para* to good electron-releasing groups in benzene (and condensed benzene) derivatives.[3c,17] While intrinsic *ortho*:*para* selectivity is not great (ca. 3:1 with anisole and from 2.5:1 to 9:1 in some *N*-acylanilides[3c]), the preparation of (**12**)-(**15**) by the direct fluorination of the corresponding hydrocarbon illustrates the utility of the method.[3c,17a,c,d]

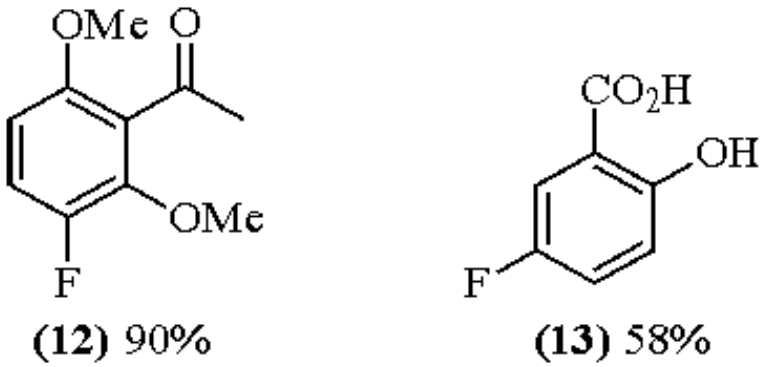

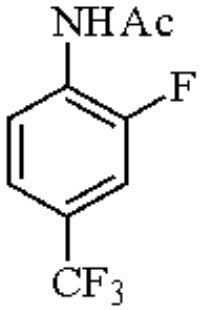

(14) 60%

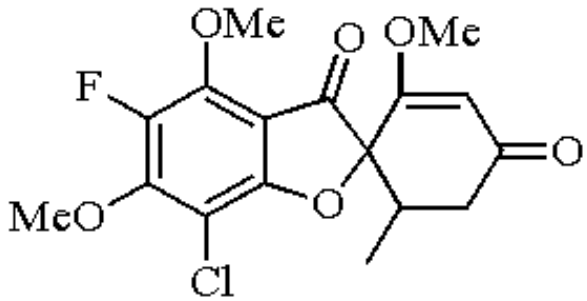

(15) 65%

AcOF has been also used for direct fluorination, but it is a good deal less reactive.

Hydroxy substituted aromatics with *o*- or *p*-alkyl or fluorine substituents tend to undergo *ipso* fluorination to give α- or γ-fluorocyclohexadienones; thus (**16**)[18] and (**17**)[17a] were prepared by fluorination of the corresponding phenols, while (**18**)[17a,b] was obtained from fluorination of either the acetate or the methyl ether. Enforced *ipso* fluorination of pentafluorophenol is the key step in a convenient synthesis of perfluorocyclopentadiene.[19]

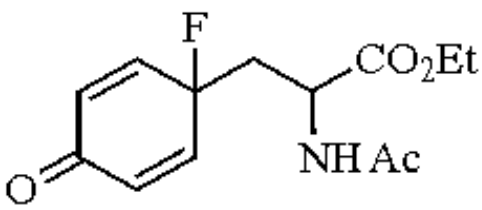

(16)

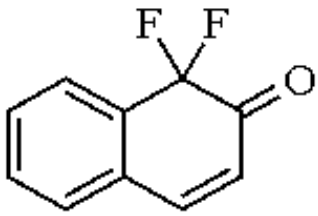

(17)

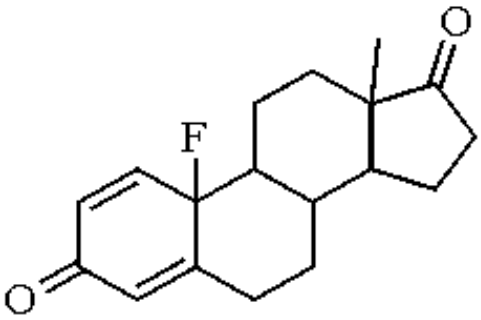

(18) 65%

CF_3OF tends to give addition products (rather than substitution) with deactivated aromatics, the K region of polycyclics[20] and heterocyclics (such as *N*-acylindole and benzofuran).[21]

5-Fluoropyrimidines (and Nucleosides).

CF_3OF in polar solvents converts pyrimidines into addition products, e.g. (**19**) -> (**20**) (eq 5) (X = OH, OMe, or other nucleophile derived from the solvent).[22] If R^3 = H (otherwise the adducts are stable), heating[22a] or treatment with ***Triethylamine***[22b] causes elimination of HX leading to a 5-fluoro pyrimidine, (**20**) -> (**21**). The latter procedure is favored as it permits the direct preparation of analogs of cytosine (Y = NH)[22b] as well as those with X = O and allows for the direct fluorination of nucleosides[22b] (R^1 = ribosyl, deoxyribosyl, etc.).

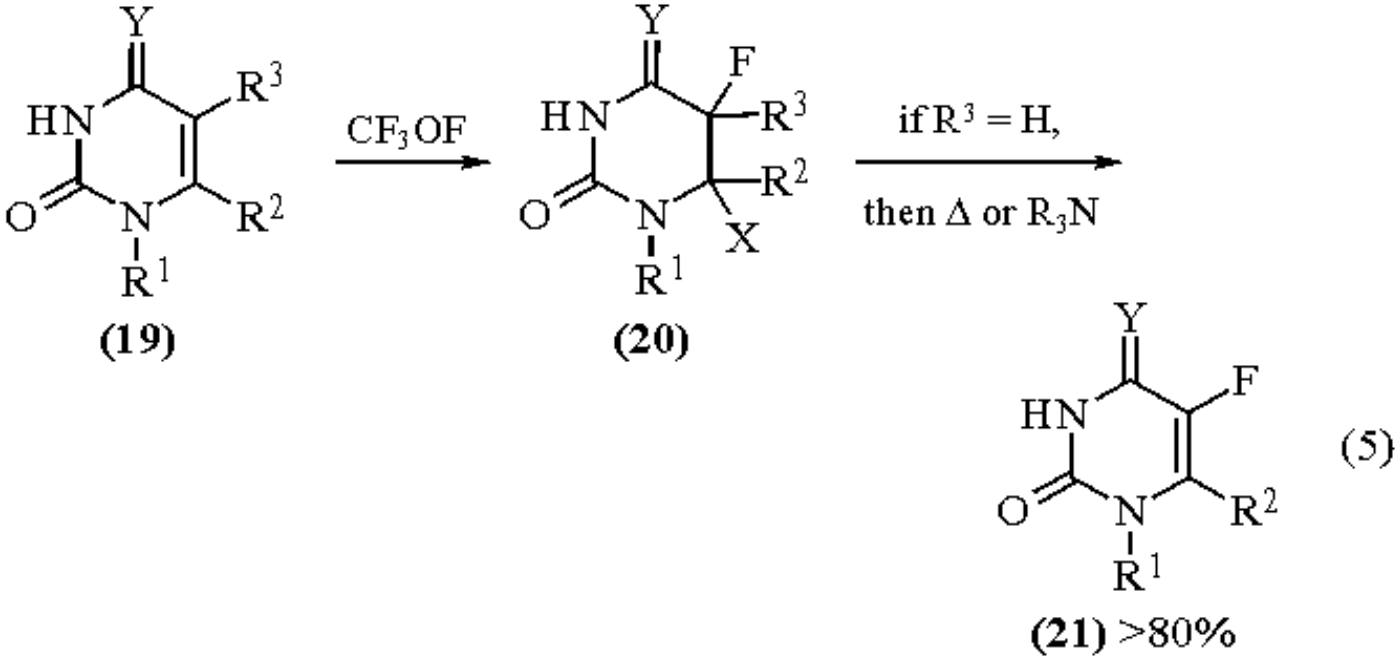

A variety of 5-F pyrimidines (and nucleosides) of biological interest have been so prepared.[22c] Radiolabeled 5-F compounds are conveniently prepared through direct fluorination of the readily available 5-H compounds.[23] Barbituric acid analogs (R^2 = OH) are also converted into 5-F compounds.[22a] (Pyrimidines have been fluorinated by F_2,[24] and 5-fluorouracil (**21**) (X = O, R^1 = R^2 = H) is prepared commercially on a quite large scale with F_2).[25]

N-Fluoro Amides and *N,N*-Difluoramines.

CF_3OF reacts with amides, first producing an N-F amide which may be further fluorinated (and cleaved) in a second step to give a difluoramino compound and an acyl derivative (X = F or OCF_3) (eq 6).[18]

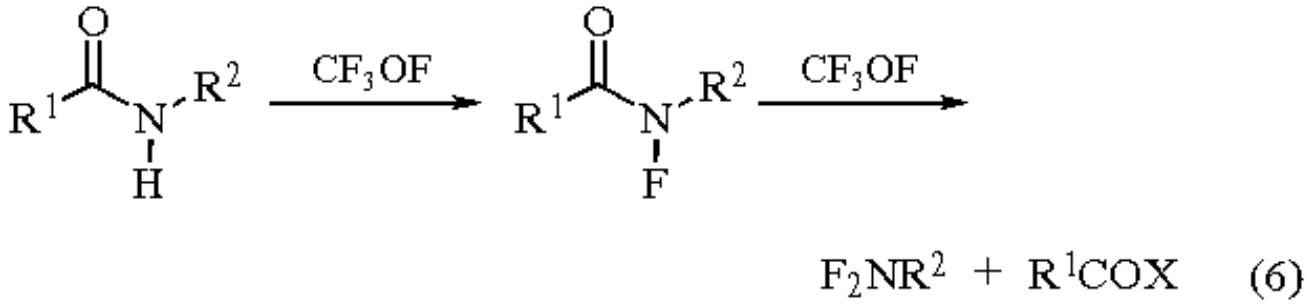

Although the rapidity of the second step impairs the synthesis of N-F carboxamides, fluorination at low conversion leads to acceptable yields (50-70%) of rather complex products[26] (i.e. **22**). N-F sulfonamides (**23**) are formed in good yield,[18] as are N-F phosphoramides, e.g. (**24**).[26]

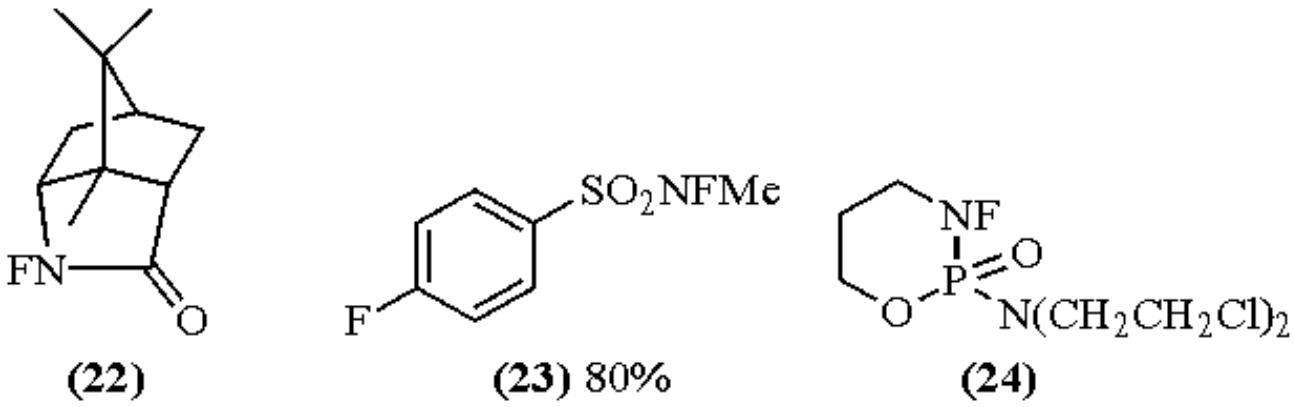

As amide nitrogen reacts with CF_3OF rather more slowly than activated aromatic rings,[18] this method is limited to the preparation of *N,N*-difluoramines bearing more robust substituents. This limitation is circumvented by fluorination of imino ethers (readily prepared by

alkylation of amides) (eq 7), e.g. preparation of (**24**) and (**25**) from the corresponding imino ethers having R^1 = Ph.[18]

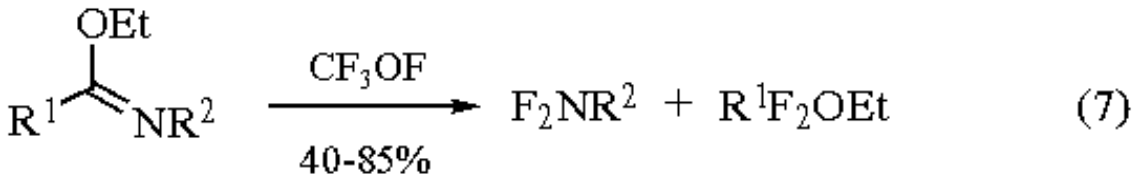

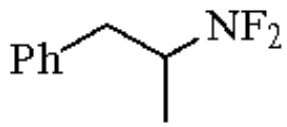

(25) 85%

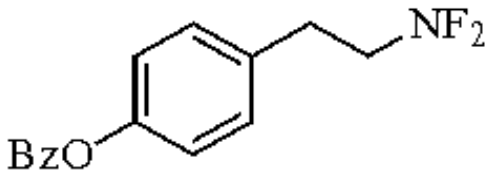

(26) 52%

Schiff bases react with CF_3OF,[27] and if the reaction is carried out in the presence of an alcohol[27b] the final cleavage is highly regioselective, affording RNF_2 (eq 8); in the absence of alcohol the alternative cleavage giving $ArCF_2NF_2$ intrudes.

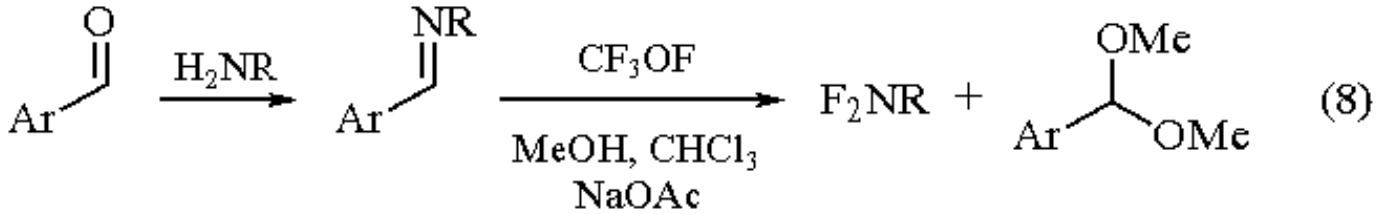

Use of Ar = Ph leads to easy purification of compounds such as (**27**), while use of Ar = *p*-NaO_2C-C_6H_4 leads to easy recovery of the neutral compounds, e.g. (**28**).

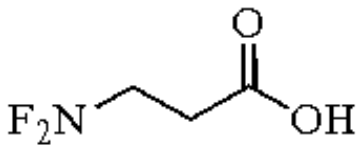

(27) 64%

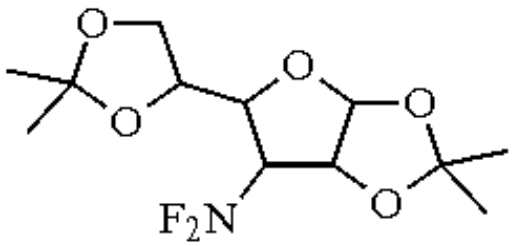

(28) 71%

Direct Replacement of sp^3 H by F.

CF_3OF reacts slowly with saturated hydrocarbons in the presence of a radical chain inhibitor (O_2, $PhNO_2$, etc., the absence of which leads to nonselective radical fluorination) to selectively replace tertiary hydrogen atoms with F.[28] This remarkable electrophilic reaction is quite regioselective (virtually restricted to tertiary H and extremely sensitive to remote electron-withdrawing groups); note (**29**)-(**31**), each obtained by fluorination of the corresponding hydrocarbon. The same regioselectivity and comparable (or superior) yield can be obtained with F_2.[28]

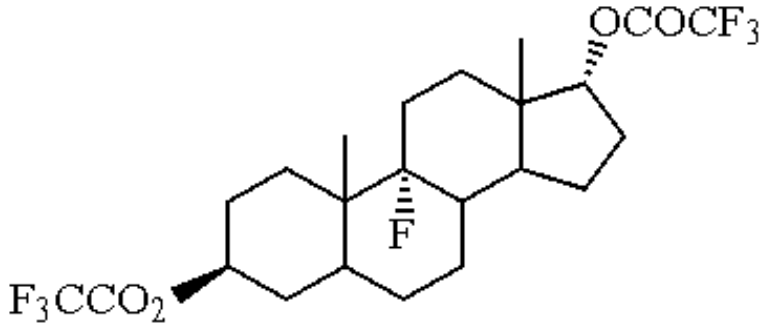

(29) >40%

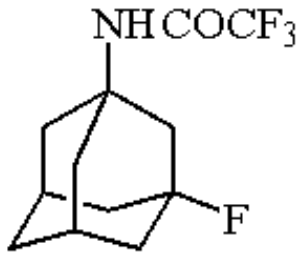

(30) 90%

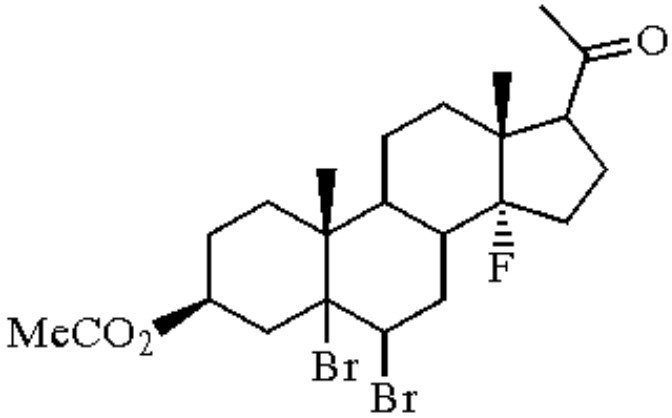

(31) >40%

Miscellaneous Reactions.

Fluorination of diazo compounds;[29a] fluorodemetalation of organometallics;[29b] photoinitiated radical replacement of H by F;[29c] photoinitiated radical addition to alkenes.[29d]

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Trifluoromethylthiocopper(I)

CF_3SCu

[3872-23-9] · $CCuF_3S$ · Trifluoromethylthiocopper(I) · (MW 164.63)

(source of nucleophilic CF_3S for preparation of aryl and vinyl sulfides)

Physical Data: mp 113-115 °C (1:1 DMF adduct).

Solubility: sol ether.

Form Supplied in: copper-colored solid; commercially available.

Preparative Methods: can be prepared by two different procedures (eq 1). Heating of finely divided ***Copper*** powder with bis(trifluoromethylthio)mercury neat at 80-100 °C until the appearance of an orange color persists, and then heating for 30 min at 150 °C, gives the desired product upon cooling, ether extraction, and evaporation.[1,2] Stirring of copper powder and bis(trifluoromethyl) disulfide in DMF for 1 h gives trifluoromethylthiocopper as its 1:1 DMF adduct.[3,4] Additionally, this reagent has been prepared by metal exchange of trifluoromethylthiosilver with ***Copper(I) Bromide***.[5]

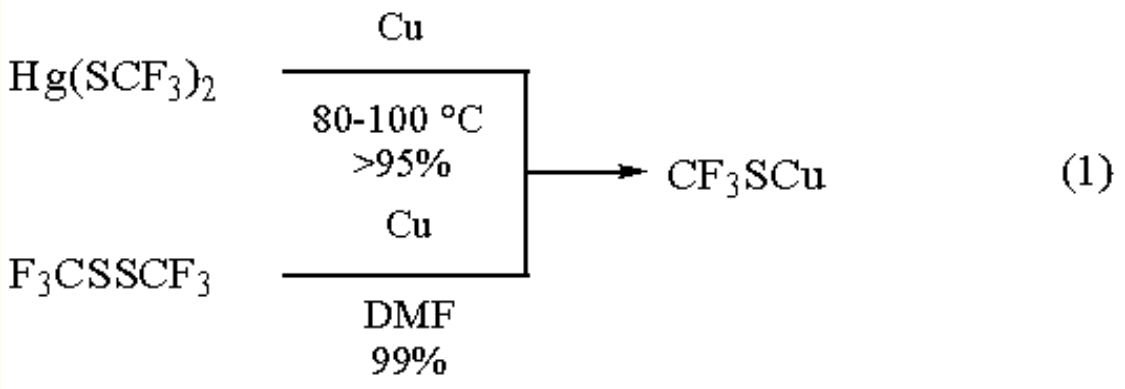

Handling, Storage, and Precautions: stable for several months when stored over phosphorus pentoxide at ambient temperature. Use in a fume hood.

Sulfide Formation.

Trifluoromethylthiocopper has been employed in reactions with bromodibenzocycloheptenones to synthesize precursors to tricyclic antipsychotic agents (eq 2).[6] Conveniently, the copper reagent is formed from its mercury salt and copper (see eq 1) in the presence of the aryl bromide, and then reacted in situ to give the aryl sulfide in high yield. These aryl sulfides have also been prepared by heating a diaryl disulfide with trifluoromethylthiocopper in acetonitrile (eq 3). 1,2-Dithioalkenes, made with trifluoromethylthiocopper, have served as precursors to 1,2-bis(trifluoromethylthio)alkynes. The alkynes are prepared in three steps from 1,2-dibromoethene in good yield (eq 4).[7]

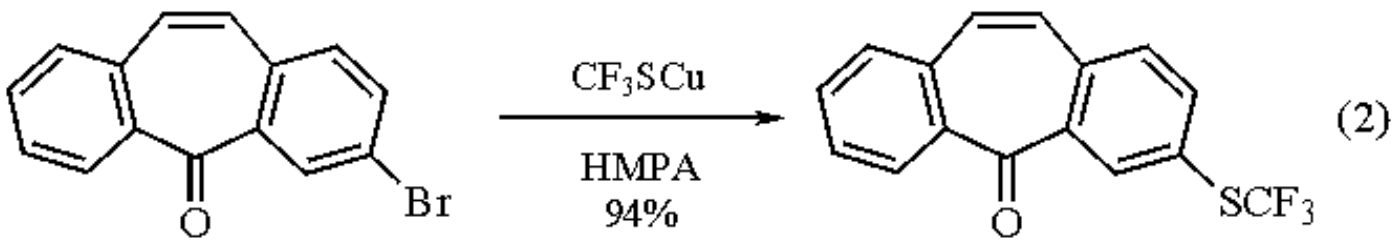

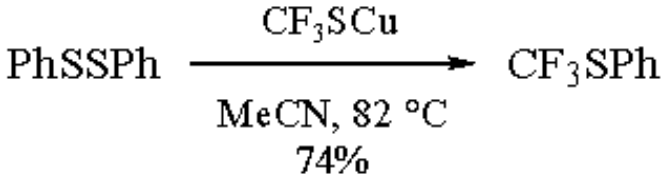

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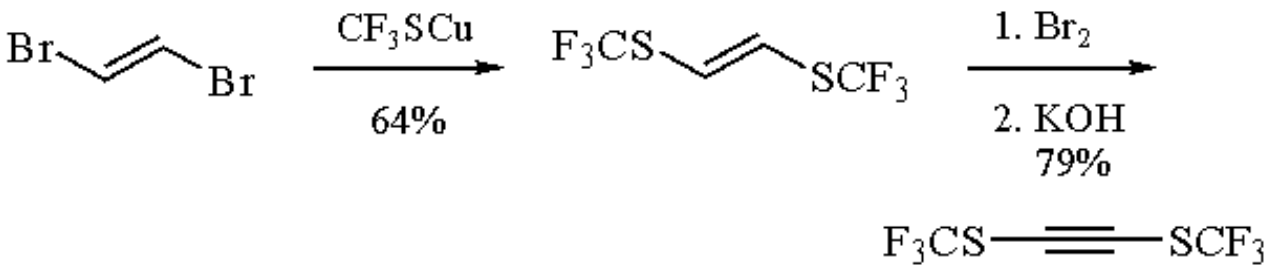

(4)

Related Reagents.

Phenylthiocopper(I).

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Trifluoromethyltrimethylsilane

Me_3SiCF_3

[81290-20-2] · $C_4H_9F_3Si$ · Trifluoromethyltrimethylsilane · (MW 142.22)

(nucleophilic trifluoromethylating agent;[1,2] difluorocarbene precursor[1])

Physical Data: bp 54-55 °C; d^{20} 0.963 g cm^{-3}.

Solubility: sol THF, ether, CH_2Cl_2.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: is prepared[2,6] based on the original procedure of Ruppert,[7] by the reaction of ***Chlorotrimethylsilane*** with the complex of trifluoromethyl bromide and hexaethylphosphorous triamide in benzonitrile (eq 1). Other less convenient procedures for its preparation are also reported.[8,9]

$$\text{TMSCl} + CF_3Br \xrightarrow[\text{benzonitrile}]{(Et_2N)_3P} \text{TMSCF}_3 \quad (1)$$

75%

Handling, Storage, and Precautions: is an acid-, base-, and moisture-sensitive compound and should be stored under anhydrous conditions in a refrigerator. Use in a fume hood.

Introduction.

$TMSCF_3$ is a valuable reagent for trifluoromethylation of electrophilic substrates under nucleophilic catalysis or initiation.[1,2] Homologous trifluoromethyltrialkylsilanes have also been used for the same purpose.[3-5]

$TMSCF_3$ reacts as a trifluoromethide equivalent with a wide variety of electrophilic substrates such as carbonyls, sulfonyl fluorides, sulfoxides, deactivated aromatics, sulfur dioxide, and alkenes, etc.

Reactions with Carbonyl Compounds.

$TMSCF_3$ reacts with aldehydes in the presence of a catalytic amount of ***Tetra-n-butylammonium Fluoride*** (TBAF) in THF to form the corresponding trifluoromethylated carbinols in good to excellent yields following aqueous hydrolysis of the silyl ethers (eq 2).[2,3,6,10] The reaction also works very well for ketones under the same conditions, with the exception of extremely hindered ones such as 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, di-1-adamantyl ketone, and fenchone. The reaction has been characterized as a fluoride-induced autocatalytic reaction.[3,10] Other initiators such as ***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate*** (TASF), ***Potassium Fluoride***, $Ph_3SnF_2^-$, and RO^- can also be used for these reactions. For the reactions of $TMSCF_3$ and perfluorinated ketones and pentafluorobenzaldehyde, excess of KF is needed.[16,17]

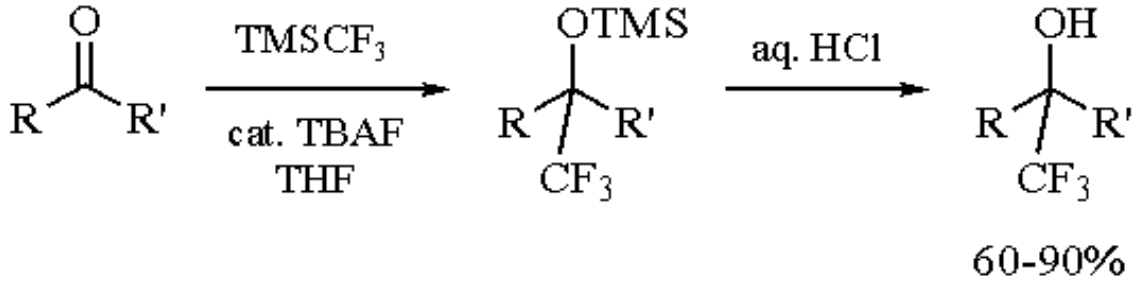

(2)

$TMSCF_3$ has been used in the preparation of polycyclic aromatic carcinogens, the key step being the addition of $TMSCF_3$ to the carbonyl group (eq 3).[11]

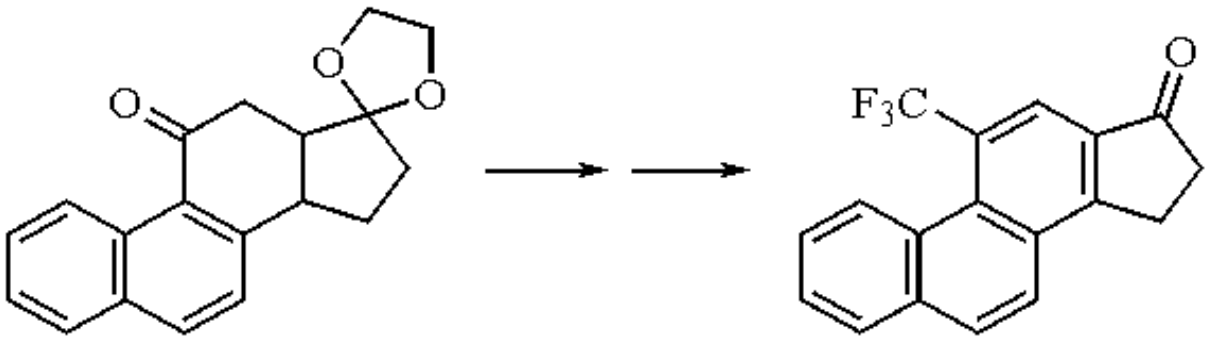

(3)

A series of tripeptides containing the trifluoromethyl group has been prepared as potent inhibitors of human leukocyte elastase (HLE) by using $TMSCF_3$.[12] $TMSCF_3$ has also been used to prepare trifluoromethyl analogs of L-fucose and 6-deoxy-D-ribose.[13] Gassman et al. have prepared 1-trifluoromethylindene starting from 1-indanone.[14]

1,2-Diketones such as benzil give only the monoadduct. On the other hand, the highly enolizable cyclohexane-1,3-dione did not give the addition product with $TMSCF_3$.[15]

A series of α,β-conjugated enones and ynones react with $TMSCF_3$ to give predominant 1,2-addition products (eq 4).[3,15]

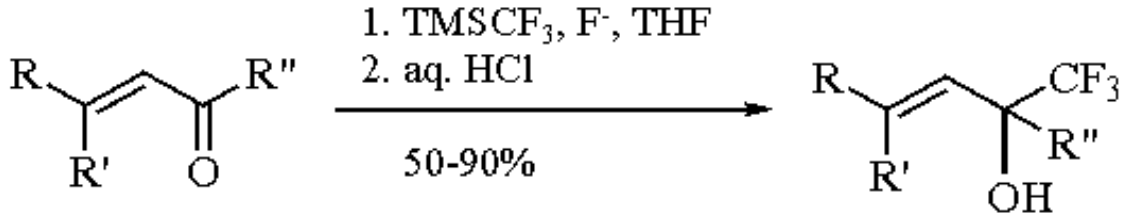

(4)

Simple unactivated esters do not react with $TMSCF_3$.[3] However, activated esters such as trifluoroacetic acid esters do react.[3] Cyclic esters, i.e. lactones, react with $TMSCF_3$ to give the corresponding adducts.[3] An efficient and simple synthesis of trifluoropyruvic acid monohydrate has been developed starting from di-*t*-butyl oxalate.[18]

Direct trifluoromethylation of α-keto esters give Mosher's acid derivatives (eq 5).[19]

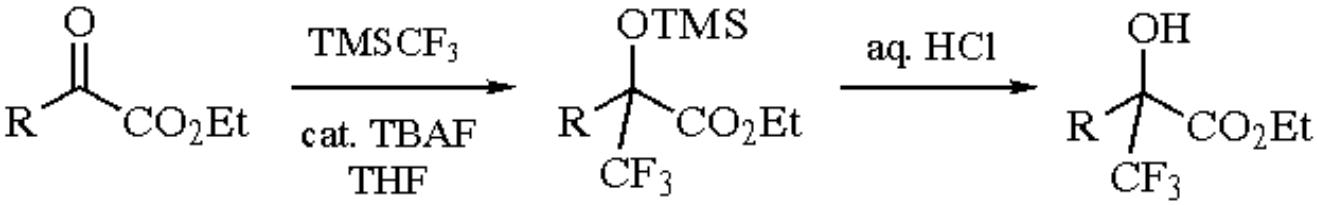

(5)

Acyl halides such as benzoyl chloride react with $TMSCF_3$ to give a mixture of the trifluoroacetophenone and hexafluorocumyl alcohol in the presence of equimolar TBAF.[3] Cyclic anhydrides react readily with $TMSCF_3$; however, a stochiometric amount of TBAF is required. Acyclic anhydrides react less cleanly.[3]

Simple amides, such as benzamide and acetamide, do not react with $TMSCF_3$ even with molar quantities of TBAF.[3] However, an

activated amide carbonyl such as in *N*-trifluoroacetylpiperidine reacts to give an adduct which upon subsequent hydrolysis gives hexafluoroacetone trihydrate.[15] Imidazolidinetriones react with $TMSCF_3$ to give 5-trifluoromethyl-5-hydroxyimidazolidine-2,4-diones upon aqueous acid workup.[20] Imides such as *N*-methylsuccinimide react smoothly to afford the hemiaminal adducts (eq 6).[15]

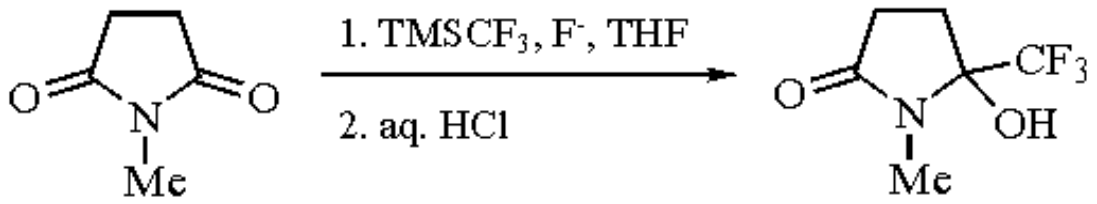

(6)

Sulfur Derivatives.

Kirchmer and Patel have reported[17] the preparation of trifluoromethylsulfinyl fluorides, sulfonyl fluorides, sulfoxides, and sulfuranes using $TMSCF_3$ in the presence of a catalytic amount of KF.

$TMSCF_3$ reacts with ***Dimethyl Sulfoxide*** in the presence of catalytic amount of TBAF to give Me_2CF_3SOTMS.[17] Arylsulfonyl fluorides react with $TMSCF_3$ to give the corresponding trifluoromethyl sulfones.[1,21]

Sulfur Dioxide reacts with $TMSCF_3$ in the presence of TMSONa to give the sodium trifluoromethyl sulfinate. The sulfinate has been further oxidized to trifluoromethanesulfonic acid in 30% overall yield.[1]

Nitroso Group.

Nitrosobenzene reacts with $TMSCF_3$ to afford the *O*-silylated trifluoromethylated hydroxylamine quantitatively.[1]

Aromatic Compounds.

Nucleophilic trifluoromethylation of aromatic compounds containing nitro, fluoro, and trifluoromethyl groups as substituents using $TMSCF_3$ has been investigated.[22,15] Yagupolskii et al. have reported that $TMSCF_3$-TASF (1:1) reacts with 1,2,4,5-tetrakis(trifluoromethyl)benzene at -30 °C to give the stable carbanion salt (eq 7).[23]

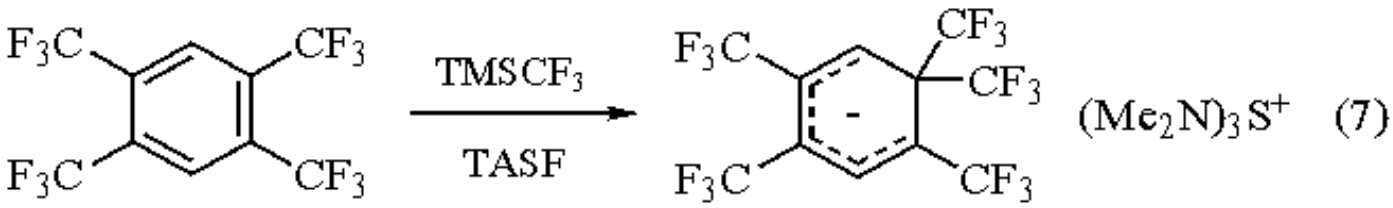

(7)

Phosphorus Compounds.

Treatment of $(BuO)_2P(O)F$ with $TMSCF_3$ and a catalytic amount of KF gave $(BuO)_2P(O)CF_3$ in 93% isolated yield.[1]

Generation of Difluorocarbene.

Treatment of $TMSCF_3$ with an anhydrous fluoride source such as TASF in THF results in the generation of singlet difluorocarbene. In the presence of an acceptor such as tetramethylethylene, the corresponding adduct can be isolated.[1]

Related Reagents.

Trifluoromethylcopper(I).

---

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Trifluoroperacetic Acid[1]

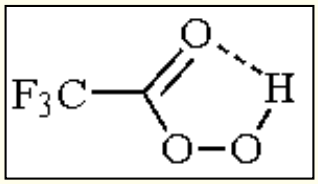

[359-48-8] · $C_2HF_3O_3$ · Trifluoroperacetic Acid · (MW 130.03)

(electrophilic reagent capable of reacting with many functional groups; delivers oxygen to alkenes, arenes, and amines;[1] useful reagent for Baeyer-Villiger oxidation of ketones[27,44])

Alternate Names: TFPAA; peroxytrifluoroacetic acid.

Solubility: sol CH_2Cl_2, dichloroethane, ether, sulfolane, acetonitrile.

Form Supplied in: not available commercially.

Analysis of Reagent Purity: assay using iodometry.[2]

Preparative Methods: the preparation and handling of TFPAA should be carried out behind a safety shield. A mixture of ***Trifluoroacetic Anhydride*** (46.2 g; 0.22 mole) and CH_2Cl_2 (50 mL) is cooled with stirring in an ice bath. 90% H_2O_2 (caution: for hazards see ***Hydrogen Peroxide***) (5.40 mL, 0.20 mol) is added in 1 mL portions over a period of 10 min. When the mixture has become homogeneous, it is allowed to warm to rt and then again cooled to 0 °C.[3] TFPAA prepared from 30% aqueous H_2O_2 and ***Trifluoroacetic Acid*** has been used for some reactions.[4-6] Hydrogen peroxide of high concentration (70%) is not widely available due to hazards involved in handling, storage, and transportation. The commercially available ***Hydrogen Peroxide-Urea*** (UHP) system, which is safe to handle, has been introduced recently as a substitute for anhydrous H_2O_2 in the preparation of TFPAA.[2,7,8]

Purification: in the preparation of TFPAA, a slight excess of trifluoroacetic anhydride is used to ensure that no water is present in the reagent. The reaction between H_2O_2 and trifluoroacetic anhydride is very fast; the reagent is ready for use after the reactants have been mixed and the solution has become homogeneous. No special purification steps are employed. Suitable buffers (Na_2CO_3, Na_2HPO_4) are used to neutralize the highly reactive and strongly acidic trifluoroacetic acid which is present along with TFPAA in the reagent.

Handling, Storage, and Precautions: the reagent can be stored at -20 °C for several weeks[9] and exhibits no loss in active oxygen content after 24 h in refluxing CH_2Cl_2.[40] However, since it can be prepared in a short time, the usual practice is to prepare the reagent when needed. Note that solutions of TFPAA in CH_2Cl_2 can lose activity by evaporation of the volatile peracid.[41] Since peroxy acids are potentially explosive, care is required while carrying out the reactions and also during workup of the reaction mixture. Solvent removal from excess H_2O_2-CF_3CO_2H experiments can result in explosions; the peroxide must be destroyed by addition of MnO_2 (until a potassium iodide test is negative) before solvent removal.[10a] For a further discussion of safety, see Luxon.[10b] This reagent should only be handled in a fume hood.

General Considerations.

Trifluoroperacetic acid oxidizes simple alkenes, alkenes carrying a variety of functional groups (such as ethers, alcohols, esters, ketones, and amides), aromatic compounds, alkanes,[11] amines and N-heterocycles. Ketones undergo oxygen insertion reactions (Baeyer-Villiger oxidation).

Epoxidations of Alkenes.

Due to the presence of the strongly electron withdrawing CF_3 group, TFPAA is the most powerful organic peroxy acid and as such is more reactive than performic[21] or 3,5-dinitroperbenzoic acids.[41] It reacts readily even with electron-poor alkenes to furnish the corresponding

epoxides (see ***m-Chloroperbenzoic Acid***).

Trifluoroacetic acid is a strong acid which opens epoxides readily.[12,44] Since TFPAA is a much weaker acid than trifluoroacetic acid (pK_a 3.7 vs. 0.3), the latter reagent can be selectively neutralized with Na_2CO_3 or Na_2HPO_4, leading to the isolation of epoxides in high yields. When the substrate is highly reactive, Na_2CO_3 is used as buffer; when the substrate reacts sluggishly, Na_2HPO_4 is used as buffer.[12] The TFPAA reagent is rapidly decomposed by Na_2CO_3.

Since monosubstituted alkenes are not electron rich, they react sluggishly with the standard organic peroxy acids. By contrast, the monosubstituted alkene 1-pentene (**1**) is epoxidized efficiently by TFPAA (eq 1).[12] TFPAA prepared from 0.3 mol of 90% H_2O_2 and 0.36 mol of trifluoroacetic anhydride in CH_2Cl_2 is added during 30 min to a stirred mixture of (**1**) (0.2 mol), Na_2CO_3 (0.9 mol), and CH_2Cl_2 (200 mL). Since the alkene is volatile the reaction flask is fitted with an efficient ice water-cooled condenser. The reaction mixture boils during the addition of the peracid. After all the reagent has been added, the reaction mixture is heated under reflux for 30 min, cooled, and the insoluble salts are removed by centrifugation. The salt is thoroughly washed with CH_2Cl_2. Fractional distillation of the combined CH_2Cl_2 extracts furnishes the epoxide (**2**) in 81% yield.

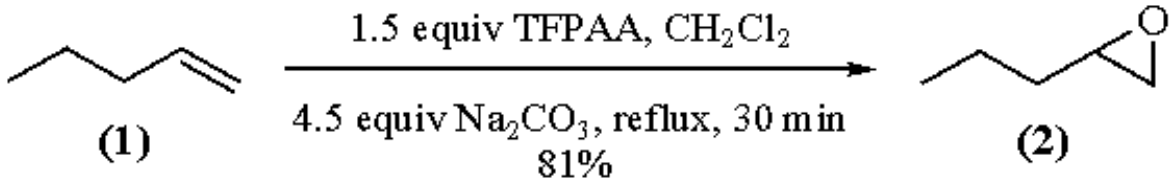

(1)

The alkene (**3**), which is resistant to epoxidation by *m*-CPBA or ***Peracetic Acid***, has been epoxidized with TFPAA to furnish in 83% yield a mixture of esters (**4**) and (**5**) (eq 2).[13] Esters (**4**) and (**5**) undergo facile deacylation when chromatographed on silica gel to furnish alcohols (**6**) and (**7**).

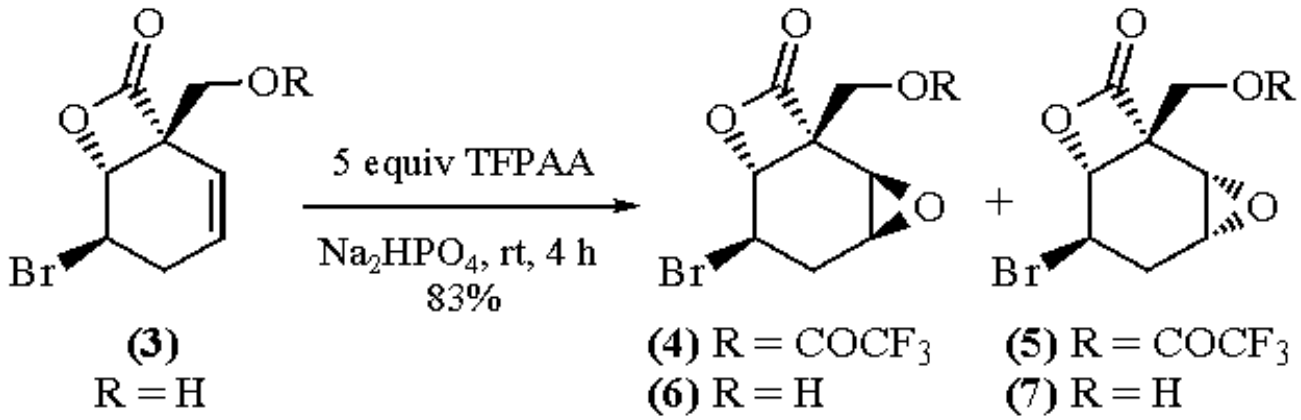

(2)

Epoxidation of allyldiphenylphosphine oxide (**8**) with TFPAA furnishes in quantitative yield the corresponding epoxide, 2-(diphenylphosphinoylmethyl)oxirane; *m*-CPBA epoxidation of (**8**) furnishes the epoxide in only 56% yield.[14] Epoxide (**9**) is obtained in 80% yield through regio- and stereoselective epoxidation of the corresponding alkene with TFPAA in CH_2Cl_2 in the presence of Na_2HPO_4 buffer.[15]

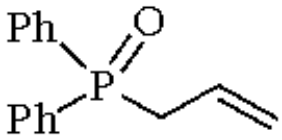

(8)

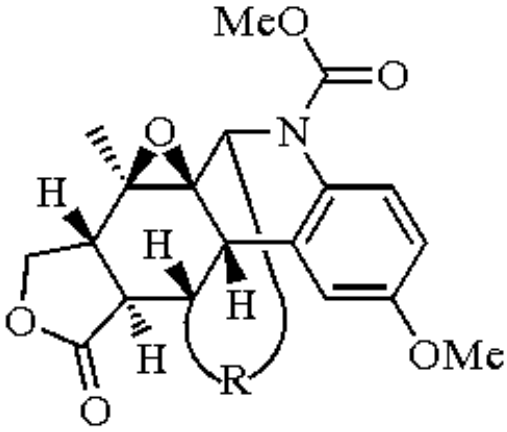

(9) R =

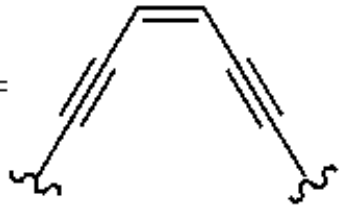

(Z)

The tertiary amine of (**10**) is expected to react more readily than the disubstituted double bond on treatment with an organic peracid. Selective epoxidation of the double bond in (**10**) was achieved by initially treating it with CF_3CO_2H. This led to salt formation due to protonation of the amine. Epoxidation of the salt with TFPAA and subsequent workup furnished the epoxide (**11**) (eq 3).[16]

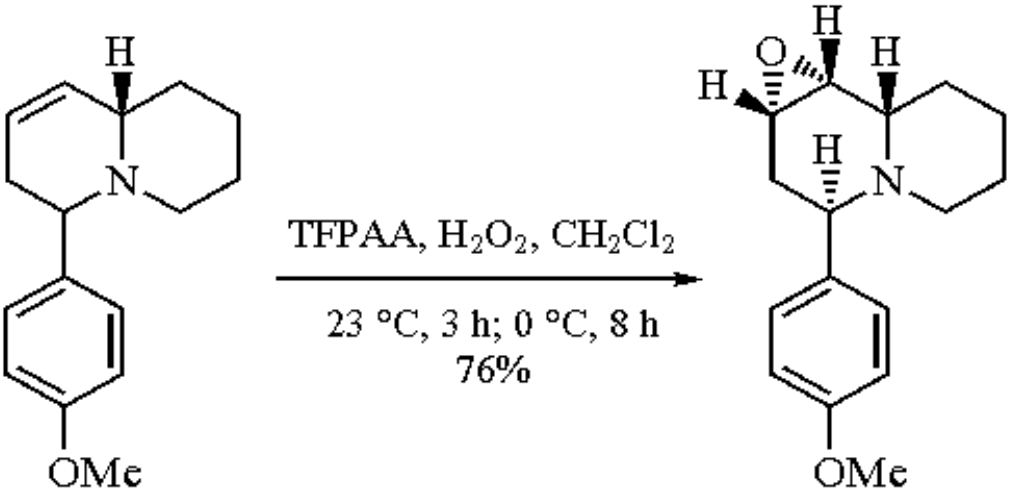

(3)

(10) **(11)**

Alkenes have been epoxidized efficiently employing TFPAA prepared by the UHP method (eq 4).[2]

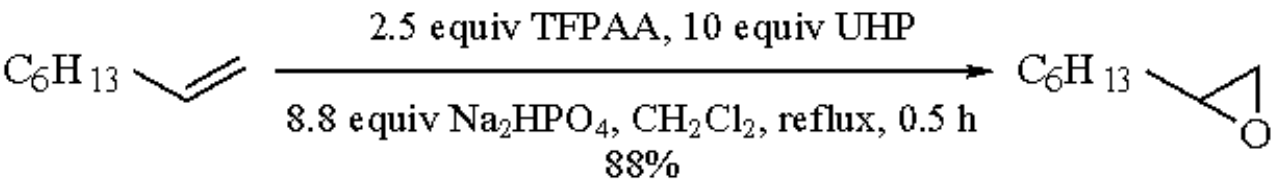

(4)

α,β-Unsaturated esters and α,β-unsaturated ketones are resistant to epoxidation by organic peracids since the double bonds are not electron rich; however, these compounds can be epoxidized by TFPAA. 1-Acetylcyclohexene[17] and methyl methacrylate[12] furnish the corresponding epoxides in 50% and 84% yields, respectively, when treated with TFPAA/Na_2HPO_4 in CH_2Cl_2 (reflux for about 0.5 h). The α,β-unsaturated ester (**12**) has been epoxidized stereoselectively by TFPAA (eq 5).[18] With *m*-CPBA, this epoxidation requires a higher reaction temperature which results in the formation of a complex mixture.

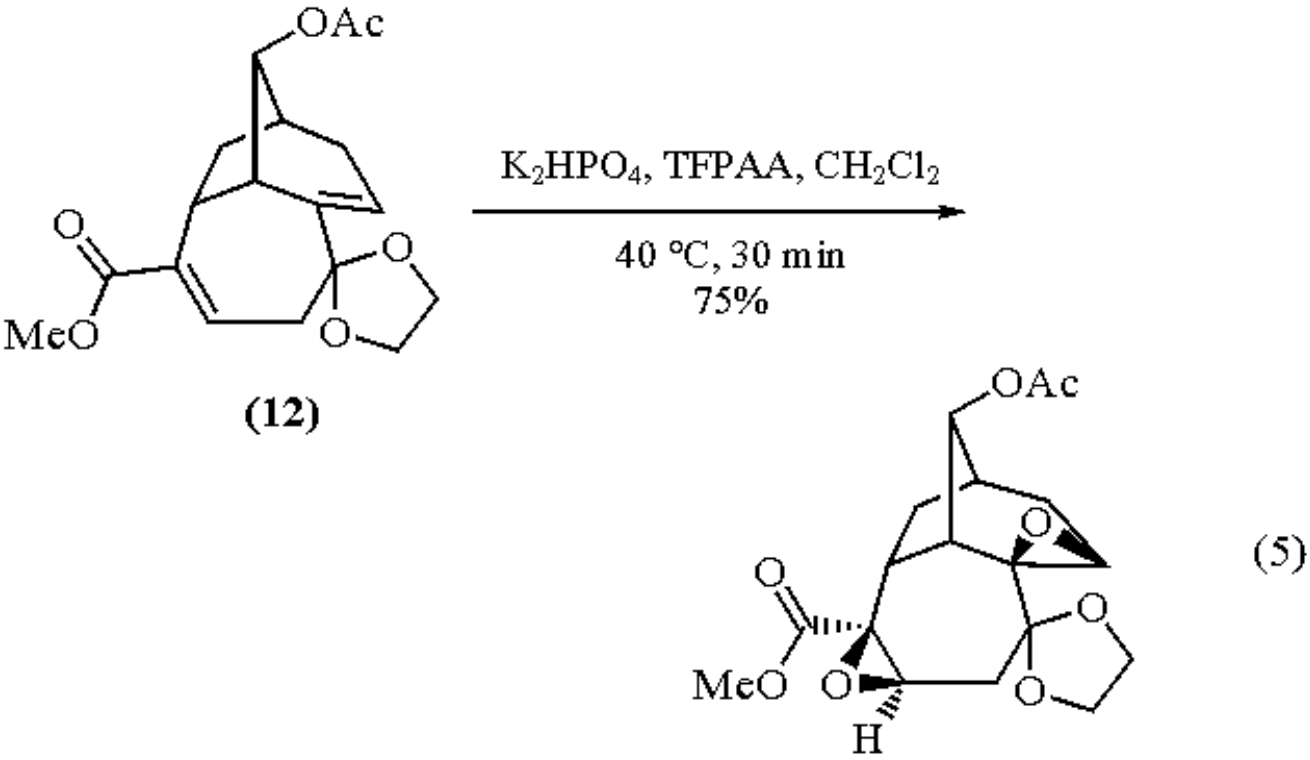

With organic peracids, allyl alcohols form hydrogen bonds involving the hydrogen of the alcohol, as in (**13**).[19] Ganem has suggested that, with TFPAA, allylic ethers form hydrogen bonds involving the hydrogen of the peracid (**14**).

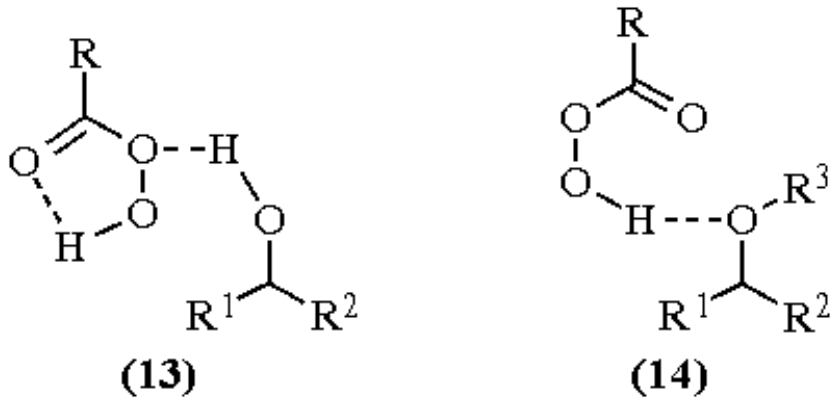

Epoxidation of (**15**) having an allylic ether substituent axially oriented is *syn* selective (*syn:anti* epoxidation = 12.4:1) (eq 6);[19] this selectivity is due to the formation of the hydrogen bond of the type shown in (**14**). The stereoselectivity in the epoxidation of (**15**) is solvent dependent. When (**15**) is epoxidized in THF (which disrupts hydrogen bonding) the ratio of *syn*:*anti* epoxides obtained is 1:12. The epoxidation of the allyl alcohol (**16**) with TFPAA is highly *syn* selective (*syn*:*anti* epoxidation = 100:1); the *syn* selectivity in the epoxidation of (**16**) with *m*-CPBA is much less (*syn*:*anti* epoxidation = 5.2:1).

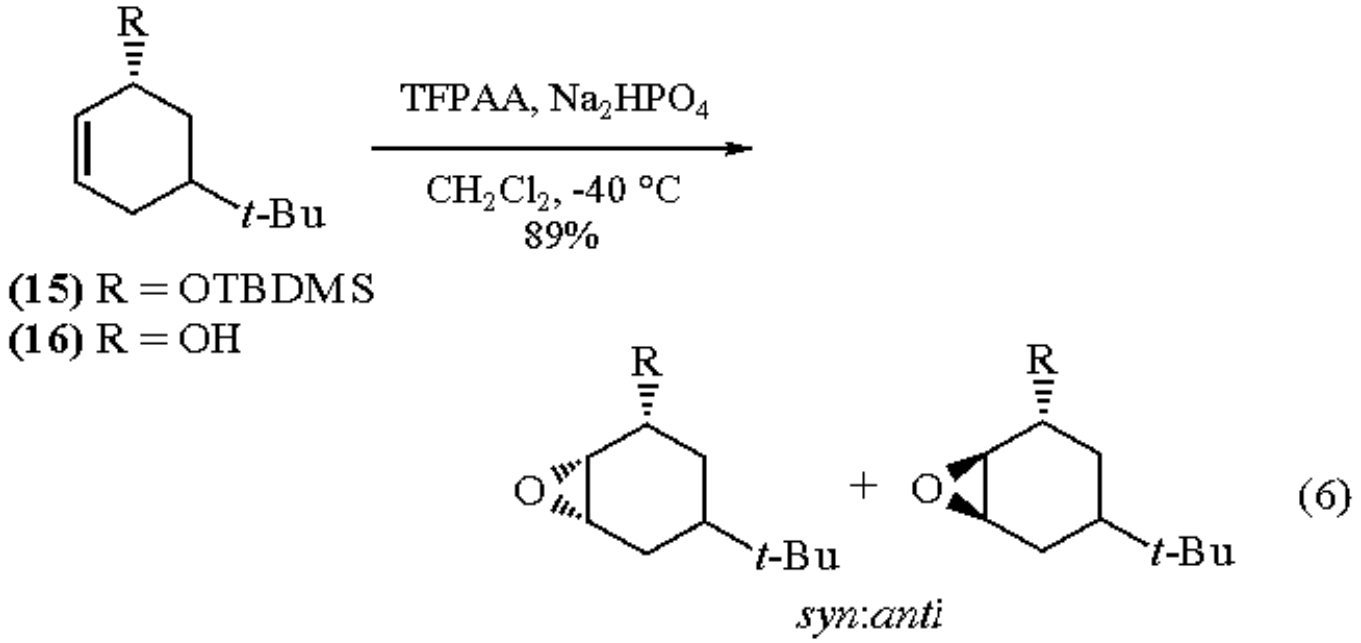

The diol (**17**) is epoxidized stereoselectively to furnish (**18**) (eq 7).[20]

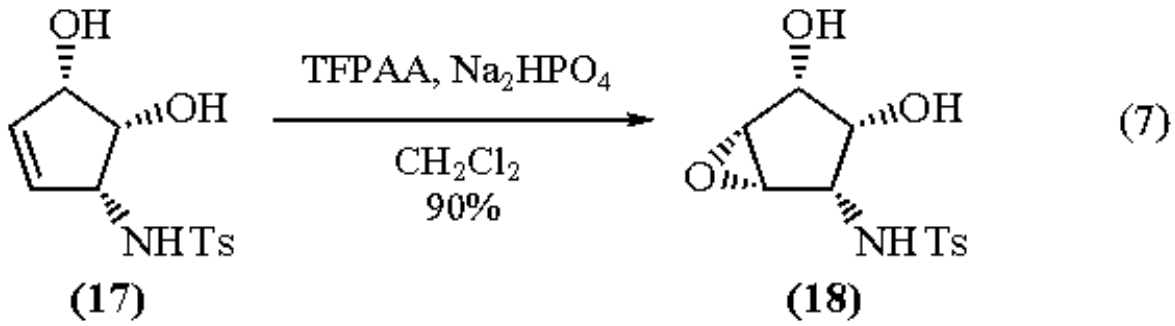

Oxidation of Alkenes to Diols and Ketones.

Alkenes react readily with a CF_3CO_3H/CF_3CO_2H mixture to furnish hydroxy trifluoroacetates, e.g. (**19**) -> (**20**) (eq 8).[21] In this reaction, high molecular weight byproducts are formed due to the condensation of hydroxy trifluoroacetates with the epoxides formed from alkenes. The formation of the byproduct can be avoided by adding triethylammonium trifluoroacetate. After the formation of the glycol ester is complete, the solvent is evaporated under reduced pressure and the crude ester is subjected to methanolysis to furnish the vicinal diol (**21**). α,β-Unsaturated esters are also hydroxylated by this procedure.

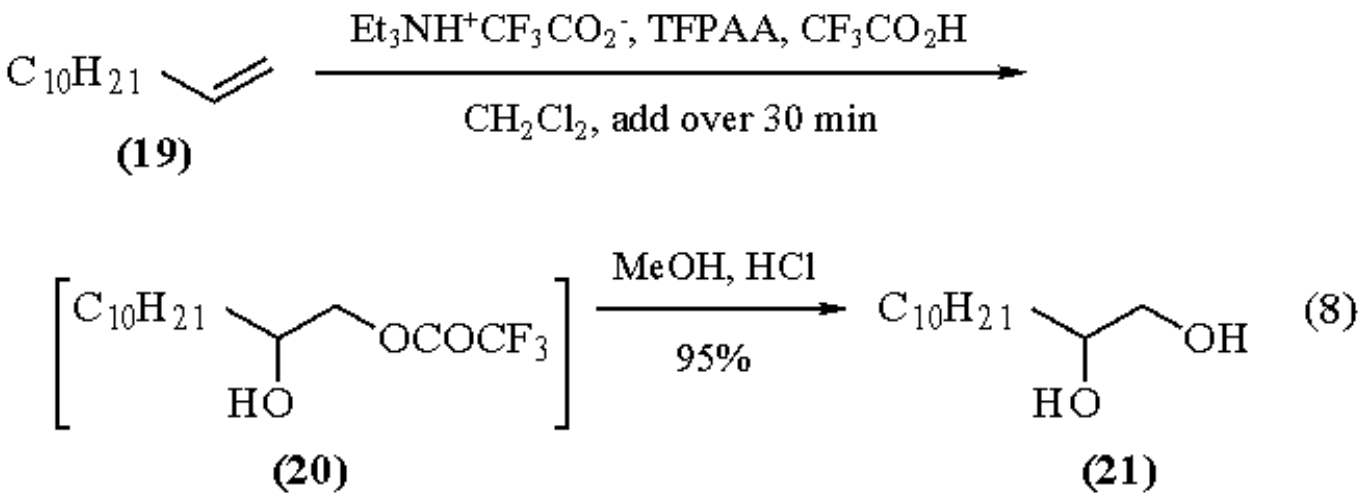

The allyl alcohol (**22**) reacted readily with TFPAA to furnish the 1,3-dioxolane (**23**) (eq 9).[8] This reaction could not be carried out with *m*-CPBA even in refluxing ethylene dichloride. The homoallyl alcohol (**22**) (R^1 = H, R^2 = OH) was reacted with TFPAA prepared from commercially available urea-hydrogen peroxide; the major product formed was the dioxolane (**23**) (R^1 = H, R^2 = OH).

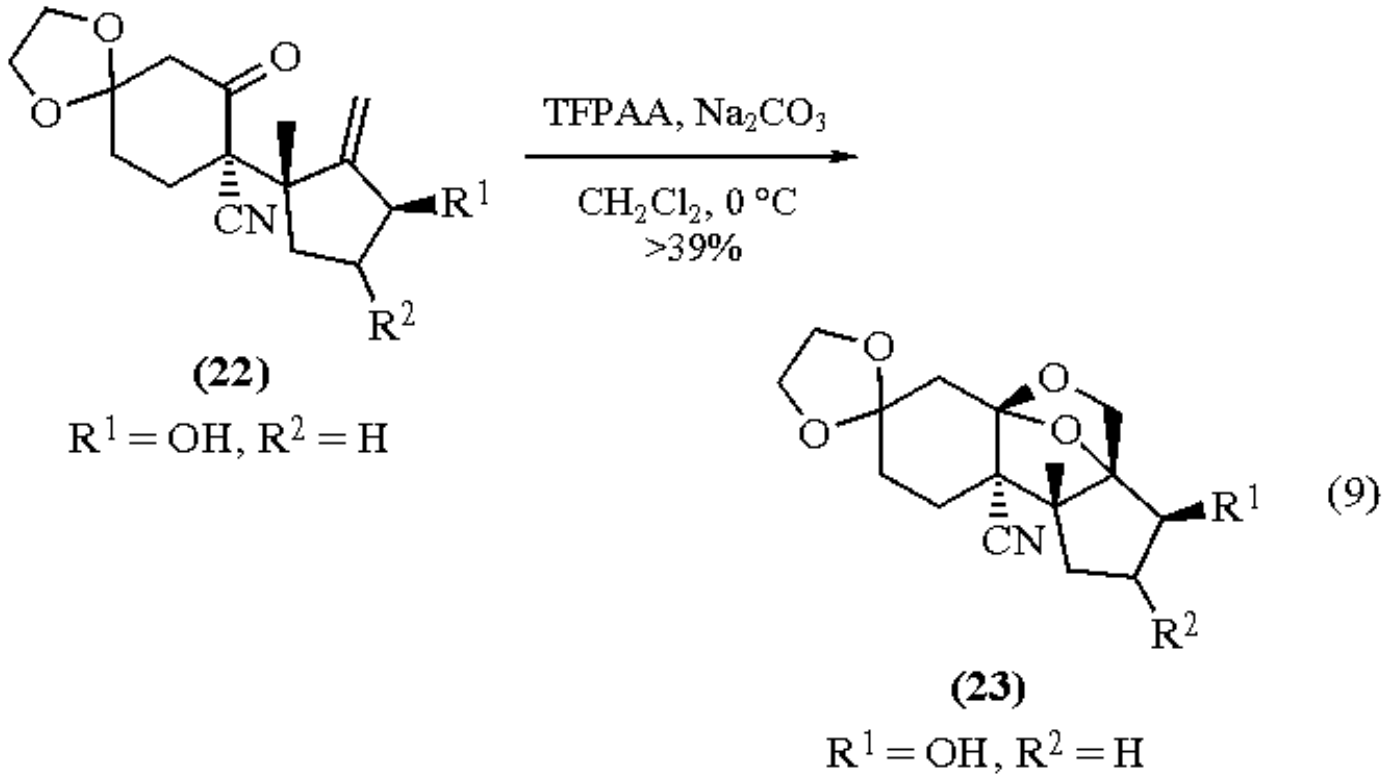

(±)-Allosamizoline (**25**) has been synthesized from the (dimethylamino)oxazoline (**24**).[22] 5.4 M TFPAA in CF_3CO_2H is added carefully to (**24**) at 0 °C. The reaction mixture is evaporated in vacuum and the resulting mixture of epoxides is solvolyzed by heating with 10% aqueous CF_3CO_2H at 40 °C. Hydrogenolysis (Pd/C, H_2, MeOH) of the solvolysis product furnishes pure (±)-(**25**) (overall yield 67%) and the epoxide (**26**) (yield 16%).

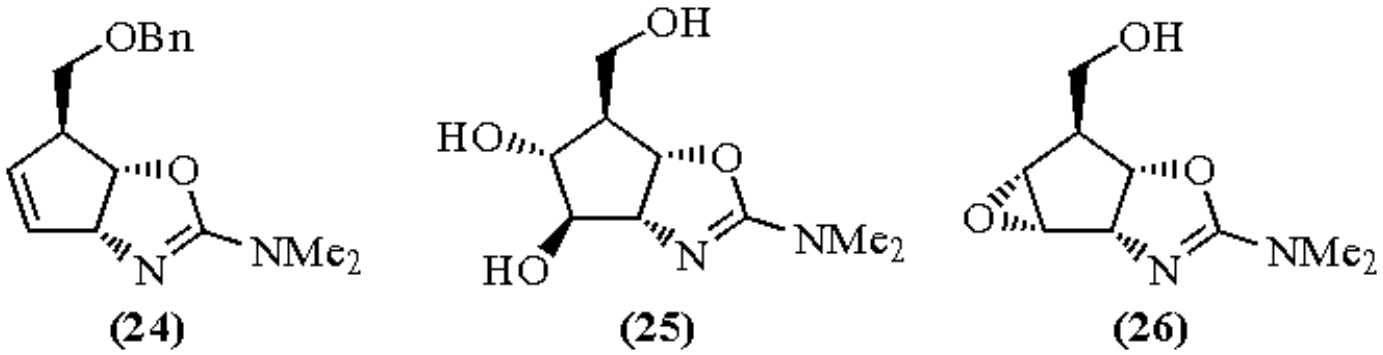

Epoxidation of sterically congested alkenes occurs with TFPAA under basic conditions (eq 10).[45]

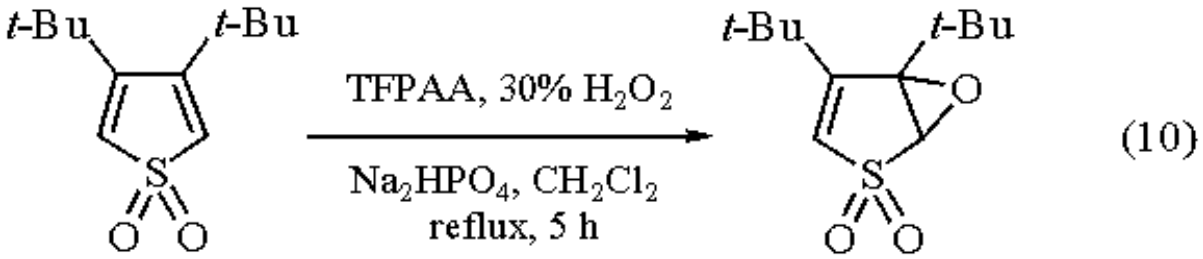

Treatment of tetrasubstituted alkenes with TFPAA/BF_3 furnishes ketones via rearrangement. 1,2-Dimethylcyclohexene has been transformed to the ketone (**27**) (eq 11);[23] the reagents TFPAA and 47% ***Boron Trifluoride Etherate*** are added simultaneously.

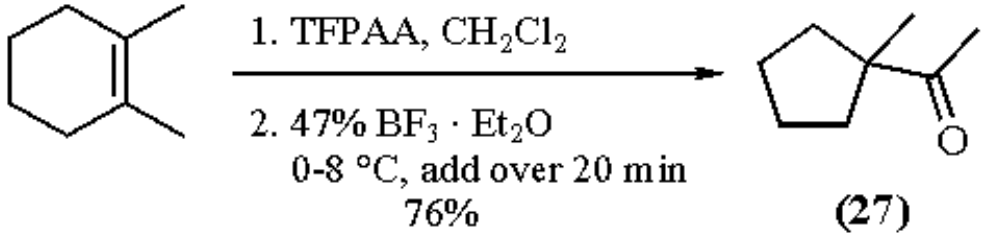

(11)

Arene Oxidation.

Arenes are exhaustively oxidized to aliphatic carboxylic acids. Heteroaromatic systems, such as pyridine, quinoline, and dibenzothiophene, are quantitatively oxidized to their *N*-oxides and sulfone rather than undergo ring oxidation. The heteroatom oxidation deactivates the ring towards electrophilic attack by TFPAA.[6] Benzene undergoes direct catalytic oxidation to phenyl trifluoroacetate using a TFPAA/Co^{III} reagent.[24]

With BF_3.

The combination TFPAA/***Boron Trifluoride*** is a potent electrophilic oxidant for π-systems.[46] As a source of positive hydroxyl, it is used to convert aromatics into cyclohexadienones (eq 12)[26a] and phenols,[25] and alkenes into ketones (eq 13).[26b] See also eq 11 above.

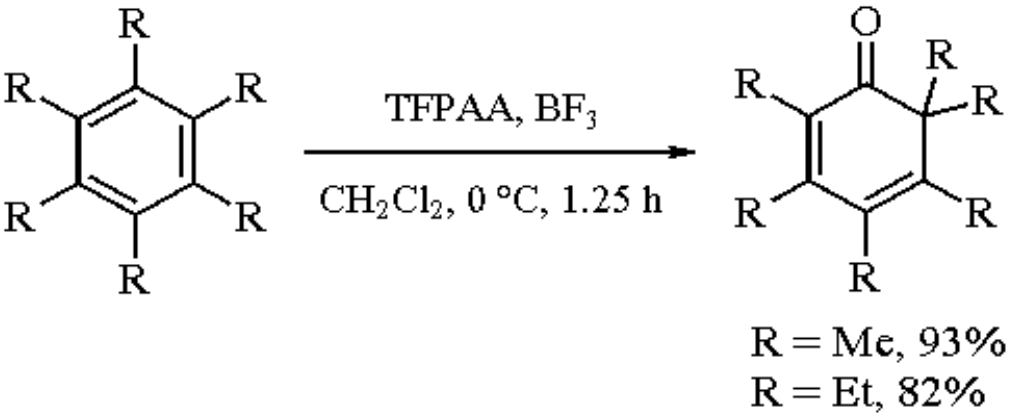

(12)

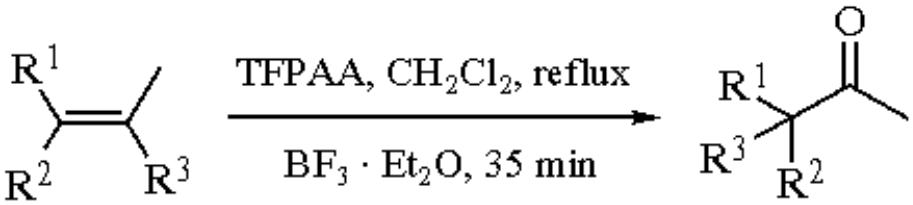

(13)

R^1	R^2	R^3	Yield
Me	Me	Me	75%
Me	Me	H	53%
Et	Me	H	70%
Me	Cl	Me	77%

Baeyer-Villiger Oxidation.

On treatment with organic peroxy acids, ketones undergo oxygen insertion reactions to furnish esters (see ***m-Chloroperbenzoic Acid***).[44] This reaction, known as the Baeyer-Villiger rearrangement, has several applications and has been reviewed recently.[27] When carrying out this oxidation with TFPAA, Na_2HPO_4 buffer is added to prevent the reaction between trifluoroacetic acid and the Baeyer-Villiger product. The ketone (**28**) reacts with TFPAA to furnish brassinolide tetracetate (**29**) (eq 14).[28] The migration of C-7 rather than C-5 carbon in this oxidation is due to the effect of the acetate groups at C-2 and C-3. A systematic study of the Baeyer-Villiger reaction of 5α-cholestan-6-ones

having substituents at C-1, C-2, and C-3 has been carried out.[29]

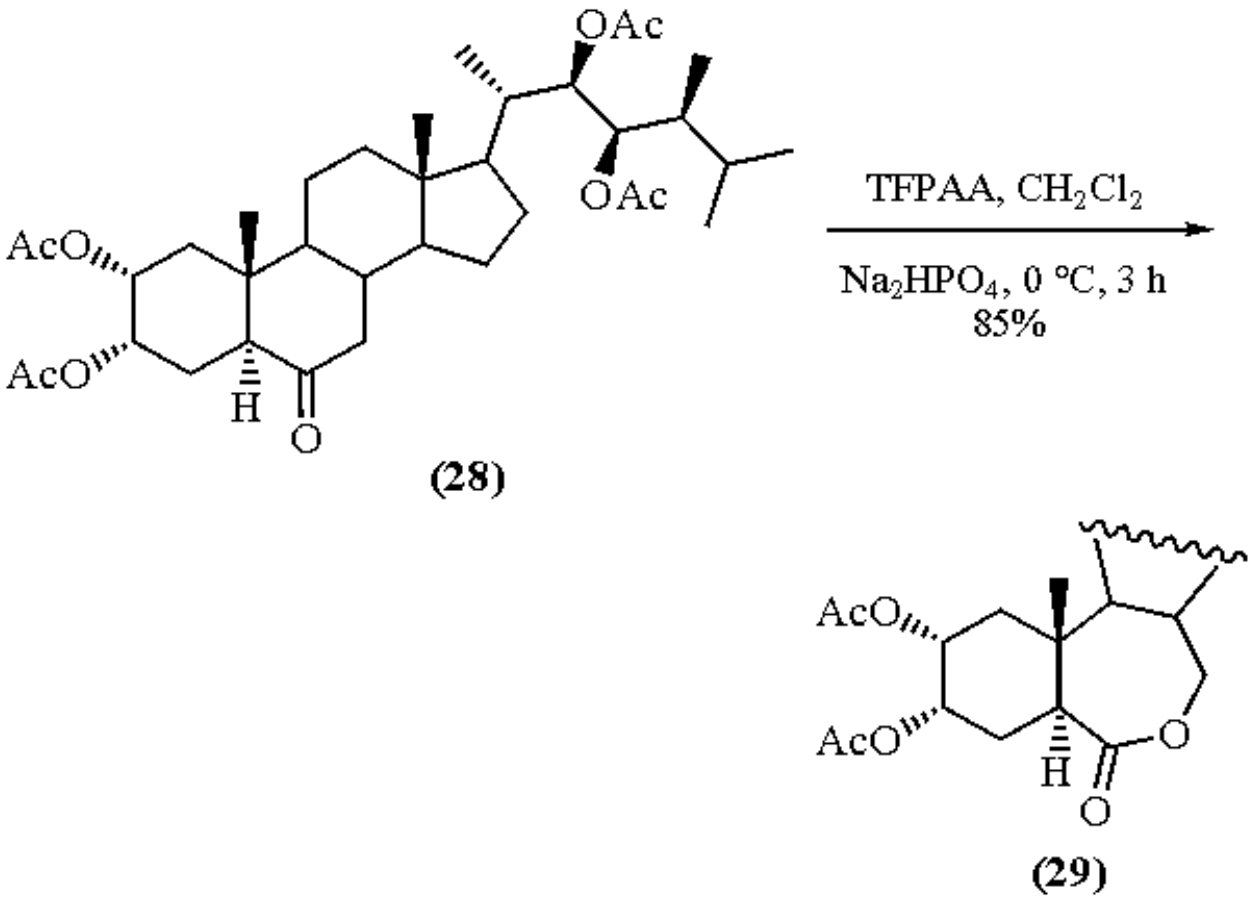

(14)

The oxidations of the ketone (**30**) and α-tetralone (**31**) have been reported (eqs 15 and 16).[30,2] Epimerization of α-substituents is generally not observed when ketones are oxidized with buffered TFPAA.[42]

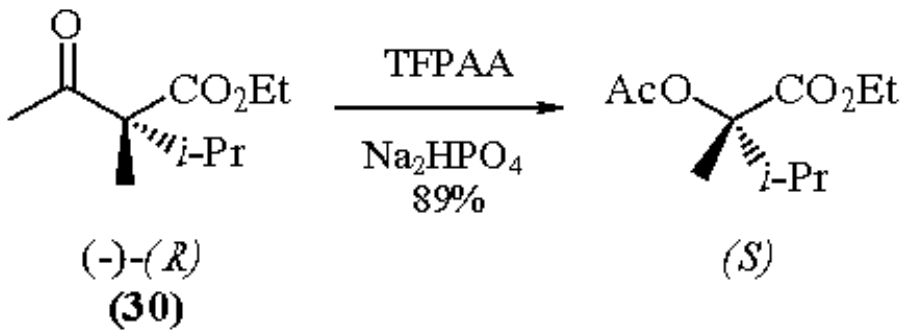

(15)

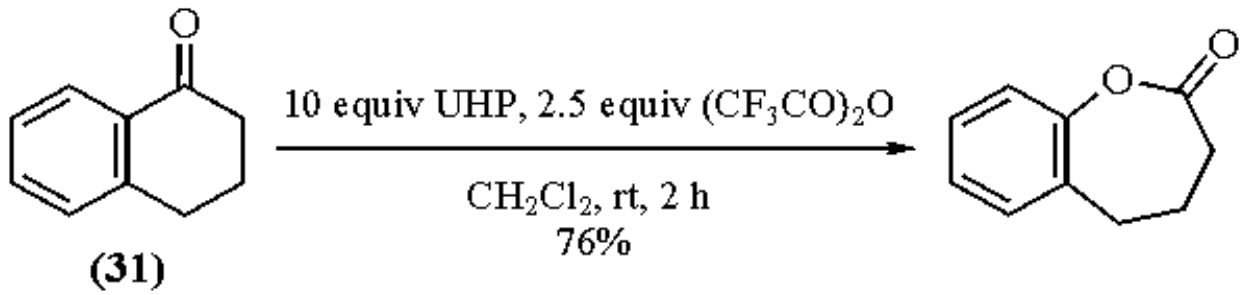

(16)

Complete stereospecificity and high regioselectivity (25:1) is observed in the oxidation of an *erythro* ketone (eq 17). Oxidation of the *threo* ketone is also stereospecific but gives a 5:3 mixture of ester regioisomers.[47]

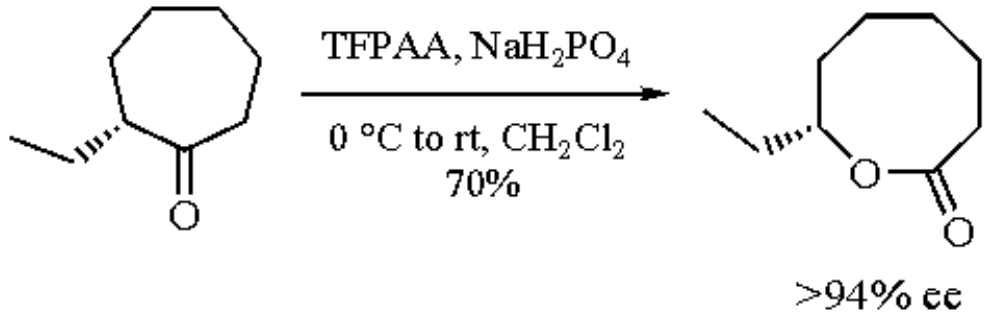

(17)

Heteroatom Oxidations.

Aromatic primary amines carrying electron-withdrawing groups are oxidized efficiently by TFPAA to the corresponding nitro compounds (eq 18).[21,31] The amine dissolved in CH_2Cl_2 is added to the peracid. The above oxidation cannot be carried out with aromatic amines such as *p*-anisidine, which are unusually sensitive to electrophilic attack; for these sensitive amines, peracetic acid is the preferred oxidant.

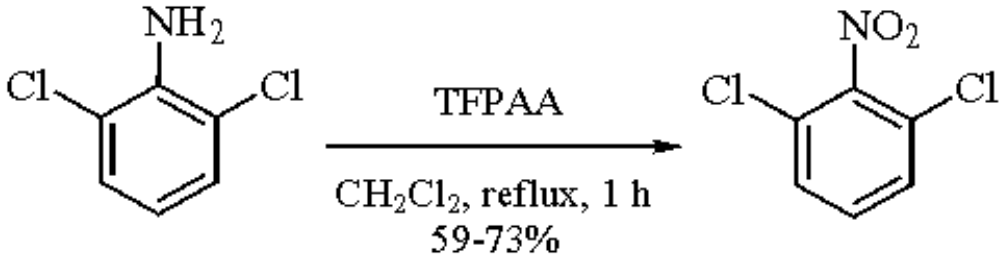

(18)

Oxidation of 2,3,4,5,6-pentachloroaniline with TFPAA in $CHCl_3$-water at rt furnishes, in 78% yield, 2,3,4,5,6-pentachloronitrosobenzene.[32] The electron-deficient heterocycle (**32**) furnishes the *N*-oxide (**33**) on oxidation with TFPAA prepared from urea-hydrogen peroxide (eq 19).[7] Electron-deficient pyridines are oxidized to the corresponding *N*-oxides with TFPAA; perbenzoic and peracetic acid are not effective for this transformation.[43]

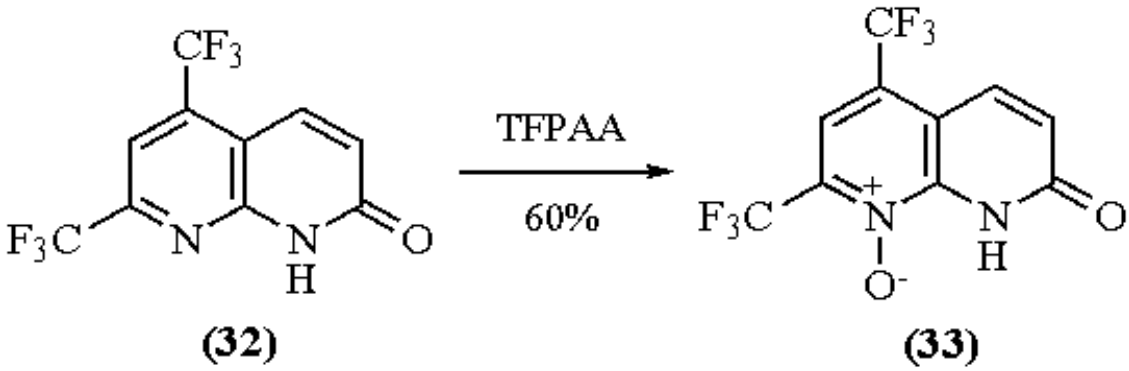

(19)

Oxidation of the isoxazoline (**34**) furnishes the hydroxy ester (**35**) (eq 20) via an initial oxaziridine intermediate.[33]

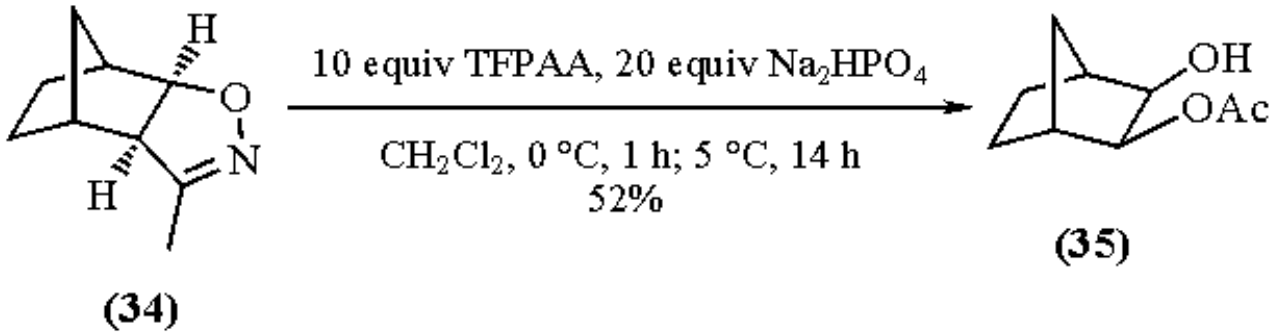

(20)

Nitro compounds have many applications in organic chemistry.[34] Strained polynitro polycyclic compounds are of interest as a new class of energetic materials.[35] Since oximes are readily available, their oxidation to nitro compounds has been studied. Oxidation of the oxime (**36**) furnishes a mixture of nitro compounds; the major component is the *cis* isomer (eq 21).[36] During the oxidation of oximes, ketones are obtained as byproducts. Hindered oximes such as camphor oxime are not oxidized by TFPAA.

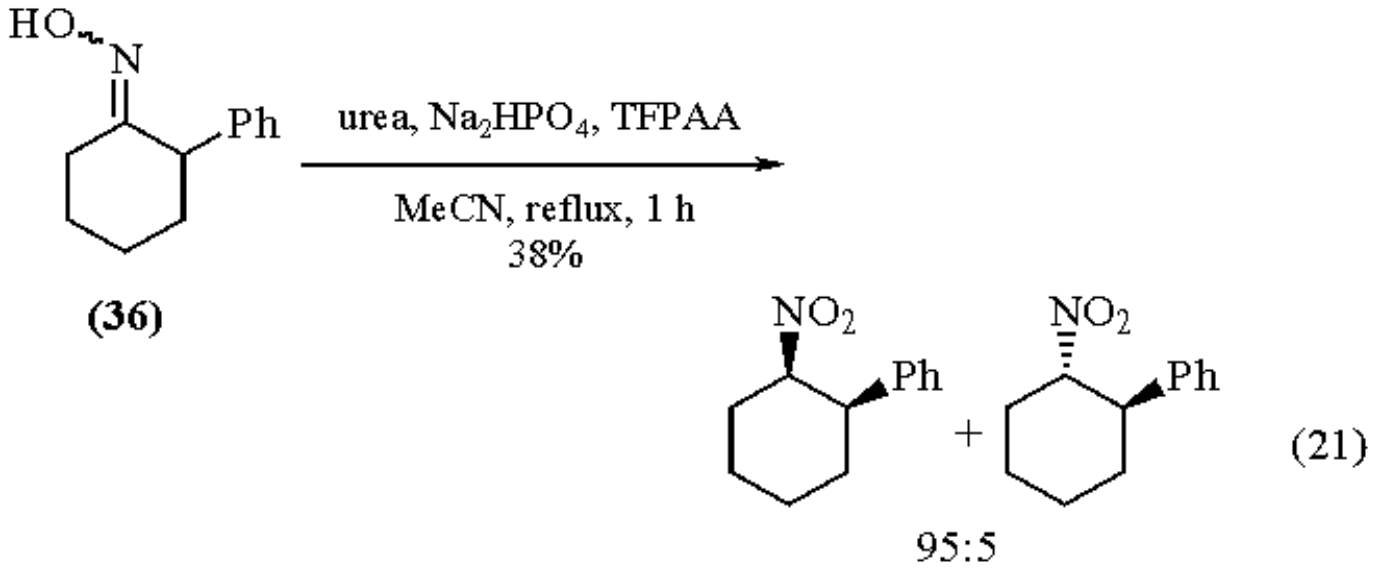

(21)

Oximes yield primary, secondary, and alicyclic nitroalkanes (72%),[48] and α-chloro ketoximes give α-nitroalkenes (31-66%).[49]

Oxidation of the oxime (**37**) furnishes a mixture of *endo,endo* and *exo,exo* isomers (eq 22).[35b] Oximes have been converted to nitro compounds using a multistep method.[35a] ***Sodium Perborate*** in glacial acetic acid oxidizes oximes to nitro compounds.[37]

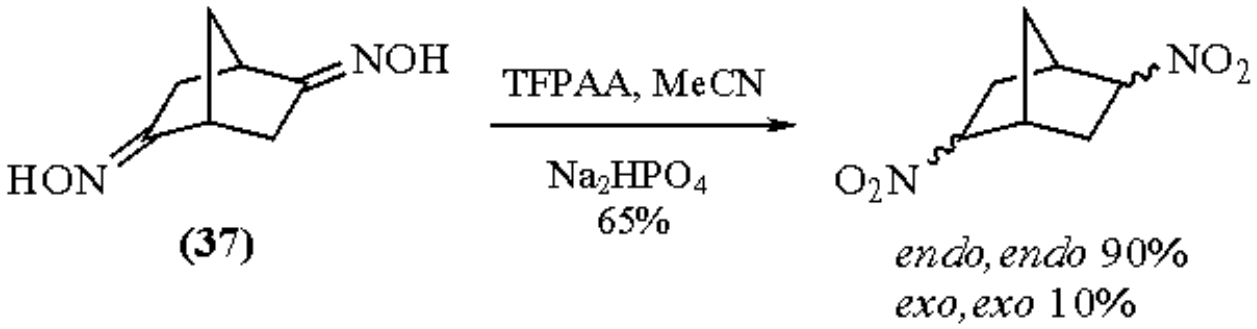

(22)

α-Unsubstituted α,β-epoxy ketoximes are oxidized to γ-hydroxy-α-nitroalkenes (eq 23).[38] Aldoximes are oxidized to nitroalkanes (60-80%) with the reagent prepared from urea-H_2O_2 and trifluoroacetic anhydride. Ketoximes fail to react with this reagent system.[50]

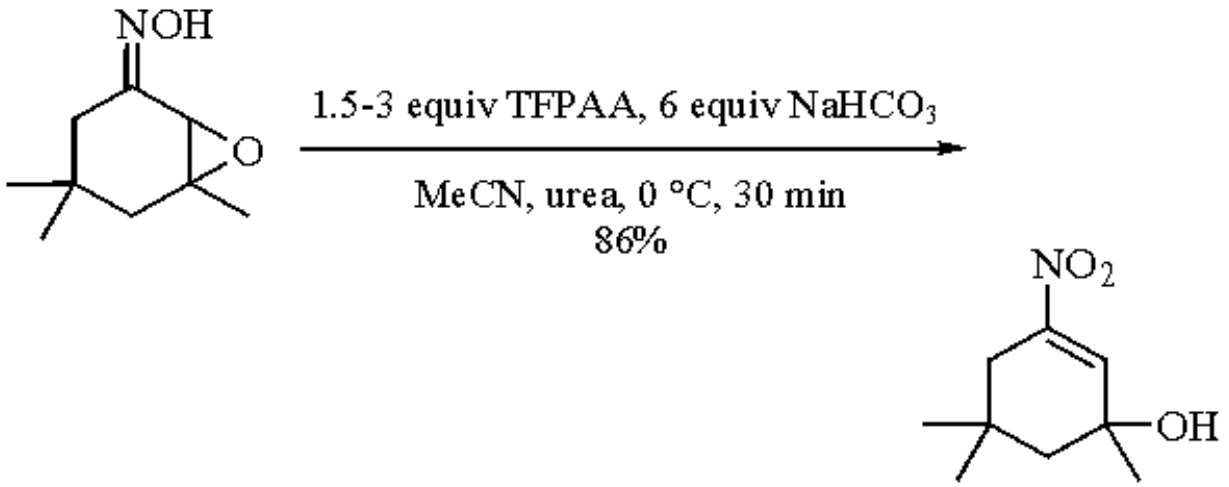

(23)

Nitroso compounds are oxidized to the corresponding nitro compounds (eq 24)[39] or to nitramines.[40,51] 30% H_2O_2 is added to a solution of the nitrosopyrimidine (**38**) in CF_3CO_3H during 1.5 h. After workup the nitro compound (**39**) is obtained in high yield; in this reaction, oxidative hydrolytic desulfurization is observed.

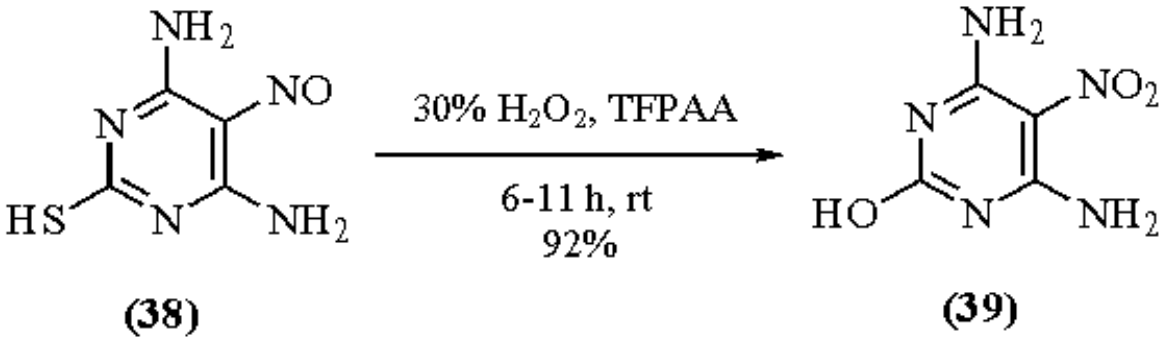

(24)

Miscellaneous Reactions.

Aromatic azines are oxidized to their azine monoxides with TFPAA.[52] Organosulfides can be oxidized by TFPAA to either sulfoxides or sulfones under mild conditions in high yield.[5,53]

Related Reagents.

m-Chloroperbenzoic Acid; ***Hydrogen Peroxide-Urea***; ***Peracetic Acid***; ***Perbenzoic Acid***.

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Triisobutylaluminum[1]

***i*-Bu$_3$Al**

[100-99-2] · $C_{12}H_{27}Al$ · Triisobutylaluminum · (MW 198.37)

(reducing agent with unique stereochemical preferences;[2] used in combination with CH_2I_2 as a selective cyclopropanation agent[16])

Physical Data: mp 0 °C; bp 46 °C/1 mmHg; *d* 0.781 g cm^{-3} (25 °C).

Solubility: freely miscible with saturated and aromatic hydrocarbons; reacts violently with H_2O and protic solvents.

Form Supplied in: as a neat liquid in a stainless container or as solutions in hexane, heptane, or toluene.

Analysis of Reagent Purity: brochures from manufacturers describe an apparatus and method for assay.

Handling, Storage, and Precautions: the reagent is indefinitely stable under an inert atmosphere. The neat liquid or the dense solutions are highly pyrophoric. Solutions more dilute than a certain concentration are not pyrophoric and are safer to handle. The nonpyrophoric limits are 20 wt % in isopentane, 22 wt % in hexane, and 25 wt % in heptane, respectively. Use of halogenated hydrocarbon as a solvent should be avoided because of possible explosive reactions sometimes observed for mixtures of CCl_4 and organoaluminums.

Carbonyl Reduction.

i-Bu$_3$Al acts primarily as a reducing agent rather than an alkylating agent toward carbonyl compounds.[2] Although the reactivity is modest and enolization sometimes competes, some unique stereochemical features are noted in the reduction of cyclic[3a] and acyclic ketones.[3b] Enones undergo mainly 1,2-reduction, whereas 1,4-reduction occurs in the presence of a Ni catalyst (eq 1).[4]

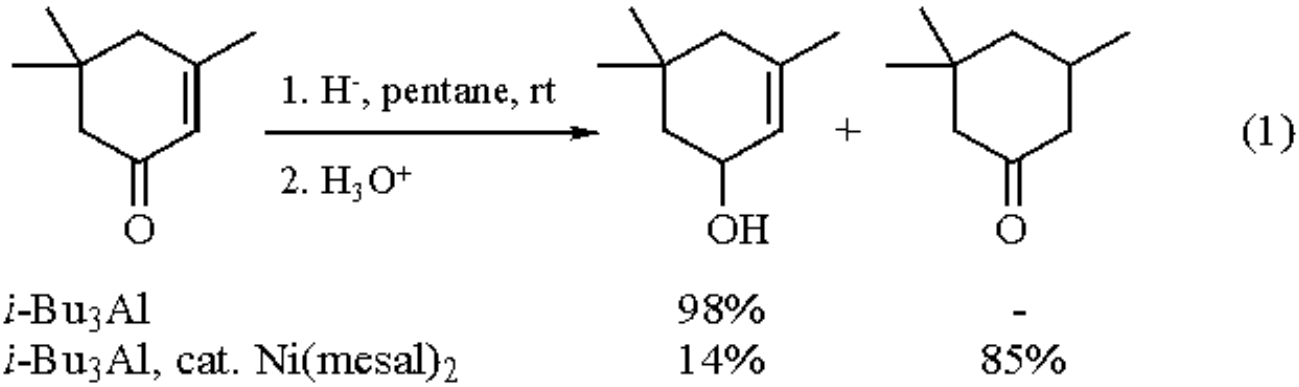

Alkylation.

Alkylation of allyl acetates[5] or glycal derivatives[6] proceeds regioselectively (eqs 2 and 3). The 1,4-addition to nitroalkenes gives, after hydrolysis, α-alkylated ketones.[7a] Application to the synthesis of alkylated dihydro-2(3*H*)-furanones[7b] (eq 4) and 1,4-diketones has been reported.[7c]

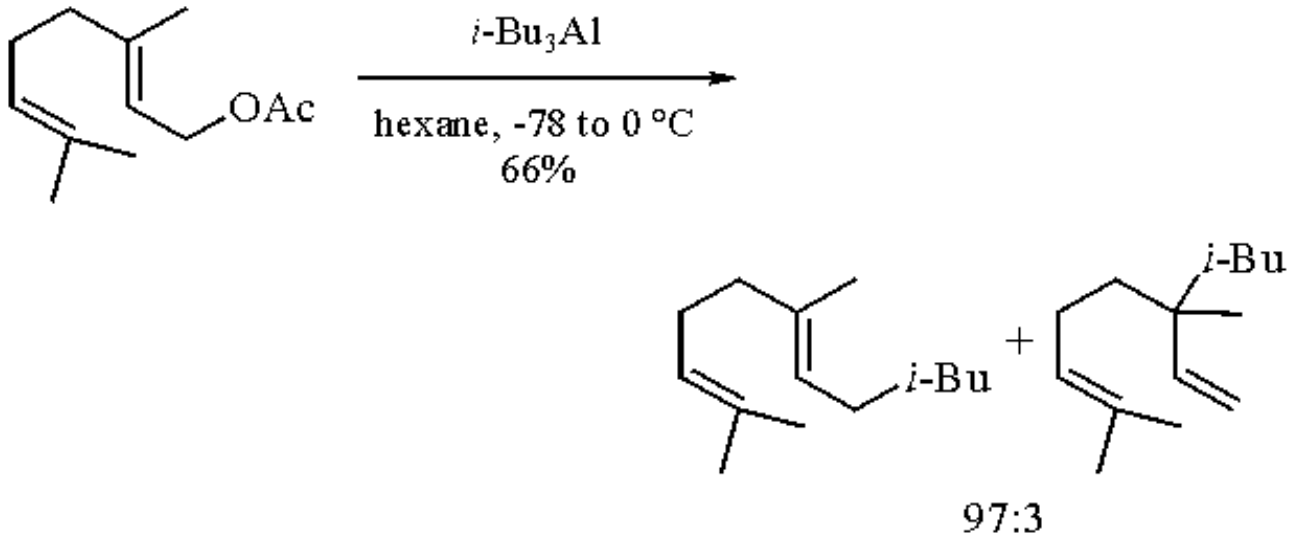

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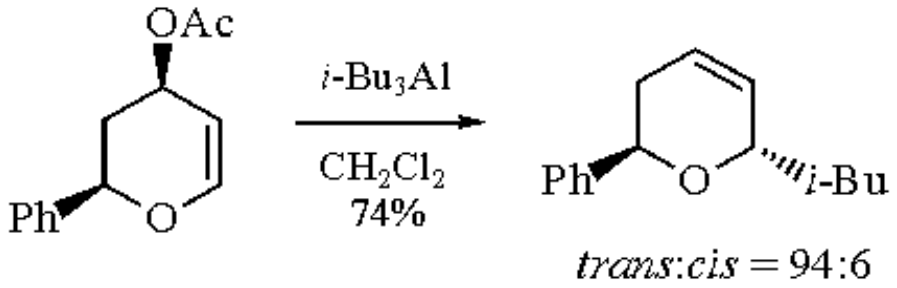

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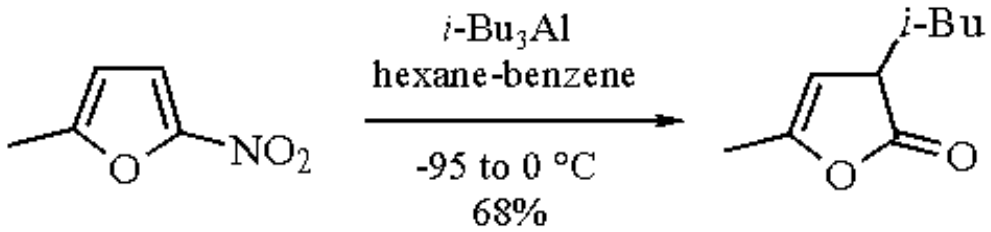

(4)

Cross couplings of *i*-Bu_3Al with carboxylic acid chlorides or thioesters can be achieved under Pd- or Cu-catalyzed conditions (eq 5).[8] A Ni catalyst is effective for coupling with alkynyl bromides (eq 6).[9] Reactions with propargyl acetates are effectively catalyzed by ***Iron(III) Chloride*** to give substituted allenes (eq 7).[10]

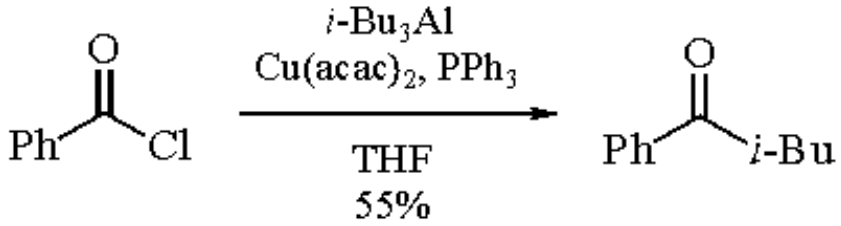

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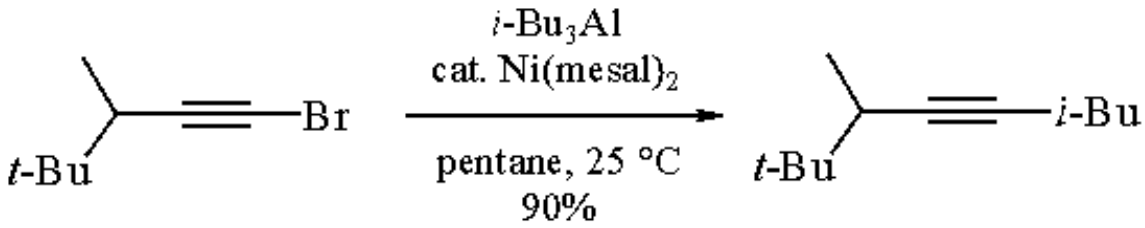

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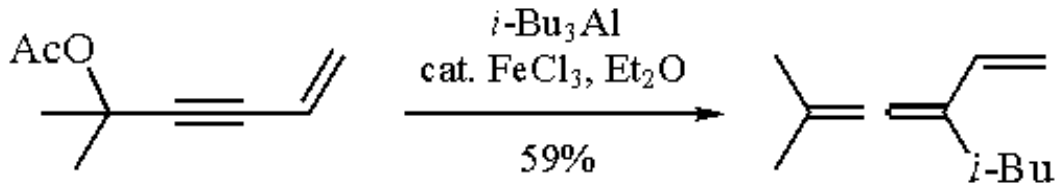

(7)

Rearrangements.

The [3,3]-sigmatropic rearrangement of allyl vinyl ethers is promoted by *i*-Bu_3Al, which also reduces intermediate aldehydes to give primary alcohols (eq 8).[11] Synthesis of a seven-membered ring via ring enlargement has been reported (eq 9).[11c] When ***Trimethylaluminum*** or ***Triethylaluminum*** are used, alkylated products are obtained. Reductive ring contraction reactions are effected by *i*-Bu_3Al to deliver cyclobutyl- or cyclopropylmethanols (eqs 10 and 11).[12]

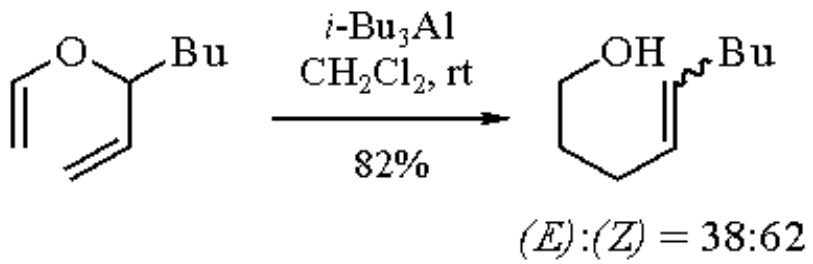

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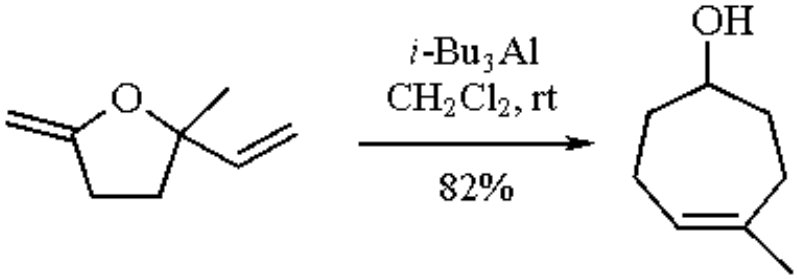

(9)

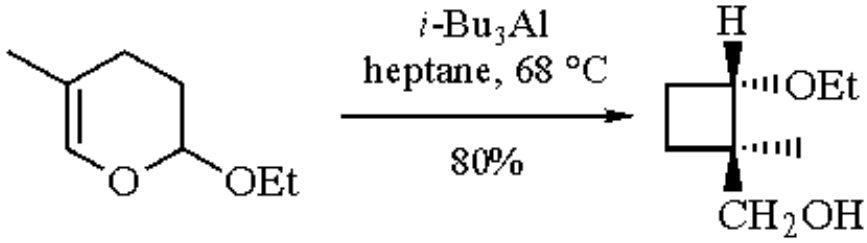

(10)

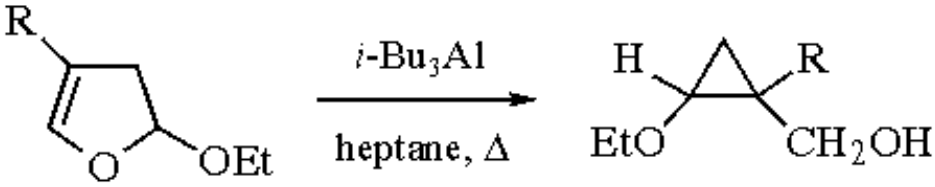

(11)

Alkylative Beckmann rearrangement of oxime sulfonates is achieved by trialkylaluminums to give, after in situ reduction with ***Diisobutylaluminum Hydride***, the rearranged amines (eq 12).[13] Related alkylative Beckmann fragmentations have also been reported (eq 13).[14]

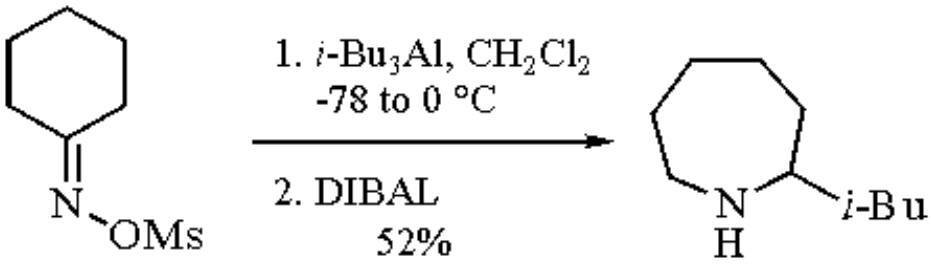

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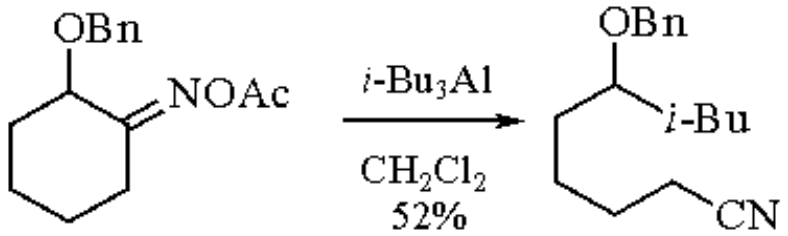

(13)

Regioselective ring cleavage of chiral acetals is effected by *i*-Bu_3Al (eq 14).[15a] Related reactions involving kinetic resolution have also been reported.[15b]

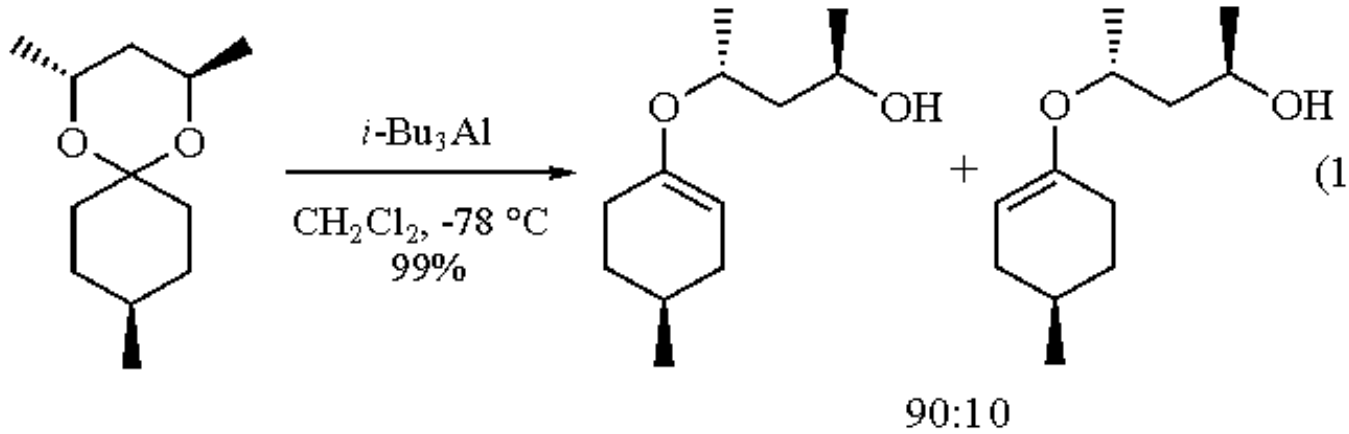

(14)

Cyclopropanation.

The reagent combination of CH_2I_2 and *i*-Bu_3Al (or other organoaluminums) leads to cyclopropanation of alkenes (eq 15).[16] The regioselectivity of this reagent is markedly different from the Simmons-Smith reaction.

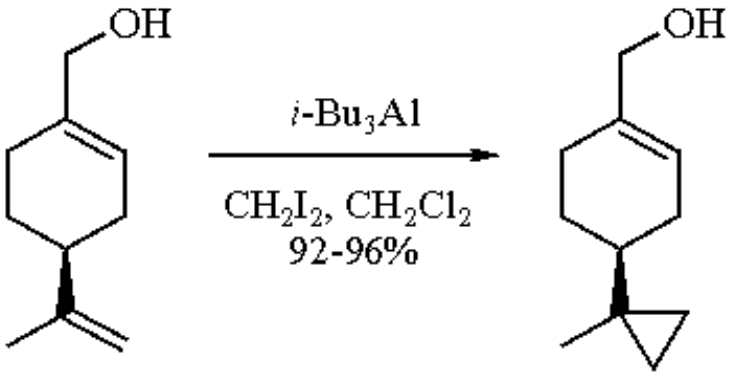

(15)

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2,4,6-Triisopropylbenzenesulfonyl Azide[1]

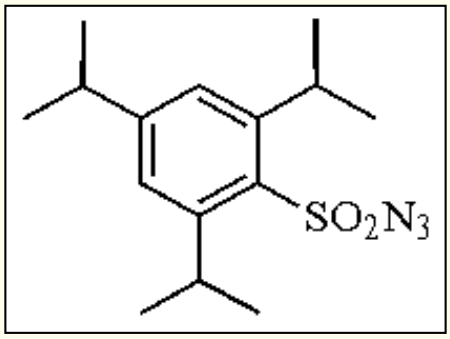

[36982-84-0] · $C_{15}H_{23}N_3O_2S$ · 2,4,6-Triisopropylbenzenesulfonyl Azide · (MW 309.48)

(agent for diazo[2] and azide[3] transfer to enolates)

Alternate Name: trisyl azide.

Physical Data: mp 41-43 °C.

Solubility: freely sol most organic solvents.

Preparative Methods: readily prepared by treatment of the commercially available triisopropylbenzenesulfonyl chloride (trisyl chloride) with sodium azide.[4]

General Considerations.

The reactions of arylsulfonyl azides with enolates have been reported to give a range of products, depending on the fragmentation of the initial adduct.[3,5] This may differ according to the nature of the enolate, the particular sulfonyl azide, and the quenching procedure. Net diazo transfer is usually observed for stabilized enolates, while azide transfer is more common with more reactive enolates.

Diazo Transfer to Ketones.

Triisopropylbenzenesulfonyl azide has been used for the direct transfer of the diazo group to ketone enolates under phase transfer conditions to furnish α-diazo ketones (eqs 1-4).[2,6-8]

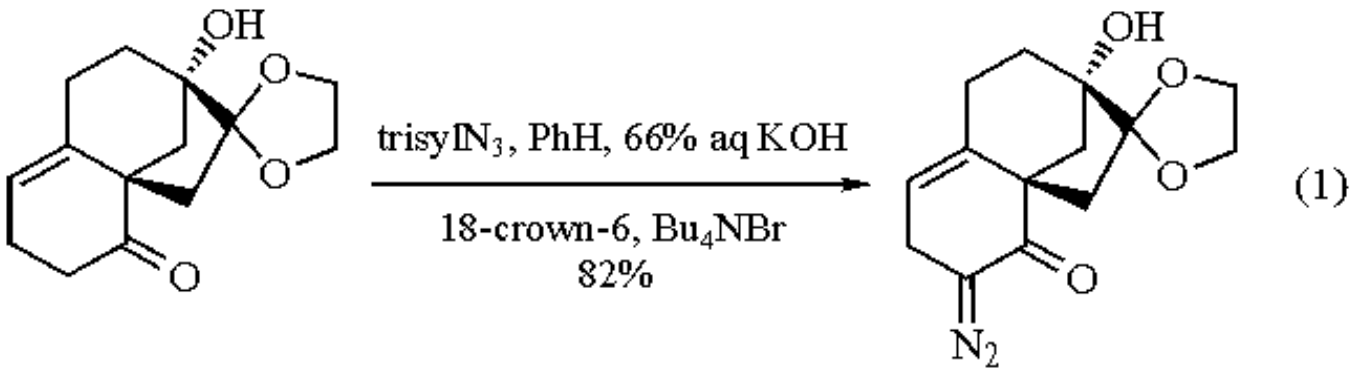

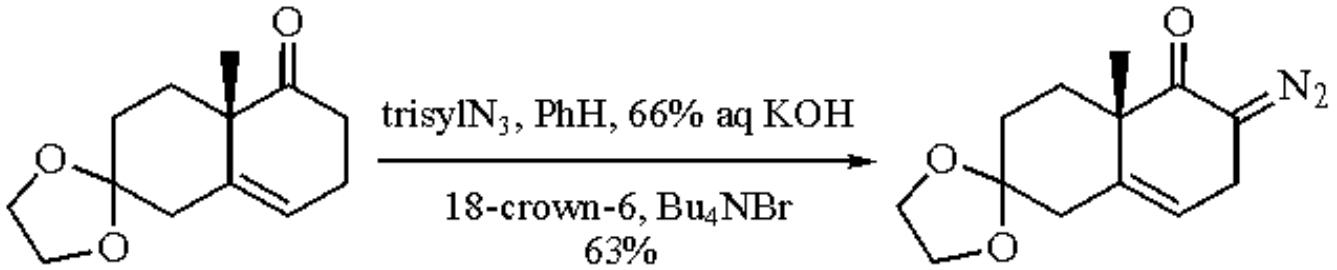

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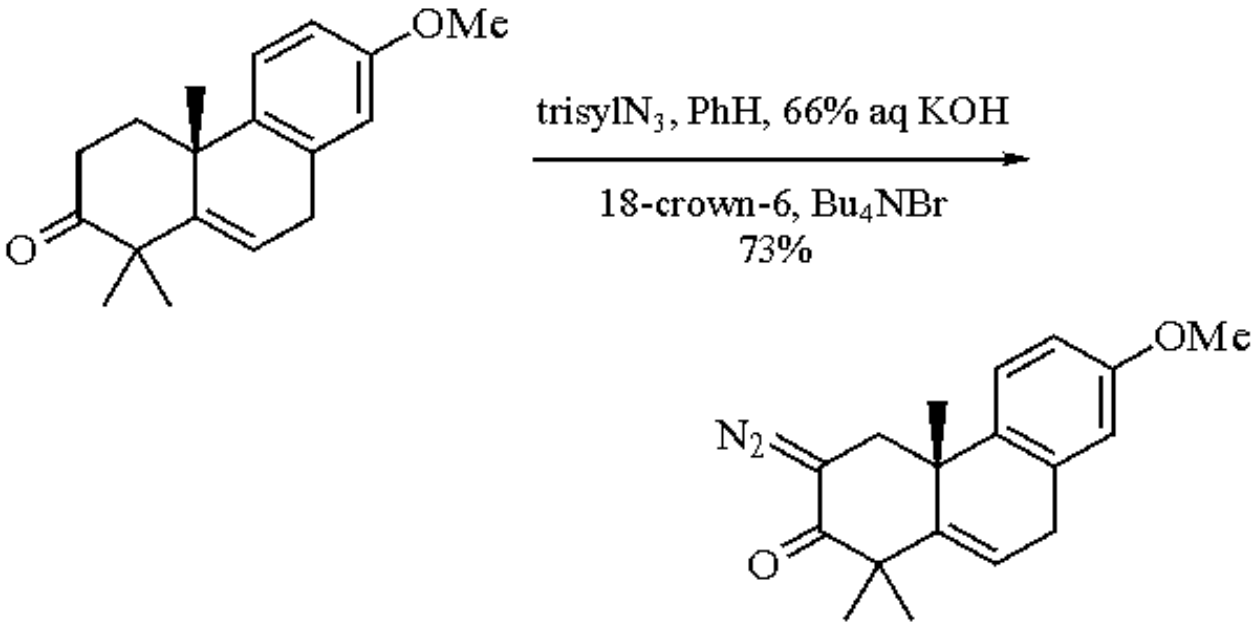

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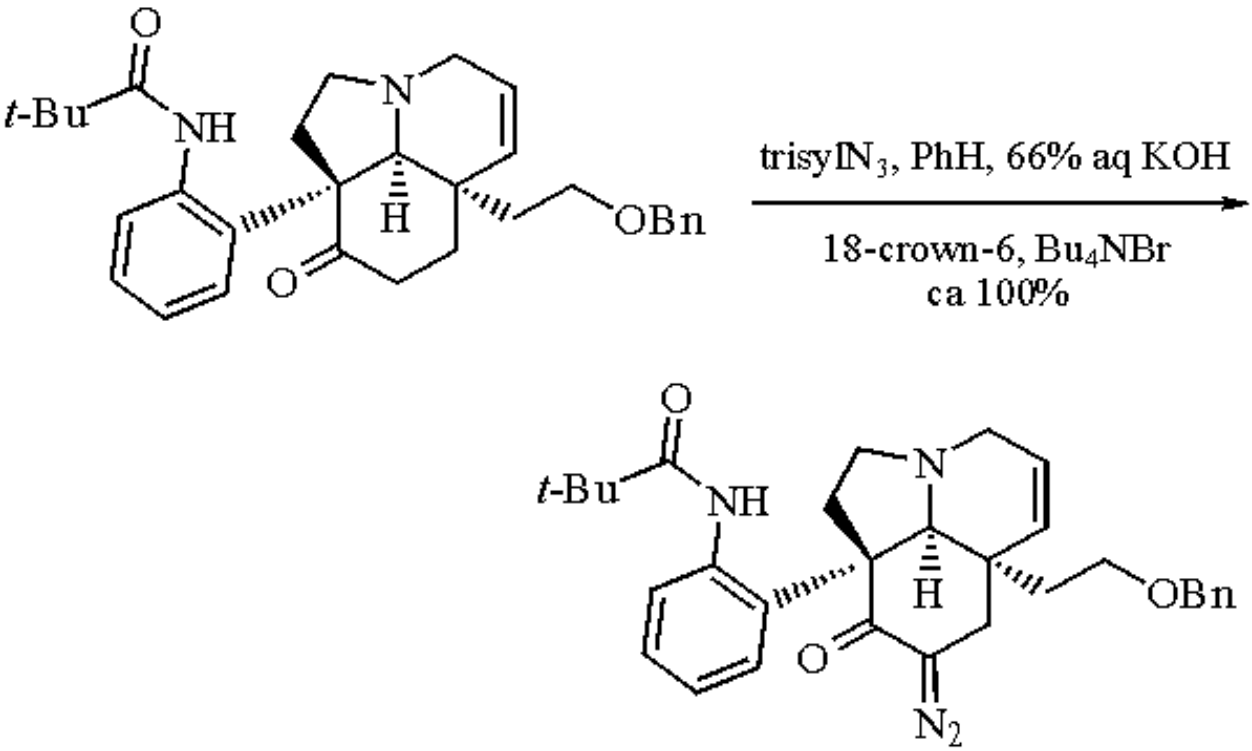

(4)

The method may be used as a more direct alternative to the stepwise procedure of hydroxymethylenation, followed by treatment with ***p-Toluenesulfonyl Azide*** and ***Triethylamine***,[9] but its greatest value lies with the reactions of sterically hindered substrates (eqs 5-9),[2,10-12] for which the two-stage process is ineffective. The utility of the trisyl azide in these conversions stems from the steric hindrance afforded by the *ortho* isopropyl groups; simpler arylsulfonyl azides are degraded too rapidly under these conditions to be useful. The method appears to be less effective with cyclopentanones (eq 9)[13] and several failures have been reported with such substrates.[14]

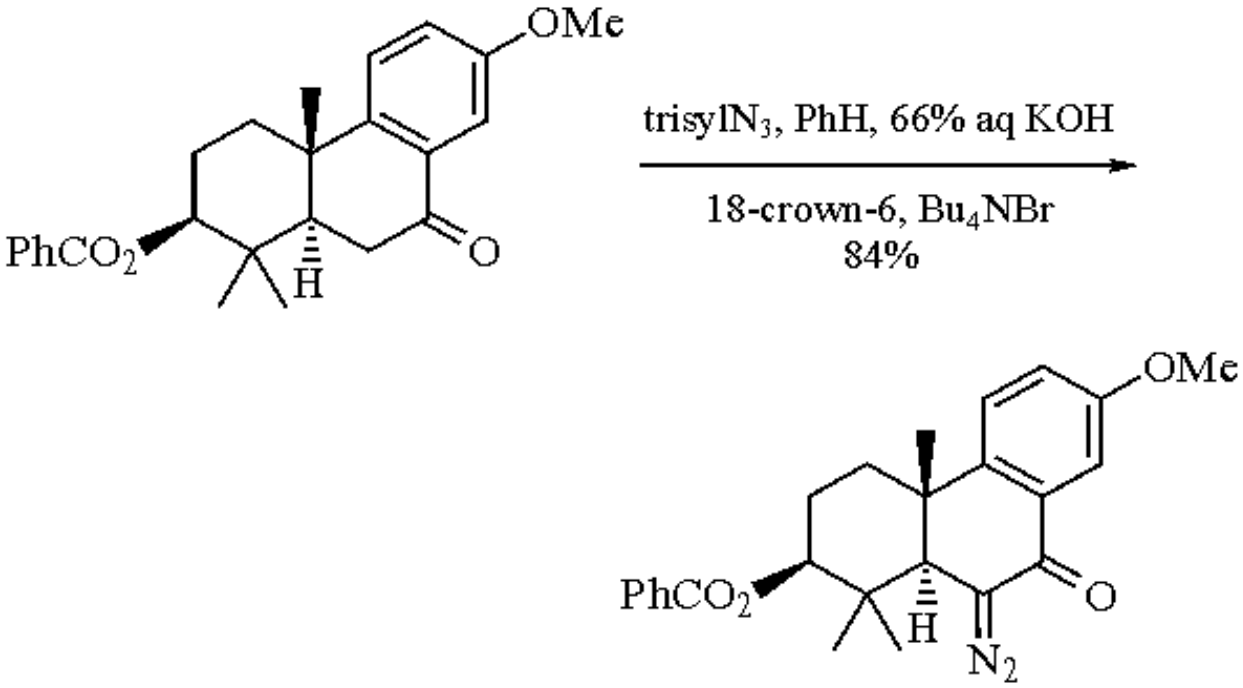
OMe
PhCO2
H
O
trisylN3, PhH, 66% aq KOH
18-crown-6, Bu4NBr
84%
OMe
PhCO2
H
O
N2

(5)

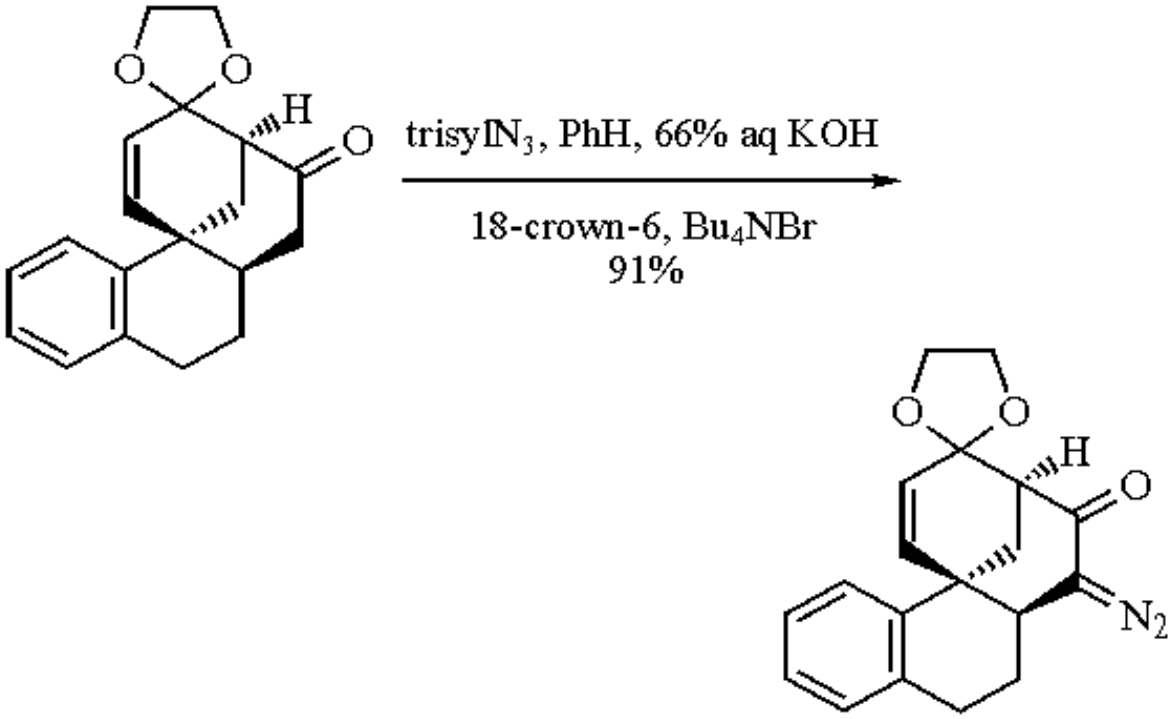
O
O
H
O
trisylN3, PhH, 66% aq KOH
18-crown-6, Bu4NBr
91%
O
O
H
O
N2

(6)

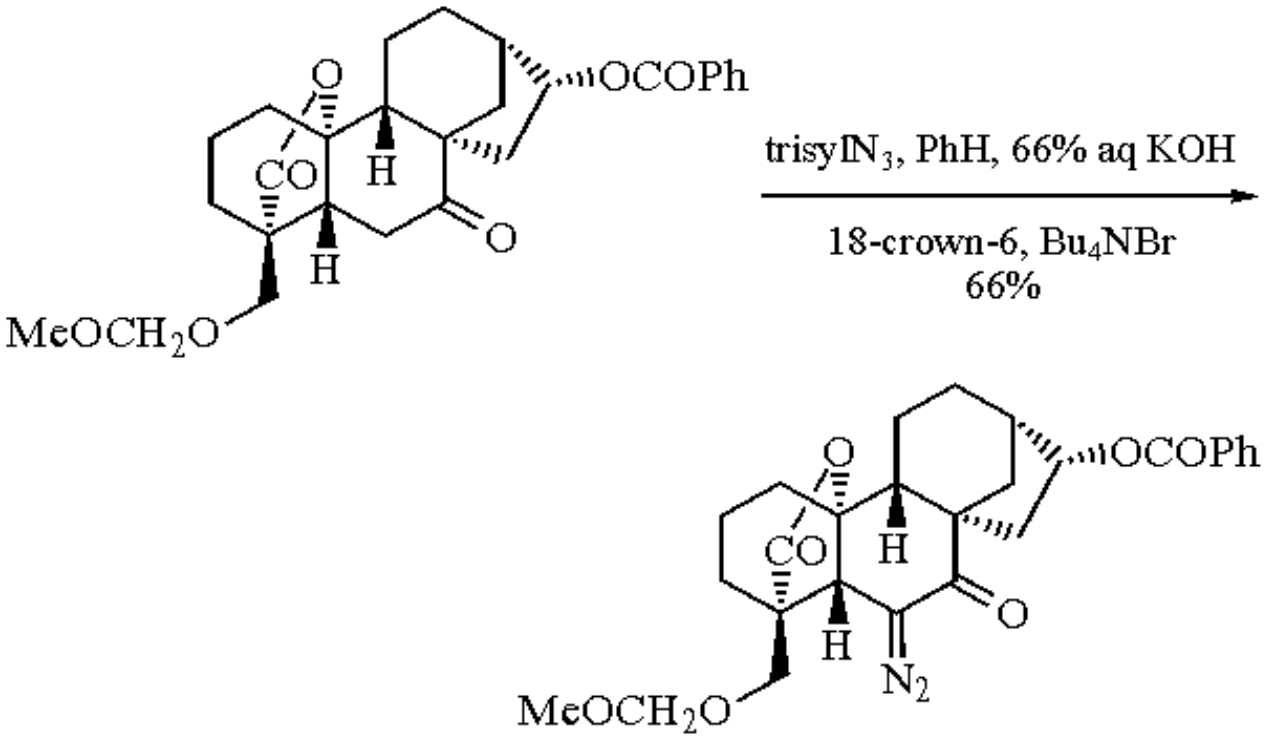
OCOPh
O
CO
H
H
O
MeOCH2O
trisylN3, PhH, 66% aq KOH
18-crown-6, Bu4NBr
66%
OCOPh
O
CO
H
H
O
N2
MeOCH2O

(7)

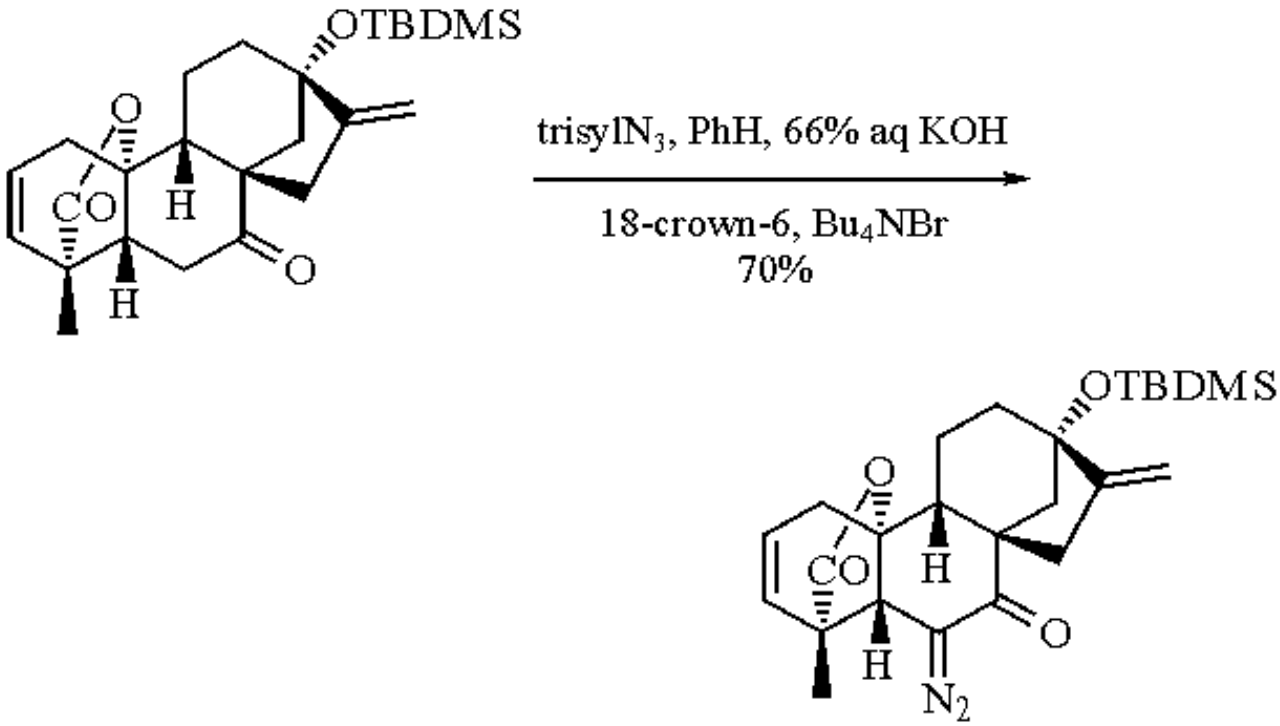
OTBDMS
O
CO
H
H
O
trisylN3, PhH, 66% aq KOH
18-crown-6, Bu4NBr
70%
OTBDMS
O
CO
H
H
O
N2

(8)

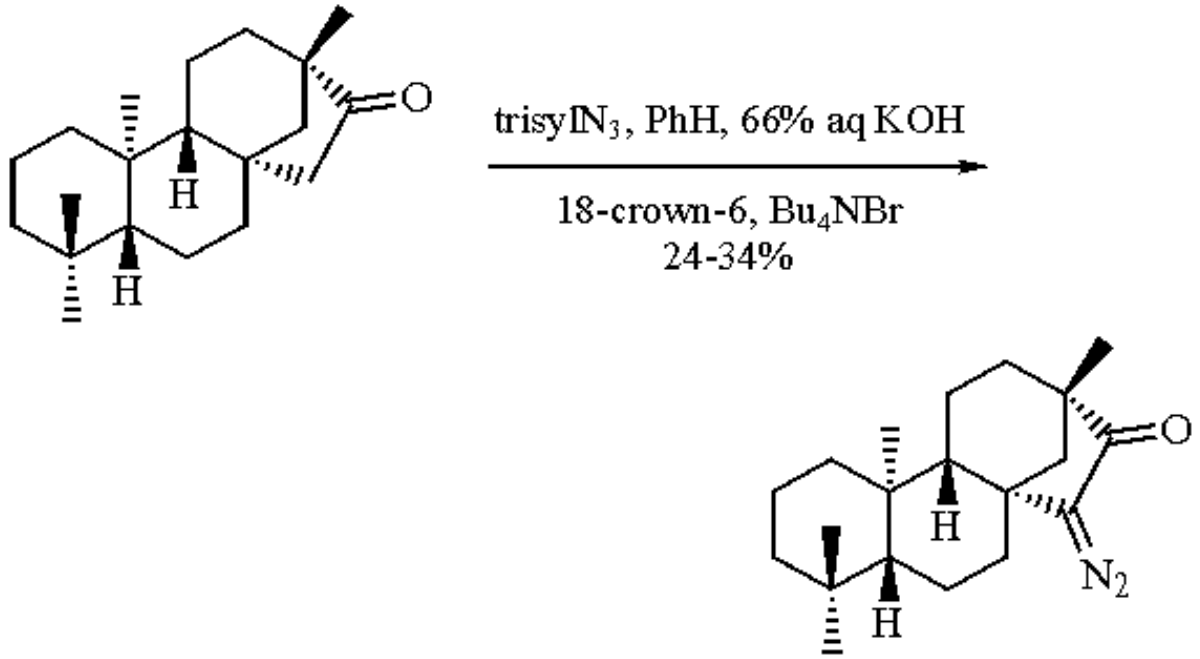

(9)

Azide Transfer to Enolates.

Kinetically controlled azide transfer to the lithium enolates of azetidinones was originally demonstrated with tosyl azide using ***Chlorotrimethylsilane*** as a quenching reagent,[15] but was found not to be general for other enolates. One of the problems is competing diazo transfer. In a systematic study of azide transfer to imide enolates,[5] it was found that azide transfer is more strongly favored by more electropositive counterions (K > Na >> Li), and by more electron-rich arylsulfonyl azides (trisyl > tosyl > *p*-nitrobenzenesulfonyl). The steric requirements of the trisyl group undoubtedly play a role also. Triazenes are implicated as intermediates and it is the treatment of these compounds which determines the product distribution rather than the initial step. Triazene (**1**) was sufficiently stable to be isolated as a mixture of tautomers and it was found that decomposition to azide (**2**) could be effected with potassium acetate, but not lithium acetate. Thus the counterion effect noted above is expressed in triazene decomposition, rather than the initial addition of the enolate to the azide.

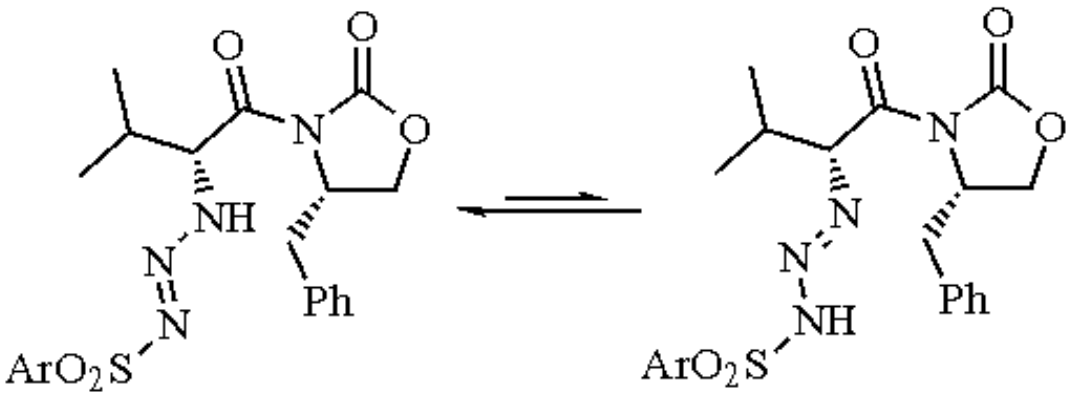

(1)

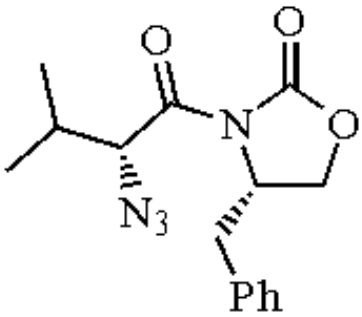

(2)

The most general protocol (eq 10) has therefore been based on ***Potassium Hexamethyldisilazide*** (KHMDS) as the base, addition of trisyl azide at -78 °C and then acetic acid at the same temperature.[5] Excellent levels of diastereoselectivity are observed with most substrates and

the method has been used widely in the enantioselective synthesis of α-amino acids from chiral imides.[16] Chemoselective azidation of an imide enolate in the presence of an ester function has been demonstrated (eq 11).[17] The product distribution is nevertheless finely balanced, as discovered with the respective dimethyl and dibenzyl ethers of the 3,5-substituted phenylacetyl imide (**3**) (eq 12).[18]

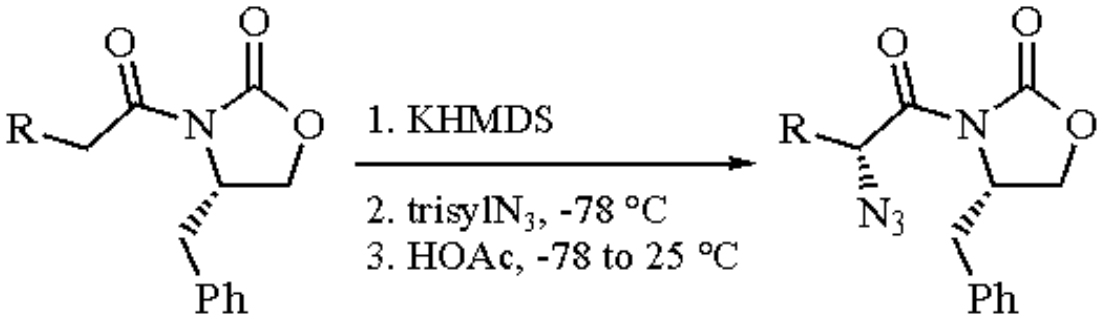

(10)

R = CH_2Ph ds = 97% (91% yield)
R = Me ds = 97% (74% yield)
R = Ph ds = 91% (82% yield)
R = *t*-Bu ds = 99% (90% yield)

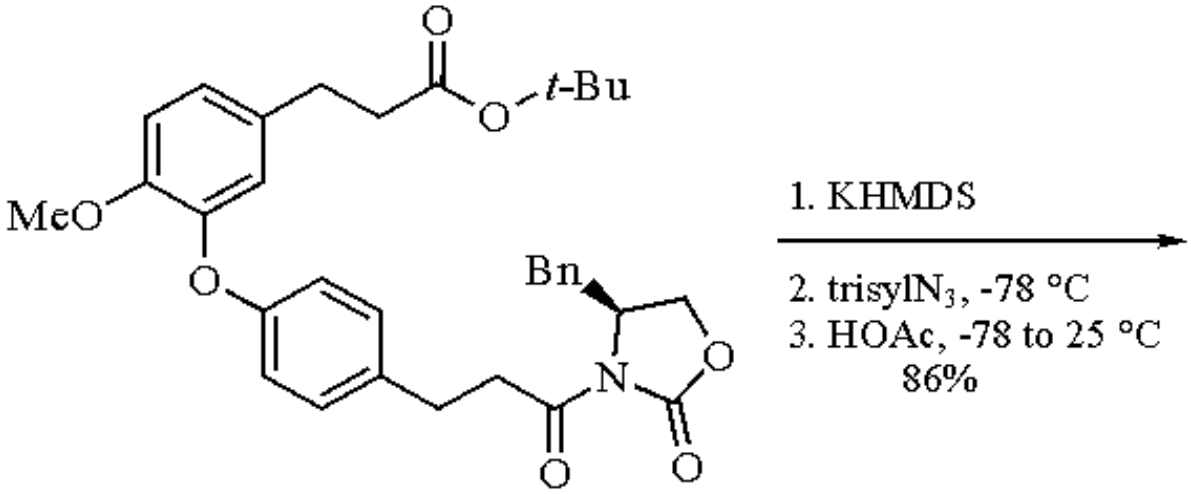

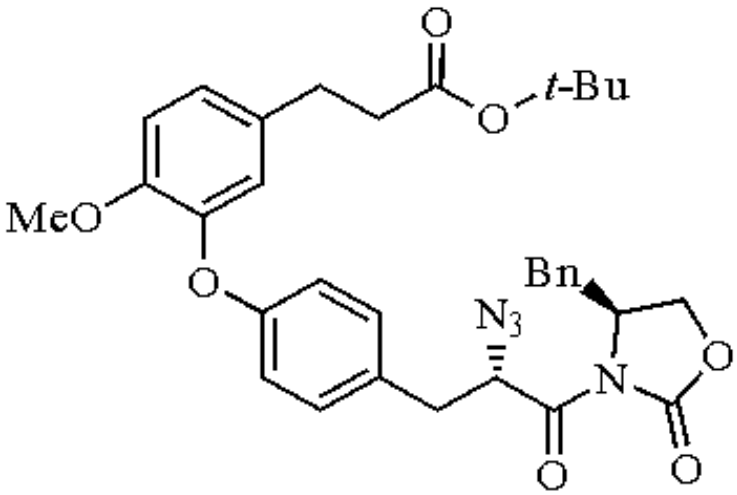

(11)

97% ds

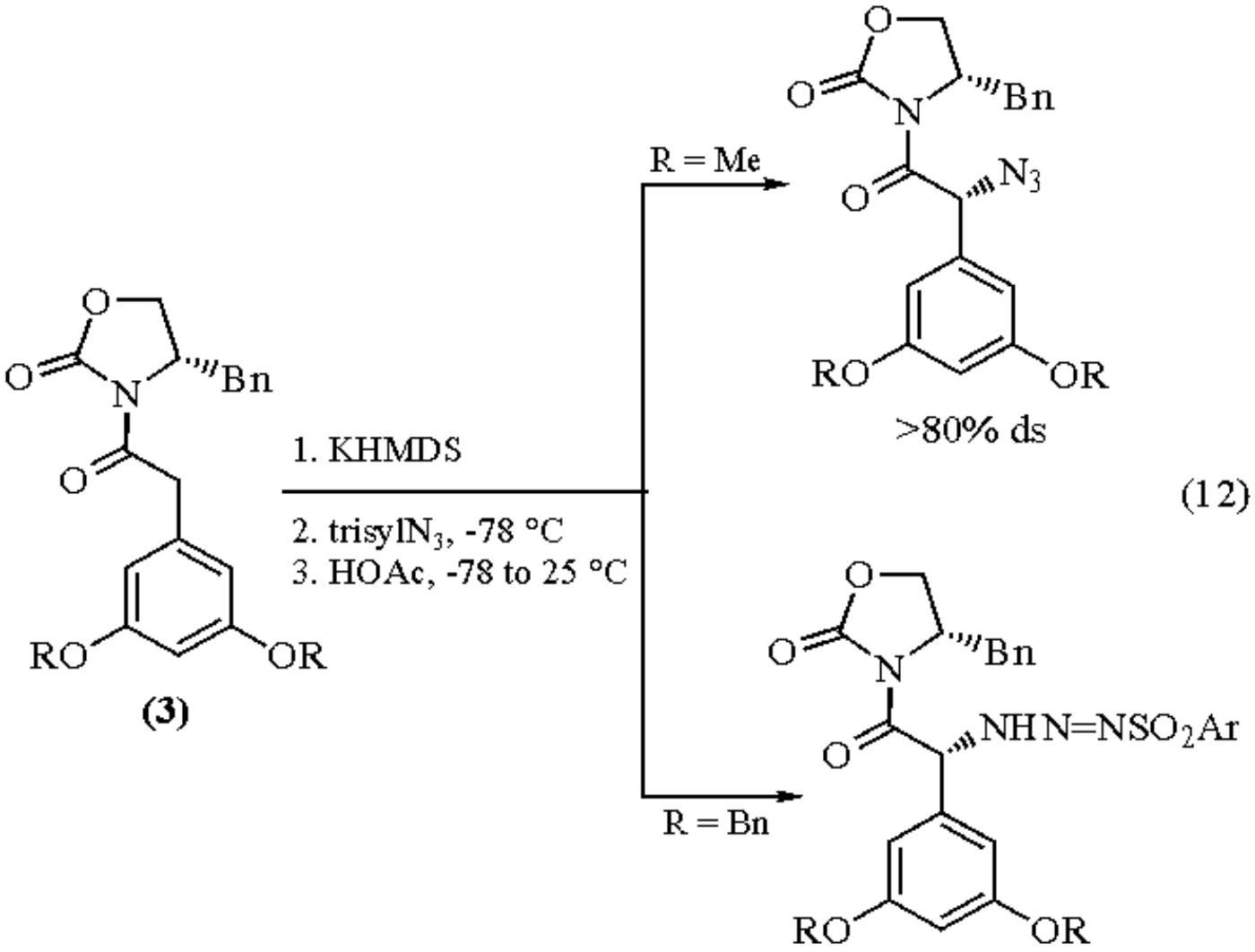

The azide transfer methodology may also be applied to a variety of esters[19] and is compatible with a number of other functional groups (eqs 13-15).[20,21] It may also be used with phosphonates (eq 16),[22] and if the counterion to the anion is lithium, as in the earlier imide study, it is possible to isolate the simple adduct retaining the sulfonyltriazine moiety (eq 17). Reaction with an *N*-hydroxy β-lactam afforded the deoxy-α-azido lactam via the *O*-sulfonate.[23]

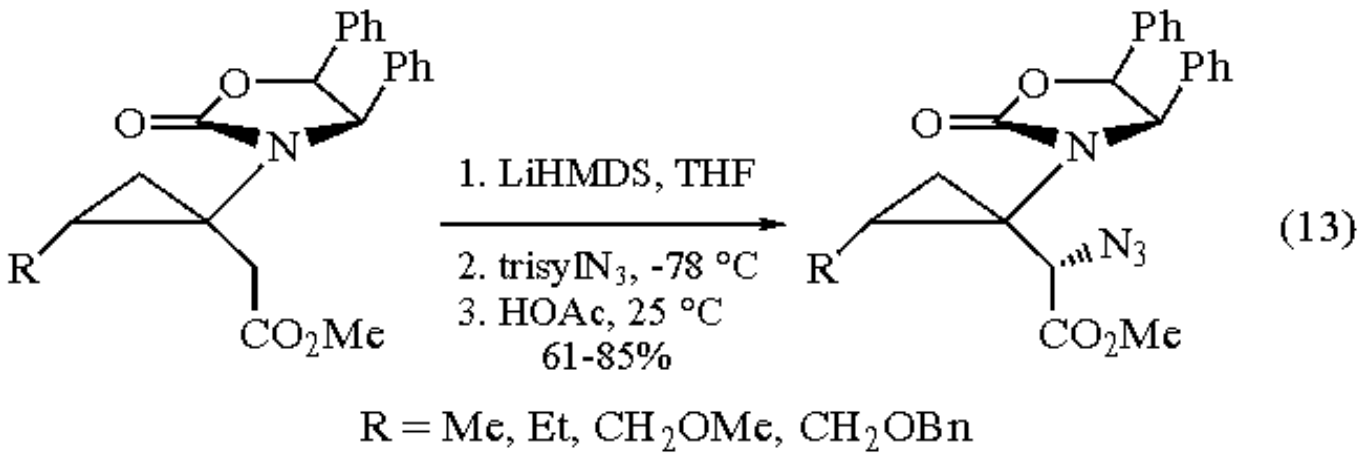

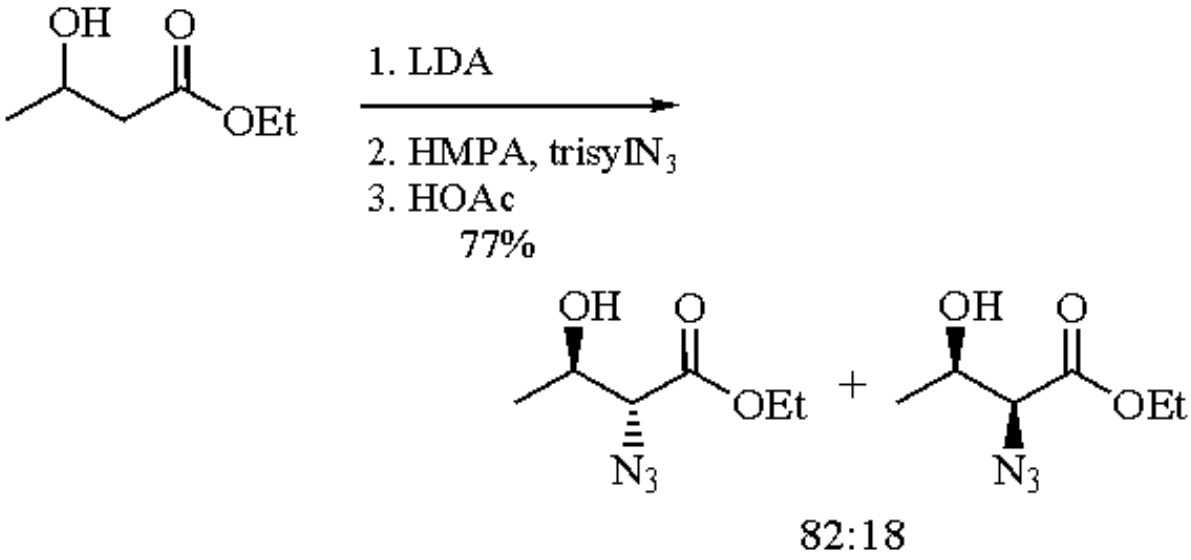

(14)

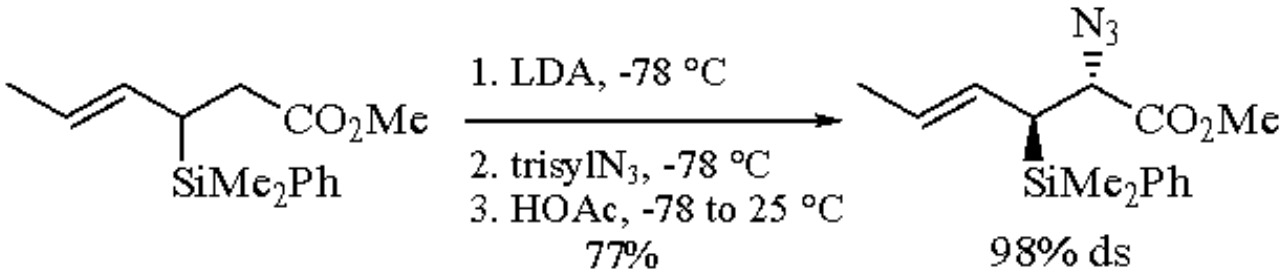

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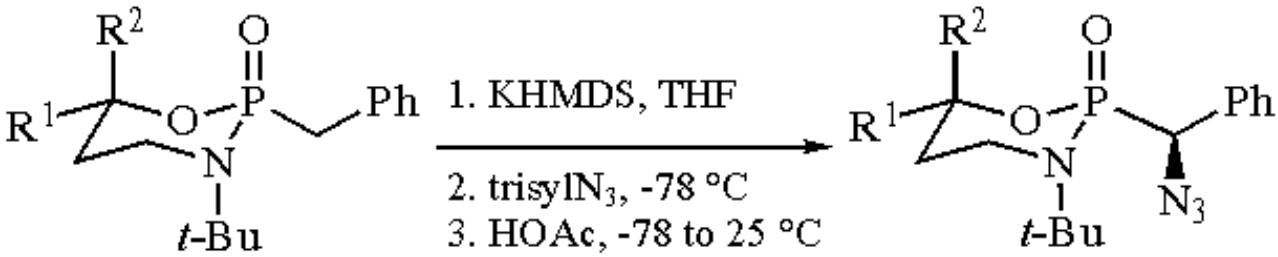

(16)

R^1, R^2 = Me; >95% ds (52-68% yield)
R^1 = Me, R^2 = H; 57% ds (52-70% yield)

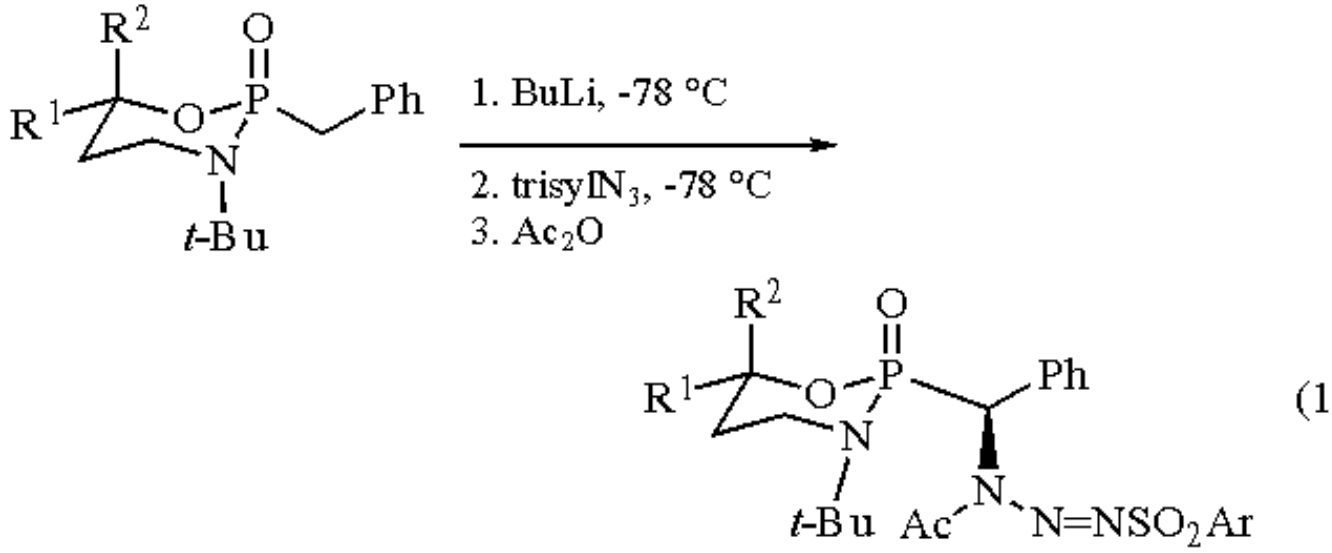

$R^1, R^2 = Me$; >95% ds (70-93% yield)
$R^1 = Me, R^2 = H$; 92% ds (75% yield)

Related Reagents.

p-Toluenesulfonyl Azide and ***Methanesulfonyl Azide*** have been used widely for diazo transfer to stabilized enolates.[9] The latter reagent simplifies isolation of the desired product,[24] but is potentially explosive and must be handled with care. Relative to other aryl analogs, the electron-deficient *p*-nitrobenzenesulfonyl analog favors diazo transfer to imide enolates.[5]

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Lewis N. Mander

2,4,6-Triisopropylbenzenesulfonylhydrazide[1]

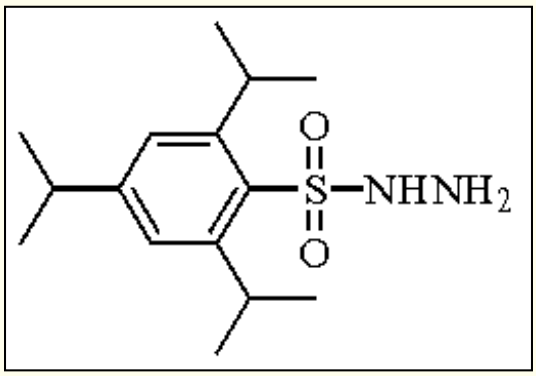

[39085-59-1] · $C_{15}H_{26}N_2O_2S$ · 2,4,6-Triisopropylbenzenesulfonylhydrazide · (MW 298.50)

(used as a diazene equivalent;[3] condensed with ketones and aldehydes to form hydrazones that can be converted into reactive intermediates such as diazoalkanes, carbenes,[13] carbenium ions, alkyllithiums,[9] or umpolung synthons)

Alternate Name: trisyl hydrazide; TPSH.

Physical Data: mp 121-122 °C (dec).

Solubility: sol virtually all ethereal, halogenated, protic, and aprotic solvents; insol water and hydrocarbon solvents.

Analysis of Reagent Purity: NMR, IR, TLC.

Preparative Methods: may be prepared in 96% yield by treating commercially available 2,4,6-triisopropylbenzenesulfonyl chloride[2] with hydrazine hydrate in THF,[3,4] being careful to keep the reaction and workup temperatures below or around 0 °C. The solid can be dried in vacuo over P_2O_5 for 24 h.

Handling, Storage, and Precautions: decomposes rapidly in solution at rt to diazene, particularly under basic or neutral conditions; acid retards this degradation significantly. It is stable in solid form at -20 °C for months and may be freed from acidic impurities as described in the literature.[3] 2,4,6-Triisopropylbenzenesulfonylhydrazide is a toxic, potentially flammable solid which should be handled with gloves under an inert atmosphere.

Alkene Reduction.

2,4,6-Triisopropylbenzenesulfonyl hydrazide (TPSH) undergoes solvent-dependent thermal degradation into diazene (diimide) between 35 and 65 °C, resulting in the in situ reduction of alkenes and other double bonds in good to excellent yields.[3-6] TPSH remains one of the best sources of diazene, and addition of amine bases increases the rate of both diazene formation and hydrogenation. It is the most reactive of the common arenesulfonylhydrazides, being 380 and 24 times more reactive than ***p-Toluenesulfonylhydrazide*** and ***Mesitylenesulfonylhydrazide***, respectively, under base-catalyzed conditions.[3]

Formation of Hydrazones.

Much of the rich chemistry exhibited by TPSH comes from its condensation products with ketones and aldehydes. Such trisyl hydrazones are typically prepared in excellent yield by mixing equimolar amounts of reagents in methanol or ethanol at room temperature with a catalytic amount of acid such as HCl and storing the reaction in the cold.[7] The product precipitates and is filtered off. Very hindered ketones such as camphor and diisopropyl ketone require stoichiometric amounts of acid and extraordinarily hindered ketones may not condense at all.[1,8]

Electrophilic Additions to Hydrazone Anions.

Trisylhydrazones can be quantitatively deprotonated with 2 equiv of ***n-Butyllithium*** to give dianions which are highly nucleophilic and participate in alkylation, aldol, halogenation, and epoxide-opening reactions at low temperature.[9] Regioselectivity of deprotonation is dictated

by three factors. First, and most important, is the geometry of the hydrazone C=N double bond, since the second equivalent of base is directed *syn* to the sulfonamide nitrogen anion in ethereal solvents.[10] Thus the mixture of azaenolates is determined by the ratio of isomeric hydrazones. TMEDA solvent negates the *syn*-directing effect and has been used extensively to deprotonate the less substituted α-carbon independent of hydrazone geometry.[11] Second, anion-stabilizing substituents in the α-position direct deprotonation. Third, is a general rule that methyl > methylene > methine in acidity. The preferred proton abstracted is illustrated with arrows in eq 1.[9d,12]

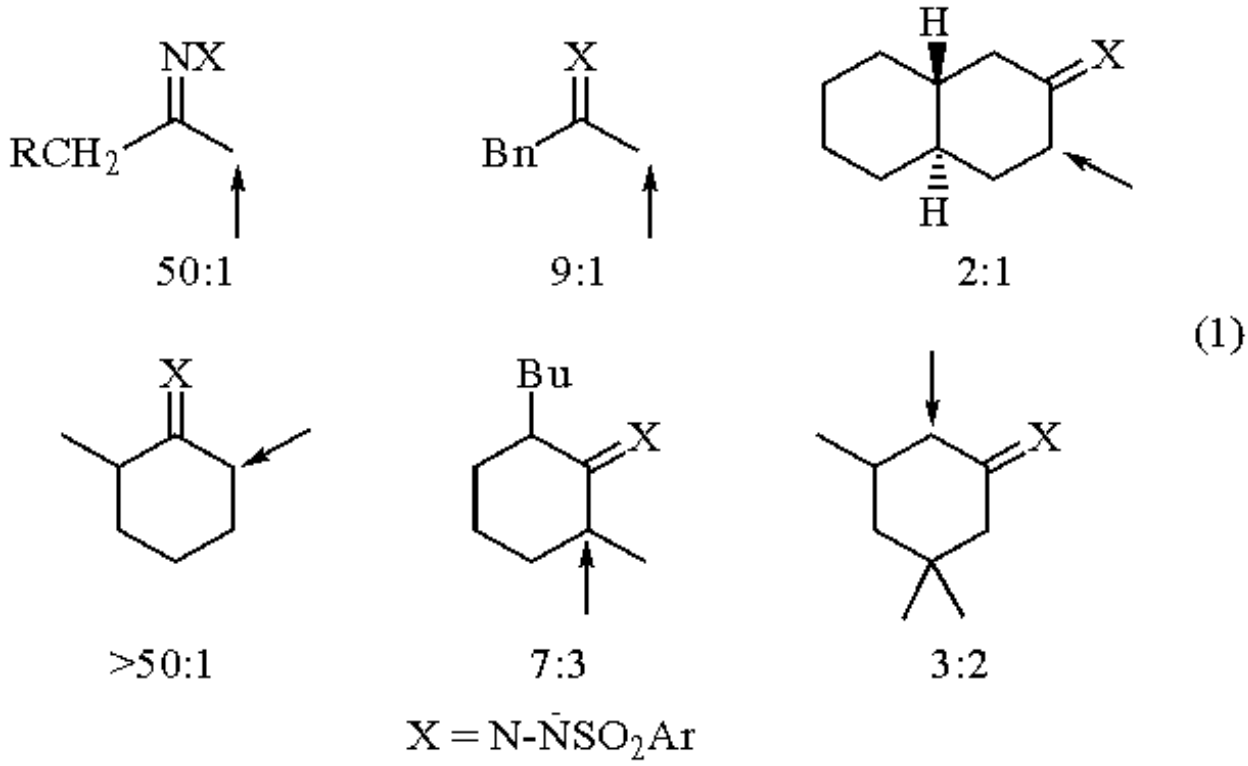

(1)

Bamford-Stevens and Shapiro Reactions.

Thermal decomposition of the monoanions of arenesulfonylhydrazones in aprotic solvents such as glyme (the aprotic Bamford-Stevens reaction[13]) is a method of choice for forming diazo compounds and carbenes. Trisylhydrazones are well suited to this end and have been shown to be the superior reagent for diazoalkane formation in several instances (eq 2).[14]

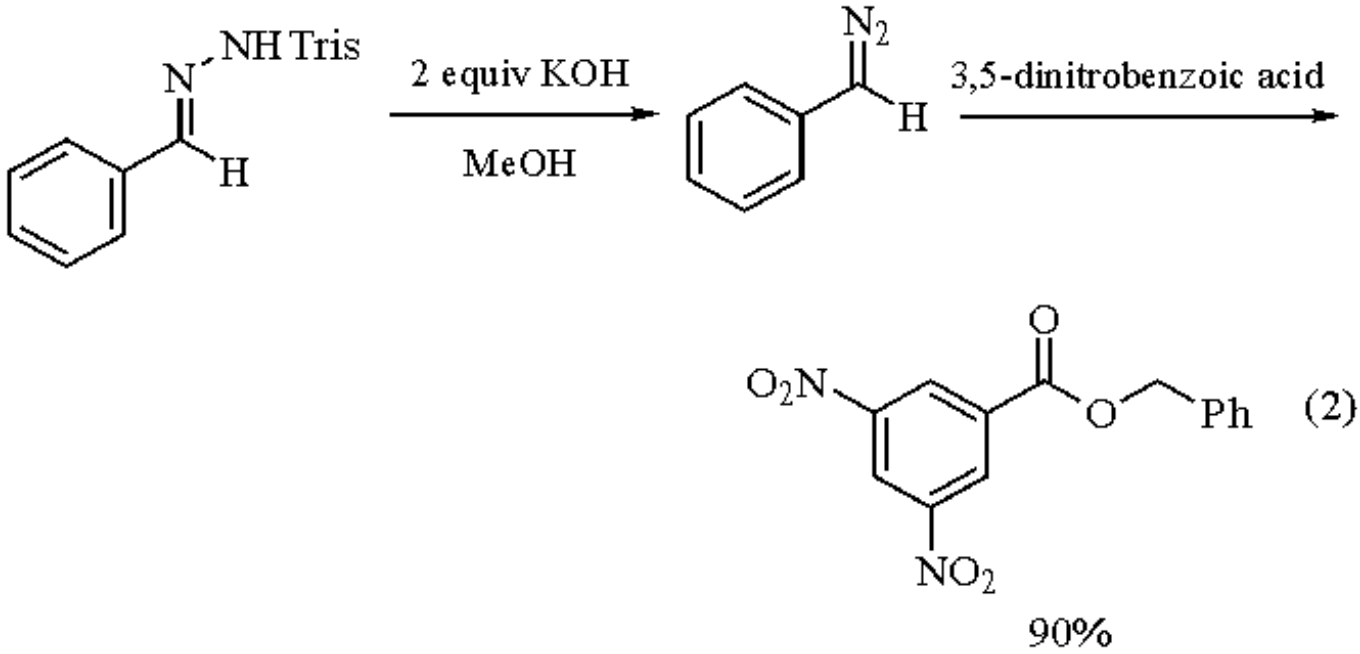

(2)

Trisylhydrazones were originally investigated as an alternative to the shortcomings of tosylhydrazones in the Shapiro reaction.[12a] The former have the advantage that their anions decompose at lower temperatures and the bulky isopropyl substituents preclude *ortho* metalation, enabling the use of stoichiometric amounts of base. Acyclic azaenolates have a strong preference for $(E)_{CC}$ geometry[10] and undergo the Shapiro elimination to stereoselectively produce alkenes of (*Z*) geometry (eqs 3 and 4). The stereochemical fidelity of the azaenolate is compromised significantly, however, if there is hydrocarbon branching at the α´-center due to allylic strain.[1]

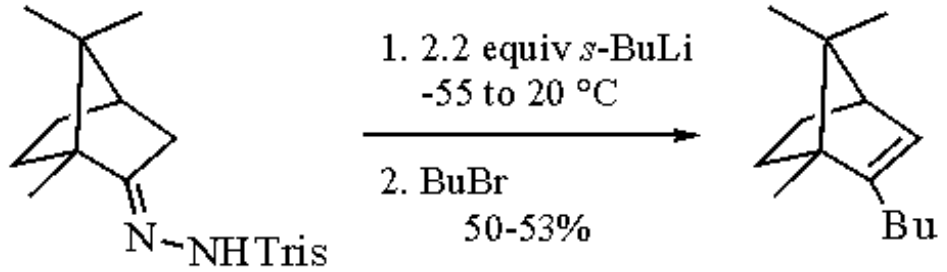

(3)

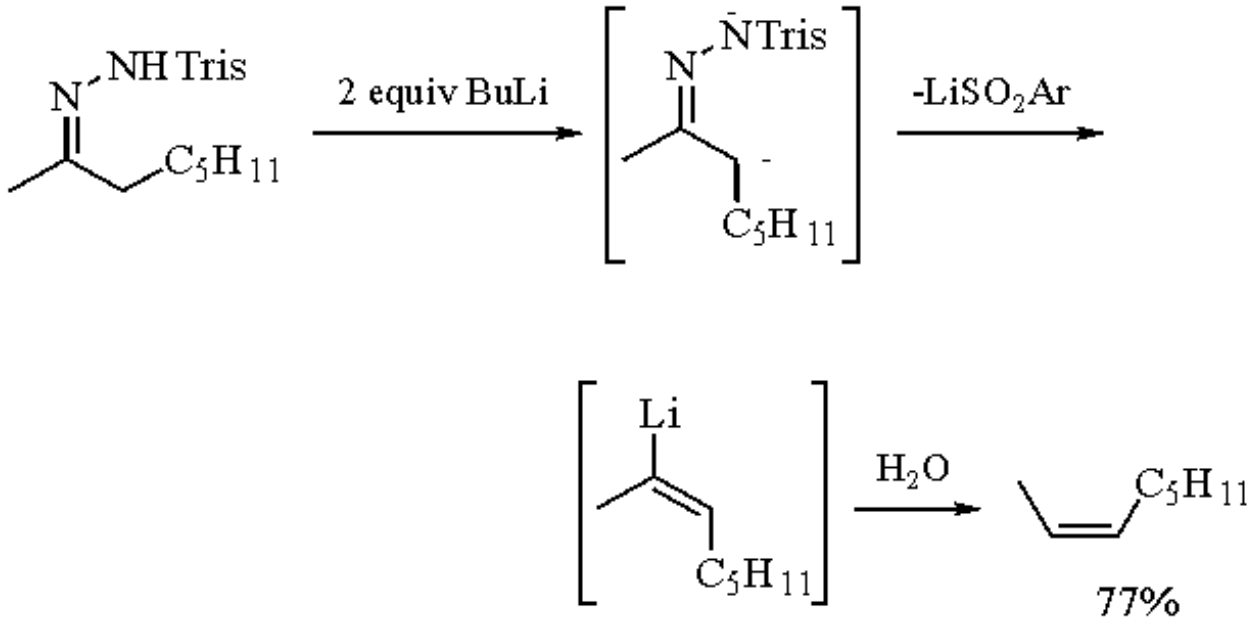

(4)

The resulting vinyllithium intermediates may be trapped with a proton or some of the representative electrophiles shown in eqs 3-6.[11,15]

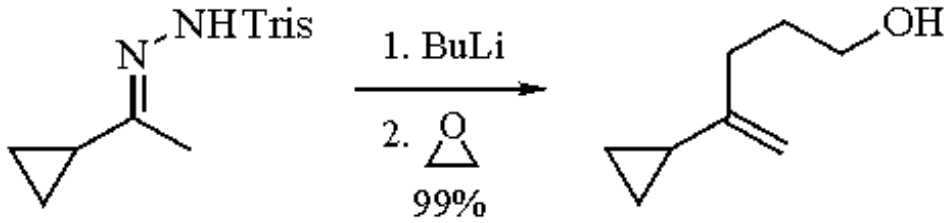

(5)

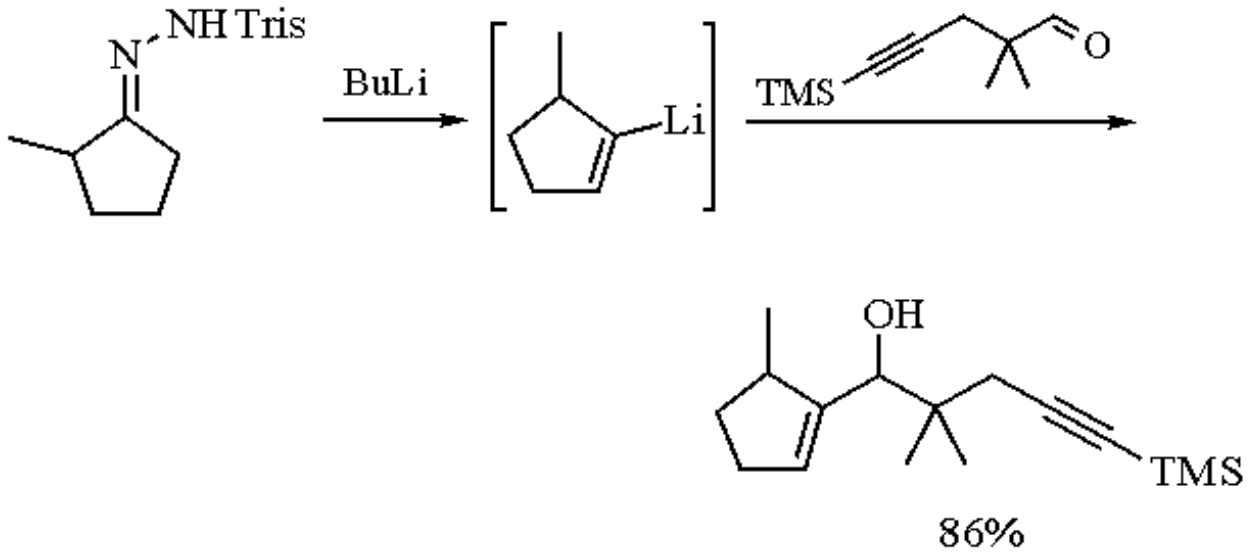

(6)

Additional electrophiles include CO_2, DMF, formaldehyde, ethyl chloroformate, ketones, D_2O, halophosphines, halides, and propargylic tosylates.[9d,11,12a,16]

The Shapiro elimination also provides access to a diverse array of one-pot electrophile-substituted double bonds (eqs 7 and 8).[9]

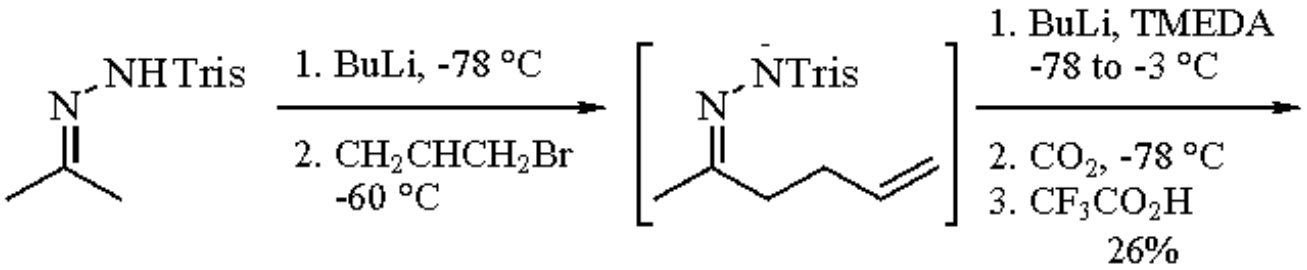

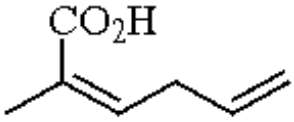

(7)

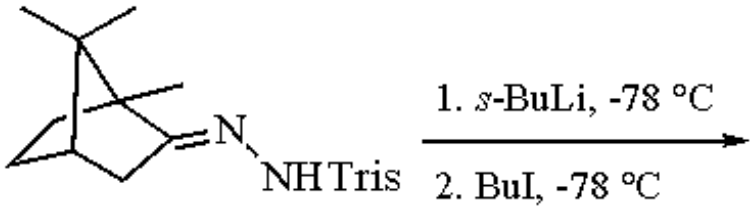

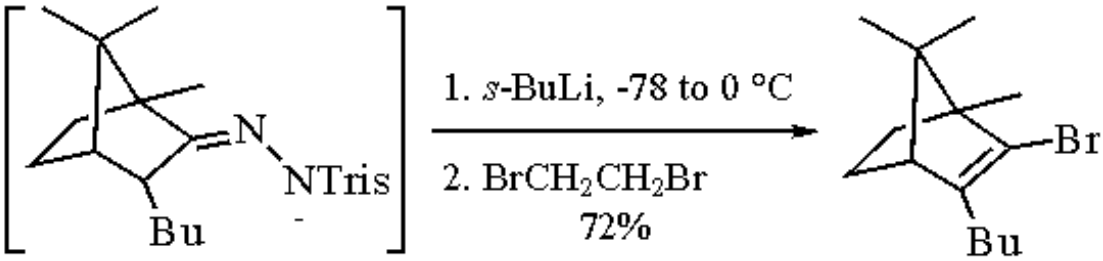

(8)

Several investigators have attenuated the potent nucleophilicity of vinyllithium intermediates by transmetalation or trapping. Vinylstannanes,[17] chromium-carbene complexes,[18] and particularly vinylsilanes[19,20] have been prepared. Alkenyllithiums react faithfully to give 1,2-addition products with α,β-unsaturated ketones, and mixed cuprate reagents have also been prepared with some success by trapping vinyllithiums with phenylthiocopper for 1,4-addition (eq 9).[21,22]

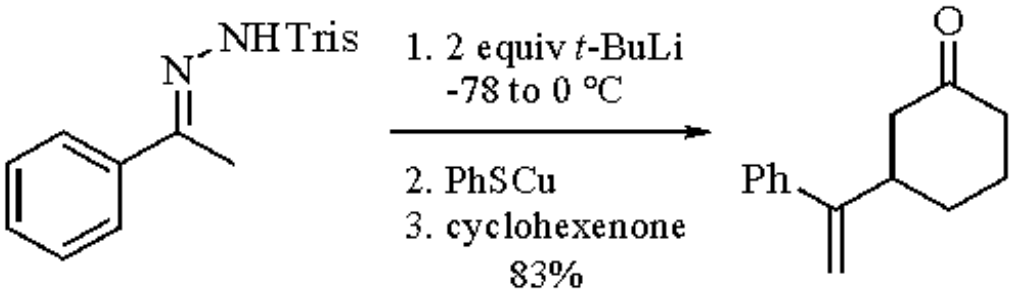

(9)

Intercepting the vinyllithium with a trialkylboron Lewis acid (eq 10) forms an ate complex that can then undergo iodine-promoted alkyl migration and elimination to give excellent yields of hindered trisubstituted alkenes.[23,24] This transformation constitutes a formal S_N2 displacement of a secondary halide and appears generally applicable to cyclic and acyclic ketones.

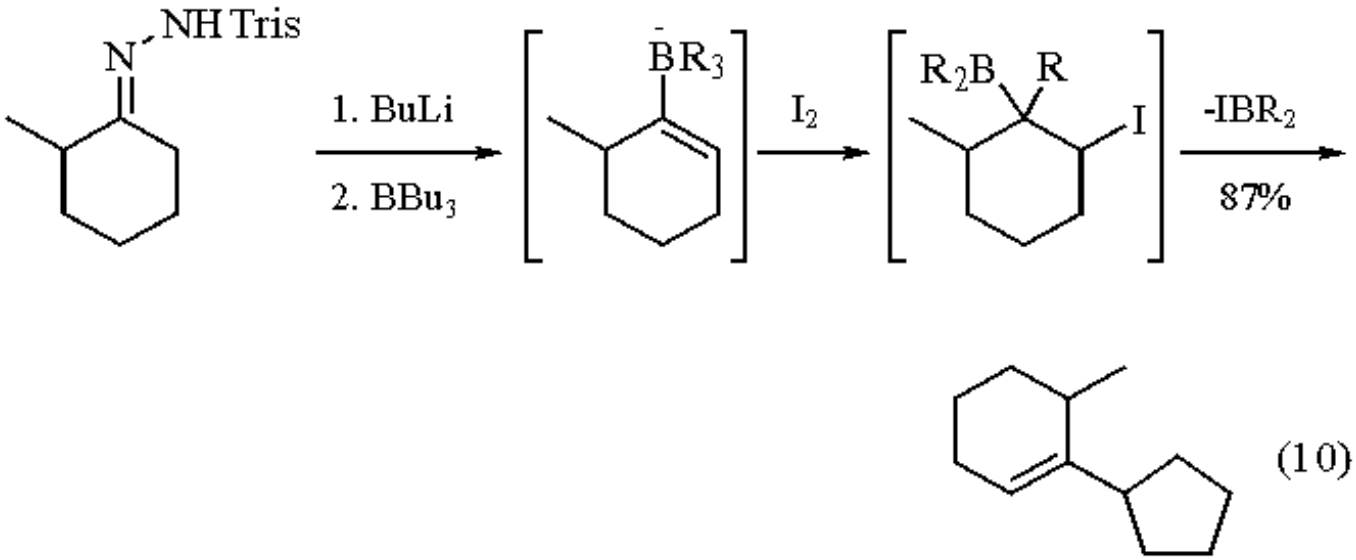

(10)

Intramolecular vinyllithium trapping has been used as an alternative to radical cyclization. Five- to seven-membered ring alkylidene cycloalkanes are formed via S_N2 displacement of a hydrocarbon-tethered leaving group by an alkenyllithium intermediate in 30-72% yield.[25] Another more general alternative is an analogous alkenyllithium condensation with a tether containing an unactivated terminal alkene (eqs 11 and 12).[26,27]

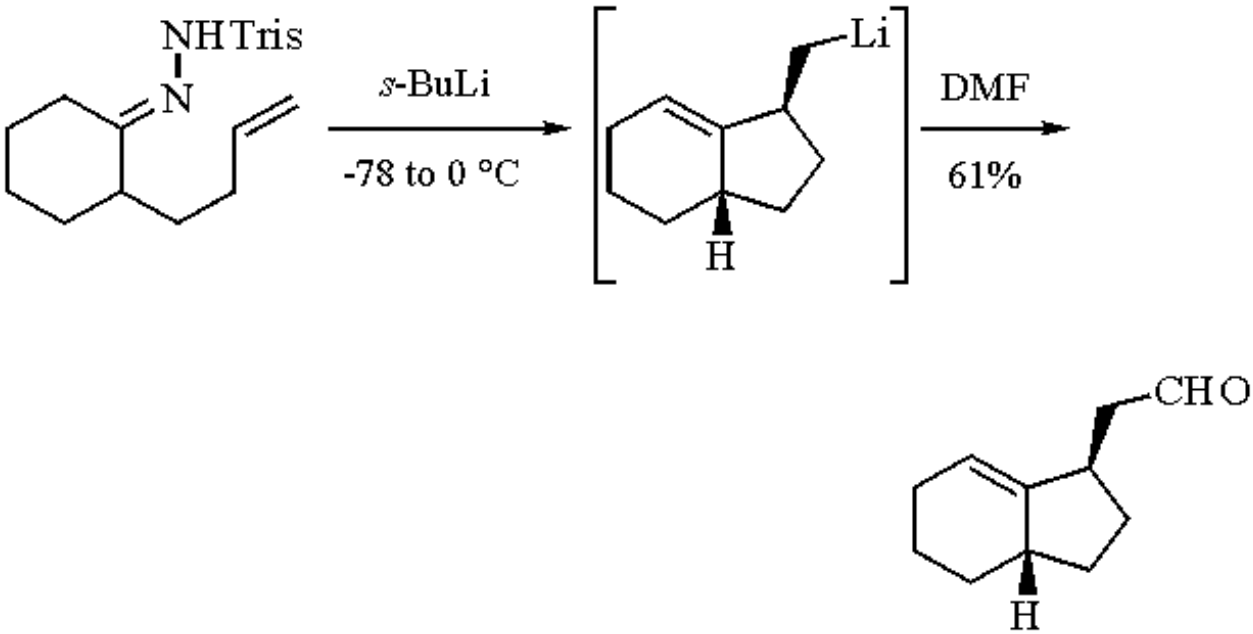

(11)

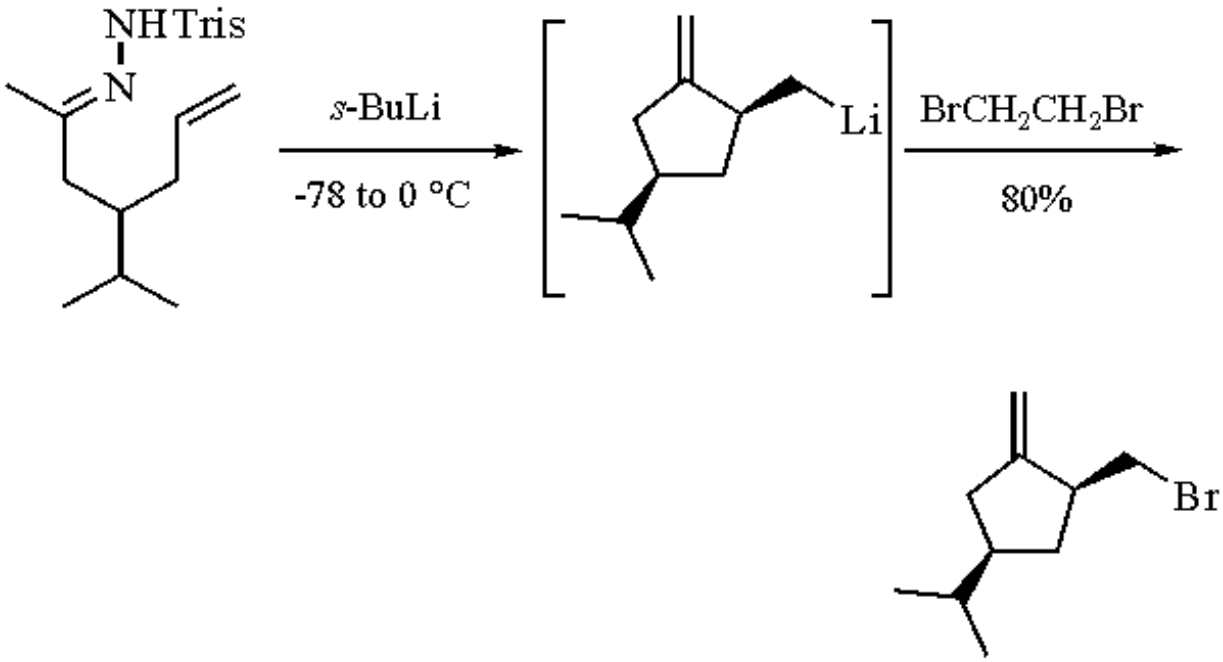

(12)

The resulting alkyllithium produced after cyclization has also been successfully trapped with several electrophiles in fair to excellent yield. This annulation stereoselectively gives the *syn* isomer in 10:1 to >50:1 but is limited to five-membered ring formation and has not been applied to highly functionalized carbocycles.

Condensation of trisylhydrazones with α,β-unsaturated ketones yields hydrazones that are selectively deprotonated α rather than γ to form 2-lithioalkadienes or quenched to form dienes (eqs 13 and 14).[28] 2-Halo ketone hydrazones give the same intermediate after treatment with strong base.[29]

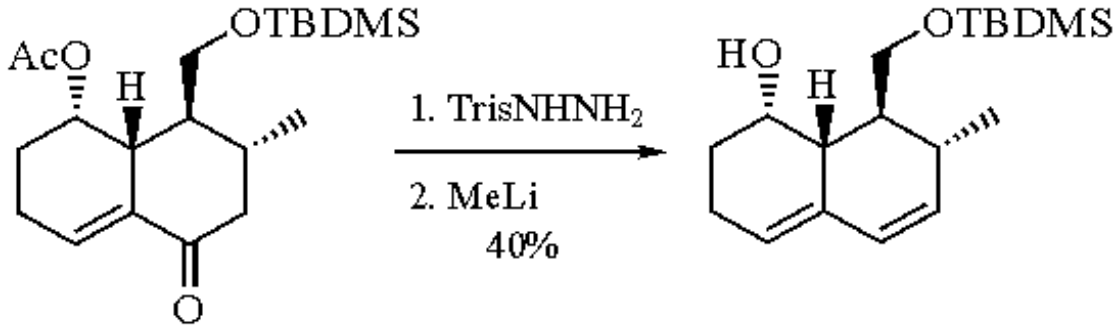

(13)

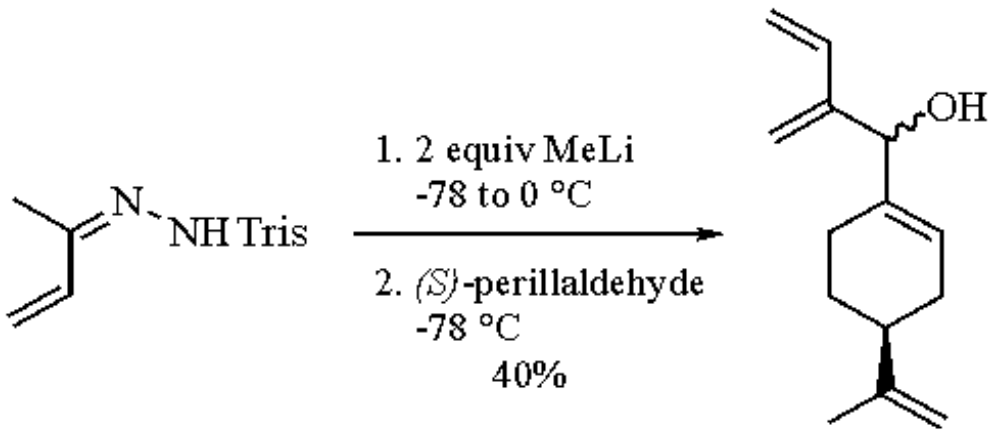

(14)

Miscellaneous.

Ketones may be homologated by one carbon in moderate yield by forming the trisylhydrazone and reacting it with cyanide ion in boiling methanol.[30] 1,2-Carbonyl transpositions are possible in good to excellent yield by sulfenylation of a trisylhydrazone dianion, Shapiro elimination, and hydrolysis of the thioenol ether.[31] Vinylsilanes have been used to the same end.[32] Hydrazones of amides (amidrazones) have been prepared indirectly by treatment of a trisyl carbazate with ***Phosphorus(V) Chloride*** and then ***Morpholine***. These compounds act as acyl anion equivalents and may also undergo the Shapiro elimination to form a lithio enamine which can be attacked by two electrophiles.[33] Finally,

trisylhydrazones of α-keto amides may be indirectly synthesized from isocyanides; when treated with alkyllithium base, they undergo the Shapiro reaction to give allenylates. These intermediates react with electrophiles to give α-substituted-α,β-unsaturated amides in good to excellent yield.[34]

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Triisopropyl Borate

B(O-*i*-Pr)$_3$

[5419-55-6] · $C_9H_{21}BO_3$ · Triisopropyl Borate · (MW 188.11)

(used for the preparation of boronic acids and esters;[1a] also used as Lewis acid catalyst or additive in many reactions)

Physical Data: bp 139-141 °C; *n*20D 1.3764; *d* 0.815 g cm^{-3}.

Solubility: very sol ether, ethanol, isopropanol, benzene; dec in H_2O.[2]

Form Supplied in: colorless liquid, about 98% pure.

Purification: by distillation.

Handling, Storage, and Precautions: moisture sensitive; must be stored under nitrogen in a cool dry place; irritating to the skin and to the eyes.[3]

Synthesis of Borinic and Boronic Acids and Esters.

B(O-*i*-Pr)$_3$ is a useful reagent for the preparation of isopropyl borinates (eq 1)[1b] or diisopropyl boronates (eq 2)[1a,1c-i] by reaction with 2 or 1 equiv of the appropriate organolithium or Grignard reagent, followed by addition of just 1 equiv of HCl. B(O-*i*-Pr)$_3$ is superior to B(OMe)$_3$ for these reactions.

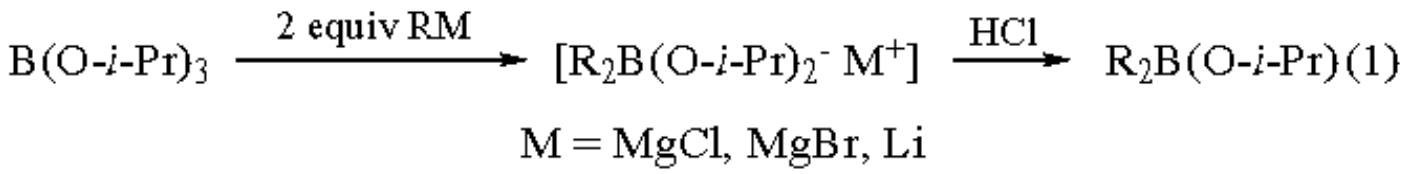

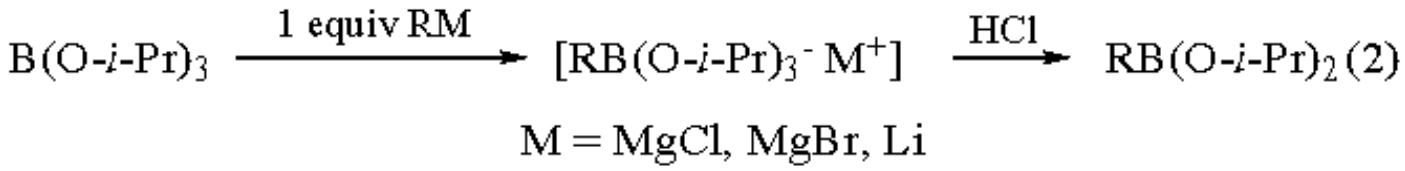

Borinic esters are useful intermediates for the preparation of tertiary alcohols, ketones, α-haloborinic esters, lithium dialkylborohydrides, and new types of dialkylboranes.[1b] Boronic esters can be easily converted into the corresponding boronic acids by aqueous hydrolysis,[1c] with or without the presence of an acid (see also ***Trimethyl Borate***). An improved procedure for the preparation of both borinic and boronic isopropyl esters involves the pyrolysis of the intermediate ate complexes.[1e] Many boronic esters and acids can be prepared by the procedure summarized in eqs 1 and 2; some examples include allyl (substituted or not),[1f,g] 1-alkynyl,[1h] and 1-alkenyl[1j] boronic esters. Usually B(O-*i*-Pr)$_3$ gives better yields in boronic acids synthesis (especially for methylboronic acid) than B(OMe)$_3$ or other trialkyl borates.[1a,1d,1g]

Reaction of triisopropyl borate with ***Chloromethyllithium***,[1a] ***Bromomethyllithium***,[4a] or α-haloallyllithium[4b] represents an efficient entry into α-haloboronates, which can in turn undergo various substitution reactions.

Use of Boronic Esters and Acids.

One of the main uses of diisopropoxyboranes is their conversion into other boronates, passing through the corresponding boronic acids.

These new boronates are usually cyclic and can be chiral either on the diol residue[1f,g] used for the esterification, on the R-B moiety,[1a] or both.[1i] Allyl and substituted allyl boronates have been used in stereoselective C-C bond formation, by reaction with aldehydes (for a series of examples see ***Trimethyl Borate***).[1a,f,g,5] They can also react with C=N electrophiles, such as aldoximes, imines, and sulfenimides,[5] although more slowly than with aldehydes.

The reaction of $BrCH_2Li$ with simple boronates (achiral or chiral) inserts a CH_2 group into the carbon-boron bond, affording homologated boronates.[4a] Reaction with Cl_2CHLi inserts the CHCl group.[1a] The resulting α-haloboronic esters are useful starting materials for various substitution reactions. The same applies for α-haloallylboronates.[4b]

Diisopropyl boronates[1a] and boronic acids have been employed as nucleophilic partners in palladium-catalyzed cross-coupling reactions. However, only few have been prepared from $B(O\text{-}i\text{-}Pr)_3$ (usually boronic acids are prepared using $B(OMe)_3$ and ***Catecholborane*** as boron reagents), including some arylboronic acids used in the synthesis of 5-arylnicotinates.[6] (1-Alkynyl)diisopropoxyboranes can be used in ***Boron Trifluoride Etherate***-catalyzed conjugate addition to α,β-unsaturated ketones to provide 3-alkynyl ketones.[1h] Finally, a regiospecific synthesis of 2-fluoro-3-*O*-methylestrone (**2**) was realized by electrophilic displacement of boronic acid (**1**) with ***Cesium Fluoroxysulfate*** (CFS) (eq 3);[7] boronic acid formation was regiospecific in position 2 when the metalation [1. *n*-BuLi; 2. $B(O\text{-}i\text{-}Pr)_3$] was performed on the η^6-arenetricarbonylchromium(0) complex, derived from estrone.

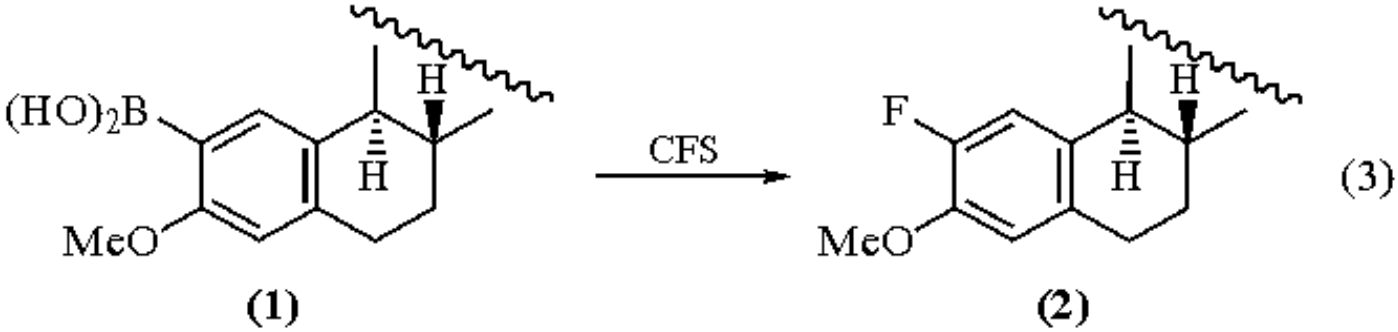

Miscellaneous.

$B(O\text{-}i\text{-}Pr)_3$ has been used to prepare a boron reagent from lithium (trimethylsilyl)acetonitrile, which was employed for the stereoselective alkenation of aldehydes to give α,β-unsaturated nitriles. Compared to Li, Ti, and Mg reagents, this boron reagent gives the best results in regard to chemical yields and (*Z*/*E*) ratios.[8] $B(O\text{-}i\text{-}Pr)_3$, together with other trialkyl borates, has been used to transform unactivated bromides (R^1 = alkyl, vinyl, aromatic) into the corresponding homologated ester, via a carbonylation reaction catalyzed by 1,5-hexadienerhodium(I) chloride dimer and ***Tetrakis(triphenylphosphine)palladium(0)***;[9a] the same reaction can also be performed on benzyl chlorides in the presence of iodide ion and the above mentioned Rh^I catalyst (eq 4).[9b]

$$3\ R^1CH_2X + B(OR^2)_3 + 3\ CO \xrightarrow{\text{cat.}} 3\ R^1CH_2CO_2R^2 + BX_3 \quad (4)$$

Finally, the reaction of $B(O\text{-}i\text{-}Pr)_3$ with KH[10] gives ***Potassium Triisopropoxyborohydride***, a mild reducing agent for carbonyl compounds, disulfides, and haloboranes.

---

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Luca Banfi, Enrica Narisano & Renata Riva

Triisopropyl Phosphite[1]

(i-PrO)$_3$P

[116-17-6] · $C_9H_{21}O_3P$ · Triisopropyl Phosphite · (MW 208.27)

(corresponding phosphonate esters afford high (*E*) selectivity in Wadsworth-Emmons alkenations[4,5])

Physical Data: bp 63-64 °C/11 mmHg; n_D 1.411; *d* 0.844 g cm^{-3}; fp 67 °C.

Solubility: sol organic solvents.

Form Supplied in: clear liquid; widely available.

Purification: by distillation at reduced pressure to avoid decomposition by Michaelis-Arbuzov reaction.

Handling, Storage, and Precautions: moisture sensitive, toxic (RTECS# TH2800000). Stable at rt for extended periods of time. Use in a fume hood.

Phosphonate/Phosphate Formation.

The reactions of the triisopropyl ester of P(OH)$_3$ are only marginally different from those of the triethyl or trimethyl esters. It may be used advantageously in situations which require a higher reaction temperature or a more sterically congested center (e.g. to prevent dealkylation of phosphonate esters). It can be used as a source of phosphonates (Michaelis-Arbuzov reaction)[1] for Wadsworth-Emmons alkenation reactions.[2] Control of the stereochemistry of the α,β-unsaturated ester may be possible by proper choice of the phosphonate ester. In contrast to the high (*Z*) selectivity observed[3] using the bis(trifluoroethyl) phosphonate, diisopropyl phosphonates[4,5] afford high (*E*) selectivity in some cases (eq 1).[5] This has been attributed to the increased bulk of the phosphorus ester, but other reports[6] dispute this and attribute the improved stereoselectivity to other factors.

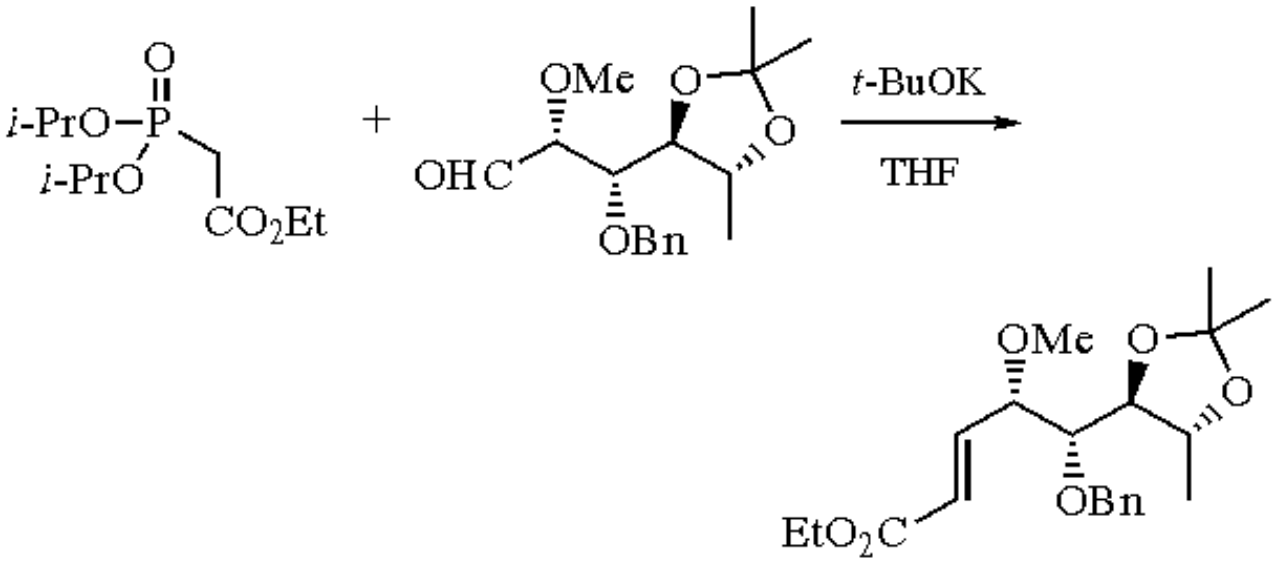

(1)

Reaction with α-halo ketones affords enol phosphates (Perkow reaction),[7] which can be converted to alkenes (eq 2).[6]

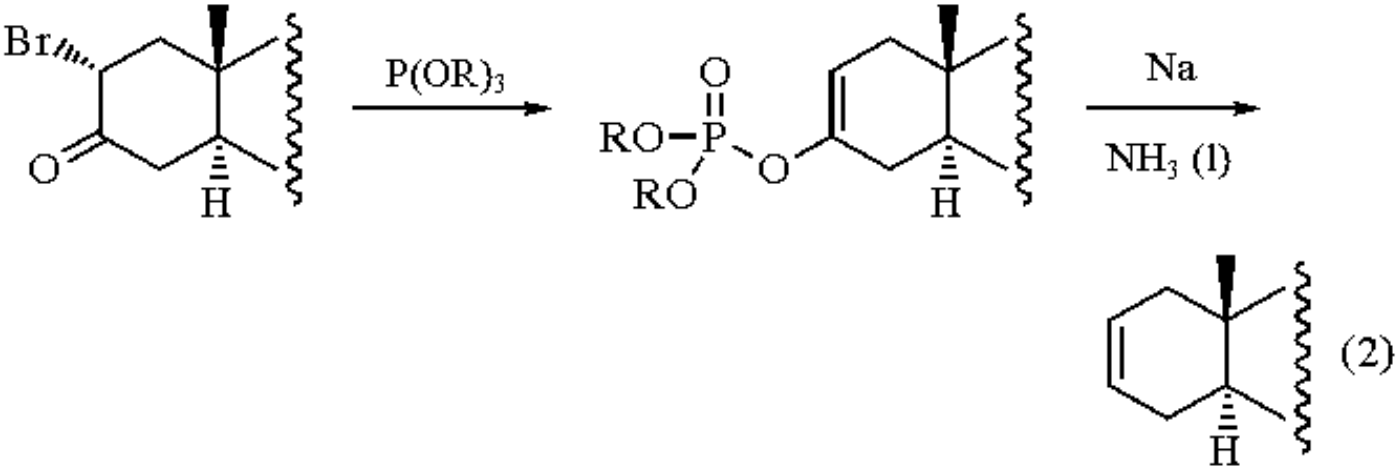

Like all phosphites, triisopropyl phosphite can be used as a reagent for removal of O,[8] S,[9] Hal,[10] etc. from organic substrates (e.g. epoxides, episulfides, thiadiazolines). Like most reactions of trivalent phosphorus derivatives (phosphites or phosphines) with organic substrates, these reactions begin by formation of an alkoxyphosphonium salt or a derivative. Subsequent decomposition of the addition products leads to various products, depending on the functional groups involved. The use of triisopropyl phosphite as a ligand for transition metals is common. The much larger cone angle of triisopropyl phosphite[11] relative to the ethyl and methyl esters can be advantageous. Phosphites are less basic and less nucleophilic than phosphines (trialkyl or triaryl).

Reduction of Carbonyl Groups.

Triisopropyl phosphite has been used as a simple alternative to the Clemmensen or Wolff-Kischner reductions.[12] Refluxing the aldehyde or ketone with excess phosphite affords the deoxygenated reduced product in good yield under essentially neutral conditions (eq 3). A mechanism similar to the Meerwein-Pondorf-Verley reduction was proposed.

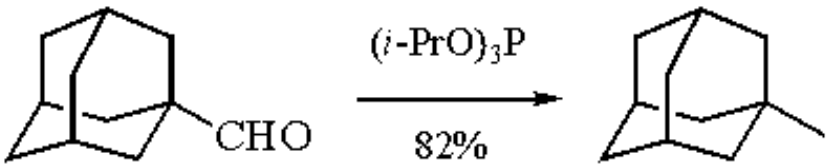

(3)

Related Reagents.

Triethyl Phosphite; ***Triethyl Phosphonoacetate***; ***Trimethyl Phosphite***; ***Trimethyl Phosphonoacetate***.

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Triisopropylsilyl Chloride

***i*-Pr$_3$SiCl**

[131154-24-0] · $C_9H_{21}ClSi$ · Triisopropylsilyl Chloride · (MW 192.84)

(hydroxy protecting group;[1,2] formation of triisopropylsilyl ynol ethers;[3] *N*-protection of pyrroles;[4,5] prevents chelation with Grignard reagents[6])

Alternate Names: TIPSCl; chlorotriisopropylsilane.

Physical Data: bp 198 °C/739 mmHg; *d* 0.901 g cm^{-3}.

Solubility: sol THF, DMF, CH_2Cl_2.

Form Supplied in: clear, colorless liquid; commercially available (99% purity).

Analysis of Reagent Purity: bp; NMR.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: moisture sensitive; therefore should be stored under an inert atmosphere; corrosive; use in a fume hood.

Hydroxy Protecting Group.

Several hindered triorganosilyl protecting groups have been developed to mask the hydroxy functionality. Although the *t*-butyldiphenylsilyl (TBDPS) and *t*-butyldimethylsilyl (TBDMS) groups are the most widely used, the triisopropylsilyl group (TIPS) has several properties which make it particularly attractive for use in a multi-step synthesis.[1,2]

Introduction of the TIPS group is most frequently accomplished using TIPSCl and ***Imidazole*** in DMF,[1] although several other methods exist, including using TIPSCl and ***4-Dimethylaminopyridine*** in CH_2Cl_2. It is possible to silylate hydroxy groups selectively in different steric environments. For example, primary alcohols can be silylated in the presence of secondary alcohols (eq 1)[7] and less hindered secondary alcohols can be protected in the presence of more hindered ones (eq 2).[8]

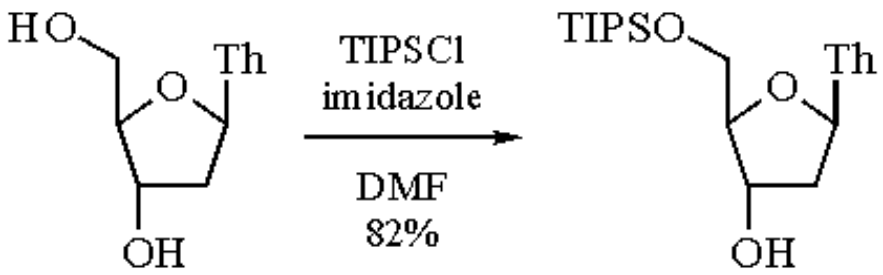

(1)

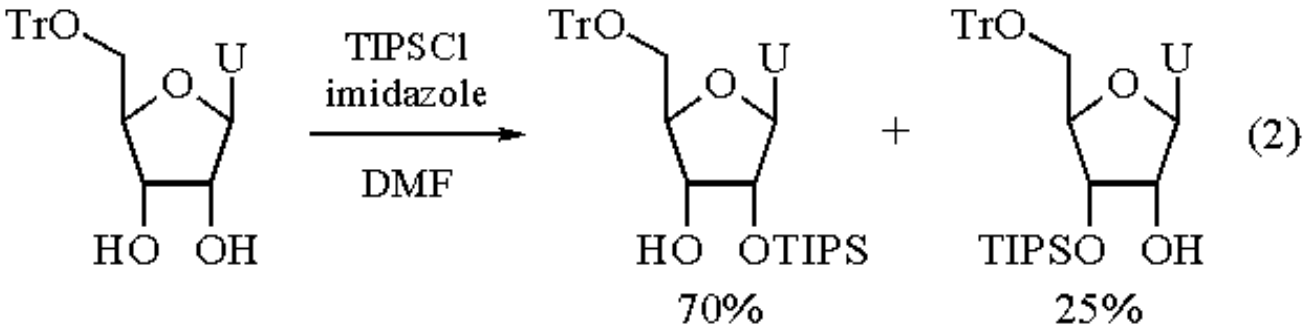

A comparison of the stability of different trialkylsilyl groups has shown that TIPS ethers are more stable than TBDMS ethers but less stable than TBDPS ethers toward acid hydrolysis.[2] The rate difference is large enough that a TBDMS group can be removed in the presence of a TIPS group (eq 3).[7] Under basic hydrolysis, TIPS ethers are more stable than TBDMS or TBDPS ethers.[2] The cleavage of TIPS ethers can also be accomplished by using ***Tetra-n-butylammonium Fluoride*** (TBAF) in THF at rt.[1] This is most convenient if only one silyl protecting group is present or if all of those present can be removed in one synthetic step.

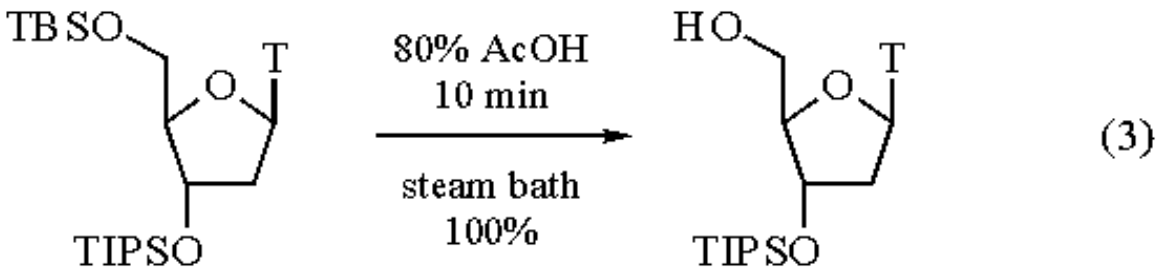

An additional feature of TIPS ethers is that they are volatile enough to make them amenable to GC and MS analysis. In fact, MS fragmentation patterns have been used to discern the structures of isomeric nucleosides.[9]

Formation of Silyl Ynol Ethers.

Esters can also be transformed into triisopropylsilyl ynol ethers.[3] The ester is first converted to the ynolate anion, followed by treatment with TIPSCl to furnish the TIPS ynol ether (eq 4). This method has even proven successful with lactones as starting materials (eq 5).

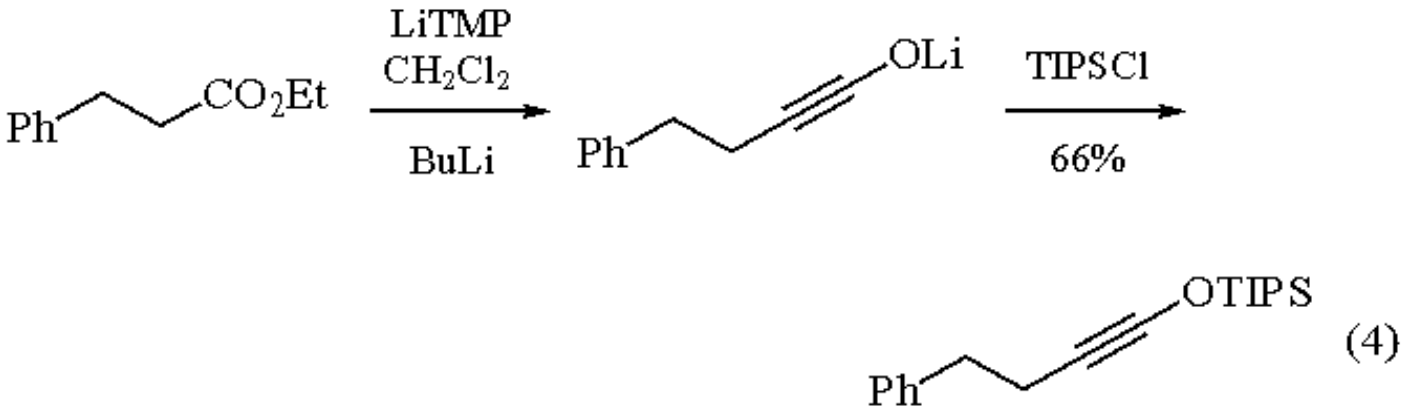

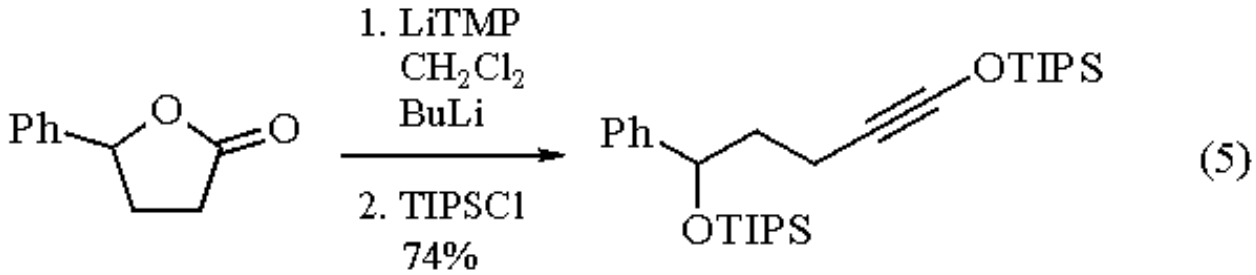

N-Protection of Pyrroles.

Pyrroles typically undergo electrophilic substitution at the α-(2)-position, but when protected as *N*-triisopropylsilylpyrroles, substitution

occurs exclusively at the β-(3)-position (eq 6).[4] It has been shown that 3-bromo-1-(triisopropylsilyl)pyrrole undergoes rapid halogen-metal exchange with ***n-Butyllithium*** to generate the 3-lithiopyrrole, which can be trapped by electrophiles to provide the silylated 3-substituted pyrrole (eq 7).[5] As expected, the silyl group can be removed with TBAF to furnish the 3-substituted pyrrole. It should also be mentioned that the *N*-TIPS group also enhances the stability of some pyrroles. For example, 3-bromopyrrole is very unstable, but the *N*-silylated derivative is stable for an indefinite period of time.[5]

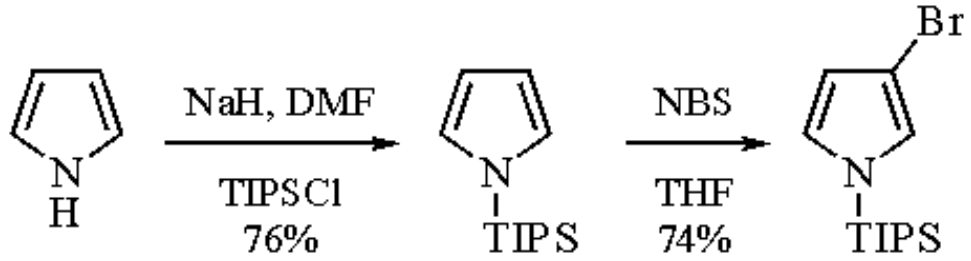

(6)

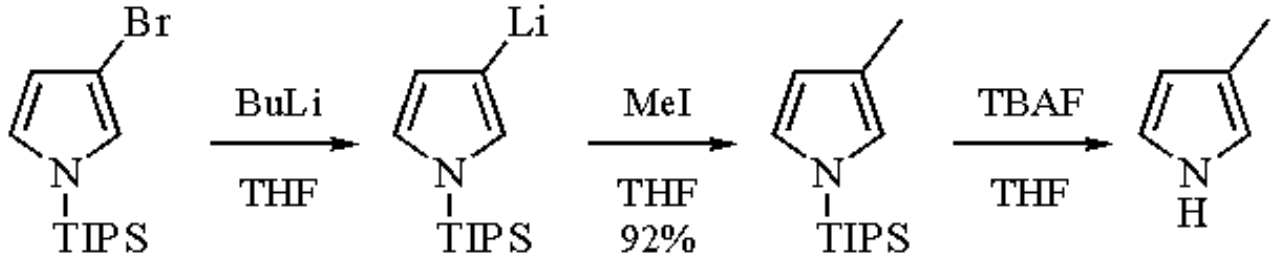

(7)

Prevention of Chelation in Grignard Reactions.

The bulky TIPS protecting group has proven extremely effective in preventing competing chelation of α- and β-oxygen functionalities during Grignard reactions (eq 8).[6] It was determined that this effect is steric and not electronic since TMS and TBDMS ethers did not affect selectivity.

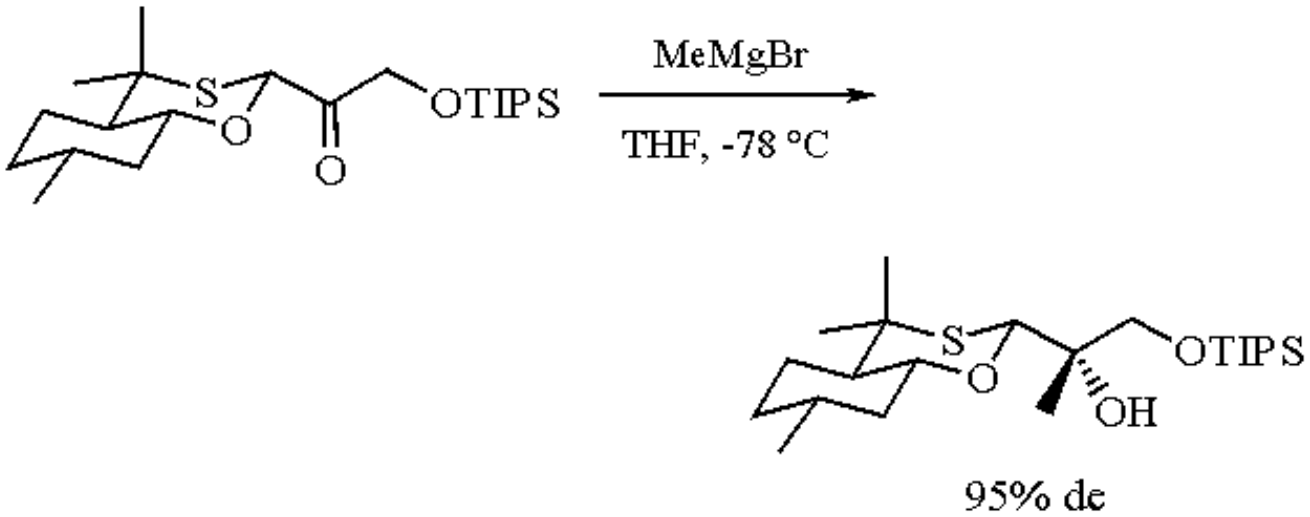

(8)

Related Reagents.

t-Butyldimethylchlorosilane; ***t-Butyldiphenylchlorosilane***.

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Triisopropylsilyl Trifluoromethanesulfonate[1]

$(i\text{-Pr})_3SiOSO_2CF_3$

[80522-42-5] · $C_{10}H_{21}F_3O_3SSi$ · Triisopropylsilyl Trifluoromethanesulfonate · (MW 306.46)

(highly reactive silylating agent and Lewis acid capable of converting primary and secondary alcohols[1] to the corresponding triisopropylsilyl ethers and converting ketones[1] and lactones[2] into their enol silyl ethers; protection of terminal alkynes;[3] promoting conjugate addition of alkynylzinc compounds to α,β-enones;[4] preparation of (triisopropylsilyl)diazomethane[5])

Alternate Name: TIPS triflate.

Physical Data: colorless oil; bp 83-87 °C/1.7 mmHg; *d* 1.173 g cm^{-3}.

Solubility: sol most organic solvents, such as pentane, CH_2Cl_2, etc.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^1H NMR ($CDCl_3$) δ 1.6-1.05 (m).

Preparative Methods: to 38.2 g (0.242 mol) of triisopropylsilane at 0 °C under argon is added 23.8 mL (0.266 mol) of ***Trifluoromethanesulfonic Acid*** dropwise. The solution is stirred at 22 °C for 16 h, at which time no further hydrogen gas evolves (removed through a bubbler). The resulting product is distilled through a 30-cm vacuum jacketed Vigreux column under reduced pressure: 71.7 g (97% yield) of TIPS triflate; bp 83-87 °C/1.7 mmHg.[1a]

Handling, Storage, and Precautions: store under argon at 0 °C; unpleasant odor; reacts rapidly with water and other protic solvents.

Silylation of Alcohols.[1]

Primary and secondary alcohols are silylated by TIPS triflate in excellent yields. Treatment of 1-phenylethanol with 1.3 equiv of TIPS triflate and 2.5 equiv of ***2,6-Lutidine*** in CH_2Cl_2 at 0 °C for 2 h provides a 98% yield of α-(triisopropylsilyloxy)ethylbenzene (eq 1).[1a]

$$\mathrm{ROH} \xrightarrow[\mathrm{CH_2Cl_2}]{(i\text{-Pr})_3\mathrm{SiOTf},\ 2,6\text{-lutidine}} \mathrm{ROSi}(i\text{-Pr})_3 \qquad (1)$$

Formations of Enol Silyl Ethers.[1,2]

Aldehydes, ketones, and lactones are readily converted into the corresponding enol TIPS ethers. Reactions of cycloalkanones with 1.1 equiv of TIPS triflate and 1.5 equiv of ***Triethylamine*** in benzene at 23 °C for 1 h gives >98% yields of the corresponding enol silyl ethers (eq 2).[1a]

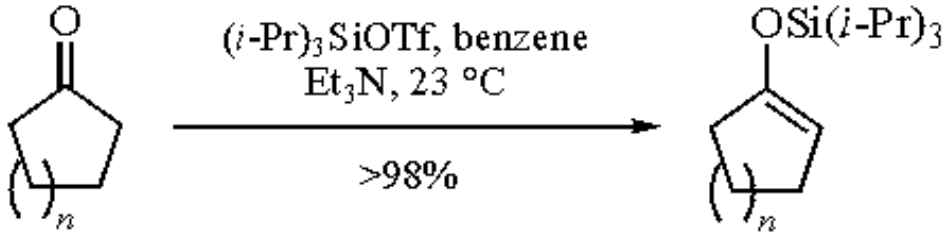

(2)

Silylation of 2-morpholinones with 1.2 equiv of TIPS triflate and 1.5 equiv of triethylamine in $CDCl_3$ for 2 min provides silyl ketene acetals, which upon standing at rt undergo Claisen rearrangement to afford pipecolic esters (eq 3).[2]

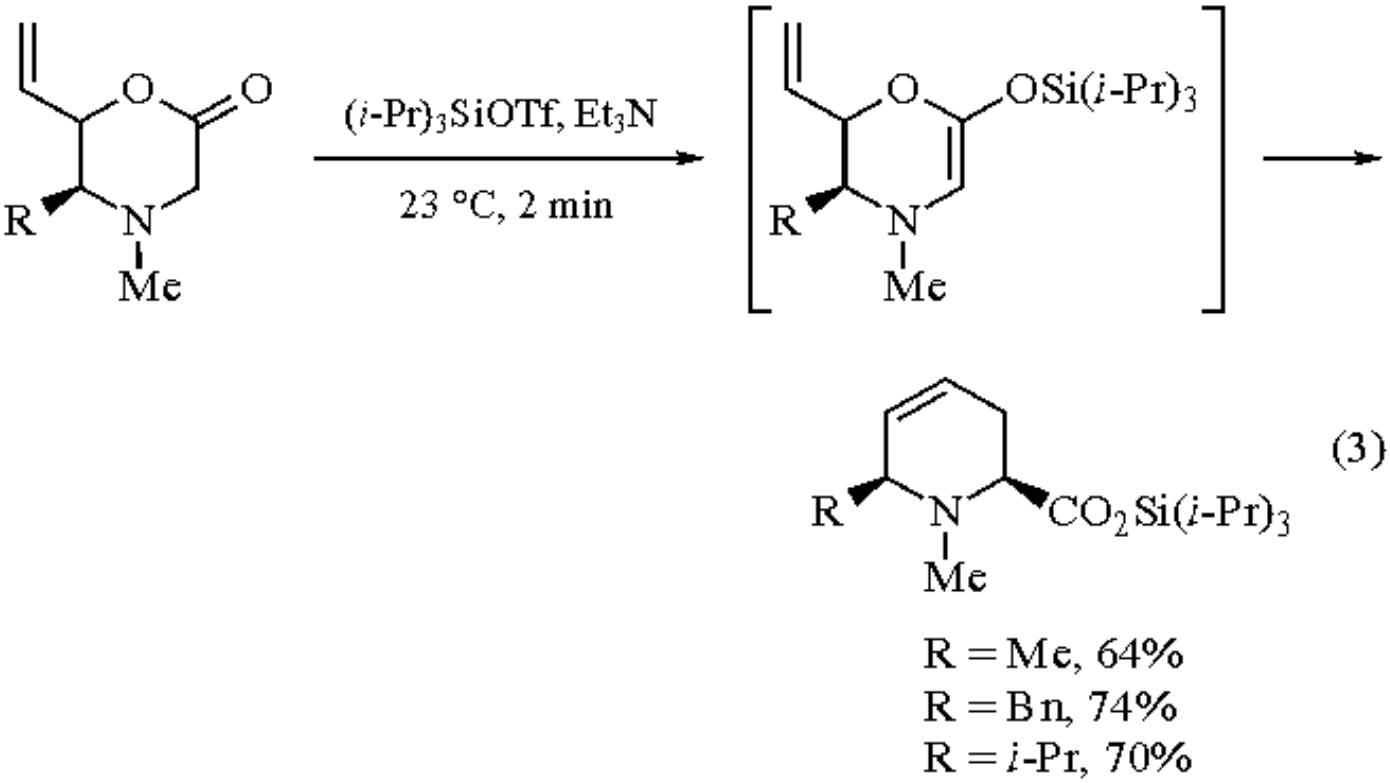

(3)

Alkynyltriisopropylsilanes.[3]

The acidic alkynic H can be protected with TIPS triflate. Silylation of 1-lithiopropyne with 1 equiv of TIPS triflate in ether at -40 to 0 °C gives an 87% yield of 1-TIPS-propyne (eq 4).[3a] 1,3-Bis(triisopropylsilyl)propyne, derived from treatment of 1-TIPS-propyne with ***n-Butyllithium*** in THF at -20 °C for 15 min followed by TIPS triflate at -78 to -40 °C (eq 5), is lithiated with *n*-BuLi in THF at -20 °C for 15 min and then allowed to react with aldehydes (eq 6). The *cis*-enynes are isolated in high yields.[3a] TIPS-propargylmagnesium bromide together with ***Copper(I) Iodide*** has been used in the displacement of the mesylate derivative of farnesol.[3b]

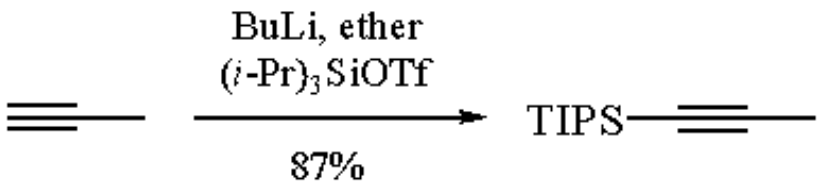

(4)

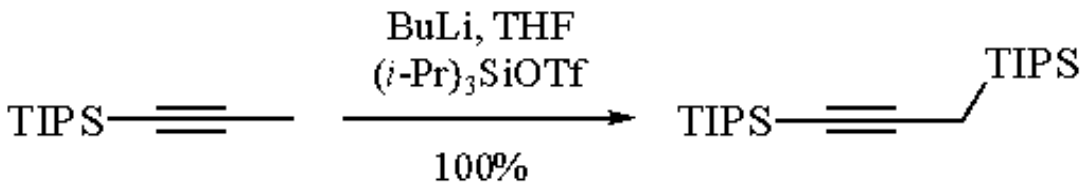

(5)

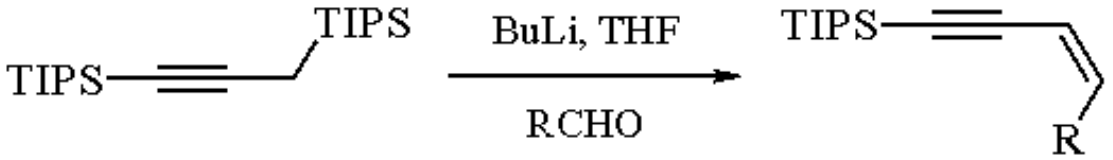

(6)

(Z):(E) = 20:1

R = Cy, 71%
R = C_6H_{13}, 57%
R = *t*-Bu, 79%

Conjugate Addition of Alkynylzinc Bromides.[4]

Alkynylzinc bromides undergo conjugate addition with α,β-unsaturated ketones in the presence of ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** or TIPS triflate (***Trimethylsilyl Trifluoromethanesulfonate*** is also effective) in ether-THF at -40 °C to give the corresponding 1,4-adducts (54-96% yields). A representative example is illustrated in eq 7.

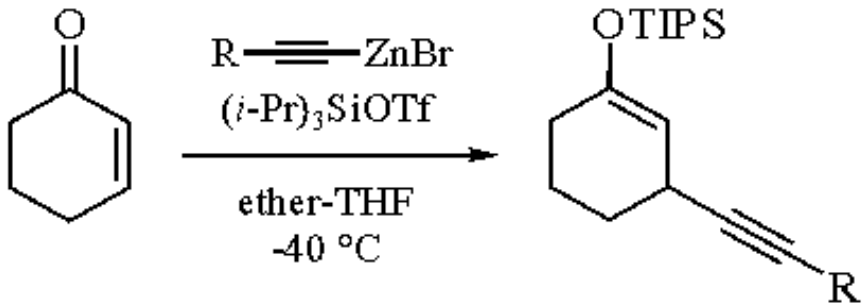

(7)

(Triisopropylsilyl)diazomethane.[5]

Silylation of ***Diazomethane*** with TIPS triflate and ***Diisopropylethylamine*** in ether at -20 °C to 25 °C gives a 45% yield of (triisopropylsilyl)diazomethane (eq 8).[5] This silylated diazomethane is used to prepare stable silyl-substituted nitrilimines.[5]

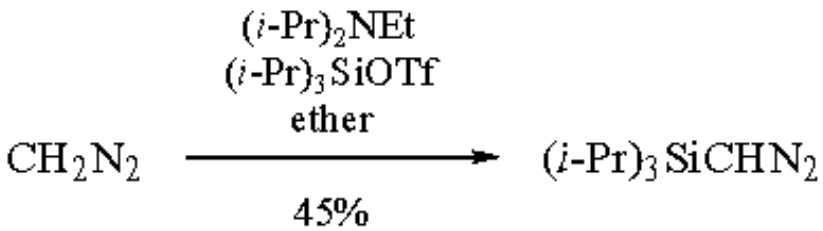

(8)

Related Reagents.

Triisopropylsilyl Chloride.

---

1. (a) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *TL* **1981**, *22*, 3455. (b) For a review of trialkylsilyltriflates: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *S* **1982**, 1.
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Duy H. Hua & Jinshan Chen

Trimethylacetyl Chloride

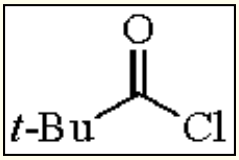

[3282-30-2] · C_5H_9ClO · Trimethylacetyl Chloride · (MW 120.59)

(ether cleavage;[1] synthesis of ketones from carboxylic acids;[2] peptide synthesis;[3] selective protection of polyols[4])

Alternate Names: pivaloyl chloride; 2,2-dimethylpropanoyl chloride.

Physical Data: bp 105-106 °C; *d* 0.979 g cm^{-3}.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: flammable; can cause severe burns and is irritating to the eyes and respiratory system; toxic by contact with the skin, by inhalation, and if swallowed. It should be used in a fume hood. During use, avoid sources of ignition and any contact. Avoid exposure to moisture.[5]

Ether Cleavage.

Ethers can be cleaved by the action of trimethylacetyl chloride (*t*-BuCOCl) and ***Sodium Iodide*** to give the corresponding trimethylacetate and alkyl iodide.[1] The reaction is regioselective, the cleavage occurring at the less substituted α-carbon-oxygen bond.[1,6] Other acyl chlorides can be used, but the reaction is more regioselective with trimethylacetyl chloride.[1] The reaction is particularly useful for cleaving methyl ethers (eq 1).[1]

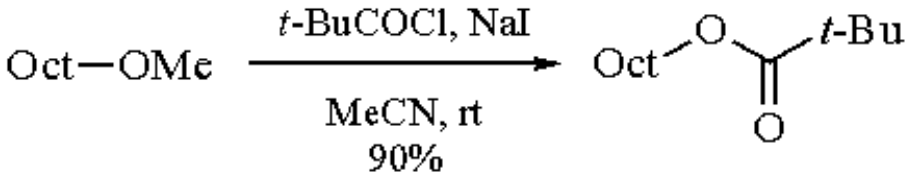

(1)

Ketone Synthesis.

Carboxylic acids can be converted to ketones by first forming the mixed anhydride with trimethylacetyl chloride and then treating it with a Grignard reagent (eq 2).[2] In addition to trimethylacetyl chloride, *ortho*-substituted benzoyl chlorides such as *o*-anisoyl chloride can be used to form the mixed anhydride. Yields were found to be slightly higher than when trimethylacetyl chloride was used.[2]

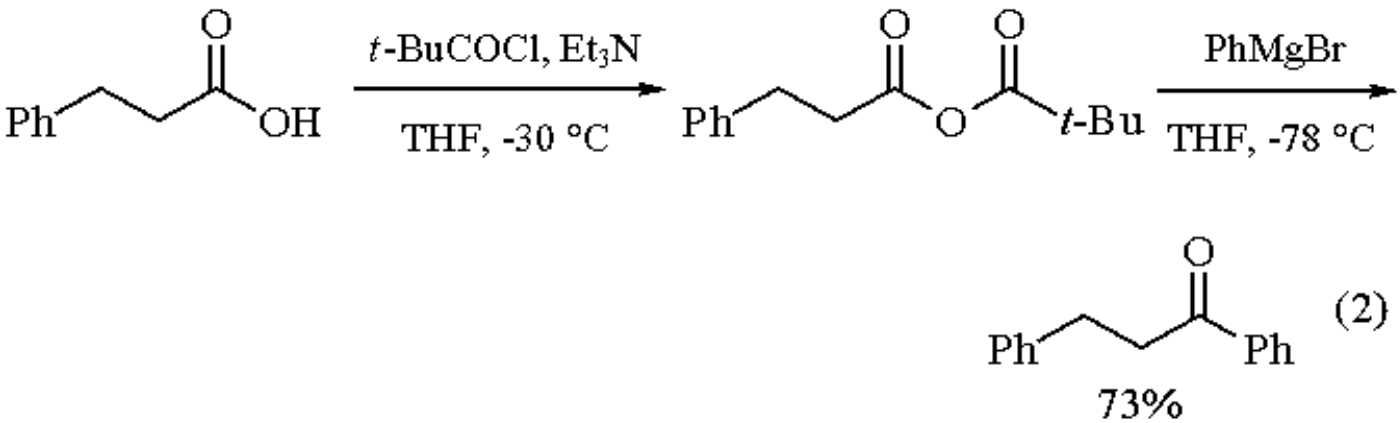

(2)

The carboxylic acid (**1**) has been converted to the ketone (**2**) via the mixed anhydride with trimethylacetyl chloride (eq 3).[7]

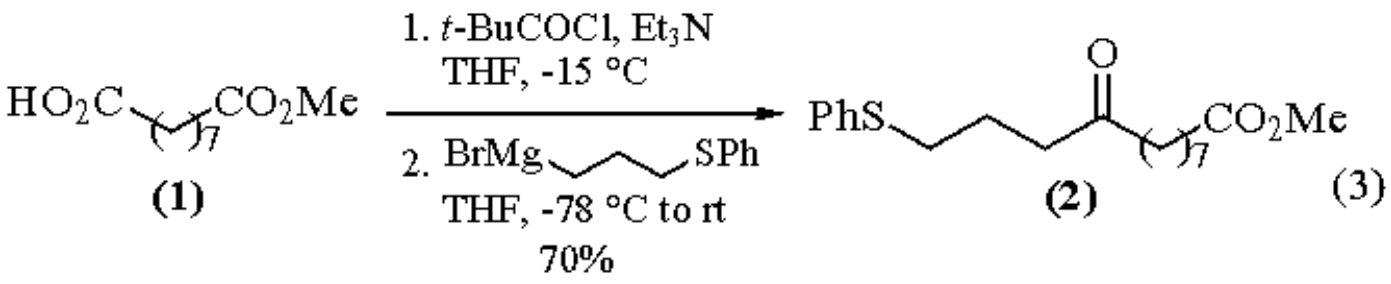

A γ-keto aldehyde synthesis has been developed using similar methodology. The ethoxy lactam (**3**) was converted to its *N*-trimethylacetyl derivative (**4**), which was then treated with a Grignard reagent. Acid workup gave the γ-keto aldehyde (**5**) (eq 4).[8]

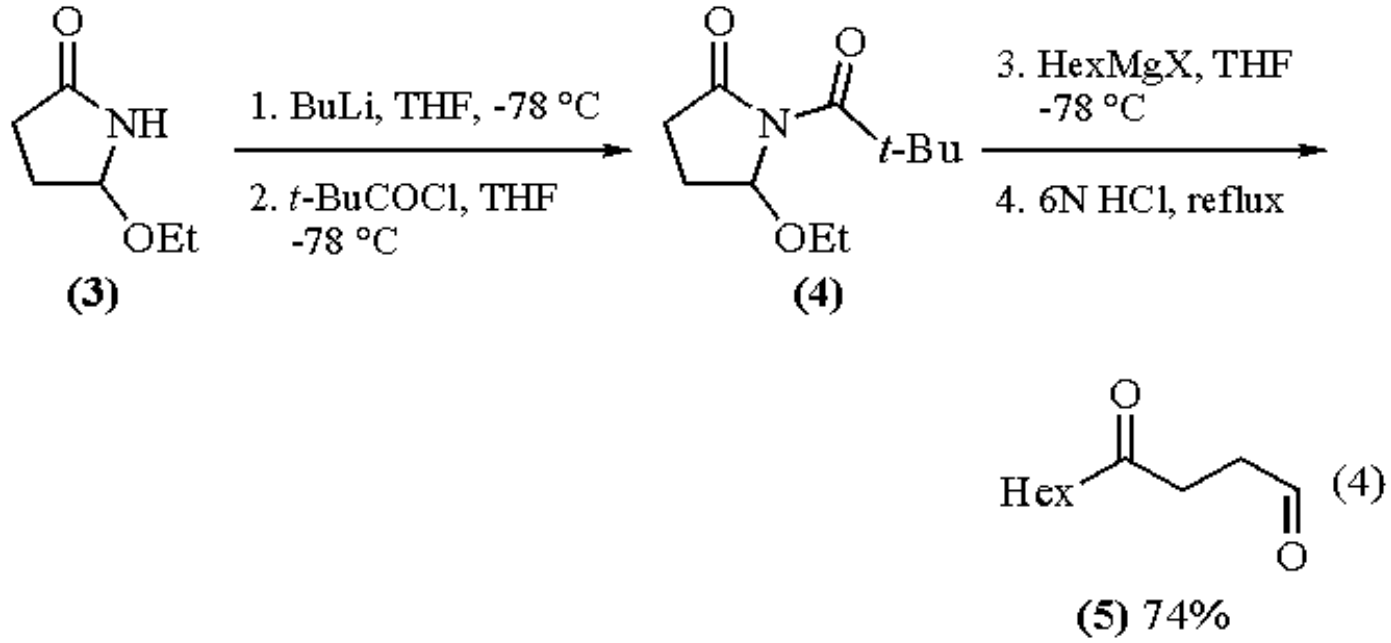

Peptide Synthesis.

Trimethylacetyl chloride has been used to synthesize peptidic bonds by the mixed anhydride method (eq 5).

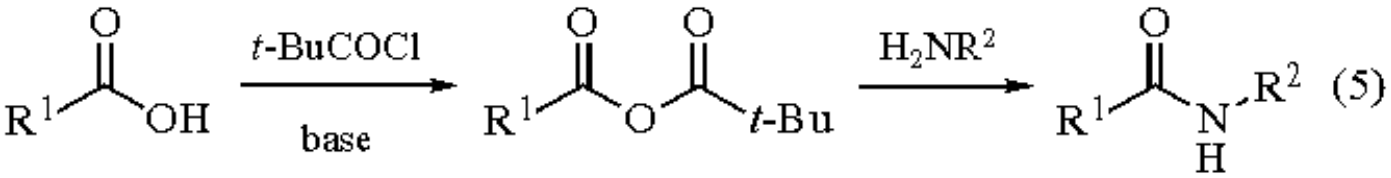

A comparison of a range of carboxylic acid chlorides showed trimethylacetyl chloride to be one of the most effective for peptide synthesis, though slightly inferior to diethylacetyl chloride.[3] The extent of racemization that occurred using various acyl chlorides has been studied and trimethylacetyl chloride was shown to give only a very small amount of racemization.[9] Trimethylacetyl chloride has been used in the synthesis of adrenocorticotrophic hormone.[10,11]

Selective Protection of Polyols.

The protection (as the trimethylacetate) of a primary alcohol in the presence of two secondary alcohols has been achieved in high yield using 1 equiv of trimethylacetyl chloride (eq 6).[4]

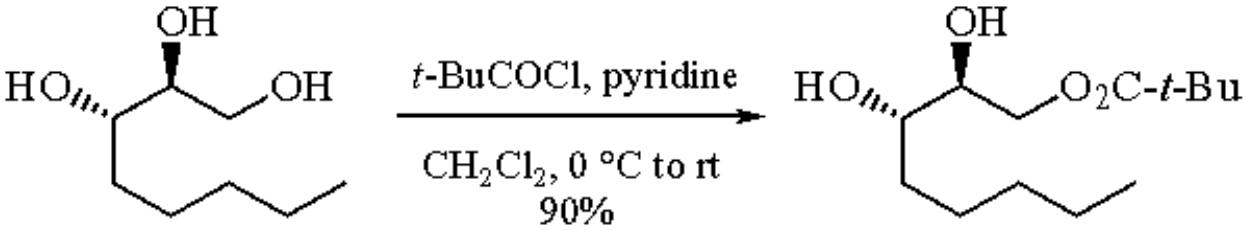

(6)

The selective protection of a less hindered primary alcohol in the presence of another more hindered one has also been achieved (eq 7).[12]

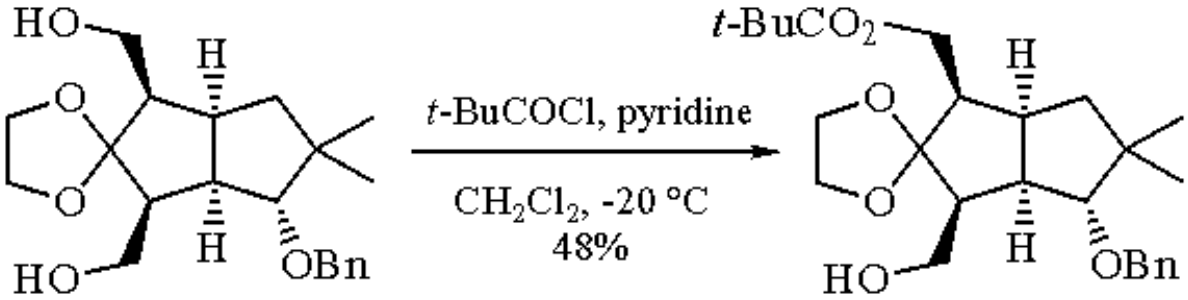

(7)

Sucrose has been selectively protected using trimethylacetyl chloride. By varying the conditions a variety of penta-, hexa-, and heptatrimethylacetates was obtained.[13]

---

1. Oku, A.; Harada, T.; Kita, K. *TL* **1982**, *23*, 681.
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Trimethylaluminum[1]

Me_3Al

[75-24-1] · C_3H_9Al · Trimethylaluminum · (MW 72.10)

(Lewis acid with methylation ability;[2-8] can effect useful C-C bond forming reactions including carboalumination,[14] methylenation,[15,16] and cyclopropanation;[17] can serve as a precursor to various sophisticated Lewis acids[27] or chiral catalysts[28,29])

Physical Data: mp 15 °C; bp 127 °C; *d* 0.743 g cm^{-3} (30 °C).

Solubility: freely miscible with saturated and aromatic hydrocarbons; reacts violently with H_2O and protic solvents.

Form Supplied in: clear colorless liquid; widely available as a neat liquid in a stainless container or 1-2 M solution in hydrocarbon solvents (hexane, heptane, toluene).

Analysis of Reagent Purity: brochures from manufacturers describe an apparatus and method for assay.

Handling, Storage, and Precautions: indefinitely stable under an inert atmosphere. Neat trimethylaluminum or concentrated solutions are highly pyrophoric. Solutions that are more dilute are not pyrophoric and are safer to handle. The nonpyrophoric limits are 11 wt % in hexane and 14 wt % in heptane. Halogenated hydrocarbons should be avoided because of possible explosive reactions sometimes observed for mixtures of CCl_4 and organoaluminums.

Methylation.

The Lewis acidity of Me_3Al has been used to activate electronegative atoms, such as oxygens, halogens, and other functional groups. It also methylates the resulting electrophilic species. Bridgehead methylation of bicyclo[2.2.2]octyl bromide (eq 1)[2a] and regioselective methylation of terpene derivatives[3a] are early examples that show these features. More recent examples include methylation of bromododecahedrane[2b] and unusual aromatic substitutions of *N*-hydroxyaniline derivatives (eq 2).[3b] Substitution reactions of glycosyl fluorides,[4] benzyl or glycal acetates,[5a,b] and sulfonyl groups[6] at activated positions can be effected with Me_3Al (eqs 3-6).

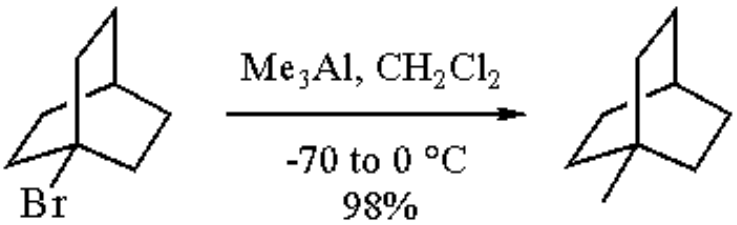

(1)

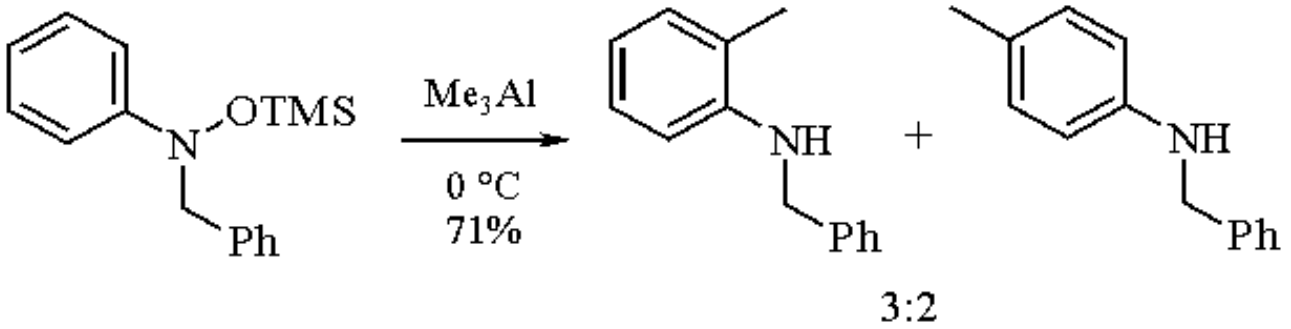

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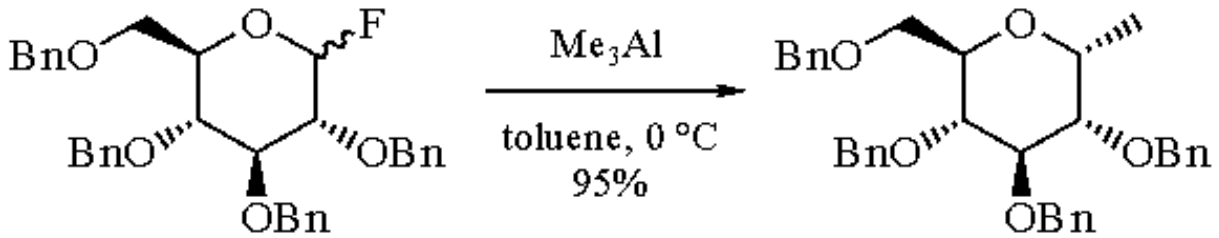

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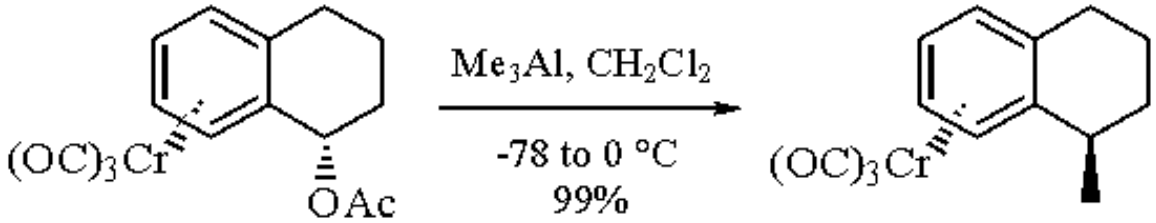

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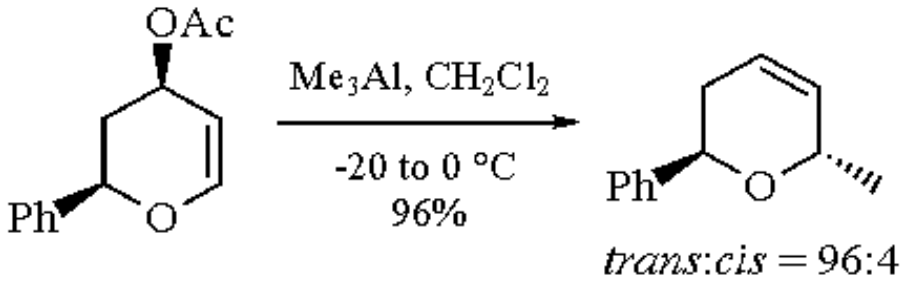

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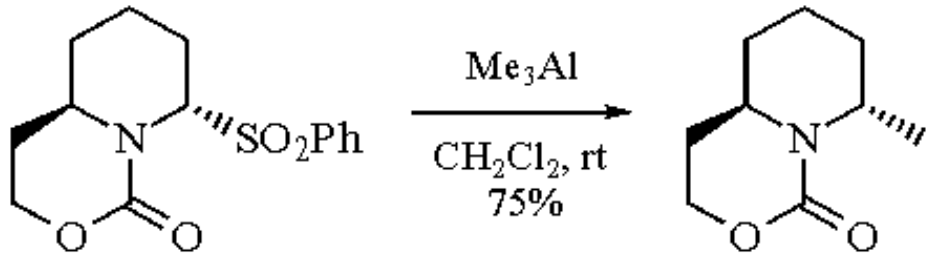

(6)

Boron Trifluoride Etherate alters the reactivity of γ- or δ-lactols toward Me_3Al (eq 7).[7] Me_3Al traps isocyanates generated from certain sigmatropic rearrangements (eq 8).[8]

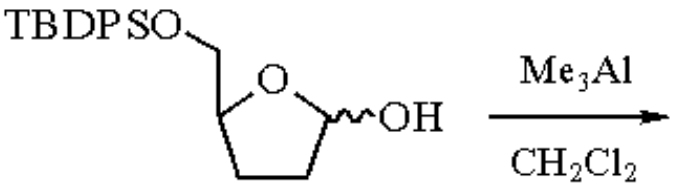

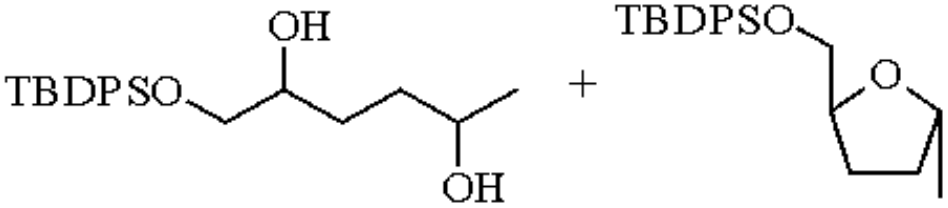

(7)

without $BF_3 \cdot OEt_2$	67%	0%
with $BF_3 \cdot OEt_2$	0%	75%
		trans:*cis* = 10:1

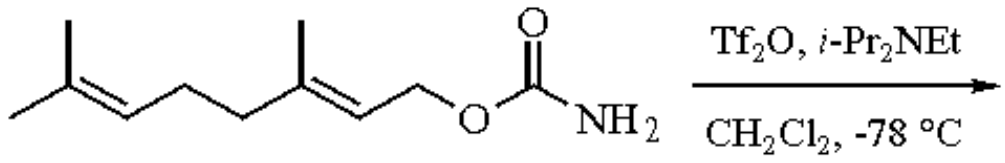

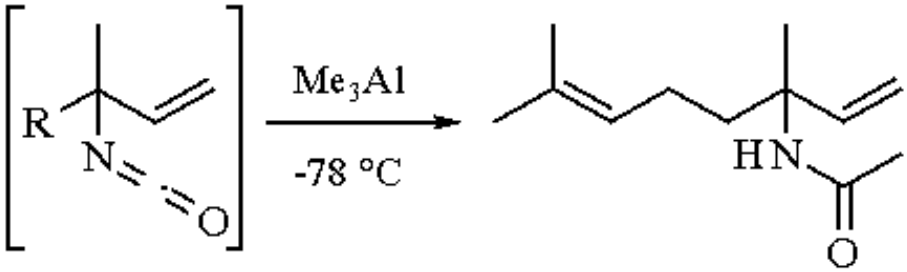

(8)

91%

In connection with the asymmetric Sharpless epoxidation, the regioselective cleavage of 2,3-epoxy alcohols and their derivatives has been well studied. In contrast to organocuprates, which provide 1,3-diols via C-2 attack, trialkylaluminiums give 1,2-diols via C-3 attack (eq 9).[9a,b] It should be noted that substrates with a phenyl group at C-3 undergo the methylation largely in retentive manner.[9c,d] ***n-Butyllithium*** catalyzes the regioselective β-addition to α- and β-alkoxy epoxides (eq 10).[10a,b] This regioselectivity also holds for epoxy acids (eq 11).[9d] A mixed reagent, Me_3Al and water (5:3), effects the regioselective and stereospecific methylation of γ,δ-epoxy acrylates (eq 12).[10c,d]

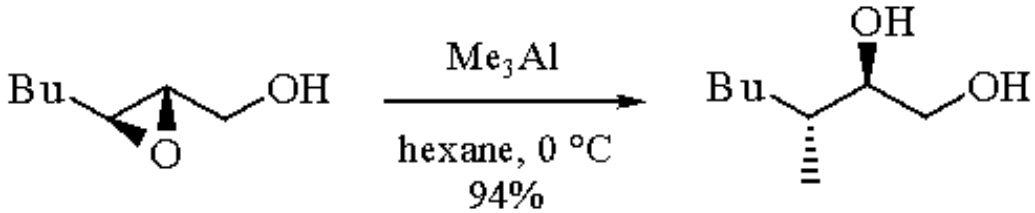

(9)

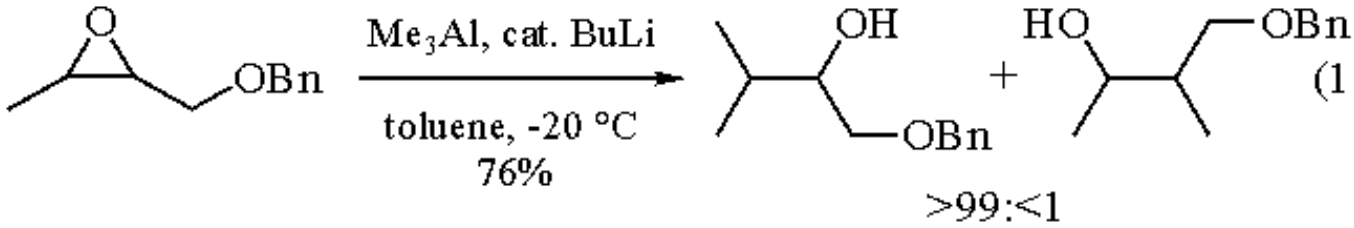

(10)

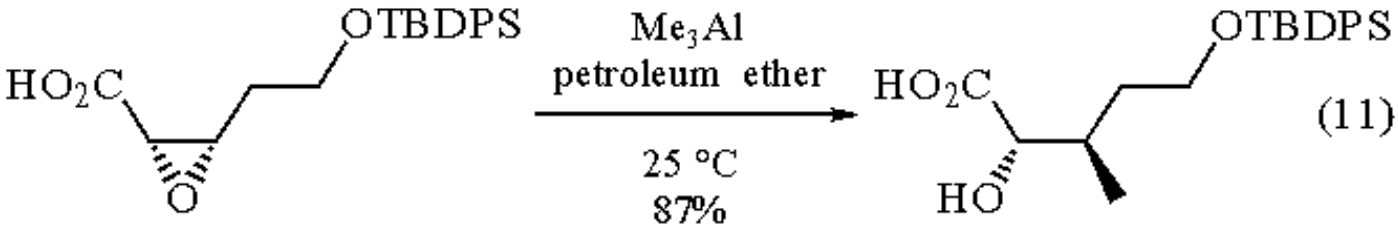

(11)

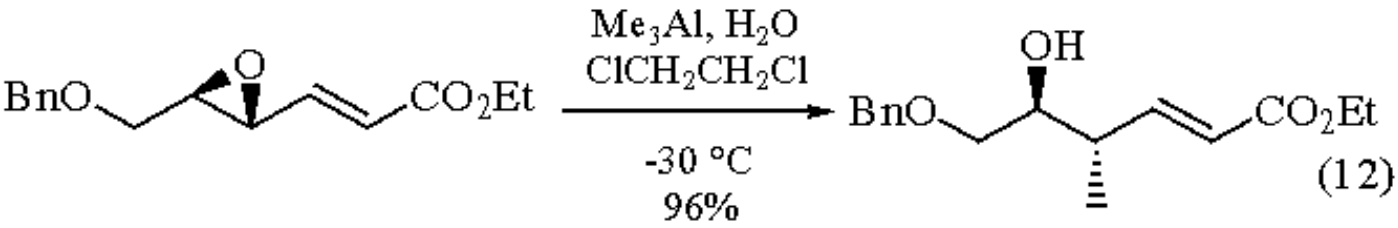

(12)

Asymmetric reactions via regioselective ring cleavage of chiral unsaturated acetals have been reported. The regioselectivity is sensitive to the solvent employed (eq 13).[11a,b] Recent developments have been described by Ishihara et al.[11c,d]

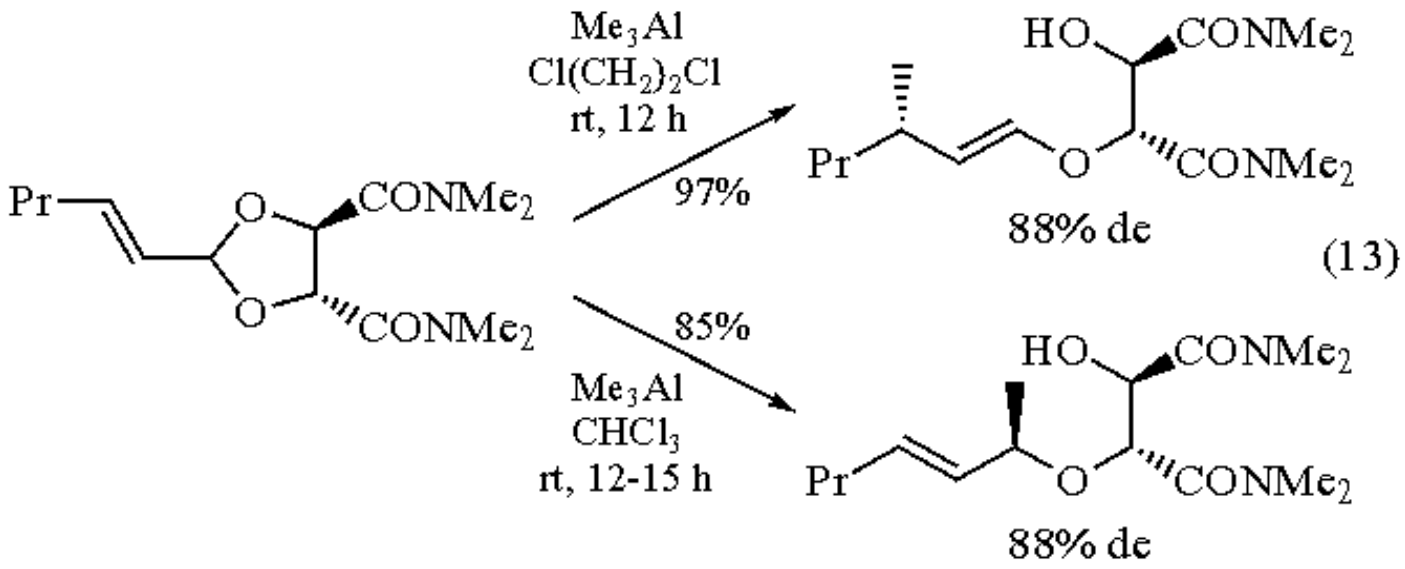

Cross couplings of organoaluminums with vinyl halides,[13b] enol phosphates,[12a] carboxylic acid chlorides, and thioesters[12b,c] are achieved by employing Pd or Cu catalysts (eqs 14 and 15). Unsaturated *N*-acylsulfoximines[13a] or *C*-alkylated purine nucleosides are thus prepared (eq 16).[13b]

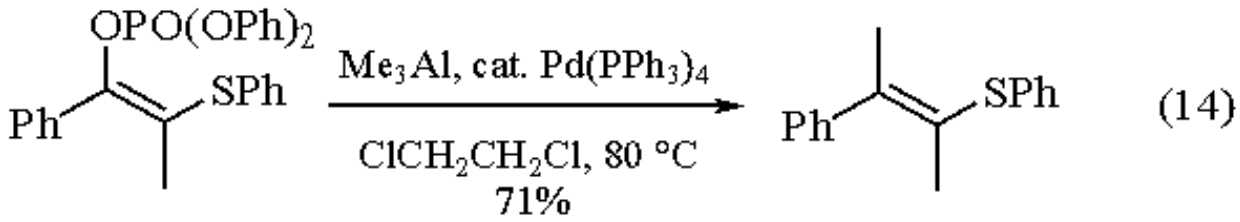

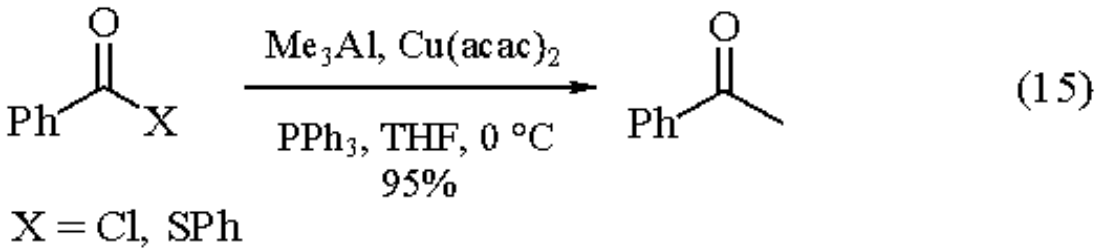

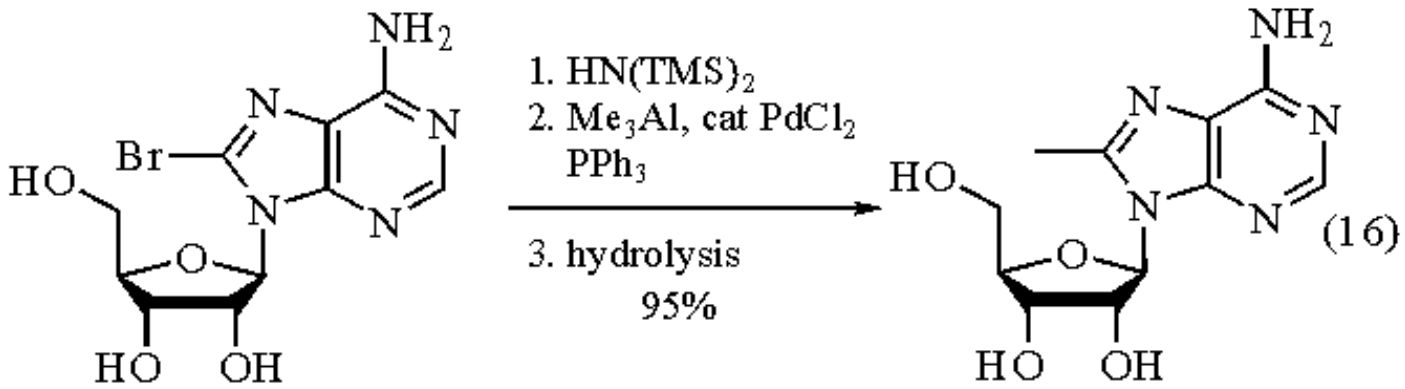

Other useful C-C bond formations using Me_3Al include the carboalumination of 1-alkynes. The procedure with ***Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)zirconium*** (eq 17) has broad applicability,[14a-c] and has been used in many natural product syntheses (eq 18).[14d] Direct manipulation of the alkenylalanes provides a stereoselective route to trisubstituted alkenes (eq 19).[14e,f]

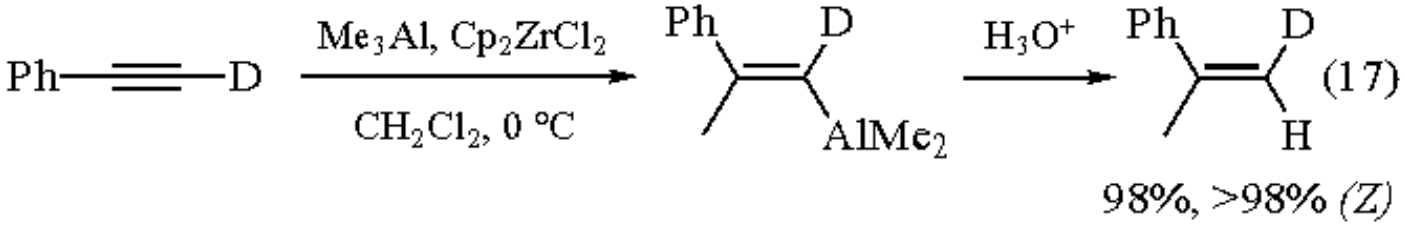

(17)

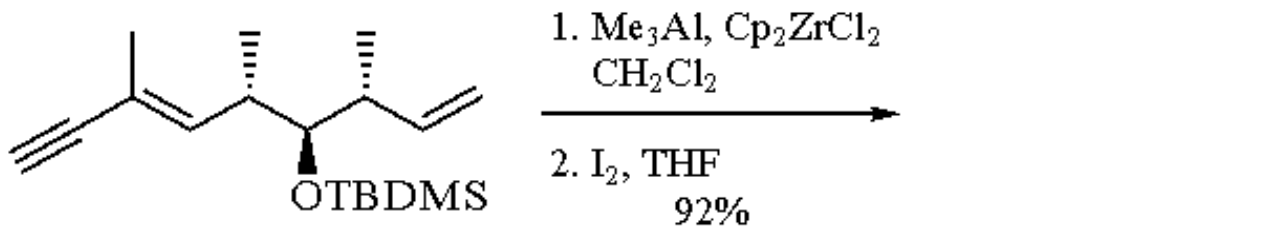

(18)

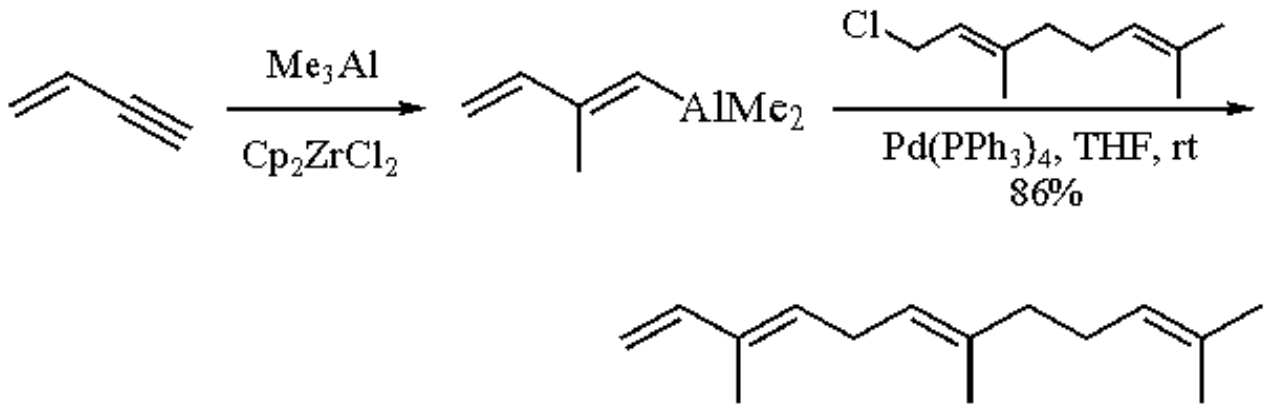

(19)

The Tebbe reagent (see μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***) is conveniently generated in situ by the reaction of ***Dichlorobis(cyclopentadienyl)titanium*** and Me_3Al, which, in contrast to the Wittig reaction, methylenates ester carbonyls to provide enol ethers (eq 20).[15] See also ***Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)titanium***. A triad reagent, ***Diiodomethane-Zinc***-Me_3Al, effects chemoselective methylenation of aldehydes (eq 21),[16] while the combination of CH_2I_2 and Me_3Al (or other organoaluminums) leads to cyclopropanation of alkenes (eq 22).[17] The regiochemical course of the latter reaction is markedly different from the Simmons-Smith reaction. Regioselective addition of polyhalomethanes to alkenes is induced by Me_3Al (eq 23).[18]

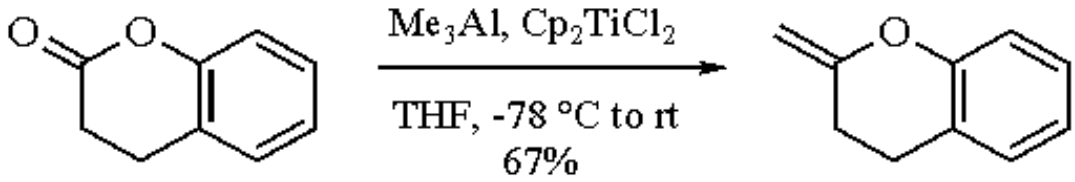

(20)

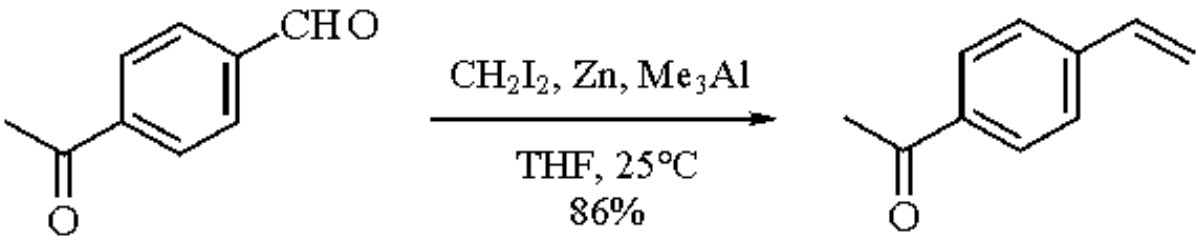

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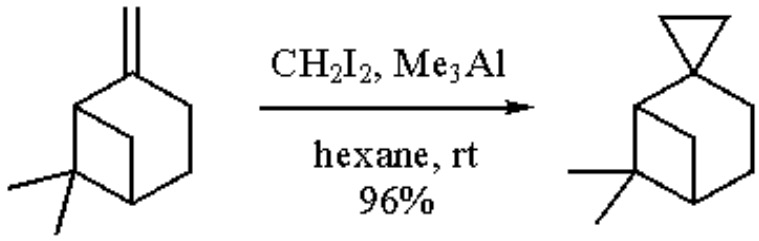

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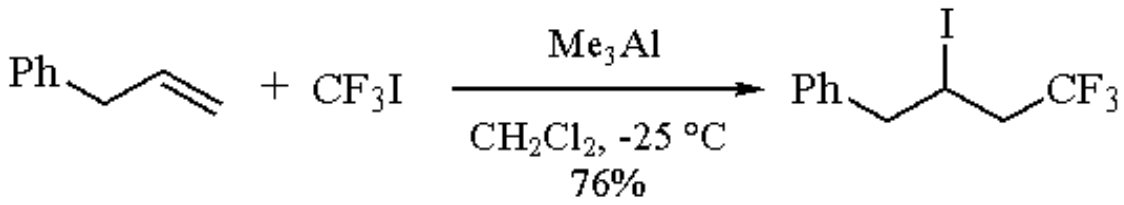

(23)

Carbon-heteroatom bond formation is often facilitated by the co-addition of Me_3Al. Aminolysis of esters is achieved by the action of amines or their hydrochlorides in the presence of Me_3Al (eq 24),[19a-c] the latter procedure being particularly useful when volatile amines are concerned (see ***Dimethylaluminum Amide***). The technique is also applicable to the synthesis of acid hydrazides.[19d] Selenoformamides are available from the corresponding formamides by reaction with $(Me_2Al)_2Se$, generated in situ from $(Bu_3Sn)_2Se$ (eq 25).[20] The corresponding tellurium chemistry works also. Me_3Al-LiSPh offers a tandem Michael-aldol approach to the oxahydrindene subunit of avermectins (eq 26).[21a]

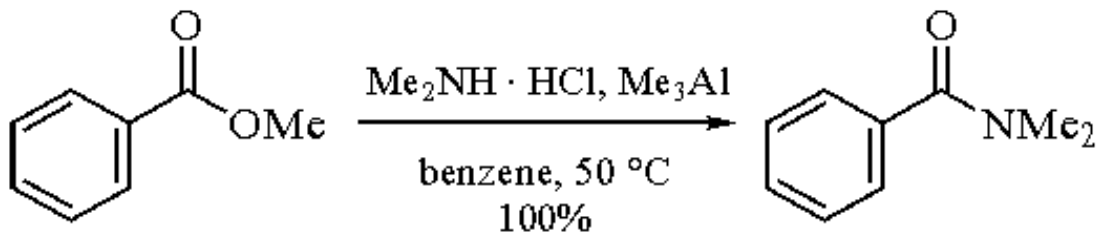

(24)

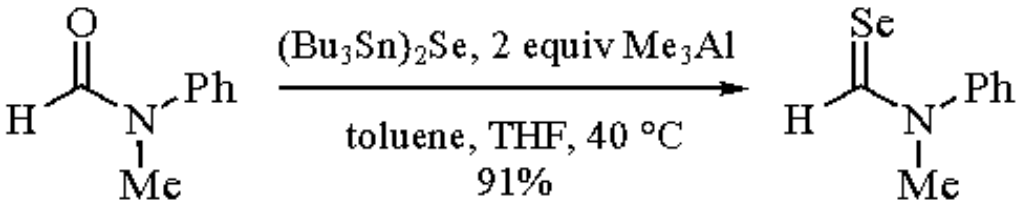

(25)

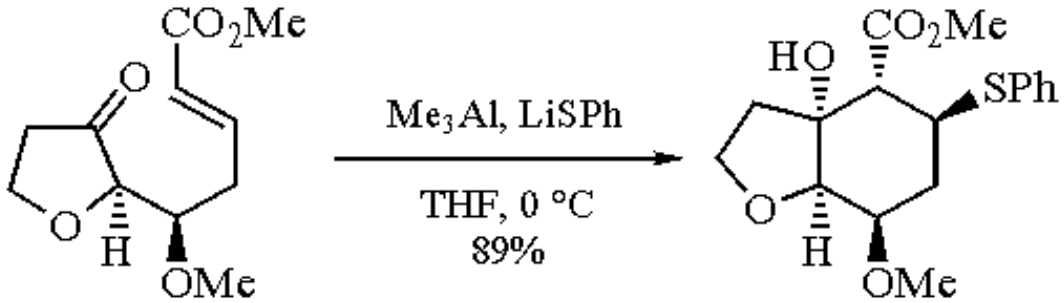

(26)

The steric course of reduction of cyclic imines is impressively reversed by a mixed reagent, ***Lithium Aluminum Hydride***-Me_3Al (eq 27).[21b]

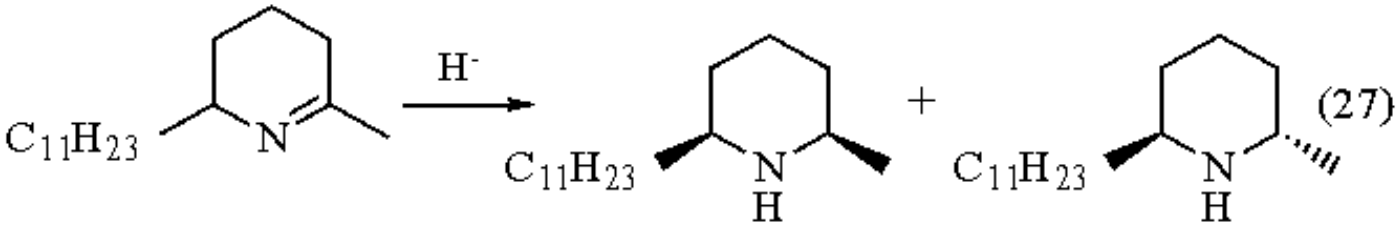

DIBAL, CH_2Cl_2	>99:<1
$LiAlH_4$-Me_3Al, THF	5:95

Rearrangements.

Allyl vinyl ethers undergo [3,3]-sigmatropic rearrangements in the presence of Me_3Al, which also captures the resulting aldehyde (eq 28).[22] In contrast, use of ***Triisobutylaluminum*** results in a primary alcohol.

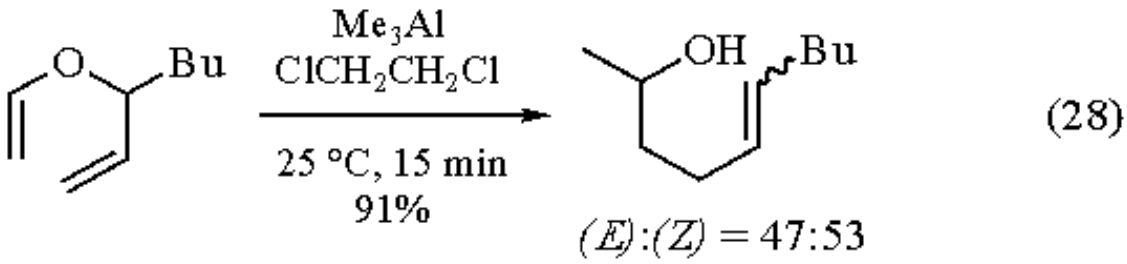

Me_3Al effects sequential Beckmann rearrangement-methylation of oxime sulfonates. The rearranged imines can be stereoselectively reduced with ***Diisobutylaluminum Hydride*** to give amines (eq 29, cf. eq 27).[23a-c] Related alkylative ring enlargement[24] or alkylative Beckmann fragmentation[23d] reactions are also known (eqs 30 and 31).

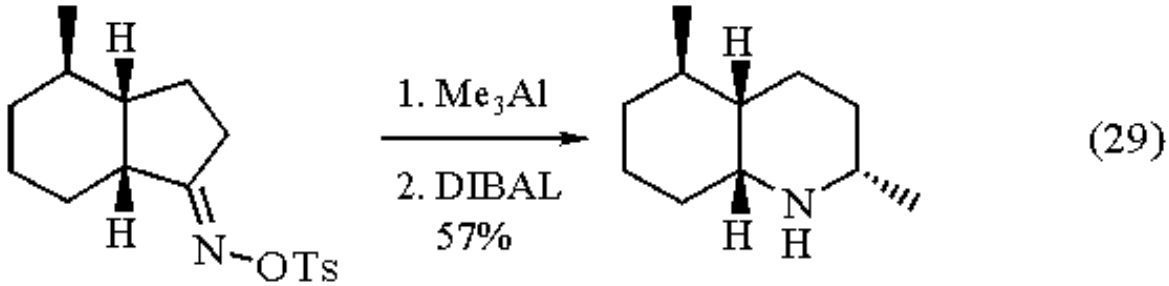

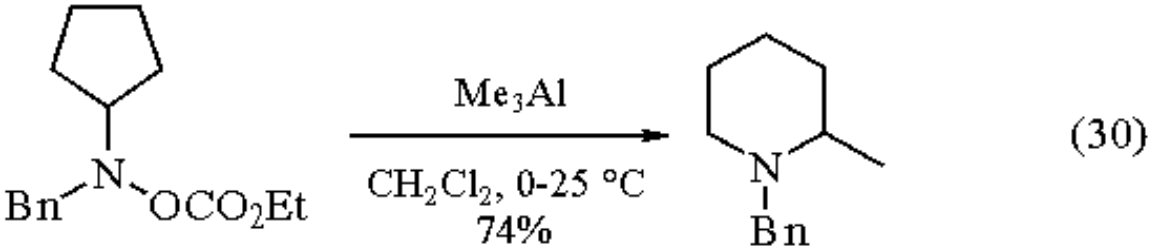

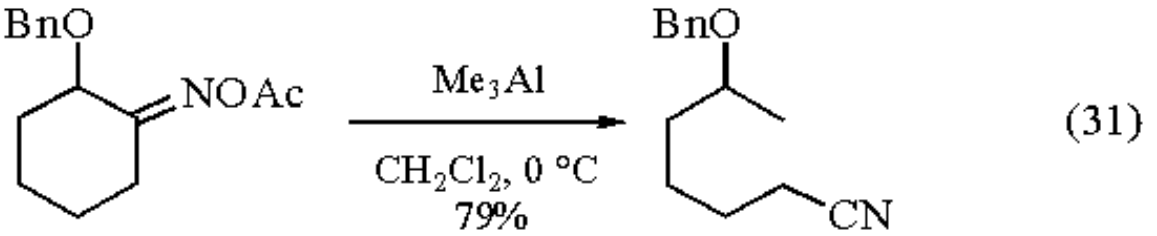

β-Hydroxy methanesulfonates or *N*-nitrosulfoximines have been activated by Me_3Al to induce asymmetric pinacol-type rearrangement (eq 32)[25] or carbocyclization reactions (eq 33).[26]

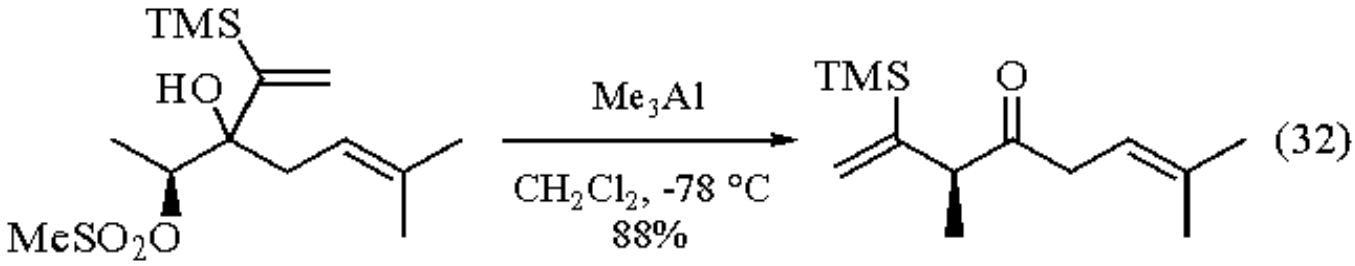

(32)

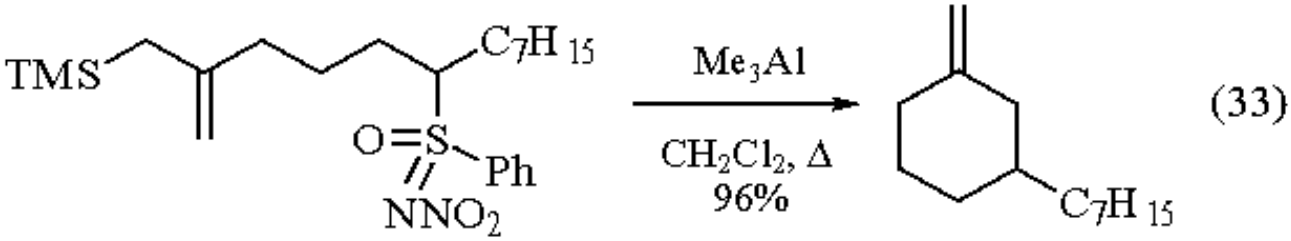

(33)

Lewis Acid.

Me_3Al serves as the precursor to various sophisticated Lewis acids with different acidities, such as $MeAl(OTf)_2$[26] and $MeAl(OC_6F_5)_2$,[11c,d] or other acids with unique spatial environments (eq 34).[27] Chiral Lewis acids, such as (**1**)[28] and (**2**),[29] serve as catalyst for asymmetric Diels-Alder reactions. The catalyst generated from (**3**) and Me_3Al has been used for asymmetric cyanohydrin synthesis.[30]

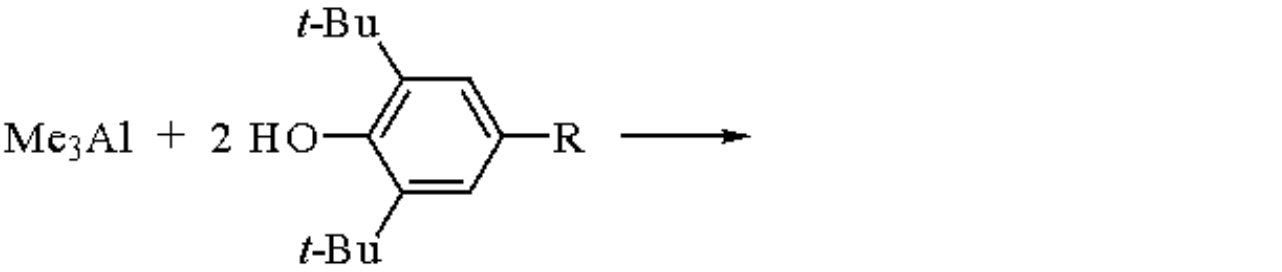

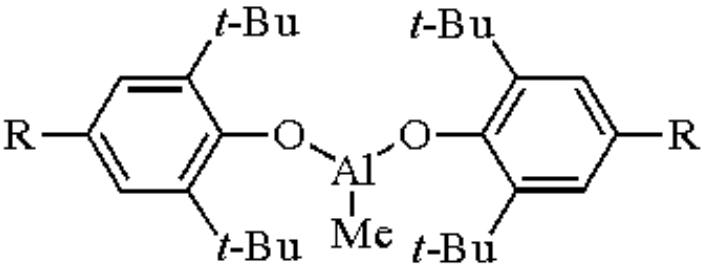

(34)

MAD R = Me
MAT R = *t*-Bu
MABR R = Br

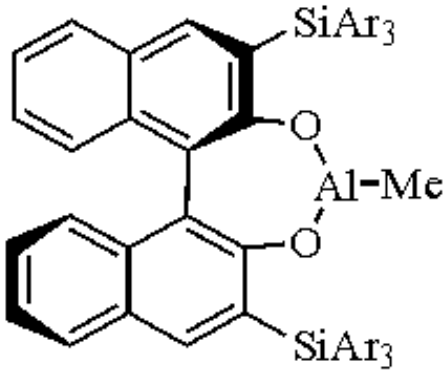

(1)

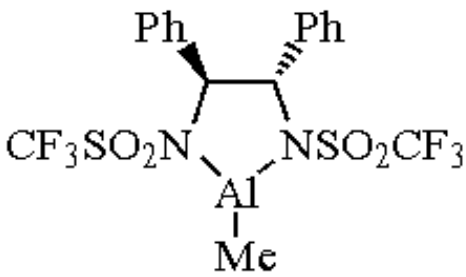

(2)

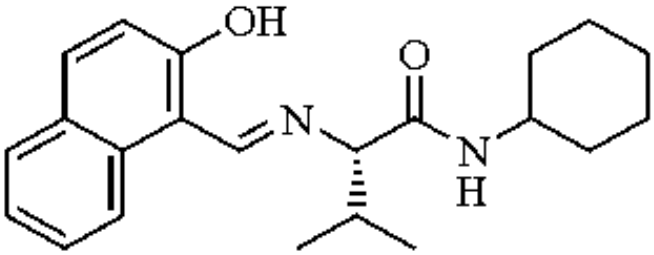

(3)

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Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)titanium

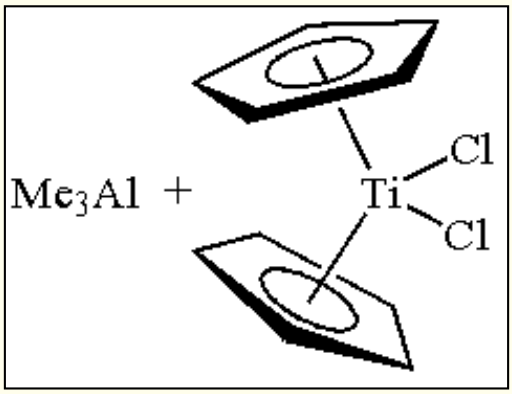

(Me_3Al)

[75-24-1] · C_3H_9Al · Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)titanium · (MW 72.10) (Cl_2TiCp_2)

[1271-19-8] · $C_{10}H_{10}Cl_2Ti$ · Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)titanium · (MW 248.98)

(carbometallation of alkynes and 1-metalloalkynes; conversion of monosubstituted alkenes to 1,1-disubstituted alkenes; preparation of the Tebbe reagent)

Physical Data: Me_3Al: bp 125 °C; *d* 0.752 g cm^{-3}. Cl_2TiCp_2: mp 287-289 °C; *d* 1.600 g cm^{-3}.

Form Supplied in: Me_3Al: liquid available neat or as solution in hexanes or toluene. Cl_2TiCp_2: bright-red crystals. Both are commercially available.

Preparative Methods: this reagent is obtained by mixing the two components.

Handling, Storage, and Precautions: Me_3Al is a very pyrophoric compound. It must be handled under an inert atmosphere.

Controlled Carbometallation of Alkynes.

The reaction of diphenylacetylene with a 1:1 mixture of ***Trimethylaluminum*** and ***Dichlorobis(cyclopentadienyl)titanium***, in 1,2-dichloroethane at 22 °C, produces, after 12 h, an alkenylmetal species, which after hydrolysis or iodinolysis gives (*Z*)-1,2-diphenylpropene or (*E*)-1-iodo-1,2-diphenylpropene, in 84 and 75% yields, respectively (eq 1).[1] Both products are >97-98% stereoisomerically pure. The current scope of this reaction is, however, much more limited than the corresponding methylmetallation with the ***Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)zirconium*** system.[2] Thus the reaction of 5-decyne produces 6-methyl-4,5-decadiene in 92% yield, rather than the expected 5-methyl-5-decene.[1] Presumably the carbometallated product undergoes dehydrometallation (eq 2). Terminal alkynes also react with Me_3Al-Cl_2TiCp_2, but the yields of carbometallated products are low.[1] Nevertheless, at least in some cases the Me_3Al-Cl_2TiCp_2 system is superior to the Me_3Al-Cl_2ZrCp_2 system. For example, the reaction of diphenylacetylene shown in eq 1 is not only faster but also higher yielding than the corresponding reaction with Me_3Al-Cl_2ZrCp_2.[1]

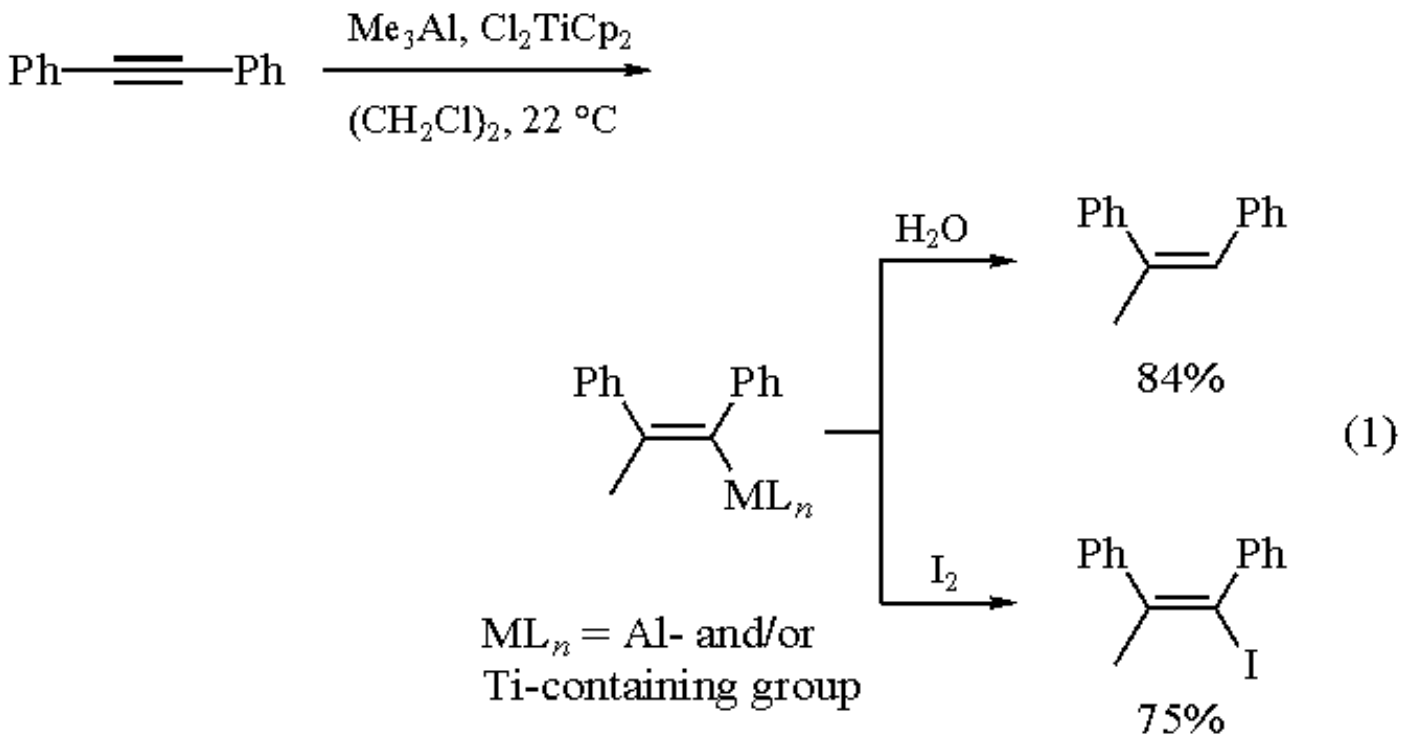

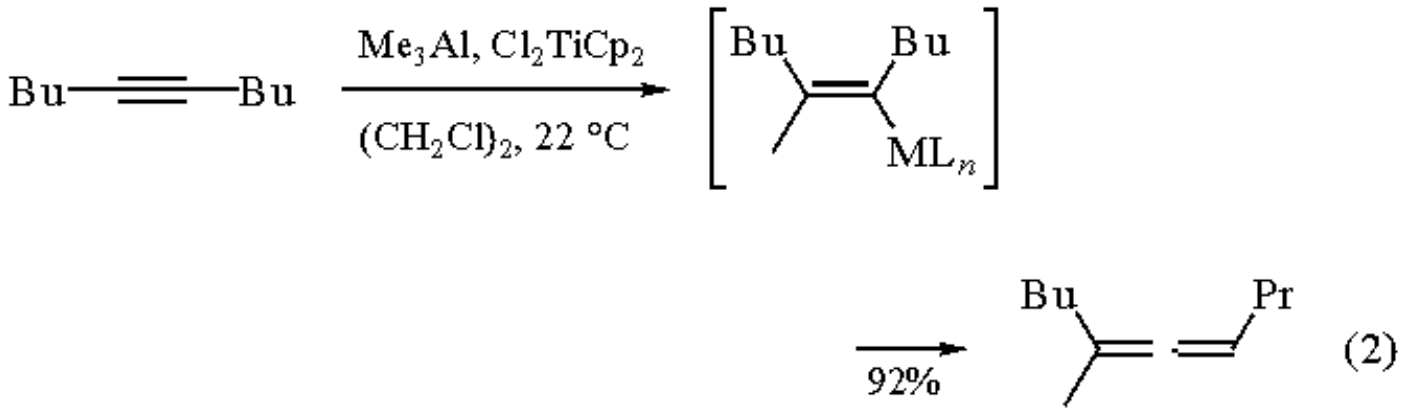

Carbometallation of 1-Metalloalkynes.

The reaction of 1-metalloalkynes, such as 1-octynylzinc chloride, 1-octynyldicyclohexylborane, and 1-octynyldimethylalane, with Me_3Al-Cl_2TiCp_2 proceeds smoothly and gives, after hydrolysis, 2-methyl-1-octene in 75, 81, and 84% yield, respectively (eq 3).[1] The reaction is >97-98% regioselective, and the intermediacy of 1,1-dimetalloalkenes is indicated by the formation of >95% pure 1,1-dideuterio-2-methyl-1-octene upon deuterolysis of (**1a**) and (**1c**). In the case of 1-octynyltrimethylsilane, the reaction produces an 80% yield of a 70:30 mixture of the desired methylmetallation product (**2a**) and an allene that can be derived from its regioisomer (**2b**) via dehydrometallation (eq 4).[1] When 1-pentynyldimethylalane is reacted with Me_3Al-Cl_2TiCp_2 (1:1) in CH_2Cl_2 at 23 °C, a 1,1-dimetalloalkene species (**3**) is formed in 90-100% yield. The reaction must involve addition of a Me-Ti bond to the alkyne, as the same compound can also be obtained by the reaction of the alkynylalane with preformed $Cl(Me)TiCp_2$.[3] Although (**3**) is formed as a single isomer, which is probably the (*E*) isomer, it undergoes a slow stereoisomerization to give a 60:40 mixture of (*E*) and (*Z*) isomers. The reaction of (**3**) with cyclohexanone or benzaldehyde gives the corresponding allenes in 83% and 67% yields, respectively (eq 5).[3]

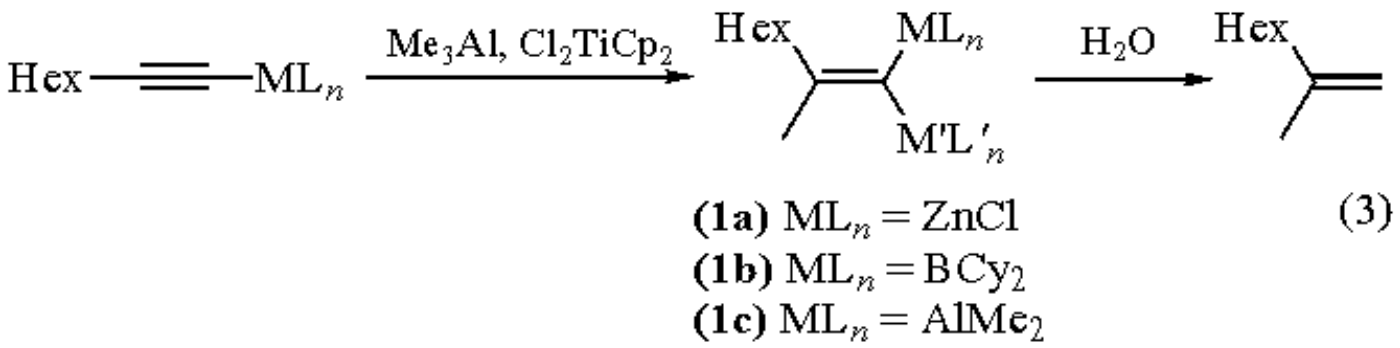

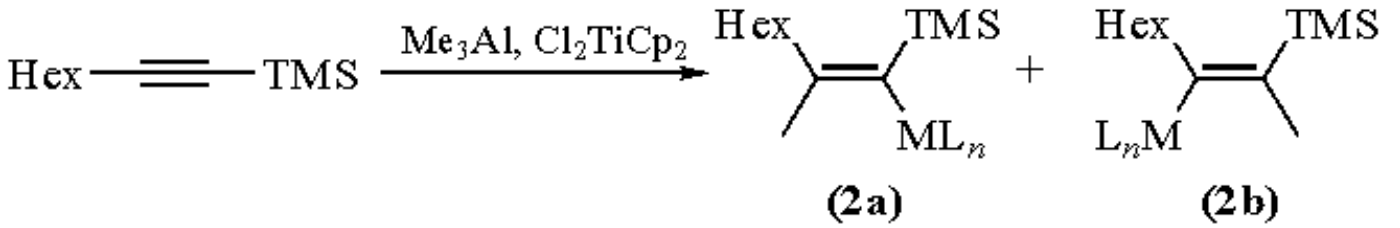

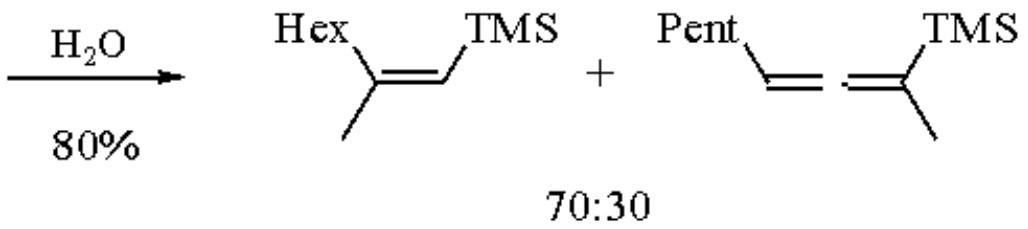

(4)

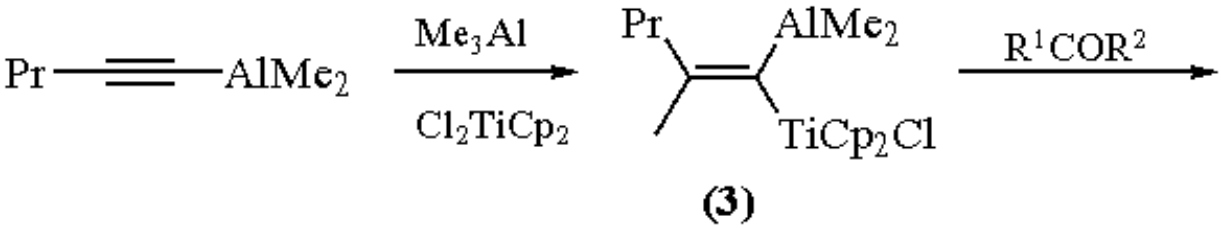

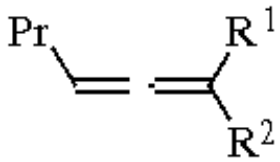

(5)

$R^1, R^2 = (CH_2)_5$, 83%

$R^1 = Ph, R^2 = H$, 67%

Reaction with Monosubstituted Alkenes.

Monosubstituted alkenes react with 1-2 equiv of a 1:1 mixture of Me_3Al and Cl_2TiCp_2 to give 2-methyl-1-alkenes in moderate to excellent yields (eq 6).[4] The reaction tolerates the presence of ester, hydroxy, and halogens such as Br, provided that these groups are not directly attached to the sp^2 carbon center. A speculative but reasonable mechanism of the reaction involves alkylation of Cl_2TiCp_2 with Me_3Al, addition of the Ti-Me bond to an alkene, and β-dehydrotitanation.

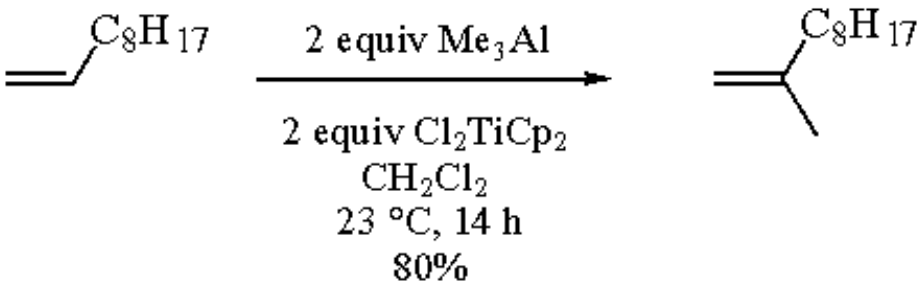

(6)

Preparation of the Tebbe Reagent.

The reaction of Me_3Al with Cl_2TiCp_2 mixed in a 2:1 ratio in toluene at rt for 2-3 d gives a titanium-aluminum reagent (**4**), commonly called the Tebbe reagent (see μ-***Chlorobis(cyclopentadienyl)(dimethylaluminum)***-μ-***methylenetitanium***), as reddish orange crystals in 80-90% yields (eq 7).[5] This complex may be isolated, stored at low temperatures, and used all under an inert atmosphere. Alternatively, it may be generated in situ and used in the same reaction vessel without purification.[6] The formation of (**4**) from 2 equiv of Me_3Al and Cl_2TiCp_2 is believed to involve the following sequence of reactions. The reaction of Me_3Al with Cl_2TiCp_2 gives $Me(Cl)TiCp_2$ and Me_2AlCl. Another molecule of Me_3Al reacts with $Me(Cl)TiCp_2$ to induce an α-hydrogen abstraction reaction assisted by Me_3Al complexed with $Me(Cl)TiCp_2$, which leads to the formation of (**4**) along with $ClAlMe_2$ and methane (eq 8).[7]

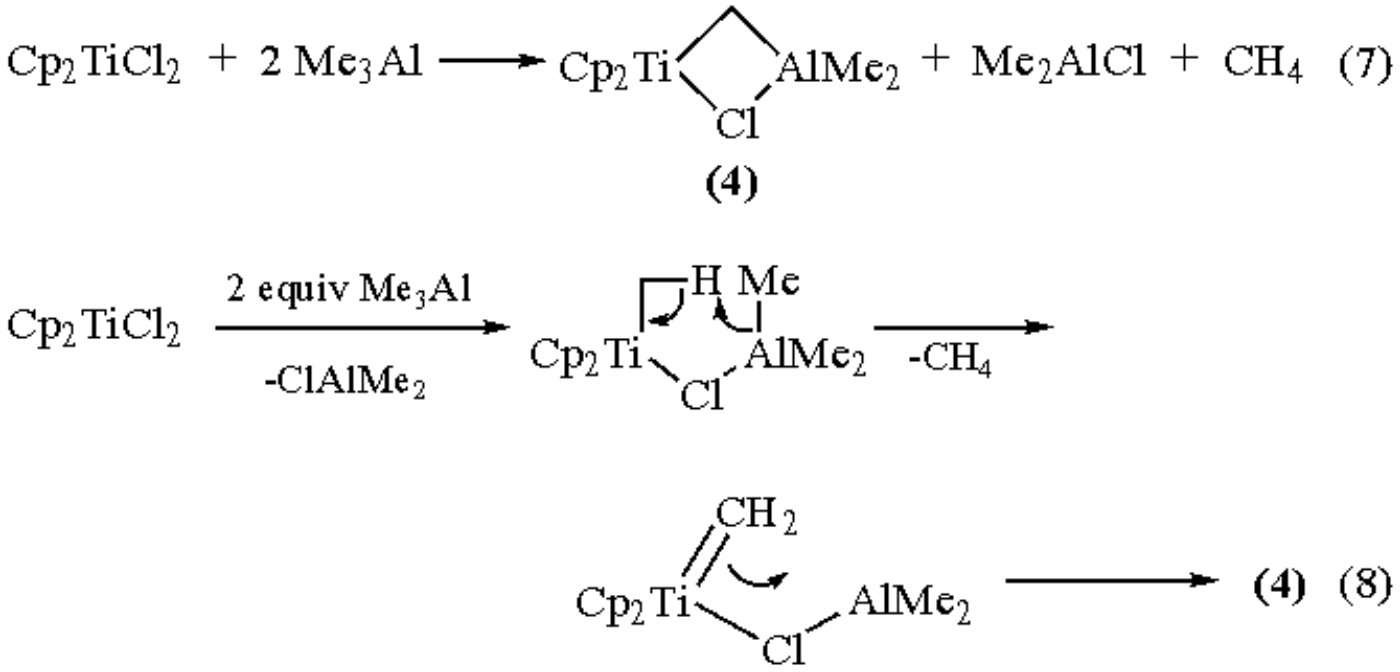

The Tebbe reagent reacts with a variety of compounds containing π-bonds, such as alkenes, alkynes, aldehydes, ketones, esters, and amides, as summarized in Scheme 1.[8]

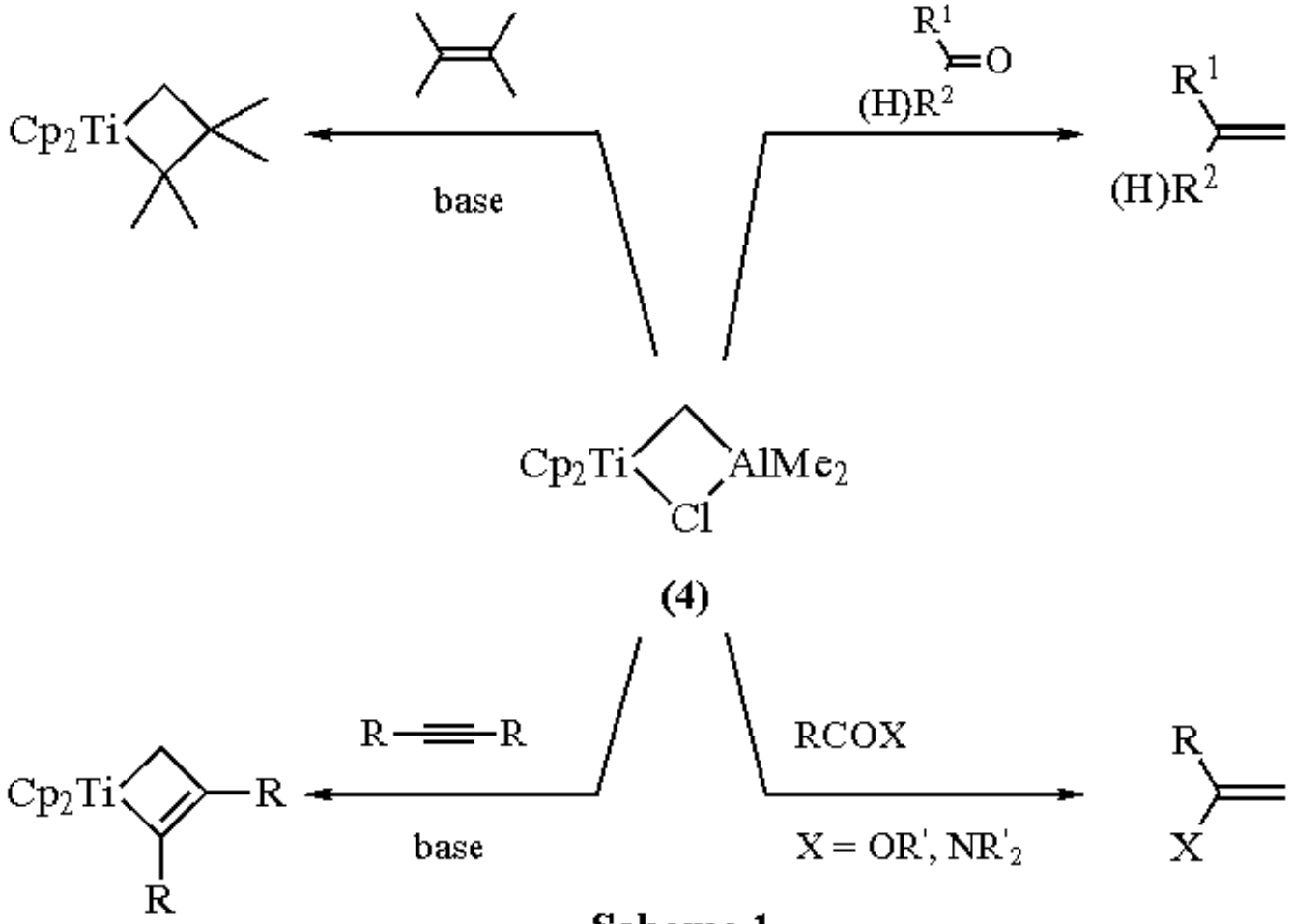

Scheme 1

The reactive species in these reactions is believed to be $Cp_2Ti{=}CH_2$, which can be generated by the interaction of (**4**) with a Lewis base, such as ***4-Dimethylaminopyridine*** or THF. Alternatively, 1,1-bis(η^5-cyclopentadienyl)-3,3-dimethyltitanacyclobutane (**5**), obtainable by the reaction of (**4**) with isobutylene (eq 9),[9] and even Cp_2TiMe_2[10] can serve as sources of $Cp_2Ti{=}CH_2$.

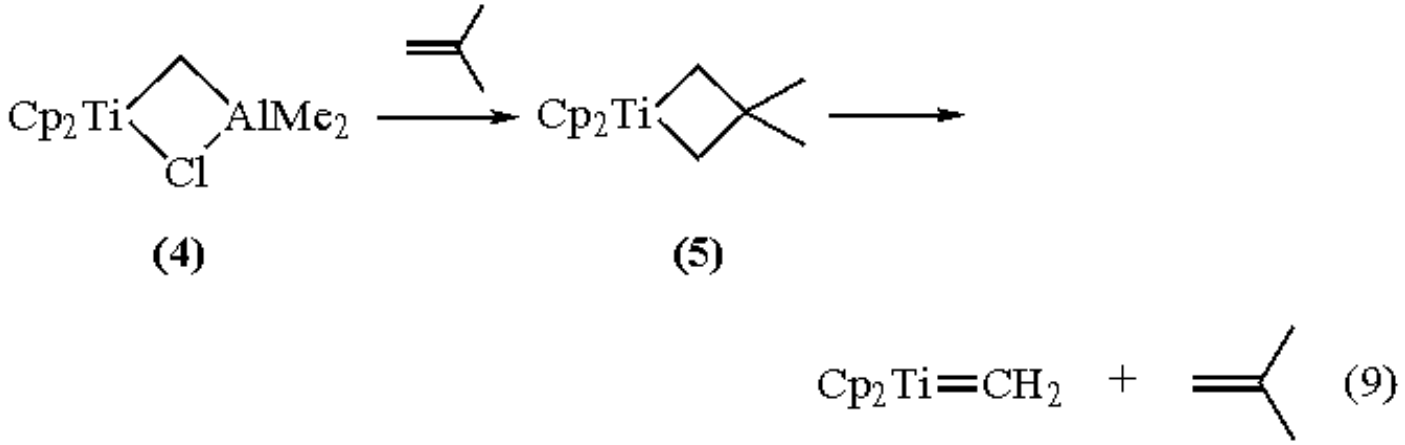

The reaction of diphenylacetylene with (**4**) to give (**6**) (eq 10)[11] is noteworthy in view of the fact that the reaction of the same alkyne with freshly mixed Me_3Al-Cl_2TiCp_2 gives the methylmetallation product (eq 1).

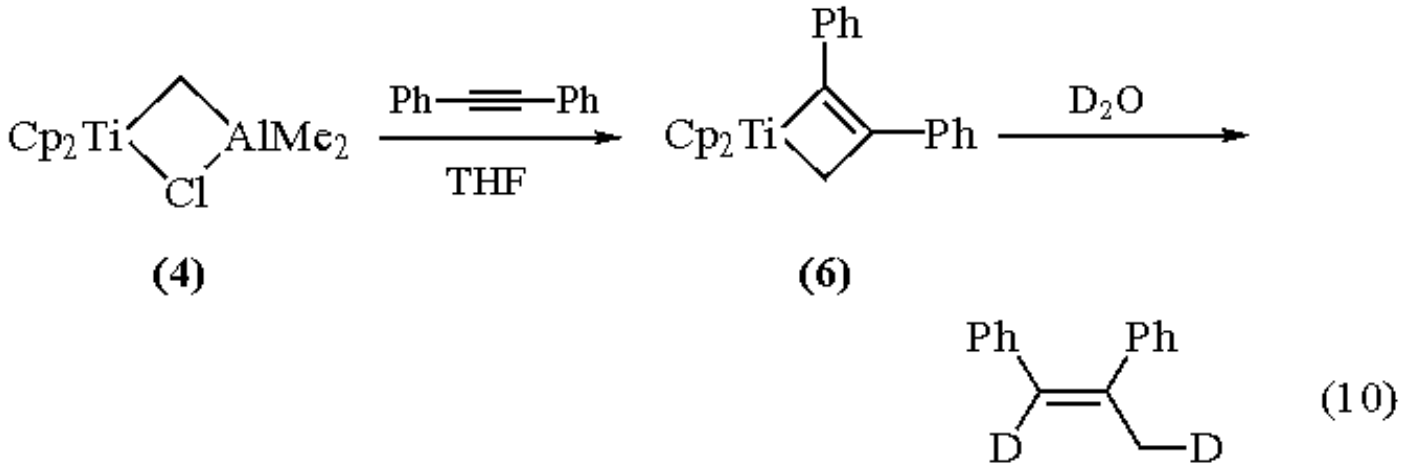

The methylenation of aldehydes and ketones with (**4**) appears to be markedly superior to the Wittig reaction in cases where the carbonyl group is hindered.[12] The most noteworthy feature of the methylenation with (**4**) is that esters and amides, which are normally inert to the Wittig reagents, can be methylenated with (**4**).[13]

Use of Me_3Al-Cl_2TiCp_2 in the Ziegler-Natta Polymerization.

Polymerization of alkenes with Me_3Al-Cl_2TiCp_2 must have been attempted. However, the literature is virtually devoid of reports on such reactions. On the other hand, various other reagent systems consisting of methylaluminum and titanocene derivatives, such as Me_2AlCl-Cl_2TiCp_2, Me_3Al-Me_2TiCp_2-H_2O, and $(MeAlO)_n$-Me_2TiCp_2, have been employed in polymerizing ethylene and other alkenes.[14]

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Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)zirconium

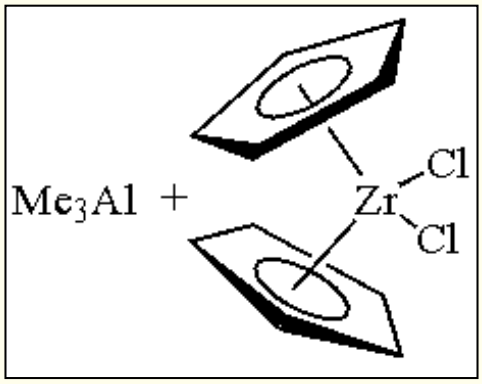

(Me_3Al)

[75-24-1] · C_3H_9Al · Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)zirconium · (MW 72.10) (Cl_2ZrCp_2)

[1291-32-2] · $C_{10}H_{10}Cl_2Zr$ · Trimethylaluminum-Dichlorobis(η^5-cyclopentadienyl)zirconium · (MW 292.32)

(regioselective and stereoselective methylalumination of alkynes; regioselective carbometallation of metallated alkynes)

Physical Data: Me_3Al: bp 125 °C; *d* 0.752 g cm^{-3}. Cl_2ZrCp_2: mp 245 °C.

Form Supplied in: Me_3Al: liquid, available neat or as solution in hexanes or toluene. Cl_2ZrCp_2: colorless crystals. Both are commercially available.

Preparative Method: obtained simply by mixing the two components.

Handling, Storage, and Precautions: Me_3Al is extremely pyrophoric and must be used and stored under an inert atmosphere of N_2 or Ar. Cp_2ZrCl_2 may be handled in air, but it appears advisable to avoid extensive exposure to air, moisture, and light. Use in a fume hood.

NMR Behavior.

The ^1H NMR spectrum of a mixture of ***Trimethylaluminum*** and ***Dichlorobis(cyclopentadienyl)zirconium*** (2:1 ratio) in 1,2-dichloroethane at 30 °C, the usual conditions under which its reactions are carried out, exhibits two broad signals (half width = 4 Hz) at δ -0.31 and 6.40 ppm. When this mixture is quenched with THF (2 equiv), the high-field Me signal splits into three, at δ 0.25, -0.75, and -0.95, while the downfield Cp signal splits into two, at δ 6.45 and 6.22. Analysis of these signals indicates that the THF-quenched mixture consists of Cl_2ZrCp_2, $Cl(Me)ZrCp_2$, $Me_3Al.THF$, and $Me_2AlCl.THF$.[1-3] Thus, under the reaction conditions, Me_3Al and Cl_2ZrCp_2 undergo Me-Cl exchange, which is rapid on the NMR timescale, to form $Cl(Me)ZrCp_2$ (eq 1).

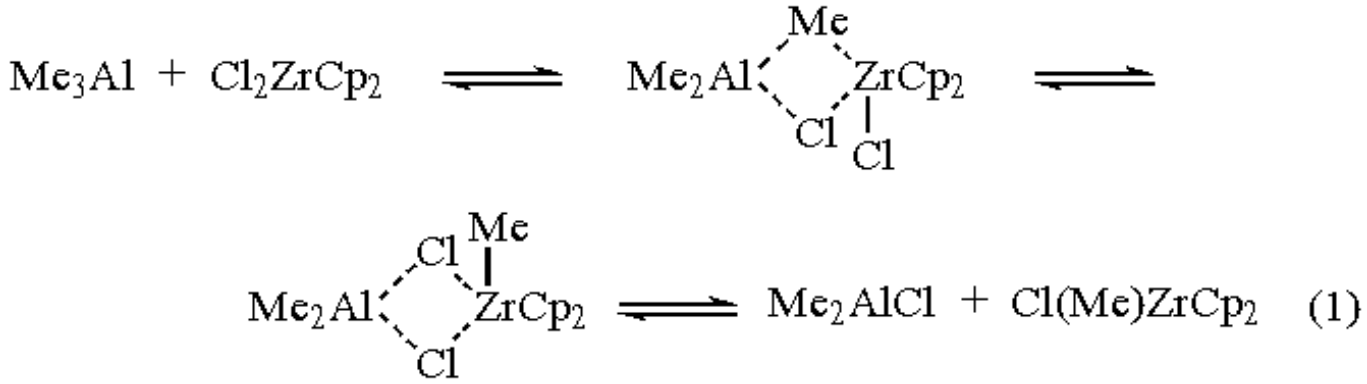

Controlled Methylalumination of Alkynes.

Controlled carbometallation of alkynes provides a very selective and efficient route to trisubstituted alkenes, many of which are important building blocks of a wide variety of natural products, especially those of terpenoid origin.[4] Alkynes react with organoalanes to give carbometallation products. However, with terminal alkynes, metallation of the terminal carbon atom is the major pathway, and the regioselectivity of the carbometallation product, obtained in generally poor yields, is low.[5,6] With internal alkynes the reaction requires higher temperatures, at which the product of initial carbometallation competes with the trialkylalane for the alkyne.[6,7] The use of transition metal complexes in conjunction with the organoalane reagent leads to a dramatic improvement of the chemo- and regioselectivity of the carboalumination reaction. Negishi and co-workers have reported that alkynes react with an organometallic reagent obtained by mixing Me_3Al and Cl_2ZrCp_2 to give alkenyl metals in high yields.[1] The reaction is not complicated by the known hydrogen abstraction of terminal alkynes with organozirconium[8] or organoaluminum[5,6] compounds. Studies by NMR spectroscopy have indicated that the product of carbometallation is largely an organoalane. Therefore the reaction is catalytic with respect to zirconium. Indeed, the reaction of 1 equiv of phenylacetylene with 2 equiv of Me_3Al in the presence of 0.1 equiv of Cl_2ZrCp_2 for 12 h at 25 °C produces, after hydrolysis, α-methylstyrene in high yield.[1] The stereoselectivity of the reaction is excellent (>98 % *cis* addition) (eq 2), as is the regioselectivity in the cases of terminal alkynes (eqs 2 and 3).[1] A recent modification of the reaction conditions by using a stoichiometric amount of H_2O leads to a remarkable acceleration of the reaction.[9] Internal alkynes can also be stereoselectively methylaluminated in high yields (eq 4).[1]

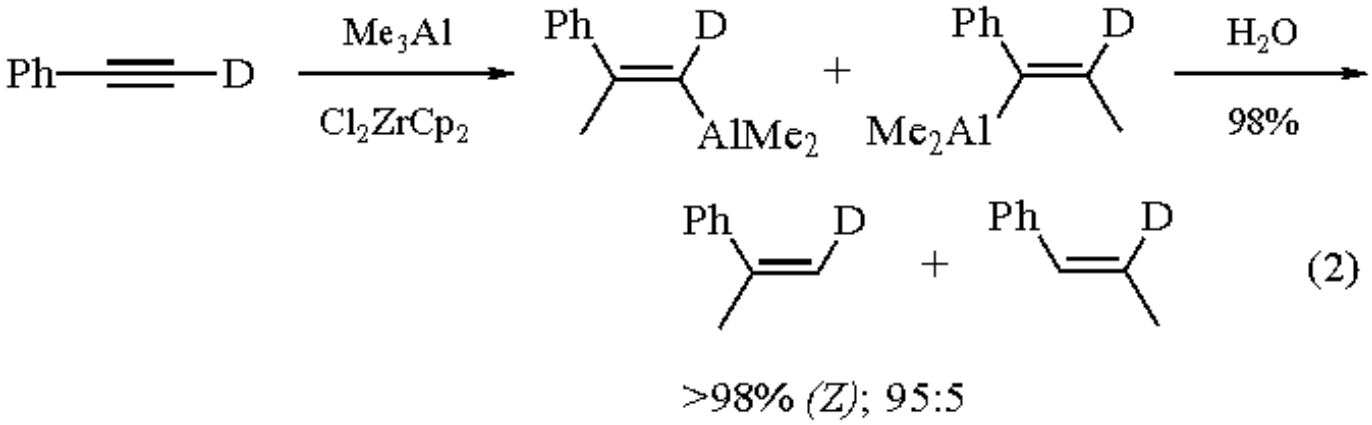

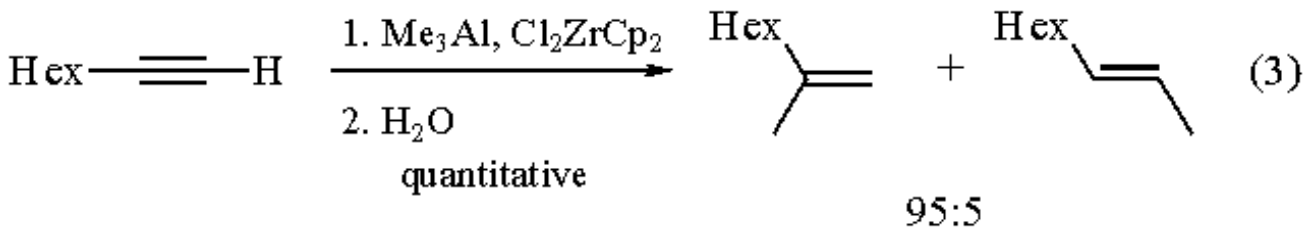

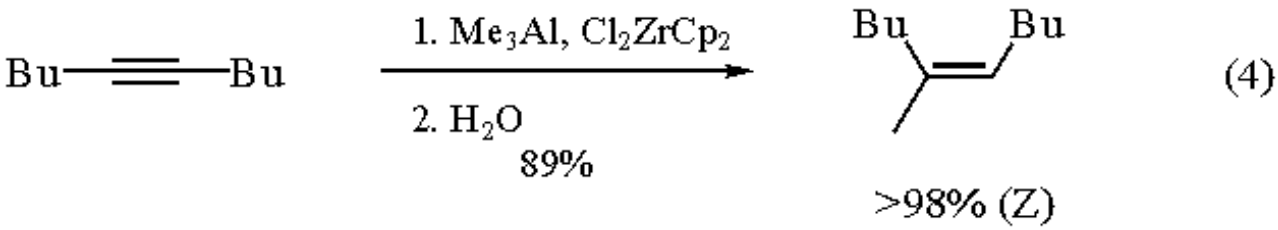

The Zr-catalyzed methylalumination can accommodate various heterofunctional groups such as OH, OTBDMS, SPh, I, and TMS.[10] Of particular synthetic utility are those alkynes containing heterofunctional groups in the propargylic or homopropargylic position. Interestingly,

and in marked contrast with some other known carbometallation reactions of propargyl and homopropargyl derivatives,[11] this reaction is very highly stereoselective (>98%) and regioselective (92-100%, except for the case of homopropargyl phenyl sulfide with which the reaction is 83% regioselective), the regioselectivity being essentially the same as that observed with simple terminal alkynes (eq 5). The yields of methylalumination products are generally in the 50-90% range. Table 1 illustrates the scope of this methylalumination reaction.

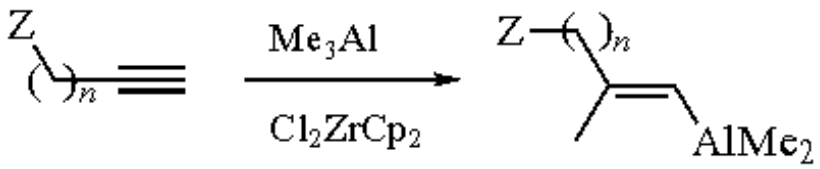

(5)

Z = OH, OTBDMS, SPh, I, TMS, etc.; n = 1 or 2

Table 1 Carboalumination of Terminal Alkynes Catalyzed by Zirconocene Dichloride

Alkyne	Major product	
	Yield (%)	Regioselectivity[a] (%)
$HC^{o}CC_6H_{13}$	³ 98	³ 95[1]
$HC^{o}CPh$	³ 98	³ 95[1]
$HC^{o}CCH{=}CH_2$	³ 86	³ 95[12]
$HC^{o}CC(Me){=}CH_2$	70	³ 95[13a]
$HC^{o}C(CH_2)_2CH{=}CMe_2$	72	³ 95[13a]
$HC^{o}CCH_2OH$	41	94[10a]
$HC^{o}CCH(OH)C_5H_{11}$	60	>98[10a]
$HC^{o}CCH_2SPh$	78	>98[10a]
$HC^{o}CCH_2SiMe_3$	63	³ 95[10b]
$HC^{o}C(CH_2)_2OH$	87	94[10a]
$HC^{o}C(CH_2)_2I$	74	>98[10a]
$HC^{o}C(CH_2)_2SPh$	78	83[10a]

[a] The major regioisomer is (*E*)-$R^1(Me)C{=}CHAlR^2_2$, and the stereoisomeric purity in each case is ³ 98%.

From the viewpoint of synthetic applications, alkenylalanes are very useful reagents. They react with a wide variety of electrophiles, and the C-Al bond can be readily converted into C-X (X = H, D, halogen, Hg, B, Zr, Cu, C, etc.) with essentially complete retention of stereochemistry via protonolysis,[6] deuterolysis,[6] halogenolysis,[13] transmetallation,[14] reactions with various carbon electrophiles such as $ClCO_2Et$, CO_2, $(CH_2O)_n$, $ClCH_2OMe$,[15] and epoxides[16] (preferably after ate complexation), and Pd- or Ni-catalyzed cross-coupling reactions.[12,17] Applications include syntheses of allylic or homoallylic alcohols,[15,16] conjugated dienes or enynes,[14c] 1,4-dienes,[12] and 1,5-dienes or enynes.[18] This methodology has been applied to the synthesis of various natural products such as geraniol,[15] farnesol,[18] monocyclofarnesol,[19] α-farnesene,[12] dendrolasin,[20] mokupalide,[20] vitamin A,[21] brassinolide,[22] milbemycin,[23] verrucarin,[24] udoteatrial,[25] and zoapatanol.[26]

The methylalumination of alkynes with Me_3Al-Cl_2ZrCp_2 appears to involve direct addition of a Me-Al bond, rather than a Me-Zr bond, to alkynes via a four-centered process which is facilitated by a $ZrCp_2$ species, as depicted in eq 6.[2] However, the reaction of 1-pentynyldimethylalane with either this reagent system or preformed $Cl(Me)ZrCp_2$ must involve direct addition of the Me-Zr bond, as depicted

in eq 7.[27]

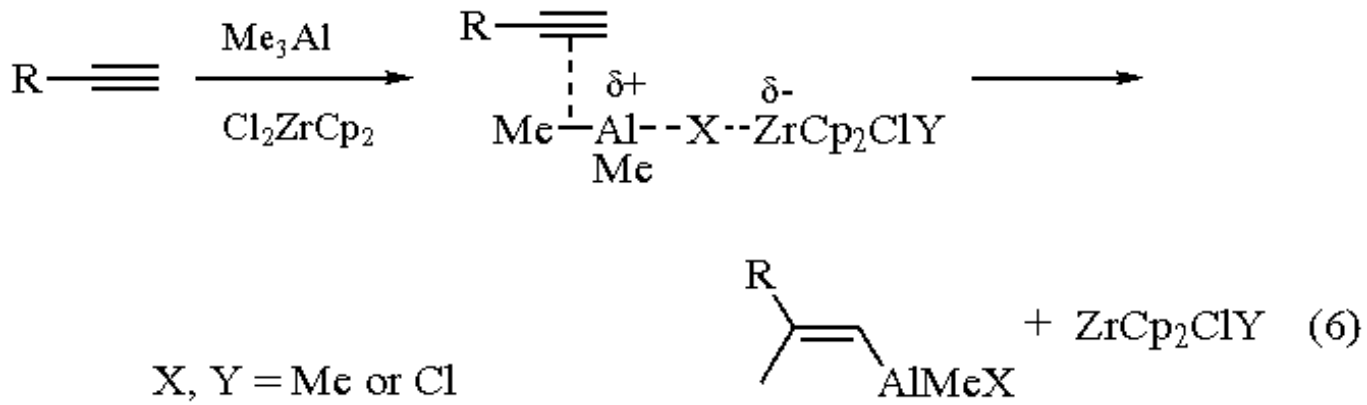

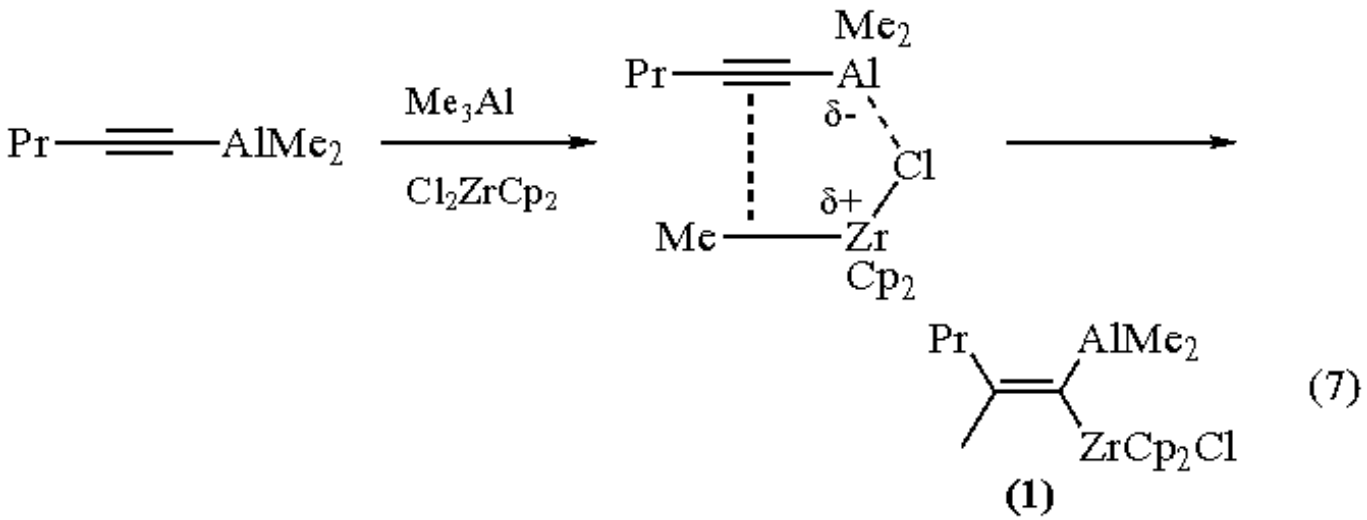

Methylalumination of 1-Metalloalkynes.

The methylmetallation reaction of 1-alkynes that are terminally metallated with $AlMe_2$ or $SiMe_3$ with Me_3Al-Cl_2ZrCp_2 is a highly regioselective process, leading to the formation of 1,1-dimetalloalkenes (eqs 7 and 8).[27,28] Whereas the reaction of alkynylsilanes gives the methylaluminated products (the reaction can proceed with a catalytic amount of Cl_2ZrCp_2),[28] that of alkynyldimethylalanes is a methylzirconation reaction which can also be achieved by using preformed $Cl(Me)ZrCp_2$.[27] It is noteworthy that the methylalumination of 1,4-bis(trimethylsilyl)-1,3-butadiyne gives exclusively the product of *trans* addition.[28]

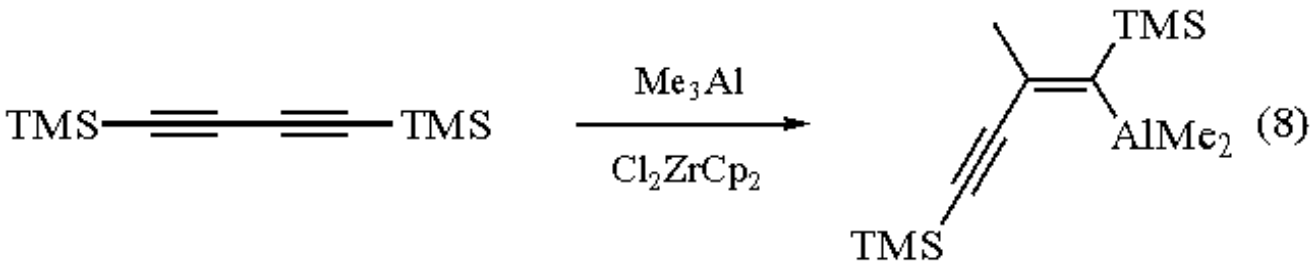

1,1-Dimetalloalkenes are of potential interest for the development of selective routes to tri- and tetrasubstituted alkenes through differentiation of the two metal groups. Some promising results have been obtained along this line. Thus, for example, treatment of (**1**) with ***Acetyl Chloride*** in the presence of ***Aluminum Chloride*** gives a 92:8 mixture of (*Z*)- and (*E*)-4-methyl-3-hepten-2-one in 61% yield.[27]

However, the most extensive synthetic application of these 1,1-dimetalloalkenes to date is the synthesis of cycloalkenylmetals. Treatment of 1-(trimethylsilyl)-4-bromo-1-butyne with Me_3Al (2 equiv) in the presence of Cl_2ZrCp_2 (1 equiv) in $(CH_2Cl)_2$ at 25 °C gives a cyclobutene (**2**) in 92% yield after 6 h, rather than the expected methylmetallation product (eq 9).[29]

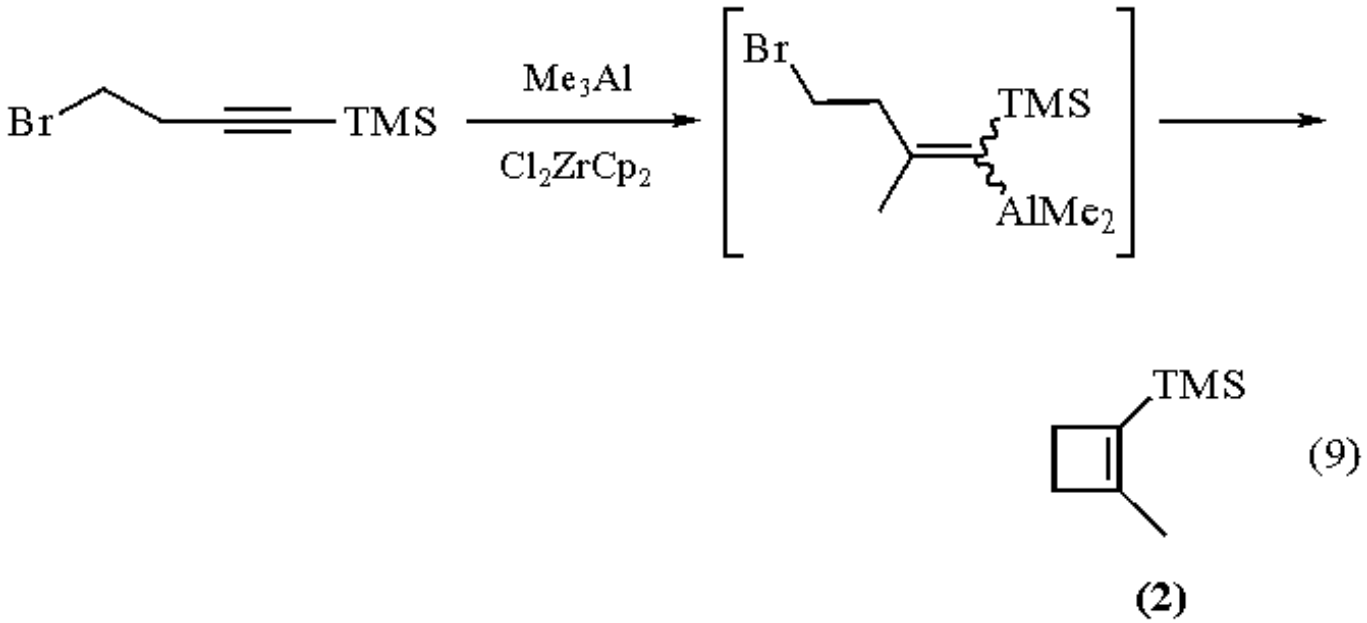

The reaction evidently involves the intermediacy of the methylalumination product shown in eq 9. A π-type cyclization involving the intermediacy of a cyclopropylcarbinyl species must be operating,[29] since (1) alkylation of alkenylalanes with alkyl halides does not occur under comparable conditions, (2) the Zr-catalyzed methylalumination is known to give exclusively or predominantly *cis* addition products which are wrong isomers for a σ-type cyclization, and (3) the reaction is regioselective but nonregiospecific (eq 10).[30] These results are consistent with the mechanism shown in eq 11.

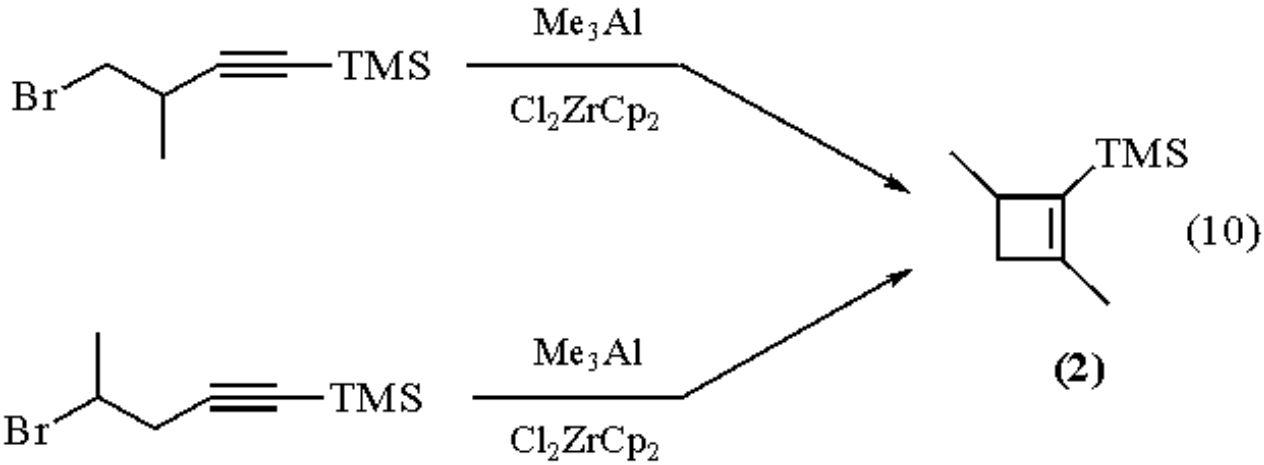

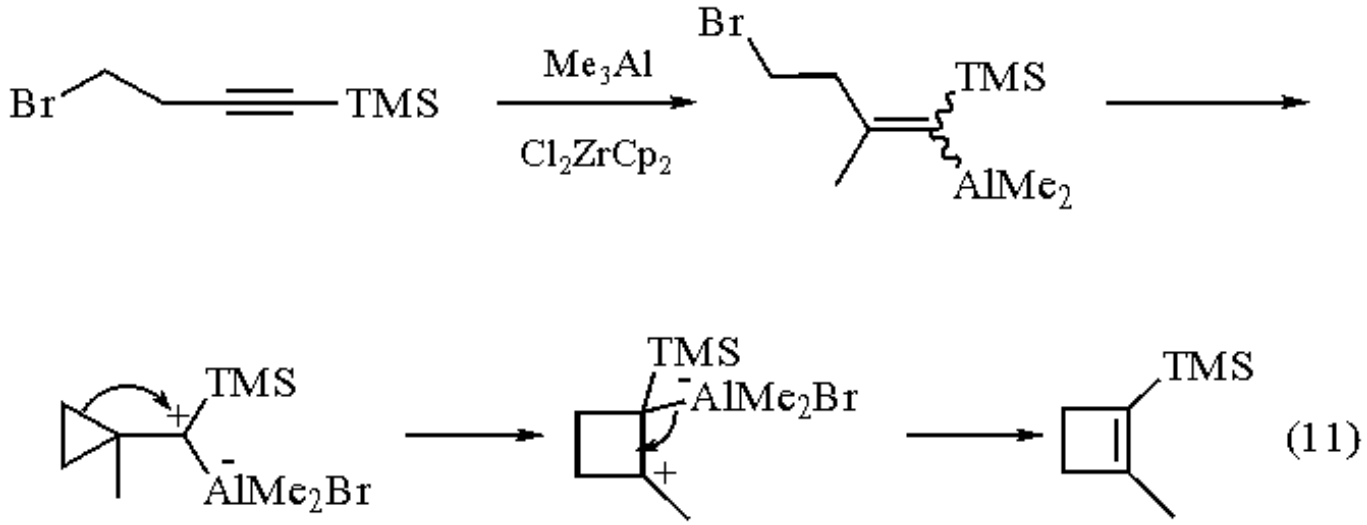

The reaction is not limited to the formation of four-membered rings. The methylalumination reaction of 1-(trimethylsilyl)-6-bromo-1-hexyne gives 1-(trimethylsilyl)-1-cyclohexene as the major product.[31] On the other hand, the corresponding reaction of 1-(trimethylsilyl)-5-bromo-1-pentyne gives only the noncyclized methylalumination product.[31]

Synthetically more attractive is the reaction of o-halo-1-alkynylalanes (**3**) with Me_3Al-Cl_2ZrCp_2, which gives the corresponding cycloalkenylmetals (**4**), readily convertible to a wide variety of cyclobutenyl derivatives (eq 12).[30] The same method can be applied to the synthesis of cyclopentenyl or cyclohexenyl analogs of (**4**), such as (**5**) and (**6**), in good yields.[32]

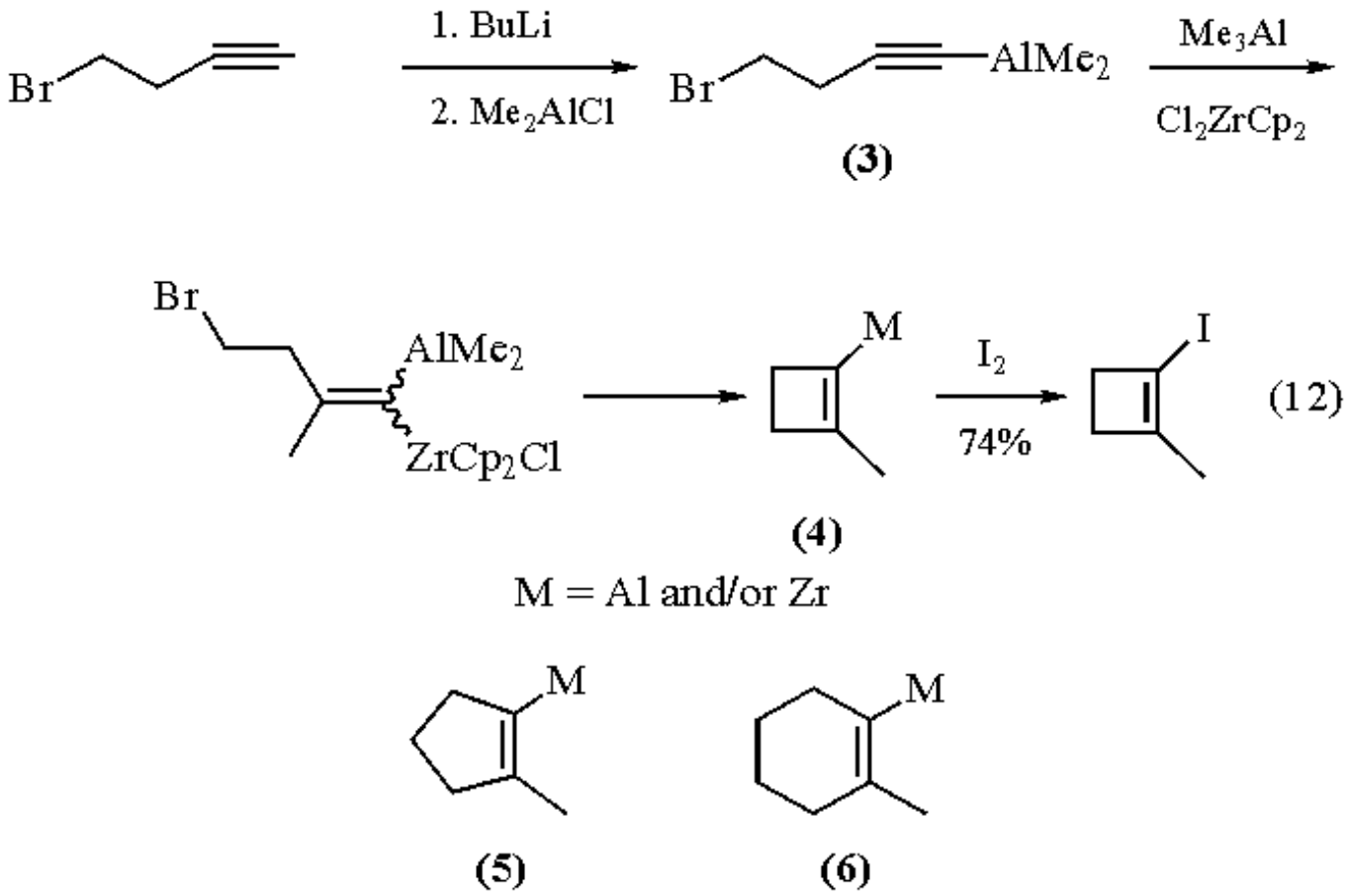

Ziegler-Natta Polymerization of Alkenes.

Some reagent systems consisting of methylaluminum and zirconocene derivatives have been used as homogeneous Ziegler-Natta polymerization catalysts. Satisfactory activity levels have been attained through the use of an additional component. For example, the use of Al_2O_3, $MgCl_2$, or SiO_2-supported Cl_2ZrCp_2 with Me_3Al promotes the polymerization of propene with a fairly good activity.[33] The most satisfactory Cl_2ZrCp_2-based system known to date makes use of methylaluminoxanes which are obtained by controlled hydrolysis of Me_3Al.[34]

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Trimethylamine

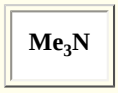

[75-50-3] · C_3H_9N · Trimethylamine · (MW 59.13)

(low boiling tertiary amine used as base in dehydrochlorinations, nucleophilic substitutions, 1,4-additions, and aldol-type condensations)

Physical Data: bp 2.9 °C; mp -117 °C; *d* 0.656 g cm^{-3}.

Solubility: sol alcohols, H_2O, ethers, benzene, toluene, xylene, ethylbenzene, $CHCl_3$.

Form Supplied in: anhydrous trimethylamine is supplied as liquefied gas in steel cylinders; 23-25% aqueous solutions are available.

Handling, Storage, and Precautions: corrosive; toxic; lachrymator. The vapors are harmful and care should be taken to avoid absorption through the skin. Use in a fume hood.

Dehydrochlorinations: Ketene Generation.

The use of trimethylamine as the base in generating ketenes from 2-arylpropionic acid chlorides allows for selective asymmetric esterifications with a variety of chiral non-racemic α-hydroxy esters.[1] Treatment of the acid chloride of racemic ibuprofen with a large excess of trimethylamine in heptane at rt generates the unisolated ketene, which is further reacted with ethyl (*S*)-lactate at -78 °C to afford, in high diastereo- and enantioselectivity, the corresponding (*S*,*S*)-2-arylpropionate (eq 1). The more sterically demanding tertiary amines, such as ***Triethylamine*** or ***Diisopropylethylamine***, lead to much lower diastereoselectivities.

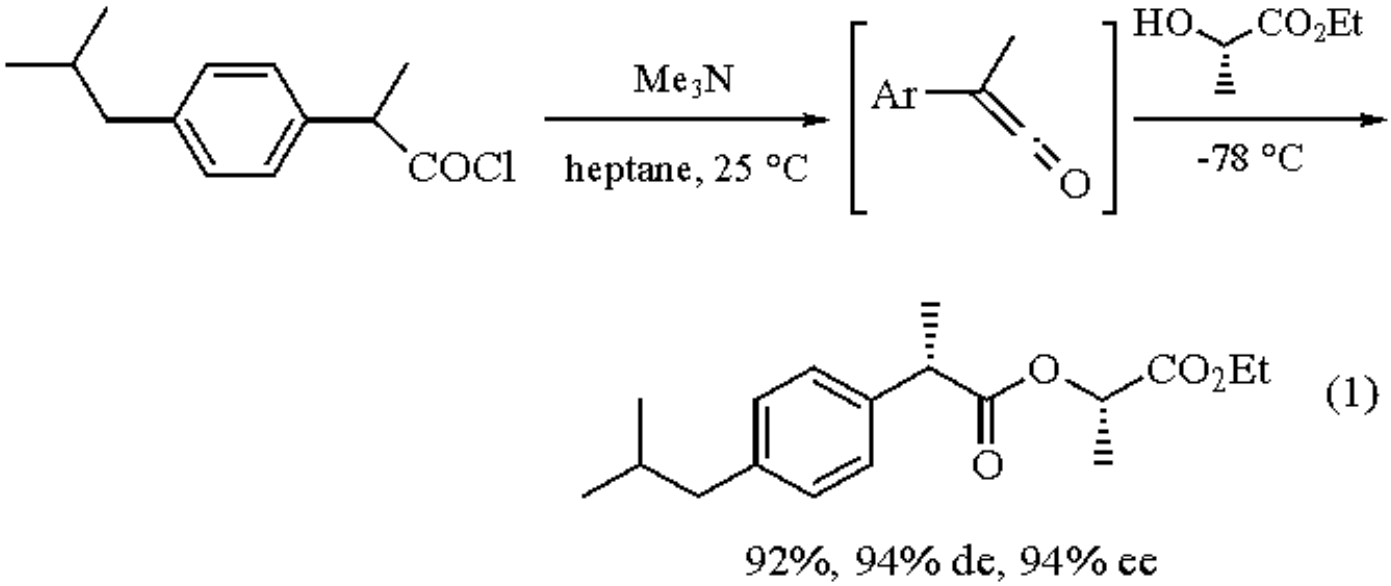

Nucleophilic Substitutions.

2-Amino-6-chloropurines react with trimethylamine and β-hydroxypropionitrile in the presence of ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** (DBU) to generate the corresponding guanines in high yields.[2] The mechanism of the overall hydrolysis consists of a series of nucleophilic displacements involving the intermediacy of the 6-trimethylammonium salt and 6-(2-cyanoethoxy) derivatives. Base-induced β-elimination of acrylonitrile from the cyanoethoxy intermediate completes the reaction sequence and leads to guanines in good overall yields (eq 2). Similarly, treatment of *O*-6-sulfonated guanosines with trimethylamine and alcohols leads to the *O*-alkylated guanosine derivatives in good yield (eq 3).[3] In related chemistry, treatment of triacetyl-2-chloroadenosine with trimethylamine in MeCN at an elevated temperature leads

to the 2-(*N*,*N*-dimethylamino)adenosine derivative in a near quantitative yield (eq 4). The reaction mechanism involves a chloride ion induced dealkylation of the trimethylammonium salt intermediate.[4]

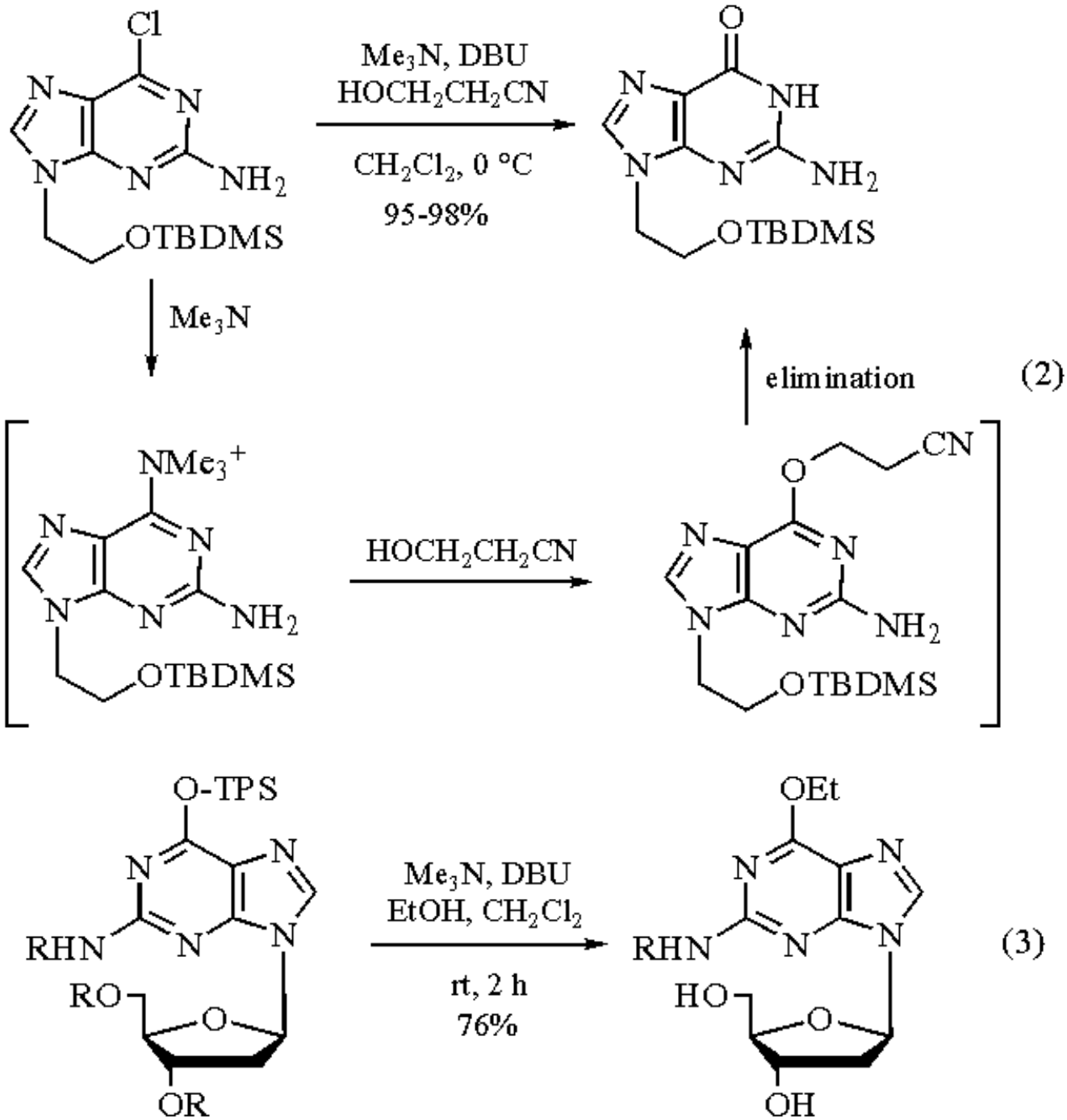

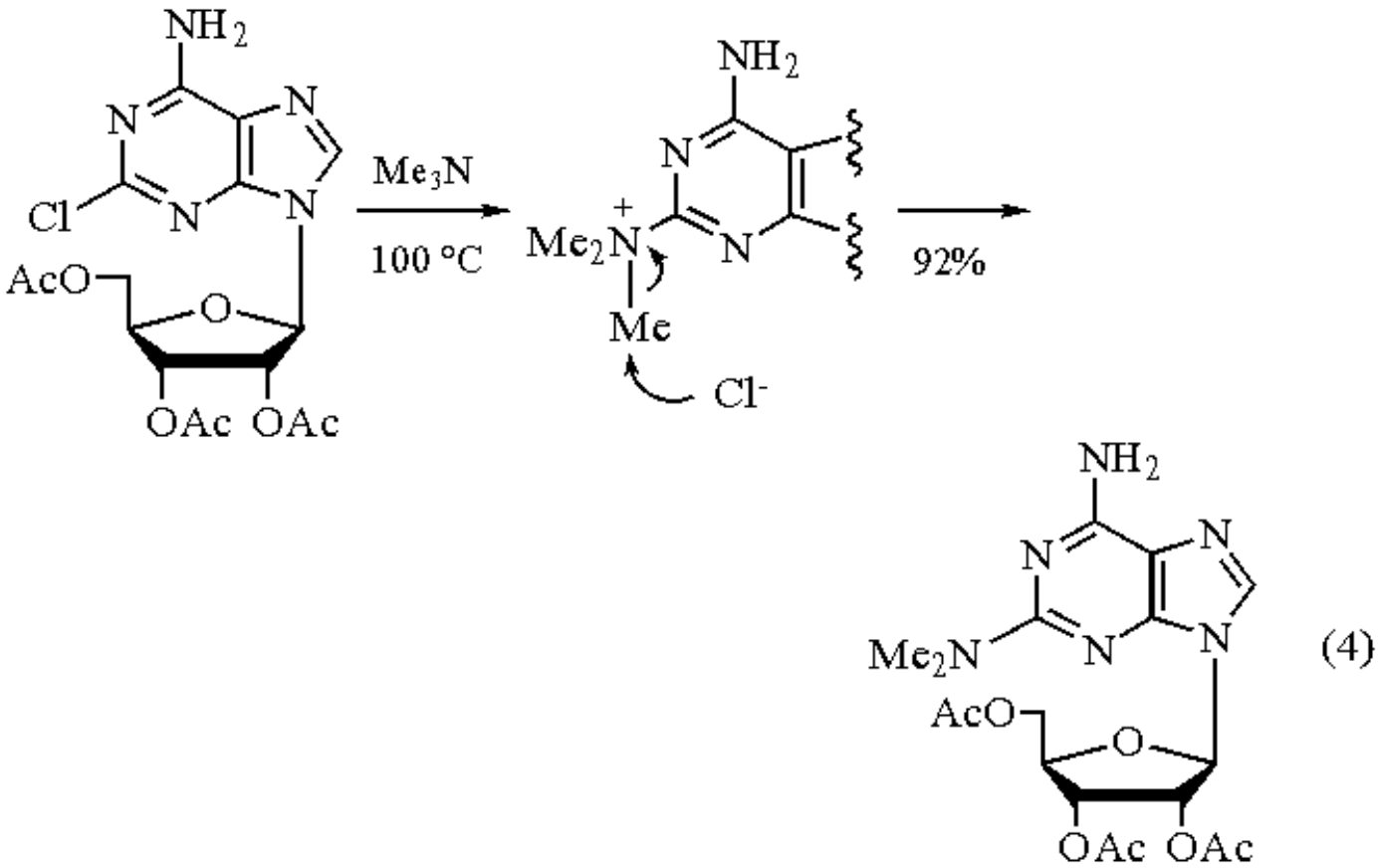

(4)

Trimethylammonium salt intermediates prepared from chloropyrimidines and chloroquinazolines react efficiently with ***Tetraethylammonium Cyanide*** to produce the heterocyclic nitriles in excellent yields.[5] Trimethylamine in ether (or toluene) reacts with 3-chloro-2-cyclopentenone to produce the trimethylammonium salt derivative in 90% yield. Subsequent treatment with an aqueous solution of ***Potassium Cyanide*** generates the 3-cyanocyclopentenone derivative in 79% yield (eq 5).[6]

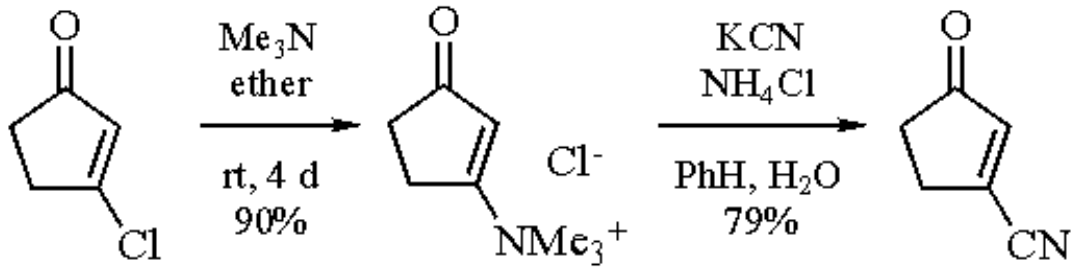

(5)

Treatment of cyclic phosphotriesters with an amine, for example anhydrous trimethylamine, and a slight excess of ***Trimethylsilyl Trifluoromethanesulfonate*** at 0 °C effects nucleophilic ring opening to afford phosphate diesters in good yields (eq 6).[7]

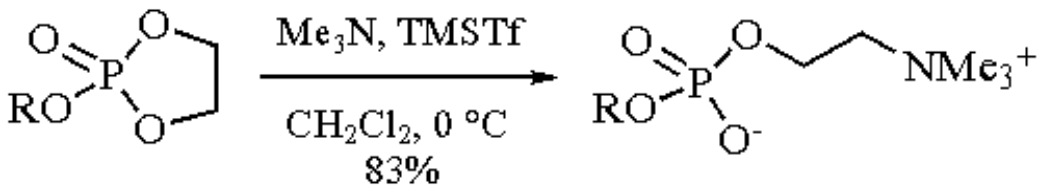

(6)

1,4-Additions.

Trimethylamine (25% aqueous solution) adds in a 1,4-fashion to alkyl propiolates with accompanying hydrolysis of the ester group to generate the (*E*)-(carboxyvinyl)trimethylammonium betaine as the sole isomer (eq 7).[8] In contrast, addition of trimethylammonium tetrafluoroborate to methyl propiolate in refluxing MeOH results in a 57:43 ratio of (*E*)- and (*Z*)-β-trimethylammonium acrylate esters (eq 8).[9] Remarkable stereochemical control is encountered with other alkynes containing electron-withdrawing groups. Trimethylammonium tetrafluoroborate adds selectively to 3-butyn-2-one to generate the (*E*)-isomer exclusively, while propiolonitrile, under identical reaction conditions, affords only the (*Z*)-isomer (eq 9).[9]

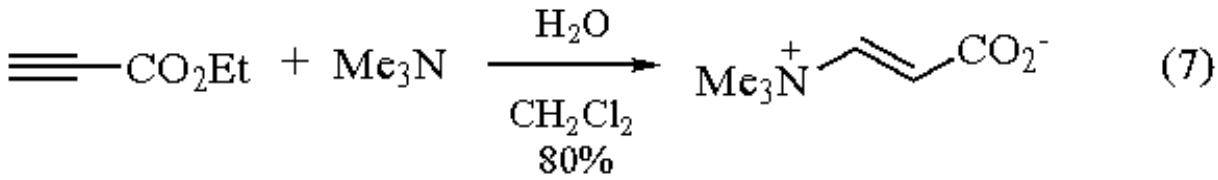

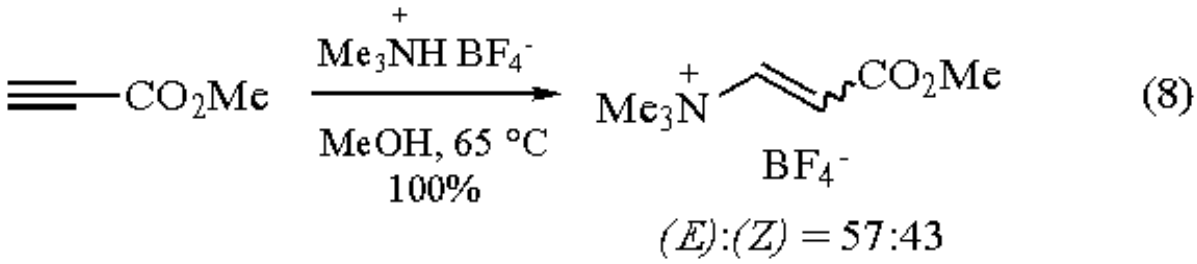

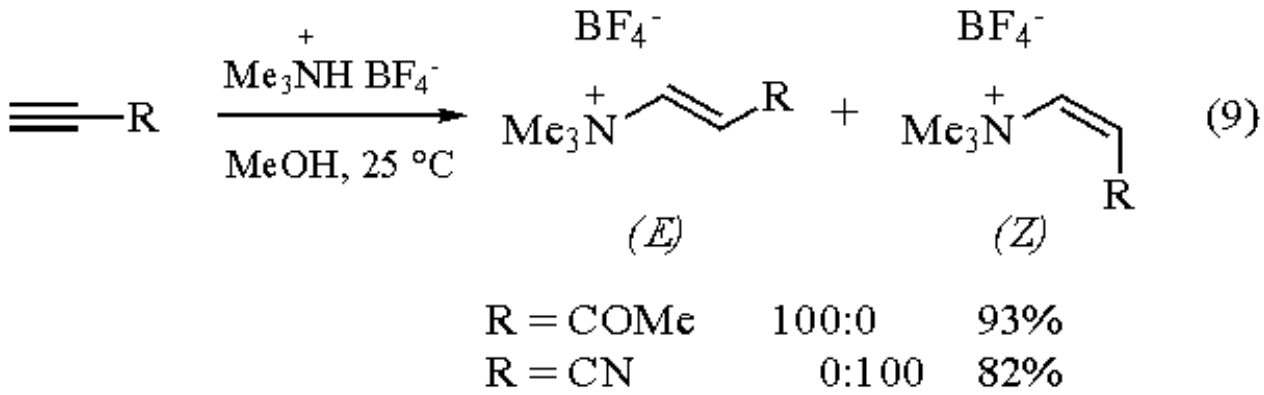

Aldol-Type Condensations.

α-Ketoaldehyde hemiacetals combine with nitroalkanes in the presence of methanolic trimethylamine to produce α-diketones in high yields. This variation of the Henry nitro-aldol reaction involves the addition of the nitroalkane to the aldehyde followed by base-induced β-elimination of nitrite (eq 10).[10]

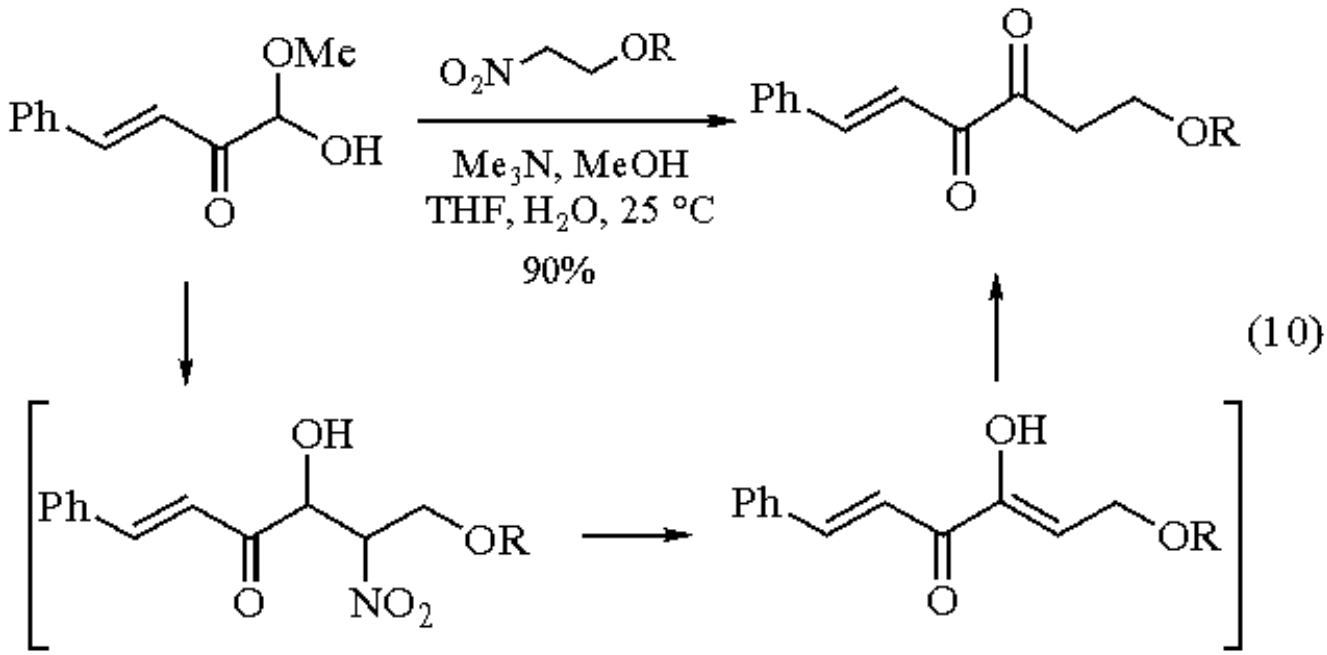

Conversions of Hydrazones to Vinyl Halides.

Treatment of hydrazones with iodine in the presence of a tertiary amine leads to vinyl iodides in good yields.[11] In reactions where isomeric vinyl iodides may be produced, the steric nature of the tertiary amine seems to exert a minor influence on the regiochemical outcome (eq 11).[12]

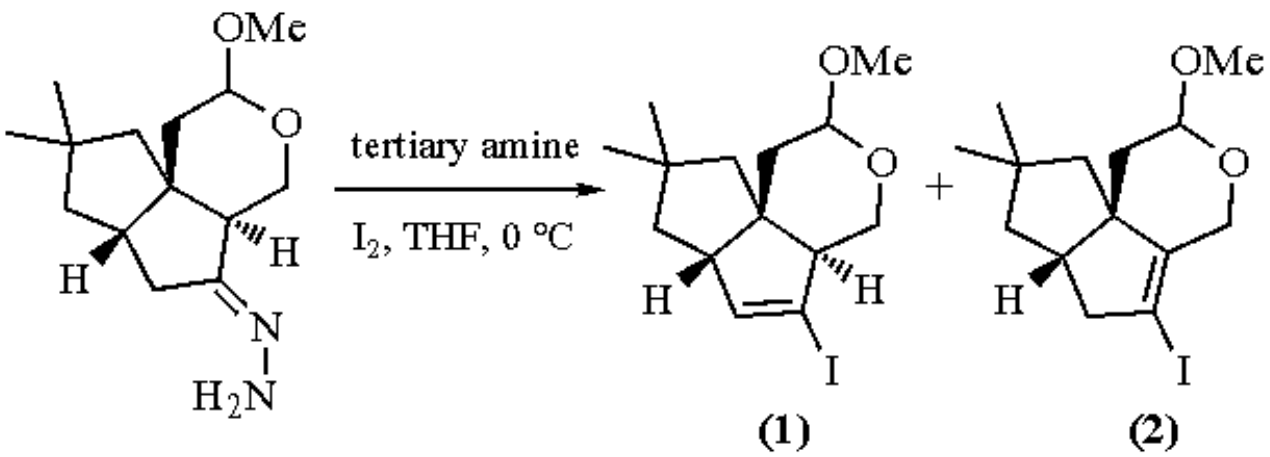

Tertiary amine	Ratio (1):(2)
DIPEA	57:43
Et_3N	58:42
DMAP	59:41
TMG	61:39
TMEDA	69:31
Me_3N	69:31

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Trimethylamine *N*-Oxide

Me_3NO

[62637-93-8] · C_3H_9NO · Trimethylamine *N*-Oxide · (MW 75.13)

(reagent for conversion of alkyl halides and sulfonates to aldehydes and ketones; precursor for azomethine ylide useful for synthesis of *N*-methylpyrrolidines; reagent for decomplexation of tricarbonyldieneiron complexes)

Alternate Name: TMANO.

Physical Data: mp 213-214 °C (dec).[1] Various melting points have been reported, ranging from 208 °C[2] to 225-227 °C. The dihydrate, $Me_3NO.2H_2O$, is a white solid, mp 96 °C.

Solubility: sol H_2O, EtOH; insol Et_2O benzene, and other hydrocarbon solvents; sparingly sol hot $CHCl_3$.

Form Supplied in: the dihydrate is commercially available as a white solid.

Preparative Methods: aqueous ***Trimethylamine*** (100 mL, 33%) is mixed with a pure 3% aqueous solution of ***Hydrogen Peroxide*** (600 mL) and is set aside at rt for 24 h. The solution is evaporated to dryness, and the product is recrystallized from EtOH-Et_2O to give the dihydrate as needles, mp 96 °C.[3,4] Several procedures are available for preparing the anhydrous reagent. The dihydrate is heated at 105 °C and 15 mmHg for several hours, after which it is sublimed at 180-200 °C and 15 mmHg. A more convenient procedure is to remove water by azeotropic distillation with benzene or toluene (Dean-Stark trap), or by co-distillation from a suspension of the reagent in DMF, followed by solvent removal in vacuo.

Handling, Storage, and Precautions: no reported hazards for this reagent. The anhydrous material is hygroscopic and should be prepared and used fresh or stored at rt in a vacuum desiccator over P_2O_5. Trimethylamine *N*-oxide is an oxidizer and should be stored away from reducing agents.

Preparation of Aldehydes and Ketones.

Alkyl bromides, iodides, and tosylates react with Me_3NO in $CHCl_3$ to give reasonable yields of aldehydes and ketones (eqs 1-3).[5]

$$RCH_2X \xrightarrow[50\text{-}60\ ^\circ C]{Me_3NO,\ CHCl_3} RCHO \qquad (1)$$

$R = C_5H_{11}$, X = I, 31%; $R = C_5H_{11}$, X = Br, 48%
$R = C_7H_{15}$, X = I, 50%; $R = C_7H_{15}$, X = OTs, 55%

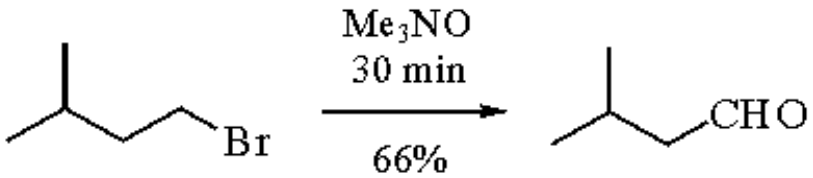

(2)

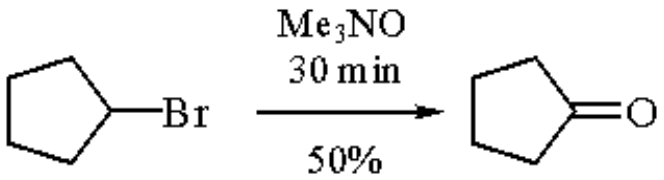

(3)

Oxidation of Organoboranes.

Trimethylamine *N*-oxide is a useful alternative to alkaline ***Hydrogen Peroxide*** for the conversion of intermediates from the hydroboration of alkenes and alkynes to alcohols, especially in those cases where the product is sensitive to either high pH or H_2O_2. For example, cyclopropanols are reported to be unstable to alkaline H_2O_2, making hydroboration of cyclopropenes problematic. Oxidation of the intermediate boranes with Me_3NO in hot toluene, followed by methanolysis of the derived tricyclopropylborate, gives cyclopropanols in good overall yield (eq 4).[6]

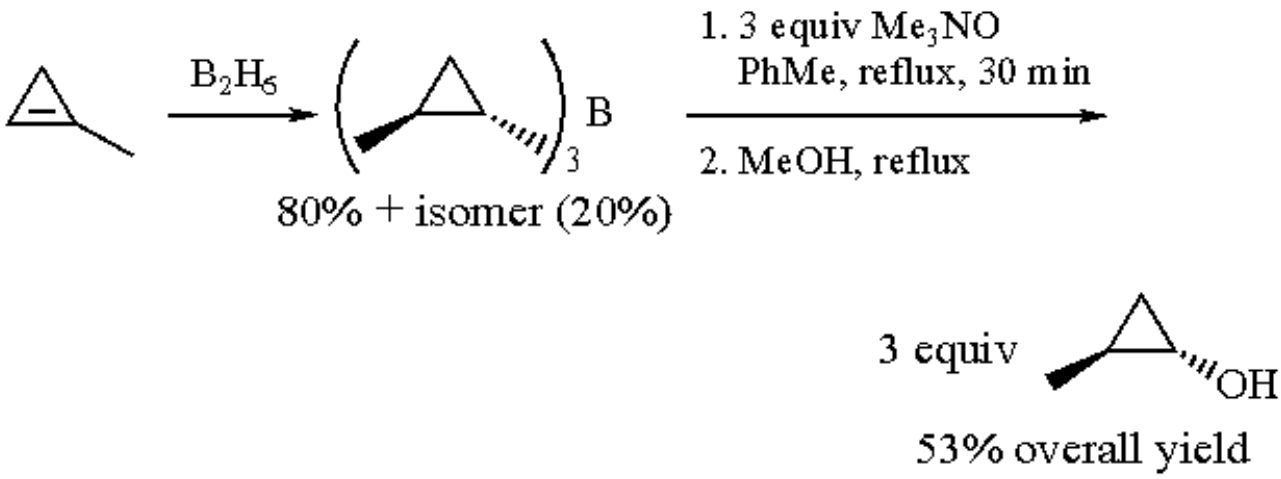

(4)

Later studies by Kabalka and Hedgecock[7] have shown that commercially available Me_3NO dihydrate is an effective reagent for organoborane oxidation, and tolerates a wide variety of functional groups. Owing to the fact that the amine oxide is not appreciably soluble in organic solvents such as THF, toluene, and $CHCl_3$, it is recommended that the oxidation is carried out with vigorous stirring.[8] Rates of oxidation are sensitive to the nature of the alkyl group (secondary cycloalkyl > secondary alkyl > *n*-alkyl > β-branched primary alkyl), and the second and third alkyl groups are removed more slowly. Choice of solvent does not appear to affect the rate of oxidation; the recommended reaction conditions are diglyme at reflux. Two simple examples are given in eqs 5 and 6.

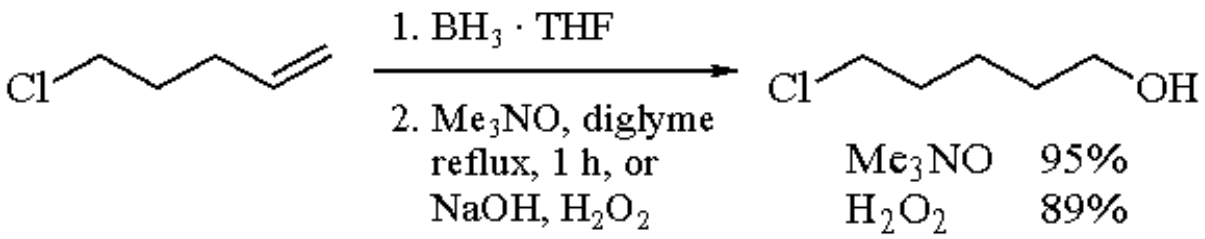

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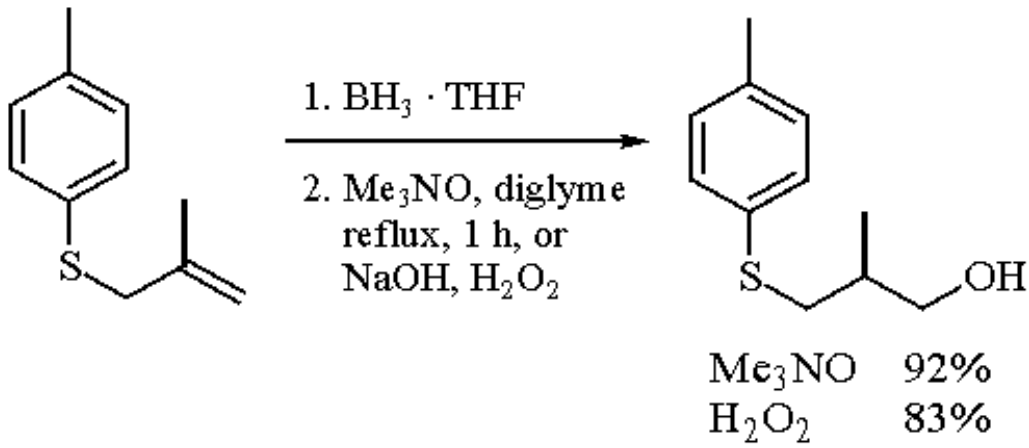

(6)

A useful example of the application of Me_3NO for borane oxidation is found in the formal total synthesis of (±)-perhydrohistrionicotoxin by

Carruthers and Cumming (eq 7).[9] Oxidation of the borane intermediate from the azaspirocycle by using alkaline hydrogen peroxide proved extremely difficult and gave a low yield of the desired alcohol (34% as a mixture of stereoisomers), this being attributed to the formation of a stable aminoborane.[10] Carruthers overcame this problem by using Me_3NO in refluxing diglyme, to give a mixture of stereoisomers that could be separated by chromatography of their acetate derivatives. The alcohol shown in eq 7 is a known intermediate in a synthesis of perhydrohistrionicotoxin.[11]

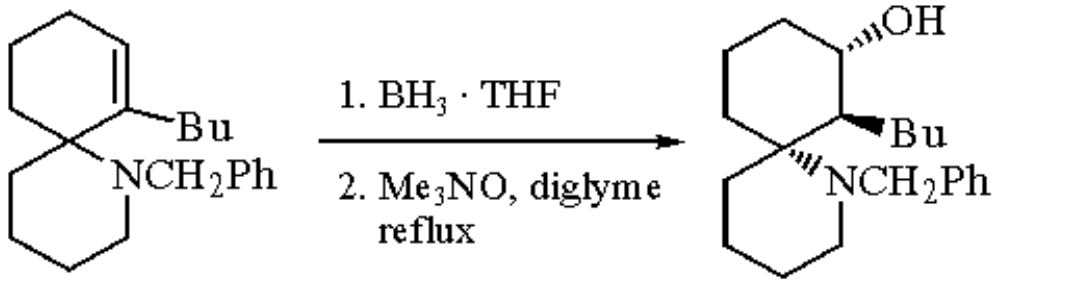

(7)

55%, + stereoisomer 5%

Trimethylamine *N*-oxide is also useful for oxidation of vinylborane intermediates formed during the hydroboration of alkynes.[12] The use of hydrogen peroxide in such reactions leads to overoxidation (eq 8), and this is avoided by using Me_3NO in refluxing THF in a one-pot procedure to generate acylsilanes from silylalkynes (Scheme 1).

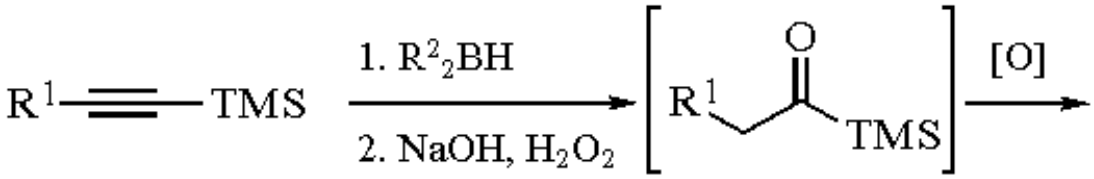

$R^1CH_2CO_2H$ (8)

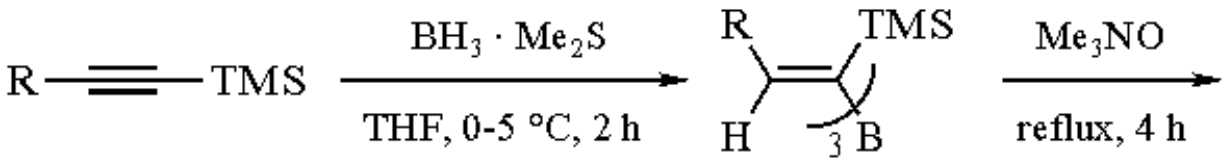

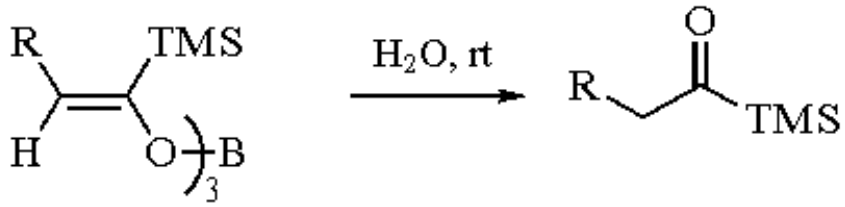

R = Bu, 86%; C_6H_{13}, 91%; Cy, 83%; *i*-Pr, 75%; $Cl(CH_2)_3$, 85%; $MeCH_2CH(OTMS)CH_2$, 76%; TMS, 75%

Scheme 1

Extension of this chemistry to the oxidation of organoaluminum derivatives has been described by Kabalka and Newton,[13] which is an extension of a reaction first reported by Köster.[14] It should be noted, however, that vinylalanes are not oxidized by this procedure; $R^1CH{=}CHAlR^2_2$ gives only the products of oxidation of the Al-R^2 bonds, with no aldehydes being detected. Examples of the procedure are shown in eq 9.

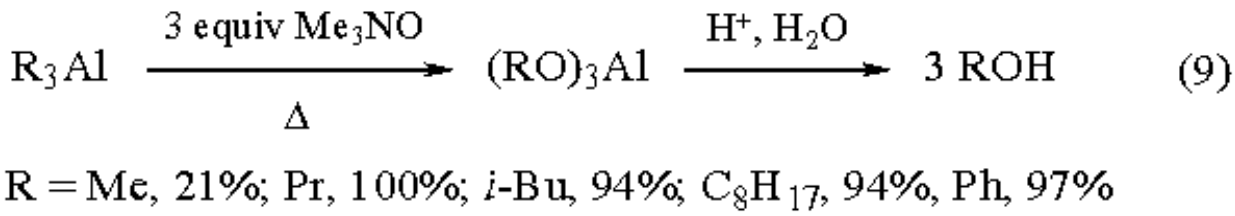

Azomethine Ylides from Me_3NO: Synthesis of *N*-Methylpyrrolidines.

Treatment of anhydrous Me_3NO with ***Lithium Diisopropylamide*** (LDA) gives an azomethine ylide which reacts in situ with alkenes in a dipolar cycloaddition to give *N*-methylpyrrolidines (eq 10).[15] Previous methods for generating azomethine ylides required electron-withdrawing or conjugatively stabilizing substituents.[16] Reaction of the azomethine ylide with dihydronaphthalenes has been described,[17] but the poor solubility of Me_3NO in THF was a problem for ylide generation, and it was found that a four-fold excess of the reagent was necessary to ensure complete consumption of all the alkene (eq 11).

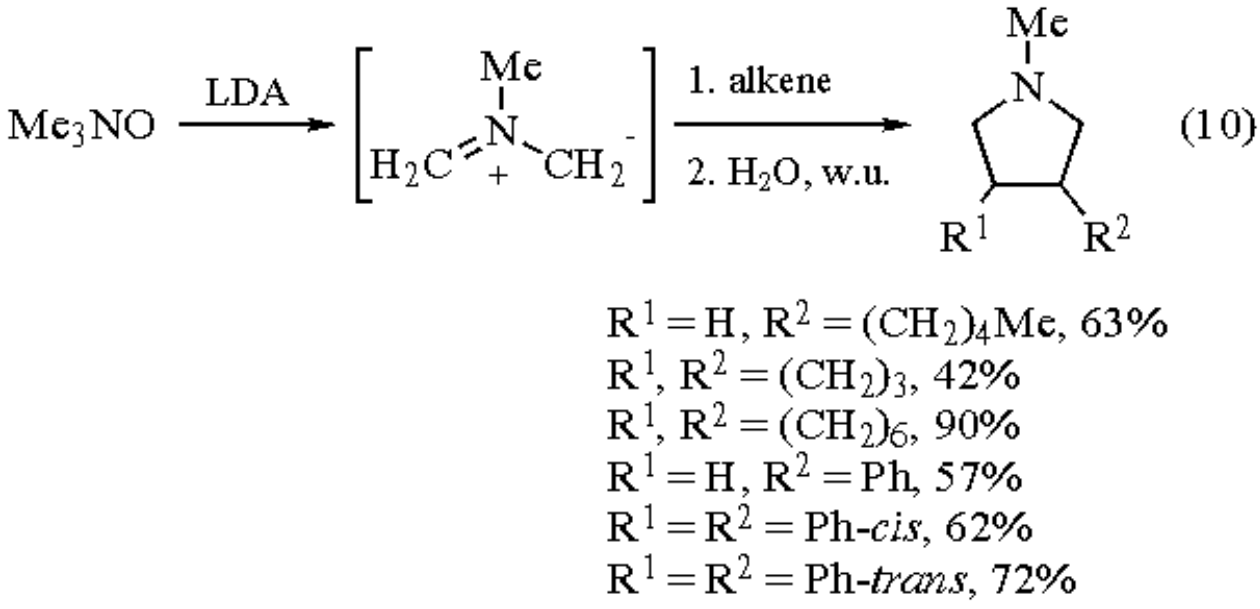

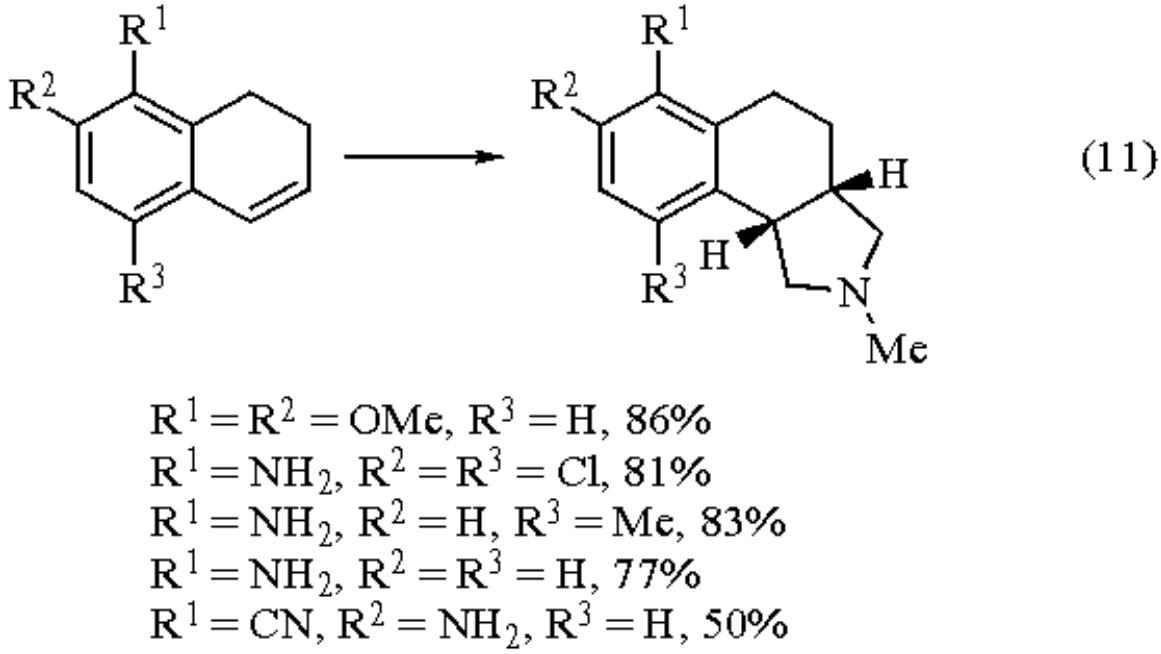

Decomplexation of Diene-$Fe(CO)_3$ Complexes.

Me_3NO has been used extensively in organometallic chemistry as a reagent for the selective removal of carbonyl ligands. An extension of this reactivity leads to applications in the decomplexation of diene-iron tricarbonyl complexes, which are being used increasingly as intermediates for organic synthesis. The first report of Me_3NO being used for this type of ligand disengagement was by Shvo and Hazum,[18]

summarized in eqs 12-15. The last two examples are particularly noteworthy, since the complexes are quite sensitive to the acidic conditions that are generated when transition metal oxidants such as ***Iron(III) Chloride*** or ***Cerium(IV) Ammonium Nitrate*** are used for decomplexation. Until the development of this method the removal of $Fe(CO)_3$ from diene complexes was considered a major obstacle to their synthetic application. The reaction conditions vary according to the diene, and must be determined empirically.

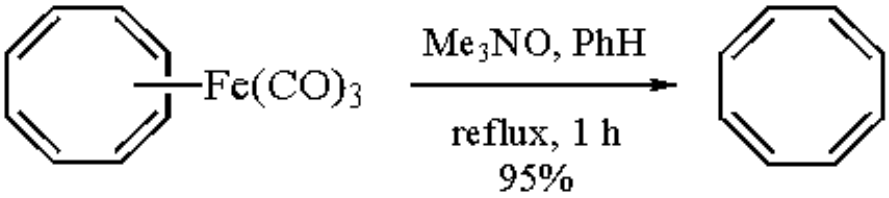

(12)

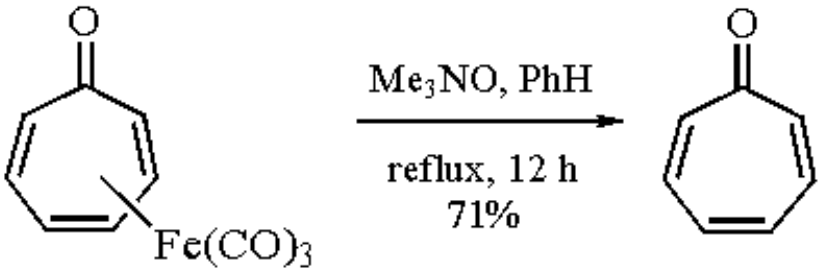

(13)

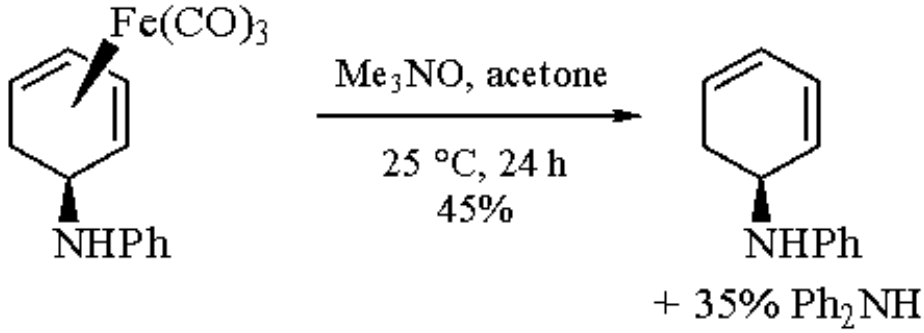

(14)

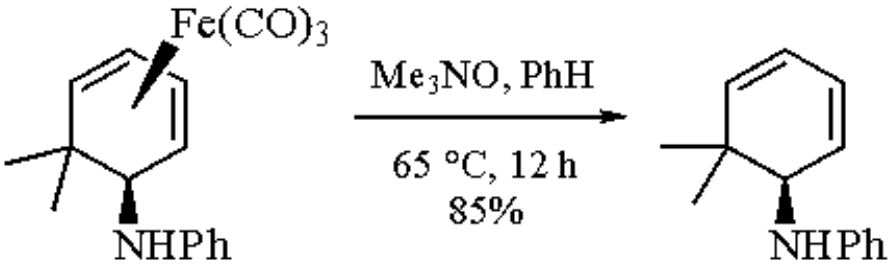

(15)

Evidence that the mechanism of the reaction involves two amine oxide molecules per diene-$Fe(CO)_3$ comes from the isolation of an intermediate that has a carbonyl ligand replaced by Me_2NH (eq 16).[19a] A plausible mechanistic explanation is shown in Scheme 2, though this is somewhat different from the mechanism proposed for reaction of Me_3NO with $Fe(CO)_5$.[19b]

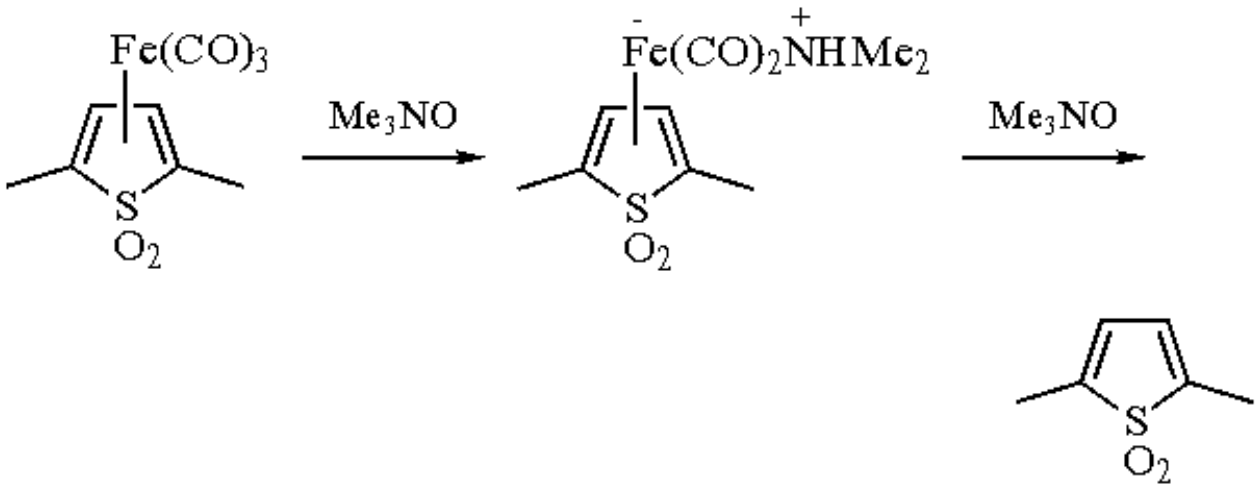

(16)

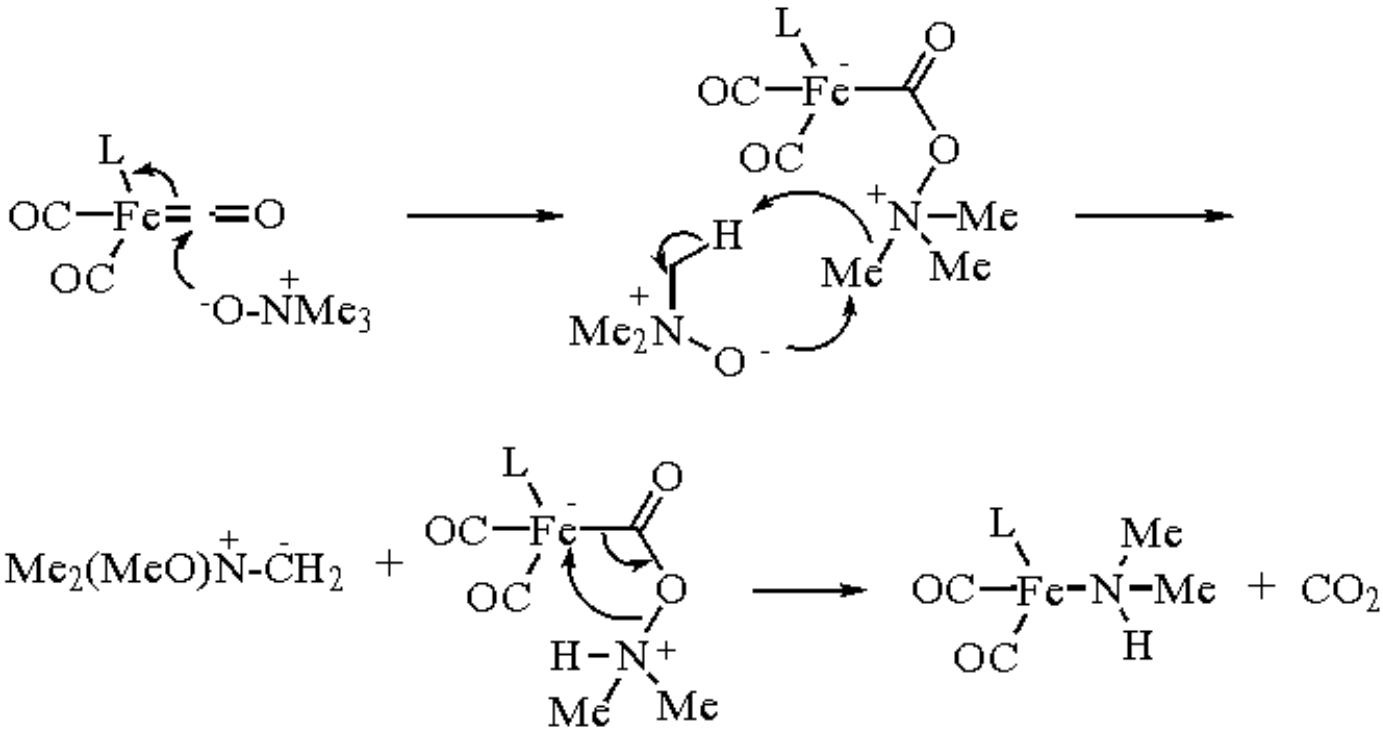

Scheme 2

A large number of examples of the use of Me_3NO for decomplexation can now be found in the synthetic literature. A comparison with iron(III) chloride is revealed by the decomplexation shown in eq 17.[20] While the methyl-substituted complex (X = Me) could be demetalated using $FeCl_3$ or Me_3NO, the use of $FeCl_3$ is problematic when X = OR, SPh, or NHR, owing to the propensity of these complexes to undergo acid-promoted scission of the C-X bond to regenerate the dienyl-$Fe(CO)_3$ cation. Me_3NO is non-acidic and does not suffer this limitation.

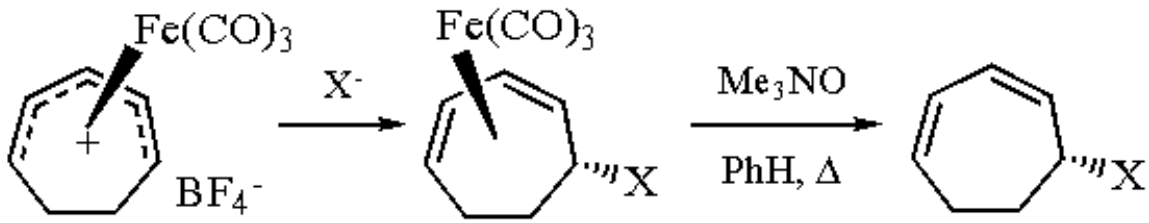

(17)

X = OMe, 42%; OPh, 39%; SPh, 33%; NMe_2, 52%; NH-*t*-Bu, 72%; Me, 48%

Similar compatibility with heteroatom substituents is observed during the synthesis of (-)-gabaculine reported by Birch et al.,[21] who also found that *N*,*N*-dimethylacetamide is an excellent solvent for decomplexation (Scheme 3), by Pearson and Ham[10] in their formal synthesis of perhydrohistrionicotoxin (eq 18), and by Pearson and Srinivasan in some approaches to cycloheptadiene triols (eqs 19 and 20).[22] The other useful aspect of Me_3NO for these decomplexations is that vinyl ether groups are not hydrolyzed to ketones under the reaction conditions.

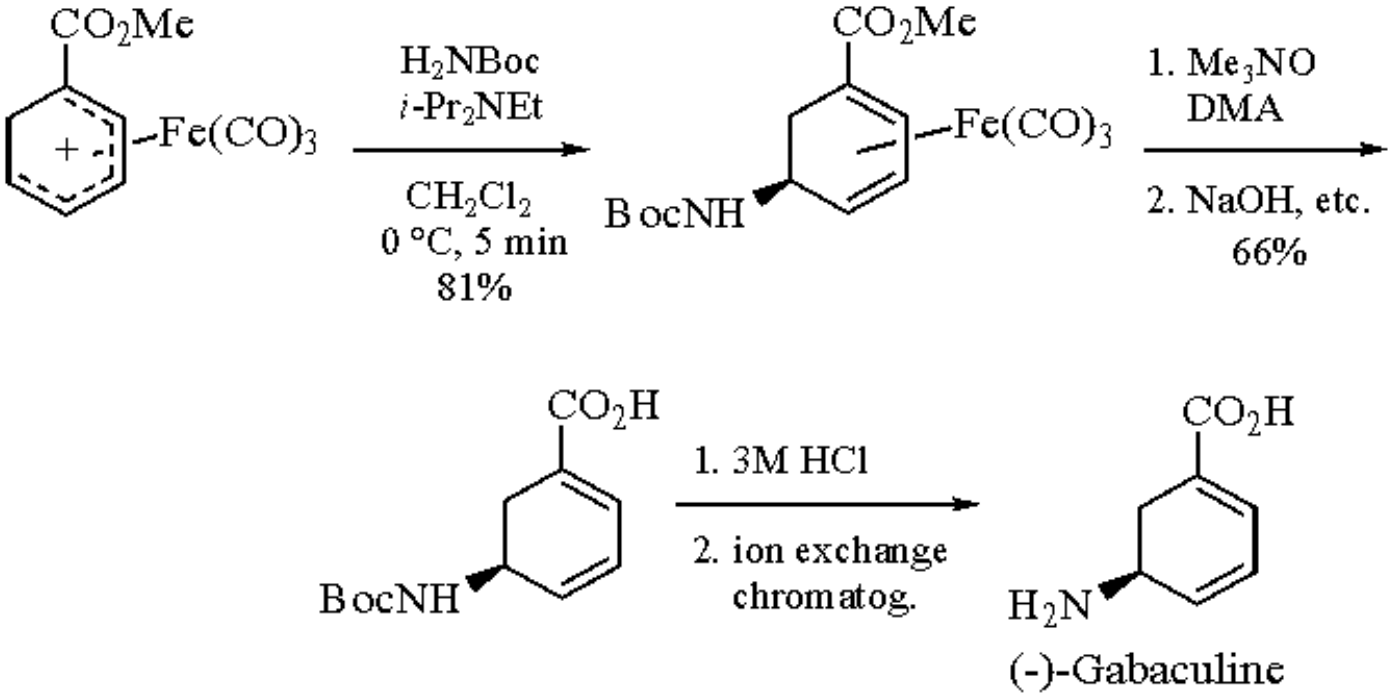

Scheme 3

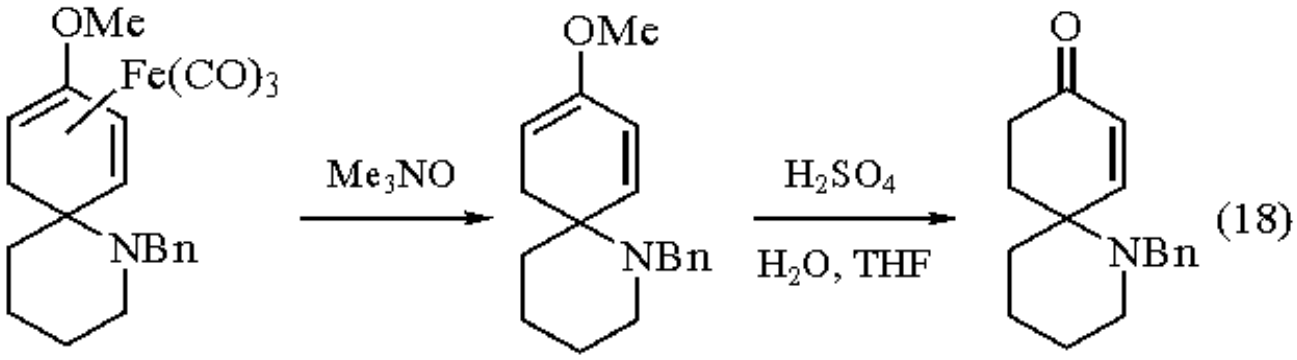

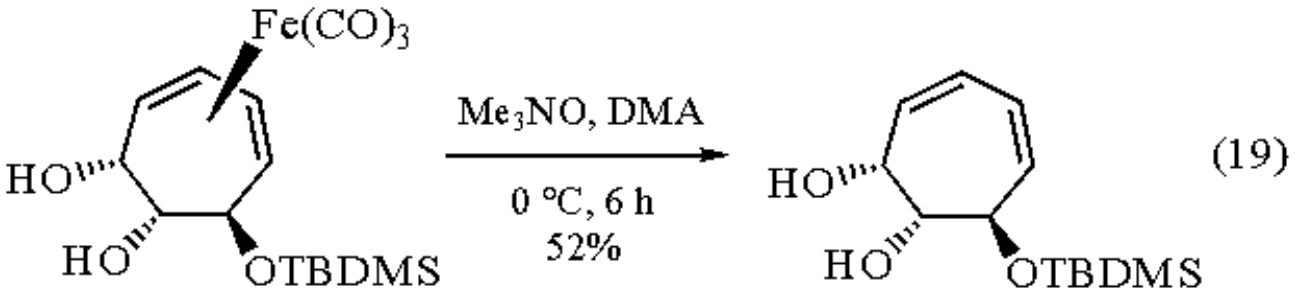

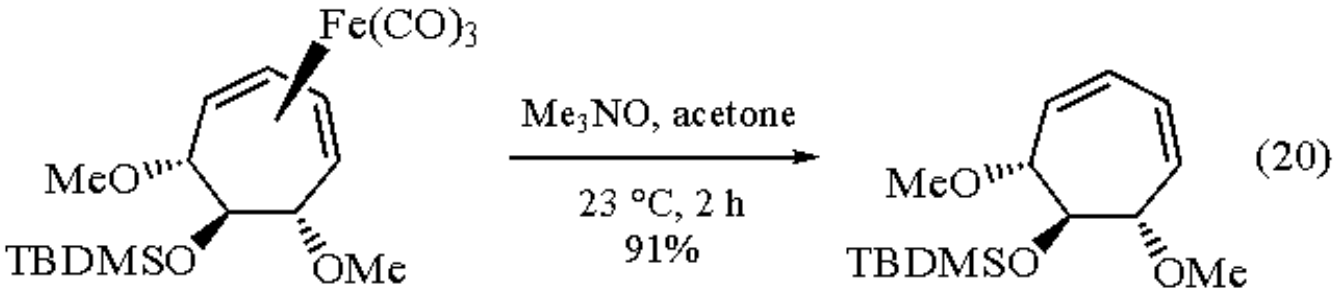

Owing to the fact that the decomplexation reaction proceeds via nucleophilic attack on a carbonyl ligand, Me_3NO is not very useful for converting diene-$Fe(CO)_2PR_3$ complexes to dienes, since the poorer π-acceptor capacity of the phosphine ligand places more electron density at the carbonyls. For this reason, it has been found better to use ***Dipyridine Chromium(VI) Oxide*** in CH_2Cl_2 for decomplexation of the phosphine-substituted derivatives (eq 21).[23]

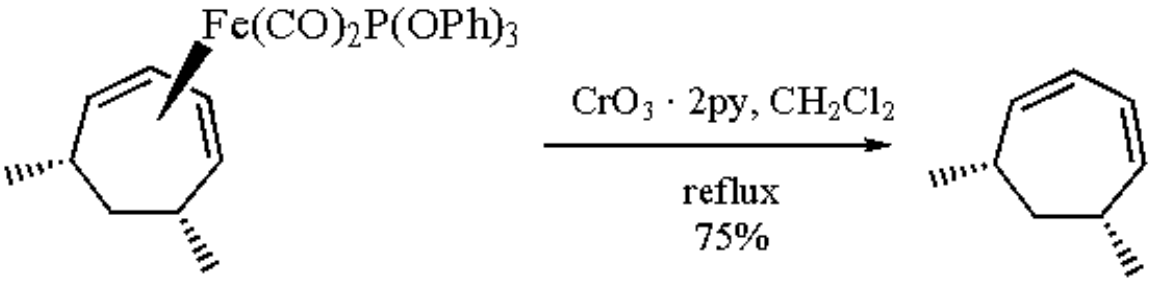

(21)

Shvo and Hazum have also reported the use of Me_3NO as promoter during the conversion of dienes to diene-$Fe(CO)_3$ complexes.[24] Reaction of $Fe(CO)_5$ with Me_3NO at controlled temperature leads to the formation of a coordinatively unsaturated $Fe(CO)_4$ derivative by a mechanism related to that shown in Scheme 2. In the presence of a diene, rapid coordination of alkene occurs, followed by a second CO loss and alkene coordination to give the diene complex (eqs 22 and 23). It should be noted that the normal conditions for $Fe(CO)_5$ -> diene-$Fe(CO)_3$ conversion are refluxing in di-*n*-butyl ether (ca. 140 °C).

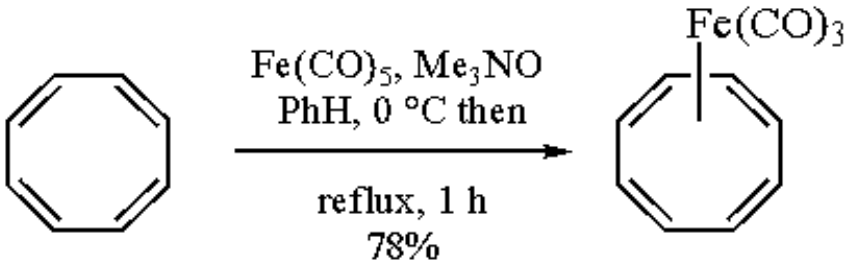

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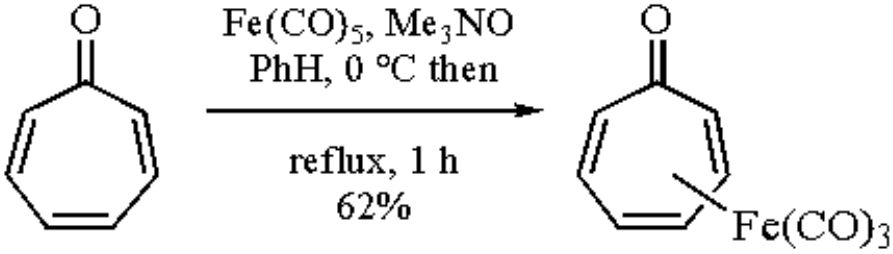

(23)

This observation, coupled with the fact that diene-$Fe(CO)_2PR_3$ complexes are quite resistant to Me_3NO, leads to a mild method for the conversion of diene-$Fe(CO)_3$ to diene-$Fe(CO)_2PR_3$ complexes (eqs 24-26).[22,25,26] The examples in eq 24 (R^1 or R^2 = OMe) are especially interesting because other methods for ligand exchange (thermal or photochemical) with these electron-rich diene complexes either fail completely or give very low yields.

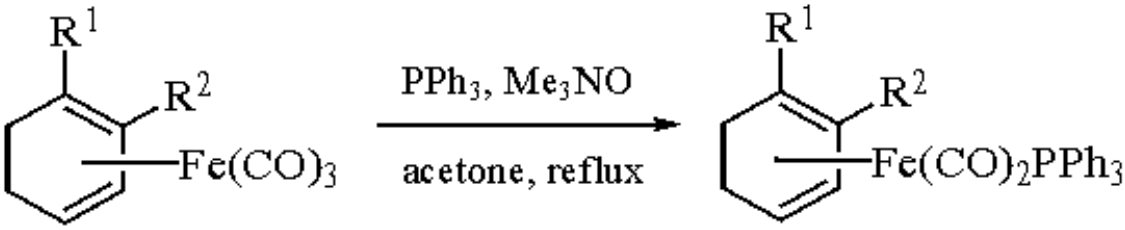

(24)

$R^1 = R^2 = H$, 64%
$R^1 = H$, $R^2 = OMe$, 48%
$R^1 = OMe$, $R^2 = H$, 54%
$R^1 = H$, $R^2 = CO_2Me$, 78%
$R^1 = CO_2Me$, $R^2 = H$, 81%

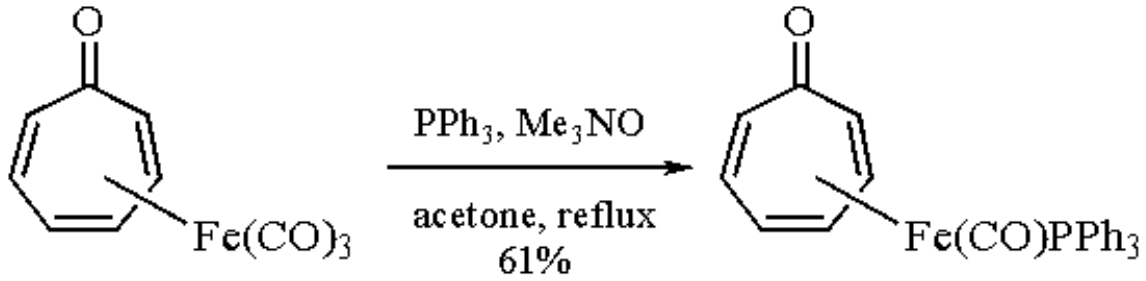

(25)

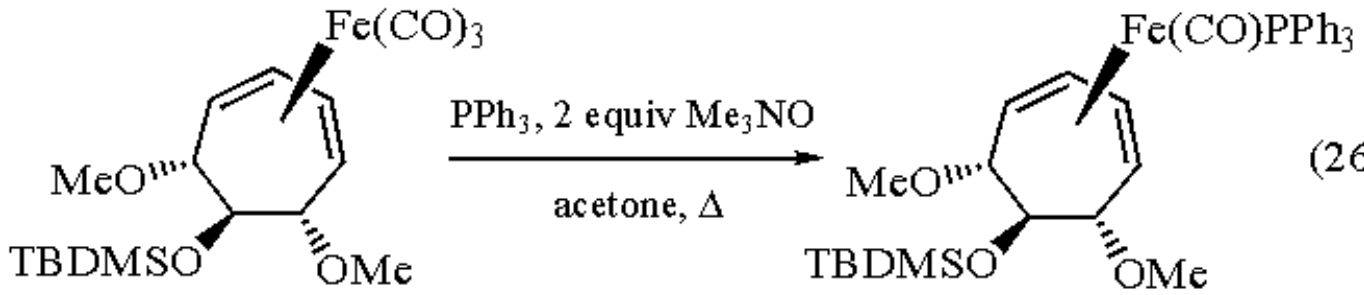

(26)

Related Reagents.

N-Benzyl-N-(methoxymethyl)-N-trimethylsilylmethylamine; ***Cerium(IV) Ammonium Nitrate***; ***Hydrogen Peroxide***; ***Iron(III) Chloride***; ***N-[(Tri-n-butylstannyl)methyl]benzaldimine***.

---

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Trimethylaminoacetohydrazide Chloride[1]

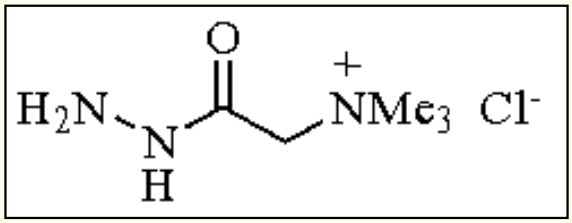

[123-46-6] · $C_5H_{14}ClN_3O$ · Trimethylaminoacetohydrazide Chloride · (MW 167.67)

(separation of aldehydes and ketones from impurities;[2] dehydration of aldols to enones[4])

Alternate Name: Girard T reagent.

Physical Data: mp 188-192 °C (dec).

Solubility: very sol H_2O; sol MeOH, cold EtOH; very sol acetic acid.

Form Supplied in: white solid; widely available.

Purification: recrystallization from EtOH.

Handling, Storage, and Precautions: very hygroscopic; develops a strong odor upon standing in air; store under inert gas.

Trimethylaminoacetohydrazide chloride has been used primarily to separate lipophilic ketones and aldehydes from various impurities via their water-soluble hydrazones (eqs 1 and 2). Several procedures for its use are published.[2]

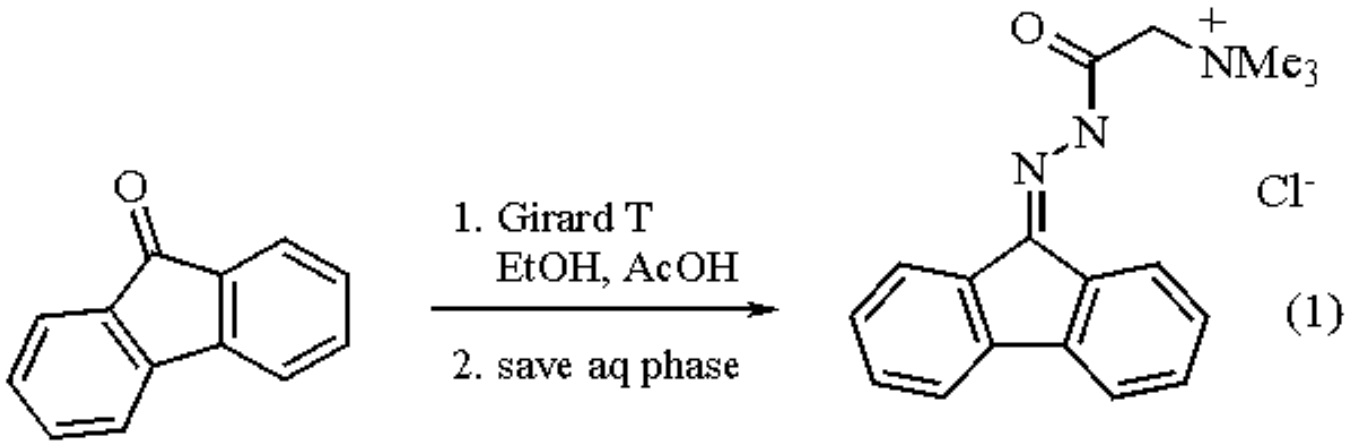

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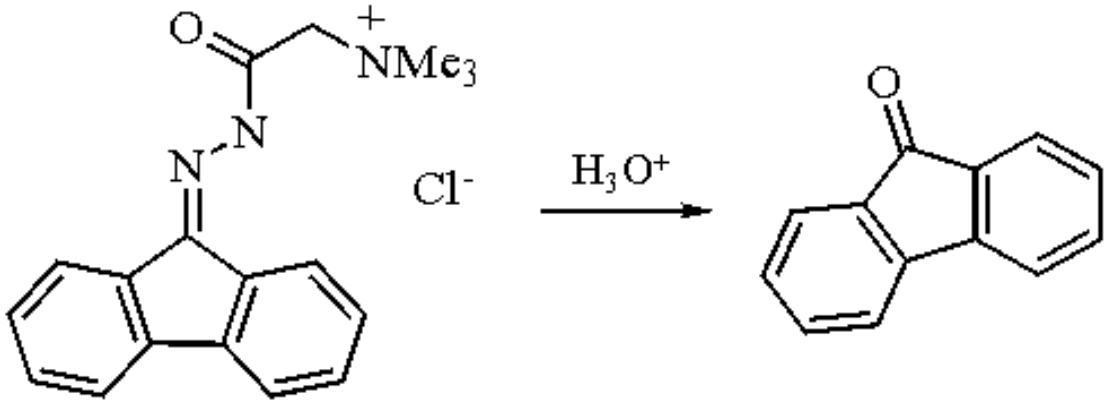

(2)

With the advent of column and flash chromatography techniques, this procedure has not been widely utilized in the organic literature for some time. It was commonly employed to separate ketonic steroids from nonketonic components in extraction-isolation protocols.[1] Recently, the reagent supported on silica gel has been used to isolate ketones and aldehydes.[3]

Dehydration of 3-keto-5β-hydroxy steroids to Δ^4-3-keto steroids can be effected by refluxing with the reagent in acetic acid (eq 3).[4]

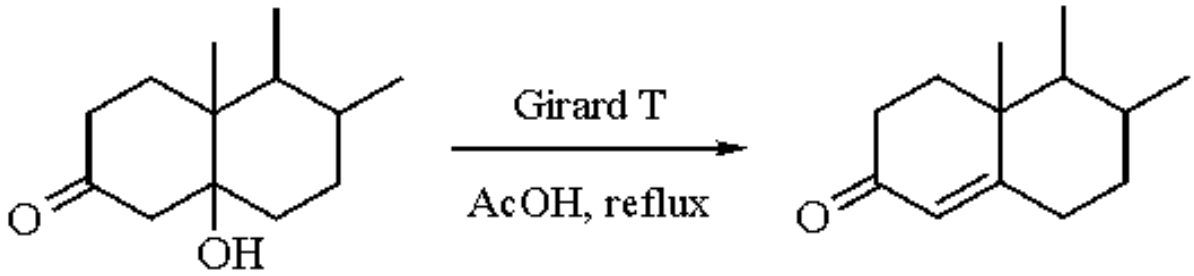

(3)

Related Reagents.

Semicarbazide.

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2. (a) Girard, A.; Sandulesco, G. *HCA* **1936**, *19*, 1095. (b) Girard, A. *OSC* **1943**, *2*, 85. (c) *FF* **1967**, *1*, 410.
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2,4,6-Trimethylbenzoic Acid

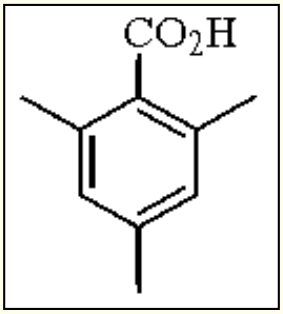

[480-63-7] · $C_{10}H_{12}O_2$ · 2,4,6-Trimethylbenzoic Acid · (MW 164.22)

(mild, hindered Brønsted acid; protecting group for carbohydrates)

Alternate Names: mesitoic acid; mesitylenecarboxylic acid.

Physical Data: needles (prisms from pet ether); mp 154-155 °C; pK_a 4.43 (25 °C); pK_{a1} 3.45 (25 °C).[1]

Solubility: sol alcohol, ether, acetone, $CHCl_3$; slightly sol H_2O.

Form Supplied in: crystalline solid.

Preparative Method: many are described, including the addition of CO_2 to the Grignard reagent derived from bromomesitylene.[10]

Purification: crystallized from H_2O, pet ether, or CCl_4.[11]

Handling, Storage, and Precautions: gloves should be worn while handling; may cause irritation.

Catalysis of Sigmatropic Rearrangements.

Mesitoic acid has been used on numerous occasions for orthoester Claisen rearrangements and related processes, where its character as a mild, not readily esterified, Brønsted acid is of virtue. The examples cited (eqs 1-3)[2-4] are typical; see also Trudell and Cook.[5]

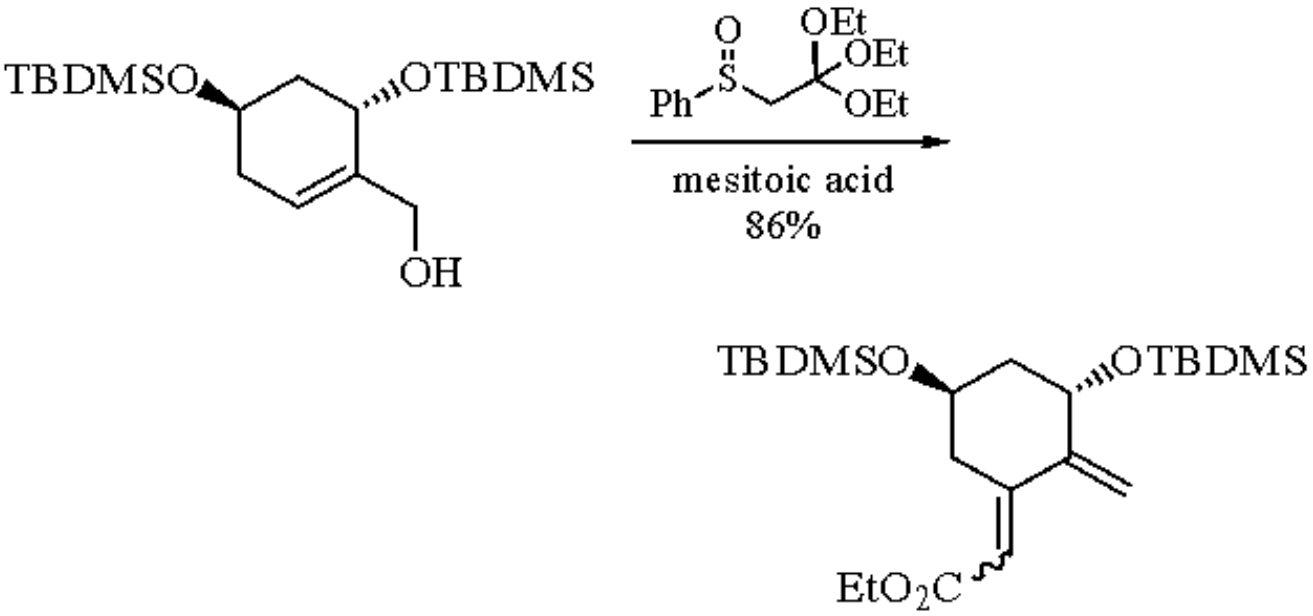

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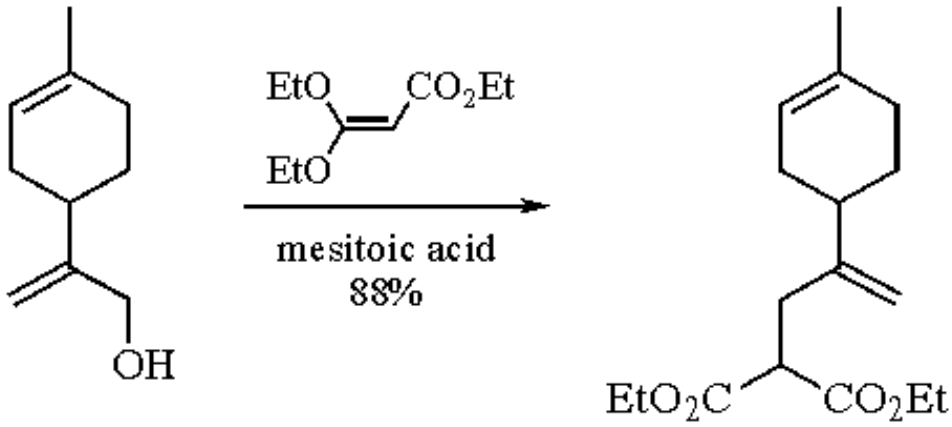

(2)

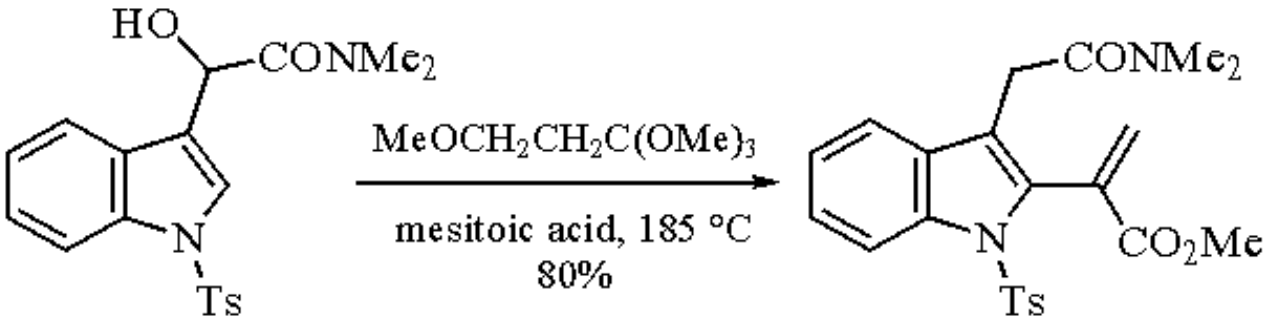

(3)

Reductive Carbonylation.

In the presence of mesitoic acid and 1,10-phenanthroline, palladium metal on alumina support is an effective catalyst for the reductive carbonylation of nitrobenzenes to generate isocyanates, ArNCO;[6] the additional presence of alcohols results in the formation of urethanes.[7]

Synthesis of Sugar Derivatives.

In a recent synthesis of 6-deoxy-6-fluorolactosides, the mesitoyl moiety was utilized as a protecting group (eq 4). Esterification of the free hydroxy groups of disaccharide (**1**) was accomplished using the mixed anhydride of mesitoic acid and ***Trifluoroacetic Acid***. Use of mesitoyl groups in (**2**) allowed for the selective hydrolysis of the butyrate ester. Following incorporation of a fluorine into the molecule, the mesitoyl groups were removed reductively with AlH_3 without affecting the C-F bond.[8]

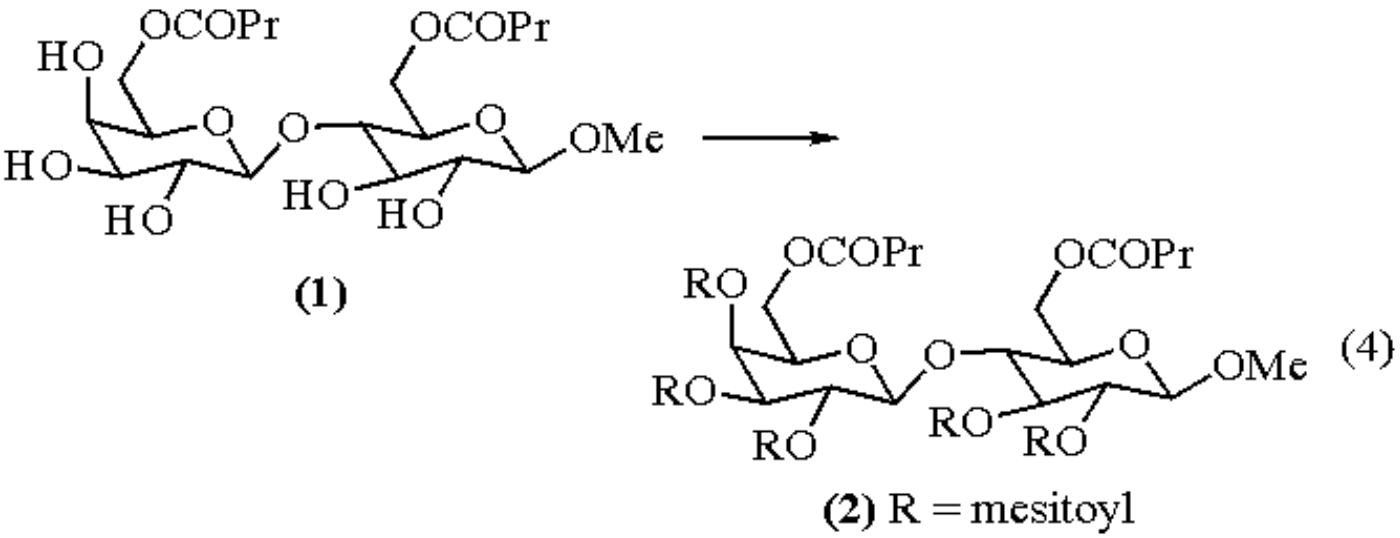

Mesitoyl groups have also been used for the selective protection of 1,4:3,6-dianhydro-D-glucitol.[9]

Related Reagents.

Acetic Acid; ***Hydrochloric Acid***; ***Methanesulfonic Acid***; ***Oxalic Acid***; ***p-Toluenesulfonic Acid***.

---

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Trimethyl Borate

$B(OMe)_3$

[121-43-7] · $C_3H_9BO_3$ · Trimethyl Borate · (MW 103.93)

(used for the preparation of boronic acids and esters;[1a] also used as Lewis acid catalyst or additive in various reactions)

Physical Data: mp -34 °C; bp 68-69 °C; *n*20D 1.3568; *d* 0.915 g cm^{-3}.

Solubility: sol in every proportion in Et_2O and MeOH; very sol EtOH; sol benzene; dec in H_2O.[2]

Form Supplied in: colorless liquid, with purity &egt;99%; azeotrope with methanol (bp 53-58 °C); MeOH is usually present as an impurity.

Preparative Methods: an improved preparation has been recently reported.[3]

Purification: if necessary, the small quantities of MeOH can be removed by adding anhydrous lithium chloride to the bottle of commercial reagent; the mixture is allowed to stand with occasional stirring. The upper layer is then decanted and distilled.[4]

Handling, Storage, and Precautions: is moisture sensitive; must be stored under nitrogen in a cool dry place. It is extremely flammable and forms explosive mixtures in air. Container explosion may occur under fire conditions. $B(OMe)_3$ is irritating to the skin and, as a vapor, to the eyes, mucous membranes, and upper respiratory tract.[5]

Synthesis of Boronic Acids and Esters.

Trimethyl borate is an inexpensive starting material for the preparation of dimethyl boronates, precursors of boronic acids. The classical synthesis involves the reaction with Grignard or alkyllithium reagents (eq 1); treatment with an aqueous acid, followed by extraction with an organic solvent, permits the direct isolation of the boronic acids (eq 2).[1] Various conditions have been used to hydrolyze boronic esters: ***Acetic Acid***,[4a] ***Hydrochloric Acid***,[4b,6] ***Sulfuric Acid***,[7] aqueous ammonium chloride.[8] In some cases, a direct exchange of the OMe group with another alcoholic residue can be effected.[9]

$$RM \xrightarrow{B(OMe)_3} [RB(OMe)_3^-M^+] \longrightarrow RB(OMe)_2 \qquad (1)$$

$$RB(OMe)_2 \xrightarrow{H_3O^+} RB(OH)_2 \qquad (2)$$

$$M = MgCl, MgBr, Li$$

A wide variety of boronic esters or acids can be prepared by this methodology: alkyl- and arylboronic acids are available from both Grignard and lithium reagents,[1,10] allylboronic acid and esters from ***Allylmagnesium Bromide***,[6] γ-substituted allylboronic acids and esters from organolithium reagents,[8] and allenylboronic esters as the only product starting from propargyl Grignard reagents.[11] Vinylboronic esters can be obtained in a stereospecific manner from the corresponding Grignard reagents.[1a,7] The organometallic reagent which reacts with trimethyl borate can also contain an heteroatom, such as sulfur[12a] or silicon,[12b] α to the carbon-metal bond. Finally, lithium derivatives of pyrrole[13a] and furan[13b] can be transformed into the corresponding boronic esters.

For boronic acid synthesis, other electrophilic boron reagents, e.g. ***Fluorodimethoxyborane Diethyl Etherate*** or ***Triisopropyl Borate***, can be used. In the case of substituted allylboronic acids and esters, these two reagents have been employed preferentially.[14]

Use of Boronic Acids and Esters.

Boronic acids and esters are versatile intermediates which have found many applications in organic synthesis, especially in the field of stereocontrolled C-C bond formation.

Dimethyl alkyl- or arylboronates react with H_2O_2 to give the corresponding alcohols or phenols. Coupled with the above described condensation of $B(OMe)_3$ with Grignard or lithium reagents, this reaction allows the overall hydroxylation of organometallic compounds. Applications include the synthesis of phenols[4b] from aryl bromides and of 4-hydroxyisoxazolines[4c] from isoxazolines via the 4-lithio derivative.

Reaction of dimethyl vinylboronates with bromine furnishes the corresponding vinyl bromides with inversion of configuration, allowing the transformation of a (*Z*)- or (*E*)-vinyl bromide into the corresponding (*E*) or (*Z*) diastereoisomer.[1a]

Boronic acids (with R^1 = allyl, substituted allyl, allenyl, and vinyl; R^2 = H; eq 3), obtained from trimethyl borate, can be easily transformed into acyclic boronates, cyclic boronates, or 1,3,2-oxazaborolidines by reaction with the appropriate aliphatic alcohol,[1a,6] a chiral (e.g. phenylbornanediol, diisopropyl tartrate, pinanediol) or achiral diol (pinacol, ethylene glycol)[1a,6] or a chiral or an achiral 2-amino alcohol.[6] This procedure allows the preparation of very pure reagents, in which the single organic group is totally differentiated from a chemical point of view from the alkoxy ligands; in this way the carbon-boron linkage can be utilized very efficiently. Chiral allylboronates can be used for enantio- and diastereoselective C-C bond forming reactions[1,14] with aldehydes (eq 3); the chirality can be present either α to the boron atom (when R^4 &neq; H) or in the chiral auxiliary R^1; also the aldehyde can be achiral or chiral. Finally, if the reaction is carried out between a chiral allylboronic ester and a stereochemically matched chiral aldehyde, greater stereoselectivity can be obtained in taking advantage of double stereodifferentiation effects.

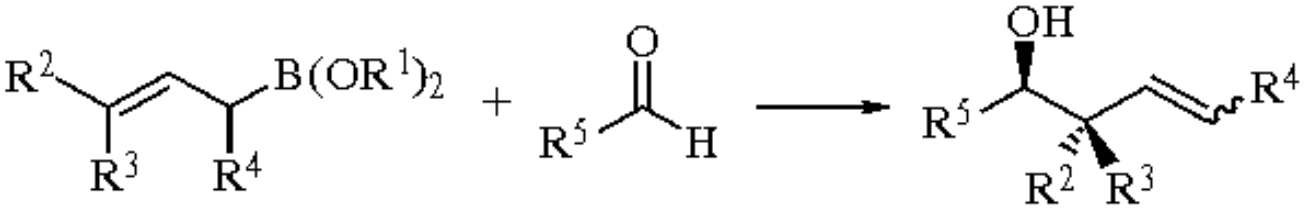

(3)

Allylboronates also react with C=N electrophiles such as aldoximes, imines, and sulfenimides,[14] although the reactions are considerably slower than those with aldehydes.

Boronic acids or esters are also suitable reagents for cross-coupling reactions, used for the formation of a C-C single bond (eq 4); this method is especially useful for the preparation of unsymmetrically substituted biaryls. One or both components can also be heterocycles. Organoboronic acids and esters used for this kind of reaction have R^1 = phenyl,[15a] various aryl,[10,15a] 2-[15a] and 3-furyl,[13b] 2-thienyl,[15a] *N*-Boc-pyrrolidin-2-yl;[13a] R^2 is usually hydrogen except for R^1 = 3-furyl, where the dimethyl boronate is used directly.[13b] R^3 is usually an aromatic or heteroaromatic moiety, but alkenyl or allyl derivatives have also been used. X is a halogen (bromine or iodine)[10,13b] or a triflate.[13b] This coupling reaction has also been used for a new synthesis of hemispherands.[15b]

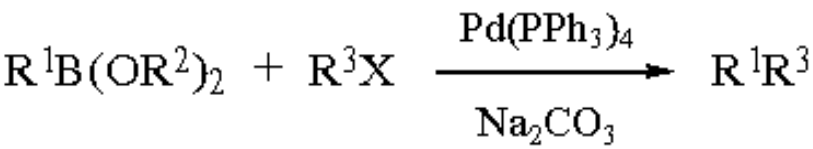

(4)

A stereocontrolled synthesis of terminal (*E*)- and (*Z*)-dienes can be performed by reacting pinacol (*E*)-1-trimethylsilyl-1-propene-3-boronate with aldehydes; the intermediate β-trimethylsilyl alcohols can then be transformed into both (*E*)- and (*Z*)-dienes.[8] Vinylboronates are also prepared from the reaction of the anion of a trimethylsilyl methaneboronic ester (derived from trimethyl borate) and various aldehydes or ketones.[12b]

Anions prepared from cyclic bis(phenylthio)methaneboronic esters, derived from the corresponding dimethyl boronates, can be used to prepare ketene dithioacetals through homologation of carbonyl compounds (eq 5).[12a]

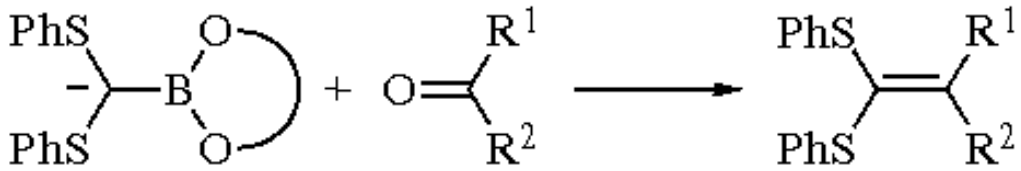

(5)

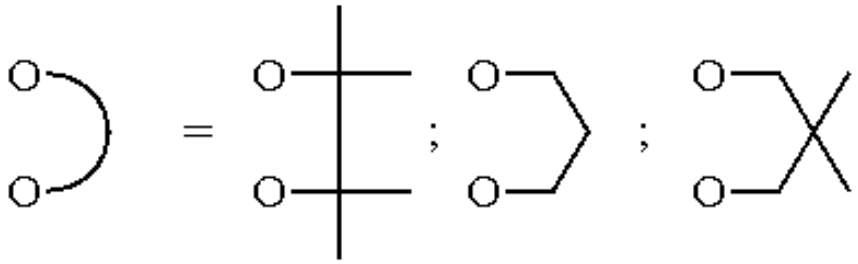

More recently, an arylboronic acid has been used as an intermediate for the preparation of 2-borono-1,3-xylyl crown ethers.[16]

Boronic esters can be reduced by ***Lithium Aluminum Hydride*** to the corresponding lithium alkylborohydrides, which are easily converted into monoorganylboranes,[17a] such as tripylborane, a compound similar to thexylborane, but considerably more stable.[17b]

Use of Trimethyl Borate as Catalyst or Additive.

Trimethyl borate has been used, like other boron compounds, as a catalyst for the reduction of esters to alcohols by ***Lithium Borohydride***.[18a] Trimethyl borate also promotes a rapid ionic reaction of methyl hypobromite with alkenes and dienes.[18b] Finally, trimethyl borate, as with other boronic acids and various boranes, has been used to catalyze anti-Markovnikov hydration of alkenes in the presence of dichloroaluminum hydride under dry air.[18c]

Trimethyl borate has been successfully used to improve the yields in the Reformatsky reaction.[19] This is due to the mildly acidic properties of the boron reagent which neutralizes the zinc alkoxides, so that base-catalyzed side reactions of starting materials are prevented.

Reactions of aldehydes with 1,3-bis(trimethylsilyl)propenyl anion are poorly stereoselective. However, when this condensation was carried out in the presence of $B(OMe)_3$, only *anti* compound (**1**) was obtained (eq 6); (**1**) can in turn be stereospecifically transformed into either (1*E*,3*E*)- or (1*E*,3*Z*)-1-trimethylsilylbuta-1,3-dienes.[20]

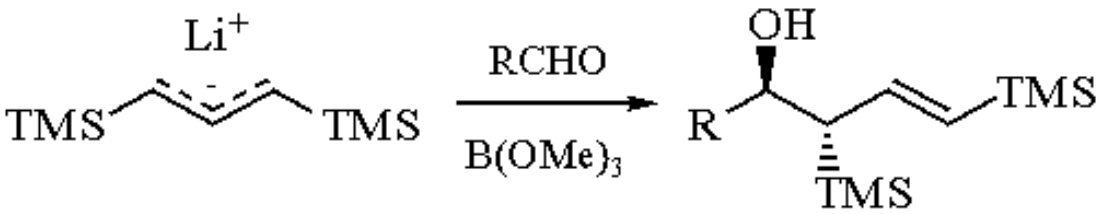

(6)

(1)

Miscellaneous.

Trimethyl borate has been used as an electrophilic reagent to trap the product of the regio- and stereoselective ***Dichlorobis(cyclopentadienyl)zirconium***-catalyzed ethylmagnesation of allylic[21a] and homoallylic[21b] alcohols (eqs 7 and 8).

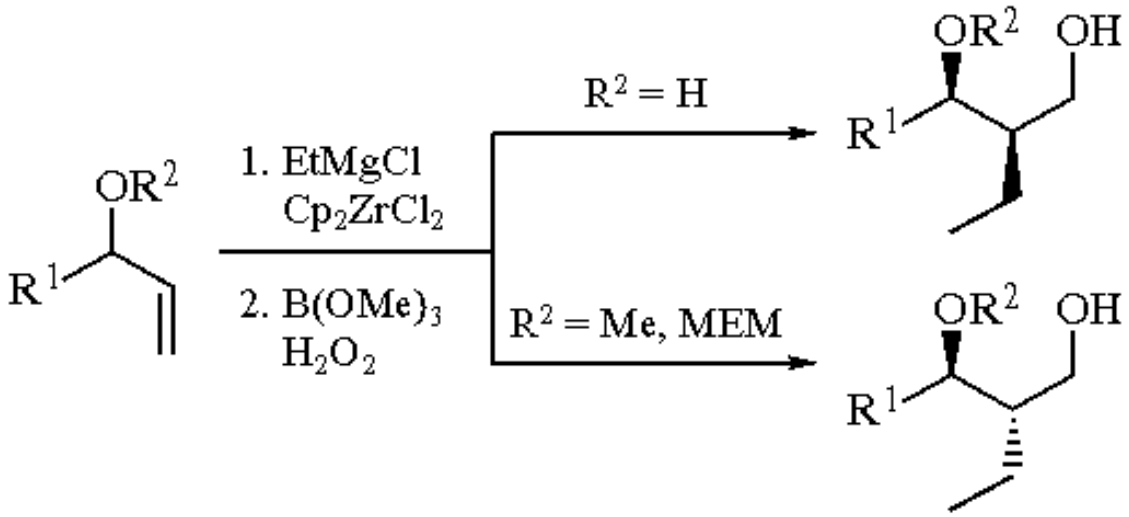

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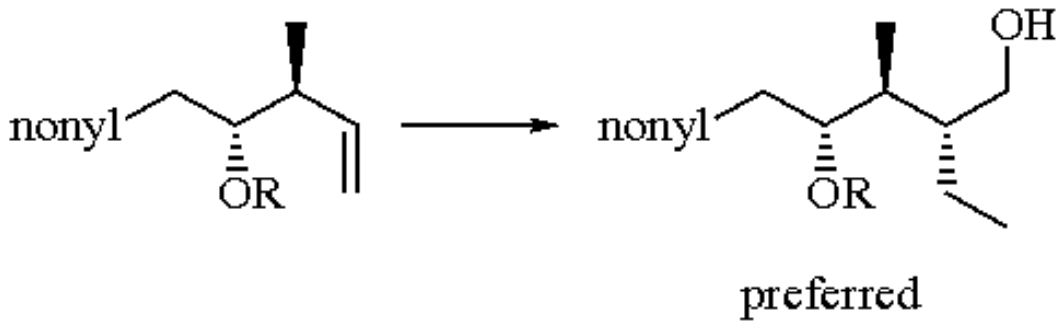

(8)

$B(OMe)_3$, in the presence of ***Borane-Dimethyl Sulfide***, has been used to promote the chemoselective reduction of a carboxylic acid to an alcohol in the presence of an ester.[22]

Trimethyl borate was used also to prepare other borates or tetraalkoxy boron ate compounds. For example, functionalized borate (**2**), obtained by in situ treatment of juglone with $B(OMe)_3$ and a tartaric acid derived chiral diol, has been used as dienophile in an asymmetric Diels-Alder reaction (eq 9).[23]

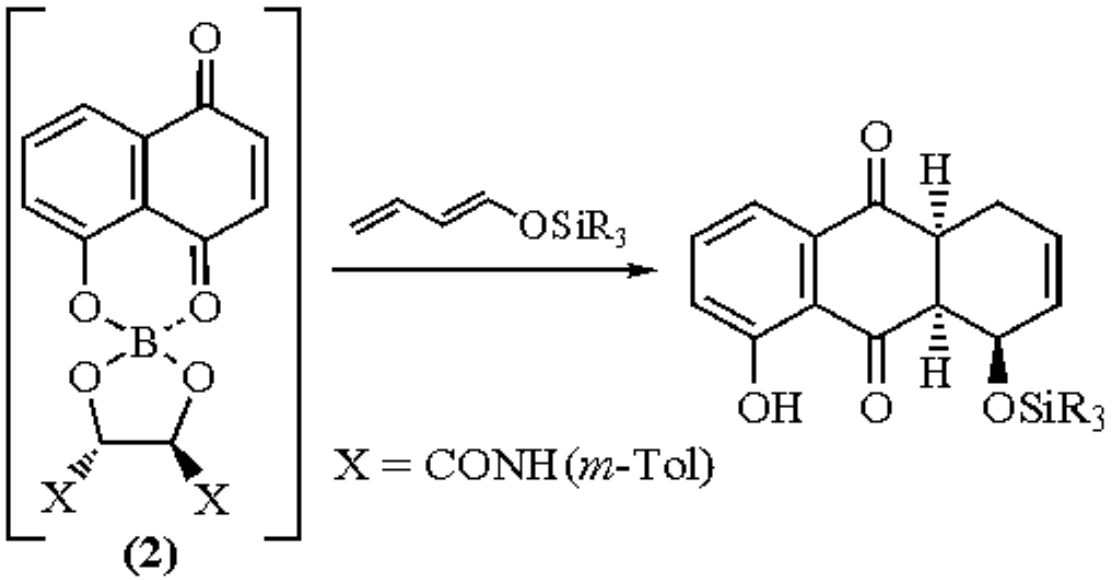

(9)

Finally, in the synthesis of aplasmomycin, a boron-containing antibiotic, the boron ate unit was introduced as the last step by the reaction of deboro aplasmomycin with $B(OMe)_3$.[24]

Related Reagents.

Fluorodimethoxyborane Diethyl Etherate; ***Triisopropyl Borate***.

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2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one[1]

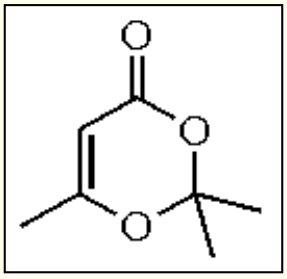

[5394-63-8] · $C_7H_{10}O_3$ · 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one · (MW 142.17)

(acetylketene equivalent, used for acetoacetylation and cycloaddition reactions; can be functionalized to provide substituted acylketenes; diketene equivalent)

Alternate Name: diketene-acetone adduct.

Physical Data: mp 12-13 °C; bp 65-67 °C/0.2 mmHg; *d* 1.088 g cm^{-3}.

Solubility: miscible with most organic solvents.

Form Supplied in: neat liquid; 95% (major impurity acetone).

Analysis of Reagent Purity: GC (keep injector port 200-225 °C); NMR.

Preparative Methods: the diketene-acetone adduct (**1**) is one of a series of 1,3-dioxin-4-ones which can be prepared by the reaction of diketene with an aldehyde or ketone in the presence of an acidic catalyst[2] or a quaternary ammonium salt (eq 1).[3] An alternate preparatory method is the reaction of a β-keto acid with acetone.[4]

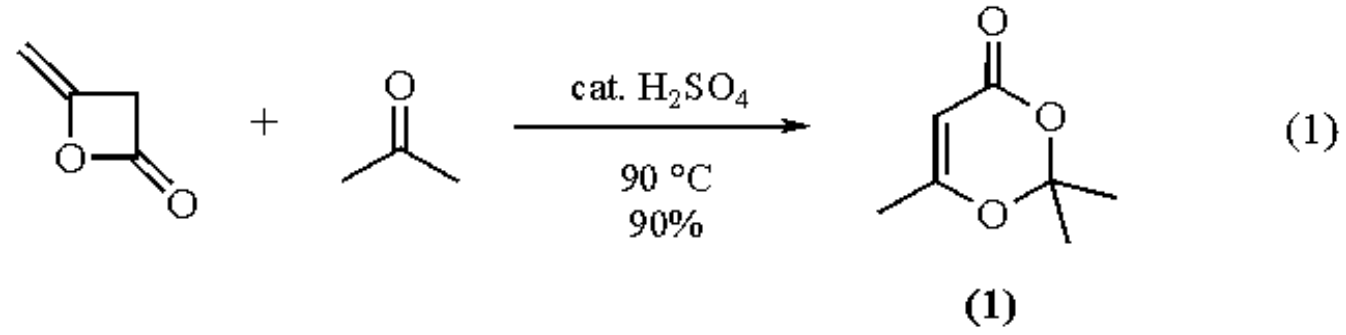

Purification: high-vacuum distillation at temperatures below 80 °C.

Handling, Storage, and Precautions: generally nonhazardous; anticipate release of acetone upon heating over 80 °C; will also produce CO_2 if heated in presence of water; extremely good solvent: will dissolve some plastic tubing. Use in a fume hood.

Chemical Transformations: Acetylketene Generation.

Dioxinone (**1**) generates acetylketene (**2**) and acetone upon heating at temperatures around 120 °C,[5] via a retro Diels-Alder reaction. The acetylketene thus produced reacts in situ with nucleophiles, including alcohols, amines, and thiols, to provide acetoacetic acid derivatives, e.g. (**3**) (eq 2).[6] The diketene-acetone adduct is thus a convenient, safe, and nonlachrymatory alternative to diketene. In practice, dioxinone (**1**) is often added to a solution of the nucleophile in xylene at 110 °C and the acetone is removed by evaporation or distillation; no catalyst is required. Most of these acetoacetylation reactions are complete within 20 min at 120 °C if the acetone is removed efficiently, although polymeric nucleophiles may require higher reaction temperatures or longer times. Changing the substituents at C-2 will alter the temperature at which the acetylketene is liberated (see below). Irradiation at 254 nm will also provide acetylketene from (**1**).[7] Nucleophilic ring opening

can also be effected with base (***Potassium Carbonate***, MeOH).[8]

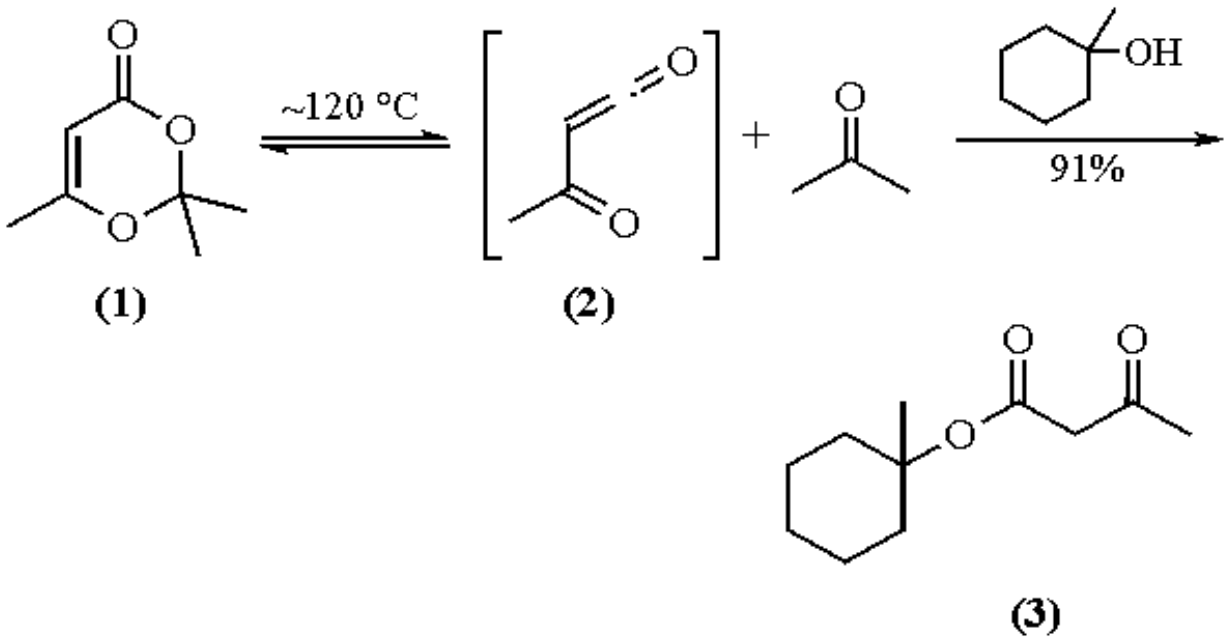

(2)

Virtually every synthetic transformation which utilizes dioxinone (**1**) ultimately involves the generation of an acylketene or a β-keto ester, often following elaboration of the dioxinone nucleus.

Preparation of Heterocycles.

Dioxinone (**1**), as an acetylketene equivalent, reacts with a wide variety of functional groups in a manner analogous to diketene[9] to provide heterocycles. For example, heating dioxinone (**1**) in the presence of electron-rich alkenes, such as enamines or enol ethers, will provide the corresponding pyrone derivative (**4**) via a [4 + 2] cycloaddition reaction, as illustrated in the preparation of 2,6-dideoxy sugar (**5**) (eq 3).[10,11]

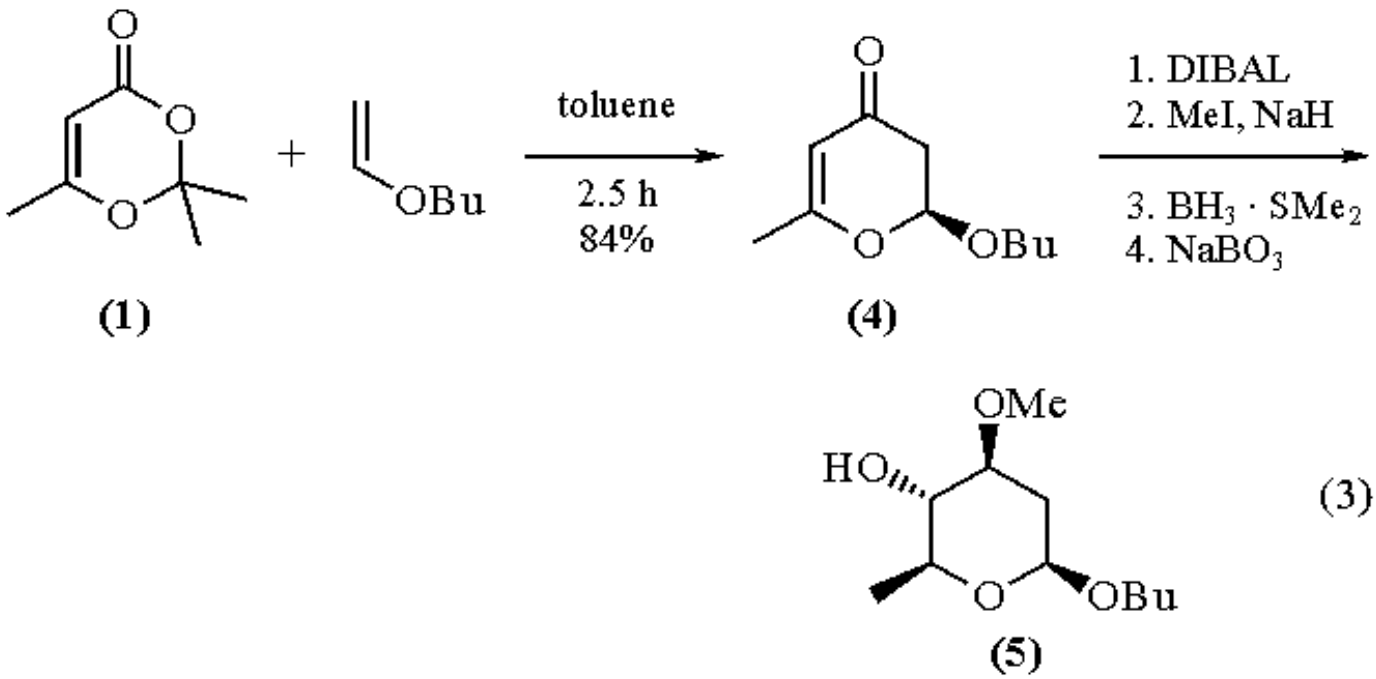

(3)

DeMayo Reactions.

The [2 + 2] photocycloaddition of alkenes to dioxinone (**1**) (eq 4), followed by reduction and then cyclization of the resultant retro-aldol product, affords cyclohexenones (**6**).[12]

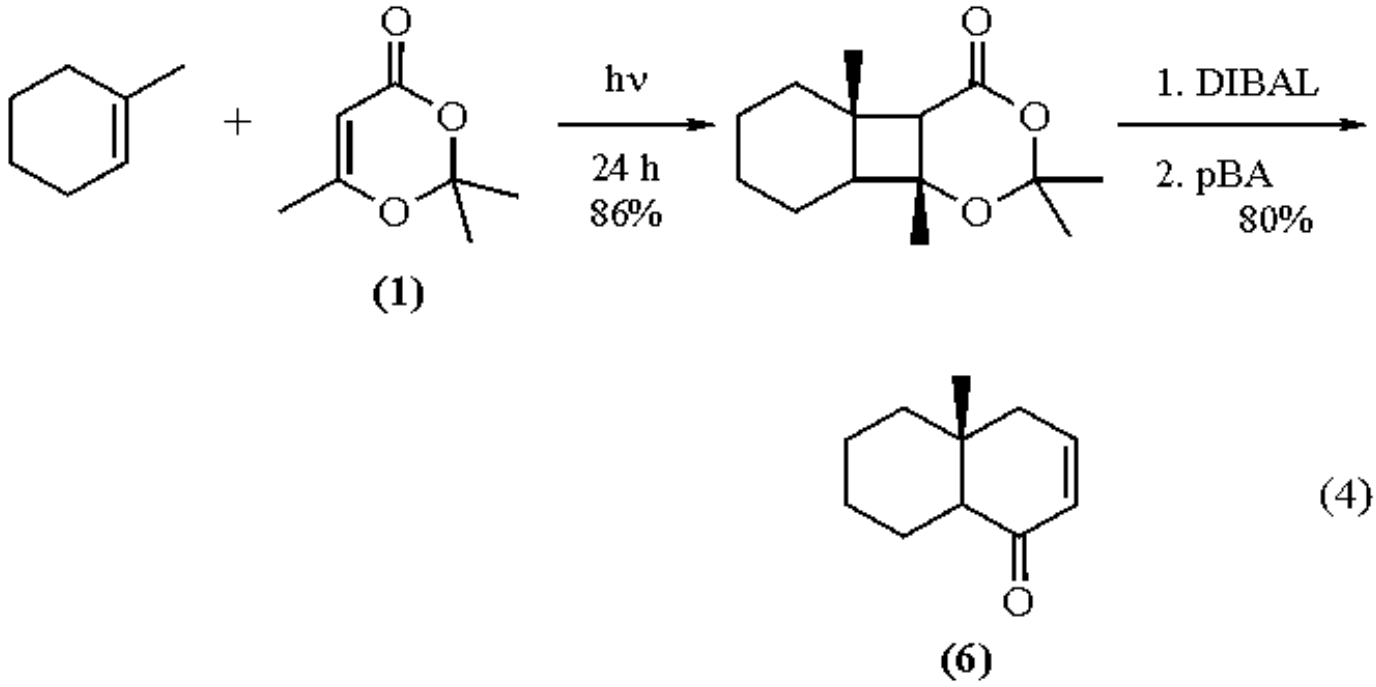

(4)

Synthesis of Modified Dioxinones.

Many dioxinones are modified prior to acylketene generation, either at C-5 or on the C-6 methyl group, to enhance the synthetic utility.[1] Thus dioxinone (**1**) can be halogenated[13] at C-5 or on the 6-methyl group[14] prior to further synthetic elaboration (eqs 5 and 6). The latter bromomethyl dioxinone (**7**) is readily converted into a Wittig[15] or Horner-Emmons reagent.[14]

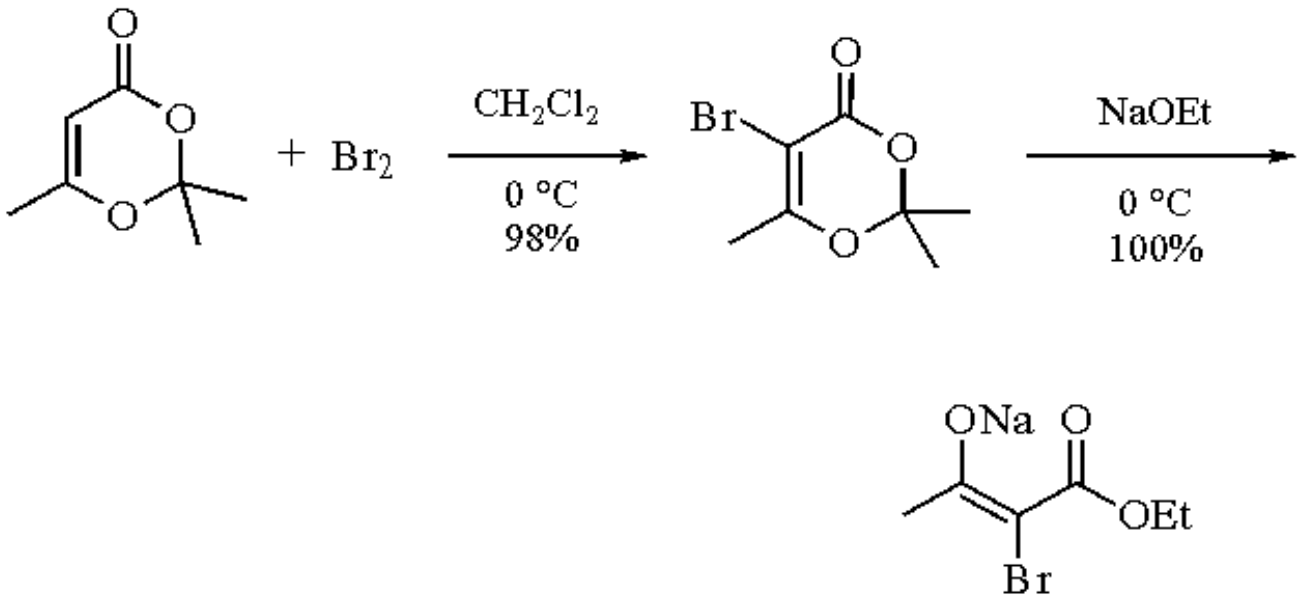

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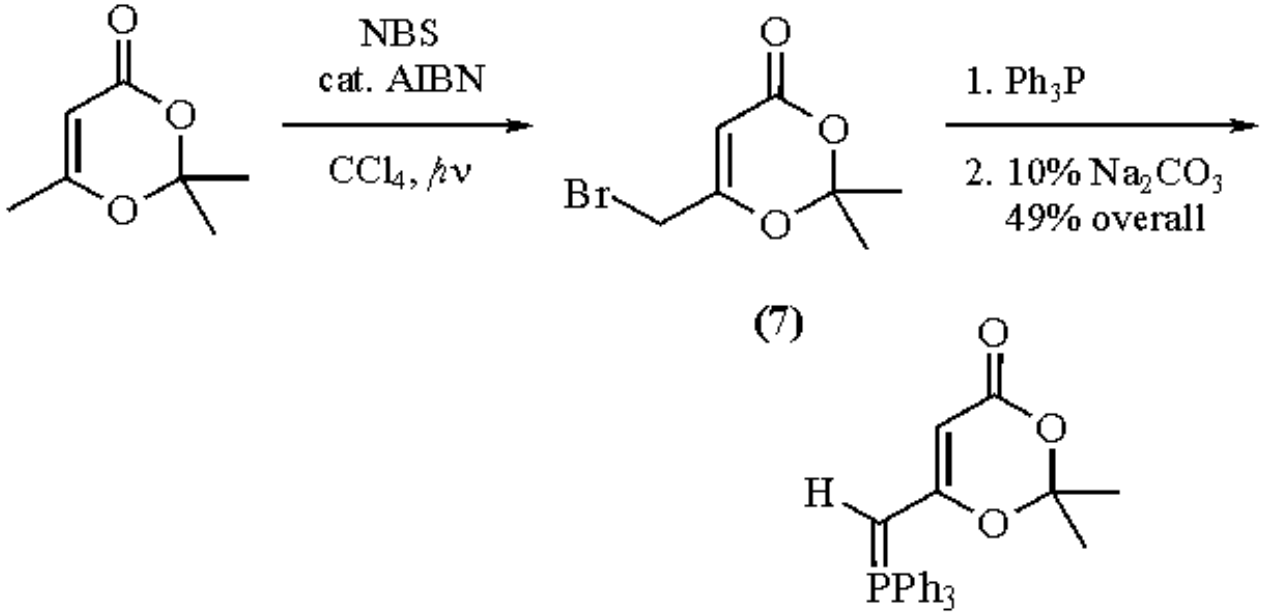

(6)

An alternate approach to modification of dioxinone (**1**) on the C-6 methyl group is via deprotonation (eq 7),[16] sometimes accompanied by silyl enol ether formation (eq 8).

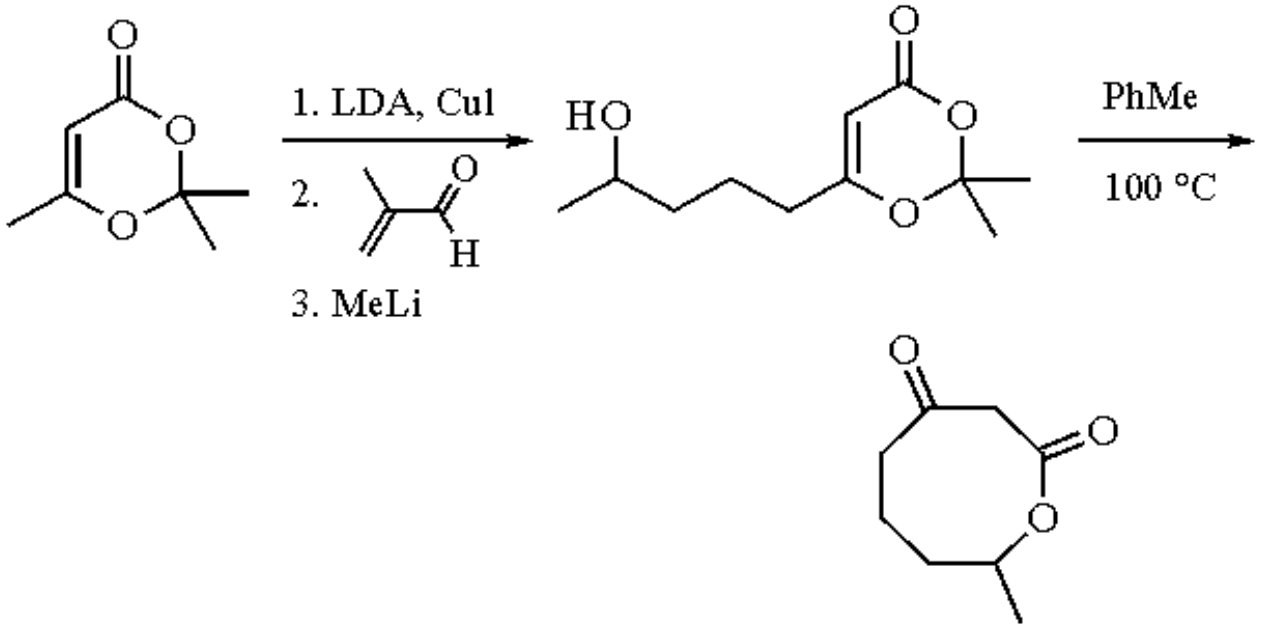

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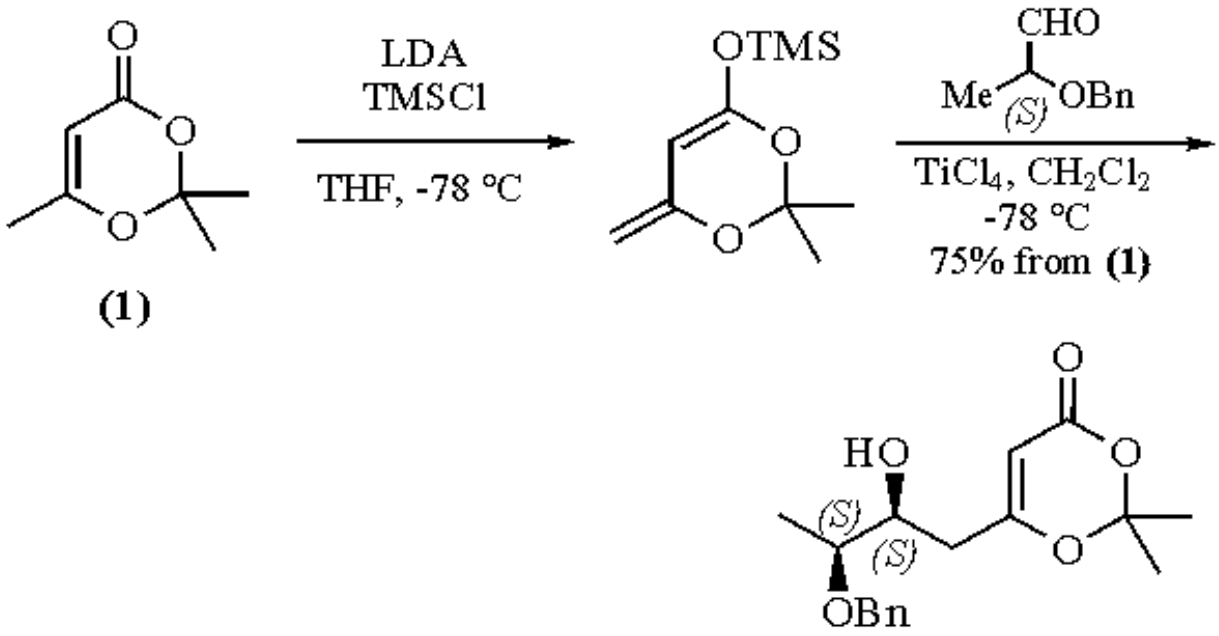

(8)

The resulting elaborated dioxinones have been used to effect ring closure of large rings via intramolecular ketene trappings,[16] methoxide-mediated ring openings to the β-keto esters,[16c,17] and in intramolecular photocycloaddition reactions (eq 9),[18] thereby demonstrating the synthetic utility and versatility of the diketene-acetone adduct (**1**). Both (*R*)- and (*S*)-2-*t*-butyl dioxinones are enantiopure acetoacetate derivatives that are useful for asymmetric synthesis.

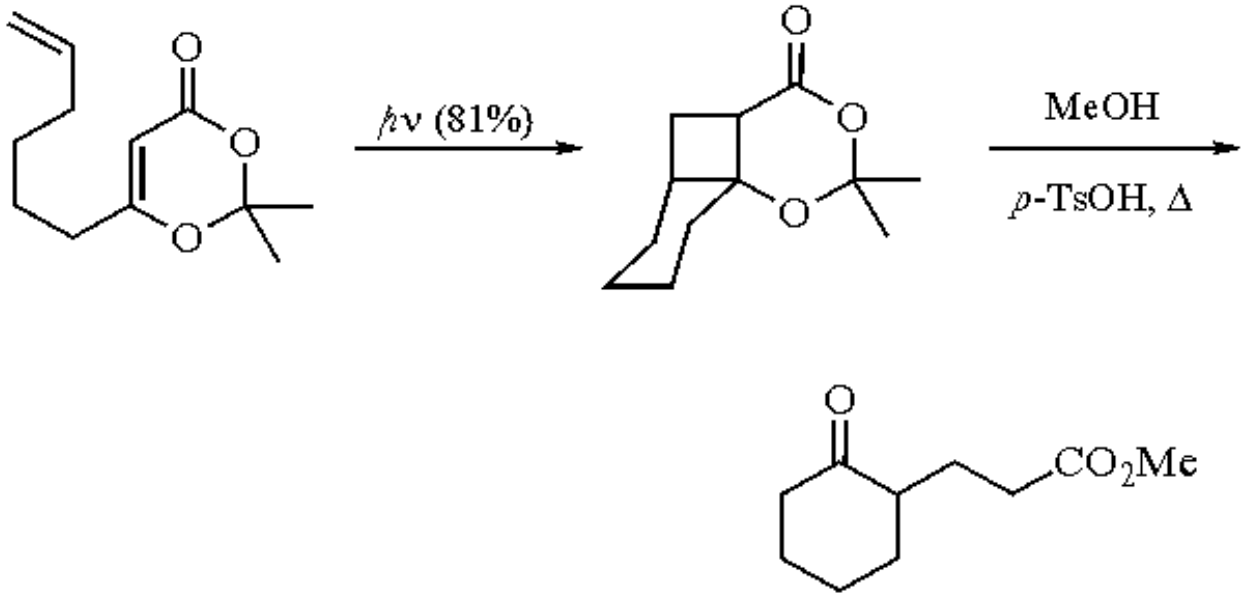

(9)

Related Reagents.

Acetoacetic Acid; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***Diketene***; ***Ethyl Acetoacetate***; ***Ethyl 4-Chloroacetoacetate***; ***Ethyl 3-Hydroxybutanoate***; ***Ethyl 4-(Triphenylphosphoranylidene)acetoacetate***; ***Methyl Dilithioacetoacetate***.

---

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Trimethylene Oxide

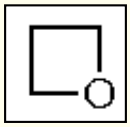

[503-30-0] · C_3H_6O · Trimethylene Oxide · (MW 58.09)

(three-carbon homologation)

Alternate Name: oxetane.

Physical Data: bp 50 °C; *d* 0.893 g cm^{-3}.

Solubility: sol H_2O and most common organic solvents.

Form Supplied in: commercially available in 97% purity.

Preparative Methods: from 3-chloropropyl acetate and ***Potassium Hydroxide***;[1] from ***1,3-Propanediol*** and ***Diethyl Azodicarboxylate/Triphenylphosphine***.[2]

Purification: by distillation.

Reaction with Carbon Nucleophiles.

Trimethylene oxide readily undergoes ring opening with a variety of carbon nucleophiles to give the three-carbon homologated alcohol. Substituted oxetanes undergo analogous reactions. Grignard reagents and alkyllithiums react cleanly, although reduced yields are obtained with secondary Grignard reagents (eq 1).[3] Alkyl cuprates,[4] alkenyllithium,[5] alkenylaluminum,[6] alkynyllithium,[7] and allyllithium[8] reagents have been used to open oxetane. Reaction with ester and amide enolates provides access to 5-hydroxy esters and amides (eq 2)[9] and ketone imine salts react with oxetane (eq 3) as well.[10] ***Boron Trifluoride Etherate*** is frequently used to assist the ring opening. Oxetane reacts with allylsilanes and ***Titanium(IV) Chloride*** to give the ring-opened products (eq 4).[11]

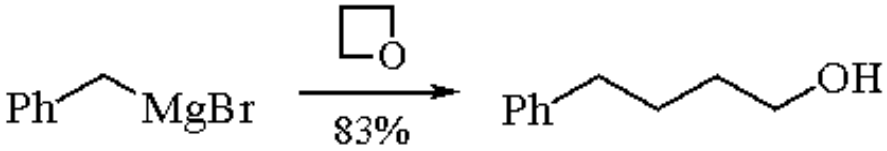

(1)

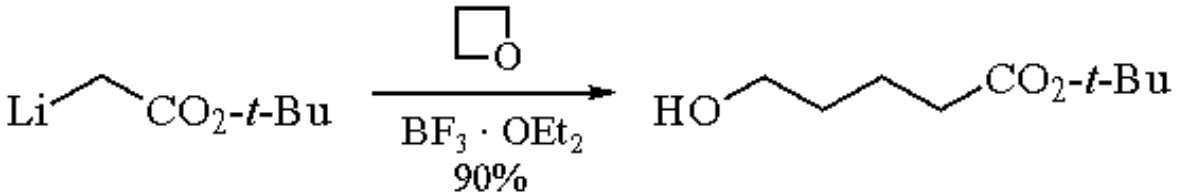

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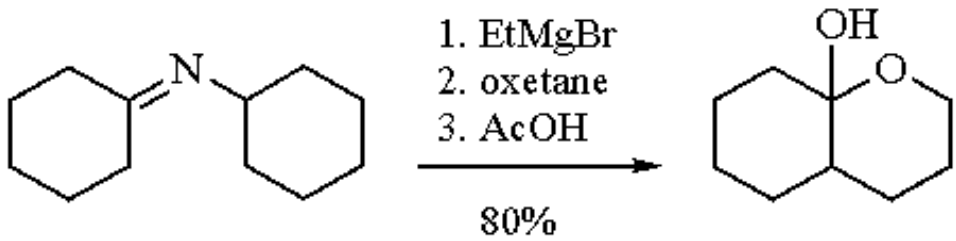

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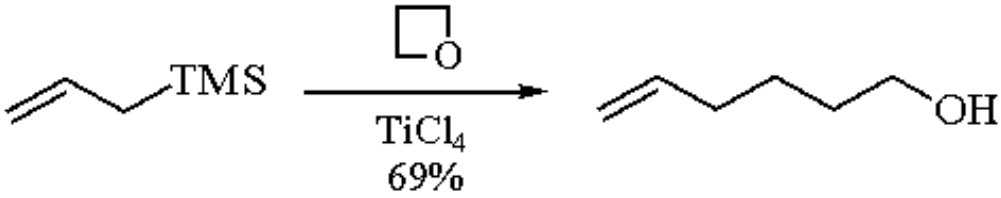

(4)

Reaction with Heteroatom Nucleophiles.

Trimethylene oxide undergoes ring opening with a wide variety of heteroatom nucleophiles. Reaction with ***Cyanotrimethylsilane*** gives, after hydrolysis of the isocyanide, 3-aminopropanol (eq 5).[12,13] 3-Hydroxydimethylsulfonium salts are obtained on reaction with ***Trifluoromethanesulfonic Acid*** and ***Dimethyl Sulfide***.[14] Phosphonium salts are obtained on reaction with ***Triphenylphosphine*** and ***Trifluoroacetic Acid*** or triflic acid (eq 6).[15] Reaction with phosphine anions gives the 3-hydroxypropylphosphines.[16] Trimethylene oxide is readily opened by selenium nucleophiles, such as phenylselenide anion, which gives 3-hydroxypropyl phenyl selenide.[17]

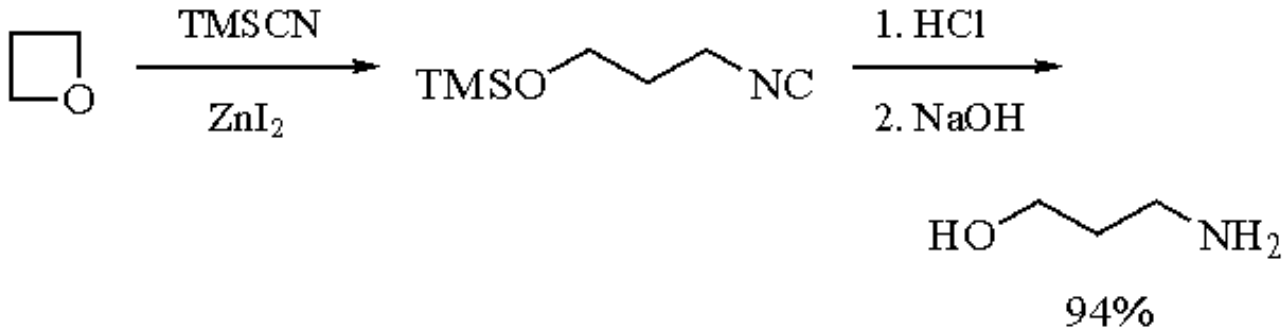

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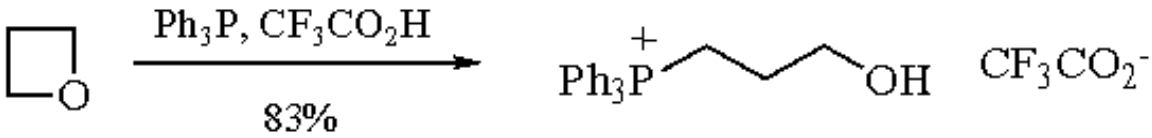

(6)

Reductive Opening of Oxetane.

Reduction with ***Lithium 4,4´-Di-t-butylbiphenylide*** (LDDB) gives the 3-lithioalkoxide, which reacts with a wide variety of electrophiles (eq 7).[18] A similar opening occurs with the ***Potassium/18-Crown-6*** complex.[19]

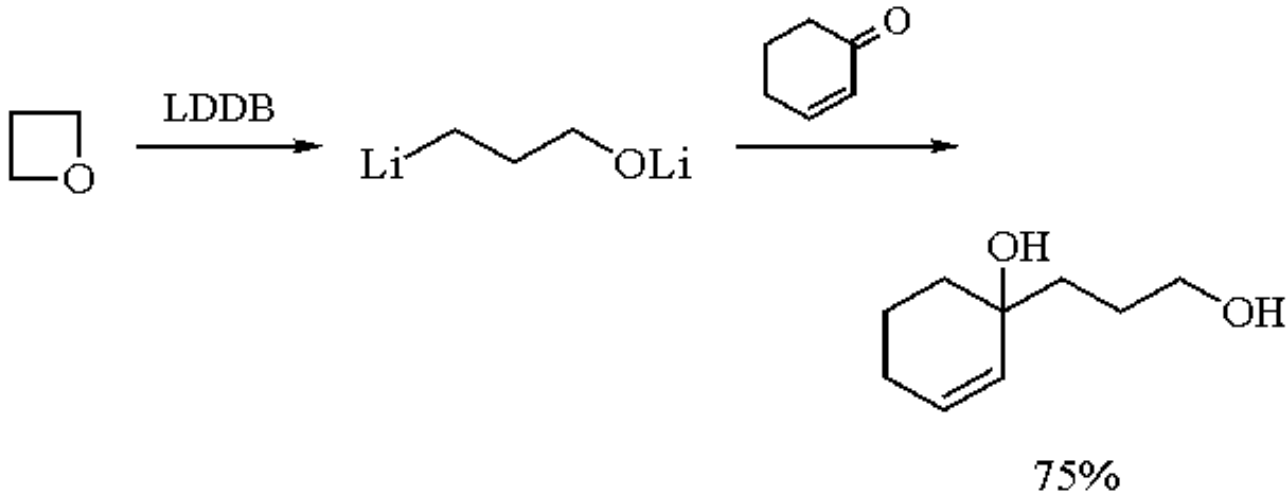

(7)

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Trimethylironlithium

Me_3FeLi

[26220-97-3] · C_3H_9FeLi · Trimethylironlithium · (MW 107.91)

(alternative to ***Lithium Dimethylcuprate***[1] for constructing new carbon-carbon bonds by its reaction with alkenones,[5] alkyl halides,[2] vinyl halides, and allyl halides)

Alternate Name: lithium trimethylferrate.

Preparative Method: prepared in situ by reaction of FeI_2 and MeLi in ether.

Handling, Storage, and Precautions: decomposes in solution at 0 °C after several hours.

Carbon-Carbon Bond Formation.

Methylation of Organohalides.

Alkylation of alkyl halides using organocopper reagents has been widely studied.[1] Other organometallic reagents have also been studied for their efficacy in carbon-carbon bond formation, including trimethylironlithium.[2]

The reagent appears to work most effectively with vinyl, phenyl, and primary alkyl halides. However, it is generally ineffective with secondary and tertiary alkyl halides, under the conditions examined (Table 1). The reaction between trimethylironlithium and organohalides is considerably faster than similar reagents prepared from manganese or cobalt. The reaction of tri-*n*-butylironlithium with organohalides failed.

Table 1 Methylation of Organohalides with Trimethylironlithium in Ether[2]

Halide	Temp. (°C)	Time (h)	Product	Yield (%)
1-Iododecane	- 78	3	*n*-Undecane	2
Iodocyclohexane	- 20	1	Methylcyclo-hexane	10
3-Bromocyclohexane	- 20	1	3-Methylcyclo-hexene	50
Iodobenzene	- 78	3	Toluene	50
trans-1-Iodo-1-nonene	- 78	1	*trans*-2-Decene	90
trans-1-Bromo-2-phenylethylene	- 78	1.5	*trans*-1-Phenyl-propene	83
1-Bromocyclohexene	- 78, 0	3, 12	1-Methylcyclo-	75

1-Bromocyclohexene	- 78, 0	3, 12	1-Methylcyclo-hexene	75
7,7-Dibromonorcarane	- 78, 0	4, 12	7,7-Dimethyl-norcarane	65

In general, trialkylironlithium appears to be inferior to organocuprates in effecting carbon-carbon bond formation. However, it has been found to be superior to organocuprates and other methylating reagents in special cases.[3] For instance, the methylation of allyl bromide (**1**) gave the corresponding alkene (**2**) in excellent yield, without an allylic transposition[4] that was found to occur with lithium dimethylcuprate (eq 1).

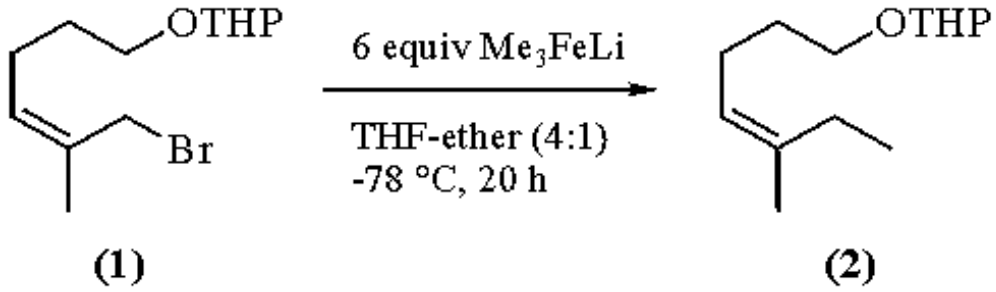

(1)

Methylation of Cycloalkenones.[5]

The methylation of cyclohexenone (**3**) with trimethylironlithium gave the conjugate addition product, 3-methylcyclohexanone (**4**), in 26% yield, and cyclohexenol (**5**), in 28% yield (eq 2). Greater regioselectivity to produce cyclohexanone (**4**) is achieved with organocuprates and organomanganese reagents.

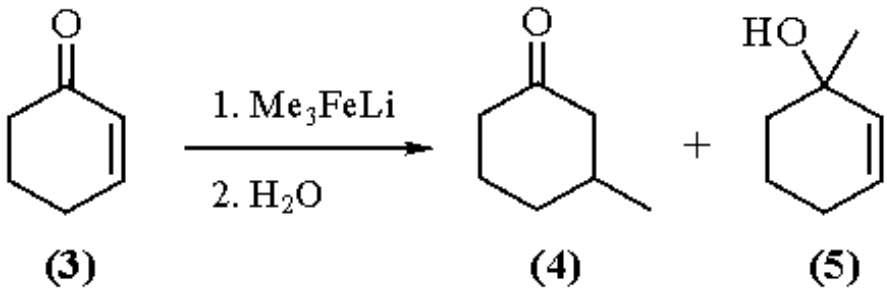

(2)

Miscellaneous Reactions.

The reaction of trimethylironlithium with epoxyvinyl sulfone (**6**) gave predominantly ketone (**7**) and reduction product (**8**) rather than the anticipated 1,2- and 1,4-addition products (eq 3).[6]

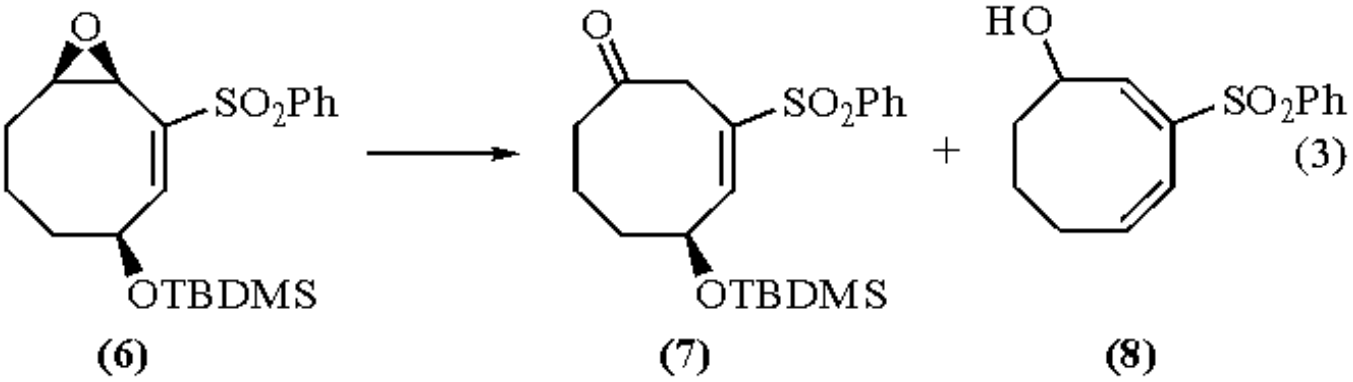

(3)

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Trimethyl(3-methyl-2-butenyl)stannane

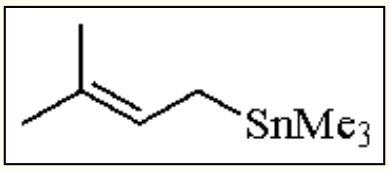

[17314-40-8] · $C_8H_{18}Sn$ · Trimethyl(3-methyl-2-butenyl)stannane · (MW 232.97)

(γ-regioselective prenylation of aldehydes and ketones; α-regioselective prenylation of quinones; palladium-catalyzed regioselective coupling with electrophiles)

Alternate Name: prenyl trimethylstannane.

Physical Data: bp 56-57 °C/15 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: by the reaction of ***Trimethylstannyllithium*** with 3-methyl-2-butenyl bromide.[1] Alternatively, it is prepared from 3-methyl-2-butenylmagnesium bromide and ***Chlorotrimethylstannane***.[2]

Handling, Storage, and Precautions: is air- and moisture-stable. However, it should be kept under N_2 in a refrigerator for prolonged storage.

Prenylation of Aldehydes and Ketones.

Prenyltrimethylstannane reacts with aldehydes and ketones in the presence of ***Boron Trifluoride Etherate*** at low temperatures to give the corresponding homoallyl alcohols in high yield (eq 1).[3] The $BF_3.OEt_2$-mediated reaction of the prenyltin reagent with acenaphthenequinone affords the γ-adduct exclusively (eq 2), whereas the photochemical reaction in MeCN produces a 68:32 mixture of the α- and γ-adducts in 87% yield.[4] An α-regioselective prenylation occurs in the photochemical reaction of benzil with the prenyltin reagent (eq 3).[4]

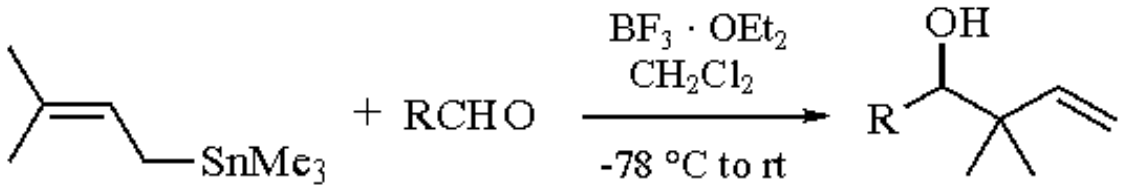

(1)

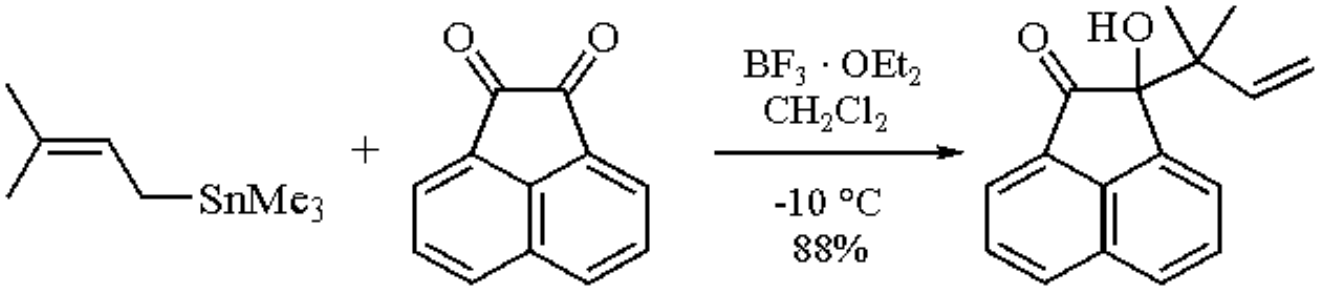

(2)

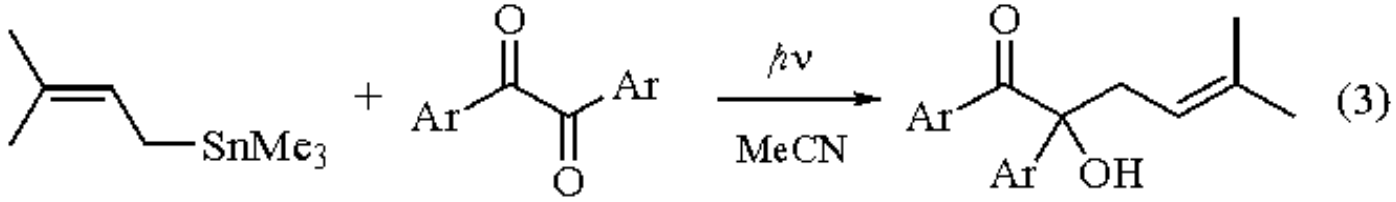

Prenylation of Quinones.

Lewis acid (BF_3) mediated allylation of α,β-unsaturated ketones with allylstannanes affords only 1,4-addition products.[3] However, the $BF_3.OEt_2$-mediated reaction of *o*-quinones, such as 9,10-phenanthrenequinone and acenaphthenequinone, with allylstannanes gives exclusively 1,2-addition products (quinols) (eq 2). Similarly, *p*-quinones, such as 2,6-dimethoxybenzoquinone and 2-methoxy-1,4-naphthoquinone, afford only 1,2-adducts (quinols).[1] On the other hand, the allylation of simple benzoquinone with allyltrialkylstannane produces allylhydroquinone (1,4-adduct) in high yield, which is converted to allylbenzoquinone upon oxidation with ***Silver(I) Oxide*** or ***Iron(III) Chloride***.[1] The reaction of benzoquinone with 3-methyl-2-butenyltributylstannane gives the α-1,4 adduct (eq 4).[1] Similarly, α-1,4-addition products are obtained from 2,3-dimethyl-, 2,5-dimethyl-, 2,6-dimethyl, and trimethylbenzoquinone, 2-methyl-1,4-naphthoquinone, and 2,3-dimethoxy-5-methylbenzoquinone. 2-Acetyl-1,4-naphthoquinone, in which the C-3 position is sterically crowded, gives a 70:30 mixture of γ-1,4 and α-1,4 adducts in 80% yield upon treatment with the title reagent.[5]

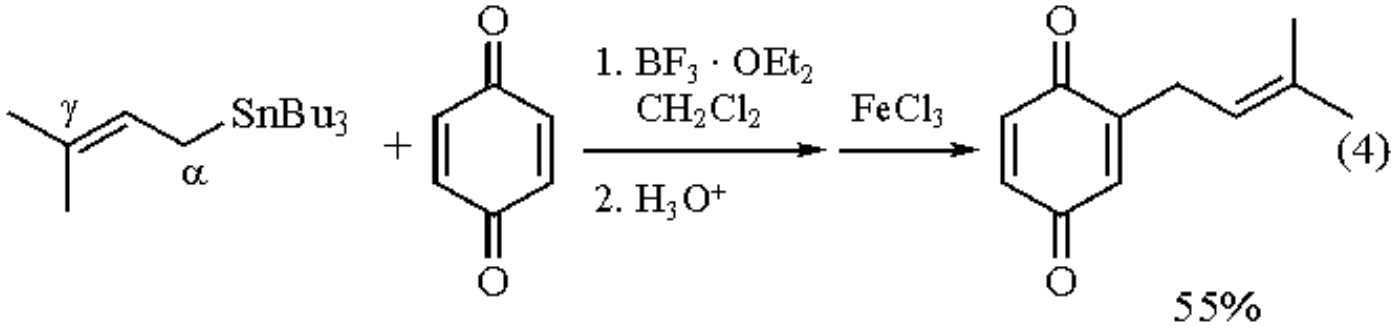

Substitution with Allylic Substrates and Vinyl Epoxides.

The allylic-allylic coupling of trimethyl(3-methyl-2-butenyl)stannane with allylic acetates promoted by bis(diethylaluminum) sulfate affords, in general, a mixture of the γ-α´ and γ-γ´ products (eq 5).[2] It should be noted that the coupling takes place at the γ-position of the tin reagent. The coupling with allylic ethers and halides results in lower yields. The coupling between allylic stannanes and allylic halides takes place at rt in CH_2Cl_2 at high pressures (~10 kbar) to give head-to-tail coupling products (γ-α´ adducts), with allylic rearrangement of the tin reagents, in high yields.[6] The $BF_3.OEt_2$-mediated reaction of the tin reagent with vinyl epoxides normally gives 1,2-addition products, with 1,3-allylic rearrangement of the allylstannane, in high yields (eq 6).[7]

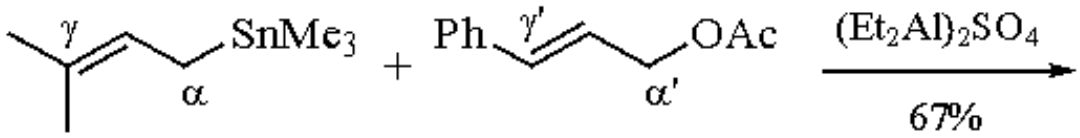

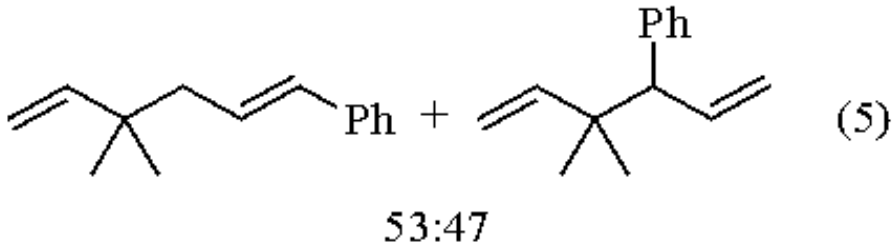

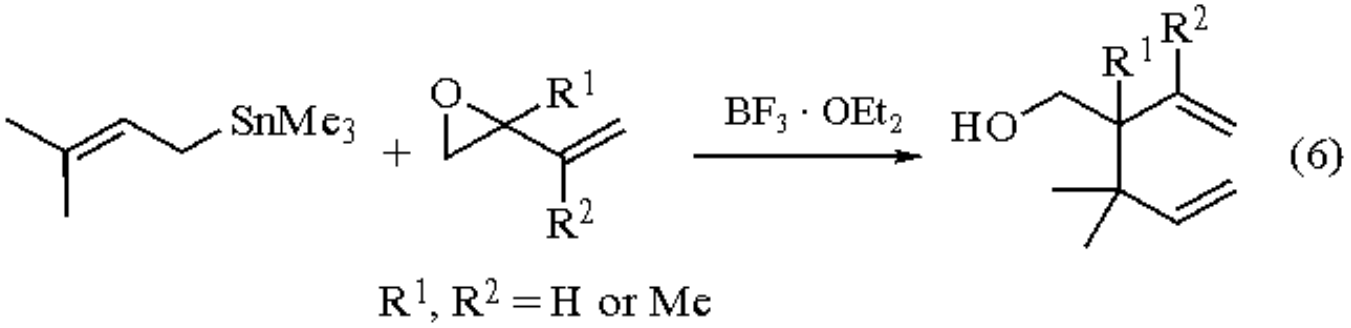

Palladium-Catalyzed Coupling.

The palladium-catalyzed coupling reaction of organotin reagents with organic electrophiles, such as acid halides, allylic halides, aromatic and benzylic halides, vinyl iodides and triflates, and α-halo esters, takes place under mild conditions in high yields.[8] A wide variety of organic halides and organotin compounds can be coupled either directly or in the presence of carbon monoxide (to yield a ketone R^1COR^2). Moreover, a wide variety of functional groups (e.g. CO_2R, CN, OH, and even CHO) are tolerated on either reaction partner. In addition, the coupling of allylic components (i.e. allylstannane or allyl halide) is regioselective and occurs stereospecifically with inversion of configuration at sp^3 carbon centers bound to tin and/or halogen. Usually retention of configuration of the double bond is observed, regardless of which reactant contains the double bond. The palladium-catalyzed direct coupling of prenyltributyltin with allyl bromide occurs with preferential allylic rearrangement of the tin reagent (eq 7).[9] However, no allylic rearrangement takes place in coupling reactions of the prenyl bromide partner (eq 8). In contrast to direct coupling, carbonylative coupling occurs without allylic rearrangement of the allylic tins and allylic halides, and CO insertion takes place exclusively at the least hindered site (eq 9).[10]

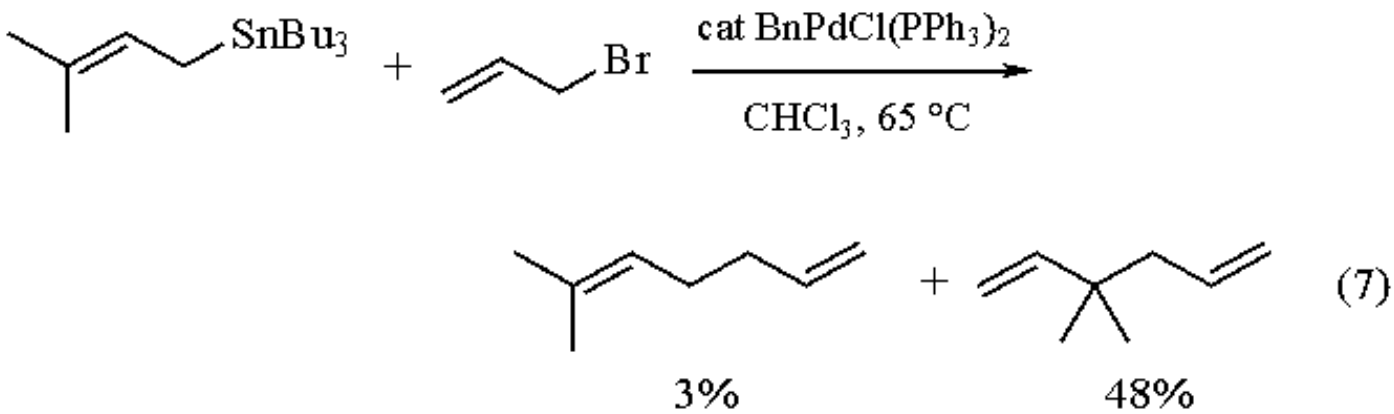

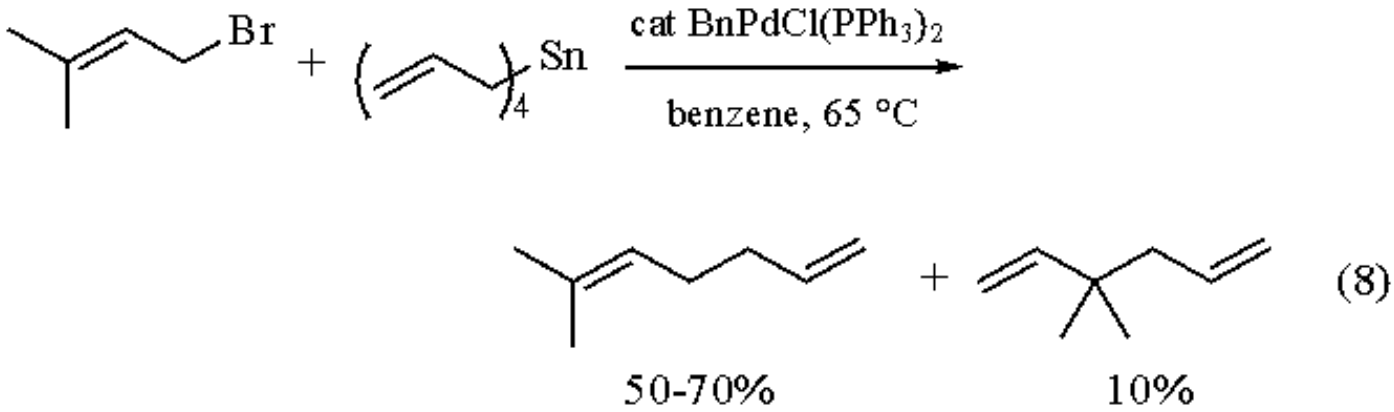

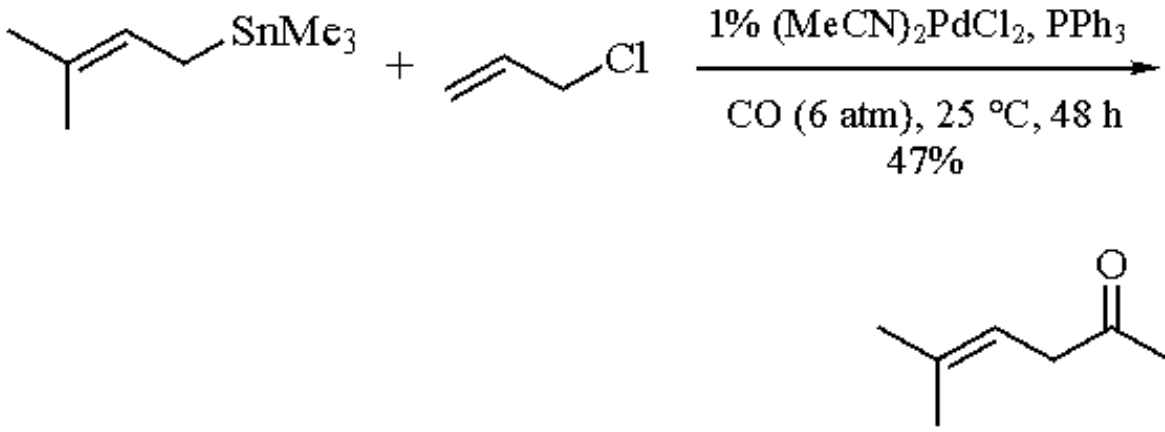

(9)

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1. Naruta, Y. *JACS* **1980**, *102*, 3774.
2. Hosomi, A.; Imai, T.; Endo, M.; Sakurai, H. *JOM* **1985**, *285*, 95.
3. (a) Hosomi, A.; Iguchi, H.; Endo, M.; Sakurai, H. *CL* **1979**, 977. (b) Naruta, Y.; Ushida, S.; Maruyama, K. *CL* **1979**, 919.
4. Takuwa, A.; Nishigaichi, Y.; Yamashita, K.; Iwamoto, H. *CL* **1990**, 639.
5. Uno, H. *JOC* **1986**, *51*, 350.
6. Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *CC* **1984**, 548.
7. Naruta, Y.; Maruyama, K. *CL* **1987**, 963.
8. Stille, J. K. *AG(E)* **1986**, *25*, 508.
9. (a) Kosugi, M.; Migita, T. *J. Syn. Org. Chem. Jpn.* **1980**, *38*, 1142. (b) Godschalx, J. P.; Stille, J. K. *TL* **1980**, *21*, 2599.
10. Merrifield, J. H.; Godschalx, J. P.; Stille, J. K. *OM* **1984**, *3*, 1108.

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2,4,4-Trimethyl-2-oxazoline

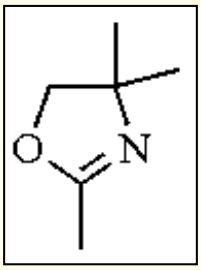

[1772-43-6] · $C_6H_{11}NO$ · 2,4,4-Trimethyl-2-oxazoline · (MW 113.18)

(a masked ethyl acetate equivalent; generation of the anion with *n*-BuLi followed by treatment with electrophiles affords homologated acetic acids and esters, β-hydroxy esters, β-keto esters, α,β-unsaturated esters, and γ-butyrolactones[1])

Alternate Name: 4,5-dihydro-2,4,4-trimethyloxazole.

Physical Data: bp 112-113 °C.

Form Supplied in: commercially available.

Preparative Method: can be prepared by the thermal condensation (98-110 °C) of acetic acid and 2-amino-2-methyl-1-propanol in 73% yield (eq 1).[2]

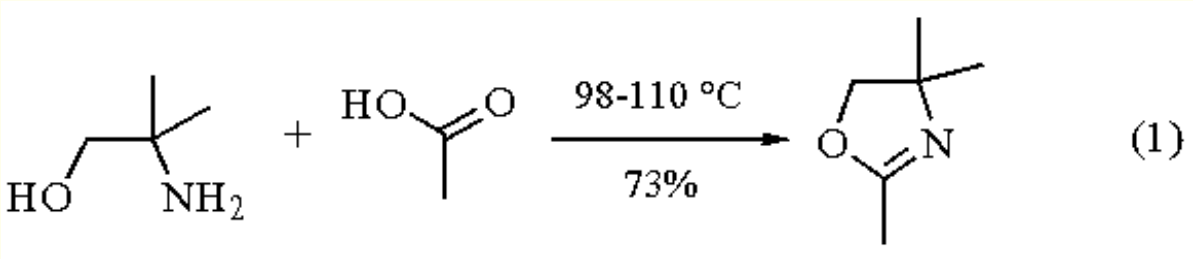

Handling, Storage, and Precautions: no special precautions are warranted.

Preparation of Analogs.

Other 2-substituted oxazolines can be prepared in a similar fashion to the preparation of the title reagent, from the appropriate carboxylic acid. Substituted oxazolines can be formed under milder conditions by cyclocondensations with the corresponding orthoesters (DMF, 110 °C) or imino ether hydrochlorides (MeOH, 0 °C).[3] 2-Alkyl- and 2-aryl-4,4-dimethyl-2-oxazolines may also be prepared by rearrangement of *N*-acyl-2,2-dimethylaziridines.[2b]

α-Alkylations.

Lithiation of the C-2 methyl group of the title compound occurs with ***n-Butyllithium***. Treatment of the resulting anion with electrophiles forms substituted oxazolines (eq 2). One of the remaining methylene protons from the same position can be abstracted in a similar fashion and the resulting anion alkylated again. Subsequently, the mono- or dialkylated oxazoline can be easily transformed to the corresponding carboxylic acid or ethyl ester. Thus the title compound functions as an acetic acid synthon. Some illustrative examples of this methodology are listed in Table 1.[3,5-8] This protocol has been used to synthesize radiolabelled amino acids.[4]

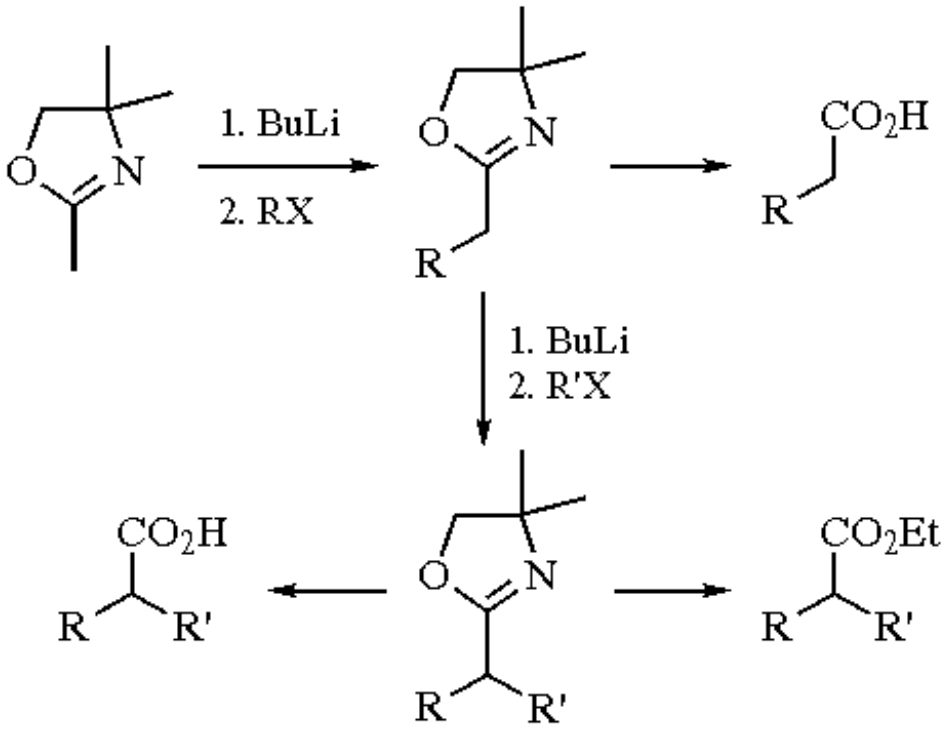

(2)

Table 1 Homologated Acetic Acids, Produced According to Eq 2

RX	Product	Yield (%)
		80[3,5]
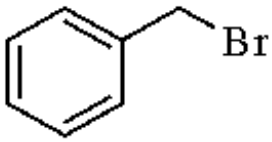	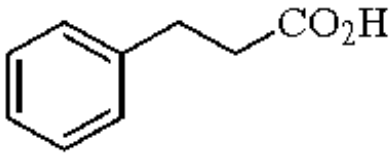	95[3,5]
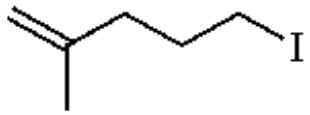	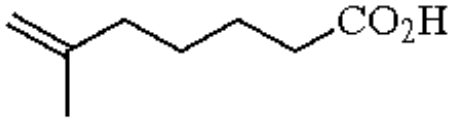	94[3]
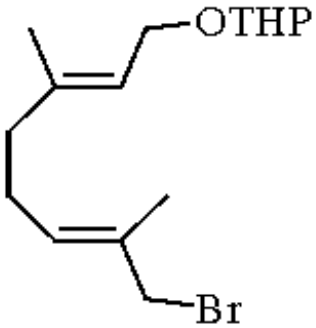	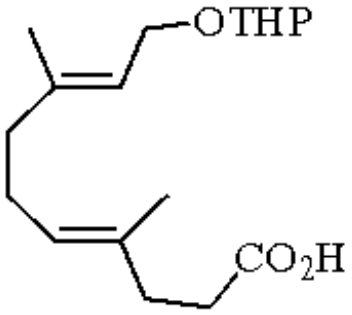	37[6]
(-)-*(S)*-Menthyl *p*-toluenesulfinate	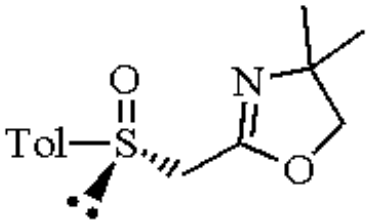	83[7]
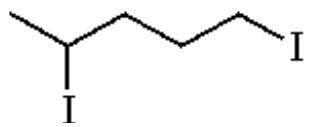	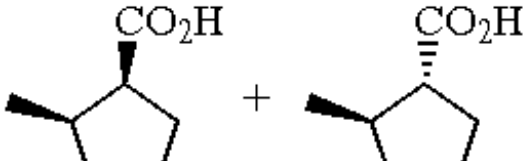	70[8]

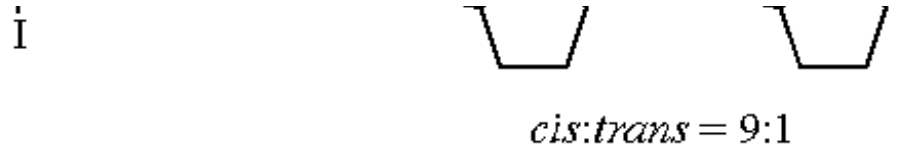

The initial 2-alkylated 4,4-dimethyl-2-oxazoline can also be prepared directly from homologs of acetic acid. α-Branching substituents can then be introduced by alkylation of the 2-alkyloxazoline. Thus *n*-butyric acid is converted to the desired oxazoline by condensation with 2-amino-2-methyl-1-propanol in 88% yield (eq 3).[3] The standard protocol of metalation, electrophile addition, and oxazoline hydrolysis affords the 2-substituted butyric acid in 61% yield (eq 3).[3] Since hydrolysis of the *N*-methylated heterocycle can be carried out under basic conditions, acid-labile groups such as the 1,3-dioxolane can be incorporated into the carboxylic acid product.

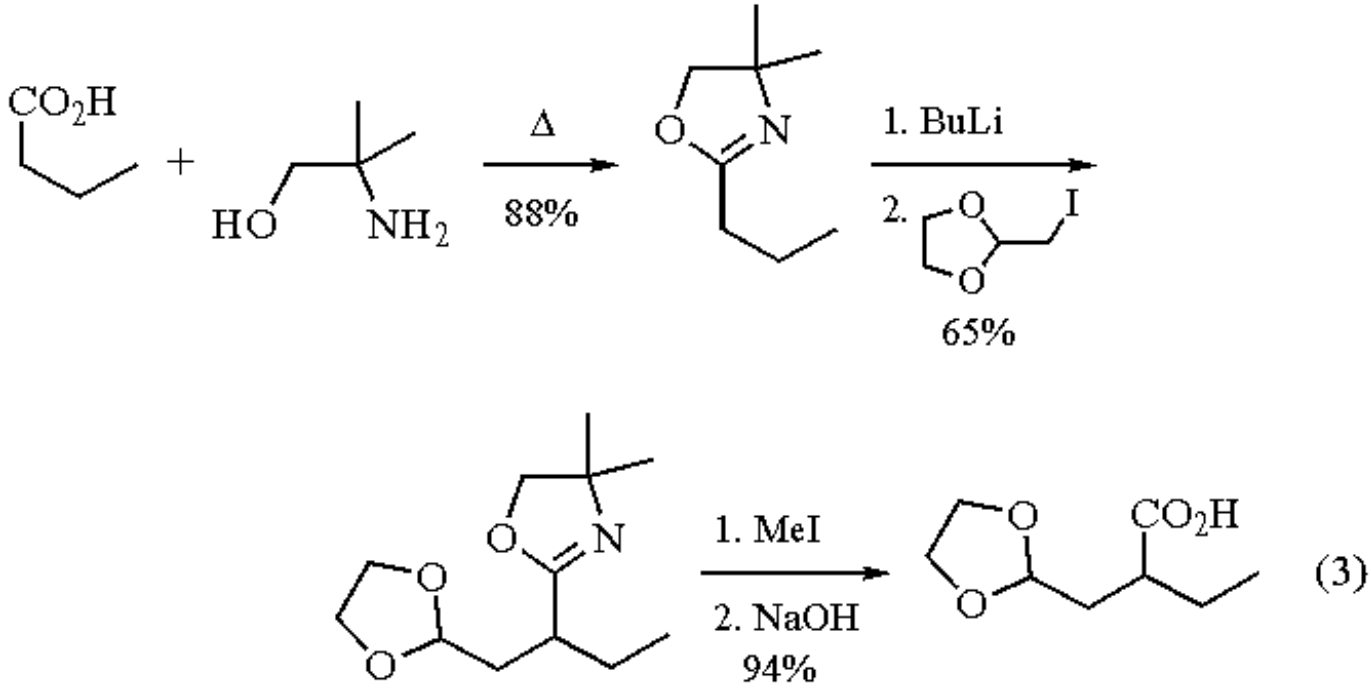

The stability of the anion of 2,4,4-trimethyl-2-oxazoline allows efficient alkylation with epoxides to form, after oxazoline hydrolysis, the corresponding γ-butyrolactone or γ-hydroxy acids (Table 2).[9,10]

Table 2 Lactones, Produced According to Eq 2

Epoxide	Product	Yield (%)
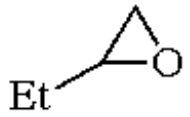	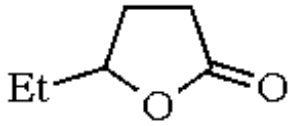	85[9]
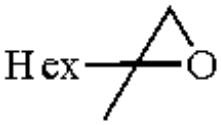	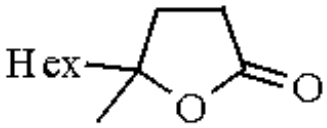	70[9]
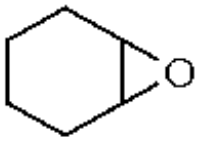	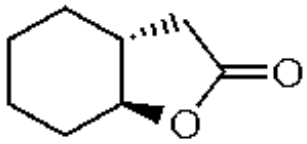	65[9]
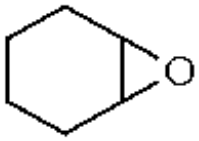	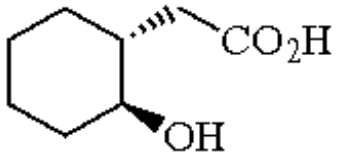	–[10]

Aldol Condensations.

The lithiated title reagent also adds cleanly to aldehydes and ketones. Acidic hydrolysis of the oxazoline gives a mixture of the α,β- and β,γ-unsaturated acids or esters (eqs 4 and 5).[3,5,11] When the hydrolysis is performed with lower concentrations of acid, it is possible to isolate the β-hydroxy ester (eq 4).[5]

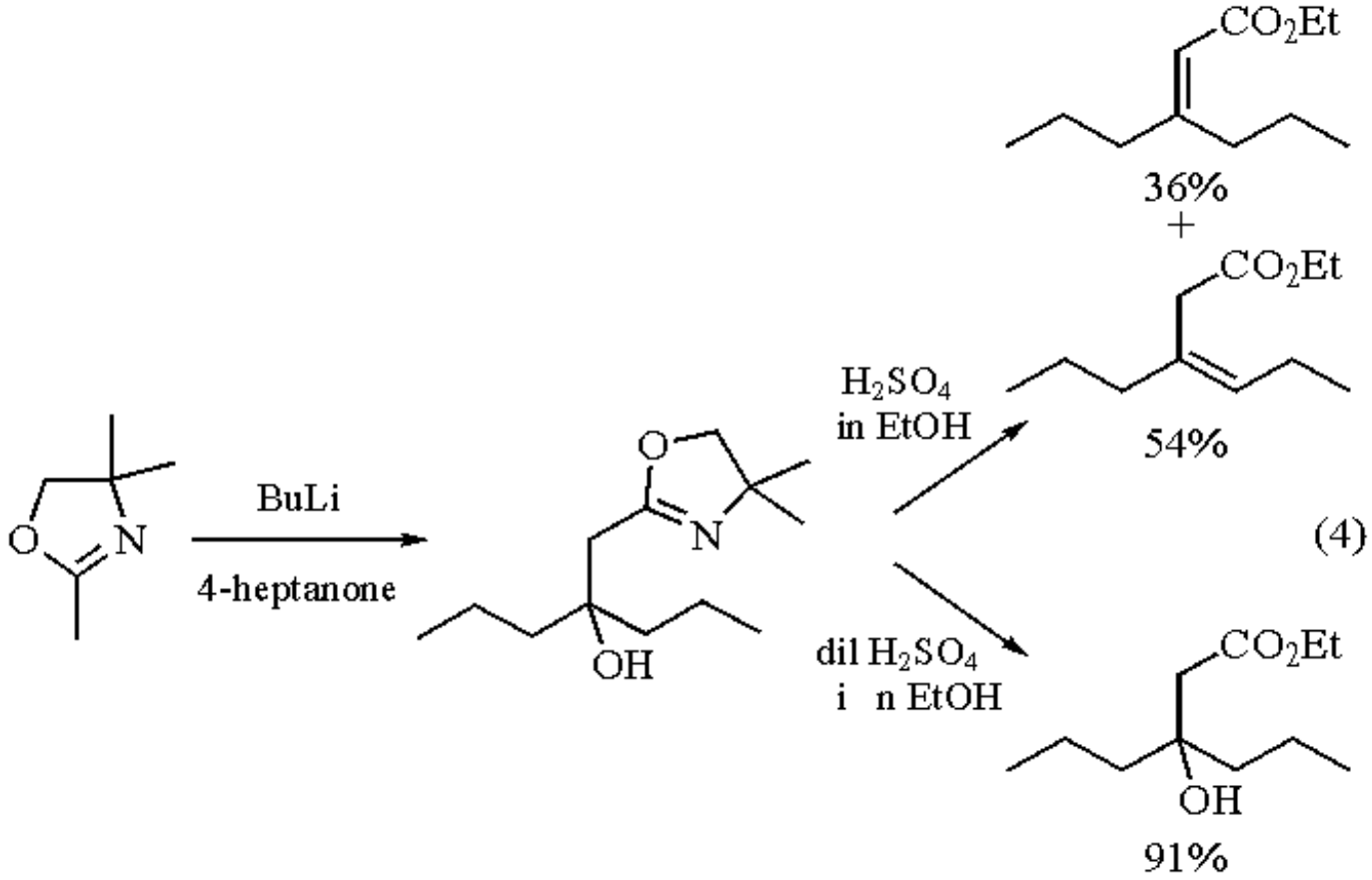

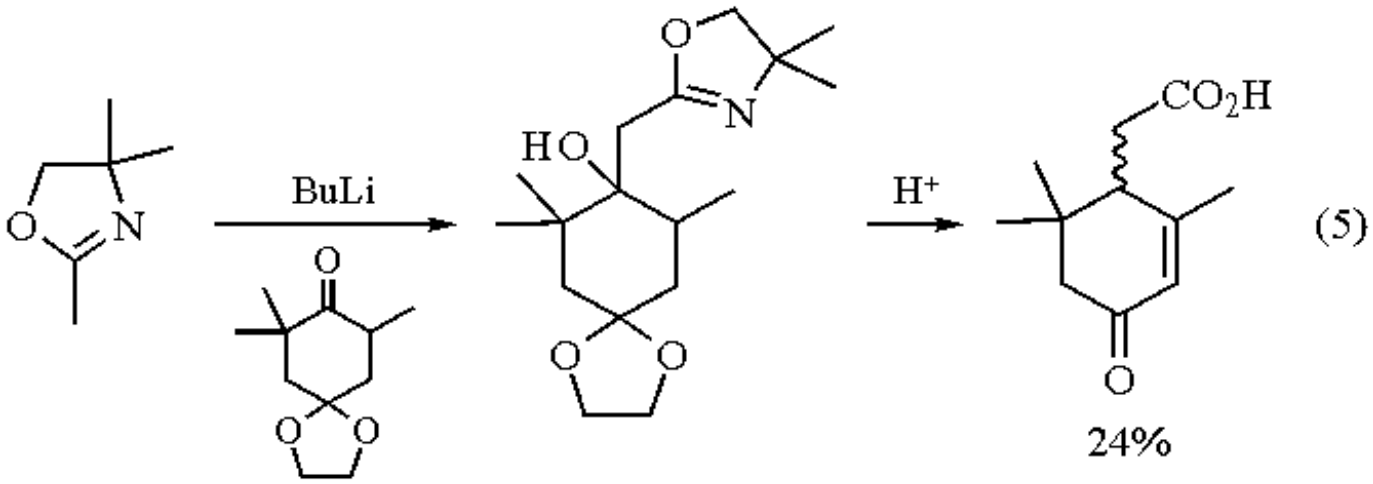

The lithiated oxazoline can also be used as an enol acetate equivalent in the aldol reaction.[12] The chiral sulfoxide (entry 5, Table 1), prepared from 2,4,4-trimethyl-2-oxazoline, has been used in the aldol reaction as an enol acetate equivalent, albeit with moderate enantiomeric enrichment (ee <= 53%).[7]

Acylation Reactions.

In addition, the lithium anion of 2,4,4-trimethyl-2-oxazoline undergoes *C*- and *N*-acylation with acid chlorides.[13] Further alkylation leads to a stable enol, which is a masked β-keto acid or ester (eq 6). These oxazoline enols are also accessible from the reaction of 2-alkylated 4,4-dimethyl-2-oxazolines with acid anhydrides in the presence of $AlCl_3/Et_3N/MeCN$ followed by treatment with KOH/MeOH.[14]

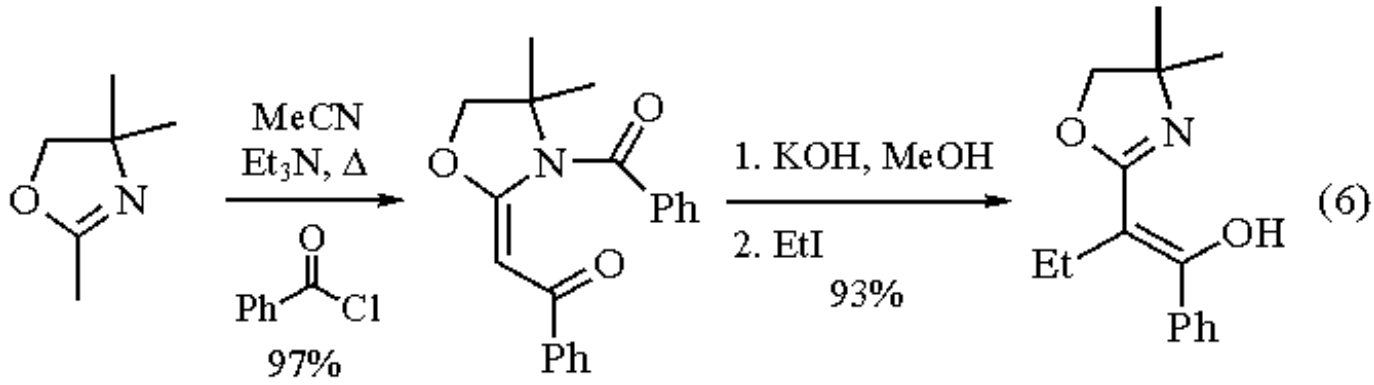

Addition of the lithio anion to nitriles forms the corresponding enamino oxazolines (eq 7).[15,16]

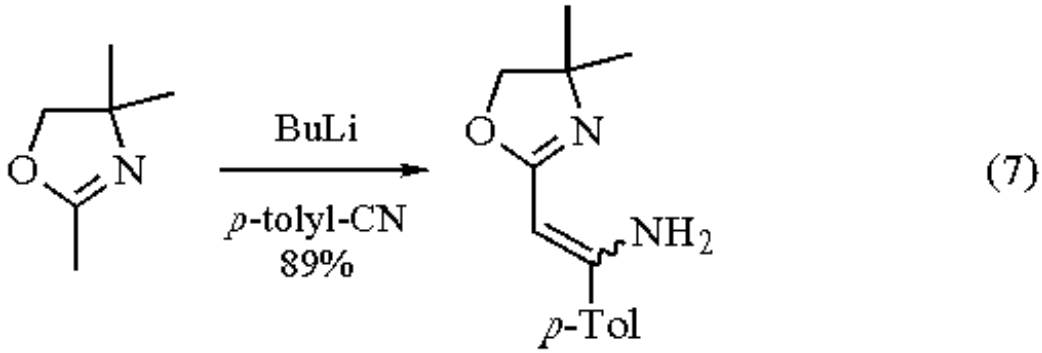

1,3-Dipolar Cycloadditions of Oxazoline *N*-oxides.

The *N*-oxide of 2,4,4-trimethyl-2-oxazoline has been utilized in [3 + 2] cycloadditions (eq 8).[17]

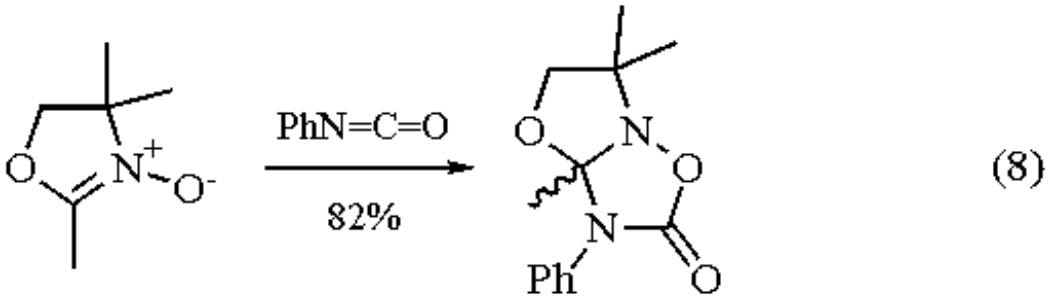

Asymmetric [3 + 2] cycloadditions have been accomplished by utilizing the *N*-oxides of chiral oxazolines.[18]

Carboxyl Protection.

2-Alkyl-2-oxazolines can also serve as protected forms of esters and carboxylic acids[19] because they are resistant to attack by Grignard reagents[5] and ***Lithium Aluminum Hydride***.[20] The oxazolines can be converted to ethyl esters (3 M HCl, EtOH) or carboxylic acids (MeI, 25 °C; 1 M NaOH, 25 °C).[19]

Related Reagents.

5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4H)-oxazine; ***Dilithioacetate***; ***Ethyl Lithioacetate***; ***2-(o-Methoxyphenyl)-4,4-dimethyl-2-oxazoline***; ***Methoxy(phenylthio)trimethylsilylmethane***; ***2-Methylbenzothiazole***; ***2-Methyl-2-thiazoline***; ***N,4,4-Trimethyl-2-oxazolinium Iodide***.

---

1. (a) Gant, T. G.; Meyers, A. I. *T* **1994**, *50*, 2297. (b) Reuman, M.; Meyers, A. I. *T* **1985**, *41*, 837.
2. (a) Allen, P.; Ginos, J. *JOC* **1963**, *28*, 2759. (b) Meyers, A. I.; Temple, D. L., Jr.; Nolen, R. L.; Mihelich, E. D. *JOC* **1974**, *39*, 2778.
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16. Poindexter, G. S.; Catt, J. D.; Sasse, P. A.; Kercher, M. A. *H* **1993**, *36*, 295.
17. (a) Ashburn, S. P.; Coates, R. M. *JOC* **1985**, *50*, 3076. (b) Kobayakawa, M.; Langlois, Y. *TL* **1992**, *33*, 2353. (c) Hisano, T.; Harano, K.; Matsuoka, T.; Watanabe, S.; Matsuzaki, T. *CPB* **1989**, *37*, 907.
18. Bérranger, T.; André-Barrès, C.; Kobayakawa, M.; Langlois, Y. *TL* **1993**, *34*, 5079.
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N,4,4-Trimethyl-2-oxazolinium Iodide

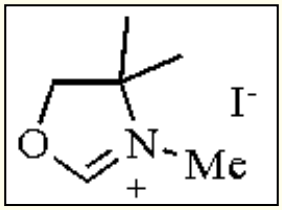

[30093-97-1] · $C_6H_{12}INO$ · *N*,4,4-Trimethyl-2-oxazolinium Iodide · (MW 241.09)

(a formylation and deuteroformylation reagent for aryl, benzyl, vinyl, and alkynyl Grignard reagents[1,2])

Physical Data: mp 215 °C (dec).

Preparative Method: by alkylation of commercially available 4,4-dimethyl-2-oxazoline with ***Iodomethane*** (eq 1). Filtration and purification affords the 2-oxazolinium salt in 80% yield.[1]

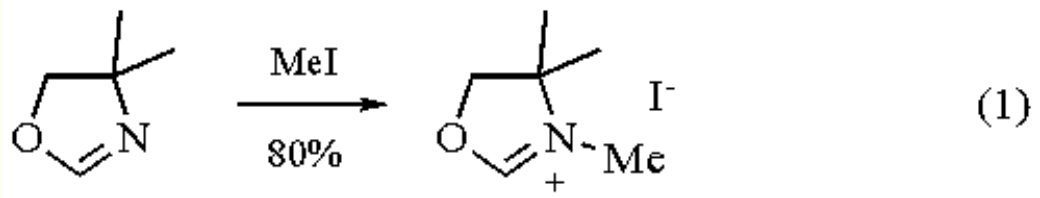

Handling, Storage, and Precautions: slightly hygroscopic; store under an inert atmosphere; use in a fume hood.

Synthetic Utility.

N,4,4-Trimethyl-2-oxazolinium iodide is used as a formylating reagent. Aryl, vinyl, benzyl, and alkynyl Grignard reagents react with the title compound in the presence of HMPA to form the corresponding oxazolidine adducts (eq 2, Table 1).[1] Hydrolysis of the oxazolidine with ***Oxalic Acid*** releases the free aldehyde. However, aliphatic Grignard reagents do not successfully enter into this protocol.[1,2]

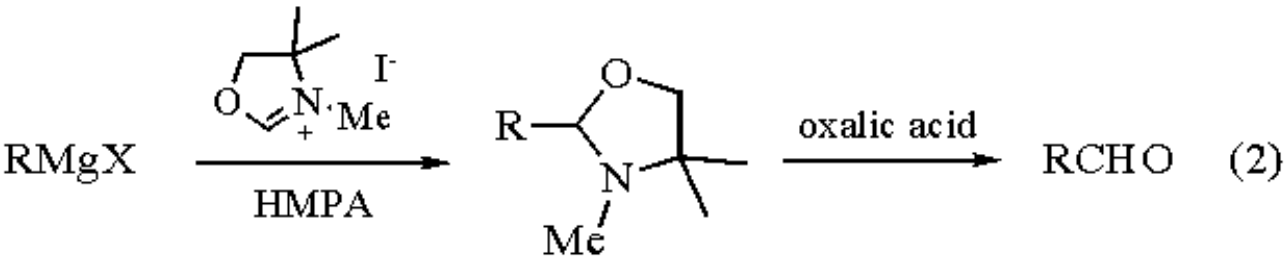

Table 1 Aldehyde Formation

Grignard reagent	Aldehyde	Yield (%)
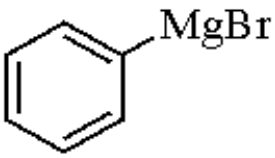	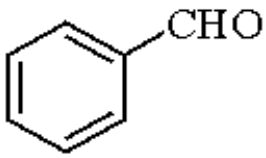	69
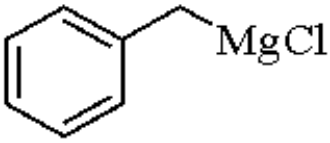	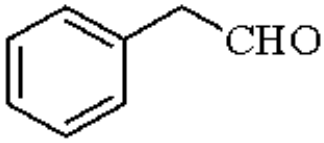	87
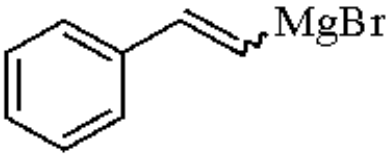	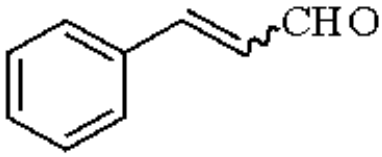	64
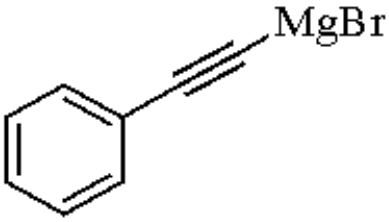	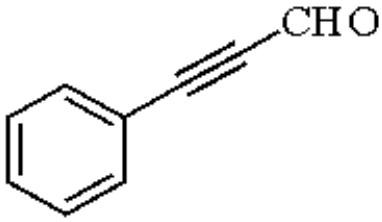	51

Utilization of deuterated *N*,4,4-trimethyl-2-oxazolinium iodide affords the corresponding deuterated aldehyde (eq 3).[1]

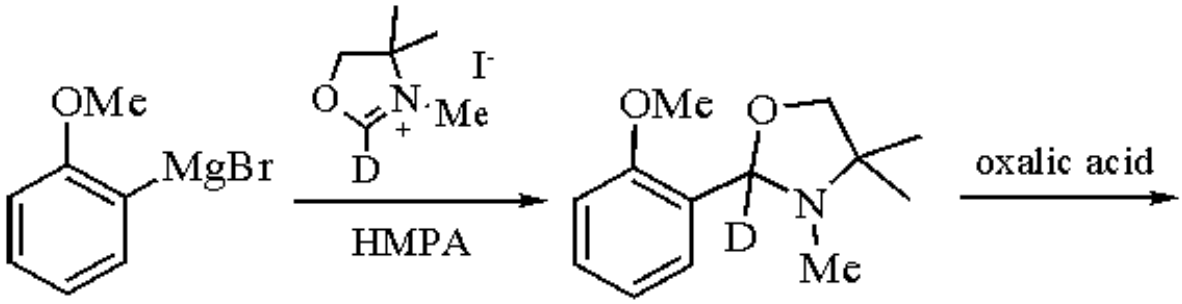

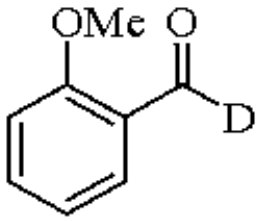

(3)

70%

Related Reagents.

Diethyl Phenyl Orthoformate; ***N,N-Dimethylformamide***; ***N,N-Dimethylformamide Diethyl Acetal***; ***N,O-Dimethylhydroxylamine***; ***1,1,3,3-Tetramethylbutyl Isocyanide***; ***Triethyl Orthoformate***.

1. Meyers, A. I.; Collington, E. W. *JACS* **1970**, *92*, 6676.
2. Brinkmeyer, R. S.; Collington, E. W.; Meyers, A. I. *OSC* **1988**, *6*, 64.

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Trimethyloxonium Tetrafluoroborate[1]

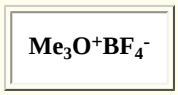

[420-37-1] · $C_3H_9BF_4O$ · Trimethyloxonium Tetrafluoroborate · (MW 147.93)

(methylating agent;[1] activates C-X multiple bonds;[2] esterifies polyfunctional carboxylic acids;[3] catalyst for polymerization of cyclic sulfides and ethers; Beckmann rearrangement of oximes[4])

Physical Data: mp 179.6-180.0 °C (sealed tube, with dec).

Solubility: sol nitrobenzene, nitromethane, $CHCl_3$, acetone (hot), SO_2 (liq); slightly sol CH_2Cl_2; insol common organic solvents.

Form Supplied in: white crystalline solid; commercially available; is contaminated by ethyldimethyloxonium tetrafluoroborate.

Analysis of Reagent Purity: ^{1}H NMR (CD_2Cl_2/SO_2) δ 4.68 (s, CH_3); ^{13}C NMR (CD_2Cl_2/SO_2) δ 78.8 (CH_3).

Purification: highly pure oxonium salt is obtained from dimethoxycarbenium tetrafluoroborate and dimethyl ether.[5] The resulting solid is vacuum dried at 50 °C/1 mmHg for 30 min.

Handling, Storage, and Precautions: when prepared according to Curphey,[6] the oxonium salt is stable, nonhygroscopic, and may be readily handled in the air for short periods of time. The dry oxonium salt should be stored under argon at -15 °C or as a suspension in CH_2Cl_2 at -20 °C for prolonged periods. Batches stored in this manner for over a year have been successfully used for alkylations. Highly pure samples[5] showed no change in spectral data after this time. Reactions of the reagent should be performed under an argon or a nitrogen atmosphere; dry solvents are also necessary. Because of its caustic nature and potent properties as an alkylating agent, direct contact with the skin must be avoided.

Functional Group Methylations.

The powerful alkylating property of trimethyloxonium tetrafluoroborate allows methylation of sensitive or weakly nucleophilic functional groups. Smooth alkylation of a variety of anions or uncharged molecules has been reported. Examples include carboxylic acids,[7] ketones,[2,8] lactones,[4,9] nitriles,[4,10] *O*-acetals,[4] *S*-acetals,[11] sulfoxides,[12] sulfides,[13] thioamides,[14] thiophenes,[13g] and sulfonium ylides.[14] As should be expected for strongly electrophilic agents,[1c] the hard oxonium salt yields considerable amounts of products derived from methylation at the site of the highest electron density (HSAB principle) when it reacts with ambident nucleophiles. *O*-Methylation of sulfoxides,[15] *N*-methylation of sulfoximides,[16] sulfinyl amines,[17] sulfodiimides, and nitriles[10] and *S*-methylation of thioamides[14b] have been observed. The very reactive cationic intermediates (e.g. carboxonium, carbosulfonium, or nitrilium ions) as primary products in those reactions are versatile intermediates for synthetic transformations. Ketones can be converted into α-acetoxy ketones via *N*-methylation of the oxime acetates (eq 1)[18] and thioamides to amides (eq 2).[14a,b]

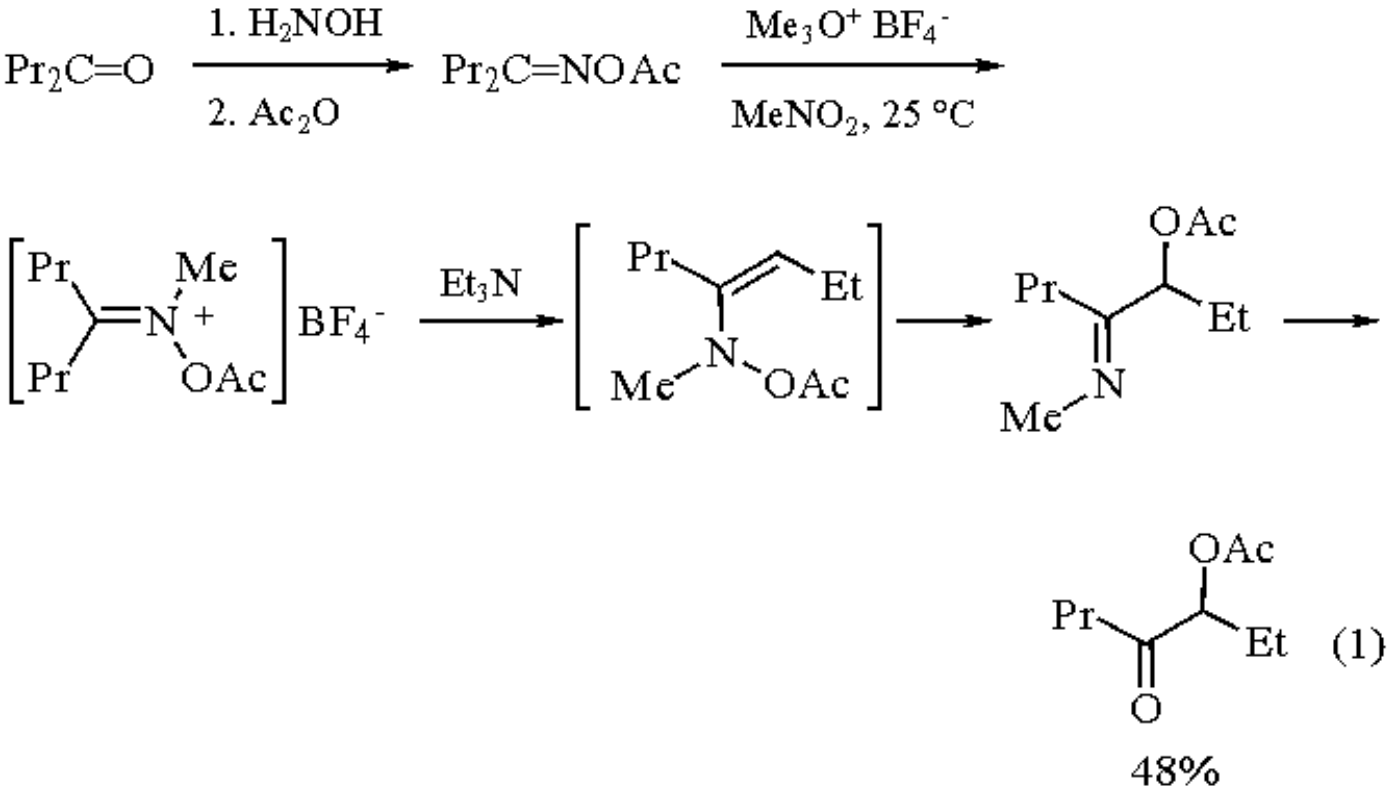

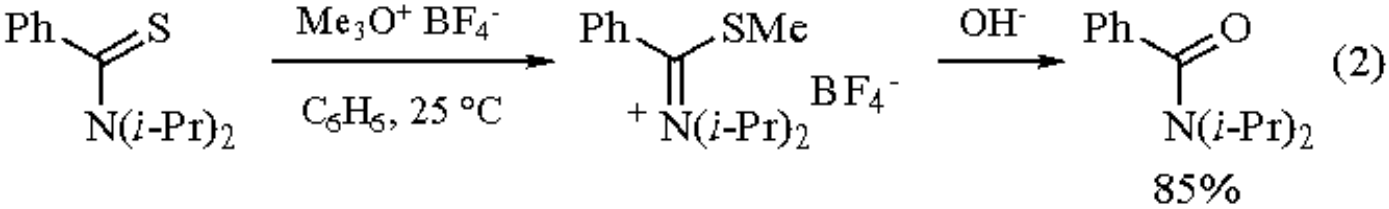

The reactions of thioacetals with $Me_3O^+BF_4^-$ constitute a high-yielding method for deprotection of thioacetals to give ketones (eq 3).[11a,19]

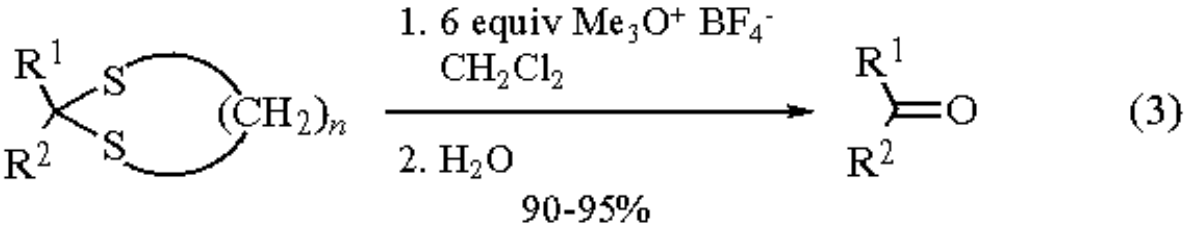

The reagent has been employed as a quaternizing agent for a variety of N-heterocycles.[20] Regioselective *N*-methylation has been observed (eq 4).[20c] Thiazoles are exclusively *N*-methylated,[20a,b] whereas tetrazoles yield regioisomeric products.[20d,h] The dication of squaric acid bis(amidine) is prepared by regioselective *N*-methylation (eq 5).[21]

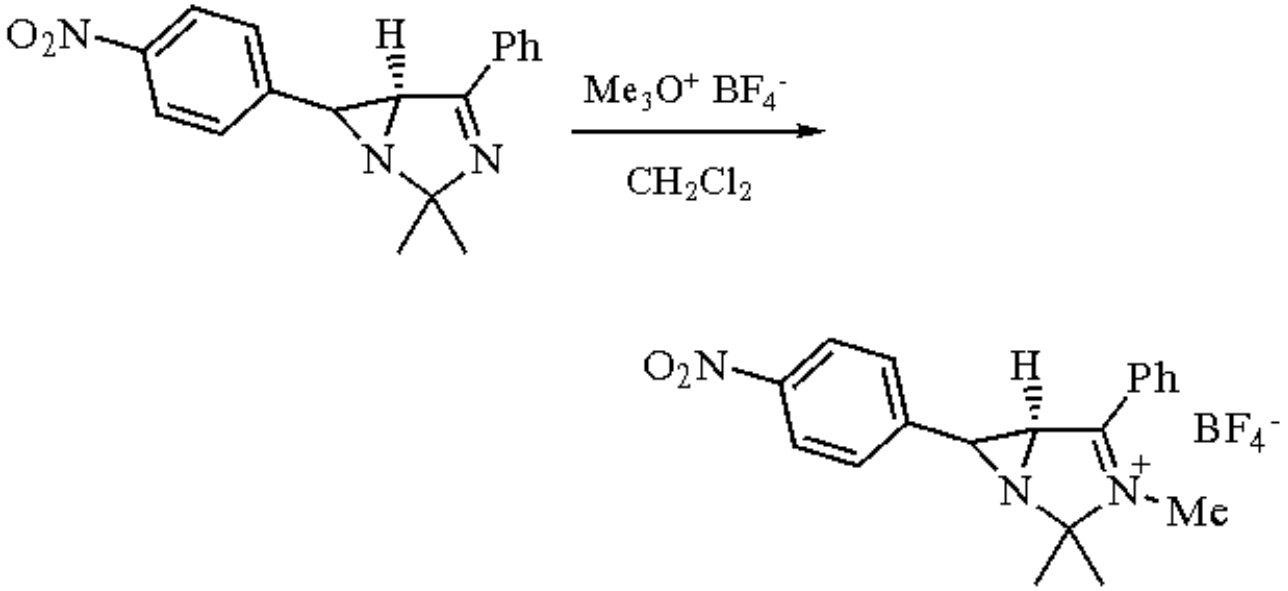

(4)

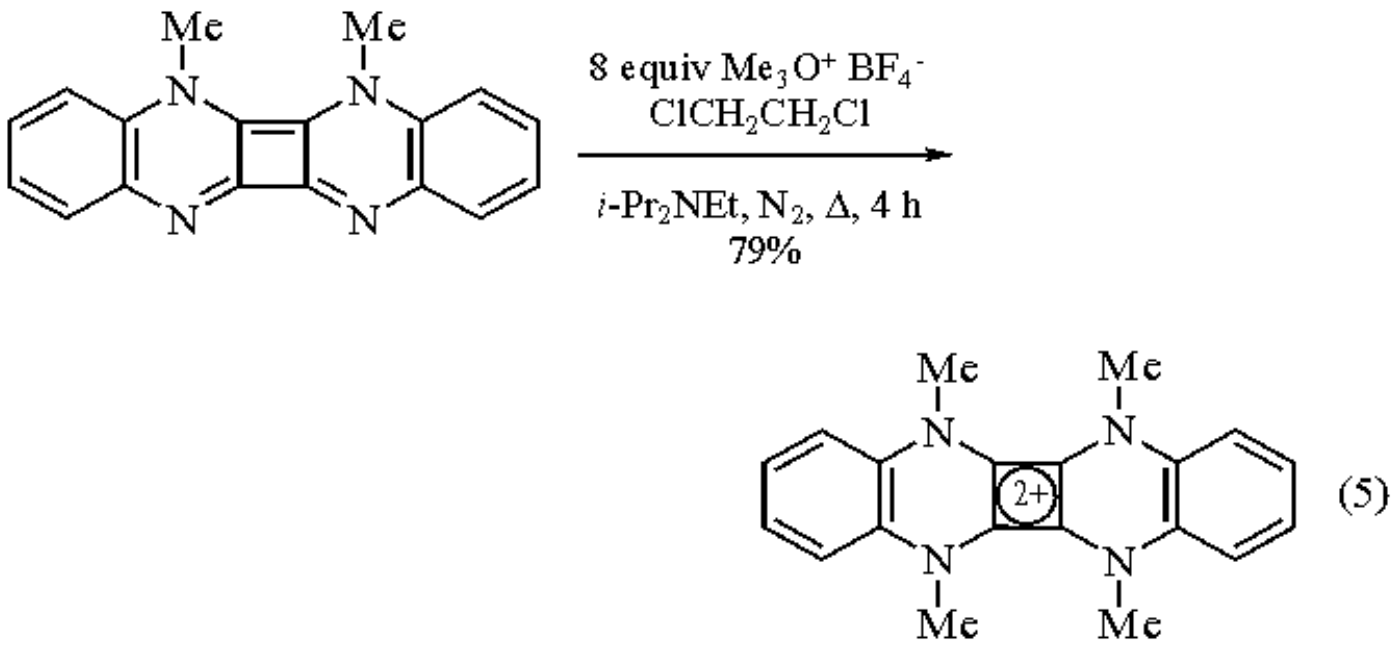

(5)

1,3-Benzothiazolines react preferentially at nitrogen,[22] whereas heterocycles containing dipolar carbonyl groups usually yield products resulting from *O*-methylation.[2,23] Furthermore, $Me_3O^+BF_4^-$ is the reagent of choice for the synthesis of higher alkylated products which are otherwise not obtainable. Examples are the preparation of vinylidene disulfonium salts (eq 6),[13c] dionium salts of *N*,*S*-[13b] and *S*,*S*-acetals,[11a-c,24] or 1,4-dithianium ditetrafluoroborates (eq 7),[19] and a heterocyclophane-type tetrasulfonium salt (eq 8). The latter introduces a hydrophobic cavity into the aqueous phase, thus serving as an inclusion catalyst.[25]

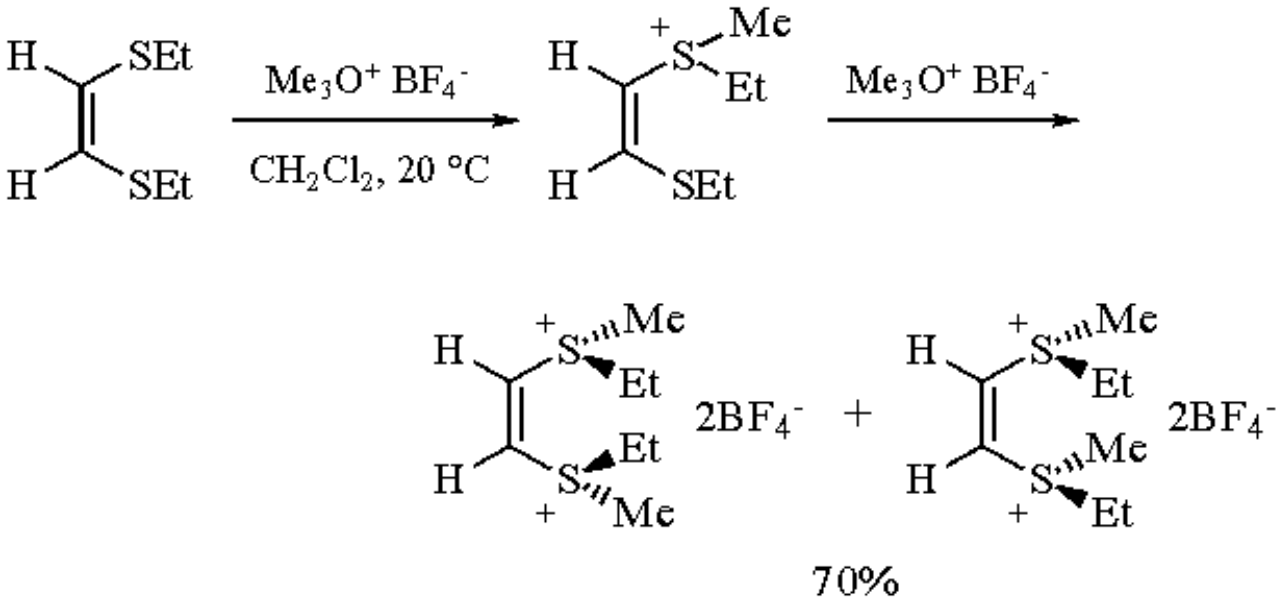

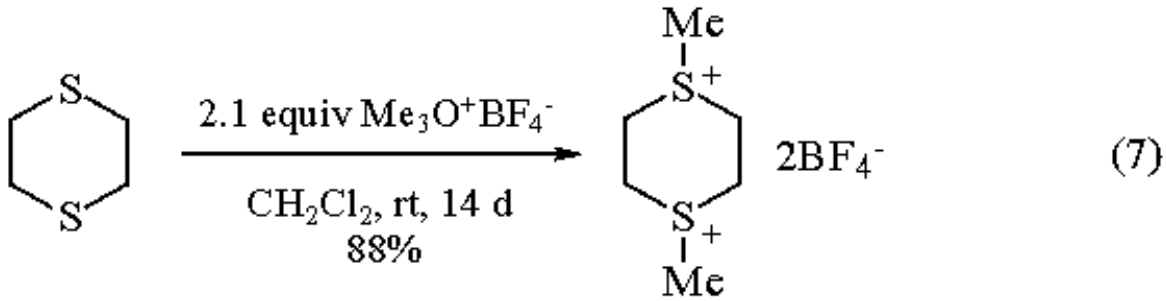

mixture of two stereoisomers

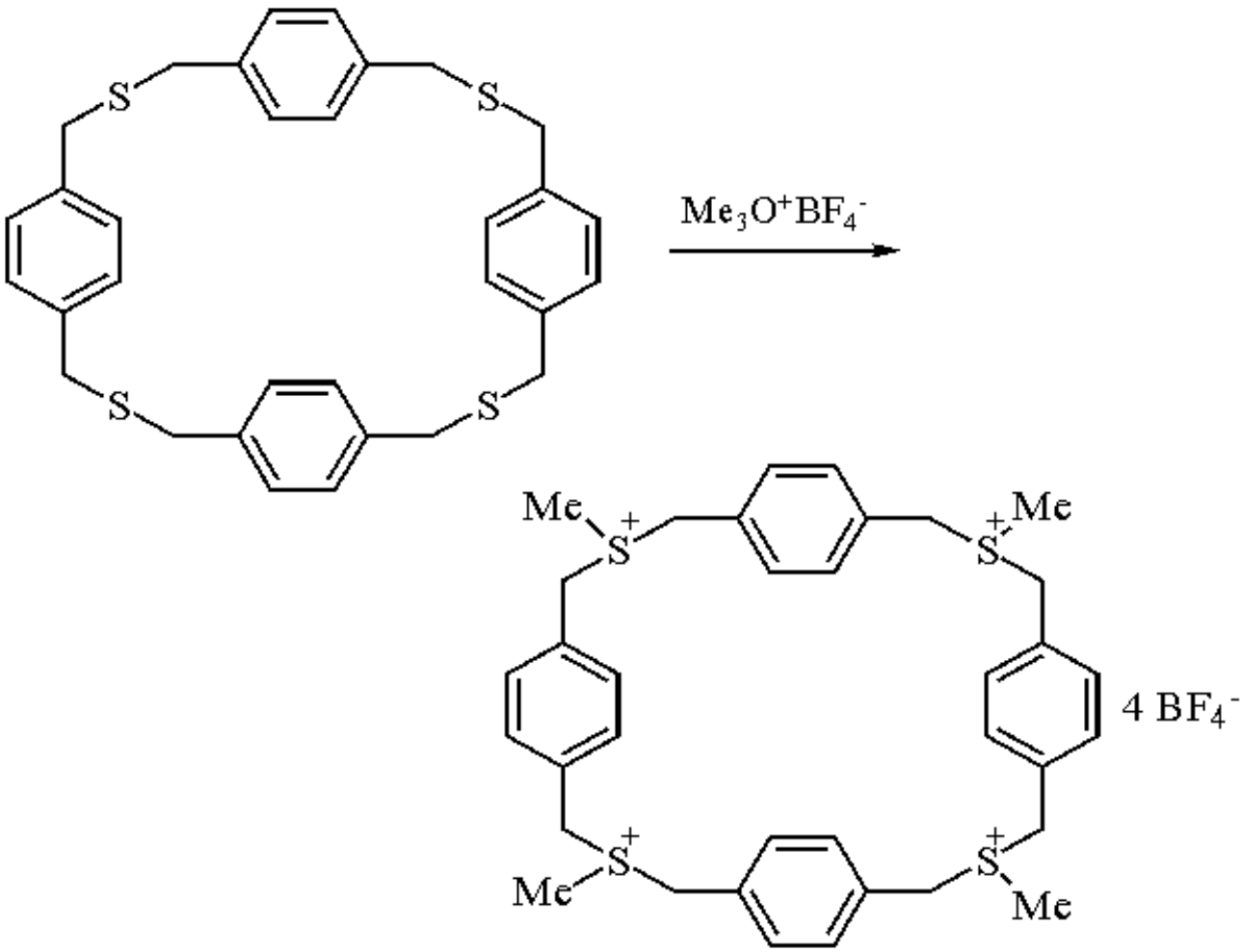

Trialkyloxonium salts such as $Me_3O^+BF_4^-$ are excellent reagents for the generation of cyclopropenylium cations by *O*-methylation of suitable cyclopropenones (eq 9).[26]

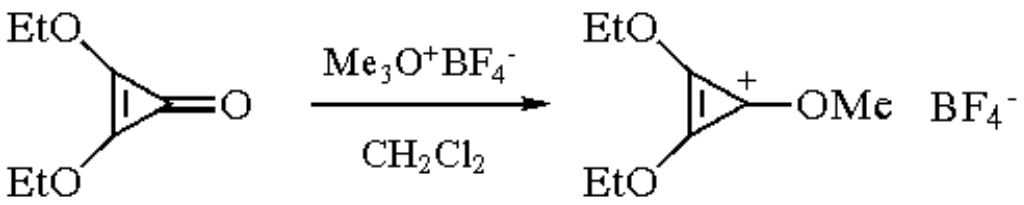

(9)

The reaction of trialkyloxonium salts with carboxylic acids is a mild, general esterification procedure that does not require the use of more hazardous reagents such as ***Hexamethylphosphoric Triamide-Thionyl Chloride***, ***Iodomethane***, ***Dimethyl Sulfate***, ***3-Methyl-1-p-tolyltriazene***, or ***Diazomethane***. The reaction proceeds smoothly with sterically hindered acids, as well as with acids containing various functional groups such as amides or nitriles (eq 10).[3,7]

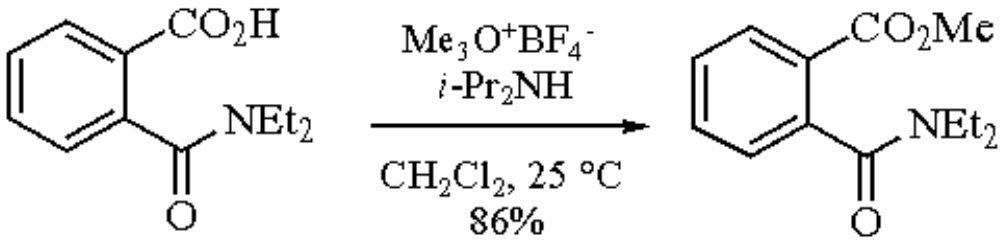

(10)

One of the major advantages of the use of oxonium salts is that alkylations can be effected under reaction conditions that are generally much milder than those necessary with conventional alkyl halides and sulfonates. $Me_3O^+BF_4^-$ has been used as a suspension in CH_2Cl_2 or dichloroethane, or as a solution in nitromethane or liquid SO_2. Alkylations in water[27] and trifluoroacetic acid[28] have been described, and direct fusion has been used in cases where other conditions failed.[29] An S_N2 mechanism must be assumed in the reaction of the reagent with nucleophiles. The rates of the complete hydrolysis decrease in the sequence $Me_3O^+ >> Et_3O^+ > Pr_3O^+ > c\text{-}C_5H_{10}{+}OEt$.[30] Comparative studies on the alkylating ability of common methylating agents[31] show that Me_3O^+ ions are more reactive than the trifluoromethanesulfonate ester (factor 5 to 12), following the order $Me_3O^+ > MeOSO_2CF_3 > MeOSO_2F > MeOClO_3$. In terms of availability, stability, and freedom from hazards, however, oxonium salts often appear the reagents of choice (including comparisons with other powerful alkylating agents such as dialkoxycarbenium ions,[32] dialkylhalonium ions,[33] and haloalkanes in the presence of silver salts[34]). While the carcinogenic properties of other potent alkylating agents are well documented,[35] any such dangers associated with trialkyloxonium salts are presumably minimized by the fact that these compounds are water-soluble, nonvolatile, crystalline solids which are rapidly solvolyzed in aqueous solution.[1b,36] Although ***Triethyloxonium Tetrafluoroborate*** is the cheaper and much more used oxonium salt in synthetic chemistry, $Me_3O^+BF_4^-$ effects alkylations which the triethyl analog does not.[11,37]

Use in Transition Metal Chemistry.

$Me_3O^+BF_4^-$ has been successfully used in the generation of transition metal carbene complexes by direct methylation of lithium acylcarbonylmetalates (eq 11).[38] Oxidative addition processes by which metal-carbon σ-bonds are formed have also been observed.[39] $Me_3O^+BF_4^-$ also serves as a halide acceptor in the reaction with square planar platinum(II) complexes.[40]

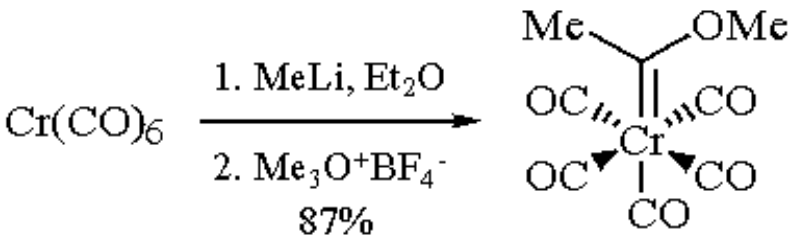

(11)

Catalytic Properties.

$Me_3O^+BF_4^-$ has been used as a catalyst for the polymerization of cyclic sulfides and in the polymerization of THF to macrocyclic ethers.[4] A valuable modern application is the catalytic Beckmann rearrangement of oximes in homogeneous liquid phase,[41] the active species being a formamidinium salt.

Other Reactions.

The reaction of γ-alkenyl-γ-butyrolactones with allylsilanes in the presence of $Me_3O^+BF_4^-$ as the lactone-activating agent is reported to proceed with high regio- and stereoselectivity to afford methyl (*E*)-4,8-alkadienoates in high yields (eq 12).[42]

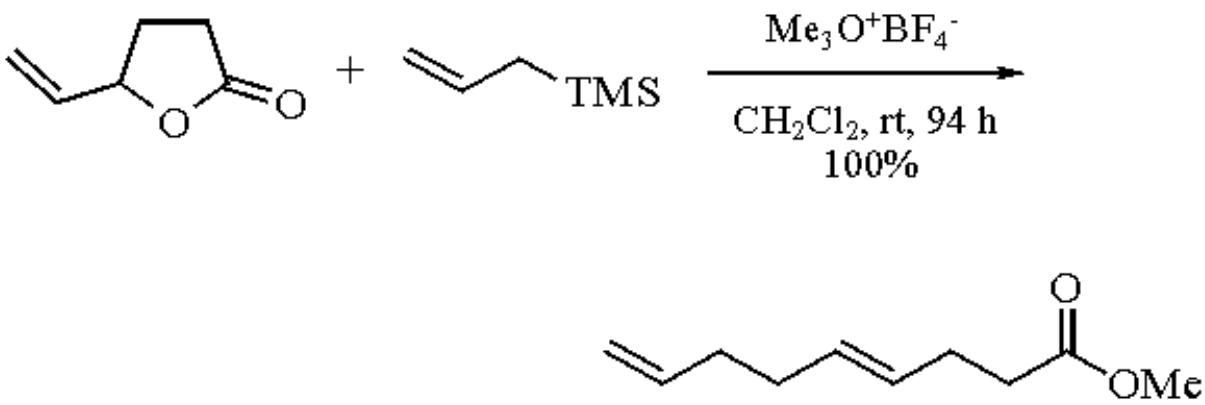

(12)

$Me_3O^+BF_4^-$ has also been used as a methylating agent of the lithium enolate of a β-keto sulfoxide, leading to a mixture of isomeric dienol ethers, which are of potential interest as substrates for asymmetric Diels-Alder cycloadditions (eq 13).[43]

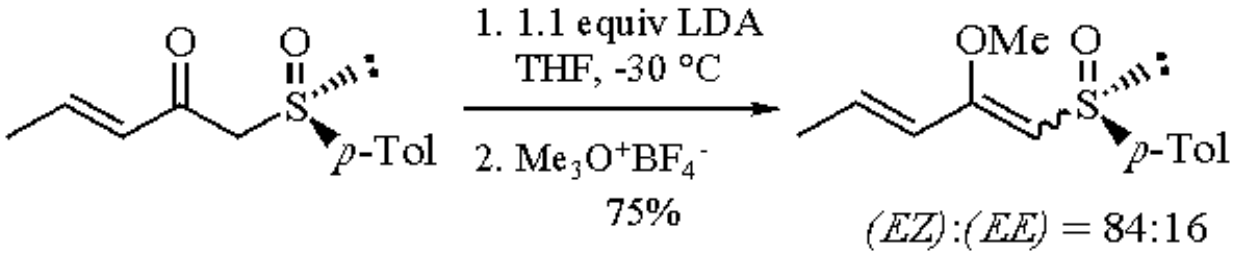

(13)

Related Reagents.

Dimethyl Sulfate; ***Iodomethane***.

---

1. (a) Meerwein, H. *MOC* **1965**, *6/3*, 335. (b) Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie: Weinheim, 1971. (c) Granik, V. G.; Pyatin, B. M.; Glushkov, R. G. *RCR* **1971**, *40*, 747. (d) Perst, H. In *Carbonium Ions*; Olah, G. A.; Schleyer, P. v. R., Eds.; Wiley: New York, 1976; Vol. 5, pp 1961-2047.
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Trimethyl Phosphate

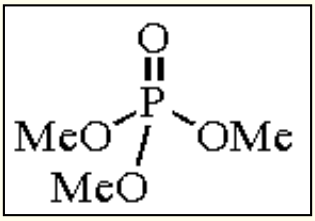

[512-56-1] · $C_3H_9O_4P$ · Trimethyl Phosphate · (MW 140.09)

(esterification of carboxylic acids;[1] *N,N*-dimethylation of anilines;[2] *N*-methylation of nitrogen heterocycles[3])

Physical Data: bp 197 °C; *d* 1.197 g cm^{-3}.

Solubility: sol H_2O (1 g mL^{-1}), ethanol, ether.

Form Supplied in: liquid; widely available.

Purification: distillation at ambient or reduced pressure.

Handling, Storage, and Precautions: stable for extended periods of storage. It is a cancer suspect agent and possible mutagen and should be handled with due caution.

Esterification of Carboxylic Acids.

Trimethyl phosphate is an effective reagent for the preparation of methyl esters of hindered carboxylic acids (eq 1)[1a] and serves as an alternative to toxic ***Dimethyl Sulfate***.[4] It can also effect the *O*-methylation of unprotected amino acids,[1b] although some *N,O*-dimethylated product is observed.

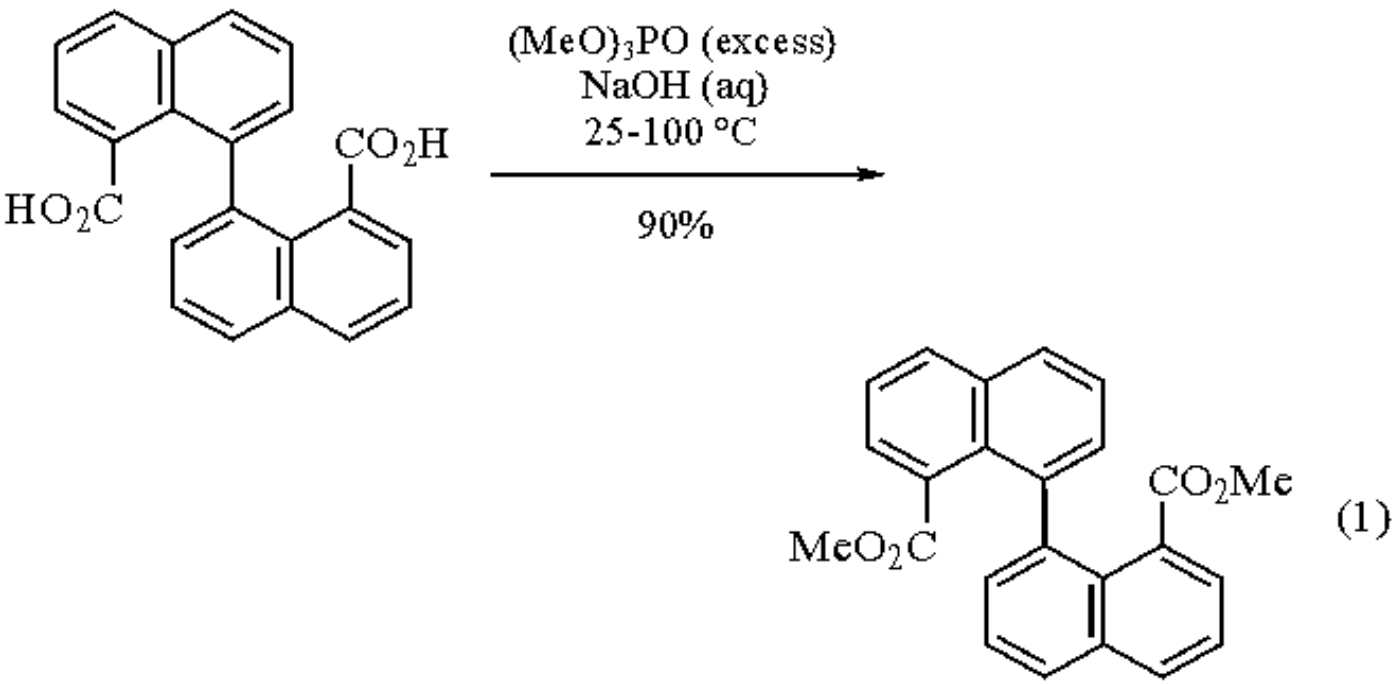

(1)

N,N-Dialkylation of Anilines.

Trimethyl phosphate reacts with anilines to give *N*,*N*-dimethylated products (eq 2).[2a,b] A wide variety of substitution is tolerated, although substituents which significantly decrease the basicity of nitrogen, such as *p*-nitro, are not. All three methyl groups of the reagent molecule are utilized in these alkylations.

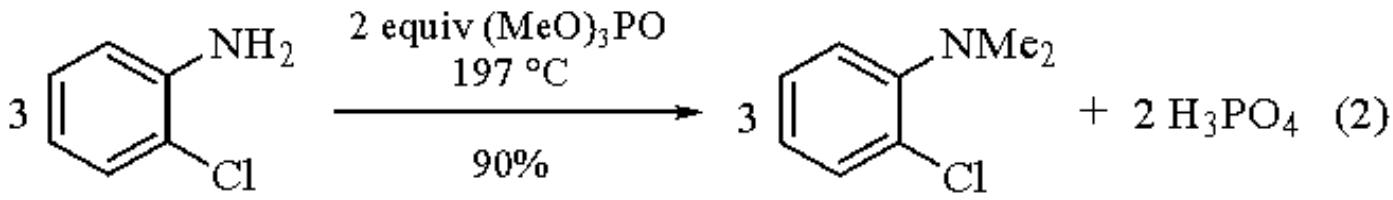

N-Alkylation of Nitrogen Heterocycles.

The title reagent has been used to *N*-methylate a wide variety of nitrogen heterocycles, including imidazoles,[3a] benzimidazoles (eq 3),[3a] pyrazoles,[3a] 1,2,4-triazoles,[3a] benzotriazoles,[3a] quinolines,[3b] purines,[3c,d] pyrimidines,[3e,f] and phenothiazines.[3g]

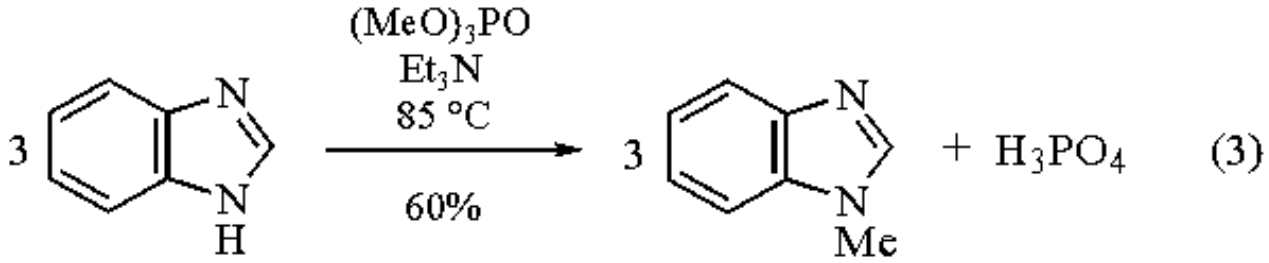

Ring Opening of Isoxazolidines.

Trimethyl phosphate reacts with *N*-alkylisoxazolidines to form, depending on the substitution pattern of the isoxazolidine, α,β-enones[5a] (eq 4) or tertiary allylic alcohols.[5b]

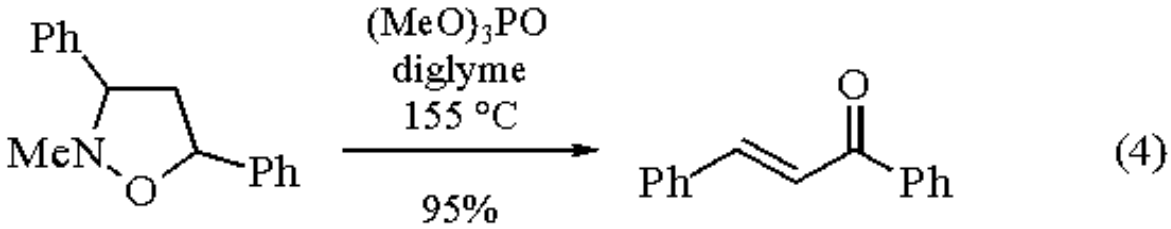

Methylation of α-Lithio Sulfoxides.

Trimethyl phosphate reacts with α-lithio sulfoxides to form the corresponding α-methyl sulfoxides.[6] The coordinating ability of the reagent with the lithium counterion can lead to a reversal of product stereochemistry compared with similar alkylations with ***Iodomethane***.[6a,b]

Use as a Solvent.

Trimethyl phosphate is an excellent dipolar aprotic solvent for a variety of synthetic transformations. In aromatic halogenation reactions[7] and the halogenative cleavage of cyclic acetals,[8] trimethyl phosphate acts as an acid scavenger, very rapidly reacting with liberated hydrogen halide to form methyl halide. Trimethyl phosphate also has an accelerating effect on the diphosgene-mediated conversion of carboxamides to nitriles,[9] and on the phosphoryl chloride-mediated direct phosphorylation of unprotected nucleosides to 5´-nucleotides.[10]

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Trimethyl Phosphite[1]

$(MeO)_3P$

[121-45-9] · $C_3H_9O_3P$ · Trimethyl Phosphite · (MW 124.09)

(reducing agent for various functional groups; can function as a potent thiophile for sulfur extrusion; forms a stable complex with copper(I) iodide and methylcopper)

Physical Data: bp 111-112 °C/760 mmHg; *d* 1.052 g cm^{-3}.

Solubility: sol most organic solvents.

Form Supplied in: clear, free flowing liquid; commercially available in >99% purity.

Purification: treatment with sodium (to remove water and dialkyl phosphonate), followed by decanting and distillation.[2]

Handling, Storage, and Precautions: store in a dry place, preferably in a fume hood due to its pungent odor; purified material should be stored over activated molecular sieves.

Use in the Arbuzov and Perkow Reactions.

Although used less frequently than ***Triethyl Phosphite***, trimethyl phosphite has seen significant application in the synthesis of organophosphonates (eq 1)[3] and phosphates (eq 2)[4] via Arbuzov and Perkow reactions, respectively. For example, an interesting α-diazophosphonate reagent developed by Seyferth has been applied to the one-step conversion of aldehydes to terminal alkynes (eq 3).[5] Since the potentially hazardous diazophosphonate is purified by distillation, use of the relatively volatile dimethyl derivative is warranted.

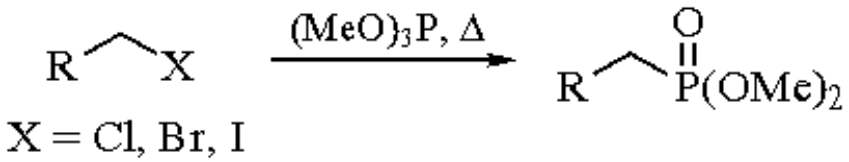

(1)

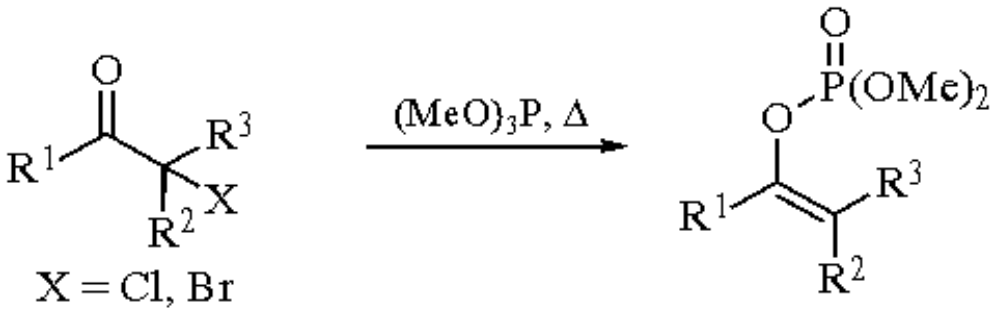

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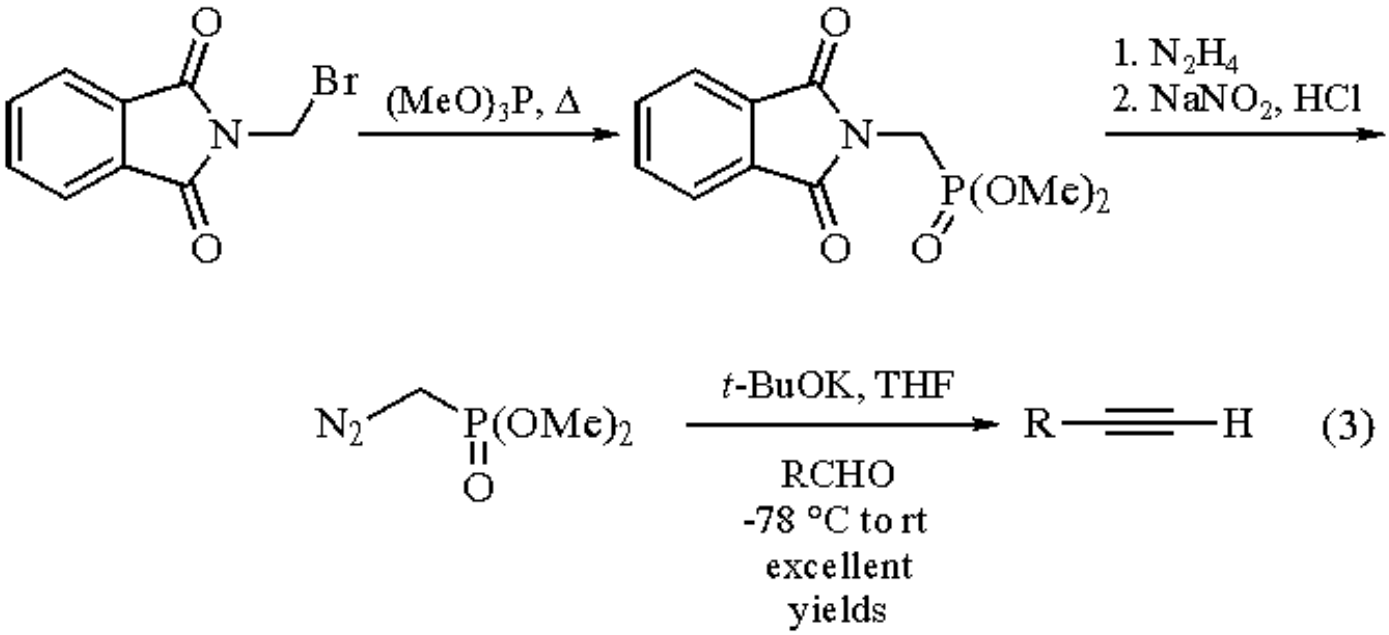

Carbonyl Adducts.

Trimethyl phosphite reacts readily with 1,4- and 1,2-benzoquinones to give methyl esters of hydroquinone monophosphates (eq 4)[6] and cyclic oxyphosphoranes (eq 5),[6] respectively. Ramirez and co-workers reported that trimethyl phosphite promotes the dimerization of methyl pyruvate to give, after basic hydrolysis, a mixture of diastereomeric tartrates (eq 6).[7]

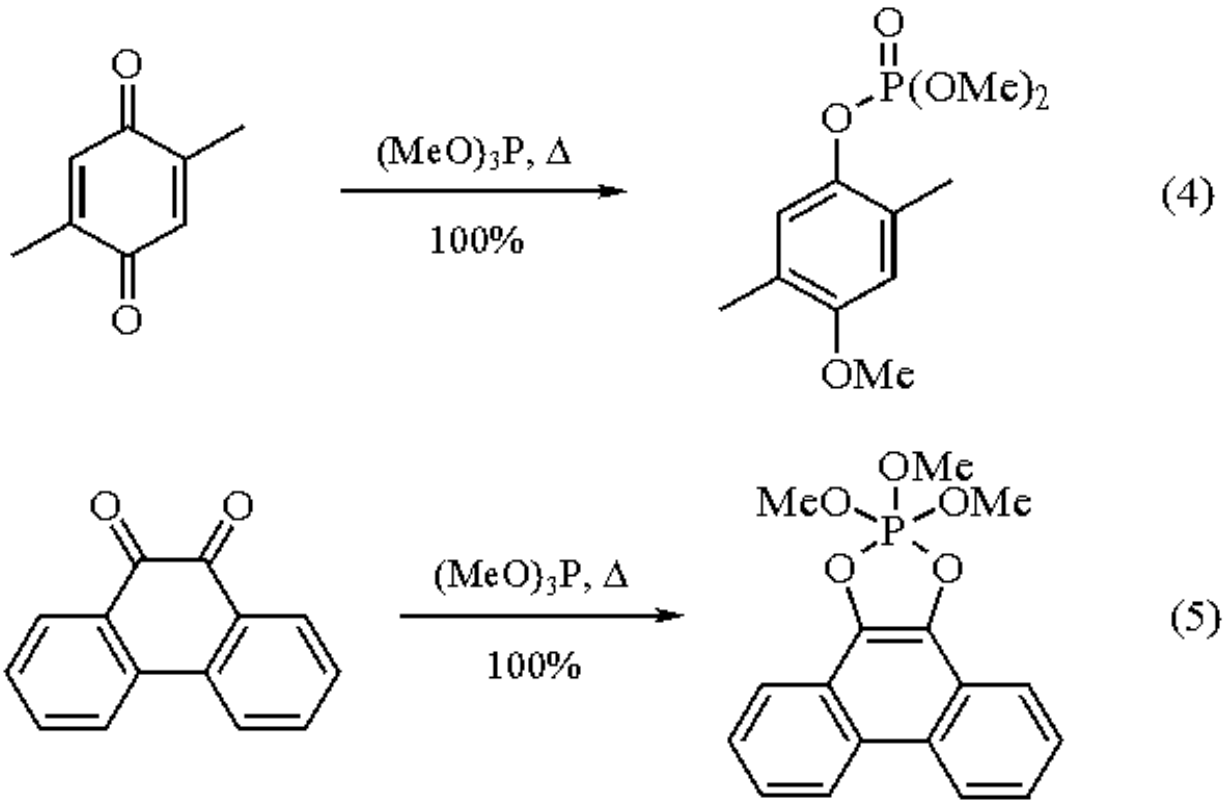

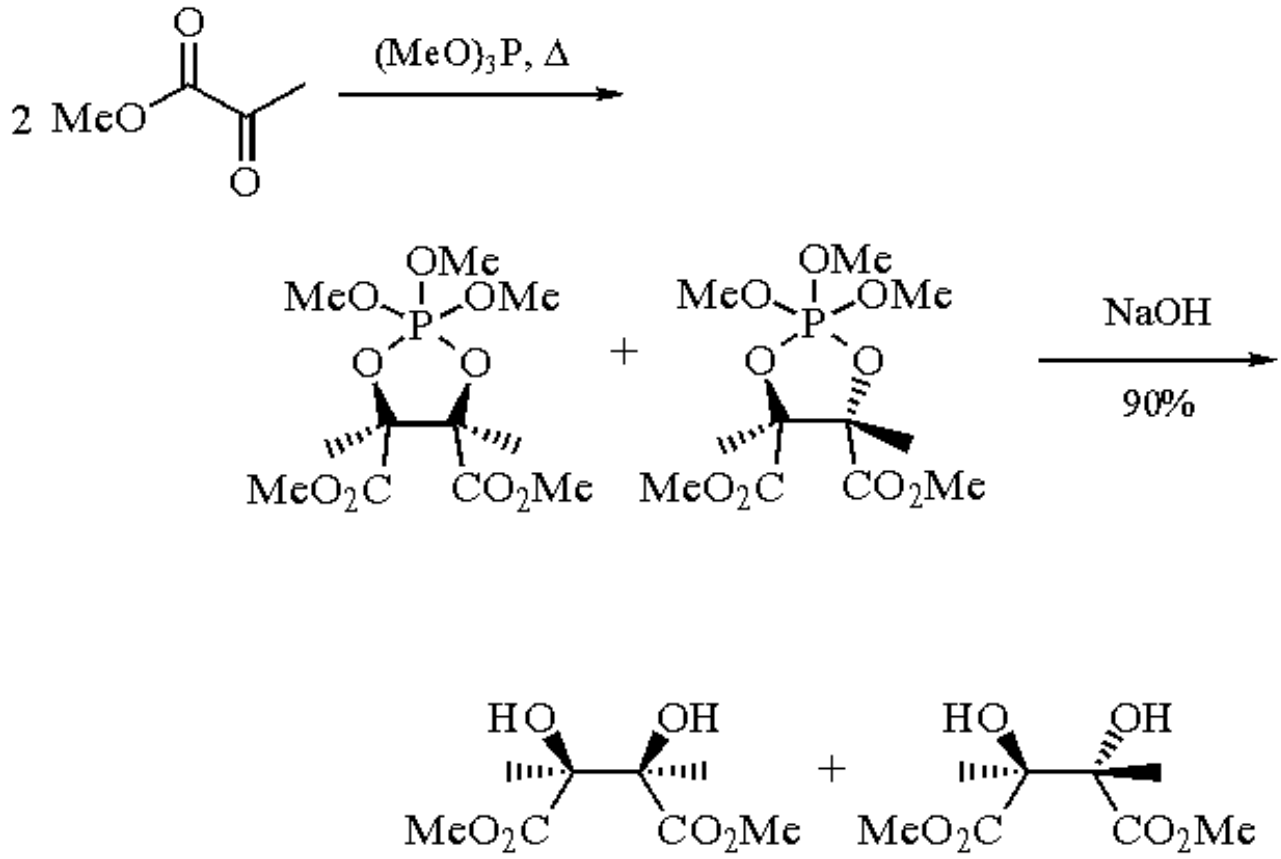

Deoxygenation.

The reductive decomposition of ozonides can be conveniently accomplished using trimethyl phosphite (eq 7).[8] The innocuous byproduct, trimethyl phosphate, is easily removed from the crude reaction mixture either by extraction or evaporation.

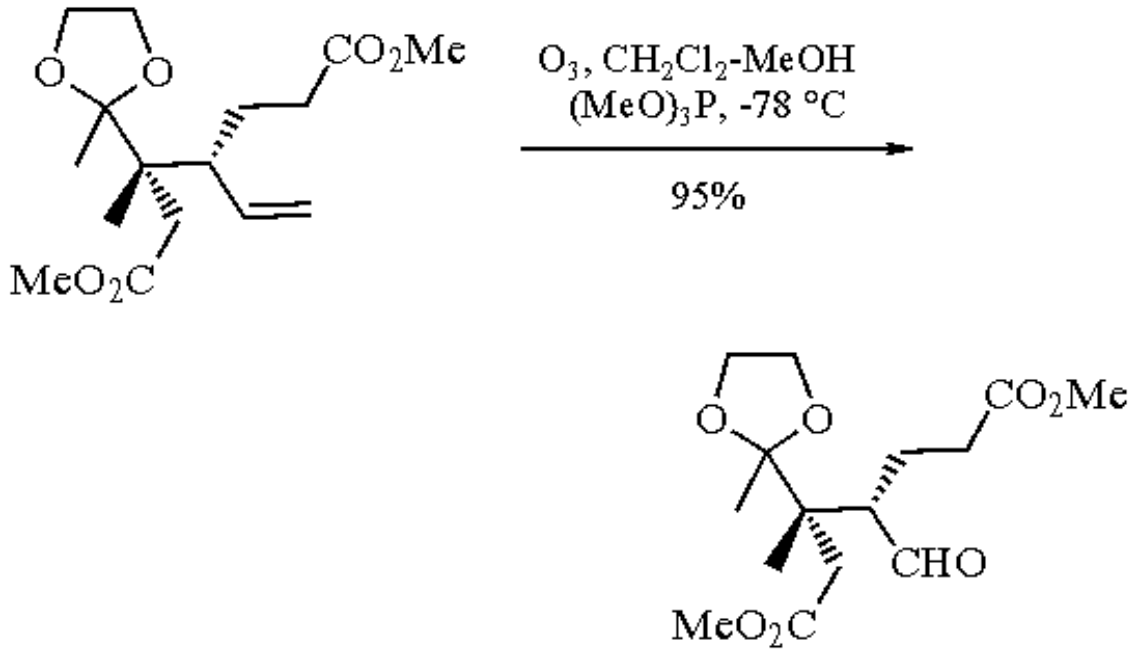

The reagent has been equally efficacious in the conversion of nitrile oxides to nitriles (eq 8).[9] Additionally, Seebach and co-workers have reported the synthesis of a cyclic ε-tetrazine via reduction of the corresponding *N*-oxide (eq 9).[10]

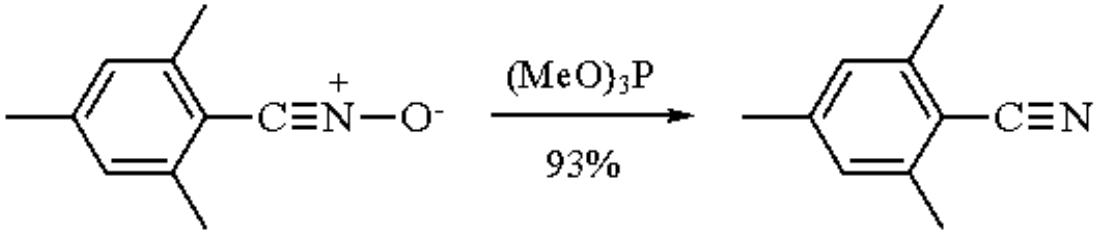

(8)

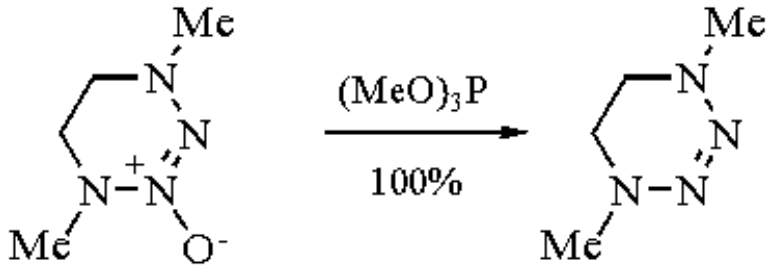

(9)

Desulfurization.

Trimethyl phosphite (in addition to triethyl phosphite) has been applied successfully to the Corey-Winter alkene synthesis.[11] The key step of the sequence involves phosphite-mediated decomposition of a thiocarbonate derivative which proceeds stereospecifically and often results in good yields of desired alkene (eqs 10 and 11).[12] Alkynes have also been synthesized using this method, albeit in lower overall yields (eq 12).[13]

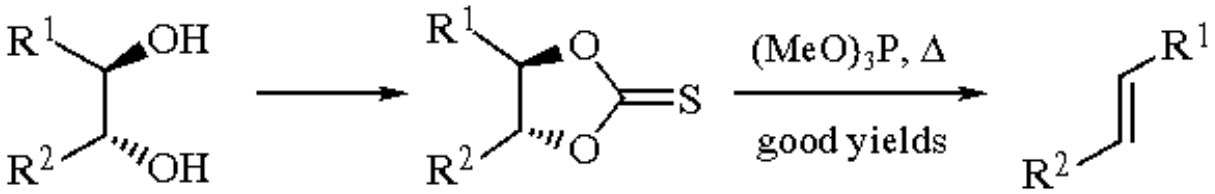

(10)

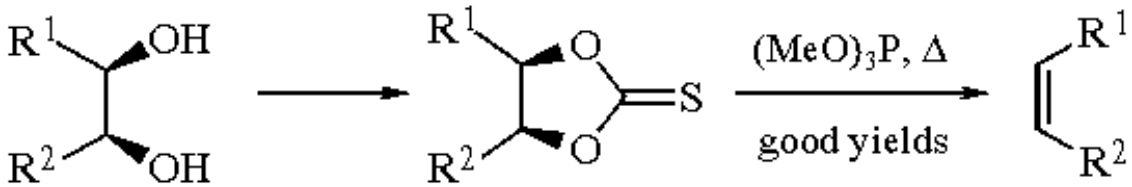

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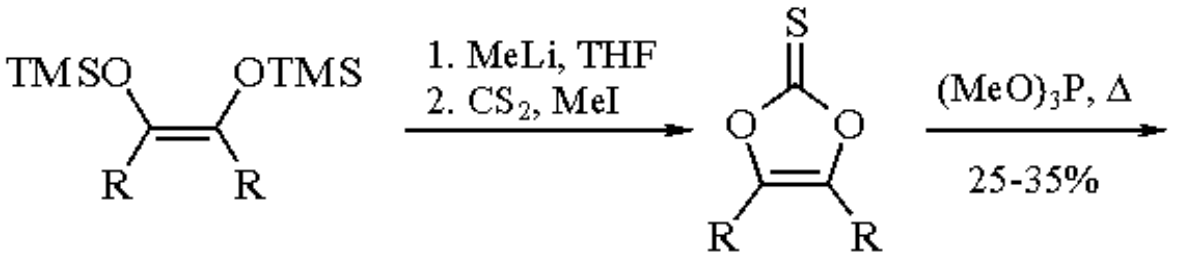

(12)

Treatment of 1,3-dithiacyclohexane-2-thione[14] with trimethyl phosphite affords the corresponding ylide quantitatively. The phosphorane has been applied the one-carbon homologation of aldehydes to carboxylic acids (eq 13).[15]

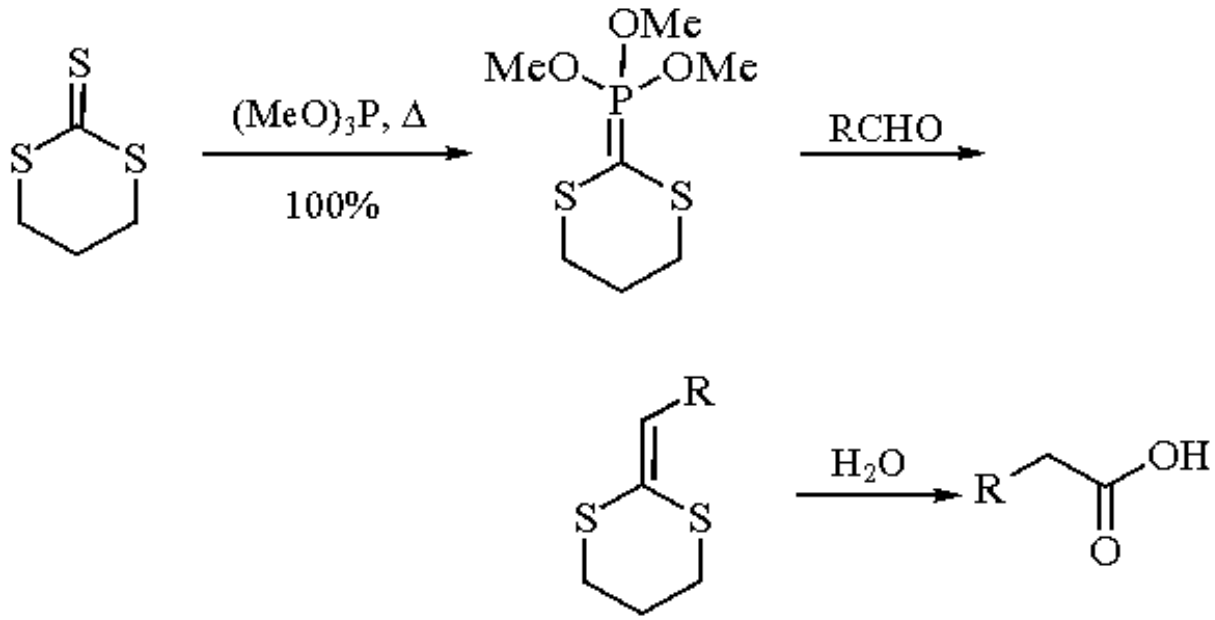

(13)

In addition, trimethyl phosphite has been used to capture intermediates formed during [2,3]-sigmatropic rearrangement of allylic sulfoxides (eq 14)[16] and in the conversion of penicillin derivatives to azetidinones (eq 15).[17]

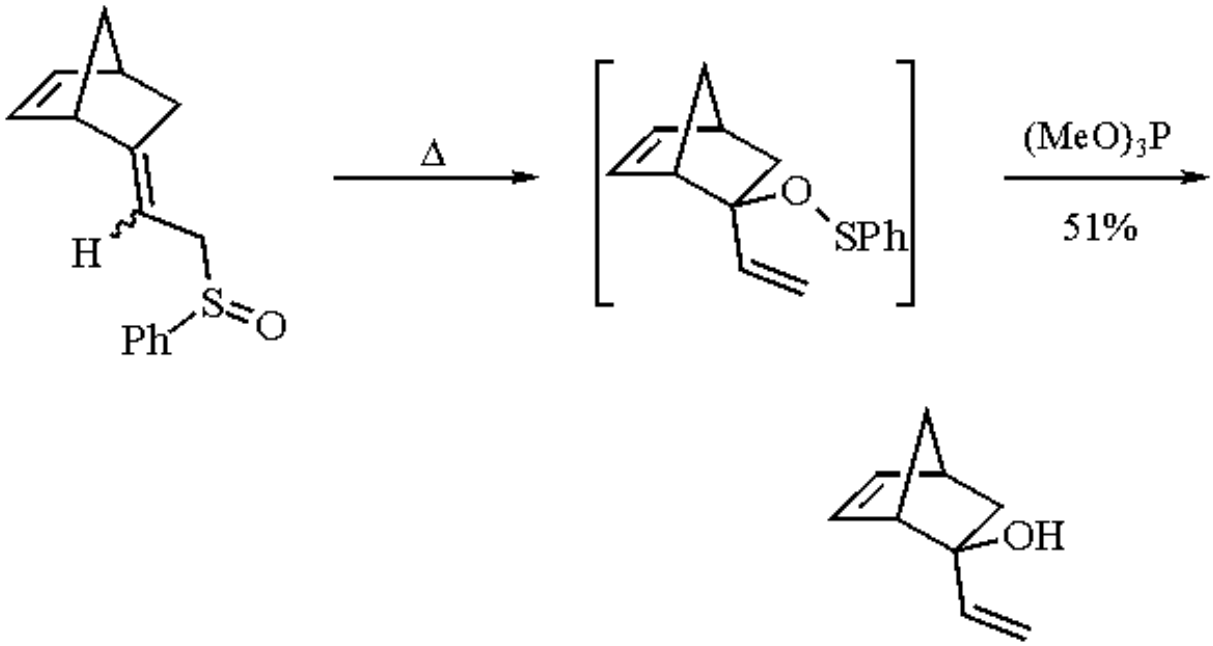

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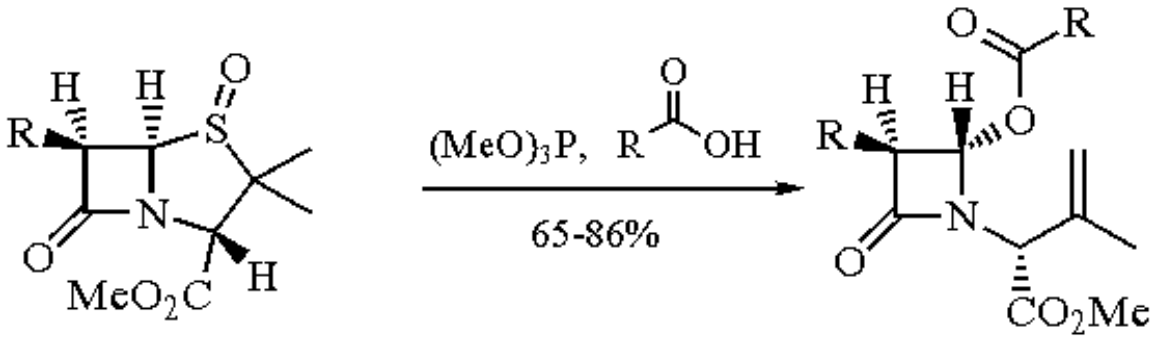

(15)

Dehalogenation.

Dershowitz[18] has reported that vicinal dibromides are smoothly converted to alkenes by heating in the presence of trimethyl phosphite. The reagent was successfully applied to systems where other reagents, such as ***Sodium Iodide*** or ***Zinc*** dust proved unsatisfactory (eq 16). The dehydrohalogenation of a steroidal allylic bromide has also been reported (eq 17).[19]

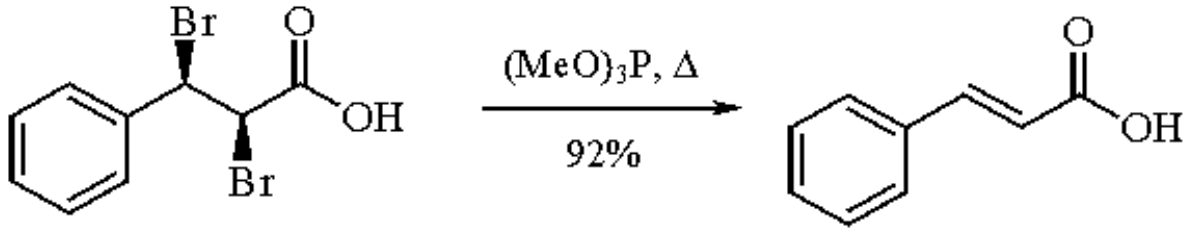

(16)

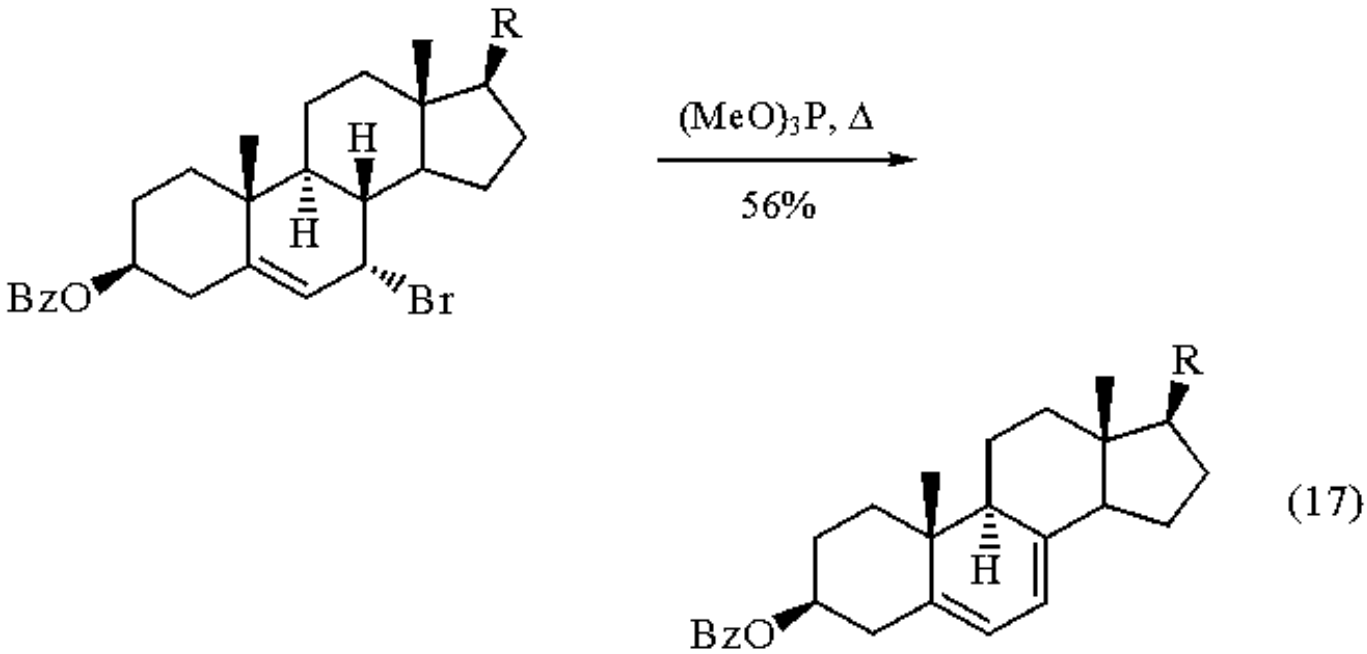

(17)

Copper Complexes.

Copper(I) Iodide-Trimethyl Phosphite is formed in 84% yield by the reaction of trimethyl phosphite and ***Copper(I) Iodide*** in refluxing benzene.[20] The salt has been used as a catalyst in the decomposition of diethyl diazomalonate to give ethers (eq 18)[21] and cyclopropanes (eq 19).[20] Furanones have been prepared using related methodology (eq 20).[22]

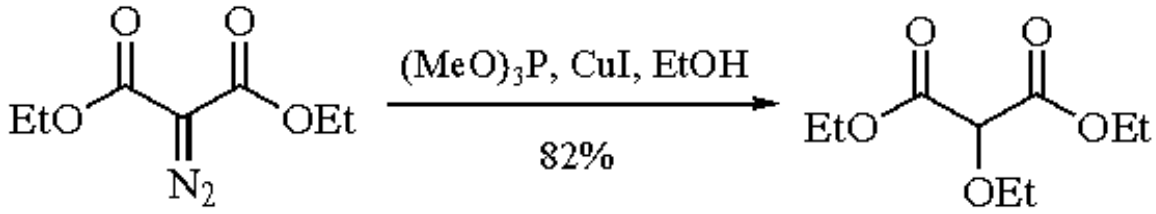

(18)

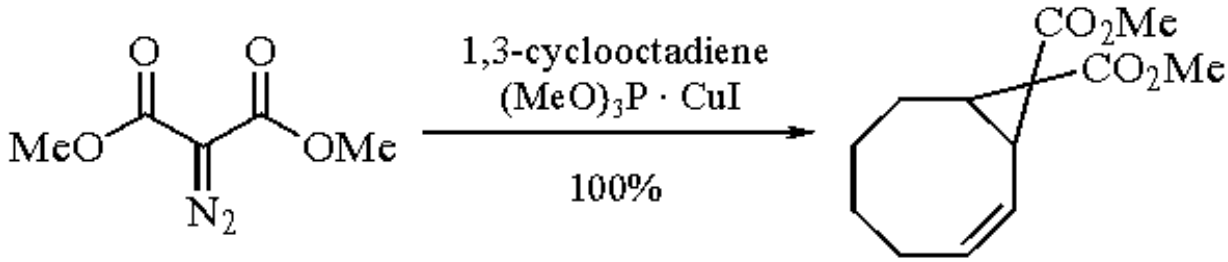

(19)

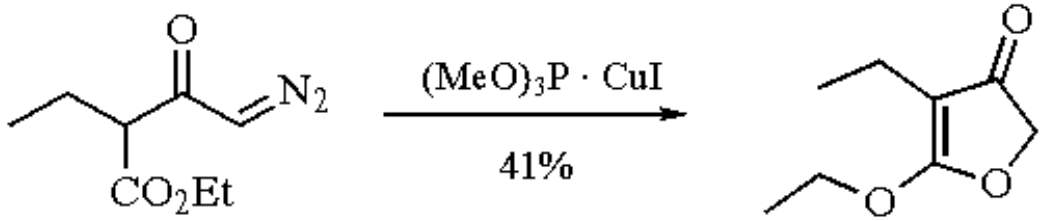

(20)

Trimethyl phosphite-methylcopper is a relatively stable complex of ***Methylcopper***. The reagent adds readily, in a conjugate sense, to

cyclohexenones, with a strong preference for axial attack (eq 21).[23]

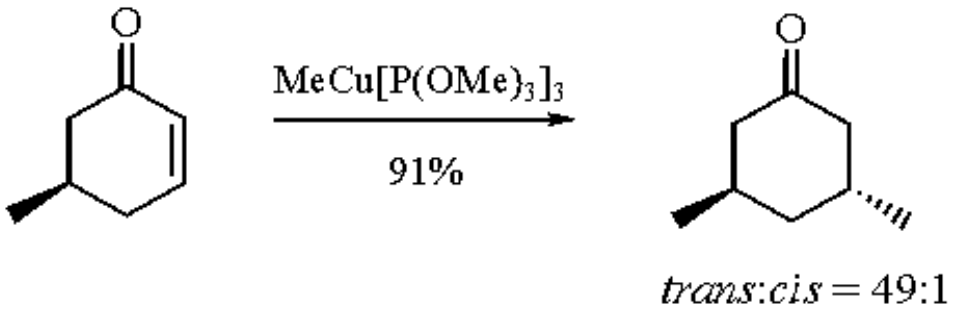

(21)

Esterification.

Trimethyl phosphite has been used in the conversion of a sensitive indolecarboxylic acid to the corresponding methyl ester under neutral conditions (eq 22).[24]

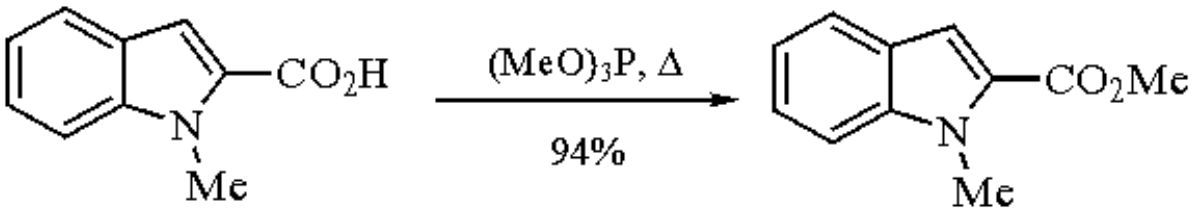

(22)

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Trimethyl Phosphonoacetate[1]

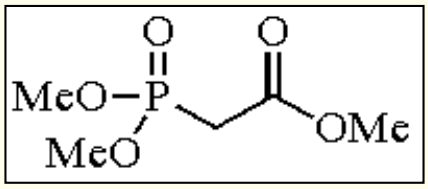

[5927-18-4] · $C_5H_{11}O_5P$ · Trimethyl Phosphonoacetate · (MW 182.13)

(with a base gives a phosphoryl-stabilized carbanion that reacts with aldehydes,[1] ketones,[1a-c] ketenes,[2] pyrylium salts,[3] triflates,[4a] alkyl halides,[4b] alcohols,[5] amines,[5] azides,[6] and CS_2[7])

Alternate Name: dimethyl (methoxycarbonyl)methylphosphonate.

Physical Data: bp 118 °C/0.85 mmHg; *d* 1.125 g cm^{-3}.

Solubility: sol common organic solvents.

Form Supplied in: colorless liquid; widely available.

Handling, Storage, and Precautions: store under N_2.

Reactions with Aldehydes and Ketones.

n-Butyllithium,[1d,8] ***Sodium Amide***,[9] ***Sodium Hydride***,[1d,10b] ***Potassium Hydride***,[1d] ***Potassium t-Butoxide***,[8,10] ***Sodium Methoxide***,[11] KOMe,[12] ***Potassium Hexamethyldisilazide*** (KHMDS),[13] and other bases deprotonate $(MeO)_2P(O)CH_2CO_2Me$ in solvents such as THF, DME, MeCN, DMF, DMSO, MeOH, benzene, toluene, and dioxane to give a phosphoryl-stabilized carbanion, $[(MeO)_2P(O)\text{-}CHCO_2Me]X^+$. The anion reacts with aldehydes and ketones to give an (*E*)-α,β-unsaturated ester as the major product (eq 1)[14] in a Horner-Wadsworth-Emmons (HWE) reaction (see also ***Triethyl Phosphonoacetate***). Hemiacetals (eq 2)[15] also react with $[(MeO)_2P(O)\text{-}CHCO_2Me]X^+$ to give an α,β-unsaturated ester. In some instances, $(MeO)_2P(O)CH_2CO_2Me$ and the aldehyde undergo a Knoevenagel condens ation (eq 3).[16]

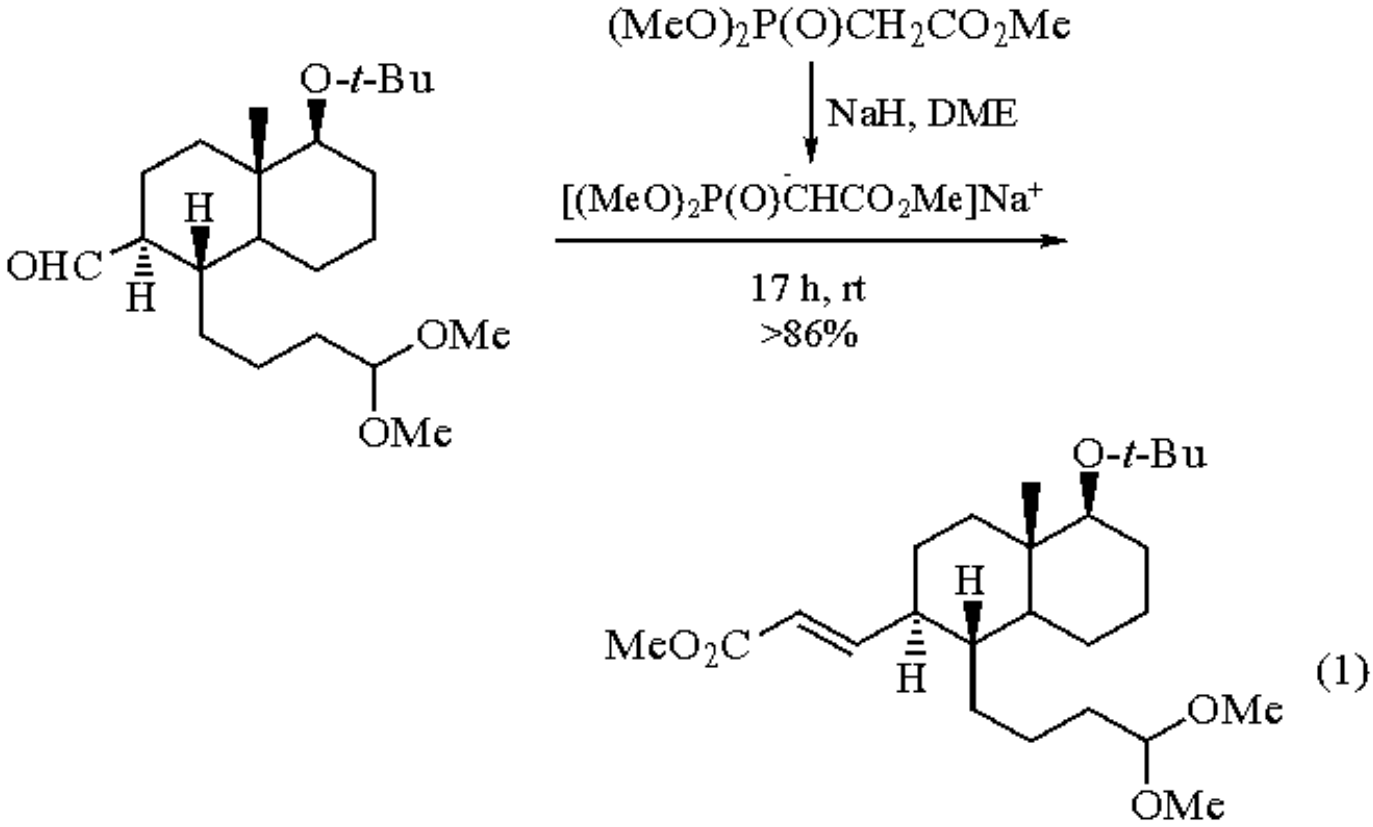
(MeO)2P(O)CH2CO2Me
NaH, DME
[(MeO)2P(O)CHCO2Me]Na+
17 h, rt
>86%
O-t-Bu
OHC
H
OMe
OMe
MeO2C
(1)

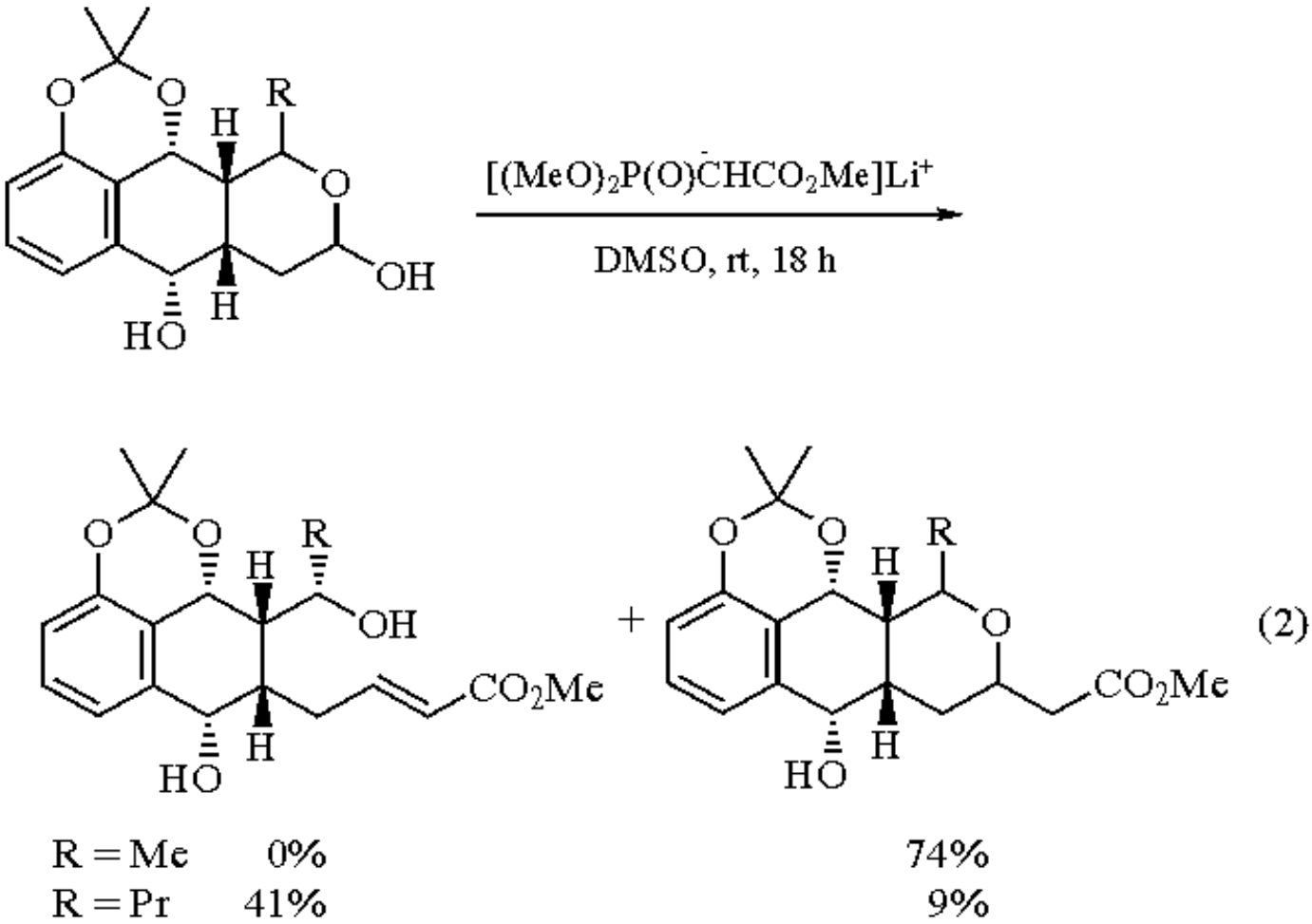
[(MeO)2P(O)CHCO2Me]Li+
DMSO, rt, 18 h
R
OH
HO
CO2Me
(2)
R = Me 0% 74%
R = Pr 41% 9%

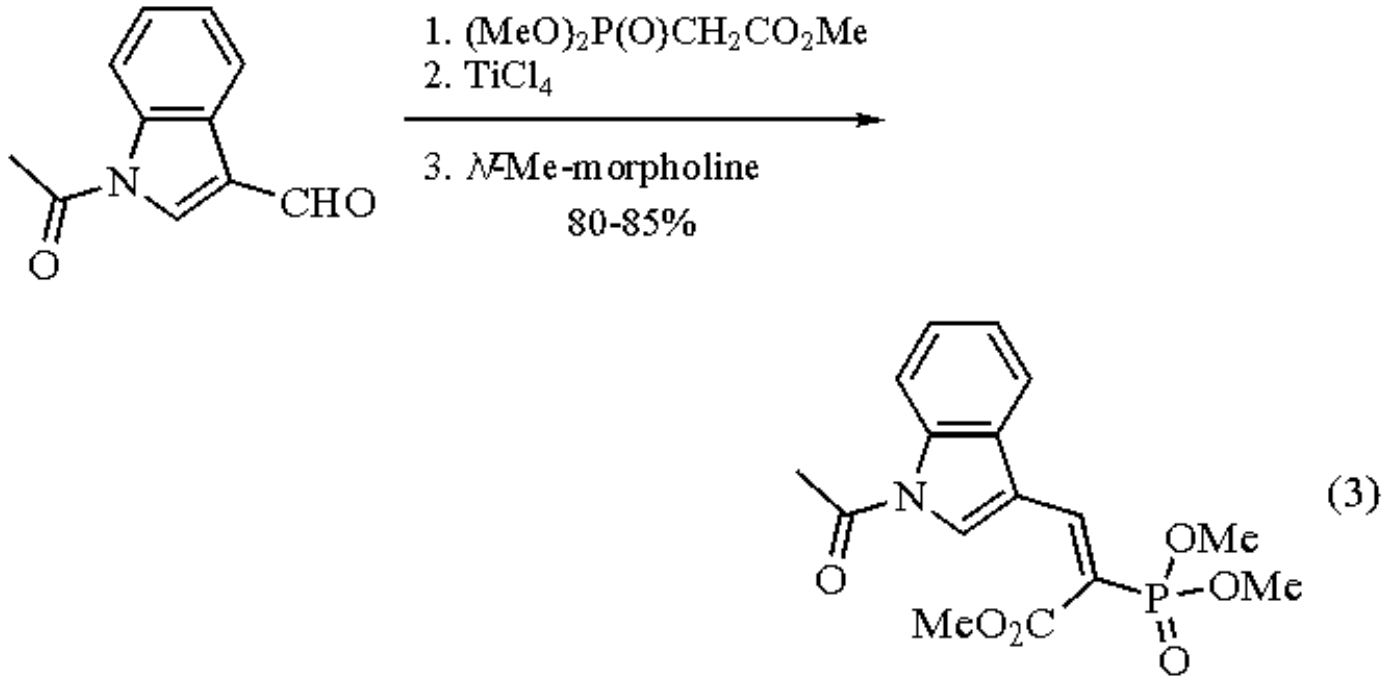

The aldehyde reactivity in HWE reactions with $(MeO)_2P(O)CH_2CO_2Me$ is seemingly unaffected by complexation (eq 4)[2,17a] or conjugation (eqs 4 and 5).[17] Cyclohexanones with a C-2 equatorial alkyl group are unreactive to $[(MeO)_2P(O)\text{-}CHCO_2Me]X^+$ under normal conditions.[18] Reaction occurs if the substituent can readily attain a conformation or configurational (epimerization) conversion to an axial position. Compounds containing 2 equivalent carbonyl groups undergo a double HWE reaction.[19]

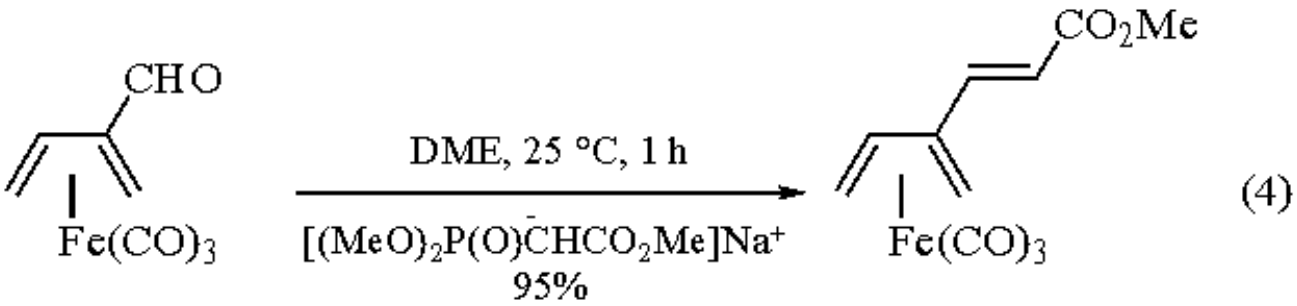

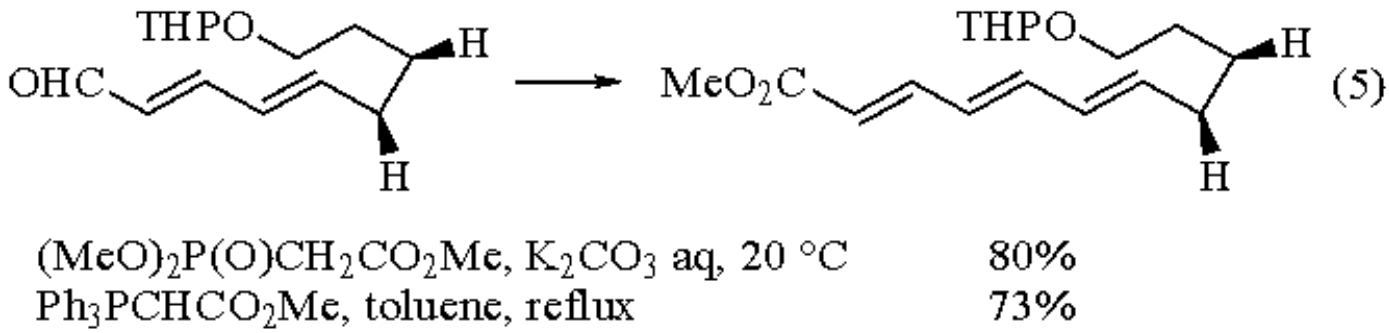

Other basic conditions for the HWE reaction with $(MeO)_2P(O)CH_2CO_2Me$ have been developed to accommodate base-sensitive aldehydes and to minimize undesired side reactions.[11c,16] ***Potassium Carbonate*** has been used in heterogeneous liquid-liquid conditions in the absence of organic solvents (eq 5).[17b,20,21] ***Sodium Hydroxide*** has also been used in liquid-liquid conditions[20] in the presence of a phase-transfer catalyst and both NaOH[20] and K_2CO_3[20] have been used in solid-liquid two-phase conditions. Other bases used include ***Cesium Carbonate***,[15c,20] ***Barium Hydroxide***,[20] ***Lithium Hydroxide***,[22] and a combination of ***Lithium Chloride*** and either ***Diisopropylethylamine*** (DIPEA) (eq 6),[20,23] ***1,8-Diazabicyclo[5.4.0]undec-7-ene***,[20] or ***Triethylamine***.[20] HWE reactions have also been carried out in the presence of crown ethers[13b] and the treatment of polymer-bound phosphonates at rt with aldehydes and ketones gives alkenes in high yields and with high (*E*) stereoselectivity.[24]

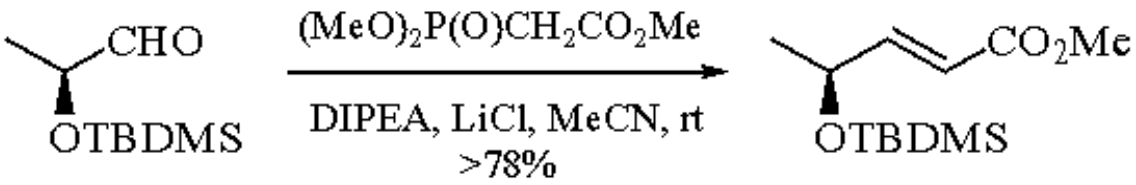

(6)

The (*E*/*Z*) ratio of unsaturated esters formed in the reaction of $[(MeO)_2P(O)\text{-}CHCO_2Me]X^+$ with aldehydes is dependent on the metal cation (X^+), reaction temperature, solvent, and the degree of α-substitution of the aldehyde.[1d] None of the effects alone is very large, but the combination of effects allows for a degree of control on the stereoselectivity of the reaction. (*E*) Selectivity is promoted with α-trisubstituted aldehydes, Li^+, rt, and nonchelating solvents such as benzene and DME. Formation of (*Z*)-unsaturated esters is promoted with α-mono and disubstituted aldehydes, and Na^+ or K^+ at -78 °C in THF. The (*E*/*Z*) stereochemistry in HWE reactions of trialkyl phosphonates is also influenced by the nature of the phosphonate carboxylic ester substituent.[1c]

A comparison of the alkenation of ketones and aldehydes using $(MeO)_2P(O)CH_2CO_2Me$ under HWE conditions and Ph_3PCHCO_2Me under Wittig conditions suggests that the former gives superior (*E*) stereoselectivity and occurs under milder reaction conditions (e.g. eq 5).[17b,25] α,β-Unsaturated esters are prepared from aromatic, saturated, and unsaturated aliphatic aldehydes with high (*Z*) stereoselectivity under Still-modified HWE conditions, using bis(trifluoroethyl) phosphonoesters $(CF_3CH_2O)_2P(O)CHRCO_2Me$ (R = H, Me) and/or strongly dissociated base systems like $KN(TMS)_2$/18-crown-6.[13a,25c,26] A predominance of (*Z*)-alkene has also been reported using $(MeO)_2P(O)CH_2CO_2Me$ under these conditions (eq 7).[13b,26a]

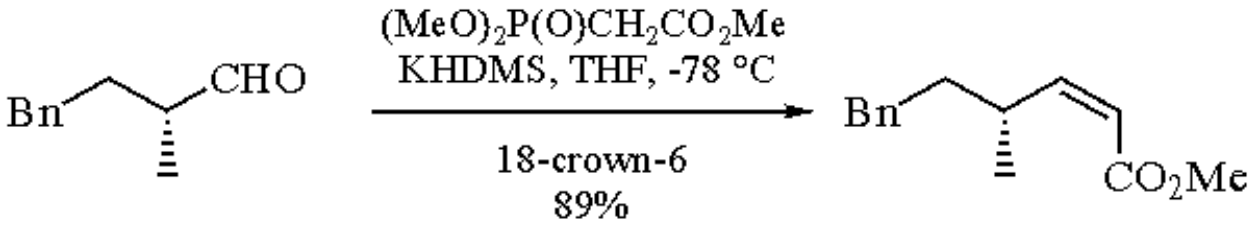

(7)

The reduction of a saturated ester or lactone with ***Diisobutylaluminum Hydride*** at -78 °C in the presence of $[(MeO)_2P(O)\text{-}CHCO_2Me]Na^+$ gives a good yield (60-80%) of the homologous ester with little or no overreduction of the starting material or product ester (eq 8).[20,27]

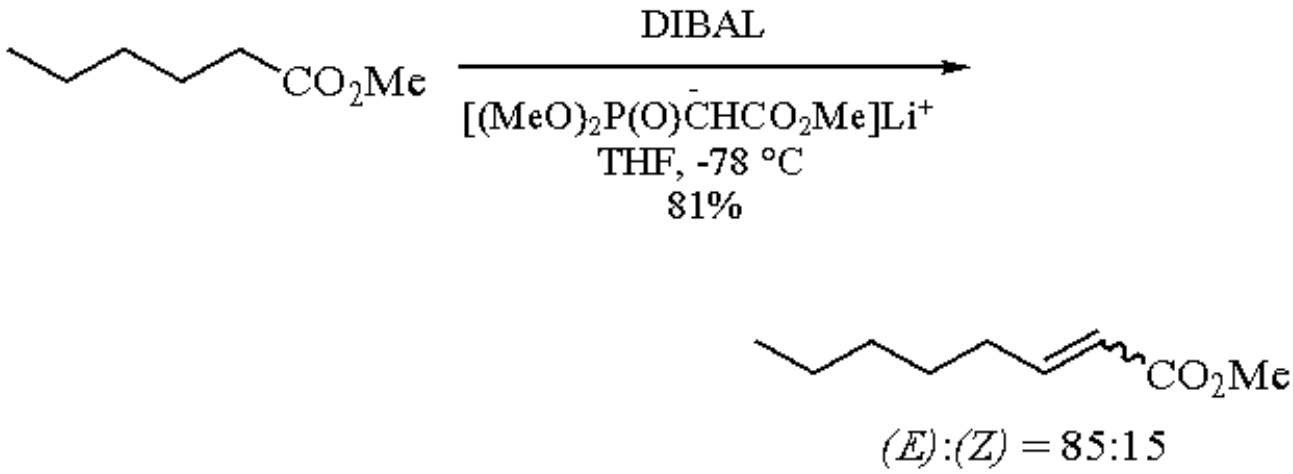

(8)

Reactions with Ketenes.

The anion of trimethyl phosphonoacetate, derived from reaction with ***Sodium Hydride***, reacts with tricarbonyl(vinylketene)iron(0) complexes to give (*E*)- and (*Z*)-tricarbonyl(vinylallene)iron(0) complexes in the ratio of 7:3 (eq 9).[2] Oxidation of the vinylallene complexes with ***Iron(III) Chloride*** leads to the release of the organic ligands as 5-alkyl-5-styrylfuran-2(5*H*)-ones (eq 9).[2]

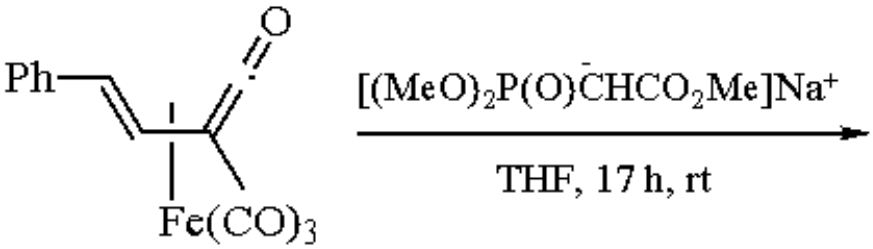

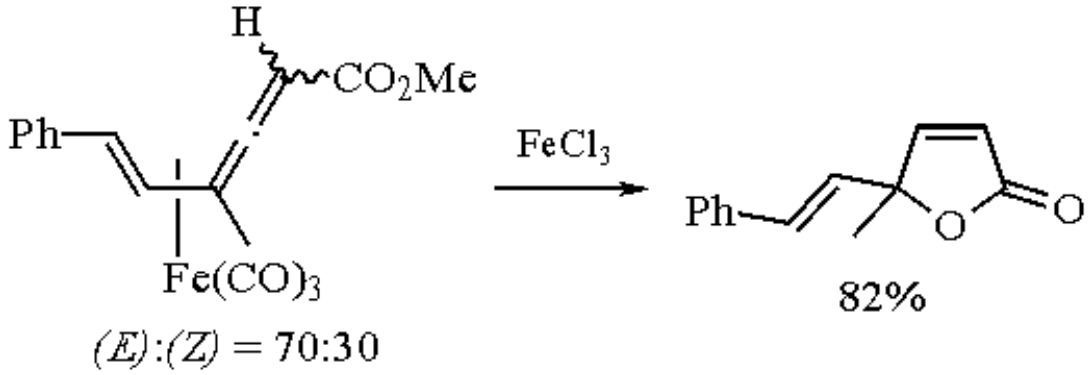

(9)

Other Reactions.

$[(MeO)_2P(O)\text{-}CHCO_2Me]Na^+$ reacts with pyrylium salts (eq 10).[3] α-Substituted phosphonates are prepared by alkylating $[(MeO)_2P(O)\text{-}CHCO_2Me]Na^+$ with either an alkyl triflate (eq 11)[4a] or iodide[4b] (see also ***Triethyl Phosphonoacetate***). Differentially substituted phosphonoacetates and phosphonoacetamides are prepared by reacting $(MeO)_2P(O)CH_2CO_2Me$ with ***4-Dimethylaminopyridine*** and an alcohol or amine, respectively.[5] The reaction of $[(MeO)_2P(O)\text{-}CHCO_2Me]Na^+$ with an azide gives an α-diazo phosphonate.[6] Reaction with CS_2 gives an 1,1-alkenedithiolate (eq 12) that can be alkylated, oxidized, protonated, and phosgenated.[7] Trialkyl phosphonates react with epoxides,[20] but only under forcing conditions.[28]

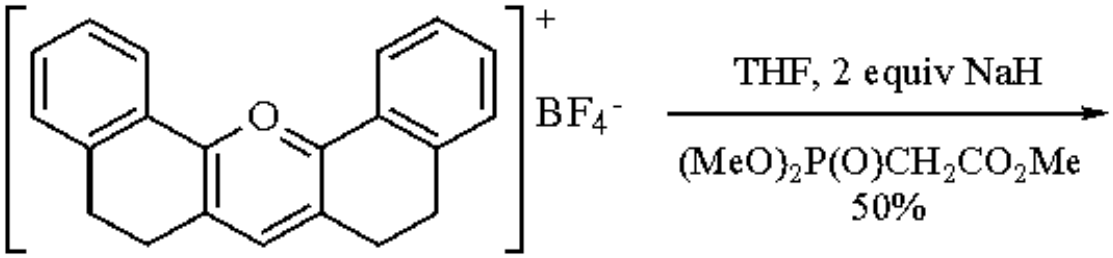

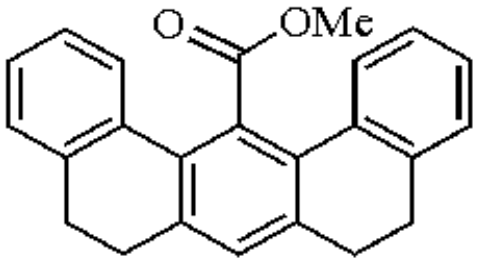

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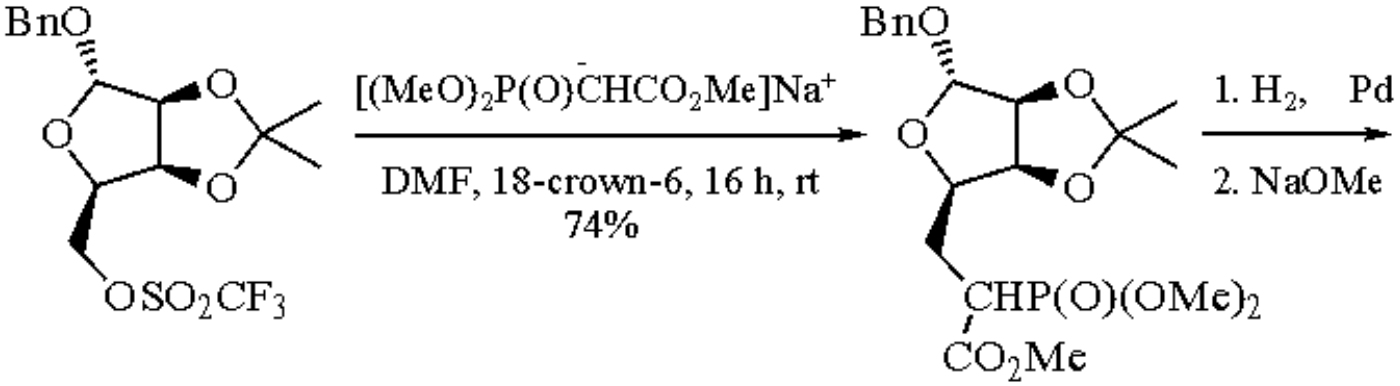

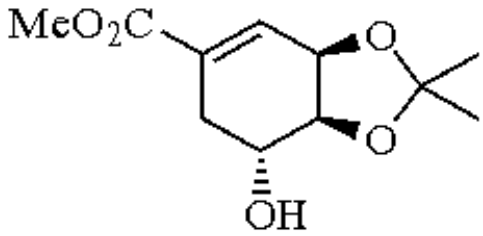

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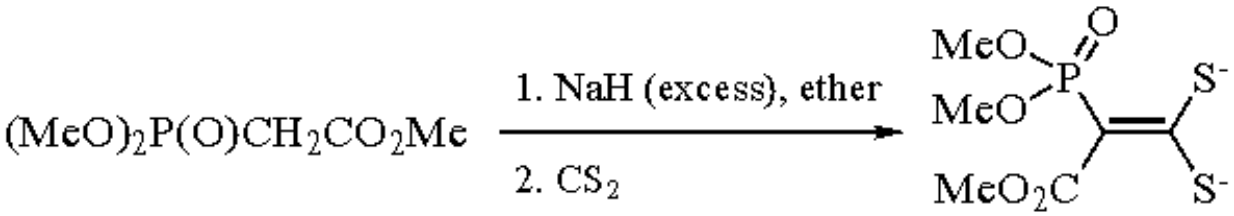

(12)

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Trimethyl 2-Phosphonoacrylate

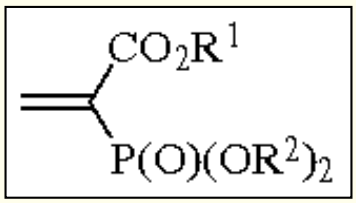

(**1**; R^1 = Me, R^2 = Me)

[55168-74-6] · $C_6H_{11}O_5P$ · Trimethyl 2-Phosphonoacrylate · (MW 194.14) (**2**; R^1 = Et, R^2 = Et)

[20345-61-3] · $C_9H_{17}O_5P$ · Triethyl 2-Phosphonoacrylate · (MW 236.23) (**3**; R^1 = Me, R^2 = Et)

[993-88-4] · $C_8H_{15}O_5P$ · Diethyl Methyl 2-Phosphonoacrylate · (MW 222.20)

(reactive, bifunctional Michael acceptor for tandem conjugate addition-alkenation and annulation reactions; useful enophile for ene reactions and dienophile for Diels-Alder reactions)

Physical Data: (**1**) bp 90-92 °C/0.1 mmHg. (**2**) bp 98.5-99.5 °C/0.13 mmHg. (**3**) bp 95-98 °C/0.15 mmHg.

Solubility: sol Et_2O, THF, EtOH, and most polar organic solvents.

Form Supplied in: (**1**) is commercially available; (**2**) and (**3**) must be synthesized.[2,3]

Analysis of Reagent Purity: IR and NMR spectroscopy and GC.

Preparative Method: (**1**) is prepared by heating ***Trimethyl Phosphonoacetate*** at reflux with a mixture of ***Paraformaldehyde***, MeOH, and ***Piperidine*** (previously heated at reflux).

Handling, Storage, and Precautions: commercial (**1**) is supplied with 0.5% 2,6-di-*t*-butyl-*p*-cresol as a stabilizer.

Conjugate Addition-Alkenation.

3-Substituted 2-phosphonomethylacrylates[1] can be prepared using phosphorus nucleophiles which undergo Michael addition to trimethyl 2-phosphonoacrylate. The resulting carbanion undergoes Horner-Emmons-type alkenation with aldehydes (eq 1). A similar sequence can be utilized to prepare functionalized dienes,[1] trienes, and their analogs (eq 2).

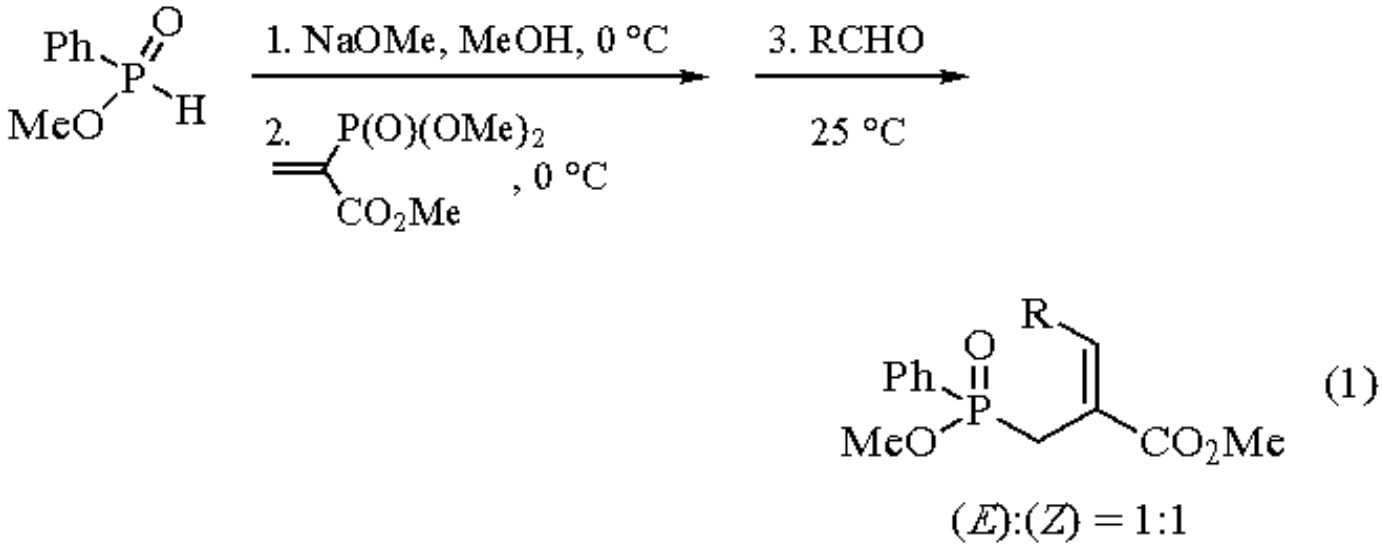

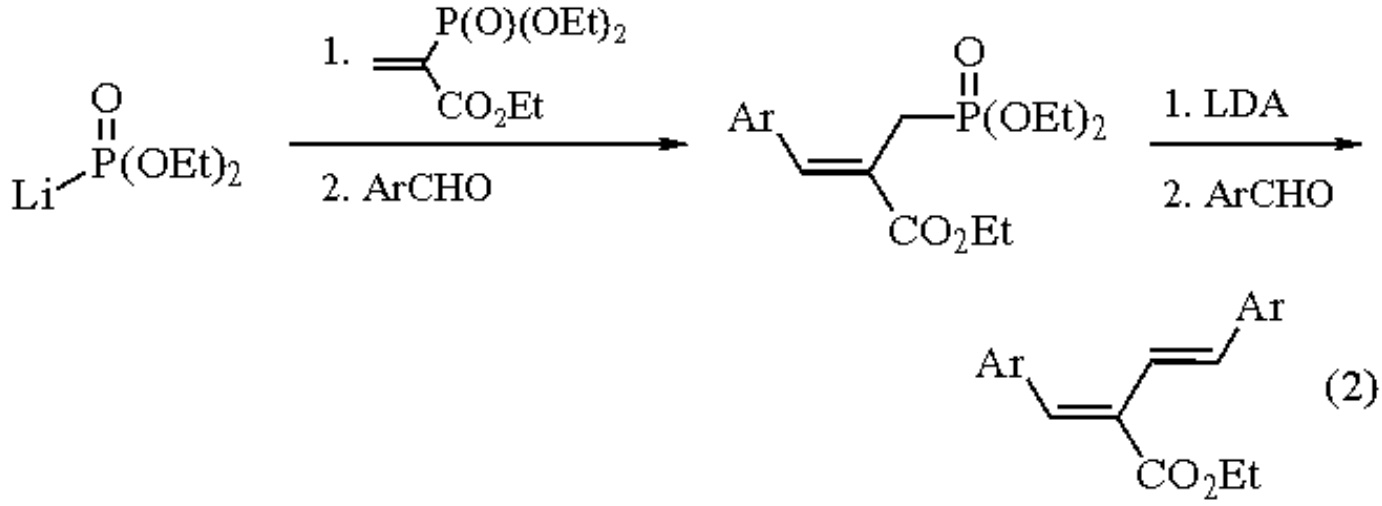

A variety of carbanion nucleophiles add to vinyl phosphonates to produce stabilized phosphonate anions capable of undergoing reactions with aldehydes and ketones to give unsaturated esters (eq 3).[2]

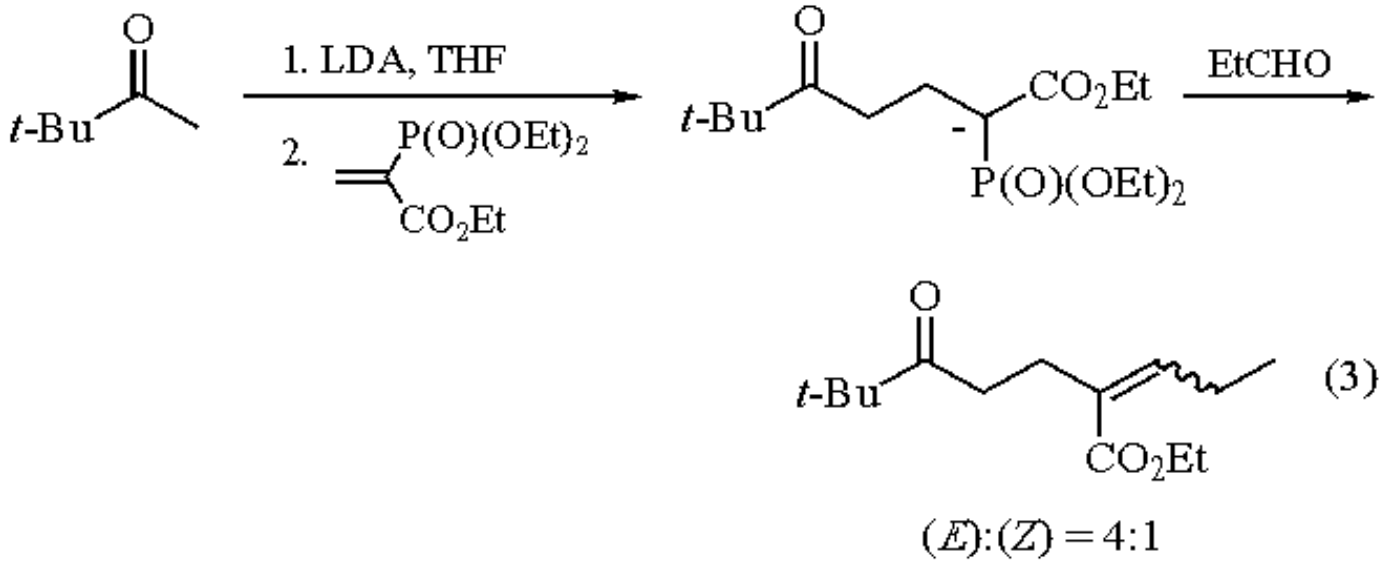

Annulation.

Oxygen and nitrogen nucleophiles add to phosphonoacrylates and lead to the formation of heterocyclic compounds (eq 4). Michael addition of *N*-lithio-4-vinylazetidin-2-one to vinyl phosphonate gives an addition product which can be converted to Δ^1-carbapenems[4] via ozonolysis and intramolecular Horner-Wittig reaction (eq 5). An imine-enamine annulation was used in the synthesis of the indoloquinolizidine alkaloid (±)-deplancheine.[4] Similarly, synthesis of six-membered carbocyclic compounds can be achieved by 2:1

condensation reactions of the phosphonoacrylate with cyclopentanone enolates (eq 6). Phosphonoacrylate annulation was also used in the construction of a [3.3.0]pyrazolidinone[4] from the monocyclic pyrazolidinone.

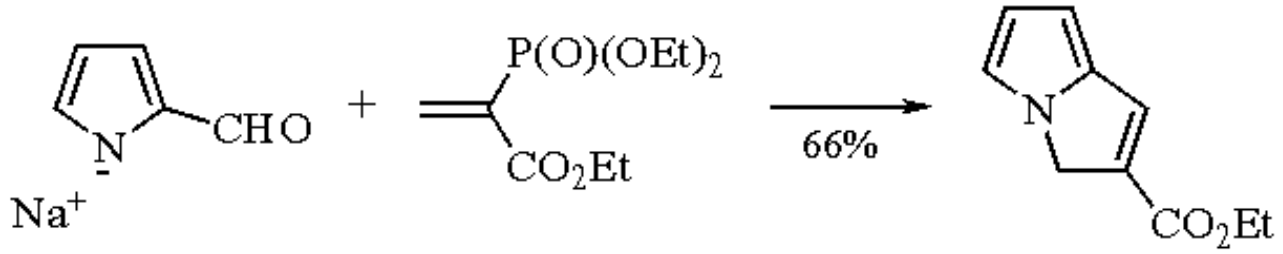

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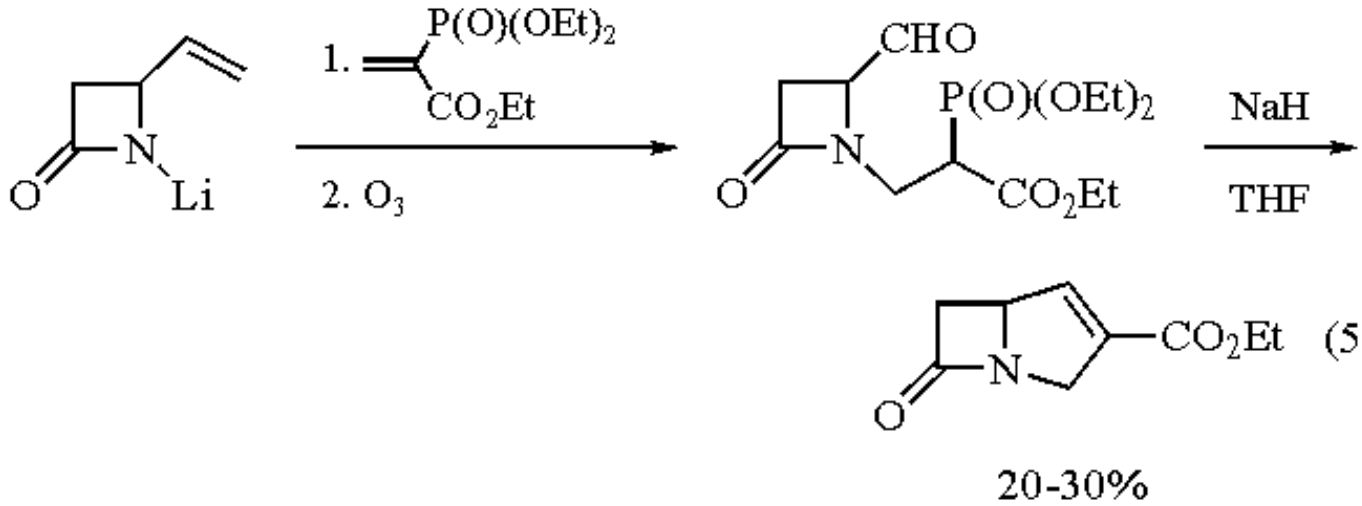

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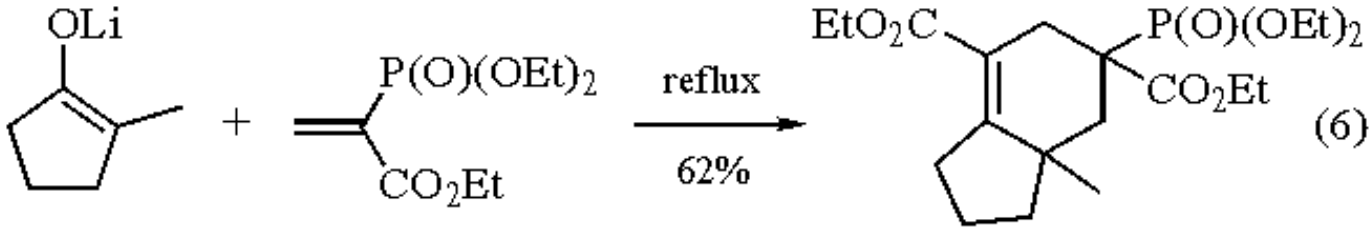

(6)

Sulfur Nucleophiles.

Michael addition of mercaptoacetaldehyde to phosphonoacrylate gives methyl 2,5-dihydrothiophene-3-carboxylate, which thermally decomposes to methyl 1,3-butadiene-2-carboxylate (eq 7). Similarly, sulfur nucleophiles[5] such as phenylthiolate and isopropylthiolate have been utilized in the synthesis of β-acetoxy- and β-hydroxy-α-methylene-γ-butyrolactones (eq 8),[5] confertin,[5] and arteannuin B.[5]

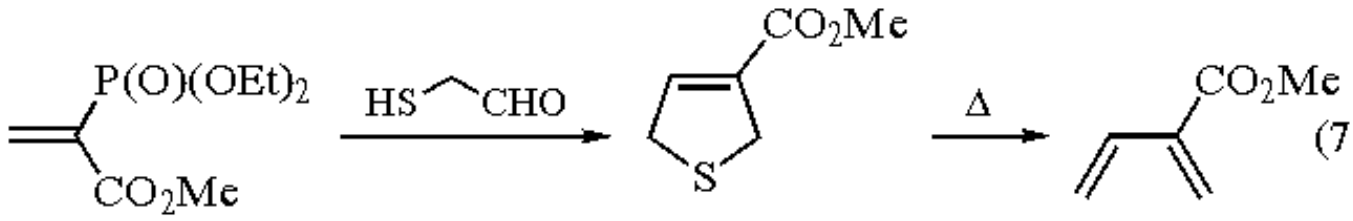

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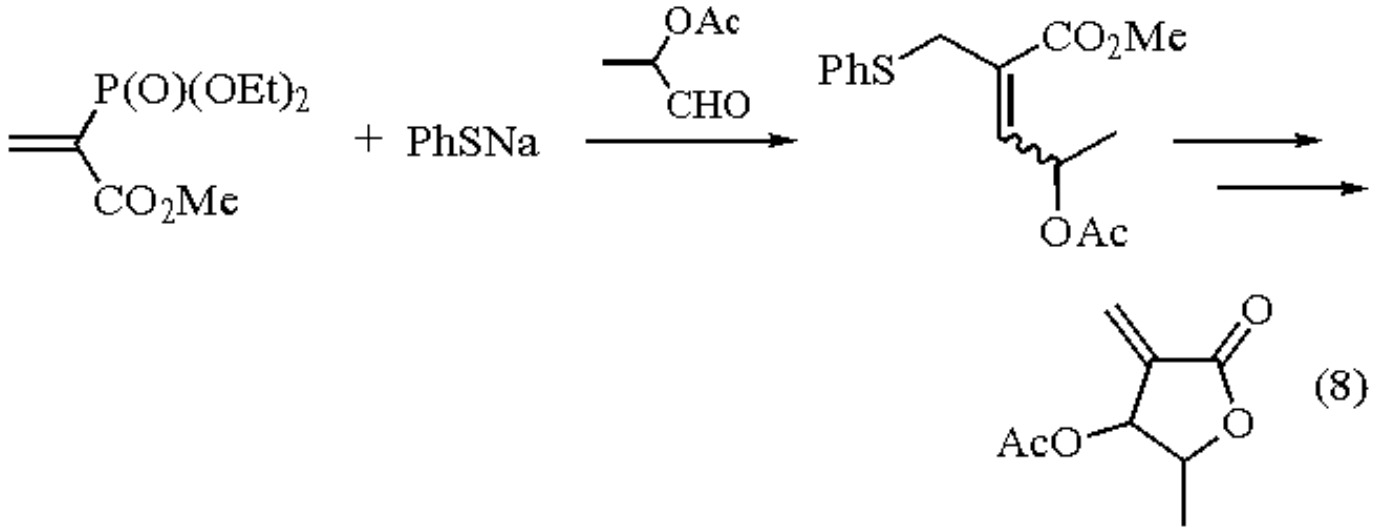

Ene and Diene Reactions.

Trimethyl 2-phosphonoacrylate undergoes facile ene reactions[6] with a variety of alkenes, using ***Ethylaluminum Dichloride*** as a Lewis acid catalyst (eq 9). It also undergoes [4 + 2] cycloadditions with isoprene (eq 10) and 6,6-diphenylfulvene.[6] Irradiation of acyl-*N*-hydroxy-2-thiopyridones in the presence of trimethyl 2-phosphonoacrylate affords derivatives of phosphonic analogs of nucleotides.[7]

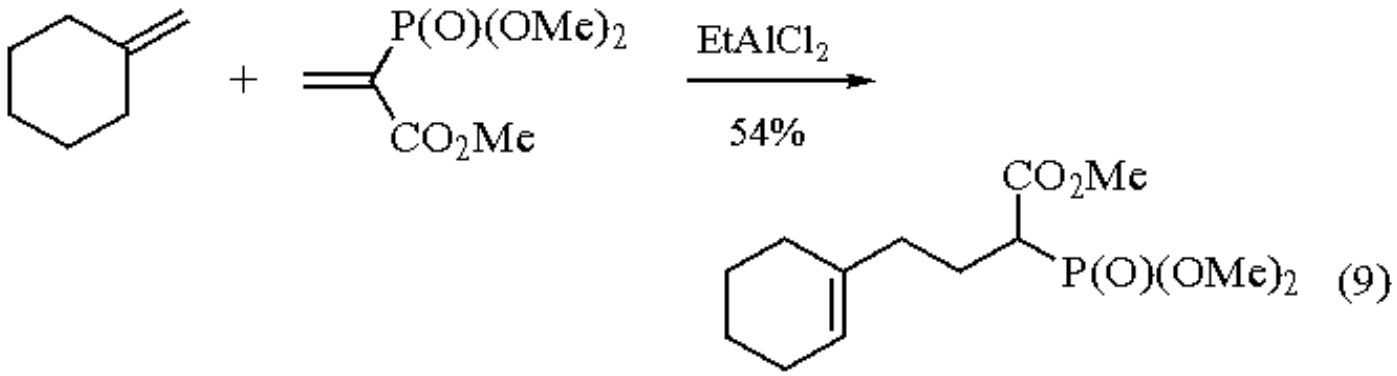

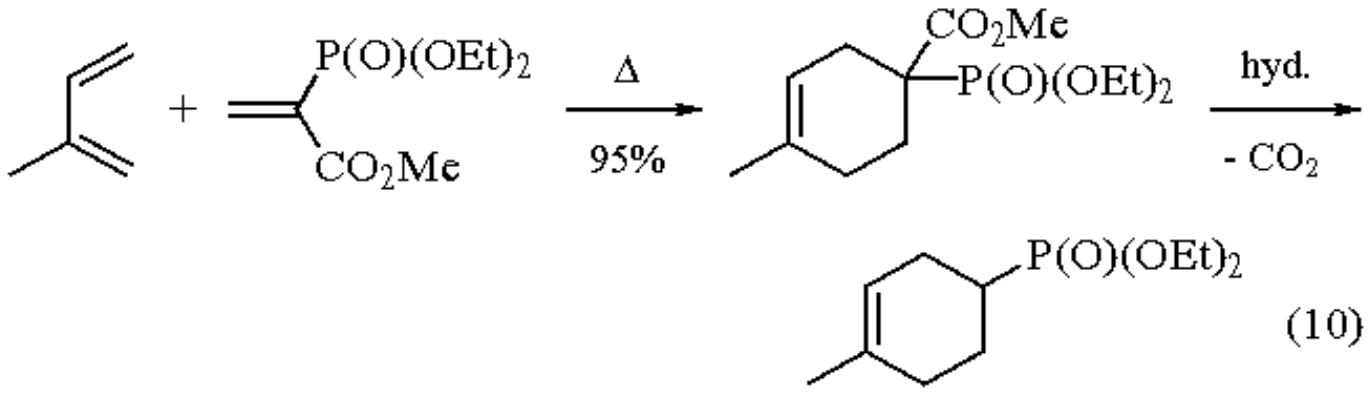

Related Reagents.

Diethyl Phosphonite; ***Ethyl Acrylate***; ***Methyl 2-Methylthioacrylate***; ***Methyl 2-Trimethylsilylacrylate***; ***Triethyl Phosphite***; ***Triethyl Phosphonoacetate***; ***Vinyltriphenylphosphonium Bromide***.

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2,4,6-Trimethylpyrylium Tetrafluoroborate[1,2]

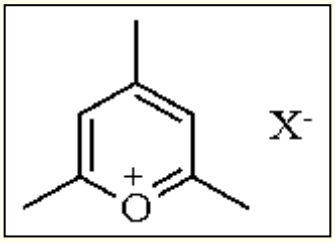

(**1**; $X^- = BF_4^-$)

[773-01-3] · $C_8H_{11}BF_4O$ · 2,4,6-Trimethylpyrylium Tetrafluoroborate · (MW 210.00) (**2**; $X^- = ClO_4^-$)

[940-93-2] · $C_8H_{11}ClO_5$ · 2,4,6-Trimethylpyrylium Perchlorate · (MW 222.64) (**3**; $X^- = CF_3OSO_2^-$)

[40927-60-4] · $C_9H_{11}F_3O_4S$ · 2,4,6-Trimethylpyrylium Triflate · (MW 272.27) (**4**; $X^- = HO_2CCH_2SO_3^-$)

[80731-12-0] · $C_{10}H_{14}O_6S$ · 2,4,6-Trimethylpyrylium Sulfoacetate · (MW 262.31)

(synthon reacting with various nucleophiles)

Physical Data: (**1**) mp 244 °C (dec). (**2**) mp 244 °C (dec). (**3**) mp 119-120 °C. (**4**) mp 115-116 °C.

Solubility: (**1**) sol H_2O, AcOH, CF_3CO_2H. (**2**) sol CF_3CO_2H. (**3**) sol H_2O, $CHCl_3$, MeOH, EtOH, $(ClCH_2)_2$. (**4**) sol H_2O, MeOH, EtOH, AcOH; insol Et_2O, Me_2CO.

Form Supplied in: white solids.

Preparative Methods: 2,4,6-trimethylpyrylium salts were the first pyrylium salts devoid of hydroxy or alkoxy substituents to be obtained, by Baeyer and Piccard in 1911.[3] Until then, protonated or alkylated γ-pyrones were the only known pyrylium salts. At that time, pyrones were puzzling nitrogen-free bases; the discussion about which of their two oxygen atoms was attacked lasted a long time and eventually led to the clarification of the concepts of aromaticity and aromatic sextet. Pertinent references may be found in reviews.[1]

A low-yield synthesis[3] was based on the reaction of 2,6-dimethyl-4-pyrone with methylmagnesium iodide, followed by treatment with acid (perchloric acid was then favored).

The preferred syntheses of 2,4,6-trimethylpyrylium perchlorate (**2**) are based either on the diacetylation of ***Isobutene*** (eq 1),[4] or on the acetylation of mesityl oxide (eq 2),[5] using ***Acetic Anhydride*** and 60-70% perchloric acid. In the former synthesis, instead of the gaseous isobutene, one uses *t*-butanol which is dehydrated in situ.[6]

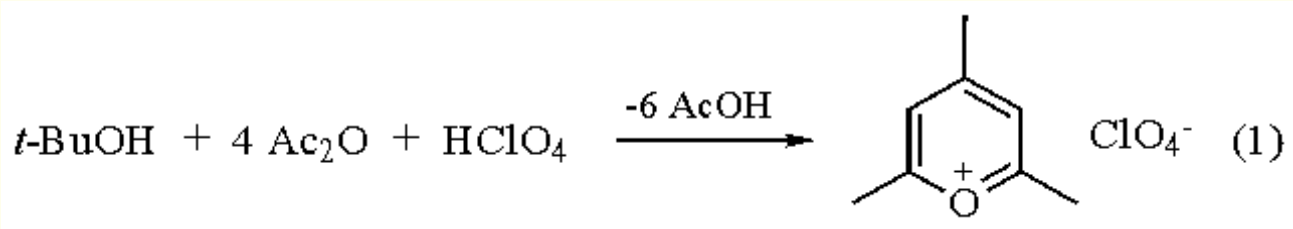

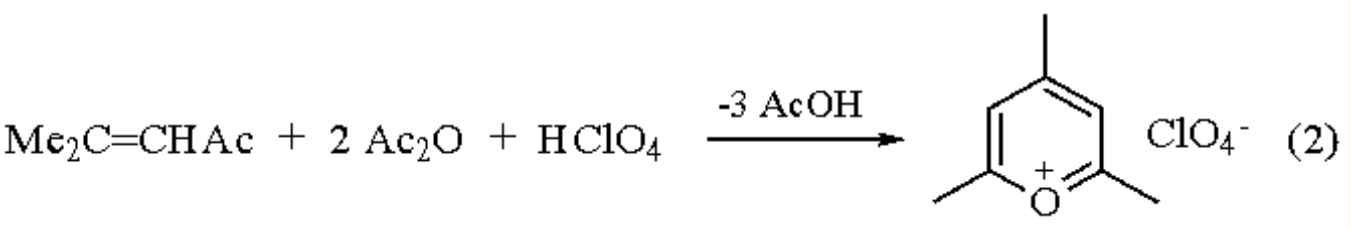

In both methods, isomesityl oxide is the actual reaction intermediate. The reaction mechanism is shown in eq 3.

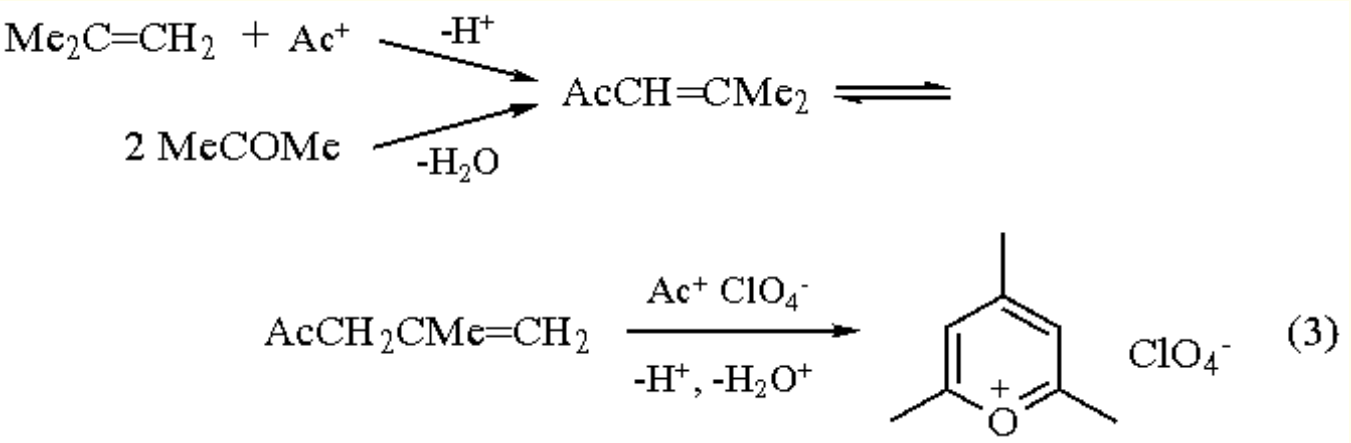

Since organic perchlorates may explode on impact when dry, other anions have lately been preferred, namely tetrafluoroborate or trifluoromethanesulfonate (triflate), obtained from *t*-butanol with Ac_2O and the corresponding acid, analogously to eq 1. When using 48% fluoroboric acid, the yield of fluoroborate (**1**) is 50%,[7] and when using anhydrous triflic acid, the yield of triflate (**3**) is 42%.[8]

2,4,6-Trimethylpyrylium sulfoacetate (**4**) can be prepared inexpensively on a large scale (in kg amounts) according to published procedures[9] starting either from isobutene or from *t*-butanol (eq 4). Excess acetic anhydride is no longer required for reacting with the water from $HClO_4$ or HBF_4 solutions. The sulfoacetate (**4**) crystallizes from the reaction mixture on addition of acetone, in which it is insoluble. It has a high solubility in water.

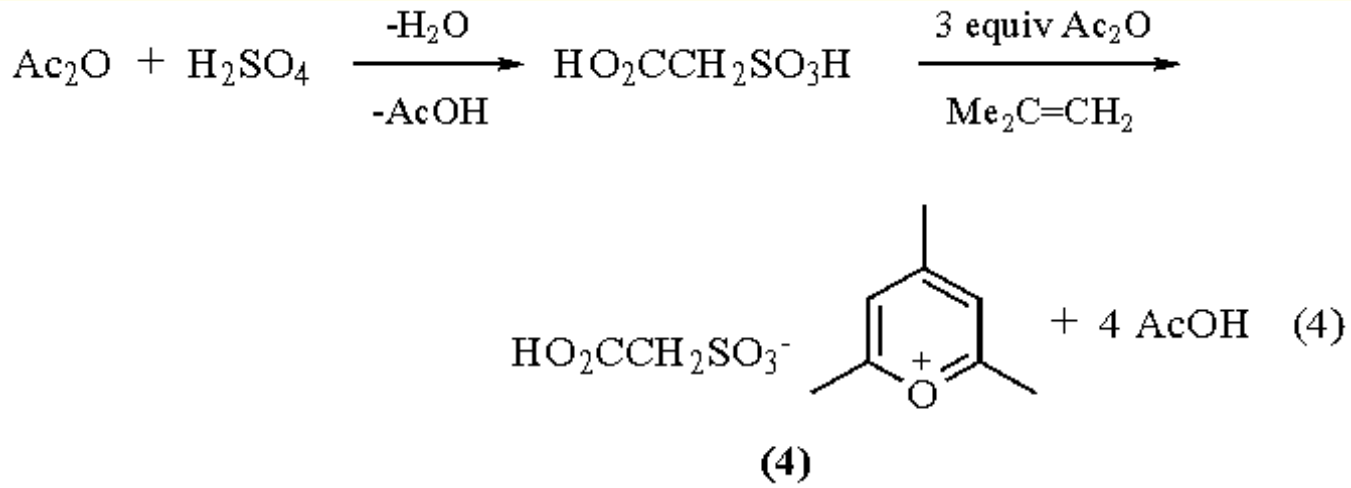

Purification: recrystallize from: (**1**), EtOH, MeOH; (**2**), H_2O, AcOH; (**3**), dioxane-AcOH (7:1) or $CHCl_3$-CCl_4 (2:1); (**4**), MeOH-Me_2CO.

Handling, Storage, and Precautions: all salts may be stored indefinitely. Reports on possible mutagenic activity make it desirable to avoid direct contact with skin. The perchlorate (**2**) is explosive; therefore it should be prepared only in the required amount for further use. The dry perchlorate should be handled with great care, and never be heated, crushed, rubbed, or pushed through a narrow opening. It may be kept in a cork-stoppered flask when moistened with water or dry THF. Use in a fume hood.

Reactions.

Like other pyrylium salts, the title products (**1**)-(**4**) react readily with many nucleophiles, yielding adducts initially (usually 2*H*-pyrans, but exceptionally 4*H*-pyrans with hydrides or Grignard reagents). The 2*H*-pyrans are valence isomeric with open-chain 2,4-pentadien-1-ones, which then may recyclize to a variety of products, mainly aromatic or heteroaromatic. The result is the incorporation of the pyrylium five-carbon chain with its substituents into new acyclic, carbocyclic, or heterocyclic systems, triggered by the initial reaction with the nucleophile.[2] In the following, (**2**) or (**3**) may always replace (**1**), and the same is true for (**4**), but in this case one must take into account the CO_2H group of the anion which may sometimes interfere with the nucleophile.

In some cases, the recyclization involves one of the α-methyl groups in (**1**). Thus 3,5-dimethylphenol (**5**) is formed by boiling (**1**) with aqueous alkali hydroxides (eq 5), and similar reactions occur with other pyrylium salts having α-methyl or α-methylene groups.[5a,10] With secondary amines, (**1**) affords *N*,*N*-dialkyl-3,5-dimethylaniline derivatives similarly (**6**).[11]

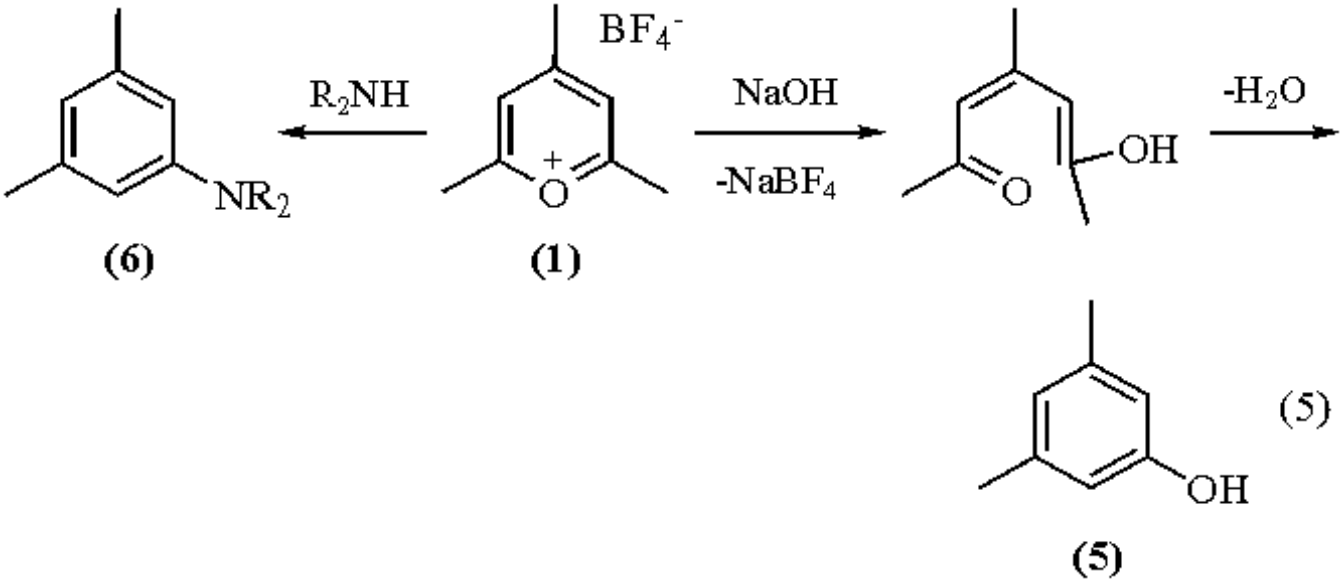

Reactions With Oxygen Nucleophiles.

Hydrogen Peroxide converts (**1**) into 2-acetyl-3,5-dimethylfuran.[12] The yield is increased appreciably if the reaction is carried out in a phosphate buffer; enol esters have been identified as byproducts.[13]

Reactions With Nitrogen Nucleophiles.

Ammonia and primary amines (RNH_2) react with (**1**), yielding *sym*-collidine and *N*-substituted collidinium salts, respectively. In the latter reaction, depending on the R group, an aniline derivative (secondary amine) analogous to the tertiary amine (**6**) may be obtained as a byproduct, but in some cases this may become the main product.[14] Amino acids and terminal amino groups in polypeptides give rise to pyridinium salts on reacting with (**1**); this reaction may have biochemical significance.[15]

The *N*-substituted pyridinium salts prepared from isopropylamine (**7a**) or from amino alcohols or their esters (**7b-7d**) present ^1H and ^{13}C NMR chemical shift nonequivalence of their α-methyl peaks; the intramolecular rotation barriers ΔG^+ are 13-15 kcal mol^{-1} for (**7a**) and (**7b**), 17 kcal mol^{-1} for (**7c**), and 19 kcal mol^{-1} for (**7d**). Such values are among the highest for sp^2-sp^3 single bonds.[16]

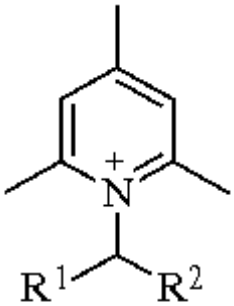

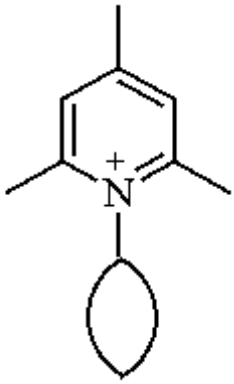

(7a) $R^1 = R^2 = Me$
(7b) $R^1 = Ph,\ R^2 = CH_2OH$
(7c) $R^1 = Me,\ R^2 = CH_2OH$
(7d) $R^1 = Et,\ R^2 = CH_2OH$

(8)

X-ray crystallography showed that the dihedral angle of *N*-phenyl-2,4,6-trimethylpyridinium perchlorate is 85°.[17] The *N*-aryl ring current therefore strongly shields the six α-methyl protons and deshields slightly the three γ-methyl protons relative to *N*-alkyl-2,4,6-trimethylpyridinium. The chemical shift difference between the two α/γ methyl peaks in (**8**), when the sizes of *N*-aryl or -hetaryl groups are similar, measures the relative ring current in these groups.[18]

Hydroxylamine affords 2,4,6-trimethylpyridine *N*-oxide with (**1**).[6a,19] An indolizine (**10**) synthesis is based on the reaction between (**1**) and aminoacetaldehyde acetals (**9**) (R = Me or Et) (eq 6).[20]

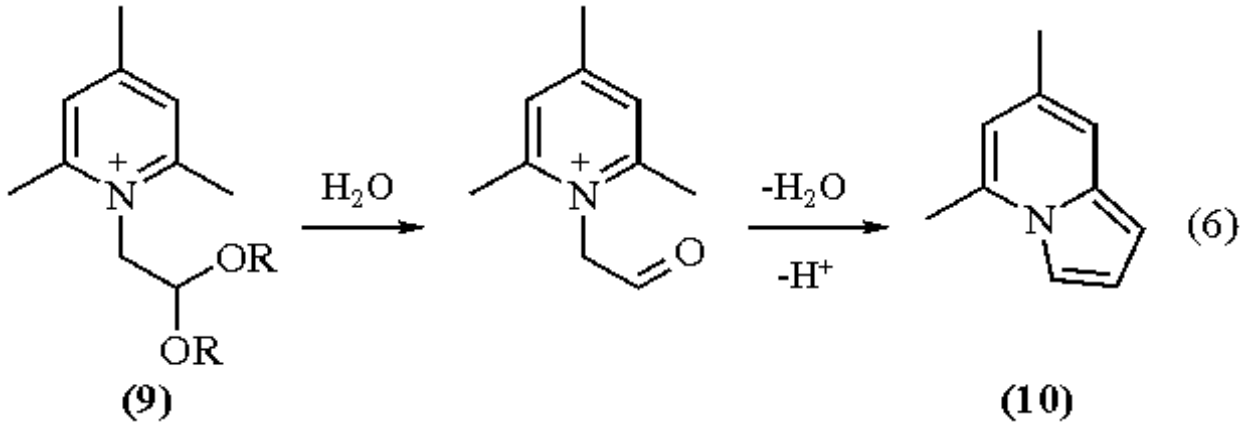

Reactions With Carbon Nucleophiles.

With sodium cyclopentadienide, (**1**) yields 4,6,8-trimethylazulene.[21] Alkali cyanides react with (**1**), yielding (*Z*)-5-cyano-2,4-dien-1-ones; these are converted to (*E*)-isomers by cold mineral acids.[22] Benzylmagnesium chloride attacks (**1**) in the γ-position, yielding a 4*H*-pyran which, on treatment with strong acids, undergoes ring opening and recyclizes to 1,3-dimethylnaphthalene, splitting off acetone (eq 7).[23] Since the 2,4,6-trimethylpyrylium cation may be synthesized from acetone and acetylacetone in the presence of strong acids,[24] it was logical to devise a synthesis of naphthalene derivatives from 1,3-diketones and benzylmagnesium chloride.[25]

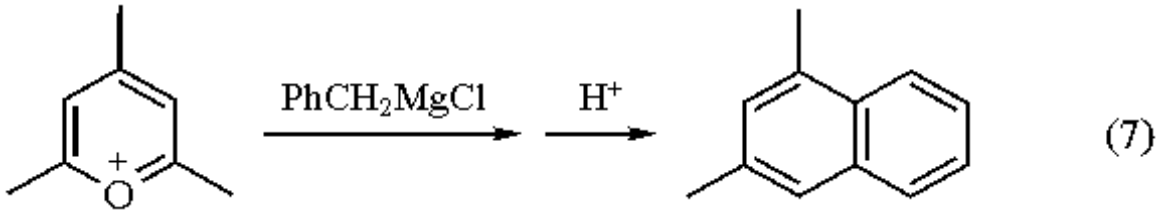

Nitronate anions (e.g. ***Nitromethane*** with 2 equiv of ***Potassium t-Butoxide***) convert (**1**) into aromatic nitro derivatives (i.e. 2,4,6-trimethylnitrobenzene).[26] With acetylacetone or ***Ethyl Acetoacetate***, (**1**) affords 2,4,6-trimethylacetophenone, whereas with ***Ethyl Cyanoacetate*** it forms mesitonitrile;[27] such reactions exemplify the versatility of pyrylium synthons.[2]

Isotopic Exchange of Methyl Hydrogens.

Brief heating of (**1**) in D_2O, namely for 10 min at 80 °C (the less-soluble perchlorate (**2**) works even better because it crystallizes at the end of the isotopic exchange), leads mainly to γ-methyl deuteration. On further refluxing in D_2O for 1 h, all nine methyl hydrogens are deuterated. If this fully deuterated salt is heated in H_2O for 20 min, only the γ-methyl is de-deuterated (eq 8). Thus, specifically methyl-deuterated 2,4,6-trimethylpyrylium salts (i.e. only in γ, only in α, or in both α and γ) may be obtained and converted afterwards, without loss of isotopic labels, into pyridines, azulenes, benzene derivatives, etc.[28] Secondary isotope effects of deuterium in specifically labeled 2,4,6-trimethylpyridine were thus investigated, proving that lanthanide shift reagents feel only the smaller size of CD_3 vs. CH_3, pK_a differences are due only to the higher donor ability of CD_3 groups, and quaternization by CH_3I or CD_3I is affected comparably by both steric and electronic differences between CH_3 and CD_3 groups.[29]

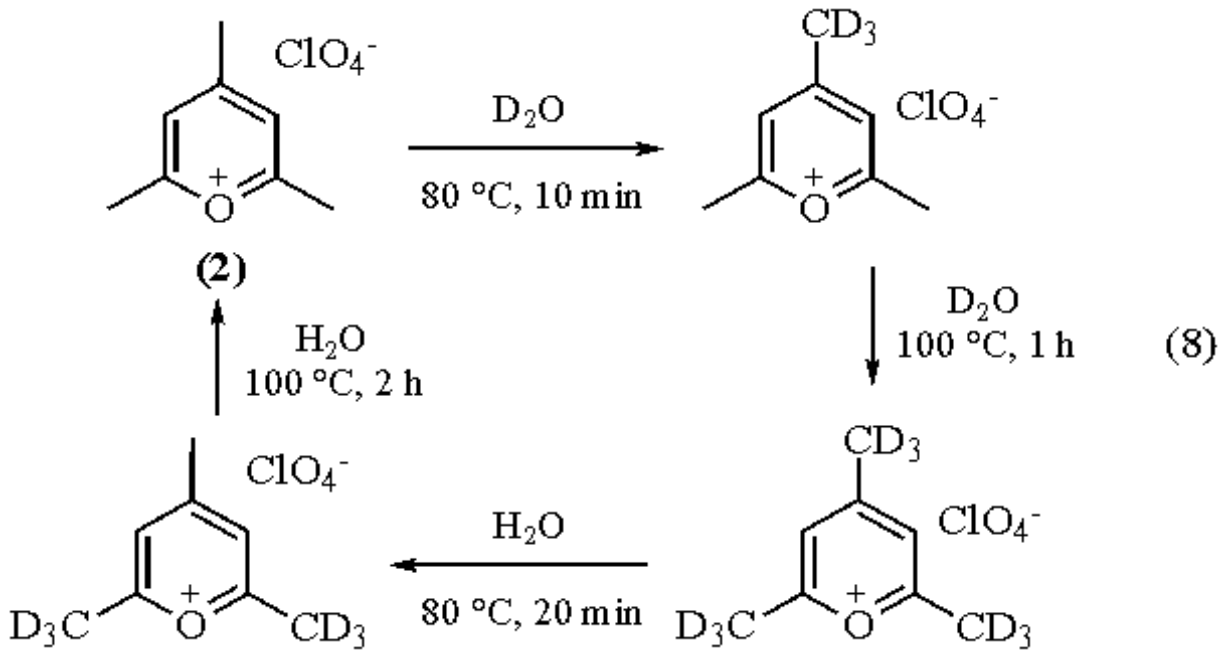

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&

Trimethylselenonium Hydroxide

Me_3SeOH

[44124-85-8] · $C_3H_{10}OSe$ · Trimethylselenonium Hydroxide · (MW 141.09)

(methylating agent for relatively nonnucleophilic heteroatoms[1])

Solubility: sol H_2O, MeOH.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: solution concentration can be determined by titration with 0.1 N hydrochloric acid.

Preparative Method: a solution in methanol-water can be generated by addition of ***Silver(I) Oxide*** (1 equiv) to a solution of trimethylselenonium iodide (1.3 equiv).[1] Typical concentrations of ~0.7 N are obtained.

Handling, Storage, and Precautions: the solution is stable at temperatures below 10 °C, undergoing ~5% decomposition after 1 month. The solution is alkaline, and therefore would not be compatible with acidic solvents. Since one of the byproducts of the reaction is dimethyl selenide, reactions should be carried out in a fume hood.

Methylation Reactions.

Trimethylselenonium hydroxide is a mild methylating agent, reacting with carboxylic acids, thiols, phenols, and other weakly basic heteroatoms.[1] The reactions are typically performed by adding the substrate (1.0 equiv) to a solution of the electrophile (1.1 equiv) in methanol-water and concentrating the mixture on a rotary evaporator.[1] The reaction flask is then equipped with a distillation head and heated with stirring. In the case of solid nucleophiles, DMF is added prior to heating the reaction mixture.[1] The dimethyl selenide (bp 56-57 °C) produced in the reaction is collected in the distillation, and could be reused by regeneration of trimethylselenonium iodide with ***Iodomethane***.[2] The pure methylated products could then be purified by direct distillation or recrystallization of the crude residue.

The reactions with carboxylic acids (eq 1), phenols (eq 2), and thiols (eq 3) are complete within 15 min and progress in quantitative yield.[1] Ring amines in aromatic heterocycles are also smoothly converted to the methylated derivatives as well (eq 4).[1] Alcohols and both aliphatic and aromatic amines do not react under these conditions. Selective methylations can thus be readily performed (eq 5).[1] Multiple methylations can be effected in a single pot, as in the synthesis of caffeine (eq 6).[1] Trimethylselenonium hydroxide and triethylselenonium hydroxide can also be used to quantitatively alkylate fatty acids on a GC (eq 7).[3]

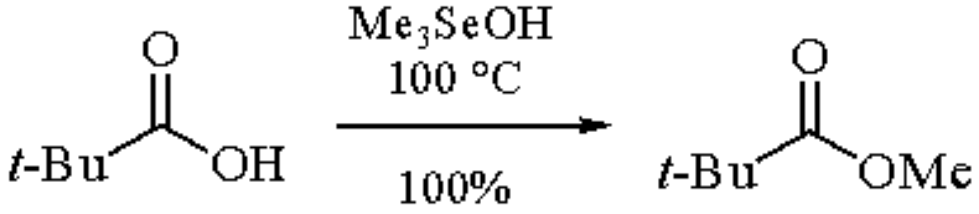

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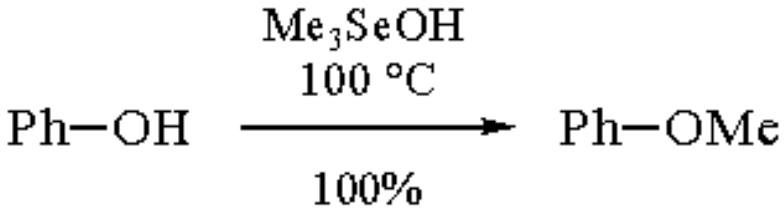

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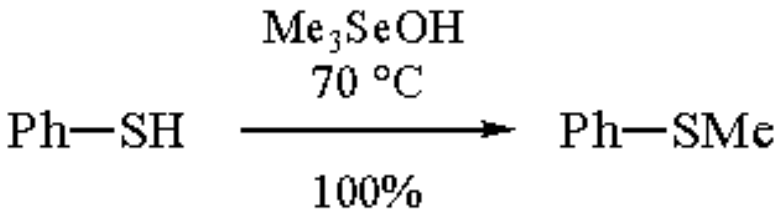

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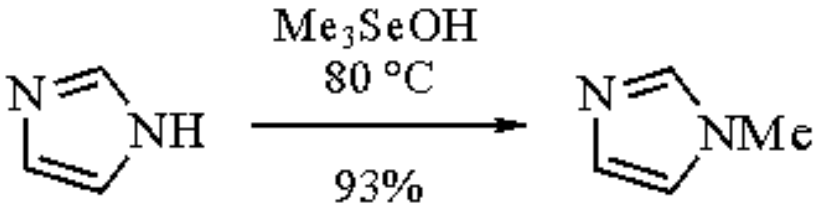

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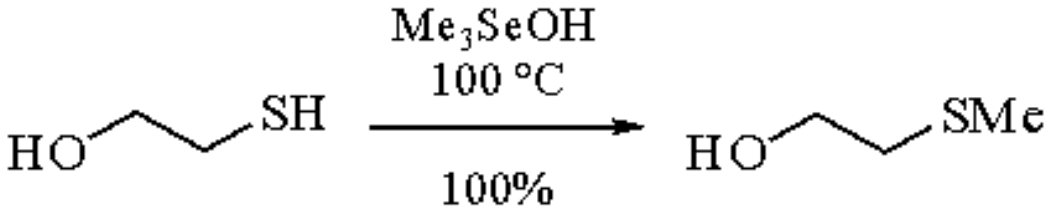

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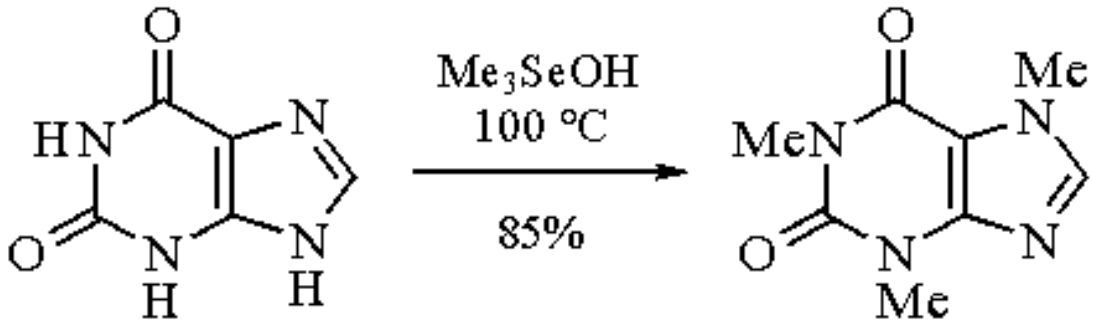

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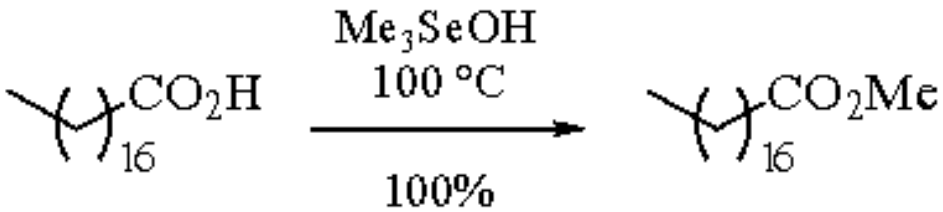

(7)

Trimethylselenonium hydroxide is the most reactive of the onium hydroxides, which generally follow the reactivity order of Me_3SeOH > Me_3SOH > Me_3SO_2H > $PhMe_3NOH$ (see also ***Trimethylsulfonium Hydroxide***).[1] Trimethylselenonium hydroxide has several advantages over more conventional methylating agents. Purification is

facilitated as compared with MeI or ***Dimethyl Sulfate*** because no inorganic salts are generated. Due to the carcinogenicity of ***Diazomethane***, as well as its *N*-nitroso precursors, trimethylselenonium hydroxide should be considered as a safer alternative. Finally, since the dimethyl selenide can be recovered and reused, the relatively high cost of this starting material is less of a deterrent.

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N-Trimethylsilylacetamide

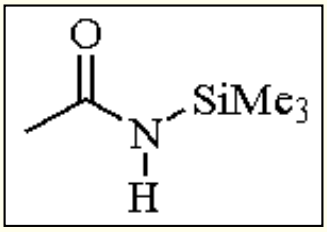

[13475-12-6] · $C_5H_{13}NOSi$ · *N*-Trimethylsilylacetamide · (MW 131.28)

(silylating agent of alcohols[2] and carboxylic acids;[4] acetamide dianion equivalent;[7] aminating agent)

Alternate Name: MSA.

Physical Data: mp 46-49 °C; bp 84 °C/18 mmHg; fp 57 °C.

Form Supplied in: moist white crystals.

Handling, Storage, and Precautions: handle and store under nitrogen; combustible and easily hydrolyzed.

Silylating Reagent.

N-Trimethylsilylacetamide has poor silylation potential[1] and although not as frequently used as ***N,O-Bis(trimethylsilyl)acetamide*** (BSA) as a silylating agent, this reagent has found a number of uses. *N*-Trimethylsilylacetamide has been used to silylate alcohols,[2] the hydroxy groups of sugars,[3] carboxylic acids,[4] amino groups,[5] and the oxygen of phosphate esters (eqs 1 and 2).[6]

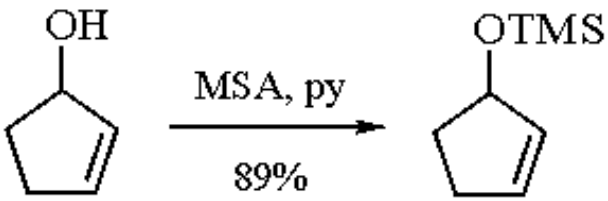

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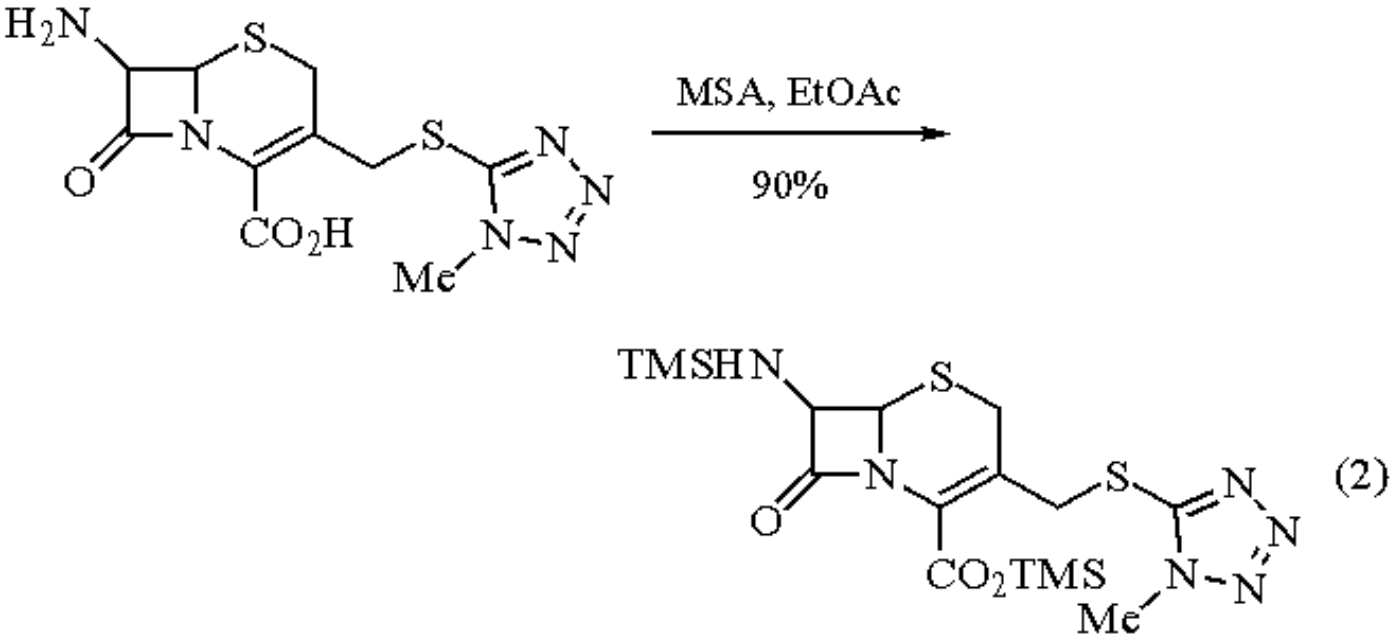

Acetamide Dianion Equivalent.

The dianion of *N*-trimethylsilylacetamide can be used as a soluble alternate to the insoluble acetamide dianion. The dianion can be alkylated or acylated at carbon (eqs 3-5).[7]

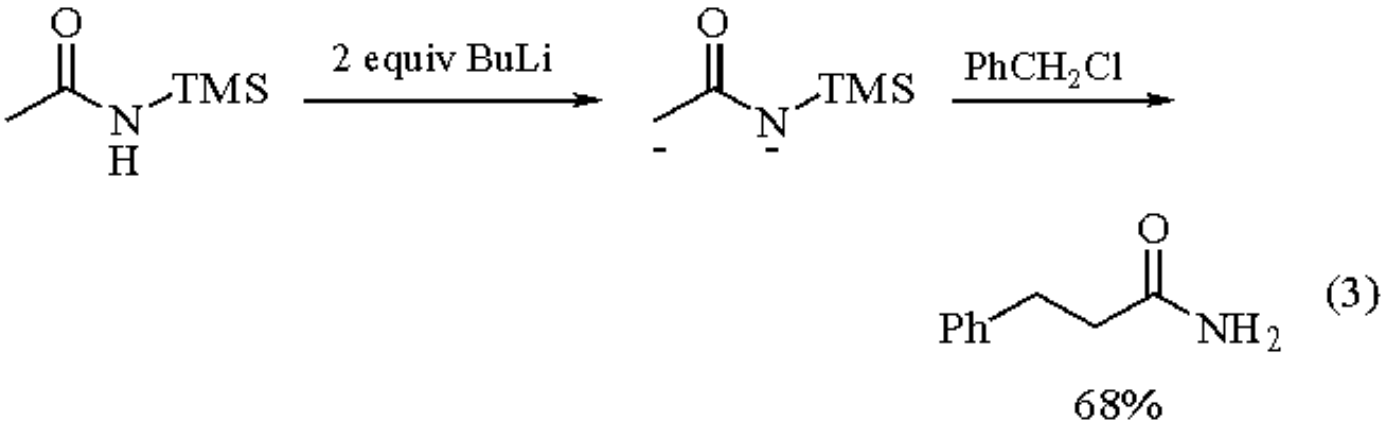

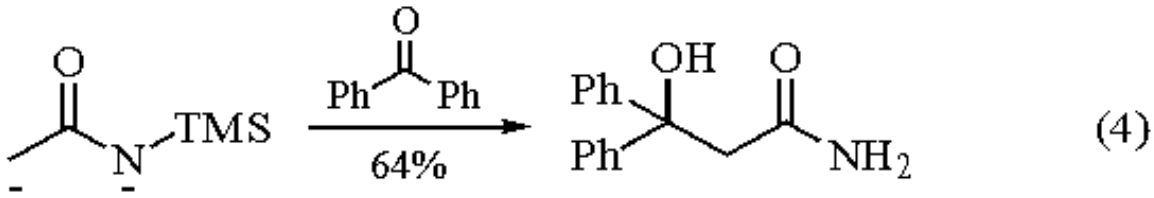

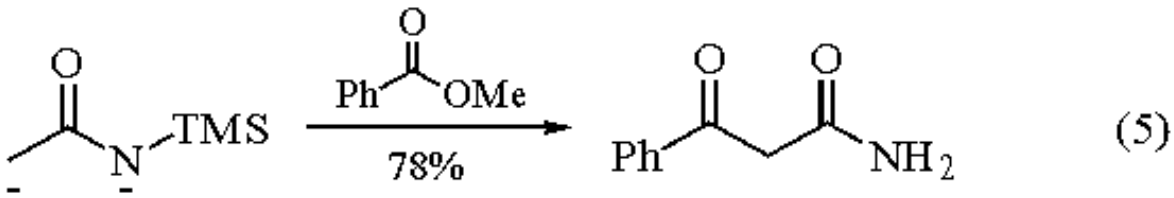

In an unusual reaction, *N*-trimethylsilylacetamide in the presence of ***Trifluoromethanesulfonic Anhydride*** can be used to *N*-glycosylate the anomeric positions of sugars (eq 6).[8]

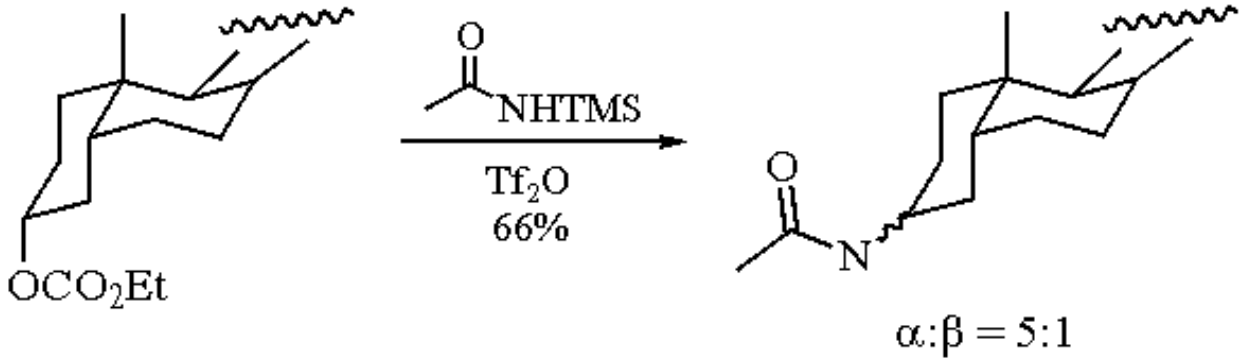

(6)

Related Reagents.

N,N´-Bis(trimethylsilyl)urea.

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Trimethylsilylacetic Acid[1]

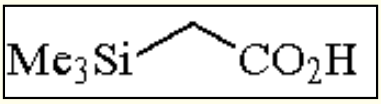

[2345-38-2] · $C_5H_{12}O_2Si$ · Trimethylsilylacetic Acid · (MW 132.26)

(preparation of α,β-unsaturated carboxylic acids and α-trimethylsilylbutyrolactones[2])

Physical Data: mp 40 °C.

Solubility: sol ethereal solvents.

Preparative Methods: obtained from the reaction of ***Trimethylsilylmethylmagnesium Chloride*** with ***Carbon Dioxide***;[3] can also be prepared by reaction of ***Acetic Acid*** with 2 equiv of ***Lithium Diisopropylamide***, followed by ***Chlorotrimethylsilane*** and hydrolysis.[4]

Handling, Storage, and Precautions: prone to isomerization and should not be stored for extensive periods.

Anionic Reactions.

In a manner similar to α-silyl esters, trimethylsilylacetic acid (**1**) can be used to prepare α,β-unsaturated carboxylic acids from carbonyl compounds by a Peterson alkenation reaction (eq 1).[1] However, the dianion of acid (**1**) is required.[2] The yields are generally inferior to analogous reactions with α-silyl esters.[5]

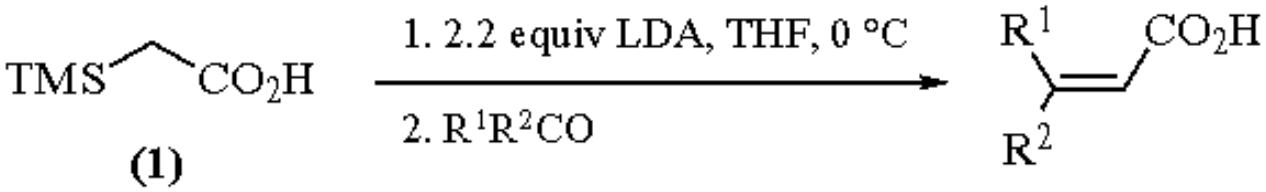

(1)

The dianion of acid (**1**) also reacts with alkyl halides to afford substituted α-trimethylsilylcarboxylic acids.[2] With epoxides, the dianion provides γ-hydroxy acids that cyclize to α-silylbutyrolactones (eq 2).[2] The resultant α-silyl lactones (**2**) are precursors to a wide variety of functionalized derivatives. The direct conversion of a butyrolactone to its α-silyl analog is complicated by the competition of the *O*-silylation pathway.

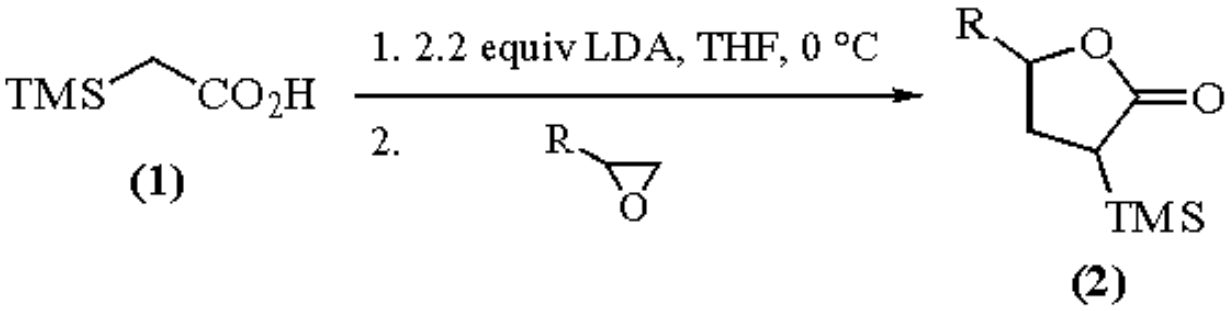

(2)

Derivatives.

Trimethylsilylacetyl thiolesters, which have been used as precursors to β-lactams, are prepared by reaction of the appropriate thiol

with the acid chloride derivative of (**1**).[6] Acid (**1**) has also been used as a precursor to 1-diazo-3-trimethylsilylacetone, which provides cyclopropyl trimethylsilylmethyl ketones upon reaction with alkenes, through reaction of the acid chloride or a mixed anhydride derivatives of the acid (**1**) with ***Diazomethane***.[4]

Silylacetic acids undergo a thermal rearrangement to afford the silyl ester (eq 3). The same migration of the silyl group is observed at lower temperatures when base catalysis is employed.[7]

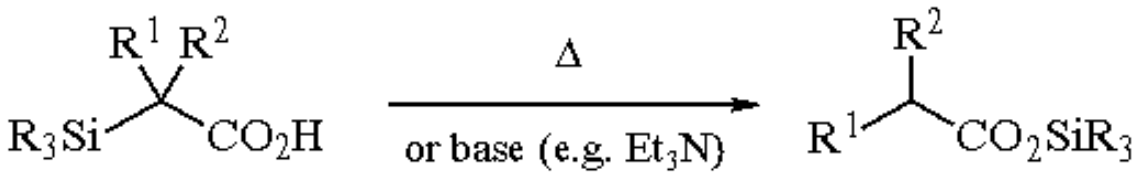

(3)

Related Reagents.

t-Butyl α-Lithiobis(trimethylsilyl)acetate; ***t-Butyl Trimethylsilylacetate***; ***Dilithioacetate***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl Trimethylsilylacetate***.

---

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Trimethylsilylacetone[1]

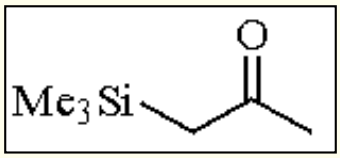

[5908-40-7] · $C_6H_{14}OSi$ · Trimethylsilylacetone · (MW 130.29)

(reacts with Grignard or organolithium reagents to provide, after elimination, 2-substituted 2-propenes;[2] in combination with fluoride ion, gives chemistry of the corresponding enolate ion;[3] can direct electrophilic substitution to either side of the carbonyl group[3b,4])

Physical Data: clear liquid; bp 74 °C/96 mmHg; *d* 0.8274 g cm^{-3} (26 °C), *n*26D 1.4188.

Preparative Methods: the best procedure for the preparation of trimethylsilylacetone is the reaction of ***Trimethylsilylmethylmagnesium Chloride*** or bromide with ***Acetic Anhydride***.[5] Other useful preparative methods for α-trimethylsilyl ketones involve the reaction of trimethylsilylmethylmagnesium chloride with acid chlorides,[6] or with aldehydes followed by oxidation of the resulting β-hydroxysilane to the ketone.[2e] When the trialkylsilyl group is very large, particularly the triisopropylsilyl group, a rearrangement from the silyl enol ether to the α-silyl ketone is possible.[7]

Handling, Storage, and Precautions: α-trimethylsilyl ketones thermally rearrange to the more stable silyl enol ethers at temperatures above approximately 100 °C and normally within 1 h at 140 °C or above; they hydrolyze to the parent ketone upon treatment with acid or base and are difficult to purify by chromatography due to desilylation; use in a fume hood.

Preparation of 2-substituted α-Alkenes.

The reaction of trimethylsilylacetone with Grignard and organolithium reagents has been employed in the synthesis of 2-substituted propenes via the formation of a β-hydroxysilane, which is then subjected to a Peterson elimination (eq 1).[2] It was also used to prepare β,γ-unsaturated esters, nitriles, and amides (eq 2).[2b]

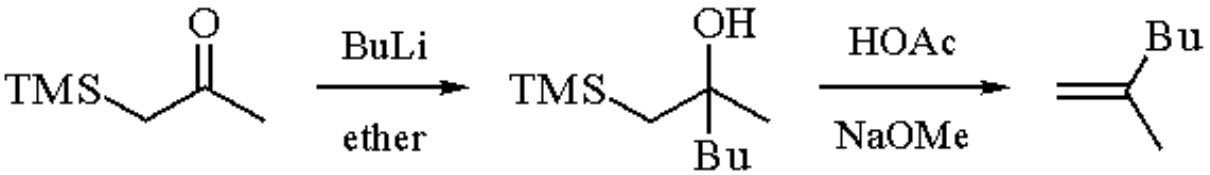

(1)

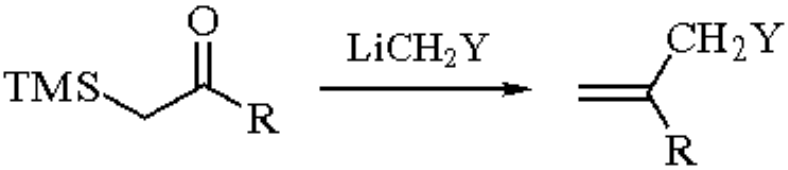

(2)

Y = CO_2-*t*-Bu, CN, $CONMe_2$

The reaction of acid chlorides with 2 equiv of a trimethylsilylmethyl organometallic reagent, where the metal can be chloromagnesium, lithium, or, best, dichlorocerium, proved to be an excellent direct synthesis of allylsilanes via the intermediacy of an α-trimethylsilyl ketone (eq 3).[2d] By reaction of α-trimethylsilyl ketones with ***Vinylmagnesium Bromide***, one can prepare 2-substituted 1,3-butadienes (eq 4).[2c,2f]

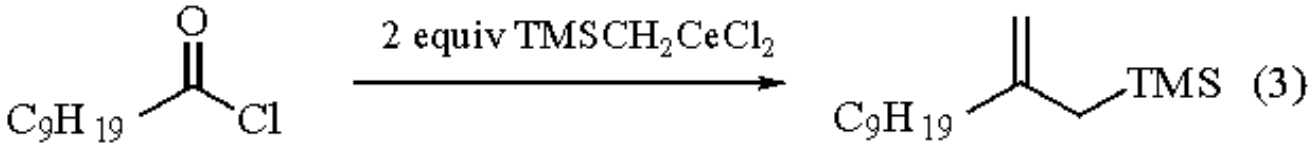

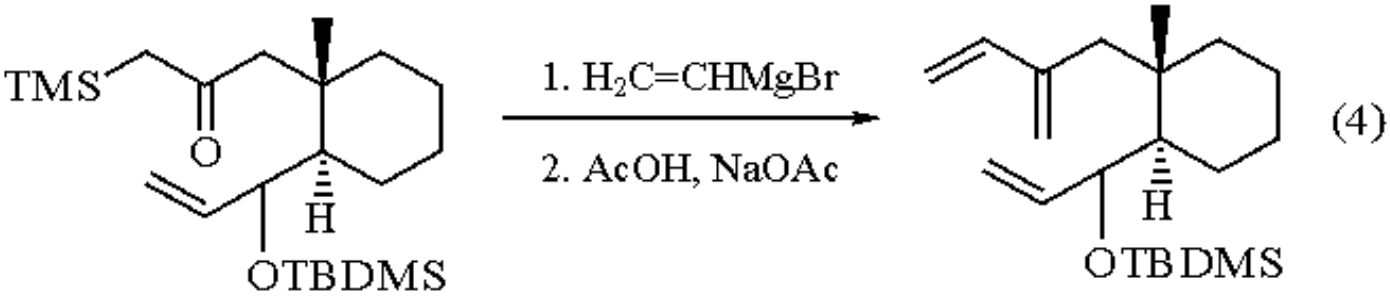

Reaction with Electrophiles.

The electrophilic substitution of α-silyl ketones gives the same products as those derived from the corresponding silyl enol ether. Thus reaction with ***Bromine*** or ***Thionyl Chloride*** gives the α-bromo (or chloro) ketone, with the halogen replacing the trimethylsilyl group (eq 5).[4a,b]

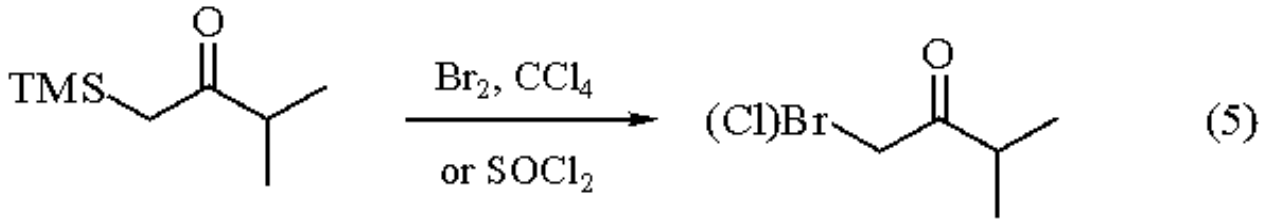

The Lewis acid-catalyzed reaction with aldehydes results in aldol condensation to give the β-hydroxy ketone with substitution on the side of the trimethylsilyl group as would be the case with the silyl enol ether. One potential advantage of this reaction is the ability to control the regioselectivity through the synthesis of the α-silyl ketone (eq 6).[3b]

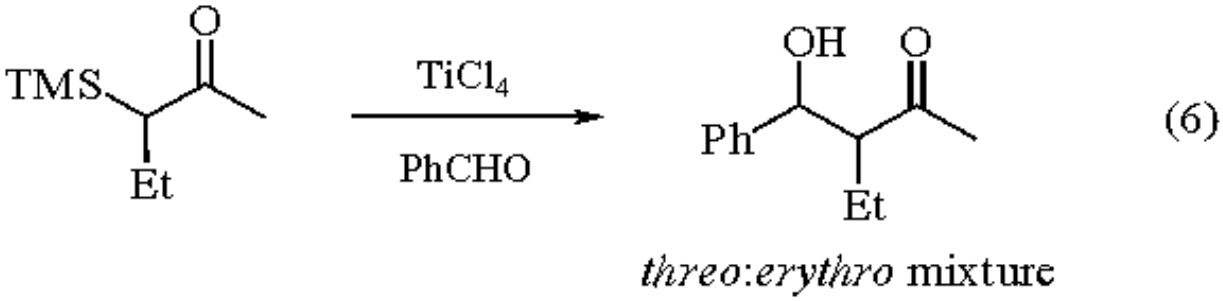

Electrophilic reaction with acetals is also possible, as shown with the optically active acetal (eq 7), which gives very high diastereoselectivity.[8] This has been employed in an approach to aklavinone[9] and *cis*-2-substituted 6-methylpiperidines.[4e]

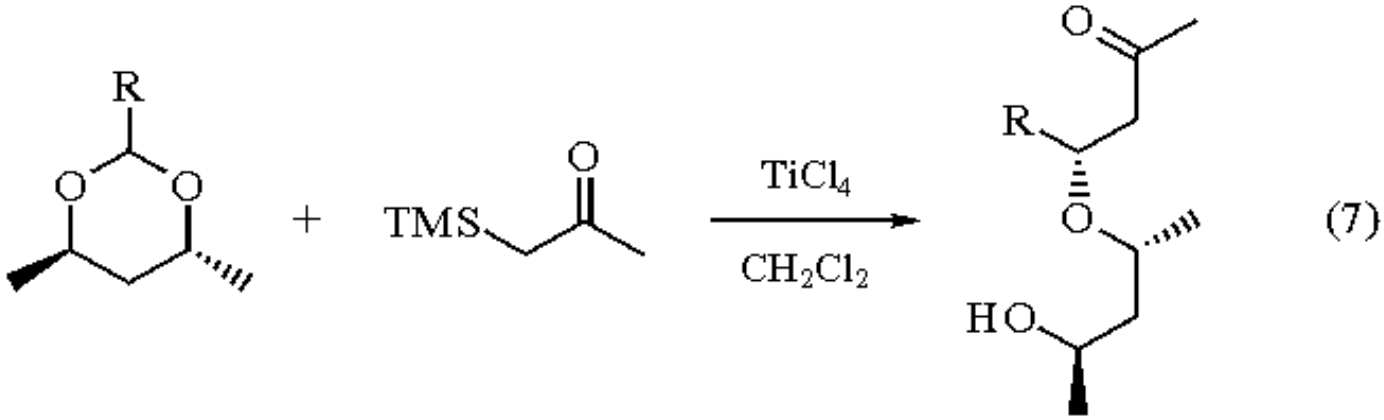

<3% of other diastereomer

Reaction with Fluoride Ion.

The reaction of α-trimethylsilyl ketones with fluoride ion results in attack of the fluoride ion on the trimethylsilyl group and formation of the corresponding enolate ion. This represents an in situ method for regioselective generation of the enolate ion in the presence of the electrophile (eqs 8 and 9). This can be especially advantageous when the more substituted enolate ion is desired.[3]

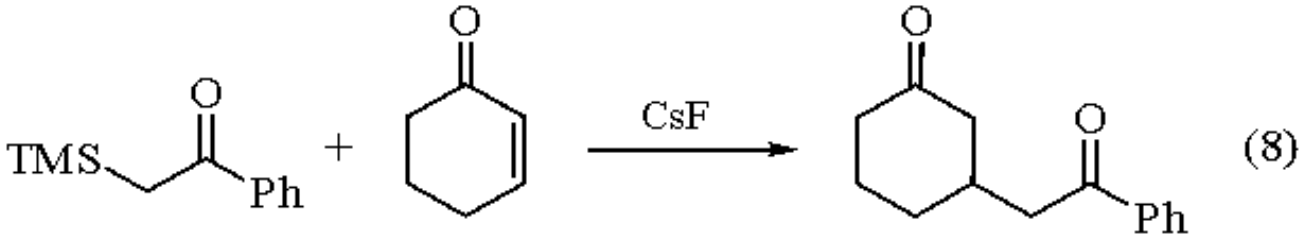

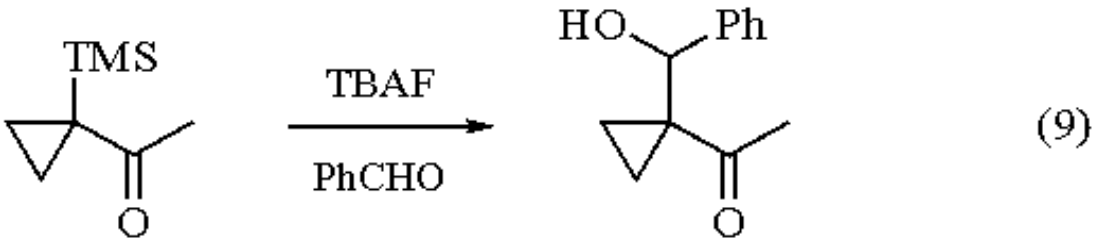

Reaction with Strong Bases.

Trimethylsilylmethyl ketones that do not carry another α-substituent can be regioselectively deprotonated on the side bearing the trimethylsilyl group (eq 10). This can lead to α,β-unsaturated ketones when the resulting enolate reacts with aldehydes (eq 11).[10]

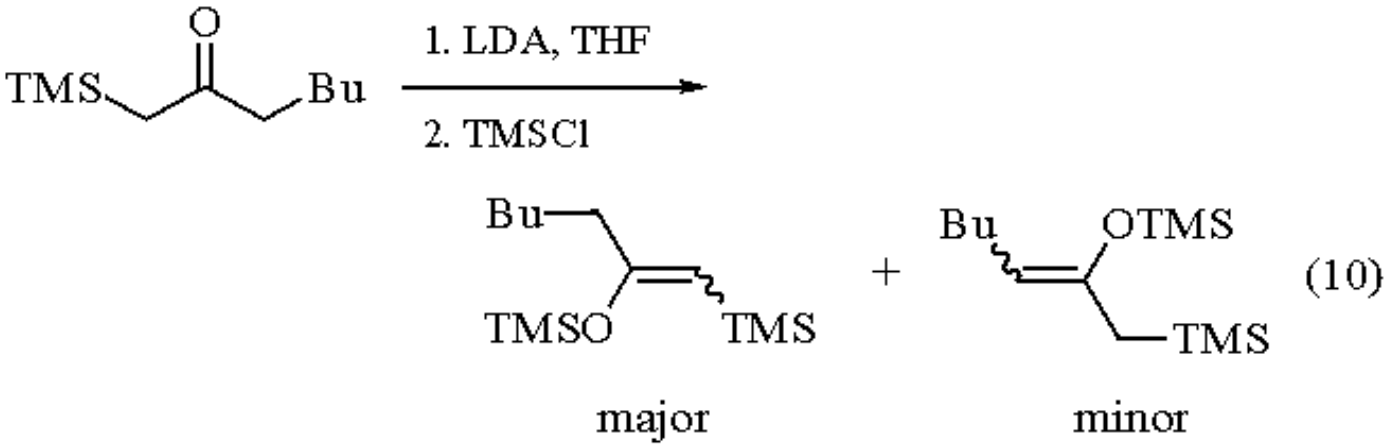

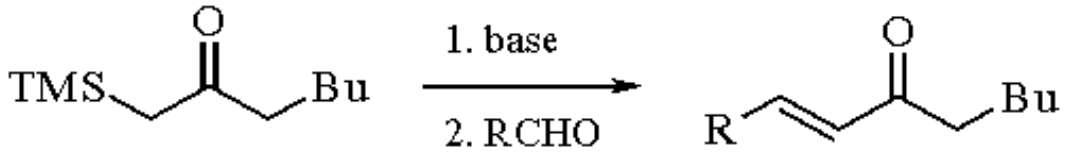

(11)

The enolate chemistry of α-substituted α-trimethylsilyl ketones can be directed to either side of the ketone. Thus deprotonation with LDA occurs away from the trimethylsilyl side for steric reasons (eq 12), whereas Lewis acid-catalyzed reactions occur on the trimethylsilyl side of the molecule (eq 13).[10]

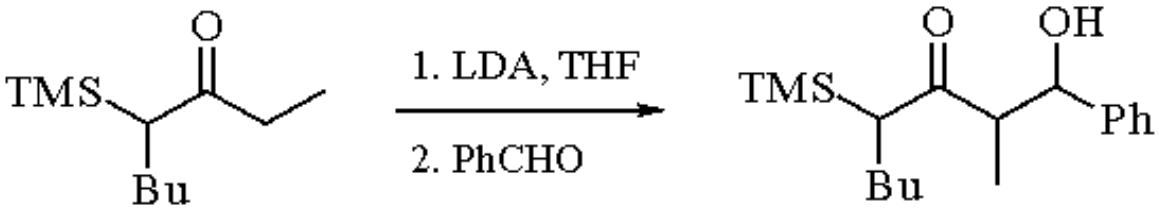

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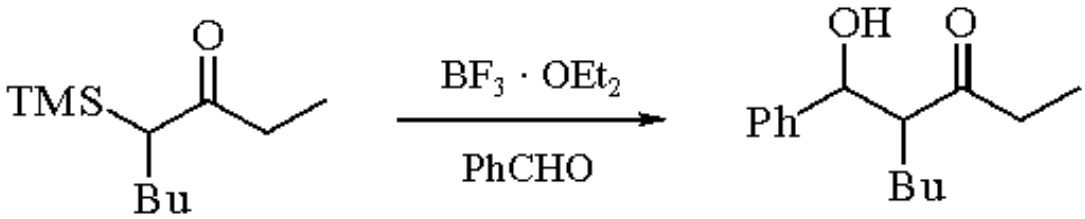

(13)

Related Reagents.

t-Butyl Trimethylsilylacetate; ***N,N-Dimethyl-2-(trimethylsilyl)acetamide***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***Ethyl Trimethylsilylacetate***; ***Trimethylsilylacetic Acid***.

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Trimethylsilylacetonitrile

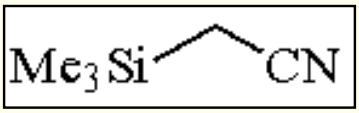

[18293-53-3] · $C_5H_{11}NSi$ · Trimethylsilylacetonitrile · (MW 113.26)

(α-carbanion is a useful alternative to $LiCH_2CN$ for nucleophilic cyanomethylation; (*Z*)-selective Peterson alkenation)

Physical Data: bp 84-85 °C/54 mmHg,[1] 66 °C/35 mmHg,[2] 65-70 °C/20 mmHg;[3] *d* 0.827 g cm^{-3}.

Solubility: sol most common organic solvents.

Form Supplied in: liquid; commercially available.

Preparative Methods: from ***Chlorotrimethylsilane***, ***Zinc***, and XCH_2CN, (X = Cl, 61% yield; X = Br, 81% yield).[3]

Handling, Storage, and Precautions: is an organic cyanide and should be handled with due care in a fume hood.

Metalation.

Exposure to ***Lithium Diisopropylamide*** or ***n-Butyllithium*** in ether[3] or THF at -78 °C generates lithiotrimethylsilylacetonitrile [*70980-14-2*], which is stable at -78 to -20 °C.[3-5]

Peterson Alkenation (Cyanomethylenation).

The anion, typically lithiotrimethylsilylacetonitrile, undergoes Peterson alkenations with aldehydes to furnish α,β-unsaturated nitriles, principally as the (*Z*) isomer (eq 1),[6-9] in contrast to the Horner-Emmons-Wittig condensation, which gives predominantly the (*E*) isomer.[9] Use of the boronate-stabilized anion of trimethylsilylacetonitrile, especially in the presence of HMPA, increases the (*Z*) selectivity (eq 1) but no effect is observed in the case of benzaldehyde.[6,7] Acyclic α-chlorocarbonyl compounds[8] exhibit poor (*E*/*Z*) stereoselectivity. Other trialkylsilylacetonitriles (e.g. Ph_3SiCH_2CN, *t*-$BuMe_2SiCH_2CN$)[6,7] exhibit similar (*E*/*Z*) stereoselectivity, but higher homologs of trimethylsilylacetonitrile (e.g. $Me_2PhSiCH(Me)CN$, $Me_2PhSiCH(Et)CN$) give 1:1 (*E*/*Z*) mixtures.[10]

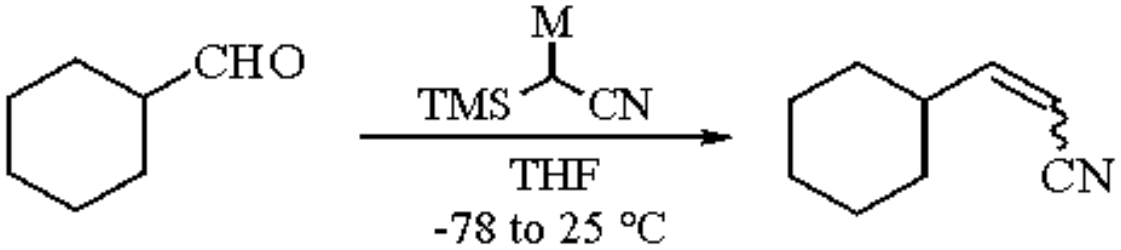

(1)

M = Li, 82%, (*Z*):(*E*) = 7:1
M = B(O-*i*-Pr)$_2$, 90%, (*Z*):(*E*) = 12:1

Michael Addition.

The reaction of α,β-unsaturated aldehydes[3,6] and ketones[11,12] with trimethylsilylacetonitrile proceeds with 1,2- and 1,4-regioselectivity, respectively. A synthesis of (+)-sesbanimide[11,13] highlights the utility of trimethylsilylacetonitrile in a Michael addition to an α,β-unsaturated ester: lithiotrimethylacetonitrile gives exclusively the 1,4-addition product, whereas ***Lithioacetonitrile*** gives mainly the 1,2-addition product. Desilylation of the former adduct results in the product of overall 1,4-addition of lithioacetonitrile.

Reactions with Other Electrophiles.

The anion of trimethylsilylacetonitrile reacts with allylic, propargylic, and benzylic bromides,[14] with some alkyl bromides and iodides,[5,14] with epoxides to afford γ-(trimethylsilyloxy)nitriles,[3] and with Me_3GeCl,[15] Me_3SiCl,[16] and $(Me_3SiO)_2$[17] to afford the expected α-substitution products. Trimethylsilylacetonitrile also reacts with (*n*-Bu)$_3$SnOMe[18] to afford (*n*-Bu)$_3$SnCH$_2$CN.

Cyanomethylation.

Trimethylsilylacetonitrile is a useful synthetic equivalent for the anion of acetonitrile in condensation reactions with carbonyl compounds[19-21] and glycosyl fluorides,[22] leading to β-(trimethylsilyloxy)nitriles (eq 2)[21] and cyanomethyl glycosides, respectively. However, the addition of trimethylsilylacetonitrile to hindered ketones using cyanide catalysis fails;[20b] enolizable ketones may form silyl enol ethers;[19,20b] and the β-(trimethylsilyloxy)nitriles derived from cyclic ketones undergo spontaneous elimination to give α,β-unsaturated nitriles.[19]

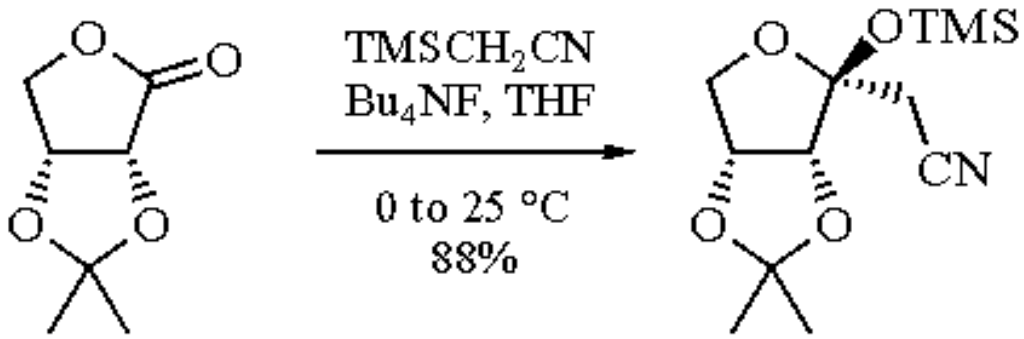

(2)

Related Reagents.

t-Butyl Trimethylsilylacetate; ***N,N-Dimethyl-2-(trimethylsilyl)acetamide***; ***Ethyl Lithio(trimethylsilyl)acetate***; ***Ethyl 2-(Methyldiphenylsilyl)propanoate***; ***Ethyl Trimethylsilylacetate***; ***Lithioacetonitrile***.

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Trimethylsilylacetylene

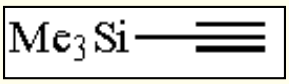

[1066-54-2] · $C_5H_{10}Si$ · Trimethylsilylacetylene · (MW 98.24)

(ethynylation by palladium(0)-catalyzed coupling/condensation with aryl and vinyl halides[1] and triflates,[2] or by nucleophilic attack of the corresponding acetylide on electrophilic centers;[3,4] reacts with alkyl iodides,[5] tin hydrides,[6] and dichloroketene[7] in a regioselective and stereoselective manner)

Alternate Names: trimethylsilylethyne; TMSA.

Physical Data: bp 53 °C; *d* 0.695 g cm^{-3}.

Solubility: sol all organic solvents.

Form Supplied in: colorless transparent liquid; supplied in ampules.

Handling, Storage, and Precautions: once transferred from the ampule to a sample bottle, it can be stored for long periods without loss of purity and material if stored cold. It is a flammable liquid classified as an irritant. Use in a fume hood.

Ethynylations.

All ethynylation processes involve two steps: (a) coupling of the trimethylsilylethynyl group to the substrate either by a palladium(0)-catalyzed reaction or by nucleophilic attack of the derived acetylide on an electrophilic center; and (b) replacement of the trimethylsilyl group with a proton. Although ***2-Methylbut-3-yn-2-ol*** can be used for ethynylation and is a much cheaper reagent than TMSA, the advantage of TMSA is in the mild conditions needed for removal of the trimethylsilyl group. Deprotection of the 2-methyl-2-hydroxybutynyl group requires heating in toluene at >70 °C with NaH[8] or NaOH,[9] whereas replacement of the trimethylsilyl group occurs at room temperature and can be effected with dilute aqueous methanol solutions of NaOH or KOH,[10] with LiOH in aqueous THF,[11] or with mild bases such as K_2CO_3[12] or Na_2CO_3[13] in MeOH and KF in aqueous DMF.[14] The yields usually range from good to high.

Palladium(0)-Catalyzed Coupling Reactions.

Treatment of the title reagent with vinyl (eq 1)[1b] and aryl (eq 2)[1c] halides and triflates (eqs 3 and 4)[2c,d] and an appropriate Pd catalyst affords vinylalkynes in good yield. For halides, the order of reactivity is I > Br >> Cl.[15] Vinyl chlorides undergo this reaction, and one-step diethynylation of dichloroethylenes can be achieved in good yield (eq 5).[16] Aromatic chlorides, however, undergo ethynylation with terminal alkynes only if there is a strong electron-withdrawing group, such as nitro, on the ring.[15]

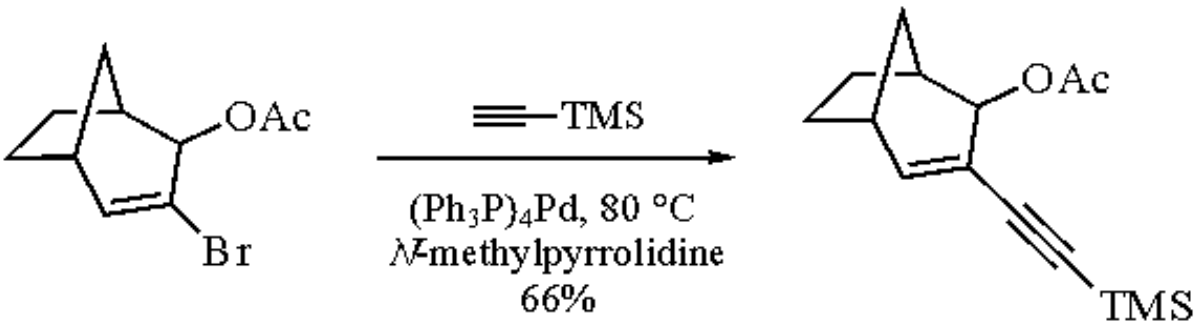

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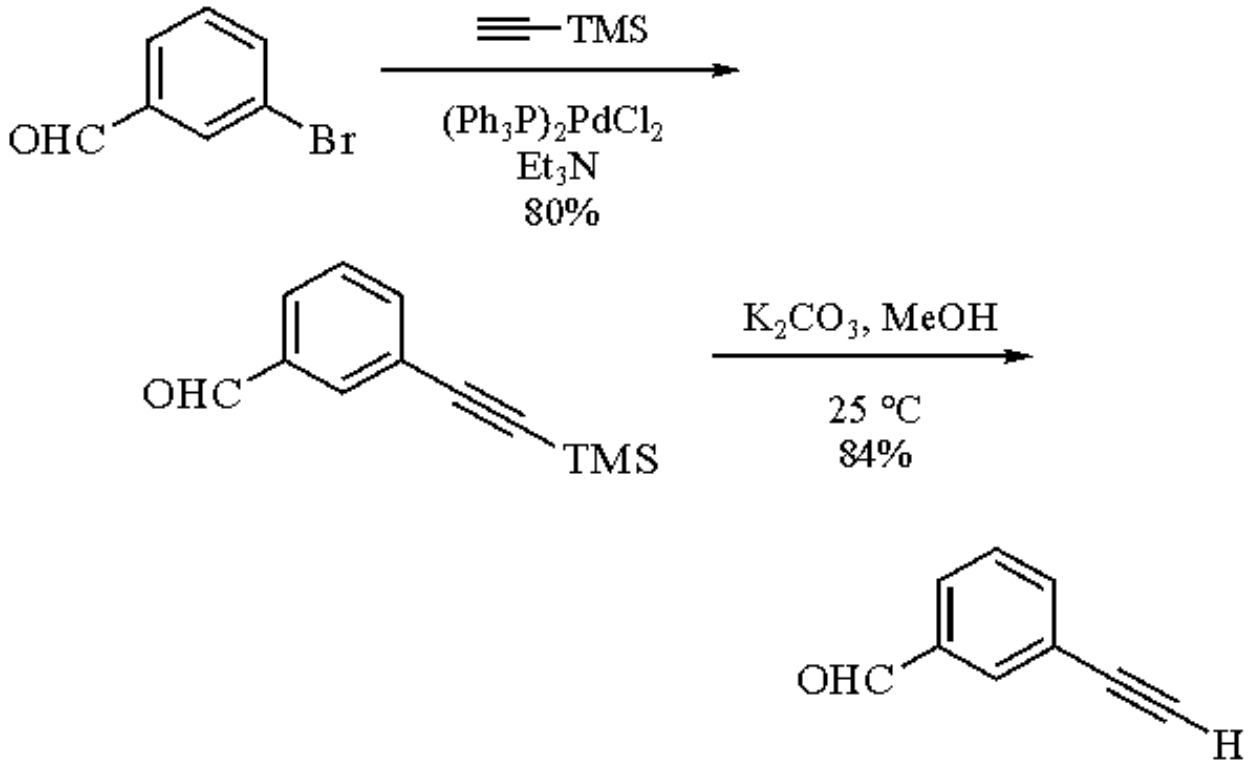

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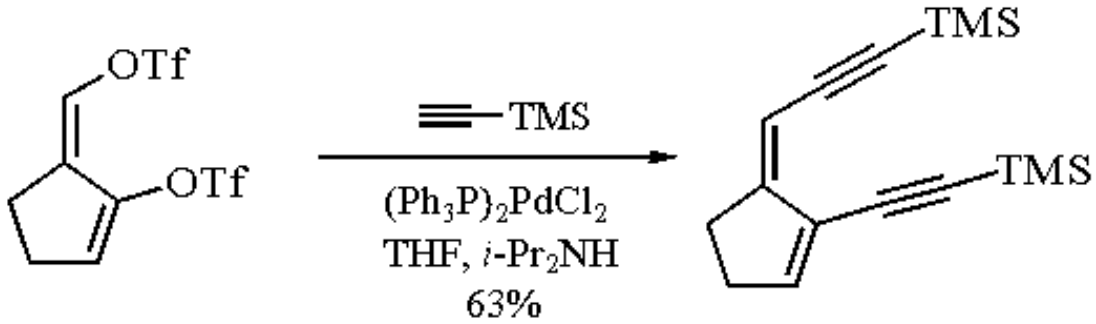

(3)

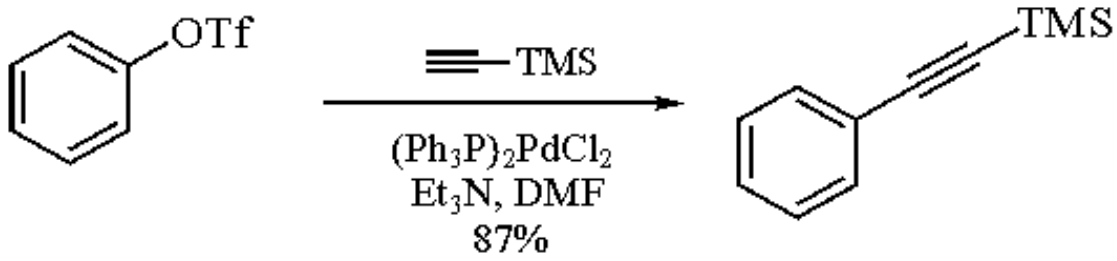

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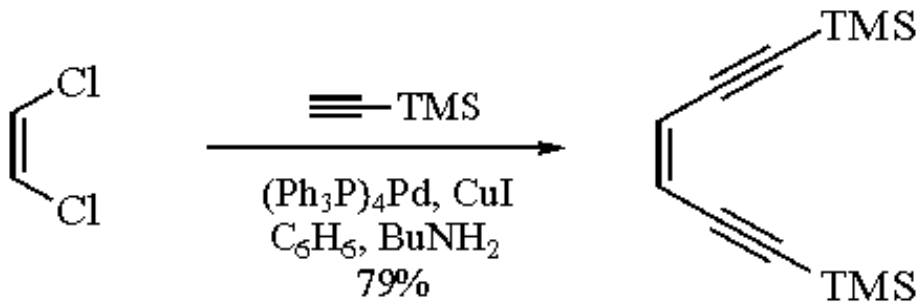

(5)

Heteroaromatic and heterocyclic vinyl halides and triflates can also be effectively ethynylated using TMSA (eqs 6 and 7).[17] The product heterocycles can be elaborated into polycyclic compounds (eq 8).[18]

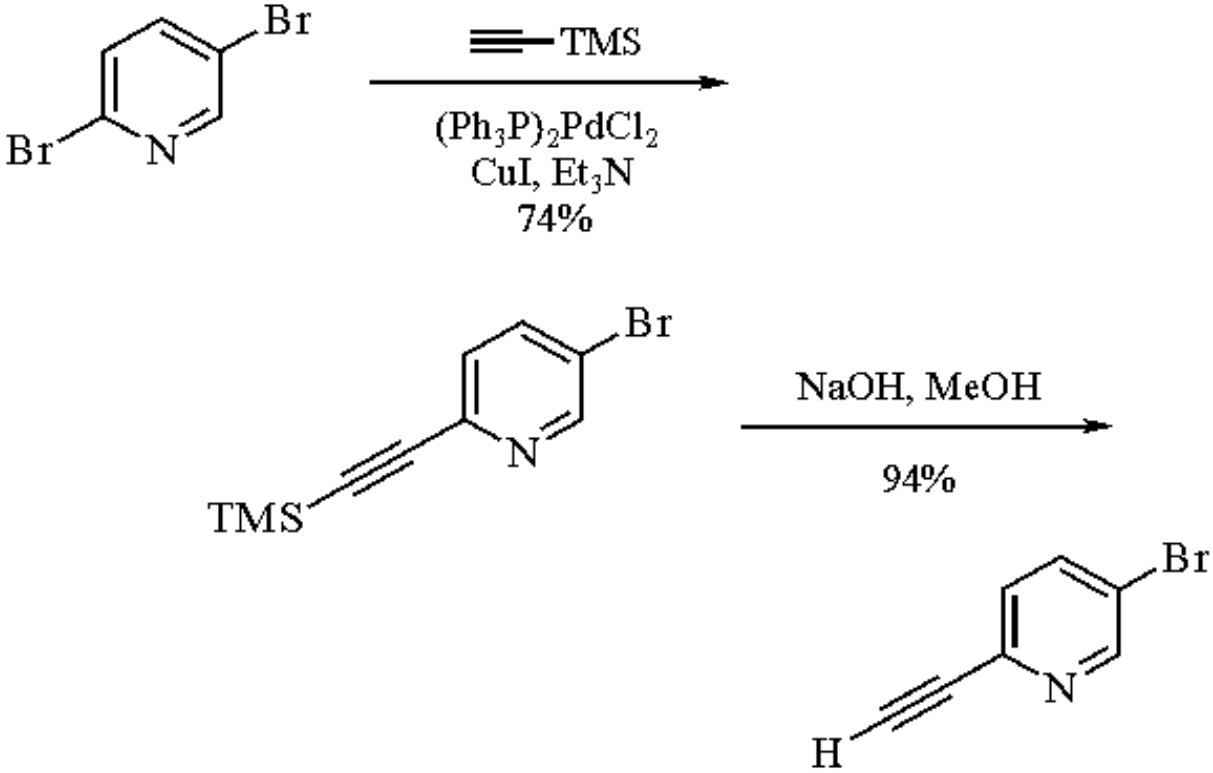
Br
Br
N
TMS
(Ph3P)2PdCl2
CuI, Et3N
74%
Br
TMS
N
NaOH, MeOH
94%
Br
N
H

(6)

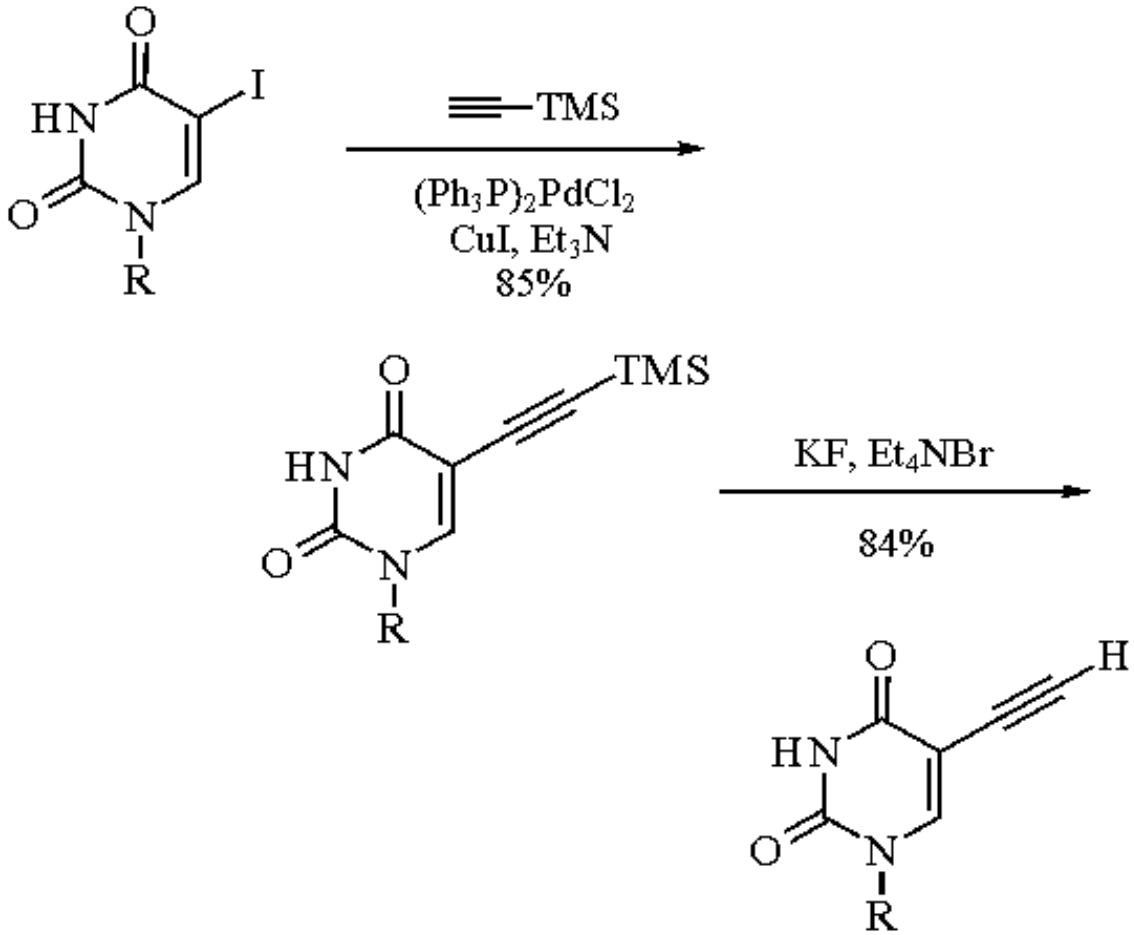
O
HN
I
O
N
R
TMS
(Ph3P)2PdCl2
CuI, Et3N
85%
O
TMS
HN
O
N
R
KF, Et4NBr
84%
O
H
HN
O
N
R

(7)

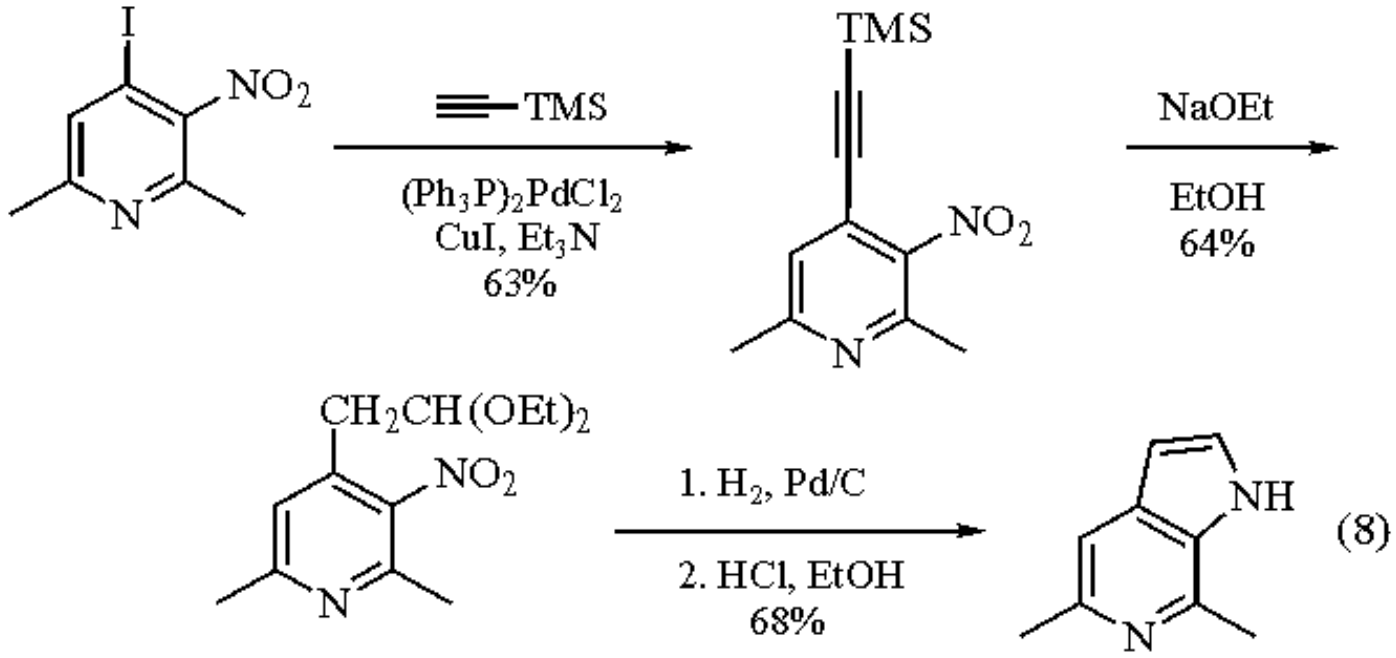

(8)

Aromatic compounds with nitro groups *ortho* to the alkyne have been converted into indoles (eq 9).[19] Alkynic ketones have been prepared from either the corresponding acyl halides[20] or by carbonylative ethynylation[21] of vinyl halides and triflates with TMSA.

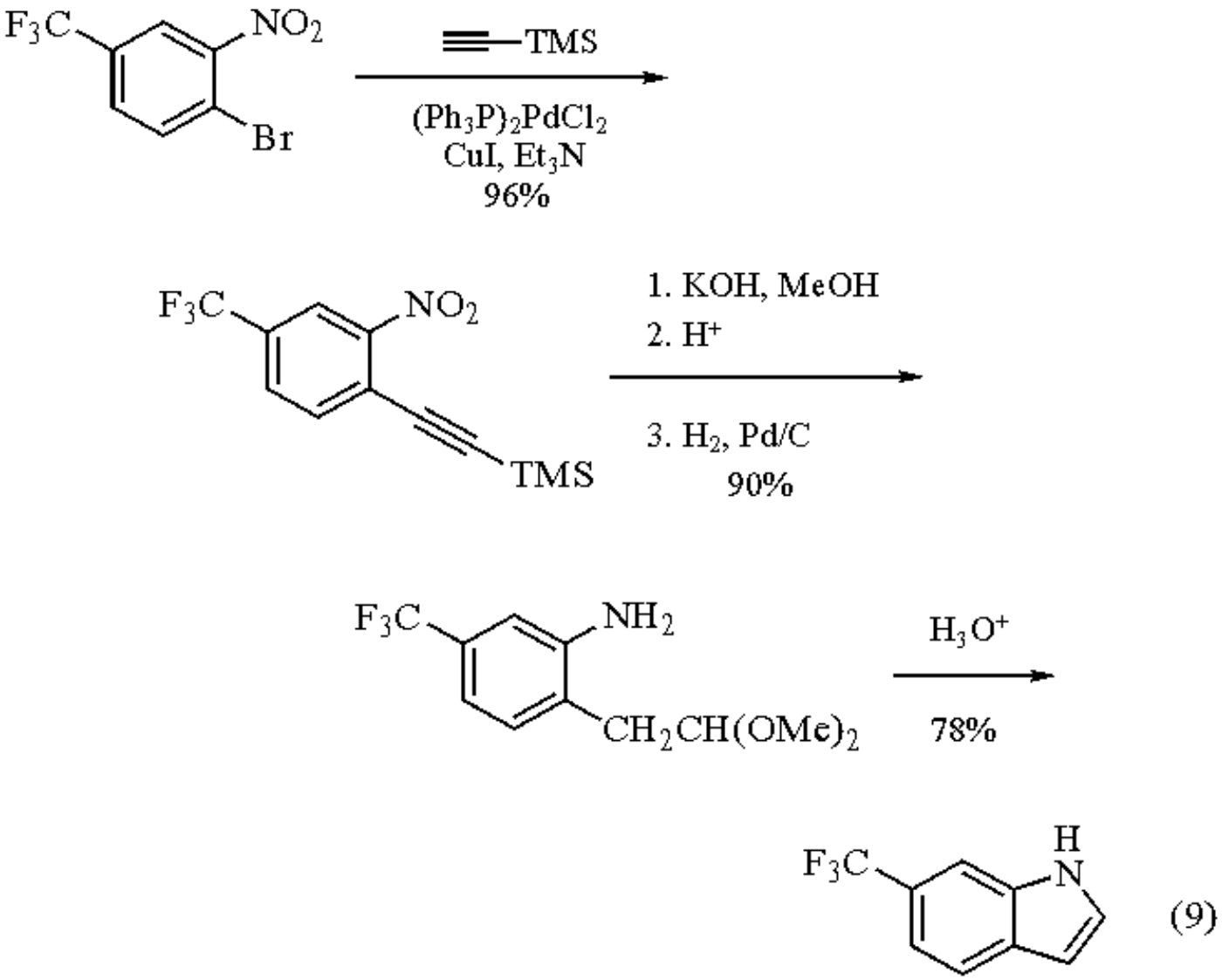

(9)

Generally, the palladium(0)-catalyzed reaction requires a base to deprotonate the terminal alkyne. Often, the solvent for the reaction is an amine which also serves as base. Alternatively, the amine can be used in slightly more than a stoichiometric amount in nonbasic solvents such as THF,[2c] benzene,[16b] or DMF.[1b,22] Sodium alkoxides[22] and acetate[2a] have also been used as bases. Various Pd^{II} and Pd^{0} complexes

are effective for the coupling reaction. In one case, Pd^0-catalyzed coupling of TMSA with a vinyl halide gives appreciable amounts (40-45%) of a fulvene instead of the expected enyne when the reaction is conducted using $(MeCN)_2PdCl_2$ in the absence of CuI (eq 10).[23] With appropriate choice of reaction conditions, however, it is possible to reduce or totally eliminate this fulvene formation (eq 10).

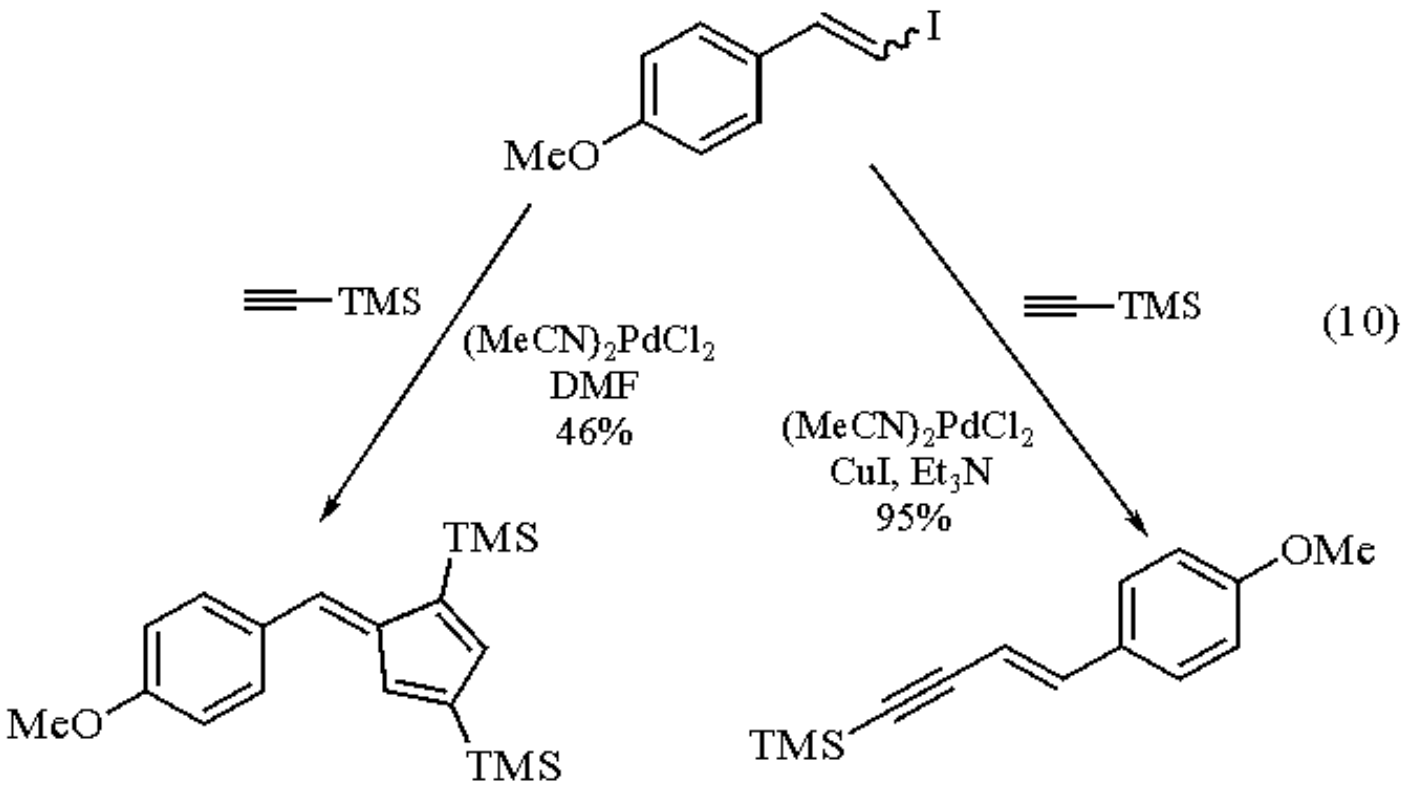

(10)

Reaction of Trimethylsilylacetylides with Electrophiles.

Lithium (Trimethylsilyl)acetylide is easily generated from TMSA and ***n-Butyllithium***[4c,3b] or ***Methyllithium***[24] at low temperatures. The corresponding Grignard reagent can be prepared from TMSA and ***Ethylmagnesium Bromide***. The zinc chloride derivative can be generated by transmetalation of the lithium acetylide.[4a] A cerate derivative has also been described.[25] All of these acetylides add to the carbonyl group of ketones[26] and aldehydes[3,24] to generate alcohols. The tertiary sulfide shown in eq 11 reacts smoothly with zinc acetylides without elimination, a complication that occurs with the more basic Li and Mg acetylides.[4a]

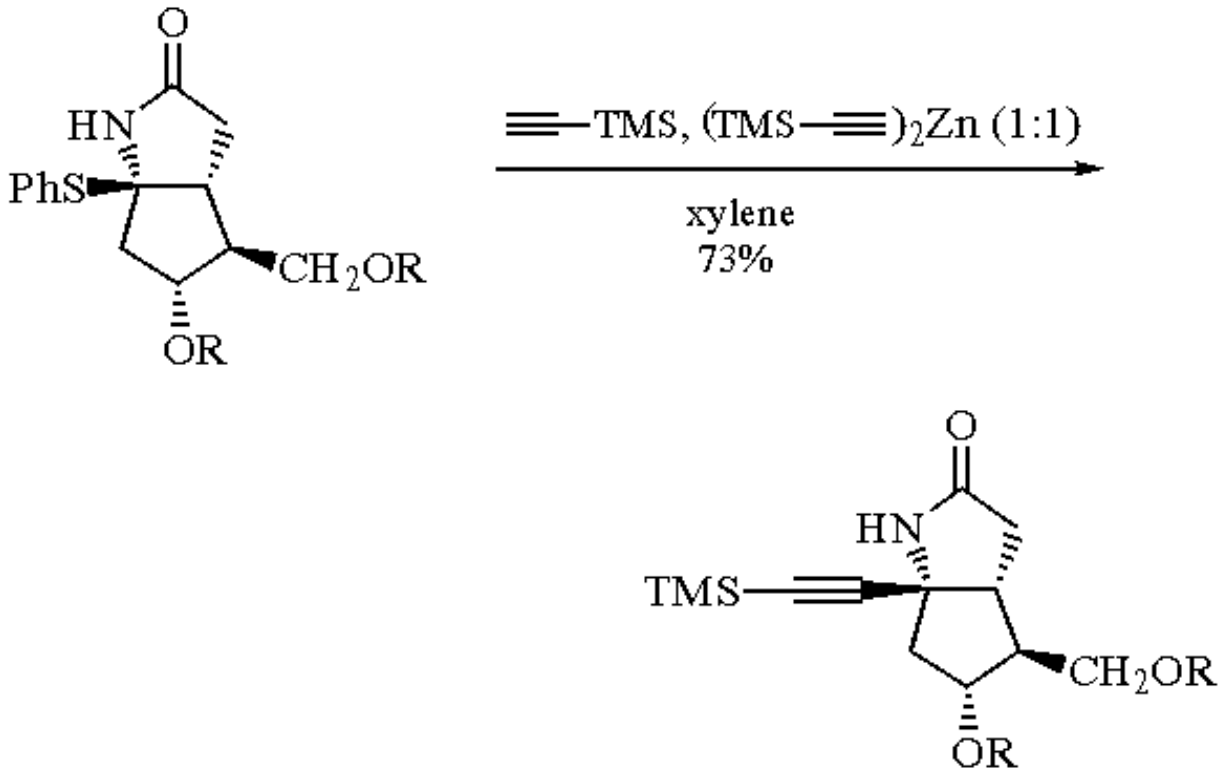

(11)

Radical-Initiated and Transition Metal-Catalyzed Additions.

Some radical and transition metal-catalyzed additions to TMSA are unique when compared with additions to other terminals alkynes, because they show remarkable regioselectivity and/or stereoselectivity. The regioselectivity of a metal-catalyzed addition may be complementary to that of a radical-initiated process (eq 12). For example, rhodium[27] and molybdenum[28] complex-catalyzed additions of trialkyltin or triaryltin hydrides to TMSA give mainly the 1,1-disubstituted ethylenes, whereas radical hydrostannylation through sonication[29] or ***Triethylborane***[6] initiation gives the 1,2-adducts with the (*E*)-isomers predominating. Other terminal alkynes undergo radical or metal-catalyzed hydrostannylation with either poorer or reverse selectivity.

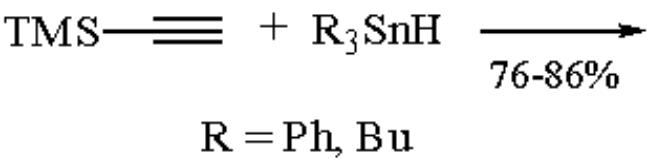

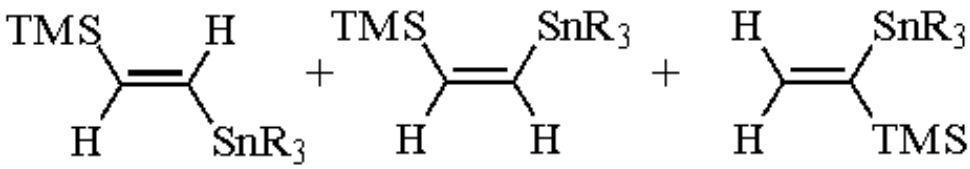

(12)

(*E*)-1,2- (*Z*)-1,2- 1,1-

Et_3B-initiated radical addition of various alkyl iodides to TMSA occurs with high regioselectivity, giving (*Z*)-1-iodo-1-trimethylsilyl-2-alkylethylenes stereospecifically (eq 13).[5]

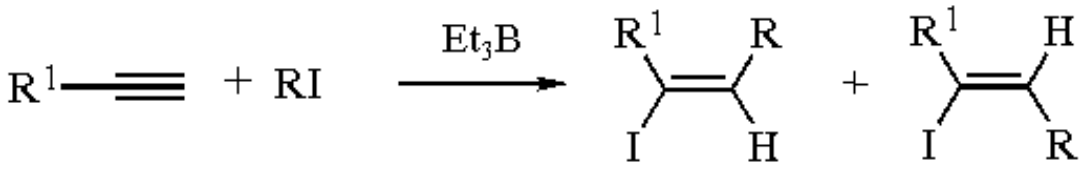

(13)

(*E*) (*Z*)

R^1 = TMS, R = *i*-Pr, 79% 0:100

R^1 = Ph, R = *i*-Pr, 81% 21:79

Cycloaddition Reactions.

Unlike [2 + 2] additions involving other alkynes, TMSA adds to dichloroketene[7,30] and keteniminium salts[31] in a highly regioselective manner to give cyclobutanones (eqs 14 and 15). The regiochemistry in this cycloaddition is opposite to that predicted from the electronic effects of the trimethylsilyl group and has been explained using MO considerations.[30] The cycloaddition of TMSA to Fischer carbene complexes to provide naphthoquinones has also been reported (eq 16).[32]

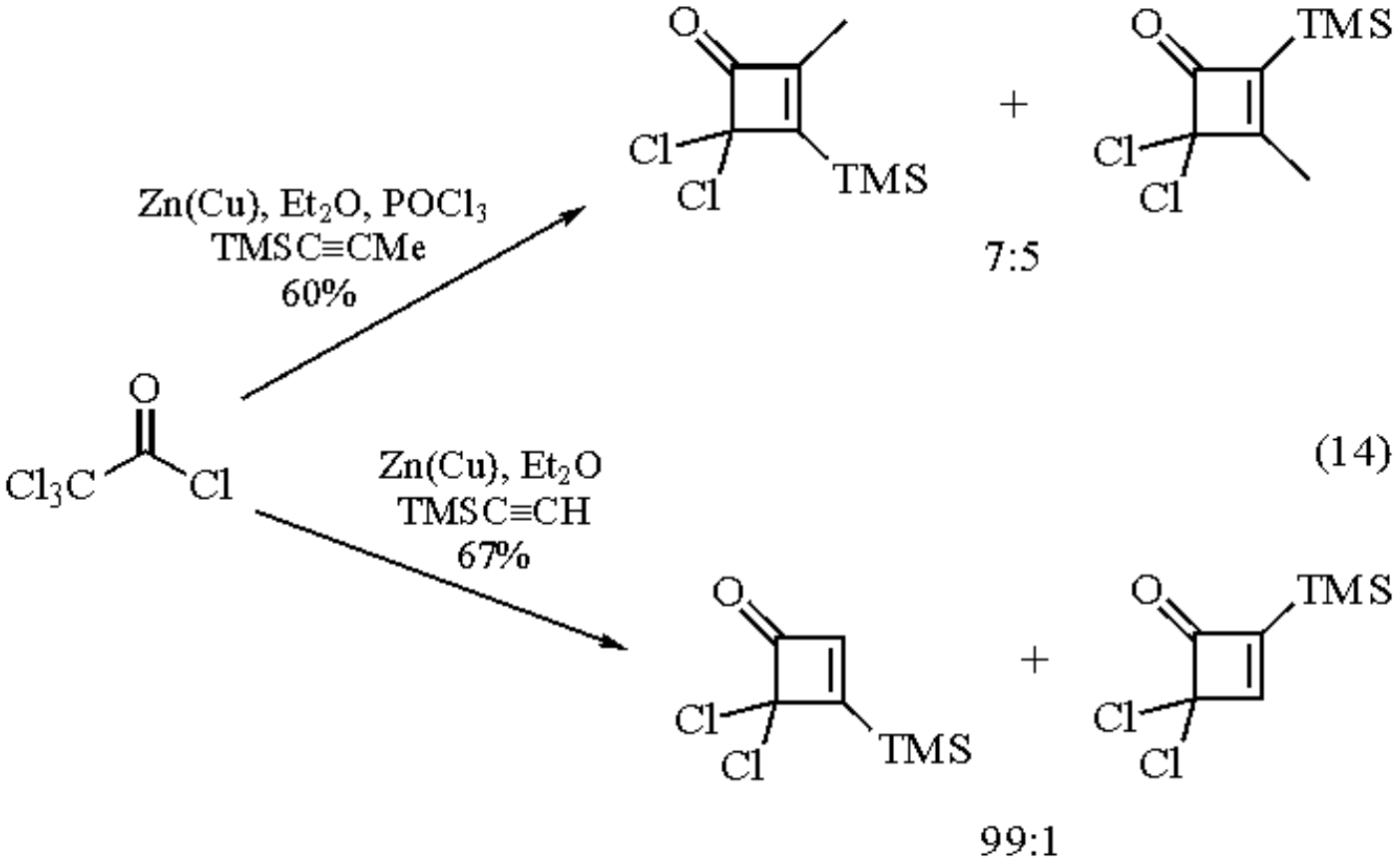

(14)

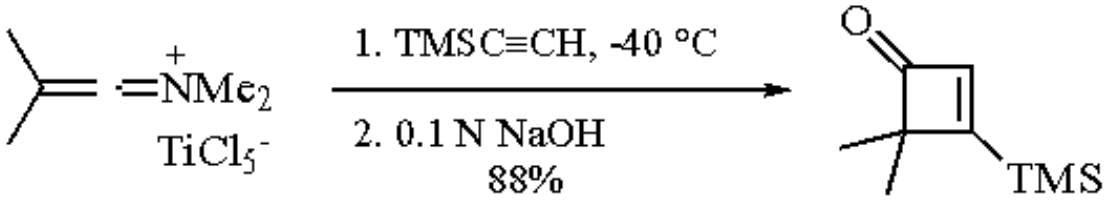

(15)

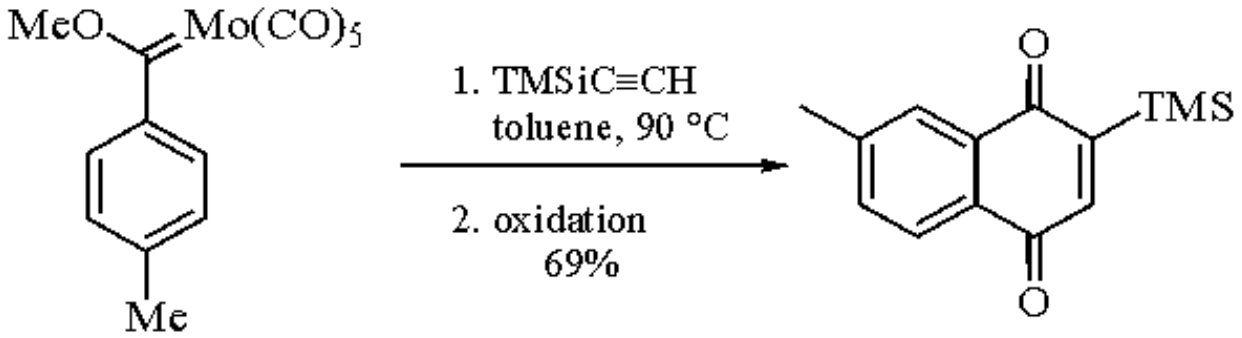

(16)

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(Trimethylsilyl)allene[1]

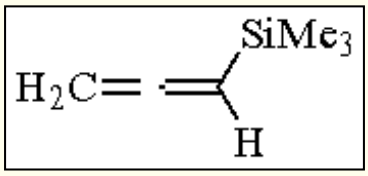

[14657-22-8] · $C_6H_{12}Si$ · (Trimethylsilyl)allene · (MW 112.27)

(propargylic anion equivalent;[2-4] substrate for ene reaction[5])

Alternate Name: trimethyl-1,2-propadienylsilane.

Physical Data: bp 90-93 °C.

Solubility: sol CH_2Cl_2, benzene, most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Analysis of Reagent Purity: IR (tf) 2955, 2900, 1935, 1250, 1210, 1055, 840, 800, 750, and 690 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.15 (s, 9H), 4.27 (d, 2H, *J* = 7.7), 4.88 (dd, 1H, *J* = 6.6, 7.7).[4b]

Preparative Methods: two methods have been reported for the preparation of (trimethylsilyl)allene [(TMS)allene] (**1**). Reductive deoxygenation of the tosylhydrazone derivative affords the title compound in 51% yield.[4b] The tosylhydrazone is readily prepared from the corresponding aldehyde, which in turn is accessed by formylation of (trimethylsilyl)ethynylmagnesium bromide with DMF (eq 1).[6] (TMS)allene has also been prepared by flash vacuum pyrolysis of methyl (trimethylsilyl)propargyl ether, which is obtained from silylation of methyl propargyl ether (eq 2).[7]

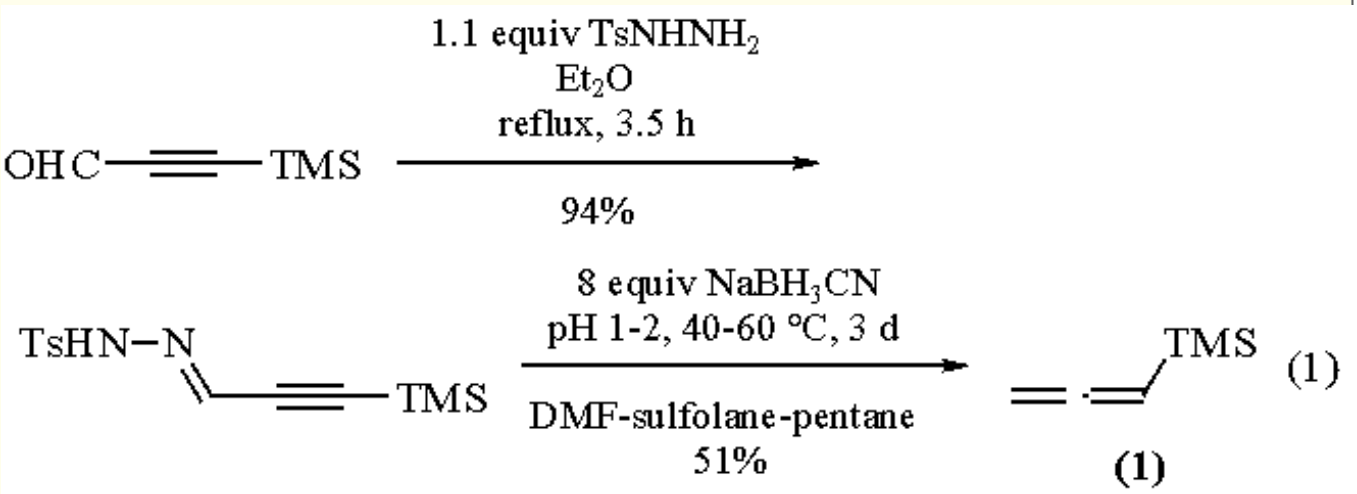

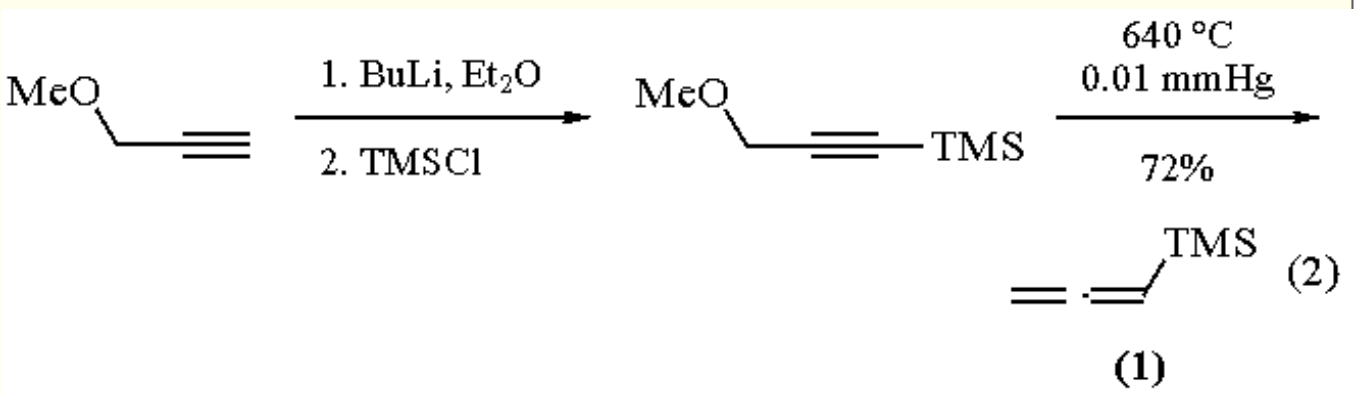

Purification: distillation at atmospheric pressure.[4b]

Handling, Storage, and Precautions: stable indefinitely when stored under nitrogen in the refrigerator.

Propargylic Anion Equivalent.

(TMS)allene reacts with electrophiles at the C-3 position in an S_E2' process analogous to electrophilic substitution reactions of allyl- and propargylsilanes.[8] For example, upon treatment with trimethylsilyl chlorosulfonate or ***Sulfur Trioxide-1,4-Dioxane***, (TMS)allene yields silyl esters of sulfonic acids (eq 3).[2] (TMS)allene undergoes conjugate addition with α,β-unsaturated acyl cyanides to yield δ,ε-acetylenic acyl cyanides.[3]

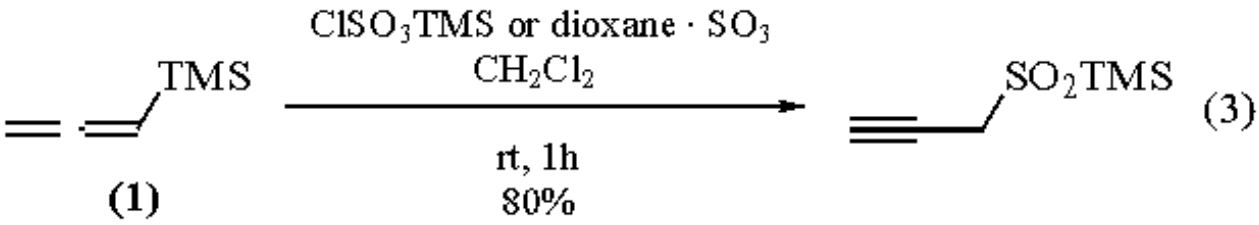

Particularly important is the reaction of (TMS)allene with aldehydes and ketones, which provides a convenient route to secondary and tertiary homopropargylic alcohols, respectively. Treatment of (**1**) (1.1-1.5 equiv) with a mixture of carbonyl compound and 1.1-1.5 equiv of ***Titanium(IV) Chloride*** in methylene chloride produces mixtures of homopropargylic alcohols and (trimethylsilyl)vinyl chlorides. Exposure of the crude reaction product to 2.5 equiv of ***Potassium Fluoride*** in DMSO[9] then furnishes the desired homopropargylic alcohols (eq 4).[4]

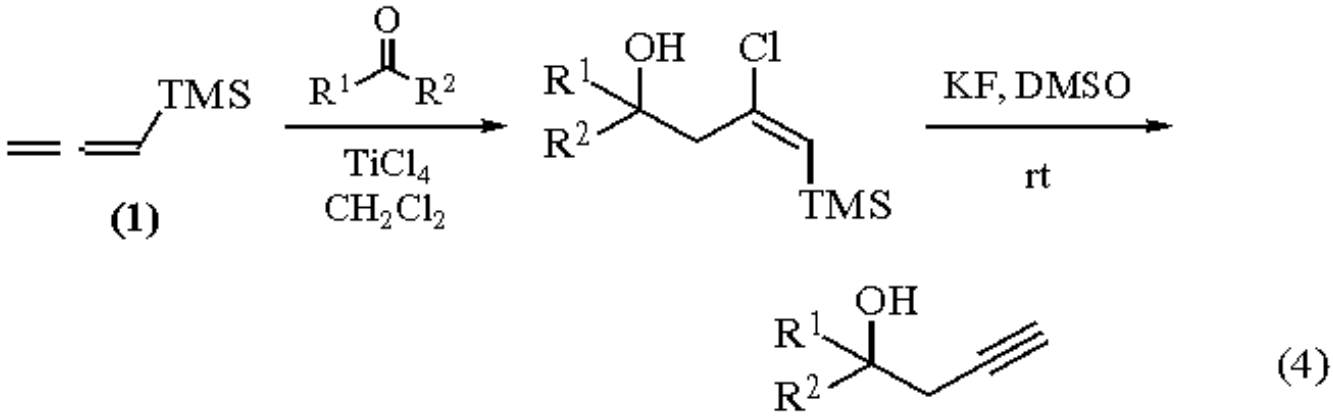

Carbonyl compound	% Yield
$PhCH_2CH_2CHO$	84
$PhCH_2COMe$	72
Cyclohexanone	89

Several alternative reagents function as propargylic anion equivalents.[10] Homopropargylic alcohols can be prepared by the addition of allenylboronate esters to aldehydes (though not to ketones).[11] Brown has recently reported that 9-allenyl-9-BBN reacts with aldehydes and ketones to produce homopropargylic alcohols in good yields.[12] ***Allenyllithium*** unfortunately combines with carbonyl compounds to afford mixtures of allenic and acetylenic alcohols.[13] Allenylmagnesium bromide reacts with carbonyl compounds to furnish homopropargylic alcohols in poor yields; in some cases, mixtures of allenic and alkynic products are obtained.[12] Diallenyltin dibromide, which is generated by reaction of propargyl bromide with tin metal in the presence of aluminum, reacts with both aldehydes and ketones to afford homopropargylic alcohols in good yield.[14] Alternatively, triisopropylsilyl derivatives of these alkynes can be prepared by the reaction of the lithium derivative of 1-(triisopropylsilyl)propyne with ketones and aldehydes by using the procedure described by Corey and Rucker.[15] Trimethylsilyl analogs of these alkynes have been prepared using the Reformatsky reagent derived from trimethylsilylpropargyl bromide: zinc-mediated condensation of trimethylsilylpropargyl bromide with aldehydes and ketones delivers homopropargylic alcohols (eq 5).[16]

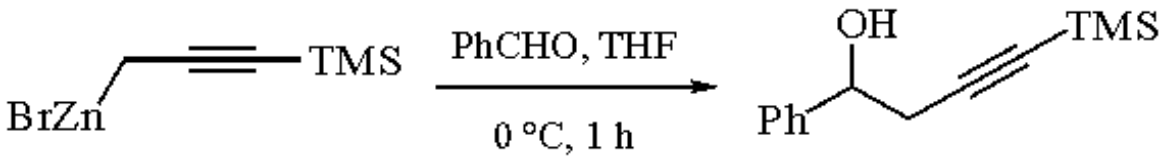

(5)

Synthesis of Silylacetylenes via Ene Reaction.

(TMS)allene undergoes ene reactions with ***4-Phenyl-1,2,4-triazoline-3,5-dione*** and other reactive enophiles to give silylacetylenes.[5]

Related Reagents.

Allenyllithium; ***1-Methyl-1-(trimethylsilyl)allene***; ***Allyltrimethylsilane***; ***Propargylmagnesium Bromide***; ***3-Trimethylsilyl-1-propyne***.

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Trimethylsilylallyllithium[1]

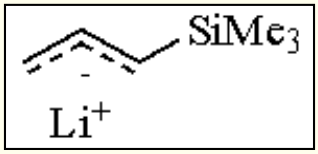

[67965-38-2] · $C_6H_{13}LiSi$ · Trimethylsilylallyllithium · (MW 120.22)

(addition to ketones and aldehydes;[2] synthesis of dienes with defined stereochemistry;[3] reaction with alkyl halides,[4] epoxides,[5] and other electrophiles[6])

Alternate Name: [1-(trimethylsilyl)-2-propenyl]lithium.

Physical Data: ^{1}H and ^{13}C NMR solution studies of the TMEDA complex in THF[7a] and the X-ray structure of the TMEDA complex of a closely related reagent have been reported.[7b]

Solubility: sol THF, ether.

Preparative Method: prepared in situ, under an inert atmosphere, by reaction of ***Allyltrimethylsilane*** with ***n-Butyllithium*** or with ***s-Butyllithium***.[1,7a]

Handling, Storage, and Precautions: solutions are inflammable. Preclude contact of the solutions with air and moisture.

Addition to Ketones and Aldehydes.[2]

Trimethylsilylallyllithium (**1**) adds to most aldehydes and ketones to give γ-(*E*)-vinylsilanes (eq 1) and only very small amounts of α-condensation products or Peterson elimination products.[2] The stereoselectivity has been investigated by NMR studies carried out in solution, which show that (**1**) exists exclusively in the *exo* conformation.[7]

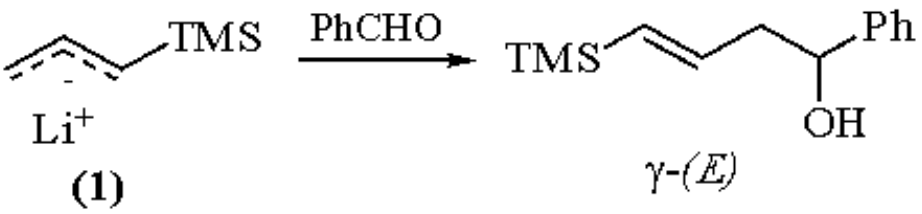

(1)

However, other types of silylallyllithium compounds with internal complexing capabilities are suspected to exist in the *endo* conformation under certain conditions. For example, (dialkylaminomethyl)dimethylsilylallyllithiums give the usual γ-(*E*)-vinylsilane products with reasonable selectivity when they react with aldehydes and ketones in toluene. However, if a small amount of 1,2-dimethoxyethane is added to the reagent, the stereoselectivity of the reaction is reversed, giving the γ-(*Z*)-vinylsilane as the major product (eq 2).[8]

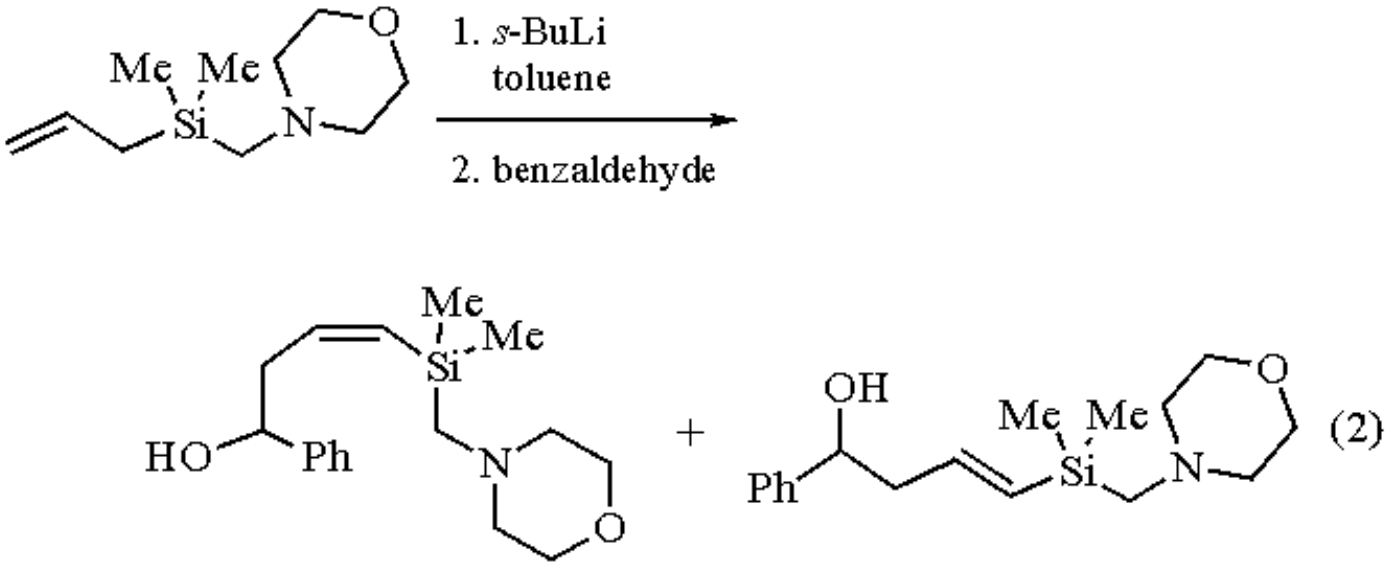

DME at -90 °C	7:1	72%
-78 °C	1:10	82%

These γ-condensation products are useful in organic synthesis. For example, the vinylsilane portion of the molecule can be used as an internal nucleophile in cyclization reactions, as demonstrated in the synthesis of substituted aromatic compounds (eq 3).[9] They can also be used as lactone precursors (eq 4), as demonstrated in the synthesis of the steroidal 17-spiro-γ-lactone (**2**).[2]

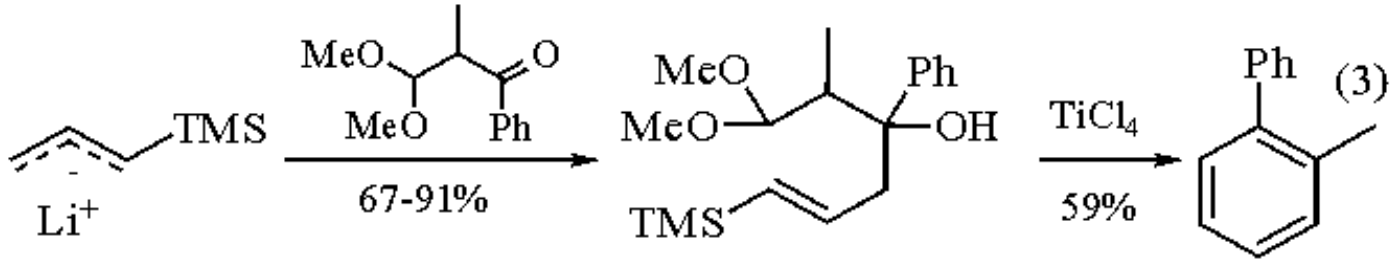

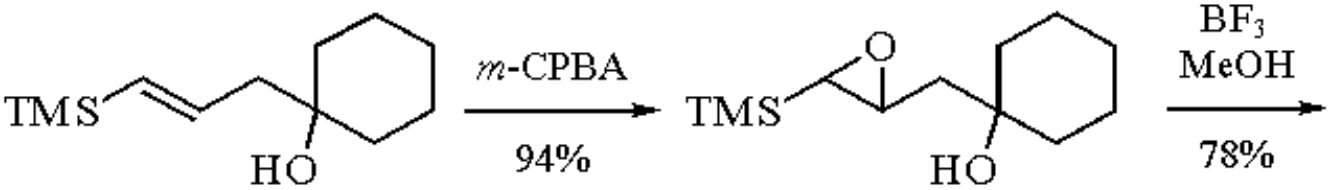

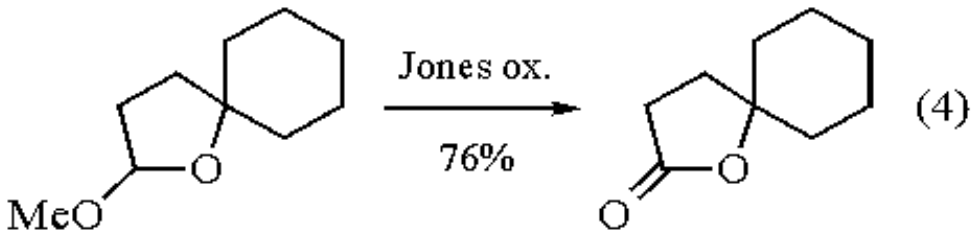

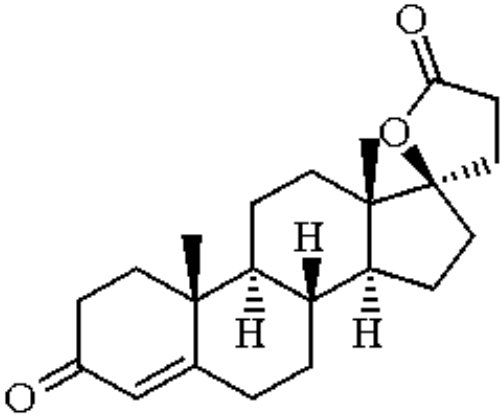

(2)

The reactivity of the double bond in these hydroxyvinylsilane products is affected by the trimethylsilyl group. The reaction of (**3**) with ***N-Bromosuccinimide*** leads to the formation of a β-bromooxetane at 0 °C or of a diene product at 40 °C (eq 5). The expected formation of the tetrahydrofuran product has not been observed.[2]

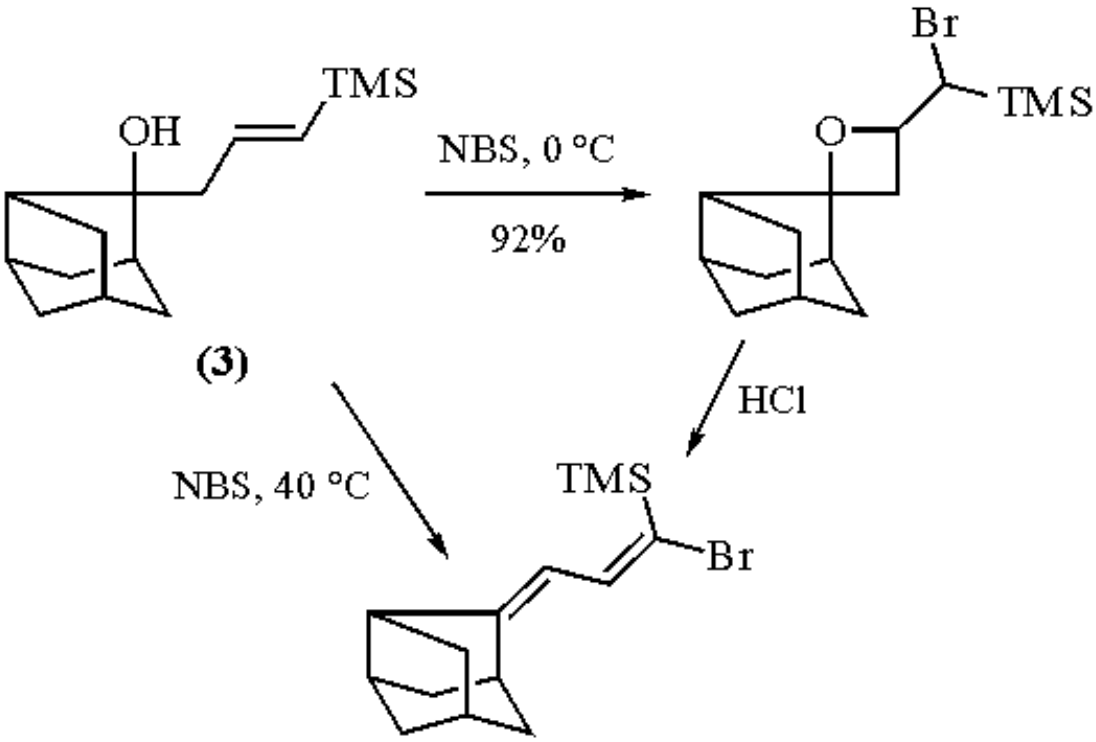

(5)

Synthesis of Dienes with Defined Stereochemistry.[3]

The normal γ-regioselectivity in the reaction of (**1**) with ketones and aldehydes can be modified by the use of other metal counter-ions. Thus α-substitution products can be obtained selectively if ***Magnesium Bromide*** or other Lewis acids are added to the reaction media (eq 6). The resulting alcohols are also diastereomerically enhanced. These observations are explained by the formation of a six-membered ring transition state (**4**) where the metal ion M^+ coordinates with the carbonyl oxygen. Other reagents used to control the regio- and stereoselectivity of the reactions of (**1**) with aldehydes are shown in eq 7.[2c,3c-g] The alcohols are useful for the stereospecific formation of dienes by the Peterson alkenation reaction (eq 6).[3a] The same logical approach has been used to obtain (*E*)- or (*Z*)-4-aryl (or alkyl)-(*E*)-1-(trimethylsilyl)-1,3-butadienes from the deprotonation of 1,3-bis(trimethylsilyl)propene, an α-trimethylsilylated equivalent of (**1**), and reaction with benzaldehyde (eq 8).[3b]

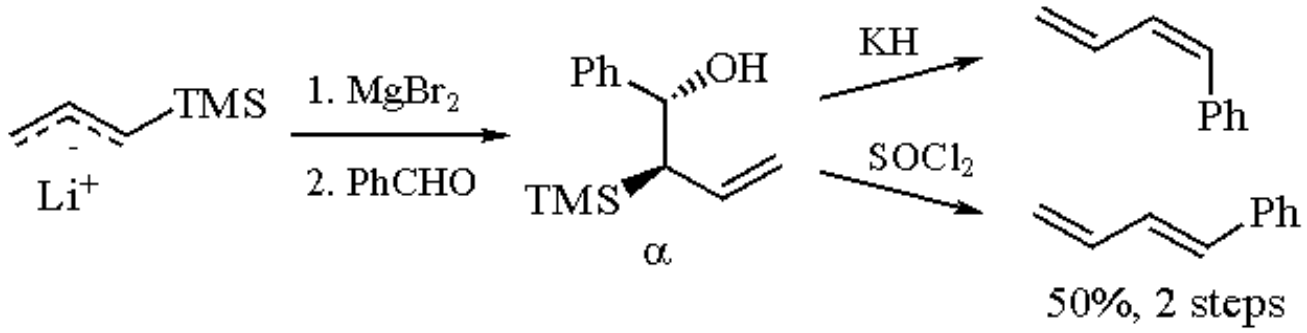

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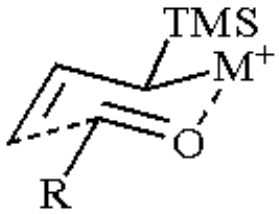

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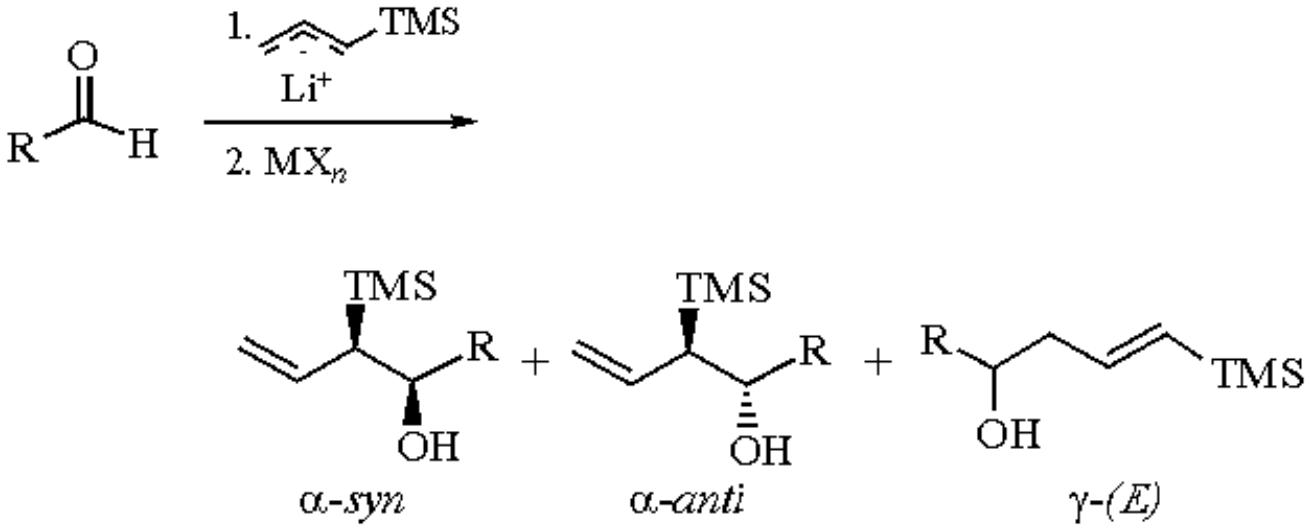

(7)

MX_n	RCHO	Relative amount of α-*syn*	α-*anti*	γ-(*E*)	Combined yield (%)
$ZnEt_2$	Benzaldehyde	100*	-	-	74[3c]
BR_2Cl	Isobutyraldehyde	-	100	-	60[3d]
CuCN	Cinnamaldehyde	-	-	100	75[2c]
$AlEt_3$	Benzaldehyde	37	43	2	51[3d,e]
$AlEt_2Cl$	Benzaldehyde	4	88	2	66[3d,e]
$SnBu_3 + BF_3$	Benzaldehyde	100*	-	-	77[3d]
$TiCp_2Cl$	Benzaldehyde	-	100*	-	95[3f]
$Ti(O\text{-}i\text{-}Pr)_4$	Benzaldehyde	-	>99	<1	80-83[3g]

*The ratios were inferred from the stereochemistry of the dienes obtained after Peterson eliminations of the α-condensation products

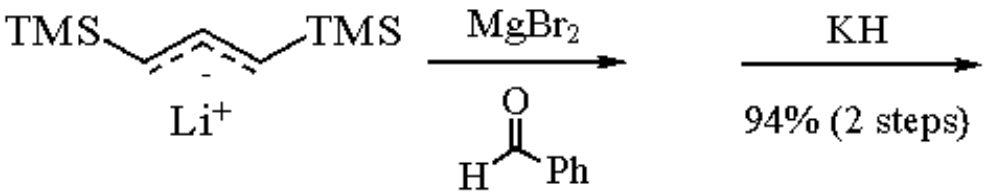

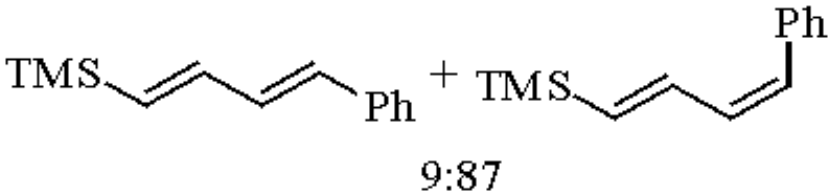

(8)

Reaction with Alkyl Halides, Epoxides, and Other Electrophiles.[4-6]

Trimethylsilylallyllithium reacts with alkyl halides at low temperature, giving mixtures of α- and γ-(*E*) products in ratios that vary with the electrophile and the reaction conditions (eq 9).[4] In these reactions the γ-(*E*)-alkylation product generally predominates. For example, when trimethylsilylallyllithium is formed by deprotonation of allyltrimethylsilane with *n*-butyllithium in the presence of potassium *t*-butoxide in THF, the (*E*)-vinylsilane alkylation product is obtained in better then 85% yield (eq 10). This has been exploited in the synthesis of (*Z*)-9-tricosene epoxide, the sex pheromone of the gypsy moth.[4a]

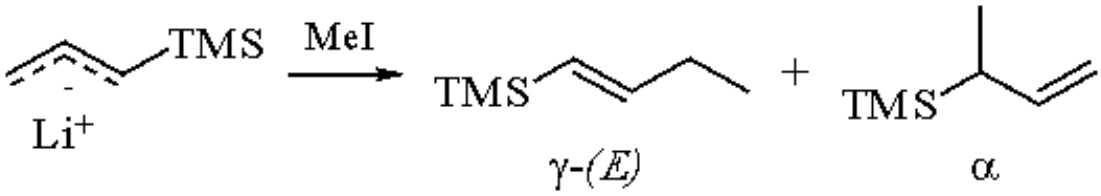

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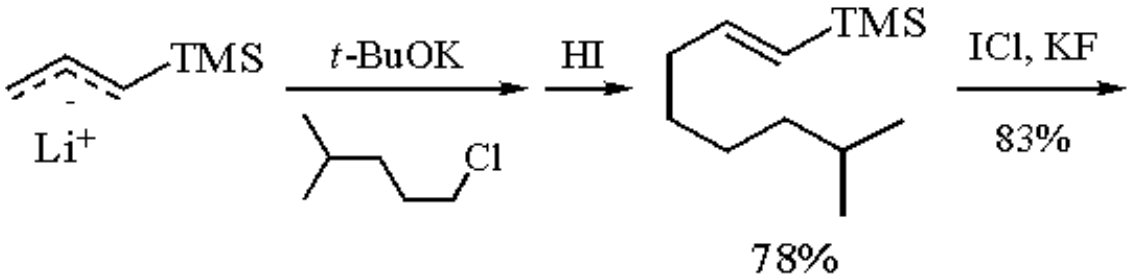

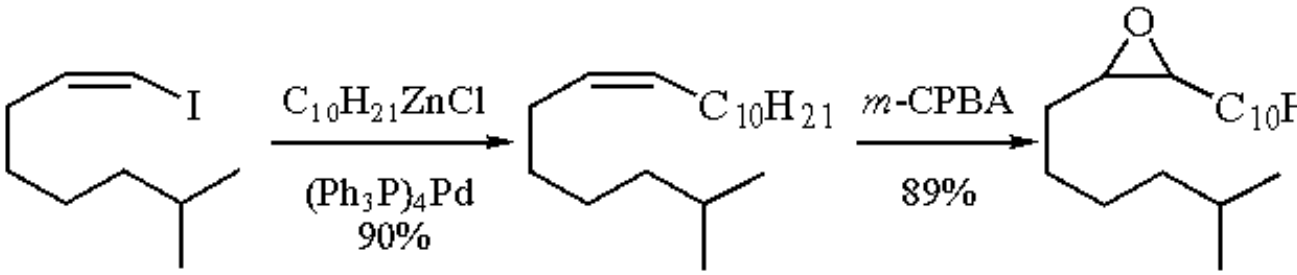

(10)

This γ-regioselectivity can be further improved by the use of bulky substituents attached to the silicon atom.[4a,b] In recent years, attempts have been made at developing reagents closely related to trimethylsilylallyllithium that will permit α-alkylation in high regio- and diastereoselectivity. In some instances, significant changes in regioselection can be achieved once the silicon is substituted with alkoxy or aminomethyl groups.[4c,4e] In particular, the use of chiral, lithium-chelating, amino groups attached to silicon as shown in eq 11, has been successfully applied to the regio- and diastereoselective alkylation of allylsilanes.[4c,e] This same approach gives even better results in the synthesis of chiral propargylic alcohols (eq 12).[4d]

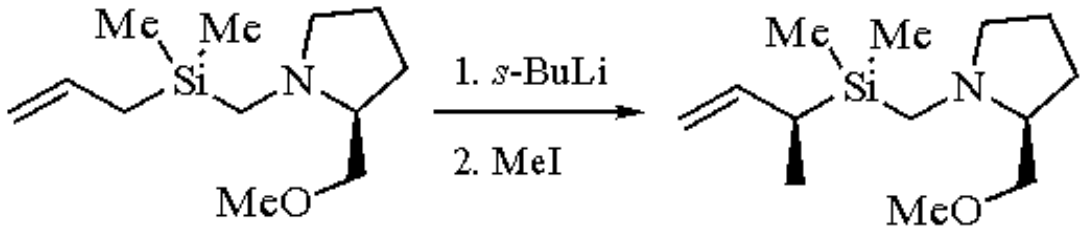

(11)

α:γ = 85:15
one diastereomer

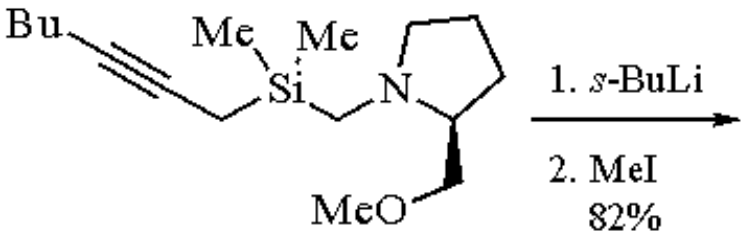

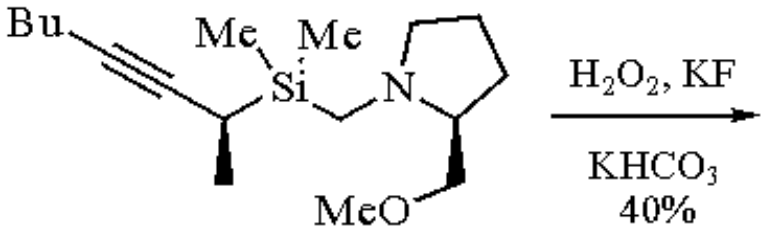

(12)

α:γ >98:2 >99% ee

Trimethylsilylallyllithium reacts with epoxides (at -40 °C in THF for 2 h) to give alcohols in good yields. Highest α-selectivity is obtained with smaller monosubstituted epoxides; larger trisubstituted epoxides give γ-products. In unsymmetrical epoxides, attack is on the less hindered side[5a] with the notable exception of trimethylsilyl-substituted ones, where the attack occurs predominantly on the carbon bearing the trimethylsilyl group. This approach has been used to synthesize 1-silyl-substituted 1,4-dienes (eq 13).[5b] Trimethylsilylallyllithium also reacts with many other electrophiles including imines,[6a] carbon dioxide,[6b] substituted naphthalene,[6c] selenocyanogen,[6d] and dimethylformamide.[2a]

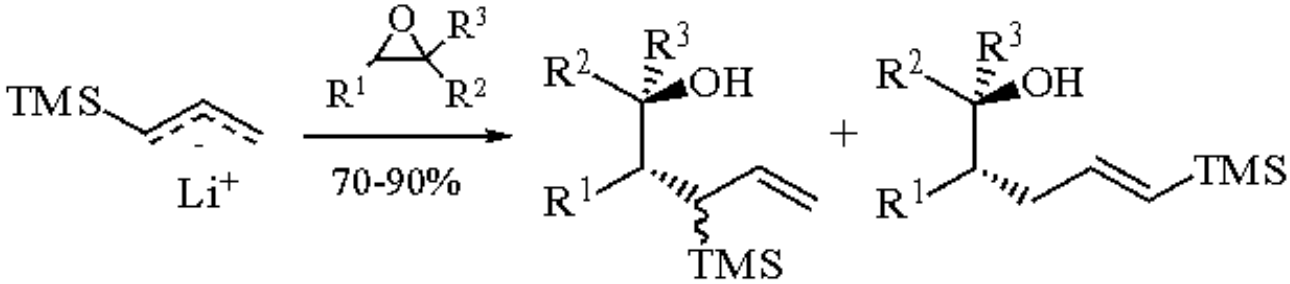

(13)

$R^1 = R^2 = R^3 = H$	10:1
$R^1 = R^2 = Me$, $R^3 = H$	1:2
$R^1, R^2 = -(CH_2)_4-$, $R^3 = Me$	1:10

Related Reagents.

The literature contains numerous examples of reagents having different substitutions on the silicon moiety. The introduction of bulky and/or aromatic groups on the silicon atom, for example in (**5**) (R = Ph, *p*-tolyl, vinyl, *t*-Bu),[6b] (**6**),[6b] and (**7**) (R = OMe, Ph, Et, *i*-Pr),[2a,4a,6b,10] has been used to modify the reactivity of the allylic anion. The influence exerted by these groups is mediated through their steric and/or electronic interactions with the allylic anion and with its counter ion. It is not surprising then that the presence of chelating amino or ether

functions on the silicon atom, for example in (**5**) [R = NEt_2, $N(i\text{-}Pr)_2$, $NH(CH_2CH_2NMe_2)$, pyrrolidino, CH_2(methoxymethylpyrrolidine), $CH_2N(CH_2CH_2OMe)_2$], also modifies the reactivity of the allyllithium attached to it.[4c,11] The silylallyllithium reagents are normally obtained by deprotonation of the corresponding allylsilanes. However, γ-deprotonation of vinylsilanes can also be used for the same purposes, as is the case when either (**8**) or (**9**) are used to give the corresponding silylallyllithium reagent.[12] Other reagents (**10**)-(**17**) having heteroatom substituents on the allyl group have also been used.[3b,7b,13-19]

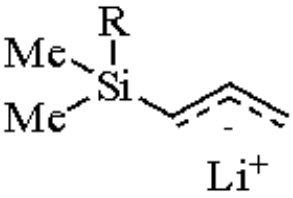

(**5**)

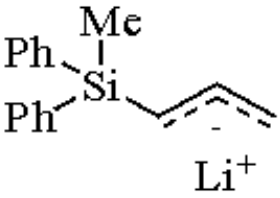

(**6**)

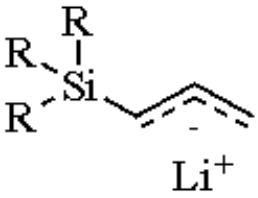

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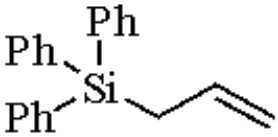

(**8**)

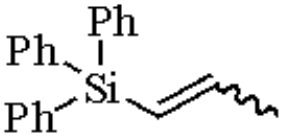

(**9**)

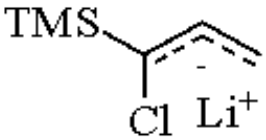

(**10**)

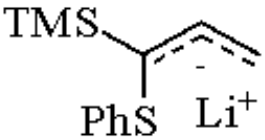

(**11**)

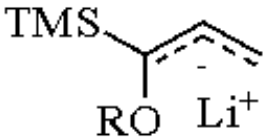

(**12**)

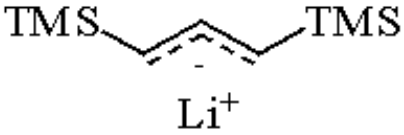

(**13**)

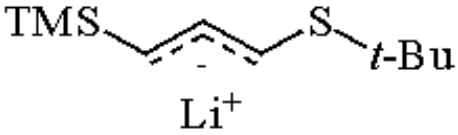

(**14**)

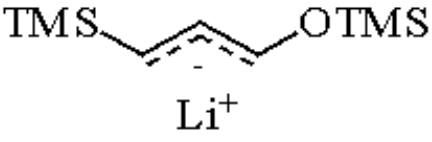

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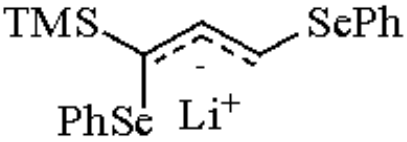

(**16**)

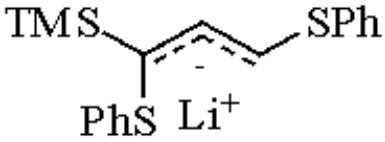

(**17**)

A few carbon-substituted reagents (**18**)-(**20**) have also been prepared.[4b,6b,20] Of these, reagent (**18**) has been used in the synthesis of frontalin, a natural product. The last three examples (**21**)-(**23**) show interesting steric and electronic effects on the regio- and stereoselectivity of the alkylation and condensation reactions.[4e,21,22]

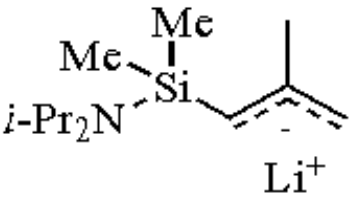

(**18**)

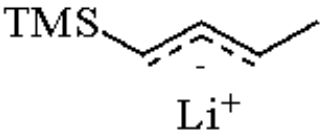

(**19**)

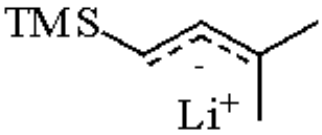

(**20**)

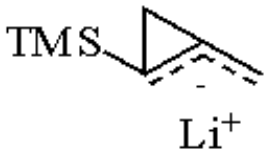

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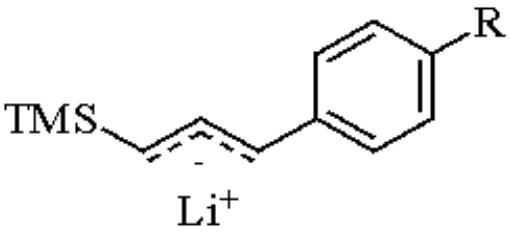

(22) R = H or OMe

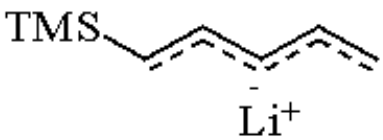

(23)

Related Reagents.

Allyllithium; ***Crotyllithium***; ***9-[1-(Trimethylsilyl)-2(E)-butenyl]-9-borabicyclo[3.3.1]nonane***; ***5-Trimethylsilyl-1,3-pentadiene***.

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2-Trimethylsilyl-1,3-benzothiazole

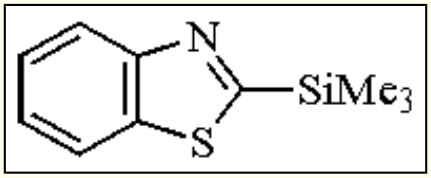

[32137-73-8] · $C_{10}H_{13}NSSi$ · 2-Trimethylsilyl-1,3-benzothiazole · (MW 207.40)

(silyl heterocycle that reacts with a variety of electrophiles)

Physical Data: bp 139 °C/15 mmHg; *n*25D = 1.57.

Solubility: sol all organic solvents.

Analysis of Reagent Purity: NMR.

Purification: vacuum distillation.

Handling, Storage, and Precautions: can be stored indefinitely in the refrigerator in the absence of moisture.

Reaction with Carbon Electrophiles.

The ability of this reagent to transfer the benzothiazol-2-yl unit to carbon electrophiles, is demonstrated by reactions with aldehydes, acyl halides, and chloroformates that give trimethylsilyl carbinols, ketones, and esters (eq 1).[1]

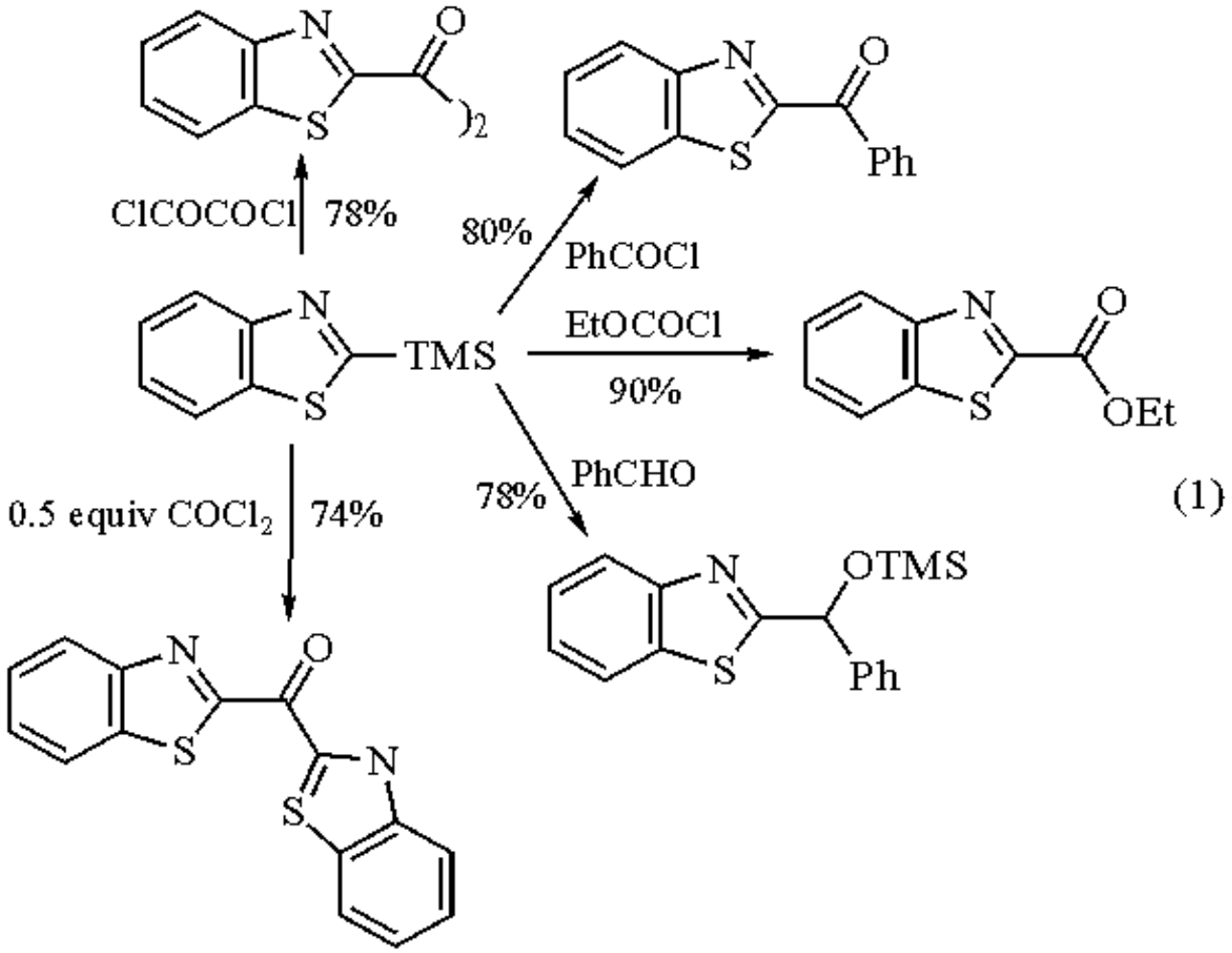

The reaction with benzaldehyde is performed under a dry nitrogen atmosphere at 160 °C for 40 h; acyl halides and ***Ethyl Chloroformate*** react under milder reaction conditions. The reaction of 2 equiv of 2-trimethylsilyl-1,3-benzothiazole and ***Phosgene***[2] occurs at 0 °C and provides a bis-heteroaryl ketone; ***Oxalyl Chloride***[2] is converted to the (benzothiazol-2-yl)-substituted diketone. In these reactions the use of the corresponding stannylated derivative leads in several cases to complex product mixtures. The reactivity toward electrophiles is increased in the presence of a catalytic amount of fluoride ion.[3] The easy F^--catalyzed desilylation, promoted by ***Cesium Fluoride*** or SiO_2-supported ***Tetra-n-butylammonium Fluoride***, allows reaction with a wider range of electrophiles such as saturated lactones (eq 2). δ-Valero- and ε-caprolactone react smoothly under F^- catalysis, affording the corresponding keto alcohols from acyl-oxygen bond cleavage. Ring size effects are also seen; reaction of β-propiolactone fails because of ring opening and polymerization, whereas γ-butyrolactone gives only modest conversion yields (15%). With cyclohexen-2-one as an electrophile, conjugated addition of the benzothiazol-2-yl carbanion occurs, with formation of the Michael adduct.

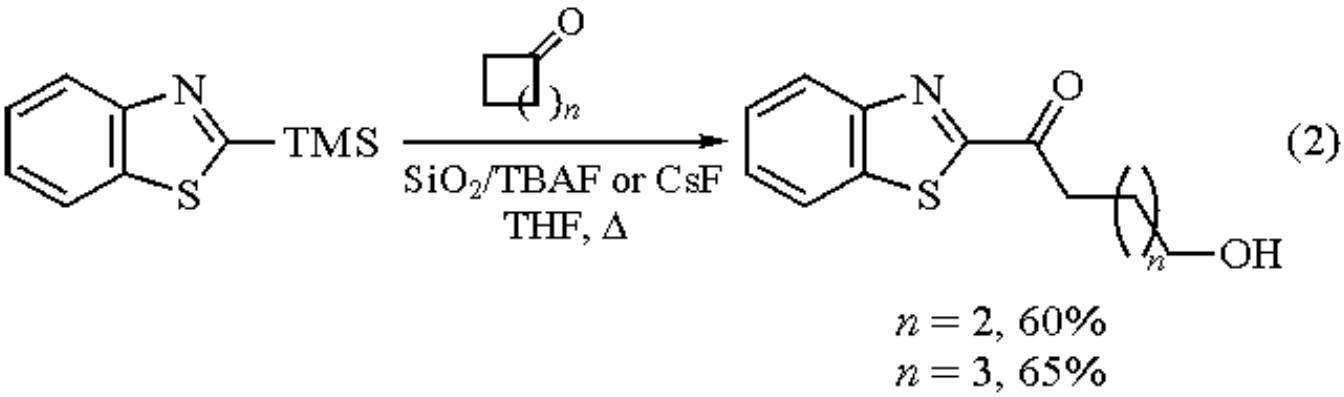

Stereoselective Additions.

The addition of 2-trimethylsilyl-1,3-benzothiazole to α-asymmetric aldehydes proceeds[4] under mild conditions in good chemical yield and with significant stereoselectivity. In particular, the reaction with D-glyceraldehyde gives the *anti*-isomer with 80% diastereomeric purity (eq 3). The diastereoselectivity appears to vary depending on the azole nucleophile. Reaction of 2-lithiobenzothiazole with the same aldehyde (Et_2O, -78 °C) shows a complete lack of stereoselectivity. Unmasking the formyl group, using suitable procedures from the literature,[5a,b] allows 2-trimethylsilyl-1,3-benzothiazole to be used as a formyl anion equivalent in the diastereoselective synthesis of α-

hydroxy carbonyl derivatives.

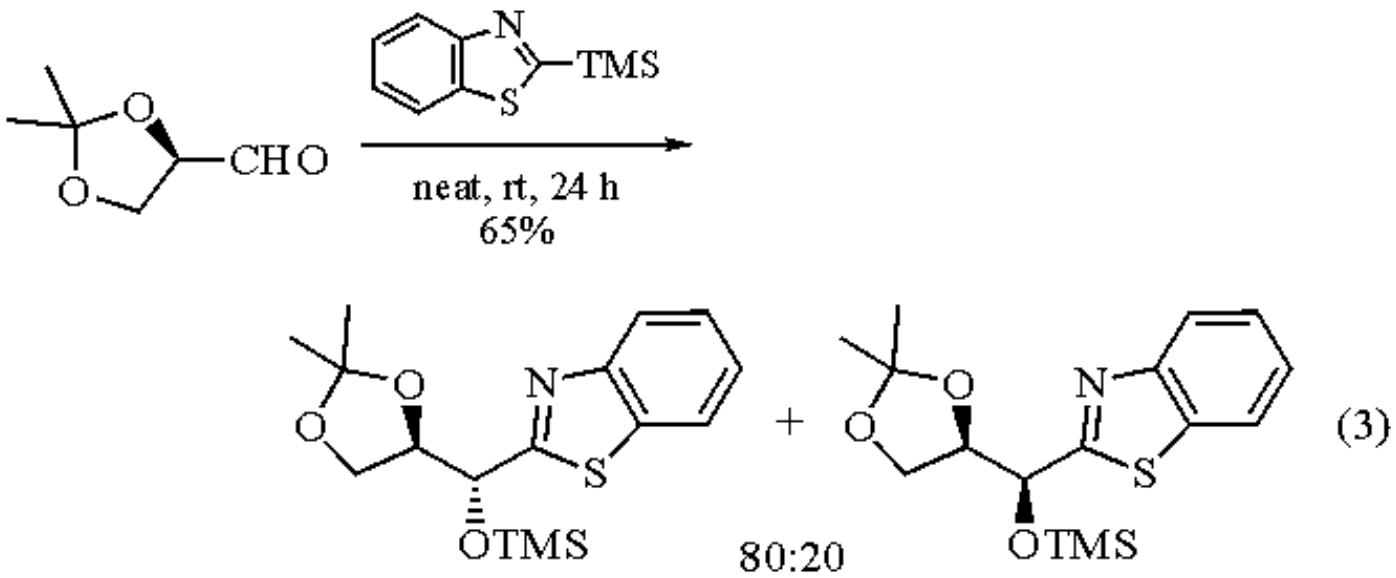

Synthesis of Heterocyclic-Substituted Tertiary Phosphines.

Electrophilic cleavage of the C-Si bond of 2-trimethylsilyl-1,3-benzothiazole by ***Phosphorus(III) Chloride***, $PhPCl_2$, and Ph_2PCl, affords the tris-, bis-, and mono(benzothiazol-2-yl)phosphines in good yields (eq 4). The procedure involves the electrophilic cleavage of the C-Si bond and formation of a C-P bond.[6] The reactions are conducted neat and the phosphorus derivatives appear quite air-stable even at room temperature. Attempts to prepare tris(benzothiazol-2-yl)phosphines by reaction of the corresponding heteroaryl organolithium reagent and PCl_3 were unsuccessful.

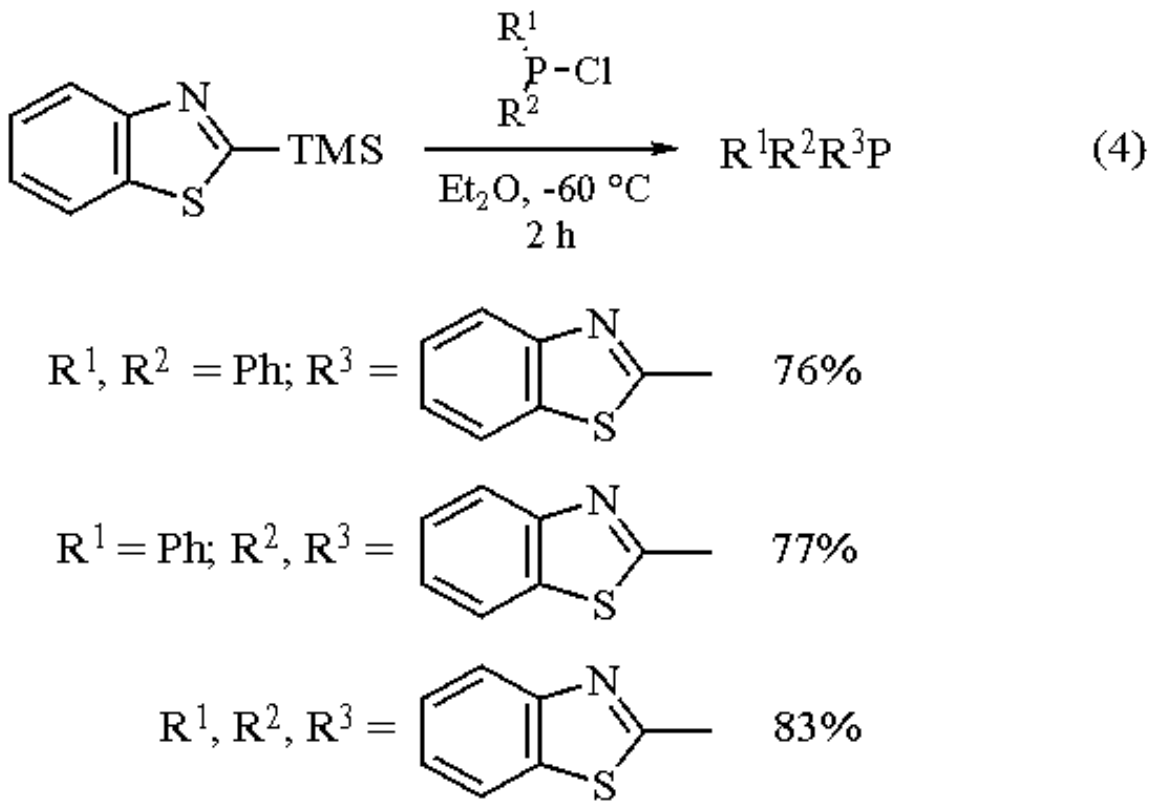

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(*E*)-1-Trimethylsilyl-1,3-butadiene[1]

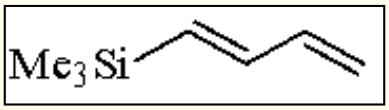

[71504-26-2] · $C_7H_{14}Si$ · (*E*)-1-Trimethylsilyl-1,3-butadiene · (MW 126.30)

(diene for Diels-Alder reactions,[2,3] creating allylsilanes that can be converted to a variety of functionalized cyclohexenes with a shift of the double bond from its original position in the cycloaddition;[3] synthesis of a chiral allylborane;[4] synthesis of allylsilanes[5,6] and trienes[7])

Physical Data: bp 110-115 °C, 70-74 °C/210 mmHg.

Solubility: freely sol all organic solvents.

Analysis of Reagent Purity: NMR: δ ($CDCl_3$) 6.6-4.9 (5H, m), 0.02 (9H, s).[3] UV: λ_{max} (EtOH) 231 nm (ε 22 000).[2]

Preparative Methods: prepared geometrically pure by Wittig[2] or Peterson[3] reactions on (*E*)-3-trimethylsilylpropenal,[8] by pyrolysis of silylated 3-sulfolenes,[9] and by coupling (*E*)-2-trimethylsilylvinyl bromide with ***Lithium Divinylcuprate***.[10] It can also be prepared geometrically impure, but largely (*E*), from ***Allyltrimethylsilane*** by a vinylogous Ramberg-Bäcklund reaction,[11] and from ***1,3-Butadienyl-1-magnesium Chloride*** and ***Chlorotrimethylsilane***.[4]

Handling, Storage, and Precautions: reasonably stable in the absence of air and radical initiators. It should be kept in a stoppered flask or sealed ampule in the presence of hydroquinone. Its toxicity is unknown, but the presence of a trimethylsilyl group is generally benign.

Diels-Alder Reactions.

(*E*)-1-Trimethylsilyl-1,3-butadiene undergoes Diels-Alder reactions with the usual dienophiles, with unimpaired *endo* stereoselectivity, but at a somewhat slower rate than 1,3-butadiene itself (eq 1).[2,3] The regioselectivity with unsymmetrical dienophiles is poor (eq 2).[2,3] The adducts are allylsilanes, which react with electrophiles in the usual way (eqs 3 and 4) to give cyclohexenes with a double bond shifted from the original position.[3]

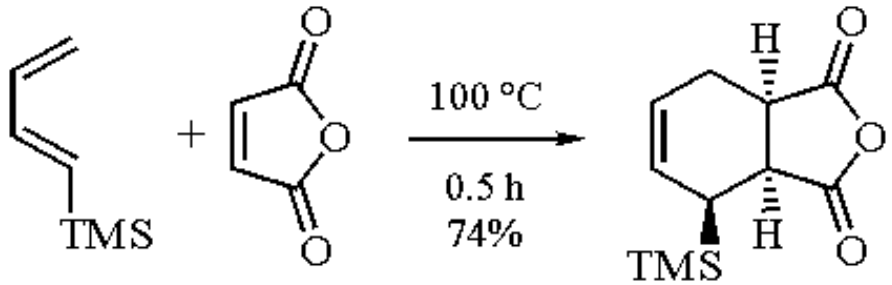

(1)

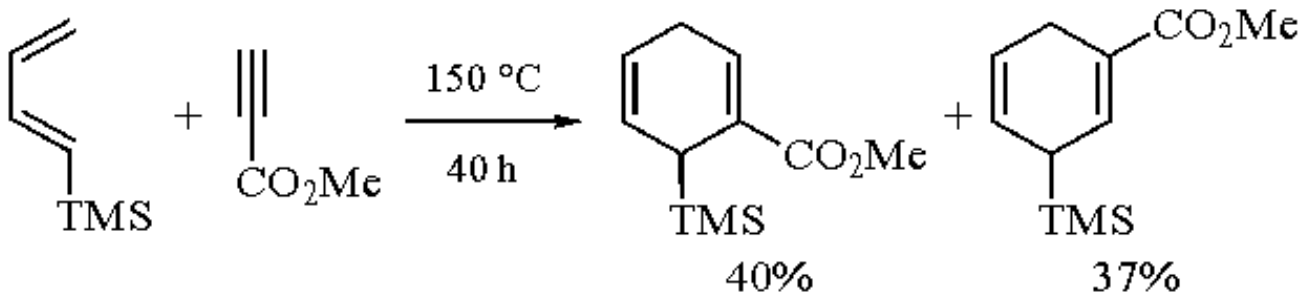

(2)

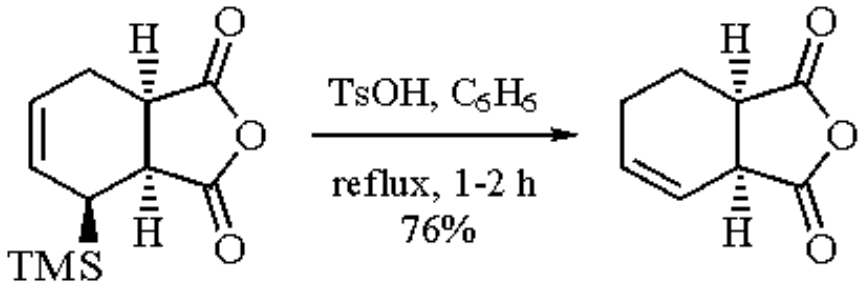

(3)

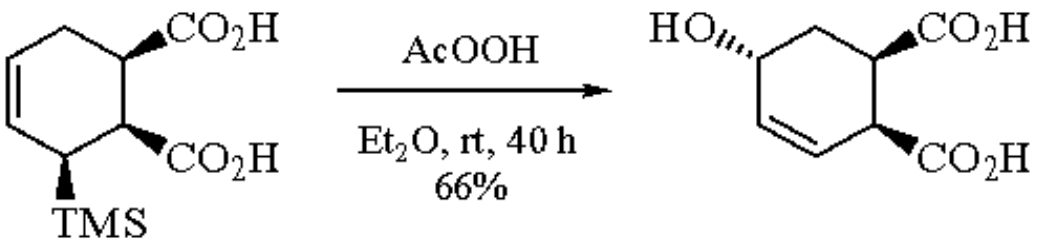

(4)

Because of the low level of regiocontrol imparted by the silyl group, other substituents on 1-silylated dienes can impart better regiocontrol (eq 5).[3]

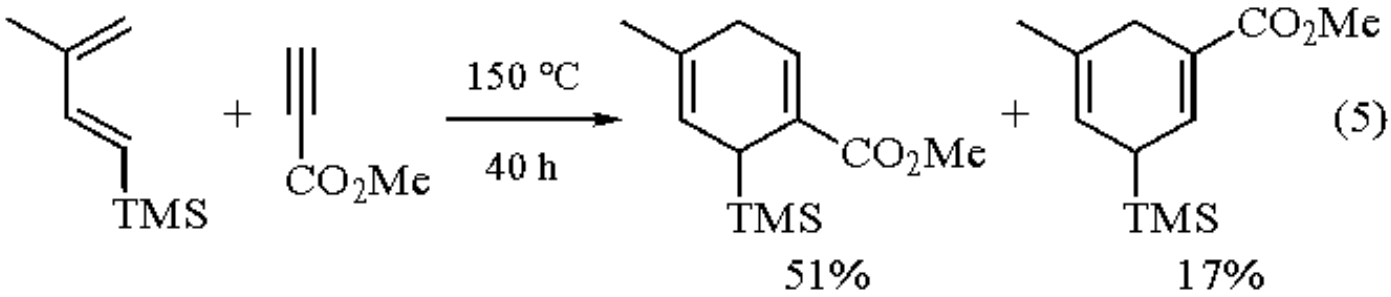

(5)

Trimethylsilylallylboranes.

The diene is used as a starting material for the synthesis of the chiral allylborane (**1**) or its enantiomer (eq 6).[4]

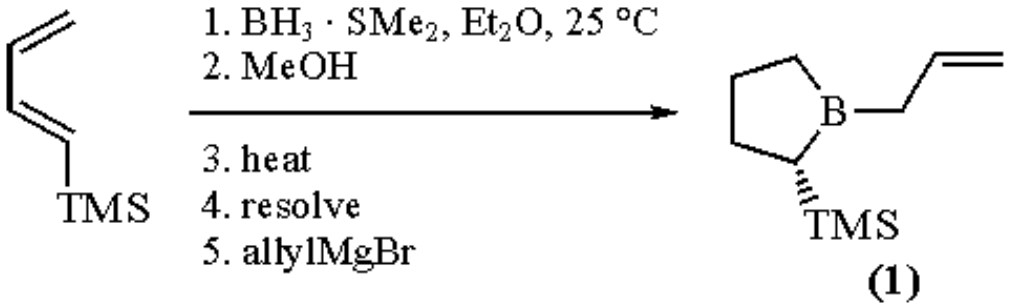

(6)

Allylsilanes.

Reduction of the diene with ***Lithium*** and *t*-butanol in liquid ammonia gives ***Crotyltrimethylsilane***,[5] and reaction with Grignard reagents gives longer chain (*E*)-allylsilanes (eq 7).[6]

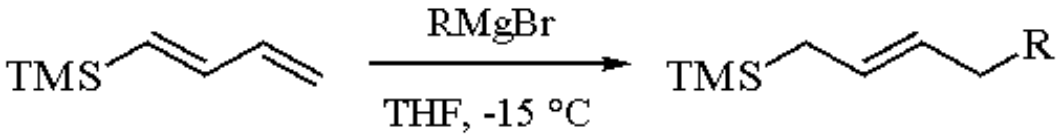

(7)

Triene Synthesis.

Like other vinylsilanes, 1-trimethylsilyl-1,3-butadiene can be used in a Hiyama coupling reaction with vinyl iodides (eq 8).[7]

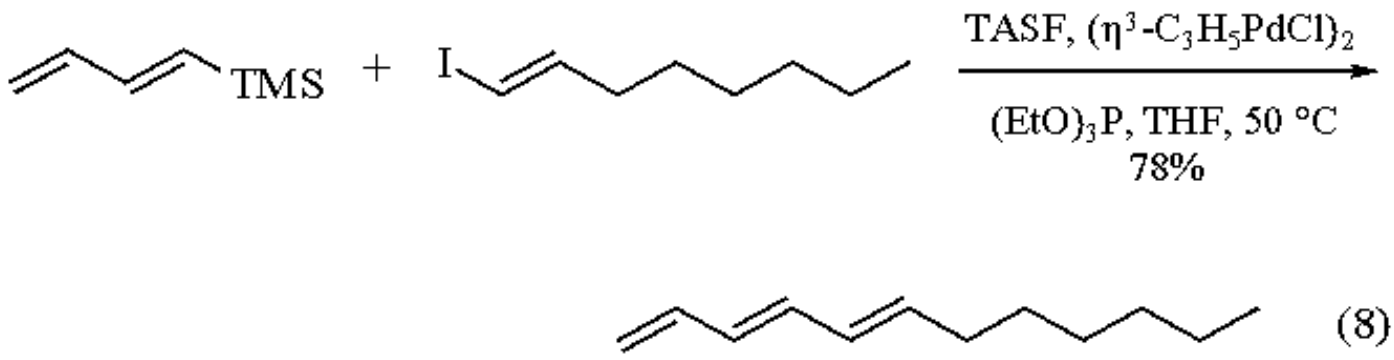

(8)

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3-Trimethylsilyl-3-buten-2-one

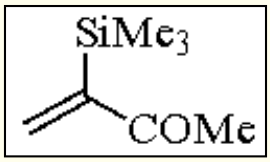

[43209-86-5] · $C_7H_{14}OSi$ · 3-Trimethylsilyl-3-buten-2-one · (MW 142.30)

(methyl vinyl ketone homolog[1] useful as a Michael acceptor in annulation reactions,[2,3] γ,δ-unsaturated ketone formation,[4] and Peterson condensations;[5] precursor to a stabilized Diels-Alder diene[6])

Physical Data: bp 72 °C/50 mmHg.

Analysis of Reagent Purity: ^{1}H NMR (CCl_4): δ 6.53 (d, *J* = 2 Hz, 1H, C*H*), 6.18 (d, *J* = 2 Hz, 1H, C*H*), 2.23 (s, 3H, CH_3), 0.14 [s, 9H, Si(CH_3)$_3$]. Analysis by gas chromatography on a 1.85m 3% silicon gum rubber (SE-30) column at 25 °C gives a single peak.

Preparative Methods: prepared by the reaction of ***(1-Bromovinyl)trimethylsilane*** with ***Acetaldehyde***.[1] An alternative synthesis from ***Acrolein*** has been published.[7]

Handling, Storage, and Precautions: shows no tendency to deteriorate when stored under an argon atmosphere at -20 °C.

Annulation.

3-Trimethylsilyl-3-buten-2-one has been employed as a ***Methyl Vinyl Ketone*** homolog in an improved method for the annulation of ketones.[2] Based on work by Stork and Ganem,[3] who employed ***3-Triethylsilyl-3-buten-2-one*** as a Michael acceptor in the Robinson annulation reaction, Suzuki and co-workers[8] prepared a functionalized bicyclic ketone via a silyl enol ether as shown in eq 1. In general, the annulation of 2-alkylcycloketones with methyl vinyl ketone and its homologs produces rather poor yields of the desired cyclized products.

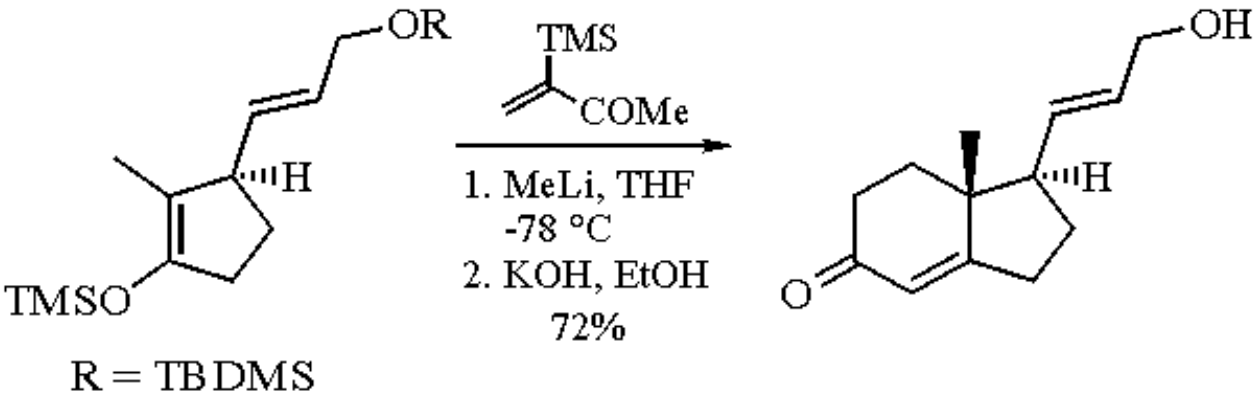

(1)

The conjugate addition of enolate anions to activated 3-trimethylsilyl-3-buten-2-one helped solve another long-standing problem in organic synthesis by permitting the annulation reaction to be carried out in aprotic solvents under conditions where enolate equilibration is avoided. The annulation of thermodynamically unstable lithium enolates with MVK, where equilibration to the more stable enolate occurs prior to Michael addition, often yields a mixture of structural isomers.[9] For example, Boeckman successfully employed 3-trimethylsilyl-3-buten-2-one in a Robinson annulation sequence (eq 2). Thus treatment of cyclohexenone with ***Lithium Dimethylcuprate*** in diethyl ether and then with 3-trimethylsilyl-3-buten-2-one gives the desired Michael adduct, which is converted into the functionalized octalone in 52% overall yield.[10]

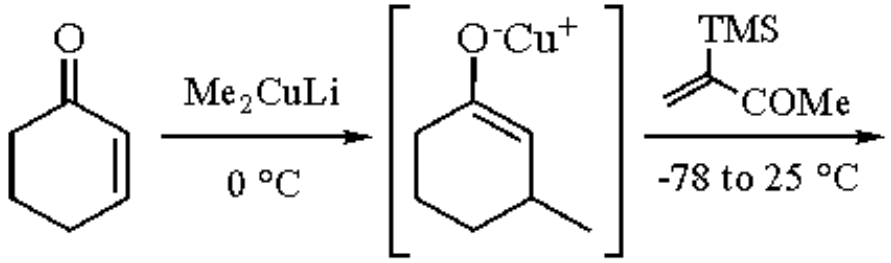

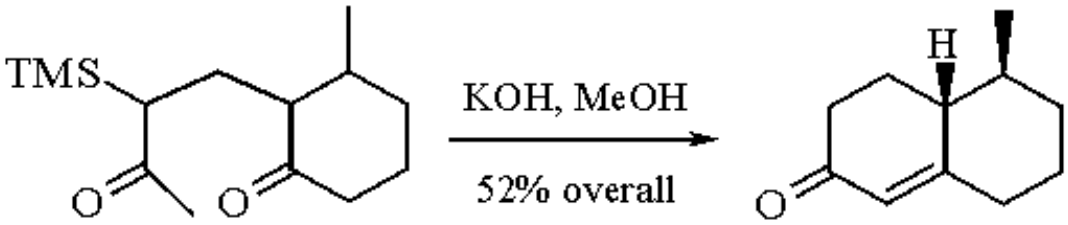

(2)

Boeckman originally postulated that the enolate copper bond played a part in the success of this sequence. In 1974, however, Boeckman[11] and Stork and Singh[12] reported simultaneously that lithium enolates can be used under aprotic conditions for regiospecific annulation with 3-trimethylsilyl-3-buten-2-one (eq 3).

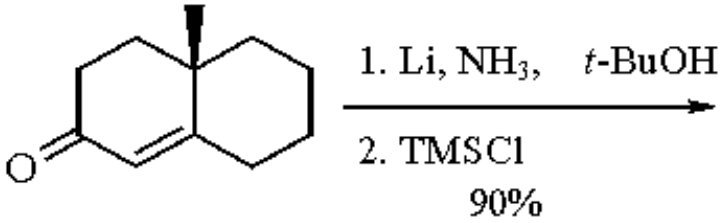

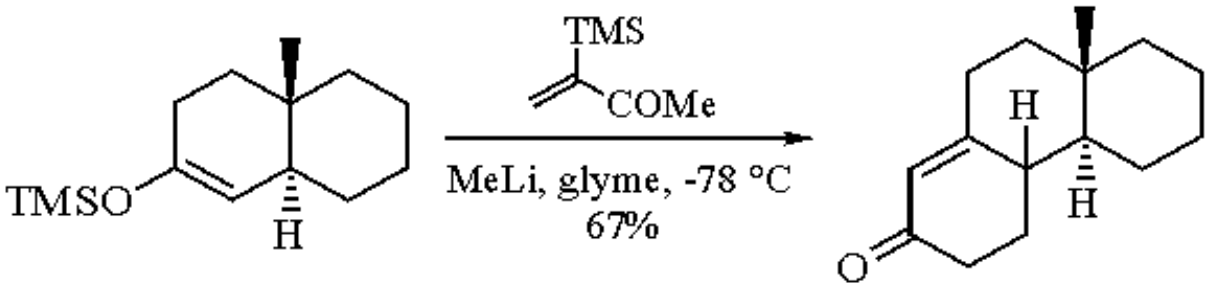

(3)

The most general annulation procedure is to first generate an enolate by lithium-ammonia reduction of an enone in the presence of *t*-butanol; the enolate is then trapped as the trimethylsilyl enol ether, which can be examined spectroscopically to establish homogeneity. The enolate is then regenerated with ***Methyllithium*** in dry glyme or diethyl ether at -78 °C prior to the addition of the α-silylated vinyl ketone. In this case, only traces of the linear tricyclic ketone are formed. The trimethylsilyl group helps stabilize the intermediate carbanion formed by conjugate addition, relative to that of the starting ketone, thus facilitating the forward reaction and at the same time discouraging equilibration of the enolate of the starting ketone.

Michael Condensation.

In 1988, Hagiwara and co-workers extended this annulation technology to include the two-fold Michael reaction of kinetic enolates derived from 1-acetylcyclohexenes (eq 4).[13] The kinetic enolates of 1-acetylcyclohexenes are generated from the corresponding trimethylsilyl enol ethers by treatment with MeLi in THF prior to the addition of 3-trimethylsilyl-3-buten-2-one. This one-pot annulation produces the desired decalone as a single isomer in 39% yield.

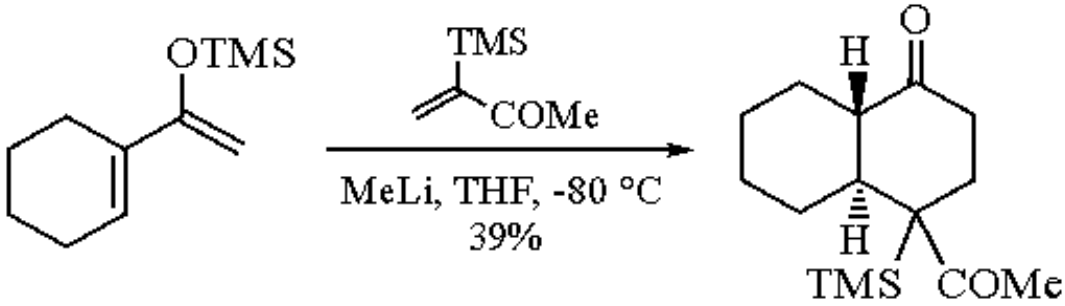

(4)

1-Alkenyldialkoxyboranes also react with 3-trimethylsilyl-3-buten-2-one in the presence of ***Boron Trifluoride Etherate*** through a facile 1,4-addition to give γ,δ-unsaturated ketones in good yields with high regio- and stereoselectivity (eq 5). Without BF_3 etherate this reaction does not occur and other Lewis acids, such as $AlCl_3$, $TiCl_4$, $SnCl_4$, and $ZnCl_2$, are less effective.[4]

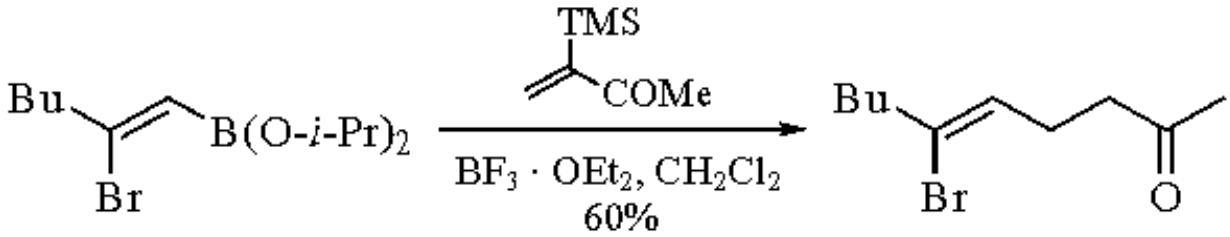

(5)

Michael-Peterson Condensation.

3-Trimethylsilyl-3-buten-2-one also undergoes smooth Michael addition with Grignard reagents (R = Me, *n*-Pr, *i*-Pr, *t*-Bu, Ph), generating magnesium enolates which are then trapped with benzaldehyde to give (*E*)- and (*Z*)-enone isomers after Peterson condensation (eq 6).[5] For example, treatment of the α-silyl vinyl ketone with methylmagnesium iodide followed by reaction with benzaldehyde yields a 7:1 mixture of (*E*)- and (*Z*)-isomers of 3-ethyl-4-phenyl-3-buten-2-one in 45% yield. (*E*)-Alkenes become the major products under thermodynamic control when the condensation with benzaldehyde is carried out at room temperature in diethyl ether. (*Z*)-Isomers are favored as kinetically controlled products at -78 °C in THF.

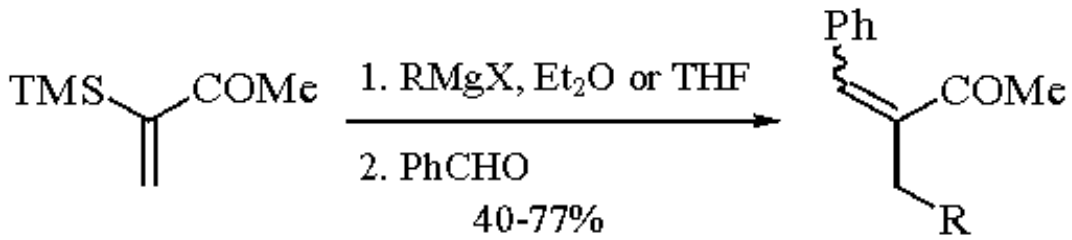

(6)

Diene Adduct.

3-Trimethylsilyl-3-buten-2-one undergoes a Shapiro reaction to give the 2,3-bis(trimethylsilyl)buta-1,3-diene in 32% yield (eq 7). This compound undergoes Diels-Alder reactions with a number of dienophiles (e.g. maleic anhydride, benzoquinone) in benzene at 60 °C to give silylated cycloaddition adducts.[6]

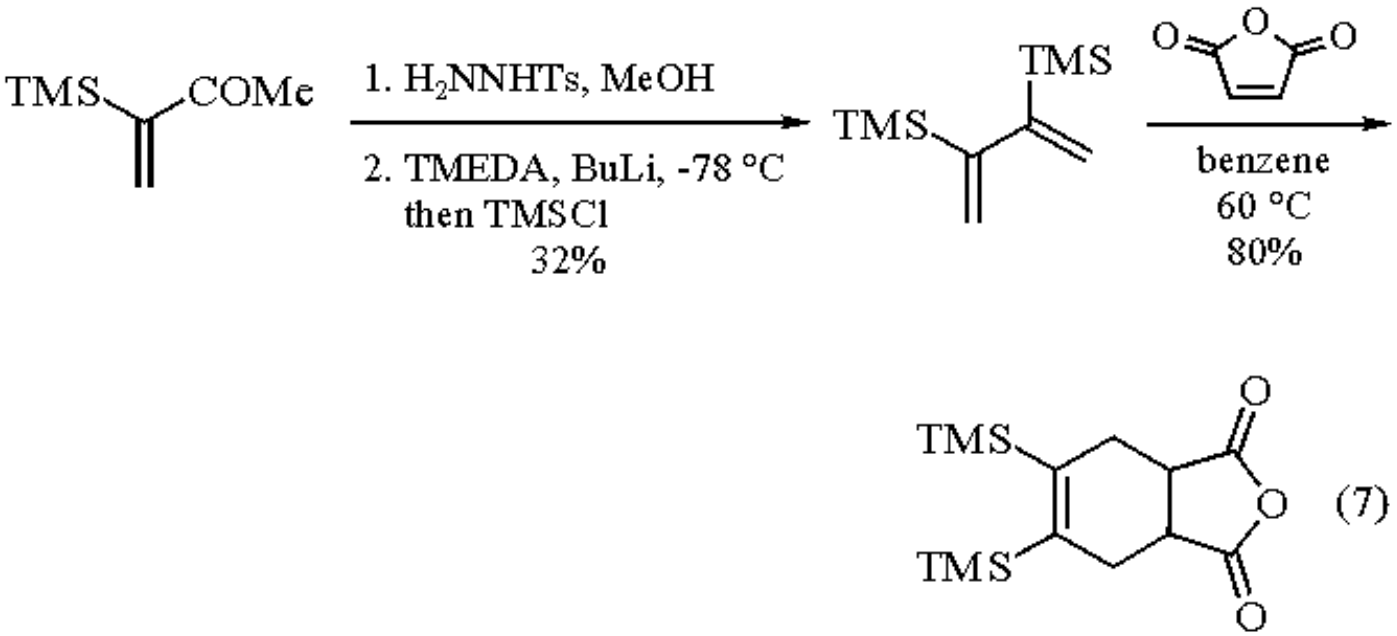

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2. (a) Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. *JCS(P1)* **1986**, 837. (b) Bonnert, R. V.; Jenkins, P. R. *CC* **1987**, 6. (c) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *JACS* **1988**, *110*, 1985. (d) Rigby, J. H.; Kierkus, P. C.; Head, D. *TL* **1989**, *30*, 5073. (e) Paquette, L. A.; Sauer, D. R.; Cleary, D. G.; Kinsella, M. A.; Blackwell, C. M.; Anderson, L. G. *JACS* **1992**, *114*, 7375.
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13. Hagiwara, H.; Akama, T.; Okano, A.; Uda, H. *CL* **1988**, 1793.

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9-[1-(Trimethylsilyl)-2(*E*)-butenyl]-9-borabicyclo[3.3.1]nonane

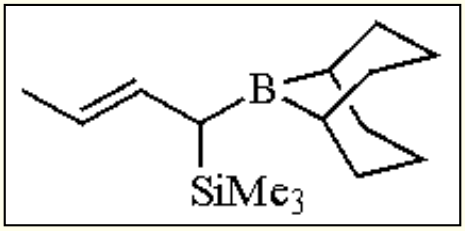

[100701-75-5] · $C_{15}H_{29}BSi$ · 9-[1-(Trimethylsilyl)-2(*E*)-butenyl]-9-borabicyclo[3.3.1]nonane · (MW 248.34)

(*anti*-(*Z*)-selective allylation reagent for aldehydes and pyruvates;[2] stereoselective synthesis of (*Z*)-2-butenylsilane[1])

Alternate Name: 9-trimethylsilylcrotyl-9-borabicyclo[3.3.1]nonane.

Physical Data: bp 85-87 °C/0.03 mmHg.

Solubility: sol most organic solvents.

Preparative Methods: prepared as described by Yatagai et al.[1]

Handling, Storage, and Precautions: the neat liquid must be handled and stored in the absence of air. May be kept as CH_2Cl_2 or THF solutions under a N_2 atmosphere. Use in a fume hood.

Anti-(*Z*)-Selective Crotylation of Aldehydes.

The reaction of α-trimethylsilyl-substituted crotyl-9-BBN with aldehydes in the presence of ***Pyridine*** affords *anti*-homoallyl alcohols having (*Z*) double bond geometry (eq 1).[2] The use of 1 or 2 equiv of pyridine is essential to obtain high stereoselectivity. Without pyridine, a complex mixture of products, coupled both at the α- and γ-position of the crotyl reagent, are obtained. Perhaps pyridine coordinates the boron atom to form the corresponding ate complex, which prevents allylic rearrangement of the crotylboron. The reaction with aldehydes proceeds through a six-membered chair transition state in which the trimethylsilyl group adopts an axial position, giving (*Z*) geometry of the double bond in the homoallyl alcohol products. The *anti*-(*Z*)-alkenylsilanes thus obtained are useful for the further elaboration of complex molecules. For example, epoxidation with ***m-Chloroperbenzoic Acid*** proceeds with high diastereoselectivity to give the corresponding epoxides in good yield (eq 2).

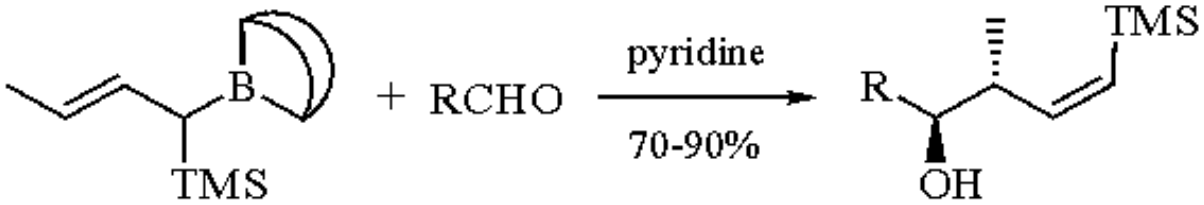

(1)

R = Ph, Bu, PhCH=CH

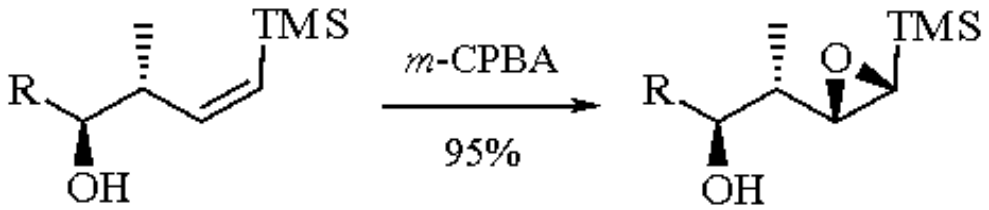

(2)

The reaction of methyl pyruvate with α-silyl-substituted crotyl-9-BBN gives the *anti*-(*Z*)-adduct as a single diastereoisomer in 60% yield along with the α-adduct (35%) (eq 3).[3] ***n-Butyllithium*** is used instead of pyridine for converting the crotylboron reagent to the corresponding ate complex. The *anti*-(*Z*)-adduct can be converted into *cis*-crobarbatic acid methyl ester via the procedure[4] of Magnus (eq 4). The reaction of simple crotyl-9-BBN with pyruvates produces the *anti*-isomers either predominantly or exclusively. The *anti* diastereoselectivity can be improved by increasing the steric bulk of the ester groups; *anti*/*syn* = 73:27 in the case of the methyl ester, whereas the ratio becomes 100:0 in the case of the 2,6-di-*t*-butyl-4-methylphenyl ester. However, as mentioned above, the α-silyl-substituted crotyl-9-BBN produces a 100:0 selectivity even in the case of the methyl ester.

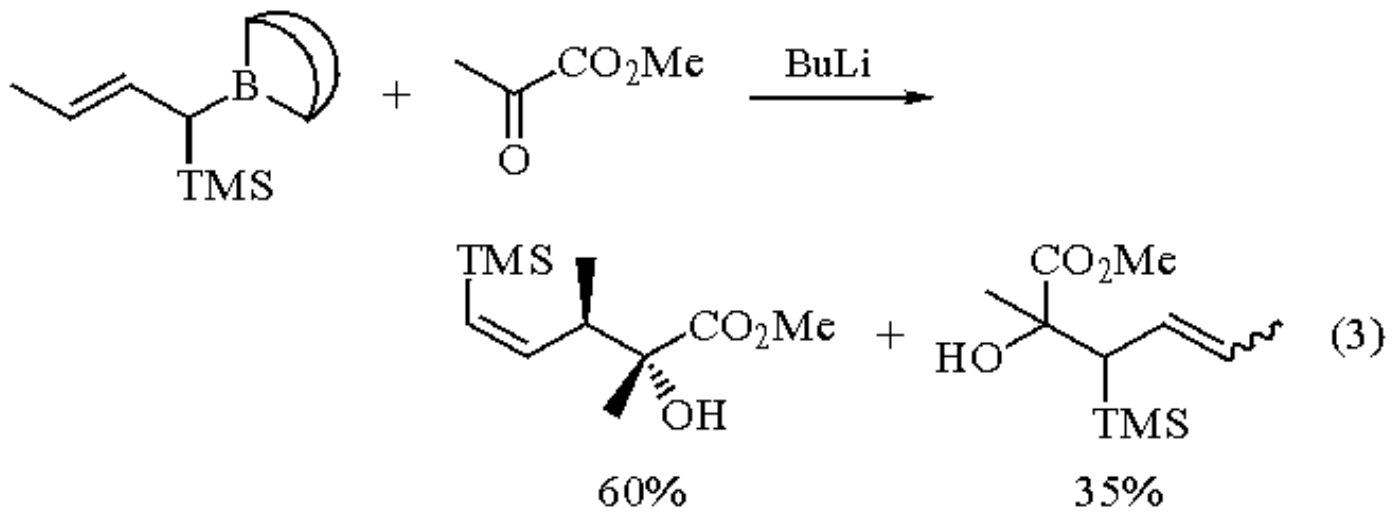

(3)

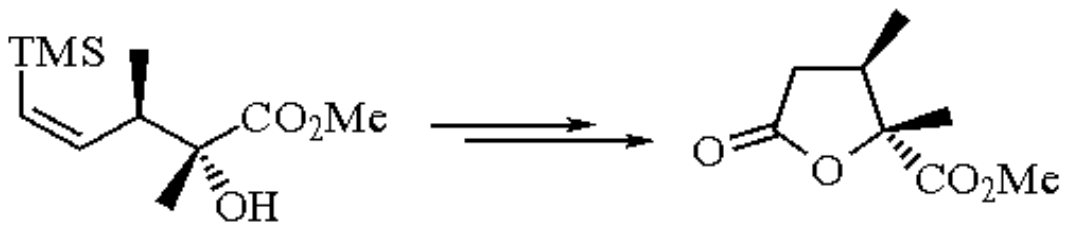

(4)

α-Trimethylstannylallyl-9-BBN, prepared by a procedure similar to the synthesis of α-trimethylsilylallyl-9-BBN, also exhibits *anti*-(*Z*) diastereoselectivity in reactions with aldehydes and pyruvates, as observed in the case of the silyl reagent.

Synthesis of (*Z*)-2-Alkenylsilanes.

Protonolysis of 2-alkenyl-1-trimethylsilyl-9-BBN affords (*Z*)-2-alkenylsilanes with high stereoselectivity (eq 5).[1] Similarly, protonolysis of 2-alkenyl-1-trimethylstannyl-9-BBN gives (*Z*)-2-alkenylstannanes.

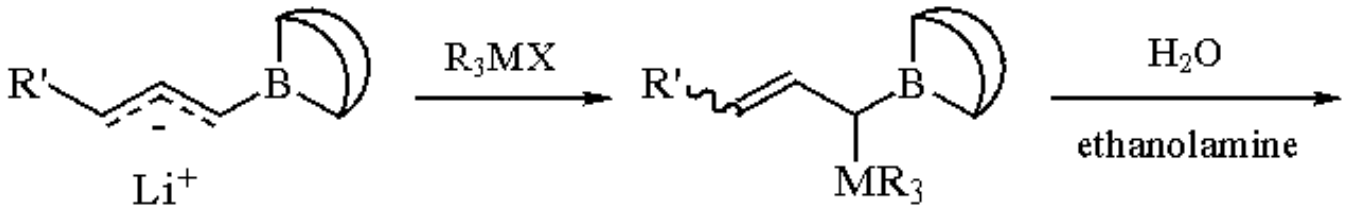

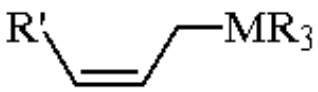

(5)

$R_3M = Me_3Si, Me_3Sn, Bu_3Sn$

Related Reagents.

B-Allyl-9-borabicyclo[3.3.1]nonane.

1. Yatagai, H.; Yamamoto, Y.; Maruyama, K. *JACS* **1980**, *102*, 4548.
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4. Ehlinger, E.; Magnus, P. *JACS* **1980**, *102*, 5004.

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Trimethylsilyl-*t*-butylamine

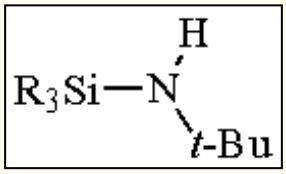

(R = Me)

[5577-67-3] · $C_7H_{19}NSi$ · Trimethylsilyl-*t*-butylamine · (MW 145.36) (R = Et)

[17940-20-4] · $C_{10}H_{25}NSi$ · *t*-Butyldimethylsilyl-*t*-butylamine · (MW 187.45) (R_3Si = $MePh_2Si$)

[91308-43-9] · $C_{17}H_{23}NSi$ · Methyldiphenylsilyl-*t*-butylamine · (MW 269.50) (R_3Si = *t*-$BuMe_2Si$)

[93066-37-6] · $C_{10}H_{25}NSi$ · Triethylsilyl-*t*-butylamine · (MW 187.45)

(precursor of a strong, hindered base for the regioselective deprotonation of unsymmetrical ketones;[1] the derived lithium amide reacts with chloromethyl ethers to give alkoxymethylamines, which can be converted to substituted *t*-butylamines[2])

Physical Data: R = Me: bp 119 °C; *n*20D 1.4076; d^{20} 0.574 g cm^{-3};[3] pK_a 33.1 (cf. 35 for dialkylamines).[4] R = Et: bp 101 °C. R_3Si = $MePh_2Si$: bp 109 °C/0.4 mmHg. R_3Si = *t*-$BuMe_2Si$: bp 84 °C/27 mmHg.

Solubility: sol most organic solvents; reacts with protic solvents. The derived lithium trialkylsilyl-*t*-butylamides have solubilities similar to, or greater than, those of lithium diisopropylamide, with THF or THF/hexane being excellent solvents.

Form Supplied in: not commercially available; best prepared immediately prior to use.

Preparative Methods: these lithium reagents are prepared by the reaction of the parent amines with ***n-Butyllithium*** in THF/hexane. The parent amines are prepared by the reaction of lithium *t*-butylamide and the corresponding chlorosilanes (eq 1). Trimethylsilyl-*t*-butylamine can be prepared by the reaction of ***t-Butylamine*** and ***Chlorotrimethylsilane*** (eq 2).[2,3]

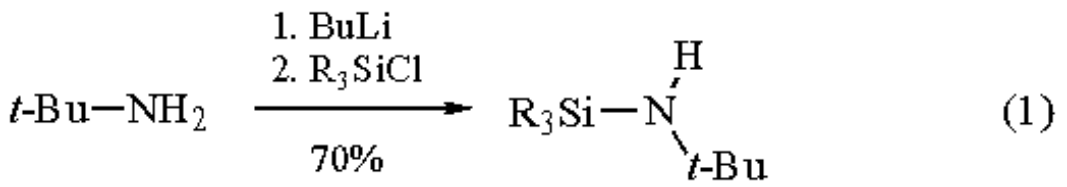

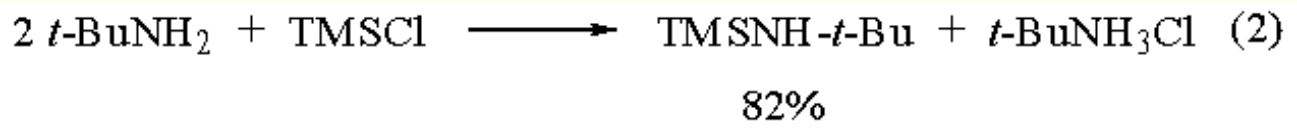

Purification: best purified by distillation.

Handling, Storage, and Precautions: aminosilanes react readily with protic solvents, especially water, and must be maintained in a dry environment. They are thermally stable. Use in a fume hood.

Deprotonation of Unsymmetrical Ketones.

The lithium amides of hindered amines have been employed with great success in the deprotonation of aldehydes, ketones, esters, lactones, amides, and lactams.[5] In the search for greater regio- and stereoselectivity, more hindered systems have been sought.[6] The trialkylsilyl-*t*-butylamines are readily prepared and their lithium reagents are strong bases with high regioselectivity in the deprotonation of unsymmetrical ketones. The results of a study of the deprotonation of six representative unsymmetrical ketones as outlined in eq 3 are given in Table 1.

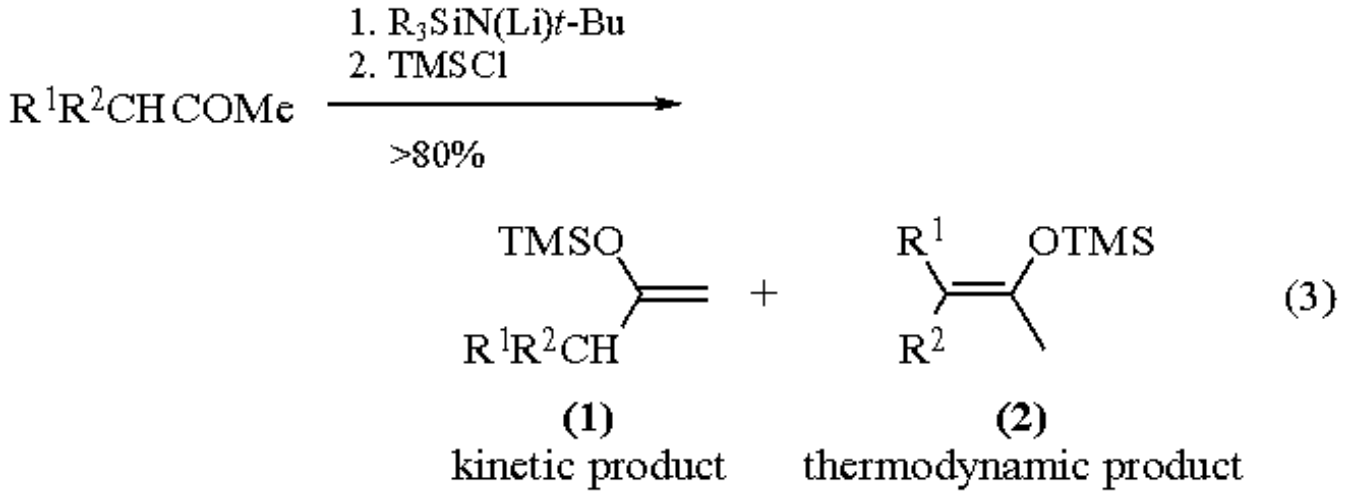

Table 1 Regiospecificity of Deprotonation of Unsymmetrical Ketones According to eq 3[a]

Ketone	LDA	Ratio of kinetic enolate (**1**) to thermodynamic enolate (**2**) (**3a**)	(**3b**)	(**3c**)	(**3d**)
2-Heptanone	93:7	98:2	98:2	92:8	96:4
Phenylacetone	34:66	25:75	48:52	62:38	18:82
3-Methyl-2-pentanone	>99:1	96:4	99:1	98:2	>99:1
4-Methyl-2-pentanone	97:3	97:3	99:1	99:1	97:3
2-Methylcyclohexanone	98:2	>99:1	97:3	>99:1	>99:1
Trimethylsilylacetone	81:19	98:2	97:3	>99:1	>99:1

[a] (**3a**) lithium trimethylsilyl-*t*-butylamide; (**3b**) lithium triethylsilyl-*t*-butylamide; (**3c**) lithium *t*-butyldimethylsilyl-*t*-butylamide; (**3d**) lithium methyldiphenylsilyl-*t*-butylamide.

As can be seen from the data presented in Table 1, the lithium trialkylsilyl-*t*-butylamides are excellent hindered bases for the stereospecific deprotonation of unsymmetrical ketones. Of particular interest is the increased ability of these bases to provide the kinetic enolate of phenylacetone, where the thermodynamic enolate benefits from the presence of the phenyl group. Also of interest is the effect of the trimethylsilyl group in ***Trimethylsilylacetone***, where the selectivity is very high with the silylated amides as opposed to that of LDA. This effect of the trimethylsilyl group in the ketone is presumably due to the fact that the steric effect of the silyl group and its longer bond in the silyl amides better matches that of the longer C-Si bond in trimethylsilylacetone.

Preparation of Substituted *t*-Butylamines.

The reaction of lithium trimethylsilyl-*t*-butylamide with chloromethyl ethers gives alkoxymethylamines (eq 4). Organomagnesium, -aluminum, or -zinc reagents react to give nucleophilic displacement of the alkoxy group, providing substituted amines (eqs 5 and 6), which after desilylation can give substituted *t*-butylamines.[2]

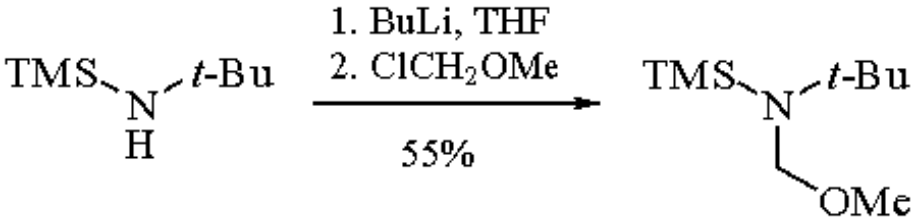

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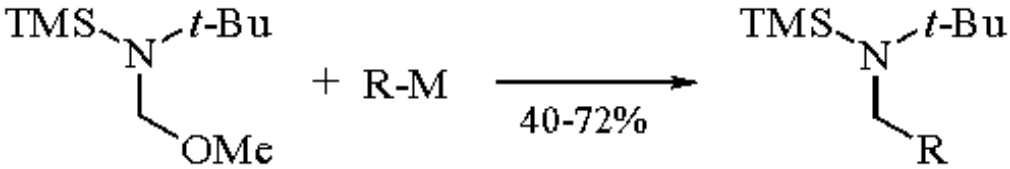

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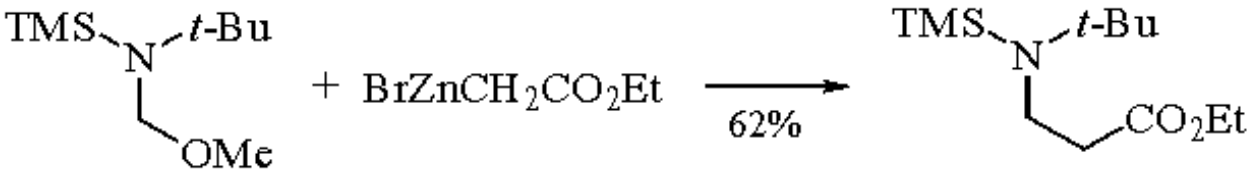

(6)

Related Reagents.

Diisopropylamine; ***Hexamethyldisilazane***.

---

1. Prieto, J. A.; Suarez, J.; Larson, G. L. *SC* **1988**, *18*, 253.
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6. Corey, E. J.; Gross, A. W. *TL* **1984**, *25*, 495.

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Trimethylsilylcopper[1]

Me_3SiCu

[91899-54-6] · C_3H_9CuSi · Trimethylsilylcopper · (MW 136.76)

(nucleophilic silylmetal reagent useful for the regioselective preparation of allyltrimethylsilanes from allylic halides,[2-4] allylic sulfonates,[4] and allylic phosphates[5])

Preparative Method: prepared in situ by adding 1 equiv of ***Copper(I) Iodide*** dissolved in dimethyl sulfide (2.5 M solution) to a vigorously stirred solution of 1 equiv of ***Trimethylsilyllithium***[6] (prepared from hexamethyldisilane and methyllithium-lithium bromide complex) in HMPA at 0-5 °C under argon.[2] The reagent is used immediately in silylation reactions.

Handling, Storage, and Precautions: prepared and used under dry air-free conditions (argon atmosphere, dry solvents, etc.). Since reactions with this reagent employ HMPA (a carcinogen) as solvent, suitable precautions should be taken. Use in a fume hood.

Silylcopper Reagents.[1]

Trimethylsilylcopper (TMSCu) is one of the many silylcopper reagents which were developed in the 1980s and used in the synthesis of allylsilanes from various allylic substrates. Other well-studied silylcopper reagents include $(Me_3Si)_2CuLi$,[7] $(Me_3Si)Cu(CN)Li$,[8] $(PhMe_2Si)_2CuLi$,[7,9-11] and $(PhMe_2Si)_2Cu(CN)Li_2$.[12-14] In all cases, these reagents are prepared in situ from 1 equiv of a silyllithium reagent (Me_3SiLi or $PhMe_2SiLi$) by reaction with 0.5-1.0 equiv of copper(I) iodide or copper(I) cyanide.

Synthesis of Allylsilanes.

TMSCu reacts with a variety of allylic substrates to form allylsilanes stereoselectively and in good to excellent yields. Thus the reagent reacts readily with primary allylic halides,[2-4] sulfonates from secondary and tertiary alcohols,[4] and primary and secondary allylic phosphates[5] to yield a variety of allylsilanes. Representative examples of these reactions are shown in eqs 1-3. This methodology seems particularly attractive for the synthesis of 3-trimethylsilyl-1-alkenes which are presently unavailable by other methods. For example, (*E*)-8-*t*-butyldiphenylsilyloxy-2,6-dimethyl-3-trimethylsilyl-1,6-octadiene, a key intermediate in Corey's synthesis of tricyclohexaprenol, has been prepared from a primary allylic chloride using this methodology (eq 4).[15] Moreover, this method has been used in the preparation of 2,3-bis(trimethylsilyl)alk-1-enes (eq 5)[4] and ***(2-Bromoallyl)trimethylsilane*** (eq 6),[2] a useful intermediate in organic synthesis.[8]

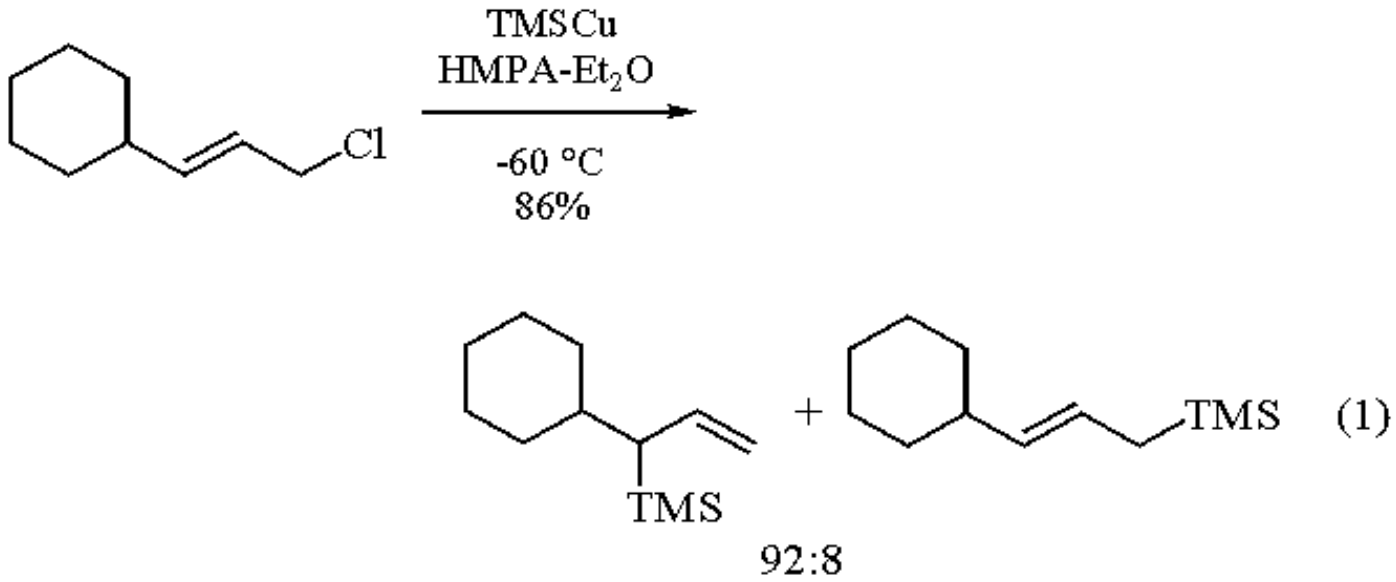

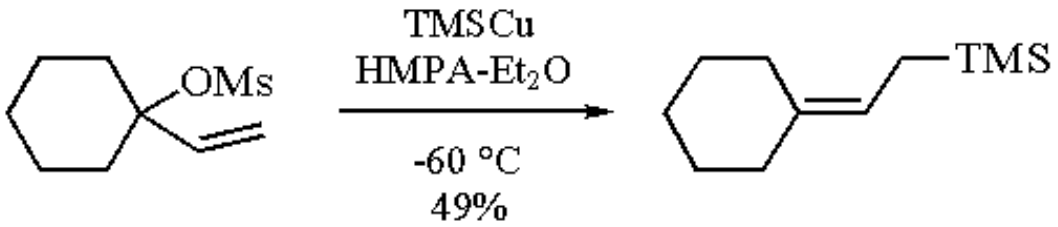

(2)

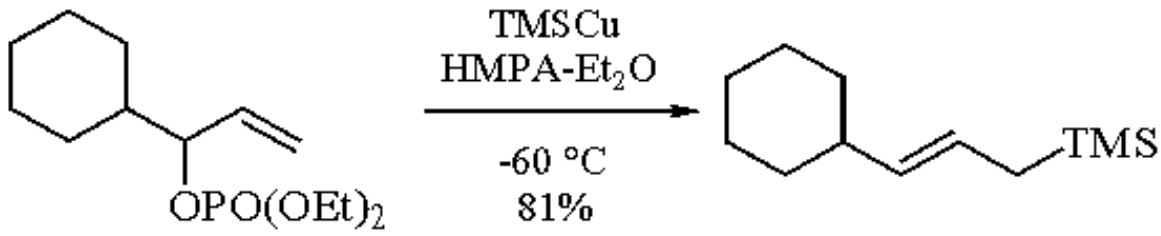

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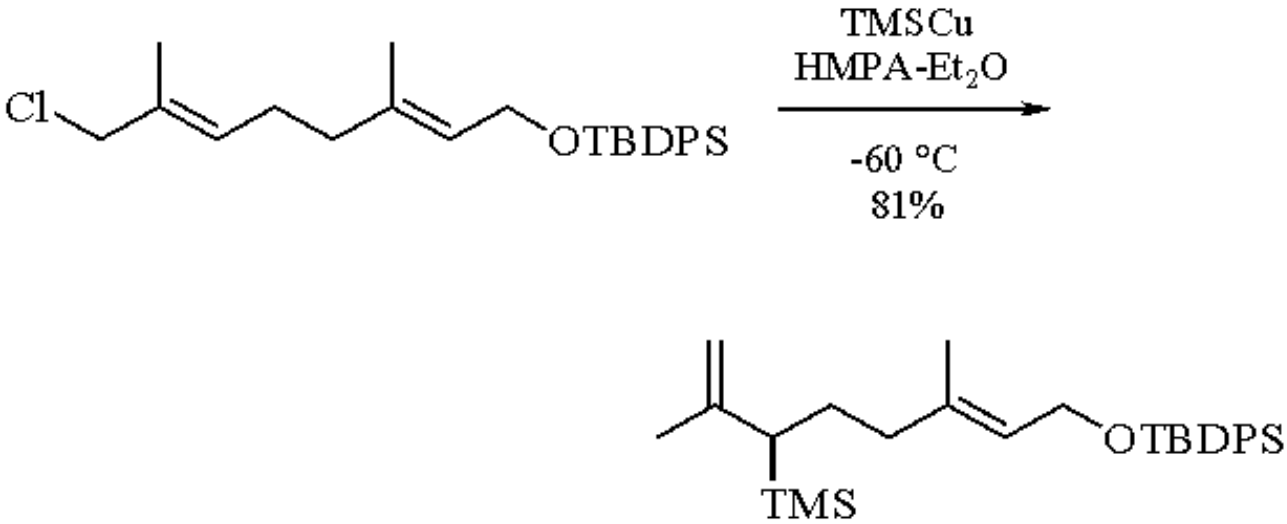

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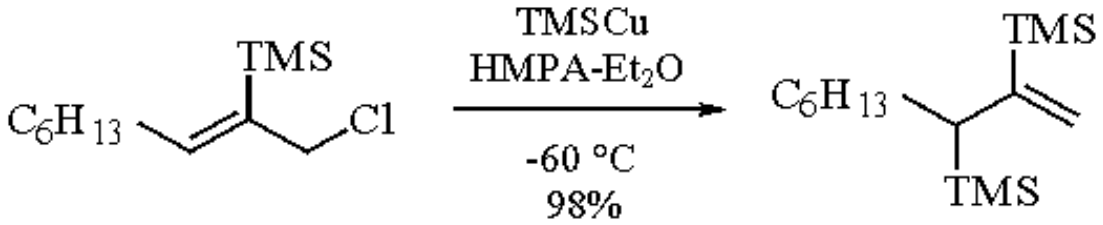

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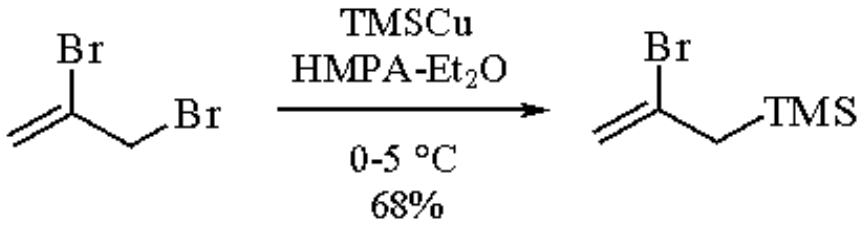

(6)

The reactions of TMSCu are in marked contrast to the reactions of ***Trimethylsilyllithium*** with similar substrates.[3,4] Whereas treatment of a 1-chloro-2-alkene with TMSCu affords a 3-trimethylsilyl-1-alkene, reaction of TMSLi with these same starting materials yields terminal (*E*)-allylsilanes where the stereochemistry of the double bond is retained in the product (eq 7). Thus a single allylic halide yields either of two regioisomers by proper choice of reaction conditions. With allylic phosphates, TMSCu affords as major product the allylsilane resulting from attack by what is formally an S_N2'-like reaction. With TMSLi, however, the major product is always the isomeric allylsilane having a more substituted internal double bond (eq 8).

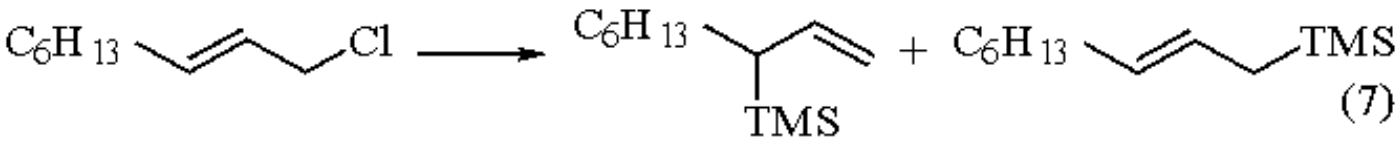

TMSCu 87% 98:2
TMSLi 78% 0:100

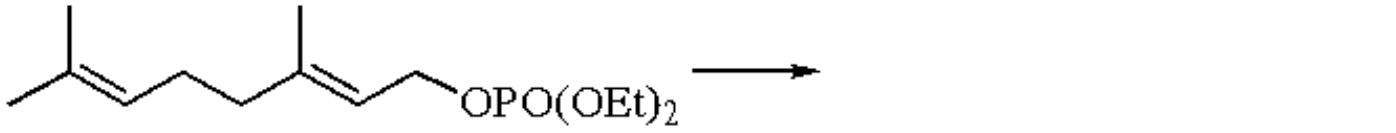

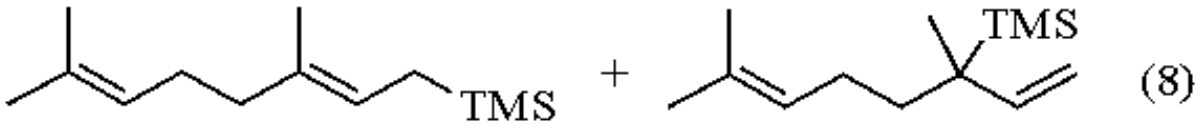

TMSCu 92% 25:75
TMSLi 69% 100:0

Other silylcuprate reagents have also been used to prepare allylsilanes from allylic halides,[10] acetates,[11,13] and urethanes.[13c,14,16] Moreover, other silylmetal reagents have been used in similar preparations of allylsilanes. For example, silylaluminum reagents have been used to prepare allylsilanes from allylic acetates[17] and allylic phosphates,[18] and silylmanganese reagents react with allylic sulfides and allylic ethers.[19] One advantage that the present methodology has over many other methods is that it utilizes a *trimethyl*silylmetal reagent to afford an allyl*trimethyl*silane. The silyl byproducts obtained in the preparation and reaction of these allylsilanes are volatile and easily separable from the desired product. Many of the other existing methods yield allylsilanes where one or more of the alkyl groups on the silicon is replaced by phenyl.

Related Reagents.

Lithium Cyano(dimethylphenylsilyl)cuprate; ***Trimethylsilyllithium***.

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19. (a) Fugami, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *TL* **1986**, *27*, 2161. (b) Fugami, K.; Hibino, J.; Nakatsukasa, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *T* **1988**, *44*, 4277.

Trimethylsilyldiazomethane[1]

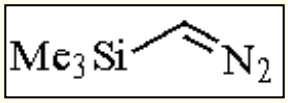

[18107-18-1] · $C_4H_{10}N_2Si$ · Trimethylsilyldiazomethane · (MW 114.25)

(one-carbon homologation reagent; stable, safe substitute for diazomethane; [C-N-N] 1,3-dipole for the preparation of azoles[1])

Physical Data: bp 96 °C/775 mmHg; *n*25D 1.4362.[2]

Solubility: sol most organic solvents; insol H_2O.

Form Supplied in: commercially available as 2 M and 10 w/w% solutions in hexane, and 10 w/w% solution in CH_2Cl_2.

Analysis of Reagent Purity: concentration in hexane is determined by ^1H NMR.[3]

Preparative Method: prepared by the diazo-transfer reaction of ***Trimethylsilylmethylmagnesium Chloride*** with ***Diphenyl Phosphorazidate*** (DPPA) (eq 1).[3]

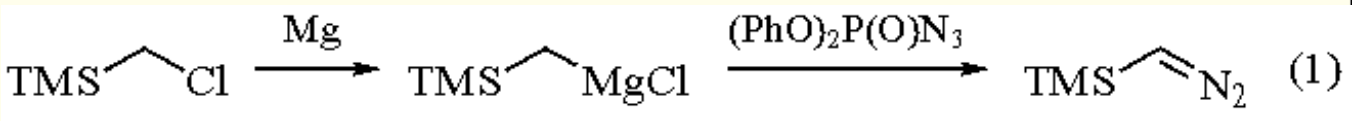

Handling, Storage, and Precautions: should be protected from light.

One-Carbon Homologation.

Along with its lithium salt, which is easily prepared by lithiation of trimethylsilyldiazomethane ($TMSCHN_2$) with ***n-Butyllithium***, $TMSCHN_2$ behaves in a similar way to ***Diazomethane*** as a one-carbon homologation reagent. $TMSCHN_2$ is acylated with aromatic acid chlorides in the presence of ***Triethylamine*** to give α-trimethylsilyl diazo ketones. In the acylation with aliphatic acid chlorides, the use of 2 equiv of $TMSCHN_2$ without triethylamine is recommended. The crude diazo ketones undergo thermal Wolff rearrangement to give the homologated carboxylic acid derivatives (eqs 2 and 3).[4]

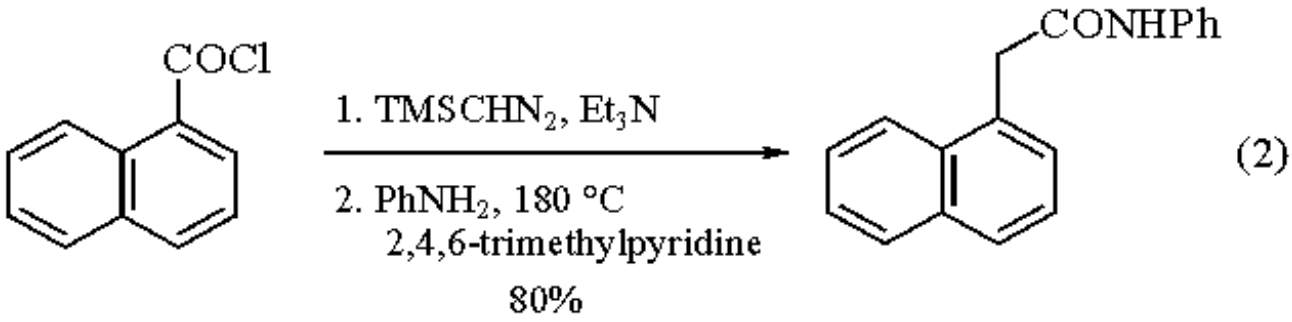

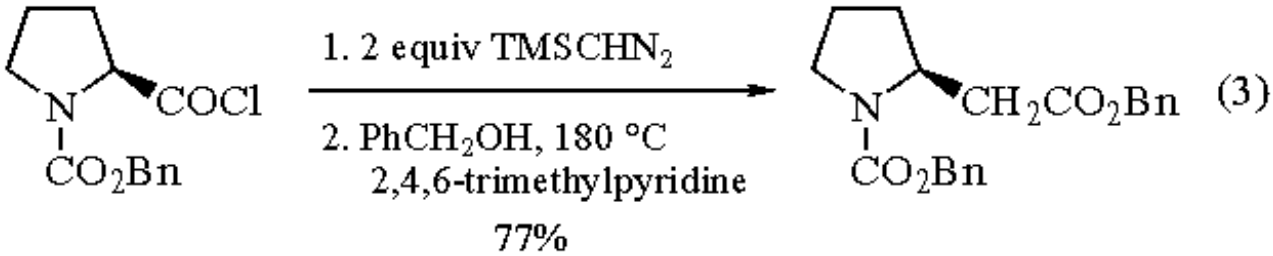

Various ketones react with $TMSCHN_2$ in the presence of ***Boron Trifluoride Etherate*** to give the chain or ring homologated ketones (eqs 4-6).[5] The bulky trimethylsilyl group of $TMSCHN_2$ allows for regioselective methylene insertion (eq 5). Homologation of aliphatic and alicyclic aldehydes with $TMSCHN_2$ in the presence of ***Magnesium Bromide*** smoothly gives methyl ketones after acidic hydrolysis of the initially formed β-keto silanes (eq 7).[6]

$$PhCOCH_2Ph \xrightarrow[\substack{CH_2Cl_2,\ -15\ °C,\ 1\ h \\ 74\%}]{TMSCHN_2,\ BF_3 \cdot Et_2O} PhCOCH_2CH_2Ph \qquad (4)$$

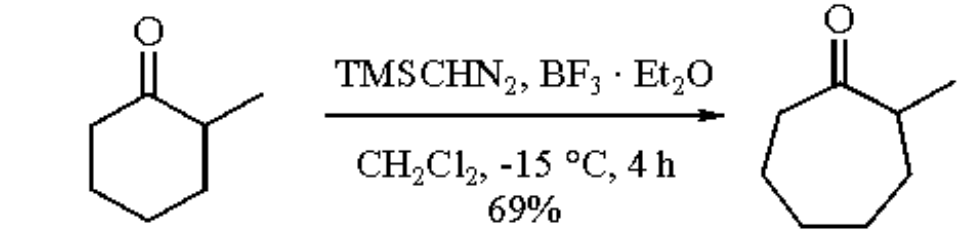

(5)

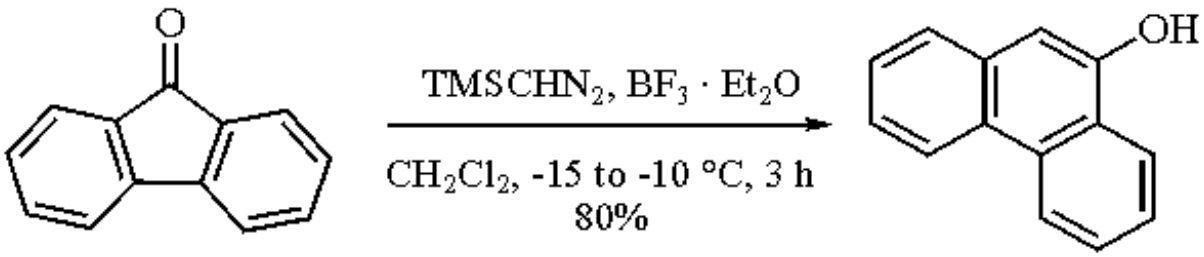

(6)

$$t\text{-}BuCHO \xrightarrow[\substack{2.\ 10\%\ aq\ HCl \\ 89\%}]{1.\ TMSCHN_2,\ MgBr_2} t\text{-}BuCOMe \qquad (7)$$

O-Methylation of carboxylic acids, phenols, enols, and alcohols can be accomplished with $TMSCHN_2$ under different reaction conditions. $TMSCHN_2$ instantaneously reacts with carboxylic acids in benzene in the presence of methanol at room temperature to give methyl esters in nearly quantitative yields (eq 8).[7] This method is useful for quantitative gas chromatographic analysis of fatty acids. Similarly, *O*-methylation of phenols and enols with $TMSCHN_2$ can be accomplished, but requires the use of ***Diisopropylethylamine*** (eqs 9 and 10).[8] Although methanol is recommended in these *O*-methylation reactions, methanol is not the methylating agent. Various alcohols also undergo *O*-methylation with $TMSCHN_2$ in the presence of 42% aq. ***Tetrafluoroboric Acid***, smoothly giving methyl ethers (eq 11).[9]

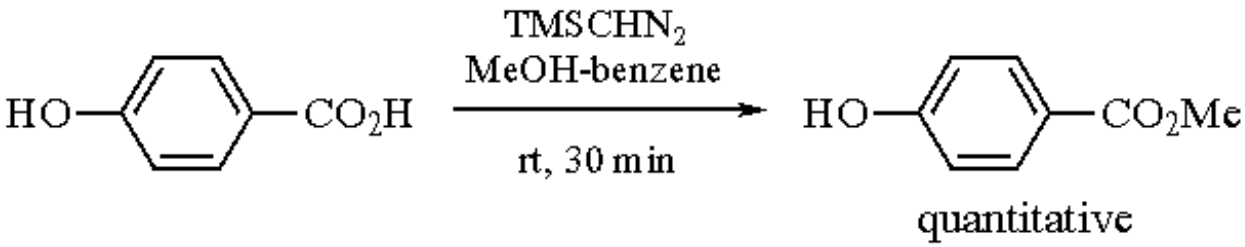

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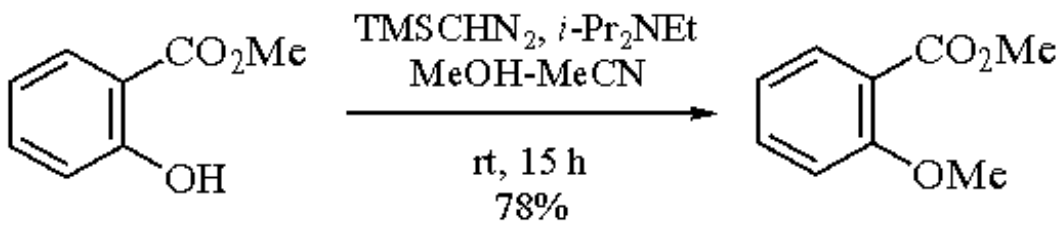

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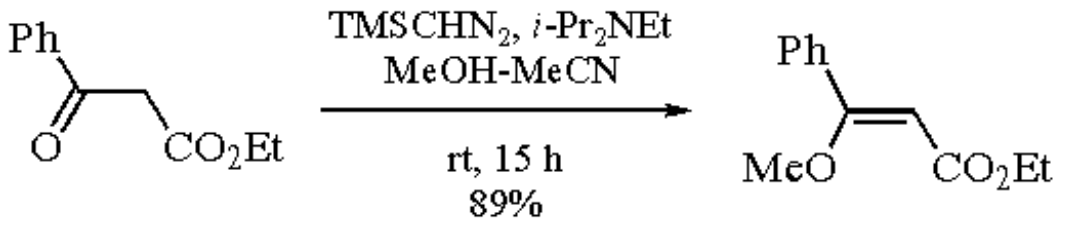

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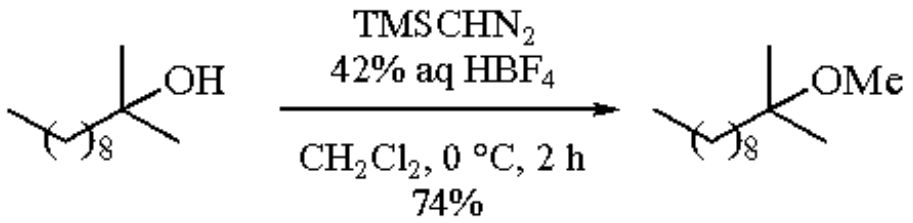

(11)

Alkylation of the lithium salt of $TMSCHN_2$ ($TMSC(Li)N_2$) gives α-trimethylsilyl diazoalkanes which are useful for the preparation of vinylsilanes and acylsilanes. Decomposition of α-trimethylsilyl diazoalkanes in the presence of a catalytic amount of ***Copper(I) Chloride*** gives mainly (*E*)-vinylsilanes (eq 12),[10] while replacement of CuCl with rhodium(II) pivalate affords (*Z*)-vinylsilanes as the major products (eq 12).[11] Oxidation of α-trimethylsilyl diazoalkanes with ***m-Chloroperbenzoic Acid*** in a two-phase system of benzene and phosphate buffer (pH 7.6) affords acylsilanes (α-keto silanes) (eq 12).[12]

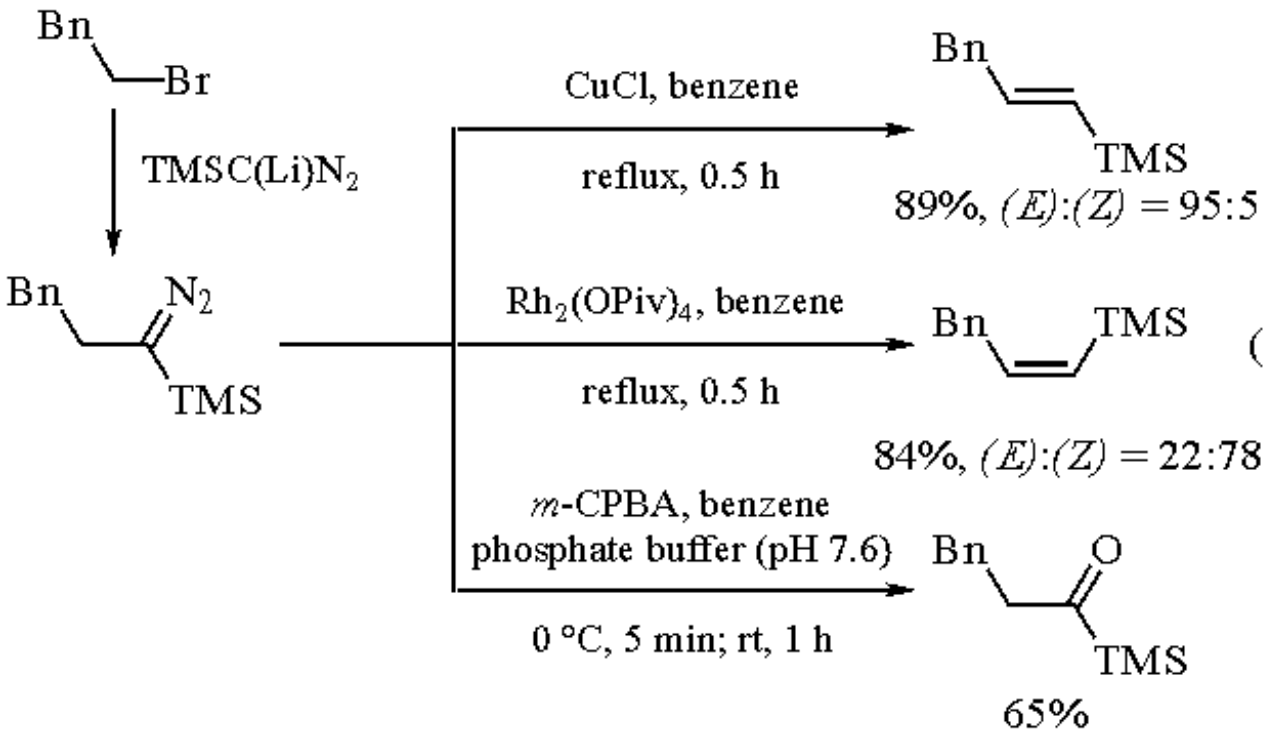

(12)

(*E*)-β-Trimethylsilylstyrenes are formed by reaction of alkanesulfonyl chlorides with $TMSCHN_2$ in the presence of triethylamine (eq 13).[13] $TMSC(Li)N_2$ reacts with carbonyl compounds to give α-diazo-β-hydroxy silanes which readily decompose to give α,β-epoxy silanes (eq 14).[14] However, benzophenone gives diphenylacetylene under similar reaction conditions (eq 15).[15]

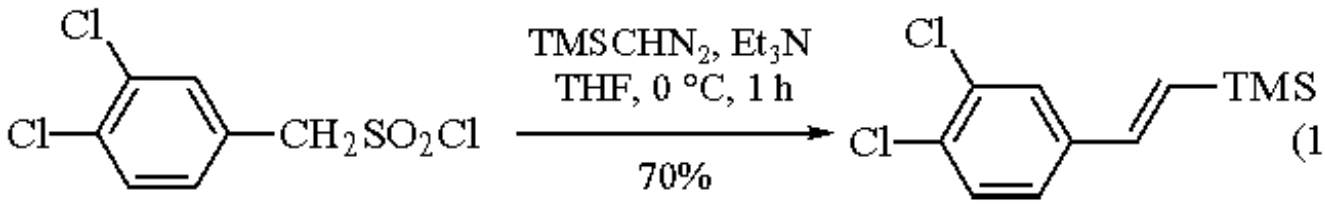

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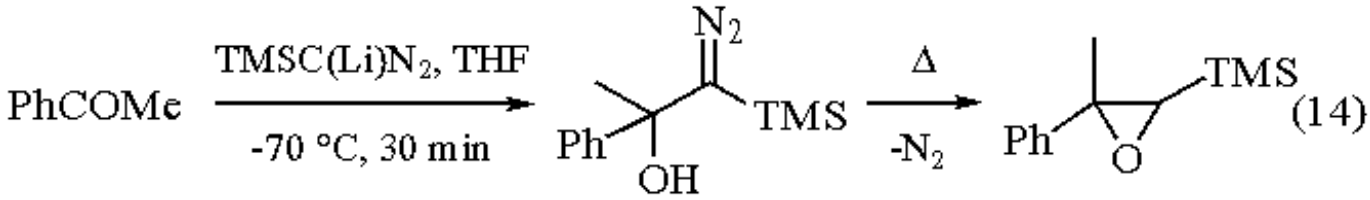

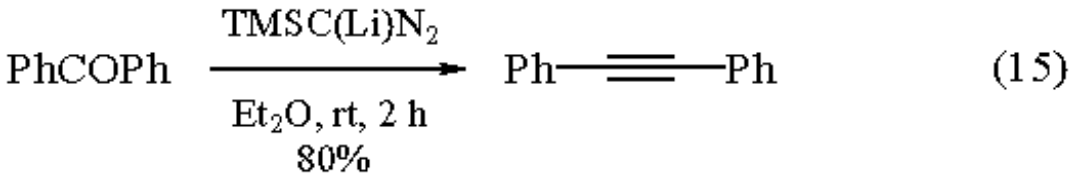

Silylcyclopropanes are formed by reaction of alkenes with $TMSCHN_2$ in the presence of either ***Palladium(II) Chloride*** or CuCl depending upon the substrate (eqs 16 and 17).[16] Silylcyclopropanones are also formed by reaction with trialkylsilyl and germyl ketenes (eq 18).[17]

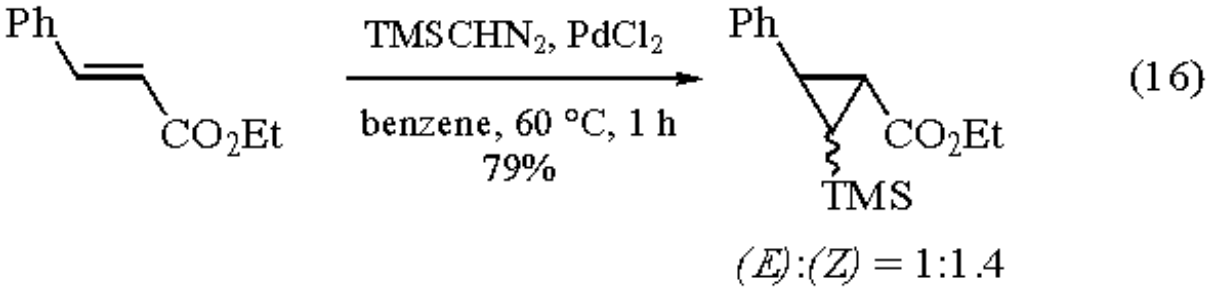

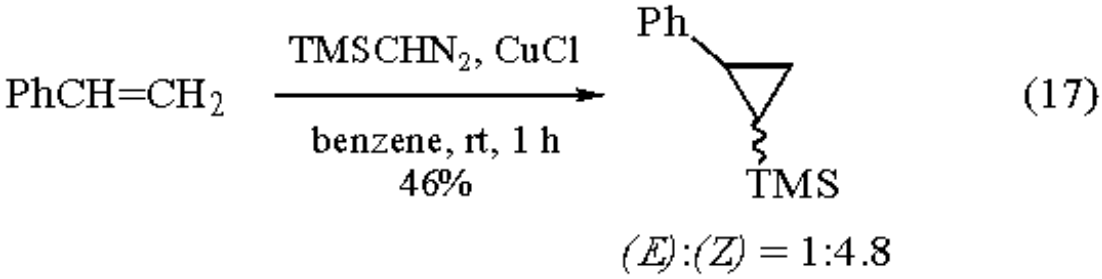

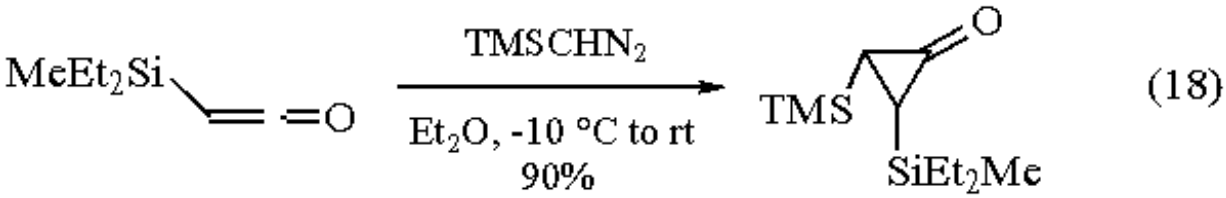

[C-N-N] Azole Synthon.

$TMSCHN_2$, mainly as its lithium salt, $TMSC(Li)N_2$, behaves like a 1,3-dipole for the preparation of [C-N-N] azoles. The reaction mode is similar to that of diazomethane but not in the same fashion. $TMSC(Li)N_2$ (2 equiv) reacts with carboxylic esters to give 2-substituted 5-trimethylsilyltetrazoles (eq 19).[18] Treatment of thiono and dithio esters with $TMSC(Li)N_2$ followed by direct workup with aqueous methanol gives 5-substituted 1,2,3-thiadiazoles (eq 20).[19] While reaction of di-*t*-butyl thioketone with $TMSCHN_2$ produces the episulfide with evolution of nitrogen (eq 21),[20] its reaction with $TMSC(Li)N_2$ leads to removal of one *t*-butyl group to give the 1,2,3-thiadiazole (eq 21).[20]

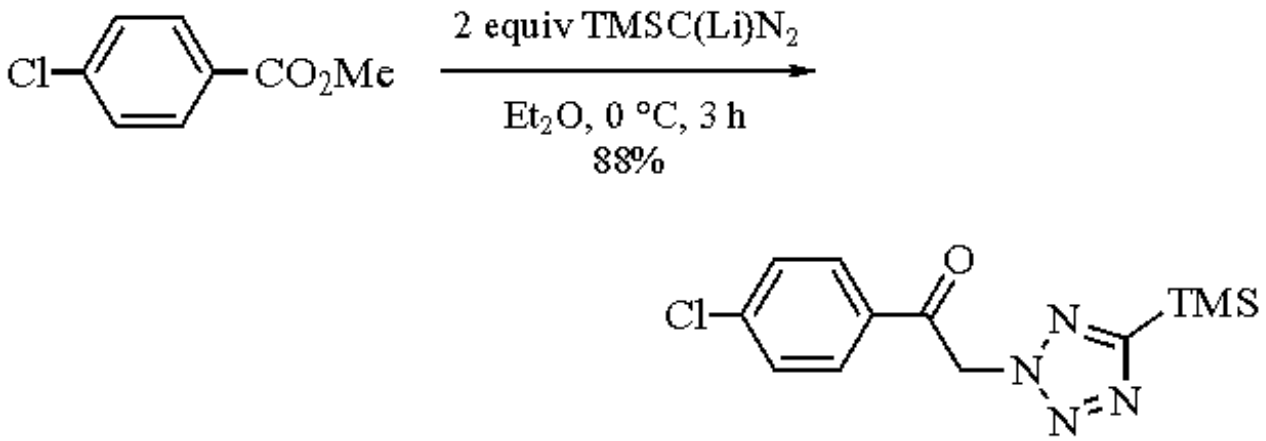

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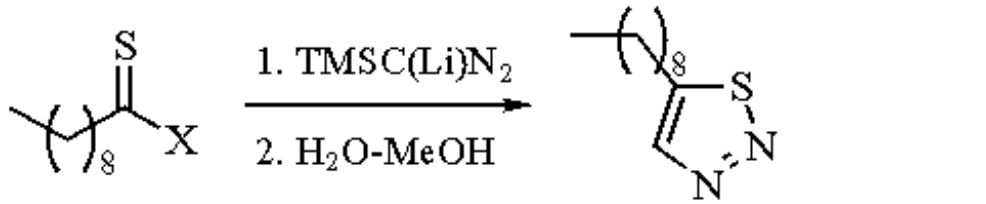

(20)

X = OMe or SMe X = OMe, 79%; SMe, 84%

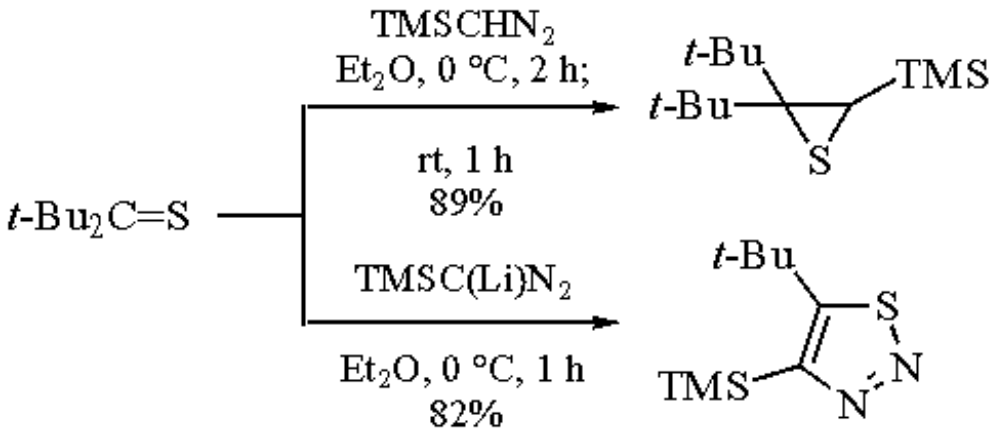

(21)

$TMSCHN_2$ reacts with activated nitriles only, such as cyanogen halides, to give 1,2,3-triazoles.[21] In contrast with this, $TMSC(Li)N_2$ smoothly reacts with various nitriles including aromatic, heteroaromatic, and aliphatic nitriles, giving 4-substituted 5-trimethylsilyl-1,2,3-triazoles (eq 22).[22] However, reaction of α,β-unsaturated nitriles with $TMSC(Li)N_2$ in Et_2O affords 3(or 5)-trimethylsilylpyrazoles, in which the nitrile group acts as a leaving group (eq 23).[23] Although α,β-unsaturated nitriles bearing bulky substituents at the α- and/or β-positions of the nitrile group undergo reaction with $TMSC(Li)N_2$ to give pyrazoles, significant amounts of 1,2,3-triazoles are also formed. Changing the reaction solvent from Et_2O to THF allows for predominant formation of pyrazoles (eq 24).[23] Complete exclusion of the formation of 1,2,3-triazoles can be achieved when the nitrile group is replaced by a phenylsulfonyl species.[24] Thus reaction of α,β-unsaturated sulfones with $TMSC(Li)N_2$ affords pyrazoles in excellent yields (eq 25). The geometry of the double bond of α,β-unsaturated sulfones is not critical in the reaction. When both a cyano and a sulfonyl group are present as a leaving group, elimination of the sulfonyl group occurs preferentially (eq 26).[24] The trimethylsilyl group attached to the heteroaromatic products is easily removed with 10% aq. KOH in EtOH or HCl-KF.

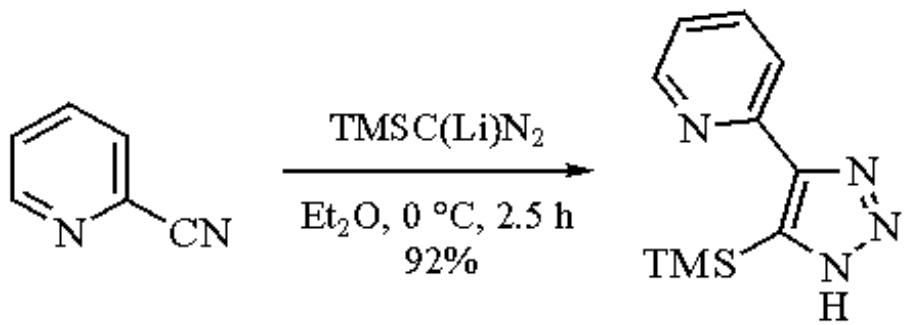

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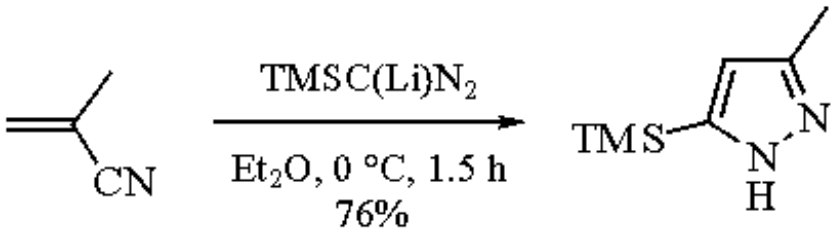

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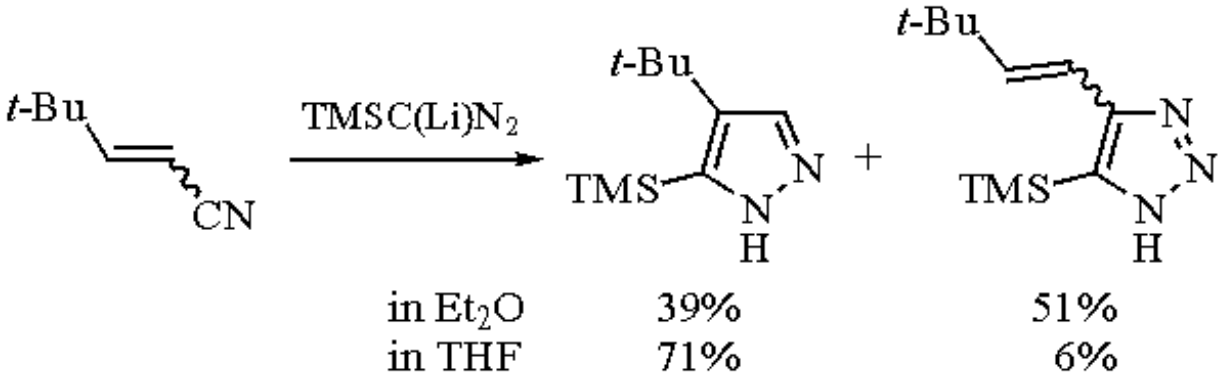

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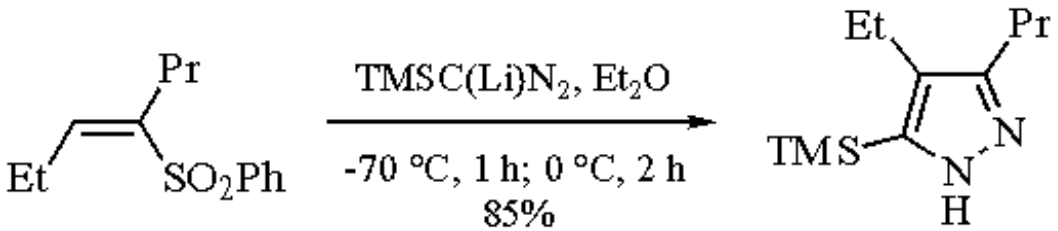

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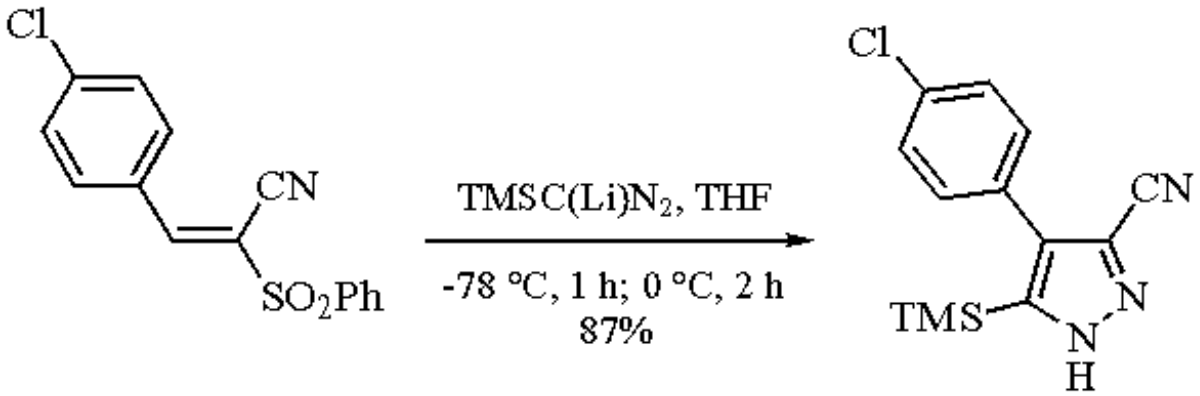

(26)

Various 1,2,3-triazoles can be prepared by reaction of TMSC(Li)N_2 with various heterocumulenes. Reaction of isocyanates with TMSC(Li)N_2 gives 5-hydroxy-1,2,3-triazoles (eq 27).[25] It has been clearly demonstrated that the reaction proceeds by a stepwise process and not by a concerted 1,3-dipolar cycloaddition mechanism. Isothiocyanates also react with TMSC(Li)N_2 in THF to give lithium 1,2,3-triazole-5-thiolates which are treated in situ with alkyl halides to furnish 1-substituted 4-trimethylsilyl-5-alkylthio-1,2,3-triazoles in excellent yields (eq 28).[26] However, changing the reaction solvent from THF to Et_2O causes a dramatic solvent effect. Thus treatment of isothiocyanates with TMSC(Li)N_2 in Et_2O affords 2-amino-1,3,4-thiadiazoles in good yields (eq 28).[27] Reaction of ketenimines with TMSC(Li)N_2 smoothly proceeds to give 1,5-disubstituted 4-trimethylsilyl-1,2,3-triazoles in high yields (eq 29).[28] Ketenimines bearing an electron-withdrawing group at one position of the carbon-carbon double bond react with TMSC(Li)N_2 to give 4-aminopyrazoles as the major products (eq 30).[29]

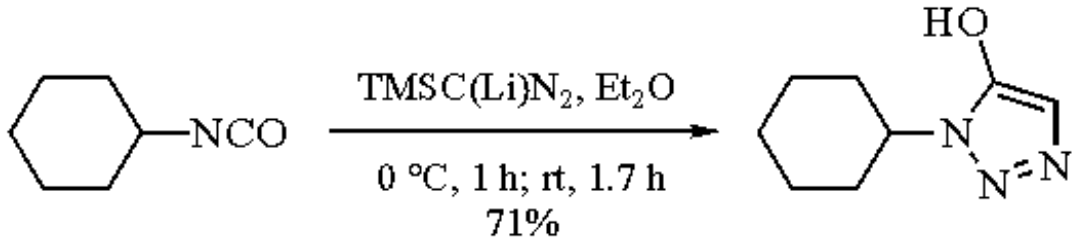

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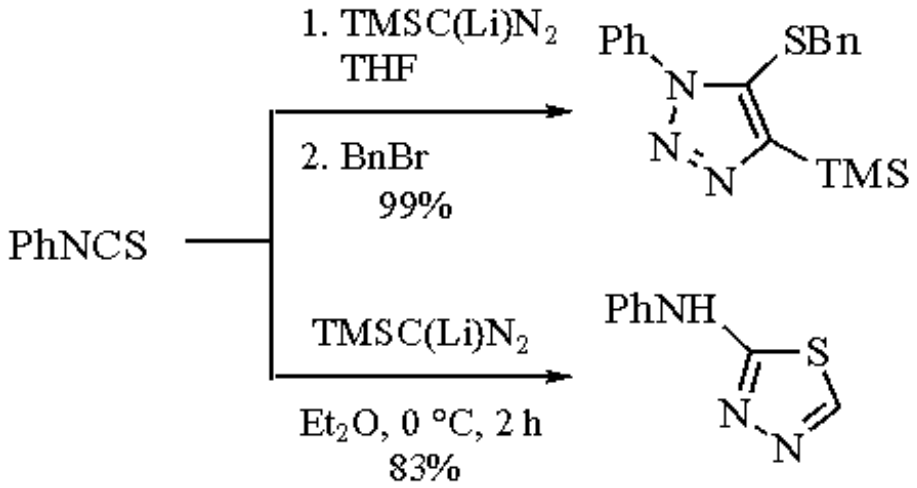

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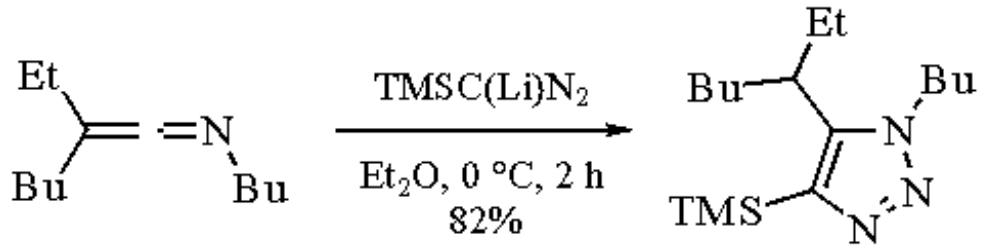

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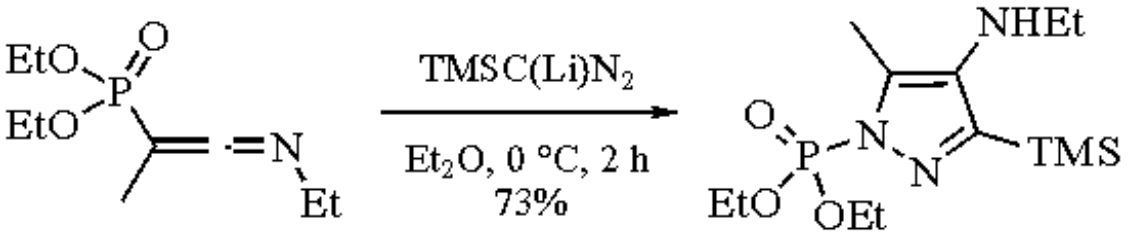

(30)

Pyrazoles are formed by reaction of $TMSCHN_2$ or $TMSC(Li)N_2$ with some alkynes (eqs 31 and 32)[24,30] and quinones (eq 33).[31] Some miscellaneous examples of the reactivity of $TMSCHN_2$ or its lithium salt are shown in eqs 34-36.[20,31,32]

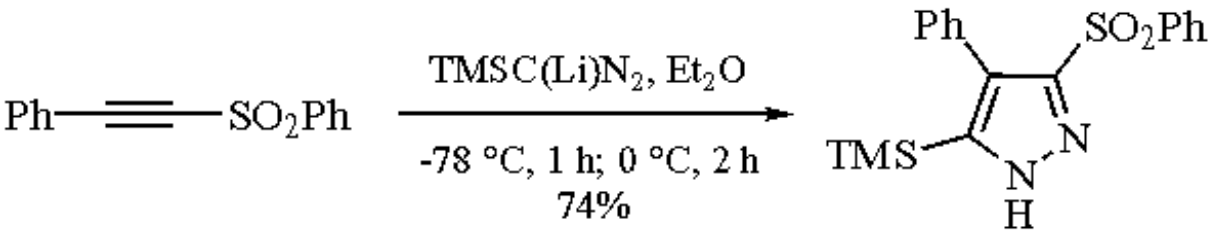

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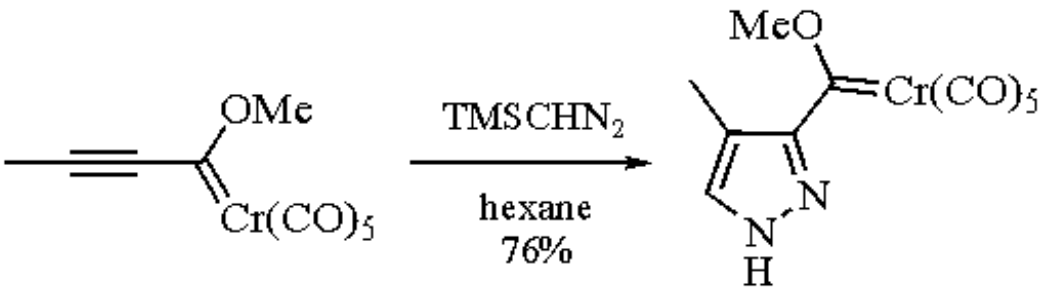

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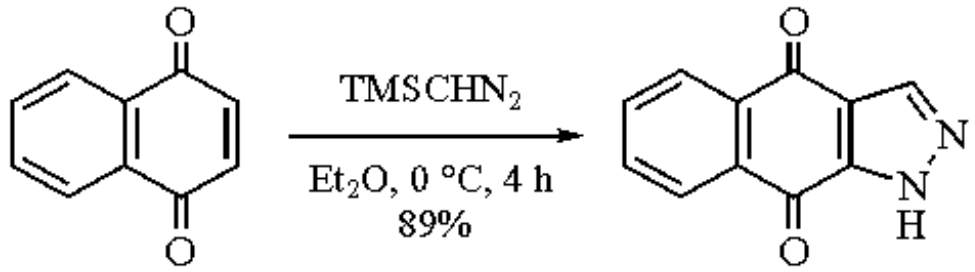

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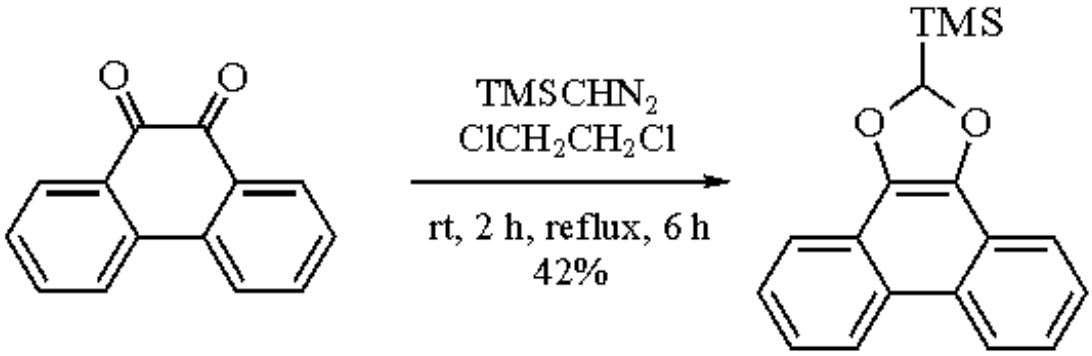

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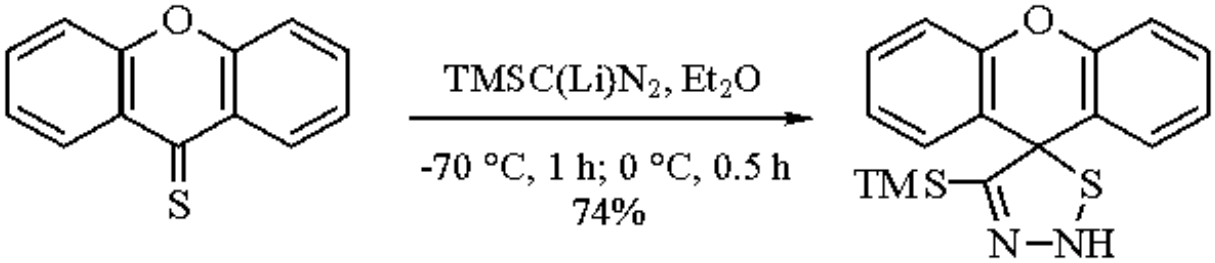

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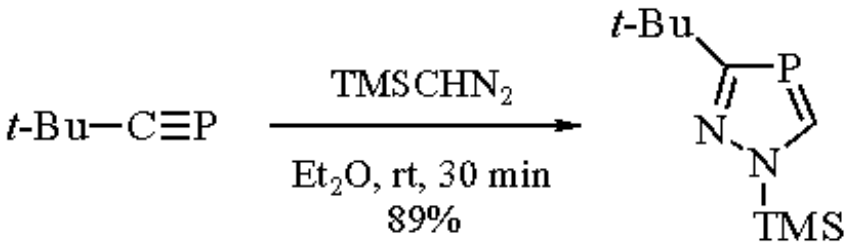

(36)

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Trimethylsilyldiethylamine[1]

Me_3SiNEt_2

[996-50-9] · $C_7H_{19}NSi$ · Trimethylsilyldiethylamine · (MW 145.36)

(selective electrophilic trimethylsilyl source;[2] nucleophilic source of the diethylamino group[3])

Physical Data: bp 127-129 °C; *d* 0.767 g cm^{-3}; *n*20D 1.4110.

Solubility: sol pentane, hexane, acetonitrile, ether, THF, acetone.

Form Supplied in: liquid; commercially available.

Analysis of Reagent Purity: NMR, GC.

Preparative Methods: prepared by reaction of diethylamine with ***Chlorotrimethylsilane***,[4] ***Hexamethyldisilazane***,[5] or ***Cyanotrimethylsilane***.[6]

Purification: distillation.

Handling, Storage, and Precautions: stable indefinitely when maintained in a dry environment; destroyed by water.

Trimethylsilyl Group Transfer.

The major use of this reagent has been in the protection of functional groups (particularly hydroxyl) as the trimethylsilyl derivatives. This is illustrated in work on brefeldin A (eq 1)[7] and in the synthesis of prostaglandin E_2 methyl ester (eq 2), where selective protection of two hydroxyl groups occurred.[2] In addition, axial alcohols are converted into trimethylsilyl ethers much faster than equatorial alcohols.[8] Another multifunctional molecule which has been protected is the alcohol produced by cleaving the enone shown in eq 3.[9]

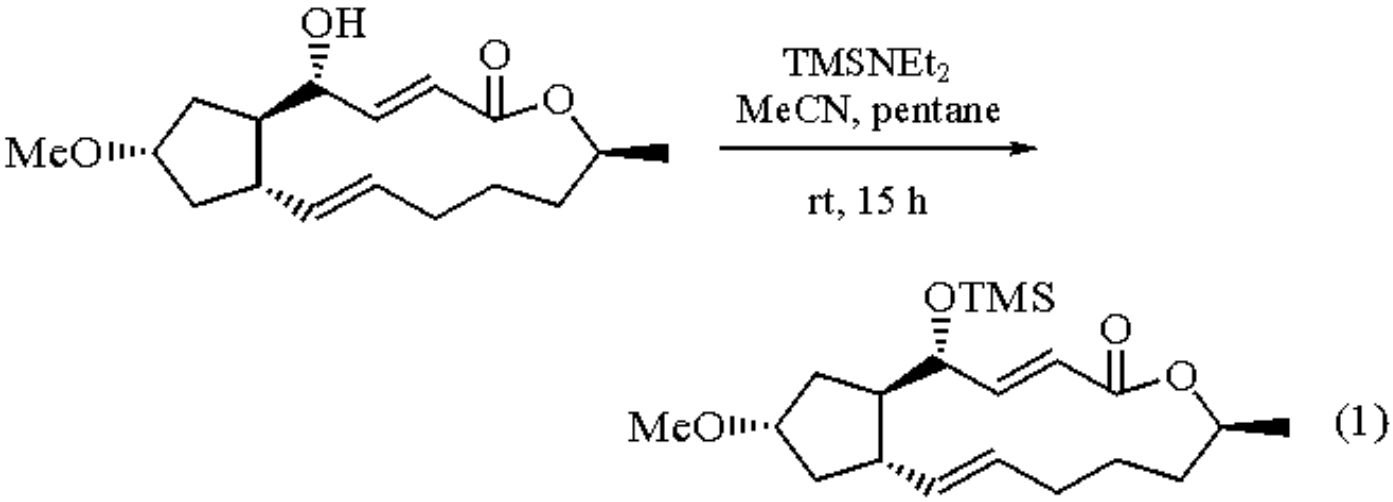

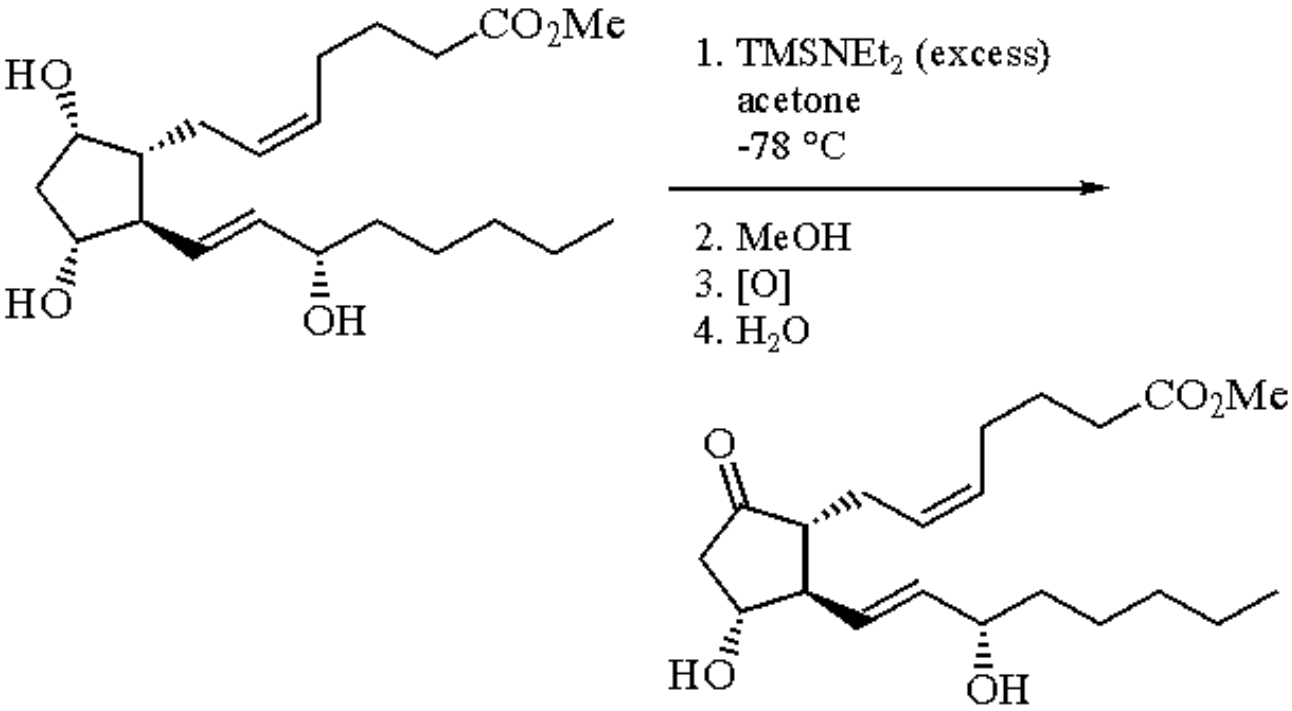

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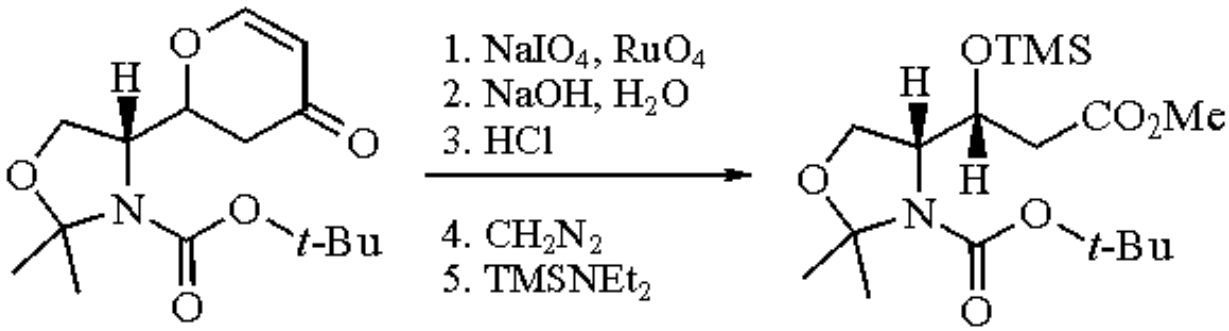

(3)

Unsaturated γ-butyrolactones are converted into 2-silyloxyfurans,[10] while the corresponding *N*-methyllactams give trimethylsilyloxypyrroles.[11] Amines can be converted into trimethylsilyl derivatives, as in the case of putrescine which forms the *N*,*N*´-bis(trimethylsilyl) compound in 95% yield.[12] Carboxylic acids can be silylated, as in the case of amino acid hydrochloride salts in DMF.[13] The hydroxyl group of acid-sensitive compounds, such as that in eq 4, can be protected so that conversion to the phosphoryl chloride moiety gives trimethylsilyl chloride instead of HCl as a byproduct, thus enabling the other groups to survive.[14]

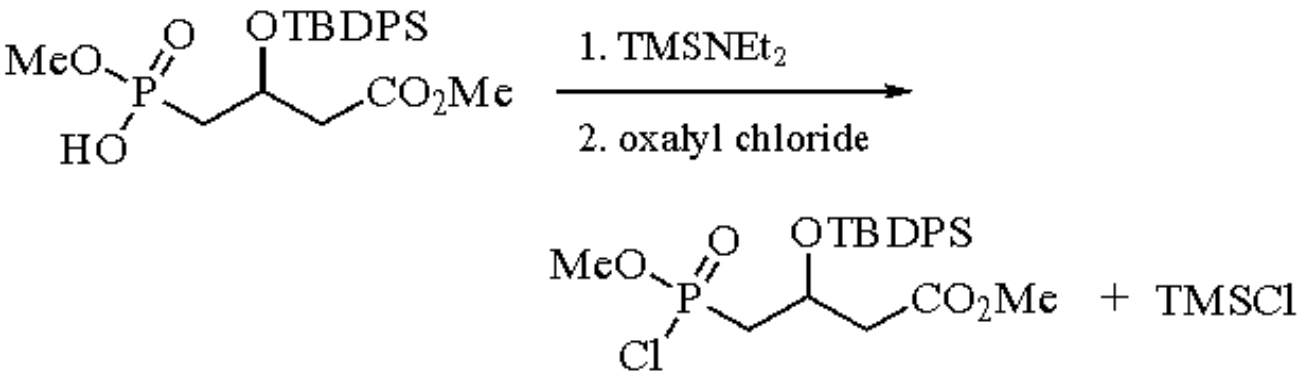

(4)

Diethylamino Group Transfer.

The diethylamino group can be transferred to electrophilic compounds. ***Oxalyl Chloride*** is converted into the monoamide with 1 equiv of $TMSNEt_2$ at -23 °C and the bisamide with excess silylamine at room temperature;[2] ***Benzeneselenenyl Chloride*** gives the selenenamide.[15] Unsaturated lactones give β-diethylamino lactones with $TMSNEt_2$ and a trace of diethylamine.[10] Conjugated enones give β-amino enol silyl ethers (eq 5),[16] while 1-triphenylsilylpropynone gives simple conjugate addition of diethylamine.[17]

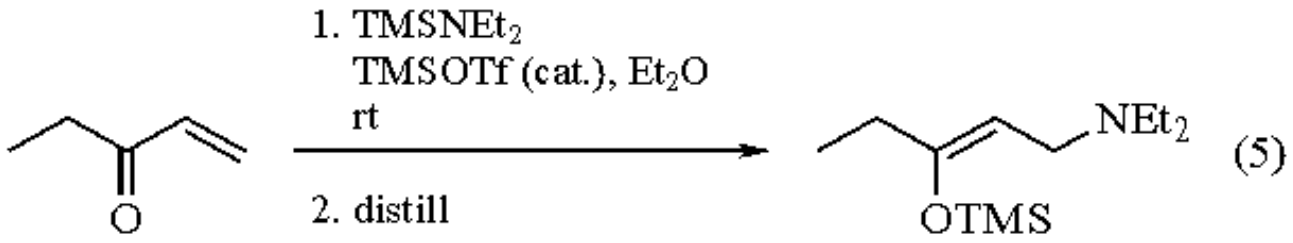

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2-Trimethylsilyl-1,3-dithiane

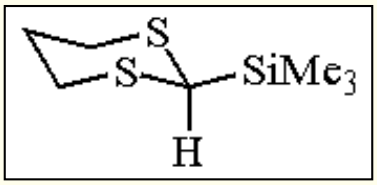

[13411-42-2] · $C_7H_{16}S_2Si$ · 2-Trimethylsilyl-1,3-dithiane · (MW 192.46)

(precursor of dithioketene acetals[1] which are good substrates for both cationic[2] and anionic[3] cyclization processes; the anion reacts with unsaturated ketones and aldehydes to give vinyl dithioketene acetals that can be used as dienes[4] or for the preparation of substituted α,β-unsaturated alkyl ketones;[5] alkylation of the anion provides a general synthesis of acylsilanes[6,7])

Physical Data: bp 54-55 °C/0.17 mmHg.

Solubility: insol H_2O; sol organic solvents.

Form Supplied in: commercially available.

Preparative Method: prepared by alkylation of ***2-Lithio-1,3-dithiane*** with ***Chlorotrimethylsilane*** (eq 1).[1]

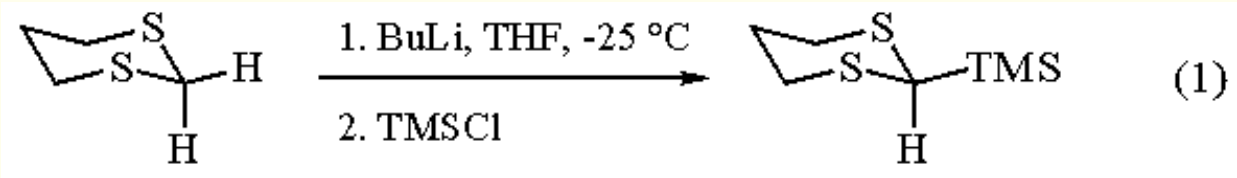

Handling, Storage, and Precautions: use in a fume hood.

2-Lithio-2-trimethylsilyl-1,3-dithiane.

This reagent (**1**) is generated from the title compound by treatment with ***n-Butyllithium*** at -78 °C (eq 2)[1] and is the species utilized in many of the following transformations.

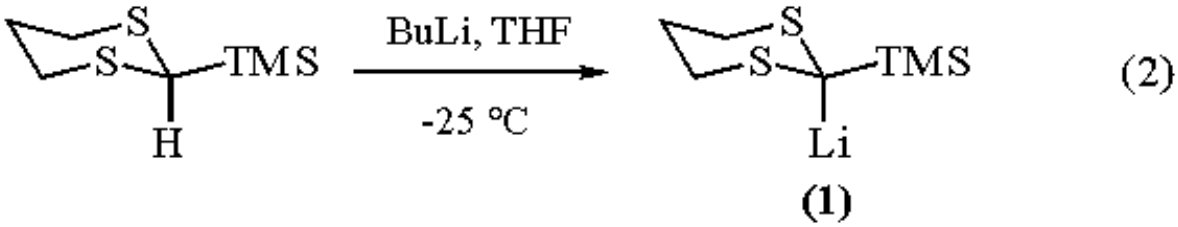

Thioketene Acetals.

Anion (**1**) reacts with aldehydes and ketones to provide the corresponding thioketene acetals;[1] aryl and unsaturated aldehydes and ketones are good substrates for this reaction (eqs 3 and 4). Enolizable alkyl ketones also react to provide thioketene acetals (eq 5). Alternative methods for the preparation of these cyclic thioketene acetals involve the use of phosphonate derivatives,[8] mixed zinc-titanium organometallic reagents,[9] and *N*,*N*-dimethyl thioamides.[10] The phosphonate reagents are more nucleophilic than (**1**) and are superior when competitive deprotonation is a problem.

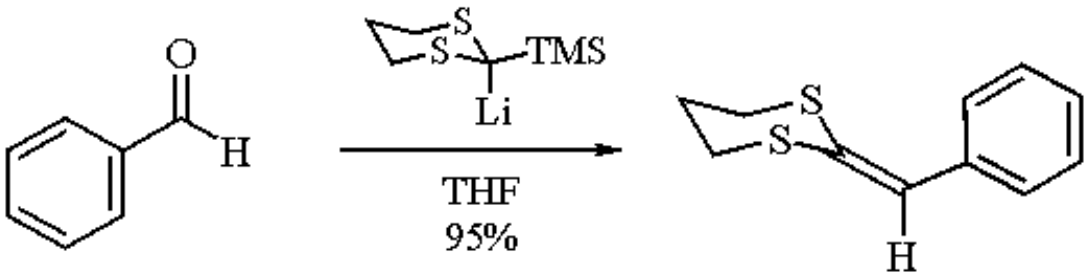

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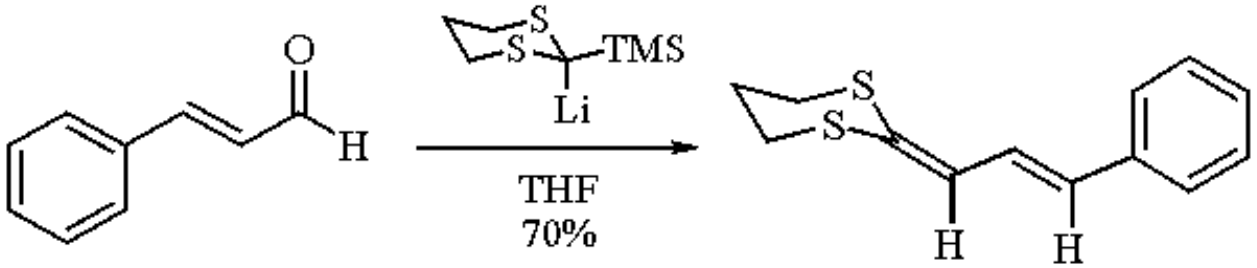

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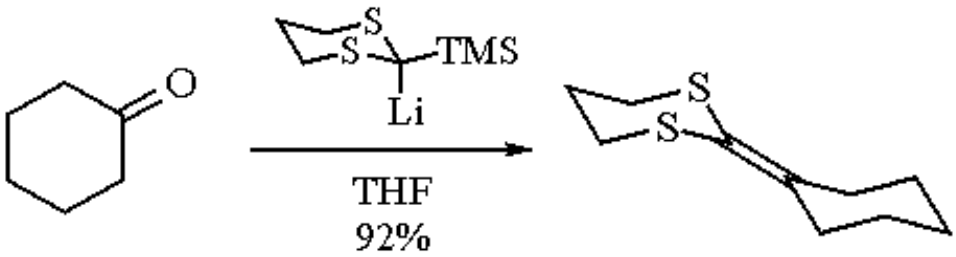

(5)

A variation of this method has also been developed for cases in which reactions with (**1**) give poor results (eq 6). Thus the carbonyl compound is treated with ***2-Lithio-1,3-dithiane*** followed by TMSCl to generate the silyl ether. Subsequent addition of a second equivalent of *n*-butyllithium effects alkenation, affording the thioketene acetal in good yield.[11]

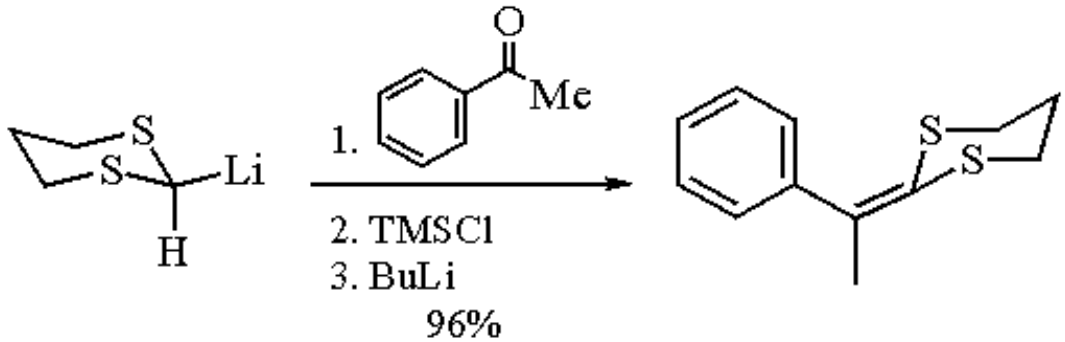

(6)

Cationic and Anionic Cyclizations.

The thioketene acetals derived from the reaction of anion (**1**) have found several applications in cyclization methodology. The thioketene acetals can be used as either electrophiles (eq 7)[2] or nucleophiles (eq 8)[3] in a cyclization process which depends on the experimental conditions.

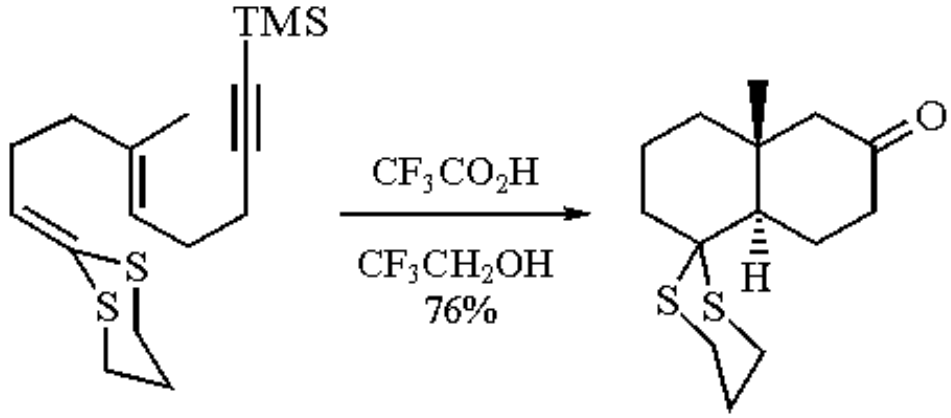

(7)

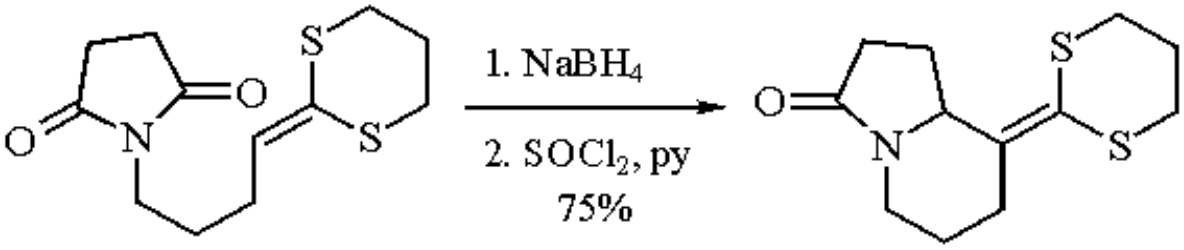

(8)

Substituted trimethylsilyldithianes can be converted into nucleophiles via fluoride ion desilylation and used in anionic cyclization strategies.[12] This anion not only undergoes condensations with carbonyls (eq 9), but it is also an effective Michael donor (eq 10).

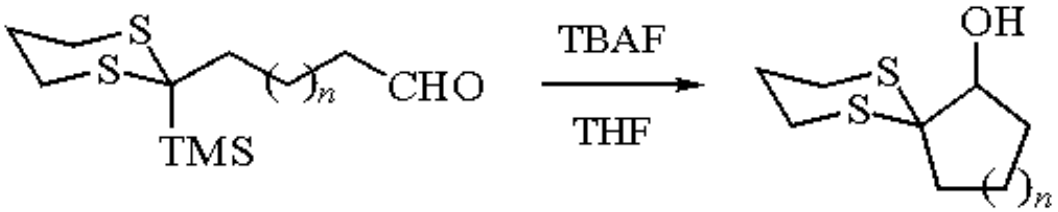

(9)

$n = 1$, 60-76%
$n = 2$, 57-61%

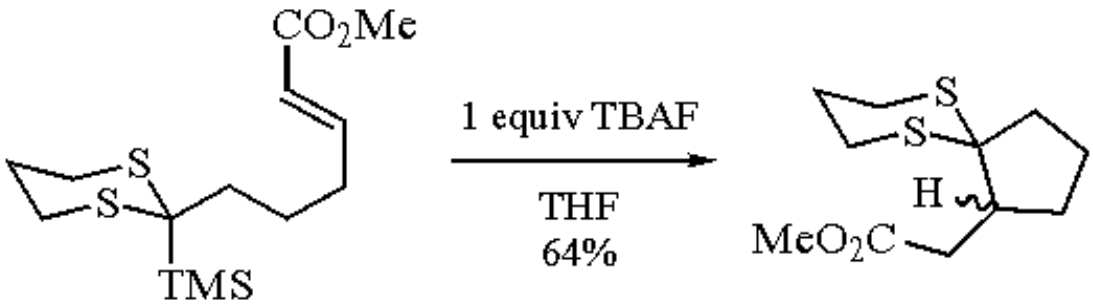

(10)

Unsaturated Dithioketene Acetals.

The reaction of anion (**1**) with various α,β-unsaturated aldehydes and ketones occurs in a 1,2-fashion and provides vinyl thioketene acetals that are acceptable dienes for Diels-Alder reactions (eq 11);[4] dienes of this type are difficult to access using other protocols. This method is also convenient for the introduction of a protected carbonyl group.

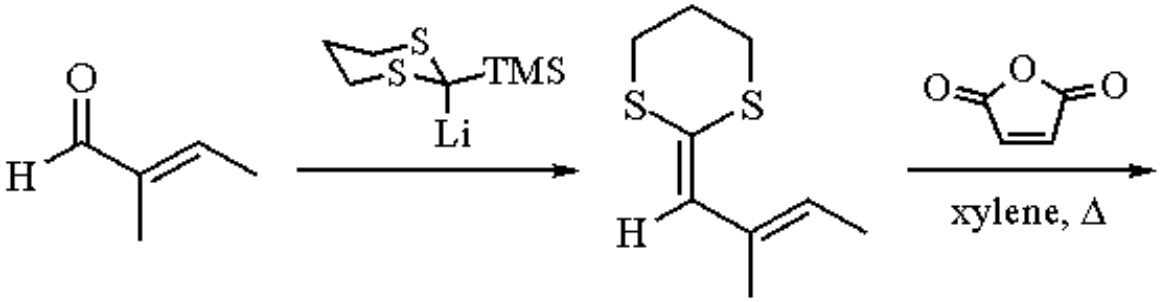

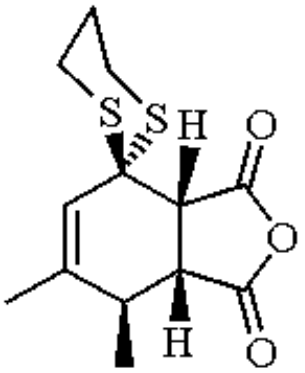

(11)

60%

Treatment of acrolein and cyclohexenone with 2-lithio-2-trimethylsilyl-1,3-dithiane provides the corresponding unsaturated dithioketene acetals (eq 12).[5a] Subsequent exposure to *n*-butyllithium followed by MeI produces protected forms of α,β-unsaturated ketones in almost quantitative yield; anion addition occurs distal to the dithiane and alkylation takes place at the dithiane stabilized anion (eqs 13 and 14).[5b] Another interesting application is the use of suitably substituted 2-aryl-2-trimethylsilyl-1,3-dithianes as precursors for *o*-quinodimethanes (eq 15).[13]

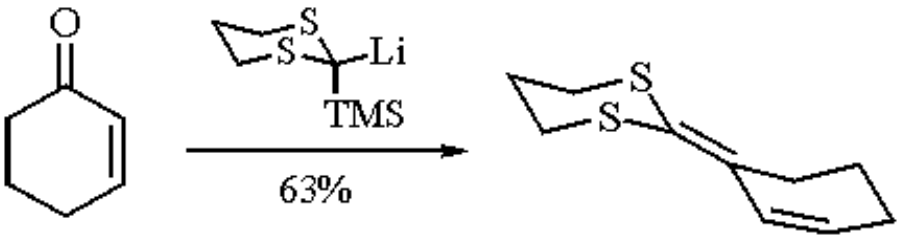

(12)

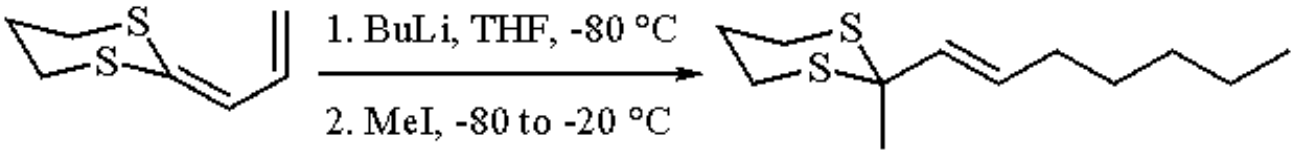

(13)

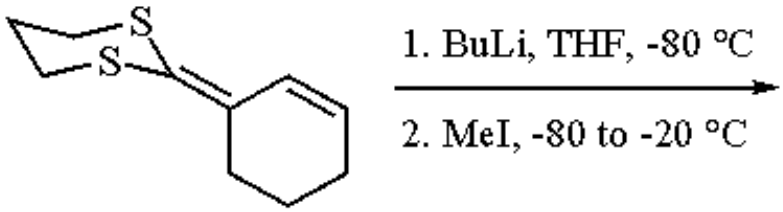

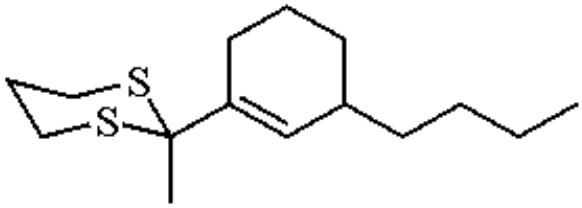

(14)

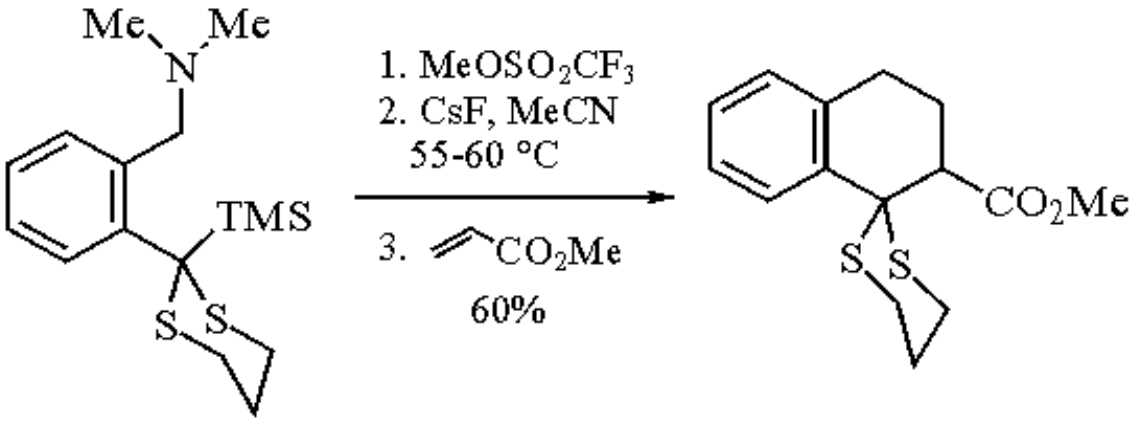

(15)

Acylsilanes.[14]

The reaction of anion (**1**) with alkyl halides generates a functionalized dithiane which, when hydrolyzed under mild conditions, provides the corresponding acylsilane (eq 16).[2] More highly substituted acylsilanes have been accessed by initial formation of the dithiane from the aldehyde, followed by deprotonation and silylation with TMSCl (eq 17). Acylsilanes have been used as sterically hindered aldehyde equivalents for regiocontrol in addition reactions (eq 18)[15] and also as precursors for silyl-substituted vinyl triflates (eq 19).[16]

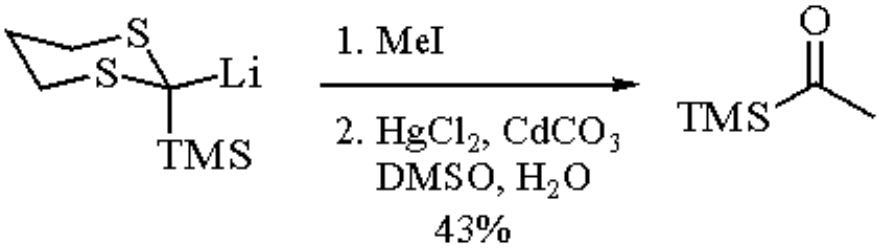

(16)

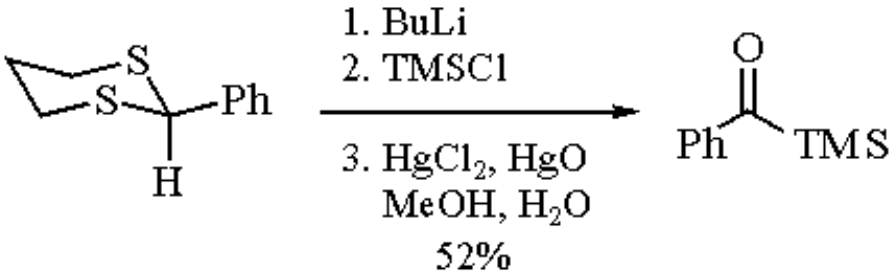

(17)

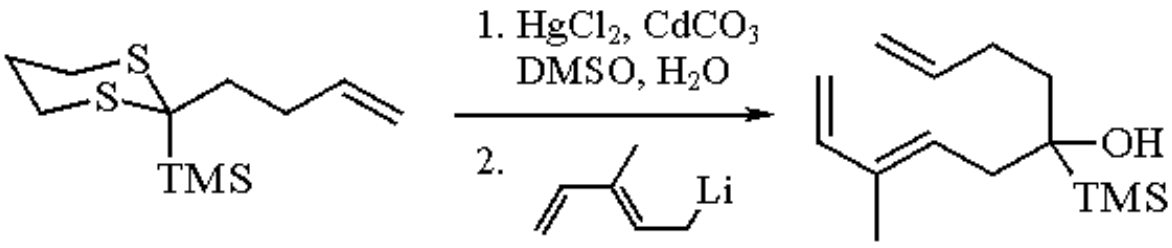

(18)

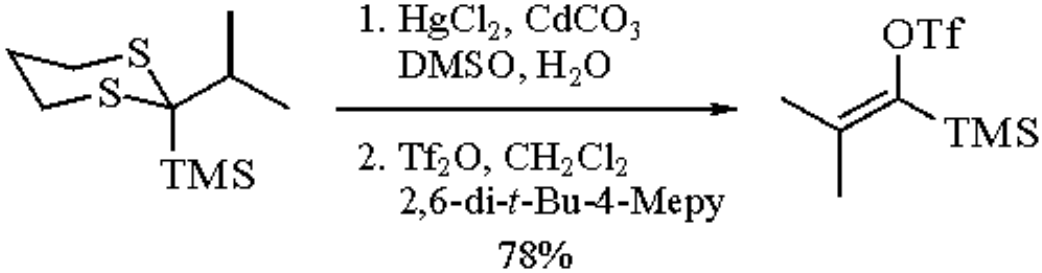

(19)

There are several alternative methods for the formation of acylsilanes; these include the reaction of silyl cuprates with acid halides,[17] palladium-assisted coupling of acyl halides with ***Hexamethyldisilane***,[18] the reaction of thiopyridyl esters with ***Tris(trimethylsilyl)aluminum*** in the presence of Cu^{I} salts,[19] and the hydroboration of trimethylsilyl-substituted alkynes.[20] While all of

these procedures are complementary, the method involving the title compound provides an easy, inexpensive route to acylsilanes.

---

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β-Trimethylsilylethanesulfonyl Chloride

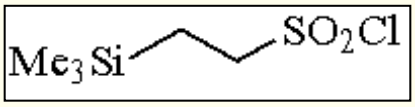

[97203-62-8] · $C_5H_{13}ClO_2SSi$ · β-Trimethylsilylethanesulfonyl Chloride · (MW 200.79)

(protection of primary and secondary amines as their sulfonamides, which are cleaved by fluoride ion[1])

Alternate Name: SESCl.

Physical Data: bp 60 °C/0.1 mmHg; yellow oil.

Solubility: sol most common organic solvents.

Preparative Methods: can be most conveniently synthesized from commercially available ***Vinyltrimethylsilane*** (**1**) (eq 1).[1] Radical addition of sodium bisulfite to the vinyl group catalyzed by *t*-butyl perbenzoate yields the sulfonate salt (**2**) which can be directly converted to SESCl (**3**) with ***Phosphorus(V) Chloride***. The chloride (**3**) can then be purified by distillation. The intermediate sulfonate salt (**2**) is commercially available. The chloride (**3**) can also be prepared in 62% yield from the salt (**2**) using ***Sulfuryl Chloride*** and ***Triphenylphosphine*** (eq 2).[2] A less convenient procedure to synthesize SESCl (**3**) using β-trimethylsilylethylmagnesium chloride (**4**) and sulfuryl chloride has also been developed (eq 3).[1]

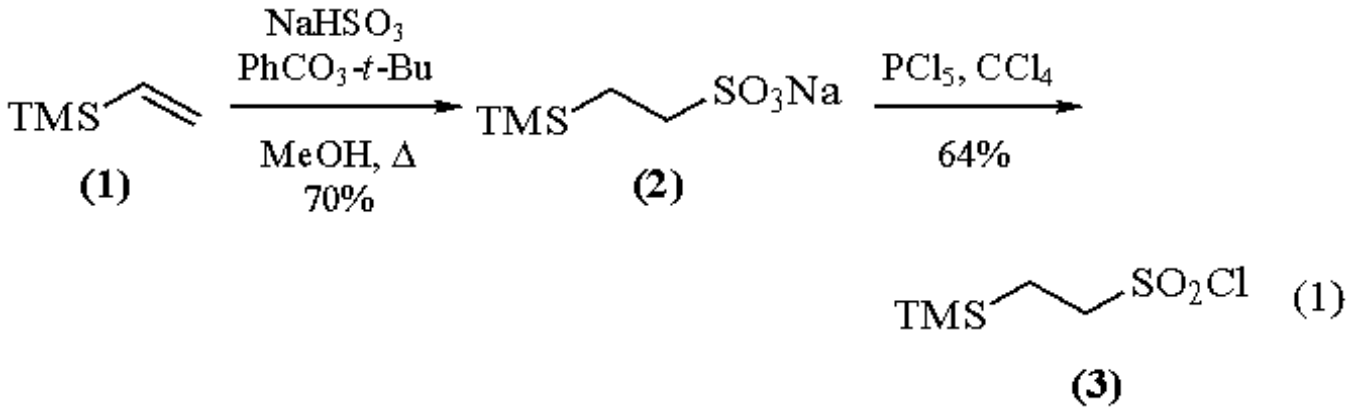

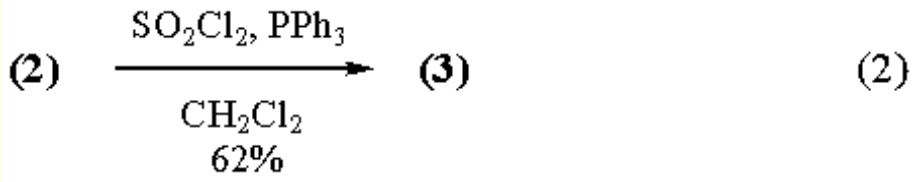

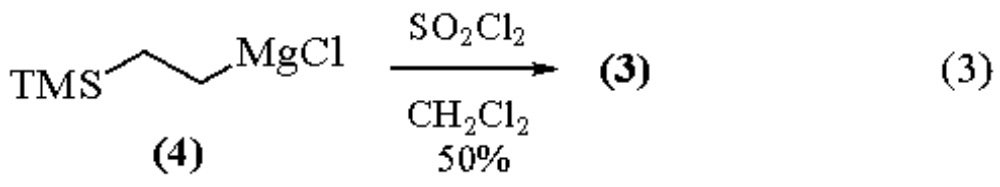

Handling, Storage, and Precautions: stable liquid that can be stored at room temperature for weeks. Prone to hydrolysis.

Protection of Amines.

Sulfonamides are among the most stable of amine protecting groups and it is this stability that detracts from their utility, since harsh reaction conditions are often needed for their removal. The advantage of using the β-trimethylsilylethanesulfonyl (SES) protecting group is that the sulfonamide (**5**) can be easily cleaved to regenerate the parent amine (eq 4)[1] in good yields with either ***Cesium Fluoride*** (2-3 equiv) in DMF at

95 °C for 9-40 h, or ***Tetra-n-butylammonium Fluoride*** trihydrate (3 equiv) in refluxing MeCN. The main disadvantage of the latter procedure is an occasional difficulty in separating tetrabutylammonium salts from some amines.

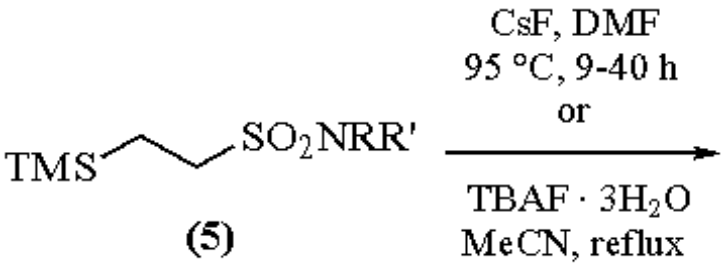

$$TMSF + H_2C{=}CH_2 + SO_2 + RR'NH \quad (4)$$

The sulfonamides can be prepared from a wide variety of primary and secondary amines using sulfonyl chloride (**3**) in DMF containing ***Triethylamine***. For aromatic and heterocyclic amines, ***Sodium Hydride*** is the preferred base. The sulfonamides are generally quite stable and are untouched by refluxing TFA, 6 M HCl in refluxing THF, 1 M TBAF in refluxing THF, $LiBF_4$ in refluxing MeCN, $BF_3.OEt_2$, and 40% HF in ethanol. Table 1 lists a few examples of various amines and their protection as SES sulfonamides and cleavage with CsF in DMF at 95 °C.[1]

Table 1 Synthesis and Cleavage of SES Sulfonamides with CsF, DMF, 95 °C

Amine	% Yield sulfonamide	% Yield of cleavage (time)
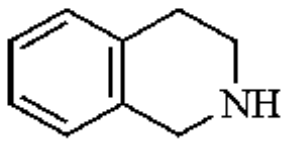	92	82 (29 h)
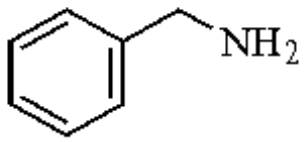	92	86 (16 h)
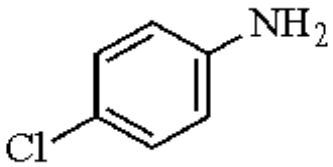	83	93 (40 h)
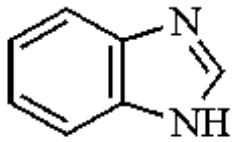	93	91 (9 h)
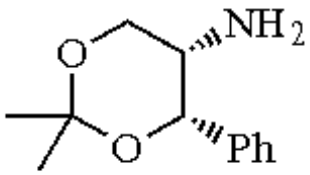	88	89 (24 h)

SESCl in Synthesis.[3]

The SES group has been used successfully in the synthesis of glycosides (eq 5).[4] Reaction of (**6**) with SES-sulfonamide and ***Iodonium Di-sym-collidine Perchlorate*** provides the iodo sulfonamide (**7**) in 82% yield. Treatment of (**7**) with (benzyloxy)tributylstannane in the presence of ***Silver(I) Trifluoromethanesulfonate*** provides the β-benzyl glycoside (**8**). Fluoride treatment of (**8**) removes both the silyl ether and the SES

group, giving the amino alcohol (**9**).

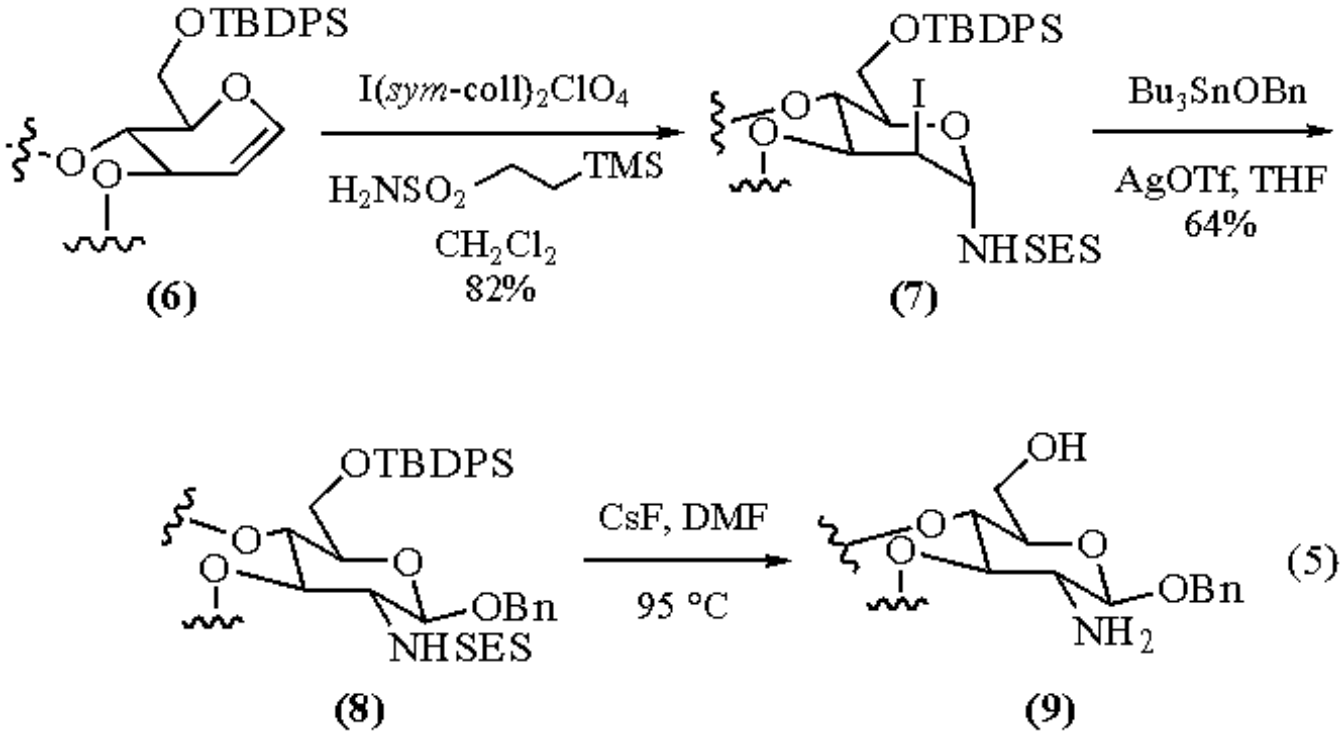

The smooth removal of the SES protecting group from pyrrole and pyrrole-containing peptides demonstrates the synthetic potential of this protecting group in heterocyclic chemistry (eq 6).[5] The SES group of (**10**) is removed with TBAF.$3H_2O$ in DMF at room temperature to yield (**11**). Other protecting groups (i.e. mesylate, triflate) cannot be removed without destruction of the substrates.

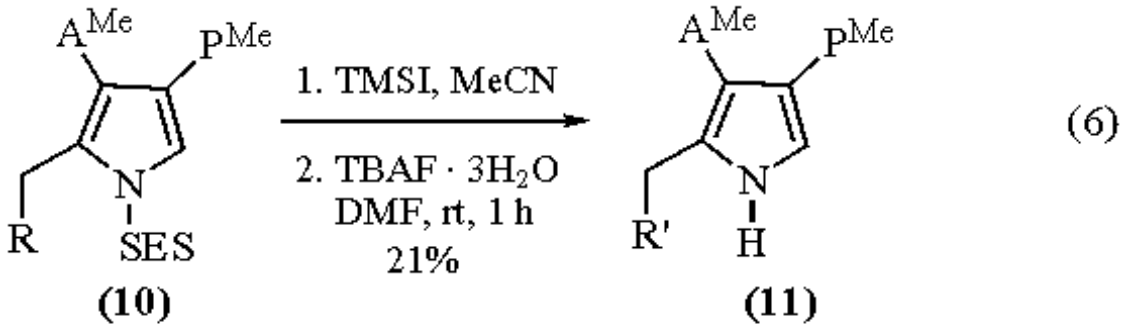

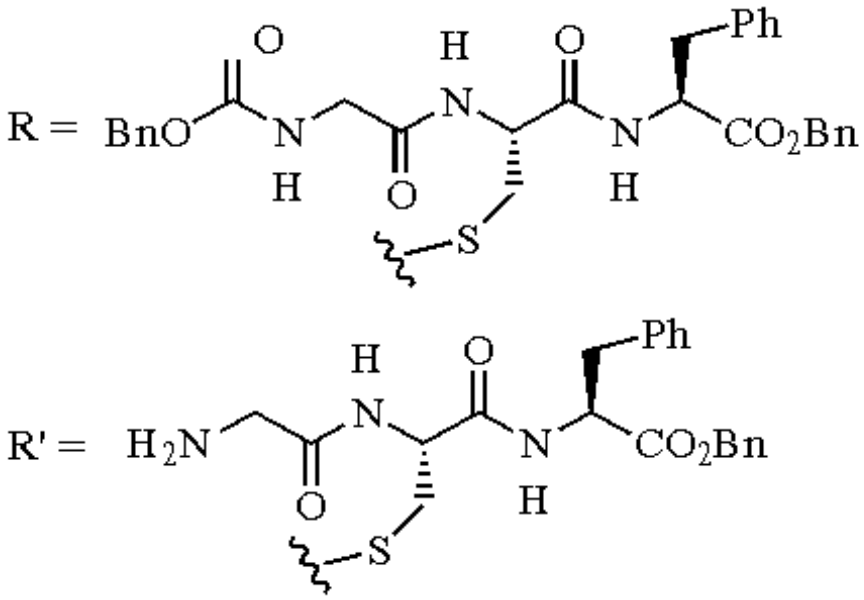

The *N*-SES group can be incorporated by treating an aldehyde with *N*-sulfinyl-β-trimethylsilylethanesulfonamide (SESNSO) (**13**), which can be made by treating the sulfonamide (**12**) with ***Thionyl Chloride*** and a catalytic amount of *N,N*-dichloro-*p*-toluenesulfonamide (eq 7) (see also ***N***-

Sulfinyl-p-toluenesulfonamide).[6] The *N*-sulfonyl imine can be used in situ in a number of reactions. For example, the *N*-sulfonyl imine from aldehyde (**14**) reacts with 2,3-dimethylbutadiene (eq 8)[7] to give the Diels-Alder adduct (**15**). Treatment of (**15**) with fluoride ion affords the bicyclic lactam (**16**). Also, the *N*-sulfonyl imine derived from isobutyraldehyde and (**13**) reacts with ***Vinylmagnesium Bromide*** to provide the allylic SES-sulfonamide (**17**) in 65% yield (eq 9).[8]

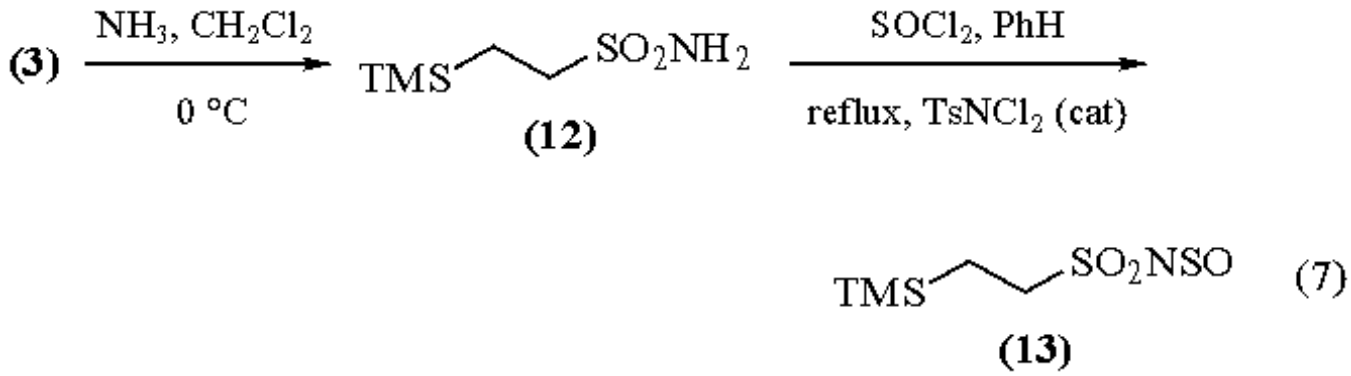

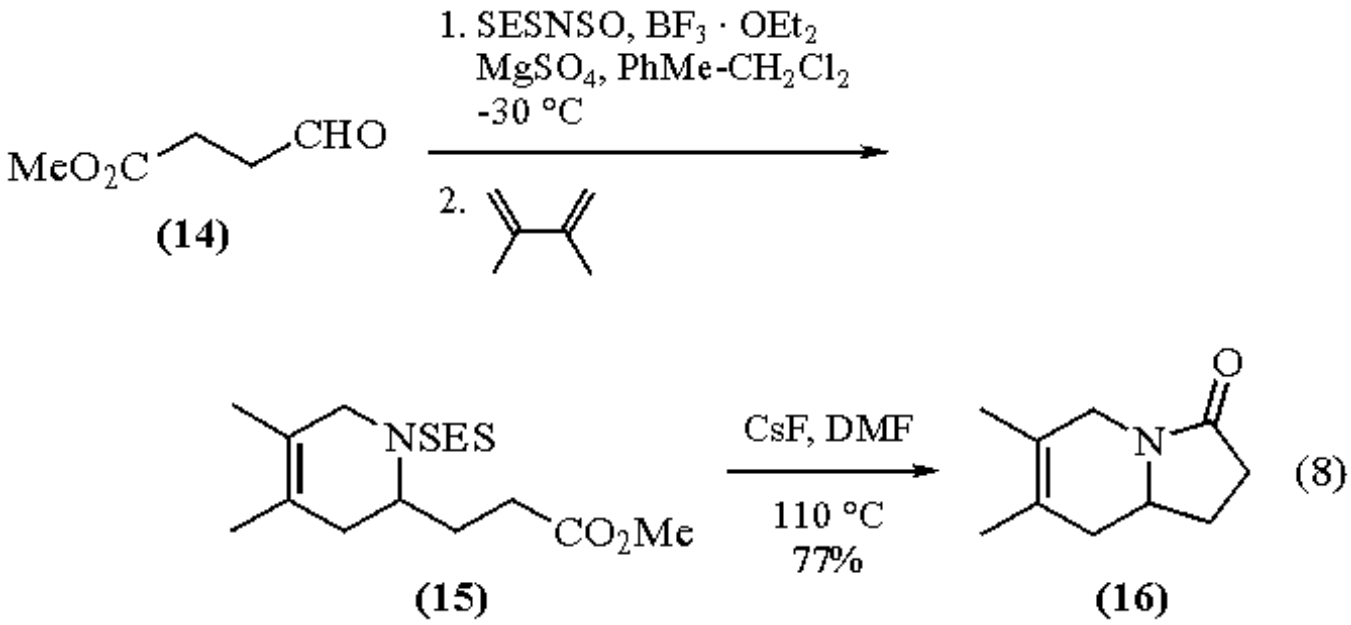

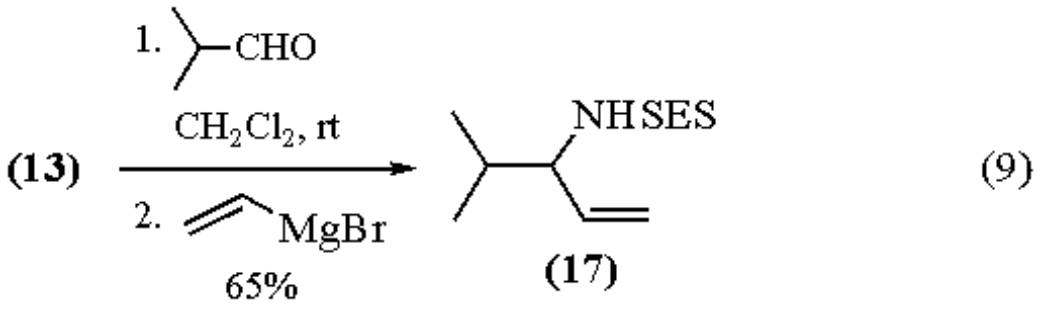

In a total synthesis of the antitumor antibiotic (-)-bactobolin (**18**), the choice of protecting group on the nitrogen was crucial (eq 10).[6] Unlike other protecting groups, the SES group is compatible with a wide variety of transformations and reagents, and is easily removed at the end of the synthesis.

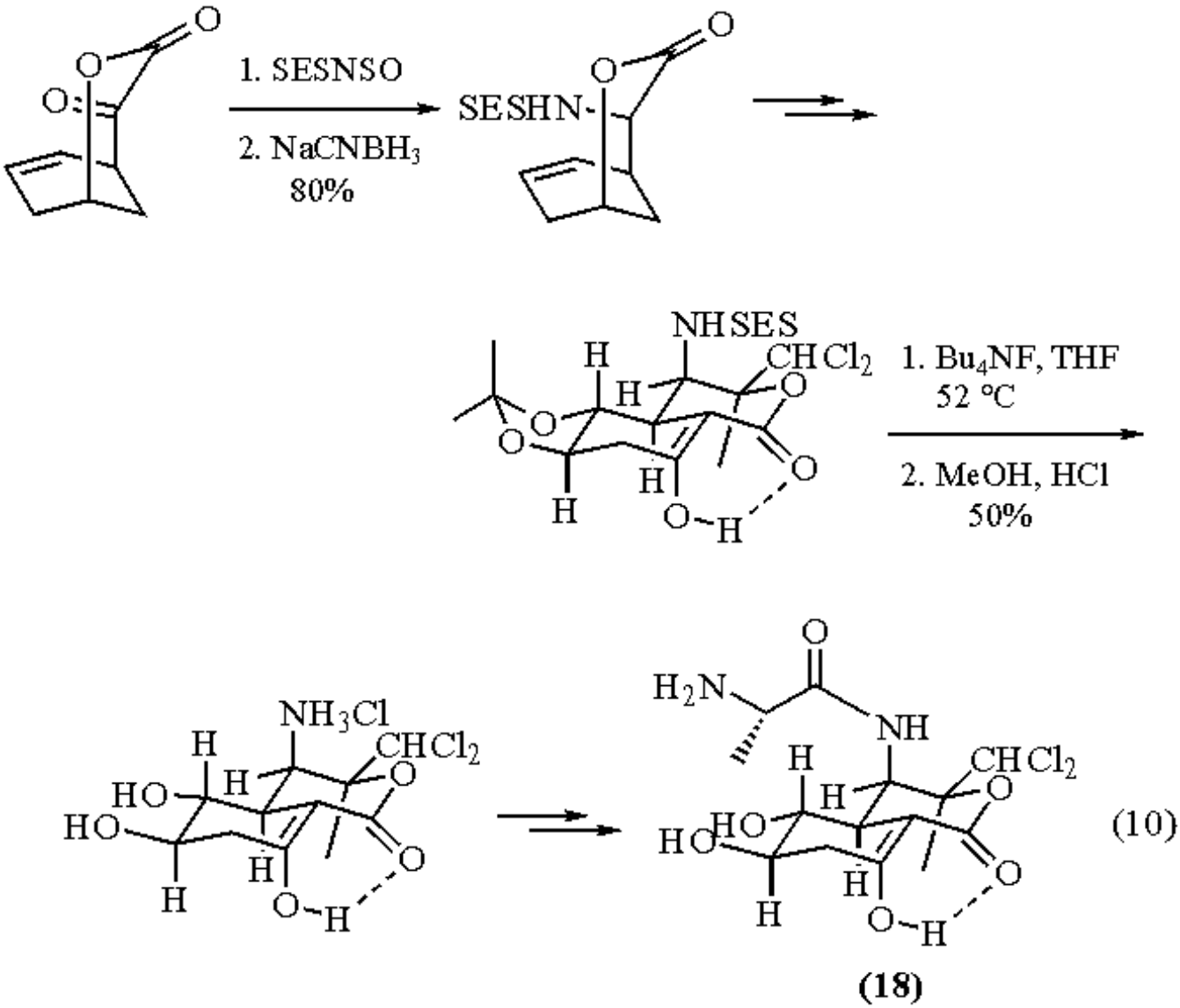

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The Pennsylvania State University, University Park, PA, USA

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2-(Trimethylsilyl)ethanol

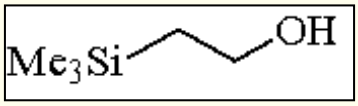

[2916-68-9] · $C_5H_{14}OSi$ · 2-(Trimethylsilyl)ethanol · (MW 118.28)

(protecting reagent for carboxyl, phosphoryl, hydroxyl, and amino groups)

Physical Data: bp 50-52 °C/10 mmHg, 71-73 °C/35 mmHg; *d* 0.825 g cm^{-3}.

Form Supplied in: colorless liquid; 99% purity; widely available.

Preparative Methods: three methods of preparation have been reported: (a) from the treatment of ethyl bromoacetate with ***Zinc*** followed by the reaction with ***Chlorotrimethylsilane***[1] and subsequent reduction of the resultant ***Ethyl Trimethylsilylacetate*** with ***Lithium Aluminum Hydride***[2,3] or ***Borane-Tetrahydrofuran***[4] (eq 1); (b) from the hydroboration/oxidation[5,6] or oxymercuration/demercuration[7] of ***Vinyltrimethylsilane*** (eq 2); and (c) most conveniently, by the reaction of the Grignard reagent formed from ***(Chloromethyl)trimethylsilane*** with ***Paraformaldehyde*** (eq 3).[8]

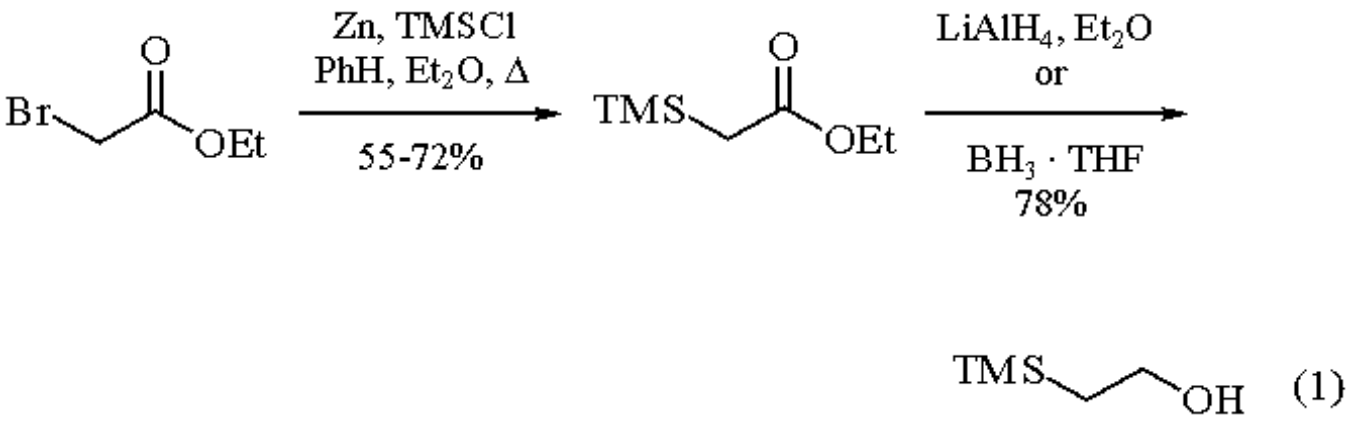

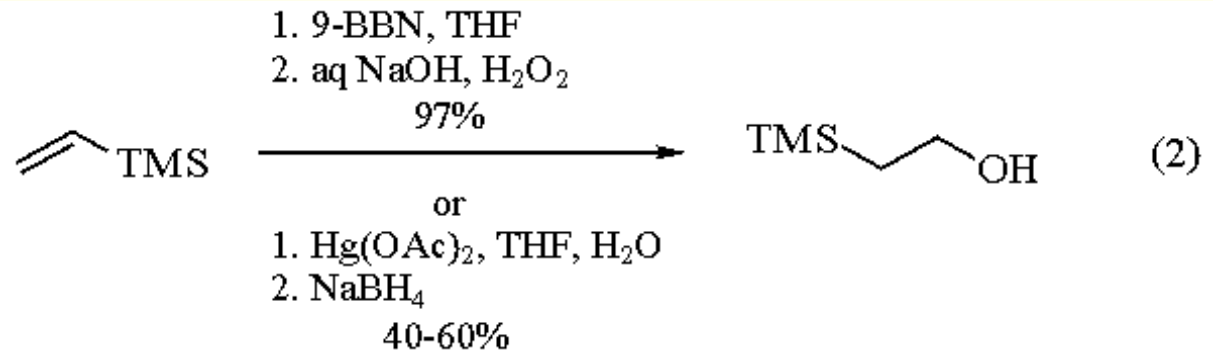

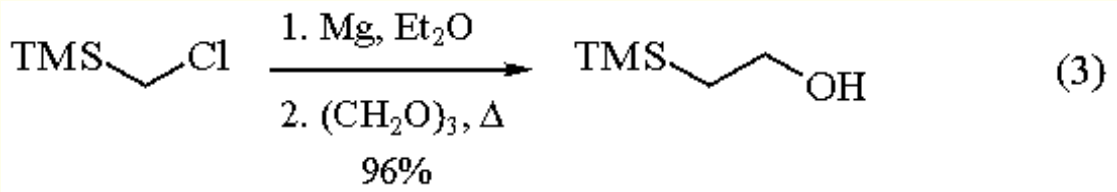

Handling, Storage, and Precautions: corrosive; irritant.

A variety of methods are available for the protection of carboxylic acids as 2-(trimethylsilyl)ethyl esters.[9] 2-(Trimethylsilyl)ethyl esters are stable to conditions used in peptide synthesis. Deprotection of the ester is readily accomplished by treatment with ***Tetra-n-butylammonium Fluoride*** (TBAF).[9] Hemisuccinates have been prepared indirectly under nonacidic conditions by monoprotection of succinic anhydride as 2-

(trimethylsilyl)ethyl esters followed by esterification (eq 4) and then selective deprotection of the resultant diester (eq 5).[10]

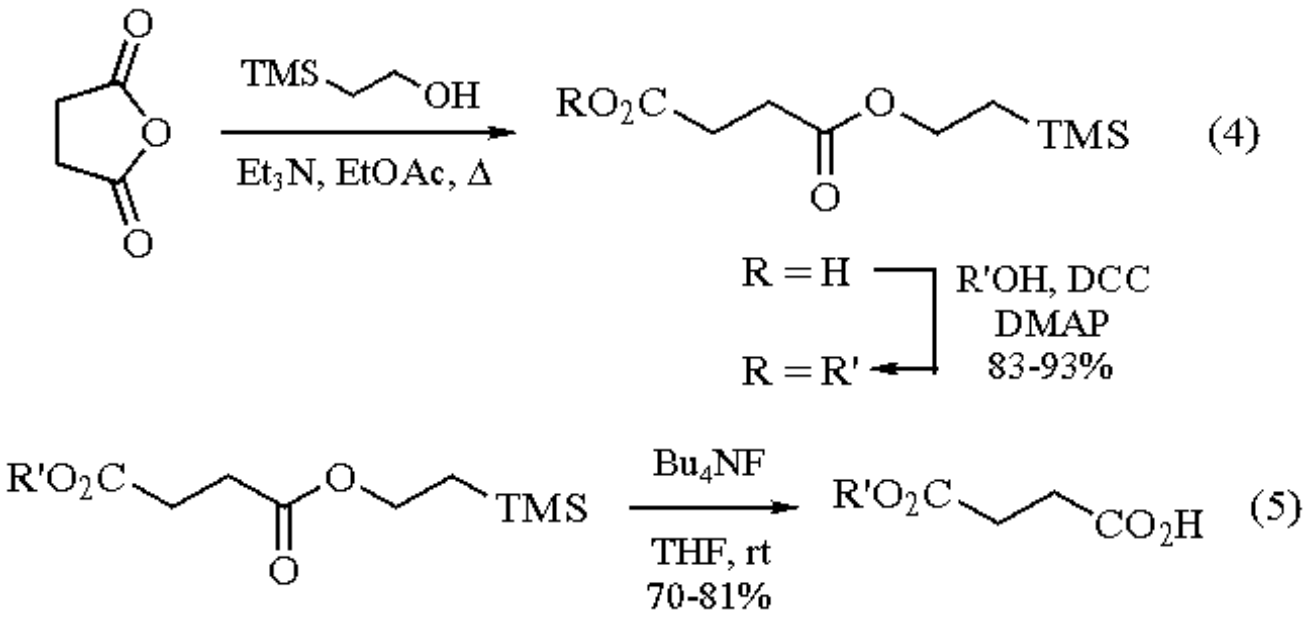

Transesterification of methyl esters to 2-(trimethylsilyl)ethyl esters under mild and neutral conditions takes place in the presence of ***Titanium Tetraisopropoxide*** (eqs 6-8).[11] Deprotection of the 2-(trimethylsilyl)ethyl ester in the presence of an *O*-TBDMS protected secondary hydroxyl group has been achieved (eq 9).[11b] An alternative method for the transesterification uses ***1,8-Diazabicyclo[5.4.0]undec-7-ene/Lithium Bromide*** and 2-(trimethylsilyl)ethanol.[12]

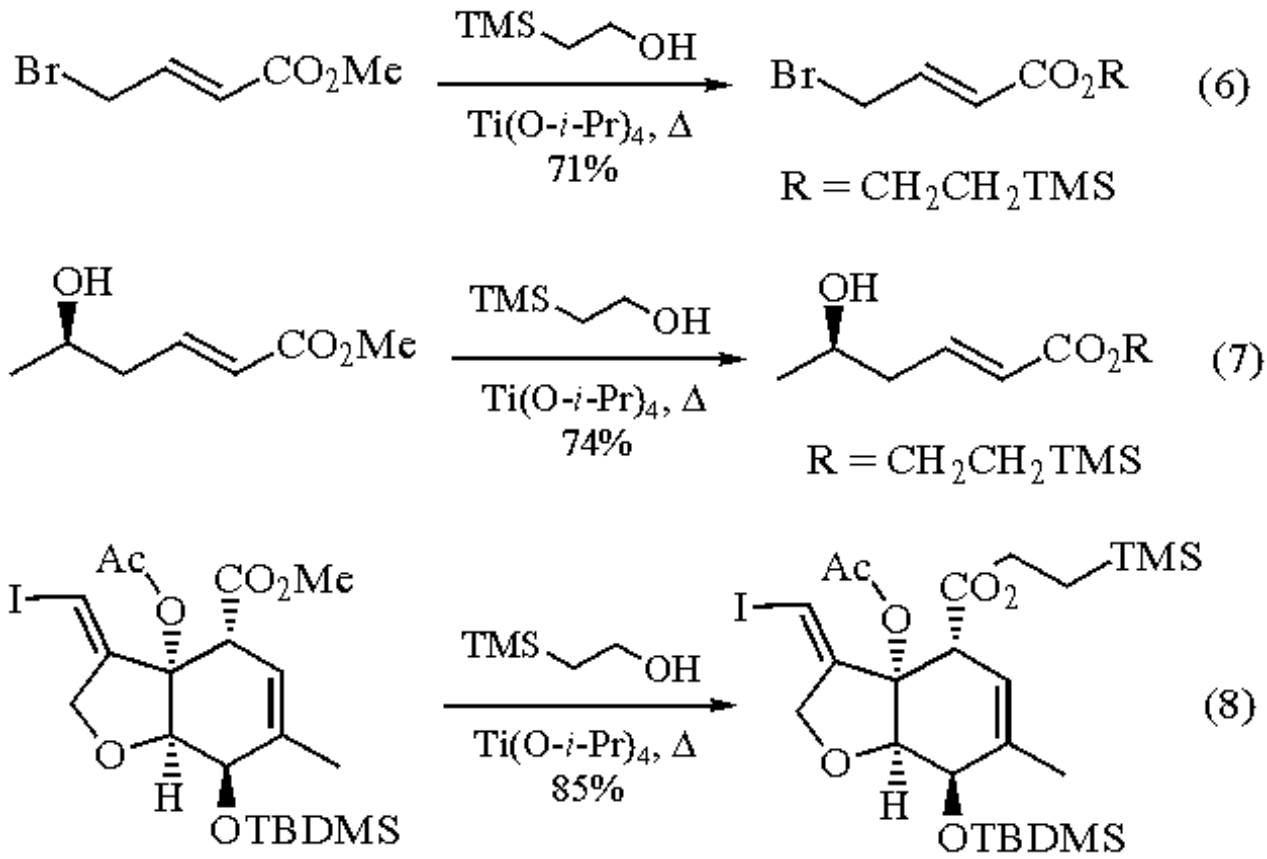

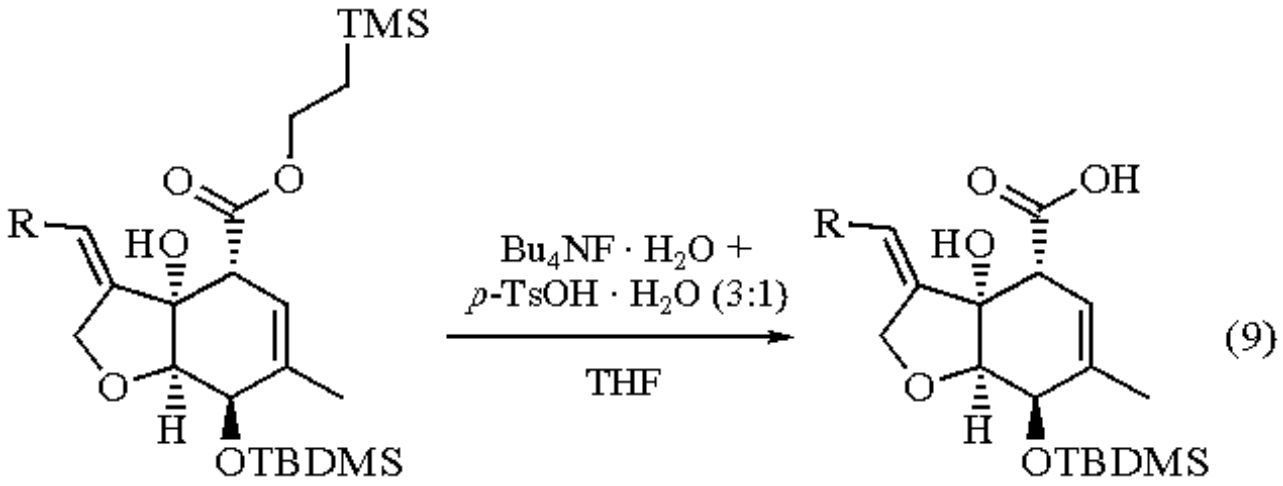

Protection of hydroxyl groups as 2-(trimethylsilyl)ethyl ethers[13a] and 2-(trimethylsilyl)ethyl carbonates[13b] (eq 10) has been utilized as illustrated below. The 2-(trimethylsilyl)ethyl carbonate group can be cleaved under mild conditions using TBAF in dry THF (eq 11).[13b]

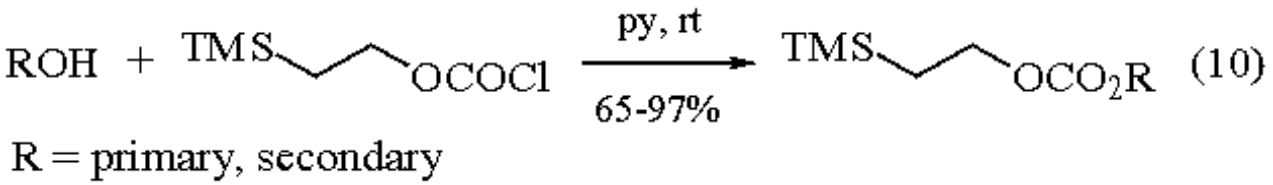

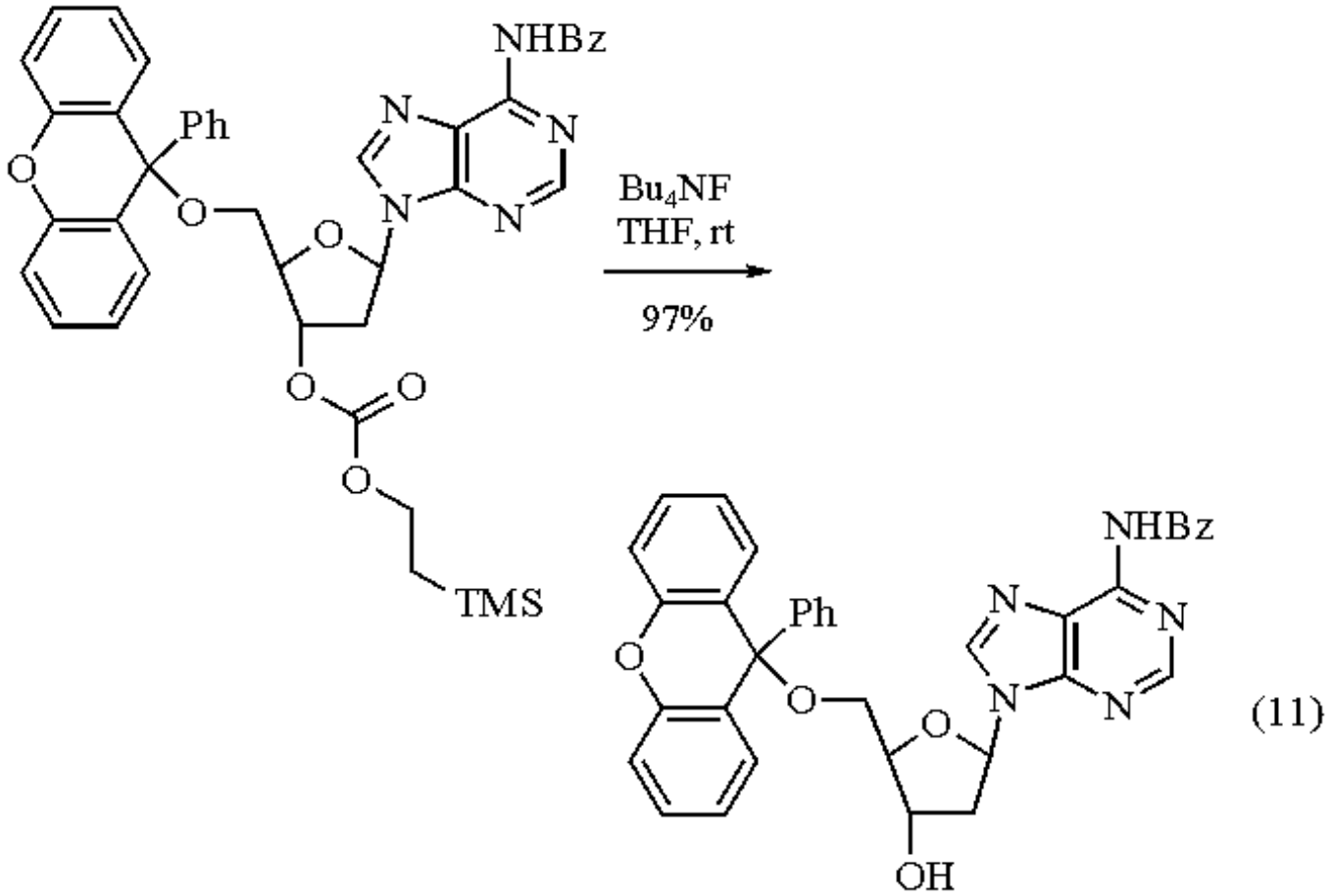

Methods for the protection of pyranosides and furanosides as 2-(trimethylsilyl)ethyl glycosides (eq 12) and deprotection using dry ***Lithium Tetrafluoroborate*** in MeCN have been developed (eq 13).[14]

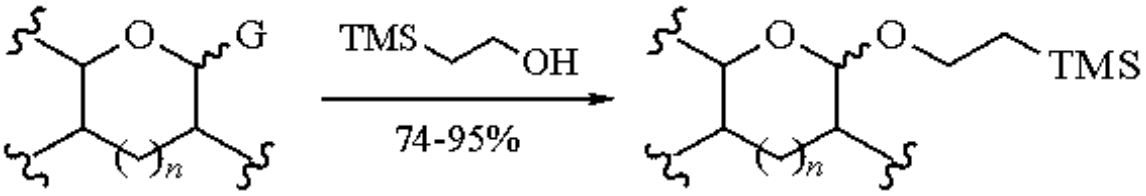

(12)

G = OH, halogen; $n = 0, 1$

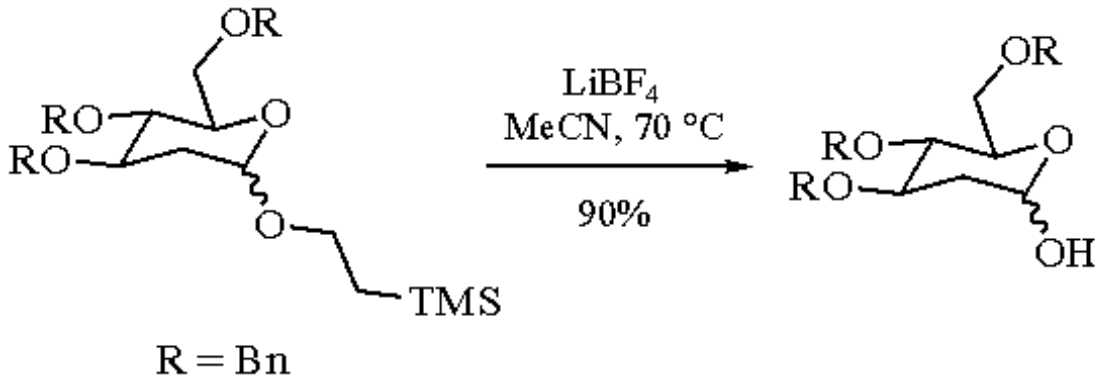

(13)

2-(Trimethylsilyl)ethanol has been used as a protecting group in phosphate monoester synthesis and involves the use of 2-(trimethylsilyl)ethyl dichlorophosphite (eq 14).[15] Bis[2-(trimethylsilyl)ethyl] *N*,*N*-diisopropylphosphoramidite has been prepared from dichloro(diisopropylamino)phosphine and 2-(trimethylsilyl)ethanol and used as a phosphitylating agent in the synthesis of phosphotyrosine containing peptides (eq 15).[16]

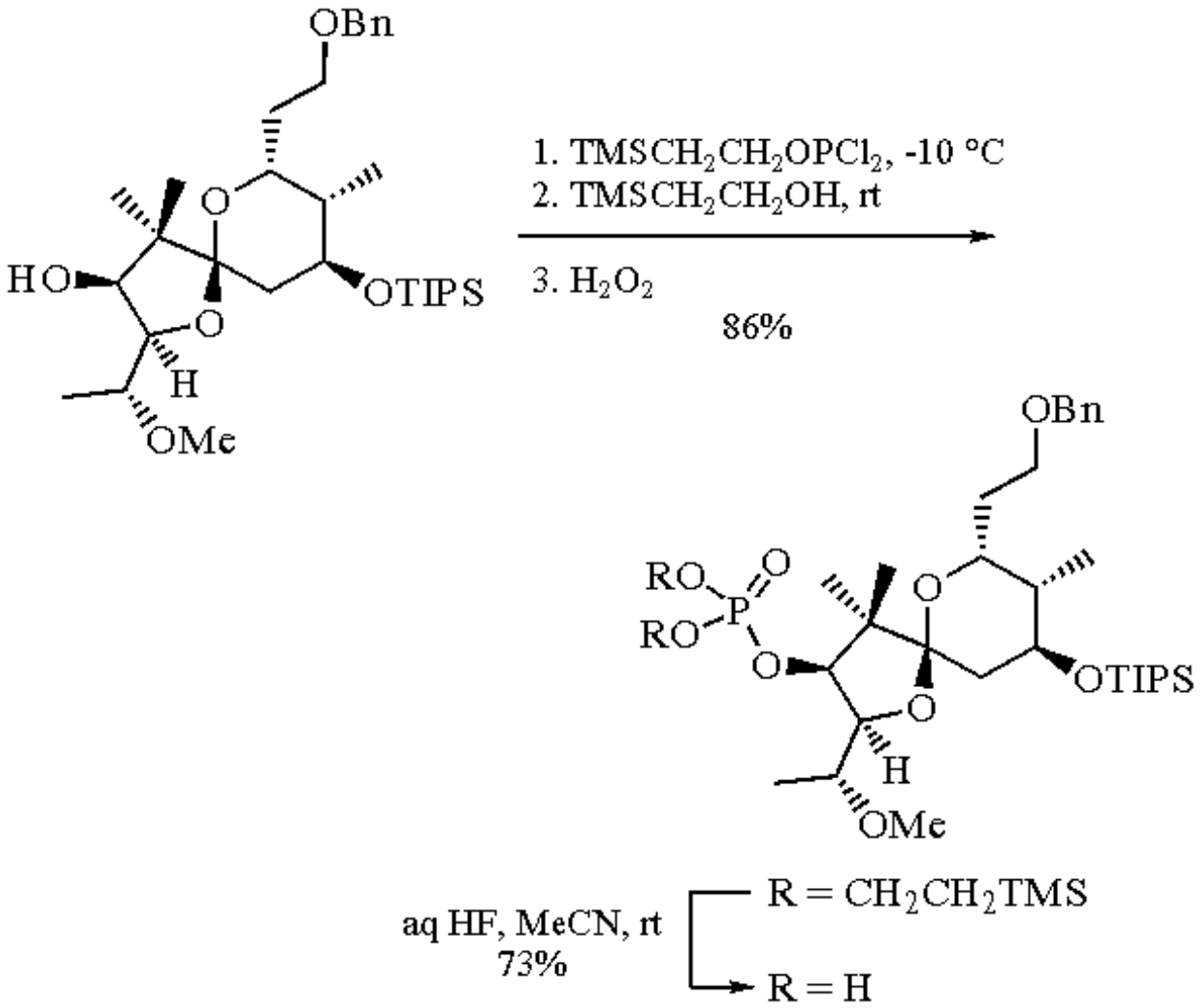

(14)

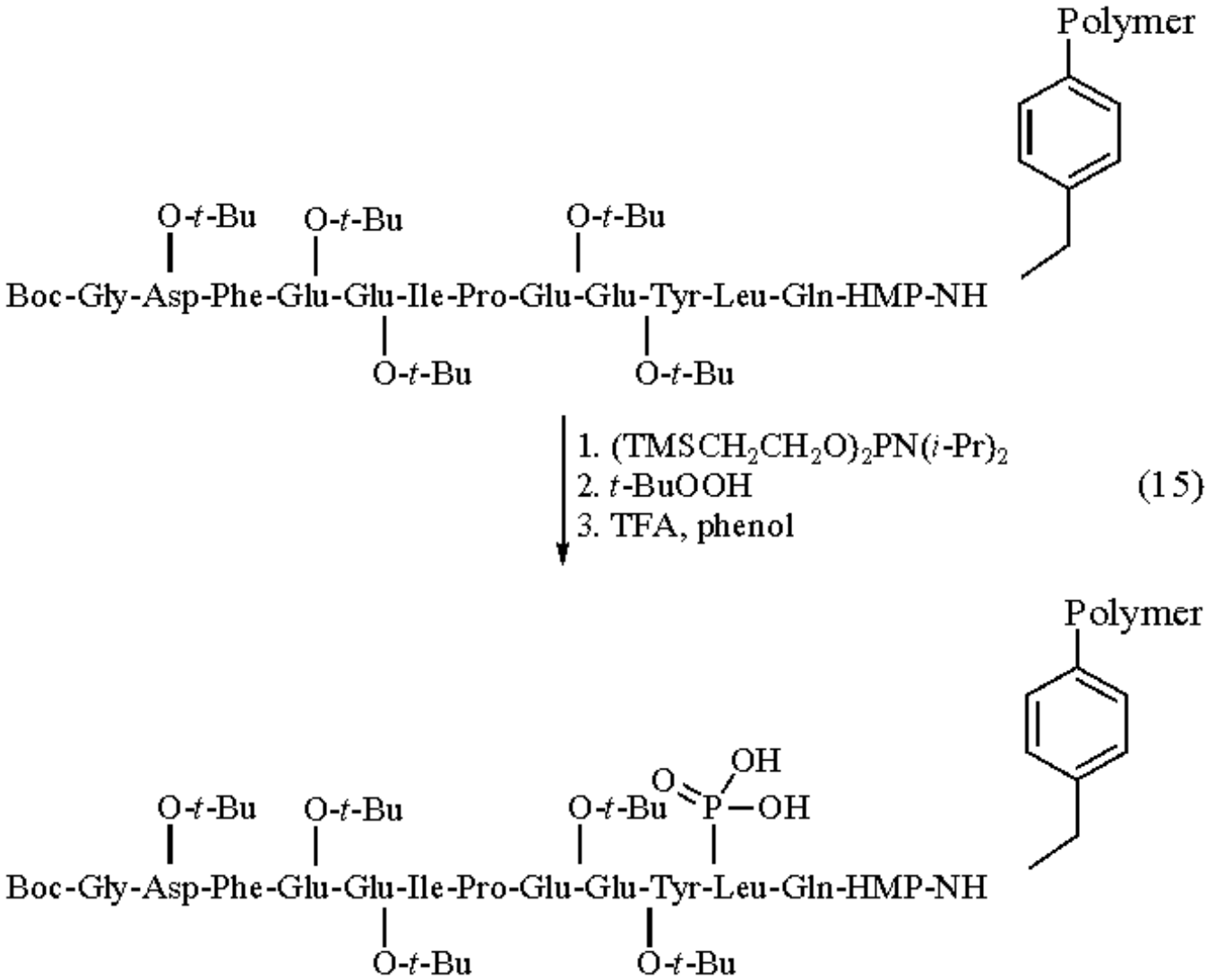

2-(Trimethylsilyl)ethoxycarbonyl (Teoc) groups have been used to protect amine functionalities (eq 16).[17] Using a mixture of tetra-*n*-butylammonium chloride and KF.2H_2O deprotects the Teoc group.[18] *N*-Debenzylation and concurrent protection as *N*-Teoc results when tertiary *N*-benzylamines are treated with ***2-(Trimethylsilyl)ethyl Chloroformate***.[19]

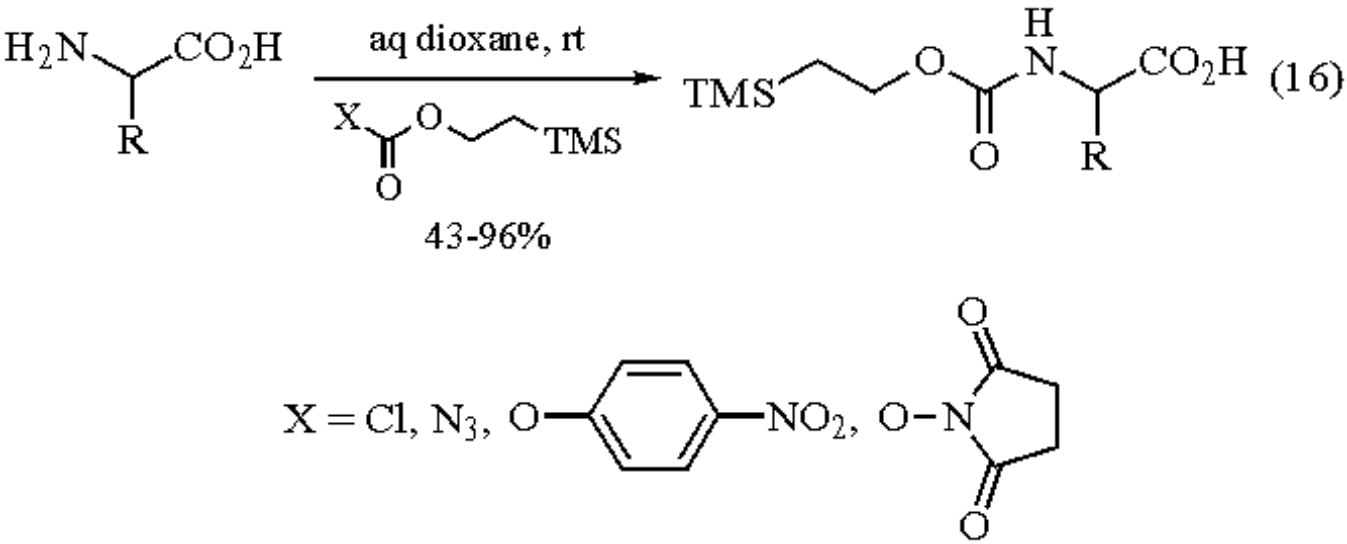

A new method for the synthesis of imidazolones involves the replacement of the C-2 nitro group of *N*-protected dinitroimidazoles by nucleophilic addition of the sodium salt of 2-(trimethylsilyl)ethanol (eq 17).[20]

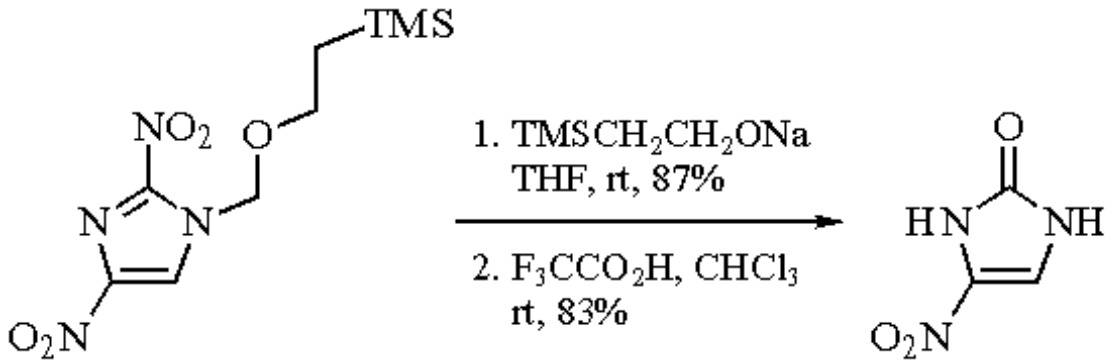

(17)

Reaction of 2-(trimethylsilyl)ethyl benzenesulfenate with halides in the presence of TBAF yields phenyl sulfoxides (eq 18).[21] 2-(Trimethylsilyl)ethyl benzenesulfenate is prepared by the reaction of ***Benzenesulfenyl Chloride*** and the lithium salt of 2-(trimethylsilyl)ethanol.

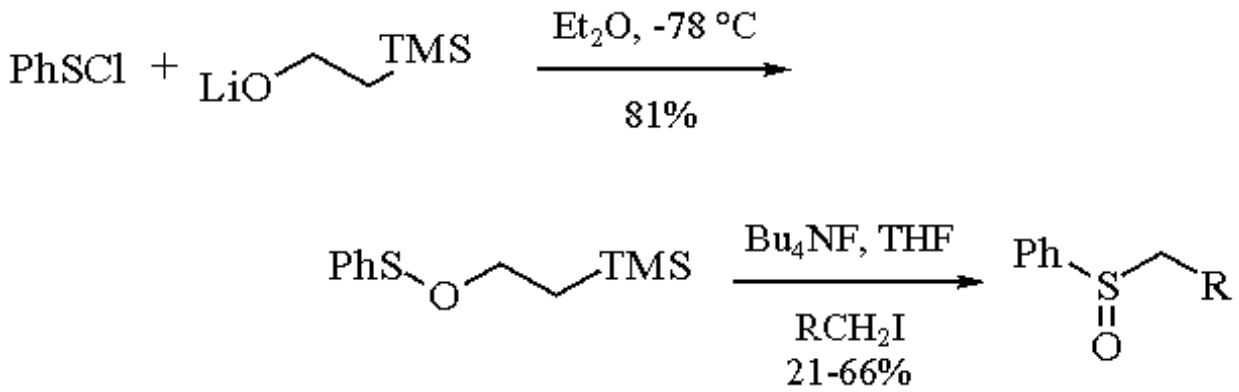

(18)

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2-(Trimethylsilyl)ethoxymethyl Chloride[1]

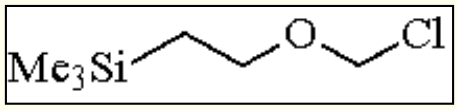

[76513-69-4] · $C_6H_{15}ClOSi$ · 2-(Trimethylsilyl)ethoxymethyl Chloride · (MW 166.75)

(protection of alcohols,[1,2] secondary aryl amines,[3] and imidazole, indole, and pyrrole nitrogens;[4-6] electrophilic formaldehyde equivalent;[7] acyl anion equivalent[8])

Alternate Name: SEM-Cl.

Physical Data: bp 57-59 °C/8 mmHg; *d* 0.942 g cm^{-3}.

Solubility: sol most organic solvents (pentane, CH_2Cl_2, Et_2O, THF, DMF, DMPU, HMPA).

Form Supplied in: liquid; commercially available 90-95% pure; HCl is typical impurity.

Analysis of Reagent Purity: GC.

Preparative Methods: several syntheses have been reported.[2,9-12]

Handling, Storage, and Precautions: water sensitive; corrosive; should be stored in a glass container under an inert atmosphere; a lachrymator; flammable (fp 46 °C).

Reagent for the Protection of Alcohols.

Lipshutz and co-workers introduced the use of SEM-Cl for the protection of primary, secondary, and tertiary alcohols (eq 1).[2] SEM-Cl is now widely employed in organic synthesis for the protection of hydroxyl functionalities (eqs 2 and 3).[13,14]

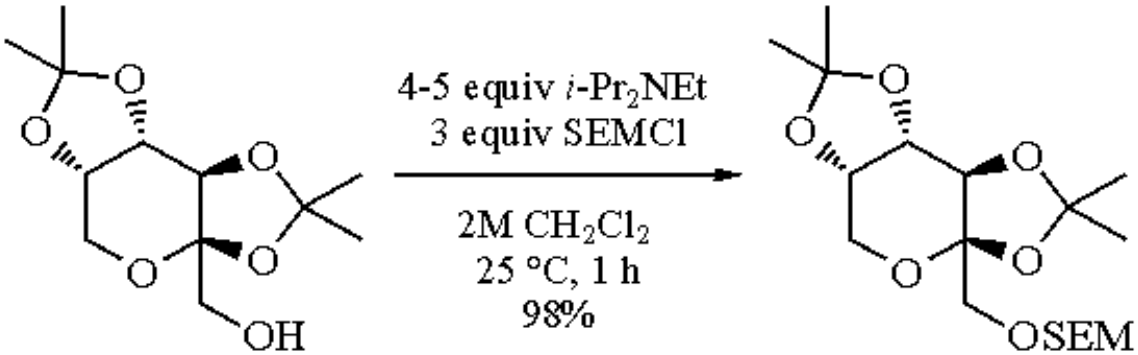

(1)

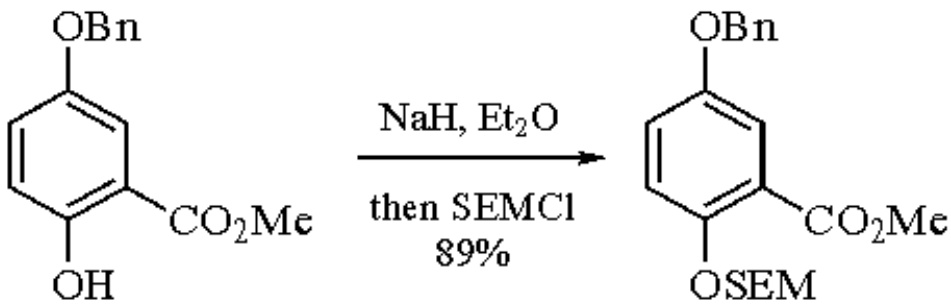

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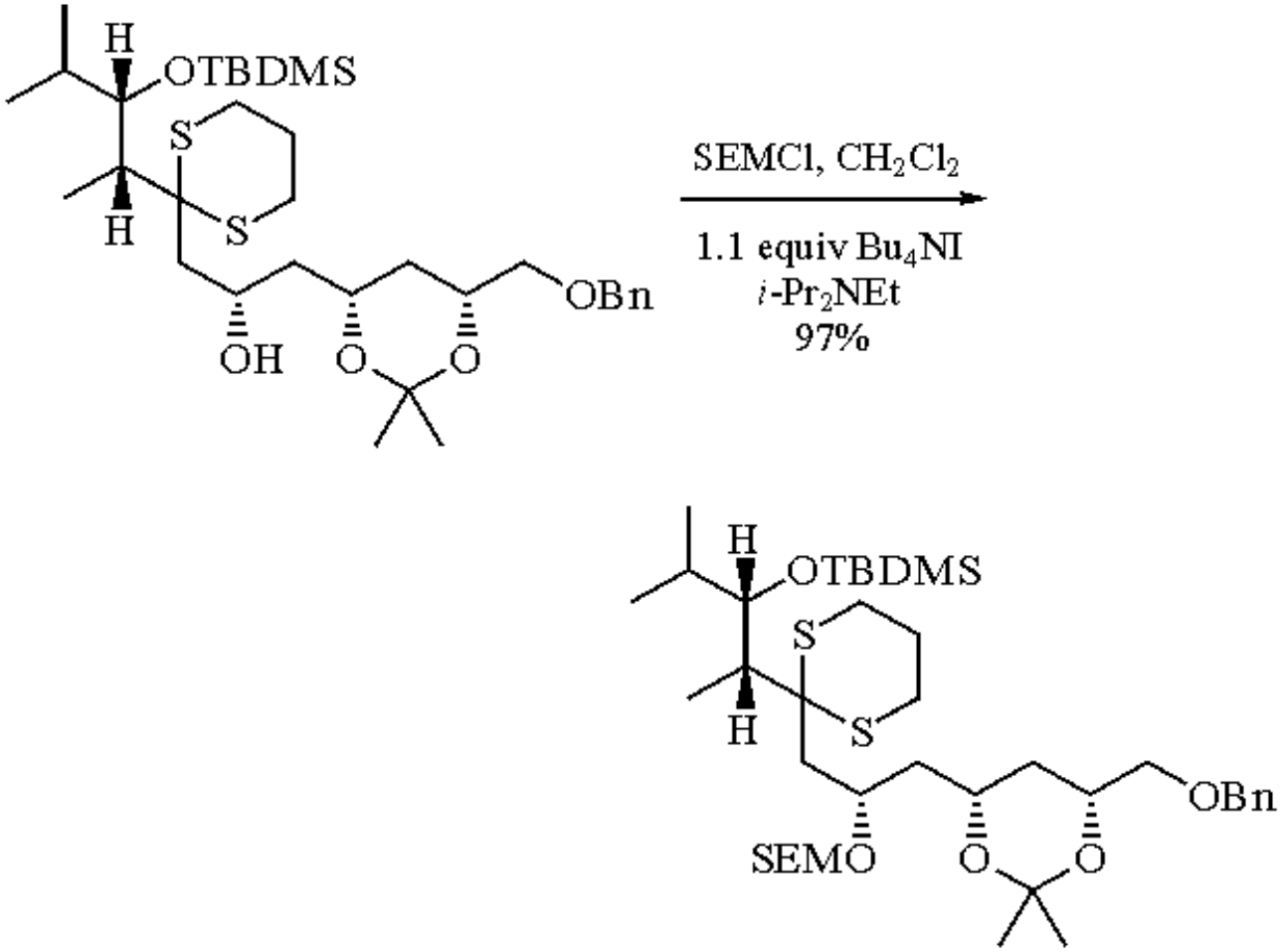

(3)

The resulting SEM ethers are stable under a variety of conditions. Most SEM ethers are cleaved with a fluoride anion source (eqs 4 and 5),[2,15-17] although this fragmentation is generally much less facile than fluoride-induced cleavage of silyloxy bonds. Therefore the selective deprotection of other silyl ethers in the presence of SEM ethers is possible (eq 6).[15] Vigorous conditions with anhydrous fluoride ion are required for the cleavage of some tertiary SEM ethers (eq 7).[18,19]

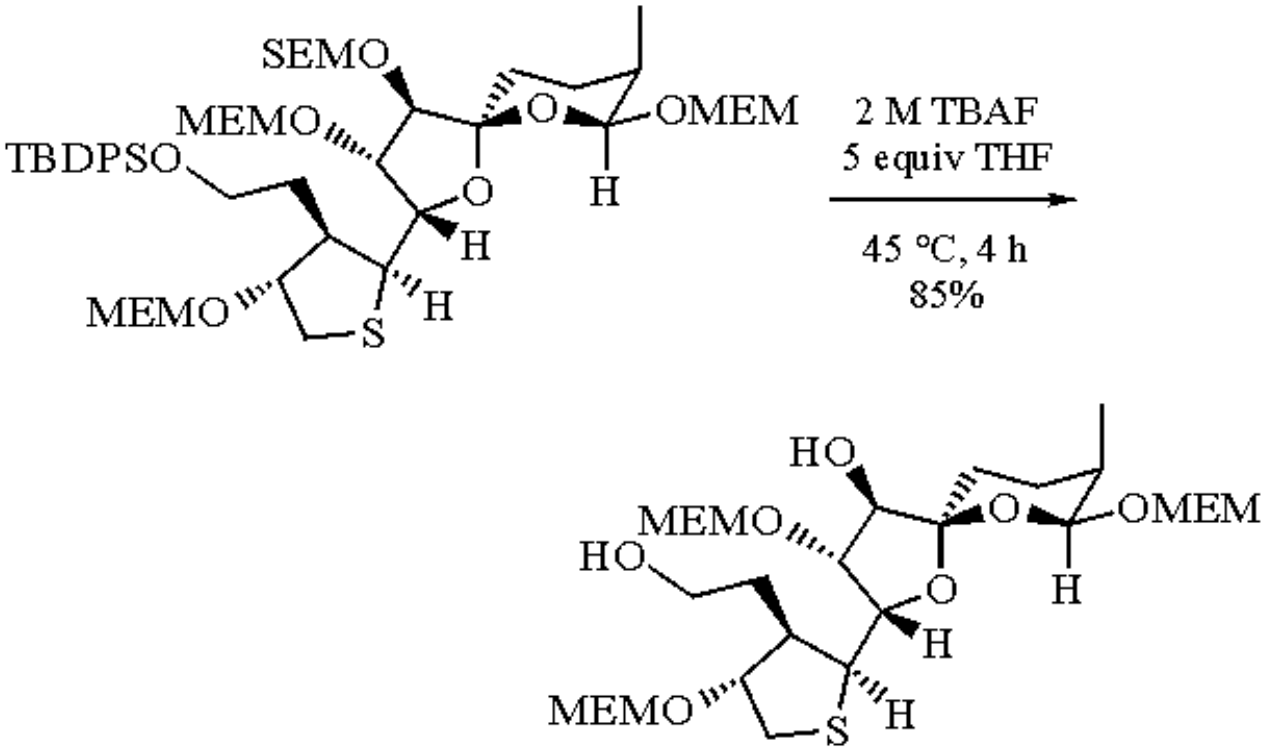

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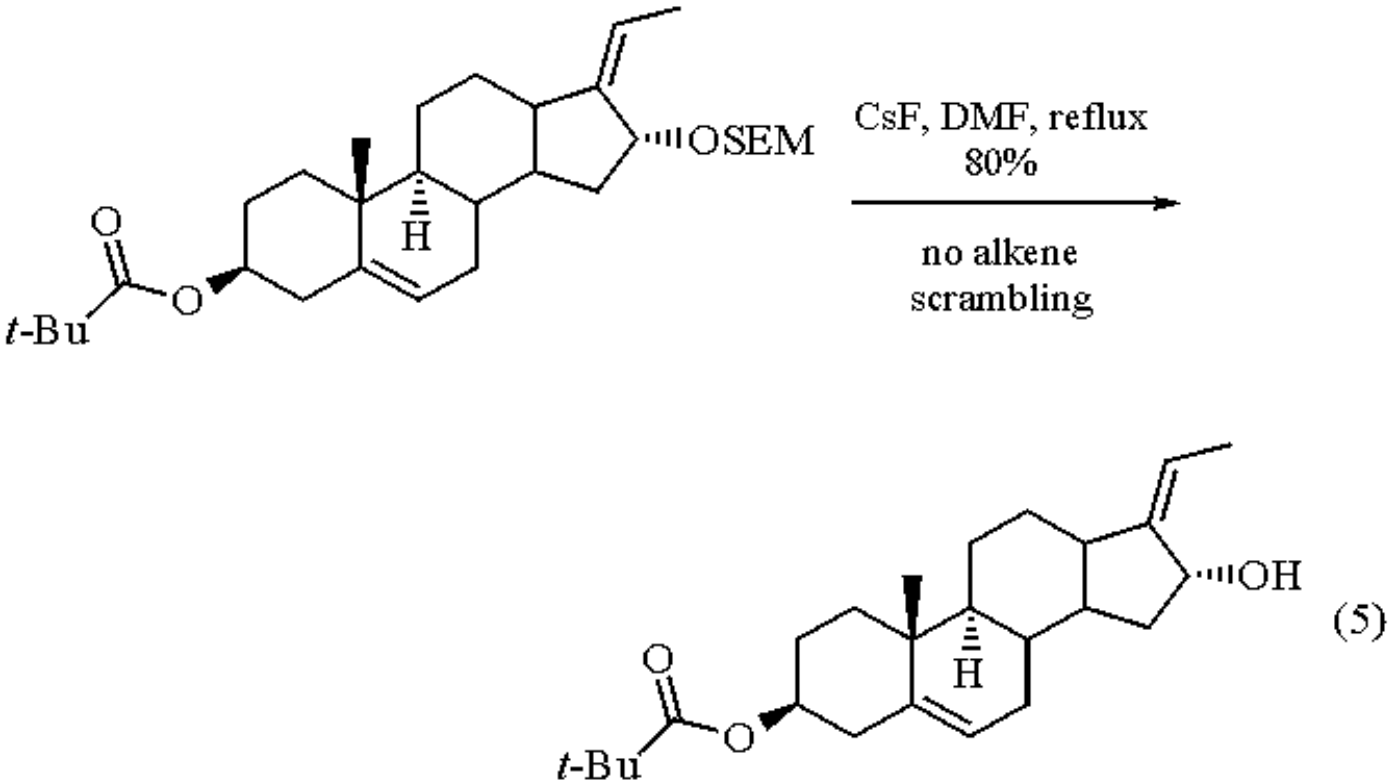

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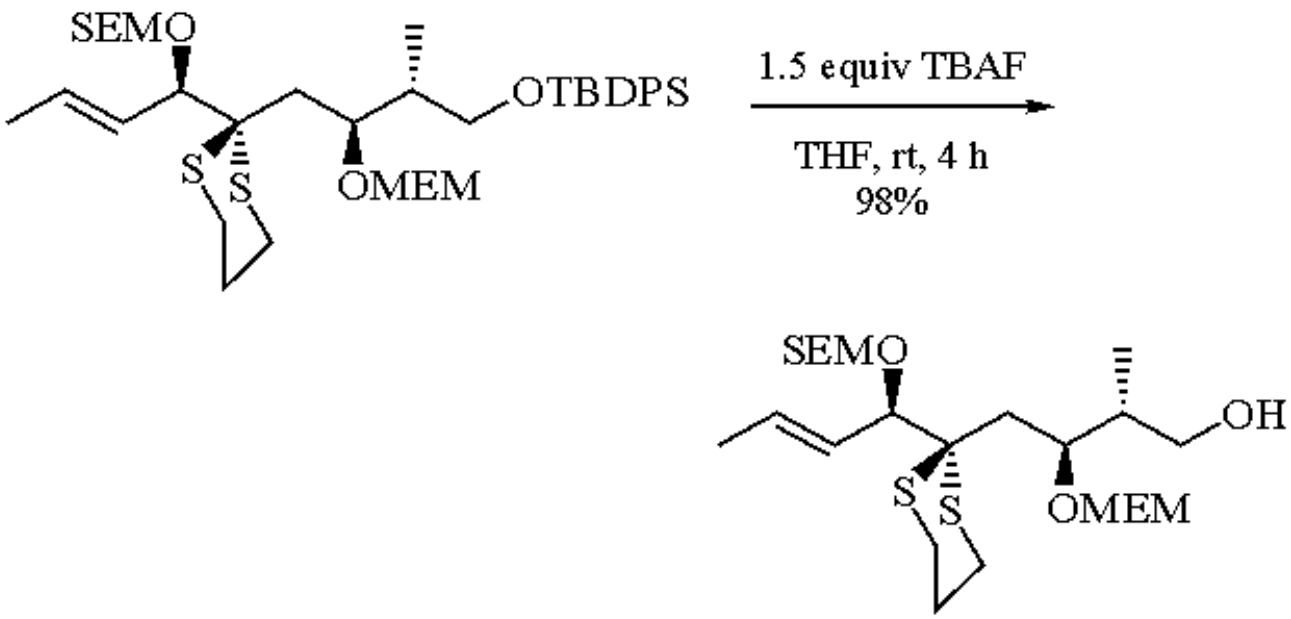

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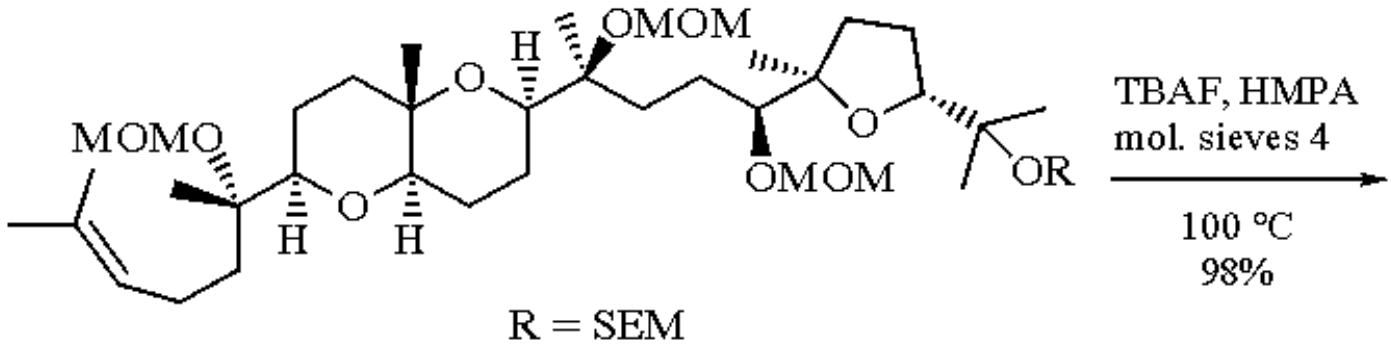

R = H (7)

The stability of SEM ethers has necessitated the development of a variety of other deprotection methods. SEM protective groups are stable to the acidic conditions used to hydrolyze THP, TBDMS, and MOM ethers (AcOH, H_2O, THF, 45 °C),[2] but can be removed under strongly acidic conditions with ***Trifluoroacetic Acid***.[20] SEM, MTM, and MOM ethers are selectively cleaved in the presence of MEM, TBDMS, and

benzyl ethers with ***Magnesium Bromide*** (eq 8).[21] SEM, MOM, and MEM phenolic protective groups are removed with ***Diphosphorus Tetraiodide*** (eq 9).[22]

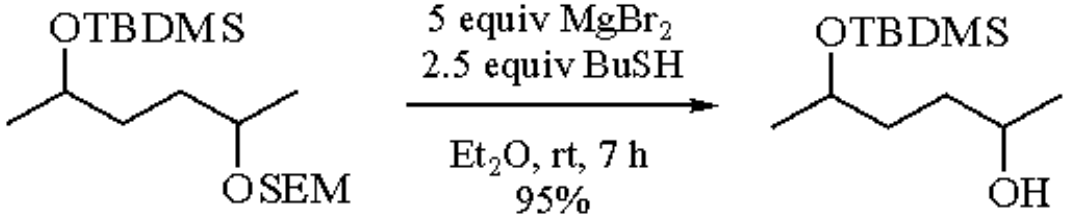

(8)

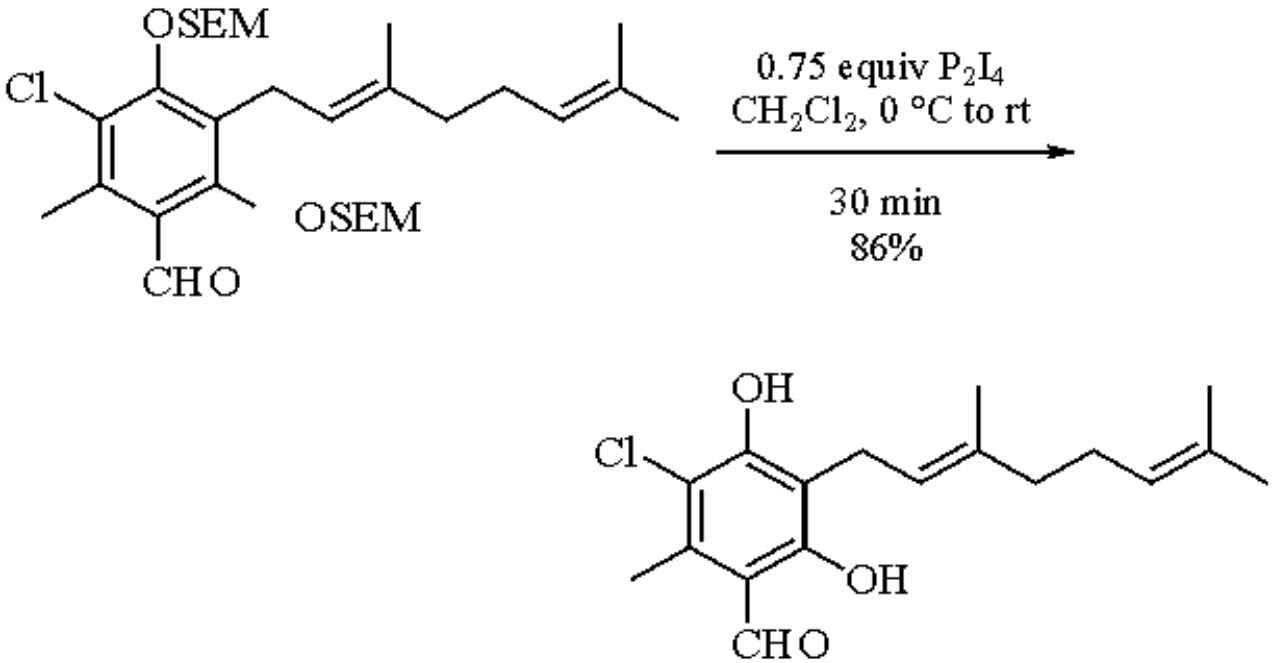

(9)

SEM-Cl has also proven useful in carbohydrate synthesis where the resulting SEM ethers can be cleaved under less acidic conditions than those required for the cleavage of MOM and MEM ethers (eq 10).[23]

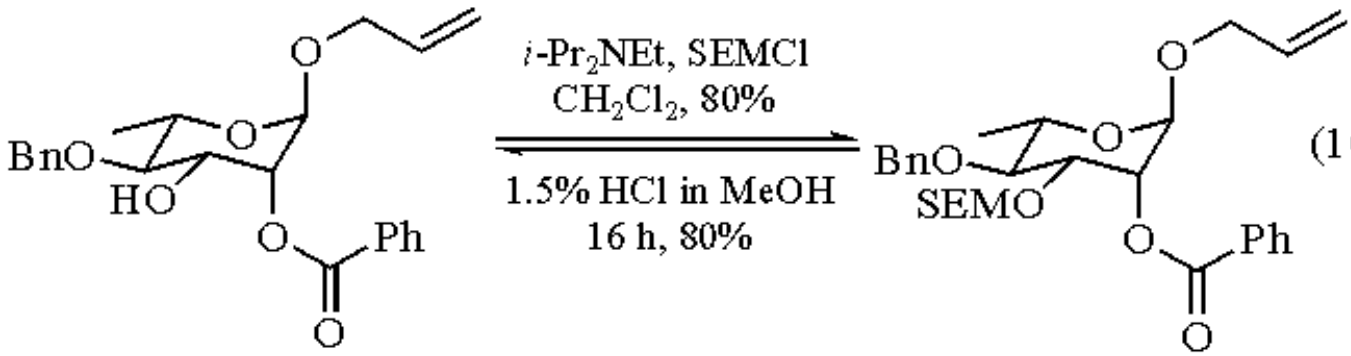

(10)

Reagent for the Protection of Acids.

Carboxylic acids can be protected as SEM esters (eq 11).[24,25] Cleavage of the SEM esters occurs with refluxing methanol[24] or magnesium bromide (eq 12).[25,26]

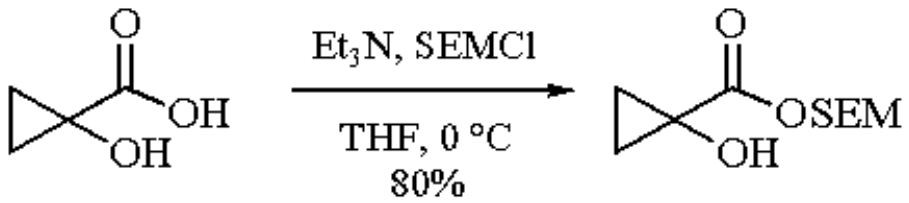

(11)

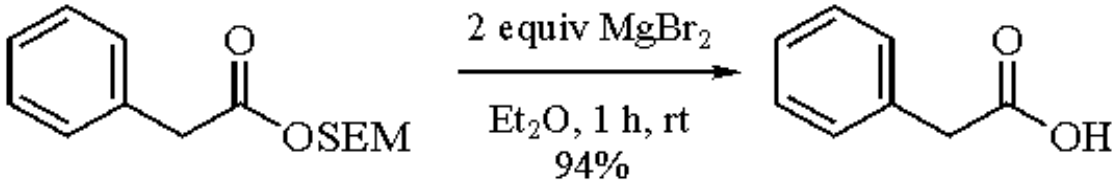

(12)

Reagent for the Protection of Secondary Amines.

SEM-Cl can be used to protect secondary aromatic amines (eq 13),[3] and is an ideal reagent for the protection of imidazoles, indoles, and pyrroles (eqs 14-16).[4-6,27] Many functional groups are compatible with the introduction and cleavage of SEM amines, and the SEM substituent is unusually stable to further functionalization of the molecule.[4-6,27] Recently, a one-pot method for protection and alkylation of imidazoles employing ***n-Butyllithium*** and SEM-Cl has been developed (eq 17).[28-30]

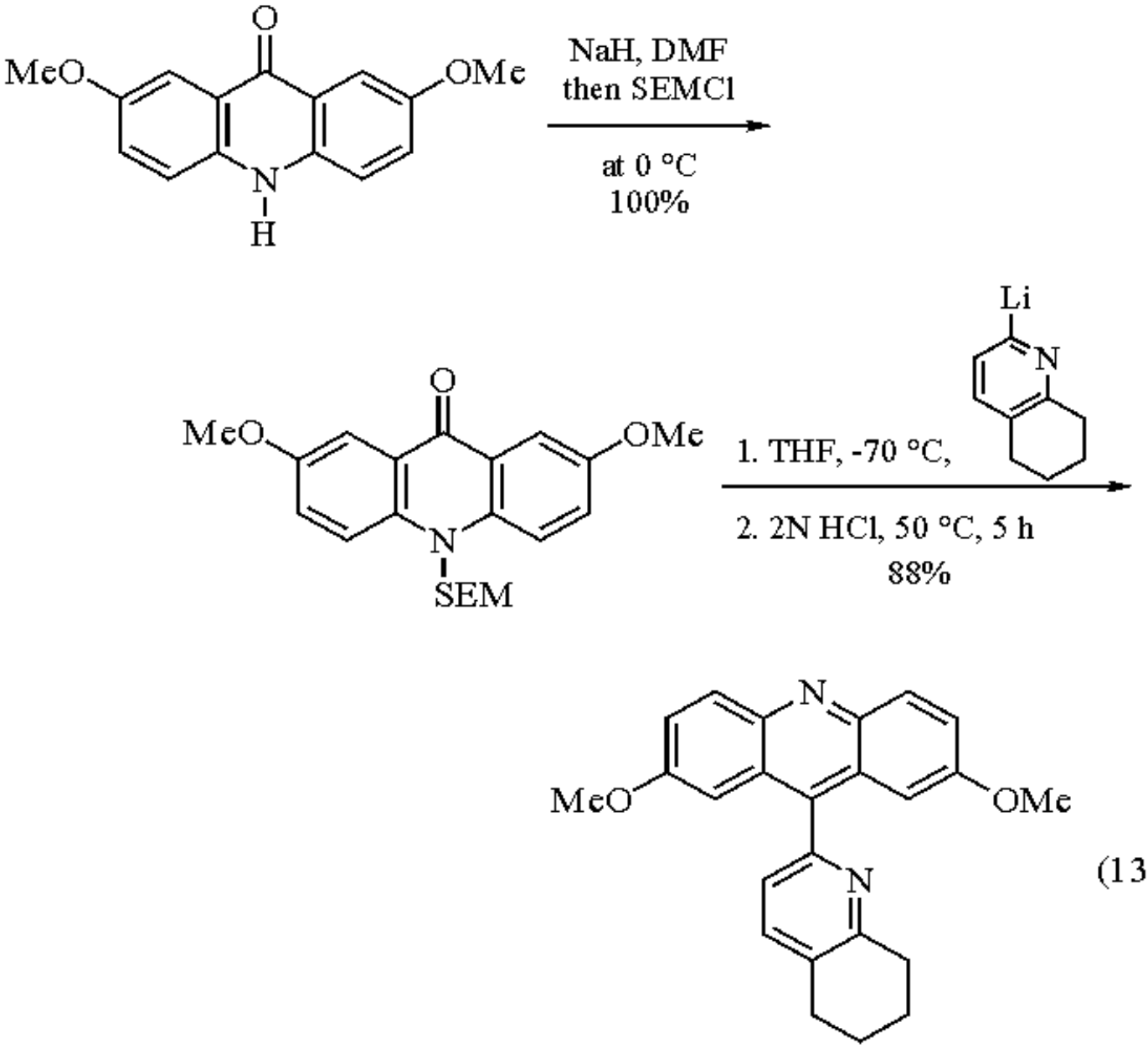

(13)

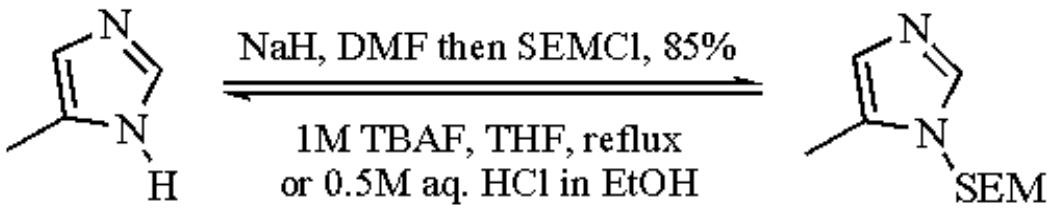

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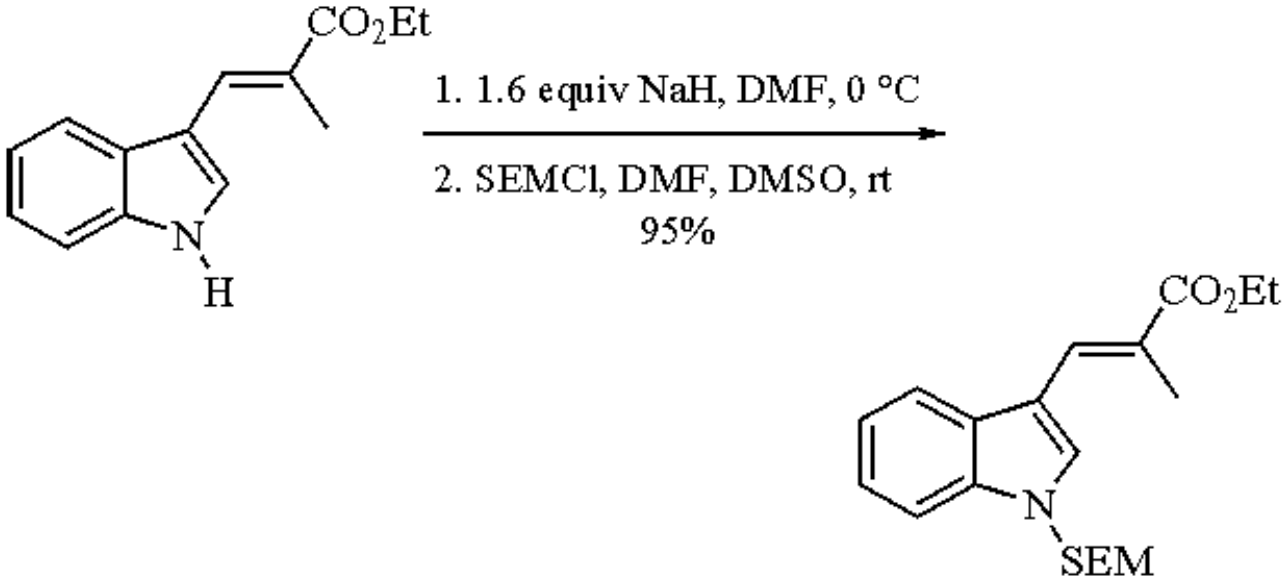

(15)

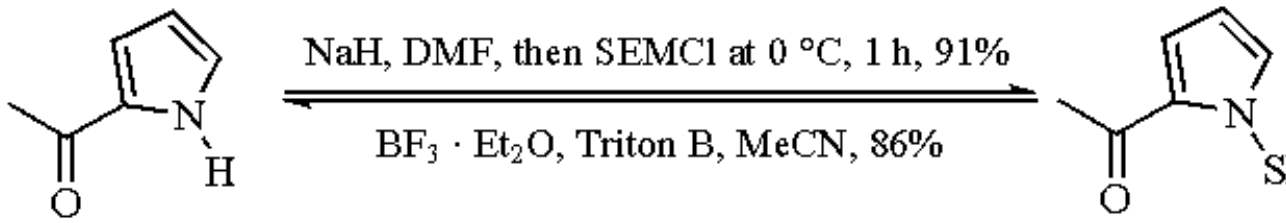

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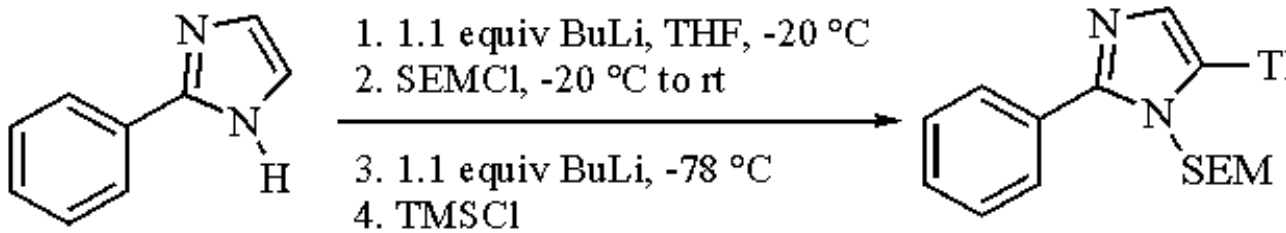

(17)

One-Carbon Homologations.

SEM-Cl has functioned as an alternative to the use of ***Formaldehyde*** (eq 18).[7] The enolate of the lactone (**1**) undergoes *C*-alkylation with SEM-Cl, and the resulting SEM substituent can be subsequently treated with trifluoroacetic acid to afford the alcohol (**2**).

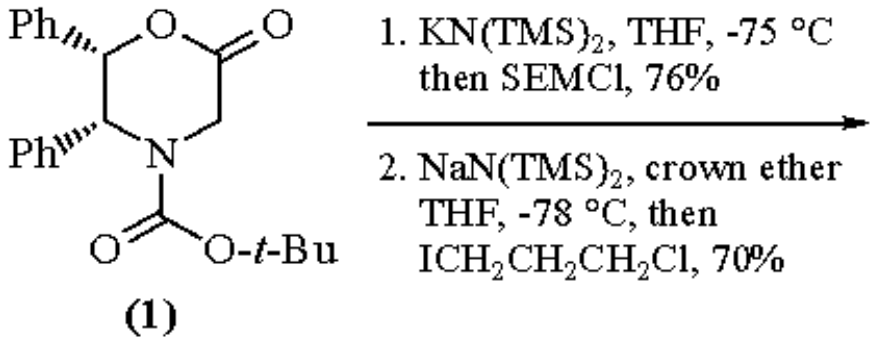

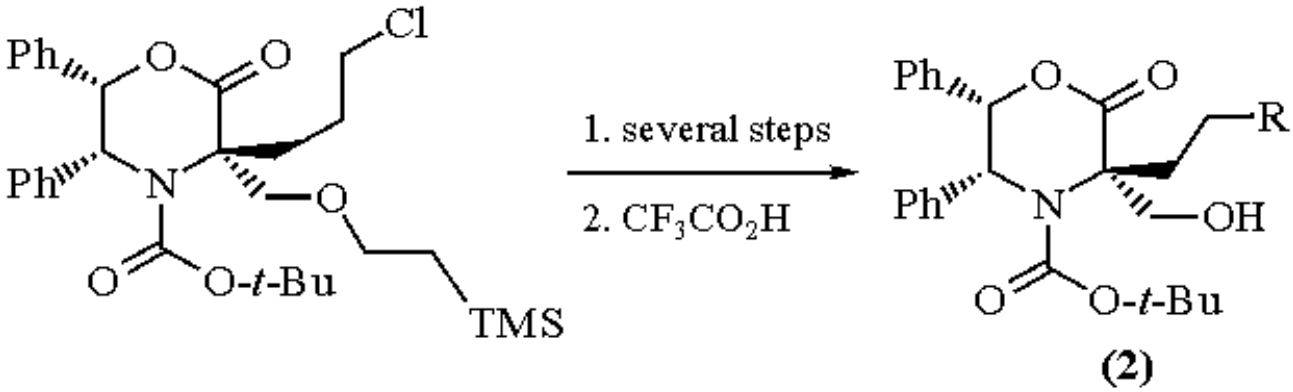

(18)

SEM-Cl has been transformed to a formaldehyde carbanion equivalent.[8] SEM-Cl is converted to the ylide upon treatment with ***Triphenylphosphine*** and ***Sodium Hydride***. This ylide reacts with a variety of aldehydes and ketones affording enol ethers (eq 19).[8] Hydrolysis with 5% aqueous HF gives the corresponding aldehyde.

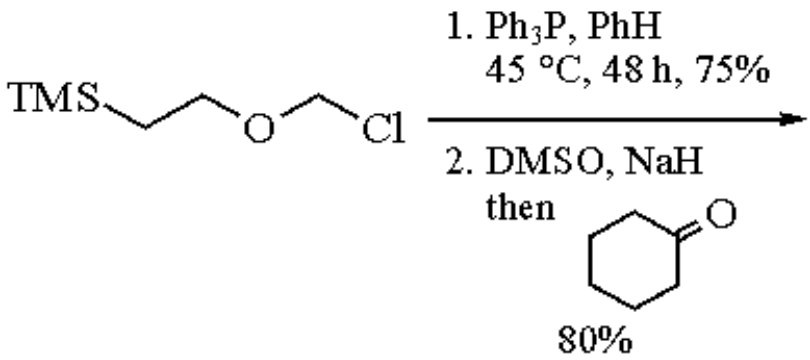

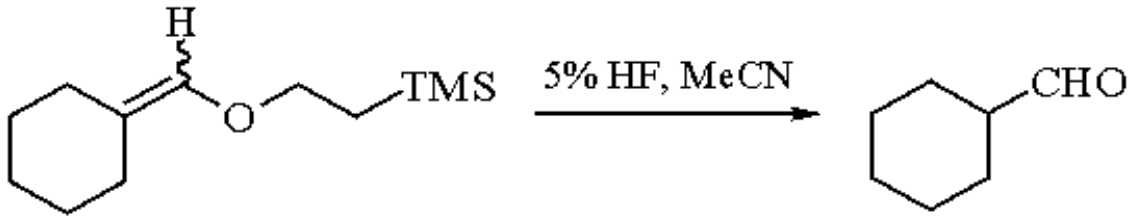

(19)

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30. For a similar method with pyrroles, see Ref. 13.

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2-(Trimethylsilyl)ethoxycarbonylimidazole

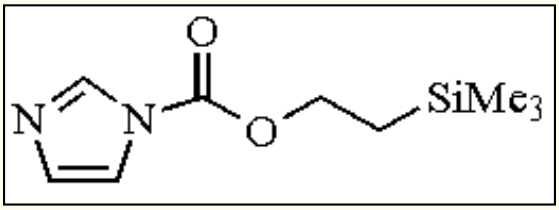

[81616-20-8] · $C_9H_{16}N_2O_2Si$ · 2-(Trimethylsilyl)ethoxycarbonylimidazole · (MW 212.36)

(introduction of the trimethylsilylethoxycarbonyl protecting group[1])

Physical Data: mp 29-30.5 °C;[1] bp 99-100 °C/1 mmHg.[3]

Solubility: insol H_2O; sol benzene, ether, THF, chloroform.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: NMR.[1]

Preparative Method: from ***2-(Trimethylsilyl)ethanol*** and ***N,N´-Carbonyldiimidazole***.[1]

Purification: silica gel chromatography.[1]

Handling, Storage, and Precautions: stable crystalline solid; possibly moisture sensitive.

Protecting Group Formation.

2-(Trimethylsilyl)ethoxycarbonylimidazole (**1**) is a useful reagent for the introduction of the 2-trimethylsilylethoxycarbonyl (Teoc) alcohol protecting group. For example, (**1**) has been used to protect the secondary hydroxyl group of verrucarol (**2**) as the Teoc derivative (eq 1).[1] Note that the apparently low yield (54%) of this reaction is due to the presence of a second reactive hydroxyl group in (**2**). The yield based on consumed (**2**) is a more respectable 81%. Although other examples of the use of (**1**) have not yet been reported, the reagent appears to have significant potential for the protection of alcohols and amines.

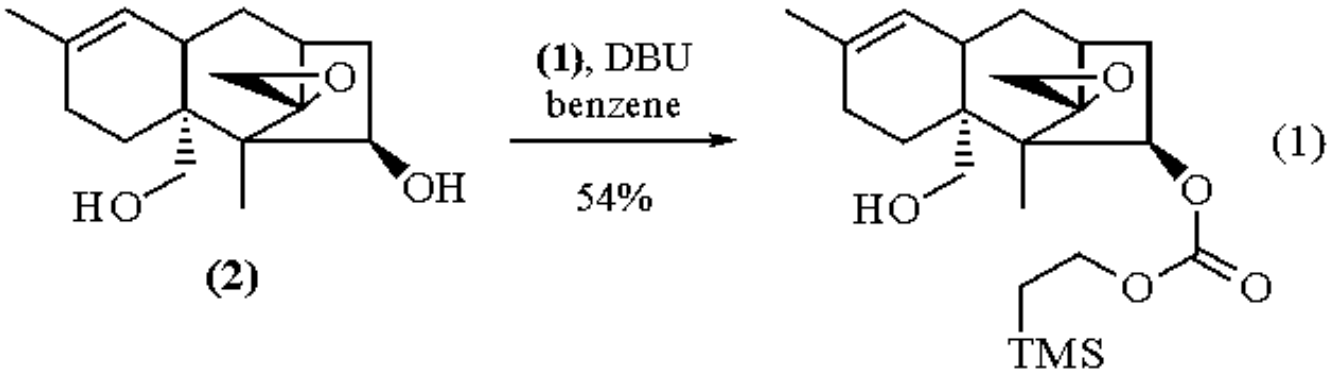

Alternative reagents for the introduction of the Teoc group include ***2-(Trimethylsilyl)ethyl Chloroformate*** (**3**; X = Cl),[2] trimethylsilylethyl azidoformate (**3**; X = N_3),[2] trimethylsilylethyl methoxyvinyl carbonate (**4**),[3] trimethylsilylethyl 4-nitrophenyl carbonate (**5**),[4] and the aminoxy carbonates (**6**).[7] Of these, only the 4-nitrophenyl carbonate (**5**) is commercially available. The carbonate (**5**) has been used to block NH groups in amino acids[4,5] and indoles.[6]

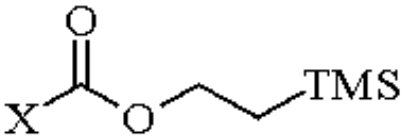

(3)

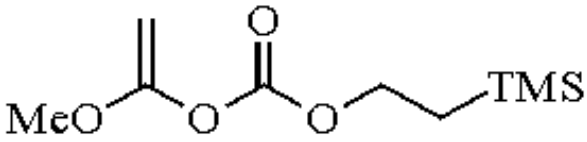

(4)

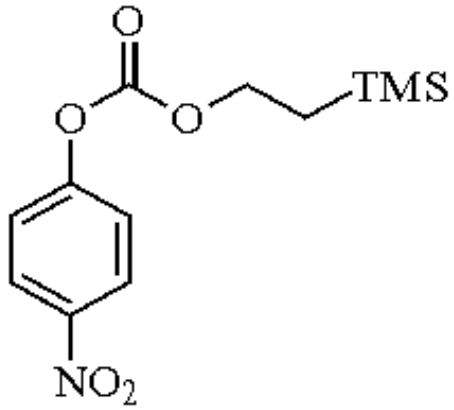

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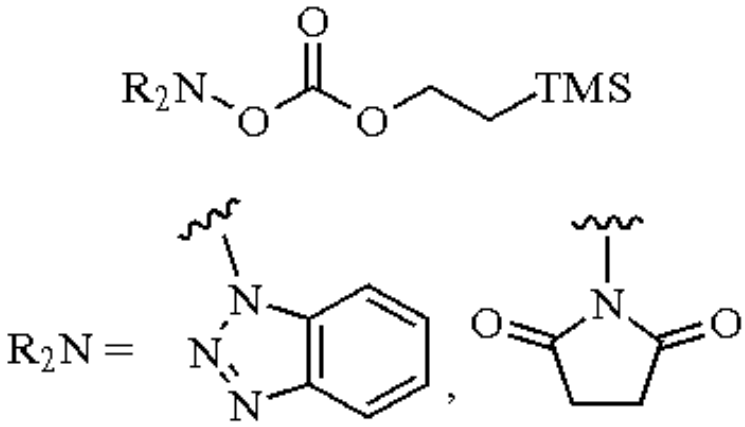

(6)

Although (**1**) is not commercially available, it is a stable, crystalline solid which is readily prepared in excellent yield by condensation of commercially available 2-trimethylsilylethanol and carbonyldiimidazole (eq 2).[1] This procedure avoids the use of potentially dangerous phosgene gas which is required for the preparation of the other reagents. Alternatively, (**1**) may be prepared in a somewhat less convenient manner from (**4**).[3] The stability, easy preparation, and reactivity of (**1**) combine to make it an excellent reagent for the introduction of the Teoc protecting group.

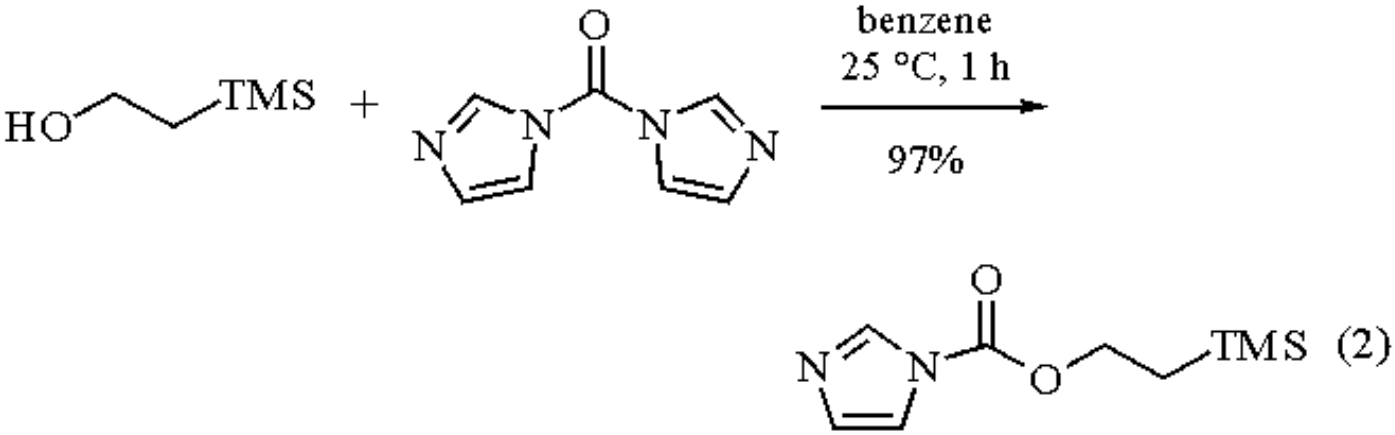

(2)

(1)

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2-(Trimethylsilyl)ethyl Chloroformate

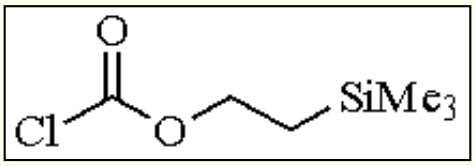

[20160-60-5] · $C_6H_{13}ClO_2Si$ · 2-(Trimethylsilyl)ethyl Chloroformate · (MW 180.73)

(introduction of the trimethylsilylethoxycarbonyl (Teoc) protecting group for amines[1-3] or alcohols;[4,5] activation of tertiary amines for dealkylation[6] or ring opening;[7-10] starting material for alternative reagents for introduction of the trimethylsilylethoxycarbonyl protecting group[11])

Physical Data: bp 34 °C/1 mmHg;[6] bp 42-43 °C/4 mmHg;[12] *d* 0.9944 g cm^{-3}.[1]

Solubility: insol H_2O; sol benzene, ether, THF, chloroform.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: NMR.

Preparative Method: prepared from ***2-(Trimethylsilyl)ethanol*** and ***Phosgene***.[6,11,12]

Purification: distillation.

Handling, Storage, and Precautions: moisture sensitive; stable for three months under nitrogen at 0 °C;[6] probably toxic; handle in a fume hood.

Protection of Amines.[1]

2-(Trimethylsilyl)ethyl chloroformate (**1**) is a useful reagent for the introduction of the trimethylsilylethoxycarbonyl (Teoc) protecting group for amines.[1-3] For example, *p*-chloroaniline reacts with (**1**) to form the expected trimethylsilylethyl carbamate (eq 1).[1] The Teoc protecting group is stable to hydrogenation (H_2, ***Palladium on Carbon***) and mild acid or base. It can be removed with fluoride ion or with a strong acid (e.g. ***Trifluoroacetic Acid***). It is possible to selectively cleave a *t*-butyldimethylsilyl (TBDMS) ether in the presence of a trimethylsilylethyl carbamate (eq 2).[3] For a discussion of alternative reagents for the introduction of the Teoc group, see ***2-(Trimethylsilyl)ethoxycarbonylimidazole***.

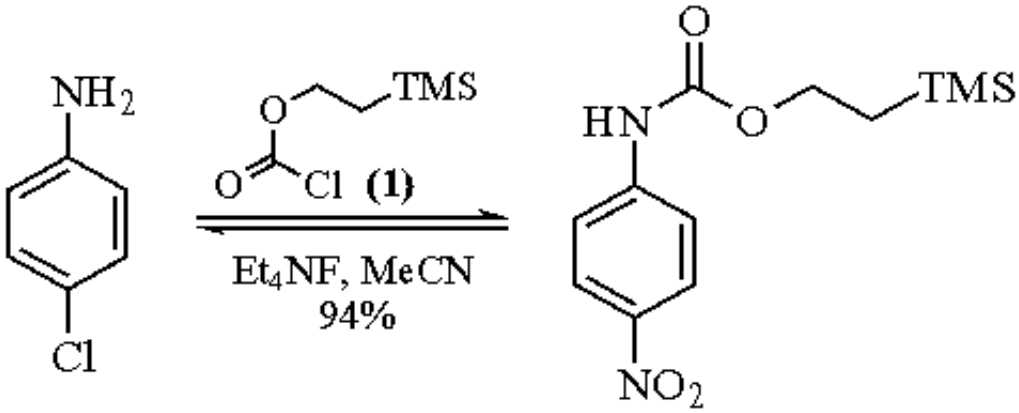

(1)

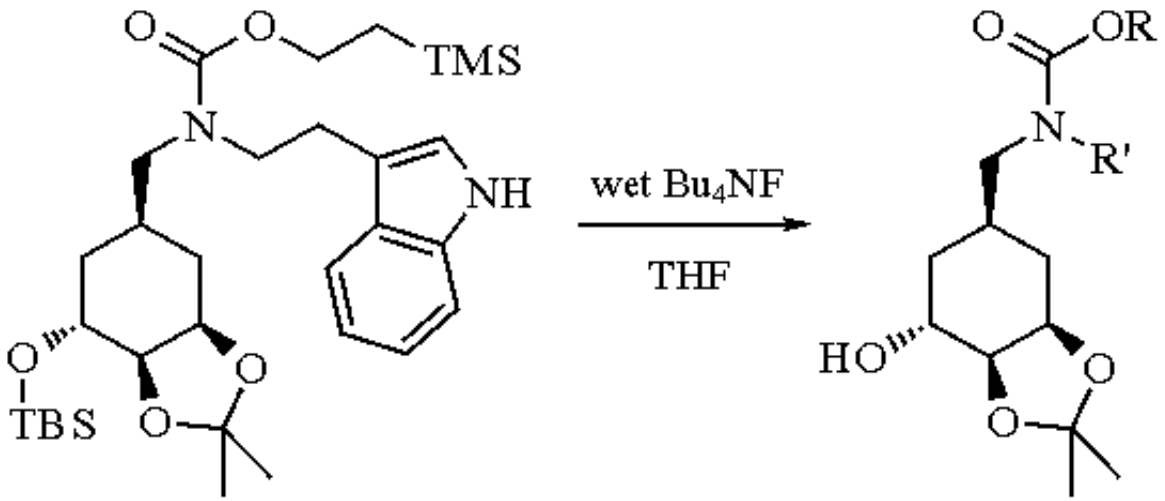

(2)

Protection of Alcohols.[4]

2-(Trimethylsilyl)ethyl chloroformate (**1**) is also useful for the introduction of the trimethylsilylethoxycarbonyl (Teoc) protecting group for alcohols.[4,5] The Teoc protecting group is stable to mild acid but it is base sensitive. It can be cleaved with fluoride ion or with ***Zinc Chloride*** or ***Zinc Bromide*** (eq 3).[4]

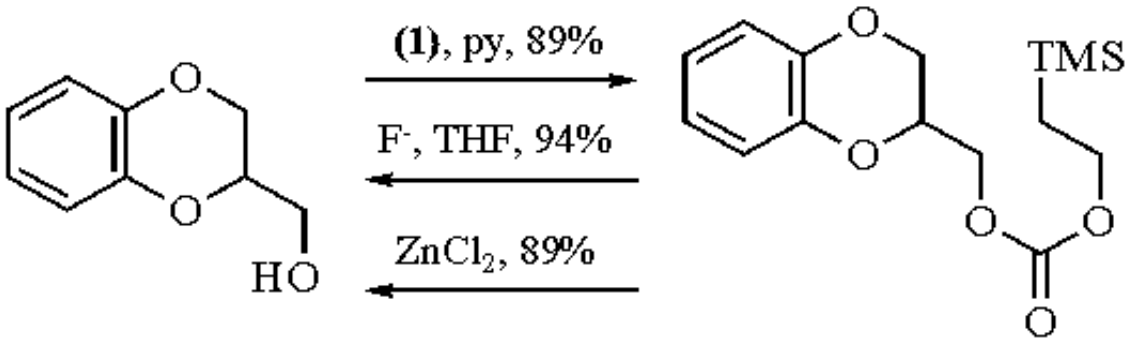

(3)

Dealkylation or Ring Opening of Tertiary Amines.[6-10]

Under certain conditions, 2-(trimethylsilyl)ethyl chloroformate (**1**) is reactive enough to acylate a tertiary amine. The resulting quaternary ammonium species is a sufficiently good leaving group for one of the carbon-nitrogen bonds to be cleaved by reaction with a suitable nucleophile. This process has been used to debenzylate tertiary amines (eq 4).[6] Subsequent removal of the Teoc group (see above) to afford the free amine results in a net debenzylation of the tertiary amine. Demethylation of tertiary amines is also possible but yields are generally lower.[6] Alternatively, for cyclic tertiary amines, acylation of the nitrogen followed by reaction with a nucleophile can result in a ring-opening reaction (eq 5).[7] In a strained ring system (e.g. an aziridine), acylation of the nitrogen followed by reaction with a nucleophile can result in ring opening even for secondary amines (eq 6).[8]

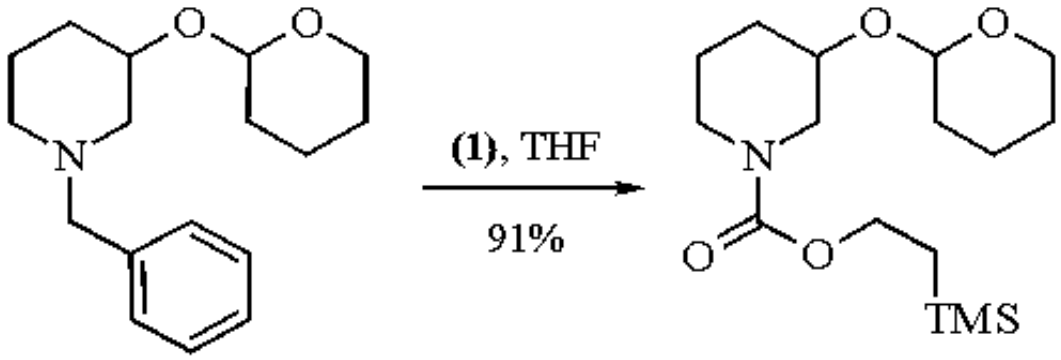

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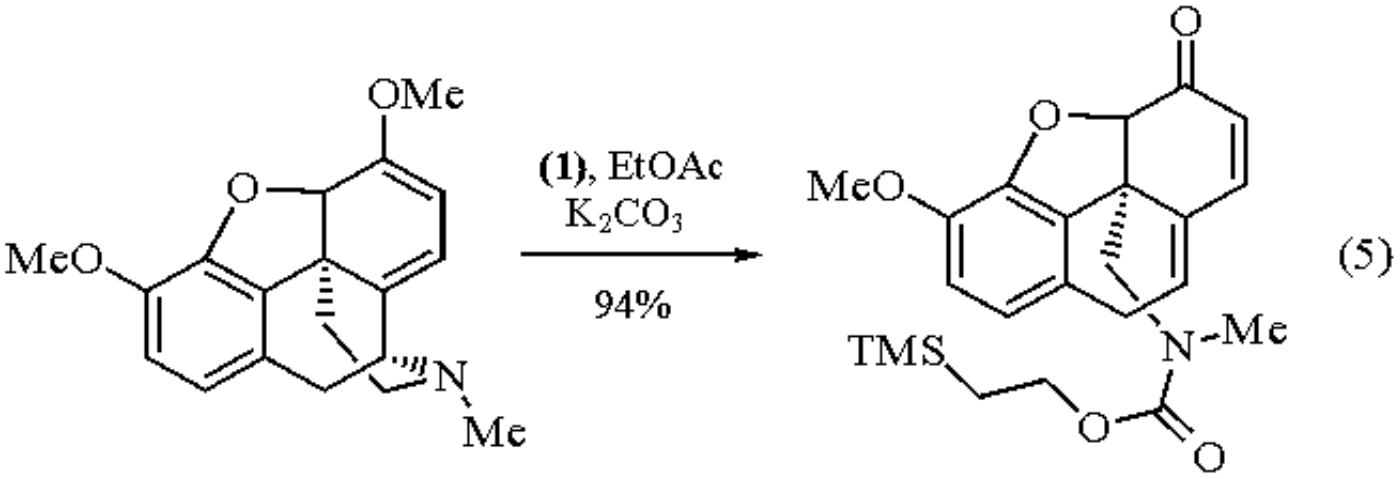

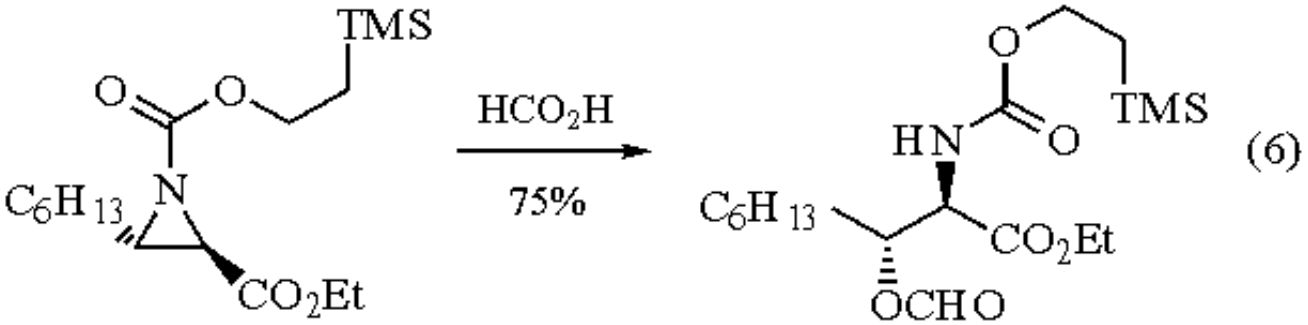

Synthesis of Alternative Teoc Reagents.[11]

The chloroformate (**1**) has been used as a starting material for the preparation of alternative reagents for the introduction of the Teoc group (eq 7).[11] For a discussion of additional alternative reagents for the introduction of the Teoc group, see ***2-(Trimethylsilyl)ethoxycarbonylimidazole***.

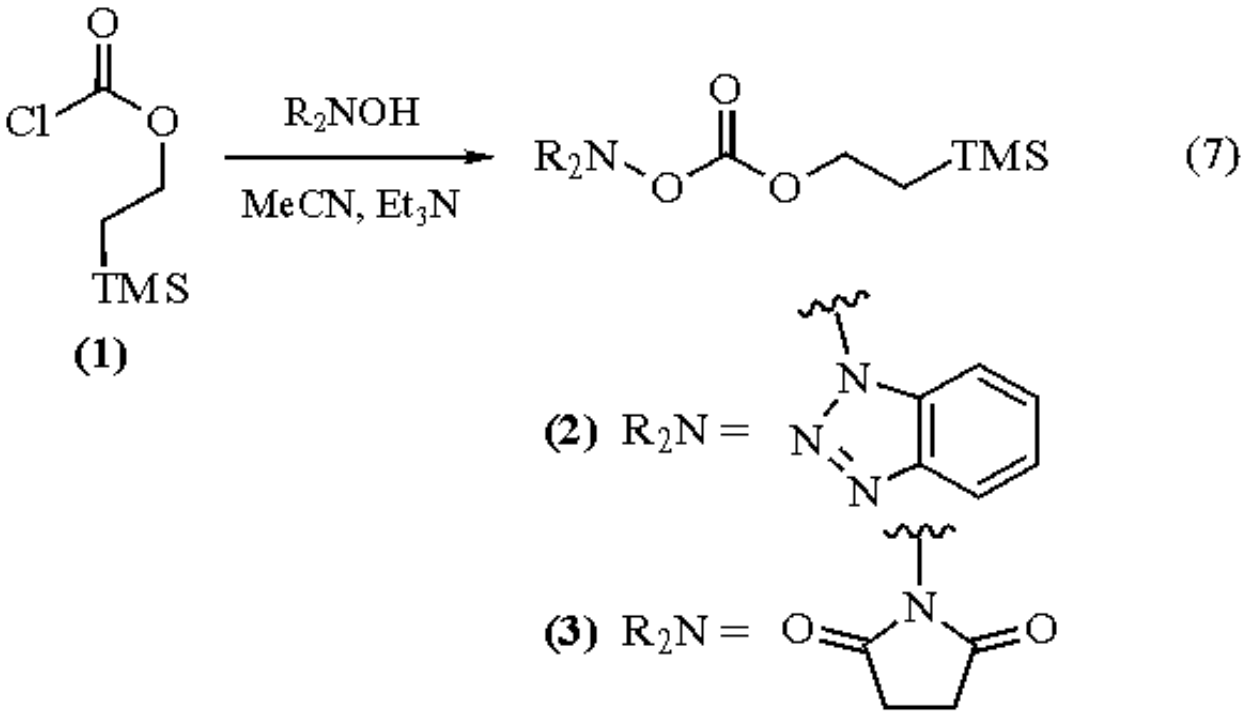

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(Trimethylsilyl)ethynylcopper(I)[1]

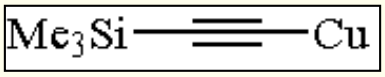

[53210-13-2] · C_5H_9CuSi · (Trimethylsilyl)ethynylcopper(I) · (MW 160.78)

(coupling agent for introduction of the (trimethylsilyl)ethynyl group;[2] preparation of mixed cuprates[3])

Alternate Name: copper(I) trimethylsilylacetylide.

Physical Data: orange-red unstable solid.

Solubility: sol THF, THF-HMPA mixtures; insol ether.

Preparative Methods: by treatment of ***Trimethylsilylacetylene*** with ***Copper(I) t-Butoxide***,[2] by addition of $CuBr.SMe_2$ (see ***Copper(I) Bromide***) to a THF solution of ***Lithium (Trimethylsilyl)acetylide***,[4] or by treatment of trimethylsilylacetylene with ***Triethyl Phosphite*** and ***Copper(I) Chloride***.[5]

Handling, Storage, and Precautions: best generated in situ and used immediately.[2] THF solutions are unstable above -20 °C.[2] The solid is unstable, and all such copper(I) acetylides are potentially explosive. Use in a fume hood.

Coupling Agent.

Copper trimethylsilylacetylide is a versatile coupling agent for introduction of the trimethylsilylethynyl group to activated molecules. Due to the instability of the reagent, the Castro coupling reaction cannot be attempted, but additions to acyl chlorides,[2] activated amines,[6] and terminal (methoxy)iodoallenes have been reported.[7] This last reaction proceeds via an S_N2' mechanism, and a similar addition has been observed with α-acetoxy alkynes (eq 1) giving allenic alkynes in high yield.[8] Coupling between copper TMS-acetylide and 1,2-dichloroalkenes has also been demonstrated.[9,10] Coupling of the copper acetylide (generated in situ) to give the biologically important enediyne framework can be achieved using palladium catalysis (eq 2).[10]

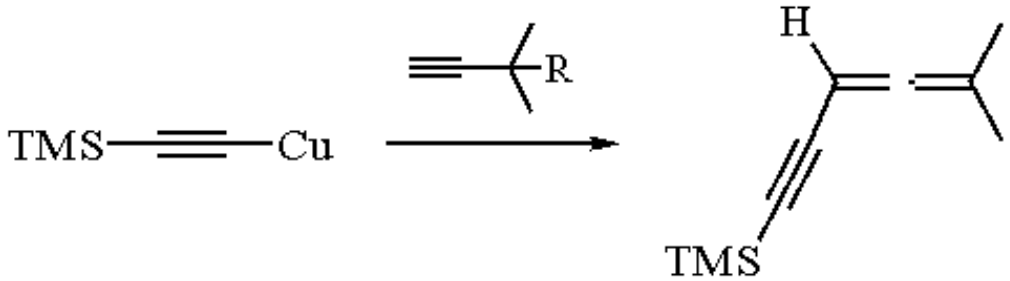

(1)

R = Br, 33%; OAc, 98%; OSOMe, 98%

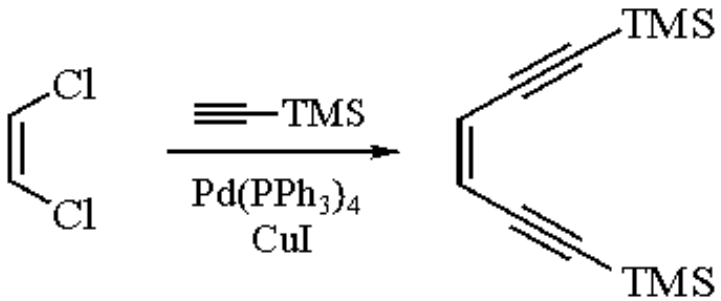

(2)

Mixed Organocuprates.

The trimethylsilylethynyl group acts as a nontransferable dummy ligand (see also ***1-Pentynylcopper(I)-Hexamethylphosphorous Triamide***, ***1-Hexynylcopper(I)***, ***(3-Methoxy-3-methyl-1-butynyl)copper(I)***) when copper trimethylsilylacetylide is converted to a mixed alkyl or vinyl cuprate.[3,11,12] In one report, utilization of a mixed cuprate derived from a terminally lithiated allene allows chemoselective conjugate delivery of the allenic moiety to an α,β-unsaturated system (eq 3), which gives a functionalized and versatile enone system on hydrolysis.[3] The effects of ***Chlorotrimethylsilane*** on such conjugate additions have been studied.[11] On using a mixed cuprate derived from combination with ***n-Butyllithium*** in the presence of TMSCl, smooth and efficient 1,4-butylation ensues (eq 4).[11] The stoichiometry of the TMSCl employed has a marked effect on the reaction profile. Mixed magnesioorganocuprates have also been employed in conjugate addition reactions.[12] The highest yields of the corresponding 1,4-addition products are recovered using a stoichiometry of 3:1 Grignard reagent-copper TMS-acetylide.[12]

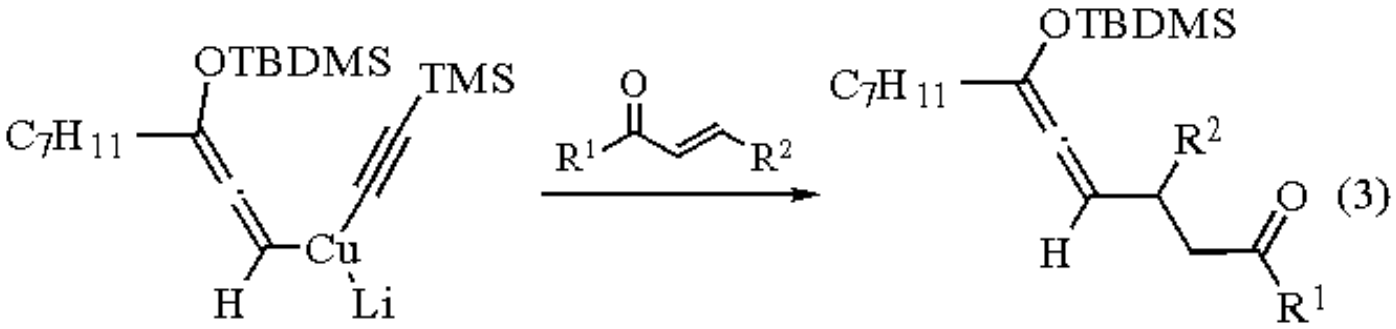

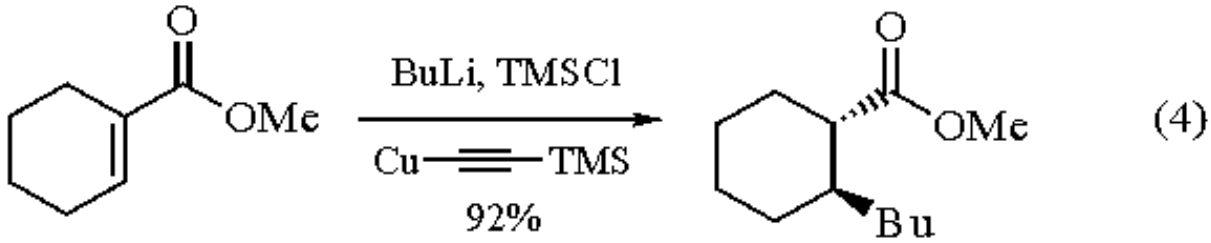

Copper Homoenolates.

Magnesium homoenolates, typically generated by addition of ***Vinylmagnesium Bromide*** to an acyltrimethylsilane, undergo conjugate addition to enones (eq 5) in the presence of copper trimethylsilylacetylide, giving easy access to 1,6-diketones.[4,13] The reaction presumably proceeds via a mixed copper homoenolate, with the trimethylsilylethynyl group acting as a nontransferable ligand.

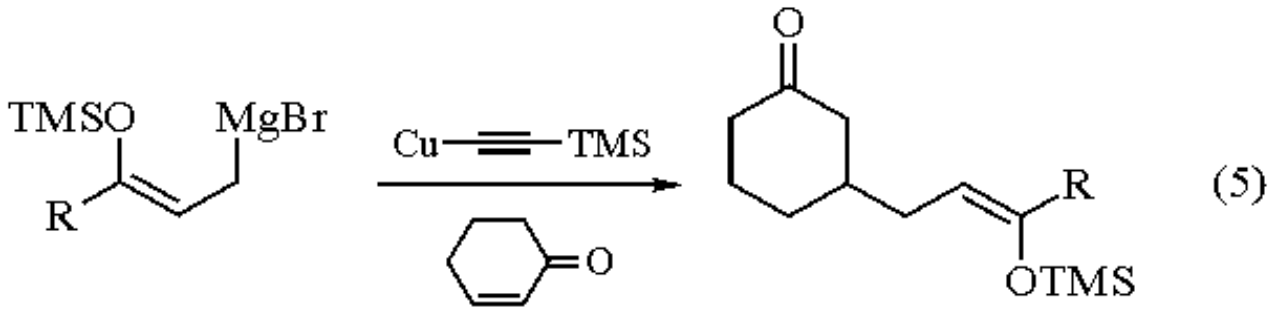

Related Reagents.

3-Trimethylsilyl-2-propynylcopper(I).

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1. (a) Normant, J. F. *S* **1972**, 63. (b) Sladkov, A. M.; Gol'ding, I. R. *RCR* **1979**, *48*, 868. (c) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (d) *FF* **1977**, *6*, 148.
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13. Enda, J.; Matsutani, T.; Kuwajima, I. *TL* **1984**, *25*, 5307.

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N-(Trimethylsilyl)imidazole[1]

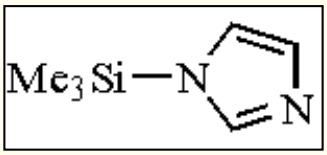

[18156-74-6] · $C_6H_{12}N_2Si$ · *N*-(Trimethylsilyl)imidazole · (MW 140.29)

(silylating agent for alcohols and 1,3-dicarbonyl compounds;[2] reaction with esters to give imidazolides; preparation of *O*-trimethylsilyl monothioacetals; aromatization of the A-ring of steroids)

Physical Data: bp 93-94 °C/14 mmHg; fp 5 °C; *d* 0.956 g cm^{-3}.

Form Supplied in: liquid.

Handling, Storage, and Precautions: flammable. Harmful by inhalation, in contact with skin, and if swallowed. Possible carcinogen. Use in a fume hood. When using, wear protective gear and clothing. Handle and store under N_2. Store in a cool dry place.

General Discussion.

N-(Trimethylsilyl)imidazole is a powerful silylating agent for alcohols (eq 1).[2] 1,3-Dicarbonyl compounds, although usually existing mostly in the enol form, are not efficiently silylated by standard methods. *N*-(Trimethylsilyl)imidazole has proved to be an ideal reagent for this transformation (eq 2).[3]

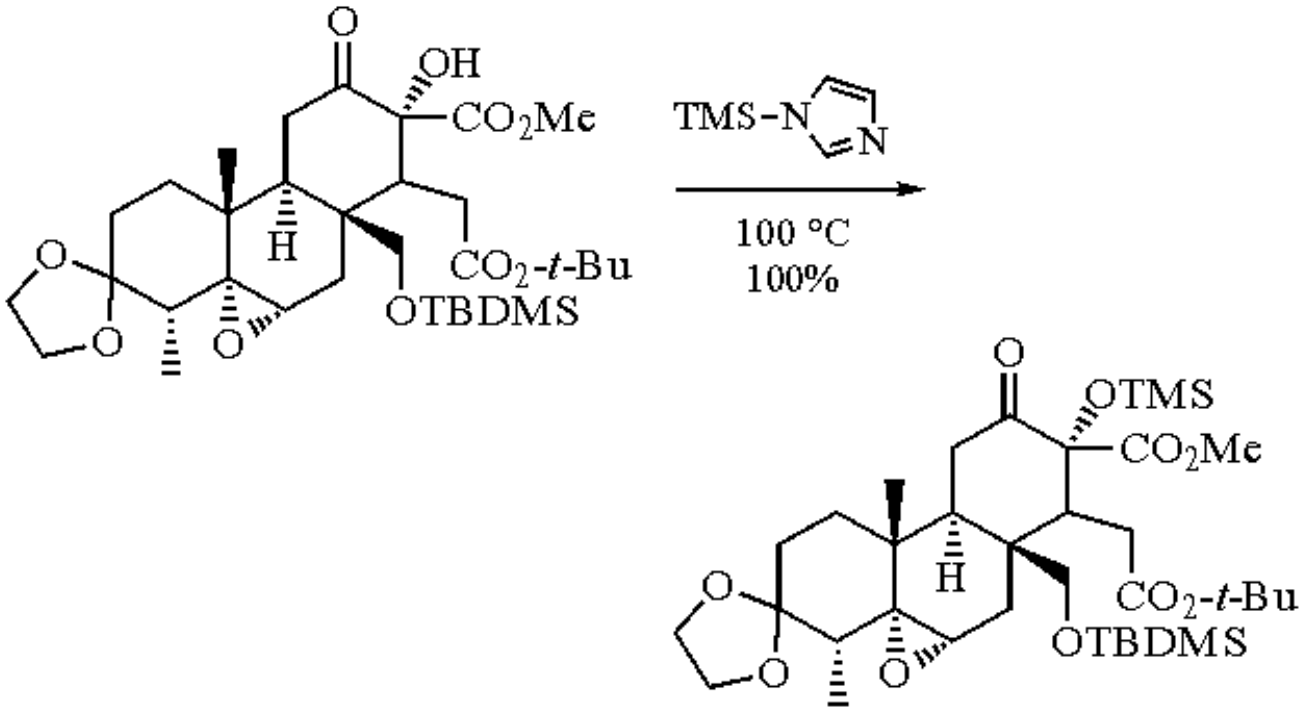

(1)

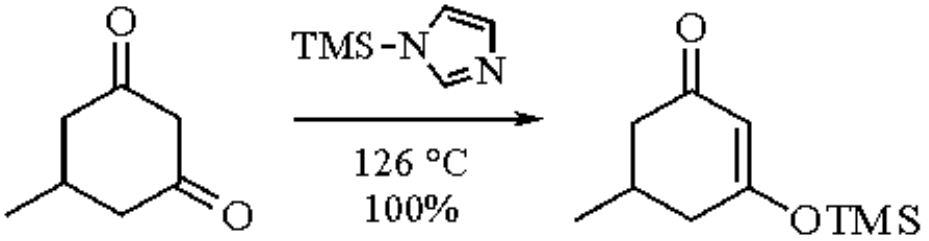

(2)

N-(Trimethylsilyl)imidazole reacts with phenyl and 2,2,2-trifluoroethyl esters under base catalysis to give acylimidazolides (eq 3).[4] These imidazolides show reactivity similar to acyl chlorides and therefore are useful in synthesis.[5]

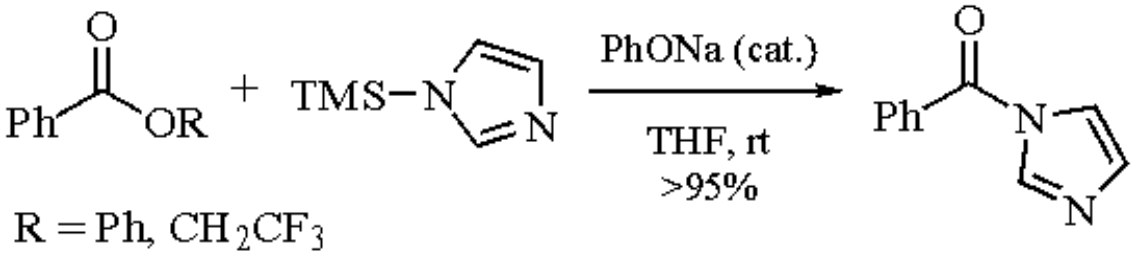

(3)

N-(Trimethylsilyl)imidazole is used in the preparation of *O*-trimethylsilyl monothioacetals directly from corresponding carbonyl compounds and thiols (eq 4).[6] The basicity of the medium due to the imidazole generated during the reaction effectively prevents dithioacetalation.

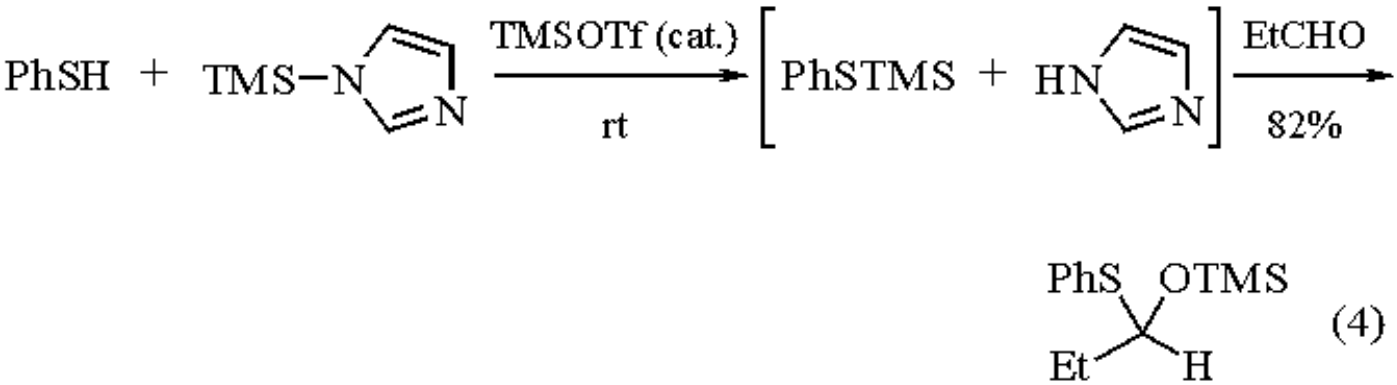

(4)

Aromatization of the A-ring of steroid systems has been achieved by the use of *N*-(trimethylsilyl)imidazole (eq 5).[7]

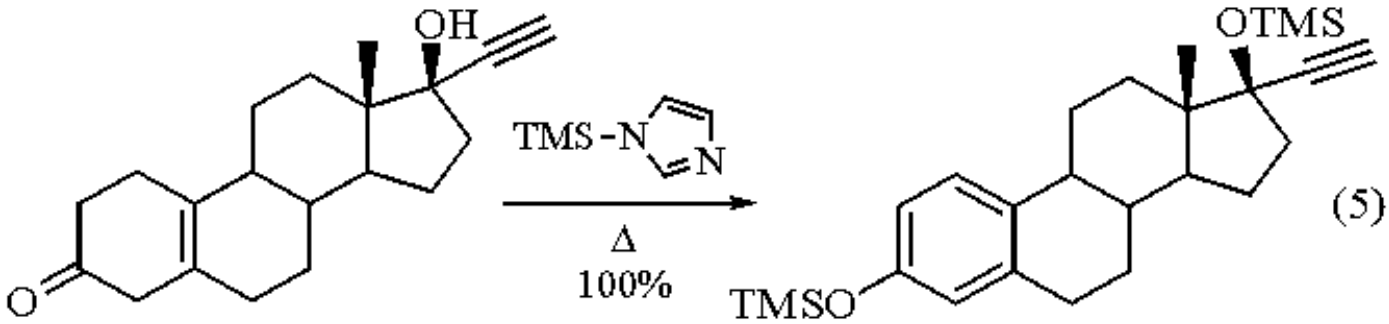

(5)

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1. For reviews on silylations, see: (a) Birkofer, L.; Ritter, A. *AG(E)* **1965**, *4*, 417. (b) Klebe, J. F. *ACR* **1970**, *3*, 299. (c) Colvin, E. W. *CSR* **1978**, *7*, 15. (d) Cooper, B. E. *CI(L)* **1978**, 794. (e) Fleming, I. *CSR* **1981**, *10*, 83. (f) Lalonde, M.; Chan, T. H. *S* **1985**, 817.
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Janet Wisniewski Grissom & Gamini Gunawardena

Trimethylsilylketene[1]

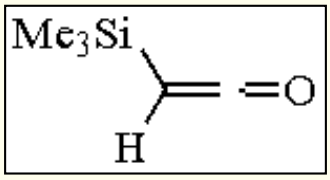

[4071-85-6] · $C_5H_{10}OSi$ · Trimethylsilylketene · (MW 114.24)

(reactive acylating agent for amines and alcohols;[2] building block for synthesis of coumarins;[3] synthesis of α-silyl ketones via the addition of organocerium reagents;[4] treatment with stabilized ylides forms trimethylsilyl-substituted allenes;[2a] cycloaddition with aldehydes affords β-lactones;[5] forms small rings with diazomethane;[6] treatment with *n*-BuLi forms a ketene enolate[7])

Physical Data: [2a,7] bp 81-82 °C; *d* 0.80 g cm^{-3}.

Solubility: sol CH_2Cl_2, $CHCl_3$, CCl_4, THF, diethyl ether, and most standard organic solvents; reacts with alcoholic and amine solvents.

Form Supplied in: colorless oil; not commercially available.

Analysis of Reagent Purity: [8] IR (CCl_4) 2130 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.65 (s, 1 H), 0.12 (s, 9 H) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 179.4, 0.5, -0.2 ppm.

Preparative Methods: most often prepared (eq 1) by pyrolysis of ***Ethoxy(trimethylsilyl)acetylene*** at 120 °C (100 mmol scale, 65% yield).[2a] Recently, pyrolysis of *t*-butoxy(trimethylsilyl)acetylene has been shown to be a convenient alternative for the preparation of trimethylsilylketene (**1**). Thermal decomposition of *t*-butoxy(trimethylsilyl)acetylene causes elimination of 2-methylpropene slowly at temperatures as low as 50 °C and instantaneously at 100-110 °C (30 mmol scale, 63% yield).[8] The main advantage of this method is that it is possible to generate trimethylsilylketene in the presence of nucleophiles, leading to in situ trimethylsilylacetylation (eq 2). Increased shielding of the triple bond prevents problems such as polymerization and nucleophilic attack that occur when the ketene is generated in situ from (trimethylsilyl)ethoxyacetylene. Trimethylsilylketene can also be prepared (eq 3) via the dehydration of commercially available ***Trimethylsilylacetic Acid*** with ***1,3-Dicyclohexylcarbodiimide*** (DCC) in the presence of a catalytic amount of ***Triethylamine*** (100 mmol scale, 63%).[9] Other typical methods used for ketene generation such as dehydrohalogenation of the acyl chloride[10] and pyrolysis of the anhydride[10b,11] have been applied to the preparation of (**1**); however, both methods afford low yields.

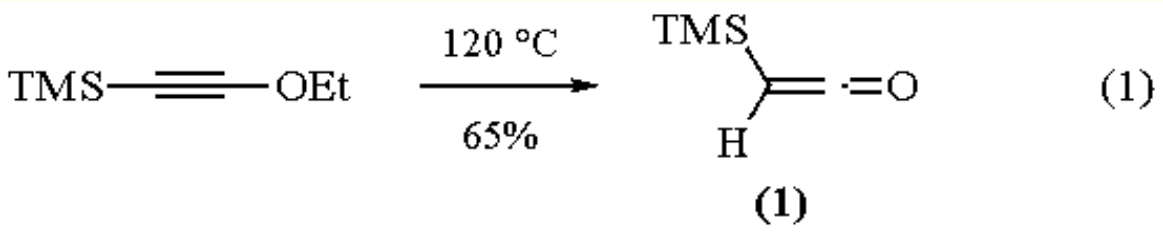

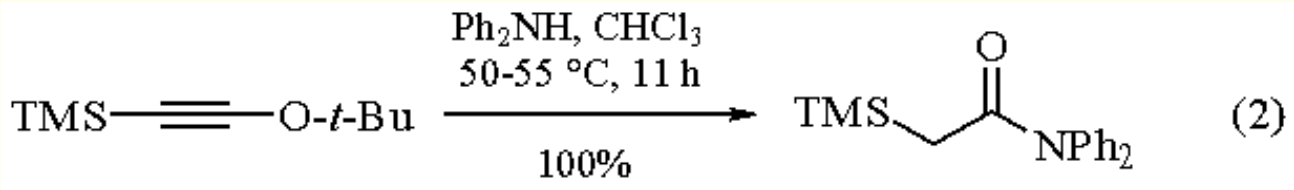

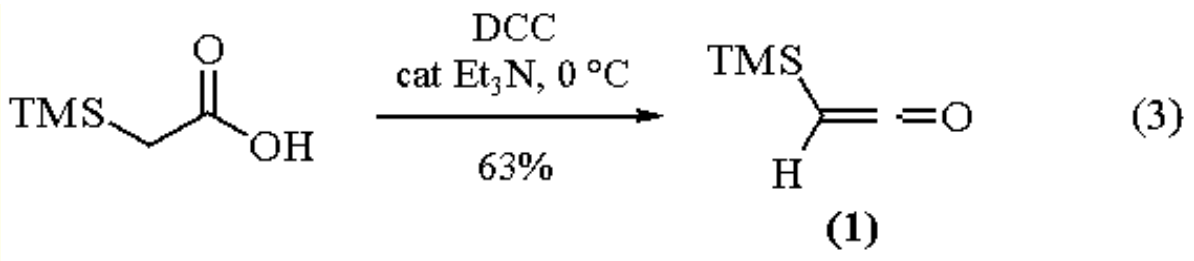

(3)

Purification: purified by distillation at 82 °C/760 mmHg.

Handling, Storage, and Precautions: unusually stable for an aldoketene with respect to dimerization and decomposition. Samples stored neat under nitrogen at room temperature show no noticeable decomposition after several months.

Trimethylsilylacetylation of Alcohols and Amines.

Trimethylsilylketene (**1**) has been used as a potent acylating agent for amines and alcohols (eq 4).[2a] It reacts almost instantaneously with hindered amines to form α-silyl amides in quantitative yield. Reaction with alcohols such as *t*-butanol is much slower (CCl_4, 48 h, rt, 80% yield). However, ***Boron Trifluoride Etherate*** strongly catalyzes α-silylacetate formation. Hindered tertiary alcohols that cannot be acylated by standard reagents such as benzoyl chloride, acetyl chloride, and acetic anhydride (even in the presence of DMAP) can be acylated by (**1**). Desilylation can be effected using ***Potassium Fluoride*** in methanol to produce the acetate directly (eq 5).[12] When the addition of alcohols to (**1**) is catalyzed by zinc halides, a high degree of functionality can be tolerated in the substrate, including carbonyl, acetal, thioacetyl, epoxy, and alkenic groups.[2b] In contrast, $BF_3.Et_2O$ catalysis results in partial product desilylation with alcohols containing carbonyl groups and also causes cleavage of acetal groups. Other reactions used to prepare α-silyl acetates including the Reformatsky reaction,[13] *C*-silylation of esters,[14] and silyl migration from acylsilanes[15] are incompatible with many active functional groups. Functionalized α-silyl acetates serve as useful precursors to butenolides (eq 6).[2b]

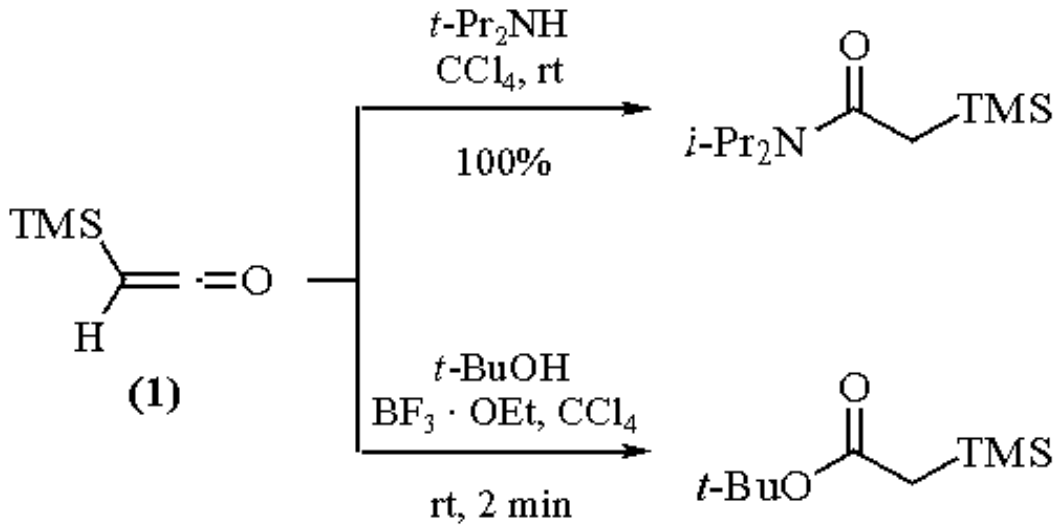

(4)

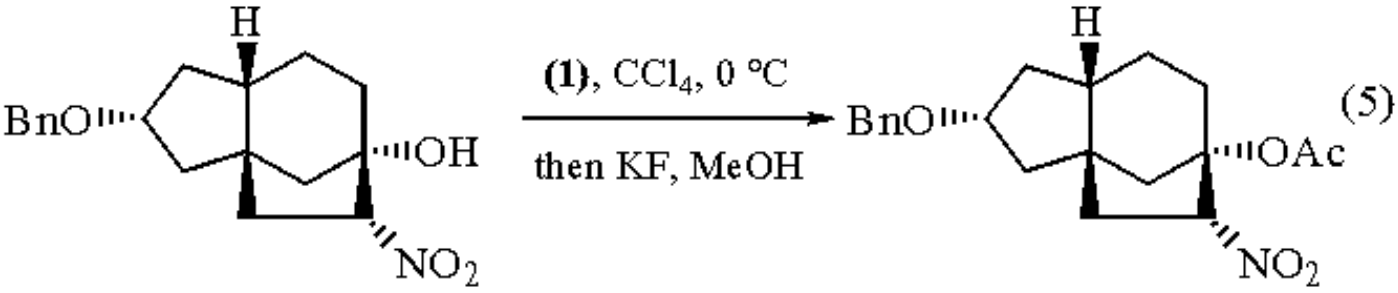

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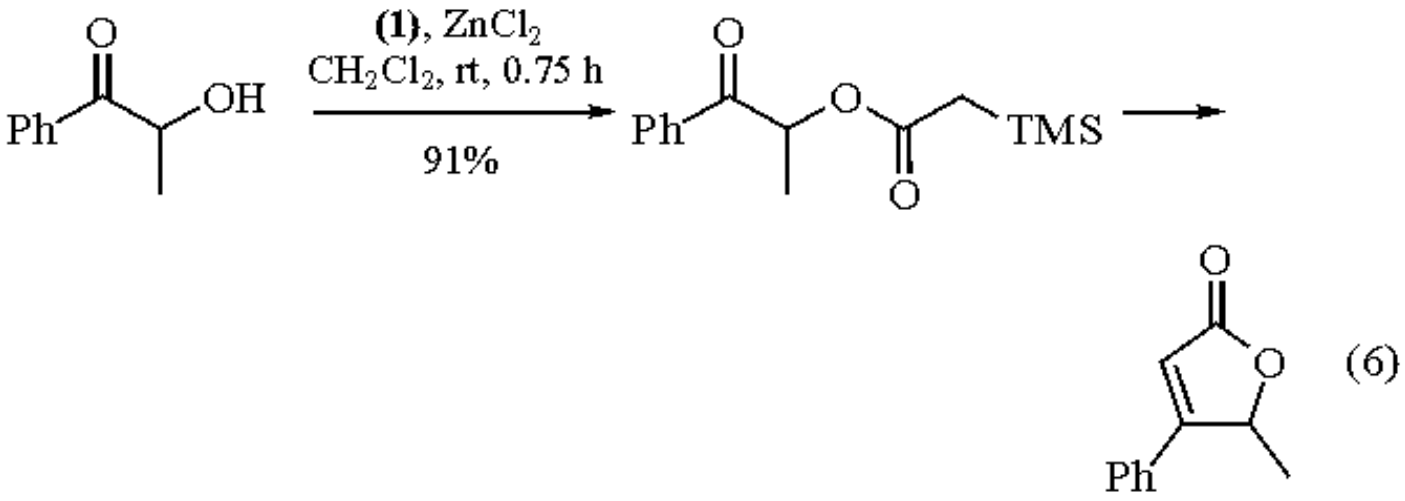

Synthesis of Coumarins via Cyclization-Elimination.

Reaction of (**1**) with *o*-acylphenols affords coumarins in high yields in a one-pot reaction (eq 7).[3] The reaction is applicable to a variety of functionalized aromatic systems. Coumarins form more readily in somewhat higher yield using this procedure as compared to a similar method involving the use of a cumulated phosphorus ylide reagent, ***Ketenylidenetriphenylphosphorane***.[16] Workup and product isolation is easier in view of the triphenylphosphine oxide byproduct formed in the ylide reaction. Other methods used to convert *o*-acylphenols to coumarins include approaches based on Knovenagel[17] and Pechmann[18] reactions. The method described above involves milder conditions and often provides coumarins in higher yields.

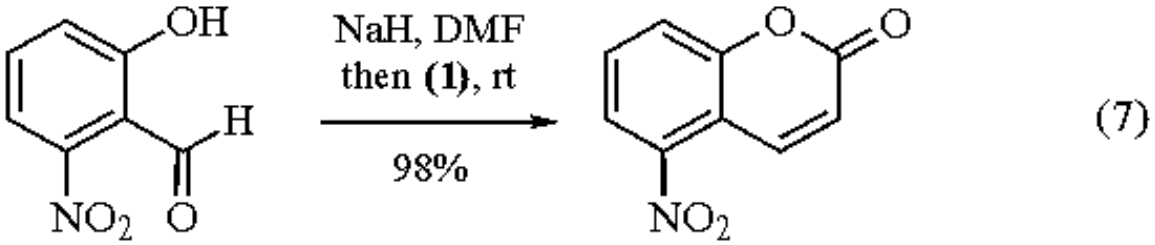

One-pot Formation of α-Silyl Ketones.

α-Silyl ketones can be prepared in a one-pot synthesis by the addition of organocerium reagents to (**1**) followed by subsequent quenching with aqueous ammonium chloride or alkyl halides (eq 8).[4] The organocerium reagents can be easily prepared from ***Cerium(III) Chloride*** and an alkyl- or aryllithium. Organolithium reagents are not suitable for this reaction because proton abstraction is preferred resulting only in complicated reaction mixtures of products.[7] A variety of other methods have been reported for the synthesis of α-silyl ketones, including methods based on 1,3-O to C silyl migration from lithiated silyl enol ethers,[19] other types of migration from silicon-containing compounds,[20] isomerization of silicon-containing allyl alcohols,[21] and Si-H insertion reactions of diazo ketones,[22] as well as classical preparations involving carboxylic acid derivatives[23] and the oxidation of β-hydroxy silanes.[21,23] However, most of these methods require multistep procedures and are less convenient.

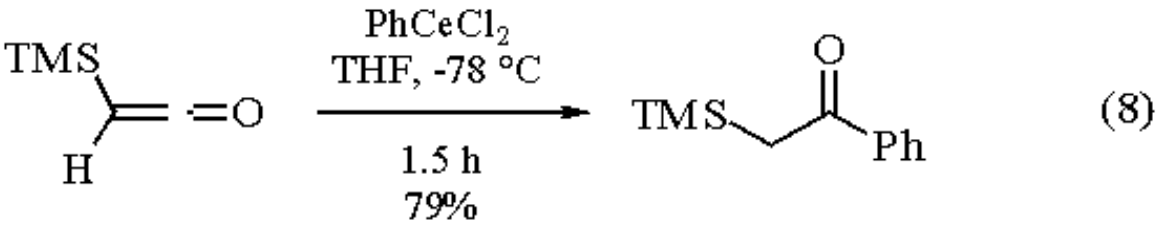

Preparation of Trimethylsilyl-Substituted Allenes.

Treatment of (**1**) with a stabilized phosphorus ylide, ***(Ethoxycarbonylmethylene)triphenylphosphorane***, affords the silyl substituted allenic ester in 85% yield (eq 9).[2a] These alkenation reactions only occur with stabilized phosphorus ylides; unstabilized ylides reportedly form complex mixtures with trimethylsilylketene.

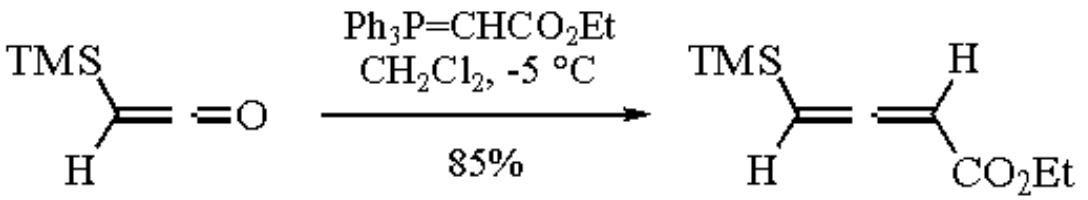

(9)

Preparation of β-Lactones.

Reaction of (**1**) with saturated aldehydes in the presence of $BF_3.Et_2O$ results in mixtures of both *cis*- and *trans*-2-oxetanones (eq 10). Ketones are reported not to undergo cycloadditions with (**1**).[5c,d] Cycloadditions have been described with both saturated and α,β-unsaturated aldehydes. Distillation is reported to promote a 1,3-shift of the organosilyl group accompanied by ring opening to yield the trimethylsilyl dienoate ester.[5a]

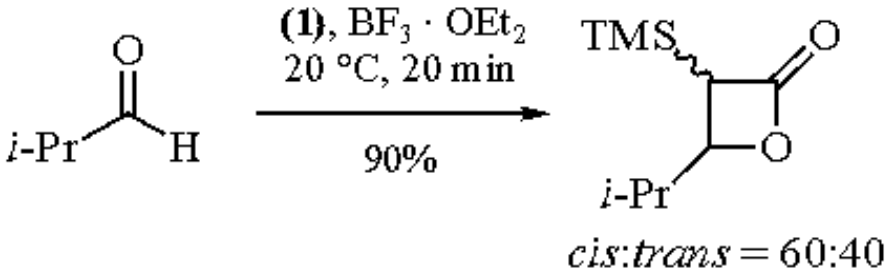

(10)

Recently, a method for the stereoselective preparation of the *cis*-substituted β-lactones using catalytic ***Methylaluminum Bis(4-bromo-2,6-di-t-butylphenoxide)*** has been described (eq 11).[5e] This method is reported to work well for alkyl, aryl, and unsaturated aldehydes. Stoichiometric amounts of catalyst lead to desilylation followed by ring opening to afford (*Z*)-alkenoic acids.

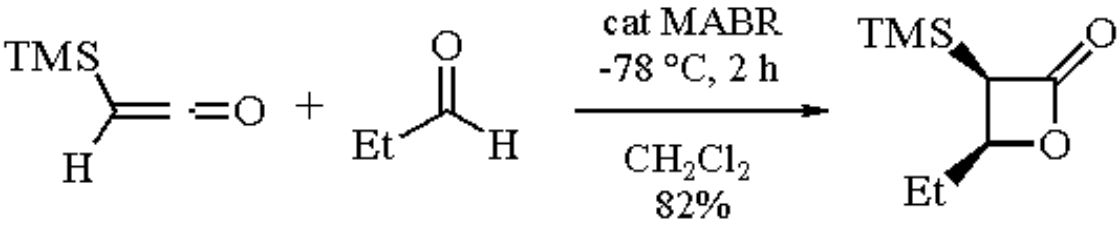

(11)

Reaction with Diazomethane to Form Silylated Cyclopropanes and Cyclobutanones.

The reaction of (**1**) and ***Diazomethane*** results in a mixture of products. Treatment of equimolar amounts of (**1**) with diazomethane at -130 °C leads to (trimethylsilyl)cyclopropanone in moderate yield (eq 12).[6] The product obtained can then react with a second equivalent of diazomethane upon warming to -78 °C, resulting in ring expansion to a mixture of 2- and 3-(trimethylsilyl)cyclobutanones. Alternatively, these isomeric products may be obtained directly with 2 equiv of diazomethane. Treatment of the isomeric (trimethylsilyl)cyclobutanone mixture with methanol makes it possible to obtain pure 3-substituted isomer in 84% yield.[24] This 3-(trimethylsilyl)cyclobutanone derivative can also be formed by a more elaborate route via the regioselective [2 + 2] addition of ***Dichloroketene*** to ***Trimethylsilylacetylene*** followed by hydrogenation and reductive removal of the two chlorine atoms.[25] ***Trimethylsilyldiazomethane*** has also been reported to react with (**1**) to form bis-silyl substituted cyclopropanones.[26]

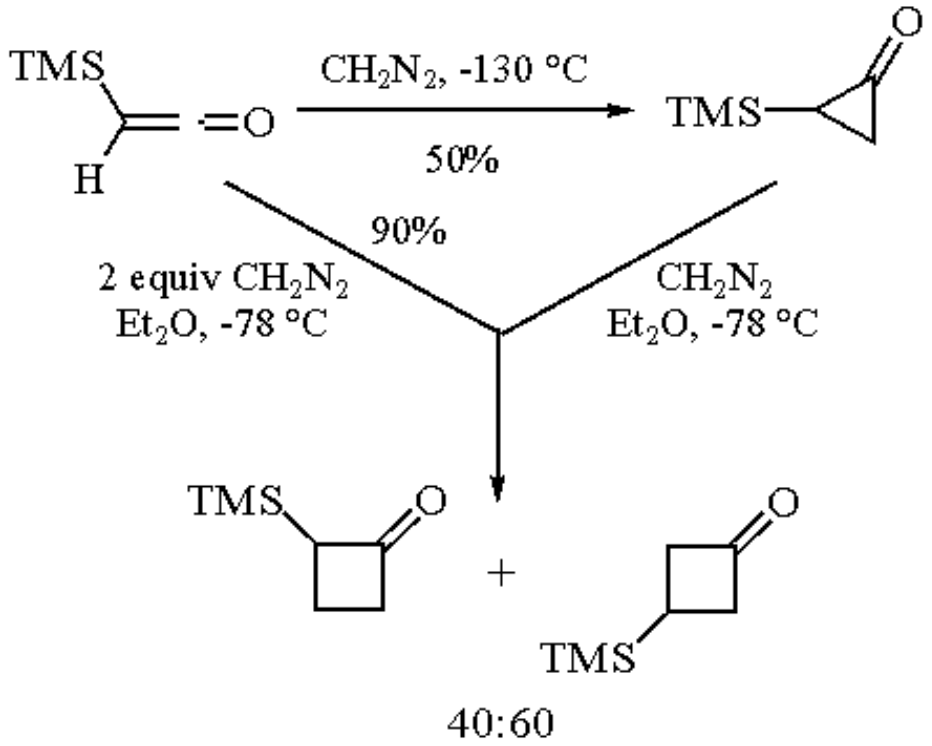

(12)

Formation of the Ketene Enolate.

Addition of (**1**) to a solution of ***n-Butyllithium*** at -100 °C presumably forms the ketene enolate. Quenching with ***Chlorotrimethylsilane*** then affords the bis-silylketene in high yield (eq 13).[7] Attempts to trap the enolate with other electrophiles have been unsuccessful. Other methods[27] affording bis(trimethylsilyl)ketene have been reported including a very similar method involving deprotonation of (**1**) with ***Triethylamine*** and quenching with ***Trimethylsilyl Trifluoromethanesulfonate***.[28] However, the yield for this reaction is much lower (48%). Other reactions report bis(trimethylsilyl)ketene as a byproduct.[29]

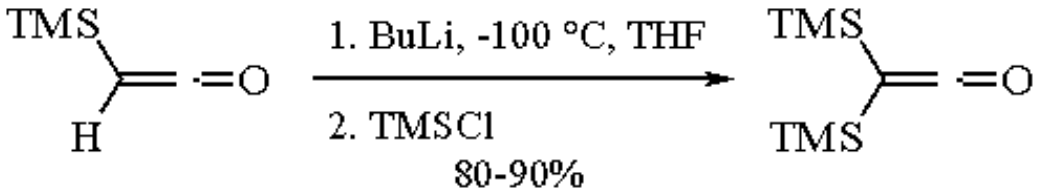

(13)

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Trimethylsilyllithium

Me_3SiLi

[18000-27-6] · C_3H_9LiSi · Trimethylsilyllithium · (MW 80.15)

(synthesis of β-silyl ketones;[1] homologation of sterically hindered ketones;[2] inversion of alkene stereochemistry[3])

Preparative Method: by the reaction of ***Hexamethyldisilane*** and ***Methyllithium*** in HMPA.

Handling, Storage, and Precautions: should be used immediately after preparation. The red HMPA solution of trimethylsilyllithium is sensitive to air and moisture. HMPA is carcinogenic and should be used only in a well-ventilated hood. Contact with eyes and skin should be avoided.

General Discussion.

Triorganosilyl alkali metal species in which at least one substituent on silicon is an aryl group were prepared by cleavage of the corresponding hexaorganodisilanes by alkali metals in the 1950s; however, the hexaalkyldisilanes are inert to metal cleavage.[4] The generation of trimethylsilyl alkali metal species has more recently been accomplished by the reaction of hexamethyldisilane and potassium methoxide,[3] sodium methoxide,[5] or methyllithium[1] in HMPA. ***Trimethylsilylpotassium*** (TMSK) and trimethylsilylsodium have also been obtained by the reaction of hexamethyldisilane and KH or NaH in HMPA.[6] The most useful method for the generation of trimethylsilyllithium (TMSLi) is the procedure reported by Still.[1] A deep red solution of TMSLi is obtained upon reaction of hexamethyldisilane with methyllithium in HMPA at 0 °C in 15 min (eq 1); however, further reaction leading to a disilane anion is possible (eq 2).[7] The solid state structure of TMSLi has been determined by single crystal X-ray analysis as a hexameric species.[8]

$$\text{TMS-TMS} \xrightarrow[\text{HMPA, 0 °C}]{\text{MeLi}} \text{TMSLi} + Me_4Si \qquad (1)$$

$$\text{TMS-TMS} + \text{TMSLi} \longrightarrow \text{TMS-SiMe}_2\text{Li} + Me_4Si \qquad (2)$$

TMSLi adds to cyclohexenone in THF-HMPA to give exclusively the 1,4-addition product (eq 3).[1] The intermediate enolate may be stereoselectively alkylated at carbon with alkyl halides, or *O*-silylated with ***Chlorotrimethylsilane*** to provide the enol ether. Nucleophilic 1,4-addition to cyclohexenones is quite stereoselective. Reaction of 5-methylcyclohex-2-enone with TMSLi occurs predominantly by axial attack, resulting in a 92:8 ratio of axial to equatorial products.[9] TMSLi also undergoes diastereoselective nucleophilic addition to 1-naphthyloxazolines (eq 4);[10] however, the addition of the silyl nucleophile is not as selective as the addition of simple alkyllithium reagents. The diminished diastereoselection is presumably due to the presence of HMPA required in the generation of TMSLi.

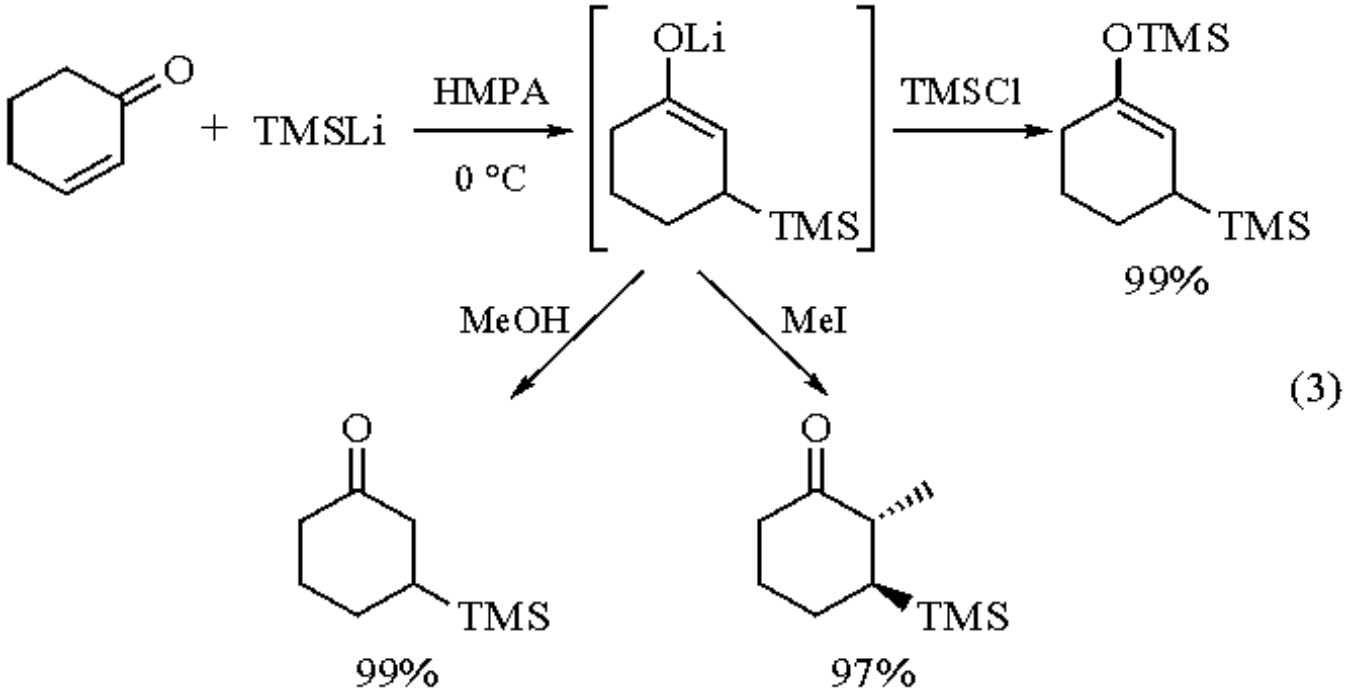

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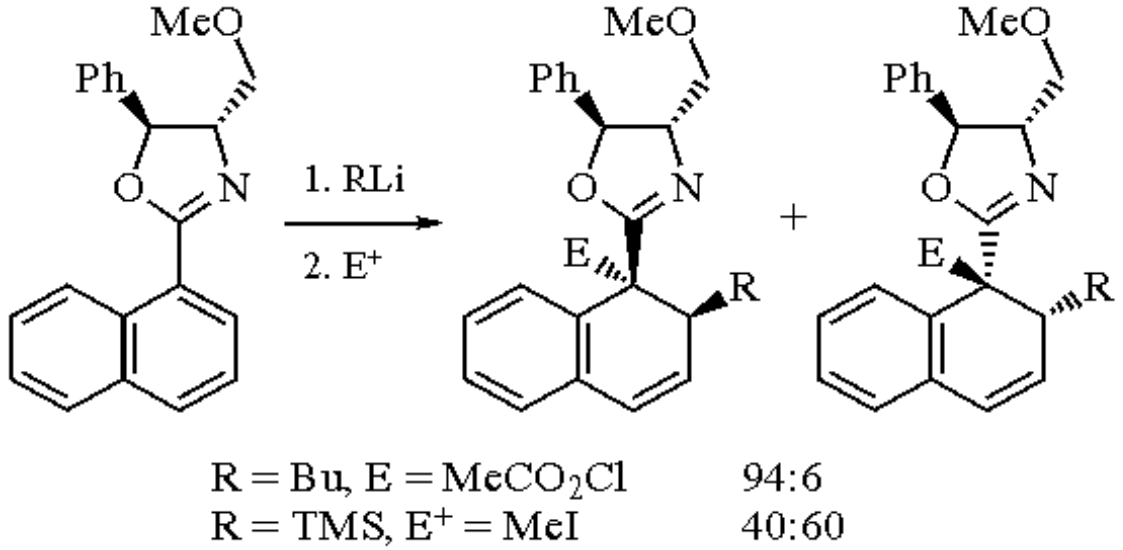

(4)

R = Bu, E = $MeCO_2Cl$ 94:6
R = TMS, E^+ = MeI 40:60

The β-silyl ketones obtained by 1,4-addition of TMSLi have been employed in the synthesis of alkenic acids by means of a silicon directed Baeyer-Villager oxidation (eq 5).[11] Peracid oxidation of the β-silyl ketone results in formation of the unstable seven-membered ring lactone which undergoes acid-catalyzed ring opening with concomitant stereoselective 1,2-migration of the trimethylsilyl group to provide the stable six-membered ring lactone. Saponification followed by stereoselective alkene generation, either via *anti*-elimination using ***Boron Trifluoride Etherate*** or *syn*-elimination using ***Potassium Hydride***, leads to the *trans*- or *cis*-alkene, respectively. The directed Baeyer-Villager approach has been applied to the stereoselective synthesis of *exo*- and *endo*-brevicomin.[12] The regioselectivity of the β-silyl-directed oxidation is not completely controlled. Quaternary carbons migrate preferentially over a less substituted β-silyl alkyl group.

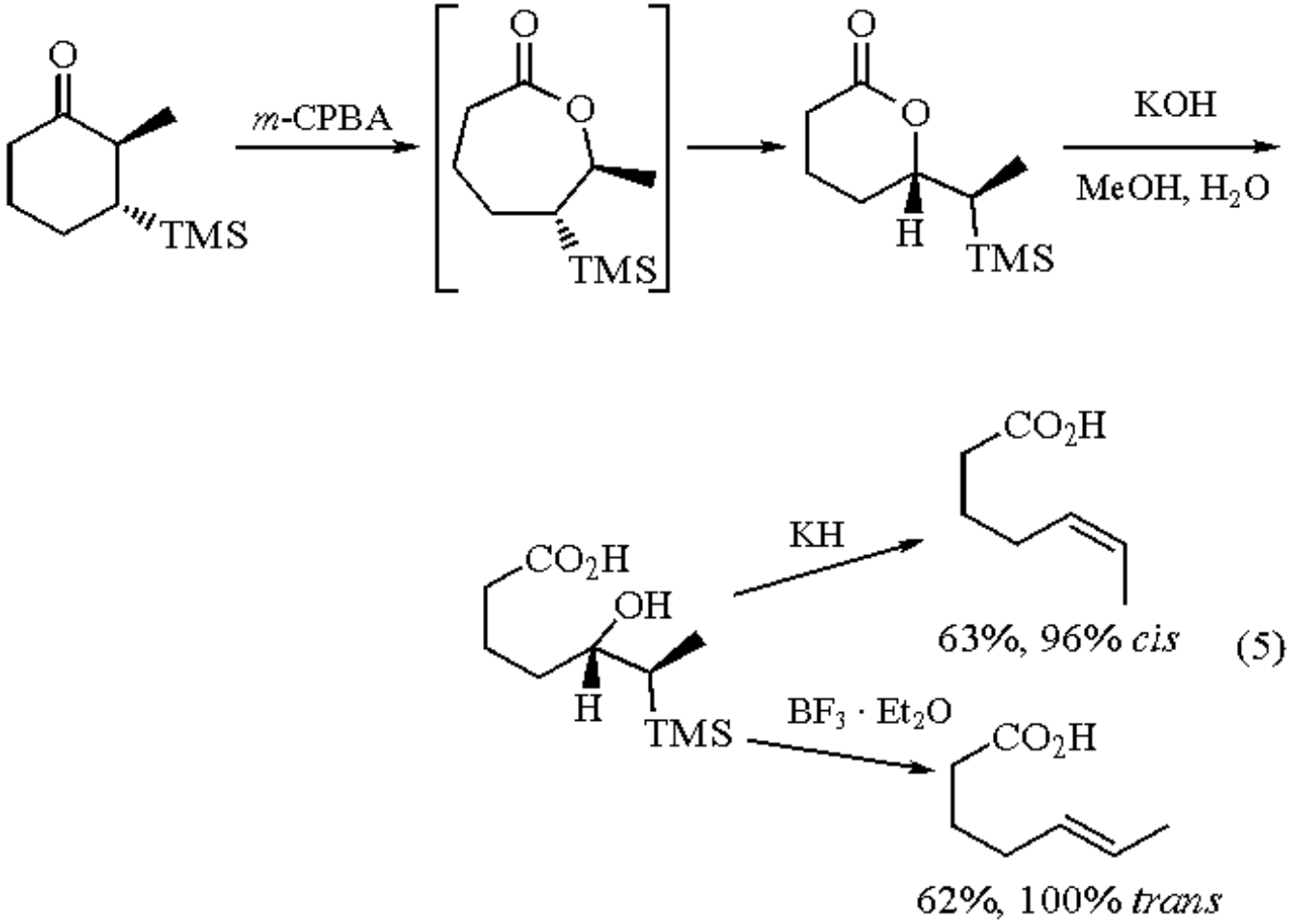

TMSLi also undergoes direct nucleophilic 1,2-addition to saturated ketones and aldehydes. A novel route for the homologation of sterically hindered ketones which involves the addition of TMSLi to the α-trimethylsilyloxy aldehyde derived from the cyanohydrin of a ketone has been developed.[2] The initial alkoxide undergoes an intramolecular oxygen-to-oxygen silyl migration, leading to a β-hydroxy silane (eq 6). Treatment of the β-hydroxy silane with excess base induces alkene formation by a Peterson alkenation reaction. Hydrolysis of the silyl enol ether product then provides the homologated aldehyde. Reduction of the aldehyde to the hydroxymethyl group provides a key intermediate in the synthesis of aphidicolin (eq 6),[2] stemodin, and stemodinone.[13]

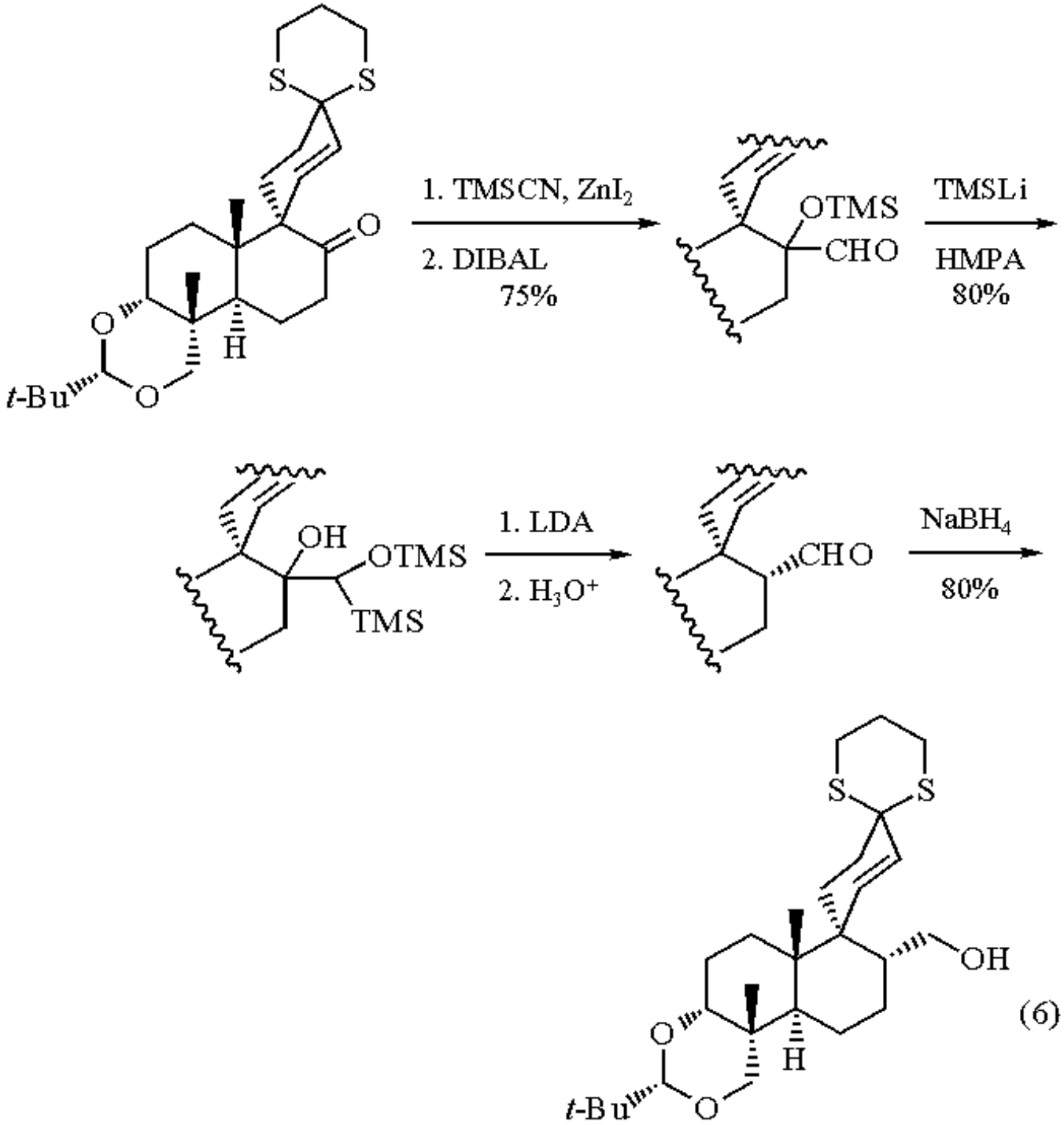

(6)

Stereoselective nucleophilic addition of TMSLi to 2-methylcyclohexanone provides an intermediate for the study of the stereochemistry of the aliphatic Brook rearrangement (eq 7).[14] The reverse Brook rearrangement has provided a method for the synthesis of a variety of (α-hydroxyalkyl)trialkylsilanes which does not require the difficult preparation of trialkylsilyl anions.[15] The method involves nucleophilic addition of readily available ***Tri-n-butylstannyllithium*** to a carbonyl, *O*-silylation, and subsequent O-to-C migration of the silyl group induced by Sn-Li transmetalation (eq 8). The yields of (α-hydroxyalkyl)trimethylsilanes obtained by this procedure are frequently greater than the yields obtained by the direct addition of TMSLi. Direct addition of TMSLi[16] or TMSK[3] to epoxides has also been reported. Due to the stereospecific nature of the Peterson alkenation reaction, the epoxidation and TMSK deoxygenation of an alkene can result in stereospecific inversion of the double bond stereochemistry (eq 9). The epoxidation-deoxygenation sequence has been employed as a method to protect an alkene during catalytic hydrogenation.[16] Allylsilanes may be prepared by the S_N2 displacement of allyl chlorides.[17] The reaction appears to be a direct nucleophilic displacement and does not involve electron transfer processes. TMSLi can also undergo transmetalation to a variety of other organometallic species such as ***Trimethylsilylcopper***. Vinylsilanes can be obtained by the reaction of an alkyne with TMSLi in the presence of Mn^{II} and methylmagnesium chloride.[18] TMSLi has not been used as extensively as the more readily accessible dimethylphenylsilyllithium for generation of other silyl organometallic reagents.[4,19]

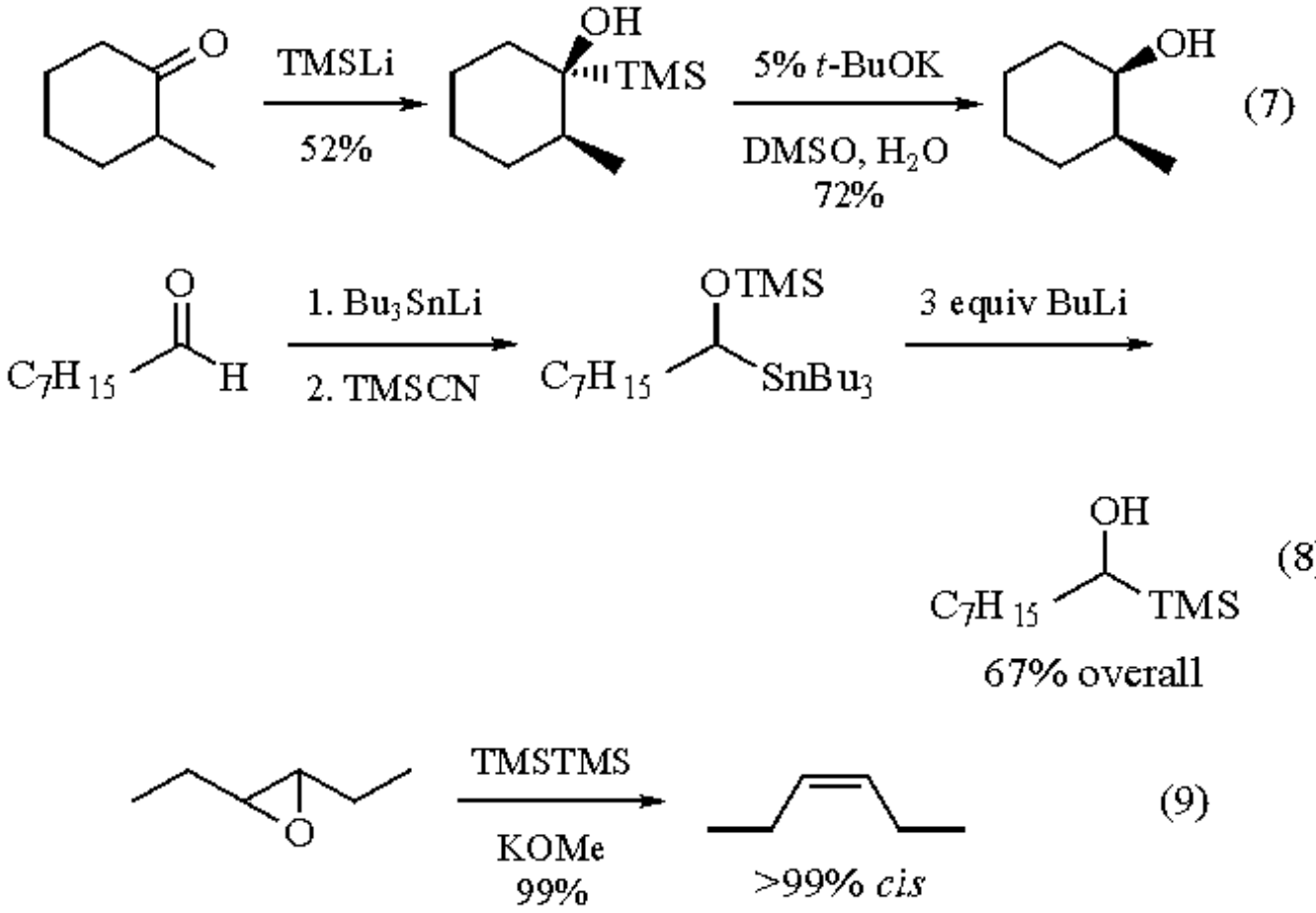

Related Reagents.

Dimethyl(phenyl)silane; ***Hexamethyldisilane***; ***Trimethylsilylpotassium***.

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Trimethylsilyl Methanenitronate[1]

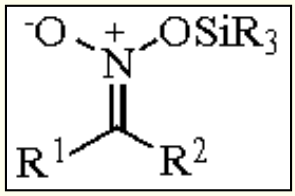

($R^1 = R^2 = H$, R_3Si = TMS)

[51146-35-1] · $C_4H_{11}NO_2Si$ · Trimethylsilyl Methanenitronate · (MW 133.25) ($R^1 = C_5H_{11}$, $R^2 = H$, R_3Si = TBDMS)

[75157-17-4] · $C_{12}H_{27}NO_2Si$ · *t*-Butyldimethylsilyl 1-Hexanenitronate · (MW 245.49) ($R^1R^2 = (CH_2)_5$, R_3Si = TBDMS)

[75157-19-6] · $C_{12}H_{25}NO_2Si$ · *t*-Butyldimethylsilyl Cyclohexanenitronate · (MW 243.47)

(react with alkenes in a 1,3-dipolar cycloaddition reaction;[1c,3-5] undergo Bu_4NF-mediated diastereoselective carbonyl addition to aldehydes;[6-12] react with alkyllithium reagents to give oximes;[13] oxidative coupling leads to 1,2-dinitro alkanes;[14,15] cross coupling with silyl enol ethers or enamines gives β-nitro carbonyl derivatives;[15] conversion of thiocarbonyl to carbonyl groups;[1c,16] can be converted into carbonyl compounds (cf. Nef reaction)[17])

Alternate Name: [(trimethylsilyl)-*aci*-nitro]methane.

Physical Data: $R^1 = C_5H_{11}$, $R^2 = H$, R_3Si = TBDMS: bp 80-90 °C/0.02 mmHg. $R^1R^2 = (CH_2)_5$, R_3Si = TBDMS: bp 150 °C/0.01 mmHg. A more complete list of silyl nitronates is given by Torssell.[1c]

Solubility: sol pentane and in all nonprotic common organic solvents.

Preparative Methods: a large number of silylation conditions can be applied to primary or secondary nitroalkanes,[1,2] including: R_3SiCl/Et_3N (or Ag^+ or Li_2S), R_3SiOTf, LDA/R_3SiCl, R_3SiCl/DBU,[17a] silylated amides, etc. The first reports were published by Ioffe, Tartakovskii, and their colleagues in the early 1970s.[1] The silyl nitronates are isolated by nonaqueous workup and purified by bulb-to-bulb distillation, with the TBDMS derivatives being much more thermally stable than the TMS derivatives.[2] From crystal structure analyses and NMR studies it is concluded that the silyl group migrates rapidly from one nitronate oxygen to the other and that the more stable configuration of silyl nitronates derived from primary nitroalkanes is (*E*).[2,8]

Handling, Storage, and Precautions: although there are indications that some trimethylsilyl nitronates are thermally unstable,[1c] there have been no reports of violent decompositions. Silyl nitronates are, of course, extremely sensitive to moisture, and they are more resistant to base than to acid. All silyl nitronates should be kept under an inert atmosphere and stored in a freezer.

Reactions of Silyl Nitronates with C-C Bond Formation.

Silyl nitronates are synthetically equivalent to nitrile oxides in [3 + 2] cycloadditions. The [3 + 2] adducts shown in eq 1 lose trialkylsilanol very readily, with formation of Δ^2-isoxazolines.[1c,3-5] Silyl nitronates are somewhat less reactive than nitrile oxides, which is not a disadvantage in intramolecular cycloadditions.[3] The reaction is also applicable to the CF_3-substituted silyl nitronate ($R^1 = CF_3$, $R^2 = H$).[18] Depending upon the method of reduction, either the amino alcohol (**1**) or its epimer (**2**) can be obtained with a diastereoselectivity of ca. 4:1. When the silyl nitronate is derived from a secondary nitroalkane, no silanol elimination can occur; the corresponding isoxazolidines undergo a rearrangement to nitroso silyl ethers such as (**3**).[1d,19] The isoxazolidines derived from primary nitroalkanes are not only precursors to amino alcohols but also to β-hydroxy ketones. Thus the nitrile oxide/silyl nitronate [3 + 2] cycloaddition route constitutes an alternative access to aldols.[1c,20,21] This method becomes especially attractive when rendered enantioselective. Addition of a silyl nitronate from a primary nitroalkane to a chiral acrylamide (such as ***10,2-Camphorsultam***,[4] ***trans-2,5-Dimethylpyrrolidine***,[22] or Kemp-Rebek acid derivatives[5]), silanol elimination, and reductive removal of the auxiliary gives 3-substituted Δ^2-isoxazoline-5-methanols in either enantiomeric form (eq 2).

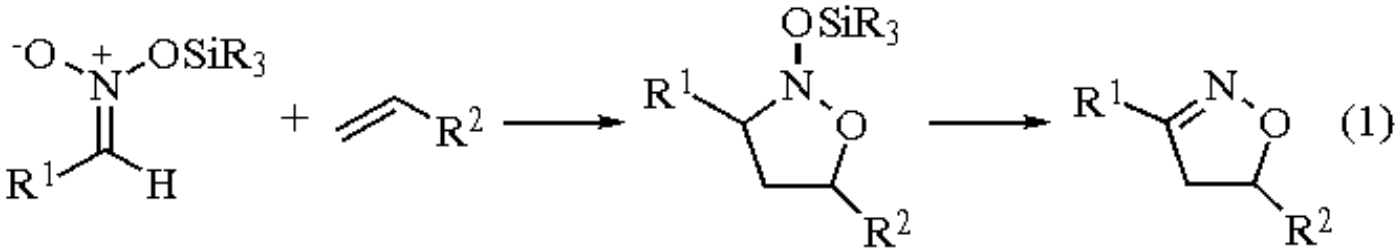

(1)

R^2 = alkyl, vinyl, phenyl, COR, $CONR_2$, CO_2R

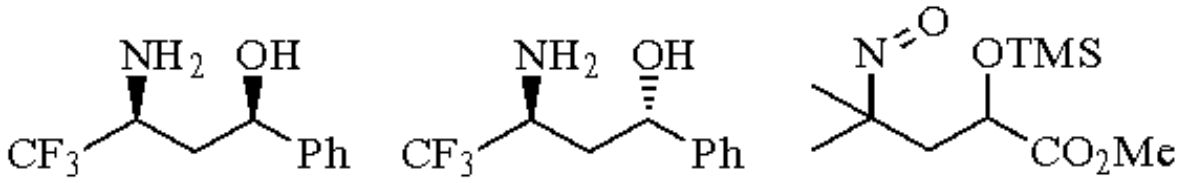

(1) (2) (3)

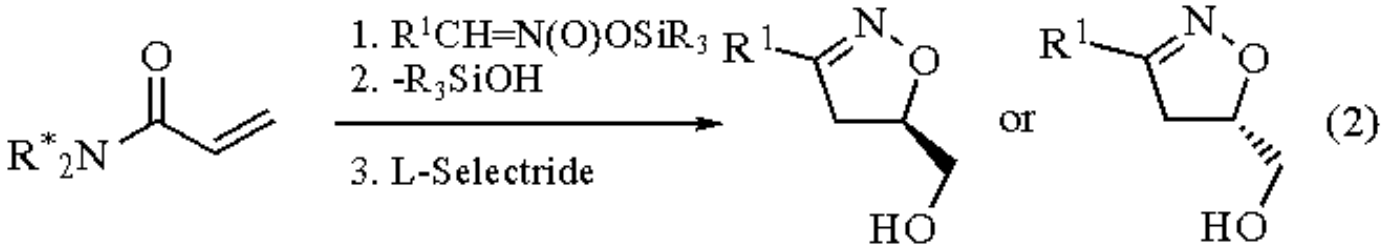

(2)

The second most important synthetic application of silyl nitronates in C-C bond-forming reactions is their fluoride-mediated addition to aldehydes.[6-12] Silyl nitronates from secondary nitroalkanes lead to free nitro aldols such as (**4**),[8] while those from primary nitro alkanes give silylated products. In contrast to the classical Henry reaction, the silyl variant is highly diastereoselective with aldehydes, furnishing *erythro-O*-silylated nitro aldols (e.g. **5**).[9] It is important that the reaction temperature does not rise above 0 °C, otherwise *threo*/*erythro* equilibration takes place. The same *erythro*-nitro aldol derivatives are available by diastereoselective protonation of silyloxy nitronates (eq 3) (usually the dr is >20:1), while the nonsilylated *threo*-epimers (R^3 = H, dr = 7:3-20:1) are formed by kinetic protonation of lithioxy lithio nitronates in THF/DMPU (eq 4).[9] Other recent modifications of the nitroaldol addition using titanium nitronates[23] or $ClSiR_3$ in situ[24] are less selective. It should also be mentioned that there are recent reports[25] about the enantioselective addition of nitromethane to aldehydes in the presence of rare earth binaphthol complexes.

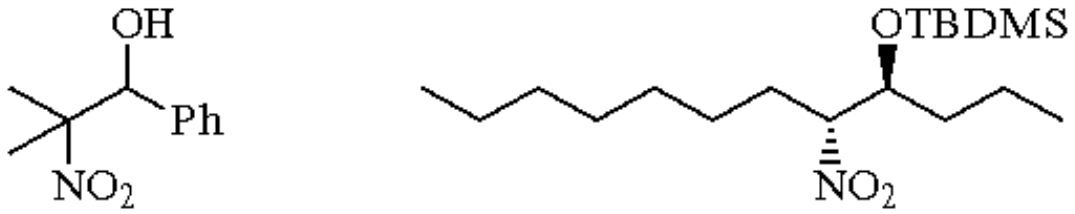

(4) (5) dr >95:5

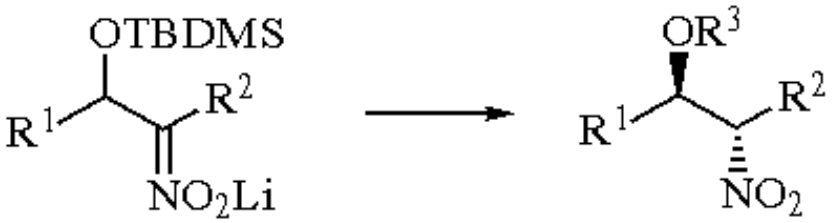

(3)

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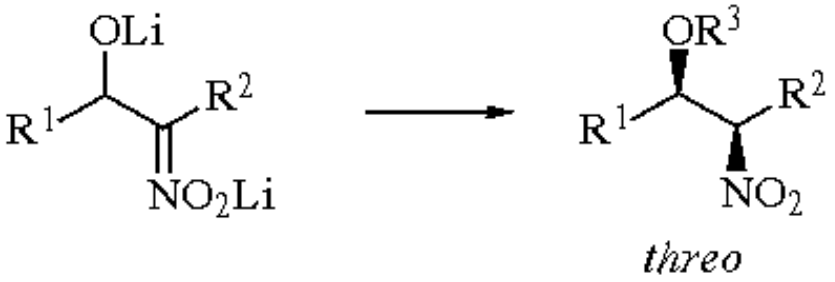

(4)

Reactions of Silyl Nitronates with Strong Base.[13]

With 2 equiv of an alkyllithium, the nitronates from primary nitroalkanes give oximes with the newly introduced alkyl group attached to the oxime carbon (eq 5). The analogous reaction of silyl nitronates from secondary nitroalkanes produces oximes in which chain extension has occurred in the α-position (eq 6). These reactions take place when alkyllithium is added to 0.1 molar silyl nitronate in THF at dry-ice temperature, with subsequent warming to room temperature before aqueous workup. Probably a nitrile oxide is the intermediate in the first case and a nitroso alkene in the second case. Finally, oxidative cross couplings of silyl nitronates with silyl enol ethers, ketene acetals, or enamines produce β-nitro carbonyl compounds (eq 7) or, by HNO_2 elimination, α,β-unsaturated ketones and esters.[15]

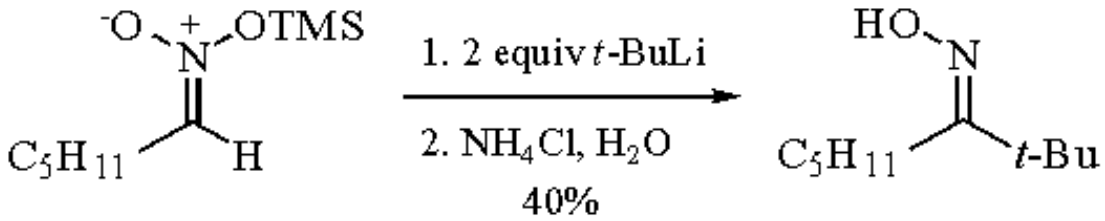

(5)

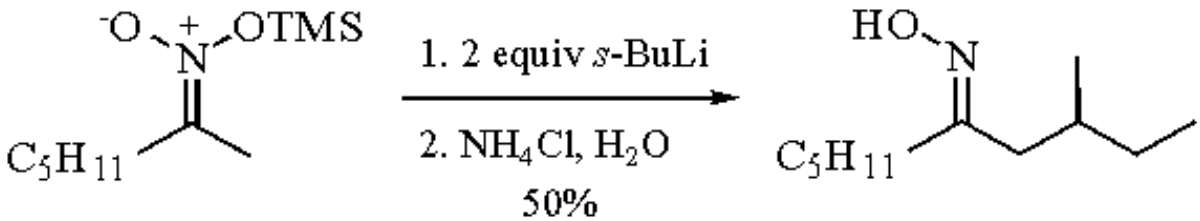

(6)

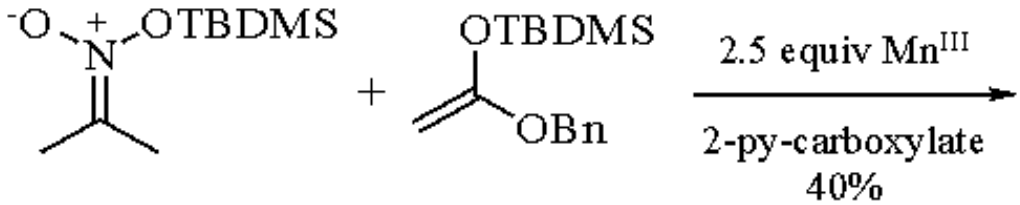

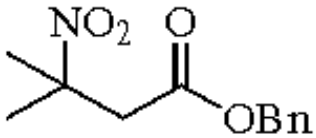

(7)

Functionalization Reactions of Silyl Nitronates.

Silyl nitronates can be used for a number of transformations in which the carbon skeleton is not changed. Thus they are intermediates en route from nitroalkanes to ketones (the transform[26] of the Nef reaction). Peroxy acid treatment converts silyl nitronates, which would not survive the classical conditions of the Nef reaction, to ketones[17a] (eq 8). Aldehydes can be obtained analogously, using stannyl nitronates.[17b]

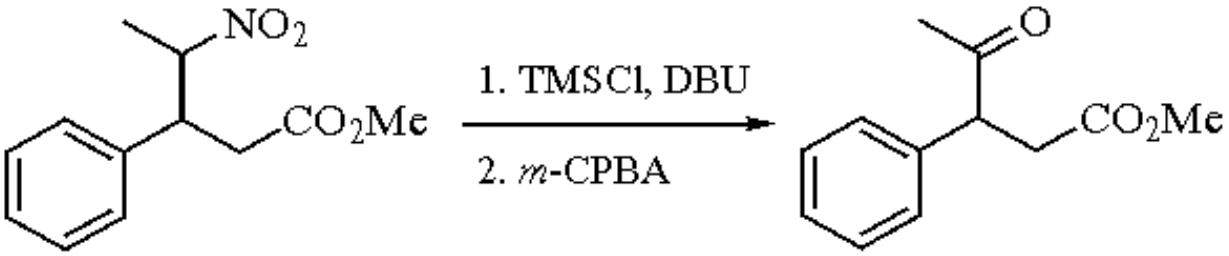

(8)

Silyl nitronates can also be further silylated to the interesting *N*,*N*-bis(silyloxy)enamines (eq 9).[27] In contrast to the *N*,*N*-bis(lithioxy)enamines, the double bond in the bis(silyloxy)enamines appears to have electrophilic rather than nucleophilic reactivity. With primary and secondary amines, α-amino oximes are produced (eq 9)[27] in a kind of S_N' substitution, followed by hydrolytic desilylation. In this manner, the bis(silyloxy)enamine is reacting as a nitroso alkene.

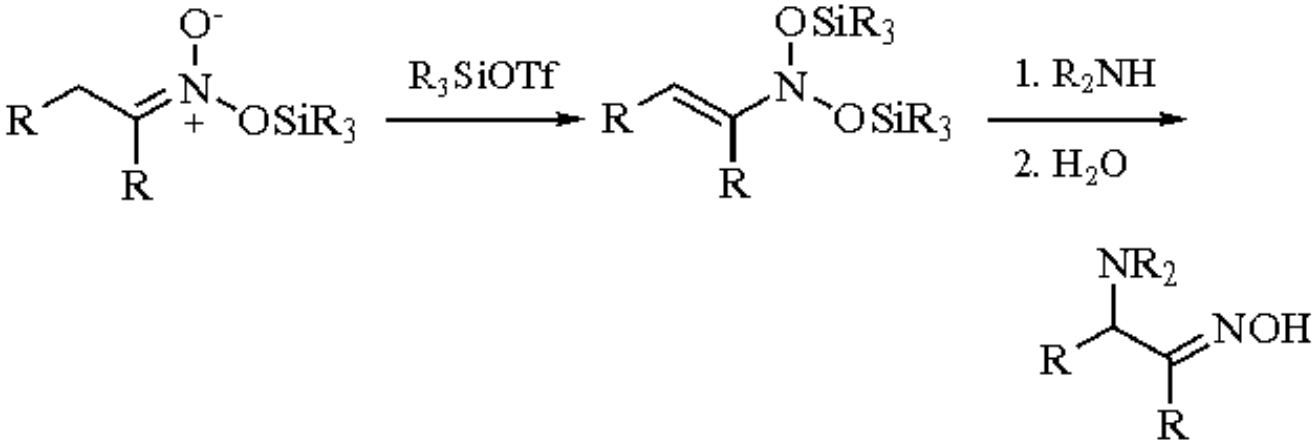

(9)

Conversion of Thioketones to Ketones.[16]

Thioketones generated by a Norrish-type photofragmentation of a sulfenyl acetophenone are trapped in situ by [3 + 2] dipolar cycloaddition with a silyl nitronate (eq 10). Fluoride treatment of the resulting heterocycle produces the ketone.[16b] This transformation is compatible with a variety of functional groups and has been used as part of a synthetic manipulation in which an α-acyl cyclic thioether is converted stereoselectively, with ring enlargement, to a ketolactone (methynolide synthesis).[16a]

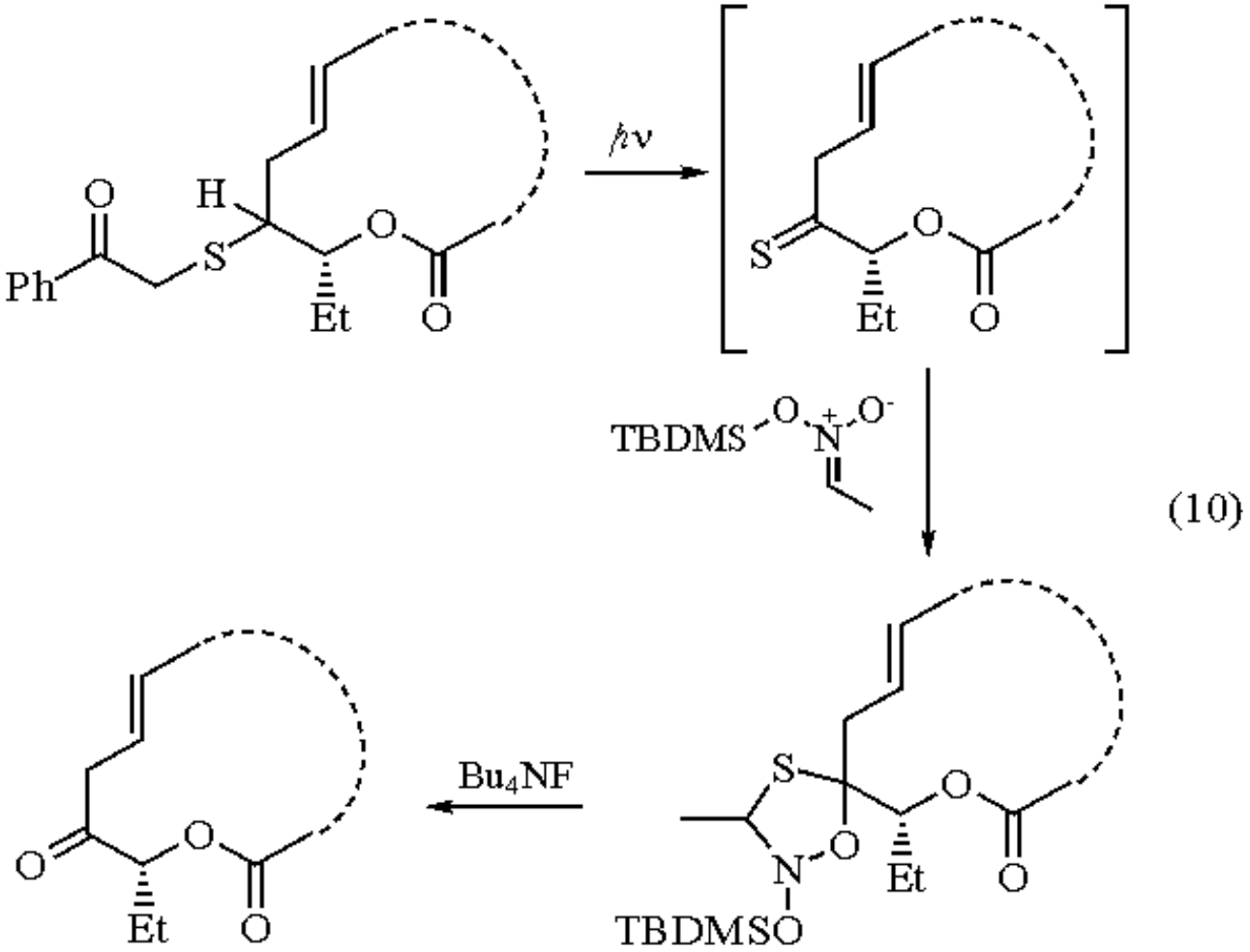

(10)

Silyl Nitronate Reactivity Pattern.

As illustrated by the examples described above, silyl nitronates provide a^1 and d^1 acyl and aminoalkyl synthons (**6** and **7**), as well as a^2 α-carbonyl and aminoalkyl synthetic building blocks (**8** and **9**).[1e,28]

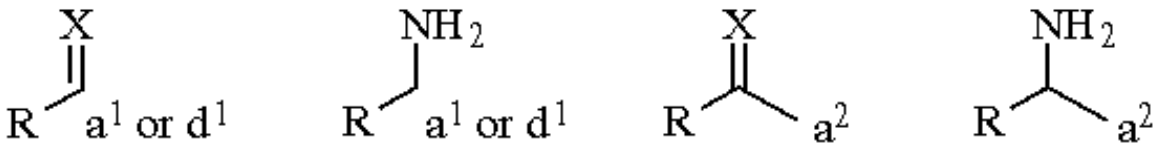

(6) **(7)** **(8)** **(9)**

X = O, NR, NOH

Related Reagents.

Lithium α-Lithiomethanenitronate; ***Nitroethane***; ***Nitromethane***; ***1-Nitropropane***; ***Phenylsulfonylnitromethane***.

---

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(Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride

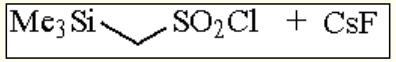

($Me_3SiCH_2SO_2Cl$)

[18143-34-5] · $C_4H_{11}ClO_2SSi$ · (Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride · (MW 186.76) (CsF)

[13400-13-0] · CsF · (Trimethylsilyl)methanesulfonyl Chloride-Cesium Fluoride · (MW 151.91)

(source of free sulfene in solution;[1] source of silylated sulfene[8])

Physical Data: $Me_3SiCH_2SO_2Cl$ is a colorless liquid, bp 50-52 °C/0.6 mmHg, 57 °C/1 mmHg; mp 18 °C, *n*20D 1.4700,[3] 1.4680.[7a] See also ***Cesium Fluoride***.

Solubility: acetonitrile is the preferred solvent due to solubility of CsF and absence of hydrogen bonding; $Me_3SiCH_2SO_2Cl$ is soluble in most organic solvents.

Preparative Methods: $Me_3SiCH_2SO_2Cl$ is: (1) formed in 58% isolated yield via reaction of ***(Chloromethyl)trimethylsilane*** with ***Thiourea*** in ethanol followed by concentration and chlorination in water, extraction, and distillation;[2] (2) formed in 63% isolated yield by ***Peracetic Acid*** oxidation of (trimethylsilyl)methanethiol followed by treatment with ***Phosphorus(V) Chloride***;[2] (3) formed in 84% yield through reaction of Me_3SiCH_2Cl with ***Magnesium*** followed by sequential reaction of the Grignard reagent with ***Sulfur Dioxide*** followed by ***Chlorine***;[3] and (4) formed in 53% yield through reaction of tetramethylsilane with ***Sulfuryl Chloride***.[7a]

Handling, Storage, and Precautions: like most sulfonyl chlorides, the title compound hydrolyzes slowly to produce HCl and therefore should be kept dry. The byproduct of hydrolysis is hexamethyldisiloxane. Hydrolysis is very rapid with 5% NaOH solution.[7a]

Formation of Sulfene Adducts.

A widely used procedure for the generation of sulfene involves the treatment of ***Methanesulfonyl Chloride*** with ***Triethylamine***. While adducts of sulfene, generated by this route, can usually be isolated in satisfactory yield, the amine or its acid salt may isomerize or decompose base- or acid-sensitive reaction partners. Furthermore, the interpretation of reaction mechanisms can sometimes be complicated by the presence of the amine. Thus the amine may form a complex with sulfene prior to its reaction with other substrates. In the presence of a fluoride ion source such as CsF, $Me_3SiCH_2SO_2Cl$ undergoes fluorodesilylation to give sulfene which can be trapped with ***Cyclopentadiene*** giving the Diels-Alder adduct 2-thiabicyclo[2.2.1]hept-5-ene 2,2-dioxide in 69% yield (eq 1). The same reaction fails when mesyl chloride-triethylamine is used as a sulfene source. Additional examples of sulfene adducts, including a number of thietane *S*,*S*-dioxides, formed from $Me_3SiCH_2SO_2Cl$ are given in Table 1.[1,2,5,8] This procedure can also be used with homologs of $Me_3SiCH_2SO_2Cl$ such as $Me_3SiCHRSO_2Cl$, $(Me_3SiCH_2SO_2)_2O$, $(Me_3SiCHRSO_2)_2O$, $Me_3SiCH_2S(O)Cl$,[4] and 1-(trimethylsilyl)cyclopropanesulfonyl chloride.[5,6] If $Me_3SiCH_2SO_2Cl$ is treated with triethylamine in the presence of the electron-rich alkene ***Ketene Diethyl Acetal***, then the silylated sulfene trimethylsilylthioformaldehyde *S*,*S*-dioxide ($Me_3SiCH{=}SO_2$) is trapped.[8] The mechanism of hydrolysis of $Me_3SiCH_2SO_2Cl$ in the presence of KF has been studied.[3]

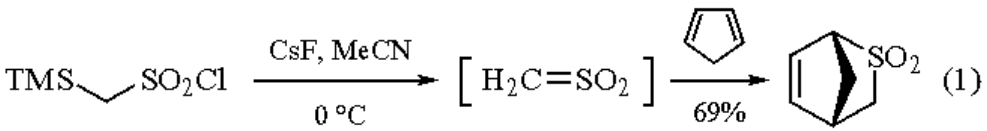

(1)

Table 1 Sulfene Adducts from (Trimethylsilyl)methanesulfonyl Chloride and Related Compounds

Substrate	Reagent	Product	Yield (%)	Ref.
	$TMSCH_2SO_2Cl$, CsF		69	1

	$TMSCH_2SO_2Cl$, CsF		69	1
	$(TMSCH_2SO_2)_2O$, CsF		75	2
	$(TMSCHEtSO_2)_2O$, CsF		76	2
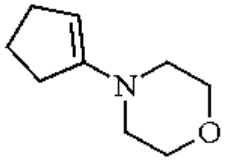	$TMSCH_2SO_2Cl$, CsF	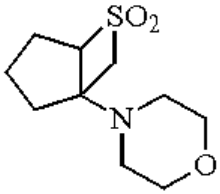	81	1
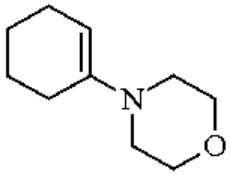	$TMSCH_2SO_2Cl$, CsF	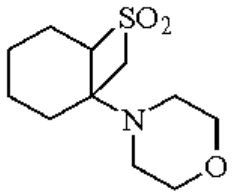	65	1
$MeC{\equiv}CNEt_2$	$TMSCH_2SO_2Cl$, CsF	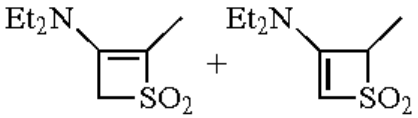 1:1	90	1
$MeC{\equiv}CNEt_2$	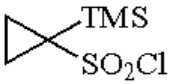 , CsF	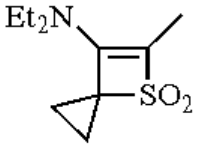	56	5
$H_2C{=}C(OEt)_2$	$TMSCH_2SO_2Cl$, Et_3N	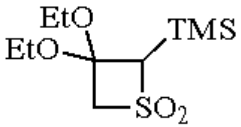	95	8

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1-Trimethylsilyl-1-methoxyallene[1]

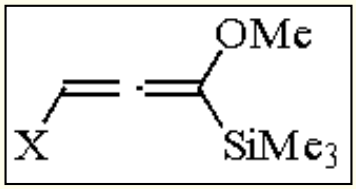

(X = H)

[77129-88-5] · $C_7H_{14}OSi$ · 1-Trimethylsilyl-1-methoxyallene · (MW 142.30) (X = Li)

[82200-98-4] · $C_7H_{13}LiOSi$ · 3-Lithio-1-trimethylsilyl-1-methoxyallene · (MW 148.23)

(precursor to acylsilanes, 2-trimethylsilylfurans, and dihydrofurans)

Physical Data: bp 40-43 °C/28 mmHg.[2]

Solubility: sol THF, ether.

Preparative Method: from methoxyallene by deprotonation with ***n-Butyllithium*** and quenching the allenyl anion with ***Chlorotrimethylsilane***.[3]

Handling, Storage, and Precautions: best stored at -20 °C or below, over anhydrous K_2CO_3. Hydrolysis, desilylation, or polymerization take place in the presence of acid.

α,β-Unsaturated Acylsilanes.

Deprotonation at C-3 of 1-trimethylsilyl-1-methoxyallene (**1**) takes place with *n*-BuLi in THF. Trapping the lithioallene with an alkyl halide, followed by hydrolysis of the methyl enol ether with ***Trifluoroacetic Acid***, leads to the (*E*)-acylsilane (eq 1).[3] Fluorodesilylation with ***Tetra-n-butylammonium Fluoride*** prior to the hydrolysis step produces the corresponding α,β-unsaturated aldehyde.

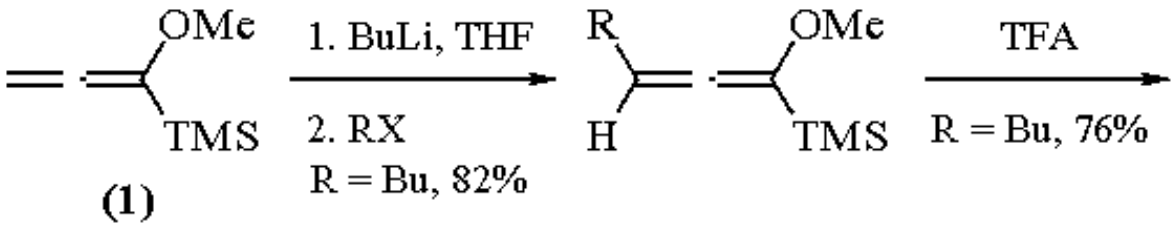

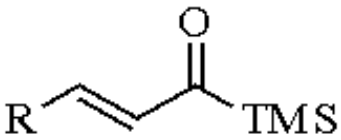

(1)

Furan and Dihydrofuran Synthesis.

Trapping the 3-lithio derivative of (**1**) with decanal leads to the allenic alcohol (eq 2). Aqueous acid under carefully controlled conditions produces 2-trimethylsilyl-5-nonylfuran.[2] The addition product of the 3-lithio derivative of (**1**) with cyclopentanone undergoes acid-catalyzed conversion to the butenolide (**2**) (eq 3). This unusual transformation apparently takes place through formal loss of Me_3Si^- from a cyclic intermediate.[2]

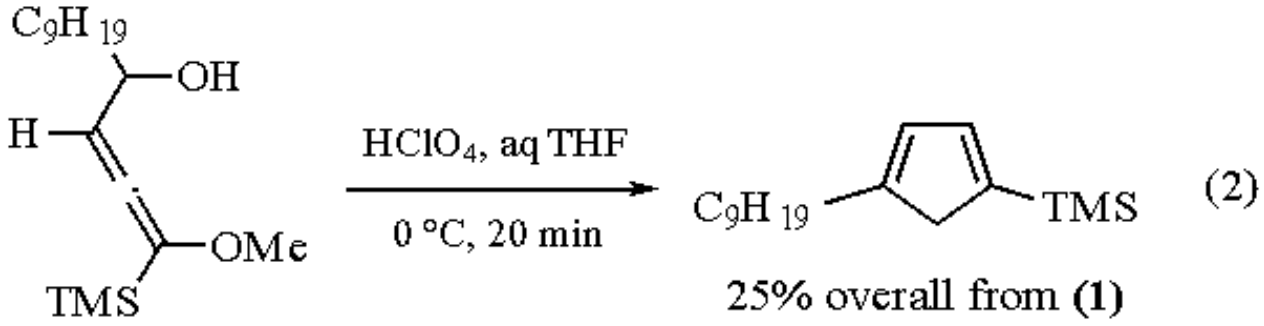

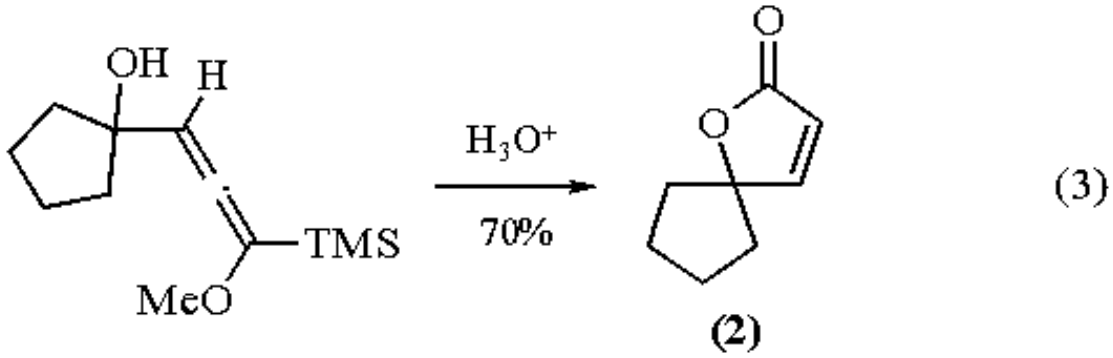

Deprotonation of (**1**) with ***Lithium Diethylamide*** takes a different course (eq 4). The initially formed allenyl anion isomerizes to the acetylide, which is trapped with ketones or aldehydes to produce propargyl alcohols (**3**).[4] The isomerization is postulated to take place through proton transfer steps mediated by diisopropylamine. This is consistent with the observation that no such isomerization takes place with alkyllithium reagents. The propargyl alcohols (**3**) are converted to methoxydihydrofurans (**4**) with catalytic ***Potassium Hydride*** in DMSO.[4]

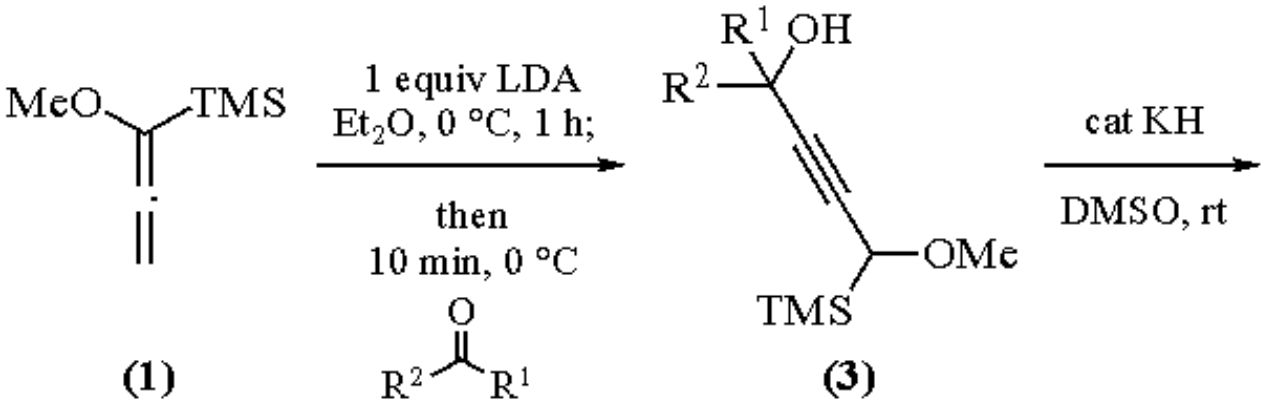

R^1	R^2	(3)	(4)
-$(CH_2)_5$-		89%	71%
-$(CH_2)_6$-		86%	77%
C_8H_{17}	H	83%	56%

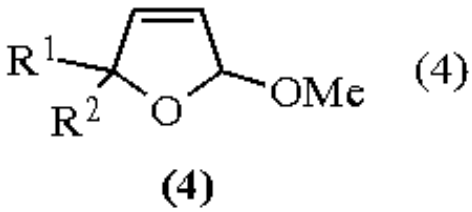

Related Silanes.

1-Trimethylsilyl-1-(ethoxyethoxy)allene (**5**) undergoes efficient reaction with electrophiles to produce substituted unsaturated acylsilanes (eq 5).[5] The reaction products can be converted to diverse 2-silyloxy-1,3-butadienes. Exposure of (**5**) to ***Boron Trifluoride Etherate*** leads to rearrangement in which an oxonium ion is intercepted at C-2 of the allene (eq 5).[6] This rearrangement proceeds via an intermolecular pathway. Acylstannanes can also be prepared through this method.

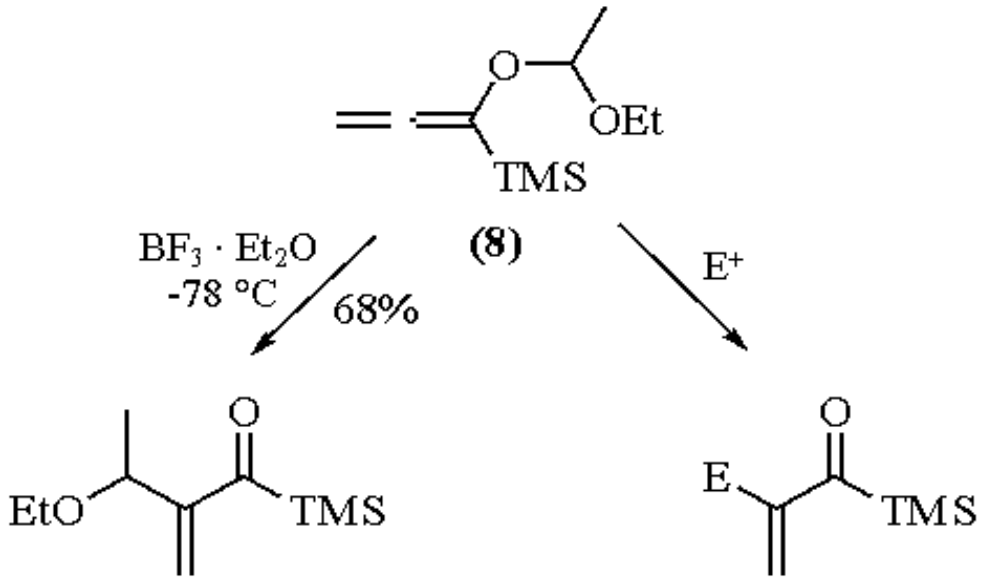

(5)

E^+	E	Yield
H_2SO_4	H	65%
PhSeCl	PhSe	73%
SO_2Cl_2	Cl	65%

Epoxidation of *t*-butyldimethylsilyl-1-(ethoxyethoxy)allene (**6**) with ***m-Chloroperbenzoic Acid*** leads to an α-keto acylsilane,[6] presumably through an allene oxide intermediate (eq 6). Deprotonation of (**6**) at C-3 and trapping of the anion with ***Selenium***, followed by ***Iodomethane***, produces an allenyl selenide. The reaction of this material with peracid follows a different course, leading to an acetylenic acylsilane, presumably via [2,3]-sigmatropic rearrangement of an allenyl selenide (eq 6).[7]

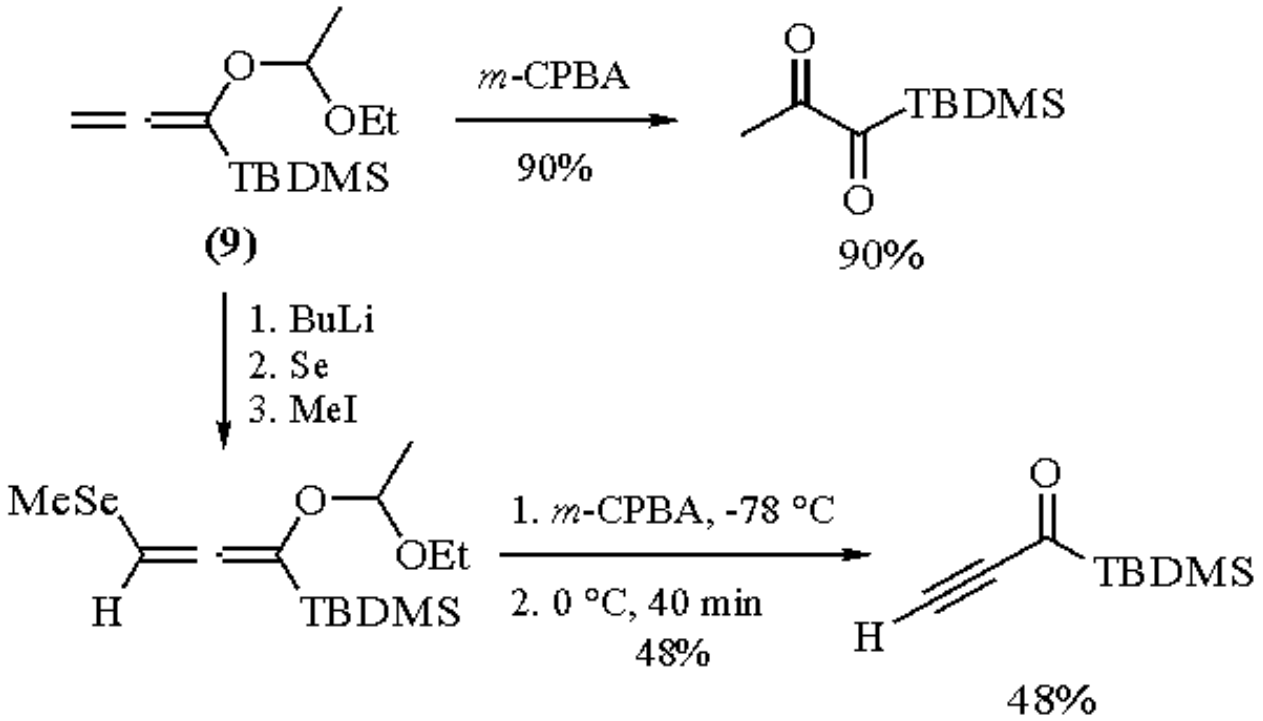

(6)

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Trimethylsilylmethyl Azide[1]

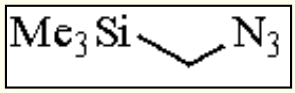

[87576-94-1] · $C_4H_{11}N_3Si$ · Trimethylsilylmethyl Azide · (MW 129.27)

(amination of organometallic compounds; preparation of heterocyclic compounds; precursor of azomethine ylide)

Physical Data: bp 43 °C/43 mmHg; IR ν_{max} 2100 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.12 (s, 9H), 2.75 (s, 2H); MS *m/z* 129, 73.

Solubility: sol organic solvents; insol water.

Form Supplied in: colorless liquid.

Preparative Method: obtained in high yield by reaction of ***Sodium Azide*** and ***(Chloromethyl)trimethylsilane*** in DMF[1a] or HMPA[1b] at 80 °C.

Handling, Storage, and Precautions: useful, safe substitute for methyl azide, bp 20 °C, which is explosive. Trimethylsilylmethyl azide is stable to temperatures of at least 120 °C and can be stored in a refrigerator for more than 6 months.

Amination.

Trimethylsilylmethyl azide reacts with aryl Grignard reagents at room temperature to give aniline derivatives in 70-95% yield (eq 1).[1a] An intermediate of the reaction is probably a triazene, which is hydrolyzed by neutral water to yield an amine. Amination of Grignard reagent with other azides (sulfonyl azide and thiomethyl azide) is known, but relatively drastic conditions are required to decompose the intermediate.[2] The azide also reacts with aryllithium compounds to afford amines (eq 2), but yields are generally lower.[1a,3]

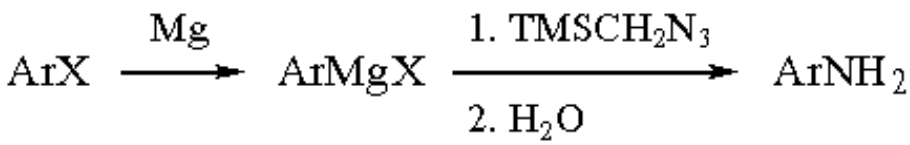

(1)

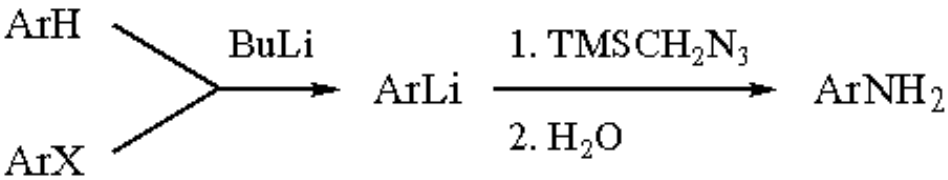

(2)

Azomethine Ylide Precursor.

The azide is readily converted into a precursor of azomethine ylides (eq 3).[4,5] Reactions of the ylides with carbon-carbon multiple bonds and carbonyl group are used in a synthesis of pyrroline and oxazole derivatives (eq 4).[6-8]

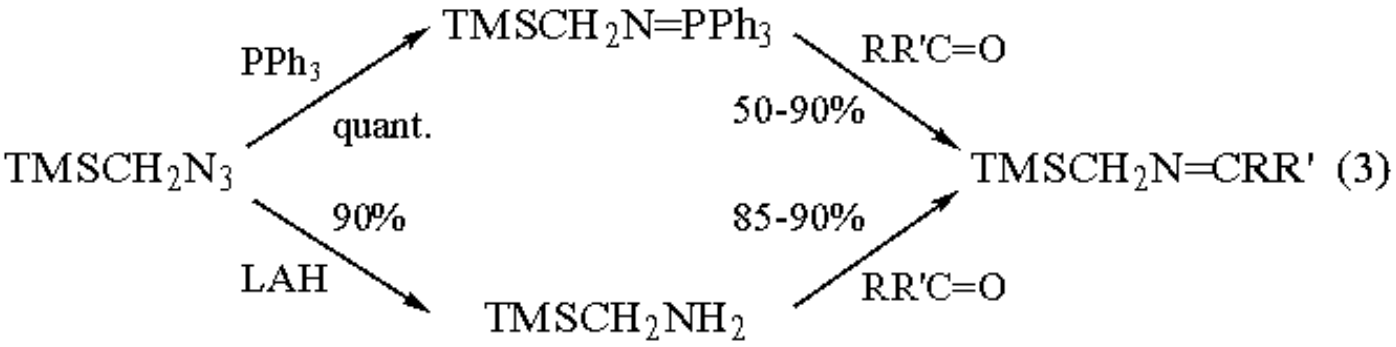

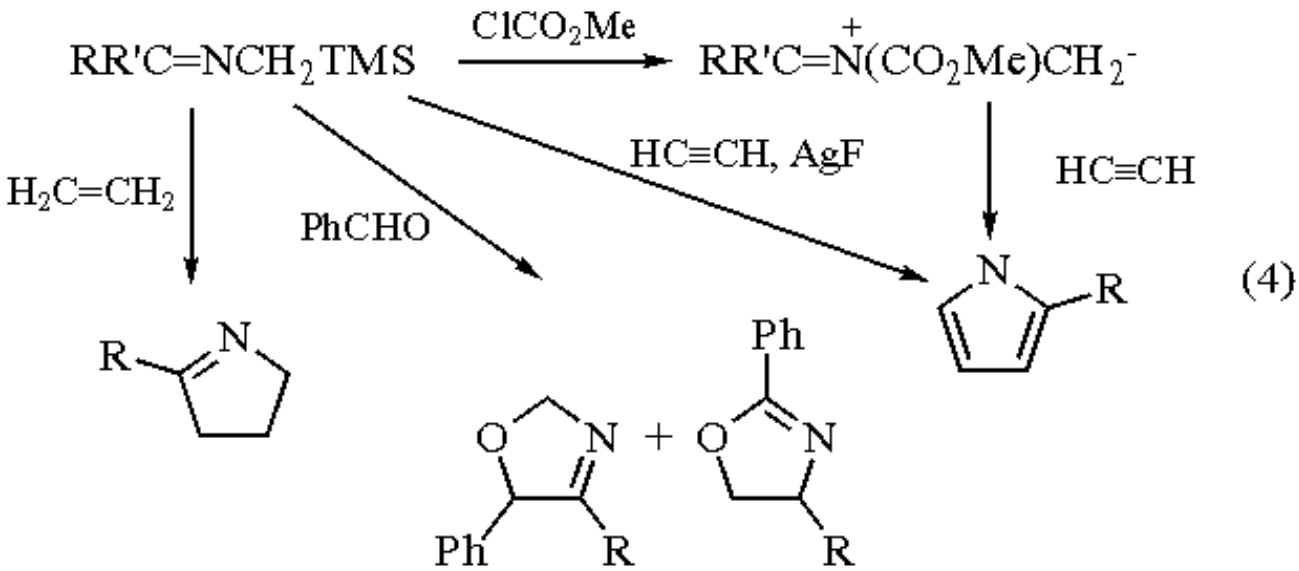

Silylmethyl-Substituted Heterocumulenes.

(Trimethylsilylmethyl)iminotriphenylphosphorane is obtained from a one-pot reaction of the azide and ***Triphenylphosphine*** (eq 3). The reactions of the phosphorane with ***Carbon Dioxide*** or ***Carbon Disulfide*** (eq 5) give trimethylsilylmethyl isocyanate or trimethylsilylmethyl isothiocyanate in 68 and 94% yields, respectively.[4]

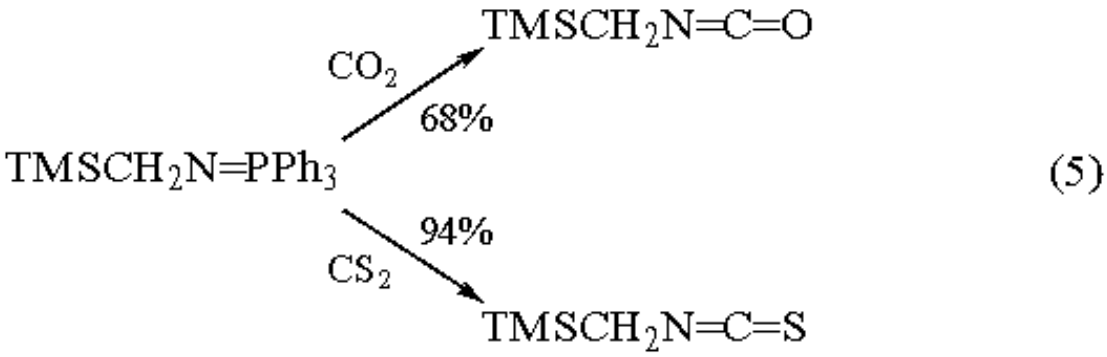

[3 + 2] Cycloaddition.

The azide reacts with alkynes (eq 6),[1b] phosphaalkynes (eq 7),[9] and isothiocyanates (eq 8)[10] to give [3 + 2] cycloaddition products, which can be used as synthons for the preparation of a large variety of other heterocycles.

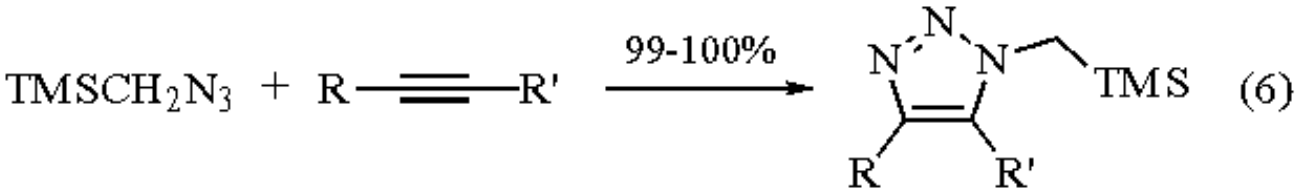

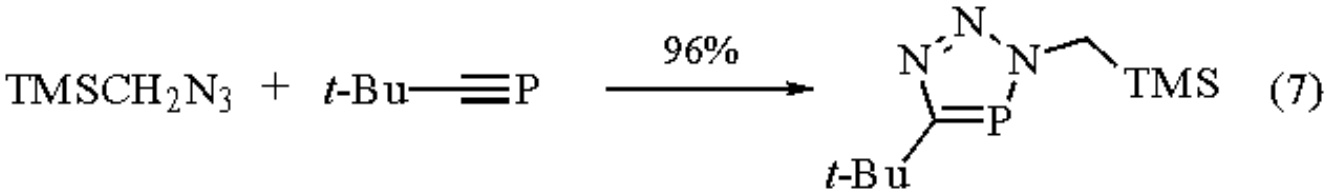

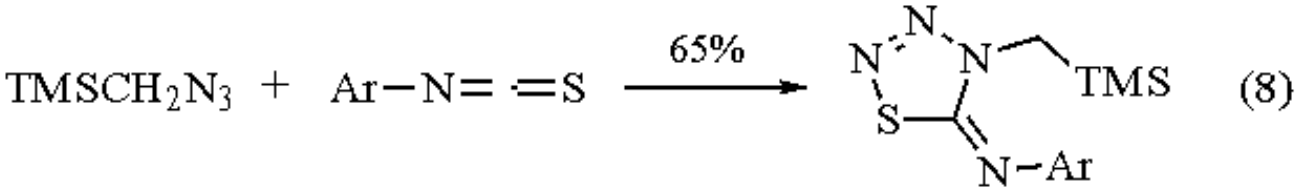

Miscellaneous.

The azide is used for the preparation of other heterocyclic compounds. Typical examples are the formations of disilaaziridine (eq 9)[11] and *s*-triazine (eq 10)[12] derivatives.

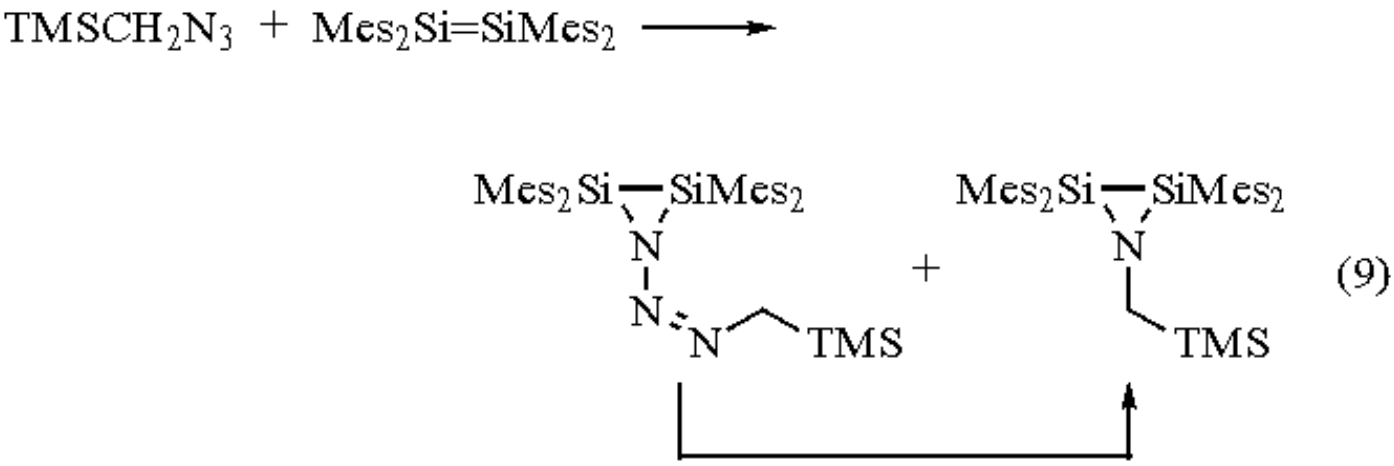

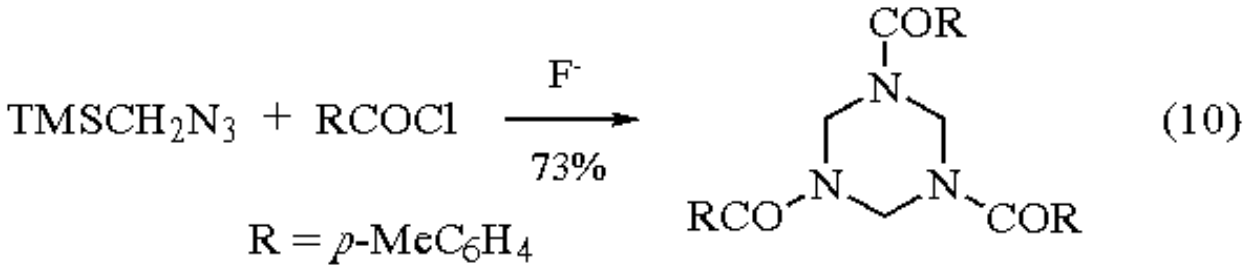

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1. (a) Nishiyama, K.; Tanaka, N. *CC* **1983**, 1322. (b) Tsuge, O.; Kanemasa, S.; Matsuda, K. *CL* **1983**, 1131.
2. Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *JOC* **1969**, *34*, 3430; Trost, B. M.; Pearson, W. H. *JACS* **1981**, *103*, 2483.
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2-Trimethylsilylmethyl-1,3-butadiene[1]

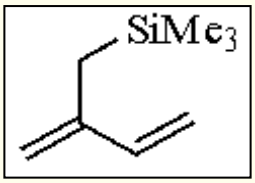

[70901-64-3] · $C_8H_{16}Si$ · 2-Trimethylsilylmethyl-1,3-butadiene · (MW 140.33)

(isoprenylation reagent;[1] Diels-Alder diene[1])

Physical Data: bp 69-70 °C/80 mmHg.

Analysis of Reagent Purity: ^{1}H NMR.

Purification: by distillation.

Solubility: sol common organic solvents.

Preparative Methods: prepared most conveniently by the coupling reaction of the Grignard reagent prepared from ***(Chloromethyl)trimethylsilane*** with 2-chloro-1,3-butadiene (chloroprene) in the presence of a catalytic amount of $Ni[Ph_2P(CH_2)_3PPh_2]Cl_2$ (91% yield) (eq 1).[2] Alternatively, it can be prepared by the reaction of the same Grignard reagent with allenylmethyl phosphate in 57-73% yield (eq 2).[3] Direct metalation of ***Isoprene*** followed by the reaction with ***Chlorotrimethylsilane*** gives 2-trimethylsilylmethyl-1,3-butadiene in low yield.[4] Thermal isomerization of 1-trimethylsilylmethylcyclobutene to 2-trimethylsilylmethyl-1,3-butadiene has also been reported.[5]

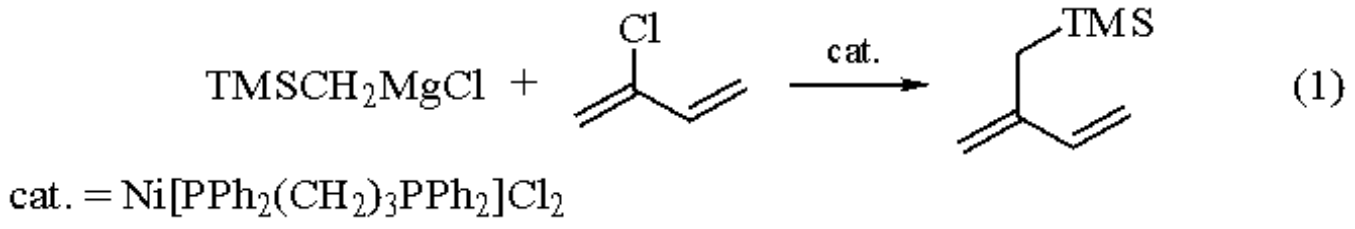

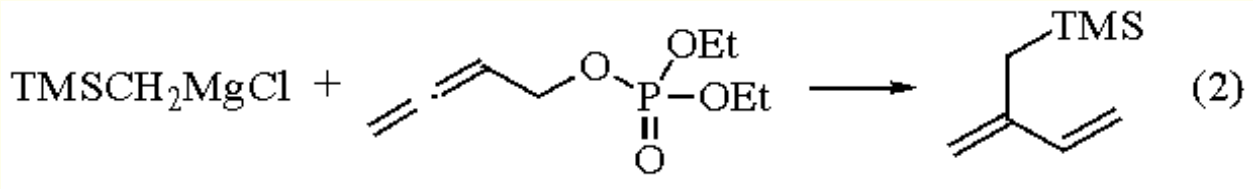

Handling, Storage, and Precautions: can be stored in a glass bottle under nitrogen.

Isoprenylation.

Like other allylic silanes, 2-trimethylsilylmethyl-1,3-butadiene reacts with various electrophilic species such as acetals, acid chlorides, and carbonyl compounds with the aid of a Lewis acid to give the corresponding isoprenylated compounds (eqs 3-6).

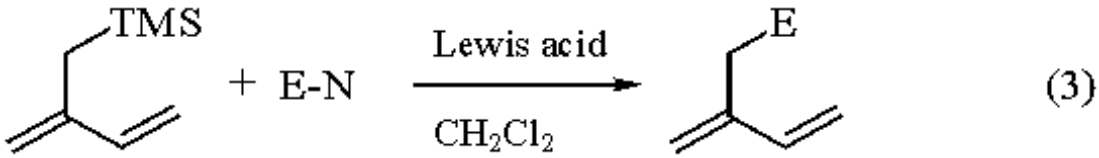

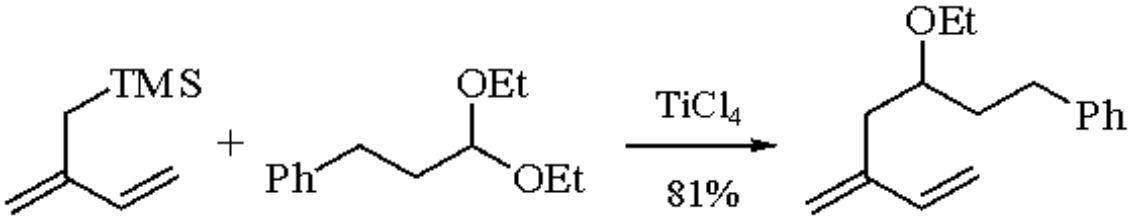

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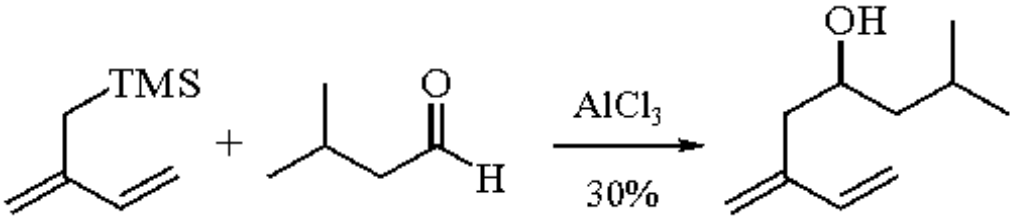

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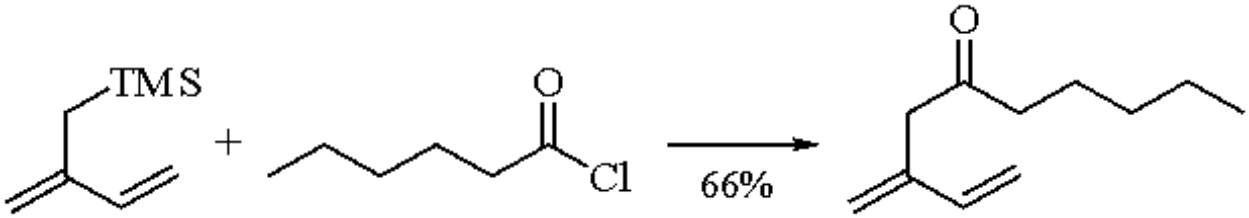

(6)

The direct reaction of 2-trimethylsilylmethyl-1,3-butadiene with isovaleraldehyde gives (±)-ipsenol (2-methyl-6-methylene-7-octen-4-ol) in rather low yield (30%) (eq 5). However, ipsenol is obtained in 62% overall yield by the reaction of 2-trimethylsilylmethyl-1,3-butadiene with isovaleryl chloride, followed by reduction with ***Diisobutylaluminum Hydride*** (eq 7). Similarly, (±)-ipsdienol (2-methyl-6-methylene-2,7-octadien-4-ol) is obtained by reduction of myrcenone, prepared by the reaction of 2-trimethylsilylmethyl-1,3-butadiene with 3,3-dimethylacryloyl chloride, in 75% overall yield (eq 8).

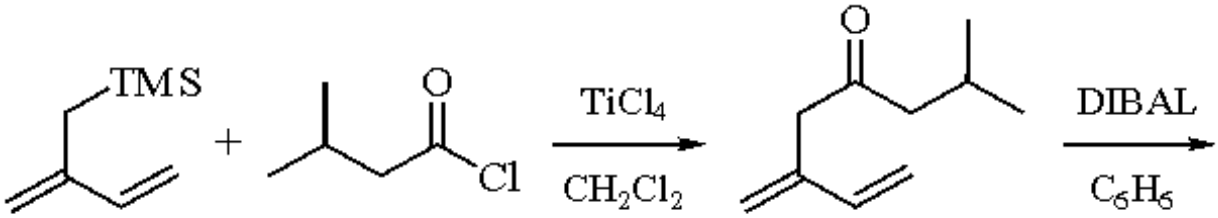

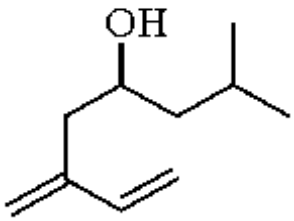

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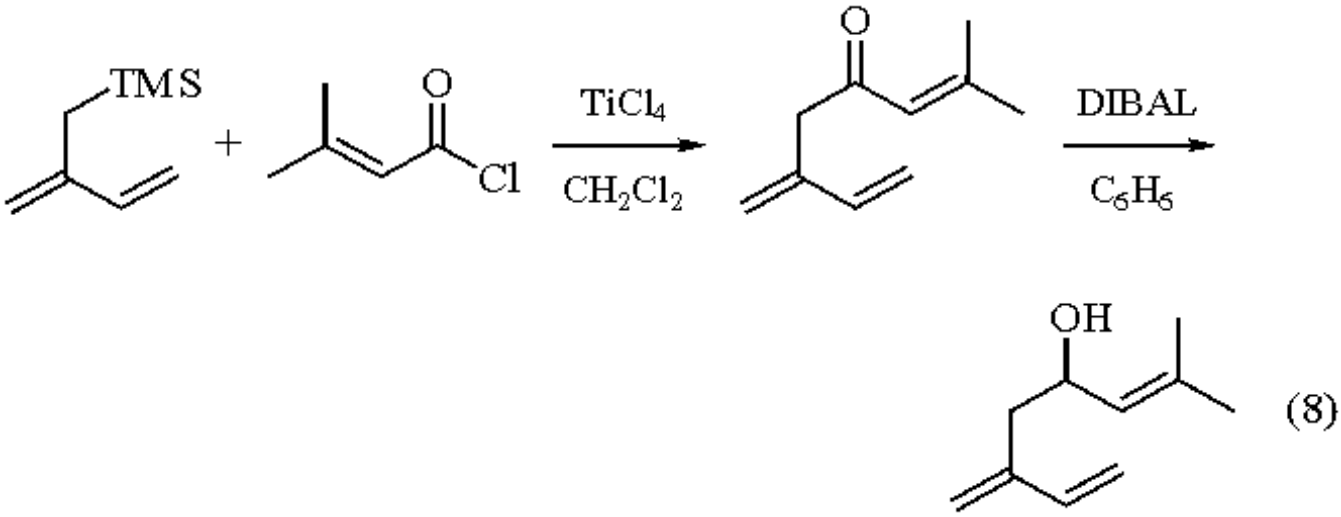

The methyl ether of ipsenol can be prepared by the reaction of 2-trimethylsilylmethyl-1,3-butadiene and isovaleraldehyde dimethyl acetal with ***Iodotrimethylsilane*** catalysis (90%) (eq 9)[6] and from methyl 1-chloro-3-methylbutyl ether (72%).[7] Isoprenylation of carbonyl compounds with 2-trimethylsilylmethyl-1,3-butadiene initiated by a catalytic amount of ***Tetra-n-butylammonium Fluoride*** (TBAF) (eq 10) is the most convenient route to ipsenol and ipsdienol.[8] Reactions with γ-vinylbutyrolactone[9] and *N*-alkylmethyleneiminium salt[10] are also reported.

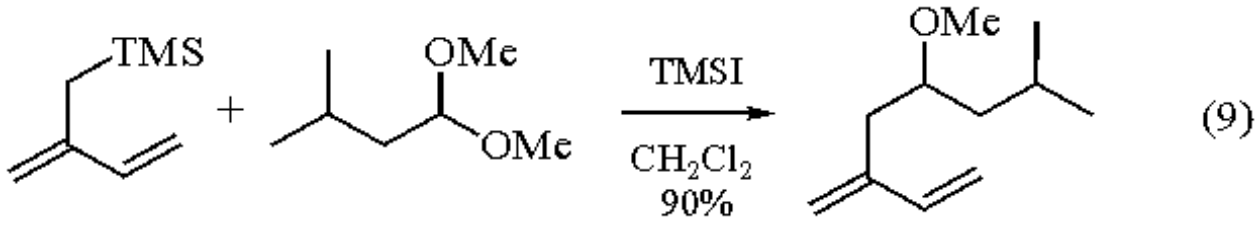

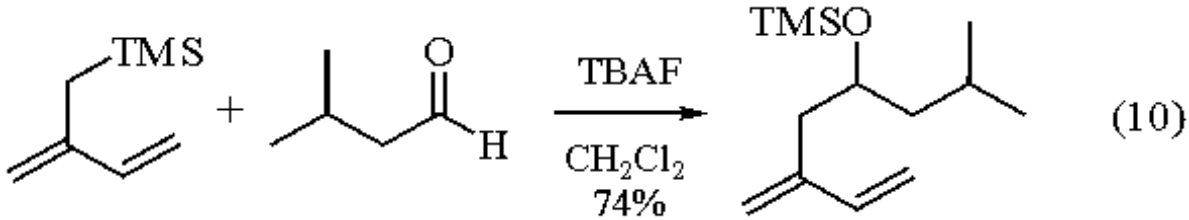

Diels-Alder Reactions.

2-Trimethylsilylmethyl-1,2-butadiene and ***2-Trimethylstannylmethyl-1,3-butadiene*** undergo facile cycloaddition with dienophiles (eq 11). The reactions of 2-trimethylsilylmethyl- and 2-trimethylstannylmethyl-1,3-butadiene with unsymmetrical dienophiles give the so-called *para* product predominantly, and the selectivity is much higher in the reactions with 2-trimethylsilylmethyl- and 2-trimethylstannylmethyl-1,3-butadiene compared to reactions with isoprene. The *para*/*meta* ratios in the reactions with ***Methyl Acrylate*** (eq 12) are: 70/30 (X = H), 84/16 (X = $SiMe_3$), and 91/9 (X = $SnMe_3$).[11]

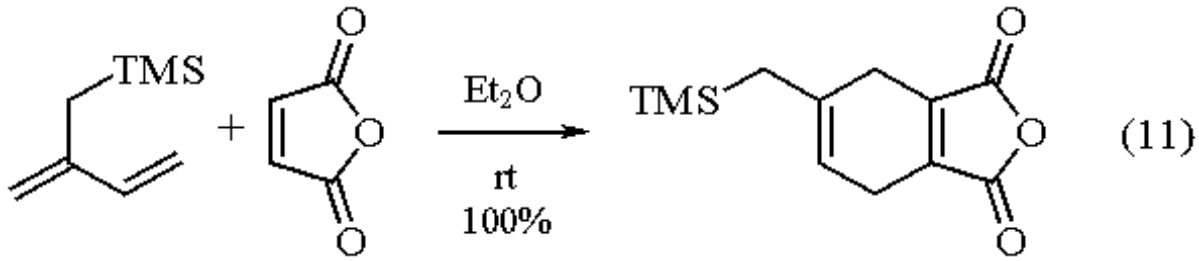

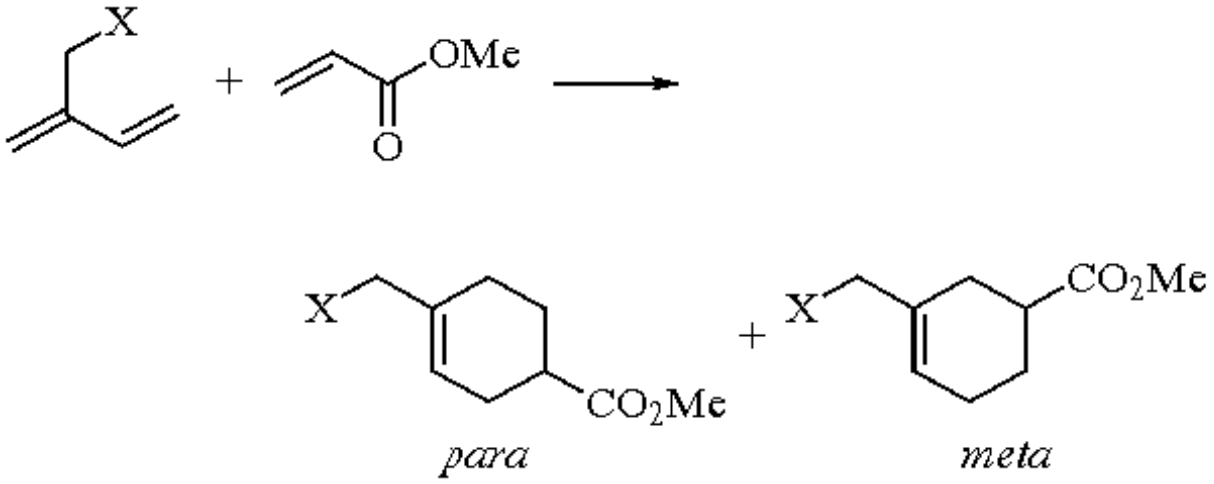

(12)

2-Trimethylsilylmethyl-1,3-butadiene undergoes highly regioselective ***Aluminum Chloride***-catalyzed Diels-Alder reactions with dienophiles such as ***Acrolein*** and ***Methyl Vinyl Ketone*** in which the *para* isomers are obtained almost exclusively (eqs 13 and 14). The adducts are converted readily to a variety of naturally occurring mono- and sesquiterpenes (eq 15).[12]

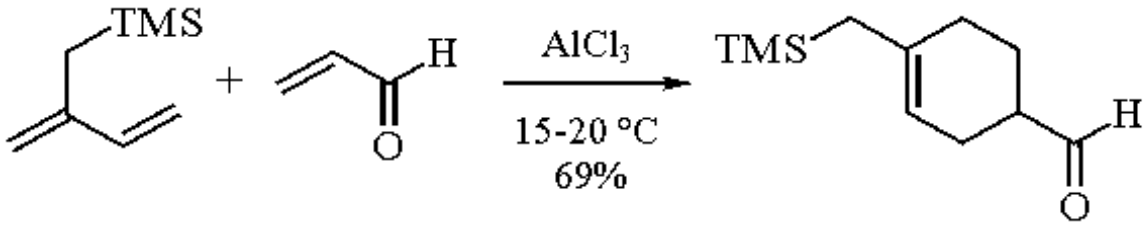

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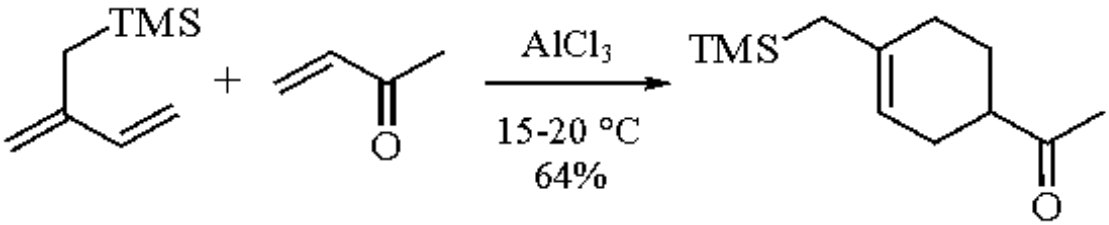

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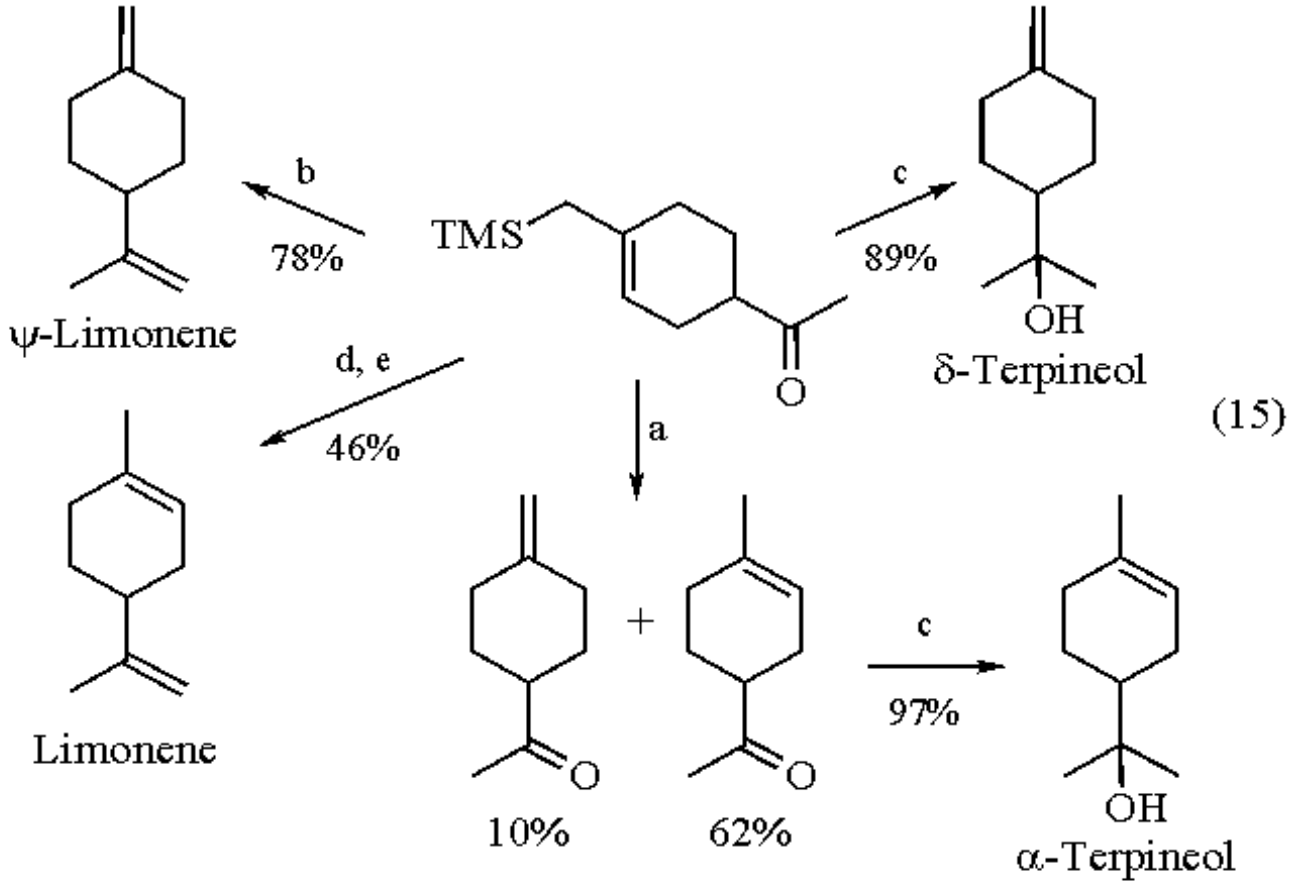

(15)

a: KF, DMSO, 120 °C, 12 h
b: 1. $TMSCH_2MgCl$, Et_2O, 35 °C, 2 h. 2. MeCOCl, MeOH, 0 °C, 15 min
c: 1. MeMgBr, Et_2O, 35 °C, 2 h. 2. HCl, MeOH, rt, 20 min
d: $TMSCH_2MgCl$, Et_2O, 35 °C, 2 h
e: CsF, DMSO, 130 °C, 3 h

Formation of π-Allylic Complex Followed by Acyldemetalation.

2-Trimethylsilylmethyl-1,3-butadiene forms a titanium(III) complex by the reaction with ***Dichlorobis(cyclopentadienyl)titanium*** and *n*-PrMgBr. The complex reacts with carboxylic acid chlorides RCOCl (R = alkyl, alkenyl) to give β,γ-unsaturated ketones (eq 16).[13]

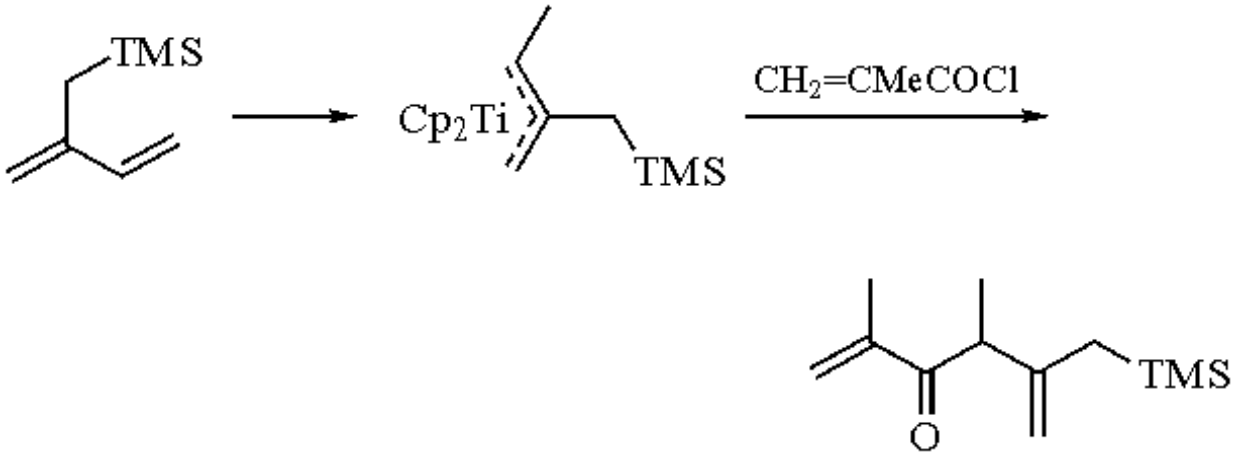

(16)

The regioselectivity of nucleophilic additions to the $Co(CO)_3BF_4$ complex has also been examined.[14] Ziegler-Natta polymerization of 2-trimethylsilylmethyl-1,3-butadiene catalyzed by ***Triethylaluminum*** and ***Titanium(IV) Chloride*** gives predominantly *cis*-1,4-polymer. However, anionic polymerization yields a polymer whose microstructure is composed of *cis*-1,4-, *trans*-1,4-, and 3,4-units.[15]

Related Reagents.

Allyltrimethylsilane; ***2-Trimethylstannylmethyl-1,3-butadiene***.

---

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Trimethylsilylmethylcopper[1]

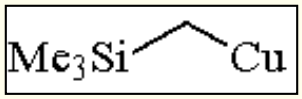

[48003-18-5] · $C_4H_{11}CuSi$ · Trimethylsilylmethylcopper · (MW 150.79)

(organocopper reagent which undergoes smooth S_N2' and addition reactions)

Physical Data: exists in tetrameric form;[2] tetrakis[trimethylsilylmethylcopper(I)] consists of discrete, centrosymmetric, tetrameric units containing a square plane of copper atoms (Cu-Cu 2.42 Å), with the methylene carbons lying in the same plane and bridging the edges.

Solubility: sol THF.

Preparative Method: prepared under an inert atmosphere of argon by addition of ***Trimethylsilylmethylmagnesium Chloride*** (prepared starting from (trimethylsilyl)methyl chloride) to a solution of $LiCuBr_2$ in THF at -65 °C and then stirring for 15 min.

Handling, Storage, and Precautions: air- and moisture-sensitive reagent prepared in situ. Use in a fume hood.

Substitution Reactions.

Trimethylsilylmethylcopper is a suitable reagent to convert α-acetylenic oxiranes, α-allenic oxiranes and α-allenic methanesulfinates, as well as disulfonates, into the corresponding 1,3-substitution products in good yield (80-90%) (eq 1). These reactions proceed with good regiospecificity. The advantage of trimethylsilylmethylcopper over R_2CuM is that RCu generally gives cleaner reaction products, especially when propargylic compounds are the substrates. Trimethylsilylmethylcopper is more effective than R_2CuM in reactions with sulfinates because R_2CuM attacks the sulfinate functionality itself.[3] This conversion consists of two successive 1,3-substitution reactions (eq 2).

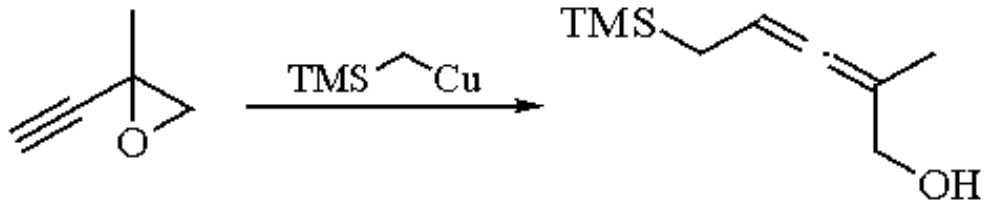

(1)

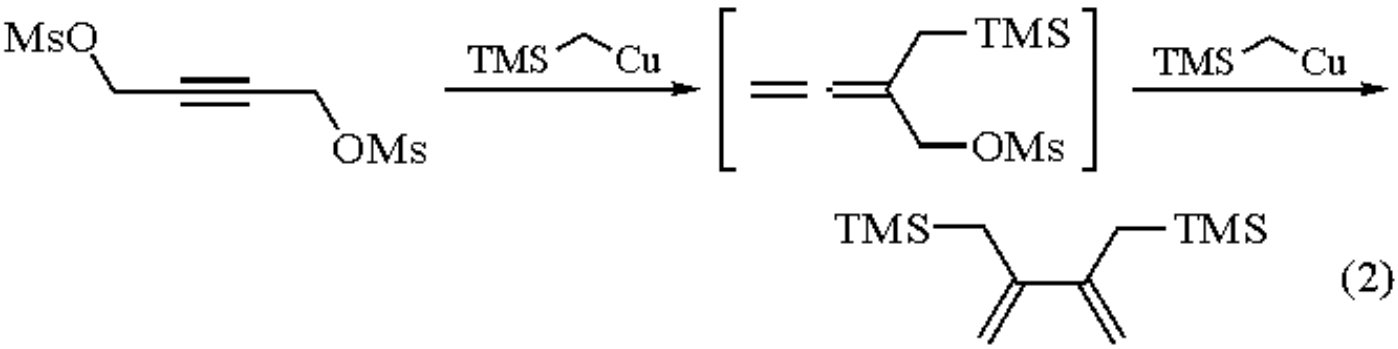

(2)

Addition Reactions.

Trimethylsilylmethylcopper adds smoothly to a variety of activated carbon-carbon triple bonds (eq 3). The adducts are formed predominantly in a stereoselective or even stereospecific *cis*-addition in good yields (70-95%).

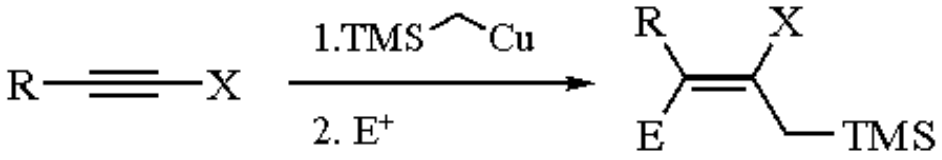

(3)

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Trimethylsilylmethylenedimethylsulfurane

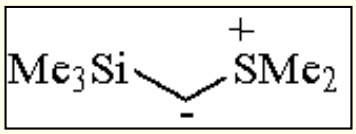

[28872-77-7] · $C_6H_{16}SSi$ · Trimethylsilylmethylenedimethylsulfurane · (MW 148.38)

(vinyl sulfide preparation; preparation of silylcyclopropyl ketones from α,β-unsaturated ketones)

Physical Data: bp 46 °C/7 mmHg.

Analysis of Reagent Purity: ^{1}H NMR.

Preparative Methods: from trimethylsilylmethyldimethylsulfonium iodide by treatment with ***n-Butyllithium*** in Et_2O,[1] ***s-Butyllithium*** in THF,[2] or ***Potassium t-Butoxide*** in DMSO.[3]

Purification: distillation at reduced pressure or fractional condensation in a -45 °C trap.

Handling, Storage, and Precautions: undergoes thermal decomposition; best prepared in situ with *s*-BuLi.

General Discussion.

The addition of this ylide to α,β-unsaturated ketones affords silylcyclopropyl ketones in moderate yields (36-65%) (eq 1).[2] The choice of conditions is very important as silylcyclopropanation is observed only with the reagent prepared in situ from trimethylsilylmethyldimethylsulfonium iodide and *s*-BuLi in THF.

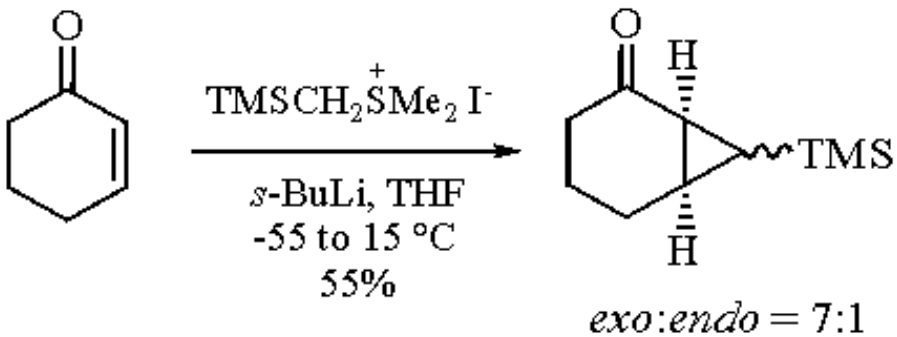

(1)

Treatment of aryl or saturated ketones with trimethylsilylmethylenedimethylsulfurane affords vinyl sulfides (eq 2).[2] The use of *t*-BuOK in DMSO leads to desilylation of the vinylsulfonium intermediate, giving a mixture of products depending upon the substrate used.[3] The most predominant product results from elimination of trimethylsilanol followed by a 2,3-sigmatropic rearrangement of the allyl substituted sulfurane intermediate (eq 3).

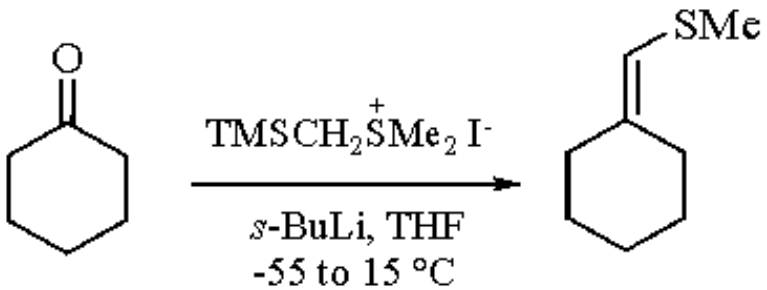

(2)

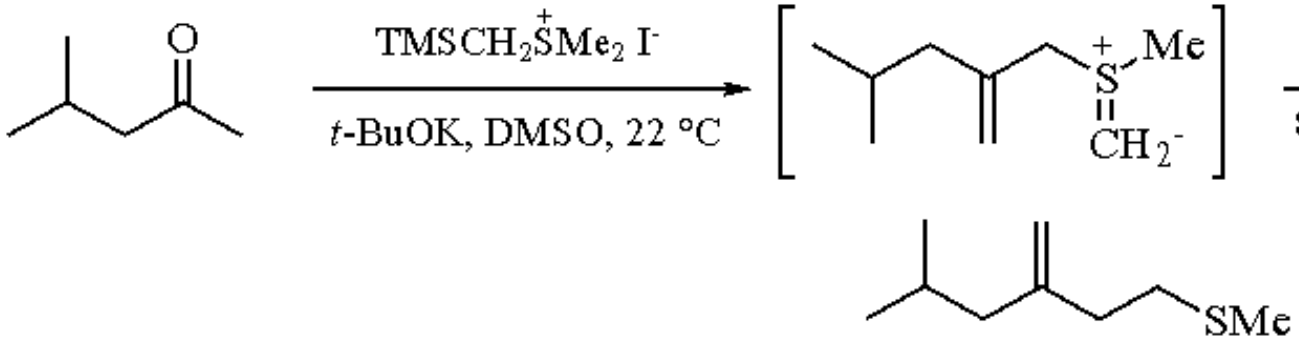

(3)

1. McMullen, J. C.; Miller, N. E. *IC* **1970**, *9*, 2291.
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3. Fleischmann, C.; Zbiral, E. *T* **1978**, *34*, 317.

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Trimethylsilylmethyllithium[1]

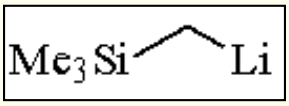

[1822-00-0] · $C_4H_{11}LiSi$ · Trimethylsilylmethyllithium · (MW 94.18)

(methylenation of carbonyl compounds;[1b] reacts with carboxylic acid derivatives to provide α-silyl ketones;[1d,2] synthesis of allylsilanes[1k,3])

Physical Data: mp 112 °C.

Solubility: sol ethereal solvents; reacts with protic solvents.

Preparative Methods: obtained by reaction of ***(Chloromethyl)trimethylsilane*** with ***Lithium*** metal in an inert solvent.[4] It is also available by displacement of a heteroatom group based on sulfur,[5] silicon,[6] or tin.[7]

Handling, Storage, and Precautions: reacts with protic solvents. It should be prepared and handled in inert solvents under an atmosphere of dry nitrogen or argon.

Peterson Alkenation.

Trimethylsilylmethyllithium (**1**) provides an alternative to a Wittig approach for the preparation of methylene compounds from carbonyl precursors.[1b,c,7] In some cases the use of (**1**) is superior to the Wittig approach.[8] Condensation of (**1**) with a carbonyl compound results in the formation of a β-hydroxysilane. Elimination to the alkene can be accomplished by use of acidic or basic conditions (eq 1).[1a,b,9] ***Acetyl Chloride*** or ***Thionyl Chloride*** can also be used to accomplish this elimination.[10] A wide variety of aldehydes and ketones have been used as substrates in this reaction.[1b] The use of ***Cerium(III) Chloride*** has been advocated with reagent (**1**) to favor nucleophilic addition with enolizable carbonyl compounds. The use of the lithium agent (**1**) gives superior yields compared to the use of ***Trimethylsilylmethylmagnesium Chloride*** with cerium.[11]

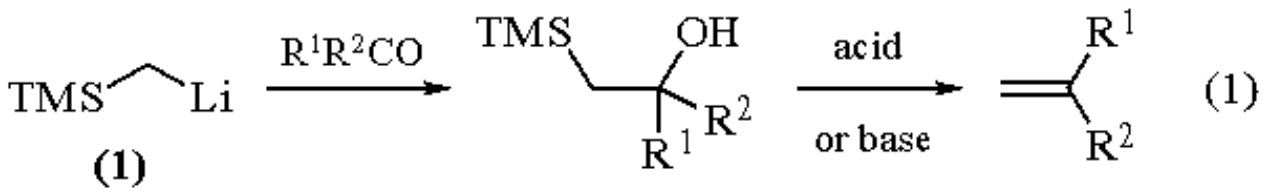

The carbonyl compound can also contain additional functionality.[1b,12] Thus, treatment of an α,β-epoxy ketone with excess lithium reagent (**1**) provides the allyl alcohol (**2**) (eq 2).[13] The use of an α-phenyl selenoaldehyde as electrophile allows either an allyl selenide or a β-silyl aldehyde to be obtained, depending upon the reaction conditions used with the hydroxysilane (eq 3).[14] With α,β-unsaturated ketones, the lithium reagent (**1**) adds in the 1,2-sense; the Grignard analog can provide 1,4-addition.[15] The cuprate derived from (**1**) undergoes the expected reactions for this class of compounds, such as 1,4-addition.[16]

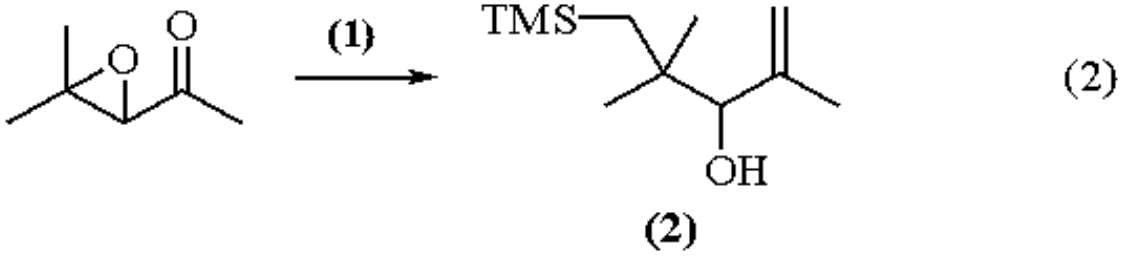

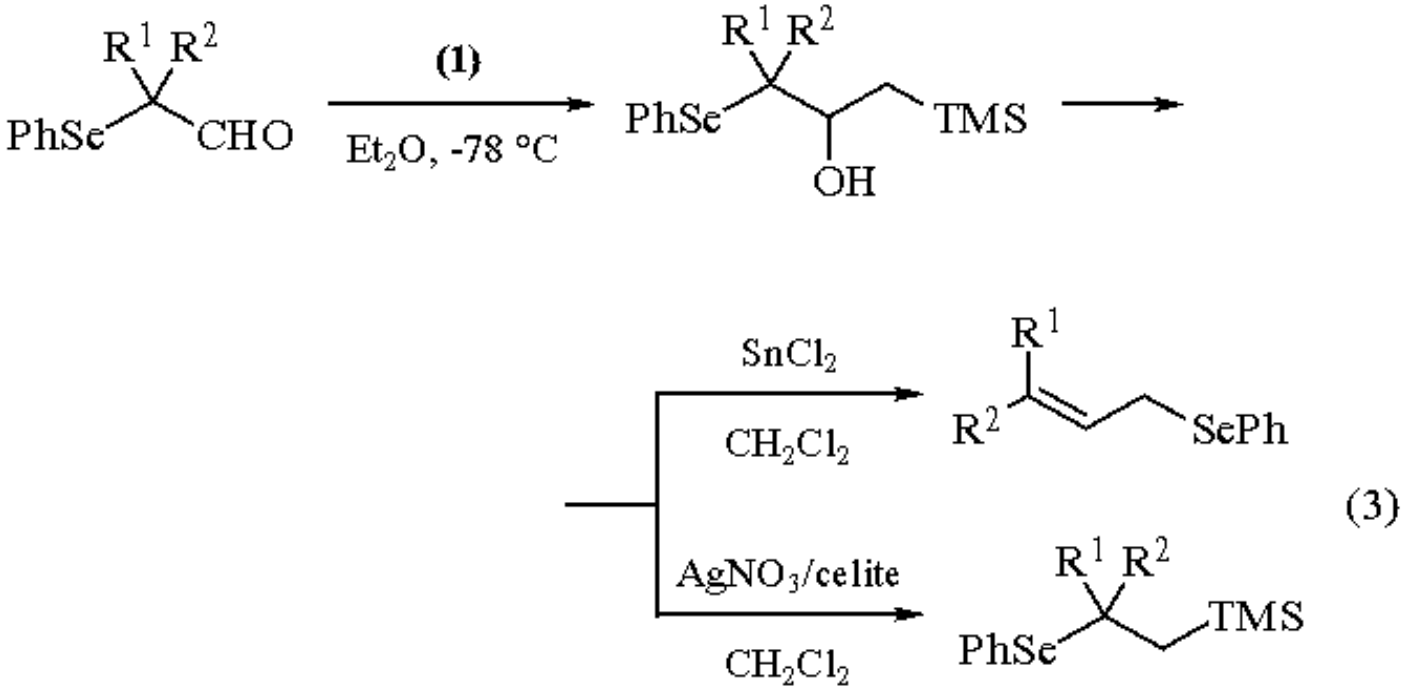

Reaction with Carboxylic Acid Derivatives.

Reaction of (**1**) with carboxylic acid derivatives provides β-silyl ketones (**3**) (eq 4). The reaction yield is very dependent upon the presence of α-hydrogens in the substrate; lower yields are obtained when deprotonation can occur at this center.[2] The reaction occurs with esters, lactones, acid chlorides, and the parent carboxylic acids.[7,17] The resultant β-silyl ketones can be desilylated by simple hydrolysis,[2] or used as a substrate in a Peterson alkenation approach to enones.[1b] The use of a cerium reagent with the acid chloride has been advocated for the preparation of allylsilanes.[18]

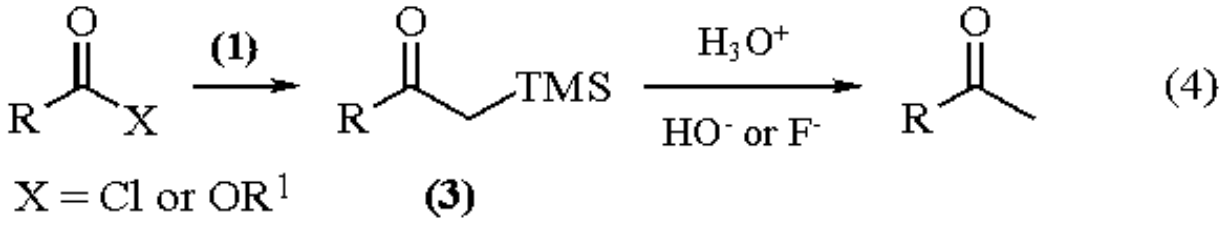

Other Electrophiles.

A mixed higher order cuprate derived from (**1**) allows for the stereoselective preparation of allylsilanes through an epoxide ring opening (eq 5); use of a lower order cuprate results in low yields and mixtures of products.[3]

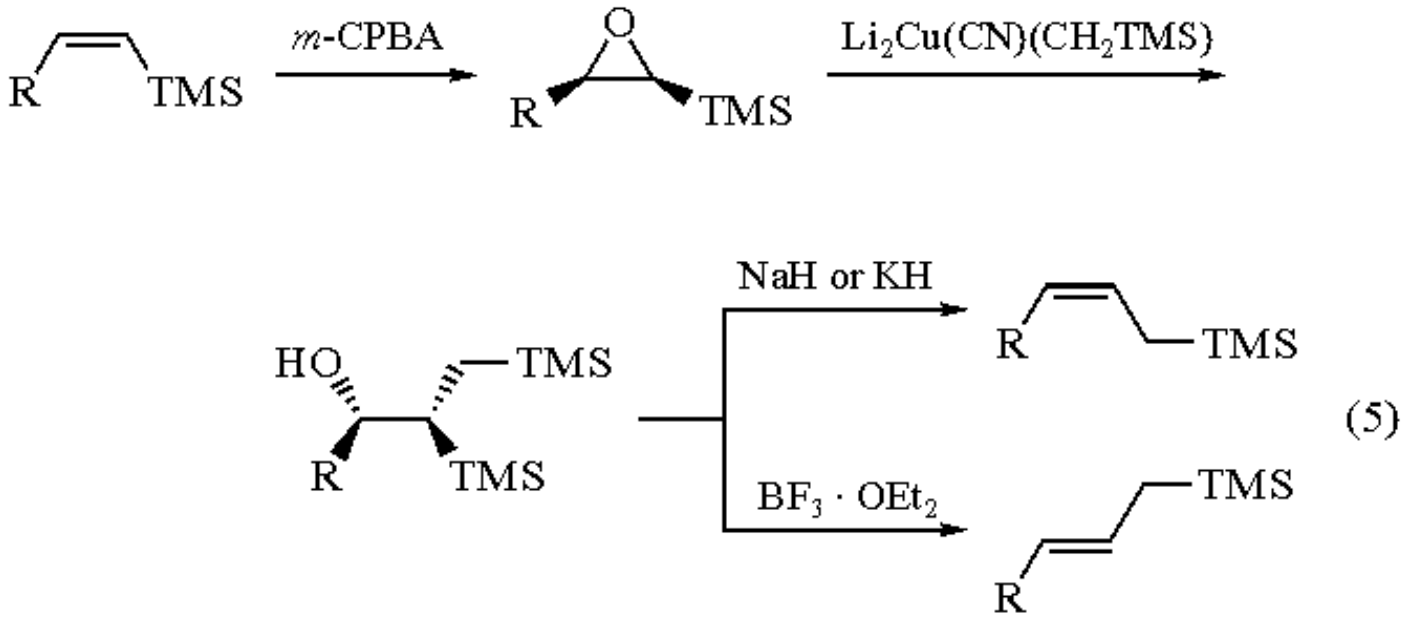

The organolithium reagent (**1**) also reacts with a wide variety of other electrophiles, including silyl chlorides to provide bis(silyl)methane derivatives,[4a,19] and nitriles to provide β-silyl amines after in situ reduction of the intermediate imine derivative.[20] α-Silyl epoxides are opened to provide the substituted vinylsilane.[21] Reaction of (**1**) with arenesulfonyl fluorides provides α-silyl sulfones,[16c] key intermediates for the preparation of vinyl sulfones.[5b,c,22] Reaction of the lithium reagent (**1**) with ***Aluminum Chloride*** followed by a vinyl triflate results in formation of an allylsilane (eq 6).[23] With ***Carbon Monoxide*** as an electrophile with (**1**), a rapid entry to acylsilanes, or silyl enol ethers by subsequent reaction with ***Chlorotrimethylsilane***, can be realized.[24] The alkyllithium (**1**) is the precursor to a wide variety of organometallic compounds that contain the trimethylsilylmethyl ligand.[25]

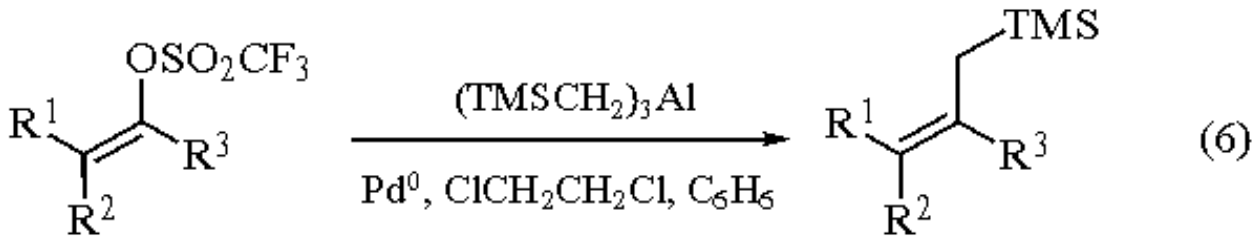

Analogs.

The displacement of a heteroatom to introduce the lithium allows for a wide range of substituted analogs of the reagent (**1**) to be prepared.[1b,5,26] The presence of an aromatic group on the same carbon atom as the silyl moiety allows for direct deprotonation by butyllithium to form the lithium reagent.[27] Higher alkyl analogs of (**1**) are also available by the addition of an alkyllithium to a vinylsilane.[1a,10,27,28] All of these higher homologs react with carbonyl compounds and other electrophiles, as expected.[1b,d]

Related Reagents.

Bis(trimethylsilyl)methane; ***(Diisopropoxymethylsilyl)methylmagnesium Chloride***; ***Trimethylsilylmethylmagnesium Chloride***; ***(Trimethylstannylmethyl)lithium***.

---

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28. Tamao, K.; Kanatani, R.; Kumada, M. *TL* **1984**, *25*, 1905.

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Trimethylsilylmethylmagnesium Chloride[1]

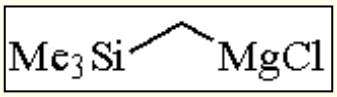

[13170-43-9] · $C_4H_{11}ClMgSi$ · Trimethylsilylmethylmagnesium Chloride · (MW 147.00)

(methylenation of carbonyl compounds;[1b,2] provides a variety of methods to prepare allylsilanes[1k])

Solubility: sol ethereal solvents; reacts with protic solvents.

Preparative Method: from ***(Chloromethyl)trimethylsilane*** and ***Magnesium*** in an ethereal solvent.[3,4]

Handling, Storage, and Precautions: this Grignard reagent reacts with protic solvents.

Peterson Alkenation.

Trimethylsilylmethylmagnesium chloride (**1**) reacts with carbonyl compounds to give β-hydroxysilanes (**2**).[2,4,5] These silanes can then be eliminated to provide an alkene under acidic or basic conditions, such as with ***Sodium Hydride*** or ***Potassium Hydride*** (eq 1).[1a,1b,5,6] The elimination can also be accomplished by ***Acetyl Chloride*** or ***Thionyl Chloride***.[7] For the introduction of *exo*-methylene groups, reagent (**1**) has been found to be superior to a Wittig approach;[8] the silicon reagent reacts rapidly and the byproduct is simple to remove.[1b]

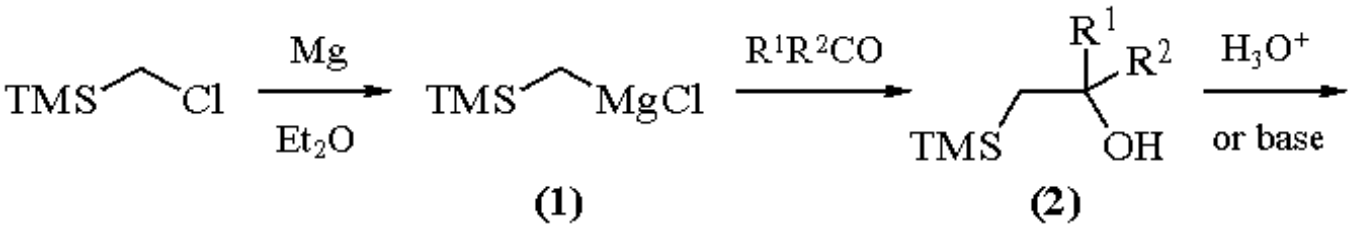

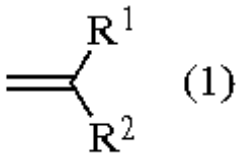

(1)

This methodology has found application in the carbohydrate field for homologation of a saccharide,[9] as other functional groups can be tolerated.[1b,10] The resultant alkene can be functionalized in a wide variety of ways.[11] The use of ***Paraformaldehyde*** as electrophile provides a simple method to ***2-(Trimethylsilyl)ethanol***.[12]

Many of the uses of the Grignard reagent (**1**) are complementary to those of ***Trimethylsilylmethyllithium***, although the cerium reagent derived from the lithium analog provides higher yields with enolizable aldehydes and ketones.[13]

With α,β-unsaturated carbonyl compounds the Grignard reagent reacts in a 1,2-manner,[14] although 1,4-addition can be observed in certain cases.[15] The resultant β-hydroxysilane from a 1,2-addition can be isomerized to the β-ketosilane with a rhodium catalyst.[16] In the presence of copper(I), the Grignard reagent (**1**) reacts in a 1,4-manner with α,β-unsaturated carbonyl compounds.[15,17]

The use of substituted carbonyl compounds allows for the formation of functionalized alkenes; for example, α,β-epoxy ketones afford the monoepoxide of a diene.[18] The successive treatment of α-chlorocarbonyl compounds with (**1**) and ***Lithium*** powder provides a regioselective entry to allylsilanes (eq 2).[19]

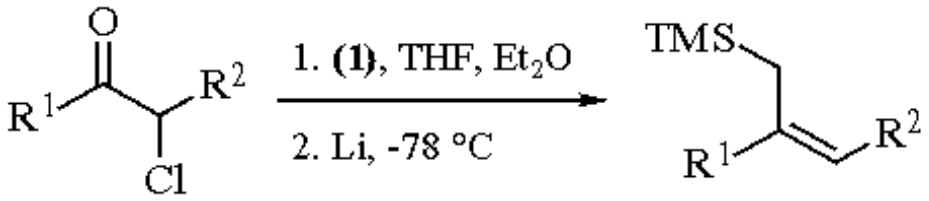

(2)

Reagent (**1**) does also react with imines that, in turn, can be generated in situ.[20]

Reaction with Carboxylic Acid Derivatives.

In addition to carbonyl compounds, reagent (**1**) also reacts with carboxylic acid derivatives.[4] Thus lactones provide hydroxy allylsilanes (**3**) (eq 3).[21]

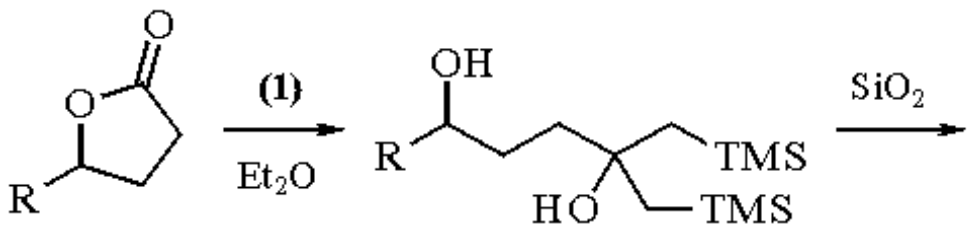

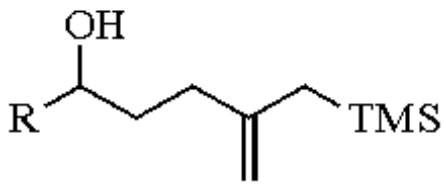

(3)

(3)

Reaction of excess (**1**) with esters provides the tertiary alcohol in an analogous manner,[1d] and subsequent elimination provides the allylsilane.[22] The addition of the second equivalent of (**1**), however, is dependent on the steric requirements of the intermediate β-silyl ketone.[23] The addition of ***Chlorotrimethylsilane*** to the reaction mixture has been advocated as higher yields of the resultant allylsilane are obtained.[24] The use of ***Cerium(III) Chloride*** with Grignard reagent (**1**) promotes nucleophilic attack on esters, and the allylsilanes can be obtained in high yield (eq 4).[25] The yields seem to be higher than for the analogous reaction between an acid chloride and the cerium reagent prepared from trimethylsilylmethyllithium.[26] 1,2-Addition is observed with α,β-unsaturated esters.[25] Other functional groups, such as acetals, thioacetals, halogens, hydroxy, acetates, and sulfides, can be incorporated at the α-position of the ester group without detrimental effects.[27]

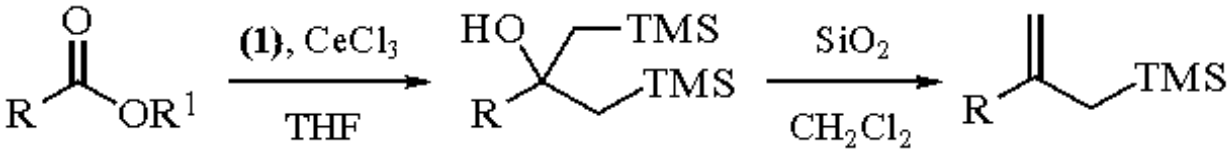

(4)

Reaction with diketene in the presence of a nickel catalyst gives 3-(trimethylsilylmethyl)but-3-enoic acid (**4**) (eq 5).[28]

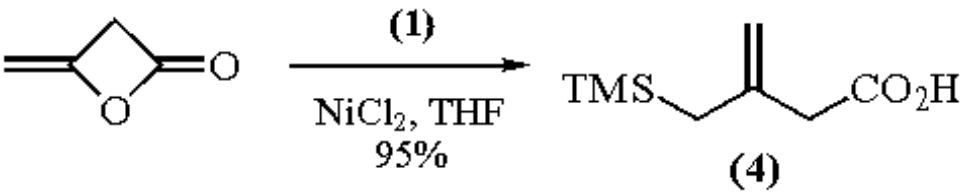

(5)

(4)

The Grignard reagent (**1**) does react with acid chlorides to provide ketones after hydrolytic workup.[2] The use of a copper(I) catalyst allows isolation of β-silyl ketones (eq 6).[29]

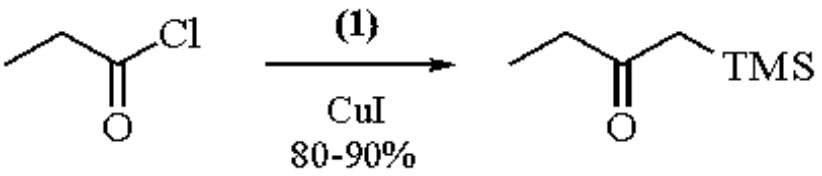

(6)

β-Silyl ketones are hydrolytically unstable and can be converted to the desilylated ketone by simple acid or base treatment,[30] or used in a Peterson alkenation reaction to provide enones.[1b,29a] They are also precursors to silyl enol ethers by rearrangement.[29c,31] Reaction of the β-silyl ketone with a vinyl Grignard reagent provides a rapid entry to 2-substituted 1,3-dienes by a Peterson protocol.[32]

Reaction of (**1**) with ***Carbon Dioxide*** provides ***Trimethylsilylacetic Acid***,[33] while treatment of (**1**) with ***Ethyl Chloroformate*** gives ***Ethyl Trimethylsilylacetate***.[34] The use of ethyl oxalyl chloride as substrate for (**1**) provides a simple preparation of ethyl 2-(trimethylsilylmethyl)propenoate.[35] Condensation of (**1**) with benzonitrile resulted in isolation of acetophenone (64%) and desoxybenzoin (45%).[4]

Reaction with Alkyl Halides.

The Grignard reagent (**1**) can be alkylated by allyl halides to afford the homoallylsilane.[4,36] The use of a nickel(II) catalyst facilitates coupling of the Grignard reagent (**1**) to vinyl halides[37] and aryl halides, triflates and *O*-carbamates[38] and provides a useful method for the preparation of allyl- and benzylsilanes (eq 7). Palladium catalysis is also effective to couple (**1**) with vinyl halides.[37b,39]

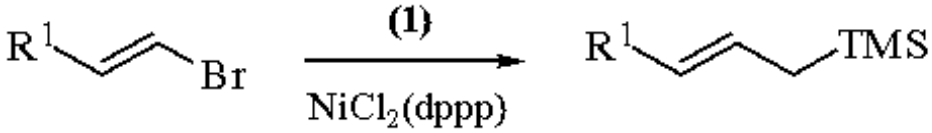

(7)

Reaction with Sulfur Compounds.

In a similar coupling reaction to those of alkyl halides, (**1**) reacts in the presence of a nickel catalyst with allylic dithioacetals to yield 1-(trimethylsilyl)butadienes (eq 8).[40]

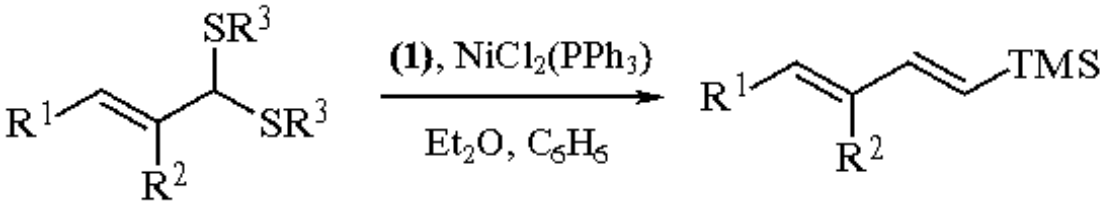

(8)

Dithioacetals derived from alkyl aryl ketones react with the Grignard reagent (**1**) in the presence of a nickel catalyst.[41,42] The use of an orthothioester as substrate in place of a thioacetal provides 1,3-bis(trimethylsilyl)propenes as a mixture of the (*E*)- and (*Z*)-isomers.[43] With α-oxoketene dithioacetals (**5**), the Grignard reagent (**1**) reacts, in the presence of ***Copper(I) Iodide***, to provide 1-trimethylsilyloxy-3-thiadienes (eq 9).[44]

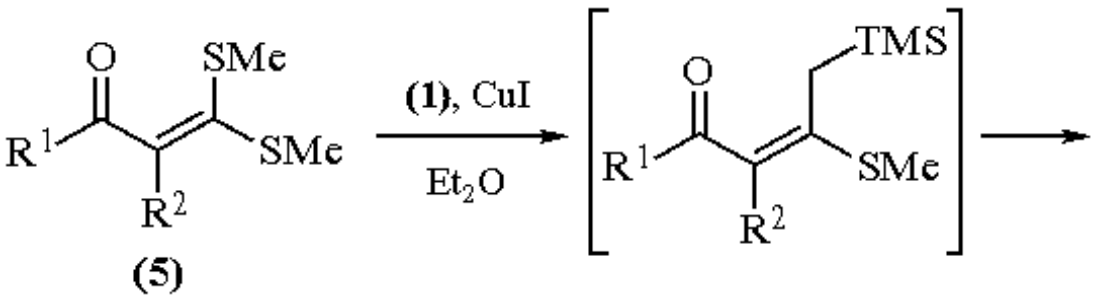

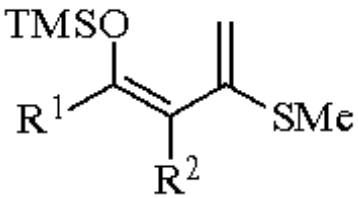

(9)

Reaction with Other Electrophiles.

Reaction occurs between (**1**) and epoxides to yield γ-hydroxysilanes.[45] Michael addition is observed with nitroalkenes; the silyl group can then promote a Nef reaction to afford β-silyl ketones (eq 10).[46]

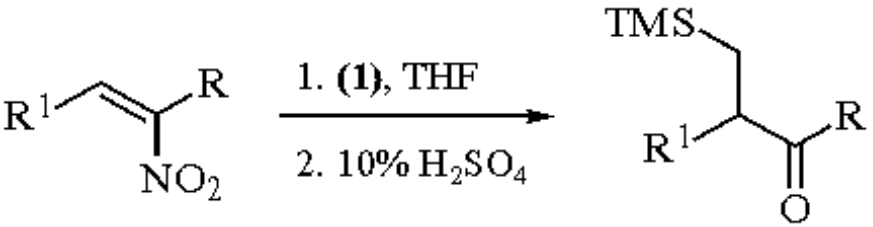

(10)

With aromatic nitro compounds, nucleophilic addition of (**1**) occurs on the aromatic nucleus (eq 11).[47]

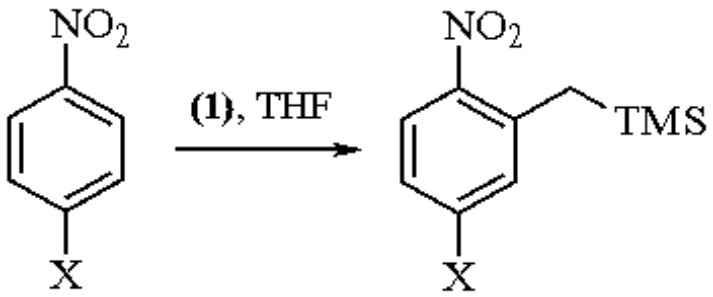

(11)

A nickel catalyst allows reaction between (**1**) and an enol phosphate,[48] silyl enol ether,[49] or substituted dihydrofurans[50] and dihydropyrans[51] to afford allylsilanes. Additional functionality can be tolerated in the substrate.[52]

Coupling of (**1**) with propargylic tosylates, mesylates, or acetates in the presence of copper(I) leads to α-trimethylsilylallenes,[53] while the use of a propargyl alcohol substrate leads to the substituted allylsilane (eq 12).[54]

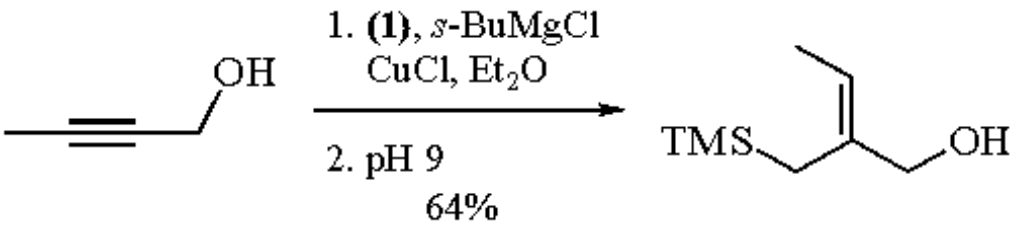

(12)

With alkynes, copper-catalyzed addition of the Grignard reagent (**1**) provides the allylsilane.[55] The intermediate vinylcopper reagent can also be trapped with electrophiles.[56]

The reagent (**1**) also reacts with wide variety of electrophiles, including carbon dioxide,[33] cyanogen,[57] silyl chlorides,[3,58] metal halides,[59] and ***Phosphorus(III) Chloride***.[59a] With methyl phenyl sulfinate, reaction of (**1**) leads to the formation of (phenylthio)(trimethylsiloxy)methane, a protected form of formaldehyde, by a sila-Pummerer rearrangement.[60]

The Grignard reagent (**1**) is the precursor of numerous organometallic compounds that contain the trimethylsilylmethyl ligand.[61]

Related Reagents.

(Diisopropoxymethylsilyl)methylmagnesium Chloride; ***Trimethylsilylmethylpotassium***; ***(Trimethylstannylmethyl)lithium***.

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2-Trimethylsilylmethyl-2-propen-1-ol[1]

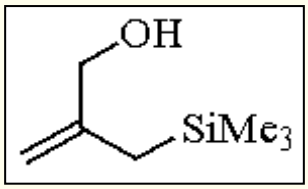

[81302-80-9] · $C_7H_{16}OSi$ · 2-Trimethylsilylmethyl-2-propen-1-ol · (MW 144.32)

(derivatives function as trimethylenemethane (TMM) precursors and undergo cyclopentannulation reactions; methylenecyclopentanes; 2-acetoxymethyl-3-trimethylsilylpropene;[2] [3 + 2] annulation;[3] three-carbon condensative expansion;[4] cyclocontraction-spiroannulation[5])

Alternate Names: 2-(hydroxymethyl)-3-trimethylsilylpropene; 2-(hydroxymethyl)-2-propenyltrimethylsilane; (hydroxymethyl)allyl trimethylsilane; 2-(trimethylsilylmethyl)allyl alcohol.

Physical Data: bp 54-56 °C/2 mmHg; *n*20D 1.454; *d* 0.861 g cm^{-3}; fp 71 °C.

Solubility: insol water; sol all organic liquids.

Form Supplied in: liquid, 90% pure; remainder of the mixture (approx. 10%) is 3-trimethylsilyl-2-methyl-2-propen-1-ol or 3-trimethylsilylmethyl-2-propen-1-ol.

Preparative Method: prepared in four steps from methallyl alcohol. The synthesis begins with the metalation with ***n-Butyllithium*** (2 equiv) producing the dianion which is bis-silylated by trapping with ***Chlorotrimethylsilane*** to generate the allylsilane. The TMS ether is subsequently removed by hydrolysis (eq 1). The primary allylic alcohol serves as a precursor to more functionalized reagents.

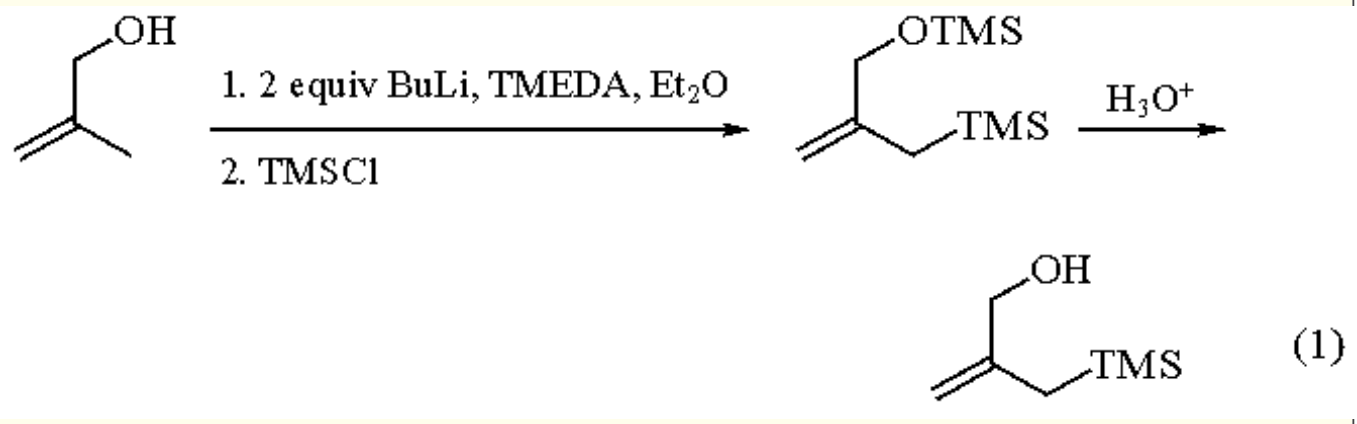

Useful derivatives of the alcohol are the primary allylic chloride, mesylate, and acetate. These are easily prepared in a short number of steps as shown (eq 2) or by functionalization of the primary allylic alcohol.

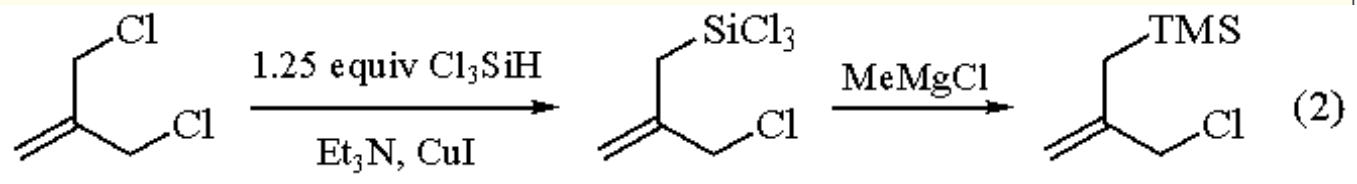

Purification: by distillation under reduced pressure.

Handling, Storage, and Precautions: flammable liquid; irritant; store at 0-4 °C.

Introduction.

The title allylsilane reagent has been employed as a conjunctive reagent which is considered to be a synthetic equivalent of a zwitterionic, bifunctional compound possessing a nucleophilic allylic anion synthon and an electrophilic cation synthon in the same molecule (**1**).

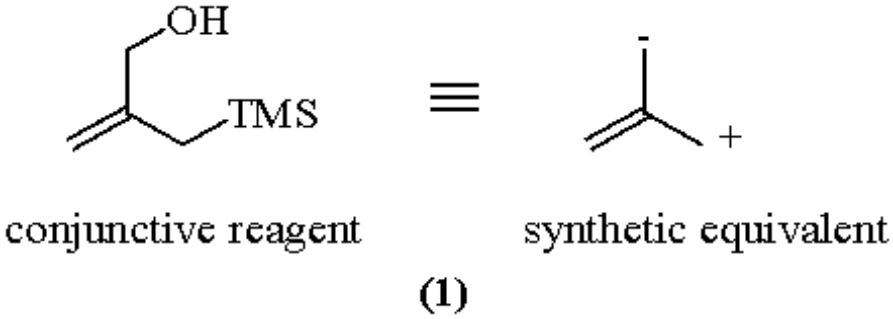

(1)

[3 + 2] Annulations.

The primary allylic halide ***2-Chloromethyl-3-trimethylsilyl-1-propene*** or the mesylate derived from the corresponding alcohol behaves as a bifunctional reagent possessing both nucleophilic and electrophilic reaction centers. For example, they have been shown to participate in [3 + 2] carbon annulations for the construction of methylenecyclopentanes. The reaction proceeds through a Lewis acid-promoted conjugate addition (Sakurai reaction) followed by an internal alkylation of the derived ketone enolate (eq 3).

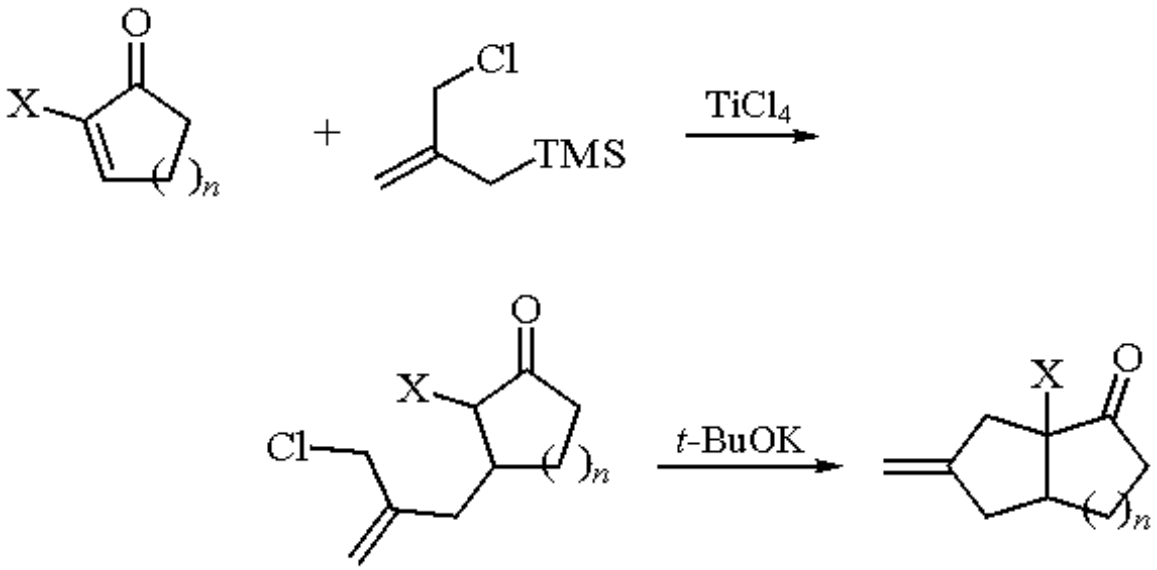

(3)

n	X	Yield (%)	Yield (%)
2	H	80	60
1	H	8	-
2	SPh	80	79
1	SPh	63	73

In a related study, the annulation is combined with a ring expansion reaction. The reaction utilizes a β-keto sulfone as the two-carbon component along with an allylic mesylate as the bifunctional reagent. The alkylation/cyclization process is outlined in eq 4. The subsequent ring expansion appears to be a general process except for cases involving fused six- and seven-membered ring systems (eq 5).

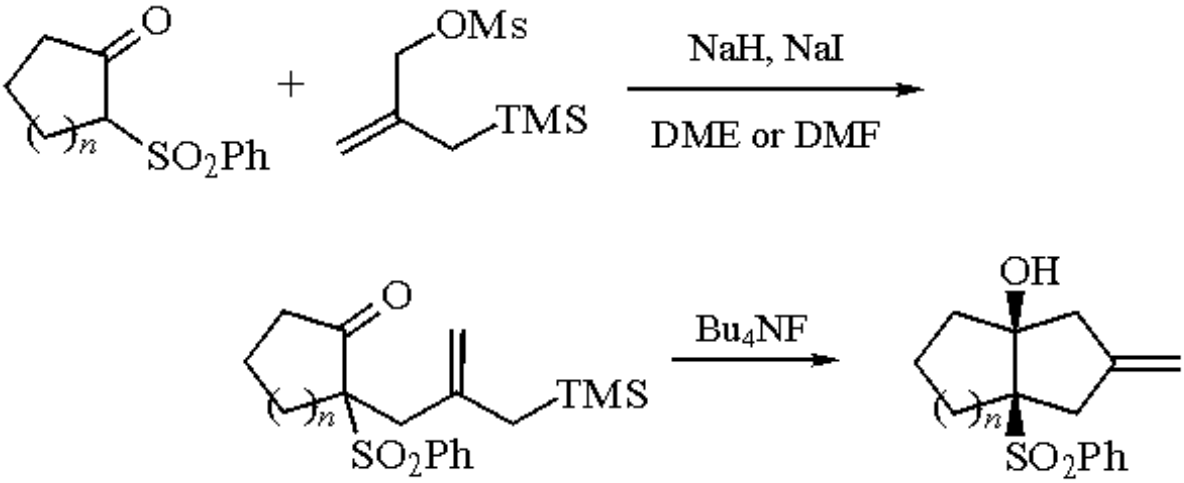

(4)

n	Alkylation yield (%)	Cyclization yield (%)
1	81	94
2	71	79
3	80	79

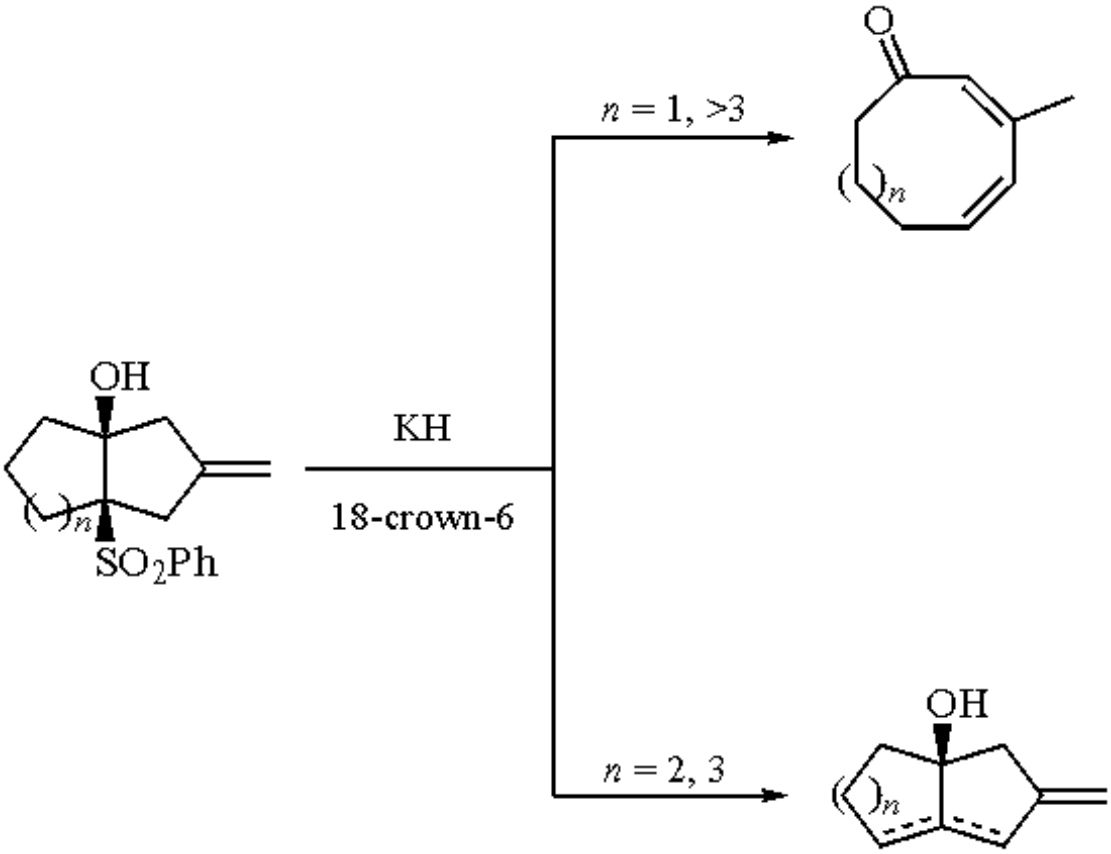

(5)

Methylenecyclopentane Annulation.

The acylated derivative 2-acetyloxymethyl-3-trimethylsilylpropene is known to be an effective three-carbon component in cyclopentane annulations. It has been demonstrated that 2-acetoxymethylallyltrimethylsilane adds to a variety of electron-deficient alkenes in the presence of a catalytic amount of ***Tetrakis(triphenylphosphine)palladium(0)*** and ***1,2-Bis(diphenylphosphino)ethane*** to produce methylenecyclopentanes (eqs 6-8).

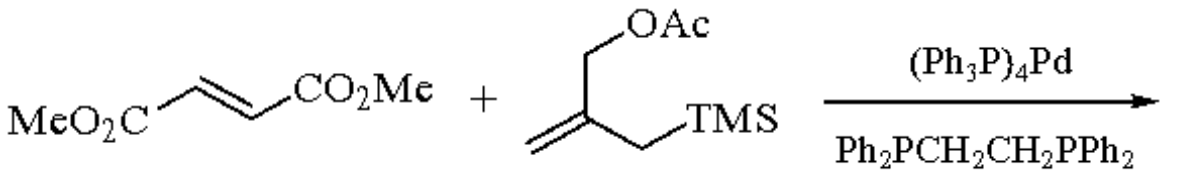

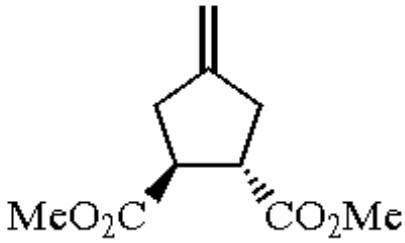

(6)

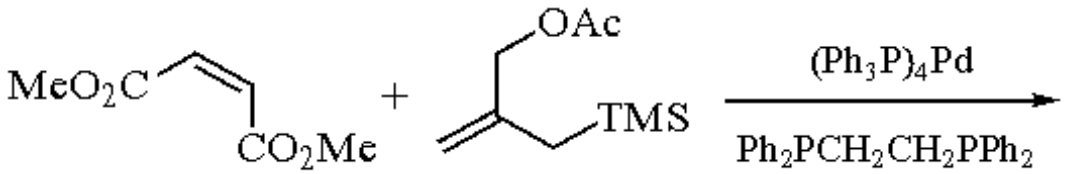

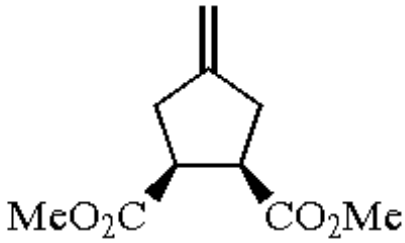

(7)

cis:*trans* = 1.3:1

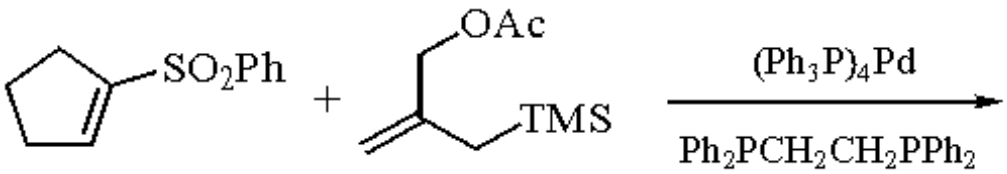

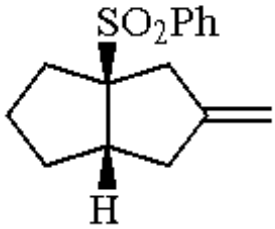

(8)

Cyclocontraction-Spiroannulation.

The mesylate derivative of 2-hydroxymethyl-3-trimethylsilylpropene participates in an interesting annulation reaction involving a β-keto sulfone as the two-carbon component (eq 9).

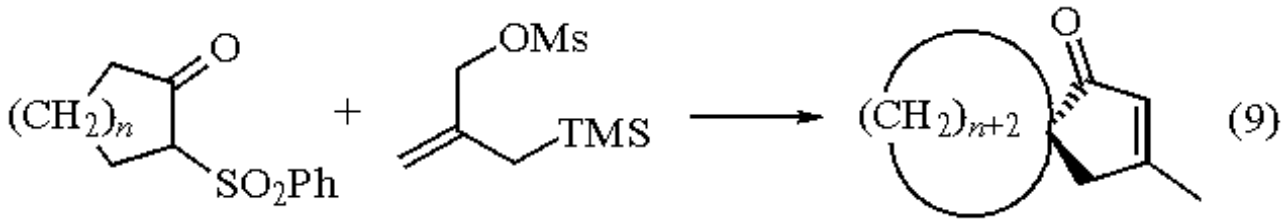

The reaction is thought to involve a pinacol-type rearrangement in which the phenylsulfonyl group serves as a leaving group in the presence of a Lewis acid (eq 10).

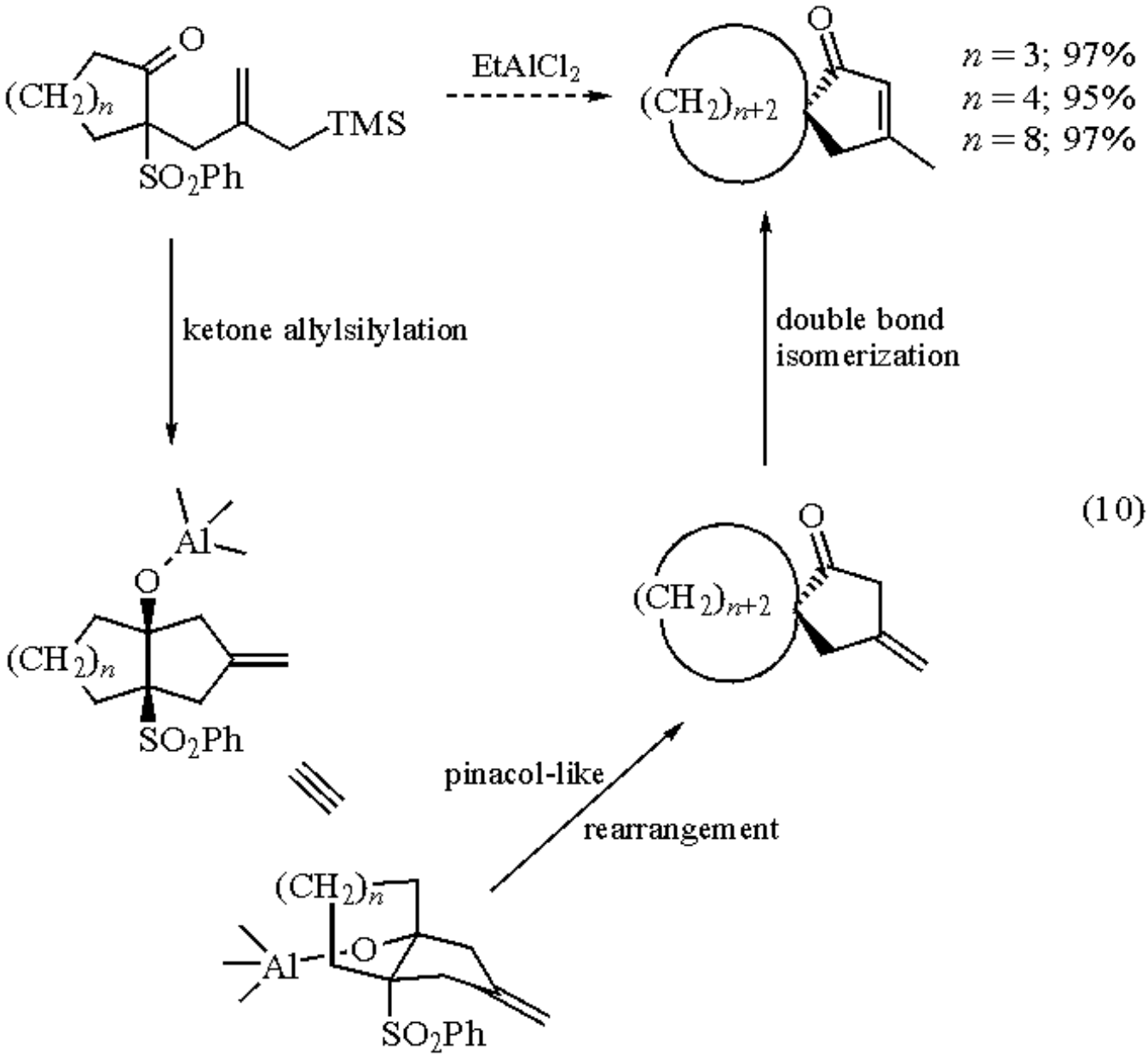

Related Reagents.

3-Acetoxy-2-trimethylsilylmethyl-1-propene; ***3-Iodo-2-trimethylsilylmethyl-1-propene***.

---

1. Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *OS* **1984**, *62*, 58.
2. Trost, B. M.; Chan, D. M. T. *JACS* **1979**, *101*, 6429.
3. Knapp, S.; O'Connor, U.; Mobilio, D. *TL* **1980**, *21*, 4557.
4. Trost, B. M.; Vincent, J. E. *JACS* **1980**, *102*, 5680.
5. Trost, B. M.; Adams, B. R. *JACS* **1983**, *105*, 4849.

James S. Panek & Pier F. Cirillo

Trimethylsilylmethylpotassium[1]

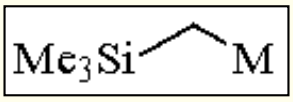

(**1**; M = K)

[53127-82-5] · $C_4H_{11}KSi$ · Trimethylsilylmethylpotassium · (MW 126.34) (**2**; M = Na)

[53127-81-4] · $C_4H_{11}NaSi$ · Trimethylsilylmethylsodium · (MW 110.23)

(can act as a strong base with benzylic and allylic compounds[2])

Preparative Methods: trimethylsilylmethylpotassium (**1**) and -sodium (**2**) are prepared by reaction of ***Bis(trimethylsilyl)mercury*** with the appropriate metal as a suspension in cyclohexane.[2,3] Trimethylsilylmethylsodium can also be prepared by reaction of ***Bis(trimethylsilyl)methane*** with ***Sodium Methoxide*** in HMPA.[4]

Handling, Storage, and Precautions: both of these organometallic reagents should be prepared just prior to use and not stored for extended periods. All reactions with these reagents should be performed under an inert atmosphere.

Base Reactions.

Both metal reagents (**1**) and (**2**) act as bases. The tricyclic ether (**3**) is readily deprotonated by the hindered base (**1**), but pentylsodium or butylpotassium proved superior in other cases.[2] However, reagent (**1**) provides an alternative to the ***n-Butyllithium-Potassium t-Butoxide*** system (eq 1).[1]

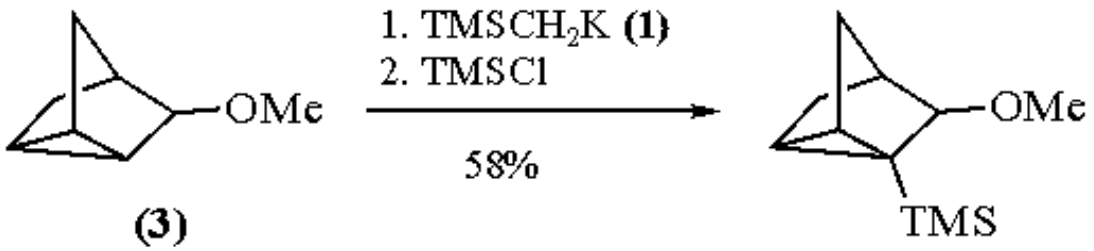

(1)

Both reagents (**1**) and (**2**) react with benzylic compounds to afford benzyl anions. The reaction can accommodate alkyl or silyl groups on the benzylic position or as substituents on the aromatic ring (eq 2).[2,3]

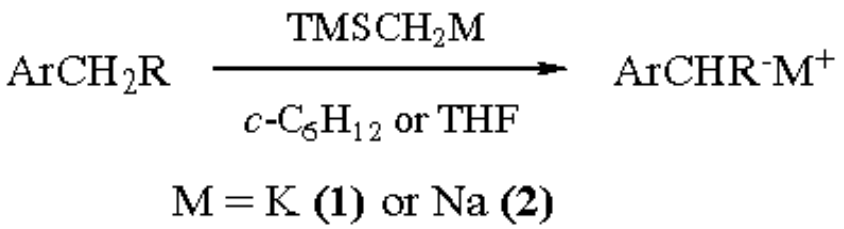

(2)

The use of trimethylsilylmethylpotassium (**1**) as a base also allows deprotonation of allylic positions. The allyl carbanions produced by the action of substrate with (**1**) react with ***Ethylene Oxide*** to afford the 4-en-1-ol product; unsymmetrical allylic anions can result in a mixture of products, although reaction is favored at the least substituted center (eq 3).[5]

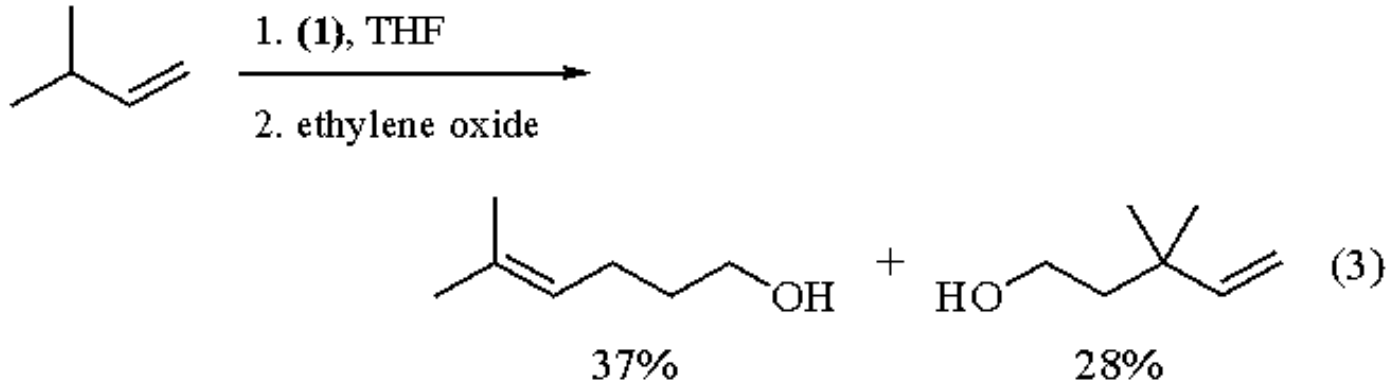

The potassium reagent (**1**) will deprotonate simple alkenes to give allylic anions.[2] Subsequent reaction with a chloroborane results in the allylic borane, which, in turn, can be converted to an allyl alcohol (eq 4).[6]

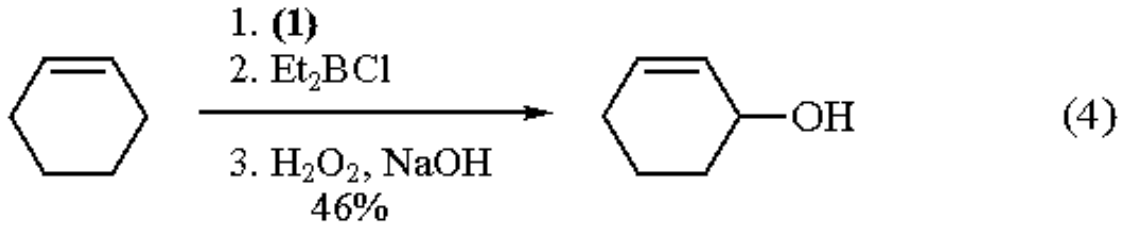

Pentadienyl-type organometallic reagents are available by reaction of (**1**) with homoconjugated and conjugated dienes, without significant polymerization. The regioselectivity of the metalation is dependent on the structure of the substrate, U-shaped delocalized systems usually being preferred.[7] However, the factors affecting the regioselectivity are subtle, as illustrated by reaction at the 14-position of 7-dehydrocholesterol (**4**) (eq 5).[8]

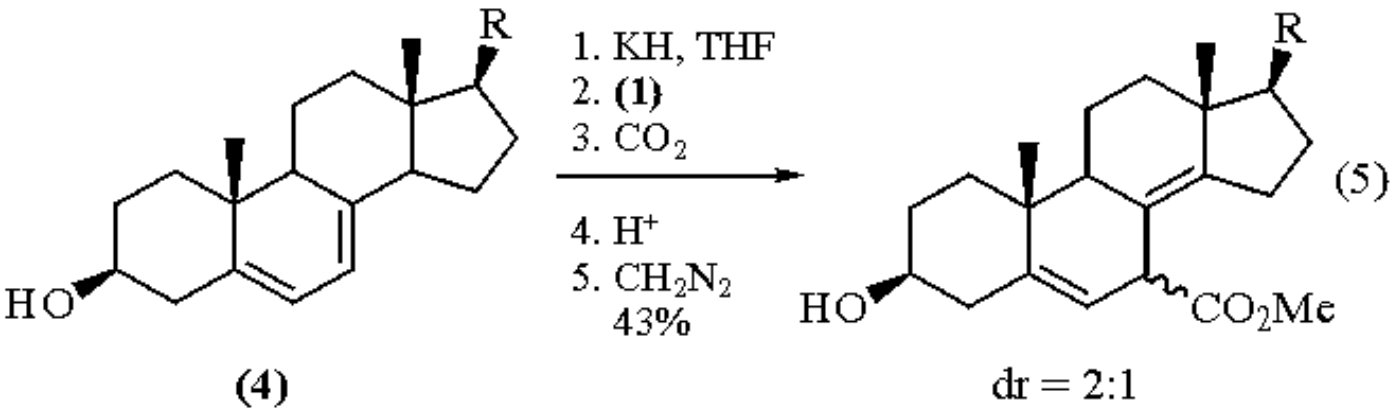

Peterson Alkenation.

Trimethylsilylmethylsodium (**2**) is prepared in situ by the action of sodium methoxide on bis(trimethylsilyl)methane (**5**),[4] and reacts with nonenolizable carbonyl compounds to provide alkenes by a Peterson alkenation reaction (eq 6). Alternative procedures are available that circumvent the use of HMPA, and allow reaction with enolizable carbonyl compounds.[9]

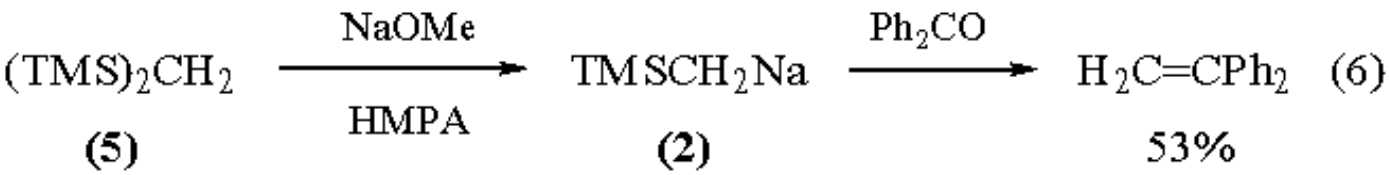

Related Reagents.

Trimethylsilylmethyllithium; ***Trimethylsilylmethylmagnesium Chloride***.

1. Schlosser, M. *AG(E)* **1974**, *13*, 701.
2. Hartmann, J.; Schlosser, M. *HCA* **1976**, *59*, 453.
3. Hart, A. J.; O'Brien, D. H.; Russell, C. R. *JOM* **1974**, *72*, C19.
4. Sakurai, H.; Nishiwaki, K.-i.; Kira, M. *TL* **1973**, 4193.
5. Hartmann, J.; Schlosser, M. *S* **1975**, 328.
6. Zaidlewicz, M. *JOM* **1985**, *293*, 139.
7. (a) Schlosser, M.; Rauchschwalbe, G. *JACS* **1978**, *100*, 3258. (b) Bosshardt, H.; Schlosser, M. *HCA* **1980**, *63*, 2393. (c) Schlosser, M.; Bosshardt, H.; Walde, A.; Stähle, M. *AG(E)* **1980**, *19*, 303.
8. Moret, E.; Schlosser, M. *TL* **1984**, *25*, 1449.
9. (a) Ager, D. J. *OR* **1990**, *38*, 1. (b) Johnson, C. R.; Tait, B. D. *JOC* **1987**, *52*, 281.

David J. Ager

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Trimethylsilylmethyl Trifluoromethanesulfonate[1]

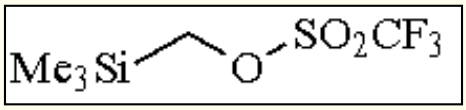

[64035-64-9] · $C_5H_{11}F_3O_3SSi$ · Trimethylsilylmethyl Trifluoromethanesulfonate · (MW 236.32)

(preparation of azomethine ylides, sulfonium ylides, ammonium ylides, and phosphonium ylides from imines, amines, sulfides, or phosphines via alkylation[1,2,3a] and fluoride-induced desilylation[1,2,3b])

Alternate Name: trimethylsilylmethyl triflate.

Physical Data: bp 156-158 °C,[2] 49-51 °C/9 mmHg.[4a]

Solubility: miscible with common organic solvents (ethers, halocarbons, hydrocarbons).

Form Supplied in: colorless oil.

Analysis of Reagent Purity: ^{1}H NMR ($CDCl_3$, ppm): δ 0.19 (9 H, s) 4.27 (3 H, s).

Preparative Methods: Me_3SiCH_2OH + ***Trifluoromethanesulfonic Anhydride/Pyridine*** in CH_2Cl_2 (68%);[2,4a] Me_3SiCH_2OMe + ***Trimethylsilyl Trifluoromethanesulfonate*** (93%);[4b] ***Diazomethane*** + $Me_3SiOSO_2CF_3$ (81%).[4c]

Purification: distillation.

Handling, Storage, and Precautions: can be stored indefinitely in the refrigerator under anhydrous conditions.

Azomethine Ylides from Imines.

An imine is alkylated with the title reagent ($TMSCH_2OTf$) to give a salt such as (**1**) which is not isolated, but is treated with ***Cesium Fluoride*** to generate the reactive azomethine ylide (**2**). In the presence of ***Dimethyl Acetylenedicarboxylate*** as the dipolarophile, (**2**) is trapped by [2 + 3] cycloaddition to afford a pyrroline (eq 1). Azomethine ylides (**3**)-(**8**)[2,5] can be generated and trapped in the same way with external dipolarophiles, while (**9**)[5h] undergoes the analogous internal [2 + 3] cycloaddition process.[5] Other desilylation approaches to azomethine ylides have been developed since the initial report in 1979,[1] and the topic has been reviewed.[2,6]

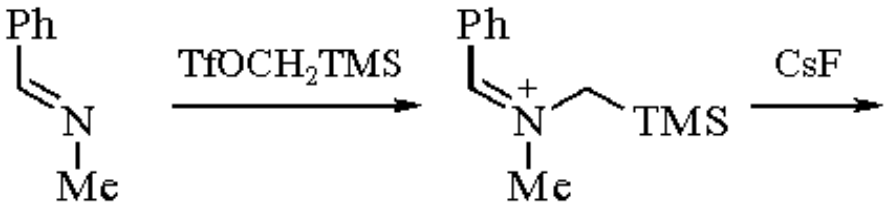

(1)

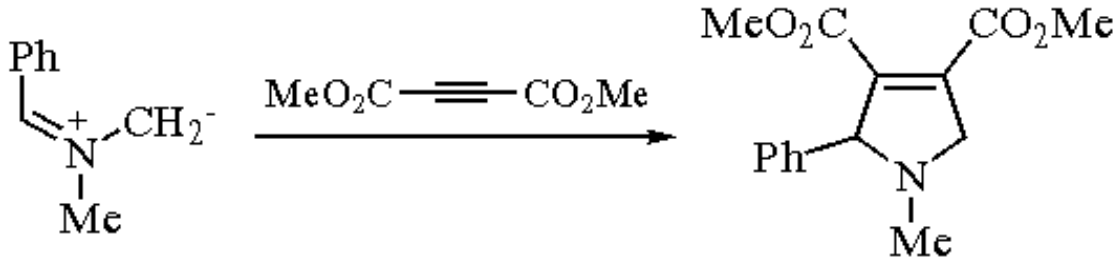

(2) (1)

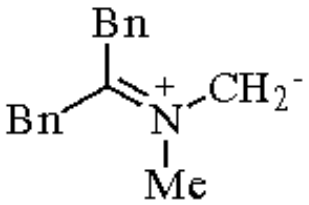

(3)

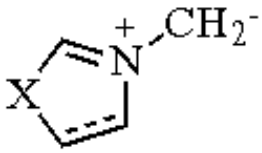

(4a) X = O
(4b) X = BnN

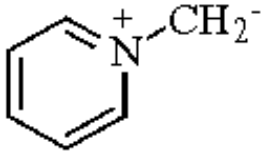

(5)

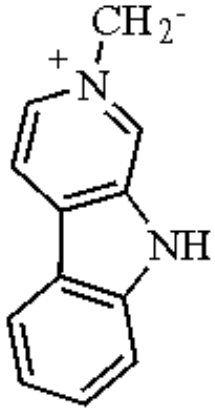

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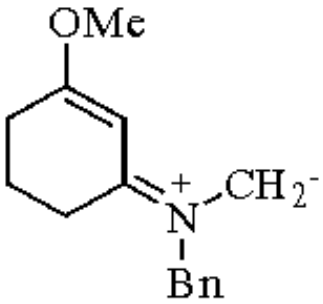

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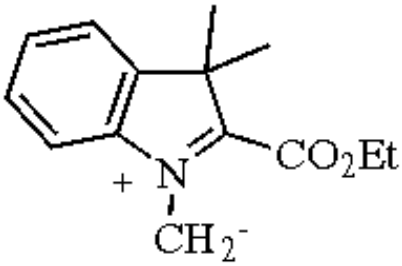

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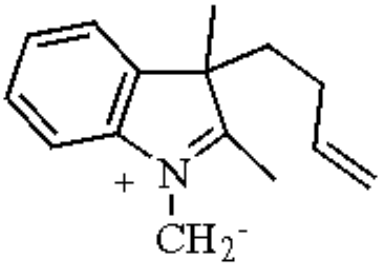

(9)

2,3-Sigmatropic Rearrangement.

The desilylation approach permits regiospecific methylide generation from sulfides or amines. If the ylide also contains an allylic group as a heteroatom substituent, then 2,3-sigmatropic rearrangement (eq 2) occurs smoothly. This process has been demonstrated for the ammonium ylide (**10**),[2] and the sulfonium ylides (**11**)[2] and (**12**).[7] Rearrangement by 2,3-shift can also involve an aromatic double bond in ylide (**13**), as shown in eq 3.[8] In this case, two nonaromatic intermediates can be detected, but chromatography affords the aromatized product 2,3-dimethyl(methylthiomethyl)benzene. Similar intermediates have been reported in the rearrangement of *N*-benzylammonium methylides generated by the desilylation method.[9]

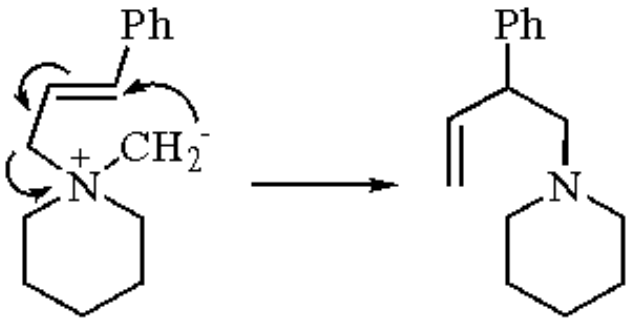

(2)

(10)

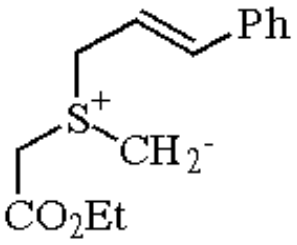

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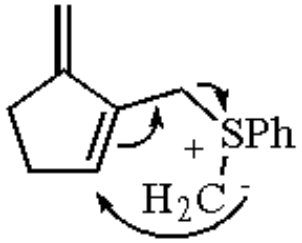

(12)

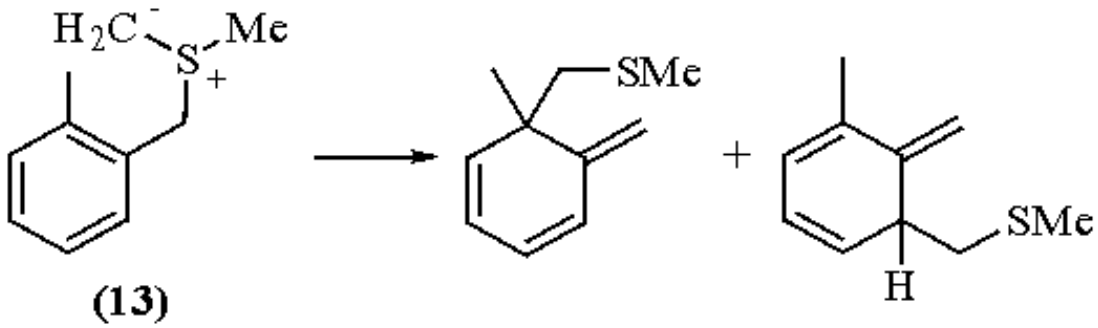

(3)

(13)

Miscellaneous Applications.

Alkene formation is possible via sulfide alkylation with $TMSCH_2OTf$, followed by ylide generation with CsF.[2] The process involves a five-center elimination (eq 4). The same procedure leads to the ammonium ylide (**14**), and spontaneous fragmentation occurs at room temperature to give (*E*)-cyclododecene (70%).[2] Sulfonium methylide generation and trapping by intramolecular attack at a C=O bond is also known, resulting in the formation of epoxides or fragmentation products.[10] Treatment of ***Triphenylphosphine*** with $TMSCH_2OTf$ followed by desilylation with CsF in the presence of benzophenone results in the in situ generation and Wittig trapping of the phosphonium ylide $Ph_3P{=}CH_2$.[2] Finally, $TMSCH_2OTf$ can also be used for the *C*-alkylation of α-lithio vinylcarbamates.[11]

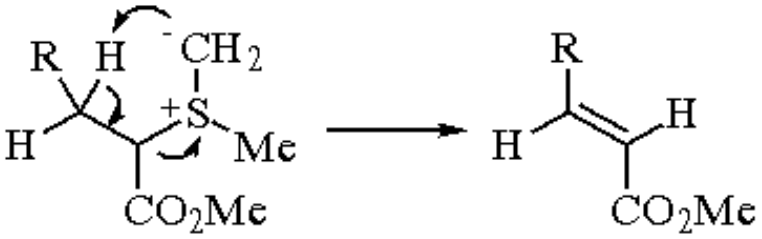

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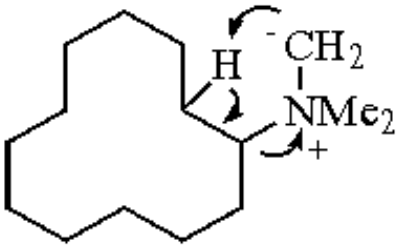

(14)

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1. Vedejs, E.; Martinez, G. R. *JACS* **1979**, *101*, 6452.
2. Vedejs, E.; West, F. G. *CRV* **1986**, *86*, 941.
3. (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *S* **1982**, 85. (b) Block, E.; Aslam, M. *T* **1988**, *44*, 281. (c) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *CRV* **1993**, *93*, 1371.
4. (a) Baum, K.; Lerdal, D. A.; Horn, J. S. *JOC* **1978**, *43*, 203. (b) Cunico, R. F.; Gill, H. S. *OM* **1982**, *1*, 1. (c) Lee, J. G.; Ha, D. S. *S* **1988**, 318.
5. (a) Oxazole: Padwa, A.; Venkatramanan, M. K.; Chiacchio, U. *CC* **1985**, 1108. (b) *N*-Benzylimidazoline: Jones, R. C. F.; Nichols, J. R.; Cox, M. T. *TL* **1990**, *31*, 2333. (c) Tsuge, O.; Kanemasa, S.; Kuraoka, S.; Takenaka, S. *CL* **1984**, 279. (d) Miki, Y.; Hachiken, H.; Ikeda, M.; Takemura, S. *H* **1984**, *22*, 701. (e) Poissonnet, G.; Theret, M. H.; Dodd, R. H. *H* **1993**, *36*, 435. (f) Padwa, A.; Haffmanns, G.; Tomas, M. *TL* **1983**, *24*, 4303. (g) Fishwick, C. W. G.; Jones, A. D.; Mitchell, A. B.; Eggleston, D. S.; Baurer, P. W. *SL* **1990**, 359. (h) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *TL* **1989**, *30*, 4447.
6. (a) Vedejs, E. *Adv. Cycloaddition* **1988**, *1*, 33. (b) Terao, Y.; Aono, M.; Achiwa, K. *H* **1988**, *27*, 981. (c) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231. (d) Grigg, R. *CSR* **1987**, *16*, 89.
7. Cohen, T.; Yu, L. C.; Suzuki, K.; Kosarych, Z. *JOC* **1985**, *50*, 2965.
8. Padwa, A.; Gasdaska, J. R. *T* **1988**, *44*, 4147.
9. Shirai, N.; Watanabe, Y.; Sato, Y. *JOC* **1990**, *55*, 2767.
10. Watanabe, Y.; Takeda, T.; Anbo, K.; Ueno, Y.; Toru, T. *CL* **1992**, 159.
11. Sengupta, S.; Snieckus, V. *JOC* **1990**, *55*, 5680.

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Trimethylsilyl Nonaflate

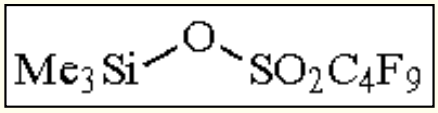

[68734-62-3] · $C_7H_9F_9O_3SSi$ · Trimethylsilyl Nonaflate · (MW 372.32)

(Lewis acid capable of generating enol silyl ethers from ketones;[1] selective Friedel-Crafts catalyst for nucleoside formation from silylated heterocycles and peracylated sugars;[2] catalyzes *cis*/*trans* equilibration of substituted cyclopropanes;[3] used in the formation of mixed iodonium sulfonates[4])

Physical Data: bp 70-72 °C/12 mmHg.[5]

Solubility: sol most organic solvents.

Preparative Methods: can be conveniently generated in situ by the addition of ***Chlorotrimethylsilane*** to a suspension of potassium nonaflate.[1] Other methods of preparation exist;[5,6] however, the aforementioned method appears to be the most efficient.

Handling, Storage, and Precautions: should be used as prepared.

General Discussion.

It has been shown that enolizable ketones can be efficiently converted to their corresponding enol silyl ethers by the reaction of trimethylsilyl nonaflate and ***Triethylamine*** at the temperature of refluxing cyclohexane (eqs 1 and 2).[1]

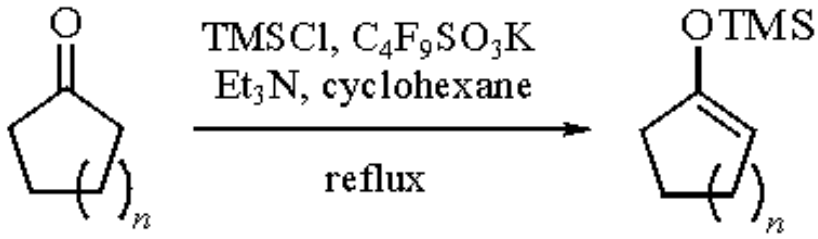

(1)

$n = 1$, 72%; $n = 2$, 82%

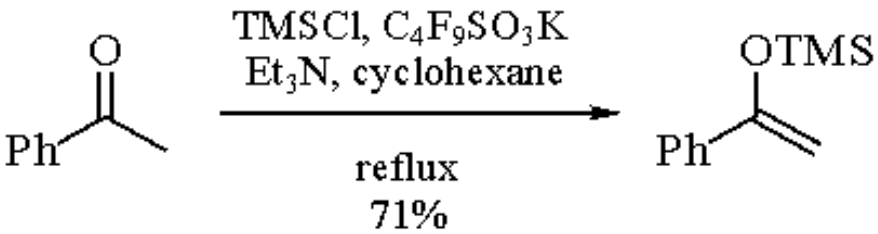

(2)

Trimethylsilyl nonaflate as well as ***Trimethylsilyl Trifluoromethanesulfonate*** and ***Trimethylsilyl Perchlorate*** have been shown to be selective and efficient Friedel-Crafts catalysts for the formation of nucleosides from silylated heterocycles and peracylated sugars. They are also useful catalysts for the rearrangement of persilylated protected nucleosides.[2] The aforementioned catalysts are more advantageous to the typically employed ***Tin(IV) Chloride*** owing to their reduced Lewis acidity.

Trimethylsilyl nonaflate is also an effective Lewis acid catalyst for the low-temperature *cis*/*trans* equilibration of methyl 2-trimethylsiloxycyclopropanecarboxylates via heterolytic cleavage of a carbon-carbon bond (eq 3).[3]

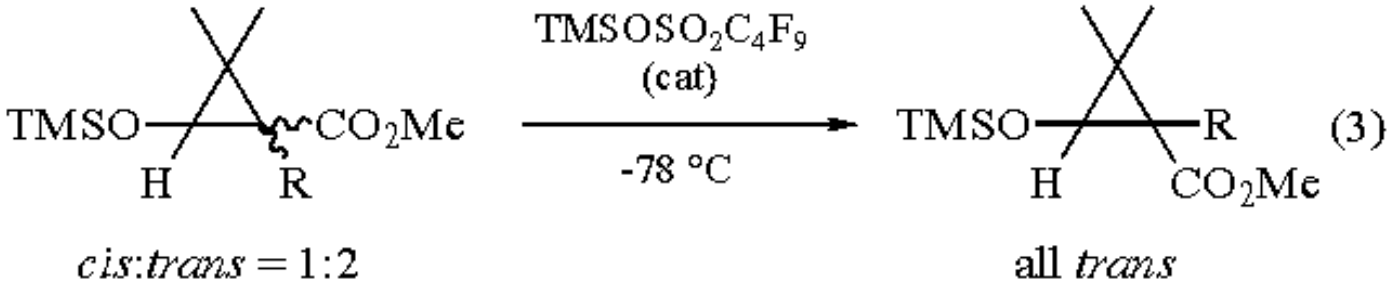

Mixed iodonium sulfonates of the type $PhI(CN)OSO_2C_4F_9$ can be generated in a one-pot procedure by the reaction of PhIO and trimethylsilyl nonaflate followed by the addition of ***Cyanotrimethylsilane***.[4]

Related Reagents.

Iodotrimethylsilane.

---

1. Vorbruggen, H.; Krolikiewicz, K. *S* **1979**, 34.
2. Vorbruggen, H.; Krolikiewicz, K.; Bennua, B. *CB* **1981**, *114*, 1234.
3. Reissig, H.-U.; Bolm, I. *TL* **1983**, *24*, 715.
4. Zhdankin, V.; Crittel, C.; Stang, P.; Zefirov, N. *TL* **1990**, *31*, 4821.
5. Frasch, M.; Sundemyer, W.; Waldi, *JBC* **1992**, *125*, 1763.
6. Habich, D.; Effenberger, F. *S* **1978**, *10*, 755.

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1-Trimethylsilyloxy-1,3-butadiene

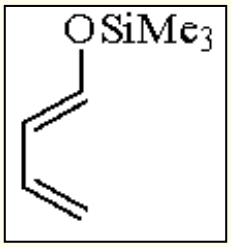

[6651-43-0] · $C_7H_{14}OSi$ · 1-Trimethylsilyloxy-1,3-butadiene · (MW 142.30)

(easily prepared[1] reactive diene for Diels-Alder reactions and other cycloadditions;[2-21] reactive silyl enol ether for aldol and Michael reactions,[22-28] and electrophilic additions[29-32])

Physical Data: bp 131 °C, bp 49.5 °C/25 mmHg; *d* 0.811 g cm^{-3}.

Solubility: sol most standard organic solvents.

Form Supplied in: liquid commercially available (98% purity) as an approximately 85:15 mixture of (*E*)- and (*Z*)-isomers.

Preparative Methods: can be prepared easily.[1]

Handling, Storage, and Precautions: is a flammable liquid and is moisture sensitive.

Diels-Alder Reactions and Other Cycloadditions.

Although commercially available, 1-trimethylsilyloxy-1,3-butadiene (**1**) can be easily prepared by silylation of ***Crotonaldehyde***.[1] It has often been used as a reactive diene in Diels-Alder reactions. For example, reaction with ***Dimethyl Acetylenedicarboxylate*** (**2**) affords the cyclohexadiene diester (**3**) in 68% yield. This initial Diels-Alder adduct can be converted into two different aromatic products by the proper choice of conditions: namely, thermal elimination affords the phthalate (**4**), while oxidation produces the phenol (**5**), both in good yield (eq 1).[2] Reaction with ***Methyl 3-Nitroacrylate*** (**6**) followed by hydrolysis of the initial adduct (**7**) and elimination of the β-nitro group leads to the cyclohexadienol (**8**) (eq 2).[3] Many other Diels-Alder reactions of this type have been carried out using (**1**), as shown in Table 1.[4] In general, the *endo* adduct is favored, especially at lower temperatures.

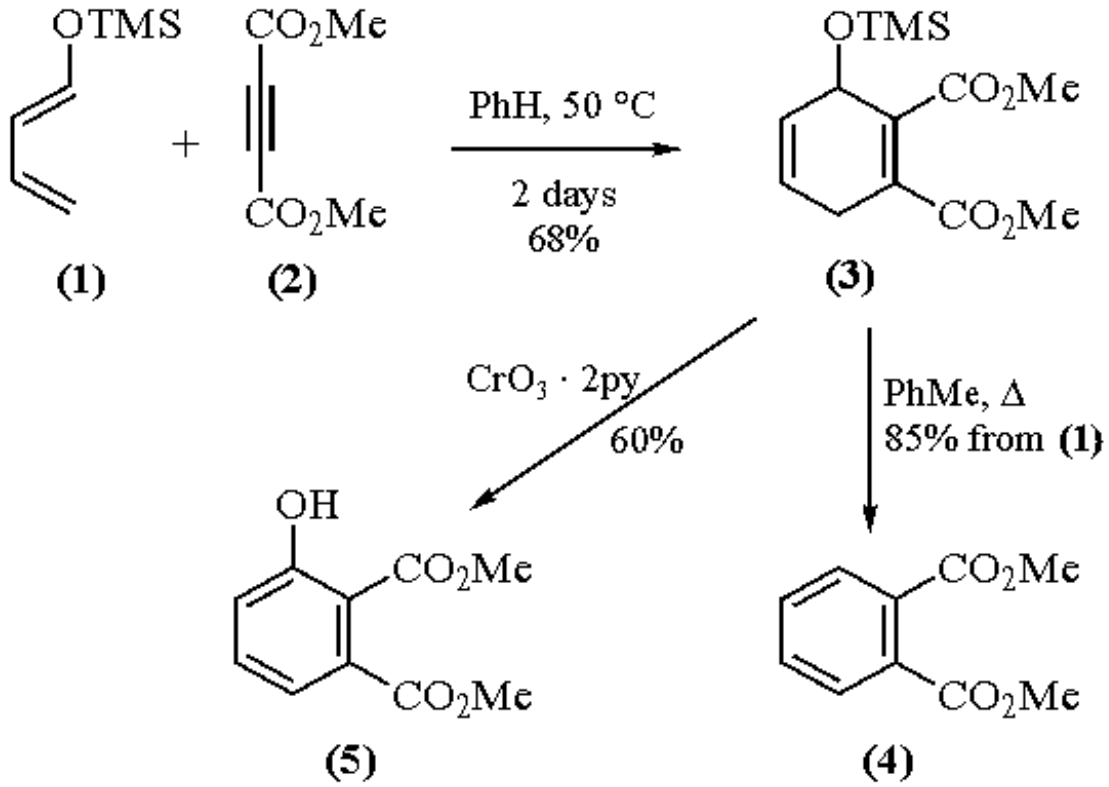
OTMS
CO2Me
CO2Me
PhH, 50 °C
2 days
68%
OTMS
CO2Me
CO2Me
(1)
(2)
(3)
CrO3 · 2py
60%
PhMe, Δ
85% from (1)
OH
CO2Me
CO2Me
CO2Me
CO2Me
(5)
(4)

(1)

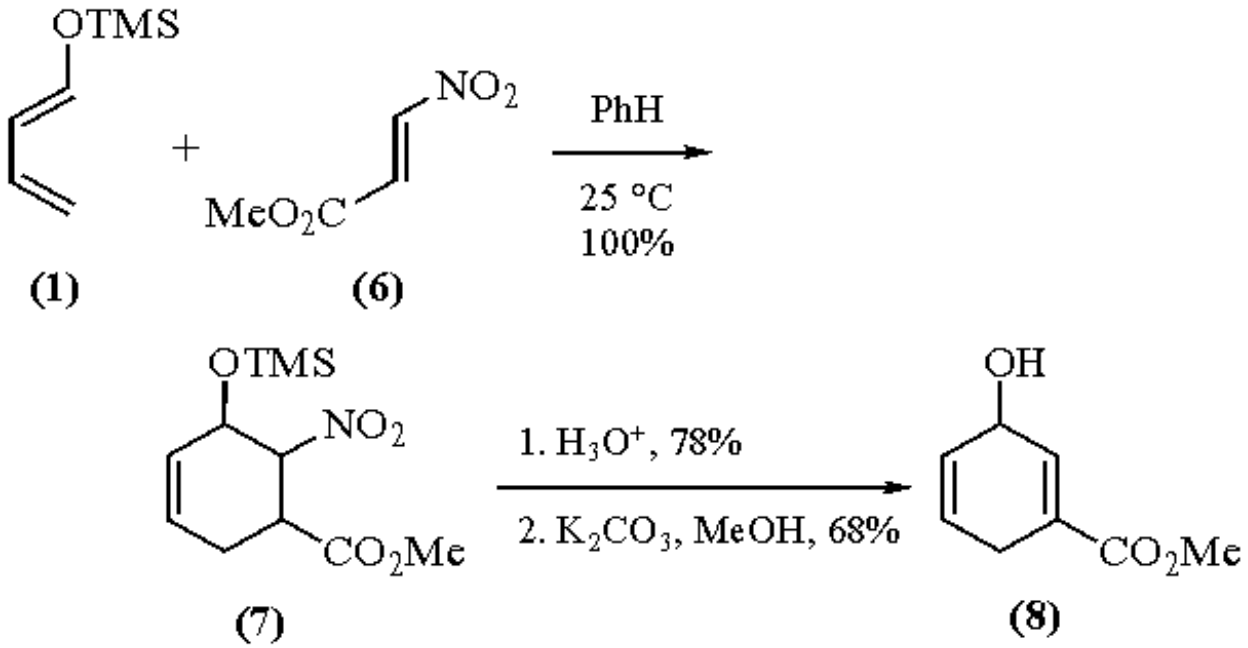
OTMS
NO2
MeO2C
PhH
25 °C
100%
(1)
(6)
OTMS
NO2
CO2Me
1. H3O+, 78%
2. K2CO3, MeOH, 68%
OH
CO2Me
(7)
(8)

(2)

Table 1 Diels-Alder Reactions of 1-Trimethylsilyl-1,3-butadiene (**1**)

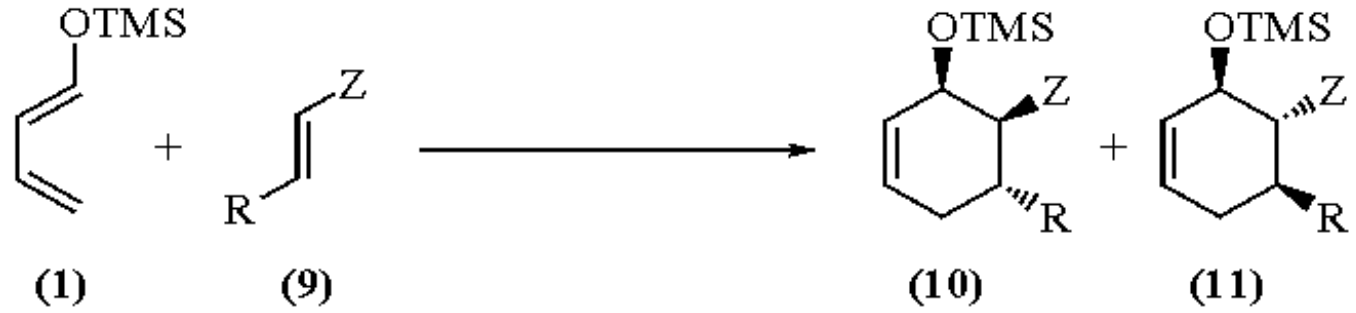

Dienophile	Conditions	Yield	Ratio (**10**):(**11**)
Z = CHO, R = H	50 °C, 48 h	88%	11:1[4a]
Z = CHO, R = H	130 °C, 7 h	53%	86:14[4b]
Z = CHO, R = Me	150 °C, 7 h	69%	65:35[4b]
Z = CHO, R = CO_2Me	40 °C, 48 h	>90%	83:17[4c]
Z = R = COPh	80 °C, 5 h	93%	no stereochem. given[4d]
Z = NO_2, R = TMS	100 °C, 37 h	83%	100:0[4e]
Z = NO_2, R = OCOPh	25 °C	90%	6:1[4f]

Cyclic enones, lactones, and lactams have also been used often as dienophiles in Diels-Alder reactions with (**1**), again giving mainly the *endo* adduct,[5] e.g. (**12**) reacted with (**1**) to give (**13**) as the major product in 74% yield (eq 3).[5a] As mentioned earlier, the initial adducts are often oxidized (either directly or after hydrolysis of the silyl ether) with Jones reagent to the corresponding enone,[6] e.g. (**14**) to give (**15**) (eq 4).[6a] This corresponds to the annulation of a cyclohexenone unit onto an existing enone or unsaturated lactone unit and has been used often in synthesis, e.g. in the preparation of aureolic acid derivatives such as (**17**) from (**16**) and (**1**) (eq 5).[6c]

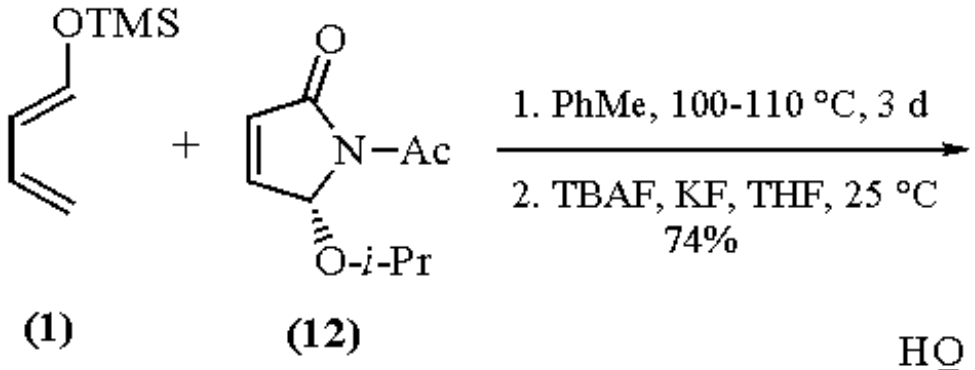

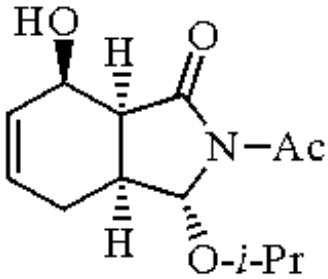

(3)

(**13**)

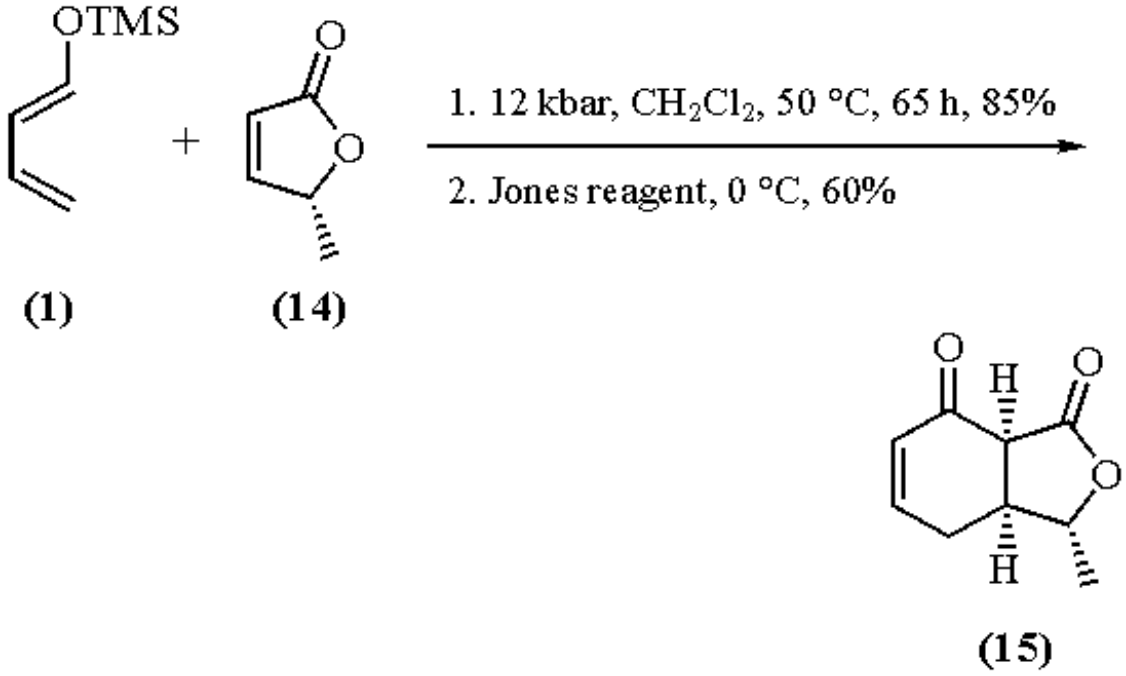

(4)

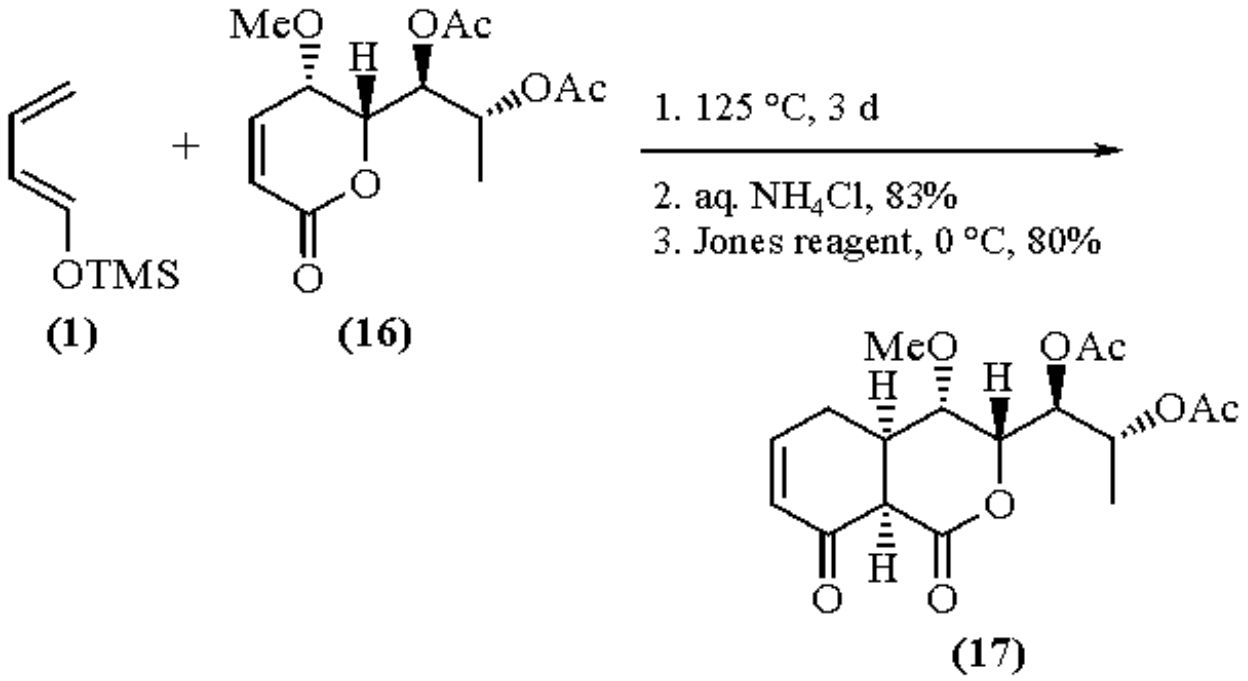

(5)

There are some exceptions to the preference for *endo* stereochemistry, especially with unsaturated sulfones.[7] A curious and useful reversal of the stereochemical preference has been reported, namely Diels-Alder cycloaddition of the pyrazolecarboxylate (**18**) with (**1**) followed by photochemical elimination of nitrogen gave mainly the *endo* adduct (**19n**) (eq 6), whereas cycloaddition of (**1**) with the cyclopropenecarboxylate (**20**) gave nearly exclusively the *exo* adduct (**19x**) (eq 7).[8]

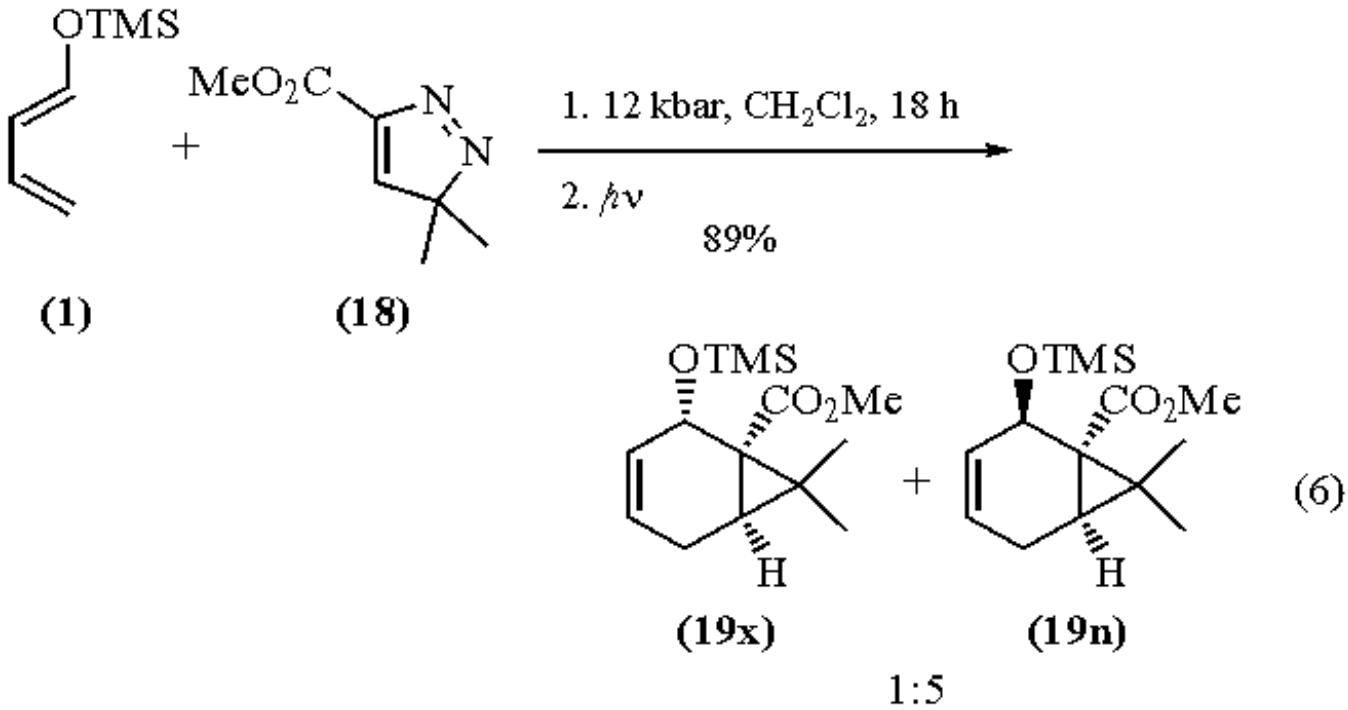

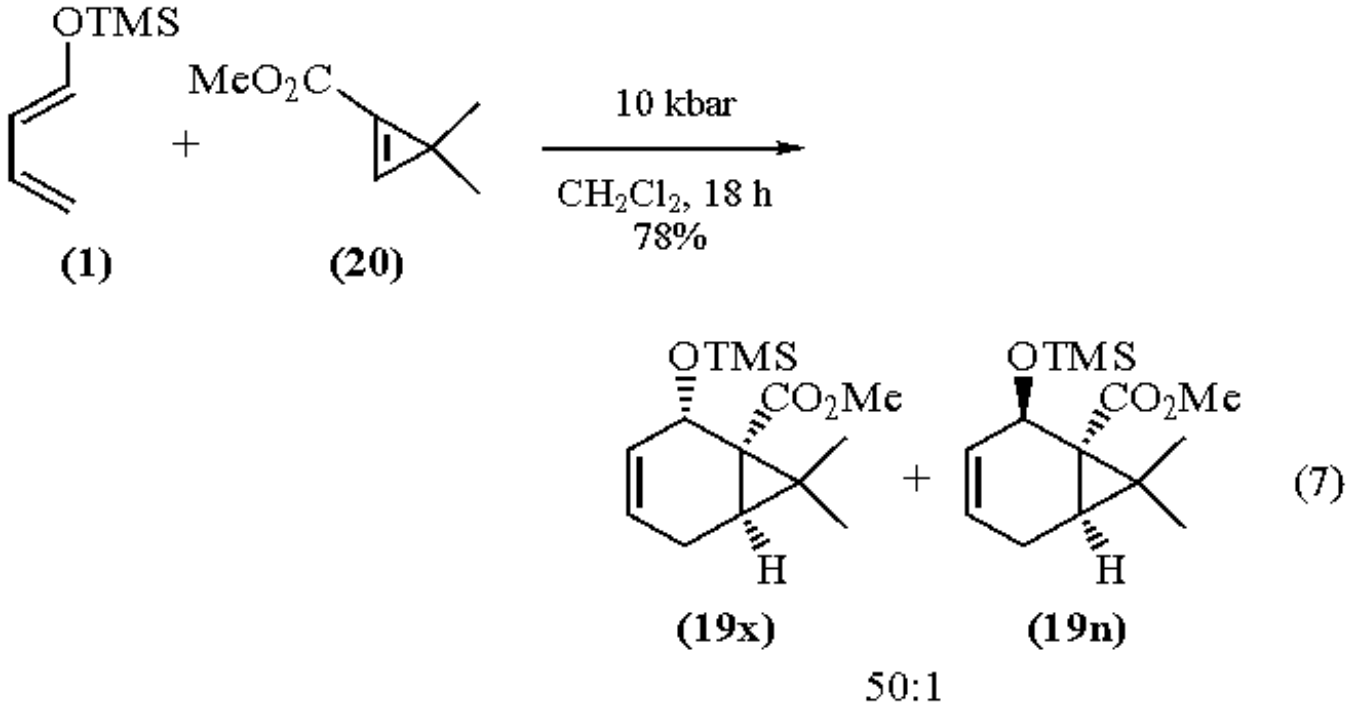

Stereocontrol with acyclic dienophiles can also be high,[9] e.g. (**21**) giving only (**22**) (eq 8),[9a] although the relative stereochemistry of the adjacent allylic center can cause nearly stereorandom addition as well.[9a] The versatility of the initial adducts has been evidenced most clearly in the synthesis of anthraquinones and their derivatives. The adducts of (**1**) with various quinones and substituted quinones have been transformed into simple aromatics,[10] phenols,[11] e.g. (**23**) gave (**24**) (eq 9),[11a] cyclohexenones,[12] e.g. (**25**) gave (**26**) (eq 10),[12a] and allylic alcohols,[13] all in excellent yields.

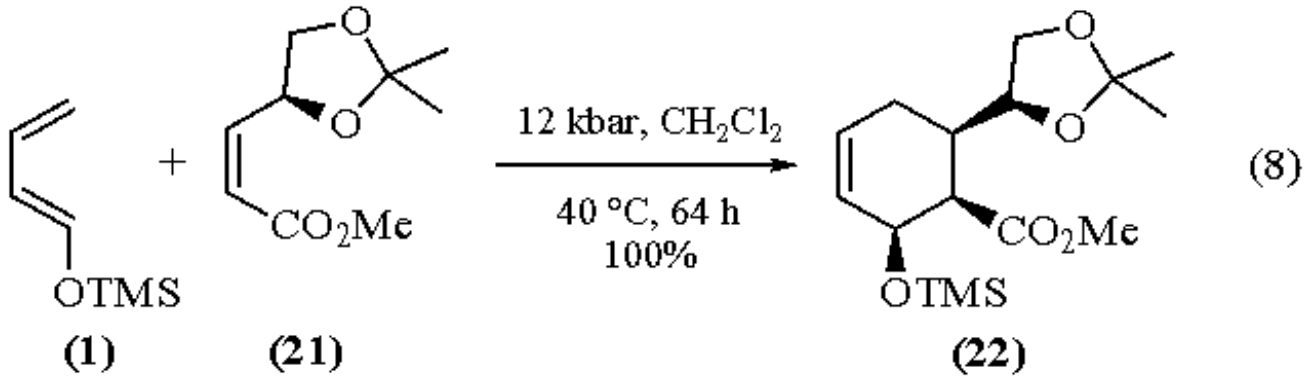

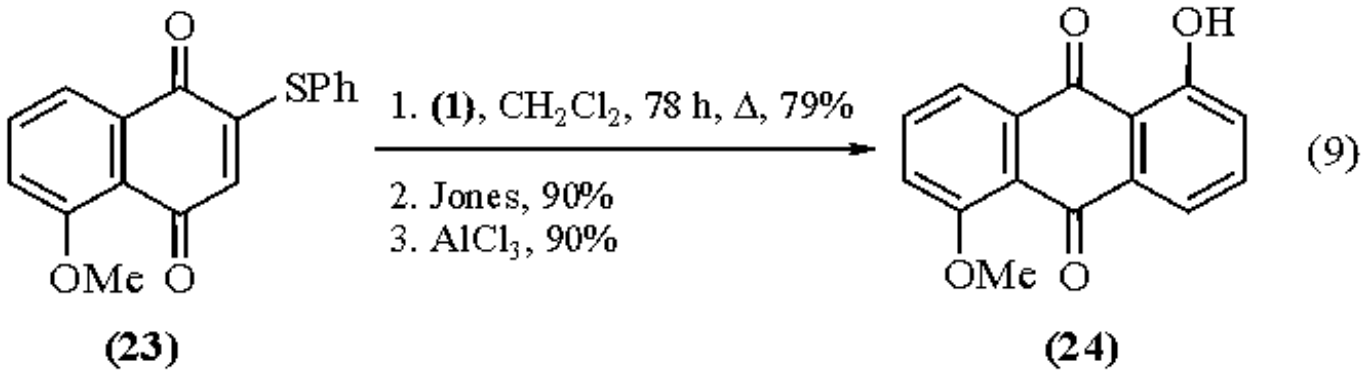

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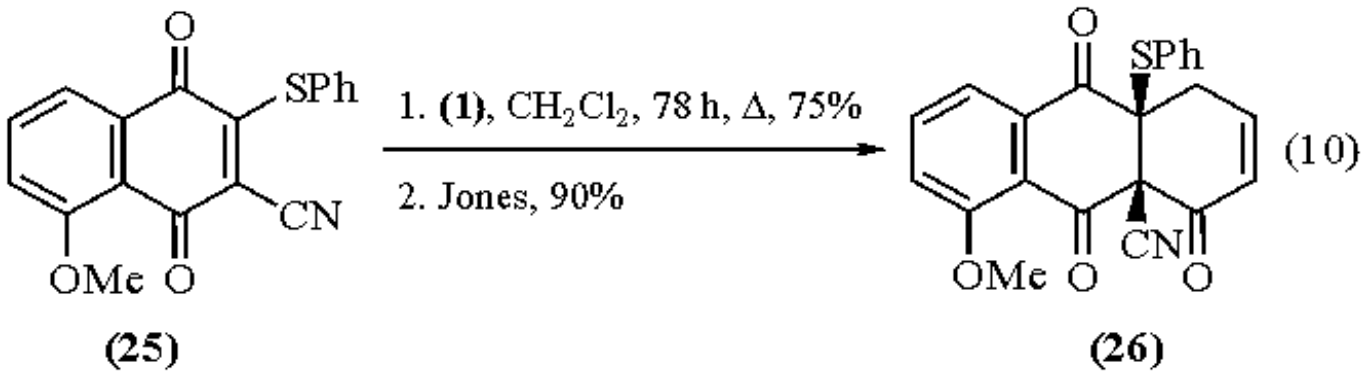

(10)

The reaction can be carried out with excellent enantiocontrol (generally 80% or better) using juglone (**27**) and a catalyst prepared from ***Trimethyl Borate*** and a tartaramide to give (**28**) (eq 11).[13a] Finally, with metal complexes of tropene and tropone systems, one can obtain either normal [4 + 2] cycloadditions[14a] or novel [6 + 4] cycloadditions, e.g. (**29**) giving (**30**) (eq 12).[14b,c] Other [4 + 2] cycloadditions have also been reported, using as dienophiles aldehydes[15] to give pyran derivatives such as (**31**), vinyl chlorides,[16] singlet oxygen,[17] nitrosoalkanes[18] to give compounds such as (**32**), and phosphaalkenes (eq 13).[19] Several [2 + 2] cyclizations are known, namely carbene and ketene additions to (**1**), all of which occur at the unsubstituted double bond.[20] One clever use of (**1**) in synthesis is the tandem [2 + 2]-Cope process which converts (**33**) into (**34**) (eq 14).[20d] Finally, a nickel(0)-catalyzed [4 + 4] cyclization of (**1**) gives the *trans*-3,4-bis(silyloxy)-1,5-cyclooctadiene (**35**) in excellent yield (eq 15).[21]

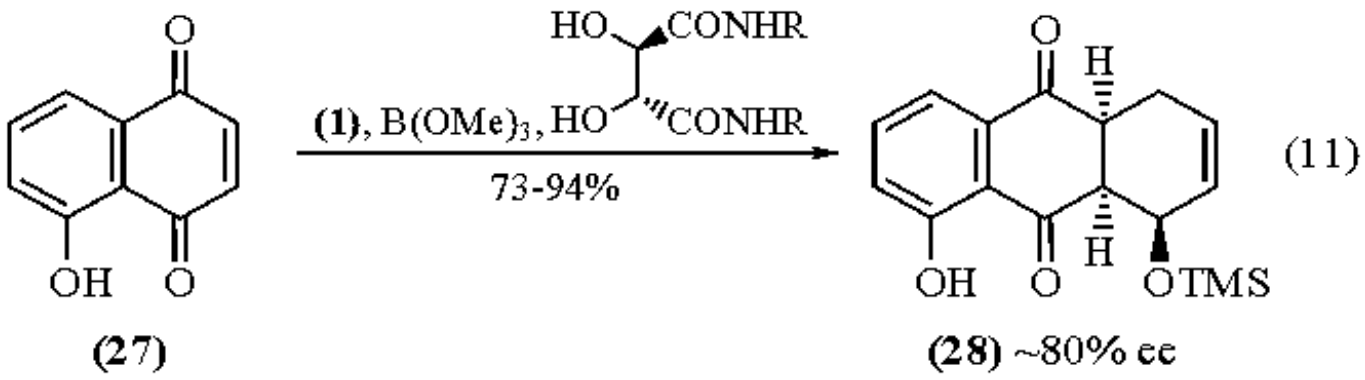

(11)

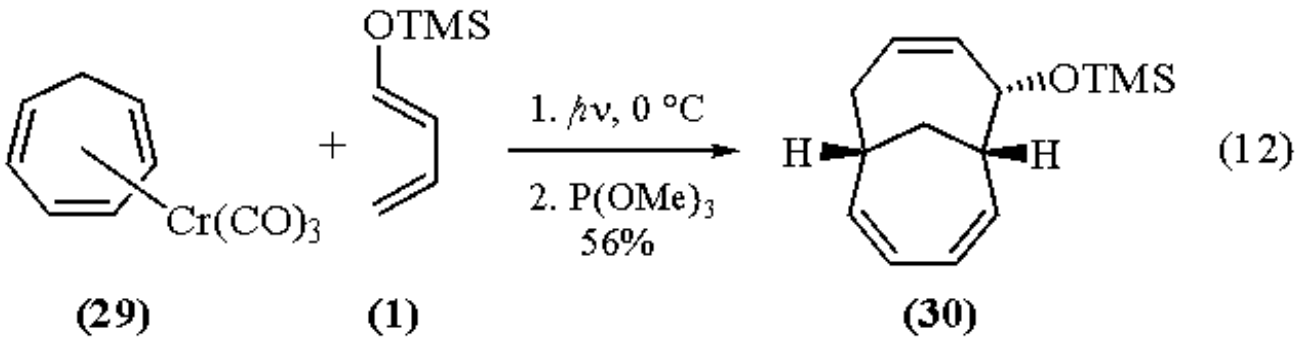

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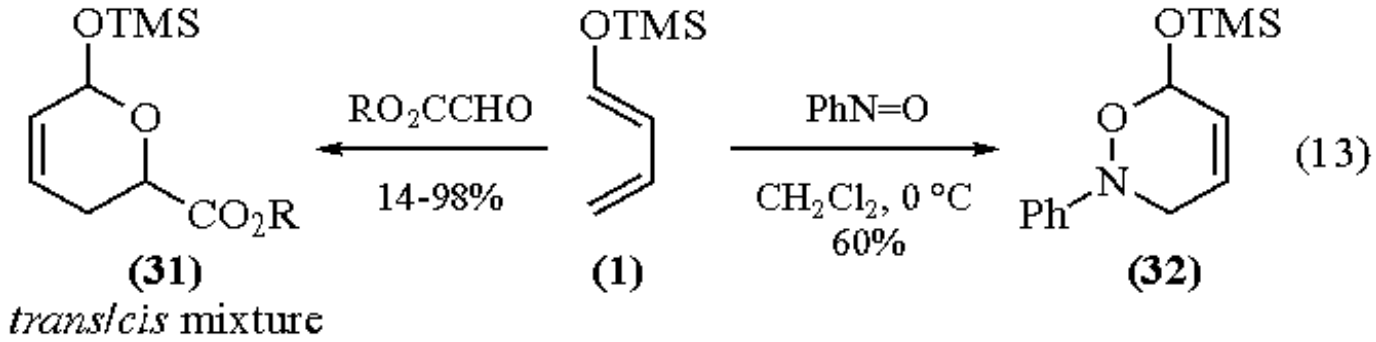

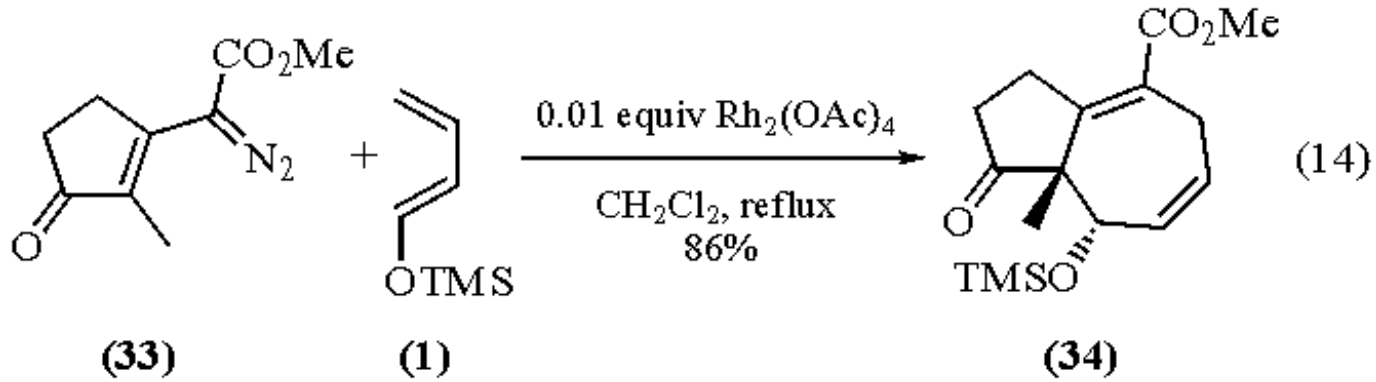

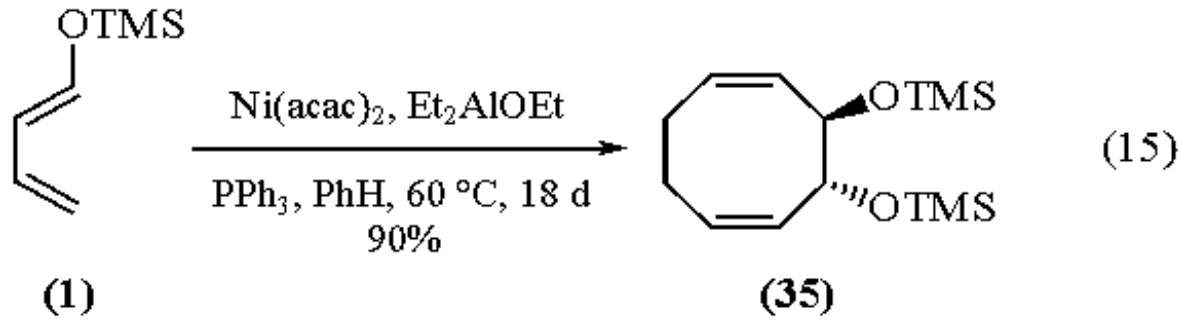

Aldol Condensations.

The nucleophilicity of the γ-carbon atom in 1-trimethylsilyloxy-1,3-butadiene (**1**) allows Lewis acid-catalyzed aldol condensations to be carried out, with (**1**) acting as the equivalent of the enolate of crotonaldehyde.[22-26] The products usually have the (*E*) stereochemistry about the newly formed double bond. Orthoesters are good electrophiles;[22,1d] when orthoformate is used as the electrophile, the (*E*)-monoacetal of glutacondialdehyde (**36**) is formed in good yield.[22e] This was then used in a very short synthesis of the antiviral agent AZT (**37**) (eq 16).[22e] 1,3-Dithienium salts and 2-alkoxydithiolanes have also been used to produce the dithioacetals corresponding to (**36**).[23] Simple acetals and α-chloro ethers can be used as the electrophiles with (**1**) to generate initially δ-alkoxy-α,β-unsaturated aldehydes and then the doubly unsaturated aldehydes after treatment with base.[24,1c] A clever approach to the synthesis of indole from pyrrole involves the condensation of (**1**) with the endoperoxides derived from *N*-alkoxycarbonylpyrrole as shown in eq 17.[25a] An approach to the piperidine alkaloids uses similar chemistry.[25b,c]

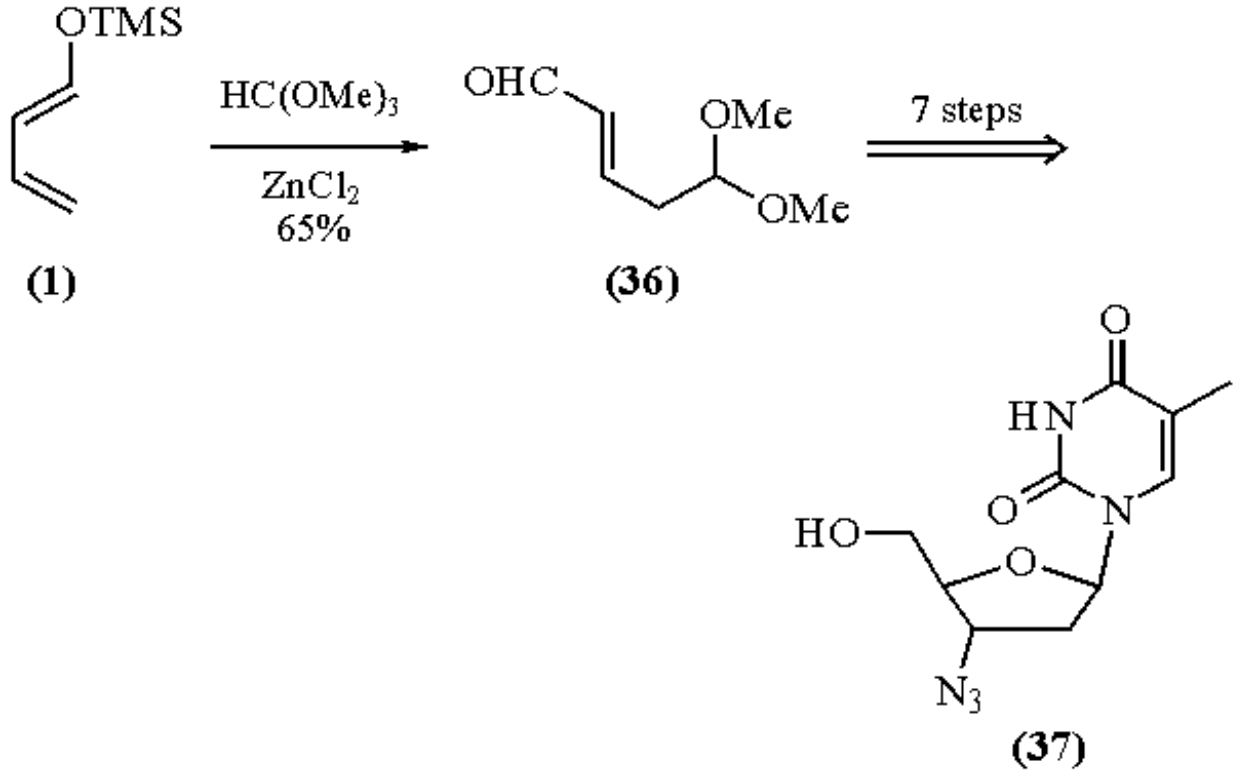

(16)

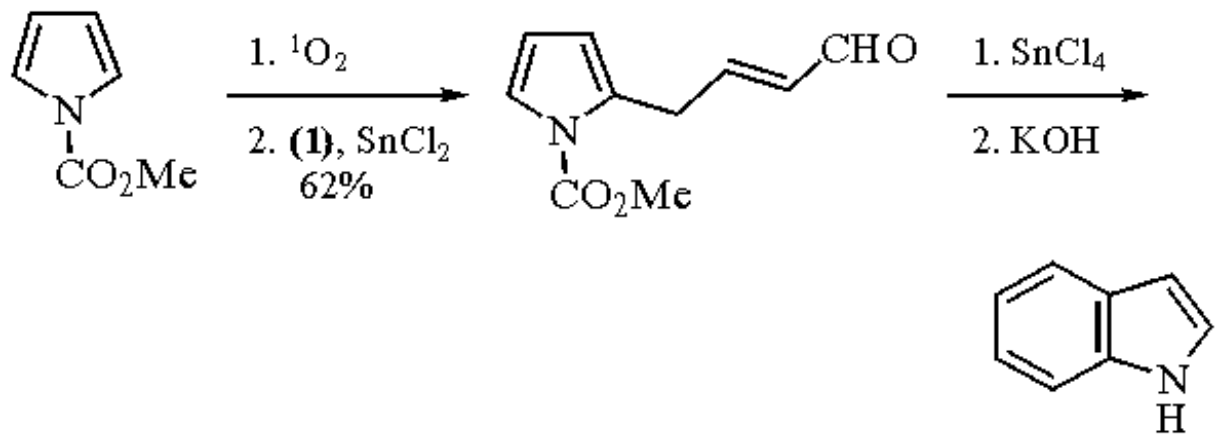

(17)

Finally, a conceptually similar reaction involves the addition of (**1**) to an acyl imminium salt to give an intermediate (**38**) (eq 18) which was then used in an intramolecular Diels-Alder approach to the heteroyohimboid alkaloids.[26] A Michael adduct is formed when (**1**) is allowed to react with 2,2-bis(phenylsulfonyl)styrene, probably as the result of a Diels-Alder reaction in which the adduct reverses to a zwitterion and internally deprotonates.[27] Also the lithium enolate derived from (**1**) has been added in a Michael fashion to α,β-unsaturated ketones to give, after silylation, the same adducts as the direct Diels-Alder reaction but at much lower temperatures.[28]

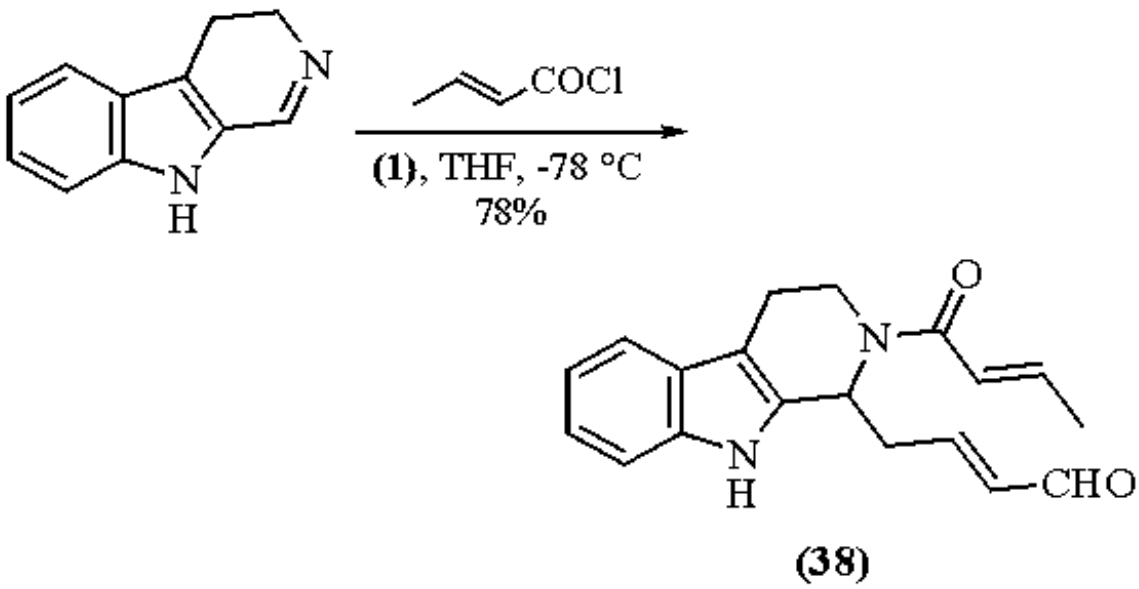

(18)

Electrophilic Additions.

Finally, various electrophiles (other than the carbon species in aldol and other condensations) have been added to (**1**) in good yield, namely: ***Benzenesulfenyl Chloride***,[29] ***Bromine*** or ***N-Bromosuccinimide***,[30] and ***t-Butyl Hypochlorite***.[31] There are also several reports of the reaction of (**1**) with various transition metal electrophiles which generate either a silyloxydiene bound to the metal[32] or a crotonaldehyde unit bound to the metal.[33]

Related Reagents.

1-Acetoxy-1,3-butadiene; ***2-Methoxy-1,3-butadiene***; ***2-Methoxy-3-phenylthio-1,3-butadiene***; ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***; ***2-Trimethylsilyloxy-1,3-butadiene***.

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2-Trimethylsilyloxy-1,3-butadiene

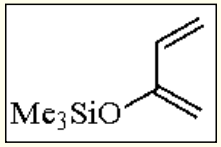

[38053-91-7] · $C_7H_{14}OSi$ · 2-Trimethylsilyloxy-1,3-butadiene · (MW 142.30)

(easily prepared[1] reactive diene for Diels-Alder reactions[2-40] and other cycloadditions;[41-44] reactive silyl enol ether for aldol, Michael reactions, and electrophilic additions[45-46])

Physical Data: bp 50-55 °C/50 mmHg; *d* 0.811 g cm^{-3}.

Solubility: sol most standard organic solvents.

Form Supplied in: liquid available commercially.

Preparative Methods: can be prepared easily from methyl vinyl ketone.[1]

Handling, Storage, and Precautions: is a flammable liquid and is moisture sensitive.

Diels-Alder Reactions.

Although commercially available, 2-trimethylsilyloxy-1,3-butadiene (**1**) can be easily prepared by silylation of ***Methyl Vinyl Ketone***.[1] It has been often used as a reactive diene in Diels-Alder reactions. In nearly all cases with a strongly activated dienophile, the trimethylsilyloxy group ends up 1,4 to the activating group in the adduct. Several representative examples are shown in Table 1.[1-14] The initial Diels-Alder adduct is a silyl enol ether and as such can be converted into several different products by simple silyl enol ether chemistry, e.g. the adduct (**3**) from the reaction of (**1**) with ***Dimethyl Fumarate*** (**2**) (eq 1) can be hydrolyzed to the cyclohexanone (**4**) in either acid or base, converted into the α-bromo or α-hydroxy ketone (**5**) or (**6**) on treatment with ***Bromine*** or ***N-Bromosuccinimide*** and ***m-Chloroperbenzoic Acid***, respectively, and finally via a Mukaiyama-type aldol (PhCHO/***Titanium(IV) Chloride***) to the enone (**7**).[1b,2]

Table 1 Diels-Alder Reactions of 2-Trimethylsilyl-1,3-butadiene **(1)**

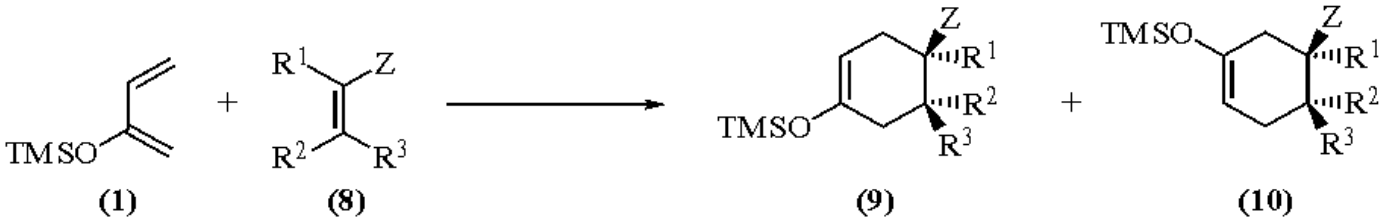

Z	R^1	R^2	R^3	Conditions	Yield (%)	Ratio	Ref.
CN	CN	CN	CN	PhH, 25 °C	90	100:0	1f
CO_2Me	H	H	H	toluene, 110 °C, 18 h	35	100:0	1b, 2
COMe	H	H	H	toluene, 110 °C, 18 h	60	100:0	1b, 2
CO_2Et	H	CO_2Et	H	toluene, 110 °C, 18 h	77	100:0	1b, 2
CO_2Et	H	H	CO_2Et	toluene, 110 °C, 18 h	39	100:0	1b, 2
CO_2Et	H	H	CO_2Et	toluene, 140 °C, 7 h	95	100:0	1c
CHO	H	H	H	toluene, 110 °C, 24 h	81[b]	100:0	3
CO_2Me	Me	H	H	xylene, 140 °C, 48 h	68	100:0	4
CHO	Me	H	H	toluene, 110 °C, 45 h	54	100:0	5
NO_2	H	CO_2Me	H	PhH, 25 °C, 42 h	100 (72)[a]	100:0	6
NO_2	H	OCOPh	H	-	95	100:0	7
CO_2Me	H	CO_2-*t*-Bu	H	CH_2Cl_2, -20 °C, MAD, 50 h	48	99:1	8
SO_2Ph	SO_2Ph	H	H	CH_2Cl_2, 20 °C, 24 h	100 (79)[a]	100:0	9
SO_2Ph	SO_2Ph	Me	H	$LiClO_4$, Et_2O, 50 °C, 24 h	95	100:0	10
SO_2Ph	SO_2Ph	Ph	H	$LiClO_4$, Et_2O, 50 °C, 24 h	90	100:0	10
SO_2Ph	H	CF_3	H	toluene, 110 °C, 4 h	89 (68)[a]	66:23	11
CF_3	H	H	H	neat, 150 °C, 72 h	17	76:24	12
$CO_2CMe_2O_2C$		$(CH_2)_2CX_2(CH_2)_2$		PhH, 80 °C, 22 h	97	100:0	13
COCR=CRO		H	H	toluene, 110 °C, 12 h	(53)[a]	100:0	14

[a] Yield of cyclohexanone after hydrolysis. [b] Product is 93% pure.

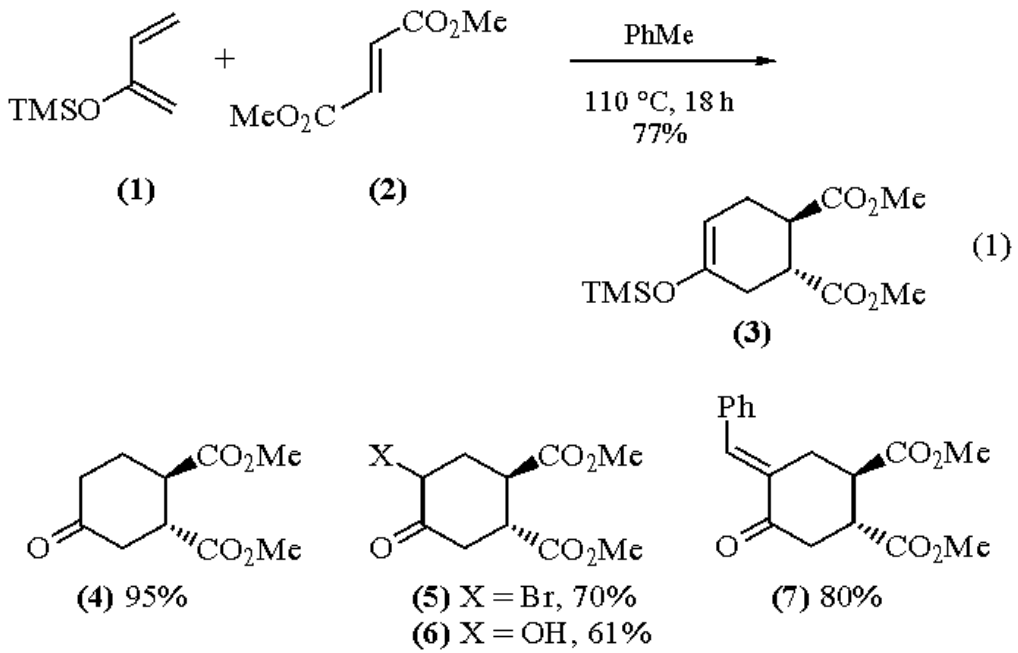

Alkynic dienophiles also work well, e.g. ethyl propiolate and (**1**) produce the expected cyclohexadiene ester in 77% yield.[15] In addition to simple dienophiles, a number of allenic dienophiles have also been utilized, as shown in Table 2.[16-19] Cyclic dienophiles, enones, lactams, etc., are often reacted with (**1**) to give fused bicyclic systems, but generally the yields are only in the 25-45% range,[20-24] e.g. reaction of (**1**) with (**13**) gives (**14**) in 27% yield (eq 2).[20b]

Table 2 Allenic Dienophiles in Diels-Alder Reactions with **(1)**

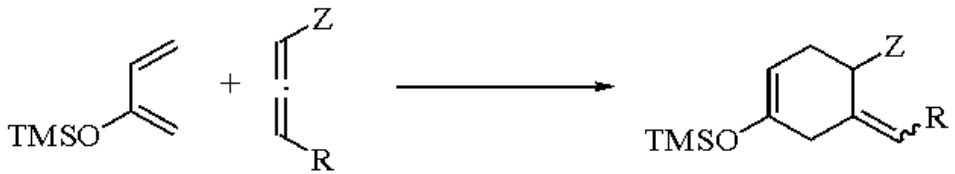

(1) **(11)** **(12)**

Z	R	Conditions	Yield (%)	Ref.
CO_2TMS	CO_2TMS	PhH, 82 °C, 20 h	80	16
CO_2Et	CO_2Et	PhH, 82 °C, 14 h	97	17
SO_2Ph	H	160 °C, 3 h	79	18
CO_2TMS	$CH_2OTBDMS$	PhMe, 110 °C, 24 h	62	19

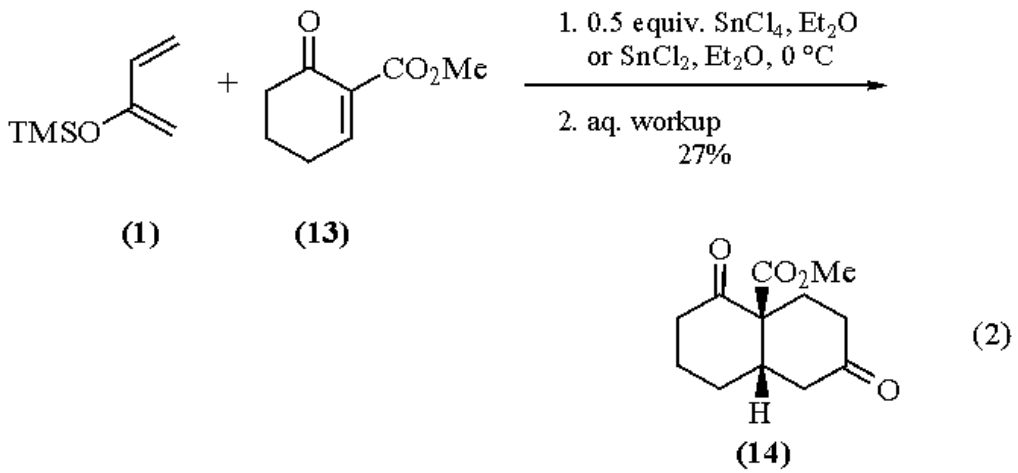

(2)

More reactive dienophiles, e.g. β-nitroenones,[21] enediones,[22] 1,2-disulfonylethylene,[23] etc., give higher yields, as do Lewis acids,[24] e.g. ***Zinc Bromide*** (eq 3),[24a] and the use of high pressure.[25] Stereofacial differentiation of (**1**) with cyclic enones,[26] lactones,[27] and lactams[28] is generally excellent, e.g. (**1**) reacts with (**17a,b**) to give (**18a,b**) with high selectivity in good yield (eq 4).[26] Reaction of (**1**) with quinones has often been used[29] in syntheses of anthraquinones and their derivatives, e.g. to prepare the A ring of the anthracyclines.[29b-g] Double Michael reactions[30] have been used quite often instead of Diels-Alder reactions to provide the same products, often in higher yields. The preparation of the azabicyclic ketone (**20**) is an interesting example of a tandem Diels-Alder reaction-aldol-type condensation (eq 5).[31] An example of an aldol reaction followed by a Diels-Alder is also known.[32]

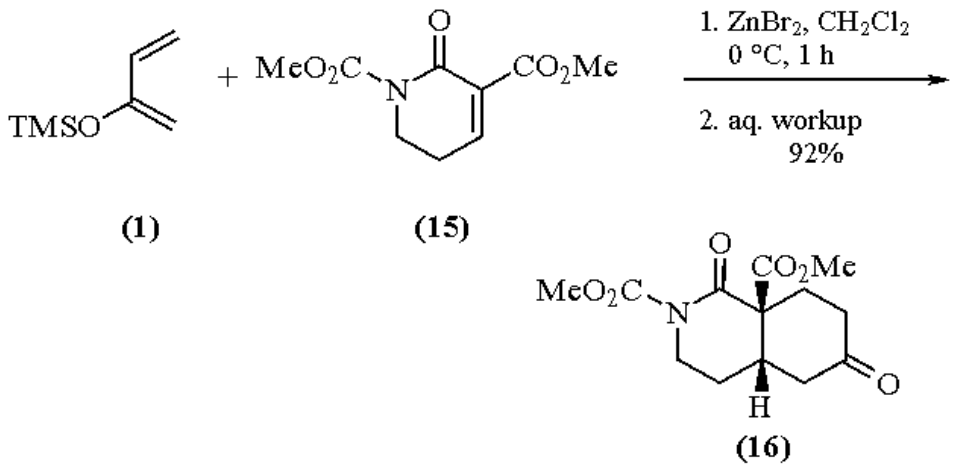

(3)

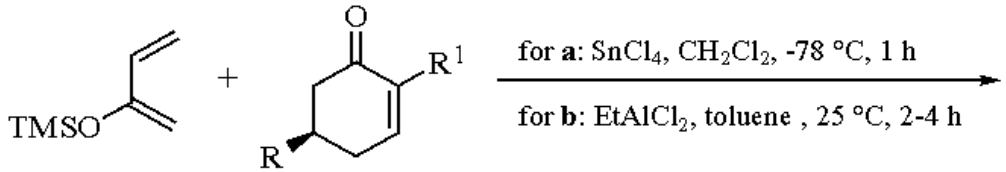

(1) **(17a)** R = TMS, R^1 = H
(17b) R = C(Me)=CH_2, R^1 = Me

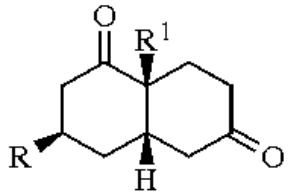

(4)

(18a) 66% 100:0
(18b) 73% 95:5

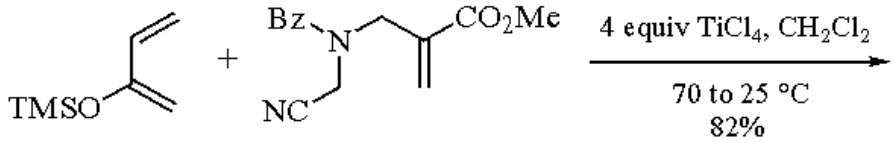

(1) **(19)**

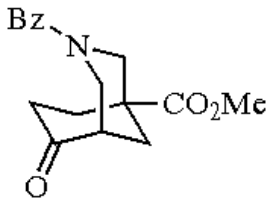

(5)

(20)

Finally, there is one example of (**1**) acting as the dienophile, namely in the Diels-Alder reaction with α-nitrosostyrene, where 6-vinyl-6-silyloxy-4,5-dihydrooxazine is formed in 65% yield.[33]

Heterodienophiles.

Many heterodienophiles have been reacted with (**1**).[34-37] Mesoxalate, glyoxalate, and hexafluoroacetone all give the 4-pyranone silyl ether derivatives in fair yield.[34] The corresponding thiomesoxalate affords the 3-thiopyranone-4,4-diester in good yield,[35a,b] as does an α-oxosulfine,[35c] while alkyl thioformates yield the 4-thiopyranones.[35d] By far the largest group of heterodienophiles used are imine derivatives.[36-37] Activated imines, e.g. diacyl imines,[36] afford the 4-piperidones, while aryl-fused dihydropyridines, e.g. (**21**), furnish fused 4-piperidones, e.g. (**22**), in good yield when reacted with (**1**) in the presence of a Lewis acid (eq 6).[37]

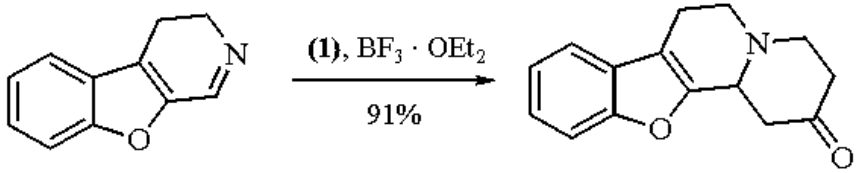

(21) (22) (6)

Finally, several imines give products of an aldol-type condensation rather than Diels-Alder reaction when reacted with (**1**) in the presence of Lewis acids.[38] Phosphaalkenes react with (**1**) to give ultimately the aromatic phosphinine[39] and dimethyl azodicarboxylate affords the expected [4 + 2] adduct in 83% yield.[40]

[2 + 2] and Other Cycloadditions, Carbene Additions.

Several [2 + 2] cyclizations of (**1**) with various alkenes are known.[41] Quite often these vinyl cyclobutyl silyl ethers can be thermally rearranged to the normal Diels-Alder product,[16,19,41] e.g. (**23**) giving (**25**) via (**24**) (eq 7).[41a] These [2 + 2] adducts can also be transformed via palladium catalysis into α-methylenecyclopentanones[41d,e] in good yield, e.g. (**26**) gives (**28**) via (**27**) (eq 8).[41d] Metal complexes of ***1,3,5-Cycloheptatriene*** react with (**1**) to give a novel [6 + 4] cycloaddition, e.g. (**29**) giving (**30**) (eq 9).[42]

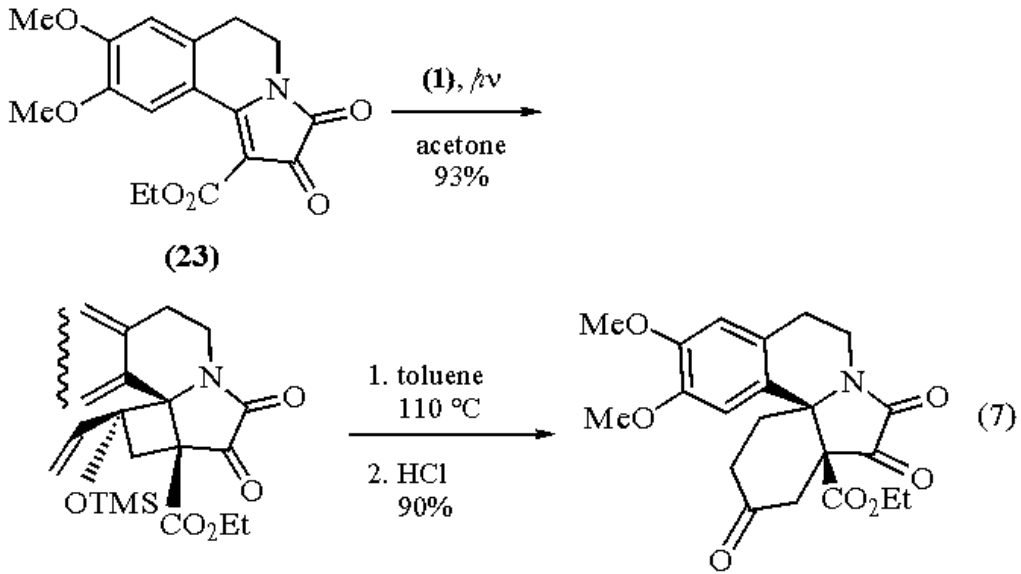

(23) (24) (25) (7)

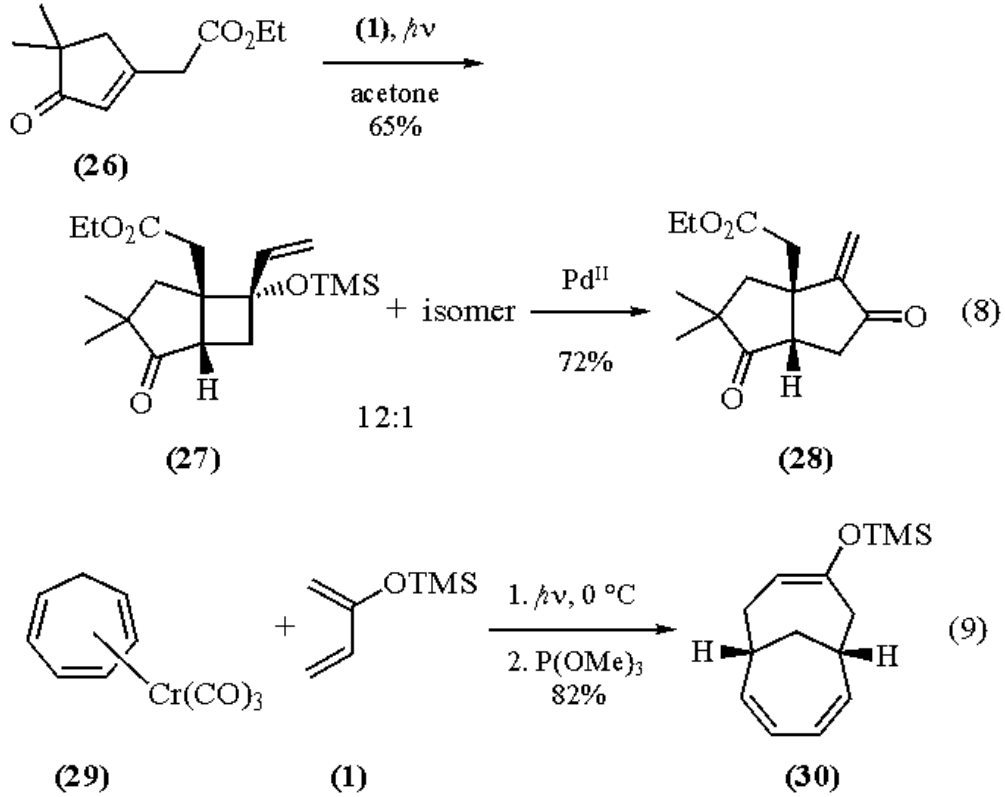

Even [3 + 2] cycloadditions occur when cyclopropyl ketones are treated with (**1**) under photolytic or Lewis acid conditions to produce cyclopentane systems.[43] Cyclopropanations of (**1**) are well known, in all cases adding to the more electron-rich silyloxy alkene.[1a,44] The vinylcyclopropanol silyl ethers can be converted into a number of different products, e.g. cyclopentanones, 2-methylcyclobutanones, vinyl ketones, and β-alkoxy ketones (eq 10). One clever use of (**1**) in synthesis is the tandem [2 + 2]-Cope process which converts (**34**) into (**35**) (eq 11).[44i]

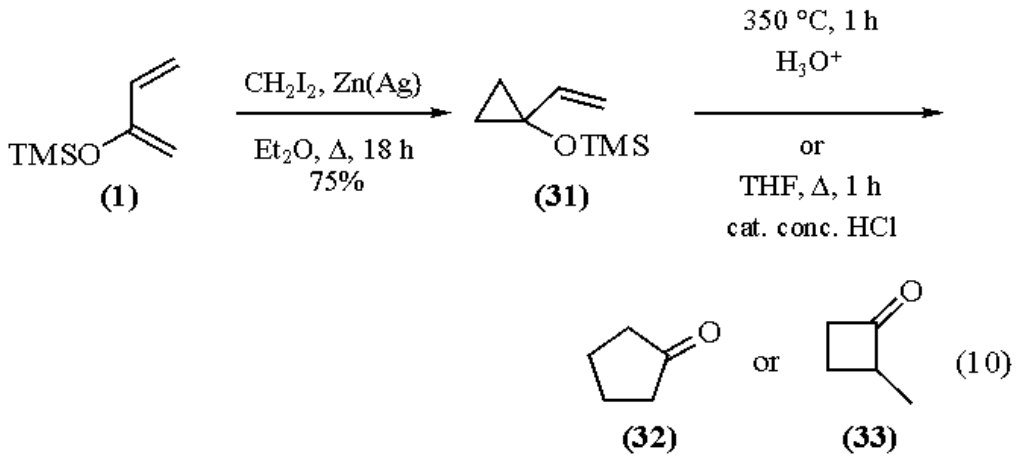

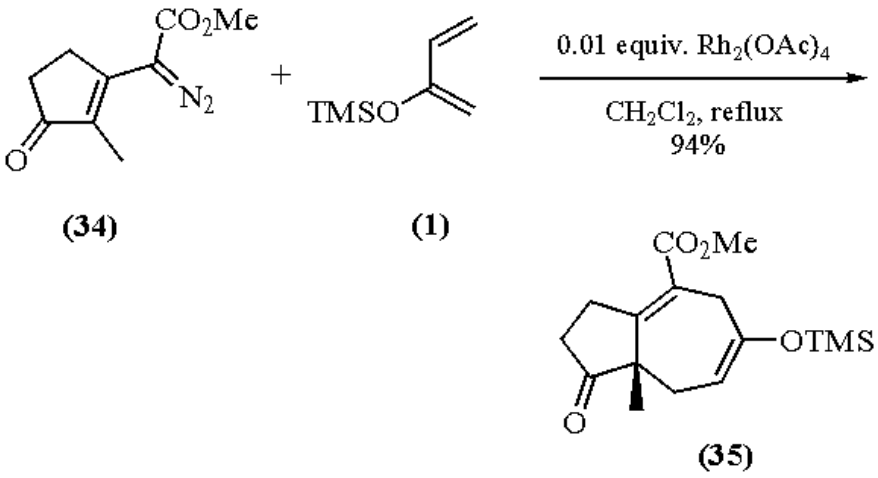

(11)

Aldol Condensations and Electrophilic Additions.

2-Trimethylsilyloxybutadiene (**1**) can act as the enolate of methyl vinyl ketone (MVK) towards reactive carbon atoms in an aldol- like process to give the products of overall addition of MVK to reactive centers.[45] Various strong electrophiles have been added to (**1**), e.g. bromine, NBS, *m*-CPBA, alkylating agents, and acylating agents, usually reacting at the carbon of the silyl enol ether to give α-bromo, α-silyloxy, or α-alkyl ketones in good yields.[46] With acylating agents, however, the *O*-acylated products are obtained.[46e]

Related Reagents.

1-Acetoxy-1,3-butadiene; ***2-Methoxy-1,3-butadiene***; ***1-Methoxy-3-trimethylsilyloxy-1,3-butadiene***; ***1-Trimethylsilyloxy-1,3-butadiene***.

---

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2-Trimethylsilyloxyfuran[1]

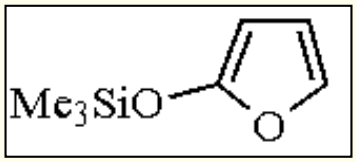

[61550-02-5] · $C_7H_{12}O_2Si$ · 2-Trimethylsilyloxyfuran · (MW 156.28)

(provides 5-substituted 2(5*H*)-furanones by alkylation,[2] aldolization,[3] and conjugate addition;[4] transforms quinones into furo[3,2-*b*]benzofurans;[5] useful for the four-carbon elongation of sugars[6])

Alternate Name: TMSOF.

Physical Data: bp 44-46 °C/17 mmHg; *d* 0.93 g cm^{-3}.

Solubility: sol most organic solvents, e.g. CH_2Cl_2, Et_2O, benzene, THF, MeCN.

Form Supplied in: colorless liquid; commercially available (98% pure) but expensive.

Preparative Method: accessible by silylation of 2(5*H*)-furanone,[1c,5b] which is obtained at very low cost by oxidation of furfural (see also α,β-***Butenolide***).

Handling, Storage, and Precautions: flammable liquid; sensitive to moisture. To avoid hydrolysis, it should be kept under Ar at -18 °C or below. For best results, reactions should be performed under strictly anhydrous conditions in aprotic solvents. Use in a fume hood.

Synthetic Applications.

In recent years, 2-trimethylsilyloxyfuran has emerged as a keystone for the rapid assembly of a wide variety of 5-substituted 2(5*H*)-furanones. This is readily achieved by reaction with an electrophile and desilylation. Electrophilic attack usually occurs exclusively at C-5;[3-10] products arising by C-3 attack are observed only rarely.[2c,11] Consequently, this electron-rich furan is viewed as a stable, readily accessible synthon for the γ-anion of 2(5*H*)-furanone (**1**).

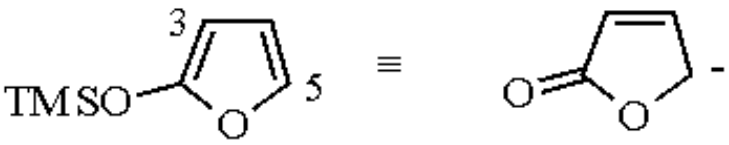

(1)

Carbon-Heteroatom Bond Formation.

Bromination of 2-trimethylsilyloxyfurans affords the corresponding 5-bromo-2(5*H*)-furanones in quantitative yields (eq 1).[1a] Similarly, reaction with ***Lead(II) Acetate*** provides 5-acetoxy-2(5*H*)-furanones (eq 2).[8] Oxidation can also be effected by using ***Iodosylbenzene*** in conjunction with a nucleophile, such as ***p-Toluenesulfonic Acid***, and ***Boron Trifluoride Etherate*** (eq 3).[9] Replacement of TsOH by ***Azidotrimethylsilane*** in eq 3 provides 5-azido-2(5*H*)-furanone.[9]

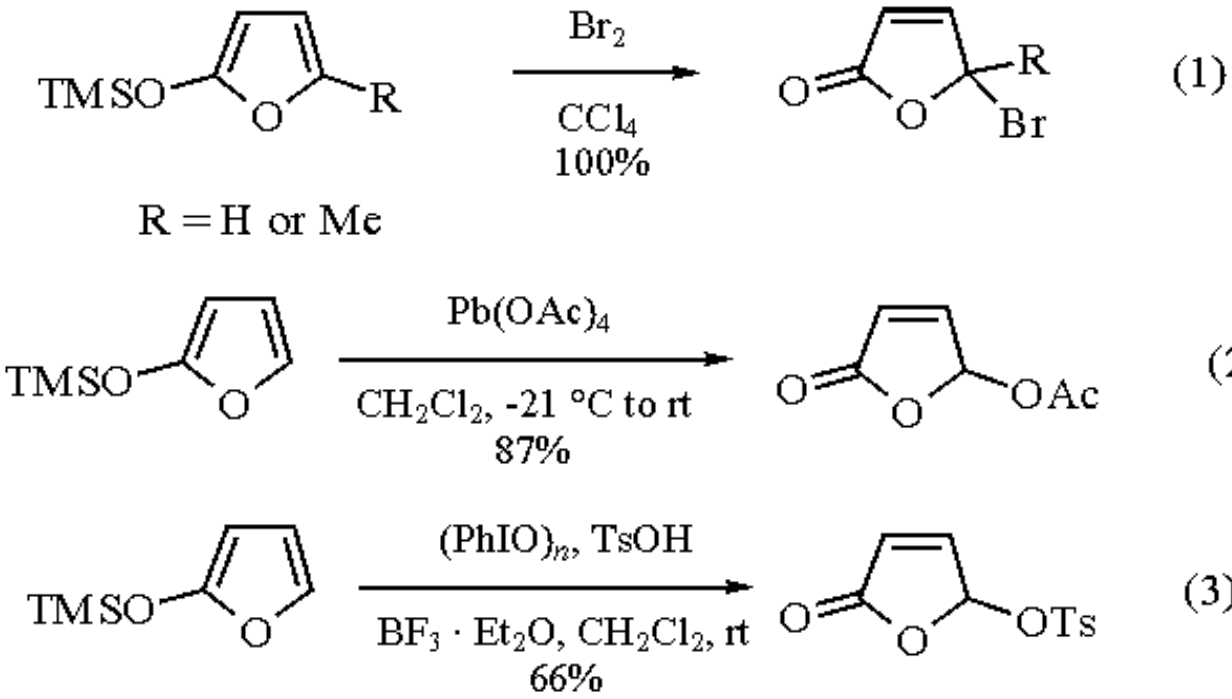

Alkylation.

Upon activation with ***Silver(I) Trifluoroacetate***, primary alkyl iodides and allylic bromides are readily transformed into 5-alkyl- and 5-allyl-2(5*H*)-furanones, respectively (eq 4).[2] Significantly, typical S_N1-unreactive halides such as ethyl iodoacetate work equally well.[2b] This method has served as a basis for short syntheses of several natural products,[13] including eldanolide[2a] and the Whisky lactones.[2c]

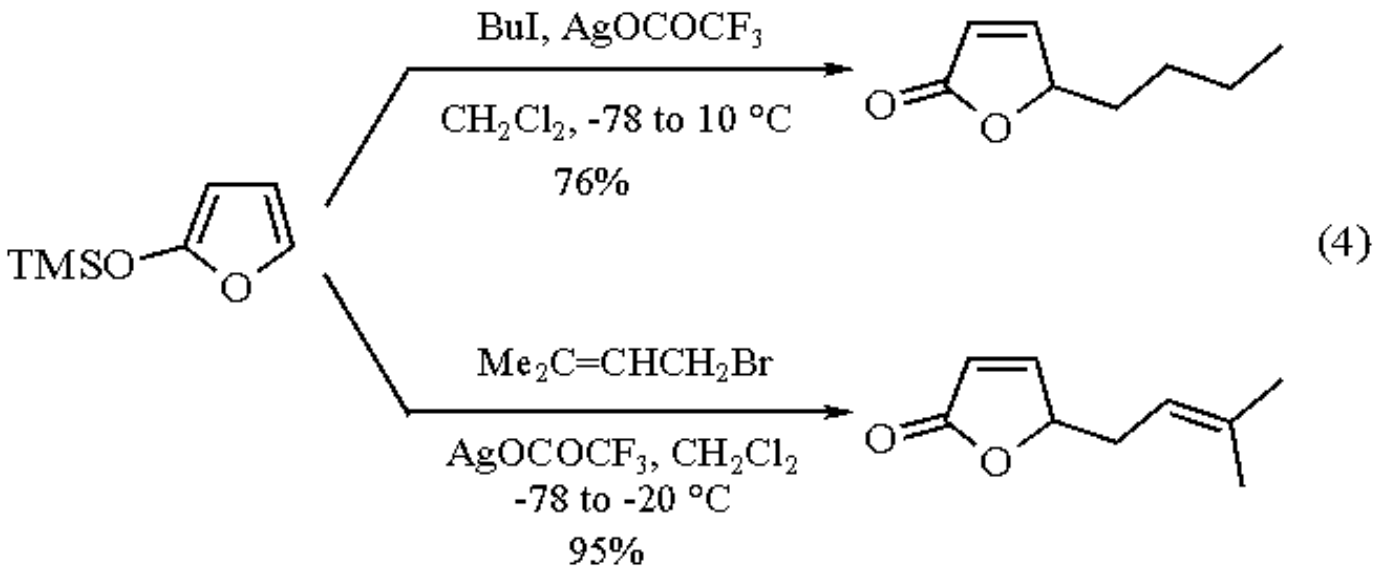

Alternatively, 5-allyl-2(5*H*)-furanones can be obtained from TMSOF and allylic acetates using ***Lithium Perchlorate*** in ether.[13] 5-Propargyl-2(5*H*)-furanones are prepared by coupling with hexacarbonyldicobalt complexes of propargylium cations (eq 5).[10] Reaction of the intermediate complex with ***Cerium(IV) Ammonium Nitrate*** removes the cobalt. Fluoroalkylation is achieved by using bis(fluoroalkanoyl) peroxides in 1,1,2-trichloro-1,2,2-trifluoroethane (Freon 113) (eq 6).[14] This process is believed to involve combination of a fluoroalkyl radical with the furan-derived radical cation.

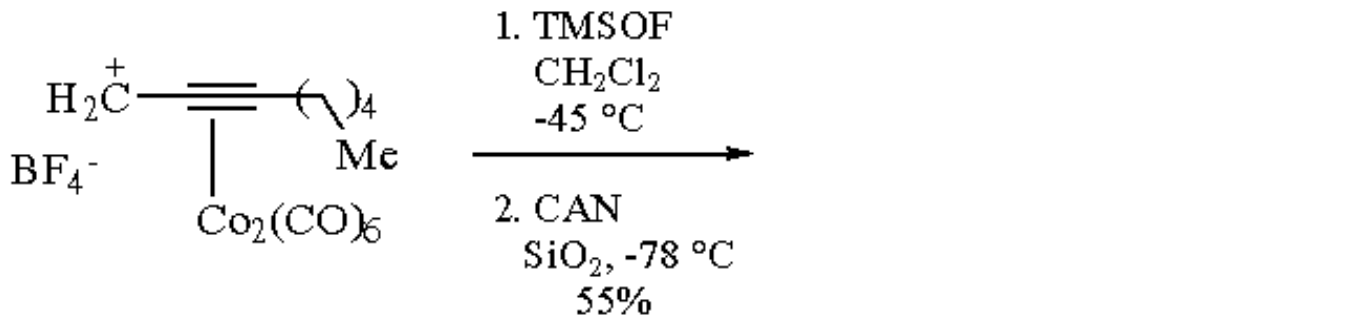

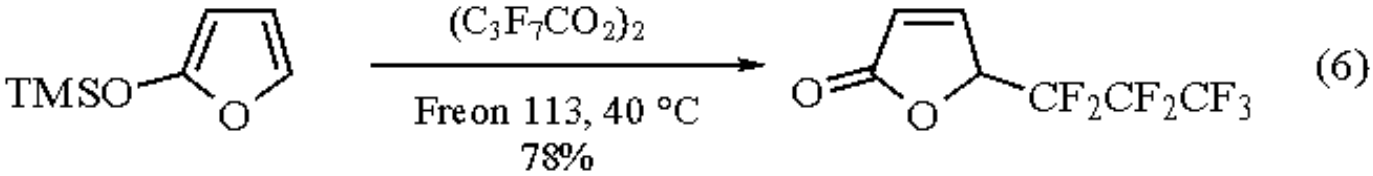

Aldol-Type Reactions.

The facile condensation of 2-trialkylsilyloxyfurans with carbonyl compounds[3] and their derivatives[7a] has spawned many synthetic applications.[15-19] Aldol products derived from aldehydes, ketones, or acetals can be readily transformed into 4-ylidenebutenolides.[3a] Dehydration of 5-(1´-hydroxyalkyl)-2(5*H*)-furanones is achieved by using ***Acetic Anhydride*** and 4-pyrrolidinopyridine (PPY) in ***Triethylamine*** (eq 7).[3a]

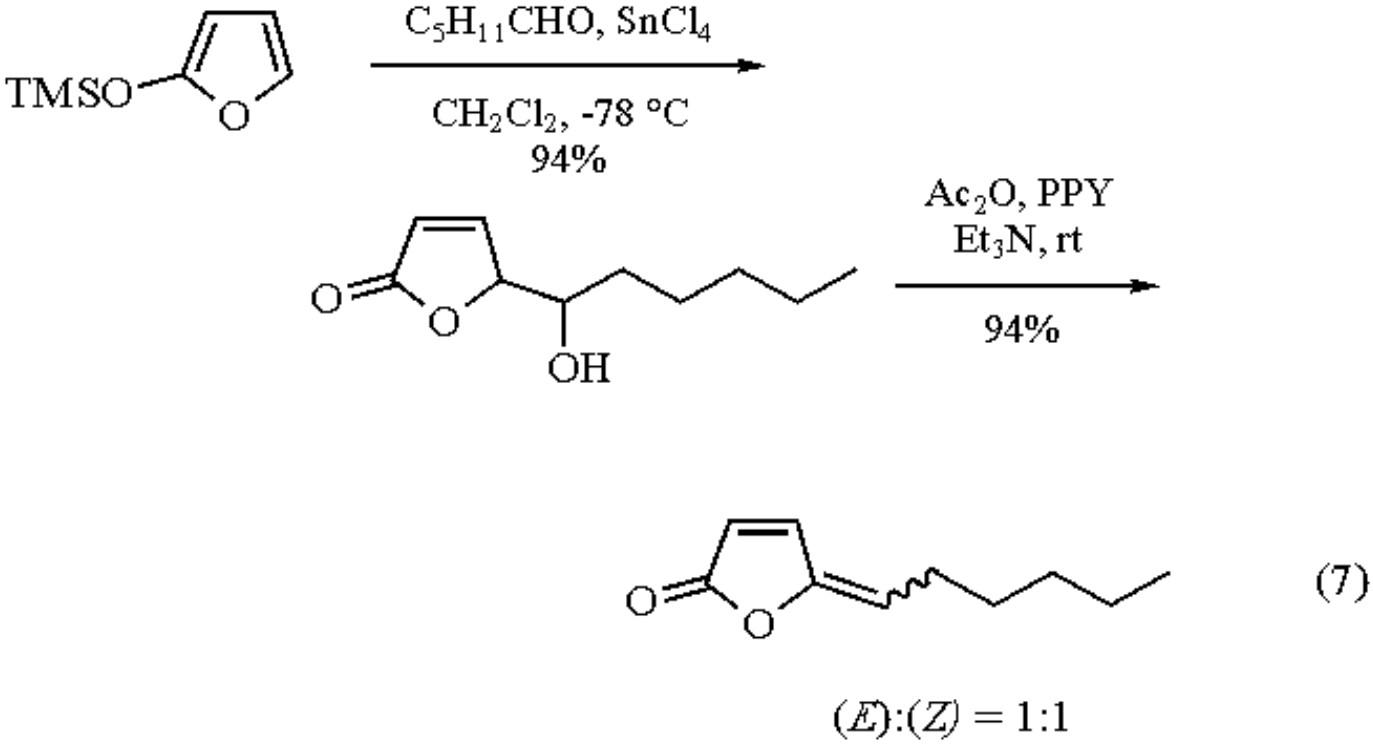

The diastereoselectivity of the reaction of TMSOF with aldehydes can be controlled by the choice of catalyst. Lewis acids such as ***Triethylsilyl Trifluoromethanesulfonate*** (TESOTf), $BF_3.OEt_2$, and ***Tin(IV) Chloride*** favor *syn* selectivity, while the use of fluoride ion confers *anti* selectivity (eq 8).[3b] In both situations, open transition states are involved.[3b] Impressive diastereofacial preference is encountered in the aldol reaction of TMSOF with chiral aldehydes (eq 9).[6a] This chemistry is particularly useful for the four-carbon elongation of sugars.[6]

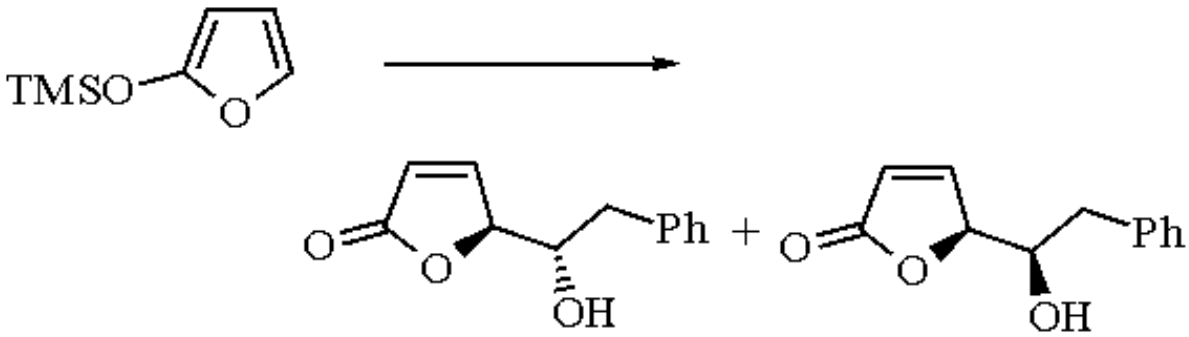

(8)

BnCHO, TESOTf, -78 °C, 92% 82:18
BnCHO, Bu_4NF, -78 °C, 73% 19:81

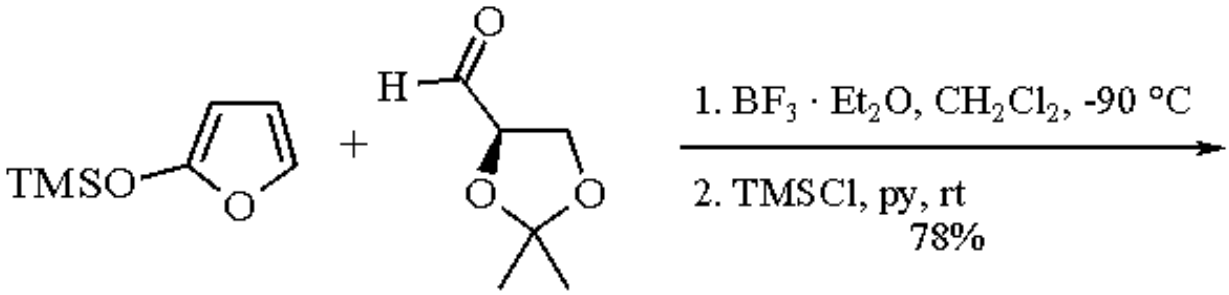

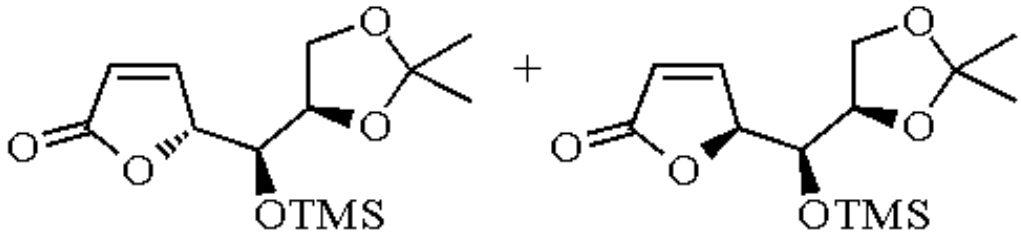

(9)

≥95:5

Ketones,[16] orthoamides,[17] and *N*-acyl-*N*,*O*-acetals[18] also undergo diastereoselective condensation with TMSOF in the presence of Lewis acids. Thus 1-benzyloxycarbonyl-2-ethoxypyrrolidine leads preferentially to the *syn* product (eq 10).[19]

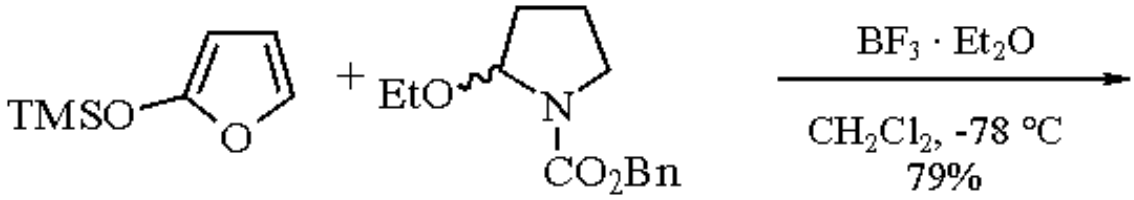

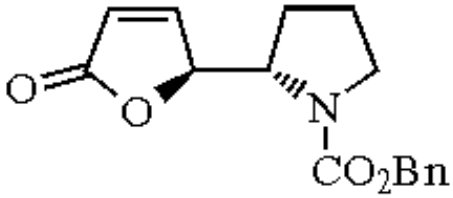

(10)

syn:*anti* = 5:1

Conjugate Addition.

In comparison to aldol condensation, the conjugate addition of 2-trialkylsilyloxyfurans to enones has received only scant attention.[8,20] Yet some interesting applications have already surfaced. Especially noteworthy is the high level of stereochemical discrimination in the few recorded cases.[21] For example, full diastereoselectivity is observed in the fluoride ion-induced addition of TMSOF to a chalcone (eq 11).[4]

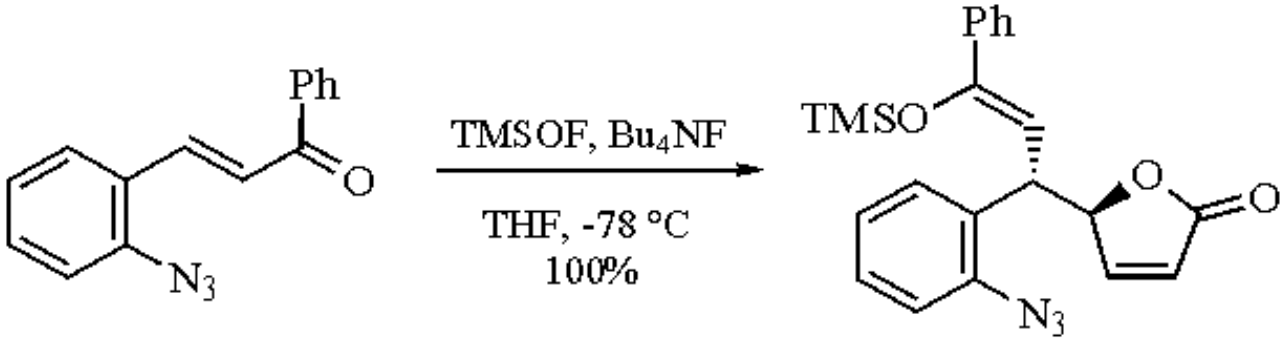

(11)

Activated quinones undergo uncatalyzed reaction with TMSOF to produce furo[3,2-*b*]benzofurans (eq 12).[22] Furofuran annulation is explicable by initial conjugate addition of the furan, subsequent aromatization, and eventual intramolecular conjugate addition of the resulting hydroxy group onto the butenolide.[5] This protocol is of relevance to the synthesis of pyranonaphthoquinone antibiotics.[23]

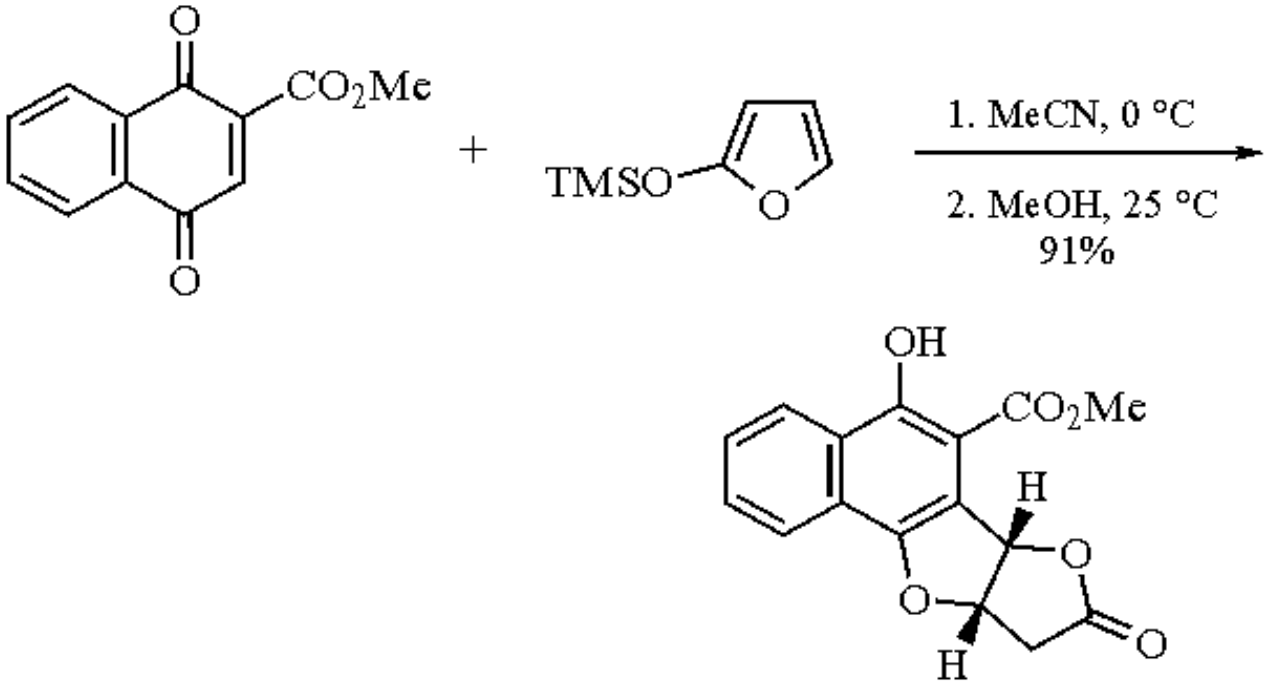

(12)

Diels-Alder Reaction.

In view of the propensity of furans to undergo [4 + 2] cycloadditions,[24] 2-trialkylsilyloxyfurans are potentially useful for the rapid construction of various phenol derivatives.[25] Although TMSOF performs poorly in Diels-Alder reactions, some of its more substituted analogs are highly effective.[26] An illustration is provided by the short synthesis of a naturally occurring hydroxyphthalide (**2**) via cycloaddition of 3,5-dimethyl-2-(trimethylsilyloxy)furan with ***Maleic Anhydride*** (eq 13).[26] Unlike TMSOF, the more stable 2-pivaloyloxyfuran is strongly recommended for similar transformations.[27]

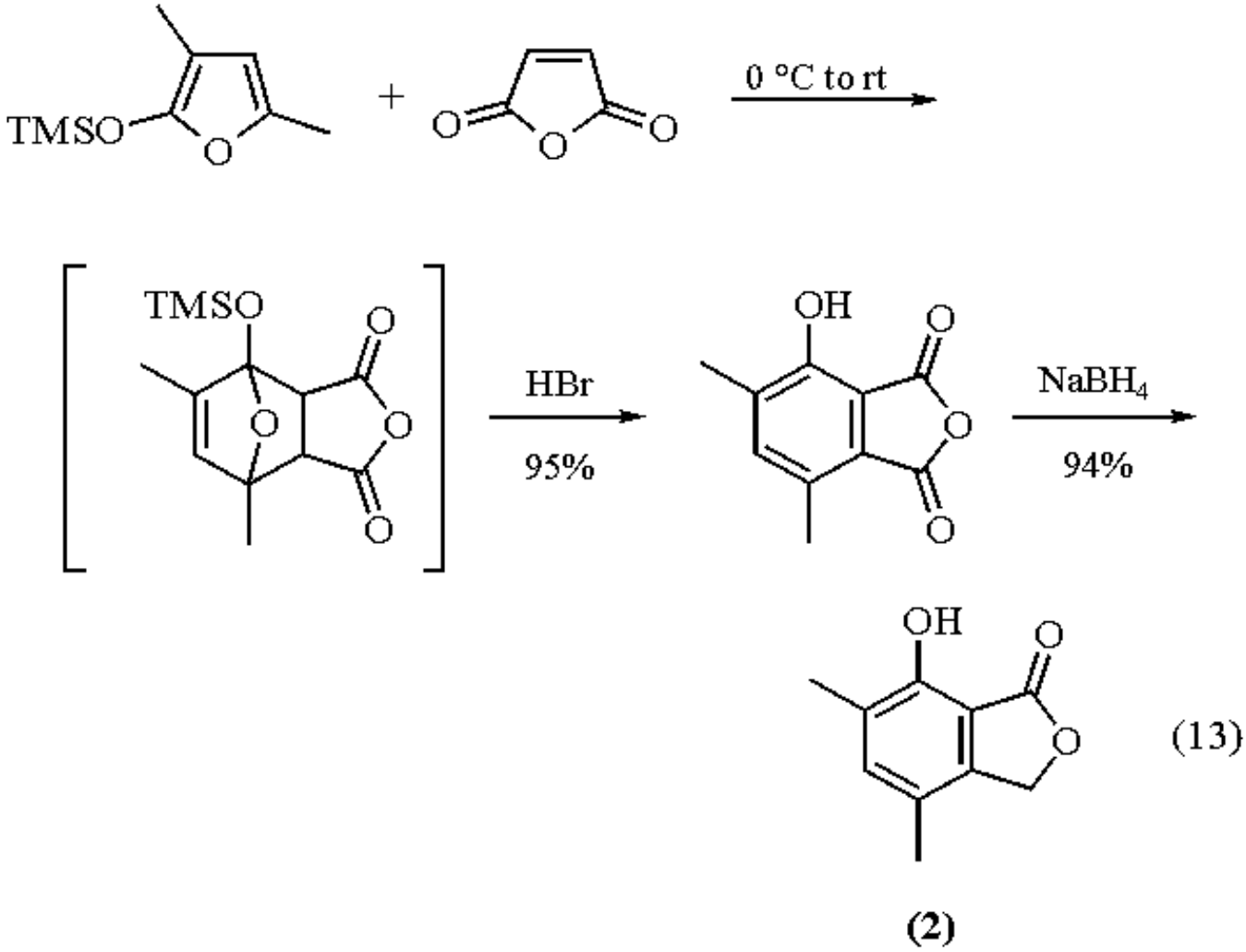

Related Reagents.

Several other 2-trialkylsilyloxyfurans have served as building blocks for the synthesis of natural products[28a,b] and analogs.[28c] The commercially available (4-methoxy-2-(trimethylsilyloxy)furan (**3**) is especially useful for preparing 5-substituted methyl tetronates.[29] 5-Ethylthio-2-(trimethylsilyloxy)furan (**4**)[21a] has been employed for the synthesis of mitomycins.[21] The easily prepared 2-(*t*-butyldimethylsilyloxy)-3-methylfuran (**5**)[12a] is the reagent of choice for constructing furanosesquiterpenes[12] and spirocyclic alkaloids of the *Ergot* family.[30]

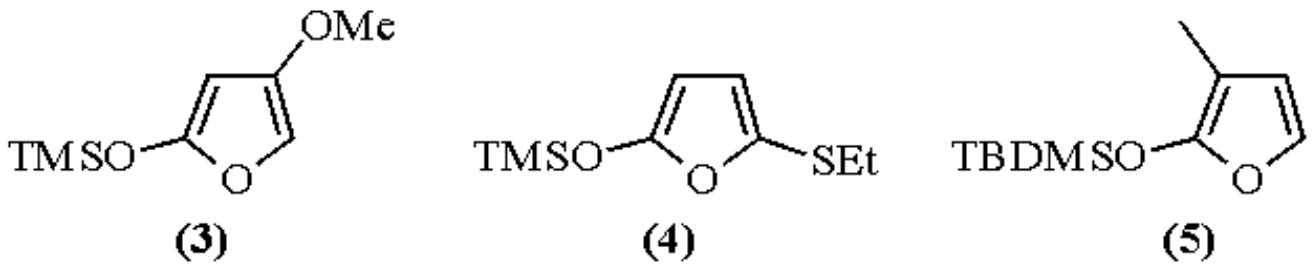

(3) (4) (5)

Other related reagents are γ-***Butyrolactone***, ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***, ***2,5-Dihydro-2,5-dimethoxyfuran***, ***Furan***, ***5-Lithio-2,3-dihydrofuran***, and β-***Vinyl***-α,β-***butenolide***.

---

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(*Z*)-2-(Trimethylsilyloxy)vinyllithium

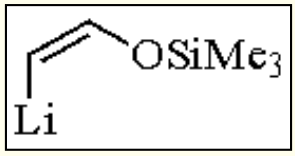

[78108-48-2] · $C_5H_{11}LiOSi$ · (*Z*)-2-(Trimethylsilyloxy)vinyllithium · (MW 122.19)

(vinylogation of aldehydes and ketones under mild conditions; preparation of β-methoxy aldehydes and β-silyl silyl enol ethers)

Solubility: sol Et_2O, THF.

Preparative Methods: bromine-lithium exchange starting from ***(Z)-2-Bromo-1-(trimethylsilyloxy)ethylene*** in dry Et_2O (0.15 M) and ***t-Butyllithium*** at -70 °C under inert atmosphere.[1] One equivalent of *t*-BuLi is sufficient if (*Z*)-(trimethylsilyloxy)vinyllithium is condensed with reactive electrophilic reagents which are added 10-20 min after the end of the addition of *t*-BuLi.[1,2] In other cases, two equivalents of *t*-BuLi are needed, the second equivalent is used to destroy *t*-BuBr formed during the exchange[3] and the electrophilic reagents are added after the end of addition of *t*-BuLi.

Handling, Storage, and Precautions: when prepared with 2 equiv of *t*-BuLi the reagent is stable in Et_2O over 20 h at -70 °C;1 from -60 °C it begins to decompose with formation of ***Acetylene***.[4]

General Discussion.

(*Z*)-(Trimethylsilyloxy)vinyllithium (**1**) has essentially been used for a one-pot vinylogation of carbonyl compounds. Condensation of (**1**) with aldehydes and ketones (**2**) occurs readily at low temperature (-70 °C); then treatment of the reaction mixture with an acidic solution in mild conditions (1 N ***Hydrochloric Acid***, 0 °C to rt) produces the α,β-unsaturated aldehydes (**3**), without double bond migration. The (*E*) isomers are obtained alone (from aldehydic compounds) or very predominantly (from ketonic compounds). The intermediate adducts, γ-hydroxy enol ethers (**4**), can be isolated by slightly basic mild hydrolysis (eq 1).[1]

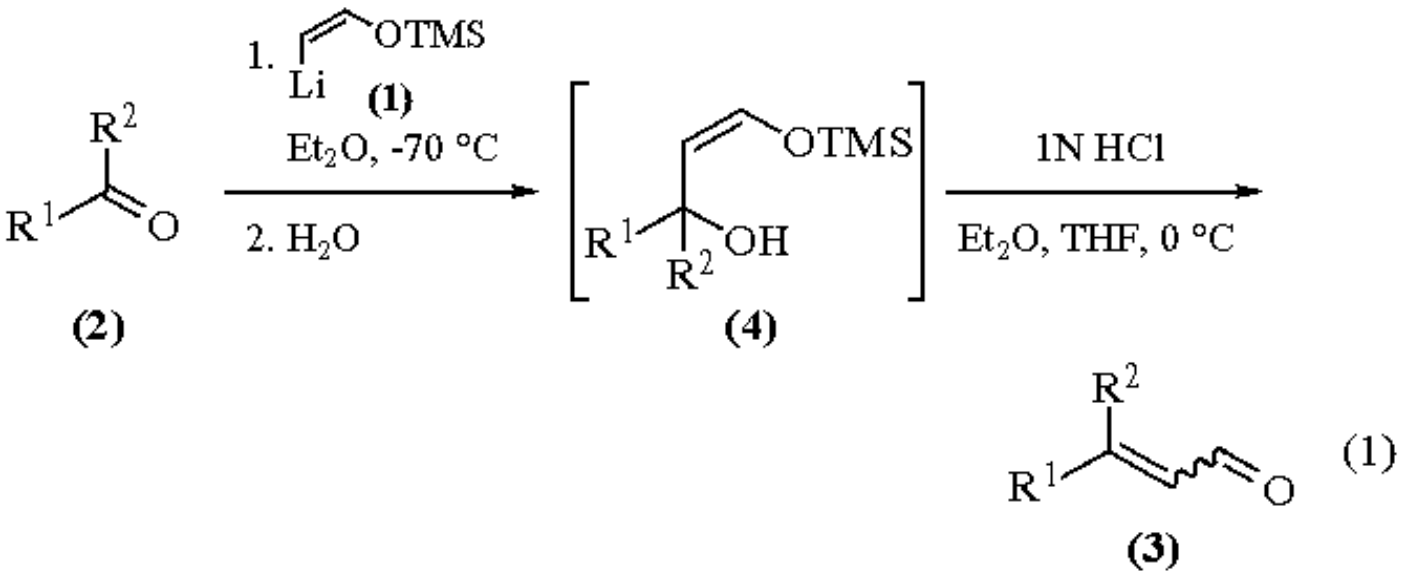

(1)

As condensation with α,β-unsaturated compounds occurs exclusively in a 1,2-fashion,[1,2] this reagent has been used in terpene synthesis. A synthesis of retinal (**3b**) in three steps from β-ionone (**2a**) (via β-ionylideneacetaldehyde and C_{18} ketone) was reported using reagent (**1**) for the first and third steps (eq 2).[5]

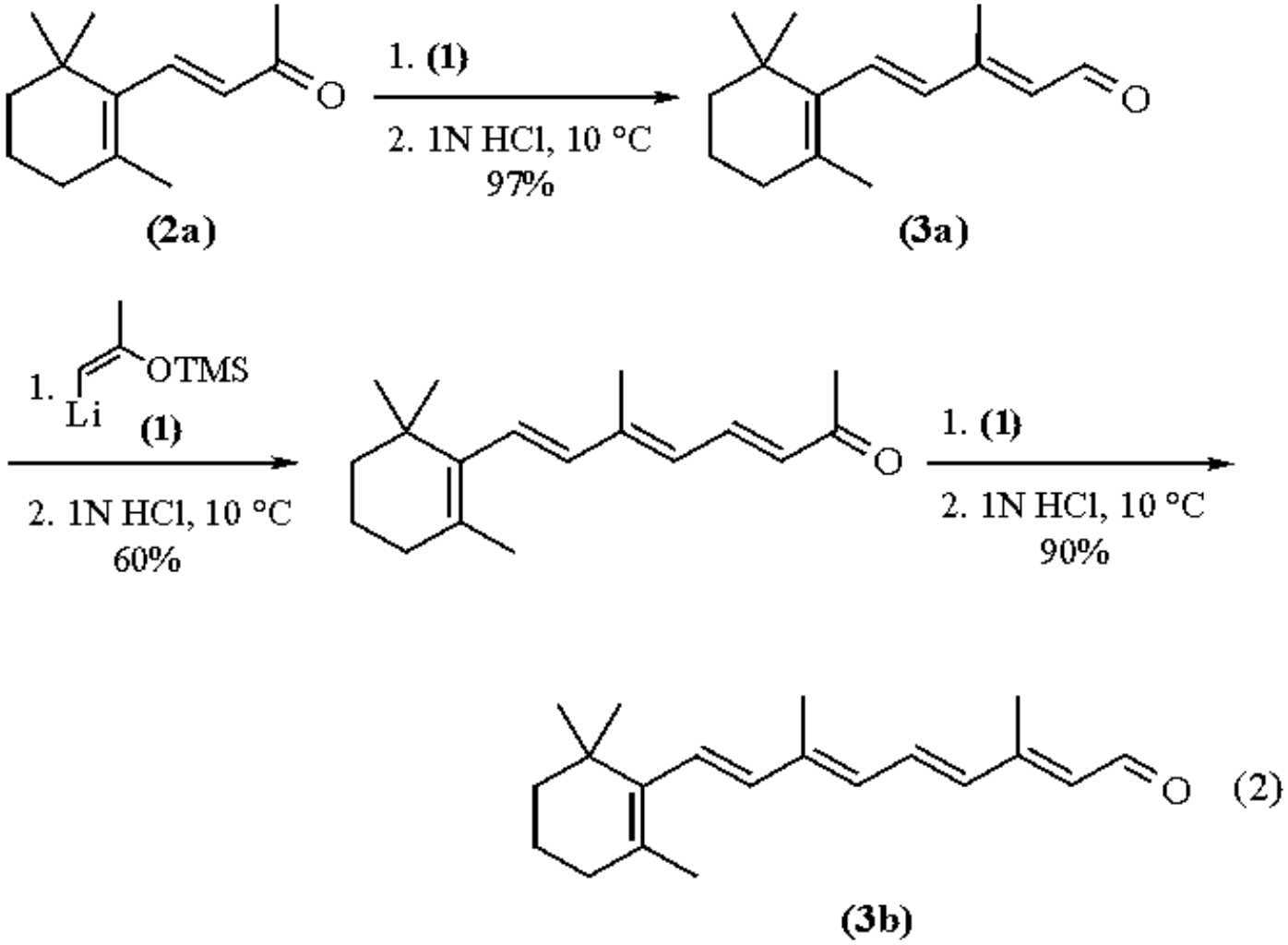

(2)

For the step (**2a**) -> (**3a**), reagent (**1**) competes favorably with other classical vinylogation reagents: ***Formylmethylenetriphenylphosphorane*** (0%);[6] lithium cyclohexylvinylamide (2 steps, 34%);[7] lithio salt of ***5,6-Dihydro-2,4,4,6-tetramethyl-1,3(4H)-oxazine*** (3 steps, 54%);[8] lithium *t*-butyl-2-trimethylsilylvinylamide (1 step, 88%)[9] (see Duhamel et al.[2] for other comparative studies).

Thus (*Z*)-(trimethylsilyloxy)vinyllithium (**1**) is an excellent reagent for the preparation of building blocks such as (**4**), (**5a**), and (**5b**) (eq 3), which are useful for short convergent syntheses of terpenoid compounds (eqs 4 and 5).[10]

Condensation of acetylacetaldehyde dimethyl acetal with reagent (**1**) leads to the δ-aldolacetal (**3c**) in 90% yield, which has been transformed by classical methods into bromoacetal (**4**) and bromo enol ethers (**5a,5b**) (eq 3).[10]

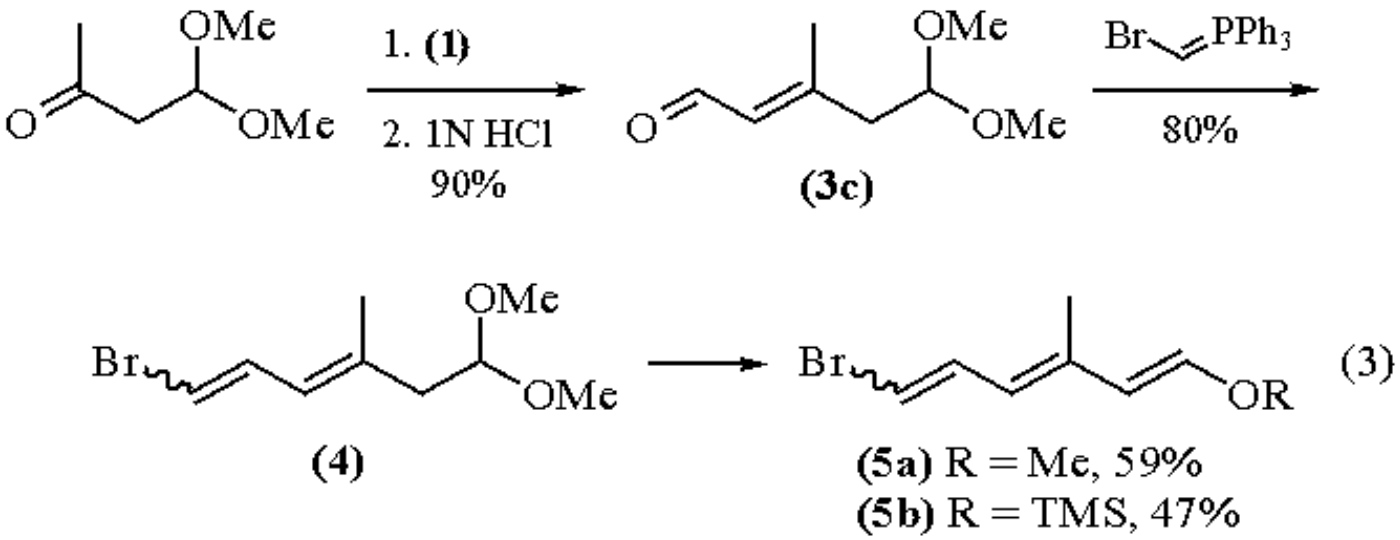

(3)

For the first time a one-step synthesis of retinal (**3b**) from β-ionone (**2a**) was reported, using reagents (**5a**) and (**5b**) (eq 4),[10] whereas two-step syntheses of dehydrocitral from acetone (60%), *pseudo*-retinal from *pseudo*-ionone (61%), and retinal from β-ionone (55%) were

described using reagent (**4**).[10]

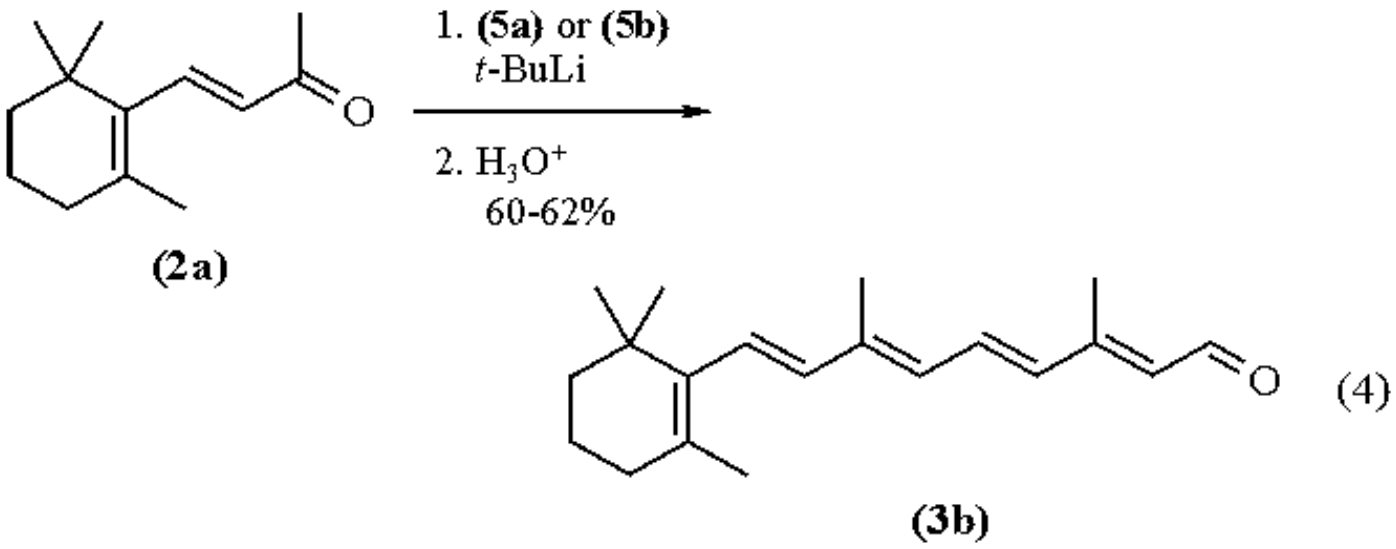

A short synthesis of phytol (**6**) from 6-methyl-5-hepten-2-one was described using reagents (**1**) and (**4**). Condensation of 6-methyl-5-hepten-2-one with (**4**) yielded the hydroxy acetal (**7**), which was converted in one pot into *pseudo*-phytone (**8**). Catalytic hydrogenation of (**8**) gave phytone, which was transformed into phytol (**6**) after condensation with (**1**) followed by reduction (eq 5).[11]

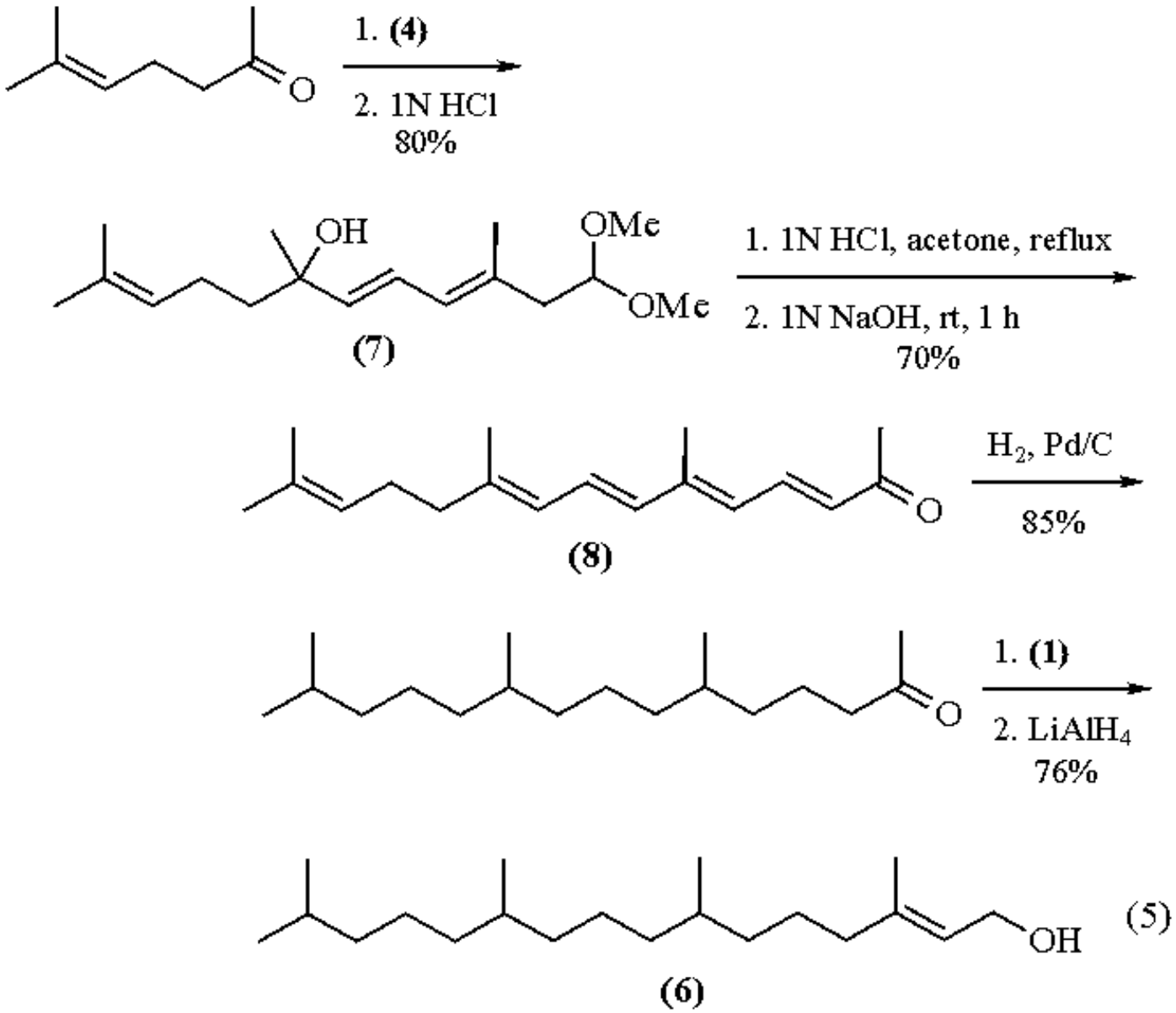

The adduct of (**1**) with carbonyl compounds can be trapped by methyl fluorosulfonate, leading to γ-methoxy enol ethers (**9**) precursors of β-

methoxy aldehydes (**10**) (eq 6).[12]

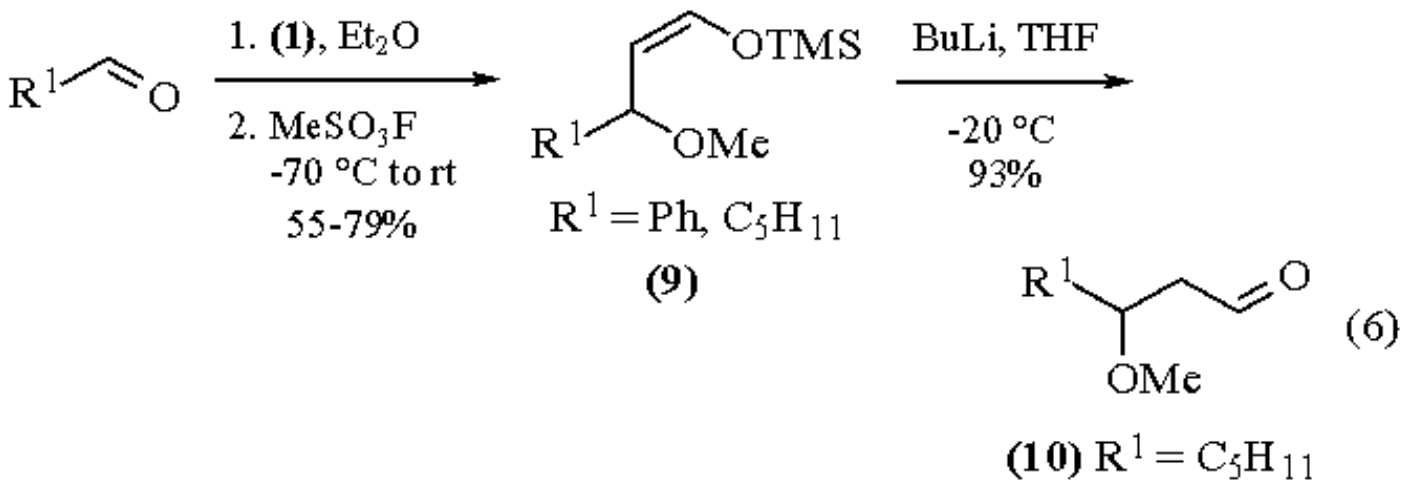

Depending on the experimental conditions, reaction of (**1**) with ***t-Butyldimethylsilyl Trifluoromethanesulfonate*** leads either to the expected β-trimethysilyl enol ether (**11**), or to its isomer (**12**) formed by a 1,3-migration of the trimethylsilyl group from the oxygen atom to the carbon atom (**1** -> **13**). Reaction with ***t-Butyldimethylchlorosilane*** always gives (**12**).[13] Trimethylsilyl enol ether (**11**) is easily hydrolyzed to 2-(*t*-butyldimethylsilyl)acetaldehyde (**14**) (eq 7).[14]

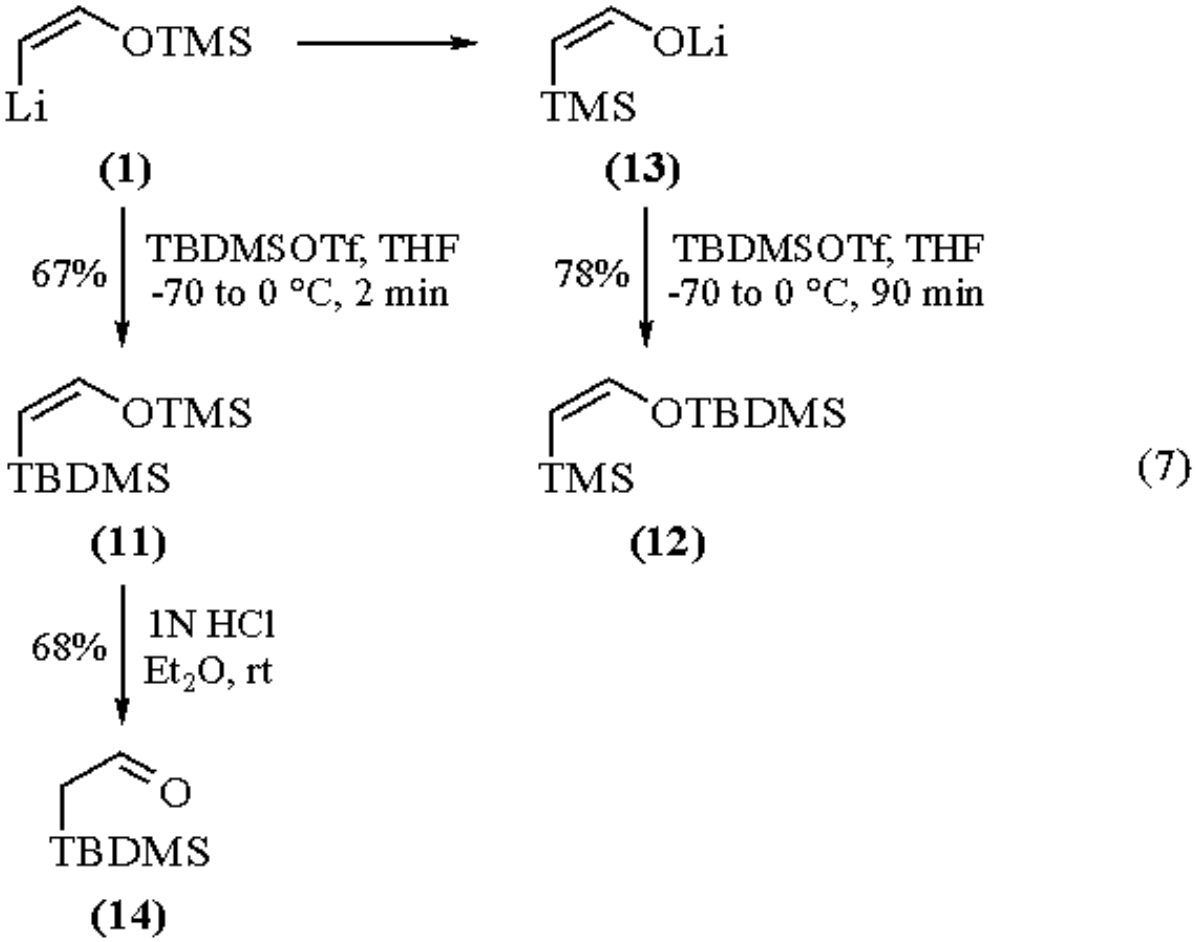

The study of the ^{1}H NMR spectra of (**1**) in Et_2O-d_{10} at -70 °C is in agreement with the proposed structure; the isomeric enolate (**13**) is not normally detected (eq 7), but in THF at -70 °C it slowly forms.[4]

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5-Trimethylsilyl-1,3-pentadiene

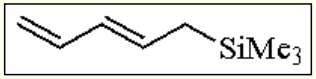

[72952-73-9] · $C_8H_{16}Si$ · 5-Trimethylsilyl-1,3-pentadiene · (MW 140.33)

(useful pentadienylation reagent;[1] an allyl silane;[7] a precursor for 1-trimethylsilyldienes and intramolecular Diels-Alder substrates[2])

Alternate Name: 2,4-pentadienyltrimethylsilane.

Physical Data: bp 41 °C/36 mmHg or 105 °C/760 mmHg; *n*20D 1.4570.

Solubility: sol hexane, benzene, CH_2Cl_2, ether, THF.

Analysis of Reagent Purity: by NMR, GC (8.4 min on 3 mm × 3 M 5% Apiezon L on Chromosorb W at 80 °C) or TLC: 5% $AgNO_3$/silica gel (4:1 hexane/benzene).

Preparative Method: may be prepared in 85% yield by the reaction of ***Pentadienyllithium*** with ***Chlorotrimethylsilane*** in THF at room temperature.[1-3] Generally the product is ~95% (*E*) isomer as judged by IR (strong band at 1000 cm^{-1}) or NMR (*trans* coupling constant of 15.2 Hz for proton at C-3, 5.92 ppm).

Handling, Storage, and Precautions: stable liquid; the toxicological properties of this reagent are unknown. It should be handled in a well ventilated hood.

General Discussion.

2,4-Pentadienyltrimethylsilane is used as a stable (storable) nucleophilic substitute for pentadienyllithium. This compound reacts with Lewis acid (***Boron Trifluoride Etherate***, ***Iodotrimethylsilane***, ***Titanium(IV) Chloride***) activated electrophiles in the same manner as allylsilanes (eq 1). Generally only ε-substitution is observed (cf. Table 1).[1,4,5,7]

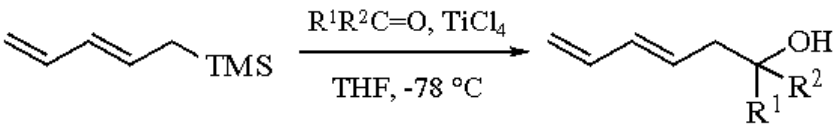

(1)

Table 1 Reaction of $H_2C{=}CHCH{=}CHCH_2MMe_3$ with Typical Electrophiles

Entry	Electrophile (E^+)	M	Lewis acid	Product	Yield (%)	Ref
1	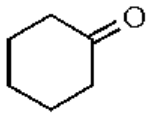	Si	$TiCl_4$	ε-adduct	64	1
2	$PhCH(OMe)_2$	Si	$BF_3 \cdot OEt_2$	ε-adduct	85	4, 5
3	PhCHO	Si	$BF_3 \cdot OEt_2$	ε-adduct	16	5
4	*t*-BuCOCl	Si	$BF_3 \cdot OEt_2$	34% ε-adduct, 25% γ-adduct	-	5
5	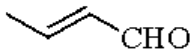	Si	$BF_3 \cdot OEt_2$	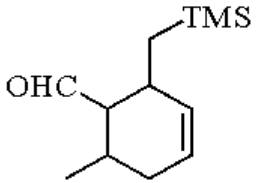	40	1, 7
6	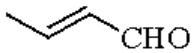	Sn	$BF_3 \cdot OEt_2$	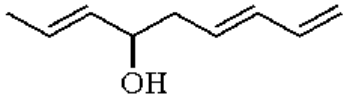	70	7
7	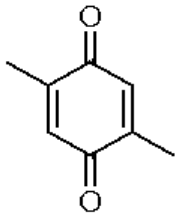	Si	$BF_3 \cdot OEt_2$	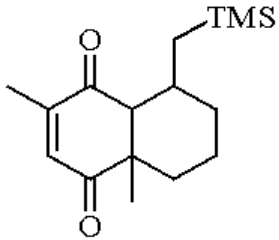	91	7
8	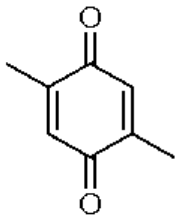	Sn	$BF_3 \cdot OEt_2$	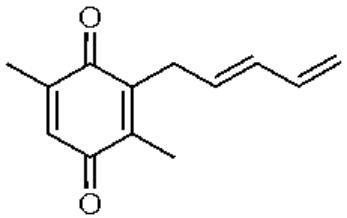	85[a]	7

[a] After reoxidation to the quinone.

Other electrophiles which have been used include acetals,[4] acid chlorides,[5] and heteroatom-based electrophiles. A useful varient of the title compound is the more reactive 2,4-pentadienyltrimethylstannane (Table 1, entries 6 and 8).[6,7] Lewis acid-catalyzed conjugate addition reactions have been observed with the tin analog,[7,8] but are not observed with 2,4-pentadienyltrimethylsilane due to a competing Diels-Alder reaction (Table 1, entries 5 and 7).

In a typical reaction of 2,4-pentadienyltrimethylsilane with electrophiles, a carbonyl compound was dissolved in CH_2Cl_2 and cooled to -40 °C and 0.3 equiv $TiCl_4$ (or $BF_3.OEt_2$) was added. After 5 min, 0.66 equiv 2,4-pentadienyltrimethylsilane was added and the mixture warmed to 5-25 °C over a 5 min to 2 h period (depending on the reactivity of the electrophile). After quenching with $NaHCO_3$ the product was extracted with ether.

2,4-Pentadienyltrimethylsilane may also be deprotonated adjacent to silicon with ***Lithium Diisopropylamide***, forming the 1-(Me_3Si)-pentadienyl anion.[2] This anion reacts with many electrophiles to give ε-substituted dienes (eq 2) which are ideal candidates for protodesilyation or intramolecular Diels-Alder reactions.

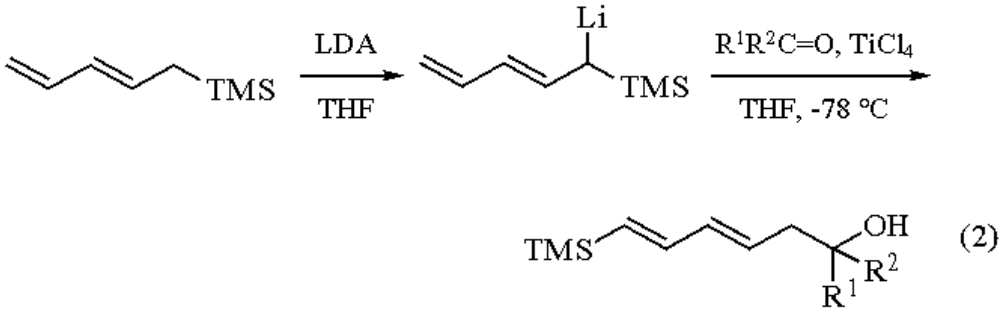

(2)

The reaction of the 1-(Me_3Si)-pentadienyl anion with cyclohexanone gives a 59/41 mixture of γ- and ε-regioisomers.

---

1. Seyferth, D.; Pornet, J. *JOC* **1980**, *45*, 1722.
2. Oppolzer, W.; Burford, S. C.; Marazza, F. *HCA* **1980**, *63*, 555.
3. Seyferth, D.; Pornet, J.; Weinstein, R. M. *OM* **1982**, *1*, 1651.
4. Sakurai, H.; Sasaki, K.; Hosomi, A. *TL* **1981**, 745.
5. Hosomi, A.; Saito, M.; Sakurai, H. *TL* **1980**, 3783.
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7. Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *CL* **1983**, 1683.
8. Nishigaichi, Y.; Fujimoto, M.; Takuwa, A. *JCS(P1)* **1992**, 2581.

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Trimethylsilyl Perchlorate[1]

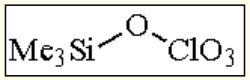

[18204-79-0] · $C_3H_9ClO_4Si$ · Trimethylsilyl Perchlorate · (MW 172.66)

(nucleoside synthesis;[1] selective cleavage of *t*-Boc group;[2] disiloxane[3] formation and general silylation characteristics[4,5])

Alternate Name: TMSP.

Physical Data: bp 35-38 °C/14 mmHg.

Preparative Method: prepared by a silver salt-trimethylsilane anion exchange (eq 1).[6] Not commercially available.

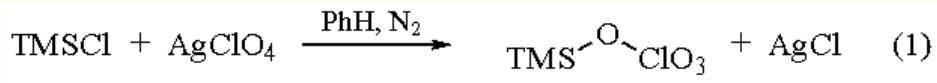

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: explosive; fumes when exposed to air. Use in fume hood.

Catalytic Synthesis of Nucleosides from Silylated Heterocycles and 1-*O*-Acyl or 1-*O*-Alkyl Sugars.[1]

Trimethylsilyl perchlorate, prepared in situ, acts as a strong Lewis acid suitable as a Friedel-Crafts catalyst in the reaction of silylated heterocycles, like uracil (**1**), with 1-*O*-acyl or 1-*O*-alkyl sugars such as 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**). This Friedel-Crafts reaction produces the nucleoside 4-*O*-silylated ribosyl benzoate (**3**) (eq 2).

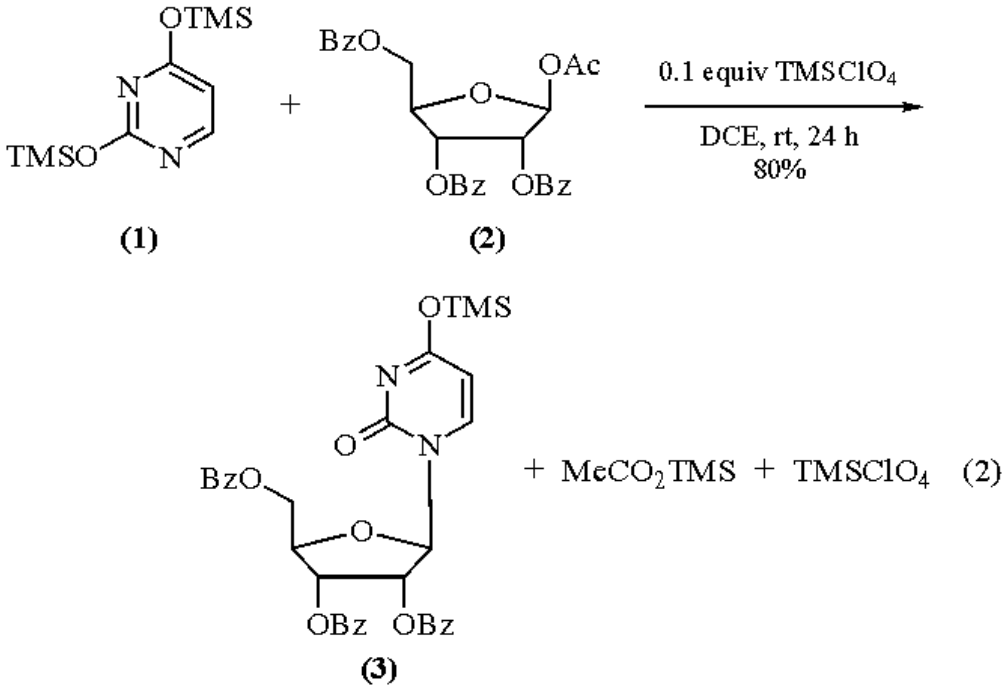

Since trimethylsilyl perchlorate is produced by the reaction, it can be used catalytically. Workup of these Friedel-Crafts reactions is effected by $NaHCO_3/CH_2Cl_2$. The use of this reagent as the catalyst is an improvement over the past nucleoside synthesis which employed ***Tin(IV) Chloride***, where isolation and purification were complicated by the formation of emulsions and colloids. This rate of nucleoside formation is also greatly enhanced by an increase in temperature. Trimethylsilyl perchlorate can be effectively substituted with ***Trimethylsilyl Trifluoromethanesulfonate***. Yields ranged from 60-90%.

Selective Acidic Cleavage of the *t*-Butoxycarbonyl Group.[2]

Trimethylsilyl perchlorate enables selective cleavage of *t*-Boc groups in the presence of the benzyloxycarbonyl (*Z*) group and *t*-butyl esters. This difficult selective cleavage is executable at rt over a 5 min period in benzene, CH_2Cl_2, or benzene/acetonitrile with 1.0 equiv of trimethylsilyl perchlorate as the promoter. Yields are quantitative (Table 1).

Table 1 Cleavage of *t*-Boc Groups Using TMSP

Peptide	Solvent	Product	Yield (%)
(1) Boc Ala Phe OMe	C_6H_6	H Ala Phe OMe·$HClO_4$	87
(2) Boc Val Leu OMe	C_6H_6	H Val Leu OMe·$HClO_4$	~100
(3) Z Lys (Boc)Arg (NO_2)OMe	C_6H_6/MeCN (1:1)	Z Lys Arg(NO_2) OMe·$HClO_4$	~100
(4) Boc Gly Ile Val Glu(O-*t*-Bu) OBn	C_6H_6/MeCN (1:1)	H Gly Ile Val Glu(O-*t*-Bu) OBn·$HClO_4$	~100

Disiloxane Formation[3] and Silylations.

$(Me_3Si)_3CSiMe_2OH$, a sterically hindered silanol, gives the disiloxane $(Me_3Si)_3CSiMe_2OSiMe_3$ in 87% yield, when treated with 4.5 equiv of trimethylsilyl perchlorate in benzene at room temperature for 10 min (eq 3). The same result may be effected with ***Iodotrimethylsilane***, ***N,O-Bis(trimethylsilyl)acetamide***, or ***Methyllithium*** followed by ***Chlorotrimethylsilane***.

$$(TMS)_3CSiMe_2OH + 4.5\ \text{equiv}\ TMSOClO_3 \xrightarrow[87\%]{\text{rt, 10 min}} (TMS)_3CSiMe_2OTMS + HClO_4 \qquad (3)$$

The above disiloxane formation is an example of a silylation. The active nucleophilic species and kinetics of different silylations have been studied. The ideal silylation mixture should consist of a polar solvent to stabilize salts, a highly electrophilic silane, such as trimethylsilyl perchlorate, trimethylsilyl iodide, or trimethylsilyl trifluoromethanesulfonate, a strong nucleophile, such as ***N-Methylimidazole***, ***4-Dimethylaminopyridine***, or ***Hexamethylphosphoric Triamide*** and a proton acceptor like ***Triethylamine***.[4] It has also been shown that trimethylsilyl perchlorate forms bis(trimethylsilyl)imidazolium salts which are postulated to be active intermediates in other silylation reactions.[5]

---

1. Vorbruggen, H.; Krolikiewicz, K. *AG* **1975**, *14*, 421.
2. Vorbruggen, H.; Krolikiewicz, K. *AG* **1975**, *14*, 818.
3. Eaborn, C.; Safa, K. D. *JOM* **1982**, *234*, 7.
4. Bassindale, A. R.; Stout, T. *TL* **1985**, *26*, 3403.
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6. (a) Eaborn, C. *JCS* **1955**, 2517. (b) Wannagat, U.; Liehr, W. *AG* **1957**, *69*, 783.

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Trimethylsilyl Polyphosphate

(can activate functional groups containing an oxygen atom; cyclodehydration agent for synthesis of heterocycles)

Alternate Names: polyphosphoric acid trimethylsilyl ester; PPSE.

Solubility: sol dichloromethane, chloroform, 1,2-dichloroethane, benzene, toluene, xylene, 1,2-dichlorobenzene.

Form Supplied in: colorless or pale yellow, viscous liquid; commercially available.

Preparative Methods: prepared by heating a mixture of ***Phosphorus(V) Oxide*** and ***Hexamethyldisiloxane*** (2-3.5 moles per mole P_4O_{10}) in a solvent such as dichloromethane or without solvent (eq 1).[1,2]

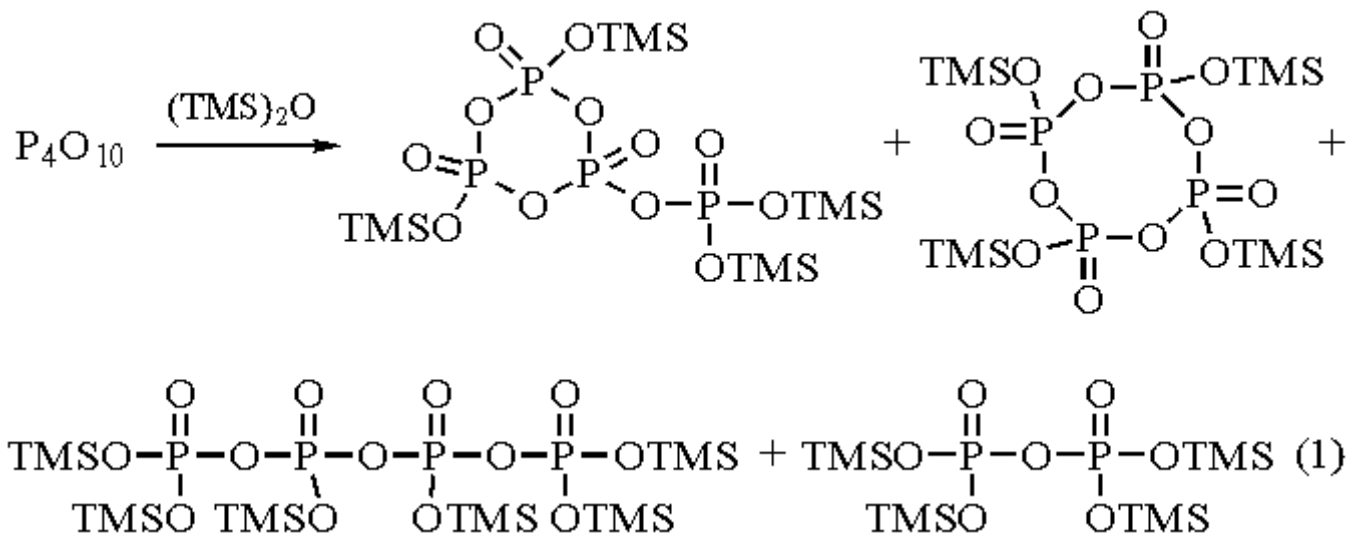

PPSE consists mainly of three tetraphosphoric acid trimethylsilyl esters together with a small amount of tetrakis(trimethylsilyl) pyrophosphate.[3]

Handling, Storage, and Precautions: PPSE is hygroscopic, and should be stored strictly in the absence of moisture.

Transformations of Functional Groups Containing an Oxygen Atom.

PPSE is capable of activating functional groups containing an oxygen atom by interaction with a phosphorus atom or a trimethylsilyl moiety. These reactivities of PPSE in conjunction with its aprotic nature and high solubility in organic solvents render this reagent useful in transformations of some functional groups. Thus amides are smoothly dehydrated by PPSE at reflux in chloroform to give nitriles (eq 2).[4] Ketoximes are readily subjected to the Beckmann rearrangement to yield amides.[1] Acetophenone oximes possessing OH, NH_2, or SH groups at *ortho* positions are converted to 2-methylbenzoxazole, 2-methylbenzimidazole, and 2-methylbenzothiazole, respectively, via the Beckmann rearrangement and cyclization (eq 3).[3] On the other hand, aldoximes are dehydrated by PPSE to afford nitriles.[5] It is noted that aromatic nitriles are conveniently prepared from aromatic aldehydes by refluxing with ***Hydroxylamine*** hydrochloride and PPSE (eq 4).[4]

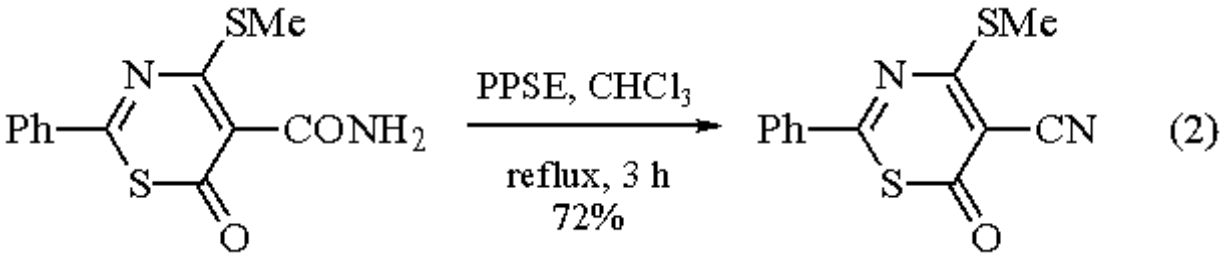

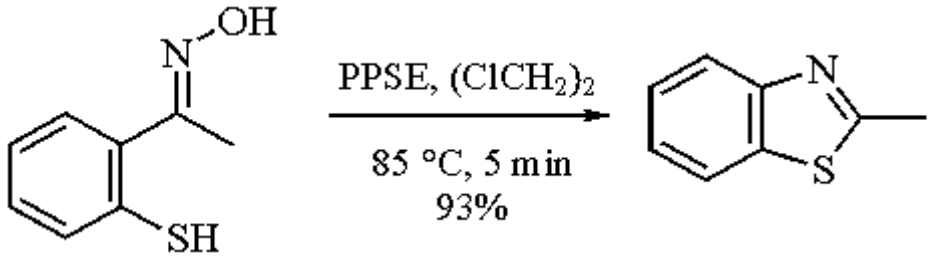

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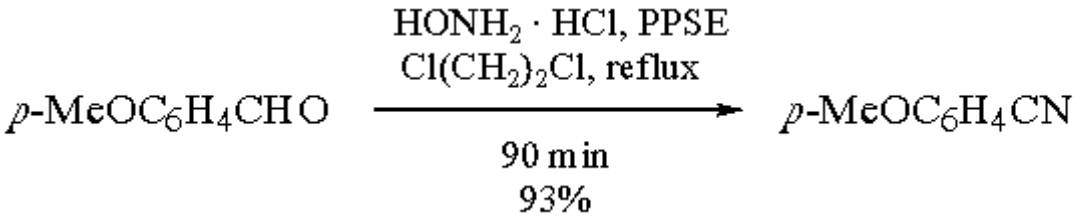

(4)

Primary and secondary alcohols are converted to the corresponding alkyl iodides by treatment with the ***Sodium Iodide***-PPSE reagent system (eq 5).[6] The reaction of optically active secondary alcohols results in the formation of virtually racemized alkyl iodides. Carboxylic acids are activated by PPSE, undergoing condensation with two equivalents of amines to afford amidines in high yields (eq 6).[7]

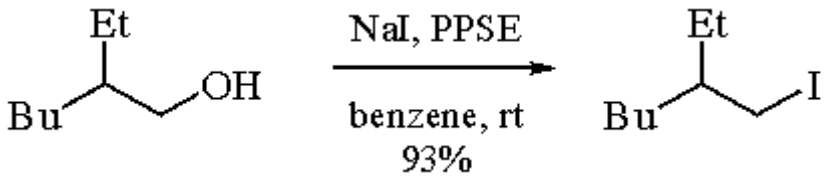

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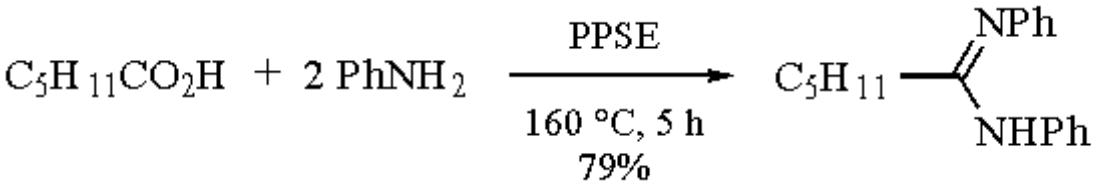

(6)

Reagent for Cyclodehydration.

PPSE can be used as a condensation agent for the preparation of such heterocycles as 1,3-dioxane derivatives (eq 7),[2] 9*H*-selenoxanthen-9-ones and related sulfur and oxygen congeners (eq 8),[8] 1,3-oxazin-6-ones,[9] 2*H*-1,2,4-benzothiadiazine derivatives,[10] and benzoxazoles (see also ***Polyphosphoric Acid*** (PPA) and ***Polyphosphate Ester*** (PPE)).[11,12]

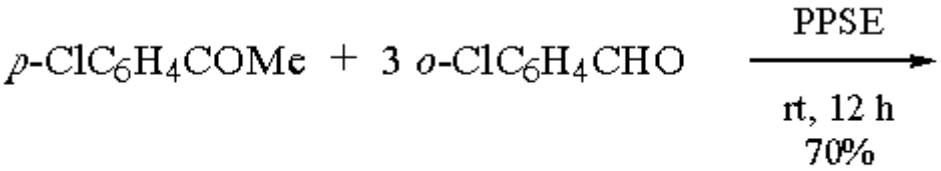

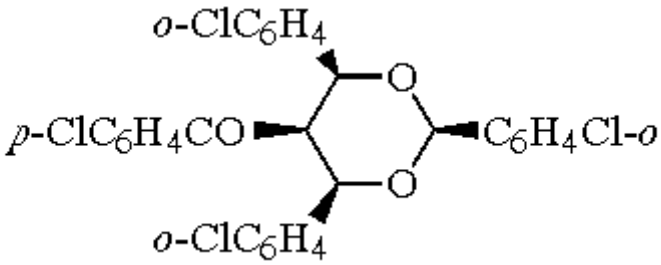

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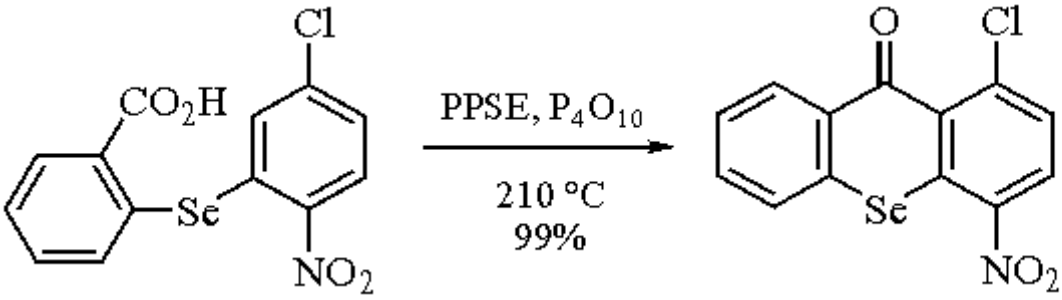

(8)

1. Imamoto, T.; Yokoyama, H.; Yokoyama, M. *TL* **1981**, *22*, 1803.
2. Imamoto, T.; Matsumoto, T.; Yokoyama, H.; Yokoyama, M.; Yamaguchi, K. *JOC* **1984**, *49*, 1105.
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5. Aizpurua, J. M.; Palomo, C. *NJC* **1983**, *7*, 465.
6. Imamoto, T.; Matsumoto, T.; Kusumoto, T.; Yokoyama, M. *S* **1983**, 460.
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12. Flouzat, C.; Guillaumet, G. *S* **1990**, 64.

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Trimethylsilylpotassium

Me_3SiK

[56859-17-7] · C_3H_9KSi · Trimethylsilylpotassium · (MW 112.31)

(highly reactive nucleophile and one-electron transfer reagent;[1-3] deoxygenates substituted epoxides with inversion of stereochemistry[4,5])

Solubility: sol DME, THF, HMPA, hexane.

Analysis of Reagent Purity: ^{13}C NMR (HMPA) δ 4.2.[6]

Preparative Methods: prepared quantitatively by the cleavage of the silicon-silicon bond of ***Hexamethyldisilane*** with ***Potassium Hydride*** or potassium alkoxides (KOMe or ***Potassium t-Butoxide***) (eqs 1 and 2).[1,2,7-9] It can also be conveniently prepared by deprotonation of Me_3SiH with KH (eq 3).[2,3] These procedures circumvent the need to handle volatile organomercury compounds that previous routes required.[10]

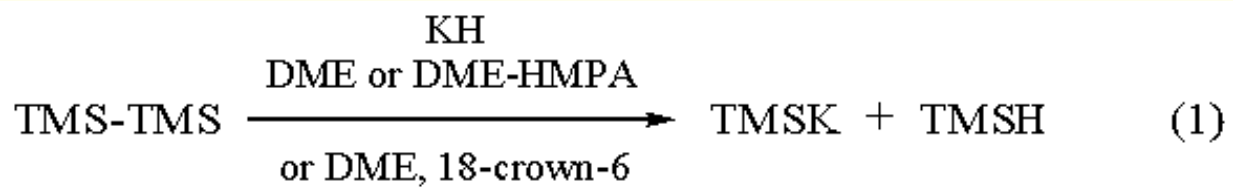

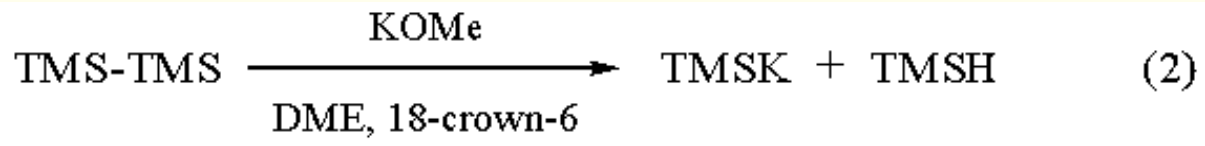

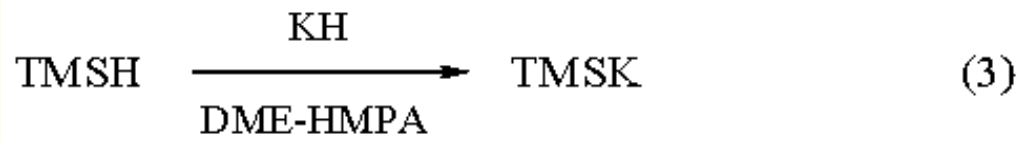

Handling, Storage, and Precautions: solutions of Me_3SiK are air and moisture sensitive and must be handled under inert atmospheres. The toxicity of Me_3SiK is not currently known; however, the preparations employing ***Hexamethylphosphoric Triamide*** and ***18-Crown-6*** necessitate handling these solutions in a fume hood using chemically resistant gloves.

Nucleophilic and Electron Transfer Reactions.

Me_3SiK is a highly reactive nucleophile and one-electron transfer reagent. It readily couples with halides and enones via S_N2 and 1,4-additions (eqs 4 and 5). When 1-bromohex-5-ene and benzophenone are treated with Me_3SiK, electron transfer induced cyclization and dimerization occur (eqs 6 and 7). The course of these reactions can be substantially influenced by the nature of the solvent, resulting in enhancement of either nucleophilic substitution or electron transfer.[1-3]

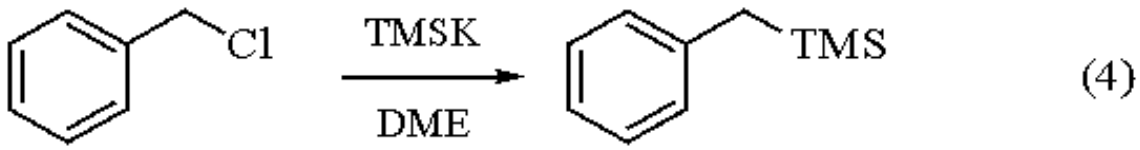

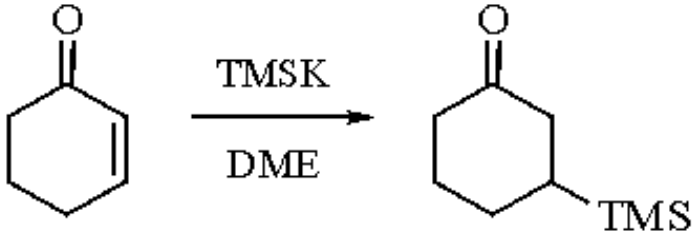

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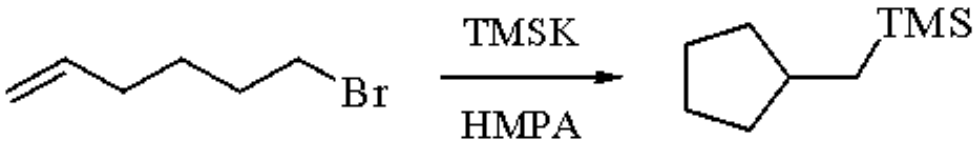

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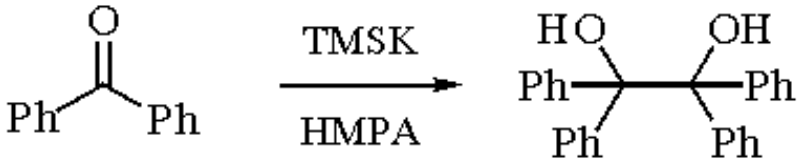

(7)

Aryl halides can be converted in one step to aryl trimethylsilanes in good yields with Me_3SiK (eq 8).[11] These are particularly useful intermediates for directing electrophilic substitutions on carbon.[12]

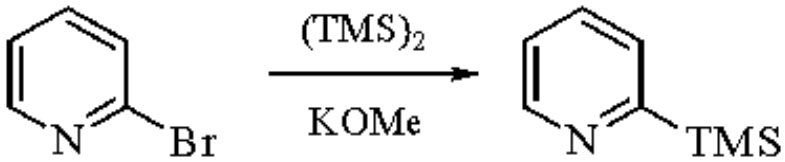

(8)

Deoxygenation of Epoxides with Inversion.

Me_3SiK stereospecifically deoxygenates substituted epoxides with inversion of stereochemistry. Reactions of *cis*- and *trans*-epoxides with $Me_3SiSiMe_3$ and KOMe give the *trans*- and *cis*-alkenes, respectively (eqs 9 and 10).[4,5]

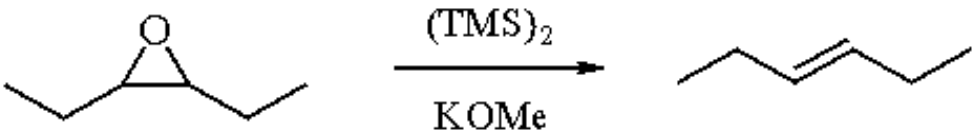

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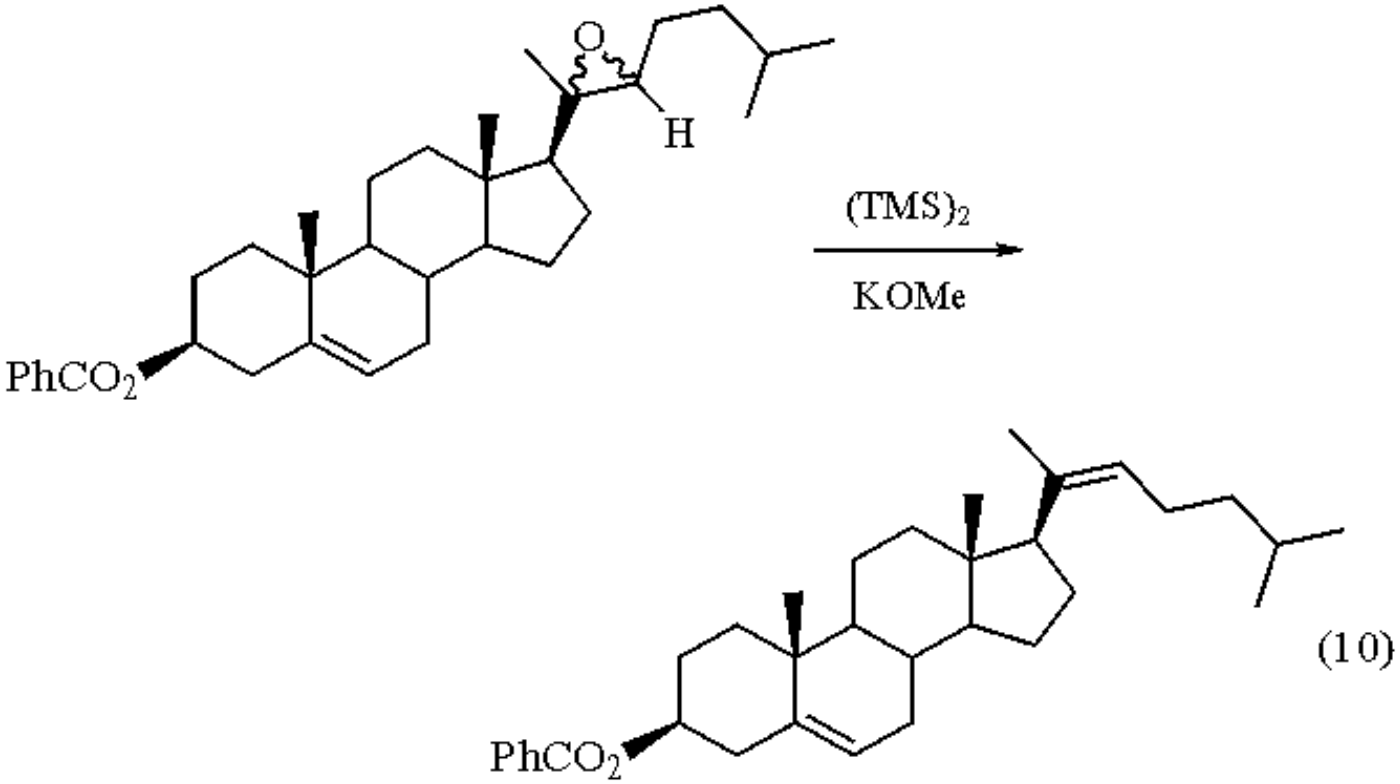

1. Sakurai, H.; Kondo, F. *JOM* **1975**, *92*, C46.
2. Corriu, R. J. P.; Guérin, C. *CC* **1980**, 168.
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12. Eaborn, C. *JOM* **1975**, *100*, 43.

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3-Trimethylsilyl-2-propen-1-yl Acetate

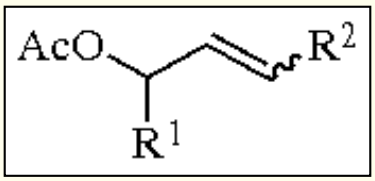

(**1**; R^1 = H, R^2 = (*E*)-$SiMe_3$)

[86422-21-1] · $C_8H_{16}O_2Si$ · 3-Trimethylsilyl-2-propen-1-yl Acetate · (MW 172.33) (**2**; R^1 = H, R^2 = (*Z*)-$SiMe_3$)

[86422-22-2] (*E* + *Z*)

[80401-14-5] (**3**; R^1 = $SiMe_3$, R^2 = H)

[80401-11-2]

(preparation of vinylsilanes via the corresponding allylmetal complexes;[1] oxygenated allylsilane reagents for nucleophilic addition and substitution reactions[2])

Preparative Methods: (i) from 3-trimethylsilyl-2-propyn-1-ol by reduction (***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (Red-Al), 70%)[3] and acetylation (***Acetyl Chloride***, ***Pyridine***, 78%);[4] (ii) from 3-trimethylsilyl-2-propyn-1-ol by reduction (P-2 ***Raney Nickel***, H_2, 86%)[5] and acetylation; (iii) from allyloxytrimethylsilane by a metalation-rearrangement sequence (***t-Butyllithium***, 90%)[2a,6] and acetylation (***Acetic Anhydride***, ***Triethylamine***, 76%).[2a]

Handling, Storage, and Precautions: use in a fume hood.

Preparation of Vinylsilanes.

Both (*E*)- and (*Z*)-3-trimethylsilyl-2-propen-1-yl acetates (**1** and **2**), together with their allylic isomer (**3**) (1-trimethylsilyl-2-propen-1-yl acetate) are useful reagents for the formation of vinylsilanes by way of transition metal-catalyzed allylic alkylations. Reaction of the π-allylpalladium intermediate generated from (**1**)-(**3**) with several types of nucleophiles has been studied.[4,7] In general, these alkylations exhibit high regioselectivity, with reaction occurring at the position γ to silicon. ***Diethyl Malonate*** sodium enolate reacts with either (**2**) or (**3**) in the presence of Pd^0 to give alkylated products in good yields and favoring the (*Z*)-vinylsilane isomer (eq 1).[1] Cyclohexanone enamine participates in the alkylation reaction, giving the (*E*)-vinylsilane as the sole product (eq 2).[1] Although lithium enolates are problematic, addition of tri-*n*-butyltin trifluoroacetate allows product formation in good yield (eq 3).[8]

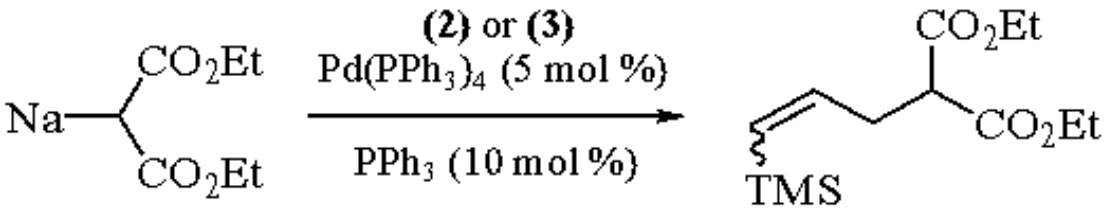

(1)

Reagent	Yield (%)	(*E*):(*Z*)
(2)	72	22:78
(3)	65	27:73

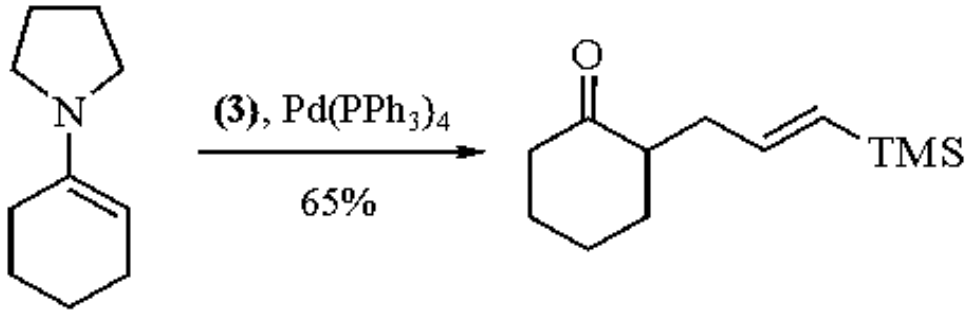

(2)

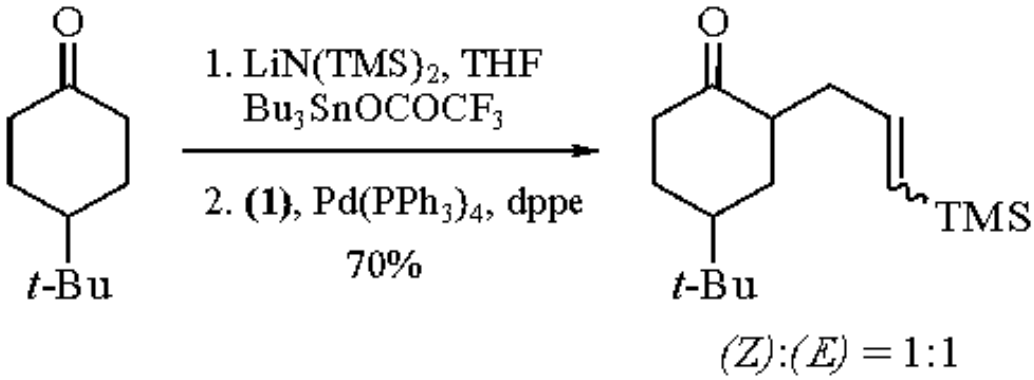

(3)

Other metals besides palladium are also effective.[9] Reaction of the cationic allyltetracarbonyliron complex derived from (**1**) or (**2**) with silyl enol ethers, *O*-silyl ketene acetals, or allylstannanes, followed by oxidative decomplexation, gives the vinylsilane products.[10] The process was shown to occur with near complete retention of stereochemistry (cf. eqs 4 and 5).[10]

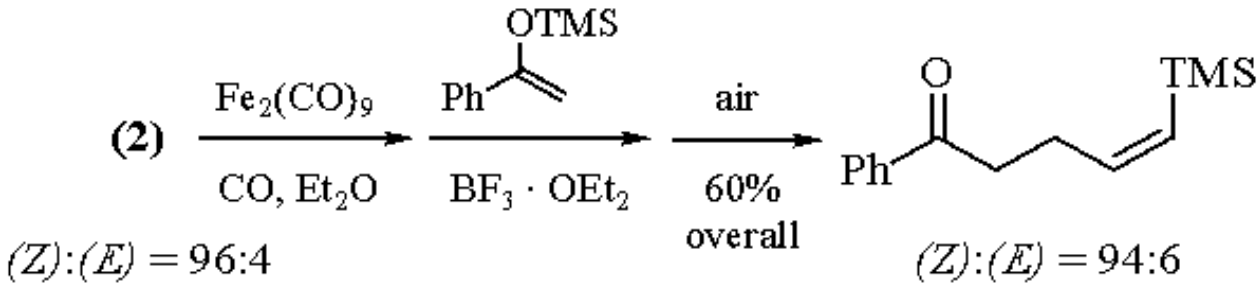

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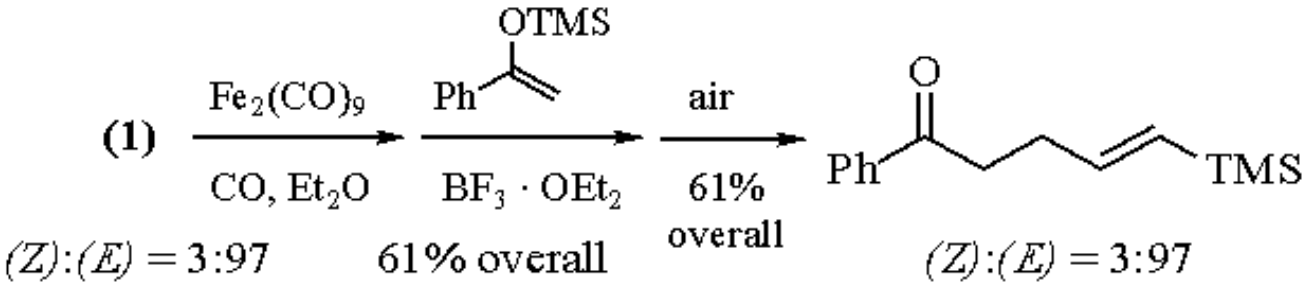

(5)

Nucleophilic Addition and Substitution Reactions.

Allylsilane (**3**) has been shown to undergo conjugate addition to enones in the presence of ***Tetra-n-butylammonium Fluoride*** (eq 6).[2a] The reaction demonstrates high regioselectivity, as no products arising from 1,2-addition to the enone or attack at the γ-position of the allylsilane were isolated. Stereoselective *C*-glycosidation can be effected by reaction of allylsilane (**3**) with D-mannopyranoside derivatives in the presence of ***Boron Trifluoride Etherate*** (eq 7).[2b] The α-*C*-glycoside arises from axial addition to the pyranoside oxonium ion.

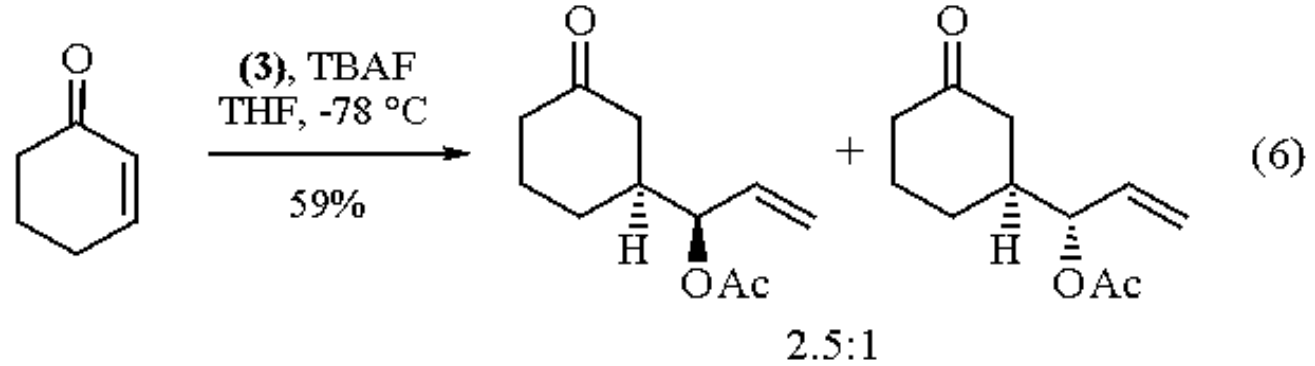

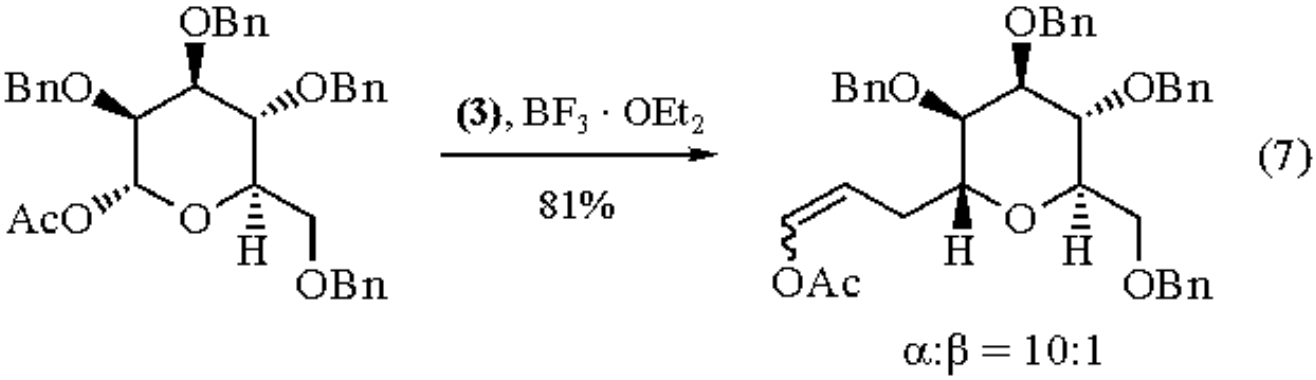

Related Reagents.

Allyltrimethylsilane; ***3-Bromo-1-trimethylsilyl-1-propene***; ***1-Pyrrolidino-1-cyclohexene***; ***Tetrakis(triphenylphosphine)palladium(0)***; ***Trimethylsilylallyllithium***.

---

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2. (a) Panek, J. S.; Sparks, M. A. *TL* **1987**, *28*, 4649. (b) Panek, J. S.; Sparks, M. A. *JOC* **1989**, *54*, 2034. (c) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *TL* **1992**, *33*, 1549.
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9. For use of $Mo(CO)_6$, see: Trost, B. M.; Lautens, M. *OM* **1983**, *2*, 1687.
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2-(3-Trimethylsilyl-1-propenyl)magnesium Bromide-Copper(I) Iodide[1]

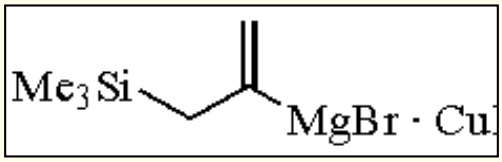

[103559-91-7] · $C_6H_{13}BrMgSi$ · 2-(3-Trimethylsilyl-1-propenyl)magnesium Bromide-Copper(I) Iodide · (MW 217.49)

[7681-65-4] · CuI · 2-(3-Trimethylsilyl-1-propenyl)magnesium Bromide-Copper(I) Iodide · (MW 190.45)

(used in methylenecyclopentane annulation via conjugate addition to enones;[2b] can serve as hydroxymethylvinyl anion equivalent[3])

Preparative Methods: copper(I) iodide-catalyzed reactions of 2-(3-trimethylsilyl-1-propenyl)magnesium bromide (**1**) have been carried out in ether or THF by combining (**1**) with a catalytic amount of ***Copper(I) Iodide*** at -30 to 0 °C. Two different preparations of (**1**) have been reported.[2a,3]

Handling, Storage, and Precautions: use in a fume hood.

Methylenecyclopentane Annulation.

Trost and Coppola[2b] applied the copper(I) iodide-catalyzed addition of (**1**) to enones; the conjugate adducts were converted to the corresponding methylenecyclopentanes in good yield (eqs 1-3). Attempts to generate stoichiometric cuprates were complicated by oxidative dimerization.

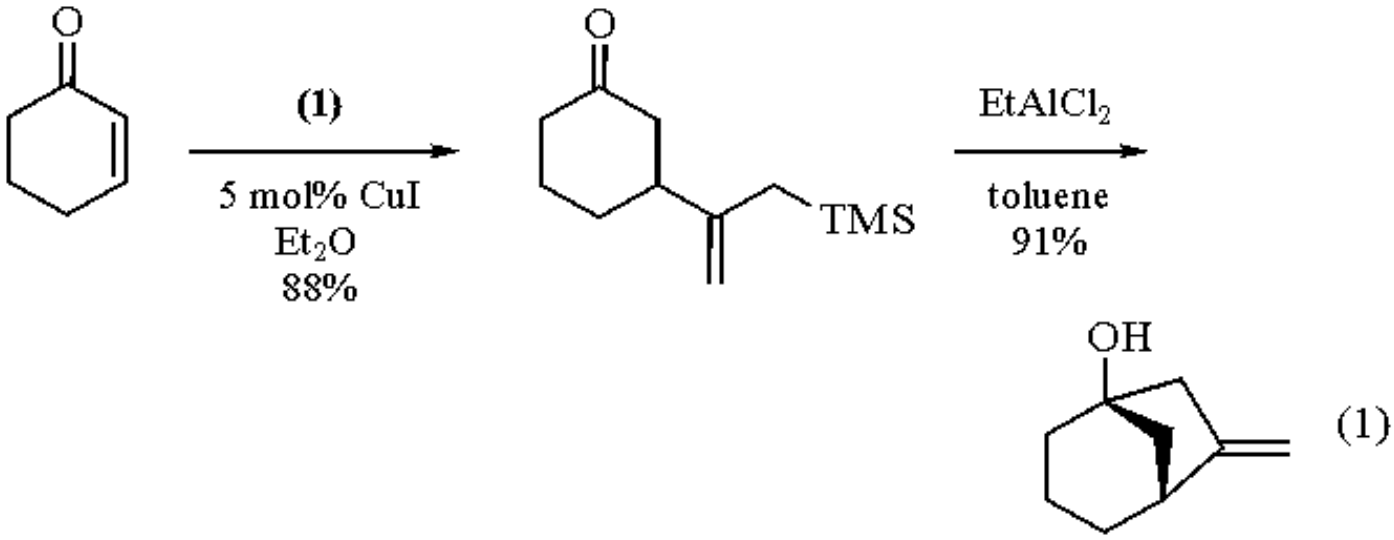

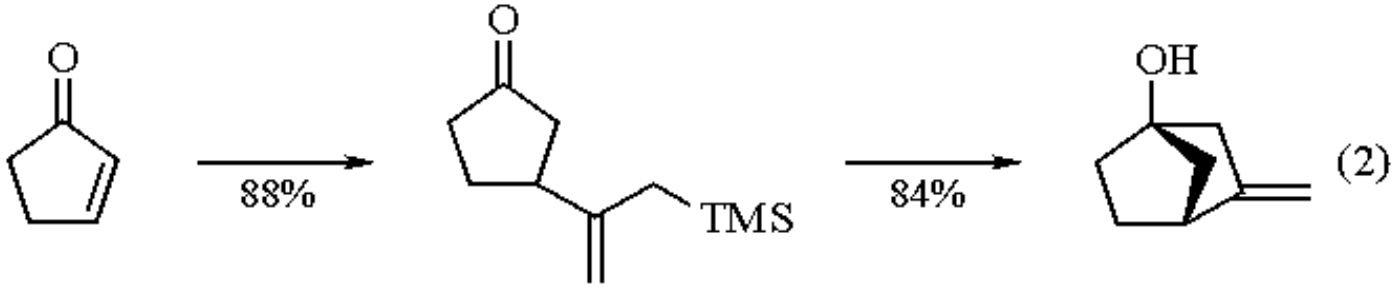

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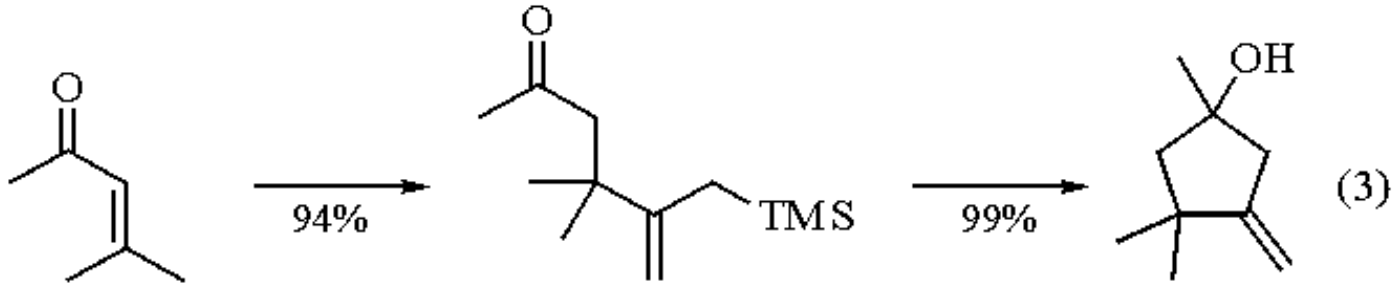

(3)

1-Hydroxymethylvinyl Anion Equivalent.

Copper(I) iodide-catalyzed addition of (**1**) to epoxides affords allylsilanes (**2**) (eq 4).[3] Oxidation of (**2**) to the corresponding allylic alcohols (**3**) constitutes formal addition of a hydroxymethylvinyl anion to an epoxide (eq 5). Alcohols (**3**) were converted to the corresponding α-methylene-γ-lactones (**4**) upon further oxidation (eq 6).

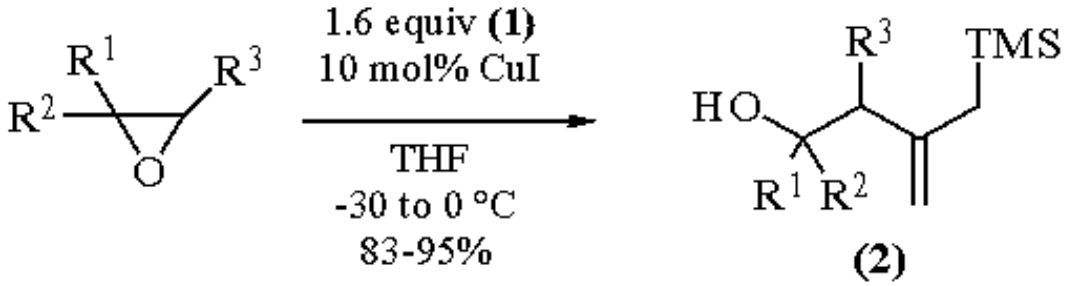

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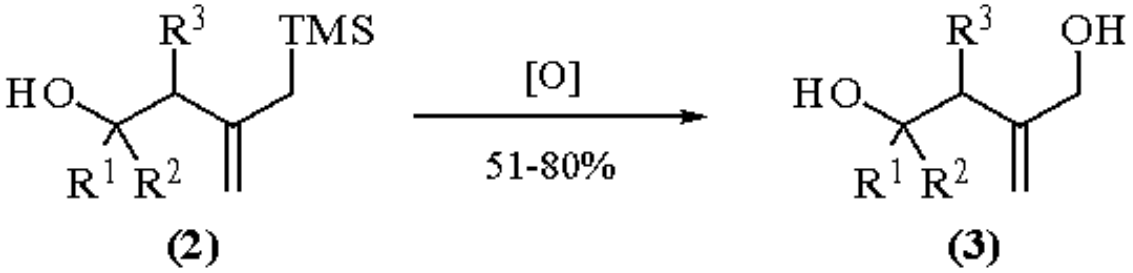

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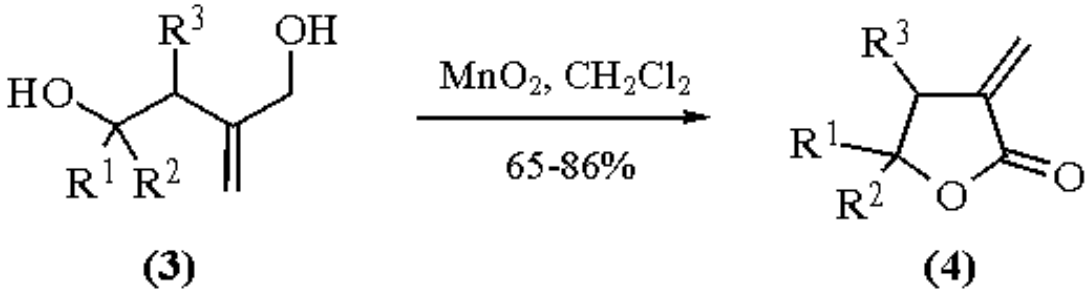

(6)

Related Reagents.

2-Bromo-3-trimethylsilyl-1-propene; ***Isopropenylmagnesium Bromide***; ***2-Propenylmagnesium Bromide-Copper(I) Iodide***; ***1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide***.

1. For a recent review of organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135.
2. (a) Trost, B. M.; Chan, D. M. T. *JACS* **1982**, *104*, 3733. (b) Trost, B. M.; Coppola, B. P. *JACS* **1982**, *104*, 6879.
3. Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *TL* **1982**, 1267.

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3-Trimethylsilyl-1-propyne

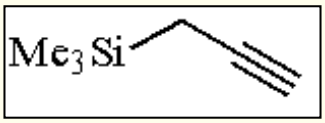

[13361-64-3] · $C_6H_{12}Si$ · 3-Trimethylsilyl-1-propyne · (MW 112.27)

(propargylation agent; allenylation agent; can give addition reactions on the triple bond)

Alternate Name: propargyltrimethylsilane.

Physical Data: bp 91-93 °C/760 mmHg; 40 °C/140 mmHg; *d* 0.753 g cm^{-3}; *n*20D 1.4140. IR (cm^{-1}, neat): 3320 s, 2120 m (C&tbond;CH); 1250 s, 845 s, 755 w (Si-C). ^1H NMR: (CCl_4, δ ppm): 0.11 (s, 9H, $SiMe_3$); 1.41 (d, *J* 2.5 Hz, 2H, CH_2); 1.66 (t, *J* 2.5 Hz, 1H, CH).[1-4]

Solubility: sol ether, THF, CH_2Cl_2.

Form Supplied in: colorless liquid, commercially available.

Analysis of Reagent Purity: IR and NMR.

Preparative Methods: the main method of preparation is shown in eq 1.[1-3] The title reagent can be obtained by other methods,[4] but in poor yields.

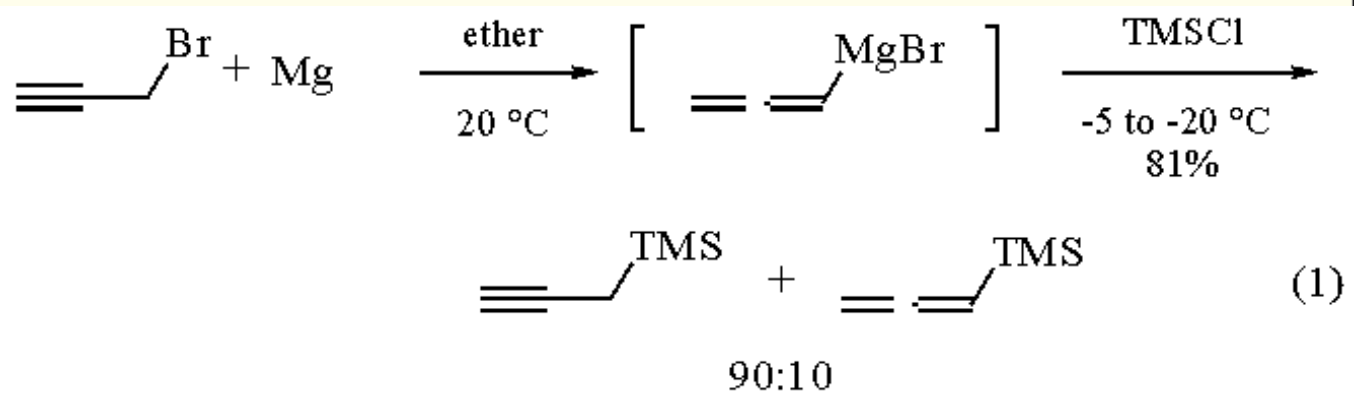

(1)

Purification: by distillation.

Handling, Storage, and Precautions: usually stored in a refrigerator. The reagent should be handled in a well-ventilated hood.

Reactivity.

3-Trimethylsilyl-1-propyne is the simplest of the propargylic silanes, which are convenient reagents in organic synthesis.[5,6]

Propargylation Reactions.

3-Trimethylsilyl-1-propyne is metalated easily by using an organomagnesium or a lithium compound, leading to the corresponding alkynic organometallic reagent which can react with many electrophiles.

Alkylation Reactions.[7-9]

These reactions may be obtained with various halides, a number of them having other functionalities (eqs 2 and 3).

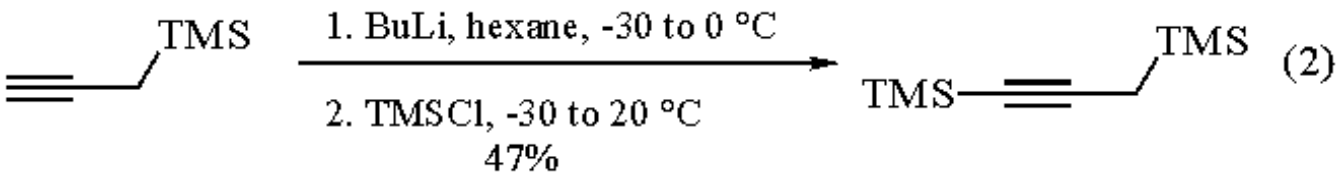

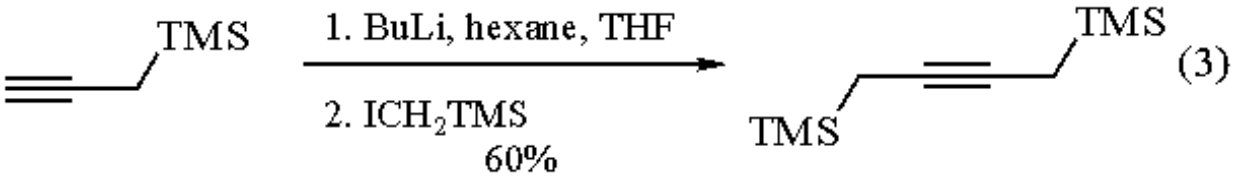

Reactions with Epoxides.[10,11]

These reactions allow preparation of β-alkynic alcohols (eq 4); the use of ***n-Butyllithium***, followed by ***Diethylaluminum Chloride***, may increase the yield.

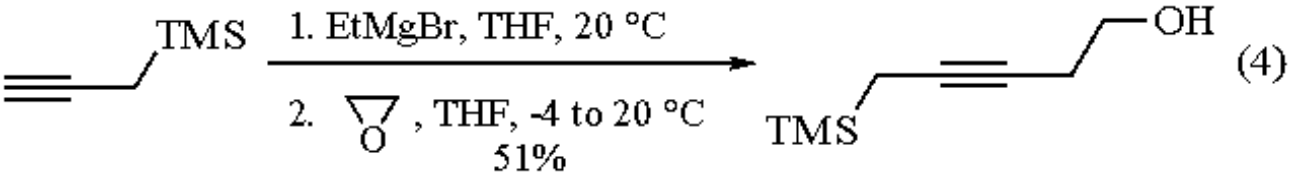

Reactions with Aldehydes and Ketones.[12-16]

These are exemplified by eqs 5 and 6. Under the conditions of eq 6, the major product results from further reaction between the initial alcoholate and the excess ***Formaldehyde***. Secondary and tertiary alcohols are also obtained easily (eq 7). The yields are best when *n*-BuLi is used as the base and when HMPA is used as a cosolvent in the reaction with the ketone.

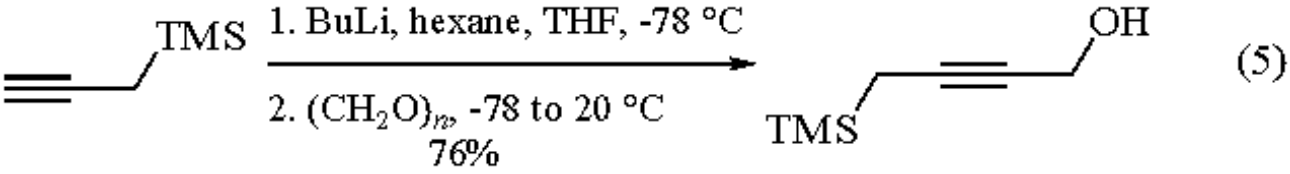

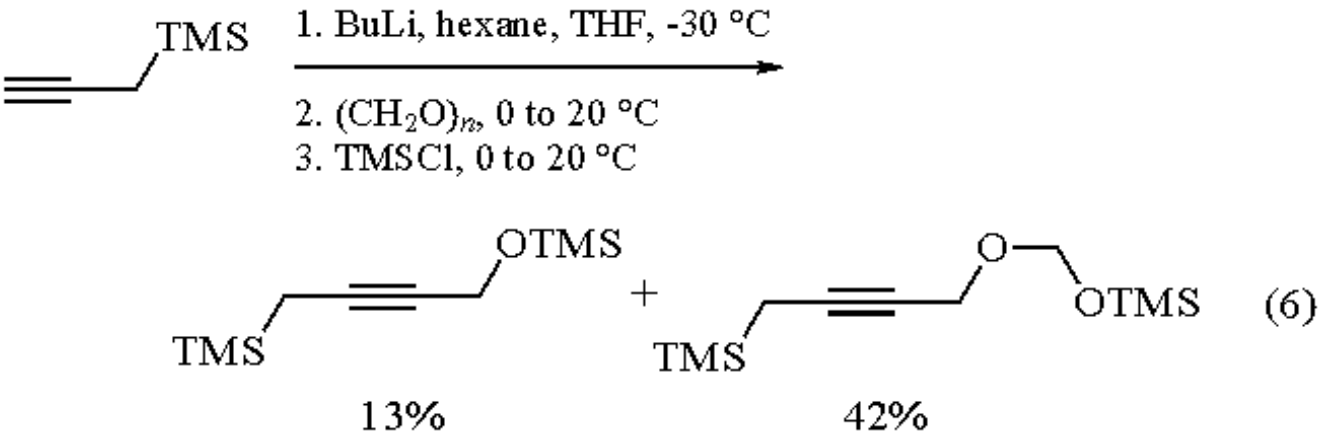

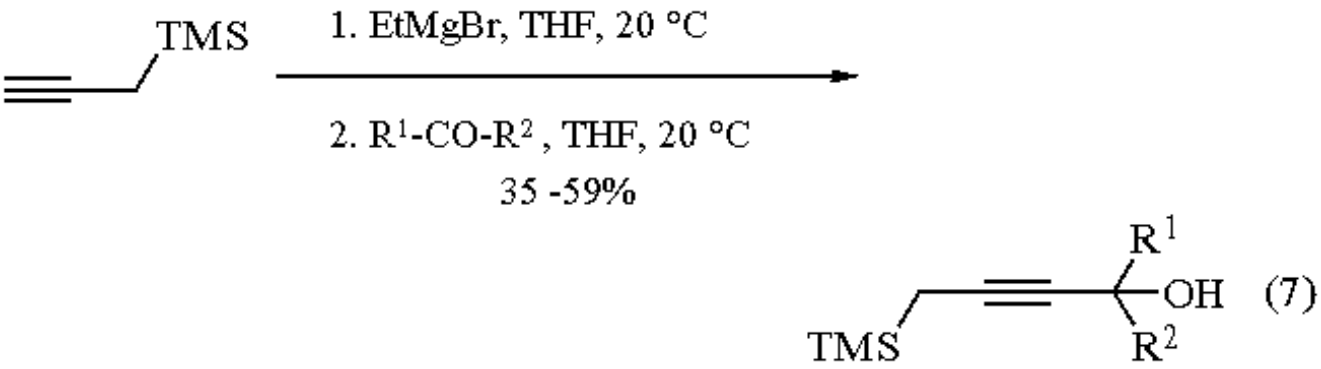

Reactions with Chloroformates.[17]

These are exemplified by eq 8.

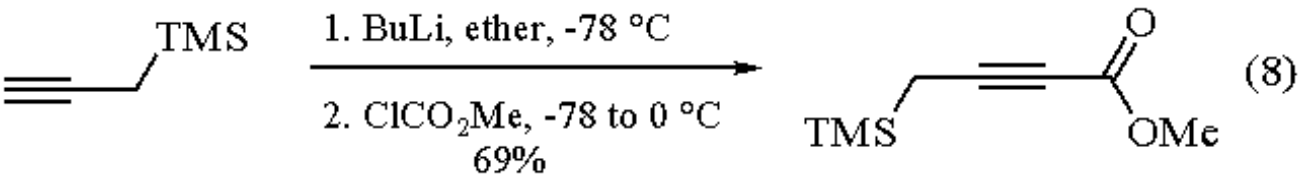

Reactions with Polyoxymethylene and Amines[13] (Mannich Reaction).

These are exemplified by eq 9.

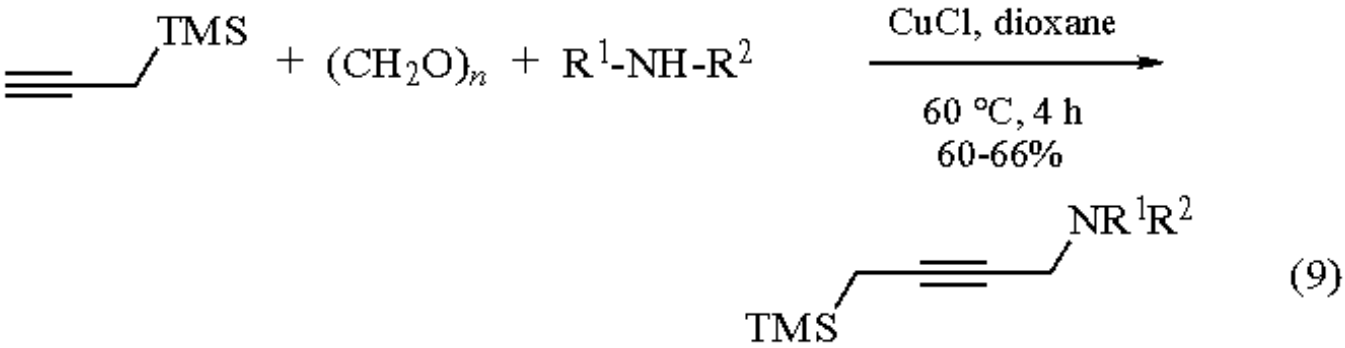

Allenylation Reactions.

The propargyltrimethylsilanes undergo Lewis acid-catalyzed reactions with electrophiles, with regiospecific rearrangement, to give substituted allenes eq (10)[18-21]. The catalysts usually employed are ***Aluminum Chloride***, ***Boron Trifluoride Etherate***, and ***Titanium(IV) Chloride***.

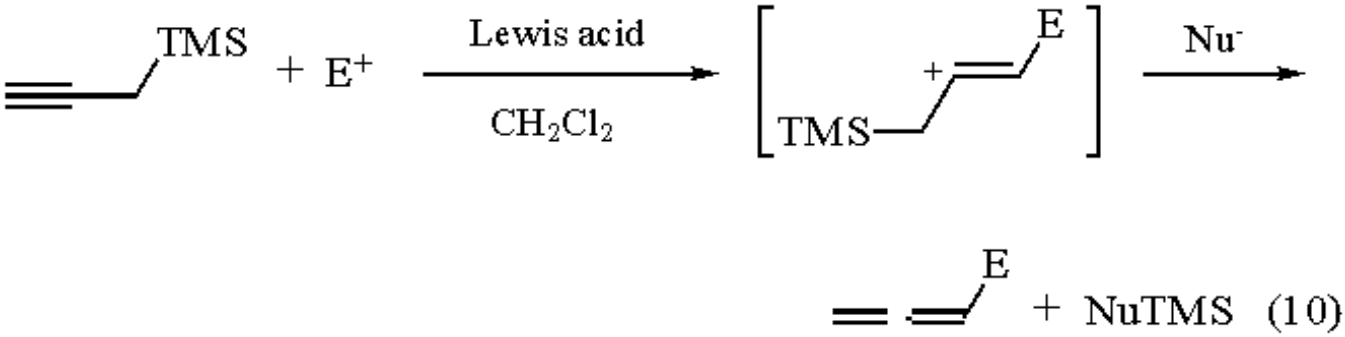

Substitution Reactions.

Few examples have been described. Generally, the reaction occurs with regiospecific rearrangement. Substitution of halides[18] is shown in eq 11, and of OH, $OSiMe_3$, and OCOR groups[19,20] in eq 12.

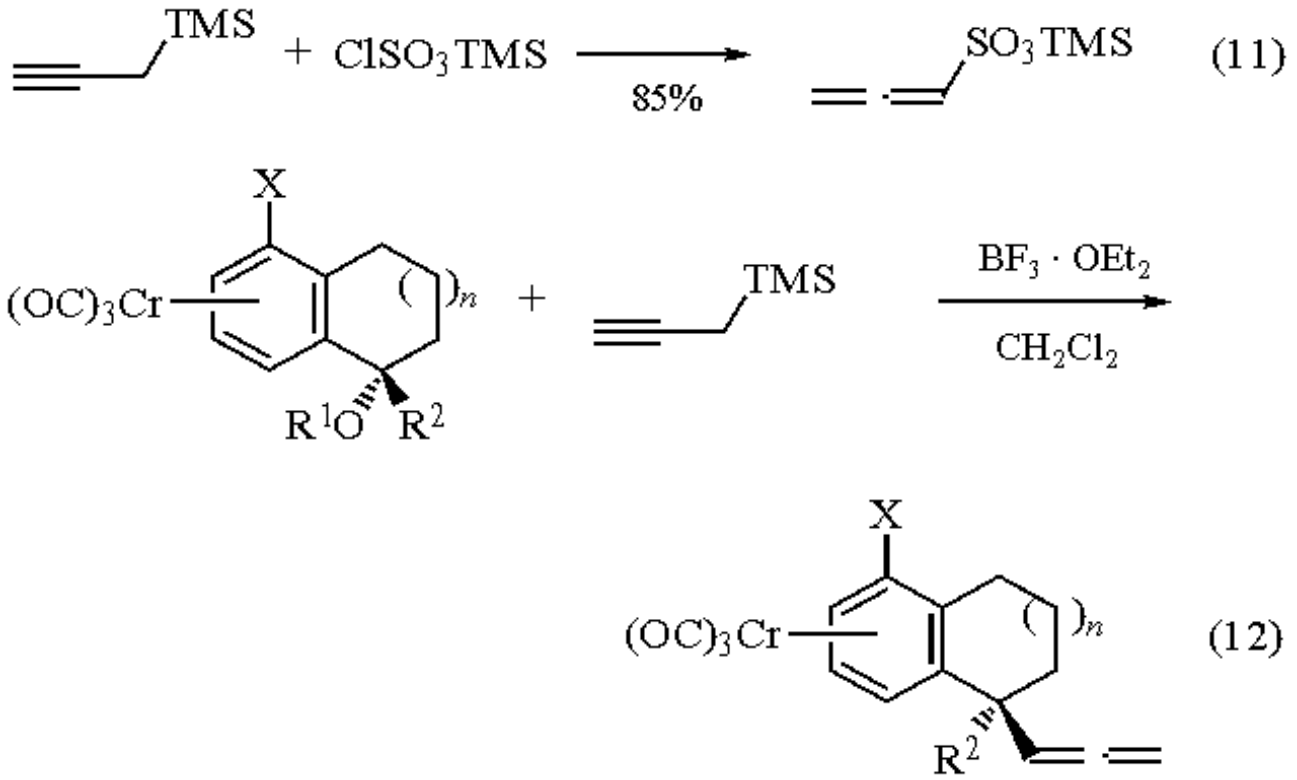

Ortho-propynyliodoarenes are obtained by reductive iodono-Claisen rearrangement of allenyliodinanes (eq 13).[21] When both *ortho* positions and the *para* position of aryliodinanes are occupied, *ipso*-propynylarenes are formed (eq 14).

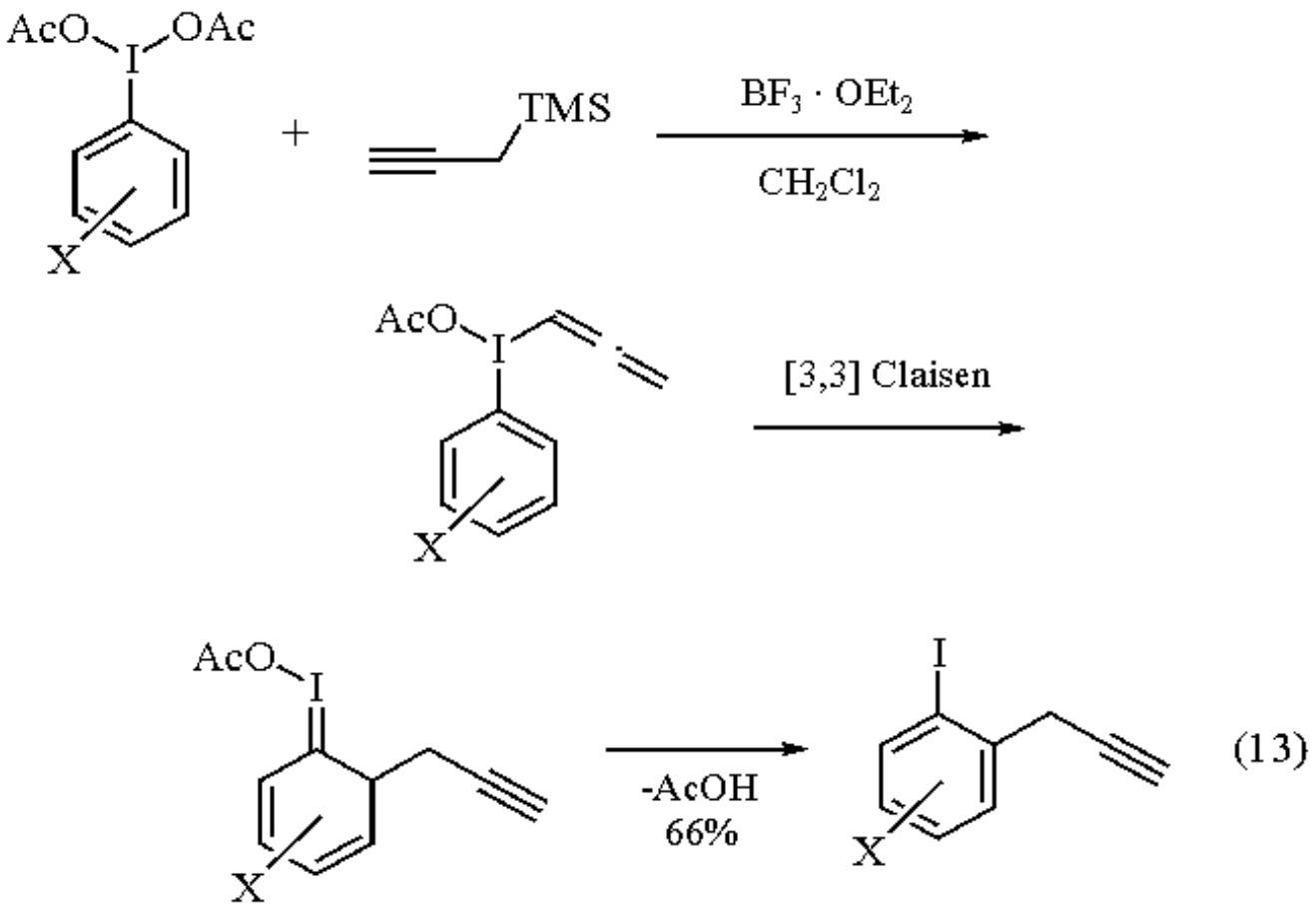

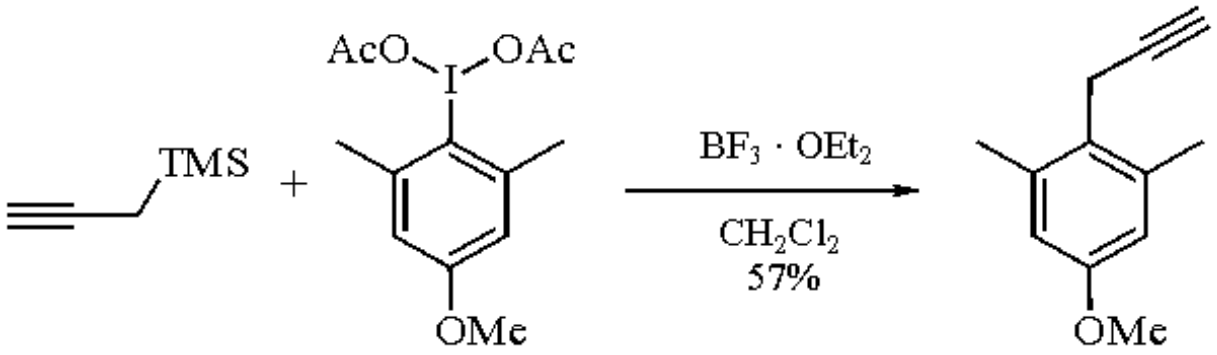

(14)

Reactions with Acetals[22,23] and Hemiacetals.[24-26]

These are exemplified by eqs 15 and 16. The synthesis of *C*-glycosides bearing an allenyl group has been accomplished[25,26] by use of 3-trimethylsilyl-1-propyne.

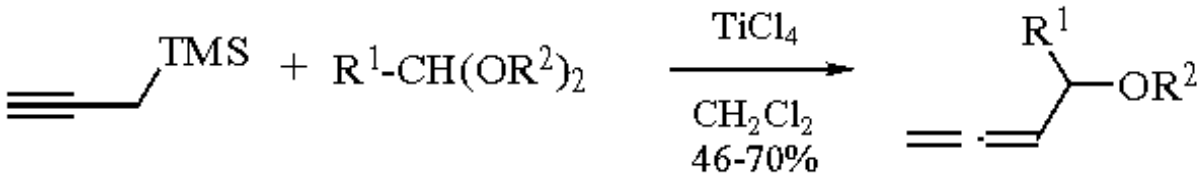

(15)

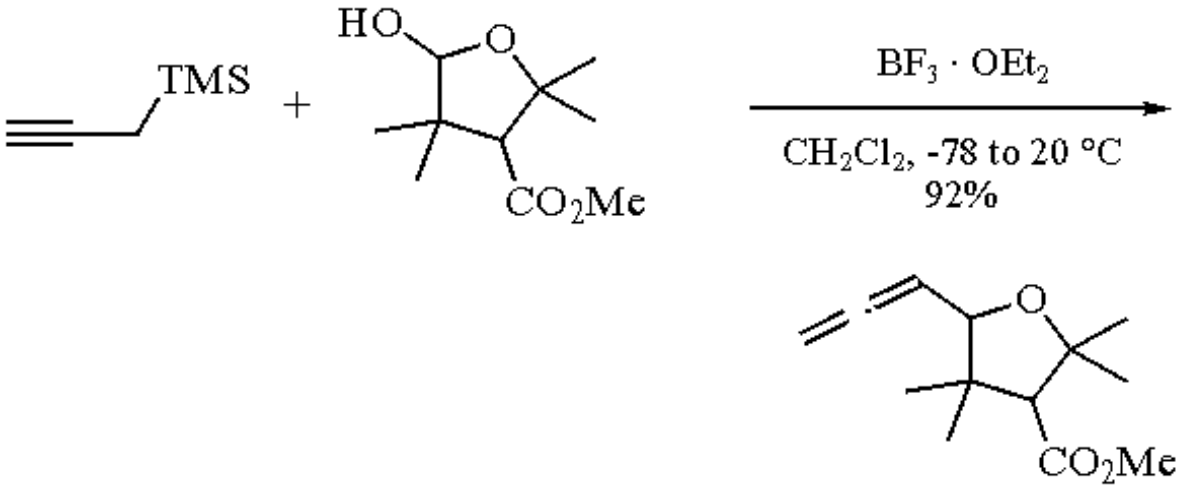

(16)

Reactions with Aldehydes and Ketones.[22,27-29]

These reactions generally lead to α-allenyl alcohols (eq 17). With titanium(IV) chloride as catalyst, the major product is a chloroprenic derivative formed from the α-allenyl *O*-silylated alcohol (eq 18).[22] The yields are good with aliphatic aldehydes bearing a primary or a secondary group and with activated ketones; they are poorer with aliphatic ketones (23-25%). With two equivalents of an aldehyde, the formation of a heterocyclic compound may be observed (eq 19).[28] By using ***Tetra-n-butylammonium Fluoride*** as catalyst, α-allenyl alcohols are easily obtained[29] with aliphatic and aromatic aldehydes (eq 20).

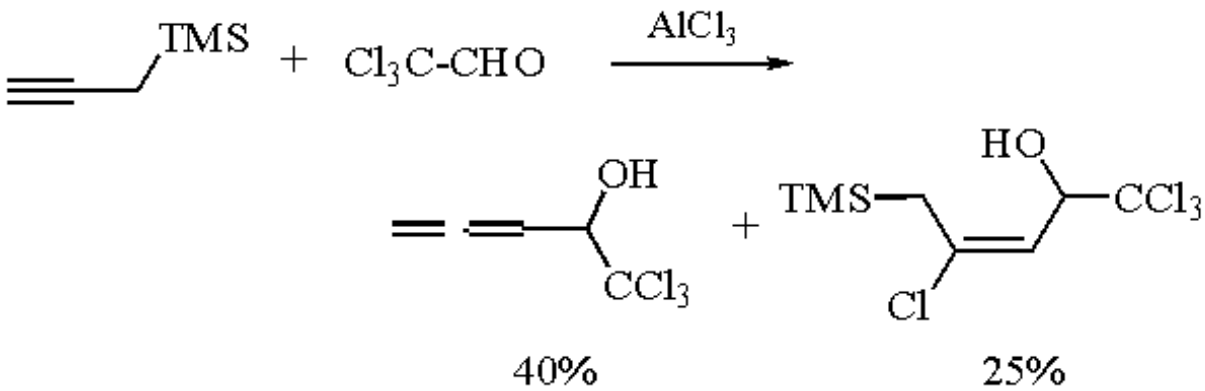

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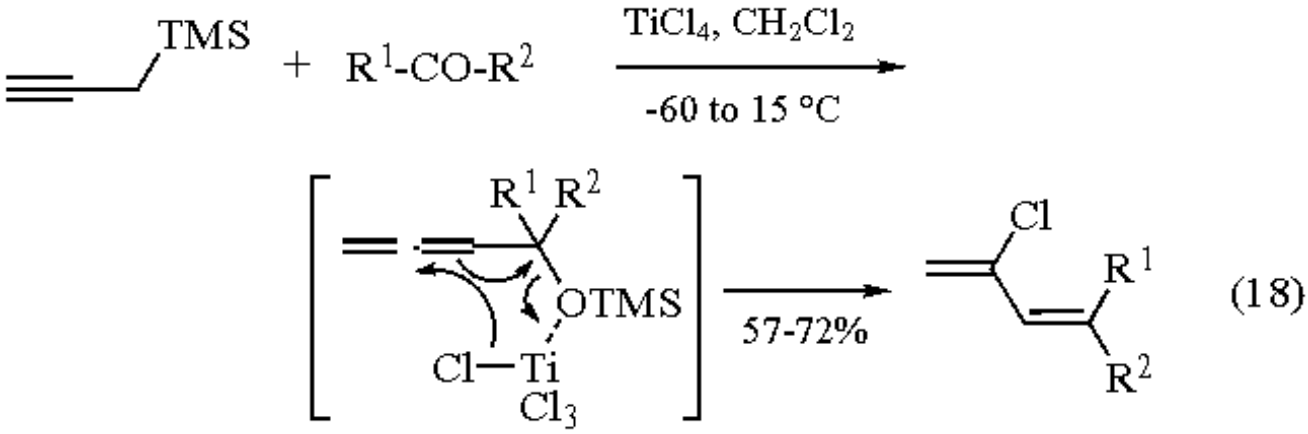

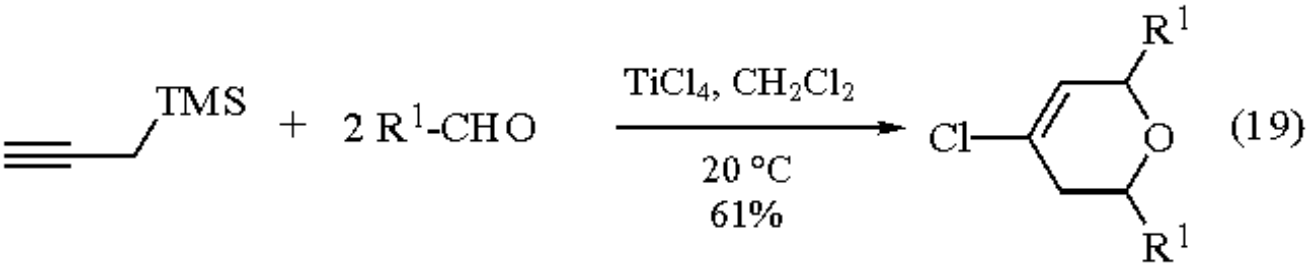

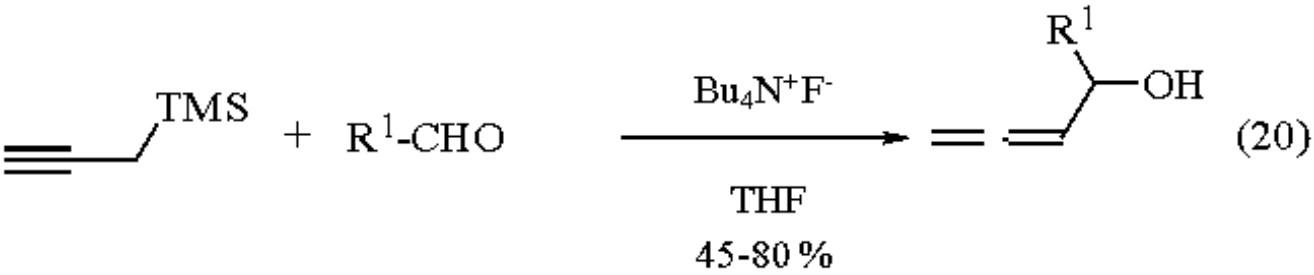

Reactions with in situ Generated Iminium and α-Acyl Iminium Ions.[30-32]

These reactions allow the preparation of α-allenyl amines and amides (eqs 21 and 22). The photoinduced addition reaction leads to a mixture of two products (eq 23).[32]

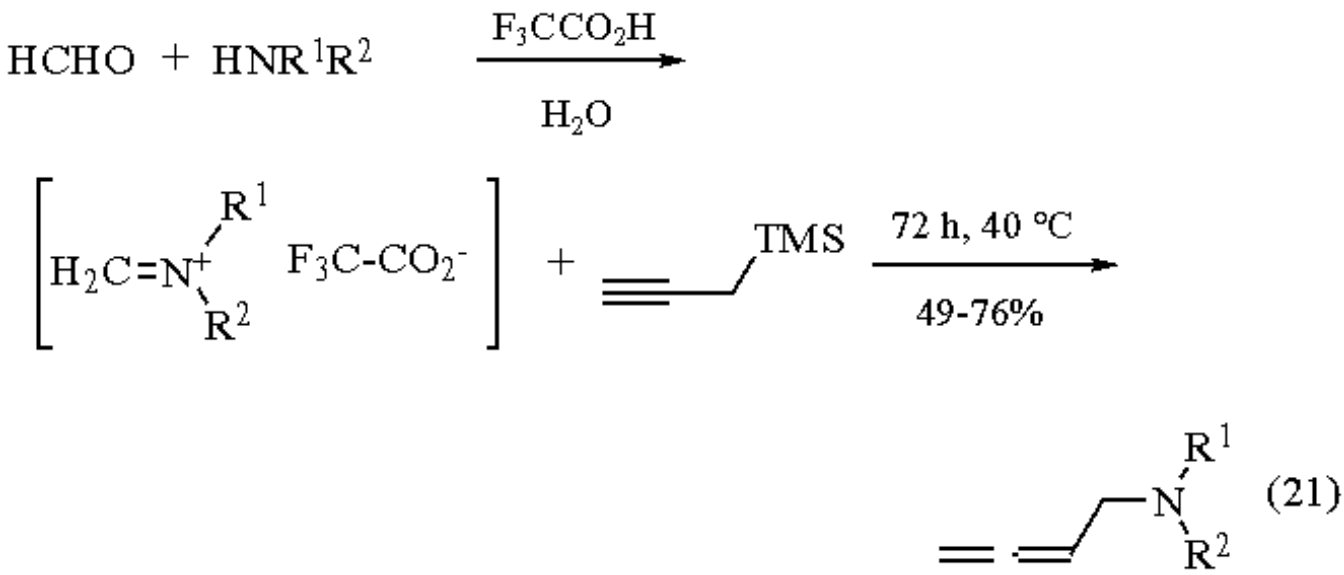

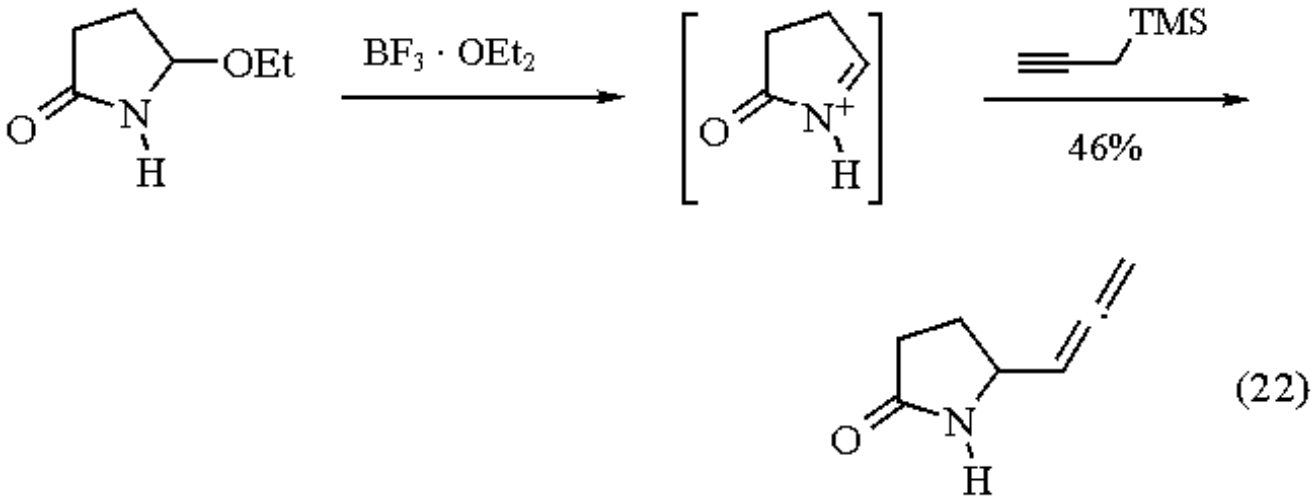

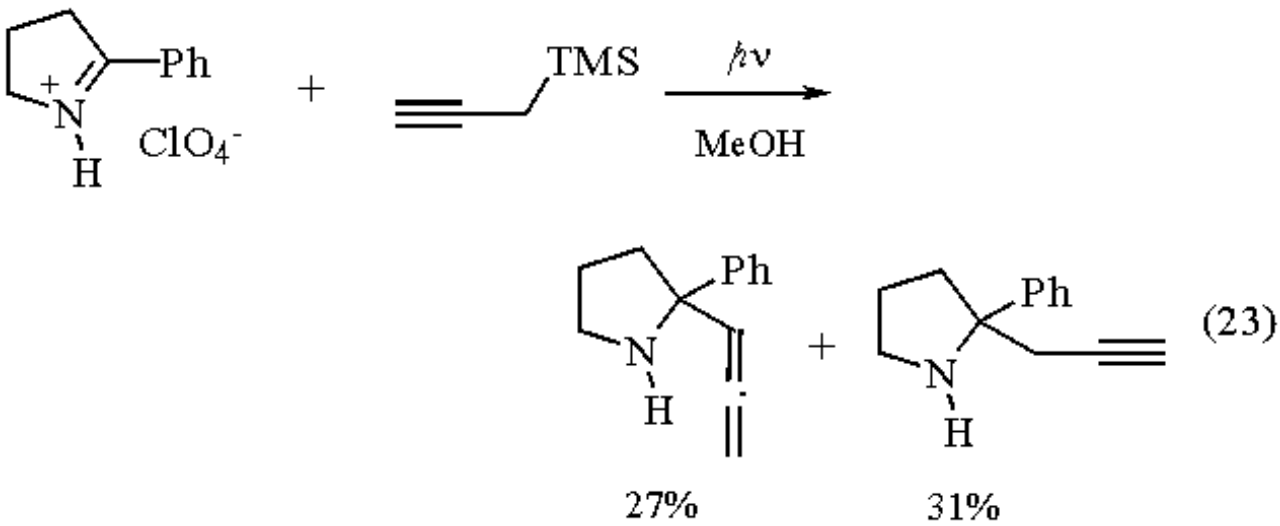

Reactions with Acid Chlorides.[33]

These reactions lead to α-allenyl ketones (eq 24).

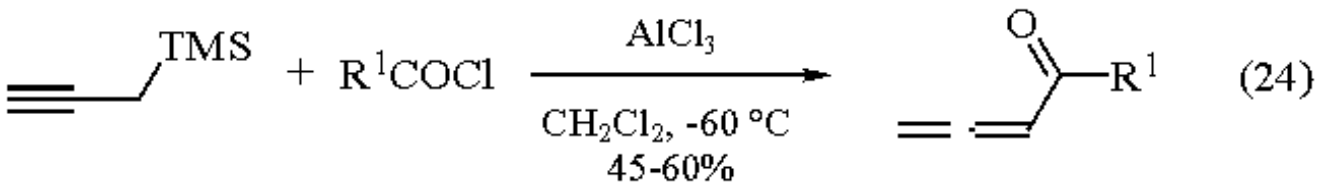

Reactions with Conjugated Heteroatomic Systems.[3a,34]

3-Trimethylsilyl-1-propyne seems unable to undergo 1,4-addition to monofunctional conjugated carbonyl derivatives such as R´CH=CH-CO-R´´, R´CH=CH-CO_2R´´, or R´CH=CH-CN, but readily undergoes 1,4-addition reactions with alkylidenemalonates and analogs (eq 25)[3a] and with conjugated acyl cyanides (eq 26).[34] Similar results are obtained with alkylideneacetylacetates and -cyanoacetates (45-65%).[3a]

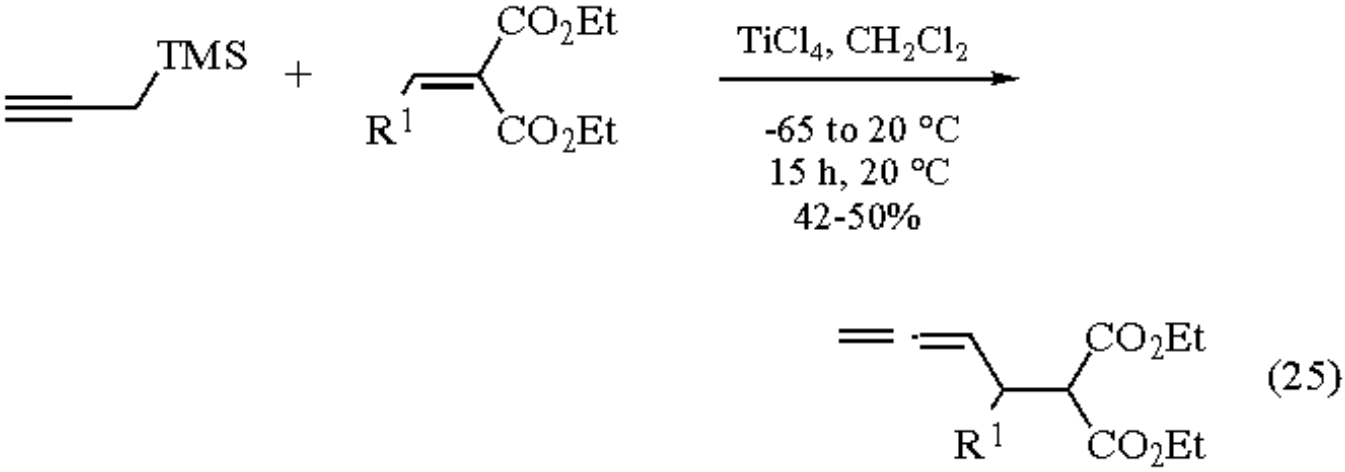

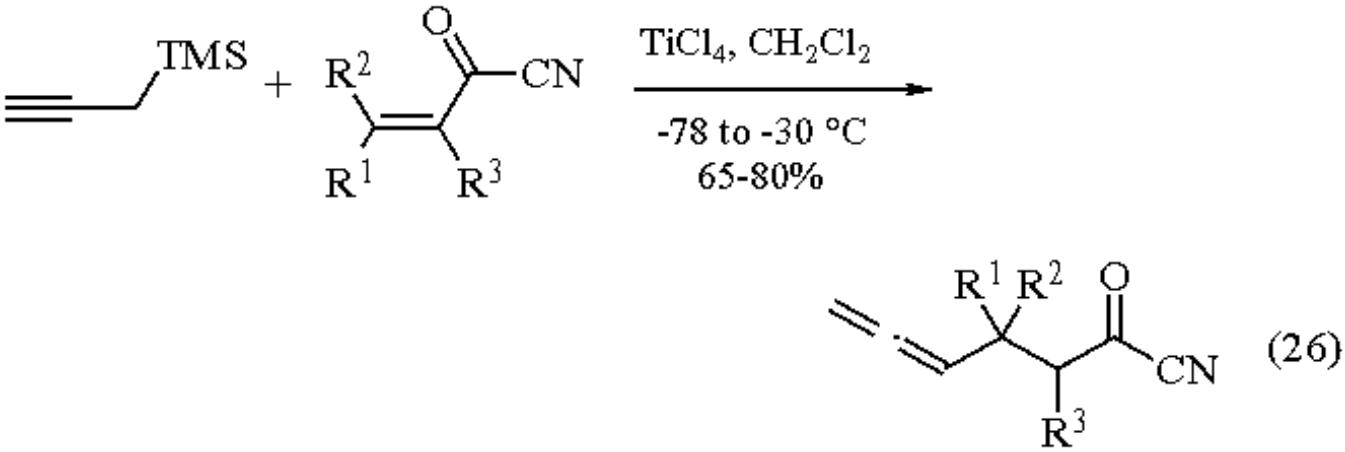

Reactions of the Triple Bond.

Preparation of Complexes with Transition Metals.[5b,35]

3-Trimethylsilyl-1-propyne reacts with ***Octacarbonyldicobalt*** to give the complex shown in eq 27.[35] This complex can react with alkenes to lead to 2-trimethylsilylmethylcyclopentenones (28-30%).

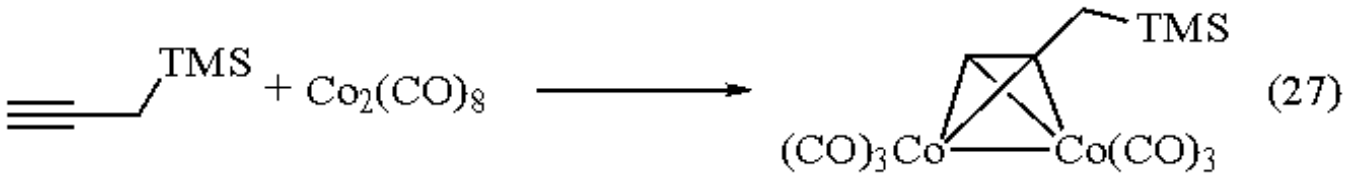

Preparation of a Bis-silylated Conjugated Enyne.[36]

This is shown in eq 28.

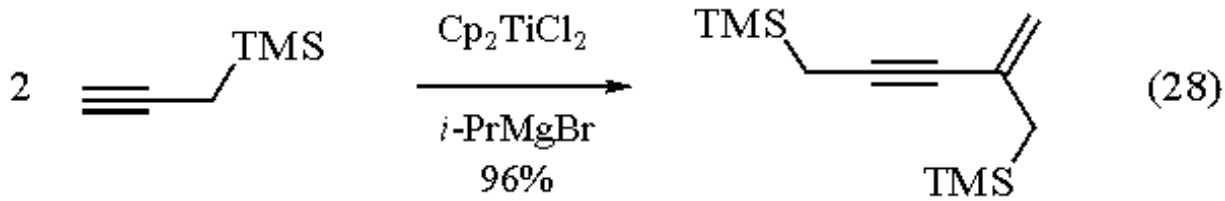

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(Trimethylsilyl)allene.

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18. Bourgeois, P.; Mérault, G. *CR(C)* **1971**, *273*, 714.
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20. Uemura, M.; Kobayashi, T.; Hayashi, Y. *S* **1986**, 386.
21. (a) Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y. *JACS* **1991**, *113*, 1319. (b) Ochiai, M.; Ito, T.; Masaki, Y. *CC* **1992**, 15. (c) Ochiai, M.; Ito, T.; Shiro, M. *CC* **1993**, 218.
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36. Akita, M.; Yasuda, H.; Nakamura, A. *BCJ* **1984**, *57*, 480.

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3-Trimethylsilyl-2-propynylcopper(I)[1]

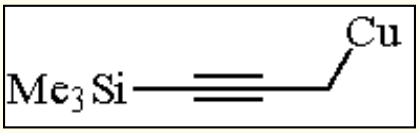

[55630-32-5] · $C_6H_{11}CuSi$ · 3-Trimethylsilyl-2-propynylcopper(I) · (MW 174.81)

(agent for the introduction of the trimethylsilylpropynyl group via 1,6-conjugate additions[2] and vinyl substitutions;[3] preparation of lithium bis(trimethylsilylpropynyl)cuprate[4])

Alternate Name: trimethylsilylpropargylcopper

Physical Data: brown heterogenous solution in ether.

Solubility: sol pyridine, THF; slightly sol ether.

Analysis of Reagent Purity: addition of aqueous ammonium chloride gives >95% conversion to 1-trimethylsilylpropyne.[2]

Preparative Method: a solution of ***1-Lithio-3-trimethylsilyl-1-propyne*** containing ***N,N,N´,N´-Tetramethylethylenediamine*** (TMEDA) in ether[2] or THF is added to a slurry of ***Copper(I) Iodide*** in ether at -78 °C, then warmed to -10 °C and used immediately.[3]

Handling, Storage, and Precautions: dry copper(I) acetylides are potentially explosive. Use in a fume hood.

Coupling Reactions.

Trimethylsilylpropynylcopper adds to conjugated esters in a 1,6-manner if facilitated, giving mixtures of products dependent on the nature of the system.[2] Addition to an unsubstituted (*E*)-dienoic ester gave an 8:2 mixture of allene:propynyl-substituted adducts (eq 1).

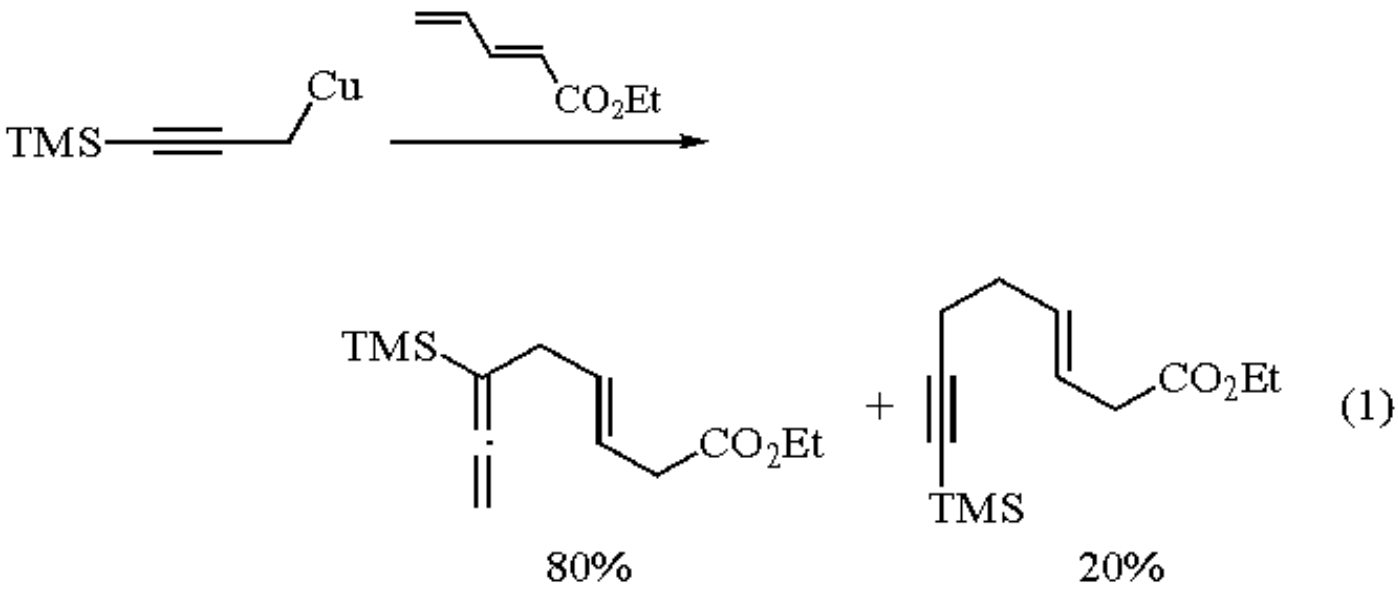

Best conversion yields (80%) are obtained by using 3.5 equiv of the copper reagent; use of 1.2 equiv results in a lower yield (42%) but an unaltered ratio.[2] If a δ-substituted dienoic ester is employed, the ratio reverses (eq 2), showing marked sensitivity to steric effects in this region;[2] for best conversion to products (70%), 3.5 equiv of copper reagent are employed.[2]

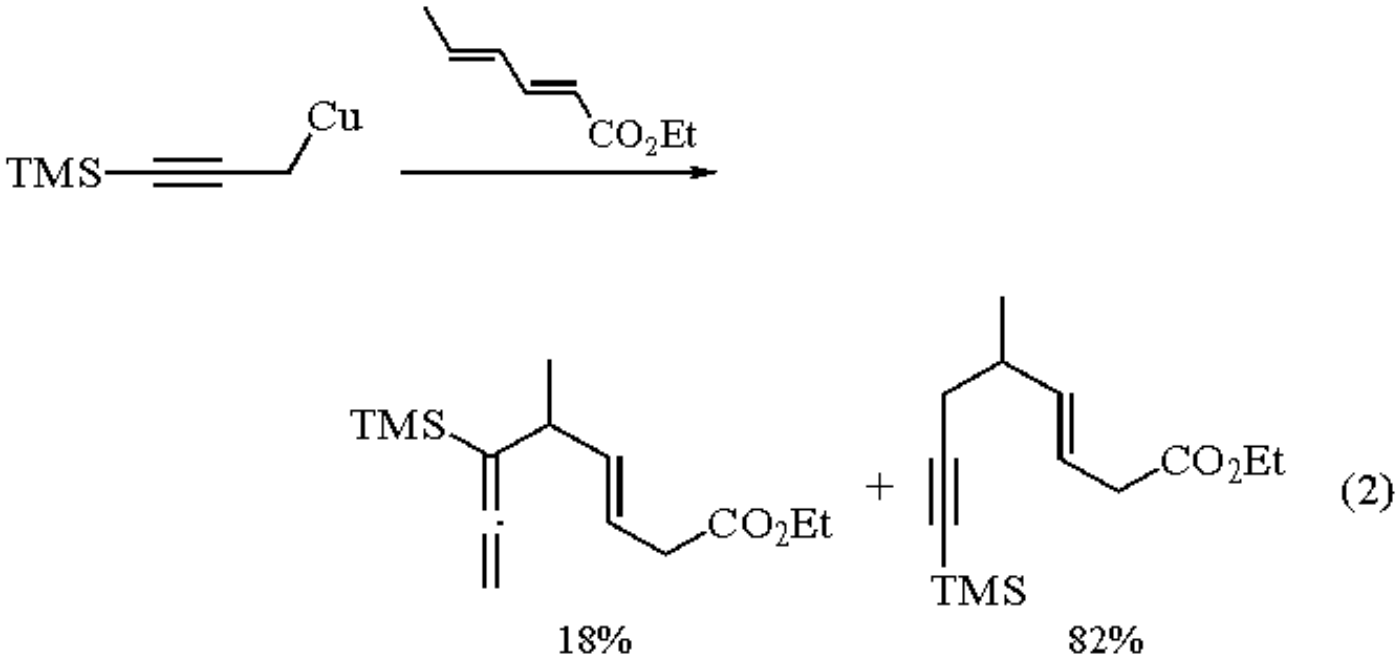

Finally, if a β,γ-disubstituted dienoic ester is used, selectivity reverses in favor of the allenic adduct (eq 3), pointing to the δ-carbon as the single most important dictator of steric control in this reaction (in this sequence, only 1.2 equiv of cuprate were employed, accounting for the low (35%) overall conversion to products). Results obtained using *t*-butyldimethylsilylpropynylcopper paralleled those indicated above. As expected, however, the ratios of products showed sensitivity towards this more sterically bulky coupling agent, with a 95:5 ratio of allene:alkyne products in the addition to the unsubstituted dienoate (eq 1) and a 97:3 ratio of alkyne:allene in the addition to the δ-substituted system (eq 2).[2] Vinyl substitution has been reported, using an iodohexene and 2 equiv of trimethylsilylpropynylcopper; the corresponding adduct was obtained in 80% yield (eq 4).[3] Using 1 equiv of copper acetylide, however, the yield drops to 63%. A mechanism has been proposed to account for this coupling, and is assumed to involve a four-centered transition state assembly.[3]

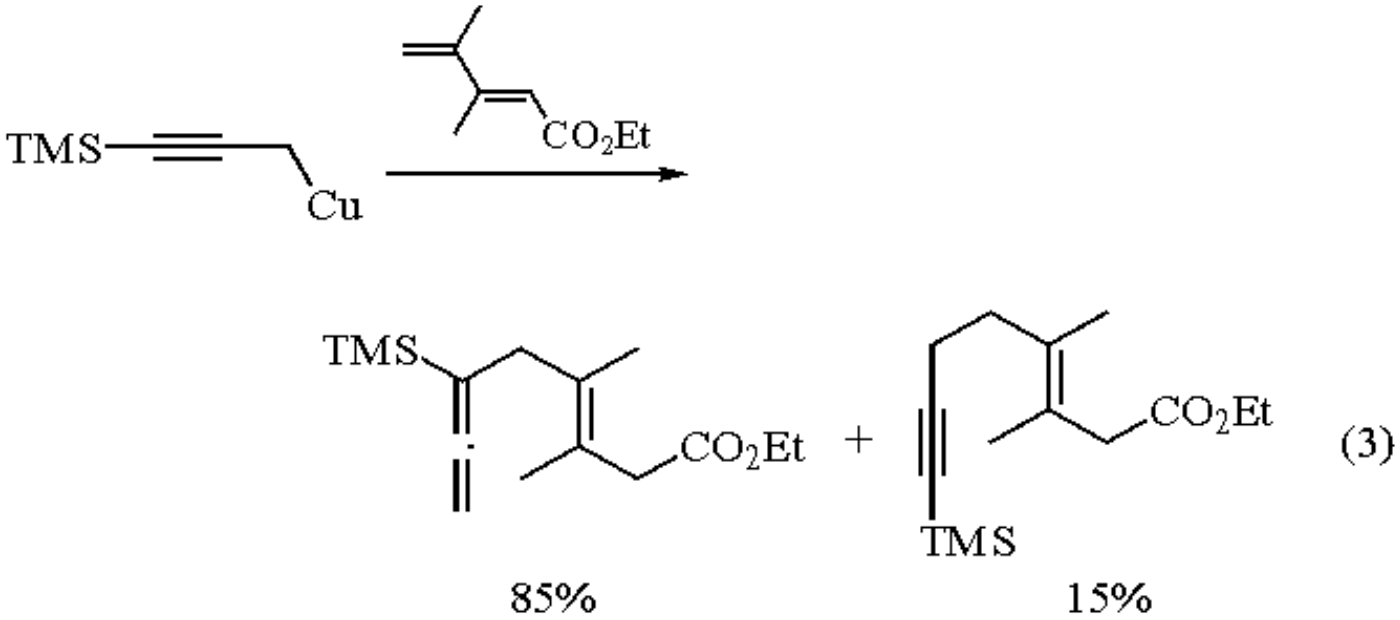

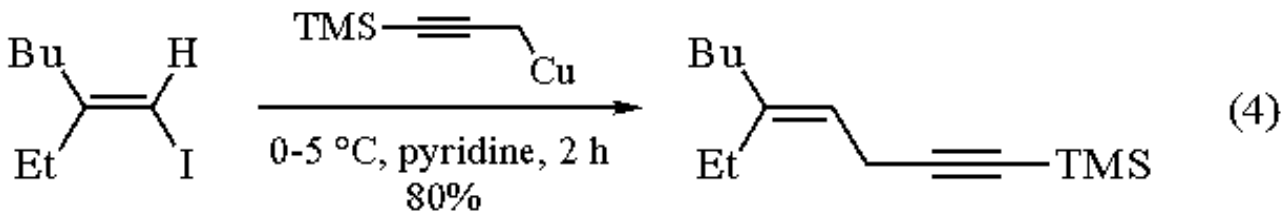

Lithioorganocuprates.

Lithium bis(trimethylsilylpropynyl)copper, prepared by addition of lithium trimethylsilylpropyne to copper(I) iodide, has been used as a nucleophilic source of the trimethylsilylpropynyl group (eq 5).[4] Chemoselective 1,2-addition resulted in a 90% isolated yield of the desired

secondary alkynyl alcohol (eq 5); use of the corresponding lithium or bromomagnesium acetylides resulted in substantial recovery of allenic products.[4]

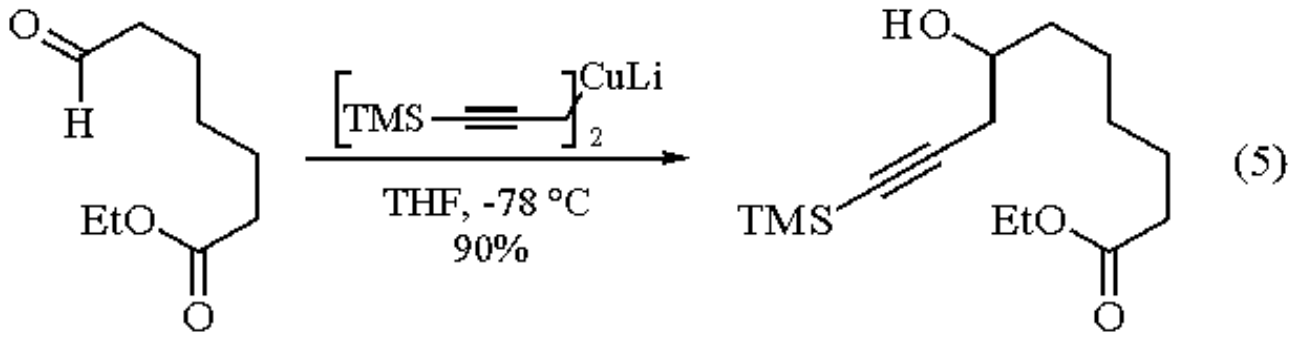

Related Reagents.

1-Hexynylcopper(I); ***1-Pentynylcopper(I)***; ***(Trimethylsilyl)ethynylcopper(I)***.

---

1. (a) Normant, J. F. *S* **1972**, 63. (b) Sladkov, A. M.; Gol'ding, I. R. *RCR* **1979**, *48*, 868. (c) Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135. (d) *FF* **1977**, *6*, 638.
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2-(Trimethylsilyl)thiazole[1]

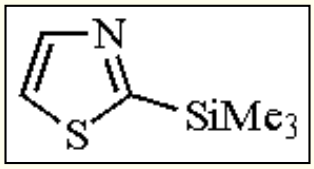

[79265-30-8] · $C_6H_{11}NSSi$ · 2-(Trimethylsilyl)thiazole · (MW 157.34)

(useful formyl anion equivalent;[1] effective one-carbon homologating reagent of alkoxy aldehydes, amino aldehydes, and dialdoses[2])

Physical Data: bp 51-53 °C/10 mmHg; *d* 0.992 g cm^{-3}; n_D 1.4980.

Solubility: insol H_2O; very sol CH_2Cl_2, diethyl ether, THF.

Form Supplied in: liquid; widely available.

Analysis of Reagent Purity: ^1H and ^{13}C NMR.

Purification: distillation under reduced pressure.

Preparative Method: although 2-(trimethylsilyl)thiazole (**1**) is commercially available, it can be easily prepared on a multigram scale from 2-bromothiazole, ***n-Butyllithium***, and ***Chlorotrimethylsilane*** as shown in eq 1.[3]

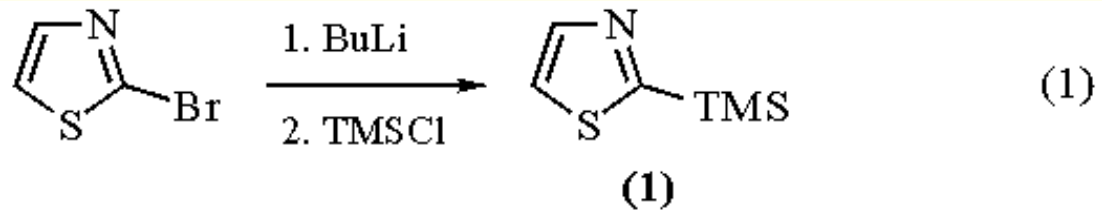

Handling, Storage, and Precautions: is stable upon storage under an inert atmosphere in a refrigerator. Nevertheless, it should be freshly distilled for best results. Irritating to the eyes, respiratory system, and skin. Wear suitable protective clothing, gloves and eye/face protection. Use in a fume hood.

General Discussion.

2-(Trimethylsilyl)thiazole (**1**) reacts with various C-electrophiles such as azolium halides (eq 2),[4] ketenes (eq 3),[5,6] acyl chlorides (eq 4),[6,7] ketones, and aldehydes (eq 5)[6-8] under mild conditions to give the corresponding 2-substituted thiazoles in very good isolated yields. No catalysts are required in these carbodesilylation reactions.

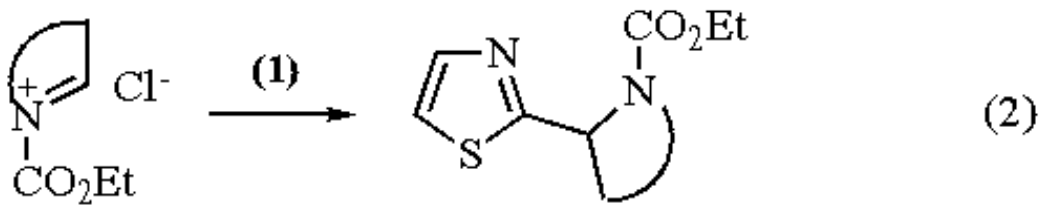

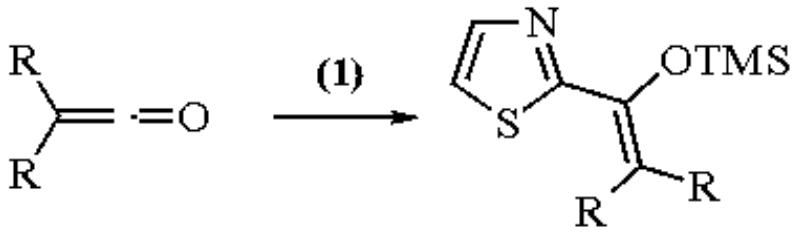

(3)

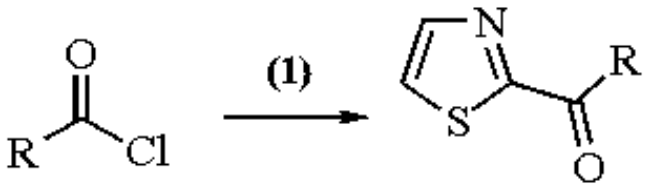

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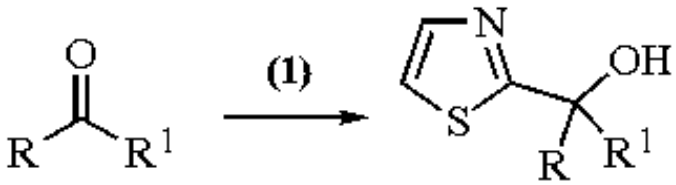

(5)

R = H, CF_3

The general mechanism via an *N*-thiazolium-2-ylide, earlier proposed for all these reactions,[6,7] has found substantial support in the identification of spirodioxolane intermediates in the reaction of (**1**) with aldehydes.[9]

The reaction of (**1**) with chiral alkoxy aldehydes led to the discovery of a new methodology for the one-carbon chain elongation of these compounds.[2a,b] The methodology proved to be capable of iteration and therefore suitable for the stereoselective synthesis of polyalkoxy aldehydes (carbohydrate-like materials).

The homologation of D-glyceraldehyde acetonide (**2**) serves to illustrate the method.[3] This consists of two sequential operations: first, addition of 2-(trimethylsilyl)thiazole (**1**) to the aldehyde (**2**) followed by in situ desilylation and protection as the *O*-benzyl derivative (**3**) (eq 6); secondly, aldehyde release in the resultant adduct[10] by a three-step sequence involving methylation of the thiazole ring to the *N*-methylthiazolium salt; reduction to thiazolidine; hydrolysis to α-benzyloxy aldehyde (**4**) (eq 7).

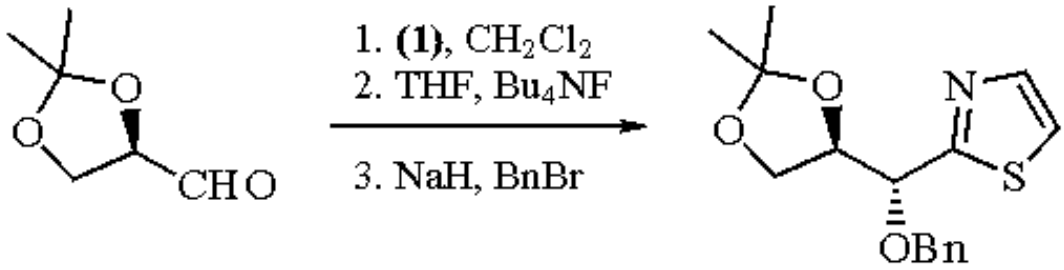

(6)

(2)

(3)

ds [3] 95%

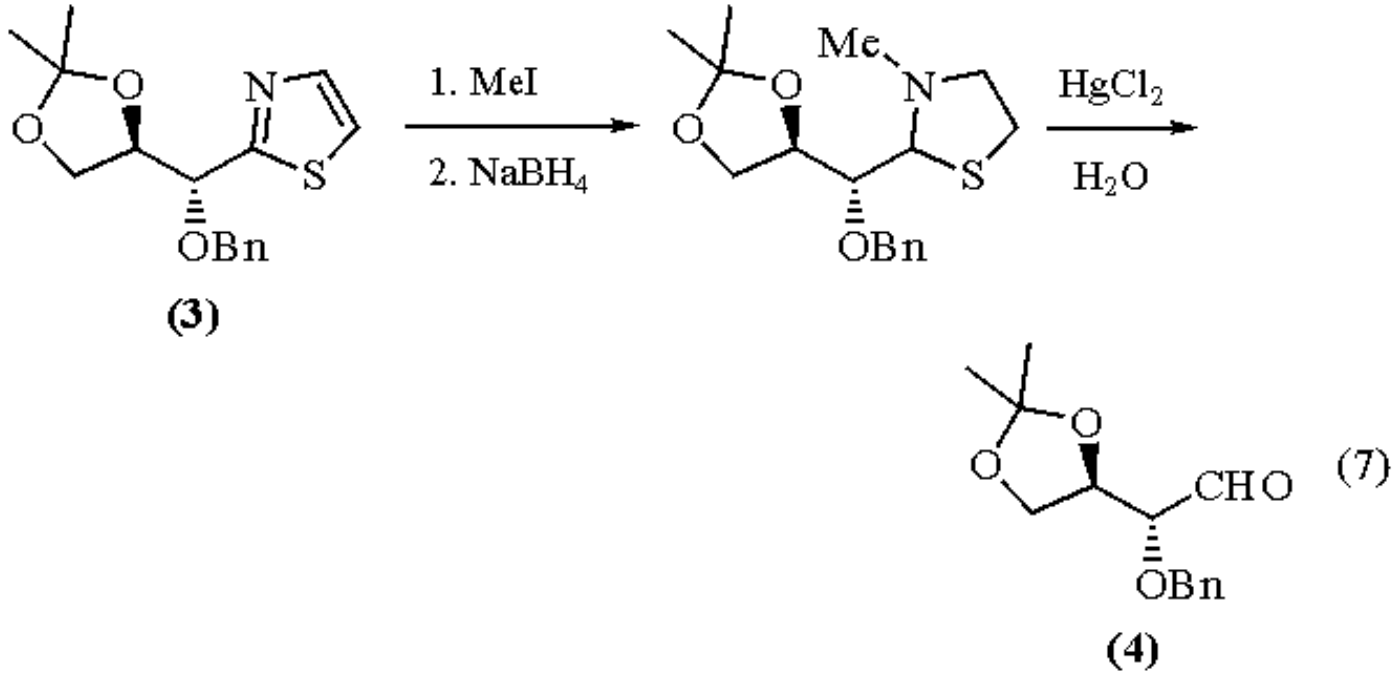

Hence, (**1**) serves as a synthetic equivalent for the formyl anion synthon which adds to the aldehyde in a stereoselective manner, creating a new chiral hydroxymethylene center. The repetition of the first and second operational sequences above over six consecutive cycles with high levels of diastereoselectivity and chemical yields in each cycle provided a series of protected D-aldoses[2c] having up to nine carbons in the chain (eq 8).

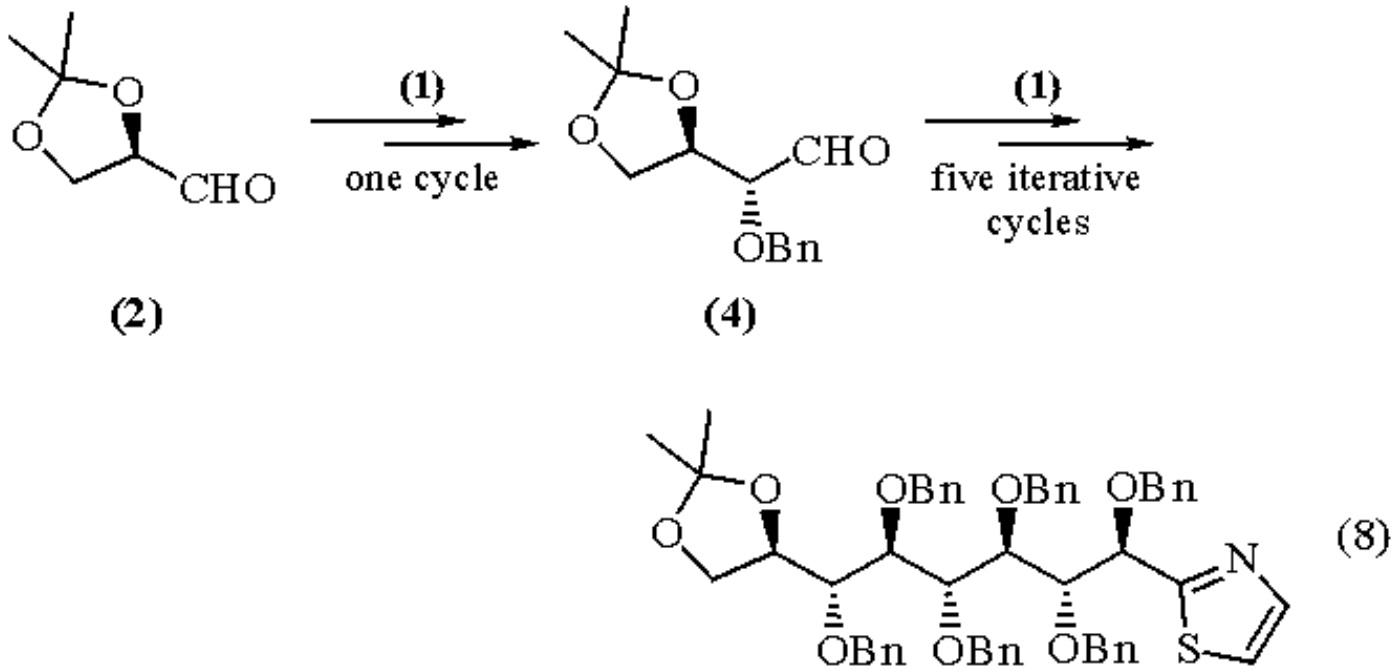

The utility of this approach to long-chain sugars (thiazole route to carbohydrates) is illustrated by the conversion of protected L-threose (**5**) and dialdogalactopyranose (**6**) into higher homologs (eqs 9 and 10).[2c,d] The extension of this methodology to other dialdoses has been reported.[11]

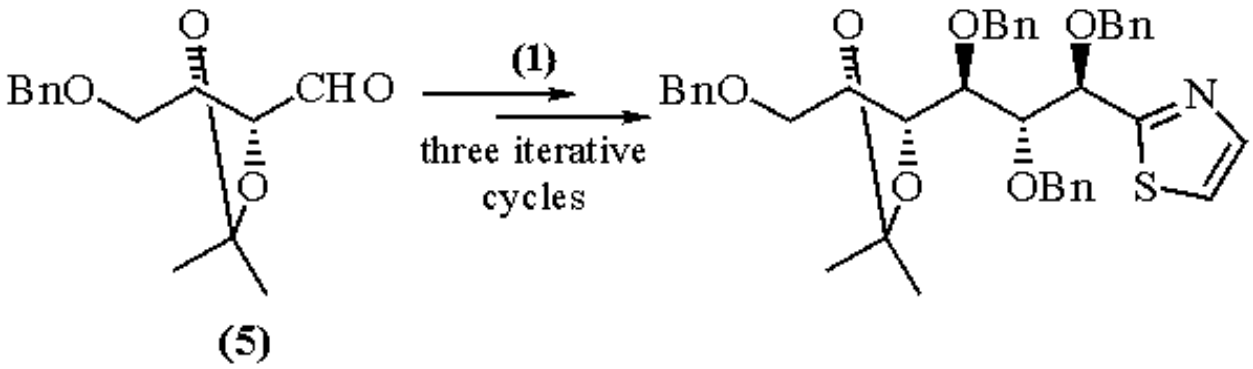

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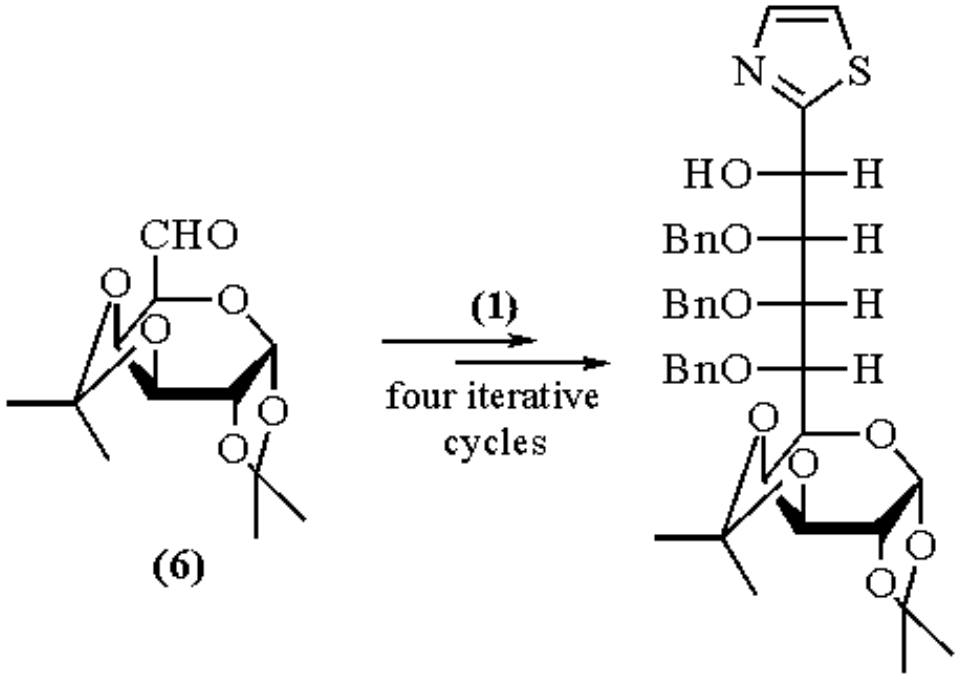

(10)

This technique, in combination with an inversion of configuration of the carbon adjacent to the thiazole ring, has been employed[2e] for the chain extension of D-glyceraldehyde acetonide (**2**) into all possible tetrose and pentose homologs (eq 11).

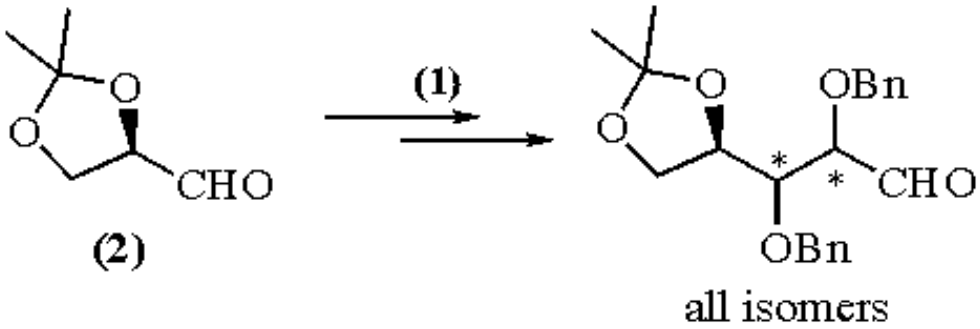

(11)

The 2-(trimethylsilyl)thiazole-based one-carbon extension strategy was also used for the construction of amino tetroses as well as amino pentoses[12] using α-amino aldehydes as chiral educts. An interesting finding was that the reactions of (**1**) with the *N*-diprotected α-amino aldehydes were *anti* selective (eq 12), whereas those with the *N*-monoprotected α-amino aldehydes were *syn* selective (eq 13).

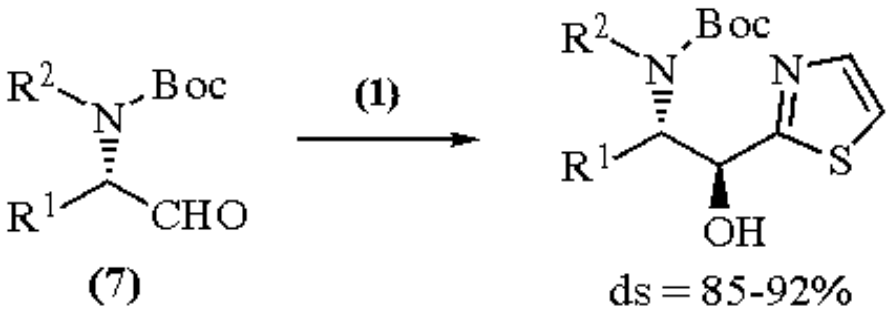

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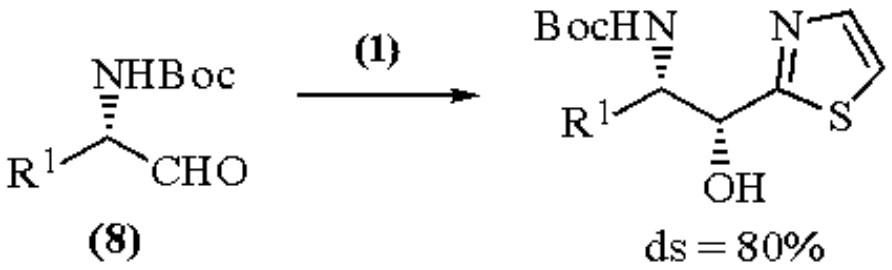

(13)

These opposite diastereoselectivities were explained by assuming a Felkin-Anh-Houk model (*anti* addition) and a proton-bridged Cram cyclic model (*syn* addition) for the case of differentially protected α-amino aldehydes (**7**) and (**8**). The resulting 1,2-amino alcohols proved to be convenient precursors to L-amino sugars and sphingosines.[12]

This strategy has been also employed for the synthesis of a dipeptide mimic,[13] as illustrated in eq 14.

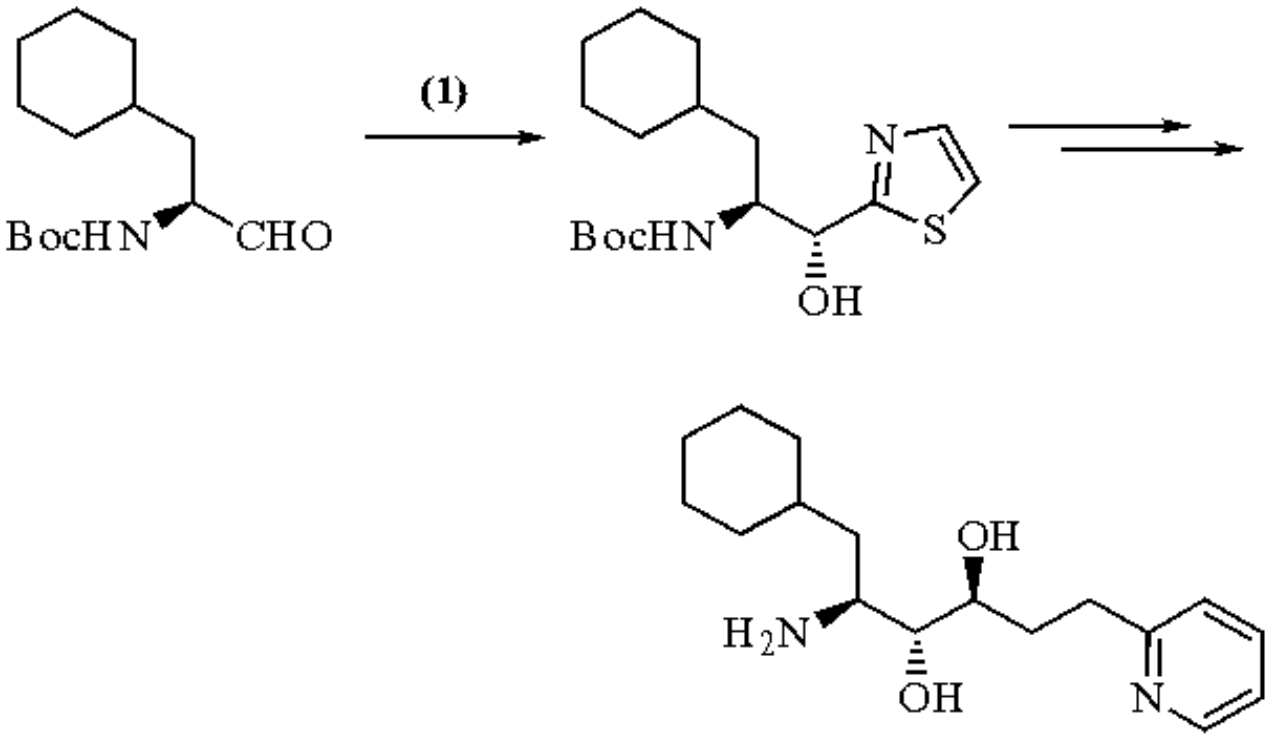

(14)

In summary, 2-(trimethylsilyl)thiazole (**1**) appears to be a useful formyl anion equivalent.[14] The advantages over other precursors to the formyl anion (see ***Benzothiazole***) can be found in the stability of the thiazole ring to a wide range of reaction conditions and its ready conversion into the formyl group under mild and neutral conditions. Few of the many formyl anion equivalents[14] have been demonstrated to be capable of producing labile α-alkoxy aldehydes without racemization.

Related Reagents.

(4aR)-(4aα,7α,8aβ)-Hexahydro-4,4,7-trimethyl-4H-1,3-benzoxathiin; ***2-Lithio-1,3-dithiane***; ***1,1,3,3-Tetramethylbutyl Isocyanide***.

---

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2. (a) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *TL* **1985**, *26*, 5477. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *AG(E)* **1986**, *25*, 835. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *JOC* **1989**, *54*, 693. (d) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *T* **1987**, *43*, 3533. (e) Dondoni, A.; Orduna, J.; Merino, P. *S* **1992**, 201.
3. Dondoni, A.; Merino, P. *OS* **1993**, *72*, 21.
4. Dondoni, A.; Dall'Occo, T.; Galliani, G.; Mastellari, A.; Medici, A. *TL* **1984**, *25*, 3637.
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6. Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *JOC* **1988**, *53*, 1748.
7. Medici, A.; Fantin, G.; Fogagnolo, M.; Dondoni, A. *TL* **1983**, *24*, 2901.
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9. Dondoni, A.; Douglas, A. W.; Shinkai, I. *JOC* **1993**, *58*, 3196.
10. For a modification of the original procedure, see: Dondoni, A.; Marra, A.; Perrone, D. *JOC* **1993**, *58*, 275.
11. (a) Maillard, Ph.; Huel, C.; Momenteau, M. *TL* **1992**, *33*, 8081. (b) Khare, N. K.; Sood, R. K.; Aspinall, G. O. *CJC* **1994**, *72*, 237.
12. (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *CC* **1988**, 10. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *JOC* **1990**, *55*, 1439.
13. Wagner, A.; Mollath, M. *TL* **1993**, *34*, 619.
14. (a) Dondoni, A.; Colombo, L. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni A., Ed.; JAI Press: London, 1993: (b) Ager, D. J. In *Umpoled Synthons*; Hase, T. A.; Ed.; Wiley: New York, 1987; Chapter 2.

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Trimethylsilyl Trifluoromethanesulfonate[1]

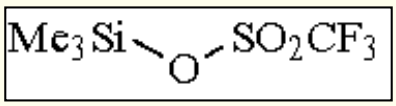

[88248-68-4; 27607-77-8] · $C_4H_9F_3O_3SSi$ · Trimethylsilyl Trifluoromethanesulfonate · (MW 222.29)

Alternate Name: TMSOTf.

Physical Data: bp 45-47 °C/17 mmHg, 39-40 °C/12mmHg; *d* 1.225 g cm^{-3}.

Solubility: sol aliphatic and aromatic hydrocarbons, haloalkanes, ethers.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: may be prepared by a variety of methods.[2]

Handling, Storage, and Precautions: flammable; corrosive; very hygroscopic.

Silylation.

TMSOTf is widely used in the conversion of carbonyl compounds to their enol ethers. The conversion is some 10^9 faster with TMSOTf/***Triethylamine*** than with ***Chlorotrimethylsilane*** (eqs 1-3).[3-5]

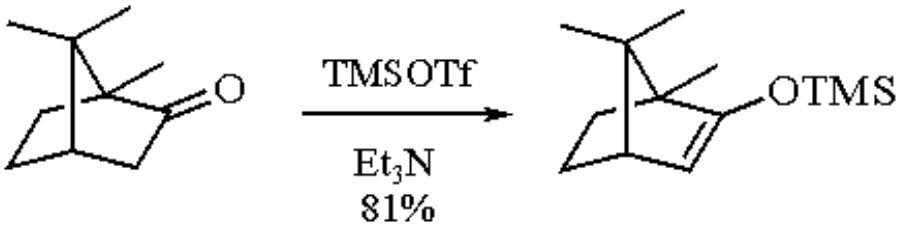

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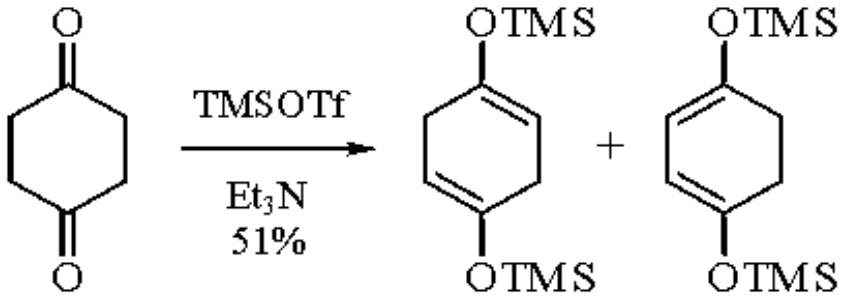

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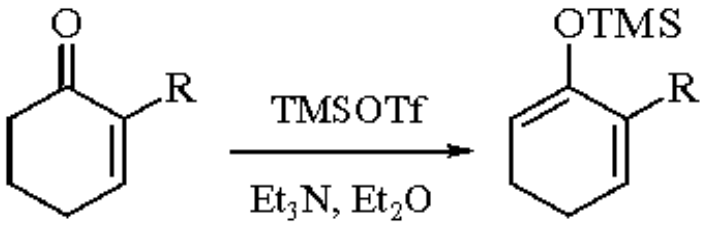

(3)

Dicarbonyl compounds are converted to the corresponding bis-enol ethers; this method is an improvement over the previous two-step method (eq 4).[6]

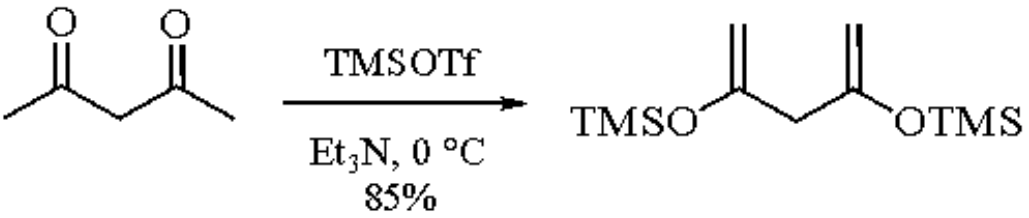

(4)

In general, TMSOTf has a tendency to *C*-silylation which is seen most clearly in the reaction of esters, where *C*-silylation dominates over *O*-silylation. The exact ratio of products obtained depends on the ester structure[7] (eq 5).[8] Nitriles undergo *C*-silylation; primary nitriles may undergo *C*,*C*-disilylation.[9]

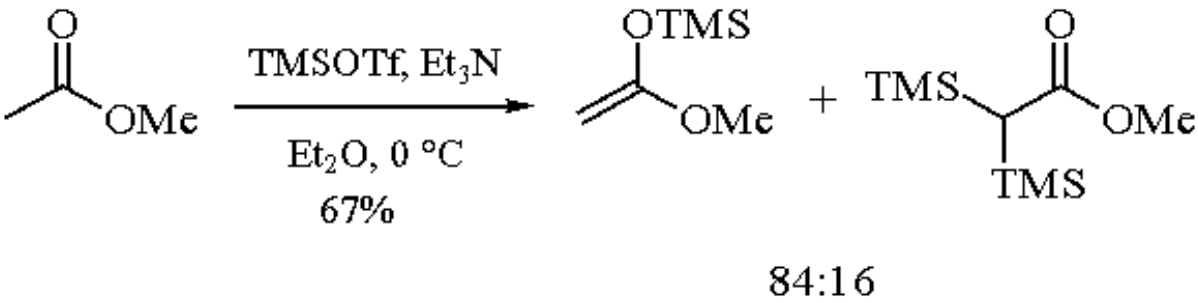

(5)

TMS enol ethers may be prepared by rearrangement of α-ketosilanes in the presence of catalytic TMSOTf (eq 6).[10,11]

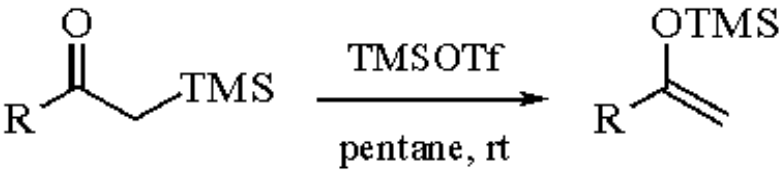

(6)

Enhanced regioselectivity is obtained when trimethylsilyl enol ethers are prepared by treatment of α-trimethylsilyl ketones with catalytic TMSOTf (eq 7).[12]

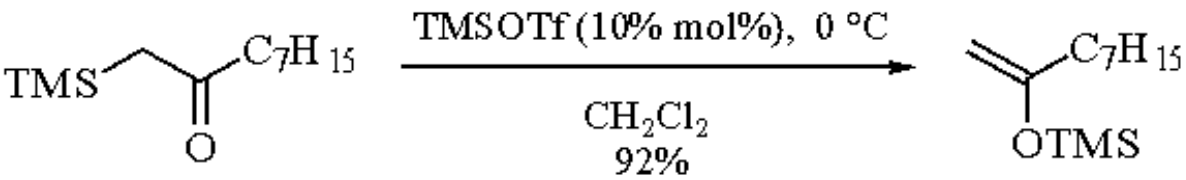

(7)

The reaction of imines with TMSOTf in the presence of Et_3N gives *N*-silylenamines.[13]

Ethers do not react, but epoxides are cleaved to give silyl ethers of allylic alcohols in the presence of TMSOTf and ***1,8-Diazabicyclo[5.4.0]undec-7-ene***; The regiochemistry of the reaction is dependent on the structure of the epoxide (eq 8).[14]

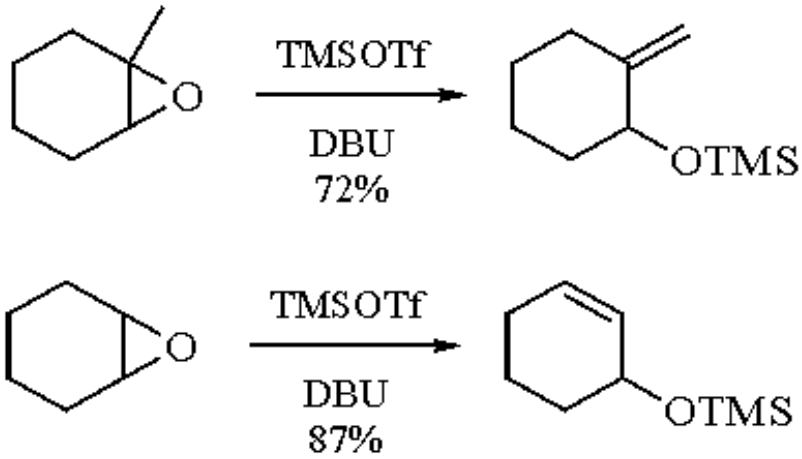

(8)

Indoles and pyrroles undergo efficient *C*-silylation with TMSOTf (eq 9).[15]

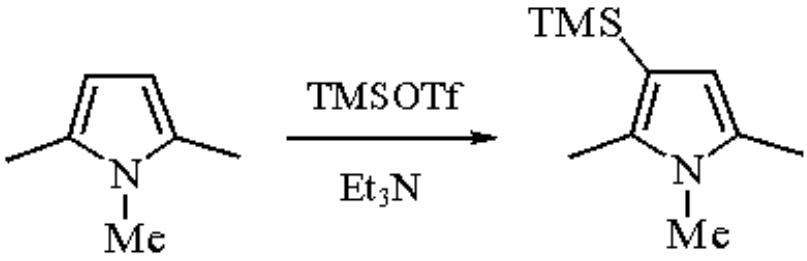

(9)

t-Butyl esters are dealkylatively silylated to give TMS esters by TMSOTf; benzyl esters are inert under the same conditions.[16]

Imines formed from unsaturated amines and α-carbonyl esters undergo ene reactions in the presence of TMSOTf to form cyclic amino acids.[17]

Carbonyl Activation.

1,3-Dioxolanation of conjugated enals is facilitated by TMSOTf in the presence of 1,2-bis(trimethylsilyloxy)ethane. In particular, highly selective protection of sterically differentiated ketones is possible (eq 10).[18] Selective protection of ketones in the presence of enals is also facilitated (eq 11).[19]

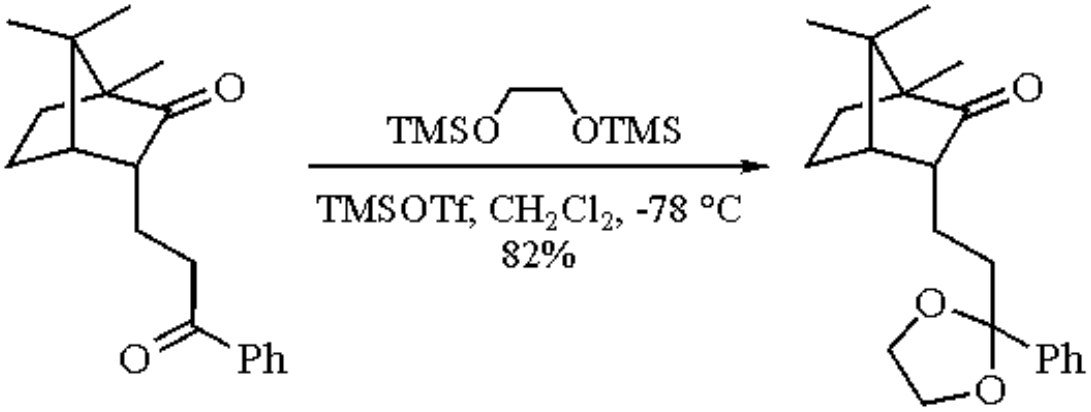

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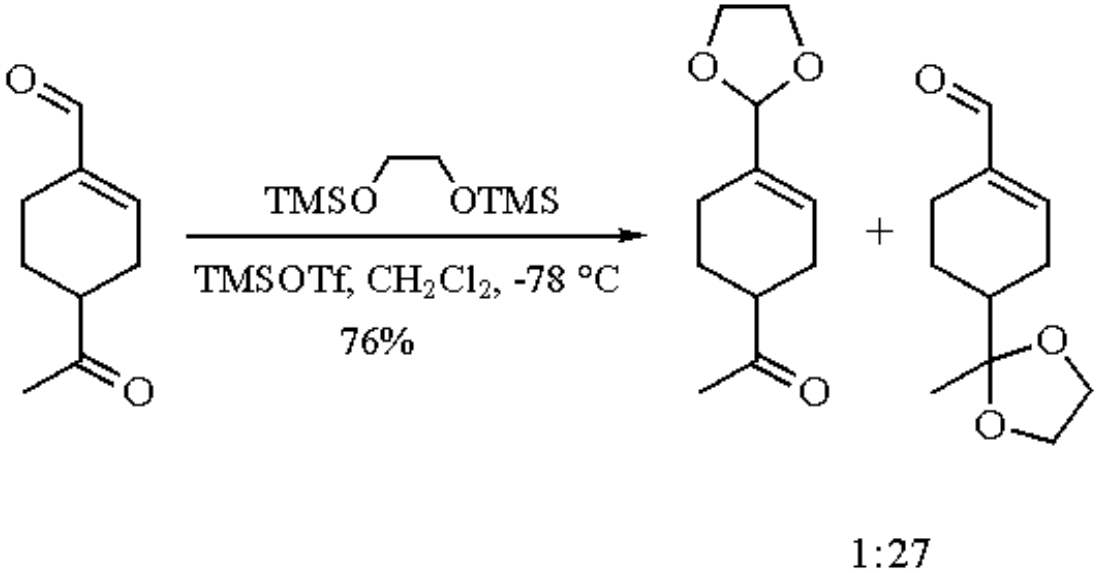

(11)

The similar reaction of 2-alkyl-1,3-disilyloxypropanes with chiral ketones is highly selective and has been used to prepare spiroacetal starting materials for an asymmetric synthesis of α-tocopherol subunits (eq 12).[20]

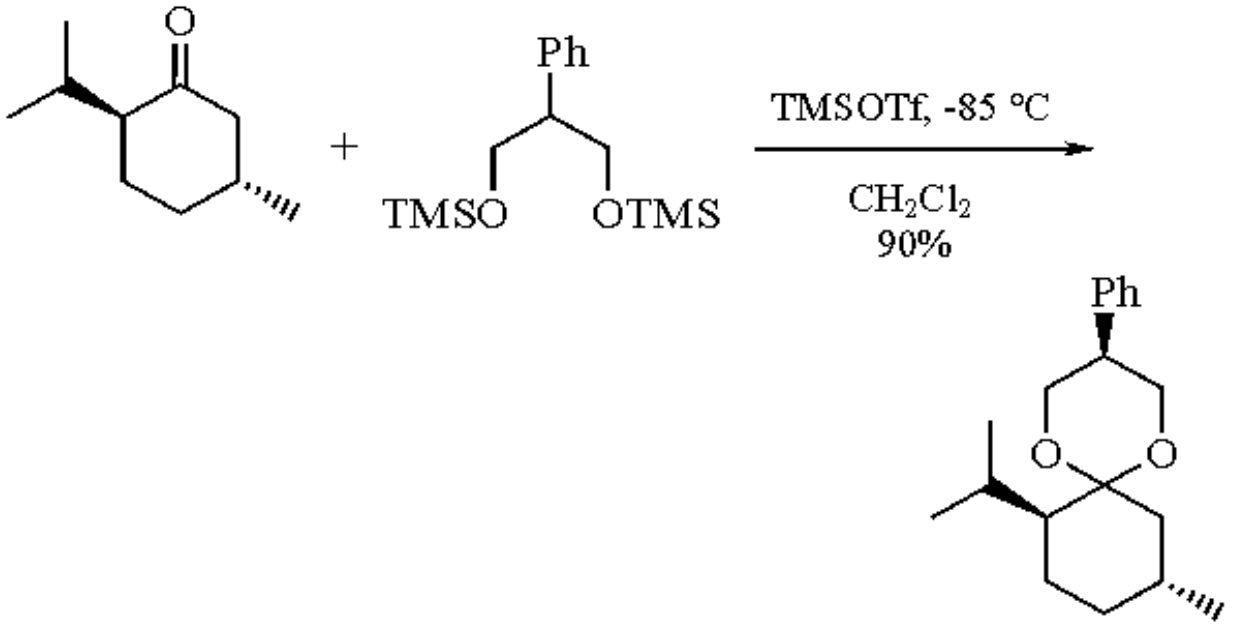

(12)

The preparation of spiro-fused dioxolanes (useful as chiral glycolic enolate equivalents) also employs TMSOTf (eq 13).[21]

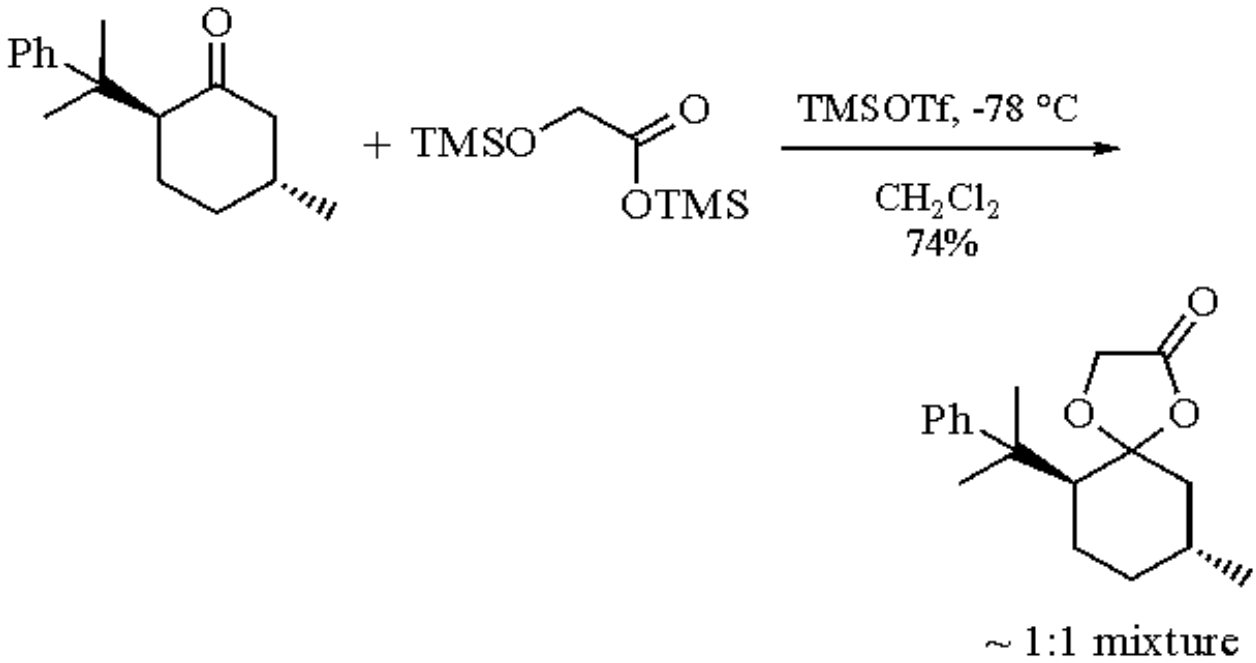

(13)

TMSOTf mediates a stereoselective aldol-type condensation of silyl enol ethers and acetals (or orthoesters). The nonbasic reaction conditions are extremely mild. TMSOTf catalyzes many aldol-type reactions; in particular, the reaction of relatively nonnucleophilic enol derivatives with carbonyl compounds is facile in the presence of the silyl triflate. The activation of acetals was first reported by Noyori and has since been widely employed (eq 14).[22,23]

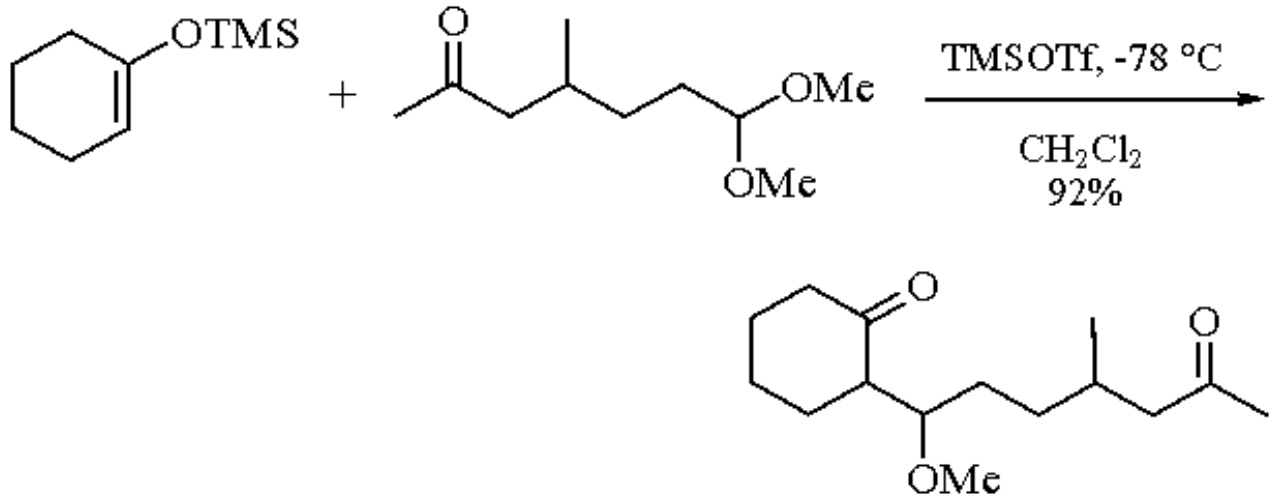

(14)

In an extension to this work, TMSOTf catalyzes the first step of a [3 + 2] annulation sequence which allows facile synthesis of fused cyclopentanes possessing bridgehead hydroxy groups (eq 15).[24]

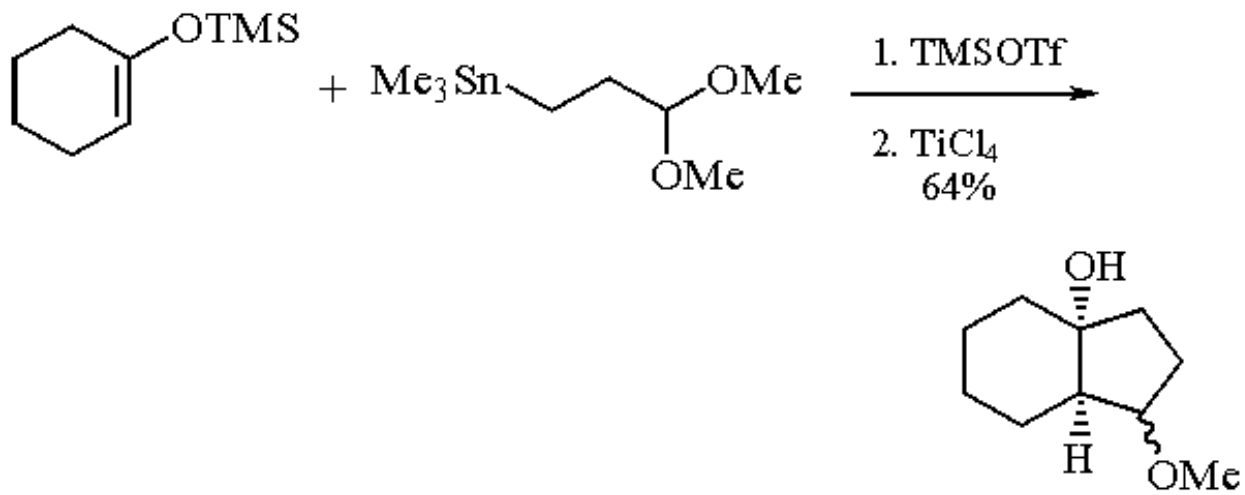

(15)

The use of TMSOTf in aldol reactions of silyl enol ethers and ketene acetals with aldehydes is ubiquitous. Many refinements of the basic reaction have appeared. An example is shown in eq 16.[25]

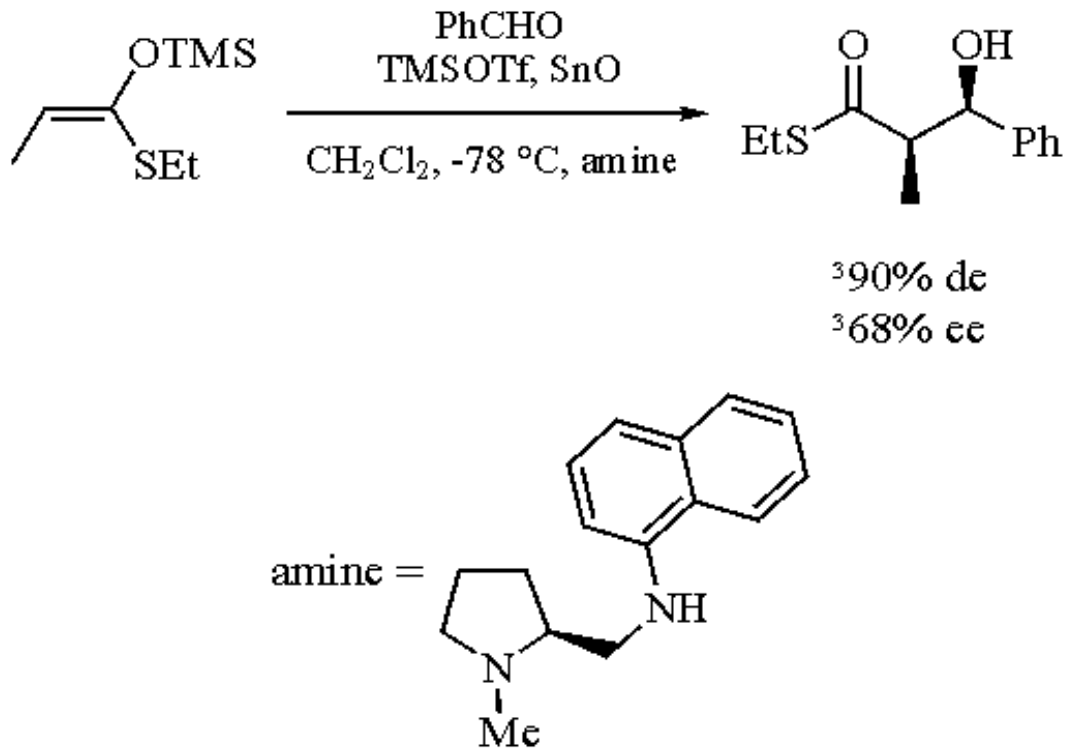

(16)

The use of TMSOTf in the reaction of silyl ketene acetals with imines offers an improvement over other methods (such as Ti^{IV}- or Zn^{II}-mediated processes) in that truly catalytic amounts of activator may be used (eq 17);[26] this reaction may be used as the crucial step in a general synthesis of 3-(1´-hydroxyethyl)-2-azetidinones (eq 18).[27]

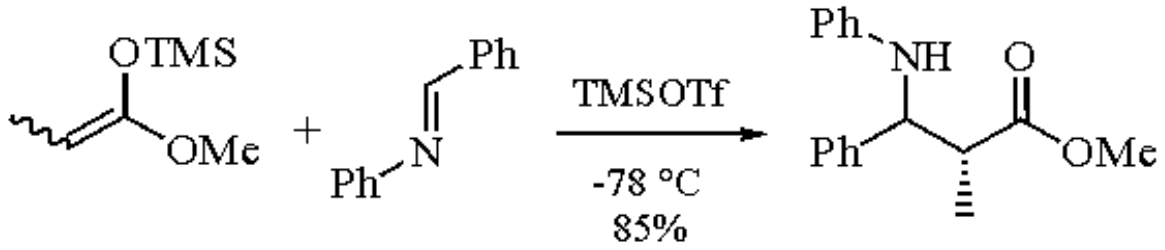

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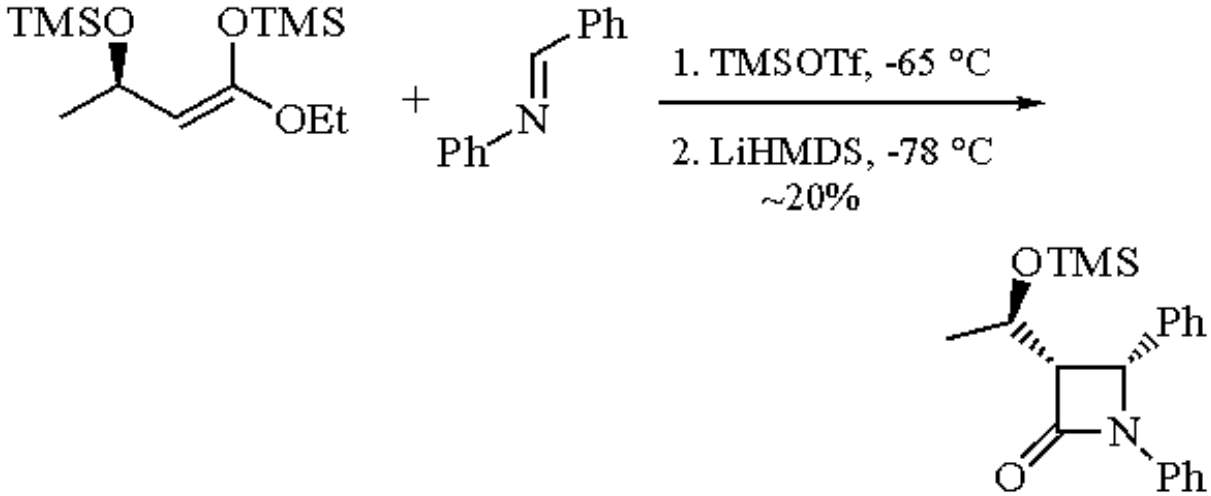

(18)

Stereoselective cyclization of α,β-unsaturated enamide esters is induced by TMSOTf and has been used as a route to quinolizidines and indolizidines (eq 19).[28]

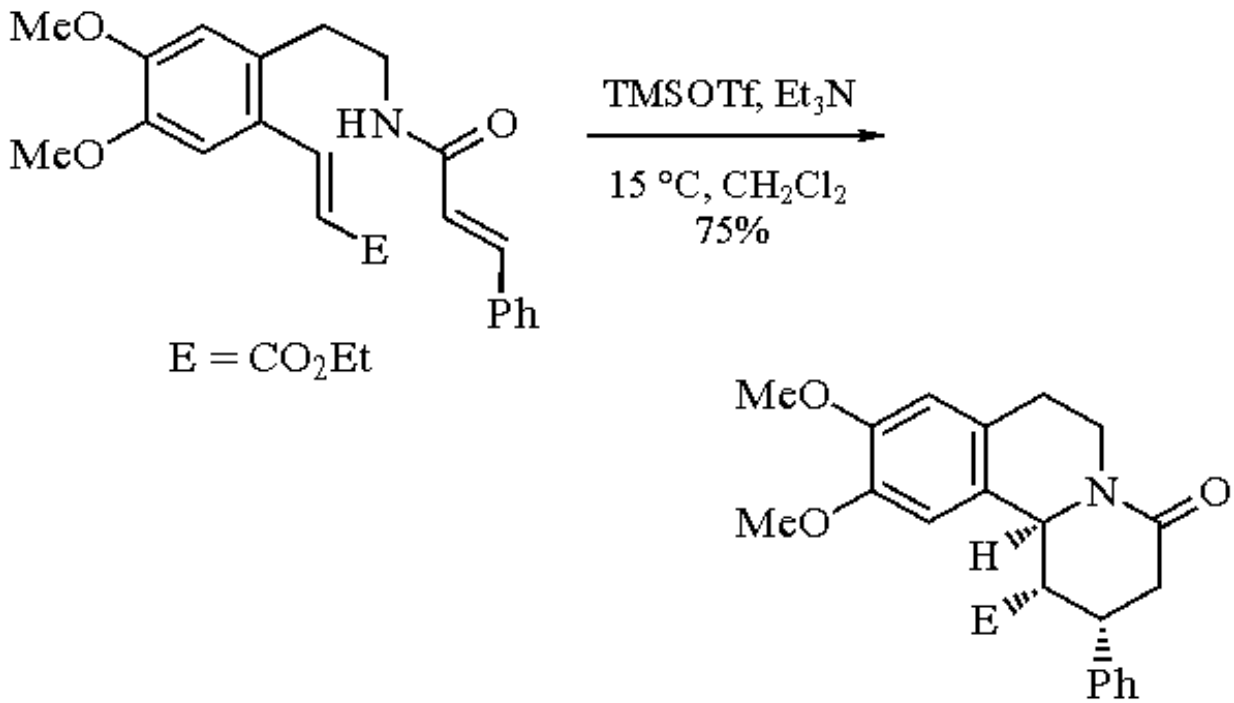

(19)

The formation of nitrones by reaction of aldehydes and ketones with ***N-Methyl-N,O-bis(trimethylsilyl)hydroxylamine*** is accelerated when TMSOTf is used as a catalyst; the acceleration is particularly pronounced when the carbonyl group is under a strong electronic influence (eq 20).[29]

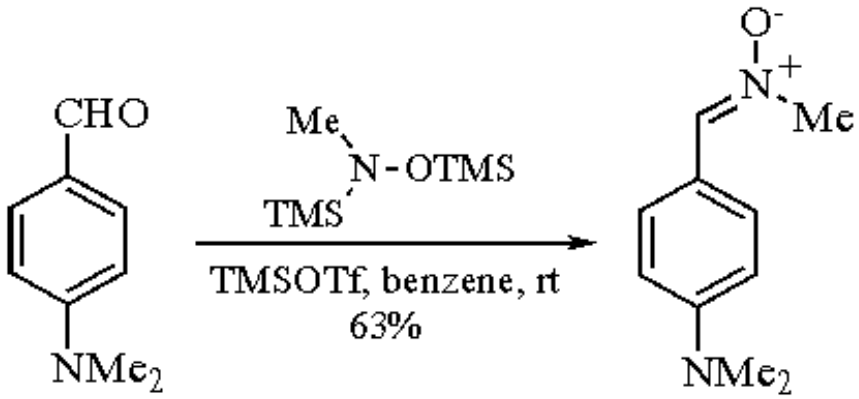

(20)

β-Stannylcyclohexanones undergo a stereoselective ring contraction when treated with TMSOTf at low temperature. When other Lewis acids were employed, a mixture of ring-contracted and protiodestannylated products was obtained (eq 21).[30]

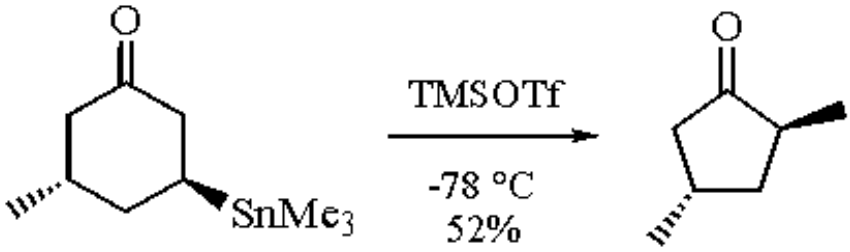

(21)

The often difficult conjugate addition of alkynyl organometallic reagents to enones is greatly facilitated by TMSOTf. In particular, alkynyl zinc reagents (normally unreactive with α,β-unsaturated carbonyl compounds) add in good yield (eq 22).[31] The proportion of 1,4-addition depends on the substitution pattern of the substrate.

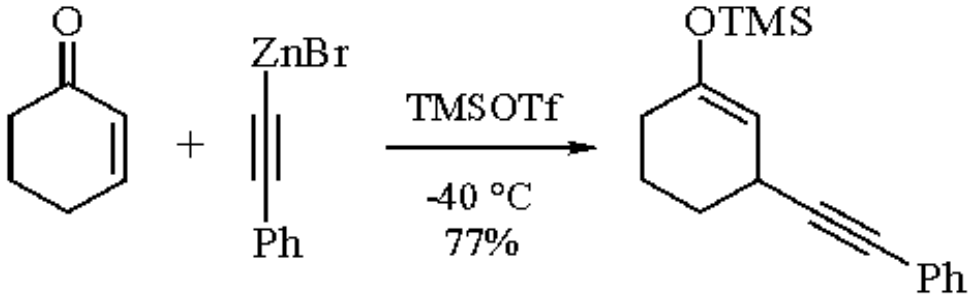

(22)

The 1,4-addition of phosphines to enones in the presence of TMSOTf gives β-phosphonium silyl enol ethers, which may be deprotonated and alkylated in situ (eq 23).[32]

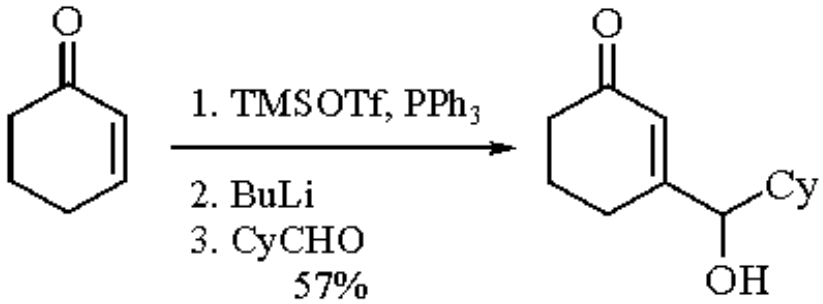

(23)

Miscellaneous.

Methyl glucopyranosides and glycopyranosyl chlorides undergo allylation with allylsilanes under TMSOTf catalysis to give predominantly α-allylated carbohydrate analogs (eq 24).[33]

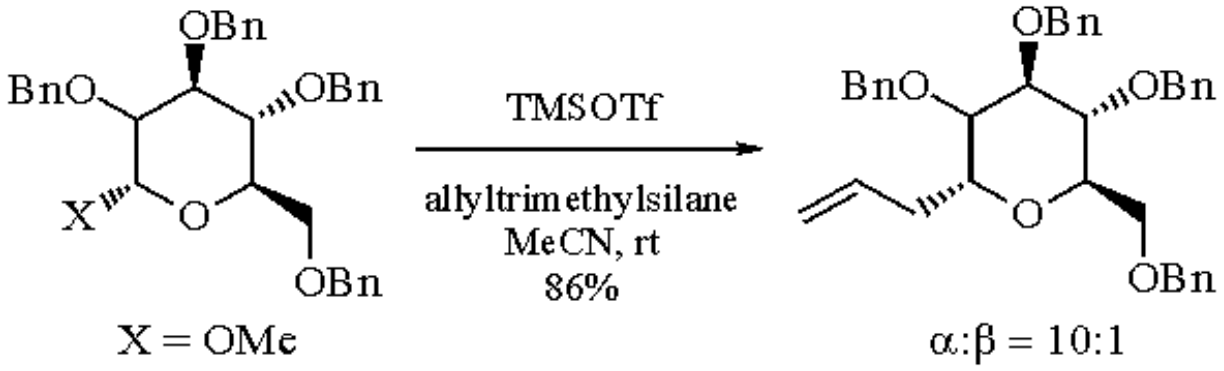

(24)

Glycosidation is a reaction of massive importance and widespread employment. TMSOTf activates many selective glycosidation reactions (eq 25).[34]

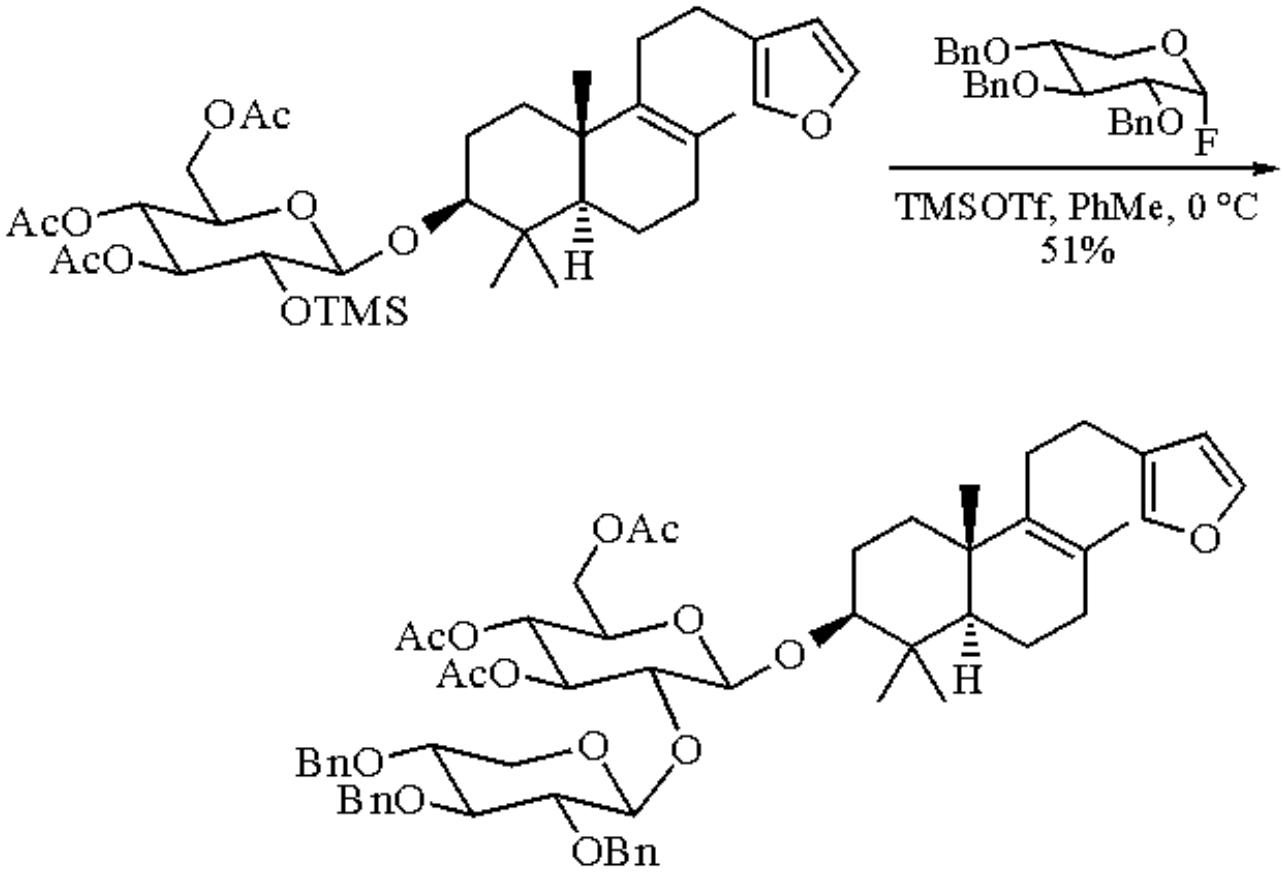

(25)

TMSOTf activation for coupling of 1-*O*-acylated glycosyl donors has been employed in a synthesis of avermectin disaccharides (eq 26).[35]

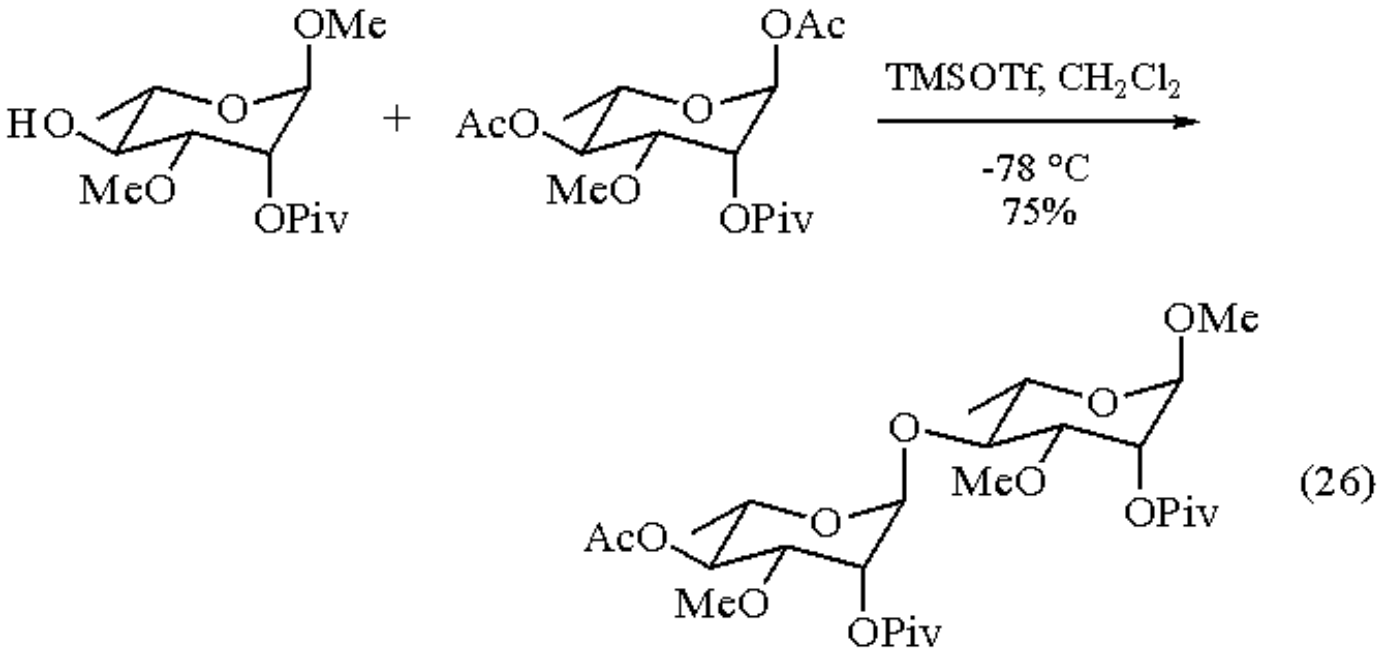

Similar activation is efficient in couplings with trichloroimidates[36] and *O*-silylated sugars.[37,38]

2-Substituted Δ^3-piperidines may be prepared by the reaction of 4-hydroxy-1,2,3,4-tetrahydropyridines with a variety of carbon and heteronucleophiles in the presence of TMSOTf (eqs 27 and 28).[39]

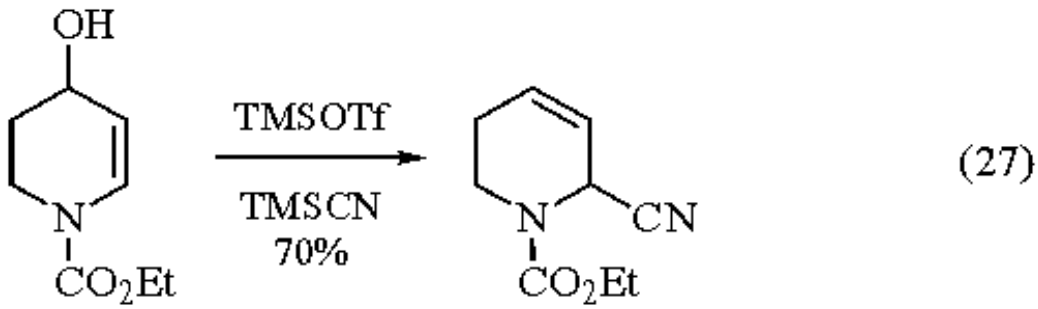

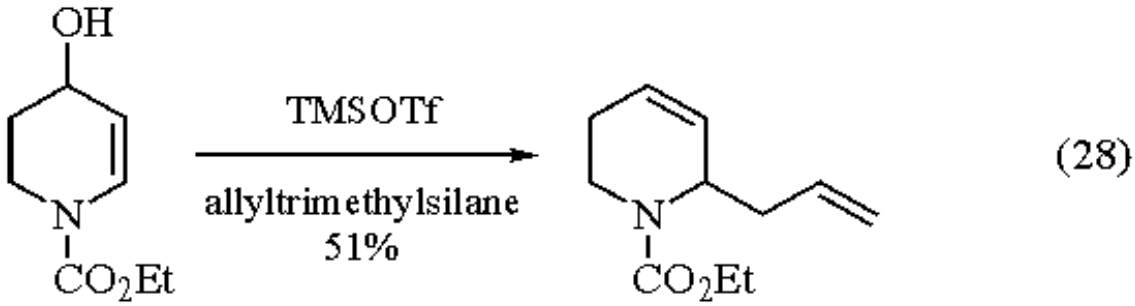

Iodolactamization is facilitated by the sequential reaction of unsaturated amides with TMSOTf and ***Iodine*** (eq 29).[40]

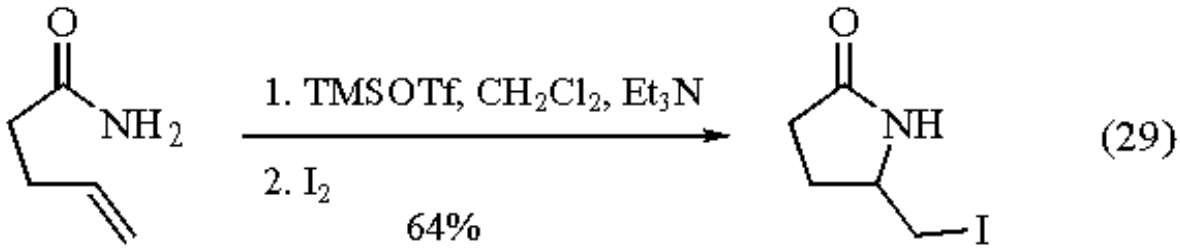

By use of a silicon-directed Beckmann fragmentation, cyclic (*E*)-β-trimethylsilylketoxime acetates are cleaved in high yield in the presence of catalytic TMSOTf to give the corresponding unsaturated nitriles. Regio- and stereocontrol are complete (eq 30).[41]

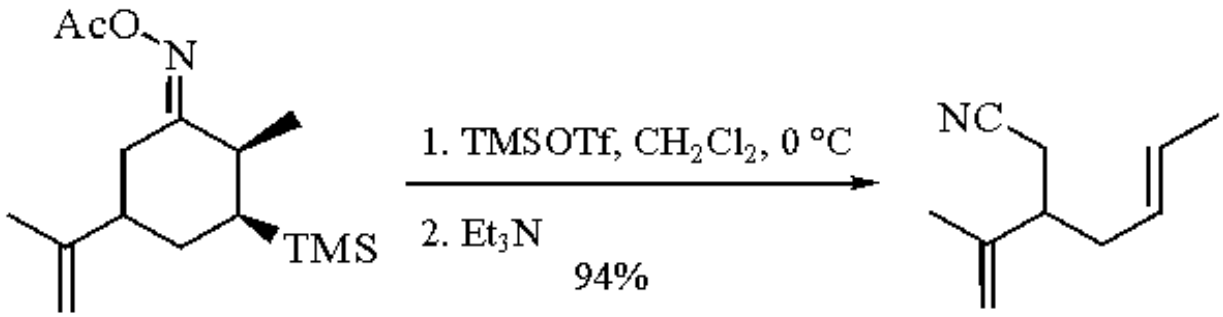

(30)

A general route to enol ethers is provided by the reaction of acetals with TMSOTf in the presence of a hindered base (eq 31).[42] The method is efficient for dioxolanes and noncyclic acetals.

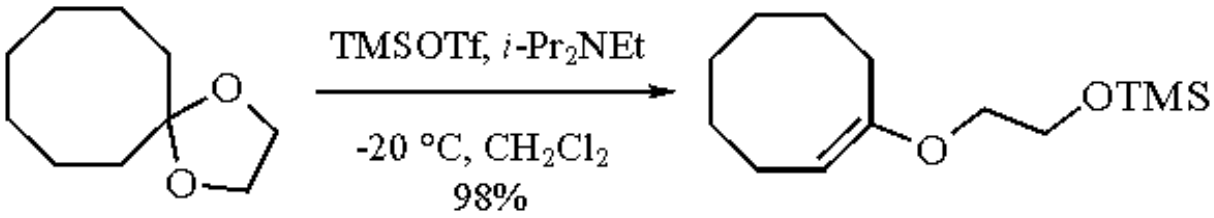

(31)

α-Halo sulfoxides are converted to α-halovinyl sulfides by reaction with excess TMSOTf (eq 32),[43] while α-cyano- and α-alkoxycarbonyl sulfoxides undergo a similar reaction (eq 33).[44] TMSOTf is reported as much superior to ***Iodotrimethylsilane*** in these reactions.

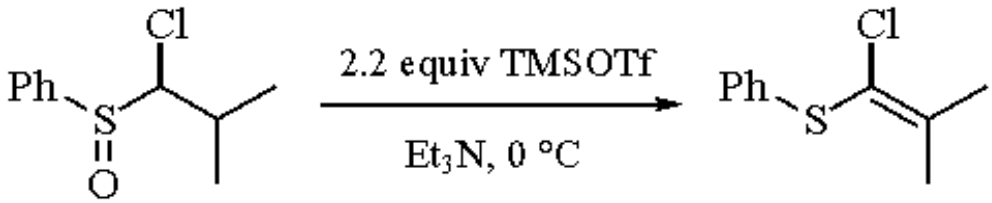

(32)

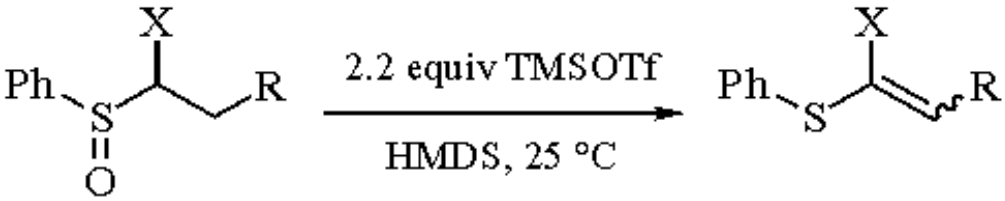

(33)

X = CN or CO_2R'

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44. Miller, R. D.; Hässig, R., *TL* **1985**, *26*, 2395.

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3-Trimethylsilyl-3-trimethylsilyloxy-1-propene[1]

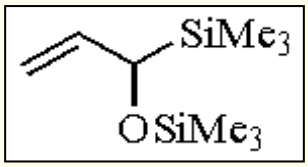

[66662-17-7] · $C_9H_{22}OSi_2$ · 3-Trimethylsilyl-3-trimethylsilyloxy-1-propene · (MW 202.49)

(homoenolate anion[2] and homoenolate dianion[3] equivalents; synthesis of acylsilanes)

Physical Data: bp 62 °C/35 mmHg; *n*20D 1.4228.

Preparative Methods: allyl trimethylsilyl ether is lithiated with ***s-Butyllithium*** in THF-HMPA to give a rapidly equilibrating mixture of a carbanion and a silylallyloxy anion (eq 1). Silylation of the mixture with ***Chlorotrimethylsilane*** affords 3-trimethylsilyl-3-trimethylsilyloxy-1-propene (**1**) exclusively. Several other derivatives with bulky substituent(s) on the silyloxy group were also prepared.[2]

Handling, Storage, and Precautions: use in a fume hood.

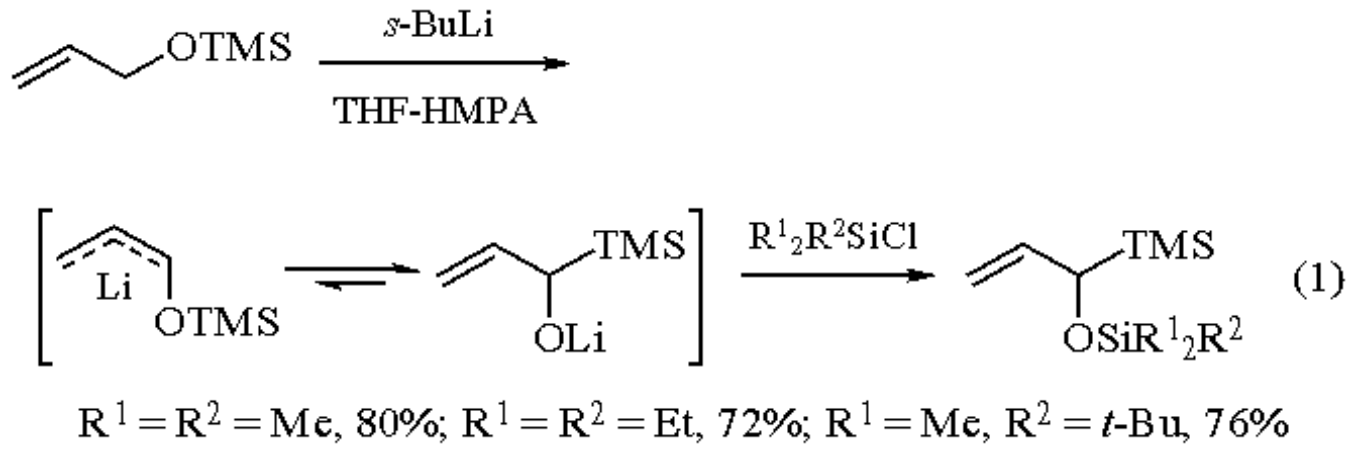

Homoenolate Anion Equivalent.

The reaction of (**1**) with acid chlorides in the presence of ***Titanium(IV) Chloride*** affords the corresponding γ-keto aldehydes after hydrolysis (eq 2).[2] *O*-Acylation to form the 1-silyl allyl ester (17-30%) competes with the S_E' alkylation of the double bond. Bulkier silyloxy derivatives give γ-keto aldehydes in higher yield.

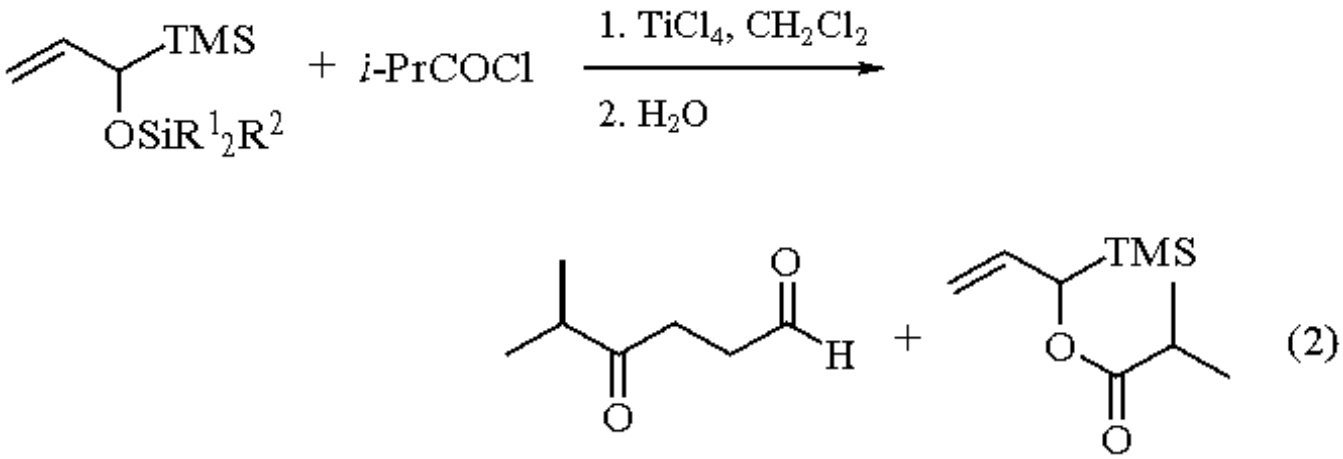

$R^1 = R^2 = Me$	20%	30%
$R^1 = R^2 = Et$	43%	17%
$R^1 = Me$, $R^2 = t$-Bu	45%	-

Homoenolate Dianion Equivalent.

The intermediate in the reaction is believed to be an enol silane and/or enol titanate which gives the expected product with carbon electrophiles such as acetals (eq 3).[3]

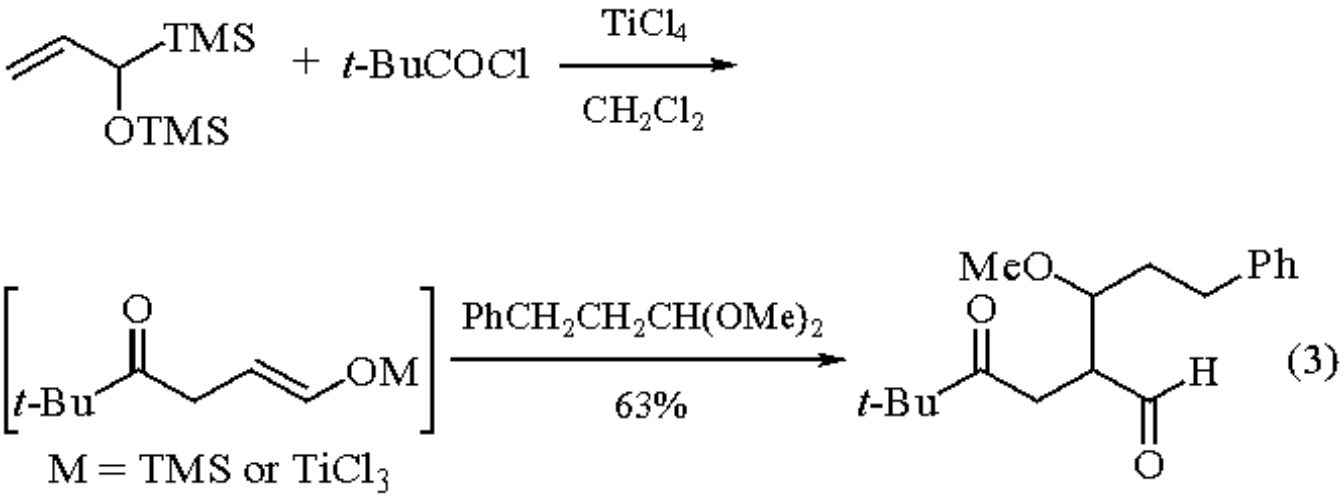

Synthesis of Acylsilanes.

The title reagent (**1**) and other related derivatives undergo sequential isomerization to α-silylalkenyl ethers upon treatment with ***Palladium on Carbon*** which subsequently give acylsilanes by hydrolysis (eq 4).[4]

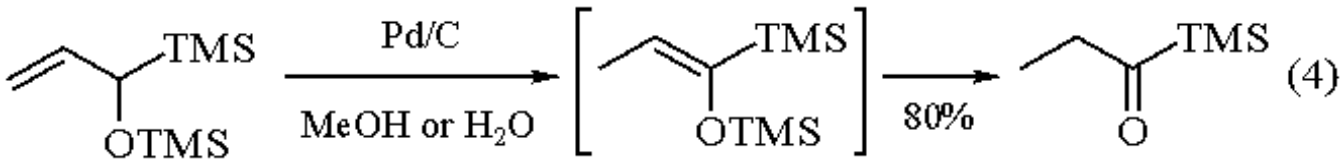

Related Reagents.

Allyltrimethylsilane; ***1-Ethoxy-1-(trimethylsilyloxy)cyclopropane***; ***1-Methoxyallyllithium***; ***Trimethylsilylallyllithium***.

---

1. Fieser, M. *FF* **1980**, *8*, 485.
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(*E*)-1-Trimethylsilyl-2-trimethylstannylethylene[1,2]

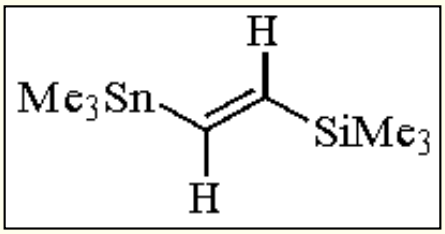

[58207-97-9] · $C_8H_{20}SiSn$ · (*E*)-1-Trimethylsilyl-2-trimethylstannylethylene · (MW 263.08)

(reagent for Pd^0-catalyzed cross-coupling reactions with aryl and vinyl halides or triflates;[1,2] source of β-trimethylsilylvinyllithium[3])

Physical Data: bp 22 °C/0.04 mmHg; n_D 1.4723.

Solubility: sol ether, DMF, hydrocarbon, aromatic solvents.

Analysis of Reagent Purity: ^{1}H NMR (CCl_4/CH_2Cl_2) δ 0.12 (s, 9H, Me_3Si), 0.17 (s, 9H, Me_3Sn), 6.30-7.20 (AB pattern, J_{AB} = 22 Hz, 2H, vinyl).

Preparative Method: trans-1,2-bis(tri-*n*-butylstannyl)ethylene is treated successively with ***n-Butyllithium***, ***Chlorotrimethylsilane***, *n*-BuLi, and ***Chlorotrimethylstannane*** to give (*E*)-trimethylsilyl-2-trimethylstannylethylene in good yield.[3]

Handling, Storage, and Precautions: organotin reagents are extremely toxic and readily absorb through the skin.[4] The reagent should be handled at all times in an efficient fume hood, wearing the appropriate personal safety equipment (i.e. gloves, safety eyewear).

Palladium-Catalyzed Coupling Reactions.

Vinyl and aromatic halides undergo palladium-catalyzed cross-coupling reactions with trimethylsilyl-2-trimethylstannylethylene to give substituted 1,3-dienes and styrenes, respectively (eqs 1 and 2).[5,6] Vinyl triflates also undergo cross-coupling reactions to give 1,3-dienes, provided that ***Lithium Chloride*** is added to the reaction (eq 3).[7,8]

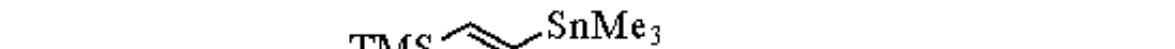

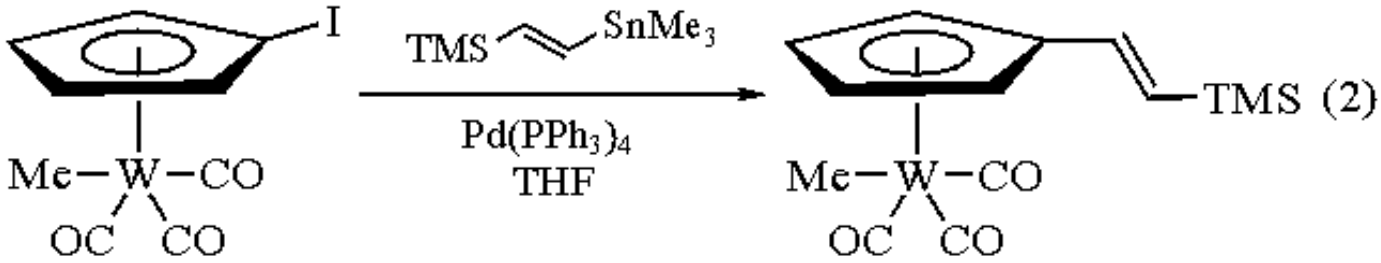

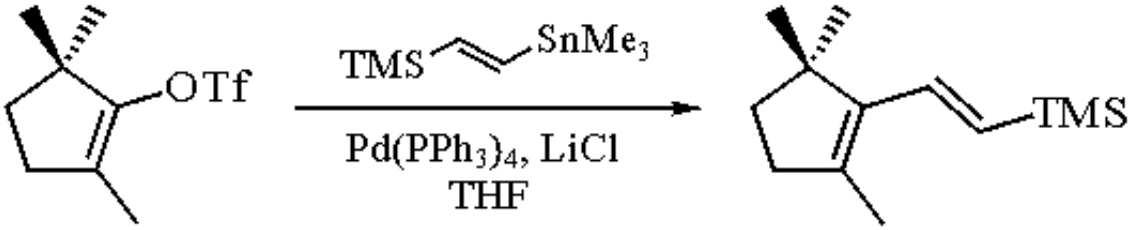

(3)

The reactions employ mild conditions, are regioselective and stereospecific, and give high yields of products. In addition, tedious protection-deprotection steps are not necessary because the reactions tolerate a wide variety of functional groups.[5,6]

When the coupling of vinyl triflates is carried out in the presence of ***Carbon Monoxide*** and lithium chloride, carbon monoxide insertion occurs, yielding unsymmetrical divinyl ketones (eqs 4 and 5).[9,10] This is a particularly useful procedure for the formation of intermediates for the Nazarov cyclization reaction.[11]

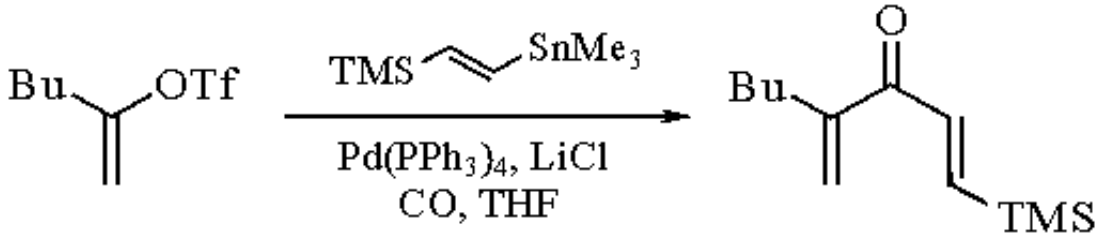

(4)

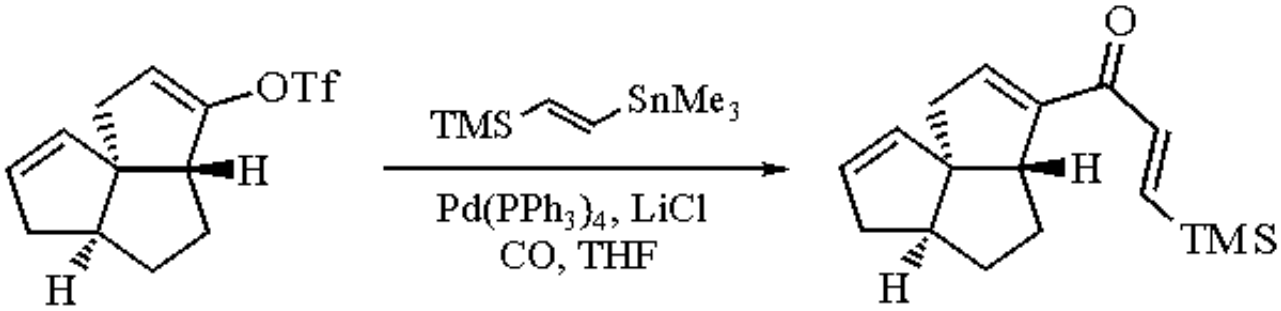

(5)

For additional discussion about palladium-catalyzed coupling reactions, see also those entries dealing with organopalladium complexes (e.g. ***Tetrakis(triphenylphosphine)palladium(0)***, ***Tris(dibenzylideneacetone)dipalladium***, and/or ***(E)-1-Tri-n-butylstannyl-2-trimethylsilylethylene***).

Transmetalation Reactions.

Transmetalation of trimethylsilyl-2-trimethylstannylethylene at low temperature with *n*-BuLi affords ***(E)-2-(Trimethylsilyl)vinyllithium*** in high yield (eq 6).[3]

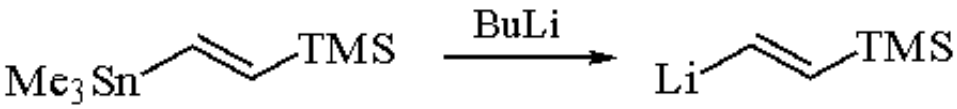

(6)

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(Trimethylsilyl)vinylketene

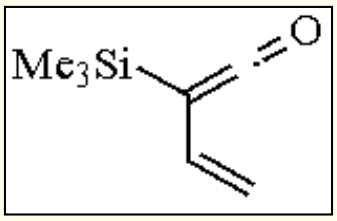

[75232-81-4] · $C_7H_{12}OSi$ · (Trimethylsilyl)vinylketene · (MW 140.28)

(reactive diene for [4 + 2] cycloadditions[1])

Alternate Name: 2-(trimethylsilyl)-1,3-butadien-1-one.

Physical Data: bp 49.0-50.5 °C/1.6 mmHg.

Solubility: sol CH_2Cl_2, $CHCl_3$, CCl_4, toluene, benzene, hexane, most organic solvents.

Form Supplied in: yellow-green liquid; not commercially available.

Analysis of Reagent Purity: IR ($CDCl_3$) 2085, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.25 (s, 9 H), 4.82 (dd, *J* = 1, 10 Hz, 1 H), 4.88 (dd, *J* = 1, 17 Hz, 1 H), 5.92 (dd, *J* = 10, 17 Hz, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ -1.0 (q), 22.3 (s), 111.6 (t), 125.1 (d), 183.7 (s) ppm.

Preparative Methods: conveniently prepared as outlined in eq 1. Treatment of 1-(trimethylsilyl)propyne (**2**)[2] with 1.1 equiv of ***Diisobutylaluminum Hydride*** (25 °C, 21 h) and 1.1 equiv of ***Methyllithium*** (0 °C, 0.5 h) in ether-hexane,[2] followed by reaction of the resulting vinylalanate with anhydrous ***Carbon Dioxide***,[3] yields (*Z*)-2-(trimethylsilyl)-2-butenoic acid (**3**) in 68% yield. Exposure of the potassium salt of this acid (**4**) to 1.1 equiv of ***Oxalyl Chloride*** in pentane containing a catalytic amount of ***N,N-Dimethylformamide*** (0-25 °C, 1.5 h) then produced a mixture of the acid chloride (**5**) and its geometric isomer, which was dehydrohalogenated without further purification. A solution of (**5**) in pentane was added dropwise over 1-2 h to a solution of 0.9 equiv of ***Triethylamine*** in pentane at 25 °C, and the resulting mixture was heated at reflux for 15-24 h and then filtered with the aid of pentane. Solvent was evaporated at -50 °C (0.5 mmHg), and the residue was distilled at 25 °C (1 mmHg) and then again at 5 mmHg into a receiver cooled at -78 °C. In this manner a yellow-green liquid of (trimethylsilyl)vinylketene (**1**) was obtained in 39-50% overall yield (from **3**).

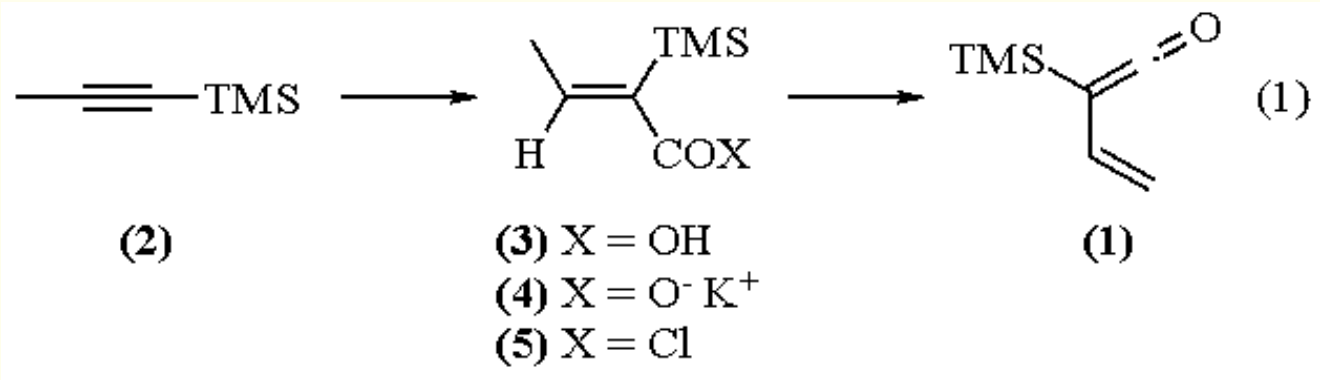

Handling, Storage, and Precautions: purified vinylketenes can be stored under nitrogen in solution at 0 °C without appreciable decomposition for 1-2 weeks.

Reactive Enophile in [4 + 2] Cycloadditions.

Vinylketenes are not effective as dienes in Diels-Alder reactions because they undergo only [2 + 2] cycloaddition with alkenes, as predicted by frontier molecular orbital theory. However, silylketenes exhibit dramatically different properties from those found for most

ketenes.[4] (Trimethylsilyl)vinylketene (**1**) is a relatively stable isolable compound which does not enter into typical [2 + 2] cycloadditions with electron-rich alkenes. Instead, (**1**) participates in Diels-Alder reactions with a variety of alkenic and alkynic dienophiles. The directing effect of the carbonyl group dominates in controlling the regiochemical course of cycloadditions using this diene. For example, reaction of (**1**) with ***Methyl Propiolate*** produced methyl 3-(trimethylsilyl)salicylate with the expected regiochemical orientation. Protodesilylation of this adduct with ***Trifluoroacetic Acid*** in chloroform (25 °C, 24 h) afforded methyl salicylate in 78% yield (eq 2).

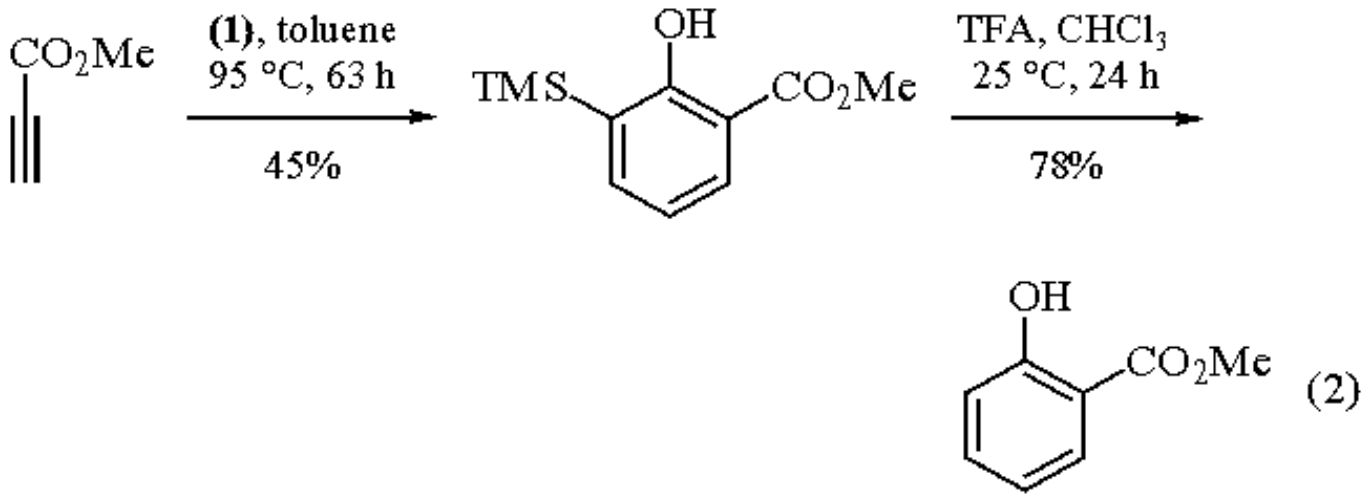

Diels-Alder addition of (**1**) to alkenic dienophiles furnishes cyclohexenone derivatives (eqs 3 and 4). Addition of (**1**) to naphthoquinone afforded a mixture of several cycloadducts which could be oxidized to a single anthraquinone (eq 5).

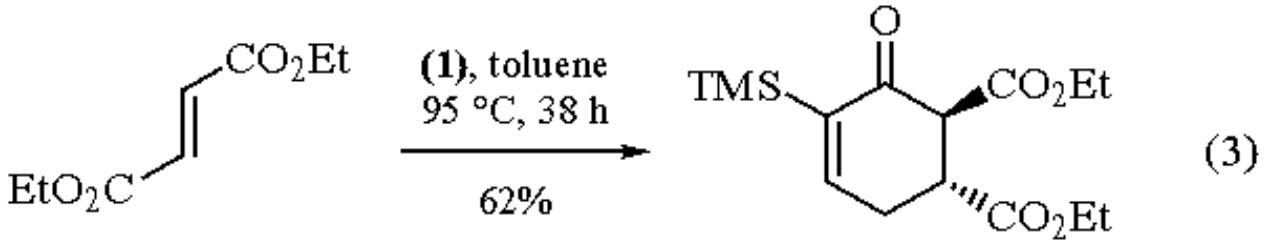

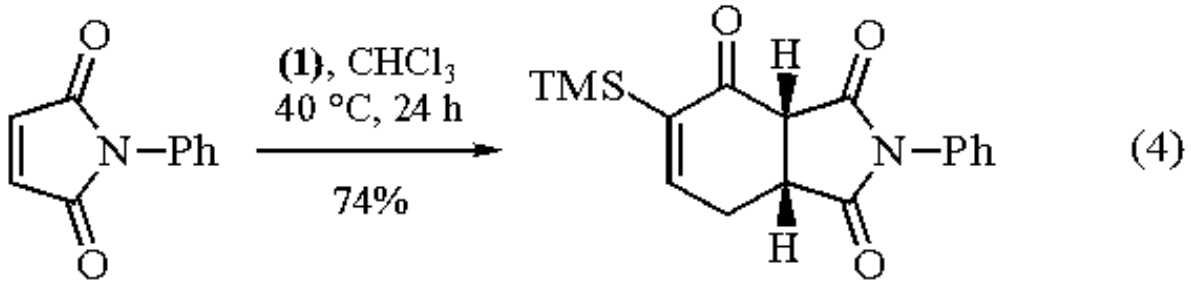

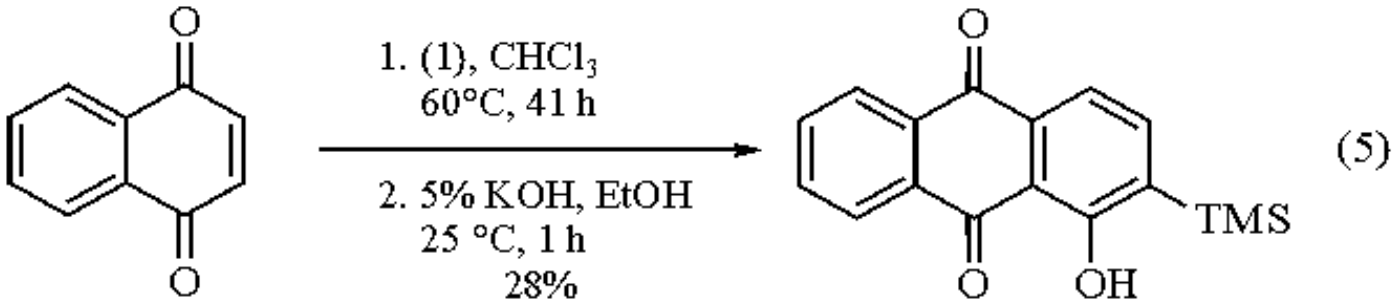

The reactivity of (trimethylsilyl)vinylketene compares favorably to previously reported vinylketene equivalents. Both vinylketene acetals[5] and thioacetals[6] have been reported to undergo [4 + 2] cycloadditions in good yield. However, due to the limited reactivity of hindered (*Z*)-dienes, only highly electrophilic dienophiles react. Specially activated vinylketene thioacetal substrates have been made with an electron-donating group at the 3-position of the diene to promote reaction with weaker dienophiles. Unfortunately, due to their strong nucleophilic character, these dienes were found to participate in a stepwise Michael-type process. Concerted [4 + 2] cycloadditions were only seen with a few dienophiles.[6c] Vinylketenimines are shown to be isolable by distillation, are stable at room temperature, and undergo [4 + 2] cycloadditions in moderate to good yield. Again, reaction only occurs with electron-deficient dienophiles.[7]

A general route to substituted (silyl)vinylketenes has been developed and several substituted ketenes have been prepared. The synthesis of 1-(1-cyclohexenyl)-2-triisopropylsilylketene is representative of this general approach (eq 6).[10]

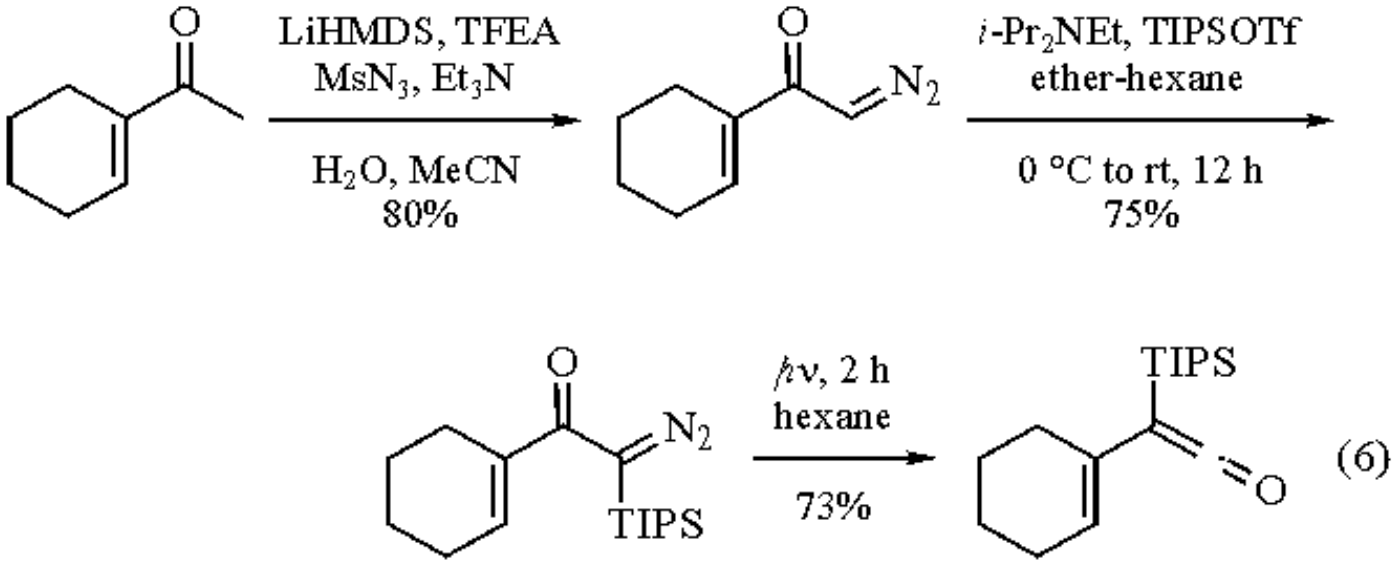

Thus detrifluoroacetylative diazo transfer[8] furnished the diazo ketone in 80% yield, which was converted to the silyl diazo ketone in 75% yield by the method of Maas.[9] The key photolysis step was effected by irradiating a degassed 0.1 M solution of the silyl diazo ketone in hexane in a Vycor tube using a low-pressure mercury lamp (300 nm) for 2 h. Concentration and chromatographic purification furnished the desired (silyl)vinylketene in 73% yield.[10]

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1. Danheiser, R. L.; Sard, H. *JOC* **1980**, *45*, 4810.
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10. Danheiser, R. L.; Loebach, J. L. unpublished results.

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1-(Trimethylsilyl)vinyllithium

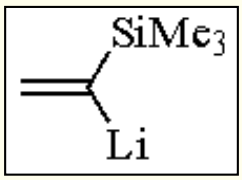

[51666-94-5] · $C_5H_{11}LiSi$ · 1-(Trimethylsilyl)vinyllithium · (MW 106.19)

(adds 1,2 to ketones and aldehydes;[1] 1,4-additions to enones via the cuprates;[2] diene synthesis;[3] formation of vinylsilanes[4])

Alternate Names: 1-lithio-1-(trimethylsilyl)ethylene; α-(trimethylsilyl)vinyllithium.

Solubility: sol THF, ether.

Preparative Method: prepared in situ under an inert atmosphere by lithium-halogen exchange of ***(1-Bromovinyl)trimethylsilane*** with ***t-Butyllithium***.

Handling, Storage, and Precautions: solutions are inflammable; it is critical to preclude contact with air and moisture.

Addition to Ketones and Aldehydes.[1]

α-(Trimethylsilyl)vinyllithium (**1**) adds to ketones and aldehydes. The adducts do not undergo the expected Peterson elimination reaction when treated with ***Sodium Hydride*** or ***Potassium Hydride***, but the corresponding allene can still be obtained if the alcohol is converted to the chloride followed by fluoride-catalyzed β-elimination (eq 1).[5a,b] Other uses have also been made of the allyl chlorides made in this manner: they react with cuprates,[5c] or they can be oxidized to the epoxides to serve as precursors to allene oxides.[5d-l]

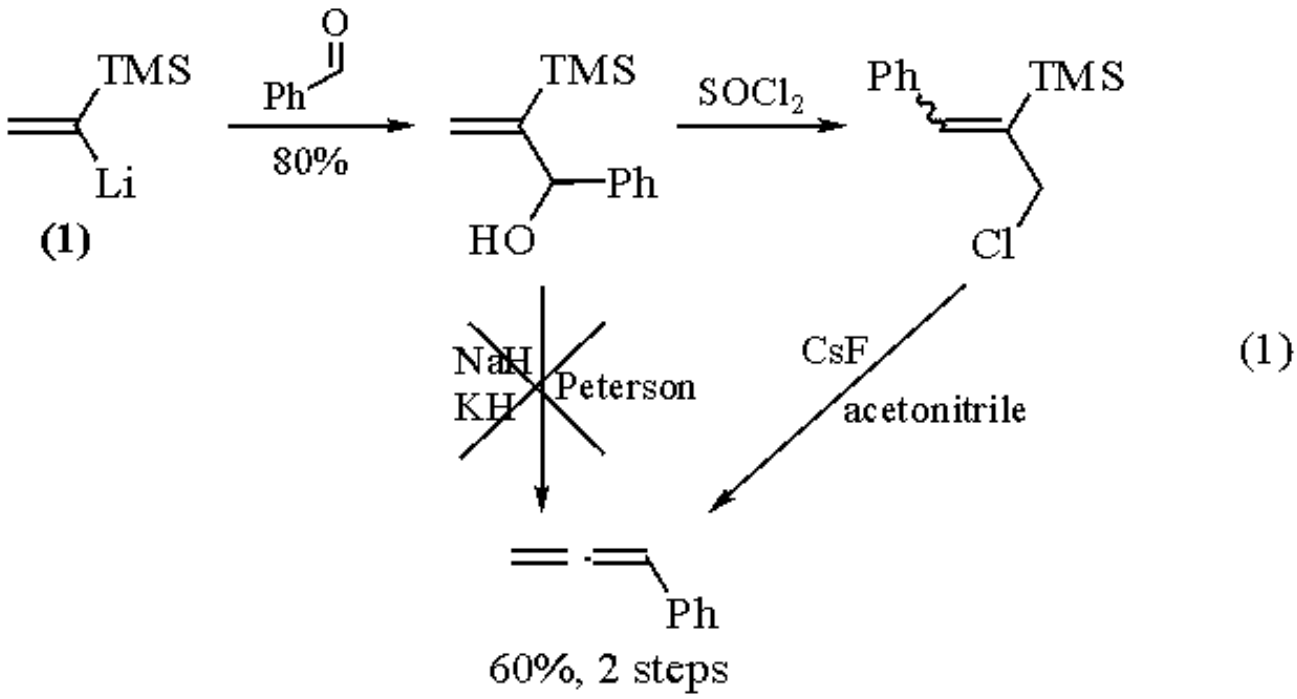

(1)

Under certain conditions (KH in HMPA), products from the homo-Brook rearrangement are observed (eq 2).[6] This is therefore a good method of desilylation of β-hydroxyvinylsilanes to the corresponding vinyl alcohols. Other conditions for desilylation were found to give better yields (eq 3).[7] Since α-(trimethylsilyl)vinyllithium was found to add to chiral aldehydes with better diastereoselectivity than ***Vinyllithium***, the overall sequence is an improvement for chelation controlled 1,2-asymmetric induction.[7a] In the sequence of eq 3, diastereoselectivity varied as the protecting group R´ was changed; it was 20:1 for R´-benzyl. This illustrates the usefulness of α-

(trimethylsilyl)vinyllithium in stereoselective polyol synthesis.[7]

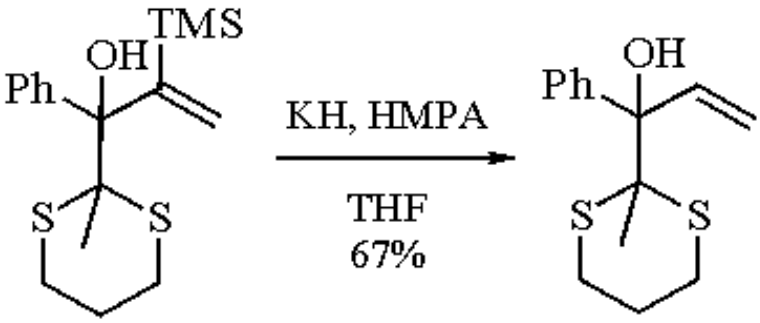

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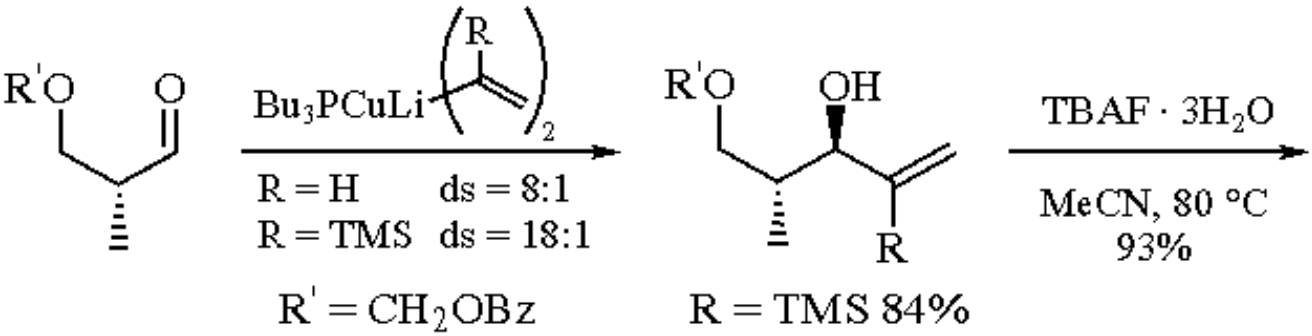

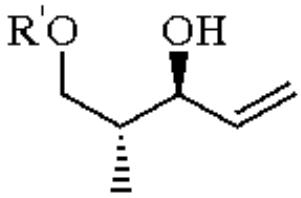

(3)

The alcohol adducts from α-(trimethylsilyl)vinyllithium and aldehydes have found many uses in organic synthesis. The ketones obtained by oxidation (eq 4) are especially good Michael acceptors and have been used in a modified Robinson annulation reaction for the construction of cyclohexenones.[8] Cyclopropanation leads to cyclopropylsilane adducts, which can be converted into a variety of cyclopentenes (eq 5).[9] Halogenation followed by stannylation gives synthons (eq 6) useful for making substituted vinylsilanes through radical reactions.[10]

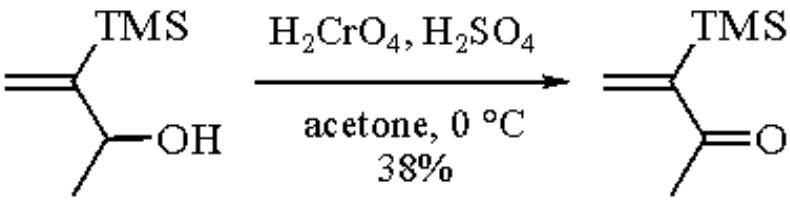

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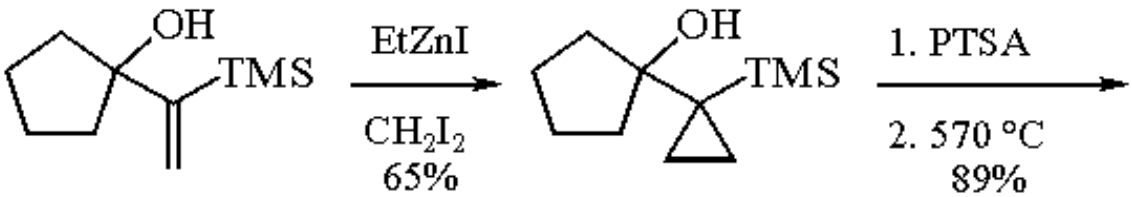

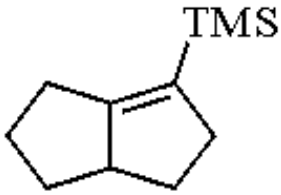

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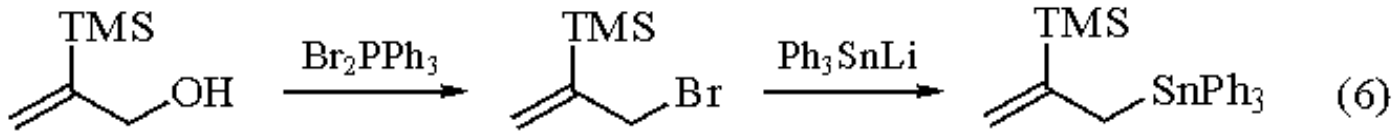

Rearrangements of alcohols bearing an epoxide functionality give ketones that can be stereoselectively reduced. The new stereocenter formed is of opposite configuration when the trimethylsilyl group R is present on the vinyl moiety (eq 7).[11b,c] Thus α-(trimethylsilyl)vinyllithium can be viewed as a large vinyl anion equivalent (e.g. eq 3) which complements vinylmagnesium and lithium chemistry.[11] These reactions were elegantly used in the total syntheses of avenaciolide, isoavenaciolide,[11b,c] and (+)- and (-)-eldanolide.[11f]

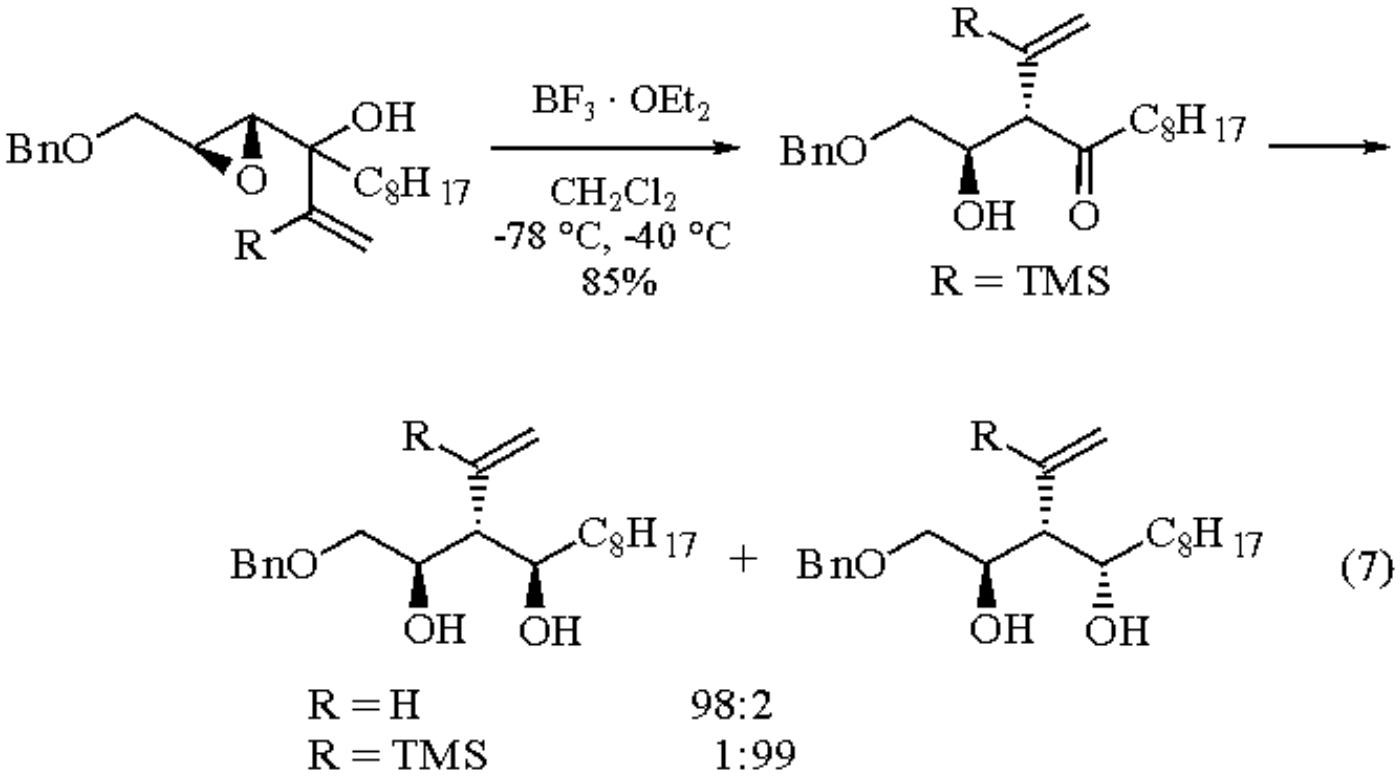

1,4-Additions to Enones via the Cuprates.[2]

α-(Trimethylsilyl)vinyllithium undergoes Michael addition to enones, in good yields, in the presence of copper salts (eq 8).[2] The vinyl group can be oxidized to the epoxide, which is then converted to the acyl group.[2,12] The overall transformation is the addition of an acyl anion equivalent. α-(Trimethylsilyl)vinyllithium compares favorably with other acyl anion equivalents, particularly with the vinyl ether analogs which do not add well to hindered enones.[13]

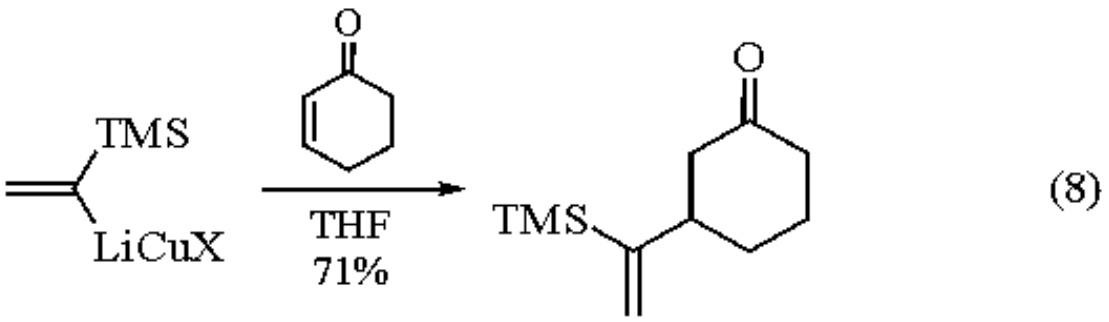

Diene Synthesis.[3]

α-(Trimethylsilyl)vinyllithium dimerizes in the presence of ***Copper(I) Iodide***. This reaction was first observed as a side product during the formation of organocuprates,[3a] then developed for the synthesis of 2,3-bis(trimethylsilyl)buta-1,3-diene (eq 9).[3b]

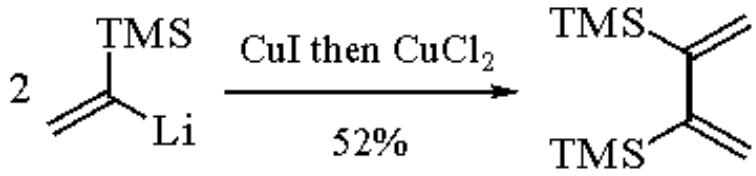

(9)

Reactions with Other Electrophiles.[4]

α-(Trimethylsilyl)vinyllithium reacts with ethylene oxide to give an intermediate which has been used to set up an impressive eight-membered ring cyclization for the synthesis of (-)-laurenyne (eq 10).[4a] Here, vinyltrimethylsilane was preferred over the simple vinyl moiety because of its greater reactivity.

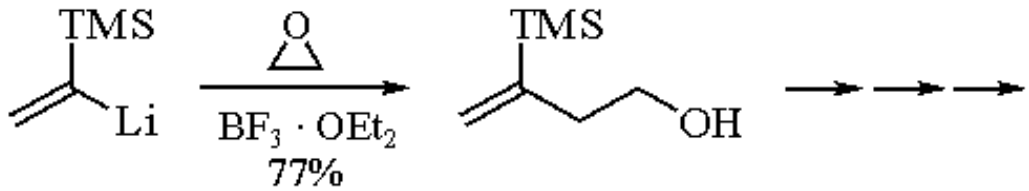

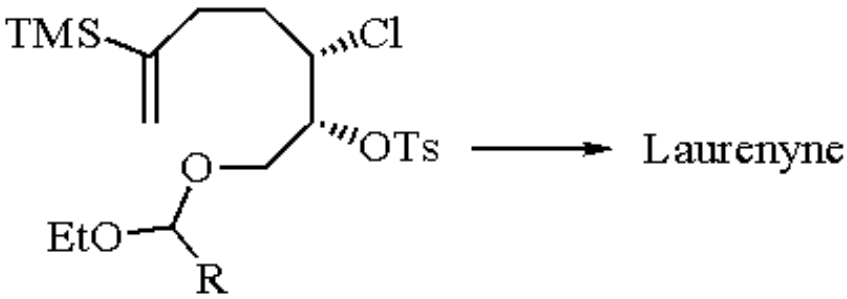

(10)

The reaction of this anion with carbon monoxide leads to the formation of an interesting cyclopropyl product (eq 11).[4c] Other electrophiles, for example selenium cyanide,[4d] ***Iodine***,[4f] chlorosilanes,[4g] and imines,[4h] react with α-(trimethylsilyl)vinyllithium to give the corresponding adducts.

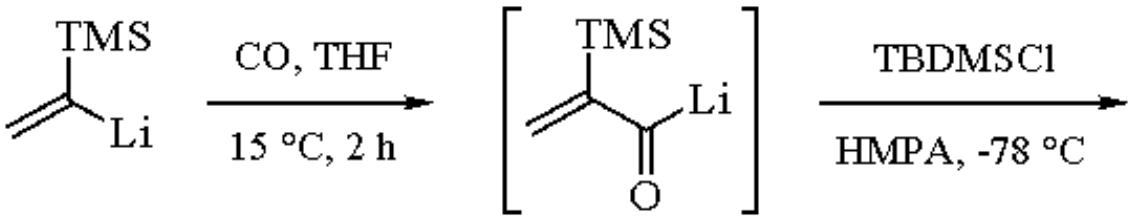

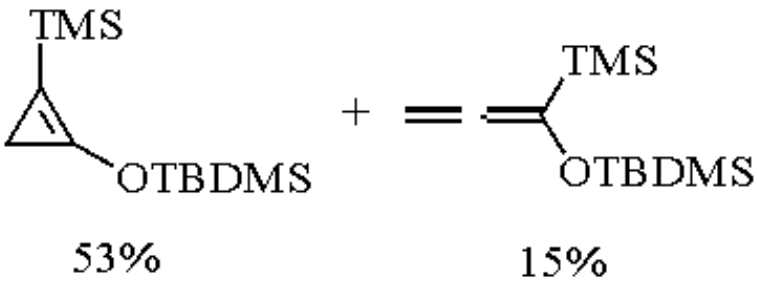

(11)

Related Reagents.

Other types of 1-lithio-1-vinylsilanes have been made, mainly through the lithium-halogen exchange reaction described before. For example, one or all of the methyl groups on silicon can be substituted by phenyls. The compounds (**2**)[4c] and (**3**)[14] have properties similar to α-(trimethylsilyl)vinyllithium.

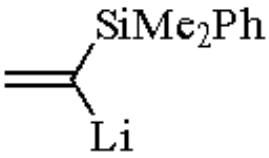

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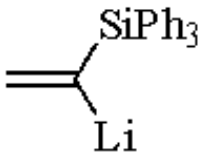

(3)

Monosubstitution in the 2-position on the vinyl moiety has been extensively exemplified in the literature. The stereochemistry of the double bond implies two possible types of reagents. For example, the 2-(*Z*)-monosubstituted (**4**,[15] **5**[11d]) and the 2-(*E*)-monosubstituted (**6**,[16a] **7**[16b]) 1-lithiovinylsilanes have been treated with carbonyl and alkyl electrophiles.

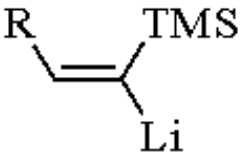

(4) R = C_6H_{13}
(5) R = $PhCH_2OCH_2$

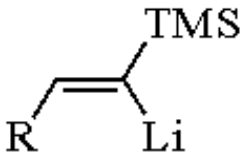

(6) R = *i*-Pr
(7) R = Ph

The stereochemistry of the 1-lithiovinylsilanes is easily lost, as exemplified in eq 12 where (**9**), prepared by a transmetalation reaction, subsequently equilibrates to a mixture containing (**9**) and (**10**).[15,16b]

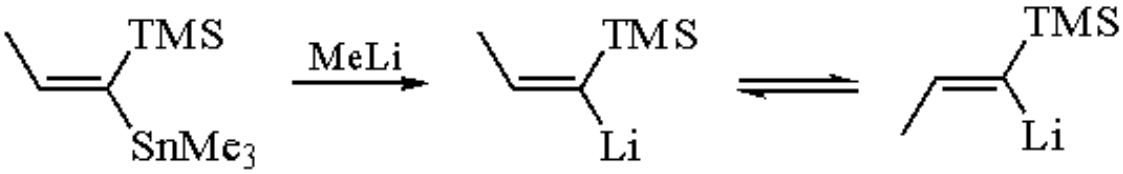

(8) **(9)** **(10)** (12)

One other related reagent includes the species (**11**),[17] obtained from silylcupration of the corresponding lithium acetylide. This is yet another way to obtain 1-lithiovinylsilanes substituted in the β-position.

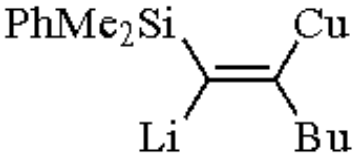

(11)

See also ***Lithium (Trimethylsilyl)acetylide***, ***(E)-2-(Trimethylsilyl)vinyllithium***, and ***Vinyllithium***.

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(*E*)-2-(Trimethylsilyl)vinyllithium

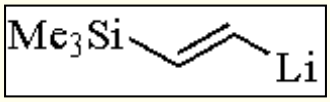

[55339-31-6] · $C_5H_{11}LiSi$ · (*E*)-2-(Trimethylsilyl)vinyllithium · (MW 106.19)

(for introduction of the β-(trimethylsilyl)vinyl moiety; the resulting alkenylsilanes undergo useful electrophilic substitutions of the TMS group[1])

Form Supplied in: not available commercially; prepared in situ in either THF or diethyl ether.

Preparative Methods: attempts to produce synthetically useful quantities of (*E*)-2-(trimethylsilyl)vinyllithium (**1**) by reaction of ***Lithium*** metal with ***(2-Bromovinyl)trimethylsilane*** (**2**) failed because of concomitant metalation-elimination processes involving (**1**) and (**2**).[2] However, the transmetalation process between (**2**) and excess ***t-Butyllithium*** has been effectively used to provide (**1**) (eq 1).[3] An alternative route to (**1**) employs the transmetalation of a 1-(trimethylsilyl)-2-stannylethylene with organolithium reagents (eqs 2 and 3).[4,5]

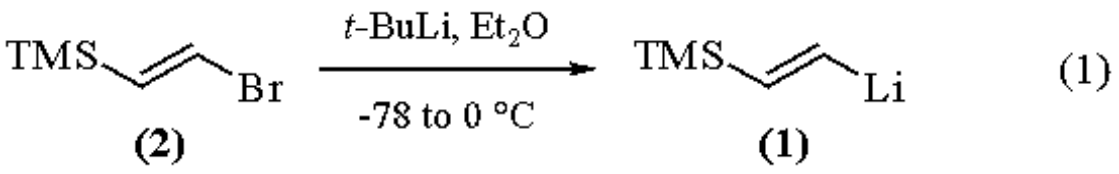

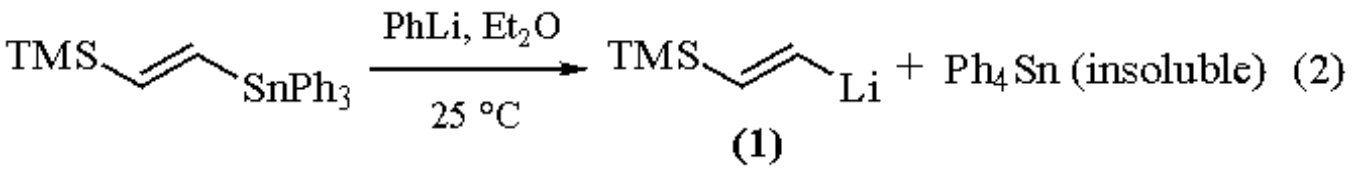

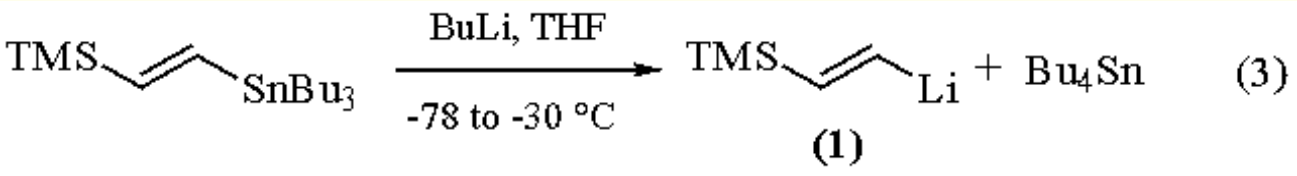

Handling, Storage, and Precautions: must be prepared and transferred under inert gas (Ar, N_2) to exclude oxygen and moisture.

Substitution Reactions.

Alkylating agents containing primary alkyl or methyl groups react with (**1**) in synthetically useful yields (eqs 4 and 5).[4,5] Reaction of (**1**) with ***1,2-Dibromoethane*** affords (**2**),[4] while the use of metal or metalloidal halides generally results in high yields of coupling products (eqs 6-9).[4-7]

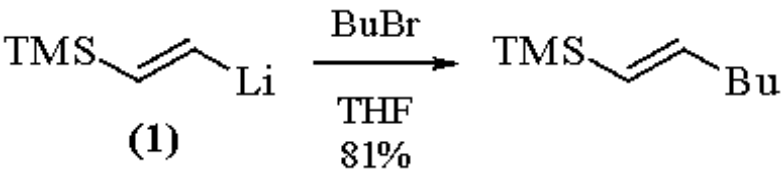

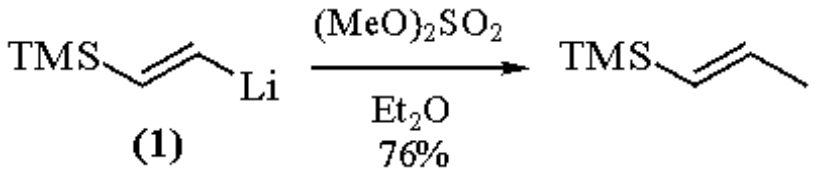

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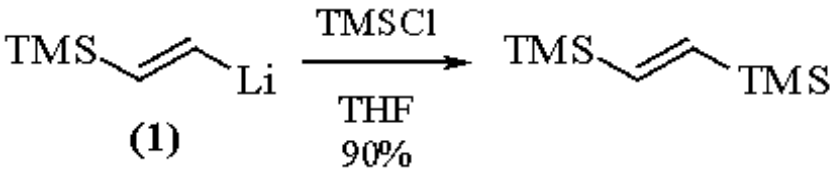

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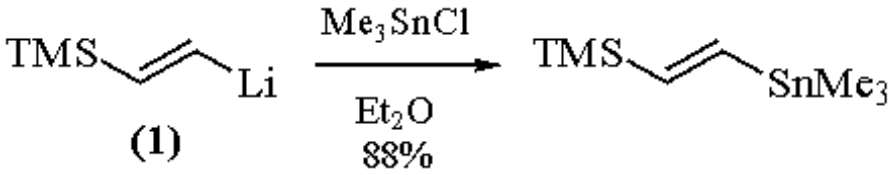

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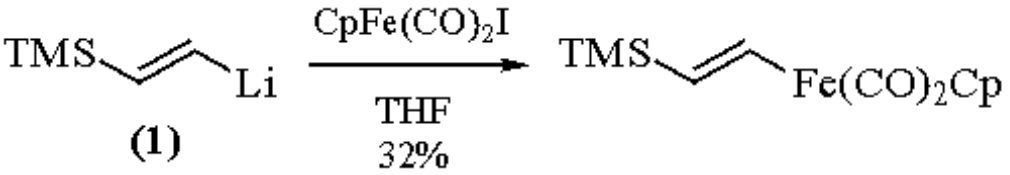

(9)

An important subset of the reaction with metal halides is the conversion of (**1**) into more discriminating reagents. Thus the reaction of (**1**) with ***Copper(I) Iodide*** forms a diorganocuprate (**3**) which adds in a 1,4-fashion to conjugated enones (eqs 10 and 11).[3a,b,8] In this same vein, (**2**) was transformed into an alkenylzinc reagent which displayed selectivity between adjacent aldehyde and ester functionalities (eq 12).[9]

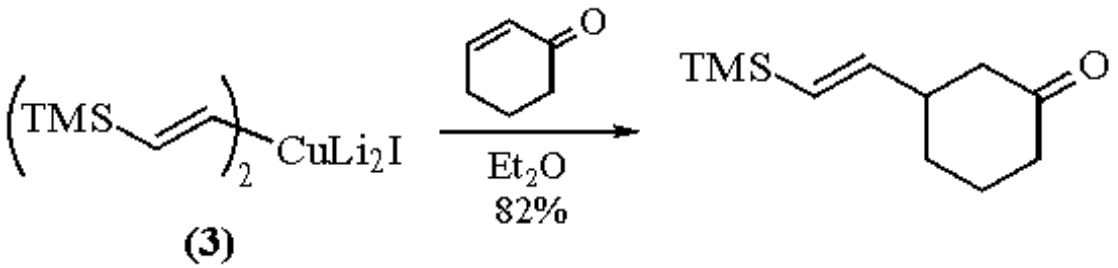

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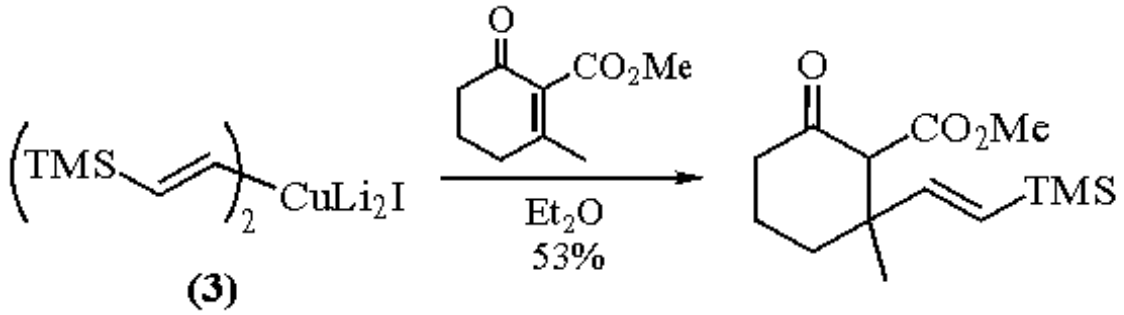

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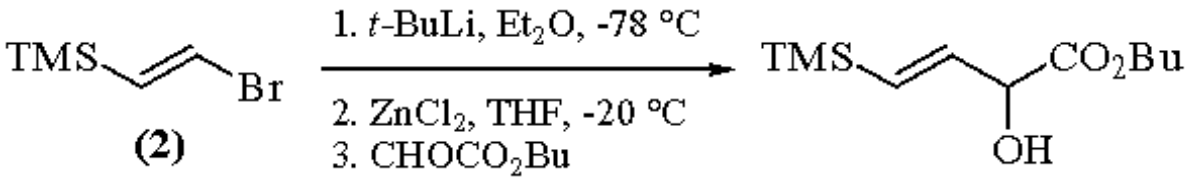

(12)

Addition Reactions.

The behavior of (**1**) with carbonyl-containing compounds is completely straightforward, with aldehydes (eqs 13 and 14),[10,11] ketones (eqs 15 and 16),[12,13] and ***Carbon Dioxide*** (eq 17)[4] leading cleanly to expected products. Sato and co-workers have observed (**1**) to display considerable chemoselectivity in favor of an aldehyde functionality when presented with an ester as the alternative (eq 18).[13]

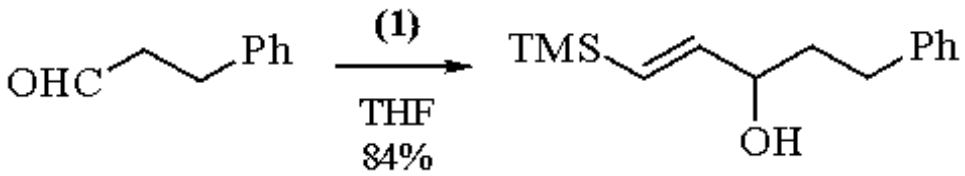

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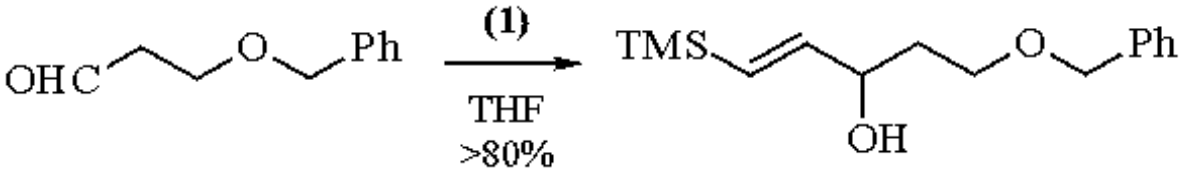

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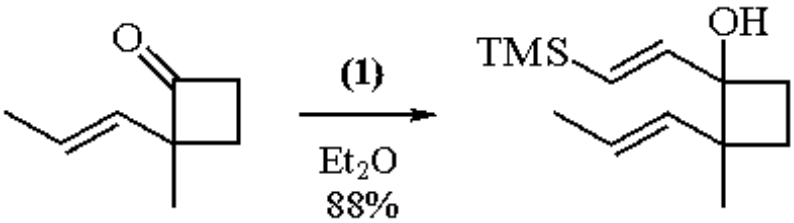

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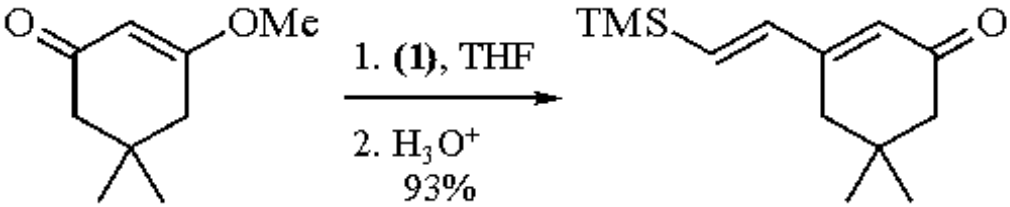

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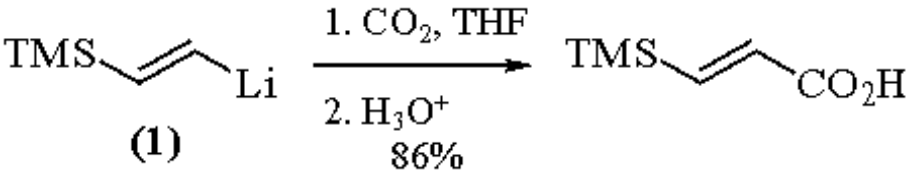

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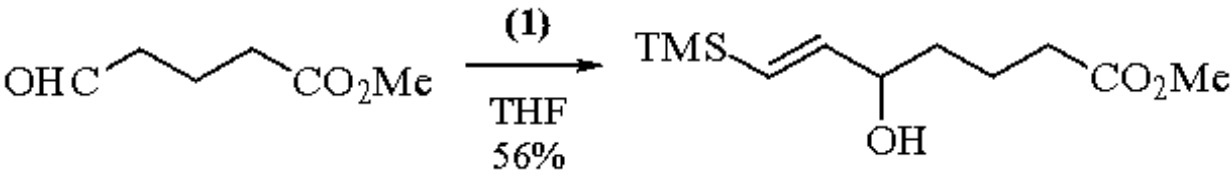

(18)

Related Reagents.

(2-Bromovinyl)trimethylsilane; ***(E)-1-Lithio-2-tributylstannylethylene***; ***(E)-1-Tri-n-butylstannyl-2-trimethylsilylethylene***.

---

1. Alkenylsilane chemistry reviews: (a) Fleming, I.; Dunogues, J.; Smithers, R. *OR* **1989**, *37*, 57. (b) Blumenkopf, T. A.; Overman, L. E. *CRV* **1986**, *86*, 857. (c) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981.
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3. (a) Boeckman, Jr., R. K.; Bruza, K. J. *TL* **1974**, 3365. (b) Boeckman, Jr., R. K.; Bruza, K. J. *JOC* **1979**, *44*, 4781. (c) Miller, S. A.; Gadwood, R. C. *JOC* **1988**, *53*, 2214.
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1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide[1]

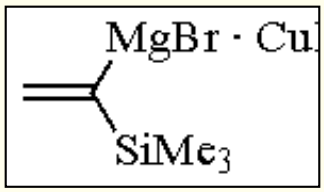

[49750-22-3] · $C_5H_{11}BrMgSi$ · 1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide · (MW 203.46)

[7681-65-4] · CuI · 1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide · (MW 190.45)

(reacts with epoxides to give homoallylic alcohols useful for the synthesis of α-methylenebutyrolactones;[2] can function as a synthon for epoxides;[3,4] adds to D-glyceraldehyde acetonide to give epoxy alcohols and D-threose derivatives[3,4])

Preparative Methods: prepared in situ under anhydrous conditions by reacting 1-(trimethylsilyl)vinylmagnesium bromide (**1**) with ***Copper(I) Iodide*** (**2**) in various molar ratios.

Handling, Storage, and Precautions: use in a fume hood.

α-Methylenebutyrolactone Synthesis.

Epoxides react with (**1**) in the presence of catalytic amounts of (**2**) to give homoallylic alcohols (**3**) (eq 1) which were used in a synthesis of α-methylene lactones (**4**) (eq 2).[2] In the absence of (**2**) the reaction fails to give the desired homoallylic alcohols (**3**).

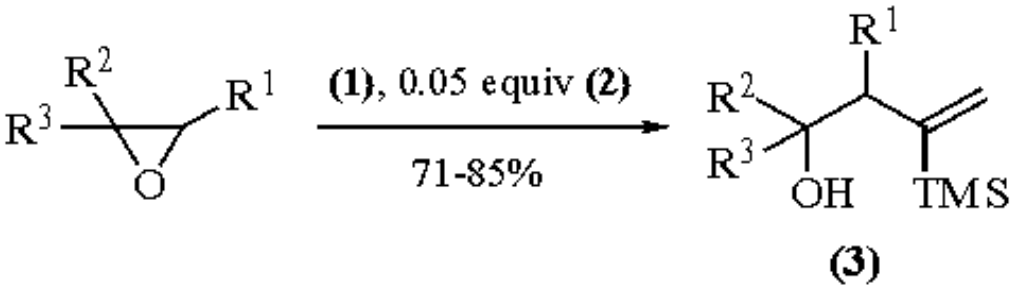

(1)

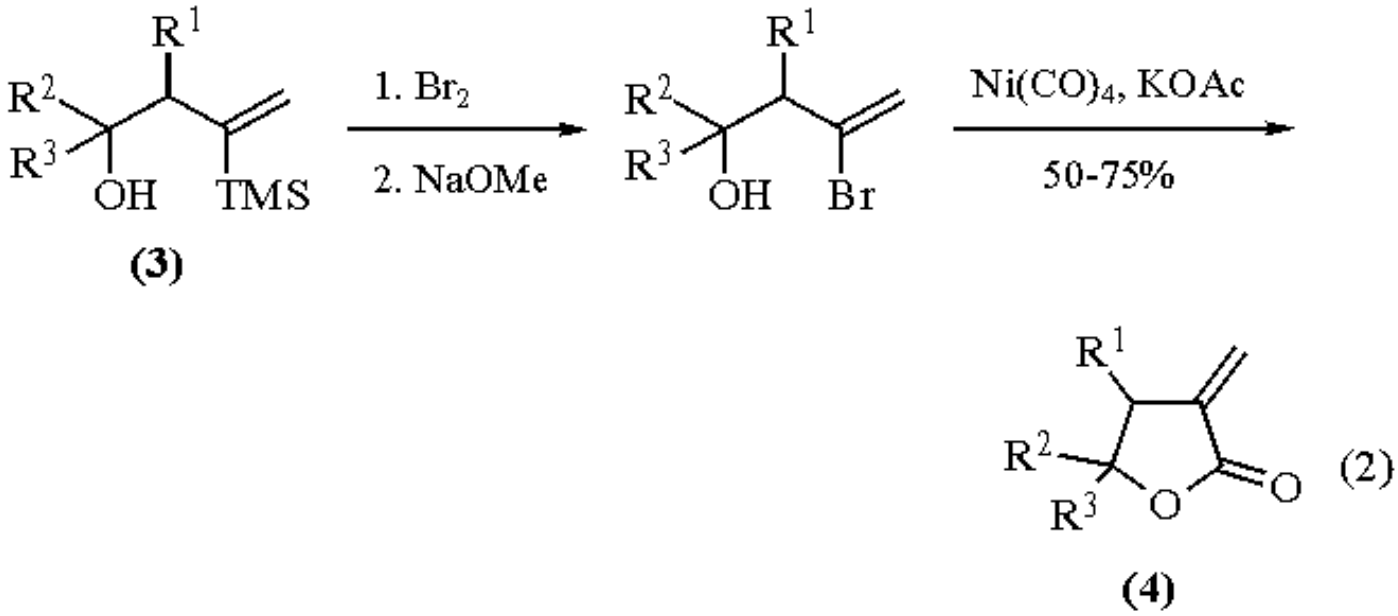

Addition to D-Glyceraldehyde Acetonide: Preparation of Epoxy Alcohols and D-Threose Derivatives.

2,3-*O*-isopropylideneglyceraldehyde (**5**) reacts with (**1**) in the presence of excess (**2**) to give the *syn* addition product (**6**) with high diastereoselectivity (>98:2 *syn*:*anti*, eq 3).[3,4] Sharpless epoxidation of (**6**) followed by protodesilylation gave epoxy alcohol (**7**) (eq 4).[3] Alternatively, (**6**) can be converted to the D-threose derivative (**8**) by a sequence of three steps: protodesilylation, protection, and ozonolysis.[4] Replacement of ***Copper(I) Cyanide*** and ***Methyllithium*** for CuI in this reaction gives predominantly the *anti* addition product in 87% yield.

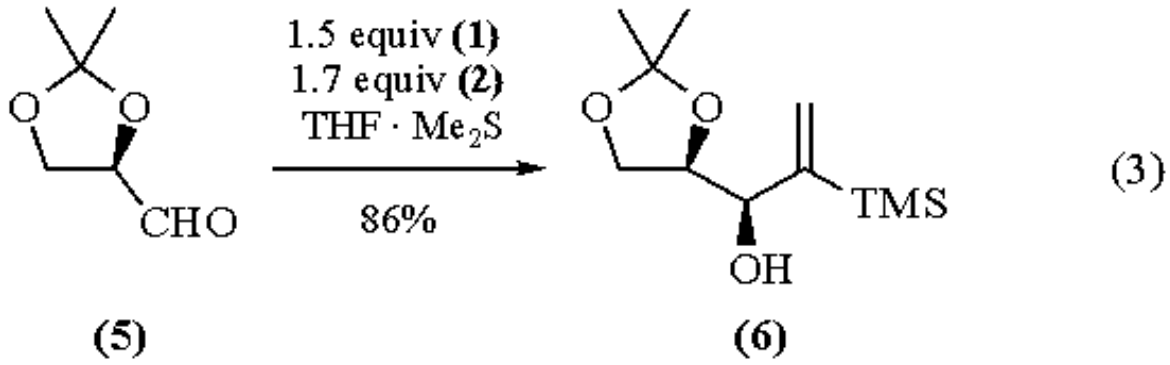

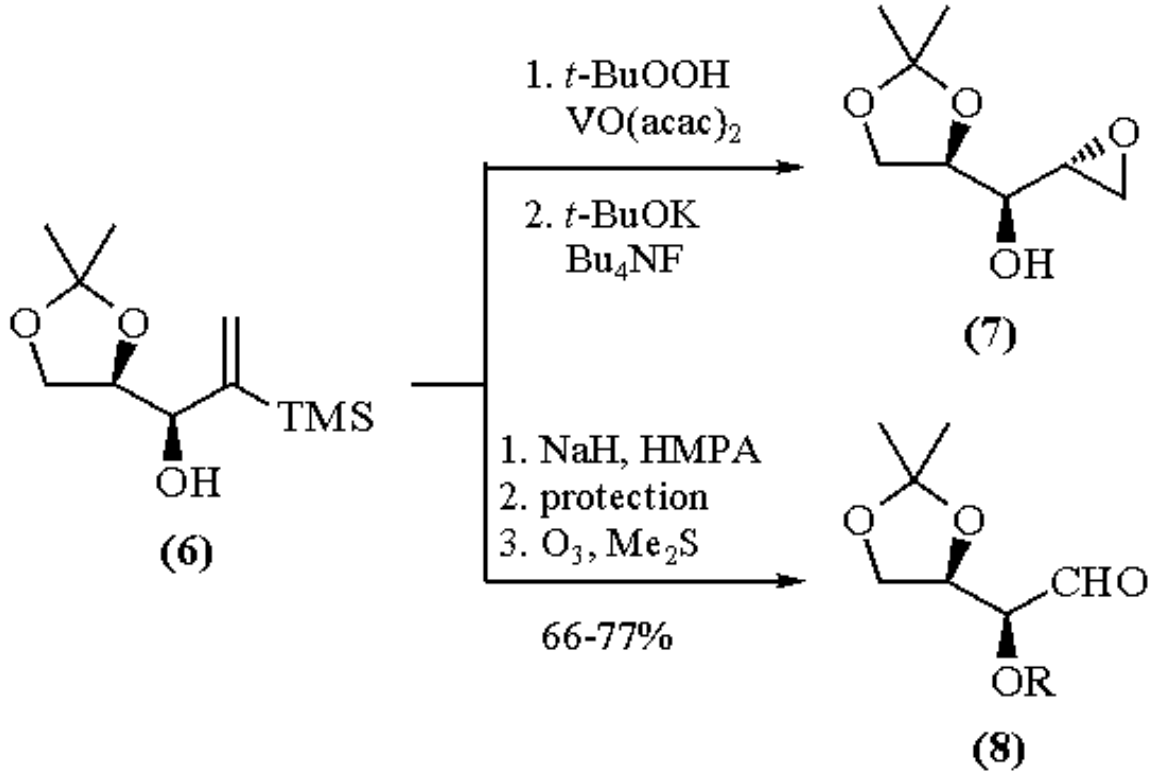

(4)

Related Reagents.

2-(3-Trimethylsilyl-1-propenyl)magnesium Bromide-Copper(I) Iodide; ***Vinylmagnesium Bromide***; ***Vinylmagnesium Bromide-Copper(I) Iodide***.

---

1. For a recent review of organocopper reagents, see: Lipshutz, B. H.; Sengupta, S. *OR* **1992**, *41*, 135.
2. Matsuda, I. *CL* **1978**, 773.
3. Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *CC* **1985**, 1636.
4. Kusakabe, M.; Sato, F. *CL* **1986**, 1473.

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Trimethylstannylcopper-Dimethyl Sulfide

$Me_3SnCu.Me_2S$

[89041-25-8] · $C_5H_{15}CuSSn$ · Trimethylstannylcopper-Dimethyl Sulfide · (MW 289.53)

(transfer of trimethyltin to electrophilic substrates, including β-iodo α,β-unsaturated ketones,[1] α,β-alkynic carboxylic acid derivatives,[2-5] and terminal alkynes[6])

Physical Data: prepared in situ; its THF solution is deep red.

Solubility: sol THF.

Preparative Method: $Me_3SnCu.Me_2S$ (**2**) is readily prepared[1] by addition of solid $CuBr.Me_2S$[8] (see ***Copper(I) Bromide***) to a solution of ***Trimethylstannyllithium*** (**1**)[7b,9] in THF (eq 1). The actual structure of the stannylcopper(I) reagent is not known. Formula (**2**) is employed for convenience and on the basis of analogy with alkylcopper(I) reagents.

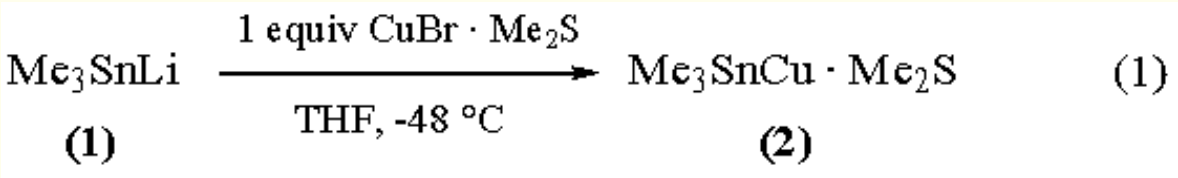

Handling, Storage, and Precautions: the reagent is sensitive to air and must be prepared in dry THF and used under an inert atmosphere. Since organotin compounds exhibit toxicity,[7a] reaction workup should be carried out only in a well-ventilated fume hood.

Reaction with α,β-Unsaturated Carbonyl Systems.

Reagent (**2**) is appreciably less reactive than the parent Me_3SnLi (**1**). Although (**1**) efficiently effects conjugate addition of the Me_3Sn function to α,β-unsaturated ketones and esters,[1,9] (**2**) reacts with these substrates sluggishly or not at all.[1] On the other hand, (**2**) is an excellent agent for the transformation of β-iodo α,β-unsaturated ketones[10] into the corresponding β-trimethylstannyl enones (eq 2).[1] The latter substances are potentially useful intermediates for organic synthesis.[11]

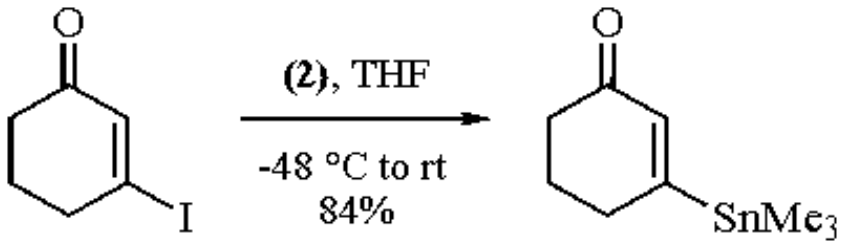

(2)

Reaction with α,β-Alkynic Carboxylic Acid Derivatives.

An important use of reagent (**2**) results in the regioselective *cis* addition of the elements of Me_3Sn-H across the triple bond of α,β-alkynic esters[2,5] and *N,N*-dimethylamides[4] (eqs 3 and 4). Attempts to trap the intermediates derived from the ester substrates with electrophiles other than protons have not been successful.[3-5,12] On the other hand, the corresponding intermediates obtained from the amide substrates can be trapped with reactive alkylating agents (eq 4).[4] The synthetic utility of alkyl (*E*)-3-trimethylstannyl-2-alkenoates (cf. **3**) has been demonstrated in a variety of contexts.[13]

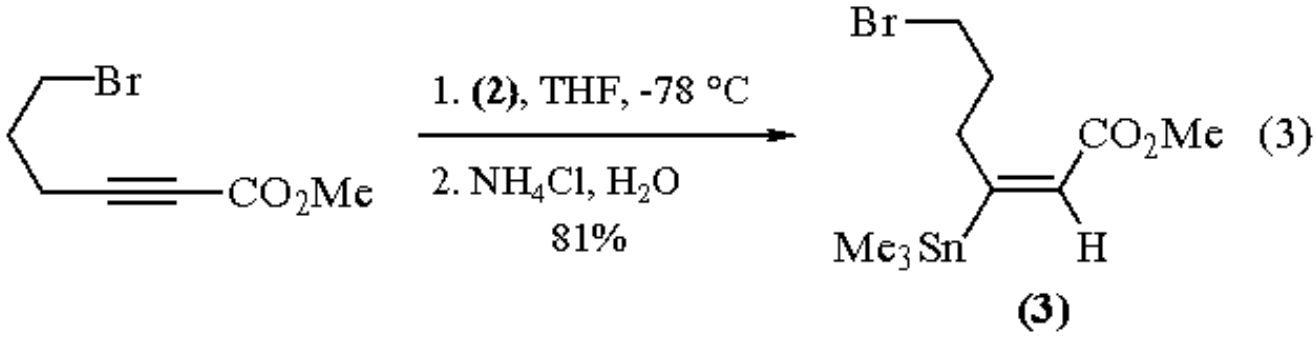

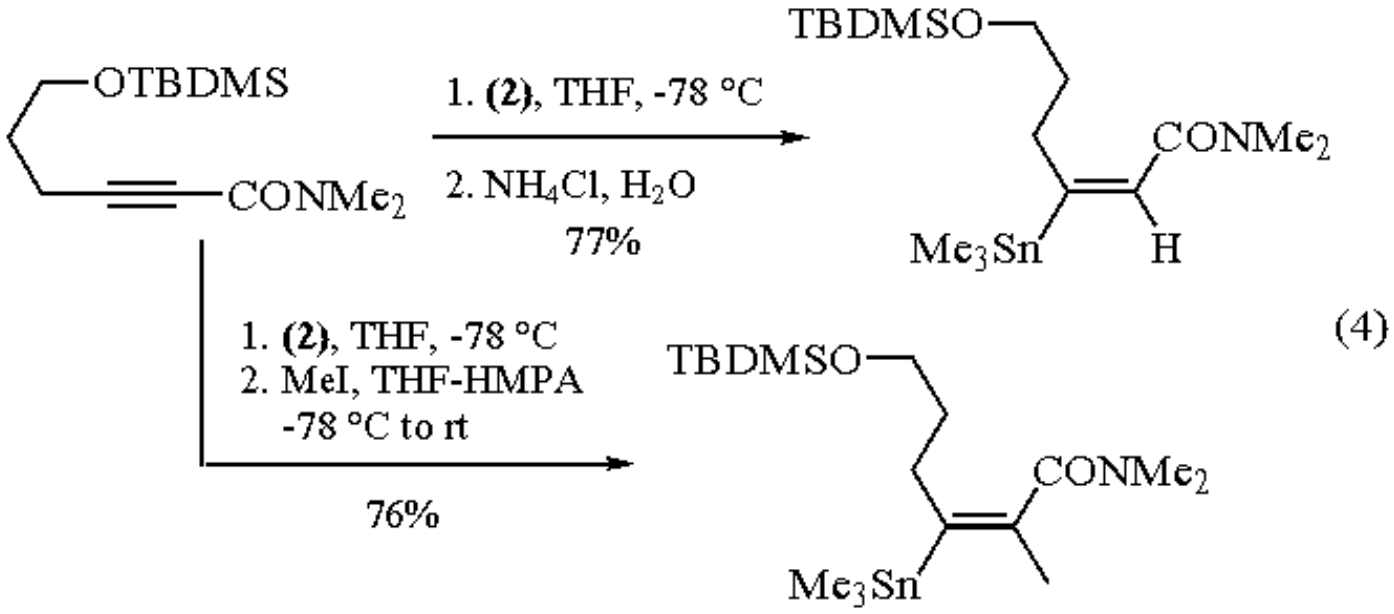

Interestingly, treatment of α,β-alkynic esters with reagent (**2**) under suitable conditions provides alkyl (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates (eq 5).[3] The latter compounds, which may also be prepared by Pd^0-catalyzed addition of ***Hexamethyldistannane*** to α,β-alkynic esters,[14a,c] are useful substrates for the stereocontrolled preparation of tetrasubstituted alkenes.[14b]

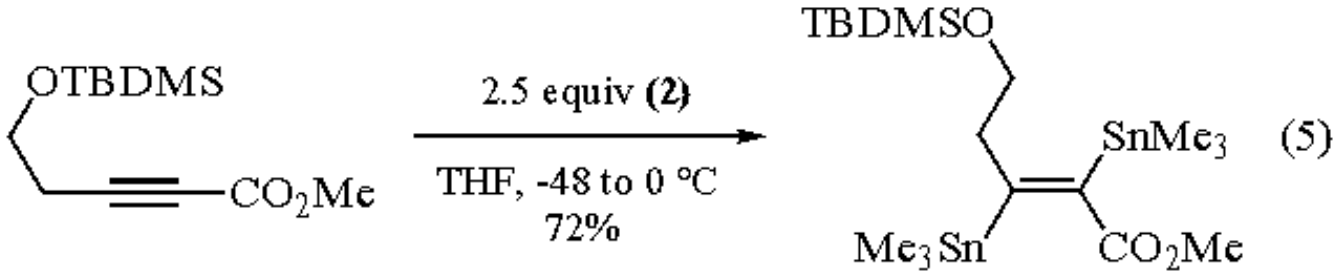

Reaction with 1-Alkynes.

Under appropriate conditions, $Me_3SnCu.Me_2S$ (**2**) reacts with 1-alkynes to provide, regioselectively, 2-trimethylstannyl-1-alkenes[6,15-22] (eq 6).[15] This process can be carried out successfully in the presence of a variety of functional groups. Functionalized 2-trimethylstannyl-1-alkenes are useful intermediates for organic synthesis[16-19,23] (see also ***4-Chloro-2-trimethylstannyl-1-butene***).

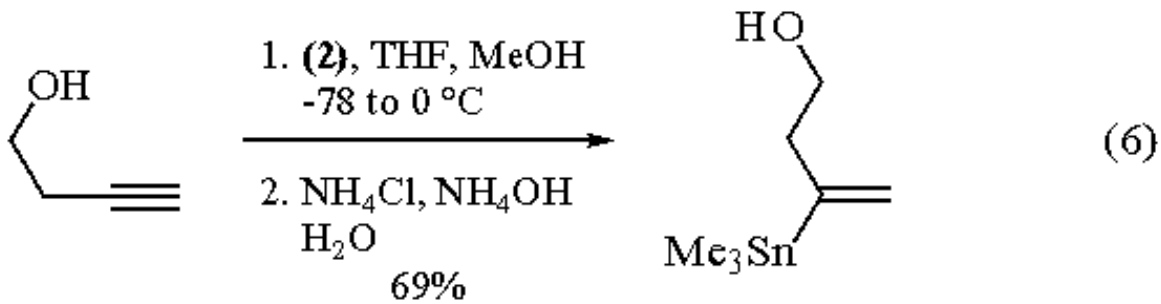

Related Reagents.

Bis(methylthio)(trimethylstannyl)methane; ***Lithium Phenylthio(trimethylstannyl)cuprate***; ***Tri-n-butylstannylcopper***; ***Tri-n-butylstannyllithium***; ***2-Trimethylstannylmethyl-1,3-butadiene***.

---

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2-Trimethylstannylmethyl-1,3-butadiene[1]

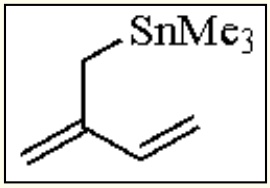

[71092-51-8] · $C_8H_{16}Sn$ · 2-Trimethylstannylmethyl-1,3-butadiene · (MW 230.95)

(isoprenylation reagent;[1] Diels-Alder diene[1])

Physical Data: bp 77-78 °C/40 mmHg.

Analysis of Reagent Purity: ^{1}H NMR δ 0.07 (9H, s), 1.89 (2H, d, *J* = 1.0 Hz), 4.65-5.20 (4H, m), 6.33 (1H, dd, *J* = 10.0, *J* = 17.4 Hz); λ_{max} (hexane) 239.5 (ε 10 000).

Solubility: sol common organic solvents but avoid hydroxylic solvents.

Purification: by distillation.

Preparative Methods: by the reaction of the Grignard reagent prepared from chloromethyltrimethylstannane and chloroprene in the presence of a catalytic amount of dichlorobis(diphenylphosphino)propanenickel(II) in 75% yield,[2] analogous to the procedure employed for the preparation of ***2-Trimethylsilylmethyl-1,3-butadiene***.[3] The reaction of ***Trimethylstannyllithium***[4] with α-bromoisoprene[5] also gives 2-trimethylstannylmethyl-1,3-butadiene in 70% yield.[6]

Handling, Storage, and Precautions: can be stored in a glass bottle under nitrogen. Organotin derivatives are known to be toxic. Therefore the reagents should be handled in a well-ventilated hood and contact with the skin and eyes should be avoided.

Diels-Alder Reaction.

2-Trimethylstannylmethyl-1,3-butadiene undergoes Diels-Alder reactions with a variety of dienophiles in high yield (eqs 1 and 2). With unsymmetrical dienophiles, the para products are obtained with higher selectivity than the reaction of the silicon analog (see ***2-Trimethylsilylmethyl-1,3-butadiene***).[2]

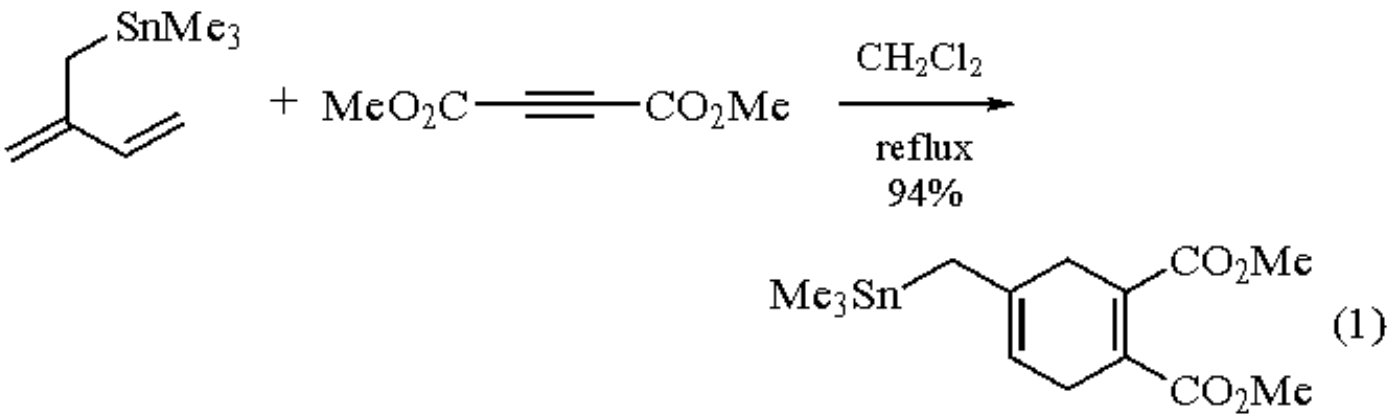

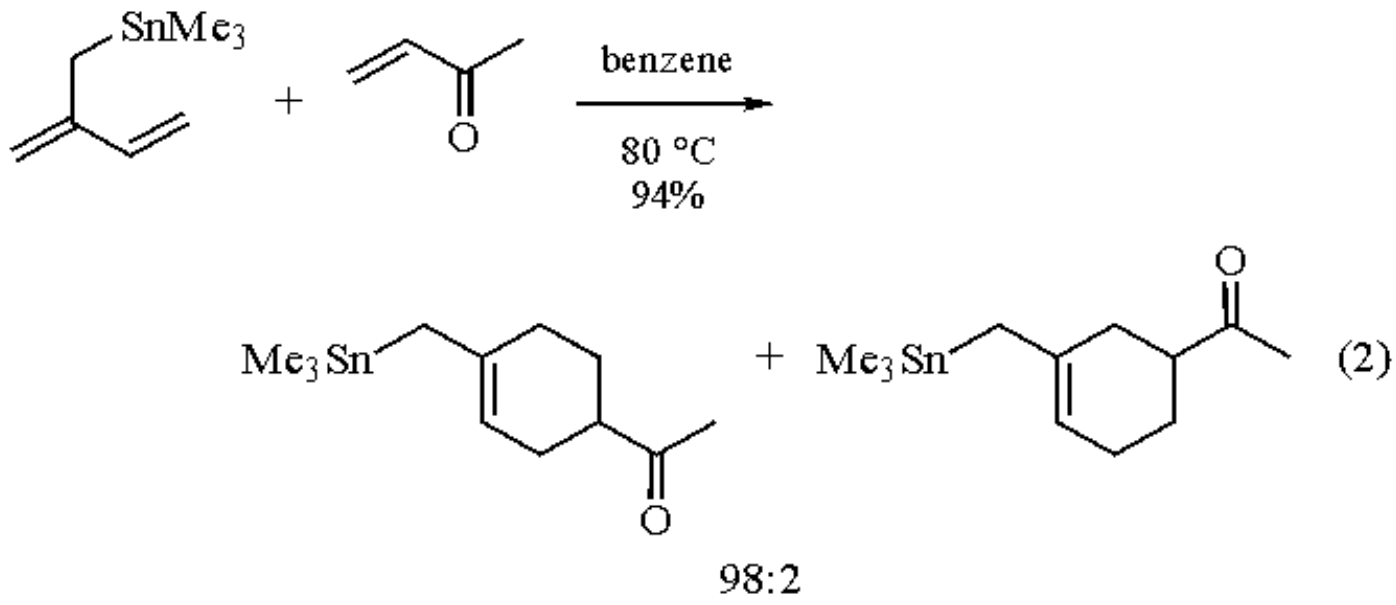

Allylation Reaction.

2-Trimethylstannylmethyl-1,3-butadiene enters the usual allylation reactions with carbonyl compounds in the presence of ***Boron Trifluoride Etherate*** (eq 3).[7]

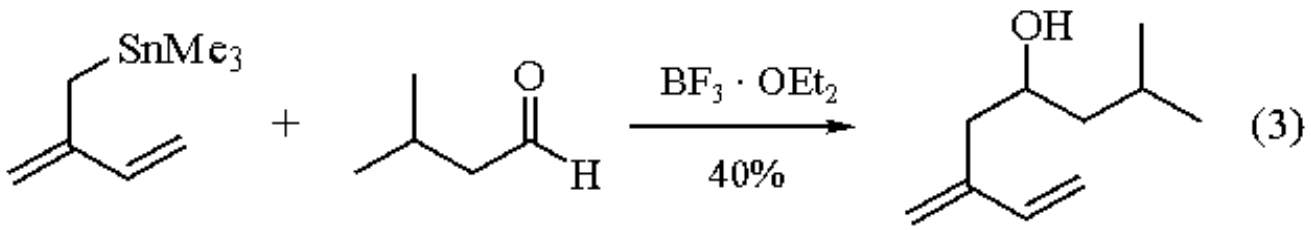

Cross-Coupling Reaction.

Zinc Chloride-catalyzed reaction with ***Allyl Bromide*** results in the formation of allyl coupling products (eq 4).

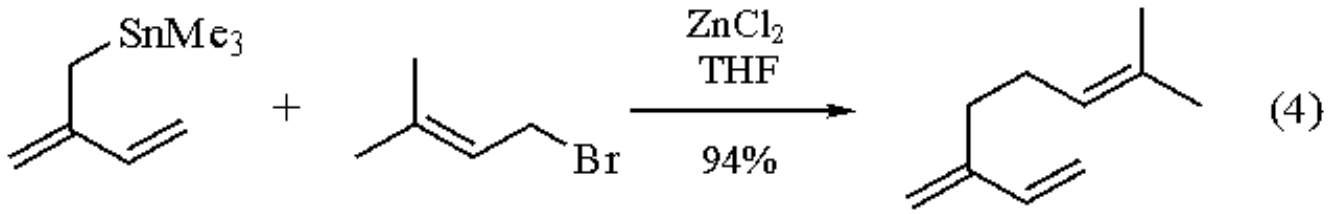

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(Trimethylstannylmethyl)lithium[1]

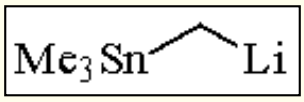

[76373-10-9] · $C_4H_{11}LiSn$ · (Trimethylstannylmethyl)lithium · (MW 184.80)

(methylenation reagent for several electrophiles;[1] methylene double anion equivalent connecting two different electrophiles with methylene bridge[1])

Solubility: sol ethers (THF, diethyl ether, DME).

Preparative Methods: treatment of bis(trimethylstannyl)methane with *n*-butyllithium or ***Methyllithium*** in dry THF.[2] Bis(trimethylstannyl)methane can be obtained by the reaction of dichloromethane with 2 equiv of trimethylstannylsodium in liq NH_3 (89%)[3] or by the reaction of ***Diiodomethane*** with ***Tin(II) Bromide*** followed by the treatment with methylmagnesium iodide.[4]

Purification: the precursor bis(trimethylstannyl)methane should be distilled under reduced pressure before use (88-92 °C/15 mmHg).

Handling, Storage, and Precautions: since organotin reagents are toxic, all experiments should be performed in a good fume hood and with gloves.

Methylenation Reagent for Carbonyl Compounds.

The title reagent (**1**) or the analogous (tributylstannylmethyl)lithium react with ketones (**2**), affording β-stannyl alcohols (**3**) which undergo Peterson-type eliminations upon acid treatment or heating to methylene compounds (**4**) (eq 1).[5]

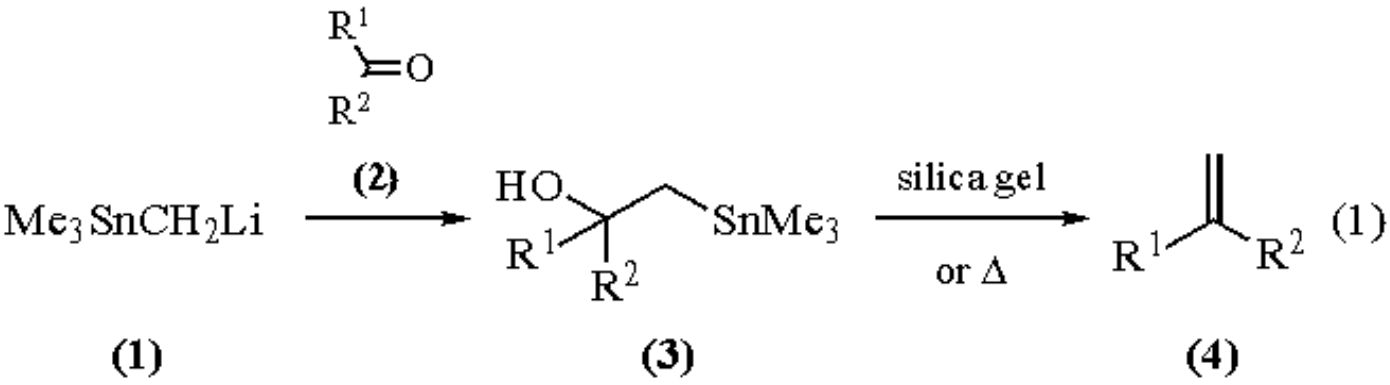

In contrast to the Wittig or Peterson reaction, which sometimes fails with enolizable ketones (5-20%),[6] the present reaction gives the desired alkenes in good yields (64-96%).[5] Remarkably, the reaction with *cis*-1-decalone in the presence of ***Hexamethylphosphoric Triamide*** proceeds with no epimerization, giving the *cis-exo* methylene compound in 91% yield, while the Wittig reaction affords the product as a mixture of *cis* and *trans* isomers in 32% yield.

Methylenation Reagent for Miscellaneous Electrophiles.

Reagent (**1**) reacts with the oxiranes (**5**) to form γ-stannyl alcohols (**6**) in the presence of 2 equiv HMPA. The alcohols (**6**) are easily converted into cyclopropanes (**7**) with Lewis acids (eq 2).[5]

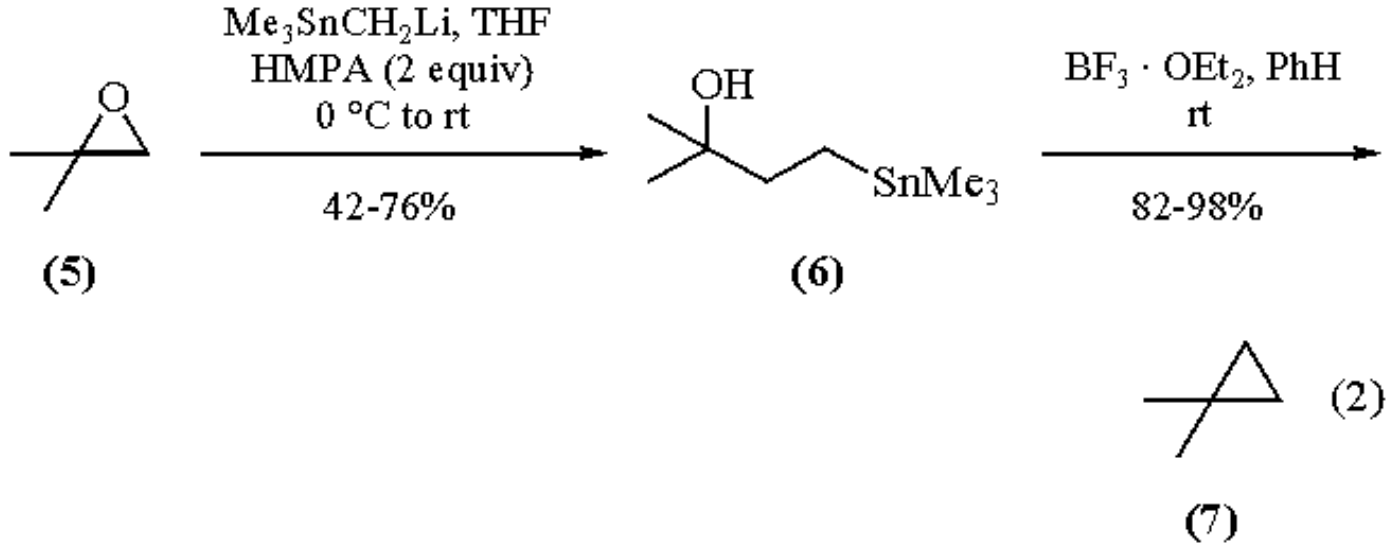

The reaction pattern of (**1**) with carbonyl groups is influenced by the presence of leaving groups at the α-position. Acyclic α,β-epoxy ketones (**8a**) produce cyclopropanols (**10**) as a single product, while cyclic ketones (**8b**) produce mixtures of (**10**) and (**12**).[7] Presumably nonselective attack of (**1**) produces the diastereomers of (**9**), which cyclize either to (**10**) or (**11**) under stereoelectronic control; β-elimination of (**11**) would produce (**12**). Cyclopropanols (**10a**) and (**10b**) can be converted into β,γ-unsaturated ketones (**13**) and (**14**), respectively, upon Lewis acid treatment. Acyclic enone (**13**) (R = Me) can be obtained in one pot in about 80% yield from the epoxy ketones (**8a**) by successive treatments with reagent (**1**) and ***Hydrogen Chloride*** (eq 3).

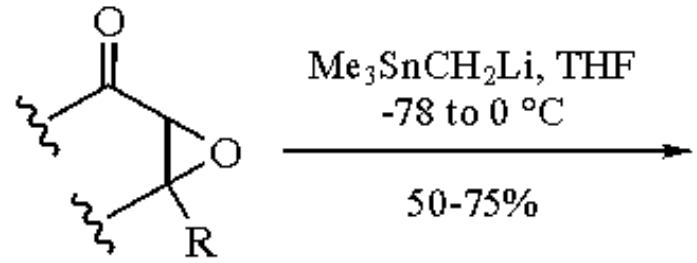

(8a) acyclic
(8b) cyclic

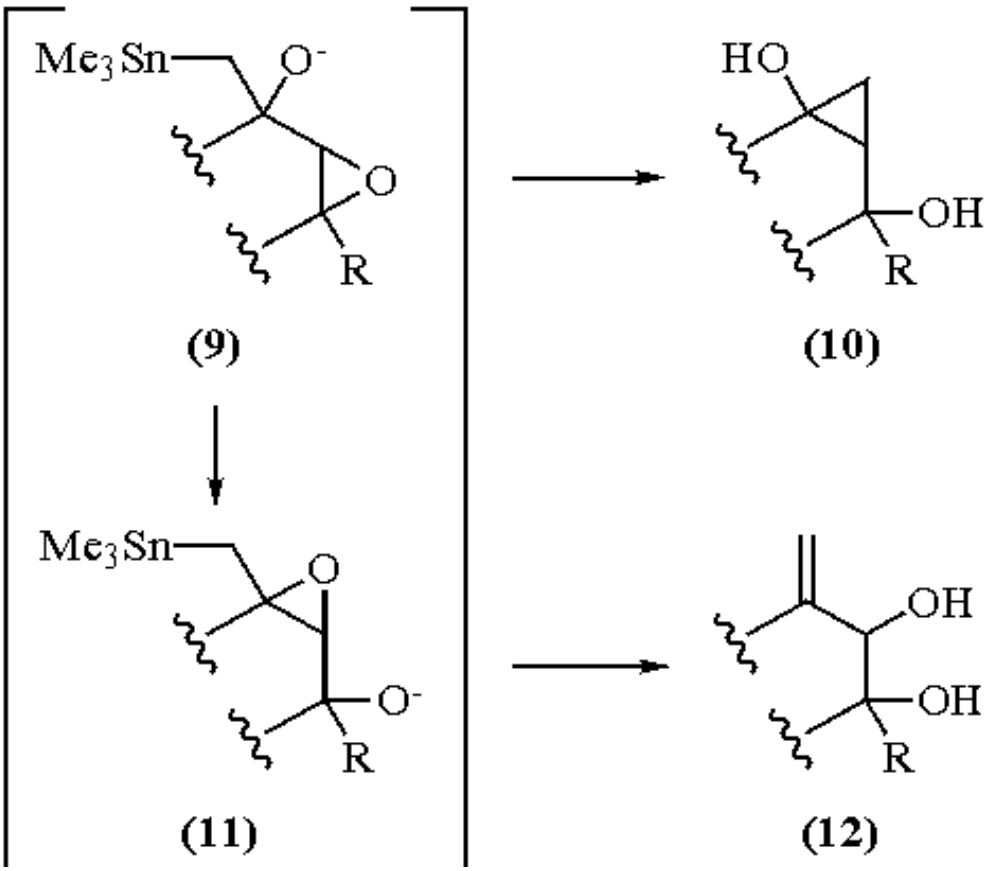

(3)

(11) (12)

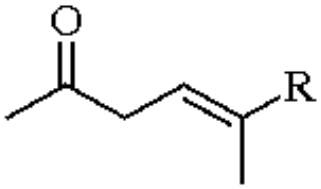

(13)

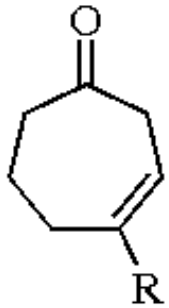

(14)

Reaction with Esters: Reagent for Connecting Two Different Kinds of Electrophiles with a Methylene Bridge.

Reagent (**1**) reacts with esters (**15**) to produce enolates (**17**), which are trapped by protons or aldehydes to afford methyl ketones or aldols, respectively (eq 4).

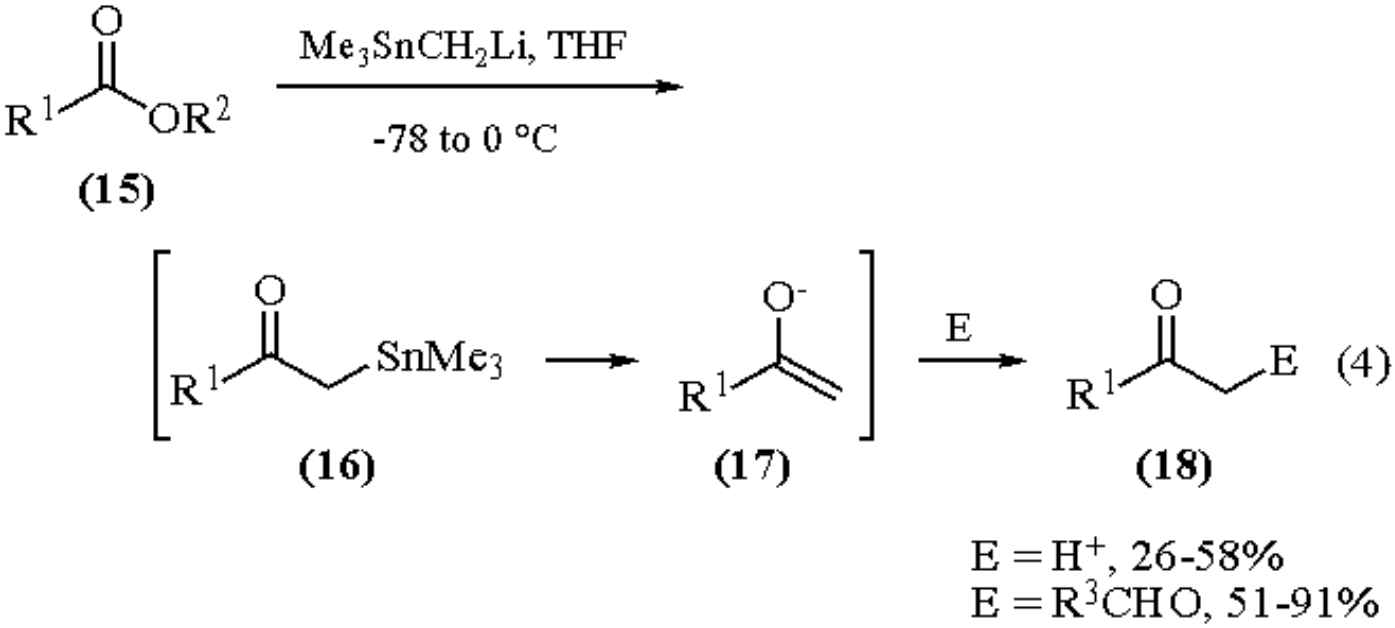

Enolates (**17**) react with methyl formate to afford β-keto aldehydes (**20**) in enol form. As an application, D-mycaroside (**22**) has been synthesized (eq 5).[8]

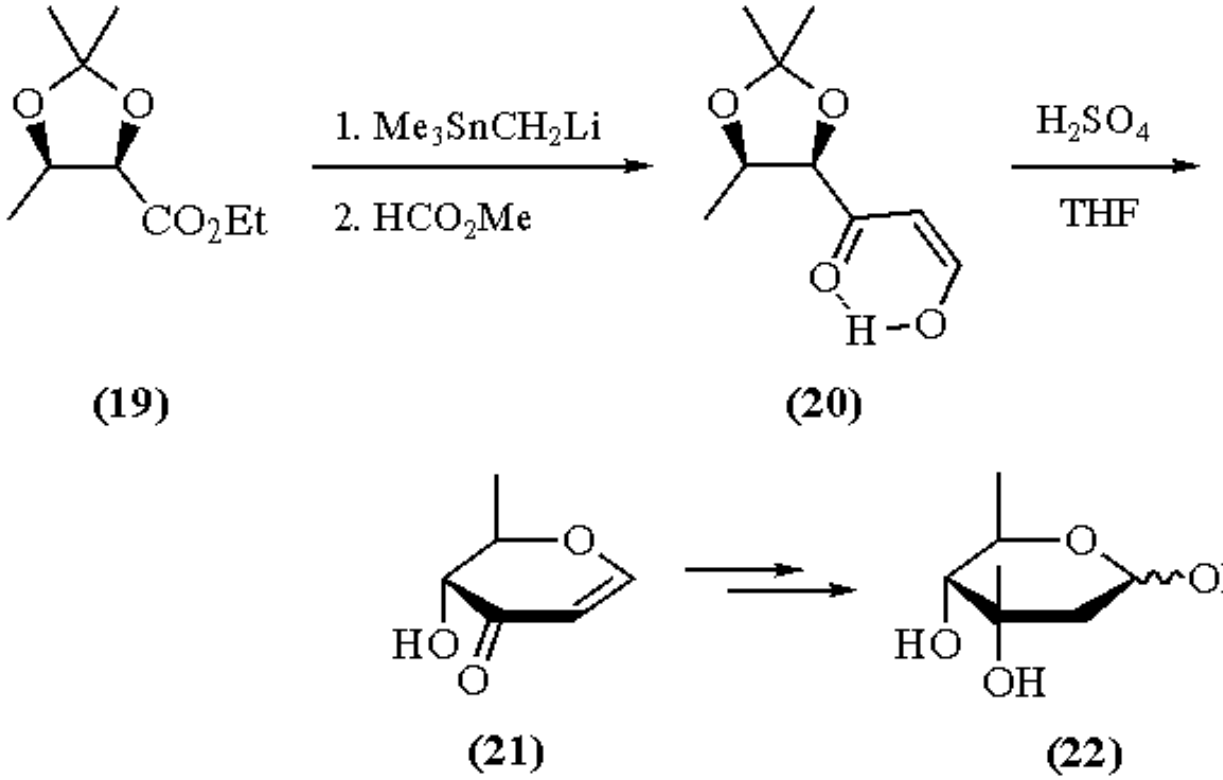

An analog of reagent (**1**), (trimethylstannyl)methylmagnesium iodide, has been used for methylenation of thioacetals (**23**) in the presence of a Ni^{II} catalyst (eq 6).[9]

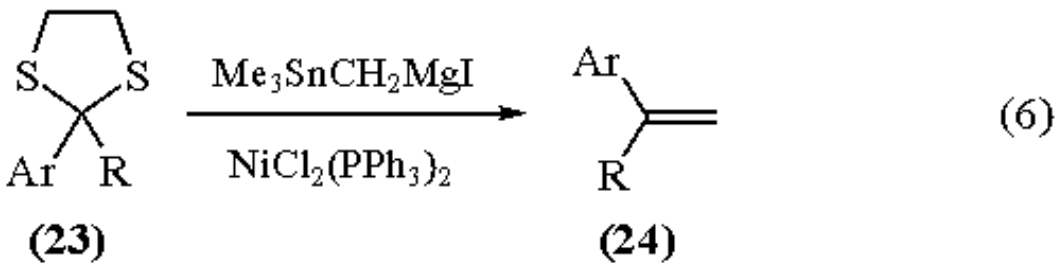

Related Reagents.

Trimethylsilylmethyllithium.

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Trimethylsulfonium Hydroxide

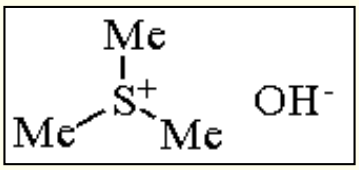

[172387-03-5] · $C_3H_{10}OS$ · Trimethylsulfonium Hydroxide · (MW 94.20)

(quantitative pyrolytic *O*-alkylation of fatty acids during gas chromatographic analysis)

Preparative Methods: by treating ***Trimethylsulfonium Iodide*** with ***Silver(I) Oxide*** in methanol;[2] by electrochemical method;[3] and in aqueous solution, by treating trimethylsulfonium iodide with ***Tetra-n-butylammonium Hydroxide*** using an extraction procedure.[1] The reagent has been reported to be stable in cool methanol for at least six months.[4]

General Discussion.

Trimethylsulfonium hydroxide is primarily referred to in the literature as a reagent for derivatizing fatty acids during gas chromatographic analysis through pyrolytic alkylation (eq 1).[5]

$$RCO_2H + Me_3S^+ OH^- \xrightarrow[-H_2O]{} RCO_2^- Me_3S^+ \xrightarrow[-Me_2S]{} RCO_2Me \quad (1)$$

The transformation takes place in the injection port, alleviating the need for more time consuming methods. Alternative methods include basic hydrolysis followed by acid-catalyzed re-esterification,[6] transesterification with sodium methoxide,[7] pyrolytic alkylation using a trialkylselenonium hydroxide,[4] and pyrolytic alkylation using a quaternary ammonium hydroxide.[8] Each of these methods has limitations. Hydrolysis and re-esterification require a significant amount of laboratory time. The transesterification using sodium methoxide fails to derivatize any free acids present in the initial mixture. Selenium reagents have handling problems due to their toxicity. Amine byproducts from a quaternary ammonium hydroxide have sufficiently long retention times to complicate a chromatogram.

Yamauchi has used trimethylsulfonium hydroxide to 2´-*O*-methylate pyrimidine ribonucleosides selectively.[9] A variety of metal ion catalysts for this methylation procedure were evaluated on a semipreparative scale.

The use of trimethylsulfonium hydroxide as a pyrolytic *O*-alkylating agent avoids many of the problems associated with other methods. The reagent is conveniently prepared from readily available starting materials and is relatively stable in solution.

---

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Trimethylsulfonium Iodide

$Me_3S^+X^-$

(X = I)

[2181-42-2] · C_3H_9IS · Trimethylsulfonium Iodide · (MW 204.09) (X = Br)

[3084-53-5] · C_3H_9BrS · Trimethylsulfonium Bromide · (MW 157.09)

(precursor of dimethylsulfonium methylide[1])

Physical Data: Me_3SI, mp 211-212.5 °C (dec); Me_3SBr, mp 201-202 °C (dec, sealed tube), 172 °C (dec).

Solubility: sol H_2O, alcohol, THF, DMSO.

Form Supplied in: Me_3SI, white crystals; Me_3SBr, white deliquescent crystals.

Preparative Methods: Me_3SI is prepared in almost quantitative yield by mixing equimolar amounts of ***Dimethyl Sulfide*** and ***Iodomethane*** at room temperature. After standing overnight, the resulting solid white cake is crushed and recrystallized from absolute ethanol to give pure trimethylsulfonium iodide.[1b,2]

To prepare Me_3SBr, a mixture of Me_2S and an excess amount (more than 3.0 equiv) of ***Bromomethane*** is heated at 100 °C for 4 h in a sealed tube. During workup the contents of the tube give out a strong irritating odor. The resulting white crystals are washed with ethyl acetate and recrystallized from a small amount of water to give white, deliquescent crystals of trimethylsulfonium bromide.[2a]

Handling, Storage, and Precautions: irritant.

Formation of Dimethylsulfonium Methylide.

Treatment of trimethylsulfonium iodide (or bromide) with strong bases such as the methylsulfinyl carbanion[1b,3] (***Potassium t-Butoxide*** in ***Dimethyl Sulfoxide***, ***Sodium Hydride*** in DMSO-THF, ***Sodium Ethoxide*** in DMSO) or ***n-Butyllithium*** in THF gave a solution of ***Dimethylsulfonium Methylide***. This heat-labile reagent generated in situ is an exceedingly selective methylene-transfer reagent which is of great use for converting carbonyl compounds into epoxides (even in the case of α,β-unsaturated carbonyl compounds).[4] This ylide also converts imines to aziridines.

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Trimethylsulfoxonium Iodide[1]

$Me_3SO^+X^-$

(X = I)

[1774-47-6] · C_3H_9IOS · Trimethylsulfoxonium Iodide · (MW 220.09) (X = Cl)

[5034-06-0] · C_3H_9ClOS · Trimethylsulfoxonium Chloride · (MW 128.64)

(precursor of dimethylsulfoxonium methylide,[1] which transfers a methylene group to ketones and aldehydes to form epoxides and to α,β-unsaturated carbonyl compounds to produce cyclopropyl derivatives;[1-3] a methylation reagent;[4] can function as a catalyst[5])

Physical Data: trimethylsulfoxonium iodide: mp 170 °C (dec), yellow crystalline powder; trimethylsulfoxonium chloride: 227 °C (subl), white powder. The vibrational spectra of both iodide and chloride salts, as well as NMR studies of molecular motion of both salts, have been investigated.[6-8] pK_a = 18.2 for sulfoxonium ion in DMSO.

Solubility: trimethylsulfoxonium iodide: 3.85 g/100 g H_2O (20 °C).[9] Trimethylsulfoxonium chloride has greater solubility in THF than trimethylsulfoxonium iodide.[10] Both sulfoxonium salts sol H_2O, DMSO, *t*-butanol.

Form Supplied in: both iodide and chloride salts are widely available in powder form.

Analysis of Reagent Purity: the purity of trimethylsulfoxonium iodide and trimethylsulfoxonium chloride can be determined by an $AgNO_3$ titration method. A miscible organic solvent, such as acetone, ethanol, or propanol, is usually adopted to carry out the titration process.[11] For precise data, the $AgNO_3$(aq) solution should be protected from light and stored in a dark glass bottle.

Purification: trimethylsulfoxonium iodide and trimethylsulfoxonium chloride are precursors of dimethylsulfoxonium methylide. Except when used under phase transfer conditions, the sulfur ylide is usually prepared by deprotonation of trimethylsulfoxonium iodide or trimethylsulfoxonium chloride with moisture-sensitive strong bases such as ***Sodium Hydride***, ***n-Butyllithium***, etc. Therefore drying the salts prior to use is crucial. Trimethylsulfoxonium iodide can be purified by recrystallization from H_2O and dried in a desiccator over P_2O_5 before use.[2,9]

Preparative Methods: trimethylsulfoxonium iodide is commonly prepared by reaction of ***Dimethyl Sulfoxide*** with ~2.5 equiv of ***Iodomethane***.[12] After refluxing for 24 h at 80 °C, the reaction mixture is cooled and the crude solid product filtered and washed with acetone to give the trimethylsulfoxonium iodide. Iodomethane has to be handled in a fume hood because of its high volatility and toxicity.[12-14] Excess MeI is used to ensure the completion

of the reaction.

Trimethylsulfoxonium chloride can be obtained by the treatment of trimethylsulfoxonium iodide with benzyltributylammonium chloride in a mixed solvent system (CH_2Cl_2/H_2O).[10] The end point is reached when two clear phases are obtained. The aqueous phase is then washed with CH_2Cl_2. After evaporation of H_2O, solid trimethylsulfoxonium chloride is obtained. Direct oxidation of trimethylsulfonium chloride with ***Sodium Hypochlorite*** in the presence of catalytic amount of ***Ruthenium(VIII) Oxide*** in H_2O at room temperature also provides trimethylsulfoxonium chloride.[15] Alternatively, trimethylsulfoxonium chloride can be synthesized by treating a hot aqueous solution of trimethylsulfoxonium iodide with AgCl. After removal of iodide salt, the aqueous filtrate is evaporated to dryness to give trimethylsulfoxonium chloride.[6]

Handling, Storage, and Precautions: both the iodide and chloride salts are hygroscopic and have to be stored in a cool, dry place. They are incompatible with strong oxidizing agents and strong base. The iodide salt is sensitive to light and needs to be protected from light as much as possible.

Preparation of Dimethylsulfoxonium Methylide.

Trimethylsulfoxonium iodide and trimethylsulfoxonium chloride are primarily utilized in the preparation of ***Dimethylsulfoxonium Methylide***, an extremely useful organic synthesis reagent.

Methylation.

Trimethylsulfoxonium iodide can be converted to ***Trimethylsulfonium Hydroxide*** in a mixture of MeOH and water in the presence of ***Silver(I) Oxide*** at room temperature. After filtration, the reaction mixture is concentrated and used directly as a methylation reagent. Uracil, thymine, and cytosine were reported to be converted to their corresponding *N*-methylated products in excellent yield using this reagent. In the same manner, uridine, thymidine, and inosine were smoothly methylated to produce corresponding *N*-methylated nucleosides.[16] Quaternization of tertiary amines is usually accomplished with MeI. Direct treatment of trimethylsulfoxonium iodide with aqueous perchloric acid also provided trimethylsulfoxonium perchlorate, which readily quaternized tertiary amines to their corresponding perchlorate salts in one step.[17]

Other Usages.

Trimethylsulfoxonium iodide is used as a catalyst in the conversion of oxathiolane to oxathiin in toluene under acidic conditions.[5] It is also used in the promotion of the reaction between ***Phosphorus(V) Sulfide*** and an alcohol to form the desired dialkyl phosphorodithioic acid.[18]

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Trimethylstannane[1]

Me_3SnH

[1631-73-8] · $C_3H_{10}Sn$ · Trimethylstannane · (MW 164.84)

(hydrostannation of alkenes and alkynes;[2] radical hydrogen source;[3] Me_3SnLi precursor[4])

Alternate Name: trimethyltin hydride.

Physical Data: bp 59-60 °C; *d* 1.477 g cm^{-3}.

Solubility: sol common organic solvents; slightly sol H_2O; insol NH_3.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: best analyzed by ^1H NMR (C_6D_6).

Preparative Method: synthesized by the reaction of ***Lithium Aluminum Hydride*** with ***Chlorotrimethylstannane*** in ethereal solvents.[5] Highest yields are obtained by using high boiling solvents such as bis(2-ethoxyethyl) ether.[6]

Purification: fractional distillation from $LiAlH_4$.

Handling, Storage, and Precautions: unstable to oxidative and photolytic processes; best used immediately upon synthesis. Neat compound can be stored up to a month in a 0 to -20 °C refrigerator, under an inert atmosphere (N_2 or Ar), protected from light. Organostannanes are toxic and should only be used in a well-ventilated hood. All glassware should be rinsed in a KOH/EtOH bath during cleaning.

Hydrostannation.

One of the primary uses of Me_3SnH is for the hydrostannation of π-bonds. Addition of tin hydride can proceed via either a radical or an ionic pathway, depending on the reaction conditions and the substituents adjacent to the π-bond. Hydrostannation can also be mediated by a Pd^0 catalyst. Hydrostannation of terminal alkynes can form three products (eq 1).[2] The major product of the ionic pathway is the α-stannane, formed by addition of the trimethyltin moiety at the most substituted position.[7] Radical hydrostannation typically affords a mixture of the *cis*-β- and *trans*-β-products, with the latter predominating.[7] The palladium-mediated reaction can form any of the above products. The stereochemistry of the product can vary with the substituents on the alkyne. A striking example of this is the palladium-mediated hydrostannation of alkynic esters versus alkynic ketones.[8] The ester gives predominantly *syn* (kinetic) addition, while the ketone gives predominantly *anti* (thermodynamic) addition. Allenes can be hydrostannated under either radical or palladium-catalyzed conditions, but typically lead to a regio- and stereochemical mixture of products.[9]

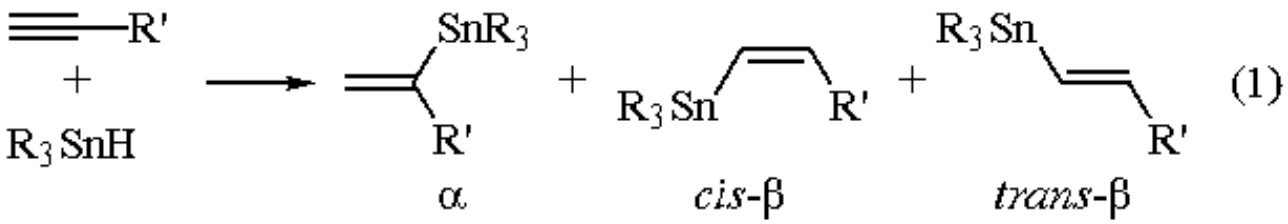

1,1-Distannyl-1-alkenes, formed by thermal radical hydrostannation of 1-stannyl-1-alkynes (eq 2), can be used to generate α-stannylvinyl anions upon treatment with ***Methyllithium***.[10] The anion can then be treated with electrophiles to form stereochemical mixtures of alkylated products (eq 3). The corresponding bis(tributylstannyl)alkene selectively affords the (*E*)-product. Addition of 2 equiv of methyllithium and electrophile forms the dialkylated product (eqs 4 and 5). Butyllithium cannot be used in this reaction due to alkyl exchange equilibria between tin and lithium.

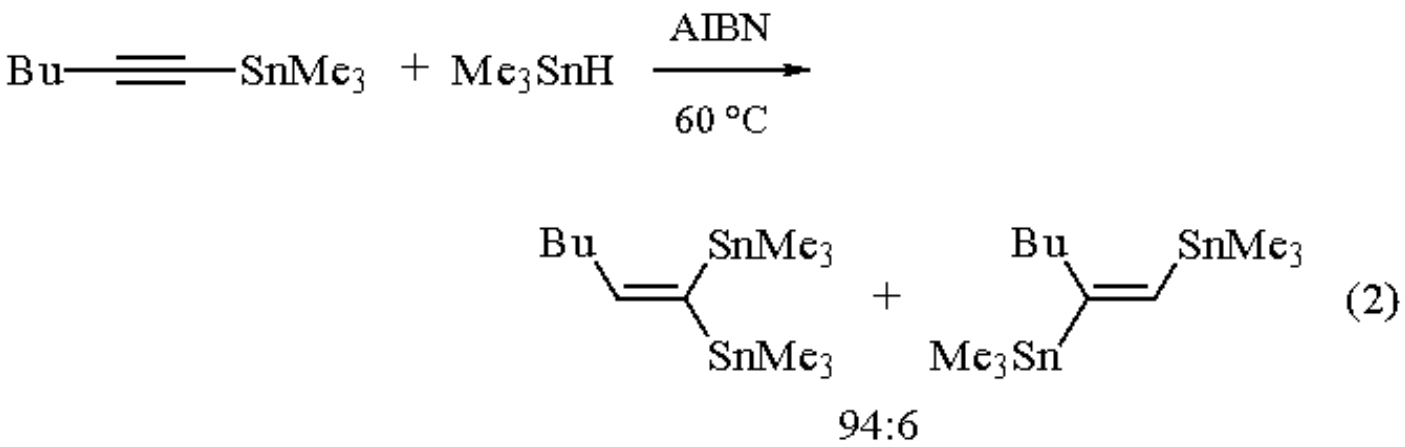

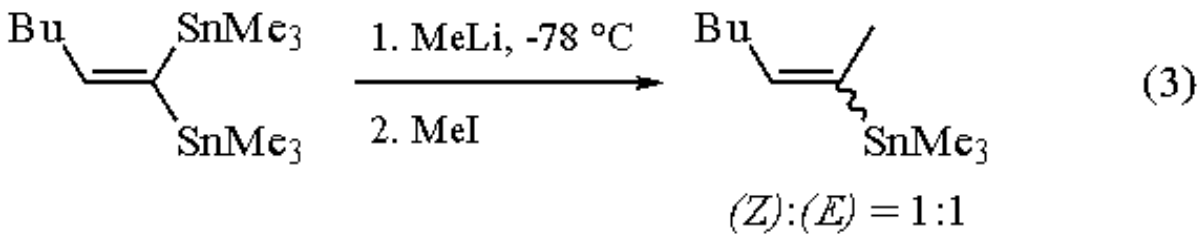

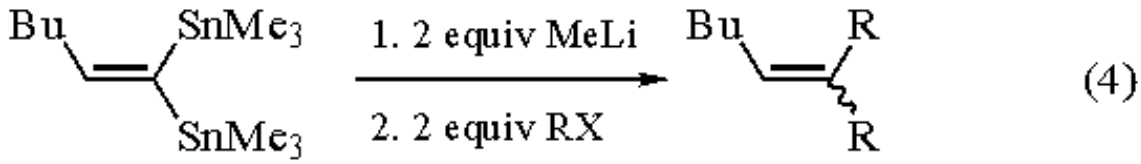

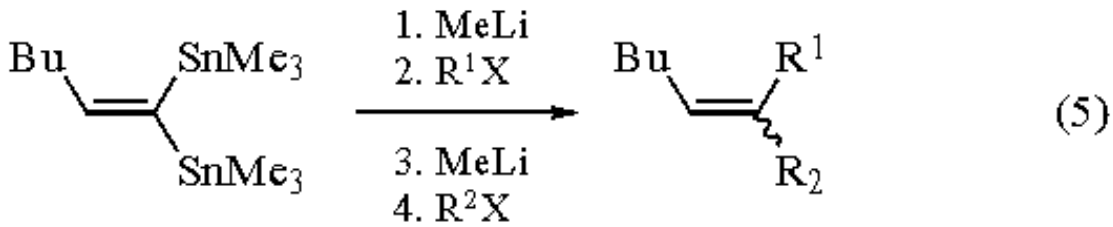

Hydrostannation of alkenes affords alkyltins. For example, (*E*)-2,3-disubstituted propenoates can be irradiated with a mercury lamp for 4.5 h in the presence of trimethyltin hydride to give the β-stannane (eq 6).[11] In this case, use of thermal free radical conditions (AIBN, 70 °C) causes reduced yields (~25%).[11]

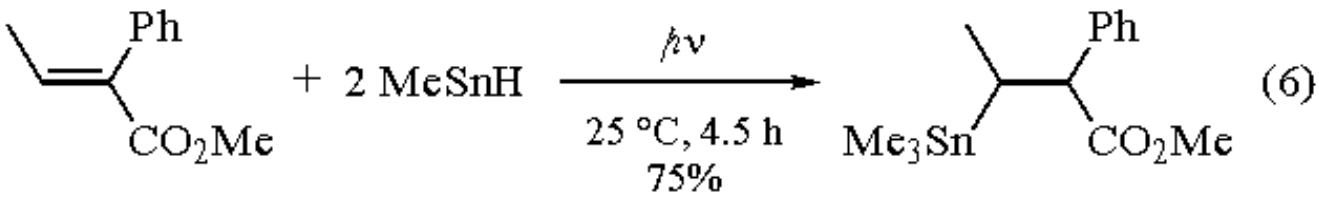

Trimethylstannyllithium.

Treatment of trimethyltin hydride with LDA affords ***Trimethylstannyllithium***, which can be used in nucleophilic reactions.[12] While less convenient than the Me_6Sn_2/MeLi generation of Me_3SnLi, this approach is also less expensive and affords fewer tin byproducts. Nucleophilic attack of trimethylstannyllithium on geminal dibromoalkenes gives the distannyl product in good yield.[13] Use of the analogous dichloro alkene gives only Me_6Sn_2 and an alkyne. Treatment of Me_3SnLi with ***t-Butyldimethylchlorosilane*** affords the silylstannane (eq 7), which can be added across an alkyne in the presence of Pd^0 (eq 8).[4]

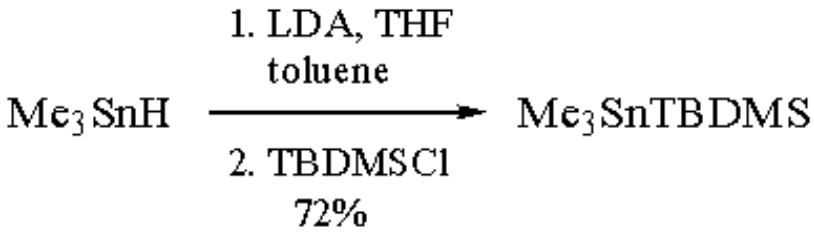

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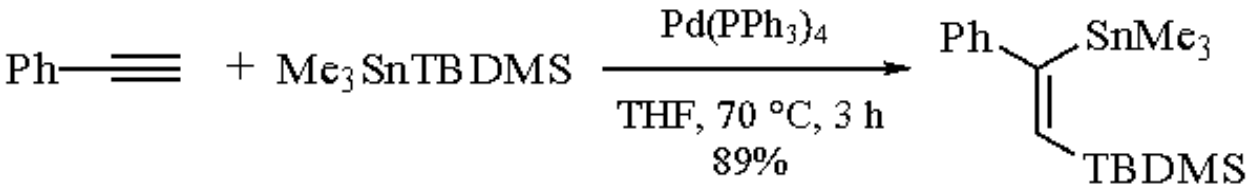

(8)

Reaction of trimethyltin hydride with a cuprate in THF at -78 °C forms the stannylcuprate, which will undergo conjugate additions.[14] Trimethylstannyllithium will also undergo conjugate addition with enones (eq 9).[15,16] After protection of the carbonyl group as an enamine, the trimethylstannyl group can be transmetalated to the alkyllithium with MeLi. Bu_3SnH can also be used for this reaction.

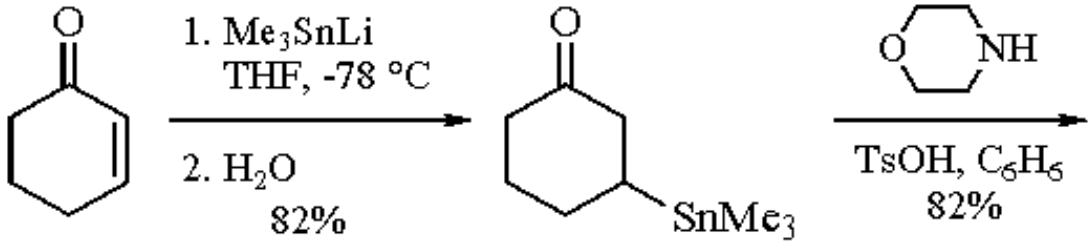

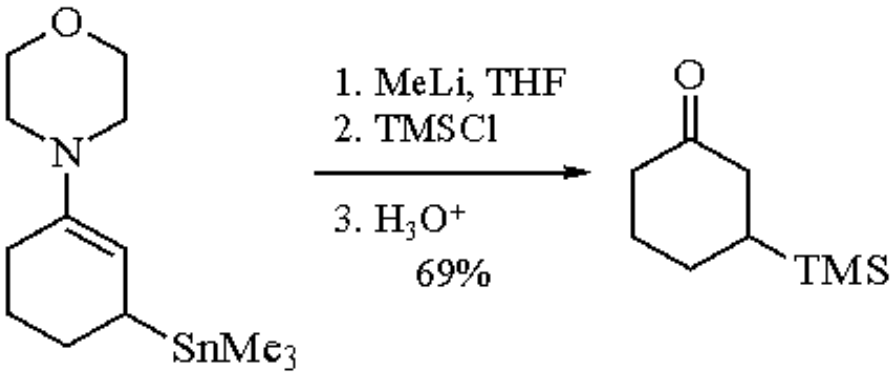

(9)

Radical Reductions.

Alkyl halides are reduced with trimethyltin hydride in the presence of radical initiators, such as ***1,1´-Azobis-1-cyclohexanenitrile*** (ACHN).[3] Tributyltin hydride will also work in this reaction.

Related Reagents.

Hexamethyldistannane; ***Tri-n-butylstannane***; ***Triphenylstannane***.

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Trimethylstannyllithium

Me_3SnLi

[17946-71-3] · C_3H_9LiSn · Trimethylstannyllithium · (MW 170.77)

(synthesis of allylstannanes,[1] vinylstannanes,[2] acylstannanes,[3] α-hydroxyalkylstannanes,[4] and β-stannyl ketones[5])

Alternate Name: trimethyltinlithium.

Preparative Methods: prepared by the reaction of ***Hexamethyldistannane*** and ***Methyllithium***, ***Chlorotrimethylstannane*** and ***Lithium*** metal, or by deprotonation of ***Trimethylstannane***.

Handling, Storage, and Precautions: should be used immediately after preparation. For some applications the purity of the starting material is critical. Trimethylstannane should be distilled immediately prior to deprotonation. Sensitive to air and moisture. Volatile organostannanes are toxic and should be used always in a well ventilated fume hood. Contact with eyes and skin should be avoided.

General Discussion.

Trimethyltinlithium is prepared by the reaction of trimethyltin chloride and lithium[6] or by the deprotonation of trimethylstannane using ***Lithium Diisopropylamide***.[5,7] In each case the generation of the reagent is a complicated reaction process, leading to several other reactive species in addition to trimethyltinlithium itself (eq 1).[8]

$$\begin{aligned} Me_3SnCl + Li^0 &\longrightarrow Me_3SnLi \rightleftharpoons [Me_2Sn:] + MeLi \\ [Me_2Sn:] + Me_3SnLi &\longrightarrow Me_5Sn_2Li \end{aligned} \qquad (1)$$

The reaction of trimethyltinlithium with alkyl halides has been the subject of intensive mechanistic study. There are three potential reaction mechanisms for the displacement of an alkyl halide with trimethyltinlithium: direct S_N2 displacement, initial electron transfer leading to the formation of radical intermediates, or initial metal-halogen exchange leading to a carbanion intermediate.[9] Several additives have been explored as a means to delineate radical versus carbanionic pathways: however, the influence of additives such as dicyclohexylphosphine or *t*-butylamine on the mechanism of the reaction has been called into question.[9] Evidence for radical pathways has been obtained by several studies using internal radical traps such as 6-bromohexene,[10] 6-bromoheptene (eq 2),[11] and cyclopropylmethyl bromide.[12] Several studies have used stereochemical probes to determine the possible mechanisms for trimethyltinlithium displacement of alkyl halides.[13] Displacement of a nonracemic secondary alkyl bromide or tosylate also results in a nonstereoselective reaction for the alkyl bromide (~40% inversion) and a stereoselective (100% inversion) process for the tosylate.[14] 4-Methyl- or 4-*t*-butylcyclohexyl bromide and tosylate have been examined as substrates for trimethyltinlithium reactions.[15] In each of these studies the cyclohexyl bromides undergo substitution with loss of stereochemistry, implying a radical process (eq 3). The corresponding tosylates are displaced with complete inversion of stereochemistry by an S_N2 process (eq 4). Radical chain processes are also implicated in the reaction of trimethyltinlithium and 1-bromo-4-iodobicyclo[2.2.2]octane.[16] In a related study using 1,4-dihalobicyclo[2.2.1]heptanes, trimethyltinlithium substitution by an $S_{RN}1$-type mechanism has been postulated; however, a polar mechanism involving formation of a carbanion effectively competes with the chain process.[17]

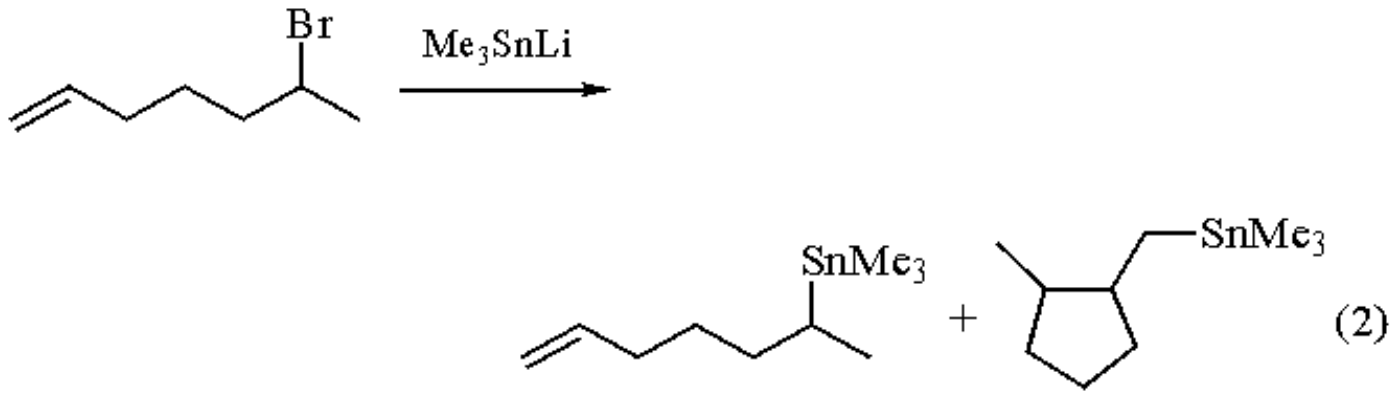

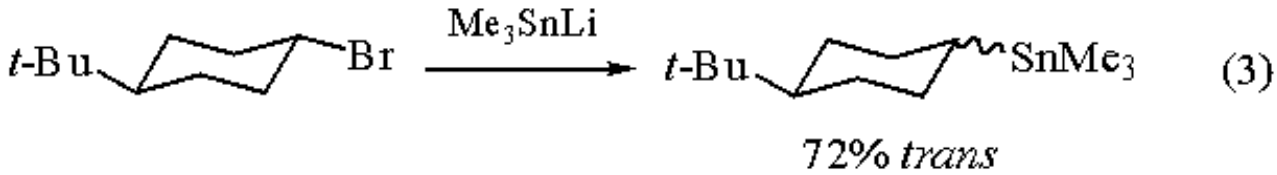

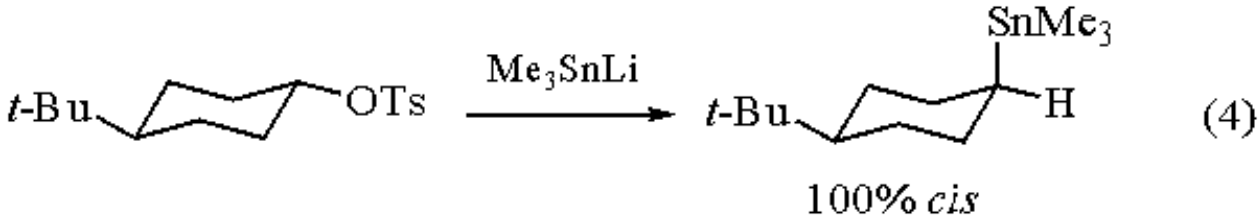

Trimethyltinlithium can be used for the synthesis of allylstannanes by the displacement of allyl halides,[1] and in the synthesis of 1-trimethylstannyl-2,4-dienes by reaction with 5-tetrahydropyranoxy-1,3-dienes (eq 5).[18] Direct displacement of vinyl halides can also be realized, providing access to 1,1-distannyl-1-alkenes.[2] Acylstannanes are obtained by the reaction of trimethyltinlithium and ethyl esters or thiophenyl esters in the presence of ***Boron Trifluoride Etherate***.[3] Direct displacement of α-chloro boronates can be accomplished leading to α-trimethylstannyl boronate esters with inversion of configuration.[19] The trimethylstannyl-substituted boronate thus obtained can undergo transmetalation with an additional equivalent of trimethyltinlithium to provide the α-lithio boronate ester. Silylation of the alkoxide intermediate obtained by addition of trimethyltinlithium to carbonyl compounds provides α-silyloxystannanes which are useful precursors for the synthesis of (α-alkoxyalkyl)trialkylsilanes.[4] (α-Alkoxyalkyl)stannanes and (α-alkoxy)trialkylsilanes can be employed in the stereoselective synthesis of acyclic ethers by means of a directed Mukaiyama aldol reaction.[20]

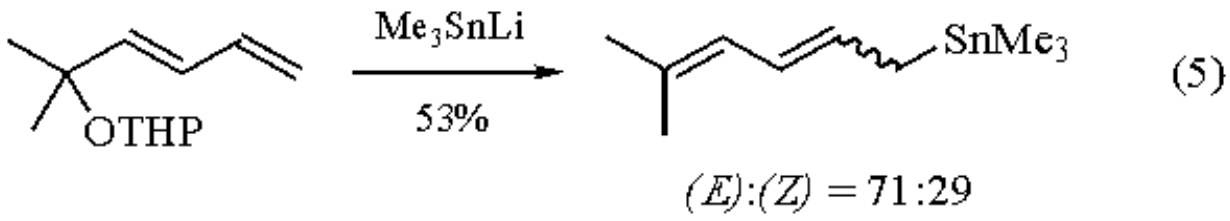

Trimethyltinlithium undergoes conjugate addition reactions with enones in THF or THF/NH_3.[5,21] This approach has been used in the synthesis of several potential chiral Lewis acids derived from conjugate addition of trimethyltinlithium to verbenone, carvone, and pinene. Subsequent regioselective cleavage of one of the methyl groups from the trimethyltin moiety is possible using ***Tin(IV) Chloride*** or ***Mercury(II) Chloride*** (eq 6).[21]

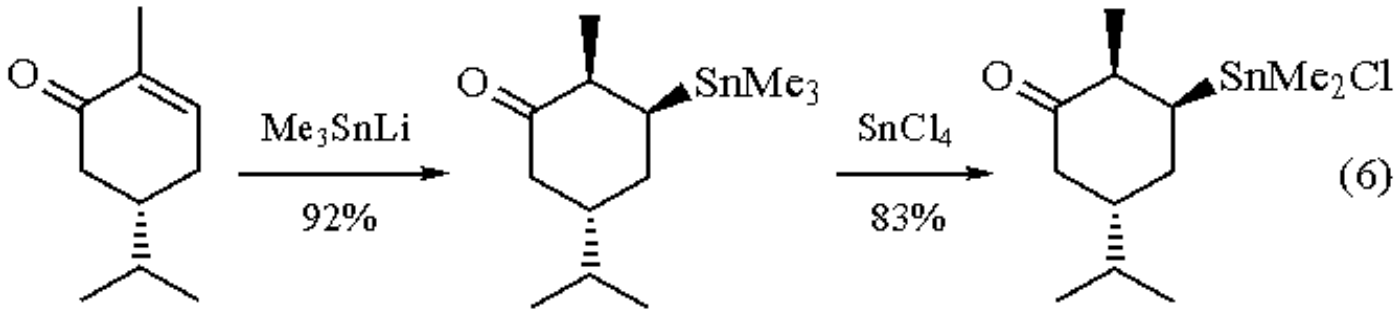

Oxidative cleavage of the trimethyltin moiety to give an alcohol has been accomplished with retention of configuration.[22] Initial 1,4-

addition of trimethyltinlithium to cyclohexenone, followed by alkylation of the enolate intermediate and reduction of the ketone, provides a β-hydroxy trimethylstannyl-substituted cyclohexane ring. Subsequent reaction with ***Bromine*** and ***m-Chloroperbenzoic Acid*** results in cleavage of the trimethyltin moiety to give the cyclohexane diol (eq 7).

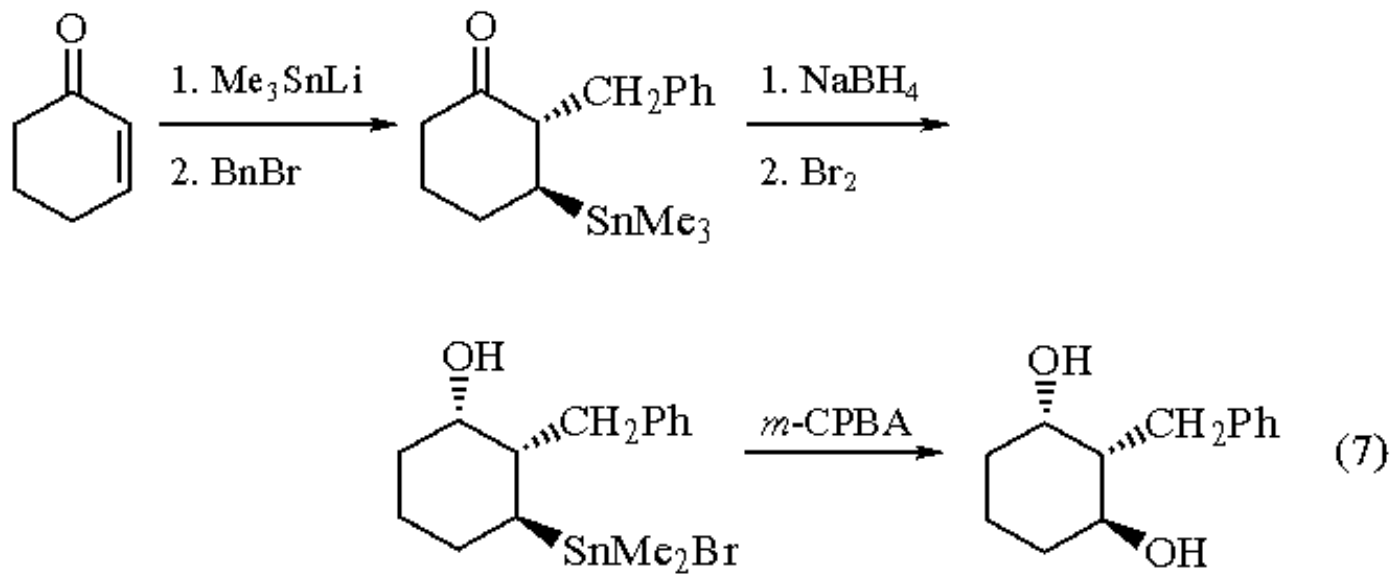

The 1,4-addition product obtained by the reaction of trimethyltinlithium and cyclohexenone has also provided a substrate for the study of the γ-effect of tin in solvolysis reactions.[23] Providing that the Sn-C-C-C-X bonds adopt a planar W orientation, the tin substituent serves to enhance solvolysis through an extended hyperconjugation effect. Oxidative fragmentation of β-hydroxy trimethylstannyl-substituted cyclohexanes by ***Lead(II) Acetate*** has also been employed in the stereospecific synthesis of (*E*)- and (*Z*)-keto alkenes (eq 8).[24] 1,4-Addition of trimethyltinlithium to cyclohexenone, followed by reduction of the ketone and oxidative fragmentation, has resulted in the synthesis of *exo*- and *endo*-brevicomin. Treatment of β-trimethylstannylcyclohexanones with Lewis acids results in the destannylated cyclohexanone or in a ring-contracted cyclopentanone through the intermediacy of a cyclopropanol (eq 9).[25] If the ketone is first transformed into an epoxide, Lewis acid treatment results in the synthesis of cyclopropane products (eq 10).[26,27] The Lewis acid-catalyzed reaction proceeds through an ionic intermediate since there is no stereochemical restriction on the reaction. Cyclopropane formation can also be induced by protic acid treatment; however, a concerted 1,3-elimination reaction occurs which places a stereoelectronic restriction on the reaction. Only stannyl epoxides which can adopt a planar W configuration of the Sn-C-C-C-OH bonds can undergo 1,3-elimination. Other conformationally restricted isomers undergo a 1,2-shift.[27] Trimethyltinlithium can undergo transmetalation to a variety of copper species which have been extensively studied by NMR.[28]

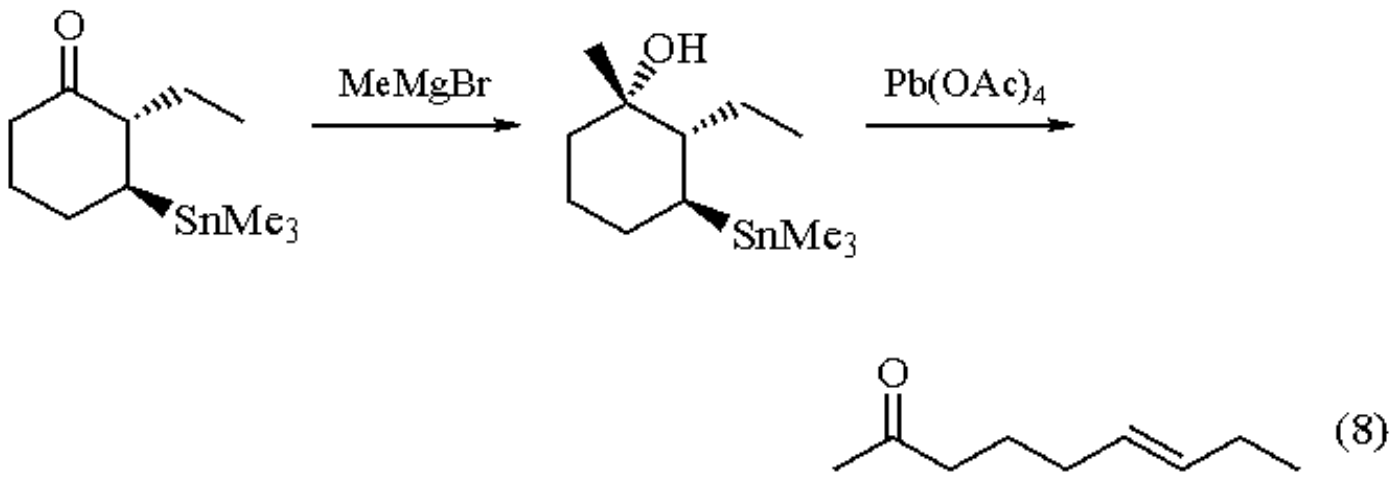

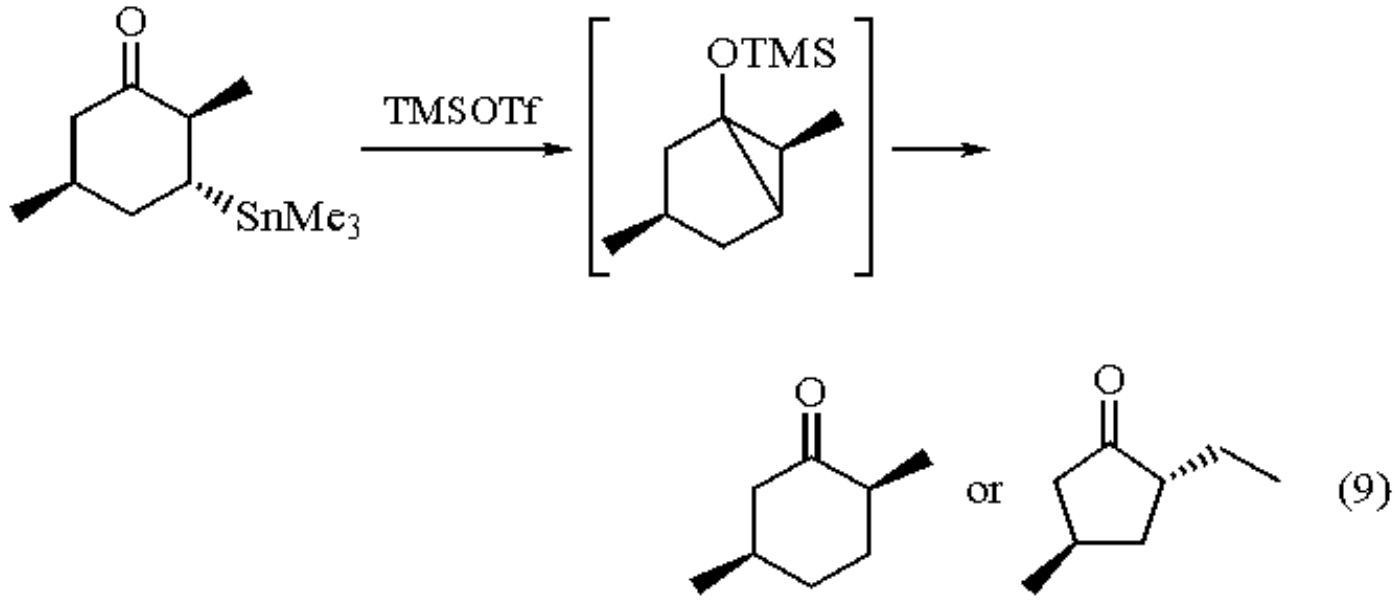

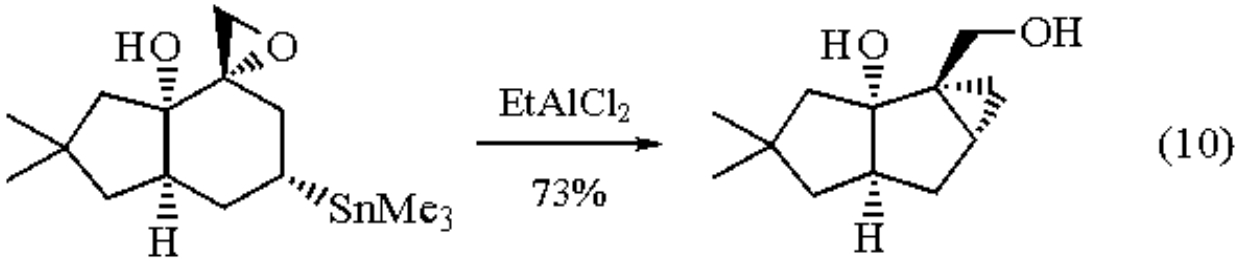

Related Reagents.

Tri-n-butylstannyllithium.

---

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Trimethyl(trifluoromethyl)stannane[1]

Me_3SnCF_3

[754-25-6] · $C_4H_9F_3Sn$ · Trimethyl(trifluoromethyl)stannane · (MW 232.84)

(a low-temperature difluorocarbene source[1])

Alternate Name: (trifluoromethyl)trimethyltin.

Physical Data: mp -57 to -53.2 °C;[2] bp 100-101 °C;[3] ^{1}H NMR (90 MHz) δ 0.42; ^{19}F NMR (84.6 MHz) δ -28;[4,5] IR (KBr) (cm^{-1}) 3080, 3010, 2940, 1330, 1220, 1210, 1205, 1160, 1075, 810, 785, 730, 541, 520.[2,3]

Solubility: sol benzene, carbon tetrachloride, DME, petroleum ether, pyridine, methylene chloride.

Preparative Methods: prepared in 81% yield by reaction of ***Hexamethyldistannane*** with ***Trifluoroiodomethane*** in a sealed tube at 80 °C for 20 h (eq 1).[3] Without compromising the yield, this reaction may also be performed at rt by irradiating for 6 h with a 250 W UV lamp.[6,7] Reaction of Me_3SnX (X = $OCOCF_3$ or Br) with an alkylating agent, such as $(CF_3)_2Cd$, may also be used to synthesize trimethyl(trifluoromethyl)tin in high yields.[8-10]

$$Me_3SnSnMe_3 + CF_3I \xrightarrow[h\nu,\ rt,\ 6\ h]{80\ °C,\ 20\ h\ \text{or}} Me_3SnCF_3 + Me_3SnI \quad (1)$$

Handling, Storage, and Precautions: prolonged contact or heating with water causes decomposition to produce fluoroform. Temperatures above 150 °C cause decomposition to trimethyltin fluoride.[3]

Thermal Generation of Difluorocarbenes.

Heating trimethyl(trifluoromethyl)tin in a sealed tube at 150 °C for 15 h is believed to produce difluorocarbene as evidenced by the formation of *gem*-difluorocyclopropanes in the presence of alkenes (eq 2).[3] Additionally, difluorocarbene insertion into an acid fluoride bond also occurs under these conditions.[11]

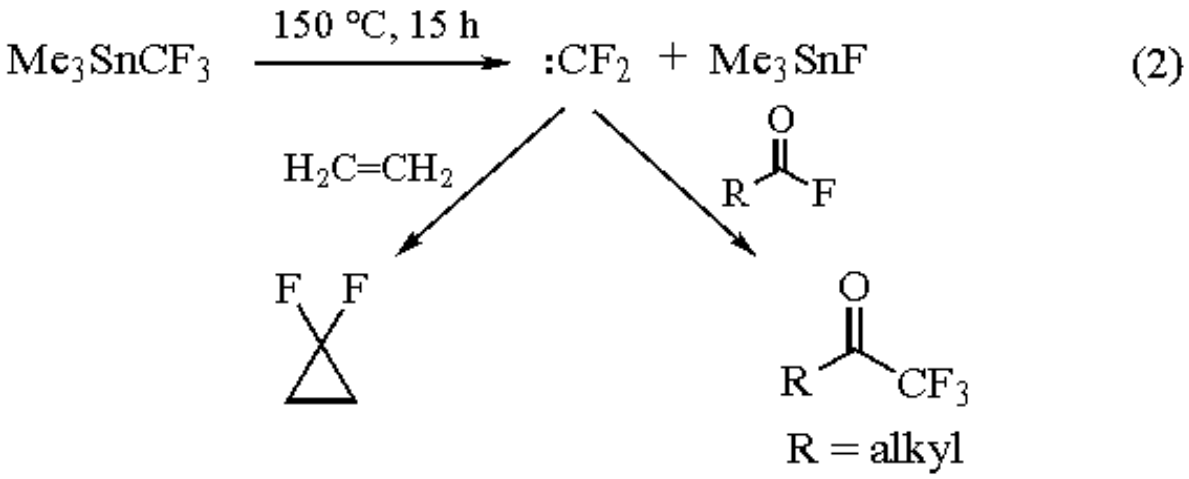

Nucleophile-Initiated Generation of Difluorocarbenes.

The addition of ***Sodium Iodide*** to trimethyl(trifluoromethyl)tin allows the generation of difluorocarbene at significantly lower temperatures (eq 3),[12,13] thereby making reactions with thermally unstable alkenes accessible. The reaction is believed to occur via a pentacoordinated trimethyl(trifluoromethyl)tin iodide intermediate. The trifluoromethyl anion, which is unstable even at -100 °C, then decomposes to produce the difluorocarbene.

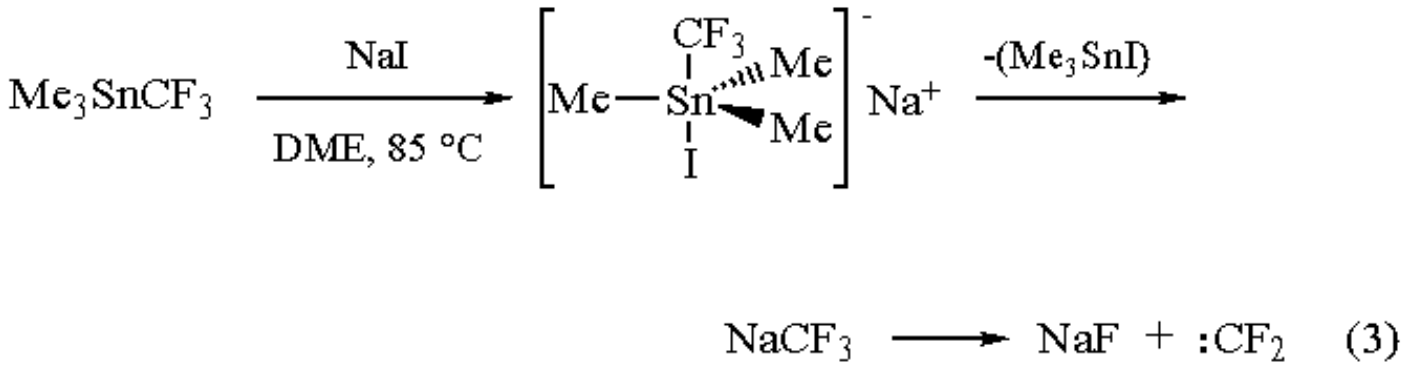

Fluoride[14] and chloride[15] anions are also effective as nucleophiles and generate difluorocarbene in good yields. The ***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate*** (TASF) catalyzed conversion of sulfonyl fluorides to aryl trifluoromethyl sulfones is an illustration of the use of the former anion (eq 4).[14] Interestingly, the corresponding silicon reagent, ***Trifluoromethyltrimethylsilane***, is as effective as the tin reagent in these reactions.[14]

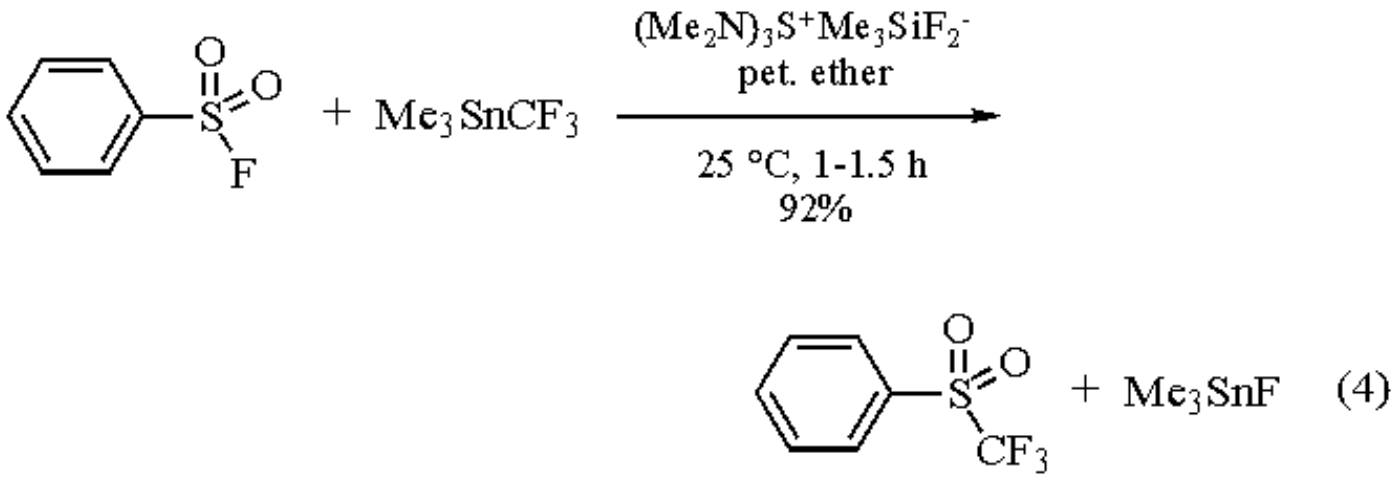

Lewis Acid-Initiated Generation of Difluorocarbenes.

Reaction of trimethyl(trifluoromethyl)tin with Lewis acids such as BX_3 (X = F, Cl) appears to produce difluorocarbene, as indicated by its insertion into the boron-halogen bond.[16,17] This too presumably occurs via the aforementioned decomposition of the trifluoromethyl anion.

---

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Triphenylacetonitrile *N*-Oxide

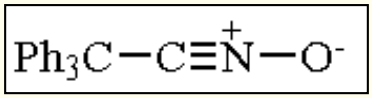

[13412-55-0] · $C_{20}H_{15}NO$ · Triphenylacetonitrile *N*-Oxide · (MW 285.36)

(1,3-dipolar reagent[1])

Physical Data: mp 152-153 °C.[2]

Solubility: sol benzene, dioxane.

Form Supplied in: colorless solid; not commercially available.

Analysis of Reagent Purity: IR 2280, 1320 cm^{-1}; the corresponding isocyanate, the primary decomposition product, has a strong band at 2250 cm^{-1}.

Preparative Methods: usually prepared[2,3] by treatment of silver fulminate with triphenylmethyl chloride. The compound is reported[4] to be readily available from triphenylacetaldehyde oxime by treatment with bromine in an $NaOH/H_2O/CCl_4$ mixture at 0 °C, but no experimental details are provided.

Purification: recrystallization from a minimum amount of benzene.

Handling, Storage, and Precautions: if the reagent is being prepared from silver fulminate, extreme caution should be exercised due to the shock sensitivity. Unlike other nitrile oxides, which are usually generated in situ, triphenylacetonitrile oxide is a fairly stable solid. Upon heating it rearranges to triphenylmethyl isocyanate. Introducing a 3- or 4-trifluoromethyl group dramatically increases the proclivity towards rearrangement.[2]

1,3-Dipolar Cycloaddition.

Like other nitrile oxides (see ***Acetonitrile N-Oxide***) this reagent is useful for 1,3-dipolar cycloaddition reactions. Alkenes give 3-triphenylmethyl-Δ^2-isoxazolines containing a labile Ph_3C group which may be used to trigger other events. For example, photolysis of 3-triphenylmethyl-Δ^2-isoxazolines fragments the heterocycle, presumably by homolysis of the Ph_3C-C bond (eq 1).[4] The triphenylmethyl group of 3-triphenylmethyl-Δ^2-isoxazolines is also the key to a novel preparation of cyclic ethers (eq 2).[5] The regiochemistry of dipolar cycloadditions of nitrile oxides containing bulky substituents has been studied.[6]

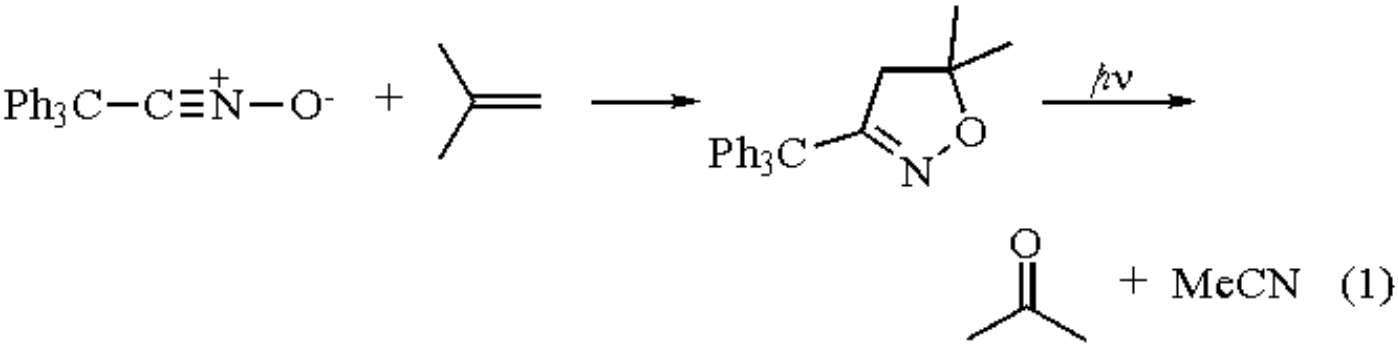

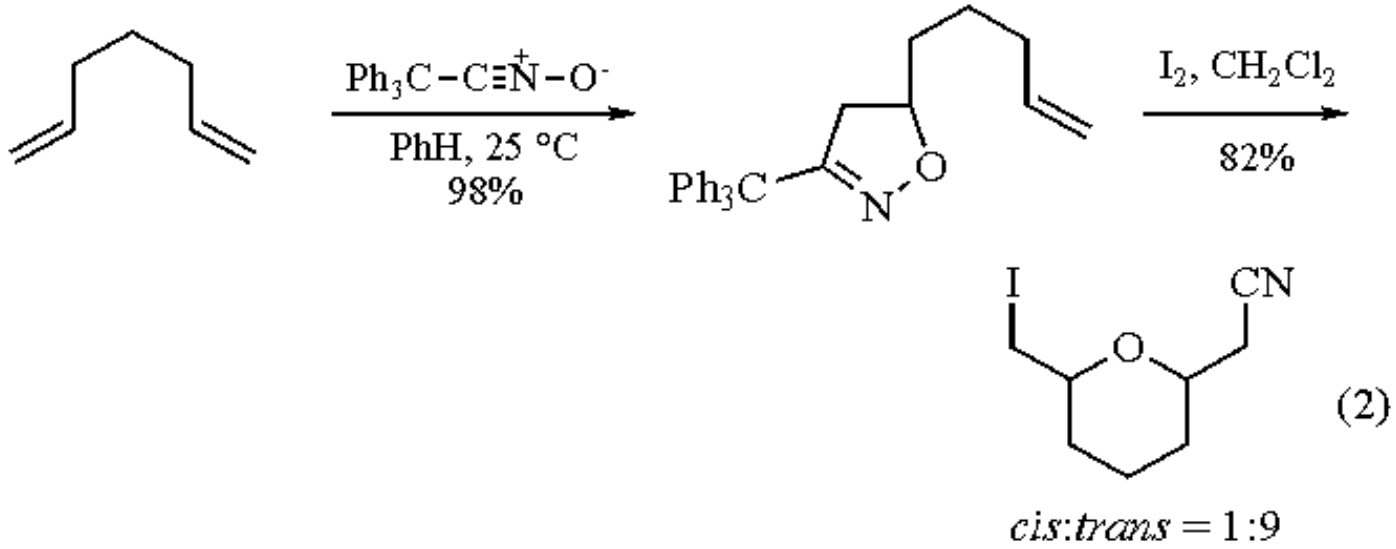

Related Reagents.

Acetonitrile N-Oxide; ***1-Pyrroline 1-Oxide***.

---

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Triphenylarsine[1]

[603-32-7] · $C_{18}H_{15}As$ · Triphenylarsine · (MW 306.25)

(nucleophilic agent for the synthesis of arsonium salts, which undergo epoxidation or alkenation reactions; can be used as a ligand)

Physical Data: plates (EtOH), mp 60.5 °C; bp 360 °C, 232-234 °C/14 mmHg.

Solubility: insol H_2O, ethanol; sol ether, THF, acetonitrile, etc.

Form Supplied in: commercially available.

Preparative Method: prepared from arsenic trichloride, chlorobenzene, and powdered sodium in benzene under reflux.[2]

Handling, Storage, and Precautions: use in a fume hood.

Introduction.

Arsonium ylides are more reactive than the corresponding phosphonium ylides since the covalent canonical form (ylene form) makes a smaller contribution to the overall structure of arsonium ylides (eq 1) than to that of phosphonium ylides.[1] This has been supported by X-ray crystallography.[3]

$$Ph_3As{=}CR^1R^2 \longleftrightarrow Ph_3\overset{+}{A}s\text{-}\bar{C}R^1R^2 \qquad (1)$$

Arsonium Salts.

Reaction of triphenylarsine with halo compounds forms arsonium salts which are converted to ylides on treatment with base. These perform alkenation reactions under PTC conditions.[4] A general procedure for the synthesis of unsaturated aldehydes, ketones, esters, and amides directly via arsonium salts in the presence of a weak base (solid ***Potassium Carbonate***) under PTC conditions at rt has been devised (eq 2).[5] All the arsonium salts are stable and can be stored for a long time. The Ph_3AsO byproduct can be easily reconverted to Ph_3As by reduction.[6]

$$R(CH{=}CH)_mCHO + Ph_3\overset{+}{A}s(CH{=}CH)_nXBr^- \xrightarrow[\text{trace } H_2O,\ rt\ \ -Ph_3AsO]{K_2CO_3\ (s),\ \text{solvent}} R(CH{=}CH)_{m+n+1}X \qquad (2)$$

$$m = 0,\ 1,\ 2;\ n = 0,\ 1$$
$$X = CHO,\ COMe,\ CO_2R,\ CONR^1R^2$$

Formylmethyltriphenylarsonium bromide (**1**) (eq 3) reacts with aldehydes to give (*E*)-α,β-enals exclusively (eq 4).[7,8]

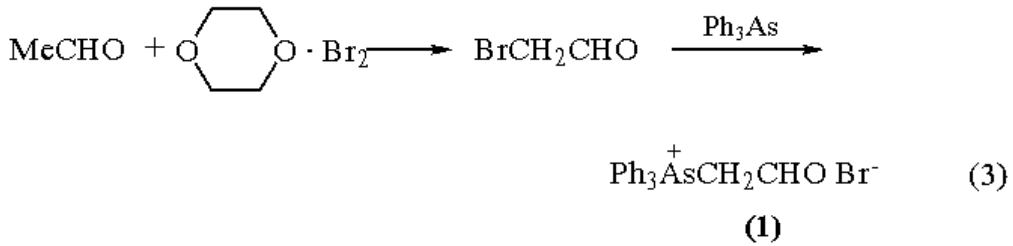

(3)

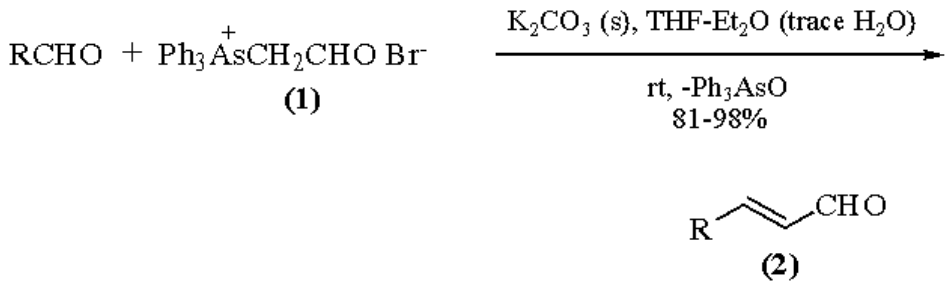

(4)

Formylallyltriphenylarsonium bromide (**3**) reacts with aldehydes to give mixtures comprising mostly (2*E*,4*E*)- with some (2*E*,4*Z*)-dienals. The latter can be isomerized to the former by treating with a catalytic amount of ***Iodine*** in daylight (eq 5).[9]

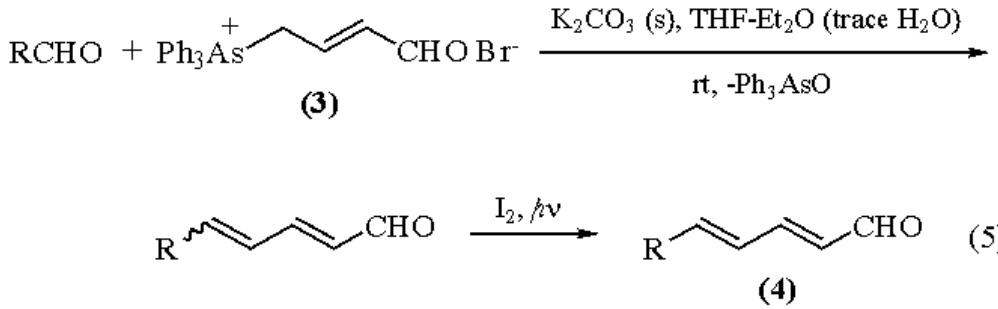

(5)

2-(Oxoamido)triphenylarsonium bromides (**5**)[10] react with saturated and unsaturated aldehydes at rt in the presence of K_2CO_3(s) to afford (2*E*)-unsaturated amides (**6**) or (2*E*,4*E*)-dienamides in excellent yields. No (*Z*) stereoisomer is detected (eq 6).[10] A vinylog (**7**)[11] reacts with aromatic aldehydes to give exclusively the (2*E*,4*E*)-products in 80-98% yield (eq 7); with aliphatic aldehydes, (2*E*,4*E*/2*E*,4*Z*) products are formed in a ratio of 85/15. The (2*E*,4*Z*) product can be isomerized to the (2*E*,4*E*) product.[11] The reactions of aldehydes with arsonium salts are listed in Table 1.

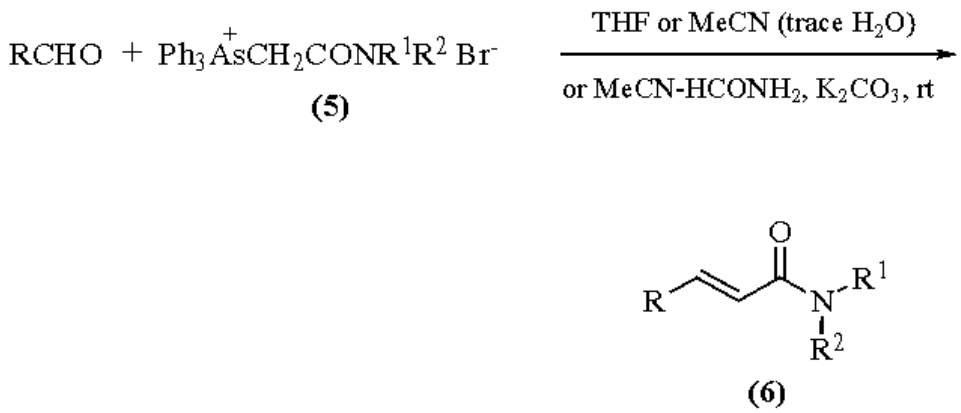
RCHO + Ph3AsCH2CONR1R2 Br-
(5)
THF or MeCN (trace H2O)
or MeCN-HCONH2, K2CO3, rt
R
O
N
R1
R2
(6)

(6)

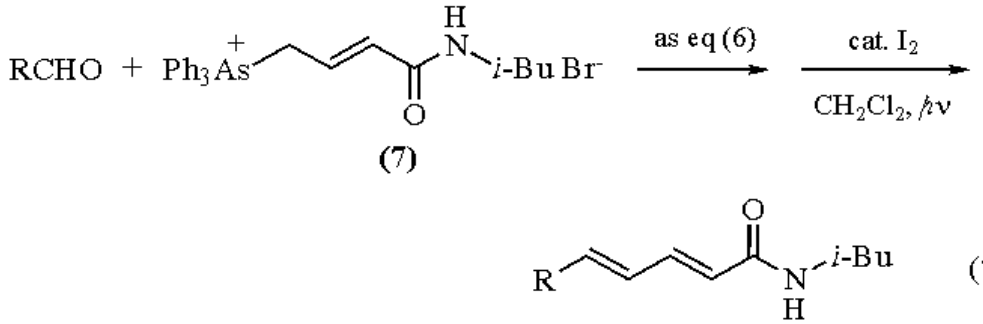
RCHO + Ph3As
H
N
i-Bu Br-
O
(7)
as eq (6)
cat. I2
CH2Cl2, hν
R
O
N
H
i-Bu

(7)

Table 1 Reaction of Aldehydes (RCHO) with Arsonium Salts

Reagent		Mp (°C)	Product	Yield (%)	Ratio of isomer
$Ph_3\overset{+}{A}sCH_2CHO\ Br^-$	**(1)**	160-161	RCH=CHCHO	81-98	only (*E*)
$Ph_3\overset{+}{A}sCH_2CH{=}CHCHO\ Br^-$	**(2)**	153-154	RCH=CHCH=CHCHO	79-98	(2*E*,4*E*):(2*E*,4*Z*) = 1:1-4:1
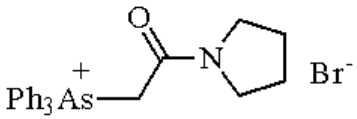	**(5a)**	191-192	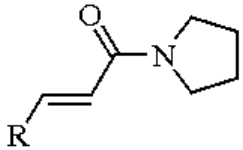	81-98	only (*E*)
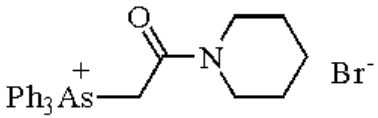	**(5b)**	167-168	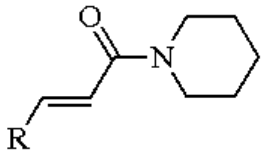	88-99	only (*E*)
$Ph_3As^+CH_2CONH\text{-}i\text{-}Bu\ Br^-$	**(5c)**	174-175	RCH=CHCONH-*i*-Bu	80-98	only (*E*)

Triphenylarsonium salts have been used to synthesize a variety of natural products under very mild conditions: (*EZ*)-,diene sex pheromones,[12] pellitorine,[10b] trichonine,[13] *Achillea* amide,[10b] *Otanthus maritima* amide,[10a] (+)-yingzhaosu A,[14] LTA_4 methyl ester,[15] 19-hydroxy-LTB_4,[16] and lipoxins A_4 and B_4[17] have all been successfully synthesized.

Since tributylarsine is more reactive towards halides than triphenylarsine, Wittig-type alkenation of carbonyl compounds can be performed catalytically. Thus the reaction of various aldehydes with ***Methyl Bromoacetate*** (or ***Bromoacetone***) in the presence of ***Triphenyl Phosphite*** and Bu_3As (0.2 equiv) provides α,β-unsaturated esters (or α,β-unsaturated ketones) in 60-87% yields and with (*E*)/(*Z*) ratios of 97:3-99:1 (eq 8).[18]

$$RCHO + BrCH_2CO_2Me + (PhO)_3P + K_2CO_3 \xrightarrow[\text{THF-MeCN, rt}]{\text{cat. } Bu_3As} RCH{=}CHCO_2Me + (PhO)_3PO \qquad (8)$$

An efficient one-pot synthesis of α-iodo- α,β-unsaturated esters, ketones, and nitriles via arsonium salts has been reported (eq 9).[19] A one-pot synthesis of *trans*-fluorovinylic epoxides has also been achieved (eq 10).[20]

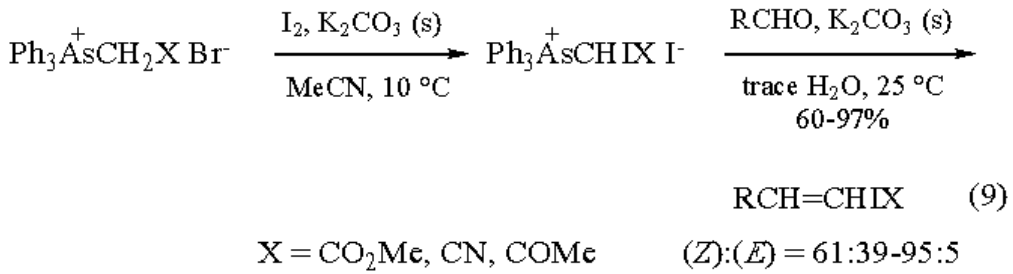

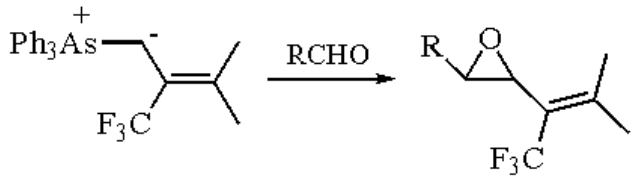

(10)

Silylated enynyl carboxylic esters can be synthesized with high stereoselectivity by the reaction of trimethylsilyl-2-propynylidenetriphenylarsorane, prepared in situ from the corresponding arsonium salt with ***n-Butyllithium***, and $BrCH_2CO_2R$ (eq 11).[21] Triphenylarsoranylideneketene reacts with 2-benzoylpyrrole in methylene chloride to give 1-phenylpyrrolizin-3-one in 85% yield (eq 12).[22]

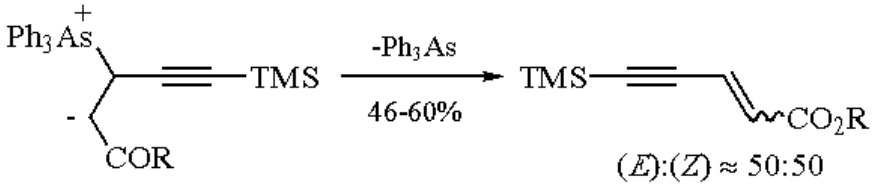

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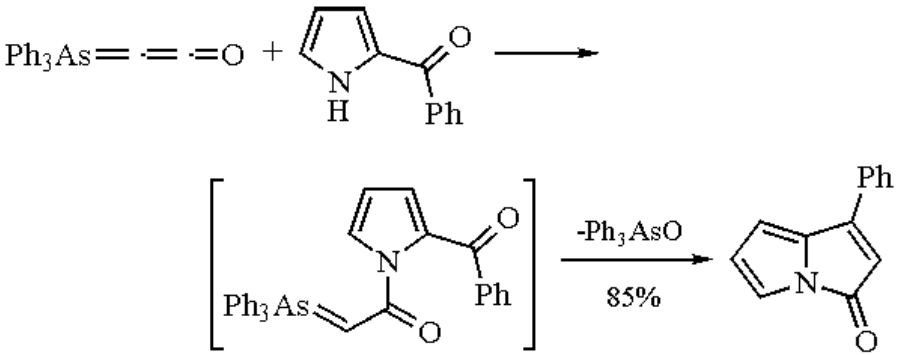

(12)

Methylenetriphenylarsorane ($Ph_3As{=}CH_2$), which is thermally unstable both in the solid state and in solution, has been isolated and characterized by analytical and spectroscopic methods.[23] Triphenylarsonium ethylide ($Ph_3As{=}CHCH_3$), prepared from triphenylethylarsonium tetrafluoroborate with ***Potassium Hexamethyldisilazide*** in THF/HMPT at -40 °C, reacts with aliphatic aldehydes to give *trans*-epoxides with high selectivity (eq 13). Stereoselection is lower with aromatic aldehydes (83% (*E*) for benzaldehyde). The reagent also reacts with ketones to form trisubstituted epoxides.[24]

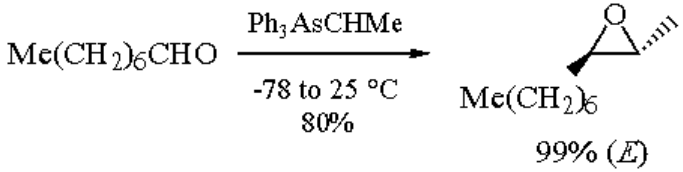

(13)

The synthesis and reactivity of (3,3-diisopropoxypropyl)triphenylarsonium ylide have been reported. This reagent can be considered as a β-formylvinyl anion equivalent (eq 14), as shown by the conversion of aldehydes to 4-hydroxy-2(*E*)-enals under very mild conditions (eq 15).[25] This route has been successfully applied to the total synthesis of (±)-hepoxilin A_3.[26]

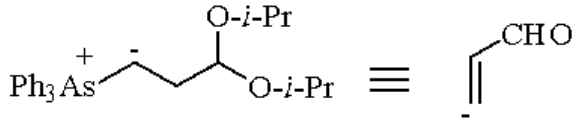

(14)

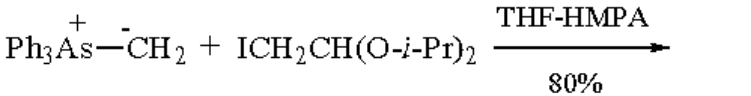

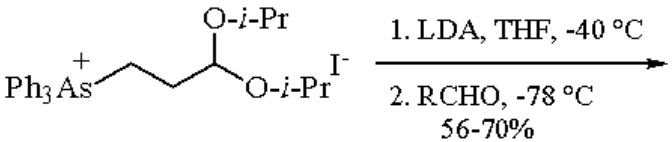

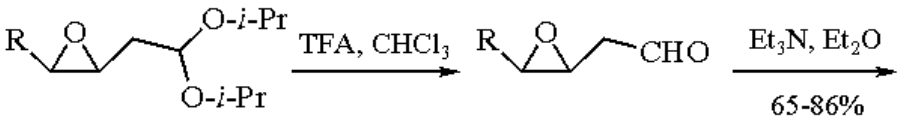

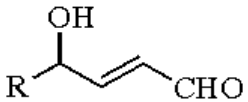

(15)

Homologation of aldehydes using (phenylthiomethylene)triphenylarsorane has been reported. Reaction with aldehydes gives exclusively α-phenylthio epoxides in THF and enol phenol thioethers in THF/HMPA. The former adducts are readily transformed to α-thiophenoxy carbonyl compounds and the latter to one-carbon homologated aldehydes (eq 16).[27]

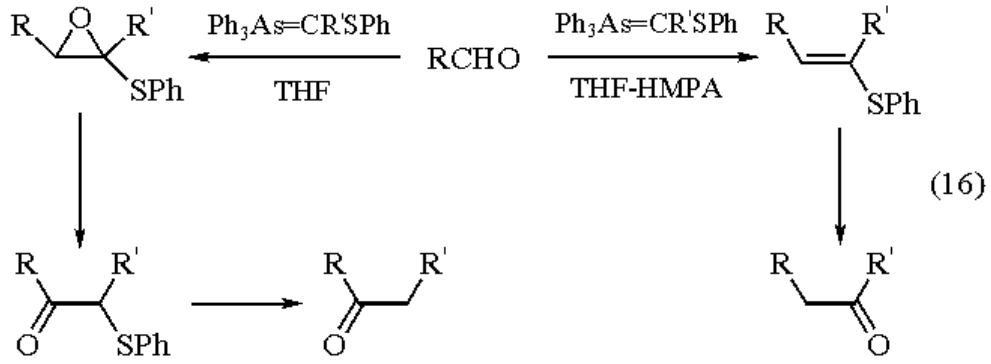

Large rate enhancement in Stille cross-coupling reactions is observed with triphenylarsine (a factor of 70 over the triphenyl phosphine-based catalyst) (eq 17).[28]

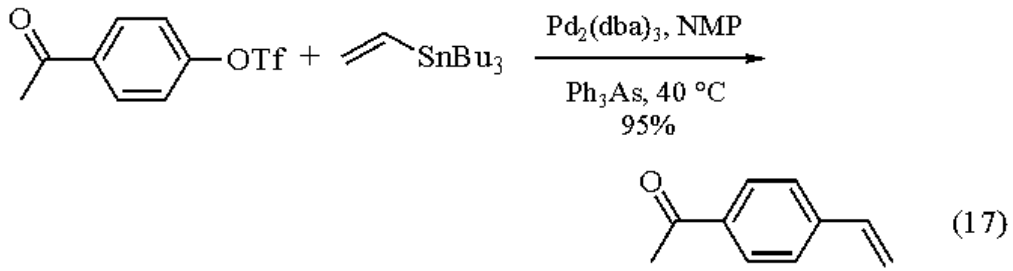

Related Reagents.

Dibutyl Telluride; ***Tri-n-butylstibine***; ***Triphenylphosphine***.

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Triphenylbismuthine[1]

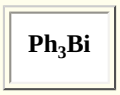

[603-33-8] · $C_{18}H_{15}Bi$ · Triphenylbismuthine · (MW 440.31)

(catalyst for glycol cleavage;[5] phenylating agent for alcohols[7] and amines;[8] source of phenyl radicals under photolytic conditions[4])

Alternate Name: triphenylbismuth.

Physical Data: mp 77.6 °C.[2]

Solubility: CH_2Cl_2, $CHCl_3$, CCl_4, benzene, toluene, ether, THF, ethyl acetate; insol H_2O, alcohols; decomposed in acidic solvents.

Preparative Method: conveniently prepared by reaction of ***Phenylmagnesium Bromide*** with $BiCl_3$ in ether.[3]

Handling, Storage, and Precautions: must be stored in dark bottles in the absence of moisture or acidic vapors. Use in a fume hood.

α-Glycol Cleavage.[5]

Triphenylbismuthine acts as a catalyst in the oxidative cleavage of α-glycols by ***N-Bromosuccinimide*** or ***N-Bromoacetamide*** in the presence of ***Potassium Carbonate*** to give the corresponding aldehydes and/or ketones. The oxidation is best performed by dropwise addition of an acetonitrile solution of NBS (4 equiv) to the mixture of the glycol, Ph_3Bi (0.01-0.1 equiv), and K_2CO_3 (4 equiv) in acetonitrile-water (99:1) in the dark at room temperature (eq 1). Yields are similar or better than those obtained with ***Lead(IV) Acetate***, periodic acid and its salts, or the stoichiometric ***Triphenylbismuth Carbonate*** reagent. In contrast with these reagents, which cleave only *cis*-decalin-9,10-diol, the catalytic system cleaves both the *cis*- and the *trans*-decalin-9,10-diol isomers at nearly the same rate.

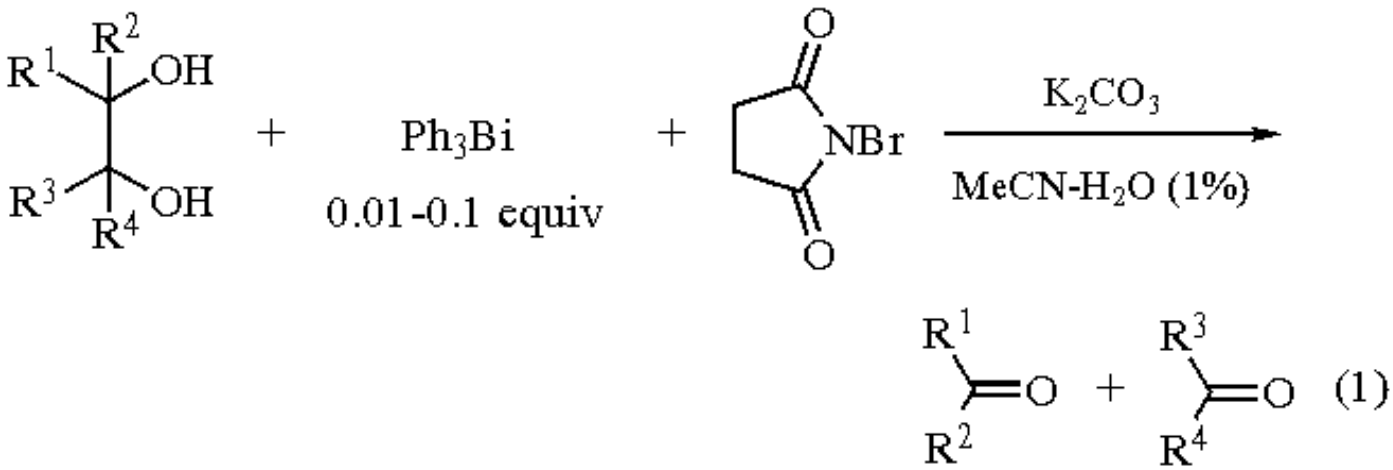

Copper-Catalyzed Phenylations.

Although there is no reaction between Ph_3Bi and ***Copper(II) Acetate***, triphenylbismuthine can transfer a phenyl group to alcohols, phenols, or amines when a stoichiometric amount of copper diacylate is used.

Alcohols and phenols.[6,7]

When primary or secondary alcohols are treated with Ph_3Bi in the presence of copper diacetate (Ph_3Bi:$Cu(OAc)_2$ = 1:2) without solvent in sealed ampules, the *O*-phenyl ethers are formed in 43-91% yields (based on the bismuth reagent) at a very slow rate (several days at rt) (eq 2). No reaction with phenol has been described under these conditions. However, when a CH_2Cl_2 solution of 3,5-di-*t*-butylphenol is treated with a mixture of Ph_3Bi (1.2 equiv), $Cu(OAc)_2$ (2 equiv), and Et_3N (4 equiv), the corresponding *O*-phenyl ether is obtained in 44% yield after 10 h at rt. These *O*-phenylation reactions, particularly of phenols, are better performed with the more general copper-catalyzed ***Triphenylbismuth Diacetate*** system.

$$\mathrm{ROH} + \mathrm{Ph_3Bi} + \mathrm{Cu(OAc)_2} \xrightarrow{\text{neat}} \mathrm{R\text{-}O\text{-}Ph} \qquad (2)$$

Amines.[7]

Amines react smoothly at rt with Ph_3Bi (1.2 equiv) and $Cu(OAc)_2$ (0.5 equiv) to give high yields of *N*-mono- or *N*,*N*-diphenylated amines. Generally, monophenylated compounds are obtained with primary amines (eq 3) in variable yields, depending upon the basicity and steric hindrance of the substrate (6% for *p*-nitroaniline, 25% for mesitylamine, but 82% for *p*-methoxyaniline). With *n*-butylamine, the monophenyl (60%) and diphenyl (38%) derivatives are obtained. This reaction is less efficient than the related copper-catalyzed triphenylbismuth diacetate system. However, since Ph_3Bi is commercially available, this reaction is of interest for the monophenylation of anilines and a variety of aliphatic and heterocyclic amines.

$$\mathrm{RNH_2} + \mathrm{Ph_3Bi} + \mathrm{Cu(OAc)_2} \xrightarrow[\text{rt}]{\mathrm{CH_2Cl_2}} \mathrm{RNH\text{-}Ph} \qquad (3)$$

Palladium-Catalyzed Phenylation.[8]

Triarylbismuthines Ar_3Bi (Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$) react with $Pd(OAc)_2$ (1 equiv) and ***Triethylamine*** (2 equiv) in HMPA to afford quantitatively the corresponding biaryl after heating for 10 min at 65 °C. When the reaction is performed in presence of acyl chlorides at 65 °C for 5 h in HMPA, phenyl ketones are obtained in 89-96% yields (eq 4). In the absence of the catalyst, phenyl ketones are also formed but in low yields.[9]

$$\mathrm{RCOCl} + \mathrm{Ph_3Bi} + \mathrm{Pd(OAc)_2} + \mathrm{Et_3N} \xrightarrow[\text{65 °C}]{\text{HMPA}} \mathrm{RCO\text{-}Ph} \qquad (4)$$

Other Uses.

Triphenylbismuthine can also function as a catalyst or cocatalyst in the polymerization of hydrocarbons,[1c] and as a source of phenyl radicals under photolytic conditions.[4]

---

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Triphenylbismuth Carbonate[1]

Ph_3BiCO_3

[47252-14-2] · $C_{19}H_{15}BiO_3$ · Triphenylbismuth Carbonate · (MW 500.32)

(oxidation of alcohols; glycol cleavage;[4], *C*-phenylation of phenols,[3] carbonyl compounds,[7] and nitrogen derivatives[7])

Physical Data: mp 164 °C.[2]

Solubility: insoluble most organic solvents; reacts with carboxylic and sulfonic acids to give the corresponding diesters.

Preparative Method: prepared by reaction of ***Triphenylbismuth Dichloride*** with ***Potassium Carbonate*** in acetone-water.[3]

Handling, Storage, and Precautions: stable white powder; can be stored in the refrigerator for months. Use in a fume hood.

Oxidation of Alcohols.[4]

Ph_3BiCO_3 is a very effective heterogeneous oxidant for primary, secondary, allylic, and benzylic alcohols, which are converted into the corresponding carbonyl derivatives under neutral conditions. Thiols are oxidized to disulfides, but the thiocarbonyl group in xanthates, *N*,*N*-dialkyl thionocarbamates, and di-*t*-butyl thioketone remain unaffected. Aniline, dimethylaniline, pyrrolidine, indole, and 3-pyrrolidinocholesta-3,5-diene are not oxidized. Hydrazo compounds are oxidized to azo compounds and hydrazones to diazo compounds.

Glycol Cleavage.

Very high yields of carbonyl derivatives are obtained upon oxidation of 1,2-glycols with Ph_3BiCO_3.[4] As an example, the monobactam polyol in eq 1 is cleaved by Ph_3BiCO_3 to the disulfide in 85% yield.[5]

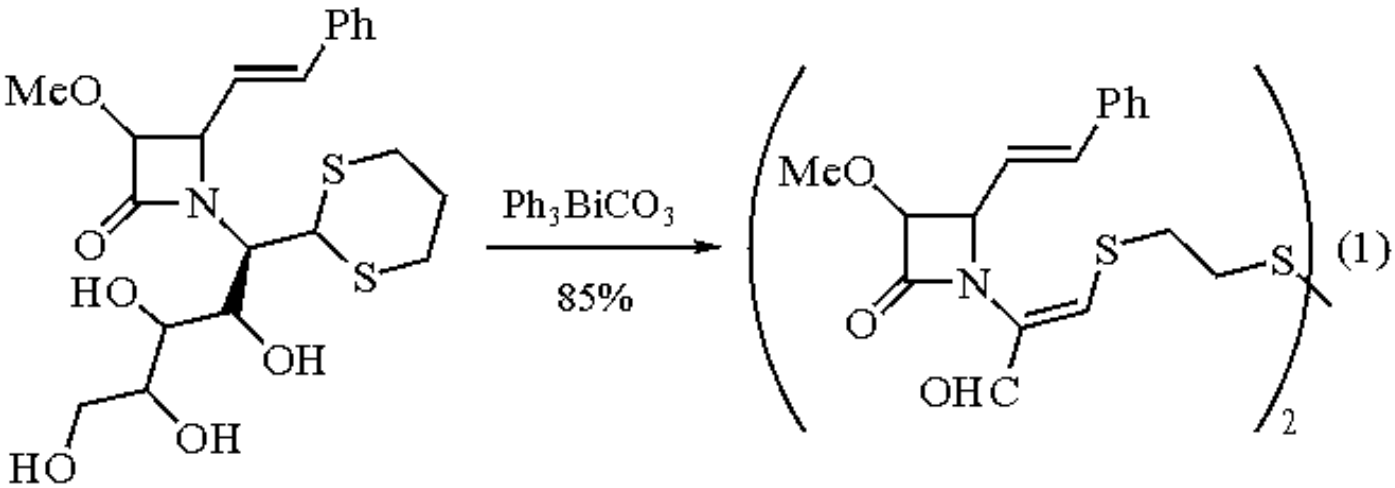

Phenylation.

Phenols.[3,6]

The nature of the product of the reaction of Ph_3BiCO_3 with phenols is very dependent upon the nature of the phenolic substrate. Thus, whereas β-naphthol reacts in the presence of TMG to give α-phenyl-β-naphthol (76%) (eq 2), 2,6-dimethylphenol gives 2,2´,6,6´-

tetramethyldiphenoquinone (92%) (eq 3), and phloroglucinol is converted to a perphenyl enedione and a small amount of 2,4,6-triphenylphloroglucinol (eq 4).

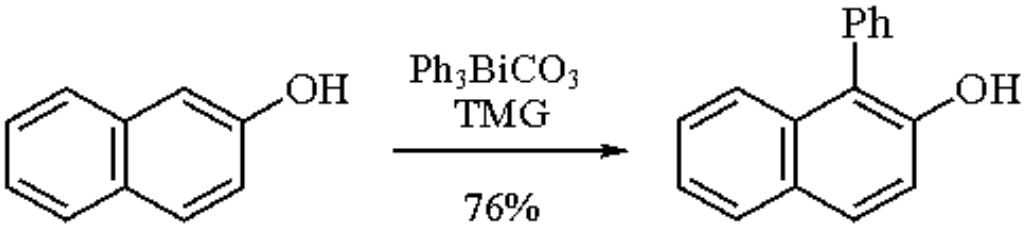

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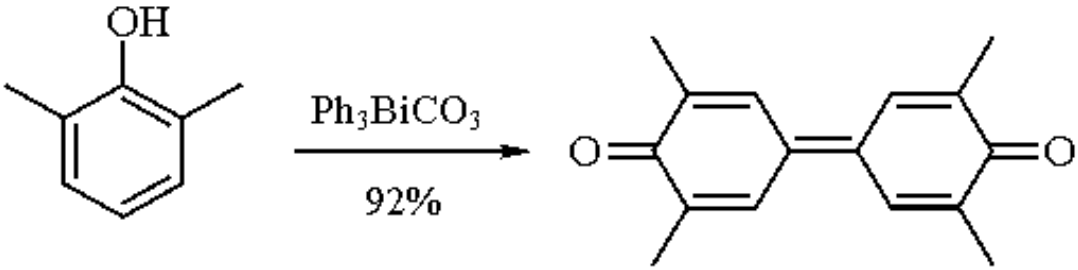

(3)

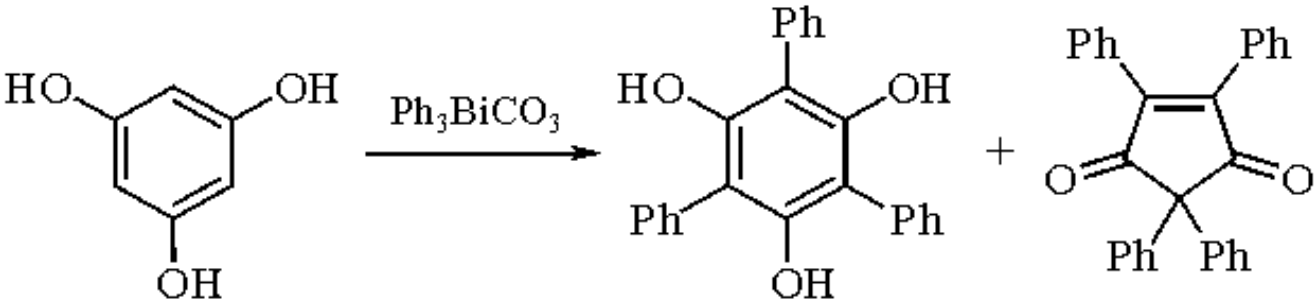

(4)

24% 40%

Carbonyl Compounds.[6,7]

The arylation of ketones by Ar_3BiCO_3 (Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$NO_2C_6H_4$) under basic conditions leads to *C*-arylation of the carbons α to the carbonyl. When a THF solution of a ketone is treated with an excess of Ph_3BiCO_3 (2-8 equiv) in the presence of KH as base, the α,α´-perphenylated products are obtained in 60-93% yield (eq 5).

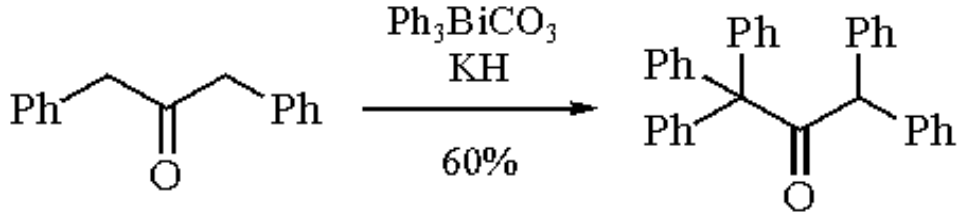

(5)

Enolic compounds, such as 1,3-dicarbonyl compounds, react with Ph_3BiCO_3 under neutral conditions to give the corresponding α-mono- or diphenyl derivatives. One major exception is dimedone, which affords a bismuthonium ylide instead of the 2,2-diphenylated compound. β-Keto sulfones also react easily with Ph_3BiCO_3 to afford the α-phenyl-β-keto sulfones;[8] this reaction can be used for a very efficient synthesis of isoflavanone and isoflavone derivatives. α-Arylglycine derivatives are obtained by the reaction of arylidene imines of glycine ethyl esters with Ar_3BiCO_3 under reflux in DMF (eq 6).[9] When the arylidene group is derived from *p*-chlorobenzaldehyde, a moderate yield of the diphenylated product is obtained, but selective monophenylation is realized with the benzophenone imine. This arylation procedure has also been extended to the synthesis of α-substituted α-phenylglycines.[10]

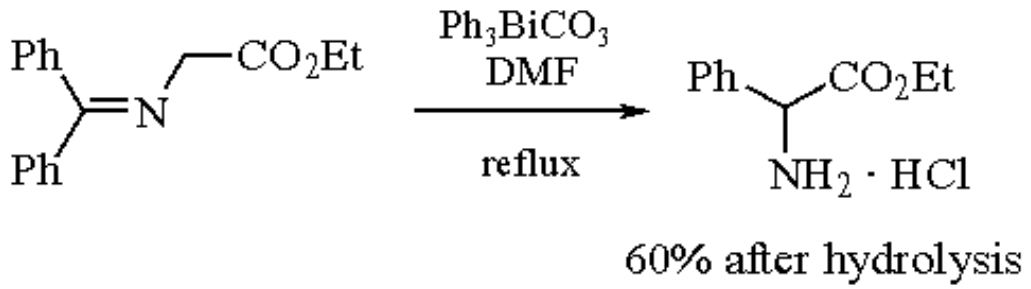

(6)

Nitrogen Derivatives.

Ph_3BiCO_3 generally does not react with amines, but with *N*-phenylhydroxylamine it gives *N*,*N*-diphenylhydroxylamine.[11] Amides are reported to be *N*-phenylated in high yield.[12] Thus *N*,*N*-diphenylacetamide (90%) is obtained from the reaction of the sodium salt of acetamide with Ph_3BiCO_3; *N*-phenyl-*N*-methylbenzamide (90%) is obtained similarly from *N*-methylbenzamide. However, these results could not be repeated, although amides have been *N*-phenylated by ***Triphenylbismuth Dichloride*** in the presence of BTMG.[13] 2-Nitropropane reacts with Ph_3BiCO_3 under basic conditions (KH in THF) to afford α-nitrocumene in 80% yield.[7]

Triarylbismuth carbonates are highly efficient and selective reagents for the arylation of phenolic and enolic substrates. A useful though not so widely applicable class of reagents, which are complementary to the organobismuth reagents for the arylation of phenols and enols, are the aryllead triacetates.

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Triphenylbismuth Diacetate[1]

$Ph_3Bi(OAc)_2$

[7239-60-3] · $C_{22}H_{21}BiO_4$ · Triphenylbismuth Diacetate · (MW 558.41)

(oxidation of alcohols and glycols;[3] *O*- and *N*-phenylation[9,14,16])

Physical Data: mp 187-189 °C.[2]

Solubility: sol CH_2Cl_2, $CHCl_3$; insol ether, MeOH.

Preparative Methods: prepared by treatment of ***Triphenylbismuth Carbonate*** with ***Acetic Acid*** in CH_2Cl_2,[3] or by ***Lead(IV) Acetate*** oxidation of ***Triphenylbismuthine***.[2a] The best yield (60%) is obtained by treatment of Ph_3Bi with $Pb(OAc)_4$ in AcOH for 2 h at rt, followed by addition of water, filtration, and recrystallization (CH_2Cl_2-ether).

Handling, Storage, and Precautions: stable white solid; can be stored under inert gas in the refrigerator for some months. Use in a fume hood.

Oxidation of Alcohols and 1,2-Glycols.

Under basic conditions (either ***Potassium Carbonate*** or an organic base such as ***1,8-Diazabicyclo[5.4.0]undec-7-ene*** or ***1,1,3,3-Tetramethylguanidine***), this reagent oxidizes alcohols to the corresponding carbonyl compounds.[3,4] In a fashion similar to Ph_3BiCO_3, $Ph_3Bi(OAc)_2$ reacts with vicinal glycols in the presence of K_2CO_3[3] or with the stannylene derivatives of vicinal glycols[5] under neutral conditions to afford the two corresponding carbonyl fragments in high yield.

Phenylation of Alcohols.

In the absence of base, $Ph_3Bi(OAc)_2$[6,7] and the related reagent $Ph_4BiOCOCF_3$[8] (prepared by reaction of Ph_5Bi with 1 equiv of CF_3CO_2H, mp 120-132 °C, $C_{26}H_{20}BiF_3O_2$, MW 630.44, *[83566-43-2]*) react with primary and secondary alcohols to afford mostly the corresponding *O*-phenyl ethers with various amounts of oxidation products. In the presence of a copper catalyst, 62-97% of the *O*-phenyl ethers can be obtained with simple alcohols and $Ph_3Bi(OAc)_2$ (eq 1). As copper catalyst, ***Copper(II) Chloride***, ***Copper(I) Chloride***, ***Copper(II) Acetate***, or metallic ***Copper*** can be used.[9]

$$\mathrm{ROH} + \mathrm{Ph_3Bi(OAc)_2} \xrightarrow{\mathrm{CuX_n}} \mathrm{R\text{-}O\text{-}Ph} \qquad (1)$$

Miscellaneous Phenylation Reactions.

In a very simple procedure, α-, β-, γ-, or δ-diols can be efficiently monophenylated by simple reflux of the diol and $Ph_3Bi(OAc)_2$ (1 equiv) in CH_2Cl_2 until disappearance of the diol (eq 2).[10] For secondary-tertiary diols, the secondary *O*-phenyl ethers are obtained, and for axial-equatorial diols, the axial ethers are obtained. With an excess of $Ph_3Bi(OAc)_2$, the bis-ether can be obtained.[9] Addition of a small amount of $Cu(OAc)_2$ (0.1 equiv or less) increases the reaction rate significantly, and the reaction can then be performed in a variety of solvents (eq 3).[9] Moreover, addition of chiral pyridine oxazolines leads to a moderate optical induction in the case of the *meso-cis*-1,2-cyclohexanediol.[11]

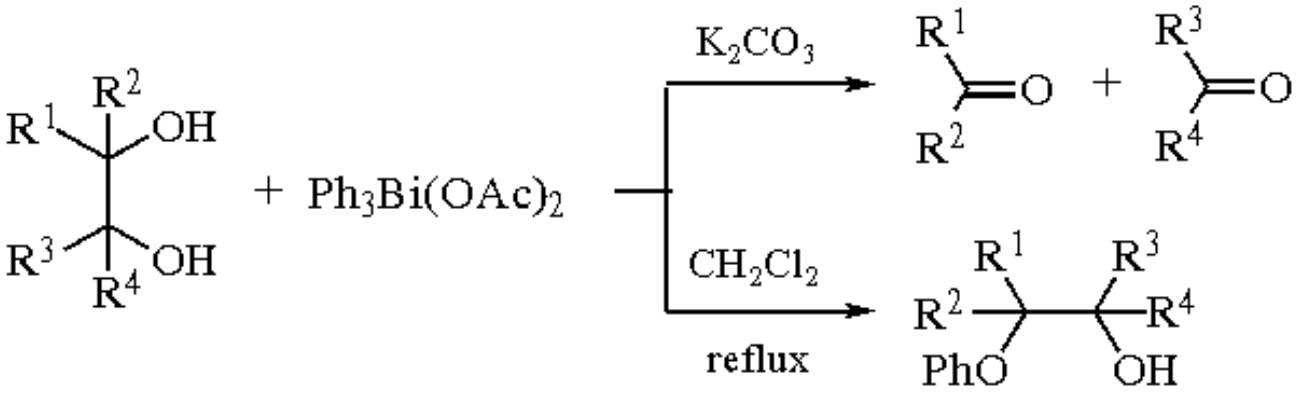

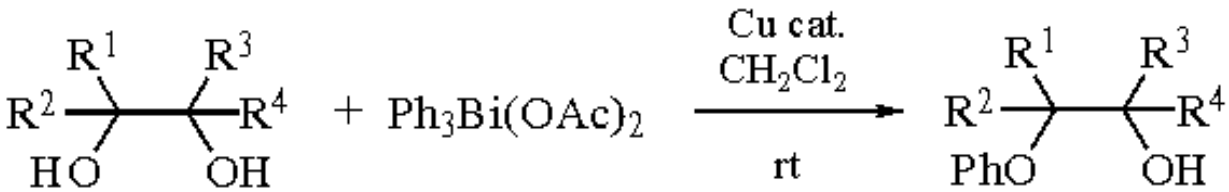

Whereas thiols are oxidized with Ph_3BiCO_3 or Ph_3BiCl_2 and base or $Ph_4BiOCOCF_3$ and base, they gave the corresponding phenyl thioether when treated with $Ph_4BiOCOCF_3$ under neutral or acidic conditions.[12] However, in the case of hydroxythiols, the copper-catalyzed reaction with $Ph_3Bi(OAc)_2$ leads to mixtures of mono- and di-*O*-phenylated disulfides.[9]

Phenols react with $Ph_4BiOCOCF_3$ (under neutral conditions or with acid catalysis) in benzene under reflux to afford moderate to good yields of the *O*-phenyl ethers.[13] Faster rates and better yields can be obtained through copper catalysis. However, $Ph_3Bi(OAc)_2$ under copper metal catalysis in CH_2Cl_2 at rt effects a more efficient and selective *O*-phenylation of electron-poor as well as electron-rich phenols (eq 4). Except for highly hindered phenols, such as 2,6-di-*t*-butylphenol, yields are generally high.[14]

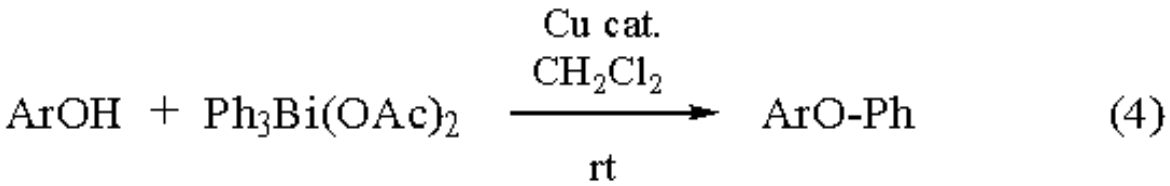

Enols are subject to mono-*O*-phenylation with $Ph_4BiOCOCF_3$ under neutral or, preferably, acidic conditions.[12] Copper catalysis leads to some improvement. Enols can also give the *O*-phenyl ethers by reaction with $Ph_3Bi(OAc)_2$ or the analogous reagent $Ph_3Bi(OCOCF_3)_2$ (prepared by action of CF_3CO_2H on Ph_3BiCO_3, mp 133 °C, $C_{22}H_{15}BiF_6O_4$, MW 666.35, *[83566-43-2]*) under copper metal catalysis. Yields are moderate to good.[14]

Phenylation of Amines.

Under metallic copper catalysis, $Ph_3Bi(OAc)_2$ and $Ph_3Bi(OCOCF_3)_2$ react with aliphatic, heterocyclic, or aromatic amines in CH_2Cl_2 at rt to give the mono-*N*-phenyl derivatives in high yields (eq 5).[15,16] A number of α-amino acid esters are also selectively mono-*N*-phenylated under these conditions.[17] A wide range of variously substituted anilines have been mono- or di-*N*-phenylated with these reagents (eq 6). The most conveniently prepared reagent [$Ph_3Bi(OAc)_2$] is less reactive than $Ph_3Bi(OCOCF_3)_2$. Thus after 45 min, mesitylamine gives 40% of *N*-phenylmesitylamine with the former reagent, but 95% with the latter. Similarly, 4-nitroaniline gives 22% and 98%, respectively. Indoles are *N*- or *C*-3 phenylated only with $Ph_3Bi(OCOCF_3)_2$ under copper catalysis.[18]

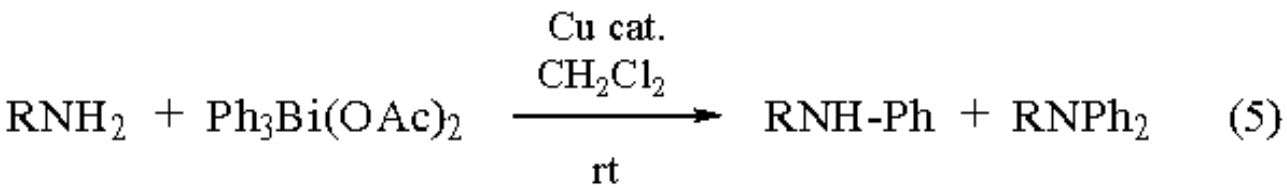

$$ArNH_2 + Ph_3Bi(OAc)_2 \xrightarrow[rt]{\substack{Cu\ cat. \\ CH_2Cl_2}} ArNH\text{-}Ph \qquad (6)$$

The system $Ph_3Bi(OAc)_2$ + copper catalysis provides a broader spectrum of reactivity than the similar aryllead triacetates under copper catalysis, which do not effect phenol *O*-arylation but which do react with anilines to give high yields of unsymmetrical diarylamines.[19]

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Triphenylbismuth Dichloride[1]

Ph_3BiCl_2

(Ph_3BiCl_2)

[594-30-9] · $C_{18}H_{15}BiCl_2$ · Triphenylbismuth Dichloride · (MW 511.21) (Ph_5Bi)

[3049-07-8] · $C_{30}H_{25}Bi$ · Pentaphenylbismuth · (MW 594.53) ($Ph_4BiOCOCF_3$)

[83566-43-2] · $C_{26}H_{20}BiF_3O_2$ · Tetraphenylbismuth Trifluoroacetate · (MW 630.44) (Ph_4BiOTs)

[83566-44-3] · $C_{31}H_{27}BiO_3S$ · Tetraphenylbismuth Tosylate · (MW 688.63)

(phenylation of phenols,[6] ketones and enols,[5] and nitro compounds[8])

Physical Data: mp 159-160 °C.[2]

Solubility: sol CH_2Cl_2, $CHCl_3$, benzene, toluene; insol ether, THF, MeOH.

Preparative Methods: easily prepared[2] by oxidation of ***Triphenylbismuthine*** either by bubbling ***Chlorine*** gas into an ethereal solution of Ph_3Bi at 0 °C, or by addition of 1 equiv of ***Sulfuryl Chloride*** to a solution of Ph_3Bi in CH_2Cl_2 at -78 °C. The action of ***Phenyllithium*** on Ph_3BiCl_2 leads to pentaphenylbismuth (mp 77-78 °C).[2] Addition of 1 equiv of a carboxylic or sulfonic acid to Ph_5Bi affords compounds of the type Ph_4BiX.[3] ($Ph_4BiOCOCF_3$: mp 120-132 °C; Ph_4BiOTs: mp 155-162 °C).

Handling, Storage, and Precautions: stable white solid; can be stored in the refrigerator in the absence of moisture. Pentaphenylbismuth is a poorly stable violet powder which can be stored under inert gas in the refrigerator for some days. $Ph_4BiOCOCF_3$ and Ph_4BiOTs are white powders which can be stored in the refrigerator under inert gas for some weeks. These reagents should be used in a fume hood.

Oxidation of Alcohols.[4]

Treatment of primary or secondary alcohols with (a) Ph_3BiCl_2 or Ph_4BiX in the presence of a strong base (e.g. ***1,1,3,3-Tetramethylguanidine***, BTMG (*t*-butyltetramethylguanidine), or ***1,8-Diazabicyclo[5.4.0]undec-7-ene***) or with (b) Ph_5Bi under neutral conditions leads to oxidation to the corresponding carbonyl compounds under mild conditions in moderate to high yields (eq 1). Because of the similar reactivity patterns of these reagents, the system Ph_3BiCl_2 + base is the reagent of choice, due to its facile preparation and stability. An excess of reagent must be avoided, as possible side reactions such as α-*C*-phenylation can occur (see below).[5] The reaction of salts of tertiary alcohols, e.g. *t*-BuOLi, with Ph_3BiCl_2 results in the formation of the *O*-phenyl ethers e.g. *t*-BuOPh.[4c] In the presence of a base such as BTMG, Ph_3BiCl_2 cleaves glycols efficiently in the same way as Ph_3BiCO_3.

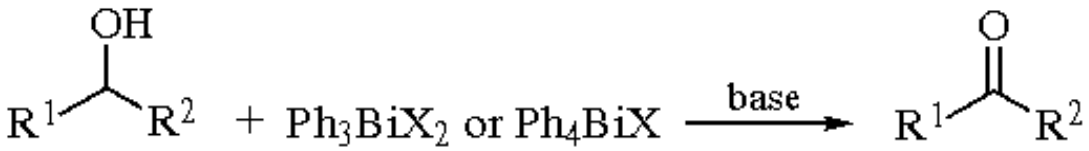

(1)

Phenylation of Phenols.[6]

The reaction of phenols with organobismuth(V) reagents leads to a variety of products (eq 2). Phenols bearing electron-donating substituents react with Ph_3BiX_2 or Ph_4BiX in the presence of a strong base (BTMG, TMG, NaH, or KH) or with Ph_5Bi under neutral conditions to give mostly or only the *o*-mono- or *o,o´*-di-*C*-phenylated derivatives. With 2,6-disubstituted phenols, either 6-phenyl-6-methylcyclohexa-2,4-dienone or 4-phenyl-2,6-di-*t*-butylphenol are obtained, in contrast to the reaction with Ph_3BiCO_3 which gives diphenoquinones. Unactivated phenols or phenols bearing *meta* electron-withdrawing substituents afford mixtures of *O*- and *ortho*-*C*-

phenylphenols. Phenols bearing *para* electron-withdrawing substituents give exclusively *O*-phenyl ethers after thermal decomposition of the aryloxybismuth intermediate. As these *O*-phenyl ethers can be obtained under milder conditions (neutral, rt) with ***Triphenylbismuth Diacetate*** under $Cu(OAc)_2$ catalysis, the present system does not compete efficiently.

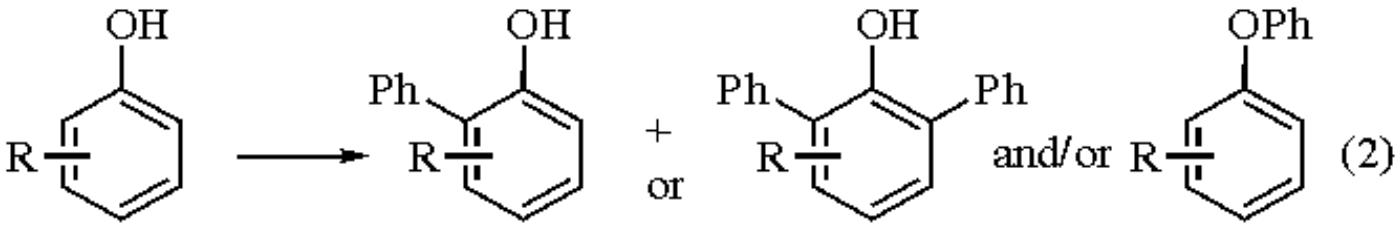

Phenylation of Ketones and Enolic Compounds.[5]

In the presence of a strong base, ketones react with Ph_3BiCl_2 or Ph_4BiX to afford mostly or only the perphenylated derivatives. For example, cyclohexanone affords 2,2,6,6-tetraphenylcyclohexanone in 80% yield with Ph_4BiOTs + KH.[7] Ph_5Bi does not react with nonenolizable ketones, but with enolizable ketones the reaction does take place. Thus 2-phenylethanol is oxidized by Ph_5Bi and the aldehyde further reacts to afford, eventually, triphenylacetaldehyde in 69% yield.[5] Enolizable compounds such as β-dicarbonyl derivatives react with Ph_5Bi under neutral conditions, or with Ph_3BiCl_2 and Ph_4BiX (both in the presence of a strong base), to afford generally the α-perphenylated derivatives. For example, this reaction occurs with acetylacetone, ethyl acetoacetate, ethyl cyclohexanone-2-carboxylate (eq 3), ethyl cyclopentanone-2-carboxylate, diethyl malonate, and dimedone.[5,8]

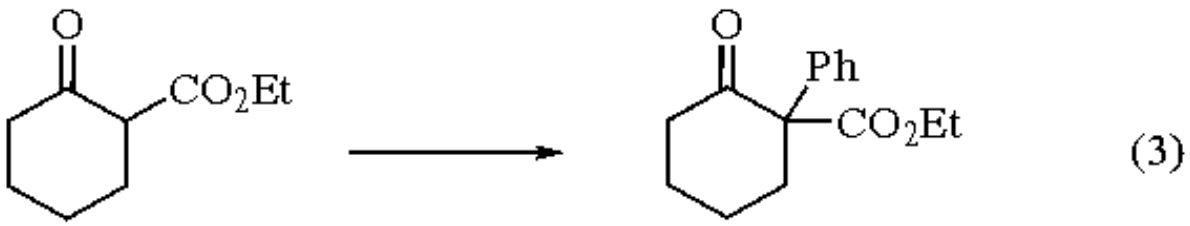

Ph_5Bi	57%
Ph_3BiCl_2, BTMG	75%
$Ph_4BiOCOCF_3$, BTMG	91%

With acetylacetone, Ph_3BiCl_2 and base leads to 3,3-diphenylacetylacetone (74%), whereas $Ph_4BiOCOCF_3$ in benzene under reflux in the absence of base gives a moderate yield of the 3-monophenyl derivative (34%). In the case of dimedone and Meldrum's acid, the reaction of their sodium salts with Ph_3BiCl_2 leads only to the stable crystalline bismuthonium ylides.[9] In an application in natural products chemistry, high yields of 3-phenyl-4-hydroxycoumarins have been obtained from the reaction of 4-hydroxycoumarins with Ph_5Bi at -23 °C.[10] With caprolactam-type malonic derivatives, completely different results are observed, depending on the reagent used. Thus 3-cyano-ε-caprolactam reacts only with Ph_5Bi to give 74% of 3-cyano-3-phenyl-ε-caprolactam; 3-ethoxycarbonyl-ε-caprolactam does not react with Ph_5Bi and gives only the *N*-phenylcaprolactam derivative through reaction with Ph_3BiCl_2 and base.[11]

Phenylation of Nitro Compounds.

In the presence of BTMG, 2-nitropropane reacts with Ph_3BiCl_2 or Ph_4BiOTs to produce α-nitrocumene (86 or 77% respectively).[8] The reaction using Ph_3BiCl_2 and TMG has been applied to the synthesis of α-methyl-α-phenylglycine via arylation of α-nitropropionic acid esters.[12]

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Triphenylcarbenium Tetrafluoroborate

$Ph_3C^+ BF_4^-$

[341-02-6] · $C_{19}H_{15}BF_4$ · Triphenylcarbenium Tetrafluoroborate · (MW 330.15)

(easily prepared[1] hydride abstractor used for conversion of dihydroaromatics to aromatics,[2-4] and the preparation of aromatic and benzylic cations;[5-8] oxidative hydrolysis of ketals[9] and thioketals;[10] conversion of acetonides to α-hydroxy ketones;[9] oxidation of acetals[11] and thioacetals;[12] selective oxidation of alcohols and ethers to ketones;[9,13-15] oxidation of silyl enol ethers to enones;[16] hydrolysis of TBS and MTM ethers;[17] oxidation of amines and amides to iminium salts;[18-20] oxidation of organometallics to give alkenes;[21-23] sensitizer for photooxidation using molecular oxygen;[24] Lewis acid catalyst for various reactions;[25] polymerization catalyst;[26] other reactions[27-30])

Alternate Name: trityl fluoroborate.

Physical Data: mp ~200 °C (dec).

Solubility: sol most standard organic solvents; reacts with some nucleophilic solvents.

Form Supplied in: yellow solid; commercially available.

Preparative Methods: the most convenient procedure involves the reaction of Ph_3CCl with ***Silver(I) Tetrafluoroborate*** in ethanol.[1b] The most economical route employs the reaction of Ph_3CCl with the anhydrous ***Tetrafluoroboric Acid***-Et_2O complex.[1c]

Purification: recrystallization of commercial samples from a minimal amount of dry MeCN provides material of improved purity, but the recovery is poor.[1a]

Handling, Storage, and Precautions: moisture-sensitive and corrosive. Recrystallized reagent can be stored at rt for several months in a desiccator without significant decomposition. This compound is much less light-sensitive than other trityl salts such as the perchlorate.[1a]

Preparation of Aromatic Compounds via Dehydrogenation.

Dihydroaromatic compounds are easily converted into the corresponding aromatic compound by treatment with triphenylcarbenium tetrafluoroborate followed by base.[2] Certain α,α-disubstituted dihydroaromatics are converted to the 1,4-dialkylaromatic compounds with rearrangement (eq 1).[3] Nonbenzenoid aromatic systems, e.g. benzazulene[4a] or dibenzosesquifulvalene,[4b] are readily prepared from their dihydro counterparts. Aromatic cations are also easily prepared by hydride abstraction, for example, tropylium ion (e.g. in the synthesis of heptalene (eq 2)),[5] cyclopropenyl cation,[6] and others, including heterocyclic systems.[7] Some benzylic cations, especially ferrocenyl cations,[8] can also be formed by either hydride abstraction or trityl addition.

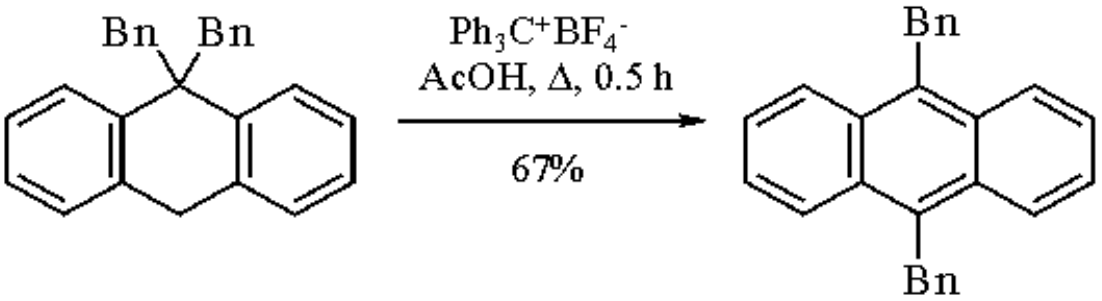

(1)

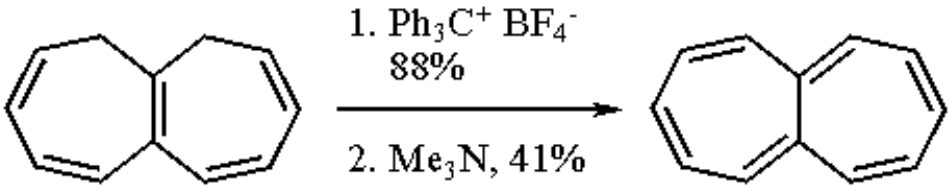

(2)

Oxidation by Hydride Abstraction.

In the early 1970s, Barton developed a method for the oxidative hydrolysis of ketals to ketones, e.g. in the tetracycline series (eq 3).[9] The same conditions can also be used to hydrolyze thioketals.[10] Acetonides of 1,2-diols are oxidized to the α-hydroxy ketones in good yield by this reagent (eq 4).[9] The hydrogen of acetals is easily abstracted (eq 5), providing a method for the conversion of benzylidene units in sugars to the hydroxy benzoates.[11] The hydrogen of dithioacetals is also abstracted to give the salts.[12] Since benzylic hydrogens are readily abstracted, this is also a method for deprotection of benzyl ethers.[9,13] Trimethylsilyl, *t*-butyl, and trityl ethers of simple alcohols are oxidized to the corresponding ketones and aldehydes in good yield. Primary-secondary diols are selectively oxidized at the secondary center to give hydroxy ketones by this method (eq 6).[14] 2,2-Disubstituted 1,4-diols are oxidized only at the 4-position to give the corresponding lactones.[15] Trimethylsilyl enol ethers are oxidized to α,β-unsaturated ketones, thereby providing a method for ketone to enone conversion (eq 7).[16] *t*-Butyldimethylsilyl (TBDMS) ethers are not oxidized but rather hydrolyzed to the alcohols, as are methylthiomethyl (MTM) ethers.[17] Benzylic amines and amides can be oxidized to the iminium salts,[18] allylic amines and enamines afford eniminium salts,[19] and orthoamides give triaminocarbocations.[20]

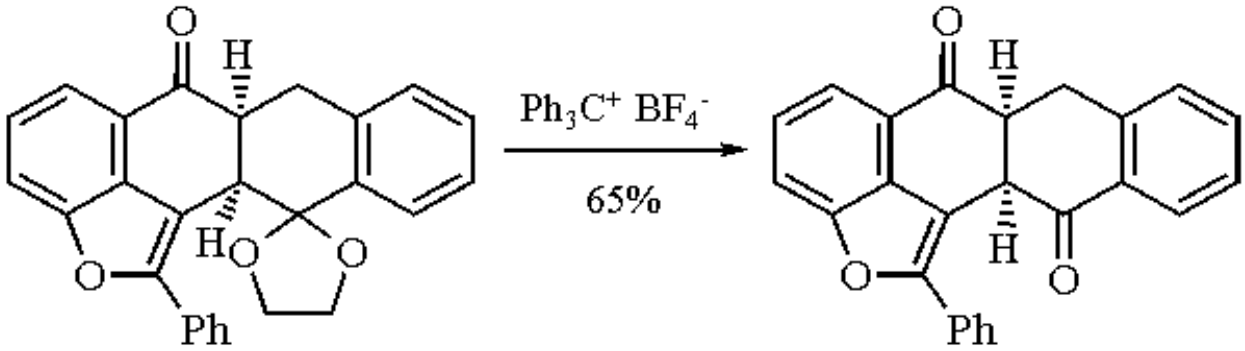

(3)

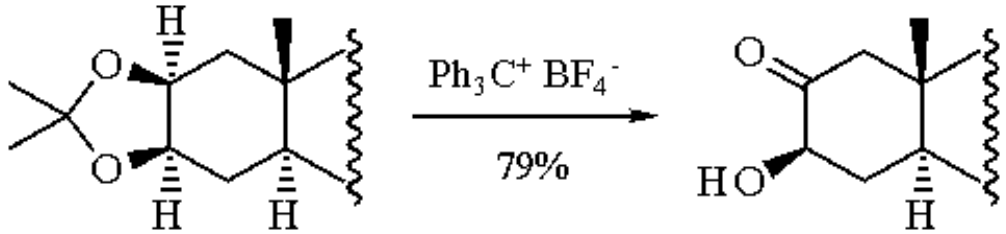

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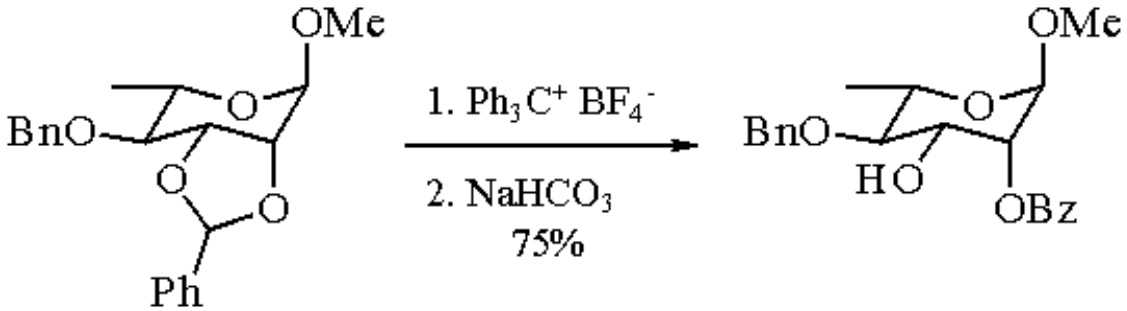

(5)

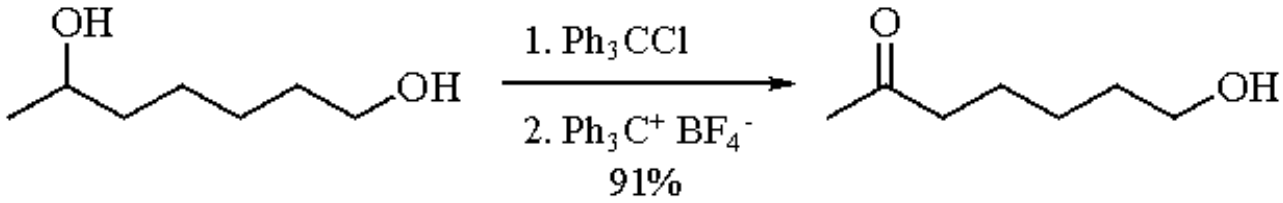

(6)

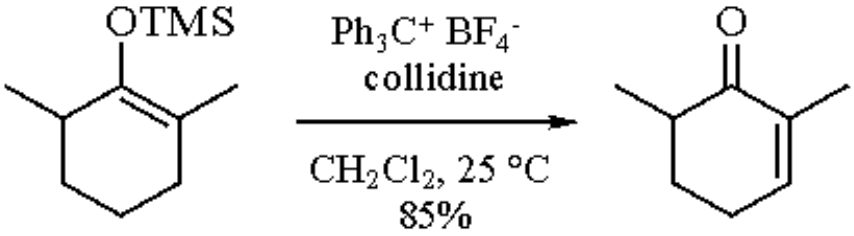

(7)

Generation of Alkenes from Organometallics.

Various β-metalloalkanes can be oxidized by trityl fluoroborate to the corresponding alkenes.[21-23] The highest yields are obtained for the β-iron derivatives (eq 8), which are easily prepared from the corresponding halides or tosylates.[21] Grignard reagents and organolithiums also undergo this reaction (eq 9),[22] as do Group 14 organometallics (silanes, stannanes, etc.).[23]

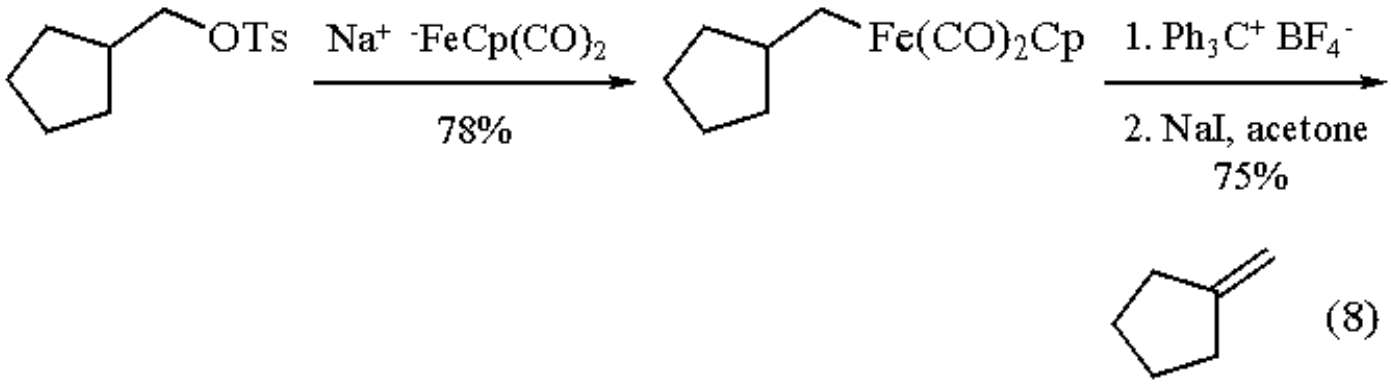

(8)

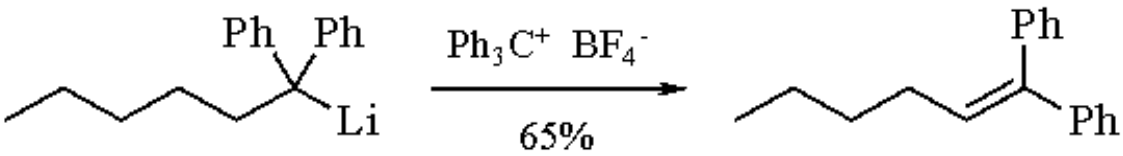

(9)

Sensitizer of Photooxygenation.

Barton showed that oxygen, in the presence of trityl fluoroborate and ordinary light, adds to cisoid dienes at -78 °C in very high yields.[24] For example, the peroxide of ergosterol acetate is formed in quantitative yields under these conditions (eq 10),[24a,b] which have been used also for photocycloreversions of cyclobutanes.[24c]

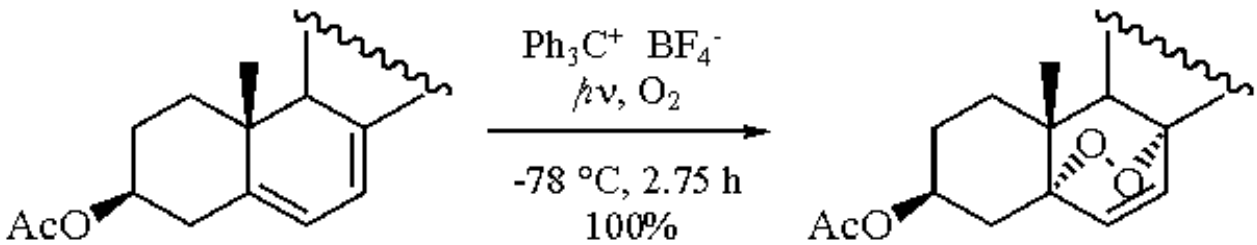

(10)

Lewis Acid Catalysis.

Trityl fluoroborate is a good Lewis acid for various transformations,[25] e.g. the Mukaiyama-type aldol reaction using a dithioacetal and silyl enol ether (eq 11).[25a] It has also been used as the catalyst for the formation of glycosides from alcohols and sugar dimethylthiophosphinates (eq 12)[25b] and for the formation of disaccharides from a protected α-cyanoacetal of glucose and a 6-*O*-trityl hexose.[25c] Michael additions of various silyl nucleophiles to conjugated dithiolenium cations also proceed well (eq 13).[25d,e] Finally, the [4 + 2] cycloaddition of cyclic dienes and oxygenated allyl cations has been effected with trityl fluoroborate.[25f]

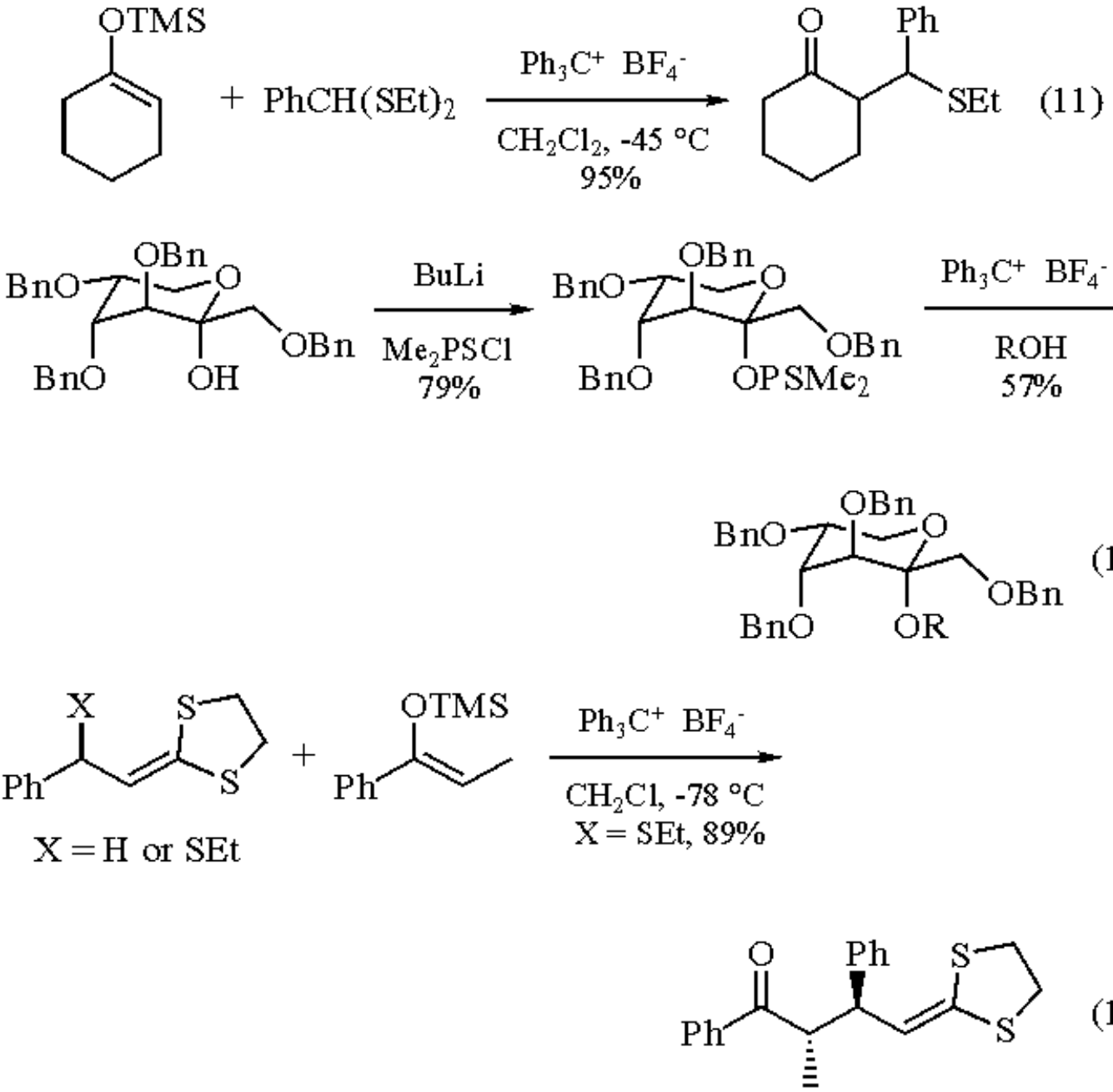

Polymerization Catalyst.

Several types of polymerization[26] have been promoted by trityl fluoroborate, including reactions of orthocarbonates[26a] and orthoesters,[26b-d] vinyl ethers,[26e-g] epoxides,[26h,i] and lactones.[26j,k]

Other Reactions.

Trityl fluoroborate has been used often to prepare cationic organometallic complexes, as in the conversion of dienyl complexes of iron, ruthenium, and osmium into their cationic derivatives.[27] It alkylates pyridines on the nitrogen atom in a preparation of dihydropyridines[28a] and acts as a tritylating agent.[28b] It has also been used in attempts to form silyl cations and silyl fluorides from silanes.[29] Finally, it has been reported to be a useful desiccant.[30]

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1,1,2-Triphenyl-1,2-ethanediol[1,2]

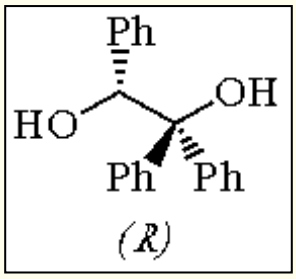

[95061-46-4] · $C_{20}H_{18}O_2$ · 1,1,2-Triphenyl-1,2-ethanediol · (MW 290.38)

(derived chiral monoesters undergo stereoselective aldol additions; formation of *O*-silyl orthoesters and cyclic phosphonates)

Physical Data: mp 126 °C. (*R*): [α]25D +214° (*c* = 1, ethanol), +220° (*c* = 1, 95% ethanol); (*S*): [α]25D -217° (*c* = 1, ethanol).

Solubility: sol dichloromethane, chloroform, THF, ethanol; insol hexane.

Form Supplied in: white solid; the (*R*)-form is commercially available.

Preparative Methods: (*R*)-1,1,2-triphenylethane-1,2-diol [(*R*)-(**1**)] is easily available from commercial (*R*)-***Mandelic Acid***, which is first esterified to give methyl mandelate and then treated with ***Phenylmagnesium Bromide*** (3.5 equiv). In an analogous way, (*S*)-(**1**) is accessible from (*S*)-mandelic acid, which is also commercially available (eq 1).[2]

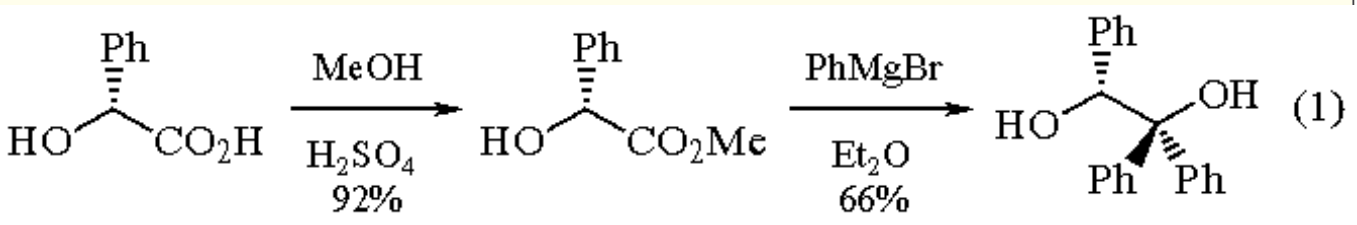

anti-Selective and Diastereofacially Selective Aldol Additions.

2-Trimethylsilyloxy-1,2,2-triphenylethyl propionate, which is prepared from (*R*)-(**1**) by esterification with propionyl chloride and subsequent silylation of the tertiary hydroxy group, reacts in a highly stereoselective manner upon deprotonation, transmetalation with ***Dichlorobis(cyclopentadienyl)zirconium***, and addition to 2-methylpropanal. The diastereoselectivity is 96:4, which is the ratio of the major product to the sum of all other diastereomers. Subsequent reduction with ***Lithium Aluminum Hydride*** affords (2*S*,3*R*)-2,4-dimethyl-1,3-pentanediol in 95% ee (eq 2).[3] *anti*-Selective aldol additions which deliver chiral nonracemic products have been a longstanding problem of asymmetric synthesis.[4] Doubly deprotonated 2-hydroxy-1,2,2-triphenylethyl propionate has been applied in a total synthesis of dolastatin.[5]

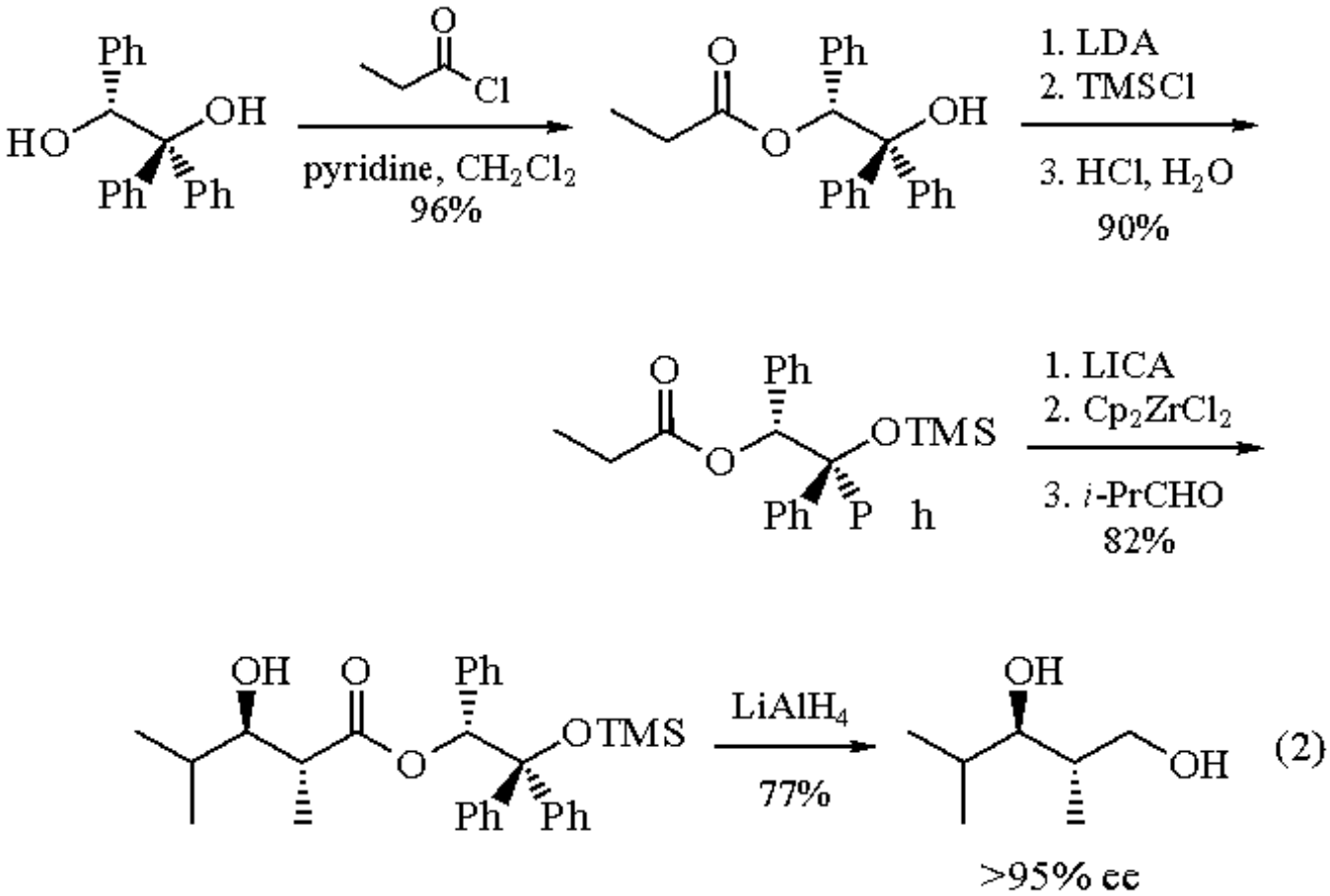

When 1,1,2-triphenylethane-1,2-diol-derived esters are submitted to a monodeprotonation and subsequently treated with ***Chlorotrimethylsilane***, the formation of 2-trimethylsilyloxy-1,3-dioxolanes results. The orthoester moiety thus obtained serves as a protecting group for carboxylic acids (eq 3); it is stable towards alkyllithium reagents and can be cleaved under nonacidic conditions by alkaline hydrolysis.[6]

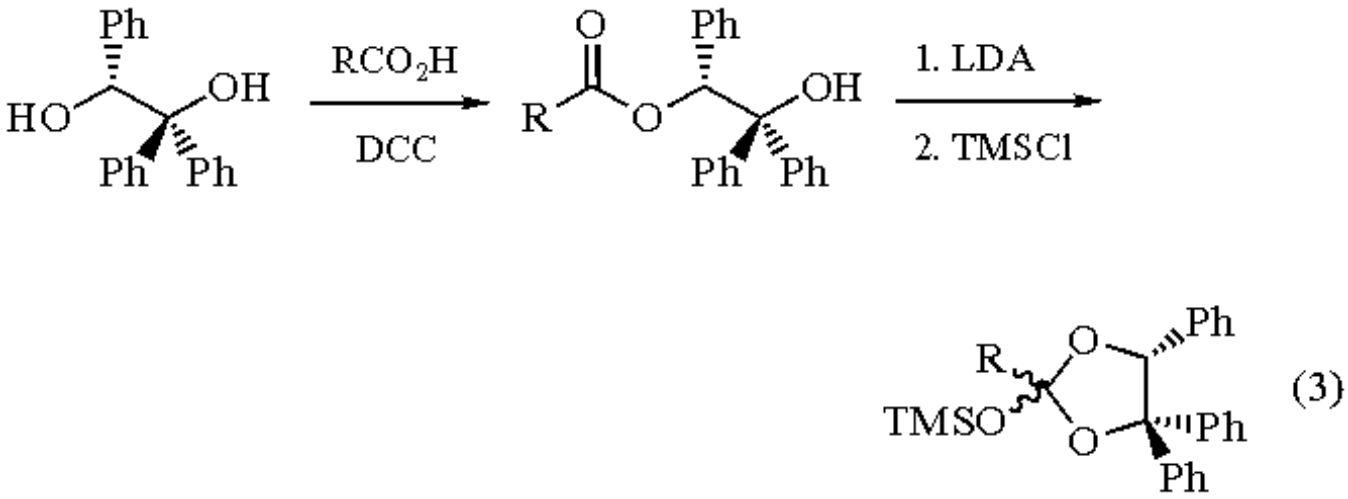

Methanephosphonyl dichloride reacts with (*R*)-(**1**) to give 2-methyl-4,4,5-triphenyl-2-oxo-1,3,2-dioxaphospholane (eq 4); the (R_P,R_C) diastereomer forms predominantly (9:1).[7]

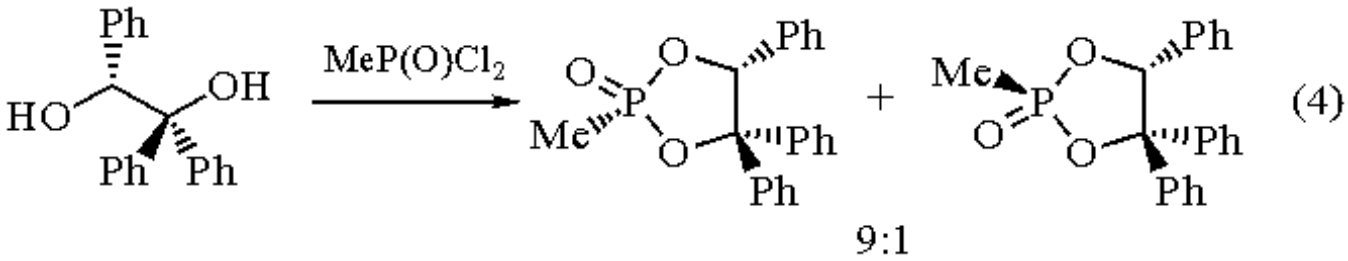

A series of enantiomerically pure 1,1-diaryl-2-phenylethane-1,2-diols is available from methyl mandelate by addition of the corresponding substituted arylmagnesium bromides or aryllithium reagents.[2b,8]

Related Reagents.

10,2-Camphorsultam; ***(R)-2-t-Butyl-6-methyl-4H-1,3-dioxin-4-one***; ***(R)-(+)-t-Butyl 2-(p-Tolylsulfinyl)propionate***; ***Chloro(cyclopentadienyl)bis[3-O-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranosyl)]titanium***; ***10-Dicyclohexylsulfonamidoisoborneol***; ***Diisopinocampheylboron Trifluoromethanesulfonate***; ***(R,R)-2,5-Dimethylborolane***; ***2-Hydroxy-1,2,2-triphenylethyl Acetate***; ***α-Methyltoluene-2,α-sultam***; ***(S)-4-Benzyl-2-oxazolidinone***; ***3-Propionylthiazolidine-2-thione***; ***(R,R)-1,2-Diphenyl-1,2-diaminoethane N,N´-Bis[3,5-bis(trifluoromethyl)benzenesulfonamide]***; ***trans-2,5-Bis(methoxymethyl)pyrrolidine***.

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Triphenylmethyl Hexafluorophosphate

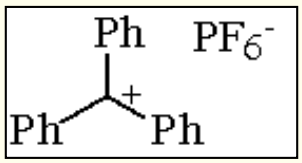

[437-17-2] · $C_{19}H_{15}F_6P$ · Triphenylmethyl Hexafluorophosphate · (MW 388.31)

(catalyst for Michael additions,[1] aldol reactions,[2] photooxygenation;[3] reagent for hydride abstraction[4] and alkoxy abstraction[5])

Alternate Names: trityl hexafluorophosphate; triphenylcarbenium hexafluorophosphate.

Physical Data: mp 145 °C (dec.)[6]

Form Supplied in: brown powder; widely available.

Handling, Storage, and Precautions: trityl hexafluorophosphate should be stored in the dark as exposure to light darkens the compound. It is rapidly hydrolyzed by exposure to moist air.[7,8]

Michael Reactions.

Silyl enol ethers and α,β-unsaturated ketones react in the presence of trityl hexafluorophosphate (2-3 mol %) to give predominantly the *anti* Michael addition products (eq 1).[1] Steroeselectivity is similar to that found when ***Triphenylmethyl Perchlorate*** is used as the catalyst.[1]

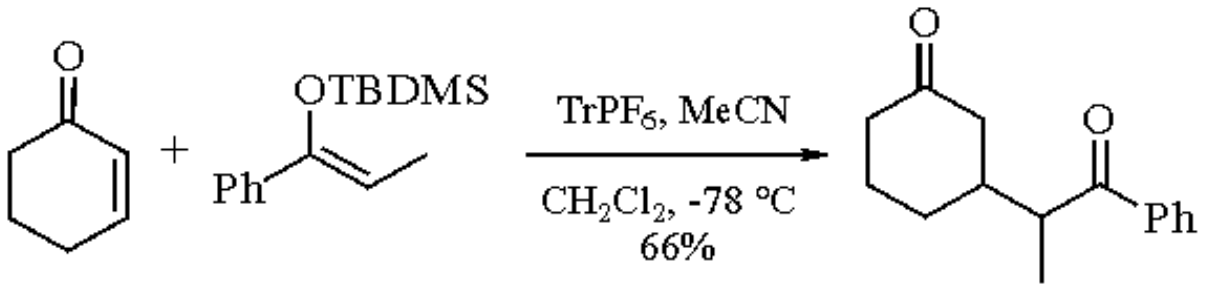

(1)

Aldol Reactions.

Trityl hexafluorophosphate catalyzes the reaction of silyl enol ethers with aldehydes to give aldol products (eq 2).[2] Yields are similar to those obtained with trityl perchlorate as catalyst, being slightly higher or lower depending on the substrate.[2]

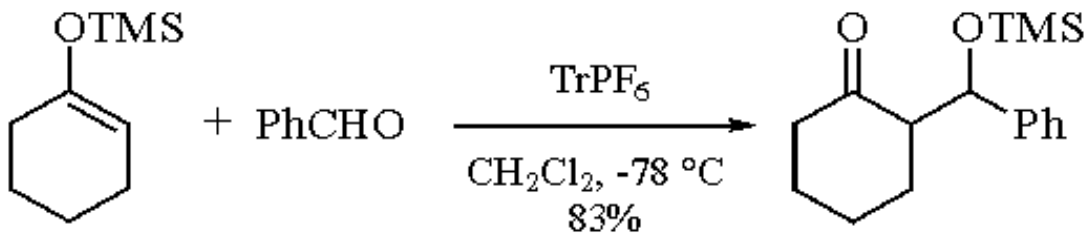

(2)

Photooxygenation.

Ergosteryl acetate can be converted photochemically to the corresponding peroxide by oxygen in the presence of trityl hexafluorophosphate (eq 3).[3] Other trityl salts can also be used.[3]

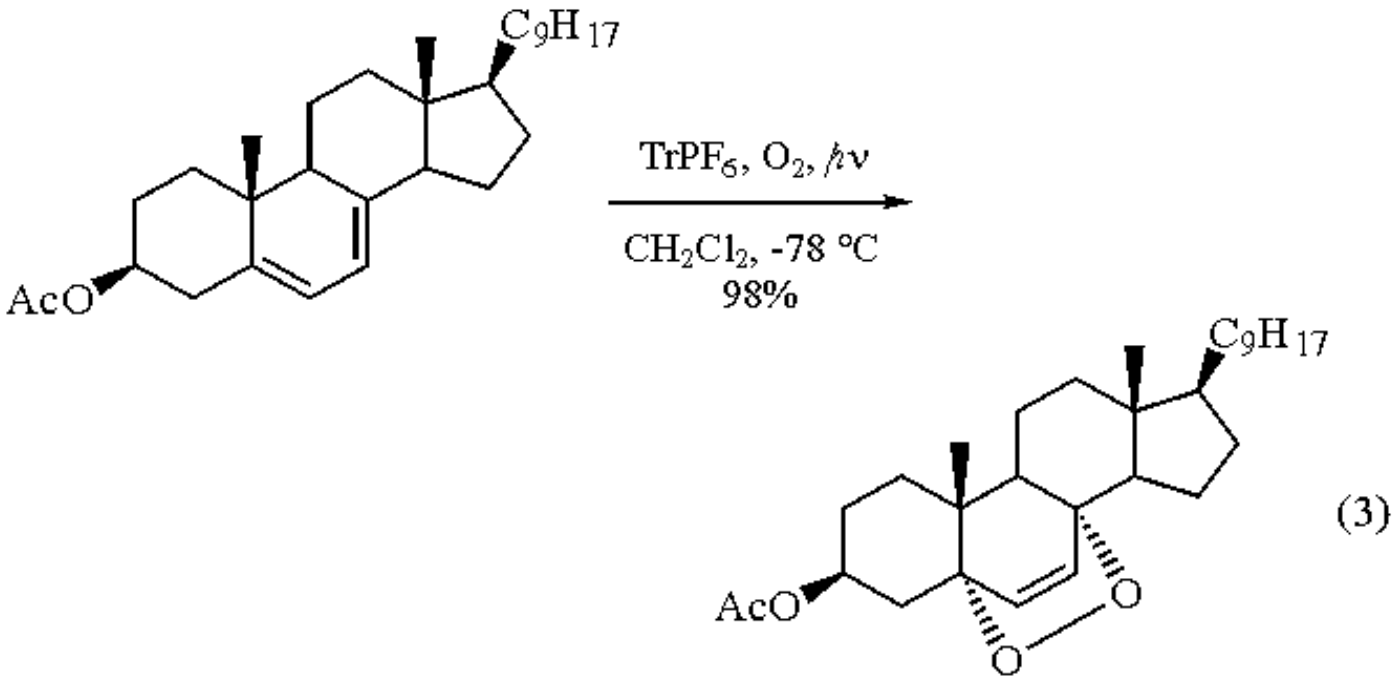

Hydride Abstraction.

Trityl hexafluorophosphate has been used with great success to abstract hydride ions from transition metal-complexed alkenic systems. For instance, with iron as the transition metal, the complex (**1**) gives the cyclobutatropylium iron complex (**2**) (eq 4).[9]

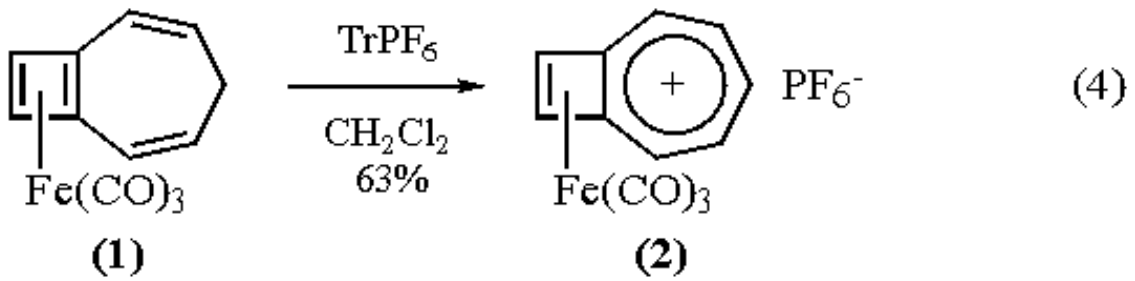

The regiochemistry of hydride abstraction by trityl hexafluorophosphate from a cycloheptadienyl iron complex can be controlled. The complex (**3**) undergoes hydride abstraction to give the iron cycloheptadienyl cation complex (**4**) (eq 5).[10,11]

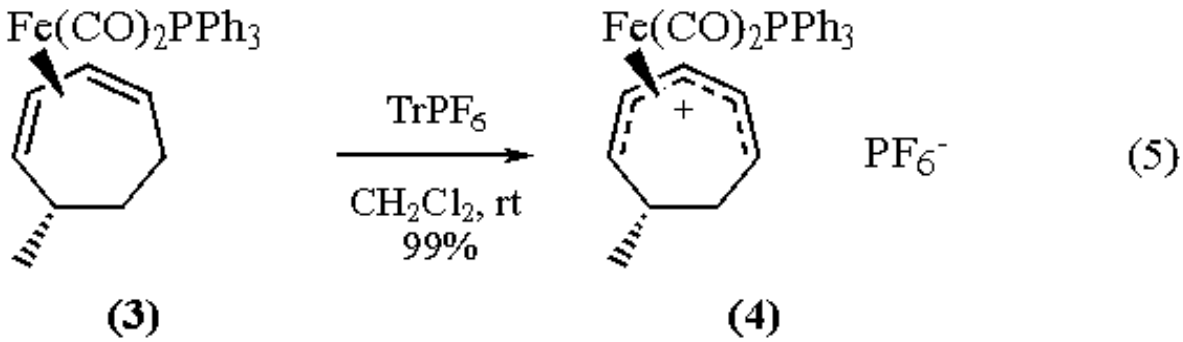

The ability of trityl hexafluorophosphate to abstract hydride from variously substituted cyclohexadiene iron complexes has been reported. The two complexes (**5**) and (**6**) undergo smooth hydride abstraction, whereas the complexes (**7**) and (**8**) are resistant to hydride abstraction with trityl hexafluorophosphate (Scheme 1).[4]

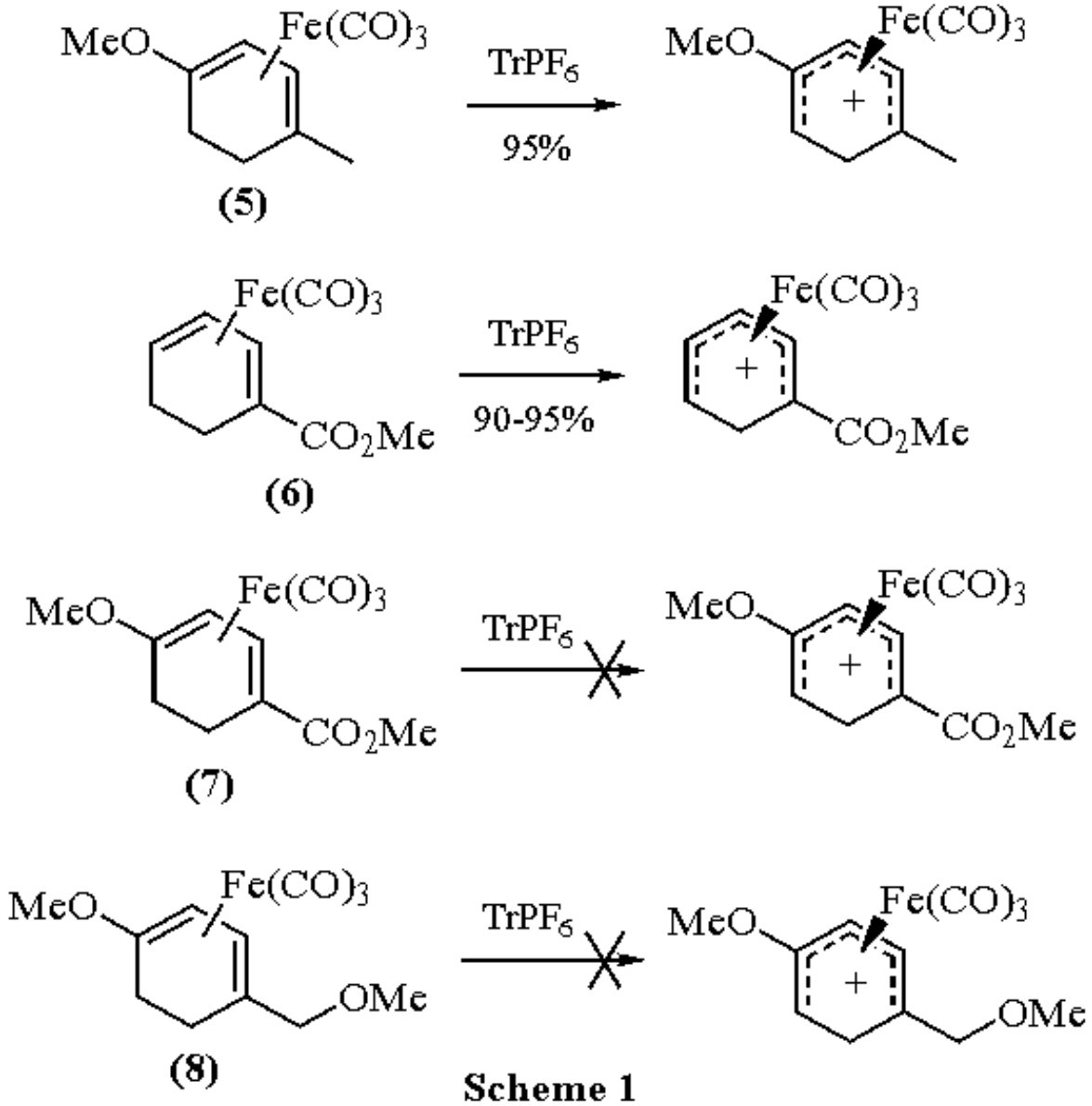

Scheme 1

Other transition metal alkene complexes are known to undergo hydride abstraction with trityl hexafluorophosphate. The π-allyl molybdenum complex (**9**) gives the cycloheptadiene complex (**10**) upon treatment with trityl hexafluorophosphate (eq 6).[12,13]

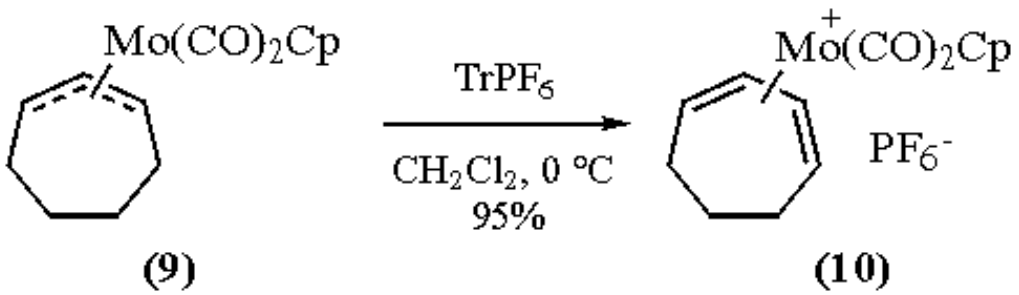

(6)

Hydride abstraction also occurs from the benzyl rhenium complex (**11**) when it is treated with trityl hexafluorophosphate; the rhenium carbene complex (**12**) results (eq 7).[14]

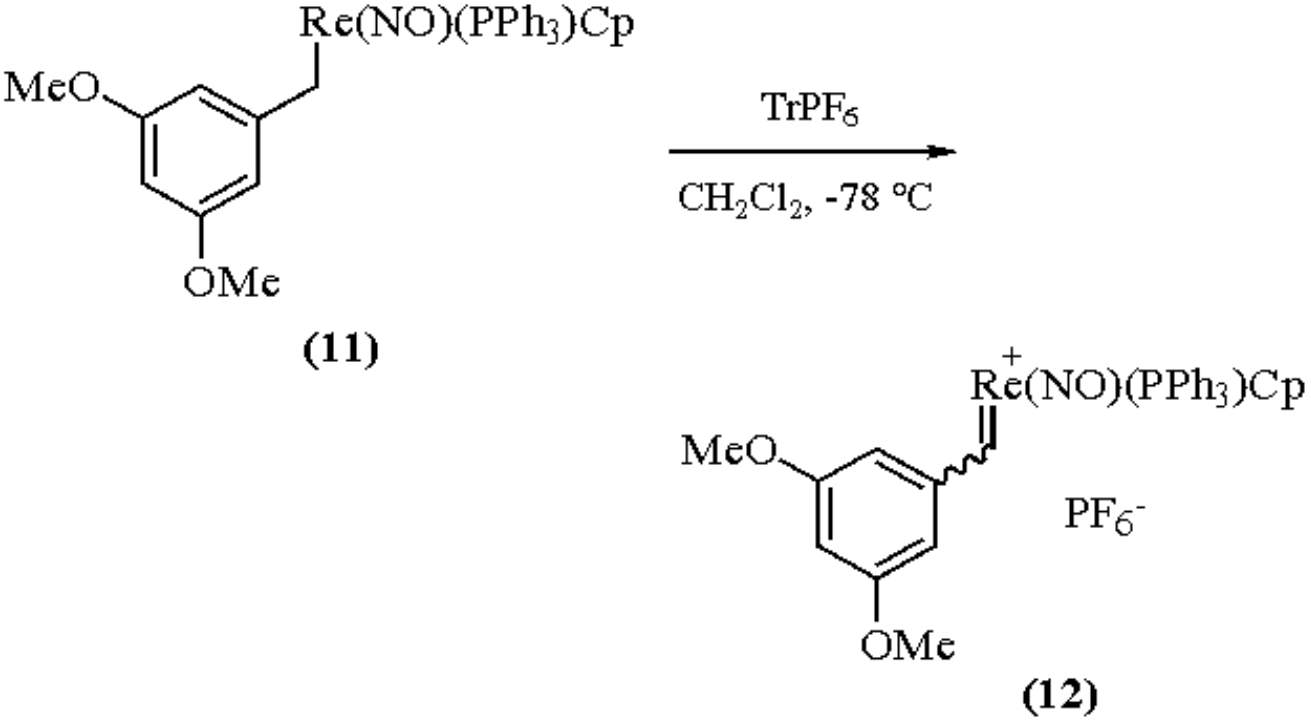

(7)

Alkoxy Abstraction.

Upon treatment with trityl hexafluorophosphate the alkoxy substituted π-allyl molybdenum complex (**13**) is ionized by ethoxy abstraction to give the complex (**14**). Fluoroboric acid failed to achieve the same ionization cleanly (eq 8).[5]

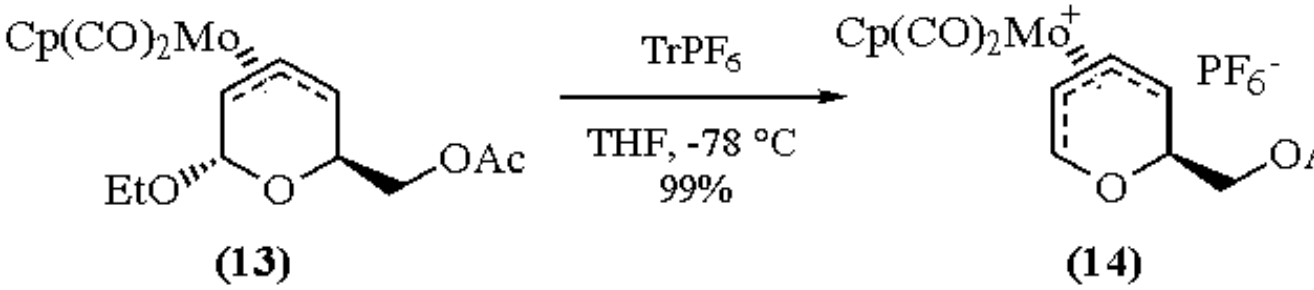

(8)

Alkoxy abstraction has also been observed with the two cyclopentadienyliron dicarbonyl complexes (**15**) and (**16**), which both give vinyl ether cyclopentadienyliron dicarbonyl complexes (**17**) and (**18**) upon treatment with trityl hexafluorophosphate (eqs 9 and 10).[15]

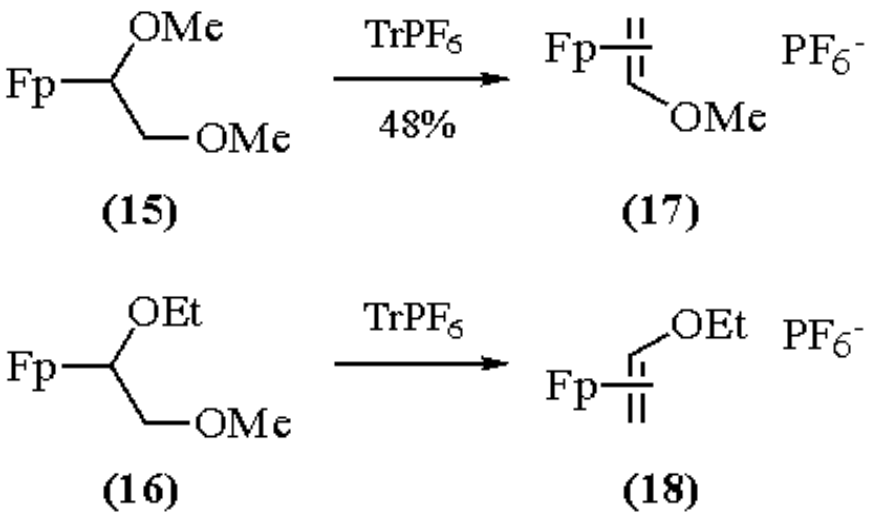

(9)

(10)

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Triphenylmethyl Hydroperoxide[1]

Ph_3COOH

[4198-93-0] · $C_{19}H_{16}O_2$ · Triphenylmethyl Hydroperoxide · (MW 276.35)

(oxidant useful for enantioselective metal-catalyzed epoxidation of allylic alcohols[2] and enantioselective oxidation of sulfides to sulfoxides[3])

Alternate Names: trityl hydroperoxide, THP.

Physical Data: mp 87.5-88.5 °C; *d* 1.27 g cm^{-3}.

Solubility: insol H_2O; sol most organic solvents.

Form Supplied in: commercially available as white, crystalline solid, 95+%.

Analysis of Reagent Purity: iodometric titration[7] (see ***t-Butyl Hydroperoxide***).

Preparative Methods: has been prepared in several ways.[4] The following method involves the acid-catalyzed reaction of triphenylmethanol with 30% ***Hydrogen Peroxide*** in acetic acid.[5] Triphenylmethanol (5.2 g, 20 mmol) is dissolved in 60 mL of glacial acetic acid, and ether (20 mL) is added to prevent solidification of the acetic acid at ice bath temperatures. Concentrated H_2SO_4 (4 drops, 0.08 mL) and 10 mL of 30% H_2O_2 are added to this solution. The solution is stirred at 0 °C for 3.5 h and then neutralized with aqueous NaOH. Care must be taken to keep the solution cold during the neutralization. The mixture is then extracted twice with ether, and the ether extracts are combined, washed sequentially with 5% $NaHCO_3$ and water, and then dried over anhydrous $MgSO_4$. The ether is removed in vacuo and the hydroperoxide is recrystallized from pentane. The yield of white solid is 5 g (91%), mp 84-86 °C. This compound consistently shows an assay purity of 99% by iodometric titration.

Purification: purified by recrystallization from ether, petroleum ether, pentane, pentane-ether, or $CHCl_3$-pentane.[6]

Handling, Storage, and Precautions: an unusually stable hydroperoxide which is relatively resistant (but still susceptible) to induced explosive decomposition. Like most alkyl hydroperoxides, it should be stored cold (ca. 0 °C) in the absence of light in a container such as a polyethylene bottle that is unlikely to shatter if there is pressure buildup. Exposing the pure hydroperoxide or concentrated solutions to heat, acid, reducing materials, or transition metal salts should be avoided. Upon completion of reactions, steps should be taken to safely destroy any remaining reagent. This can usually be done safely by exposing the reaction mixture to a mild reducing agent such as aqueous sodium sulfite, dimethyl sulfide, or triphenylphosphine. The reagent should always be handled in a fume hood.

Enantioselective Epoxidation of Allylic Alcohols.

THP can be used in place of *t*-butyl hydroperoxide (TBHP) as the oxidant in the Sharpless asymmetric epoxidation of allylic alcohols to give scalemic epoxy alcohols.[2] Usually, THP has been used for mechanistic studies and not for synthetic advantage. In one case, however, use of THP with a nontartrate ligand resulted in a reversal of enantioselectivity (eq 1).[8] With tartrate ligands, enantioselectivity is not reversed going from TBHP to THP.

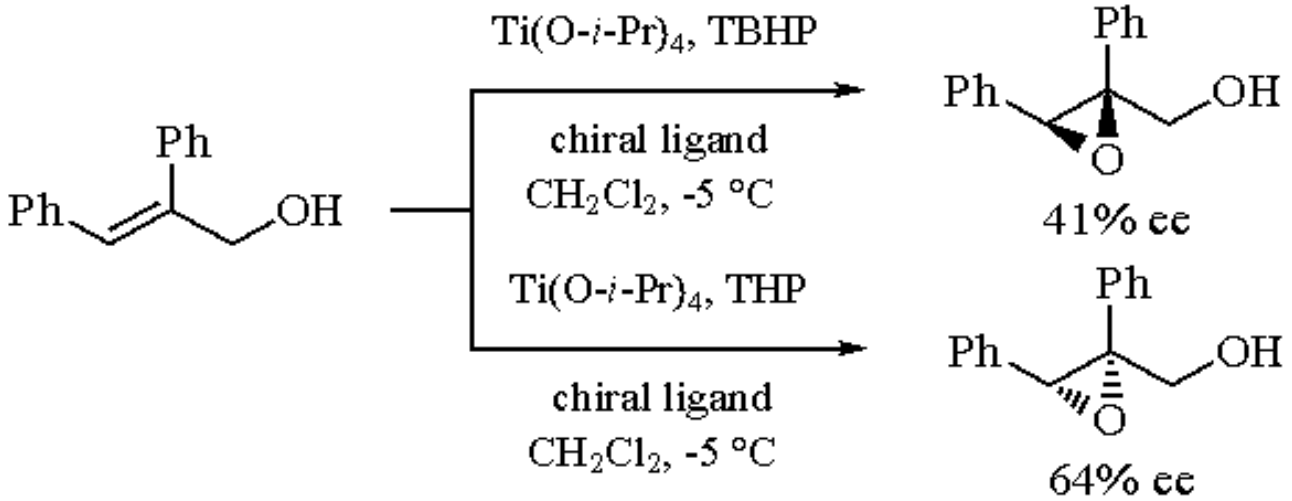

(1)

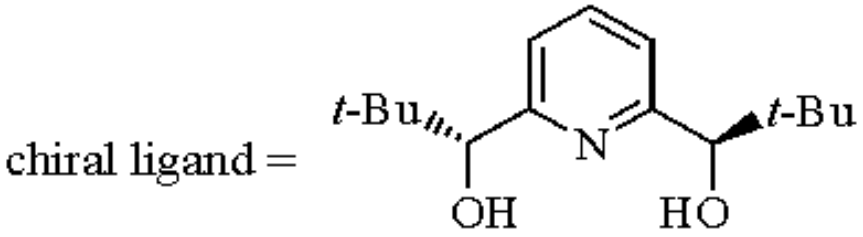

Enantioselective Oxidation of Sulfides to Sulfoxides.

THP has also been used in the titanium-tartrate catalyzed asymmetric oxidation of prostereogenic sulfides to give scalemic sulfoxides.[3] Unlike ***Cumyl Hydroperoxide*** (which gives improved results over TBHP), THP gives poor asymmetric induction (eq 2).[9]

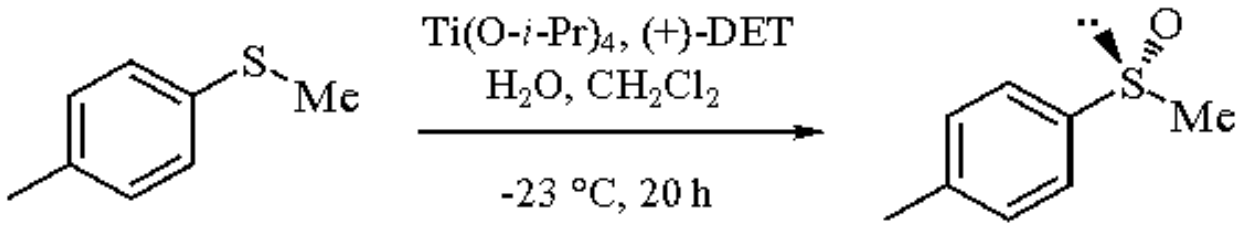

(2)

Hydroperoxide	Yield (%)	ee (%)
TBHP	90	89
CHP	93	96
THP	90	16

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Triphenylmethyl Isocyanide[1]

Ph_3C-NC

[1600-49-3] · $C_{20}H_{15}N$ · Triphenylmethyl Isocyanide · (MW 269.36)

(cyanide transfer via metal-isonitrile exchange reaction[2])

Alternate Names: trityl isocyanide; isocyanotriphenylmethane.

Physical Data: mp 130-133 °C (benzene).[3]

Solubility: insol water, cold methanol, hexane; sol common organic solvents.

Form Supplied in: white solid.

Analysis of Reagent Purity: IR ν = 2130 cm^{-1}; NMR.

Preparative Method: easily prepared in 94% yield from *N*-triphenylmethylformamide by dehydration with ***Dimethylchloromethyleneammonium Chloride*** (Vilsmeier reagent).[4]

Purification: recrystallization from benzene.

Handling, Storage, and Precautions: can be stored indefinitely at room temperature; quickly adds water in the presence of acids; easily undergoes isocyanide-nitrile rearrangement (60-80 °C in acetonitrile).[5] Since some isocyanides are known to be toxic, appropriate precautions are recommended.[6]

Reactions with Organometallic Reagents.

Addition of organolithium reagents to triphenylmethyl isocyanide leads to the formation of unstable α-metalloaldimines which readily undergo elimination reaction to give nitriles and triphenylmethyllithium (eq 1).[7] However, only when ***t-Butyllithium*** is used can the nitrile (tertiary) be isolated in high yield (88%). In all other cases, subsequent reaction of the nitrile with the organolithium reagent (used therefore in excess) gives rise to symmetrical ketones upon acid hydrolysis (eq 2). Sequential addition of *t*-BuLi and another organolithium reagent produces unsymmetrical (*t*-alkyl-alkyl) ketones in good yields (eq 3). The intermediate ketimine can also be isolated when 2 equiv of *t*-BuLi are used and the reaction mixture is hydrolyzed with water (eq 4).

$$Ph_3C\text{-}NC + t\text{-}BuLi \xrightarrow[88\%]{\text{THF, -78 °C}} t\text{-}Bu\text{-}NC + Ph_3CLi \qquad (1)$$

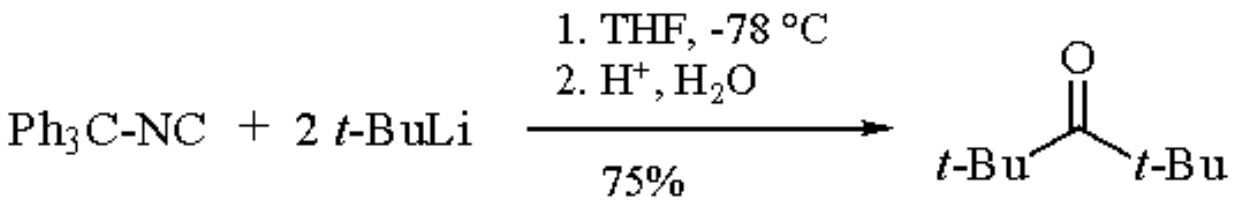

(2)

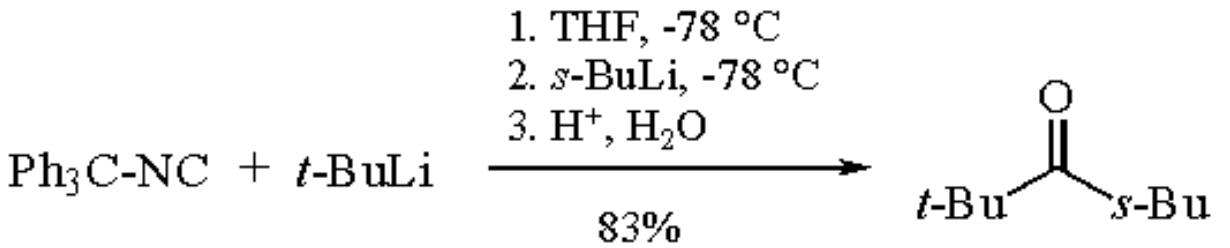

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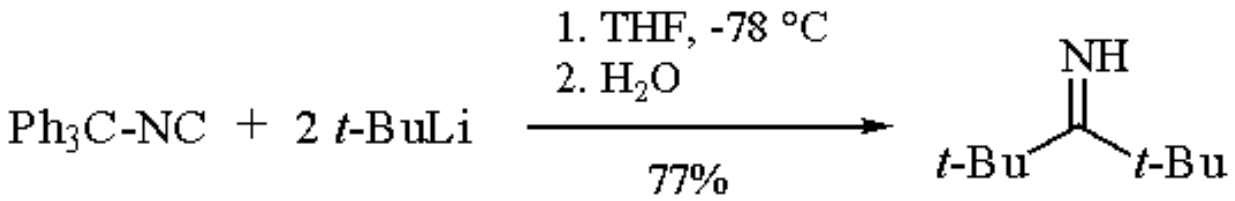

(4)

Secondary Grignard reagents react readily with triphenylmethyl isocyanide to give secondary nitriles in 70-95% yield. Tertiary and aromatic organomagnesium compounds fail to give synthetically useful reactions. Reaction of primary Grignard reagents gives neither nitriles nor ketones as main products. When *n*-butylmagnesium bromide is treated with triphenylmethyl isocyanide, 5-amino-4-cyano-4-nonene is isolated in 50-60% yield (eq 5). Reaction of triphenylmethyl isocyanide with organometallic reagents can be stopped at the nitrile stage when organocopper (dialkylcuprate) reagents are used, but low yields mitigate its use as a synthetic tool.[7]

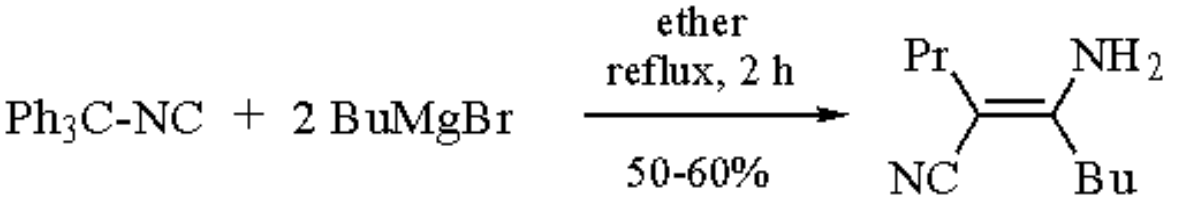

(5)

Synthesis of Masked Acyl Cyanides.

Triphenylmethyl isocyanide reacts readily with ***2-Lithio-1,3-dithiane*** to give the expected nitrile in 83% yield (eq 6).[8] The product can subsequently be alkylated with a variety of alkylating reagents in high yields.

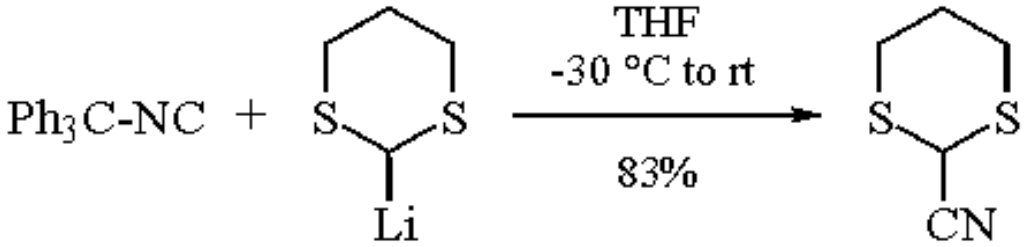

(6)

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Triphenylmethyllithium

Ph_3CLi

[733-90-4] · $C_{19}H_{15}Li$ · Triphenylmethyllithium · (MW 250.28)

(sterically hindered strong base; can function as a nucleophile)

Form Supplied in: red solution in THF, DME, and toluene; diethyl ether solution is colorless.

Analysis of Reagent Purity: the concentration of colored solutions can be determined by titration with a standard solution of 2-butanol to a colorless endpoint.[2]

Preparative Methods: solutions in ether solvents (containing some hexane) are most conveniently prepared by adding commercial solutions of ***n-Butyllithium*** in hexane to a solution of triphenylmethane in the ether, usually with ice-water cooling.[1] Crystals of the diethyl ether complex may be obtained as red needles by removal of the solvent.[3] Preparative methods up to 1959 have been reviewed.[4]

Handling, Storage, and Precautions: the red color of the reagent is rapidly discharged on exposure to air or water. Solutions in THF and diethyl ether are stable indefinitely,[3] but solutions in DME slowly lose titer at room temperature and form Ph_3CH, LiOMe, and CH_2=CHOMe.[2]

Reaction as a Base.

Triphenylmethyllithium is a strong base (the pK_a of Ph_3CH is 31.5) and rapidly converts a number of carbonyl compounds into the corresponding lithium enolates. The reagent played an important role in pioneering studies of enolate chemistry, but the more recently developed lithium dialkylamides possess significant advantages including greater base strength and faster rates of proton removal. A considerable advantage is the easier separation of dialkylamine, compared to Ph_3CH, from reaction mixtures. It has been observed that triphenylmethyllithium is now rarely used, in favor of the amide bases.[5] Nevertheless, triphenylmethyllithium has several unique characteristics which may make it the base of choice for some applications. The bright red color of triphenylmethyllithium together with the colorless nature of Ph_3CH allows a simple check for the completion of proton transfer as well as a rough estimation of the rate. For some applications, this advantage can be gained for other bases by addition of small quantities of Ph_3CH as an indicator.[6] Triphenylmethane is a relatively inert material compared to secondary amines and this fact may be advantageous for transformations subsequent to proton transfer. Quenching lithium amide-generated enolate solutions with D_2O often results in less than quantitative incorporation of deuterium because of the readily exchangeable protons of secondary amines. Of eight bases examined, triphenylmethyllithium gave the highest incorporation of deuterium in compound (**1**), an intermediate in the synthesis of the antibiotic Fludalanine (eq 1).[7]

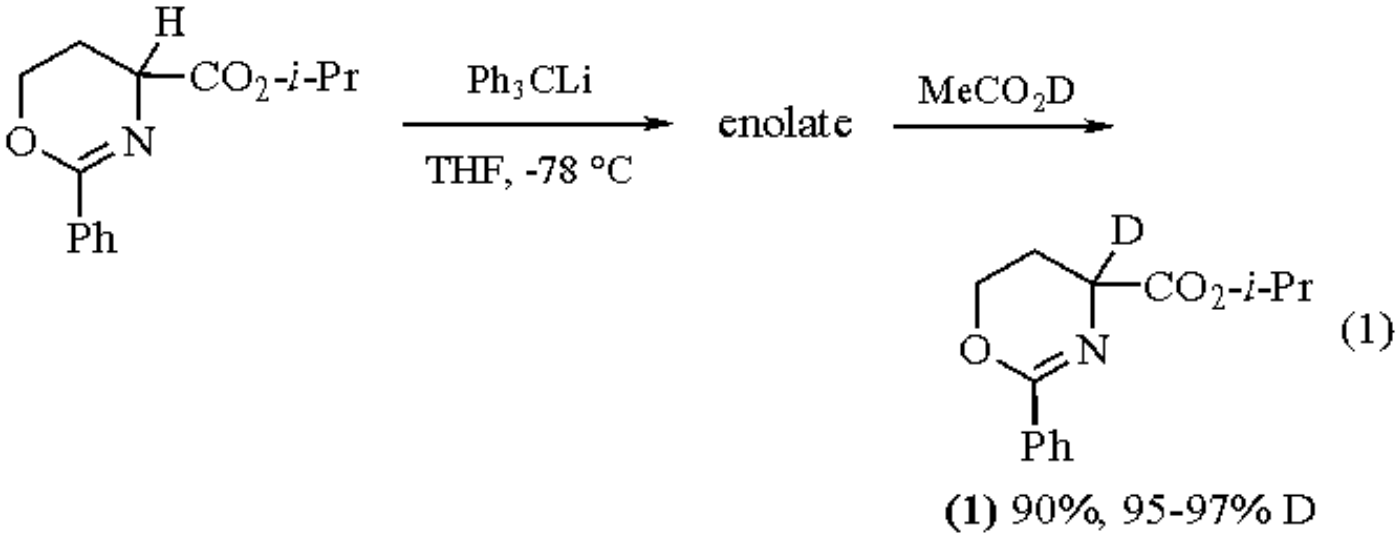

Triphenylmethyllithium can react with conjugated enones by single electron transfer,[2] and this can provide an alternate mechanism for the formation of conjugated enolates (eq 2).[8] This may account for the occasional reports of superior yields,[9] or different regiochemistry,[10] obtained for proton removal with triphenylmethyllithium in such systems.

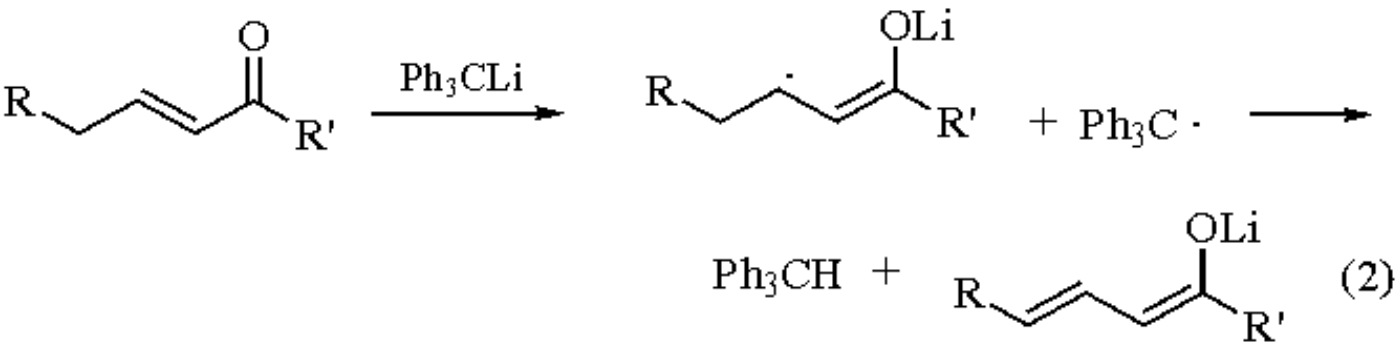

Reaction as a Nucleophile.

Triphenylmethyllithium can function as a surprisingly efficient nucleophile, especially in cases where proton transfer is not possible. Addition reactions with nonenolizable aldehydes and ketones,[4] and conjugate addition with enones, have been reported.[2,8] The reaction with organic halides and tosylates, in some cases at least, proceeds with inversion.[11,12]

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Triphenylmethyl Perchlorate

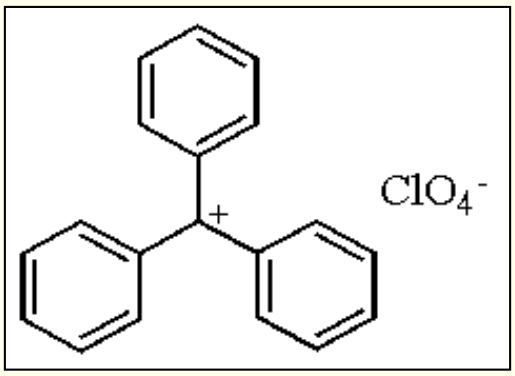

[3058-33-1] · $C_{19}H_{15}ClO_4$ · Triphenylmethyl Perchlorate · (MW 342.79)

(catalyst for Michael additions,[1] aldol reactions,[2] and glycosidation[3])

Alternate Names: trityl perchlorate; triphenylcarbenium perchlorate.

Physical Data: mp 143 °C.[4]

Preparative Methods: perchloric acid is added to triphenylmethanol in acetic anhydride. The trityl perchlorate is separated, washed with ether, and dried.[5]

Purification: recrystallize from dry acetonitrile as yellow prisms.[4]

Handling, Storage, and Precautions: trityl perchlorate should be stored in the dark as exposure to light darkens the compound.[4] It is rapidly hydrolyzed by exposure to moist air.[4] All perchlorates present a potential explosion hazard.

Michael Reactions.

Silyl enol ethers react with α,β-unsaturated ketones in the presence of catalytic amounts of trityl perchlorate (2-3 mol %[1]) to give 1,5-dicarbonyl compounds.[6] No 1,2 addition products were obtained. It is possible to isolate the intermediate silyl enol ethers, which is not the case if ***Titanium(IV) Chloride*** is used as catalyst (eq 1).[6] *Anti* Michael adducts are obtained preferentially with selectivities of up to >95:5 (eq 2).[1] Silyl enol ethers of thioesters also react to give 5-keto thiol esters.[7] Allylsilanes have been reacted with α,β-unsaturated ketones to give δ,ε-unsaturated ketones (eq 3).[8] 1,4-Benzoquinones react with silyl enol ethers to give benzofurans.[9] Trityl perchlorate was found to be a more effective catalyst for Michael addition reactions than other trityl salts.[6]

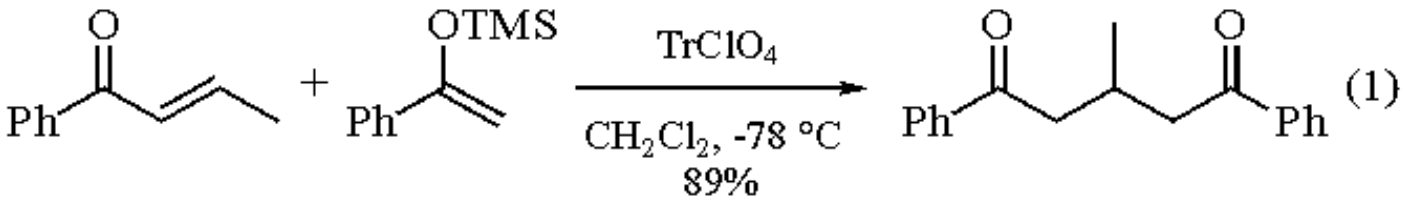

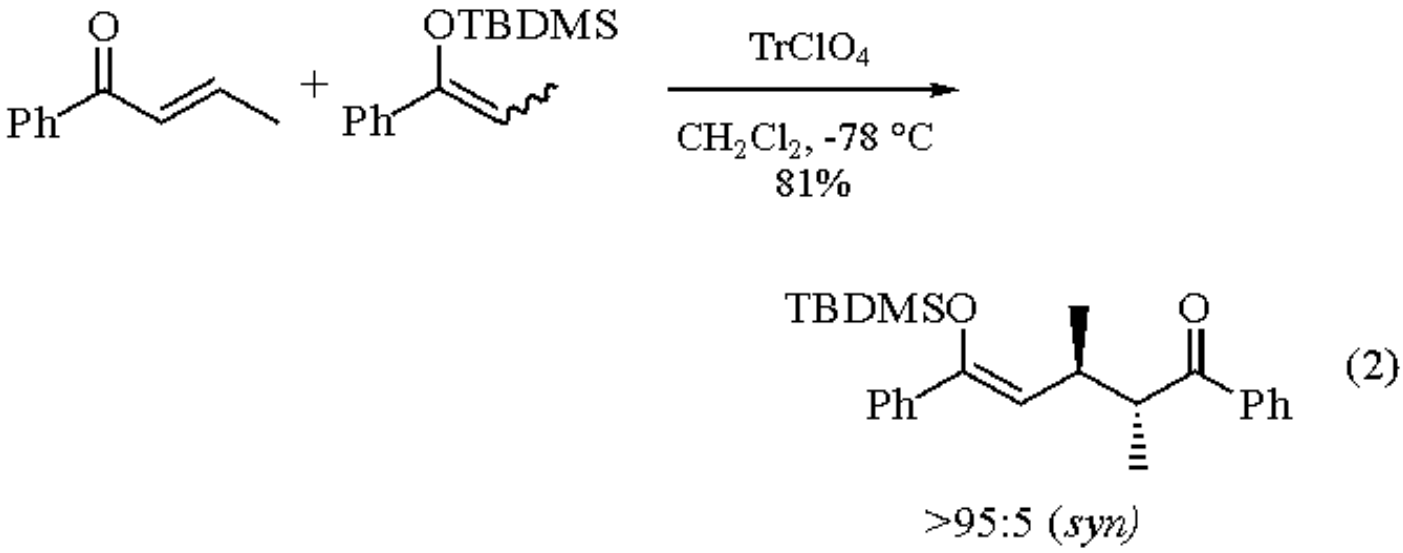

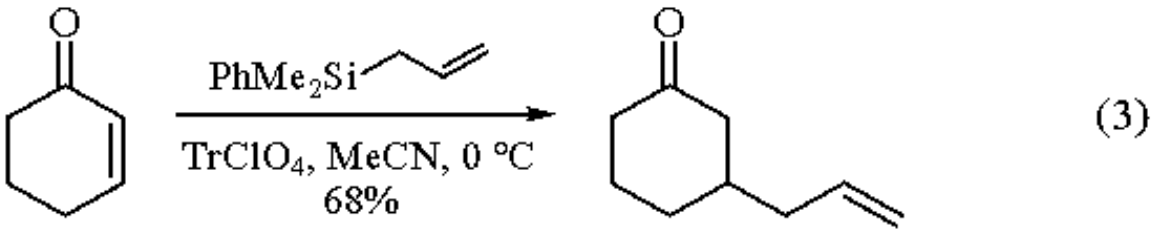

Aldol Reactions.

In the presence of a catalytic amount of trityl perchlorate (1-5 mol %), silyl enol ethers react with acetals to give β-alkoxy ketones (eq 4).[10] Orthoformates react in a similar way.[10] Aldehydes react with silyl enol ethers to give β-silyloxy ketones (eq 5).[2] The reaction can be made *threo* selective, with selectivities of up to 82:18 reported.[11] Alkyl enol ethers and acetals react in the presence of trityl perchlorate to give β-alkoxy ketones.[12] A tandem Michael-aldol reaction has been reported which gives γ-acyl-δ-hydroxy ketones (eq 6).[13]

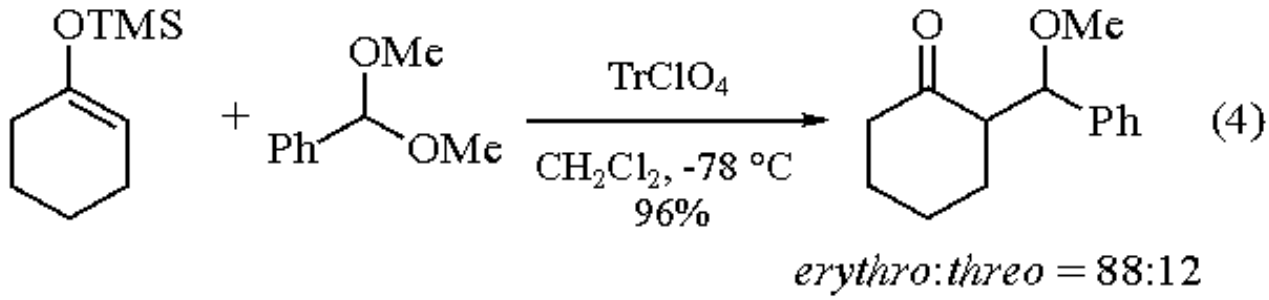

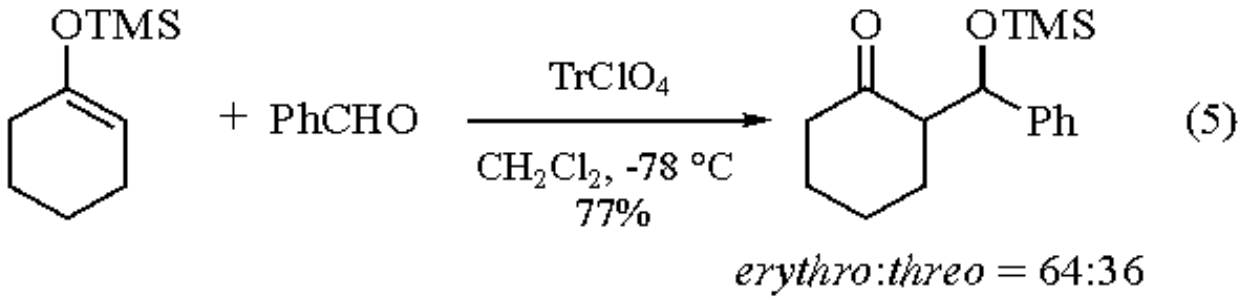

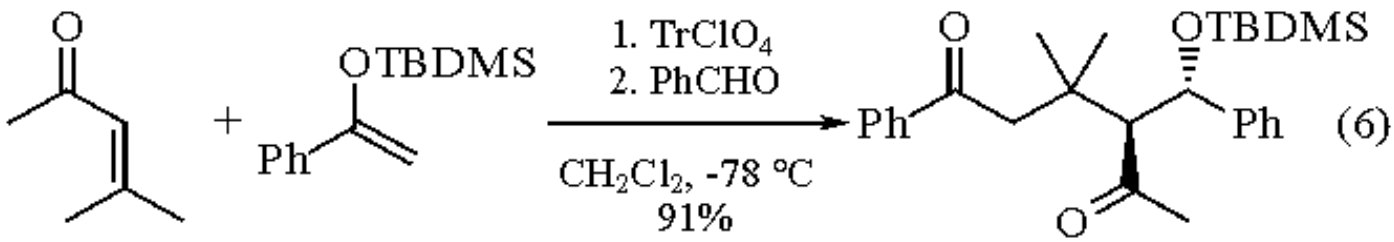

Glycosidation.

Perbenzylated 1-*O*-bromoacetyl-β-D-glucose reacts with alcohols in the presence of trityl perchlorate to give α-glucosides.[14] α-Ribosides can be prepared in a similar manner.[14] Other nucleophiles (silyl enol ethers, allylsilanes, and ***Cyanotrimethylsilane***) react with benzylated 1-*O*-acetyl ribose to give α-*C*-ribofuranosides (eq 7).[3]

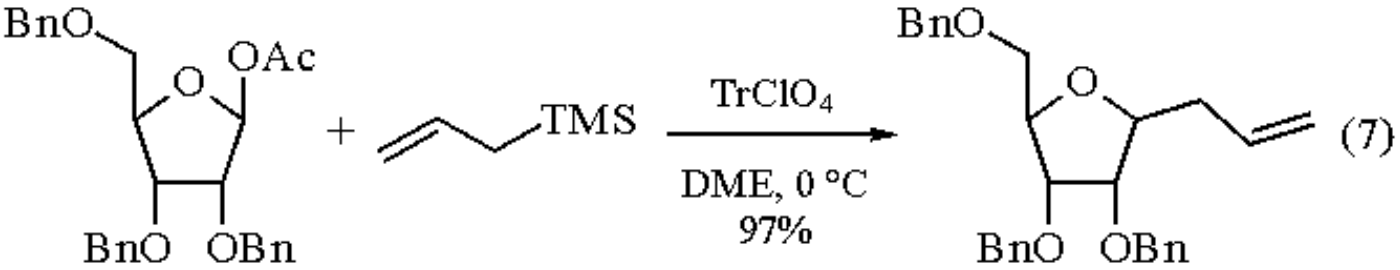

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Triphenylphosphine

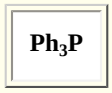

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine · (MW 262.30)

(deoxygenation of ozonides, peroxides, epoxides, and *N*-oxides; reduction of azides; reduction of organosulfur compounds; dehalogenations)

Physical Data: mp 79-81 °C; bp 377 °C; *d* (solid) 1.18 g cm^{-3}; *n*20D 1.59.

Solubility: insol H_2O; sol alcohol, benzene, chloroform; v sol ether.

Form Supplied in: white crystalline solid, widely available; polymer supported, ca. 3 mmol P per gram of resin is also available.

Purification: crystallize from hexane, methanol, or 95% ethanol; dry at 65 °C/<1 mmHg over $CaSO_4$ or P_2O_5.[1]

Handling, Storage, and Precautions: classified as an irritant upon acute exposure and a neurological hazard upon chronic exposure.[2] It is incompatible with strong oxidizing agents. Arylphosphines are less reactive toward molecular oxygen than benzyl- or alkylphosphines, but air oxidation of triphenylphosphine nonetheless occurs to an appreciable extent, particularly in solution, to give triphenylphosphine oxide.[3] Triphenylphosphine has low fire and explosion hazards, but, when heated to decomposition, it emits highly toxic fumes of phosphine and PO_x.[4] Use in a fume hood.

Introduction.

Triphenylphosphine is a fairly general reducing agent as the following examples indicate. The chemistry in which triphenylphosphine participates is, in most cases, driven by the formation of triphenylphosphine oxide, a thermodynamically favored reaction. The enthalpies of formation of triphenylphosphine and triphenylphosphine oxide are $\Delta_f H°_m$ = (207.02 ± 3.52) kJ mol^{-1} and $\Delta_f H°_m$ = -(116.41 ± 3.42) kJ mol^{-1}, respectively.[5] Triphenylphosphine oxide, however, is a highly crystalline nonvolatile material which often requires chromatography to effect its removal from desired reaction products. While less relevant to its chemistry, it is noteworthy that triphenylphosphine is a considerably weaker base than trialkylphosphines; its pK_a is 2.73 compared to, for instance, tributylphosphine with a pK_a of 8.43.[6]

Deoxygenations.

Triphenylphosphine has found widespread use in the reduction of compounds containing the hydroperoxide or endoperoxide functionality to form, depending upon the substrate, alcohols, carbonyl compounds, or epoxides. The primary driving force behind this class of reactions is the formation of the strong P=O bond at the expense of the relatively weak (45-50 kcal mol^{-1}) O-O bond.[7] For example, triphenylphosphine constitutes a mild, selective method for the reductive decomposition of ozonides to ketones and aldehydes. Compared to triphenylphosphine, ***Dimethyl Sulfide*** has enjoyed more popularity for this purpose,[8] probably because of its comparable mildness and the relative ease in removing the byproduct dimethyl sulfoxide compared to triphenylphosphine oxide. Nevertheless, the convenience of handling of triphenylphosphine and its lack of unpleasant odor render it an attractive alternative, as its use in the following examples illustrates (eqs 1 and 2).[9,10]

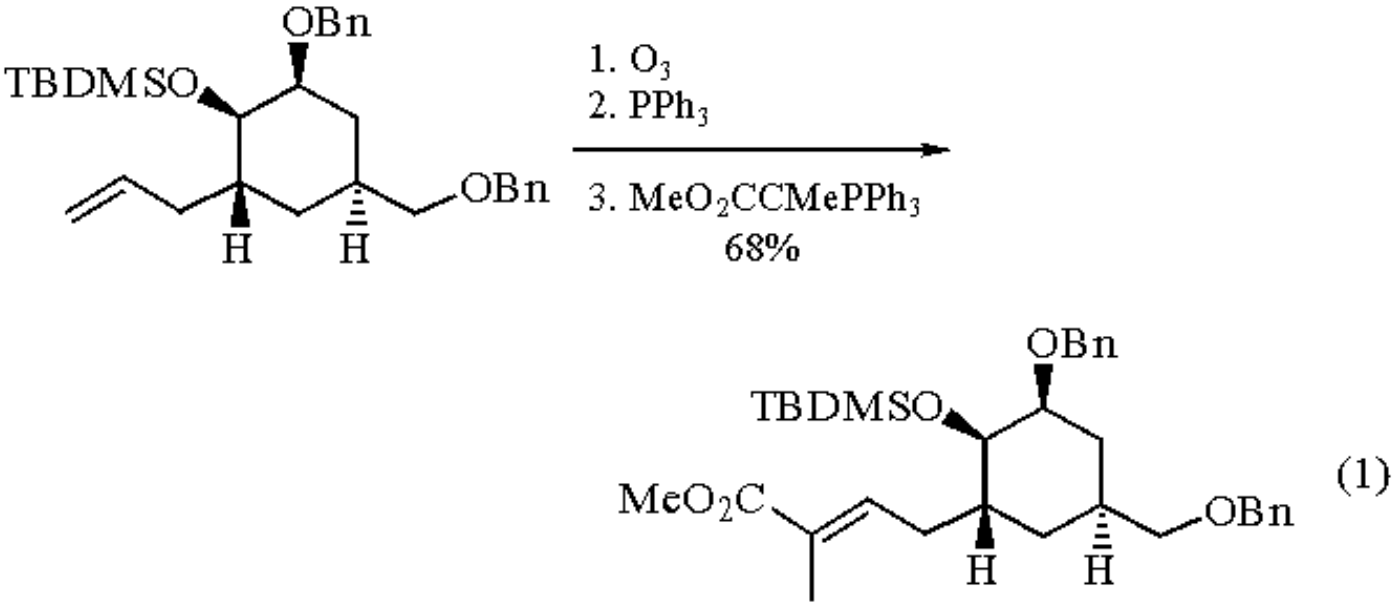

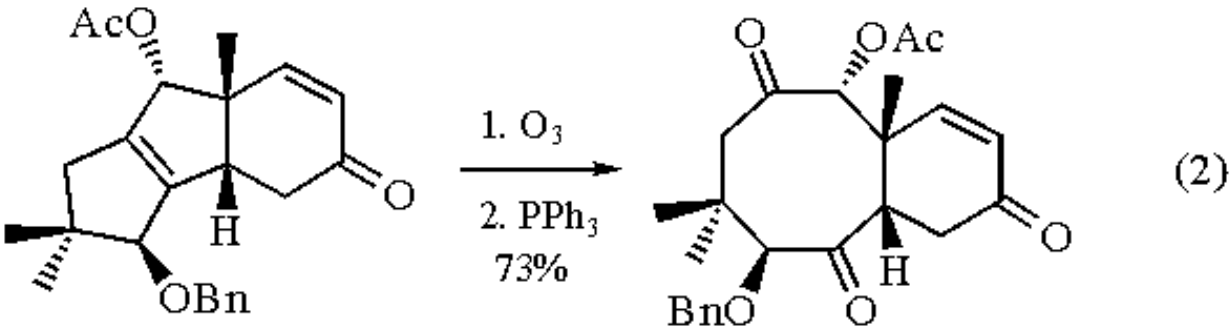

Treatment of hydroperoxides with triphenylphosphine affords the corresponding alcohols in high yields under mild conditions and with retention of configuration at the carbon bearing the peroxide (eqs 3 and 4).[11,12] The reaction of endoperoxides, on the other hand, affords epoxides with inversion of configuration at one of the two carbon atoms (eq 5).[13] Vinylogous endoperoxides react with triphenylphosphine to afford the allylic epoxides (eq 6).[14] These examples should not imply that reaction of endoperoxides with triphenylphosphine is necessarily facile, since certain endoperoxides have been shown to be inert to PPh_3.[15] Nevertheless, the transformation of the α-methylene-β-peroxy lactone to afford the β-lactone (eq 7)[16] illustrates the wide scope of the peroxide deoxygenation capability of triphenylphosphine.

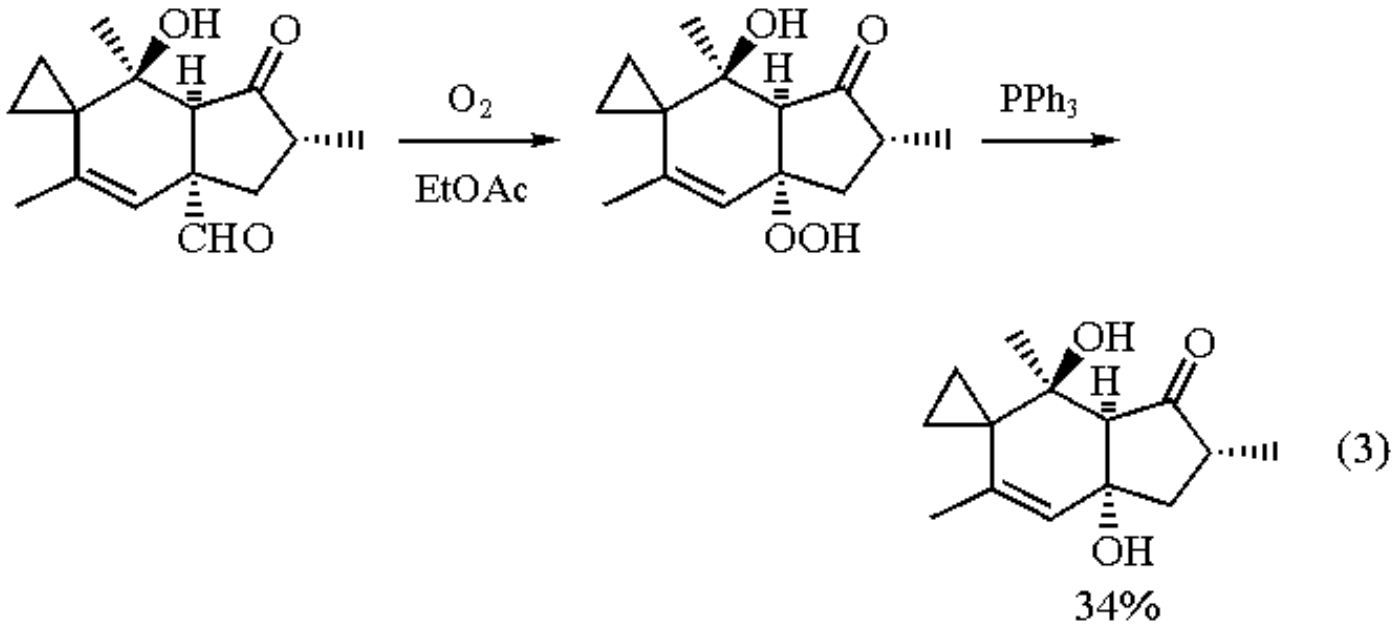

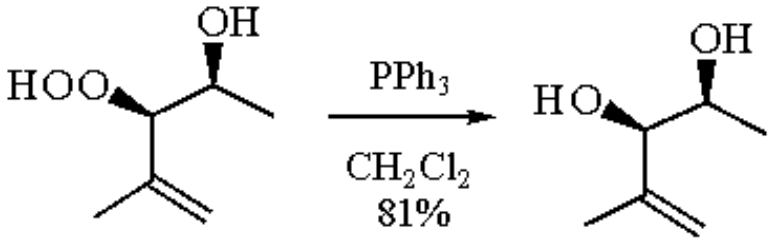

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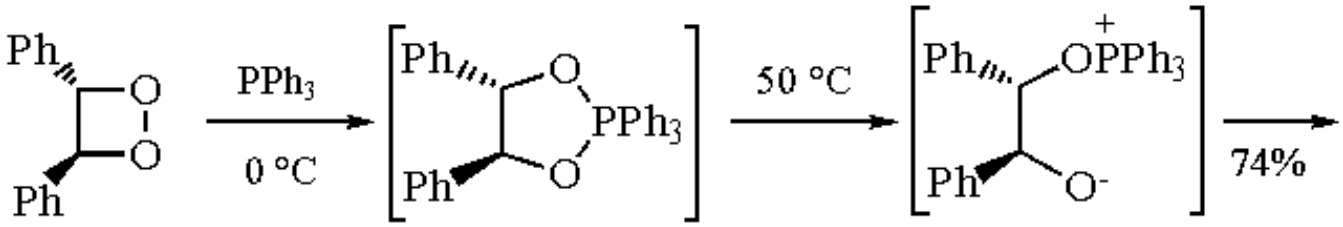

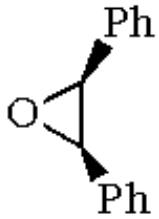

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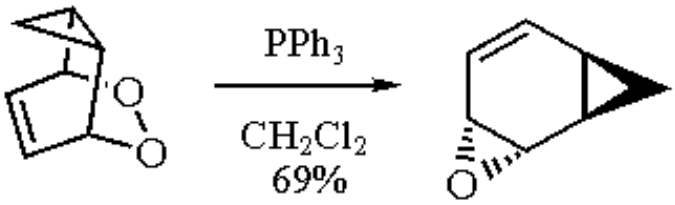

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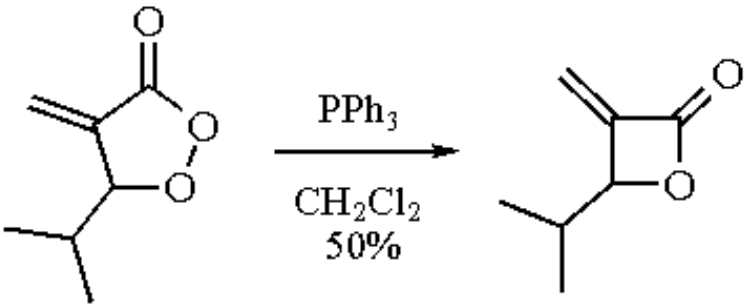

(7)

The deoxygenation of epoxides affords the corresponding alkenes and results in an inversion in the stereochemistry of substitutents attached to the double bond.[17] While the reaction has been known since the mid 1950s,[18] it has not found widespread use. Triphenylphosphine has found utility as a reducing agent of *N*-oxides. While several alternative reagents and conditions are available, these often require fairly strong reducing conditions which are incompatible with a wide range of functionality.[19] In fact, triphenylphosphine-mediated reductions of *N*-oxides require much more vigorous conditions than do the corresponding reductions of peroxides. For example, reduction of trimethylamine oxide with trialkylphosphines requires refluxing in glacial acetic acid,[20] and the reduction of pyridine *N*-oxide derivatives is best carried out at temperatures above 200 °C in the absence of solvent.[21] However, it has been found that aromatic amine oxides are reduced in high yield with triphenylphosphine at room temperature with irradiation (eq 8).[22] While not general, under special conditions triphenylphosphine is also capable of reducing aromatic nitroso[23] and nitro groups (eq 9).[24]

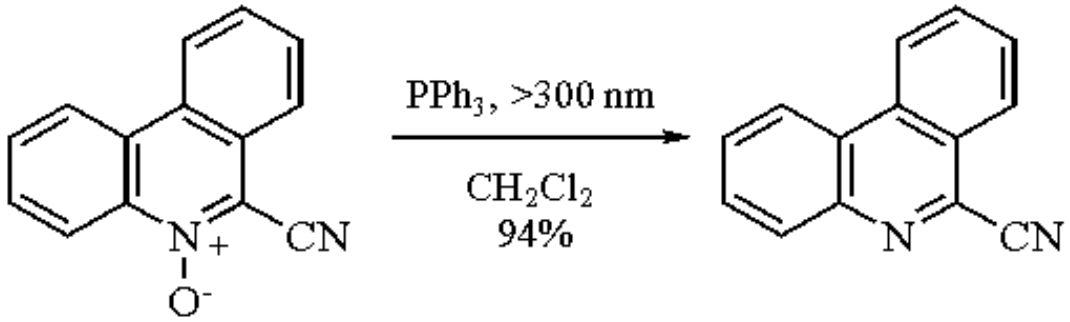

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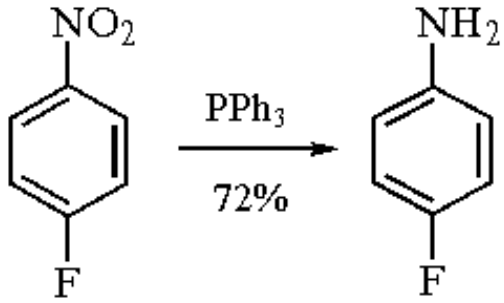

(9)

Reduction of Azides (Staudinger Reaction).

In 1919, Staudinger and Meyer[25] reported that the addition of triphenylphosphine to organic azides produced iminophosphoranes. This reaction proceeds by attack on nitrogen by phosphorus to produce an unstable phosphazide which extrudes dinitrogen to give the iminophosphorane (eq 10). This is known as the Staudinger reaction.[26]

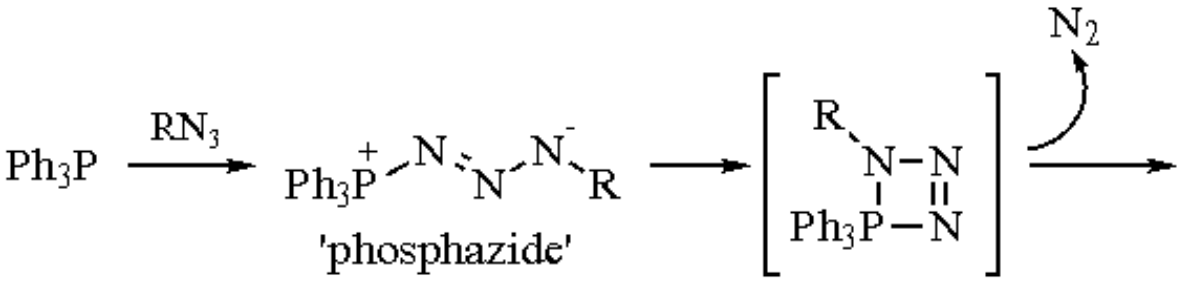

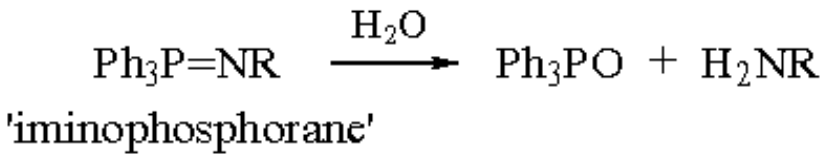

(10)

The iminophosphorane is a useful functional group for synthesis and can be isolated, although it is usually generated and used in situ. Iminophosphoranes can be hydrolyzed to amines. This forms the basis for the conversion of azides to amines using triphenylphosphine in the presence of water (eqs 11-13).[27] This mild and chemoselective reduction is an attractive alternative to other known methods (***Lithium Aluminum Hydride***, ***Diborane***, catalytic hydrogenation) that effect this transformation.[28] The reduction shown in eq 14 attests to the chemoselectivity of triphenylphosphine for this transformation. This reaction is sensitive to steric effects, but even tertiary azides can be reduced. Reduction of azides at a chiral center produce amines with the same configuration.

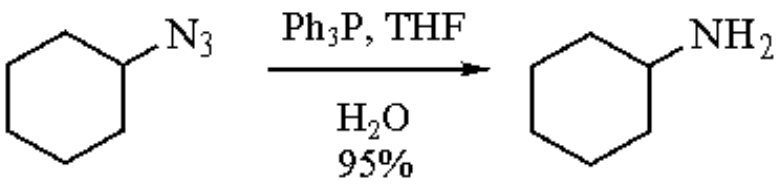

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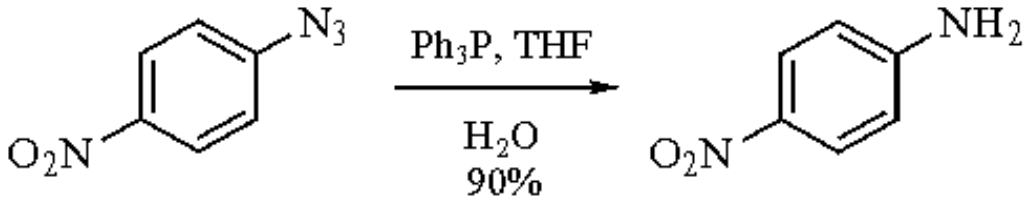

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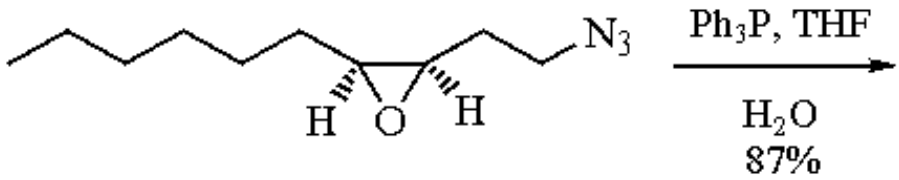

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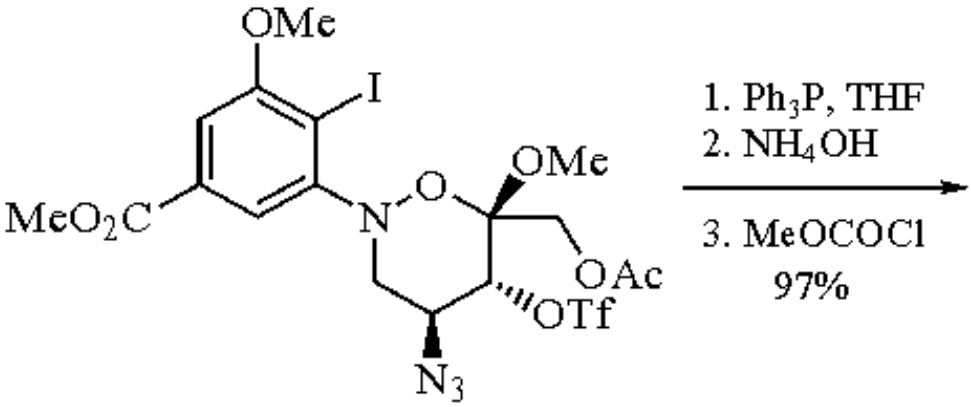

(14)

Reactions of Iminophosphoranes.

Iminophosphoranes are reactive nucleophilic ylides; electrophiles react with the nitrogen.[29] Aldehydes and ketones are particularly favored reaction partners with iminophosphoranes, producing imines and triphenylphosphine oxide.[30,31] This reaction is analogous to the Wittig reaction and is known as the aza-Wittig reaction. Again, the driving force for this reaction is the formation of triphenylphosphine oxide (eq 15). Two intramolecular examples are shown in eqs 16 and 17.[32,33]

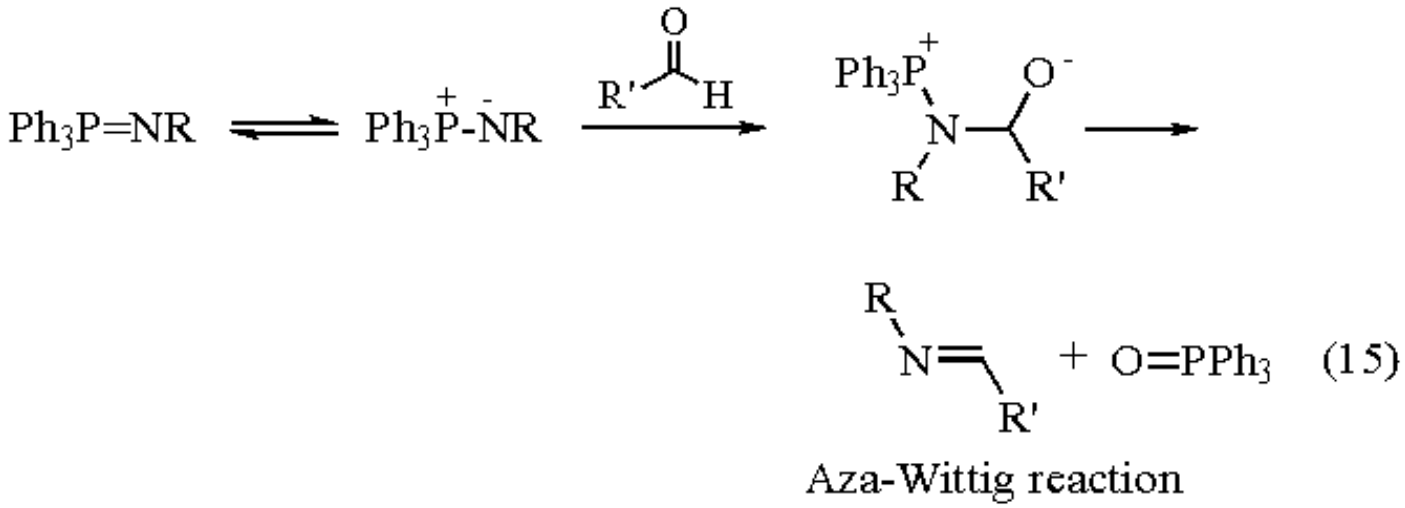

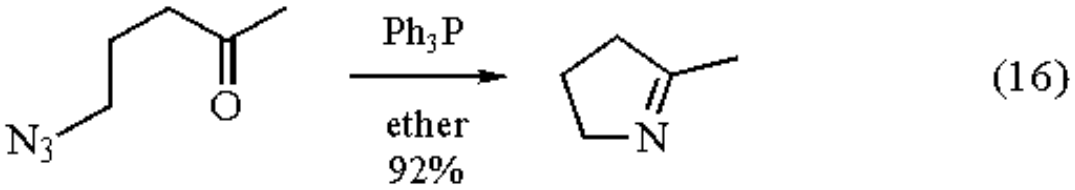

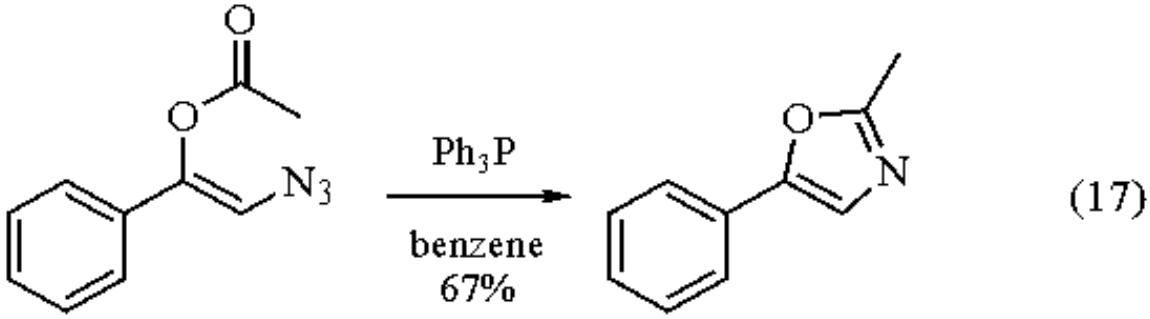

Two other examples of reactions proceeding through the intermediacy of an iminophosphorane are shown in eqs 18 and 19.[34,35] Both reactions result in aziridine formation, and the driving force is the production of triphenylphosphine oxide.

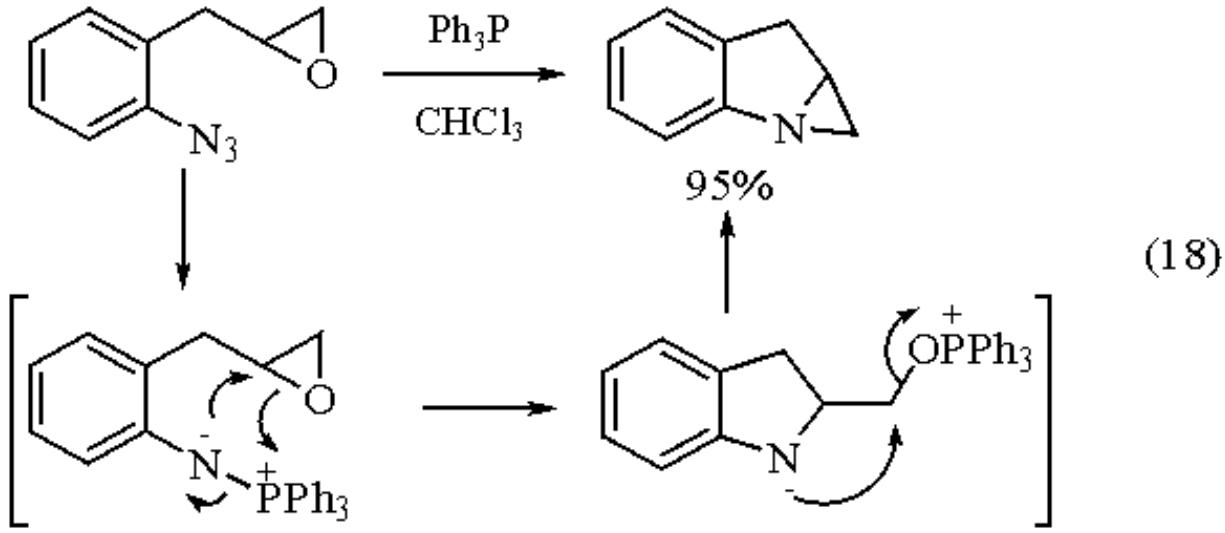

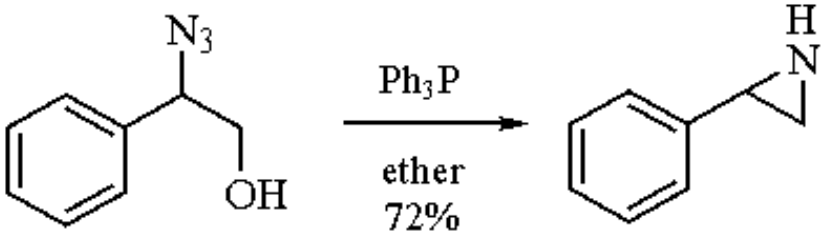

(19)

Reduction of an azide with triphenylphosphine in the presence of phthalic anhydride results in the formation of a phthalimide, a common protecting group for an amine (eq 20).[36] This reaction is facilitated by the addition of 0.1 equiv of tetrabutylammonium cyanide. If the reduction is performed in the presence of a carboxylic acid, an amide is formed (eq 21).[37] This reaction works with either aromatic or aliphatic (primary, secondary) azides and either aromatic or aliphatic carboxylic acids.

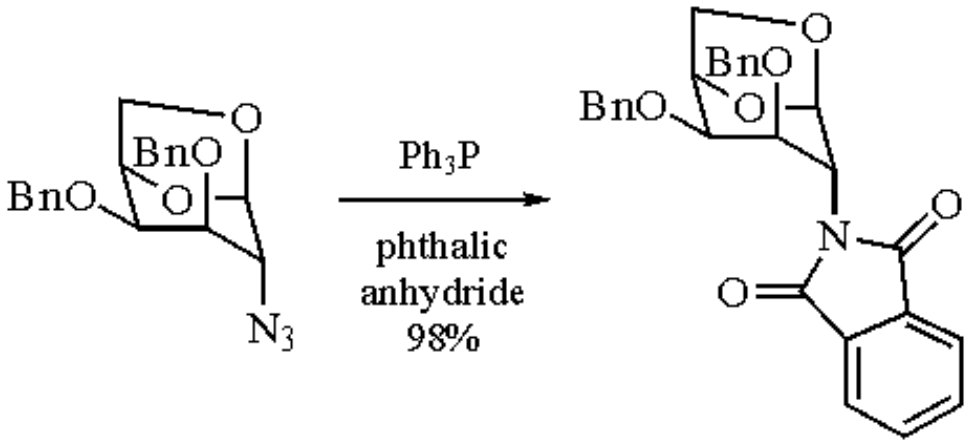

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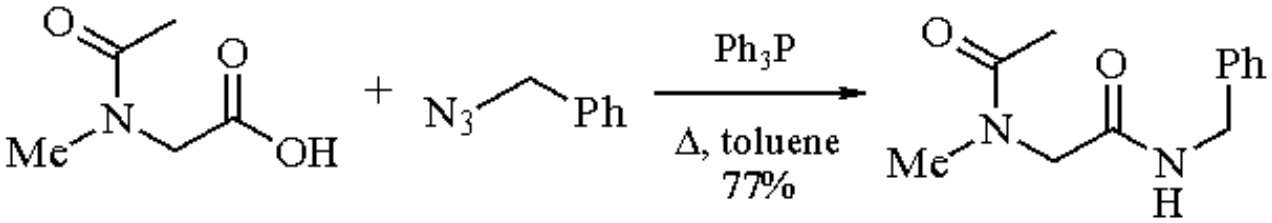

(21)

Reduction of Organosulfur Compounds.

Triphenylphosphine converts episulfides to alkenes[38] smoothly at room temperature (eq 22). In contrast to the reaction of triphenylphosphine with epoxides, the reduction is stereospecifically *syn*.[39] This *syn* elimination can also be promoted with alkyllithiums,[40] lithium aluminum hydride,[41] and excess ***Iodomethane***,[40] and by exposure to carbenes.[42] This sulfur extrusion reaction plays a crucial role in Barton's method of alkene formation from carbonyl compounds.[43] This process (eq 23) is particularly effective for the formation of tetrasubstituted and highly hindered alkenes, where a paucity of methods exist for effective formation of these compounds. For example, cyclohexanone is easily converted to the azosulfide (**1**) in two steps, which, upon heating to 100 °C in the presence of triphenylphosphine, gives bicyclohexylidene via the episulfide (**2**) in good overall yield.

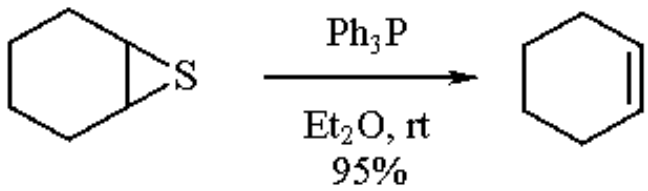

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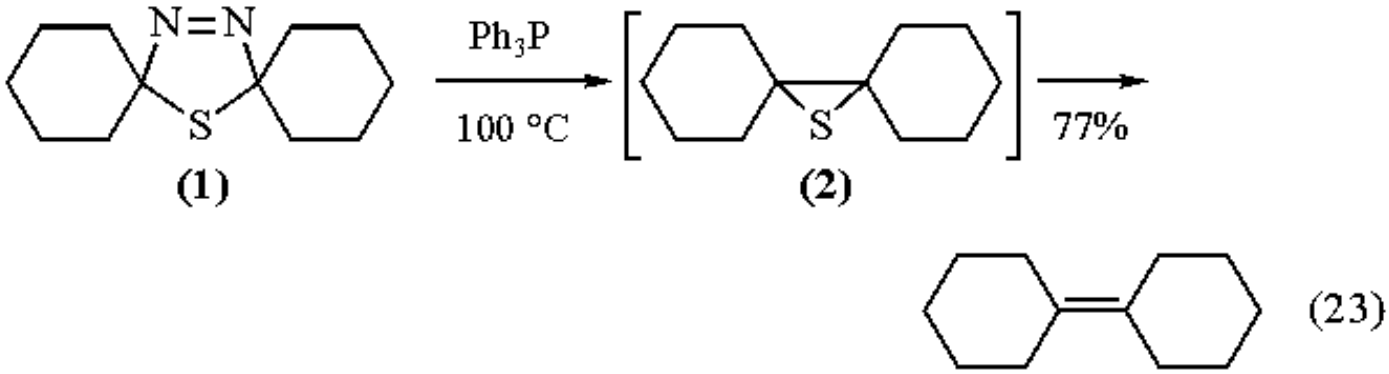

(23)

Aryl disulfides can also be reduced to aryl thiols with triphenylphosphine in aqueous dioxane (eq 24).[44] The resulting aryl thiols are easily removed from the triphenylphosphine oxide byproduct by extraction with aqueous base. The rate of reaction is faster for arenes with electron-withdrawing groups and is susceptible to catalysis by either acid or base. This reaction can also be accomplished with $LiAlH_4$, ***Sodium Borohydride***, and ***Zinc*** and dilute acid,[45] or by heating with alkali.[46]

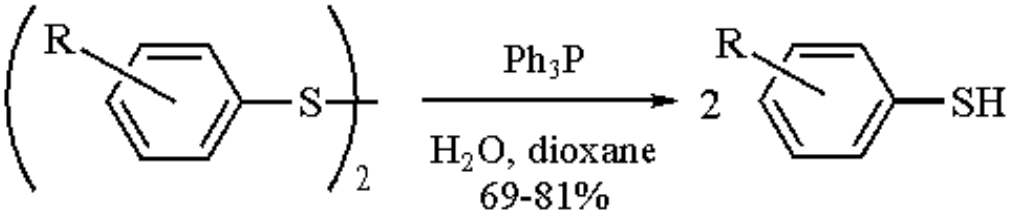

(24)

In addition, arenesulfonic acids, their sodium salts, and alkyl arenesulfonates can be reduced to the corresponding aryl thiols by triphenylphosphine and a catalytic amount of ***Iodine*** (eq 25).[47] Since no reaction occurs in the absence of iodine or triphenylphosphine, the initial reduction is presumably mediated by iodotriphenylphosphonium iodide. The reaction can be greatly accelerated by the addition of a tertiary amine such as ***Tri-n-butylamine***. Use of bromine in place of iodine results in a considerably lower yield of thiol.

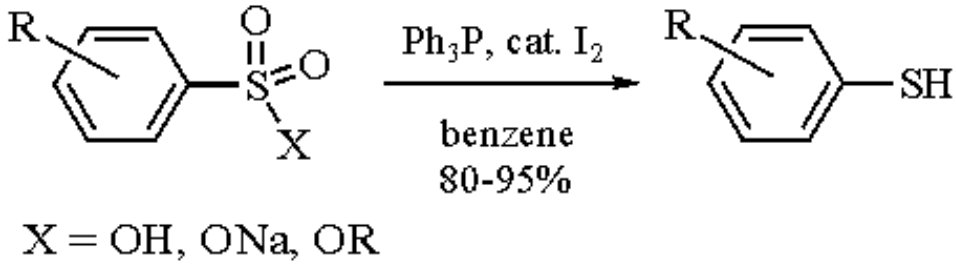

(25)

Triphenylphosphine has also been used to convert α-aryl-α-chloro sulfides to stilbenes.[48] The reaction (eq 26) requires addition of PPh_3 to the α-chloro sulfide prior to base addition; reversing the order of addition leads to negligible stilbene formation. The mechanism is not clear, but studies have shown that the phosphonium salt is not an intermediate in the process.

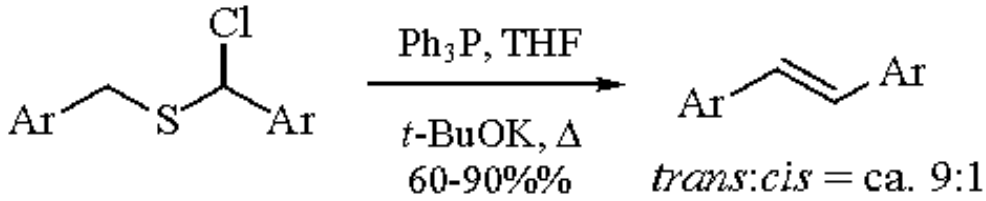

(26)

Eschenmoser[49] has used triphenylphosphine in an alkylation-sulfide contraction sequence useful in preparing secondary vinylogous amides and enolizable β-dicarbonyl compounds (eq 27). Although the precise mechanism is not known, an episulfide intermediate has been postulated. Addition of 0.1-0.2 equiv of a base such as ***Potassium t-Butoxide*** is necessary in some cases to promote enolization of the starting material.

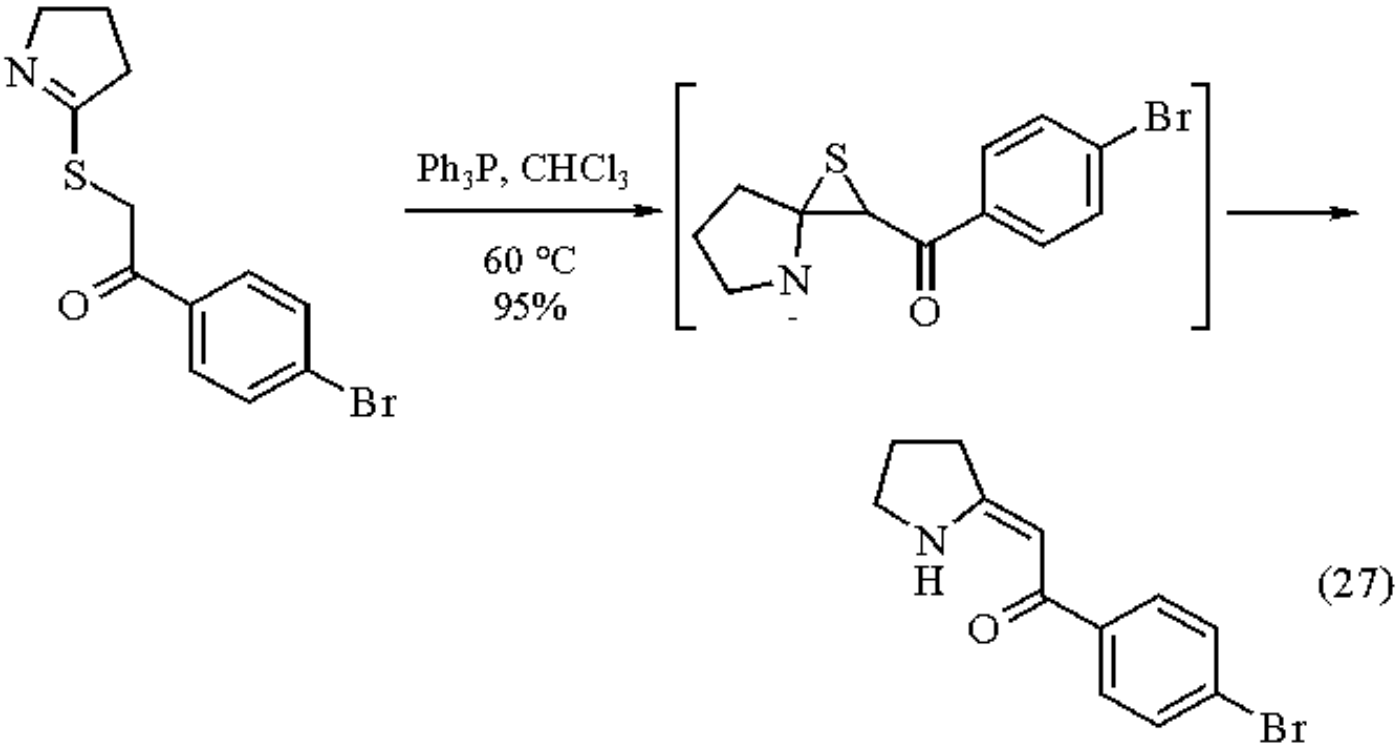

(27)

Dehalogenation.

Triphenylphosphine has been used to reduce bromine or iodine atoms in the *ortho* or *para* positions of phenols (eq 28).[50] The procedure consists of heating the phenol and 1 equiv of triphenylphosphine in benzene at 100-150 °C for 1-5 h followed by alkaline hydrolysis. The corresponding aryl chlorides do not undergo this reaction. In the case of 2,4-dibromophenol, the *ortho* bromine atom is reduced preferentially.

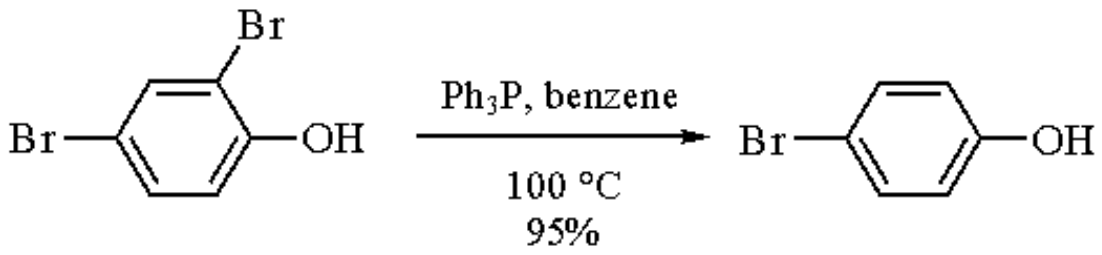

(28)

Secondary and tertiary α-bromo ketones react with triphenylphosphine in refluxing benzene-methanol to afford the debrominated ketone in 60-70% yields (eq 29).[51] No quaternary phosphonium salts resulting from nucleophilic displacement of bromide are observed. The intermediacy of enol phosphonium salts has been proposed. Under conditions similar to those employed for bromo ketones, 2-chlorohexanone is dechlorinated to only a slight extent and direct quaternization is not detected.

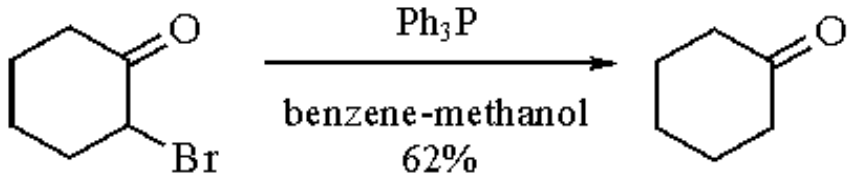

(29)

Triphenylphosphine debrominates ethyl methacrylate dibromide and methyl acrylate dibromide to the unsaturated esters (eq 30).[52] Dehydrobromination or displacement of bromide is not observed. Triphenylphosphine also debrominates α-bromodiphenylacetyl bromide at room temperature to generate ***Diphenylketene*** (eq 31).[53] The mildness of this method avoids problems of other approaches such as the use of unstable intermediates such as phenylbenzoyldiazomethane and polymerization of the ketene.

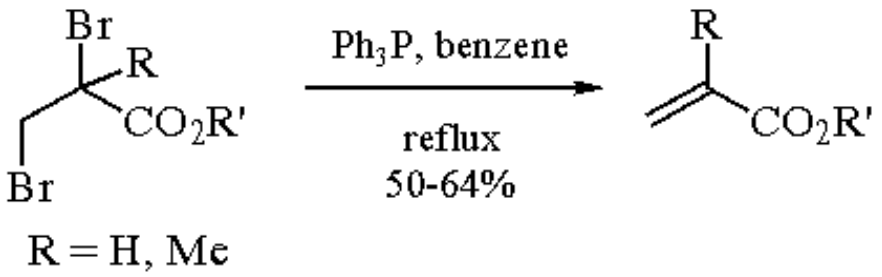

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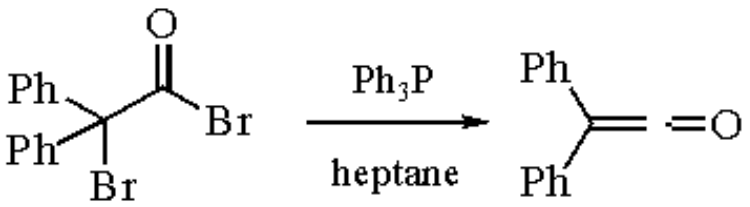

(31)

Finally, triphenylphosphine has been utilized in the preparation of alkyl-substituted thiirene dioxides via a 1,3-elimination of bromine from bis(α,α-dibromoalkyl) sulfones (eq 32).[54] The tetrabromo sulfones are synthesized from ***Dimethyl Sulfone*** in two steps.[55]

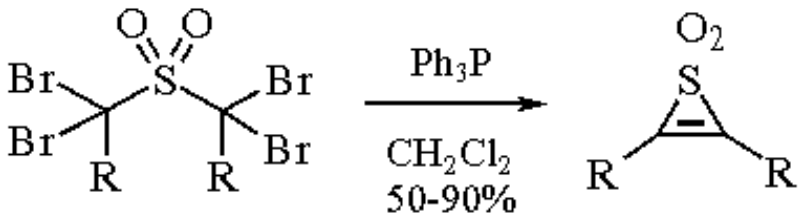

(32)

Miscellaneous.

Trost[56] has reported that triphenylphosphine catalyzes the isomerization of ynones, ynoates, and ynamides to their corresponding diene-carbonyl compounds (eq 33). Conjugation of the alkyne with an electron-withdrawing group is necessary for the reaction to occur, and the reactivity order with respect to the electron-withdrawing group is ketone > ester > amide. Esters and amides require the addition of a weak protic acid such as ***Acetic Acid*** to facilitate the isomerization. Several examples of selectivity with polyfunctional alkynes have been reported (eq 34). The mildness and selectivity of this method over transition metal-catalyzed alkene redox reactions[57] allows for greater functional group compatibility.

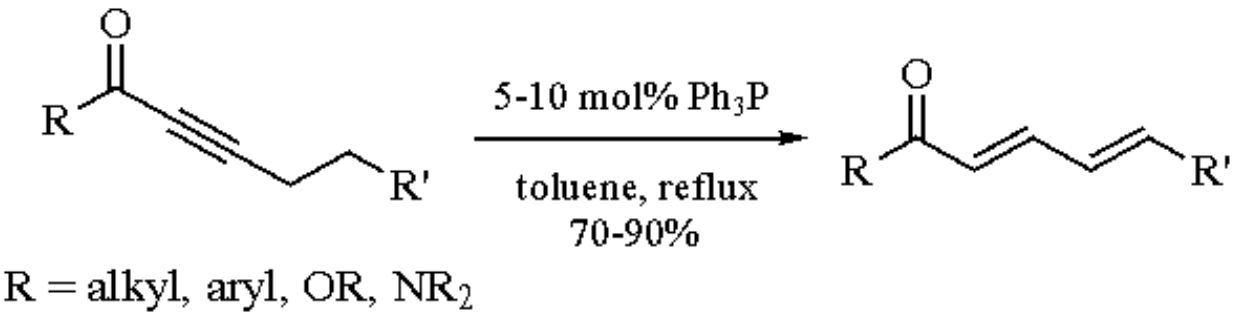

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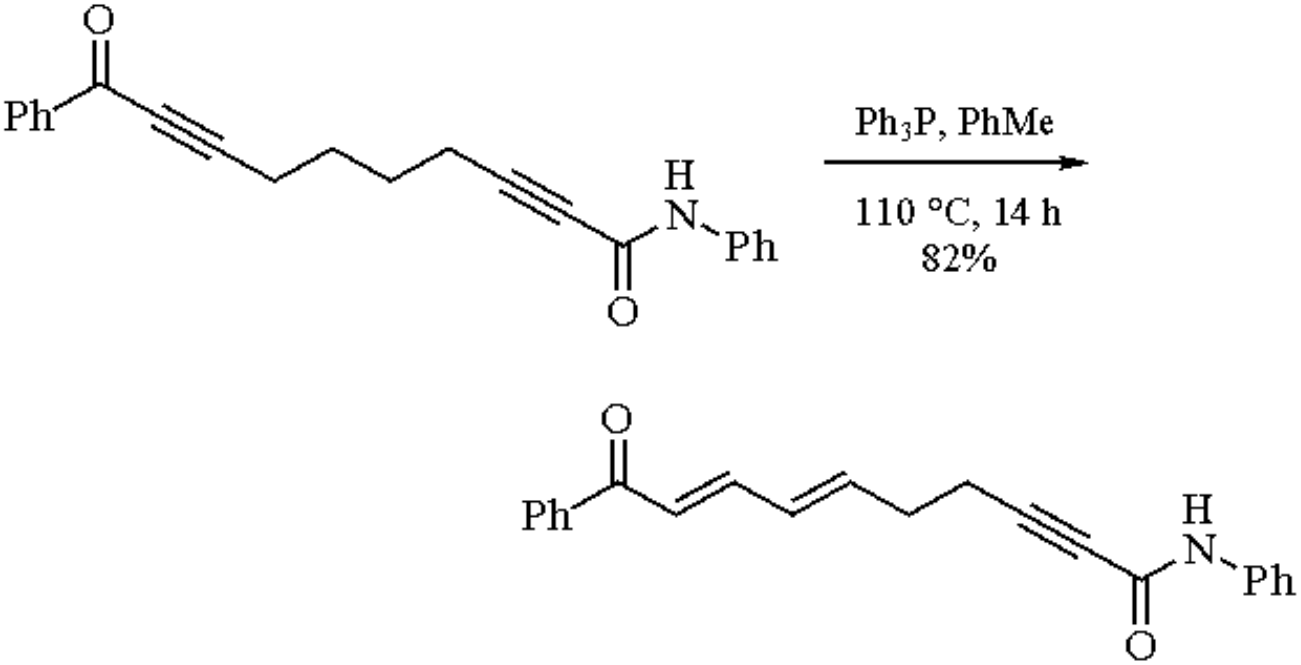

(34)

Treatment of arylbromonitromethanes with an equimolar amount of triphenylphosphine in an inert solvent such as benzene leads to formation of ***Benzonitrile Oxide***,[58] which can be isolated as diphenylfuroxan; use of methyl acrylate as the solvent leads to isoxazolines via a [3 + 2] cycloaddition of the benzonitrile oxide generated in the reaction with ***Methyl Acrylate*** (eq 35). However, reaction of 2 equiv of triphenylphosphine with alkyl-1-bromo-1-nitromethanes leads to formation of the corresponding nitriles,[59] presumably via reduction of an intermediate nitrile oxides by the second equivalent of triphenylphosphine (eq 36). The putative alkyl nitrile oxide intermediate cannot be isolated or trapped by conducting the reaction in a solvent such as stilbene.

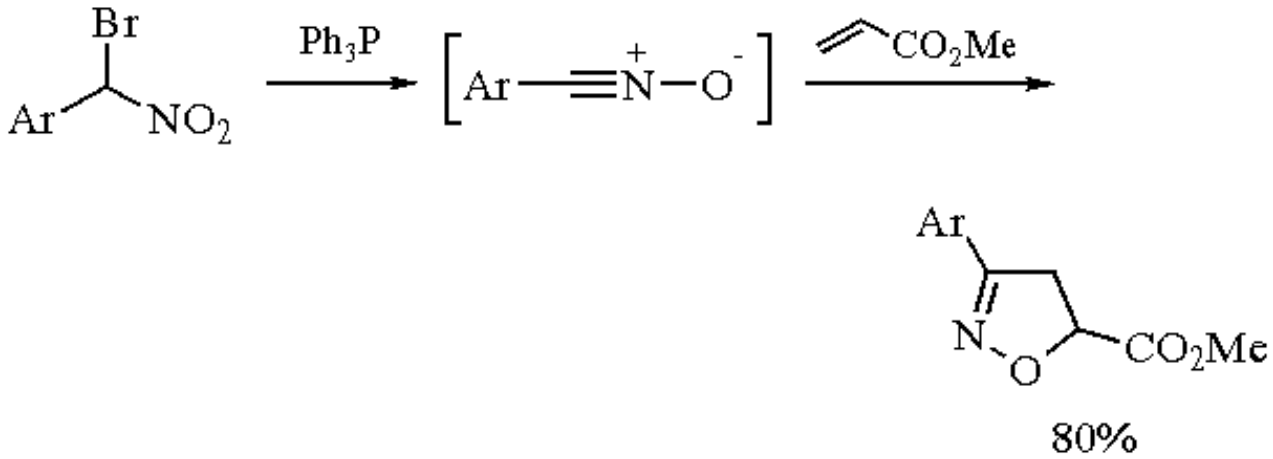

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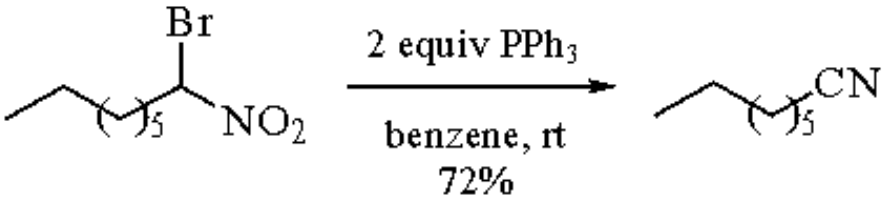

(36)

Triphenylphosphine in refluxing acetonitrile has also been used in the dequaternization of pyridinium salts (eq 37).[60] Placement of an electron-withdrawing group on the pyridine ring facilitates the dequaternization reaction.

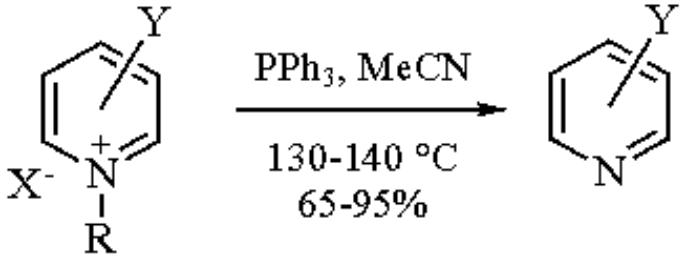

(37)

R = alkyl; Y = CN, COMe, Et

Triphenylphosphine has found wide application as a coreagent with a variety of other compounds including diethyl azodicarboxylate and carbon tetrachloride. These reagent combinations are covered in subsequent articles.

Related Reagents.

Molybdenum(V) Chloride-Triphenylphosphine; ***Triphenylphosphine-N-Bromosuccinimide***; ***Triphenylphosphine-Carbon Tetrabromide***; ***Triphenylphosphine-Carbon Tetrabromide-Lithium Azide***; ***Triphenylphosphine-Carbon Tetrachloride***; ***Triphenylphosphine-Diethyl Azodicarboxylate***; ***Triphenylphosphine-Hexachloroacetone***; ***Triphenylphosphine-Iodine***; ***Triphenylphosphine-Iodoform-Imidazole***; ***Triphenylphosphine-2,4,5-Triiodoimidazole***.

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Triphenylphosphine-*N*-Bromosuccinimide[1]

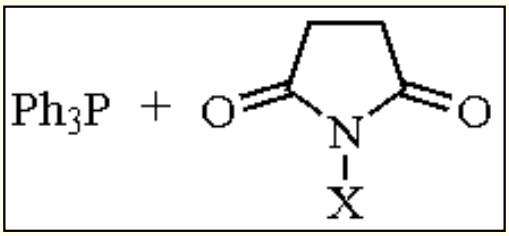

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-*N*-Bromosuccinimide · (MW 262.30) (NBS)

[128-08-5] · $C_4H_4BrNO_2$ · Triphenylphosphine-*N*-Bromosuccinimide · (MW 177.99) (NCS)

[128-09-6] · $C_4H_4ClNO_2$ · Triphenylphosphine-*N*-Chlorosuccinimide · (MW 133.54) (NIS)

[516-12-1] · $C_4H_4INO_2$ · Triphenylphosphine-*N*-Iodosuccinimide · (MW 224.99)

(conversion of primary alcohols to alkyl halides)

Physical Data: See ***Triphenylphosphine***, ***N-Bromosuccinimide***, ***N-Chlorosuccinimide***, and ***N-Iodosuccinimide***.

Preparative Methods: the mixed reagent is prepared in situ as needed by combining triphenylphosphine, the alcohol, and *N*-halosuccinimide in a suitable solvent (usually DMF) and heating.

Handling, Storage, and Precautions: precautions in handling should be made as described for the individual reagents. This mixed reagent is not appropriate for storage. Recrystallization of the triphenylphosphine and *N*-halosuccinimide is necessary to achieve the most efficient halogenation reaction. In addition, the use of anhydrous solvent is important for the success of the reaction.

Introduction.

The combination of triphenylphosphine and *N*-halosuccinimide was applied by Hanessian[2] to the preparation of primary halides from carbohydrate precursors. This method is related to a number of other methods for hydroxyl substitution via oxyphosphonium salts as described in a comprehensive review.[1]

Conversion of Alcohols to Alkyl Halides.

The typical procedure[2] as applied to the preparation of methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-D-ribofuranose (eq 1) involves the addition of 2 equiv of *N*-iodosuccinimide followed by 2 equiv of triphenylphosphine to a cooled solution of the alcohol in anhydrous DMF and heating the mixture to 50 °C for 20 min. Methyl alcohol is added to destroy excess reagent, followed by *n*-butanol to aid in the removal of DMF under reduced pressure. After concentration, the product is purified from the byproducts (succinimide and triphenylphosphine oxide) by addition of ether and aqueous extraction followed by column chromatography. Isolated yields of 70-85% are regularly obtained using this procedure for the preparation of chlorides, bromides, and iodides. In addition, the reaction conditions allow the preparation of primary halides in the presence of many functional groups used in carbohydrate chemistry, including the ester, amide, lactone, benzylidene acetal, and acetonide groups (eq 2). In fact, moderate yields (49-82%) of a number of primary halides are obtained using this procedure on sugars containing one or more free secondary hydroxyl groups (eq 3).[2-4]

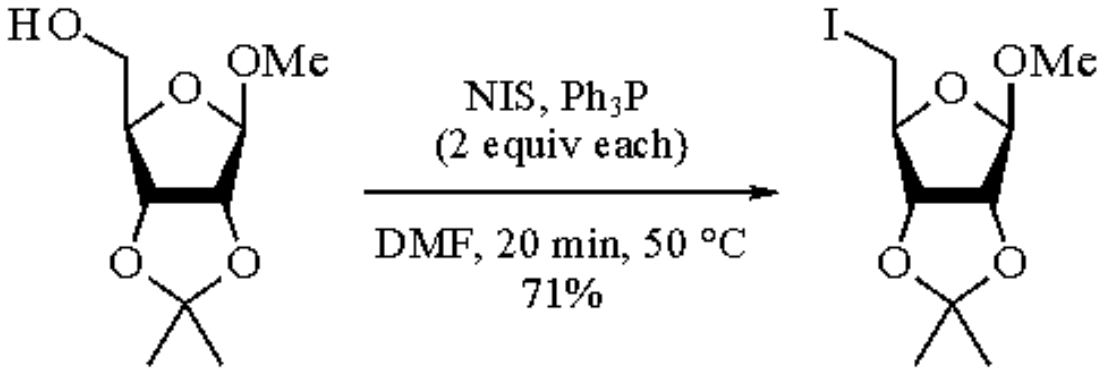

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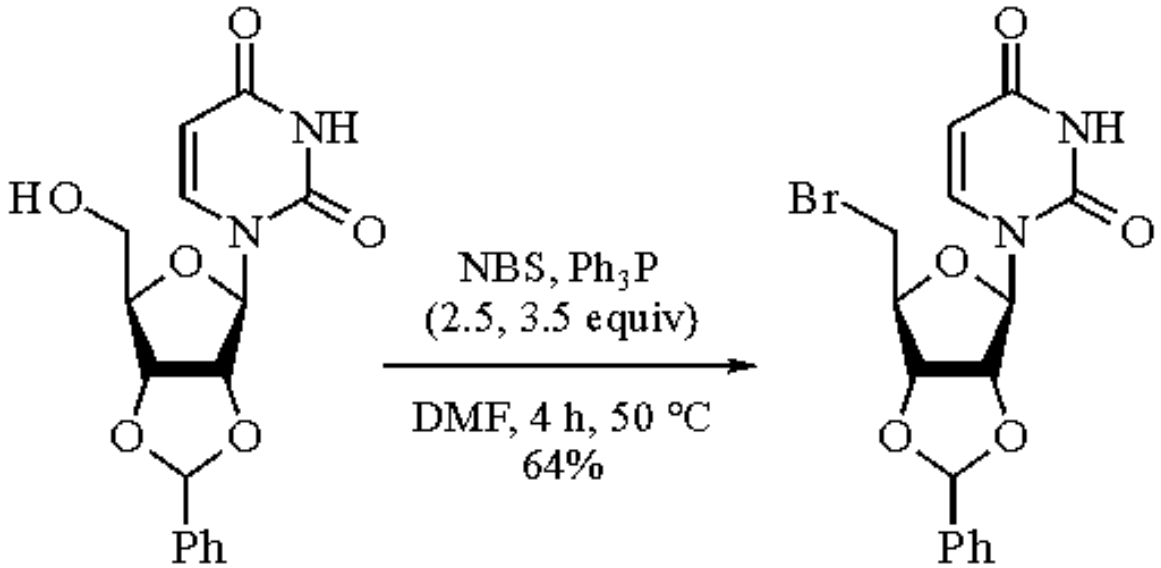

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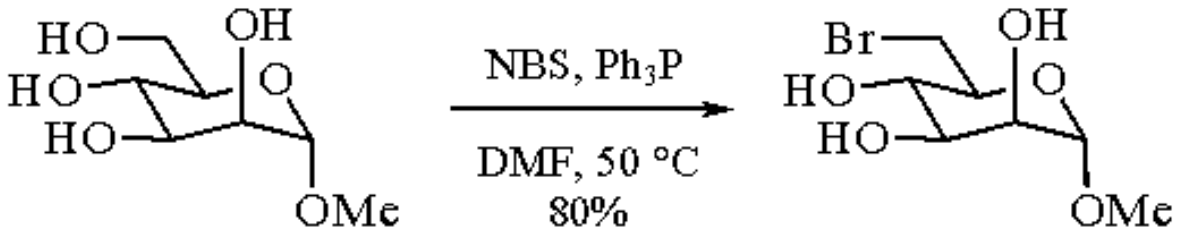

(3)

Other examples of the use of this method include the preparation of tetrahydrofurfuryl bromide,[5] 3α-cholestanyl bromide (using THF as solvent, 85% yield),[6] and intermediates toward the syntheses of alkaloids (eqs 4 and 5).[7] The reaction of the reagent with DMF alone generates the formamidinium salt which can ultimately result in the isolation of the formate ester derivative of the alcohol substrate (eq 6).[1,8] It is therefore important that the *N*-halosuccinimide is added last for the preparation of alkyl halides. Other solvents used for this reaction include CH_2Cl_2 (which can facilitate the workup of the reaction products) and HMPA.[9]

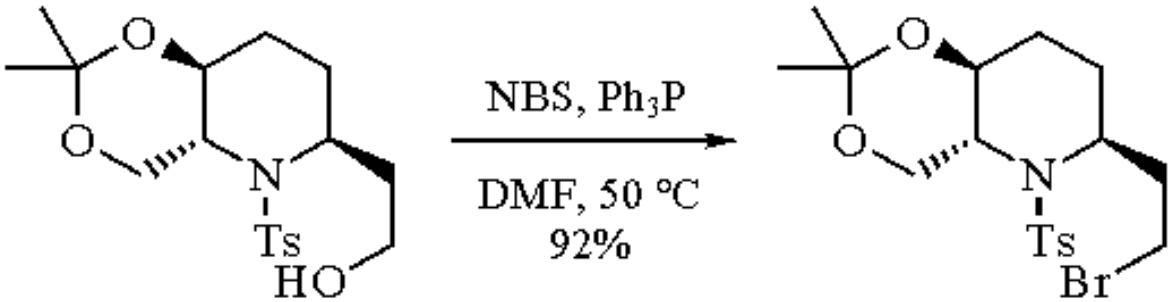

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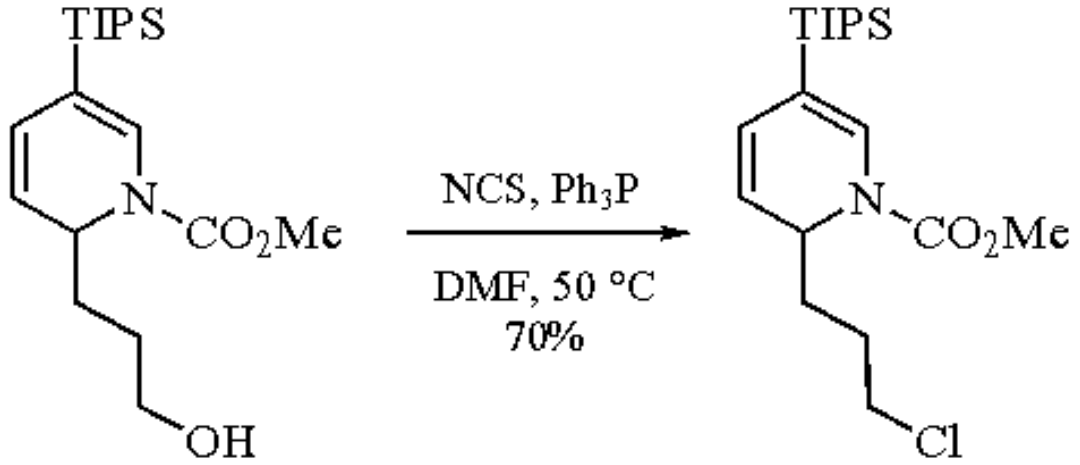

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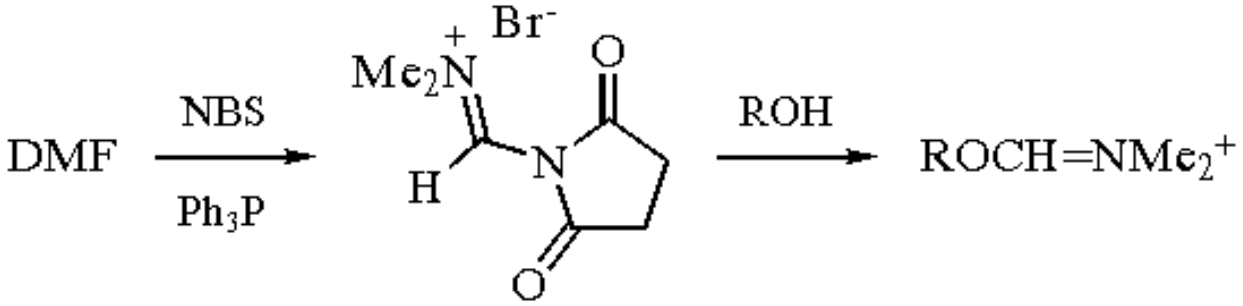

(6)

The standard procedure has often been found to be unsatisfactory for substrates which are prone to acid-catalyzed rearrangements (including migration of acetonide protecting groups) and cleavage and is also not suitable for substrates containing labile protecting groups such as THP ethers.[10,11] In some cases this problem has been circumvented by the addition of various bases such as $BaCO_3$ (eq 7),[12] ***Pyridine***, and ***Imidazole***. A recent study has achieved the preparation of 3-bromo-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose by addition of 2 equiv of *N*-halosuccinimide to a refluxing solution of the secondary alcohol and 2 equiv each of PPh_3 and imidazole in toluene or chlorobenzene (eq 8). Previous applications of PPh_3 and *N*-halosuccinimide alone afforded only the primary halide products resulting from acetonide migration. The use of pyridine and imidazole have also been found to play an essential role in the conversion of carbohydrates to halides using the reagents ***Triphenylphosphine-Iodine*** and ***Triphenylphosphine-Carbon Tetrachloride***, respectively.[13]

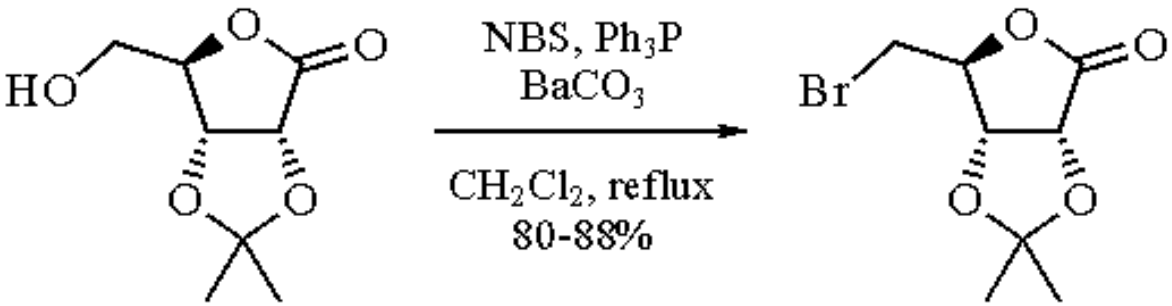

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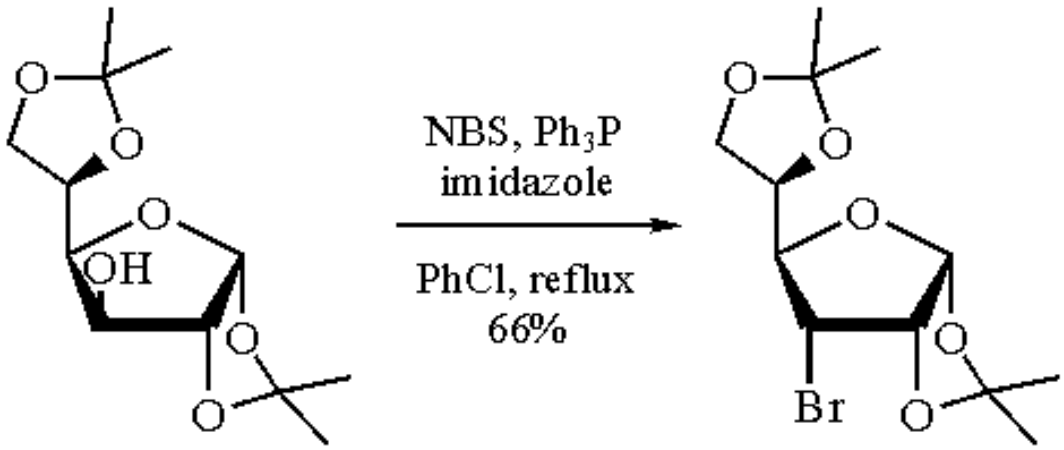

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Triphenylphosphine-Carbon Tetrabromide[1]

Ph_3P-CBr_4

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Carbon Tetrabromide · (MW 262.30) (CBr_4)

[558-13-4] · CBr_4 · Triphenylphosphine-Carbon Tetrabromide · (MW 331.61)

(reagent combination for the conversion of alcohols to bromides, aldehydes and ketones to dibromoalkenes, and terminal alkynes to 1-bromoalkynes; carboxyl activation)

Physical Data: Ph_3P: mp 79-81 °C; bp 377 °C; *d* 1.0749 g cm^{-3}. CBr_4: mp 90-91 °C; bp 190 °C; *d* 3.273 g cm^{-3}.

Solubility: sol MeCN, CH_2Cl_2, pyridine, DMF.

Preparative Method: the reactive species is generated in situ by reaction of Ph_3P with CBr_4.

Handling, Storage, and Precautions: Ph_3P is an irritant; CBr_4 is toxic and a cancer suspect agent. All solvents used must be carefully dried because the intermediates are all susceptible to hydrolysis. This reagent should be used in a fume hood.

Conversion of Alcohols to Alkyl Bromides.

The reaction of alcohols with ***Triphenylphosphine*** and ***Carbon Tetrabromide*** results in the formation of alkyl bromides. The conditions are sufficiently mild to allow for the efficient conversion of alcohols into the corresponding bromides. The uridine derivative (eq 1) is transformed into its bromide with Ph_3P and CBr_4.[2]

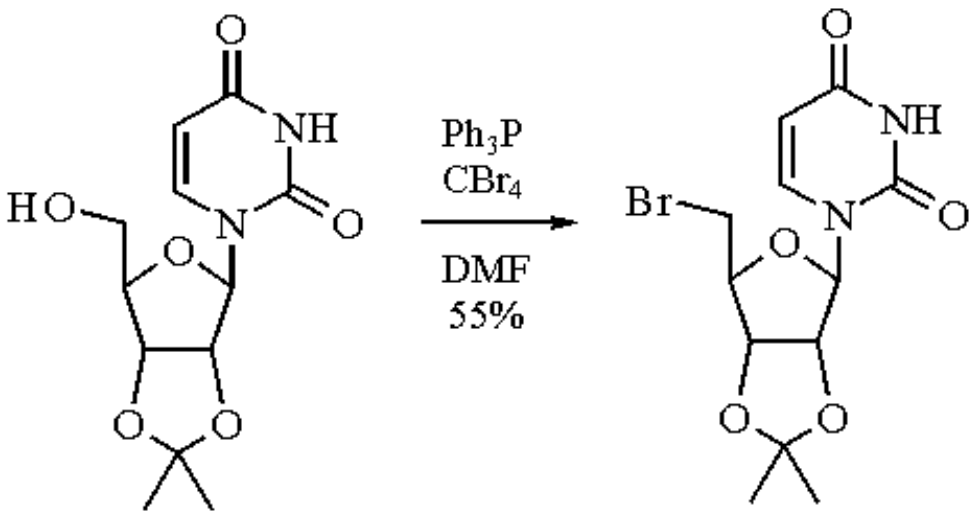

(1)

The geometry about the double bond of an allylic alcohol is usually not compromised (eq 2).[3] Allylic rearrangement is also not commonly observed. Although ketones are known to react with this reagent combination, the reaction of an allylic alcohol has been selectively achieved in the presence of a ketone (eq 3).[4]

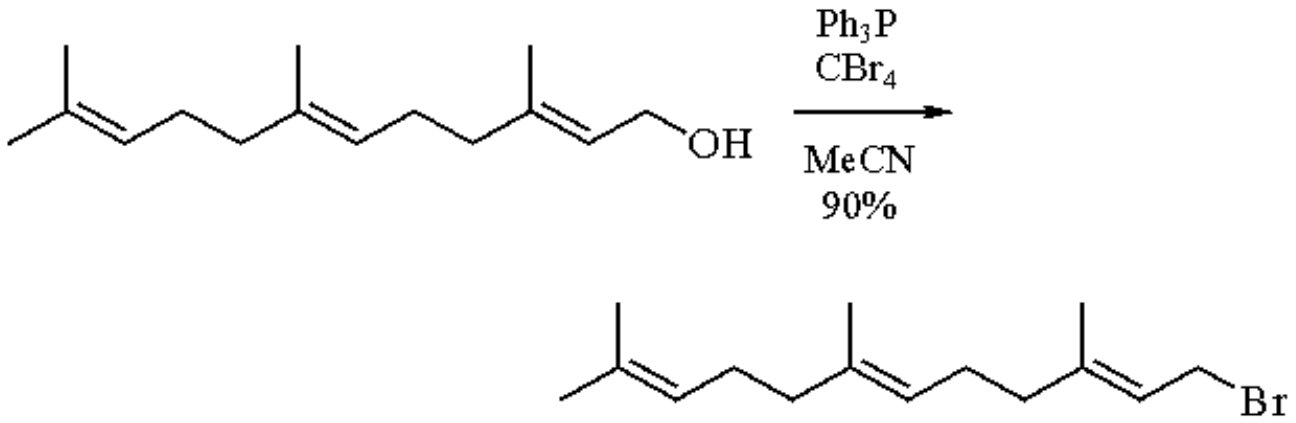

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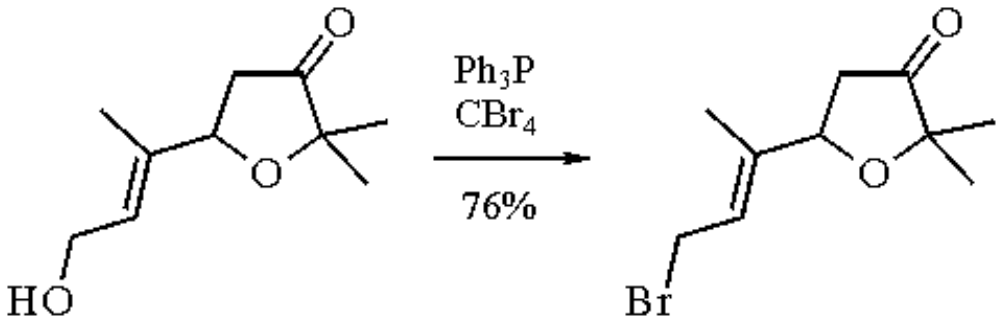

(3)

Regioselective bromination of primary alcohols in the presence of secondary alcohols is possible. These reactions are usually performed in pyridine as solvent. The reaction of the methyl glucopyranoside (eq 4) results in the selective formation of the primary bromide in 98% yield.[5] An investigation of this reaction with a chiral deuterated neopentyl alcohol yielded a partially racemized bromide.[6]

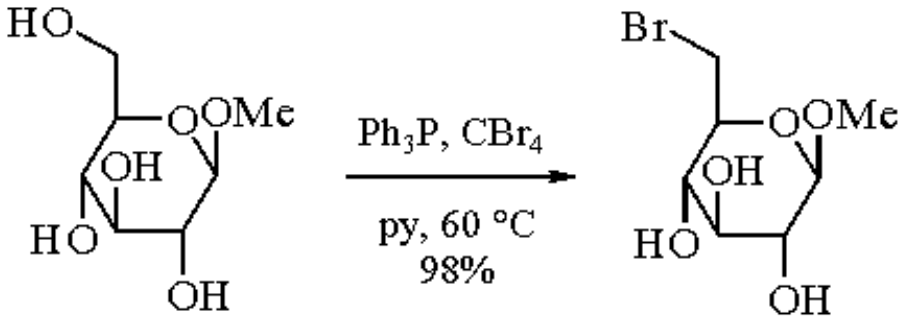

(4)

Silyl ether protected alcohols (eq 5) have been converted directly into the corresponding bromides with Ph_3P and CBr_4. The reaction works best if 1.5 equiv of acetone are added.[7] Tetrahydropyranyl ether protected alcohols have also been directly transformed into the bromides using this reagent combination. The reaction has been reported to proceed with inversion of configuration (eq 6).[8] If unsaturation is appropriately placed within a tetrahydropyranyl (eq 7) or a methoxymethyl (eq 8) protected alcohol, cyclization occurs to afford tetrahydropyrans.[9] The conversion of an alcohol to the bromide without complications with a methoxymethyl protected alcohol in the molecule is possible (eq 9).[10]

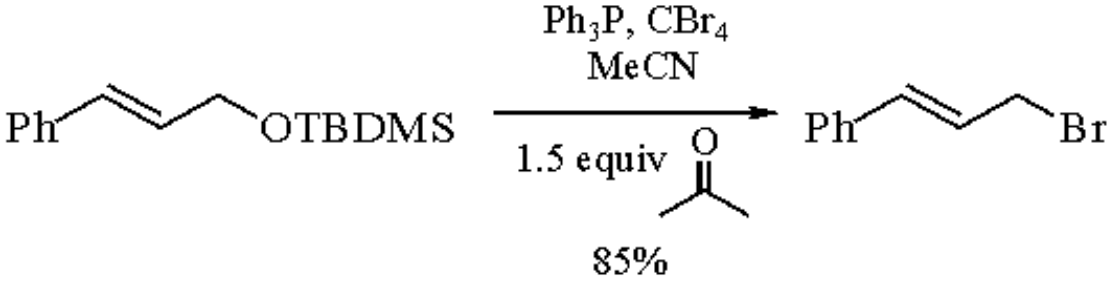

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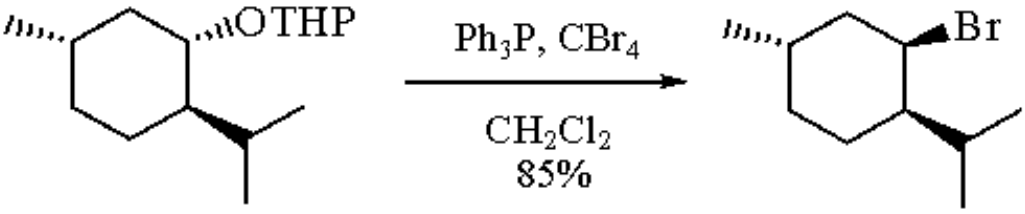

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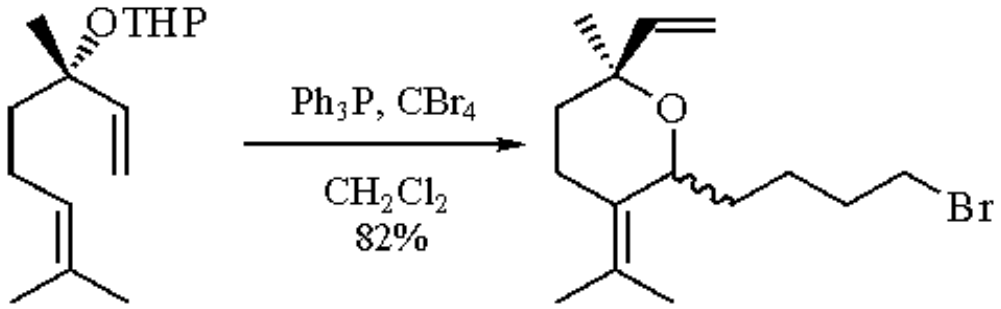

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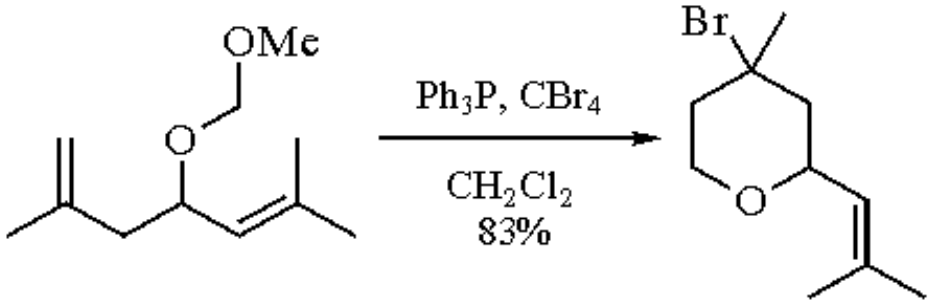

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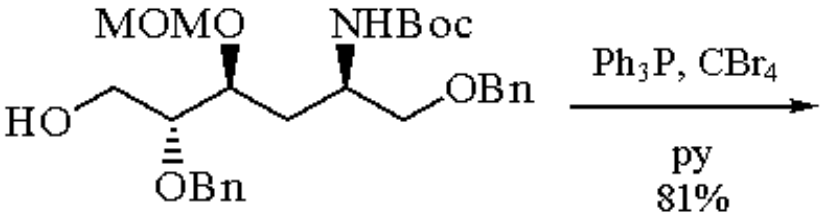

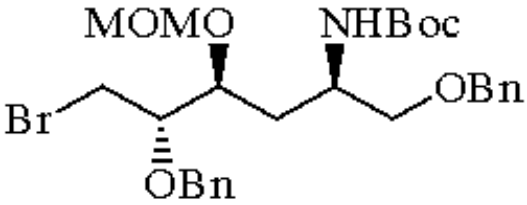

(9)

Amides from Carboxylic Acids.

N-Methoxy-*N*-methyl amides can be prepared from carboxylic acids and the amine hydrochlorides. In the case of an α-phenyl carboxylic acid (eq 10), the amide is formed in 71% yield and no racemization is detected.[11]

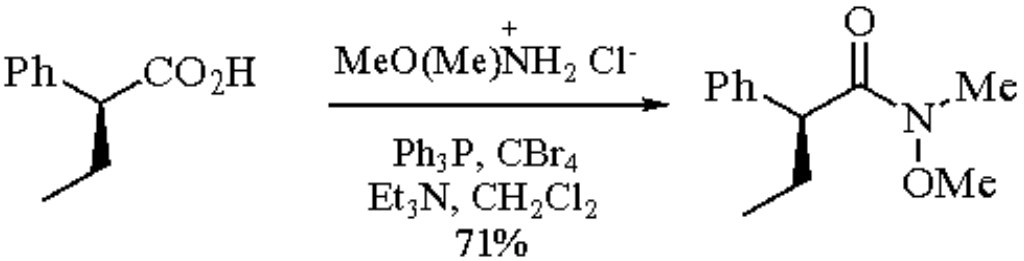

(10)

Dibromoalkenes from Aldehydes and Ketones.

Benzaldehyde is transformed into the dibromoalkene in 84% yield when treated with Ph_3P and CBr_4 (eq 11).[12] An alternative procedure for the conversion of an aldehyde to the dibromoalkene uses ***Zinc*** dust in place of an excess of the phosphine. This allows the amount of Ph_3P and CBr_4 to be reduced to 2 equiv each as opposed to 4 equiv. This procedure gives comparable results to the original procedure. The dibromoalkenes can be reacted with ***n-Butyllithium*** to form the intermediate lithium acetylide. The acetylides can then be reacted with electrophiles such as H_2O (eq 12) and CO_2 (eq 13). This offers a convenient method for the formyl to ethynyl conversion.[13]

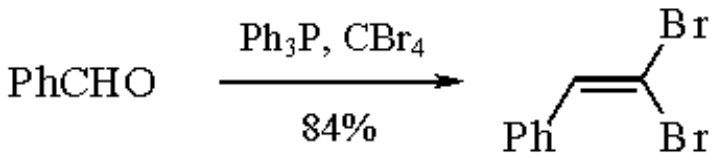

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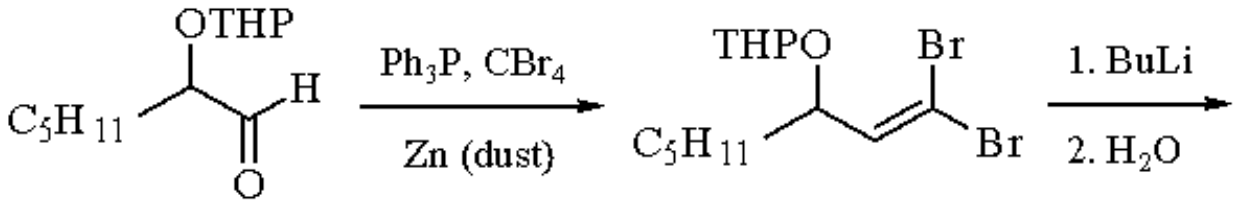

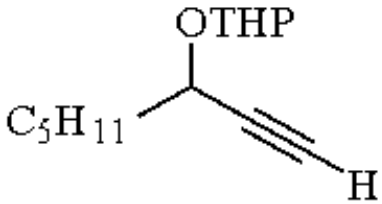

(12)

62% overall

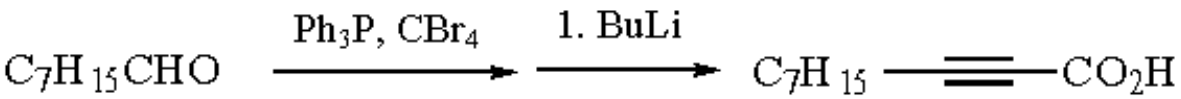

(13)

~78% overall

Ketones are converted to dibromomethylene derivatives. These intermediates can be transformed to isopropylidene compounds by reaction with ***Lithium Dimethylcuprate*** and ***Iodomethane*** (eq 14).[14] No racemization was reported for the chain extension of the aldehyde derived from (*S*)-ethyl lactate under the reaction conditions (eq 15).[15]

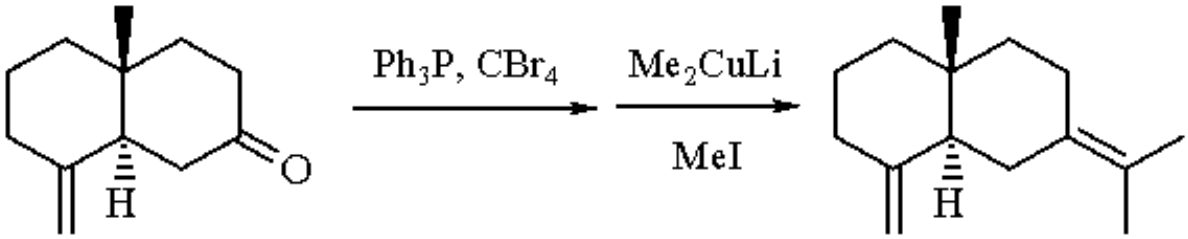

(14)

~80% overall

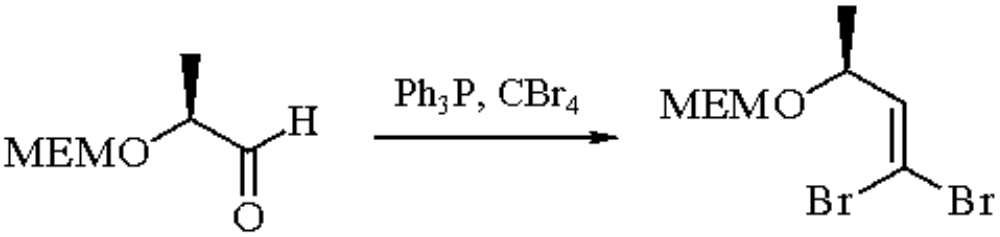

(15)

~70% from *(S)*-ethyl lactate

β-Bromo Enones from 1,3-Diketones.

The reaction of Ph_3P and CBr_4 with a 1,3-diketone efficiently converts it to the β-bromo enone (eq 16).[16]

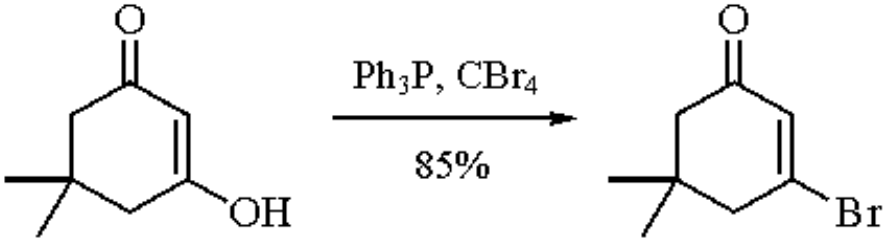

(16)

1-Bromoalkynes from Terminal Alkynes.

Terminal alkynes on reaction with Ph_3P and CBr_4 afford 1-bromoalkynes in high yield (eq 17).[17]

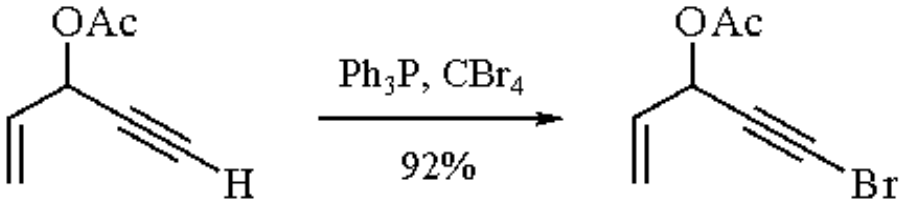

(17)

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Triphenylphosphine-Carbon Tetrabromide-Lithium Azide

Ph_3P-CBr_4-LiN_3

(PPh_3)

[603-53-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Carbon Tetrabromide-Lithium Azide · (MW 262.30) (CBr_4)

[558-13-4] · CBr_4 · Triphenylphosphine-Carbon Tetrabromide-Lithium Azide · (MW 331.61) (LiN_3)

[19597-69-4] · LiN_3 · Triphenylphosphine-Carbon Tetrabromide-Lithium Azide · (MW 48.97)

(reagent combination for the conversion of alcohols to azides)

Physical Data: Ph_3P: mp 79-81 °C; bp 377 °C; *d* 1.0749 g cm^{-3}. CBr_4: mp 90-91 °C; bp 190 °C; *d* 3.273 g cm^{-3}. LiN_3: mp 115-298 °C (dec).

Solubility: sol DMF.

Preparative Method: reactive intermediates are generated in situ by reaction of Ph_3P, CBr_4, and LiN_3.

Handling, Storage, and Precautions: Ph_3P is an irritant; CCl_4 is toxic and a cancer suspect agent; use in a fume hood. All solvents used must be carefully dried because the intermediates are all susceptible to hydrolysis. All azides are potentially explosive; workup with halogenated solvents is not recommended.

5´-Azido Nucleosides.

Introducing the azido group selectively to the 5´-position of various nucleosides can be accomplished with a combination of ***Triphenylphosphine***, ***Carbon Tetrabromide***, and lithium azide. This works well for uridine (eq 1) and thymidine. The yields are somewhat lower for *N*4-benzoylcytidine (eq 2) and *N*6-benzoyladenosine. The method is unsuccessful at introducing the azido group into the 5´-position of *N*2-benzoylguanosine.[1]

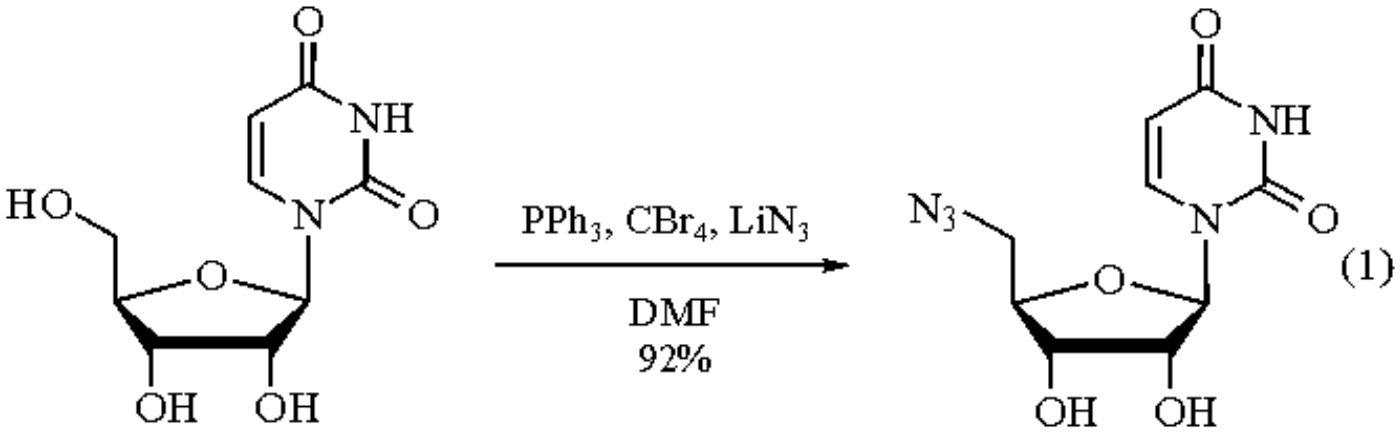

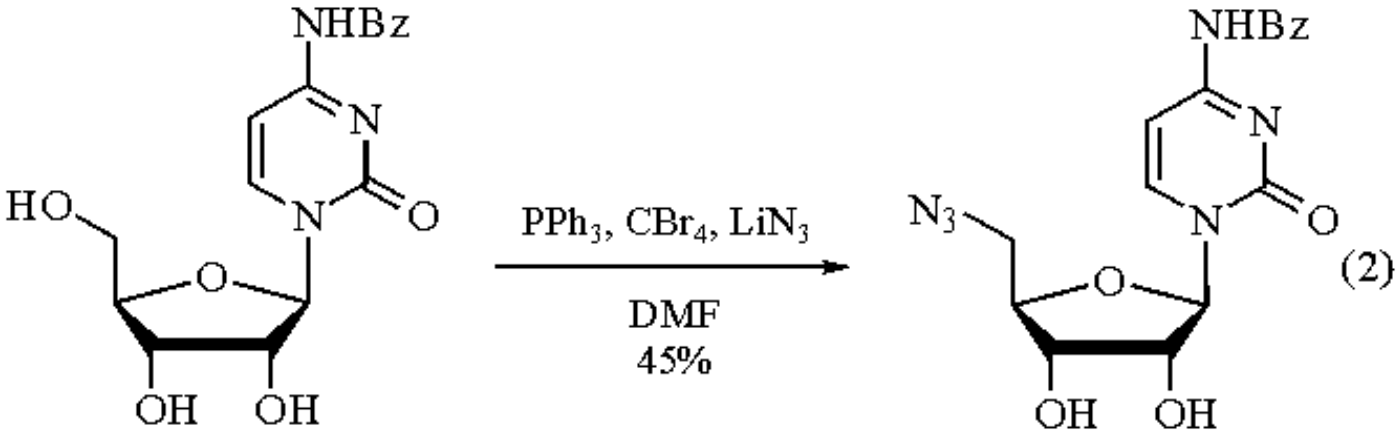

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Triphenylphosphine-Carbon Tetrachloride[1]

Ph_3P-CCl_4

(Ph_3P)

[605-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Carbon Tetrachloride · (MW 262.30) (CCl_4)

[56-23-5] · CCl_4 · Triphenylphosphine-Carbon Tetrachloride · (MW 153.81)

(reagent combination for the conversion of a number of functional groups into their corresponding chlorides and for dehydrations)

Physical Data: Ph_3P: mp 79-81 °C; bp 377 °C; *d* 1.0749 g cm^{-3}. CCl_4: mp -23 °C; bp 77 °C; *d* 1.594 g cm^{-3}.

Solubility: sol CCl_4, MeCN, CH_2Cl_2, 1,2-dichloroethane.

Preparative Method: reactive intermediates are generated in situ by reaction of Ph_3P and CCl_4.

Handling, Storage, and Precautions: Ph_3P is an irritant; CCl_4 is toxic and a cancer suspect agent; use in a fume hood. Solvents must be carefully dried because the intermediates are all susceptible to hydrolysis.

Combination of Triphenylphosphine and Carbon Tetrachloride.

This reagent combination is capable of performing a range of chlorinations and dehydrations. The reactions are typically run using the so-called two-component or three-component systems. Carbon tetrachloride can function as both the reagent and solvent. However, the rates of the reactions are highly solvent-dependent, with MeCN providing the fastest rates.[1]

Conversion of Alcohols to Alkyl Chlorides.

The reaction of alcohols with ***Triphenylphosphine*** and carbon tetrachloride results in the formation of alkyl chlorides.[2] The mild, neutral conditions allow for the efficient conversion of even sensitive alcohols into the corresponding chlorides (eqs 1 and 2).[3,4] The reaction typically proceeds with inversion of configuration.[5] In eq 3, it is interesting to note that the reaction not only proceeds with inversion of configuration but also no acyloxy migration is observed.[6]

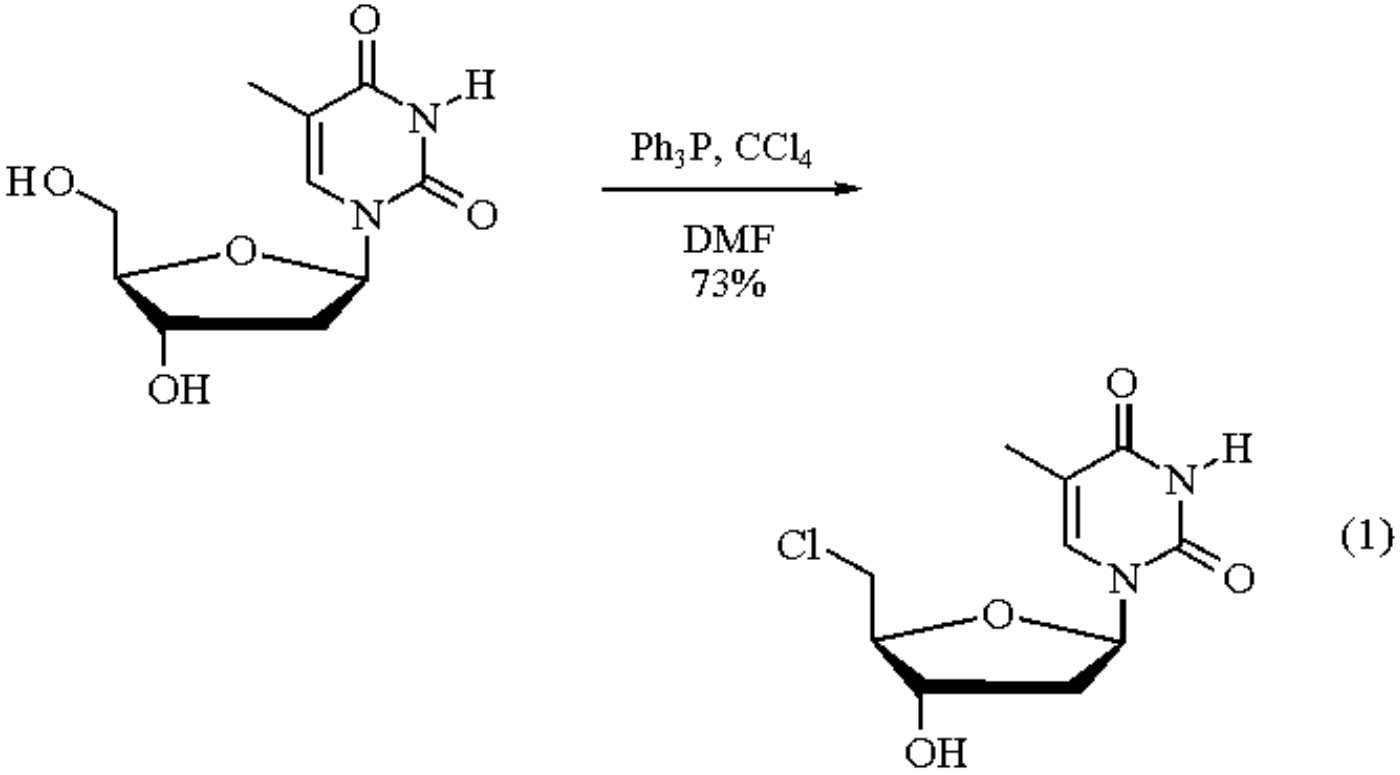

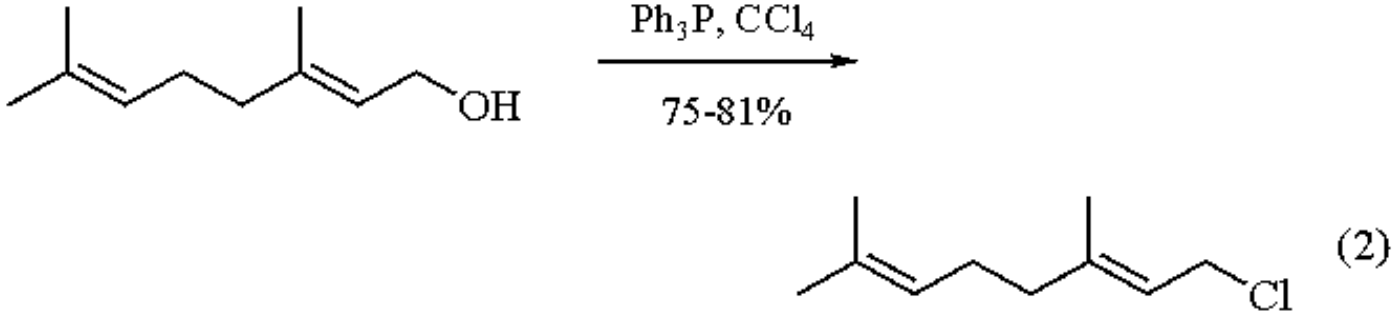

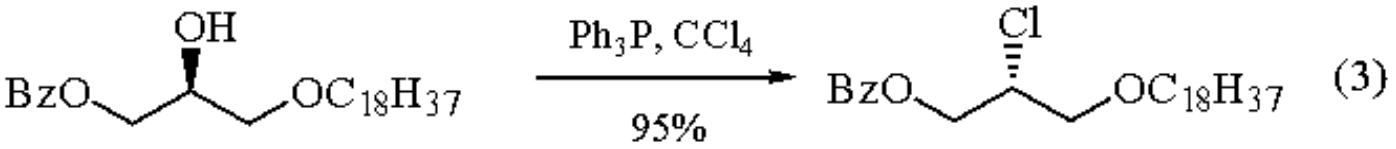

The conversion of an allylic alcohol to an allylic chloride occurs with no or minimal allylic rearrangement (eqs 4 and 5).[7] For the synthesis of low boiling allylic alcohols, it is advantageous to substitute hexachloroacetone (HCA) for CCl_4 (eq 6). The stereochemical integrity of the double bond also remains intact under these conditions.[8]

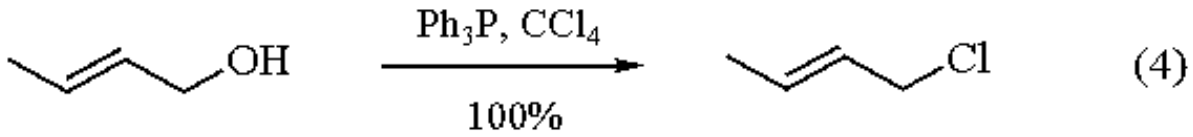

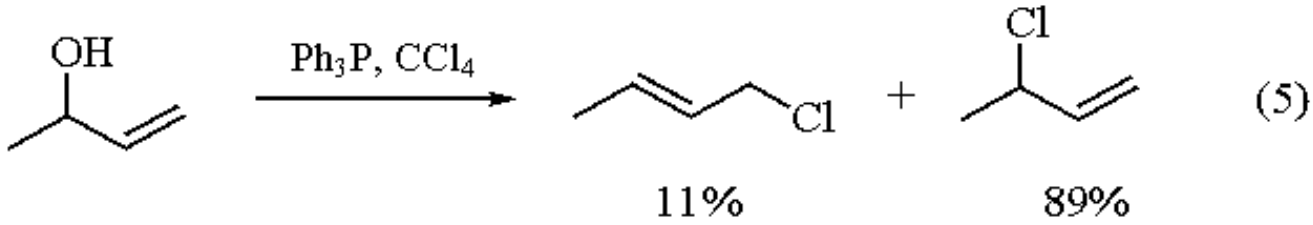

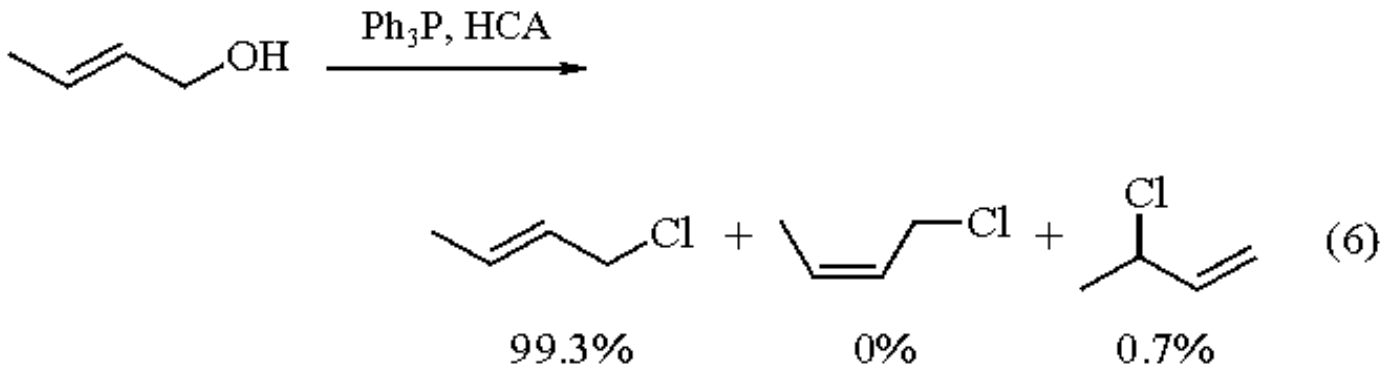

If the conversion of the alcohol to the chloride is attempted in refluxing MeCN, dehydration to form the alkene occurs (eqs 7 and 8).[9] Occasionally the separation of the product from the triphenylphosphine oxide produced in the reaction can be problematic. This can be overcome by using a polymer-supported phosphine.[10] Simple filtration and evaporation of the solvent are all that is required under these conditions. Not only is the workup facilitated, but the rate of the reaction is also increased by employing the supported reagent.[10c]

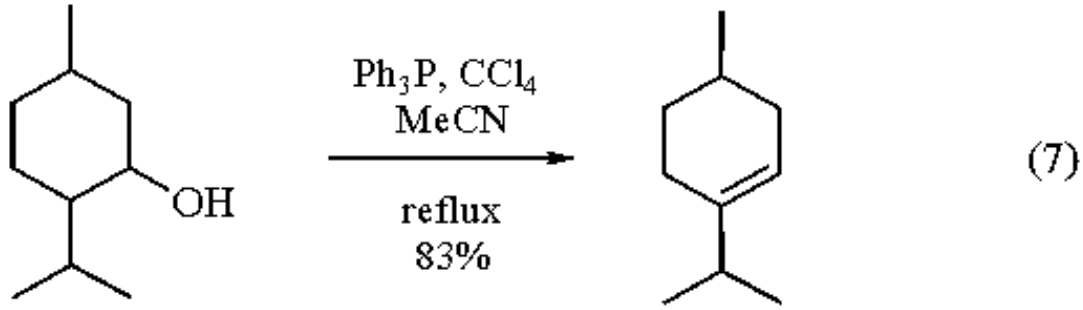

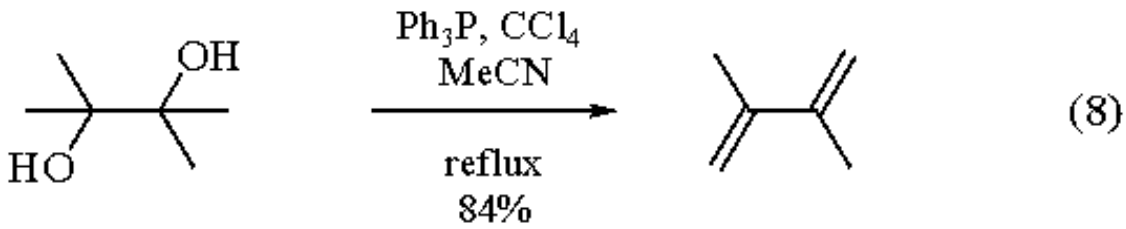

Conversion of Acids to Acid Chlorides.

The reaction of carboxylic acids with triphenylphosphine-CCl_4 reportedly produces acid chlorides in good yield under mild conditions (eq 9).[11] These conditions will allow acid sensitive functional groups to survive. Phosphoric mono- and diesters are successfully converted into the phosphoric monoester dichlorides and diester chlorides, respectively. The reaction of the diethyl ester does not produce the acid chloride. Instead, the anhydride is formed. Phosphinic acid chlorides can also be prepared from the corresponding phosphinic acid under these conditions (eq 10).[12]

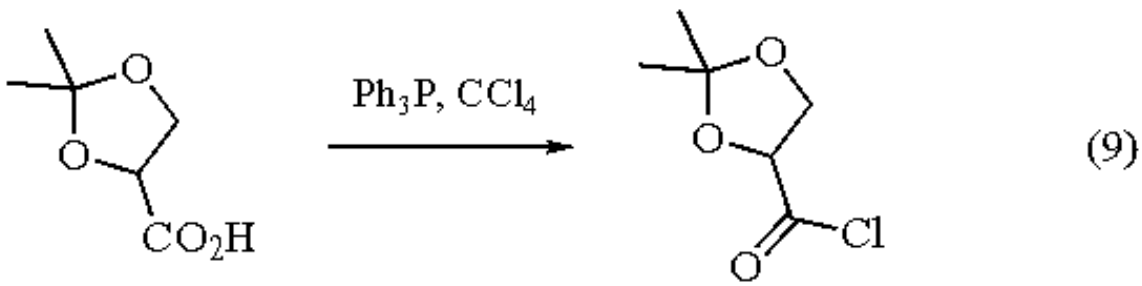

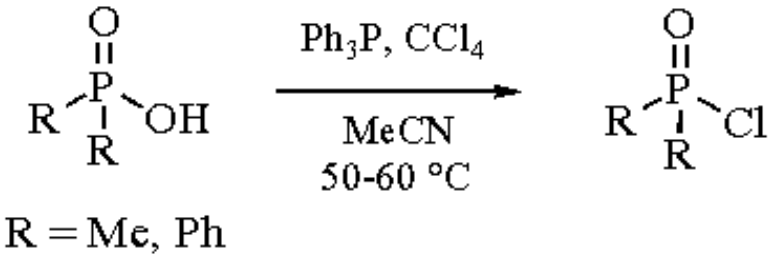

(10)

Epoxides to *cis*-1,2-Dichloroalkanes.

Epoxides are converted into *cis*-1,2-dichlorides by the action of triphenylphosphine in refluxing CCl_4.[13] Cyclohexene oxide forms *cis*-1,2-dichlorocyclohexane (eq 11) contaminated by a trace of the *trans*-isomer. Cyclopentene oxide gives only the *cis*-isomer.

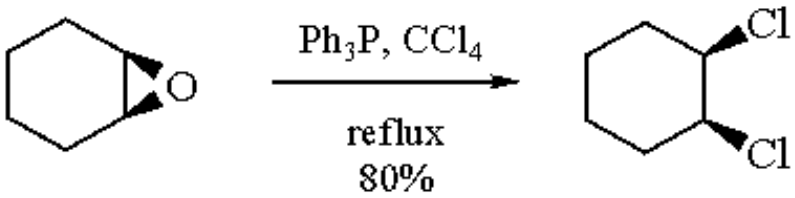

(11)

Dehydrations.

Diols may be cyclodehydrated to the corresponding cyclic ethers. The reaction is most effective for 1,4-diols (eq 12). Dehydration of 1,3- and 1,5-diols is not as successful, except in the case of the configurationally constrained 1,5-diol shown in eq 13.[14] The reaction of *trans*-1,2-cyclohexanediol with the reagent affords *trans*-2-chlorocyclohexanol with none of the *cis*-isomer or the *trans*-dichloride being detected. If the reaction is performed in the presence of K_2CO_3 as an HCl scavenger, the epoxide is formed (eq 14).[14] The yields are not as good with substituted acyclic diols.[15]

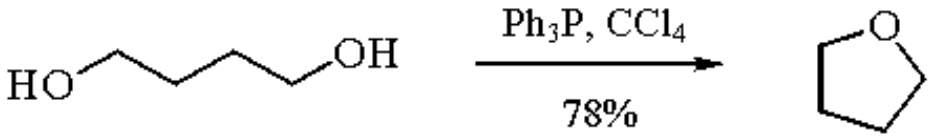

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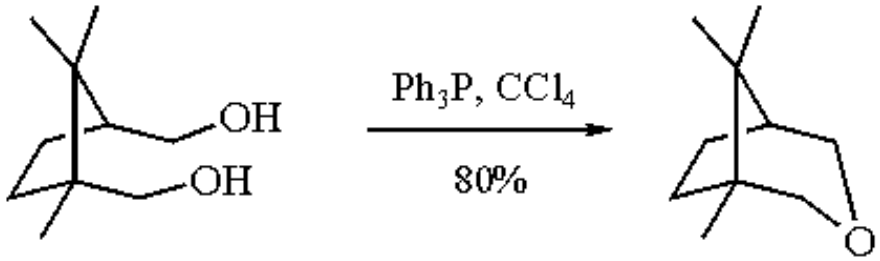

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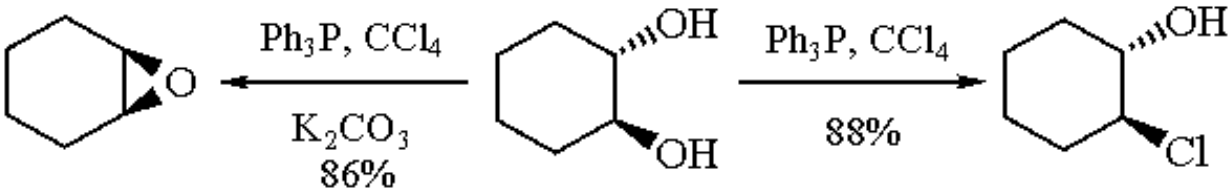

(14)

Dehydration of *N*-substituted β-amino alcohols with triphenylphosphine-CCl_4 and ***Triethylamine*** produces aziridines in good yield (eq 15).[16] This reaction has been successfully employed in the preparation of stable arene imines (eq 16).[17] Azetidines can be obtained from the corresponding 3-aminoalkanols (eq 17).[18] Additionally, reaction of 2-(3-hydroxypropyl)piperidine under these conditions yields octahydroindolizine (eq 18).

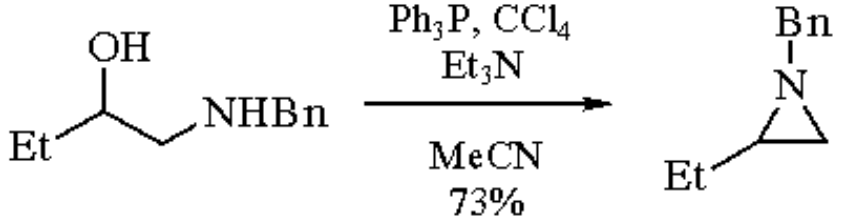

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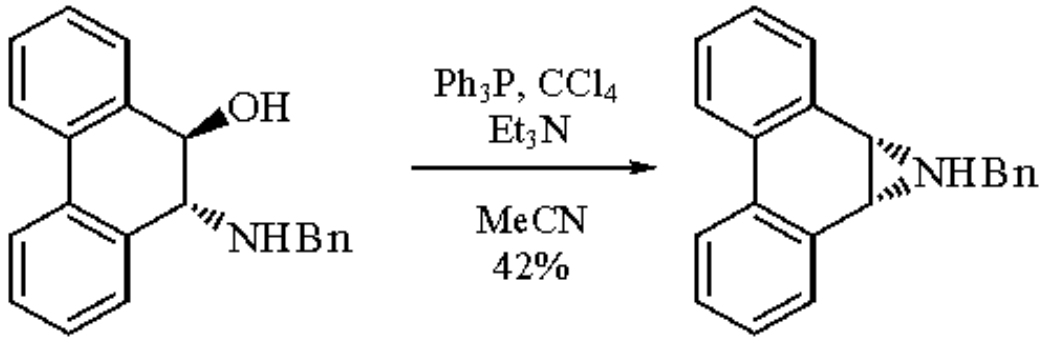

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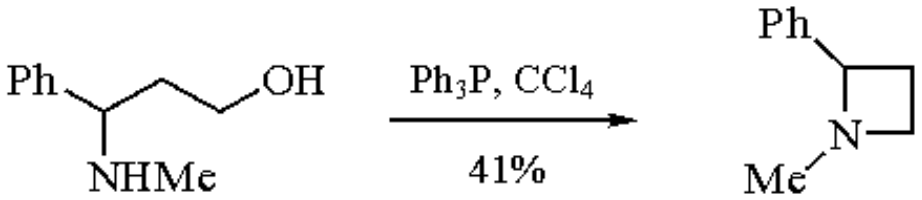

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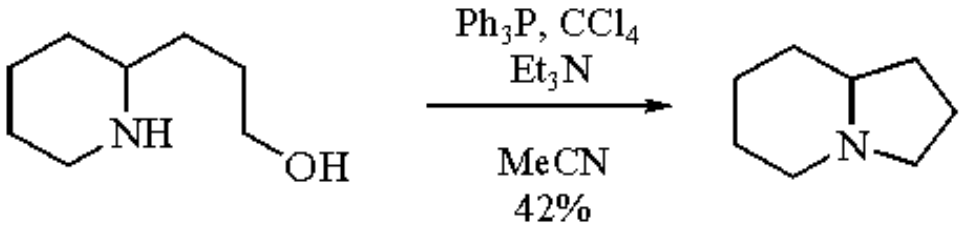

(18)

Substituted hydroxamic acids successfully cyclize to form β-lactams as long as Et_3N is present (eq 19). In the absence of the base, complex mixtures are formed.[19] Unsubstituted amides can be converted into nitriles via dehydration (eq 20).[20] This is the reagent of choice for the transformation of the amide to the nitrile in eq 21.[21]

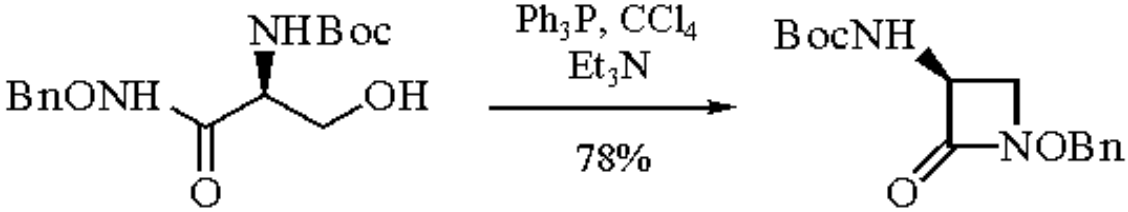

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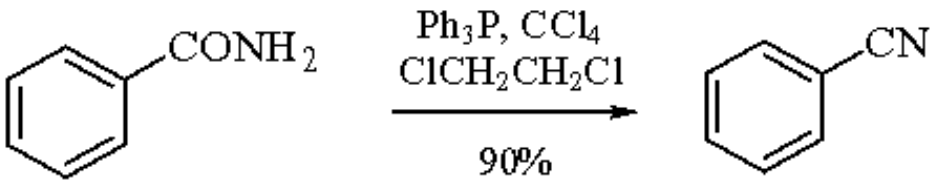

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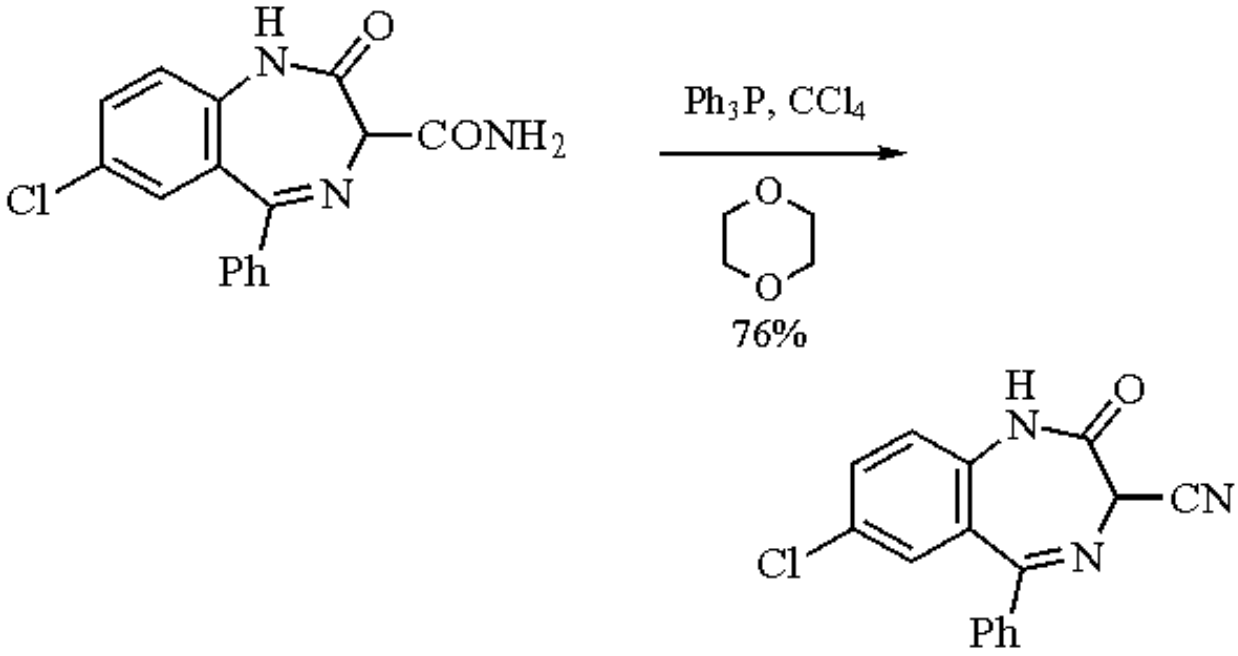

(21)

Nitriles can also be obtained from aldoximes using this reagent (eq 22).[22] Ketoximes produce imidoyl chlorides via a Beckmann rearrangement under these conditions (eq 23).[23] Imidoyl chlorides are also available by the reaction of monosubstituted amides with Ph_3P-CCl_4 in acetonitrile (eq 24).[24]

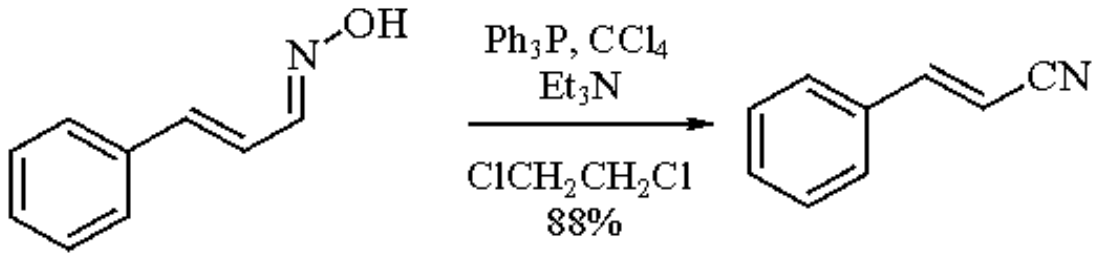

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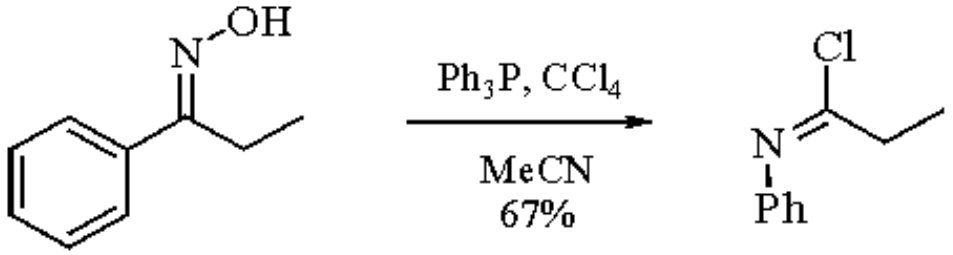

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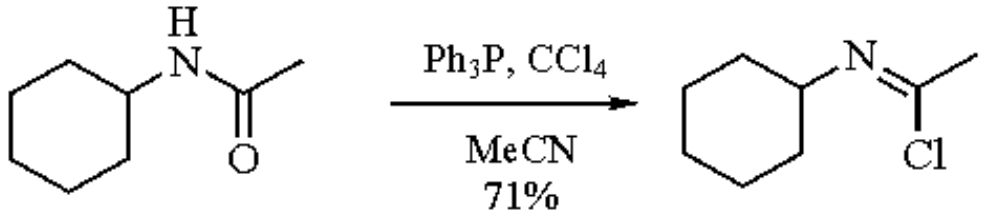

(24)

N,*N*,*N*´-Trisubstituted ureas afford chloroformamidine derivatives (eq 25),[25] while *N*,*N*´-disubstituted ureas and thioureas produce carbodiimides (eq 26).[26] When carbamoyl chlorides are treated with the reagent in MeCN, they are converted into isocyanates (eq 27).[27] Dehydration of *N*-substituted formamides provides access to isocyanides (eq 28).[28]

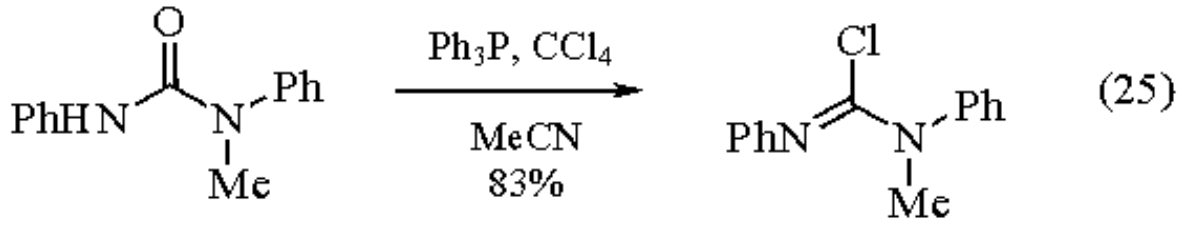

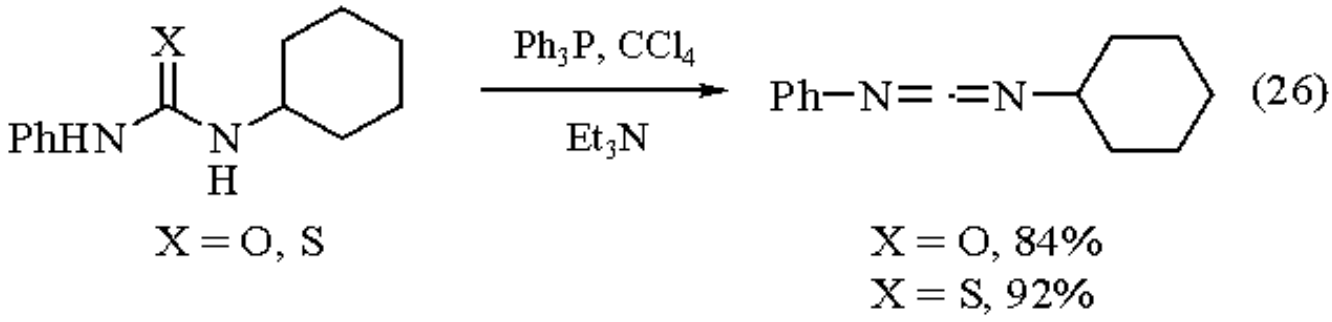

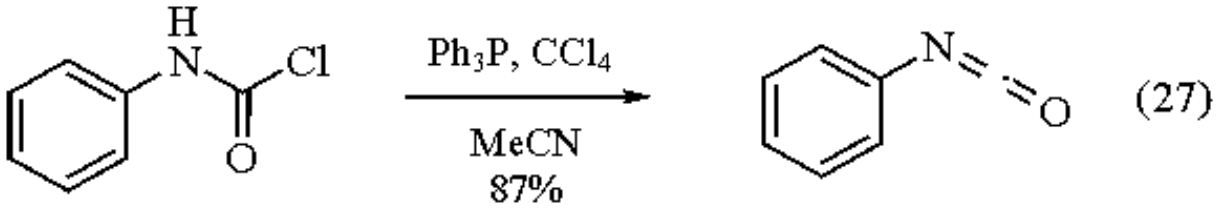

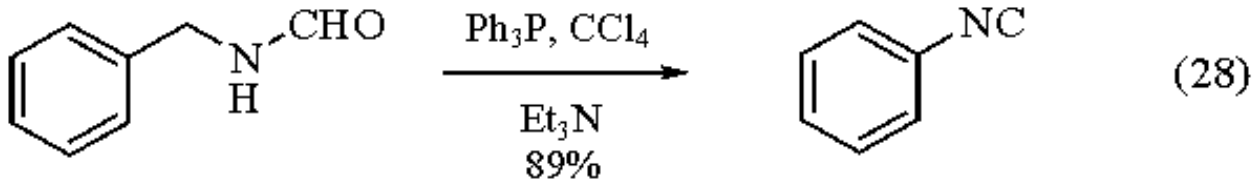

Amide Formation.

The synthesis of an amide can be accomplished by initial reaction of an acid with Ph_3P-CCl_4 and then reaction of the intermediate with 2 equiv of the appropriate amine. A tertiary amine, such as ***Diisopropylethylamine***, can be employed as the HCl scavenger in cases where one would not want to waste any of a potentially valuable amine.[29] This method has been used in the construction of an amide in the synthesis of the skeleton of the lycorine alkaloids (eq 29).[30]

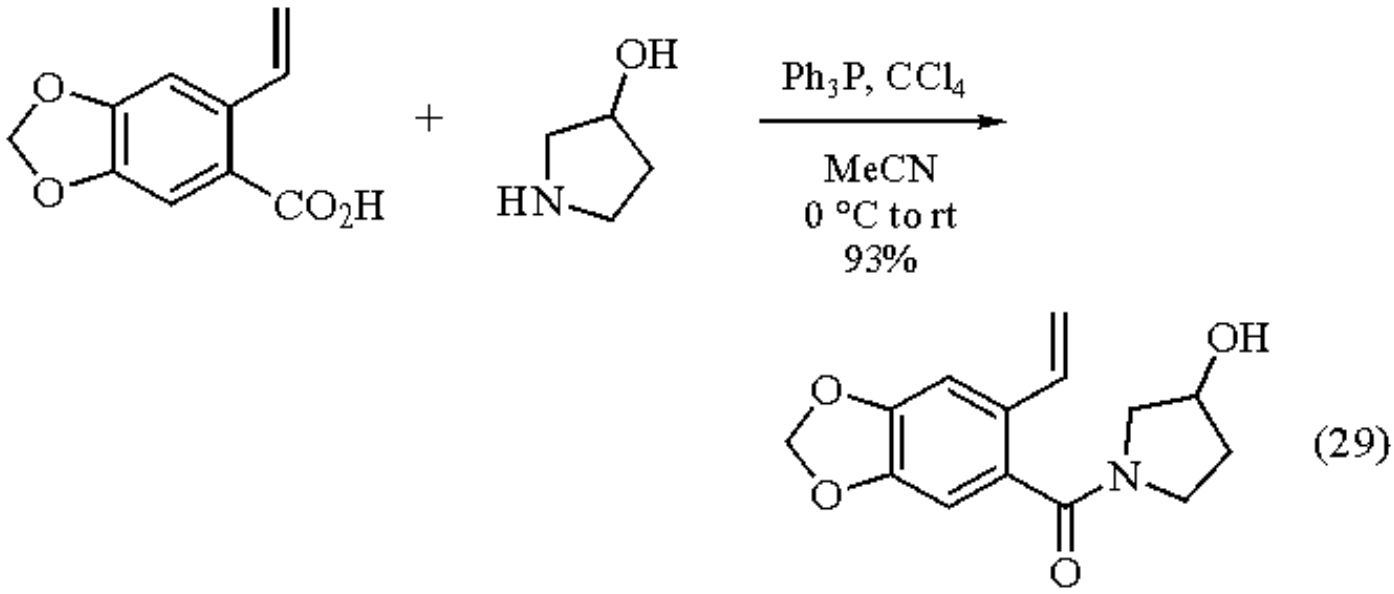

The method is effective for peptide coupling in that the yields are typically good; however, the reaction is often accompanied by racemization of the product.[31] The racemization problem can be suppressed, but this involves a change in the phosphine employed[32] or

slightly modified reaction conditions. These modified conditions have been used successfully in the construction of a hexapeptide without racemization (eq 30).[33]

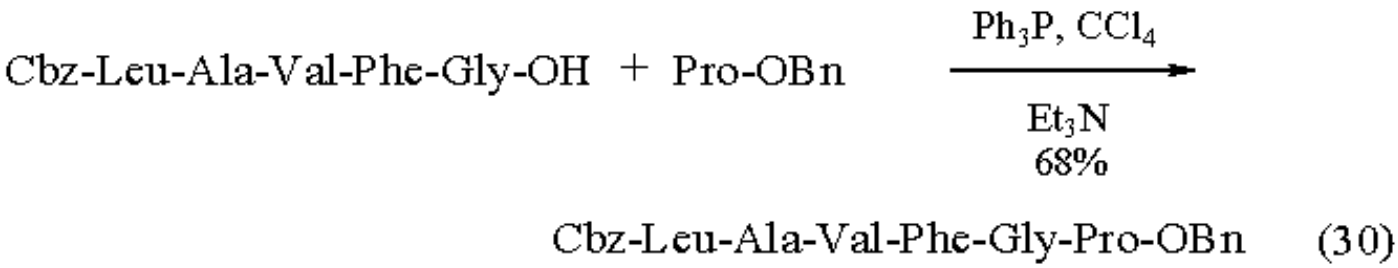

If amino alcohols, amino thiols, or diamines are used, the intermediate amides cyclodehydrate under the reaction conditions to form Δ^2-oxazolines (eq 31), Δ^2-oxazines, Δ^2-thiazolines, or Δ^2-imidazolines.[33] The reaction requires the use of 3 equiv of the Ph_3P-CCl_4 reagent. The reaction is reported to fail if a commercial sample of the polymer-supported phosphine is used instead of triphenylphosphine.

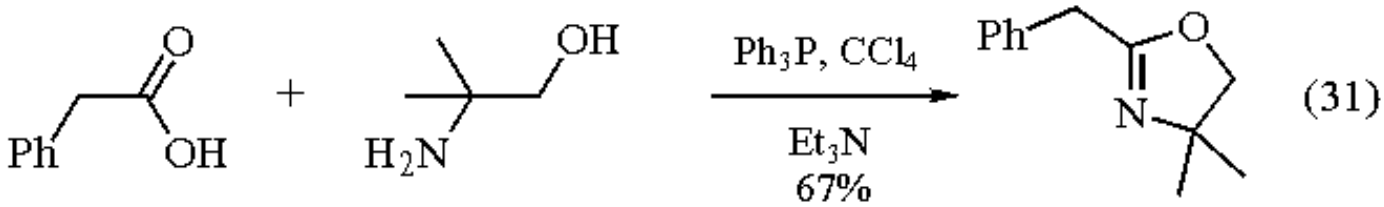

1,1-Dichloroalkenes and Vinyl Chlorides.

The reaction of aldehydes produces a mixture of the 1,1-dichloroalkene and the dichloromethylene derivatives. These are the result of reaction of the in situ generated ***Dichloromethylenetriphenylphosphorane*** and ***Triphenylphosphine Dichloride***, respectively. Benzaldehyde (eq 32) produces a 1:1 mixture of the dichloroalkene and benzal chloride in 72% yield.[34]

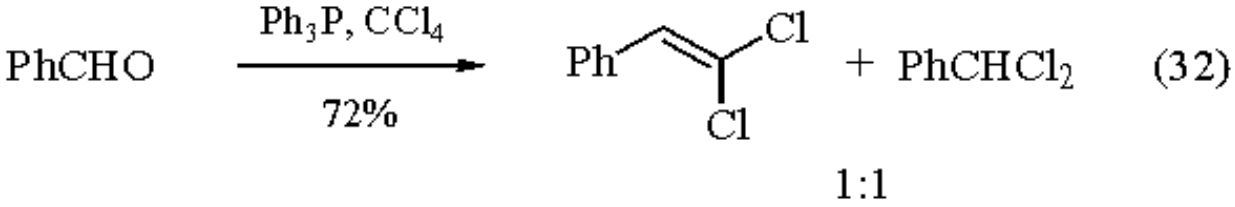

Ketones can also be used in this transformation, but sometimes enolizable ketones lead to the formation of the vinyl chloride derived from the enol. This is usually more of a problem for six-membered ring ketones than for five-membered ring ketones. Cyclopentanone yields predominantly the 1,1-dichloroalkene (eq 33), while cyclohexanone provides mainly the vinyl chloride (eq 34).[35]

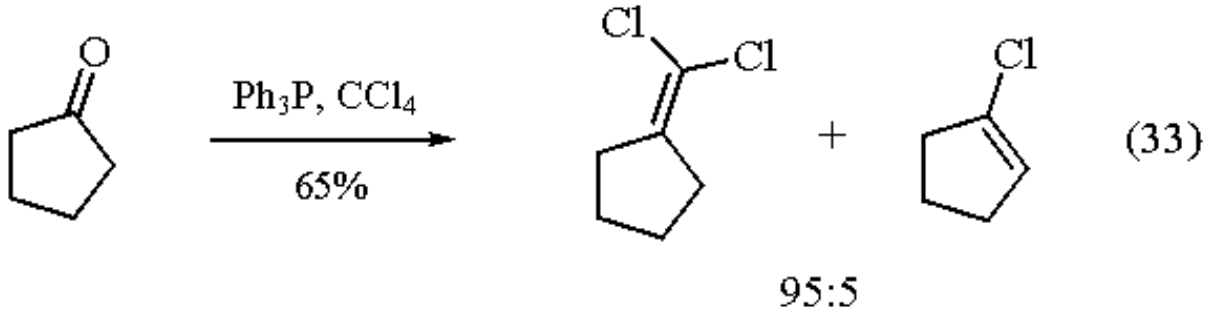

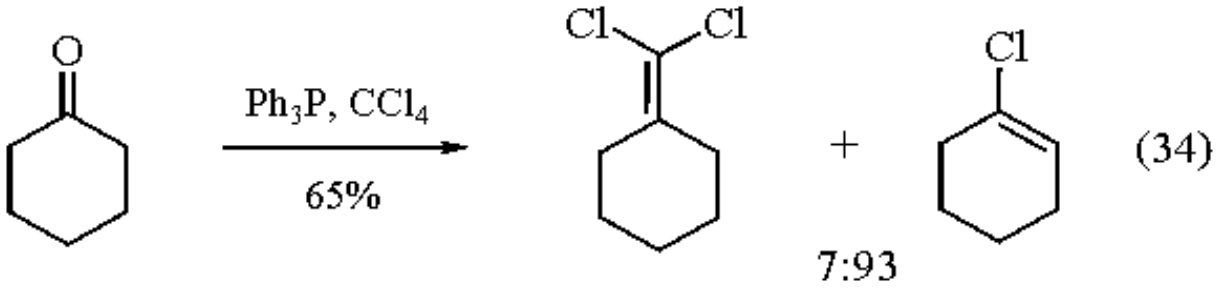

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Triphenylphosphine Dibromide[1]

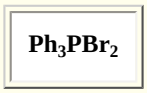

[1034-39-5] · $C_{15}H_{18}Br_2P$ · Triphenylphosphine Dibromide · (MW 389.10)

(bromination of alcohols,[3,4] phenols,[22] and enols;[3] cleavage of ethers[23,32,33] and acetals[25] to alkyl bromides; cyclization of amino alcohols[34,35] to cyclic amines; conversion of carboxylic acid derivatives into acyl bromides;[36,37] bromination[39] or dehydration[38] of carboxamide groups)

Alternate Names: bromotriphenylphosphonium bromide; dibromotriphenylphosphorane.

Physical Data: adduct:[2] colorless crystalline solid; mp 235 °C (dec). Ph_3P: mp 80.5 °C; bp 377 °C (in inert gas); *d*254 1.194 g cm^{-3}; *n*80D 1.6358. Br_2: mp -7.2 °C; bp 59.5 °C; *d*254 3.12 g cm^{-3}.

Solubility: adduct: sol CH_2Cl_2, MeCN, PhCN, DMF; less sol PhH, PhCl. Ph_3P: sol ether, PhH, $CHCl_3$, AcOH; less sol alcohol; pract. insol. H_2O. Br_2: sol H_2O (3.58 g/100 mL); very sol. alcohol, ether, $CHCl_3$, CCl_4, CS_2.

Form Supplied in: adduct: hygroscopic solid; commercially available; purity 95-96%. Both parent compounds, Ph_3P and Br_2, are widely available. Ph_3P: odorless platelets or prisms; purity ~99%; typical impurity Ph_3PO ~1%. Br_2: dark reddish liquid, volatile, with suffocating odor; vaporizes rapidly at rt; purity >99.5%.

Analysis of Reagent Purity: adduct: ^{31}P NMR (CH_2Cl_2) +49 ppm (ionic form);[2] Raman (solid phase) 239 cm^{-1} (P-Br). Typical impurities, Ph_3P and Ph_3PO: ^{31}P NMR (various solvents) -5 to -8 ppm and +25 to +29 ppm, respectively.

Preparative Methods: several preparations are described,[2,23b,32b] but in most cases the hygroscopic reagent is prepared just before use by addition of ***Bromine*** to ***Triphenylphosphine*** in a dry solvent with cooling.

Handling, Storage, and Precautions: adduct: corrosive; very hygroscopic; moisture sensitive; incompatible with strong oxidizing agents and strong bases; may decompose on exposure to moist air or water; do not get in eyes, on skin, or on clothing; keep containers tightly closed and store in a cool dry place; these reagents should be handled in a fume hood.

Introduction.

The Ph_3PBr_2 adduct was first used in synthesis in 1959[3] for the preparation of alkyl and acyl bromides from alcohols and carboxylic acids, and for the dehydration of amides and oximes to nitriles. Since then it has been widely employed as a versatile reagent for a number of synthetic reactions.

Conversion of Alcohols into Alkyl Bromides.

It has been established that Ph_3PX_2 reagents present considerable advantages over phosphorus halides (i.e. PX_3, PX_5) for which only two replaceable groups would be necessary and desirable.[4a] The mechanism[4b] of the reaction of Ph_3PBr_2 with an alcohol involves initial rapid formation of an alkyloxyphosphonium bromide,[4,5,7a] which then collapses slowly to the phosphine oxide and an alkyl bromide (eq 1). S_N2 substitution and high yields are generally observed with primary and secondary alcohols.[3,4a] This reagent shows little tendency to induce either carbonium ion rearrangement in the carbon skeleton or elimination reactions; this is illustrated by the preparation of neopentyl bromide from neopentyl alcohol (eq 2)[4a] and in the steroid field,[6] in which cholesterol and 3β-cholestanol give respectively 3β-bromocholest-5-ene and 3α-bromocholestane in yields of about 80%. Inversion of configuration is found in the S_N2 reactions of (+)-*endo*-norbornanol (eq 3)[7a,8] and 7-norbornanol. However, a similar reaction with (-)-*endo*-norbornanol leads mainly to racemic bromide via a nonclassical norbornyl cation intermediate.[7b] Likewise, little rearrangement is observed in the bromination of 3-methyl-2-butanol (eq 4).[9] Greater amounts of rearranged product are formed in the same reaction with Ph_3PCNBr (3%), ***Bromine-Triphenyl Phosphite*** (55.6%), or ***Triphenylphosphine-Carbon Tetrabromide*** (6-10%).

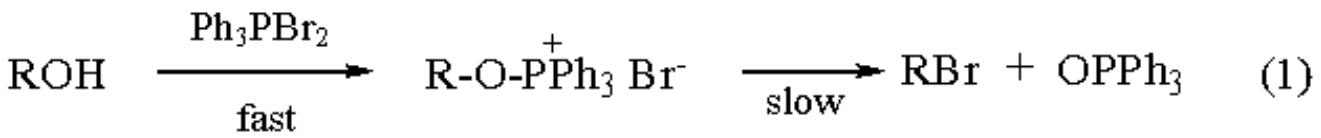

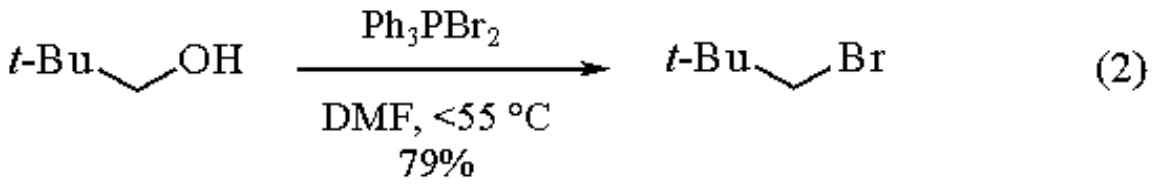

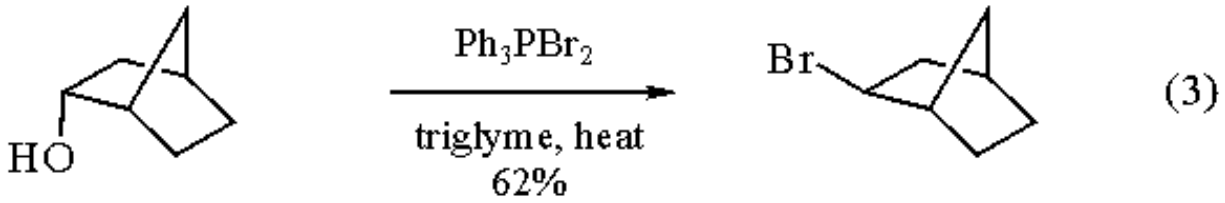

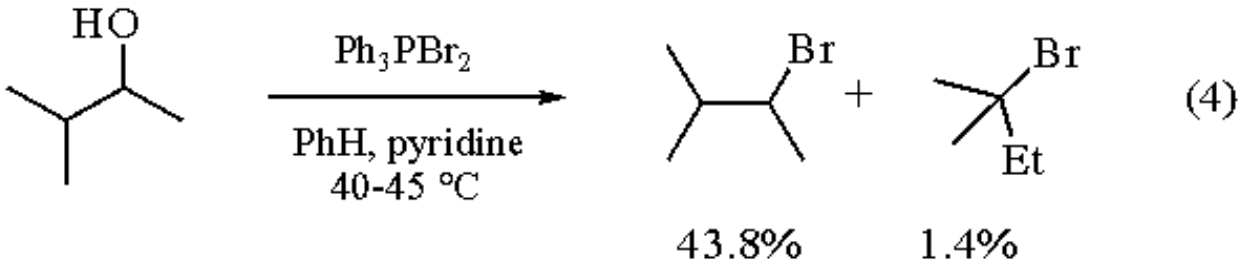

Ph_3PBr_2 can be used with sensitive substrates which incorporate cyclopropyl rings (e.g. cyclopropyl carbinol[11,12]) or unsaturation[10,13] (e.g. cinnamyl alcohol and alkynediols) with little if any side reactions. Cyclopropyl carbinols are transformed into bromides in good yield without ring opening or ring expansion, with the formation of only trace amounts of homoallylic bromides; no bromocyclobutane derivatives are detected (eq 5). Ph_3PBr_2 also proves superior to ***Phosphorus(III) Bromide*** for the bromination of alkynediols to dibromoalkynes (eq 6).[13]

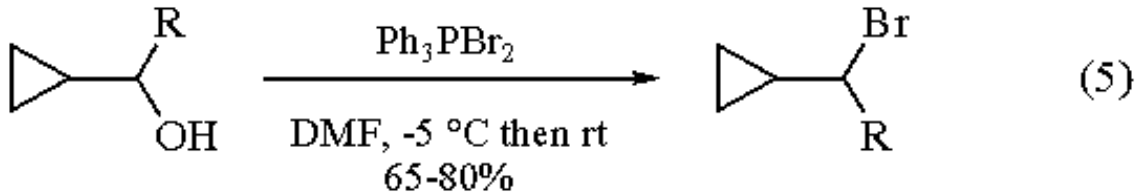

R = H, Me, Et, Pr, Bu, *i*-Pr, *t*-Bu

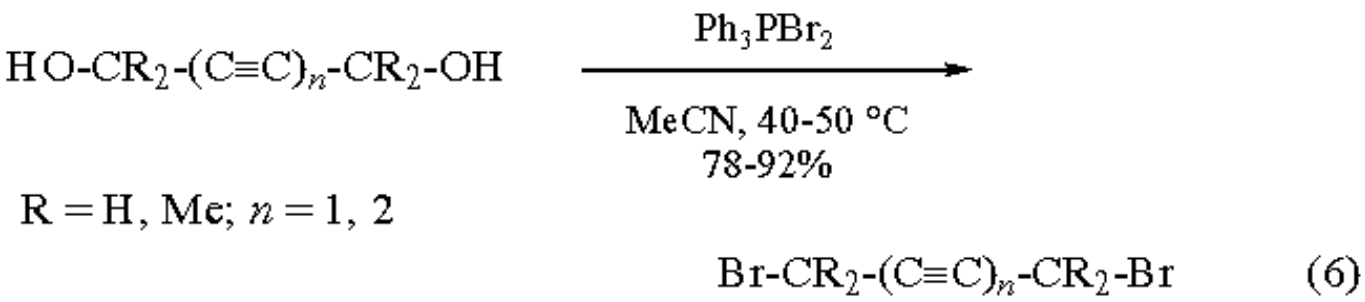

Ph_3PBr_2 provides comparable yields to Ph_3P/CBr_4 in the bromination of diethyl 1-hydroxyalkylphosphonates.[14] A number of other primary,[15] secondary,[11-14] and even tertiary alcohols are brominated with Ph_3PBr_2, but with preponderant elimination[4a,6,16] in the latter case. A polymer-supported Ph_3PBr_2 reagent[17] has been successfully applied to alcohol bromination in refluxing $CHCl_3$; product isolation is facilited by the ready separation of supported from the nonsupported species. However, note that a polymer-supported Ph_3P/CBr_4 reagent leads to better bromination results than the Ph_3PBr_2 system in a number of cases.

Similar mono- and dibrominations have also been achieved in the carbohydrate field (eq 7).[18] Configurational inversion at chiral centers is

observed throughout. Ph_3PBr_2/***Imidazole*** (ImH) or Ph_3P/2,4,5-tribromoimidazole/ImH combinations in refluxing PhMe or in PhMe-pyridine mixtures are preferred in some cases. In the nucleoside field,[19] double activation is achieved with Ph_3PBr_2 in pyridine, leading both to bromination of the 5´-position of the sugar moiety and to substitution on the C-6 position of the adenine part (eq 8).[19b]

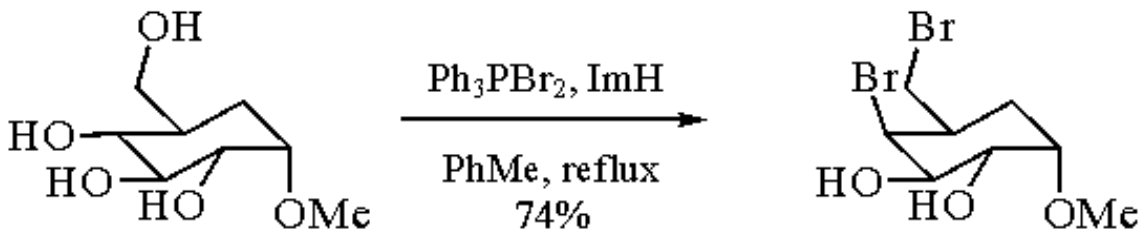

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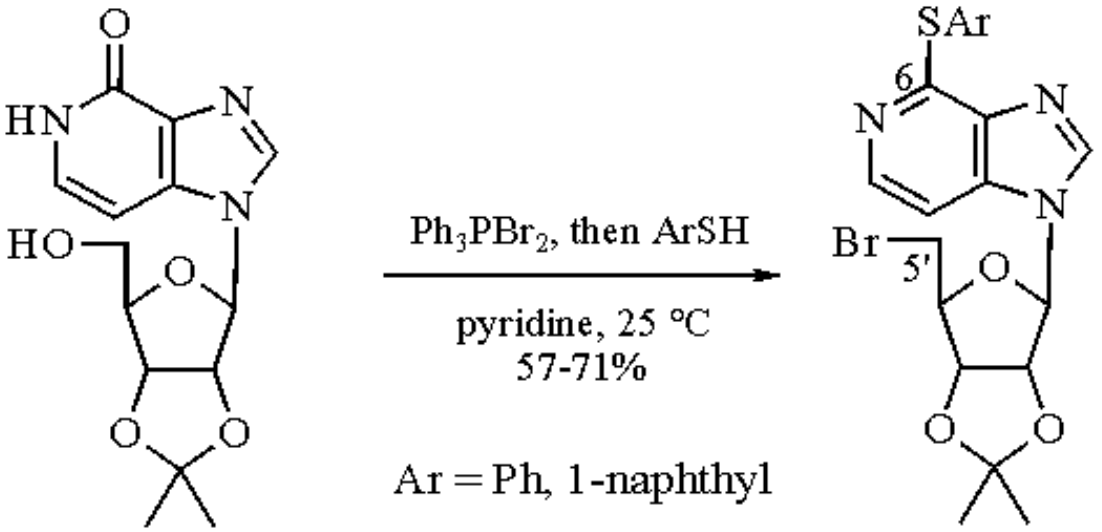

(8)

A variety of solvents such as CCl_4, PhH, triglyme, $CHCl_3$, PhMe, pyridine, NMP, MeCN, DMF, and mixtures of these have been employed in these bromination reactions, depending on substrate solubility. Both *O*- and *C*-formylations are encountered in some cases when DMF is the solvent. Ph_3PBr_2 and both Ph_3PX_2 analogs (X = Cl, I) can react with DMF according to the sequence in eq 9.[20] The intermediate alkoxyimonium bromide (**3**) affords either the expected bromide by heating, or the formyl ester by hydrolytic workup with secondary[20] or tertiary[16] alcohols (e.g. eq 10). Vilsmeier-type formylation reactions on nucleophilic carbon atoms can also take place, as developed early[38a] and then encountered later as a side reaction in the steroid field.[21] Such *O*-formylation of secondary alcohols is interestingly used in the differentiation of diols, leading to a new synthesis of bromo formates (eq 10).[20b] Under mild conditions, primary alcohols still afford bromides whereas secondary ones are converted almost exclusively to the corresponding formate esters.

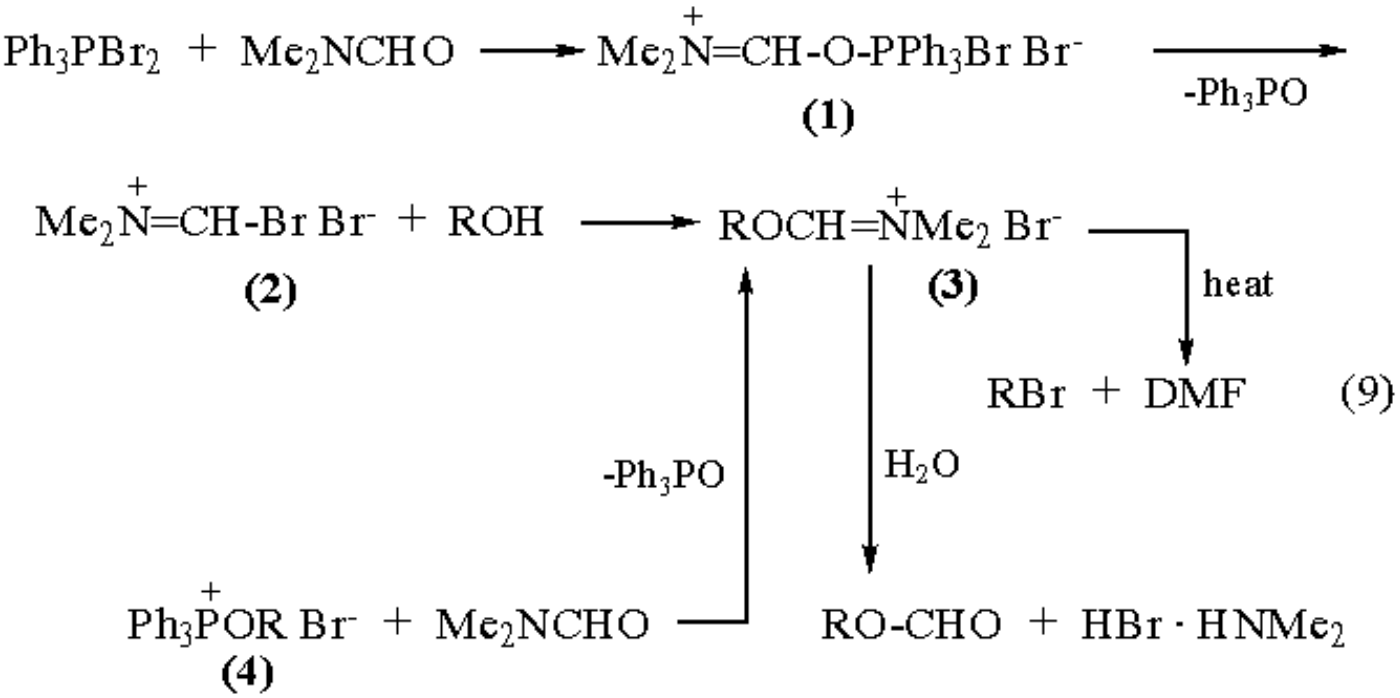

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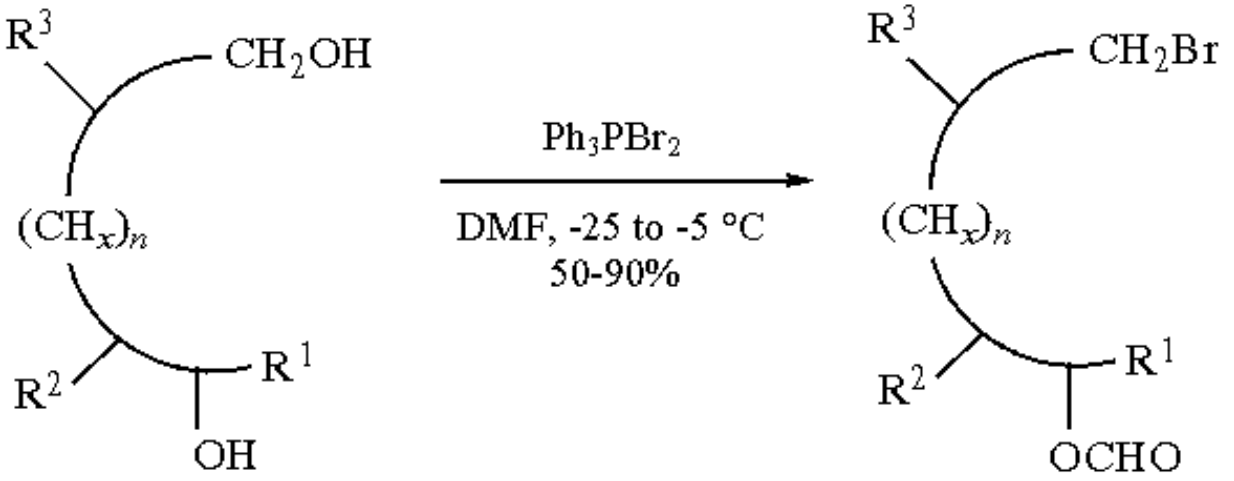

(10)

$x = 1, 2; R^1 \neq H; R^2, R^3 = H, Me, (CH_x)_n$

Synthesis of Aryl Bromides from Phenols.

Already developed in the pioneering work,[4a] the preparation of aryl bromides from phenols with Ph_3PBr_2 was later extended to a number of substrates (eq 11).[22]

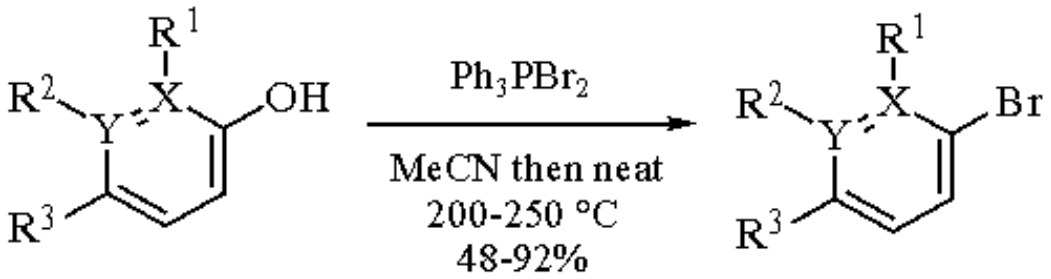

(11)

$X, Y = C, N; R^2 = H; R^3 = H, Cl, NO_2, MeO;$

$R^1 + R^2 = Ph; 2,3\text{-pyridyl}; R^2 + R^3 = Ph, 3,4\text{-phenol}$

Alkyl Bromides from Ethers and Acetals.

Ph_3PBr_2 cleaves dialkyl ethers to give the two alkyl bromides under essentially neutral conditions.[23] This reaction offers obvious advantages as it avoids both the strongly acidic and basic media which are usually employed for ether cleavage. Brominations are generally conducted at reflux in high boiling solvents such as PhCl, PhCN, DMF, or NMP. Primary and secondary alkyl groups provide good yields of bromides without rearrangement in PhCl or PhCN, at 60 to 120 °C,[23a,b] as illustrated in eq 12.[23c] Phenyl alkyl ethers initially afford aryloxyphosphonium bromides which collapse to bromobenzene only by heating at higher temperature (>230 °C as seen before). Alkyl *t*-butyl ethers are cleaved more easily in DMF[23b] or in MeCN,[24] usually between 60 and 110 °C; the *t*-butyl group is converted into isobutene in this process. In a related reaction, endoxides are transformed into arenes[28] by Ph_3PBr_2 treatment in PhCl. Aromatization takes place via HBr elimination from the initially formed dibromide.

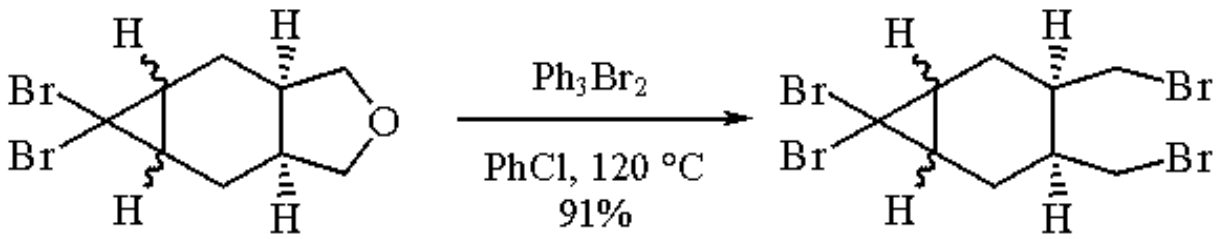

(12)

Direct conversion of tetrahydropyranyl (THP)[25] and tetrahydrofuranyl ethers[26] (THF) to bromides can be achieved by Ph_3PBr_2 treatment under milder conditions (eq 13).[25a] THP and THF ethers afford good yields of acyclic, saturated, and unsaturated,[25c] primary, secondary,

and even tertiary alkyl bromides; under the same conditions, cyclohexyl THF ethers provide mainly cyclohexene derivatives. In view of the fact that the preceding reaction of THP ethers can be stopped (at low temperature) at the stage of either the alkoxyphosphonium (see eq 1) or the pentacovalent $ROPPh_3Br$ intermediate, hydrolysis of the reaction mixture at -50 °C, leads to the corresponding alcohols in good yield (74-97%) (eq 14).[29] The method is efficient for the deprotection of secondary and tertiary THP ethers, as well as for acyclic acetal ether, dialkyl acetals, and *O*-glucosides. Acetal functions can be removed with retention of stereochemistry, as illustrated in the conversion of (-)-menthol THP ether into (-)-menthol with full recovery of the optical activity. This procedure is not applicable to primary THP ethers, where the corresponding bromides are formed under these conditions.

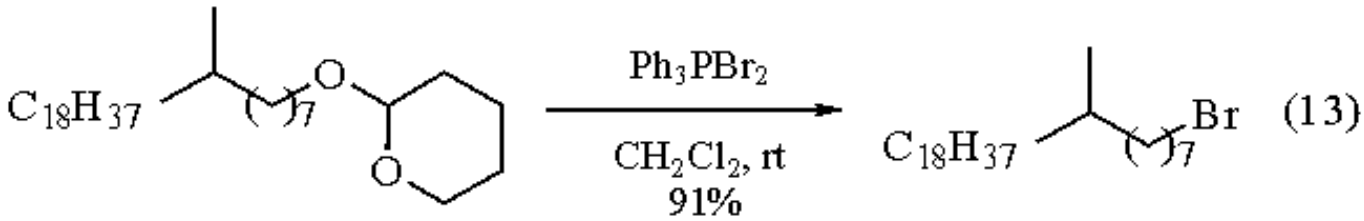

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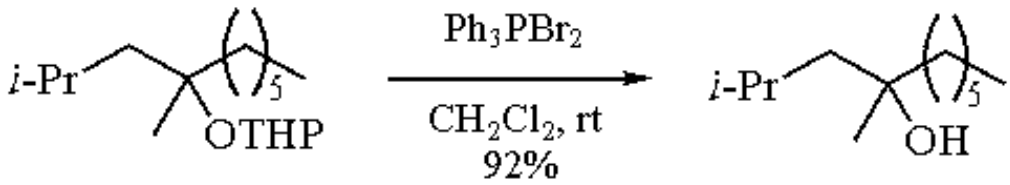

(14)

Reaction of hindered trialkylsilyl ethers with Ph_3PBr_2 in CH_2Cl_2 at rt affords primary and secondary alkyl bromides in excellent yield (70-94%); the reaction is valuable in the β-lactam field.[27a] The reaction rate is increased by addition of a catalytic amount of ***Zinc Bromide***. Silylated enol ethers, such as trimethylsilyl(1-phenylvinyloxy)silane, provide vinyl bromides such as α-bromostyrene with Ph_3PBr_2 in refluxing CCl_4.[27b]

α-Alkynyl Ketones and β-Bromo-α-Vinyl Ketones from β-Diketones.

The previously described bromination of alcohols can be applied to the enol form of β-diketones. The first attempts in this field were conducted with the Ph_3PBr_2/***Triethylamine*** system on dibenzoylmethane, leading to phenylethynyl phenyl ketone.[30a] Elimination at the oxyphosphonium stage or HBr elimination from the initially generated vinyl bromide is probably involved in this reaction. Analogously, reaction of unsymmetrical β-diketones[30b] with excess Ph_3PBr_2/Et_3N proceeds with the formation of 3:1 mixtures of α,β-ynones in good overall yield (eq 15). Ethynyltriphenylphosphonium bromides are similarly obtained[30c] starting from (benzoylmethylene)- and (carbamoylmethylene)triphenylphosphoranes.

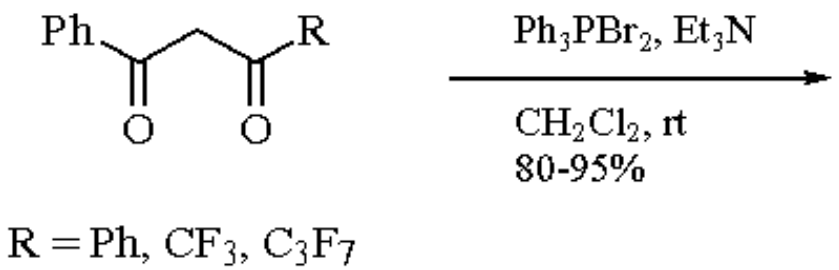

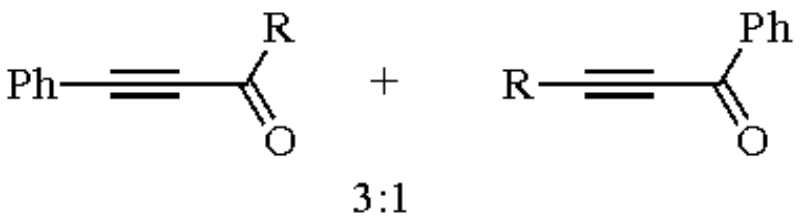

(15)

Similar treatment of unconjugated β-diketones[31] in PhH or MeCN as solvent leads to β-bromo-α,β-unsaturated ketones with superior results relative to the same transformation with PBr_3 as the brominating agent (eq 16).[31c] The reaction of acyclic 2,4-pentanedione with Ph_3PBr_2/Et_3N in PhH-MeCN[31c] or in CH_2Cl_2,[31d] but in the absence of Et_3N, appears not to be totally stereoselective, since a mixture of the geometrically isomeric bromo enones is produced, with 88% (*E*/*Z* ~ 87/13) and 85% (*E*/*Z* ~ 93/7) yields, respectively.

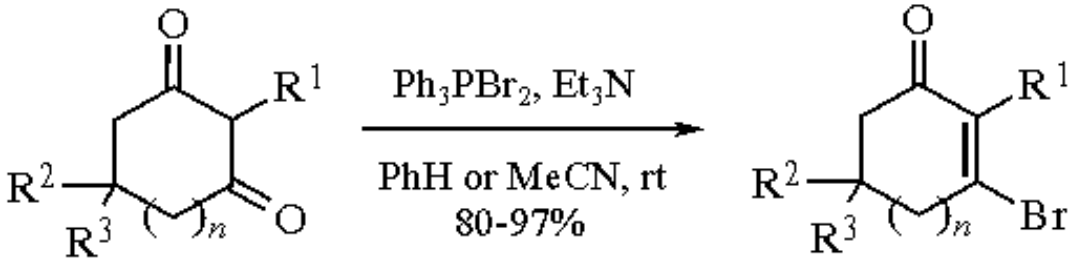

(16)

R^1 = H, Me, allyl, 2-cyanoethyl

n = 0, 1; R^2 = H, Me; R^3 = H, Me

Epoxide Opening to Vicinal Dibromides or Bromohydrins.

Epoxide ring opening with Ph_3PBr_2[32a] takes place in MeCN or PhH at 20-50 °C, affording vicinal dibromides (32-74%); *cis-trans* isomer mixtures are obtained in the case of cycloalkene epoxides. This reaction involves initial cleavage of the epoxide C-O bond at the most substituted epoxide carbon; bromoalkoxyphosphonium salts are thus formed, and these undergo subsequent substitution to give dibromides and Ph_3PO. In further studies,[32b] reaction of *cis*-epoxides in PhH produced *erythro*-dibromides exclusively (eq 17); *trans*-epoxides exhibit less specificity, leading to a mixture of *threo*- and *erythro*-dibromides. Use of a more polar solvent such as CH_2Cl_2 or MeCN, instead of PhH, with *cis*-epoxides provides *erythro-threo* mixtures (60-40 to 50-50). By reacting epoxides first with HCl and then with Ph_3PBr_2, it is possible to obtain vicinal bromochlorides stereospecifically that are also products of two S_N2 displacements.

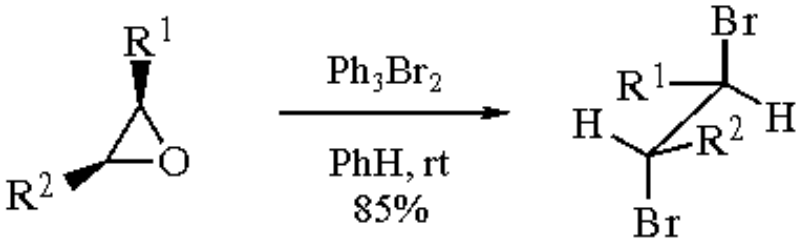

(17)

R^1 = nonyl; R^2 = Bu

The reaction can also be carried out so as to give bromohydrins. In the steroid field[33a] with conformationally rigid epoxides, oxirane cleavage appears to be quite stereoselective and leads only to the bromohydrin resulting from the usual *anti* opening of the ring in high yield (90-97%). Less hindered and rigid substrates afford regioisomeric mixtures of cyclic *trans*-bromohydrins. Equivalent results[33b] are obtained, in the steroid series, by use of polymeric Ph_3PBr_2 for the transformation of epoxides to bromohydrins under mild nonacidic conditions; oxirane ring opening remains regio- and stereoselective.

Cyclization of β- and γ-Amino Alcohols to Aziridines and Azetidines.

β-Amino alcohols undergo cyclization upon Ph_3PBr_2/Et_3N treatment,[34] providing the corresponding aziridines along with substituted piperazines as dimeric byproducts (eq 18). Walden inversion is observed in the ring closure of both *threo*- and *erythro*-ephedrine and this supports the postulated 1,2-*trans*-elimination. Application of this procedure to the synthesis of 1-monosubstituted aziridines is unsuccessful, giving only the piperazine byproduct. *N*-Aryl γ-amino alcohols are cyclized to azetidines by Ph_3PBr_2/Et_3N in MeCN (eq 19).[35a] Under these conditions, some starting material is recovered unchanged along with mixed tetrahydroquinolines as side products and the expected *N*-arylazetidine. Comparable results are obtained (45-65%)[35b] with some other *N*-protecting groups.

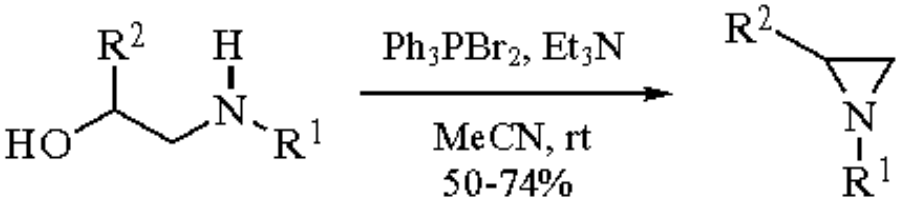

(18)

R^1 = Bu, *t*-Bu, cyclohexyl, benzyl; R^2 = Me, Ph

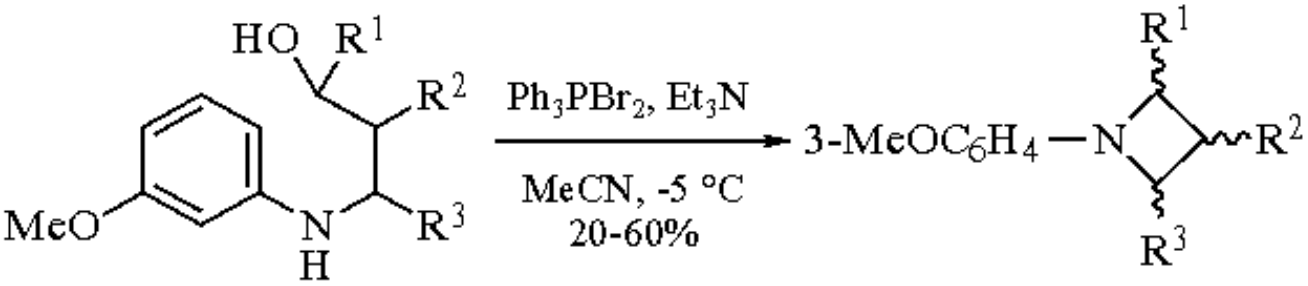

(19)

R^1 = Me, Ph; R^2 = H, Me; R^3 = H, Me, Ph

Acyl Bromides from Carboxylic Acids, Anhydrides, and Esters.

Carboxylic acid bromides are prepared by reaction of Ph_3PBr_2 with various carboxylic acids and anhydrides in boiling PhCl.[36a] Milder conditions and better yields were later obtained in a comparative study[36b] by using CH_2Cl_2 at rt (eq 20). Further improvements are observed through the use of the corresponding trimethylsilyl esters; acyl bromides are thus obtained under mild and neutral conditions, allowing reactions with sensitive acid substrates without side reactions (eq 20). This transformation is also applicable to generate the acyl bromides of more hindered trialkylsilyl esters such as the TBDMS, TIPS, and TBDPS carboxylates; in CH_2Cl_2, the reaction rate increases in the presence of a catalytic amount of $ZnBr_2$.[27a]

$$RCO_2Z \xrightarrow{Ph_3PBr_2} RCOBr \qquad (20)$$

Z = H; PhCl, reflux	50-80%
Z = H; CH_2Cl_2, rt	64-90%
Z = TMS; CH_2Cl_2, rt	70-90%

R = Ph, 2-ClC_6H_4, 4-ClC_6H_4, Et, $PhCH_2CH_2$, PhCH=CH, $PhCH(CO_2Z)$, MeCH=CH

Direct reaction of less reactive alkyl esters and lactones[37] with Ph_3PBr_2 affords both acyl and alkyl bromides. This reaction is achieved at MeCN reflux[37a-c] for α-halogenated esters such as CF_3CO_2R, but only at higher temperatures and with longer reaction times for unhalogenated ones. The reaction of an ester with Ph_3PBr_2 presumably forms an oxonium salt, which then undergoes cleavage through reaction with bromide ion. Prolonged heating (80-110 °C) of lactones with Ph_3PBr_2 gives the expected acyl alkyl dibromides, but in low yield (<=50%) due to a concomitant degradation.[37d]

Dehydration of Ureas and Amides to Carbodiimides, Nitriles, Isocyanides, and Ketenimines.

Dehydration of *N,N´*-disubstituted ureas by heating with Ph_3PBr_2/Et_3N in PhH or PhCl at 70-80 °C affords carbodiimides[38a] in good yields. Subsequent improvements[38d] involving milder conditions provides access to certain unstable derivatives from *N,N´*-disubstituted ureas; this procedure compares favorably with previous ones and with another related approach using the ***Triphenylphosphine-Carbon Tetrachloride*** reagent system (eq 21). Reaction of *N,N´*-dialkylidene ureas with Ph_3PBr_2 in PhH leads to α-haloalkyl carbodiimides.[38e]

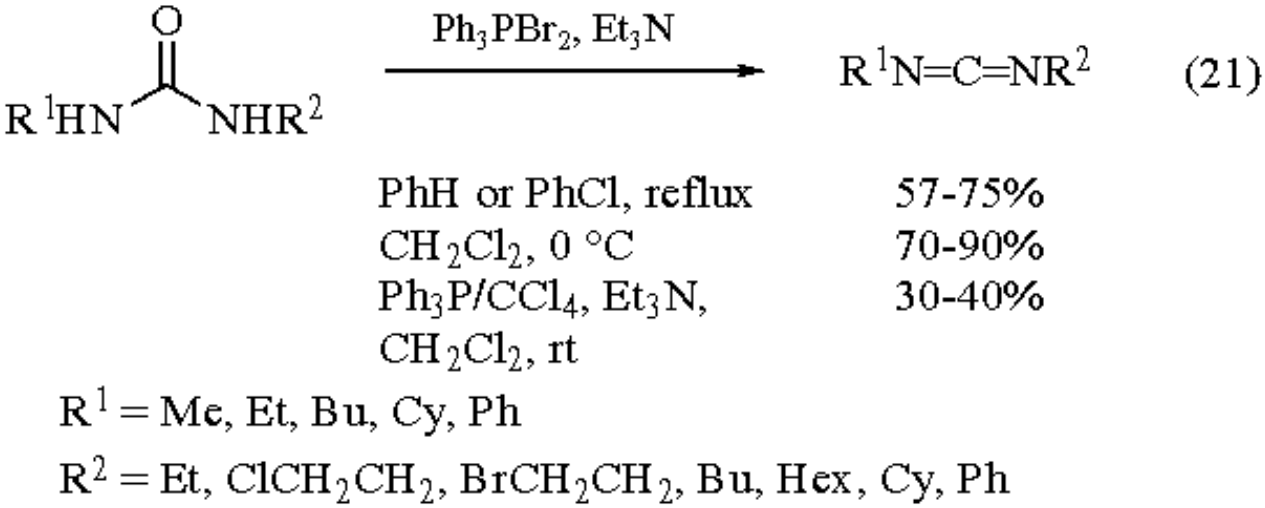

By the same Ph_3PBr_2/Et_3N procedure carried out in refluxing PhH, disubstituted cyanamides such as Me_2NCN are obtained from the *N*,*N*-disubstituted urea Me_2NCONH_2 (67%); similarly, isocyanides result from monosubstituted formamides (56-73%),[38a,40b] and nitriles from primary amides and oximes (58-68%).[3] Via the same route, ketenimines ($R^1R^2C{=}C{=}NR^3$) are prepared[38a,40b] in CH_2Cl_2 at reflux by dehydration of secondary amides having a C-H bond adjacent to the carbonyl function (45-93%). Application of this procedure to sulfimides gives highly reactive ketenimines, which are used for further reactions without isolation; [2 + 2] cycloaddition of such species with Schiff bases provides, in good yield, *N*-(tosyl)azetidin-2-imines related to β-lactam derivatives (eq 22).[38b] The diphosphorylated ketenimine $[(EtO)_2(O)P]_2C{=}C{=}NPh$ is obtained analogously in 87% yield with Ph_3PBr_2/Et_3N from the α,α-diphosphorylated acetanilide.[38c]

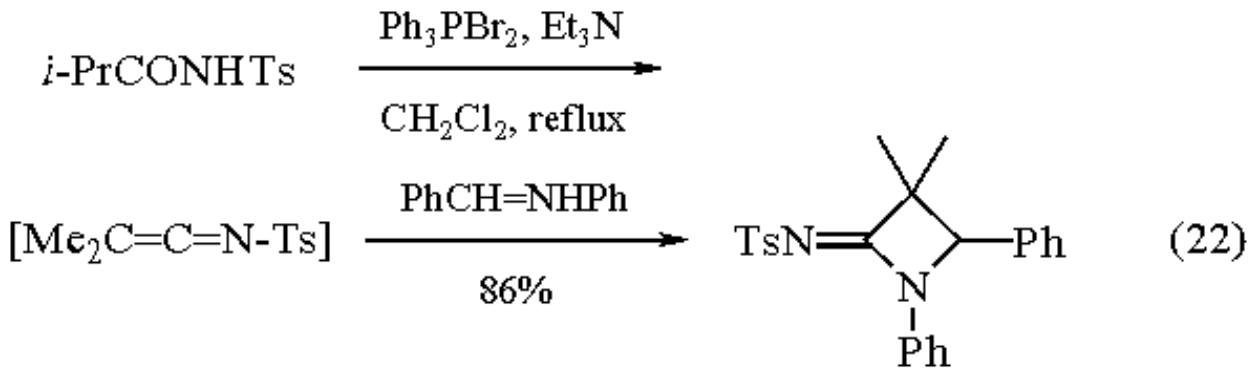

Imidoyl Bromides from Secondary Amides.

In the case of the secondary diarylamide benzanilide, reaction with Ph_3PBr_2/Et_3N in refluxing PhH provides *N*-phenylbenzimidoyl bromide in 65% yield, whereas a 70% yield is attained with the Ph_3P/CBr_4 reagent system.[39] The closely related *N*-methylbenzamide affords a dimeric compound[40b] with Ph_3PBr_2 in boiling CH_2Cl_2 by intermolecular *N*-imidoylation (see below for a similar intramolecular process) between generated imidoyl bromide or oxyphosphonium species and the starting carboxamide. Cyclodehydration of secondary carboxylic diamides with Ph_3PBr_2/Et_3N affords intramolecular *O*-imidoylation products with a benzoxadiazepine structure.[40] Without Et_3N, intramolecular *N*-imidoylation products with an o-imino lactam structure are obtained; *O*-imidoylated products rearrange to *N*-analogs under acidic conditions.

Iminophosphoranes from Amines, Hydrazines, and Related Derivatives.

Compounds containing a P=N bond, such as iminophosphoranes, are widely used as synthetic intermediates, especially in the heterocyclic field. Aromatic primary amines are generally transformed into iminotriphenylphosphoranes, and aliphatic amines into aminophosphonium bromides with Ph_3PBr_2/Et_3N in PhH, PhCl, CCl_4, or CH_2Cl_2 as solvent;[41a,b] more basic conditions are usually required to convert an alkylaminophosphonium salt into the corresponding iminophosphorane.[41b] As protected primary amines, these phosphinimines (iminophosphoranes) can then be subjected to monoalkylation, the Ph_3P protecting group being cleaved in a subsequent step to provide secondary amines (eq 23).[41a-c]

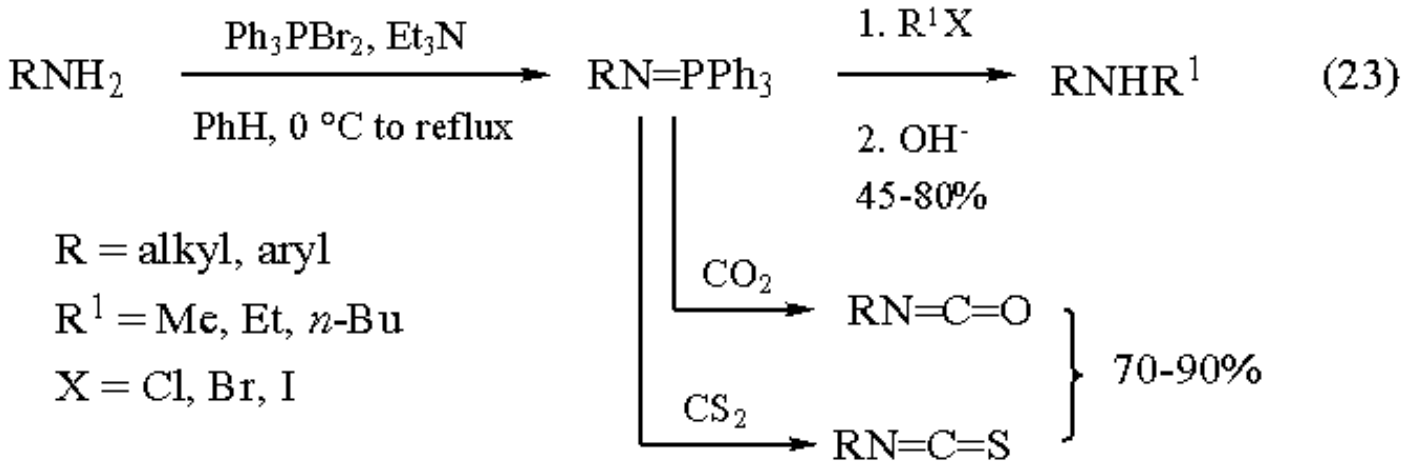

Some aliphatic and aromatic phosphinimines (prepared as above) undergo a Wittig-like condensation with CO_2 or CS_2, giving rise to isocyanates and isothiocyanates, respectively (eq 23).[41d] Dehydration reactions promoted by Ph_3PBr_2/Et_3N are used for intramolecular cyclizations involving an imide carbonyl group and an aromatic amine;[42] an aza-Wittig reaction of a phosphinimide intermediate is assumed to occur. Iminophosphoranes derived from hydrazines[43a] and acylhydrazines[43b,c] are also used as intermediates in heterocyclic synthesis. Reactions of metalated amines RNHMgX with Ph_3PBr_2 in PhH-ether can also provide aminophosphonium salts $Ph_3{+}PNHR\ Br^-$ in fair to good yields (33-74%).[43d]

Other Applications.

Reaction of Ph_3PBr_2 with benzoins in MeCN at rt provides diaryl α-diketones in excellent yields (75-98%).[44] Ph_3PBr_2 is used as a precursor in the synthesis of dialkoxytriphenylphosphoranes such as $(CF_3CH_2O)_2PPh_3$[45] and $(t\text{-}BuCH_2O)_2PPh_3$,[46] which are used as alkylating or acylating and cyclodehydration agents, respectively. Direct synthesis of β-lactams by [2 + 2] cycloaddition between carboxylic acids and imides, thus avoiding the use of acid halides, is achieved with Ph_3PBr_2 (40-55%).[47] Ph_3PBr_2, as a dehydrating agent, effects esterification reactions with tertiary alcohols,[48a] such as *t*-BuOH in PhH-HMPA, and with aromatic or aryl allylic acids and primary or secondary aliphatic alcohols in petroleum ether (27-85%).[48b]

Preparation of ***Bromotrimethylsilane*** in quantitative yield occurs by deoxygenation of $(Me_3Si)_2O$ with Ph_3PBr_2 (in 1,2-dichlorobenzene at reflux) in the presence of a catalytic amount of Zn; a one-pot preparation of pseudohalogenosilanes, in excellent yield (80-95%), can follow by subsequent addition of the appropriate salt XM in DMF (X = N_3, NCO, CN; M = K, Na,).[49] Treatment of Ph_3PBr_2 with ***Iodotrimethylsilane*** in CH_2Cl_2 at 0 °C yields Ph_3PI_2 (86%).[50] Reaction of Ph_3PBr_2/Et_3N with $EtO_2CCH_2CH{=}CHCO_2Et$ in PhH leads to the corresponding alkylidenephosphonium ylide in 80% yield.[51] Beckmann rearrangement of cycloalkanone oximes into lactams (74-81% yields) is effected by Ph_3PBr_2 in dry PhH at 50-60 °C.[52] The Ph_3PBr_2-Et_3N reagent system compares favorably with a number of other related phosphorus reagents for the rearrangement of *N*-allylamides into nitriles under mild conditions via 3-aza-Claisen reaction.[53]

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Triphenylphosphine Dichloride[1]

Ph_3PCl_2

[2526-64-9] · $C_{18}H_{15}Cl_2P$ · Triphenylphosphine Dichloride · (MW 333.20)

(conversion of alcohols,[6-10] phenols,[13] and enols[15] into alkyl chlorides; synthesis of *vic*-dichlorides[16] or chlorohydrins[17] from epoxides; conversion of carboxylic acids[11] and derivatives[20] into acyl chlorides; chlorination[23,24] or dehydration[11] of the CONH group; production of iminophosphoranes from amines and related compounds[27-29])

Alternate Names: dichlorotriphenylphosphorane; triphenyldichlorophosphorane; chlorotriphenylphosphonium chloride.

Physical Data: adduct:[2] white crystalline solid; mp 85-100 °C;[4] fp 20 °C. Ph_3P: mp 80.5 °C; bp 377 °C (in inert gas); *d*254 1.194 g mL^{-3}; *n*80D 1.6358. Cl_2: mp -101 °C; bp -34.6 °C; d^0 3.214 g L^{-1}.

Solubility: adduct: slightly sol ether, THF, PhMe; sol CCl_4, CH_2Cl_2, DMF, MeCN, pyridine; insol petroleum ether. Ph_3P: sol ether, PhH, $CHCl_3$, AcOH; less sol alcohol; pract insol H_2O. Cl_2: sol CCl_4, alcohol.

Form Supplied in: very hygroscopic solid; commercially available; purity ~80%; the remainder is 1,2-dichloroethane. The precursors Ph_3P and Cl_2 are both widely available. Ph_3P: odorless platelets or prisms; purity ~99%; typical impurity is Ph_3PO ~1%. Cl_2: greenish-yellow gas, with suffocating odor; purity &egt;99.3%; typical impurities are Br_2, C_2Cl_6, C_6Cl_6, and H_2O.

Analysis of Reagent Purity: adduct:[2,3] ^{31}P NMR (various solvents and solid state) +47 to +66 (ionic form), -6.5 to +8 (covalent form); Raman (solid state) ν(P-Cl) 593 cm^{-1} (ionic form), 274 cm^{-1} (covalent form). Typical impurities, Ph_3P and Ph_3PO: ^{31}P NMR (various solvents) -5 to -9 and +25 to +42, respectively.

Preparative Methods: various preparations have been described;[5] the adduct is usually prepared just before use by addition of a stoichiometric amount of ***Chlorine*** to ***Triphenylphosphine*** in a dry solvent.[2]

Handling, Storage, and Precautions: adduct: exceedingly sensitive to moisture; incompatible with strong oxidizing agents and strong bases; may decompose on exposure to moist air or water; do not get in eyes, on skin, or on clothing; keep containers closed and store in a cool dry place; these reagents should be handled in a fume hood.

Alkyl Chlorides from Alcohols and Ethers.

The reaction of Ph_3PCl_2 with alcohols provides an excellent synthetic method for the preparation of alkyl chlorides.[6] Mechanistic studies[6c] suggest the rapid initial formation of an alkyloxyphosphonium intermediate which then undergoes slow conversion into Ph_3PO and alkyl chloride (eq 1).[6b,c] It is assumed that chlorination takes place by an S_N2 reaction in most cases; thus, inversion of configuration is observed in the transformation of (-)-menthol to (+)-neomenthyl chloride (eq 2).[6a] As illustrated in eq 1, primary,[6b,7] secondary,[6] and even tertiary[6b] alcohols are chlorinated with Ph_3PCl_2, although reactions of tertiary alcohols are often accompanied by elimination (10%).

$$\mathrm{ROH} \xrightarrow[\text{fast}]{Ph_3PCl_2} \mathrm{R\overset{+}{O}PPh_3\ Cl^-} \xrightarrow[\text{slow}]{S_N2} \underset{90\text{-}99\%}{\mathrm{OPPh_3} + \mathrm{RCl}} \qquad (1)$$

R = Bu, neopentyl, Cy, *t*-Bu; DMF, reflux

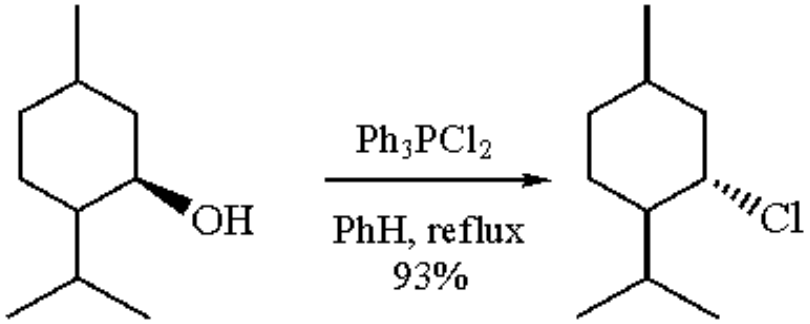

(2)

Ph_3PCl_2, generated in situ from Ph_3P and ***Hexachloroacetone*** (HCA) has proven to be a very efficient reagent for the regio- and stereoselective chlorination of allylic alcohols (eq 3),[8] and for the regioselective conversion of sterically hindered cyclopropylcarbinyl alcohols into cyclopropylcarbinyl chlorides (eq 4).[9] Chlorination of allylic alcohols occurs in less than 20 min, with total preservation of the double bond geometry and with >99% inversion of configuration for optically active alcohols. Primary and secondary alcohols give predominantly the unrearranged chlorides, while tertiary alcohols provide mostly rearranged products, with elimination to dienes becoming an important side reaction with more highly substituted systems. Similarly, cyclopropylcarbinyl alcohols yield the corresponding chlorides with no trace of homoallylic chlorides or cyclobutane derivatives.

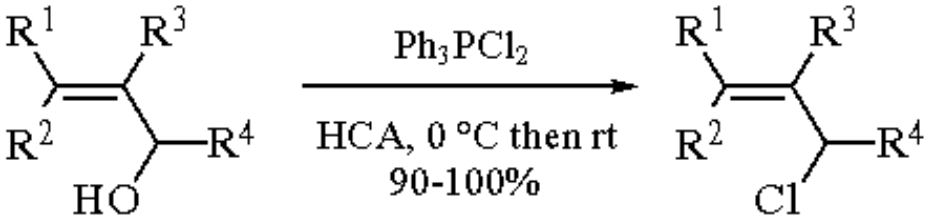

+ γ-isomer (3)

α-isomer

$R^1, R^2, R^3, R^4 = H, Me$ α:γ = 100:0 to 82:18

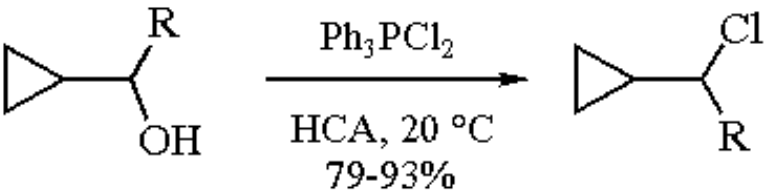

(4)

R = H, Me, Et, Pr, Bu, *i*-Pr, *t*-Bu

In the carbohydrate field, primary and secondary alcohols are chlorinated in excellent yield (80-95%) with the Ph_3PCl_2/ImH (***Imidazole***) reagent system in PhMe, MeCN, or a MeCN/pyridine mixture at rt to reflux temperature.[10] Polymer-supported Ph_3PCl_2,[11] prepared by the $Ph_3PO/COCl_2$ (***Phosgene***) procedure,[5b] has been used to transform $PhCH_2OH$ to $PhCH_2Cl$ (88%) in MeCN as a solvent; the simple workup consists of filtration of polymeric phosphine oxide and solvent removal. Several examples have been reported of the direct conversion of ethers into chlorides, as in eq 5.[7] Enol ethers such as acetophenone trimethylsilyl ether give α-chlorostyrene (30%) by Ph_3PCl_2 treatment at CCl_4 reflux.[12]

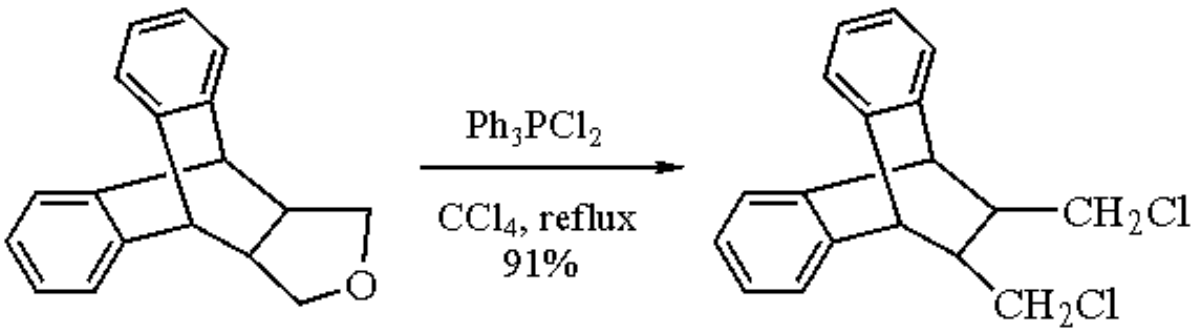

(5)

Aryl Chlorides from Phenols and Arenes.

Heating phenols with Ph_3PCl_2 at 120-140 °C leads to the corresponding aryl chlorides in good yield (eq 6).[13] A related chlorination reaction employs the Ph_3PCl_2/BSPO (***Bis(trimethylsilyl) Peroxide***) reagent system as the electrophilic chlorine source. With this reagent, in MeCN at rt, aromatic hydrocarbons bearing electron-donating substituents, such as 2,4,6-tri-*t*-butylbenzene and mesitylene, afford 1-monochloroarenes, while anisole gives a mixture of 2- and 4-chloro derivatives, in moderate to good yields (44-86%).[14a] Similar aromatic *para* chlorination has also been observed by heating anisole with Ph_3+PCl PCl_5^-, albeit in low yield (33%).[14b]

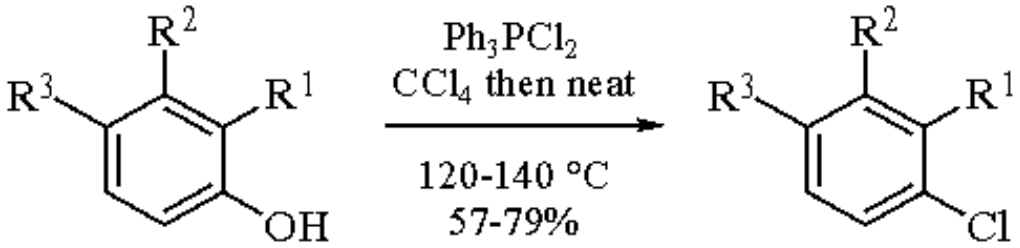

(6)

$R^1 = H, NO_2, Me; R^2 = H; R^3 = H, Me, NO_2, Ph$
$R^1 + R^2, R^2 + R^3 = Ph$

Vinyl Chlorides, Alkynyl Ketones, and β-Chloro-α-vinyl Ketones from Ketones and β-Diketones.

1-Chlorocyclohexene (45%) and α,α-dichlorotoluene (59%) are produced by the reaction of cyclohexanone and benzaldehyde with Ph_3PCl_2/***Triethylamine*** and Ph_3PCl_2 alone, respectively, in refluxing PhH.[6a] In MeCN as solvent, polymer-supported Ph_3PCl_2 converts acetophenone into α-chlorostyrene (75%).[11] In a similar fashion, unsymmetrical fluorinated β-diketones give 3:1 mixtures of α,β-ynones (eq 7) in good overall yields (slightly lower than those obtained with ***Triphenylphosphine Dibromide***).[15a] β-Chloro-α,β-unsaturated ketones are prepared in high yield from cyclic β-diketones (eq 8).[15b,c]

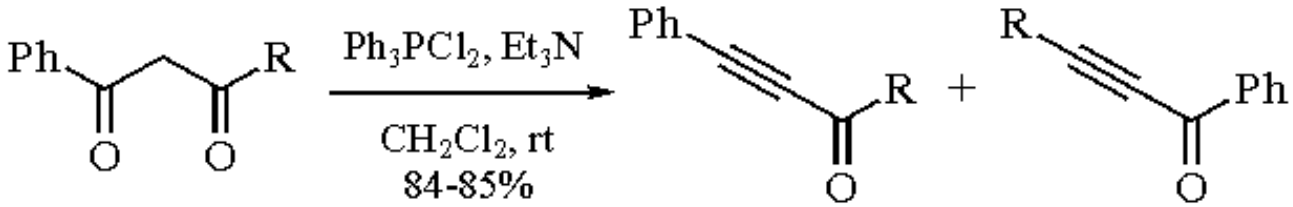

(7)

$R = CF_3, C_3F_7$

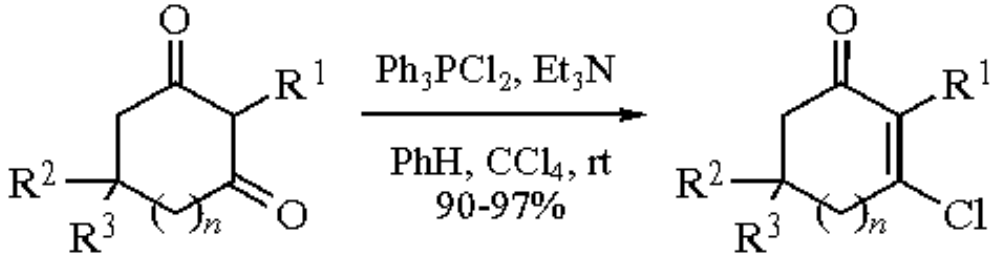

(8)

$R^1, R^2, R^3 = H, Me; n = 0, 1$

Epoxide Cleavage to Vicinal Dichlorides and Chlorohydrins.

Early reports of work in this area described the ring opening of ethylene oxide with Ph_3PCl_2 in CCl_4 at rt, leading to 1,2-dichloroethane.[16a] Subsequently,[16b,c] excellent yields were reported in the reaction of Ph_3PCl_2 with aliphatic epoxides to produce the corresponding vicinal dichlorides. The ring opening takes place stereospecifically with both *cis* and *trans* epoxides in PhH or CH_2Cl_2 at reflux, in each case providing the dichloride derived from S_N2 displacement on each C-O bond (eq 9).[16c] Alkoxyphosphonium chloride intermediates have even been isolated and characterized in a study involving ethylene oxide derivatives.[16d]

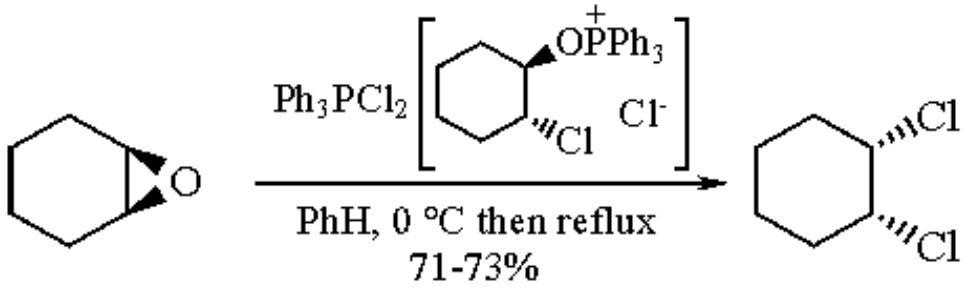

(9)

The reaction of epoxides with Ph_3PCl_2 in anhydrous CH_2Cl_2 at rt[17a] results in chlorohydrins in generally high yields (90-96%). With conformationally rigid epoxides the oxirane ring cleavage appears to be quite stereoselective, leading only to the products resulting from the usual *anti* opening of the ring. Less hindered and rigid cyclic substrates provide regioisomeric mixtures of cyclic *trans*-chlorohydrins. The reaction of the polymer-supported Ph_3PCl_2 reagent proceeds in a similar fashion with even higher yields and easier workup; simple filtration and evaporation provides the product (eq 10).[17b]

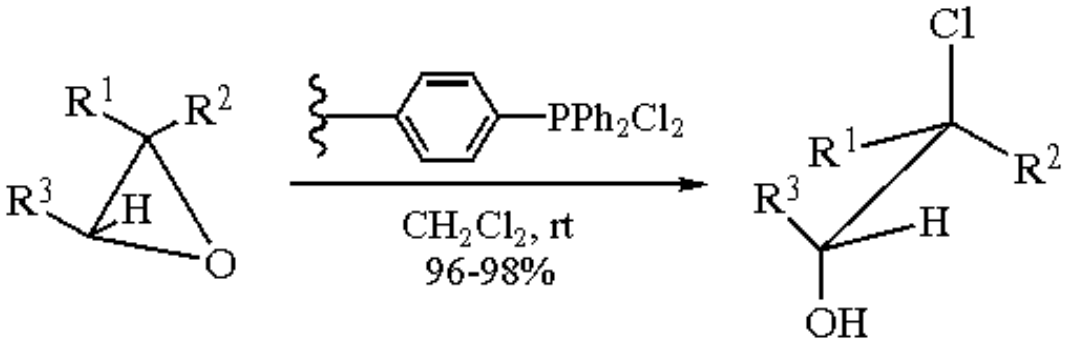

(10)

Acid Chlorides from Acids and Esters.

Mono- and dicarboxylic acids give acyl chlorides on reaction with Ph_3PCl_2[6a] or polymer-supported Ph_3PCl_2[11] in PhH, CH_2Cl_2, or MeCN (eq 11).[11] On similar Ph_3PCl_2 treatment in PhH at -10 °C to rt, sulfamic acid (H_2NSO_3H) is transformed into $Ph_3P{=}NSO_2Cl$ in 95% yield.[18] Analogously, Ph_3PCl_2, generated in situ from Ph_3P and $(EtO)_2P(=O)SCl$, reacts with Et_3N and $(EtO)_2P(O)SH$ at -78 °C to provide the corresponding acid chloride $(EtO)_2P(S)Cl$.[19]

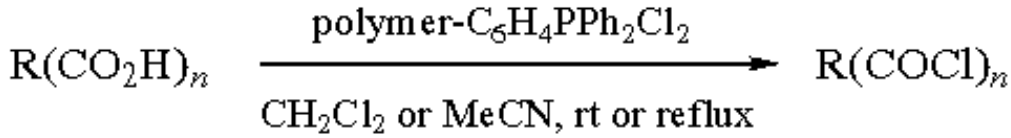

(11)

$$R = PhCH_2,\ 4\text{-}MeC_6H_4\ (n = 1);\ 1,4\text{-}C_6H_4,\ 1,3\text{-}C_6H_4\ (n = 2)$$

Direct cleavage of esters or lactones[20] to both acid and alkyl chlorides is achieved with Ph_3PCl_2; halogenated esters (RCO_2Me; R = CF_3, CCl_3, CH_2Cl) are readily cleaved in refluxing MeCN, while esters of nonhalogenated acids and lactones (eq 12) require higher temperatures or/and the use of additives such as ***Boron Trifluoride***. Cleavage is considerably retarded by steric hindrance in the alkoxy fragment. A mechanism involving initial nucleophilic cleavage of the O-alkyl bond with Cl^- is proposed for halogenated esters, whereas an initial electrophilic attack by Ph_3+PCl on the carbonyl oxygen is assumed for the cleavage of nonhalogenated esters.

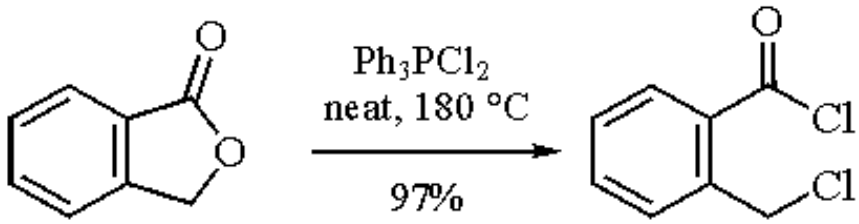

(12)

Similar transformations of esters to acid chlorides have also been achieved in the phosphonate diester field[21] and in the conversion of trialkyl phosphites into dialkyl chlorophosphites.[22] Ph_3PCl_2 acts as a mild reagent for the replacement of a single ester linkage by a chloride in phosphonate diesters (eq 13).

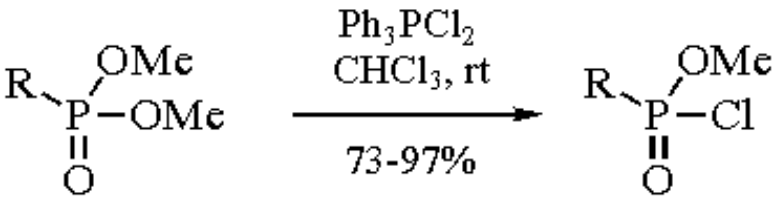

(13)

R = Me, Pr, allyl, MeOCO, *i*-PrOCO, PhOCO

Chlorination and Dehydration of Substituted Carboxamide Groups.

Secondary amides and *N*,*N*,*N*´-trisubstituted ureas possessing an N-H bond are converted to imidoyl chlorides[11,23] and chloroformamidines,[5a,24] respectively, by reaction with Ph_3PCl_2 (eqs 14 and 15). Unsupported or polymer-supported reagent has been used, with or without Et_3N, in a variety of solvents. Under very similar conditions, with Ph_3PCl_2 in CH_2Cl_2 at reflux, the primary amide $PhCONH_2$ is dehydrated to the nitrile PhCN (78%),[11] while aryl-substituted arylhydroxamic acids are dehydrated to the corresponding aryl isocyanates.[25] In the latter case, dehydration occurs via Lossen-type rearrangement of a phosphorane intermediate. In a related reaction, chlorination-dehydrochlorination of *N*-acylated hydrazines with the Ph_3PCl_2/Et_3N system is a smooth one-pot procedure to generate nitrilimines.[26] Thus, by such treatment, PhCONHNHPh affords [PhC&tbond;+N--N-Ph] in situ; this reacts with alkenic or alkynic dipolarophiles to give pyrazolines and pyrazoles.

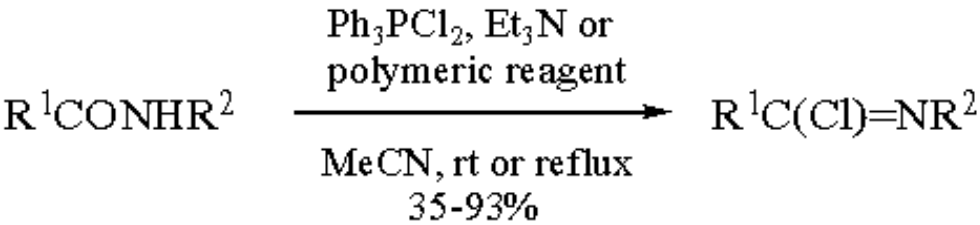

(14)

R^1 = Ph, Me; R^2 = Ph, Cy

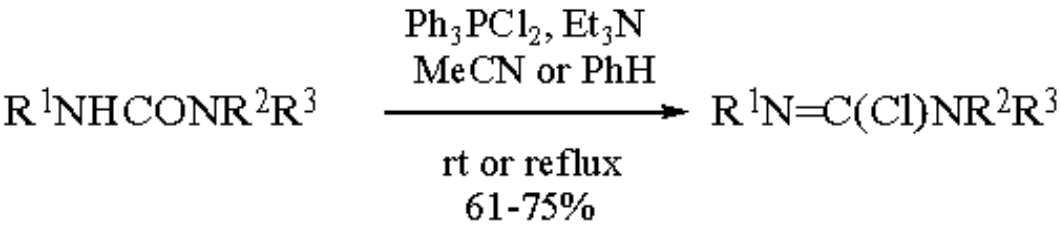

(15)

R^1 = Et, Pr, Ph; R^2 = Et, Bu, Ph; R^3 = Me, Et, Bu

Iminophosphoranes from Amines, Hydrazines, and Related Derivatives.

Iminophosphoranes (or phosphinimines) are commonly used as intermediates, especially in heterocyclic synthesis. Phosphinimines can be obtained via phosphorylation of primary amines with Ph_3PCl_2 alone,[27] or in the presence of Et_3N,[28] if necessary, to ensure the last dehydrochlorination step. In the heterocyclic β-enamino ester field, iminophosphoranes are submitted to vinylogous alkylation[28a] or cycloaddition (eq 16)[28a,b] with ring enlargement. The $=PPh_3$ moiety, which serves as a temporary amino protecting group, is then cleaved hydrolytically. Reaction of phosphinimines with aryl isocyanates affords carbodiimides,[28c] whereas iminophosphoranes of acyl hydrazines undergo dimerization to tetrazines.[28d] Other phosphinimines and phosphonium salts have been prepared from phosphorylation of amino derivatives, such as hydrazines,[29a] urethanes,[29b] and *N*-silylated imines,[29c] with Ph_3PCl_2.

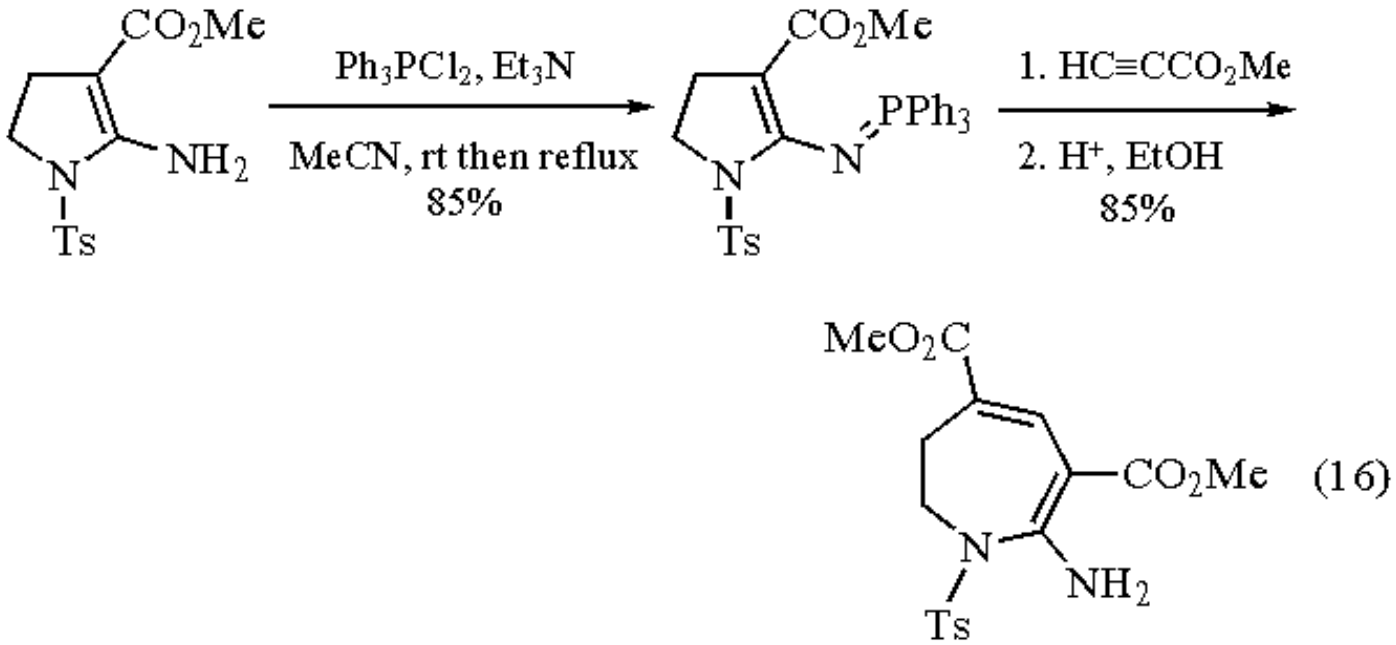

Other Applications.

Ph_3PCl_2 is a good condensation reagent for the synthesis of ketones (48-90%) from carboxylic acids and Grignard reagents. The versatility of the method is illustrated by the chemoselective reaction of carboxylic acids possessing such functional groups as halogen, cyano, and carbonyl (eq 17).[30]

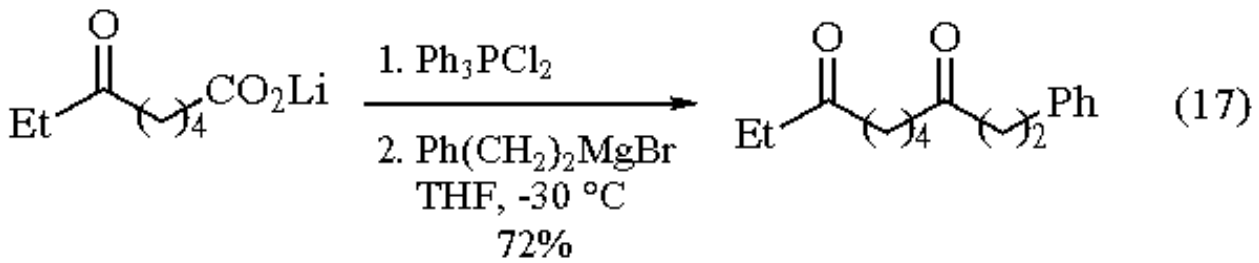

Beckmann rearrangement of benzophenone oxime to PhC(Cl)=NPh (82%) is promoted by Ph_3PCl_2/Et_3N in CH_2Cl_2 at rt.[31a] Cyclopentanone and cyclohexanone oxime are converted to δ-valero- and ε-caprolactam (76 and 86%) with Ph_3PCl_2 in PhH at 50-60 °C.[31b] The action of heat (120-130 °C) on a mixture of Ph_3PCl_2 with the highly fluorinated propanol $(CF_3)_2C(OH)CH_2SO_2CF_3$ leads to elimination of the CF_3SO_2 group and formation of the vinylic chloride $(CF_3)_2C{=}CHCl$.[32] Ph_3PCl_2 reacts with $Pb(SCN)_2$ to form $Ph_3{+}P{-}N{=}C{=}S\ SCN^-$, another reagent of the pseudohalophosphonium type, which is used for converting hydroxy groups into thiocyanate and isothiocyanate functions.[33] Ylides such as triphenylphosphonio(vinylsulfonylphenylsulfonylmethanide), $CH_2{=}CHSO_2{-}C{-}{-}(+PPh_3)SO_2Ph$, can be prepared by reaction of Ph_3PCl_2 with the very activated methylene derivative $CH_2{=}CHSO_2CH_2SO_2Ph$.[34] Heating Ph_3PCl_2 with $(Me_3Si)_2S$ at 60-70 °C leads to the formation of Ph_3PS (85%) after distillation of the Me_3SiCl byproduct.[35] Ph_3PCl_2 is reduced to Ph_3P with formation of alkyl or aryl chlorides by reaction with organometallic reagents (Mg, Li).[36]

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1. Castro, B. R. *OR* **1983**, *29*, 1.
2. The Ph_3PCl_2 adduct can be prepared by different routes; the most common involves the reaction of Ph_3P and Cl_2, both being generally used in solution, in order to ensure a correct 1/1 stoichiometry. As illustrated by physical studies,3 the resultant product is often a mixture of several compounds depending on starting materials (Ph_3P, Ph_3PO, Cl_2, $COCl_2$, CCl_3CCl_3, CCl_3COCCl_3), on their stoichiometries, and on the polarity of the solvent used for the preparation. ^{31}P NMR studies under various conditions, and solid state Raman measurements, lead to different values for ionic P^{IV} and molecular P^{V} species or to average values corresponding to equilibrated mixtures of the both structures according to the polarity of the solvent.
3. (a) Al-Juboori, M. A. H. A.; Gates, P. N.; Muir, A. S. *CC* **1991**, 1270. (b) Dillon, K. B.; Lynch, R. J.; Reeve, R. N.; Waddington, T. C. *JCS(D)* **1976**, 1243, and literature cited therein.
4. Another preparation from Ph_3P and CCl_3CCl_3 in MeCN provides material of higher mp: 207-210 °C (from MeCN-petroleum ether); see Appel, R.; Schöler, H. *CB* **1977**, *110*, 2382.
5. Apart from the classical $Ph_3P + Cl_2$ method, the following routes have been reported: (a) $Ph_3P + COCl_2$: Appel, R.; Ziehn, K. D.; Warning, K. *CB* **1973**, *106*, 2093, and literature cited therein. (b) $Ph_3PO + COCl_2$: Masaki, M.; Kakeya, N. *AG(E)* **1977**, *16*, 552, and

literature cited therein. (c) Ph_3P + CCl_4 in the presence of RNHCOCl: Appel, R.; Warning, K.; Ziehn, K. D.; Gilak, A. *CB* **1974**, *107*, 2671. (d) With Ph_3P + CCl_4 alone, a mixture of equal amounts of Ph_3PCl_2 and $Ph_3P{=}CCl_2$ is obtained: Rabinowitz, R.; Marcus, R. *JACS* **1962**, *84*, 1312; Appel, R.; Knoll, F.; Michel, W.; Morbach, W.; Wihler, H.-D.; Veltmann, H. *CB* **1976**, *109*, 58. (e) Ph_3P + CCl_3CCl_3, e.g. Ref. 4 and: Appel, R.; Halstenberg, M. In *Organophosphorus Reagent in Organic Synthesis*, Cadogan, J. I. G., Ed.; Academic: New York, 1979; Chapter 9 and literature cited therein. (f) Ph_3P + CCl_3COCCl_3 for in situ preparation of Ph_3PCl_2: see Ref. 8 and 9. (g) Ph_3PO or Ph_3P + PCl_5: Dillon, K. B.; Reeve, R. N.; Waddington, T. C. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1439, and literature cited therein.

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Triphenylphosphine-Diethyl Azodicarboxylate[1]

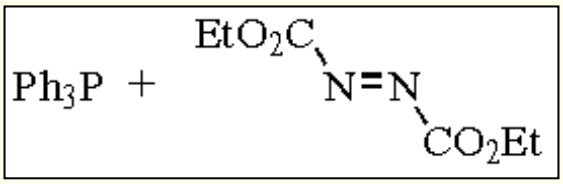

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Diethyl Azodicarboxylate · (MW 262.30) (DEAD)

[1972-28-7] · $C_6H_{10}N_2O_4$ · Triphenylphosphine-Diethyl Azodicarboxylate · (MW 174.18)

(reagent in the Mitsunobu reaction, which is a versatile, mild dehydration reaction, widely used for the synthesis of esters and ethers, for the formation of C-N, C-S, and C-halogen bonds, and for inverting the configuration of a stereogenic carbon containing an OH group[1])

Physical Data: see ***Triphenylphosphine*** and ***Diethyl Azodicarboxylate***.

Handling, Storage, and Precautions: all reagents and solvents must be anhydrous. In general, the Mitsunobu betaine (**1**) is generated in situ from the phosphine and the azodicarboxylate; however, in some cases it is essential to preform the betaine. The betaine is an unstable, colorless, crystalline solid, rapidly hydrolyzed on contact with moisture. It can be crystallized from dry THF or $CHCl_3$/hexane.

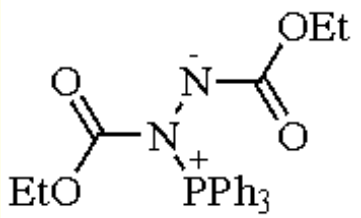

(1)

The Mitsunobu Reaction.

A mixture of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) is generally used; however, diisopropyl azodicarboxylate (DIAD) is cheaper and works just as well. The overall reaction enables the replacement of the hydroxyl group of an alcohol by a nucleophile X (eq 1).

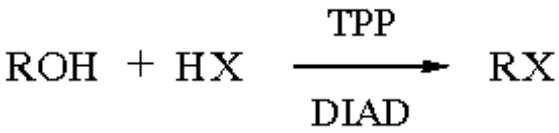

(1)

The phosphine accepts the oxygen (to give triphenylphosphine oxide) while the azodicarboxylate accepts the two hydrogens (to give the corresponding hydrazine derivative). The reaction occurs under mild (0-25 °C), essentially neutral conditions, can be carried out in the presence of a wide range of functional groups, and usually gives good yields (60-90%). In general, the reaction proceeds well with primary and secondary alcohols, and inversion of configuration is observed.[1] Retention of configuration may result from neighboring group participation,[2] or a change in mechanism if the alcohol is very hindered.[3a] Racemization may result if the C-O bond is prone to S_N1 cleavage.[4] Examples of H-X in the reaction (eq 1) include carboxylic acids, thioacids, phenols, thiols, imides, sulfonamides, hydrazoic acid, heterocyclic compounds, hydrogen halides, phosphate diesters, phosphinic acids, and certain active methylene compounds. The pK_a of H-X should generally be less than 13. LiX or ZnX_2 sometimes give better results than HX.[1c] THF is the most commonly used solvent, but other solvents such as dichloromethane, chloroform, benzene, toluene, ethyl acetate, DMF, and HMPA can also be used. The reaction is faster in nonpolar solvents; for example, formation of ethyl benzoate is about 30 times faster in $CHCl_3$ than in MeCN.[5a] A problem commonly encountered with the Mitsunobu reaction is the separation of the product from triphenylphosphine oxide. This can be overcome by the use of a phosphine containing a basic group such as diphenyl(2-pyridyl)phosphine[6] or (4-dimethylaminophenyl)diphenylphosphine,[7] where an aqueous acid wash removes the corresponding phosphine oxide,

or by using a polymer-bound phosphine.[8] Similarly, dimethyl azodicarboxylate (the corresponding hydrazine is water soluble)[9] and a polymer-supported azodicarboxylate[10] can be used to facilitate product isolation. The reaction is best explained by assuming successive formation of the betaine (**1**), the protonated *N*-phosphonium salt (**2**), and the alkoxyphosphonium salt (**3**), which collapses in S_N2 fashion (eq 2).

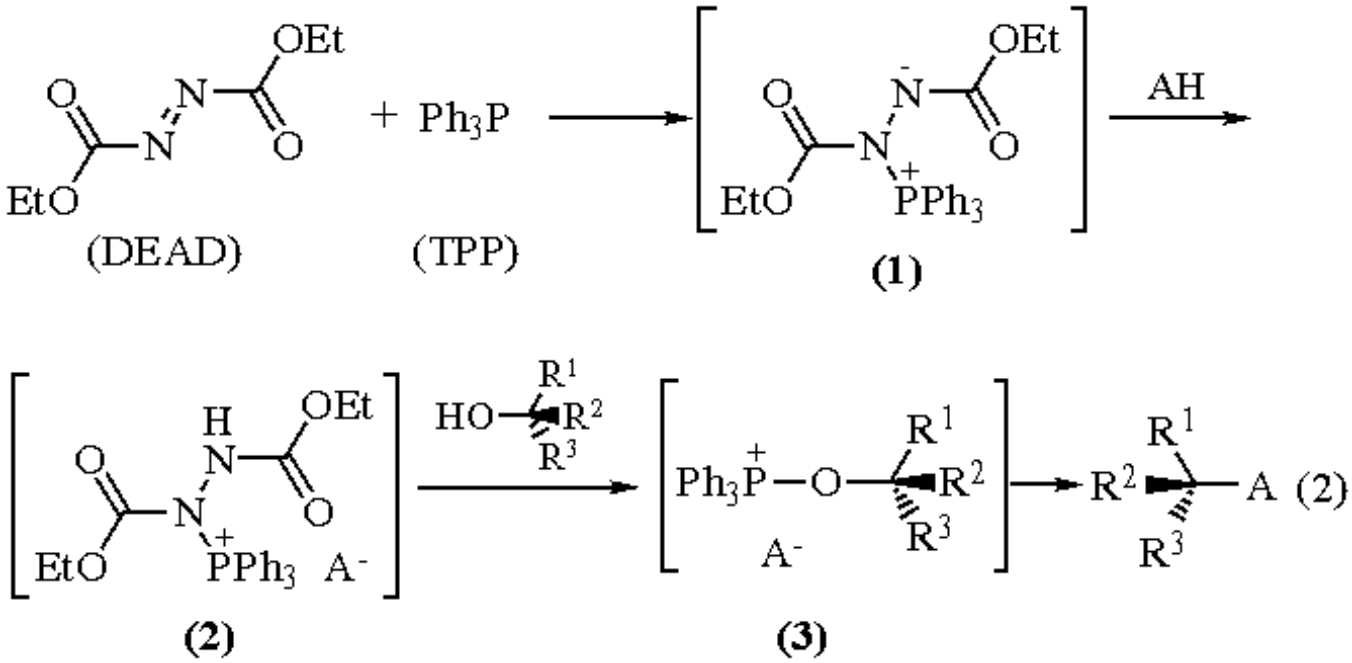

Without acidic components, *N*-alkylhydrazinedicarboxylates (**4**) can be formed.[5b,11] NMR studies of the reaction of alcohols with DEAD and TPP in the absence of acidic components have revealed that the key intermediate is the pentavalent dialkoxyphosphorane (**5**).[1c,5] In the presence of an acidic component, phosphorane intermediates are present in equilibrium with the oxyphosphonium salt (**3**).[3]

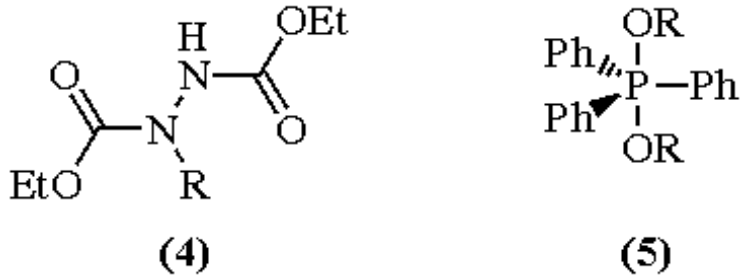

The combination of DEAD and TPP has been utilized most often as the condensation reaction system, but dimethyl, diisopropyl, and di-*t*-butyl azodicarboxylates (**6**) can also be used instead of DEAD; the azodicarboxamide (**7**) has been used as well.[1,12] Triphenylphosphine can be substituted by a variety of trivalent phosphorus compounds, including substituted triarylphosphines and trialkylphosphines.[1c]

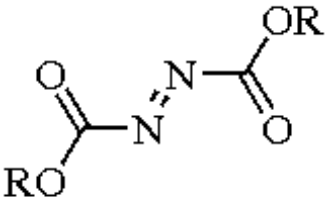

(6)

R = Me: DMAD
R = Et: DEAD
R = *i*-Pr: DIAD
R = *t*-Bu: DBAD

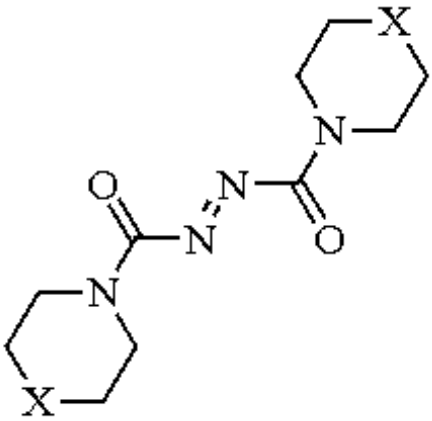

(7)

X = CH_2: ADDP
X = O, NMe

Order of Addition of the Reagents.

The order of addition can be crucial. The most commonly used procedure is to dissolve the alcohol (ROH), the acid (HX), and triphenylphosphine in THF, cool to 0 °C, add the DEAD (or DIAD) slowly with stirring, and then stir at room temperature for several hours. If this procedure fails to give the desired product, the betaine (TPP-DEAD adduct) should be preformed (addition of DEAD to TPP in THF at 0 °C) before addition of a mixture of the ROH and the HX,[13] or addition of ROH followed by slow addition of HX or HX and a buffering salt (strong acids),[14,15] or addition of HX followed by ROH (weak acids).[16] The advantage of preforming the betaine is that X^- is not generated in the presence of a powerful oxidant (the azodicarboxylate). Preformation of the betaine should minimize radical-induced side-reactions (radicals are produced when TPP and DEAD are mixed[17]).

Ester Formation.

A variety of alcohols react at room temperature with carboxylic acids in the presence of DEAD and TPP to produce the corresponding esters.[1] When polyols are used, the reaction generally takes place at the less hindered hydroxyl group, as exemplified in the reaction of 1,3-butanediol (eq 3).[18,19] When 1,2-propanediol or styrene glycol is used, however, the more sterically encumbered C-2 benzoate is predominantly obtained with complete inversion of the stereochemistry.[19] This result has been explained by the formation of a dioxaphospholane (**8**) as the key intermediate (eq 4).[3b,19,20a] With acyclic 1,4-diols such as isomaltitol,[20b] five-membered cyclic ether formation takes place in preference to esterification.

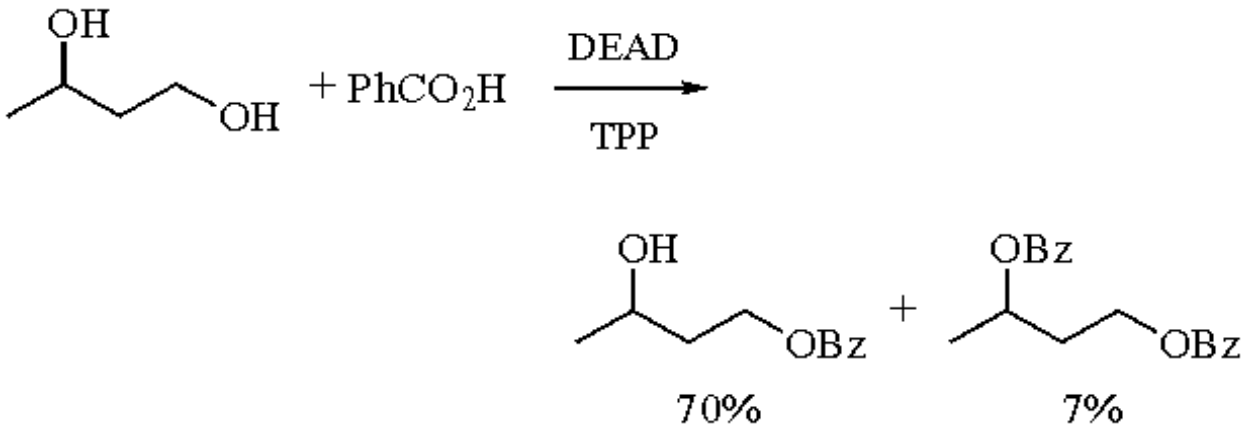

(8)

Thymidine (**9**) reacts with aromatic carboxylic acids to give 5´-*O*-aroylthymidines (**10**) (eq 5). The yield of esters increases with the acidity of the carboxylic acid, indicating the importance of the protonated *N*-phosphonium salt (**2**).[21,22]

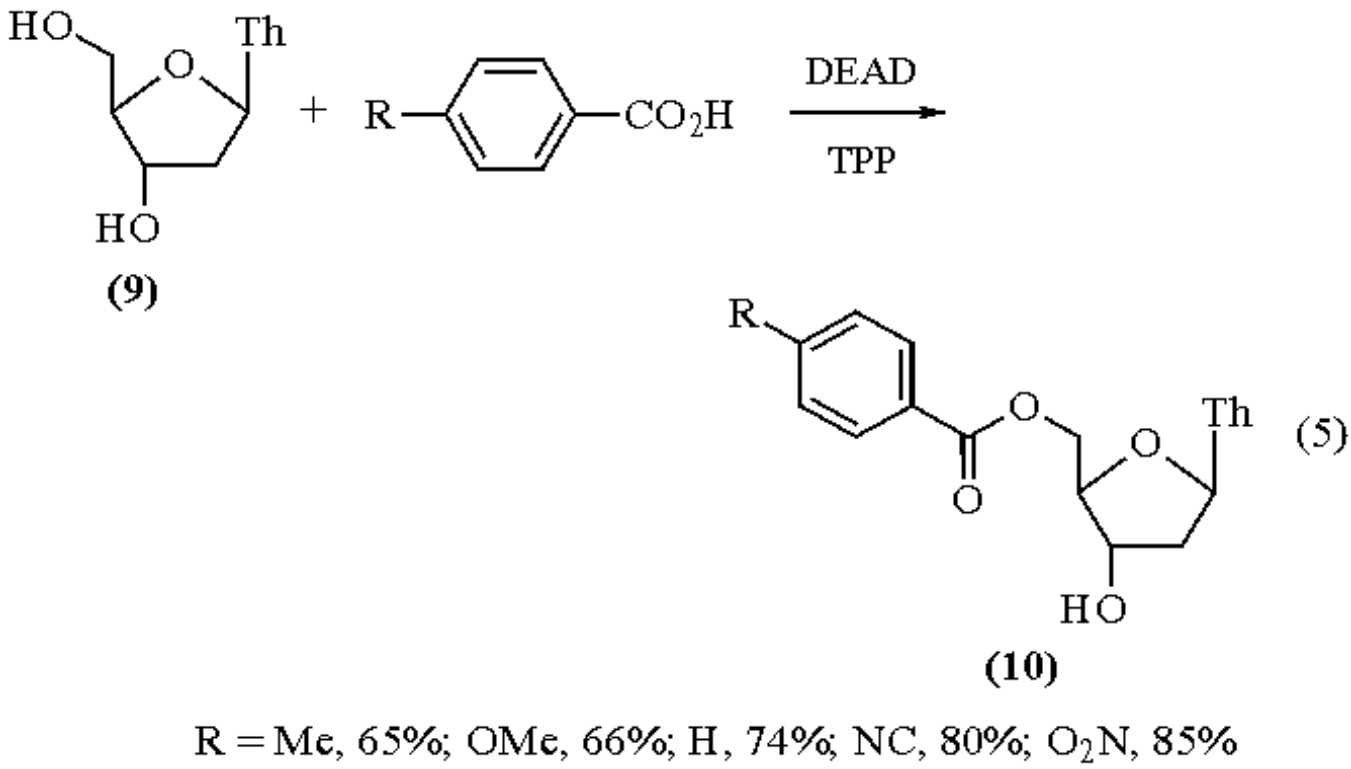

The reaction of chiral secondary carbinols with carboxylic acids, DEAD, and TPP gives the corresponding esters with inverted configuration. Removal of the carboxyl group affords the enantiomer of the parent alcohol (eqs 6-9).[23-27] For the purpose of inverting the stereochemistry of a secondary carbinol center, 3,5-dinitrobenzoic acid,[28] *p*-nitrobenzoic acid,[22b] and chloroacetic acid[29] have been recommended, because of increased yield and ease of purification and removal of the carboxyl group from the resulting esters.

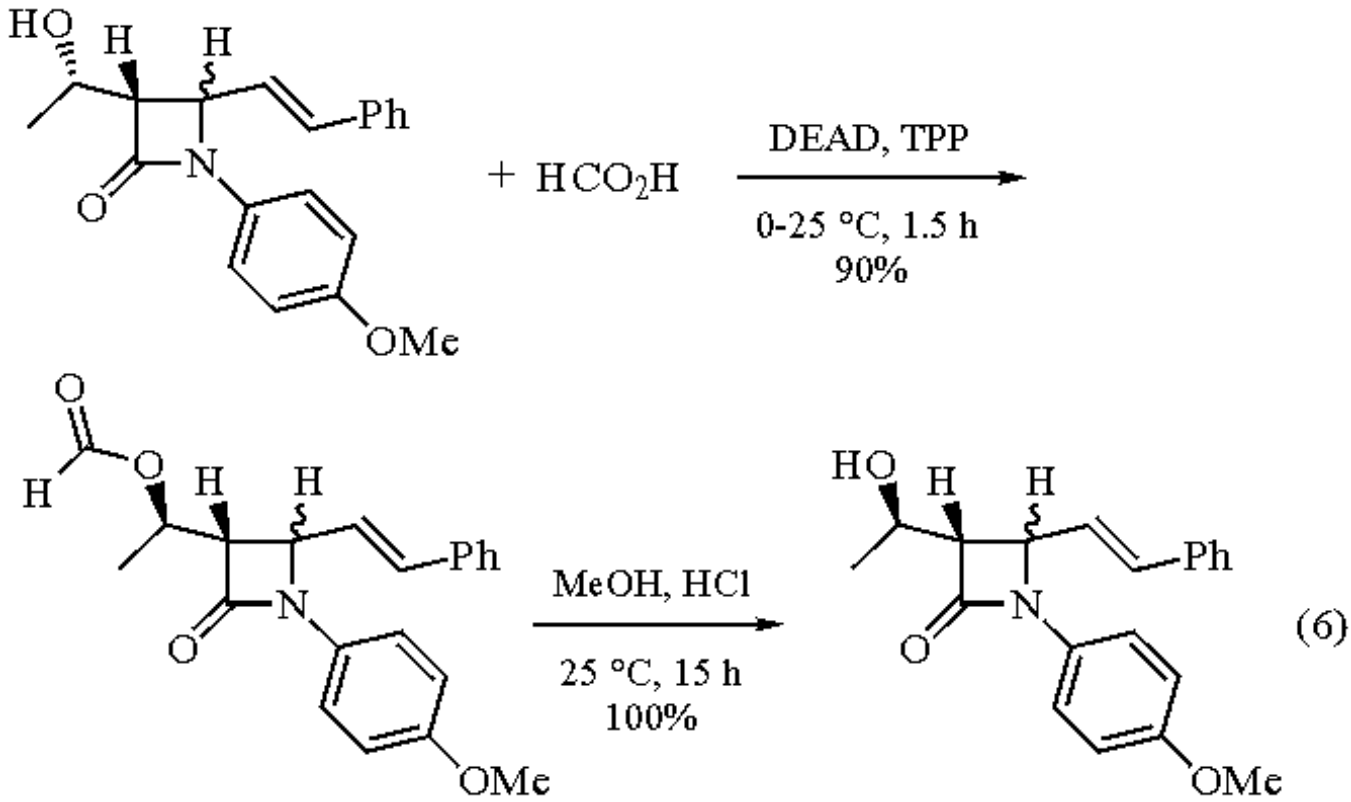

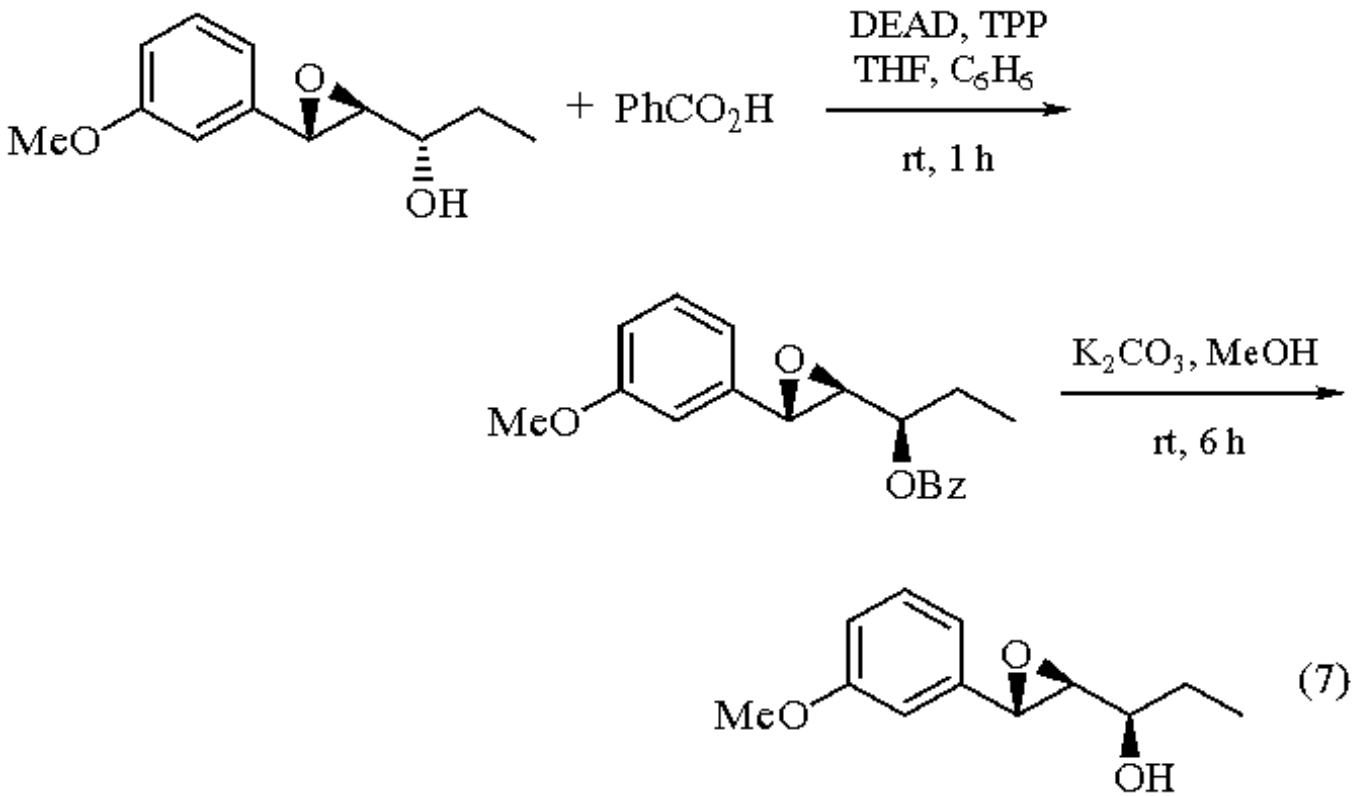
MeO
O
OH
+ PhCO2H
DEAD, TPP
THF, C6H6
rt, 1 h
MeO
O
OBz
K2CO3, MeOH
rt, 6 h
MeO
O
OH

(7)

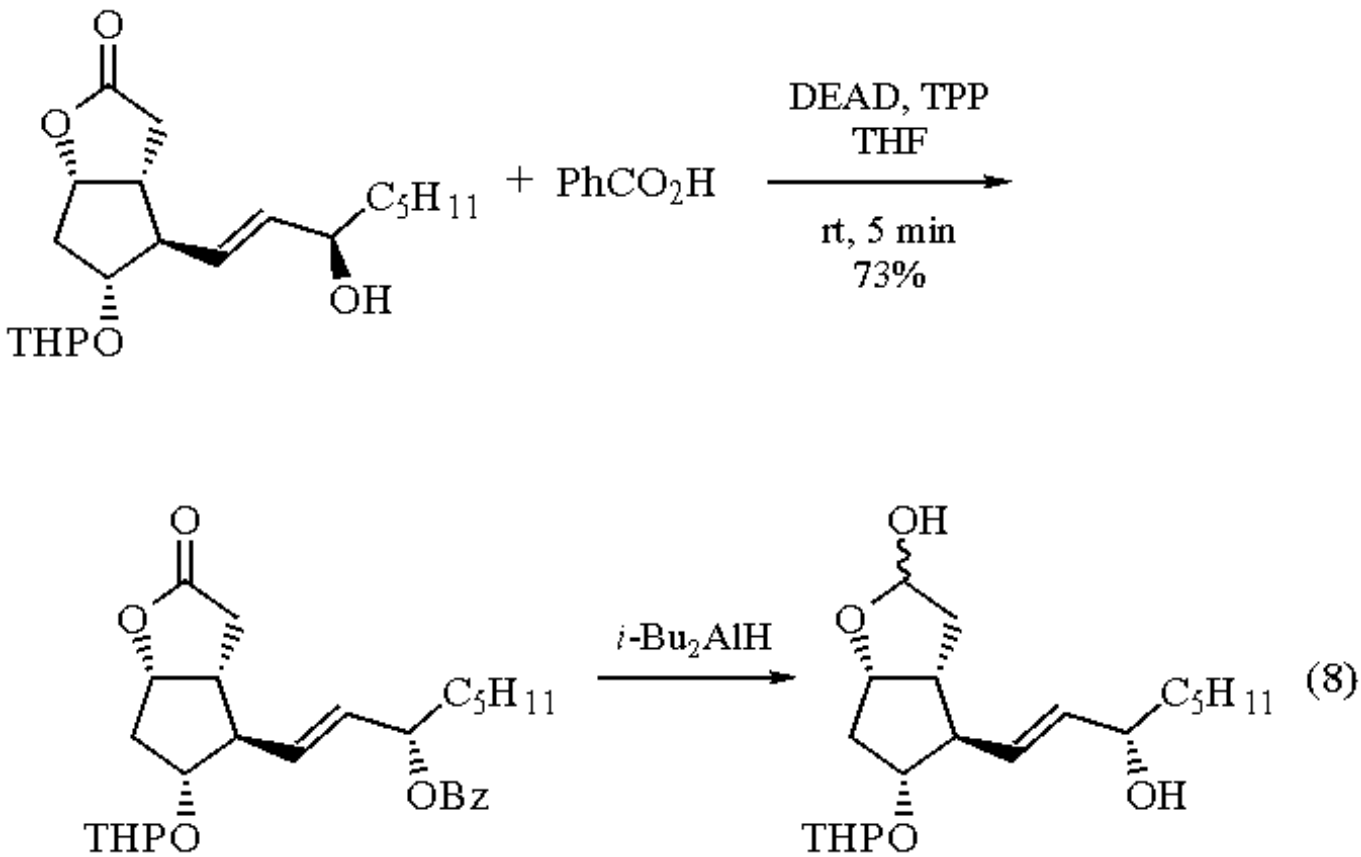
O
O
C5H11
OH
THPO
+ PhCO2H
DEAD, TPP
THF
rt, 5 min
73%
O
O
C5H11
OBz
THPO
i-Bu2AlH
OH
O
C5H11
OH
THPO

(8)

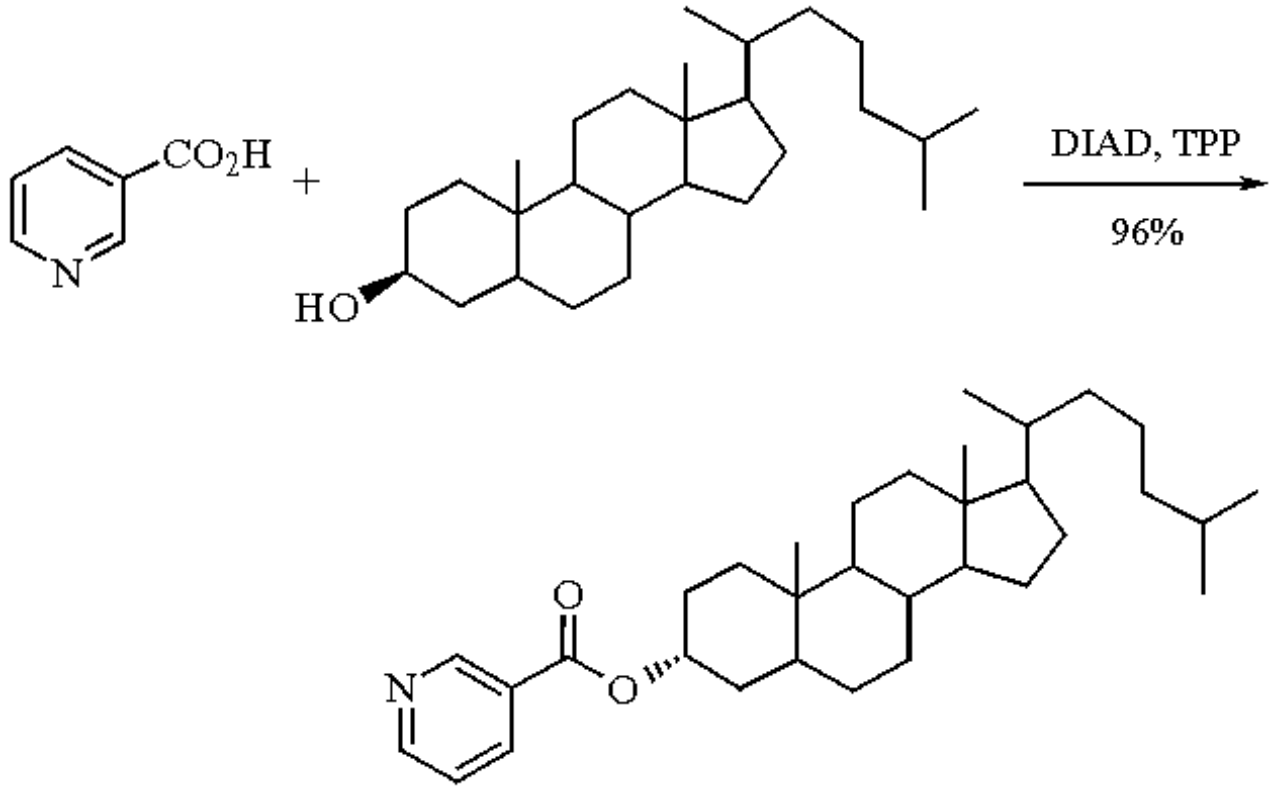

(9)

With some exceptions, a primary hydroxyl group is generally more reactive than a secondary one.[22a,30] Steric congestion and electronic effects sometimes retard the reaction and/or result in the formation of a complex mixture.[31]

The solvent also plays an important role in the success of the reaction. In general, reaction in benzene or toluene gives higher yields of inverted products.[1,22b,32] Although pyridine is not suitable in the preparation of nucleotides,[33a] pyridine can be used for the synthesis of sucrose epoxide,[33b] and a mixture of dioxane-pyridine (9:1) can be utilized in the preparation of sugar carboxylates.[22a] Mixed solvent systems may be necessary when the acid and alcohol components have widely differing solubilities. Thus a mixture of HMPA and dichloromethane works well in the synthesis of lipophilic carbohydrate esters such as cord factor.[33c]

Allylic and benzylic cyanohydrins react with carboxylic acids, DEAD, and TPP to give inverted esters with 92-99% ee, while extensive racemization takes place with benzaldehyde cyanohydrins containing strongly electron-donating substituents (eq 10). Saturated aliphatic cyanohydrins afford esters in which the original configuration is retained.[34]

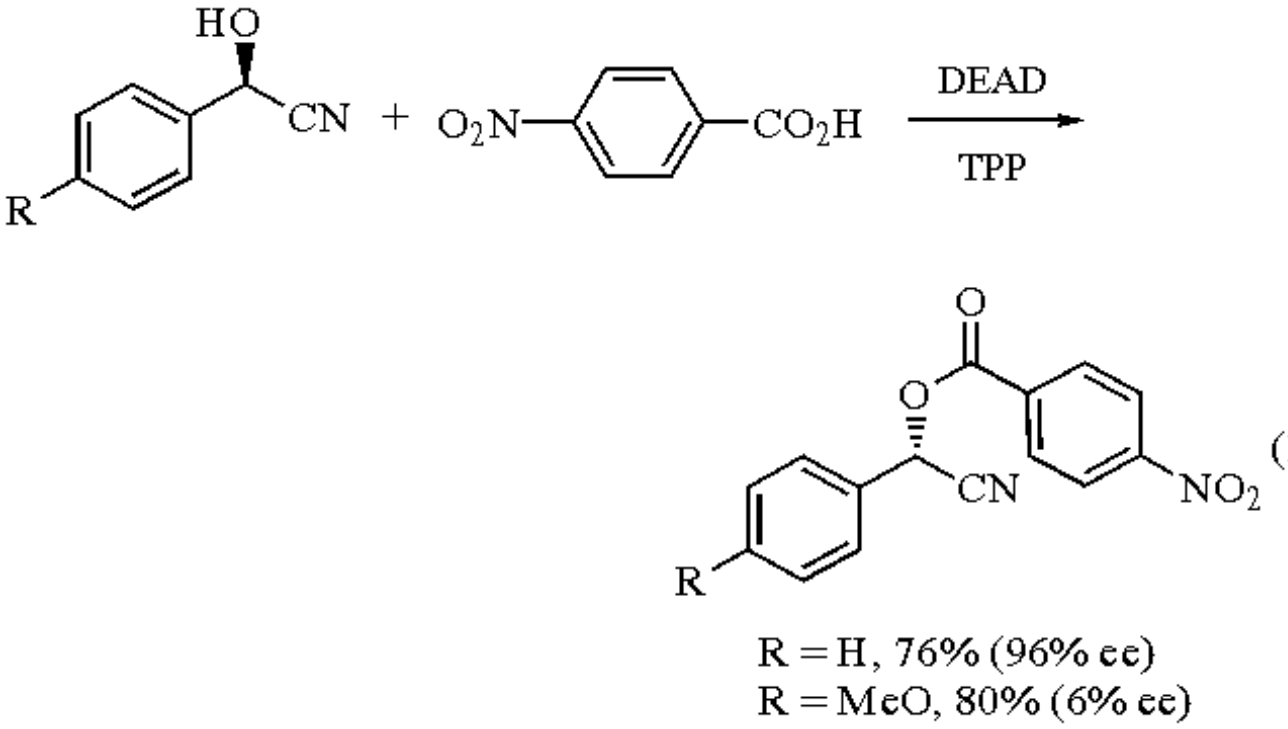

(10)

Propargylic alcohols react with carboxylic acids, DEAD, and TPP to give the corresponding inverted esters without formation of allenic alcohols.[35] Similarly, in allylic alcohols where no bias exists against the normal S_N2 process, clean regiospecific inversion is invariably observed

or implied.[1,36] In specific cases where the S_N2 pathway is hindered for some reason, such as eclipsing of substituents, allylic rearrangement can occur (eqs 11-13).[1,37] When compound (**11**) reacts with benzoic acid, DEAD, and TPP, (**13**) and (**14a,b**) (**a**/**b** = 4:1) are obtained in a ratio of 1:1. Similar treatment of (**11**) in the presence of $PdCl_2$ (0.1 equiv) results in the nearly exclusive production of (**14a,b**) (73%; **a**/**b** = 10:1) via (**12**).[37d]

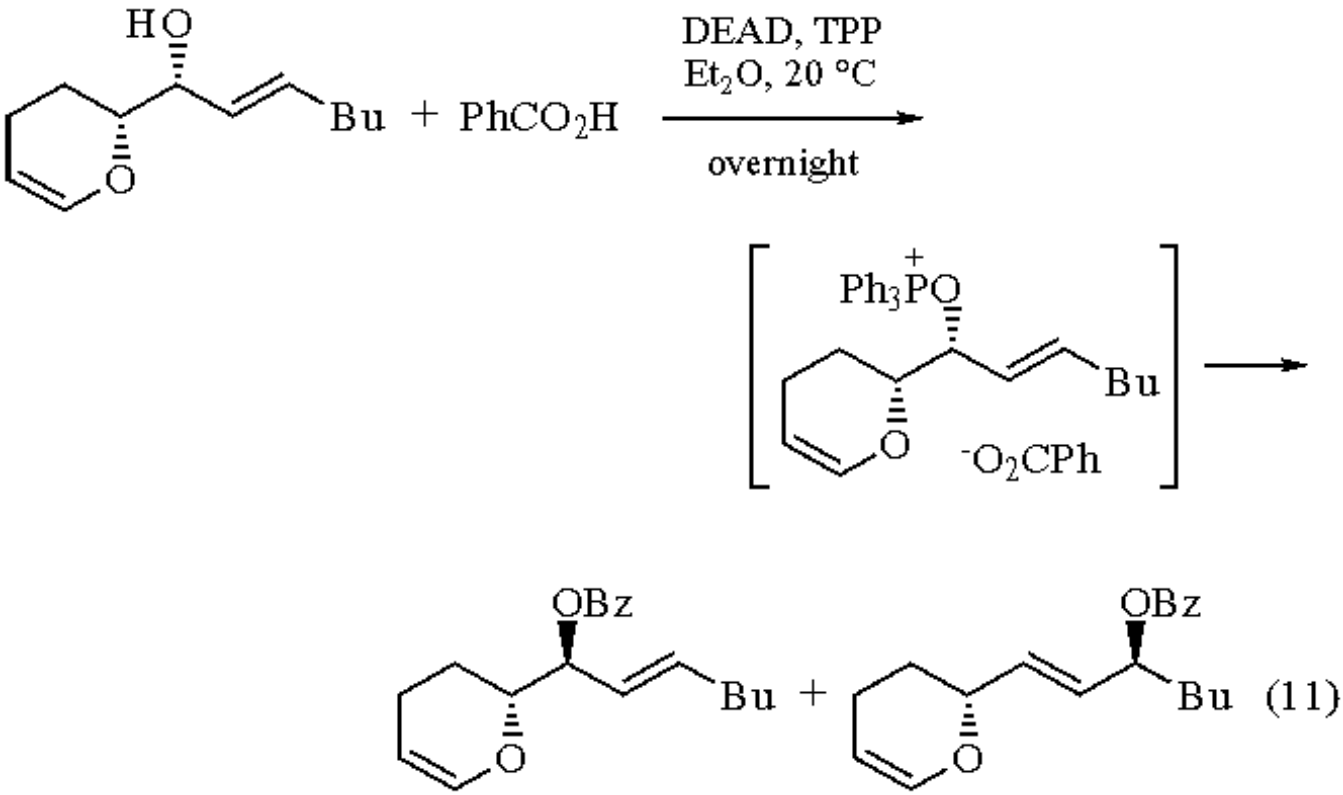

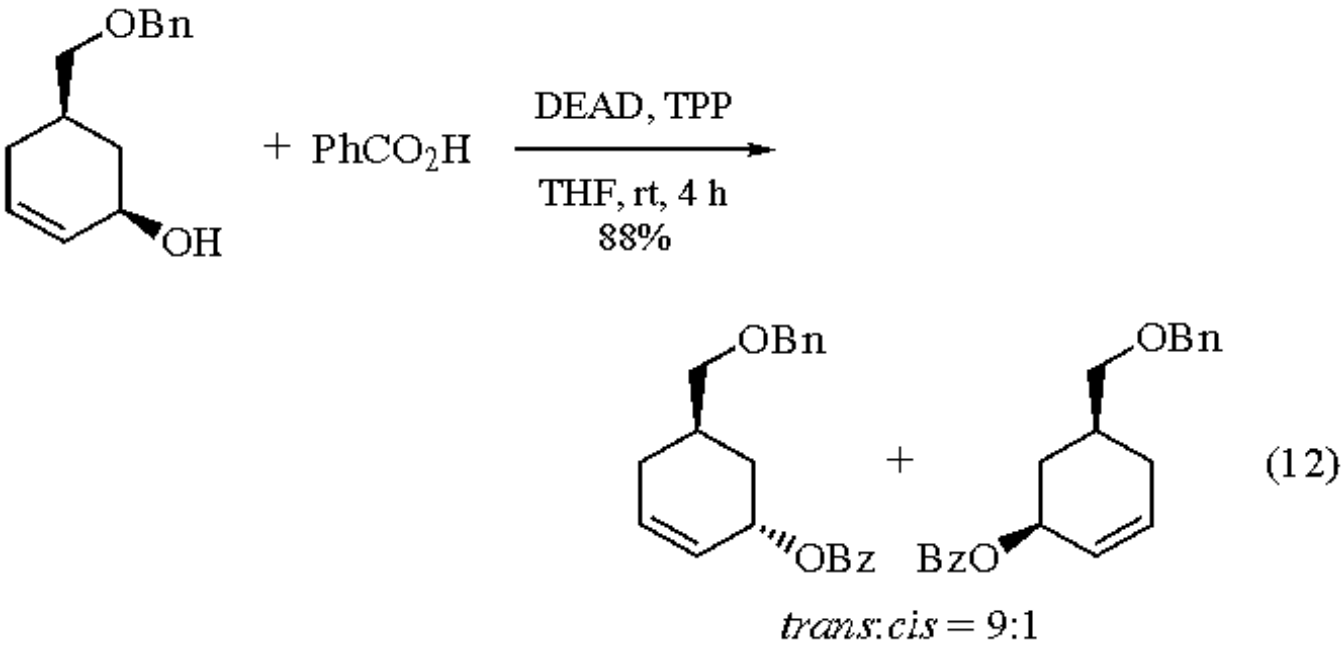

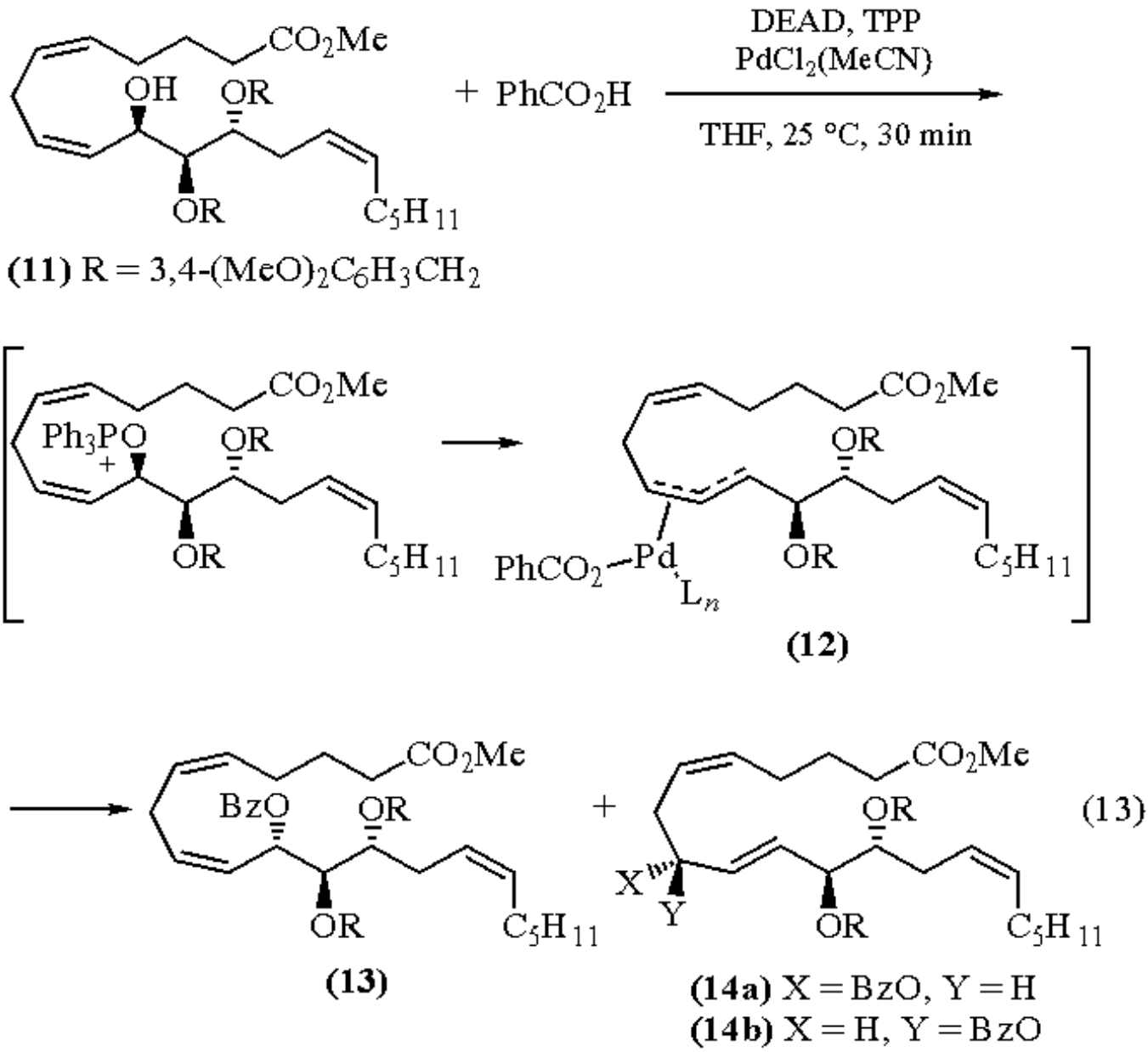

(13)

Reaction with Thiocarboxylic Acids, Phosphoric Acids, Sulfonic Acids, and their Derivatives.[1]

Thiocarboxylic acids,[38,13] dithiocarboxylic acids,[39] and dimethyldithiocarbamic acid zinc salt,[40] as well as various phosphorus oxyacids[41] and phosphorus thioacids,[42] can also be utilized. α,o-Mercapto alcohols form cyclic thioethers whereas thiols react with both DEAD and TPP-DEAD to form disulfides.[43a] 2-Mercaptoazoles also react with alcohols in the presence of DEAD and TPP.[43b] Although arenesulfonic acids do not enter into the reaction, a combination of DEAD-TPP with methyl *p*-toluenesulfonate as a nucleophile carrier gives the corresponding alkyl sulfonates (eq 14).[44] Alternatively, ***Zinc p-Toluenesulfonate*** reacts with a variety of secondary alcohols to produce the desired tosylates with clean inversion and in good yields, with some exceptions (eq 15).[45]

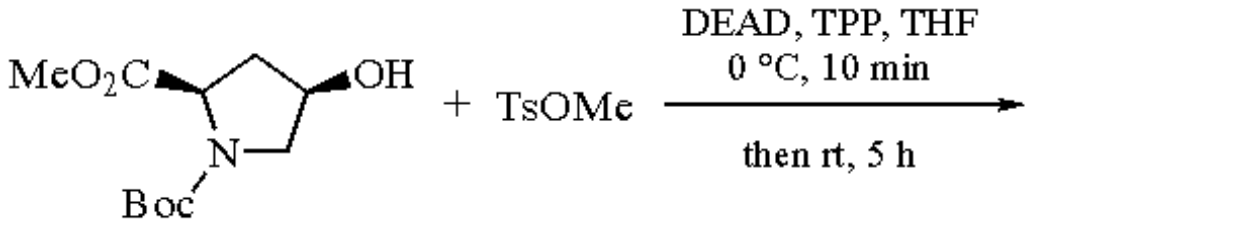

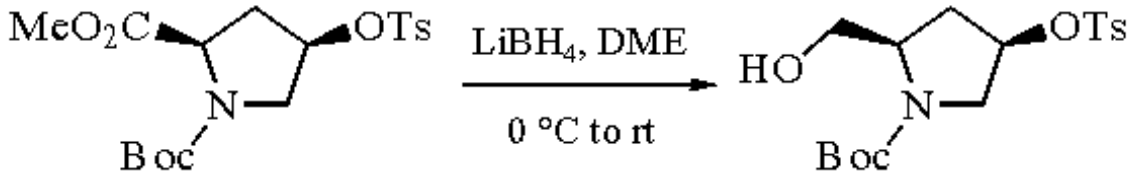

(14)

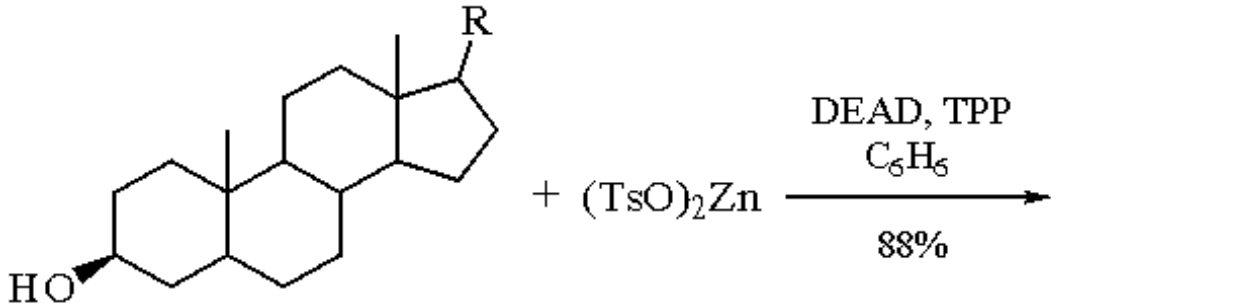

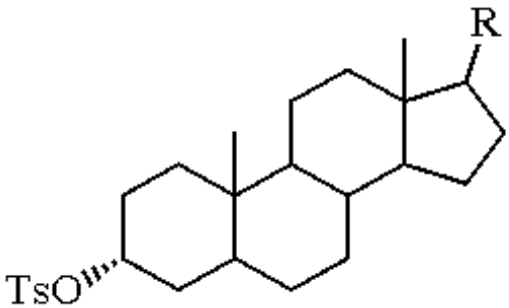

(15)

Reaction with Hydroxy Acids.

A study of reactions of *threo*-3-hydroxycarboxylic acids (**15**) with DEAD and TPP revealed that both hydroxyl group activation (HGA) and carboxyl group activation processes (CGA) are involved. With small R^1 and R^2, the zwitterion (**16**) is more stable than (**17**), so that HGA is exclusively observed, resulting in the formation of alkenes. On the other hand, the CGA process via (**17**) is progressively preferred as the size of R^1 and R^2 increases (eq 16).[46a,b] When the reaction is carried out in acetonitrile, CGA predominates.[46c]

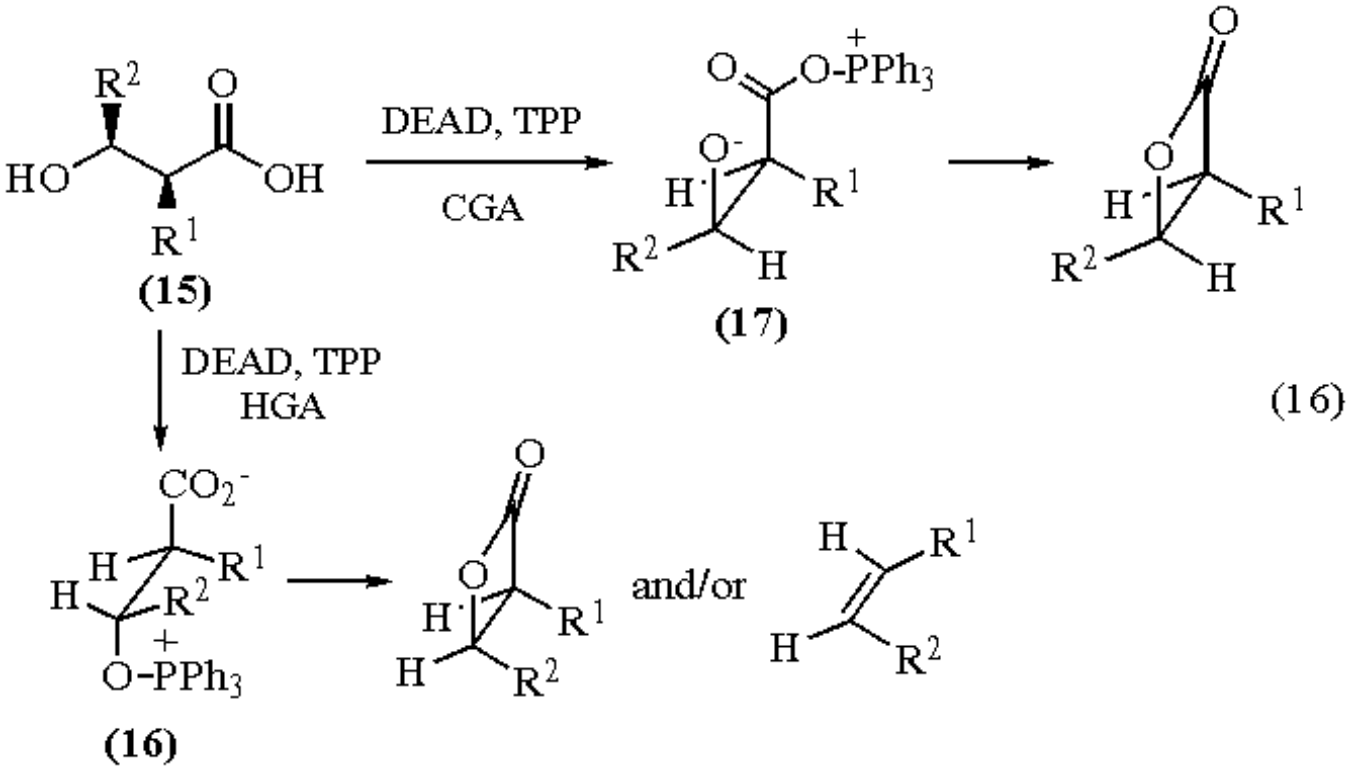

Hydroxy acids HO-$(CH_2)_n$-CO_2H with *n* &egt; 3 react with DEAD and TPP to afford the corresponding lactones.[1] This procedure can be utilized in the preparation of macrolide antibiotics and related compounds. Macrolactonization by the use of DEAD-TPP depends on the reaction conditions and the structure of the seco acids. Thus dropwise addition of the hydroxy acid (**18**) over a period of 10 h to a mixture of DEAD (7.7 equiv) and TPP (7.5 equiv) affords the lactone (**19**) in 59% yield as well as the unwanted dilactide (**20**) in a yield of <1%. On the other hand, the reaction of (**18**) with DEAD (5.0 equiv) and TPP (5.0 equiv) at 25 °C for 18 h gives (**19**) and (**20**) in 2% and 40% yields, respectively (eq 17).[47]

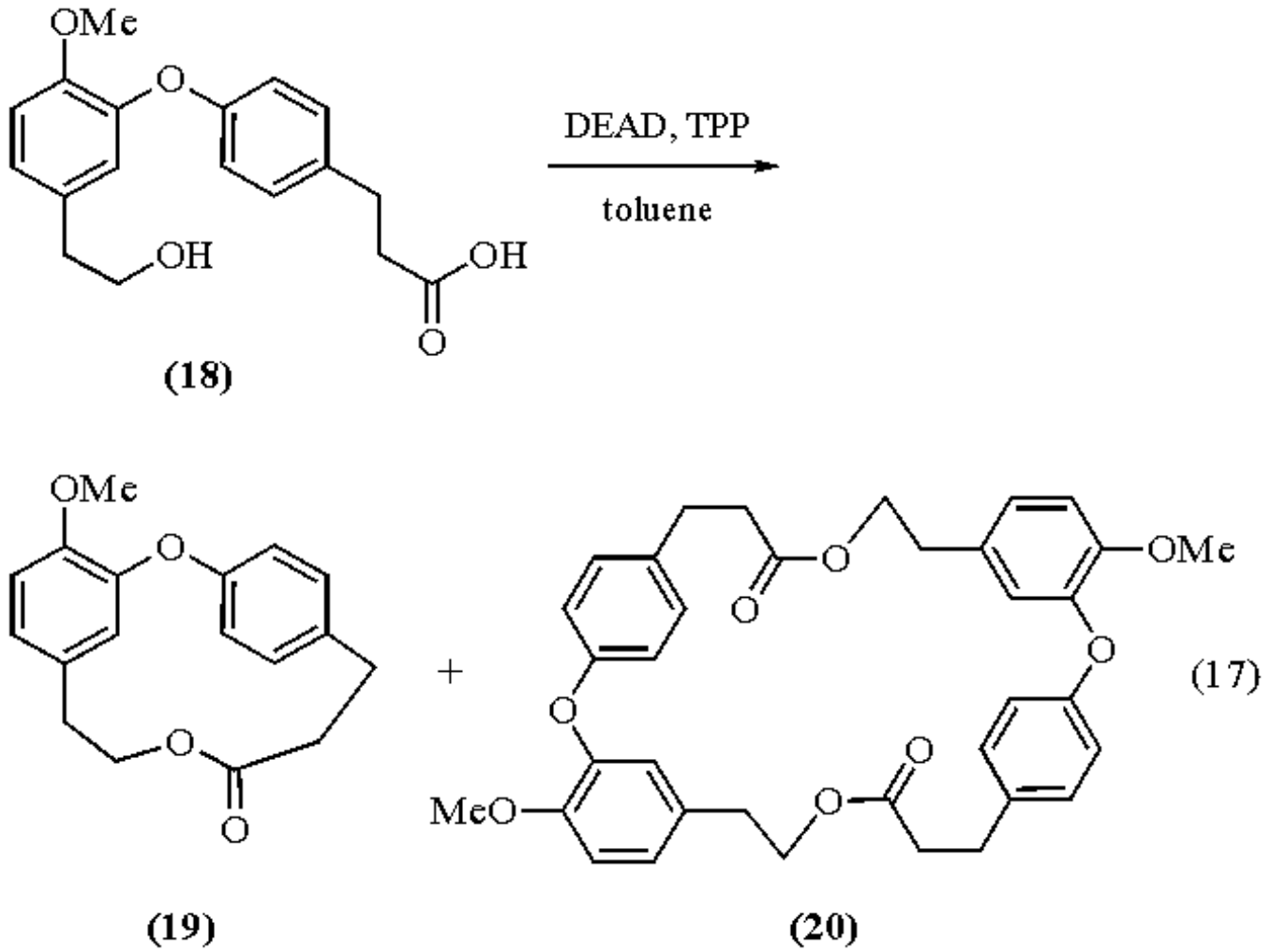

The reaction of the seco acid (**21**) of colletodiol with DEAD and TPP gives the lactone (**22**) in 45% yield after recrystallization (eq 18),[48a] while

the seco acid (**23**), which has a closely related structure to (**21**), affords the corresponding lactone (**24**) in only 4% yield (eq 19).[48b,49]

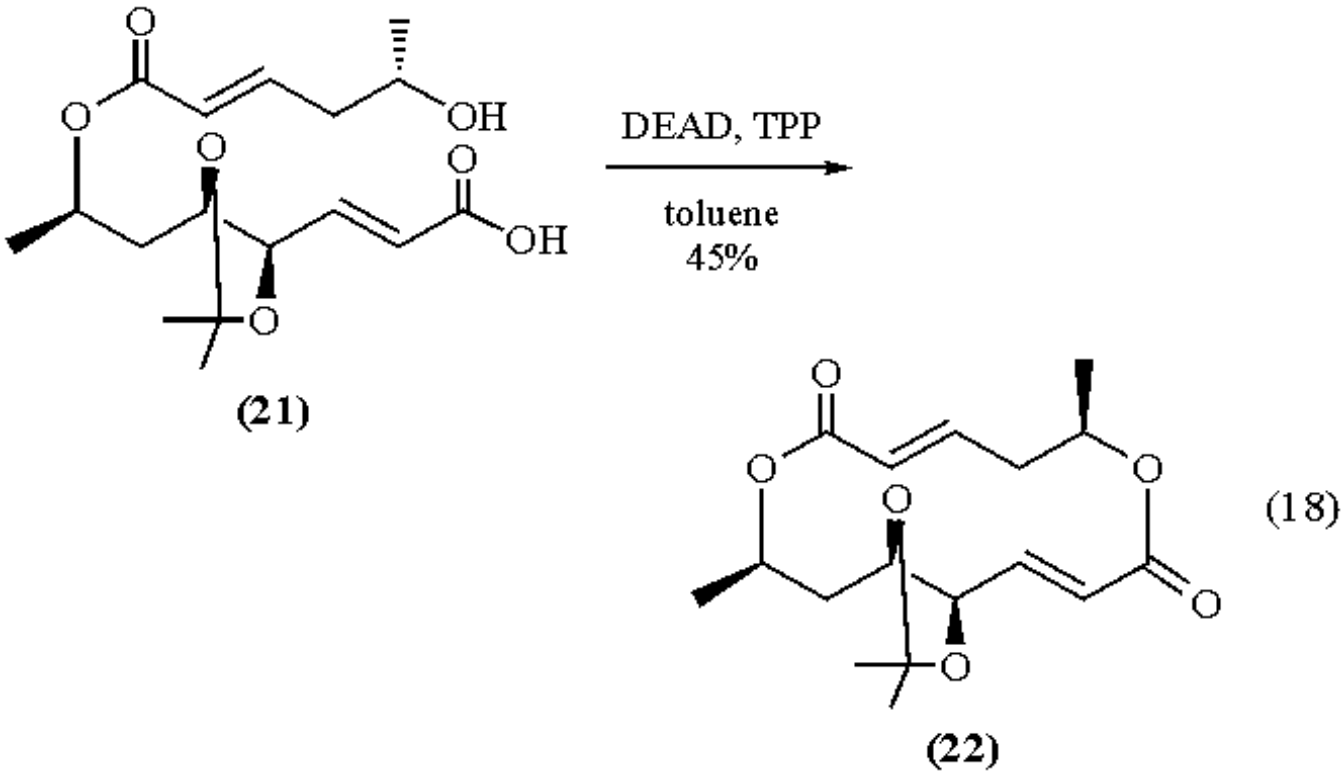

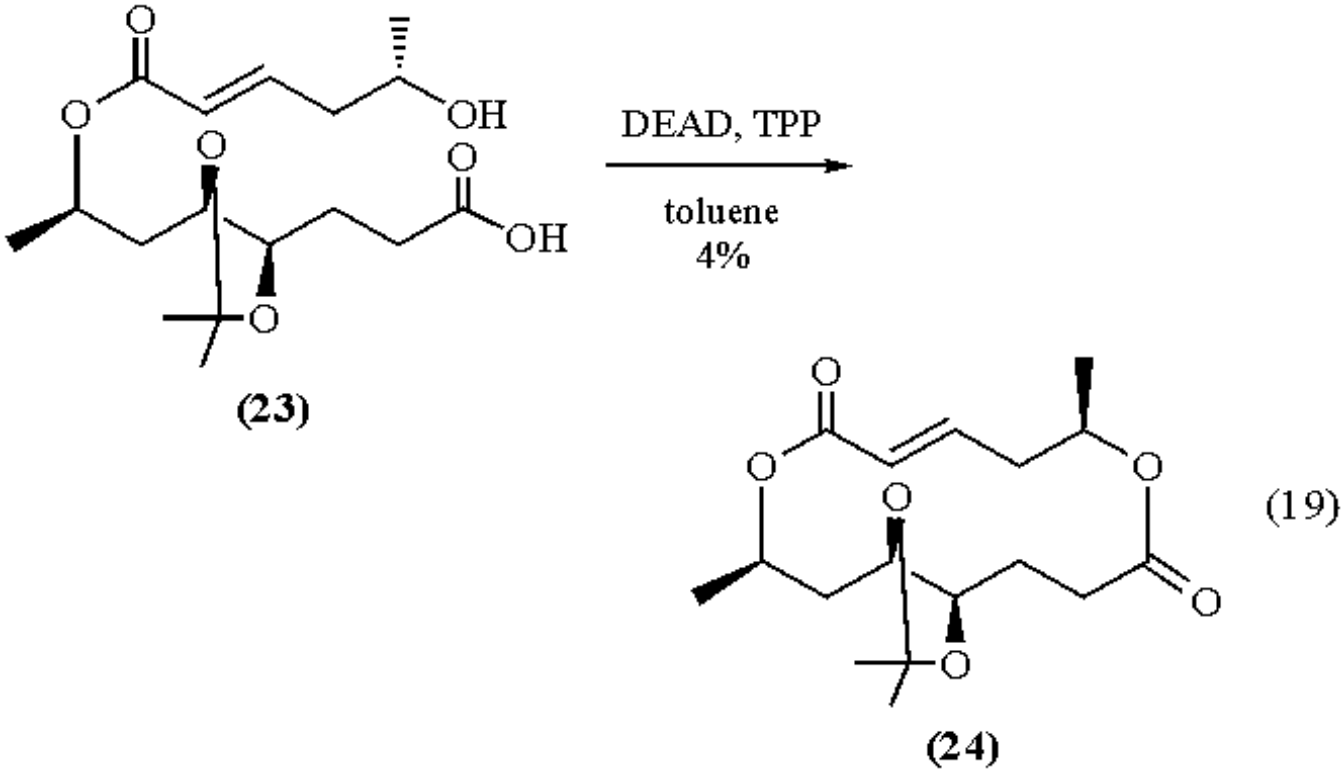

Reaction with Phenols and Other Oxygen Nucleophiles.

When alcohols react with phenols, DEAD, and TPP, the corresponding aryl alkyl ethers are produced. A tertiary amine may facilitate the reaction.[50a] In general, the reaction proceeds with clean inversion of chiral secondary carbinol centers (eq 2; AH = a phenol).[50b] Depending on the structure of the substrate, allylic rearrangement[51,52] and neighboring group participation can be observed.[2,53] Phenols having a hydroxyalkyl chain in a suitable position for cyclization afford the corresponding cyclic aryl ether.[54] Silanols react with phenols and with alcohols in the presence of DEAD and TPP to afford the corresponding silyl ethers.[55] Oximes[56] and *N*-hydroxy imides[57] can also be utilized as acidic components.

Reaction with Di- and Polyols.

Although intermolecular dehydration between two molecules of alcohols to afford acyclic ethers usually does not occur with the DEAD-TPP system, intramolecular cyclization of diols to produce three to seven-membered ethers is a common and high yielding reaction. Contrary to an early report,[58a] 1,3-propanediol does not form oxetane.[5b] Oxetanes can be formed, however, using the trimethyl phosphite modification of the Mitsunobu reaction.[1c] The reaction of (*S*)-1,2-propanediol and (*R*)-1,4-pentanediol with DEAD and TPP affords the corresponding cyclic ethers with 80-87% retention of stereochemistry at the chiral carbon, while (*S*)-phenyl-1,2-ethanediol affords racemic styrene oxide. In contrast to the reaction of the same 1,2-diols with benzoic acid (eq 4), oxyphosphonium salts (**25a**) and (**25b**) have been postulated as key intermediates in the present reaction (eq 20).[58b,e]

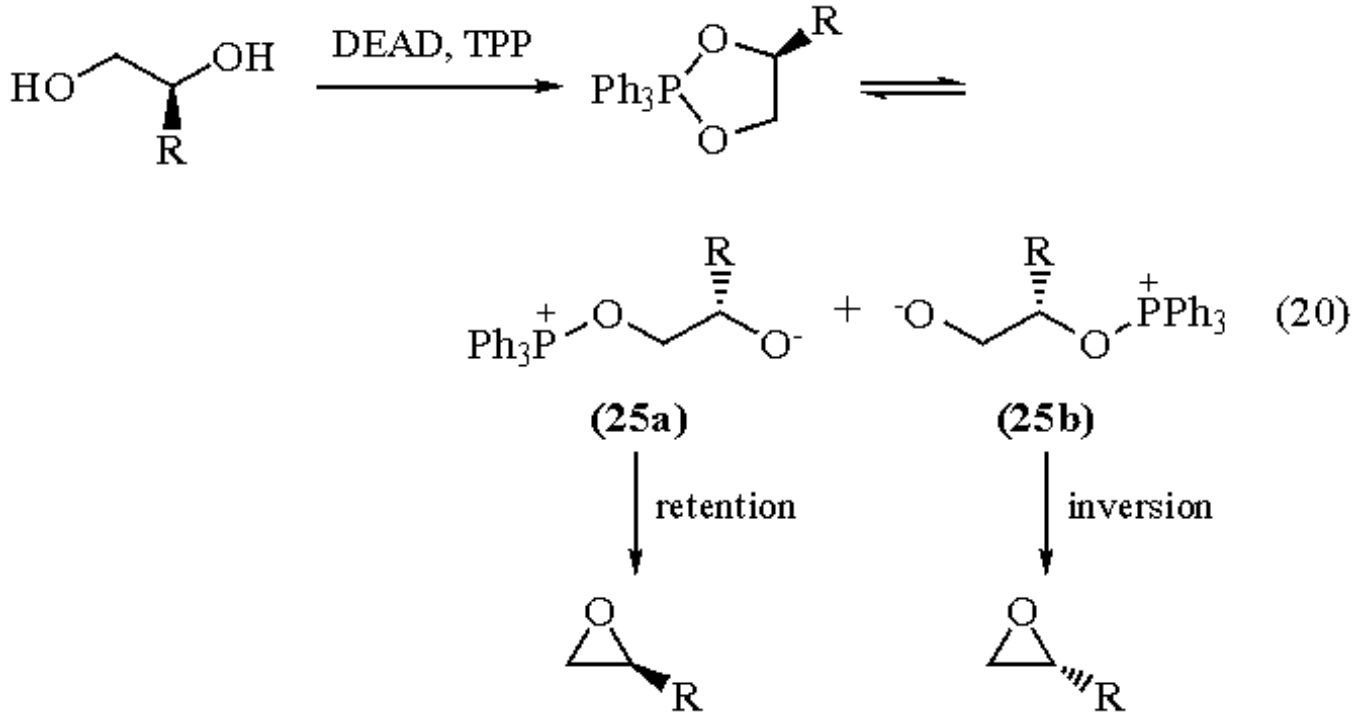

The reaction of cyclic *trans*-1,2-diols with DEAD and TPP generally gives the corresponding oxiranes via phosphoranes.[1,33b,59] Cyclic *cis*-1,2-diols also react with DEAD/TPP to afford primarily phosphoranes (**26**) which decompose into final product(s) such as oxiranes (with retention of configuration) (eq 21)[60] and dehydrated alcohols and/or ketones (eq 22).[61]

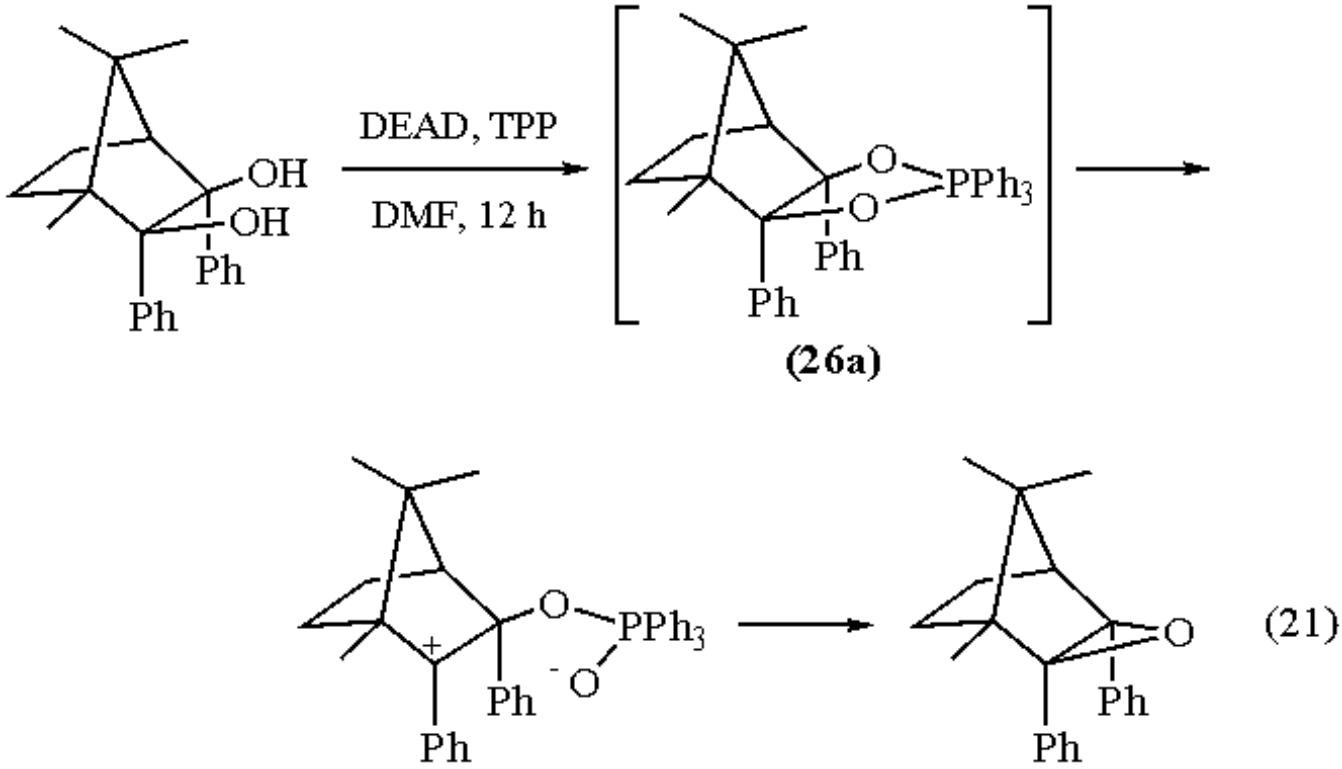

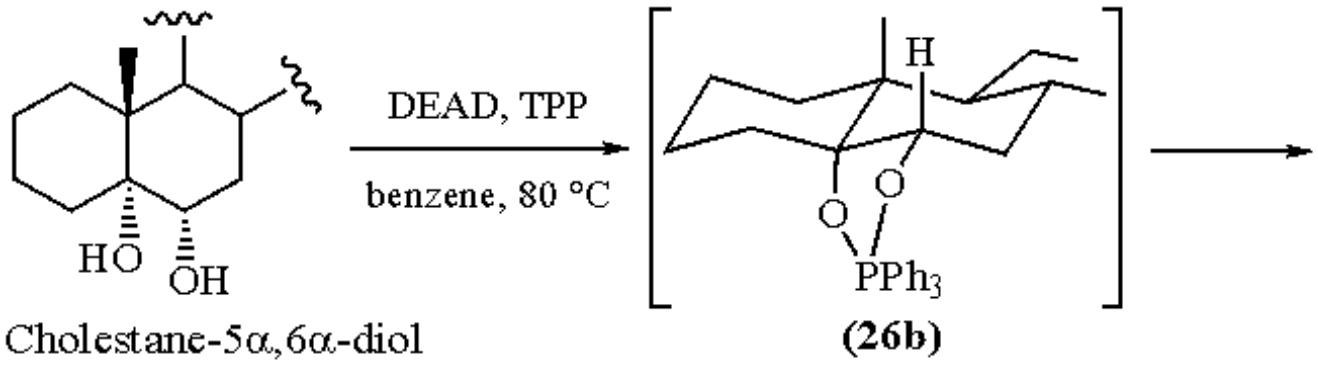

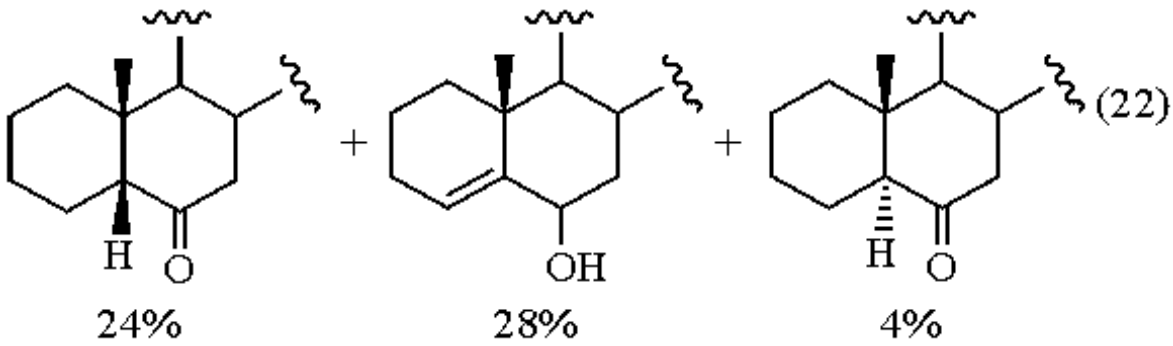

Carbon-Nitrogen Bond Formation.

Phthalimide reacts with alcohols, DEAD, and TPP to give the corresponding *N*-alkylphthalimides with inversion of configuration (eq 2; HA = phthalimide).[1] Nitrophthalimide is more reactive than phthalimide.[22a] If the reaction site is hindered and an S_N1 process favored, some stereochemical scrambling is observed. For example, the reaction of (**27**) with phthalimide in the presence of DEAD and TPP results in complete epimerization, giving (**28a**) and (**28b**) in a ratio of 1:1 (eq 23).[62] Neighboring group participation is also possible in some cases.[63]

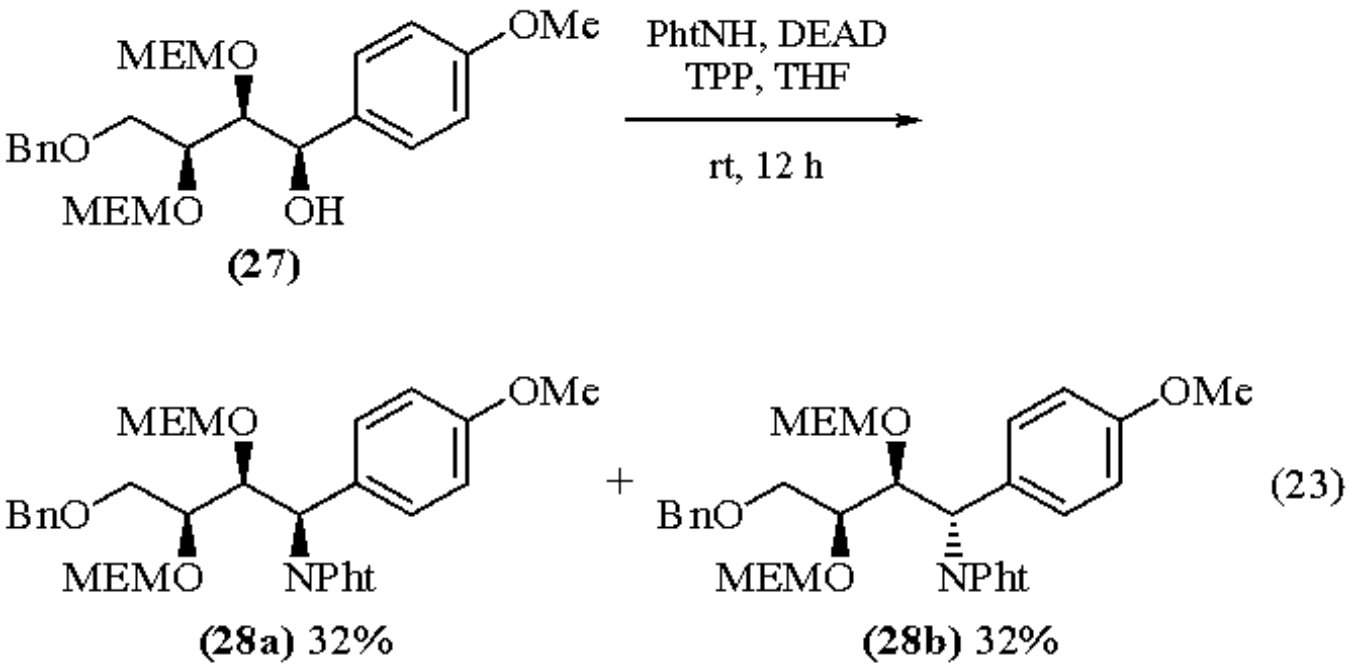

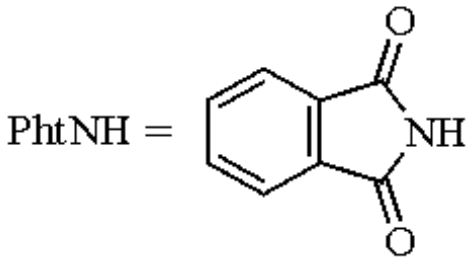

Alcohols having an acidic hydrogen atom adjacent to the hydroxyl group may undergo dehydration rather than substitution.[1] Thus the reaction of diethyl maleate (**29**) with phthalimide, DEAD, and TPP gives diethyl fumarate without any detectable formation of the substituted product.[64a] With ***Hydrazoic Acid***, however, (**29**) gives the expected azido succinate (**30**) in 74% yield (eq 24).[44a] Dehydration is regioselective in some cases.[64b,c]

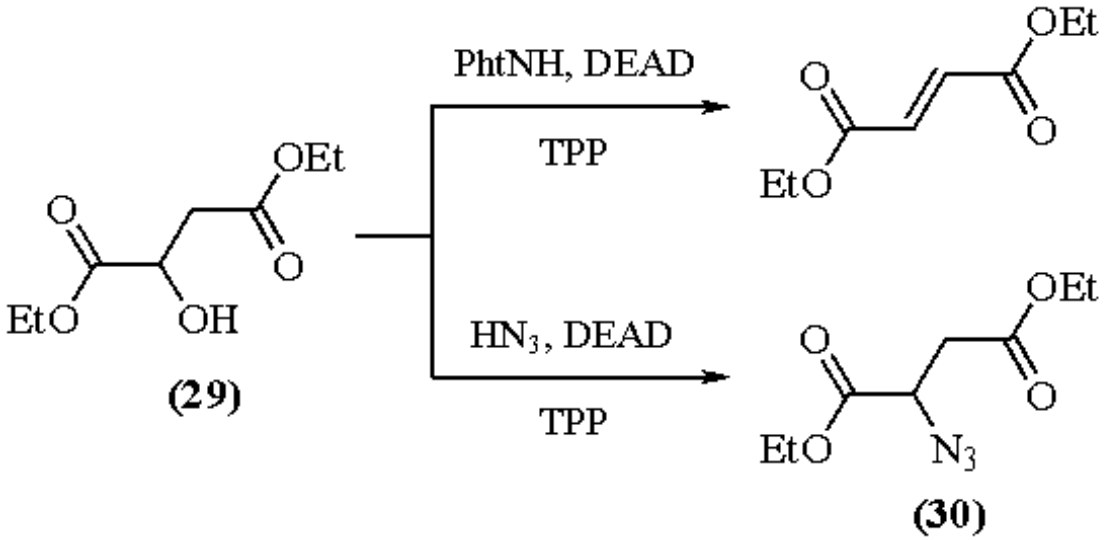

(24)

Since azides are very useful in organic synthesis (especially for the introduction of primary amino groups and the construction of heterocyclic systems), the direct conversion of alcohols into azides has been extensively studied (eq 2; HA = HN_3).[1,65] ***Diphenyl Phosphorazidate***[66] and the zinc azide/bis-pyridine complex[67] can be used instead of HN_3. Treatment of alcohols with hydrazoic acid, DIAD, and excess TPP in THF, followed by addition of water or aqueous acid, affords amines in moderate to good yields (eq 25).[68]

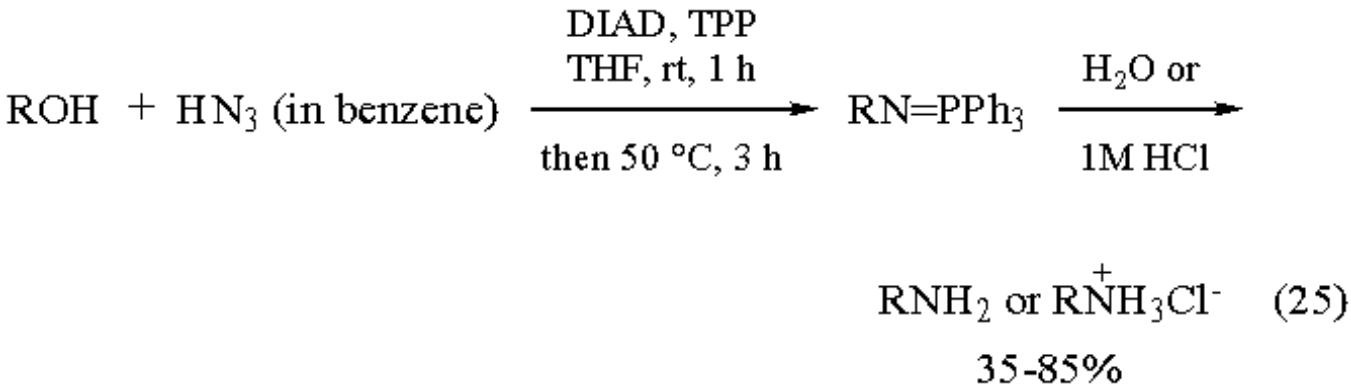

(25)

Acyclic amides and imides with pK_a < 13 can be expected to function as acidic components in the present reaction system. Thus the reaction of *N*-benzyloxycarbonylbenzamide with ethyl (*S*)-(-)-lactate gives the inverted *N*-alkylated product (**31a**) and the *O*-alkylated product (**31b**) in 19% and 48% yields, respectively (eq 26).[69] This result suggests that the alkoxyphosphonium salt (**3**) is a hard alkylating reagent.

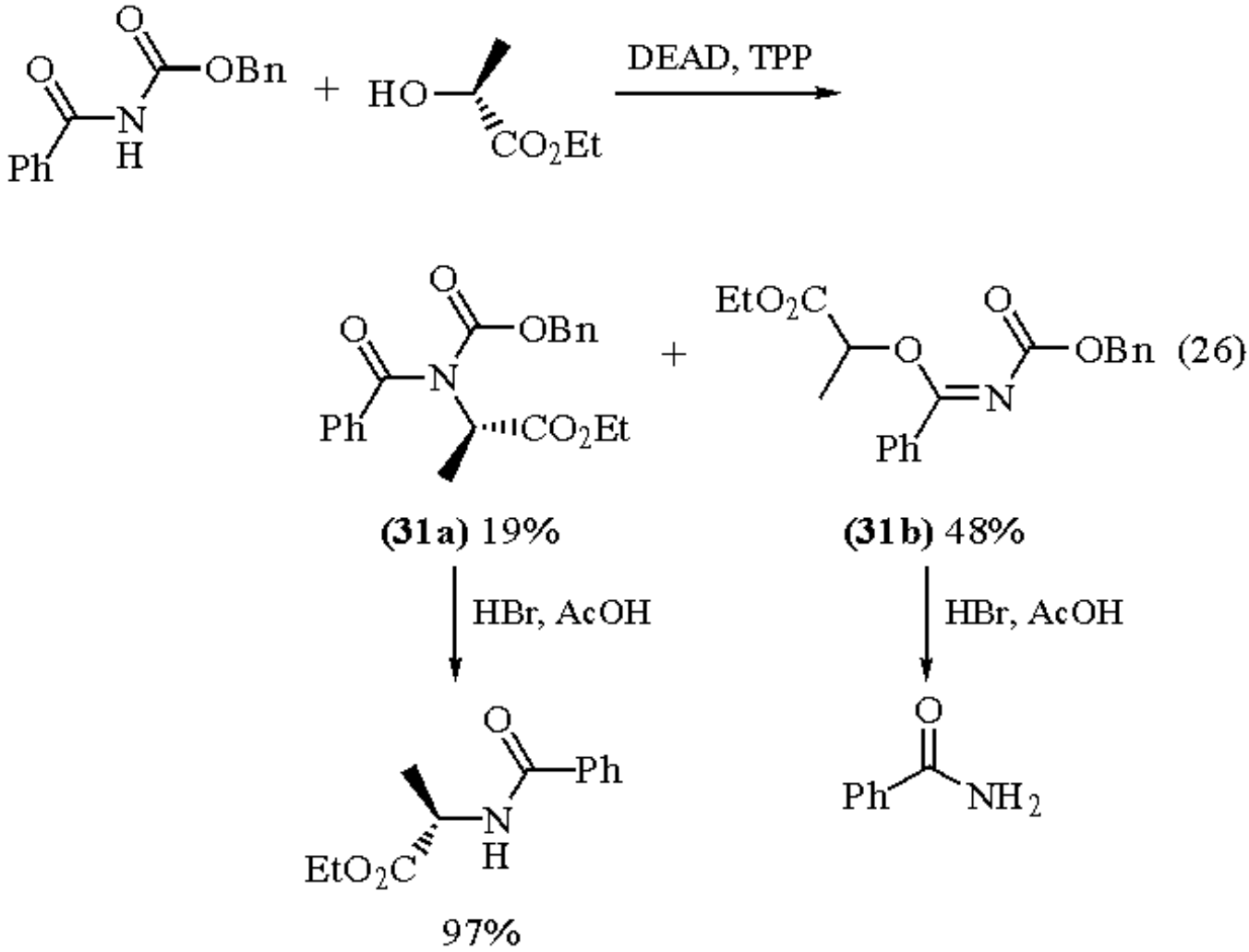

In the alkylation of imidodicarbonates and tosylcarbamates, the yield of alkylated product increases as the acidity of the NH acids increases. Thus imidodicarbonates and tosylcarbamates with pK_a < 13 give the corresponding *N*-alkylated products in 83-93% yields, while lower yields are obtained with less acidic substrates.[70a] The combination of ***1,1´-(Azodicarbonyl)dipiperidine*** (ADDP) with ***Tri-n-butylphosphine*** appears to be superior to that of DEAD with TPP in the alkylation of amides.[12] In the presence of DEAD and TPP, dibenzyl imidodicarbonate does not react with alcohols, but it does react with α-hydroxy stannanes to give the corresponding *N*-alkylated products (eq 27).[71]

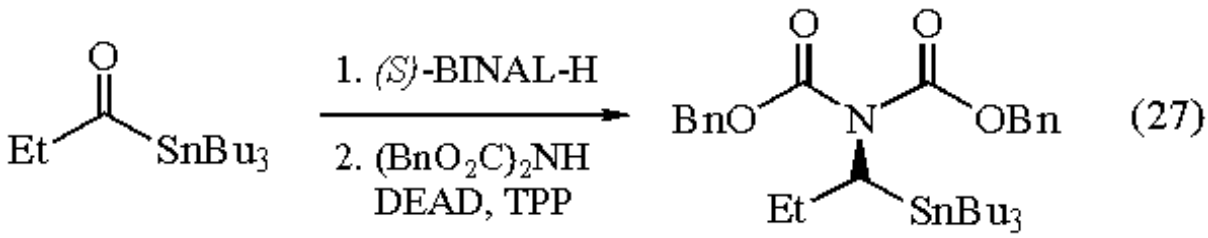

The *O*-acylhydroxamate (**32a**) (pK_a 6-7) reacts with benzyl alcohol, DEAD, and TPP to give *N*- and *O*-alkylated products, while the less acidic *O*-alkylhydroxamate (**32b**) (pK_a 9-10) gives only the *N*-alkyl product (eq 28).[72a]

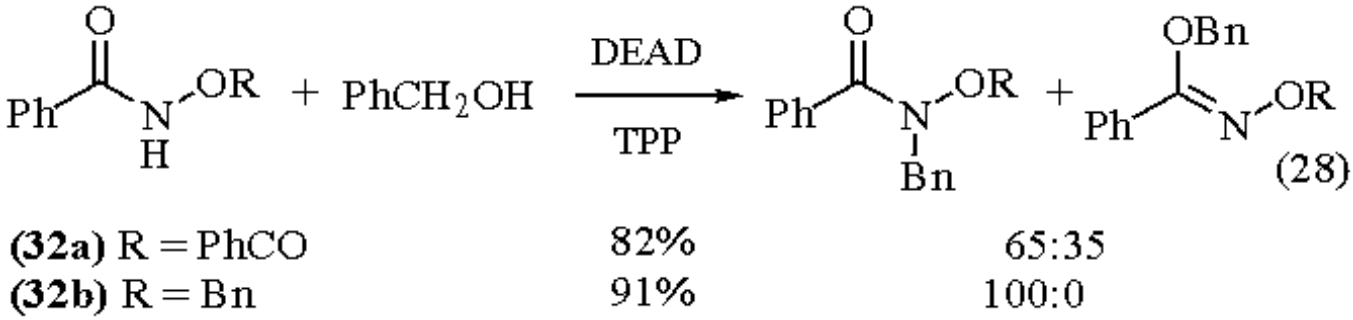

Intramolecular dehydration of 3-hydroxy carboxamides affords the corresponding β-lactams. Side reactions include elimination and formation of aziridines and oxazolidines (eq 29).[72,73] The efficiency of β-lactam formation is dependent on substrate substituents (including protecting groups

for the side-chain amino group) as well as on the choice of azodicarboxylate and P^{III} compound.[1c,74-76] For example, the dipeptide (**33**) reacts with DEAD and TPP to give a 2:1 mixture of the β-lactams (**34a**) and (**34b**). Control of the labile C-5 stereocenter can be achieved by use of ***Triethyl Phosphite*** instead of TPP; (**34a**) and (**34b**) are obtained in a >50:1 ratio (eq 30).[75] 3-Hydroxy *O*-alkylhydroxamates can also be converted into the corresponding β-lactams (eq 31).[1c,77]

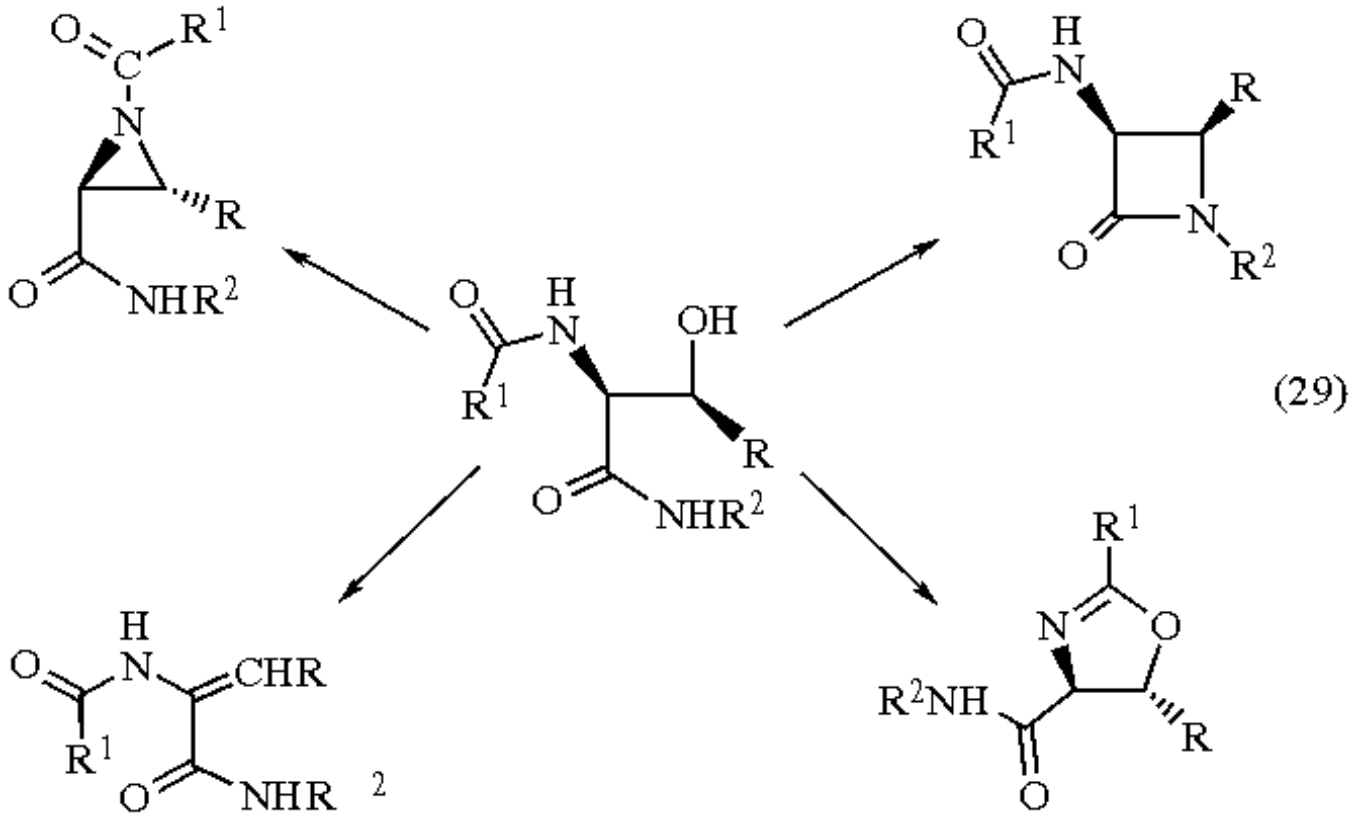

(29)

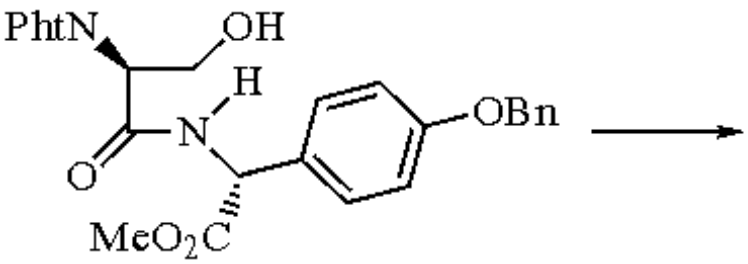

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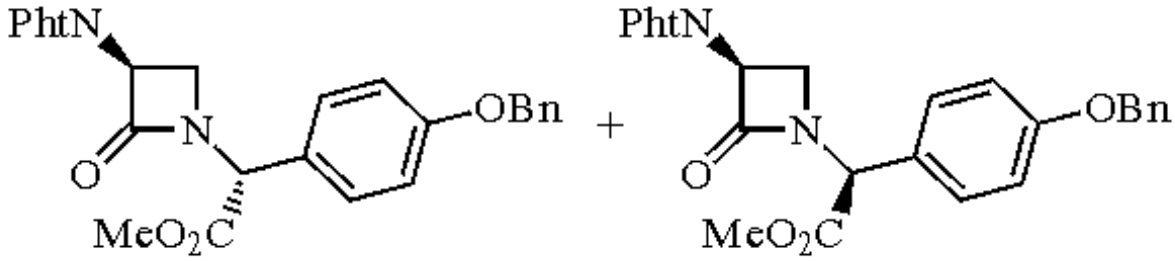

(30)

(34a) **(34b)**

DEAD-TPP	2:1
DEAD-$(EtO)_3P$	50:1

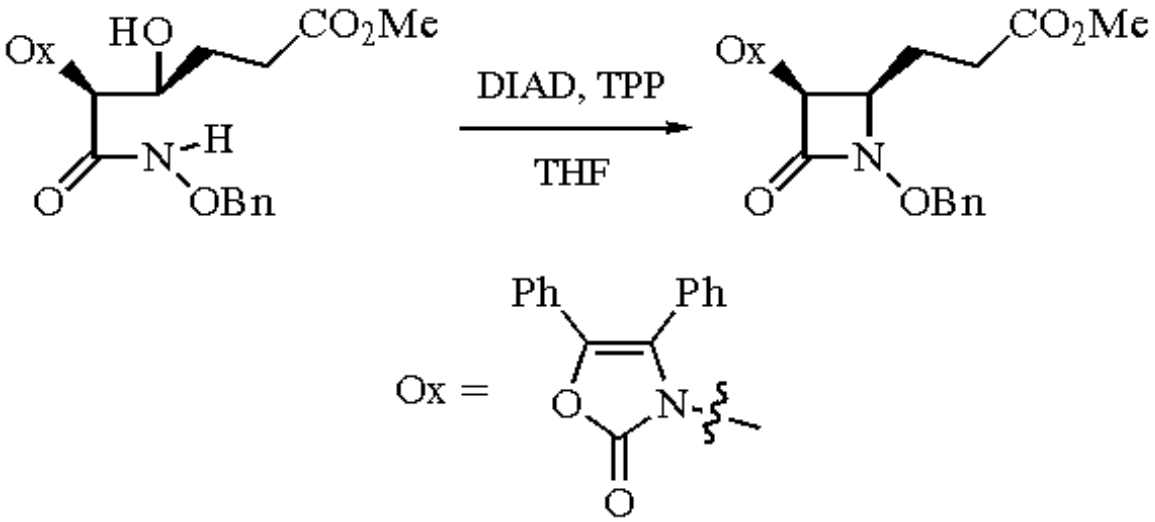

(31)

Purines and pyrimidines react with various alcohols in the presence of DEAD and TPP (eq 32).[78] The alcohol (**35**) gives a carbocyclic nucleoside (**36**) in 65% yield along with a small amount (9%) of the 7-substituted purine derivative (eq 33).[79-81]

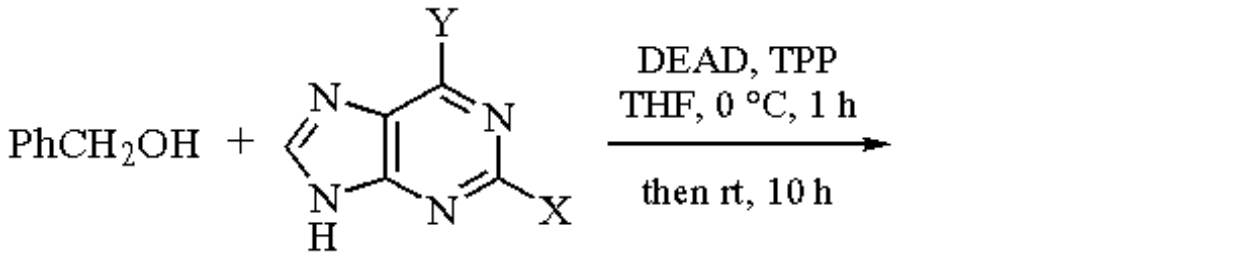

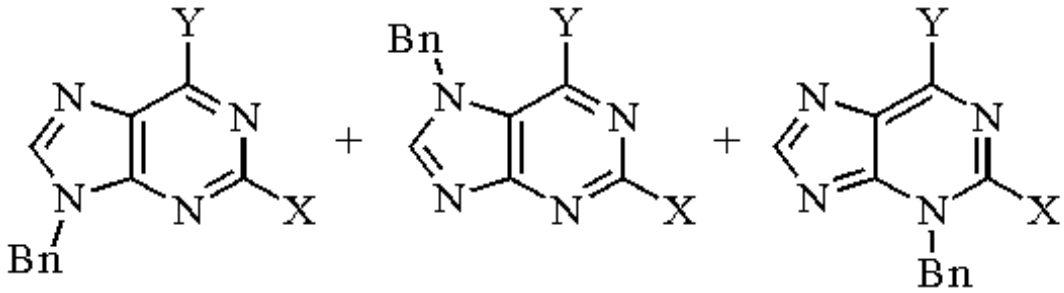

(32)

X = Y = H	70%	9%	21%
X = H, Y = Cl	67%	23%	9%
X = Y = Cl	69%	26%	-

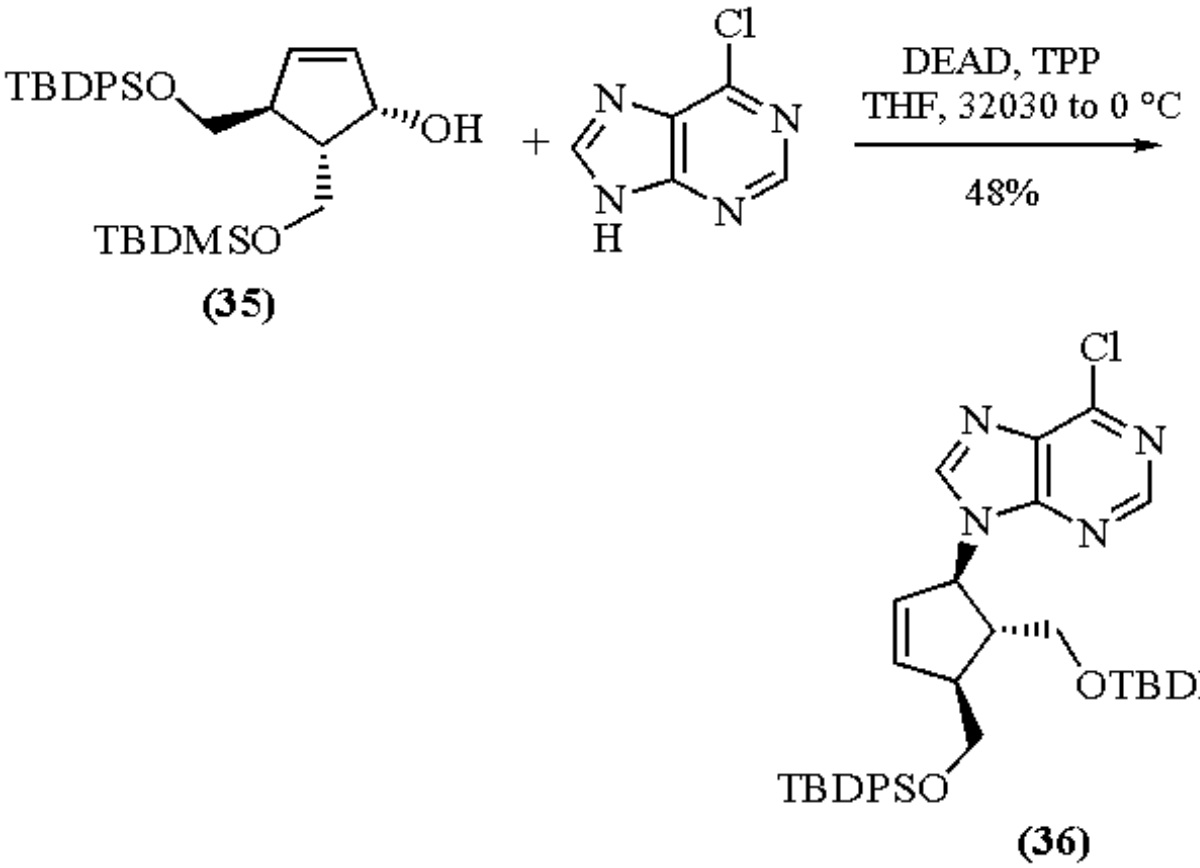

(33)

Reaction with Amino Alcohols and Related Compounds.

Both secondary and tertiary carbamates bearing a vicinal hydroxyl group react with carboxylic acids in the presence of DEAD and TPP to afford the corresponding esters with inversion of configuration (eq 34).[82] Reaction of *N*-*t*-butoxycarbonylserine with methanol, DEAD, and TPP gives the corresponding methyl ester in >98% yield (eq 35).[83] Without methanol, *N*-benzyloxycarbonyl- or *N*-*t*-butoxycarbonylserine reacts with the preformed adduct of DEAD and TPP to afford the β-lactone (eq 35).[84] The *N*-protected serine methyl ester (**37a**) and threonine methyl ester (**37b**) react with DEAD and TPP to give the dehydrated products (**38a**) and (**38b**) (eq 36).[85]

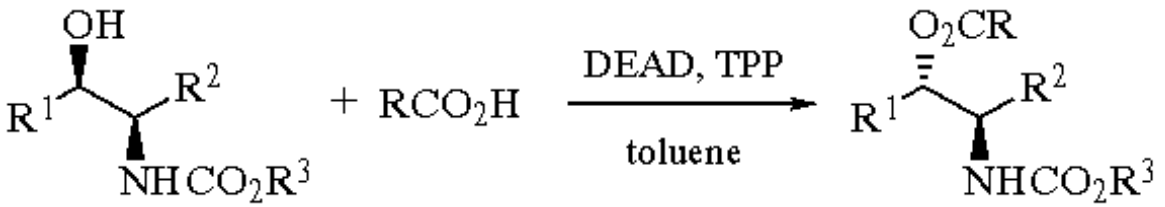

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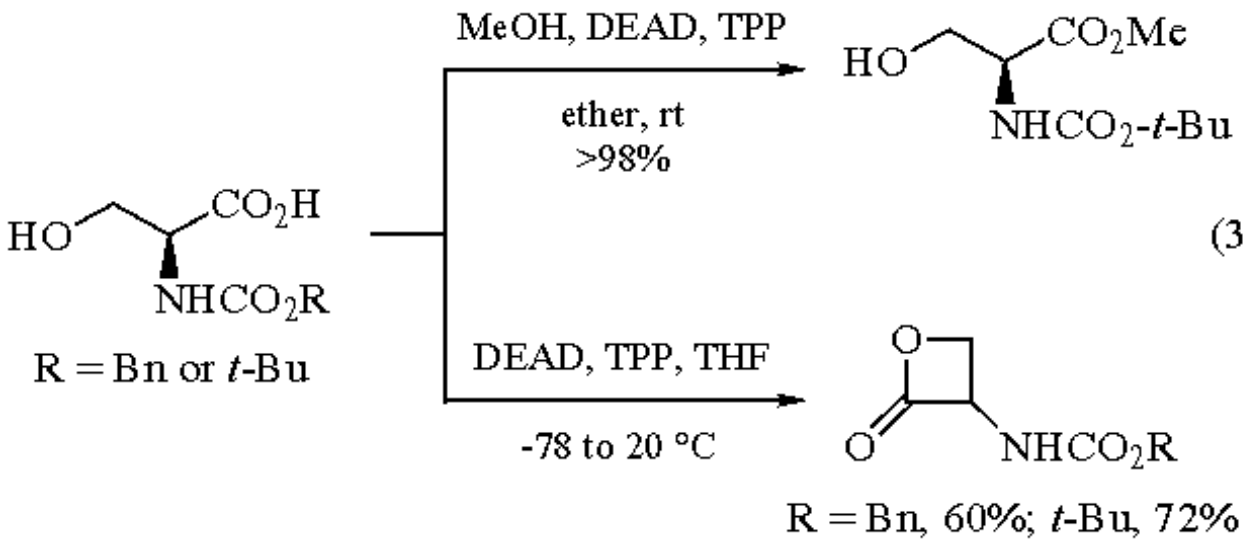

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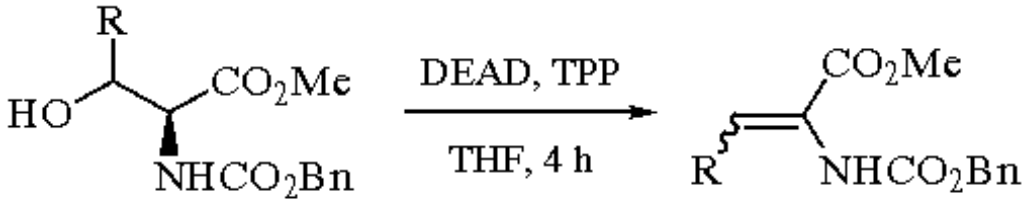

(36)

(37a) R = H
(37b) R = Me

(38a) R = H, 63%
(38b) R = Me, 55%

In the absence of an acidic component, β-(*N*-carbonylamino) alcohols afford aziridines or oxazolines, depending on the structure of the substrate. Contrary to the case of (**37**), the *N*-benzyloxycarbonylamino alcohol (**39**), with no acidic hydrogen present at the position adjacent to the hydroxyl group, affords the aziridine (**40**) in 85% yield (eq 37),[86,87] while the *N*-acylamino alcohols (**41**) give the oxazolines (**42**) in 31-68% yields (eq 38).[88]

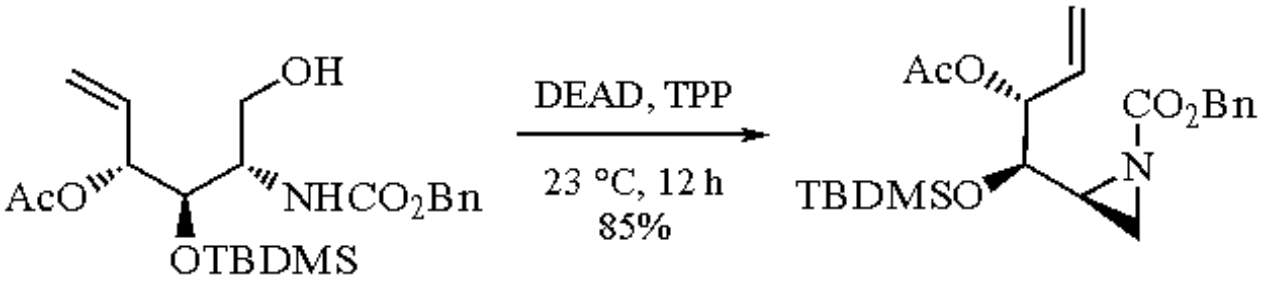

(37)

(39) **(40)**

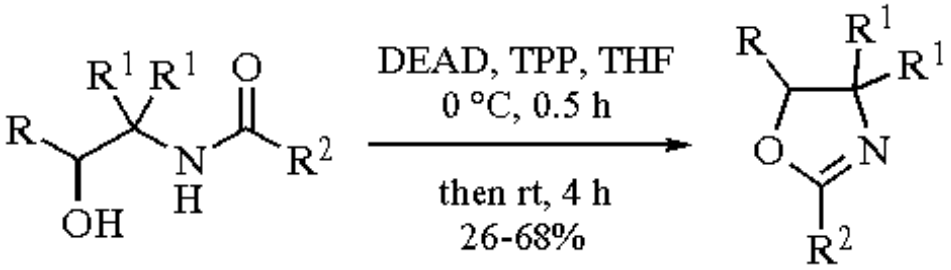

(38)

(41) **(42)**

Protection of the amino group by an electron-withdrawing group is not necessarily required for the cyclization. Amino alcohols of general structure HO-$(C)_n$-NHR react with DEAD and TPP to form the corresponding cyclic amines. Thus 2-aminoethanols give aziridines in 18-90% yields.[89] The reaction of the tetrafluoroborate salt of 3-(benzylamino)-1-propanol with DEAD and TPP gives the corresponding azetidine in 50% yield (eq 39).[90] Five- and six-membered cyclic amines are also prepared by the reaction of amino alcohols with DEAD and TPP (eqs 40 and 41).[91] Although azepines are not formed from straight-chain amino alcohols, compound (**43**) gives the azepines (**45a**) and (**45b**) by S_N2' substitution of the intermediate phosphorane (**44**) (eq 42).[92]

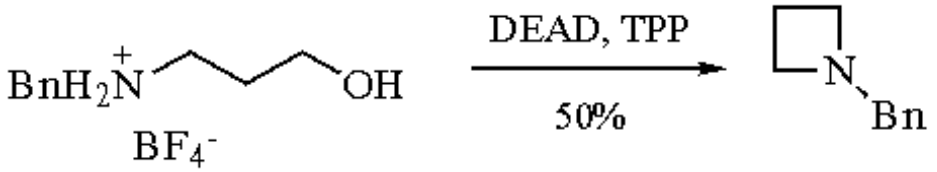

(39)

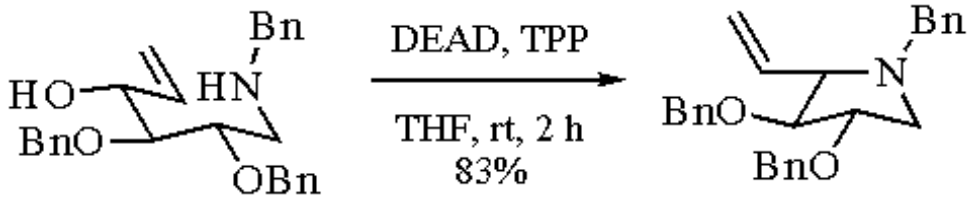

(40)

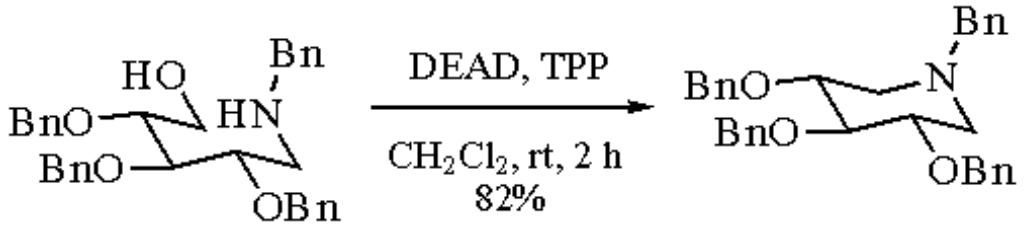

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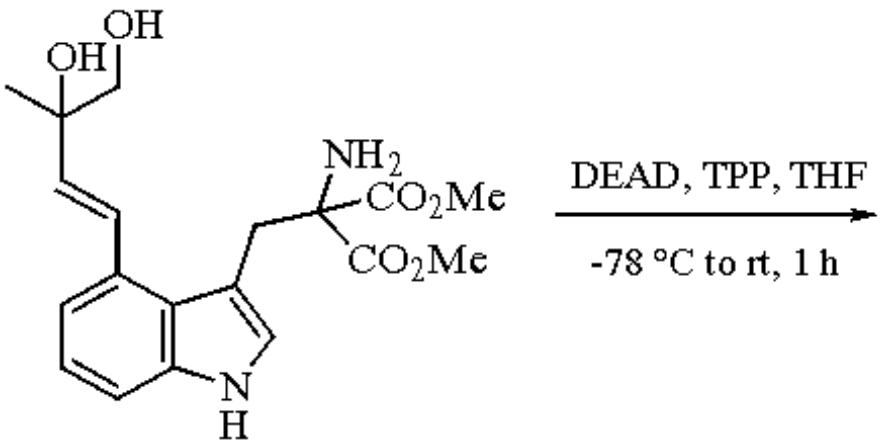

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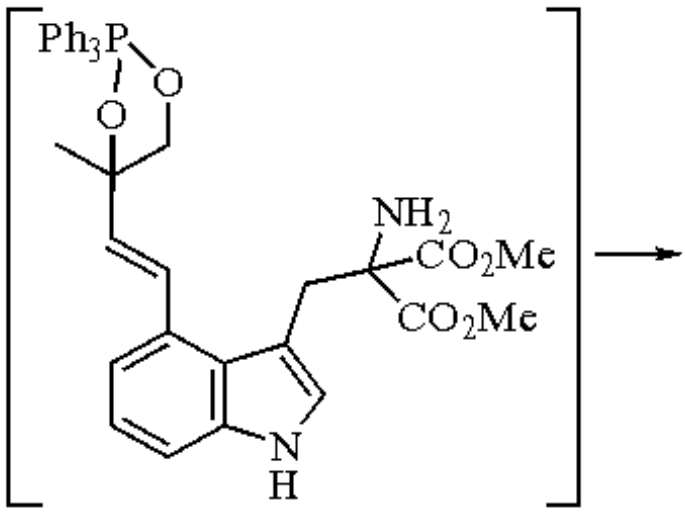

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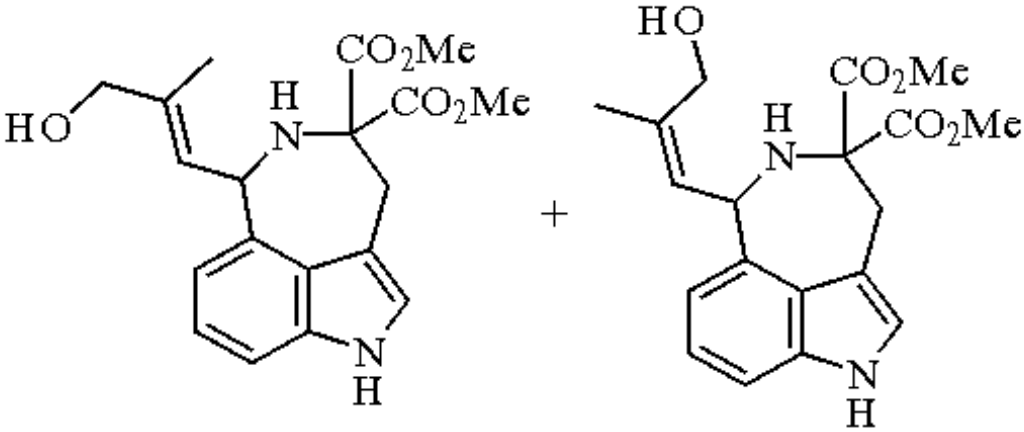

(42)

(45a) 85% **(45b)** 3%

O-Glycosidation with Phenols.

Monosaccharides possessing a free anomeric hydroxyl group react with phenol, DEAD, and trivalent phosphorus compounds to give phenyl glycosides. The yield is higher with trialkylphosphines (Bu_3P, Pr_3P).[93] Coupling of phenols and 2-α-(phenylthio)- or 2-α-(phenylseleno)-α-D-pyranoses by the use of DEAD and TPP gives aryl 2-deoxy-β-D-glycosides in 70-85% yields with high stereoselectivity (inversion of anomeric center) (eq 43).[94] Intramolecular phenolic glycosidation is also possible.[95]

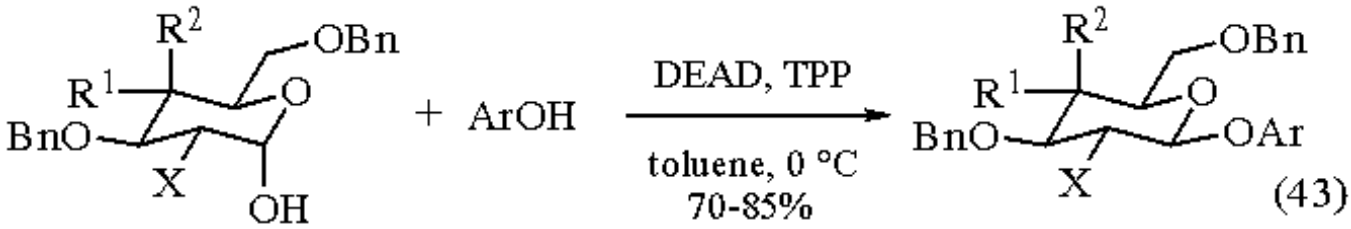

selectivity = 87:13 to 95:5

$R^1 = H, R^2 = BnO$ or $R^1 = BnO, R^2 = H$
X = PhS or PhSe; ArOH = 2-naphthol, phenol, or 2-cresol

O-Glycosidation with Carboxylic Acids.

Reaction of carbohydrates having a free anomeric hydroxyl group with carboxylic acids gives the corresponding glycosyl esters (eq 44).[96] Intramolecular glycosidation of (**46**) can be accomplished by the use of the preformed Bu_3P-DEAD betaine at low temperature (eq 45).[97]

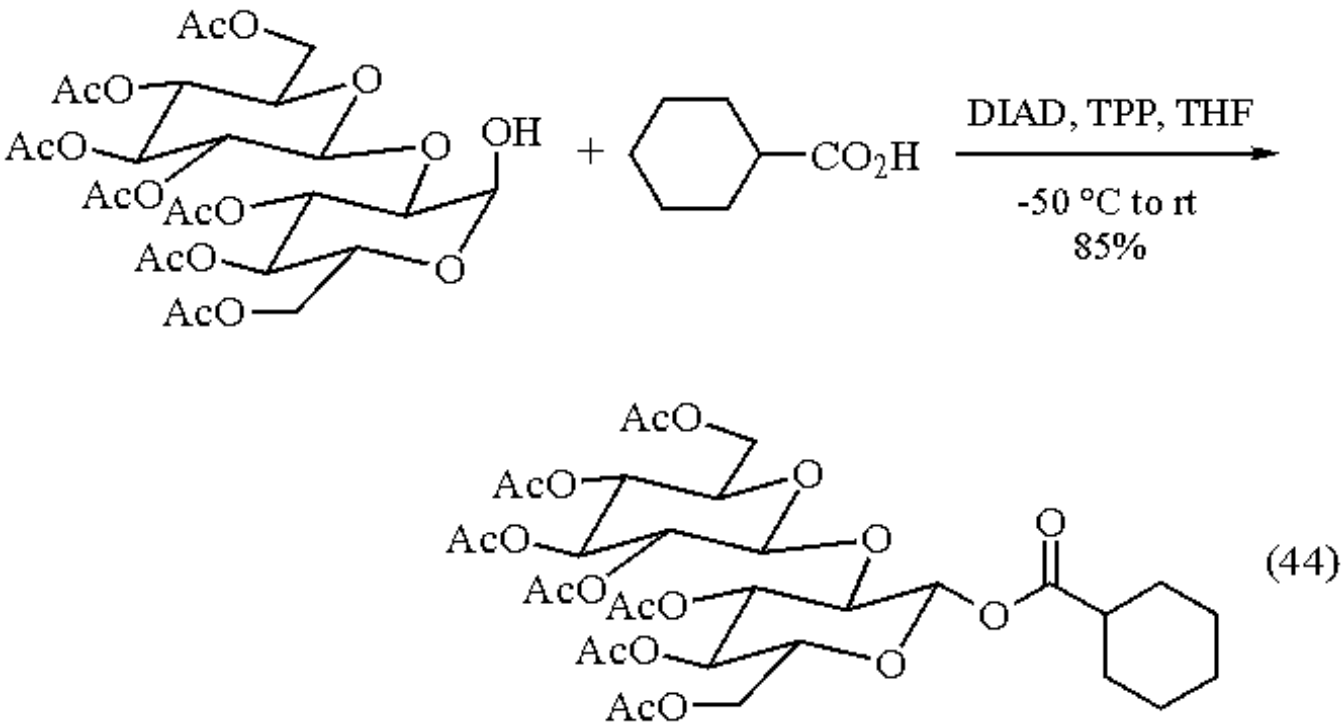

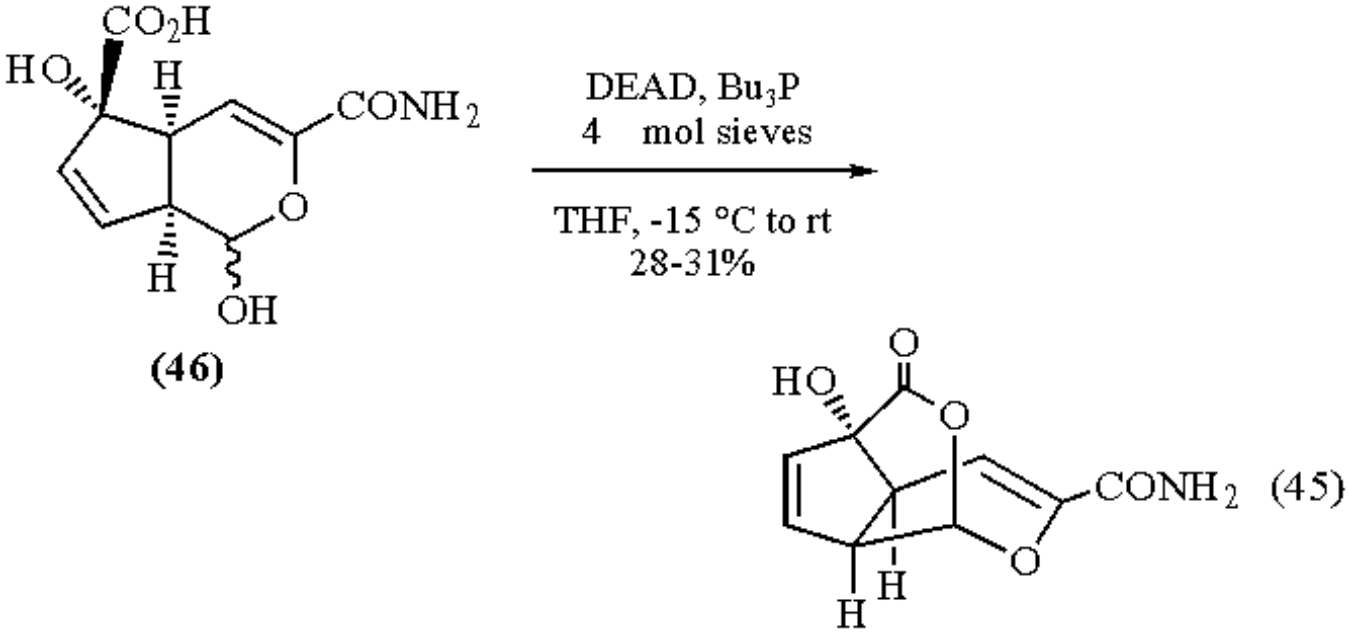

Glycosidation with Nitrogen Nucleophiles and *N*-Hydroxy Compounds.

Reaction of an anomeric hydroxyl group with nitrogen nucleophiles and with *N*-hydroxy heterocycles affords the corresponding glycosides.[1,98,99] The α-lactol (**48**) (α:β = ca. 8:1) reacts with *N*-hydroxyphthalimide, DIAD, and TPP to give the β-glycoside (**49**) (eq 46).[100]

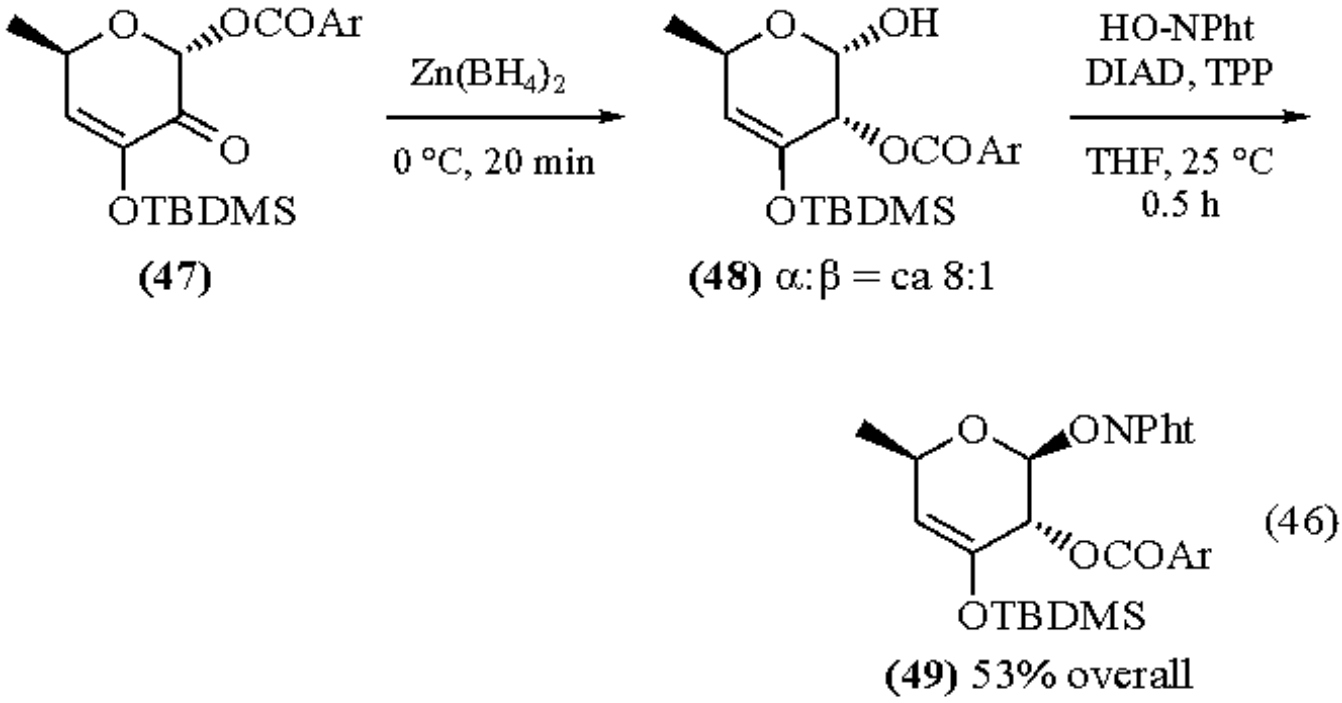

Carbon-Carbon Bond Formation.

Direct coupling of an alcohol with a carbon acid by the use of DEAD/TPP has been limited to only a few examples because of the lack of carbon acids with pK_a < 13. If enolizable carbonyl compounds are used, alkylation generally takes place on oxygen.[69a,101] Thus the reaction of 1,3-cyclohexanedione with isopropanol, DEAD, and TPP affords exclusively the *O*-alkylated product (eq 47).[101a] Cyanoacetate reacts at the carbon

atom, while diethyl malonate is unreactive.[101a] However, the reaction of diethyl malonate with alcohols in the presence of ADDP and Bu_3P affords *C*-alkylated products in 3-56% yields (eq 48).[12] Ethyl nitroacetate and nitromalonate oxidize the alcohol via an *aci*-nitro ester (eq 49).[102] *o*-Nitroarylacetonitriles of general formula (**50**) undergo alkylation on carbon (eq 50).[16,103]

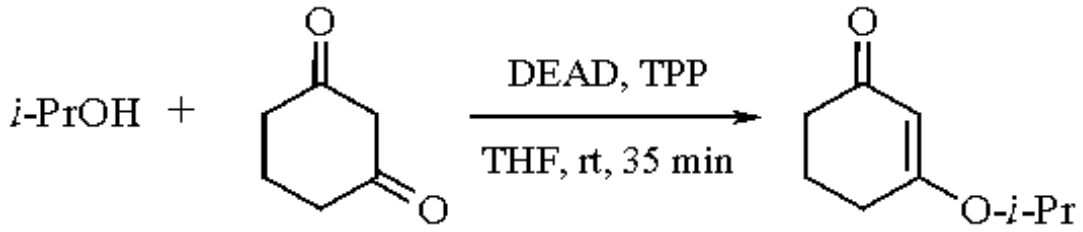

(47)

$$CH_2(CO_2Et)_2 + ROH \xrightarrow[\text{benzene, rt, 24 h; 3-56\%}]{\text{ADDP, } Bu_3P} RCH(CO_2Et)_2 \quad (48)$$

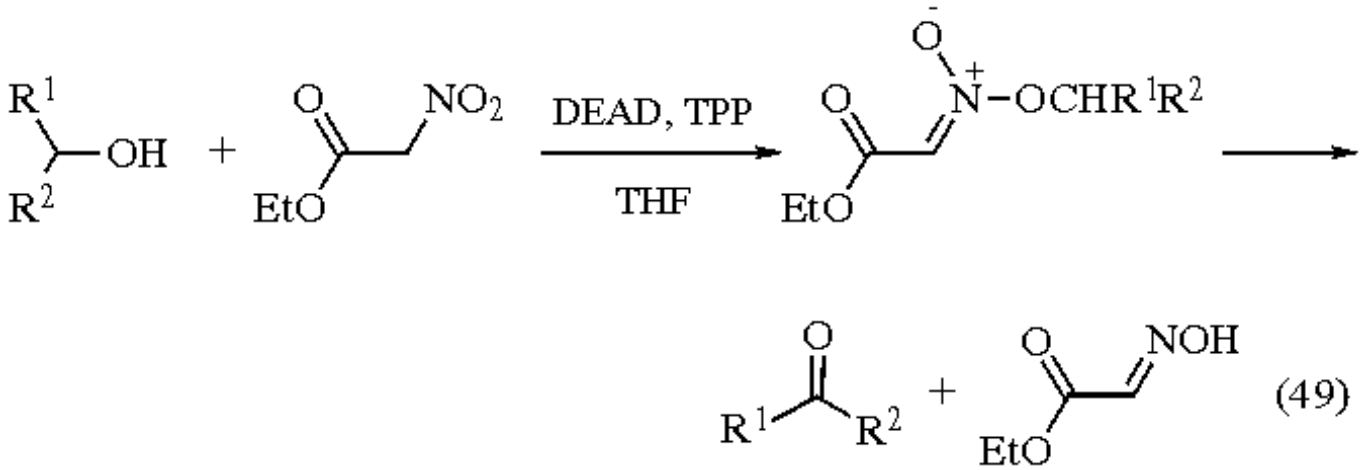

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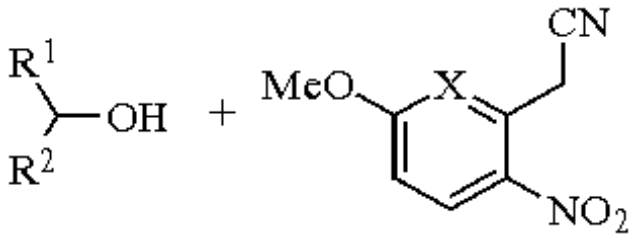

(50)

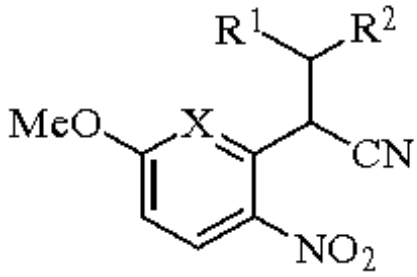

(50)

X = CH or N

γ-Nitro alcohols react with DEAD and TPP to afford α-nitrocyclopropanes in good to excellent yields (eq 51).[104a] On the other hand, nitro alcohols bearing electron-withdrawing or unsaturated substituents at the α-carbon experience exclusive intra- and intermolecular *O*-alkylation and furnish good to excellent yields of alkyl nitronates (eq 52). In contrast, 1-phenylsulfonyl-1-nitro-3-propanol affords the corresponding cyclopropane.[104b] Bis-sulfones readily undergo alkylation by alcohols.[104c] Novel intramolecular S_N2 and S_N2' type arylation occurs with certain aromatic and allylic alcohols (eqs 53 and 54).[105]

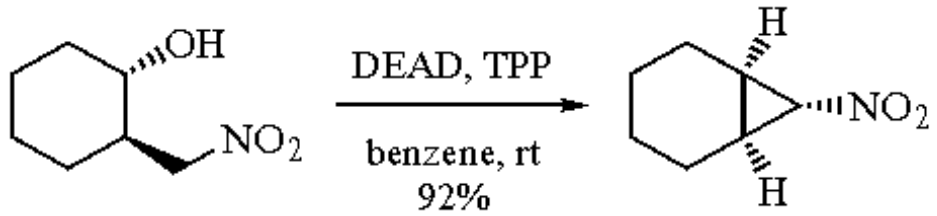

(51)

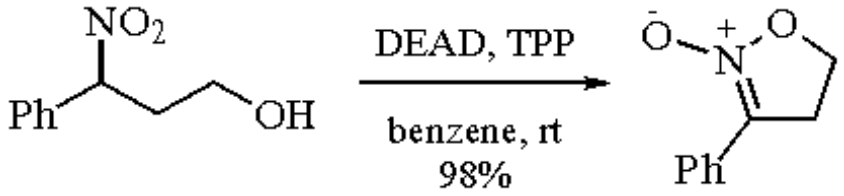

(52)

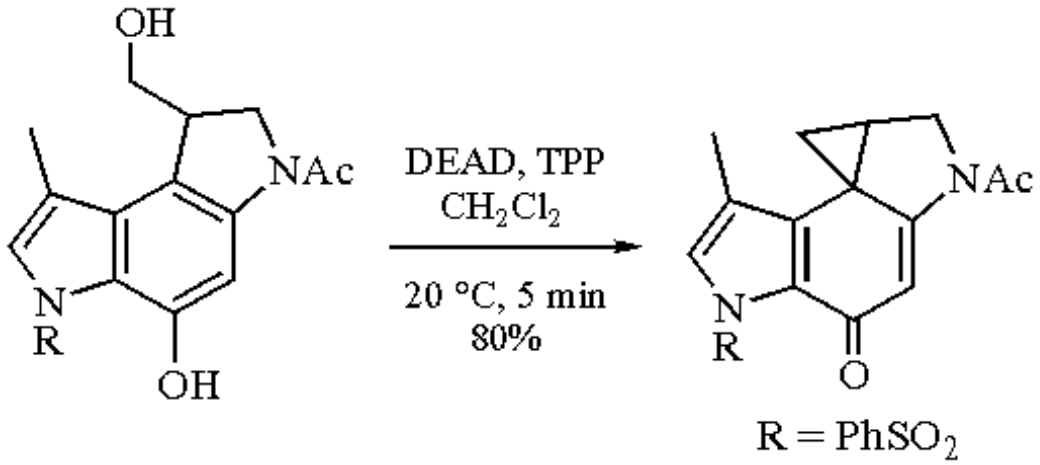

(53)

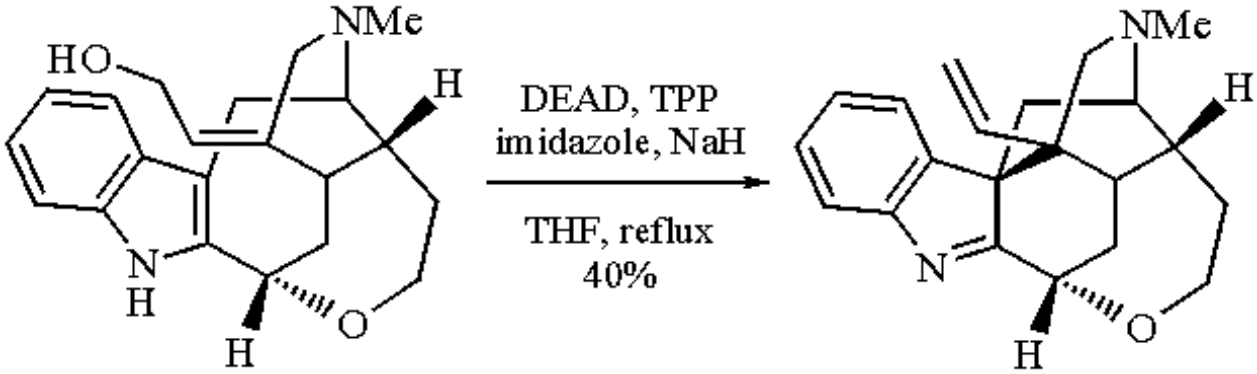

(54)

Miscellaneous Reactions.

Dialkyl phosphonates react with alcohols in the presence of DIAD and TPP to give trialkyl phosphites (eq 55).[5a] TPP-DIAD reacts with KHF_2 or HF-pyridine to form difluorotriphenylphosphorane (eq 56).[106]

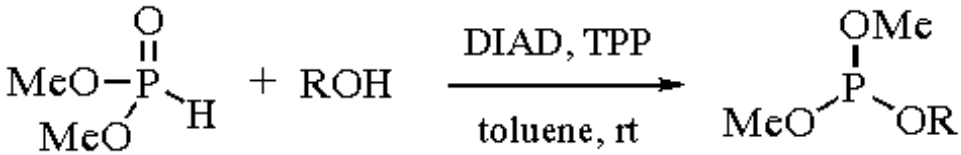

(55)

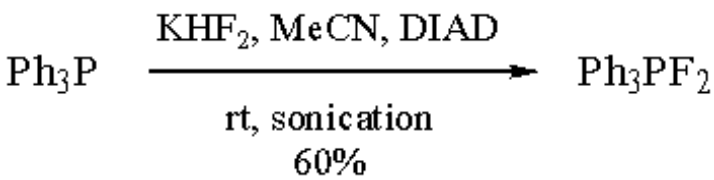

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Triphenylphosphine-Hexachloroacetone

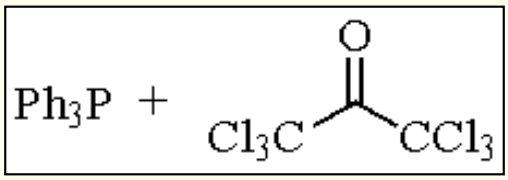

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Hexachloroacetone · (MW 262.30) (HCA)

[116-16-5] · C_3Cl_6O · Triphenylphosphine-Hexachloroacetone · (MW 264.73)

(conversion of alcohols, particularly allylic alcohols, into chlorides with high regio- and stereoselectivity)

Physical Data: Ph_3P: see ***Triphenylphosphine***. Hexachloroacetone: mp -3 °C; bp 202 °C, 66 °C/6 mmHg; *d* 1.74 g cm^{-3}.

Solubility: hexachloroacetone: slightly sol H_2O; sol acetone, benzene, chloroform, ether.

Form Supplied in: hexachloroacetone: liquid, widely available.

Handling, Storage, and Precautions: hexachloroacetone: toxic, irritant.

General Discussion.

The conversion of allylic alcohols into chlorides (eq 1) presents difficulties not encountered with saturated compounds. A successful synthesis will be: (a) regiospecific (exclusive formation of either the α- or γ-substituted product); (b) stereoselective or stereospecific (preservation of the β,γ-double bond geometry when unrearranged product is formed; complete inversion or retention of configuration in the unrearranged product when the α-carbon is stereogenic); and (c) gentle (the conditions of the reaction, isolation, and workup should cause neither allylic rearrangement nor decomposition of the product).

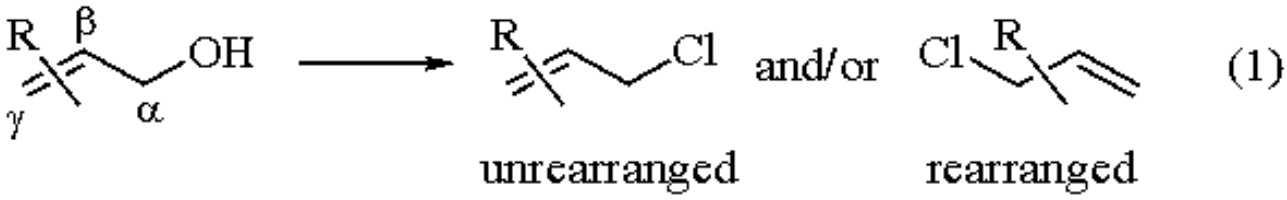

There is, at present, no single method that meets all of these criteria for every type of allylic alcohol. Conventional reagents like $SOCl_2$ and PCl_3 have been used, but with mixed results.[1] Some recently developed and frequently used methods are: (a) $MeSO_2Cl$/LiCl/DMF/collidine;[2a] (b) RLi/HMPA, then TsCl, then LiCl/HMPA;[2b] and (c) *N*-chlorosuccinimide/Me_2S/CH_2Cl_2.[2c] All of these are successful with primary substrates, but less so with secondary and tertiary allylic alcohols.[1a,3] The combination ***Triphenylphosphine-Carbon Tetrachloride*** has had notable success, not only for transforming saturated alcohols into chlorides, but also for a variety of condensation reactions.[4] Mechanistic studies[5] have revealed that chloride formation succeeds even for alkyl groups that are prone to rearrange and that it proceeds with inversion of configuration at the alcohol center. The relative mildness of this system prompted Snyder[6] to test it with allylic alcohols (eqs 2 and 3); crotyl alcohol (as an unspecified mixture of (*E*)- and (*Z*)-isomers) reacts without rearrangement, whereas 3-buten-2-ol proceeds regioselectively to an 89:11 mixture of products. One of the drawbacks to this procedure is that low molecular weight allylic chlorides have boiling points very close to those of carbon tetrachloride and its reaction product chloroform, thus making the isolation of product(s) difficult. It was principally for this reason that it was decided to replace CCl_4 with a higher boiling source of Cl^+; hexachloroacetone (HCA) was chosen, not only for its high boiling point, but also because the anionic intermediate after Cl^+ removal would benefit from resonance stabilization.[7]

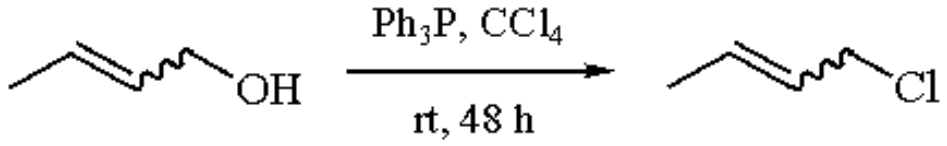

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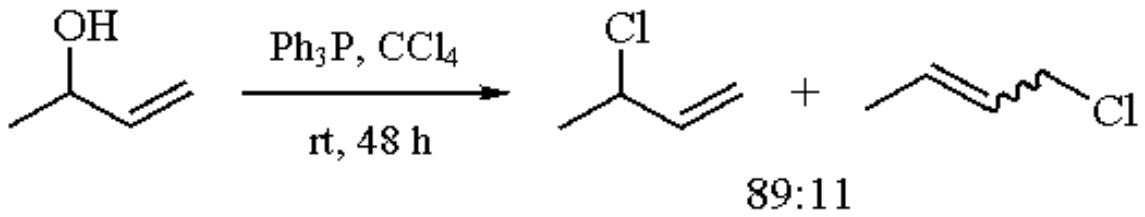

(3)

In fact, not only does the triphenylphosphine-hexachloroacetone system work admirably for a wide variety of allylic alcohols, but the conditions of the reaction and isolation are especially mild. Typically, a slight excess of solid Ph_3P is added to an ice-cold solution of the allylic alcohol in hexachloroacetone solvent (although the order of mixing of the reagents appears to be unimportant); after about 10-15 minutes the solution is warmed to room temperature and the product flash-distilled (at about 1-3 mmHg), yielding the allylic chloride(s) in nearly quantitative yield, uncontaminated by Ph_3P, HCA, or their reaction products. If desired, the reaction can be run with a stoichiometric quantity of hexachloroacetone in sulfolane; indeed, it is found that two chlorines (but not more) per HCA molecule can be used in this reaction. Saturated alcohols (1- and 2-butanol, neopentyl alcohol) give excellent yields of unrearranged chloride. The results shown in eqs 4-6[7b] are typical of the behavior of a total of sixteen allylic alcohols. Primary alcohols give essentially 100% unrearranged chloride with total preservation of double bond stereochemistry. Secondary alcohols tend toward ca. 90/10 mixtures of unrearranged/rearranged product. When the α-carbon is stereogenic, the reaction proceeds with complete inversion of configuration. The method fails only for tertiary alcohols, which give significant amounts of rearranged chloride and elimination product.

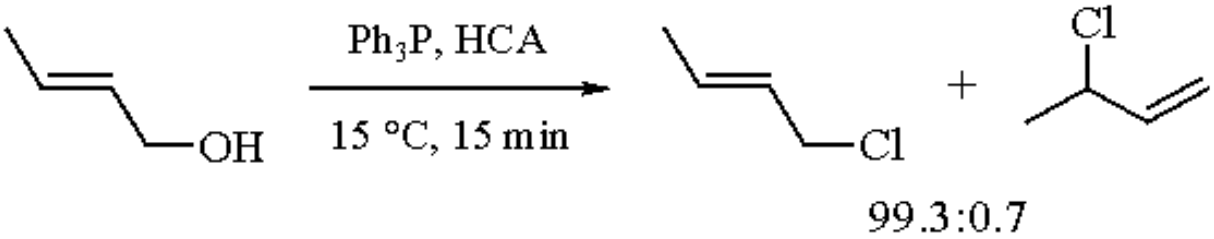

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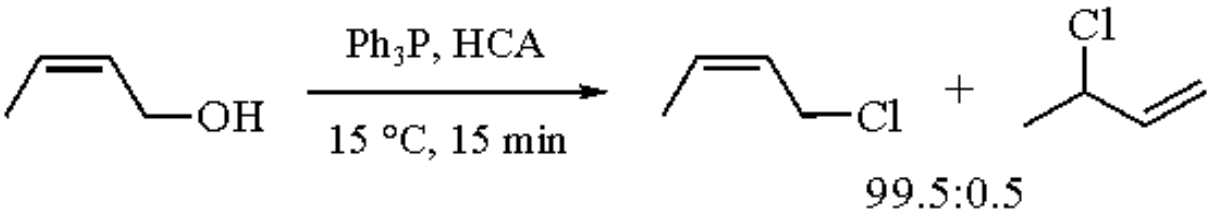

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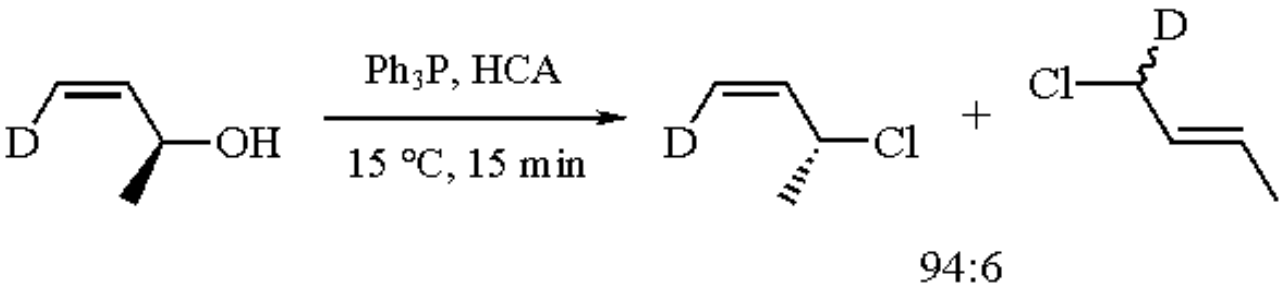

(6)

The system Ph_3P/HCA has also found use with cyclopropylcarbinyl alcohols.[8a] HCA can be replaced by hexabromoacetone in order to make allylic bromides.[8b] HCA, by itself, reacts with enamines,[8c] alcohols in DMF,[8d] tertiary amines,[8e] and miscellaneous nucleophiles.[8f]

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Triphenylphosphine Hydrobromide

$Ph_3P.HBr$

[6399-81-1] · $C_{18}H_{16}BrP$ · Triphenylphosphine Hydrobromide · (MW 343.21)

(mild source of anhydrous HBr;[1] catalyst for formation of THP ethers from tertiary alcohols;[2] preparation of phosphonium salts[3,4])

Alternate Name: triphenylphosphonium bromide.

Physical Data: mp 196 °C (dec).

Solubility: sol CH_2Cl_2, $CHCl_3$; slightly sol THF, benzene; insol ether.

Form Supplied in: commercially available white powder.

Analysis of Reagent Purity: acidometric titration.

Preparative Methods: addition of anhydrous ***Hydrogen Bromide*** to an ethereal solution of ***Triphenylphosphine***;[2] addition of Ph_3P to 48% aqueous HBr followed by $CHCl_3$ extraction and drying.[1]

Purification: recrystallization from CH_2Cl_2/Et_2O, or by washing with warm EtOAc to remove excess Ph_3P.

Handling, Storage, and Precautions: corrosive and hygroscopic; keep dry.

Source of Anhydrous HBr.

Triphenylphosphine hydrobromide (**1**) is a convenient, crystalline source of anhydrous HBr for a wide variety of applications, including as a gas.[1] This reagent has found an important use in the glycosidation of glycals[5,6] without interference from allylic (Ferrier) rearrangement (eq 1). There is a distinct preference for the α-anomer, even when the incoming nucleophile is not sterically demanding. Other commonly used acid sources (***Hydrogen Chloride***, ***Hydrogen Fluoride***, Amberlyst H-15 resin, ***p-Toluenesulfonic Acid***) and Lewis acids (***Boron Trifluoride Etherate***) catalyze allylic rearrangement.

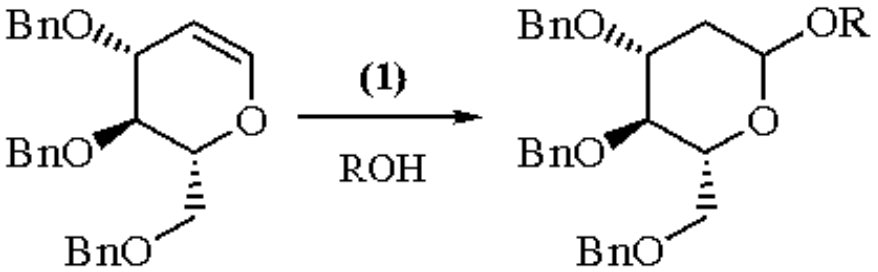

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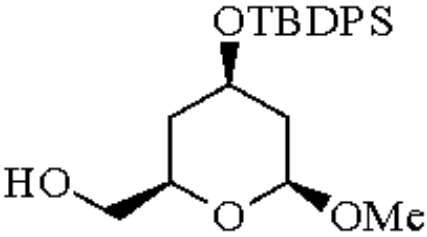

60% yield, α:β = >95:5

$MeCO_2H$ 71% yield, α:β = 92:8

MeOH 87% yield, α:β = 70:30

Catalyst for Formation of THP Ethers.

Tetrahydropyranylation, particularly of tertiary alcohols, can be catalyzed by (**1**) (eq 2).[7] Depending on the substrate, these reactions are complete in about 20 h, and the conditions are quite mild when compared with those needed with catalysts such as ***Pyridinium p-Toluenesulfonate***. Other acid catalysts such as TsOH can lead to elimination or polymerization of sensitive tertiary alcohols.

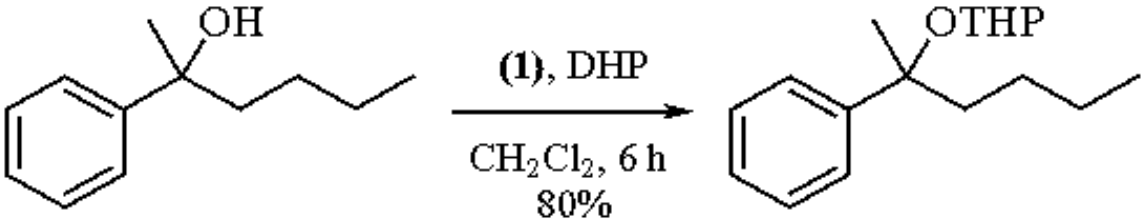

(2)

Preparation of Phosphorus Ylides.

Treatment of alkyl chlorides with (**1**) results in the formation of phosphonium salts. Rather than a direct displacement of chloride by phosphorus, this reaction proceeds by initial conversion of RCl to RBr, followed by formation of the phosphonium salt.[8] A wide variety of primary alcohols can be converted directly to the phosphonium bromides in high yield by treatment with (**1**).[3] Both aliphatic and allylic alcohols react with (**1**) in sealed tubes at 160 °C within 2 h (eq 3). Secondary (and presumably tertiary) alcohols suffer dehydration under these conditions. Allylic alcohols (such as the carotenoid precursor (**2**))[9] do not undergo allylic transposition (eq 4), although there have been cases where reactive alkenes have produced phosphonium salts upon heating with (**1**).[10]

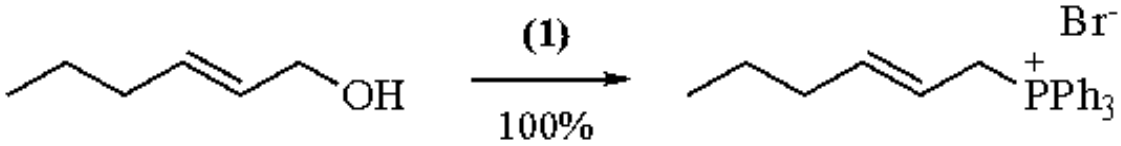

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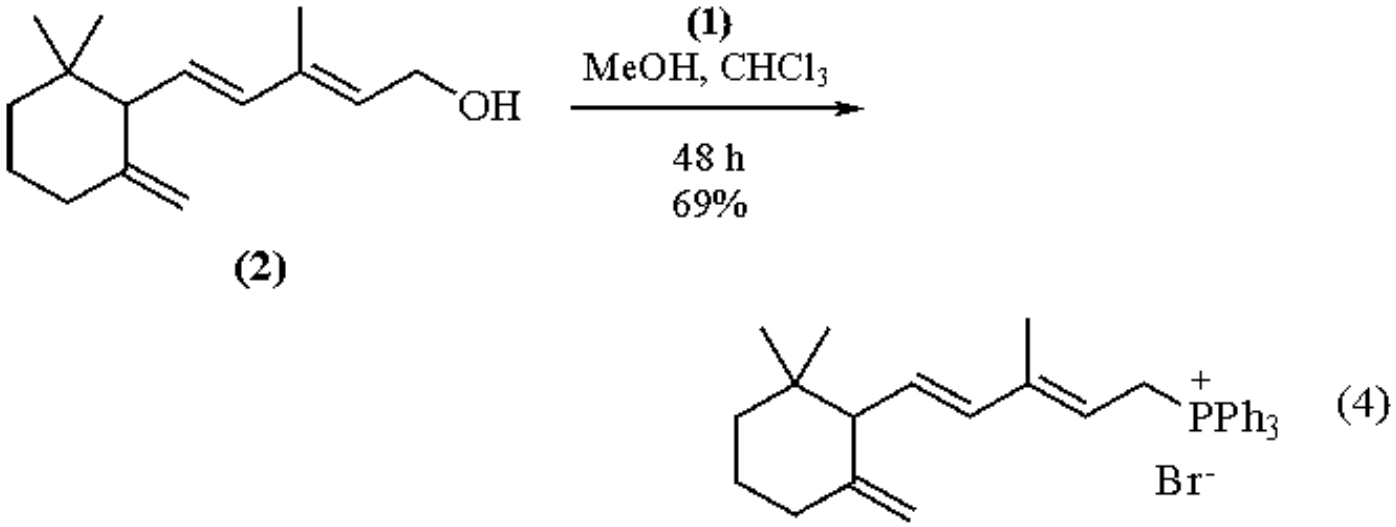

Under similar conditions (heating in a sealed tube for 4 h at 180 °C), lactones react to form the free acid phosphonium salt in excellent yield (eq 5).[3] Reactive alkenes such as enol ethers,[4] indene, and α,β-unsaturated carbonyl compounds[11] also undergo addition of (**1**) when other nucleophiles are not present. This reaction has been used to prepare a novel three-carbon Wittig reagent bearing a protected aldehyde function.[11]

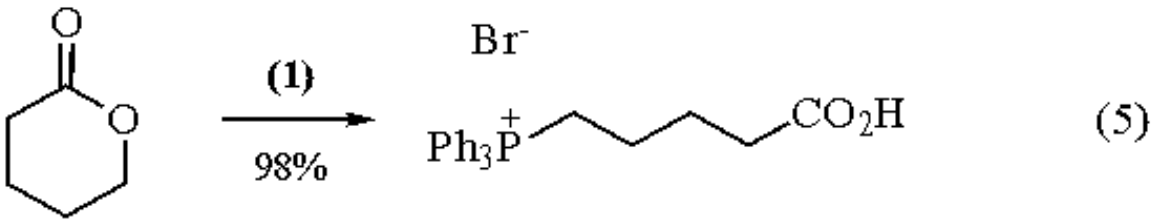

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Triphenylphosphine-Iodine[1]

$Ph_3P.I_2$

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Iodine · (MW 262.30) (I_2)

[7553-56-2] · I_2 · Triphenylphosphine-Iodine · (MW 253.80) ($Ph_3P.I_2$)

[80800-01-2] · $C_{18}H_{15}I_2P$ · Triphenylphosphine-Iodine · (MW 516.10)

(conversion of alcohols,[6,7] thiols,[11c] and enols[9] into iodides; reduction of various sulfur derivatives to sulfides or thiols;[11c] reduction of epoxides,[13] iodohydrins,[16] and vicinal diols[17a] to alkenes; production of iodohydrins from epoxides;[14] esterification of carboxylic acids;[18] acetalizations of carbonyl groups[19])

Alternate Names: triphenylphosphine diiodide; iodotriphenylphosphonium iodide; diiodotriphenylphosphorane.

Physical Data: adduct:[2,4] bright yellow solid (from ether). Ph_3P: mp 80.5 °C; bp 377 °C (in inert gas); *d*254 1.194 g cm^{-3}; *d*804 (liq) 1.075 g cm^{-3}; *n*80D 1.6358. I_2: mp 113.6 °C; bp 184.3 °C; *d* 4.93 g cm^{-3}.

Solubility: Ph_3P: sol ether, PhH, $CHCl_3$, AcOH; less sol alcohol; practically insol H_2O. I_2: sol ether (25.2 g/100 mL), PhH (14.1 g/100 mL), alcohol (21.4 g/100 mL), MeOH (23 g/100 mL), $CHCl_3$, CCl_4; less sol H_2O (0.03 g/100 mL).

Form Supplied in: the adduct is not commercially available. Ph_3P: odorless monoclinic platelets or prisms; purity ~99%; typical impurity: Ph_3PO ~1%. I_2: bluish-black scales or plates with metallic luster; characteristic odor; sharp, acrid taste and violet corrosive vapor; purity &egt;99.8%

Analysis of Reagent Purity: adduct.[2] Ph_3P and Ph_3PO: ^{31}P NMR (PhMe/MeCN, MeCN, pyridine; CCl_4) -5 to -8 and +29 to +25.

Preparative Method: for synthetic purposes the reagent is generally prepared in situ just before use, by addition of ***Iodine*** to ***Triphenylphosphine*** (or vice versa) in different solvents.

Handling, Storage, and Precautions: Ph_3P: irritant; harmful; do not get in eyes, on skin, or on clothing; avoid contact and inhalation; use with adequate ventilation; keep containers tightly closed and store in a cool dry place; incompatible with strong oxidizing agents. I_2: harmful; corrosive; severe lachrymator; do no get in eyes, on skin, or on clothing; avoid prolonged or repeated exposure; keep containers tightly closed in a cool dry place; incompatible with Mg, Zn, Al, Sb, and NH_3; reacts violently with acetaldehyde. These reagents should be handled in a fume hood.

Alkyl Iodides from Alcohols and Thiols.

The $Ph_3P.I_2$ adduct contains two replaceable iodo groups which can be substituted by nucleophiles. Its reaction with alcohols involves the rapid and irreversible formation of an alkoxyphosphonium iodide that decomposes by a slow S_N2 reaction, leading to an alkyl iodide (eq 1).

$$Ph_3\overset{+}{P}I\ I^- + ROH \xrightarrow{fast} Ph_3\overset{+}{P}OR\ I^- + HI \xrightarrow{slow} RI + Ph_3PO \quad (1)$$

Primary and secondary alcohols are converted into alkyl iodides[5-8] by use of the $Ph_3P.I_2$ reagent. The iodination of β-cholestanol in boiling PhH gives α-iodocholestane with inversion of configuration, albeit in low yield (25%); use of the more polar solvent DMF, at 75 °C, leads to complete epimerization to the thermodynamically more stable β-iodide.[6] Retention of configuration, observed in the nucleoside field,

occurs via double inversion; initial formation of the cyclic O^2,3´-anhydro derivative (**2**) is followed by ring opening by iodide ion (eq 2).[5a,b]

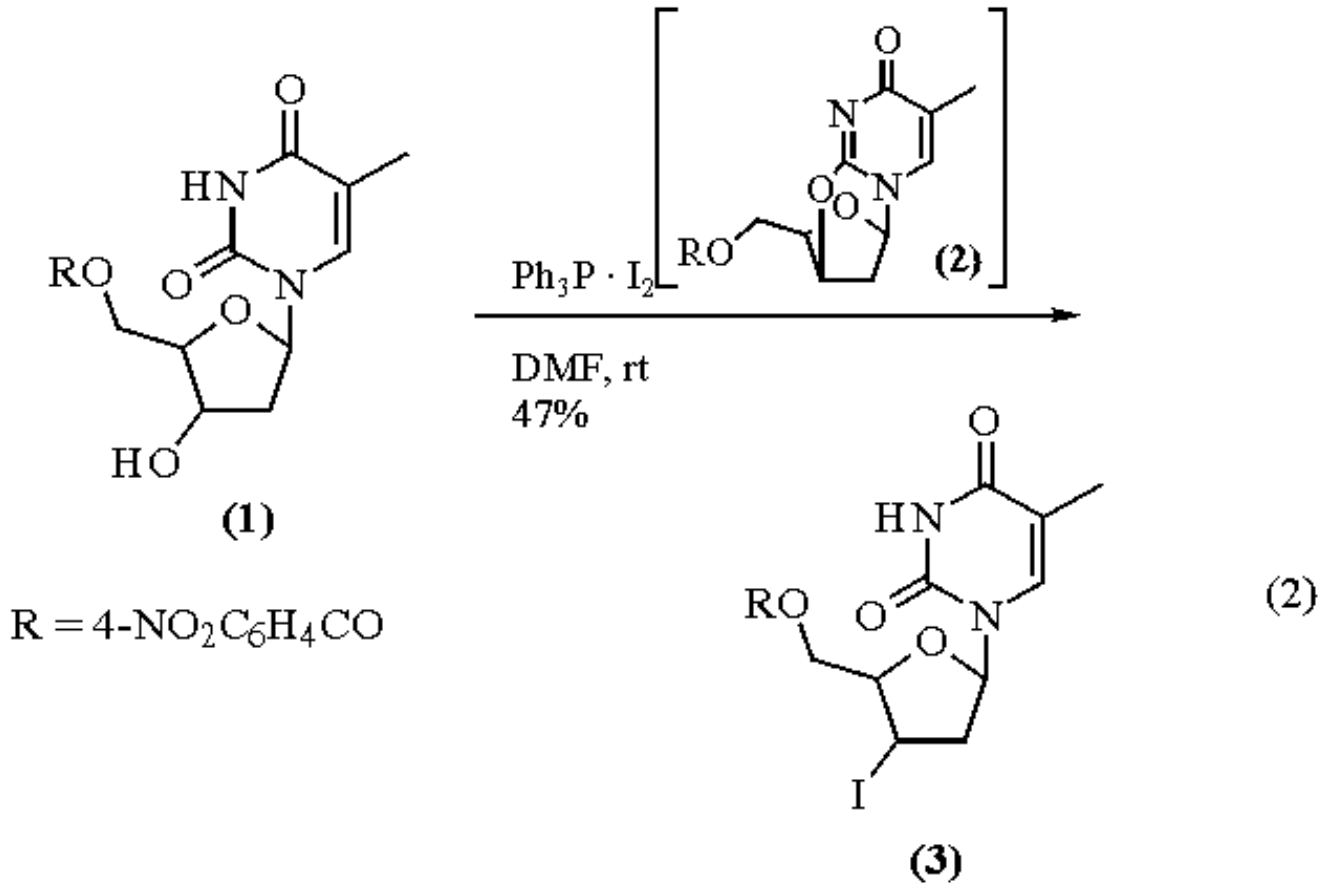

$Ph_3P.I_2$ provides better yield[5c] than the related reagent ***Methyltriphenoxyphosphonium Iodide*** (MTPI) in the iodination of the primary alcohol (**4**) (eq 3), whereas MTPI is more efficient in the preceding conversion of the secondary alcohol (**1**) into the iodide (**3**) (70%).[5a]

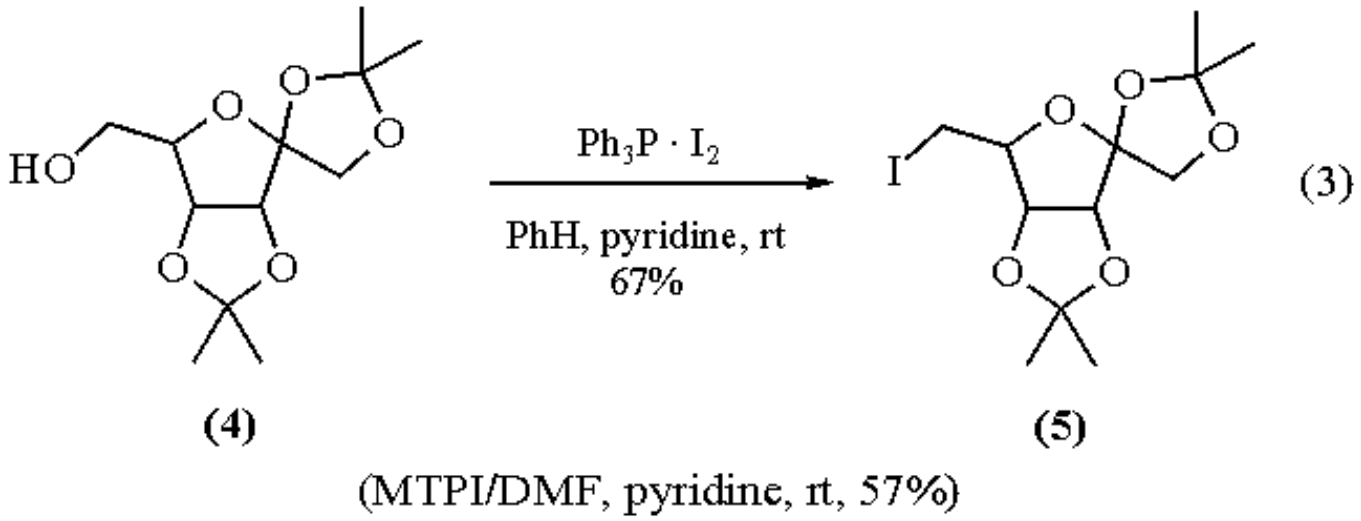

Although MeCN, $(PhO)_3PO$,[5d] and DMF are often recommended as solvents for these reactions, the latter can react with the Ph_3PX_2 reagent to produce halomethylene-*N*,*N*-dimethyliminium halide (**6**).[8] In the case of $Ph_3P.I_2$, this iminium iodide then reacts in turn with the alcohol to form an alkoxymethylene-*N*,*N*-dimethyliminium iodide (**7**), which gives mixtures of both iodide and formate after heating and hydrolytic workup; the same result could be obtained by assuming reaction of DMF with the alkoxyphosphonium iodide (**8**) (eq 4). Consequently, reactions of secondary alcohols with $Ph_3P.I_2$ in DMF can lead to formylation to the ester together with iodination.[8]

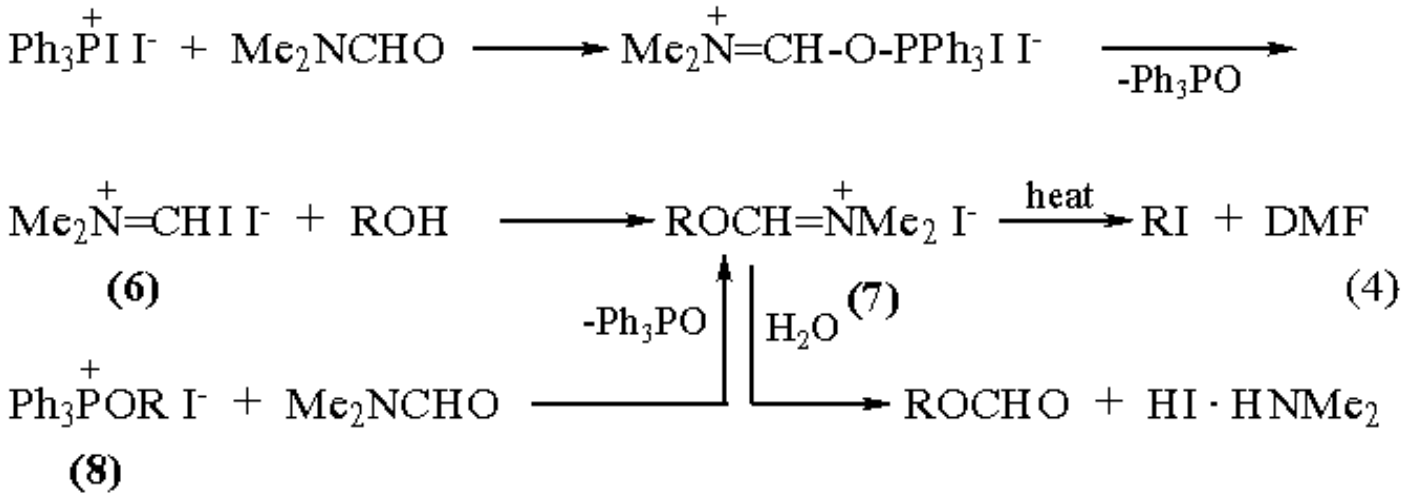

Addition of ***Imidazole*** to the $Ph_3P.I_2$ reagent leads to better yields. Alternatively, the 2,4,5-triodo derivative of imidazole and Ph_3P alone can be used. In the carbohydrate field especially,[7] higher yields are obtained in the conversion of primary (70-97%) and secondary (60-87%) alcohols, with inversion of configuration for the latter. At lower temperatures, primary hydroxyl groups may be selectively replaced by iodo groups.[7b,d] Besides the initially preferred refluxing PhMe,[7a,b] mixed solvents such as PhMe-MeCN (2:1) have been used,[7c,d] allowing certain transformations which are difficult to achieve with PhMe alone as solvent.

Alkanesulfonic acids, sulfinic acids, disulfides, thiosulfonic *S*-esters, and sulfonates are readily reduced to the corresponding thiols by treatment with a mixture of Ph_3P and a catalytic amount of I_2 (see below). Upon treatment with a mixture of Ph_3P and an excess of I_2, however, all these aliphatic sulfur compounds are eventually transformed to the corresponding alkyl iodides (67-100%) (eq 5).[11b,c]

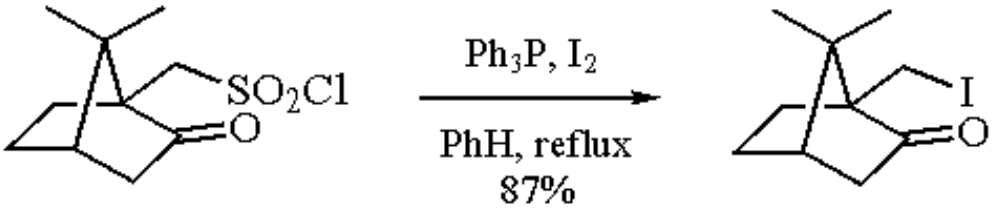

(5)

Vinyl Iodides from Enols.

Treatment of cyclic β-diketones with $Ph_3P.I_2$, in MeCN at reflux in the presence of NEt_3, affords β-iodo-α,β-unsaturated ketones in good yields (eq 6).[9] Unsymmetrical 1,3-cyclohexanediones give isomeric mixtures of 3-iodo-α,β-unsaturated ketones accompanied by deconjugated iodo enones. In MeCN-HMPA this reagent stereoselectively and regioselectively transforms α-hydroxymethylenecyclohexanone and -pentanone into (*E*)-2-iodomethylenecyclohexanone (94%) and -pentanone (73%).[9b] Other reagents useful for similar syntheses of alkyl iodides include ***Methyltriphenoxyphosphonium Iodide***,[1,5a,c] Ph_3P/CI_4,[1,5b] and Ph_3P/*N*-iodosuccinimide.[5b]

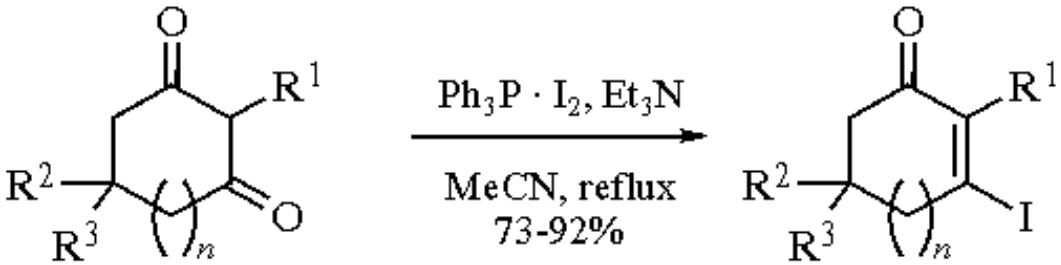

(6)

$R^1 = H, Me, allyl, (CH_2)_2CH{=}CH_2;\ R^2 = H, Me;\ R^3 = H, Me;$
$n = 0, 1$

Reduction of Sulfur Derivatives to Sulfides or Thiols.

Aryl and alkyl sulfoxides are readily deoxygenated to sulfides with the $Ph_3P/I_2/NaI$ reagent system in refluxing MeCN (eq 7).[10a] Use of the more reactive $(Me_2N)_3P$ instead of Ph_3P[10b] provides a good alternative to the previous reagent; it requires no heating and leads to an easily removed (unlike Ph_3PO) water-soluble HMPA byproduct.

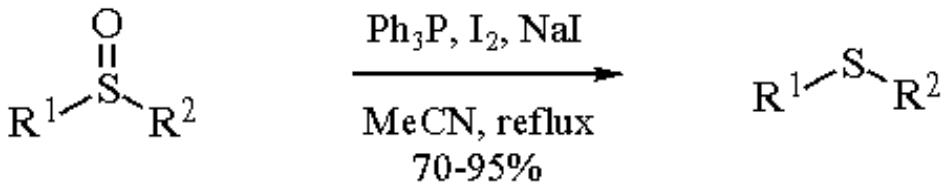

(7)

$R^1, R^2 = Pr, Bu, PhCH_2, Ph, 4\text{-}MeC_6H_4, \text{-}(CH_2)_4\text{-}$

Arylsulfonic acids, their sodium salts, halides, esters and thioesters, and arylsulfinic acids and their salts are also readily reduced to the corresponding aromatic thiols in good yields with Ph_3P (3-5 mol equiv) in the presence of I_2 (0.5-1 mol equiv) (eq 8).[11a,c]

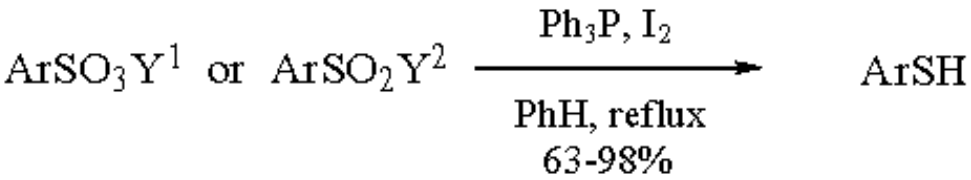

(8)

$Ar = Ph, 4\text{-}MeC_6H_4, 4\text{-}ClC_6H_4, 1\text{-naphthyl}, 2\text{-naphthyl},$
$2,4\text{-diMeC}_6H_3, 4\text{-}C_{12}H_{25}C_6H_4$
$Y^1 = H, Na, R, Ar^1; R = Et, CH_2\text{-}t\text{-}Bu, C_5H_{11}; Ar^1 = Ph$
$Y^2 = H, Na, Cl, SPh$

Reduction of Allylic Alcohols.

The reduction of allylic alcohols to the corresponding hydrocarbons by $Ph_3P.I_2$ is another valuable reduction achieved by this reagent.[12] This transformation takes place through the corresponding iodide, which is further reduced to the hydrocarbon by the HI resulting from the preceding step. Several allylic alcohols have been reduced in this fashion in moderate yields to the corresponding unsaturated hydrocarbons (24-95%).

Reduction of Epoxides and Iodohydrins to Alkenes.

Attempts to prepare vicinal diiodides from reaction of vicinal iodohydrins with the $Ph_3P.I_2$ reagent lead not to the expected products, but instead directly to the corresponding alkenes.[13] The reaction proceeds in high yields and is a stereospecific *trans* elimination (>98%). As iodohydrins may be obtained by *anti* opening of epoxides with HI, this reaction serves as the basis for a convenient method for the deoxygenation of epoxides to alkenes with retention of configuration. The transformation is typically achieved employing 1.1 equiv each of $Ph_3P.I_2$ and $Ph_3P.HI$ (eq 9). Despite the fact that only 1 equiv of Ph_3P is consumed and that HI and I_2 act only as catalysts, the first attempts to reduce the stoichiometry in reagents were unsuccessful; this problem was later solved[16] by using other reaction conditions (see below).

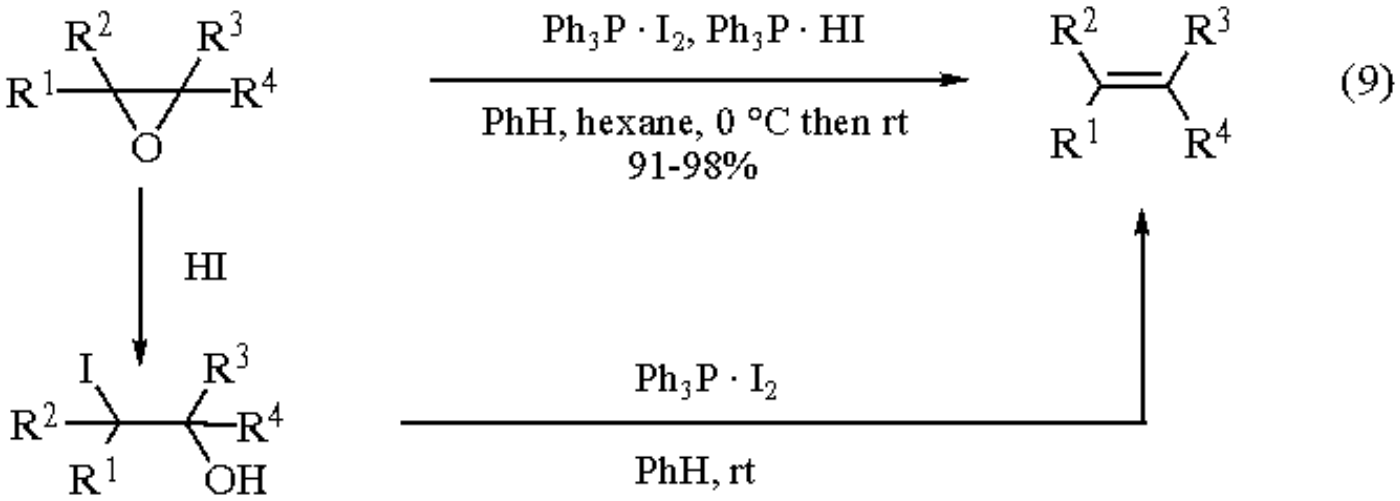

Iodohydrins from Epoxides.

Contrasting results[14,15] have been reported in the steroid field in the transformation of identically trisubstituted epoxides with $Ph_3P.I_2$. Although the experimental conditions were apparently the same in both cases ($Ph_3P.I_2$, 1.1 equiv, CH_2Cl_2, rt), the reaction products are halohydrins in the first case,[14a,b] and alkenes in the second one.[15] As mentioned elsewhere,[13,16] iodohydrins are readily transformed into alkenes by several routes (e.g. with HI or I_2 and H_2O as catalyst, in the presence of Ph_3P); the presence of traces of water in the solvent or further transformation during workup or the purification steps (in the second case[15]) would account for such discrepancies. The former preparation[14a,b] of iodohydrins under anhydrous conditions was later confirmed[14c] by the use of a polymer-supported phosphine-I_2 adduct. The method requires only a filtration and evaporation for product isolation, avoiding the often tedious Ph_3PO removal. Oxirane-ring opening remains regio- and stereoselective, the yields being somewhat higher than with Ph_3P, most probably due to the simplified workup procedure (eq 10).

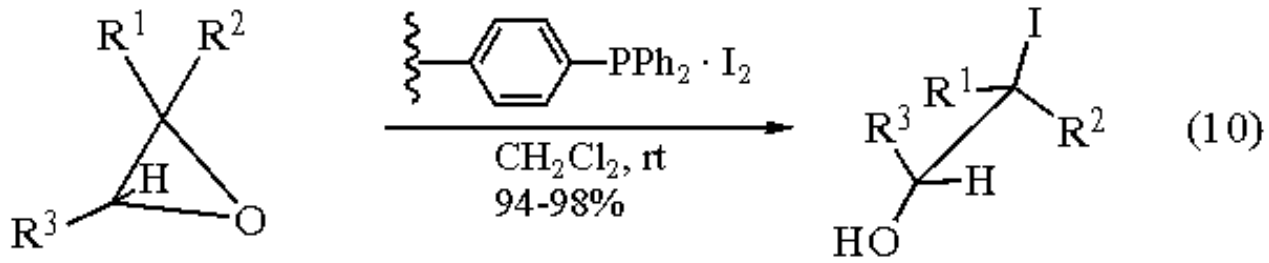

Further work[16] with $Ph_3P.I_2$ in moist MeCN clearly demonstrates the importance of both reagent stoichiometry and the presence of water in determining the reaction pathway. The active species is in fact HI, generated in situ from $Ph_3P.I_2$ in moist MeCN. Use of 0.5 equiv of $Ph_3P.I_2$ in moist MeCN provides iodohydrins (75-85%) from epoxides; alkenes are obtained from both iodohydrins (70-90%) and epoxides (70-95%) using respectively 0.6:0.1-0.6:1 and 1.1:0.6:1 molar ratios of Ph_3P, I_2, and substrate, at 80 °C (eq 11).

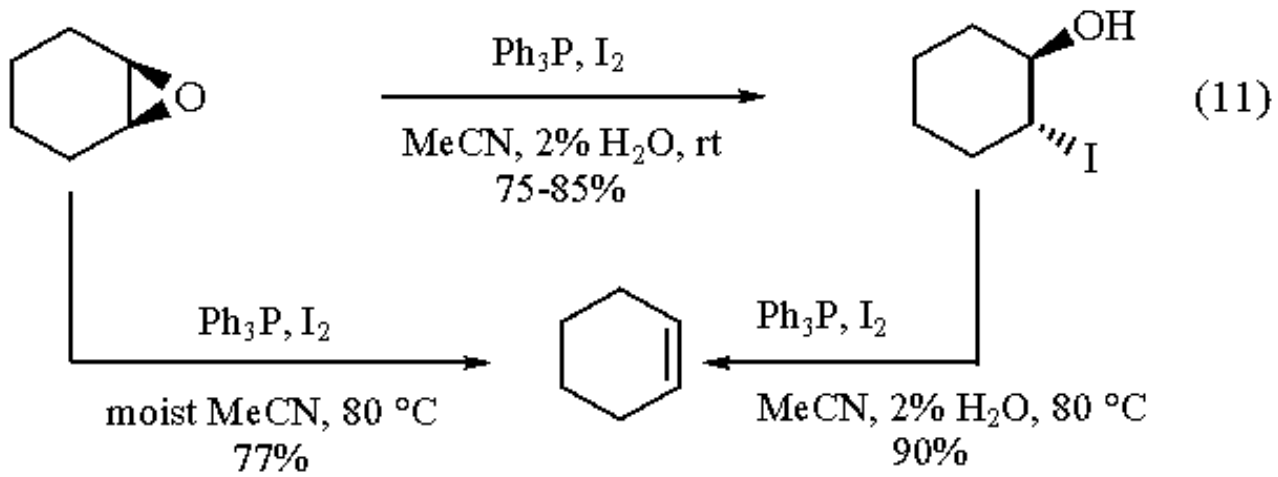

Alkenes from Vicinal Diols.

The combination of Ph_3P, I_2, and imidazole[17a] in refluxing toluene (or better, in the mixed solvent PhMe-MeCN[17c]) at 50 °C effects the conversion of vicinal diols into alkenes. Hexopyranosidic diols are transformed to alkenes in fair to good yields (eq 12). A further significant improvement over the original system can be achieved by using the combination of Ph_3P alone with 2,4,5-triiodoimidazole and imidazole (ImH).[17b]

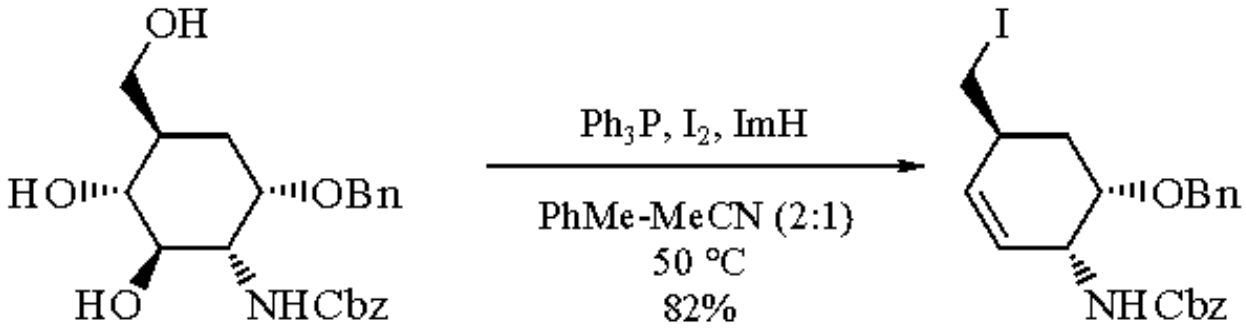

(12)

Esterification of Carboxylic Acids.

The adduct of polystyryl(diphenyl)phosphine with iodine,[14c] previously used to convert epoxides into iodohydrins, is a convenient condensing agent for the esterification of carboxylic acids[18] under very mild conditions. The reaction is assumed to proceed via the acyl iodide. The iodine adduct proves to be the most convenient among the three halogen adducts since the chloride complex provides somewhat sluggish ester formation and the use of the bromine analog is inadvisable with unsaturated material due to the occurrence of some bromination of the double bond. The reaction has been applied to a number of acids using MeOH and also cumbersome, difficult to esterify alcohols such as 5α-cholestan-3-ol (eq 13). The high yield and easy isolation of the ester (by a simple filtration and evaporation process) are among the attractive features of this preparation.

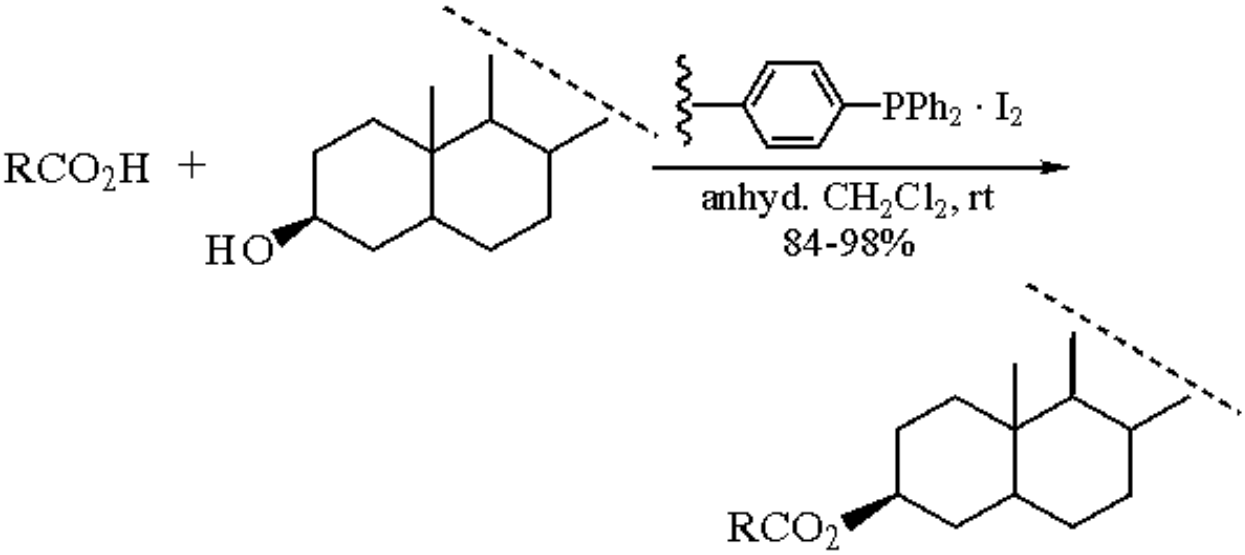

(13)

RCO_2H = acetic, benzoic, octanoic, palmitic, stearic, linoleic, 4-$MeC_6H_4CO(CH_2)_2CO_2H$, 4-$MeOC_6H_4CO(CH_2)_2CO_2H$

Acetalization of Carbonyl Compounds.

Carbonyl compounds are smoothly and rapidly acetalized by treatment with alcohols or thiols in anhydrous MeCN in the presence of the polystyryl(diphenyl)phosphine-iodine adduct as a dehydrating agent.[19] Open-chain and cyclic acetals, including 1,3-dioxolanes, 1,3-oxathiolanes, and 1,3-dithiolanes, of miscellaneous aldehydes and ketones have been successfully prepared in this way with high yields (eq 14). The isolation of the product is easily performed by simple filtration of the polymer-linked Ph_3PO which is formed during the reaction.

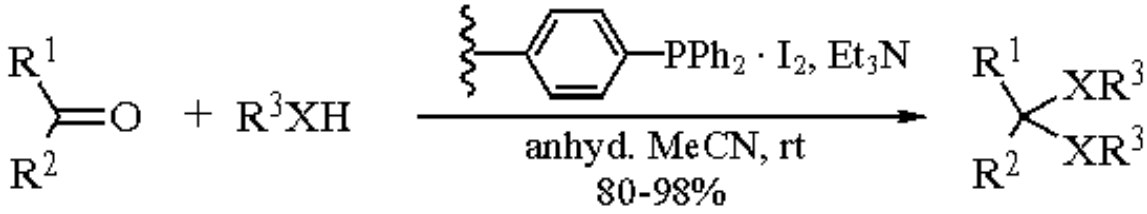

(14)

Other Applications.

In combination with imidazole as described previously, $Ph_3P.I_2$ allows the one-pot synthesis of alkyl nitrates from alcohols.[20] Treatment of alcohols with the Ph_3P-I_2-ImH reagent system, followed by in situ reaction of the generated iodides with the $AgNO_3$ in ether/MeCN mixture, leads to the formation of alkyl nitrates. The $Ph_3P.I_2$ reagent has also been used to promote the Beckmann rearrangement;[21] the reaction of cycloalkanone oxime with iodine in the presence of Ph_3P provides lactams in one step. In the presence of Et_3N, the $Ph_3P.I_2$ adduct, acting as a dehydrating agent, effects the 3-aza-Claisen rearrangement of α-heteroatom substituted *N*-allyl amides into the corresponding nitriles under very mild conditions.[22] Other phosphine-halogen adducts are studied for this purpose in the same work.

---

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2. There are only three recent references (including 3b,c) in the chemical literature. The adduct must be prepared under an inert atmosphere, in strictly anaerobic and anhydrous conditions using standard Schlenk techniques.3 Physical studies3 show that the balance between four-coordinate covalent and ionic forms, and the five-coordinate covalent form, in solution is solvent dependent; solid material prepared in ether exhibits a four-coordinate covalent form of charge-transfer complex type, while solid samples from $PhNO_2$ display a four-coordinate ionic form. Raman (nujol) 160 (I-I) (solid form from ether: Ph_3P-I-I); ^{31}P NMR (1,2-$ClCH_2CH_2Cl$, MeCN, or $CHCl_3$): +45 to +49 (ionic form); ^{31}P NMR (solid form NMR, PhMe/MeCN or pyridine) -18 to -21 (covalent form). Other physical studies on the related Ph_3P-dihalide adducts also conclude that the extent of ionic behavior is a function of the solvent polarity.
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Triphenylphosphine-Iodoform-Imidazole

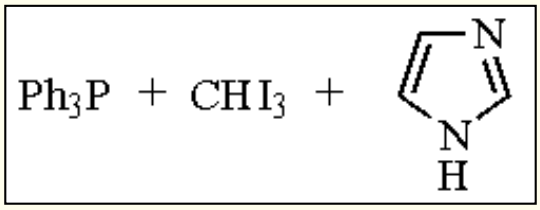

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-Iodoform-Imidazole · (MW 262.30) (CHI_3)

[75-47-8] · CHI_3 · Triphenylphosphine-Iodoform-Imidazole · (MW 393.72) (imidazole)

[288-32-4] · $C_3H_4N_2$ · Triphenylphosphine-Iodoform-Imidazole · (MW 68.09)

(deoxygenation of vicinal diols and epoxides to form alkenes;[1] particularly useful in the synthesis of unsaturated sugars)

Physical Data: see ***Triphenylphosphine***, ***Iodoform***, and ***Imidazole***.

Preparative Method: Bessodes et al.[1] reported that treatment of *cis*- or *trans*-1,2-diols with 4 equiv of triphenylphosphine, 2 equiv of iodoform and 2 equiv of imidazole in refluxing toluene (typically for 1 h) effects elimination of the vicinal diols to form the corresponding alkene.

General Discussion.

Methods for the conversion of vicinal diols to alkenes have found utility in organic synthesis, particularly in the synthesis of unsaturated or dideoxy sugars, and a number of alternative methods have been developed.[2] The use of a mixture of triphenylphosphine, iodoform, and imidazole to accomplish the reductive elimination of vicinal diols was introduced by Bessodes et al.[1] For example, the *cis*- and *trans*-1,2-diols in eq 1 are converted to the corresponding unsaturated sugars in moderate to good yields, the better yields being obtained from the *trans*-isomers. The methodology was introduced as an alternative to the methods of Garegg and Samuelsson which employ a mixture of triphenylphosphine-***Iodine***-imidazole[3] or a mixture of ***Triphenylphosphine-2,4,5-Triiodoimidazole***.[4]

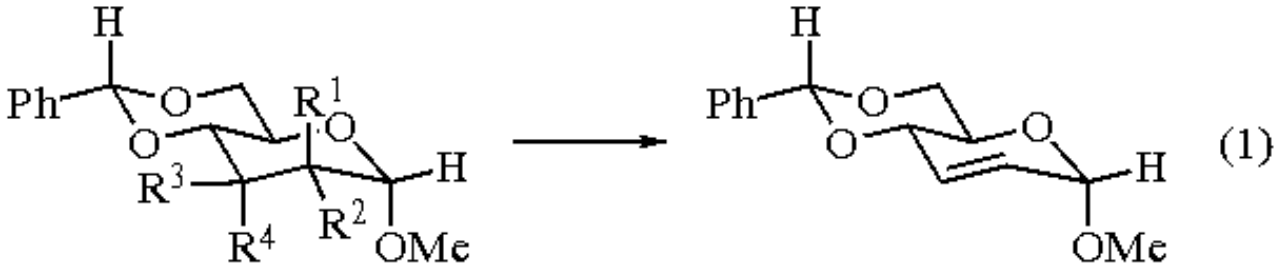

(a) $R^1, R^4 = H$; $R^2, R^3 = OH$; 80%
(b) $R^2, R^3 = H$; $R^1, R^4 = OH$; 65%
(c) $R^2, R^4 = H$; $R^1, R^3 = OH$, 45%

Nagarajan and Rao[5] used the triphenylphosphine-iodoform-imidazole reagent for the reductive elimination of a xylose-derived benzoate in 85% yield (eq 2). The procedure was used by Wee[6] for the reductive elimination of a methyl glucoside derivative bearing both benzoyl and *t*-butyldiphenylsilyl protecting groups. The dehydro-sugar is formed in 94% yield (eq 2). In this latter case the corresponding dimesylate derivative is reported[7] to desilylate under an alternative set of reductive elimination conditions, the Tipson-Cohen method (NaI, Zn, DMF).[8] Reported attempts to apply the method to furanoside substrates were unsatisfactory.[9,10]

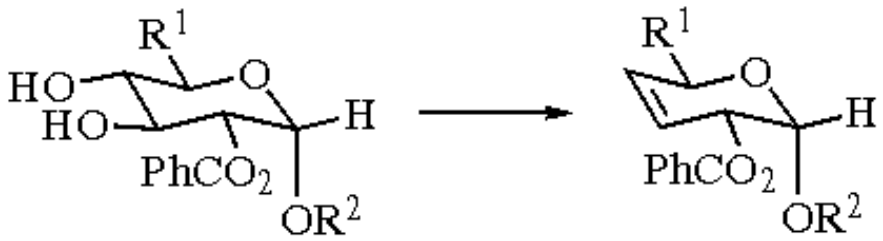

(2)

(a) $R^1 = H$, $R^2 = CH_2Ph$, 85%
(b) $R^1 = CH_2OTBDPS$, $R^2 = Me$, 94%

The methodology may have some application in nucleoside synthesis. Chu and co-workers[11] found that treatment of a dimethylpseudouridine derivative affords the dideoxycytidine analog in modest yield (40%) (eq 3). In this case the authors found that ***Tri-n-butylstannane*** reduction of the corresponding dimethyl xanthate is superior, proceeding in an overall 76% yield for the two steps. Halmos and co-workers[12] used the procedure in the preparation of certain keto nucleosides with greater success. Deoxygenation affords the theophylline derivative in 70% yield (eq 4). The authors found this method to be superior to deoxygenation via the thionocarbonate or the 1-dimethylamino(methylene) acetal.

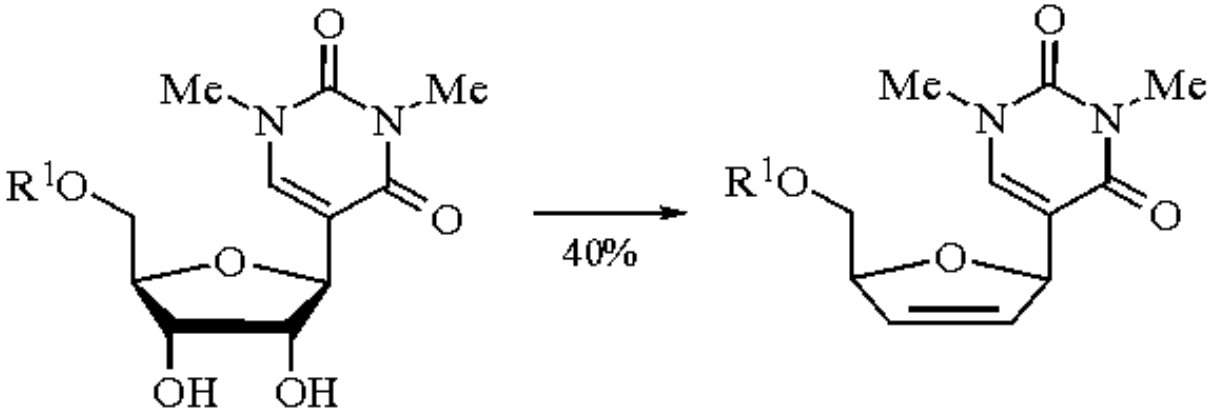

(3)

$R^1 = TBDMSO$

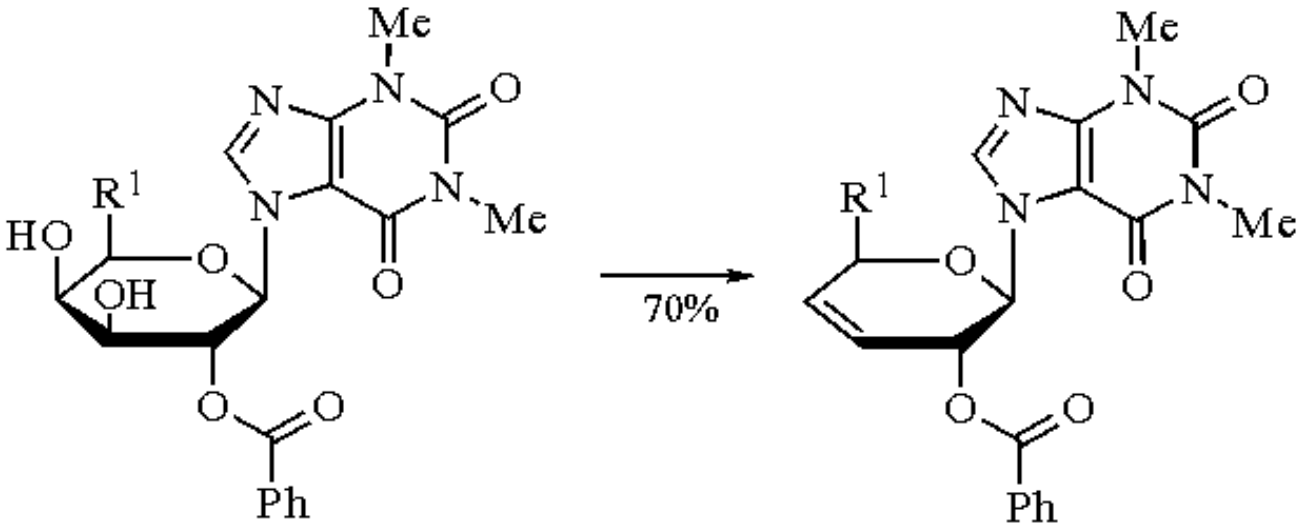

(4)

$R^1 = CH_2O(CH_2)_6OCOPh$

Lichtenthaler and co-workers[13] found that the triphenylphosphine-iodoform-imidazole reagent system is also effective in the deoxygenation of an epoxide. The epoxide derived from fructose is converted to the 3,4-unsaturated dihydropyran in 84% yield (eq 5), although unlike the reported conversions of diol substrates, reaction of the epoxide required two days in refluxing toluene.

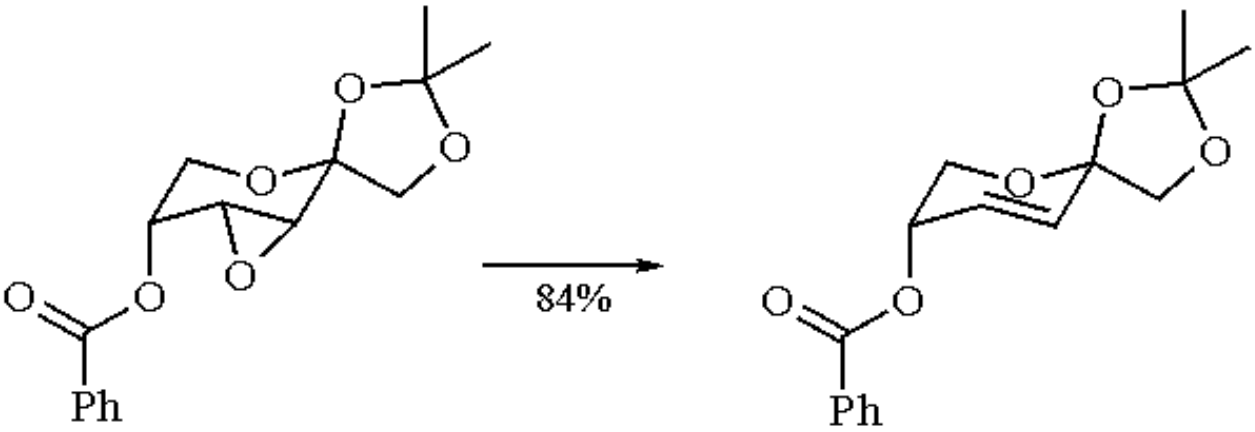

(5)

Related Reagents.

Triphenylphosphine-2,4,5-Triiodoimidazole.

---

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Triphenylphosphine Selenide

$Ph_3P{=}Se$

[3878-44-2] · $C_{18}H_{15}PSe$ · Triphenylphosphine Selenide · (MW 341.26)

(conversion of epoxides into alkenes[1])

Physical Data: mp 187-188 °C.[2]

Solubility: very sol dichloromethane; moderately sol on heating in acetonitrile, benzene, 1-butanol, ethanol, methanol; insol ether, water.[2]

Form Supplied in: white solid; commercially available.

Preparative Methods: prepared from ***Triphenylphosphine*** and either ***Potassium Selenocyanate***[2] or elemental ***Selenium***.[3,4]

Purification: recrystallization from ethanol.[2]

Handling, Storage, and Precautions: toxic;[2] use in a fume hood.

Conversion of Epoxides into Alkenes.[1]

Addition of ***Trifluoroacetic Acid*** to a dichloromethane solution of an epoxide and an excess of triphenylphosphine selenide results in deoxygenation of the epoxide to the corresponding alkene. The reaction is stereospecific (eqs 1-3). Other phosphine selenides can also be used.[5]

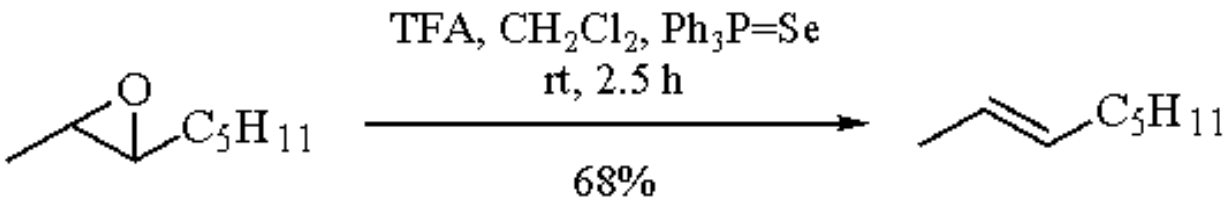

(1)

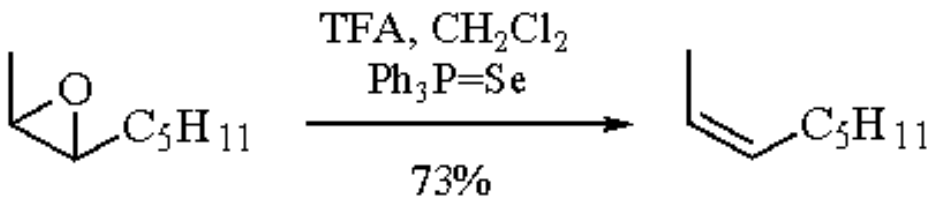

(2)

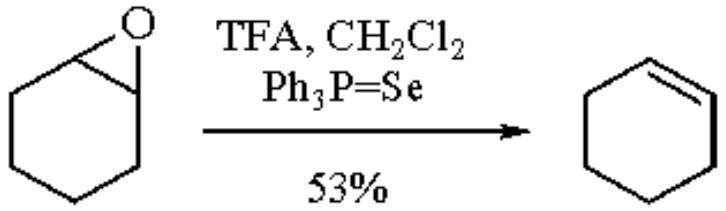

(3)

Conversion of Phosphorus Ylides into Alkenes.[6]

Several nonstabilized ylides, $Ph_3P{=}CHR$, give near thermodynamic mixtures of (*Z*)- and (*E*)-alkenes when treated with a catalytic amount of triphenylphosphine selenide in hot (90 °C) toluene (eq 4).

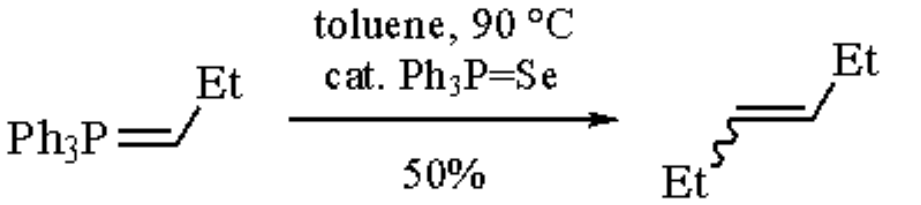

(4)

$(Z):(E) = 17:83$

Reduction of Selenoxides.[7,8]

Simple selenoxides (e.g. dibenzyl selenoxide), that do not undergo elimination, are reduced slowly (24 h to 13 days) at rt to the corresponding selenides by the action of triphenylphosphine selenide in chloroform (eq 5).

$$(PhCH_2)_2Se{=}O \xrightarrow[\text{rt, >24 h}]{Ph_3P{=}Se,\ CHCl_3} (PhCH_2)_2Se \qquad (5)$$

Formation of Ureas and Carbamates.

Aromatic nitro compounds can be converted into ureas[9] or carbamates[10,11] in processes mediated by elemental selenium (eq 6); elemental selenium is derived in situ from triphenylphosphine selenide, which serves as a carrier for selenium.

$$ArNO_2 + CO + ROH \xrightarrow[\text{25 bar, 160 °C, 30 min}]{Ph_3P{=}Se,\ H_2O_2} ArNHCO_2R \qquad (6)$$

Related Reagents.

Triphenylphosphine Sulfide.

---

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Darrin L. Mayhew & Derrick L. J. Clive

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Triphenylphosphine Sulfide

$Ph_3P{=}S$

[3878-45-3] · $C_{18}H_{15}PS$ · Triphenylphosphine Sulfide · (MW 294.37)

(conversion of epoxides into thiiranes[1])

Physical Data: mp 161 °C.[2]

Solubility: insol hexane, water, ether; sol acetone, benzene, carbon disulfide, chloroform, ethanol.[2-5]

Form Supplied in: white solid; commercially available.

Preparative Methods: prepared by a number of methods; most easily prepared from ***Triphenylphosphine*** and ***Sulfur***,[4] or from benzene, sulfur, and ***Phosphorus(III) Chloride*** in the presence of ***Aluminum Chloride***.[5]

Purification: recrystallization from ethanol[2,4] or aqueous acetone.[3,5]

Conversion of Epoxides into Thiiranes.[1]

Addition of ***Trifluoroacetic Acid*** (1 equiv) to a benzene solution of an epoxide and triphenylphosphine sulfide (1 equiv or an excess) serves to convert the epoxide into the corresponding episulfide (eq 1). The reaction is stereospecific, and can also be done using tributylphosphine sulfide (eq 2).[1]

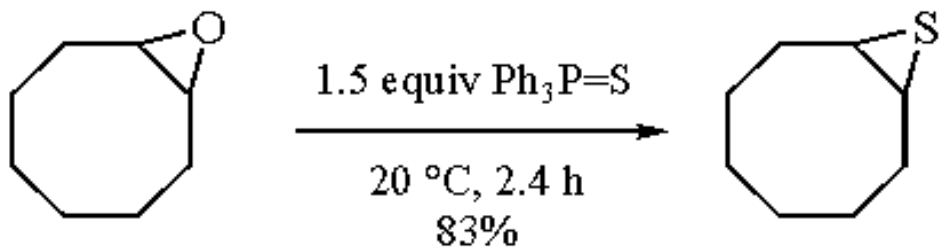

(1)

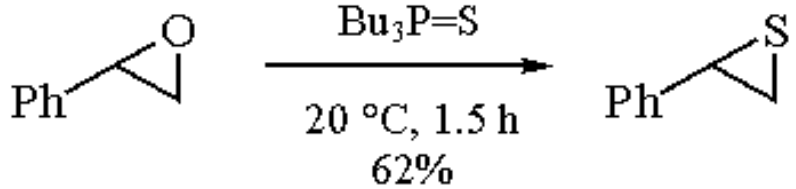

(2)

Conversion of Phenols into Dihydric Phenols.[6]

Phenols can be converted into mixtures of dihydric phenols using ***Hydrogen Peroxide***, in the presence of a ketone, and a catalytic amount of triphenylphosphine sulfide (eq 3).

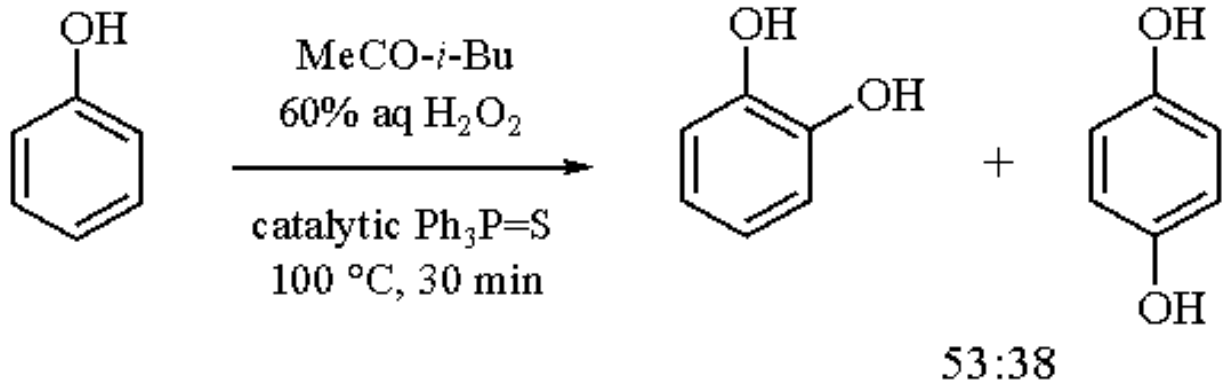

(3)

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Triphenylphosphine-2,4,5-Triiodoimidazole

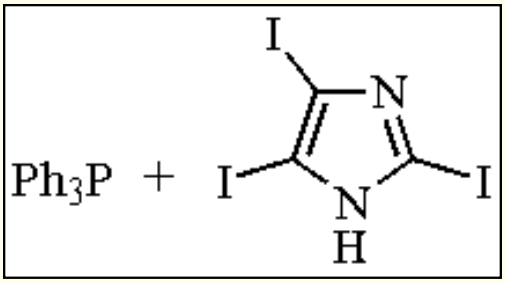

(Ph_3P)

[603-35-0] · $C_{18}H_{15}P$ · Triphenylphosphine-2,4,5-Triiodoimidazole · (MW 262.30) (2,4,5-triiodoimidazole)

[1746-25-4] · $C_3HI_3N_2$ · Triphenylphosphine-2,4,5-Triiodoimidazole · (MW 445.76)

(deoxygenation of vicinal diols[1] and epoxides to form alkenes; conversion of alcohols to iodides)

Physical Data: see ***Triphenylphosphine***; 2,4,5-triiodoimidazole, mp 190-192 °C.

Preparative Methods: the reagent reported by Garegg and Samuelsson[1,2] is prepared in situ by the combination of a 1:2 ratio of ***Triphenylphosphine*** and 2,4,5-triiodoimidazole in toluene or, preferably, toluene/acetonitrile.[3] 2,4,5-Triiodoimidazole is prepared via the treatment of ***Imidazole*** with ***Iodine*** and ***Sodium Hydroxide*** in a two-phase reaction in water/petroleum ether and recrystallized from methanol.[3]

General Discussion.

Triphenylphosphine-2,4,5-triiodoimidazole-imidazole was introduced as a alternative to the combination of triphenylphosphine-iodine-imidazole[4-8] for the deoxygenation of vicinal diols. Subsequently, the mixture ***Triphenylphosphine-Iodoform-Imidazole***[9] and, more recently, ***Chlorodiphenylphosphine***-iodine-imidazole[10] were introduced as other alternative phosphine-derived reagents for diol reductive elimination. Methods for the conversion of vicinal diols to alkenes have found significant utility in organic synthesis and a number of nonphosphine-based methods have also been developed.[11] Treatment of methyl 2,6-dibenzyl-α-D-glucopyranoside with triphenylphosphine-2,4,5-triiodoimidazole in a 2:1 excess over the substrate affords the unsaturated sugar in a reported 95% yield (eq 1).[1] This conversion was recently used in the preparation of hexose nucleoside analogs.[12]

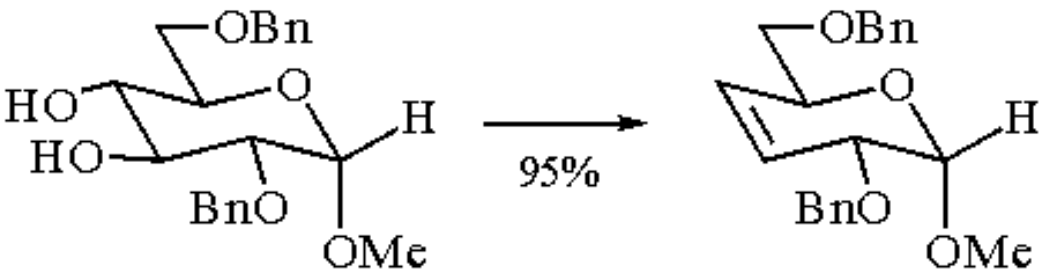

(1)

Samuelsson[1] and others[13] report that the reagent works best in the case of *trans*-diequatorial or *trans*-diaxial diols; however, Ozaki and co-workers[14] used the reagent effectively on a mixture of *cis*- and *trans*-diols. Treatment of a 2:3 *cis*:*trans* mixture of diols affords the alkene (73% yield) (eq 2), which can subsequently be used in the synthesis of optically active inositol derivatives.

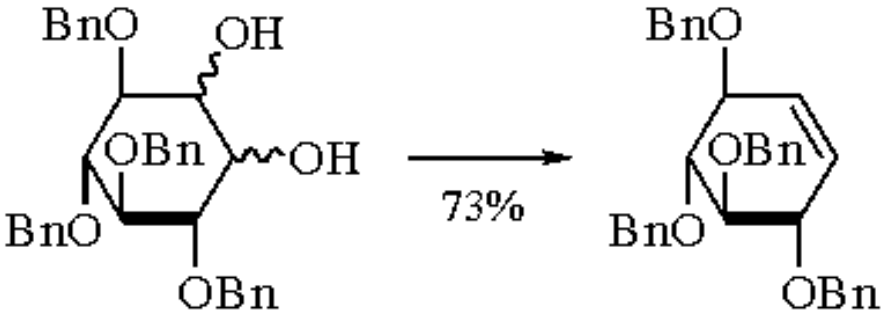

(2)

Kibayashi[15] found the reagent useful in a synthesis of indolizidine 195B (gephyrotoxin 195B). Deoxygenation of the *trans*-diol affords the unsaturated nitrogen heterocycle in 79% yield (eq 3). Small amounts of the corresponding epoxide are isolated, suggesting that the deoxygenation proceeds via initial formation of the epoxide. Kibayashi modified the Samuelsson procedure with the addition of ***Zinc*** powder, a modification that had earlier been employed for the phosphine-iodine based deoxygenation of epoxides.[4] Kibayashi suggests that the deoxygenation is stereospecific, although to date only the reactions of cyclic diols have been reported.

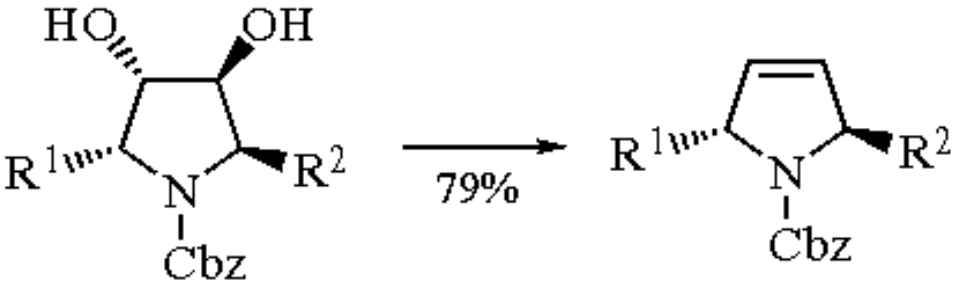

(3)

$R^1 = CH_2{=}CH(CH_2)_3\text{-}$, $R^2 = Bu$

It is reported that the deoxygenation of a furanoside leads to formation of a furan,[16] but Yoda employed Kibayashi's modified procedure to prepare optically active butenolides in 59-78% yield (eq 4).[17]

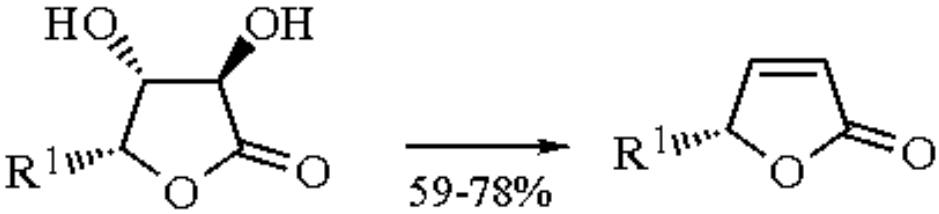

(4)

$R^1 = Bu, C_8H_{17}, C_{13}H_{27}$

The triphenylphosphine-2,4,5-triiodoimidazole-imidazole mixture has also found use as an alternative to the more frequently used triphenylphosphine-iodine-imidazole[2] mixture for the conversion of alcohols to iodides. For example, the iodide in eq 5 is prepared in 69% yield and used in the total synthesis of the antibiotic A23187.[18] Furthermore, the conversion proceeds with clean inversion of configuration and the conditions are sufficiently mild to tolerate the presence of a benzyloxymethyl protecting group (eq 6).[19,20]

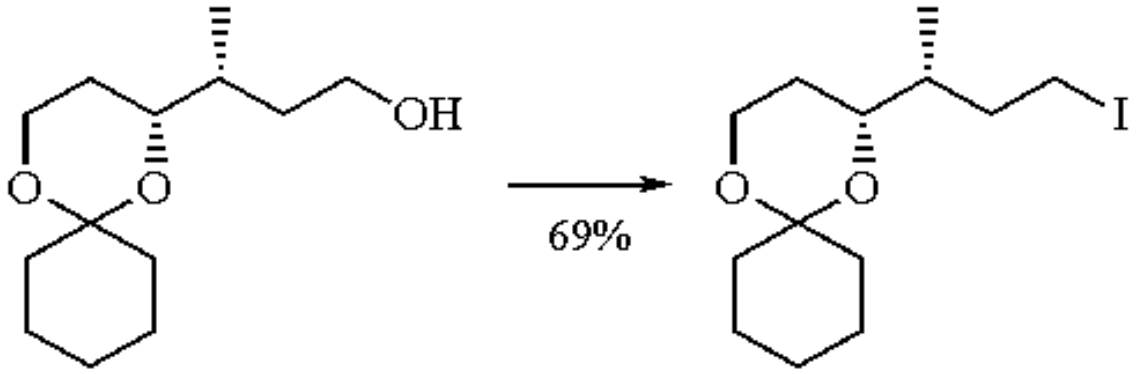

(5)

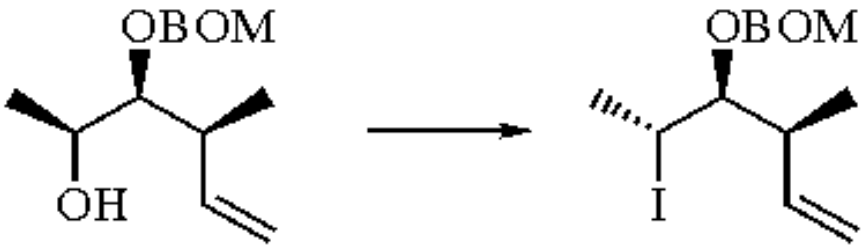

(6)

The reagent has found use in the conversion of hydroxy groups to iodides in carbohydrate substrates. For example, treatment of the protected furanose in eq 7 affords the corresponding iodide with clean inversion of configuration (78% yield).[2,21] In some cases, secondary hydroxyl groups need not be protected. For example, treatment of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside with 4 equiv of triphenylphosphine and 2 equiv of 2,4,5-triiodoimidazole in toluene-acetonitrile (2:1) affords the corresponding 6-iodo derivative in 70% yield (eq 8).[3] Toluene-acetonitrile solvent is reported to be superior to toluene alone, and other solvent systems may be applicable.[22] Other selective substitutions in carbohydrates substrates are often possible.[3,23]

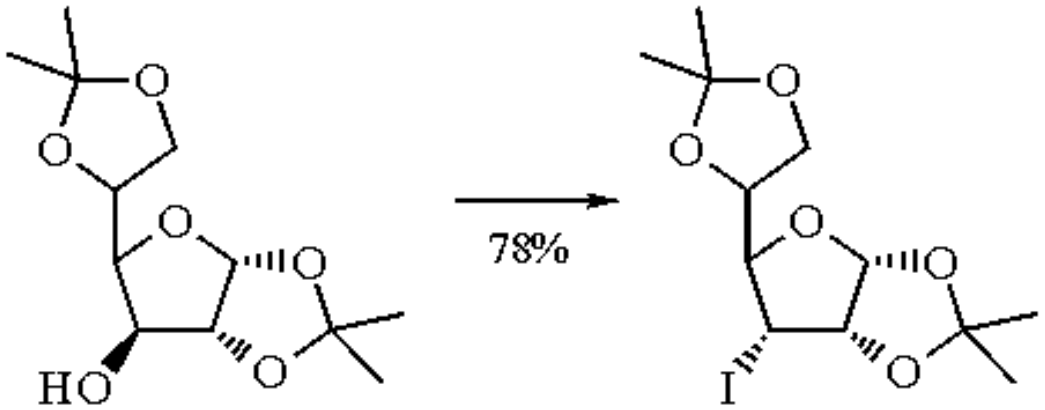

(7)

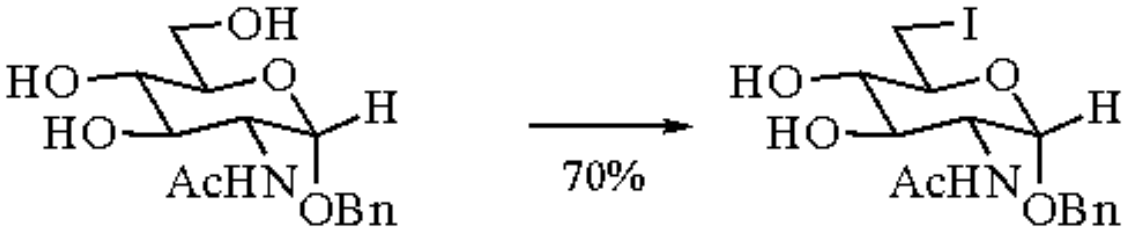

(8)

The corresponding triphenylphosphine-2,4,5-tribromoimidazole reagent behaves similarly.[3,20,24]

---

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Triphenyl Phosphite[1]

$(PhO)_3P$

[101-02-0] · $C_{18}H_{15}O_3P$ · Triphenyl Phosphite · (MW 310.30)

(mildly nucleophilic phosphite for converting alcohols to alkyl halides;[3] coupling agent in peptide and related syntheses,[1b,12] as its ozone adduct, a low-temperature source of singlet oxygen[1b])

Physical Data: mp 22-25 °C; bp 360 °C, 180-189 °C/1 mmHg; *n*25D 1.5890; δ ^{31}P 125-129.

Solubility: insol H_2O (hydrolyzes to $(PhO)_2P(O)H$); miscible most organic solvents; alcoholic solvents may transesterify.

Form Supplied in: colorless liquid, 97% pure, widely available, showing only one peak in ^{31}P NMR. The balance is largely phenol.

Purification: an ethereal solution is washed with aqueous alkali, dried, and distilled.

Handling, Storage, and Precautions: fairly safe to handle, but it is a skin sensitizer and will usually contain phenol.

General Discussion.

The ester converts alcohols to alkyl halides in the presence of a hydrogen halide, a halogen, or another alkyl halide (eqs 1 and 2), the two last being mild and convenient procedures.[2,3] Good yields are obtained, even with neopentyl halides, and the reaction proceeds with inversion at carbon.[4] The intermediate phosphonium salts may be prepared independently but are very susceptible to hydrolysis and are conveniently generated and used as required. Methyltriphenoxyphosphonium iodide has also found use in the deoxygenation of epoxides[5] (with retention of stereochemistry) and the dehydration of secondary alcohols.[6] Phenyl esters of carboxylic acids can be made from the salts and a carboxylate ion[7] or from the free acid and the neutral ester[8] (eqs 3 and 4). Phosphorus[9] and sulfur[10] acids may be esterified similarly.

$$(PhO)_3P + X_2 + ROH \longrightarrow RX + (PhO)_2P(O)X + PhOH \quad (1)$$

$$R^1OH + (PhO)_3P + RCH_2X \longrightarrow R^1X + RCH_2P(O)(OPh)_2 \quad (2)$$

$$X = Cl, Br, I;\ R = \text{primary or secondary alkyl};\ R^1 = Ph, H$$

$$(PhO)_3\overset{+}{P}Me + RCO_2^- \longrightarrow (PhO)_2P(O)Me + RCO_2Ph \quad (3)$$

$$(PhO)_3P + RCO_2H \longrightarrow (PhO)_2P(=O)H + RCO_2Ph \quad (4)$$

The adduct of $(PhO)_3P$ and ***Ozone***,[1b] apparently a cyclic phosphorane (δ ^{31}P -63), is stable below -35 °C and on warming liberates oxygen. It functions in many ways as a convenient low-temperature source of singlet oxygen (eq 5),[11] though there are some significant differences and it functions similarly at temperatures as low as -70 °C where the adduct is quite stable.

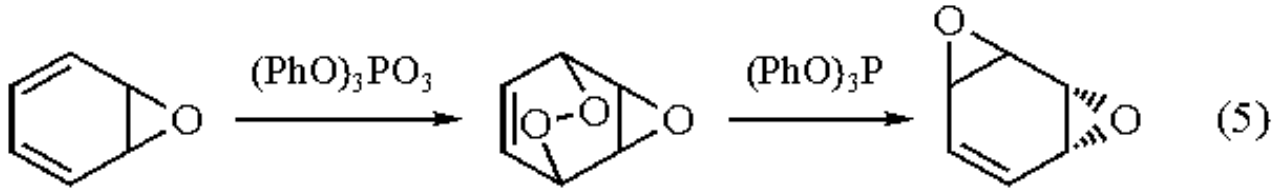

In the presence of bases, particularly ***Imidazole***, $(PhO)_3P$ acts either alone[12] or with ***2,2´-Dipyridyl Disulfide***[13] as a coupling agent for peptide synthesis (eq 6) with very little if any racemization. With ***2,2´-Dipyridyl Diselenide***, it has found use in the preparation of nucleoside phosphoranilidates[14] and oligonucleotides.[15] The ester has been occasionally used as a mild deoxygenation agent (eq 5), and in the cyclization of 2-acylaminobenzoic acids to the corresponding 4*H*-3,1-benzoxazin-4-ones.[16] It is a convenient reagent for purifying ***Thionyl Chloride***.[17]

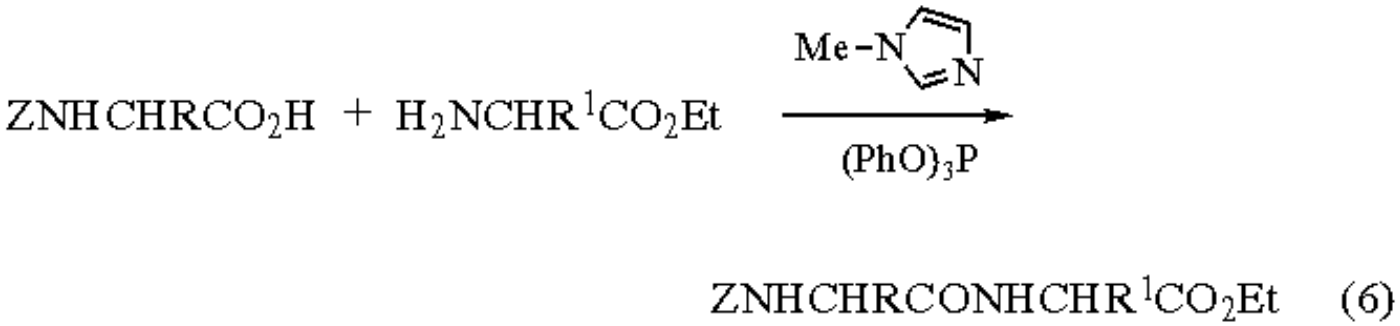

Related Reagents.

Bromine-Triphenyl Phosphite.

---

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Triphenyl Phosphite Ozonide[1]

$(PhO)_3PO_3$

[29833-83-8] · $C_{18}H_{15}O_6P$ · Triphenyl Phosphite Ozonide · (MW 358.30)

(source of singlet oxygen;[2] avoids complicating effects of radiation on reactants and products sometimes associated with photochemical generation of singlet oxygen; can also transfer dioxygen in a bimolecular process[3] not involving singlet oxygen)

Physical Data: reagent is labile and is prepared and used in situ.

Solubility: sol dichloromethane, carbon tetrachloride, benzene, acetonitrile, trichlorofluoromethane, toluene, chlorobenzene, methanol, isopropyl alcohol, acetone, diethyl ether, and pyridine.

Form Supplied in: reagent is prepared as needed.

Analysis of Reagent Purity: ^{31}P NMR.

Preparative Methods: a solution of triphenyl phosphite in CH_2Cl_2 is added to O_3-saturated (blue color) CH_2Cl_2 at -78 °C. Ozone is added periodically in order to maintain the blue color. The alternative procedure of adding ozone to a solution of the triphenyl phosphite in CH_2Cl_2 leads to lower yields of the ozonide since the phosphite reacts with the ozonide. When the ozonide is to be used as a source of singlet oxygen the solution is allowed to warm to about -25 °C in the presence of the substrate. Direct transfer of dioxygen in a bimolecular process occurs at -70 °C.[2,4,5]

Handling, Storage, and Precautions: decomposes with O_2 evolution at temperatures above about -25 °C. While solid triphenyl phosphite ozonide has occasionally been isolated[1b,6-8] this procedure is not recommended since the solid has been observed[1b,7,8] to detonate, with flashes of red light, upon warming.

Use as Singlet Oxygen Source.

In 1959, Knowles and Thompson[4] showed that ***Ozone*** forms a 1:1 adduct with ***Triphenyl Phosphite*** at low temperatures and that this adduct decomposes, with gas evolution, as the reaction solution is allowed to warm up. Corey[9] suggested that the oxygen evolved might be singlet oxygen. Experiments to investigate this possibility were initiated by Murray and co-workers in 1967. In collaboration with Wasserman and Yager[6] they were able to show that the gas evolved from solid triphenyl phosphite ozonide gave the characteristic ESR signal of singlet oxygen. Chemical evidence for the involvement of singlet oxygen was obtained by demonstrating that typical singlet oxygen products were obtained[2] from a variety of substrates when exposed to decomposing triphenyl phosphite ozonide (**1**). Thus 1,3-cyclohexadiene was converted to the endoperoxide in 67% yield (eq 1). The ene reaction was observed when 2,3-dimethyl-2-butene was converted to 2,3-dimethyl-3-hydroperoxy-1-butene in 53% yield by (**1**) (eq 2). Another example of a 1,4-cycloaddition reaction was observed in the transformation of tetraphenylcyclopentadienone to *cis*-dibenzoylstilbene in 38.2% yield. Likewise, α-terpinene was converted to ascaridole in 60% yield. Finally, in this earlier work, 9,10-diphenylanthracene was converted in 77% yield to its endoperoxide.

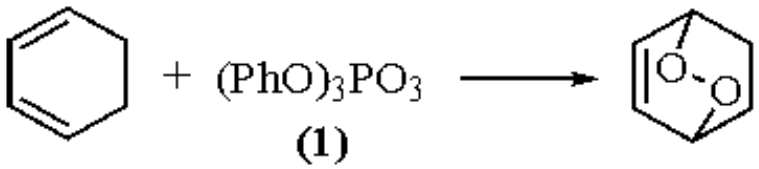

(1)

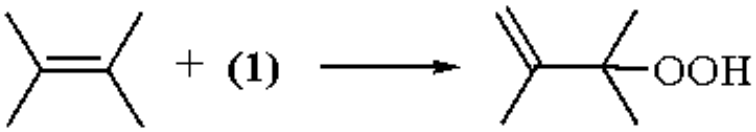

(2)

Similar work by Bartlett and Mendenhall[10] showed that (**1**) converts[9,10] dimethylanthracene (49%) and rubrene (87%) to their respective endoperoxides. When the singlet oxygen acceptor 1,3-diphenylisobenzofuran was oxidized[10] by (**1**), a 16% yield of the singlet oxygen product *o*-dibenzoylbenzene was obtained accompanied by an oxygen-1,3-diphenylisobenzofuran copolymer (eq 3).

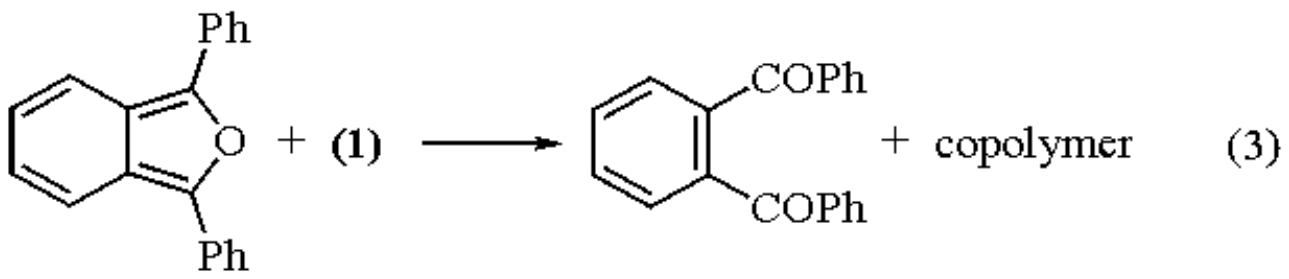

The third major reaction type ascribed to singlet oxygen has also been achieved using (**1**) as the singlet oxygen source. In this case, 2,2´-adamantylideneadamantane was converted to the dioxetane (eq 4).[11]

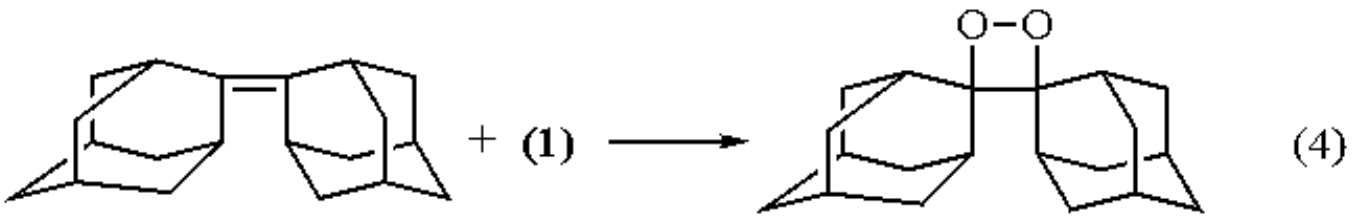

Dioxetane intermediates also seem to be involved in the conversion of 1-(2´-methoxyvinyl)pyrene and 1,1-diphenyl-2-methoxyethylene to their cleavage products.[12] Dioxetane-type intermediates have also been invoked[13] in the reaction between (**1**) and several ketenes. The reaction of the tetrathioethylene (**2**) with (**1**) is also believed[14] to proceed through the dioxetane. The products are the disulfide (**3**) and the dithiooxalate (**4**) (eq 5).

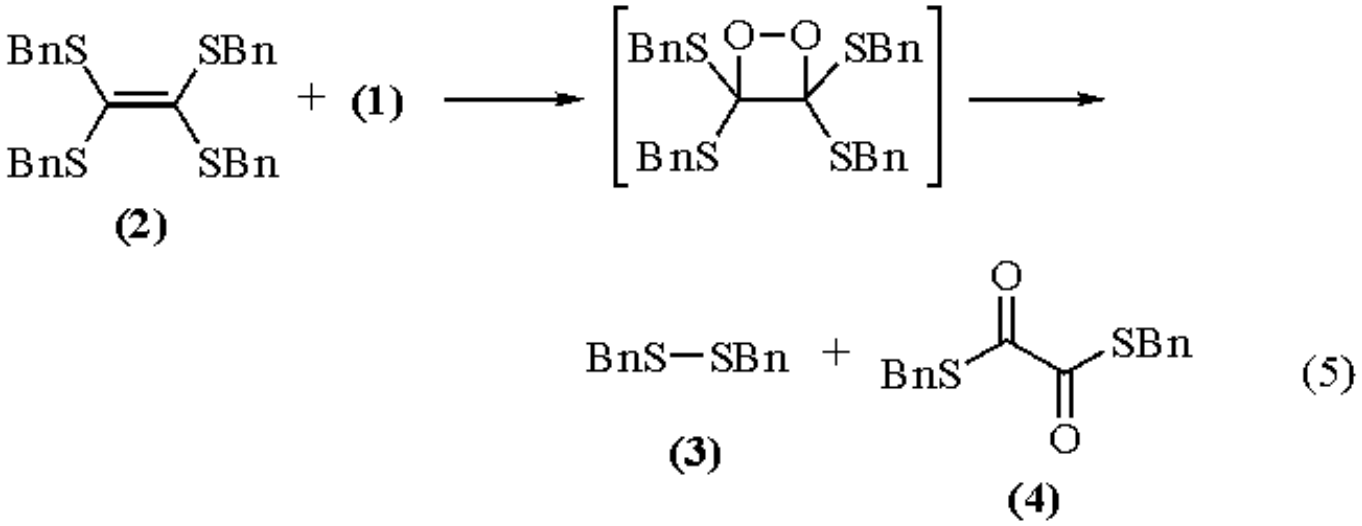

Additional evidence that (**1**) is a source of singlet oxygen was obtained by using substrates in which known singlet oxygen reactions proceed to give a characteristic product distribution. The reaction of (**1**) with 2-methyl-2-butene gives[15] two hydroperoxides with the distribution shown (eq 6). The observed ratio is not significantly different from that obtained when other sources of singlet oxygen are used. Singlet oxygen product ratios were also obtained[15,16] by two groups when the substrate is 1,2-dimethylcyclohexene. Kopecky et al.[17] showed that reaction of isopropylidenecyclohexane with (**1**) gives two hydroperoxide products in a ratio which is closer to that given in a reaction believed to involve singlet oxygen and quite different from that obtained in a base-catalyzed displacement reaction of the appropriate β-halohydroperoxide.

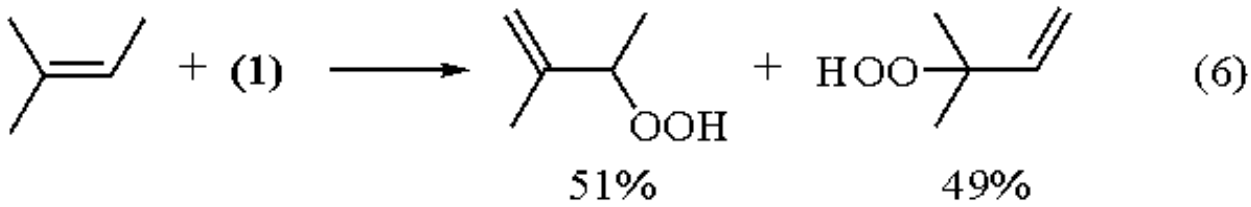

Triphenyl phosphite ozonide has been used[18] in an unusual synthesis of the *trans*-triepoxide of benzene from oxepin (eq 7). A somewhat different type of singlet oxygen reaction is observed[19] when 2,6-di-*t*-butylphenol is treated with (**1**). In this case the product *p*-benzoquinone and diphenoquinone (eq 8) are believed to be formed from radicals arising from an initial H-atom abstraction reaction of singlet oxygen with the phenol.

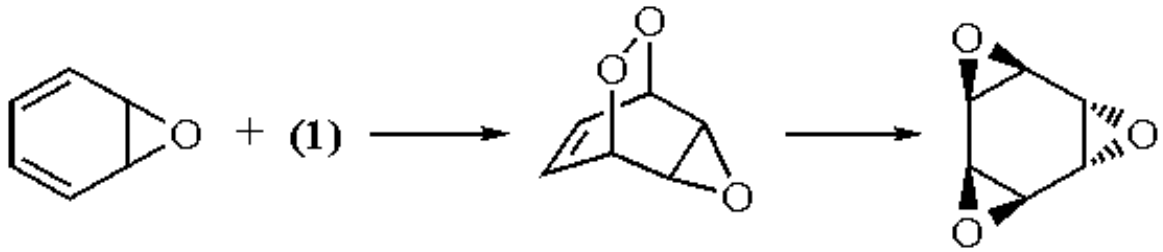

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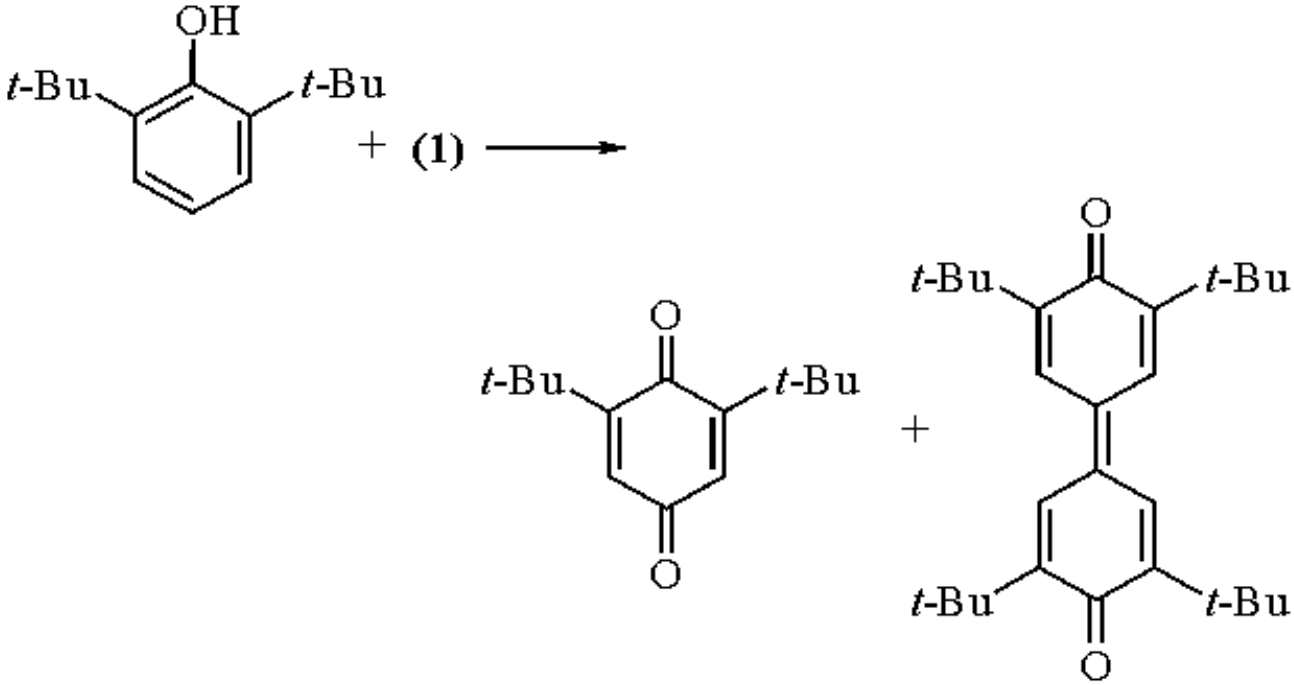

(8)

Treatment of Wittig reagents with (**1**) gives the expected aldehyde.[20] In an unusual application of this procedure, a trimethylsilyl-substituted Wittig reagent is oxidized to a trimethylsilyl ketone. A bis(trimethylsilyl) Wittig reagent gives the corresponding ketone when oxidized by (**1**) (eq 9). This ketone can be used to introduce carbonyl groups. Disulfides are converted[21] to mixtures of thiosulfinates and thiosulfonates by reaction with (**1**) (eq 10). The reaction initially favors formation of the thiosulfinate, but on standing the reaction mixture changes to give more of the thiosulfonate. This reaction was later extended to the biologically important disulfide lipoic acid,[22] where oxidation of methyl α-lipoate with (**1**) gave all four possible thiosulfinate isomers.

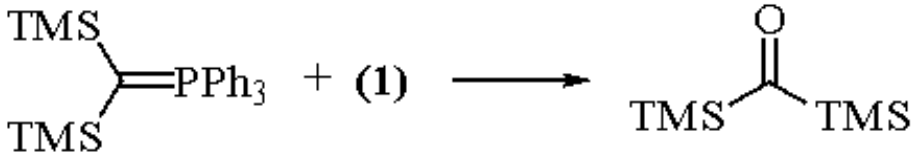

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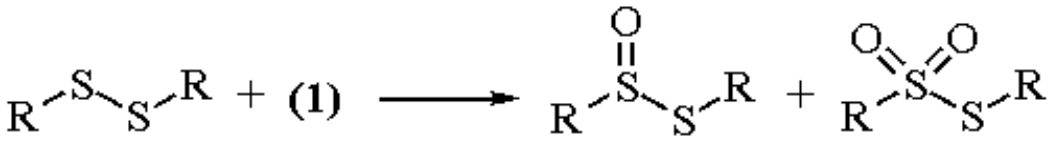

(10)

The oxidation of diazo compounds by singlet oxygen has provided an alternative route to carbonyl oxides and ozonides. This reaction can be carried out using (**1**) as a singlet oxygen source (eq 11).[23] A carbonyl oxide, produced in this manner, has been used[24] to epoxidize alkenes in low yield. However, the conditions of these reactions are such that some contribution of a direct reaction (see below) of (**1**) with the diazo compound cannot be ruled out.

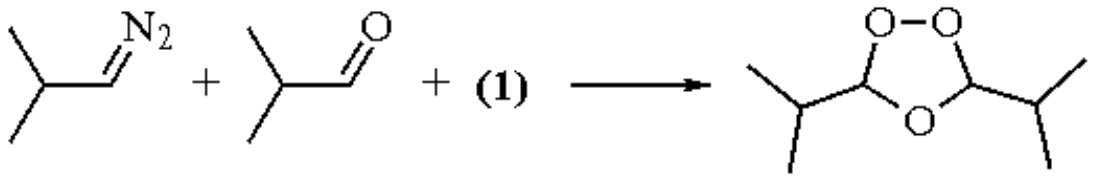

(11)

Oxidation of acetone azine by (**1**) gives acetone.[25] The reaction is believed to proceed via an electron transfer process. Triphenyl phosphite ozonide has also been used[26] to convert several cyclopropenethiones to their oxygen analogs. The insertion of dioxygen into a silicon-silicon σ-bond has been accomplished using several sources of singlet oxygen, including (**1**) (eq 12).[27a] This reaction was subsequently extended to oxadisilirane substrates, which give disilaozonides when treated with singlet oxygen.[27b]

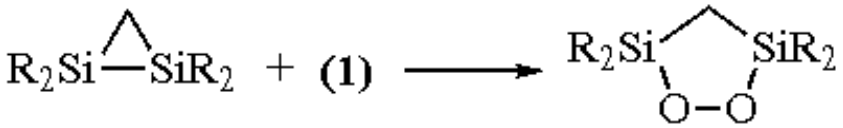

(12)

The thermal generation of singlet oxygen from (**1**) can be accelerated by the presence of methanol and pyridine.[28] A study of the mechanism of this effect indicates that it results from a successive displacement of phenoxy by methoxy groups in (**1**). The new phosphite ozonides then decompose at increased rates.

The Murray[1a] and Mendenhall[1b] articles contain some description of the chemistry of other phosphite ozonides. In general, this chemistry parallels that of (**1**) described here.

Use in Direct Bimolecular Transfer of Dioxygen.

In a number of cases the reaction of (**1**) with typical singlet oxygen substrates has been shown to proceed in a direct bimolecular manner without the release of singlet oxygen. In these cases, (**1**) is used below its decomposition temperature (usually -60 to -70 °C). Perhaps the most compelling evidence for this separate oxidation process comes from the reaction of (**1**) with *cis*- and *trans*-diethoxyethylene. This reaction gives[3] the same distribution of dioxetanes from each of the stereoisomeric substrates (eq 13). The singlet oxygen reaction is known to give the dioxetanes in a stereospecific reaction with retention. Tetramethylethylene was shown to give the characteristic singlet oxygen ene reaction product when stored with (**1**) at temperatures well below the temperature at which singlet oxygen is released.[3a,16] Relative rates of the reaction of (**1**) with typical singlet oxygen acceptors have been found to differ from those measured for singlet oxygen itself.[1b] When reacted with (**1**) at low temperature, dihydropyran gives[16] two products in a ratio which differs greatly from that given in photosensitized oxidations (eq 14). Also, tricyclopropylethylene under similar low-temperature conditions gave products[29] derived from an intermediate dioxetane, as opposed to the ene reaction products obtained when singlet oxygen is the oxidant.

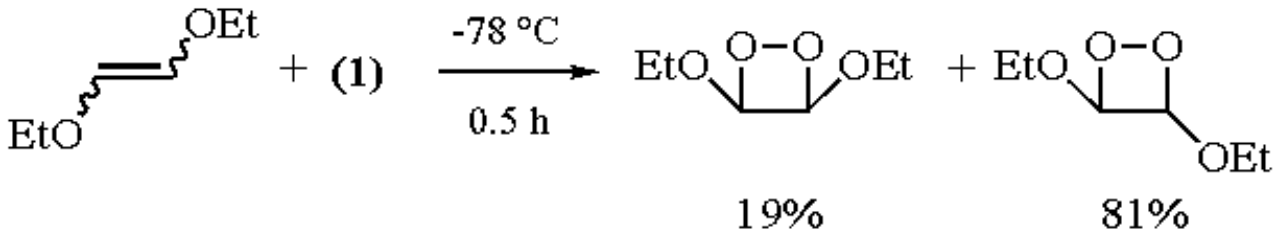

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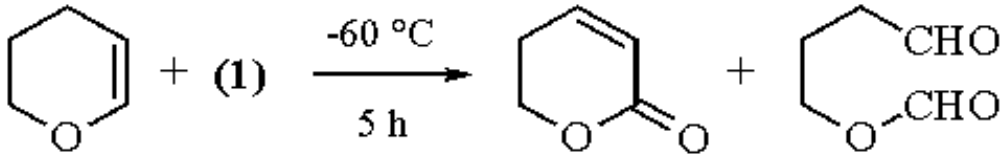

(14)

Germacrene reacts directly with (**1**) to give[30] (after reduction) an alcohol (eq 15) which is not formed in the singlet oxygen reaction. The latter reaction proceeds through two other modes of the ene reaction. Silyl enol ethers of α,β-unsaturated ketones are oxidized at low temperature by (**1**)[31] to give alcohols with stereoselectivity different from that observed with ***m-Chloroperbenzoic Acid***. An example is shown in eq 16. Several thioacetals have been oxidized by (**1**)[32] to mixtures of sulfoxides and disulfoxides under conditions where the bimolecular reaction is likely. A pyrimidine derivative has been oxidized by (**1**) to the corresponding endoperoxide.[33] The yields obtained were lower that those given by photosensitized oxidation.

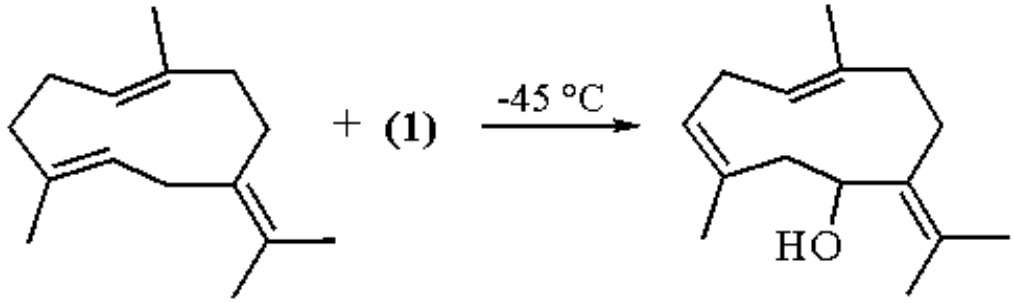

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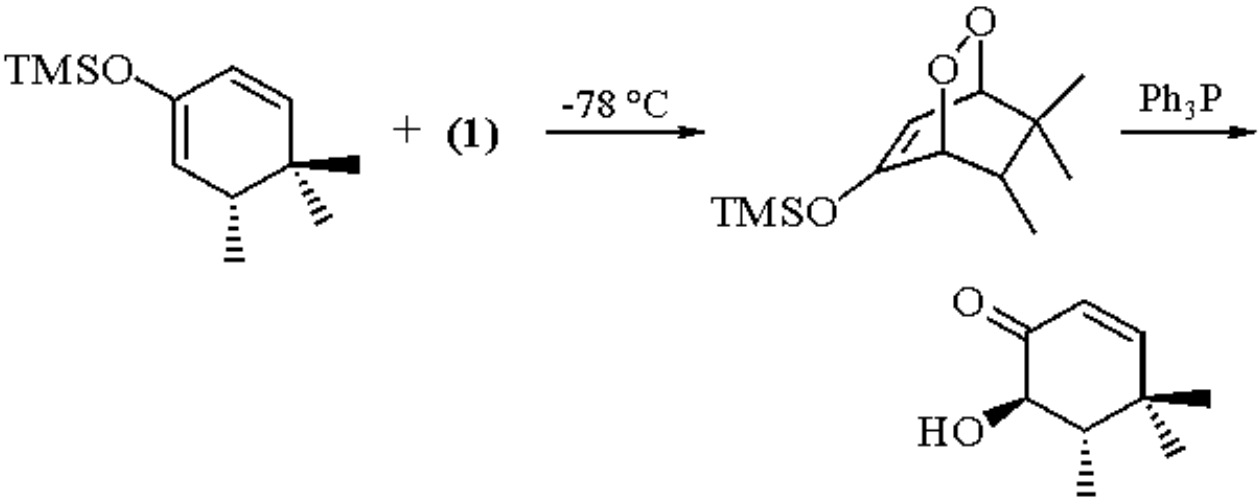

(16)

Further evidence for the bimolecular reaction is available.[16] An attempt has been made to present separately the two basic reaction modes of (**1**). However, some of the reactions presented in the section on the use of (**1**) as a singlet oxygen source were carried out under conditions such that the direct reaction may also have played a role.

Related Reagents.

Oxygen; ***Ozone-Silica Gel***; ***Singlet Oxygen***.

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Triphenylphosphonium Anhydride Trifluoromethanesulfonate

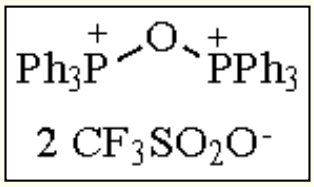

[72450-51-2] · $C_{38}H_{30}F_6O_7P_2S_2$ · Triphenylphosphonium Anhydride Trifluoromethanesulfonate · (MW 838.76)

(oxophilic reagent for net removal of water in various reactions[1,2])

Physical Data: highly hygroscopic, white crystalline solid.[3]

Solubility: slightly sol chlorocarbon solvents; insol Et_2O; reacts with THF.

Preparative Methods: triphenylphosphine oxide in CH_2Cl_2 is treated with ***Trifluoromethanesulfonic Anhydride*** in CH_2Cl_2 at 0 °C. A precipitate of the reagent forms in <15 min.

Handling, Storage, and Precautions: prepared directly before use.

Introduction.

The reagent is a potent oxophile, forming triphenylphosphonium ethers (Ph_3+P-O-R) with OH groups and ***Triethylamine*** (or preformed oxide anions). These activated ethers may be either displaced or eliminated by nucleophiles or bases, respectively, with triphenylphosphine oxide as the leaving group. The hydroxyl substrate is added to a slurry of the reagent and rapid formation of the ether is indicated by solution of the reagent. Subsequent reactions are usually fast, although higher temperatures are available using ethylene dichloride as solvent. Passage of the reaction mixture through a short silica column usually readily entraps the phosphine oxide. The reagent is generally unreactive to carbonyl groups or ethers (except epoxides, below) and is quite selective for attack at oxygen over nitrogen nucleophiles.

Carboxylic Acids.[2]

Usually, dehydration of acids to anhydrides is quickly achieved by adding a solution of the acid and TEA to the reagent slurry (2:2:1 = acid:TEA:reagent). When the α-CH of the acid is modestly acidic, however, dehydration proceeds to the ketene, as in a simple preparation of diphenylketene from diphenylacetic acid. In either case the net result is an overall dehydration of the substrate(s).

Ester formation with primary alcohols is similarly facile, requiring 15 min at room temperature with the mixed acid and alcohol, and is equally effective in acylating phenols. Since the phenol may be activated first with the reagent, its ready *O*-acylation implies a rapid equilibration of the activated species, as in eq 1. With *t*-butyl alcohol, however, the yield is only 42%, implying a large extent of elimination.

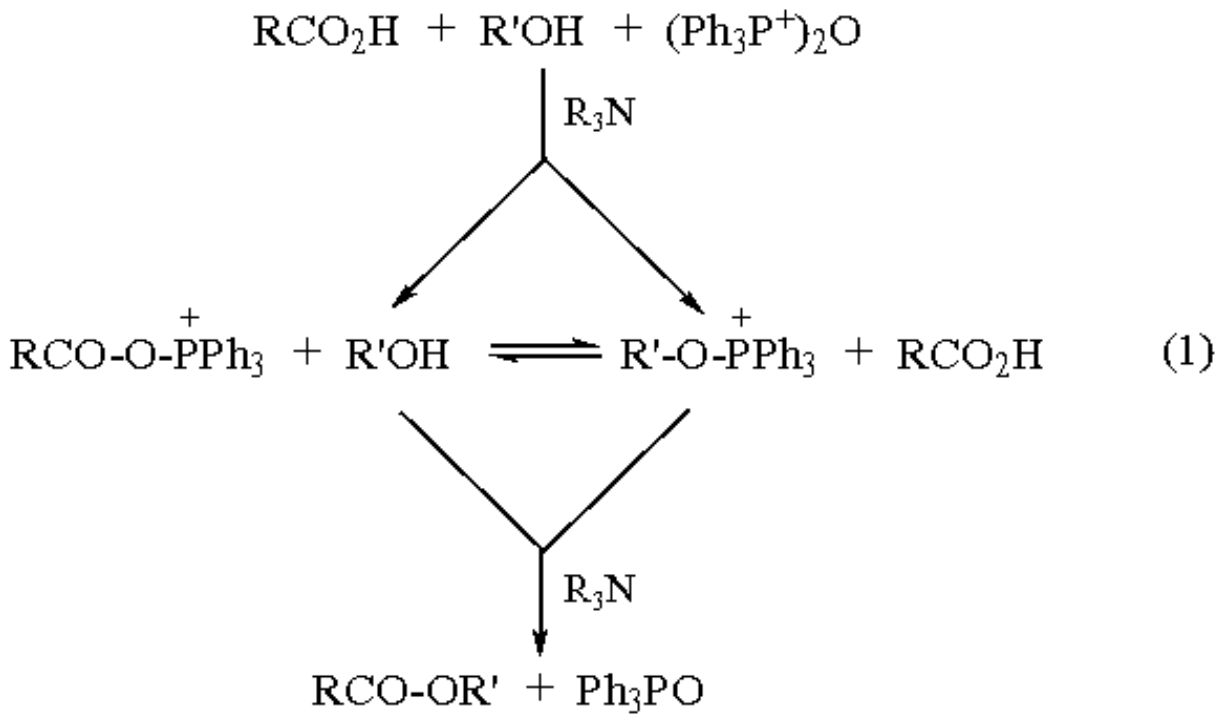

The same equilibration appears in amide formation on adding mixed acid and primary or secondary amine to the reagent. While Ph_3+P-NHR may form, it exchanges to activate the acid and then yields the amide.[2] The preference for Ph_3+P-O-R over Ph_3+P-NR_2 in the exchange may arise from the presence of two electron pairs on oxygen to back donate into the phosphorus d-orbitals, instead of only one on nitrogen. In a similar vein, amides and amines yield amidines on treatment with the reagent (eq 2; POP = reagent), although the reaction requires some 8 h at room temperature. The reagent has been used in the same fashion to convert sulfonic acid salts to their esters and amides in the synthesis of thymidine dimer analogs with sulfonic linkages.[4]

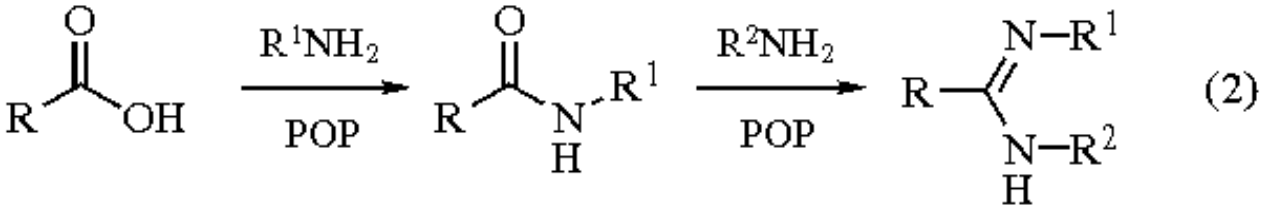

The two operations may occur successively with diamines, as in the double dehydration of benzoic acids with phenylene diamines to form benzimidazoles (eq 3; Z = NH). The conversion is complete in less than an hour at rt and appears much superior to traditional methods with higher temperatures and competing diamide formation. Similarly, benzoxazoles are conveniently formed from *o*-aminophenols and benzothiazoles from *o*-aminothiophenols (eq 3; Z = O and S, respectively)[2]. A six-membered perimidine was formed from 1,8-diaminonaphthalene and benzoic acid.

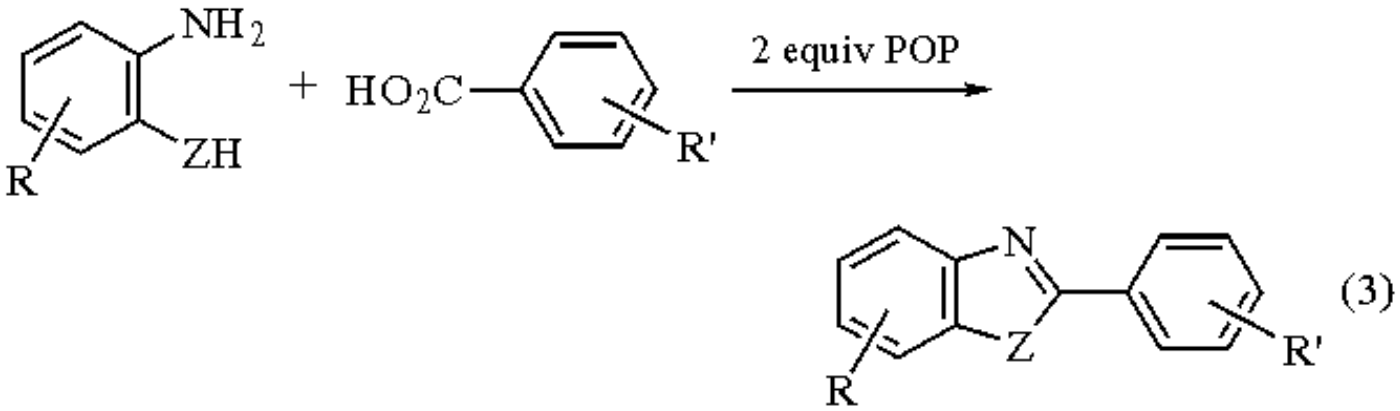

Internal cyclization of phenylalkanoic acids occurs with the reagent without bases present; the expelled triflic acid acts as a strong acid for activation, as in eq 4, to afford indanones, tetralones, and benzosuberones.[2] A case of acid-catalyzed Claisen condensation was also encountered with phenylacetic acid (eq 5).

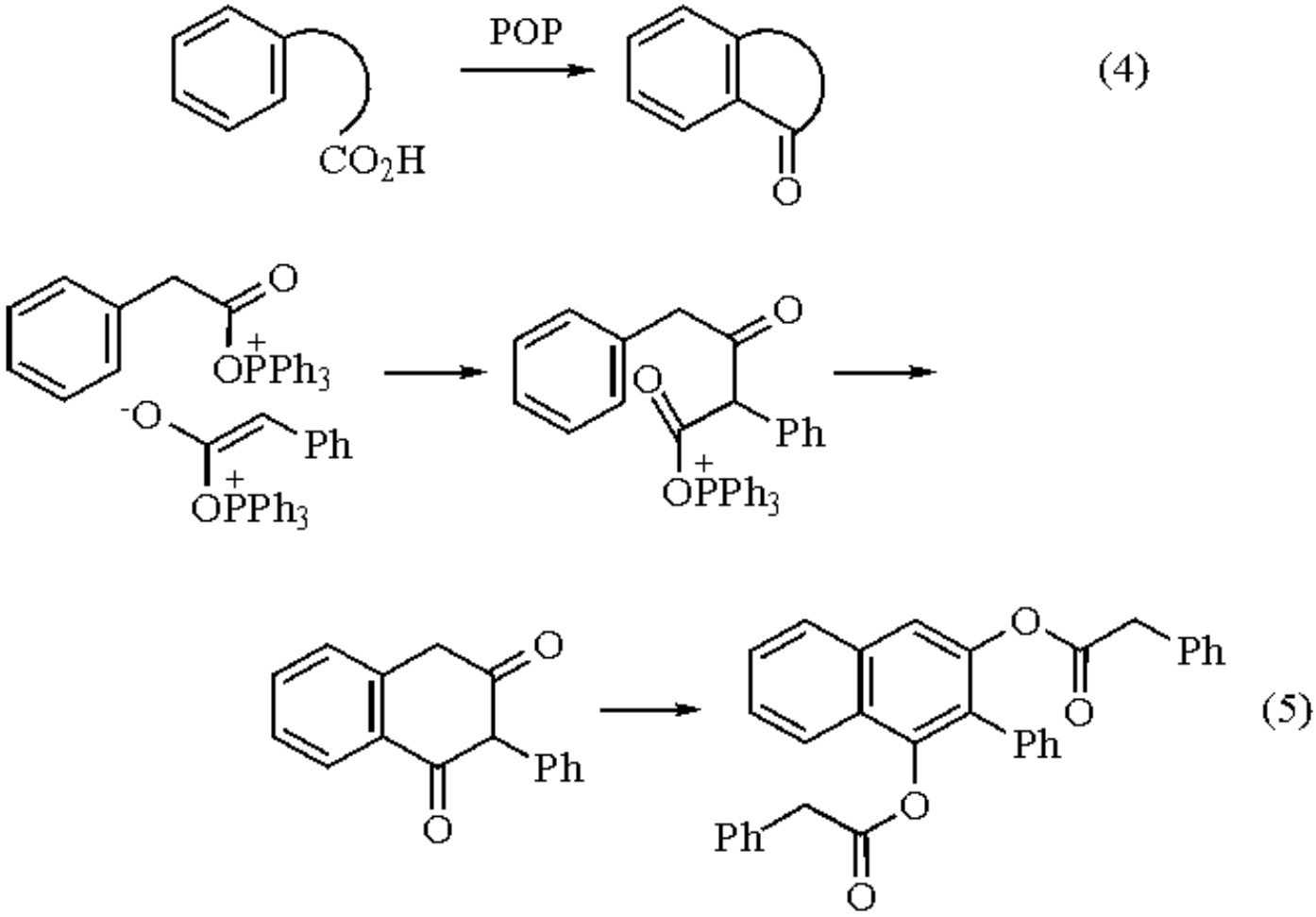

Other Substitutions.

With the exception of ketene formation, all the reactions above are substitutions at carboxylic carbons. With simple alcohols, activation has the advantage of affording the phosphonium ether without any nucleophile present except the inactive triflate; hence other nucleophiles of choice may be added for displacement. With primary and acyclic secondary alcohols, reduction with ***Sodium Borohydride*** (as a slurry in CH_2Cl_2) occurs at rt in a few hours to give the corresponding alkane.[5] Although Mitsunobu conditions presumably generate the same phosphonium ethers, borohydride reduction did not occur. On activation of cyclohexanols with the reagent, however, borohydride only generates $Ph_3P.BH_3$ and the alcohol is unchanged, apparently owing to steric hindrance. Although azide ion displaces the activated alcohols, halide ions are too unreactive.[6]

The internal displacement of the phosphonium ether is seen in the reaction of diols or amino alcohols with the reagent to form cyclic ethers or amines, respectively (eq 6), with three-, five-, or six-membered rings (the 1,3-diols for four-membered rings fragment to alkene and aldehyde).[7] The amino alcohols again imply the facile *N*/*O* exchange of the phosphonium group.

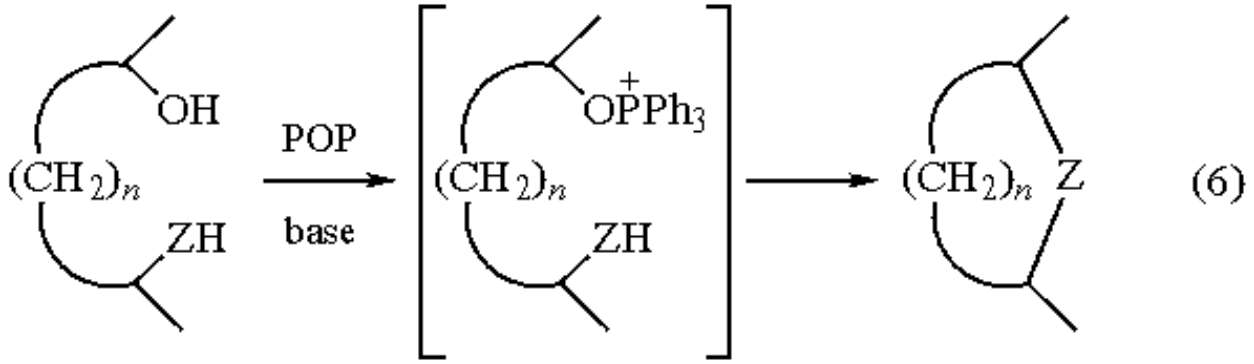

Eliminations.

Without nucleophiles present, elimination occurs instead, as with diphenylacetic acid to ketene above. Unsubstituted amides and aldoximes give nitriles at rt in minutes.[8] Tertiary alcohols eliminate with ease and phosphonium ethers of secondary alcohols eliminate with K_2CO_3 or

TEA on warming in CH_2Cl_2. Regiochemistry is not yet clear but there is an implication of favored *cis* elimination, for menthol gives both Δ^2- and Δ^3-menthenes[8] (*cis* required for the former) while only *cis* elimination occurred in two tropinol isomers[9] and a decalin case.[10]

Two other eliminations, however, have new synthetic value. Ketones activated by β-carbonyl or aryl groups are easily enolized and the reagent then serves to dehydrate the ketone to an alkyne in good yield (eq 7).[11] Dehydration of simple ketones to alkynes has not yet been perfected.

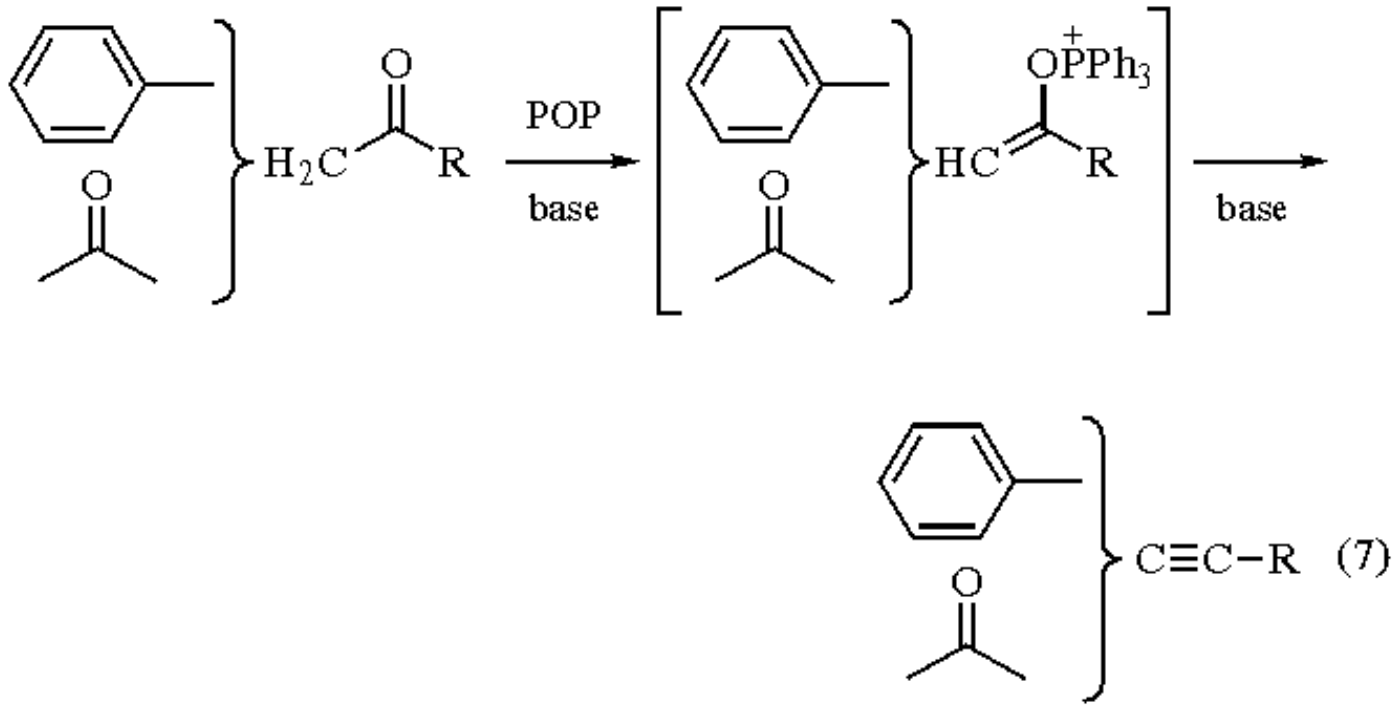

Although epoxides are easily formed from 1,2-diols with one mole of reagent, the epoxide can react further with another mole, dehydrating to the dienes.[12] This appears to provide a very convenient path for converting alkenes to dienes by successive epoxidation and dehydration, as in the case of limonene (eq 8).

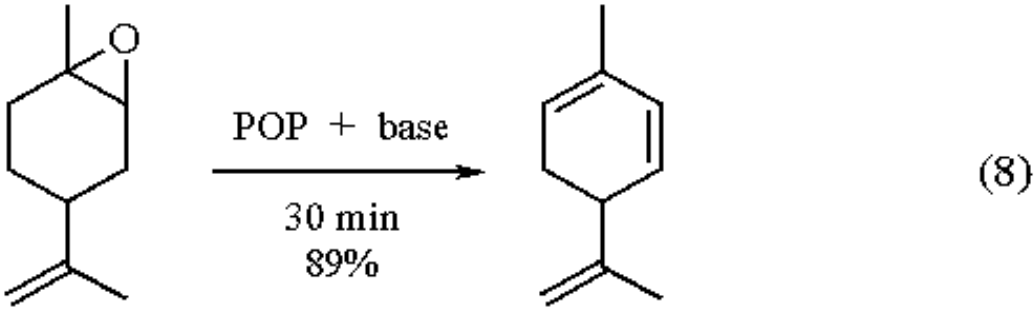

Variations.

The groups on phosphorus need not be phenyl; the related tributyl derivatives have been similarly used[13] to make 1,2-*cis*-furanoside ethers[14] and also as electrophilic catalysts for aldol and Michael reactions of silyl enol ethers.[15] To avoid the chromatographic separation of the product triphenylphosphine oxide, a basic variant of the reagent was created in the same way from $Ph_2PO\text{-}N(CH_2CH_2)_2NMe$, which is then returned from the reaction as its salt and easily extracted into water.[2]

The triphenylphosphonium ethers are also regarded as intermediates in the Mitsunobu reaction, prepared from $Ph_3P + (RO_2C\text{-}N{=})_2$ to activate an alcohol for substitution (see ***Triphenylphosphine-Diethyl Azodicarboxylate***).[16] They were earlier prepared electrochemically from Ph_3P + ROH and used for alkylation of imidazole and thiophenol[17] and carboxylic acids,[18] or applied to amides and ureas for dehydration to nitriles and carbodiimides, respectively, with bases.[19] The acyloxytriphenylphosphonium ions were similarly prepared from $Ph_3P + RCO_2H$ and converted to esters and amides as above, although in lower yields.[20]

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2,4,6-Triphenylpyrylium Tetrafluoroborate[1]

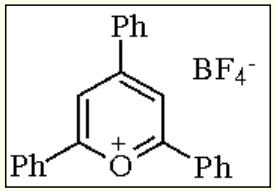

[448-61-3] · $C_{23}H_{17}BF_4O$ · 2,4,6-Triphenylpyrylium Tetrafluoroborate · (MW 396.21)

(converts primary amines into pyridinium salts which on reaction with nucleophiles NuH afford R-Nu)

Physical Data: mp 255-257 °C.

Solubility: insol H_2O, EtOH, Et_2O; sol CF_3CO_2H.

Form Supplied in: yellow solid.

Purification: recryst. from AcOH or $(ClCH_2)_2$.

Handling, Storage, and Precautions: may be stored indefinitely. Reports on possible mutagenic activity make it desirable to avoid direct contact with skin. Other 2,4,6-triphenylpyrylium salts are the commercially available sulfoacetate, and the hydrogen sulfate whose synthesis[2] is analogous to that of (**1**) as described by eq 1 below.

Syntheses.

2,4,6-Triphenylpyrylium salts may be obtained by a variety of methods.[3] The strong green fluorescence of 1,3,5-triphenylpentane-1,5-dione (benzylidenediacetophenone) in H_2SO_4 was observed as early as 1896, but the cause was discovered later (H_2SO_4 acts as a dehydrogenating and dehydrating agent, yielding the fluorescent triphenylpyrylium cation). Michael condensation of chalcone (**2**) with acetophenone yields the above 1,5-dione, and this reacts with various hydride acceptors furnishing 2,4,6-triphenylpyrylium salts in excellent yields: with ***Iron(III) Chloride*** in Ac_2O the tetrachloroferrate is obtained;[4] with ***Tetrafluoroboric Acid*** or $HClO_4$ in Ac_2O the fluoroborate (eq 1) and the perchlorate, are obtained respectively.[5] The same two salts may also be obtained using the corresponding triphenylmethyl salts as hydride acceptors,[6] which yield triphenylmethane by hydride transfer.

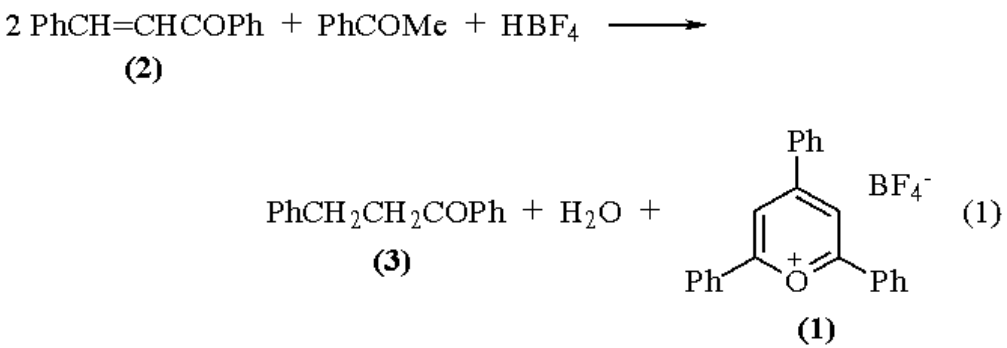

A procedure which is included in *Organic Syntheses* is based on the above reaction,[7] but the hydride acceptor is chalcone itself in acid medium ($HClO_4$ or HBF_4): its conjugate acid affords 1,3-diphenylpropan-1-one (**3**) by hydride transfer.[8] From two moles of chalcone (**2**), one mole of acetophenone, and one mole of an ethereal solution of tetrafluoroboric acid in 1,2-dichloroethane the yield of 2,4,6-triphenylpyrylium tetrafluoroborate (**1**) was 55-60%.[7]

This optimal synthetic procedure is a two-component synthesis. Other two-component syntheses of (**1**) or salts with other anions include: the replacement of acetophenone in the above reaction by its equivalent synthon, phenylacetylene (***Boron Trifluoride Etherate*** appears to be the best anion-forming reagent, leading[9] to an 80% yield of **1**); the reaction of phenylacetylene and 3-chloro-1,5-diphenylpentanedione in the presence of ***Tin(IV) Chloride***;[10] the benzoylation of dypnone (**4**) with benzoyl fluoride in the presence of boron trifluoride etherate (eq 2); the condensation of dypnone with benzaldehyde in acetic anhydride in the presence of $FeCl_3$; and the condensation of dibenzoylmethane with acetophenone in acetic anhydride with sulfuric acid, when 80% yields are attained.

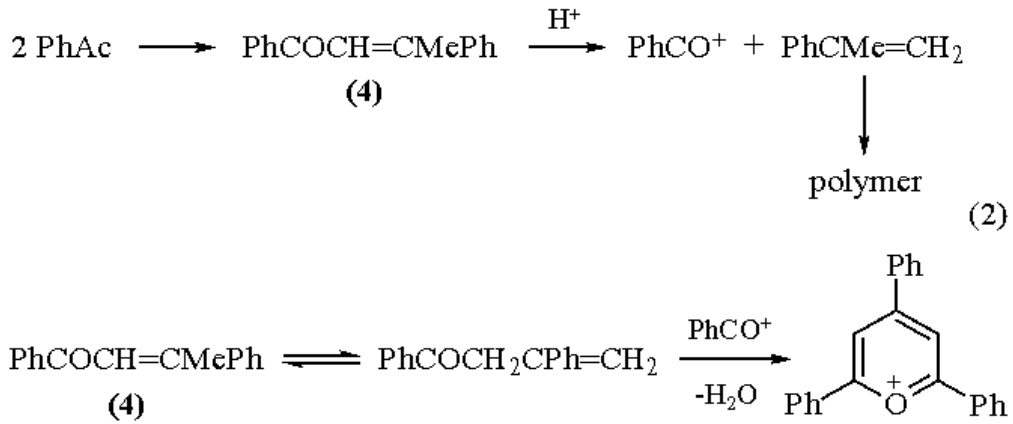

Finally, three-component syntheses have to be mentioned because they use simpler starting materials in one-step procedures: (i) condensation of two moles of acetophenone with one mole of benzaldehyde in the presence of boron trifluoride or boron trifluoride etherate;[12] the chloroferrate is produced by the same condensation in the presence of acetic anhydride and $FeCl_3$;[4] (ii) as indicated earlier, phenylacetylene may replace acetophenone,[9] and the hydride acceptor is chalcone which is formed in the condensation; (iii) a hydride acceptor becomes unnecessary when two moles of acetophenone are reacted with benzotrichloride in the presence of perchloric acid;[13] instead of benzoylating dypnone, one may react two moles of acetophenone with ***Benzoic Anhydride*** in the presence of $FeCl_3$; (iv) alternatively, one may react two moles of phenylacetylene with ***Benzoyl Chloride*** in the presence of $SnCl_4$; (v) dibenzoylation of α-methylstyrene with benzoyl chloride and ***Aluminum Chloride*** affords triphenylpyrylium tetrachloroaluminate, which can be converted into other salts.[14]

Reactions.

Weak bases (e.g. sodium acetate in aqueous ethanol) convert (**1**) or its salts with other anions into the stable crystalline triphenylpyrylium pseudobase (**5**) (1,3,5-triphenyl-2-pentene-1,5-dione) (see eq 3).

It has been reported[4,15] that substituted pyrylium salts reacted readily with ammonia or primary amines, yielding pyridines and *N*-substituted pyridinium salts, respectively. It has been observed[16] that 2,4,6-triphenylpyrylium salts react with ammonia at room temperature to yield an ether-soluble crystalline adduct which dehydrates at the melting point, resolidifying to 2,4,6-triphenylpyridine.

N-Alkyl-2,4,6-triphenylpyridinium salts may be obtained either from primary amines and 2,4,6-triphenylpyrylium salts, or by quaternization of 2,4,6-triphenylpyridine with alkyl halides. Only the former reaction is relevant to the present context.

Nucleophilic Displacement of NH_2 Groups from Primary Amines via *N*-substituted 2,4,6-Triphenylpyridinium Tetrafluoroborates.

Primary aromatic amines can be diazotized and subsequently converted into a variety of aromatic derivatives by nucleophiles which displace the diazonium group. For aliphatic primary amines, such a displacement may be achieved using pyrylium salts as the key reagents.

In 1926, Ziegler and Fries showed[17a] that 1-methyl-2,4,6-triphenylpyridinium chloride thermolyzed to 2,4,6-triphenylpyridine and presumably methyl chloride. In 1969, Susan and Balaban[17b] reported that 1-methyl-2,4,6-triphenylpyridinium iodide or chloride decomposed on melting, affording 2,4,6-triphenylpyridine and the corresponding methyl halides, which were isolated and identified; it was also observed that *N*-benzyl-2,4,6-triphenylpyridinium salts were easily solvolyzed on recrystallization from ethanol, yielding 2,4,6-triphenylpyridine. These early observations led to the development, by Katritzky and co-workers, of a synthetic method for converting primary amino groups into other functional groups by means of triphenylpyrylium and related cations.

The conversion of a primary amino group into a leaving group is achieved by reaction with 2,4,6-triphenylpyrylium tetrafluoroborate (**1**), which leads to an *N*-substituted 2,4,6-triphenylpyridinium tetrafluoroborate (**6**). The mechanism of this reaction has been studied using *n*-$BuNH_2$ in conjunction with UV and ^{13}C NMR spectroscopic methods;[18] it was concluded that when there is sufficient amine present for each mole of pyrylium salt (either &egt;2 moles of primary amine, or one mole of tertiary amine, such as triethylamine, and &egt;1 mole of RNH_2), the pyrylium salt is converted entirely to a vinylogous amide (**7**), which is then cyclodehydrated to the pyridinium cation (**6**) (eq 3). The protonations and deprotonations are assisted by the reaction solvent, which may be water or a lower alcohol (such as MeOH, EtOH, *i*-PrOH, *t*-BuOH), or dichloromethane with a small amount of acetic acid. With lower amine-to-pyrylium ratios than those mentioned above, a 1,5-diketone (**5**) (pyrylium pseudobase) is also formed from traces of water present or originating in the cyclodehydration. The rate-determining step is the cyclodehydration, which is accelerated when acetic acid is present.

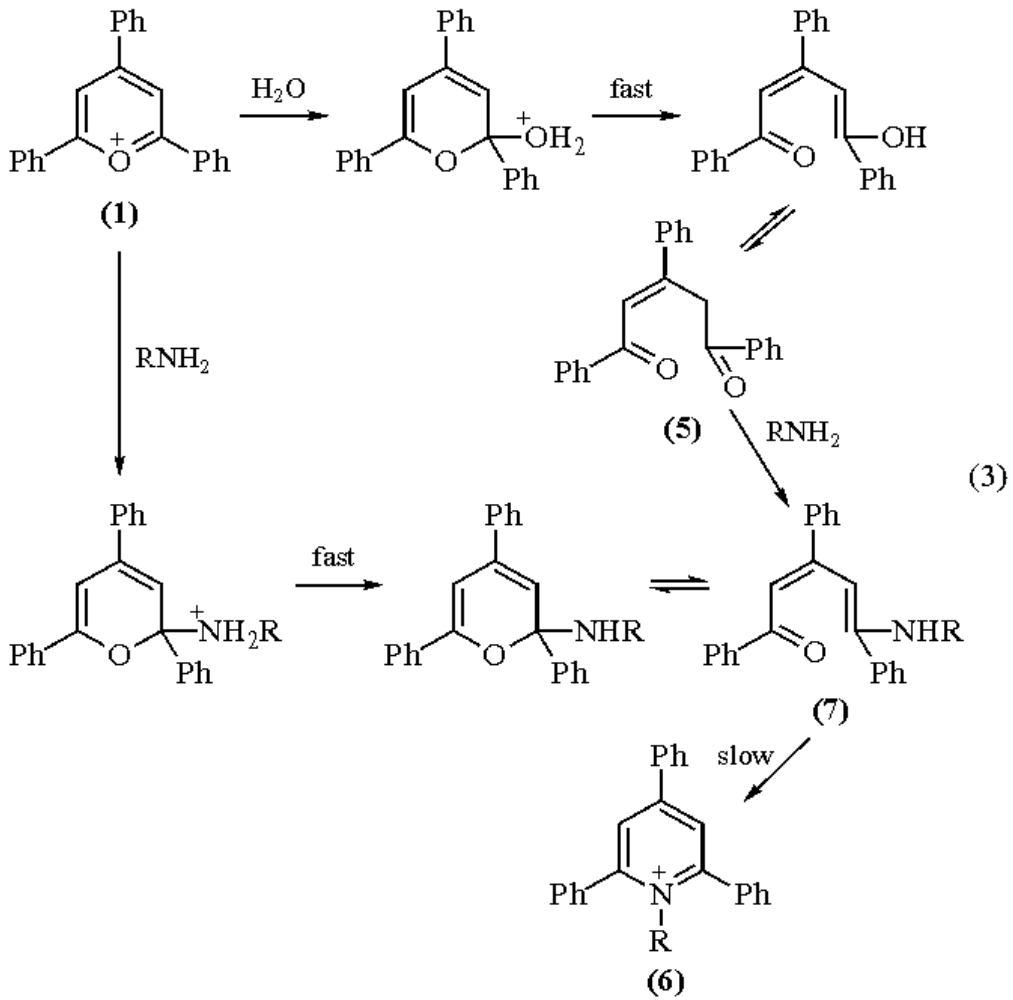

As a result of these mechanistic studies, conditions were found for rapidly obtaining good yields of pyridinium salts (**6**) at room temperature in mildly acidic or basic media from primary amines whose NH_2 group is bound to an aromatic, a primary aliphatic, or a secondary aliphatic carbon atom.

The displacement of 2,4,6-triphenylpyridine from 1-R-2,4,6-triphenylpyridinium salts (**6**) can be achieved with a variety of nucleophiles NuH, yielding RNu compounds as shown in Table 1.

Table 1 Functionalities Obtained from Primary Amines via Pyridinium Salts

Group in the Periodic Table				
1	14	15	16	17
R H^{19}	R $CH(CO_2Et)_2$[20]	R $N(COR)_2$[22]	R OAr[23]	R F[30]
	R $CH(CN)CO_2Et$	R NR_2[23]	R $OCOR$[24]	
	R $CHPhCO_2Et$	R N_3[22]	R ONO_2[25]	R Cl[31]
	R $CHRNO_2$[20,21]	R $NRSO_2Ar$[22]		
			R SO_2Ar[26]	R Br[32]
		R $\overset{+}{P}Ph_3$[23]	R SAr[23]	
			R $SC(S)OR$[27]	R I[33]
			R $SC(S)SR$[28]	
			R SCN[29]	
			R $SeCN$	

Replacement of NH_2 by Hydrogen.

Pyridinium salts (**6**) add H^- from sodium borohydride, yielding 1,2-dihydro derivatives. When R is alkyl, benzyl, arylmethyl, or heteroarylmethyl, these 1,2-dihydropyridines split off 2,4,6-triphenylpyridine on heating at around 200 °C and afford RH compounds in &egt;75% yields. Other R groups yield complex mixtures of products, but pyridinium salts formed from RNH_2 and 2,3,5,6-tetraphenylpyrylium salts react with ***Sodium Borohydride***, yielding 1,4-dihydropyridines which on pyrolysis at 180-200 °C afford RH in good yields.

Replacement of NH_2 by Carbon Nucleophiles.

When R in (**6**) is benzyl, nucleophilic attack by sodium derivatives of ***Ethyl Cyanoacetate***, ethyl phenylacetate or ***Diethyl Malonate*** in refluxing dioxane or 1,2-dimethoxyethane affords the corresponding monobenzylated esters in &egt;70% yields. With other R groups, more sterically hindered pyridinium salts have to be used, such as (**8**) (eq 4). However, (**6**) with any type of R group reacts smoothly with nitronate anions, and affords *C*-alkylated nitro compounds in good yields (unlike other agents which are *O*-alkylating).

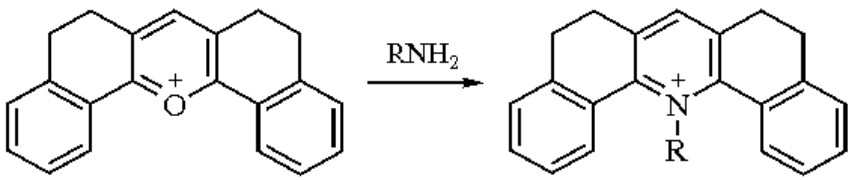

(4)

(8)

Replacement of NH_2 by Nitrogen or Phosphorus Nucleophiles.

Pyridinium salts (**6**) alkylate potassium phthalimide or sodium derivatives of succinimide, *N*-ethylbenzenesulfonamide or *N*-phenylbenzenesulfonamide; on hydrolysis of the resulting benzenesulfonamides, secondary amines RNHR´ are obtained. Tertiary amines $PhCH_2NR'_2$ can be obtained from (**6**) with piperidine or morpholine without any interference from quaternary salts; similar selectivity is obtained when the phenyl group in $PhCH_2$ is replaced by an α-, β-, or γ-pyridyl group. Quaternary salts may be obtained, however, by transferring the R group of (**6**) to pyridine or 2- or 4-picoline (&egt;70% yields). At 130 °C in DMF (**6**) reacts with ***Sodium Azide***, forming alkyl or benzyl azides in high yields. Triphenylphosphine reacts with (**6**) to yield phosphonium salts when R is benzyl or 2- or 4-picolyl.

Replacement of NH_2 by Oxygen, Sulfur, or Selenium Nucleophiles.

On heating at ca. 200 °C a powdered mixture of (**6**) with the sodium salt of a carboxylic acid (R´ = Me, Ph, Pr) in the presence of 2,4,6-triphenylpyridine, esters $R'CO_2R$ are obtained in >60% yields. Pyridinium salts whose relief of steric strain is higher, e.g. when using (**8**) instead of (**6**), require lower temperatures, e.g. 100 °C with R´ = Me. From such esters, alcohols may be obtained by hydrolysis. Starting from RNH_2 and 2,4,6-triphenylpyrylium trifluoroacetate, crystalline triphenylpyridinium trifluoroacetates are obtained; on gentle pyrolysis around 160 °C, these salts yield 2,4,6-triphenylpyridine and $ROCOCF_3$ esters, which are easily hydrolyzable to alcohols ROH. Such conversions of Alk-NH_2 into Alk-OH proceed much more cleanly and efficiently than via diazotization.

Two pathways exist for obtaining aldehydes RCHO from RCH_2NH_2 via reaction with (**1**): oxidation of the pyridinium salt (**6**) (R = $ArCH_2$) by ***Potassium Dichromate*** in the presence of Bu_4N^+ BF_4^- in refluxing 1,2-dichloroethane; and pyrolysis of (**6**) with sodium 1-oxido-4,6-diphenyl-2-pyridone. Yields are moderate.

Nitrate esters, $RONO_2$, can be obtained in good yields by pyrolyzing under vacuum 2,4,6-triphenylpyridinium nitrates prepared from RNH_2 and 2,4,6-triphenylpyrylium nitrate.

Phenoxides (sodium phenoxide or α-naphthoxide) react in refluxing dioxane with (**6**) (R = benzyl, 3- or 4-picolyl) in the presence of Bu_4N^+ BF_4^-, affording the corresponding alkyl aryl ethers.

The pyridinium salts formed from 2,4,6-triphenylpyrylium thiocyanate and primary amines afford thiocyanates RSCN on heating with triphenylpyridine; isothiocyanates RNCS are byproducts formed in low yield. An analogous reaction allows the preparation of selenocyanates Alk-SeCN. When using a pyridinium salt with high steric requirements such as (**8**), even aryl thiocyanates may be thus obtained from $ArNH_2$.

Dithiocarbonates are formed in good yield from (**6**) (R = Alk) and potassium ethyl xanthate in refluxing benzene; the more reactive salts (**6**) (R = $PhCH_2$) react similarly both in ethanol and in benzene. Thiols result by hydrolyzing the thiouronium salts formed from (**6**) and thiourea in refluxing chlorobenzene. When (**6**) (R = 4-picolyl) was refluxed in ethanol with sodium *p*-toluenesulfinate, the corresponding sulfone was formed in high yield.

Replacement of NH_2 by Halide Anions.

Primary amines RNH_2 react with 2,4,6-triphenylpyrylium fluoride in refluxing benzene-ethanol so that the resulting water is continuously removed as azeotrope. On heating the pyridinium fluorides so obtained (after careful drying) above their melting points, i.e. at 80-120 °C, the corresponding fluorides RF are formed in high yields. A reaction analogous to the Schiemann procedure, namely pyrolysis of (**6**) with KF and triphenylpyridine, results in low yields of RF contaminated with RH.

To obtain chlorides, (**6**) can be heated at 200-240 °C in a KCl-NaCl-$ZnCl_2$ eutectic, when the RCl distills out in average yields around 50%. Alternatively, one can start from 2,4,6-triphenylpyrylium chloride and RNH_2, removing water by azeotropic distillation and heating the resultant pyridinium chloride at 100-130 °C.

Starting from RNH_2 and 2,4,6-triphenylpyrylium bromide or iodide, one readily obtains the corresponding crystalline halides, which on pyrolysis afford RBr and RI, respectively. For bromides, triphenylpyridine as flux increases the yield and reduces fusion and decomposition temperatures. In the case of iodides, even $ArNH_2$ groups may afford ArI, but in this case the Sandmeyer reaction is equally effective.

In addition to the nucleophilic deaminating substitutions described above, mediated by (**1**), other reactions of (**6**) are possible with particular *N*-substituents R. Thus with R = $PhCH_2CH_2$, elimination yielding styrene occurs on pyrolysis.[34] The N^+,N^- pyridinium betaine (**6**) with R = $ArCON^-$ affords isocyanates RNCO on heating, as an alternative to the Curtius rearrangement.[35] The analogous betaine formed from (**1**) and H_2N-N=CR-NHR´ splits off triphenylpyridine on heating and rearranges to unsymmetrical carbodiimides.[36]

A synthesis of nitriles RCN from aldehydes RCHO is based on converting the aldehyde into its phenylhydrazone. Subsequent reaction with (**1**) in refluxing formamide yields triphenylpyridine and the nitrile. Alternatively, 1-amino-4,6-diphenyl-2-pyridone is reacted with the aldehyde, leading to an aldimine whose pyrolysis affords the nitrile in high yield along with 4,6-diphenyl-2-pyridone.[37]

Conversion into Other (Hetero)aromatic Systems.

In addition to the use of 2,4,6-triphenylpyrylium salts for mediating the nucleophilic displacement of amino groups, they are versatile intermediates for obtaining other interesting compounds such as 2,4,6-triphenylnitrobenzene,[38] 2,4,6-triphenylphenol and -phenoxyl,[39] -phosphabenzenes,[40] and -thiopyrylium salts.[41]

Whereas (**1**) reacts with hydrazine to form a diazepine derivative (**9**), the pseudobase (**5**) is converted by hydrazine into a monohydrazone (**10**) which cyclizes to a pyrazoline derivative (**11**) (eq 5).[42] Both the pyrylium salt and the pseudobase react with monosubstituted hydrazines (R = Ph, Me, SO_2Ar, CO_2H) in ethanol, affording monohydrazones which cyclize to pyrazoline derivatives (**11**). Strong acids split off acetophenone from these pyrazolines and afford pyrazoles (**12**) under aromatization. However, if the monohydrazone (**10**) is refluxed in acetic acid, it undergoes a different cyclization, leading to a pyridinium salt (**13**); the corresponding N^+,N^- pyridinium betaine (**14**) may be a source of nitrenes RN. Similar reactions occur when (**1**) or the pseudobase (**5**) are treated with hydroxylamine in ethanol: a crystalline isoxazoline results, and on treatment with mineral acids an analogous C-C bond splitting occurs leading to 3,5-diphenylisoxazole and PhAc. If the reaction with hydroxylamine is carried out in acetic acid, 2,4,6-triphenylpyridinium *N*-oxide results.[42,43]

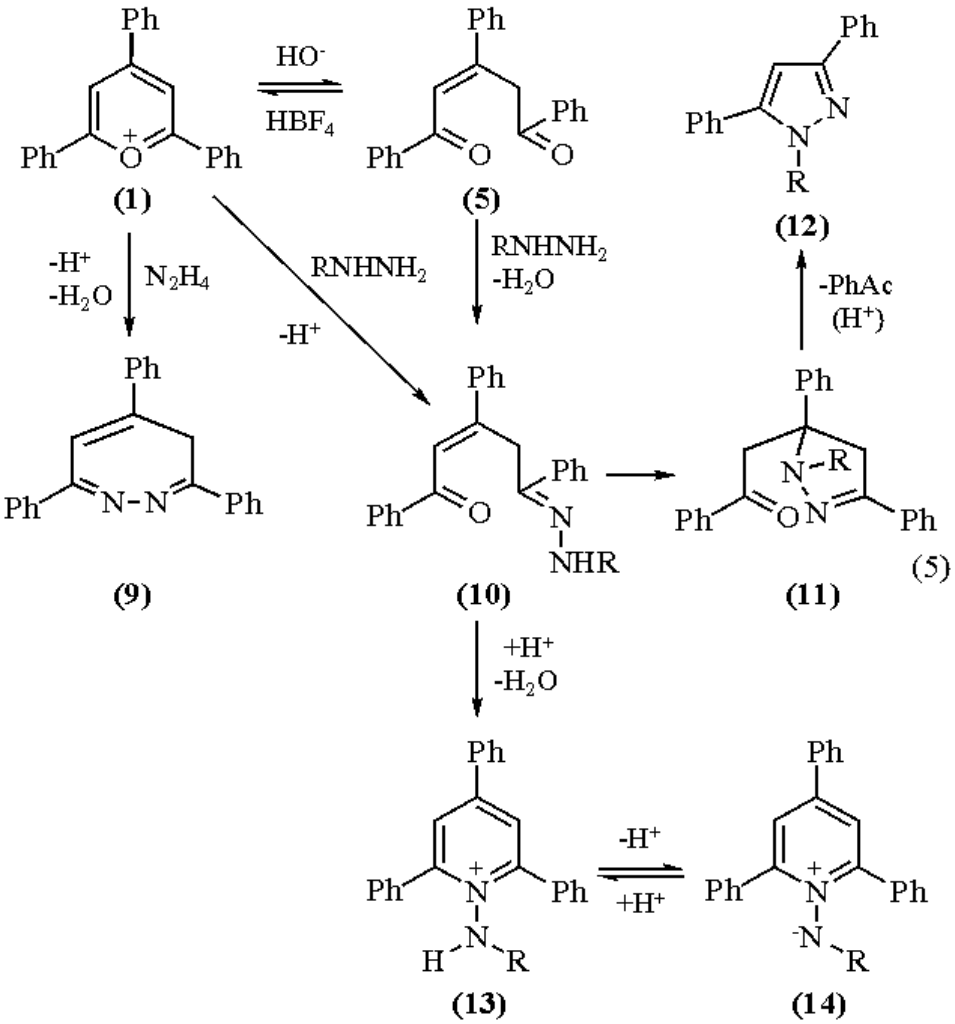

Summary of Reactions.

The primary amino group in alkyl or aralkyl amines is a very poor leaving group. By reaction with (**1**) (or other pyrylium salts with higher steric requirements), better leaving groups are obtained. Only ditosylates $RNTs_2$ are comparable, but their versatility is far smaller.

The relative reactivities increase in the order: (**6**) < (**8**) < RN_2^+, and within each of these three classes in the order: R = aryl < alkyl < benzyl. The mechanisms of substitutions or fragmentations differ and may be radical, S_N1, or S_N2.

Advantages of deaminations proceeding via pyridinium salts are the preparation of alkyl and benzyl fluorides, the *C*-alkylation of nitronate anions, the lack of rearrangement in reactions involving neopentyl derivatives,[44] and the accessibility of natural amino compounds. Some of the reactions mediated by (**6**) result in cyclizations, e.g. formation of epoxides; *N*-vinylpyridinium salts, which cannot be obtained by quaternization, may also be prepared.[45]

Optical and Electrochemical Properties.

A recent review,[46] dedicated to (**1**) as a photoinduced electron-transfer (PET) agent, outlines its advantages over cyanoaromatic photosensitizers: enhancement of radical-ion formation and reduction of back-electron transfer (both due to the absence of net charge separation associated with the electron-transfer step); efficiency as a photosensitizer in both the singlet and triplet excited states, and the possibility to favor one of these states by appropriate choice of concentration and temperature; the unique ability to study photooxygenations of organic radical cations with molecular oxygen

without interference from singlet oxygen or superoxide radical anions (both of which are formed when other photosensitizers are used). Of the PET reactions sensitized by (**1**), the above review cites: $[2_\pi; + 2_\pi]$ or $[4_\pi + 2_\pi]$ cycloadditions or cross-cycloadditions; (*Z*/*E*) isomerizations; sigmatropic rearrangements; oxygenation of alkenes yielding 1,2-dioxetanes (derived from the monomeric or dimeric alkene), epoxides, or ring-opened oxidized products; fragmentations of C-C, C-O, C-S, or C-N bonds (in the last case, dinitrogen is often extruded from azo derivatives).

The ability of pyrylium salts, including (**1**), to act as laser solutes has been reviewed.[47] The electrochemistry of pyrylium salts, including (**1**), has also recently been reviewed.[48]

Related Reagents.

2,4,6-Trimethylpyrylium Tetrafluoroborate.

---

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Alexandru T. Balaban

Triphenylsilane

Ph_3SiH

[789-25-3] · $C_{18}H_{16}Si$ · Triphenylsilane · (MW 260.43)

(reducing agent for esters, xanthates, and polychloroalkanes; protecting group for alcohols)

Physical Data: mp 47 °C; bp 152 °C/2 mmHg.

Solubility: sol most organic solvents.

Form Supplied in: white solid; commercially available.

Handling, Storage, and Precautions: this reagent is stable in air. Because the toxicogical properties are unknown, it should be handled in a well-ventilated fume hood. Contact with the eyes and skin should be avoided.

Deoxygenations.

Ph_3SiH is a useful reducing reagent under radical conditions. Esters are reduced to hydrocarbons at 140 °C by Ph_3SiH in the presence of a radical generator, ***1,1-Di-t-butyl Peroxide*** (DTBP) (eq 1).[1]

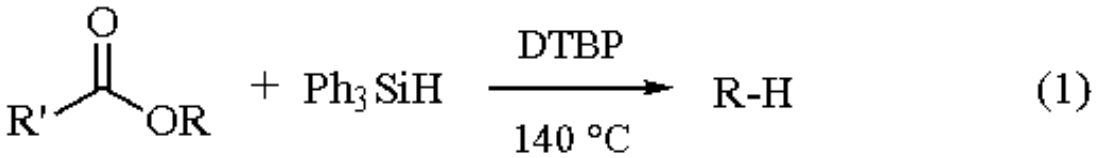

The best results are obtained with acetate esters compared with other esters, such as isobutyrate, pivalate, or benzoate. Acetates derived from primary, secondary, and tertiary alcohols are all reduced in high yield. Other silanes such as tripropylsilane and diphenylmethylsilane are not as effective, and other radical generators such as AIBN and dibenzoyl peroxide are not suitable for the deoxygenations.

This reaction can be applied to deoxygenation of carbohydrates. Thus both *O*-acetylfuranoses and -pyranoses can be converted to the corresponding deoxy sugars (eqs 2 and 3).[2]

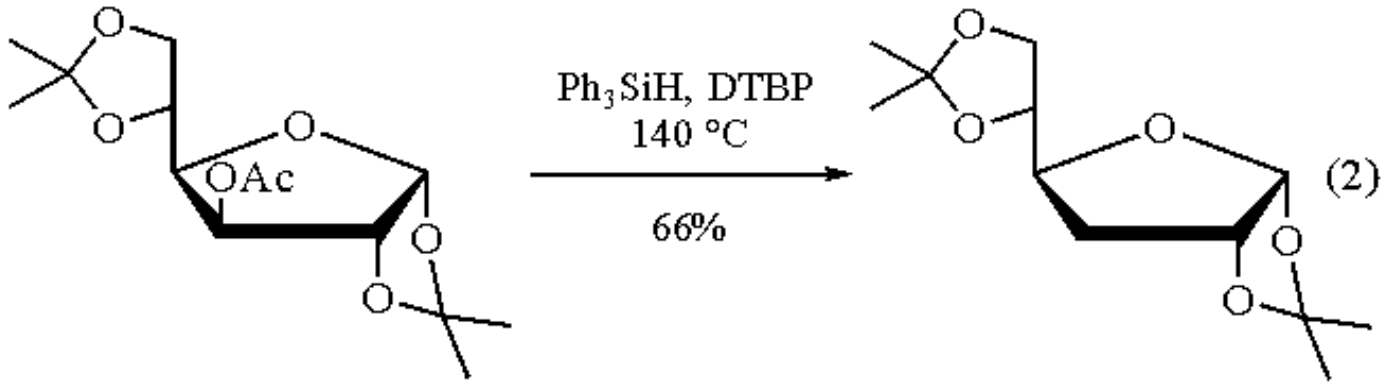

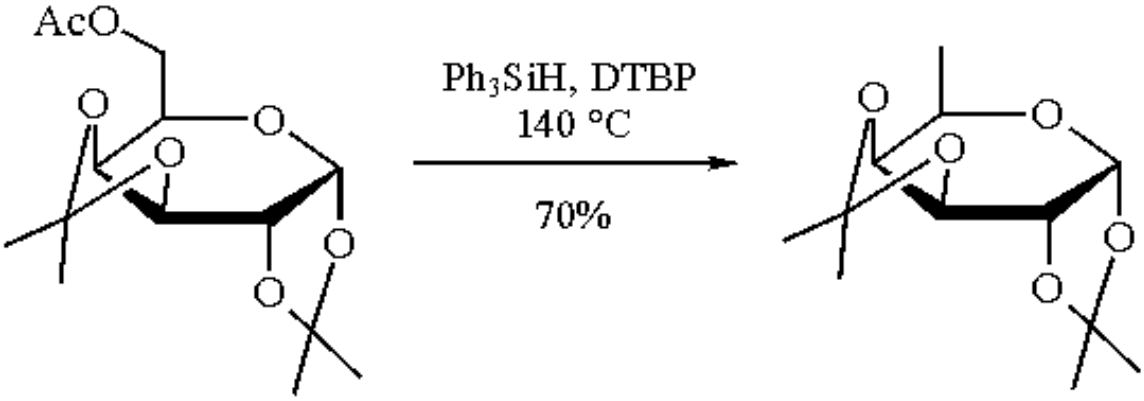

(3)

Xanthates (eq 4)[3] and perhaloalkanes[4] are also reduced by Ph_3SiH.

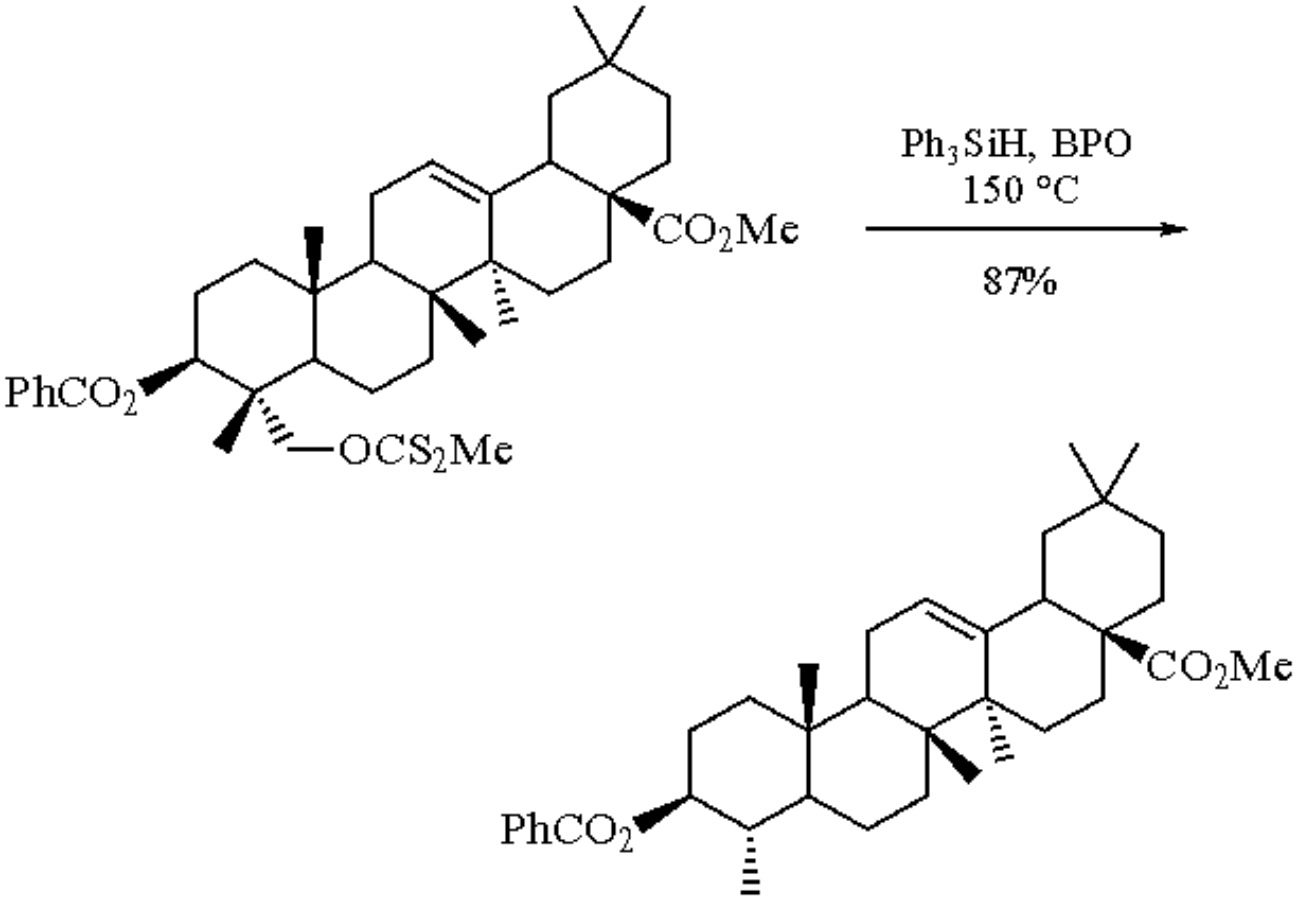

(4)

Ph_3SiH in combination with ***Trifluoroacetic Acid*** has been used for ionic deoxygenation of tertiary alcohols (eq 5).[5]

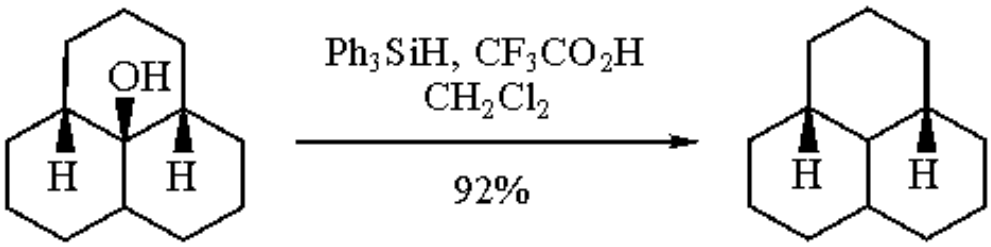

(5)

Protecting Group.

Triphenylsilane is used in certain cases for the preparation of triphenylsilyl ethers, which serve as alcohol protecting groups.[6] The triphenylsilyl group is considerably more stable (about 400 times) than the TMS group toward acidic hydrolysis.[7]

Related Reagents.

1,4-Bis(diphenylhydrosilyl)benzene; ***Triethylsilane-Trifluoroacetic Acid***.

---

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(Triphenylstannylmethyl)lithium[1]

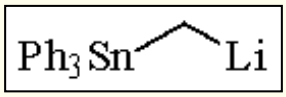

[64331-89-1] · $C_{19}H_{17}LiSn$ · (Triphenylstannylmethyl)lithium · (MW 371.01)

(methylenation reagent for several carbonyl compounds[1])

Solubility: sol several kinds of ethers; protonated in protic solvents.

Preparative Methods: iodine-lithium exchange of triphenylstannylmethyl iodide in dry ether with ***n-Butyllithium*** (98%).[1] Triphenylstannylmethyl iodide can be obtained by the reaction of ***Chlorotriphenylstannane*** with Simmons-Smith reagent (***Iodomethylzinc Iodide***) in 66% yield.[2]

Purification: recrystallization of the precursor triphenylstannylmethyl iodide from hexane (white crystalline plates, mp 86-87 °C)

Handling, Storage, and Precautions: the precursor can be stored in a desiccator. Since organotin compounds are toxic, the experiment should be performed in a good fume hood and with gloves.

Methylenation Reagent for Carbonyl Compounds.

Like ***(Trimethylstannylmethyl)lithium***, this reagent (**1**) is an effective methylenation reagent. The reagent reacts with ketones or aldehydes (**2**) to afford β-stannyl alcohols (**3**), which undergo Peterson-type elimination under acidic conditions ($HClO_4$/MeOH, 20 °C or SiO_2/THF, 20 °C, 56-68%, based on **3**)[3] or heating (110-175 °C) to produce methylene compounds (**4**). Overall yields are improved if the alcohols (**3**) are not isolated (eq 1 and Table 1).[4]

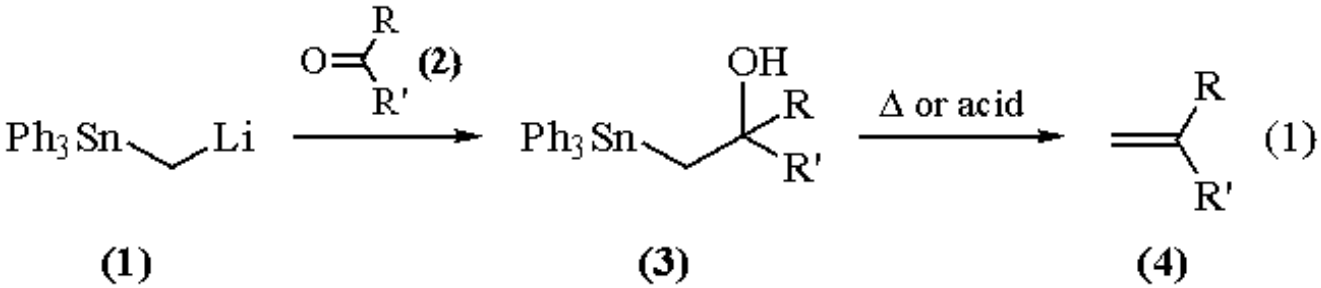

Table 1 Reaction of Reagent (**1**) with Carbonyl Compounds followed by Thermolysis

Carbonyl compound (**2**)	b-Hydroxy-stannane (**3**)	Thermo-lysis (°C)	Reaction time (min)	Alkene (**4**)	Overall yield[a] (%)
PhCHO	65	140	15	Styrene	55 (87)
		110	300		62
Ph_2CO	0				
Cyclo-	37	170	45	Methylene-	35
hexanone		132	120	cyclohexane	35 (86)
MeCOPh	41	75	45	a-Methyl-	29
		110	90	styrene	29
Butanal	31	170	60	1-Pentene	31
		132	120		31 (75)
Heptanal	26	132	180	1-Octene	18

[a] Based on carbonyl compound. Values enclosed in parentheses are overall yields without isolation of (**3**).

The analogous (tributylstannylmethyl)lithium can be generated by the same procedure (98-100%), and this reagent also methylenates esters.[5] Note that the preparation of (triphenylstannylmethyl)lithium (**1**) by iodine-lithium exchange should be performed in ether. In THF, the yield of the desired lithium reagent is decreased, producing iodomethyllithium as byproduct (eq 2).[6]

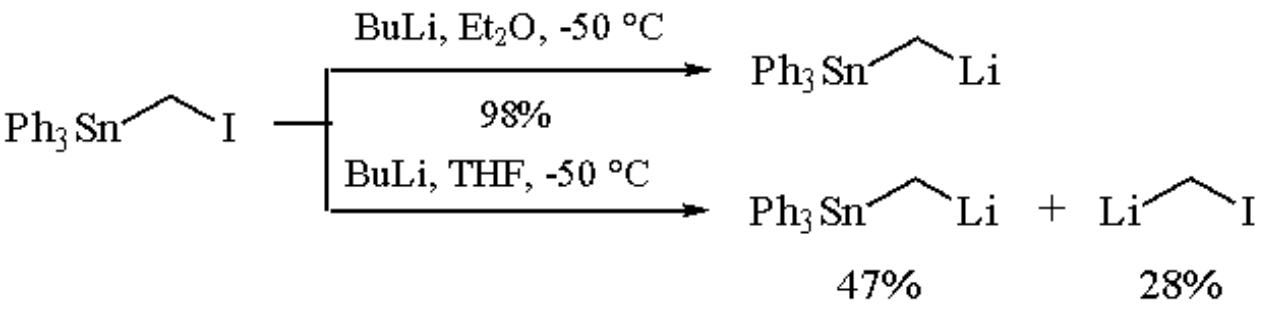

(2)

Coupling Reaction with Allyl Bromide.

Although the reagent (**1**) does not react with ***Allyl Bromide***, a copper derivative (**5**) obtained from (**1**) and ***Copper(I) Chloride*** couples with allyl bromide to afford homoallylstannane (**6**) in 57% yield.[6] This reaction is thought to proceed through the tandem oxidative addition-reductive elimination mechanism (eq 3).

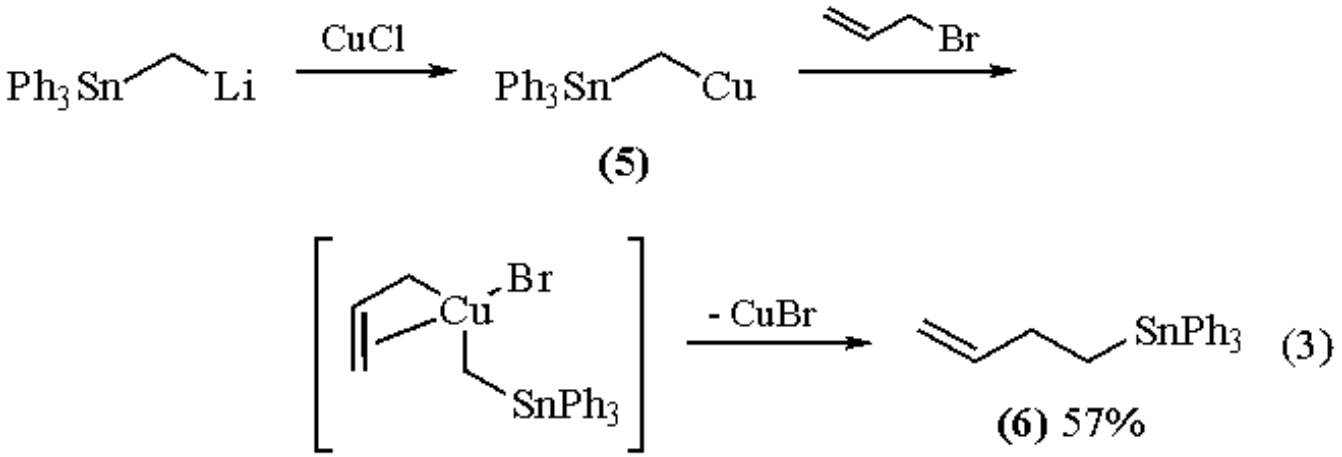

However, an unsuccessful coupling reaction of the cyanocuprate reagent (**8**), prepared from (tributylstannylmethyl)lithium and ***Copper(I) Cyanide***, with alkenyloxirane (**7**) has been reported, although the ordinary alkylcuprates react with (**7**) smoothly. The major reaction of (**8**) is the oxidative coupling of the cuprate to afford 1,2-bis(tributylstannyl)ethane (**9**) (eq 4).[7]

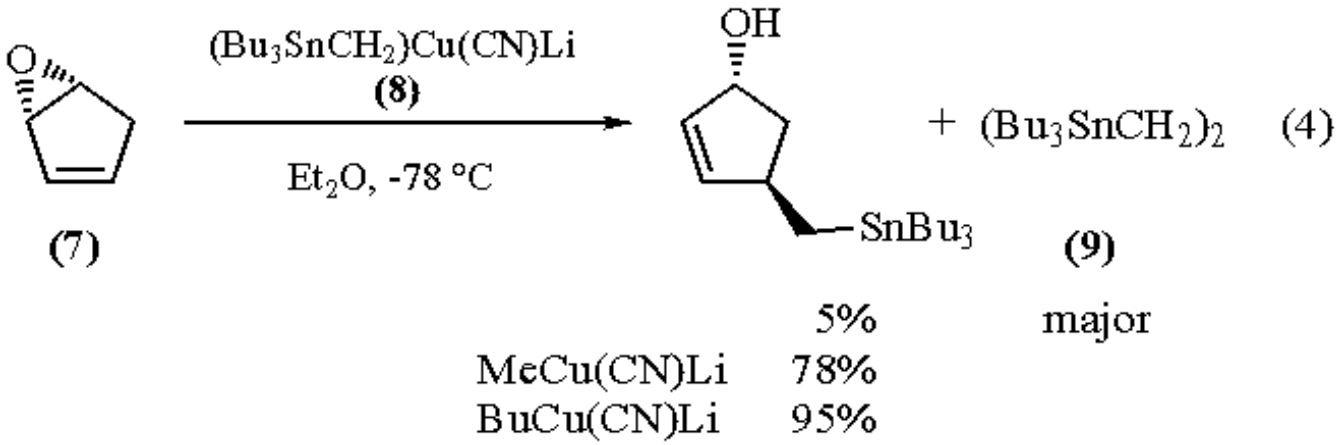

Related Reagents.

Triphenylgermylmethyllithium[8] and triphenylplumbylmethyllithium[3] have also been prepared. See also ***Trimethylsilylmethyllithium*** and ***(Diisopropoxymethylsilyl)methylmagnesium Chloride***.

---

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3-Triphenylstannyl-1-propyne

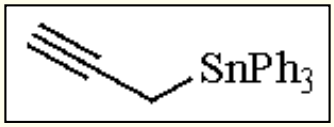

[4104-89-6] · $C_{21}H_{18}Sn$ · 3-Triphenylstannyl-1-propyne · (MW 389.10)

(addition of a propargyl or an allenyl group to aldehydes; reacts with alkyl halides to give a terminal allenyl or propargyl group; preparation of allenyl iodides and allenyl(aryl)iodinanes; isomerizes to triphenylstannylpropadiene in the presence of Lewis acids or electron donor solvents)

Alternate Name: triphenyl-2-propynylstannane; triphenylpropargylstannane.

Physical Data: mp 81-84 °C.

Solubility: typical reaction solvents include benzene and dichloromethane.

Analysis of Reagent Purity: reagent purity may be analyzed by ^{1}H NMR.[1] The most common impurity is the isomeric allene which may be detected by IR and ^{1}H NMR.

Preparative Methods: prepared from ***Propargylmagnesium Bromide*** and Ph_3SnX (X = Cl or I) in ether (70-75%).[1a,d] Also prepared by treatment of propargyl bromide with Ph_3SnLi (30%).[1b]

Handling, Storage, and Precautions: organostannane reagents are highly toxic and readily absorbed through the skin. Proper safety equipment (i.e. fume hood, gloves, protective eyewear) should be utilized at all times when handling the reagent.[2] Irradiation of 3-triphenylstannyl-1-propyne in C_6D_6 for 19 h resulted in isomerization to the allene. No isomerization was observed after heating in the dark at 70 °C for 7 h.[3] Deliberate isomerization to the allene has also been accomplished by heating the propargylstannane in electron donor solvents or in the presence of Lewis acids.[6]

Addition to Aldehydes.

The addition of 3-triphenylstannyl-1-propyne to aldehydes has been reported to give mixtures of allenyl and propargyl products.[4] Exclusive formation of the homopropargyl alcohol (β-acetylenic alcohol) may be obtained in an enantioselective manner by using the chiral bromoborane prepared from 1,2-diphenyl-1,2-diaminoethane (stilbenediamine).[5] Treatment of triphenylpropargylstannane with the chiral bromoborane gave the allenylborane, which reacted with a variety of aldehydes to form homopropargyl alcohols with excellent enantioselectivity (eq 1).

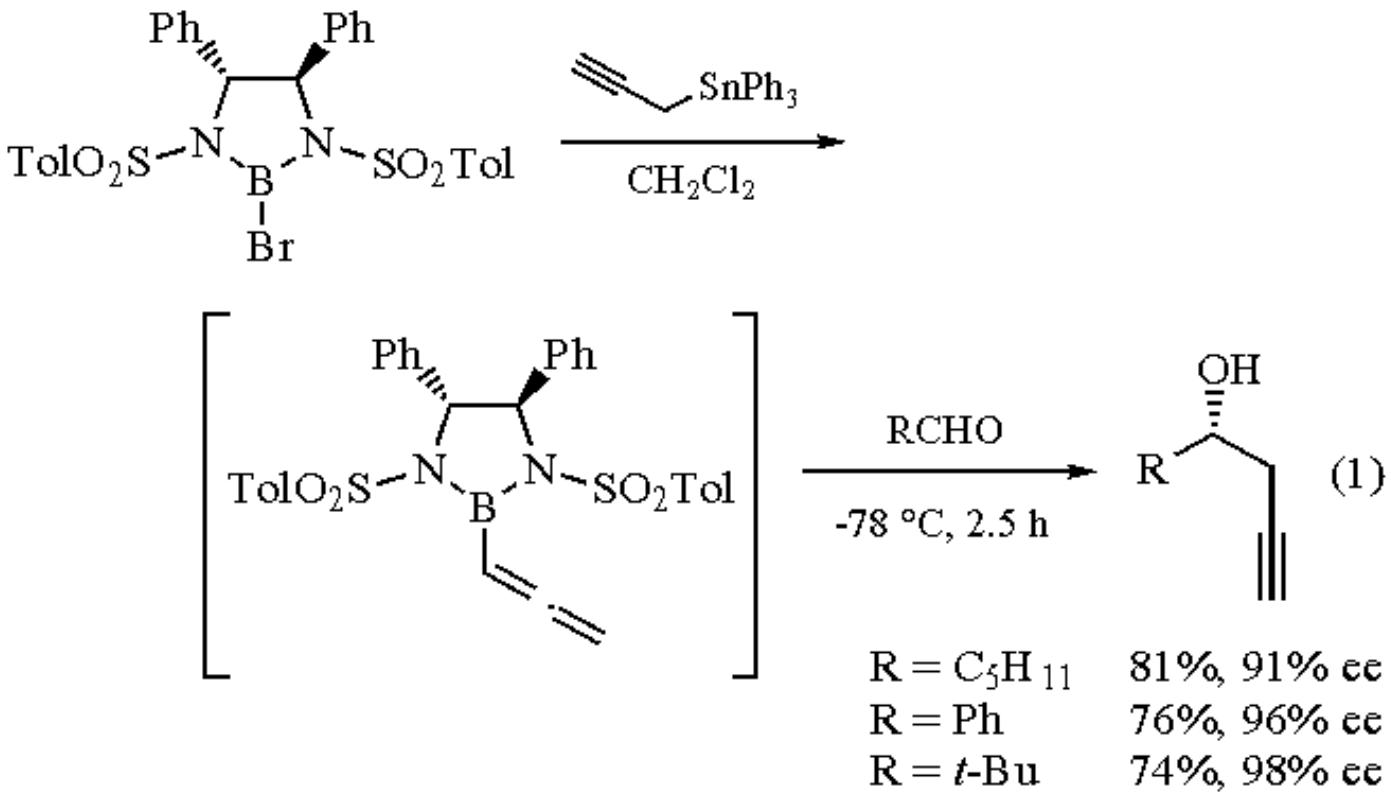

Exclusive formation of α-hydroxy allenes (α-allenic alcohols) was accomplished by using an allenylstannane, tributylstannylpropadiene, which was prepared by isomerization of the corresponding propargylstannane.[5] Isomerization of 3-triphenylstannyl-1-propyne to its allenyl derivative, triphenylstannylpropadiene, is also readily accomplished in the presence of Lewis acids or electron donor solvents.[6]

See also ***3-Iodo-1-trimethylsilylpropyne*** for the preparation of trimethylsilyl substituted α-allenic and β-acetylenic alcohols.

Reaction with Alkyl Halides.

Baldwin et al. report the formation of terminal allenes from the reaction of 3-triphenylstannyl-1-propyne with alkyl bromides and iodides in the presence of ***Azobisisobutyronitrile*** in refluxing benzene (eq 2).[7] In a related study, Hamon et al. report the formation of terminal alkynes with high diastereoselectivity from the reaction of the propargylstannane with the 8-phenylmethyl ester of *N*-Boc-2-bromoglycine (eq 3).[8] Both reactions are believed to involve radical intermediates; however, nucleophilic addition of the propargylstannane to an intermediate iminium species has also been proposed for the latter reaction (eq 3).

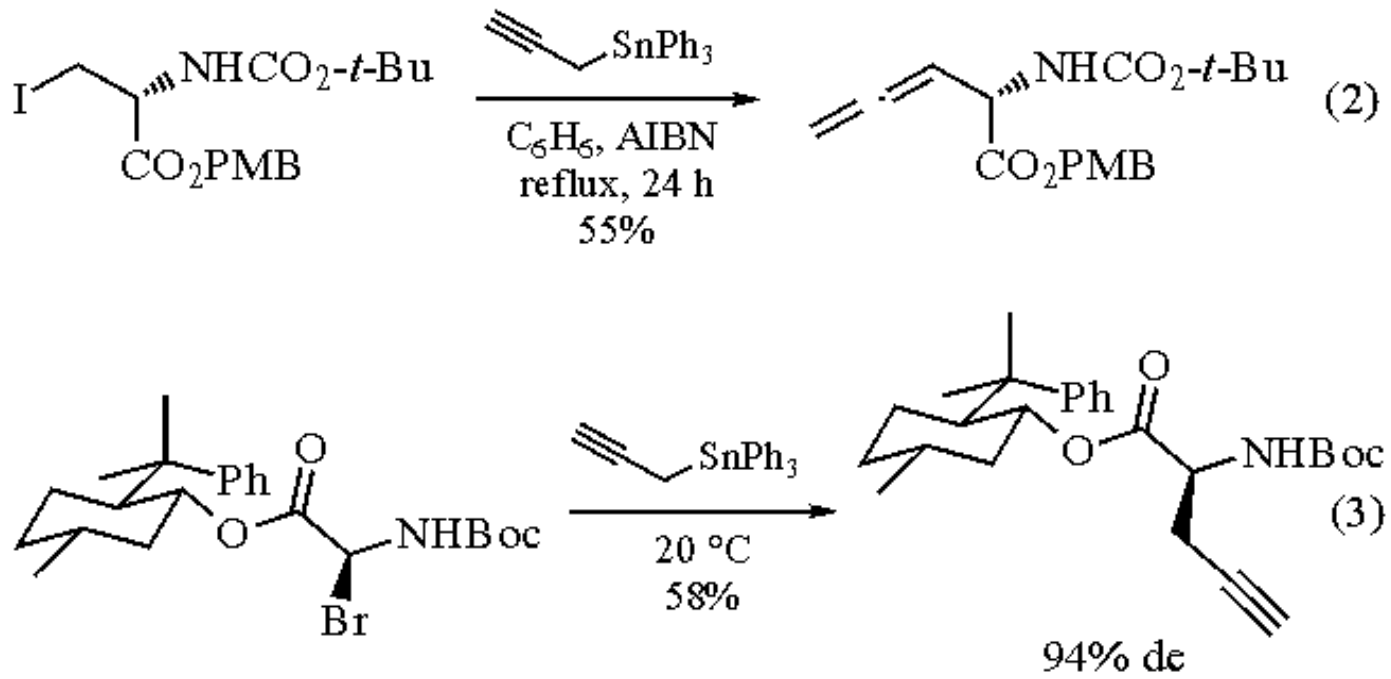

Preparation of Allenyl Iodides and Allenyl(aryl)iodinanes.

Allenyl iodides have been prepared by ***Iodine*** treatment of 3-triphenylstannyl-1-propyne (eq 4).[9] Other carbon-tin bond cleavage reactions using ***Thiocyanogen*** $(SCN)_2$ and ***Sulfur Dioxide*** are also known, giving the allenyl sulfide and the sulfur dioxide insertion product, respectively.[10,11]

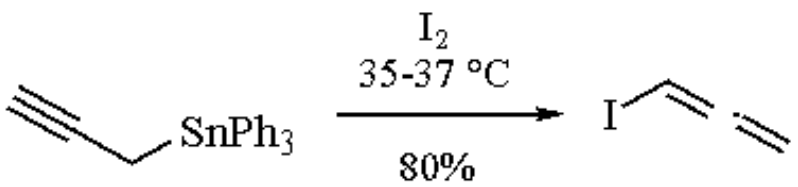

(4)

Hypervalent allenyl(aryl)iodinanes have been prepared by reaction of the propargylstannane with aryliodinanes (eq 5).[12] The product then undergoes a reductive iodonio-Claisen rearrangement to yield *o*-propargyliodoarenes.

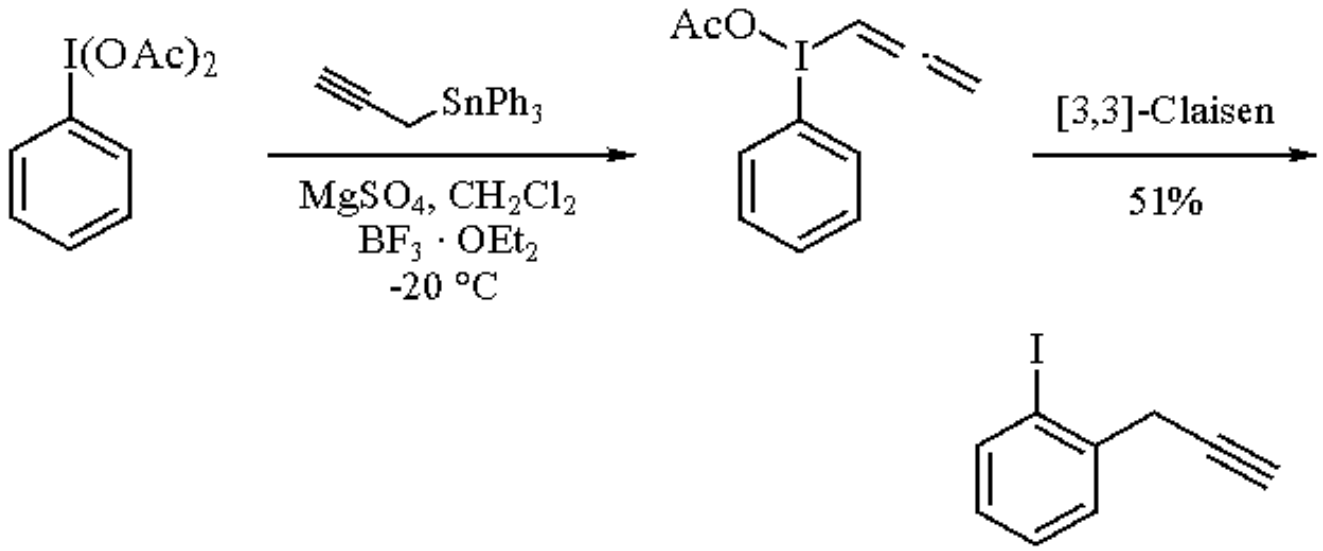

(5)

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Triphenyl Thioborate

$(PhS)_3B$

[1041-16-3] · $C_{18}H_{15}BS_3$ · Triphenyl Thioborate · (MW 338.35)

(conversion of esters and α,β-unsaturated esters into phenylthio esters,[1] and for formation of 1,3-bis(phenylthio)alkenes from aldehydes and ketones[2])

Alternate Names: phenyl thioborate; tris(phenylthio)borane.

Physical Data: pale yellow solid; mp 140-143 °C;[3] bp 196 °C/0.1 mmHg.[3]

Solubility: sol benzene, ether, acetone.[4]

Preparative Methods: can be made from ***Boron Triiodide*** and ***Diphenyl Disulfide***;[5] from ***Thiophenol*** and ***Boron Trichloride***;[6] from (phenylthio)borane trimer and thiophenol;[7] or from ***Boron Trisulfide*** and thiophenol.[2,8]

Purification: recrystallize from benzene[7] or distill in vacuo.[3]

Handling, Storage, and Precautions: sensitive to moisture and should be stored in a desiccator. Can be weighed out quickly in air, if humidity is low, but best handled in a dry box.[2]

Conversion of Esters and α,β-Unsaturated Esters into Phenylthio Esters.[1]

Esters are converted into phenylthio esters by heating with phenyl thioborate in refluxing xylene (140 °C) (eq 1), but the same transformation can be done at room temperature with phenyl thioaluminate. With the aluminum reagent, α,β-unsaturated esters give products contaminated with the β-(phenylthio) ester, but the boron reagent does not suffer from this disadvantage (eq 2).

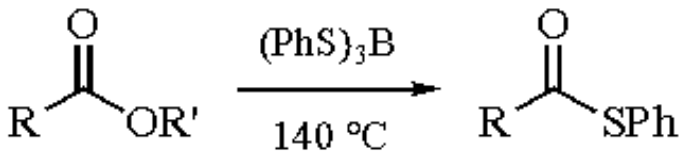

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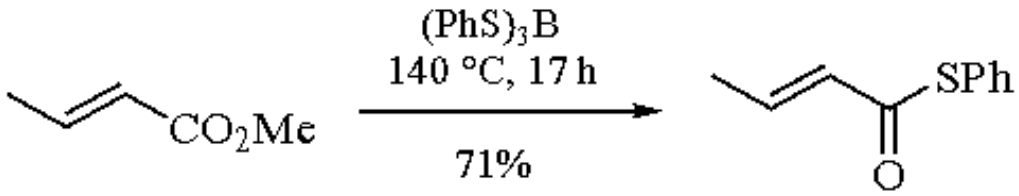

(2)

Formation of 1,3-Bis(phenylthio)alkenes from Aldehydes and Ketones.[2]

α,β-Unsaturated aldehydes and ketones form 1,3-bis(phenylthio)alkenes on treatment with phenyl thioborate (eq 3). The (phenylthio)alkenes are β-acyl vinyl anion equivalents (eq 4).

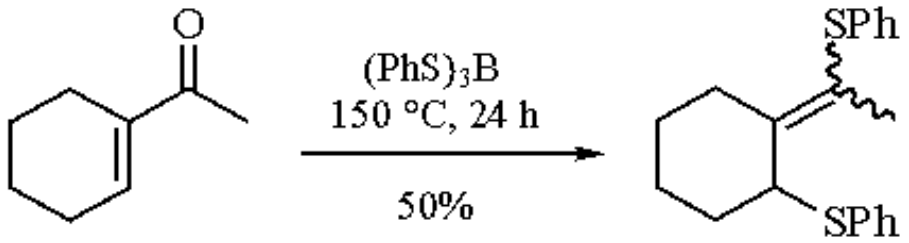

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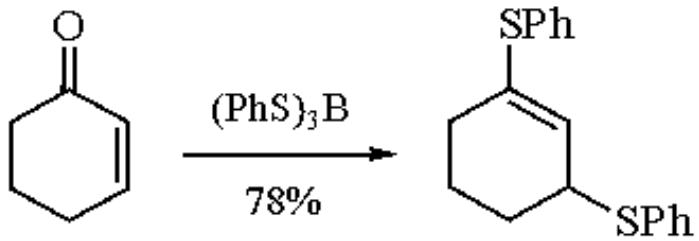

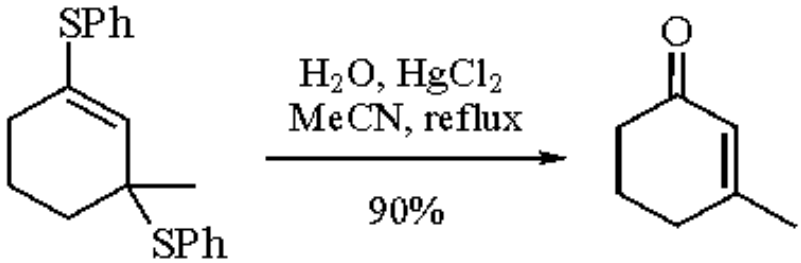

(4)

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Triphenylstannane[1]

Ph_3SnH

[892-20-6] · $C_{18}H_{16}Sn$ · Triphenylstannane · (MW 351.05)

(generation of carbon radicals from selenides,[2] halides,[3] sulfides,[4] and alkynes;[5] radical deoxygenation;[6] reduction of α,β-unsaturated aldehydes and ketones;[7] hydrostannylation of alkynes[5,8] and alkenes;[9] reversible addition of stannyl radicals to double bonds;[10] formation of metal triphenylstannates;[11] reduction of aldehydes and ketones;[12] desulfonation of β-keto phenyl sulfones;[13] hole-transfer-promoted hydrogenation[14])

Alternate Names: triphenyltin hydride; triphenylstannyl hydride.

Physical Data: white needles, mp 26-28 °C;[15,16] bp 156-158 °C/0.15 mmHg;[15] d^{25} 1.3771 g cm^{-3}.[17]

Solubility: sol many common organic solvents; usually used in benzene or toluene.

Form Supplied in: commercially available as a colorless liquid that solidifies in a refrigerator.

Analysis of Reagent Purity: titration of the derived triphenyltin chloride has been used.[18,19] Reactions of Ph_3SnH can be followed by monitoring the 1840 cm^{-1} IR absorption.[1h]

Preparative Methods: reduction of ***Chlorotriphenylstannane*** with ***Lithium Aluminum Hydride*** in ether,[12,16,20] or with ***Sodium Borohydride*** in glyme;[15] reduction of bis(triphenyltin) oxide with polymethylhydrosiloxane;[21] reduction of triphenyltin methoxide with diborane;[22] protonation of Ph_3SnLi.[17,23] The reagent has also been generated in situ from Ph_3SnCl and ***Sodium Cyanoborohydride*** in *t*-butyl alcohol.[24]

Handling, Storage, and Precautions: Ph_3SnH can be stored for several months, and is easily repurified by Kugelrohr distillation (oil-pump vacuum) before use.[25] Organotin hydrides decompose slowly at rt and are best stored at 0 °C or below.

Decomposition is catalyzed by air, silicone grease, metallic surfaces, amines and, in the case of triphenyltin hydride, by light.[1h,15,16] Manipulations of the compound are usually best done in an inert atmosphere and using thoroughly clean apparatus (KOH-MeOH is better than chromic acid for cleaning in this case[26]). Methods have been reported for removing tin species from reactions involving stannanes, but these appear to have been described explicitly only for ***Tri-n-butylstannane***.[6,27-30] Provided that skin contact and inhalation are avoided, Ph_3SnH does not present an unusual hazard.[15]

General.

Many processes with Ph_3SnH can be done also with Bu_3SnH, and vice versa; however, direct comparison of the two reagents has rarely been reported.

Formation of Carbon Radicals from Phenyl Selenides.

Many phenyl selenides have been converted into carbon radicals that have then undergone intramolecular cyclization (eq 1),[31] radical ring opening (eq 2),[32] or reduction (eq 3).[2] Tellurides (eq 4) and telluride dichlorides are also reduced to the corresponding hydrocarbon.[2,33]

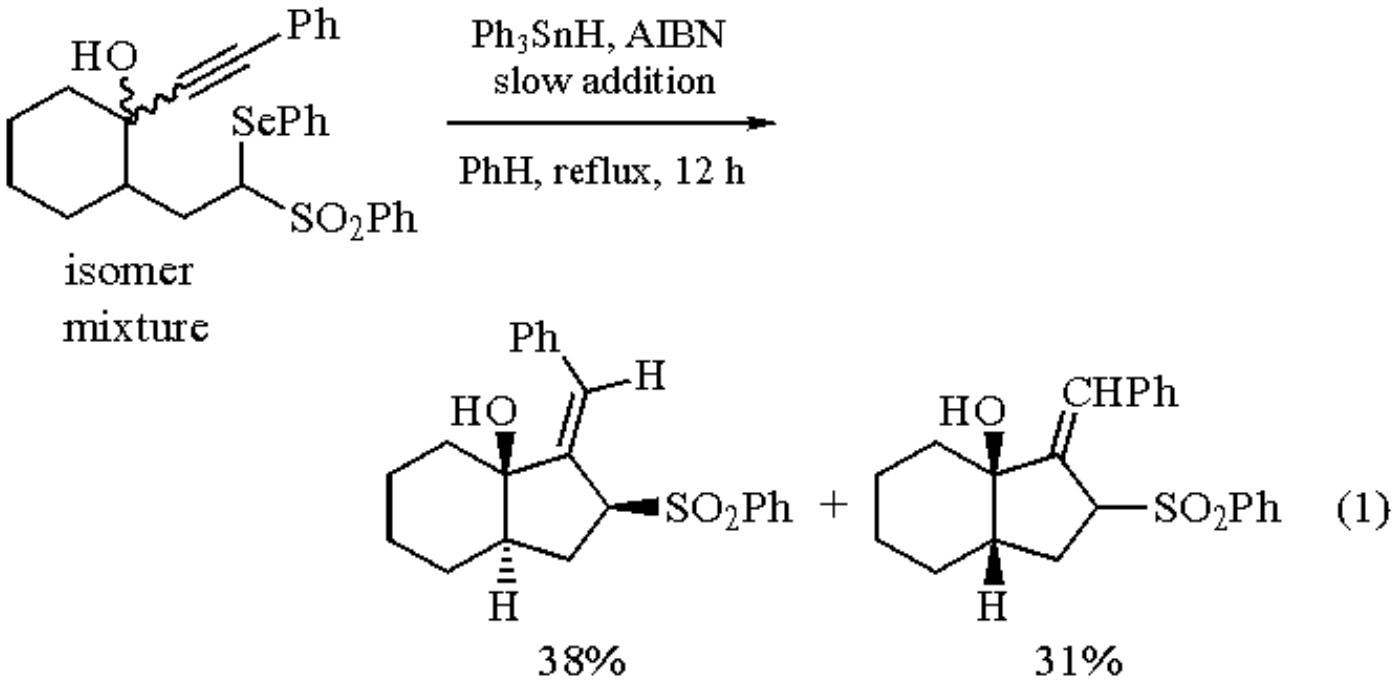

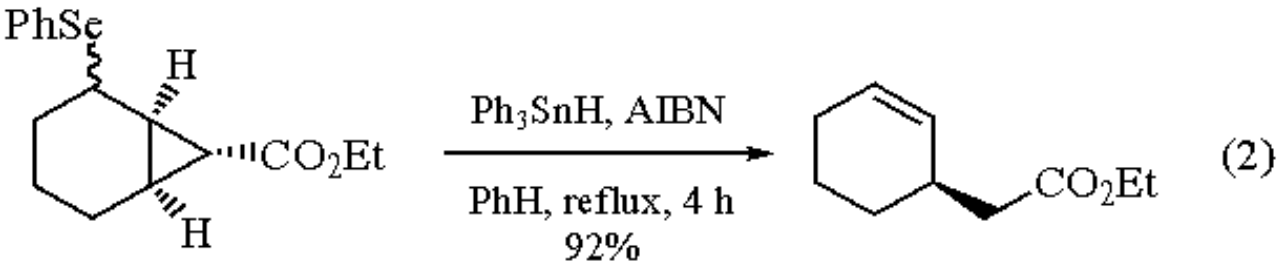

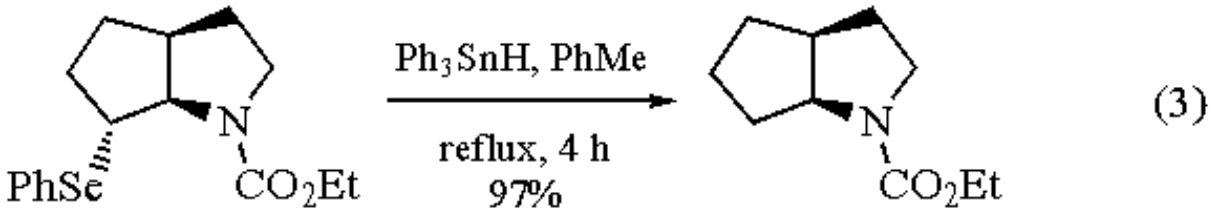

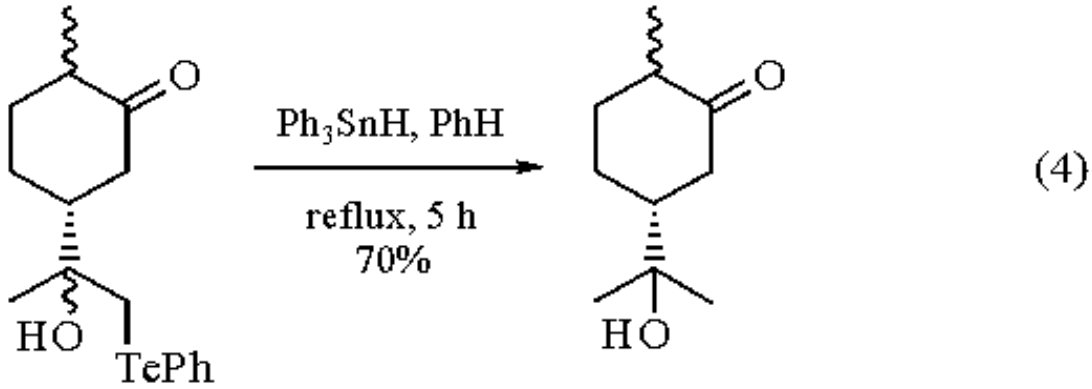

Radical Deoxygenation.

Ph_3SnH has occasionally been used for Barton deoxygenation.[6,34] In the example of eq 5, better results are obtained with Bu_3SnH than with Ph_3SnH.[6] Alcohols and carbonyl compounds (ketones or aldehydes) have been deoxygenated by conversion into the corresponding phenyl selenides or selenoacetals, respectively, followed by treatment with Ph_3SnH (eq 6).[2]

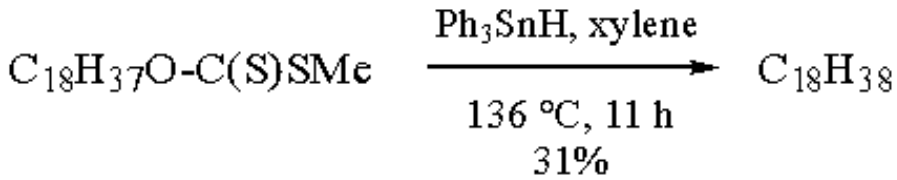

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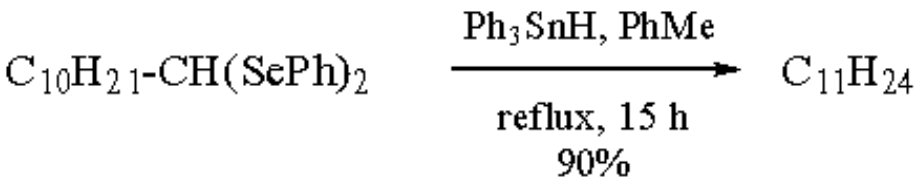

(6)

Formation of Carbon Radicals from Halides.

The triphenylstannyl radical, generated thermally[3,35-37] or electrochemically,[38] can be used for dehalogenation, the radical intermediate being captured by hydrogen transfer (eqs 7-9)[9,35,36] or by an intramolecular process (eqs 10-13).[38-41] In the last example (eq 13), Ph_3SnH gave better results than Bu_3SnH.[41]

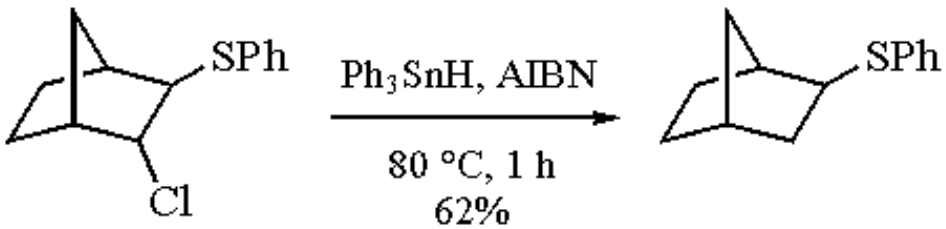

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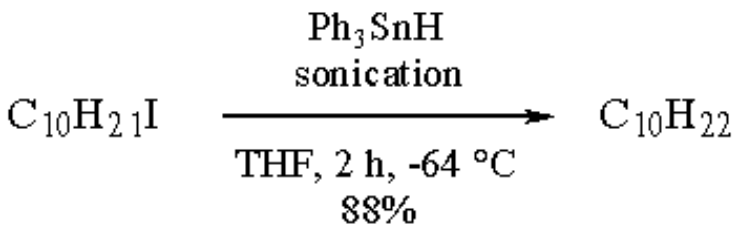

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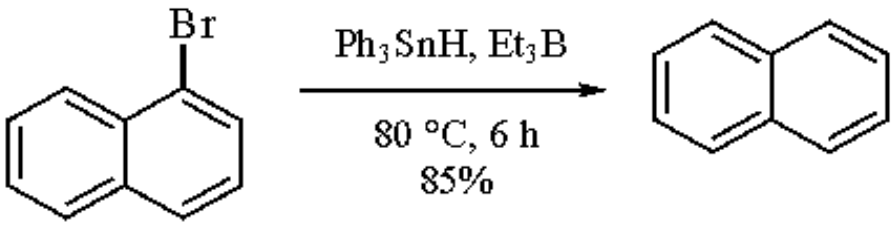

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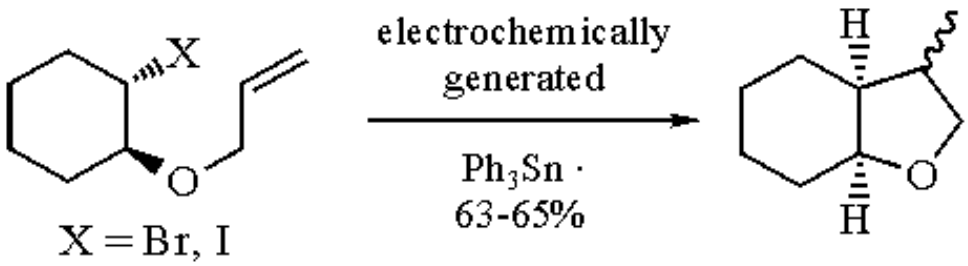

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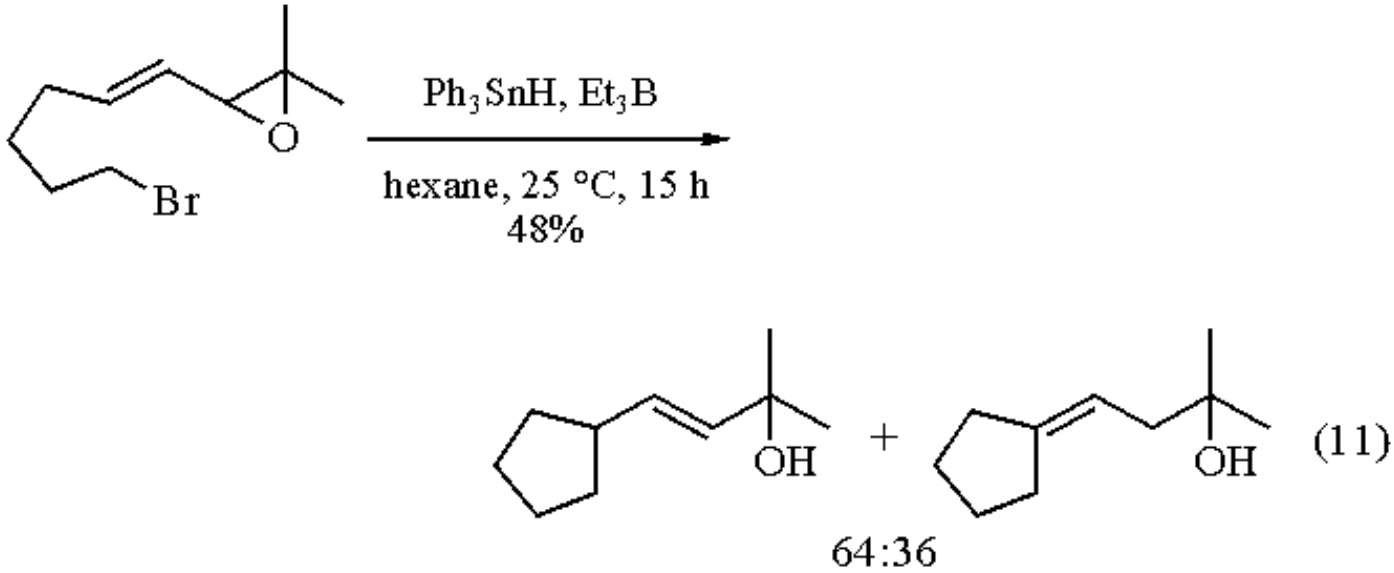

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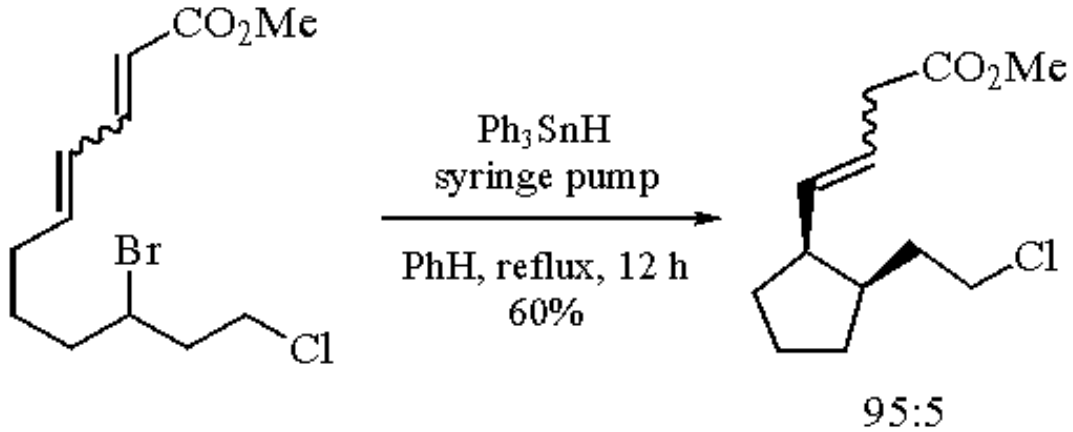

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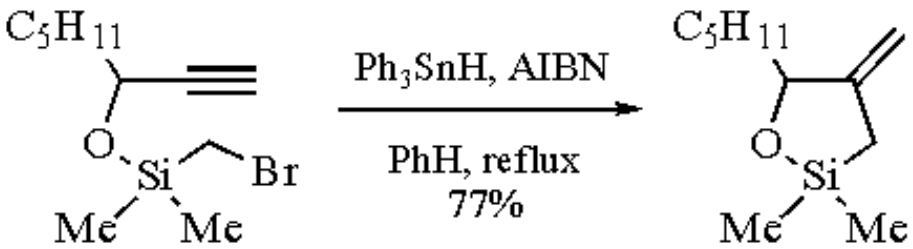

(13)

Desulfurization and Disulfide Cleavage.

Ph_3SnH has occasionally been used for desulfurization,[4,42] the process being facilitated in the example shown in eq 14 by the presence of an α-heteroatom.[4] Disulfides can also be cleaved (initially to thiyl radicals).[38,43]

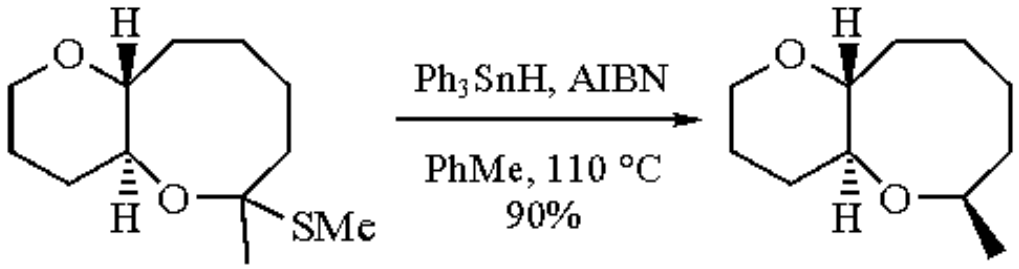

(14)

Cyclization of Acetylenic Alkenes.[5,24,44]

Acetylenic alkenes undergo cyclization on treatment with Ph_3SnH under radical conditions (eqs 15 and 16).[5,24] In the example of eq 15, and in related processes, lower yields were obtained with Bu_3SnH.[24]

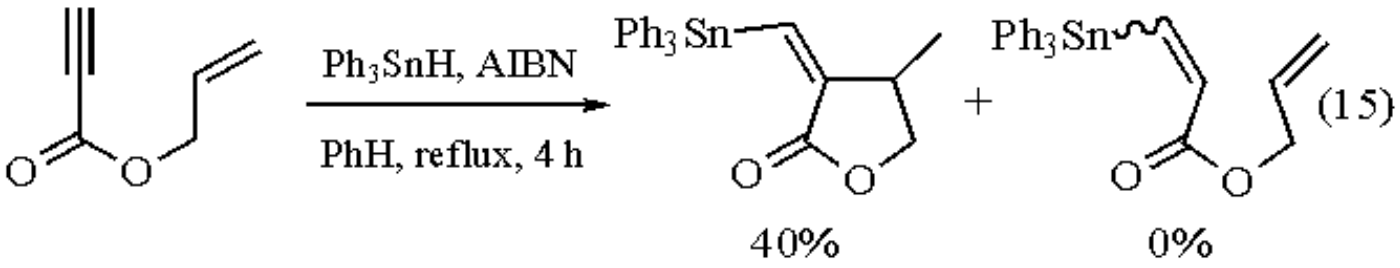

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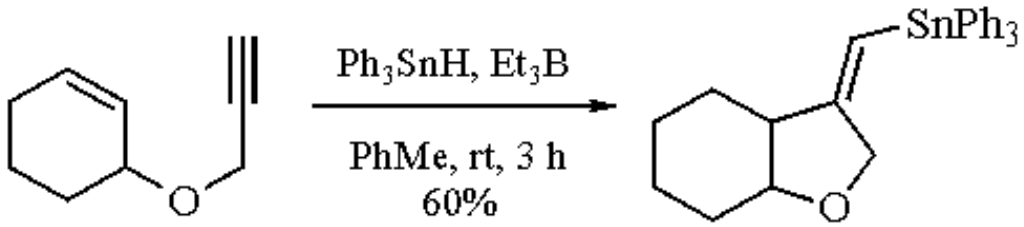

(16)

Reduction of α,β-Unsaturated Aldehydes and Ketones.[7,45 -52]

Double and (apparently) triple bonds conjugated with the carbonyl group in α,β-unsaturated aldehydes and ketones are reduced by Ph_3SnH in a radical process (eqs 17 and 18).[7]

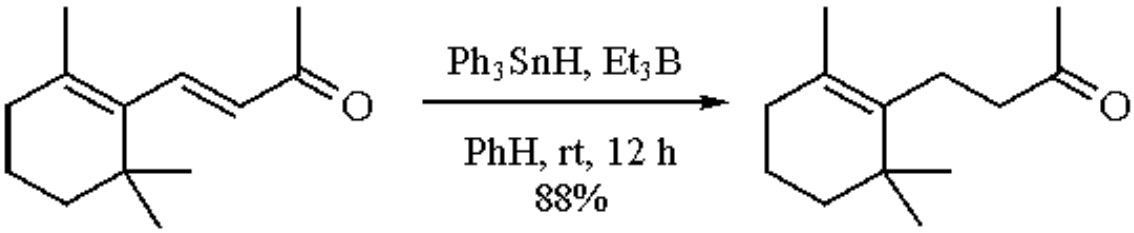

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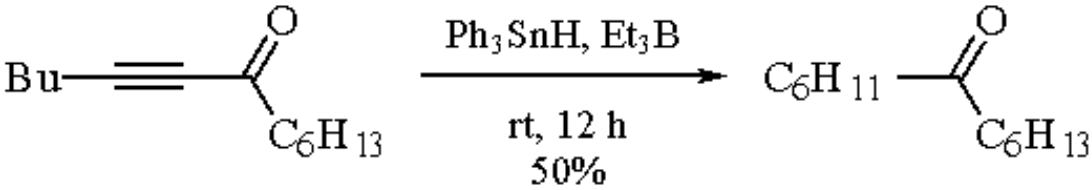

(18)

Hydrostannylation of Alkynes and Alkenes.

Allenes (eq 19)[53,54] and alkynes (eqs 20 and 21)[8,55] are hydrostannylated in the presence of a palladium catalyst. Use of Ph_3SnH rather than Bu_3SnH gives a higher proportion of the (*Z*)-isomer in (eq 19).[54]

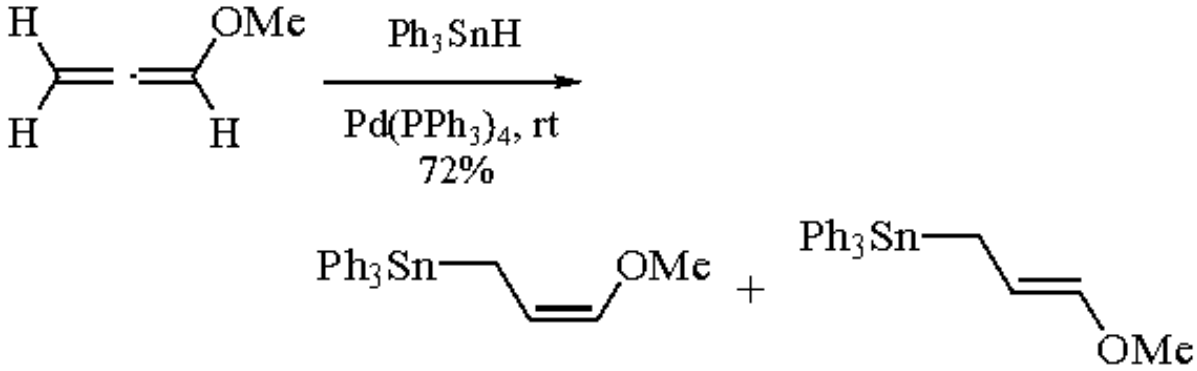

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(Z):*(E)* = 91:9

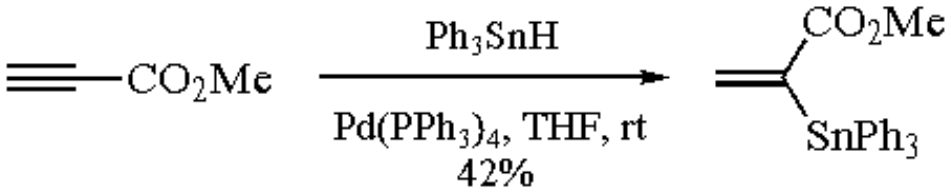

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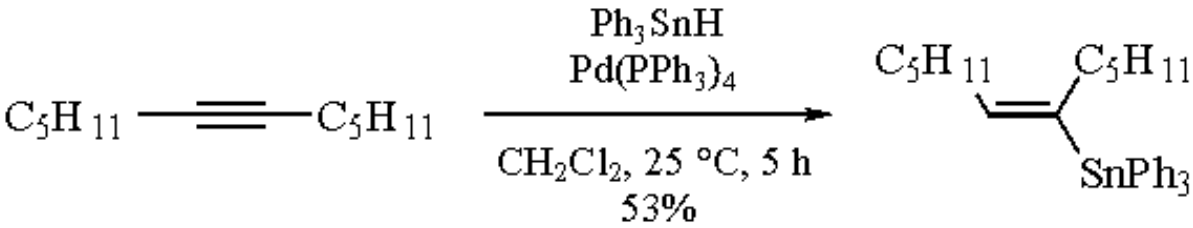

(21)

Alkynes[5,56-58] (eq 22)[5] and alkenes[9,59,60] (eqs 23 and 24)[9,59] are also hydrostannylated under radical conditions.

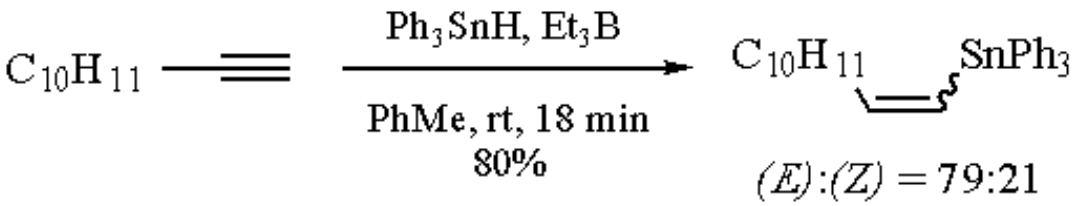

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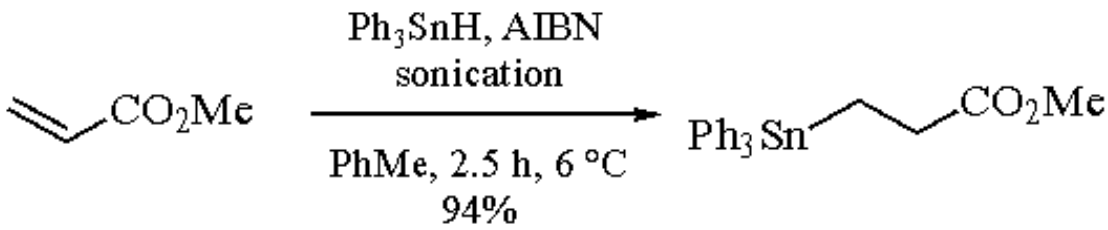

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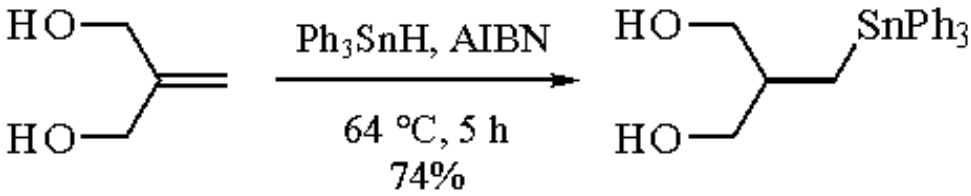

(24)

In contrast to α,β-unsaturated aldehydes and ketones (which are usually[46] reduced to the saturated carbonyl compounds), α,β-unsaturated esters[61] are generally[62,63] hydrostannylated[7,57,63-65] under mild radical conditions (eq 25). In the example of eq 25, Bu_3SnH reacted sluggishly and the process was incomplete.[7] The hydrostannylation can be highly stereoselective (eq 26).[66]

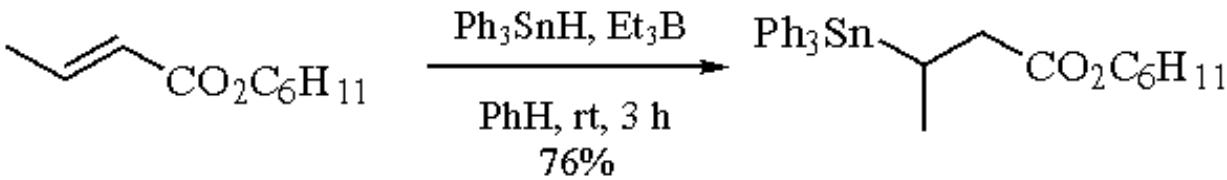

(25)

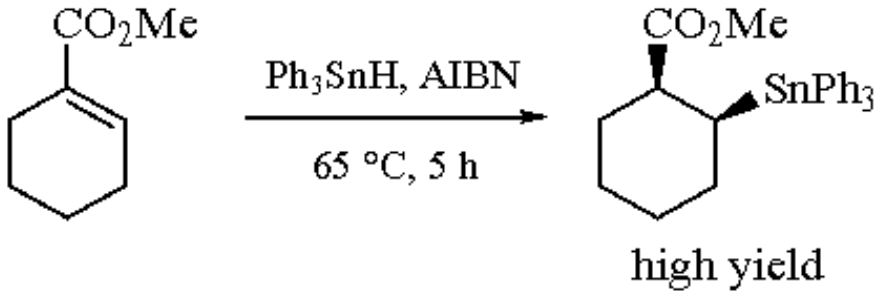

(26)

Reversible Addition of Triphenylstannyl Radicals to Double Bonds.

The process summarized in eq 27 was slightly more stereoselective with Ph_3SnH than with Bu_3SnH, but the proportion of the enone was higher.[10] Ring expansion of the type shown in eq 28 sometimes proceeded more efficiently with Ph_3SnH than with Bu_3SnH.[67]

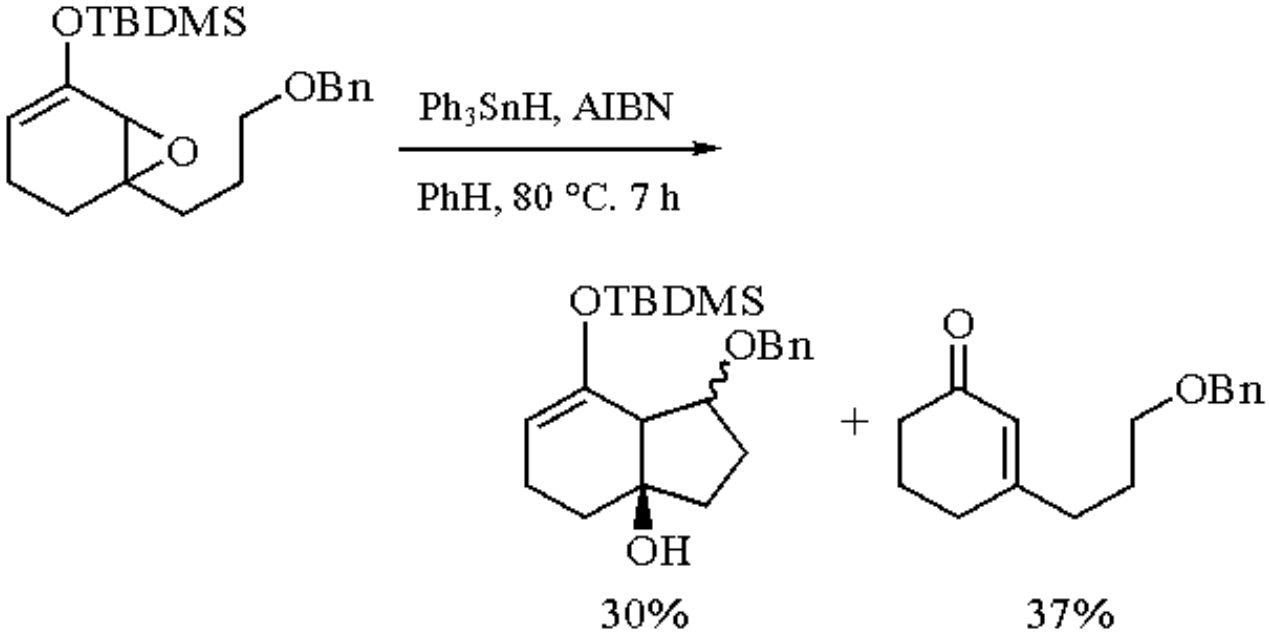

(27)

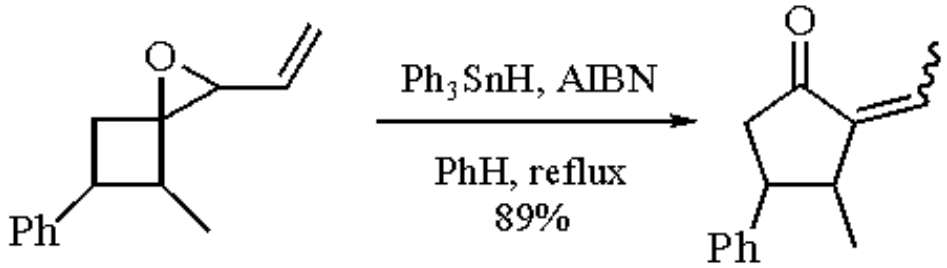

(28)

Preparation of Metal Triphenylstannates.

Ph_3SnK is easily prepared from Ph_3SnH and ***Potassium Hydride***,[68] Ph_3SnNa from the stannane and ***Sodium Hydride***,[69] Ph_3SnLi from the stannane and ***Lithium Diisopropylamide***,[11] and $(Ph_3Sn)_2Zn.TMEDA$ from the stannane and ***Diethylzinc*** in the presence of ***N,N,N´,N´-Tetramethylethylenediamine***.[70]

Reduction of Ketones and Aldehydes to Alcohols.[12,71-74]

Reduction of ketones and aldehydes with Ph_3SnH has been reported (eq 29).[12,71,72]

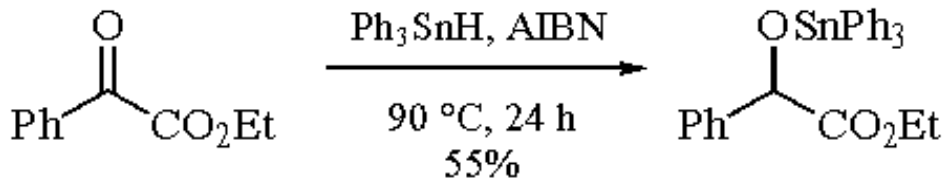

(29)

When a ketone is treated with an acid chloride in the presence of Ph_3SnH, reductive acylation of the ketone occurs (eq 30).[75]

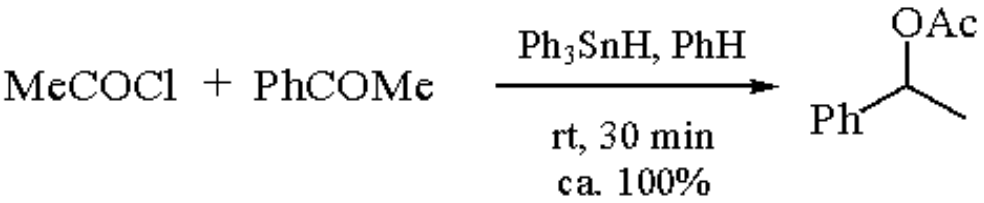

(30)

Desulfonylation of β-Keto Phenyl Sulfones.[13]

Although Bu_3SnH is usually used for desulfonylation of β-keto phenyl sulfones, Ph_3SnH gave a better yield in the case shown in eq 31.

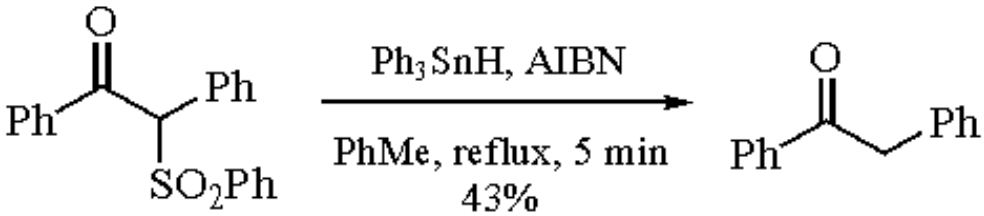

(31)

Hole-Transfer-Promoted Hydrogenation.

Ph_3SnH can be used as a source of hydrogen to saturate double bonds in a process mediated by triarylamminium ions (eq 32).[14]

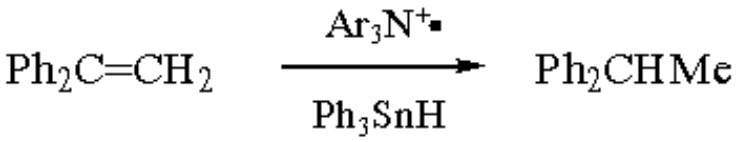

(32)

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Tripotassium Nonachloroditungstate(III)

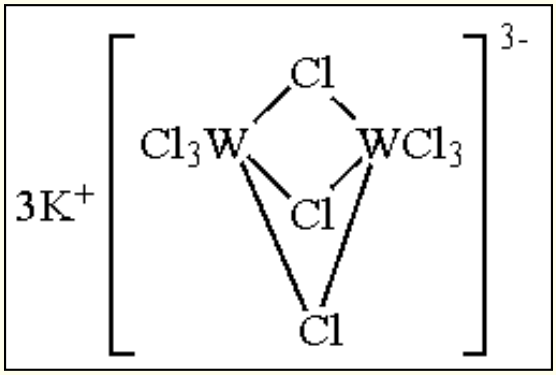

[23403-17-0] · $Cl_9K_3W_2$ · Tripotassium Nonachloroditungstate(III) · (MW 804.05)

(reduces sulfoxides to sulfides[1])

Alternate Name: potassium tri-μ-chlorohexachloroditungstate(III).

Solubility: sol methanol, water, aqueous HCl.

Form Supplied in: green crystals; not commercially available.

Preparative Methods: prepared in a three-step procedure from tungsten trioxide trihydrate.[2] First, tungsten trioxide trihydrate is treated with aqueous potassium carbonate, followed by hydrogen chloride gas, followed by reduction with tin metal.

Purification: recrystallized from aqueous HCl.

Reduction of Sulfoxides to Sulfides.

Sulfoxides are reduced to sulfides by treatment with the title reagent in refluxing methanol (eq 1).[1] The reaction is very specific for the reduction of sulfoxides and not sulfones or sulfimines. Other functional groups not reduced by this reagent include organic halides, phosphine oxides, epoxides, ketones, esters, nitriles, and aromatic nitro compounds. In one report, a vinylic sulfoxide amino acid was efficiently reduced (eq 2).[3] The major disadvantage of this reagent is that it is not commercially available. For a listing of other methods to effect this transformation, see Madesclaire.[4]

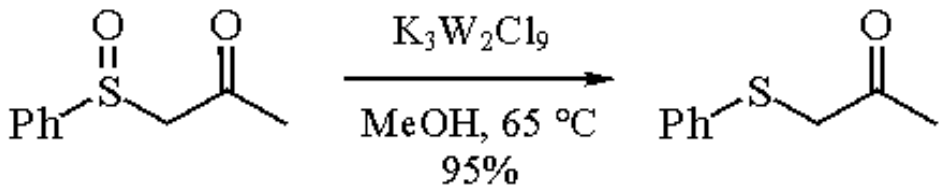

(1)

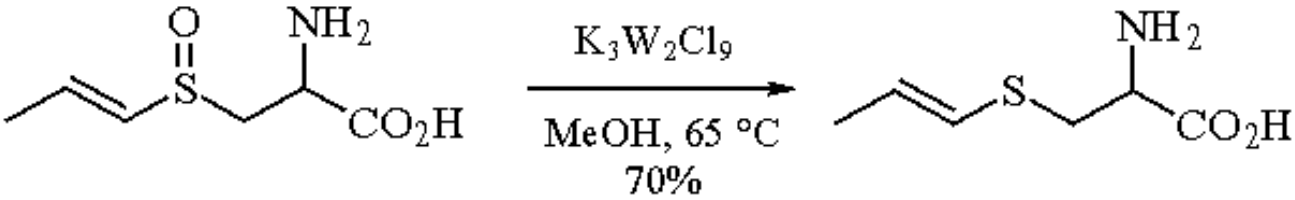

(2)

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Tripropylamine

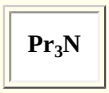

[102-69-2] · $C_9H_{21}N$ · Tripropylamine · (MW 143.31)

(in combination with trichlorosilane, for silylations, reductive silylations, and reductions;[1] used as base in preparation of activated esters with 2-chloro-*N*-methylpyridinium iodide;[2] used as base in preparation of β-lactams from activated esters and imines[3])

Physical Data: mp -93.5 °C; bp 155-158 °C; *d* 0.753 g cm^{-3}.

Solubility: sol alcohol, ether.

Form Supplied in: liquid, widely available.

Handling, Storage, and Precautions: handle with care; wear gloves and avoid breathing vapors. Use in a fume hood.

Reductive Silylations; Reductions.

Tripropylamine in combination with ***Trichlorosilane*** is an excellent reagent for reductive silylations and reductions in organic synthesis.[1] Benzylic halides are readily converted into benzylic silanes (eq 1),[4] while aromatic ketones,[5] aldehydes,[5] acid chlorides,[6] and aromatic acids[7] undergo reductive silylations with the tripropylamine-trichlorosilane combination. Aromatic ketones and aromatic aldehydes are converted to benzylic silanes which upon base hydrolysis are converted to the fully reduced compounds (eq 2).[1] The reductive silylation and hydrolysis sequence can be carried out in one pot without isolation of the intermediate benzylsilane. Aromatic carboxylic acid groups are efficiently converted into methyl groups using the reductive silylation-hydrolysis protocol.[8] The tripropylamine-trichlorosilane combination is used to reduce an aromatic carboxylic acid group selectively in the presence of an ester group (eq 3).[9] The initially formed benzylic silane esters can be isolated if desired.

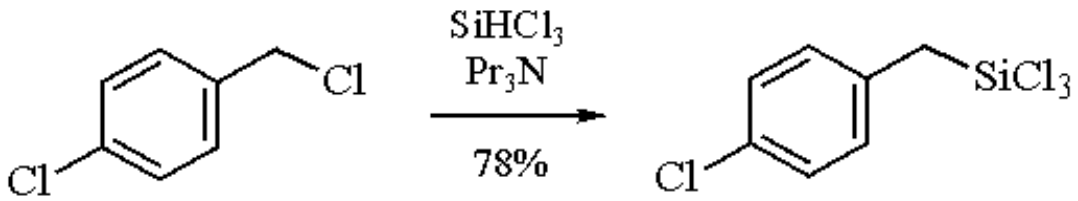

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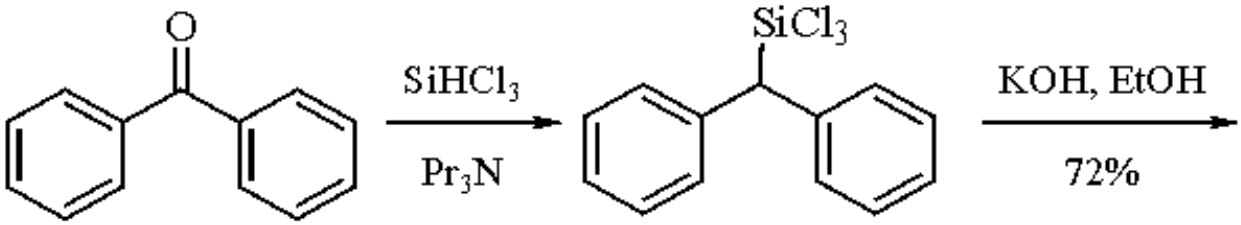

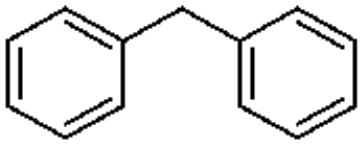

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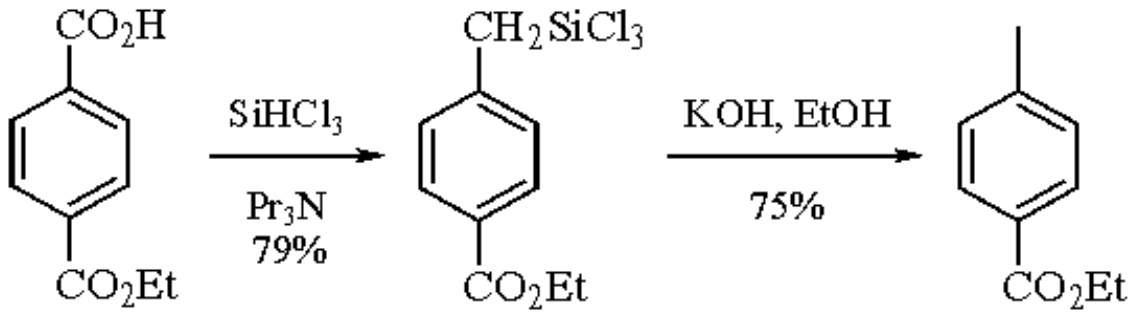

(3)

Activated Esters.

The reaction of a carboxylic acid with Mukaiyama's reagent ***2-Chloro-1-methylpyridinium Iodide*** and a tertiary amine is a convenient method for preparing activated esters. In Mukaiyama's original work,[10] ***Triethylamine***, ***Tri-n-butylamine***, and ***2,6-Lutidine*** were shown to give good results; tripropylamine was not examined. Tripropylamine has now been used with Mukaiyama's reagent and acrylic acid to efficiently prepare sulfonamidoisobornyl acrylates, nonracemic chiral intermediates for asymmetric Diels-Alder reactions (eq 4).[2] The reaction of activated esters and imines provides an important stereoselective synthesis of β-lactams via the Staudinger reaction. The use of Mukaiyama's reagent with tripropylamine (3 equiv) gives higher yields and greater stereoselectivity when compared with triethylamine or tributylamine (eq 5).[3]

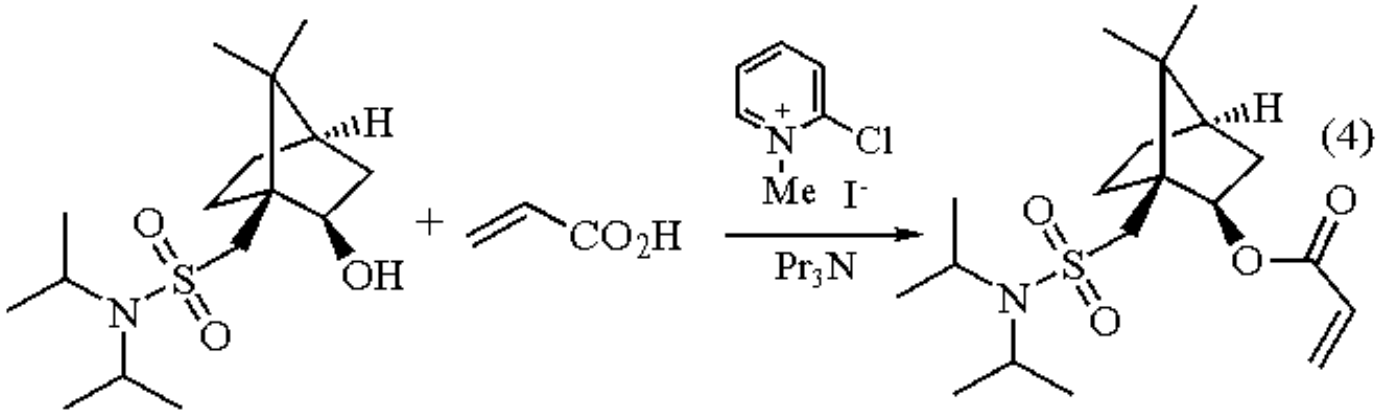

(4)

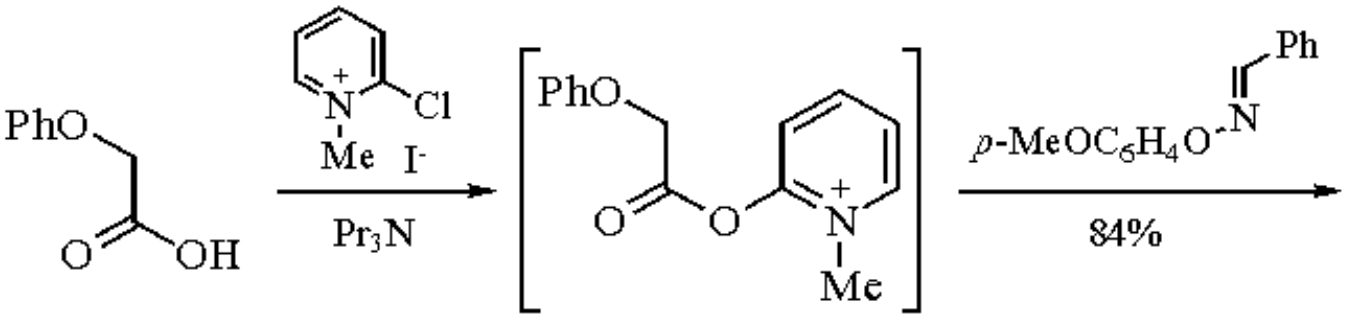

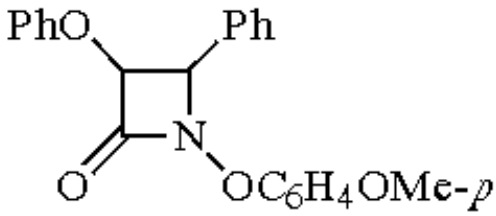

(5)

cis:*trans* = 15:1

Heterocyclic Synthesis.

The reaction of quinazoline-2,4-dione or 2,4-dichloroquinazoline with a mixture of ***Phosphorus Oxychloride***, tripropylamine, and a cyclic tertiary amine (*N*-methylpiperidine, for example) gives an excellent yield of the 4-chloro-2-substituted quinazoline.[11] The yield was

substantially reduced without the use of tripropylamine. Interestingly, the regiochemistry is opposite to that observed for the reaction of 2,4-dichloroquinazoline with primary and secondary amines, where a 4-substituted-2-chloroquinazoline is obtained.

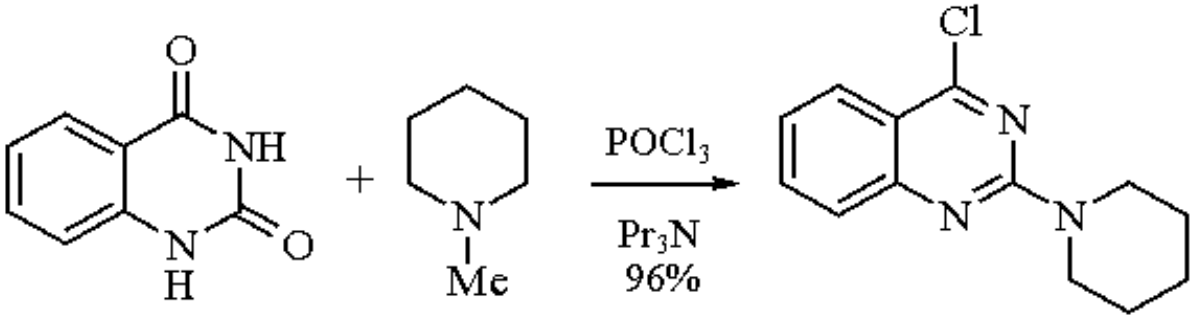

(6)

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Tris(acetonitrile)tricarbonylchromium

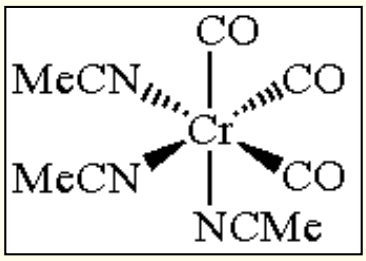

[16800-46-7] · $C_9H_9CrN_3O_3$ · Tris(acetonitrile)tricarbonylchromium · (MW 259.21)

(preparation of arene-chromium complexes[1])

Physical Data: mp 135 °C (dec).

Solubility: sol THF, acetonitrile.

Form Supplied in: not commercially available.

Preparative Methods: by refluxing ***Hexacarbonylchromium*** in ***Acetonitrile*** in an inert atmosphere. Removal of solvent under an inert atmosphere yields tris(acetonitrile)tricarbonylchromium.[2]

Purification: the crude solid obtained in the above preparation is typically used without further purification.

Handling, Storage, and Precautions: air and thermally sensitive; pyrophoric. Use in a fume hood.

Preparation of Arene-Chromium Complexes.

Treatment of aromatic compounds with tris(acetonitrile)tricarbonylchromium in THF at 65 °C leads to the corresponding (arene)tricarbonylchromium complexes (eq 1),[1] which are very useful reagents for the arylation of nucleophiles.[3] Arene-chromium complexes can be produced at lower temperatures using tris(acetonitrile)tricarbonylchromium than in the conventional procedure using hexacarbonylchromium.[4]

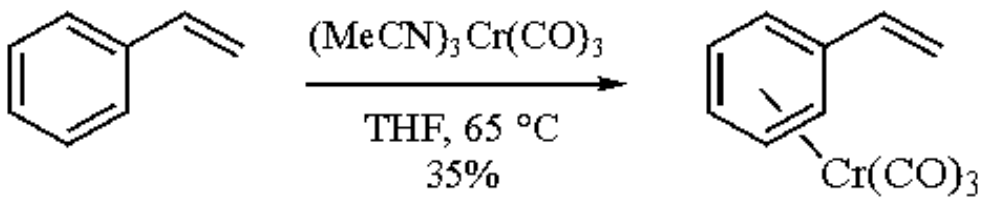

(1)

Alkene Isomerization.

Tris(acetonitrile)tricarbonylchromium catalyzes the isomerization of 1-phenylindene to 3-phenylindene (eq 2).[5] The scope and limitations of this reaction have not been tested.

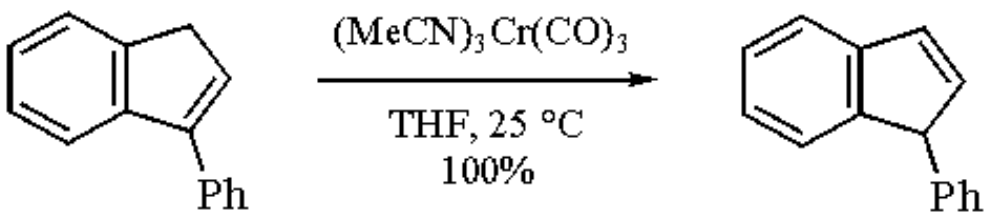

(2)

Allylic Oxidation.

Treatment of alkenes with ***t-Butyl Hydroperoxide*** in the presence of catalytic amounts of tris(acetonitrile)tricarbonylchromium (generated in situ) affords the corresponding ketone in high yield (eq 3).[6] The position of the alkene is unchanged during the oxidation.

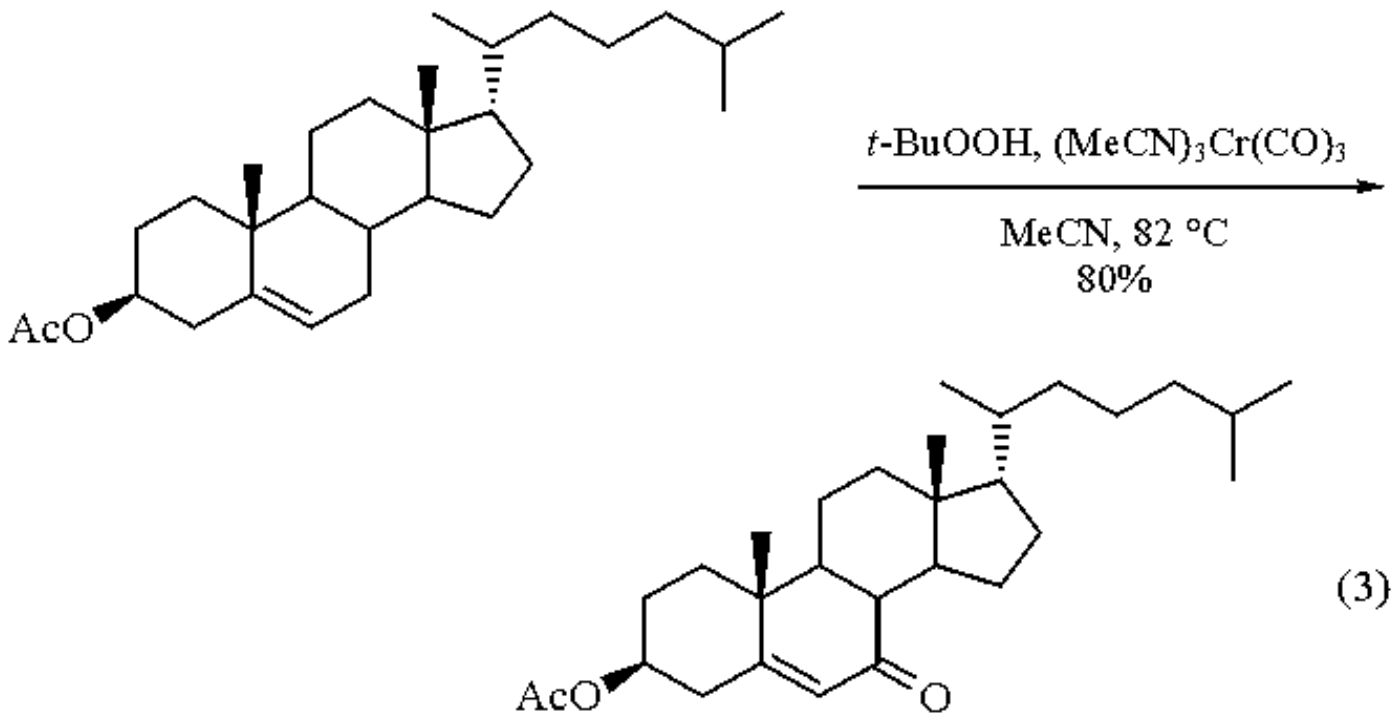

(3)

Related Reagents.

Hexacarbonylchromium; ***(η^6-Benzene)tricarbonylchromium***.

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1. Knox, G. R.; Leppard, D. G.; Pauson, P. L.; Watts, W. E. *JOM* **1972**, *34*, 347.
2. Tate, D. P.; Knipple, W. R.; Augl, J. M. *IC* **1962**, *1*, 433.
3. Semmelhack, M. F. In *COS* **1991**, *4*, 517.
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5. Berno, P.; Ceccon, A.; Gambaro, A.; Venzo, A. *TL* **1988**, *29*, 3489.
6. Pearson, A. J.; Chen, Y. S.; Hsu, S. Y.; Ray, T. *TL* **1984**, *25*, 1235.

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Tris(acetonitrile)tricarbonylmolybdenum

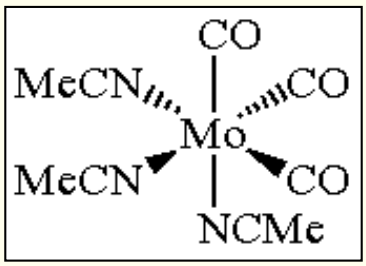

[15038-48-9] · $C_9H_9MoN_3O_3$ · Tris(acetonitrile)tricarbonylmolybdenum · (MW 303.15)

(reductively cleaves the N-O bond of isoxazolines[1])

Physical Data: mp 140 °C (dec).

Solubility: sol acetonitrile and THF.

Form Supplied in: yellow crystals; not commercially available.

Preparative Methods: by refluxing ***Hexacarbonylmolybdenum*** in ***Acetonitrile*** in an inert atmosphere. Removal of solvent under an inert atmosphere yields tris(acetonitrile)tricarbonylmolybdenum.[2]

Purification: the crude solid obtained in the above preparation is typically used without further purification.

Handling, Storage, and Precautions: air and thermally sensitive; pyrophoric; molybdenum(0) is reputed to be of low toxicity. Use in a fume hood.

Reductive Cleavage of the N-O Bond of Isoxazolines.

Treatment of isoxazolines with tris(acetonitrile)tricarbonylmolybdenum followed by silica gel leads to 3-hydroxy ketones (eq 1).[1] The conversion occurs under much milder conditions than when hexacarbonylmolybdenum is employed. The reaction is most efficient with spiro-fused cyclopropyl derivatives, where dehydration is disfavored. In other systems, mixtures of 3-hydroxy ketones and α,β-unsaturated ketones are obtained.

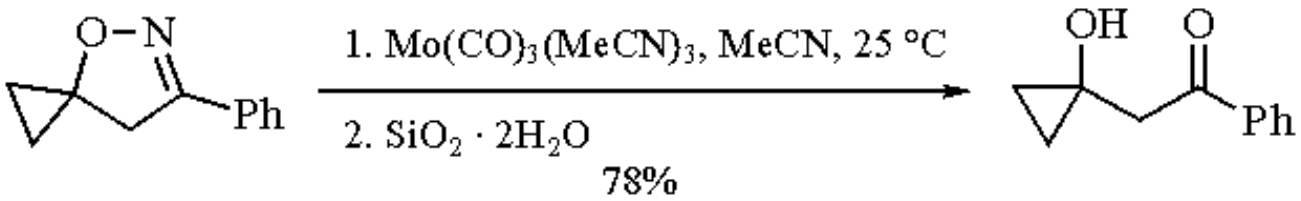

(1)

Reductive Aldol Coupling of α-Chloro Ketones.

Treatment of 2-chloroacetophenone with tris(acetonitrile)tricarbonylmolybdenum, followed by cyclopentadienyllithium, affords a mixture of the aldol product (**1**) and the secondary aldol product (**2**) (eq 2).[3] No demetallation studies have been reported for the resulting molybdenum complex. Only the yield after recrystallization was reported, suggesting that the efficiency of this reaction may be higher than indicated.

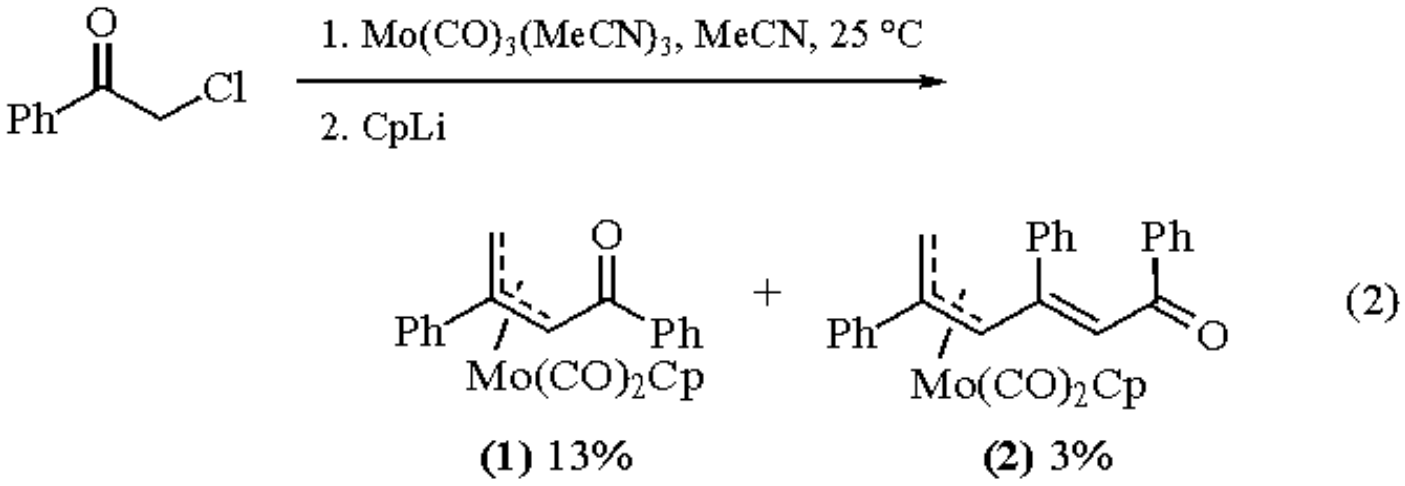

1. Guarna, A.; Guidi, A.; Goti, A.; Brandi, A.; De Sarlo, F. *S* **1989**, 175.
2. Tate, D. P.; Knipple, W. R.; Augl, J. M. *IC* **1962**, *1*, 433.
3. Faller, J. W.; Ma, Y. *OM* **1993**, *12*, 1927.

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Tris(acetonitrile)tricarbonyltungsten

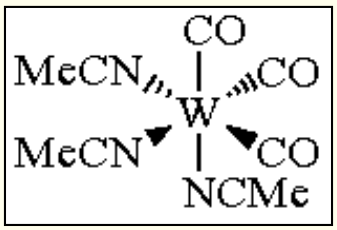

[16800-47-8] · $C_9H_9N_3O_3W$ · Tris(acetonitrile)tricarbonyltungsten · (MW 391.06)

(catalyst for nucleophilic substitution of allylic acetates[1])

Physical Data: mp 135 °C (dec).

Solubility: sol acetonitrile, nitromethane.

Form Supplied in: not commercially available.

Preparative Methods: by refluxing ***Hexacarbonyltungsten*** in ***Acetonitrile*** in an inert atmosphere. Removal of solvent under an inert atmosphere yields tris(acetonitrile)tricarbonyltungsten.[2] Solutions of the reagent can be prepared by photolysis of hexacarbonyltungsten in acetonitrile.

Purification: can be purified by recrystallization from acetone-hexane.[3] The crude solid or solution obtained in the above preparations is typically used without further purification.

Handling, Storage, and Precautions: air and thermally sensitive; pyrophoric. Use in a fume hood.

Allylic Alkylation.

Treatment of allylic acetates or carbonates with various carbon nucleophiles in the presence of tris(acetonitrile)tricarbonyltungsten and bipyridyl leads to the allylic alkylation product (eqs 1 and 2).[1] Suitable nucleophiles include those derived from carbon acids having a pK_a < ~18. The reaction proceeds with retention of configuration (eq 1) and preferentially produces the allylic regioisomer, where nucleophilic attack occurs at the carbon best able to stabilize a positive charge. This is in contrast to palladium-catalyzed allylic alkylation, where the nucleophilic attack generally occurs preferentially at the less-substituted carbon of the allylic system.[4]

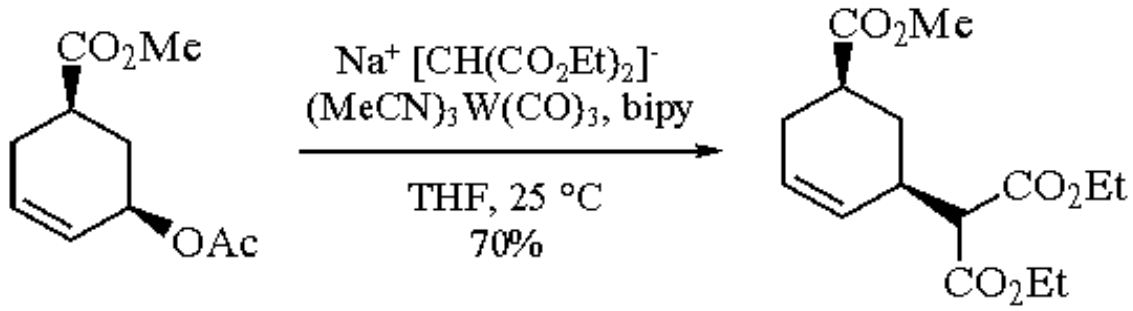

(1)

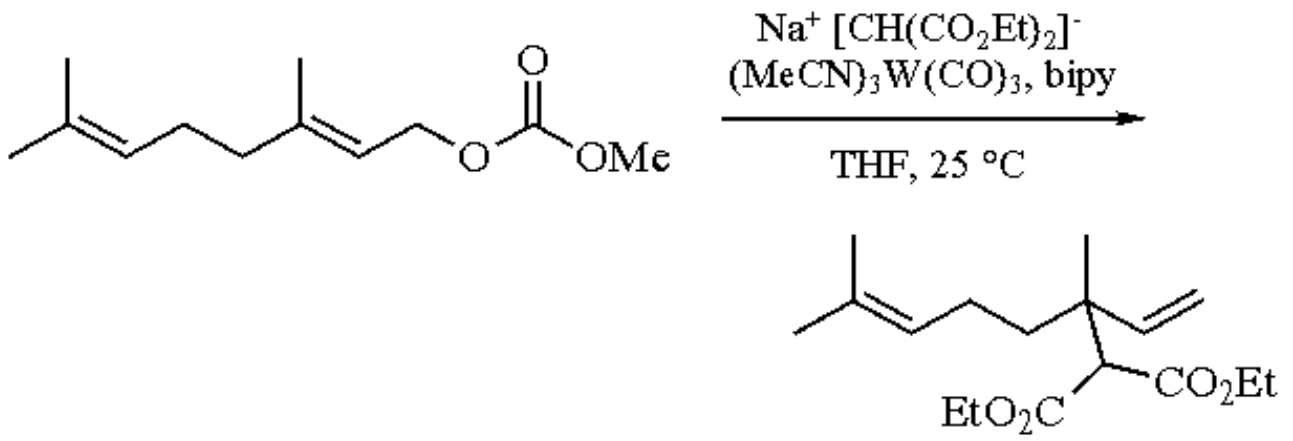

(2)

Related Reagents.

Palladium(II) Acetate; ***Palladium(II) Chloride***; ***Tetrakis(triphenylphosphine)palladium(0)***.

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1. Trost, B. M.; Hung, M. H. *JACS* **1983**, *105*, 7757.
2. Faller, J. W.; Haitko, D. A.; Adams, R. D.; Chodosh, D. F. *JACS* **1979**, *101*, 865.
3. Tate, D. P.; Knipple, W. R.; Augl, J. M. *IC* **1962**, *1*, 433.
4. Trost, B. M. *ACR* **1980**, *13*, 385.

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Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS

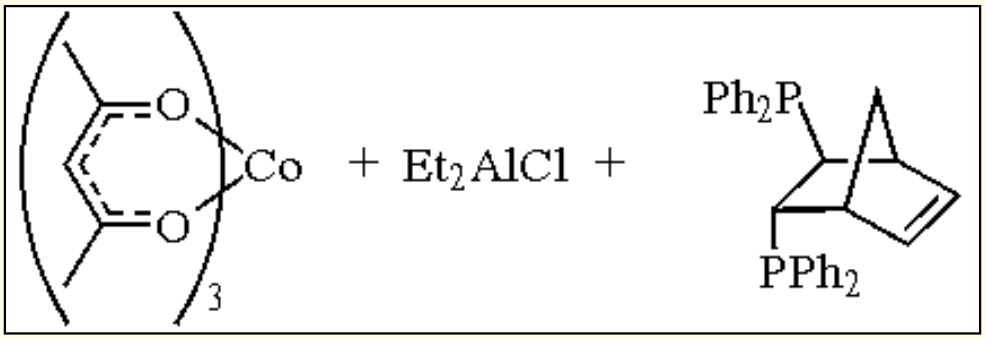

($Co(acac)_3$)

[21679-46-9] · $C_{15}H_{21}CoO_6$ · Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS · (MW 356.29) (Et_2AlCl)

[96-10-6] · $C_4H_{10}AlCl$ · Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS · (MW 120.57) ((+)-NORPHOS)

[71042-54-1] · $C_{31}H_{28}P_2$ · Tris(acetylacetonato)cobalt-Diethylaluminum Chloride-NORPHOS · (MW 462.53)

(catalyst for the formation of optically active deltacyclene derivatives by homo Diels-Alder reaction of norbornadiene with substituted acetylenes[1,2])

Physical Data: see ***Diethylaluminum Chloride*** and ***(+)-trans-(2S,3S)-Bis(diphenylphosphino)bicyclo[2.2.1]hept-5-ene*** (NORPHOS).

Solubility: sol THF, benzene, toluene.

Preparative Methods: synthesized in situ from the three components, using a 1.5 excess of the chelate phosphine; the components are commercially available or can be easily prepared.

Handling, Storage, and Precautions: the in situ catalyst should be used in an atmosphere of dry nitrogen or argon, in a fume hood. The catalyst components can be stored indefinitely. They are air stable except Et_2AlCl, which should be kept under exclusion of air.

The Homo Diels-Alder Reaction of Norbornadiene with Acetylenes.

[2 + 2 + 2] Cycloadditions of dienes such as norbornadiene with the double bonds in 1,4-position are called homo Diels-Alder reactions. Using an in situ catalyst (consisting of $Co(acac)_3$-Et_2AlCl-bis(diphenylphosphino)ethane) the products obtained with monosubstituted acetylenes, such as phenyl, *i*-propyl-, *n*-butyl-, *t*-butyl-, and trimethylsilylacetylene, are 4-substituted deltacyclenes.[1,2] In the formation of the polycyclic deltacyclene skeleton, six new stereo centers are generated in one step. Thus enantiocontrol by using optically active phosphine ligands as cocatalysts allows the synthesis of optically active cycloadducts,[3-5] as shown for the reaction of norbornadiene with phenylacetylene to give 4-phenyldeltacyclene (eq 1).

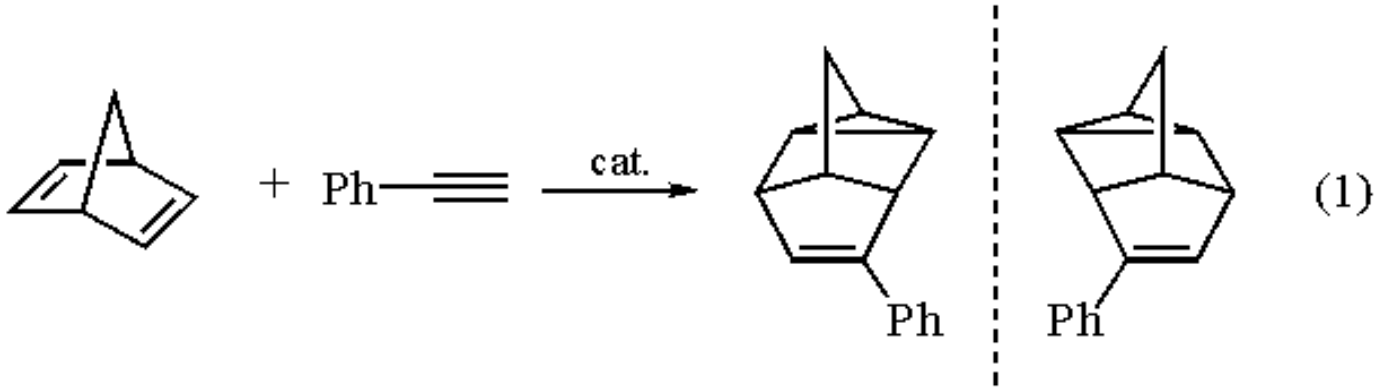

Preparation of the in situ Catalyst and Catalytic Reaction.

(This is a typical procedure for norbornadiene and phenylacetylene or 1-hexyne). Tris(acetylacetonato)cobalt (7.1 mg, 2.0×10^{-2} mmol) and (+)-NORPHOS (13.8 mg, 3.0×10^{-2} mmol) are dissolved in 1 ml of THF under dry nitrogen, using standard Schlenk techniques. Norbornadiene (1.0 mL, 10.0 mmol) and 10 mmol of phenylacetylene or 1-hexyne are added. The reaction is started by addition of 5 mL of a 1M solution of diethylaluminum chloride in hexane. The reaction mixture is kept at 35 °C for 4 h. Then 5 mL of isopropanol are added and the volatile components are removed in vacuum. The oily residue is distilled at 80 °C in high vacuum in a Kugelrohr apparatus. Chemical yield >99%; enantiomeric excess 98.4-99.6% for (+)-4-phenyldeltacyclene and 97.6-98.0% for (+)-4-*n*-butyldeltacyclene.

Product Analysis.

The distilled product is dissolved in 2 mL of dry methylene chloride and an internal standard is added (naphthalene for 4-phenyldeltacyclene, biphenyl for 4-*n*-butyldeltacyclene). The chemical yield and the enantiomeric excess of the product can be determined by GLC using a 40 m column of perpentylated β-cyclodextrin. 4-Phenyldeltacyclene: column temperature 104 °C, retention time (-)-isomer 124.7 min, (+)-isomer 128.2 min; 4-*n*-butyldeltacyclene: column temperature 65 °C, retention time (-)-isomer 78.3 min, (+)-isomer 80.8 min.

Variation of the Optically Active Phosphine Ligand (Cocatalyst) and the Solvent.[5]

In the synthesis of 4-phenyldeltacyclene, (+)-NORPHOS as the optically active ligand and THF as the solvent gave the best results, as indicated in the typical procedure. Used in benzene, the NORPHOS-containing catalyst also gives extremely high enantioselectivities but low chemical yields. With PROPHOS as the ligand, quantitative conversion in THF is only achieved after long reaction times. The enantiomeric excess in this case was ca. 80%. CHIRAPHOS and BDPP as cocatalysts result in slow conversions of the starting materials, BDPP giving high optical yields. In the case of DIOP in benzene, only low chemical and optical yields are obtained. In THF, DIOP-containing catalysts are inactive, as are BINAP-containing catalysts in benzene/THF.

For 4-*n*-butyldeltacyclene, no other cocatalyst gives the quantitative yield and 98-99% enantiomeric excess observed in the NORPHOS-containing system. The PROPHOS system gives 80% enantiomeric excess.

Variation of the Procatalyst (Metal Component) and the Acetylenic Substrate.

The in situ catalysts $Co(acac)_3$-Et_2AlCl-phosphine have proven to be well-suited for the synthesis of 4-aryl- and 4-alkyl-substituted deltacyclenes. The catalysts tolerate remote oxygen functionalities in the acetylenic substrate.[4] However, they could not be used with functionalized acetylenes such as propargylic acid derivatives.

Recently, new procatalysts have been reported. They contain different cobalt sources and reducing agents. The procatalyst CoI_2-Zn has proven valuable in the preparative homo Diels-Alder reaction.[6] It has been shown that monodentate and bidentate ligands of the aminophosphine and phosphite type, e.g. ValNOP and ProliNOP, give high optical yields in the synthesis of 4-

phenyldeltacyclene and 4-*n*-butyldeltacyclene.[7] With these new procatalysts, an extension of the homo Diels-Alder reaction to functionalized acetylenes is possible. High chemical and optical yields are obtained in the reaction of norbornadiene with substrates such as propargylic and homopropargylic ethers and esters.[8]

---

1. Lyons, J. E.; Myers, H. K.; Schneider, A. *CC* **1978**, 636.
2. Lautens, M.; Crudden, C. M. *OM* **1989**, *8*, 2733.
3. Brunner, H.; Muschiol, M.; Prester, F. *AG* **1990**, *102*, 680; *AG(E)* **1990**, *29*, 652.
4. Lautens, M.; Lautens, J. C.; Smith, A. C. *JACS* **1990**, *112*, 5627.
5. Brunner, H.; Prester, F. *JOM* **1991**, *414*, 401.
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7. Pardigon, O.; Buono, G. *TA* **1993**, *4*, 1977.
8. Buono, G.; personal communication.

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Tris(acetylacetonato)indium[1]

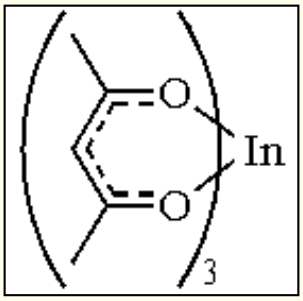

[14405-45-9] · $C_{15}H_{21}InO_6$ · Tris(acetylacetonato)indium · (MW 412.18)

(mild Lewis acid used as a cocatalyst to effect carbonyl additions[2])

Physical Data: mp 186 °C; ^{1}H NMR ($CDCl_3$) δ 2.02 (C*H*$_3$), 5.41 (C*H*); *d* 1.41 g cm^{-3}.

Solubility: readily sol toluene; moderately sol ethanol; almost insol water.

Form Supplied in: white crystalline solid; readily available. *Drying:* the freshly prepared indium compound can be recrystallized from cold acetone as colorless crystals and sublimed at 260-280 °C.

Handling, Storage, and Precautions: the dry solid can be stored in air. In(acac)$_3$ has a reputed toxicity of LD$_{50}$: 79 mg kg^{-1} with TSCA HMIS: 2-1-0-X.

1,2 vs. 1,4 Cycloadditions.

While organoindium compounds have found recent synthetic applications for a number of organic transformations including allylations,[3] cyclopropanations,[4] Reformatsky,[5] and cross-coupling reactions,[6] catalysis using indium precursors has been relatively unexplored. A recent study has shown that $InCl_3$ can be employed as a cocatalyst along with ***Chlorotrimethylsilane*** for the conversion of *O*-trimethylsilyl monothioacetals to sulfides.[7] In a similar manner, In(acac)$_3$ has been used to control the chemoselectivity in the palladium-catalyzed cycloaddition of carbonyl compounds.[2] As expected, addition of trimethylenemethane to enones in the presence of a palladium catalyst affords the 1,4-adduct exclusively.[8] However, as little as 10 mol % of In(acac)$_3$ can be utilized as a cocatalyst to alter the reaction course from conjugate to 1,2-addition (eq 1). Increasing reaction temperatures by going from refluxing THF to dioxane increases the ratio of 1,2- vs. 1,4-addition products.

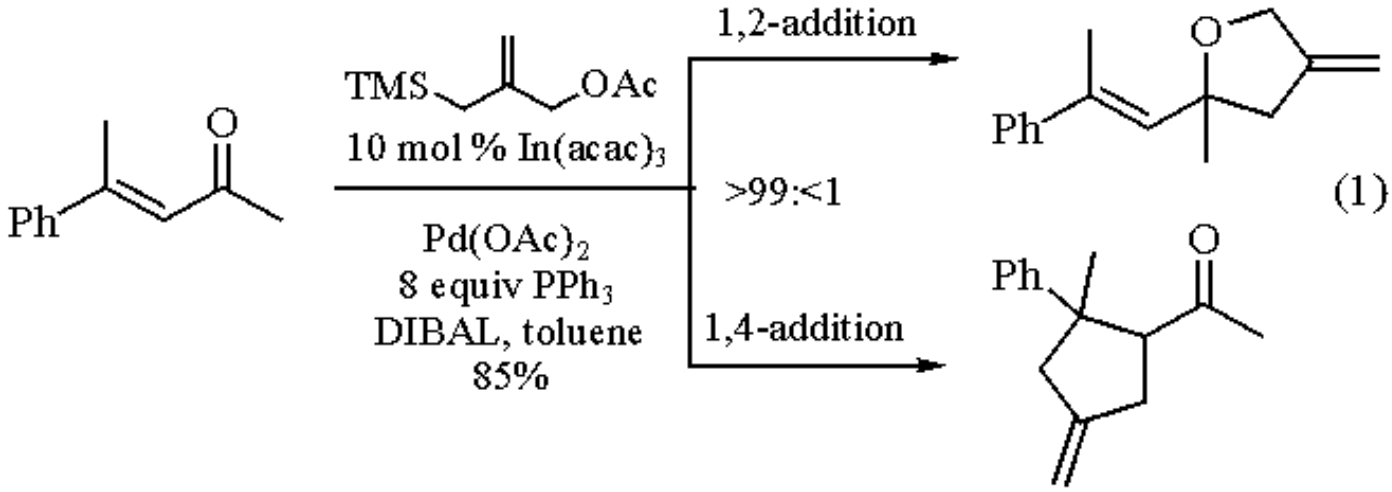

Exocyclic enone derivatives, which are particularily prone to conjugate addition, can be diverted from this pathway to give exclusive

formation of the corresponding 1,2-addition products by using an In^{III} cocatalyst (eq 2). Reactions with carbohydrates bearing several Lewis basic sites also proceed with good 1,2-selectivity and diastereoselectivity in the presence of $In(acac)_3$. Steric hindrance may inhibit 1,2-addition, however, as in the case of galactopyranose (eq 3) which gives predominant formation of the 1,4-adduct (1,2 vs. 1,4 = 1:4.2).

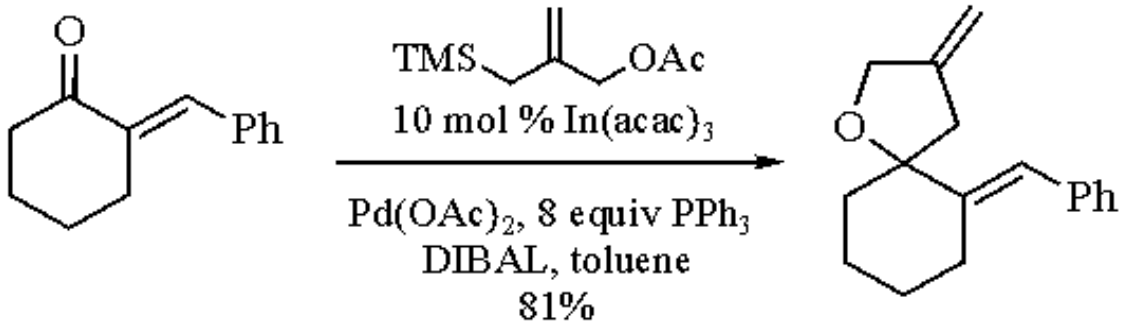

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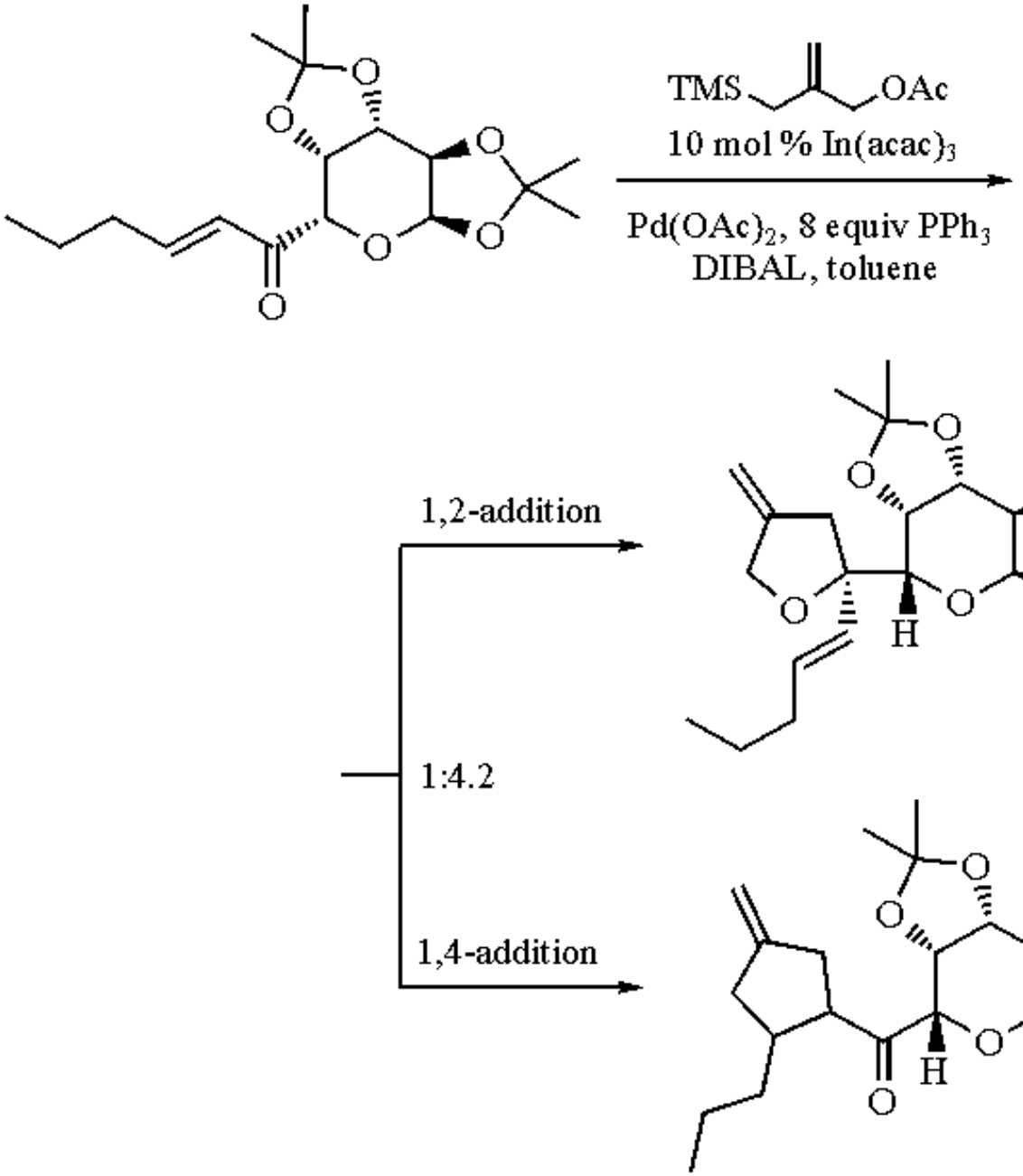

(3)

Finally, addition of trimethylenemethane to keto aldehydes affords the corresponding methylenetetrahydrofuran with enhanced diastereoselectivity (>19:1) when compared to reactions employing tin as a cocatalyst (eq 4).[9] This overall switch in chemoselectivity using indium complexes promises to be useful for a number of nucleophilic reactions.

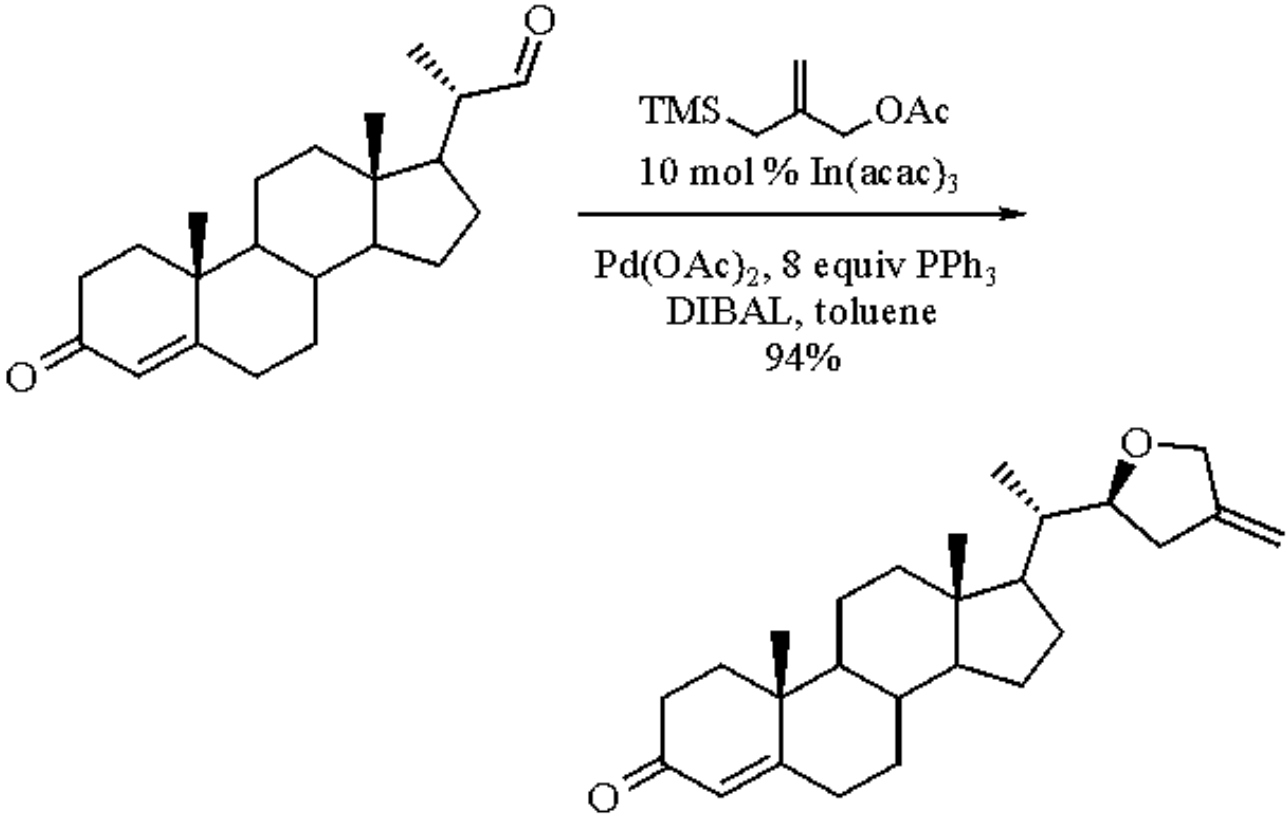

(4)

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2. Trost, B. M.; Sharma, S.; Schmidt, T. *JACS* **1992**, *114*, 7903.
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4. Araki, S.; Butsugan, Y. *CC* **1989**, 1286.
5. (a) Araki, S.; Ito, H.; Butsugan, Y. *SC* **1988**, *18*, 453. (b) Johar, P. S.; Araki, S.; Butsugan, Y. *JCS(P1)* **1992**, 711.
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Tris(acetylacetonato)iron(III)

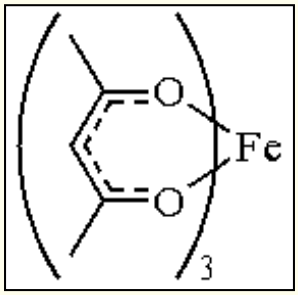

[14024-18-1] · $C_{15}H_{21}FeO_6$ · Tris(acetylacetonato)iron(III) · (MW 353.21)

(organotransition metal catalyst used in the cross coupling of acid halides or vinyl bromides with Grignard reagents, the stereoselective epoxidation of steroidal alkenes, and the reductive decyanation of alkyl nitriles)

Alternate Names: ferric acetylacetonate; ferric triacetylacetonate; iron acetylacetonate.

Physical Data: mp 182-185 °C (191 °C by differential thermal analysis[1]).

Solubility: sol alcohols, chlorinated solvents.

Form Supplied in: deep red powder.

Analysis of Reagent Purity: CH analysis (calc 57.51% C, 5.96% H).[1]

Purification: recrystallization from ethanol[2] or methanol/H_2O.[1]

Handling, Storage, and Precautions: severe eye irritant and possible teratogen. Poor thermal stability in molten state.[1]

Preparation of Ketones from Acyl Chlorides and Grignard Reagents.[3]

The inclusion of a catalytic amount of $Fe(acac)_3$ in the coupling reaction of acid chlorides and Grignard reagents gives the desired ketones without the significant formation of carbinols which accompanies the reaction in its absence (eq 1).[4] The use of other organometallic reagents[5] in place of Grignard reagents has also effected the formation of ketones without the accompanying formation of secondary and/or tertiary alcohols; however, these reagents lack the generality and convenience shown with the $Fe(acac)_3$ catalyzed reaction (Table 1). The reaction was also extended to aromatic acid chlorides and thiophenyl acid chlorides, which were coupled with long-chain di-Grignard reagents to produce symmetrical 1,*n*-diketones (*n* &egt; 8) and long-chain dicarboxylic thiol esters in moderate to good yield.[6]

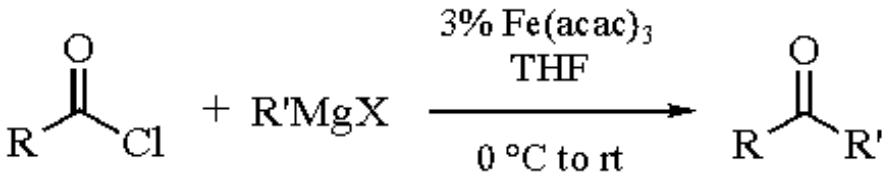

(1)

Table 1 $Fe(acac)_3$ Catalyzed Cross Coupling of Acid Halides with Grignard Reagents

R	R¢	Temp.	Yield (%)
Me	$Me(CH_2)_8$	rt	82
Ph	Me	rt	80
Ph	Ph	0 °C	75
$MeO_2C(CH_2)_2$	Bu	rt	75
$ClCO(CH_2)_3$	Et	rt	82
(*l*)(+)-$PhC(CF_3)(OMe)$	Me	rt	(*l*)(+) 76
Cycloheptatrienyl	*p*-$MeOC_6H_4$		55

Preparation of Alkenes: Cross Coupling of Vinyl Bromides,[7] Vinyl Sulfones,[8] and Vinyl Sulfoximines[9] with Grignard Reagents.

Fe^{III} complexes containing β-diketonate ligands, such as $Fe(acac)_3$, are useful catalysts for the cross coupling of vinyl bromides with Grignard reagents (eq 2).[7] The coupling reactions with vinyl bromides proceed with primary, secondary, and tertiary Grignard reagents. It is proposed that $Fe(acac)_3$ is initially reduced by the Grignard reagent to form an active Fe^{I} or Fe^{0} catalyst,[10] which has been shown to undergo an irreversible deactivation during the course of the cross-coupling reaction. A similar reagent, ***Tris(dibenzoylmethide)iron(III)***, has been shown to be more resistant to this deactivation and is the preferred iron catalyst for this reaction.[7]

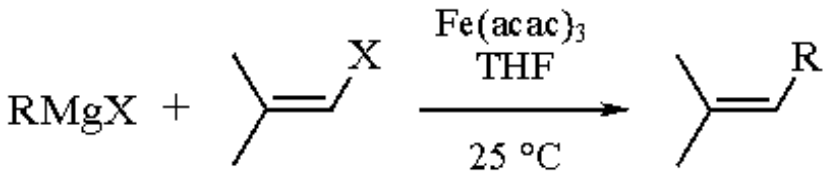

(2)

The cross coupling of Grignard reagents with vinyl sulfones in the presence of $Fe(acac)_3$ or ***Nickel(II) Acetylacetonate*** proceeds with some stereoselectivity; however, the reaction is complicated by reduction byproducts.[8] The stereoselective construction of exocyclic alkenes from the cross-coupling reaction of alkenylsulfoximines, prepared stereoselectively from the corresponding ketone, with Grignard reagents in the presence of stoichiometric amounts of $Fe(acac)_3$ and $NiCl_2$(dppp) has also been reported (eq 3).[9] This serves as a useful alternative to standard Wittig-type alkenations for the construction of exocyclic alkenes.[11]

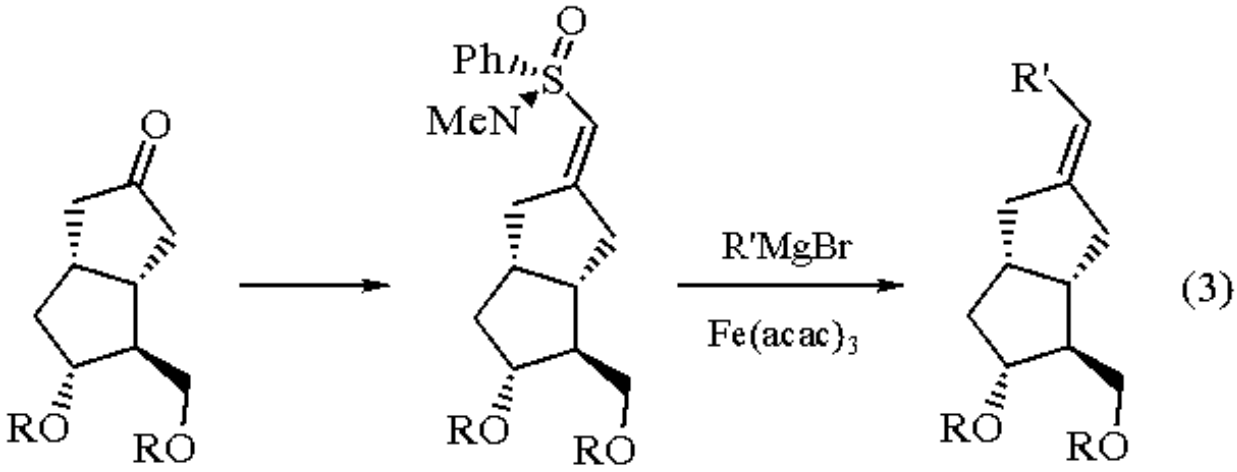

R = TBDMS R' = Ph, 74%; (*E*):(*Z*) = 4:1
R' = *m*-$C_6H_4CH_2OSiR_3$, 75%; (*E*):(*Z*) = 3:1
R' = $(CH_2)_4OSiR_3$, 34%; (*E*):(*Z*) = 7:1

Epoxidation of Steroidal Alkenes.[12]

$Fe(acac)_3$ is used to catalyze the stereoselective β-epoxidation of cholesterol derivatives (allylic alcohols) with excess ***Hydrogen Peroxide*** in acetonitrile under mild conditions (eq 4). This shows opposite stereoselectivity to epoxidation reactions using conventional organic peracids, where shielding by the angular methyl groups prevents epoxidation on the β-face. This method offers similar stereoselectivity to halohydrin methodology,[13] but the reaction is effected in a single step. The observed stereoselectivity is independent of R, unlike other methodologies.

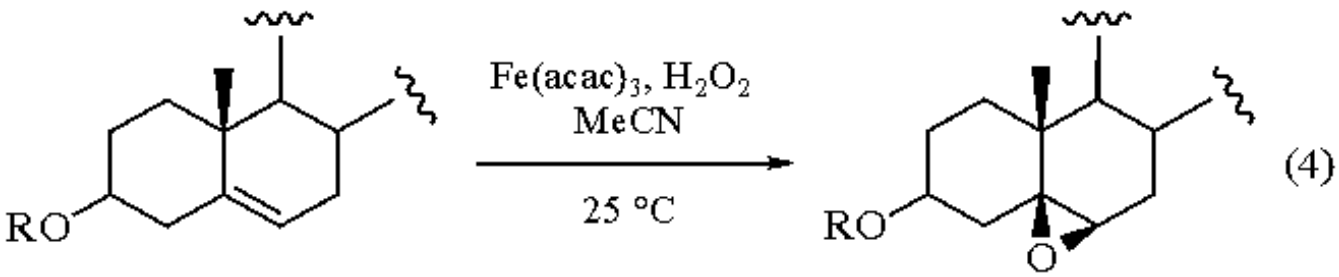

R = H, Ac

Preparation of *N*-Acylpiperidines: Ene Carbocyclization of Trienes.

The in situ generation of a (bipy)Fe^0L_n catalyst by the reaction of $Fe(acac)_3$ and ***Triethylaluminum*** is used to prepare cyclopentyl, cyclohexyl, and tetrahydropyranyl rings, as well as *N*-acylpiperidines by the formal [4 + 4] ene carbocyclization of trienes, triene ethers, and azatrienes (eq 5).[14]

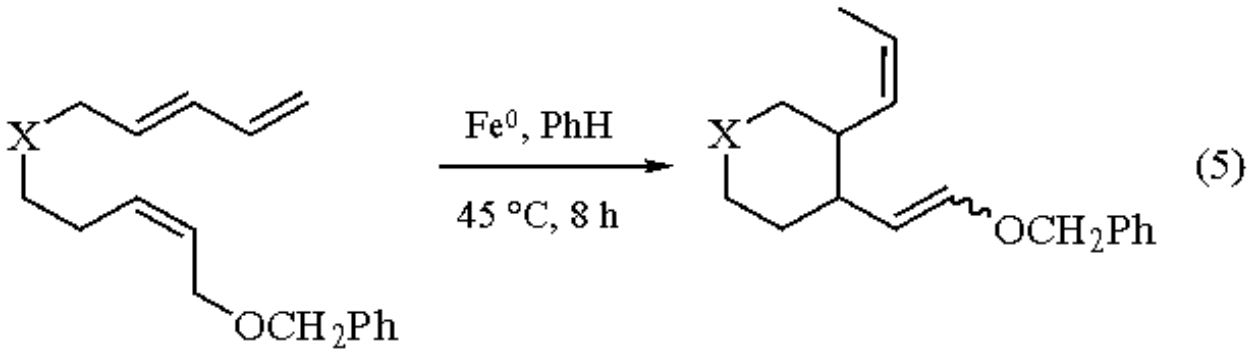

X = CH_2, O, PhC(O)N

Miscellaneous Reactions.

Hydrocarbons are produced in good to excellent yield from alkyl nitriles upon treatment with $Fe(acac)_3$ and ***Sodium*** sand in benzene.[15] The best results for this reductive decyanation were obtained with saturated alkyl nitriles. Nontransition metal promoted cleavage of primary nitriles in liquid ammonia gives inferior results.[16] The Michael addition of ethyl acetoacetates to cyclic enones was catalyzed by $Fe(acac)_3$ and an electrophilic cocatalyst.[17] Other $M(acac)_n$ compounds were also examined.

---

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Tris(4-bromophenyl)aminium Hexachloroantimonate[1]

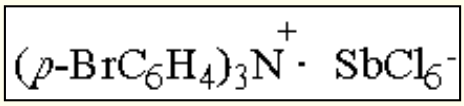

[24964-91-8] · $C_{18}H_{12}Br_3Cl_6NSb$ · Tris(4-bromophenyl)aminium Hexachloroantimonate · (MW 816.46)

(a stable radical cation[2] and one-electron oxidant[2])

Physical Data: mp 142 °C.[2]

Solubility: sol acetonitrile, dichloromethane.

Form Supplied in: dark blue crystalline solid.

Purification: one method is as follows: a solution of the title reagent (**1**) in dichloromethane (1 part) is poured into diethyl ether (3 parts) to precipitate the salt; the resulting blue needles are collected and dried under vacuum.[2]

Handling, Storage, and Precautions: is an irritant and is moisture sensitive.

Protective Group Removal.

p-Methoxybenzyl protected alcohols can be deprotected with (**1**) to give the alcohol in excellent yield in moist acetonitrile. Benzyl ethers are not affected by this reagent but can be removed with the analogous tris(2,4-dibromophenyl)aminium hexachloroantimonate.[3,4] The conversion of thioacetals to the corresponding aldehyde or ketone is effected by (**1**) in acetonitrile containing aqueous sodium bicarbonate.[5]

Glycosidation.

Alkyl, aryl, or xanthate glycosides undergo glycosidation reactions with primary or secondary alcohols of *O*-glycosides to give β-*O*-linked disaccharides. This reaction is only observed when acetonitrile is used as solvent (eq 1).[6]

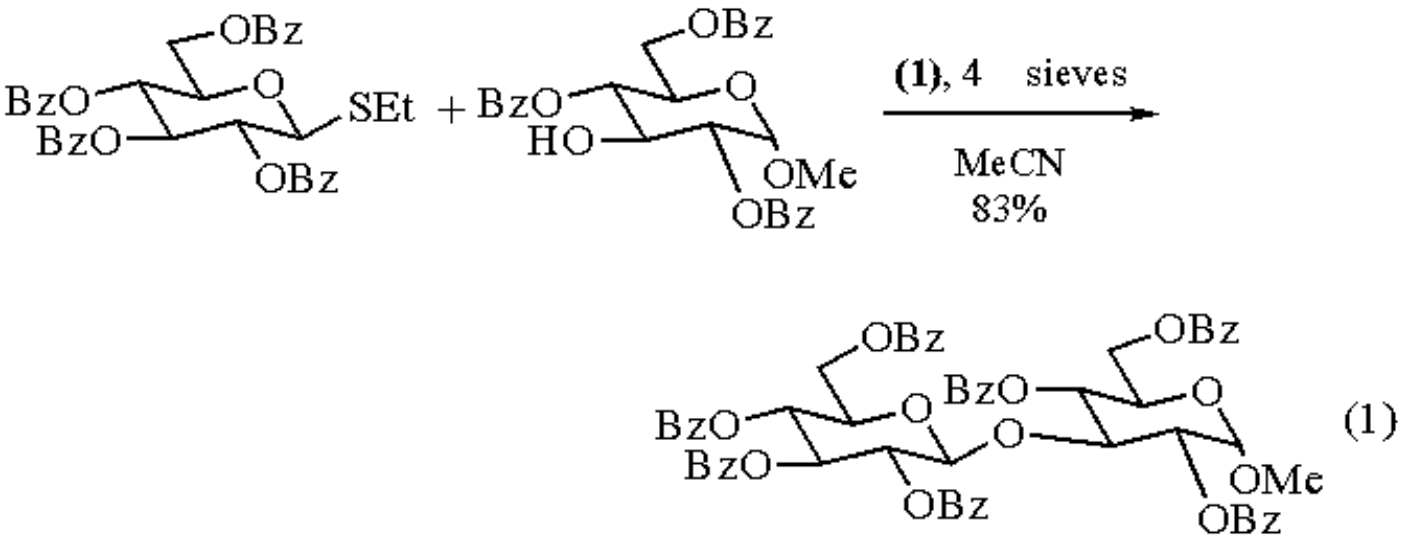

Diels-Alder and Cyclization Catalyst.

As a Diels-Alder catalyst, (**1**) has been shown to increase the rate of this reaction and give improved selectivities.[7] For example, the uncatalyzed Diels-Alder reaction of cyclohexadiene with tetramethylbutadiene proceeds in low yield at 200 °C. With a catalytic amount of (**1**) present the reaction proceeds at -25 °C with improved selectivity (eq 2).

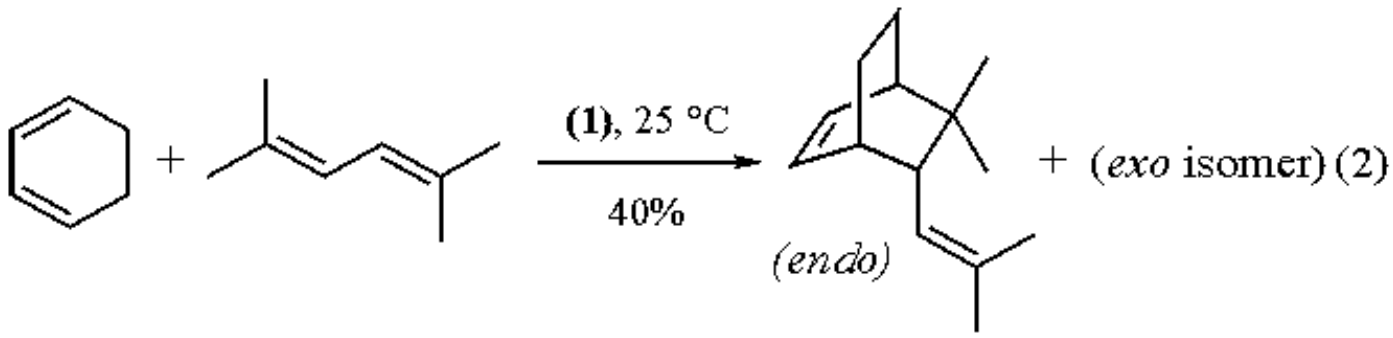

Also, (**1**) has been found to be a good catalyst for single electron acceptors and shown to provide a highly selective route for cycloadditions of neutral or electron-rich acceptors to conjugated dienes (eq 3).[7,8]

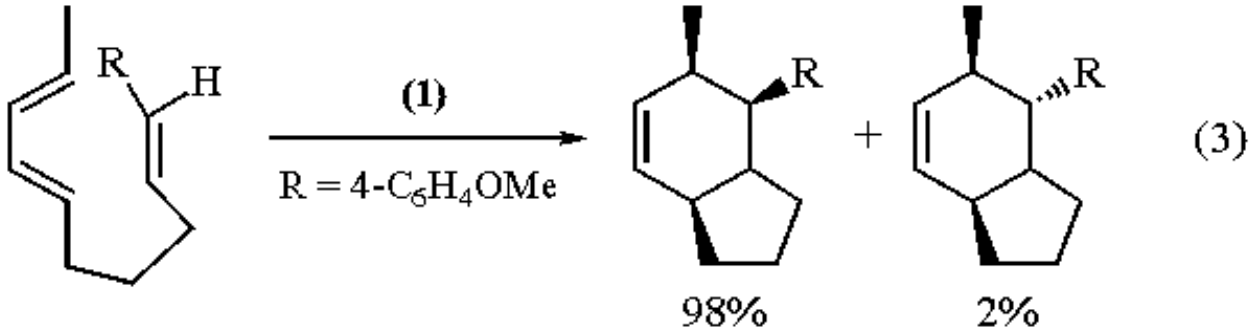

Under anhydrous conditions the cyclization of vinylbiphenyls gives the corresponding fluorene (eq 4), but if a trace of water is added the expected electrocyclization product is formed in excellent yield.[9]

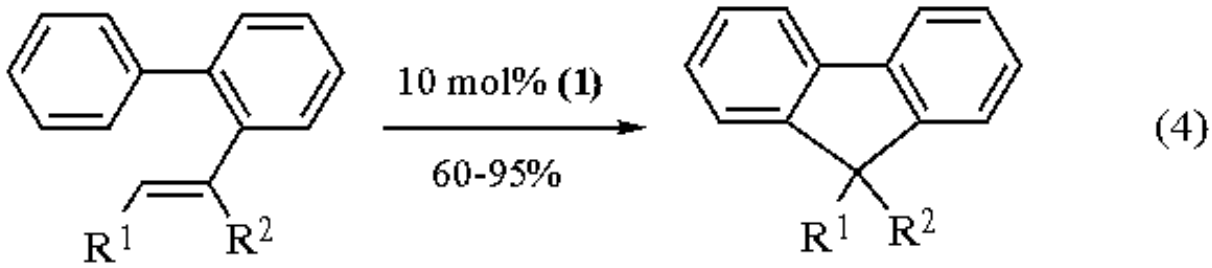

$R^1 = H$, $R^2 = Ph$ or $R^1 = R^2 = (CH_2)_n$; $n = 3$ or 4

Rearrangement of Vinylcyclopropanes.

These reactions are readily effected in acetonitrile to give cyclopentanes under mild conditions (eqs 5 and 6).[10]

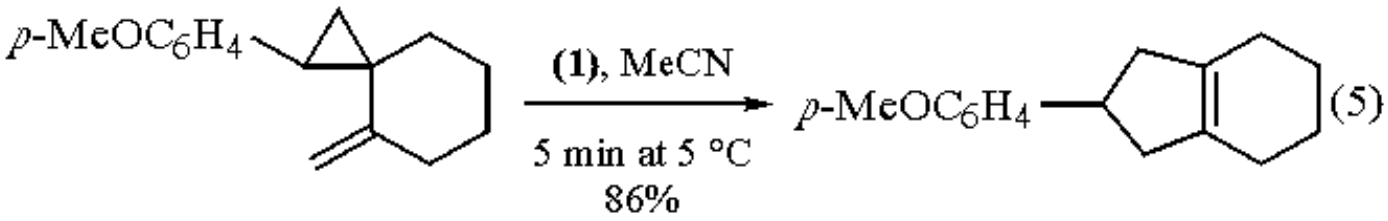

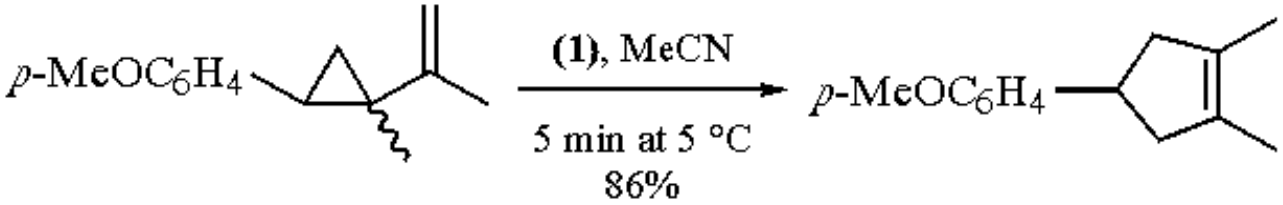

(6)

Oxidation Reactions.

Epoxides are oxidatively rearranged to ketones or esters in dichloromethane by what is thought to be a radical-type mechanism. For example, tetraphenylethylene oxide is rearranged to 2,2,2-triphenylacetophenone,[11] and the adamantyl derived epoxide in eq 7 is rearranged in quantitative yields to either the corresponding ketone or ester, depending upon the reaction temperature.[11]

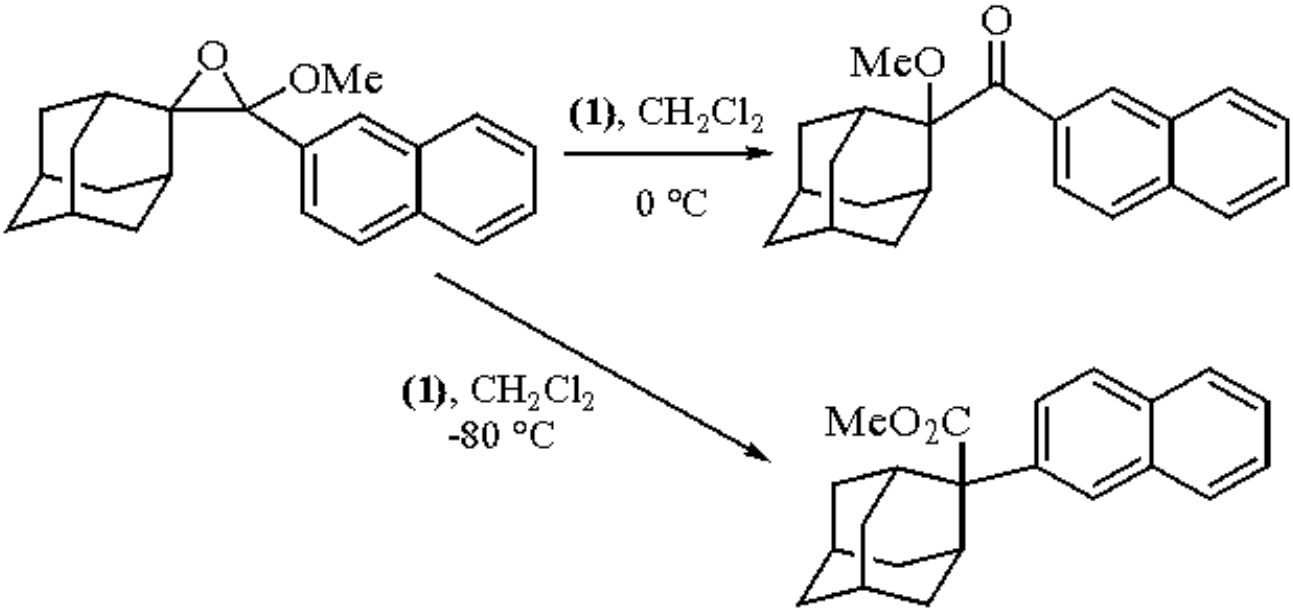

(7)

A similar reaction is observed with the epoxide of β-ionone, where a cyclohexane ring can be contracted to a cyclopentane (eq 8).[11]

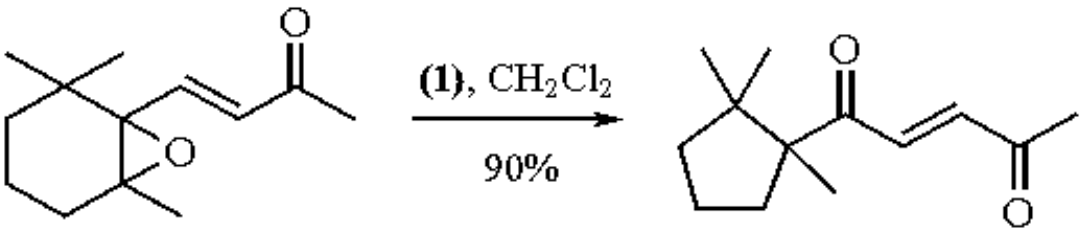

(8)

β-Ionone also undergoes allylic oxidation to give the allylic alcohol with (**1**).[12] Ketones are oxidized by (**1**) to the α-hydroxy ketone and, at higher temperatures, the α-diketone.[13] When methanol is added to the solvent (acetonitrile), the α-methoxy ketone is formed.[14]

In conjunction with ***Selenium(IV) Oxide***, (**1**) epoxidizes alkenes and enol ethers;[15] in oxygen saturated solutions of dichloromethane, (**1**) can be used to make dioxetanes[16] from alkenes or enol ethers. The oxidation of 2-nitrophenylsulfenamide protected amines or amino acids to the corresponding sulfenimine is readily brought about by (**1**) in the presence of a base such as ***2,6-Lutidine*** (eq 9).[17] Other methods for this conversion have included electrochemical oxidation.

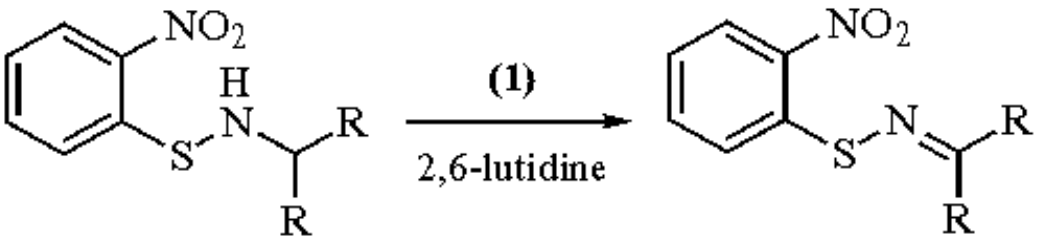

(9)

Other Reactions.

A stable adduct of (**1**) is formed in the presence of 2,3-diazabicyclo[2.2.2]oct-2-ene.[18] α,α-Dimesitylenol ethers undergo oxidative rearrangement to the monomesitylbenzofuran with (**1**),[19] and vinylferrocene undergoes dimerization upon treatment with (**1**).[20]

---

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Tris(cyclopentadienyl)lanthanum-Sodium Hydride[1]

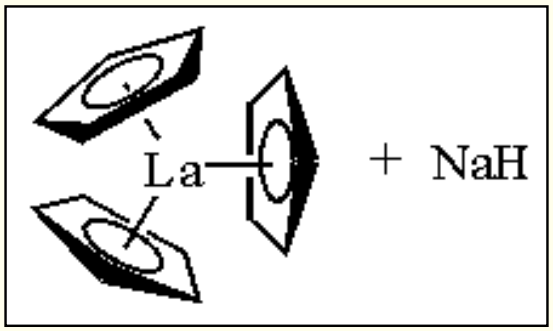

(Cp_3La)

[1272-23-7] · $C_{15}H_{15}La$ · Tris(cyclopentadienyl)lanthanum-Sodium Hydride · (MW 334.21) (NaH)

[7646-69-7] · HNa · Tris(cyclopentadienyl)lanthanum-Sodium Hydride · (MW 24.00)

(reducing agent for alkenes, organohalogen compounds, and organoheteroatom oxides; catalyst for hydrogenation and isomerization of alkenes)

Physical Data: Cp_3La: mp 395 °C (slight dec.). NaH: mp 800 °C (dec.).

Solubility: Cp_3La: sol THF; reacts with H_2O and protic solvents. NaH: slightly sol THF.

Form Supplied in: Cp_3La: white crystalline solid. NaH used as 80% dispersion in mineral oil.

Preparative Methods: because Cp_3La is sensitive to air and moisture, the preparative procedure and all subsequent operations on the compound must be carried out with Schlenk techniques under purified argon. The following procedure has proven efficacious: to a suspension of anhydrous ***Lanthanum(III) Chloride*** in THF was added 4-5 equiv of sodium cyclopentadienide in THF; the mixture was refluxed with stirring for 4 h; the solvent was removed under reduced pressure, and the dry residue was transferred to a sublimation apparatus; on heating at 250-260 °C/10^{-3}-10^{-4} mmHg, Cp_3La sublimed as a white crystalline solid. Alternatively, the residue can be recrystallized from THF to afford $Cp_3La(THF)$ as colorless crystals.

Handling, Storage, and Precautions: tris(cyclopentadienyl)lanthanum and ***Sodium Hydride*** must be used as prepared or purified, and sealed in glass ampules with argon or nitrogen for storage.

Reduction of Alkenes.

Tris(cyclopentadienyl)lanthanum and its analogs, combined with ***Sodium Hydride***, are effective reducing agents for C=C bonds,[2,3] aryl halides, vinyl halides[4,5] and certain organoheteroatom oxides.[6] Reduction of 1-hexene with Cp_3Ln/NaH (Ln = rare earth metal) in THF at 45 °C gives hexane (after hydrolysis). The reducing activity depends strongly upon the ionic radius of the trivalent ion. Generally, the activity decreases in the order: early rare

earths > mid rare earths > heavy rare earths. The reduction rate of internal C=C bonds is much slower than that of terminal ones. As a consequence, the Cp_3Ln/NaH system can be used to reduce terminal C=C bonds regioselectively (eq 1).

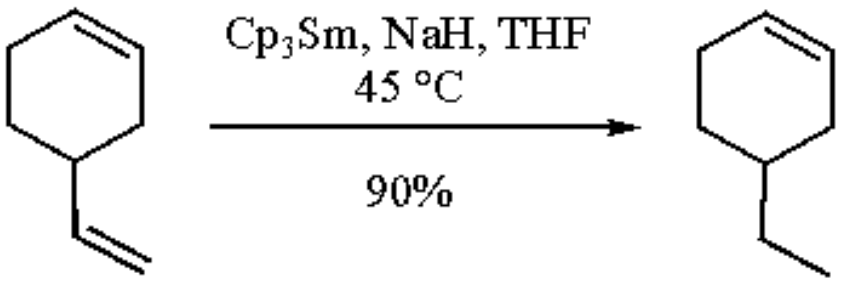

(1)

Reduction of Organohalogen Compounds.

Aryl and vinyl halides are stoichiometrically or catalytically reduced by Cp_3La/NaH systems and analogs in THF to afford the corresponding aromatics and alkenes, respectively, in excellent yields (eq 2).[4,5] The reductive activity of the light rare earth reagents is higher than that of heavy ones. The order of ease of reductive dehalogenation of aryl halides by the Cp_3La/NaH system is in agreement with that of the usual reductive dehalogenation of organic halides, i.e. I > Br > Cl > F. As a result, chemoselective reduction of *p*-bromochlorobenzene and *p*-chloroiodobenzene to chlorobenzene can be achieved. However, surprisingly, the reactivity pattern of alkyl halides with the Cp_3La/NaH system and analogs is quite different from that of aryl and vinyl halides. Treatment of alkyl halides with Cp_3La/NaH followed by hydrolysis does not generate the corresponding alkanes, but rather produces alkylated cyclopentadienes (eq 3).[5]

$$RX \xrightarrow[65\ ^\circ C]{Cp_3La,\ NaH,\ THF} RH \qquad (2)$$

R = aryl, vinyl; X = F, Cl, Br, I

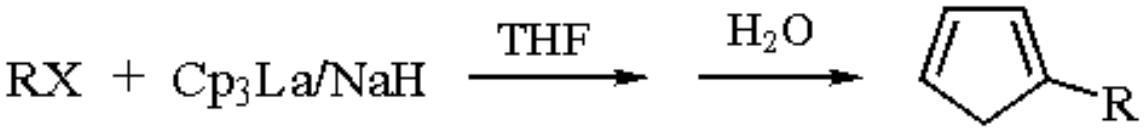

(3)

R = alkyl; X = Cl, Br, I

Other Reductions.

Some organoheteroatom oxides such as triphenylarsine oxide, diphenyl sulfoxide and pyridine *N*-oxide are smoothly deoxygenated by the Cp_3La/NaH system and analogs in THF in good yields. The suitable molar ratio of reactants is 2:8:1 (Cp_3La/NaH/oxide). Although triphenylphosphine oxide is essentially inert to Cp_3Sm/NaH, the combination of Cp_3Sm and ***Lithium Aluminum Hydride*** facilitates its reduction to phosphine.[6]

Isomerization and Hydrogenation of Alkenes.

The Cp_3La/NaH system and analogs can catalyze isomerization of 1-alkenes to *cis*- and *trans*-2-alkenes in almost quantitative yields (eq 4).[2,7] The catalytic activity seems to be related to the ionic radius of the rare earth metal. In contrast to their reducing activity, the isomerization activity of late rare earth reagents is better than that of early ones.

It is worth noting that these systems can also catalyze the isomerization of sulfur-containing alkenes such as $PhSCH_2CH{=}CH_2$,[8] while most transition metal catalysts would be deactivated by sulfur compounds. These systems are also effective for the catalytic hydrogenation of alkenes. 1-Hexene was completely converted into hexane under 4 atm pressure of hydrogen in the course of 2 days.[2]

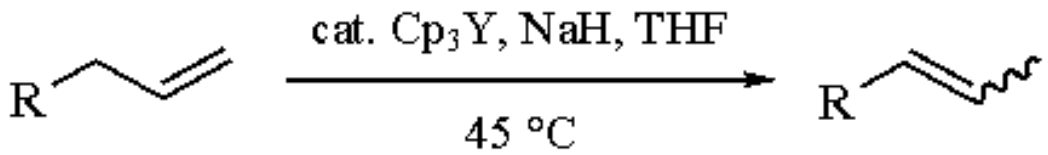

(4)

R = Pr, *i*-Pr, nonyl, Ph, etc.

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Tris(dibenzoylmethide)iron(III)

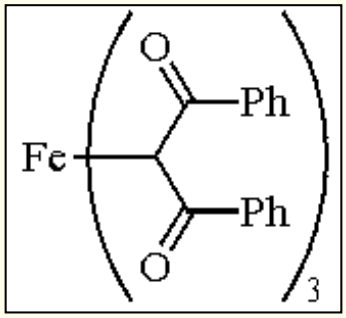

[14405-49-3] · $C_{45}H_{33}FeO_6$ · Tris(dibenzoylmethide)iron(III) · (MW 725.63)

(Fe^{III} complex containing β-diketonate ligands serves as catalyst precursor for the cross coupling of Grignard reagents with vinyl bromide[1] and for the intramolecular alkylation of ketones to give bicyclic alcohols[2])

Alternate Name: tris(dibenzoylmethanato)iron.

Physical Data: mp 240 °C (dec).

Solubility: insol hexane; sol benzene; slightly sol alcohol.

Form Supplied in: red powder.

Analysis of Reagent Purity: visible spectrum 408, 500 (sh) nm.

Preparative Methods: ***Iron(III) Chloride*** and excess dibenzoylmethane in ethanol give a red solid; add 50% aq. ammonia; filter the red solid, wash with water, and dry.

Purification: precipitate from hot benzene by addition of hot hexanes.

Handling, Storage, and Precautions: store tightly sealed in a cool, dry place.

Preparation of Alkenes.

Cross Coupling of Vinyl Bromides with Grignard Reagents.[1,3]

Tris(dibenzoylmethide)iron(III), $Fe(dbm)_3$, is an effective catalyst in the stereospecific cross coupling of vinyl bromides with primary, secondary, and tertiary Grignard reagents (eq 1 and Table 1). Improved yields were observed when dimethoxyethane replaced THF as the solvent and lower reaction temperatures were employed.[1b] The cross coupling of vinyl sulfones with Grignard reagents was also successfully accomplished in the presence of $Fe(dbm)_3$.[1c,d]

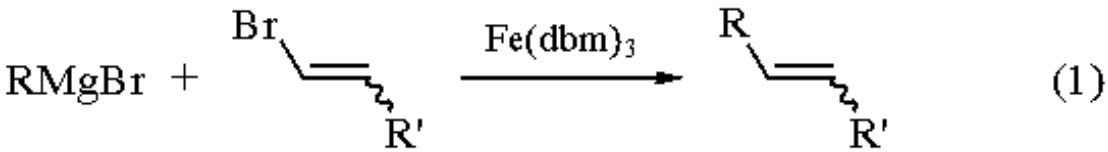

(1)

Table 1 Cross Coupling of Vinyl Bromides with Grignard Reagents (eq 1)

R	R¢	Conditions	Yield (%)
Et	Me	THF, 25 °C	58[1a]
Ph	Ph	THF, 25 °C	32[1a]
Et	Ph	THF, 25 °C	59[1a]
i-Pr	Me	THF, 25 °C	60[1a]
Cy	Me	THF, 25 °C	54[1a]
t-Bu	Me	THF, 25 °C	27[1a]
Ph	Ph	DME, - 20 °C to rt	90[1b]
Me	SPh	THF, - 78 °C to rt	75[1c]
H	SPh	THF, - 78 °C to rt	60[1c]

The superior performance compared to other Fe^{III} catalysts has been attributed to its resistance to deactivation.[1a] It is superior to other organometallic catalysts, particularly Ni, because it is used at lower concentrations and temperatures and isomerization of the Grignard reagent does not occur.[3] In general, Fe^{III} catalysts are proposed to be readily reduced to Fe^{I} or Fe^{0} species, which serve as the active catalyst in the cross coupling reactions.[3]

Preparation of Bicycloalkanols.

Intramolecular Barbier-type reactions[2] using magnesium have typically failed when used to construct six-membered cycloalkanols.[6] $Fe(dbm)_3$ used in combination with lanthanide reducing reagents, namely ***Samarium(II) Iodide***, has been shown to overcome this shortcoming. The reaction was shown to be quite stereoselective when $n = 1$ ($m = 1$ or 2), but gives poor stereoselectivity when $n > 1$ (eq 2 and Table 2).

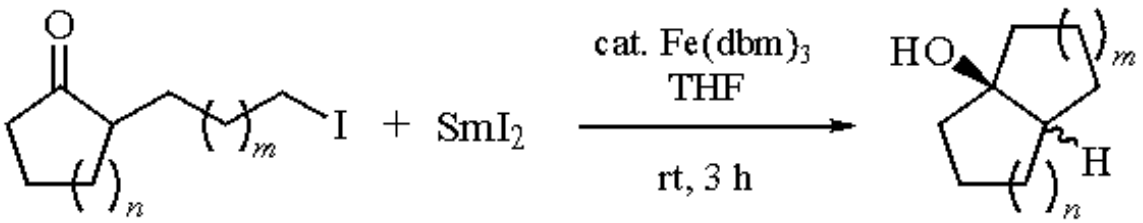

(2)

Table 2 Preparation of Bicycloalkanols using Lanthanide Reagents and Catalytic $Fe(dbm)_3$ (eq 2)[2a]

n	*m*	% GC yield (isolated)	*cis*:*trans* ratio (GC)
1	1	90 (60)	>99.5:<0.5
2	1	100 (75)	1.3:1
3	1	85 (77)	2:1
1	2	67	18:1
2	2	96 (75)	1:1.5

Indeed, numerous other organometallic reagents have been utilized to construct the desired bicycloalkanols (*m* = 0-2), including Pd,[7] Ni,[8] and other alkali metals.[9] The Barbier-type reaction with SmI_2 has also proved to be quite general for the efficient, simple construction of a variety of complex, bicyclic ring systems including bridgehead, bicyclic alcohols (eqs 3-5).[2b]

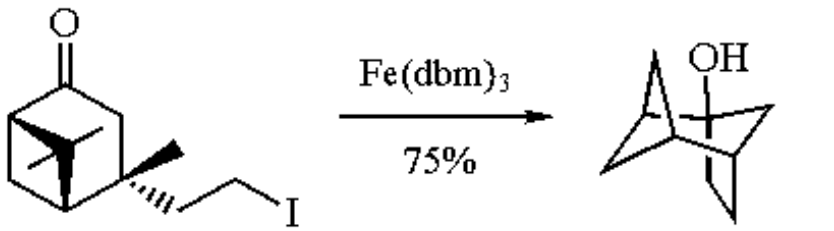

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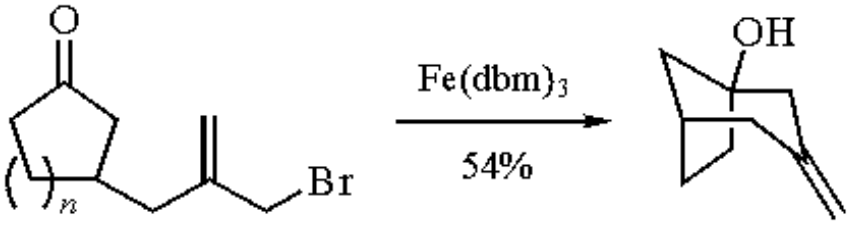

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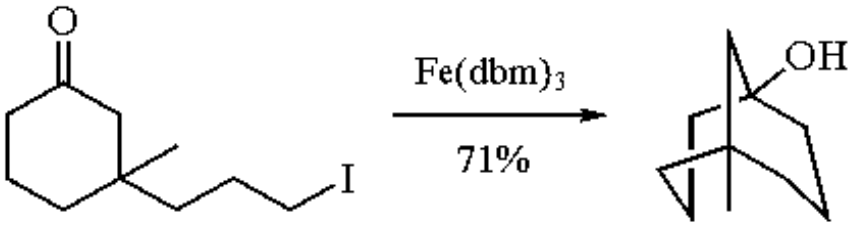

(5)

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Tris(dibenzylideneacetone)dipalladium-Chloroform

$$(PhCH{=}CHCOCH{=}CHPh)_3Pd_2 \cdot CHCl_3$$

[52522-40-4] · $C_{52}H_{43}Cl_3O_3Pd_2$ · Tris(dibenzylideneacetone)dipalladium · (MW 1035.14)

(air-stable Pd^0 complex used directly as homogeneous Pd^0 catalyst with or without ligand)

Physical Data: mp 122-124 °C (dec),[1] 131-135 °C.[2]

Solubility: insol H_2O; sol chloroform, benzene.

Form Supplied in: deep purple needle-like crystals; commercially available.

Preparative Methods: the reaction of $Na_2[Pd_2Cl_6]$ (from ***Palladium(II) Chloride*** and NaCl) and dibenzylideneacetone (dba) gives ***Bis(dibenzylideneacetone)palladium(0)***, $[Pd(dba)_2]$, which is formulated more correctly as $[Pd_2(dba)_3]dba$.[1,3] Recrystallization from chloroform displaces the uncoordinating dba with chloroform to give the title reagent as deep purple needles.[1]

Sources of Palladium(0).

Many reactions are catalyzed by Pd^0 catalysts.[4] The Pd^0 catalysts are prepared in two ways. One common method for generation of Pd^0 species involves in situ reduction of Pd^{II} salts, most conveniently ***Palladium(II) Acetate***. An alternative involves the use of air-stable, commercially available $Pd_2(dba)_3$ as a Pd^0 catalyst with or without added phosphine. The dba ligand is displaced by the addition of phosphine ligands (eq 1). Some reactions catalyzed with and without added phosphine ligands are described below.

$$Pd_2(dba)_3 + 4\,Ph_3P \longrightarrow 2\,Pd(PPh_3)_2 + 3\,dba \qquad (1)$$

Ene Reactions.

An intramolecular palladium-ene reaction that proceeds smoothly using $Pd_2(dba)_3$ in the presence of ***Triphenylphosphine*** is shown in eq 2.[5]

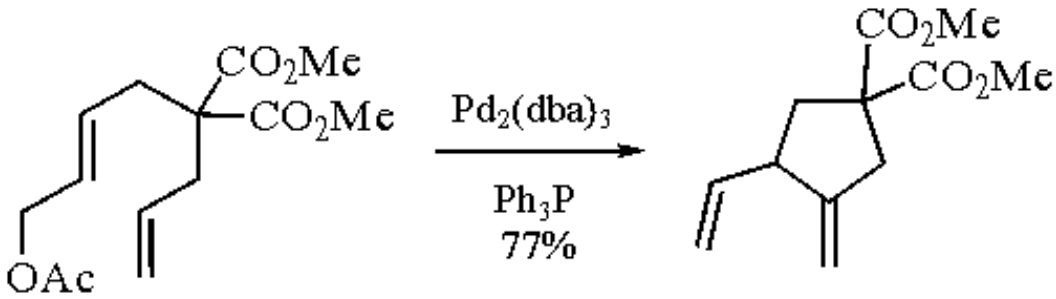

(2)

Allylation Reactions.

Silyl enol ethers react with allylic carbonates using $Pd_2(dba)_3$ and dppe (***1,2-Bis(diphenylphosphino)ethane***), yielding the allylated ketones under neutral conditions (eq 3).[6]

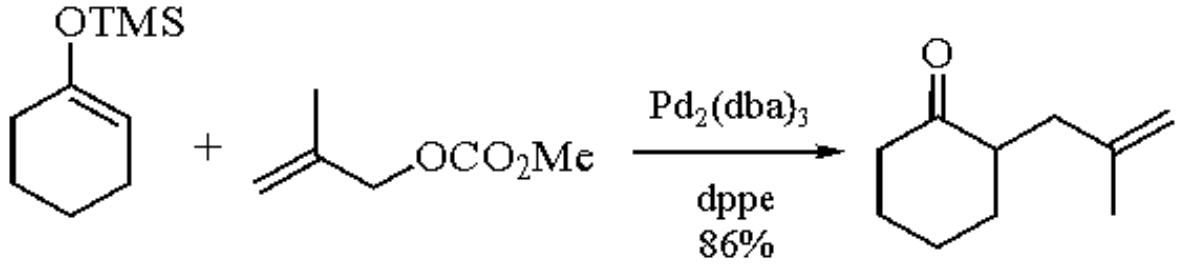

(3)

Heck Cyclizations.

Sometimes good or different results are obtained when the title reagent is used without added phosphine ligands. Dibenzylideneacetone itself is a good ligand which effects the catalytic activity of the Pd^0 differently than phosphines. The following Pd^0-catalyzed intramolecular cyclization catalyzed by $Pd_2(dba)_3$ without added phosphine ligand is more selective than in the presence of the ligand (eq 4). The cyclization under the ligandless conditions affords (**1**) and (**2**) in ratios as high as 9:1. In addition, the cyclization conducted without phosphine ligands in the presence of Ag salts occurs with virtually complete selectivity to give (**2**).[7]

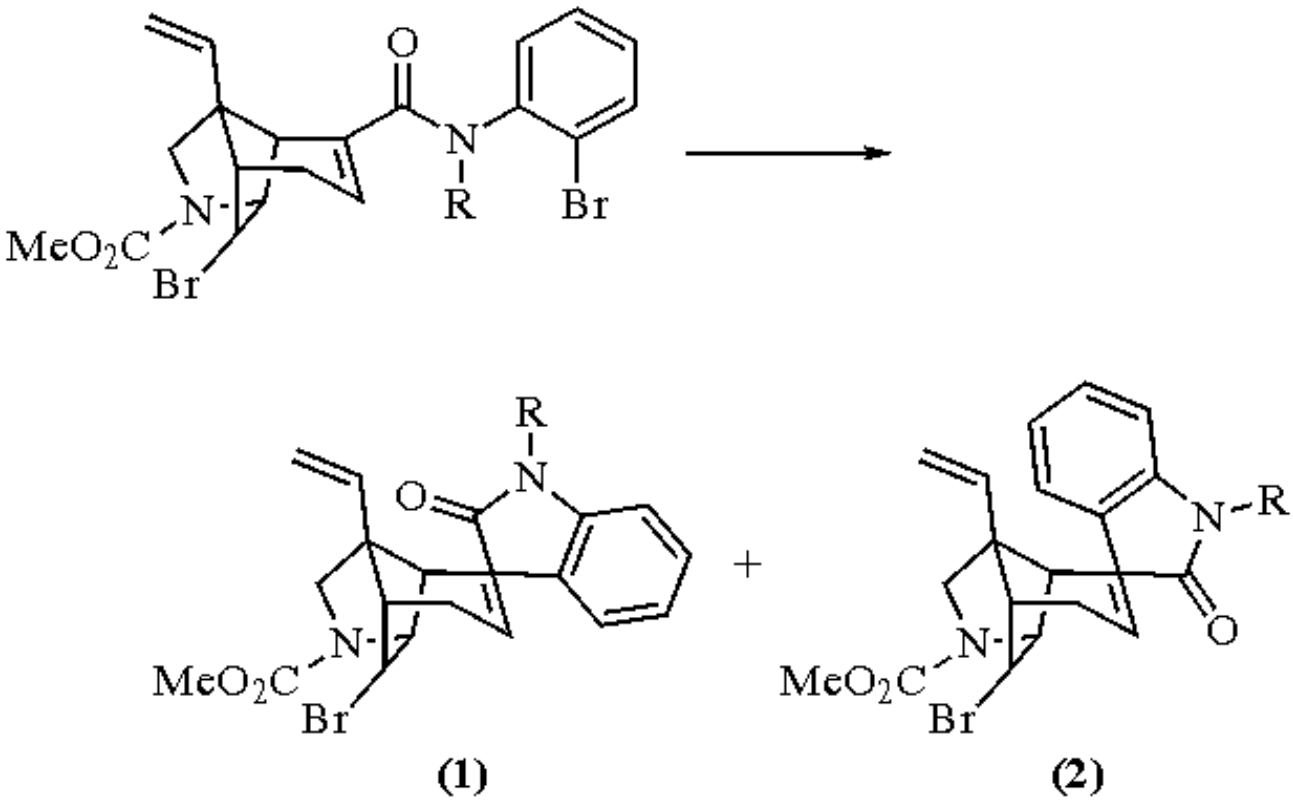

(4)

$Pd_2(dba)_3$, Et_3N, toluene, 110 °C	89:11	80%
$Pd_2(dba)_3$, Ag_3PO_4, THF, 66 °C	3:97	77%
$Pd(Ph_3P)_4$, Et_3N, MeCN, 82 °C	60:40	66%

Coupling of Enol Triflates with Organotin Reagents.

Coupling of an enol triflate with (*Z*)-1-propenyltri-*n*-butyltin proceeds smoothly using $Pd_2(dba)_3$ as a catalyst in the absence of a phosphine ligand (eq 5).[8]

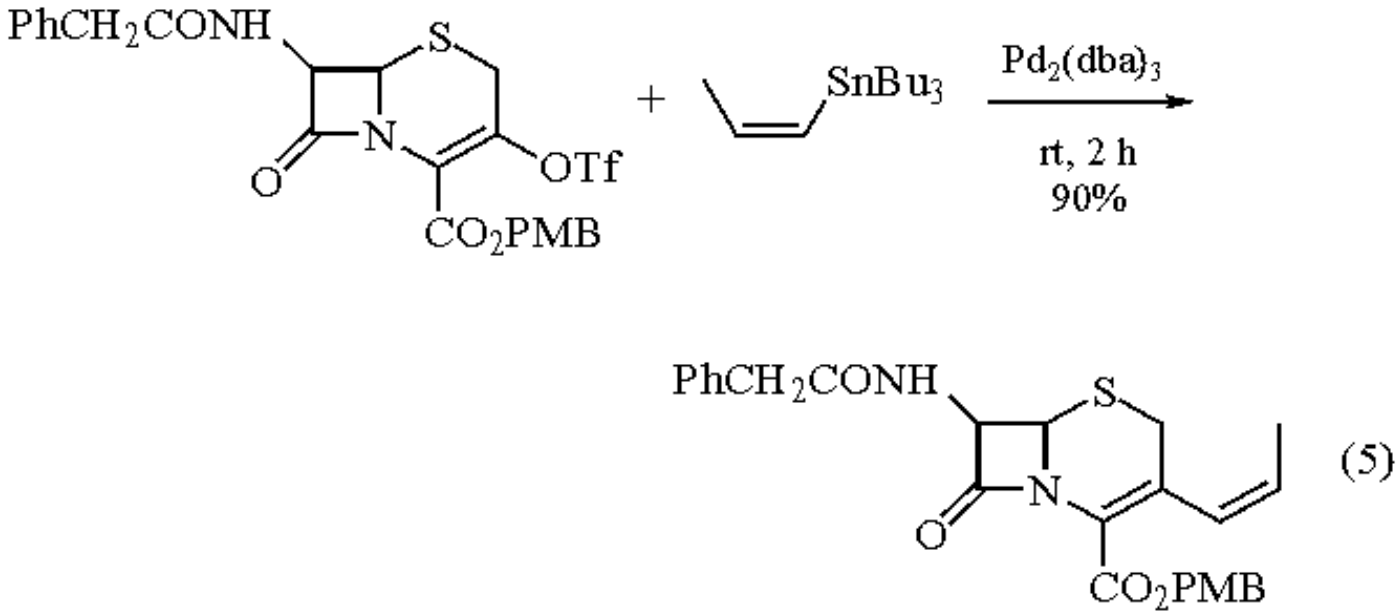

Comparison of the Catalytic Activity of $Pd_2(dba)_3$ in the Presence and Absence of a Ligand.

$Pd_2(dba)_3$ is a good catalyst, but it is not always as good as other Pd^0 catalysts. When Pd^0-catalyzed reactions of congested molecules are carried out, use of $Pd_2(dba)_3$ is not recommended. For example, in the elimination reaction of a steroidal α-allylic carbonate, the ligand-free catalyst prepared from $Pd(OAc)_2/Bu_3P$ (1:1) gives the homoannular conjugated diene regioselectively.[9] No regioselectivity is observed with the $Pd_2(dba)_3/Bu_3P$ catalyst (eq 6). Also, $Pd_2(dba)_3/Bu_3P$ is less active than $Pd(OAc)_2/Bu_3P$ in a provitamin D synthesis proceeding by the same elimination reaction of the cyclic allylic carbonates.[10]

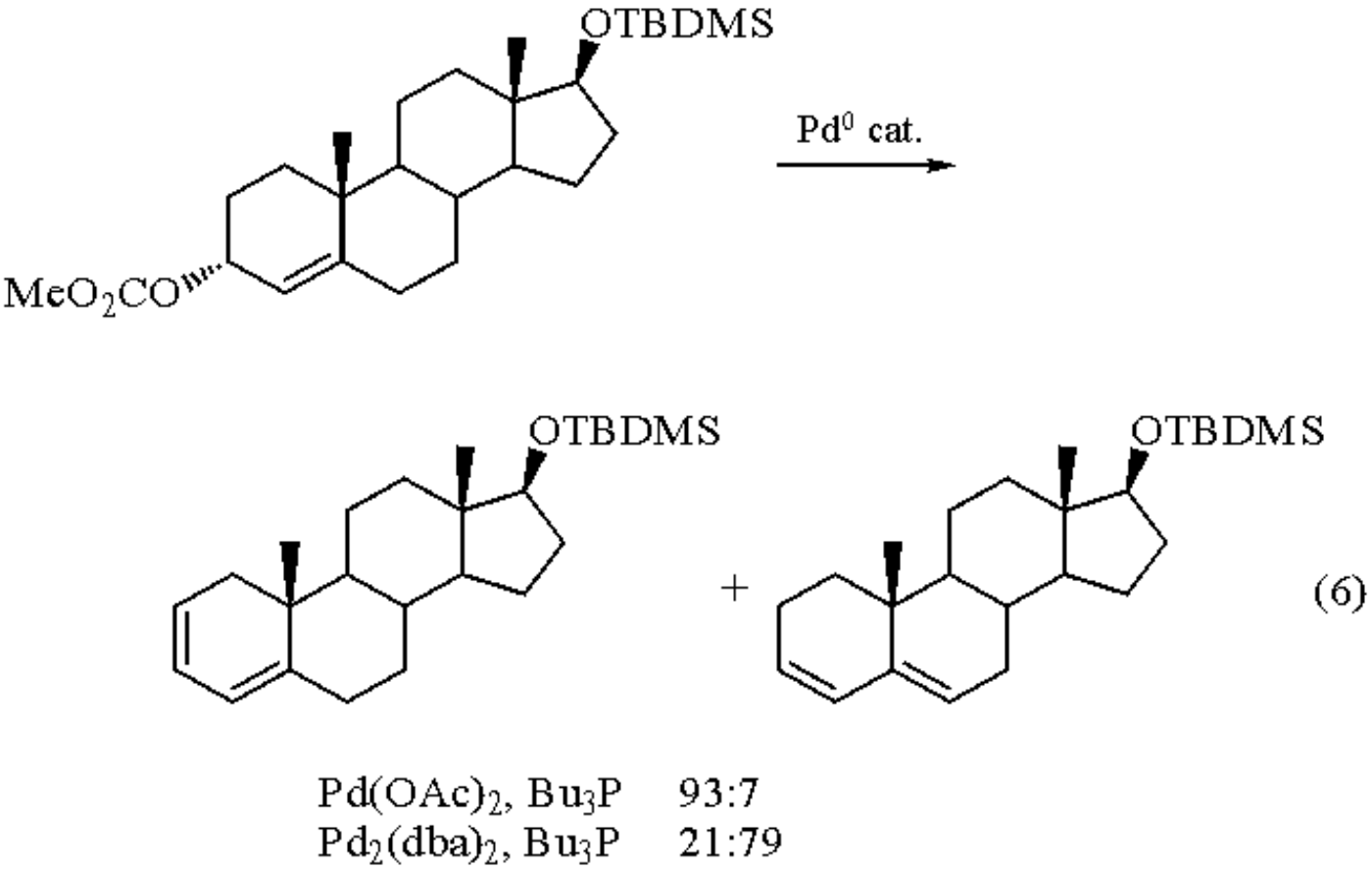

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Tris(dimethylamino)sulfonium Difluorotrimethylsilicate[1]

$(R_2N)_3S^+Me_3SiF_2^-$

(R = Me)

[59218-87-0] · $C_9H_{27}F_2N_3SSi$ · Tris(dimethylamino)sulfonium Difluorotrimethylsilicate · (MW 275.55) (R = Et)

[59201-86-4] · $C_{15}H_{39}F_2N_3SSi$ · Tris(diethylamino)sulfonium Difluorotrimethylsilicate · (MW 359.73)

(anhydrous fluoride ion source; synthesis of C-F compounds by nucleophilic displacement of sulfonates;[3] promoter for electrophilic reactions of silyl enolates of ketones and esters;[4-6] source of sulfonium cation capable of stabilizing or imparting high nucleophilic reactivity to other anions;[4,6,8a,10a] activator of vinylsilanes in Pd-catalyzed cross-coupling reactions;[7] also used for generation[8] and reactions[10] of α- and β-halo carbanions; hydrosilylation[11] and cyanomethylation[14] of ketones)

Alternate Name: TASF.

Physical Data: R = Me, mp 98-101 °C; R = Et, mp 90-95 °C.

Solubility: R = Me, sol MeCN, pyridine, benzonitrile; partially sol THF. R = Et, sol THF, MeCN. Both react slowly with MeCN.

Form Supplied in: R = Me, white crystalline solid, ~90% pure; major impurity is tris(dimethylamino)sulfonium bifluoride [$(Me_2N)_3S^+ HF_2^-$].

Analysis of Reagent Purity: mp; ^{19}F NMR δ (at 200 MHz, $CFCl_3$ standard) $TASMe_3SiF_2$ (CD_3CN) δ -60.3; $TASHF_2$ -145.8 (d, J_{HF} = 120 Hz).

Preparative Methods: the methyl derivative is prepared by the reaction of dimethylaminotrimethylsilane and ***Sulfur Tetrafluoride*** at -70 °C to rt in ether; the precipitated solid is filtered off.[1a] The ethyl derivative is best prepared by the reaction of ***N,N-Diethylaminosulfur Trifluoride*** (DAST) and diethylaminotrimethylsilane.[1b,11b]

Handling, Storage, and Precautions: because of the extreme hygroscopic nature of this compound, it is best handled in a dry box or a polyethylene glove bag filled with high purity nitrogen. Use in a fume hood.

Introduction.

The acronym TASF has been used to refer to both $(Me_2N)_3S^+F_2Me_3Si^-$ and $(Et_2N)_3S^+F_2Me_3Si^-$. To eliminate confusion, the sulfonium salt containing dimethylamino groups is referred to as TASF(Me), and the sulfonium salt containing diethylamino groups is referred to as TASF(Et). Reactions of both reagents are similar. Since both of these salts can be prepared in a rigorously anhydrous state, they have an advantage over quaternary ammonium fluorides which usually contain some water. TASF(Me) has a slight advantage over TASF(Et) in that it is highly crystalline and easier to prepare in a high state of purity, whereas TASF(Et) has an advantage over TASF(Me) in that it has greater solubility in organic solvents. The tris(dialkylamino)sulfonium cation is often referred to by the acronym TAS.

TASF is a source of organic soluble fluoride ion[2] with a bulky noncoordinating counter ion (eq 1).[9]

$$TAS^+ Me_3SiF_2^- \rightleftharpoons Me_3SiF + TAS^+ + F^- \qquad (1)$$

Fluoride Ion Source in Nucleophilic Displacements.

TASF(Me) can be used to prepare fluorides from halides[1b] and sulfonates[3] under relatively mild conditions (eq 2).

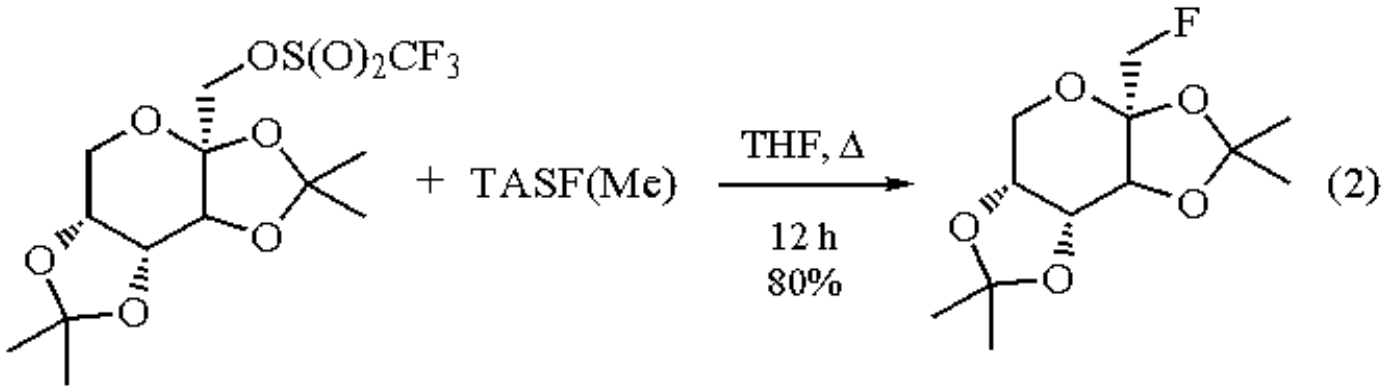

Generation of Enolates and Enolate Surrogates from Enol Silanes.

Enol silanes react with TASF(Et) to give highly reactive naked enolates which have been characterized by NMR and electrochemical measurements.[4] These enolates, generated in situ, can be regioselectively alkylated without complications from polyalkylation or rearrangements of the alkylating agent (eq 3).

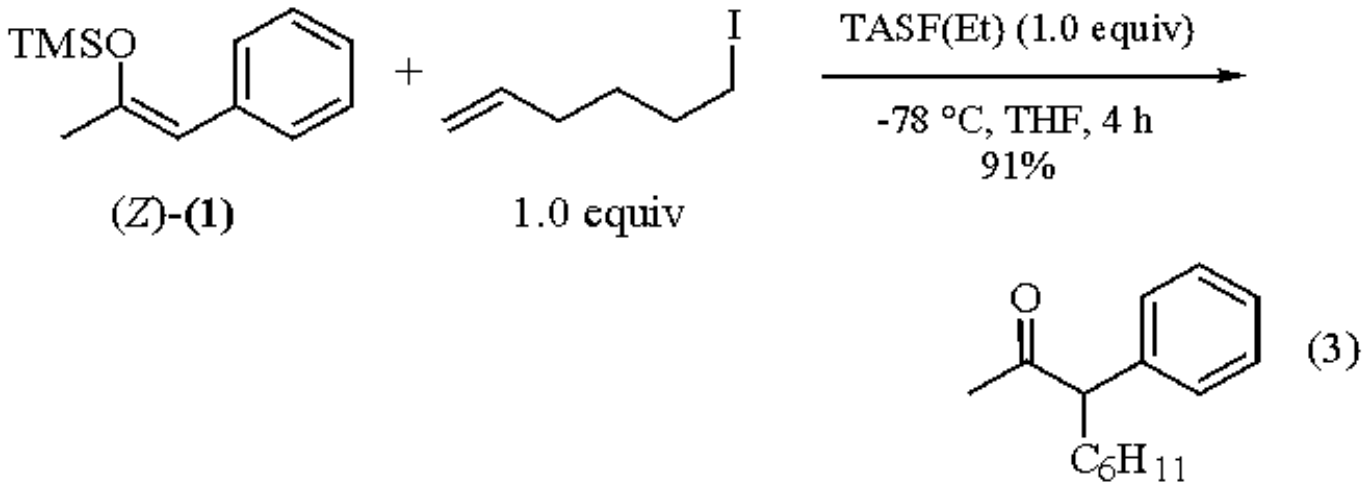

In the presence of excess ***Fluorotrimethylsilane***, TASF(Et) catalyzes aldol reactions of silyl enol ethers and aldehydes.[4] The stereochemical course of the reaction (*syn* selectivity, independent of the enol geometry, (*Z*)- or (*E*)-(**1**), eq 4), has been interpreted as arising from an extended transition state in which steric and charge repulsions are minimized.

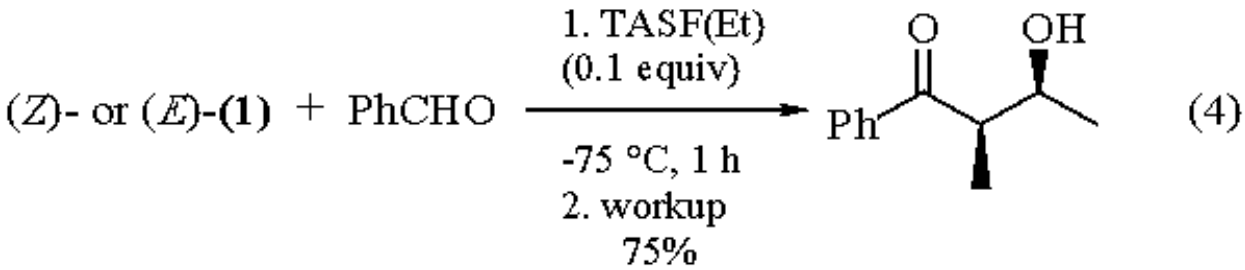

Very potent carbon nucleophiles formally equivalent to ester enolates are generated by the interaction of TASF(Me) with unhindered trialkylsilyl ketene acetals. In contrast to lithium enolates, these TAS enolates add 1,4 (nonstereoselectively) to α,β-unsaturated ketones. These adducts can be alkylated in situ to form two new C-C bonds in one pot, or they can be hydrolyzed to give 1,5-dicarbonyl compounds (eq 5).[5a]

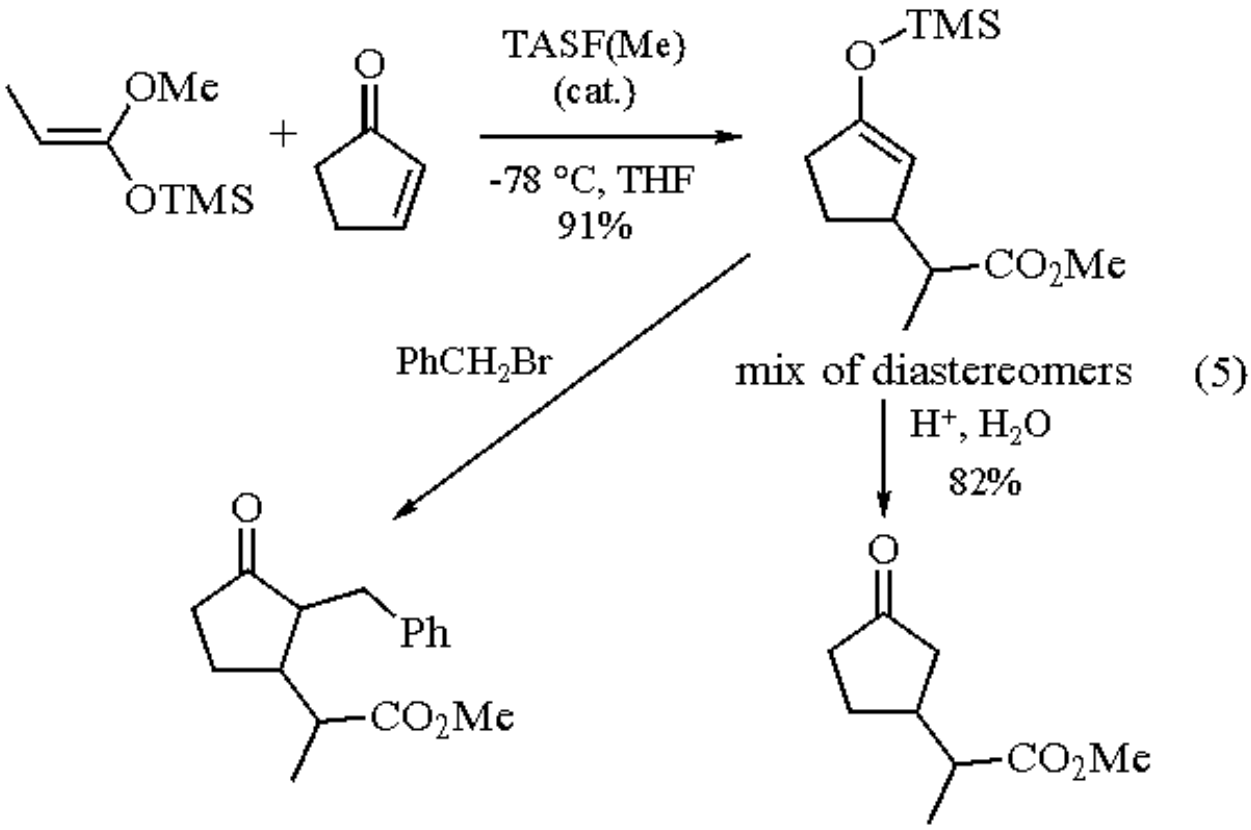

Conjugated esters undergo sequential additions to form polymers (group transfer polymerization).[5b] The molecular weight and the end group functionality of the polymer can be controlled by this method. Mechanistic studies indicate an associative intramolecular silicon transfer process via (**2**), with concomitant C-C bond formation during the polymer growth (eq 6).

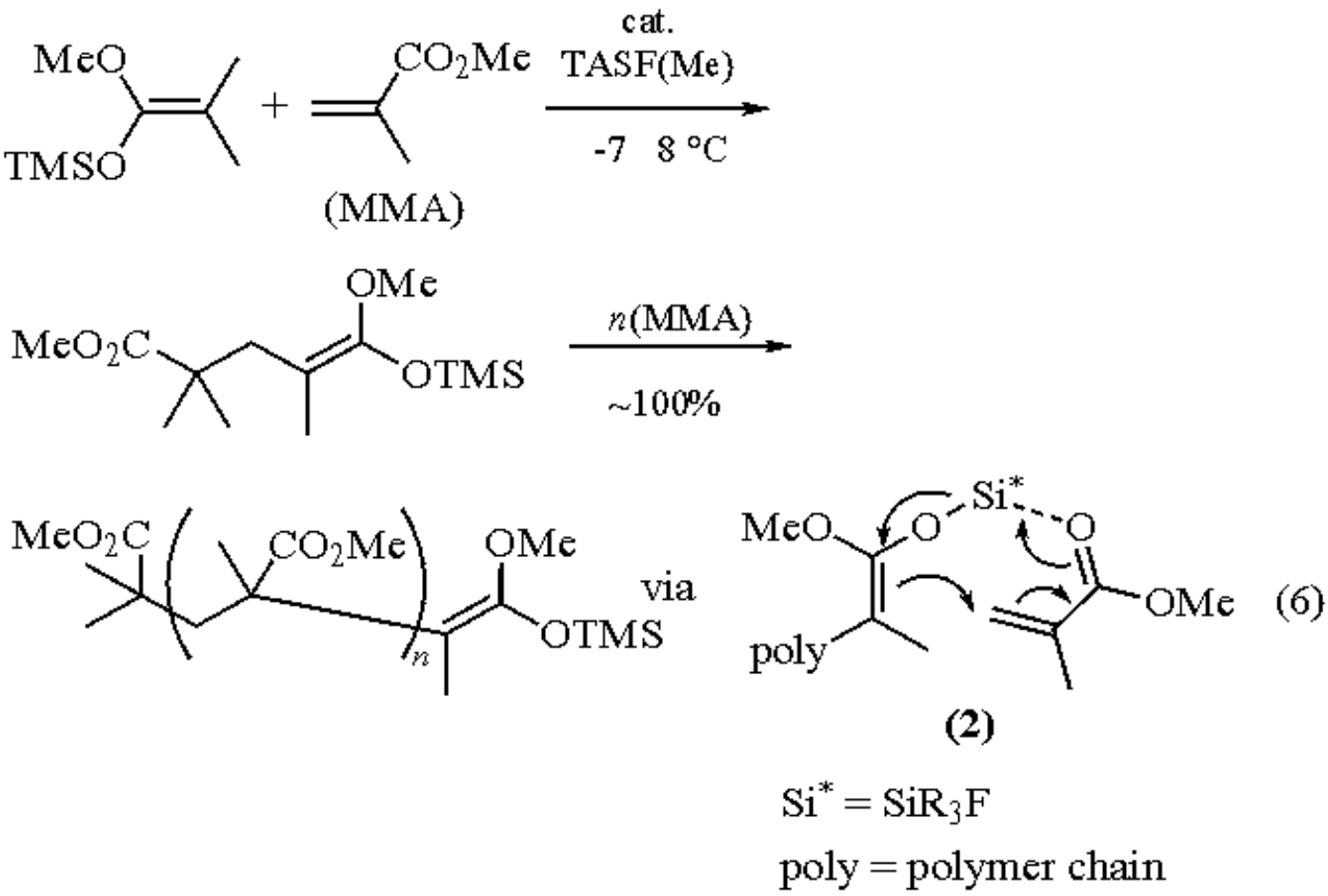

Silyl enol ethers and ketene silyl acetals add to aromatic nitro compounds in the presence of TASF(Me) to give intermediate dihydro aromatic nitronates which can be oxidized with ***Bromine*** or ***2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*** to give α-nitroaryl carbonyl compounds;[6a] the latter are precursors for indoles and oxindoles.[6b] The reaction is widely applicable to alkyl-, halo-, and alkoxy-substituted

aromatic nitro compounds, including heterocyclic and polynuclear derivatives (eq 7).

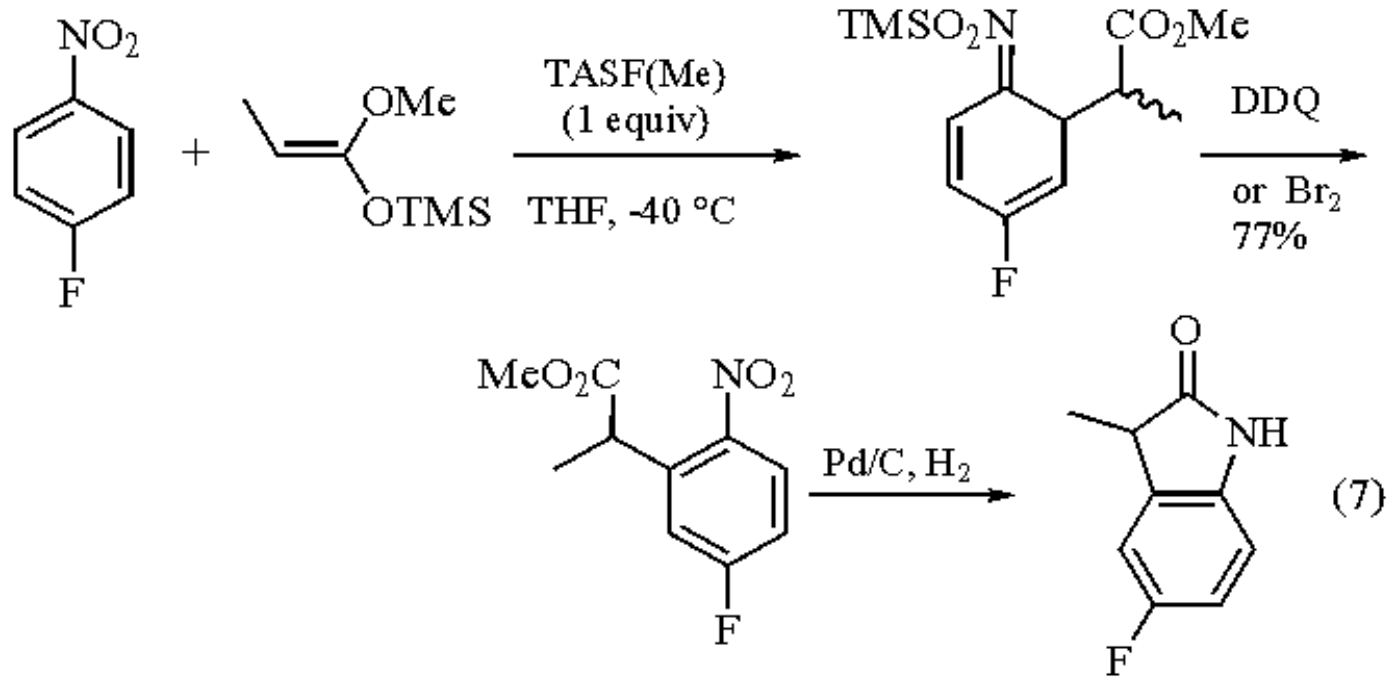

(7)

Cross-Coupling Reactions.

TASF(Et) activates vinyl-, alkynyl-, and allylsilanes in the Pd-mediated cross-coupling with vinyl and aryl iodides and bromides.[7] As illustrated in eqs 8-10, the reaction is stereospecific and chemoselective. This cross-coupling protocol is remarkably tolerant towards a variety of other functional groups such as carbonyl, amino, hydroxy, and nitro. Vinylsilanes can be synthesized from ***Hexamethyldisilane*** and vinyl iodides in the presence of TASF(Et) (eq 10) via cleavage of a Si-Si bond.[7a] Aryl iodides can also be synthesized by this method. TASF is superior to ***Tetra-n-butylammonium Fluoride*** for these reactions. In the absence of a vinylsilane reagent, one of the methyl groups from the difluorotrimethylsilicate is substituted for the halide (eq 11).[7d]

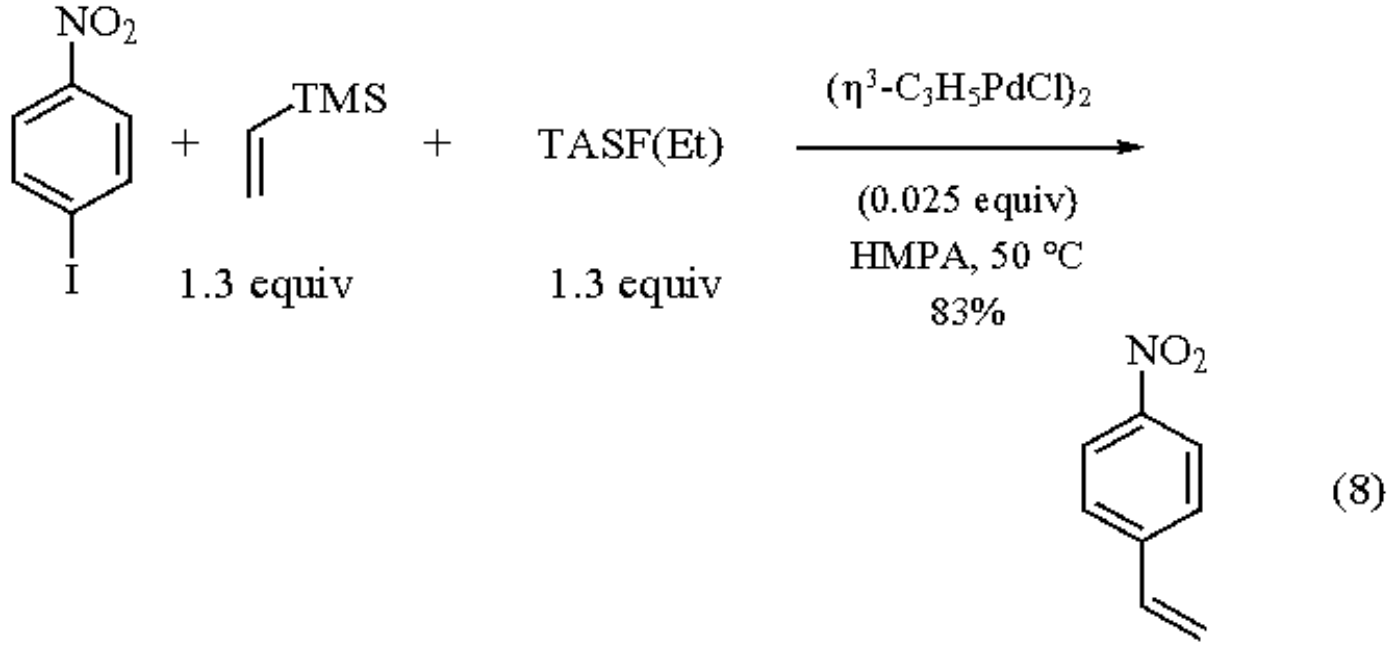

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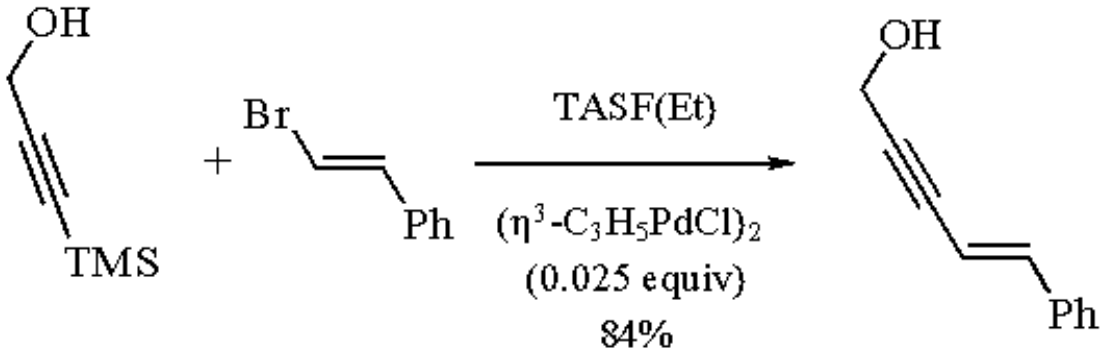

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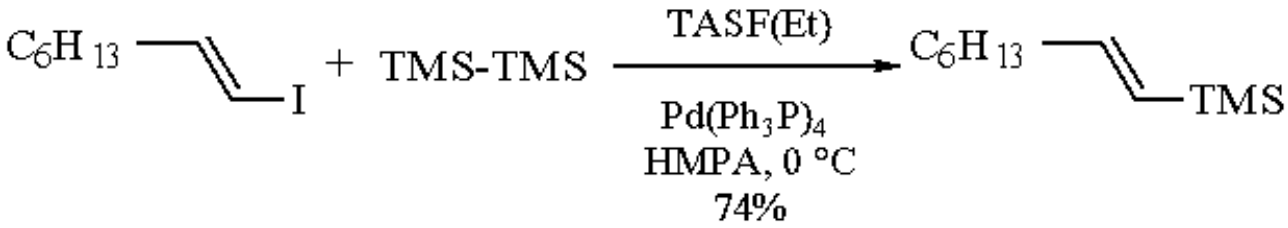

(10)

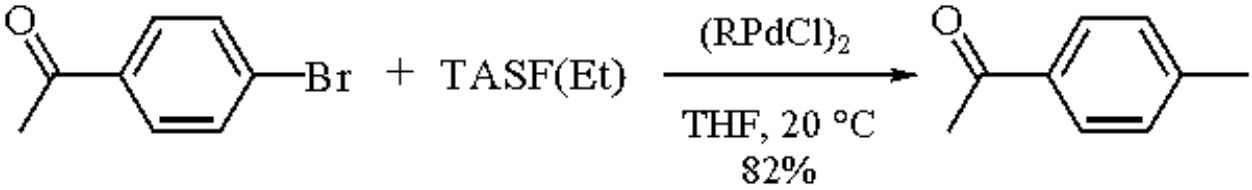

(11)

Generation and Reactions of Unusual Carbanions.

Both α- and β-halo carbanions are generally labile species and their generation and reactions require extremely low temperatures. TASF(Me) has been used to prepare several stable and isolable perfluorinated carbanions (eq 12)[8a] or alkoxides.[8b] As compared to the corresponding metal salts, the TAS^+ counterion has little coordination to the fluorines of the anion,[9] and this presumably slows the decomposition of the TAS salts to carbenoids or alkenes. Addition of α- and β-halo carbanions to carbonyl compounds may be achieved by the in situ generation of these species by the reaction of TASF(Et) with the corresponding silylated derivatives (eq 13).[10]

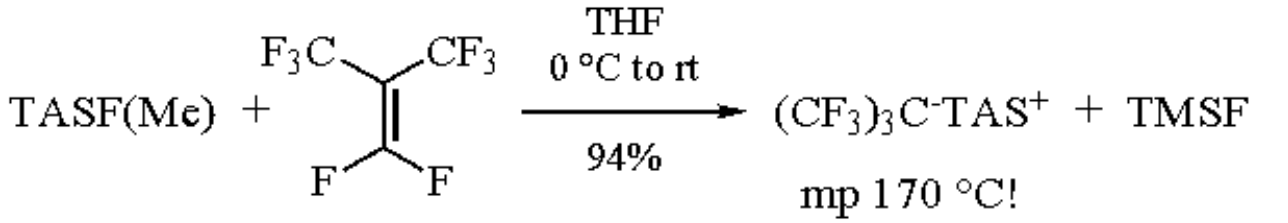

(12)

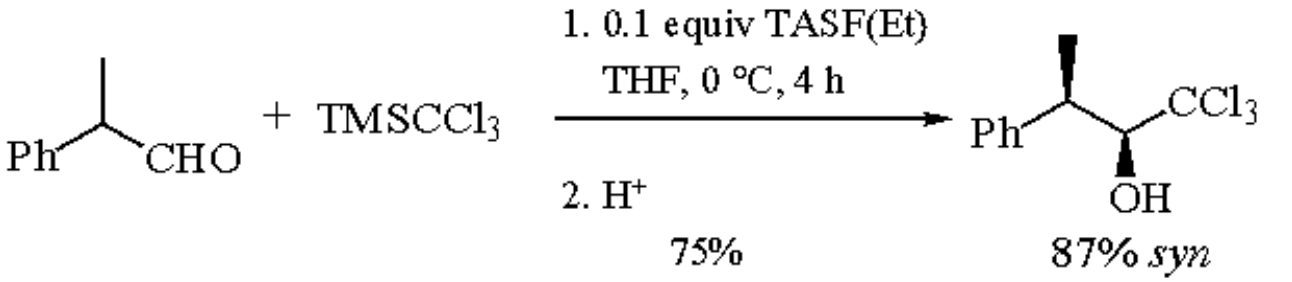

(13)

Other Applications.

TASF(Et) catalyzes the addition of ***Dimethyl(phenyl)silane*** to α-alkoxy, -acyl or -amido ketones to give the corresponding *anti* aldols (eq 14).[11] This complements the acid-catalyzed reduction which gives the *syn* isomer.

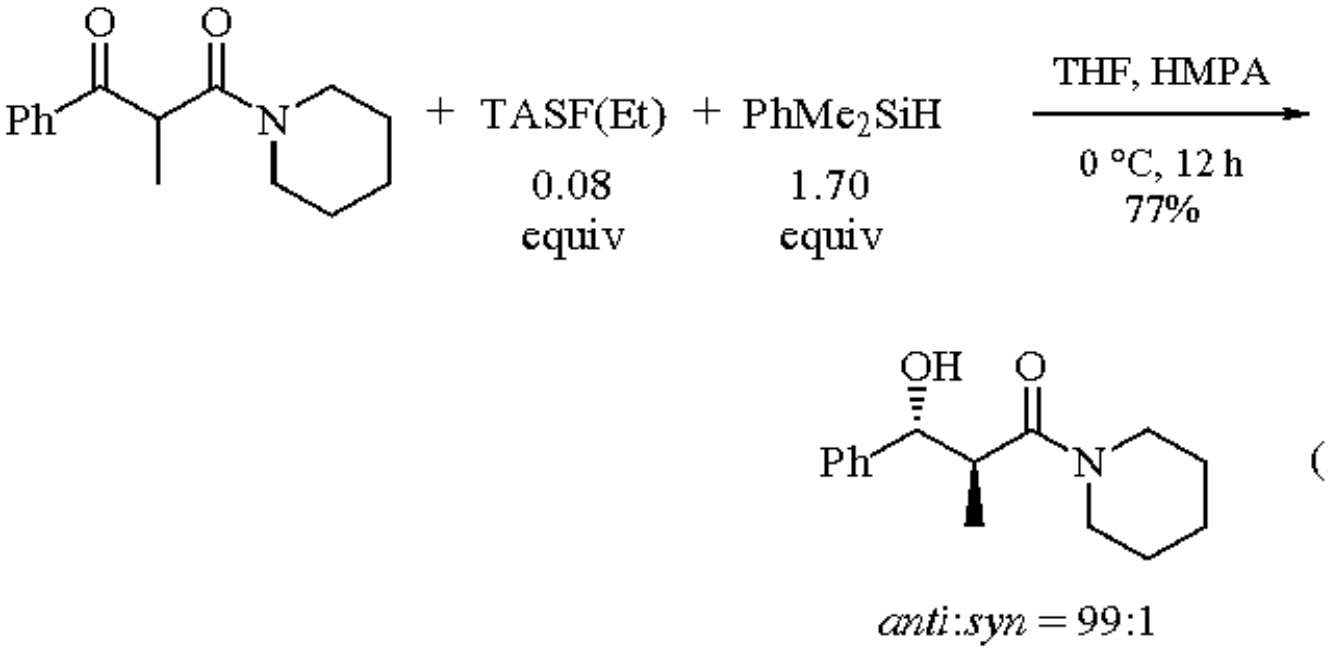

Dimethyl(phenyl)silane will reduce aldehydes and ketones to hydroxyl compounds under very mild conditions in the presence of a catalytic amount of TASF(Et).[11c]

Aryl or vinyl anions can be generated by the reaction of the corresponding vinyl iodide with Bu_3Sn anion, which in turn is produced from TASF(Et) and $Bu_3SnSiMe_3$. With an appropriately placed carbonyl group, an intramolecular cyclization ensues (eq 15).[12]

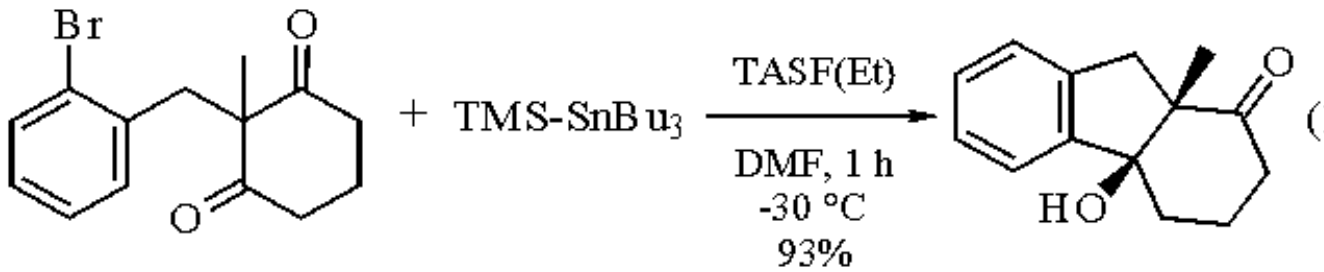

A useful variation of the Peterson alkenation relies on the generation of α-silyl carbanions from geminal disilyl compounds containing an additional stabilizing group (CO_2R, SPh, SO_2Ph, OMe, CN, Ph) at the α-carbon.[13] A related reaction is the cyanomethylation of ketones and aldehydes with ***Trimethylsilylacetonitrile*** in the presence of TASF(Me).[14] TASF(Me) was found to be the best fluoride ion source for the synthesis of aryl trifluoromethyl sulfones from the corresponding sulfonyl fluorides and ***Trifluoromethyltrimethylsilane*** or Me_3SnCF_3 (eq 16).[15]

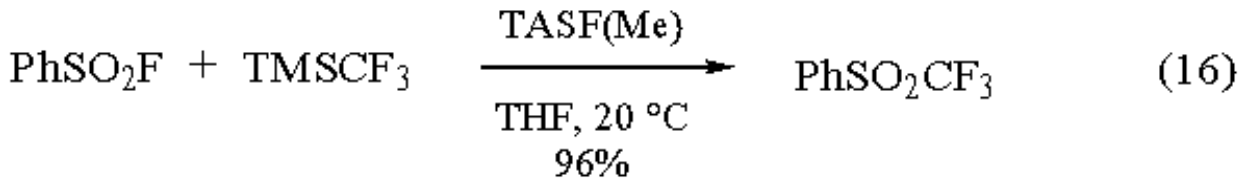

The carbanions formed by scission of a C-Si bond with TASF can also be oxygenated. Benzylic trimethylsilyl groups can be converted to hydroxyl groups in 20-95% yield by reaction with TASF(Me) in the presence of oxygen and ***Trimethyl Phosphite*** (eq 17).[16] No other source of fluoride ion was found that could replace TASF.

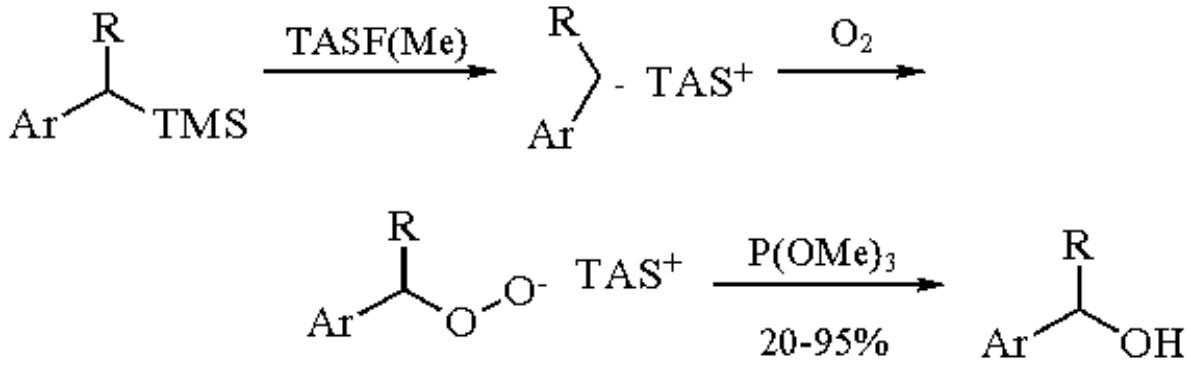

(17)

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Tris(dimethylamino)borane[1]

$B(NMe_2)_3$

[4375-83-1] · $C_6H_{18}BN_3$ · Tris(dimethylamino)borane · (MW 143.08)

(macrolactamization reagent;[4] selective monoalkylation of tetraaza macrocycles;[5] amide and enamine formation[7])

Physical Data: mp -10 °C; bp 147-148 °C; *d* 0.817 g cm^{-3}.

Solubility: sol most aprotic organic solvents; reacts readily with water and alcohols.

Form Supplied in: colorless liquid, commercially available.

Handling, Storage, and Precautions: air and moisture sensitive. Handle and store under nitrogen, use in a fume hood.

Tris(dimethylamino)borane undergoes facile transamination reactions with primary and secondary amines to give higher homologs of tris(alkylamino)boranes.[2] Reaction with triamines, such as 3,3´-diaminodipropylamine, affords unique heterocyclic aminoboranes (eq 1).[3]

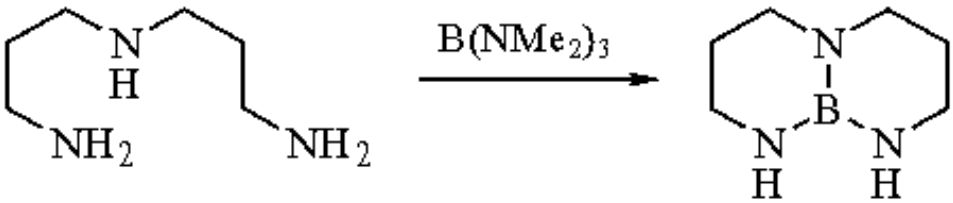

(1)

An elegant application of this reaction has been found in the synthesis of macrocyclic spermidine alkaloids. The key step in the synthesis involves a $B(NMe_2)_3$-mediated macrolactamization reaction of triamino ester (**1**) (eq 2). The reaction is carried out with $B(NMe_2)_3$ in refluxing xylene and directly affords the macrolactam (**3**) in high yield.[4] The reaction is believed to proceed via the intermediate (**2**), which allows for a boron-templated cyclization. The scope of this macrolactamization reaction is limited to triamino ester precursors. Attempted cyclization of the corresponding o-monoamino esters failed to give any lactam.

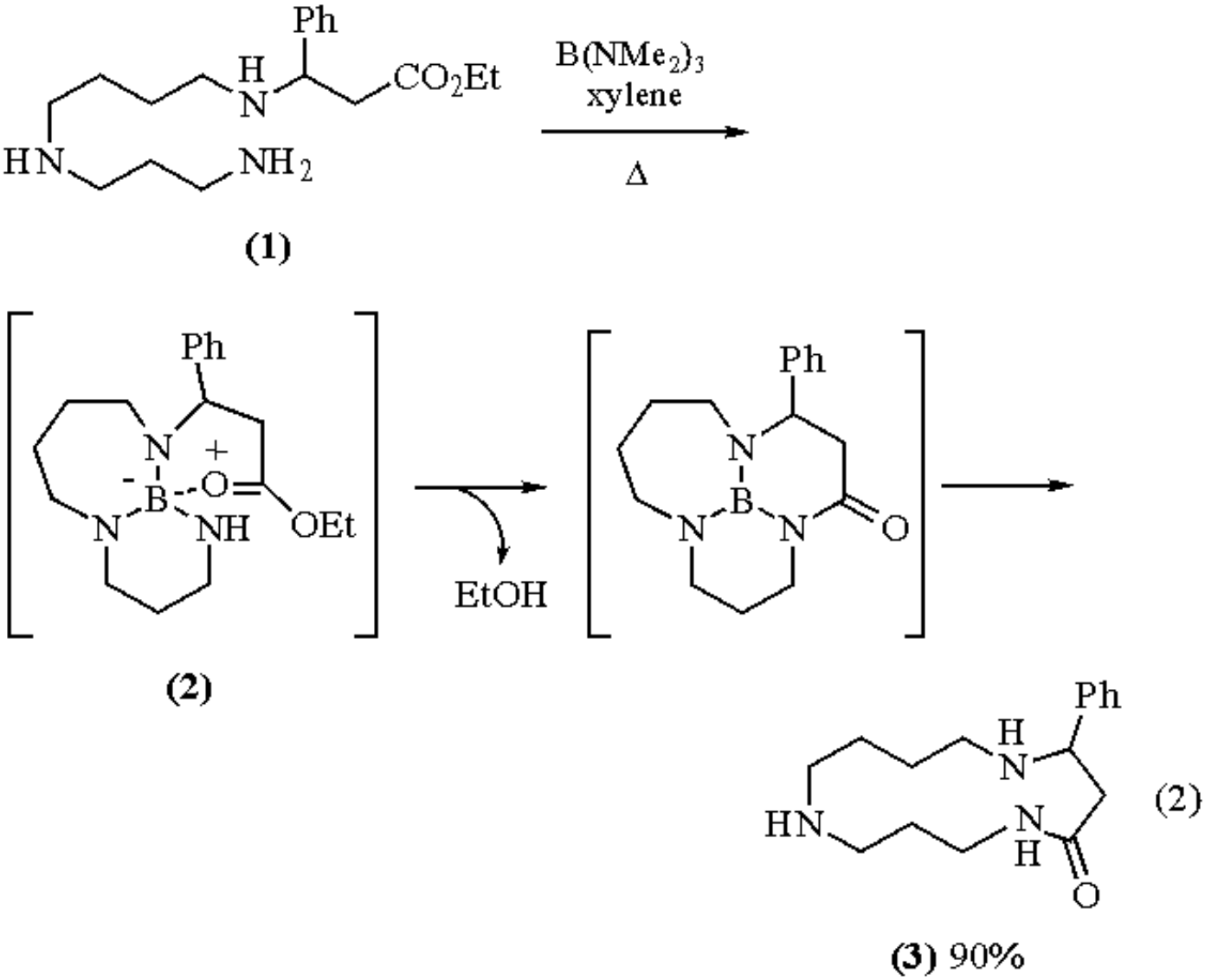

A related application of $B(NMe_2)_3$ has been utilized in the synthesis of monoalkylated derivatives of tetraaza macrocycles.[5] Reaction of $B(NMe_2)_3$ with a tetraaza macrocycle affords a polycyclic aminoborane[6] which incorporates three out of the four nitrogen atoms, thus allowing for selective monoalkylation of the single unprotected nitrogen (eq 3).

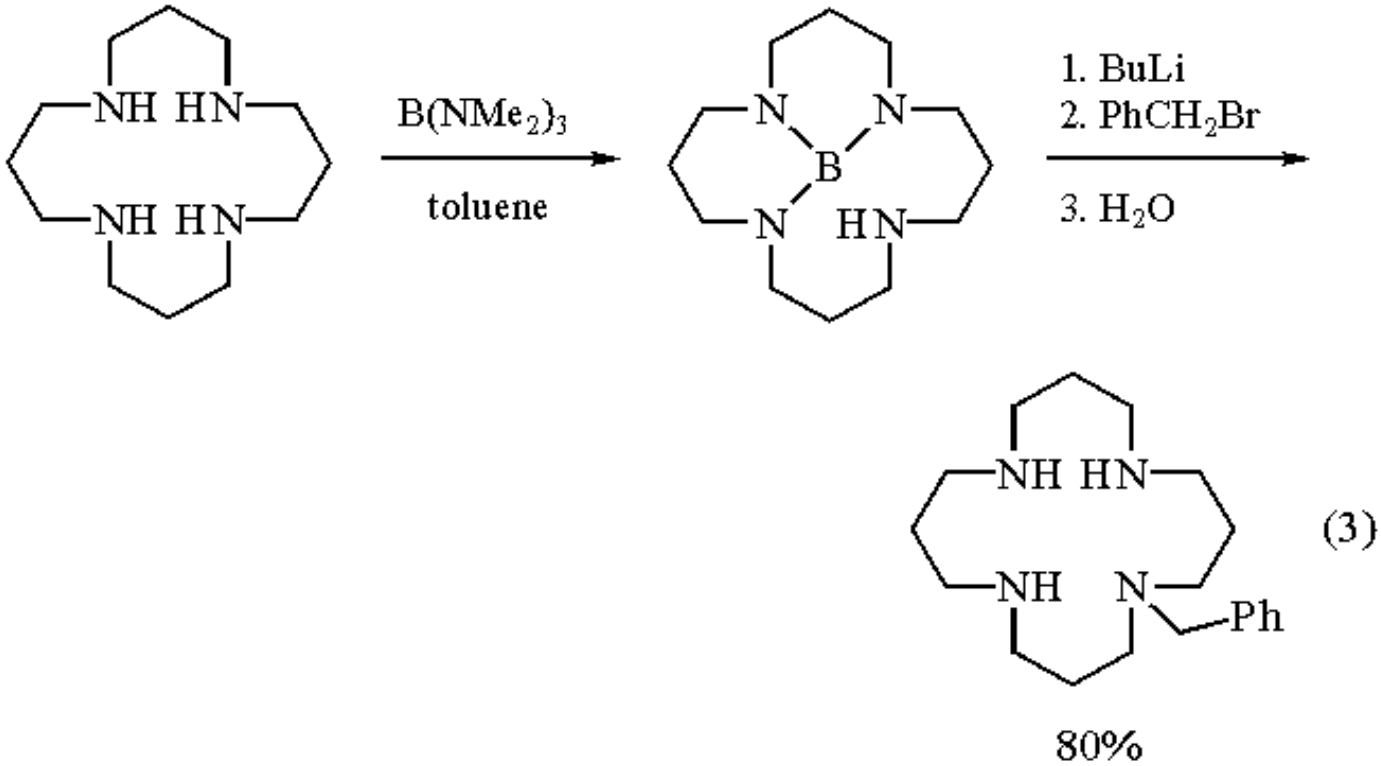

Amidation Reactions with $B(NMe_2)_3$ and Higher Homologs.

Tris(dialkylamino)boranes react readily with carboxylic acids to give amides.[7] This reaction, however, has not been widely used in recent years. The reaction is typically carried out in benzene, in the absence of any catalyst, and one molar equivalent of the boron reagent is required for complete reaction.[8] Similarly, reaction with 1,3-diketones gives enamino ketones (eq 4).[7] When the 1,3-diketone is unsymmetrical, then the least-hindered ketone is attacked selectively. Reaction with ketones to give enamines is rather slow; however, in the presence of an acid catalyst, high yields are possible.[7]

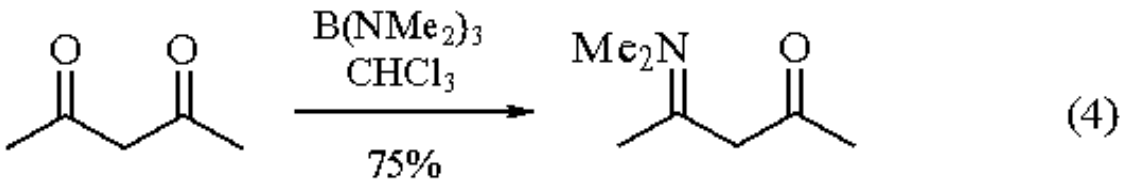

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Tris(dimethylamino)methane[1]

$(Me_2N)_3CH$

[5762-56-1] · $C_7H_{19}N_3$ · Tris(dimethylamino)methane · (MW 145.29)

(reactive aminomethylenating reagent (formylating reagent) for CH_2- and NH_2-acidic compounds; can serve as a source for bis(dimethylamino)carbene)

Alternate Names: TDAM; *N,N,N´,N´,N´´,N´´*-hexamethylmethanetriamine.

Physical Data: bp 42-43 °C/12 mmHg; *n*20D = 1.4360.

Solubility: miscible with nonpolar aprotic, water-free solvents; reacts with protic solvents such as water, alcohols, and even aprotic, weak CH-acidic solvents such as acetone and acetonitrile on heating.

Form Supplied in: colorless to light yellow liquid; strong amine smell.

Analysis of Reagent Purity: ^{1}H NMR spectrum of a neat sample.

Preparative Methods: can be prepared by reaction of lithium dimethylamide with either *N,N,N´,N´*-tetramethylformamidinium salts[2] or bis(dimethylamino)acetonitrile (eqs 1 and 2).[3] The lithium dimethylamide solution can be prepared from lithium, dimethylamine, and naphthalene in dry THF.[4] Lithium dimethylamide can be replaced by sodium dimethylamide,[2] which is accessible in situ from ***Sodium Hydride***, dimethylamine, and catalytic amounts (~20%) of ***Trimethyl Borate***.[5]

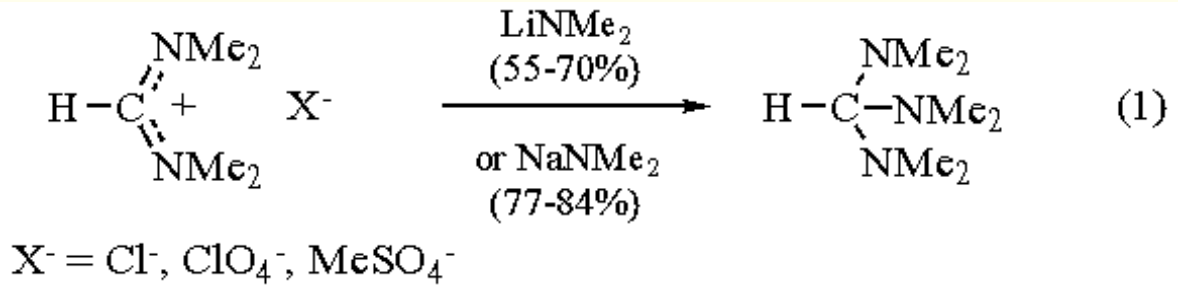

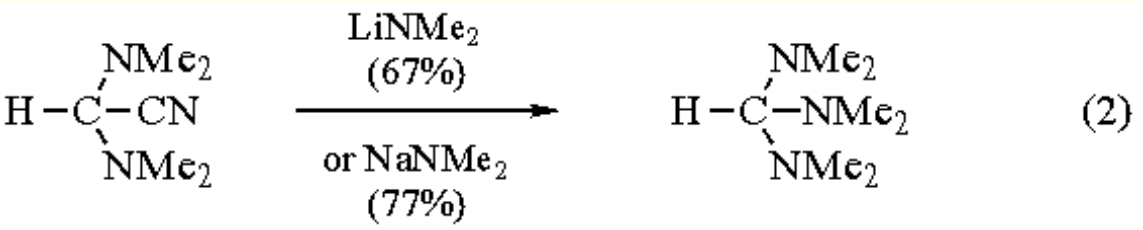

In the reaction of tetramethylformamidinium chloride with triphenylphosphonium ylides, TDAM is formed as a byproduct.[6] TDAM is also obtained as a byproduct in the synthesis of alkanethiobis(dimethylamino)methanes from sodium alkanethiolates and *N,N,N´,N´*-tetramethylformamidinium methylsulfate or from aminal esters and alkanethiols by disproportionation of the primary products.[7] ***Triethyl Orthoformate*** reacts with lithium dimethylamide (prepared in situ from lithium and dimethylamine) in HMPA to give TDAM.[8] In an equilibrium reaction, DMF acetals react with dimethylamine to give TDAM.[9] This reaction can be used on a preparative scale, if the dimethylamine is introduced at about 100 °C in the presence of 2,4,6-trimethylphenol as catalyst.[10] The transamination of bis(dimethylamino)alkoxymethanes with excess dimethylamine affords TDAM.[11] TDAM is produced in good yields in the reaction of tetrakis(dimethylamino)titanium with ***N,N-Dimethylformamide*** in ether (eq 3).[12]

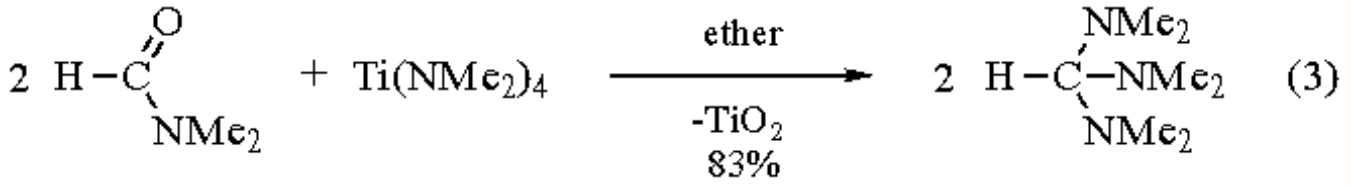

Good yields of TDAM can be obtained by reduction of *N,N,N´,N´,N´´,N´´*-hexamethylguanidinium chloride with a mixture of sodium hydride and ***Sodium Bis(2-methoxyethoxy)aluminum Hydride*** (75%)[13] or by a mixture of sodium hydride and trimethyl borate (eq 4).[5]

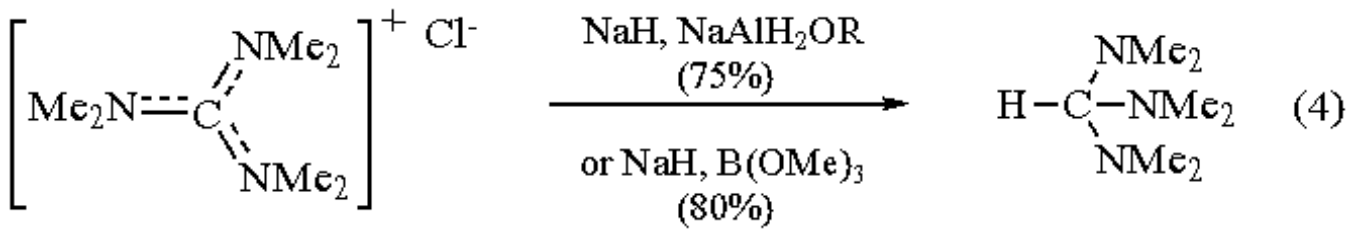

Handling, Storage, and Precautions: should be handled and used with strict exclusion of atmospheric moisture. The product should be stored in a tightly sealed container under a dry nitrogen or argon atmosphere in a refrigerator or freezer. Use in a fume hood.

General Considerations.

Conductivity measurements[4] demonstrate that tris(dimethylamino)methane dissociates into dimethylamide anions and *N,N,N´,N´*-tetramethylformamidinium cations (eq 5). This equilibrium enables an understanding of the important reactions of TDAM. Thus XH_2-acidic compounds are deprotonated by the reagent; if the anions thus formed are small and relatively unstabilized, they combine with formamidinium ions to give adducts which eliminate dimethylamine to form a dimethylaminomethylene group. This mechanism has been confirmed by ^{1}H NMR investigations.[14] If the first step involves large, well-stabilized anions, the reaction stops at the stage of ion pairs.

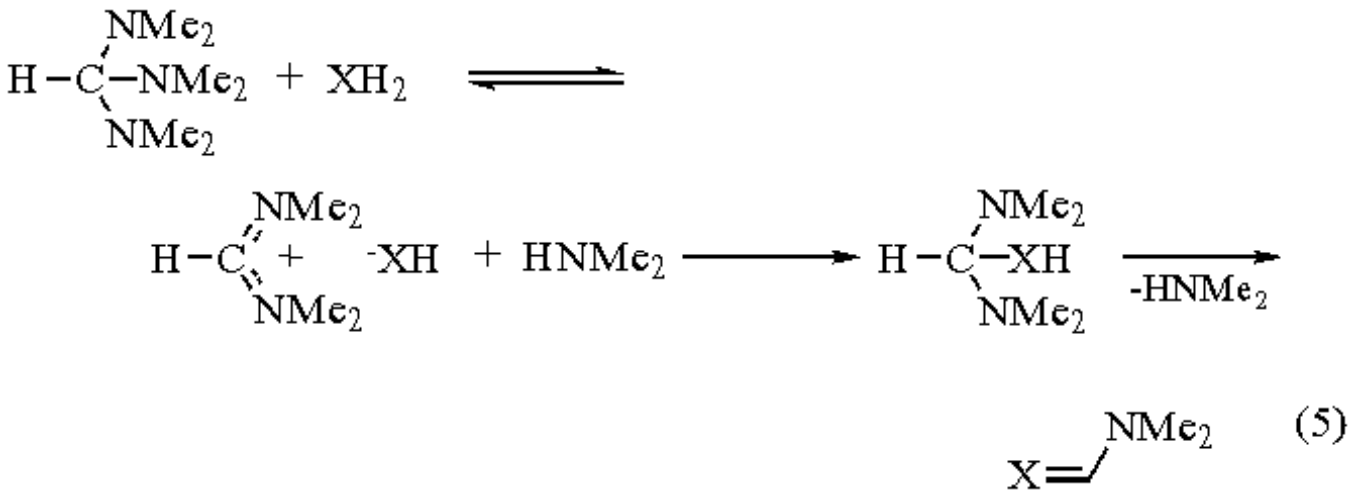

Reactions.

Even weak CH-acidic compounds such as ketones,[15-22] nitriles and dinitriles,[21,23] lactones,[24-29] 2- or 4-nitro-1-alkylbenzenes,[21,30,31] fluorene and xanthene,[14] 4-methylpyridine,[21] lactams,[15] *N*-substituted α-amino esters,[32] and methylenediphosphonates[33] react according to this scheme. The condensation products contain a masked aldehyde function and are frequently used as difunctional intermediates. Two applications are photooxidation to α-dicarbonyl compounds[15,25,28] and condensation with suitable difunctional compounds to form heterocyclic rings, including pyrimidines,[16-18,26] pyrazoles,[17,19] isoxazoles,[20] 1,4-dihydropyridines,[32] and indoles.[30,31] Eqs 6-11 show some examples.

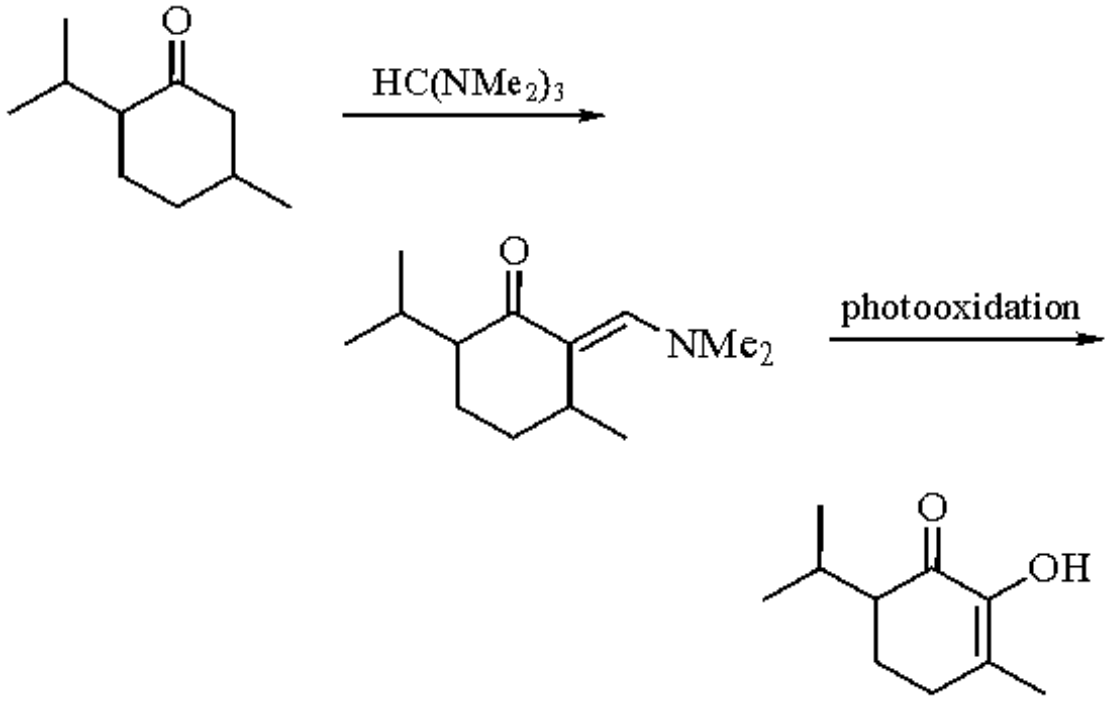
O
HC(NMe2)3
O
NMe2
photooxidation
O
OH

(6)

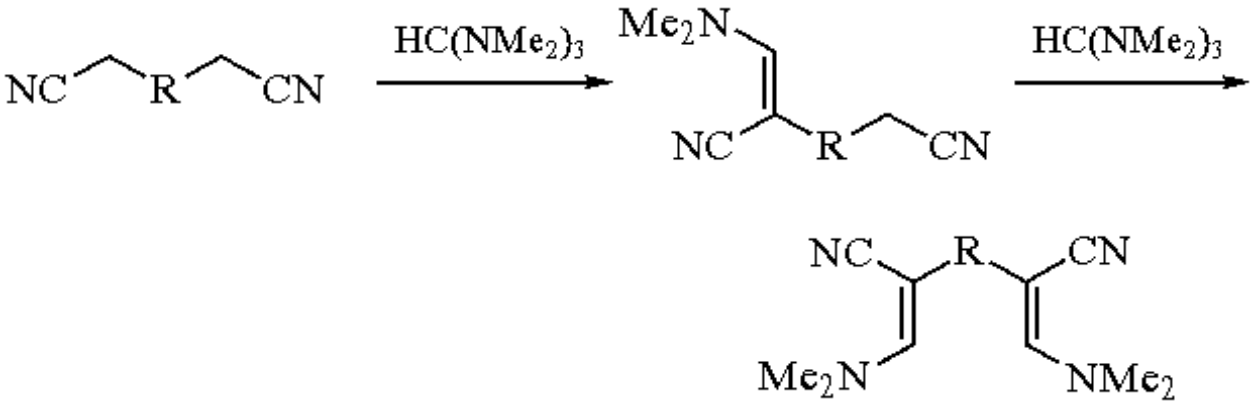
NC
R
CN
HC(NMe2)3
Me2N
NC
R
CN
HC(NMe2)3
NC
R
CN
Me2N
NMe2

(7)

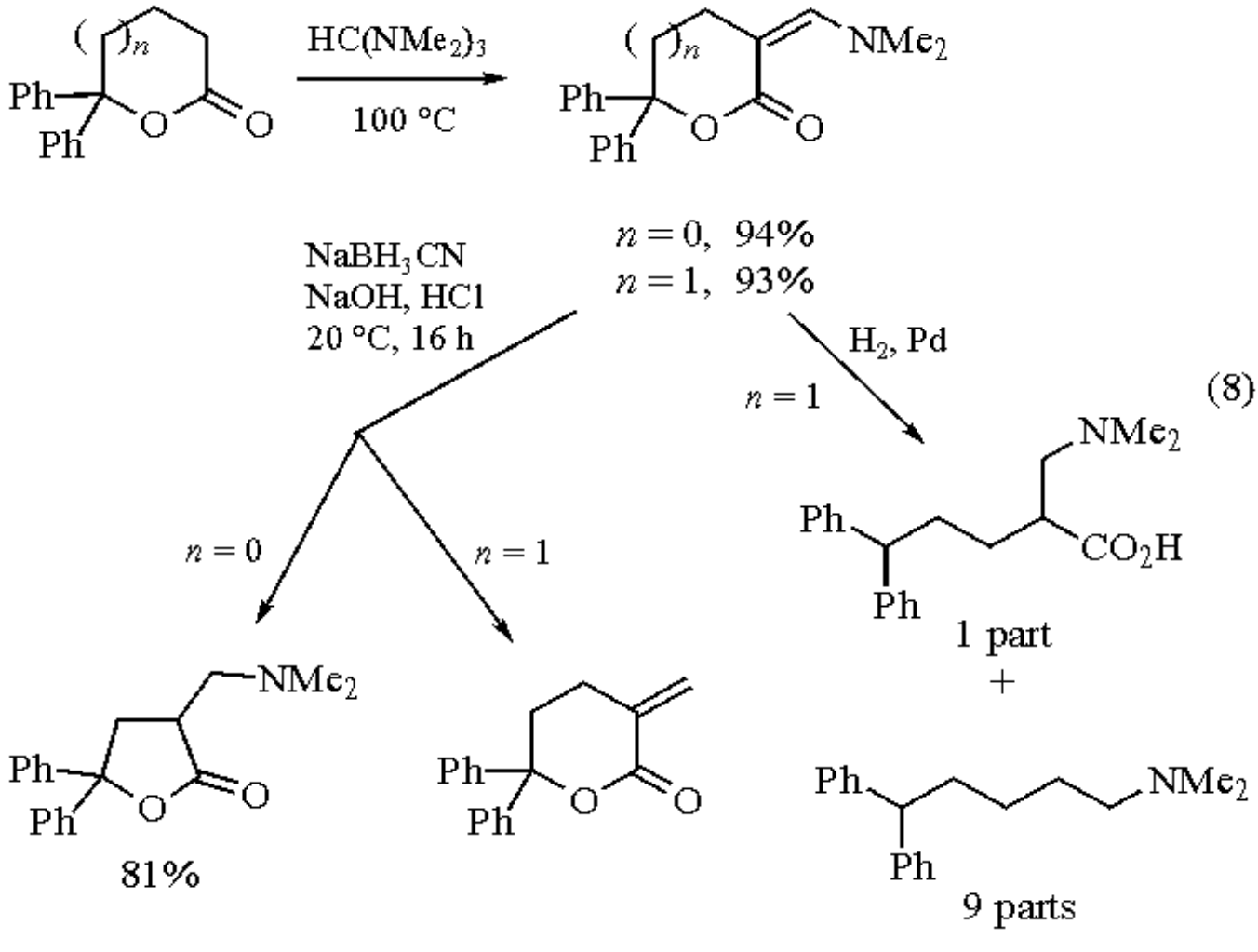
HC(NMe2)3
100 °C
n = 0, 94%
n = 1, 93%
NaBH3CN
NaOH, HCl
20 °C, 16 h
H2, Pd
n = 1
n = 0
n = 1
81%
1 part
+
9 parts

(8)

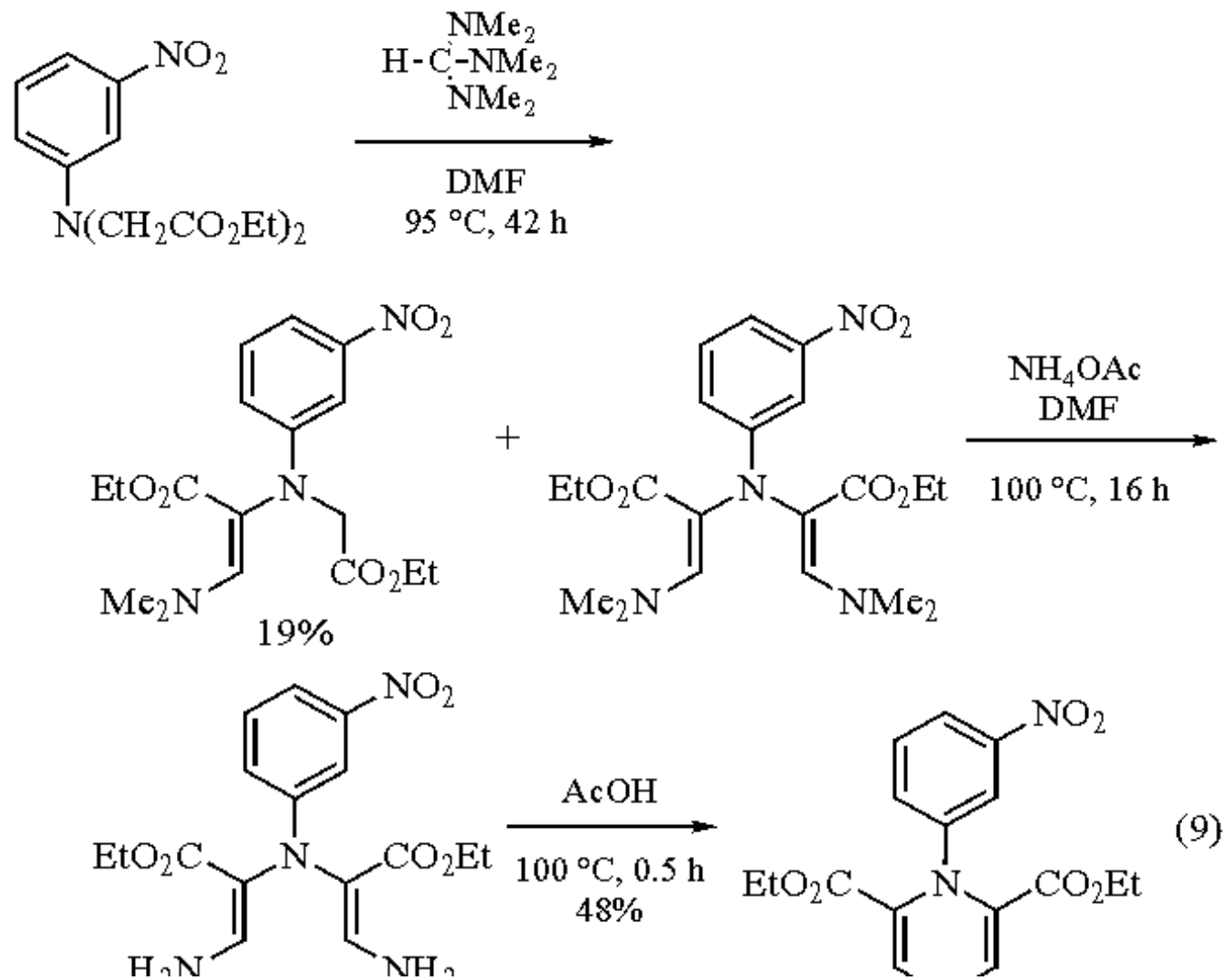
DMF
95 °C, 42 h
19%
+
NH4OAc
DMF
100 °C, 16 h
AcOH
100 °C, 0.5 h
48%

(9)

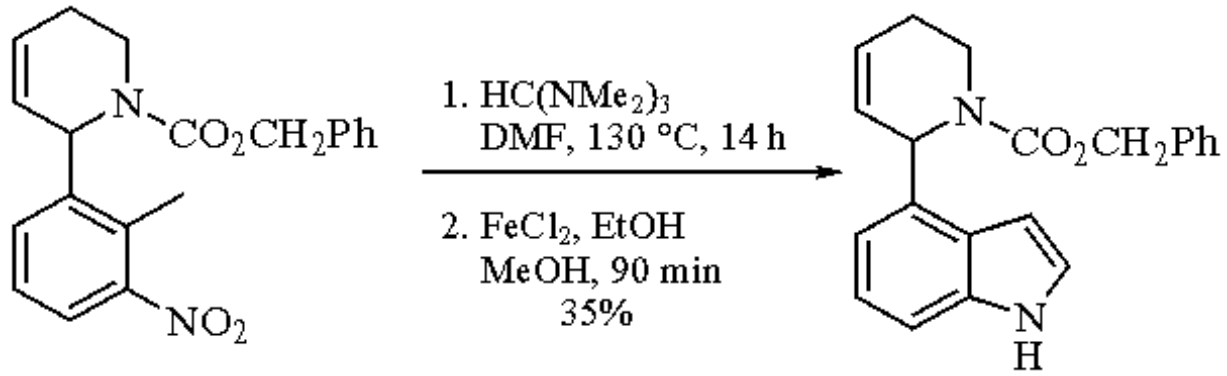

(10)

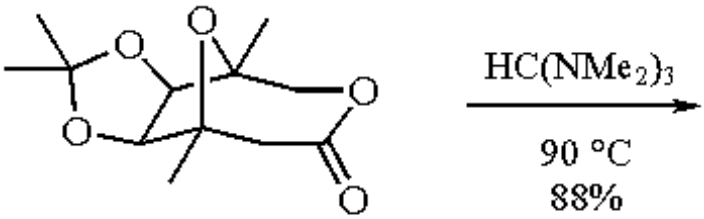

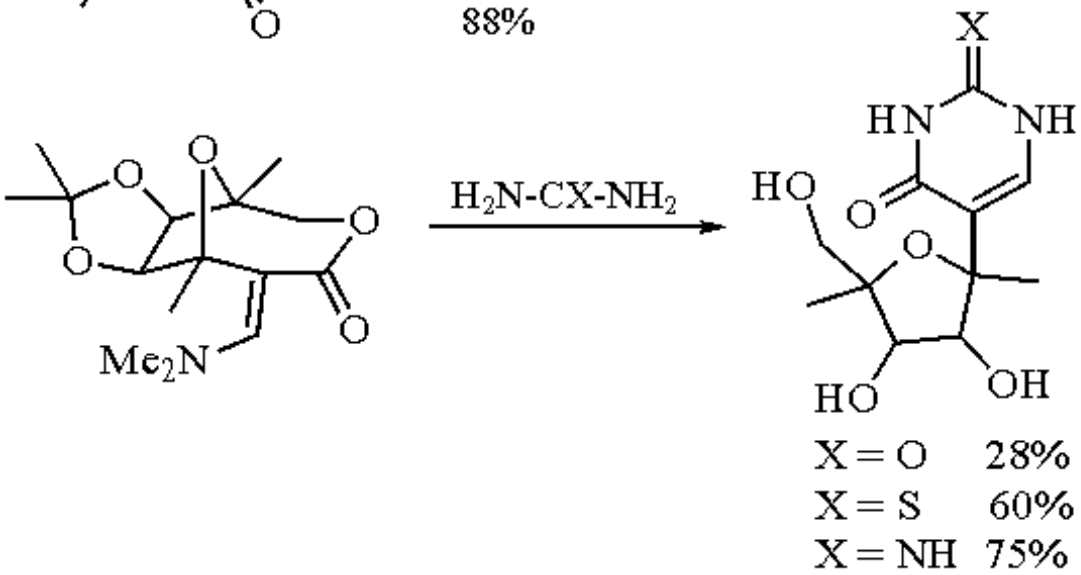

(11)

If elevated temperatures are required for reactions, it should be noted that tris(dimethylamino)methane decomposes to tetrakis(dimethylamino)ethylene at 150-190 °C (eq 12).[34]

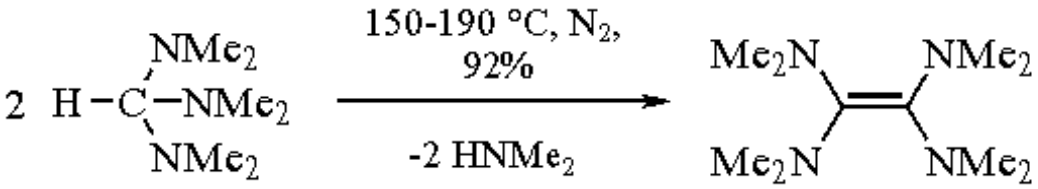

(12)

Tertiary XH-acidic compounds, such as phenylacetylene[35] and α-diazo carbonal compounds[36] undergo bis(dimethylamino)methylation with this reagent, whereas α,α-disubstituted aldehydes are converted to enamines (eqs 13-15).[37]

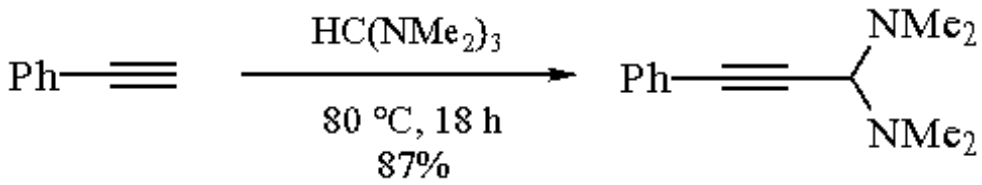

(13)

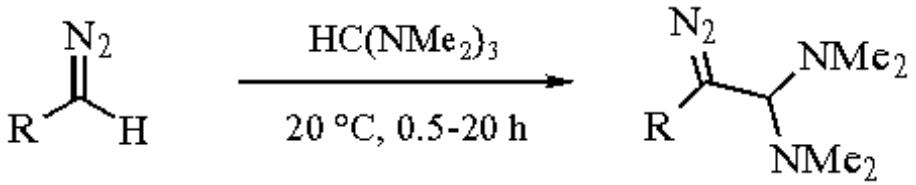

(14)

$R = CO_2R^1$, CONMePh, COMe, $PO(OR^1)_2$

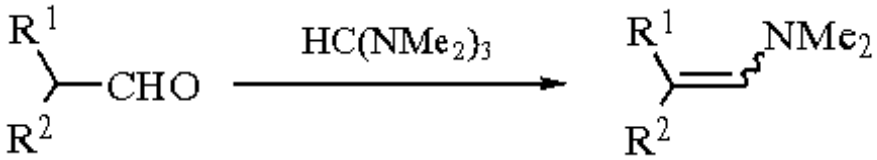

(15)

Reaction with ***Pentacarbonyliron*** affords a carbamoyltetracarbonyliron anion complex (eq 16).[38,39]

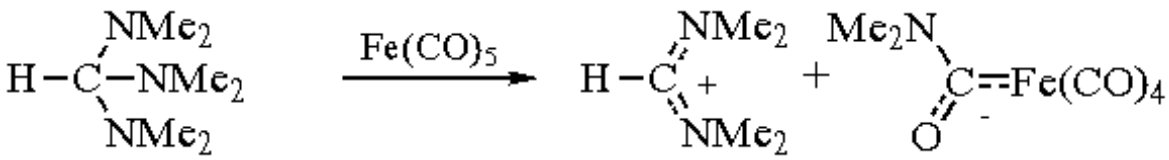

(16)

Tris(dimethylamino)methane can also serve as a strong base in deprotonation of organic compounds.[40,41] The anions thus formed can be used in further reactions (e.g. eq 17).[41]

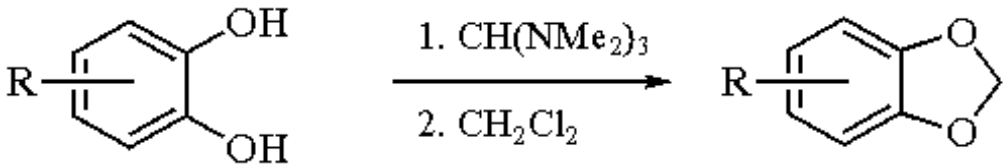

(17)

In the rhodium-catalyzed reaction of TDAM with CO and a silyl hydride, a substituted 1,2-diamino-3-silyloxypropane derivative is formed (eq 18).[42]

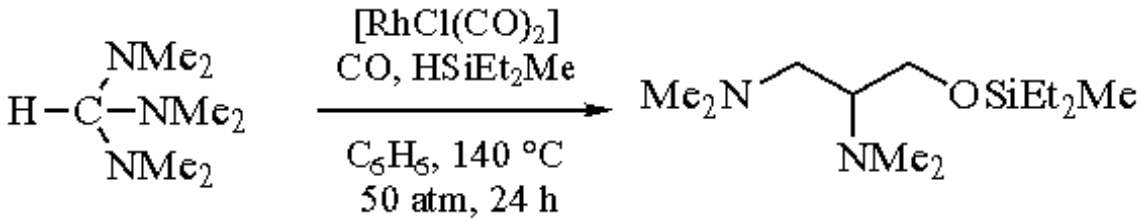

(18)

Prolonged heating of selenium and TDAM affords *N,N,N´,N´*-tetramethylselenourea;[43] bis(dimethylamino)carbene (or an equivalent species) may be an intermediate in this reaction (eq 19).

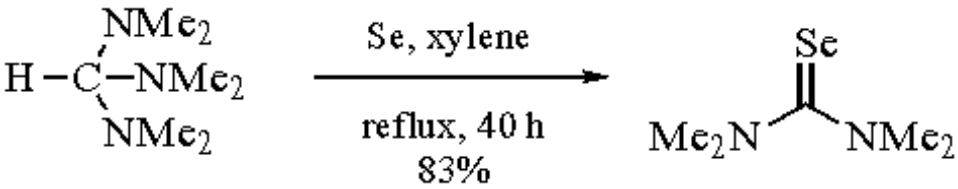

(19)

Related Reagents.

t-Butoxybis(dimethylamino)methane; ***N,N-Dimethylformamide***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Tris(formylamino)methane***.

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Tris(dimethylamino)phosphine-Carbon Tetrachloride[1]

$(Me_2N)_3P$-CCl_4

($(Me_2N)_3P$)

[1608-26-0] · $C_6H_{18}N_3P$ · Tris(dimethylamino)phosphine-Carbon Tetrachloride · (MW 163.24) (CCl_4)

[56-23-5] · CCl_4 · Tris(dimethylamino)phosphine-Carbon Tetrachloride · (MW 153.81)

(reagent combination for the conversion of hydroxyl groups to the corresponding chlorides; hydroxyl group activation; dehydrations)

Alternate Name: hexamethylphosphorous triamide-carbon tetrachloride.

Physical Data: $(Me_2N)_3P$: bp 55-58 °C/15 mmHg; *d* 0.898 g cm^{-3}. CCl_4: mp -23 °C; bp 77 °C; *d* 1.594 g cm^{-3}.

Solubility: sol CCl_4, MeCN, CH_2Cl_2, THF.

Preparative Methods: reactive species is generated in situ by reaction of $(Me_2N)_3P$ and CCl_4.

Handling, Storage, and Precautions: $(Me_2N)_3P$ is an irritant and is flammable. It is best kept under a nitrogen atmosphere. CCl_4 is toxic and a cancer suspect agent. All solvents used must be carefully dried because the intermediates are all susceptible to hydrolysis. The hexamethylphosphoramide produced as a byproduct is a cancer suspect agent. This reagent should be handled in a fume hood.

General Considerations.

The use of ***Hexamethylphosphorous Triamide*** in place of ***Triphenylphosphine*** in the phosphine-carbon tetrachloride reaction has a number of advantages. The separation of the triphenylphosphine oxide from the product can sometimes be problematic. The byproduct of the hexamethylphosphorous triamide reaction, ***Hexamethylphosphoric Triamide***, is water soluble which allows for simple separation from the desired product. The aminophosphine is more nucleophilic, resulting in milder reaction conditions. Also, the alkoxyphosphonium intermediates can sometimes be isolated.[1]

Activation of Hydroxyl Groups.

The combination of hexamethylphosphorous triamide and CCl_4 with an alcohol is a very effective method for the activation of the hydroxyl group for displacement by a variety of nucleophiles. In the absence of any external nucleophiles, the chloride ion formed in the reaction will react with the intermediate alkoxyphosphonium ion to produce the alkyl chloride (eq 1).[2]

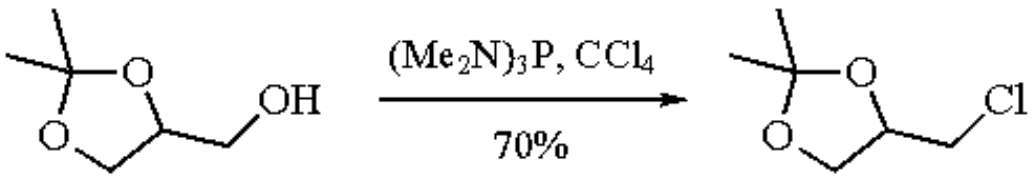

(1)

Other nucleophiles are capable of effectively competing with chloride ion for the alkoxyphosphonium ion. If ***Sodium Azide***, ***Potassium Iodide***, or ***Potassium Cyanide*** is added to the reaction mixture, the corresponding azide, iodide, or nitrile will be formed in good yield (eq 2).[3]

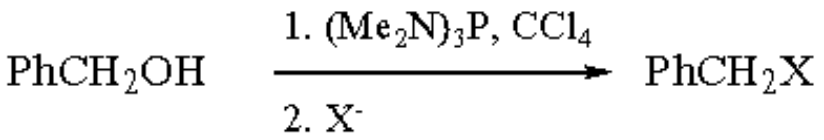

(2)

$X^- = N_3^-$, 75%; I^-, 80%; CN^-, 75%

Sometimes it is advantageous to replace the chloride counterion with less nucleophilic counterions such as BF_4^-,[4] ClO_4^-,[5] or PF_6^-.[6] This technique sometimes allows the alkoxyphosphonium salts to be isolated as stable crystalline solids (eq 3).[5] Weaker nucleophiles, such as amines (eq 4), can then be used to displace the alkoxyphosphonium ion.[5]

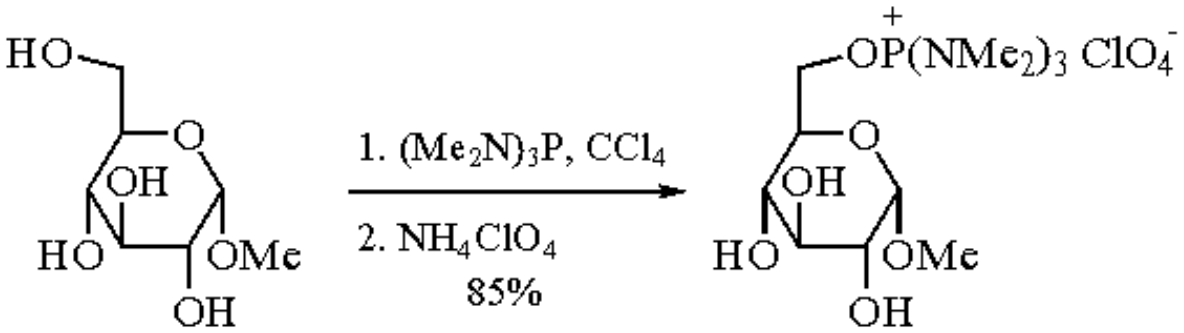

(3)

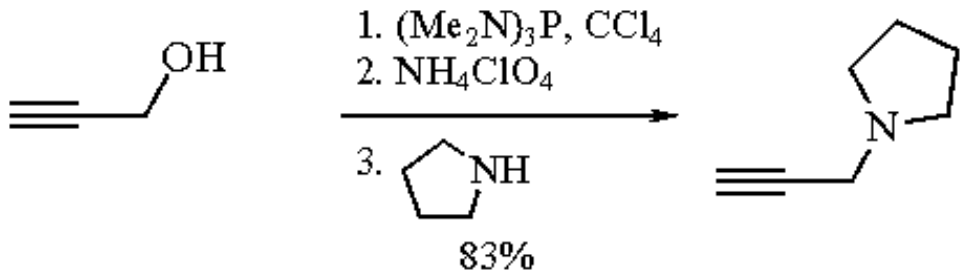

(4)

Deoxygenations.

The removal of oxygen functionality can be achieved via activation of hydroxyl groups with this reagent. The reduction of the alkoxyphosphonium ion by ***Lithium Triethylborohydride*** provides a route to deoxy sugars (eq 5).[7]

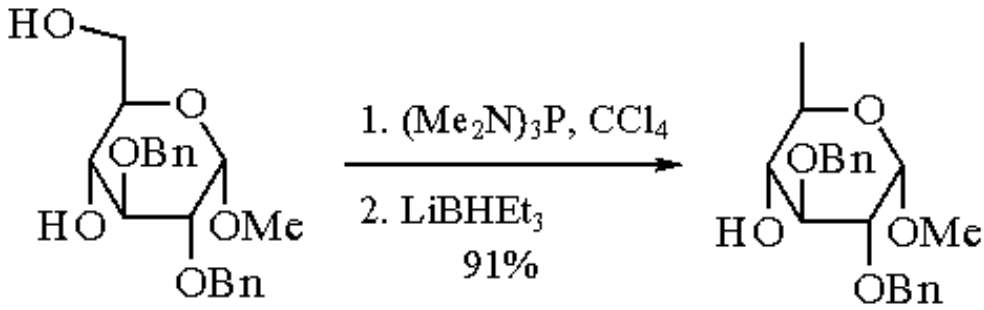

(5)

The preparation of glycals from lactols can be achieved by initial activation of the anomeric hydroxyl and subsequent Li/NH_3 reduction (eq 6).[8]

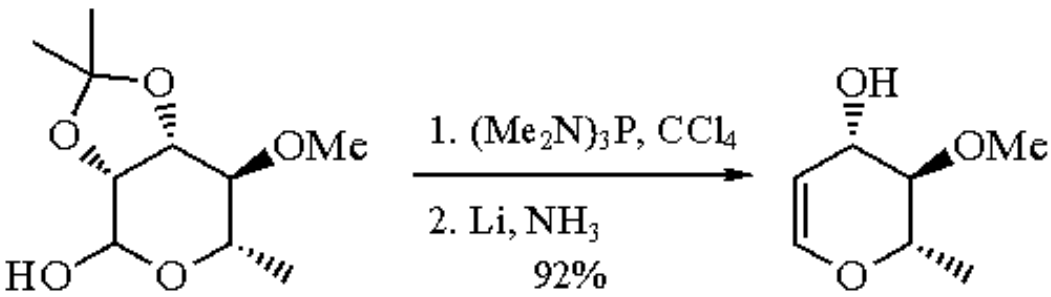

(6)

Anomeric Hydroxyl Activation.

Anomeric hydroxyl group activation can be utilized to prepare a number of glycosyl derivatives. Activation followed by reaction with ***Mesityloxytris(dimethylamino)phosphonium Azide*** affords glycosyl azides (eq 7).[9]

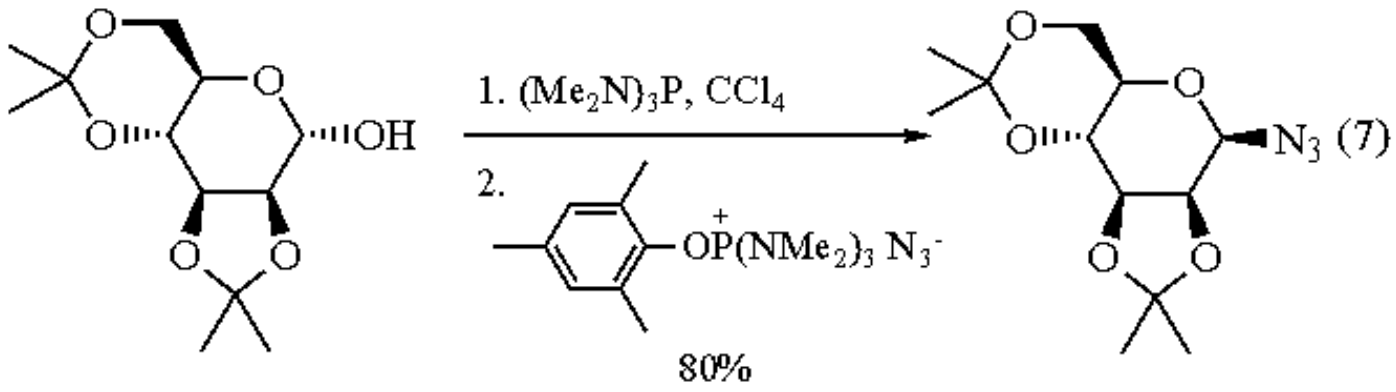

For the preparation of disaccharides, the intermediate alkoxyphosphonium ions are reacted with ***Silver(I) p-Toluenesulfonate*** prior to the addition of the second sugar (eq 8).[10]

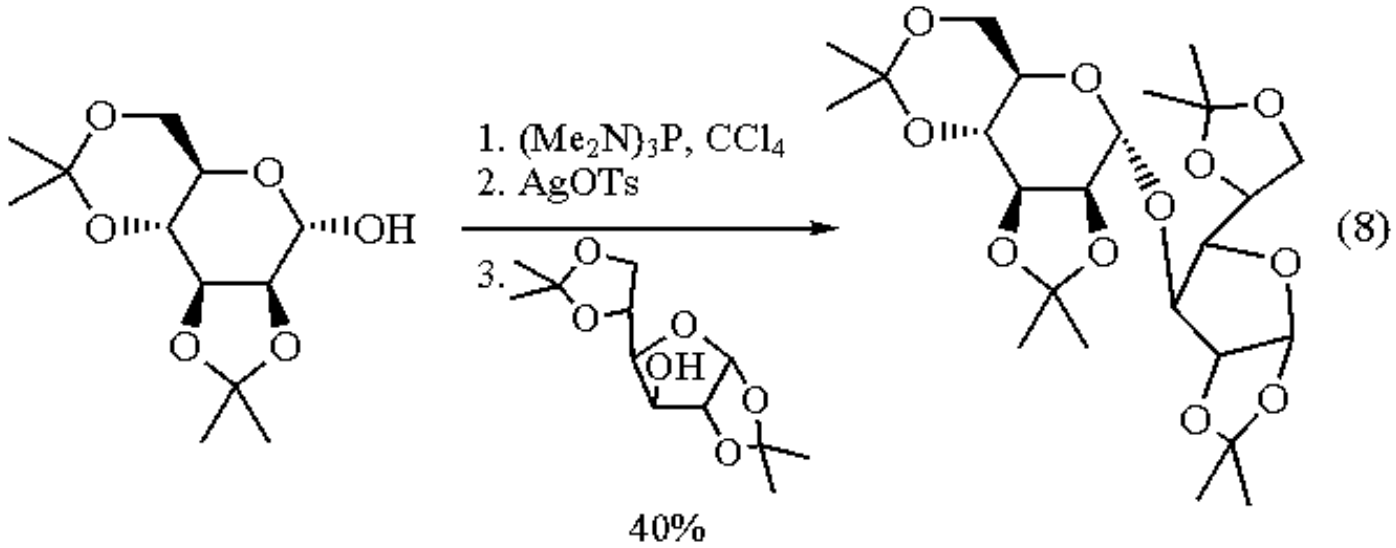

Dehydrations.

The reaction of 1,2-diols with this reagent combination can lead to the formation of epoxides (eq 9) or spirophosphoranes (eq 10). The course of the reaction is dependent on the stereochemistry of the starting diol. The reaction of *meso*-hydrobenzoin affords the epoxide while the *threo* stereoisomer provides the spirophosphorane. The *trans*-diol of cyclohexane was unaffected.[11]

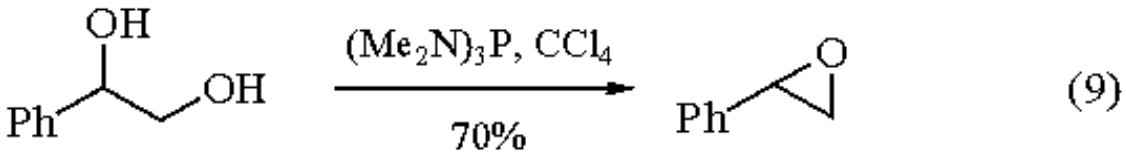

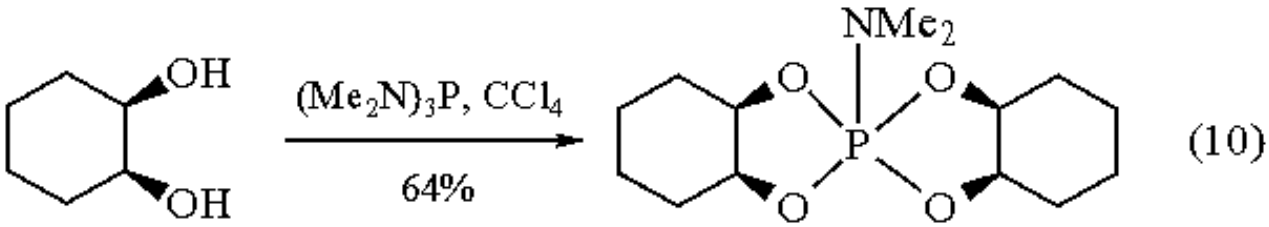

The selective monofunctionalization of a 1,3-diol is possible. Following activation, the monoalkoxyphosphonium ion can be displaced with

various nucleophiles such as iodide or azide (eq 11).[12] Alternatively, if the alkoxyphosphonium ion was reacted with base, the oxetane was formed (eq 12).[13]

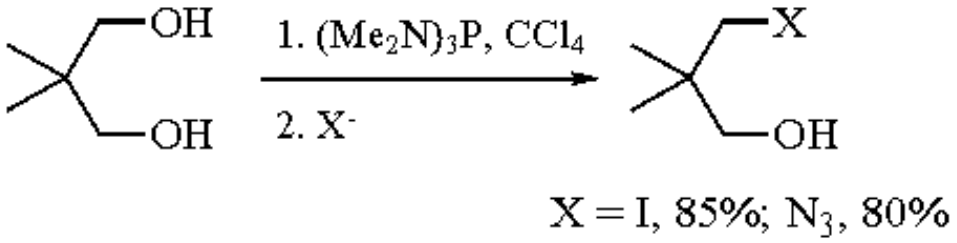

(11)

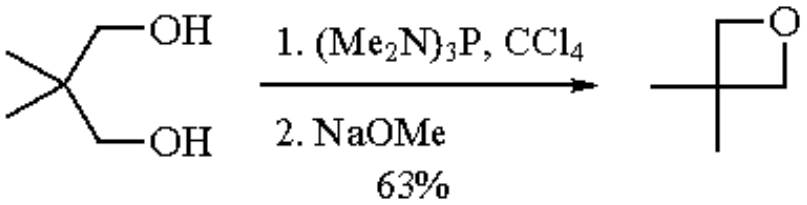

(12)

Dichloroalkenes.

Aldehydes and the intermediate trichloromethylcarbinols can be converted to dichloroalkenes.[14] Even certain γ-lactones will undergo this transformation. Treatment of the γ-lactone (eq 13) with hexamethylphosphorous triamide produced the dichloroalkene in 79% yield. The use of Ph_3P was ineffective for this transformation. Attempts to use CBr_4 in place of CCl_4 resulted in the formation of complex mixtures.[14]

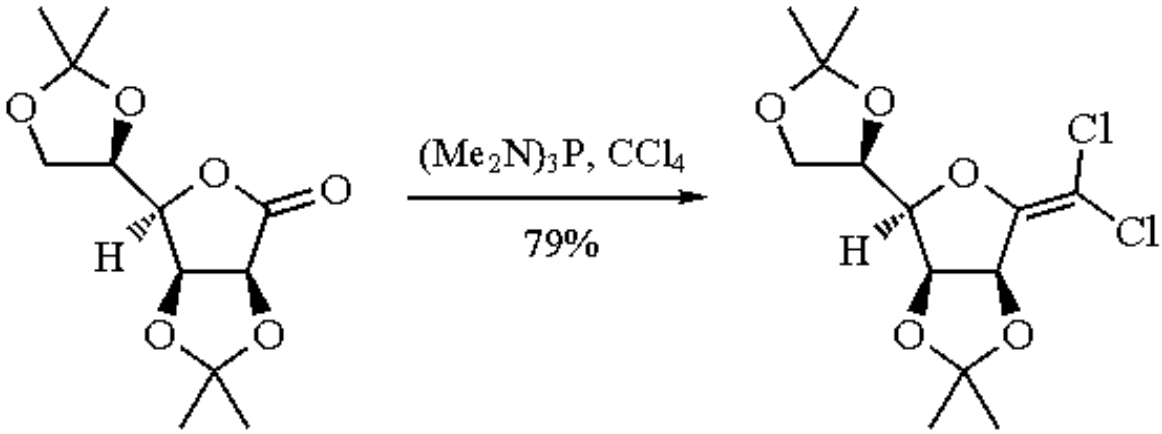

(13)

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Tris(2,2-dimethylpropyl)(2,2-dimethylpropylidene)tantalum

$Me_3CCH{=}Ta(CH_2CMe_3)_3$

[54294-45-0] · $C_{20}H_{43}Ta$ · Tris(2,2-dimethylpropyl)(2,2-dimethylpropylidene)tantalum · (MW 464.58)

(converts a carbonyl group into a neopentylidene group[1])

Physical Data: mp 71 °C.

Solubility: sol diethyl ether, hydrocarbon solvents.

Form Supplied in: not commercially available.

Preparative Methods: prepared in a two-step procedure from tantalum pentachloride.[2] First, tris(2,2-dimethylpropyl)tantalum dichloride is prepared from the reaction of tantalum pentachloride and 3 equiv of 2,2-dimethylpropyllithium. Treatment of tris(2,2-dimethylpropyl)tantalum dichloride with 2 equiv of 2,2-dimethylpropyllithium affords tris(2,2-dimethylpropyl)(2,2-dimethylpropylidene)tantalum.

Purification: recrystallized from pentane at -30 °C.

Handling, Storage, and Precautions: air and moisture sensitive.

Carbonyl Alkenation.

Treatment of carbonyl compounds with the title reagent (**1**) affords the carbonyl alkenation product.[1] In the reaction of ketones and aldehydes with (**1**), the reagent functions as a Wittig substitute (eq 1). Unlike the Wittig reaction, the carbonyl alkenation reaction also proceeds for esters (eq 2) and amides (eq 3), affording enol ethers and enamines, respectively. Reaction with carbon dioxide affords the symmetrical allene (eq 4). Only the neopentylidene unit can be transferred using the tantalum chemistry; however, the work by Schrock[1] has led to the discovery of similar reagents (Schrock carbene complexes) capable of transferring a variety of organic groups.[3]

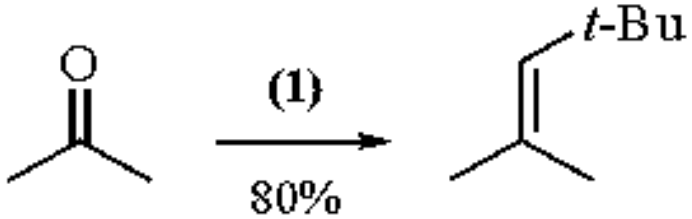

(1)

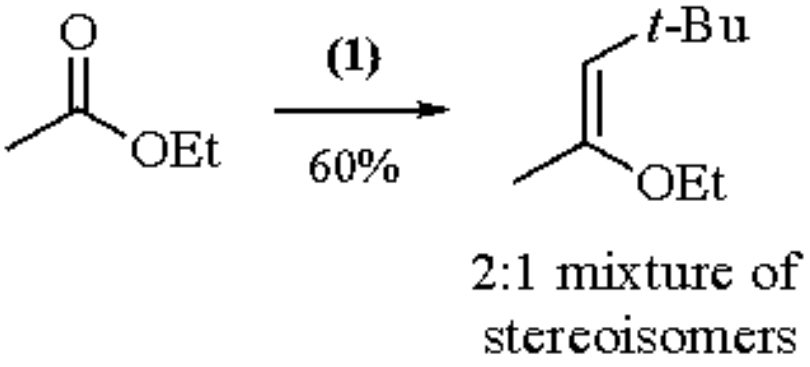

(2)

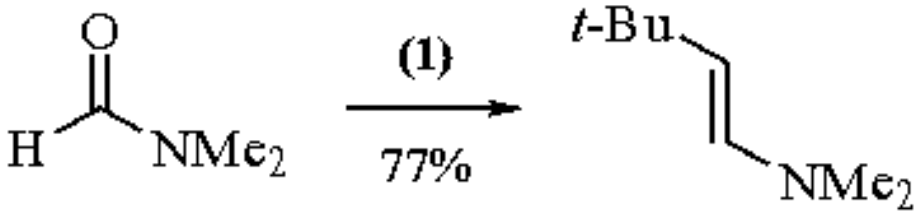

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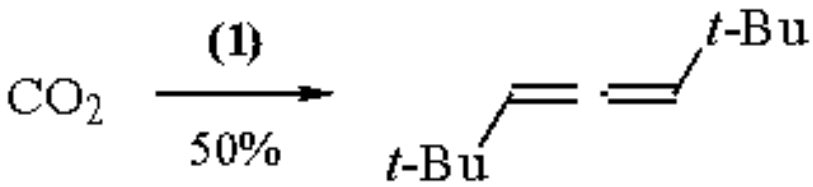

(4)

Enolate Formation.

Treatment of acid chlorides with (**1**) provides the tantalum enolate rather than the vinylic chloride (eq 5).[2] A similar reaction pathway is observed with phenyl esters. In this case, a similar type of product would be predicted from the analogous Wittig reaction.

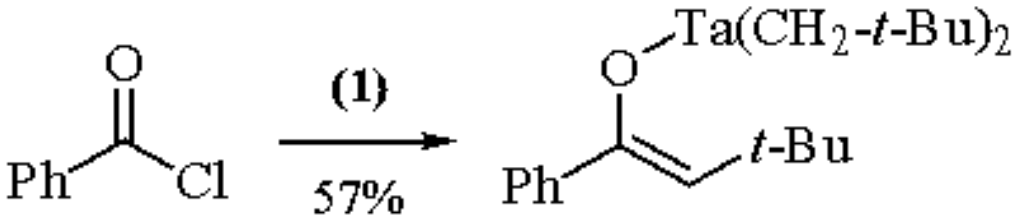

(5)

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Tris(ethylthio)borane[1]

$(EtS)_3B$

[998-26-5] · $C_6H_{15}BS_3$ · Tris(ethylthio)borane · (MW 194.23)

(used as an ethanethiol donor)

Physical Data: bp 78-81.5 °C/1.3 mmHg; *d* 1.0191 g cm^{-3}.

Preparative Methods: by reaction of bis(ethylthio)lead with boron trichloride[1,2] or sulfurated borohydride with ethanethiol.[3]

Handling, Storage, and Precautions: store and use in the absence of moisture.

General Discussion.

Like other thioboranes, tris(ethylthio)borane is a reactive intermediate for the synthesis of organic sulfur compounds, relying on the extreme lability of the B-S bond. The major application of tris(ethylthio)borane is as an alternative to ***Ethanethiol***; it is readily available and more easily handled than ethanethiol.

Tris(ethylthio)borane converts both aromatic and aliphatic carboxylic acids to the corresponding ethyl thioesters (eq 1).[2,4]

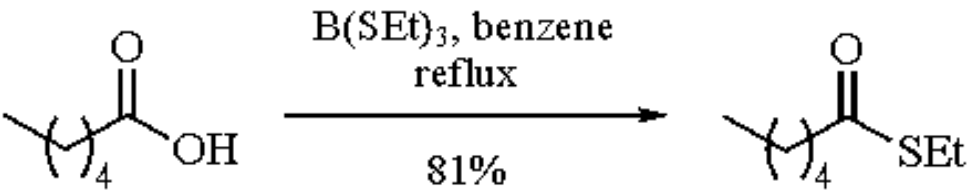

(1)

It has been shown that ketones and aldehydes are transformed to thioacetals by reaction with tris(ethylthio)borane. In contrast to the usual procedure for the formation of thioacetals, this reaction proceeds smoothly in neutral medium at ambient temperature (eq 2). The driving force is believed to be the formation of the strong B-O bond.[5]

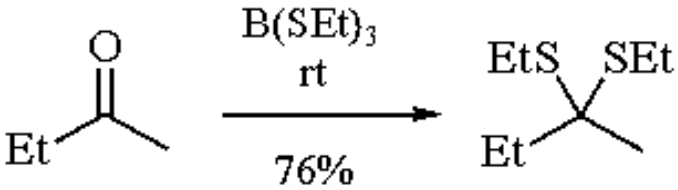

(2)

Epoxides are cleaved in the presence of tris(ethylthio)borane, with attack generally occurring at the less substituted carbon (eq 3). This procedure has been shown to be superior for these transformations.[6]

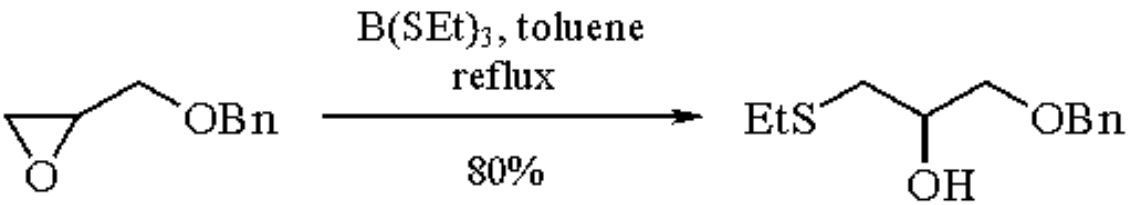

(3)

Other reactions of tris(ethylthio)borane include those with benzenesulfonic acid esters to afford asymmetric disulfides (eq 4),[7] and with isocyanates to give *N*-ethylthiocarbonylureas (eq 5).[8]

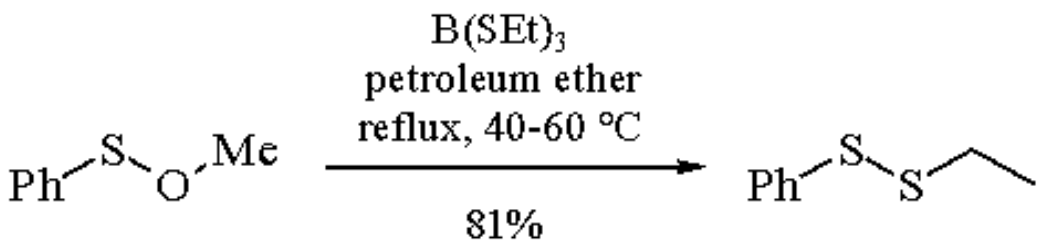

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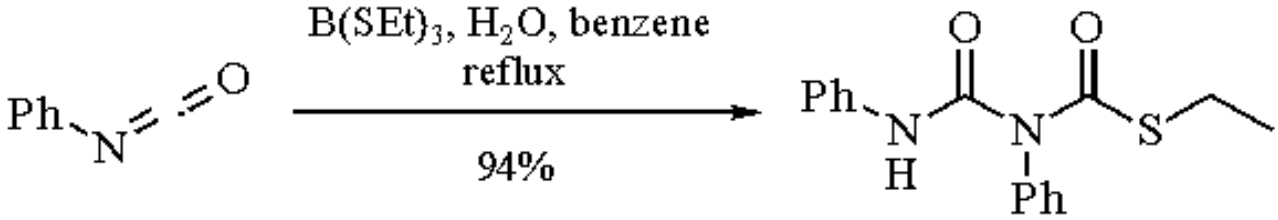

(5)

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Tris(formylamino)methane[1]

[4774-33-8] · $C_4H_7N_3O_3$ · Tris(formylamino)methane · (MW 145.14)

(a source for formamide; for *N*-formylformamidine (H_2N-CH=N-CHO); for the *N*-formylformimidoyl group (H-C=NH-CHO) as a building block in heterocyclic synthesis)

Alternate Names: TRIFO; *N,N´N´´*-methylidynetrisformamide; triformamidomethane.

Physical Data: mp 162-164 °C (dec).

Solubility: sol formamide; sol aprotic dipolar solvents such as DMF or DMA on heating.

Form Supplied in: white crystals; commercially available.

Analysis of Reagent Purity: melting point.

Preparative Methods: ***Triethyl Orthoformate*** reacts with formamide under catalysis of mineral acids to give TRIFO (eq 1).[2,3] The reaction of excess formamide with inorganic and organic acyl chlorides such as PCl_3, $POCl_3$, $SOCl_2$, acetyl chloride, benzoyl chloride, and ethyl chloroformate proceeds via iminium salts to afford TRIFO.[2,4,5] Analogously, alkylating reagents such as dialkyl sulfates, alkyl sulfonates or triethyloxonium tetrafluoroborate transform formamide to TRIFO. Alkoxymethyleneiminium salts and formamidinium salts are intermediates in these reactions.[2] Pure salts of this type are also converted to the reagent by formamide.[2] Reaction of ***Dimethyl Sulfate*** with formamide is the easiest way to prepare TRIFO.[2]

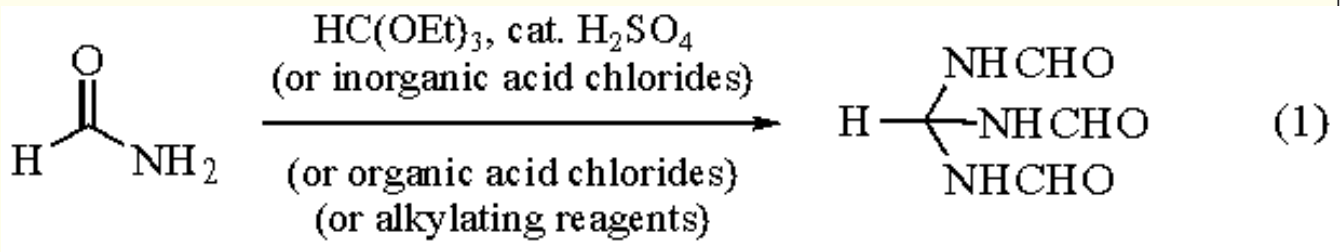

Handling, Storage, and Precautions: store at rt in closed bottles. Use in a fume hood.

Reactions.

Strong CH_2-acidic compounds such as dimethyl malonate and methyl cyanoacetate are transformed to *N*-formylaminomethylenated compounds when heated with TRIFO.[6] Heterocyclic amines are converted by TRIFO to the corresponding *N*-formylamines,[7,8] whereas primary aromatic amines react with TRIFO to give *N,N´*-diarylformamidines.[9]

Of more importance are the applications of TRIFO as a building block in heterocyclic synthesis. In the synthesis of oxazoles from TRIFO and α-halo and α-hydroxy ketones, TRIFO contributes a formamide molecule for the ring closure.[5] However, in the synthesis of 1,2,4-triazoles from hydrazines[1a,10] or amidrazones,[11] 2-alkylamino-1,3,5-triazine from *N*-alkylguanidines,[5,12-15] and pyrimido[4,5-*d*]pyrimidines from 6-aminouracils,[7,16] as well as pyrazolo[3,4-*d*]pyrimidines from 3-amino-5-pyrazolones,[17] the reagent donates (=CH-N=CH-) fragments (eqs 2-7).

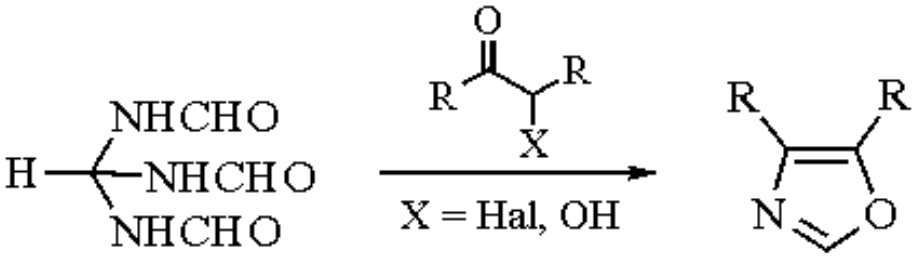

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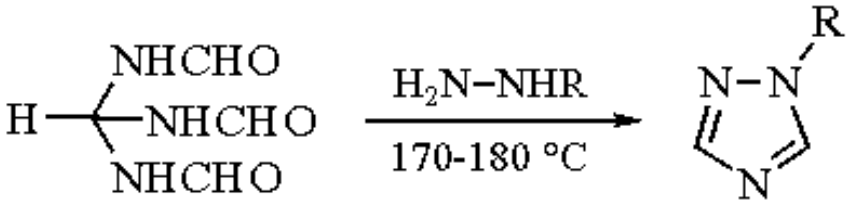

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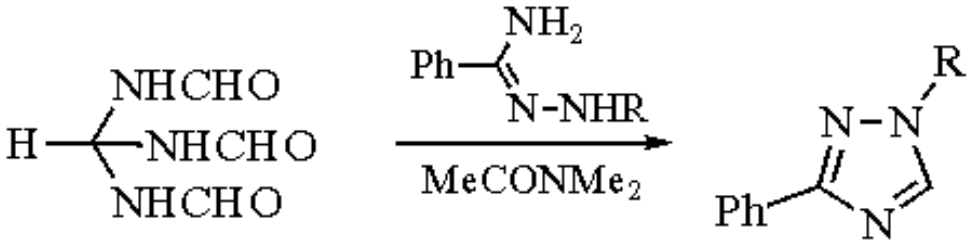

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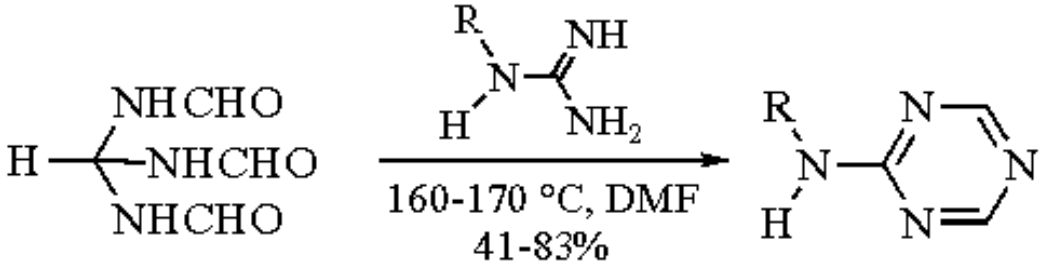

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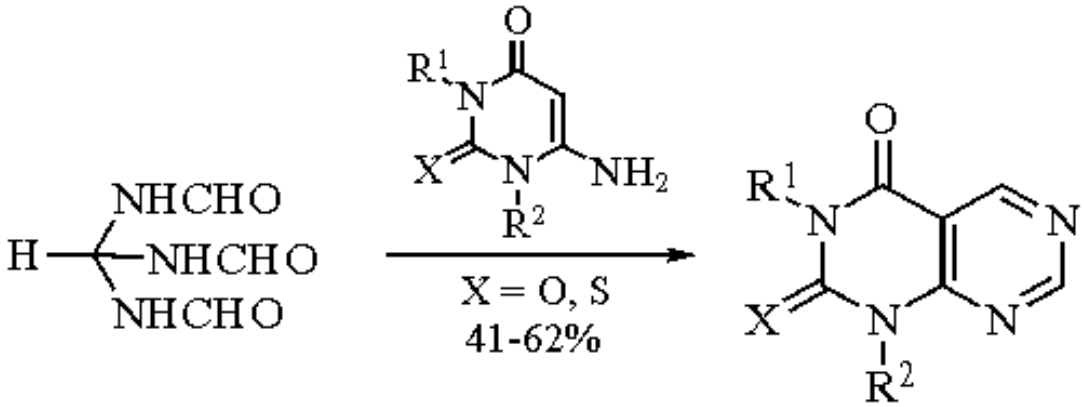

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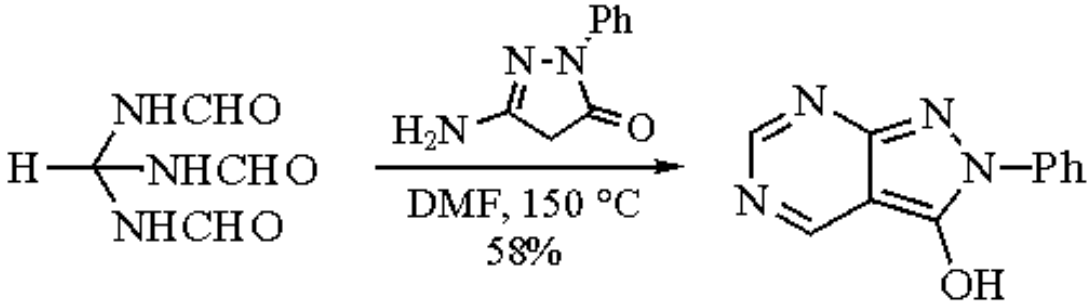

(7)

In a pyrimidine synthesis of broad scope (eqs 8-13), TRIFO acts as a donor of formylformamidine which can cyclize α-CH_2-containing ketones,[5,6,18-24] 1,3-cyclohexanediones,[20] 1,2-, 1,3-, and 1,4-dihydroxynaphthalenes,[25] tetrahydrocarbazolones,[26-30]

arylacetonitriles,[31-35] and arylacetamides,[32,33] as well as malonates, cyanoacetates,[6,36,37] and aminoacetonitriles.[31,38]

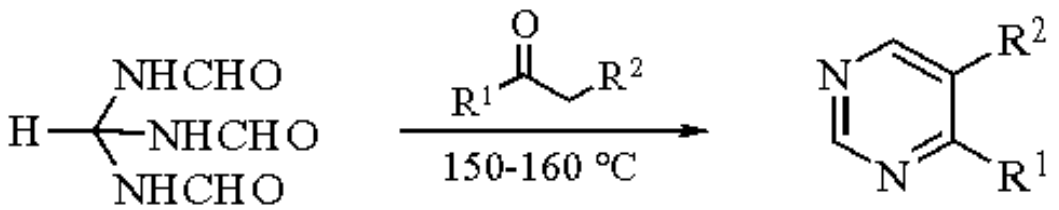

(8)

$R^1, R^2 = \text{alkyl, aryl}$

$R^1\text{-}R^2 = (CH_2)_n \ (n = 3, 4)$

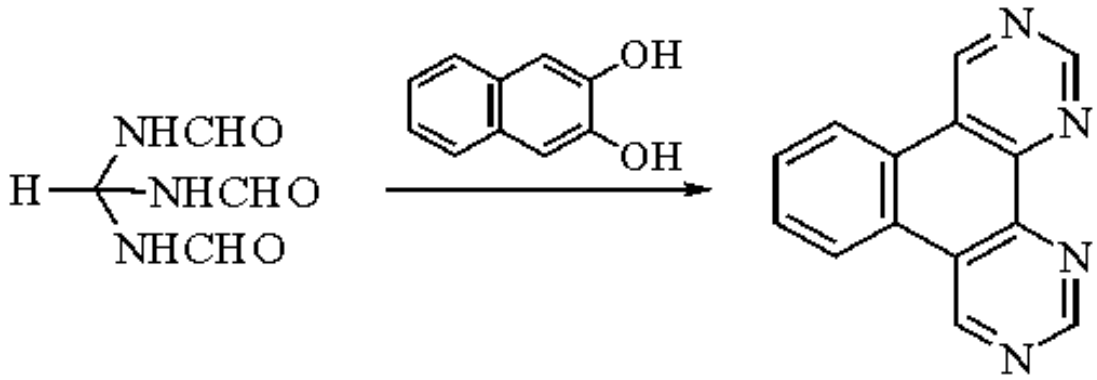

(9)

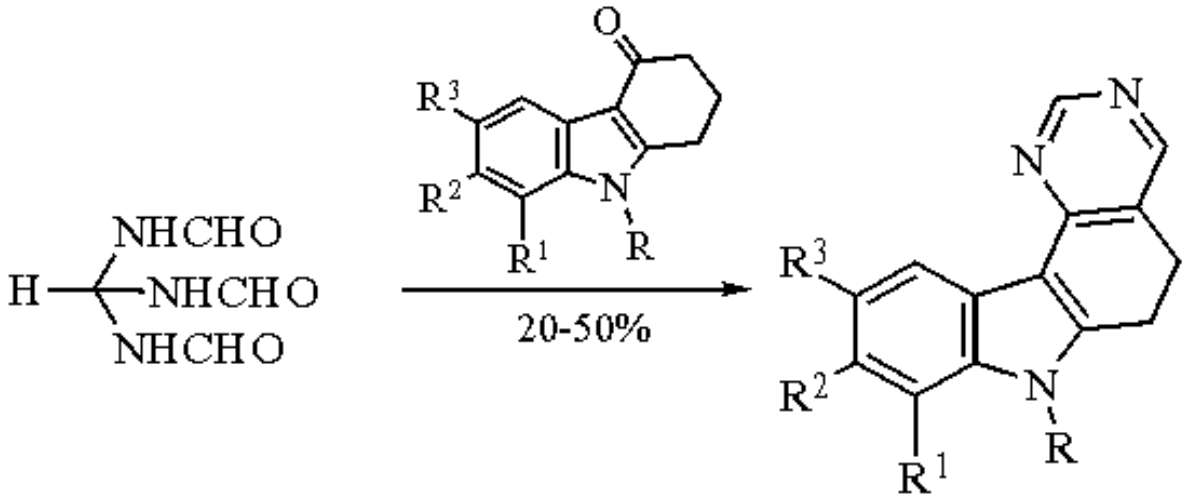

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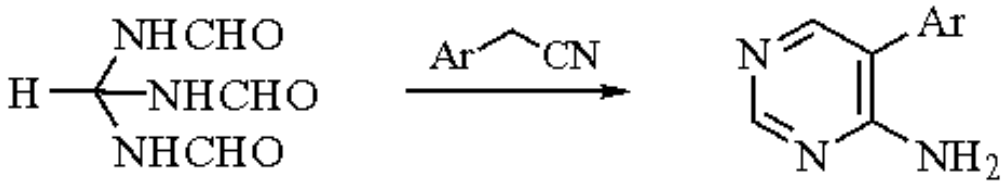

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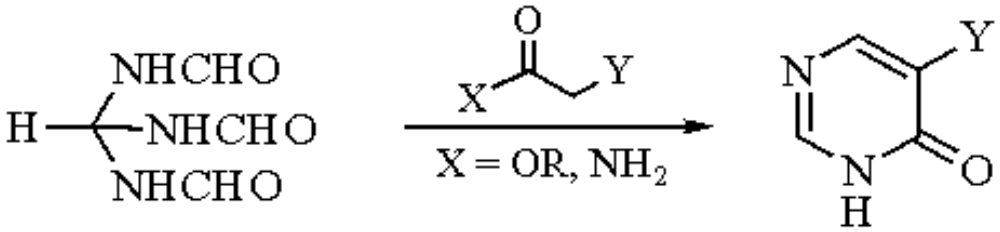

(12)

$Y = CO_2R, CN, CONH_2$

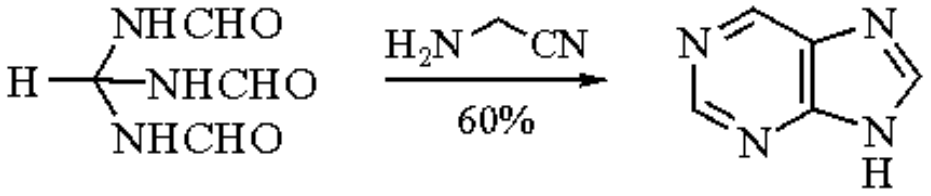

(13)

The thermolysis of TRIFO affords *s*-triazine in good yield (eq 14).[4,5,12,39] *N*-Formylformamidine is thought to be an intermediate. Some methyl heterocycles (2-methylpyridine, 2-methylquinoline, 2-methylpyrazine, and 2-methylbenzothiazole) react with TRIFO on heating in DMF to give heteroarylpyrimidines with low yields (eq 15).[40]

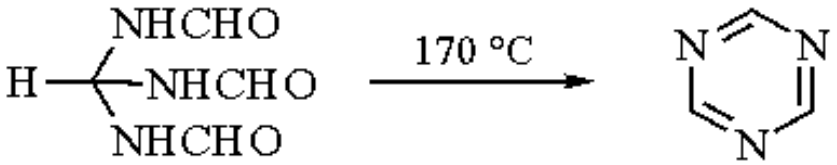

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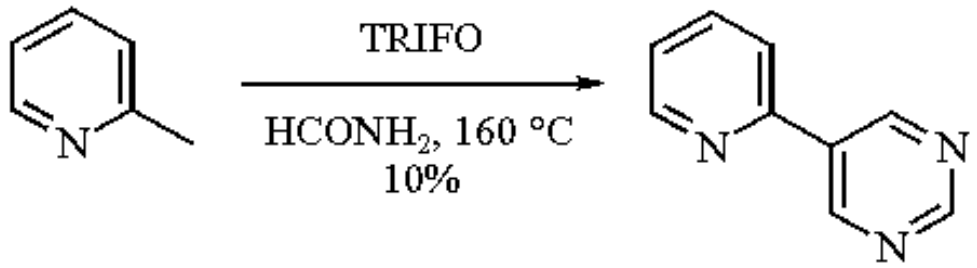

(15)

A few examples are known in which TRIFO acts as a C_1 building block in heterocyclic synthesis, e.g. *o*-phenylenediamine reacts with TRIFO to give benzimidazole (eq 16).[1a] By the same reaction, 4-amino-5-carbamoylpyrimidines can be cyclized to give pyrimido[4,5-*d*]pyrimid-4(3*H*)-ones (eq 17).[41,42] On heating urea or *S*-methylisothiourea sulfate with TRIFO, condensation of the urea derivative occurs first producing biuret and *S*,*S*′-dimethyldithioisobiuret which undergo cyclization with another TRIFO molecule to give *s*-triazines (eqs 18 and 19).[9,12,13]

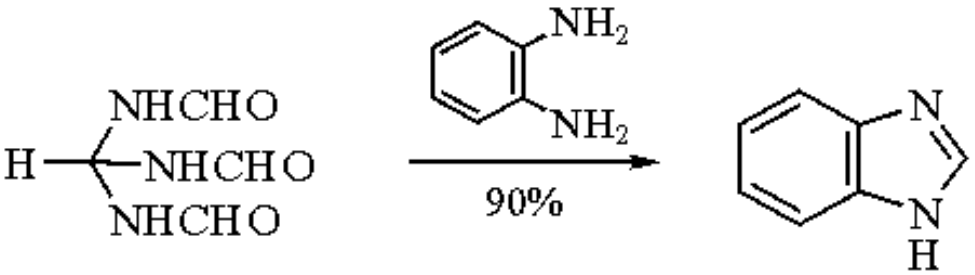

(16)

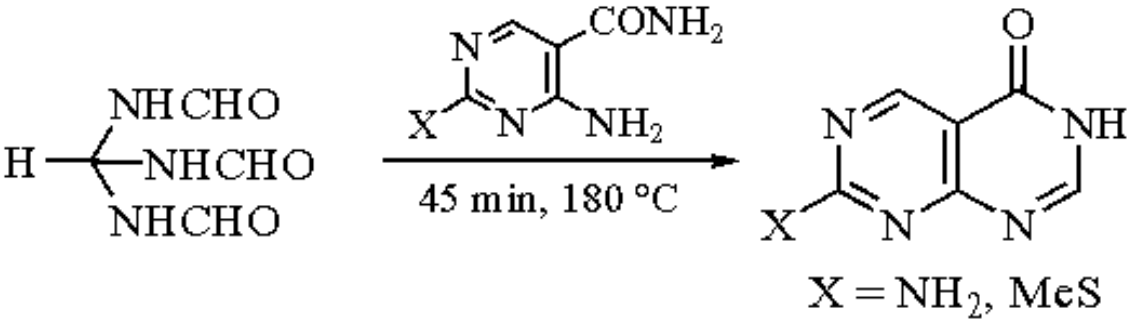

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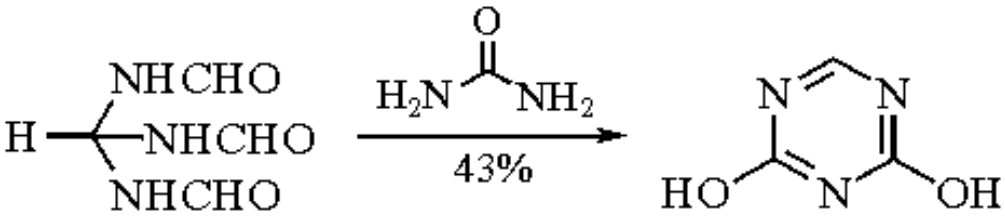

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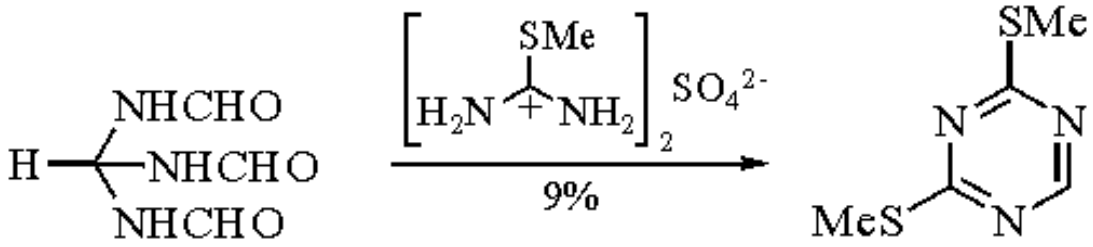

(19)

Vinylogous formamide acetals can be obtained very simply by heating TRIFO with *N*,*N*-dialkylformamide acetals in the presence of the corresponding alcohols (eq 20).[43]

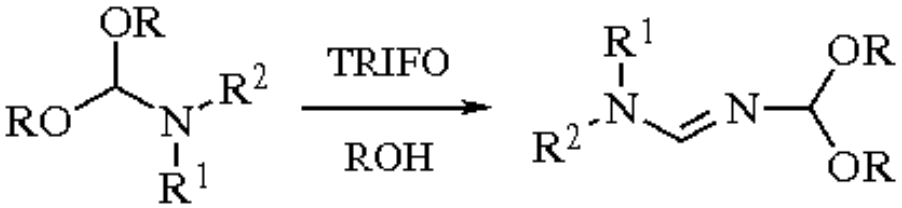

(20)

Related Reagents.

t-Butoxybis(dimethylamino)methane; ***N,N-Dimethylformamide***; ***N,N-Dimethylformamide Diethyl Acetal***; ***Tris(dimethylamino)methane***; ***Dimethylchloromethyleneammonium Chloride***.

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Tris(methylthio)methane[1]

$(MeS)_3CH$

[5418-86-10] · $C_4H_{10}S_3$ · Tris(methylthio)methane · (MW 154.35)

(precursor to tris(methylthio)methyllithium,[2] useful for the preparation of carboxylic acids,[2] esters,[3] ketene thioacetals,[4] α-hydroxy esters,[5] β-alkoxy carbonyl lactones[6] and for ring expansion of cyclic ketones to cyclic 1,2-keto thioacetals[7])

Physical Data: mp 17-18 °C;[8] bp 102 °C/15 mm;[8] *d* 1.16 g cm^{-3}; ^1H NMR (CCl_4) δ 4.63 (s, 1H), 2.16 (s, 9H).[2b]

Form Supplied in: liquid; widely available.

Handling, Storage, and Precautions: stench; irritant; use in a fume hood.

Metalation.

Tris(methylthio)methane undergoes rapid deprotonation with ***n-Butyllithium*** in THF at -78 °C (eq 1) to provide tris(methylthio)methyllithium (**1**),[2] a useful carboxylate anion equivalent. However, subsequent reactions of (**1**) with electrophiles must proceed at temperatures well below -20 °C since the anion decomposes at this temperature via a carbenoid pathway to provide tetrakis(methylthio)ethylene (eq 1).[2]

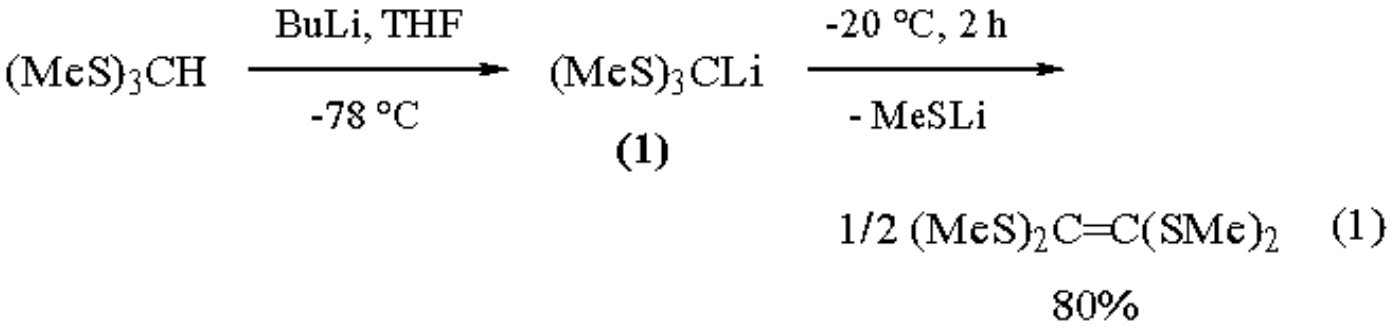

Alkylation Reactions.[2-4]

Only primary halides are suitable substrates for alkylation reactions with carbanion (**1**). Thus reaction with ethyl bromide takes place at -78 °C to afford 1,1,1-tris(methylthio)propane in 70% yield,[4a] whereas the analogous alkylation reaction using isopropyl iodide is unsatisfactory (22% yield).[2a] An alkylation reaction of carbanion (**1**) with a 1,4-cyclic sulfate has been recently examined for the purpose of preparing shikimate substrate analogs (eq 2). The alkyl sulfate and orthothioester functionalities of the resulting alkylation product were hydrolyzed to afford a deoxycarbohydrate upon concomitant lactonization (eq 2).

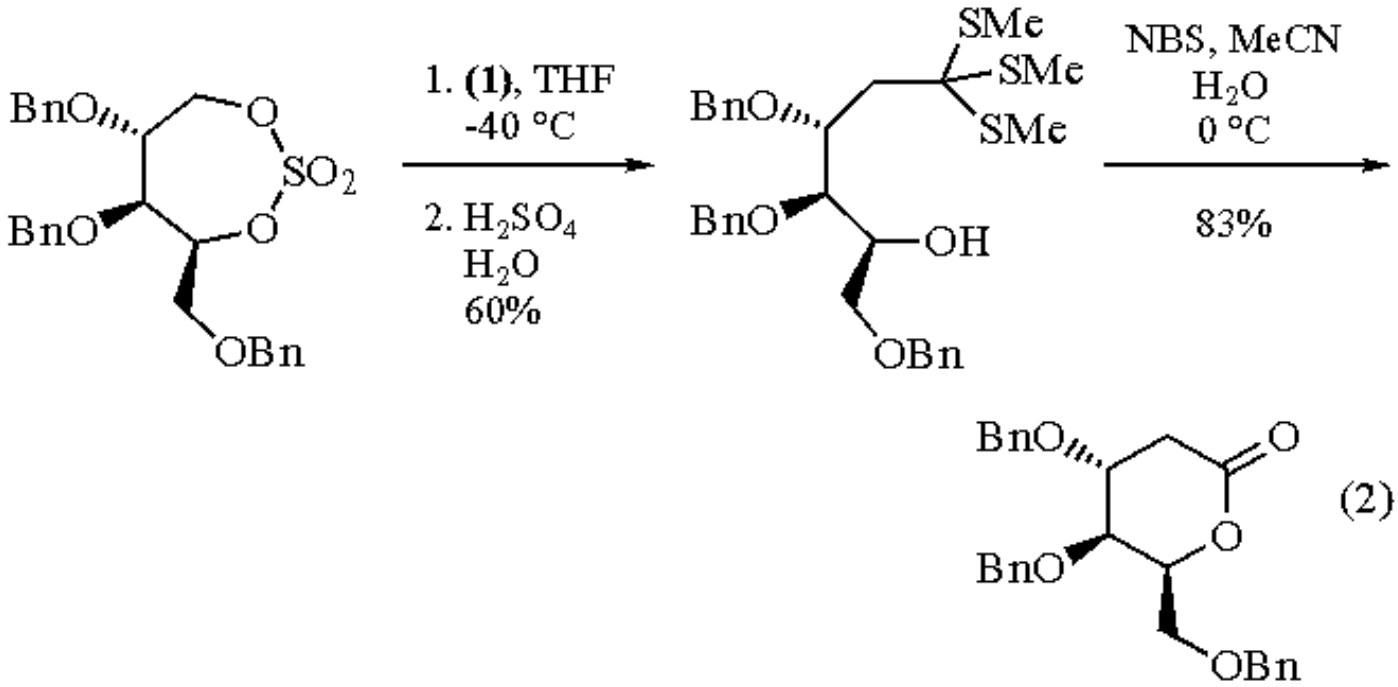

(2)

1,2-Addition Reactions with Carbonyl Compounds.

Tris(methylthio)methyllithium participates in 1,2-addition reactions with a variety of carbonyl compounds including aldehydes,[2a,5a,i] ketones,[2a,5b,c] lactones,[5d,e,f] chloroformates,[2a] and carbon disulfide.[5g] A particularly illustrative example was reported in the preparation of a BCE ring model system directed toward the total synthesis of bruceantin (eq 3).[5b] Thus stereoselective addition of (**1**) proceeded smoothly provided the reaction mixture was quenched with saturated ammonium chloride at -60 °C. The resulting alcohol tosylate (eq 3) was efficiently converted to the tetrahydrofuran ring and the orthothioester was transformed to the methyl ester functionality to afford the bruceantin BCE ring system (eq 3).

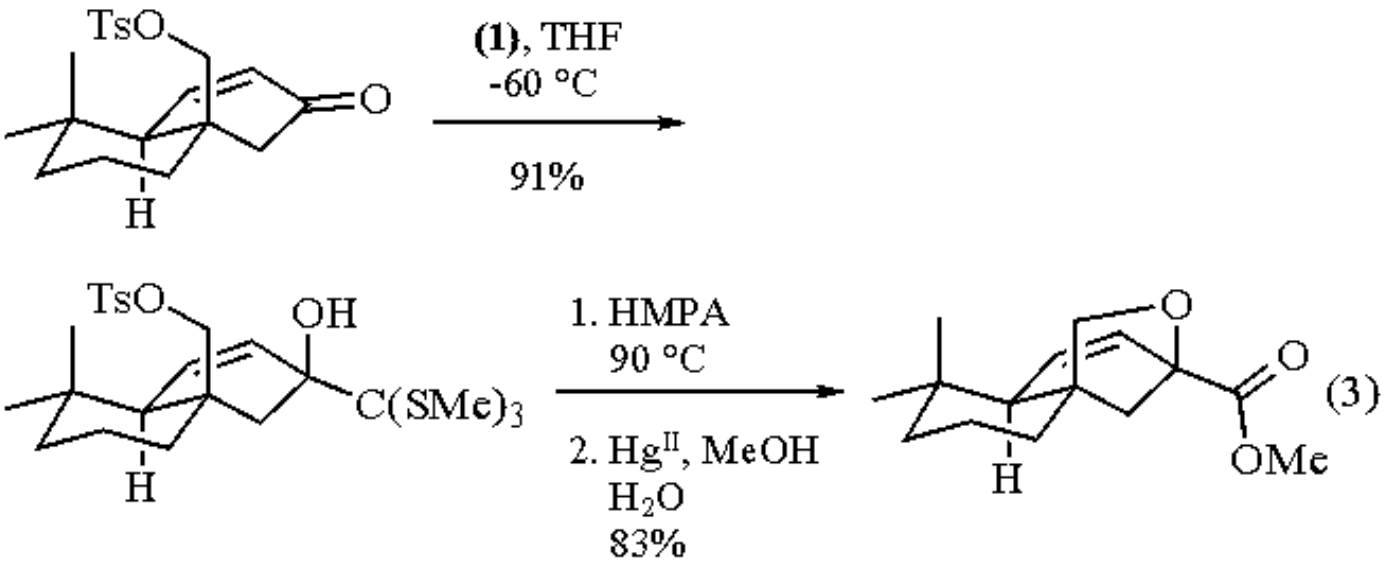

(3)

1,4-Addition Reactions to α,β-Unsaturated Carbonyl Compounds.

Conjugate addition reactions of (**1**) to butenolides,[6a,b] cyclopentenone,[6c] and nitroalkenes[6d] have been reported which are in contrast to the 1,2-addition observed for the reaction of the enone in eq 3, 2-(trimethylsilylmethyl)propenal,[5i] and cyclohexenone[5h] (which gives an equal mixture of 1,2- and 1,4-addition products).[5h,9] As expected, the enolates that result from the conjugate addition can be trapped.[6a,c] For example, conjugate addition of (**1**) to the butenolide shown in eq 4 followed by addition of gaseous formaldehyde gave a product which was easily converted to the antibiotic protolichesterinic acid.[6a]

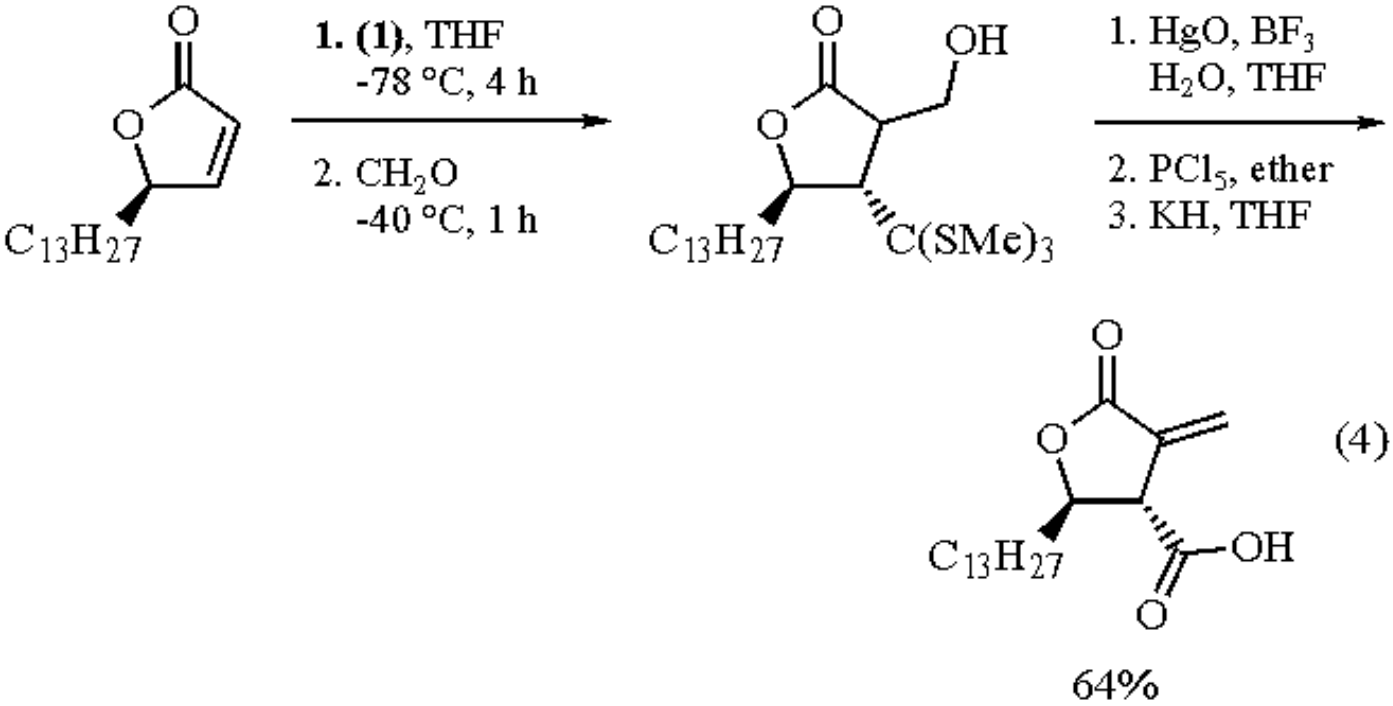

(4)

The product of a formal conjugate addition reaction to an aryl methyl ketone was obtained when the arenetricarbonylchromium complex shown in eq 5 was treated with (**1**). This gave an anionic benzocyclohexadienyl intermediate which upon methylation at the metal center underwent CO insertion and acyl transfer to afford a mixture of regioisomers, after decomplexation using triphenylphosphine.[6f]

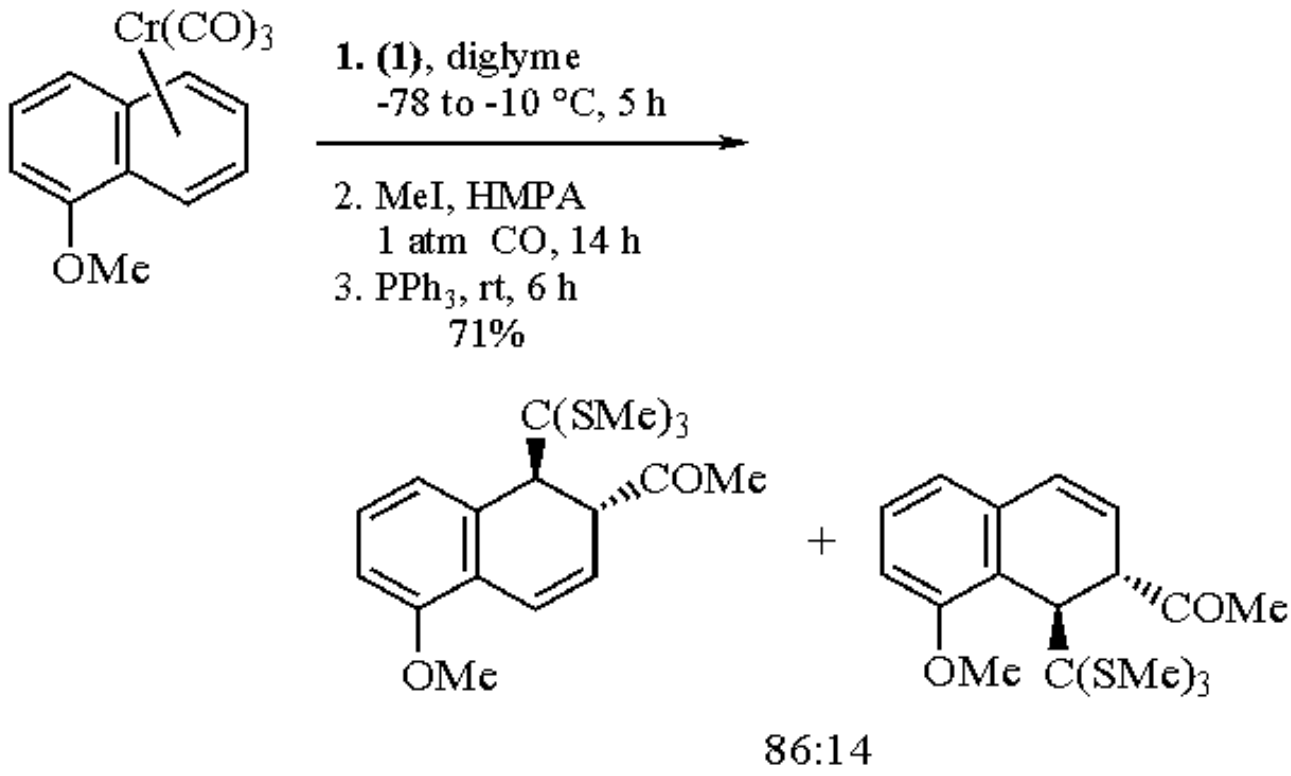

(5)

Ring Expansion of Strained Ketones.

The alcohols derived from 1,2-addition of (**1**) to cyclopentanones,[7a,b] cyclobutanones,[7a,b,d] or cyclopropyl ketones[7c] undergo Cu^{I}- or acid-promoted regioselective rearrangement to afford ring-expanded 1,2-keto thioacetal products resulting from migration of the more substituted carbon. For example, the alcohol shown in eq 6 rearranged to afford a single 1,2-keto thioacetal, which was subjected to a four-step reaction sequence in order to prepare the sesquiterpene clovene.[7d]

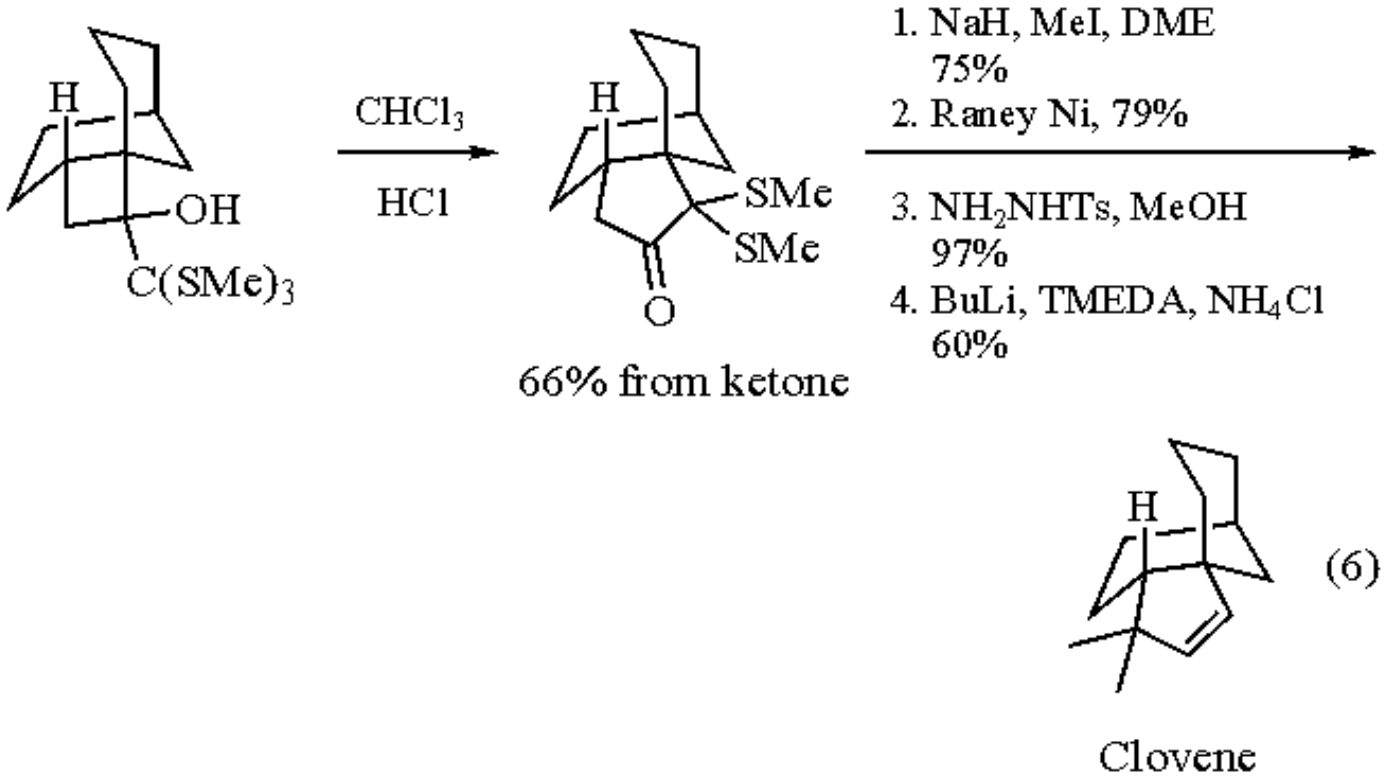

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Tris(phenylseleno)borane[1]

$B(SePh)_3$

[29680-62-4] · $C_{18}H_{15}BSe_3$ · Tris(phenylseleno)borane · (MW 479.02)

(an efficient carrier of benzeneselenolate anion equivalent in selenoacetalization reactions,[2-5] in the conversion of *O,O*-acetals into mixed *O,Se*-acetals,[3] in the opening of epoxides,[6] or in the transformation of α,β-unsaturated ketones into 1,1- and/or 1,3-bis(seleno)-2-alkenes;[7] a valuable source of phenylselenyl radicals capable of inducing hydroselenation of alkynes and cyclization of enynes;[8] used for the deoxygenation of sulfoxides[9] and of 1,2-disubstituted epoxides[6])

Physical Data: white needles, mp 152-153 °C.[1]

Solubility: sol carbon disulfide, dichloromethane, chloroform, toluene.

Preparative Methods: in a modified procedure[4] of the original,[1] ***Boron Tribromide*** (14.32 g, 57.1 mM) and dry ***Carbon Disulfide*** (100 mL) are placed in a flask cooled in an ice bath under nitrogen. ***Benzeneselenol*** (26.95 g, 171.6 mM) in 50 mL carbon disulfide is added to the well-cooled solution from the addition funnel over a period of 4 h. The reaction mixture is warmed to room temperature and stirred overnight. The nitrogen flow is stopped, and the solvent is evaporated. The residual yellow solid is suspended in 100 mL of dry pentane, and the stirred mixture refluxed under a slight static pressure of nitrogen. After cooling to rt, the yellow supernatant is removed by syringe. This washing is repeated with two more 100 mL portions of pentane. The resulting white solid is dried under vacuum, weighed (20.48 g, 74%) and stored protected from moisture.

The analogs tris(*p*-tolylseleno)borane and tris(*p*-bromophenylseleno)borane have been similarly prepared.[10] Alternatively, $B(SePh)_3$ can be synthesized[1] from BBr_3 and PhSeNa. Analogous derivatives such as $Al(SePh)_3$,[11] Al(Se-1-naphthyl)$_3$,[11] $Ti(SePh)_4$,[11] $Zr(SePh)_2$,[11] $Cr(SePh)_3$,[11] $Nb(SePh)_3$,[11] $Ta(SePh)_3$,[11] $W(SePh)_4$,[11] $Ni(SePh)_2$,[11] and $Co(SePh)_2$,[11] as well as $Me_3SiSePh$,[12,13] $Me_3GeSePh$,[12b] and $Me_3SnSePh$,[14] have been prepared.

Handling, Storage, and Precautions: stable to heat, air oxygen, and light, but sensitive to humidity which decomposes them into selenols and boric acid. Therefore they must be stored under nitrogen or argon, and all reactions conducted under anhydrous conditions. Use in a fume hood.

General Discussion.

Phenylselenoacetals can be prepared either from carbonyl compounds[2-5,15] or from the corresponding *O,O*-acetals[3] by reaction with tris(phenylseleno)borane in the presence of catalytic amounts of proton acids (eqs 1 and 2).

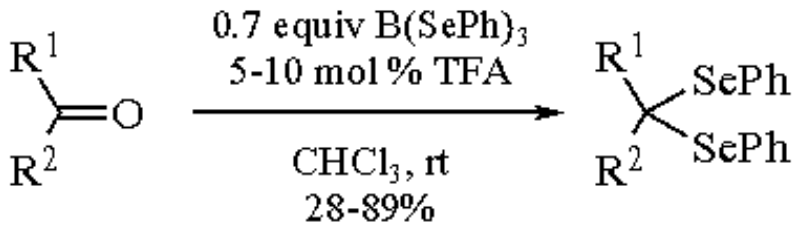

(1)

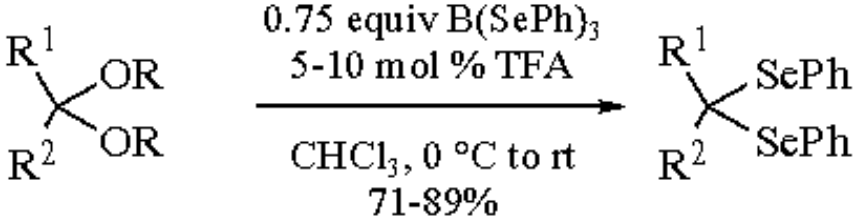

(2)

When the amount of $B(SePh)_3$ is reduced and the acid catalyst is omitted, the transacetalization reaction stops half-way, and gives mixed *O*,*Se*-acetals in excellent yield (eq 3).[3]

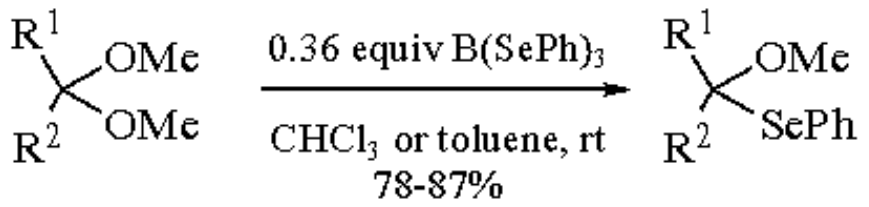

(3)

The opening of 1,2-disubstituted epoxides gives mainly β-hydroxy selenides after short reaction times (1-3 h), but gives 1,2-disubstituted alkenes after longer reaction times (24-54 h) (eq 4).[6] Trisubstituted epoxides lead to allylic alcohols.[6]

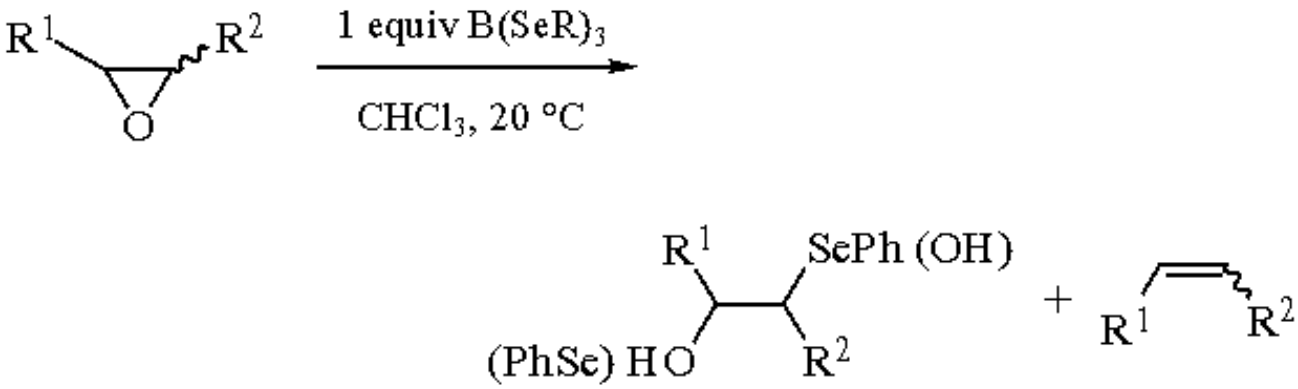

(4)

(Z): $R^1 = C_5H_{11}$; $R^2 = Me$ R = Ph, 0.8 h	77%	0%
(E): $R^1 = C_8H_{17}$; $R^2 = C_7H_{14}CO_2Me$ R = Me, 54 h	0%	71% *(E)*

Selenoacetalization of α,β-unsaturated carbonyl compounds[7] is more complicated for two reasons: 1,4-addition of the phenylselenolate species can compete with 1,2-attack; the well-known 1,3-rearrangement of allyl selenides[16,17] also affects the corresponding selenoacetals.[18] Thus the nature and composition of the products strongly depends on the substitution pattern of the starting α,β-unsaturated carbonyl derivative[7] (eqs 5 and 6).

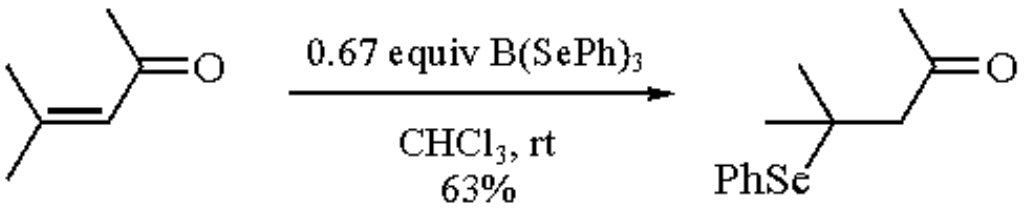

(5)

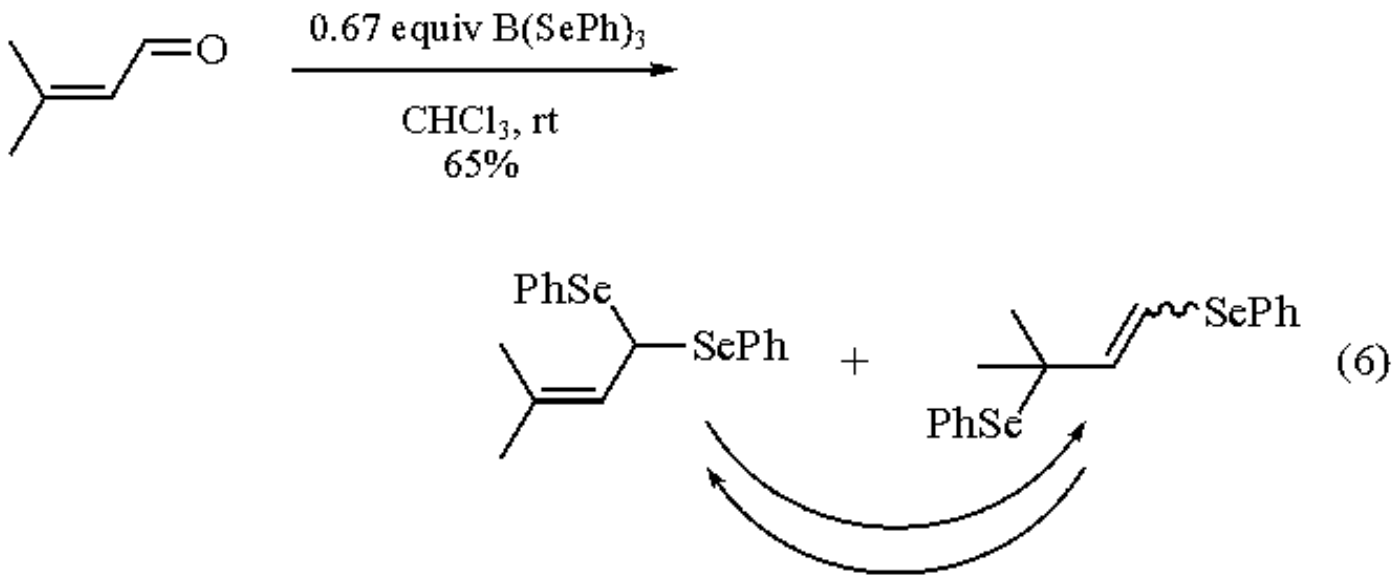

Hydroselenation of terminal alkynes proceeds best when an electron-attracting group is present on the C&tbond;C triple bond, and when oxygen is not excluded from the medium; (*Z*)-vinyl selenides are formed with high regio- and stereoselectivity (eq 7).[8]

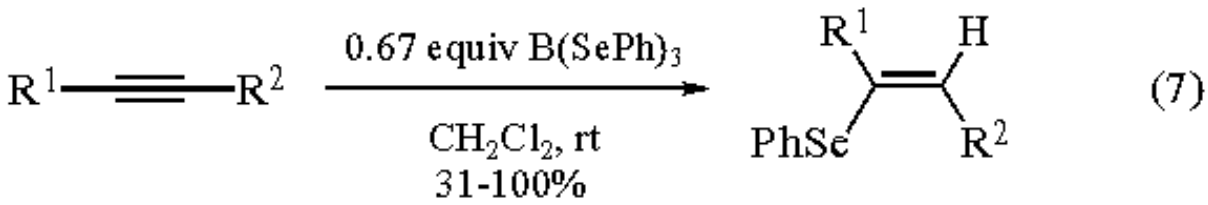

In spite of these features, a phenylselenyl radical-based mechanism is proposed mainly because the cyclization of enynes possessing a terminal C&tbond;C triple bond (eq 8) presents all the characteristics of such a mechanism.[8] Tris(phenylseleno)borane is also an efficient reagent for the deoxygenation of sulfoxides into sulfides.[8]

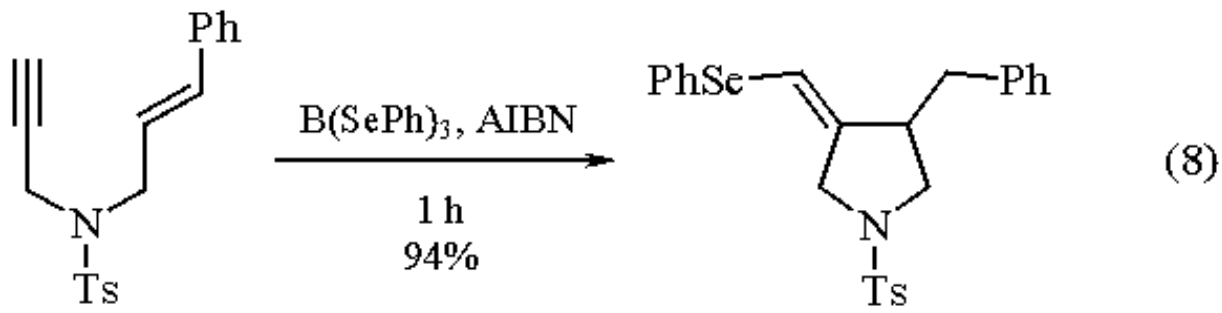

All of these reactions[19] can be effected with tris(methylseleno)borane,[20] $B(SeMe)_3$, to give products bearing the MeSe moiety.[4,7,8,13] It is surprising that the usefulness of the aluminum analogs has not been explored, except for the dimethyl derivative $Me_2AlSeMe$ which proved to be an excellent reagent for the conversion of esters into selenolesters.[21]

It is worth noting the close analogy between selenoboranes and thioboranes, both in their syntheses[22] and in their reactivity.[22b,c,23]

Related Reagents.

Dimethylaluminum Methylselenolate; ***9-Phenylseleno-9-borabicyclo[3.3.1]nonane***; ***Tris(ethylthio)borane***; ***Triphenyl Thioborate***.

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Tris(phenylthio)methane

$(PhS)_3CH$

[4832-52-4] · $C_{19}H_{16}S_3$ · Tris(phenylthio)methane · (MW 340.56)

(precursor to tris(phenylthio)methyllithium, used for nucleophilic carboxylation;[1] electrophilic formylating agent for aromatic compounds[2] and diazo esters[3])

Physical Data: mp 40-41 °C.

Solubility: freely sol most organic solvents; usually used in THF, methylene chloride, or ether.

Form Supplied in: off-white to pale yellow solid, typically 97-99% pure; commercially available.

Analysis of Reagent Purity: the NMR spectrum will establish the absence of ethyl formate, the usual precursor to the reagent. Residual thiophenol can be removed by washing an ethereal solution of the reagent with 1 N NaOH followed by standing under high vacuum.

Handling, Storage, and Precautions: is stable indefinitely if stored at ambient temperatures in tightly sealed containers to exclude moisture, which promotes hydrolysis to thiophenol and formic acid. The presence of residual thiophenol mandates that the reagent be handled in a fume hood to avoid inhalation of dust and that skin contact be avoided.

Nucleophilic Carboxylation.

The reagent, in THF or ether solution, is quantitatively converted to its lithiated derivative with 1 equiv of ***n-Butyllithium*** at -78 °C. It has also been converted to its sodium and potassium salts with the corresponding alkali metal amides.[4] The lithiated species is a useful nucleophilic carboxylating reagent for a variety of organic electrophiles. This chemistry is discussed in the article ***Tris(phenylthio)methyllithium***.

Electrophilic Formylation.

Apart from its role as precursor to tris(phenylthio)methyllithium, the utility of the reagent in organic synthesis has been very limited. Its use as an aromatic electrophilic formylating agent stems from the ability of certain Lewis acids to generate the bis(phenylthionium) cation (**1**) (eq 1).[1] In the case of intermolecular aromatic formylation, ***Dimethyl(methylthio)sulfonium Tetrafluoroborate*** (DMSTF)[5] is most effective in promoting the reaction. Yields of aldehydes are in the range 35-85%. The best yields are obtained with polycyclic aromatics such as α- or β-naphthol, although more-functionalized substrates still give acceptable results (eq 2). The hydrolysis of the thioacetal by excess DMSTF completes the sequence.

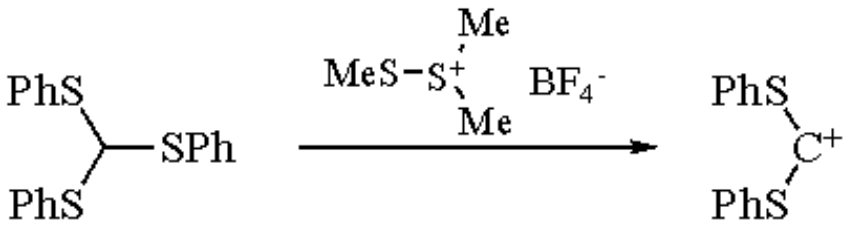

(1)

(1)

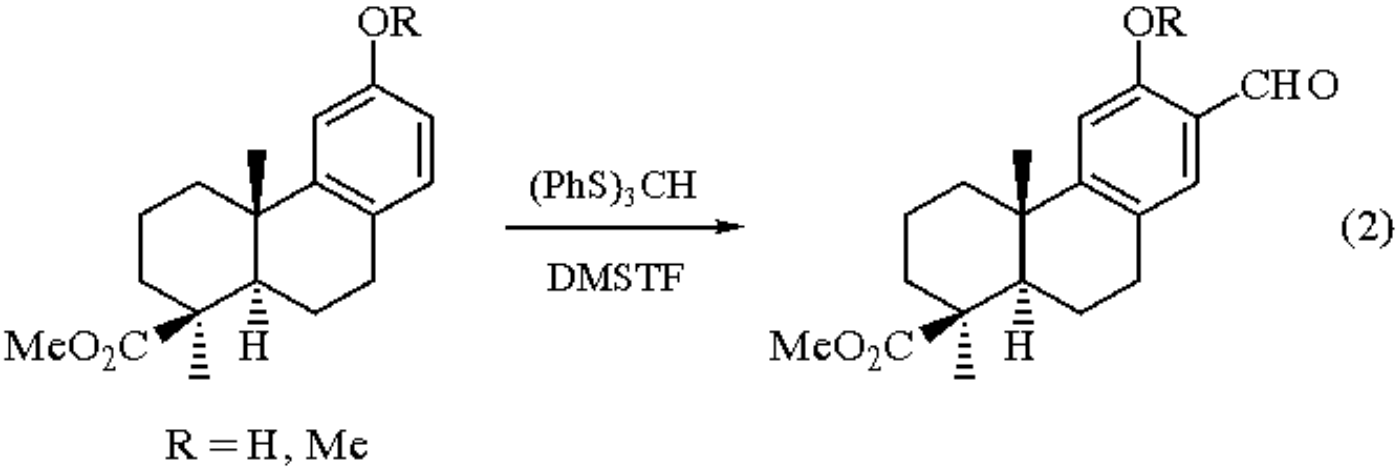

(2)

The scope of the substitution is limited to oxygen-activated aromatics. With these substrates there is a pronounced preference for formylation at the *para* position if it is available. If the *para* position is blocked, *ortho* formylation occurs with yields approximately equal to *para* formylation. Unactivated or weakly activated aromatics such as benzene or alkylbenzenes do not react with the reagent. Nitrogen-activated aromatics effectively compete with the reagent for the Lewis acid and are thus unable to react.

An extension of this chemistry has been developed for the preparation of cyclic oxygenated α-keto aromatics such as the methoxy-α-tetralone (**2**).[6] When applied in the intramolecular sense, the scope of the reaction broadens somewhat to include some alkyl-substituted substrates (for six-membered annulation). Annulation of five- or seven-membered rings onto the aromatic nucleus still requires oxygen activation. Although DMSTF was effective in promoting closure in some cases, ***Silver(I) Trifluoromethanesulfonate*** in methylene chloride proved to be a more generally effective catalyst for this reaction (eq 3).

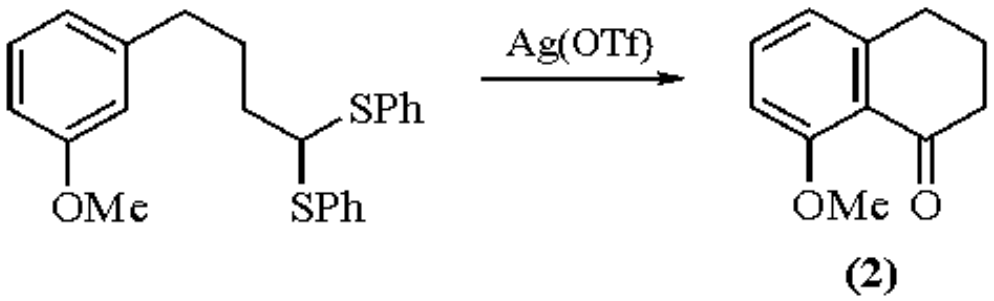

(3)

In the case of diazo esters, ***Boron Trifluoride Etherate*** was shown to promote formylation (eq 4).[3]

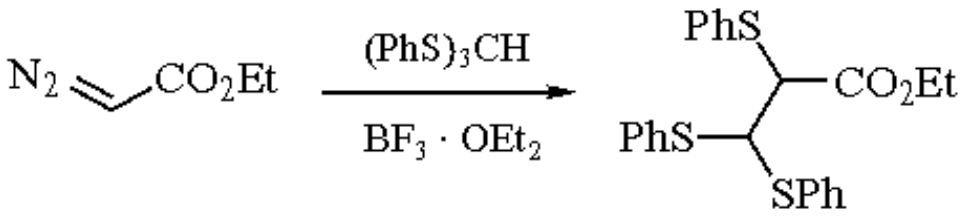

(4)

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1. (a) Seebach, D. *AG(E)* **1967**, *6*, 442. (b) Seebach, D. *AG* **1967**, *79*, 468. (c) Seebach, D. *CB* **1972**, *105*, 487 (*CA* **1972**, *76*, 99 736).
2. Smith, R. A. J.; Manas, A. R. B. *S* **1984**, 166.
3. Schönberg, A.; Praefcke, K. *CB* **1966**, *99*, 2371 (*CA* **1966**, *65*, 8752).
4. Fröling, A.; Arens, J. F.; *RTC* **1962**, *81*, 1009.
5. Trost, B. M.; Murayama, E. *JACS* **1981**, *103*, 6529.
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Tris(phenylthio)methyllithium[1]

$(PhS)_3CLi$

[14572-78-2] · $C_{19}H_{15}LiS_3$ · Tris(phenylthio)methyllithium · (MW 346.49)

(nucleophilic carboxylating agent for certain carbonyl compounds[2] and alkyl halides;[3] homologating agent for trialkylboranes;[4] carbene precursor[5])

Physical Data: not isolable; decomp above 20 °C to bis(phenylthio)carbene and lithium phenylthiolate.

Solubility: up to 2 M in THF.

Form Supplied in: not commercially available.

Analysis of Reagent Purity: titrate with D_2O or MeI.

Preparative Methods: generally prepared from ***n-Butyllithium*** and ***Tris(phenylthio)methane*** and used immediately; can also be generated from tetra(phenylthio)methane by Li-PhS exchange[2c] or from diphenyl trithiocarbonate and PhLi.[2c]

Purification: not generally practical; may contain products derived from ethyl formate used in preparation of tris(phenylthio)methane.

Handling, Storage, and Precautions: although not acutely pyrophoric, the reagent is readily hydrolyzed and should be handled under a dry, inert atmosphere. The reagent is corrosive to biological tissue. Storage, even in the cold, is not recommended because of instability. The reagent, its precursors, and reaction mixtures derived from its use, should be handled in a fume hood because of the smell of thiophenol.

Nucleophilic Carboxylation/Carbene Precursor.

Following early reports[6] of the deprotonation of trialkyl trithioorthoformates with alkali amides and their subsequent trapping with reactive electrophiles, the generation and trapping of this reagent were independently reported by Brandsma[3] and Seebach.[2a] More detailed studies of the properties of the reagent were later reported by Seebach.[7]

The reagent is quantitatively generated at -78 °C in THF by addition of 1 equiv of *n*-butyllithium to the precursor tris(phenylthio)methane. Upon raising the temperature to near ambient, the establishment of an equilibrium between the reagent and the transiently stable bis(phenylthio)carbene $(PhS)_2C$**:** was demonstrated by isolation from the reaction of products arising from its formation. These included the dimer tetraphenylthioethylene, as well as sulfur-substituted cyclopropanes obtained when ketene acetals and dithioketene acetals were added. Synthetically useful yields of cyclopropane products were obtained only when dithioketene acetals were used.[8]

These studies indicate the importance of generating and using the reagent shortly thereafter, if nucleophilic carboxylation is desired. Because the reagent is relatively bulky and has phenylthio groups as substituents, it is less reactive than the corresponding tris(methylthio) reagent (see ***Tris(methylthio)methane***). Its utility as a nucleophilic carboxylating agent is therefore more limited. Primary alkyl bromides and iodides (eq 1), allyl halides, CO_2 (eq 2), alkyl and aryl disulfides, silyl chlorides,[2a,3] and reactive ketones[9] efficiently interact with the reagent to afford the corresponding adducts. Aldehydes, saturated or unsaturated, react with the reagent to give 1,2-adducts (eq 3),[2a,5] although some variations in this behavior have been reported.[10,11] Ordinary ketones are enolized and recovered. Reactive epoxides and secondary halides give poor yields of alkylation products, apparently because the reagent adds too slowly to these electrophiles and functions as a base. However, unhindered α,β-unsaturated ketones add the reagent in the conjugate sense, affording γ-keto trithioorthotriesters in good to excellent yields (eq 4).[12] In the case of carbon electrophiles, these adducts are hydrolyzed to carboxylic acids with ***Mercury(II) Chloride***, ***Mercury(II) Oxide***, combinations of the two,[13] or $Ag(O_2CCF_3)_2$[11] in aqueous acetone, DMF, or dioxane at &egt;25 °C. Yields of carboxylation products are sometimes improved if the adducts are subjected to alcoholysis, affording the ester,[12,13a] or to partial hydrolysis, affording the thioester.[14] Conventional hydrolysis can then be employed if the carboxylic acid is desired (eq 5).[15]

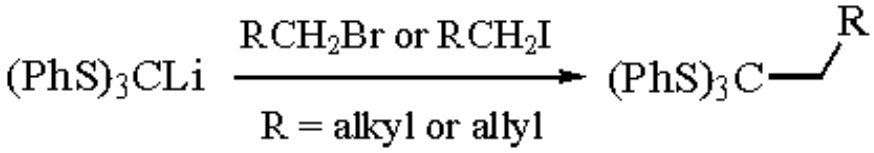

(1)

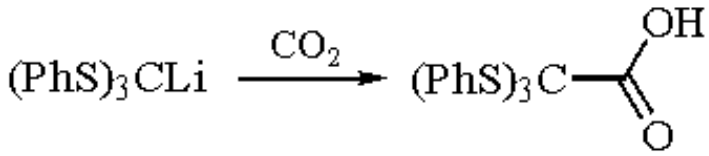

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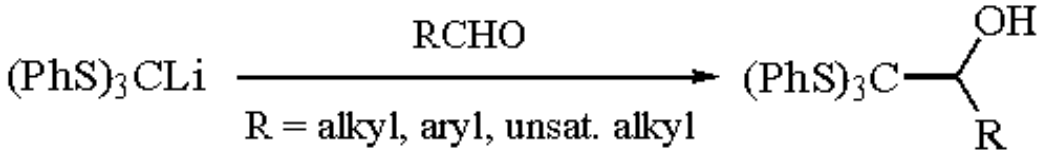

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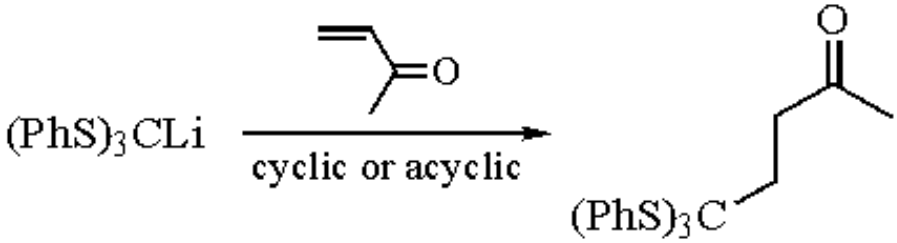

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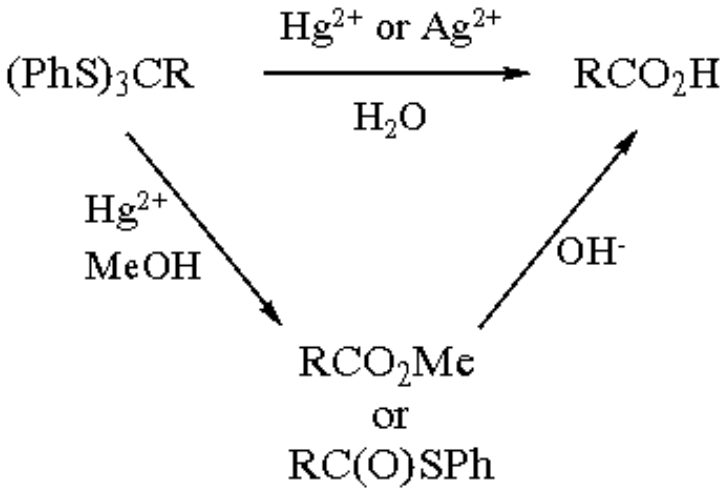

(5)

The reagent reacts with lactones such as δ-valerolactone, with various results having been reported (eq 6).[16]

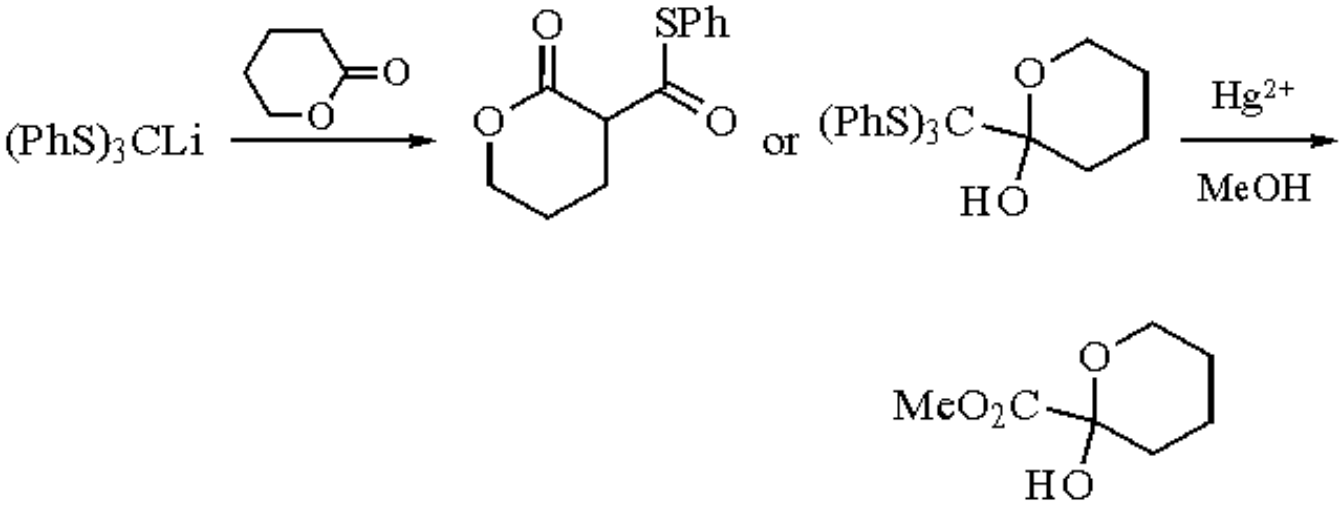

(6)

Recently, a nucleophilic carboxylation using this reagent to prepare the glyoxylate synthon tris(phenylthio)acetaldehyde, was reported (eq 7).[11]

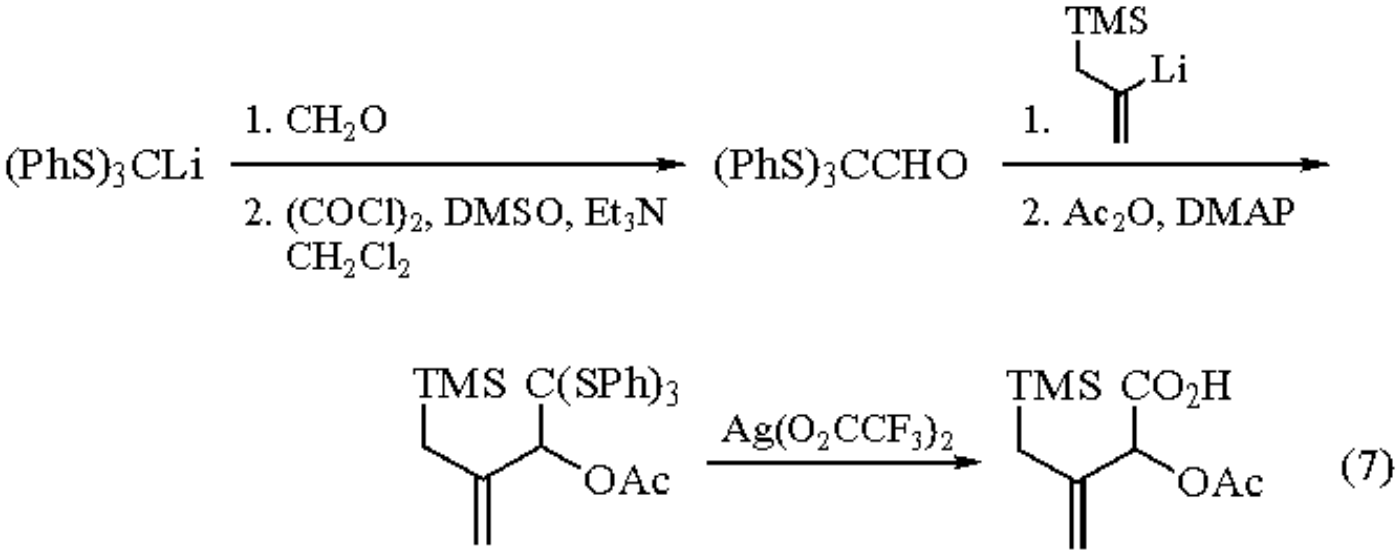

Conjugate addition of the reagent to cyclic unsaturated ketones has the feature of generating regiochemically homogenous enolates which can be trapped in situ with appropriate electrophiles (eq 8).[17]

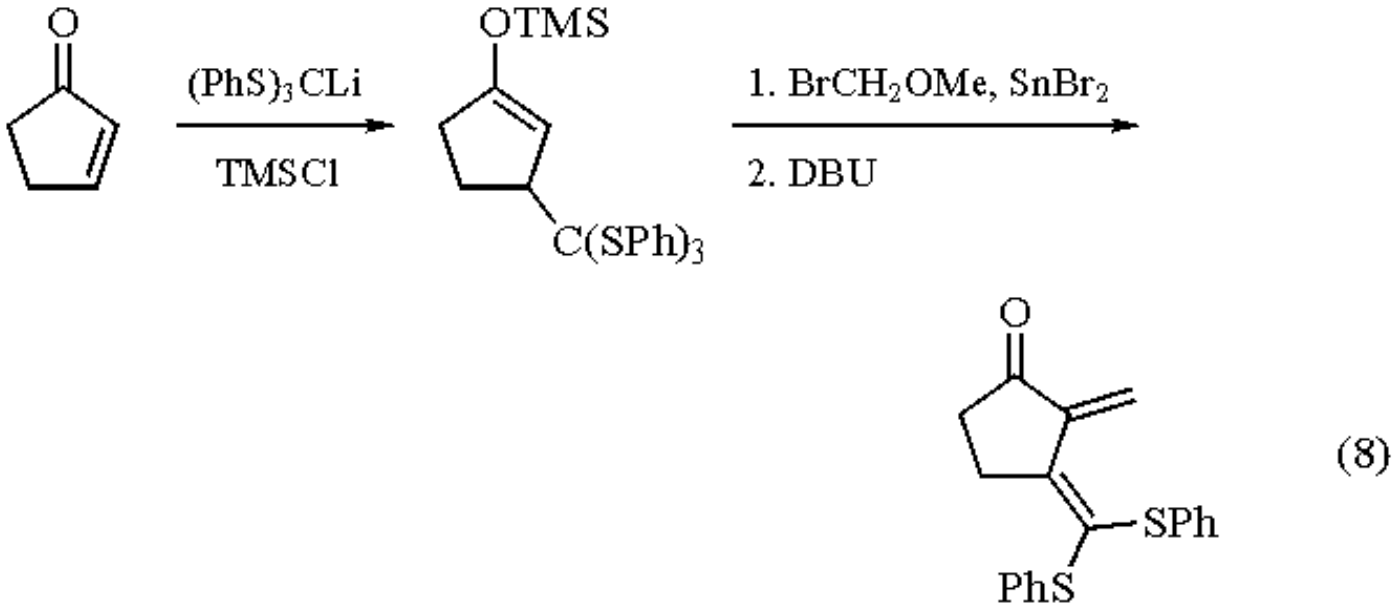

A useful property of the adducts of the reagent is their continued ability to undergo further lithiation or generate carbenes. These reactive intermediates can, if generated in the appropriate location, induce further transformations typical of carbanions or carbenes such as ring expansions,[9] hydrogen shifts,[5] and conjugate additions (eqs 9-11).[18] Although the reagent is of very limited utility in cyclopropane synthesis when used intermolecularly, intramolecular trapping of the carbenoid center by a nucleophilic alkene is an excellent route to sulfur-substituted cyclopropane-containing bicyclic ketones (eq 12).[19]

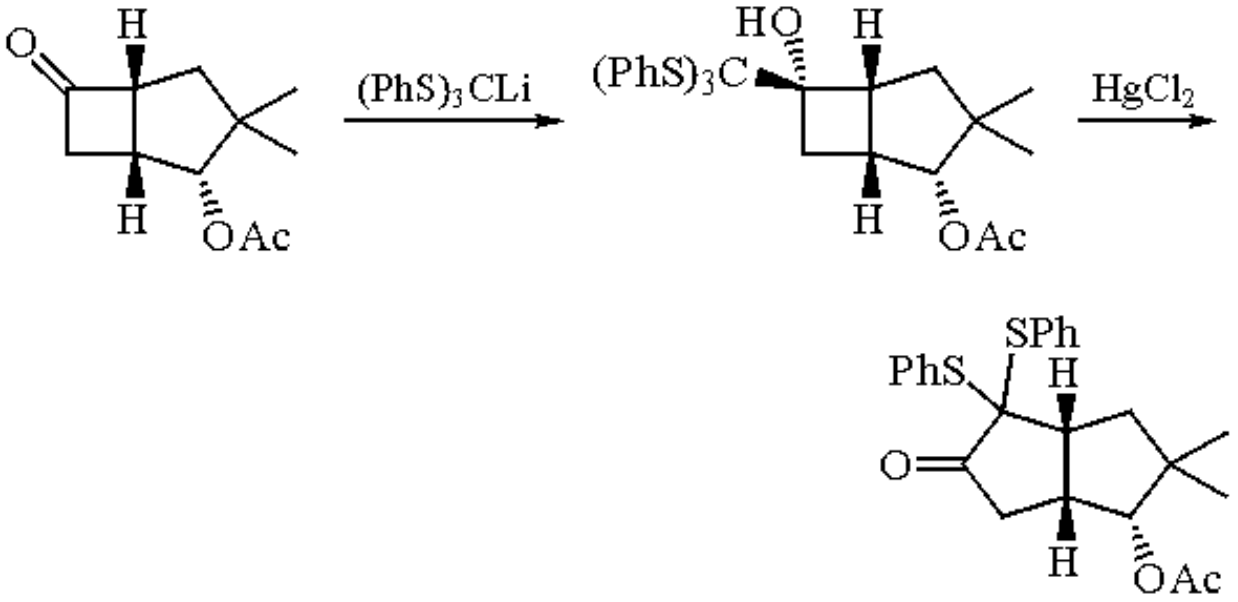
(PhS)3CLi
HgCl2
(PhS)3C
HO
H
OAc
SPh
PhS
O

(9)

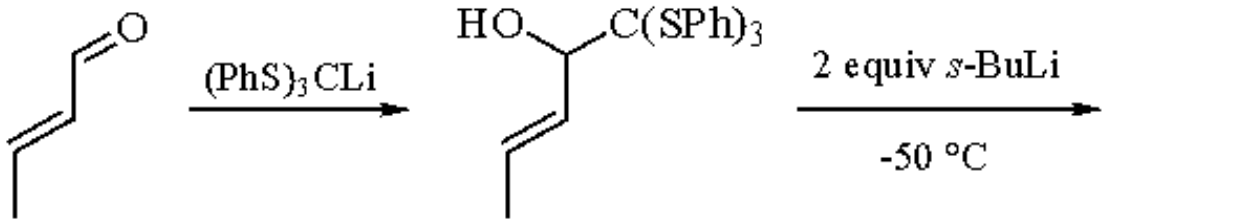
(PhS)3CLi
HO
C(SPh)3
2 equiv s-BuLi
-50 °C

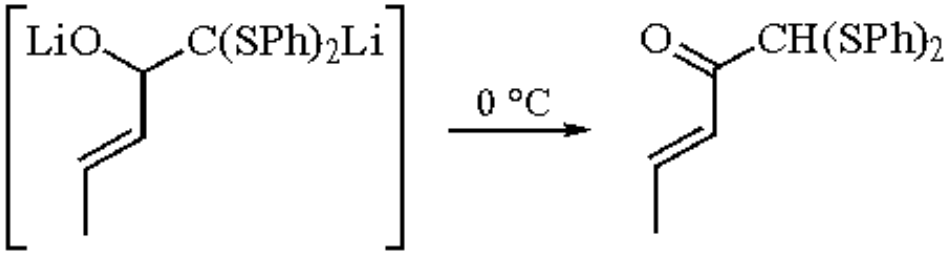
LiO
C(SPh)2Li
0 °C
O
CH(SPh)2

(10)

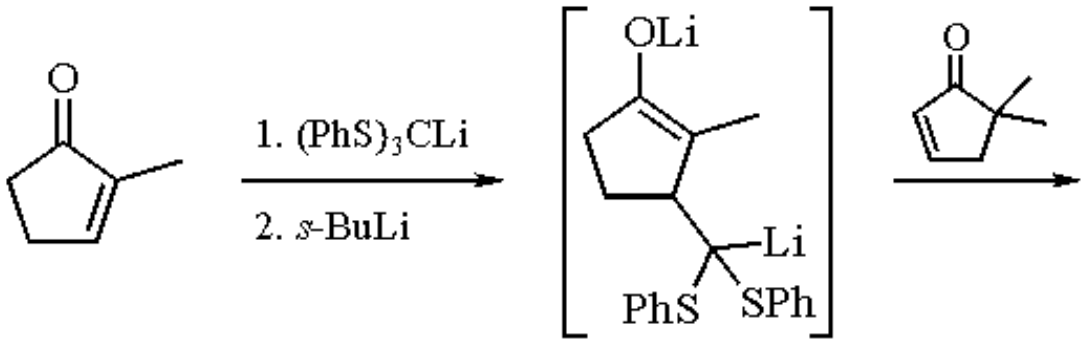
1. (PhS)3CLi
2. s-BuLi
OLi
Li
PhS
SPh
O

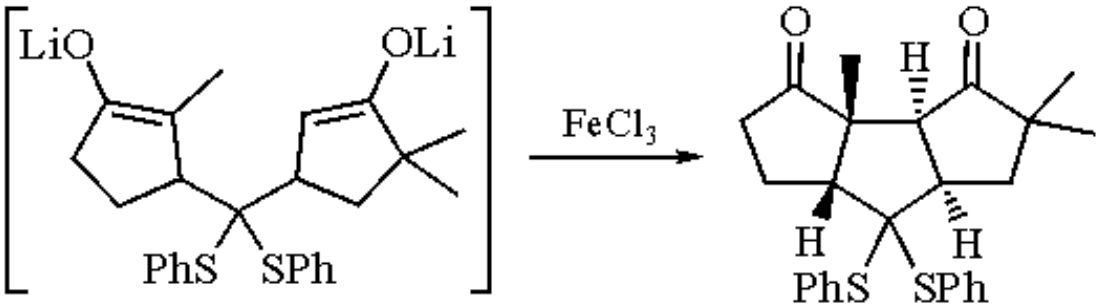
LiO
OLi
PhS
SPh
FeCl3
O
H
H

(11)

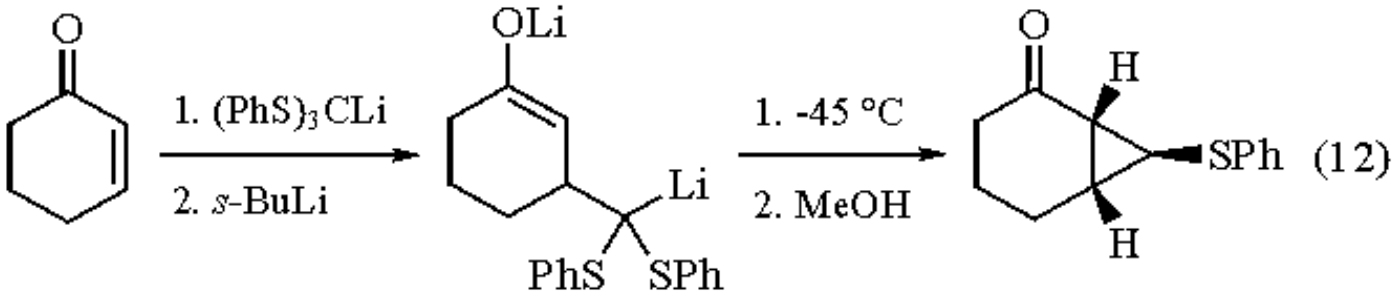

Homologation of Trialkylboranes.

When treated with relatively unhindered trialkylboranes, the reagent serves as a homologating agent, affording either ketones or tertiary alcohols. The best substrates for the reaction are boranes containing primary alkyl or cycloalkyl groups. The products are obtained after standard oxidation with basic ***Hydrogen Peroxide***, and their nature depends on the presence or absence of mercury(II) chloride. In the absence of Hg^{2+}, ketones are obtained, whereas in its presence, tertiary alcohols are the products. Primary alkyl groups migrate preferentially. The stoichiometry of the reaction is illustrated in eq 13.[4]

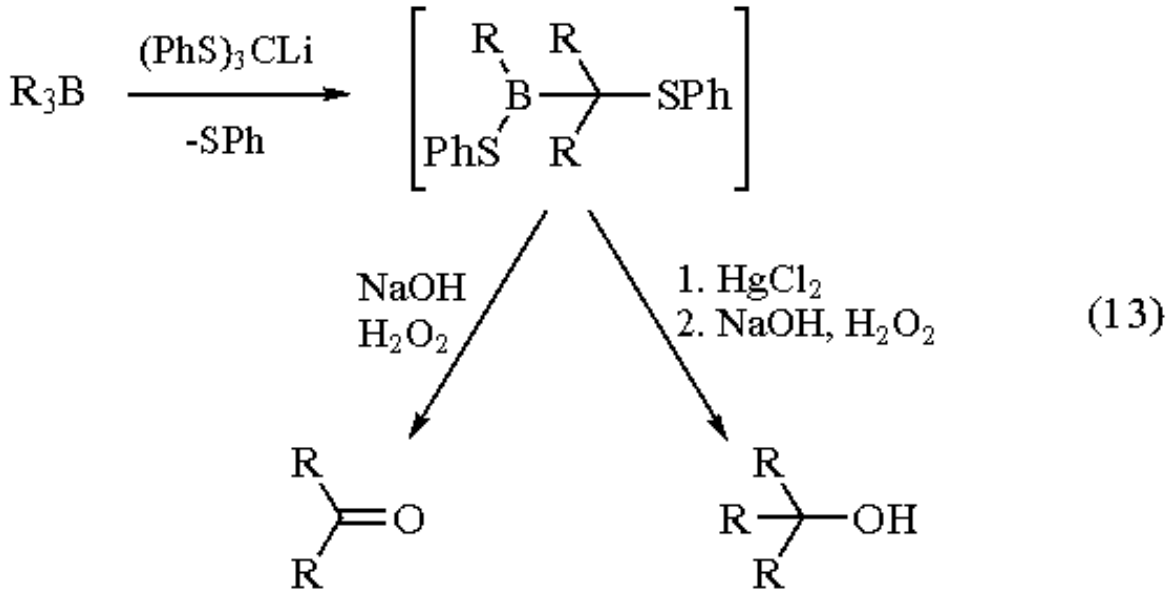

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1. Gröbel, B.-T.; Seebach, D. *S* **1977**, 357.
2. (a) Seebach, D. *AG(E)* **1967**, *6*, 442. (b) Seebach, D. *AG* **1967**, *79*, 468. (c) Seebach, D. *CB* **1972**, *105*, 487 (*CA* **1972**, *76*, 99 736).
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6. Fröling, A.; Arens, J. F. *RTC* **1962**, *81*, 1009.
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11. Trost, B. M.; Grese, T. A. *JACS* **1991**, *113*, 7363.
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15. Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *JACS* **1977**, *99*, 6756.
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18. Ramig, K.; Cohen, T.; Kuzemko, M. A.; McNamara, K. *JOC* **1992**, *57*, 1968.
19. Ramig, K.; Cohen, T.; Bhupathy, M. *JOC* **1989**, *54*, 4404.

Conrad Santini

Tris(*o*-tolyl)[(2-(trimethylsilyl)ethylidene]phosphorane[1]

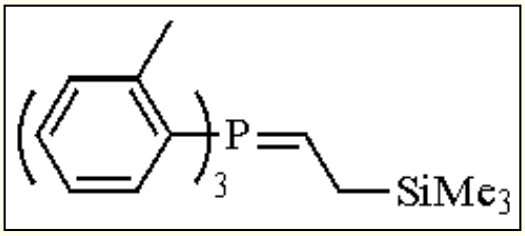

[104697-92-9] · $C_{26}H_{33}PSi$ · Tris(*o*-tolyl)[(2-(trimethylsilyl)ethylidene]phosphorane · (MW 404.65)

(*cis*-selective Wittig reaction for synthesis of allylsilanes;[1] with modification of substituents on phosphorus and silicon atoms, β-silylphosphorus ylides give allylic alcohols diastereoselectively[2])

Preparative Methods: prepared in situ from tris(*o*-tolyl)[2-(trimethylsilyl)ethyl]phosphonium iodide and ***n-Butyllithium*** in THF.[1] Tris(*o*-tolyl)phosphorus methylide (prepared in situ from methyltris(*o*-tolyl)phosphonium bromide and *n*-BuLi in THF) and ***(Iodomethyl)trimethylsilane*** were heated under reflux in THF for 5 h. The mixture was poured into H_2O and the phosphonium salt was extracted with CH_2Cl_2. Evaporation of the organic solvent gave an oily residue which was crystallized from THF-Et_2O (mp 111-113 °C). To a stirred suspension of the phosphonium salt in THF (6 mL g^{-1}) was added 1 equiv of *n*-BuLi under a nitrogen atmosphere at 0 °C and the mixture was stirred for 30 min at rt, resulting in a clear yellow ylide solution.

Handling, Storage, and Precautions: unstable to air and moisture. Should be handled under a dry nitrogen atmosphere.

Wittig Reaction with (*Z*) Selectivity.

Phosphorus ylides having silyl groups at the β-position react with aldehydes by two pathways: a Wittig reaction and a vinylation reaction that affords allylic alcohols via migration of the silyl group and elimination of phosphine. [2-(Trimethylsilyl)ethylidene]triphenylphosphorane has been used for synthesis of allylsilanes from aldehydes.[3] The reaction, however, shows low (*Z*/*E*) selectivity. In addition, allylic alcohol is formed as byproduct.[3b,4] With modification of the substituents on the phosphorus atom from phenyl to the bulkier *o*-tolyl group, the title reagent reacts with aliphatic saturated aldehydes to give allylsilanes with high (*Z*) selectivity and without formation of allylic alcohols (eq 1).[1]

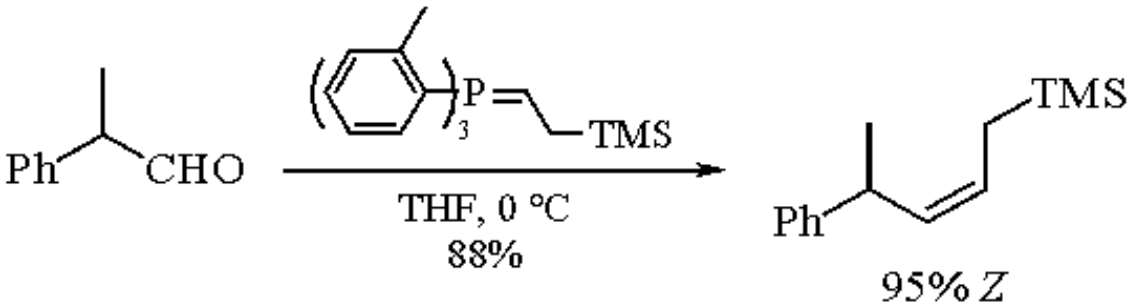

(1)

Diastereoselective Alkenylation of Aldehydes.

In the dichotomous reactivity of β-silylphosphorus ylides, electron-donating groups on the phosphorus atom and electron-withdrawing groups on silicon effect the selective formation of allylic alcohols over allylsilanes.[2] Tris(4-methoxyphenyl)[(2-(methyldiphenylsilyl)ethylidene]phosphorane [*110598-64-6*] reacts diastereoselectively with chiral aldehydes to afford allylic alcohols with suppression of the Wittig reaction. With 2-phenylpropanal the *erythro* (*syn*) product predominates[2] and with α-benzyloxy aldehydes (eq 2)[5] and α,β-epoxy aldehydes[6] the ylide gives *erythro* (*anti*) product selectively via the Felkin-Anh model. With α-*N*-Boc-amino aldehydes, [2-(trimethylsilyl)ethylidene]triphenylphosphorane gives the *threo* (*syn*) product preferentially through Cram's chelation

transition state.[7]

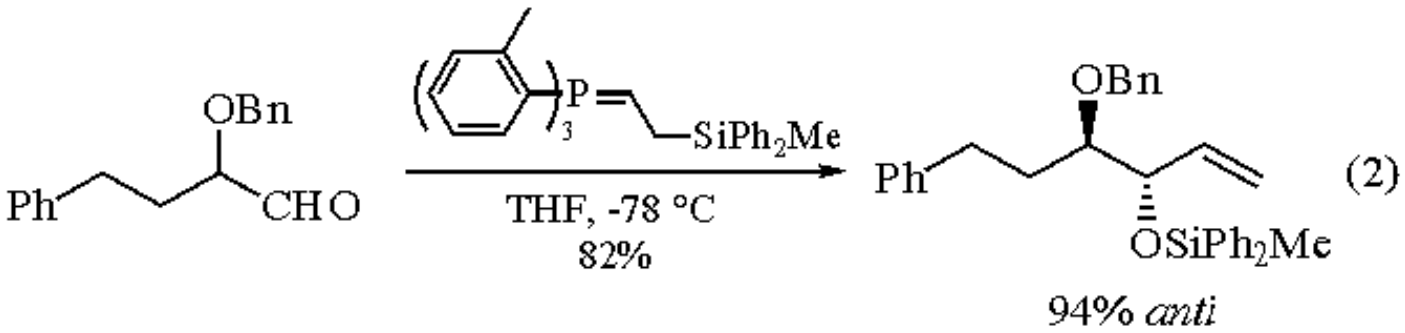

Diastereoselective isopropenylation[2] and (*E*) propenylation (eq 3)[8] are also possible using β-silylphosphorus ylides substituted with methyl groups at the α- and β-positions, respectively. The latter ylide was prepared in situ by addition of methyldiphenylsilyllithium to the propenylphosphonium salt.[8]

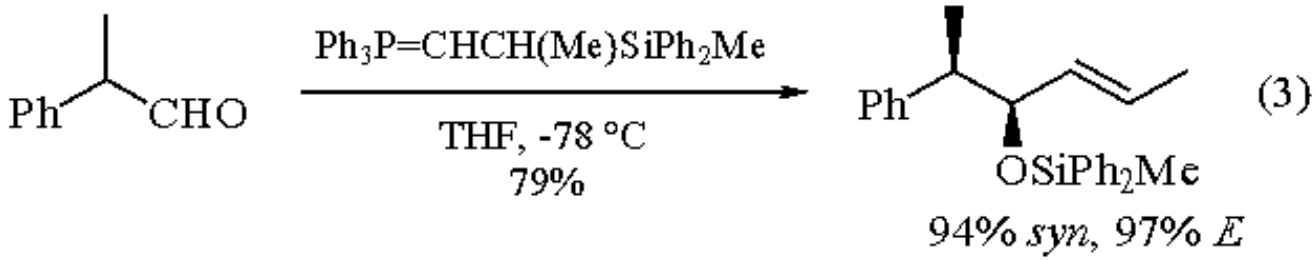

Enantioselective vinylation of aldehydes (up to 92% ee) was reported by using a β-silylphosphorus ylide carrying a chiral ferrocenyl group on the phosphorus atom.[9]

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1. (a) Iio, H.; Ishii, M.; Tsukamoto, M.; Tokoroyama, T. *TL* **1988**, *29*, 5965.
2. (a) Tsukamoto, M.; Iio, H.; Tokoroyama, T. *TL* **1985**, *26*, 4471. (b) Tsukamoto, M.; Iio, H.; Tokoroyama, T. *CC* **1986**, 880.
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6. Iio, H.; Mizobuchi, T.; Tokoroyama, T. *TL* **1987**, *28*, 2379.
7. Franciotti, M.; Mann, A.; Taddei, M. *TL* **1991**, *32*, 6783.
8. Tsukamoto, M.; Iio, H.; Tokoroyama, T. *TL* **1987**, *28*, 4561.
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Tris(trimethylsilyl)aluminum[1]

$(Me_3Si)_3Al$

[65343-66-0] · $C_9H_{27}AlSi_3$ · Tris(trimethylsilyl)aluminum · (MW 246.61) (.OEt_2)

[75441-10-0] · $C_{13}H_{37}AlOSi_3$ · Tris(trimethylsilyl)aluminum Diethyl Etherate · (MW 320.75)

(nucleophilic silylation;[2,3] silylalumination of terminal alkynes;[4] preparation of allyl-, aryl-, and alkenylsilanes[5,6])

Physical Data: mp 60 °C (dec).

Solubility: sol ethers, pentane, benzene; reacts violently with protic solvents.

Form Supplied in: white needles; not commercially available.

Preparative Methods: to ***Aluminum*** powder and granular aluminum in ether is added ***Mercury(0)*** and ***Chlorotrimethylsilane*** followed by ***Lithium*** wire. After the reaction is complete, the solution is filtered and ether is removed. The solid residue is stirred with pentane, which effects removal of insoluble $Li(Me_3Si)_4Al$. Partial concentration and cooling of the pentane solution gives $(Me_3Si)_3Al.OEt_2$ as white needles.[1b,2c]

Handling, Storage, and Precautions: ignites spontaneously in air. The reagent can be conveniently handled as a stock solution in pentane, which can be stored under an inert atmosphere in a freezer. The molarity can be determined by titration.[2c,6]

Carbonyl Additions.

The reagent is a useful nucleophilic trimethylsilyl transfer agent.[2a] Enones and enals undergo 1,2-addition in ether at room temperature, while 1,4-addition occurs at -78 °C (eq 1).[2b] Ester carbonyls, which are amenable to attack only in boiling ether in the presence of ***Aluminum Chloride***, give α,α-bis(trimethylsilyl)alkanols.[2a]

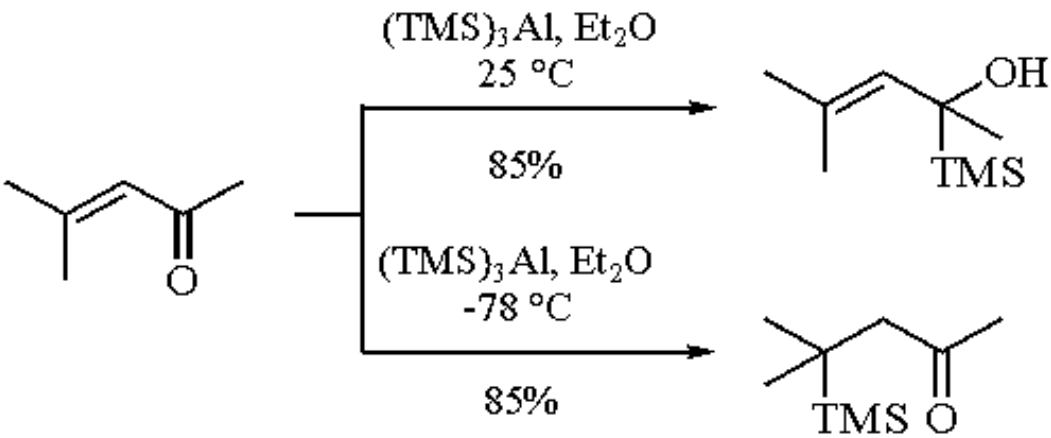

(1)

Functionalized acylsilanes are accessible by the reaction of $(Me_3Si)_3Al.OEt_2$ with (*S*)-2-pyridyl esters in the presence of stoichiometric ***Copper(I) Cyanide*** (eq 2).[3]

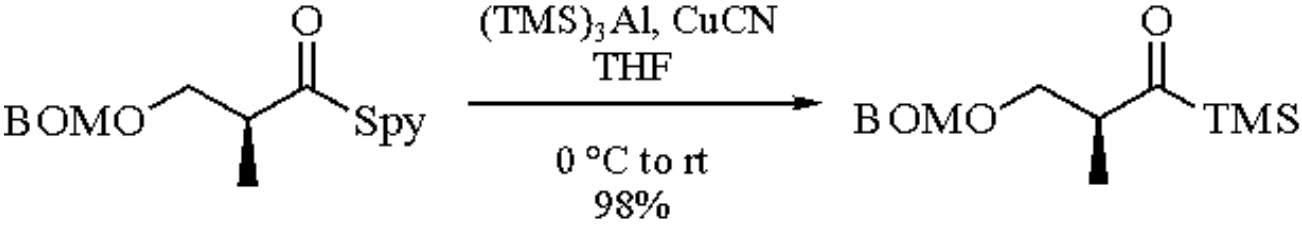

(2)

Silylalumination of Alkynes.

Silylalumination of 1-alkynes provides a convenient entry to vinylsilane derivatives in a regio- and stereoselective manner (eq 3).[4]

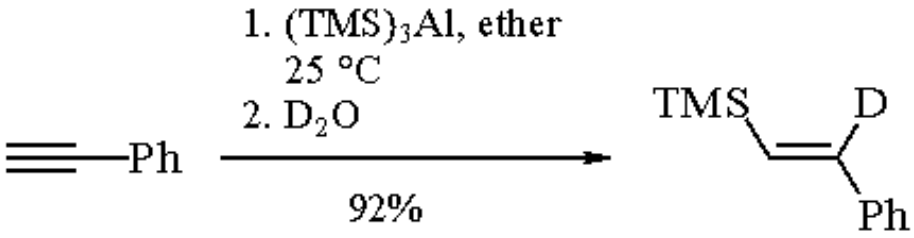

(3)

Transition Metal Promoted Coupling Reactions.

In the presence of a Ni catalyst, the reagent undergoes cross-coupling reactions with aryl bromides (eq 4).[5] Alkenyl iodides are stereospecifically converted to alkenylsilanes in the presence of a Pd catalyst (eq 5).

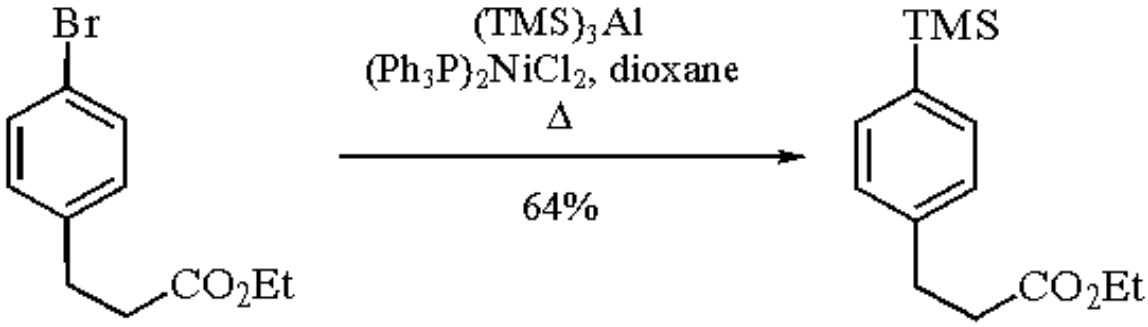

(4)

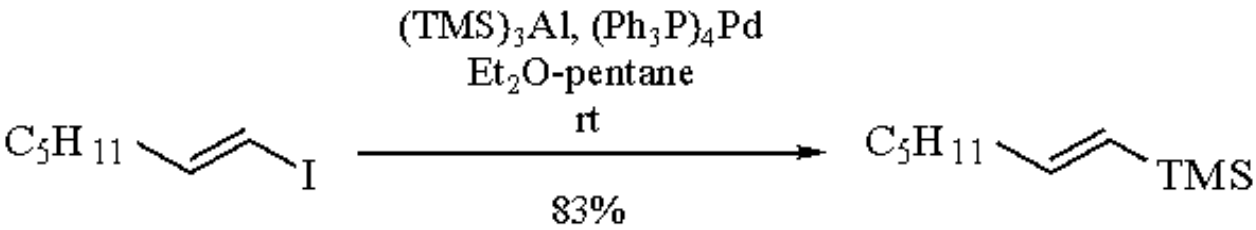

(5)

Allylic acetates are converted to allylsilanes in the presence of Pd^0 complexes or ***Hexacarbonylmolybdenum***. The regioselectivity depends on the catalyst. The Mo^0 catalyst leads to products with the silyl group attached to the less-hindered end of the allyl group. The regioselectivity of the Pd^0-catalyzed reaction depends on the solvent and, in particular, on the ligands. The two catalysts also differ with respect to stereochemistry (eq 6).[6]

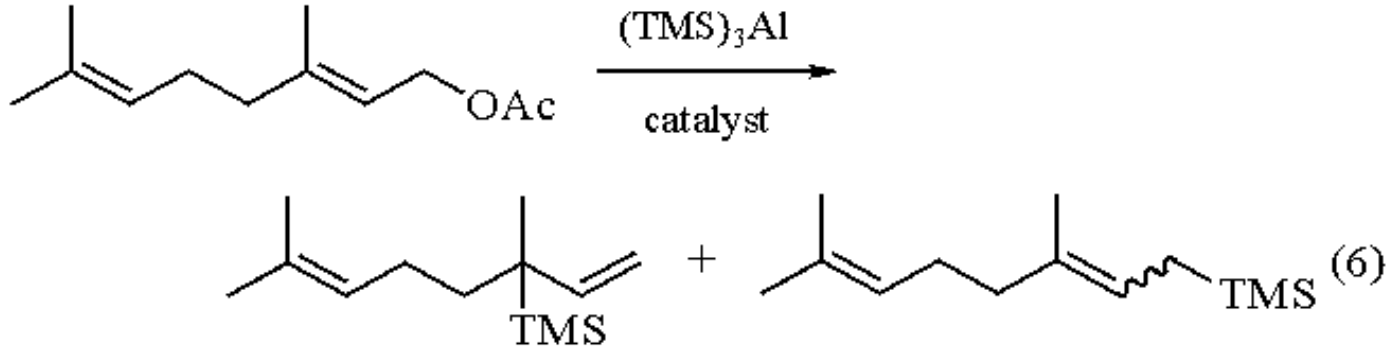

$(Ph_3P)_4Pd$, THF, 25 °C	86%	61 : 39
$Mo(CO)_6$, toluene, reflux	72%	0:100

---

1. (a) Rösch, L. *AG(E)* **1977**, *16*, 480. (b) Rösch, L.; Altnau, G. *JOM* **1980**, *195*, 47. (c) Rösch, L.; Altnau, G.; Krüger, C.; Tsay, Y.-H. *ZN(B)* **1983**, *38B*, 34.
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Tris(trimethylsilyl)ketenimine[1]

$(Me_3Si)_2C{=}C{=}N\text{-}SiMe_3$

[7351-44-2] · $C_{11}H_{27}NSi_3$ · Tris(trimethylsilyl)ketenimine · (MW 257.66)

(reactions with aldehydes; selective synthesis of (*Z*)-2-alkenenitriles and (*E*)-2-(1-hydroxyalkyl)-2-alkenenitriles)

Physical Data: bp 94-96 °C/19 mmHg.

Solubility: sol ether, THF; modestly sol aprotic solvents; reacts with H_2O and protic solvents.

Form Supplied in: colorless oil.

Analysis of Reagent Purity: IR νfilmmax 2050, 1410, 1260, 840 cm^{-1}. ^1H NMR (CCl_4) δ 0.09 (s, 18 H), 0.19 (s, 9 H).

Preparative Methods: to a solution of ***Trimethylsilylacetonitrile***[2] (3.01 g, 26.6 mmol) in dry diethyl ether (40 mL) is added ***n-Butyllithium*** (10 % w/v in hexane, 38 mL, 59.3 mmol) at -60 °C and stirring is continued for 0.5 h. ***Chlorotrimethylsilane*** (7.48 g, 68.9 mmol) is slowly added and the mixture is allowed to warm to room temperature. The mixture is concentrated and distilled at bp 94-96 °C/19 mmHg to give tris(trimethylsilyl)ketenimine (5.67 g, 83%).

Purification: distill under reduced pressure.

Handling, Storage, and Precautions: bottles of tris(trimethylsilyl)ketenimine should be kept tightly sealed to preclude contact with moisture.

General Discussion.

Tris(trimethylsilyl)ketenimine (**1**) reacts with aldehydes in the presence of ***Boron Trifluoride Etherate*** at room temperature in benzene[3] or dichloromethane to give a 1:1 adduct.[4] Upon heating, the adduct is converted quantitatively into (*E*)-2-trimethylsilyl-2-alkenenitriles (**2**) (eq 1).

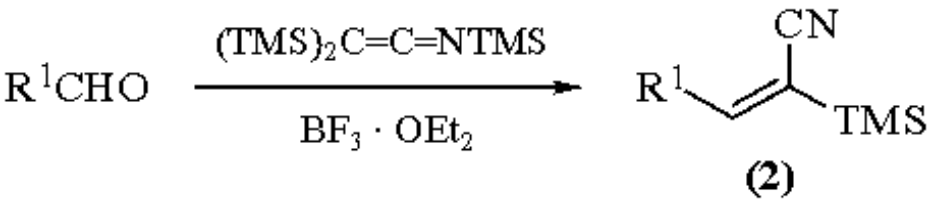

(1)

Compound (**2**) is desilylated in an alkaline medium to give pure (*Z*)-2-alkenenitriles (**3**) (eq 2).[3] Several examples are summarized in Table 1.

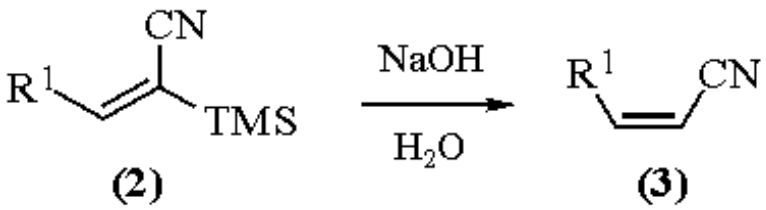

(2)

Table 1 Yields of (*E*)-2-Trimethylsilyl-2-alkenenitrile (**2**) and (*Z*)-Alkenenitriles (**3**)

R^1	Yield (%) (**2**)	Yield (%) (**3**)	Isomeric purity of (**3**) (%)
Pr	78	65	100
C_5H_{11}	74	85	100
Cy	67	85	100
Bu(Et)CH	74	91	100
Bn	78	95	100
Ph	89	97	96

Compound (**2**) also reacts with carbonyl compounds in the presence of ***Tetra-n-butylammonium Fluoride*** (TBAF) to give (*E*)-2-(1-hydroxyalkyl)-2-alkenenitriles (**4**) (eq 3).[5] Several examples of this reaction are provided in Table 2.

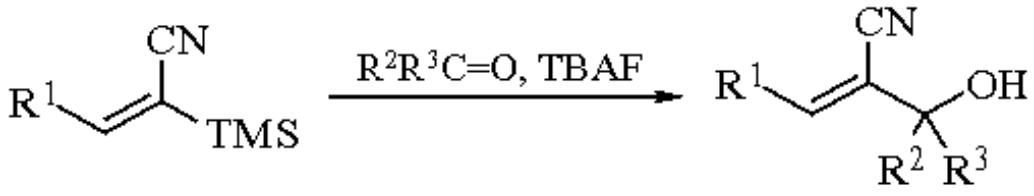

(2) (4) (3)

Table 2 Yields of (*E*)-2-(1-Hydroxyalkyl)-2-alkenenitriles (**4**)

R^1	R^2	R^3	Yield of (**4**) (%)
C_7H_{13}	H	Me	70
	H	Ph	81
	Me	Me	22
	Me	Ph	33
Bu(Et)CH	H	Me	76
	H	Ph	79
Cy	H	Me	75
	H	Ph	74
Ph	H	Me	68
	H	Ph	72

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Tris(trimethylsilyl)methane[1]

$(Me_3Si)_3CH$

[1068-69-5] · $C_{10}H_{28}Si_3$ · Tris(trimethylsilyl)methane · (MW 232.65)

(precursor of $(Me_3Si)_3CLi$, useful to introduce bulky tris(trimethylsilyl)methyl (trisyl) group; Peterson alkenation reagent)

Physical Data: bp 219 °C, 93-95 °C/13.5 mmHg; *d* 0.836 g cm^{-3}; *n*20D 1.4657.

Solubility: sol common organic solvents.

Analysis of Reagent Purity: ^1H NMR.

Purification: by distillation.

Preparative Methods: the reaction of ***Chlorotrimethylsilane***, ***Lithium*** metal, and ***Chloroform*** in THF gives tris(trimethylsilyl)methane.[2]

Handling, Storage, and Precautions: can be stored in a glass bottle.

Synthesis of Tris(trimethylsilyl)methyl Bromide.[3]

Tris(trimethylsilyl)methyl bromide (trisyl bromide) can be prepared in 75% yield by photochemical bromination of neat tris(trimethylsilyl)methane at 180-190 °C in less than 5 h (eq 1).

$$(TMS)_3CH + Br_2 \xrightarrow[75\%]{\substack{h\nu \\ 180\text{-}190\ ^\circ C}} (TMS)_3CBr + HBr \qquad (1)$$

Trisyl bromide is very reactive toward lithium, magnesium, and phenyllithium to give the corresponding organometallic reagents. These reagents are useful in the Peterson alkenation reaction.

Metalation.

Tris(trimethylsilyl)methyllithium can be prepared by metalation of tris(trimethylsilyl)methane by ***Methyllithium*** in a mixture of diethyl ether and THF (eq 2).[4] An improved procedure is described as follows. To a solution of tris(trimethylsilyl)methane in THF is added a solution of MeLi (10% excess) in diethyl ether with stirring under nitrogen. The diethyl ether is distilled off and the residual solution is boiled under reflux under nitrogen. After 2 h, about 95% of tris(trimethylsilyl)methane is converted to tris(trimethylsilyl)methyllithium. Tris(trimethylsilyl)methyllithium is important for the introduction of $(Me_3Si)_3C$ (trisyl) groups, and for use in Peterson alkenations (eq 3).

$$(TMS)_3CH + MeLi \xrightarrow{Et_2O\text{-}THF} (TMS)_3CLi \qquad (2)$$

$$(TMS)_3CLi + CH_2O \xrightarrow[70\%]{} (TMS)_2C{=}CH_2 \qquad (3)$$

Formation of Bis(trimethylsilyl)methyllithium.

The carbon-silicon bond of tris(trimethylsilyl)methane can be cleaved by lithium methoxide in HMPA to form bis(trimethylsilyl)methyllithium, which subsequently reacts with carbonyl compounds to form alkenes (eq 4).[5]

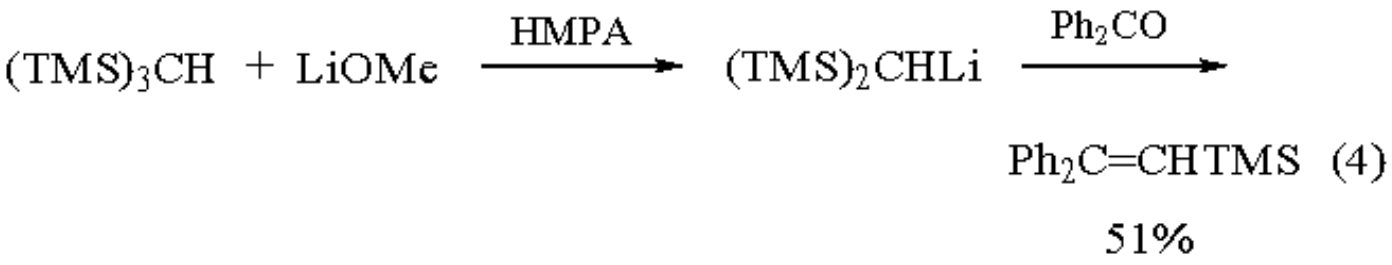

Similar cleavage of the Si-C bond occurs with fluoride ion. The in situ reaction with carbonyl compounds gives the corresponding alkenes. Thus the reaction of tris(trimethylsilyl)methane with nonenolizable carbonyl compounds in the presence of ***Tris(dimethylamino)sulfonium Difluorotrimethylsilicate*** (TASF) gives the corresponding alkenes in excellent yield (eq 5).[6]

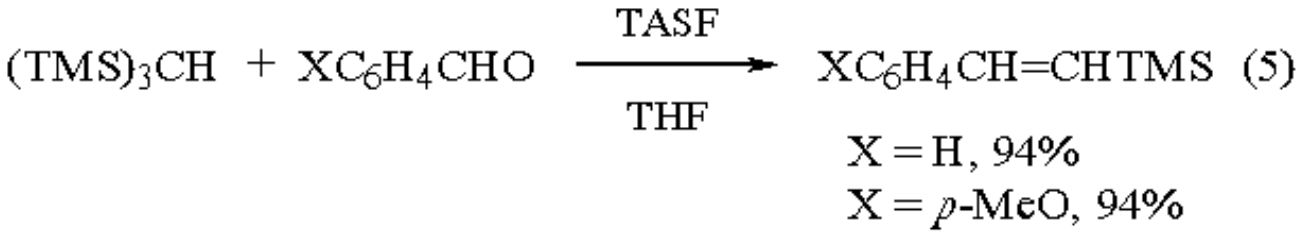

Related Reagents.

Bis(trimethylsilyl)methane.

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Tris(trimethylsilyloxy)ethylene

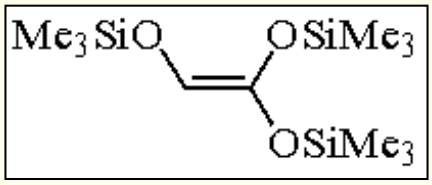

[69097-20-7] · $C_{11}H_{28}O_3Si_3$ · Tris(trimethylsilyloxy)ethylene · (MW 292.66)

(conversion of carboxylic acid chlorides to terminal α-hydroxy ketones;[1,2] conversion of aldehydes and ketones to 2,3-dihydroxyalkanoic acids[3,4])

Physical Data: bp 54-56 °C/0.1 mmHg; *d* 0.886 g cm^{-3}.[5]

Solubility: sol all organic solvents; insol in H_2O (reacts).

Form Supplied in: colorless free-flowing liquid; available commercially.

Preparative Methods: from the bis(trimethylsilyl) derivative of glycolic acid by either forming the enolate with ***Lithium Hexamethyldisilazide*** at -78 °C in THF and trapping with ***Chlorotrimethylsilane***,[1,2] or by the reaction with ***Trimethylsilyl Trifluoromethanesulfonate*** and ***Triethylamine*** at rt (eq 1).[6]

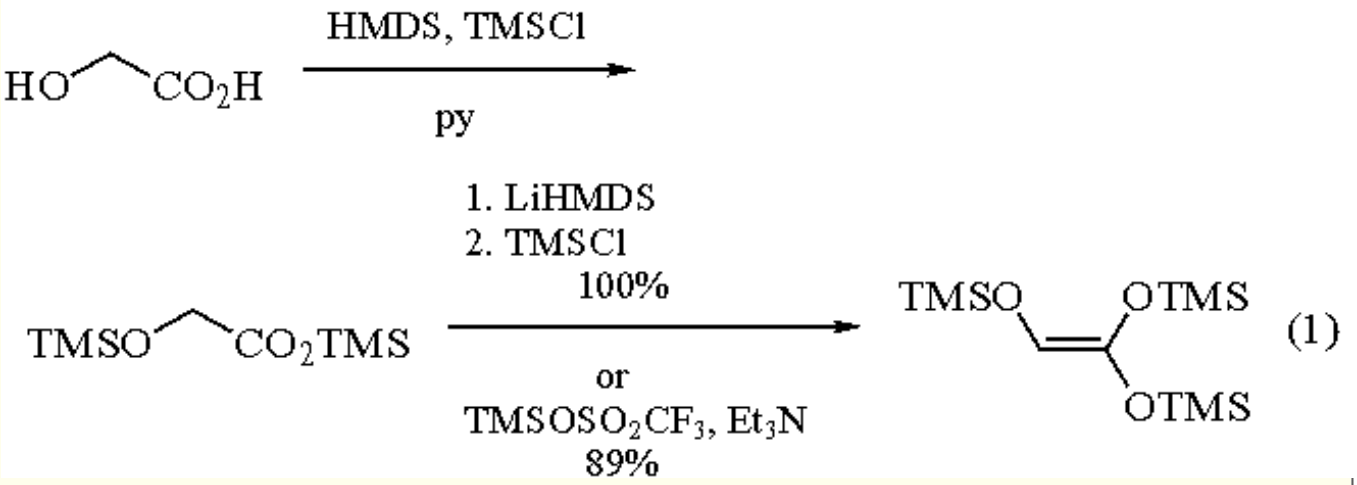

Handling, Storage, and Precautions: is readily hydrolyzed in protic solvents. It should be stored in a sealed container protected from the atmosphere. Since the reaction of the reagent with carboxylic acid chlorides and aldehydes under Lewis acid catalysis in the absence of solvent is highly exothermic, large-scale preparations may require regulation of the reaction temperature either by external cooling or by controlled addition of the reactants.

Carboxylic Acid Chlorides to Terminal α-Hydroxy Ketones.[1,2]

The reaction of 2 equiv of tris(trimethylsilyloxy)ethylene with octanoyl chloride in the absence of solvent either by heating to 90 °C for 2 h or by using a catalytic amount of ***Tin(IV) Chloride*** and allowing the reaction to freely exotherm results in the formation of (**1**), TMSCl, and bis(trimethylsilyl)-glycolic acid (eq 2). Treatment of the reaction mixture with dilute acid in THF or dioxane results in an immediate exothermic hydrolysis (presumably to β-keto acid **2**) and decarboxylation to furnish the hydroxymethyl ketone (**3**). Since the rate of the reaction of the reagent with the liberated HCl (to furnish TMSCl, and bis(trimethylsilyl)glycolic acid) is as least as fast as with the acid chloride, 2 equiv of reagent must be used to achieve complete conversion to the hydroxymethyl ketone. Both aliphatic and aromatic acid chlorides have been used successfully. Very hindered acid chlorides (e.g. 1-adamantanecarbonyl chloride) failed to react. This methodology has been applied in the total synthesis of Ajugarin-IV[7] and in the preparation of some prostaglandin analogs where the terminal hydroxymethyl ketone functional group serves as a biosteric replacement for a carboxylate group.[8]

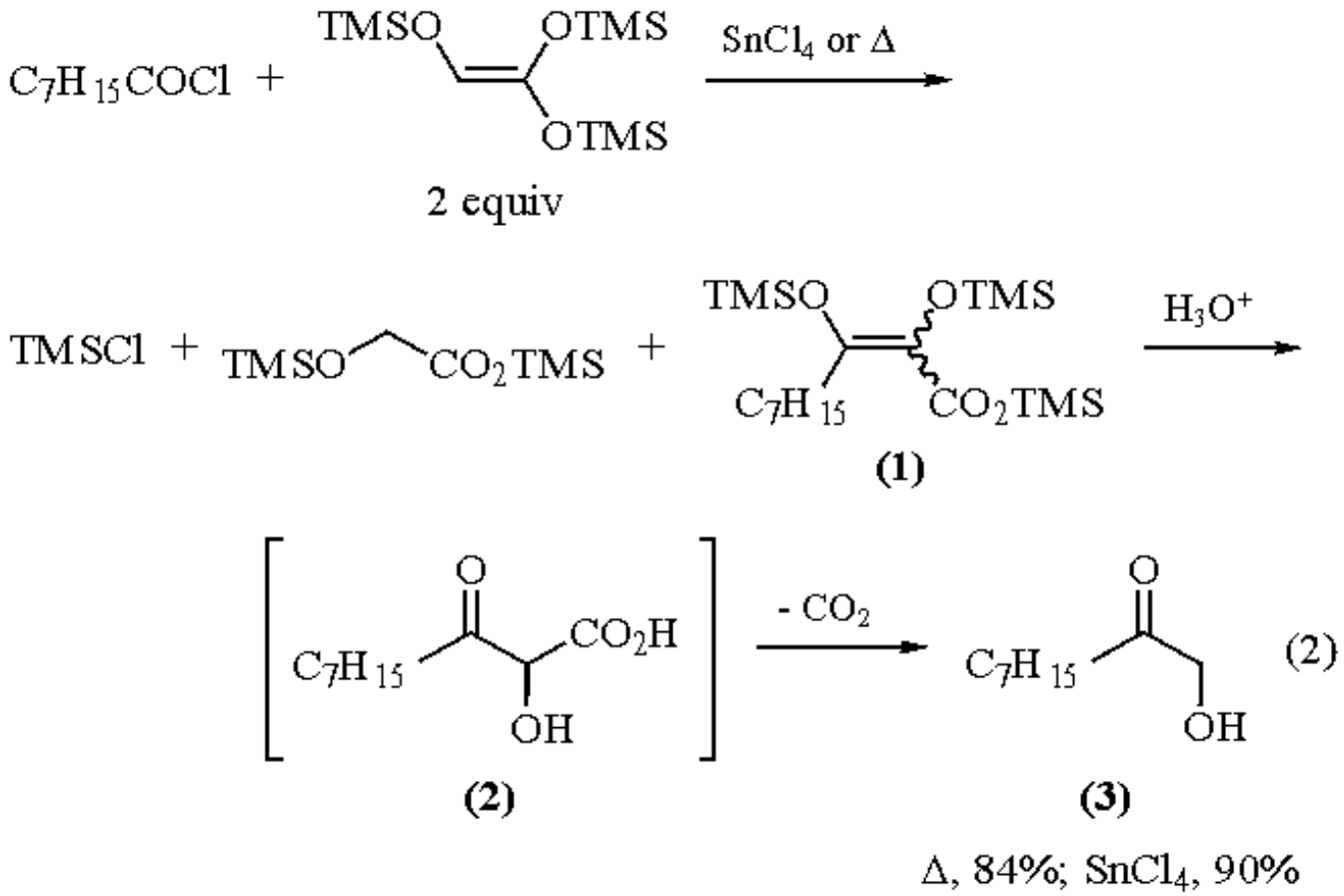

Aldehydes and Ketones to 2,3-Dihydroxyalkanoic Acids.

The reaction of tris(trimethylsiloxy)ethylene with *n*-hexanal in the absence of solvent using $SnCl_4$ as the catalyst is exothermic and furnishes the adduct (**4**). Direct hydrolysis of the reaction mixture with aqueous acetic acid in THF gives 2,3-dihydroxyoctanoic acid (**5**) as a mixture of diasteromers (eq 3).[3] Similar reactions have also been accomplished under trimethylsilyl trifluoromethanesulfonate or ***Cesium Fluoride*** catalysis.[4] Aliphatic, α,β-unsaturated, and aromatic aldehydes have been used successfully.[3,4] Aliphatic and aromatic ketones have also been used successfully under trimethylsilyl trifluoromethanesulfonate catalysis conditions.[4] This methodology usually results in poor stereoselectivity; both the *erythro* and *threo* isomers are obtained in comparable amounts.

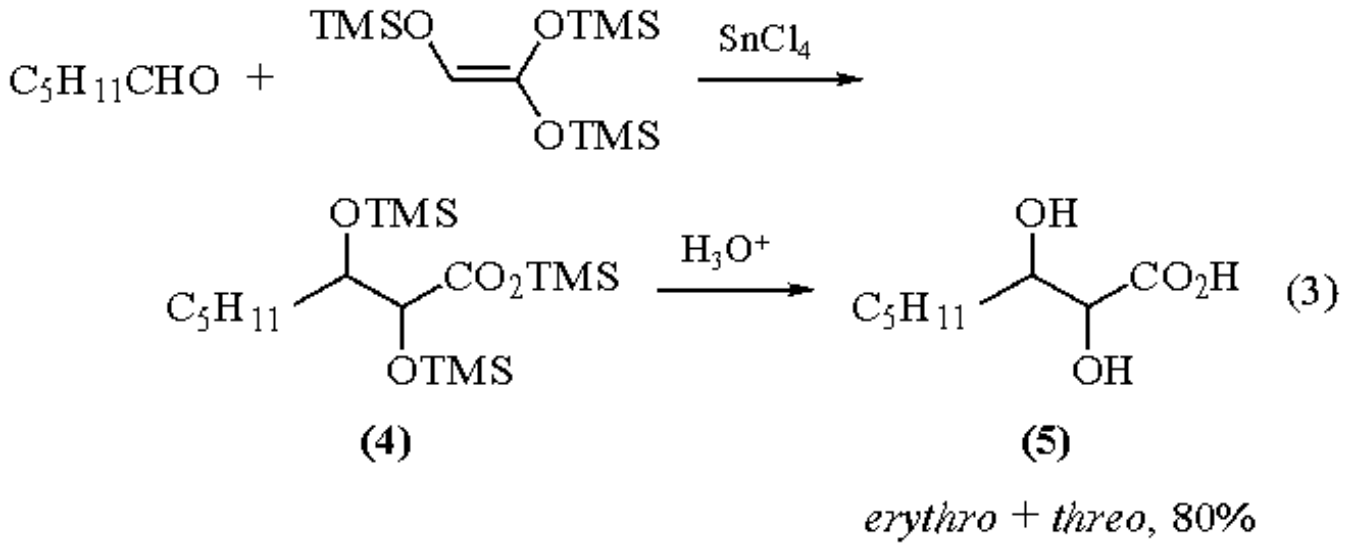

Reaction with Ketenes.

The reaction of tris(trimethylsilyloxy)ethylene with ketene generated from acetyl chloride and triethylamine furnishes the adduct (**6**) in good yield (eq 4); this compound was an intermediate in the synthesis of a series of anthragallols.[9] Similar products result from the reaction of the reagent with halogen-[10,11] and trimethylsilyl-substituted ketenes.[12]

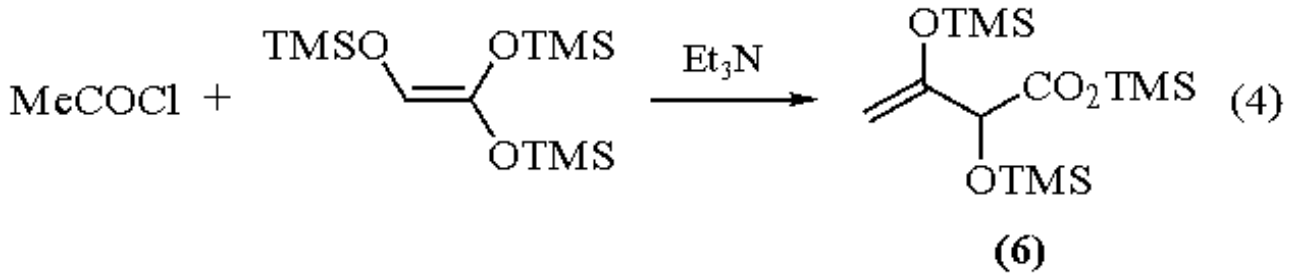

Electrophilic Addition of Acetals and Orthoesters.

With catalysis by trimethylsilyl trifluoromethanesulfonate, acetals and orthoesters undergo electrophilic addition to tris(trimethylsilyloxy)ethylene (eq 5).[4]

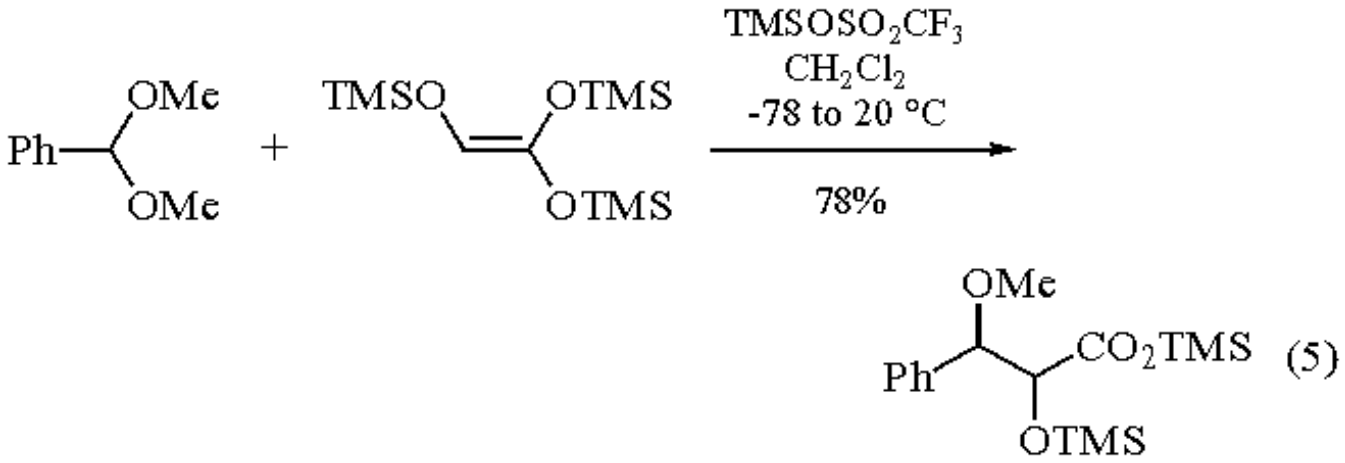

Electrophilic Addition of *t*-Alkyl and Benzyl Groups.

Compounds capable of forming a stabilized carbenium ion undergo Lewis acid-catalyzed addition to tris(trimethylsilyloxy)ethylene; these included *t*-alkyl halides[13] and benzyl acetates[14] (eq 6).

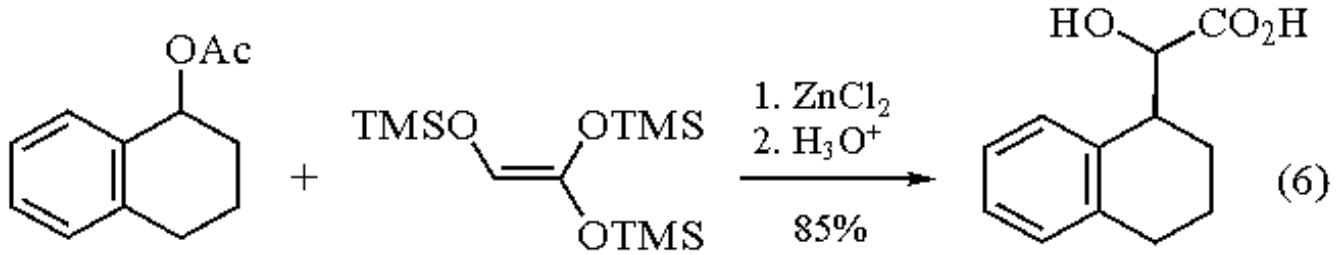

Related Reagents.

1,2-Diethoxy-1,2-bis(trimethylsilyloxy)ethylene; ***Ketene Bis(trimethylsilyl) Acetal***; ***1-Methoxy-1-(trimethylsilyloxy)propene***; ***1-Methoxy-2-trimethylsilyl-1-(trimethylsilyloxy)ethylene***; ***Methylketene Bis(trimethylsilyl) Acetal***; ***Methylketene Dimethyl Acetal***; ***Tetramethoxyethylene***.

---

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Tris(trimethylsilyl) Phosphite[1]

$P(OSiMe_3)_3$

[1795-31-9] · $C_9H_{27}O_3PSi_3$ · Tris(trimethylsilyl) Phosphite · (MW 298.60)

(preparation of bis(trimethylsilyl) phosphonate esters by the Arbuzov reaction with halogen-containing compounds or by the Abramov reaction with carbonyl compounds, followed by facile hydrolysis to the corresponding phosphonic acids, $RP(O)(OH)_2$)

Physical Data: bp 84 °C/5 mmHg,[2] 86.5 °C/18 mmHg,[3] 83-84 °C/16 mmHg,[4] 90-92 °C/16 mmHg,[4] 78-81 °C/8 mmHg; *d* 0.893 g cm^{-3}.

Form Supplied in: liquid; commercially available.

Preparative Methods: by silylation of anhydrous phosphorous acid (dried by repeated azeotropic evaporation of a solution in THF with dry benzene) with excess ***Chlorotrimethylsilane*** and excess ***Triethylamine*** in dimethoxyethane,[2] toluene,[3] or Et_2O-THF,[5] followed by evaporation of the solvent and vacuum distillation of the residue. The residue, which contains a mixture of tris(trimethylsilyl) phosphite and bis(trimethylsilyl) phosphonate [$HP(O)(OTMS)_2$], can also be heated with sodium (140 °C, 13-22 h), followed by vacuum distillation to obtain pure tris(trimethylsilyl) phosphite.[4]

Purification: vacuum distill before use.

Handling, Storage, and Precautions: extremely hygroscopic; use in a fume hood.

Arbuzov Reagent with Aliphatic Halides.

The reagent, $P(OTMS)_3$, reacts with alkyl halides such as *n*-butyl bromide[5] to give bis(trimethylsilyl) esters of phosphonic acids. 2,3-Diacyloxyiodopropanes (**1**) (*n* = 0, X = I) react with an excess of $P(OTMS)_3$; after removal of the excess $P(OTMS)_3$ and trimethylsilyl iodide under high vacuum (<1 mmHg) at 80-90 °C, bis(trimethylsilyl) 2,3-diacylphosphonates (**2**) are obtained, which are easily hydrolyzed to the corresponding phosphonic acids (**3**) (eq 1).[2,6,7] 3,4-Dipalmitoyloxy-1-bromobutane (**1**) (*n* = 1, X = Br) is converted into 3,4-dipalmitoyloxybutanephosphonic acid by the same process.[8] The advantage of $P(OTMS)_3$ compared with trialkyl phosphites in the preparation of phosphonic acids is the extreme ease with which the bis(trimethylsilyl) ester groups of (**2**) undergo neutral aqueous hydrolysis. The mild hydrolysis conditions[9] allow otherwise labile groups such as carboxylate esters to remain unaffected during desilylation.

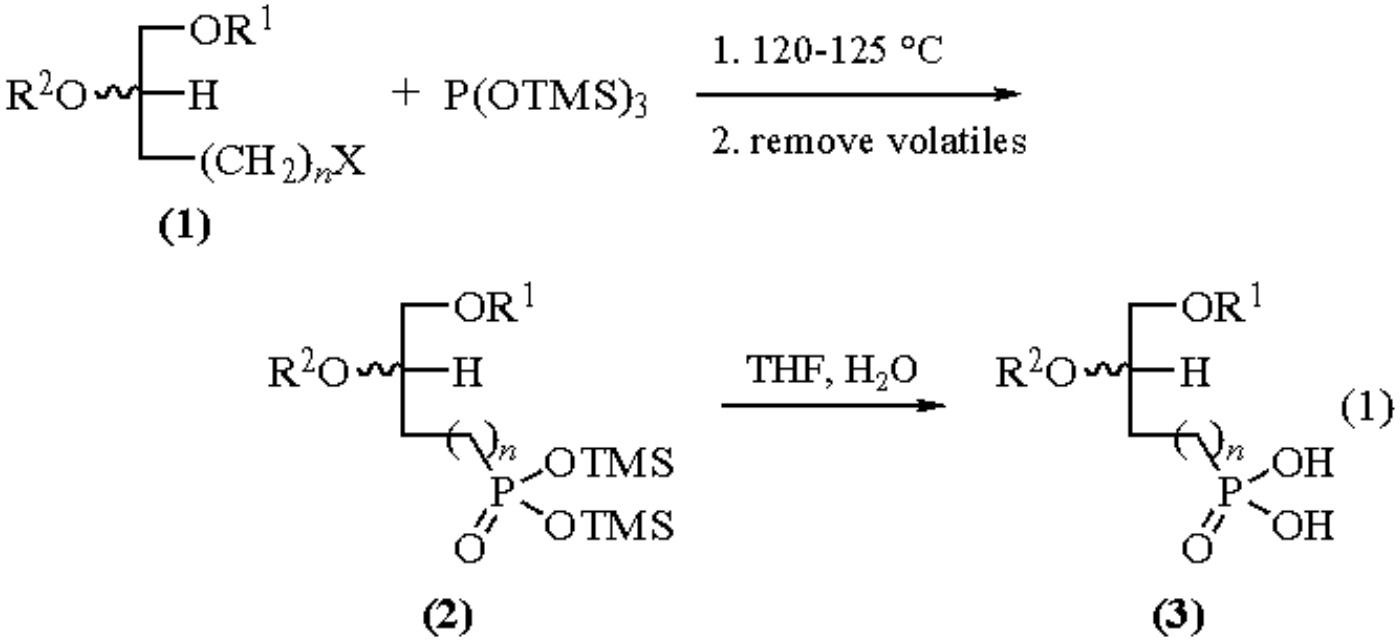

$n = 0$; X = I, $R^{1,2}$ = octanoyl (71%), myristoyl (79%), palmitoyl (43%), stearoyl (87-89%)
$n = 1$; X = Br; $R^{1,2}$ = hexadecyl (75%), R^1 = hexadecyl, R^2 = benzyl (70%)

Ether-linked phosphonolipids are available by the Arbuzov reaction of 2,3-dialkoxyiodopropanes,[7,10,11] 3,4-dialkoxy-1-bromobutanes,[7] and other long-chain alkyl bromides[12] with $P(OTMS)_3$, followed by facile desilylation (eq 1).

Formation of Alkyloxycarbonyl-, Aryloxycarbonyl-, and Acylphosphonates.

Alkyloxy- and aryloxycarbonylphosphonate bis(trimethylsilyl) derivatives, $ROCOP(O)(OTMS)_2$, are prepared from the Arbuzov reaction of alkyl or aryl chloroformates with $P(OTMS)_3$.[13,14] Pivaloyl chloride reacts with $P(OTMS)_3$ to give an acylphosphonate derivative.[15]

Formation of Thiophosphonates.

Thiophosphonic acids (**4**) are prepared from the Arbuzov reaction of thiosuccinimides and thiophthalimides containing various *S*-alkyl and *S*-aryl groups with $P(OTMS)_3$ (eq 2).[16]

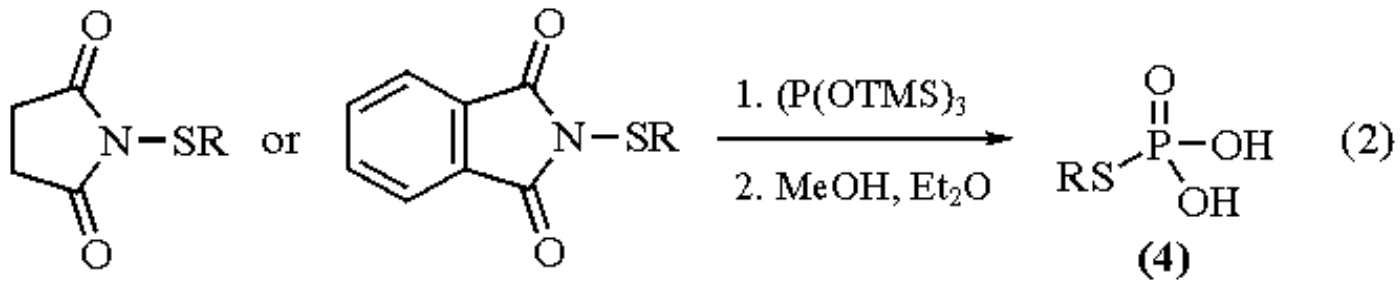

R = Bn, 77%; $C_{18}H_{37}$, 64-83%; $CH_2CH(OCOR)CH_2OCOR$, 46%

Arbuzov Reaction with Halomethyl-Containing Compounds.

A variety of chloromethyl- or bromomethyl-containing compounds react with $P(OTMS)_3$ to give the Arbuzov products, $RCH_2COCH_2P(O)(OTMS)_2$[17,18] or $RCH_2P(O)(OTMS)_2$.[19]

Other Arbuzov Reactions.

Aryl halides react with $P(OTMS)_3$ in the presence of catalytic nickel chloride, forming arylphosphonates after hydrolysis of the silyl esters.[20] 1β-Glycosyl triflates react with $P(OTMS)_3$, giving α-D-glucopyranosyl-1-phosphonic acid after hydrolysis.[21]

Addition to Carbonyl Compounds.

$P(OTMS)_3$ adds to alkyl-substituted α-halocarbonyl compounds to form 1:1 adducts, which on hydrolysis yield α-hydroxyphosphonic acids (**5**) (eq 3).[4,22] In contrast, trialkyl phosphites react with bromoacetone to give β-oxophosphonates. $P(OTMS)_3$ also adds to methyl ketones.[23]

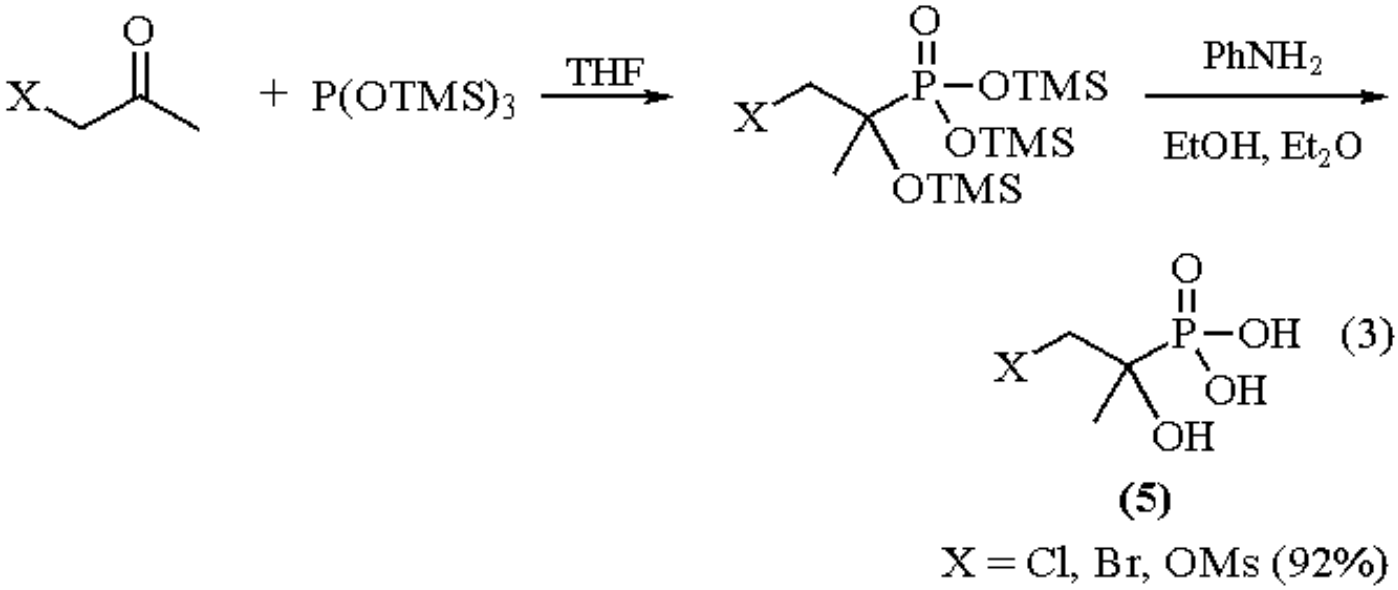

O-Silylated salicaldehyde reacts with $P(OTMS)_3$, giving a dihydroxy derivative of benzylphosphinic acid after hydrolysis.[24]

Isocyanates and isothiocyanates react with $P(OTMS)_3$ to give carbamoyl- and thiocarbamoylphosphonates, $RNHC(X)P(O)(OH)_2$ where X = O or S, after treatment with aniline in methanol.[25]

Other Addition Reactions.

Addition of excess $P(OTMS)_3$ to *N*-glycosyl-*C*-aryl nitrones at low temperature in the presence of catalytic $HClO_4$ or zinc triflate gives *N*-hydroxy-α-aminophosphonic acids.[26] Addition to aldimines yields *N*-substituted phosphonates, $(HO)_2P(O)CH(R)NH_2$.[27] *N*-(Phosphonomethyl)glycine derivatives can be made by a modified Abramov reaction of imines or imine precursors with $P(OTMS)_3$.[18a,28] Conjugate additions also take place;[1] for example, addition to acrylonitrile gives $(TMSO)_2P(O)CH_2CH(TMS)CN$ in 52% yield.[29]

Related Reagents.

Trimethyl Phosphite.

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Tris(trimethylsilyl)silane[1]

$(Me_3Si)_3SiH$

[1873-77-4] · $C_9H_{28}Si_4$ · Tris(trimethylsilyl)silane · (MW 248.73)

(mediator of radical reactions;[1,2] nontoxic substitute for tri-*n*-butylstannane in radical reactions; slower hydrogen donor than tri-*n*-butylstannane[3])

Physical Data: bp 82-84 °C/12 mmHg; *d* 0.806 g cm^{-3}; *n*20D 1.489.

Solubility: sol pentane, ether, toluene, THF; modestly sol acetone, acetonitrile; insol H_2O; decomposes rapidly in methanol and other alcohols.

Form Supplied in: colorless liquid; commercially available.

Preparative Methods: easy to synthesize.[4]

Handling, Storage, and Precautions: is slightly sensitive to oxygen and should be stored under nitrogen.[5] It showed no toxicity in several biological test systems.[6]

Functional Group Reductions.

Tris(trimethylsilyl)silane is an effective radical reducing agent for organic halides, selenides, xanthates, isocyanides,[2] and acid chlorides (Table 1).[7] The reactions are carried out at 75-90 °C in toluene in the presence of a radical initiator, i.e. ***Azobisisobutyronitrile***. Chromatographic workup affords the products. The silicon-containing byproducts are easily separated. The silane can also be used catalytically when ***Sodium Borohydride*** is employed as the coreductand.[8] If a halide (bromide or iodide) is treated under photochemical initiation conditions with an excess of sodium borohydride and a small amount of tris(trimethylsilyl)silane or its corresponding halide, the silane is continously regenerated from the silyl halide.

Table 1 Reduction of Several Organic Compounds by Tris(trimethylsilyl)silane[2,7]

RX	Yield RH (%)	RX	Yield RH (%)
	82	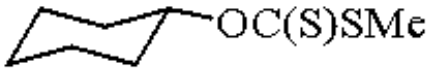	86
	90	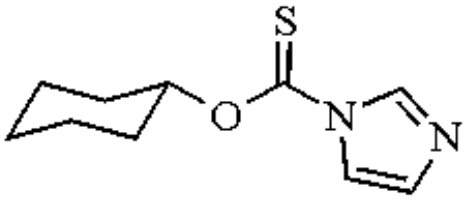	95
	97		99
	95		92

Iodides and bromides are reduced by tris(trimethylsilyl)silane to the corresponding hydrocarbons in high yield after a short reaction time (0.5

h). From tertiary to secondary and primary chlorides the reduction becomes increasingly difficult. A longer reaction time and periodic addition of initiator is required. Photochemical initiation can be used and is quite efficient.[9] Tris(trimethylsilyl)silane is superior to ***Tri-n-butylstannane*** in replacing an isocyanide group by hydrogen. The reaction with tin hydride requires high temperatures (boiling xylene for primary isocyanides) and periodic addition of initiator. Using the silane, primary, secondary, and tertiary isocyanides are reduced at 80 °C in high yields. The reduction of selenides by tris(trimethylsilyl)silane proceeds with high yields; however, the corresponding reaction of sulfides is inefficient.

Acyl chlorides are converted by tris(trimethylsilyl)silane to the corresponding hydrocarbons. Tertiary and secondary acid chlorides react at 80 °C, while the reduction of primary derivatives requires higher temperatures.[7] The radical deoxygenation of hydroxyl groups is carried out by conversion of the alcohol to a thionocarbonate, which can be reduced by tris(trimethylsilyl)silane (eq 1). This very mild method is especially useful in natural product synthesis. It has been utilized for the deoxygenation of lanosterol (eq 2)[6] and the dideoxygenation of 1,6-anhydro-D-glucose (eq 3).[10]

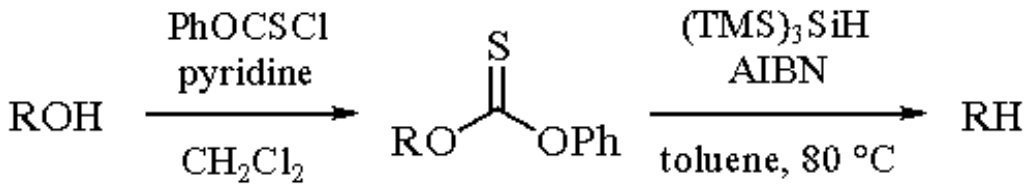

(1)

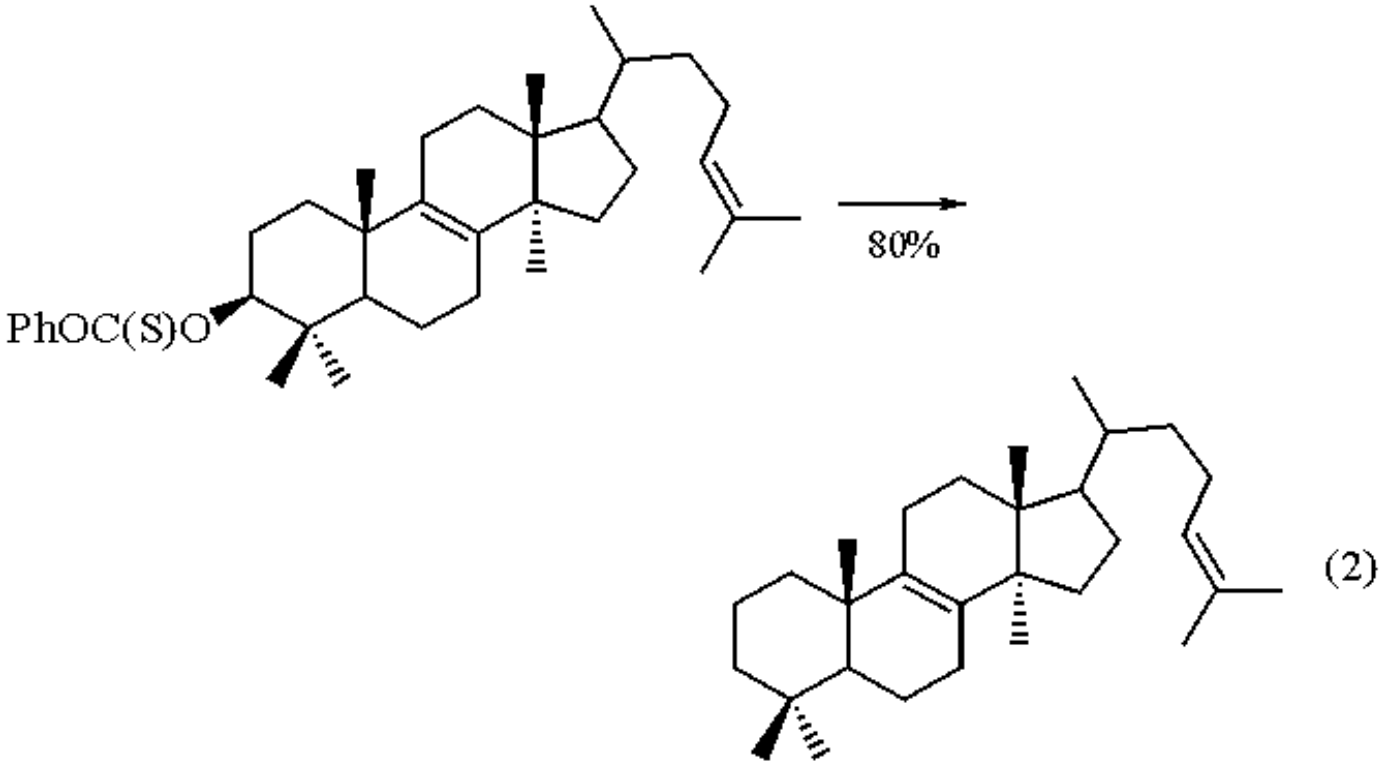

(2)

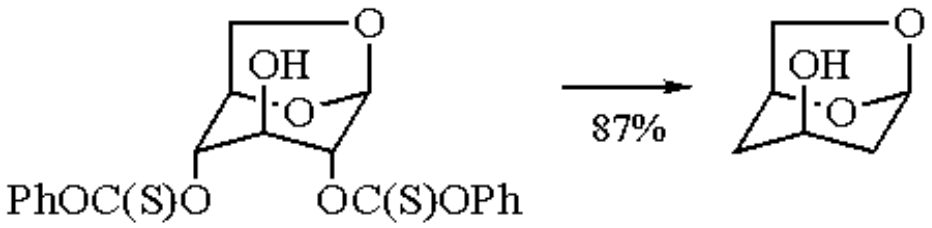

(3)

Radical deoxygenation of the *cis*-unsaturated fatty acid derivative with tris(trimethylsilyl)silane gives methyl triacont-21-*trans*-enoate together with the saturated compound (eq 4). If the reaction is carried out with tri-*n*-butyltin hydride, the configuration remains unchanged.[11]

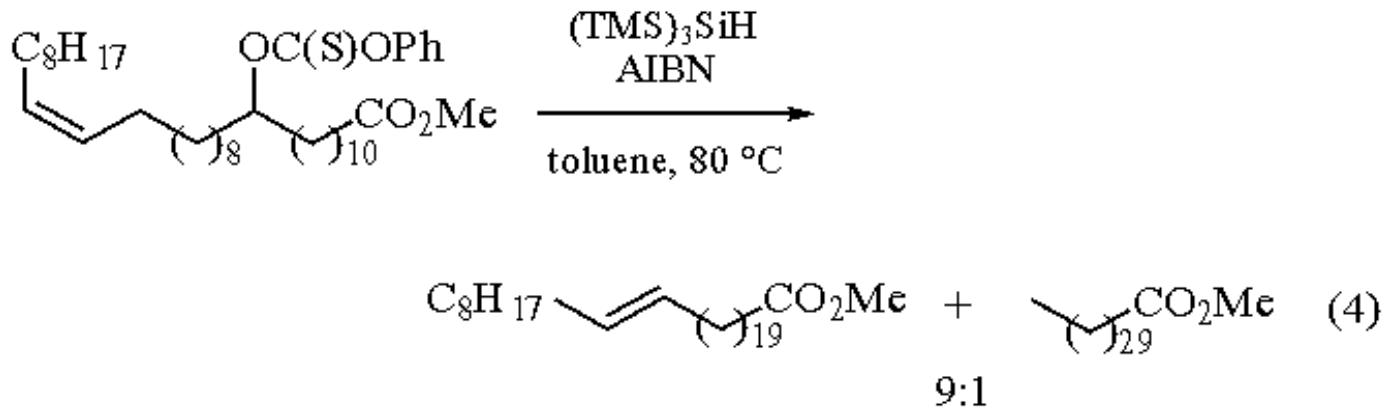

Hydrosilylation of Double Bonds.

Tris(trimethylsilyl)silane is capable of radical hydrosilylation of dialkyl ketones,[12] alkenes,[12,13] and alkynes.[13] Hydrosilylation of alkenes yields the anti-Markovnikov products with high regio- and good diastereoselectivity (eq 5). By using a chiral alkene, complete stereocontrol can be achieved (eq 6).[14] The silyl group can be converted to a hydroxyl group by Tamao oxidation.[13]

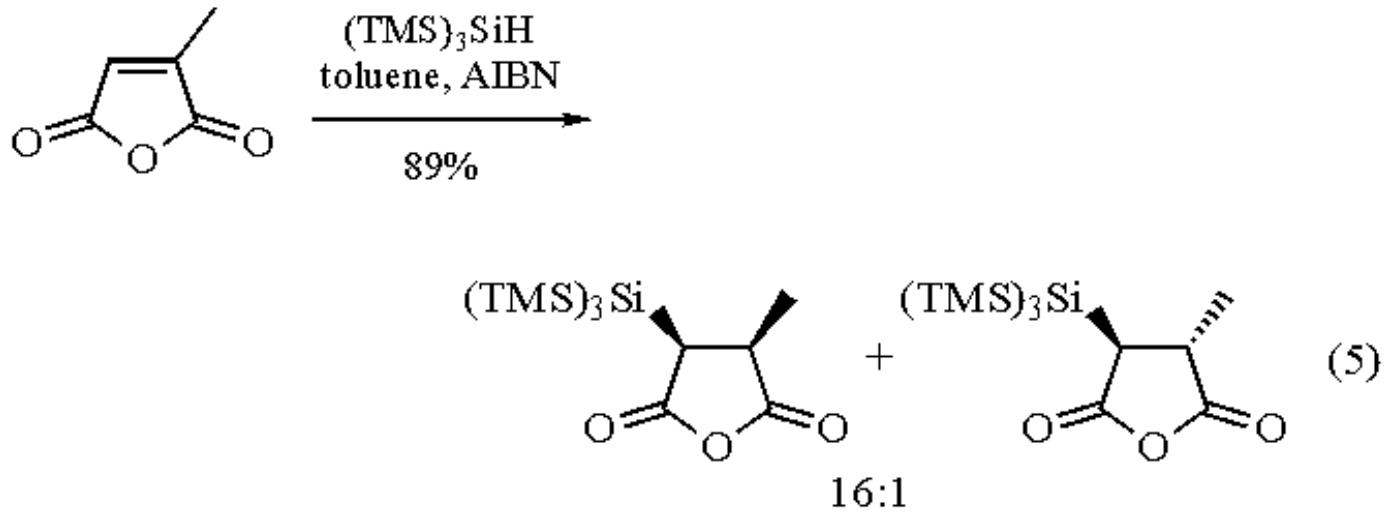

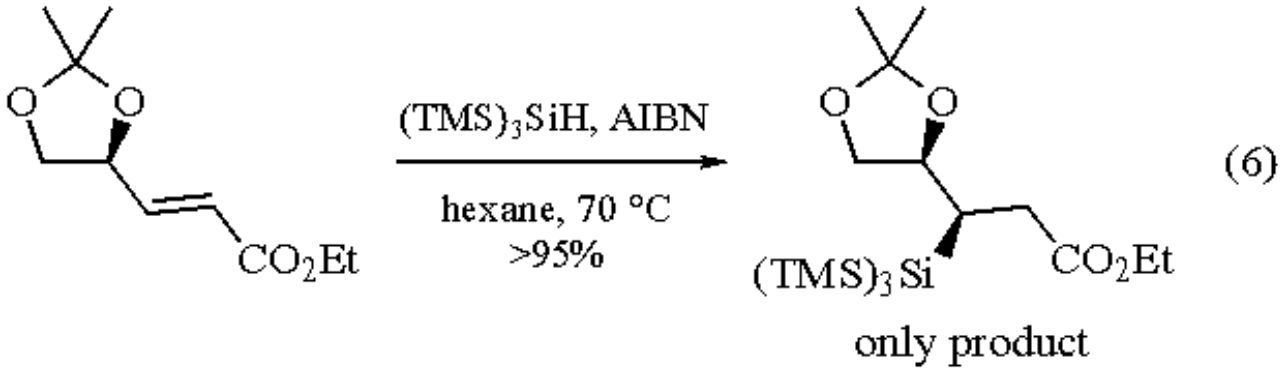

Monosubstituted alkynes give alkenes in high yield and stereoselectivity. The formation of (*E*)- or (*Z*)-alkenes depends on the steric demand of the substituents (eq 7). 1,2-Disubstituted phenylalkynes are attacked exclusively β to the phenylated alkyne carbon atom.[13] The silyl moiety can be replaced by a bromine atom with overall retention of configuration (eq 8).[13]

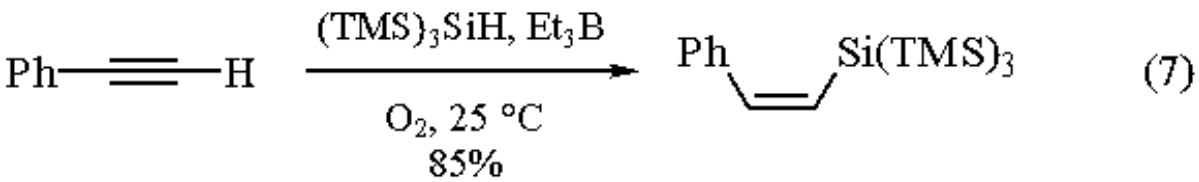

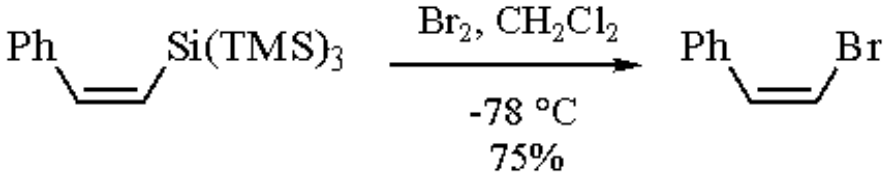

(8)

The hydrosilylation of ketones is in general slower than the corresponding reaction of alkenes and alkynes. In the case of sterically hindered ketones, a catalytic amount of a thiol is necessary to carry out the reaction.[15] The resulting silyl ethers can be easily desilylated by standard procedures. With 4-*t*-butylcyclohexanone the *trans* isomer is formed as the main product (eq 9). The hydrosilylation of a ketone bearing a chiral center in the adjacent position yields mainly the Felkin-Anh product (eq 10).[15]

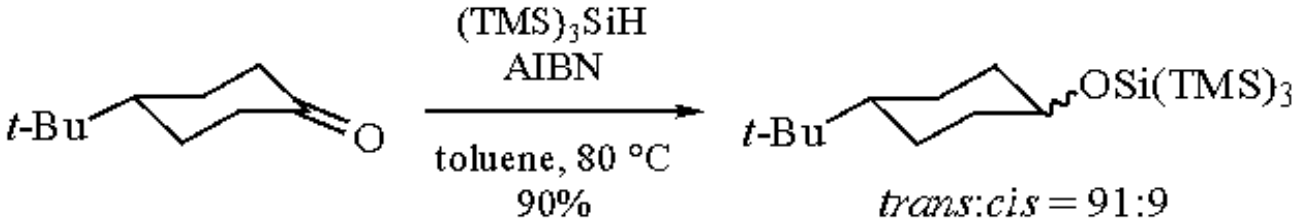

(9)

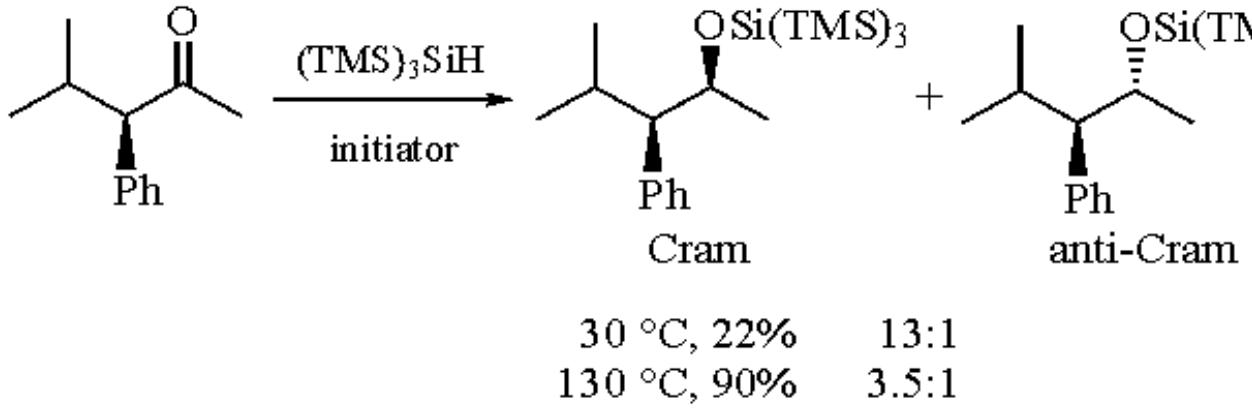

(10)

Intramolecular Reactions.

Tris(trimethylsilyl)silane is an effective mediator of radical cyclizations.[16] In addition to halides and selenides, secondary isocyanides can be used as precursors for intramolecular C-C bond formation,[17] which is impossible using the tin hydride (eq 11). Selective cleavage of the carbon-sulfur bond of a 1,3-dithiolane, 1,3-dithiane,[18] 1,3-oxathiolane, or 1,3-thiazolidine[19] derivative is an efficient process to generate carbon-centered radicals, which can undergo cyclization (eq 12).

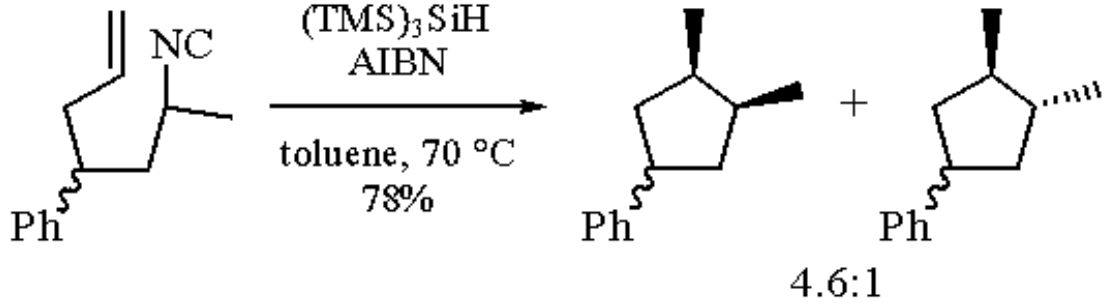

(11)

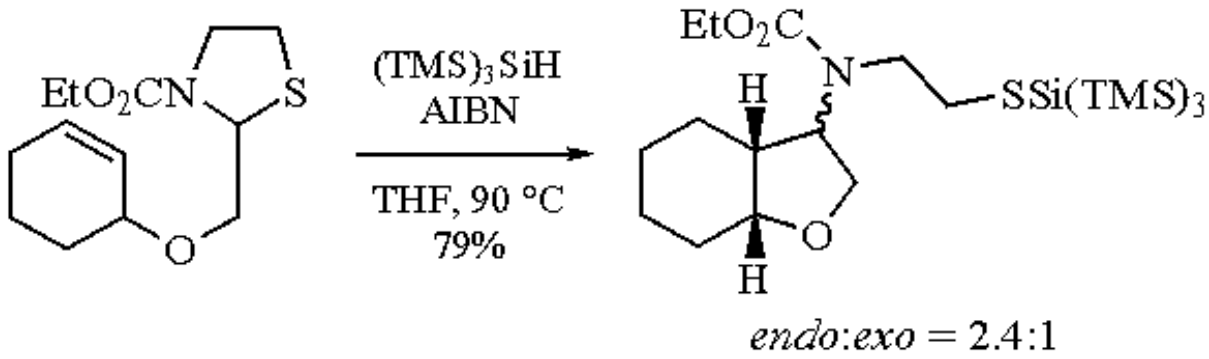

(12)

2-Benzylseleno-1-(2-iodophenyl)ethanol reacts smoothly with tris(trimethylsilyl)silane to give benzo[*b*]selenophene (eq 13).[20] A similar homolytic substitution reaction at the silicon atom yields a sila bicycle.[21]

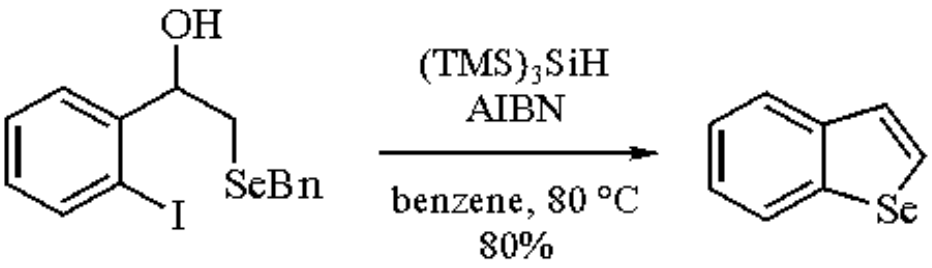

(13)

The silane is superior to the tin reagent in the radical rearrangement of glycosyl halides to 2-deoxy sugars (eq 14).[16] Aromatization of the A-ring of 9,10-secosteroids can be achieved by a mild, radical-induced fragmentation reaction of 3-oxo-1,4-diene steroids (eq 15).[22]

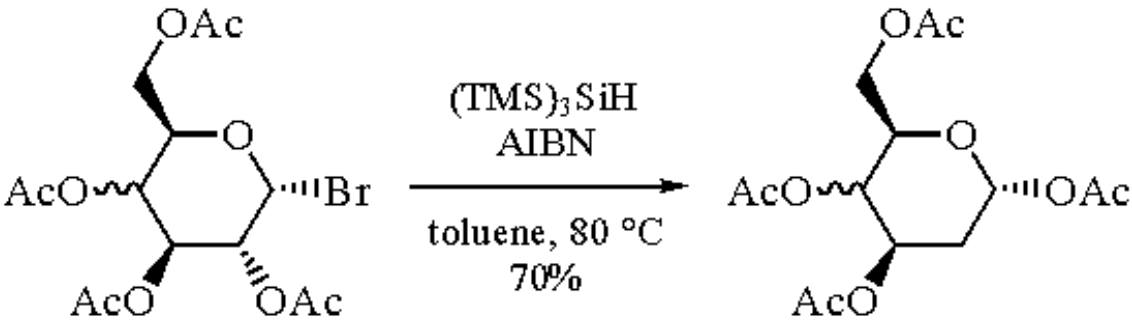

(14)

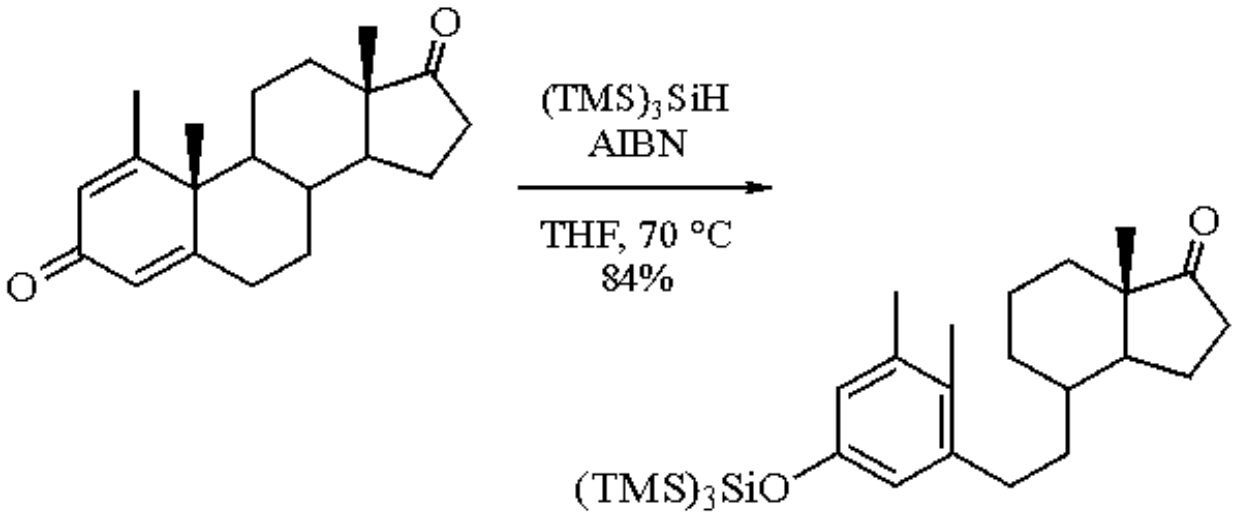

(15)

Intermolecular Reactions.

Radical carbon-carbon bond formation can be carried out with tris(trimethylsilyl)silane.[16] Again, it is possible to use isocyanides as precursors (eqs 16 and 17).[17]

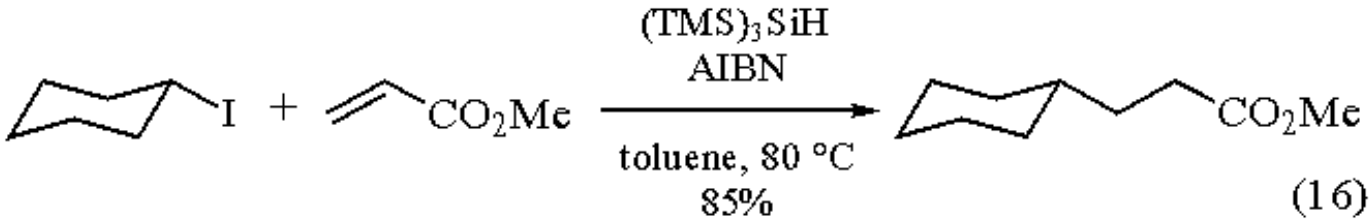

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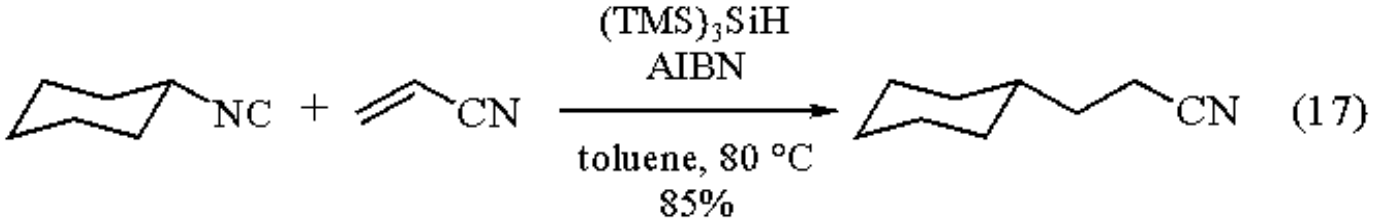

(17)

Nonradical Reactions.

Tris(trimethylsilyl)silane reacts with carbenium ions to form a silicenium ion.[23] In this case, tris(trimethylsilyl)silane is only slightly more reactive than trimethylsilane. The reaction of the silane with methyl diazoacetate in the presence of copper catalyst gives the α-silyl ester (eq 18).[24]

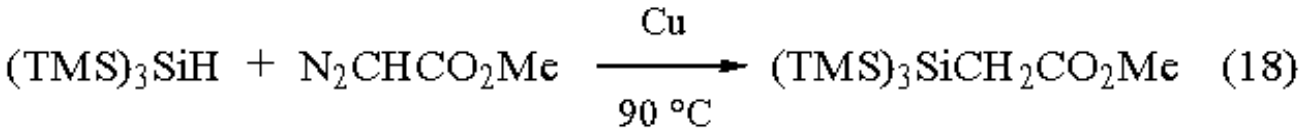

(18)

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Tris[trinitratocerium(IV)] Paraperiodate[1a,b]

$[(NO_3)_3Ce]_3H_2IO_6$

[94316-41-3] · $Ce_3H_2IN_9O_{33}$ · Tris[trinitratocerium(IV)] Paraperiodate · (MW 1203.37)

(mild oxidizing reagent for oxidation of several functional groups;[2] efficient catalyst for dimerization of thiols and selenols[3] and ring opening of epoxides[4])

Alternate Name: TTCPP.

Solubility: insol cold H_2O, THF, EtOH, acetone.

Form Supplied in: yellow solid, easily prepared.

Preparative Methods: a cold solution of potassium periodate (0.01 mol) in H_2O (100 mL) is added dropwise to a solution of ***Cerium(IV) Ammonium Nitrate*** (0.03 mol) in H_2O (30 mL) cooled in ice-bath. The precipitate is filtered and washed with H_2O and acetone, and dried (70%).

Handling, Storage, and Precautions: very air stable and can be stored for months without losing its activity; periodate and cerium are both reputed to have low toxicity.

Introduction.

TTCPP is a convenient reagent for the oxidation of several different functional groups in protic and aprotic solvents under heterogeneous conditions. Separation of the oxidant and isolation of the product are achieved simply by filtration, evaporation, and chromatographic purification. Cerium(IV) reagents usually suffer from disadvantages,[1,5,6] but many of these drawbacks are not observed when using TTCPP.[2]

Oxidations.

Benzylic hydroxyl groups are oxidized to carbonyl compounds in high yields (eq 1) with this reagent.[2]

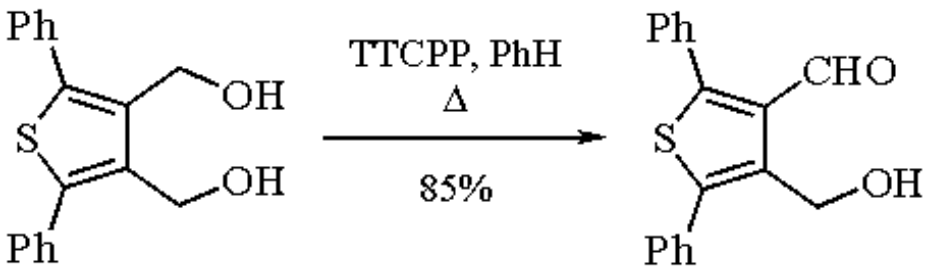

(1)

α-Hydroxy ketones are oxidized to diketones and decarboxylation occurs with α-hydroxy carboxylic acids to produce aldehydes (eqs 2 and 3).[2]

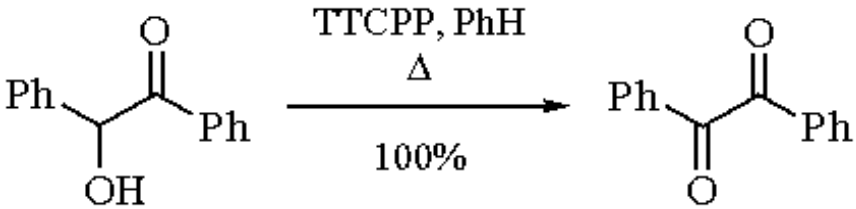

(2)

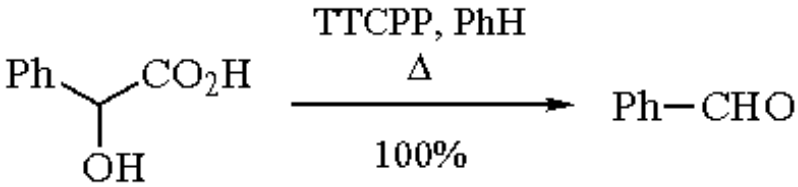

(3)

Oxidative cleavage of C-C bonds occurs in the reaction of arylethylene glycols (eq 4); TTCPP is also effective for the high-yield oxidation of phosphines (eq 5).[2]

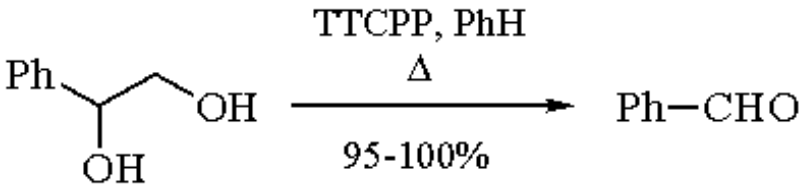

(4)

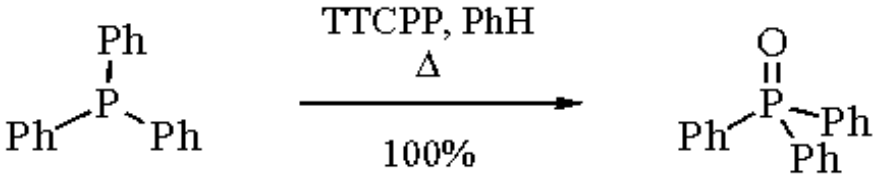

(5)

The reagent has also been employed for the oxidation of thiols to disulfides (eq 6).

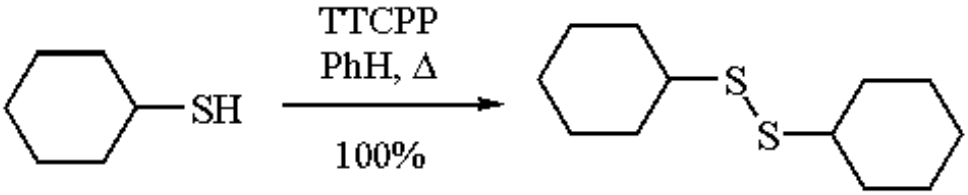

(6)

Electron-Transfer Reactions.

Catalytic amounts of TTCPP in THF dimerize both thiols and selenols efficiently at room temperature (eq 7).[3]

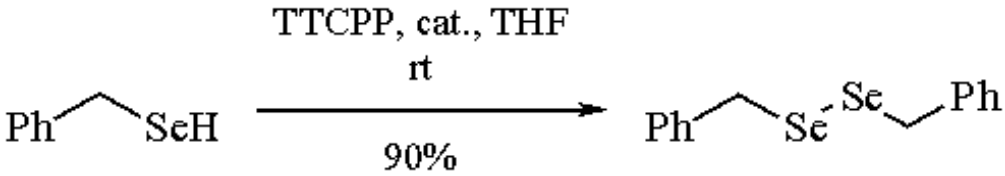

(7)

Epoxides in different types of alcohols are cleaved by catalytic amounts of TTCPP to afford β-alkoxy alcohols (eq 8).[4]

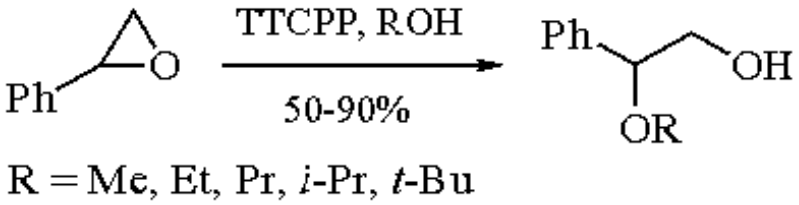

(8)

Catalytic amounts of TTCPP in acetic acid promote acetolysis of epoxides followed by abstraction of the α-hydrogen adjacent to a carbonyl group to produce β-hydroxyaryl succinates in good yields (eq 9).[4]

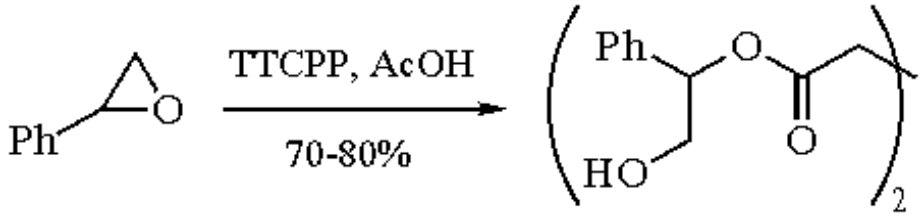

(9)

In comparison with the oxidative ability of TTCPP, ***Cerium(IV) Ammonium Nitrate*** (CAN) is relatively inactive in benzene. A comparison between TTCPP, CAN,[16,7,-10] and zinc bismuthate (ZB)[11] is shown in Table 1.

Table 1 Comparative Oxidative Abilities

Substrate	Product	TTCPP (%)	CAN (%)	ZB (%)
Benzyl alcohol	Benzaldehyde	90 95	94	80
Furoin	Furil	100	5	95
Cyclohexanethiol	Dicyclohexyl disulfide	100		99
Benzilic acid	Benzophenone	100		95
Styrene oxide	2-Methoxy-2-phenylethanol	80	90	
Epichlorohydrin	1-Chloro-3-methoxy-2-propanol	75	79	

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Tris(triphenylphosphine)nickel(0)[1]

$Ni(PPh_3)_3$

[25136-46-3] · $C_{54}H_{45}NiP_3$ · Tris(triphenylphosphine)nickel(0) · (MW 845.59)

(a source of nickel(0) useful for the coupling of aryl, alkenyl, and allyl halides;[2] oligomerization of strained alkenes;[3] oligomerization of allenes[4])

Physical Data: mp 124-126 °C (N_2).

Solubility: sol toluene, benzene, DMF, DMA, Et_2O, THF, HMPA.

Analysis of Reagent Purity: ^{1}H NMR δ 7.37 (*o*-H), 6.96 (*m*- and *p*-H).[5]

Preparative Methods: the standard preparation involves the reduction of ***Nickel(II) Chloride*** with ***Zinc*** dust in the presence of ***Triphenylphosphine***. Anhydrous $NiCl_2$ (2.6 g) was refluxed with 21 g of PPh_3 in 300 mL of acetonitrile for 1 h. After cooling to rt, 2.0 g of zinc dust was added and the mixture was stirred under nitrogen overnight. After removal of solvent, the resulting red solid was dissolved in the minimum volume of hot toluene (60 °C), removed from insoluble impurities by hot filtration, precipitated by the addition of hexane, and dried under vacuum to give a reddish-brown powder.[5] This precipitation has also been carried out in situ from the same starting materials and is currently the favored procedure.[2] Several other methods of preparation have been described.[6]

Handling, Storage, and Precautions: highly oxygen sensitive; special inert-atmosphere techniques must be used.[7] Should be stored at 0 °C.

Coupling of Aryl, Alkenyl, and Allyl Halides.

Tris(triphenylphosphine)nickel(0) reacts with organic halides by oxidative addition of nickel(0) into carbon-halogen bonds to form intermediate nickel(II) complexes.[8] These organometallic intermediates, which are usually not isolated, react with a variety of nucleophiles, leading to replacement of the original halide with the nucleophile and regeneration of a catalytic nickel(0) species. In the case of aryl halides, the arylnickel intermediates can be reacted with cyanide salts to give nitriles,[9] with acetylides to give alkynes,[10] with halide salts to give halogen exchange,[11] with phosphines to give phosphonium salts,[12] and with sodium borohydride to give overall hydrogenation.[13] Aryl amines, ethers, and carboxylic acids have also been formed catalytically through these types of reactions.[14] Aryl bromides and iodides both work well as substrates, and many functional groups are tolerated. However, *ortho* substituents tend to slow the reactions down and give lower yields. A wide array of cross-coupling reactions with Grignard and other organometallic reagents have also been performed, but using $Ni(PPh_3)_4$ as the catalyst.

Homocoupling of aryl halides requires stoichiometric amounts of nickel(0), but can be made catalytic in nickel by the addition of excess zinc, magnesium, or manganese as a reducing agent.[15] Aryl chlorides are reactive for this transformation and the yields of biphenyls from *para*-substituted aryl chlorides are better than in the corresponding stoichiometric reactions (eq 1).[16] Nitro groups destroy the catalytic acivity of the nickel complexes,[17] and *ortho* substituents strongly inhibit the reaction. The presence of acidic functionalities leads to reduction of the arene. A macrocyclic bicycle, bis[18]annulene, was synthesized by this method.[18] This coupling reaction has also been carried out intramolecularly to produce a macrocyclic pentaphenylene in 65% yield.[19]

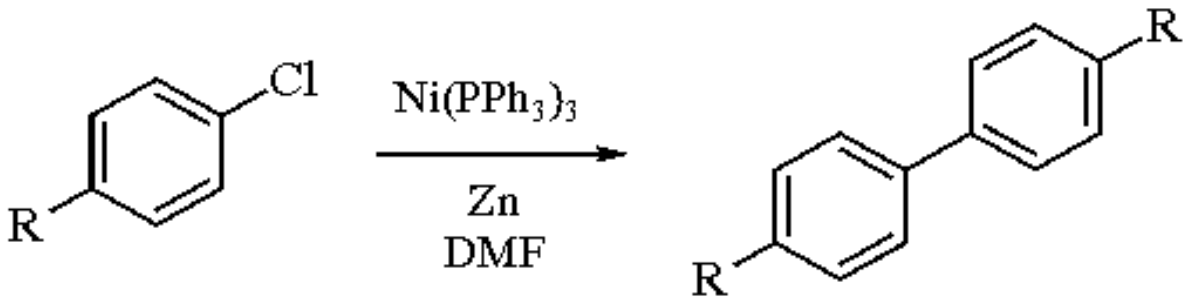

(1)

R = H, 99%; CHO, 94%; COPh, 100%; CN, 98%

In the case of alkenyl halides, oxidative addition of the nickel(0) catalyst occurs with retention of configuration of the double bond.[20] This reaction has been used for the homocoupling of vinyl bromides,[21] and to make dienoic acids by the insertion of 3-butenoic acids.[22] Allylic halides may be homocoupled as well.[2]

The coordinatively unsaturated $Ni(PPh_3)_3$ catalyst is also formed in solution from $Ni(PPh_3)_4$ by ligand dissociation and is probably the reactive species in oxidative addition reactions of $Ni(PPh_3)_4$ (see ***Tetrakis(triphenylphosphine)nickel(0)*** and ***Bis(1,5-cyclooctadiene)nickel(0)***).[23]

Oligomerization of Strained Alkenes.

3,3-Disubstituted cyclopropenes dimerize with catalytic $Ni(PPh_3)_3$ via a [2 + 2] cycloaddition pathway to form cyclobutanes.[24] Methylenecyclopropane reacts to give mixtures of cyclic and acyclic dimers and trimers (see ***Bis(1,5-cyclooctadiene)nickel(0)***).[25]

Oligomerization of Allenes.

Substituted allenes react with $Ni(PPh_3)_3$ to form dimers and trimers.[26] When carbon monoxide is added, CO insertion leads exclusively to cyclic products.[4] Reaction with a diallene, 2,7-dimethyl-2,3,5,6-octatetraene, quantitatively produced a 10-membered ring trimer (see also ***Bis(triphenylphosphine)nickel(0)***).[27]

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Tris(triphenylsilyl) Vanadate

$(Ph_3SiO)_3V{=}O$

[5590-56-7] · $C_{54}H_{45}O_4Si_3V$ · Tris(triphenylsilyl) Vanadate · (MW 893.20)

(catalyst for the 1,3-isomerization of propargylic[1] and allylic alcohols[2])

Alternate Name: oxotris(triphenylsilanolato)vanadium

Physical Data: mp 225-227 °C.

Solubility: sol xylene, benzene, mineral oil.

Form Supplied in: not commercially available.

Preparative Methods: from vanadium pentoxide and triphenylsilanol.[1]

Purification: recrystallize from xylene, benzene, or mesitylene and wash with hexane.

Handling, Storage, and Precautions: hydrolyzes in moist air.

Isomerization of Propargylic Alcohols to α,β-Unsaturated Carbonyl Compounds.

Propargylic alcohols are converted into α,β-unsaturated aldehydes or ketones by treatment with the title reagent (**1**) in mineral oil at 150 °C (eq 1).[1,3] Yields in this reaction are typically greater than 85%. The reaction proceeds via a mechanism involving a [3,3]-sigmatropic rearrangement and thus the reaction proceeds with complete allylic inversion after protonolysis of the oxyallene intermediate.

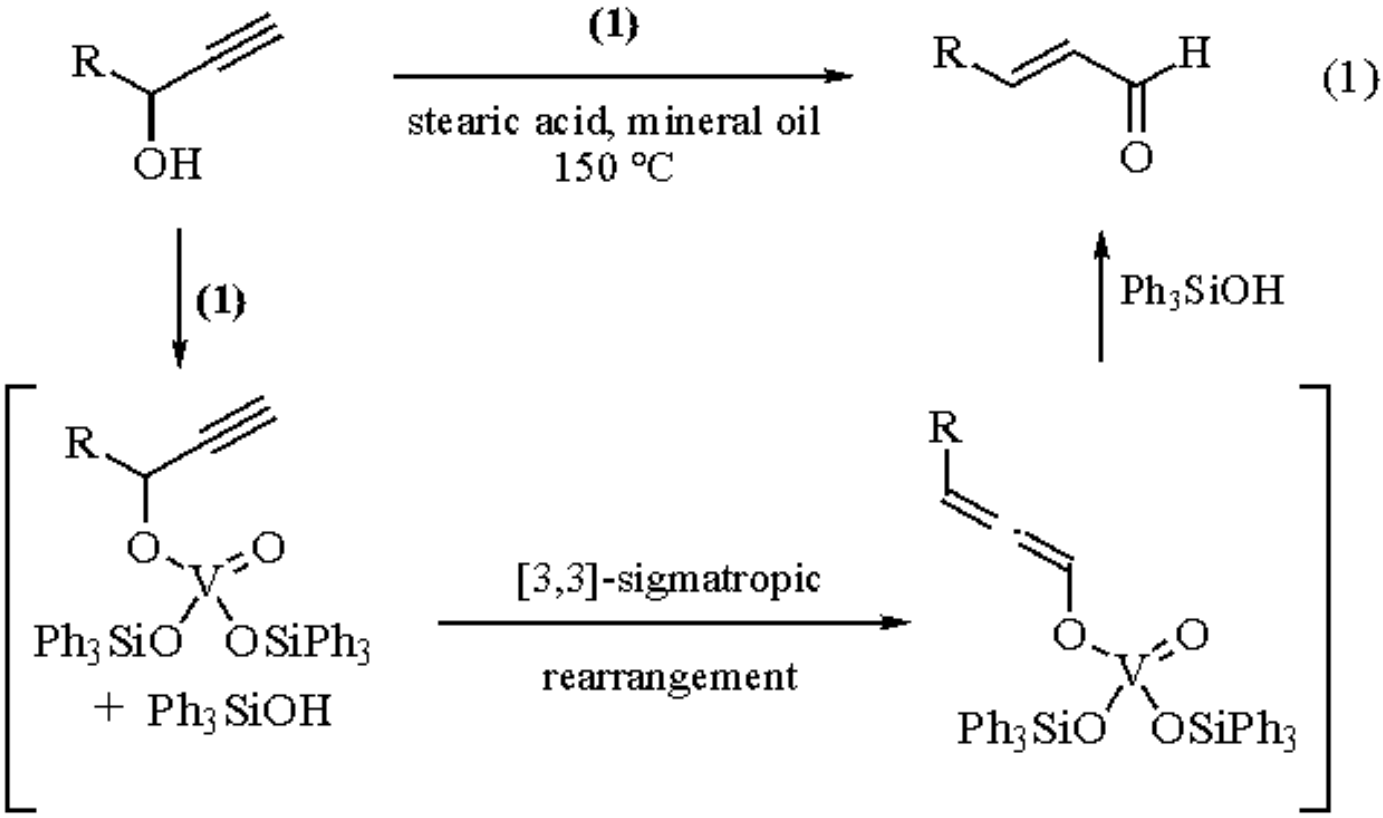

Isomerization of Allylic Alcohols.

Treatment of allylic alcohols with (**1**) in mineral oil at 150 °C effects clean allylic inversion (eq 2).[2] Since this is an equilibrium process, the reaction is probably limited to cases where the starting allylic alcohol is considerably less stable than its allylic rearrangement product. As in the above case with propargylic alcohols, the reaction proceeds via a [3,3]-sigmatropic rearrangement. In some cases, minor amounts of alcohol oxidation products were also observed. Yields for this process are typically greater than 80%.

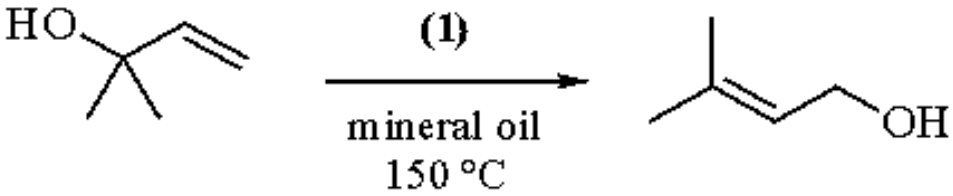

(2)

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Tropylium Tetrafluoroborate[1]

[27081-10-3] · $C_7H_7BF_4$ · Tropylium Tetrafluoroborate · (MW 177.95)

(useful precursor to azulenes,[2,3] cycloheptatrienes,[4-15] heptafulvenes,[4,9,16] 8-azafulvenes,[17] and tropones[18,19])

Alternate Names: tropylium fluoroborate, cycloheptatrienocarbonium fluoroborate.

Physical Data: mp >200 °C (dec).

Solubility: sol polar organic solvents (e.g. MeCN, DMF), and H_2O; reacts with DMSO.[19]

Form Supplied in: white powder; commercially available.

Analysis of Reagent Purity: elemental analysis; λ_{max} 218 nm; (log ε 4.70), 274 nm; (log ε 3.61).[20]

Preparative Methods: most conveniently prepared by the reaction of cycloheptatriene with PCl_3, followed by treatment with ethanolic HBF_4 at 0 °C (0.24 mol scale, 80-89% yield).[20] The reagent is obtained in 98-100% purity.

Purification: can be recrystallized from a large volume of ethyl acetate or ethyl acetate-acetonitrile; however, considerable material is lost and the purity of the reagent is not significantly improved.[20]

Handling, Storage, and Precautions: this material is a nonhygroscopic, stable source of the tropylium ion, making it a superior choice to either the halide (hygroscopic) or perchlorate (potentially explosive) salts. The reagent is a corrosive solid.

Synthesis of Azulenes.

Tropylium tetrafluoroborate ($TpBF_4$) (2 equiv) reacts with a variety of allenylsilanes to generate 2-silylazulenes in fair to excellent yield (eq 1).[2] This [3 + 2] annulation strategy allows for the synthesis of azulenes with complete regiochemical control over substituents on the newly formed five-membered ring. It is necessary to employ a nonnucleophilic acid scavenger to remove HBF_4 generated in the reaction in order to obtain good yields of azulenes; poly(4-vinylpyridine) or methyltrimethoxysilane functions best in this capacity. An analogous reaction with propargylsilanes also gives rise to 2-silylazulenes.[3] The 2-silylazulene products can be readily protodesilyated to yield 1,3-disubstituted azulenes in excellent yield. Certain substituted tropylium tetrafluoroborates will also undergo this reaction to generate azulenes. However, substituents are limited to groups bearing no α-hydrogens (to prevent heptafulvene formation,[21] e.g. *t*-butyl or phenyl).

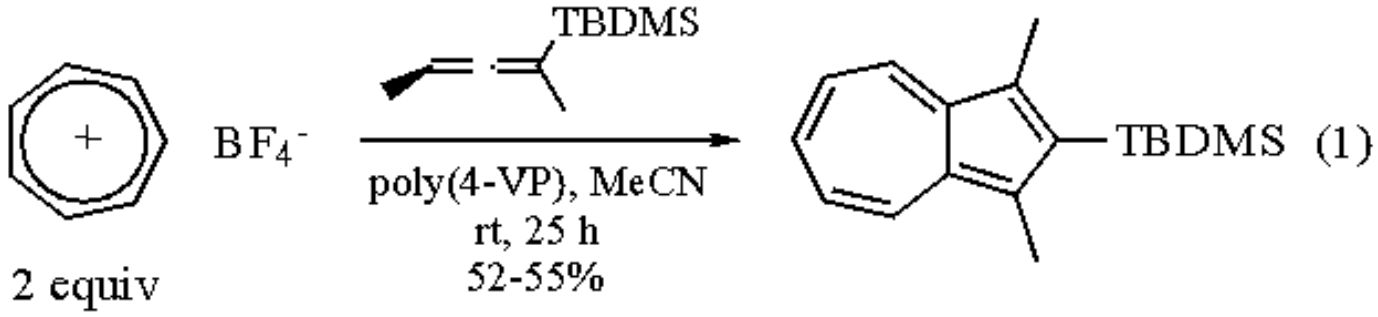

Synthesis of Substituted Cycloheptatrienes.

Tropylium salts react with a wide array of carbon- and heteroatom-based nucleophiles to provide 7-substituted cycloheptatrienes (7-CHTs). $TpBF_4$ is best suited for this reaction since it is nonhygroscopic and indefinitely stable.[20] For example, $TpBF_4$ reacts with a variety of active methylene compounds such as diethyl acetonedicarboxylate,[4] acetylacetone (eq 2),[5] and malonic acid derivatives[6] to give 7-CHTs. Alkyl-, alkenyl-, and akynyllithium reagents, as well as alkenylzinc and -aluminum derivatives, combine smoothly with $TpBF_4$ to provide access to a host of 7-CHTs.[7] α-Cycloheptatrienyl ketones are also easily prepared from $TpBF_4$ by reaction with enolizable ketones[8] or morpholinoenamines[9] in the presence of an acid catalyst. Other nucleophiles which react with $TpBF_4$ in this manner include isocyanides,[10,11] inorganic cyanides,[11] allylsilanes,[12] stabilized phosphonium ylides,[13] propargylic alcohols,[14] and allylic amines.[15]

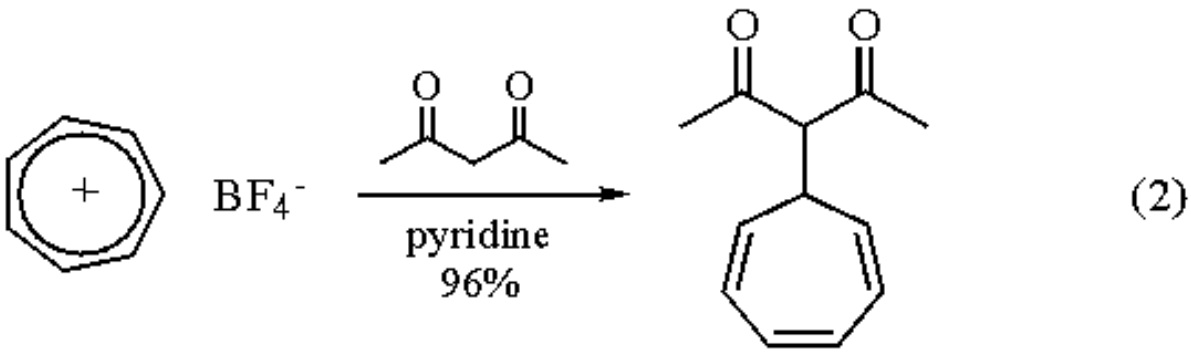

Synthesis of Heptafulvenes and 8-Azaheptafulvenes.

In a two-step procedure, $TpBF_4$ can be used to synthesize a variety of heptafulvene derivatives.[4,9,16] As previously discussed, $TpBF_4$ reacts with nucleophiles to give cycloheptatrienes. These CHTs can then be used to produce heptafulvenes. For example, treatment of $TpBF_4$ with 1,3-cyclopentanedione generates a 7-CHT. Reaction of this species with ***Phosphorus(V) Chloride*** yields a new tropylium cation, which when treated with base affords a heptafulvene derivative (eq 3).[16a] 8-Azaheptafulvenes can also be produced from $TpBF_4$ by reaction with a variety of aniline derivatives (eq 4).[17]

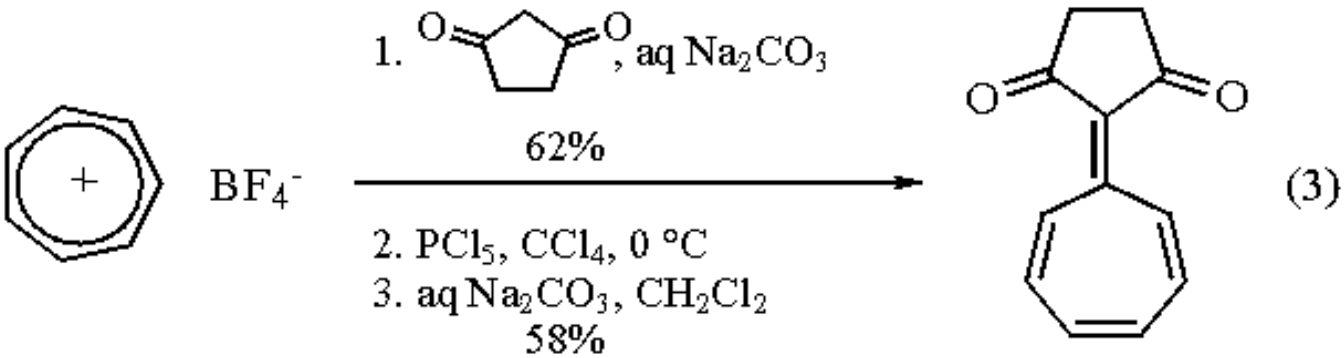

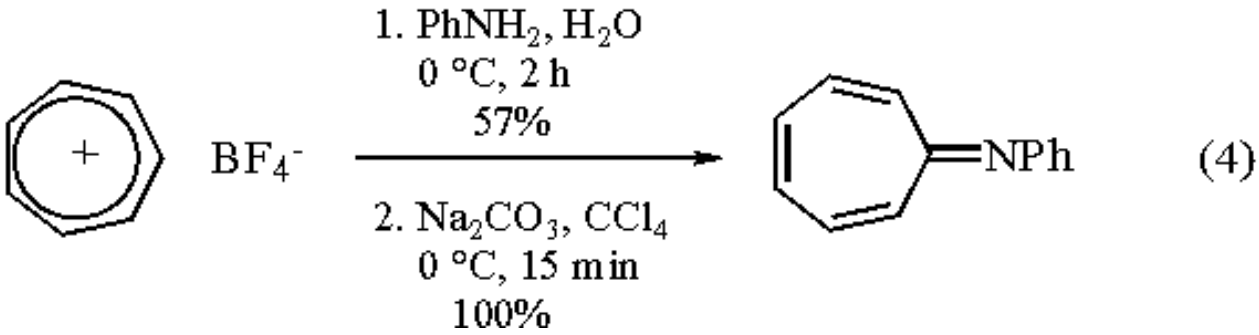

(4)

Synthesis of Tropone.

$TpBF_4$ is a convenient starting material for the synthesis of tropone in multigram quantities. This may be accomplished by treating tropyl ether (formed by the reaction of $TpBF_4$ with aq NaOH) with acid-treated silica gel (eq 5).[18] A more direct route involves heating $TpBF_4$ in DMSO; this route provides tropone in 58% yield.[19]

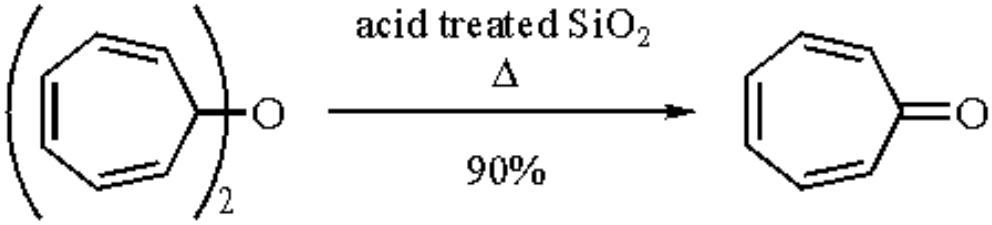

(5)

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Tungsten(VI) Chloride

WCl_6

[13283-01-7] · Cl_6W · Tungsten(VI) Chloride · (MW 396.61)

(alkene polymerization catalyst;[1] Lewis acid[2])

Physical Data: dark blue crystals; mp 275 °C; bp 347 °C.

Solubility: sol ethanol, ether, benzene, carbon tetrachloride.

Form Supplied in: sold as a solid of high purity, often packaged in ampules.

Purification: used without further purification.

Handling, Storage, and Precautions: corrosive and moisture sensitive; stored in ampules.

Decomposition of Diazo Compounds.

Diazo compounds are converted to the corresponding carbenoid species by treatment with tungsten hexachloride.[2] Tungsten hexachloride is superior to copper catalysts and common Lewis acids in effecting the [3 + 2] cycloaddition reaction between α-carbonyl carbenes and nitriles, forming isoxazoles (eq 1).

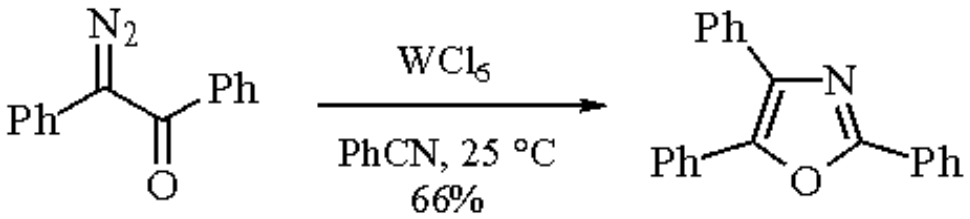

(1)

Conversion of β-Hydroxy Carboxylic Acids to Alkenes.

Treatment of β-hydroxy carboxylic acids with tungsten(VI) chloride and base leads to the β-lactones, which afford alkenes after thermal carbon dioxide expulsion (eq 2).[3] The reaction occurs in one pot and is highly stereospecific. More examples have been examined using tungsten oxychloride.

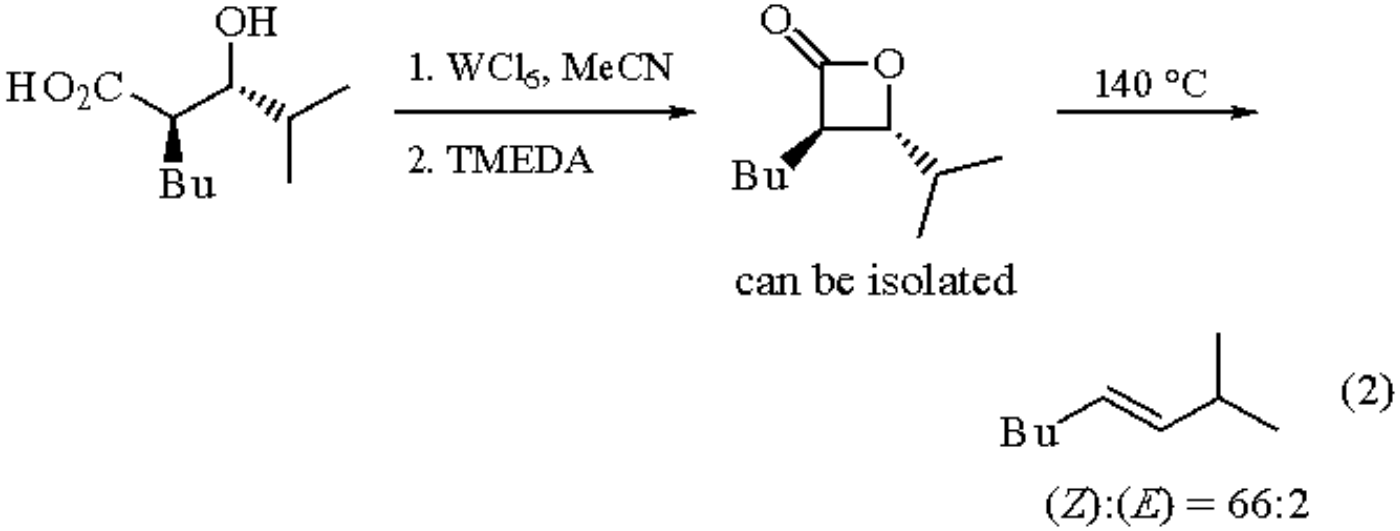

Related Reagents.

Tungsten(VI) Chloride-n-Butyllithium; ***Tungsten(VI) Chloride-Tetramethylstannane***.

---

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Tungsten(VI) Chloride-*n*-Butyllithium

WCl_6-*n*-BuLi

(WCl_6)

[13283-01-7] · Cl_6W · Tungsten(VI) Chloride-*n*-Butyllithium · (MW 396.61) (*n*-BuLi)

[109-72-8] · C_4H_9Li · Tungsten(VI) Chloride-*n*-Butyllithium · (MW 64.07)

(deoxygenation of epoxides and carbonyl compounds[1])

Physical Data: WCl_6: dark blue crystals; mp 275 °C; bp 347 °C.

Solubility: WCl_6: sol ethanol, ether, benzene, carbon tetrachloride. *n*-BuLi: sol hydrocarbon and ether solvents.

Form Supplied in: reaction of ***Tungsten(VI) Chloride*** and ***n-Butyllithium*** produces a poorly characterized species, thought to be a reduced form of tungsten. The compound obtained by mixing these two reagents is typically used without additional purification. Tungsten(VI) chloride is sold as a solid of high purity, often packaged in ampules. Butyllithium is sold as a solution in hexane, cyclohexane, or pentane.

Purification: both reagents are used without further purification.

Handling, Storage, and Precautions: WCl_6: corrosive and moisture sensitive; stored in ampules. *n*-BuLi: reacts fairly violently with water and air; can be stored indefinitely provided the container is protected from the atmosphere.

Deoxygenation of Epoxides.

The combination of tungsten(VI) chloride and butyllithium leads to a structurally uncharacterized reagent which is very efficient for the deoxygenation of epoxides, affording alkenes.[1] The reagent is stereospecific for the reduction of cyclic epoxides,[1,2] but less stereoselectivity is observed during the preparation of acyclic alkenes from the corresponding epoxides. Reduction of monosubstituted epoxides often leads to substantial amounts of chlorohydrins, which are nonstereospecifically reduced by the reagent at higher temperatures. Tungsten(VI) chloride-butyllithium is the reagent of choice for deoxygenation of highly hindered epoxides. This reagent is effective for reduction of the epoxide functionality in the complex trichothecene derivative in eq 1,[3] and the ryanodol synthesis intermediate in eq 2.[4]

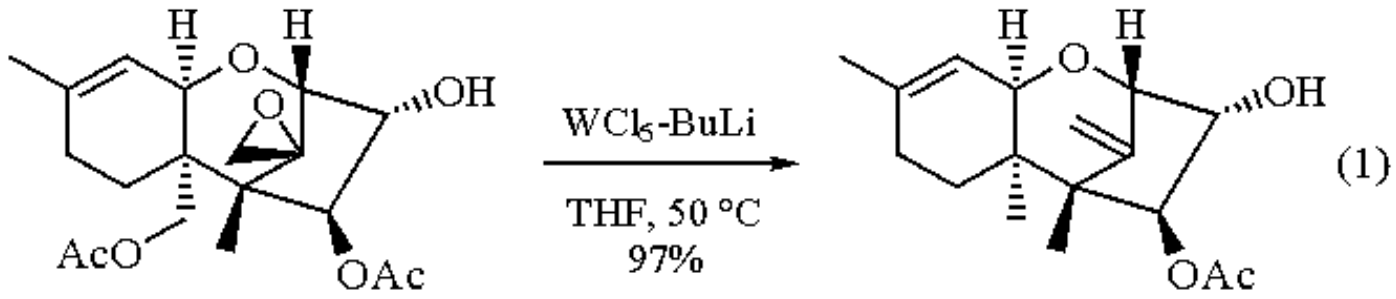

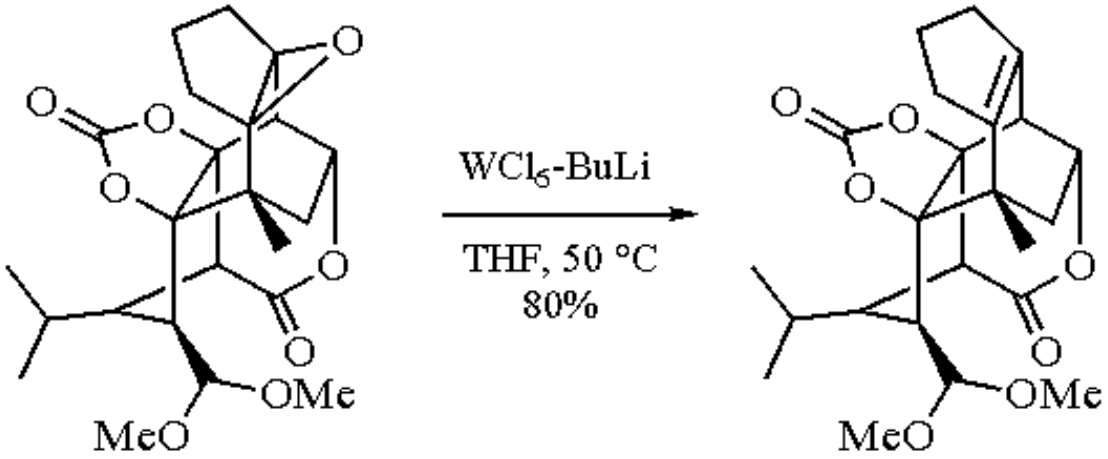

(2)

Deoxygenative Dimerization of Carbonyl Compounds.

Treatment of carbonyl compounds with tungsten(VI) chloride-butyllithium leads to the corresponding symmetrical alkenes resulting from deoxygenation and coupling of the carbonyl compounds.[1] The reaction proceeds most efficiently with aromatic aldehydes (eq 3) and less efficiently with aromatic ketones and aliphatic carbonyl compounds. The scope and limitations of this deoxygenative dimerization reaction have not been as thoroughly investigated as those employing low-valent titanium species.[5]

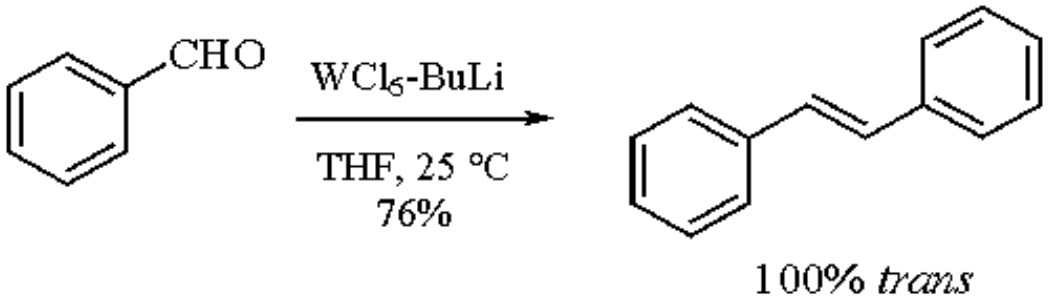

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Tungsten(VI) Chloride-Tetramethylstannane

WCl_6-$SnMe_4$

(WCl_6)

[13283-01-7] · Cl_6W · Tungsten(VI) Chloride-Tetramethylstannane · (MW 396.61) ($SnMe_4$)

[594-27-4] · $C_4H_{12}Sn$ · Tungsten(VI) Chloride-Tetramethylstannane · (MW 178.87)

(alkene metathesis catalyst[1])

Physical Data: WCl_6: dark blue crystals; mp 275 °C; bp 347 °C. $SnMe_4$: bp 74-75 °C.

Solubility: WCl_6: sol ethanol, ether, benzene, carbon tetrachloride. $SnMe_4$: sol all organic solvents.

Form Supplied in: reaction of ***Tungsten(VI) Chloride*** and ***Tetramethylstannane*** produces a poorly characterized species, which is thought to be a metal-carbene complex.[2] The compound obtained by mixing these two reagents is typically used without additional purification. Tungsten(VI) chloride is sold as a solid of high purity, often packaged in ampules. Tetramethylstannane is sold as a neat liquid.

Purification: tetramethylstannane is purified by distillation under nitrogen at atmospheric pressure.

Handling, Storage, and Precautions: WCl_6: corrosive and moisture sensitive; stored in ampules. $SnMe_4$: highly toxic; can be stored for long periods in a refrigerator. The reagent prepared by combination of tungsten(VI) chloride and tetramethylstannane is typically used immediately after mixing the two reagents.

Alkene Metathesis.

The compound generated from tungsten(VI) chloride and tetramethylstannane is a catalyst for the alkene metathesis reaction.[3] Unlike many alkene metathesis catalysts, tungsten(VI) chloride-tetramethylstannane is compatible with ester functionality.[4-7] The most important use of tungsten(VI) chloride-tetramethylstannane is in the ring opening metathesis polymerization (ROMP) of cycloalkenes;[1] however, a few examples have been presented using this reagent for organic synthesis. Self-metathesis of methyl 9-octadecenoate (*cis* or *trans*) with tungsten(VI) chloride-tetramethylstannane leads to a 2:1:1 ratio of methyl 9-octadecenoate (starting material), 9-octadecene, and dimethyl 9-octadecenedioate, respectively (eq 1).[4] This system is presumably at equilibrium. Cometathesis of cyclooctene and alkenic esters by tungsten(VI) chloride-tetramethylstannane leads to dienoic esters (eq 2).[6] Similarly, the chain length of the unsaturated fatty acid ester methyl oleate can be shortened by cometathesis with hexane (eq 3).[7] In general, the cometathesis reactions do not proceed efficiently since all possible metathesis products are produced to some extent.

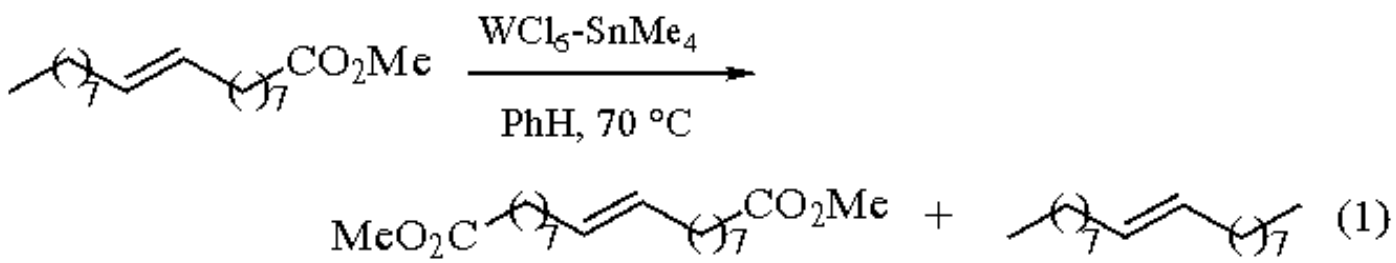

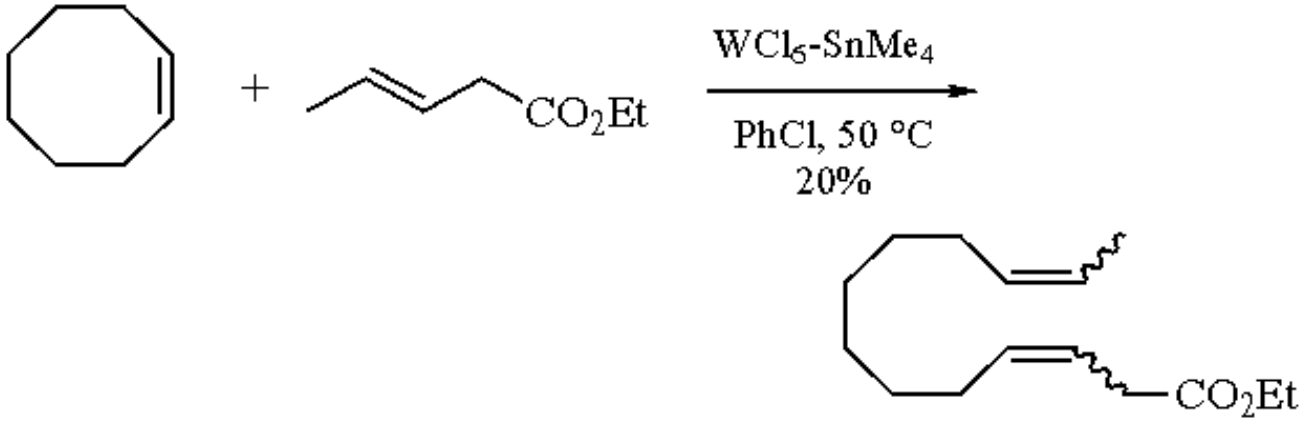

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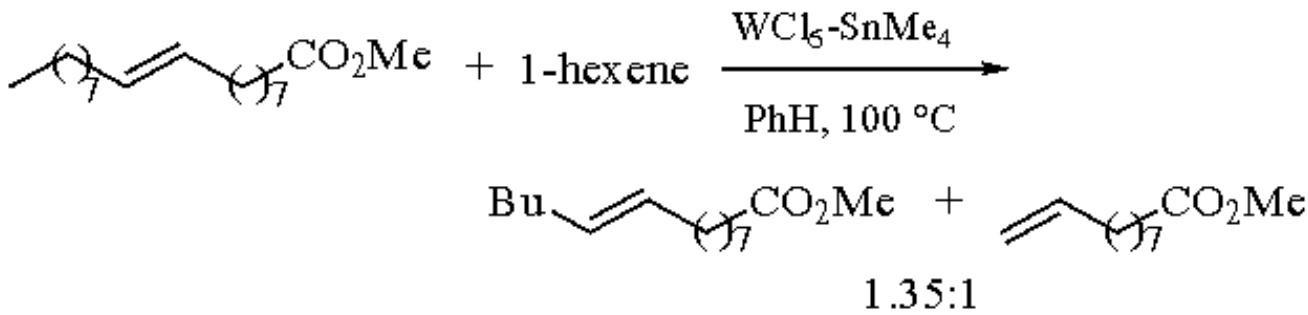

(3)

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Tungsten(VI) Fluoride

WF_6

[7783-82-6] · F_6W · Tungsten(VI) Fluoride · (MW 297.85)

(oxidant;[1] Lewis acid[1])

Alternate Name: tungsten hexafluoride.

Physical Data: mp 2.5 °C; bp 17.1 °C.

Solubility: sol nonpolar aprotic organic solvents, basic water.

Form Supplied in: gas.

Handling, Storage, and Precautions: corrosive; moisture sensitive.

Hydrolysis of *N,N*-Dimethylhydrazones and Tosylhydrazones.

Both *N,N*-dimethylhydrazones and tosylhydrazones are oxidatively hydrolyzed under neutral conditions by treatment with tungsten(VI) fluoride in chloroform/water at 0 °C (eq 1).[1] Hydrazones of aromatic aldehydes and of aromatic and aliphatic ketones are readily hydrolyzed under these conditions. In virtually all cases the yield is greater than 80%. Using tungsten(VI) fluoride, the hydrolysis proceeds at lower temperature than with other methods.[2]

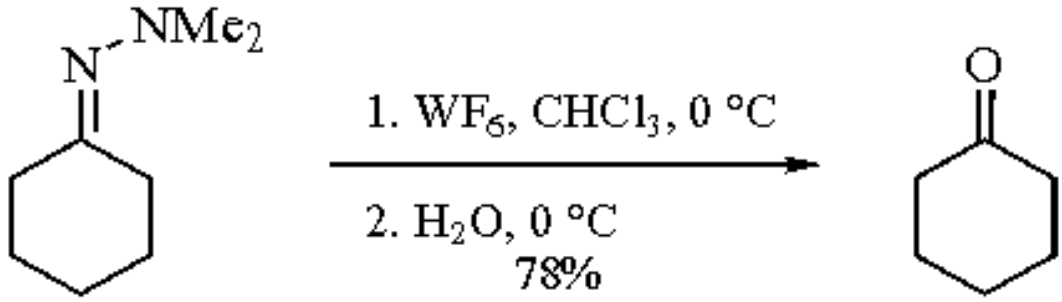

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James W. Herndon

Tungsten(VI) Oxide-Chlorosulfuric Acid

WO_3-$ClSO_3H$

(WO_3)

[1314-85-8] · O_3W · Tungsten(VI) Oxide-Chlorosulfuric Acid · (MW 231.85) ($ClSO_3H$)

[7790-94-5] · $ClHO_3S$ · Tungsten(VI) Oxide-Chlorosulfuric Acid · (MW 116.53)

(induces the coupling of α-hydroxy peroxides and epoxides, forming 1,2,4-trioxane derivatives[1])

Alternate Name: tungsten(VI) oxide-chlorosulfonic acid.

Physical Data: WO_3: mp 1473 °C; *d* 7.16 g cm^{-3}; yellow crystals. $ClSO_3H$: bp 151-152 °C/755 mmHg; *d* 1.753 g cm^{-3}.

Solubility: WO_3: sol hot alkali; slightly sol HF. $ClSO_3H$: sol $CHCl_3$, CH_2Cl_2; reactive to many organic functional groups.

Form Supplied in: WO_3: yellow solid. $ClSO_3H$: neat liquid.

Handling, Storage, and Precautions: $ClSO_3H$: reacts violently with water and alcohols; an oxidizer; corrosive.

Synthesis of 1,2,4-Trioxane Derivatives.

Coupling of α-hydroxy peroxides and epoxides in the presence of tungsten(VI) oxide and ***Chlorosulfonic Acid*** catalyst leads to the synthesis of 1,2,4-trioxane derivatives, accompanied by the ketone derived from the hydroperoxide (eq 1).[1] Overall yields of 1,2,4-trioxane derivative are generally in the range of 30-60%. Epoxides tested in this reaction include cyclohexene oxide, styrene oxide, and 1,1-diphenylethylene oxide. The α-hydroxy peroxides are generated from carbonyl compounds and 30% ***Hydrogen Peroxide***, and used without further purification. Examples tested include α-hydroxy hydroperoxides derived from decanal, benzaldehyde, and cyclohexanone. For a listing of other preparations of 1,2,4-trioxane derivatives, see Jefford et al.[2]

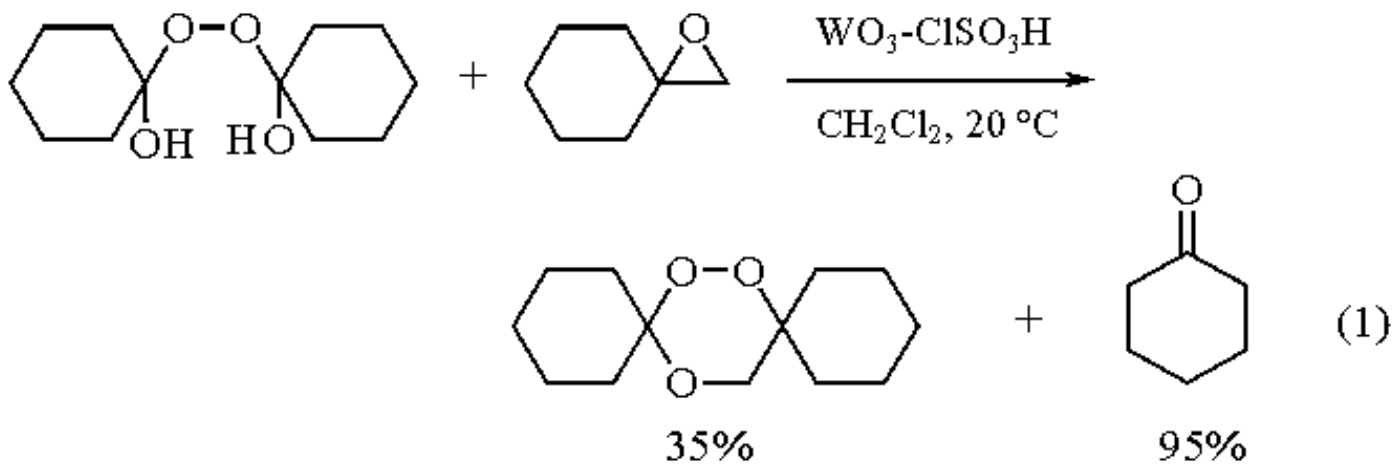

(1)

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James W. Herndon

L-Tyrosine Hydrazide

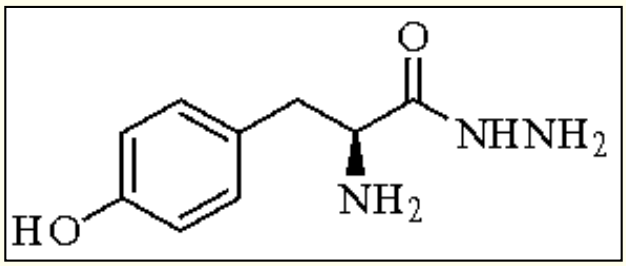

[7662-51-3] · $C_8H_{13}N_3O_2$ · L-Tyrosine Hydrazide · (MW 195.24)

(resolution of carboxylic acids and amino acids[1])

Physical Data: crystalline solid; mp 196-198 °C; [α]25D +76° (*c* 4.2, 1N HCl).

Solubility: slightly sol cold methanol or ethanol; readily sol hot methanol or ethanol.

Form Supplied in: the free base (98% purity) is available from several commercial sources. No additional purification before use is required.

Preparative Methods: the synthesis of L-tyrosine hydrazide from L-tyrosine has been described.[2] D-Tyrosine hydrazide has been obtained by resolution of DL-tyrosine hydrazide with Cbz-L-proline.[3]

Handling, Storage, and Precautions: the free base is stable in amber bottles, at room temperature, for indefinite periods of time. No special handling precautions have been described.

Introduction.

L-Tyrosine hydrazide (L-Tyr-$NHNH_2$) (**1**) is useful in the resolution of simple carboxylic acids and amino acid derivatives. It often forms highly crystalline salts with these compounds, which yield diastereomerically pure salts in just one or two recrystallizations. The yields of resolved acids tend to be high, and in many cases both enantiomers can be obtained from the same operation (the more soluble diasteromeric salt that remains in the mother liquors is often quite pure). The tyrosine hydrazide can be recovered without appreciable loss of optical activity.

Resolution of Carboxylic Acids.

A variety of racemic monofunctional carboxylic acids have been resolved with chiral α-amino acid hydrazides, including L-Tyr-$NHNH_2$ and L-leucine hydrazide, which produce mandelic acid analogs with greater than 99% ee.[4] Other examples of resolutions of simple carboxylic acids have appeared in the patent literature (eq 1).[5]

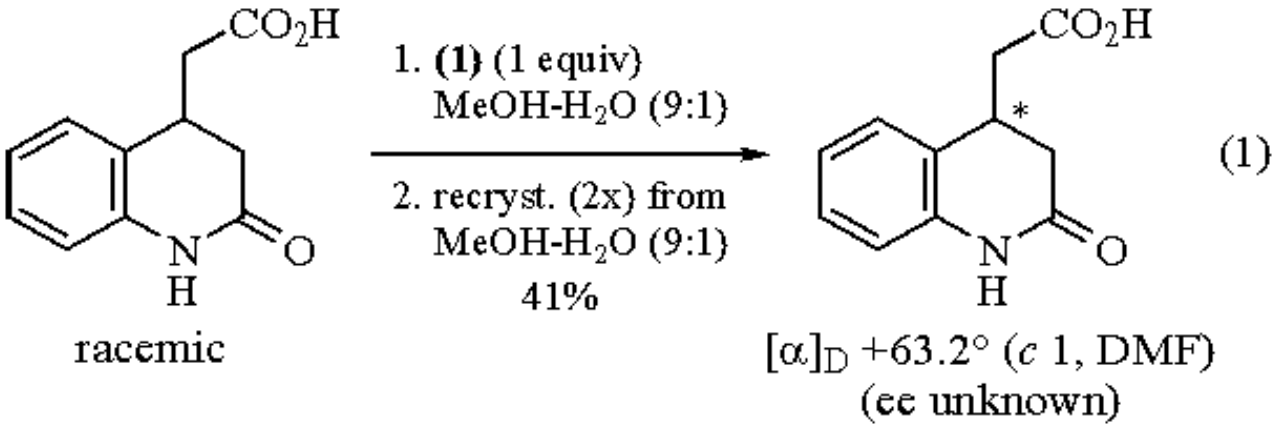

(1)

Resolution of Cyclic Amino Acid Derivatives.

L-Tyr-$NHNH_2$ has been used many times in the resolution of all types of *N*-functionalized amino acids. The high crystallinity of the salts formed has been found to be a great advantage in situations where many other common resolving agents have failed. As indicated above, multiple recrystallizations of the diastereomeric salts formed by L-Tyr-$NHNH_2$ are rarely necessary to obtain amino acids of high optical purity. In most cases, D-α-amino acid derivatives form less soluble salts with L-Tyr-$NHNH_2$ than the corresponding L-α-amino acid derivatives. One of the earliest works in this area was the resolution of (±)-Cbz-proline (eq 2).[3] (±)-Cbz-Alanine and (±)-Cbz-isoleucine (eq 3) have also been resolved.[3] In all cases, the unnatural D-α-amino acids are obtained. This procedure also allows the isolation of D-tyrosine hydrazide by resolution of (±)-Tyr-$NHNH_2$ with Cbz-L-proline.[3] Most other amino acids resolved with L-tyrosine hydrazide also have their amino group protected as the Cbz derivative. For example, both enantiomers of azetidine-2-carboxylic acid are readily available, in high yield and about 100% ee, after one single crystallization of the racemate with L-Tyr-$NHNH_2$ (eq 4).[6] Similarly, both enantiomers of pipecolic acid are obtained by resolution of (±)-*N*-Cbz-pipecolic acid with L-Tyr-$NHNH_2$ (eq 5).[7]

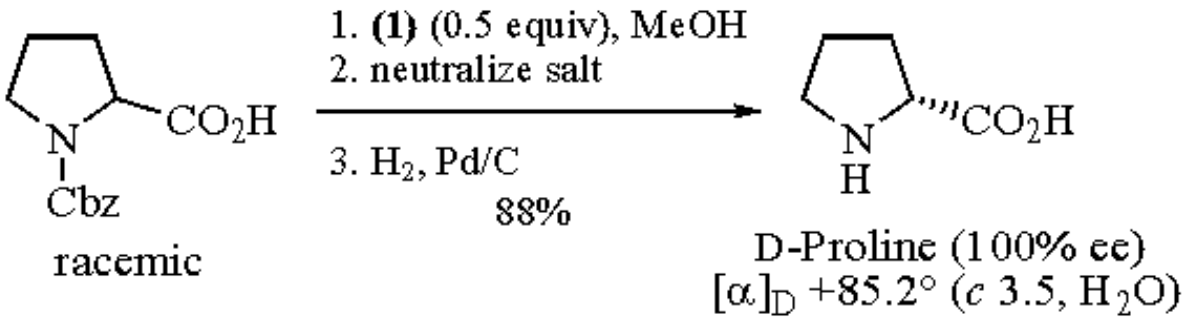

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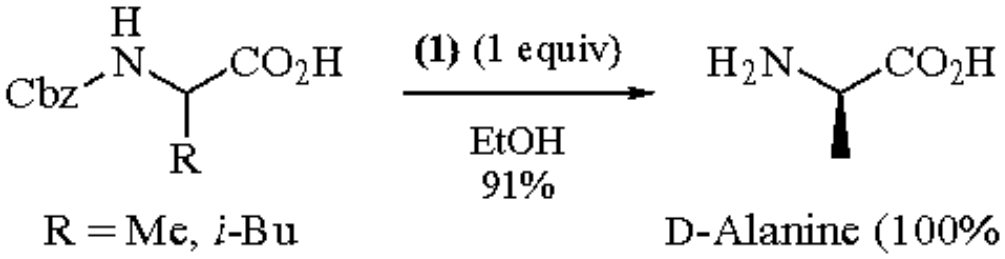

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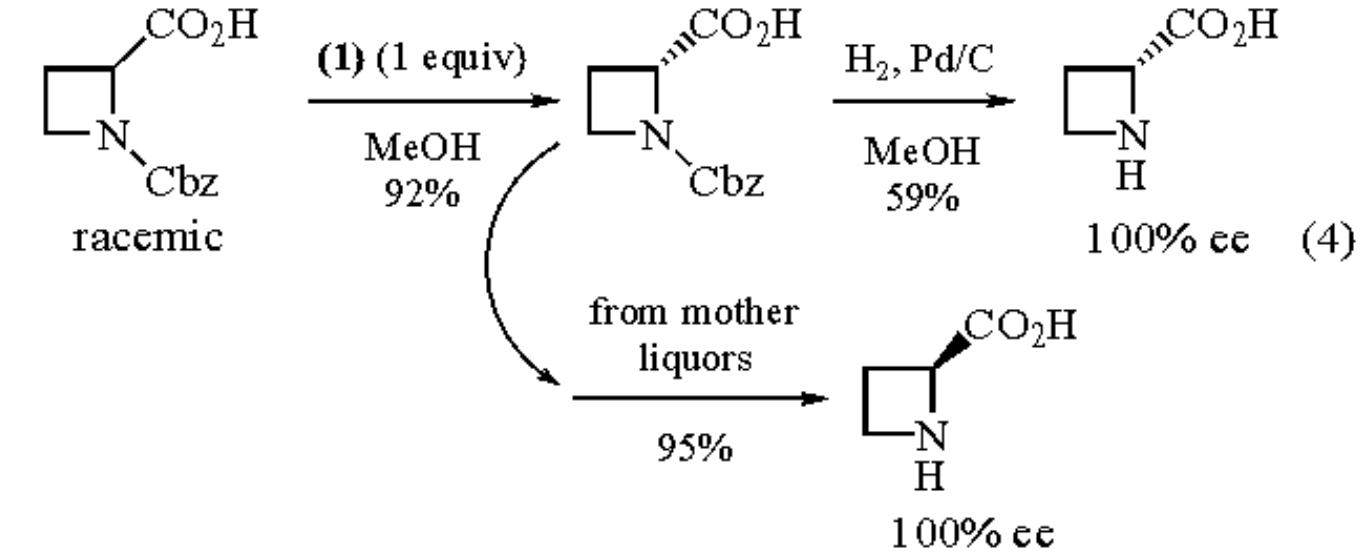

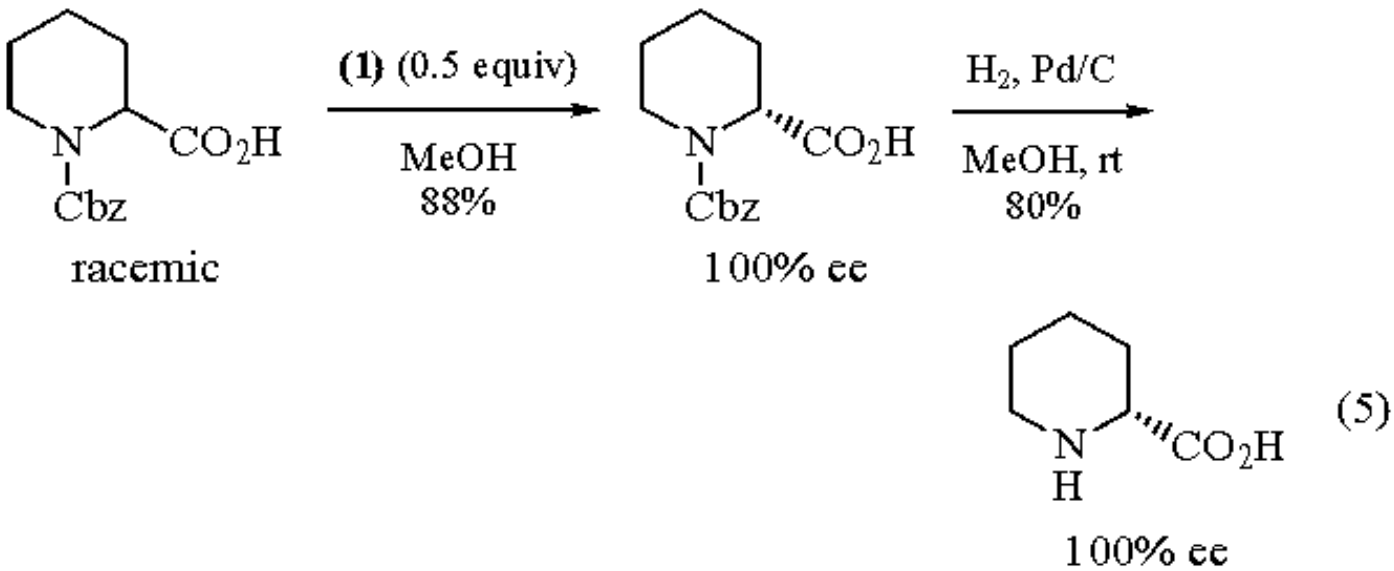

Resolution of Acyclic Amino Acid Derivatives.

D-Homoserine is readily available by resolution of (±)-*N*-Cbz-homoserine (eq 6).[8] Both enantiomers of *threo*-2-amino-3,4-dihydroxybutyric acids are available via a similar resolution with L-Tyr-$NHNH_2$.[9] *N*-Cbz-derivatives of amino dicarboxylic acids, such as α-aminosuberic acid, have been resolved with D-Tyr-$NHNH_2$. In this case, the L-amino acid derivatives crystallize preferentially with the resolving agent.[10] Finally, tetrazole analogs of α-amino acids have also been resolved with L-Tyr-$NHNH_2$. For example, racemic tetrazole analogs of *N*-protected alanine, leucine, phenylalanine, and valine are resolved with L-Tyr-$NHNH_2$ to yield, except for the phenylalanine analog, the D-enantiomers (eq 7).[11]

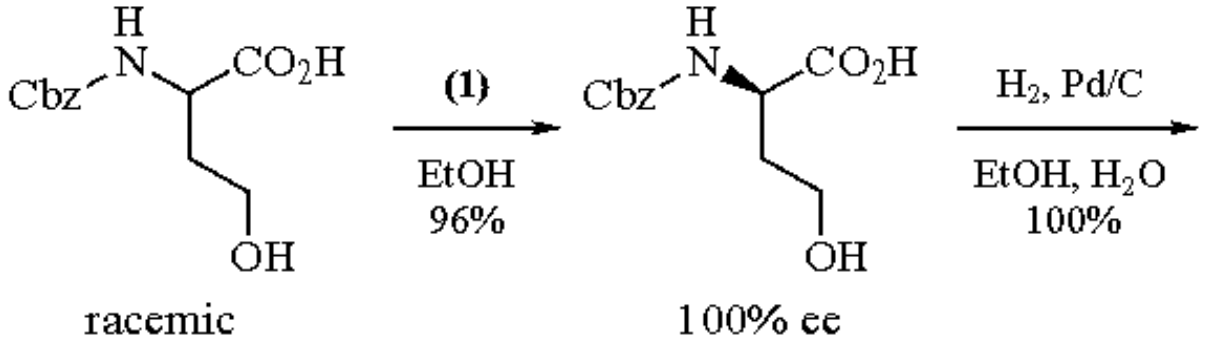

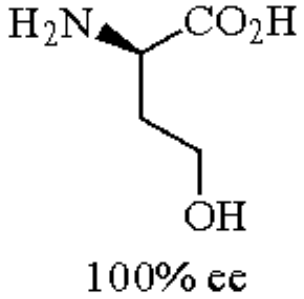

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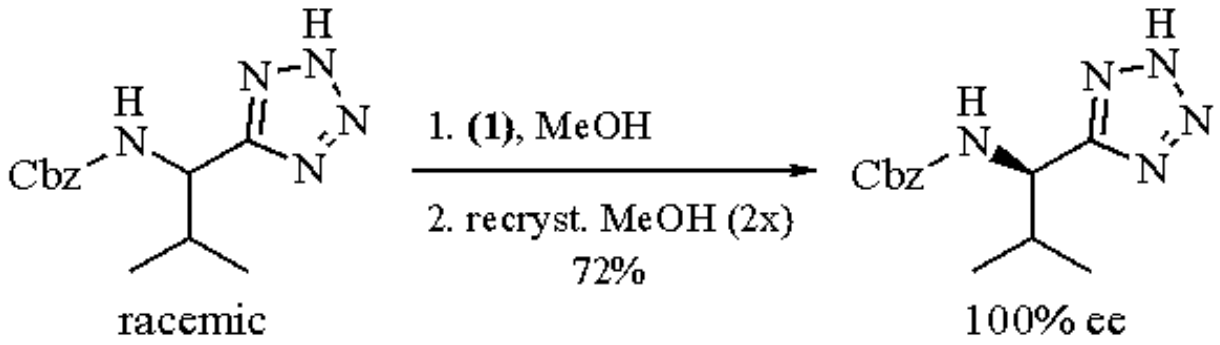

(7)

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1. All chemical yields indicated for resolution steps represent the % of the theoretical amount of pure enantiomer. For a review of resolving agents used for acids and amino acids, see: Wilen, S. H. In *Tables of Resolving Agents and Optical Resolutions*; Eliel, E., Ed.; Univ. of Notre Dame Press: Notre Dame, 1972.
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Uranium(VI) Fluoride[1]

UF_6

[7783-81-5] · F_6U · Uranium(VI) Fluoride · (MW 352.03)

(strong oxidant;[1] fluorinating agent;[2] mild Lewis acid[3])

Physical Data: mp 64.8 °C; sublimes at 56.5 °C; vapor pressure at room temperature 115 mmHg.[4]

Solubility: sol Freon, chloroform, methylene chloride.

Form Supplied in: white crystalline compound. Available in the ^{235}U depleted form as a byproduct of uranium enrichment plants.

Handling, Storage, and Precautions: UF_6, depleted of fissionable ^{235}U, contains less than 0.20% ^{235}U. It is corrosive, moisture sensitive, and mildly radioactive (low level of radiation). Caution should be exercised against these potential hazards. UF_6 is best handled in all copper apparatus. However, Freon solutions of UF_6 are stable and do not attack glass. This reagent should only be handled in a fume hood.

Oxidation.

UF_6 is a strong oxidant. Its oxidizing ability compared with that of other higher fluorides of f- and d-elements in Groups 5 and 6 is in the following sequence: $VF_5 > UF_6 > MoF_6 > WF_6 > MoF_5$.[1] Another study shows that, in acetonitrile, UF_6 is a stronger oxidant than MoF_6, NO^+, and Cu^{2+}.[5] UF_6 reacts with higher alkanes, alkenes, and arenes vigorously to give carbonaceous substances; this is of little synthetic value.[1] However, it has been used to oxidize partially oxidized organic compounds selectively. UF_6 reacts with benzylic alcohols and bromides readily to form aldehydes or ketones in moderate to good yields (eqs 1 and 2).[2] Oxidation of alkyl bromides or iodides is, however, not successful.

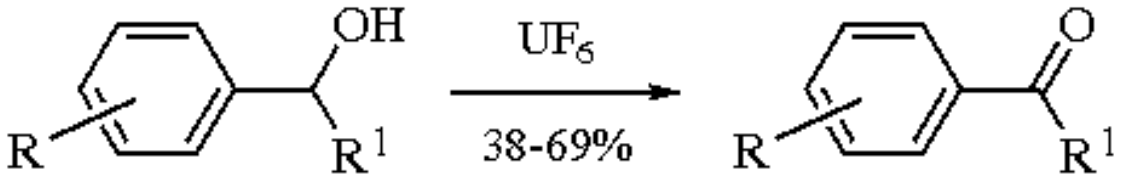

(1)

R^1 = H, alkyl, aryl

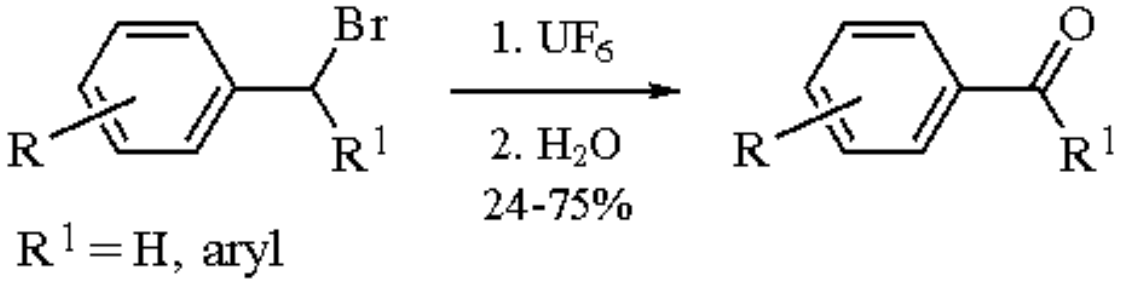

(2)

Alkyl methyl ethers are oxidatively cleaved to the corresponding carbonyl compounds (eq 3). When alkyl benzyl and alkyl benzhydryl ethers are used in the reaction, the parent alkyl alcohols are obtained together with benzaldehyde and benzophenone, respectively.[2] UF_6 is also effective in cleaving allyl ethers, but the direction of the cleavage is unpredictable. The intermediates of the oxidation can be intercepted by dithiols to form dithioacetals (eq 4). Tertiary amines (*N*,*N*-dimethylamines) react similarly with UF_6 to yield the corresponding carbonyl compounds (eq 5).

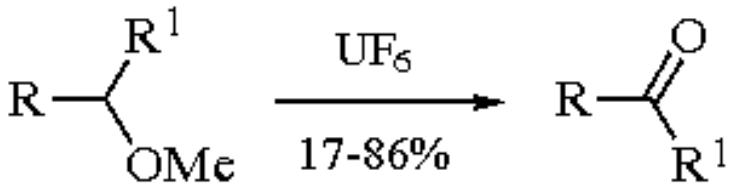

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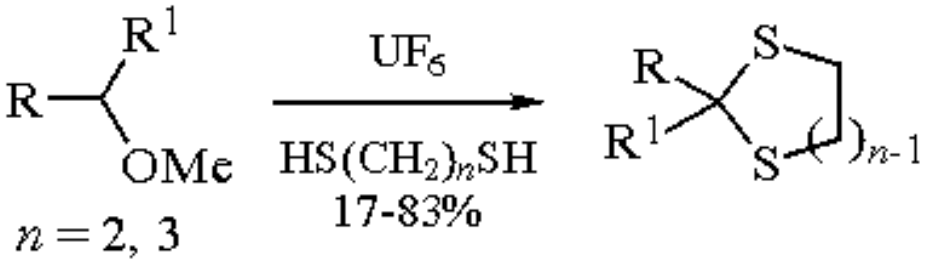

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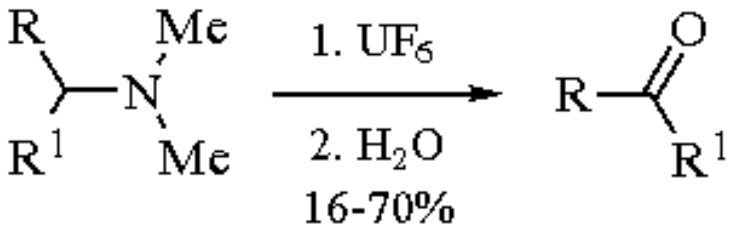

(5)

Hydrazones and oximes react with UF_6 to regenerate the parent carbonyl functions (eqs 6 and 7).[2] This offers a new alternative for these deprotections.

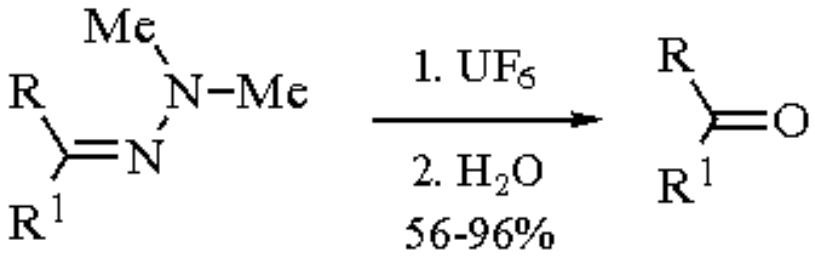

(6)

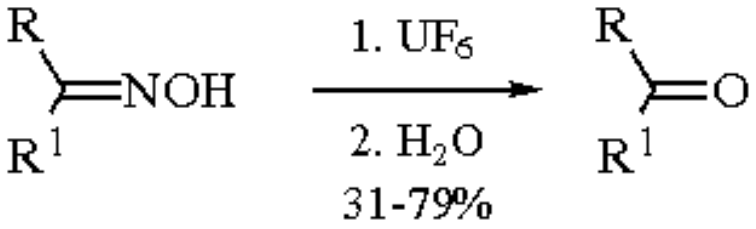

(7)

Oxidation of iodine by UF_6 in acetonitrile yields bis(acetonitrile)iodine(I) hexafluorouranate(V).[6a] In the case of bromine, oxidation generates tris(acetonitrile)bromine(I) hexafluorouranate(V) with a possible 1,3,5-triazine like structure (eq 8); this can be further utilized to brominate arenes.[6b]

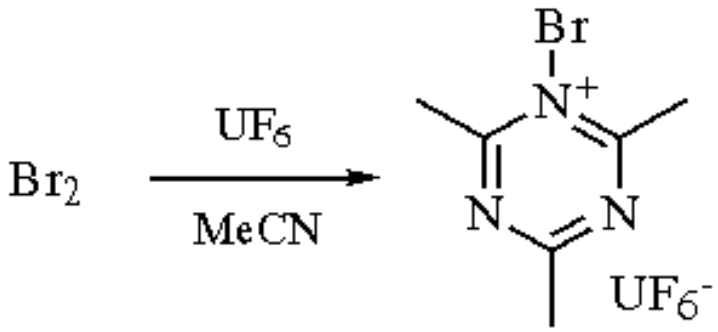

(8)

Fluorination.

Aliphatic alcohols react with UF_6 in the gas phase to form fluoroalkanes, alkenes, and ethers.[7] For primary alcohols, fluoroalkanes are the major products (eq 9). This is a valuable reaction, since it is difficult to prepare primary fluorides, especially methyl fluoride.

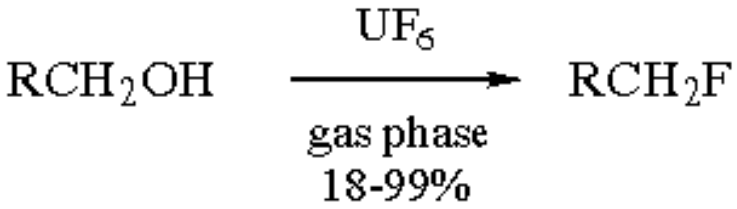

(9)

Both alkyl and aryl aldehydes have been converted to acyl fluorides in moderate yields (eq 10).[2] Adamantanone is oxidatively fluorinated to 2,2-difluoroadamantane in 41% yield (eq 11).[2] On the other hand, UF_6 behaves as a mild Lewis acid towards enolizable ketones, leading to their condensation.[8] UF_6 reacts with carboxylic acids to form acyl fluorides,[1] but in some cases this reaction is accompanied by decarboxylation.[9]

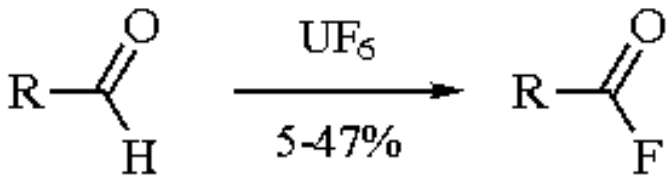

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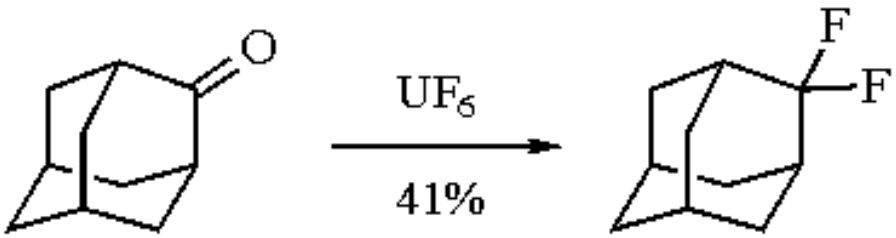

(11)

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Urea[1]

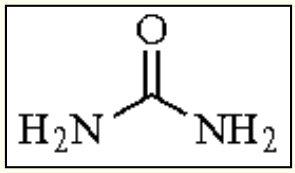

[57-13-6] · CH_4N_2O · Urea · (MW 60.07)

(nitrogen nucleophile; carbonyl cation equivalent; formation of inclusion complexes is used to purify long, slender compounds)

Physical Data: mp 132.7-132.9 °C; *d* 1.335 g cm^{-3}.

Solubility: sol H_2O (108 g/100 mL at 20 °C), EtOH (5.4 g/100 mL at 20 °C), MeOH (22 g/100 mL at 20 °C).

Form Supplied in: colorless solid.

Purification: reagent graded commercial products are sufficiently pure for most purposes. For further purification, see Perrin and Armarego.[2]

Nitrogen Nucleophile.

The three heteroatoms of urea, i.e. two nitrogens and an oxygen, are moderately nucleophilic. A number of highly regioselective alkylation reactions of urea have been developed. In most cases, the nitrogen atom is alkylated to afford the corresponding ureides or amino compounds. On heating a mixture of a carboxylic acid and urea (**1**) at around 160 °C, the corresponding amide is obtained (eq 1).[3,4] In the presence of ***Triphenyl Phosphite*** and ***Pyridine***, aromatic carboxylic acids react with urea at lower temperatures to give the corresponding arylcarbonylureas in good yields (eq 2).[5]

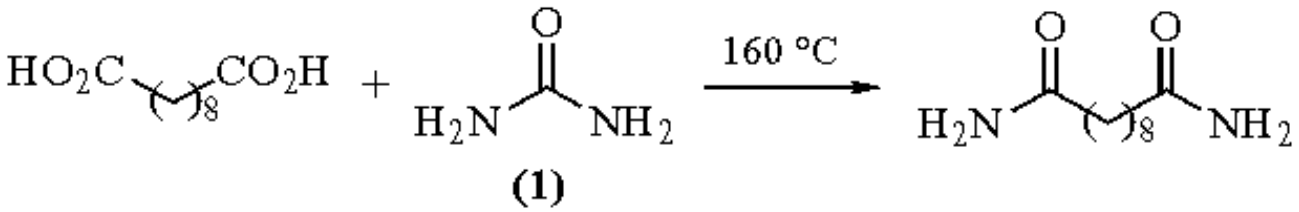

Urea serves as a nitrogen nucleophile toward tertiary carbocationic species to give *N*-*t*-alkylureas;[6,7] for example, the *t*-butyl cation, generated by treatment of *t*-BuOH with H_2SO_4, is trapped with urea to give *t*-$BuNHCONH_2$, a useful precursor of ***t-Butylamine*** (eqs 3 and 4).[6]

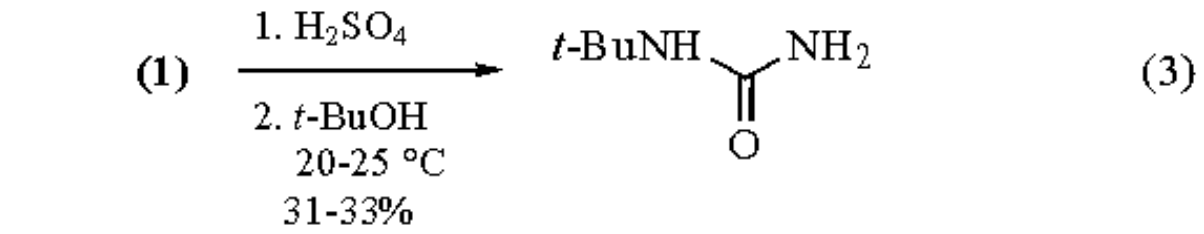

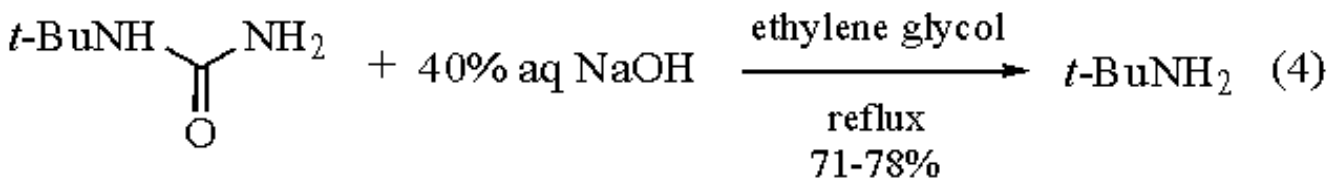

Urea reacts with orthoesters and related compounds to form alkylideneurea derivatives. The reaction with ***N,N-Dimethylformamide Diethyl Acetal*** gives *N*-carbamoyl-*N*′,*N*′-dimethylamidine (eq 5).[8] Active methylene compounds may further participate in the condensation reaction of ***Triethyl Orthoformate*** and urea to form ureidomethylene derivatives (eq 6).[9] Treatment of urea with ***Chlorine*** in the presence of ***Calcium Carbonate*** provides monochlorourea, which may be utilized as a source of ***Hypochlorous Acid*** (eq 7).[10,11]

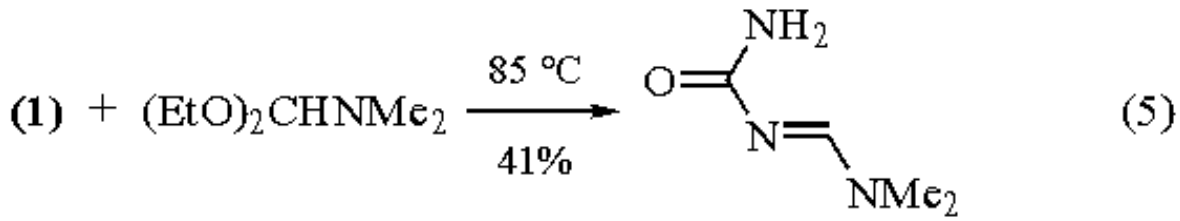

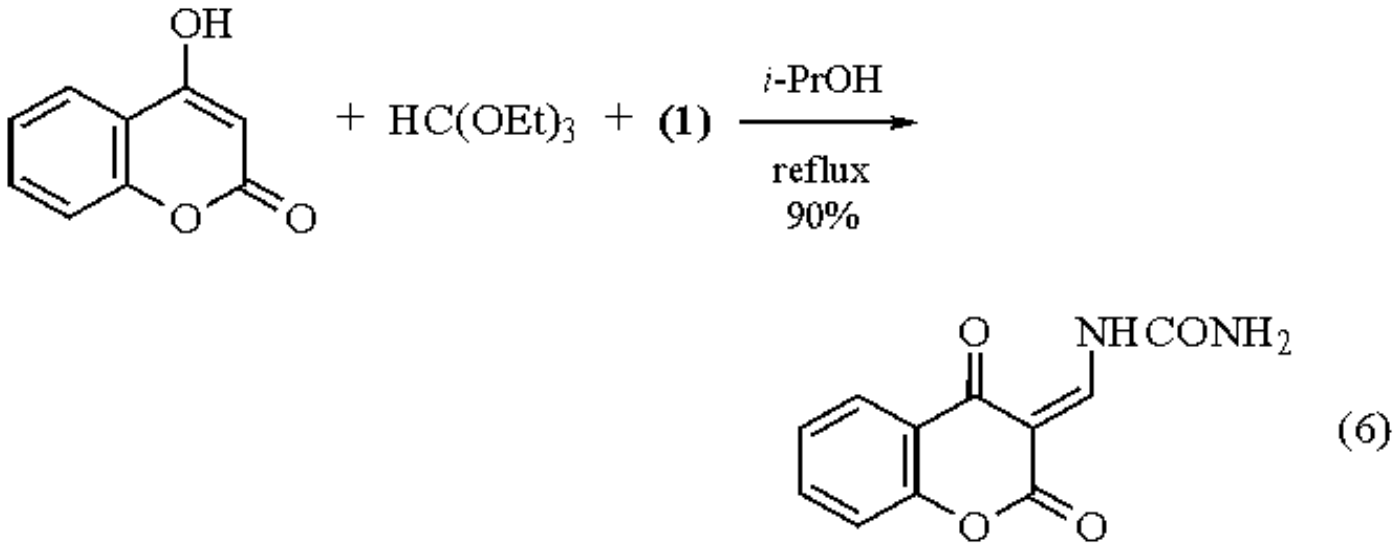

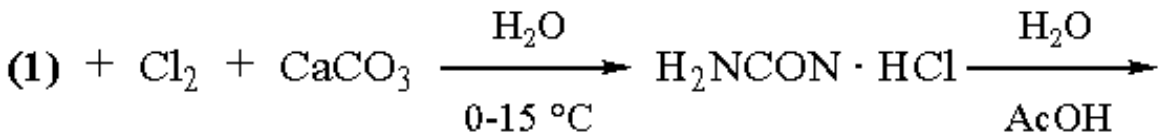

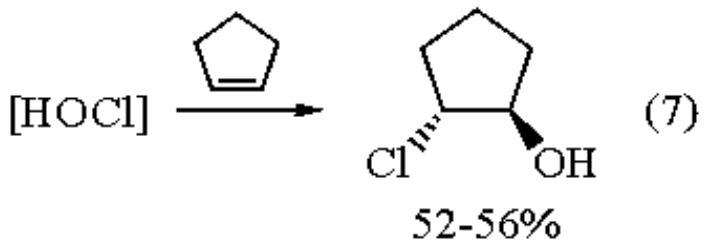

Under mild conditions, urea undergoes nucleophilic addition to carbon-carbon triple bonds (eq 8)[12] and double bonds (eq 9)[13] activated by

the coordination of Pd^{II} species. Under 1 atm of ***Carbon Monoxide***, intramolecular aminocarbonylation proceeds at 0 °C to room temperature to provide protected β-amino acids (eq 9).[13]

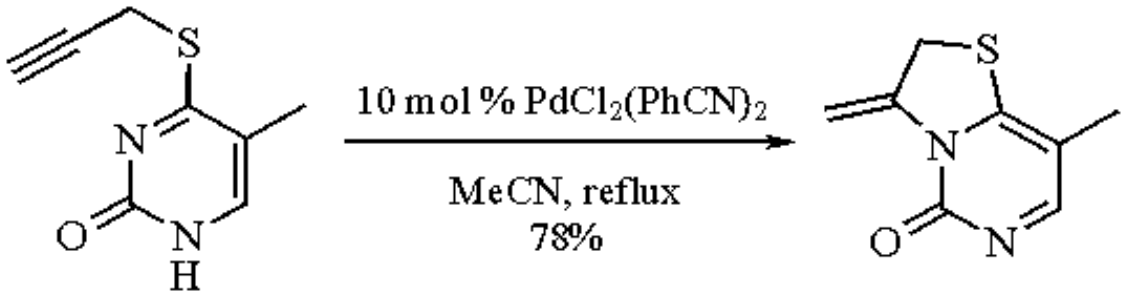

(8)

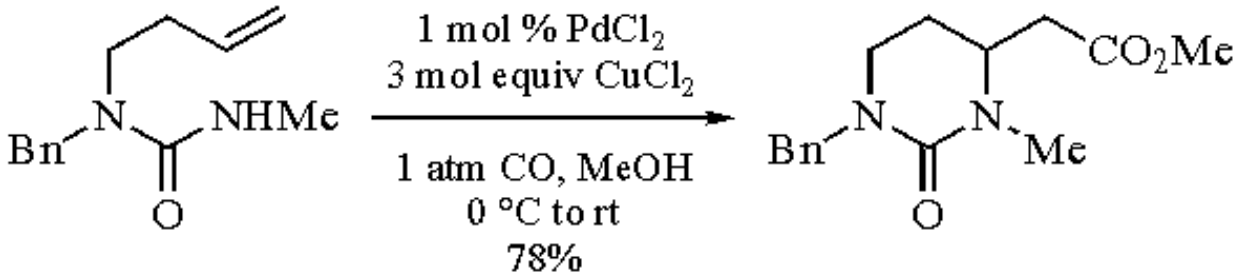

(9)

Two of the three heteronucleophilic centers of urea react with difunctionalized carbonyl compounds (e.g. dicarbonyl compounds, α-halo- or α-hydroxy carbonyl compounds, and α,β-unsaturated carbonyl compounds) to furnish a wide range of nitrogen heterocycles. The dicarbonyl compounds include ***Glyoxal***, α-diketones (eqs 10 and 11),[14-16] α-keto esters (eq 12),[17] oxalic and malonic esters (eq 13),[18,19] β-diketones (eq 14),[20] and β-keto esters (eq 15).[21] A three component connection reaction of urea, aldehydes, and β-keto esters provides dihydropyrimidines (Biginelli reaction) (eq 16).[22]

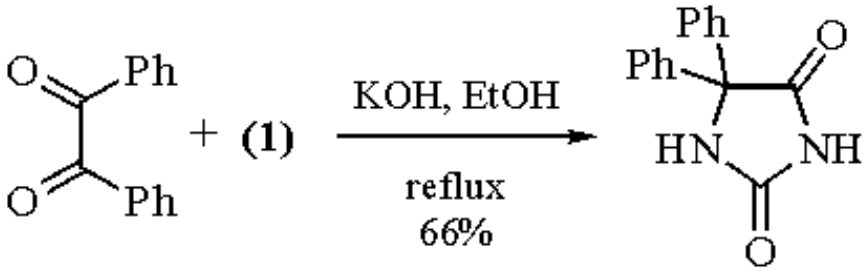

(11)

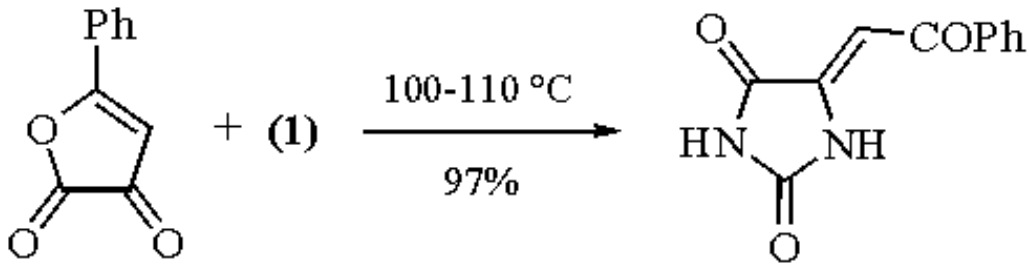

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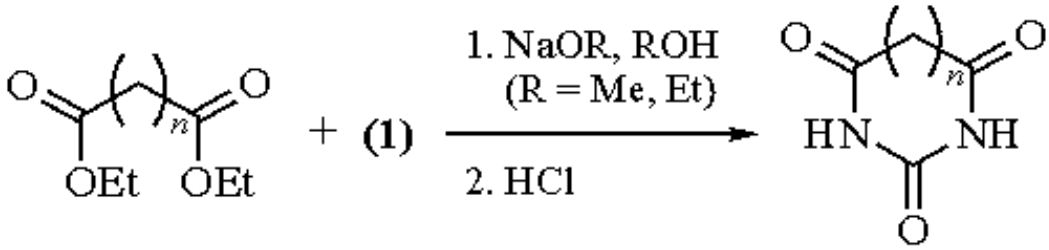

(13)

$n = 0$ parabanic acid 71.5-76%
$n = 1$ barbituric acid 72-78%

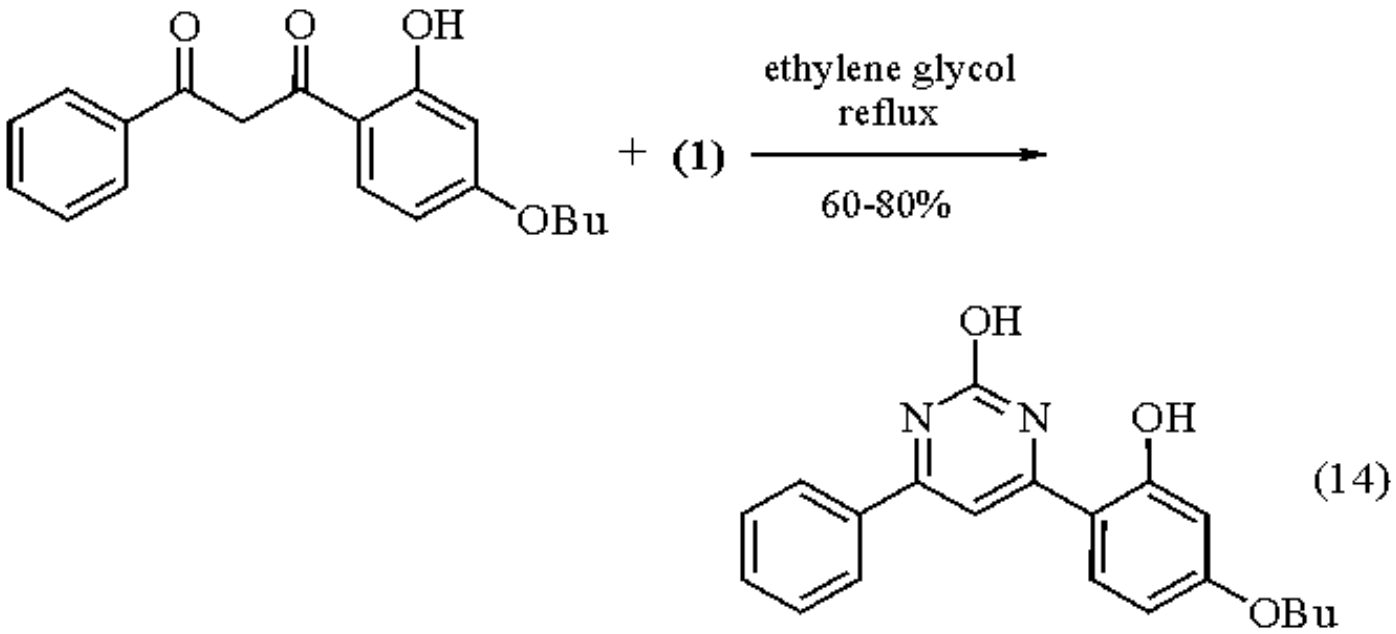

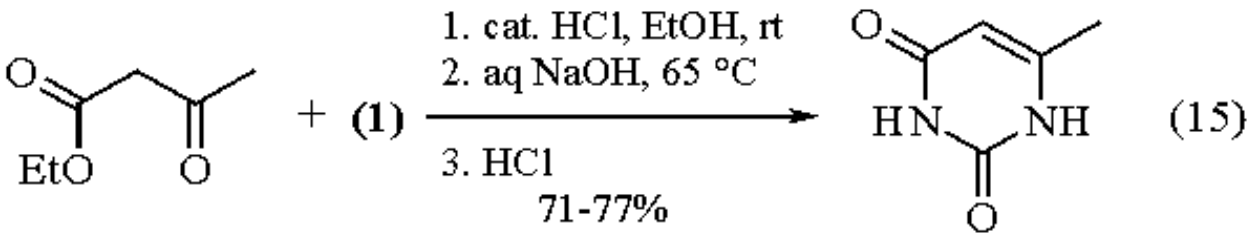

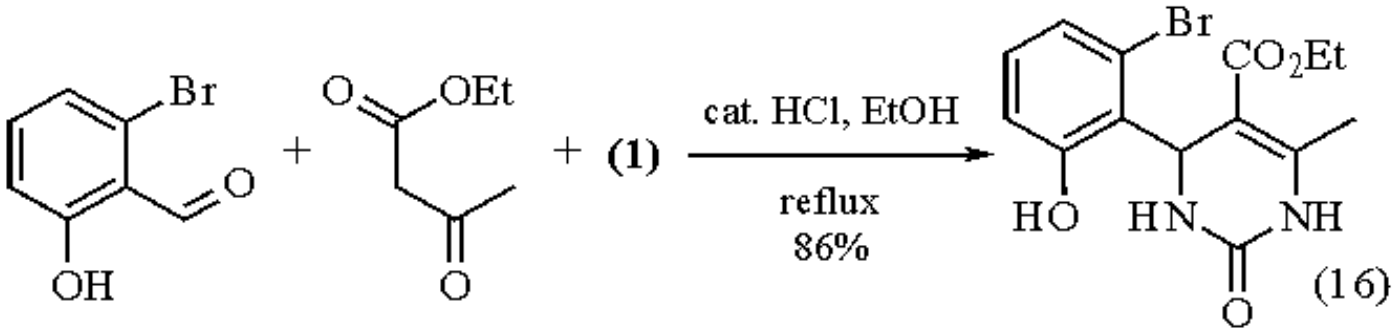

The reaction of urea and carbonyl compounds with α-substituents, such as α-hydroxy ketones[23] and α-halo ketones,[11] may afford either imidazol-2-one derivatives (eq 17) or oxazole derivatives (eq 18).[24] The latter is a rare example of the *N*,*O*-dialkylation of urea.

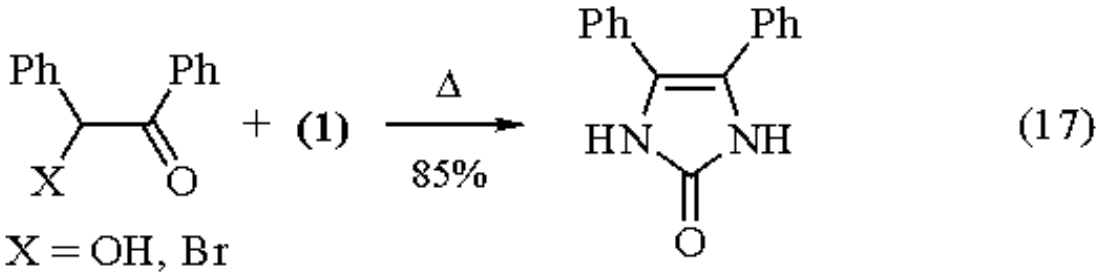

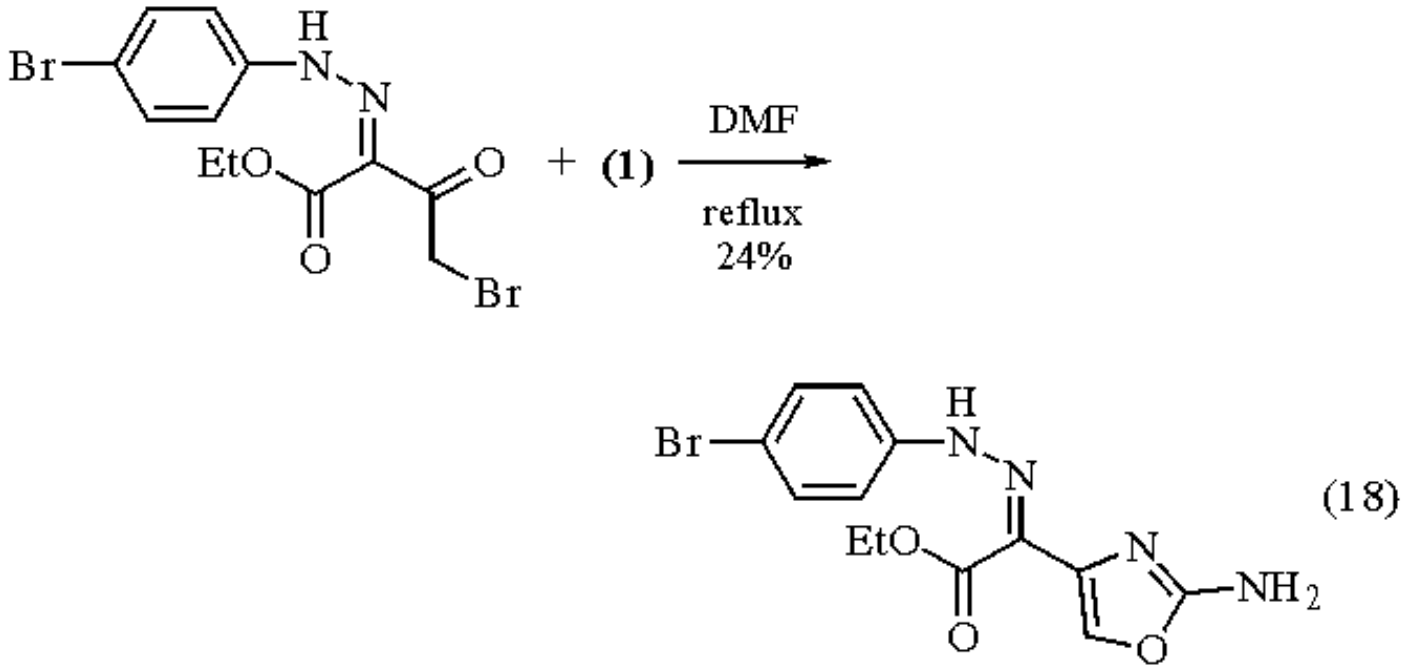

α,β-Unsaturated ketones and acids react with urea to give dihydropyrimidine derivatives (eq 19)[25] and dihydrouracils (eq 20),[26] respectively. α,β-Unsaturated aldehydes and ketones with β-substituents, such as alkoxy,[27] amino,[28] halogeno,[29] trichloromethyl,[30] etc.,[31] provide substituted pyrimidines (eq 21).

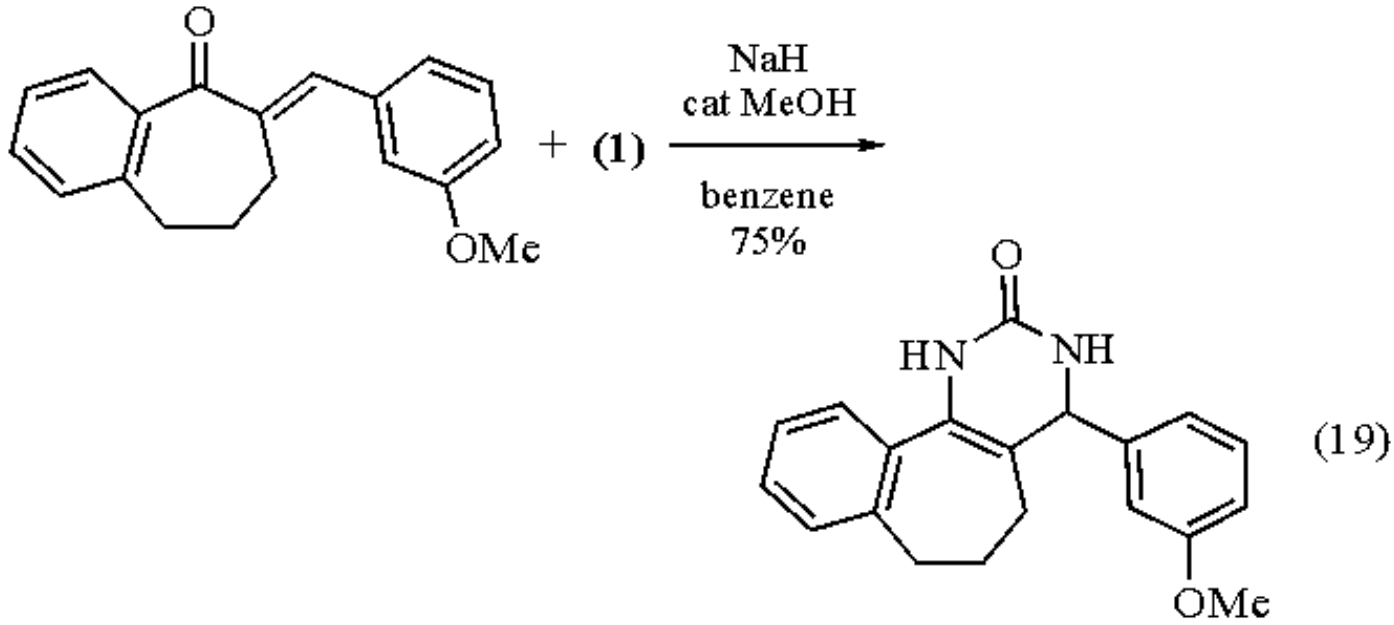

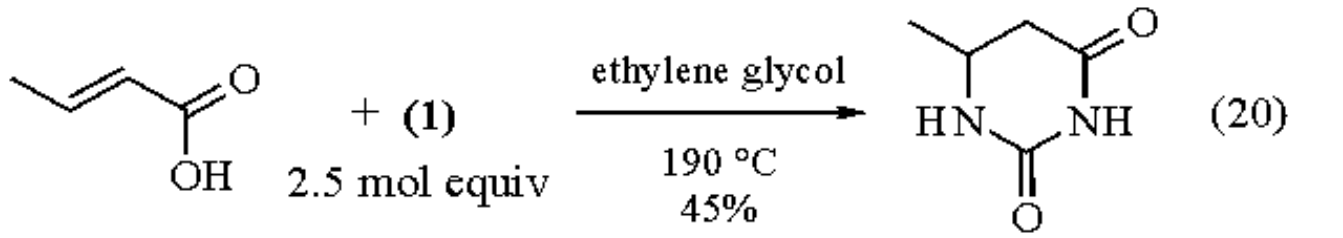

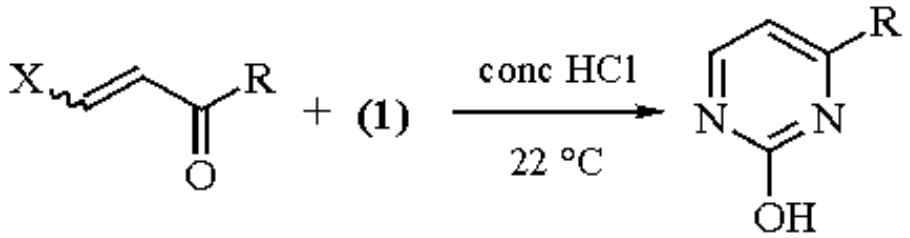

(21)

X = OEt, NMe_2, Cl, CCl_3, etc
R = H, alkyl, aryl

Carbonyl Cation Equivalent.

In the reaction with heteronucleophiles, urea acts as a carbonyl cation or dication equivalent, like phosgene and carbonates, though requiring more drastic conditions. *N*-Substituted or *N*,*N*′-disubstituted ureas can be prepared by transamination of the urea nitrogen atoms with primary amines (eqs 22 and 23).[32] Reaction of urea with *vic*-diamines (eq 24)[33] and 2-aminophenols (eq 25)[34] gives imidazolidin-2-ones and oxazolidin-2-ones, respectively. The reaction with aliphatic 2-amino alcohols, on the other hand, gives imidazolidin-2-ones via substitution by the hydroxyl group for a nitrogen of urea (eq 26).[35,36] The *cis*-1,5-dimethyl-4-phenylimidazolidin-2-ones, obtained by fusing (-)- or (+)-ephedrine hydrochloride and urea, are useful chiral auxiliaries for asymmetric syntheses.[36]

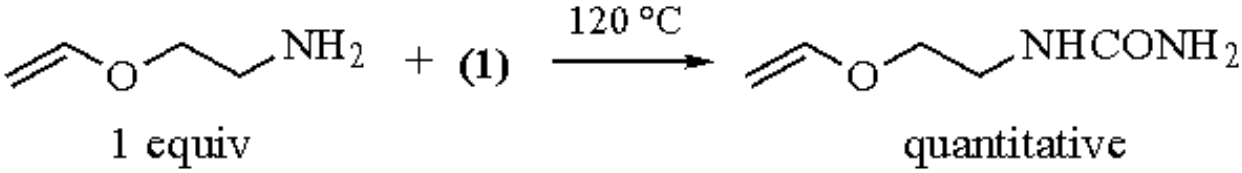

(22)

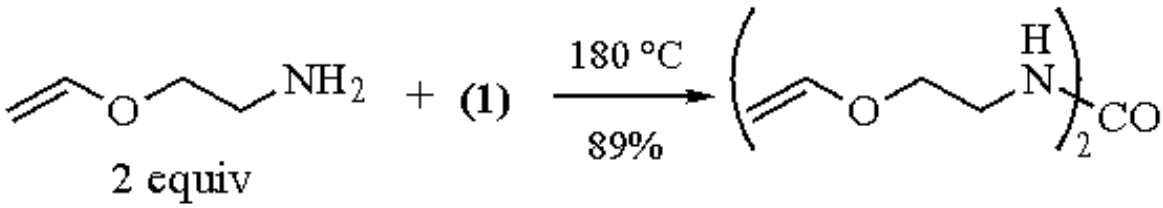

(23)

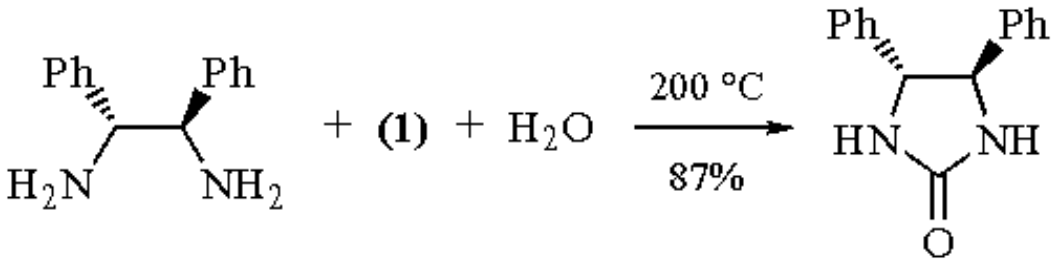

(24)

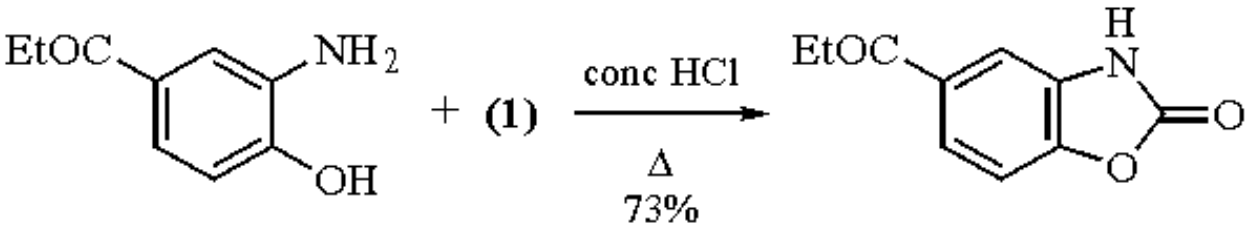

(25)

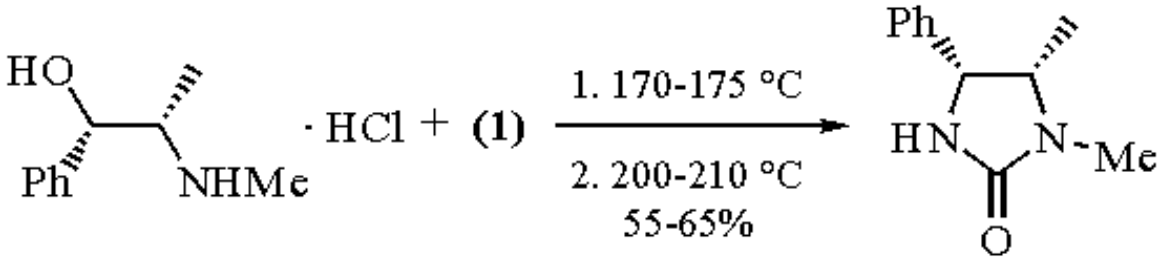

(26)

Catalyst.

The conversion of ***Tetracyanoethylene*** into dicyanoketene acetals is catalyzed by urea (eq 27).[37]

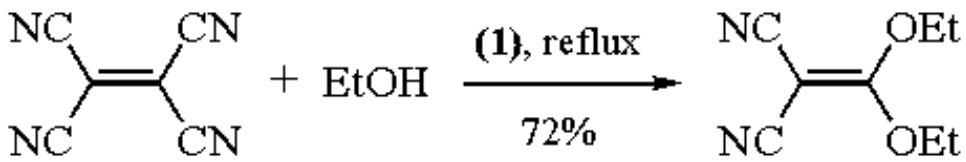

(27)

Inclusion Compounds (Differentiation of Linear Compounds from Branched Ones).[1,38]

Urea forms inclusion complexes, taking normal alkanes having six or more carbon atoms as guests.[39] In the complexes, hydrogen bonded urea molecules are oriented in a helical lattice, constructing a cylinder-shaped channel. The guest molecule is not bonded to the host but merely trapped in the cylinder. The diameter of the channel is usually about 5.25 Å. Aliphatic hydrocarbons with a single methyl branch, such as 3-methylhexadecane, that form the complex require a channel diameter of about 5.5 Å. This seems the upper limit of thickness. Not only hydrocarbons but many kinds of functionalized alkanes can be included if they are long and slender enough. Compounds that form inclusion complexes include 1-bromohexane, 1- and 2-octanol, 2-heptanone, 1-cyclopentylnonane, and 2-, 3-, and 4- methyltridecane. On the other hand, the following compounds do not form the complex: 3-ethyldodecane, 2-bromooctane, 1-cyclohexyloctane, and 2,4-dimethyldodecane.[40] Thus linear compounds, as in the former group, can be separated from a mixture with small or branched ones such as in the latter. *syn*-9,10-Dihydroxystearic acid has been separated from its *anti* counterpart.[41] The *syn*-diol (mp 95 °C), which is estimated to require a channel diameter of 5.4 Å, readily forms a urea complex. On the other hand, the *anti*-diol (mp 131 °C), which requires a channel diameter of 6 Å, does not form a complex.[38]

Related Reagents.

Hydrogen Peroxide-Urea.

---

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Urushibara Nickel[1]

Ni

[7440-02-0] · Ni · Urushibara Nickel · (MW 58.69)

(precipitated metal hydrogenation catalyst; useful principally in reduction of alkynes and alkenes to alkanes,[2] reduction of carbonyls to alcohols,[3] dehydrogenations,[1] and reductive desulfurizations[1])

Preparative Methods: Urushibara catalysts are prepared by acid (U-Ni-A), base (U-Ni-B), or neutral (U-Ni-N) digestion of precipitated nickel. Similar catalysts can be prepared using either iron or cobalt.[1]

Handling, Storage, and Precautions: Urushibara catalysts do not appear to degrade upon short exposure to air.[4] Protection from moisture is required for long-term storage.

Urushibara Catalysts.

The Urushibara catalysts are a family of precipitated metal catalysts that have been compared to the more common ***Raney Nickel*** catalysts. Although the two can catalyze many of the same reactions, Urushibara metals offer several advantages: they are nonpyrophoric, are easily generated, have a long shelf life, and can catalyze highly regio- and stereoselective reductions.

Catalytic Hydrogenation of Alkynes and Alkenes.

Alkenes and alkynes can be reduced to the corresponding alkanes using moderate to high pressures of H_2 and temperatures. In eq 1, the exocyclic alkene is hydrogenated selectively with the use of U-Ni-N. Longer hydrogenation times and use of other Urushibara catalysts result in complete reduction of this substrate. The use of Raney nickel in this example results in nonspecific reduction.[2] Aromatic rings can also be saturated; however, these reactions only proceed at high temperature or under pressure.[1]

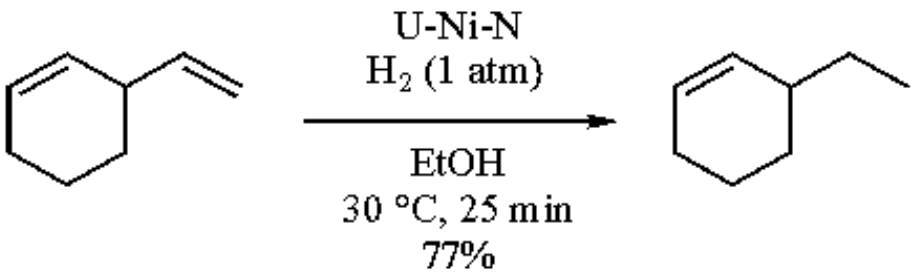

(1)

Catalytic Hydrogenation of Carbonyl Compounds.

Ketones and aldehydes can be reduced to their respective alcohols using Urushibara catalysts with hydrogen at atmospheric pressure and room temperature. Eq 2 demonstrates the regio- and stereoselectivity that can be obtained using Urushibara catalysts.[3] Use of Raney nickel results in an equimolar mixture of the two stereoisomers. Hydrogenolysis of the resulting C-O bond can occur with aryl-substituted compounds, giving the corresponding hydrocarbons.[1]

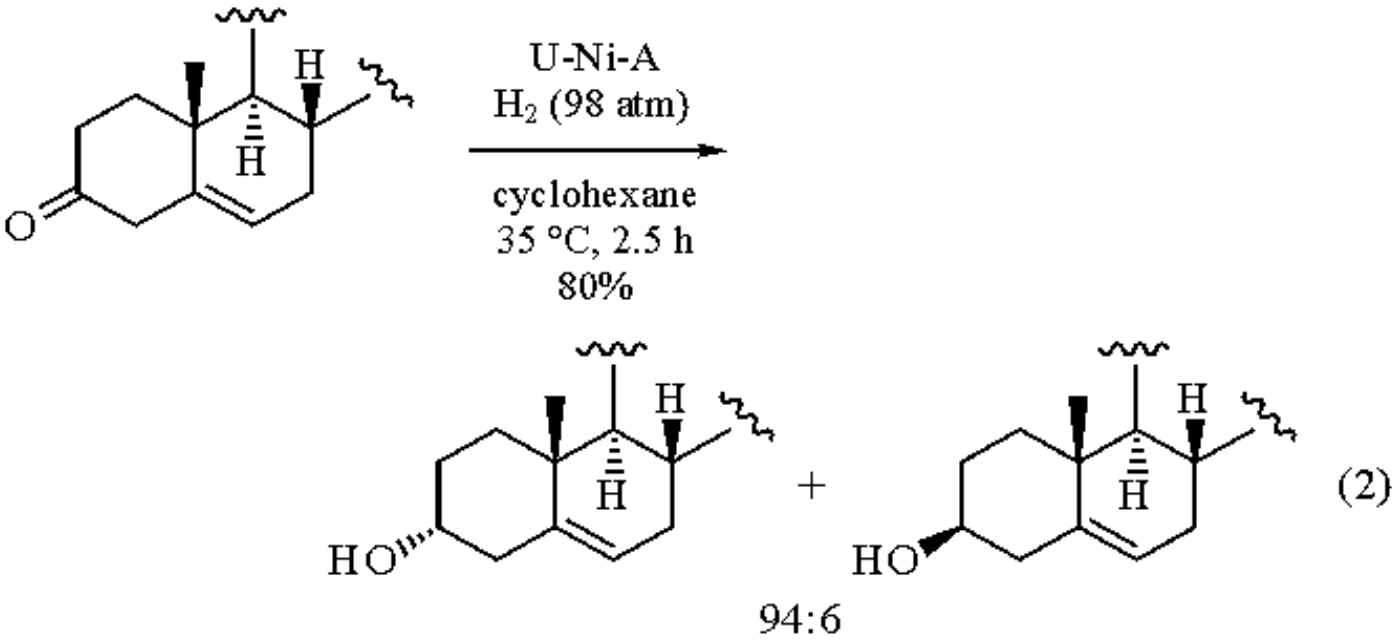

Dehydrogenations.

Urushibara catalysts have been used as dehydrogenation catalysts. Numerous examples exist with steroidal compounds using cyclohexanone as the hydrogen acceptor. In general, dehydrogenations using Urushibara catalysts are comparable to those of Raney nickel.[1]

Reductive Desulfurizations.

Urushibara catalysts, specifically U-Ni-A, have been used in desulfurizations of sulfur-containing compounds such as thiols, sulfides, disulfides, and thioacetals without competing reduction of alkenes. Reductive desulfurizations can be performed using Raney nickel with comparable yields.[1]

Miscellaneous Reductions.

Urushibara catalysts have been employed to reduce oximes, nitriles, hydroxylamines, nitro, and nitroso compounds. These reductions can be very dependent on reaction conditions. Yields of products are generally high and steric biasing can lead to high levels of stereocontrol.[1]

---

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Vanadium(IV) Chloride

VCl_4

[7632-51-1] · Cl_4V · Vanadium(IV) Chloride · (MW 192.74)

(oxidative coupling of phenols)

Alternate Names: vanadium tetrachloride; tetrachlorovanadium; vanadium chloride.

Solubility: sol with decomposition in cold water; sol abs alcohol, ether, chloroform, acetone.

Form Supplied in: commercially available as a bright red liquid.

Handling, Storage, and Precautions: moisture sensitive; spills may be neutralized with water. Toxic and corrosive; use efficient fume hood and wear plastic-covered gloves and apron (attacks neoprene).[1]

Oxidative Coupling of Phenols.

The oxidation of a number of simple phenols and aniline derivatives by vanadium tetrachloride affords dimeric products which are predominantly the result of intermolecular coupling at the *para* position.[2] For example, the addition of ca. 1 equiv of VCl_4 to phenol in dry carbon tetrachloride generates, after isolation, an 8:4:1 mixture of 4,4´-, 2,4´-, and 2,2´-biphenols, respectively (eq 1). Virtually no change in yield is observed when the ratio of phenol to VCl_4 is varied. While the related *p*- and *m*-cresol generate only polymeric products, *o*-cresol does dimerize to 3,3´-dimethyl-4-4´-dihydroxybiphenyl in 26% yield.[2]

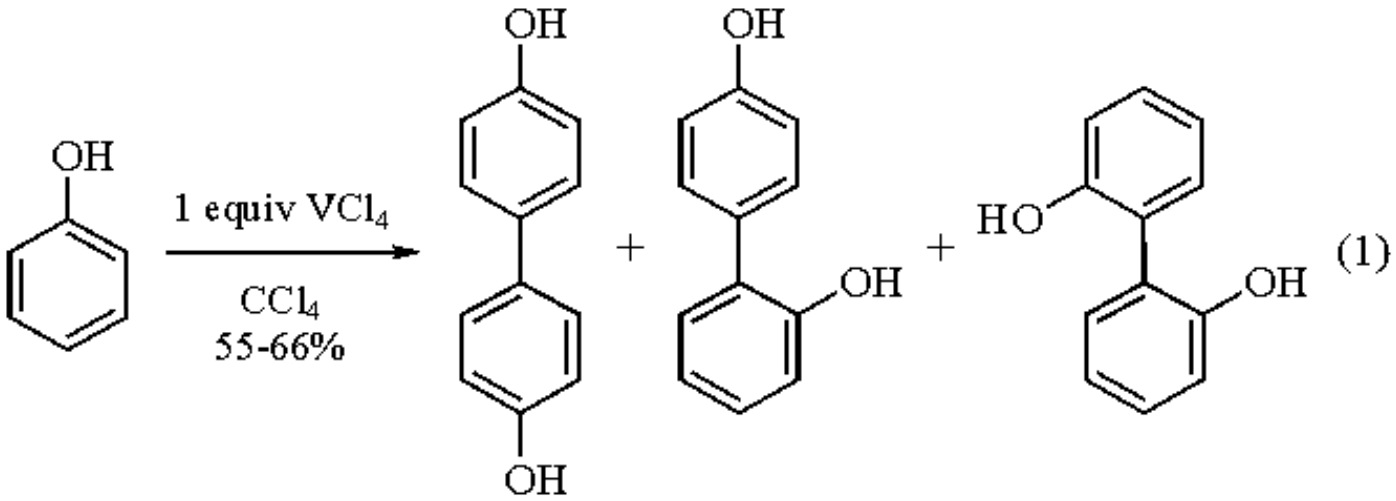

Hindered phenols have been coupled with moderate success. For example, dimerization of 3,5-dimethoxyphenol to the corresponding *para-para* adduct 2,2´,6,6´-tetramethoxy-4,4´-dihydroxybiphenyl and its *ortho-para* isomer has been effected in 10.8% overall yield as a 4:1 ratio of the respective regioisomers (eq 2).[1a] The *para-para* coupled dimer is the key intermediate in the total synthesis of the algal metabolite fucophlorethol A. Similarly, 6-*t*-butyl-3-methylphenol undergoes VCl_4-mediated coupling to a mixture of the *para-para* and the *ortho-para* products.[3] The overall yield and regioisomeric ratio are improved by reducing the reaction temperature from 20 °C to 0 °C (eq 3).

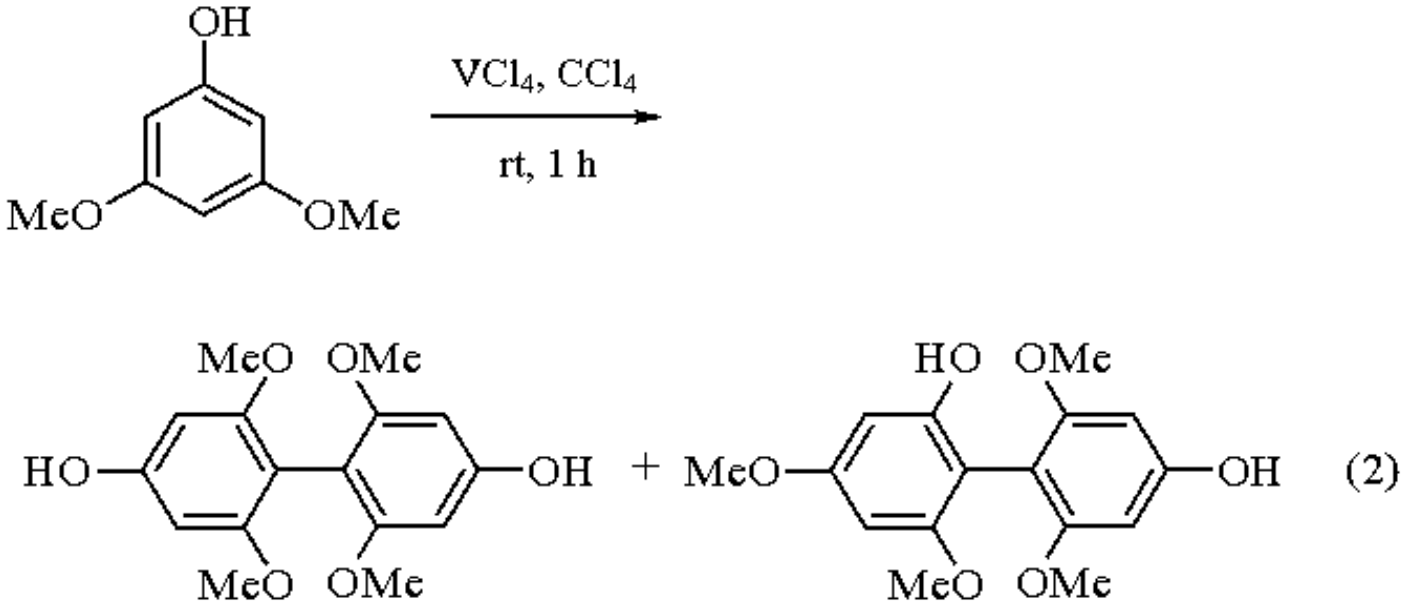

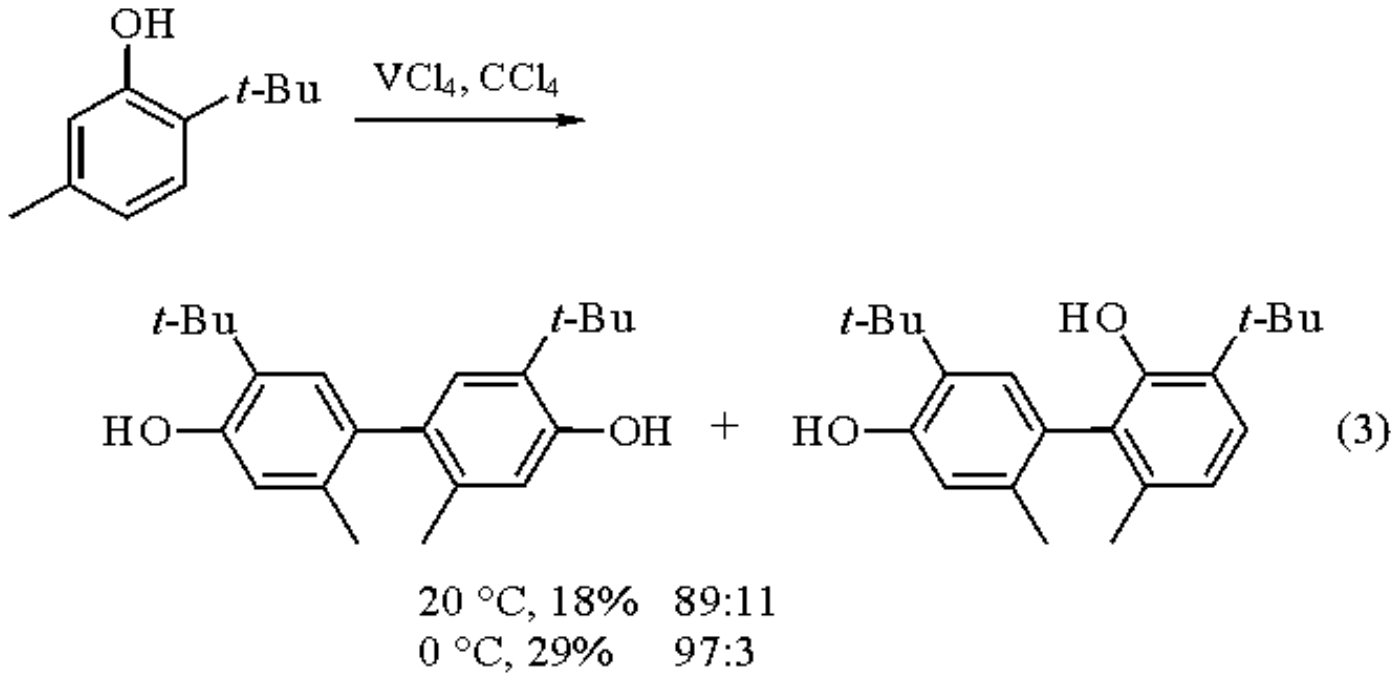

Both 1- and 2-naphthols react cleanly to generate 4,4´- and 2,2´-dihydroxybinaphthyl in 40% and 38% yields, respectively.[2] Benzene, toluene, anisole, phenyl acetate and ethyl benzoate are unreactive under standard reaction conditions. Although the attempted coupling of aniline generates little dimerized product, *N*,*N*-dimethylaniline yields *N*,*N*,*N*´,*N*´-tetramethylbenzidine in 52% yield.[2] Generally, VCl_4 complements the use of the less reactive ***Vanadyl Trichloride***

Other Vanadium(IV) Reagents.

When a diethyl ether/pentane solution of vanadium tetrachloride is treated sequentially with 3 equiv of lithium dialkylamide, 1 equiv of MeLi, and 0.8 equiv of an aromatic aldehyde, a one-pot reductive coupling reaction ensues, generating *N*,*N*,*N*´,*N*´-tetraalkyl-1,2-diarylethylenediamines[4] in yields ranging between 14% and 54% (eq 4). The active reagent in this reaction is the in situ generated tris(dialkylamino)methylvanadium(IV). Addition of *N*-methylaniline to a solution of VCl_4 affords an adduct which will effect the cyclization of nerol (**1**) to the corresponding terpinyl halide (**2**) (eq 5).[5] The related TiX_4 complex appears to be the preferred reagent in this type of reaction.

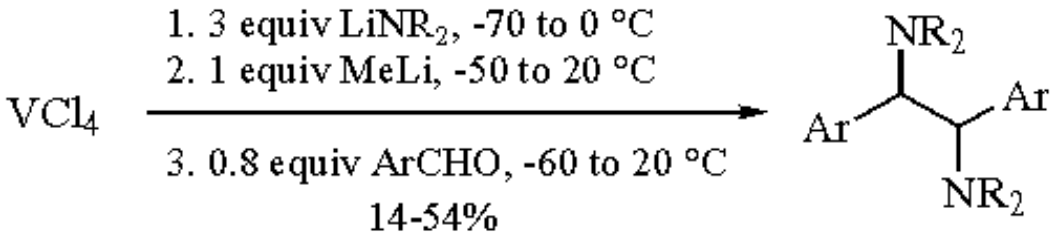

(4)

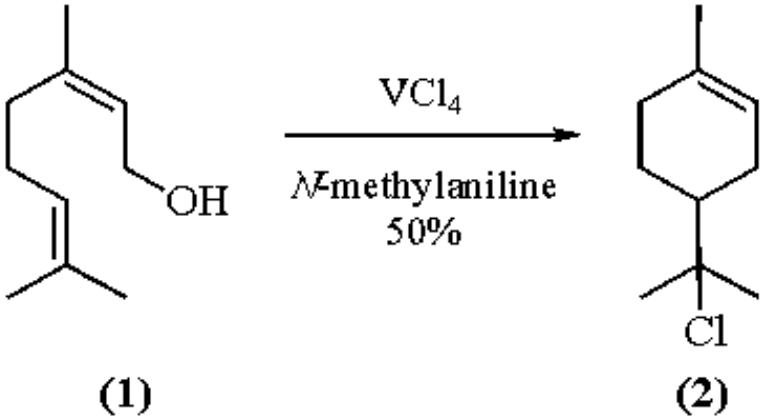

(5)

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Vanadium(II) Chloride

VCl_2

[10580-52-6] · Cl_2V · Vanadium(II) Chloride · (MW 121.84)

(nitro group to carbonyl conversion; hydrodehalogenation of α-halo ketones; reductions; reductive cleavage of oximes; reductive hydrolysis of 2,4-DNP derivatives)

Alternate Names: vanadium dichloride, vanadium chloride.

Physical Data: mp 910 °C (subl); *d* 3.23 g cm^{-3}.

Solubility: sol with decomposition in hot and cold water; sol alcohols, DMF, THF, ethers.

Form Supplied in: commercially available as a green deliquescent solid.

Vanadium(II) Chloride.

Many reagents based on chromium(II), titanium(II), and titanium(III) ions have found utility in organic synthesis because of their redox potentials (Table 1). Vanadium(II) chloride has found application in modern organic synthesis in part because its redox potential (+0.255 V) is greater than the Sn^{II}-Sn^{III} couple (-0.15 V) although lower than Cr^{II}-Cr^{III} (+0.41 V) or Ti^{II}-Ti^{III} (+0.37 V).[1] A variety of synthetic transformations have been documented.

Conversion of the Nitro Group to the Carbonyl Group.

When an aqueous solution of vanadium chloride is added to a primary or secondary aliphatic nitro compound dissolved in a mixture of water, hydrochloric acid, and DMF, a moderate to good yield (50-70% typically) of the corresponding ketone is isolated (eq 1).[2] The pH-dependent procedure involves initial reduction and subsequent hydrolysis of the resulting carbonyl imine. Several alternative methods are known[3] which will effect the same transformation.

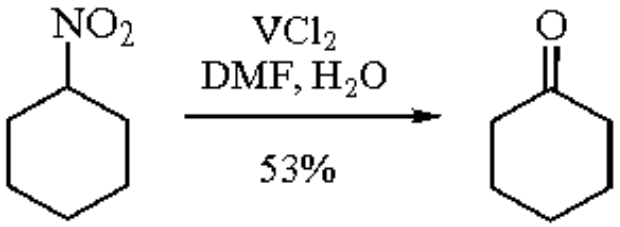

(1)

Hydrodehalogenation of α-Halo Ketones.

When an aqueous solution of vanadium chloride is added to α-halo ketones[1] in THF, a mildly exothermic reaction ensues which yields the halogen-free product after extractive workup (eq 2). Yields are generally quite high, ranging between 80 and 98%.

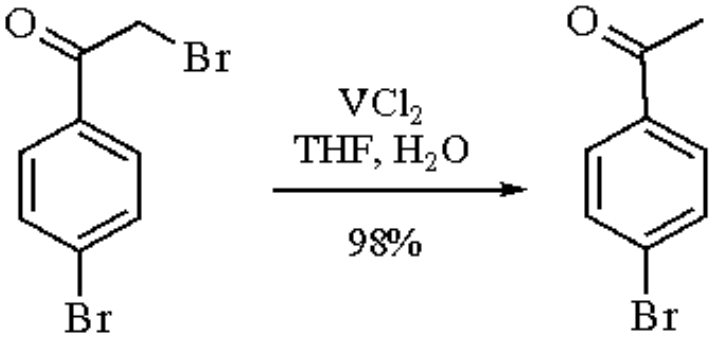

(2)

Reductions.

This reagent also reduces benzils to benzoins (THF-H_2O, 80-90% yield),[4] quinones to hydroquinones (90-95% yield),[4] and aryl azides to the corresponding amines and N_2 (70-95% yield) (eq 3).[5]

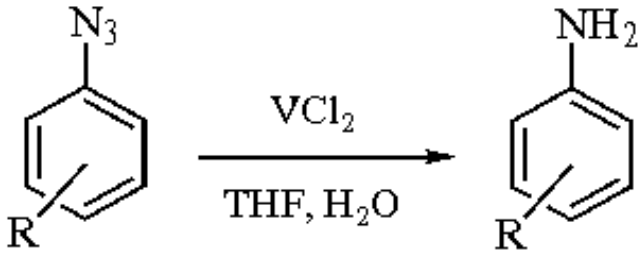

(3)

R = H, 2-Me, 4-Cl, 4-F, 2-CF_3

Reductive Cleavage of Oximes.

Aqueous solutions of VCl_2 have been employed in the mildly exothermic deoximation of oximes to the corresponding carbonyl compounds in 75-90% yield (eq 4).[6]

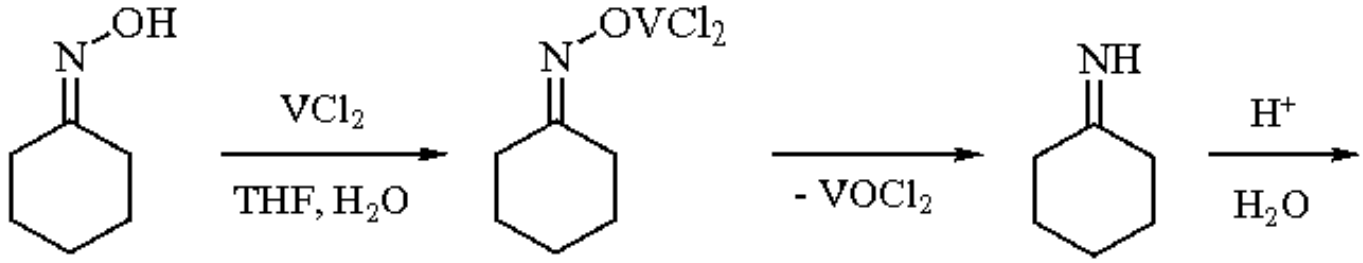

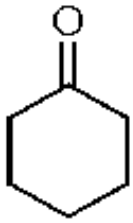

(4)

87%

Reductive Hydrolysis of 2,4-Dinitrophenylhydrazones.

The regeneration of carbonyl compounds from 2,4-dinitrophenylhydrazones is often problematic owing to the acid stability of the parent molecules. Vanadium chloride promotes the hydrolysis to the respective carbonyl moiety in 67-95% yield via initial reduction of the nitro group.[7]

Other Vanadium(II) Reagents.

Aryl and alkyl halides are reduced by a number of low-valent transition metals.[8] The complex[9] $VCl_2(py)_4$ reduces activated (e.g. Bn-Cl) but not unactivated halo compounds (e.g. vinyl halides). This reagent is selective towards the formation of coupled R-R products to the exclusion of R-H-type products. In contrast, Cr^{II} reduces[10] Bn-Cl to various ratios of bibenzyl and toluene (dependent on the reaction conditions). Bis(cyclopentadienyl)vanadium[11] (Cp_2V) is also effective in these reactions. In an extension of earlier work,[12] 2,2,2-trichloroacetanilide has been selectively reduced to 2,2-dichloroacetanilide using $VCl_2(py)_4$. Other complexes[13] of divalent vanadium having the general formula $V(amine)_4X_2$ are also known. The amine can be either aromatic (e.g. picoline) or aliphatic (e.g. ethylenediamine). The $V(amine)_4X_2$ chemistry remains largely unexplored.

Recently, a bimetallic V^{II} species, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$, prepared in situ from V^{III}, has been introduced[14] to achieve the stereoselective cross coupling of two different alkanals under mild conditions. The intermolecular pinacol cross-coupling reaction has been modified[15] to include chiral aldehydes which yield *syn*-diols in a 91:9 diastereoisomeric ratio (up to 84% ee). Reductive cyclization of δ,ε-enals has also been demonstrated[16] to proceed with excellent stereoselectivity (eq 5), in contrast to what is obtained with other reagents such as Sm^{II}.

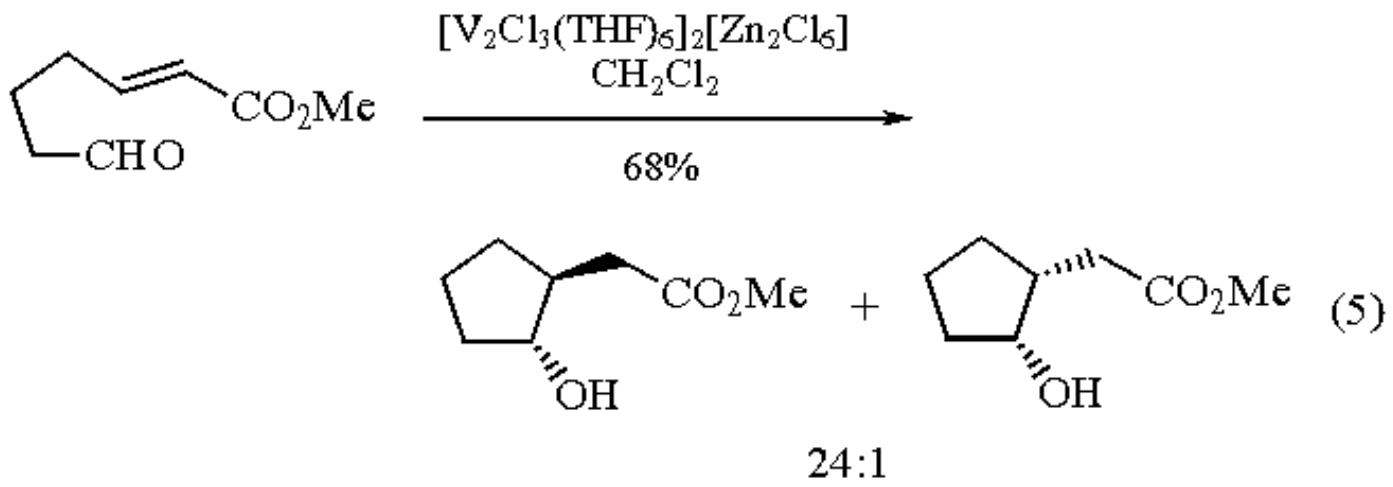

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Vanadyl Bis(acetylacetonate)[1]

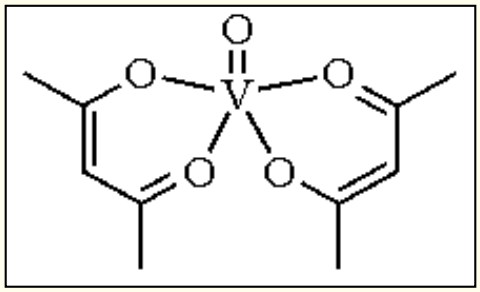

[3153-26-2] · $C_{10}H_{14}O_5V$ · Vanadyl Bis(acetylacetonate) · (MW 265.18)

(precatalyst for oxidation of several functional groups in combination with alkyl hydroperoxides or oxygen;[1] especially useful for the regio- and diastereoselective epoxidation of allylic alcohols,[2] the oxidation of tertiary amines to *N*-oxides,[3] and the oxidation of sulfides to sulfoxides[4] using an alkyl hydroperoxide as the oxidant)

Alternate Name: bis(acetylacetonato)oxovanadium(IV).

Physical Data: mp 256-259 °C; *d* 1.50 g cm^{-3}.

Solubility: insol H_2O; sol EtOH, CH_2Cl_2, $CHCl_3$, C_6H_6.

Form Supplied in: blue-green crystals; widely available.

Handling, Storage, and Precautions: generally used without further purification. Can be handled safely in the open. Should be stored in a cool, dry place in the absence of light. Contact with skin, eyes, and mucous membranes should be avoided. Toxic if swallowed. Generally performs best as an oxidation catalyst when used under anhydrous conditions. Oxidants contaminated with H_2O such as 70% *t*-butyl hydroperoxide (TBHP) are therefore usually dried prior to use with $VO(acac)_2$.

Precursor for Soluble Vanadium(V) Catalysts.

$VO(acac)_2$ is a precatalyst for the oxidation of several functional groups, usually using an alkyl hydroperoxide as the oxidant.[1b] Reaction of $VO(acac)_2$ with an alkyl hydroperoxide quickly oxidizes the vanadium from the +4 to the +5 oxidation state. The resulting organic soluble V^V complexes, whose structure can be represented as $VO(OR)_3$, are usually the actual catalysts in these reactions.[1] $VO(acac)_2$ is a commercially available, stable, crystalline, organic soluble solid and therefore a convenient source of vanadium for oxidation reactions. In contrast, organic soluble V^V compounds, suitable for these reactions, are not as widely available nor as easily handled and therefore not as convenient a source of vanadium as $VO(acac)_2$.[5]

Epoxidation of Allylic Alcohols.

Soluble V^V compounds are the preferred catalysts for nonenantioselective epoxidation of allylic alcohols to epoxy alcohols using alkyl hydroperoxides, especially ***t-Butyl Hydroperoxide***, as oxidants.[2,6] V^V compounds with alkyl hydroperoxides are also capable of epoxidation of nonfunctionalized alkenes[7] to epoxides but at rates ca. 100 times less than for the corresponding allylic alcohols.[6a] This rate differential allows the regioselective monoepoxidation of substrates like geraniol (eq 1).

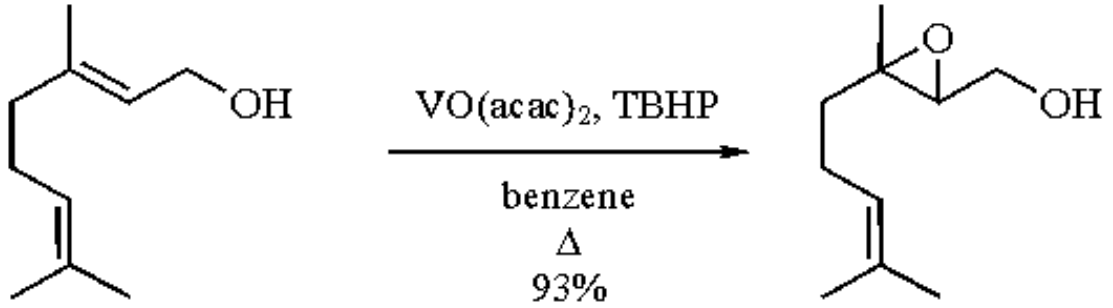

(1)

Mo^{VI}/TBHP and peracids efficiently epoxidize allylic alcohols as well but, because they also rapidly epoxidize nonfunctionalized alkenes, they tend not to be as regioselective as V^{V}/TBHP.[1] Other d^0 transition metal catalysts, such as W^{VI} and Ti^{IV}, epoxidize allylic alcohols slower and less efficiently than V^{V} and therefore are not as useful for this type of epoxidation reaction.[7] Diastereoselective epoxidation is often observed in V^{V}-catalyzed epoxidations of chiral allylic alcohols, especially cyclic allylic alcohols.[6a,8,9] Diastereoselective epoxidation of homoallylic and bishomoallylic alcohols have also been reported.[6a,10] V^{V}/TBHP often complements the diastereoselectivity of peracids and Mo^{VI}/TBHP observed for the epoxidation of secondary allylic alcohols.[6a,8] For example, epoxidation of 2-cyclooctenol gives either the corresponding *cis*- or *trans*-epoxy alcohol with high diastereoselectivity, depending on whether $VO(acac)_2$/TBHP or ***m-Chloroperbenzoic Acid*** is used (eq 2).[11]

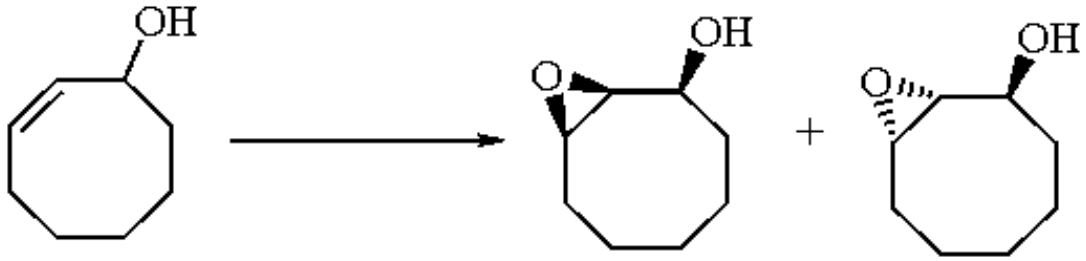

(2)

	% *cis*	% *cis*
$VO(acac)_2$, TBHP	97	3
m-CPBA	0.2	99.8
$MoO_2(acac)_2$	42	58

Hydroxyepoxidation of Alkenes.

$VO(acac)_2$ catalyzes the transformation of allylic hydroperoxides to epoxy alcohols.[12] This process presumably involves intermolecular transfer of oxygen from the hydroperoxide portion of an allylic hydroperoxide to the alkene portion of either a second allylic hydroperoxide or an allylic alcohol derived from hydroperoxide reduction (eq 3).[13]

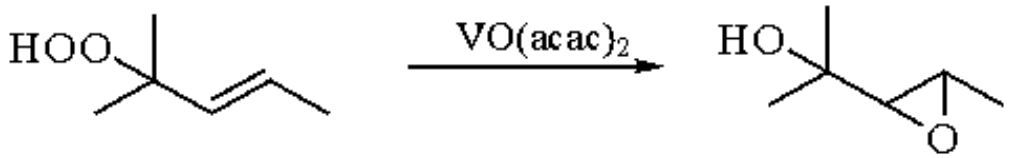

(3)

$VO(acac)_2$[14] and other forms of vanadium[15] also catalyze the transformation of alkenes to epoxy alcohols using molecular oxygen as the oxidant. This process involves initial oxidation of the alkene to an allylic hydroperoxide either by radical or photolytic processes followed by intermolecular epoxidation to give primarily the epoxy alcohol and usually several byproducts. A convenient photolytic process producing singlet oxygen in the presence of the alkene and a catalytic amount of $VO(acac)_2$ has been developed to promote this transformation in good yield and high diastereoselectivity (eq 4).[14] An obvious requirement of this reaction is that the starting alkene must readily undergo photooxygenation to give the intermediate allylic hydroperoxide. ***Titanium Tetraisopropoxide*** and molybdenyl bis(acetylacetonate) also act as catalysts in this reaction, sometimes with better yields and/or selectivity.[14]

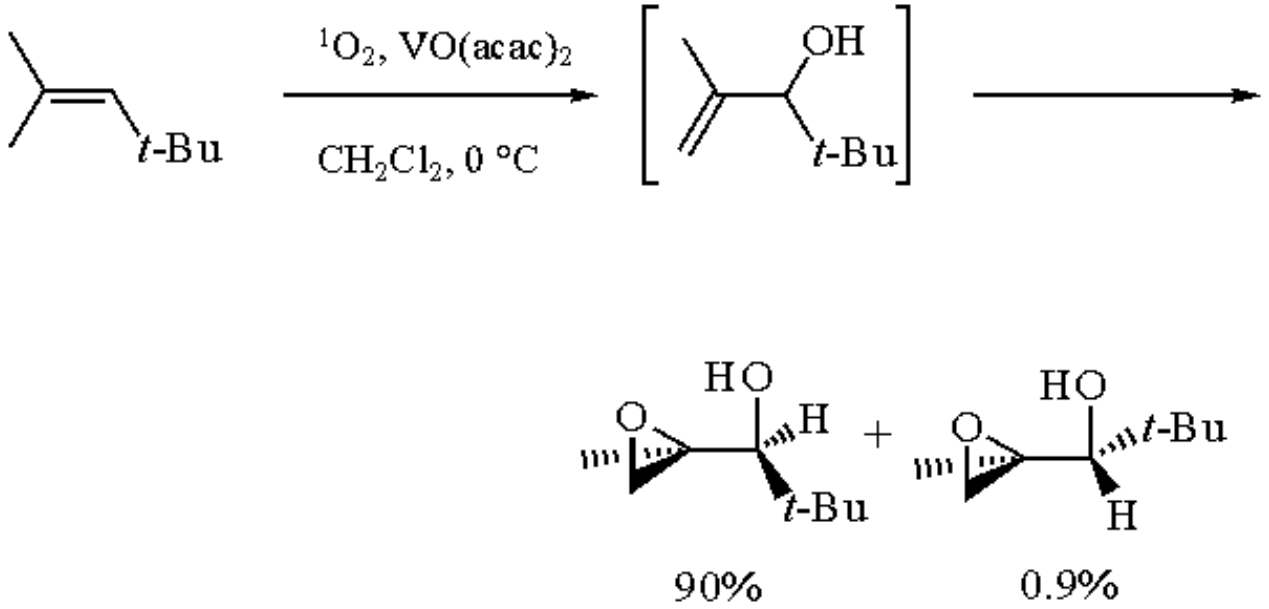

(4)

Oxidation of Amines.

V^V/TBHP efficiently oxidizes tertiary amines to *N*-oxides (eq 5).[16] The reaction is carried out under anhydrous conditions and therefore allows the preparation of anhydrous amine oxides. V^V/TBHP oxidizes aniline to nitrobenzene (eq 6).[17]

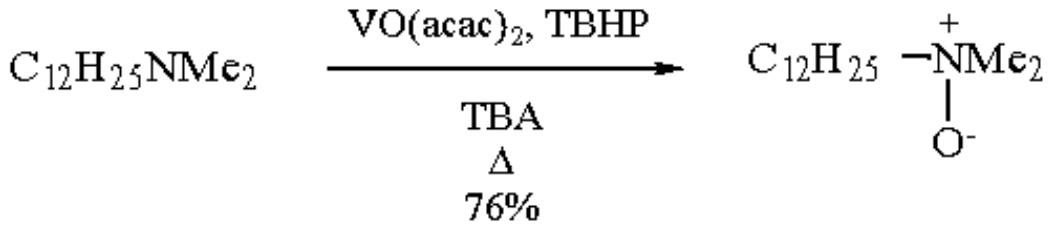

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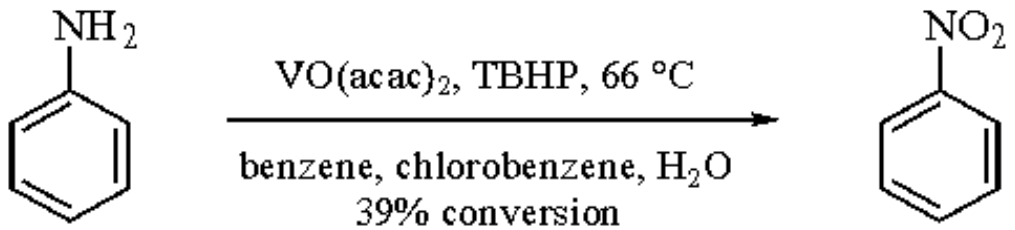

(6)

Oxidation of Sulfides to Sulfoxides.

Similar to the oxidation of tertiary amines to *N*-oxides, V^V/TBHP oxidizes sulfides to sulfoxides in high yield (eq 7).[4,18] The reaction is usually carried out at room temperature in an alcoholic solvent.

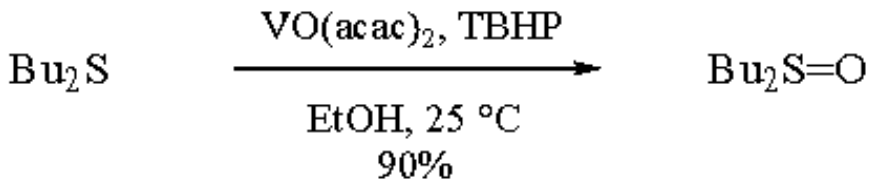

(7)

Other Oxidation Reactions.

$VO(acac)_2$ rapidly oxidizes 3,5-di-*t*-butylpyrocatechol at room temperature to the corresponding muconic acid anhydride, 2-pyrone, and *o*-quinone using oxygen as the oxidant (eq 8).[19] This method is more selective for the anhydride than oxygenation with ***Dichlorotris(triphenylphosphine)ruthenium(II)***. V^V/TBHP has also been used in the catalytic oxidation of hydrocarbons.[20] These reactions probably occur by radical mechanisms and are usually not highly selective.

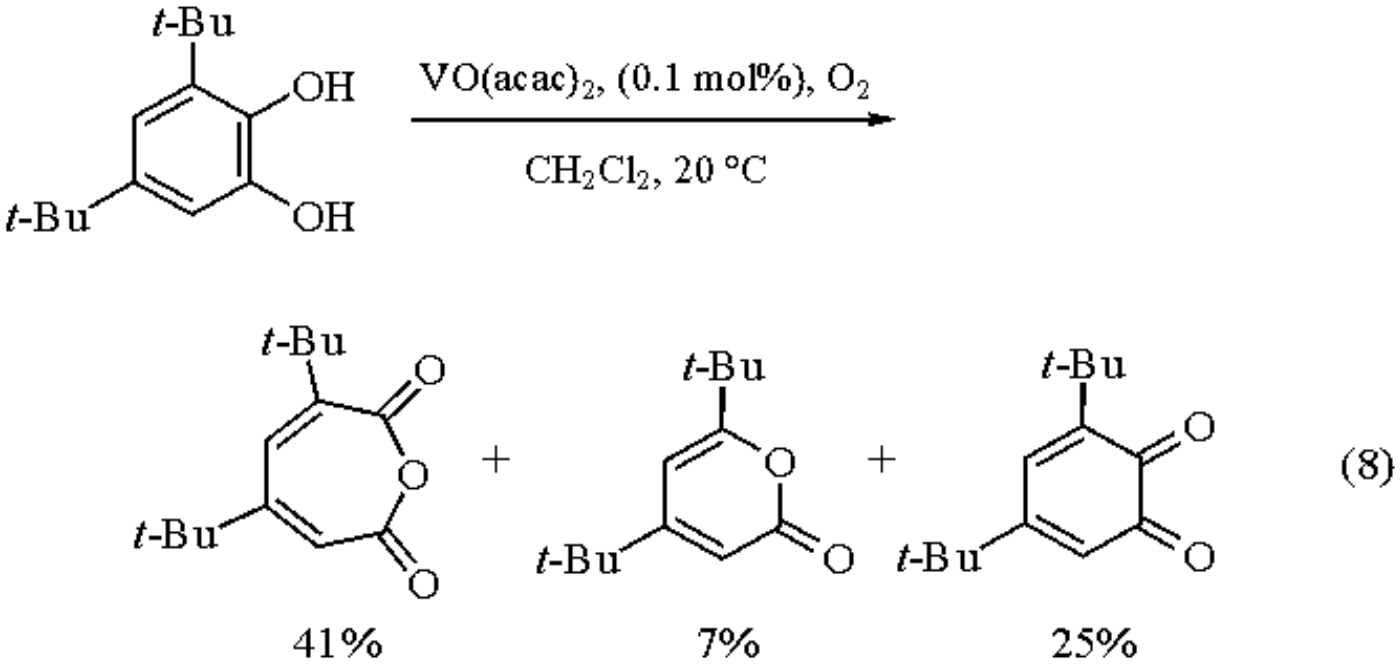

Related Reagents.

Vanadyl Bis(acetylacetonate)-Azobisisobutyronitrile.

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Bryant E. Rossiter&dead;

Vanadyl Bis(acetylacetonate)-Azobisisobutyronitrile

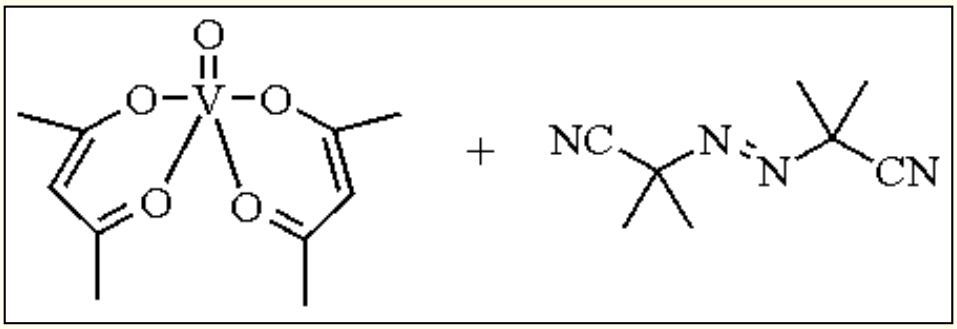

($VO(acac)_2$)

[3153-26-2] · $C_{10}H_{14}O_5V$ · Vanadyl Bis(acetylacetonate)-Azobisisobutyronitrile · (MW 265.18) (AIBN)

[78-67-1] · $C_8H_{12}N_4$ · Vanadyl Bis(acetylacetonate)-Azobisisobutyronitrile · (MW 164.24)

(catalyst for oxygen-promoted allylic oxidation coupled with hydroxyl-directed epoxidation of C=C double bonds[1])

Physical Data: AIBN: solid, mp 100 °C (dec). $VO(acac)_2$: solid, mp 250 °C (dec).

Solubility: see ***Azobisisobutyronitrile*** and ***Vanadyl Bis(acetylacetonate)***. The combination may be used in 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, acetonitrile, benzene, 1,4-dioxane, or *n*-hexane.

Form Supplied in: AIBN is sold as a white solid; $VO(acac)_2$ is sold as a green powder.

Handling, Storage, and Precautions: see the individual entries for AIBN and $VO(acac)_2$. AIBN causes convulsions.

Allylic Oxidation/Epoxidation Reactions.

The reagent combination is an effective catalyst for the oxidation of cyclic alkenes, except cyclooctene, to epoxy alcohols using molecular ***Oxygen*** as the oxidant. The conversion proceeds by way of allylic oxidation to give an allylic hydroperoxide, which is reduced by the metal to give an allylic alcohol. Hydroxyl-directed epoxidation of the latter intermediate occurs in situ to give the epoxy alcohol. Cyclohexene is converted to (**1**), together with (**2**), (**3**), and (**4**), the relative amounts of which depend on reaction conditions, primarily solvent (eq 1). Best results are obtained by using cyclohexene (20 mmol), $VO(acac)_2$ (0.01 mmol), AIBN (0.1 mmol), O_2 (1 atm), and 1,1,2-trichloroethane (2.0 mL) at 60 ± 1 °C, which gives 30% yield of a mixture of (**1**) (65%), (**2**) (17%), (**3**) (5%), and (**4**) (13%). While similar conversions can be effected by O_2 in the presence of $CpV(CO)_4$ or V_2O_5, and by $VO(acac)_2$ in the absence of AIBN, the yields and product distribution differ from those obtained by using the title reagent.

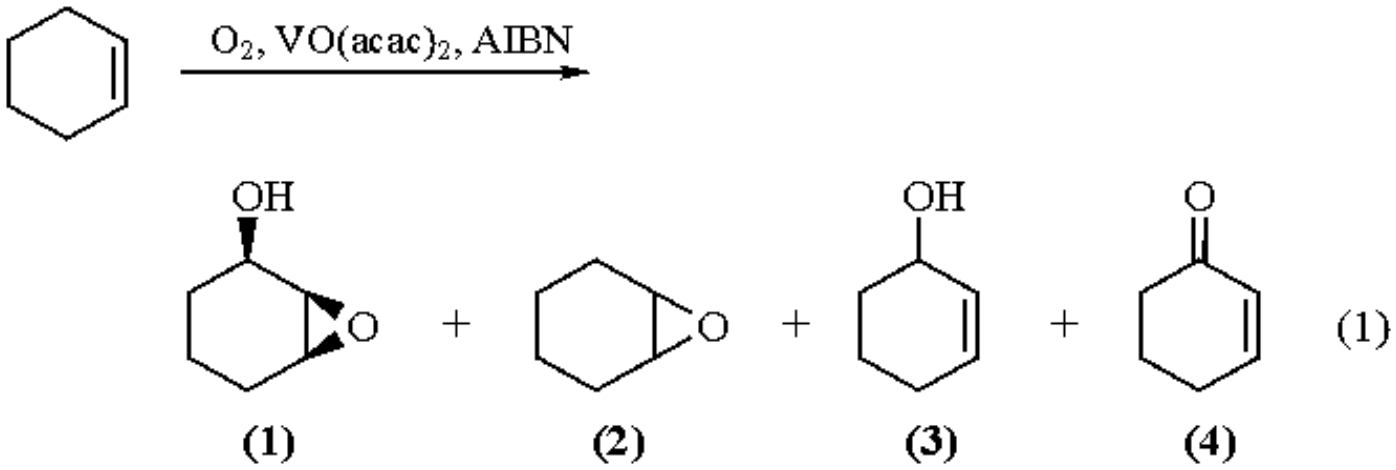

1,4-Cyclooctadiene undergoes a transannular epoxidation reaction under the above reaction conditions to give a mixture of (**5**) (43%) and four other products (57% combined yield; the published results are not clear), from which crystalline (**5**) can be obtained in 18% yield by chromatography on Florisil, followed by sublimation of the residue (eq 2).

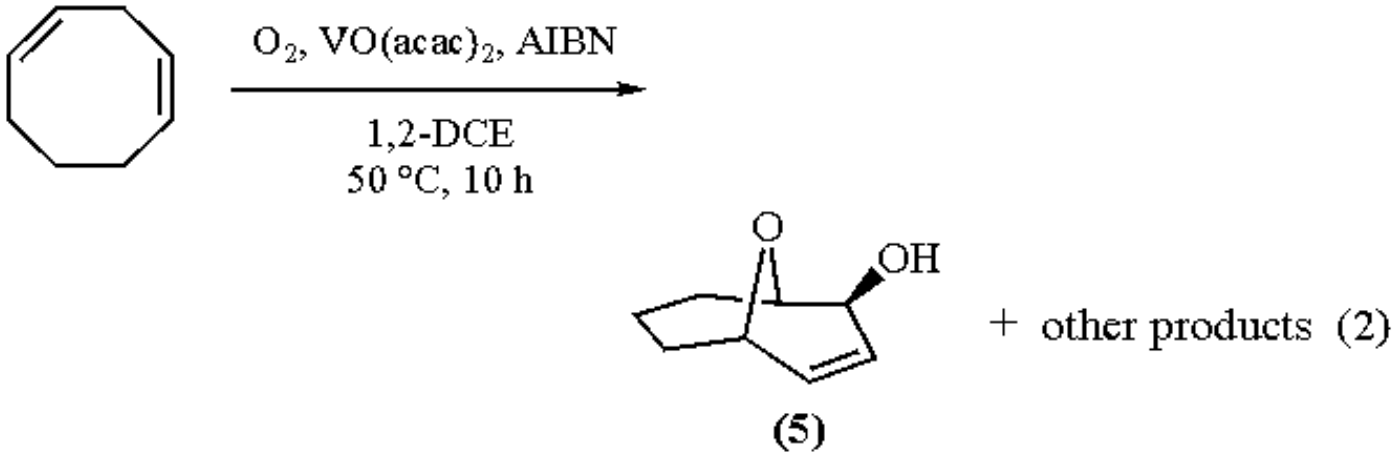

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Vanadyl Trichloride

$VOCl_3$

[7727-18-6] · Cl_3OV · Vanadyl Trichloride · (MW 173.29)

(oxidative decarboxylation; phenolic coupling)

Alternate Names: trichlorooxovanadium; vanadium oxytrichloride.

Physical Data: mp 77 °C; bp 126-127 °C; *d* 1.840 g cm^{-3}.

Solubility: sol ether, dichloromethane, benzene.

Form Supplied in: commercially available as a yellow liquid from a number of vendors.

Preparative Methods: by the action of dry Cl_2 on vanadium(III) oxide or vanadium(V) oxide.[1]

Handling, Storage, and Precautions: decomposes in the presence of moisture into vanadic acid and HCl.

Oxidative Decarboxylation-Deoxygenation.

Stoichiometric amounts of $VOCl_3$ can be utilized in the oxidative decarboxylation-deoxygenation of 3-hydroxycarboxylic acids to tri- and tetrasubstituted alkenes,[2] enabling direct conversion from the products of classical aldol condensations (eq 1). In some cases, byproducts resulting from dehydration, C-C bond cleavage, double-bond migration, and (*E*/*Z*) bond isomerization have been noted, although the latter three problems can be suppressed by the addition of ***1,8-Bis(dimethylamino)naphthalene*** (Proton Sponge). Trichloro(arylimino)vanadium(V), prepared from $VOCl_3$ and the appropriate aryl isocyanate,[2,3] can generate higher yields of alkene, free of byproducts, when used as an alternative reagent.

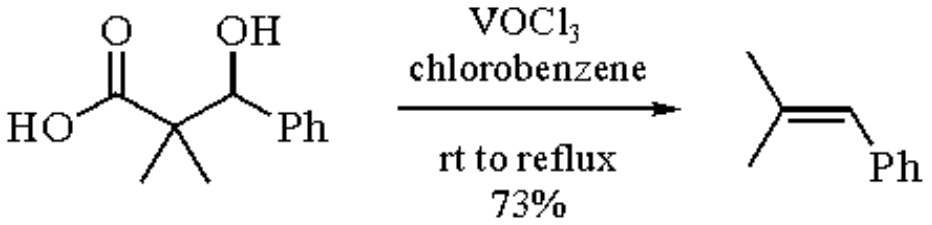

(1)

Diphenolic Oxidative Coupling.

There are a number of examples of diphenolic oxidative coupling reactions using $VOCl_3$ as the oxidizing agent. Intermolecular coupling of 1- and 2-naphthol generates 4,4´-dihydroxybinaphthyl (eq 2) and 2,2´-dihydroxybinaphthyl in 56% and 65% yield, respectively.[4] Evidence indicates that intermediate vanadium phenoxides are formed in the process. Under identical conditions, *m*-cresol yields a mixture of polymeric products. The more reactive ***Vanadium(IV) Chloride*** can be used to effect the same transformations and to some degree it complements the use of $VOCl_3$.[4]

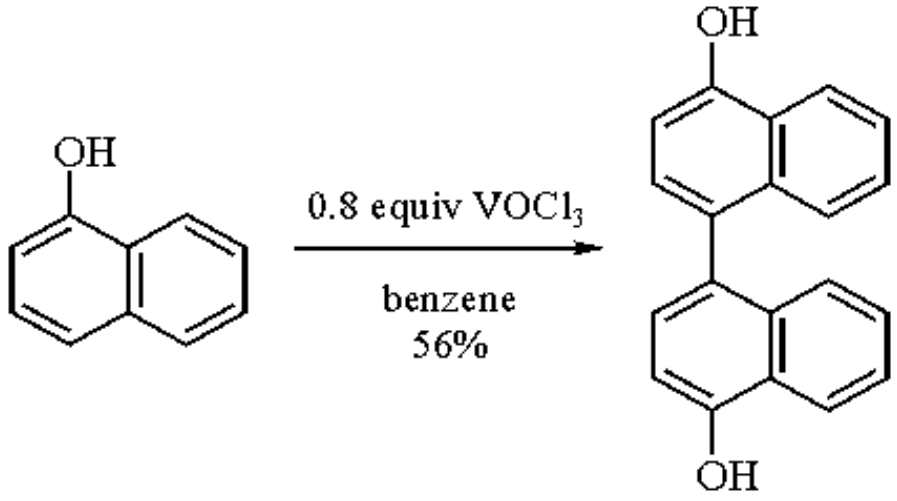

(2)

When treated with a stoichiometric amount of trichlorooxovanadium, Cbz-protected tyrosine affords the dityrosine derivative in 20% yield (eq 3).[5] A similar reaction with vanadium trifluoride doubles the yield of the desired *ortho-ortho* coupled product and is preferred due to superior functional group compatibility.

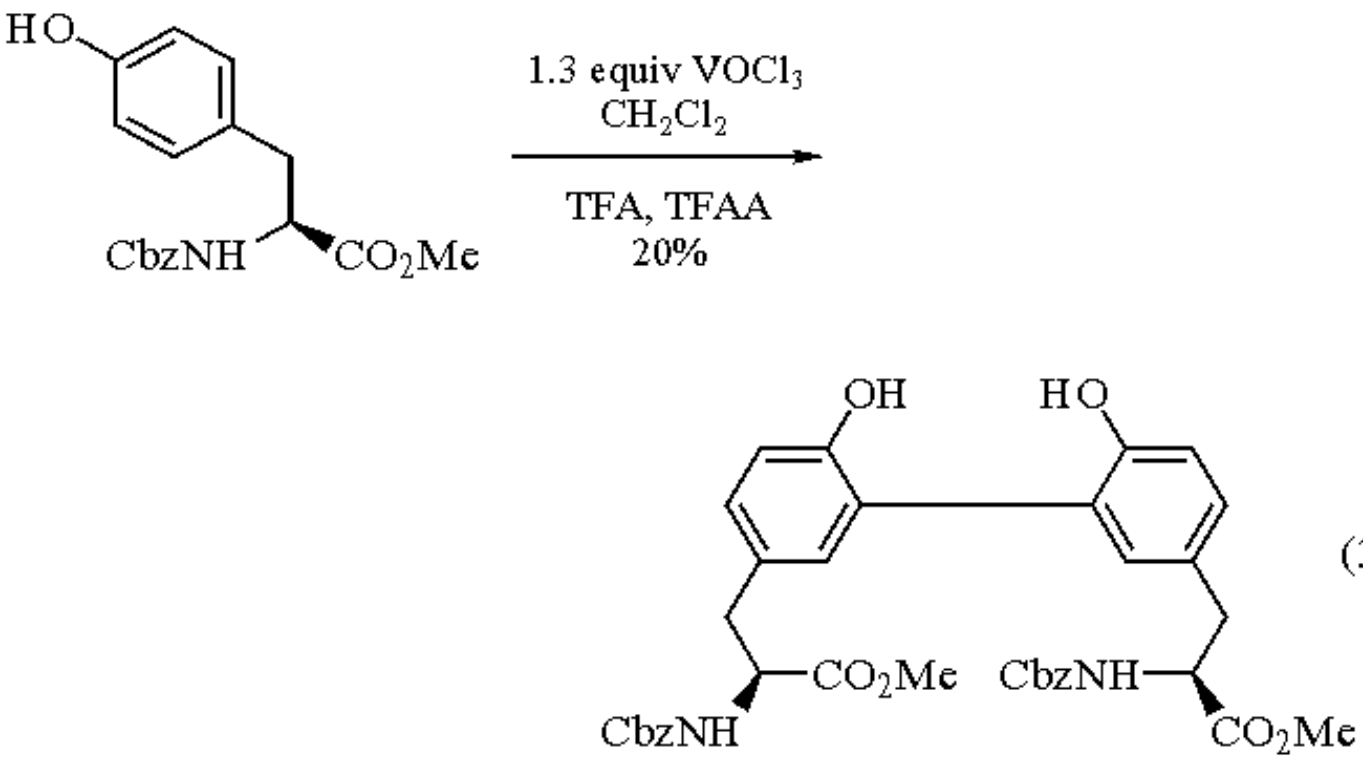

(3)

Intramolecular oxidative coupling of phenols, a key step in the biosynthesis of alkaloids and other natural products, can be effected nonenzymatically via this reagent. Although yields are high in simple systems, results are more variable in systems of increased complexity. For example, addition of an ethereal solution of 1,3-bis(hydroxyphenyl)propane to 2.5 equiv of vanadyl trichloride in ether affords the phenolic dienone in 76% yield (eq 4).[6] Initial reaction at -78 °C generates the bis(dichlorovanadate) ester which ultimately undergoes oxidative coupling at higher temperature. One-electron oxidants such as ***Potassium Ferricyanide***, ***Iron(III) Chloride***, ***Manganese Dioxide***, and ***Silver(I) Oxide*** afford low yields of coupled product due to competing polymerization reactions.[7] In a related but more complex example, vanadyl trichloride is utilized in a key coupling step (eq 5) in the total synthesis of (±)-maritidine.[8] Here the bis(hydroxyphenyl) compound is converted to the *para-para* coupled dienone in 24% isolated yield.

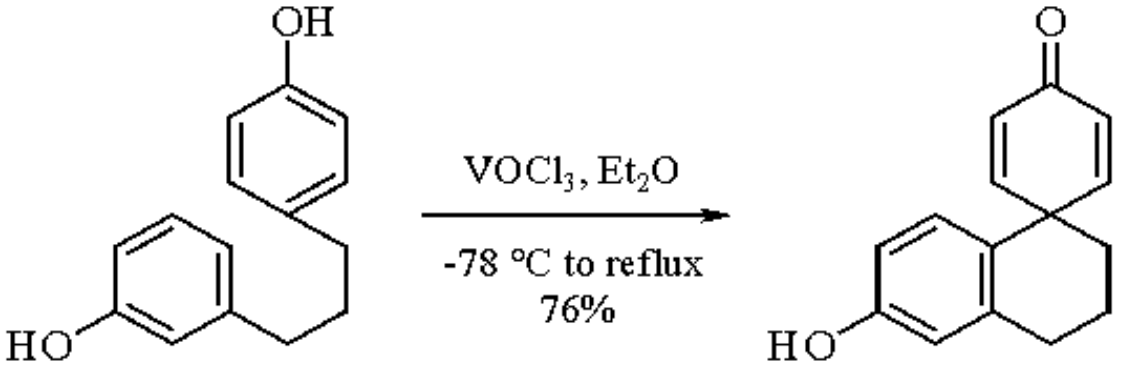

(4)

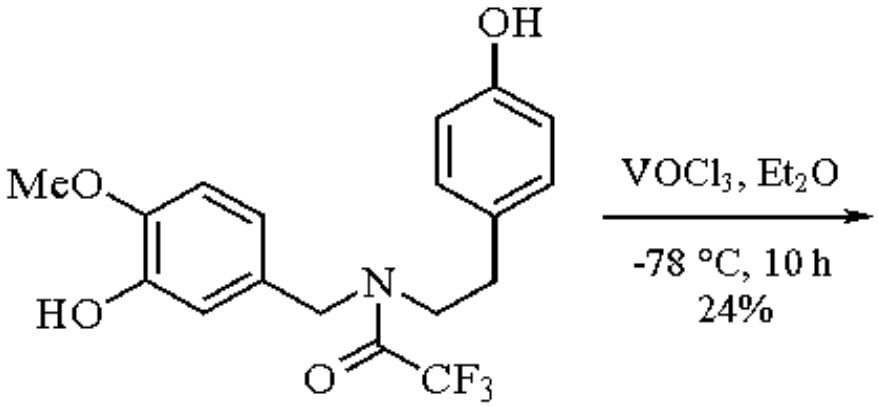

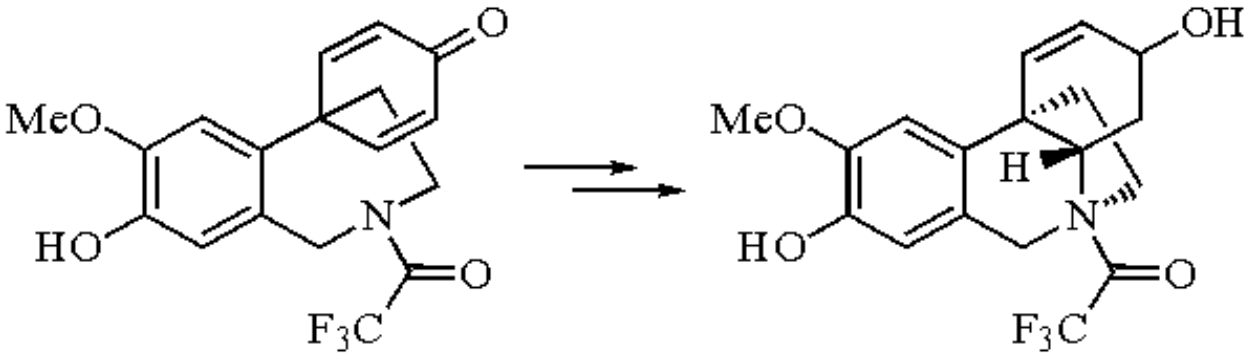

(5)

This reagent has been utilized in the intramolecular oxidative coupling of a number of benzyltetrahydroisoquinolines,[9] as exemplified by the conversion of *cis*-3,*N*-bis(methoxycarbonyl)-*N*-norreticuline to the corresponding isoboldine analog (eq 6).[10] Since four regioisomers are possible, (*para-para*/*para-ortho* morphinanes and *ortho-para*/*ortho-ortho* aporphines), directing the regiochemical outcome can be difficult. It appears that $VOCl_3$ often generates predominantly aporphine products. The effects of steric interactions have been investigated.[11] ***(Diacetoxyiodo)benzene*** and ***Thallium(III) Trifluoroacetate*** have also been utilized to effect the same transformation with less success with regard to yields and regioisomeric ratios.[9a,10]

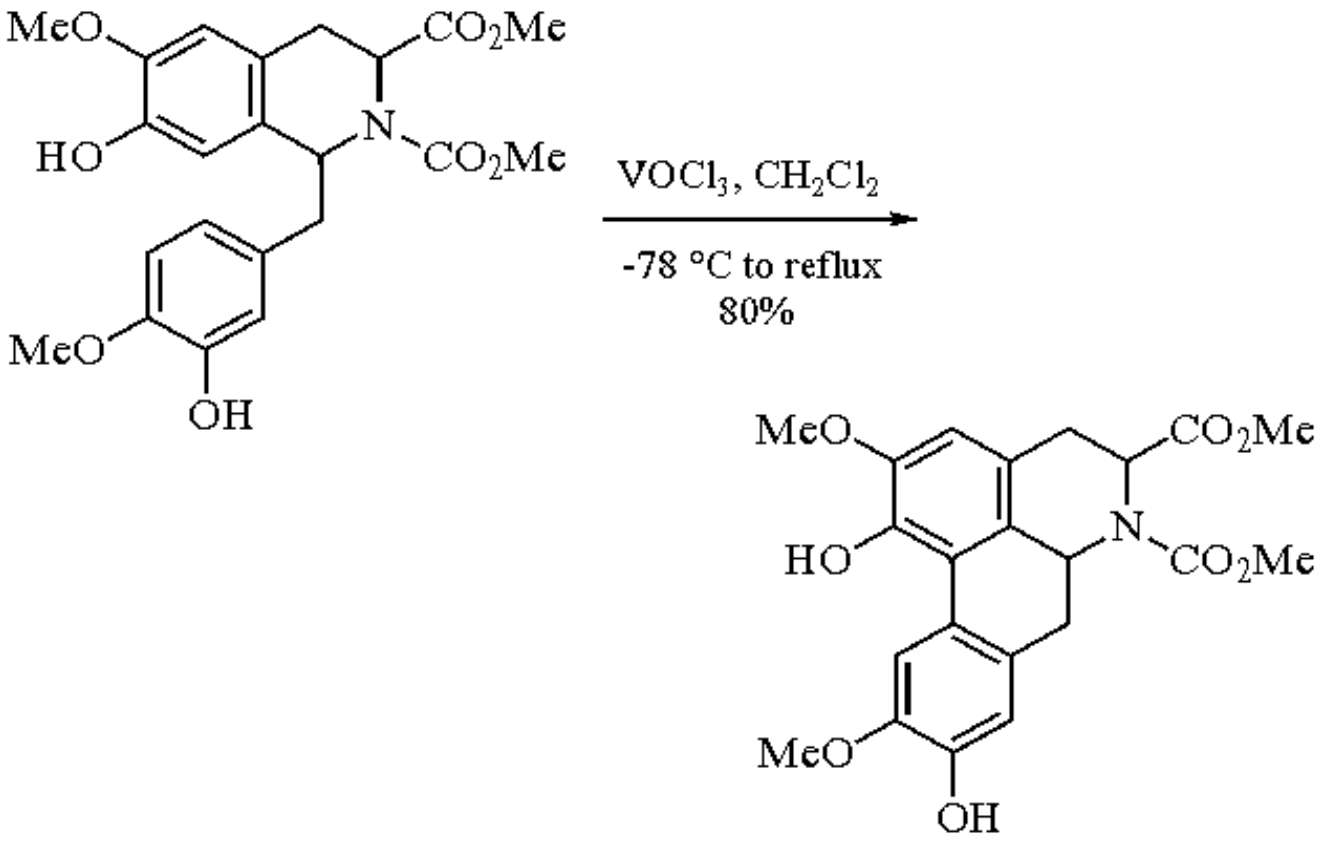

(6)

Although ***Vanadyl Trifluoride*** is often the reagent of choice,[12] intramolecular coupling of monophenols has been effected in near quantitative yield with $VOCl_3$ in dichloromethane at -78 °C (eq 7).[7,13] On the other hand, oxidative coupling of the nonphenolic substrate (R = Me) leads primarily to the dienone (via alkyl-oxygen cleavage) and a minor component (18%) resulting from coupling and subsequent rearrangement. It has been suggested that, in either case, two successive one-electron oxidations occur with coupling at the cation radical stage.[13] Trialkylamines completely inhibit this reaction. Alternative reagents such as silver bis(trifluoroacetate), thallium tris(trifluoroacetate), and vanadium oxytrifluoride[14] also induce nonphenolic coupling.

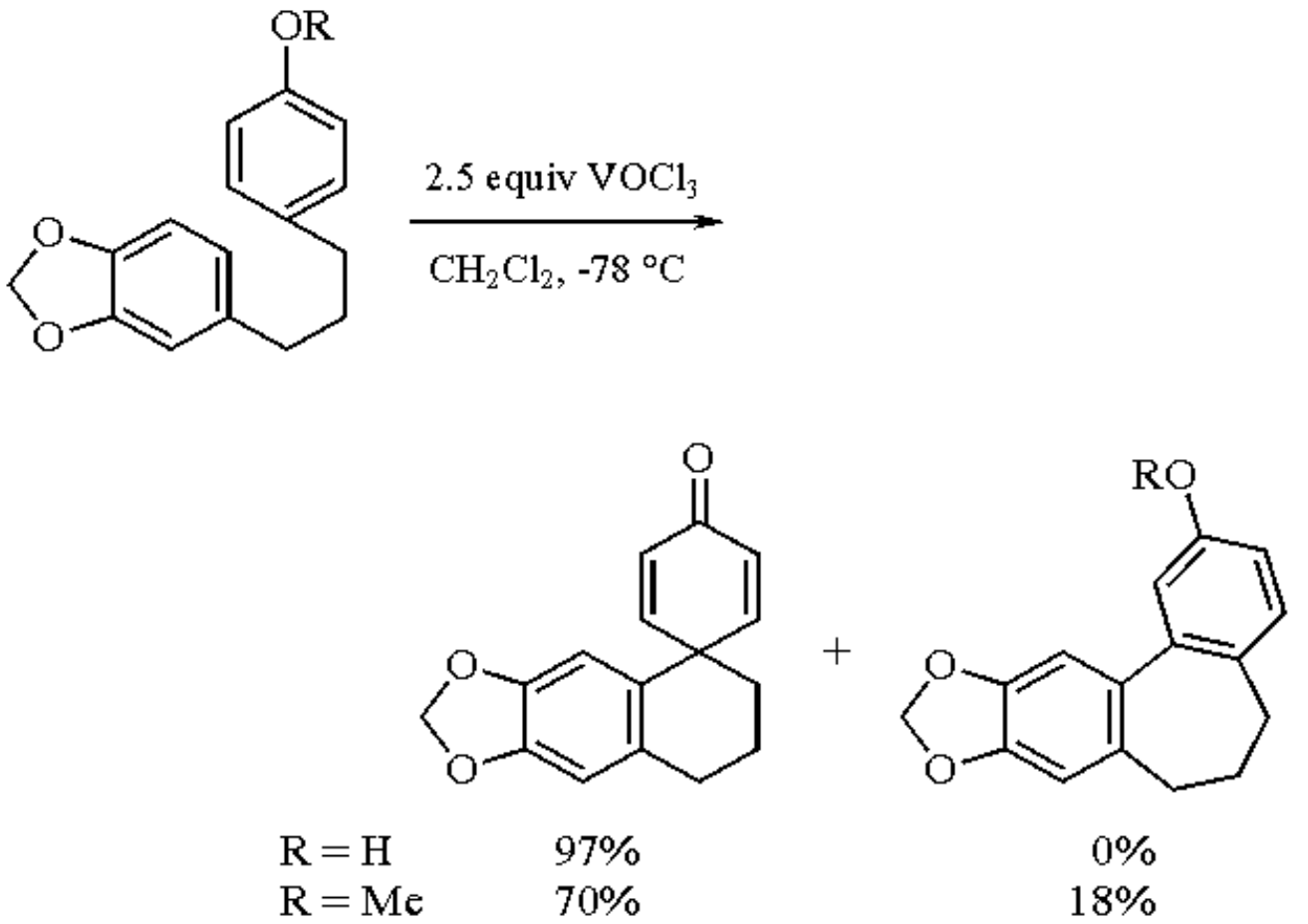

(7)

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Vanadyl Trifluoride

VOF_3

[13709-31-4] · F_3OV · Vanadyl Trifluoride · (MW 123.94)

(phenolic coupling)

Alternate Names: vanadium oxytrifluoride; trifluorooxovanadium.

Physical Data: mp 300 °C.

Solubility: sol TFA, CH_2Cl_2.

Form Supplied in: commercially available as a white solid.

Introduction.

Vanadyl trifluoride has demonstrated utility in intramolecular phenolic coupling reactions, a transformation of pivotal importance in alkaloid biosynthesis. For example, the benzyltetrahydroisoquinoline (**1**) has been converted to the oxoaporphine (**2**) in 59% yield (eq 1).[1] Although alternative reagents such as CrO_3, MnO_2/TFA, and $(CF_3CO_2)_3Tl$[2] have proven less successful in this reaction, $MoOCl_4$/TFA/$CHCl_3$ generates similar yields of oxoaporphine (62%). ***Trifluoroacetic Acid*** is an effective medium for these oxidations, particularly with moisture sensitive oxidants.[1] Reaction temperatures vary between -78 °C and ambient temperature.

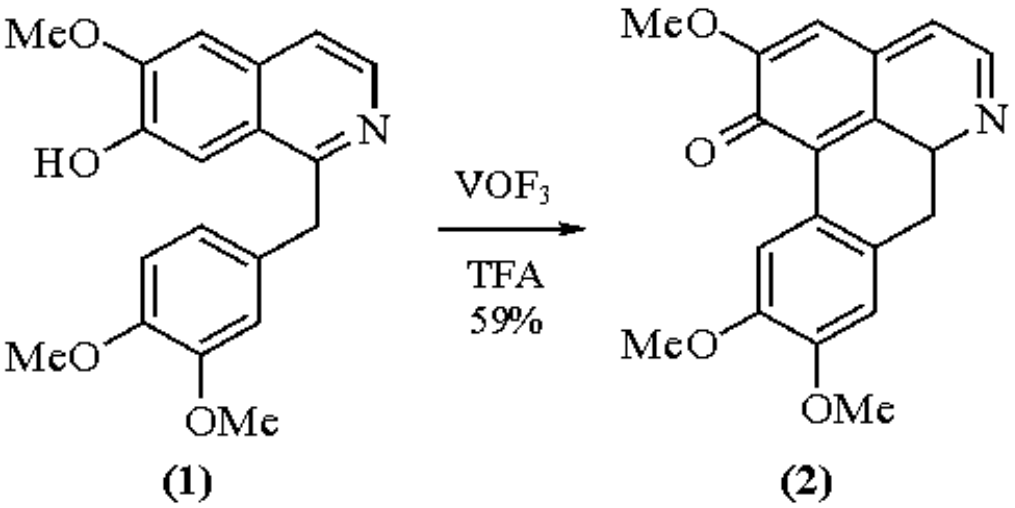

(1)

Phenyl Ether Coupling.

Vanadyl trifluoride will promote intramolecular oxidative coupling between nonphenolic aryl ethers, as exemplified in the syntheses of (±)-isostegane,[3] (±)-stegamycin,[4] and the acyl-neospirinedienones.[5] In the total synthesis of (±)-tylophorine (eq 2),[6] for instance, the reaction is complete in 1 h at room temperature in 69% yield.

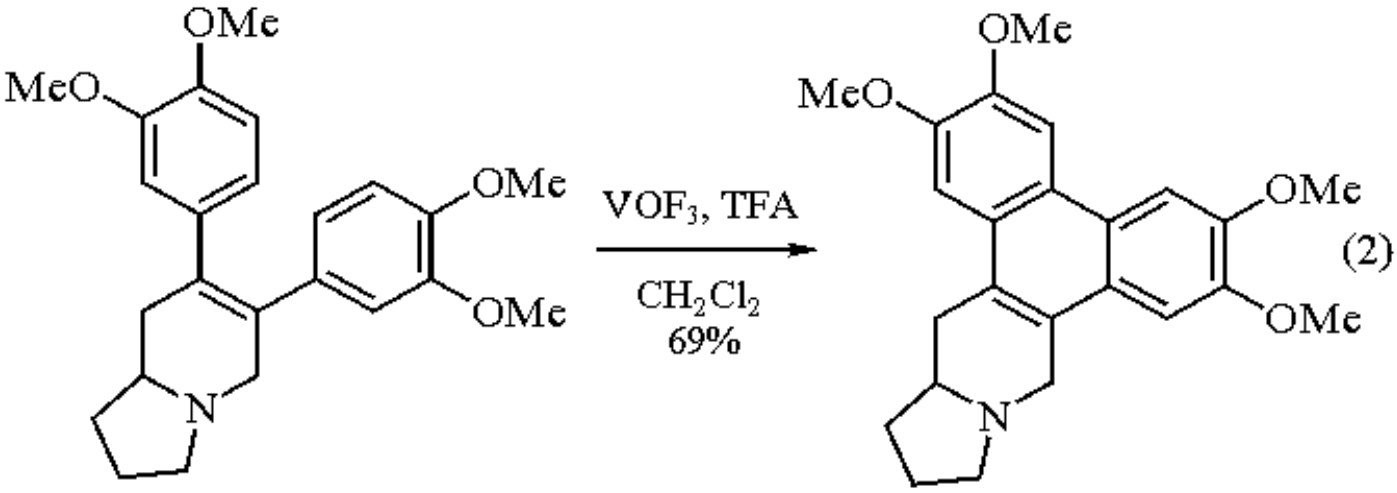

Asymmetric Synthesis.

Several asymmetric syntheses have employed VOF_3 as an intramolecular coupling agent. Syntheses of (+)-deoxyschizandrin (eq 3),[7] (+)-glaucine, and (+)-homoglaucine[8] have all utilized this reagent in the key oxidative coupling step. In the latter two cases, ruthenium tetrakis(trifluoroacetate) is an equally effective oxidant, and there have been claims that this reagent is superior to vanadyl trifluoride.[9]

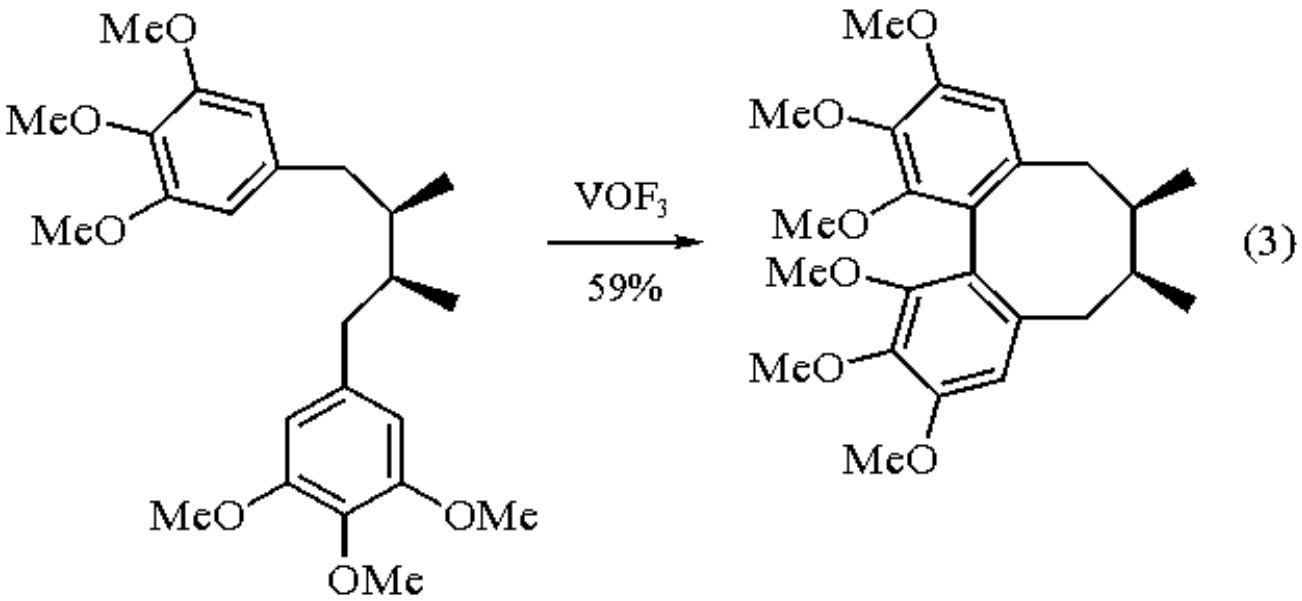

Intermolecular oxidative aryl coupling is also promoted by VOF_3, as exemplified by the synthesis of symmetrical biaryl analogs of the biphenomycin antibiotics (eq 4).[10] Moderate yields are obtained and VOF_3 is preferred over other reagents such as ***Vanadyl Trichloride*** because of higher yields and superior functional group compatibility. When these authors[10] attempted an intramolecular version of this transformation, VOF_3 failed to induce the cyclization.

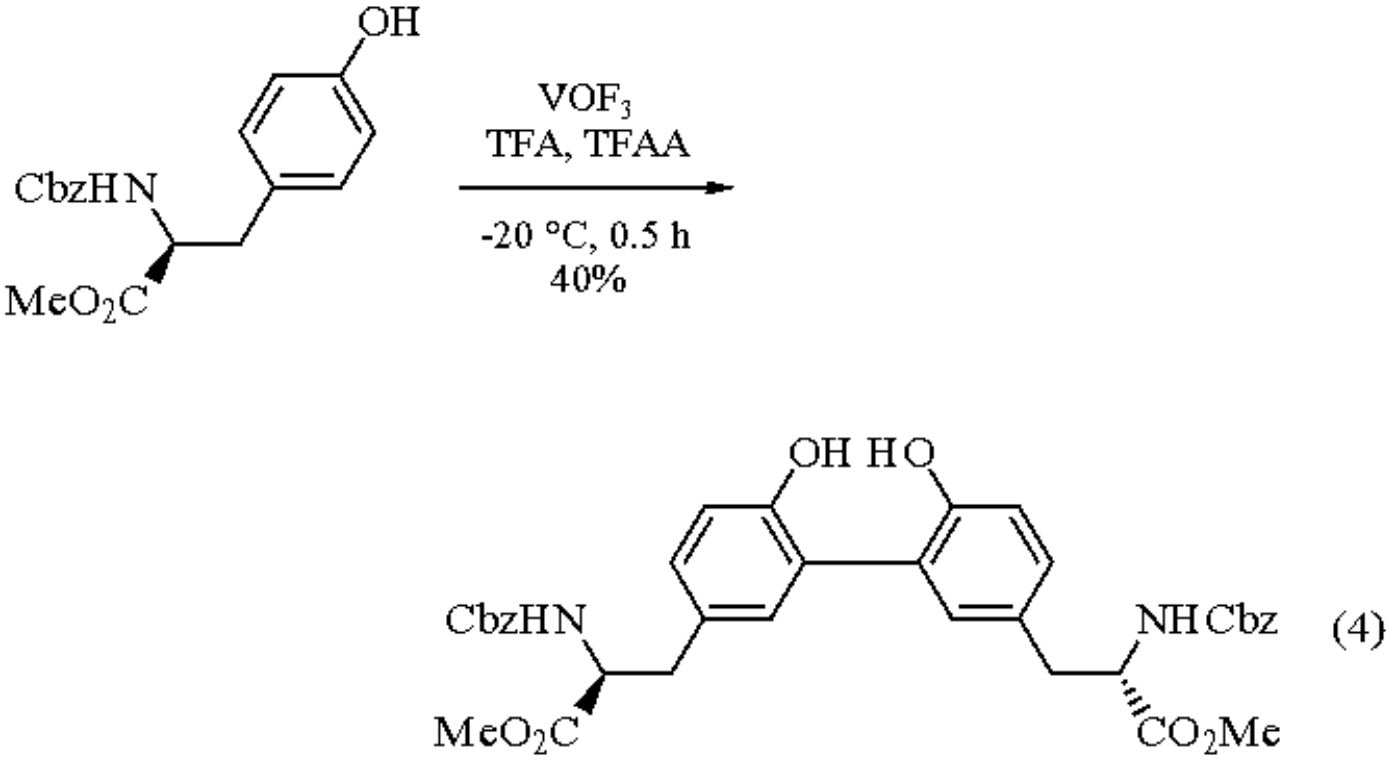

The diaryl chiral oxazolidine (**3**) (eq 5)[11] has been converted to the corresponding spirodienone (**4**) in near quantitative yield by using VOF_3. $VOCl_3$ and ***Phenyliodine(III) Bis(trifluoroacetate)*** have also been utilized to effect this transformation, albeit in lower yields. This example constitutes an efficient simulation of the biosynthetic pathway of alkaloids both in terms of yield and stereochemical outcome.

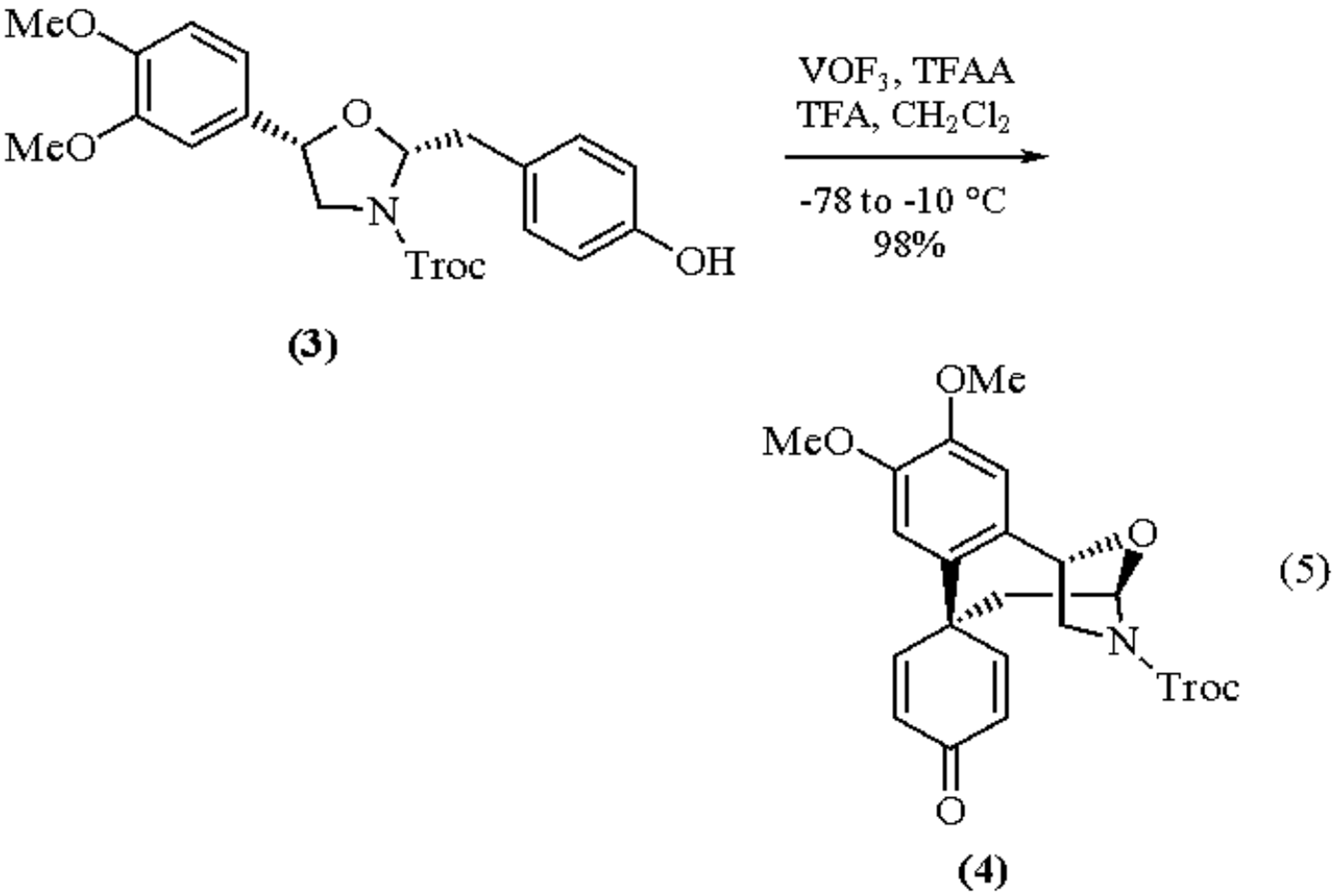

Biomimetic Oxidative Coupling.

Vanadyl trifluoride has been employed successfully in the biomimetic synthesis of the vancomycin[12] class of glycopeptides. The array of functionality present in the starting material and the degree of asymmetric induction achieved in the cyclization illustrates the utility of this

reagent in complex synthesis. Apparently, the atropdiastereoselection[13] is greatly influenced by the various protective groups on the starting tripeptide (particularly since the Boc group is unstable to these reaction conditions), the substituents on the phenyl ring, and probably the resulting A(1,3) strain, although the mechanistic details of this oxidation are unclear (eq 6). Apparently residual chloride in commercial TFA is sequestered by the Ag^{I} salts, while ***Boron Trifluoride Etherate*** prevents the attack of oxygen nucleophiles on the radical cation and the TFA/TFAA solvent combination[12] traps adventitious water. ***Manganese(III) Acetylacetonate*** is the only other reagent to effect this transformation, although in lower yield. Reagents such as $Tl(TFA)_3$, $FeCl_3$, $VOCl_3$, CoF_3, and the Pt anode failed to induce cyclization.

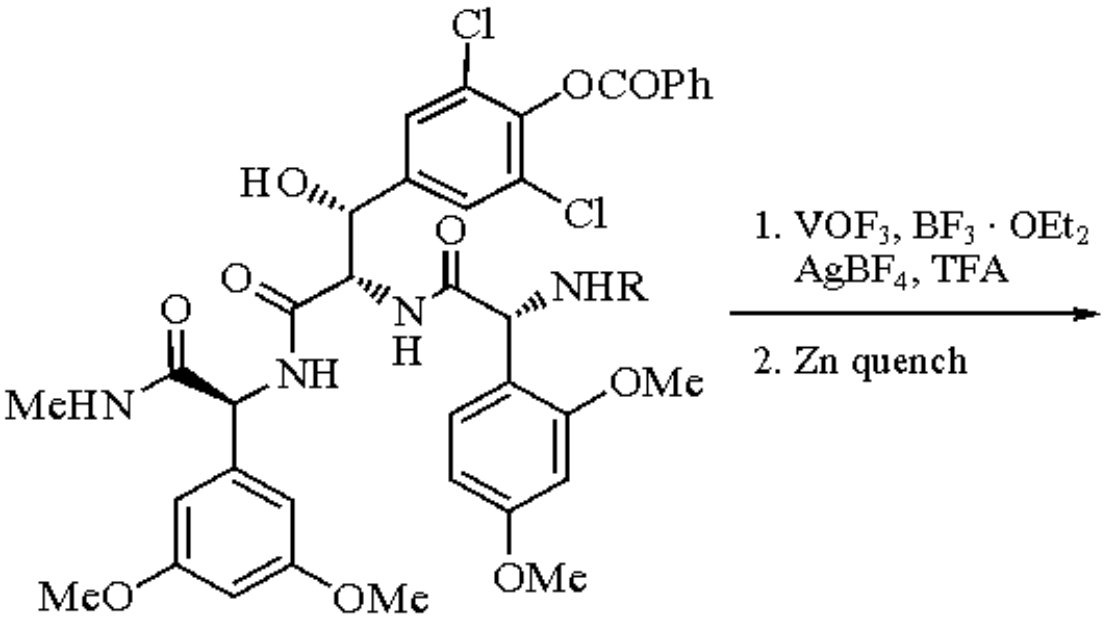

(a) R = Ac
(b) R = Boc

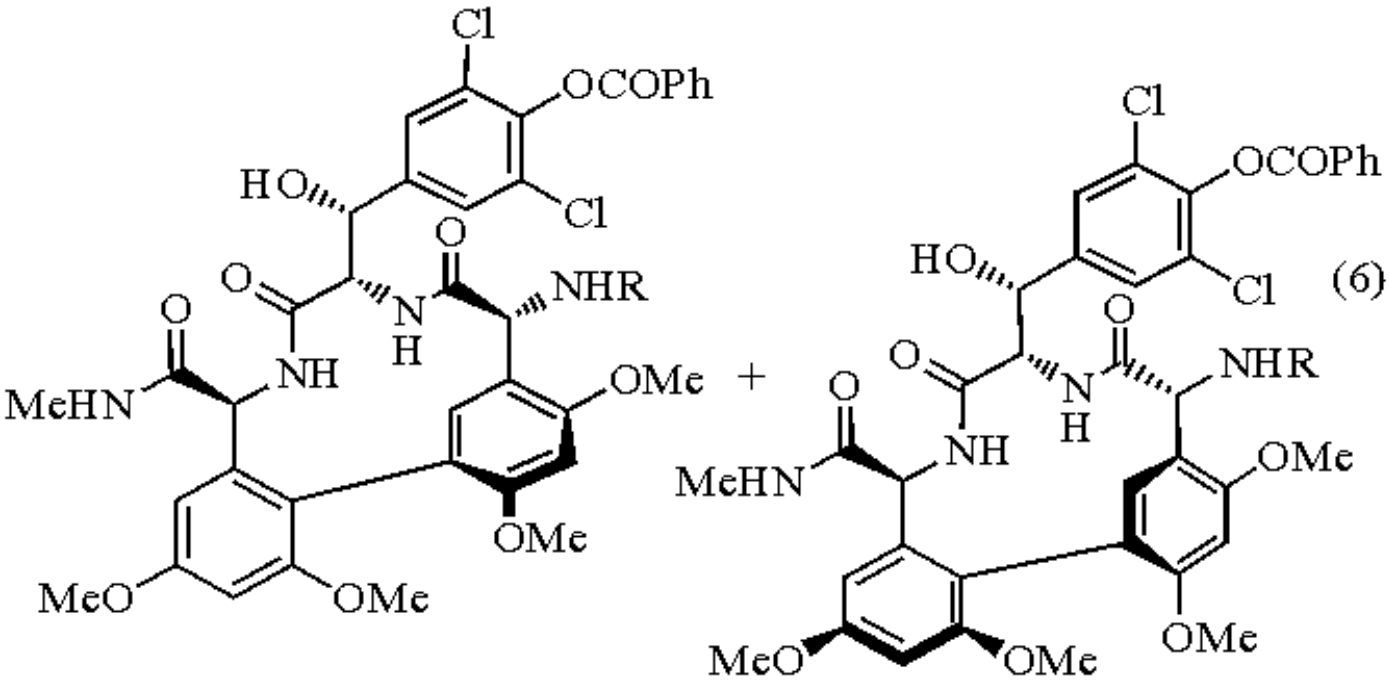

(6)

(a) R = Ac, 67%; atropdiastereoselection = >97:3
(b) R = H, 42%; atropdiastereoselection = 84:16

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Vinyl Acetate[1]

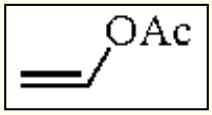

[108-05-4] · $C_4H_6O_2$ · Vinyl Acetate · (MW 86.10)

(enzyme-mediated transacetylation of alcohols; *N*- and *O*-transvinylation; acetaldehyde equivalent; cycloaddition reactions with chlorosulfonyl isocyanate to give azetidinones, nitrile oxides to give isoxazoles, nitrones to give isoxazolines, enones to give acetoxycyclobutanes, and arenes to give bi- and tricyclic adducts; source of formaldehyde oxide)

Physical Data: [2] bp 73 °C; mp -92.8 °C; *d* 0.9335 g cm^{-3}.

Solubility: soluble all common organic solvents; somewhat sol water.

Form Supplied in: colorless liquid stabilized with 4 ppm hydroquinone and 300 ppm diphenylamine.

Handling, Storage, and Precautions: extremely flammable with unusual fire and explosion hazards. Readily polymerizes, especially on exposure to light, to give a solid. Removal or loss of the inhibitors results in rapid polymerization, often quite violently. Vinyl acetate is a cancer suspect agent and may cause genetic damage. It is quite irritating to the eyes, skin, and respiratory system.[2a] Use in a fume hood.

Transacetylation.

Vinyl acetate is used extensively in irreversible enzyme-mediated transacetylation of racemic and *meso*-alcohols, usually in organic solvents, to give optically active products with excellent enantiomeric excesses.[3-9] In a typical example, enantioselective transacetylation of the glycal (**1**) with vinyl acetate is performed in dimethoxyethane at room temperature in the presence of the lipase derived from *Pseudomonas cepacia* to give the monoacetate (**2**) and diacetate (**3**), each with an enantiomeric excess of 97% (eq 1).[3] Other examples include the following preparations: the chiral auxiliaries (**5**) and (**6**) derived from racemic *trans*-phenylcyclohexanol (**4**) using an immobilized enzyme (eq 2);[4] the diltiazem intermediate (**8**) (eq 3);[5] the acetate (**11**) derived from the *meso*-diol (**10**) (eq 4);[6] and (**13**) and (**14**), the corresponding racemic alcohol (**12**) of which could not be resolved efficiently by enantioselective epoxidation (eq 5).[7] In addition, regioselective acetylation of primary and secondary alcohols with vinyl acetate in the presence of a lipase proceeds in excellent yields. In general, primary alcohols are acetylated in preference to secondary alcohols,[8a,b] and, with the latter, excellent regioselectivity is obtained depending on the stereochemistry of the alcohol (eq 6).[8c,d] See also ***Acetic Anhydride*** and ***Acetyl Chloride***.

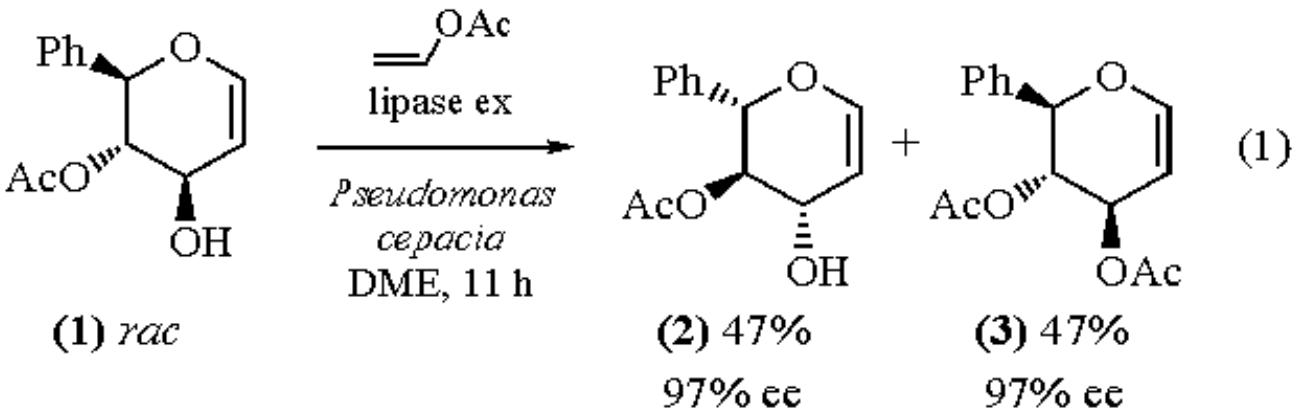

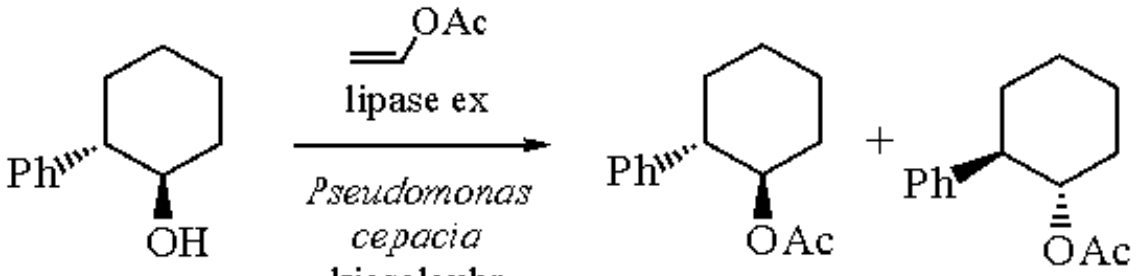

(2)

(4) *rac* **(5)** 40% 96% ee **(6)** 42% 99% ee

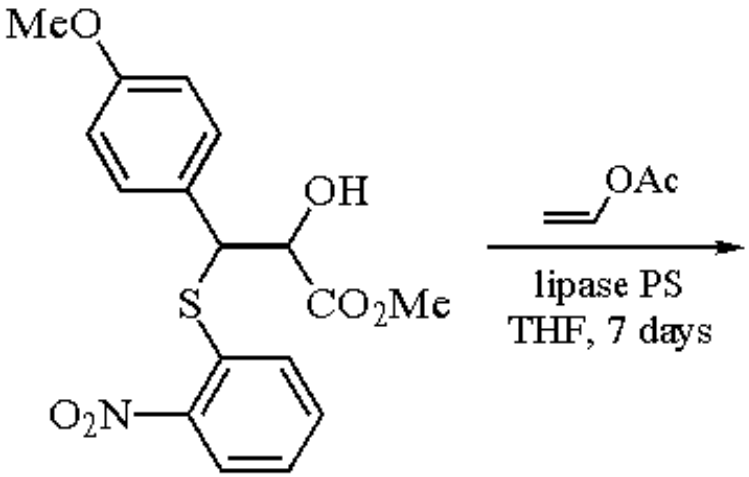

(7) *rac*

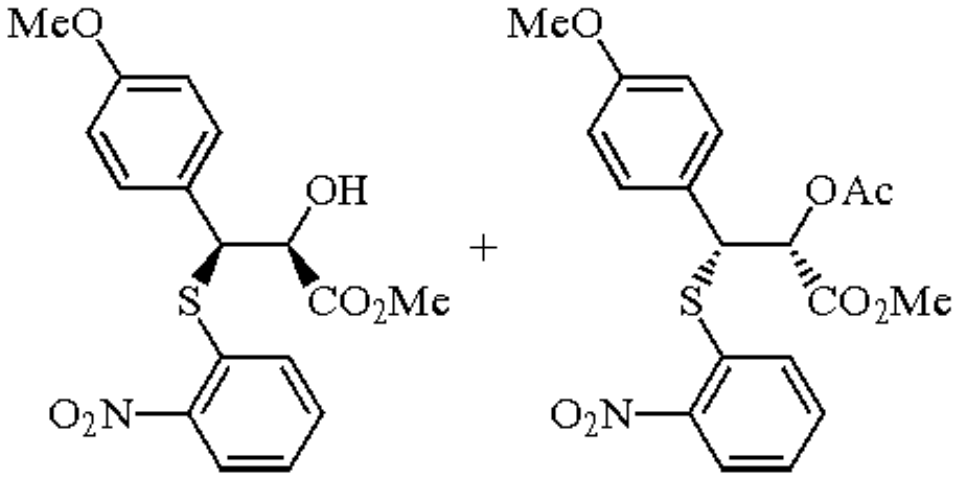

(3)

(8) 50% >95% ee **(9)** 50% >95% ee

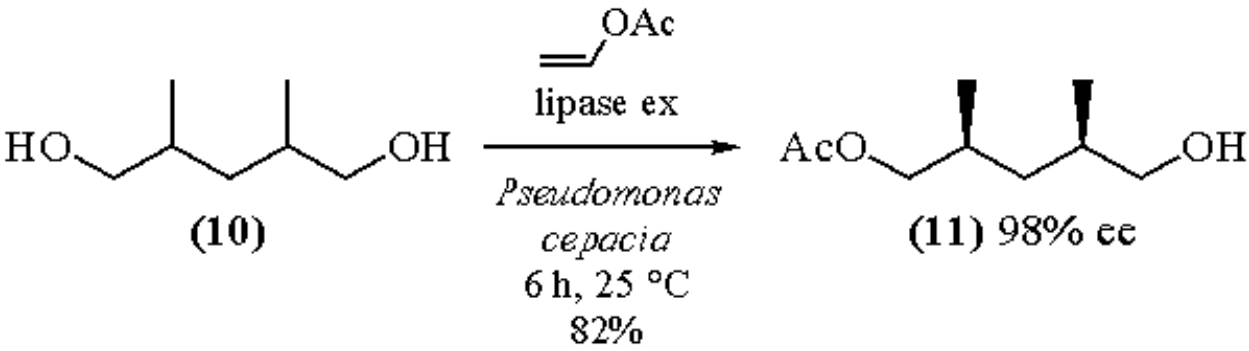

(4)

(10) **(11)** 98% ee

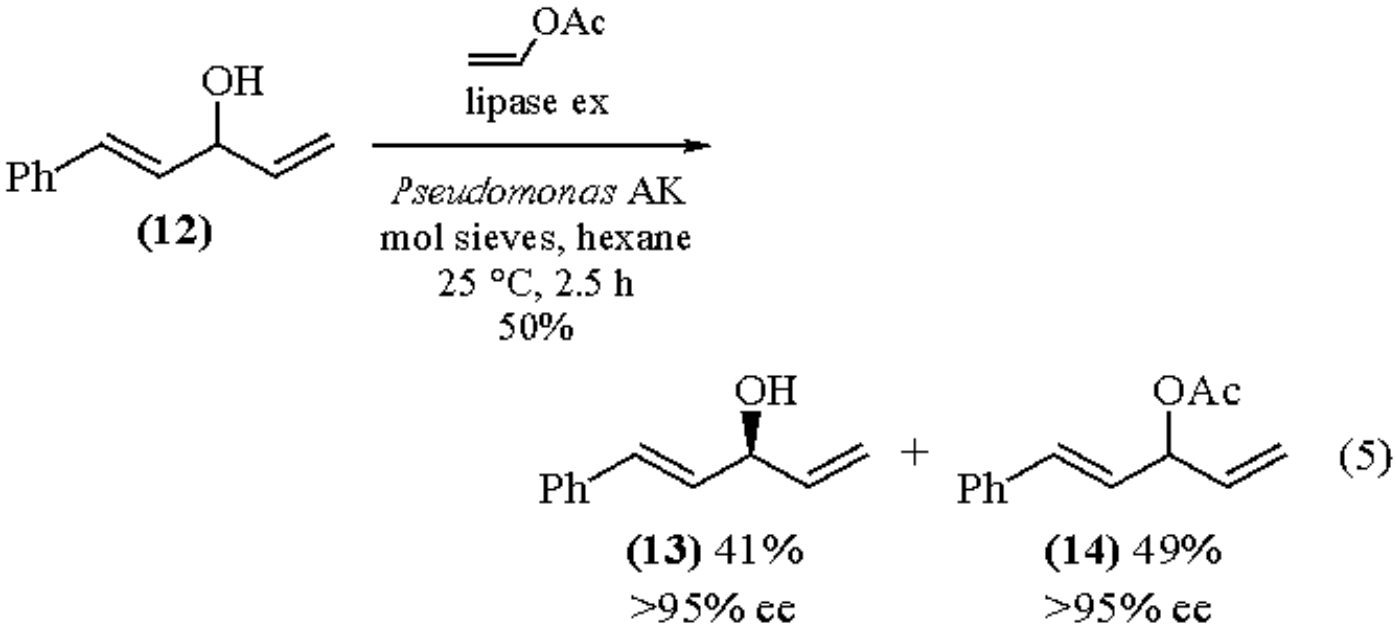

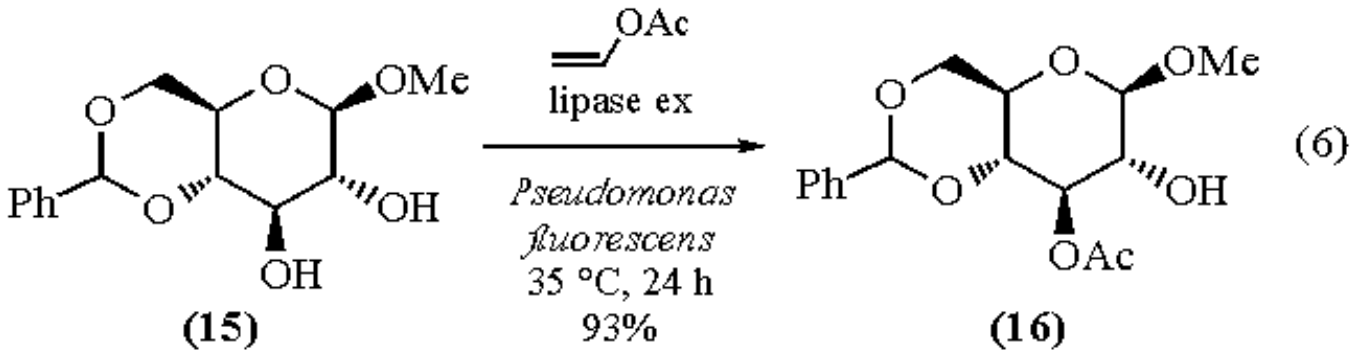

Transvinylation.

N-Vinylation with vinyl acetate is usually carried out in the presence of ***Palladium(II) Chloride***[10] or ***Mercury(II) Acetate*** (eq 7),[11] although a catalyst is apparently not required in the preparation of the alkaloid (**20**) (eq 8).[12] Vinyl esters may be prepared in moderate to good yields by heating the acid with vinyl acetate in the presence of $Hg(OAc)_2$ (eq 9)[13] or $PdCl_2$ (eq 10).[14] Vinyl esters of amino acids, prepared by transesterification with vinyl acetate in ethyl cyanoacetate, have been used as activated esters in peptide synthesis.[15] In an indole synthesis, *O*-vinylation of (**25**) with vinyl acetate in the presence of $PdCl_2$ leads directly, via a hetero-Cope rearrangement, to a regioisomeric mixture of indoles in 83% yield (eq 11).[16] Although not as widely used as ***Ethyl Vinyl Ether***, vinyl acetate has been used to prepare allyl vinyl ethers from allyl alcohols with $Hg(OAc)_2$ as the catalyst.[17]

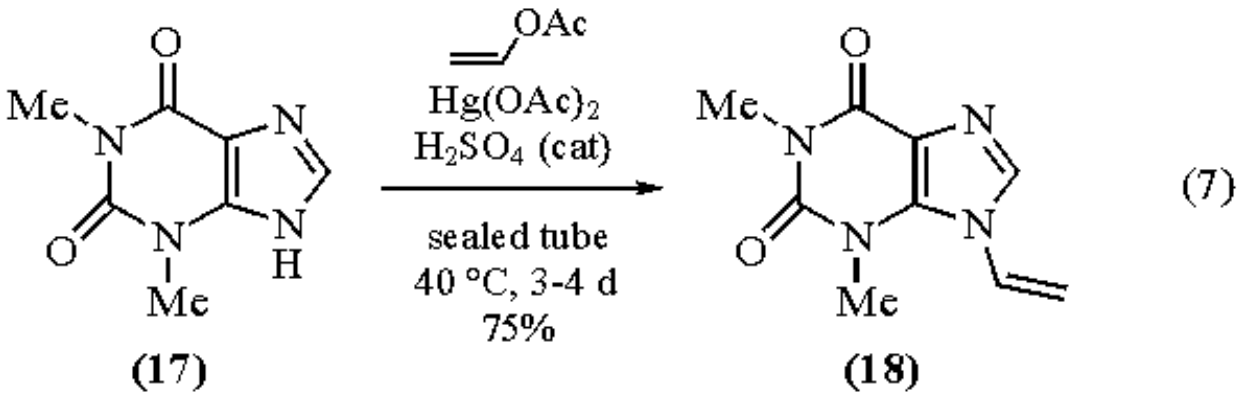

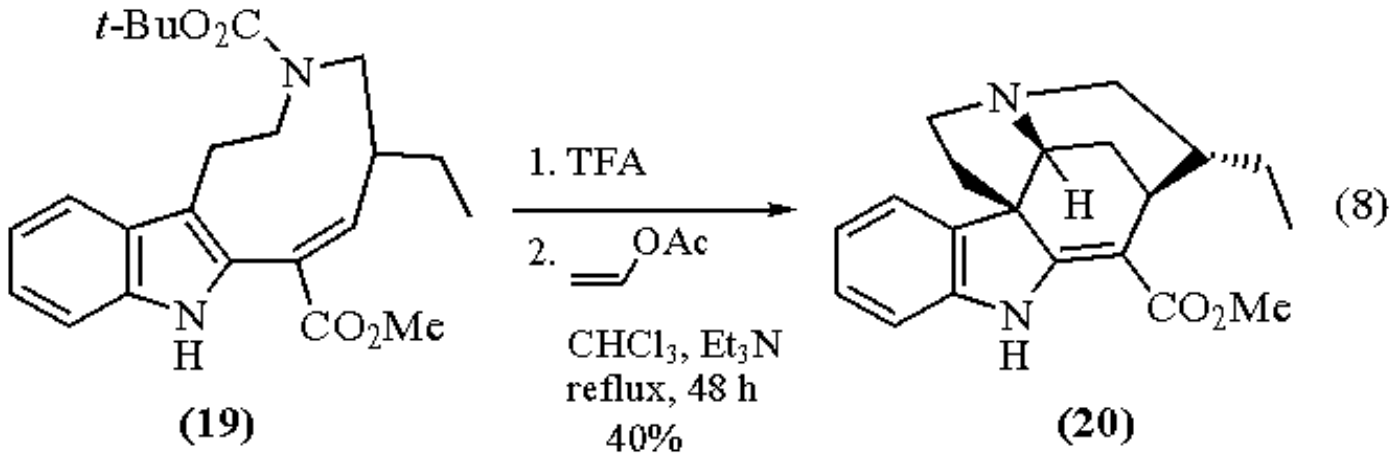

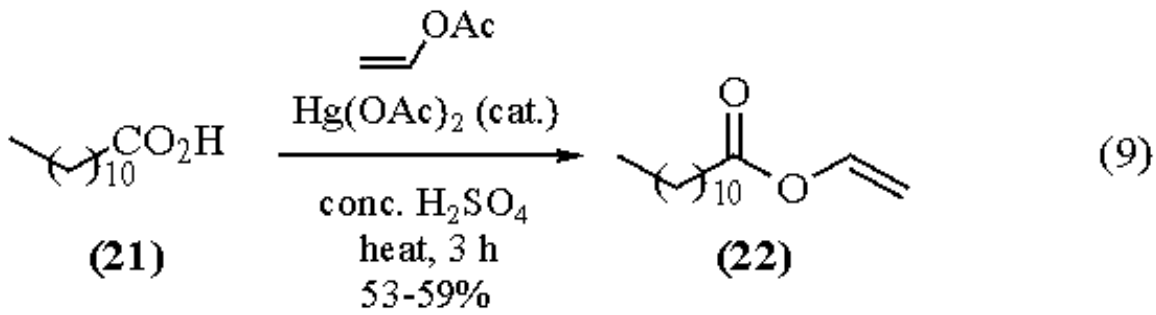

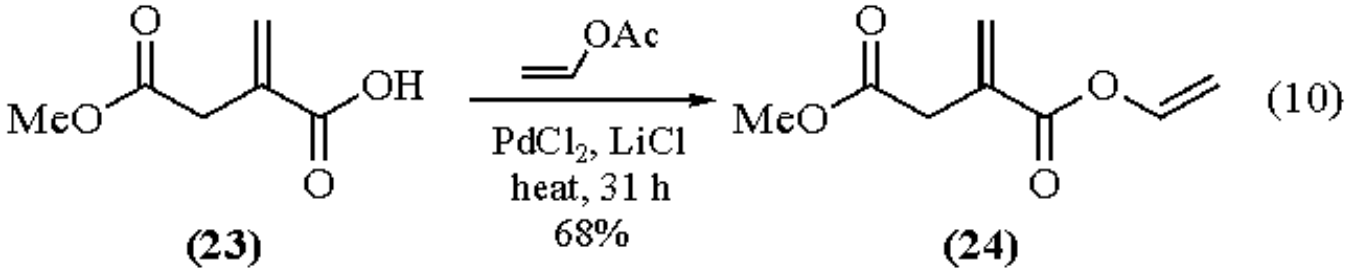

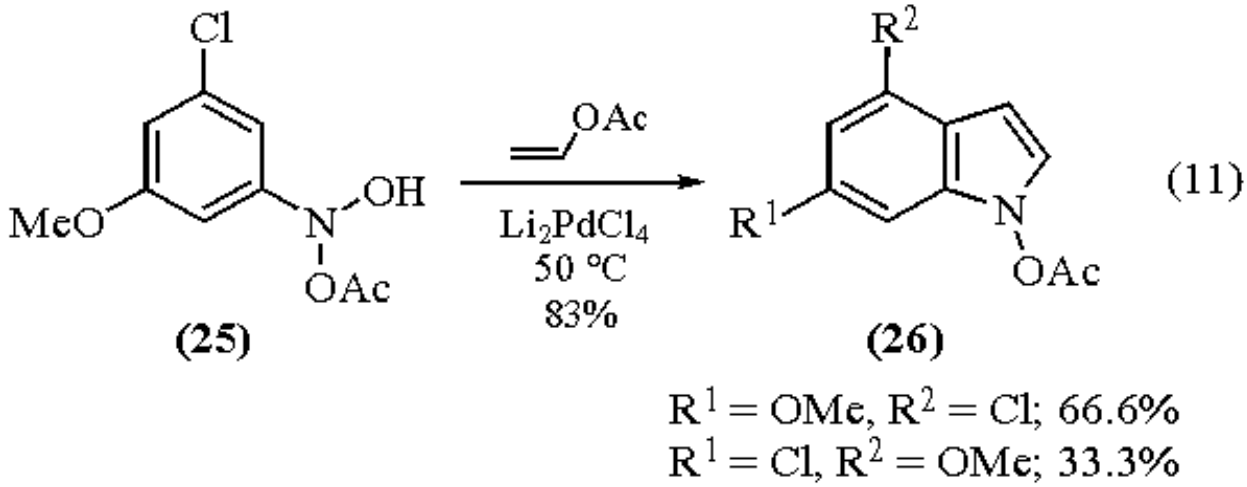

Acetaldehyde Equivalent.

The reaction of vinyl acetate with a ketone in the presence of ***Cerium(IV) Ammonium Nitrate*** gives an α-(2-acetoxy-2-nitrosylethyl) ketone, which may be solvolyzed to the corresponding acetal (eq 12).[18] A related reaction of vinyl acetate with 2,4-pentanedione leads to 2-methyl-3-acetylfuran in 56% yield (eq 13).[19] Introduction of the ***Acetaldehyde*** unit onto an aromatic ring is possible by a Meerwein reaction between a diazonium salt and vinyl acetate in the presence of ***Copper(II) Chloride*** (eq 14).[20]

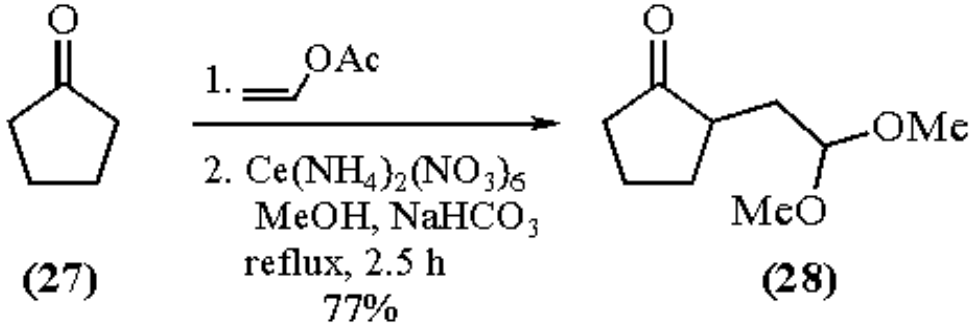

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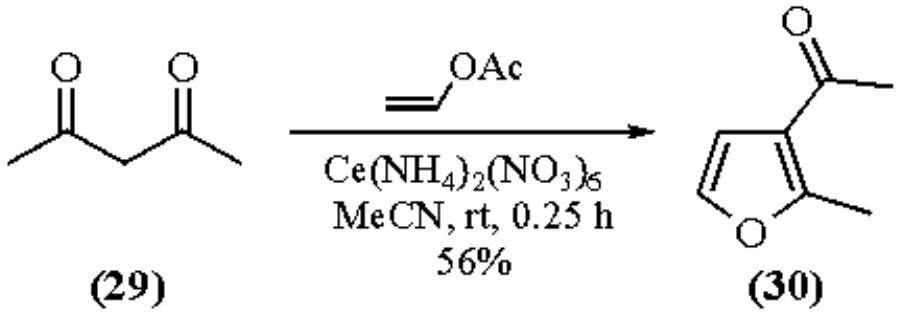

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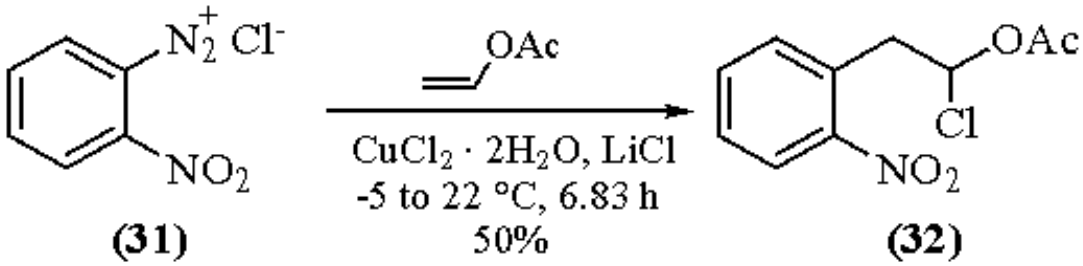

(14)

Cycloaddition Reactions.

Thermal.

Vinyl acetate reacts rapidly with ***Chlorosulfonyl Isocyanate*** at low temperatures to give, after reduction with $NaHSO_3$, 2-acetoxyazetidinone in 80% yield (eq 15).[21] However, Diels-Alder reactions with vinyl acetate are quite sluggish. With the 2*H*-pyrrole (**35**), the cycloadduct is obtained in 83% yield after 7 days (eq 16),[22] whereas the pyridine (**38**) is produced in 78% yield from the 1,2,4-triazene (**37**) (eq 17).[23] 1,3-Dipolar addition of vinyl acetate with nitrile oxides gives isoxazolines,[24] which may be converted directly to isoxazoles (eq 18);[25] isoxazoles are also obtained by heating potassium nitronates with vinyl acetate.[26] The cycloaddition of vinyl acetate to nitrones yields isoxazolines in a highly regioselective manner,[27] and can be highly stereoselective, as is found with the Cr^0-complexed nitrone (**41**) (eq 19).[28]

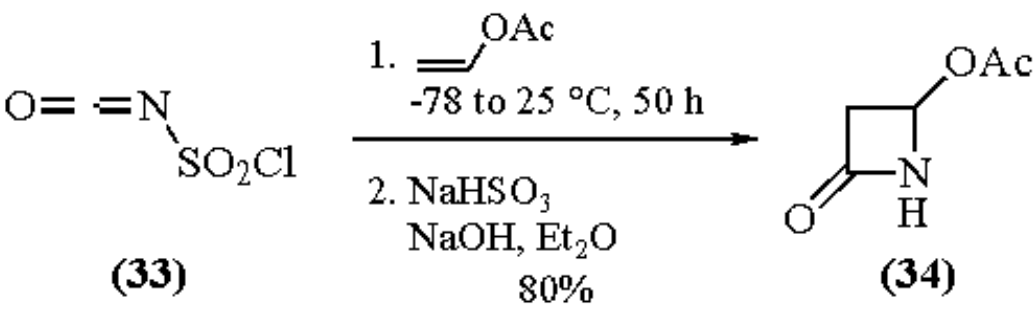

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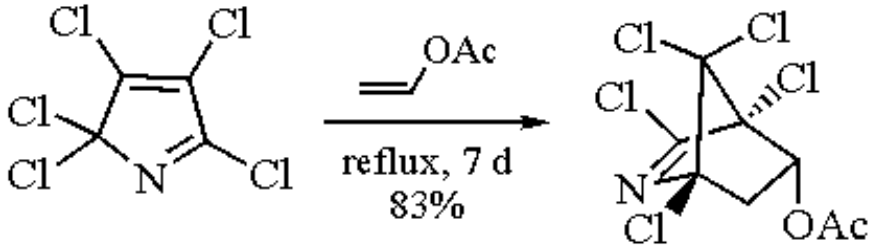

(35) (36) (16)

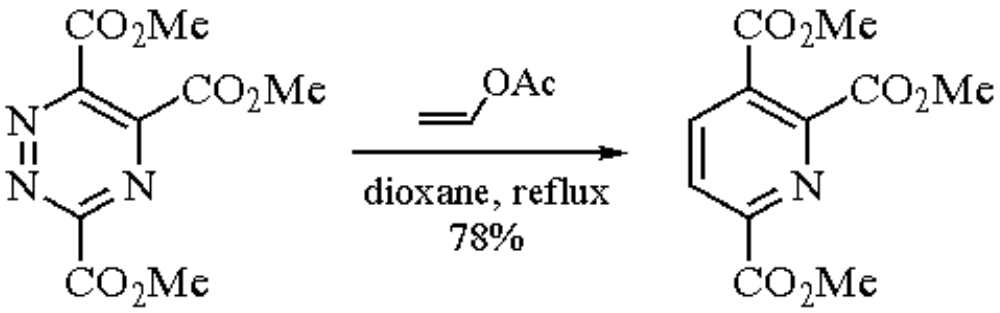

(37) (38) (17)

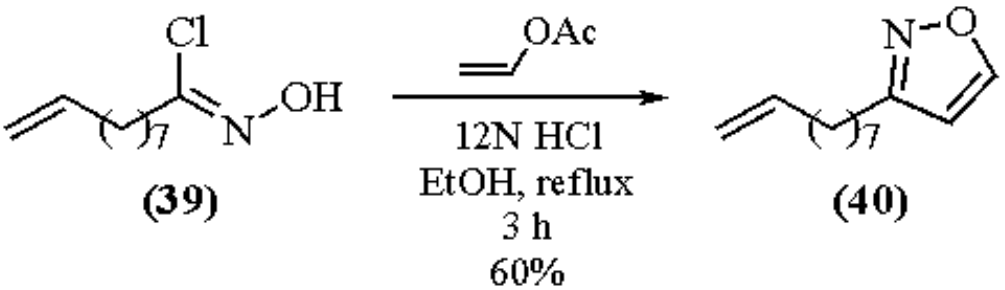

(39) (40) (18)

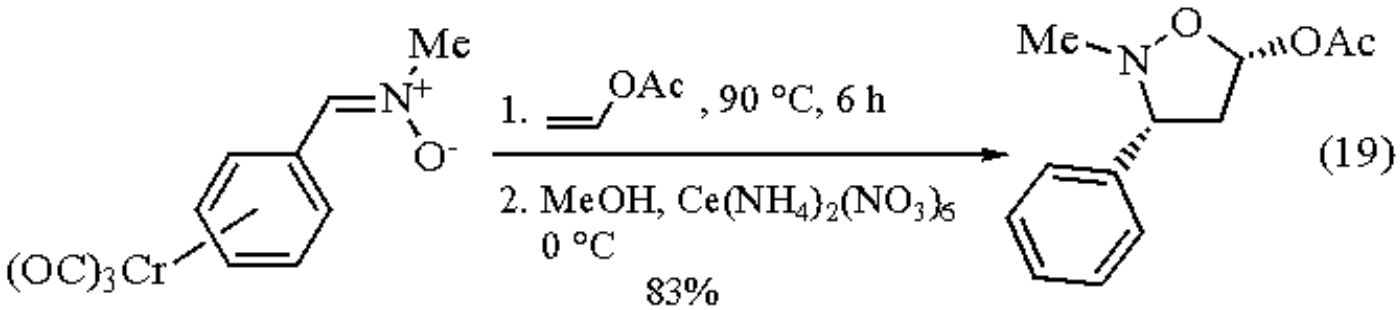

(41) (42) (19)

Photochemical.

High yields of acetoxycyclobutanes, in which the head-to-tail regioisomer predominates, are obtained from the photoaddition of vinyl acetate to cyclic enones.[29] As illustrated in an approach to the synthesis of taxol, photoaddition of vinyl acetate to the enolic form of the 1,3-dione (**43**) produces the cycloadduct (**44**) in 90% yield as a mixture of diastereomers (eq 20).[30] Similar excellent regioselectivity is realized in the photoaddition of vinyl acetate to the naphthoquinone (**45**), yielding the acetoxycyclobutane (**46**) in an almost quantitative yield (eq 21).[31]

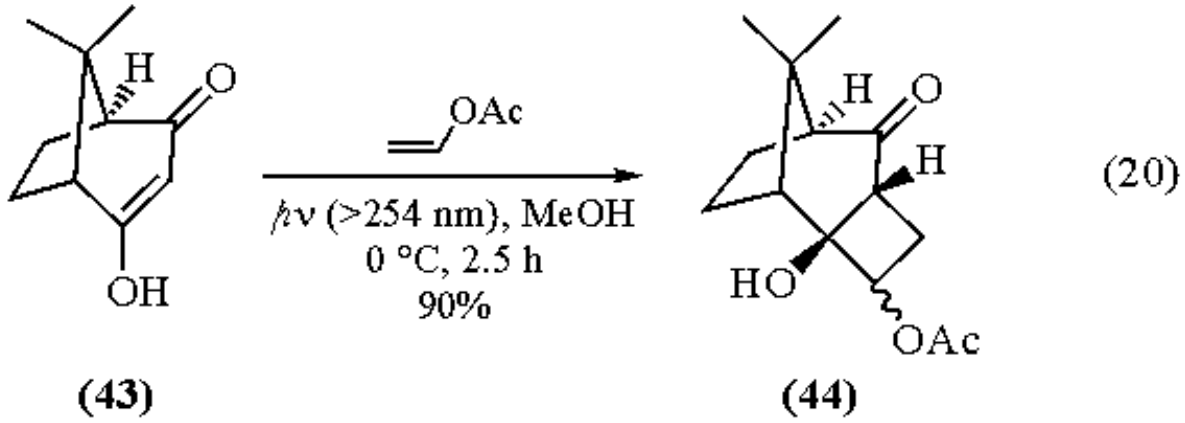

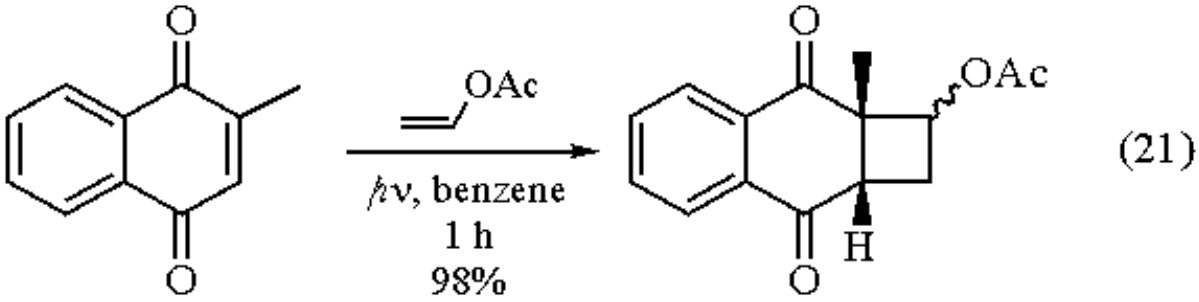

Vinyl acetate also undergoes photoaddition to arenes, producing 1,2- and 1,3-photoadducts.[29,32] Irradiation of benzene at 254 nm in the presence of a large excess of vinyl acetate gives, in low yield, a single 1,2-cycloadduct (**48**) and a regioisomeric mixture of 1,3-cycloadducts (**49**) (eq 22).[33] The latter predominates, except when there is a large difference in electron-donor/acceptor capacity between the aromatic compound and vinyl acetate, as is found with benzonitrile.[34] The photoaddition of ethenes to arenes has been used in the synthesis of several structurally complex natural products,[35] typified by the construction of the propellane system of *rac*-modhephene from the photoaddition of vinyl acetate to indan (eq 23).[36]

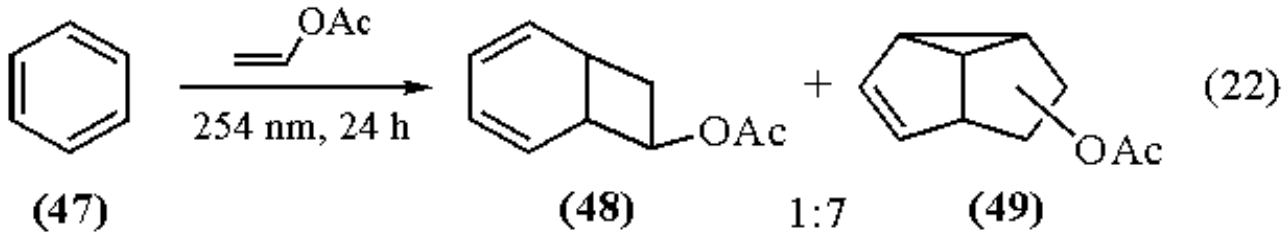

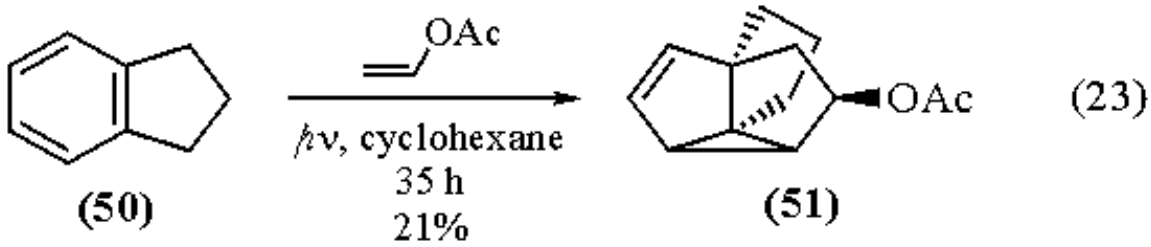

Formaldehyde Oxide.

Ozonolysis of vinyl acetate yields formaldehyde oxide, which reacts rapidly with ketones to give lactones (eq 24),[37] and is therefore an alternative to the Baeyer-Villiger oxidation.

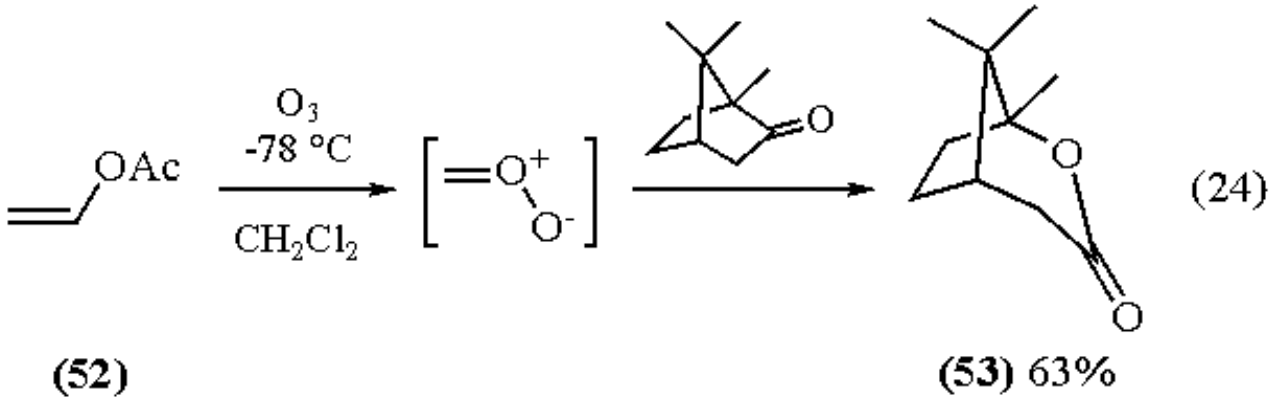

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9-Vinyl-9-borabicyclo[3.3.1]nonane

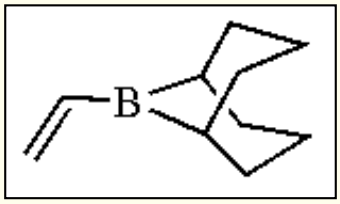

[129493-14-7] · $C_{10}H_{17}B$ · 9-Vinyl-9-borabicyclo[3.3.1]nonane · (MW 148.08)

(highly reactive and selective Diels-Alder dienophile[1])

Physical Data: bp 28-30 °C/0.25 mmHg.[1]

Preparative Method: vinylboranes are most conveniently prepared from the reaction of vinylstannanes with bromo- and chloroboranes (eq 1).[1] These preparations may be carried out in situ[2] for Diels-Alder reactions.

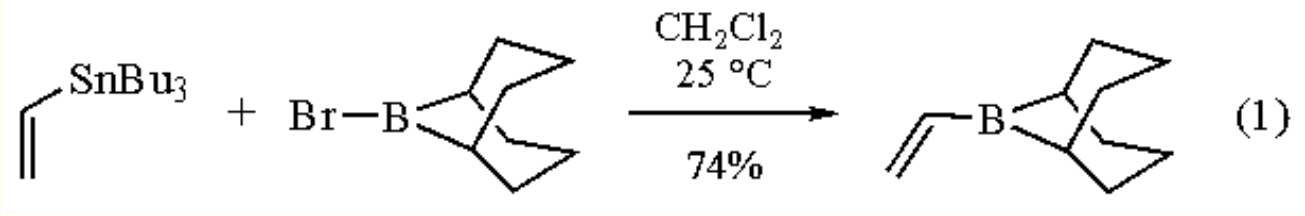

Handling, Storage, and Precautions: volatile vinylboranes are extremely pyrophoric; many problems may be avoided using the in situ procedure.[2] Vinyl-9-BBN dimerizes[3] extensively over the course of days at rt, and slowly in a freezer, but some other vinyldialkylboranes are much more stable.[3]

General Discussion.

Vinylboranes are highly reactive, regioselective, and *endo*-stereoselective dienophiles, and exhibit other useful and unusual properties in their Diels-Alder reactions. Vinyl-9-BBN is 200 times more reactive than ***Methyl Acrylate*** with ***1,3-Butadiene*** (eq 2),[1] and reacts with a wide variety of dienes at 25-55 °C. Vinyl-9-BBN is omniphilic because it displays high and surprisingly invariant reactivity with electron-rich, electron-poor, and unactivated dienes.[4]

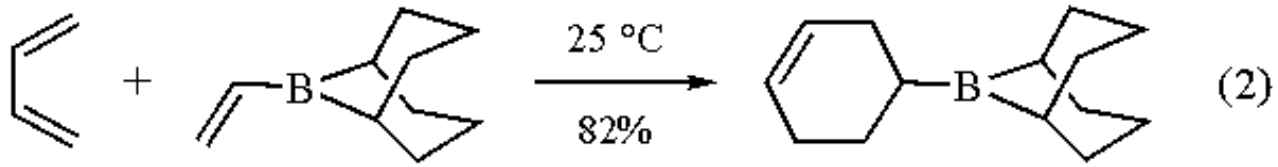

$k = 3.2 \times 10^{-6}$

The regioselectivity of vinyl-9-BBN reactions is very high (eq 3).[3] However, this selectivity appears mainly due to steric effects; less sterically demanding vinylboranes are much less selective.[3] The large role of steric effects often results in unusual regioselectivities, such as the exclusive formation of the *meta* product from piperylene and the formation of a single regioisomer from vinylcyclohexene (eq 4).[1]

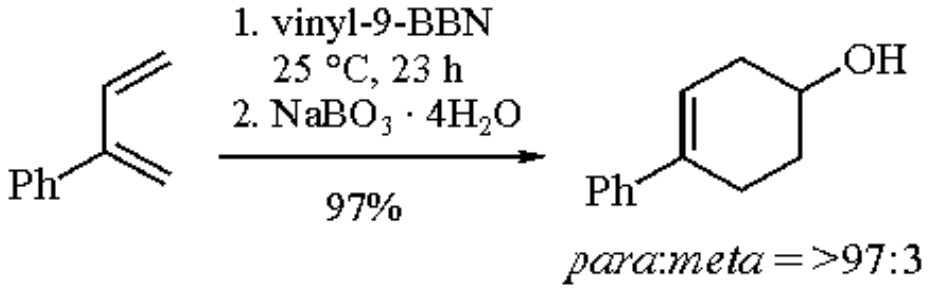

(3)

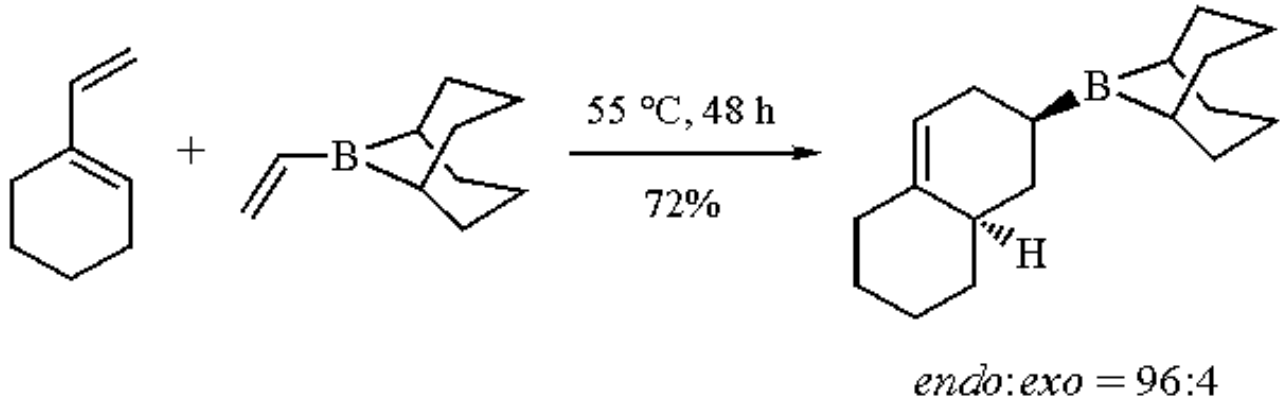

(4)

Electronic effects can also give rise to unusual regioselectivities with vinylboranes. Although vinyldihaloboranes are more reactive than vinyldialkylboranes,[5] their selectivity is low. However, 2-alkenyl- and *cis*-1-alkenyldibromoboranes are highly regioselective dienophiles and afford the unusual *meta* product (eq 5).[6] A similar *meta* regioselectivity is observed with alkynic boranes.[7] In both cases the unusual selectivity is attributed to a [4 + 3] transition state based on ab initio calculations.[8] Since the corresponding alkenyl-BBN derivatives afford the *para* products, either regioisomer may be obtained by judicious choice of borane.

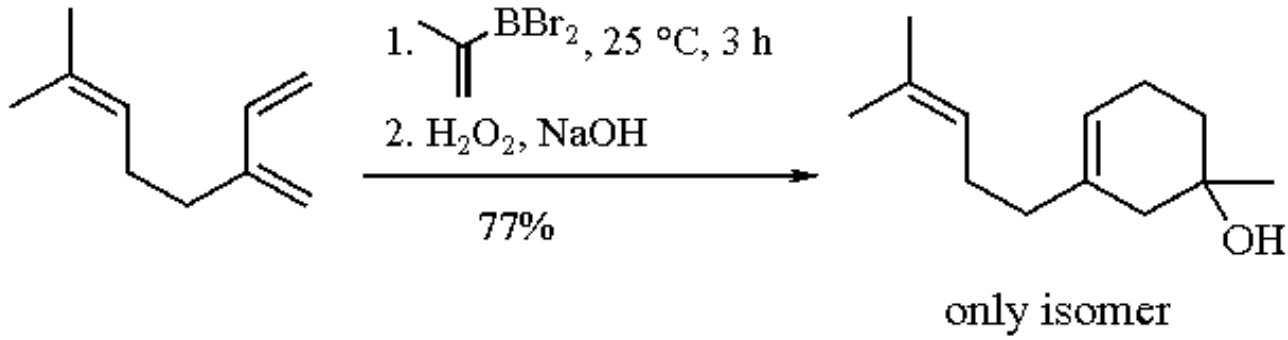

(5)

As shown in eq 4, the stereoselectivity with vinylboranes is generally >90% *endo*. Examples of lower selectivity have been improved by choice of vinyldialkylborane.[3] An exception to this selectivity has recently been observed in the reaction of 2-propenyl-9-BBN with cyclopentadiene, which affords the *exo* product with high selectivity (eq 6).[6]

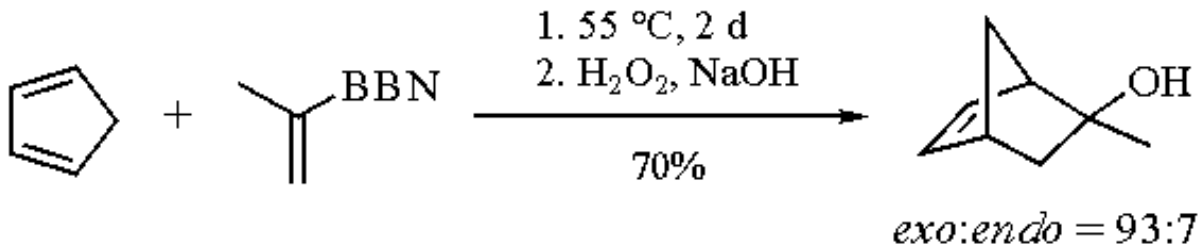

(6)

2-Trimethylsilylvinyl-9-BBN is also highly reactive.[9] Acid-catalyzed elimination of the silyl alcohol products readily affords 1,4-cyclohexadienes (eq 7), making 2-trimethylsilylvinyl-9-BBN a highly reactive ***Acetylene*** equivalent for Diels-Alder reactions.

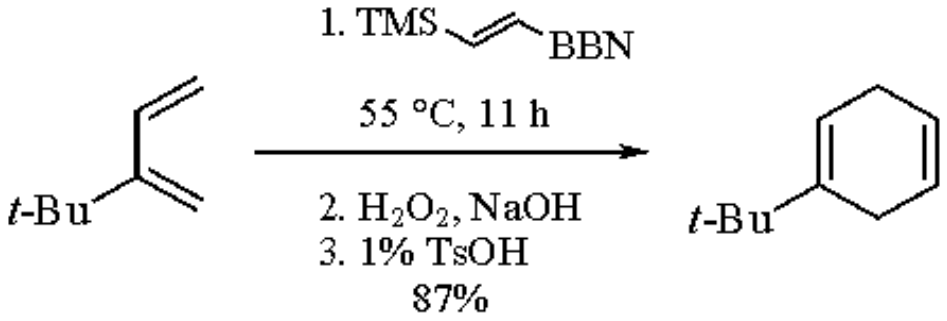

(7)

Related Reagents.

Ethyl Acrylate; ***Methyl Acrylate***; ***Methyl Vinyl Ketone***.

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1. Singleton, D. A.; Martinez, J. P. *JACS* **1990**, *112*, 7423.
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β-Vinyl-α,β-butenolide

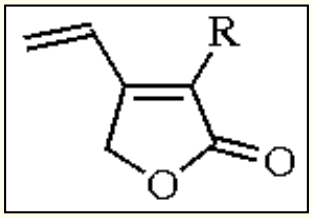

(R = H)

[54145-07-2] · $C_6H_6O_2$ · β-Vinyl-α,β-butenolide · (MW 110.12) (R = Me)

[78657-20-2] · $C_7H_8O_2$ · &AAlpha;-Methyl-β-vinyl-α,β-butenolide · (MW 124.15) (R = SPh)

[81470-07-7] · $C_{12}H_{10}O_2S$ · &AAlpha;-Phenylthio-β-vinyl-α,β-butenolide · (MW 218.29)

(lactone annulating reagent with 1,3-dicarbonyl compounds;[1,2] an acceptor in 1,6-conjugate addition reactions with various nucleophiles[3])

Alternate Name: 4-vinyl-2(5*H*)-furanone.

Physical Data: R = H, Me: oil. R = SPh: solid, mp 70 °C.

Solubility: sol CH_2Cl_2 and THF; slightly sol *n*-hexane.

Preparative Method: most conveniently prepared by sulfenylation of β-vinylbutyrolactone,[1,2,4] easily accessible from 2-butene-1,4-diol and ethyl orthoacetate,[5] followed by sulfoxide elimination (eq 1).

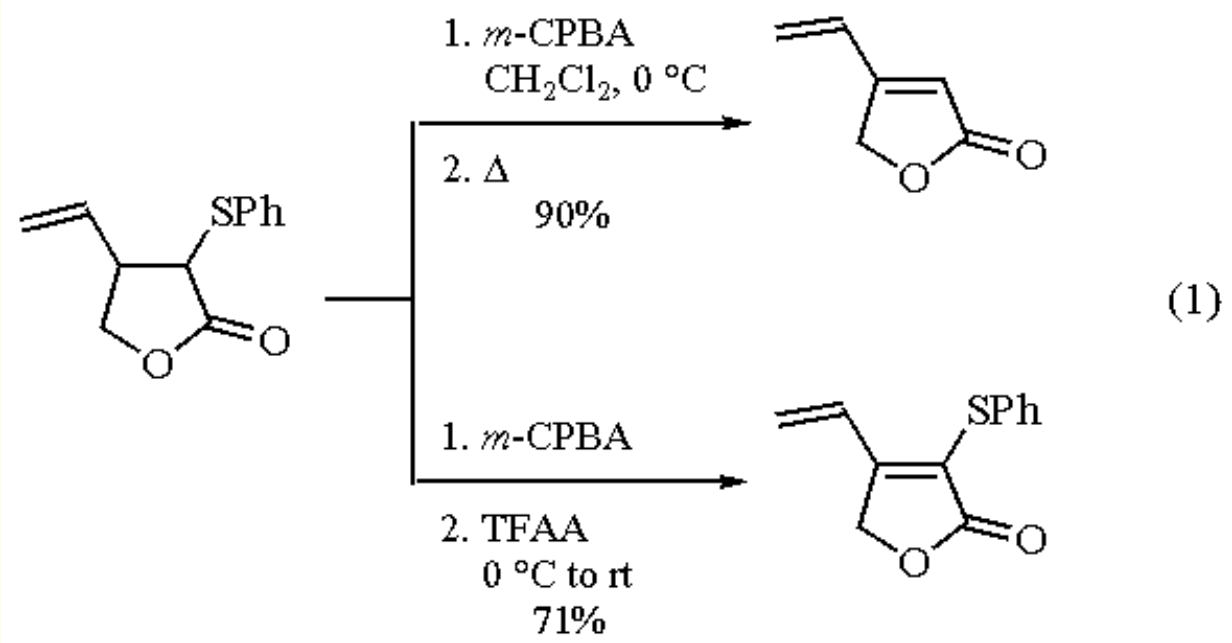

Handling, Storage, and Precautions: is relatively unstable, slowly changing into a polymeric white solid, even on refrigeration; however, α-phenylthio-β-vinylbutenolide is much more stable to storage.

Lactone Annulation.

Under basic conditions, 2-methylcyclohexane-1,3-dione adds to β-vinylbutenolide to give a 1,6-conjugate addition product, which then undergoes cyclization under the reaction conditions to yield hydroxybutenolides as a mixture of diastereomers at the C-6 position (eq 2).[1]

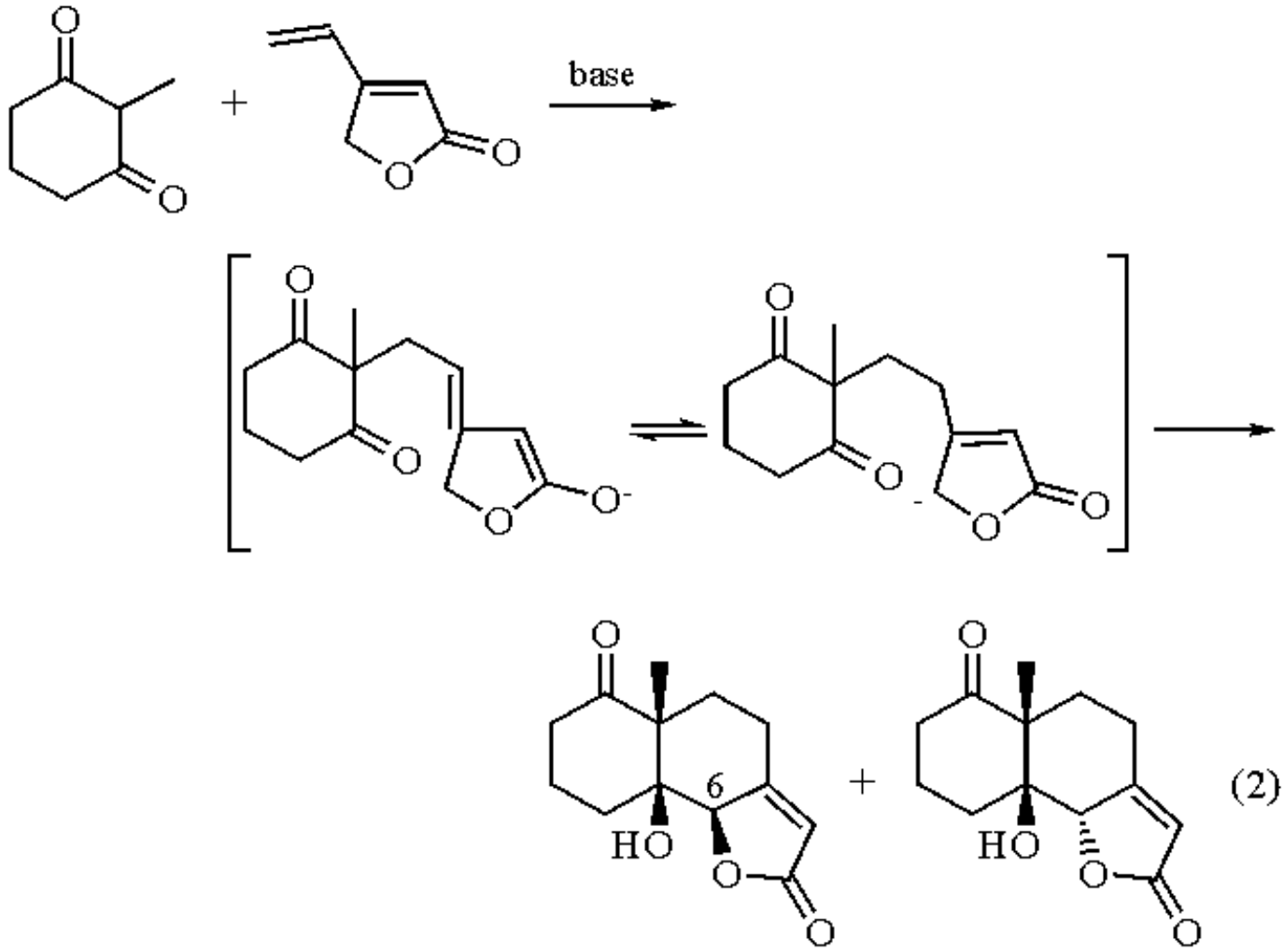

Na, THF	47%	11:1
t-BuOK, DME	22%	5:1
KF, DMSO	56%	5:1

When the sodium enolates of β-keto esters react with β-vinylbutenolide in THF or DME, annulated butenolides are produced in moderate yields (eq 3).[2] Racemic frullanolide, a typical allergenic eudesmanolide, has been synthesized from one of these annulated products.[2]

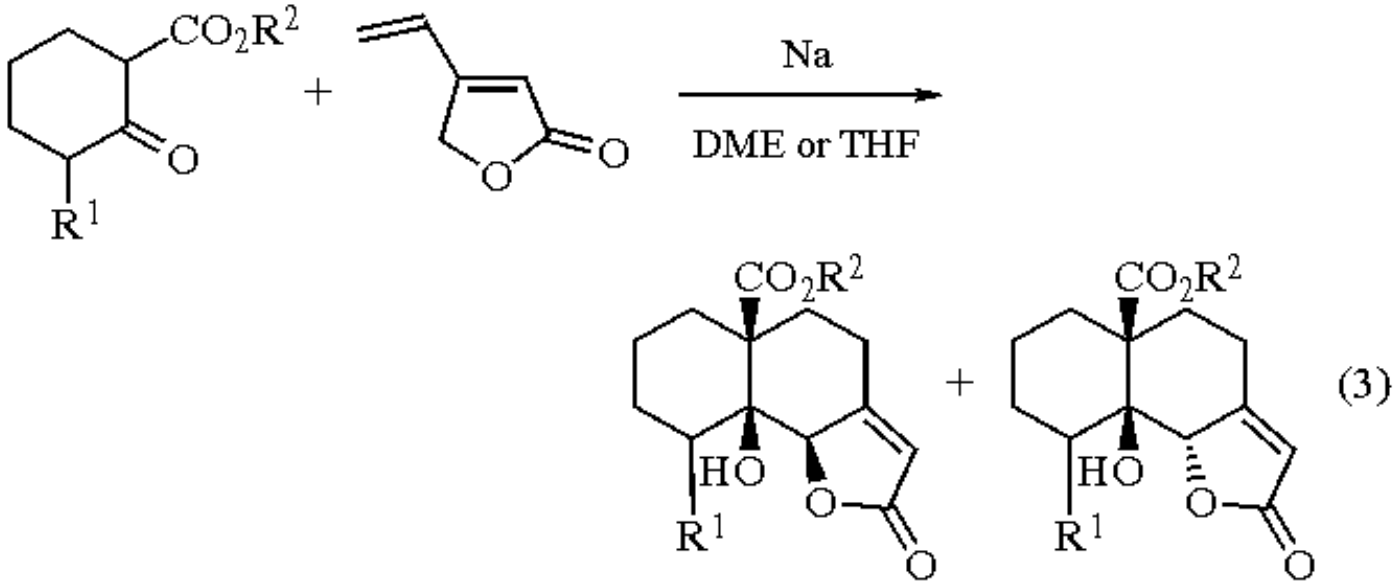

$R^1 = H$, $R^2 = Et$	57%	5:1
$R^1 = R^2 = Me$	51%	2:1
$R^1 = CO_2Me$, $R^2 = Me$	62%	0:1

1,6-Conjugate Addition.

β-Vinylbutenolide reacts with various nucleophiles in 1,6-conjugate addition reactions. For example, treatment of this butenolide with ***Benzeneselenol*** provides the 1,6-conjugate adduct, accompanied by a small amount of the isomeric 1,4-adduct (eq 4).[3]

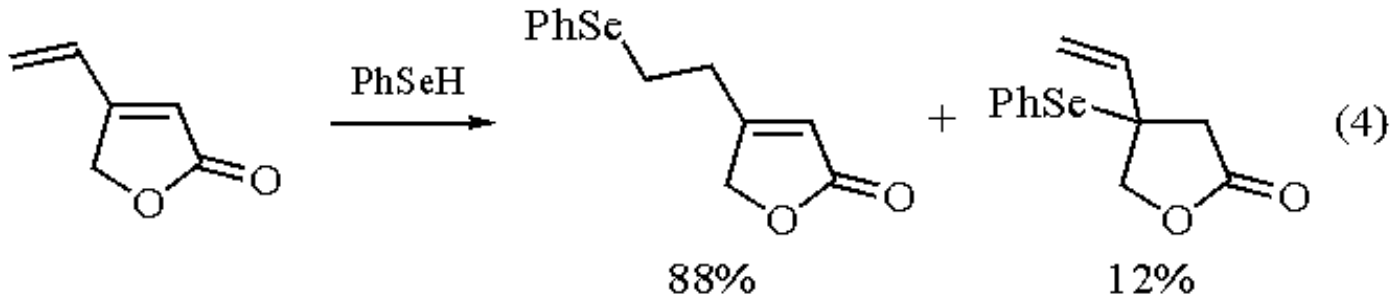

α-Phenylthio-β-vinylbutenolide.

This reagent is readily accessible from β-vinyl butyrolactone by an eliminative Pummerer rearrangement (eq 1). Annulation of activated carbonyl compounds affords oxygenated perhydrooxobenzofurans (eq 5).[6] The phenylthiobutenolide has been used in the total synthesis of paniculide A, a highly oxygenated bisabolene,[7] and avenaciolide, an antifungal mold metabolite.[8]

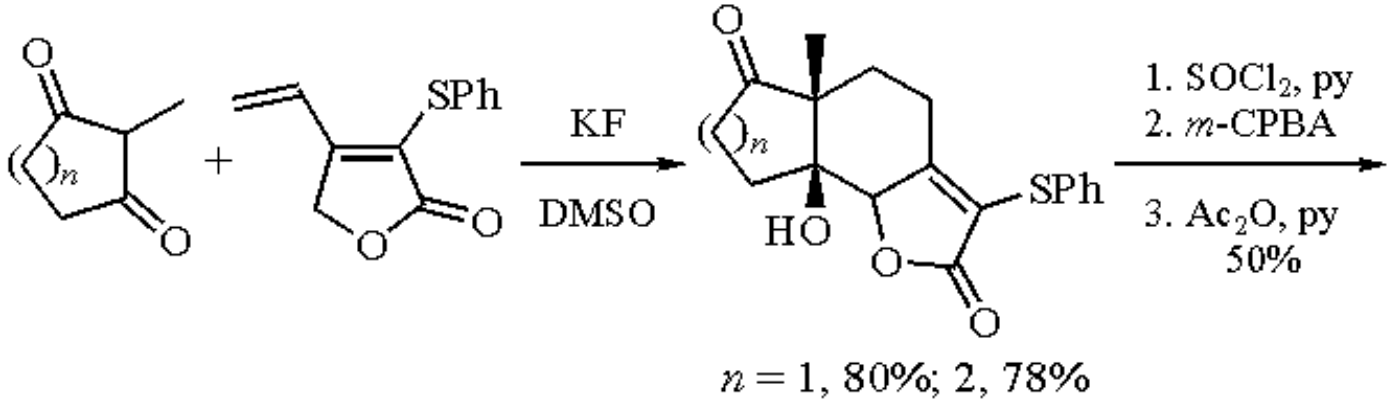

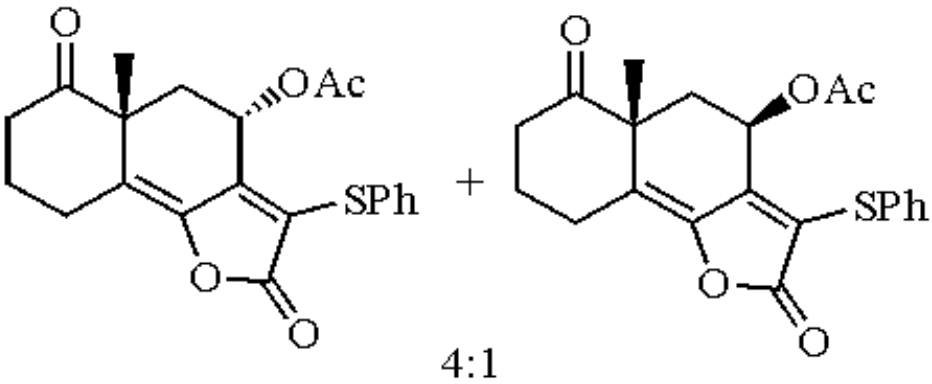

(5)

α-Methyl-β-vinylbutenolide.

This reagent is also useful for lactone annulating reactions with 1,3-dicarbonyl compounds under basic conditions.[9,10]

Related Reagents.

α,β-***Butenolide***; γ-***Butyrolactone***; ***1,3-Cyclohexanedione***; ***Dihydro-5-(hydroxymethyl)-2(3H)-furanone***; β-***Propiolactone***; β-***Ethynyl***-β-***propiolactone***; ***2-Trimethylsilyloxyfuran***.

---

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Vinyl Chloroformate

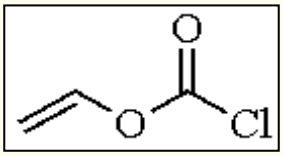

[5130-24-5] · $C_3H_3ClO_2$ · Vinyl Chloroformate · (MW 106.51)

(selective *N*-dealkylation of tertiary amines; amino protection in peptide synthesis; protection of alcohols; polymerization and polymers)

Alternate Names: vinyl chlorocarbonate; VOC-Cl.

Physical Data: bp 68-69 °C; *d* 1.163 g cm^{-3}.

Form Supplied in: colorless liquid, often stabilized with ca. 0.05% BHT; widely available.

Preparative Methods: the high price of VOC-Cl warrants some comments on its synthesis. Two processes have been used commercially. In the first, ethylene glycol is converted to its bis(chloroformate) with phosgene. This fragments to VOC-Cl in 30-40% yield when passed through a hot tube packed with glass helices at 480 °C.[1] More recently, VOC-Cl has been made commercially by a two-step route involving oxymercuration of vinyl acetate (eq 1).[2]

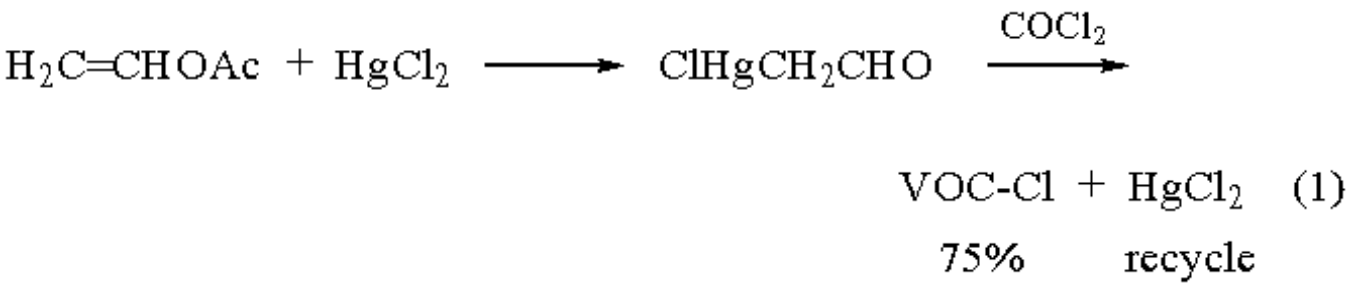

Handling, Storage, and Precautions: is slightly light-sensitive and even more reactive than other chloroformates toward trace moisture. Because the hydrolysis products, HCl and acetaldehyde, interfere in some applications, the reagent is often distilled before use. It is a strong lachrymator and skin vesicant; inhalation is particularly dangerous. Use in a fume hood.

Amino Protection in Peptide Synthesis.[3]

Amino acids are converted to their *N*-VOC derivatives by standard acylation with vinyl chloroformate (VOC-Cl), e.g. by Schnabel's pH-stat process.[4] Like Boc-amino acids, VOC-amino acids often are oils but can be characterized and stored as the crystalline dicyclohexylammonium (DCHA) salts and regenerated by acidification-extraction. The yields of VOC-peptides from the free acids or directly from the salts using ***1,3-Dicyclohexylcarbodiimide***, ***N-Ethyl-5-phenylisoxazolium-3´-sulfonate***, and active esters as the amide coupling agents are similar to those with other amine blocking groups (e.g. Boc-peptides). The crystalline products are stable and can be stored indefinitely (see Table 1).

Table 1 Representative *N*-VOC Amino Acids and Peptides

Amino acid or peptide	Mp (°C)
VOC Gly OH	95 95.5
VOC L-Phe OH	56 58
VOC L-Val OH DCHA	160 161.5
VOC L-Asn OH	157.5 158.5
VOC L-Hyp OH DCHA	179.5 181.5
VOC L-Glu(g-OMe) OH DCHA	155 156
VOC L-Ser(*O*-*t*-Bu) OH	97 97.5
VOC L-Lys(eBoc) OH DCHA	152 154
VOC L-Phe L-Leu OMe	107.5 108.5
VOC L-Glu(g-OMe) Gly OEt	88 89
VOC L-Asn Gly Gly OEt	190.5 192
VOC L-Pro L-Val L-Asn L-Leu *O*-*t*-Bu	216 (dec)
VOC L-Ser(*O*-*t*-Bu) L-Phe L-Leu *O*-Phenacyl	161 163

The high reactivity of the VOC amide C=C bond toward electrophiles is the key to the method used for deprotection.[3] Acid-induced hydrolysis with HCl or HBr in HOAc or by bubbling HCl through an inert solvent containing the peptide, followed by warming the intermediate HCl adduct in EtOH, affords the deblocked peptide salt in excellent yield. These procedures are mild enough to avoid transesterification of side chain esters (eq 2). Unmasking also can be achieved by titration of the vinyl group with Br_2 followed by warming the intermediate adduct with EtOH (eq 3). Under these conditions, Boc-protected secondary functions and *t*-butyl esters remain intact. A third scission with ***Mercury(II) Acetate*** in aqueous HOAc is rarely recommended. Carboxyl unmasking prior to removal of an *N*-VOC group can be performed with ***Zinc-Acetic Acid*** when the carboxyl is masked as a phenacyl ester. However, the VOC group is unstable to conditions required for modification-removal of most other esters (e.g. hydrazinolysis, saponification). The related isopropenyl chloroformate has no value in amine protection but is an excellent reagent of the mixed anhydride class for peptide amide bond formation (eq 4).[5]

$$\text{VOC-L-Glu}(\gamma\text{-OMe})\text{-Gly-OEt} \xrightarrow[\text{2. EtOH, }\Delta]{\text{1. HCl, }CH_2Cl_2} \text{HCl} \cdot \text{H-L-Glu}(\gamma\text{-OMe})\text{-Gly-OEt} \quad (2)$$

95%

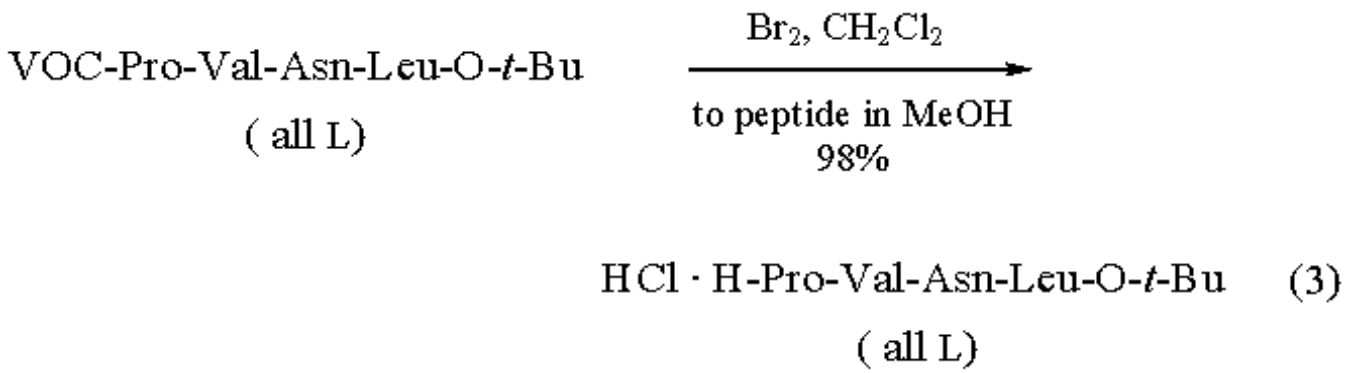

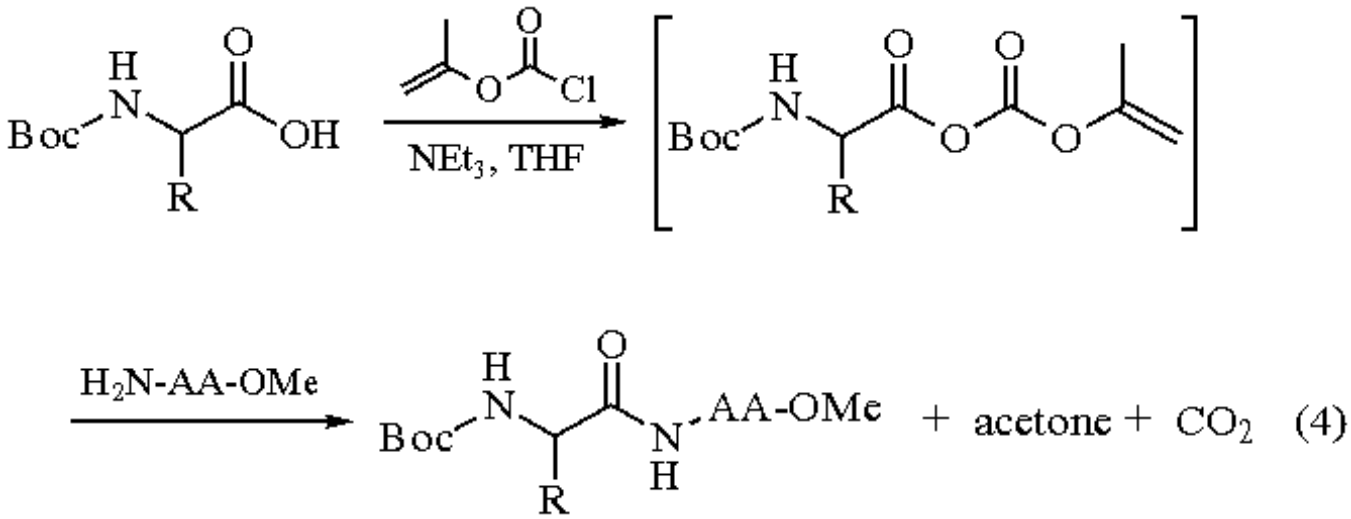

N-Dealkylation of Tertiary Amines.

The *N*-dealkylation procedure is illustrated by the selective *N*-deethylation of *N*-ethylpiperidine to obtain piperidine.HCl in 90% yield (eq 5).[6] The VOC-Cl is added to the piperidine in dichloroethane at 0 to -20 °C and the intermediate VOC-piperidine salt is then heated to reflux for a short period to obtain the intermediate carbamate. This can be isolated, but the VOC moiety usually is quantitatively removed in situ by bubbling HCl through a CH_2Cl_2 or 1,2-dichloroethane (DCE) solution and then warming the adduct in MeOH or EtOH, or by titrating the vinyl group with Br_2 and then again warming in the alcohol. Among other dealkylating agents which operate by the same principle, ***Cyanogen Bromide*** (method of von Braun) is not selective in this rigorous test system and the amine catalyzes the self-destruction of ethyl and benzyl chloroformate [ROC(O)Cl -> RCl + CO_2].[7] With phenyl chloroformate, the yield of carbamate under similar conditions is only 34%.

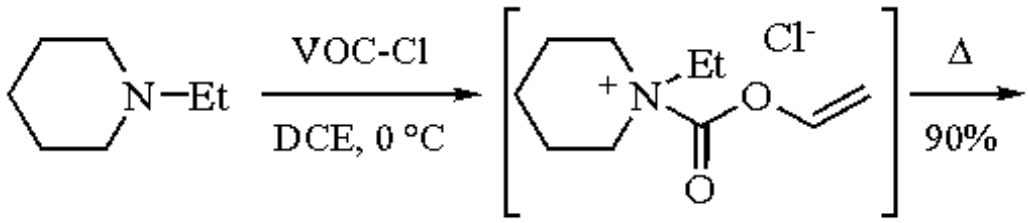

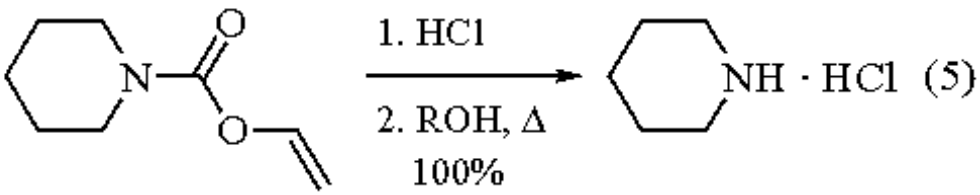

With VOC-Cl, *N*-dealkylation selectivities follow the order: benzyl, allyl, *t*-alkyl >> *s*-alkyl &egt; methyl > *n*-alkyl >> piperidine ring scission.[6,8] Weakly basic tertiary amines like *N*,*N*-dimethylaniline do not react with VOC-Cl even in refluxing DCE. Some examples of *N*-dealkylations accomplished with VOC-Cl include the *N*-demethylation of alkyl amines (eq 6)[9] and other *N*-alkylpiperidines (eq 7).[10,11] Note in eq 7 that the *N*-VOC is removed by base hydrolysis. This dealkylation process also is part of an asymmetric synthesis of α-amino esters (eq 8),[12] as well as the key step of a protocol for resolving tertiary amine enantiomers.[13] Also, VOC-Cl-induced dealkylation permits an improved synthesis of the emergency heroin antidote naloxone from oxymorphone (eq 9).[6,14] Vinyl chloroformate largely has been replaced for *N*-dealkylation by ***1-Chloroethyl Chloroformate***. This latter reagent is cheaper and shows similar dealkylation selectivities and equally facile replacement of the *N*-

alkyl by the carbamate unit.

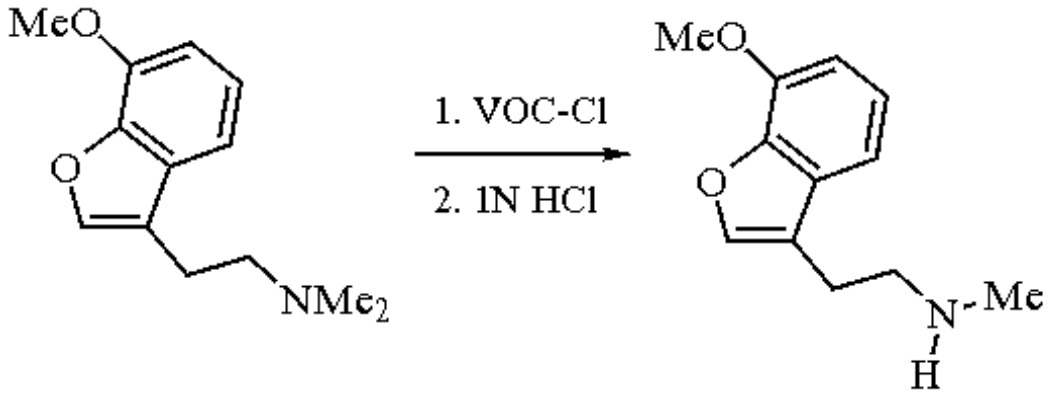

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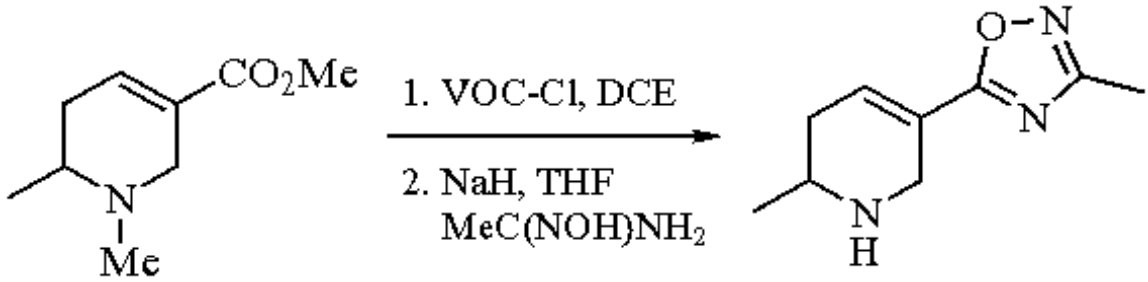

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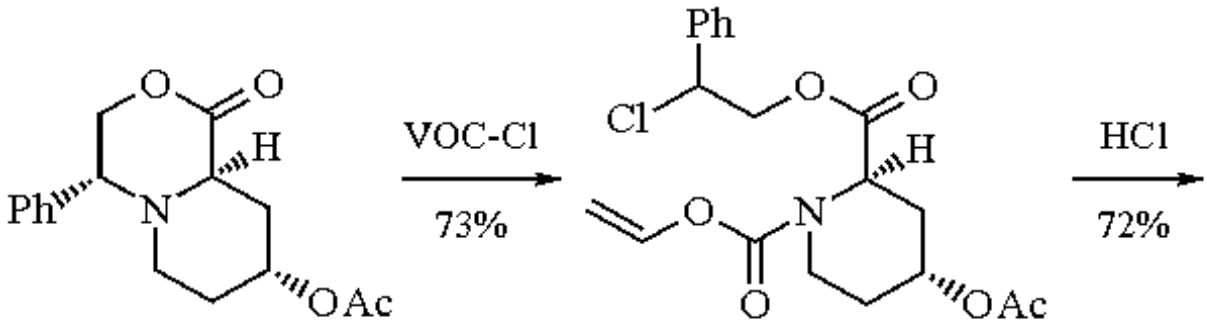

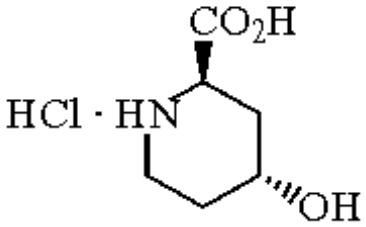

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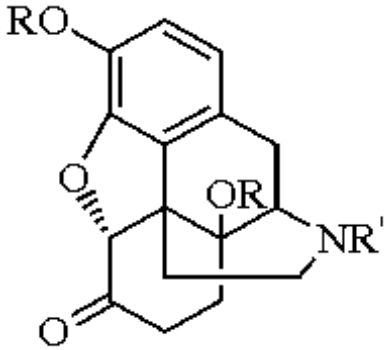

A: R = H, R' = Me (oxymorphone)
B: R = Ac, R' = Me
C: R = Ac, R' = H · HCl
D: R = R' = H
E: R = H, R' = allyl (naloxone)

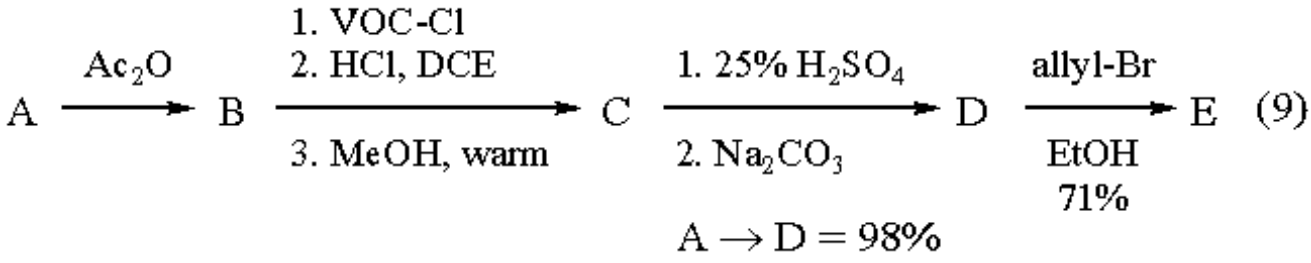

Protection of Alcohols.

Vinyloxycarbonyl esters (*O*-VOC) of phenols and alcohols are prepared from VOC-Cl by standard methods.[15] Unlike VOC derivatives of amines, *O*-VOC esters are quite stable in acid but are readily hydrolyzed in mild base, conditions under which *N*-VOC is stable (eq 10).[15] This reactivity-selectivity difference can be useful in complex syntheses involving the simultaneous protection of both amine and alcohol functions with a single blocking moiety, while retaining the flexibility to modify either site without deprotecting the other. In related blocking schemes, attempts to free the amine first usually fail because esters are generally easier to hydrolyze than amides in both acid and base. The value of this selectivity in combination with *N*-dealkylation by VOC-Cl is illustrated in a synthesis of nalorphine, the classic narcotic antagonist, from morphine in 77% overall yield (eq 11).[15]

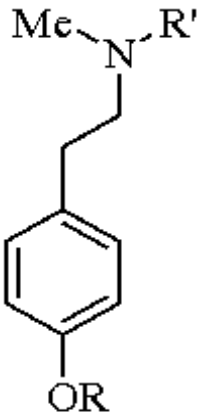

A: R = H, R' = Me
B: R = R' = VOC
C: R = VOC, R' = H · HCl
D: R = H, R' = VOC

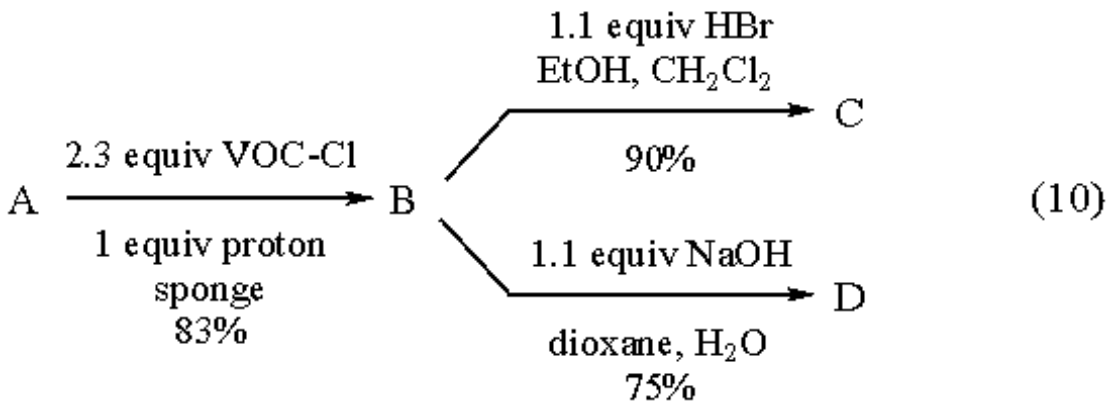

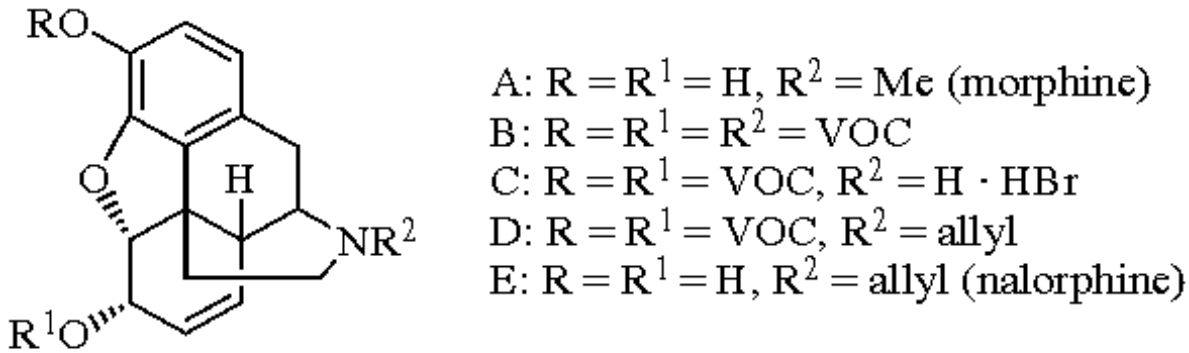

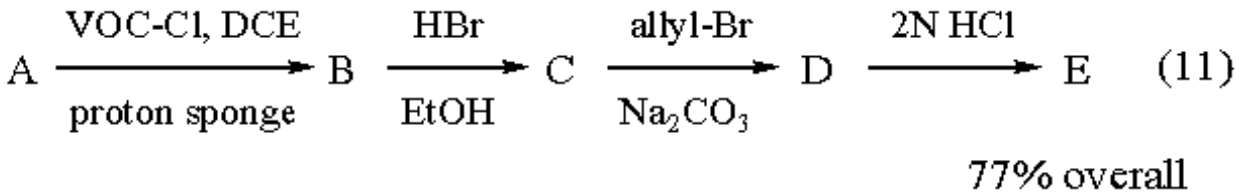

Polymerization and Polymers.

Vinyl chloroformate has been polymerized and copolymerized using standard radical initiators (e.g. peroxydicarbonates, ***Dibenzoyl Peroxide***, and ***Azobisisobutyronitrile***) to yield both high molecular weight poly(vinyl chloroformates) and random copolymers.[16,17] The polymerization is inhibited by traces of acetaldehyde. Treatment of poly(vinyl chloroformate) with amines, alcohols, and phenols affords the corresponding poly(vinyl urethanes) and poly(vinyl carbonates).[16,18] Urethanes and carbonates of VOC-Cl also can be polymerized to similar materials with radical initiators.[16-19] These materials are hard (but not brittle) clear thermoplastics with high decomposition temperatures, excellent chemical resistance, and varying glass transition temperatures.[18] Some products have value as liquid crystals[20] and detergent builders.[21] The divinyl carbonate polymerizes an order of magnitude more easily than the diallyl carbonate to a product of similar properties.[19] Polymers of carbonates of VOC-Cl and dermal drugs (e.g. benzocaine, estradiol, dexamethasone, and hydrocortisone) are recommended as hydrolyzable pro-drugs for topical use.[22]

Pummerer and Other Reactions.

Sulfoxides react with VOC-Cl to give α-chloro sulfides via the Pummerer rearrangement (eq 12). Vinyl chloroformate is more reactive than the conventional reagents, including acetic anhydride, acyl chlorides, and alkyl chloroformates. Additionally, the reaction conditions are neutral and the byproducts are readily removed.

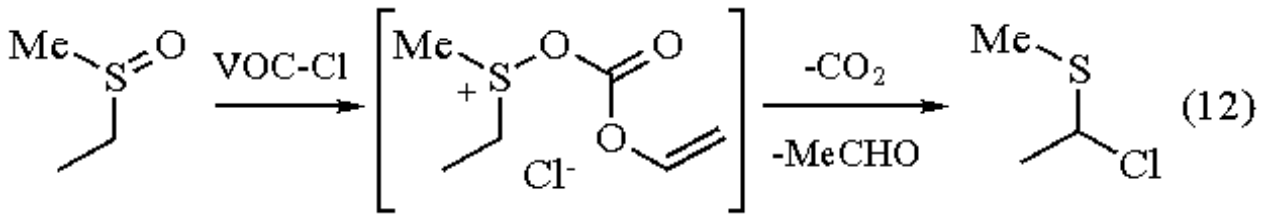

The reaction of penicillin β-sulfoxide with VOC-Cl induces a novel rearrangement which involves cleavage of the C-5-S bond (eq 13).[23] Reaction of imidazoles with VOC-Cl in weakly alkaline solution affords the corresponding imidazol-2-ones, presumably via ring opening to the isocyanate intermediate, followed by ring closure (eq 14).[24]

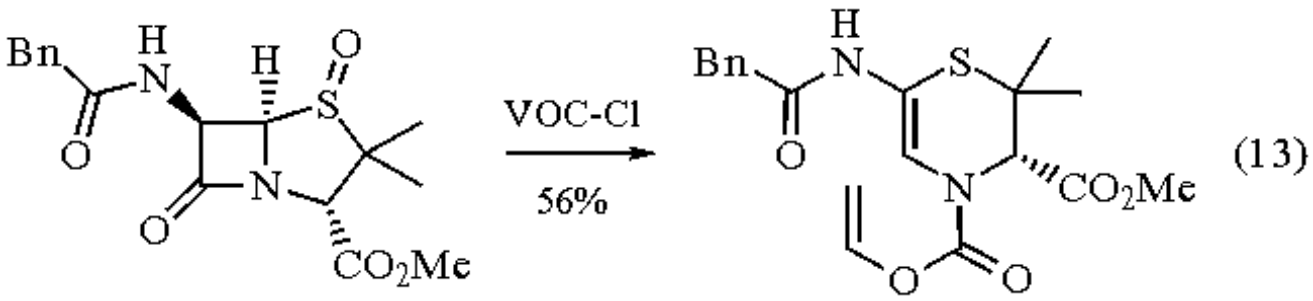

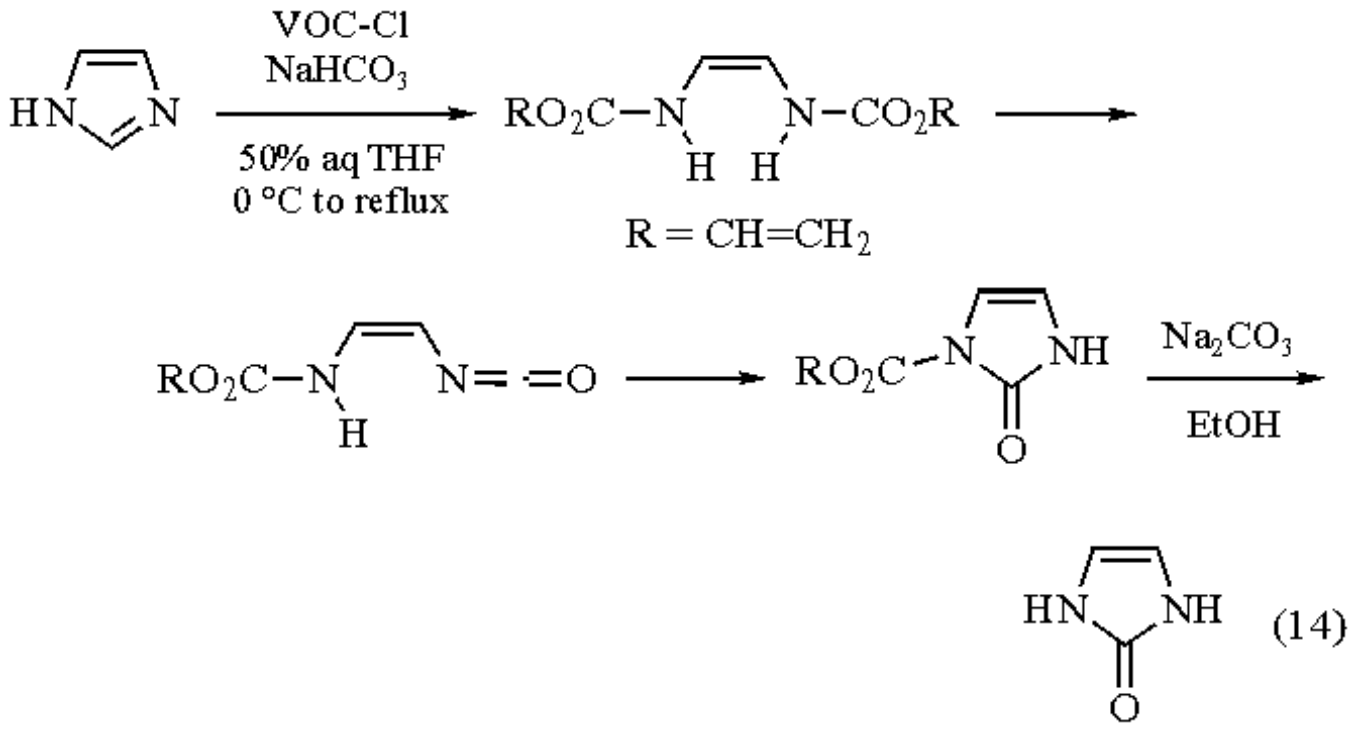

(14)

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Vinylcopper[1]

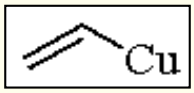

[37616-22-1] · C_2H_3Cu · Vinylcopper · (MW 90.60)

(synthesis of 1,3-dienyl esters;[2] vinyl 1,4-addition to alkynic esters[3] and enones[4])

Alternate Name: ethenylcopper.

Preparative Methods: by the reaction of ***Vinyllithium*** or vinylmagnesium halides and a copper(I) salt.

Handling, Storage, and Precautions: sensitive to air and moisture; dimerization occurs above 0 °C. Use in a fume hood.

General Discussion.

Vinylcopper was initially prepared from ***Vinylmagnesium Chloride-Copper(I) Chloride*** in THF;[5] warming the solution of vinylcopper from -40 to 20 °C results in the formation of 1,3-butadiene. ***Lithium Divinylcuprate*** was reported by House and co-workers in 1969 and shown to undergo 1,4-addition reactions with enones in very good yields.[6] However, in attempts to synthesize 1,3-dienes by the addition of lithium divinylcuprate to alkynic esters, stereochemical mixtures of double bond isomers are obtained. Corey and Chen[2] discovered that vinylcopper, prepared by the addition of 1 equiv of ***Vinyllithium*** to ***Copper(I) Iodide***-diisopropyl sulfide in ether at -78 °C, efficiently adds to alkynic esters to provide the 1,3-diene product with nearly complete stereochemical control (eq 1). Vinylcopper addition to higher homologues of alkynic esters also provides the 1,4-adduct with complete stereocontrol.[3]

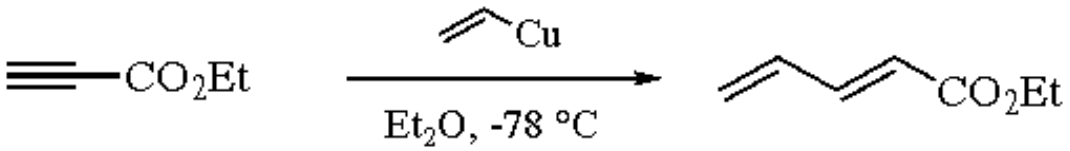

(1)

1,6-Addition of vinylcopper to 1,3-dienyl esters is also carried out at -78 to -20 °C. Quenching the reaction mixture with methanol at -20 °C provides the 3,6-heptadiene esters in greater than 95% stereochemical purity (eq 2).[2] The same reaction with lithium divinylcuprate results in a 45:55 mixture of (*E*) and (*Z*) isomers of the 3,4-double bond. Vinylcopper reagents do not readily add to γ-substituted unsaturated esters.[6] For example, no 1,4-addition of vinylcopper is observed with ethyl 4-benzyloxy-2-pentenoate. However, diastereoselective addition to a doubly activated ester does occur in reasonable yield to provide the *anti* diastereomer as the major product (eq 3). Higher yields of the 1,4-addition product are observed for lithium divinylcuprate and the corresponding higher order cyanocuprate, but the diastereoselection does not improve. The reduced reactivity of the neutral vinylcopper species prepared from ***Vinylmagnesium Bromide*** and ***Copper(I) Bromide***-dimethyl sulfide complex in THF, in comparison to that of the corresponding lithium homocuprate reagent, is advantageous in providing the 1,4-addition product in reactions with acetylenedicarboxylates.[7] Cuprate reagents tend to provide low yields of the product due to competing polymerization. Vinylcopper also readily adds to 1-alkynyl sulfoxides to form vinyl sulfoxides in high yields.[8] A useful method for the stereospecific formation of *cis*-β-substituted alkenylcopper reagents is the addition of organocopper reagents to alkynes.[9,10] The substituted vinylcopper reagent obtained in this fashion may react with a second equivalent of the same alkyne or a different alkyne to form a new vinylcopper species, or may react with an alkyl halide in the presence of HMPA.[9a] The vinylcopper reagents prepared from alkynes can also be transformed to vinyl iodides,[9b] or carbonylated[9c] with retention of double-bond stereochemistry.

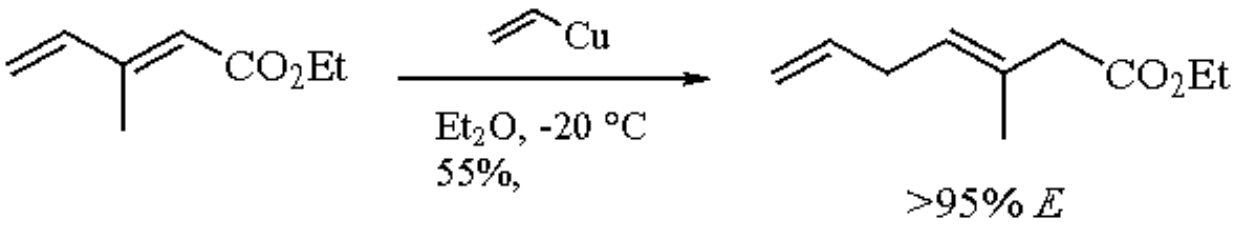

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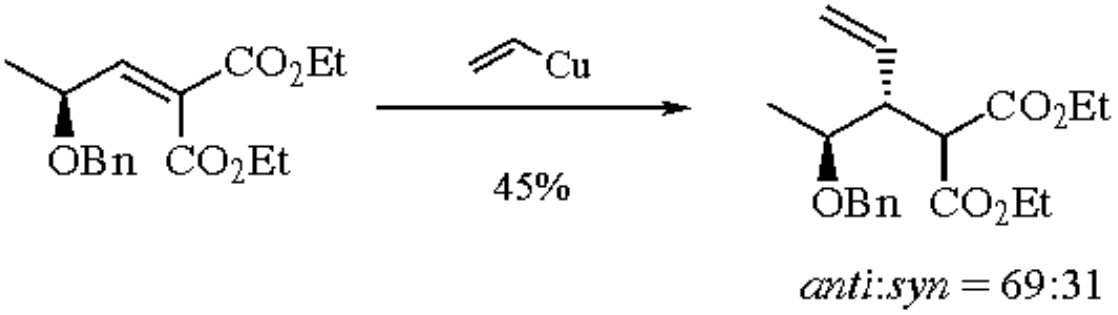

(3)

β-Substituted vinylcopper reagents derived from alkynes are also not as reactive as cuprate reagents and do not undergo 1,4-addition to enones readily. The initially formed vinylcopper species can be transformed into the more reactive cuprate by addition of an equivalent of a nontransferable ligand. Epoxides, aldehydes, and unsaturated ketones or esters can then all be used as electrophiles in subsequent reactions.[9d] β-Substituted enones are recalcitrant to 1,4-addition of vinylcopper or lithium divinylcuprate. Successful 1,4-addition of a vinyl group to isophorone is achieved only upon the addition of ***Tri-n-butylphosphine*** (eq 4).[11] Noyori and co-workers devised an efficient three-component coupling route to the prostaglandins which involves the tributylphosphine-promoted conjugate addition of neutral vinylcopper reagents to cyclopentenones.[4] A similar approach to the stereocontrolled synthesis of sterols employs a vinylcopper/tributylphosphine conjugate addition reaction (eq 5).[12] The obvious advantage of the organocopper reagents over the corresponding homocuprate reagents in the synthesis of prostaglandins and sterols is the fact that only 1 equiv of the vinyl group is required. Generation of the higher order cyanocuprate from 2 equiv of vinyllithium and ***Copper(I) Cyanide*** provides the most useful reagent for conjugate addition reactions.[1c]

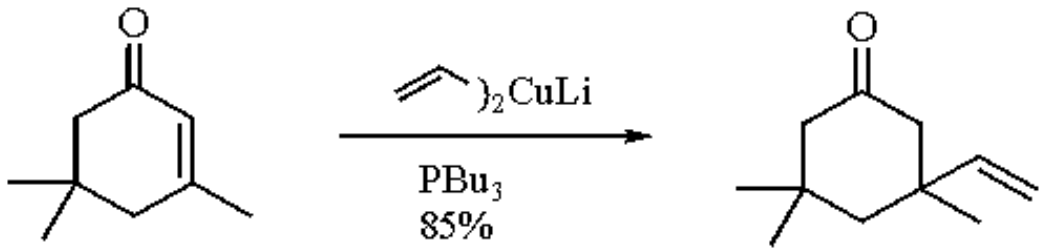

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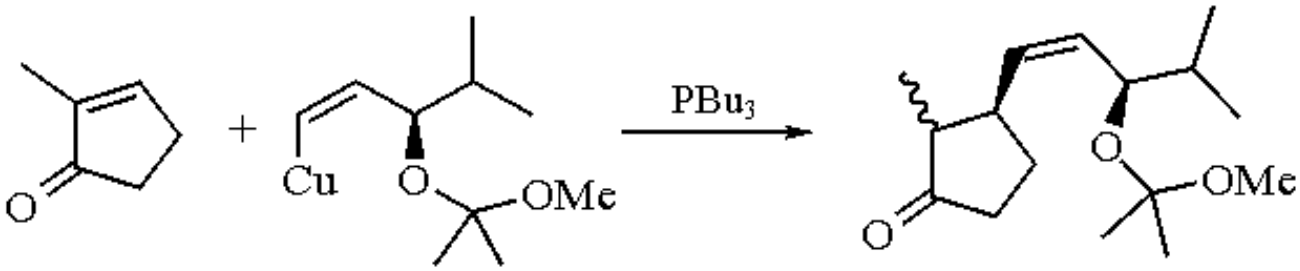

(5)

The stereoselective synthesis of dienes has also been accomplished by palladium-catalyzed coupling of neutral vinylcopper derivatives with iodoalkenes.[13] Substitution reactions of allenyl iodides by vinylcopper produces nonconjugated enyne ethers which are not readily accessible by other methods (eq 6).[14] Conjugated enynes have been prepared by trapping the vinylcopper reagent obtained by alkylcopper addition to an alkyne with alkynylphenyliodonium tosylates (eq 7).[15] The alkene geometry is maintained in the alkynylation reaction.

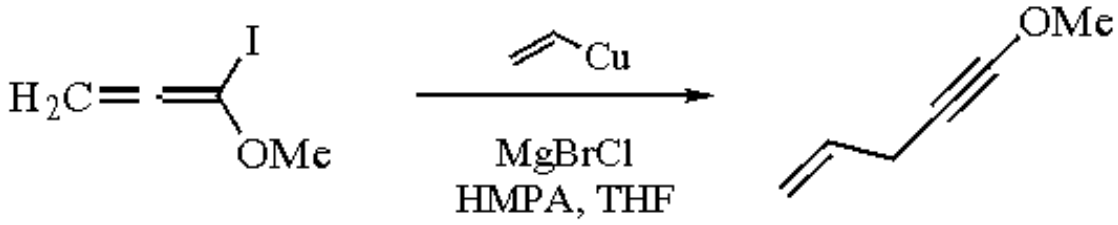

(6)

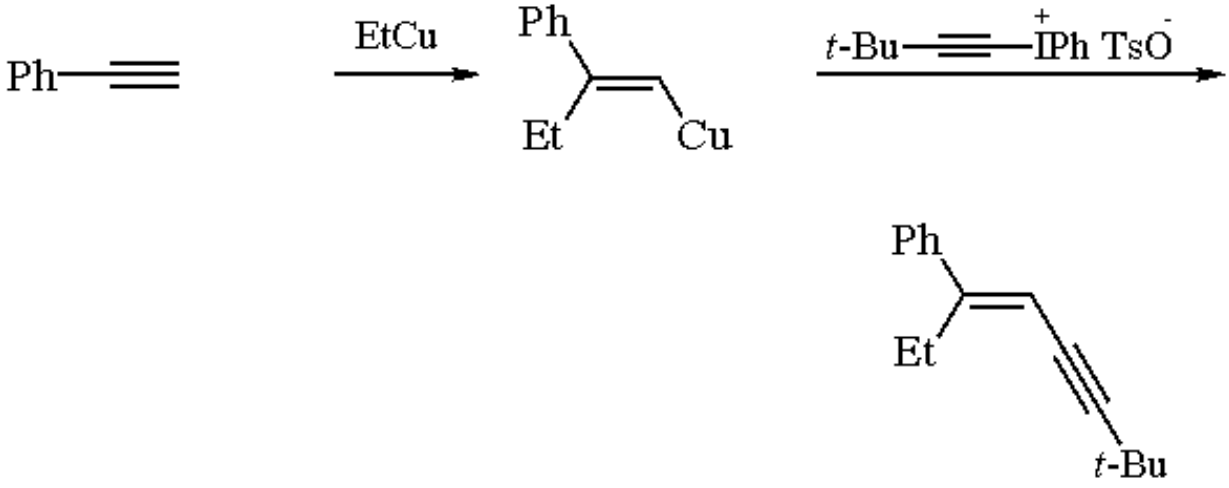

(7)

Related Reagents.

3,3-Diethoxy-1-propen-2-ylcopper; ***Lithium Divinylcuprate***; ***Lithium Divinylcuprate-Tributylphosphine***; ***1-(Trimethylsilyl)vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Chloride-Copper(I) Chloride***.

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Vinylene Carbonate

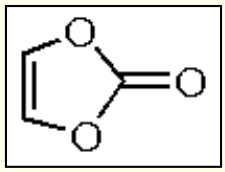

[872-36-6] · $C_3H_2O_3$ · Vinylene Carbonate · (MW 86.05)

(reacts as a dienophile[1-4] and a dipolarophile;[5-11] participates in *meta* cycloadditions[12,13] and other radical reactions[14])

Alternate Name: VC; 1,3-dioxol-2-one.

Physical Data: mp 22 °C; bp 165 °C; *d* 1.36 g cm^{-3}.

Solubility: sol Et_2O, benzene.

Form Supplied in: colorless liquid (97%), stabilized with BHT.

Handling, Storage, and Precautions: avoid contact with skin and eyes; do not breathe vapor; cancer-suspect agent. This reagent should only be used in a fume hood.

Introduction.

Since its first synthesis from ethylene carbonate, via a photochemical chlorination-dehydrochlorination sequence (eq 1),[1] vinylene carbonate (**1**) has been widely used in several thermal[15] and photochemical reactions.[16]

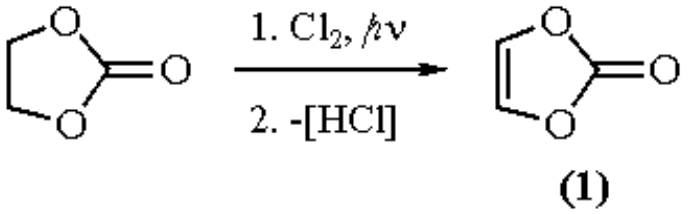

(1)

Diels-Alder Reactions.

Though reputedly a poor dienophile, VC, being a symmetrical dioxygenated alkene, has been frequently employed as a 2π participant in Diels-Alder reactions.[2] A [4 + 2] cycloaddition of isobenzofuran and vinylene carbonate takes place under mild conditions and leads to the formation of a highly oxygenated tetrahydronaphthalene (eq 2).[3] A thermal reaction between 2,4-dimethylfuran and VC provides a 7:5 mixture of cycloadducts which have been used in the total synthesis of naturally occurring citreoviral (eq 3).[4]

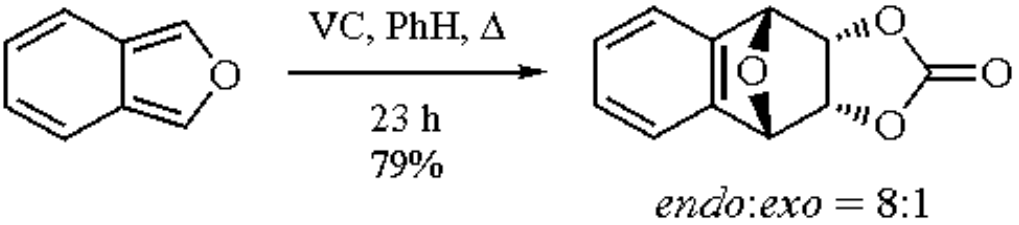

(2)

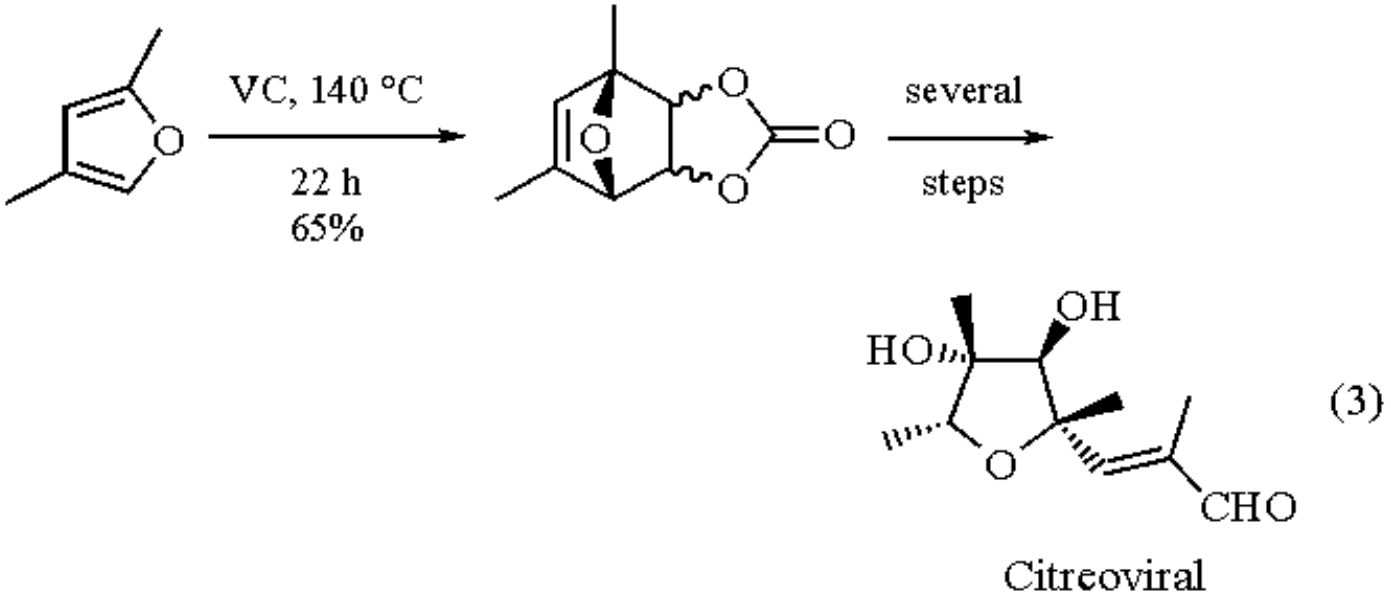

1,3-Dipolar Cycloaddition Reactions.

Whereas vinylene carbonate has been reported to be virtually unreactive towards nitrile oxides,[5] its reactivity with other 1,3-dipoles presents appealing syntheses of heterocycles.[6] The reaction of VC with hydroximic acid hydrochlorides, for instance, results in the formation of isoxazolines in modest yields (eq 4).[7]

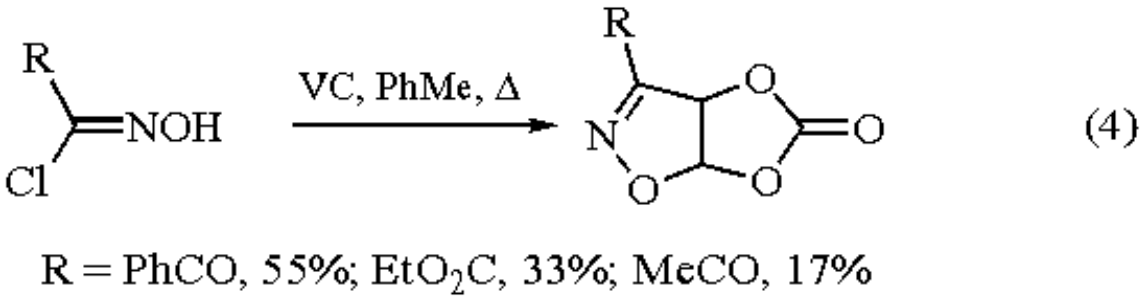

There are reports that the dipolar cycloaddition reactions of nitrones (both cyclic and open-chain) with VC lead to the formation of mixtures of *endo*- and *exo*-adducts.[8] However, nitrones bearing a chiral center on the carbon substituent of a nitrone undergo *endo* additions with achiral dipolarophiles.[9] This chemistry leads directly to the formation of masked α-hydroxy aldehydes and presents an attractive route for preparing amino sugars from noncarbohydrate precursors. Thus the [3 + 2] reaction of nitrone (**2**) and VC leads to a 1:1 diastereomeric mixture of products (both *endo*) which are readily converted into acylated derivatives of epigentosamines (eq 5).[10] A thermal dipolar reaction of an azomethine ylide with VC leads to the formation of highly functionalized pyrrolidines (eq 6).[11]

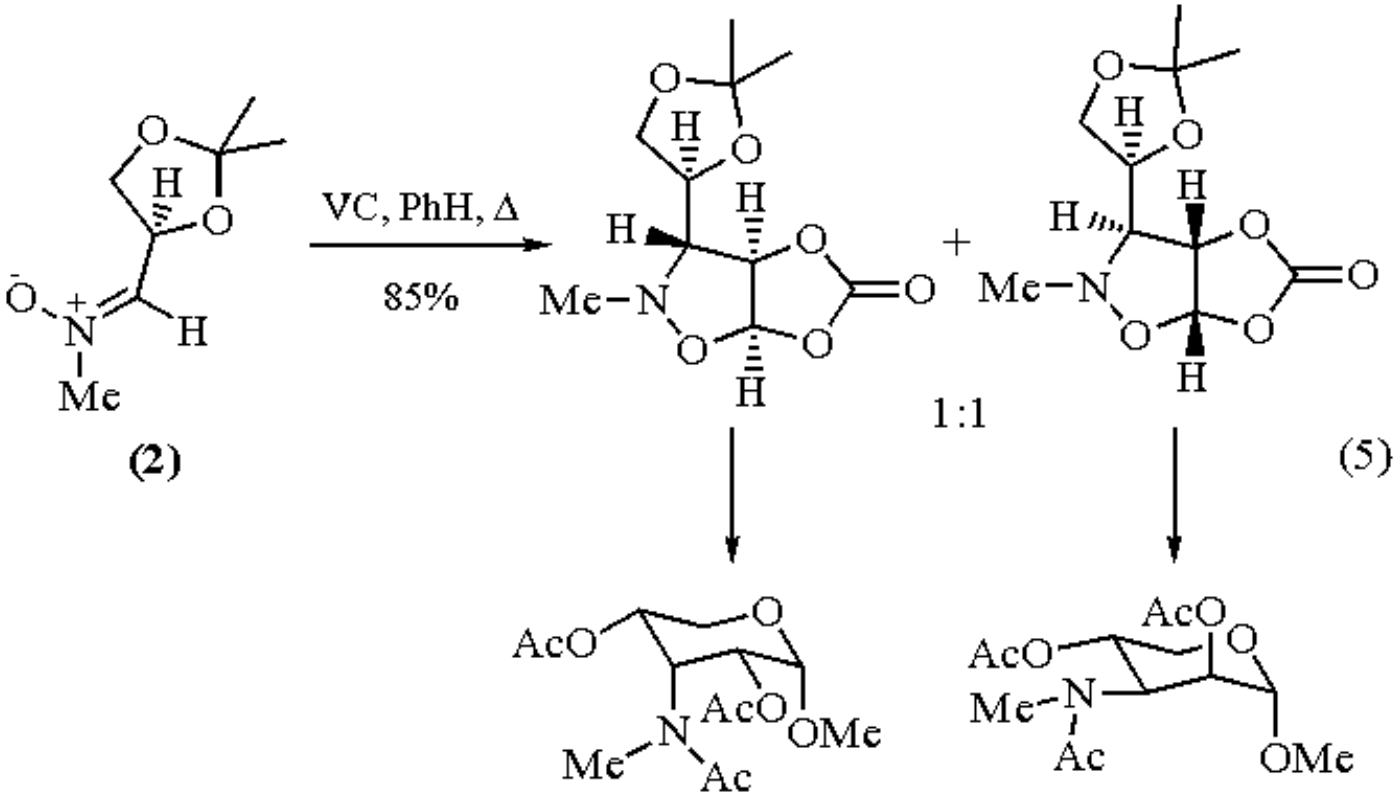

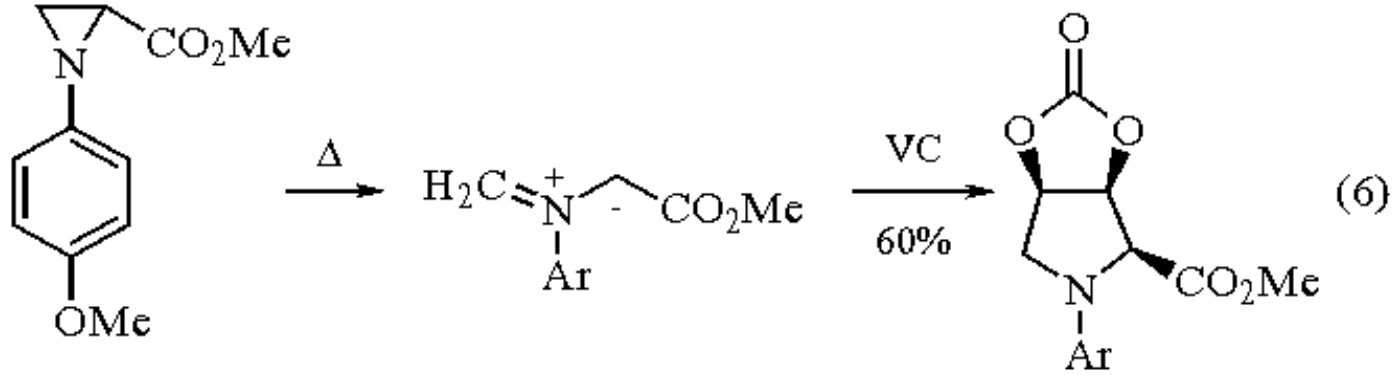

Meta Cycloadditions.

Arenes react with VC, under photochemical conditions, to provide *meta* cycloadducts.[12] The photoaddition of VC and anisole provides *meta* adducts in a 65:35 ratio (*endo*/*exo*) and some *ortho* adducts (~30%) are also observed. The reaction with benzonitrile, however, provides a regioisomeric mix of only *endo-meta* adducts.[13]

---

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Vinyllithium[1]

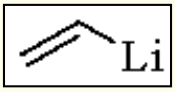

[917-57-7] · C_2H_3Li · Vinyllithium · (MW 33.99)

(introduction of vinyl groups[2,3])

Physical Data: white solid; no melting point; decomposes upon heating. The ^1H,[4] ^{13}C,[5] and ^7Li NMR[6] and UV-vis[7] spectra of vinyllithium have all been recorded.

Solubility: sol THF, ether; slightly sol pentane, hexane;[8] insol benzene.[9]

Analysis of Reagent Purity: determined by simple acid titration,[8] by reaction with vanadium pentoxide followed by titration with standard permanganate solution,[10] by hydrolysis followed by measurement of ethylene evolution,[11] or by the Gilman procedure.[12]

Preparative Methods: prepared by a variety of methods. Direct metalation of ***Ethylene*** with ***Lithium*** metal in dimethoxymethane yields vinyllithium contaminated with lithium hydride, and other organolithio species, such as butyllithium and 1,4-dilithiobutane.[13] Direct formation from ethylene can also be accomplished using ***Potassium t-Butoxide***, ***n-Butyllithium***, and TMEDA (***N,N,N´,N´-Tetramethylethylenediamine***) in hexane at -40 °C, followed by treatment of the vinylpotassium with ***Lithium Bromide***.[14] The lithium-halogen exchange reaction has been used, starting from vinyl chloride and lithium/sodium dispersions,[10,12] or from vinyl bromide with 2 equiv of ***t-Butyllithium*** in either a Trapp solvent mixture at -120 °C[15,16] or ether at -78 °C.[17] This is the most convenient procedure, but lithium halide is formed during the reaction and is present as a contaminant. Halide-free vinyllithium can be prepared by transmetalation of ***Tetravinylstannane*** with phenyl- or butyllithium,[8] of tetravinyllead with either lithium metal or ***Phenyllithium***,[9] or of divinylmercury with lithium dispersion in pentane.[11]

Purification: ether solutions can be evaporated under an inert atmosphere and the resulting solid washed with anhydrous pentane or hexane.

Handling, Storage, and Precautions: as with most alkyllithium reagents, vinyllithium reacts readily with moisture. Solid vinyllithium should be maintained at -25 °C or below, under an inert atmosphere. The solid suffers a loss in activity with time and should be used immediately upon preparation.[9] Solutions of the reagent in ether or THF, under an inert atmosphere, are stable for up to 1 week at rt.[8] Solid vinyllithium is violently pyrophoric, yielding a brilliant red flash on contact with air.[9]

Vinyl Reagents.

Vinylcuprates are easily assembled from the reaction of vinyllithium and copper species. ***Lithium Divinylcuprate*** (eq 1) has been prepared from vinyllithium using the dimethyl sulfide complex of a copper(I) halide,[18] or from ***Copper(I) Cyanide***.[19] Mixed cuprates are available by the addition of vinyllithium to (2-thienyl)Cu(CN)Li,[20] $(MeCu)_n$,[18] or ***1-Pentynylcopper(I)***.[21] In all the mixed cuprates the vinyl ligand is preferentially transferred.

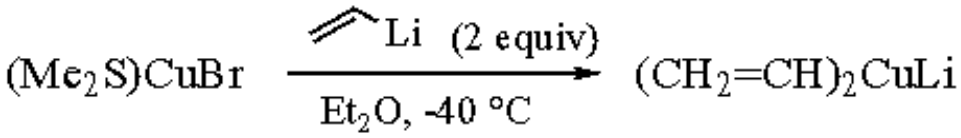

(1)

Vinylsilanes can be prepared by reaction of a silyl halide with vinyllithium.[22] Alternatively, the reaction of ***Bis(trimethylsilyl) Peroxide*** with vinyllithium yields an 80:20 mixture of ***Vinyltrimethylsilane*** and the trimethylsilyl enol ether (eq 2).[23] Use of the corresponding vinyl Grignard reagent produces exclusively the enol ether.

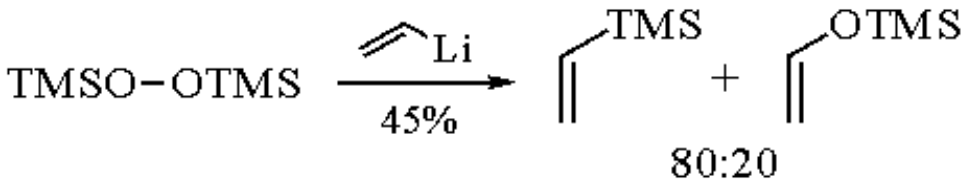

(2)

Trialkylvinylborates can be prepared by the treatment of trialkylboranes with vinyllithium in ether at 0 °C.[24] Use of a vinyl Grignard reagent to form the vinyl borate leads to lower yields in subsequent reactions. Dimesitylvinylborane is synthesized by lithium-halogen exchange of vinyllithium with fluorodimesitylborane.[25] Dialkyl disulfides[15] or diphenylphosphinodithioates (**1**)[26] react with vinyllithium to produce vinyl alkyl, or aryl, sulfides in good yields (eq 3).

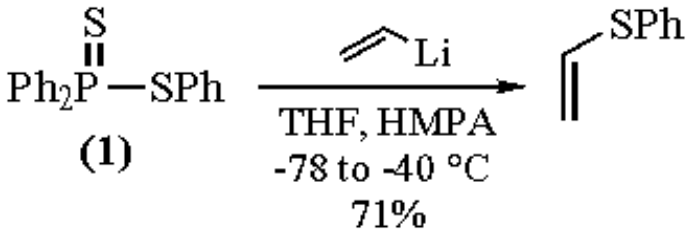

(3)

Ring Formation Reactions.

Vinyllithium reacts with carbonyl compounds, providing a convenient method for the introduction of a double bond for subsequent ring formation. Addition to a vinyl-substituted cyclobutanone, followed by treatment with ***Potassium Hydride***, gives the *cis*- and *trans*-cyclooctenones in 62% yield after Cope rearrangement (eq 4).[2] The vinyllithium addition yields only one diastereomer according to NMR and HPLC analysis. Similar sigmatropic reactions have been used in bicyclic systems. Vinyllithium adds to the carbonyl in bicyclo[3.2.0]heptan-6-ones (eq 5) which, when subsequently treated with potassium hydride, undergo a [1,3]-sigmatropic rearrangement of the 1-vinylcyclobutanols to yield the ring expanded product (**2**).[27] An oxy-Cope rearrangement has been used to construct bicyclo[5.3.1]undecenones after addition of vinyllithium to bicyclo[3.1.1]heptan-6-ones.[28] An intramolecular Diels-Alder reaction has been used to construct Isomer G, a component of thujopsene. The addition of vinyllithium to the acid (**3**) produces the precursor for the Diels-Alder cyclization (eq 6).[29] Further elaboration leads to Isomer G.

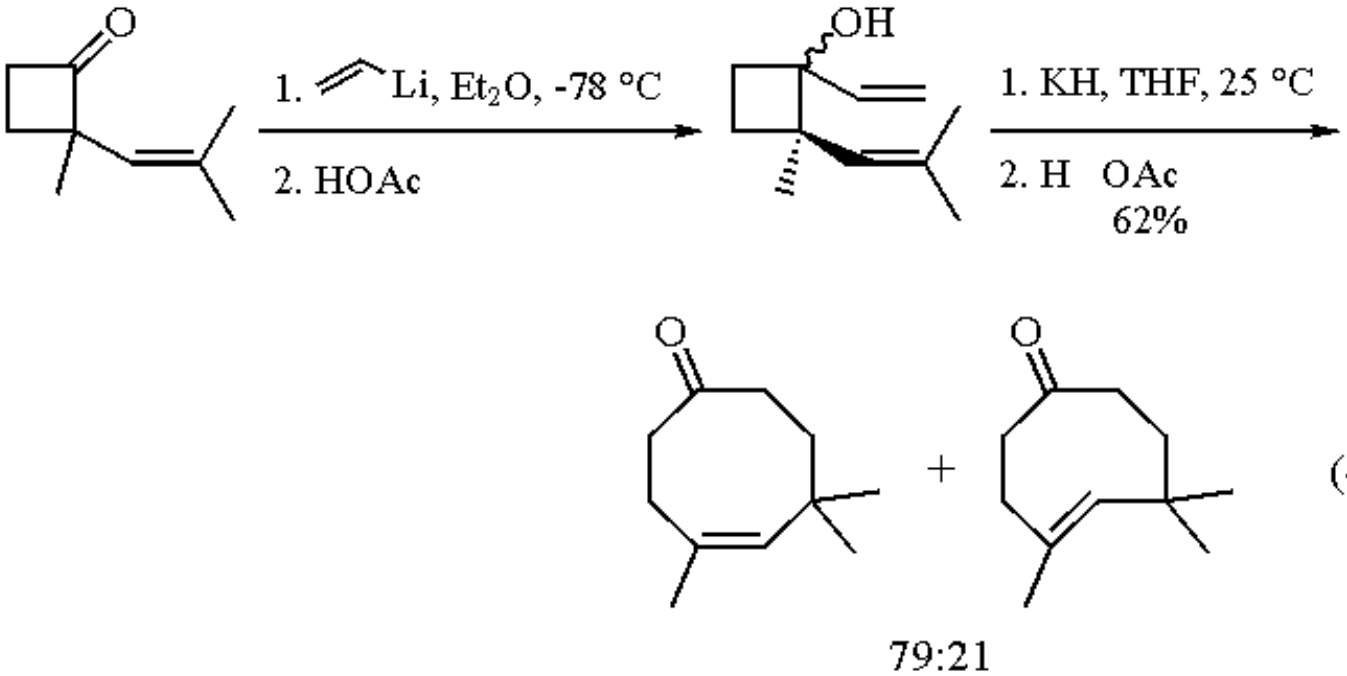

(4)

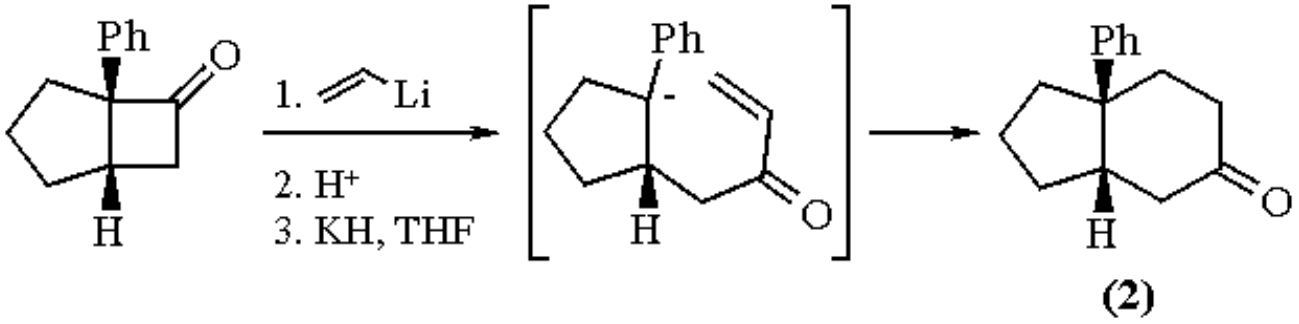

(5)

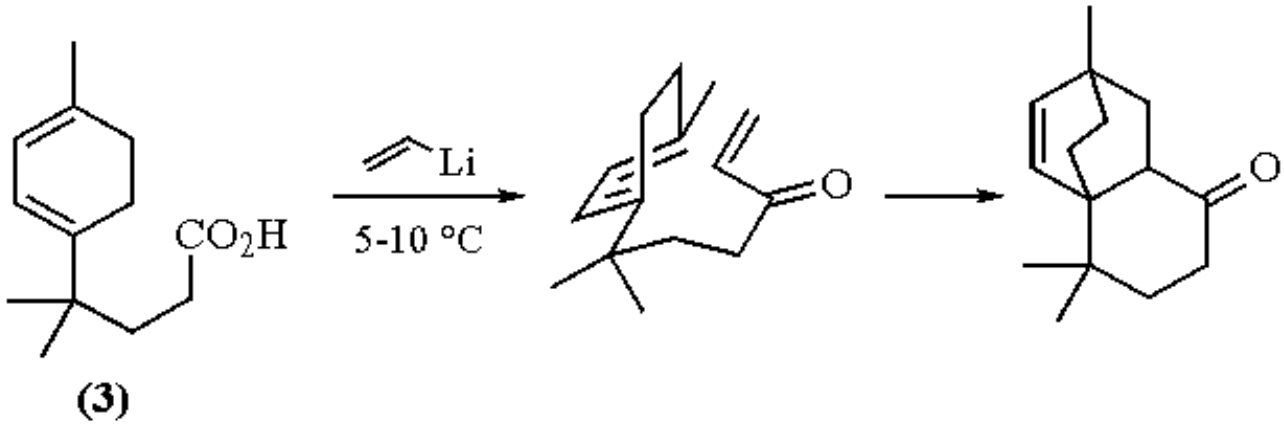

(6)

Other cyclizations have also utilized vinyl groups introduced by reaction of carbonyl groups with vinyllithium, as in the base-catalyzed cyclization used in the synthesis of aphidicolin,[30] the formation of substituted quinones from dimethyl squarate,[31] and the cyclization using sodium in THF in the synthesis of (±)-patchoulol.[32]

Nucleophilic Additions.

Reaction of vinyllithium with 1-iodooctane in THF gives 1-decene in 92% yield. The use of 1,4-dibromobutane gives 1,7-octadiene in 67% yield.[33] Alkenes are also available from the dimerization of vinyllithium with anhydrous ***Cerium(III) Chloride*** in THF.[34] Aryl or alkyl vinyl ketones are readily formed by treating carboxylic acids with 2 equiv of vinyllithium in DME at 5-10 °C. Propionic acid produces 1-penten-3-one in 92% yield.[3]

Substituted enol silyl ethers are available from vinyllithium addition to silyl ketones (eq 7). Addition of the vinyllithium to the silyl ketone results in a silyloxyallyllithium which can be trapped with various electrophiles to yield the substituted enol silyl ethers.[17] Vinyllithium can also be added to epoxides to give the ring-opened product,[35] added to aldimines in toluene at -42 °C to produce allylamines,[36] and inserted *ortho* to either a 2,6-di-*t*-butyl-4-methoxyphenyl ester substituent[37] or an oxazoline group on a naphthalene ring.[38]

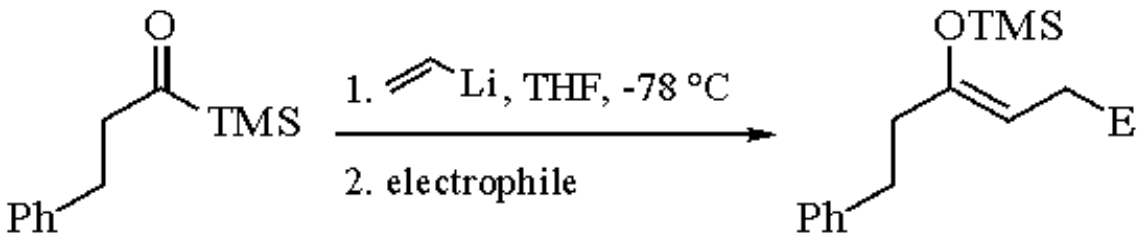

(7)

Electrophile	E	Yield
MeSSMe	MeS	89%
MeI	Me	83%
Pr—≡	H	79%

Related Reagents.

Perfluorinated vinyllithium has been prepared by transmetalation of phenyltris(perfluorovinyl)tin with 3 equiv of phenyllithium in ether at -35 to -40 °C,[39] or by lithium-bromine exchange of perfluorovinyl bromide with 2 equiv of ***t-Butyllithium*** in THF at -110 °C.[16] Vinylsodium is prepared by metalation of ethylene using pentylsodium with sodium isopropoxide.[40] Vinylpotassium is made from vinyl chloride by metal-halogen exchange using a 90% potassium/sodium alloy.[41]

Related Reagents.

1,3-Butadienyl-1-lithium; ***Isopropenyllithium***; ***1-Propenyllithium***; ***Vinylmagnesium Bromide-Methylcopper***.

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Vinylmagnesium Bromide[1]

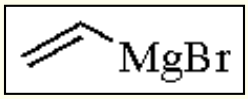

[1826-67-1] · C_2H_3BrMg · Vinylmagnesium Bromide · (MW 131.26)

(introduction of a vinyl unit)

Form Supplied in: widely available in solution in THF (1.0 M).

Preparative Methods: prepared in situ from vinyl bromide and ***Magnesium*** in THF.[3]

Handling, Storage, and Precautions: the solution in THF must be handled with care since it is flammable and may ignite on contact with moisture and air. It should be stored and handled in an inert atmosphere (argon or nitrogen) and measured or transferred by means of a hypodermic syringe or cannula. The solution may deteriorate with time and the concentration of the reagent should be titrated before use.[2]

General Discussion.

Vinylmagnesium bromide reacts with various electrophiles (e.g. aldehydes, ketones, esters, lactones, anhydrides, acid chlorides, carboxylic acids, nitriles, amides, epoxides, allyl halides) (eq 1).[1,3,4]

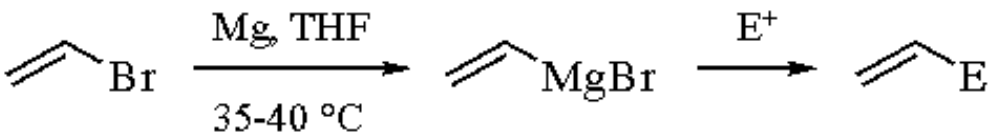

(1)

Complexation of vinylmagnesium bromide with TDA-1 [$N(CH_2CH_2OCH_2CH_2OMe)_3$] gives a powder which can react as the conventional Grignard reagent in hydrocarbon solvents (toluene, cyclohexane) (eq 2).[5]

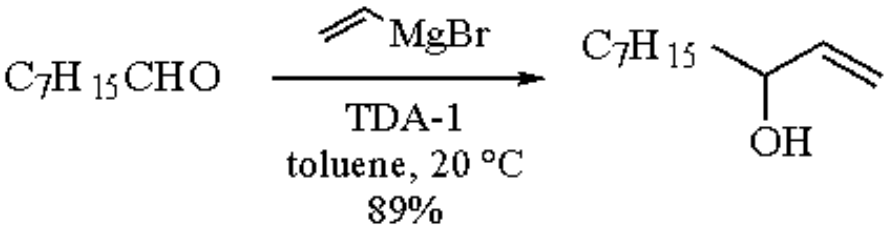

(2)

Vinylmagnesium bromide reacts with a silyl ketone to give a tertiary allylic alcohol, which is a useful intermediate for the synthesis of 2-substituted 1,3-dienes (eq 3).[6] A fluorinated 1,3-butadiene bearing a siloxy group is prepared by treatment of a trifluoroacetylsilane with vinylmagnesium bromide (eq 4).[7]

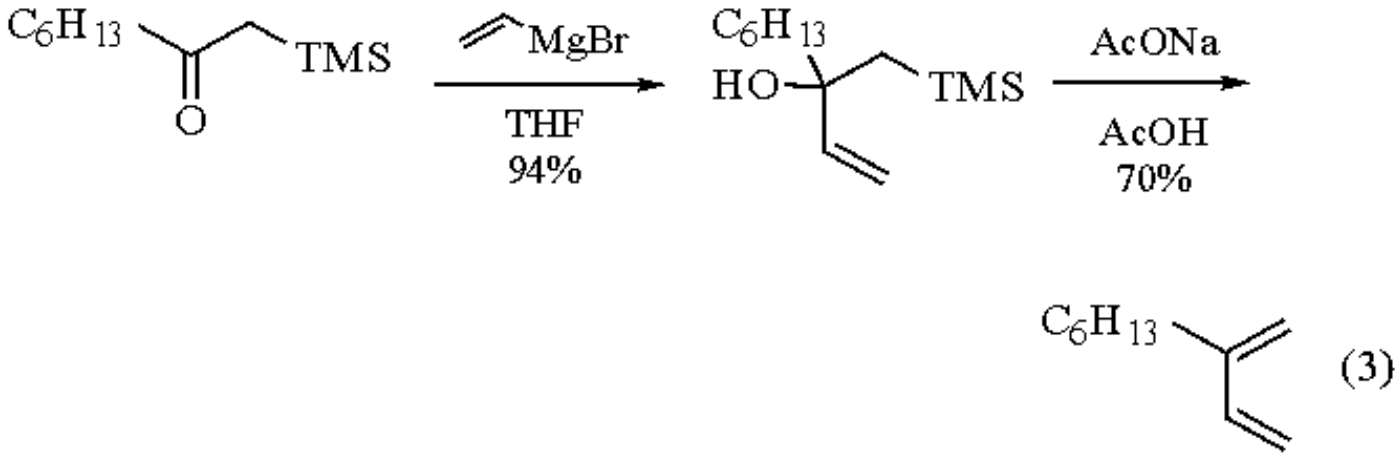

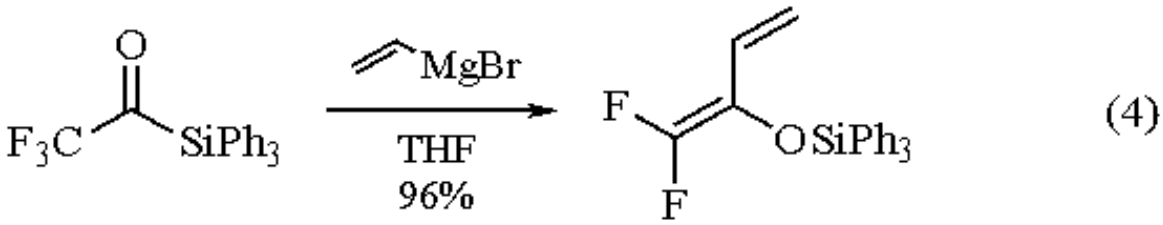

An organocerium reagent, prepared from vinylmagnesium bromide and anhydrous ***Cerium(III) Chloride***, reacts with easily enolizable ketones to afford addition products in good yield (eq 5).[8] Under copper catalysis, vinylmagnesium bromide undergoes conjugate addition to α,β-unsaturated ketones very efficiently (eqs 6 and 7).[9-11]

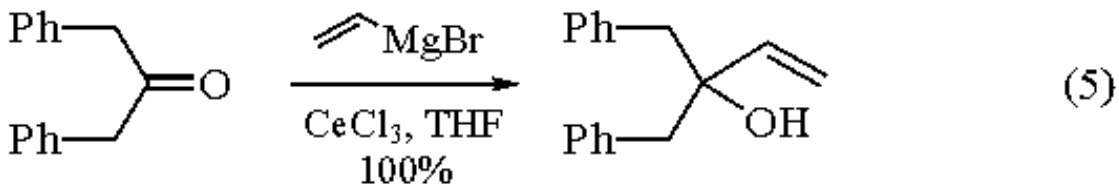

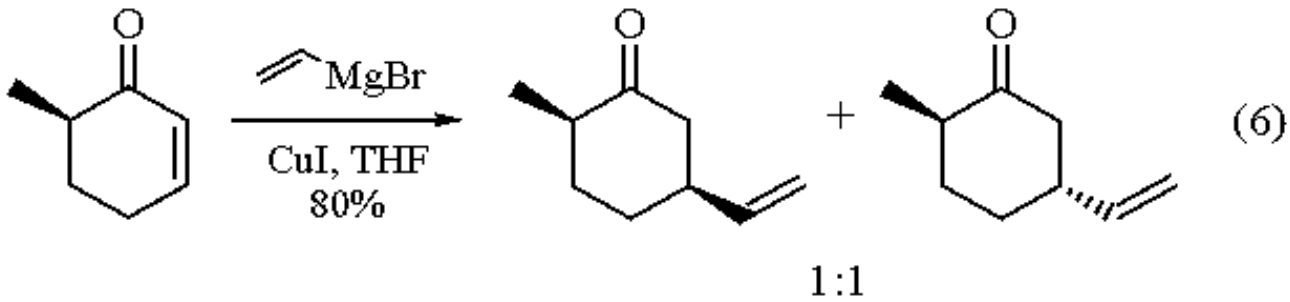

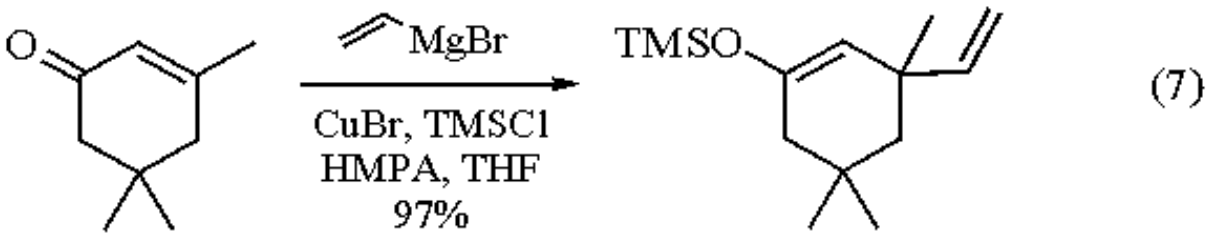

In the presence of copper(I) salts (2-10%) in THF, vinylmagnesium bromide reacts with alkyl halides (eq 8)[12] and epoxides. In the latter case, pure ***Copper(I) Iodide*** (or ***Copper(I) Bromide***-dimethyl sulfide) is needed for the ring opening of cyclohexene oxide with high stereospecificity (eq 9).[13]

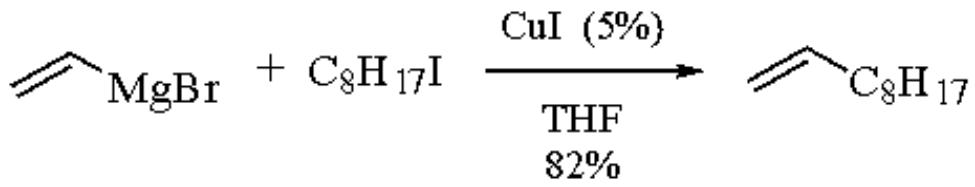

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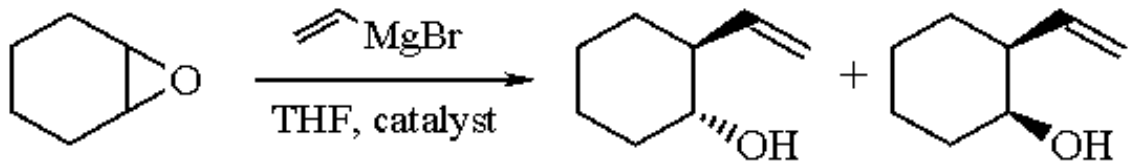

(9)

Catalyst (10%)	Yield (%)	
CuI (99.999% purity)	70%	100:0
CuI (98% purity)	70%	55:45
$CuBr \cdot Me_2S$	65%	100:0

In the presence of nickel or palladium complexes, vinylmagnesium bromide couples efficiently with aryl halides (eq 10),[14] vinyl halides (eqs 11 and 12),[15,16] and vinyl carbamates (eq 13).[17] The transmetalation of vinylmagnesium bromide occurs easily to give useful vinyl metals (eqs 14 and 15).[18,19]

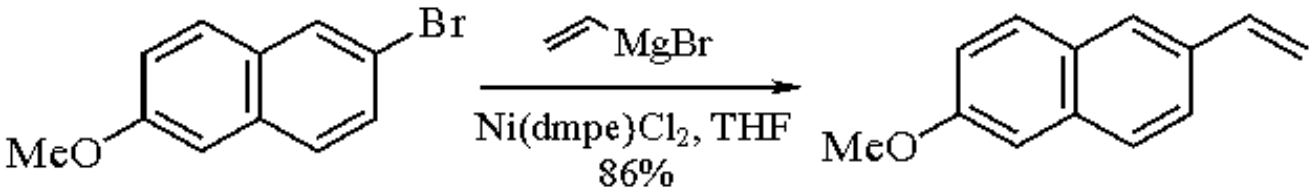

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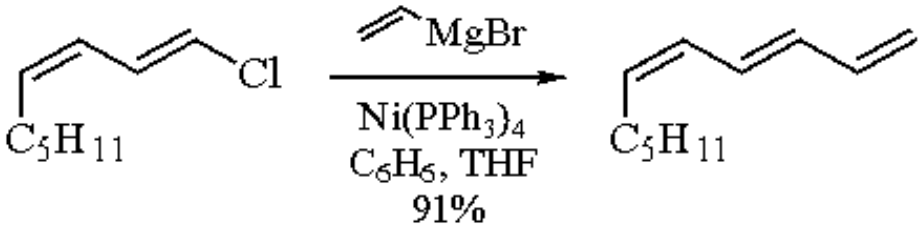

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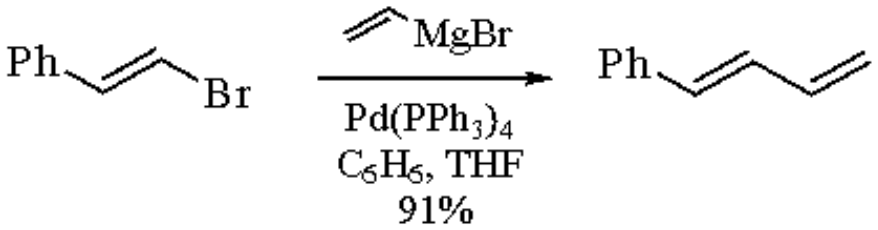

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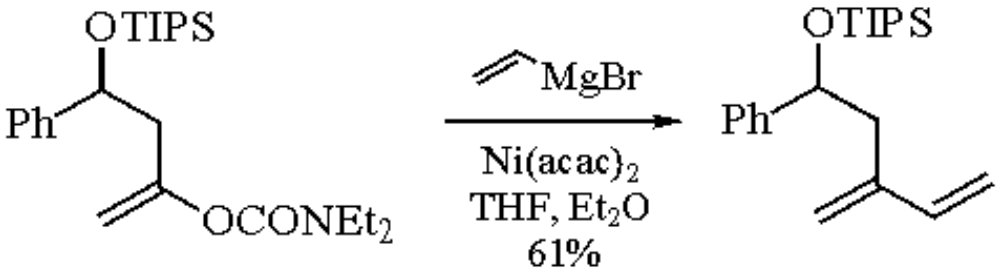

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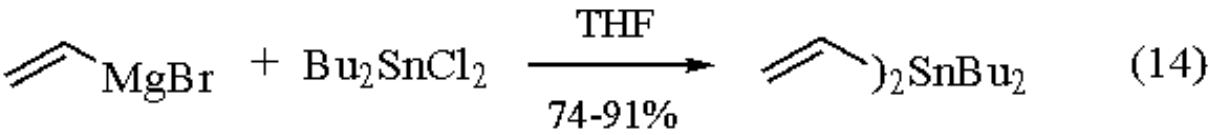

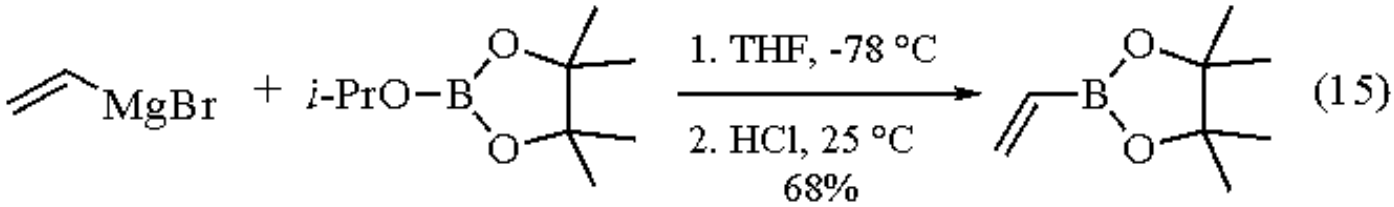

Related Reagents.

Isopropenylmagnesium Bromide; ***Vinyllithium***; ***Vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Bromide-Methylcopper***; ***Vinylmagnesium Chloride-Copper(I) Chloride***.

---

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Vinylmagnesium Bromide-Copper(I) Iodide[1]

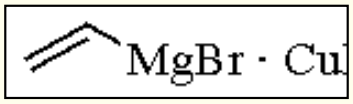

(CH_2=CHMgBr)

[1826-67-1] · C_2H_3BrMg · Vinylmagnesium Bromide-Copper(I) Iodide · (MW 131.26) (CuI)

[7681-65-4] · CuI · Vinylmagnesium Bromide-Copper(I) Iodide · (MW 190.45)

(reaction with epoxides to give optically active allylic alcohols and homoallylic epoxides;[2] ring opening of o-alkenyl lactones;[3] stereoselective Michael addition to substituted cyclohexenone[4])

Preparative Method: vinylmagnesium bromide-copper(I) iodide complexes are prepared in situ under anhydrous conditions by reacting ***Vinylmagnesium Bromide*** (**1**) with ***Copper(I) Iodide*** (**2**) in various molar ratios.

Handling, Storage, and Precautions: use in a fume hood.

Synthesis of Optically Active Allylic Alcohols and Homoallylic Epoxides.

Treatment of epoxy halides (**3**) with a preformed mixture of (**1**) and (**2**) (2 equiv of each) results in the formation of allylic alcohols (**4**) (eq 1).[2] Homoallylic epoxides (**5**) are formed by addition of (**1**) (2 equiv) to a mixture of (**2**) (0.1 equiv), (**3**) and HMPA (4 equiv) (eq 2).

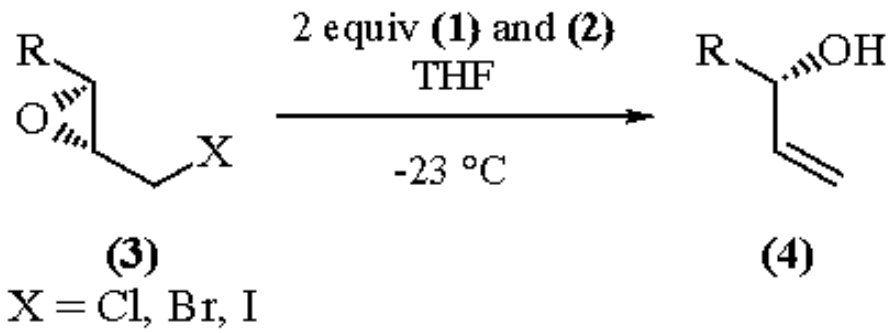

(1)

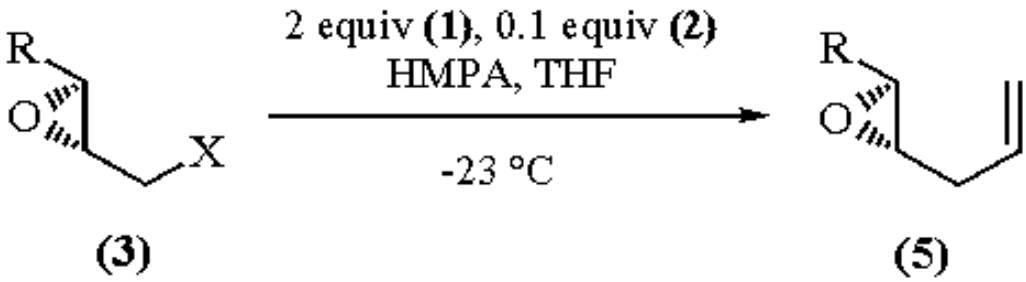

(2)

Regio- and Stereoselective Ring Opening of o-Alkenyl Lactones.

Lactones (**6**) undergo regioselective ring opening when treated with (**1**) and catalytic (**2**) in THF-Me_2S to afford alkenoic acids (**7**) in moderate yield (eq 3).[3]

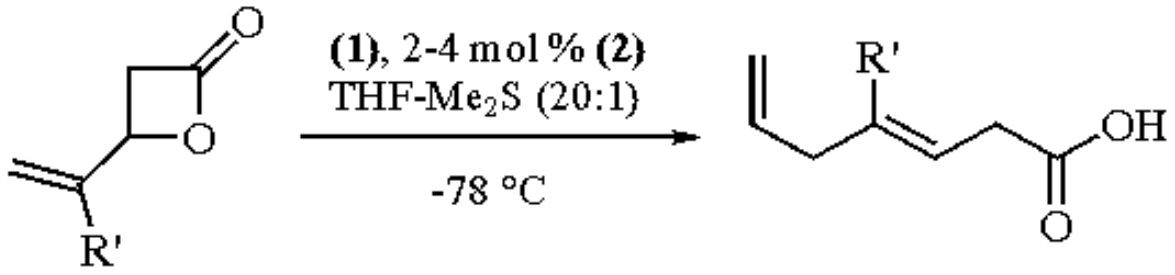

(6) (7)

R'	% yield	(*E*):(*Z*)
H	61	78:22
Cl	51	95: 5

Stereoselective Michael Addition.

The enone (**8**) reacts stereoselectively with a 1:1 mixture of (**1**) and (**2**) to give the α-addition product (**9**) (eq 4).[4] Conversely, addition of cyanide to (**8**) gives the β-addition product.

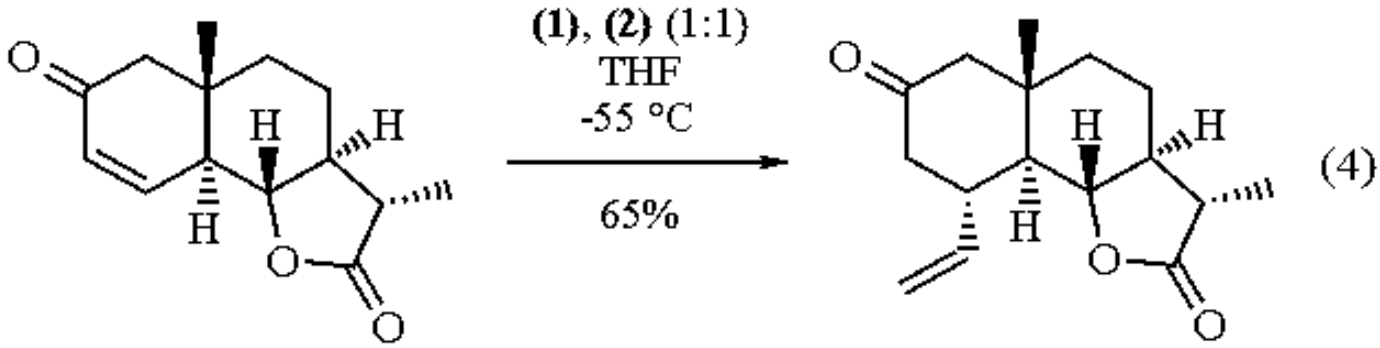

(8) (9)

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Vinylmagnesium Bromide-Methylcopper

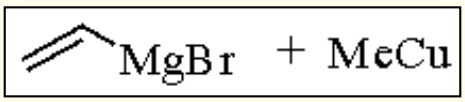

(CH_2=CHMgBr)

[1826-67-1] · C_2H_3BrMg · Vinylmagnesium Bromide-Methylcopper · (MW 131.26) (MeCu)

[1184-53-8] · CH_3Cu · Vinylmagnesium Bromide-Methylcopper · (MW 78.59)

(vinyl group transfer reagent in 1,4-addition reactions with α,β-unsaturated ketones; can reductively remove a γ-alkoxy group from α,β-unsaturated ketones)

Solubility: sol ether, THF.

Preparative Methods: generated[1,2] in situ from preformed ***Methylcopper***[3] and a commercial 1.0 M solution of ***Vinylmagnesium Bromide*** in THF. A mixture of purified[1,4] copper(I) iodide (*n* mmol) and THF (4*n* mL) is treated with a solution of methyllithium (*n* mmol) in ether at -78 °C. The suspension is warmed to 23 °C, stirred for 15 min, and then cooled to -78 °C and treated with the solution of vinylmagnesium bromide (1*n*-3*n* mmol).

Handling, Storage, and Precautions: must be generated in the absence of moisture and oxygen. It cannot be stored. Use in a fume hood.

Introduction.

The reagent is believed to consist of mixed magnesium homocuprates, $(CH_2{=}CH)_nMeCu(MgBr)_n$ (*n* = 1, 2, or 3), with the formula reflecting mainly the ratio of MeCu to CH_2=CHMgBr rather than the structure of the organocopper(I) ate complexes.[2,5] The magnesium cuprates are a useful alternative to ***Lithium Divinylcuprate***,[3] since the ***Vinyllithium*** required for the generation of $(CH_2{=}CH)_2CuLi$ is no longer available commercially.

Vinyl Group Transfer.

The selective transfer of the vinyl group in the 1,4-addition of higher order magnesium cuprates, derived from MeCu and CH_2=CHMgBr, to an enone is illustrated in eq 1.[2] There is almost no 1,2-addition. Conjugate addition products can be prepared in high yields from sterically hindered ketones (eqs 2 and 3).[1]

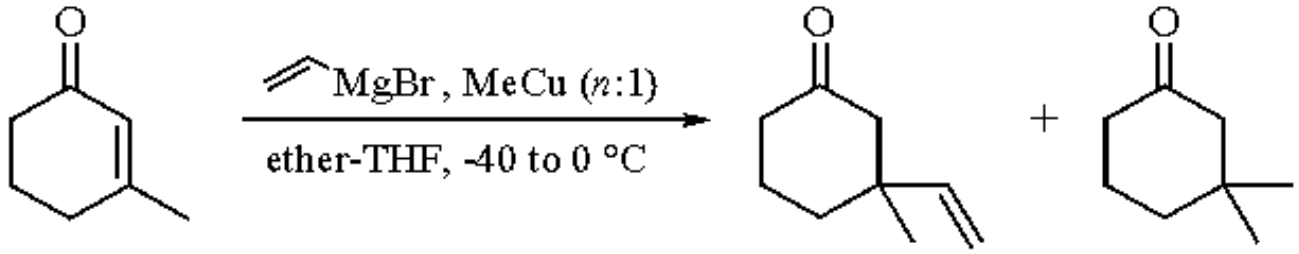

(1)

$n = 2$	69%	6.0%
$n = 3$	78%	1.6%

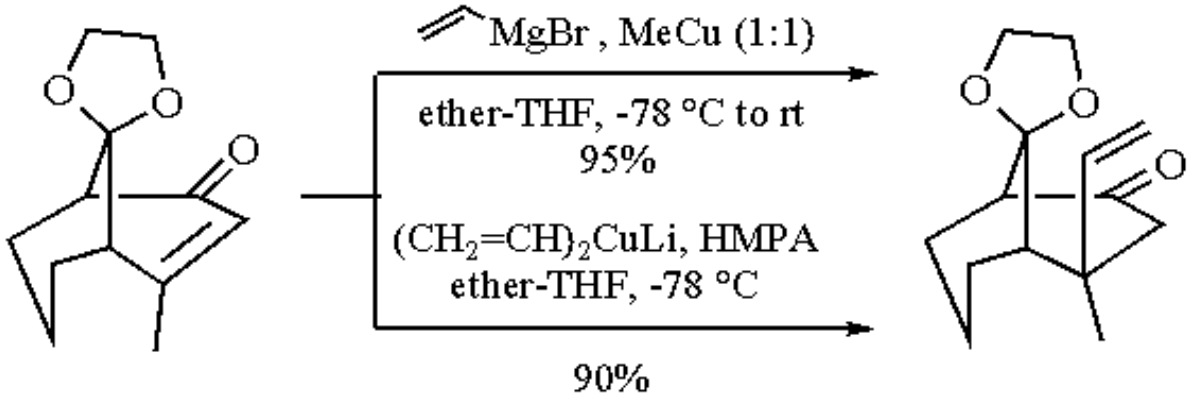

(2)

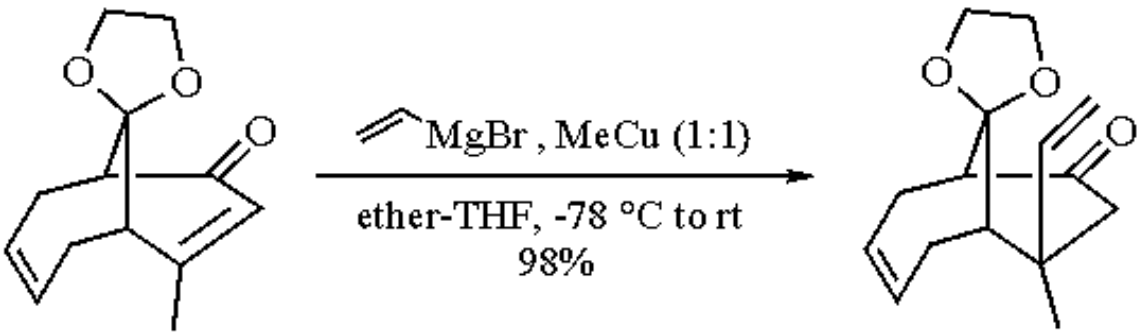

(3)

Reductive removal of the alkoxy group from a γ-alkoxy enone has been observed with the reagent derived from MeCu and CH_2=CHMgBr.[1] This problem can be overcome by the use of a divinylmagnesium cuprate[6] generated from vinylmagnesium bromide and ***Copper(I) Iodide*** (eq 4).

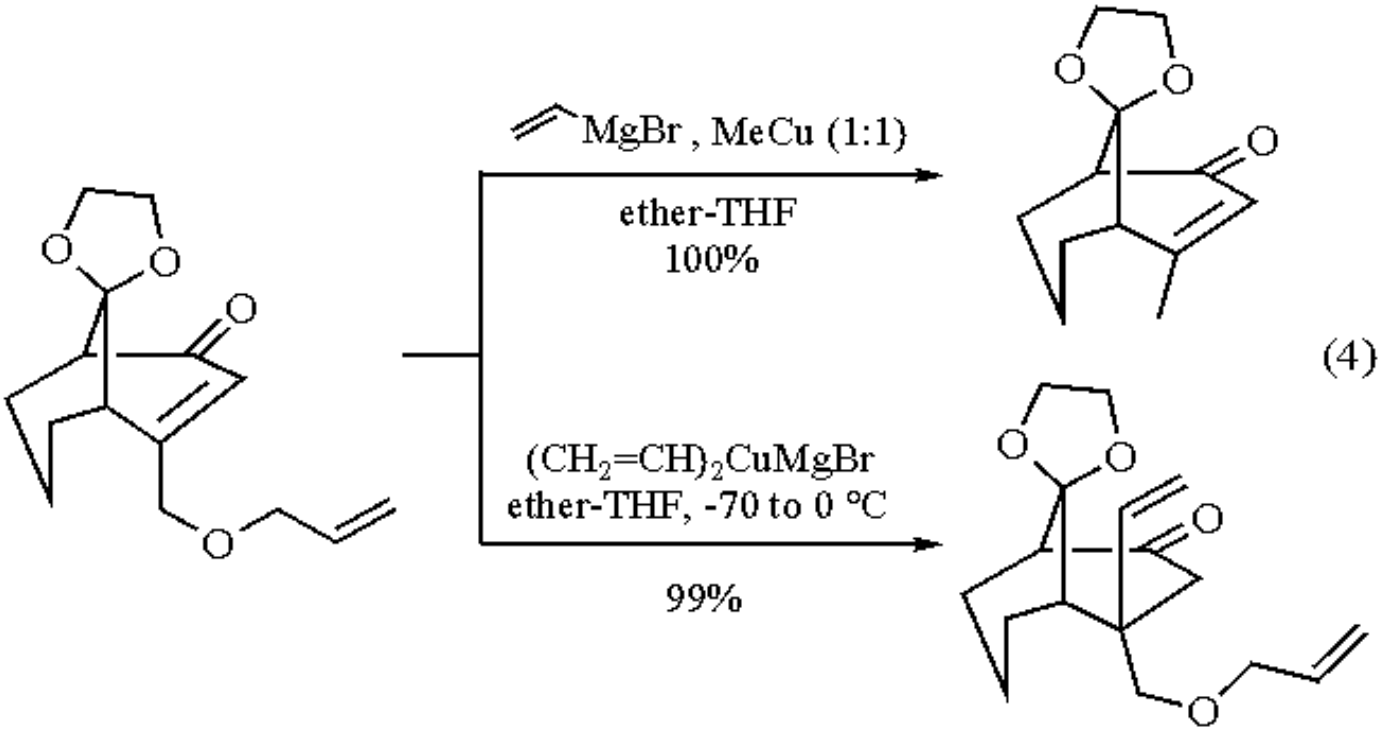

(4)

Related Reagents.

n-Butylmagnesium Bromide-Methylcopper(I); ***Vinylmagnesium Bromide-Copper(I) Iodide***; ***Vinylmagnesium Chloride-Copper(I) Chloride***.

---

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Vinylmagnesium Chloride-Copper(I) Chloride

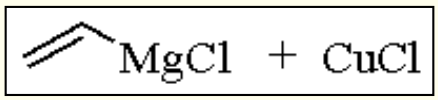

(CH_2=CHMgCl)

[3536-96-7] · C_2H_3ClMg · Vinylmagnesium Chloride-Copper(I) Chloride · (MW 86.81) (CuCl)

[7758-89-6] · ClCu · Vinylmagnesium Chloride-Copper(I) Chloride · (MW 99.00)

(mediates conjugate addition in the synthesis of β-vinyl carbonyl compounds[1-3] and 1,6-diketones[4])

Solubility: sol ether, THF.

Preparative Method: generated[2] in situ by stirring vinylmagnesium chloride[5] in THF with varying amounts of anhydrous ***Copper(I) Chloride*** below 0 °C.

Handling, Storage, and Precautions: all reactions must be conducted in the absence of moisture and oxygen. Some reactions have been conducted satisfactorily in THF under reflux conditions.[3] Use in a fume hood.

Conjugate Additions.

The reagent mediates a conjugate 1,4-addition of a vinyl group to α,β-unsaturated carbonyl compounds (eq 1) to give β-vinyl derivatives.[1] With diethyl (*E*)-2-heptenedioates as the substrates, the initial conjugate addition is followed by Dieckmann condensation of the resultant ester enolate (eq 2).[2] Ring opening of γ-lactones by this reagent produces a transient vinyl ketone, which undergoes subsequent conjugate addition with the reagent to also give β-vinyl ketones (eq 3).[3] A similar tandem reaction with esters produces the unsaturated ketones accompanied by 1,6-diketones (eq 4).[4] In a few cases studied, substitution of a carboxylic acid for the ester in this reaction results in the exclusive formation of the diketone. This synthetic approach to 1,6-diketones appears to be limited to the use of fatty acids as the substrates.[4]

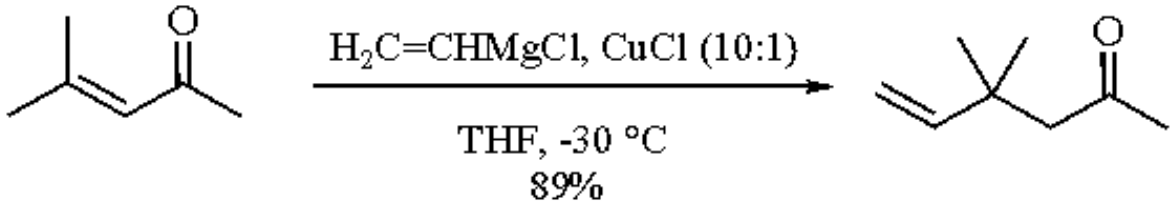

(1)

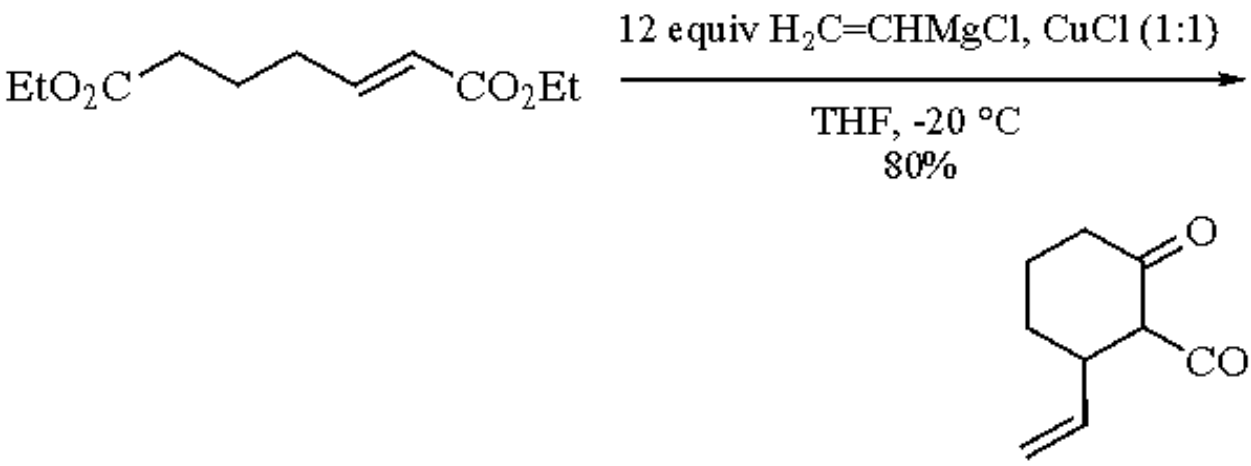

(2)

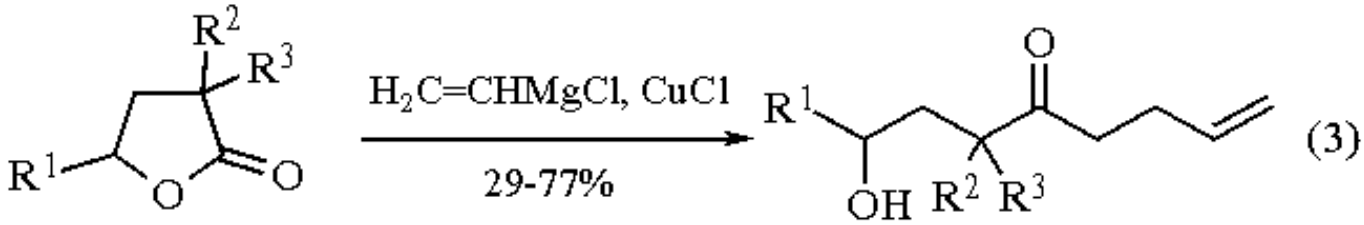

R^1 = Me, Et; R^2 = H, Me, Et, Pr, *i*-Pr; R^3 = H, Me

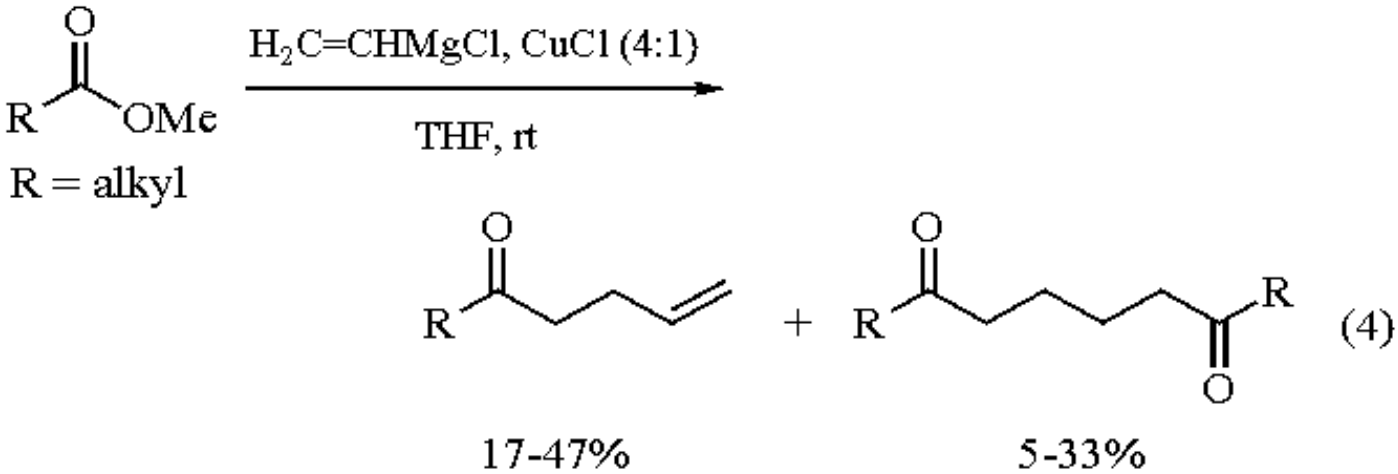

Related Reagents.

Methylmagnesium Iodide-Copper(I) Chloride; ***Vinylcopper***; ***Vinylmagnesium Bromide-Copper(I) Iodide***.

---

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Vinyltributylstannane[1]

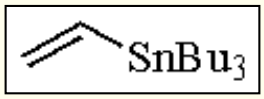

[7486-35-3] · $C_{14}H_{30}Sn$ · Vinyltributylstannane · (MW 317.15)

(vinyl nucleophile in palladium-mediated cross-coupling reactions;[2] occasionally used as a vinyllithium precursor[3])

Alternate Name: vinyltributyltin.

Physical Data: bp 104-106 °C/3.5 mmHg, 95 °C/1.5 mmHg; *d* 1.085 g cm^{-3}.

Solubility: sol common organic solvents; insol H_2O.

Form Supplied in: neat oil; widely available. Occasionally contaminated with small amounts of Bu_3SnCl.

Analysis of Reagent Purity: the pure compound shows one nonpolar spot by TLC (hexane) and one peak in the GC. ^1H NMR can also be useful.

Preparative Methods: conveniently prepared by the reaction of ***Vinylmagnesium Bromide*** with ***Tri-n-butylchlorostannane***.[4]

Purification: large quantities of material are purified by fractional distillation. Small amounts may be filtered through a plug of silica.

Handling, Storage, and Precautions: is air- and water-stable; requires no special handling or storage. Organostannanes are toxic and should only be used in a well ventilated hood. All glassware should be rinsed in a KOH/EtOH bath during cleaning.

Palladium-Mediated Cross Coupling (the Stille Reaction).

Vinyltributyltin is commonly used as a nucleophile in palladium-mediated cross-coupling reactions with organic electrophiles.[2] The electrophile may be a halide or a pseudohalide which contains an sp or sp^2 carbon at or immediately adjacent to the electrophilic center. Halide reactivity varies in the order: I > Br >> Cl. Either Pd^0 or Pd^{II} catalysts may be used to mediate the reaction, the latter being reduced in situ by excess stannane. Acid chlorides react with vinyltributyltin in the presence of ***Benzylchlorobis(triphenylphosphine)palladium(II)*** in HMPA or chloroform at 65 °C (eq 1).[5] In the latter solvent, yields are lower but the workup is significantly easier. Often the introduction of air into the reaction accelerates cross coupling of acid chlorides. Imidoyl chlorides (eq 2)[6] and vinyl halides also undergo Pd-mediated cross coupling (eqs 3 and 4).[7,8] Coupling of aryl halides typically requires electron poor aromatics or aryl iodides (eq 5).[9]

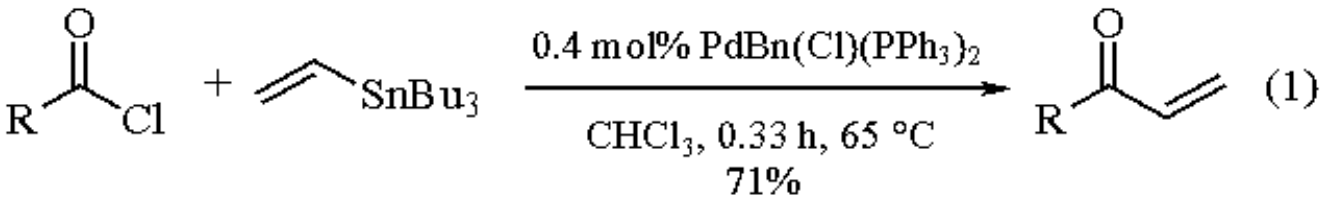

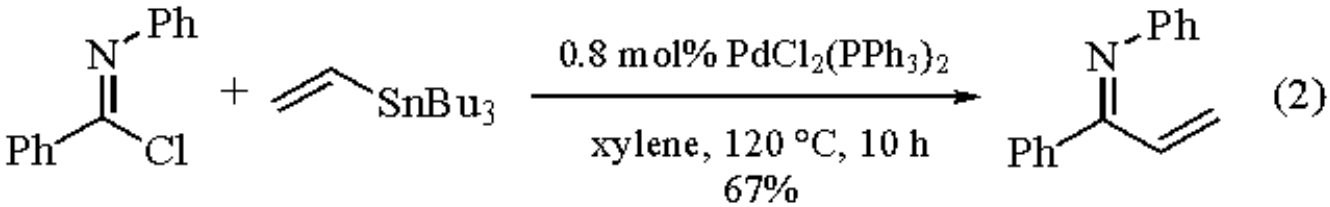

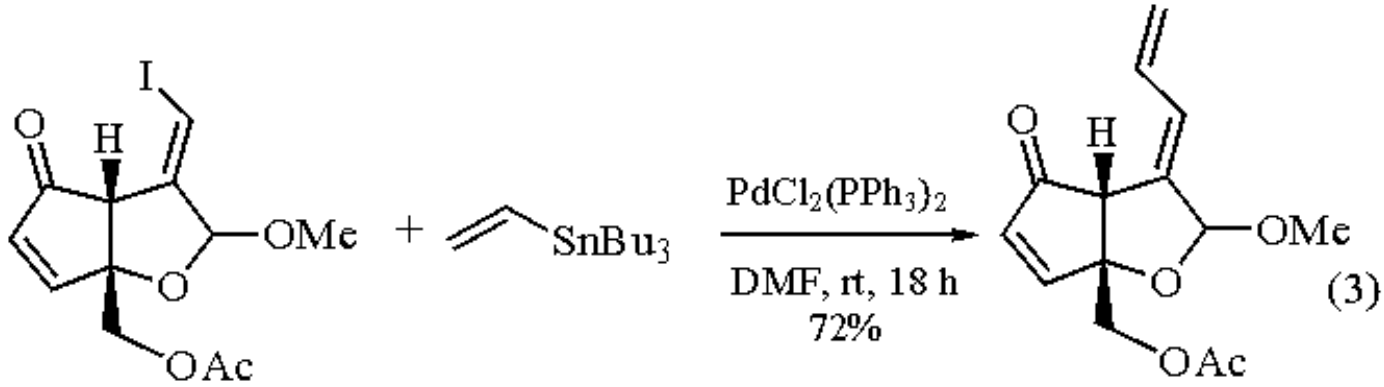

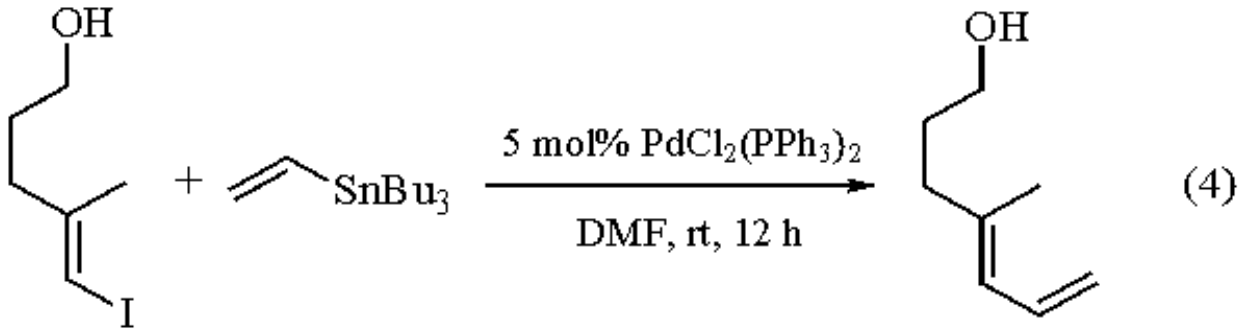

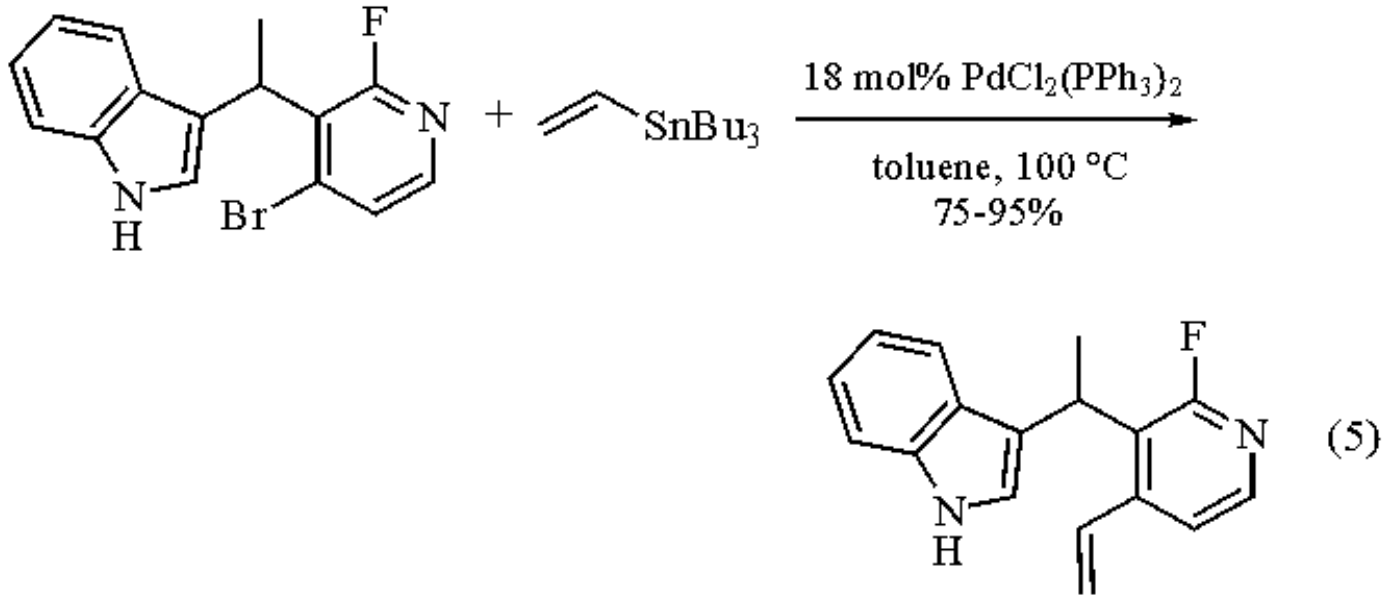

Hegedus et al. report a case in which an iodide attached to an electron-rich alkene fails to couple under normal conditions.[10] Treatment of the vinyl halide under Heck alkenation conditions in the absence of solvent gives a moderate yield of the desired product (eq 6).[10] Use of weakly donating stabilizing ligands, such as tri(2-furyl)phosphine and triphenylarsine, accelerates transmetalation, allowing coupling under conditions more gentle than those required with normal palladium catalysts [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, etc.] (eq 7).[11]

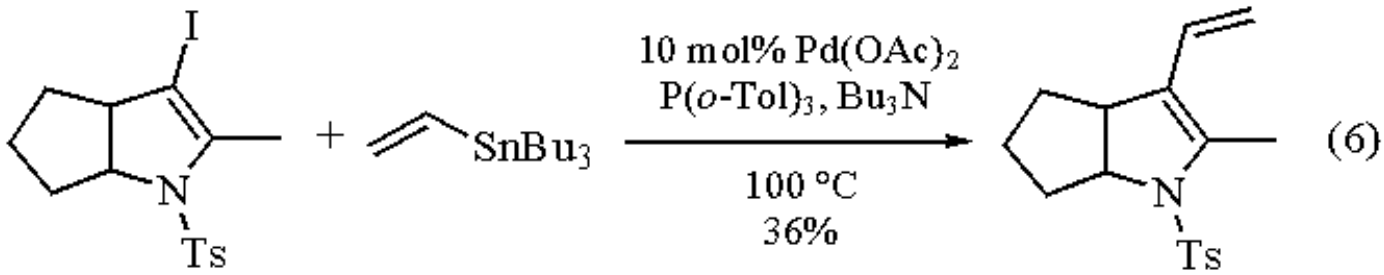

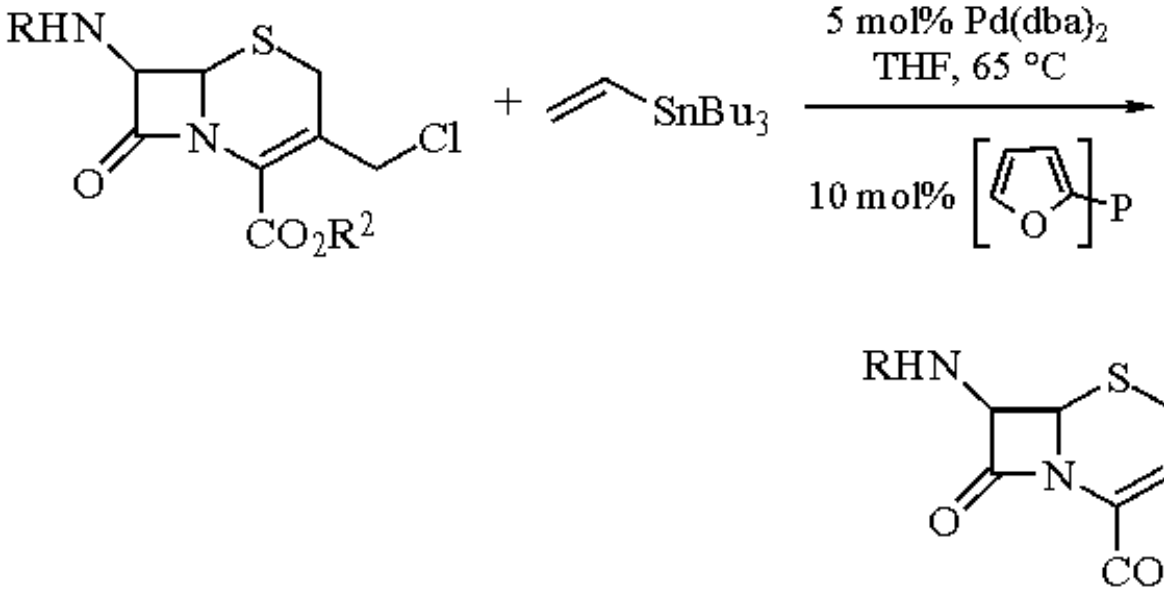

(7)

A number of pseudohalides act as electrophiles in palladium-catalyzed cross couplings. Vinyl and aryl triflates couple with a wide variety of organostannanes in the presence of excess of ***Lithium Chloride*** (eq 8).[12-14] Cross coupling with aryl triflates is more difficult that with vinyl triflates, typically requiring either a more nucleophilic catalyst [***Dichloro[1,1´-bis(diphenylphosphino)ferrocene]palladium(II)***, (dppf)$PdCl_2$)] or higher temperatures (dioxane at 98 °C) (eq 9).[15] Use of vinyl[16] or phenyl[17] fluorosulfonates allows lower cost at the expense of lower stability with respect to the analogous triflate (eq 10). Arenesulfonates have also been coupled with vinyltributyltin.[18] However, the generality of this variation is not yet clear.

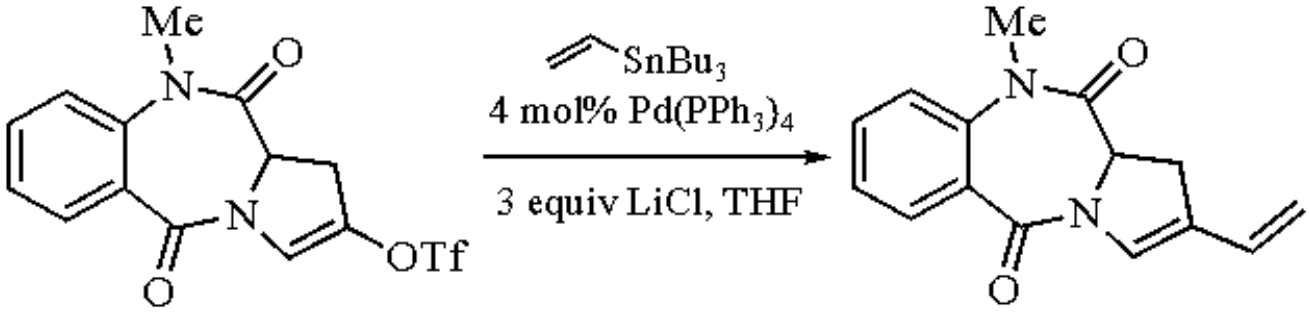

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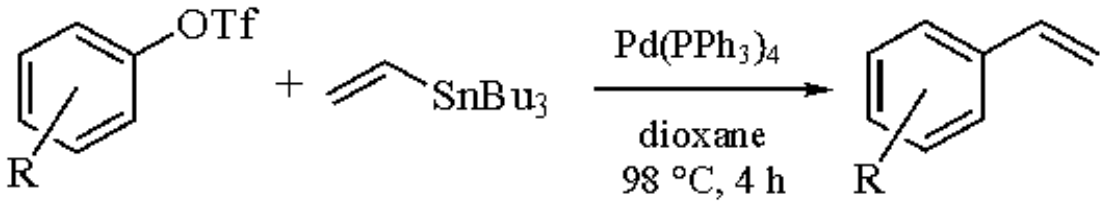

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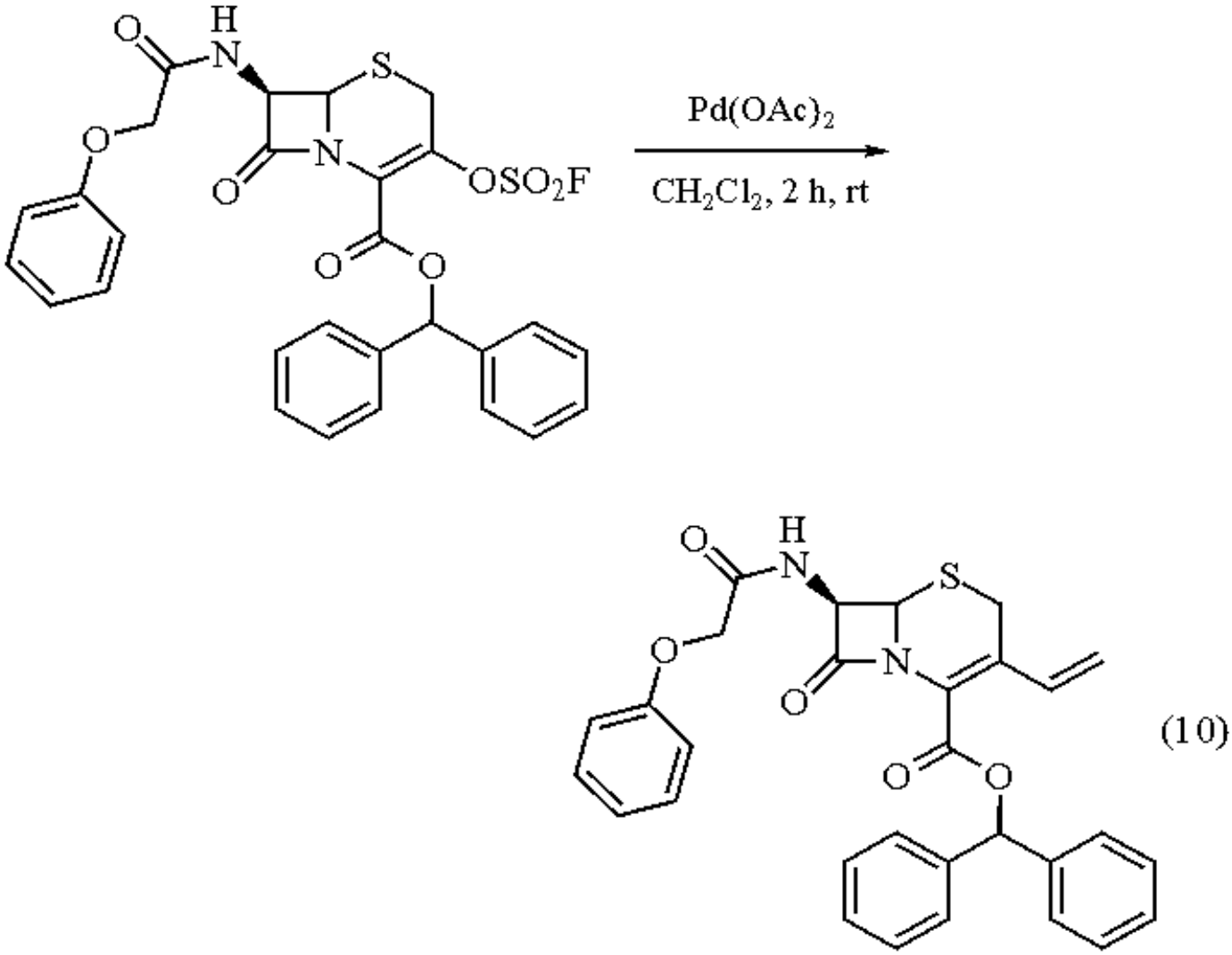

Other electrophiles which undergo cross coupling include hypervalent iodine compounds (eq 11)[19] and aryl diazonium salts (eq 12).[20] Coupling of aryl diazonium salts requires excess vinyltributyltin and 1 equiv of the catalyst to avoid significant byproduct formation.[20] Carbonylative couplings can be achieved if cross coupling is conducted under 1-3 atm of ***Carbon Monoxide*** (eq 13).[14] Vinyltributyltin has also been used in tandem Heck alkenation/Stille couplings, in which the stannane is reacted with an alkyne and an electrophile in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** (eq 14).[21,22]

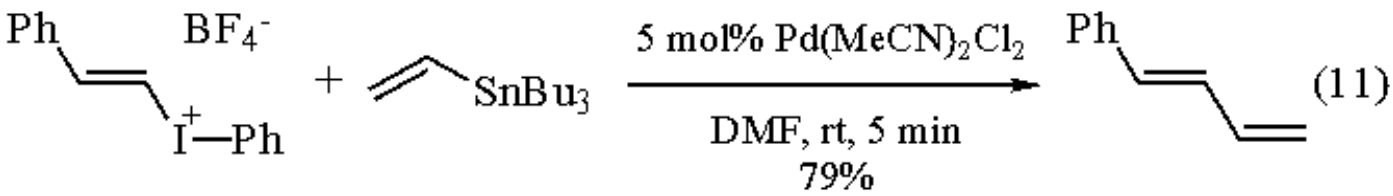

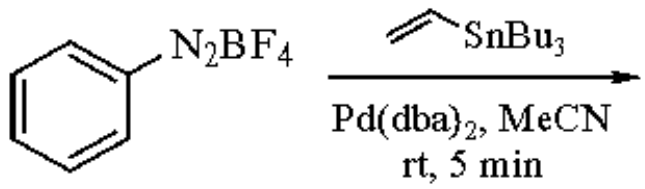

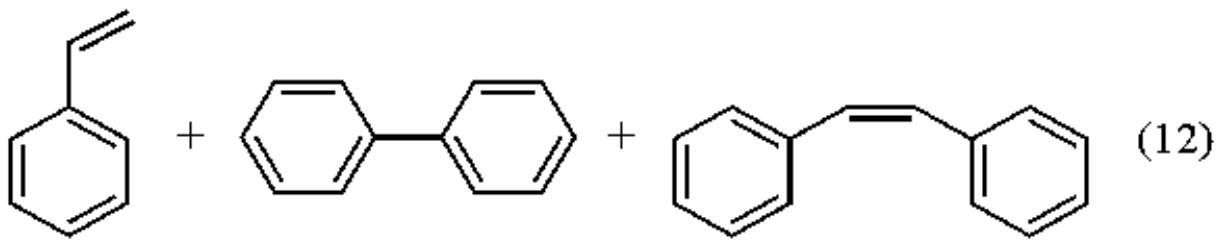

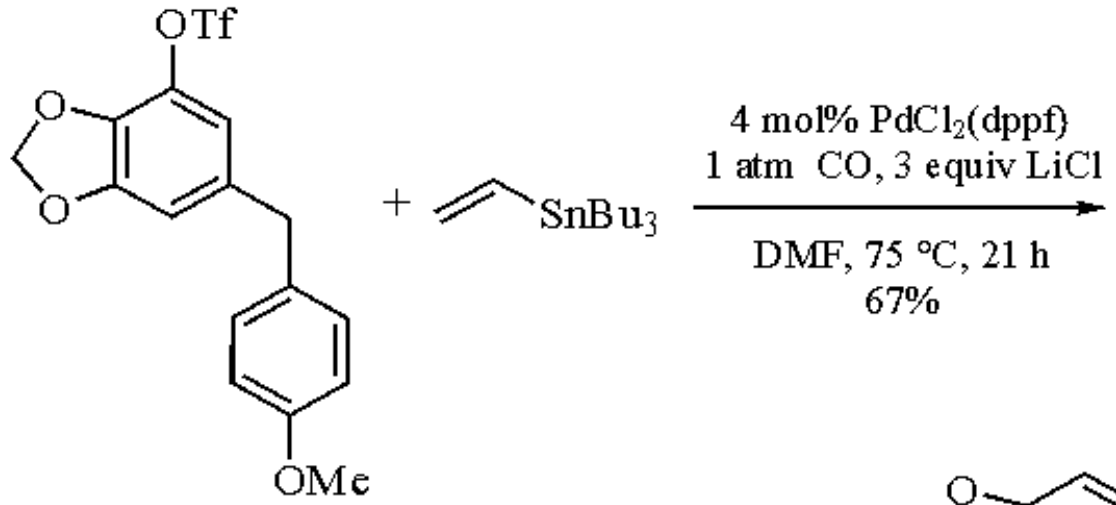

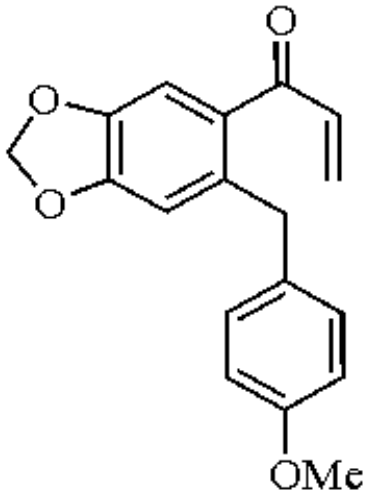

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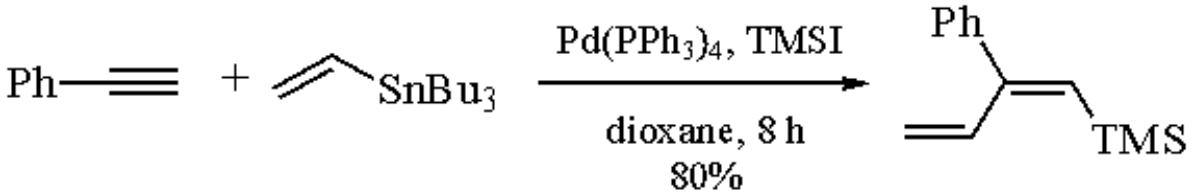

(14)

Transmetalation.

Transmetalation from tin offers a facile synthesis of vinyl nucleophiles. Treatment of vinyltributyltin with ***Methyllithium*** affords methyltributyltin and ***Vinyllithium*** (eq 15).[3] Similarly, treatment with higher order cuprates causes quantitative in situ formation of the vinylcuprate (eq 16).[23] Vinyltributyltin will transfer a vinyl group in reactions with both trimethylchlorogermane and tetrachlorogermane.[24] Transmetalation with trimethylchlorogermane requires the presence of a catalytic amount of ***Aluminum Chloride***. Treatment of an excess of vinyltributyltin with ***9-Bromo-9-borabicyclo[3.3.1]nonane*** affords ***9-Vinyl-9-borabicyclo[3.3.1]nonane*** while avoiding the manipulation of air-sensitive compounds.[25] Excess vinyltributyltin is necessary to remove adventitious protic acid, and a greater than usual amount of H_2O_2/NaOH is used during oxidative hydrolysis to allow for reaction with bromotributyltin. Iodosulfonylation of vinyltributyltin followed by elimination of HI (DBU) affords the vinyl sulfone (eq 17),[26] which can subsequently be used in Diels-Alder reactions or can be lithiated.[27]

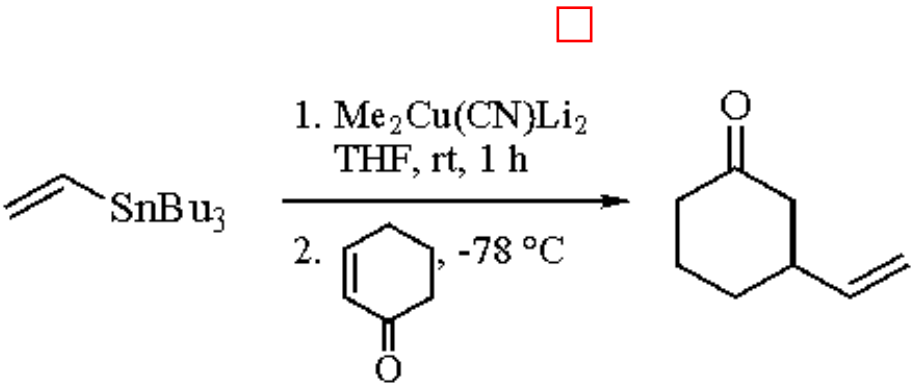

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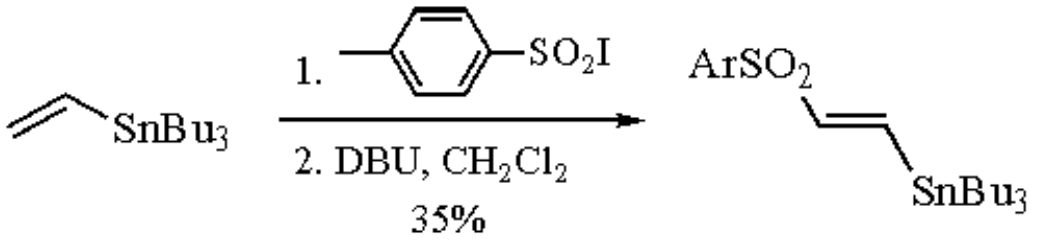

(17)

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Vinyltrimethylsilane[1]

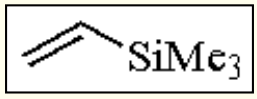

[754-05-2] · $C_5H_{12}Si$ · Vinyltrimethylsilane · (MW 100.26)

(ethylene equivalent in electrophilic substitution reactions; precursor to 3-trimethylsilyl-3-buten-2-one, a methyl vinyl ketone surrogate for Robinson annulations; homologation of aldehydes to α,β-unsaturated aldehydes)

Physical Data: bp 55-57 °C; *d*204 0.691 g cm^{-3}; *n*20D 1.391.

Solubility: sol most common organic solvents (THF, Et_2O, benzene, CH_2Cl_2, etc.)

Form Supplied in: commercially available from several suppliers.

Analysis of Reagent Purity: characterized by ^1H, ^{13}C, and ^{29}Si NMR,[2] and IR.[3] ^1H NMR (500 MHz) ($CDCl_3$): δ 0.08 (9H, s), 5.67 (1H, dd, J_{trans} = 20.3 MHz, J_{gem} = 3.8 Hz), 5.93 (1H, dd, J_{cis} = 14.7 Hz, J_{gem} = 3.8 Hz), 6.17 (1H, dd, J_{trans} = 20.3 Hz, J_{cis} = 14.7 Hz) ppm; ^{13}C NMR (125 MHz) ($CDCl_3$): δ -1.62, 130.88, 140.27 ppm; ^{29}Si NMR (19.9 MHz) ($(MeO)_4Si$): δ -71.70 ppm; IR (CCl_4): ν 1594 cm^{-1}.

Preparative Method: prepared in 67-91% yield from ***Vinylmagnesium Bromide*** and ***Chlorotrimethylsilane*** in THF.[4,5]

Purification: fractional distillation at 1 atm using an efficient Vigreux column. Some difficulty in removing trace amounts of THF (bp 67 °C) has been reported.

Handling, Storage, and Precautions: highly flammable; flash point -34 °C; hygroscopic. The reagent should be used in a well ventilated hood. Contact with the eyes and skin should be avoided.

Synthesis of Vinyl Aryl Sulfides.

Vinyltrimethylsilane functions as an ***Ethylene*** equivalent in electrophilic substitution reactions with sulfenyl chlorides (eq 1).[6] Reaction with various arylsulfenyl chlorides provides the stable adducts (**1**) in high yield. Treatment of (**1**) with fluoride ion furnishes vinyl aryl sulfides (**2**) in high yield.

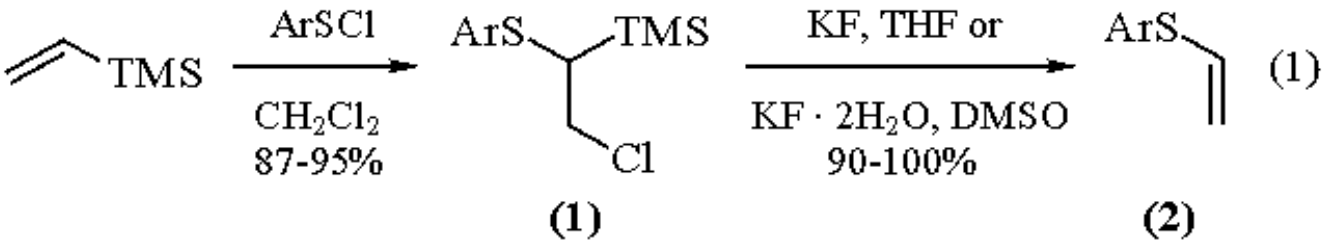

Ar = 2,4-dinitrophenyl, 2-nitrophenyl, phenyl, 4-chlorophenyl, 4-methylphenyl

Synthesis of 3-Triethylsilyl-3-buten-2-one.

Vinyltriethylsilane can be elaborated in five steps to yield ***3-Triethylsilyl-3-buten-2-one*** (**4**) (eq 2), a ***Methyl Vinyl Ketone*** surrogate useful in Robinson annulation reactions (eq 3).[7] The analogous annulation reaction using methyl vinyl ketone gives poor yields.

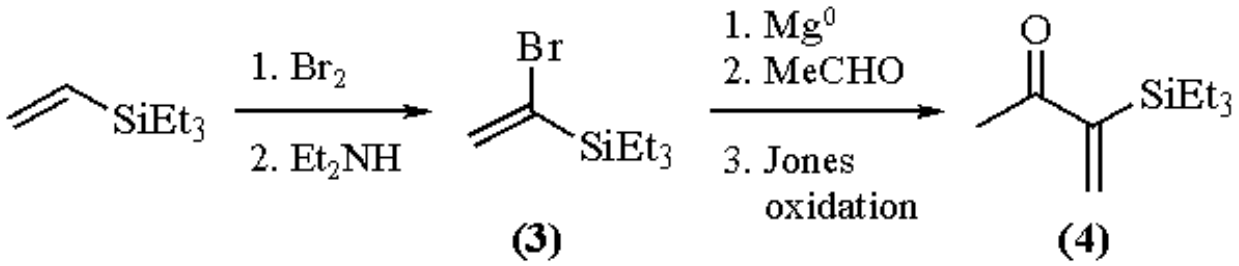

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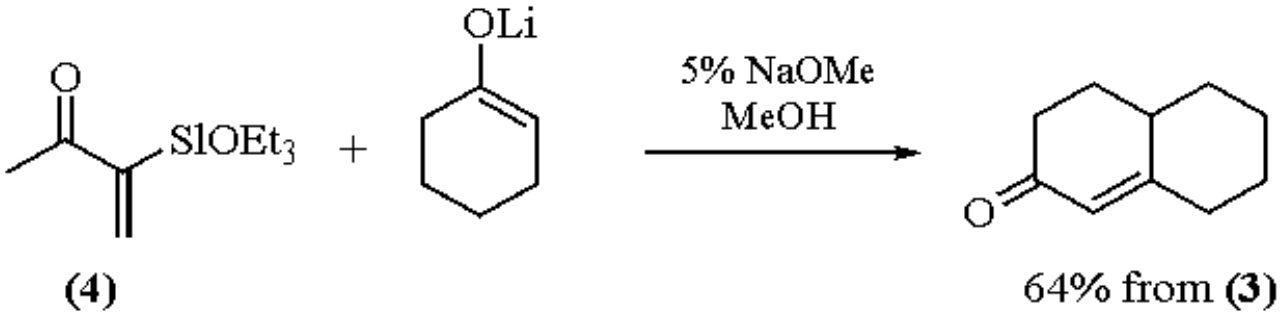

(3)

Synthesis of α,β-Unsaturated Primary Amides.

Vinylsilanes react with ***Chlorosulfonyl Isocyanate*** without the aid of Lewis acid catalysts to form β-lactams, e.g. (**5**), which subsequently undergo hydrolysis to the corresponding *trans*-α,β-unsaturated primary amides, e.g. (**6**) (eq 4).[8]

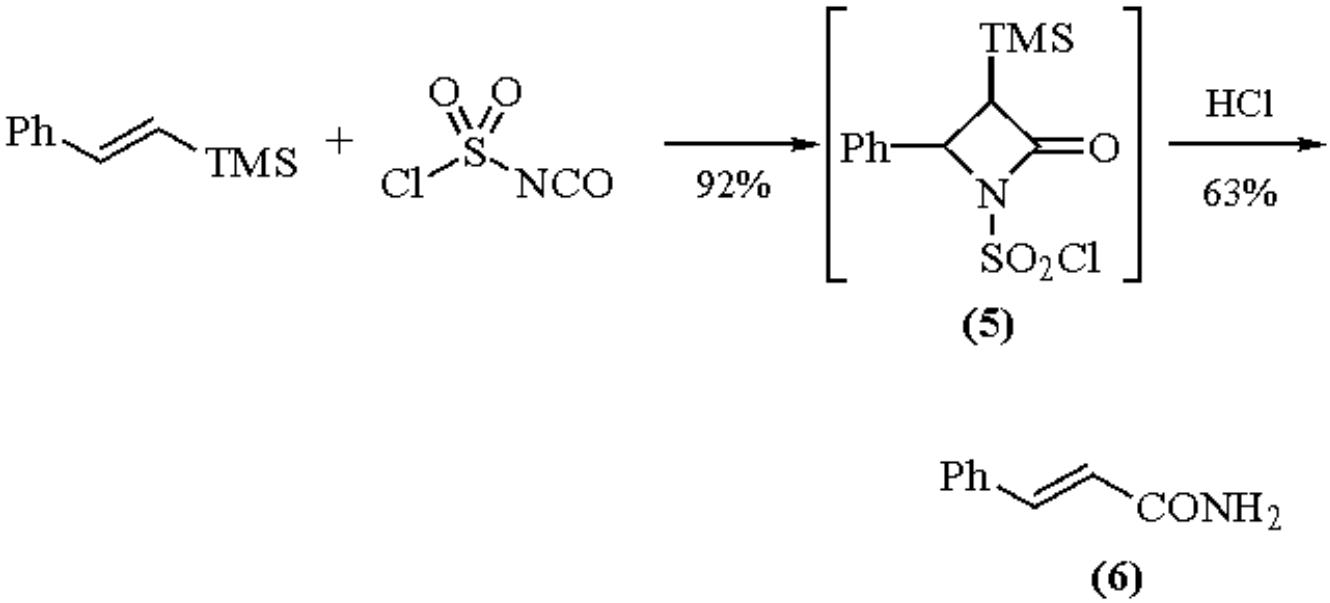

(4)

Synthesis of α,β-Unsaturated Aldehydes.

Vinyltrimethylsilane undergoes [3 + 2] cycloaddition reactions with the aldehyde-derived nitrone (**7**) to provide the corresponding (trimethylsilyl)isoxazolidine adduct (**8**) in 84% yield (eq 5).[9] Treatment of (**8**) with aqueous HF furnishes the α,β-unsaturated aldehyde (**9**) in 95% yield. This methodology is general for the homologation of aldehydes and serves as an alternative to the traditional Wittig-type alkenations.

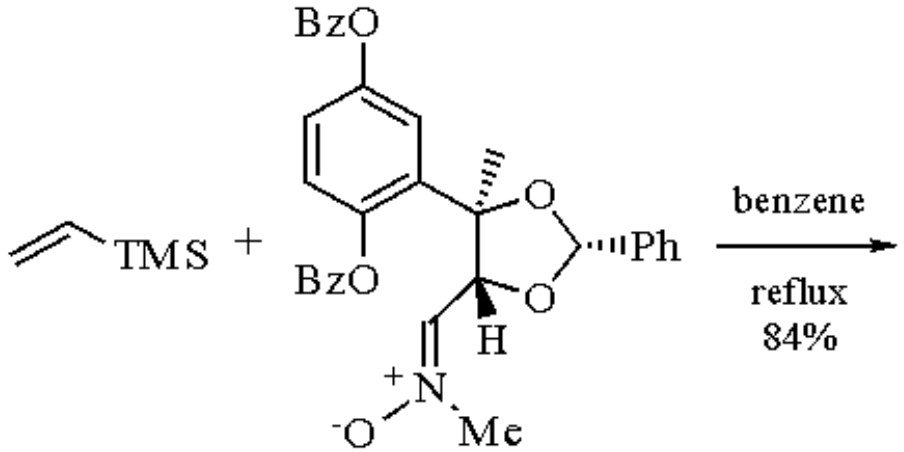

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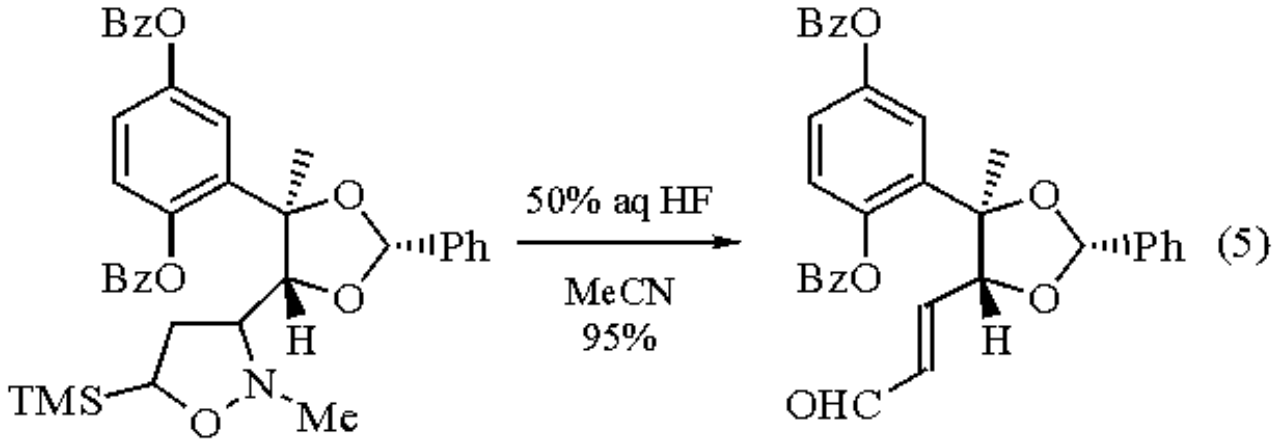

(8) (9)

Synthesis of Bicyclopentenones.

The title reagent serves as an ethylene equivalent in aliphatic Friedel-Crafts acylation reactions involving cyclic α,β-unsaturated acid chlorides. For example, the acid chloride (**10**) reacts with vinyltrimethylsilane in the presence of ***Tin(IV) Chloride*** to give the divinyl ketone intermediate (**11**), which then undergoes a Nazarov cyclization, thus producing the bicyclopentenone (**12**) in 46% overall yield (eq 6).[6,10]

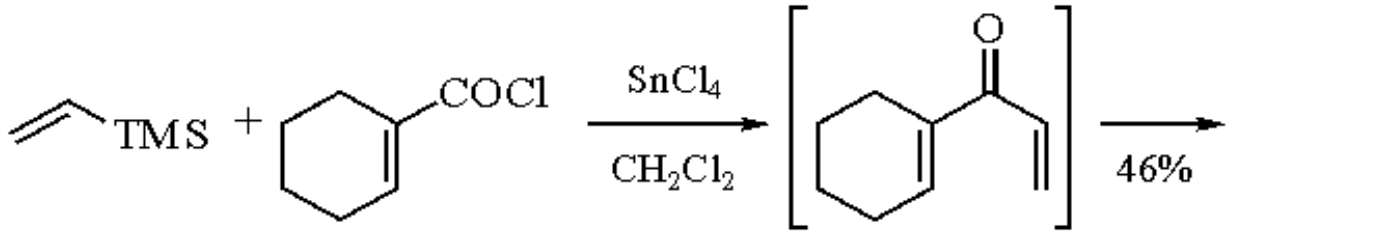

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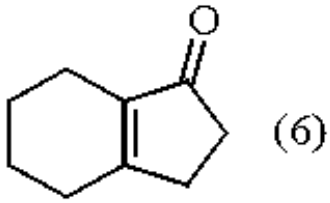

(12)

Synthesis of 1-Chlorocyclopropene.

Vinyltrimethylsilane serves as a useful precursor to 1-chlorocyclopropene (**14**).[13] Reaction of the vinylsilane with

Phenyl(trichloromethyl)mercury[12] in refluxing benzene followed by fluoride-induced elimination of TMSCl from the cyclopropane (**13**) furnishes 1-chlorocyclopropene in good yield, as evidenced in the subsequent Diels-Alder reaction with 1,3-diphenylisobenzylfuran (eq 7). A previous synthesis[13] of 1-chlorocyclopropene gave only 5-10% yield.

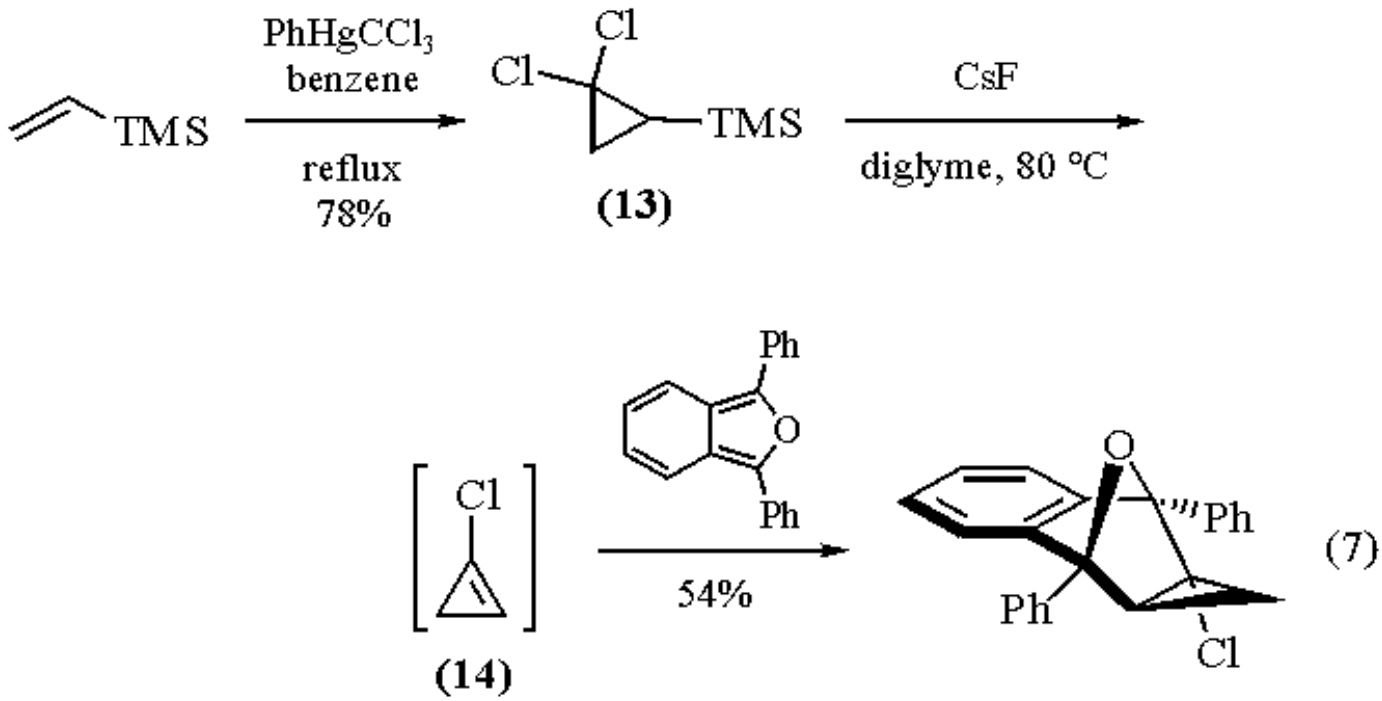

Radical Addition Reactions of Vinyltrimethylsilane.

Reaction of the title reagent with ***Benzenesulfonyl Chloride*** under radical addition conditions[14] provides ***(E)-1-Phenylsulfonyl-2-trimethylsilylethylene*** (**15**),[15] an ***Acetylene*** equivalent in Diels-Alder reactions (eq 8). In similar fashion, ***Thiophenol*** adds to vinyltrimethylsilane regioselectively.[16] Oxidation of the thiophenol adduct provides the sulfone (**16**) (eq 9), which serves as a latent exomethylene unit in the enantioselective synthesis of (1*R*)-[(methylenecyclopropyl)acetyl]-CoA (**17**).[17] The sulfone (**16**) is also used in the high yield preparation of allylsilanes, vinyl sulfones, and 2-(benzenesulfonyl)allyl alcohol derivatives.[18]

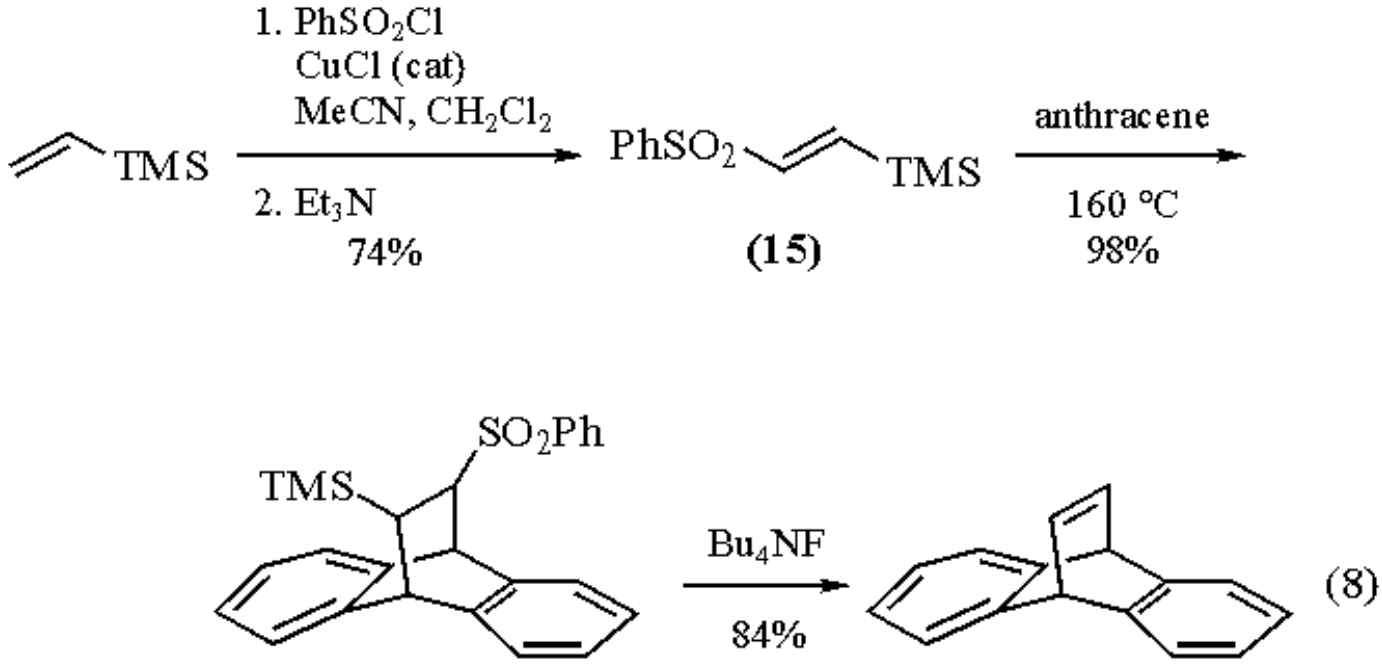

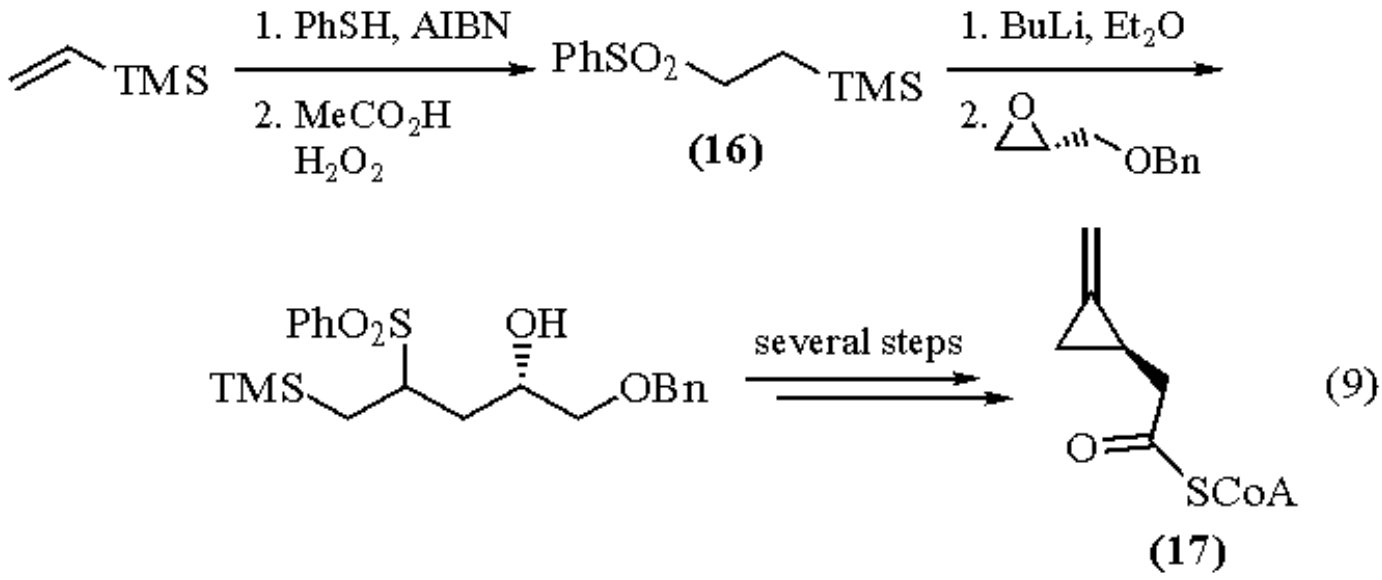

Reaction of Vinyltrimethylsilane with 2-Azaallylanions.

Reaction of vinyltrimethylsilane with the nonstabilized 2-azaallyl anion (**19**), generated in situ from the (2-azaallyl)stannane (**18**) (eq 10), produces, after quenching with MeI, the pyrrolidine (**20**) as a single diastereomer in 77% yield (eq 11).[21] Some evidence suggests that the cycloaddition is stepwise and that the W-conformation of the anion predominates in the cycloaddition sequence.

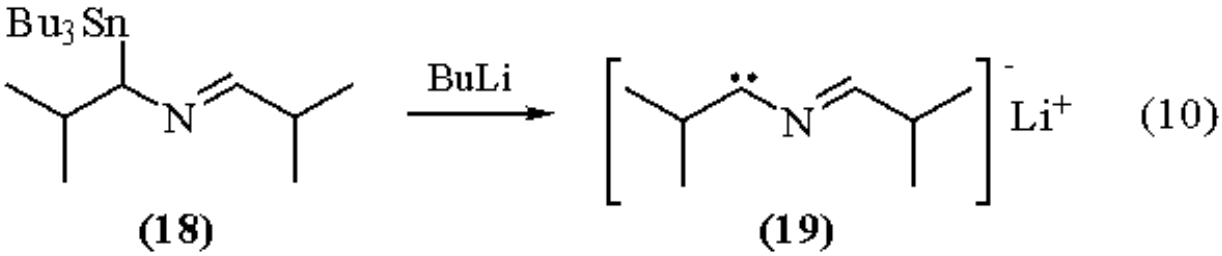

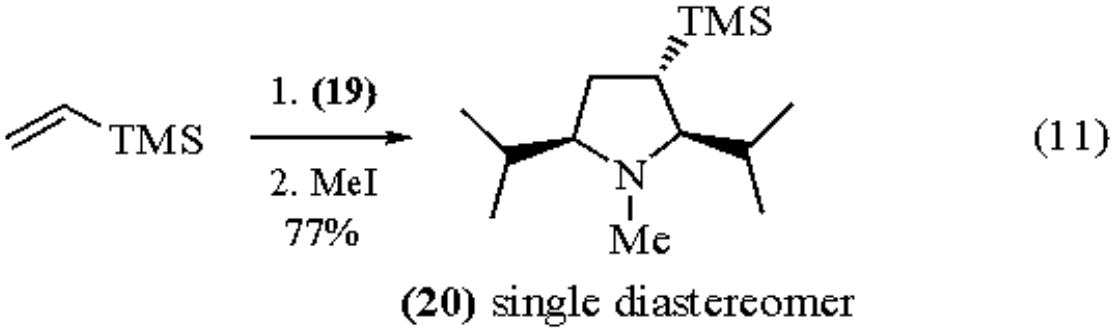

Regioselective Hydroesterification of Vinyltrimethylsilane.

Vinyltrimethylsilane undergoes highly regioselective hydroesterification reactions to furnish either ethyl 3-(trimethylsilyl)propionate (**21**) or ethyl 2-(trimethylsilyl)propionate (**22**), depending on the choice of catalyst and reaction conditions (eq 12).[20] Highly regioselective (>96% β-selective) hydroformylations of vinylsilanes containing bulky alkyl and aryl substitutents on silicon have been achieved using ***Carbonylhydridotris(triphenylphosphine)rhodium(I)*** as catalyst.[21]

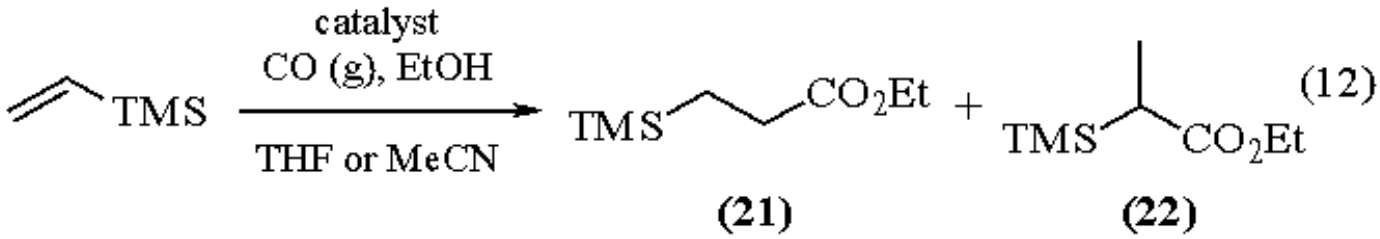

Catalyst	Yield (21)/(22)	Ratio (21):(22)	$P_{initial}(CO)$
$PdCl_2(PPh_3)_2$ (1-2 mol%)	94%	98:2	60 kg cm^{-2}
$Co(CO)_8$ (2-4 mol%)	74%	1:99	70 kg cm^{-2}

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12. Nesmeyanov, A. N.; Fiedlina, R. K.; Velchko, F. K. *DOK* **1957**, *114*, 557.
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Vinyltriphenylphosphonium Bromide[1]

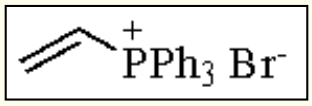

[5044-52-0] · $C_{20}H_{18}BrP$ · Vinyltriphenylphosphonium Bromide · (MW 369.25)

(phosphonioethylation; two-carbon chain-linking and alkenation; ring formation by Michael-Wittig, Michael-nucleophilic displacement, and Diels-Alder sequences[1])

Physical Data: mp 189-190 °C. The proton,[2] carbon, and phosphorus[3] NMR and the mass spectrum have been reported.[4]

Solubility: sol *t*-butanol.

Form Supplied in: white powder.

Preparative Methods: preparation of vinyltriphenylphosphonium bromide (**1**) has been accomplished by treatment of ethylenebis(triphenylphosphonium) dibromide with borate ion (32%),[5] (2-chloroethyl)triphenylphosphonium bromide with ***Triethylamine*** (72%),[6] (2-bromoethyl)triphenylphosphonium bromide with ***Silver(I) Oxide*** (85%),[7] and (2-phenoxyethyl)triphenylphosphonium bromide with boiling ethyl acetate (92%).[2]

Purification: may be recrystallized from *t*-butanol-ether[6] to give an analytically pure sample having a mp of 189-190°.[2]

Handling, Storage, and Precautions: hygroscopic; irritant; produces sneezing in many individuals. Use in a fume hood.

General Discussion.

Phosphonioethylation has been accomplished by employing a variety of nucleophiles (eq 1). Low concentrations (<=1.5 M) of aqueous ***Sodium Hydroxide*** give only (β-hydroxyethyl)triphenylphosphonium bromide (**2**) (RX = HO), whereas greater concentrations (&egt;2.0 M) of hydroxide give (**2**) (RX = HO) plus products attributable to an initial attack of hydroxide on the P atom.[8] A number of other nucleophiles have been employed to give high yields in the phosphonioethylation reactions; these include alcohols,[2,9] primary and secondary amines,[10,11] nitrosobenzene,[12] thiols,[2,9,13] and methylene groups activated by electrophilic moieties.[14-16]

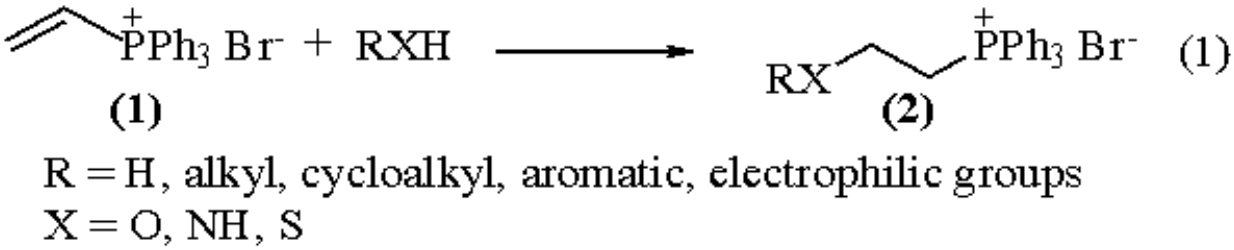

The Michael-type addition of a nucleophile to (**1**) followed immediately by a Wittig alkenation reaction has sometimes been called the Schweizer reaction (eq 2).[17] The nucleophiles (X) include various carbon, nitrogen, and oxygen species, with one example of a trimethyltin nucleophile.[18,19] Poor yields are reported for reactions of alkyllithiums (13-16%),[20] ***Phenyllithium*** (41%),[20] and diethyl ethylsodiomalonate (14%)[21] with ketones. The reaction of butyl-, vinyl-, and heptynyllithium gives none of the hoped-for product (**3**) with benzaldehyde.[7] However, cuprates give relatively good yields of (**3**). The (*Z*)-isomer predominates;[22] the addition of 5 equiv of ***Hexamethylphosphoric Triamide*** to the reaction enhances formation of the (*Z*)-isomer.[7]

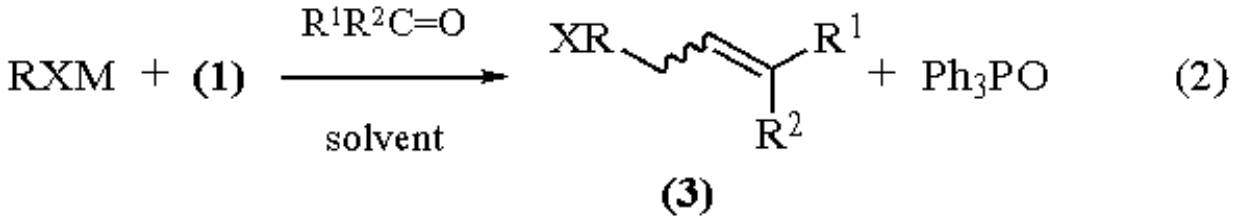

Secondary amines,[21] pyrrole,[23] sulfonamides,[21] and phthalimides,[17] as their salts, react with (**1**) and a variety of aldehydes to give allylamines. The (*Z*)-isomer is formed predominantly unless lithium salts are added.[17] The replacement of (**1**) by vinyltri-*n*-butylphosphonium bromide gives predominantly the (*E*)-isomer.[16] Primary amines have been successfully used only as the dilithio salts.[11] ***Sodium Ethoxide*** and thiophenoxide (see ***Thiophenol***) react with (**1**) and benzaldehyde to yield (**3**).[21]

The Schweizer reaction has been used mainly to prepare carbocyclic and heterocyclic species (eq 3).[24]

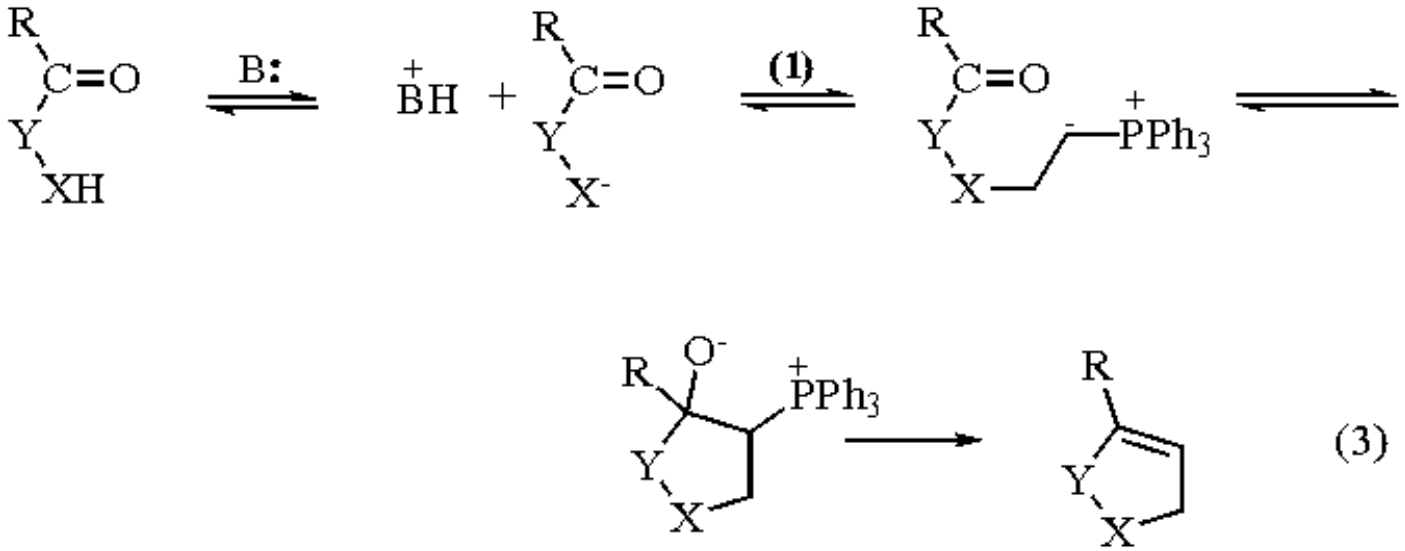

The types of ring that have been formed by this Schweizer annulation reaction are illustrated in eqs 4-12 using specific examples. Each equation is preceded by C_nX_m to illustrate the actual elemental components of the ring formed. The types of ring are: cyclopentene (eq 4);[25-27] cyclohexene (eq 5);[25,28-30] pyrrole or dihydropyrrole (eq 6);[31-40] 1,2-dihydroquinoline (eq 7);[41] 2,3-dihydropyridazine (eq 8);[40] dihydrofuran (eq 9);[14,42] 3,4-chromene (eq 10);[43] 2,5-dihydrothiophenes (eq 11);[44-48] and 3,6-dihydro-2*H*-thiopyrans (eq 12).[49]

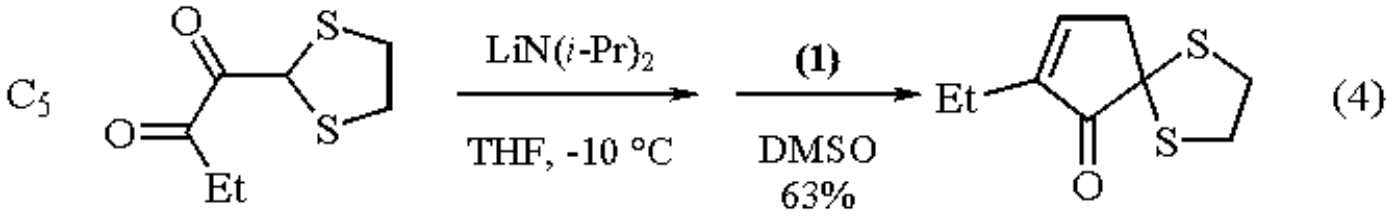

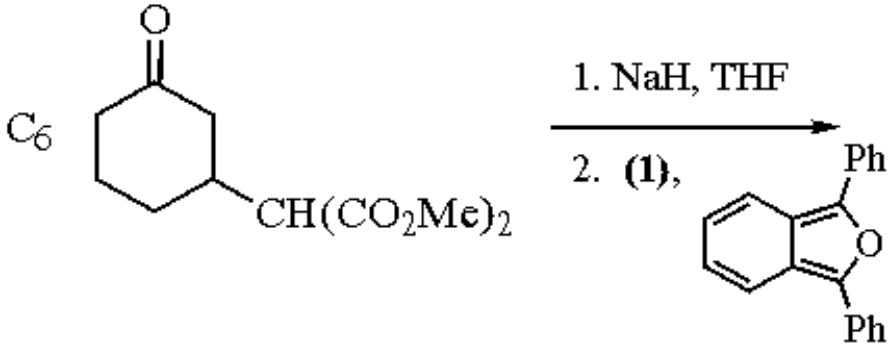
C6
O
CH(CO2Me)2
1. NaH, THF
2. (1),
Ph
O
Ph

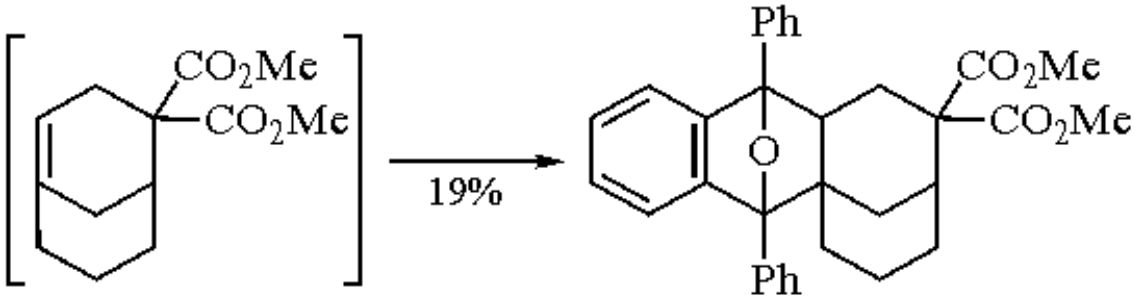
CO2Me
CO2Me
19%
Ph
O
Ph
CO2Me
CO2Me

(5)

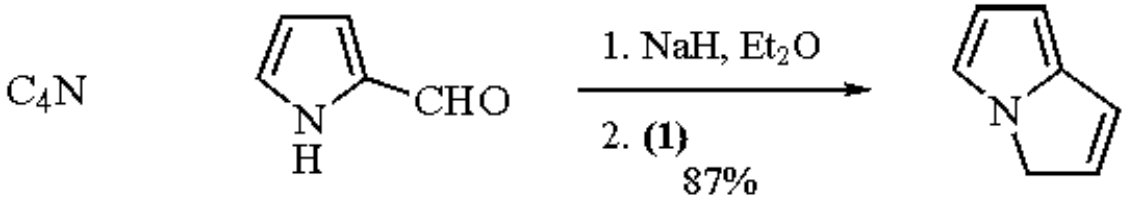
C4N
N
H
CHO
1. NaH, Et2O
2. (1)
87%
N

(6)

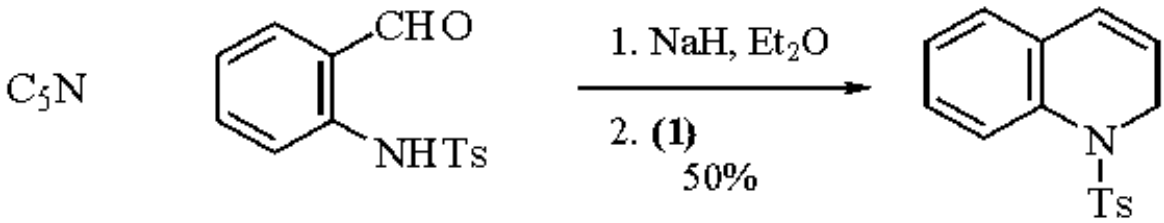
C5N
CHO
NHTs
1. NaH, Et2O
2. (1)
50%
N
Ts

(7)

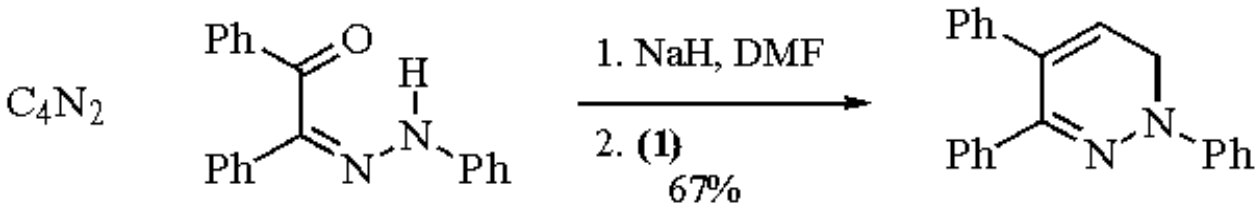
C4N2
Ph
O
H
N
Ph
N
Ph
1. NaH, DMF
2. (1)
67%
Ph
N
N
Ph
Ph
N

(8)

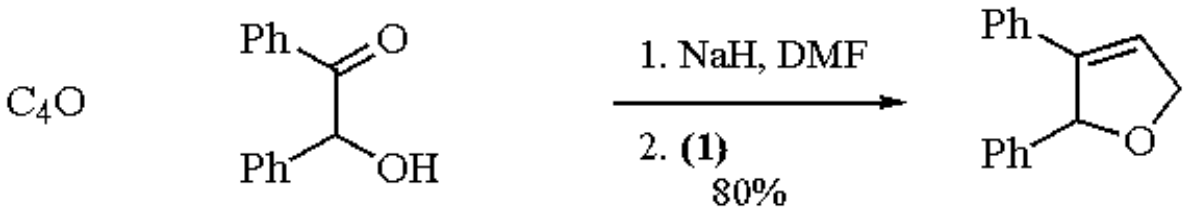
C4O
Ph
O
Ph
OH
1. NaH, DMF
2. (1)
80%
Ph
Ph
O

(9)

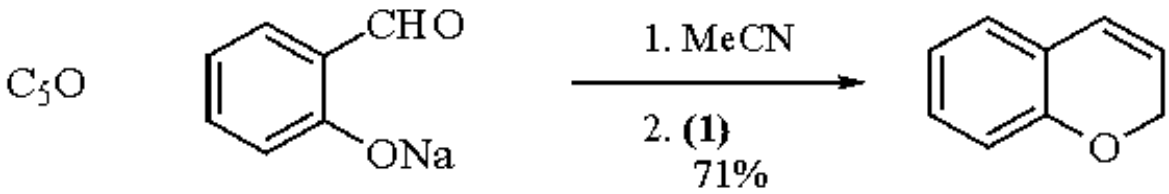
C5O
CHO
ONa
1. MeCN
2. (1)
71%
O

(10)

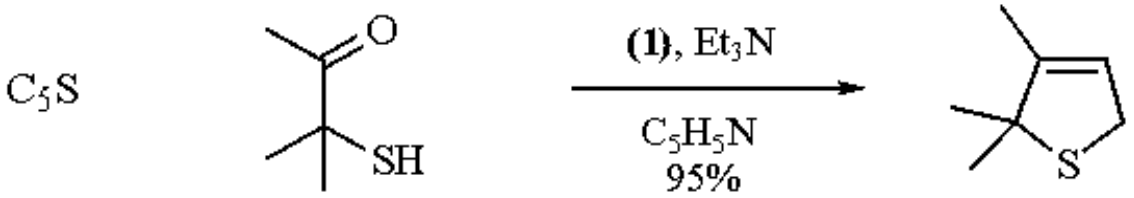

(11)

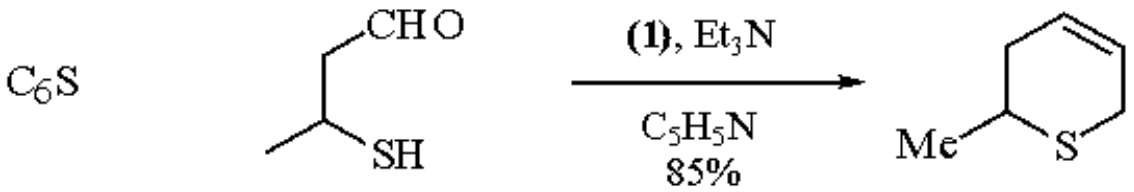

(12)

A novel extension of the Schweizer annulation reaction is a [2 + 2 + 2] annulation reaction,[50] involving two consecutive Michael-type additions followed by ring closure.[51-53] The reaction has been used successfully employing 1 mol of (**1**) and another Michael acceptor (eq 13) or 2 mol of (**1**) (eq 14).[53]

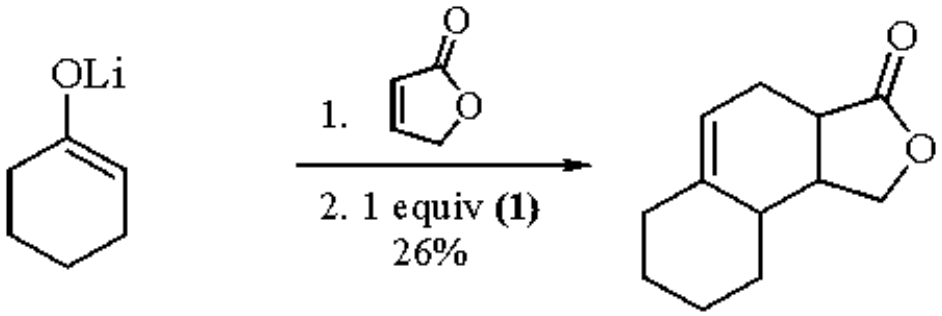

(13)

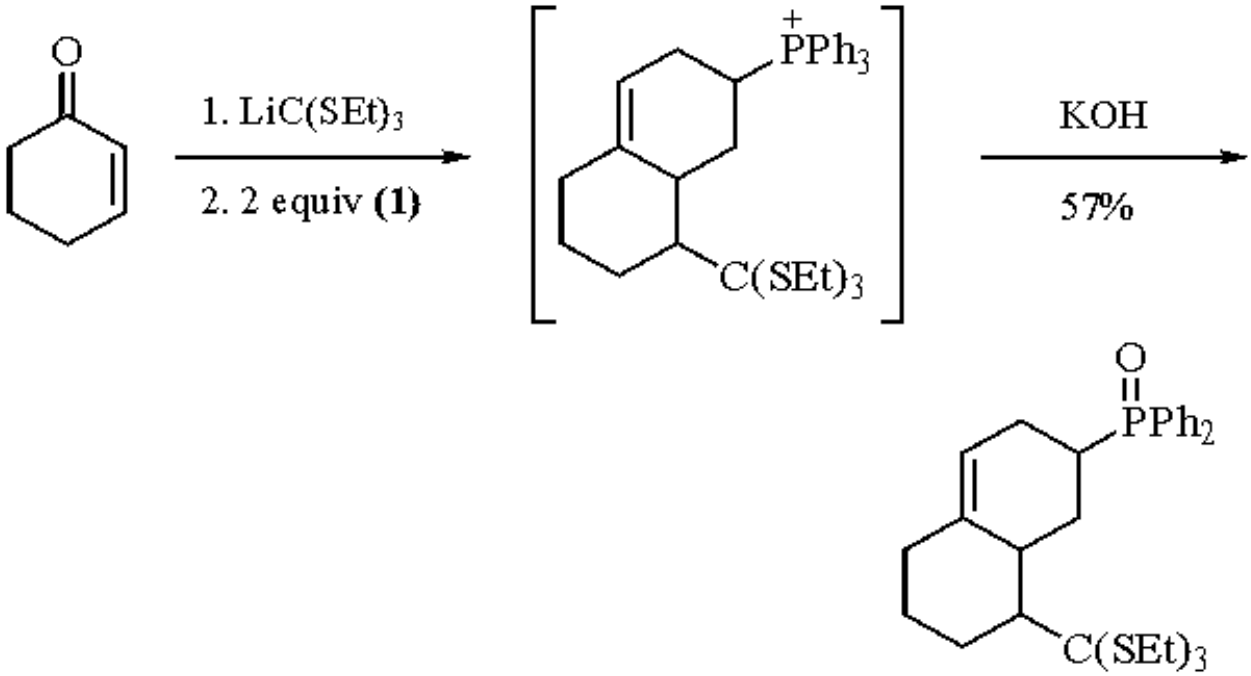

(14)

Ring formation employing (**1**) has also been accomplished with reaction sequences involving Michael-type additions followed by a nucleophilic internal substitution reaction (eq 15).[30,54-58]

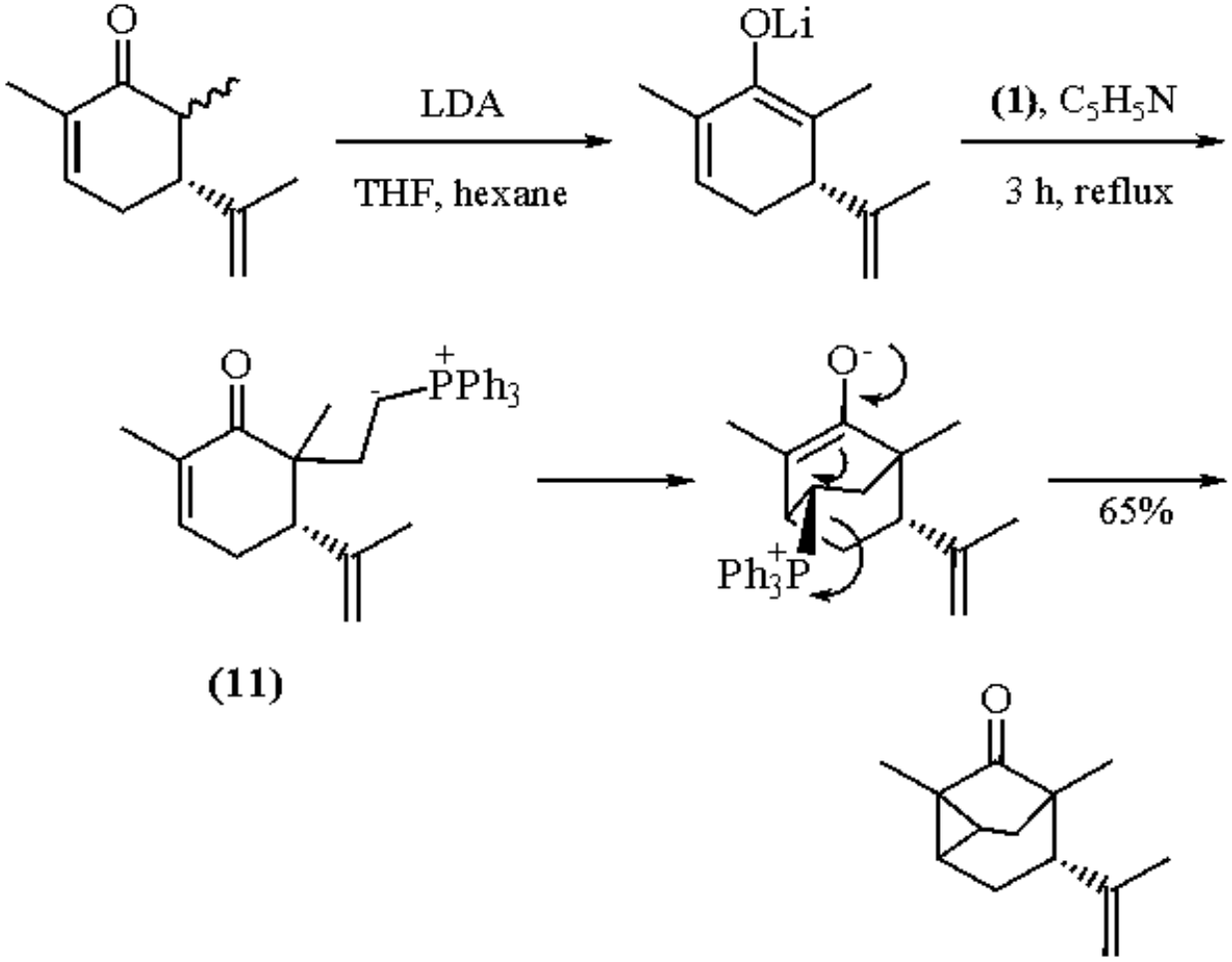

(15)

[3 + 2] Cycloadditions have yielded pyrroles (eq 16),[59] 2-pyrazolin-3-yltriphenylphosphonium bromides (eq 17),[60] pyrazoles (eq 18),[61] and the adduct from a nitrone, which decomposes spontaneously (eq 19).[62] Diels-Alder, or [4 + 2], cycloadditions have also been explored (eq 20).[63-65]

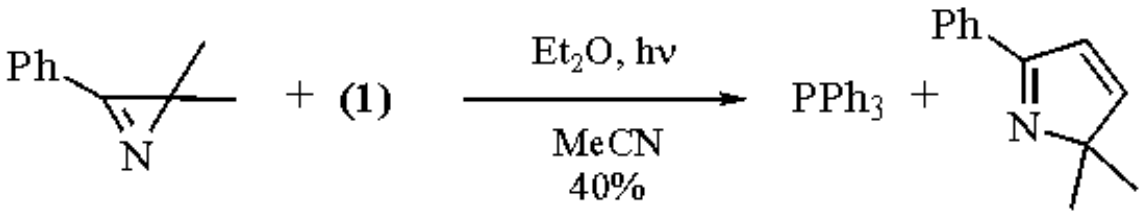

(16)

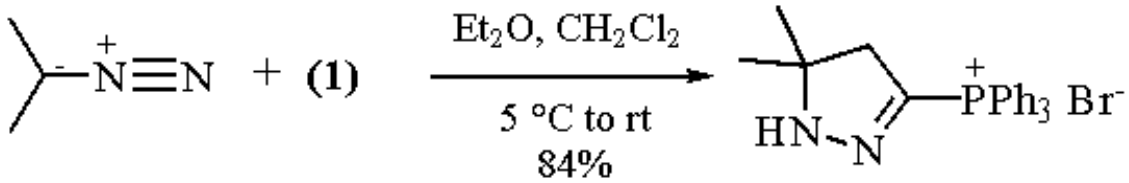

(17)

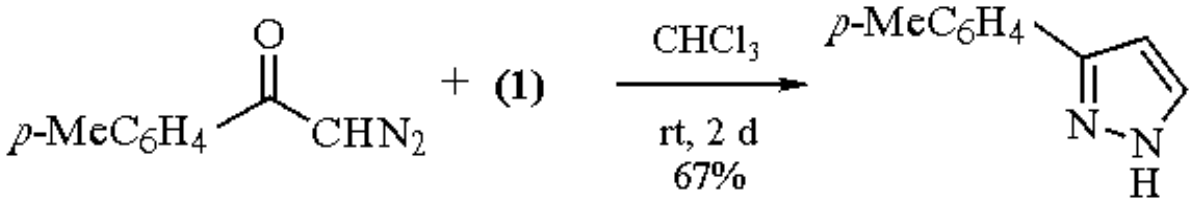

(18)

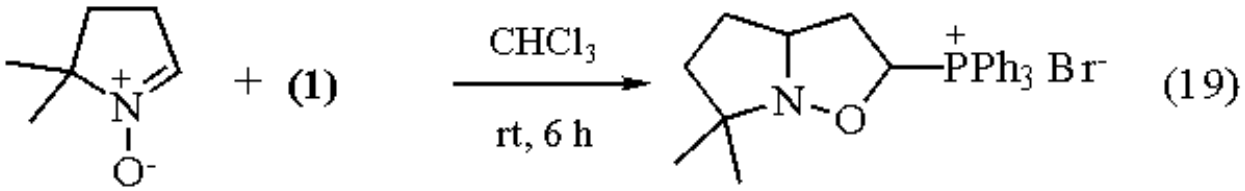

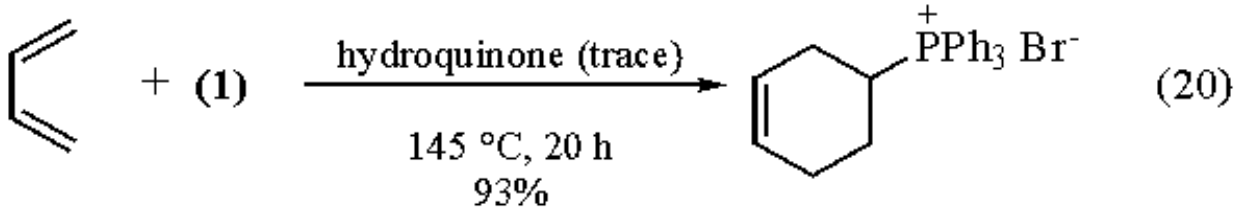

Related Reagents.

Allyltriphenylphosphonium Bromide.

---

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Vitamin B_{12}[1-3]

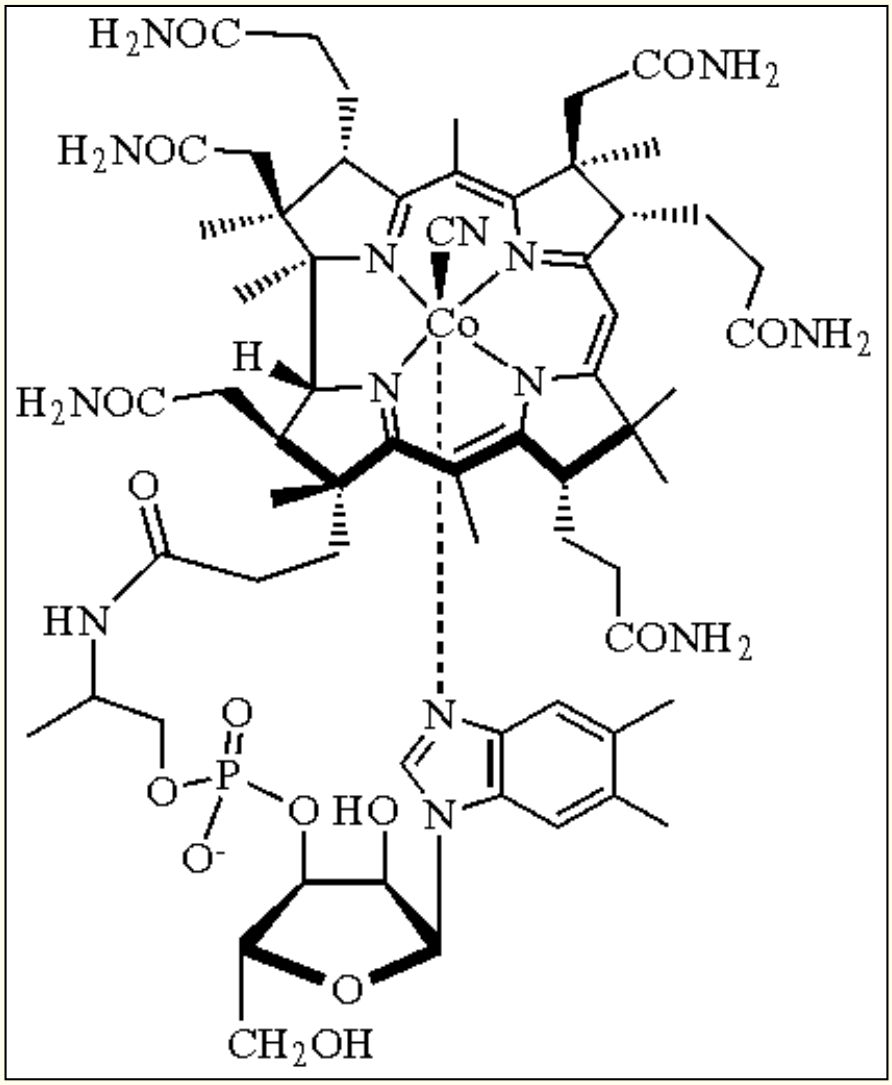

[68-19-9] · $C_{63}H_{88}CoN_{14}O_{14}P$ · Vitamin B_{12} · (MW 1355.40)

(radical source via carbon-cobalt bond homolysis; stoichiometric and catalytic radical C-C bond formation; enantioselective catalyst for molecular rearrangements)

Physical Data: odorless and tasteless, hygroscopic, dark red solid; does not have a defined melting point; darkens at 210-220 °C but is not melted at 300 °C.

Solubility: sol H_2O (1 g/80 mL), alcohol; insol acetone, chloroform, ether.

Form Supplied in: powder or crystalline solid; available from biologically oriented chemical suppliers.

Handling, Storage, and Precautions: hygroscopic; absorbs moisture from air. Hydrated crystals are air stable. Aqueous solutions slowly decompose. May be harmful by inhalation, ingestion, or skin absorption and can cause eye and skin irritation. Keep containers tightly closed and store in a cool dry place. Use in a fume hood with safety goggles and chemically resistant gloves and clothing.

Stoichiometric Processes.

In 1964, Schrauzer published the first of many papers on the synthesis and properties of alkyl cobaloximes.[1] This work led to the

development of cobaloximes and related compounds as vitamin B_{12} model compounds, e.g. (**1**)-(**4**), summarized in a review in 1976.[2] By the mid 1970's, many of the fundamental reactions of vitamin B_{12} and model complexes were well established. This work is summarized in several reviews.[3]

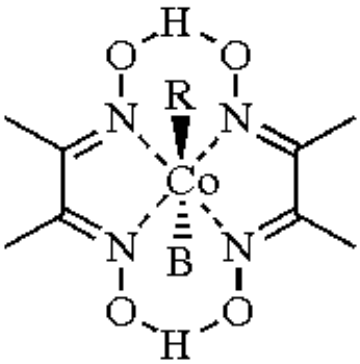

$RCo^{III}(dmgH)_2B$
(cobaloxime complex)
(1)

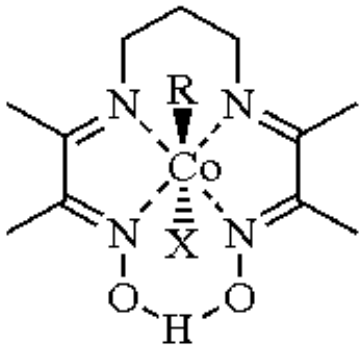

$RCo^{III}\{(DO)(DOH)PN\}X$
('DODOH' or Costa's complex)
(2)

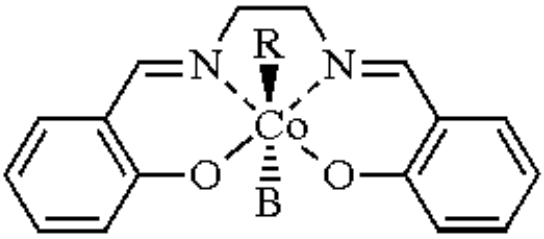

$RCo^{III}(salen)B$
(salen complex)
(3)

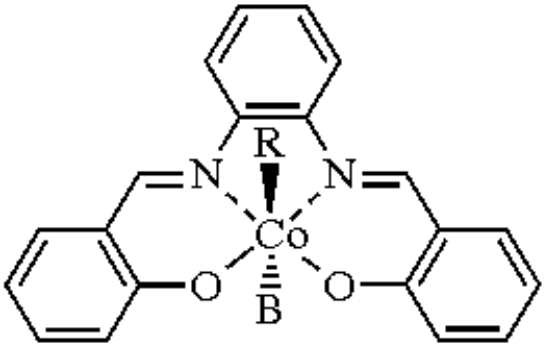

$RCo^{III}(salophen)B$
(salophen complex)
(4)

Alkylcobalt complexes provide an easy bridge between two-electron ionic chemistry and one-electron radical chemistry. This has made them popular and useful radical precursors; ionic reactions provide alkylcobalt complexes which then provide alkyl radicals via C-Co bond homolysis. In the mid 1970s and early 1980s, radical chain S_H2' reactions of allylcobaloximes were studied (eq 1).[4] These reactions were not applied to specific synthetic problems.[5]

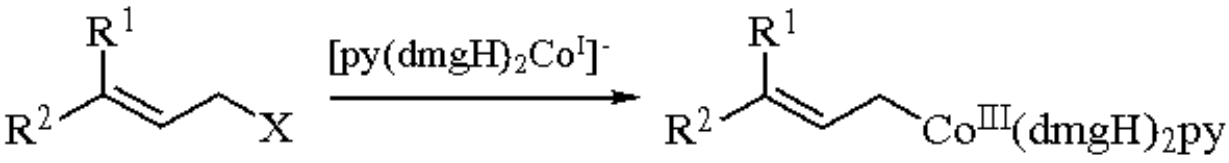

X = halide, sulfonate ester

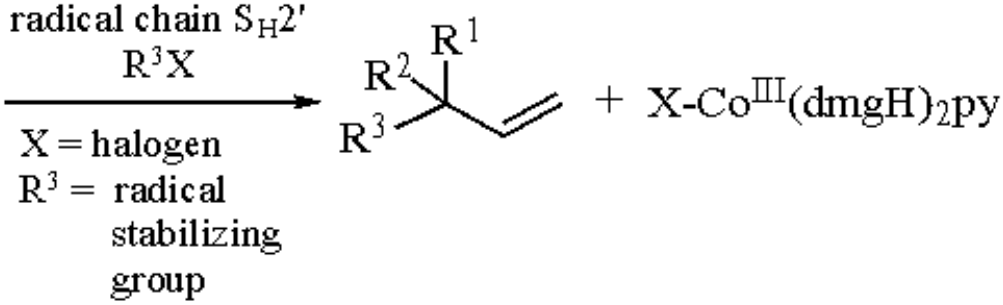

(1)

In the late 1980s, and early 1990s, stoichiometric nonchain organocobalt reactions have been developed.[6] Cobalt-based radicals, formed by carbon-cobalt bond homolysis, continue to participate in multistep radical processes to guide reaction pathways into particular directions.[7] The main practical benefits are: (1) radical-alkene additions are possible; (2) polymerization is inhibited; and (3) the alkene is regenerated in the final product by cobalt-mediated β-H elimination. A tandem radical cyclization (eq 2)[8] illustrates the main features. Oxidative addition of the cobalt anion to the alkyl bromide generates the alkyl radical which undergoes cyclization followed by trapping by the Co^{II} radical. This type of reaction was first observed in earlier studies of the mechanism of oxidative addition of Co^{I} to hindered alkyl halides.[9] Photolytic homolysis of the C-Co bond produces the alkyl radical which undergoes cyclization followed by Co^{II}-mediated β-H elimination.

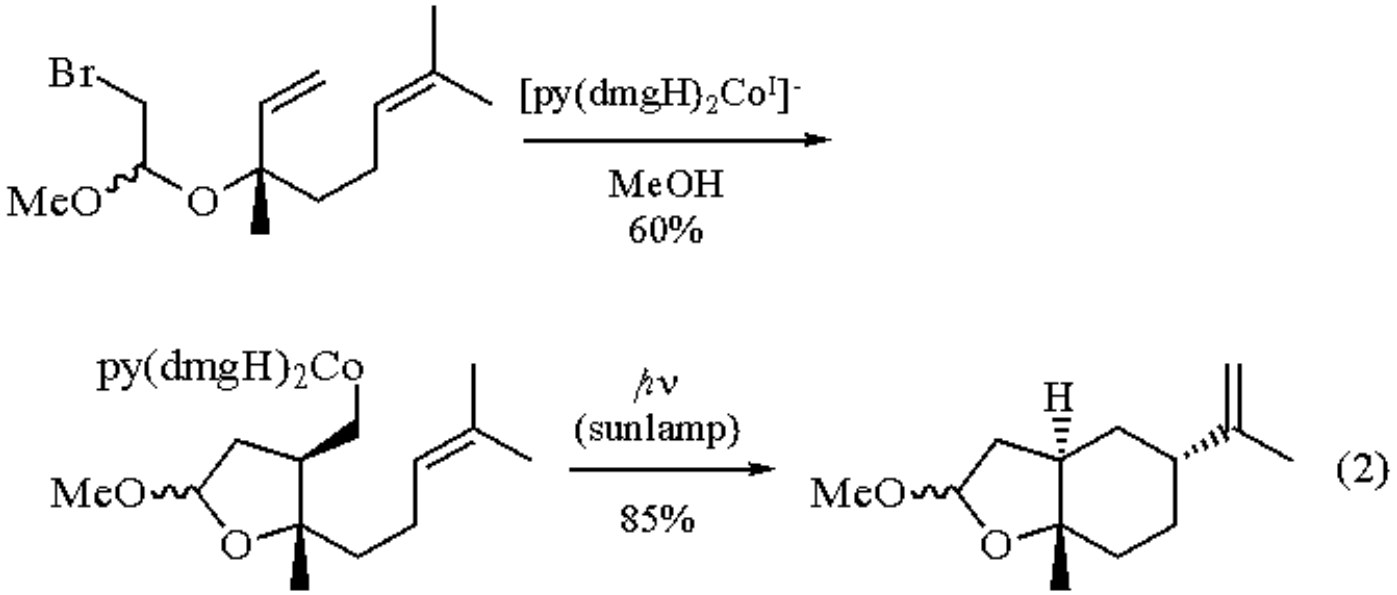

A similar strategy has been applied to the synthesis of kainoids and related compounds (eq 3).[10] Both stoichiometric and catalytic amounts of cobalt reagents have been used in these and other cyclization studies. Several examples of these types of cyclizations have been published,[11] including cyclizations using aryl halides as precursors to aryl radicals.[12]

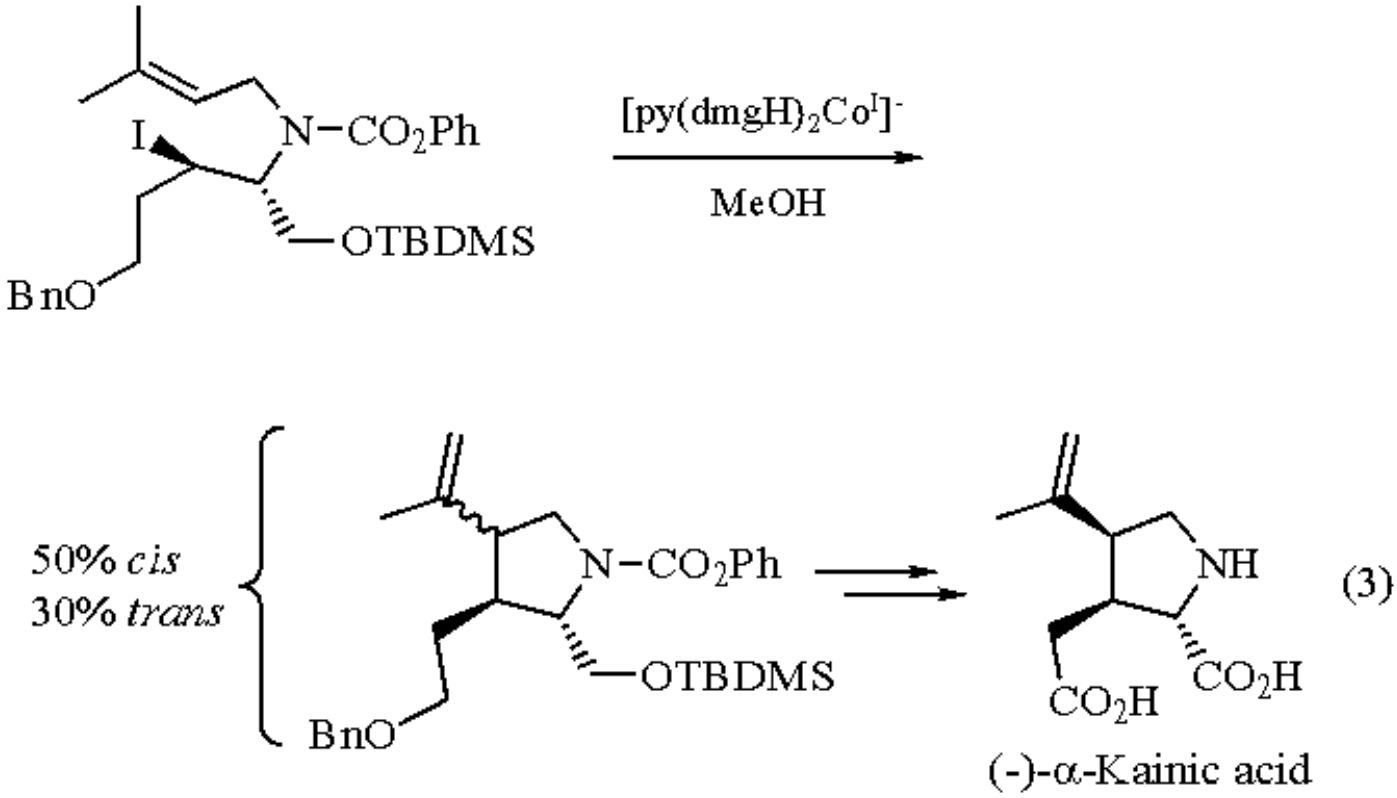

Alkylcobalt reagents are often prepared from the reaction of anionic Co^{I} complexes with alkyl halides or sulfonate esters. They can also be prepared by conjugate addition of anionic Co^{I} complexes to α,β-unsaturated carbonyl compounds and nitriles, placing the cobalt β to the activating group, or by addition of neutral Co^{III} hydrides to activated alkenes (carbonyl, nitrile, and aryl activating groups), placing the cobalt α to the activating group.[13] Anionic Co^{I} anions open epoxides regioselectively and the resulting cobaloximes show different patterns of reactivity under thermolysis versus photolysis (eq 4).[14] A mechanistic study indicates that cobalt-mediated cyclizations proceed via

radicals,[15] but the reaction mechanism in the reactions in eq 4 has not been studied in detail. Acyl radicals can be generated from readily prepared acyl cobalt complexes.[16] The key step in a formal synthesis of racemic thienamycin is illustrative (eq 5).[17]

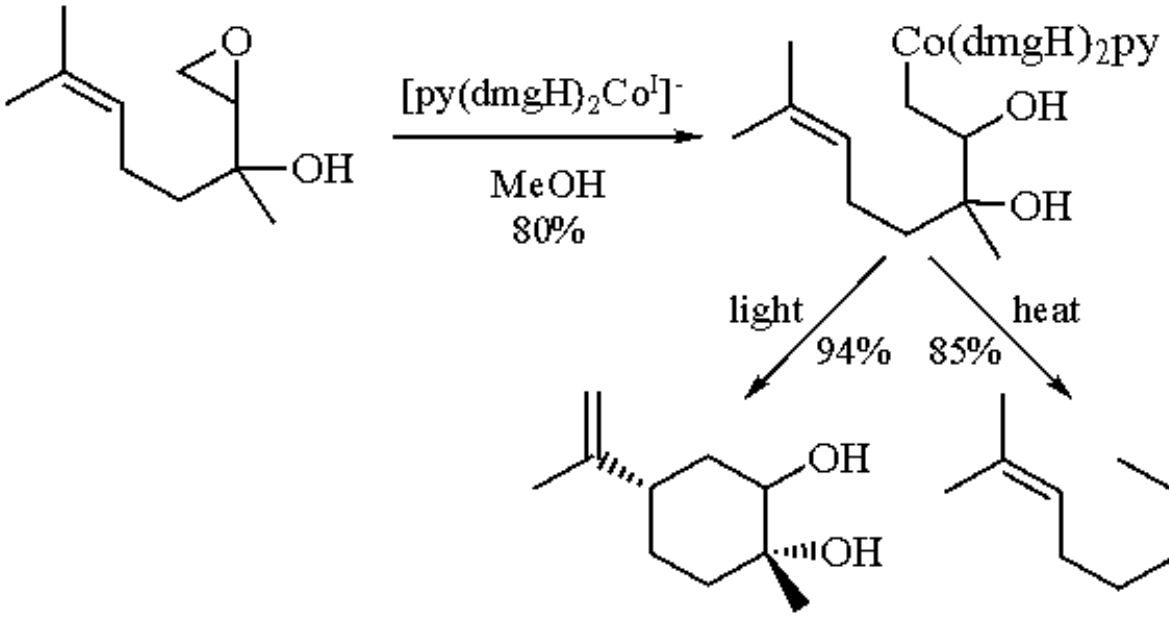

(4)

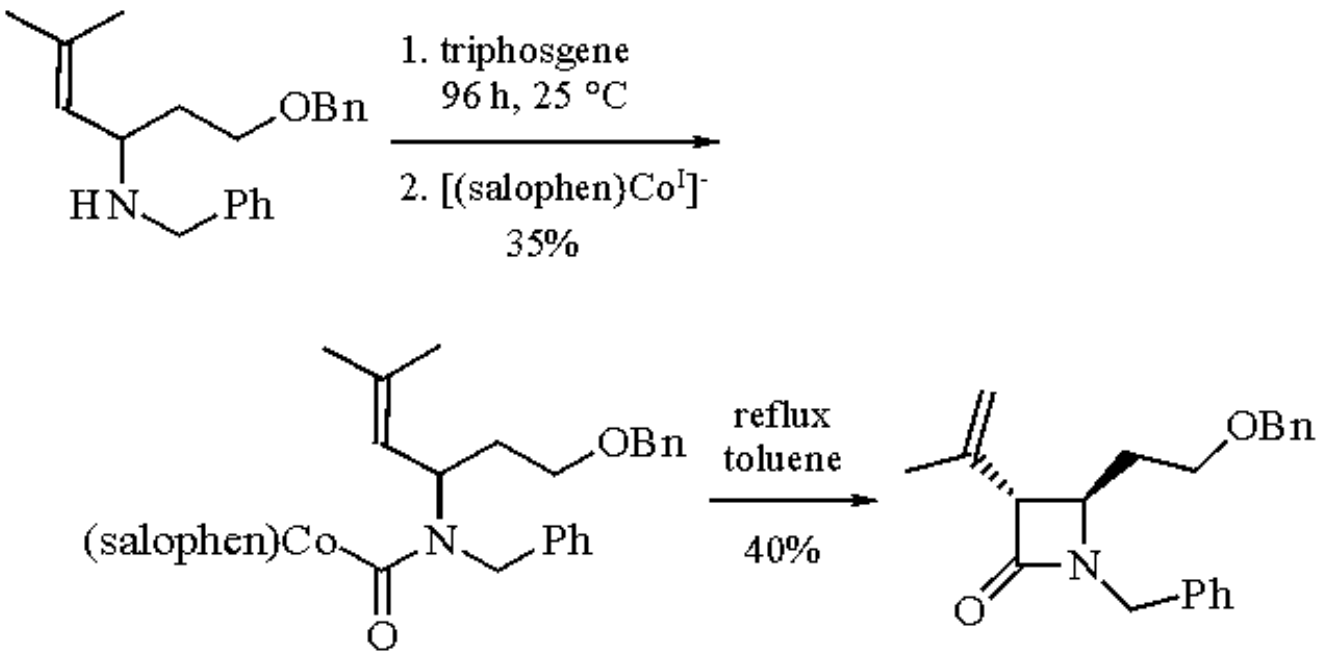

(5)

Intermolecular cross-coupling reactions have been developed.[18] One application to the synthesis of KDO takes advantage of alkene regeneration to allow further synthetic elaboration (eq 6).[19] Similar reactions have been developed for C-C bond constructions at the anomeric center of hexopyranoses,[20] leading to the production of *C*-glycosides, at C-1 of an open-chain pentose, leading to a synthesis of KDO,[21] and at C-3 of ribofuranoses.[22] Nonalkene cross-coupling partners have been used, specifically protonated heteroaromatics[23] and nitroalkyl anions.[24] Nitroalkyl anion cross couplings have been used to prepare *C*-disaccharides (eq 7).[25]

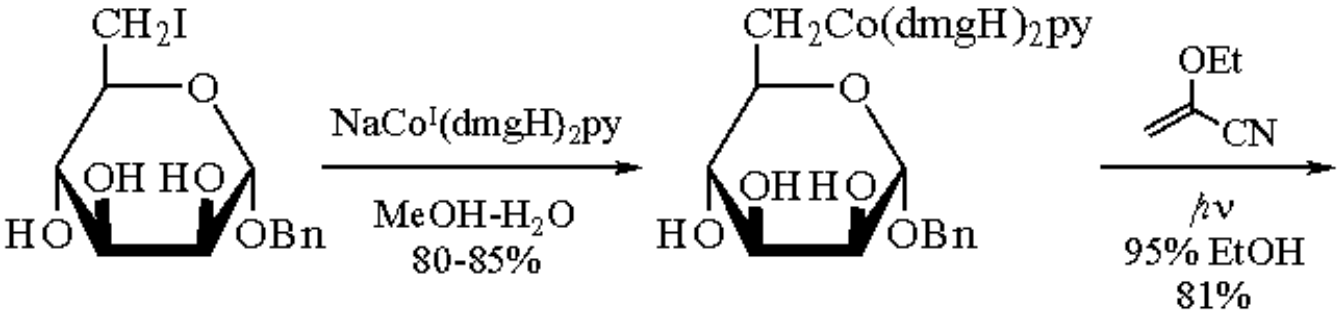

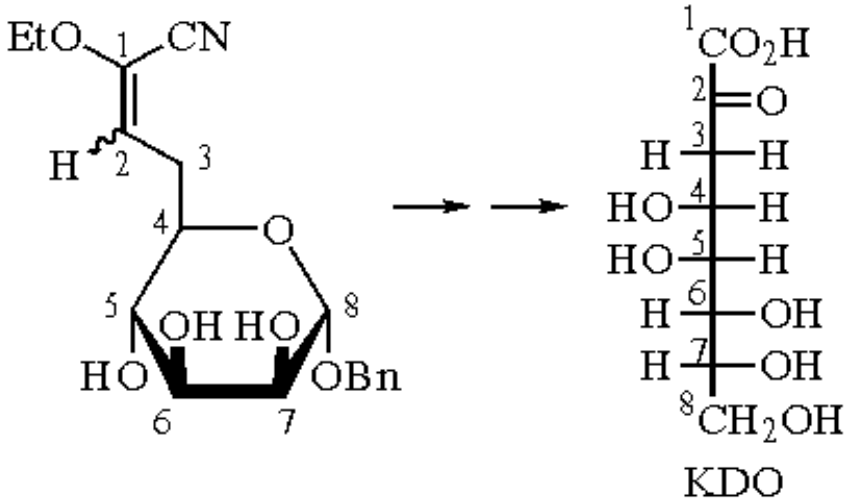

(6)

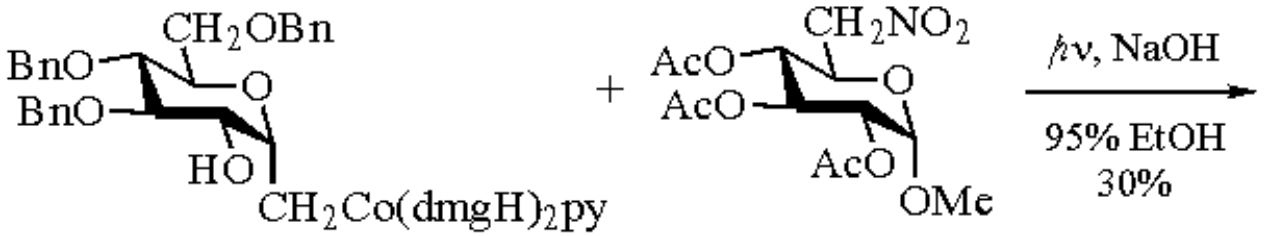

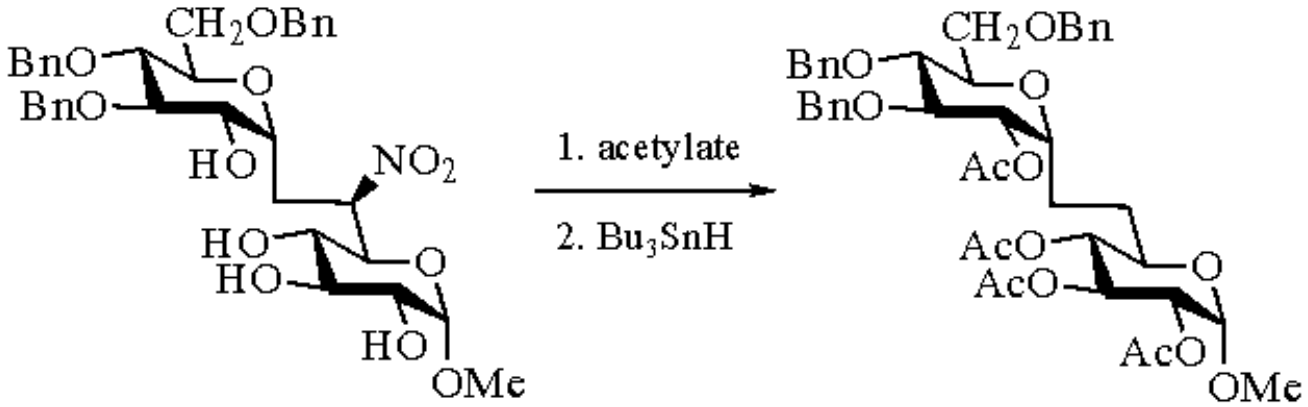

(7)

Catalytic Processes.

Catalytic processes lead to intramolecular and intermolecular C-C bond constructions which are usually directly analogous to the stoichiometric reactions. This topic was reviewed in 1983.[26] Catalytic processes often lead to reduction rather than alkene regeneration; this is more likely to happen with B_{12} as a catalyst than it is with a cobaloxime. Scheffold pioneered the use of vitamin B_{12} as a catalyst for C-C bond formation,[27] and Tada pioneered the use of model complexes such as cobaloximes.[28] Several of the reactions described in the section on stoichiometric reactions have also been performed catalytically, as mentioned in that section. Commonly used chemical reductants include ***Sodium Borohydride*** and ***Zinc*** metal. Electrochemical reduction has also been used.[29] A novel catalytic system with a Ru^{II} trisbipyridine unit covalently tethered to a B_{12} derivative has been used for photochemically driven catalytic reactions using triethanolamine

as the reductant.[30] A catalytic system using DODOH complexes can lead to reduction products or alkene regeneration depending upon the reaction conditions.[31] These catalytic B_{12} and model complex systems all utilize a Co^{I}-Co^{II}-Co^{III} redox shuttle, shown in eq 8. Several other publications have described catalytic systems such as these,[32] including B_{12}-catalyzed alkene acylations via addition of acyl radicals to activated alkenes[33] and the use of hydrophobic B_{12} derivatives which are designed to provide a binding pocket for enzyme-like catalytic reactions, usually skeletal rearrangement reactions designed to mimic reactions catalyzed by B_{12}-containing enzymes.[34] A catalytic system utilizing a Co^{II}-Co^{III} redox shuttle has been described.[35] A catalytic system for alkene oligomerization has been developed.[36] Cobalt complexes are known to catalyze radical alkene polymerization.[37]

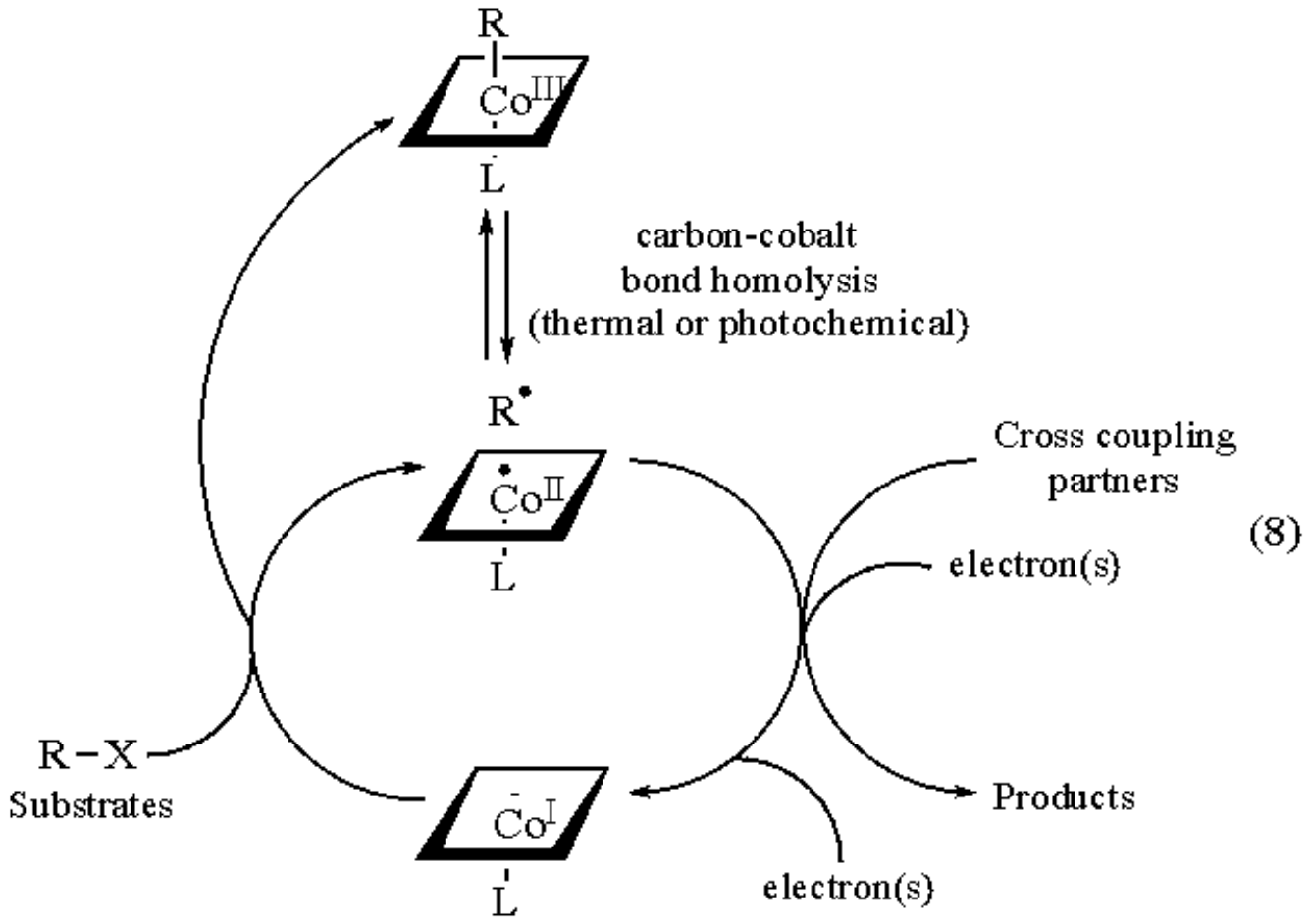

Examples of the use of vitamin B_{12} as a catalyst for enantioselective processes have been reported. The rearrangement of aziridines can proceed catalytically with ee's of up to 95% (eq 9).[38] Analogous rearrangements on achiral epoxides (typically 60% ee)[39] and achiral peroxides (low ee's)[40] have been reported.

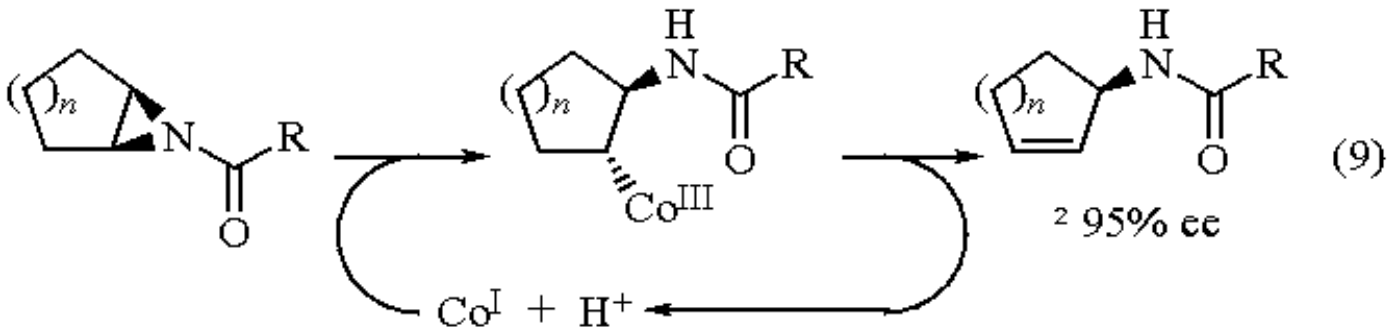

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Xenon(II) Fluoride[1]

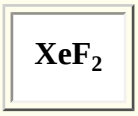

[13709-36-9] · F_2Xe · Xenon(II) Fluoride · (MW 169.29)

(relatively mild fluorine source, capable of electrophilic fluorination of carbon-hydrogen bonds; radical fluorinating agent; fluorodecarboxylation of carboxylic acids)

Physical Data: 129 °C (triple point); *d* 4.32 g cm^{-3}.

Solubility: sol H_2O (25 g/L at 0 °C), with slow decomposition; sol CCl_4, CH_2Cl_2, HF, BrF_3, MeCN.

Form Supplied in: white solid; commercially available.

Preparative Methods: prepared from xenon and fluorine.[2]

Handling, Storage, and Precautions: strong oxidizing agent; hydrolyzes in humid air. Like all other potential sources of elemental fluorine with the ability to fluorinate any substrate, it must be treated with great respect and caution, and should only be used with the proper equipment and precautions for handling reactive fluorinating agents. Contamination by XeF_4 will generate explosive XeO_3 upon hydrolysis.

Fluorodecarboxylation.

Xenon difluoride has the unique ability to convert aliphatic carboxylic acids to fluoroalkanes (fluorodecarboxylation) without fluorinating other portions of the molecule (eq 1).[3-5] This reaction is the fluorine analog of the Hunsdiecker and Kochi reactions. The substrates may contain aryl, aryloxy, and ketonic groups (Table 1).[3] Compounds containing hydroxy groups give complex mixtures. Secondary acids like cyclohexanecarboxylic acid, as well as amino acids, cholic acid, cinnamic acid, *trans*-phenylcyclopropanecarboxylic acid, and benzoic acid resist decarboxylation. Optically active α-trifluoromethyl-α-methoxyphenylacetic acid is fluorodecarboxylated to racemic α-fluoro-α-trifluoromethyl-α-methoxytoluene (**1**).[4] When this reaction is carried out in the presence of $Bu_4N^+\ {}^{18}F^-$, the $^{18}F^-$ is incorporated into (**1**) in 65% radiochemical yield.[4,5] A limitation is illustrated by the reaction of CF_3CO_2H and excess XeF_2 in benzene to give (trifluoromethyl)benzene.[5] A general procedure for fluorodecarboxylation is to combine equimolar amounts of the acid and XeF_2 in CH_2Cl_2 in a polyethylene bottle, slowly bubble HF into the solution, and store overnight at rt. The next day the solution is washed with dilute $NaHCO_3$ and purified. Although ***Bromine Trifluoride*** also promotes fluorodecarboxylation,[6]

o-Xylylene *N,N*-Diethylphosphoramidite

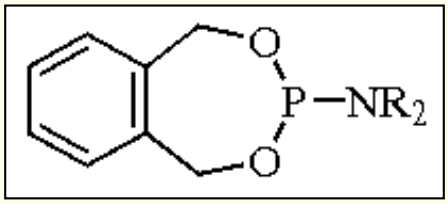

(**1**; R = Et)

[82372-35-8] · $C_{12}H_{18}NO_2P$ · *o*-Xylylene *N,N*-Diethylphosphoramidite · (MW 239.28) (**2**; R = Me)

[69813-53-2] · $C_{10}H_{14}NO_2P$ · *o*-Xylylene *N,N*-Dimethylphosphoramidite · (MW 211.22)

(phosphitylating reagents for alcohols to provide phosphoric monoesters and mixed diesters)

Physical Data: (**1**) bp 95-96 °C/0.1 mmHg; n_D 1.543. (**2**) bp 78-80 °C/0.03 mmHg; n_D 1.555.

Solubility: insol cold H_2O; sol CH_2Cl_2, THF, MeCN.

Form Supplied in: (**1**): crystalline solid; commercially available.

Analysis of Reagent Purity: δ_P (C_6H_6) +143 (**1**), +142 (**2**).

Preparative Methods: a mixture of hexaethyl- or ***Hexamethylphosphorous Triamide*** and ***1,2-Bis(hydroxymethyl)benzene*** is heated until evolution of amine ceases.

Purification: distillation under reduced pressure.

Handling, Storage, and Precautions: these reagents can be stored for extended periods (>6 months) in the absence of moisture and air. The stability of (**1**) is greater than that of (**2**).

Phosphoric Monoester Synthesis.[1]

The phosphoramidites react smoothly with a variety of sterically hindered alcohols and polyols in the presence of 1*H*-tetrazole to afford the phosphorous triesters, which are oxidized in situ with ***m-Chloroperbenzoic Acid*** to give cyclic phosphoric triesters in high yields (eqs 1-3).[2-4] The triesters are deprotected by hydrogenolysis on ***Palladium on Carbon*** to furnish phosphoric monoesters.

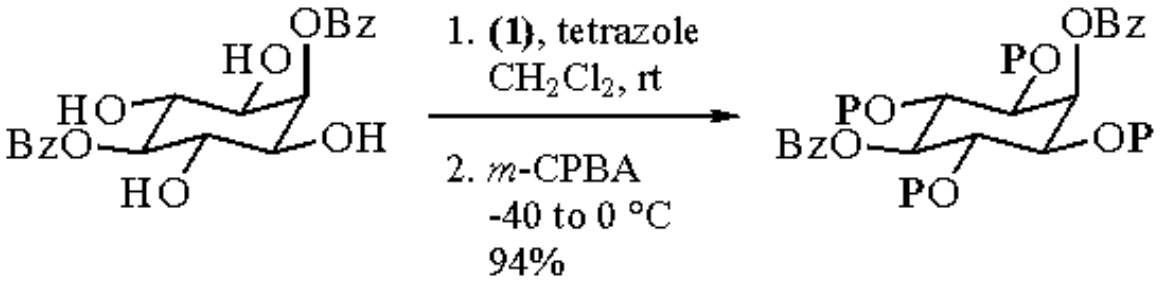

(1)

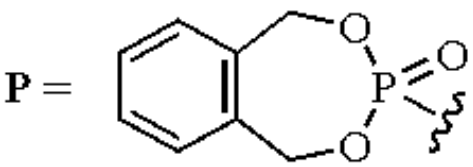

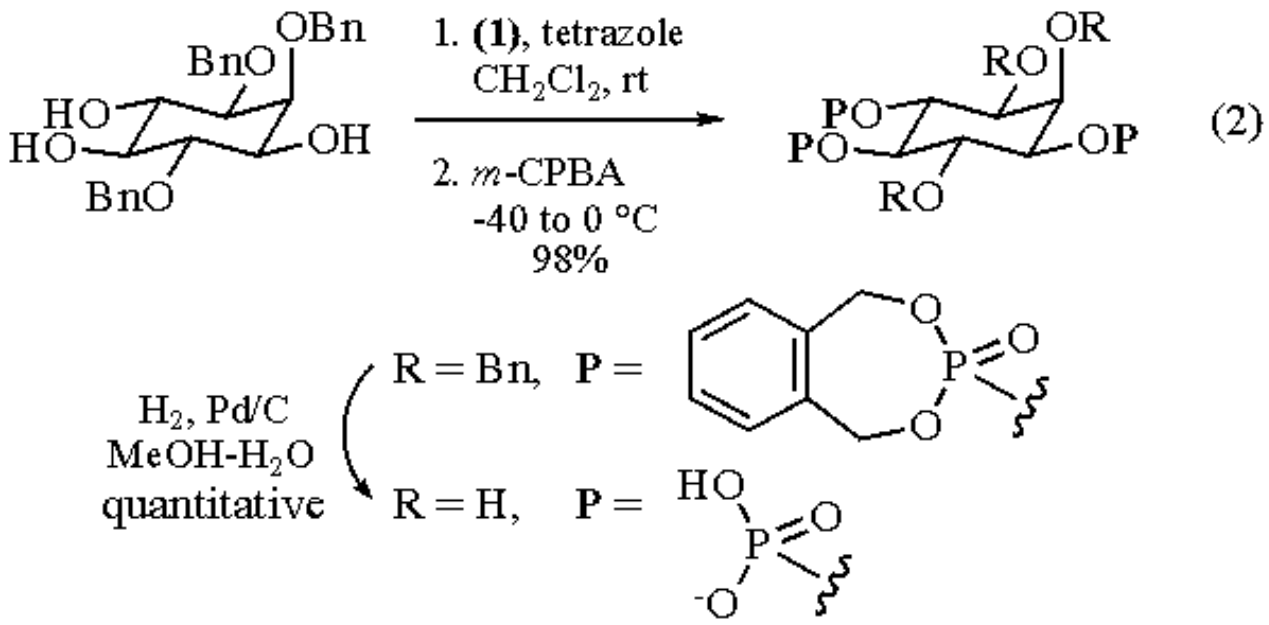

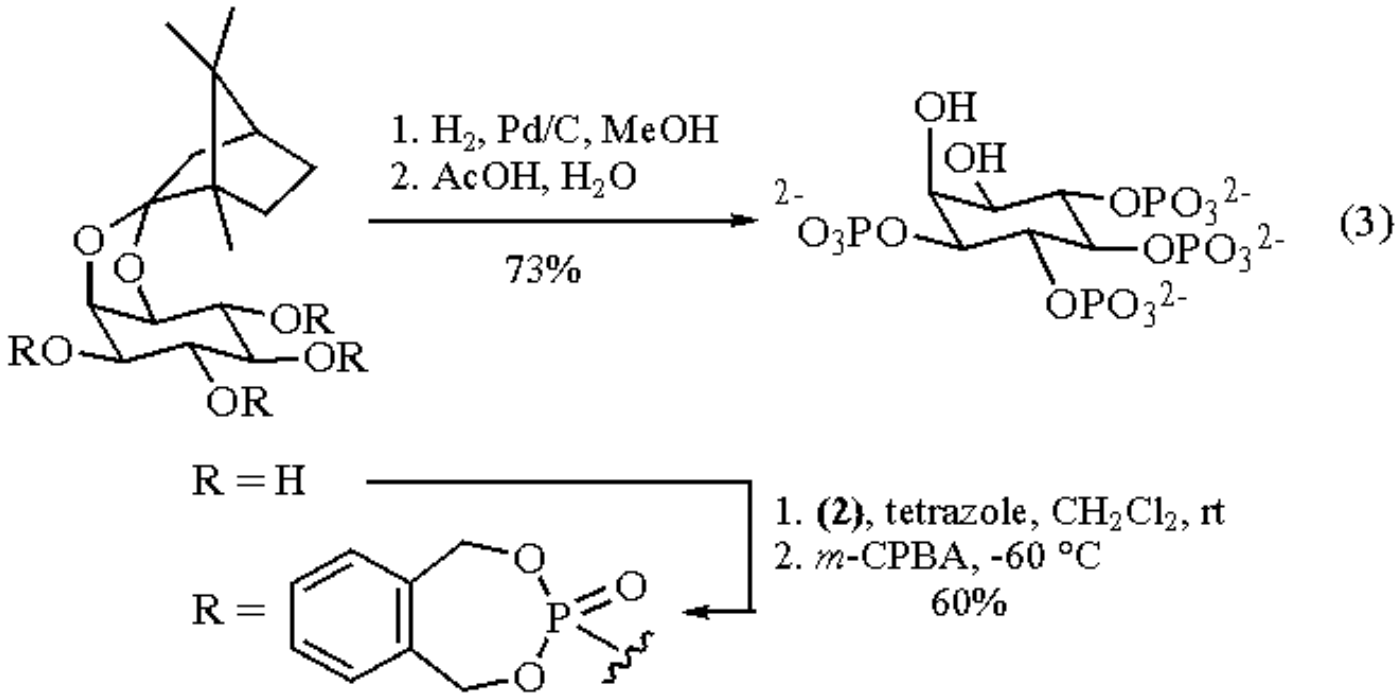

The reagents are potent alternatives to dibenzyl phosphoramidites. The former reagents can be prepared in one step and are easily purified by distillation, while the acyclic amidites require two steps. See ***Dibenzyl N,N-Diethylphosphoramidite*** and ***Dibenzyl Phosphorochloridate***; dibenzyl phosphorofluoridate and tetrabenzyl pyrophosphate are used for the same purpose.

Phosphoric Diester Synthesis.[5]

o-Xylylene *N*,*N*-diethylphosphoramidite can be used for sequential phosphorylation of two different alcohols to afford the corresponding triester (eq 4), which is converted to the phosphoric mixed diester by deprotection employing hydrogenolysis or disodium disulfide.

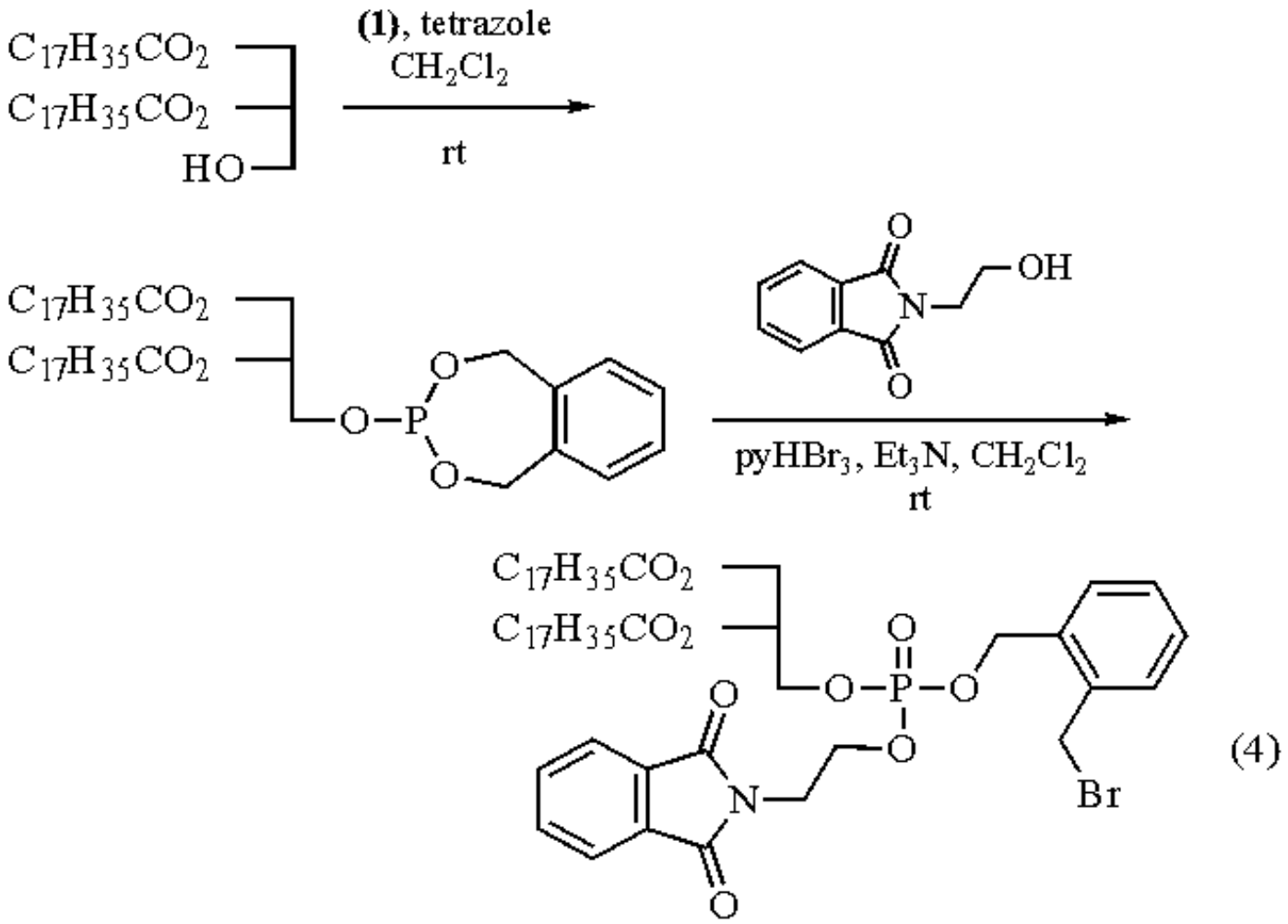

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Ytterbium(0)

Yb

[7440-64-4] · Yb · Ytterbium(0) · (MW 173.04)

(reducing agent capable of Birch-type reductions of aromatic and alkenic systems;[1-3] promotes the coupling of aldehydes and ketones to generate the corresponding pinacolic product; forms an organoytterbium complex with aromatic substrates which adds nucleophilically to ketones, epoxides, nitriles, and carbon dioxide to generate highly functionalized products[5-7])

Physical Data: mp 824 °C; bp 1427 °C; *d* 6.760 g cm^{-3}; face centered cubic structure at rt.

Form Supplied in: silvery, ductile metal; commercially available as 40 mesh powder, ingot, chip, foil.

Handling, Storage, and Precautions: is somewhat air and moisture sensitive and should be handled under an inert atmosphere.

Dissolving Metal Reductions.

Ytterbium turnings are added piecewise to dry liquid ***Ammonia***, resulting in a deep-blue solution containing the ammoniated electron. Cosolvents such as ether, THF, or *t*-butanol can be added. The blue Yb-NH_3 solution is stable for several hours at -33 °C. Quenching of the solution with water results in replacement of the deep-blue color by a transient green color, characteristic of Yb^{2+}, which changes to a brown suspension with formation of Yb^{3+} species.

Solutions of ytterbium in ammonia[8] have properties similar to those of alkali metal-ammonia solutions[9] and are strongly reducing. This is a consequence of the fact that Yb^0 ($4f^{14}6s^2$), like other lanthanides, is electropositive and dissolves readily in ammonia,[10] an excellent supporting medium for electron transfer.[11] Dissolution of ytterbium in ammonia yields two electron equivalents (eq 1) and results in Yb^{2+} which possesses the closed f shell of xenon. However, Yb^{2+} is readily oxidized in air to Yb^{3+} ($E_{Yb^0 - Yb^{3+}}$ = -2.27 V). The ionic radius of Yb^{2+} is intermediate between that of Li^+ and Na^+. Physical characteristics of ytterbium-ammonia solutions have been described.[12]

$$Yb^0 + nNH_3 \longrightarrow Yb^{2+} + 2\,e^-(NH_3)_n \qquad (1)$$

Solutions of Yb-NH_3 reduce benzenoid[13] and other aromatic rings to 1,4-dihydro aromatics and, as in the reduction with alkali metal-ammonia systems,[14] substituents exert a profound effect on the rate of the reaction and on the structure of the product. Thus benzoic acid is reduced rapidly to the 1,4-dihydro derivative (eq 2), while anisole and *p*-cresyl methyl ether are reduced more slowly to 1-methoxy-1,4-cyclohexadienes (eq 3).

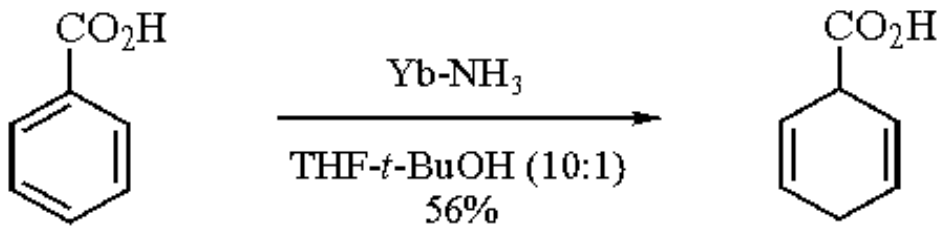

(2)

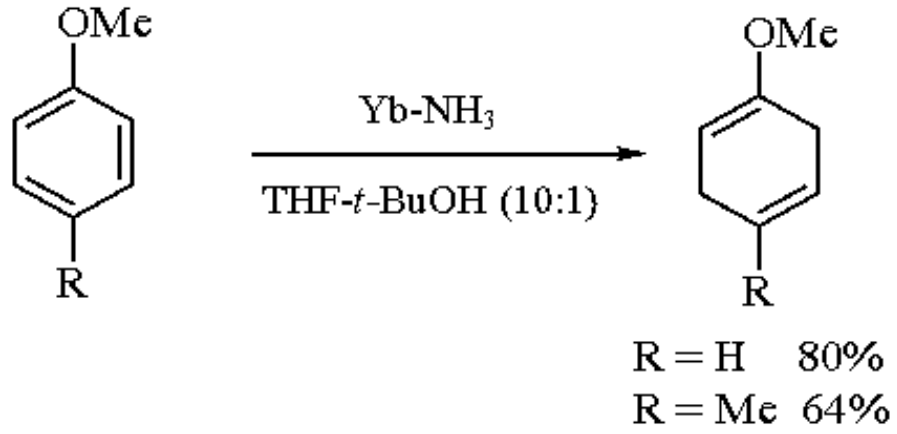

(3)

Application of this reduction to a derivative of estrone resulted, after hydrolysis of the intermediate enol ether, in dihydrotestosterone (eq 4).[15] In this case, no proton donor was added to the medium.

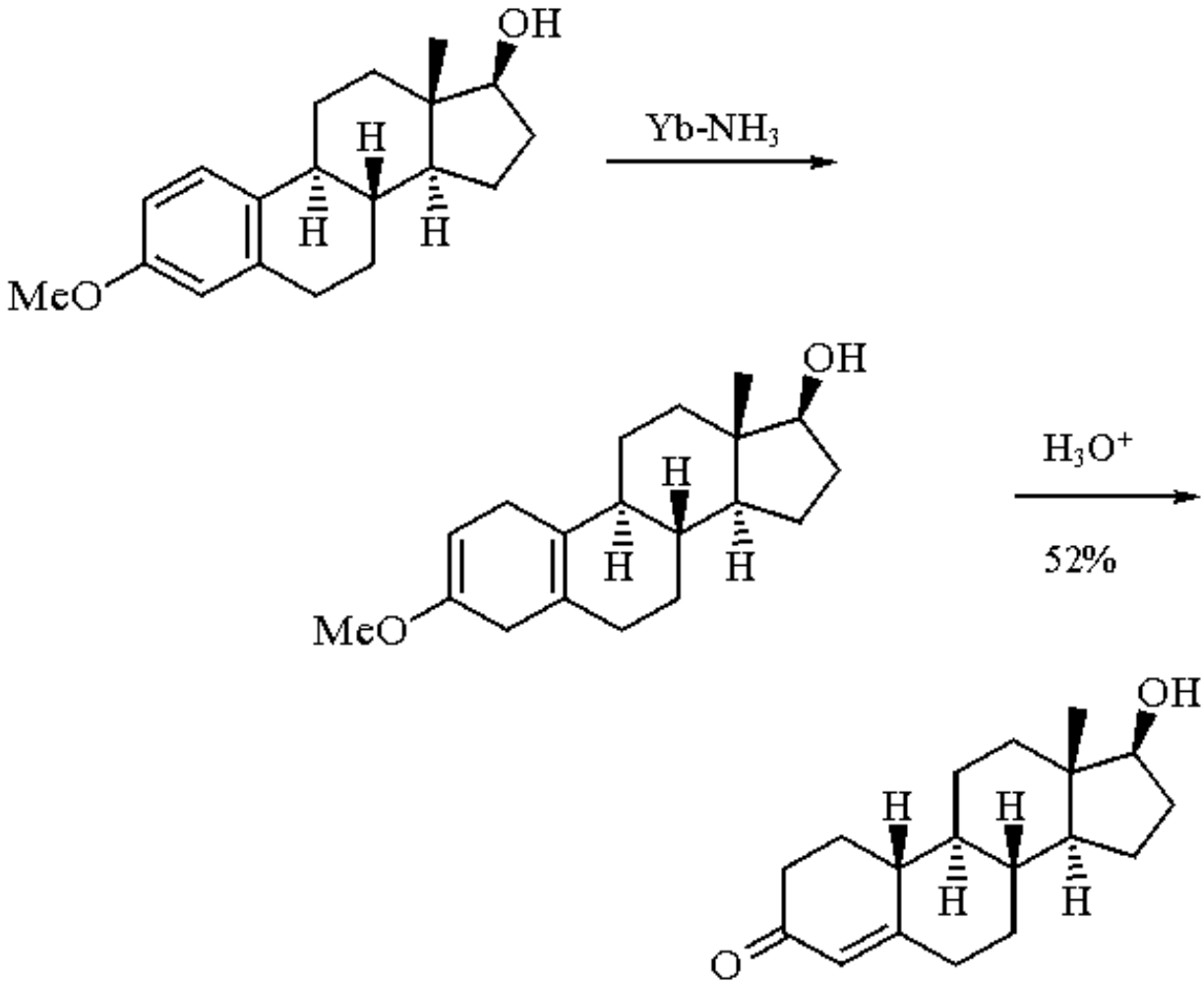

(4)

Conjugated dienes are cleanly reduced in a 1,4-manner by Yb-NH_3. An application of this reduction in a synthesis of (±)-dehalogenonidifocene resulted in a 9:1 mixture favoring the 1,4-reduction product (eq 5).[16] By contrast, Li-NH_3 gave a 1:1 mixture of 1,4- and 1,2-reduction products and Ca-NH_3 gave a 2:1 ratio of these materials. The greater selectivity of Yb-NH_3 is attributed to the weaker basicity of $Yb(NH_2)_2$ and to the consequent diminished propensity for alkene isomerization of the product.

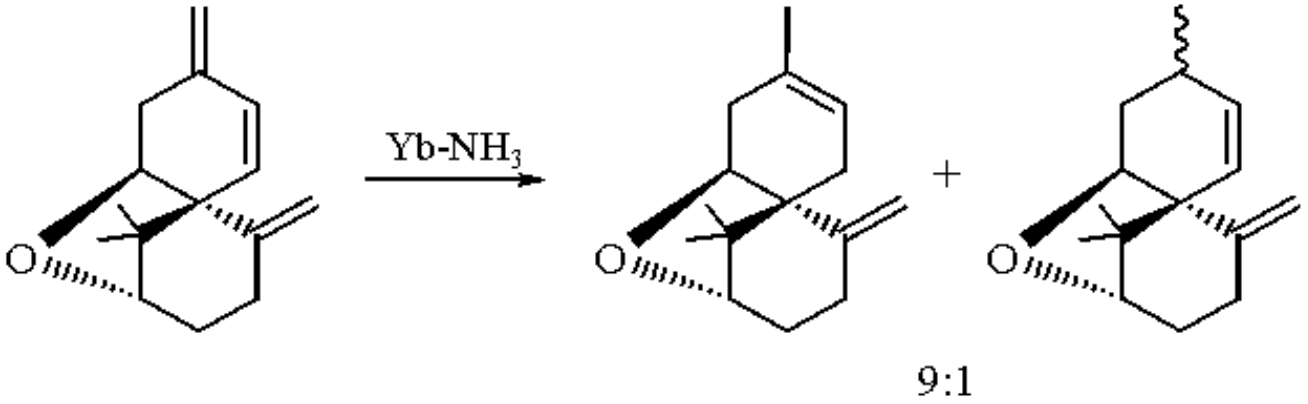

(5)

Conjugated enones are reduced with Yb-NH_3 and, in the presence of a proton source, afford the saturated ketone together with variable quantities of the alcohol resulting from further reduction (eq 6). If a proton donor is absent, a high yield of pinacol dimer is obtained, as exemplified with cholest-4-en-3-one (eq 6).[17] Pinacol coupling of aromatic ketones has been accomplished with a slurry of Yb power in THF-HMPA which, under appropriate conditions, can also lead to a high yield of cross coupled product.[4] The same reagent effects pinacol-like coupling of diaryl ketones with nitriles to give α-hydroxy ketones, and with epoxides to give 1,3-diols.[6] However, with unsymmetrical epoxides the regioselectivity can be low.[7] It is not clear that this heterogeneous form of the Yb reagent offers significant advantage over the homogeneous Yb-NH_3 system, especially since the metal must be activated (with MeI) before reduction.

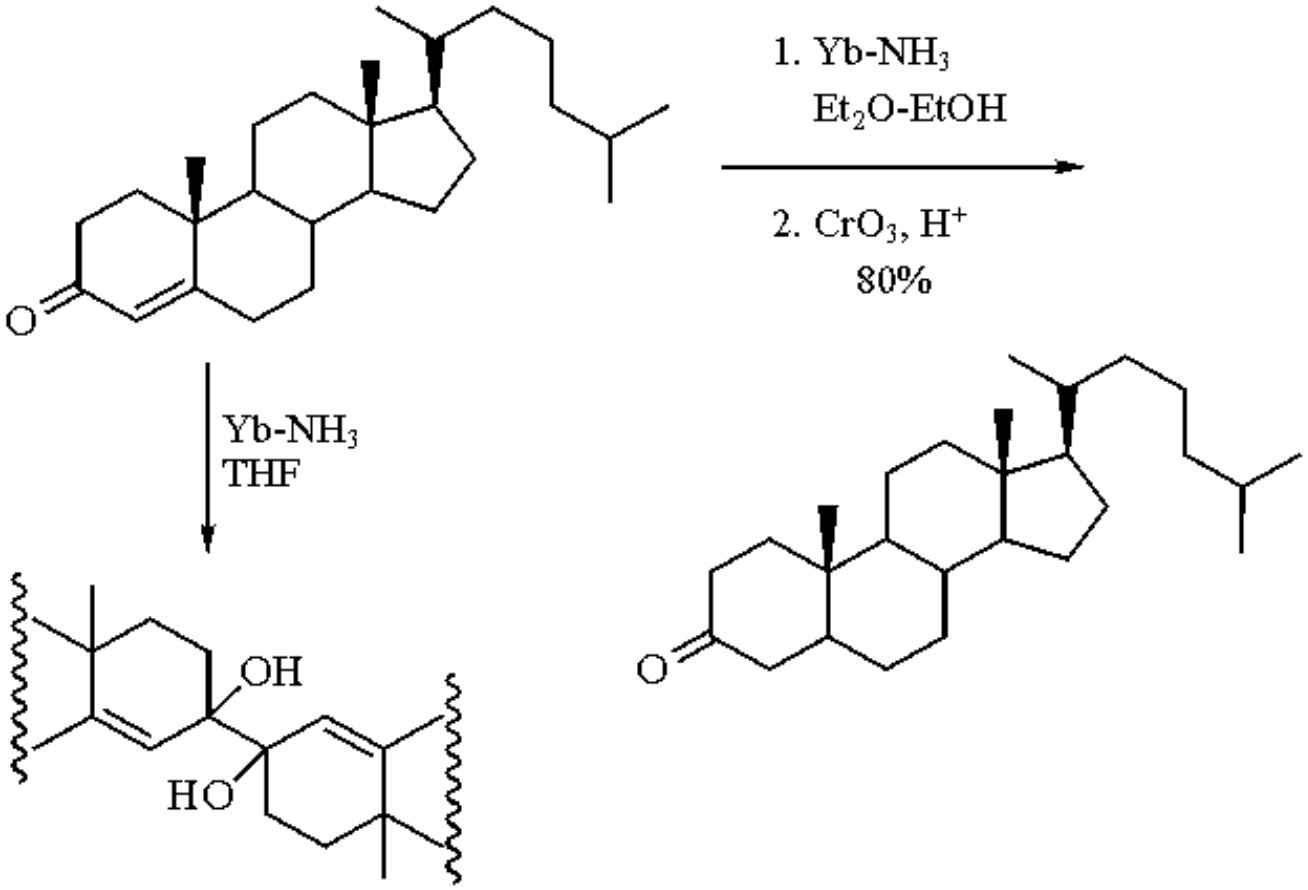

(6)

Solutions of Yb-NH_3 reduce alkynes to a *trans*-alkene (eq 7). In certain cases, strained alkenes can be reduced[18] as, for example, in the conversion of norbornadiene to bicyclo[2.2.1]heptene (eq 8).

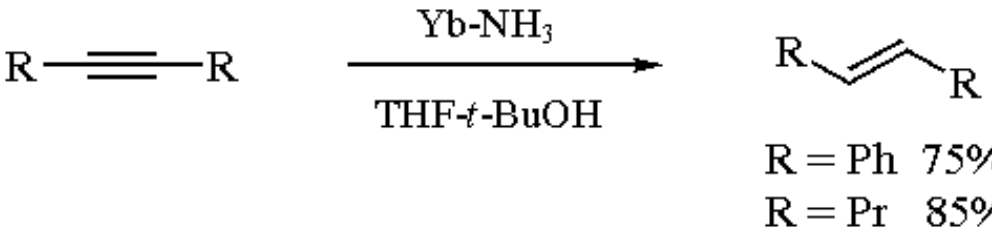

(7)

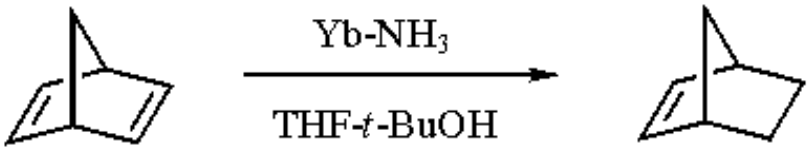

(8)

Pinacolic Coupling Reactions.

Ytterbium metal effects the coupling of pinacols (eq 9). Although pinacolic cross-coupling is difficult to achieve, ytterbium metal with diaryl ketones promotes the effective coupling of aldehydes and ketones to afford vicinal diols in good yields (eqs 10 and 11).[4-6] The utility of this protocol is limited, however, in that one of the pinacolic coupling partners must contain aromatic functionality.

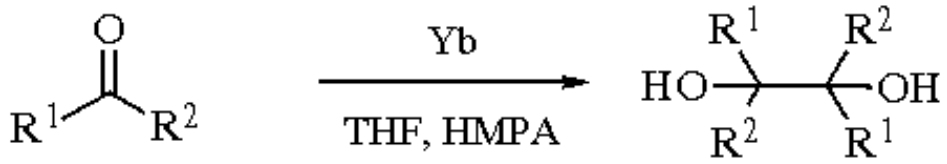

(9)

$R^1, R^2 = Ph$ 97%
$R^1 = Ph, R^2 = Me$ 73%

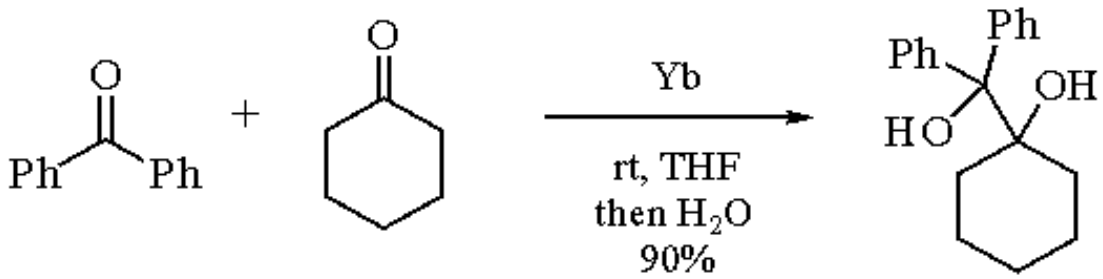

(10)

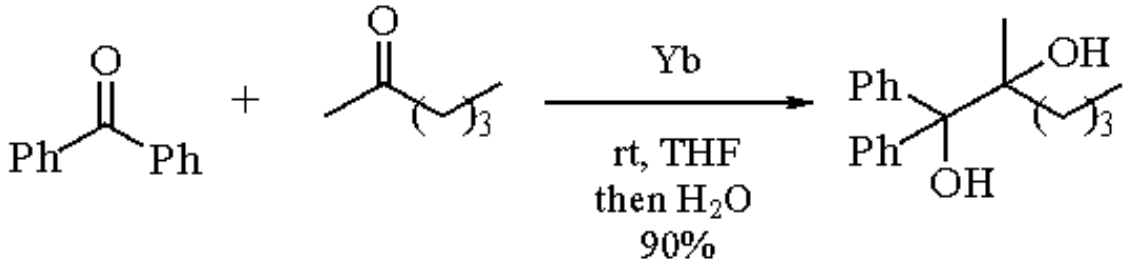

(11)

Nucleophilic Addition of Organoytterbium Complexes to Other Electrophiles.

Treatment of diaryl ketones with 1-2 equiv of Yb metal promotes the nucleophilic addition to ketones, epoxides, nitriles, and carbon dioxide to form the corresponding crossed pinacol, 1,3-diol, α-hydroxy ketone, and α-hydroxy carboxylic acid, respectively (eqs 12 and 13).[5-7]

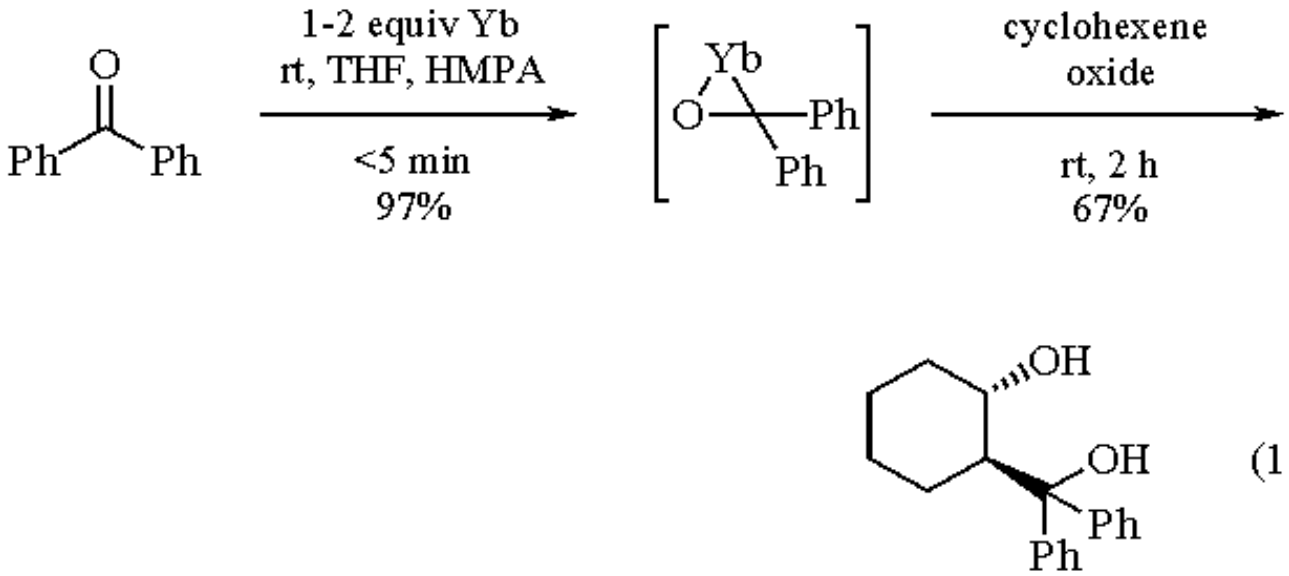

(12)

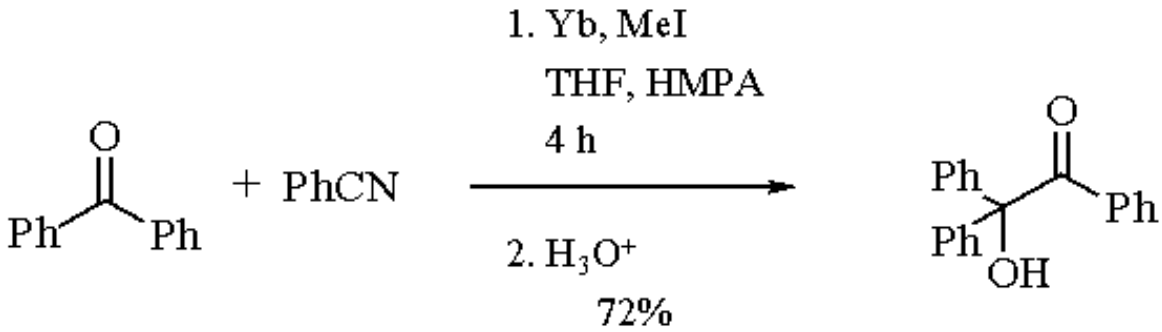

(13)

Reduction of Ketimines.

Ytterbium also provides a method for the reduction of imines (eq 14); however, considerable amounts of coupling products are observed when there are not two aromatic substituents on the substrate.[19]

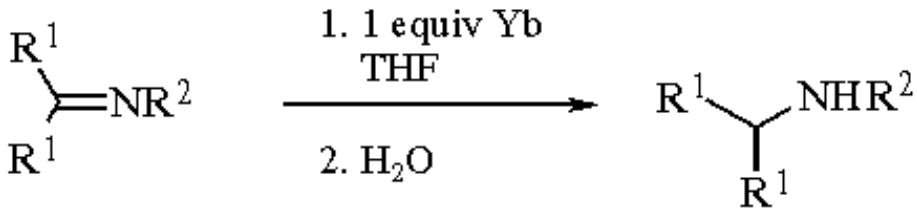

(14)

$R^1 = R^2 = Ph$	92%
$R^1 = Ph, R^2 = H$	93%

Ketimines are reduced with ytterbium metal and may subsequently be treated with carbon dioxide to generate the ytterbium salt of the α-amino acid, which is converted to the α-amino acid by acidic workup (eq 15).[20] This method too is limited to aromatic functionality on the ketimine substrate.

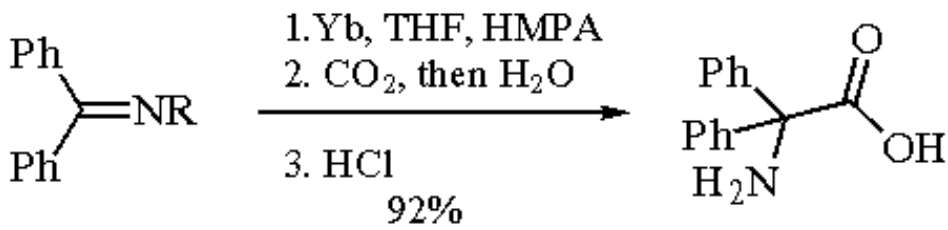

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Ytterbium(II) Chloride[1]

$YbCl_2$

[13874-77-6] · Cl_2Yb · Ytterbium(II) Chloride · (MW 243.94)

(reductive dimerization of unsaturated ketones;[2] hydroperfluoroalkylation of alkenes[3])

Physical Data: mp 720 °C; bp 1930 °C; *d* 5.08 g cm^{-3}; green rhombohedral crystals.

Solubility: sol THF; readily oxidized in H_2O.

Preparative Methods: can be obtained by reduction of the trichloride with various reagents (e.g. Na). In recent papers the trichloride is reduced in situ by ***Zinc***.

Handling, Storage, and Precautions: unstable in water and humid air; oral toxicity of ytterbium trichloride: LD_{50} 6.7 g kg^{-1} in rats.

Cyclodimerization of α,β-Unsaturated Ketones.

Ytterbium dichloride is probably the reactive species formed by reduction of the trichloride with zinc, although it was not characterized as such. This reagent was shown to be more efficient than ***Ytterbium(0)*** metal in promoting the reductive cyclodimerization of α,β-alkenic ketones to cyclopentanols.[2] Thus far, this reaction has only been observed with chalcone (eq 1).

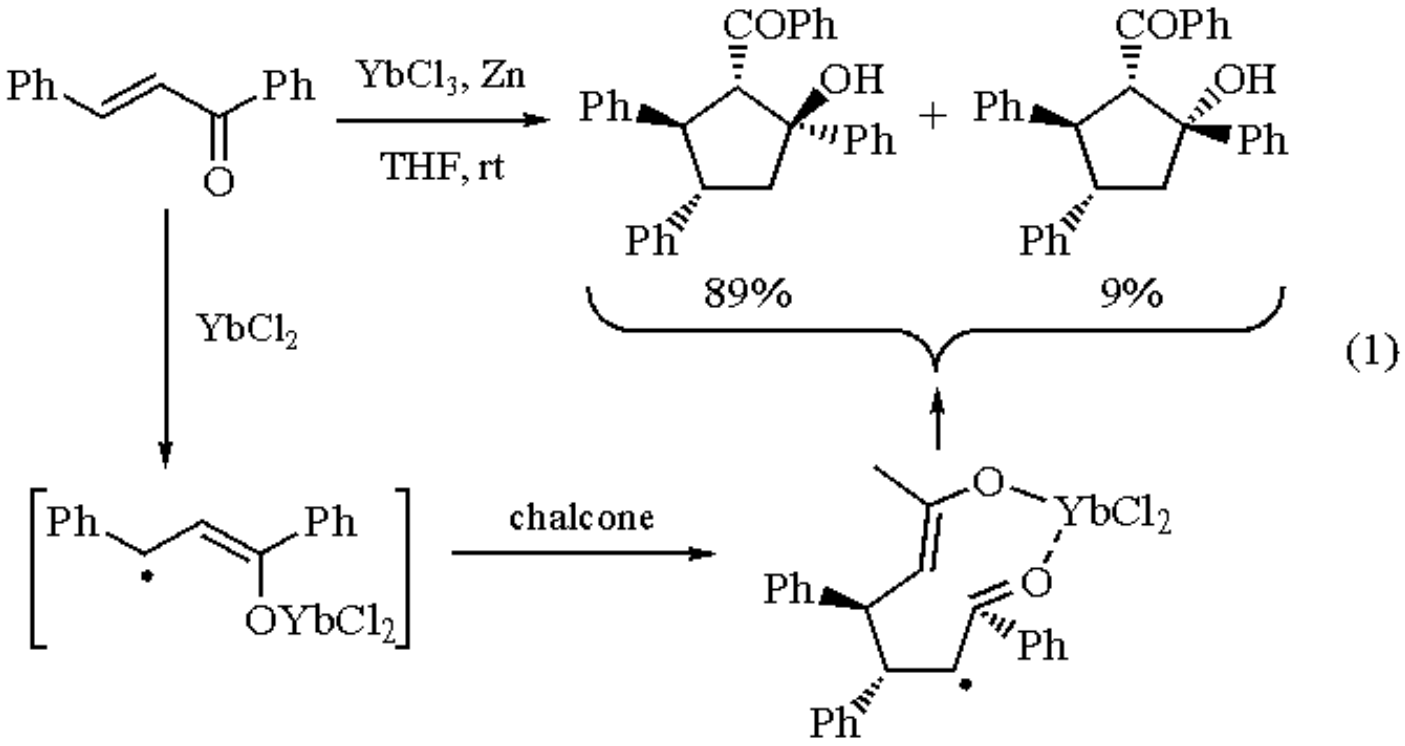

The mechanism postulated involves a single-electron transfer to the conjugated system, followed by addition of the resulting enolate radical to the starting material. The reaction exhibits significant diastereoselectivity. The radical (or the enolate derived from its further reduction) can be trapped by an aldehyde to produce the acyl or hydroxyalkyl compound (eq 2).[4] Starting from 2-propyn-1-ones, a similar process takes place, but the results are more complex. Dimerization occurs following a slightly different mechanism, with a third molecule being trapped to give an hemiacetal (eq 3). In other instances, dimerization predominates to afford either a linear (eq 4) or a cyclobutene product (eq 5).[5]

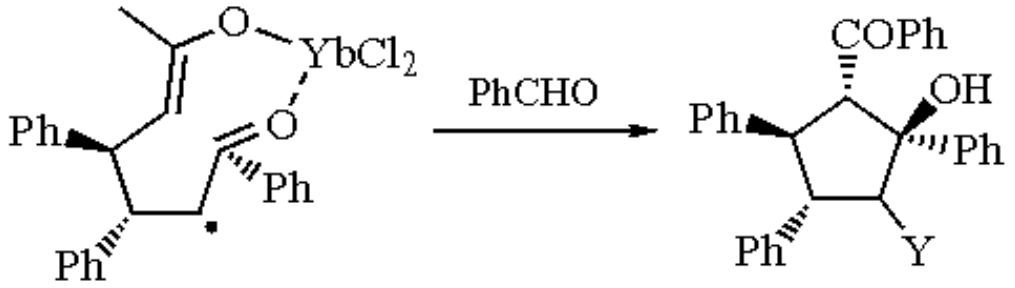

(2)

Y = COPh + CH(OH)Ph

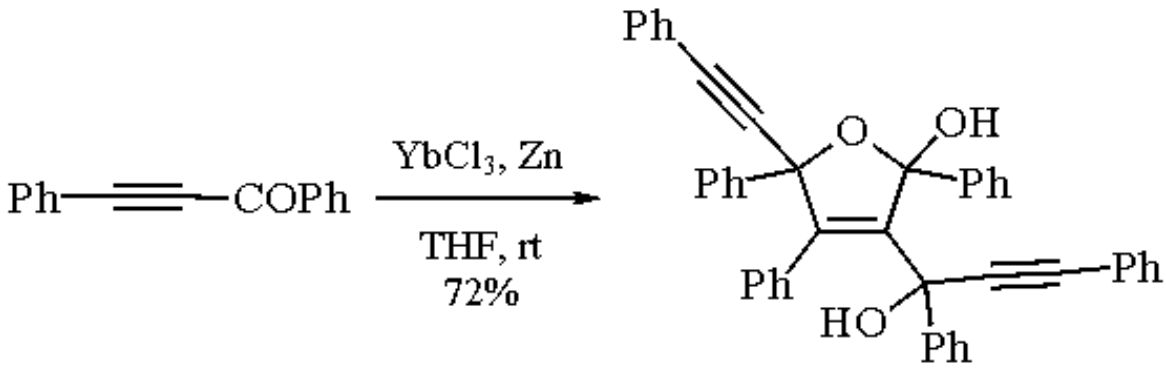

(3)

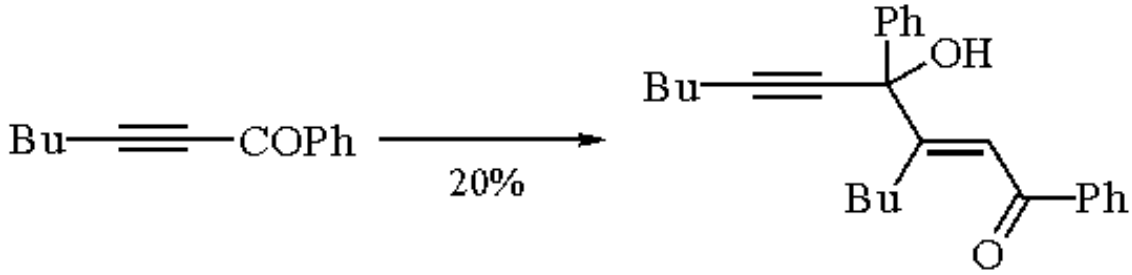

(4)

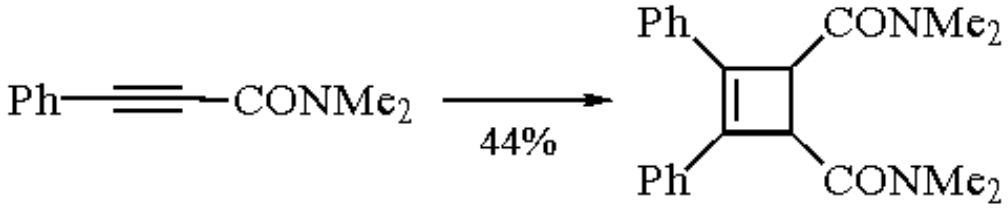

(5)

Hydroperfluoroalkylation of Alkenes.

Addition of a perfluoroalkyl group to several alkenes is easily effected using in situ-generated ytterbium dichloride. Alkenes containing ester (eq 6), ether, alcohol, and phosphonate (eq 7) groups participate in excellent yield via a rapid (5-10 min) and smooth (50-75 °C) reaction.[3]

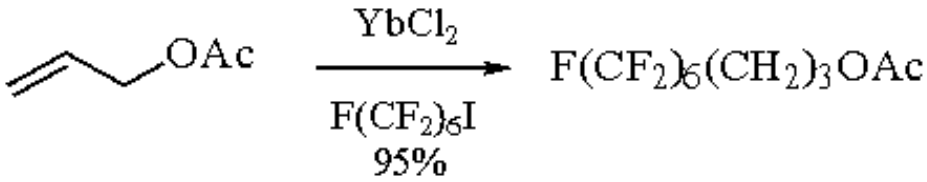

(6)

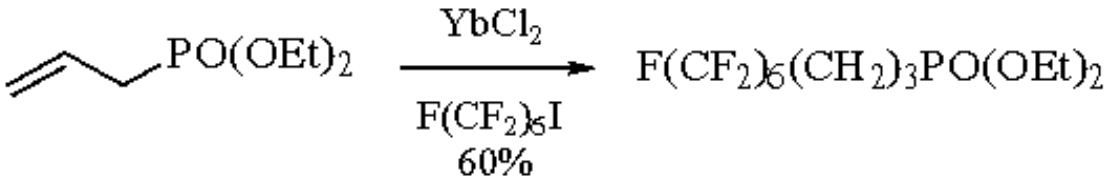

(7)

1. (a) Molander, G. A. *CRV* **1992**, *92*, 29. (b) Kagan, H. B.; Namy, J. L. *T* **1986**, *42*, 6573.
2. Takaki, K.; Nagase, K.; Beppu, F.; Fujiwara, Y. *CL* **1991**, 1665.
3. Ding, Y.; Zhao, G.; Huang, W. *TL* **1993**, *34*, 1321.
4. Beppu, F.; Fujii, N.; Nagase, K.; Takaki, K.; Fujiwara, Y. *Kidorui* **1991**, *18*, 140 (*CA* **1992**, *116*, 214 026a).
5. Takaki, K.; Nagase, K.; Beppu, F.; Shindo, T.; Fujiwara, Y. *CL* **1991**, 1669.

Jean-Louis Luche

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Ytterbium(II) Iodide

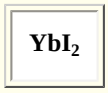

[19357-86-9] · I_2Yb · Ytterbium(II) Iodide · (MW 426.84)

(promotes the reduction of conjugated alkenes, leaving isolated alkenes unaffected;[1a,2] effects the reductive cyclization of halo ketones with good diastereoselectivities[3])

Physical Data: light yellow powder; mp 780 °C; bp 1300 °C; structure determined by X-ray diffraction.

Solubility: sol dilute acid, H_2O.

Preparative Methods: typically prepared in situ via oxidation of ***Ytterbium(0)*** metal with various organic dihalides such as ***1,1-Diiodoethane*** or ***Diiodomethane***;[1a] may also be prepared from reaction of ytterbium metal with excess HgI_2 or from the reaction of excess ytterbium metal with NH_4I and NH_3.[1b -d]

Handling, Storage, and Precautions: should be kept in an inert atmosphere; subject to hydrate formation.[1]

Reduction of Conjugated Alkenes.

Ytterbium diiodide effects the reduction of conjugated alkenes while isolated double bonds remain unchanged under the same reaction conditions.[1a] Cinnamic acid and ethyl cinnamate are cleanly reduced to the saturated carboxylic acid or ester when subjected to YbI_2 in THF/MeOH (eqs 1 and 2).[2] The analogous conjugated ketone and aldehyde, however, suffer competition between C=C and C=O reduction. Isolated ketones appear to be inert under similar reaction conditions.

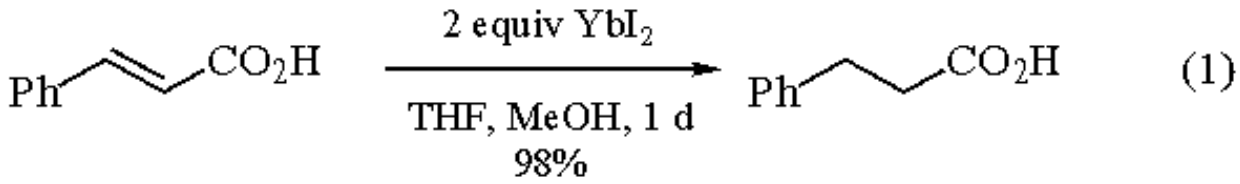

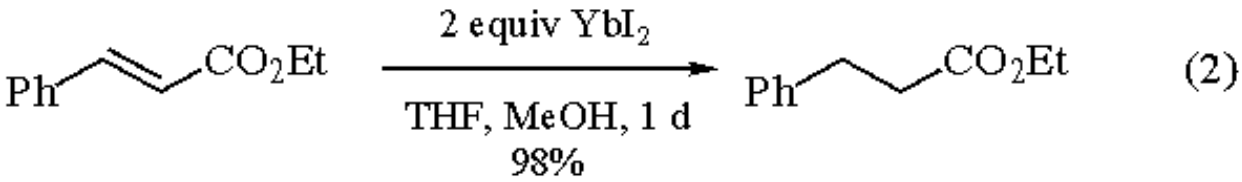

Reductive Cyclization of Halo Ketones.

Ytterbium(II) iodide has been utilized in the synthesis of five-, six-, and seven-membered rings in good yield from 2-(o-iodoalkyl)cycloalkanones (eqs 3 and 4).[3] In these examples, the ytterbium(II) iodide complex was found to give somewhat higher diastereoselectivities than ***Samarium(II) Iodide***.

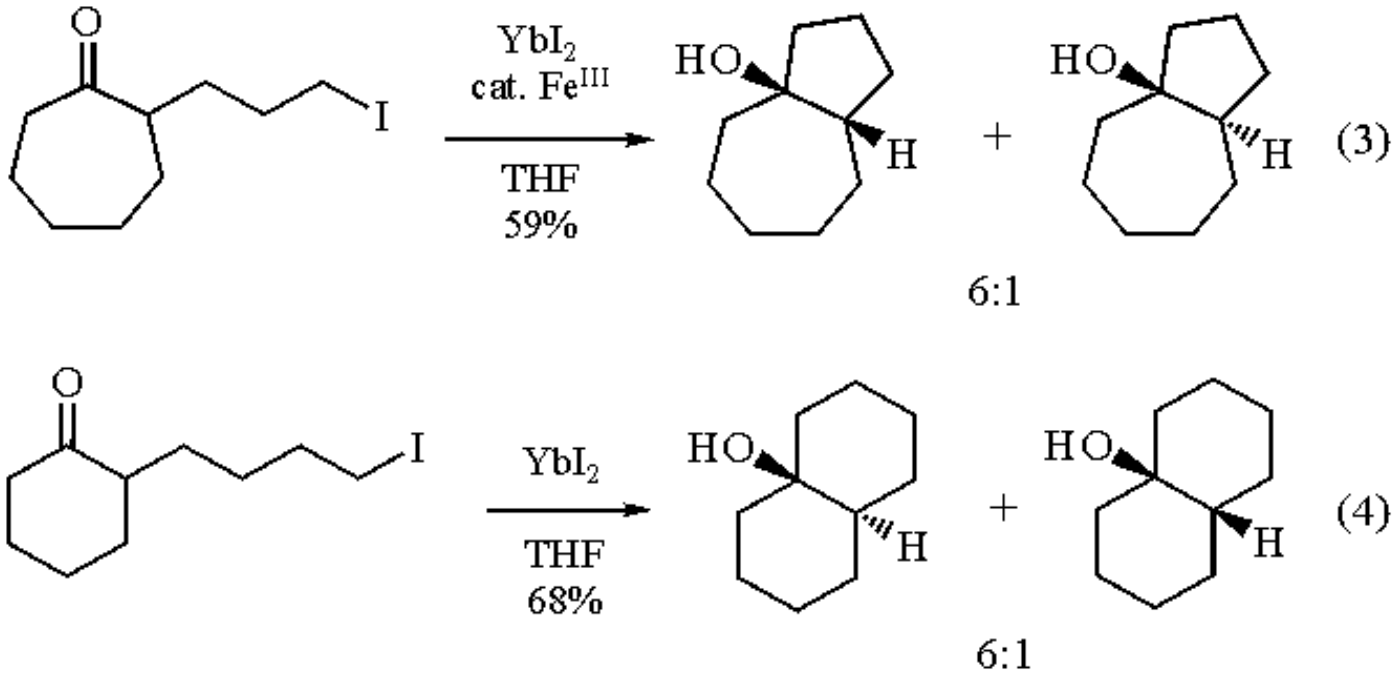

1. (a) Namy, J. L.; Girard, P.; Kagan, H. B. *NJC* **1977**, *1*, 5. (b) Kim, B. Y.; Kwapisz, R.; Eick, H. A. *J. Solid State Chem.* **1989**, *80*, 163. (c) Lasocha, W.; Voos-Esquivel, C. A.; Hodorowicz, S. A.; Kim, B. Y.; Eick, H. A. *J. Solid State Chem.* **1988**, *74*, 67. (d) Tilley, T. D.; Boncella, J. M.; Berg, D. J.; Burns, C. J.; Andersen, R. A. *Inorg. Synth.* **1990**, *27*, 146.
2. Girard, P.; Namy, J. L.; Kagan, H. B. *JACS* **1980**, *102*, 2693.
3. Molander, G. A.; Etter, J. B. *JOC* **1986**, *51*, 1778.

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Ytterbium(III) Trifluoromethanesulfonate

$Yb(OSO_2CF_3)_3$

[54761-04-5] · $C_3F_9O_9S_3Yb$ · Ytterbium(III) Trifluoromethanesulfonate · (MW 620.28)

(organometallics derived from addition of organolithiums or organomagnesiums to $Yb(OTf)_3$ display enhanced diastereoselectivities in the carbonyl addition to chiral ketones and aldehydes;[2] functions as a Lewis acid in promoting aldol reactions and hydroxymethylation reactions[4])

Alternate Name: ytterbium(III) triflate.

Preparative Methods: prepared by addition of an excess of ytterbium(III) oxide (commercially available, 99.9%) to an aqueous solution of ***Trifluoromethanesulfonic Acid*** (50% v/v) followed by heating at boiling for 0.5-1 h. The mixture is then purified by filtration to remove unreacted ytterbium oxide; residual water is removed under reduced pressure. The resultant hydrate is dried by heating under vacuum (1 mmHg) at 180 to 200 °C for 48 h. The reagent is then used without further purification.[1] The organoytterbium reagent is prepared at -78 °C from $Yb(OTf)_3$ and organolithiums or organomagnesiums.[2]

Handling, Storage, and Precautions: subject to hydrate formation in aqueous media in the presence of amines;[1] however, it survives mild aqueous workup.[4]

Addition to Ketones and Aldehydes.

Organoytterbium triflates display enhanced diastereoselectivity in carbonyl addition to chiral aldehydes and ketones. Because of the imposing steric bulk, organolanthanide reagents are suitable for achieving high diastereofacial selectivity in the addition to chiral aldehydes and ketones. Treatment of 2-methylcyclohexanone with the methylytterbium reagent produces a mixture of diastereomers in a 98:2 ratio, resulting from preferential equatorial attack of the bulky organolanthanide reagent (eq 1).[2]

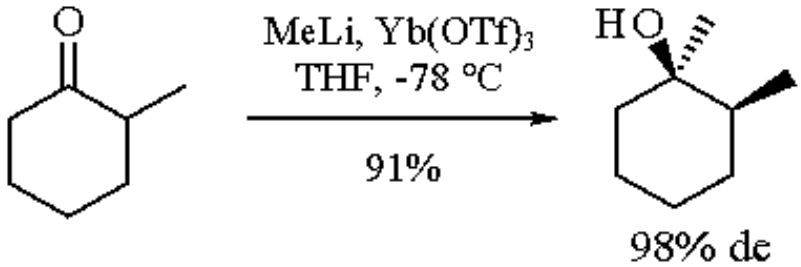

(1)

Another attractive feature of the ytterbium triflate derived organometallic reagent is the diverse organoytterbiums which may be utilized in the process. Unlike other organometallic reagents possessing similar reactivity, the organoytterbium reagent is not limited to a narrow range of organic ligands which may be incorporated onto the metal center (eq 2). Specifically, high yields and diastereoselectivities may be achieved with both alkyl- and alkenylytterbium reagents. This is in contrast to organotitanium reagents, which may provide incomplete conversion and/or low diastereofacial selectivities in additions to carbonyl substrates.[3] Additionally, tertiary organometallics can be generated and utilized without interference from β-hydride elimination processes, although enolization of the substrates does lower the yield significantly.

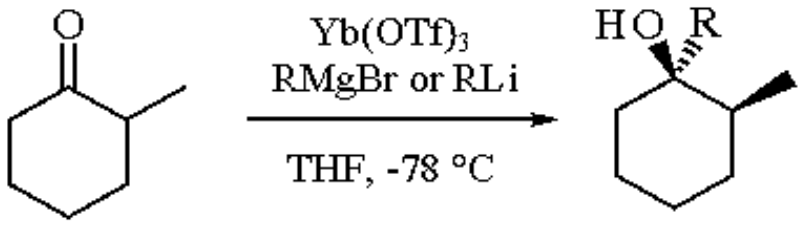

(2)

R	Yield (%)	de (%)
Bu	91	98
Ph	73	>98
trans-1-hexenyl	75	93
cis-1-hexenyl	78	95
vinyl	89	95
t-Bu	53	99

Organoytterbium triflates also show enhanced diastereofacial selectivity upon addition to acyclic chiral aldehydes (eq 3).

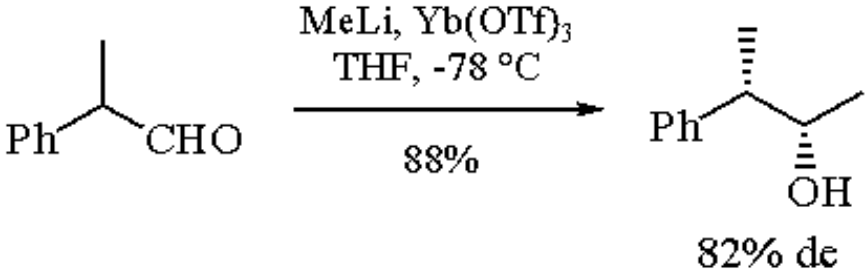

(3)

Aldol Reactions.

$Yb(OTf)_3$ serves as catalyst in promoting the aldol-type reaction between silyl enol ethers and acetals or aldehydes (eqs 4 and 5).[4]

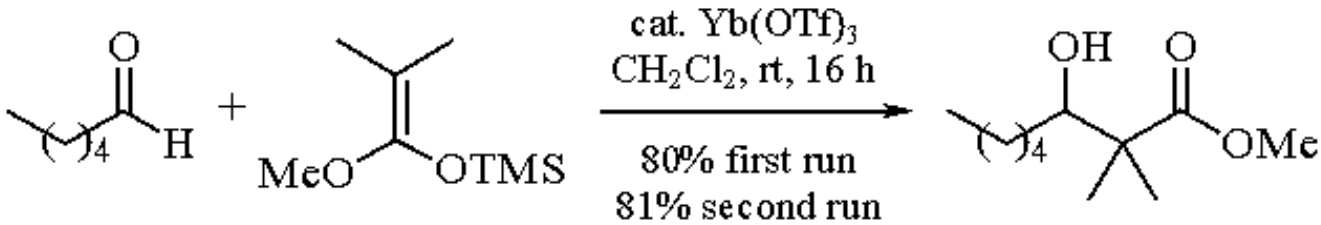

(4)

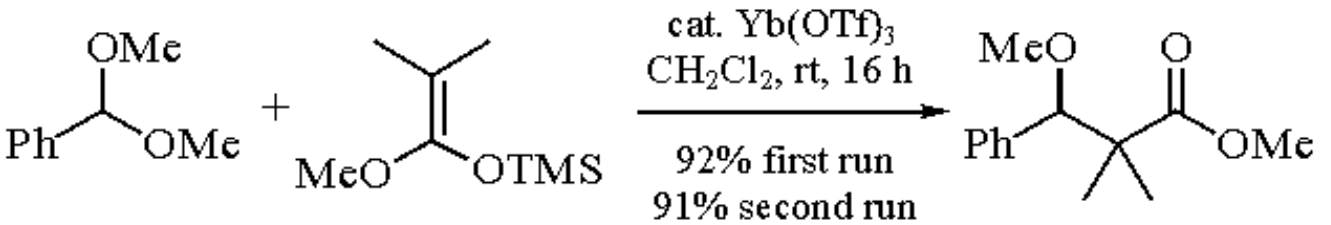

(5)

Unlike other Lewis acid catalysts capable of performing similar transformations, water does not interfere with the aldol reaction when ytterbium triflate is employed; hence, troublesome purification and dehydration steps are unnecessary when performing aldol reactions on water-soluble aldehydes. Furthermore, molecules with free hydroxyl and nitrogen functionalities are compatible with the ytterbium triflate promoted aldol reaction because these functionalities do not coordinate to ytterbium triflate. The Lewis acid thus remains active in the presence of such functional groups in contrast to other Lewis acid catalysts. Another important feature which makes ytterbium triflate attractive in these transformations is that the catalyst may be recovered from the aqueous layer after workup because $Yb(OTf)_3$ is not hydrolyzed in the presence of water.

1. Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *JOC* **1987**, *52*, 1017.
2. Molander, G. A.; Burkhardt, E. R.; Weinig, P. *JOC* **1990**, *55*, 4990.
3. (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: Berlin, 1986. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *CB* **1985**, *118*, 1441. (c) Reetz, M. T.; Kyung, S. H.; Hüllmann, M. *T* **1986**, *42*, 2931. (d) Boeckman, R. K., Jr.; O'Connor, K. J. *TL* **1989**, *30*, 3271.
4. (a) Kobayashi, S.; Hachiya, I.; Takahori, T. *S* **1993**, 371. (b) Kobayashi, S.; Hachiya, I. *TL* **1992**, *33*, 1625. (c) Kobayashi, S. *CL* **1991**, 2187.

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Zinc[1]

Zn

[7440-66-6] · Zn · Zinc · (MW 65.39)

(reducing agent;[2] used for preparation of organozinc reagents,[1,3] Reformatsky reagents,[4] and the Simmons-Smith reagent (cyclopropanation)[5])

Physical Data: mp 419 °C; bp 907 °C; *d* 7.14 g cm^{-3}.

Solubility: insol organic solvents; reacts with aqueous acidic solutions.

Form Supplied in: dust, foil, granular, wire, mossy, rod; widely available at low cost.

Handling, Storage, and Precautions: slowly oxidizes in air; no toxic properties are associated with zinc and zinc organometallics; in several cases the metal requires an activation procedure before use.[6]

Reduction of Carbon-Carbon Multiple Bonds.

Whereas isolated double bonds are rarely reduced by zinc, triple bonds are cleanly converted to alkenes using either ***Zinc/Copper Couple*** or ***Zinc Amalgam***.[7] A regio- as well as stereospecific reduction of a wide range of alkynic derivatives can be performed using zinc powder (eq 1).[8] The reduction of propargylic alcohols proves to be especially efficient (eq 2).[9] Also, the selective *cis* reduction of conjugated dienynes and trienynes proceeds well with Zn(Cu/Ag).[10] The presence of a leaving group at the propargylic position leads to the formation of allenes.[11] The conjugation of a double bond with an electron-withdrawing substituent considerably facilitates the reduction of the double bond.[12] The reduction of α,β-unsaturated ketones produces the corresponding saturated ketones.[13] Nickel catalysis allows the reduction of unsaturated aldehydes, ketones, and esters in an aqueous medium under ultrasonic irradiation (eq 3).[14]

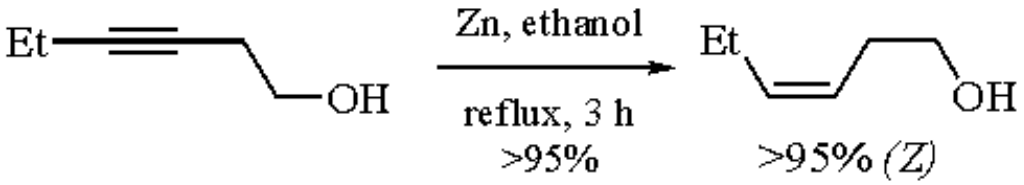

(1)

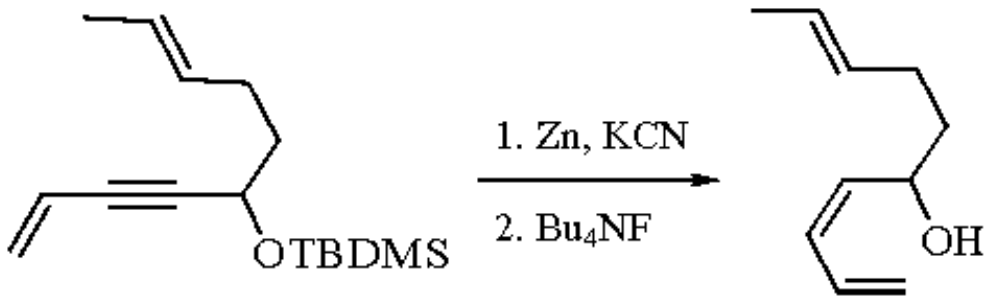

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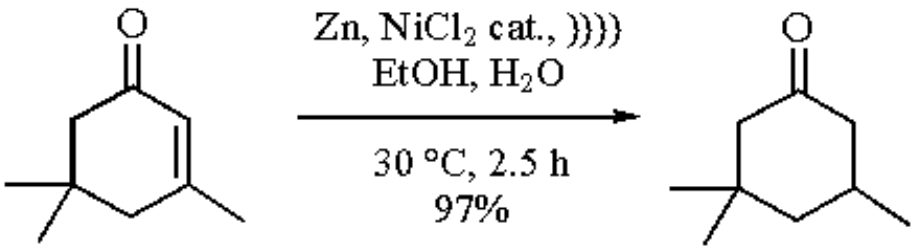

(3)

Reduction of Carbonyl Groups.

Zinc reduces ketones to either alcohols or to a methylene unit, depending on the reaction conditions and the nature of the substrate. For example, conjugation is required if reduction to a hydroxy group is desired. The reduction of aryl ketones provides benzylic alcohols (eq 4)[15] and α-diketones can be converted selectively to α-hydroxy ketones (eq 5).[16] The reduction of the carbonyl group of nonconjugated ketones to a methylene unit with zinc and hydrochloric acid in organic solvents such as ether, acetic anhydride, or benzene-ethanol proceeds in satisfactory yields with a wide range of ketones (Clemmensen reaction) (eqs 6-8).[17] The Clemmensen reduction of aromatic α-hydroxy ketones gives conjugated alkenes.[18] Finally, the Clemmensen reduction can also be performed by using zinc and ***Chlorotrimethylsilane*** in an aprotic medium, leading to alkenes (eq 9).[19] This variation has been exploited for the preparation of alkenes (eq 10)[19b] and has been used in new cyclization reactions (eqs 11 and 12).[20] Trimethylsilyl ethers can be regioselectively prepared by the zinc reduction of α-chloro ketones in the presence of TMSCl.[21] Mixed pinacol products have been prepared by using Zn(Cu) as the reducing agent (eq 13).[22]

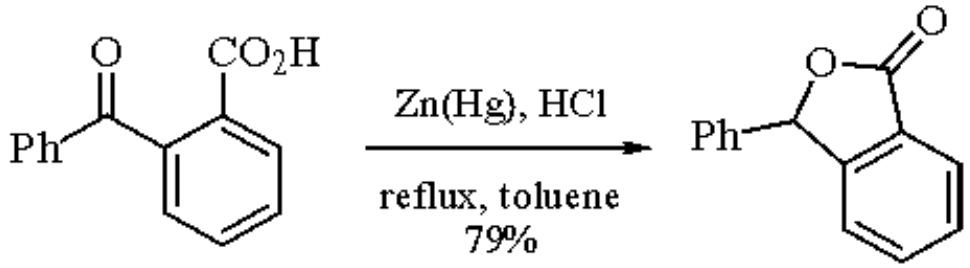

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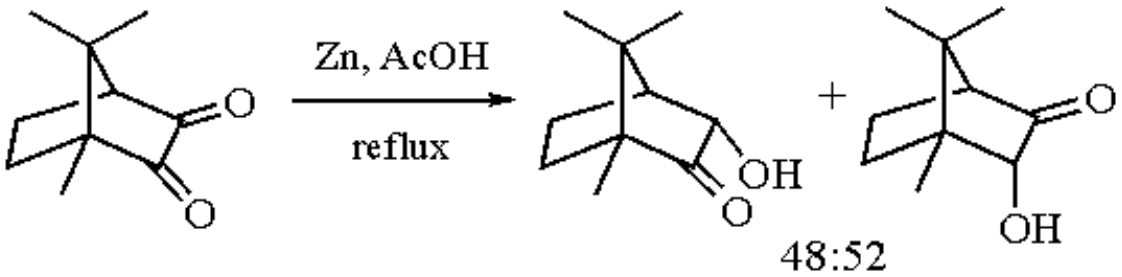

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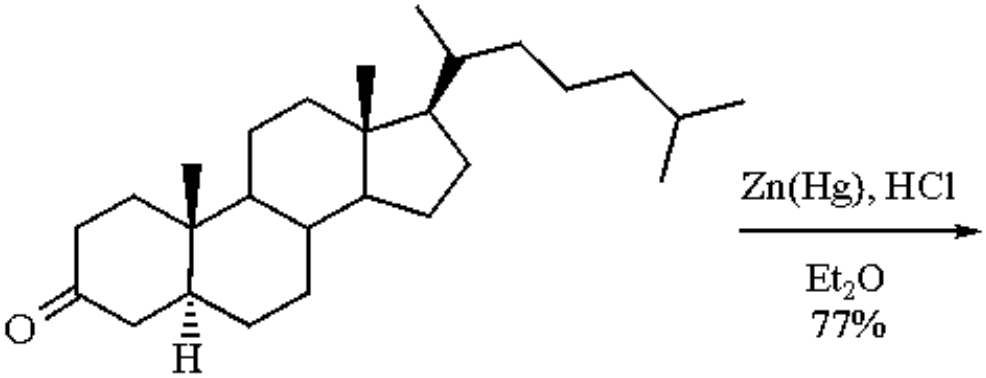

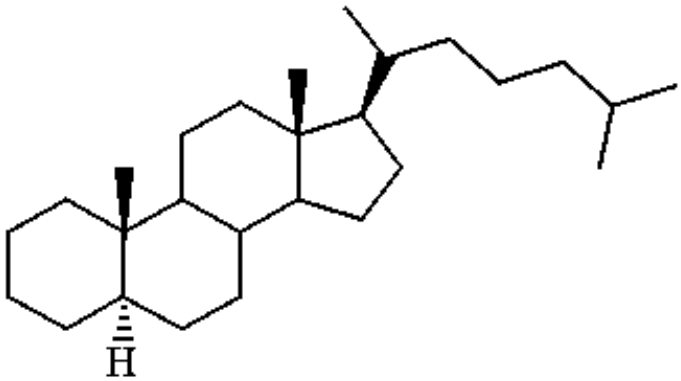

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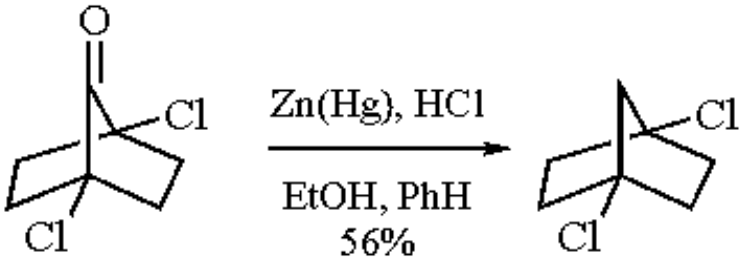
O
Cl
Cl
Zn(Hg), HCl
EtOH, PhH
56%
Cl
Cl

(7)

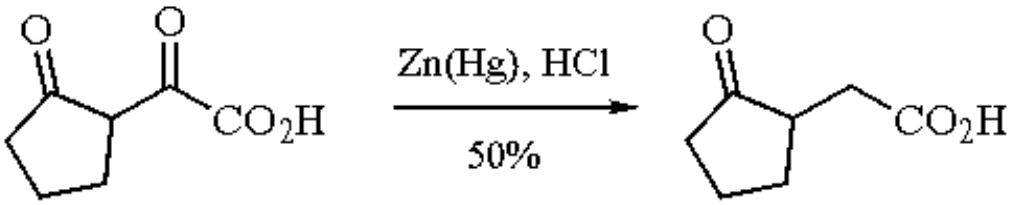
O
O
CO2H
Zn(Hg), HCl
50%
O
CO2H

(8)

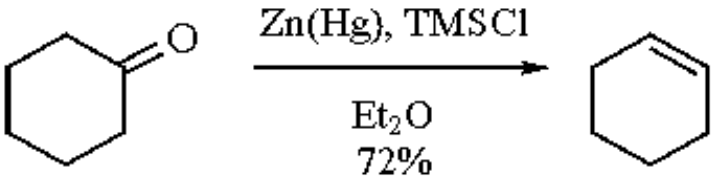
O
Zn(Hg), TMSCl
Et2O
72%

(9)

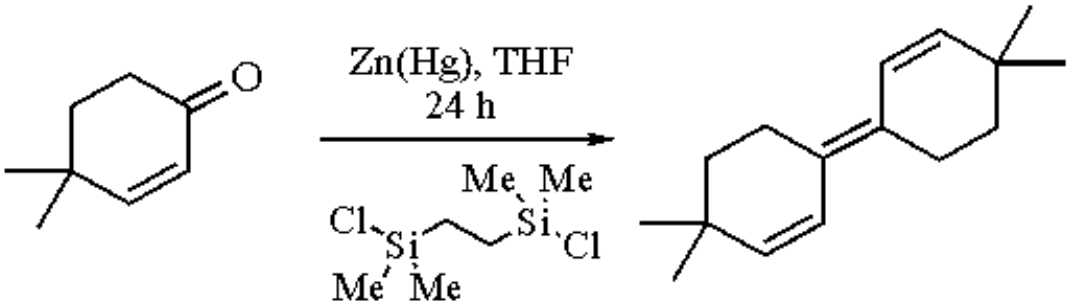
O
Zn(Hg), THF
24 h
Me Me
Cl Si Si Cl
Me Me

(10)

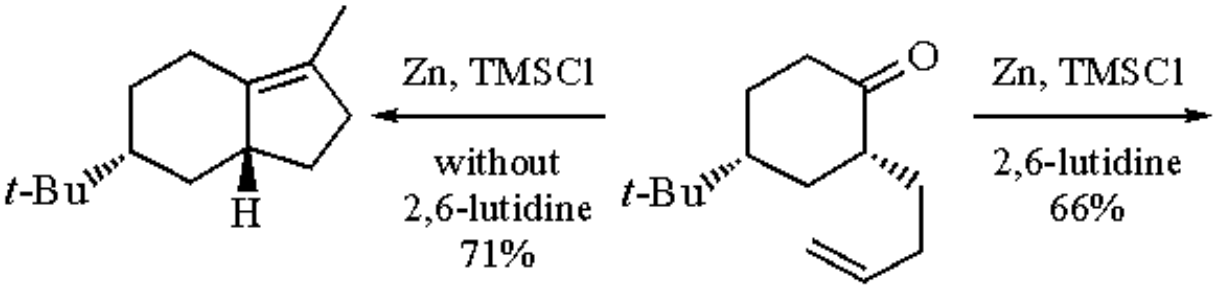
t-Bu
H
Zn, TMSCl
without
2,6-lutidine
71%
O
t-Bu
Zn, TMSCl
2,6-lutidine
66%

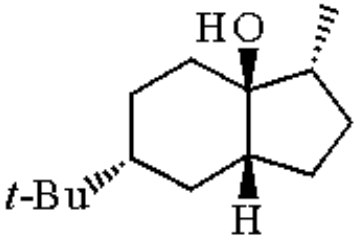
HO
t-Bu
H

(11)

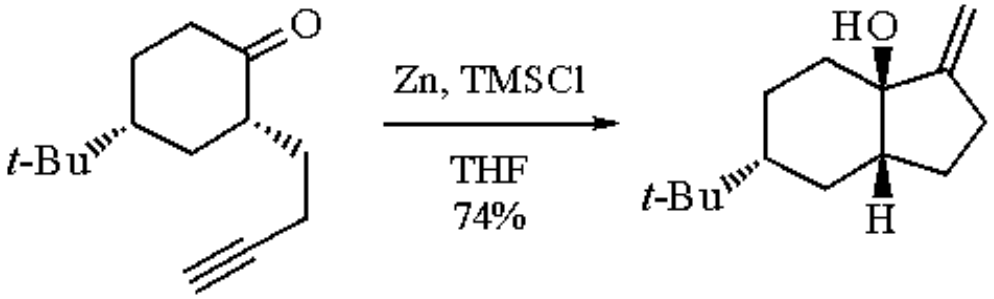

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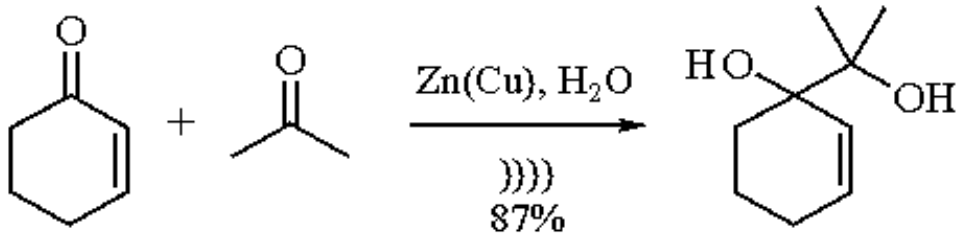

(13)

Reduction of Carbon-Oxygen Bonds.

Carbon-oxygen bonds situated α to an unsaturation are easily reduced with zinc in an acidic medium. In the case of α-hydroxy ketones, ketones are obtained in good yields (eq 14).[23] A wide range of allylic or benzylic ethers, acetates, and alcohols are reduced with zinc (eq 15).[24,25] The reduction of epoxides can lead to either alcohols (eq 16)[26] or alkenes.[26b-e] In the presence of catalytic amounts of Pd^0 and zinc dust, allylic acetates are coupled to give 1,5-dienes (eq 17).[27] Under similar reaction conditions and in the presence of an aldehyde, homoallylic alcohols are obtained in satisfactory yields (eq 18).[27b-d]

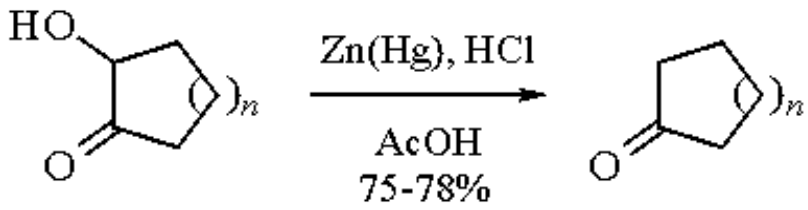

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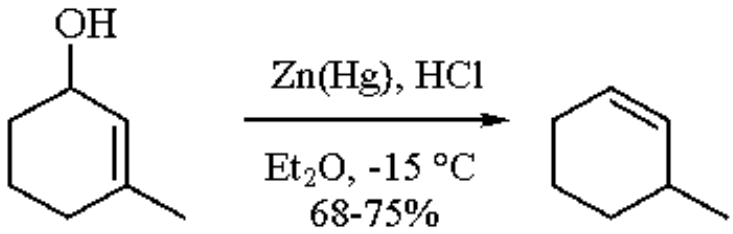

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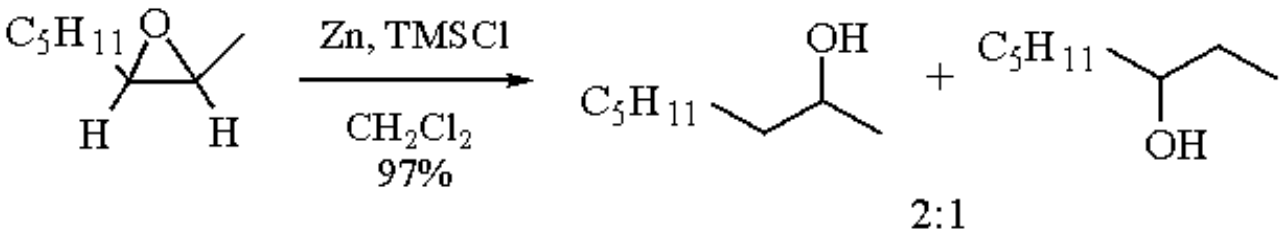

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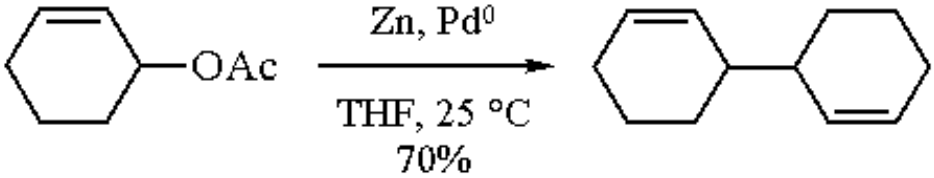

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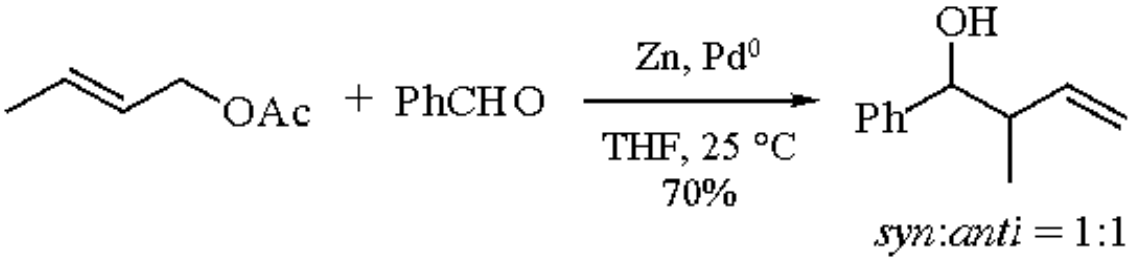

(18)

Reduction of Carbon-Halide Bonds.

Alkyl and alkenyl halides are readily reduced with zinc under various reaction conditions. The reduction produces, as an intermediate, an organic radical which can undergo carbon-carbon bond formation (Barbier reaction)[28] or can be further reduced, usually under acidic conditions. Aliphatic iodides or bromides and benzylic chlorides react readily with ***Zinc-Acetic Acid***, providing the corresponding hydrocarbon.[29] Although aromatic halides are reduced less easily, the tribromothiophene (**1**) is reduced selectively to the bromide (**2**) (eq 19).[29e,g] Various β-chloro enones are cleanly reduced to enones with ***Zinc/Silver Couple*** in methanol at rt (eq 20).[29f] α-Dihalo ketones are reduced smoothly, allowing the preparation of a variety of ketones (eqs 21 and 22).[30] The reductive couplings of α-bromo ketones, tropylium, and 1,3-dithiolylium cations have been observed.[31] In the case of 1,3-dihalides, cyclopropanes are obtained in good yields.[32] If the reduction of the carbon-halide bond is performed in the presence of an electrophile, a radical addition often occurs. Thus phenacyl halides can be coupled with methylenecyclohexanes (eq 23).[33a] Performing the reaction in the presence of an unsaturated ketone provides the 1,4-adducts. Interestingly, the reduction proceeds well in an aqueous medium supporting a radical mechanism, since zinc organometallics react instantaneously with water but only very sluggishly with enones (eq 24).[33b-h] The addition of ***Chloromethyl Methyl Ether*** to 1,2-bis-silyl enol ethers in the presence of zinc leads to ring-enlarged 1,3-cycloalkanediones after acidic treatment.[34] An interesting three-component reaction has been described (eq 25).[34b] A wide range of allylic halides undergo Barbier-type addition to carbonyl groups (eqs 26 and 27).[35,36] The reduction of α,α´-dihalo ketones with a zinc-copper couple in the presence of a diene such as ***Isoprene*** provides cycloaddition products via a zinc oxyallyl cation.[37]

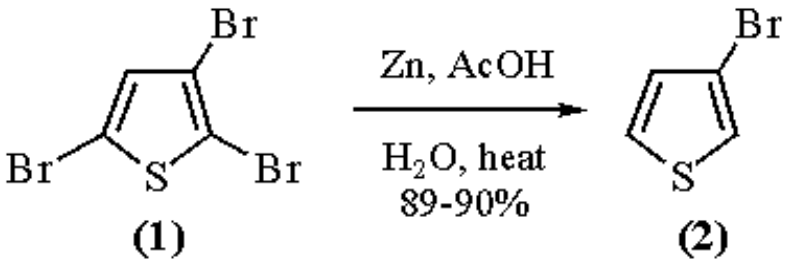

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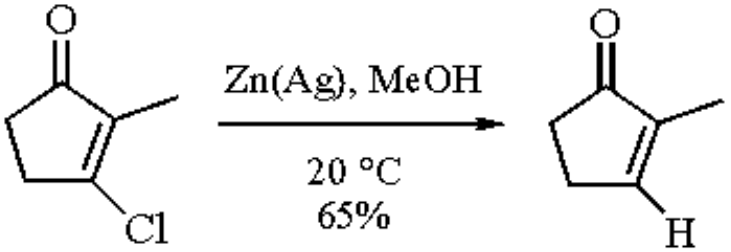

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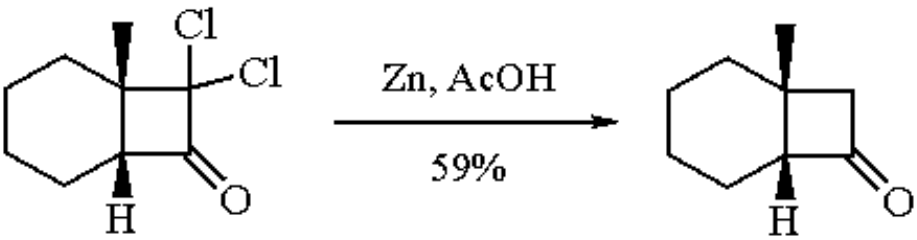

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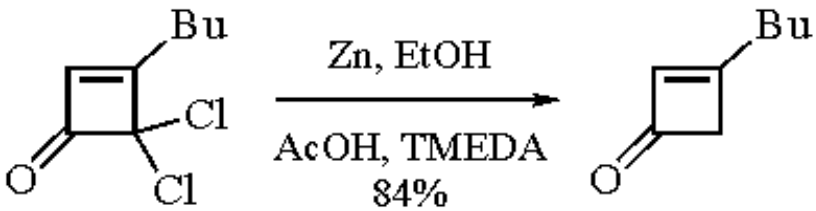

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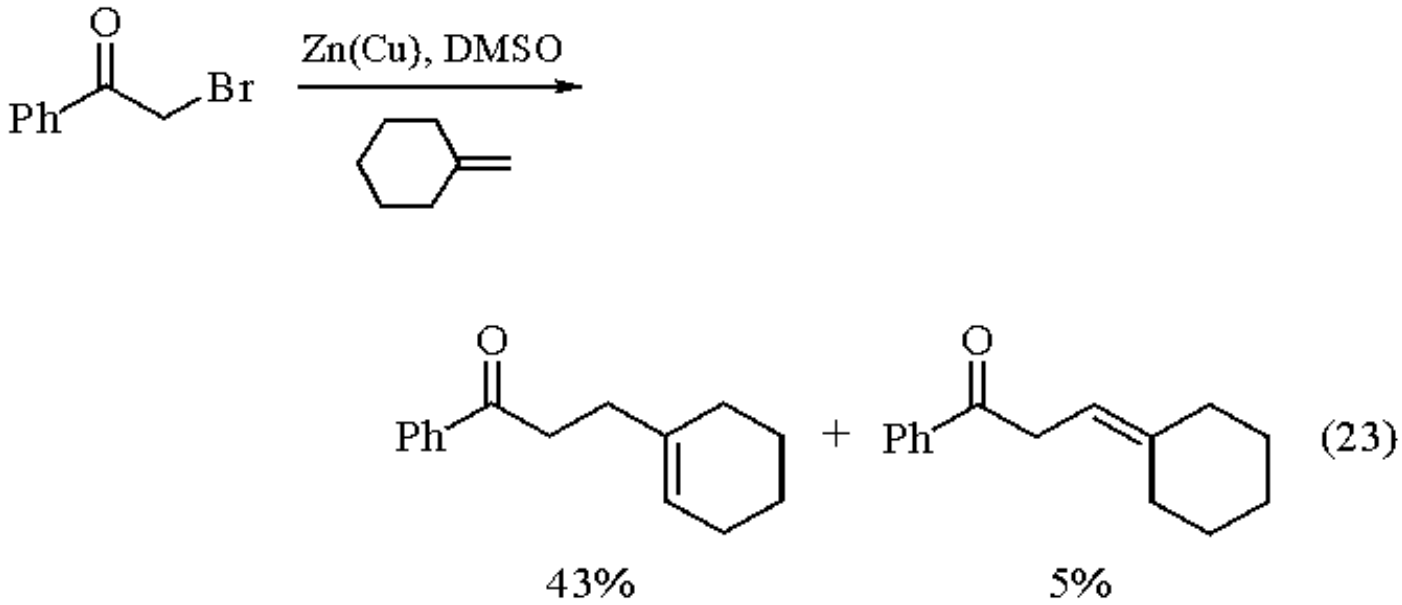
Zn(Cu), DMSO
43%
5%

(23)

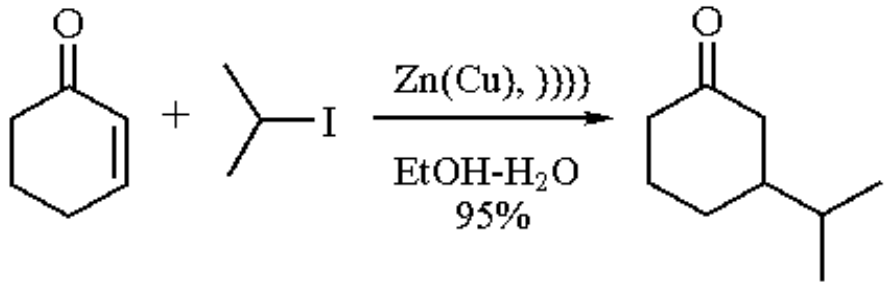
Zn(Cu),))))
EtOH-H2O
95%

(24)

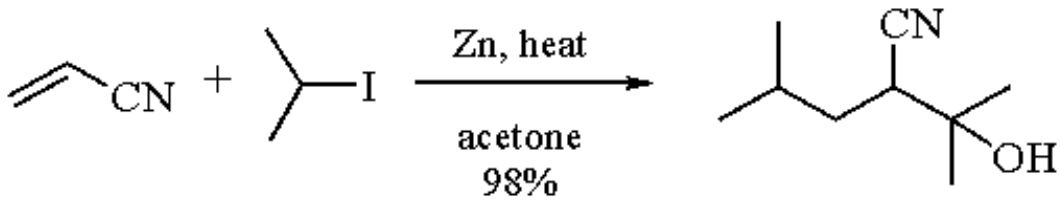
Zn, heat
acetone
98%

(25)

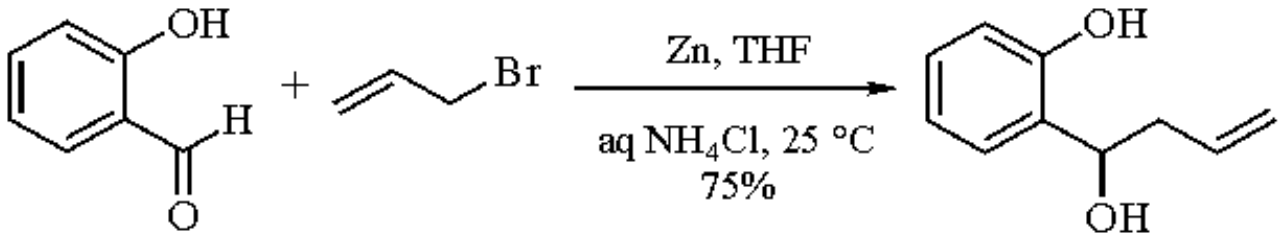
Zn, THF
aq NH4Cl, 25 °C
75%

(26)

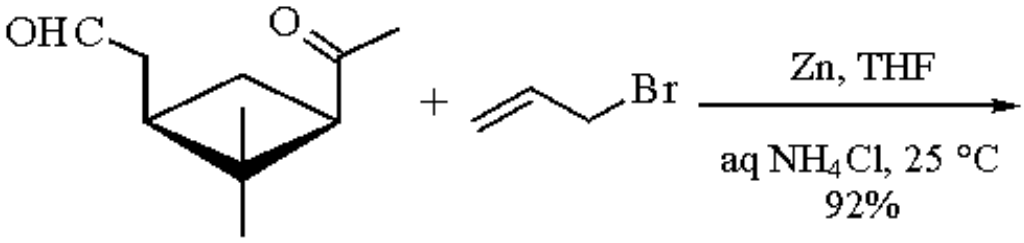

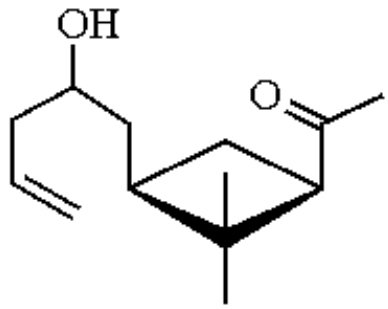

(27)

Reduction of Carbon-Nitrogen and Carbon-Sulfur Bonds.

Aldimines and oximes are converted to amines, and various heterocycles bearing carbon-nitrogen double bonds are reduced with zinc under acidic conditions.[38] Cyanamides can be cleanly cleaved leading to amines,[39a] and the zinc reduction of acylnitriles provides α-amino ketone derivatives (eq 28).[39b] Aromatic amides can be reduced with zinc dust to aromatic aldehydes.[39c] Activated carbon-sulfur bonds α to a carbonyl group[40a,b] and sulfur ylides[40c,d] can be reduced with zinc.

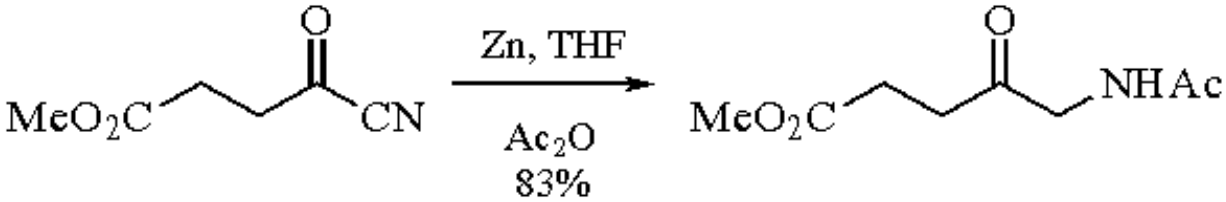

(28)

Reduction at Heteroatoms.[2]

Nitrogen-oxygen bonds of oximes,[41] nitro,[42] and nitroso[43] groups are readily reduced by zinc in acidic medium. Zinc in acetic acid has often been used for the workup procedure of alkene ozonolysis to afford aldehydes or ketones.[2] Sulfinates and thiols can be obtained selectively by the reduction of aromatic sulfonyl chlorides or disulfides.[44]

Dehalogenation and Related Reactions.[6c,45]

Zinc dust is a very efficient reducing agent for the dehalogenation of 1,2-dihalides or 1-halo-2-alkoxy derivatives, leading to alkenes. The reaction allows an access to highly reactive ketenes,[46] alkenes,[47] or alkynes[48] not readily available by standard methods (eqs 29-31). The reduction of β-alkoxy halides using ***Zinc-Graphite*** proved to be especially interesting when applied to sugar derivatives (eq 32).[6c,45e,49] The dehalogenation using zinc is such a straightforward and chemoselective reaction that several protecting groups have been devised which use this reaction as a deblocking step.[50]

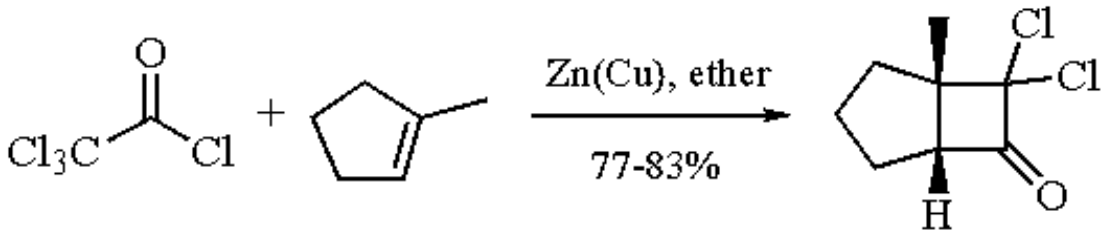

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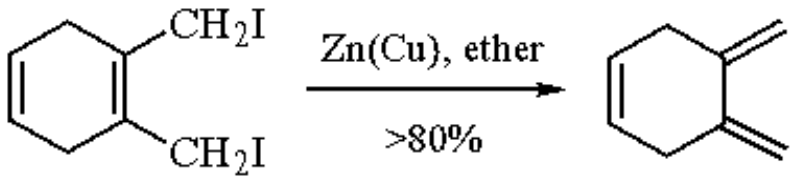

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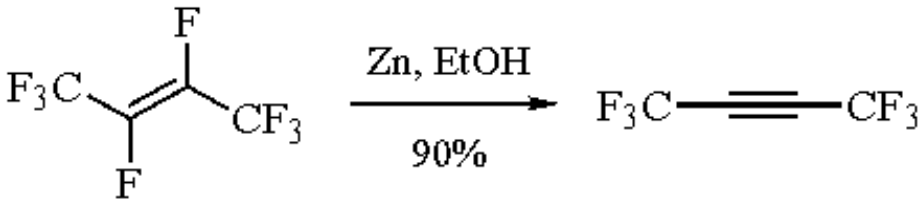

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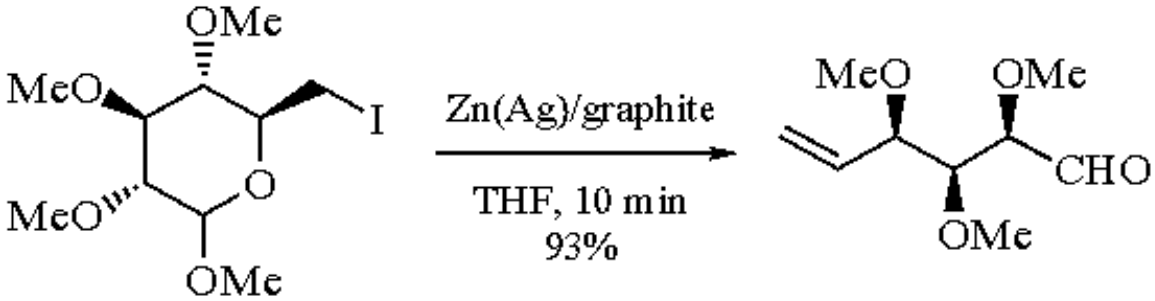

(32)

The Reformatsky Reaction.[4]

The insertion of zinc into α-halo esters produces zinc ester enolates which react readily with aldehydes or ketones, leading to aldol products. Historically, this reaction has been important since it allowed the first quantitative generation of an ester enolate. However, several modern synthetic methods for the stereoselective preparation of aldol products using metal enolates compete favorably with the Reformatsky reaction.[51] The nature of the zinc activation[6] has proved to be important for fast and quantitative zinc insertion. Remarkably, the Zn(Ag) couple on graphite reacts with ethyl bromoacetate at -78 °C within 20 min,[52a] whereas Rieke zinc requires 1 h at 25 °C,[52b] as does zinc generated from the reaction of ***Zinc Chloride*** with ***Lithium*** under ultrasound irradiation[52c] (eq 33).[52a] Interesting synthetic applications have been reported (eqs 34 and 35).[4,52] 4-Bromocrotonate reacts with ketones and Zn(Cu) with solvent-dependent regioselectivity.[52f] See also ***Ethyl Bromozincacetate***.

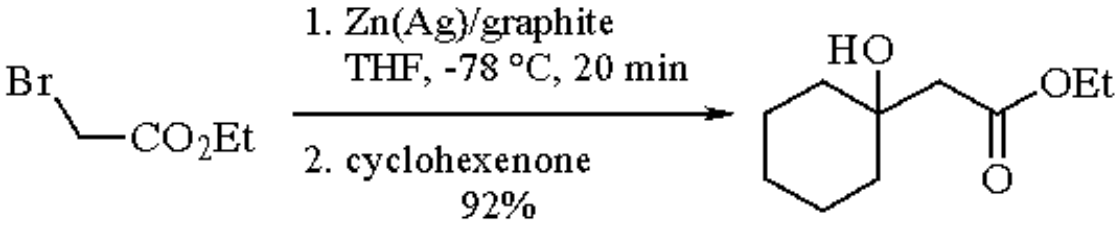

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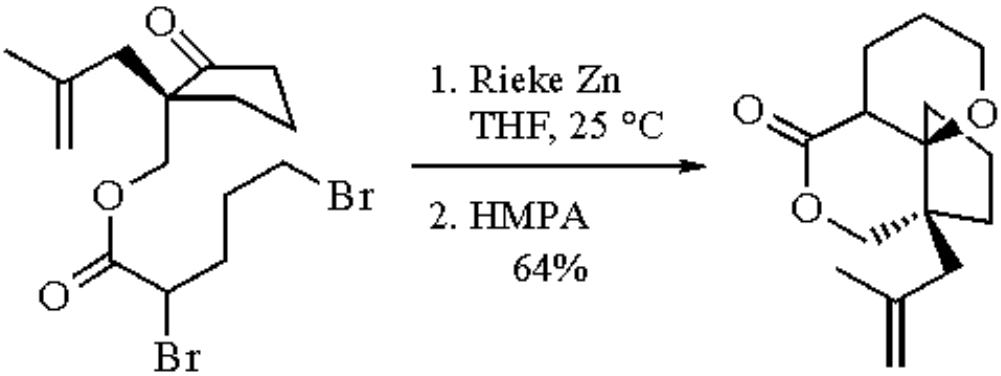

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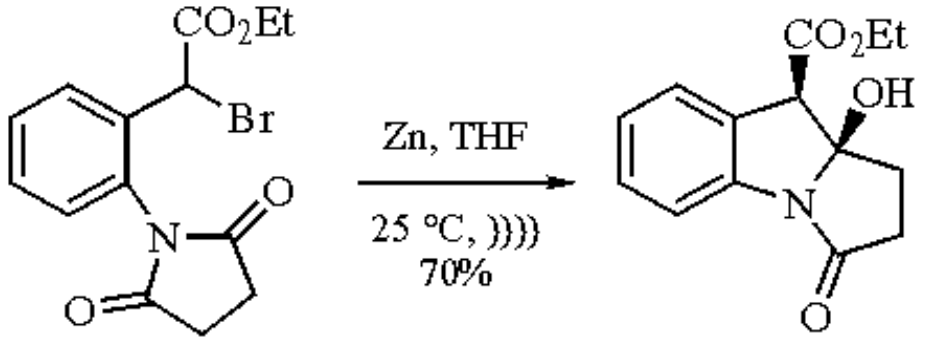

(35)

The Simmons-Smith Reaction.[5,53]

Cut Zn foil readily inserts into ***Diiodomethane*** providing iodomethylzinc iodide,[53] which cyclopropanates a wide range of alkenes in good yields (see ***Ethylzinc Iodide***, ***Iodomethylzinc Iodide***, ***Diethylzinc***, ***Ethyliodomethylzinc***). The in situ generation of iodomethylzinc iodide is often used. The Zn(Ag) couple has proved to be especially active for cyclopropanations (eq 36).[53d]

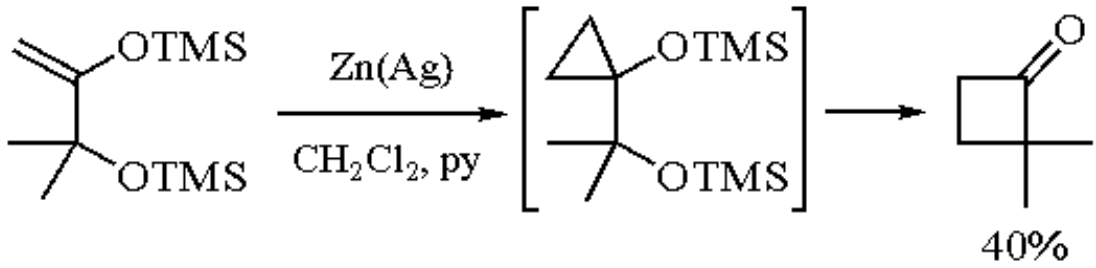

(36)

Preparation of Organozinc Reagents.[1,3a]

The insertion of zinc into organic halides provides the most general synthesis of organozinc halides. Primary and secondary organic iodides react with zinc dust (2-3 equiv) in THF between 20 °C and 50 °C, leading to organozinc iodides in high yields.[3a,54a-c] Benzylic chlorides and bromides react under even milder conditions, providing the corresponding benzylic zinc halides without the formation of significant amounts of Wurtz coupling products.[54d -f] Two remarkable properties characterize organozinc reagents: (i) their high functional group compatibility, which allows the preparation of polyfunctional organometallic zinc species bearing almost all common functional groups with the exception of nitro, azido, or hydroxy functions (see the reagents **3**,[54b] **4**,[54g,h] **5**,[54i] **6**,[54j] **7**,[54k-o] **8**,[54p] **9**,[54n,o] **10, 11**,[54q] and **12-14**,[54f] and eq 37); and (ii) their ability to undergo transmetallation with other metallic salts, such as copper salts, thus giving polyfunctional copper reagents which react readily with a wide range of electrophiles (enones,[54b,r] aldehydes,[54s] alkynes,[54t-v] nitro alkenes,[54w-y] allylic halides,[54b,z] alkynyl halides,[54g] acid chlorides,[54b,aa] and alkylidenemalonates[54ab]). Similarly, efficient transmetalations with Pd^{II} salts allow the coupling reactions to be performed (eq 38).[55,56] Zinc insertion also proceeds well with various polyfluorinated alkyl iodides[57] and with primary alkyl and benzyl phosphates and mesylates.[58] Alkenyl and aromatic halides undergo the zinc insertion far less readily and require the use of polar solvents[59] or highly activated zinc.[60] The use of a sacrificial zinc electrode offers an interesting alternative.[61] Allylic zinc halides are formed under very mild conditions and, contrary to other classes of organozinc reagents, display a high reactivity toward organic electrophiles (comparable to organomagnesium species).[36e-h,54a,62] A wide range of synthetic applications of zinc reagents for the formation of carbon-carbon bonds has been reported (eqs 39-44).[56,60a,63-66] Diorganomercurials also react with zinc dust, providing diorganozincs.[67,68]

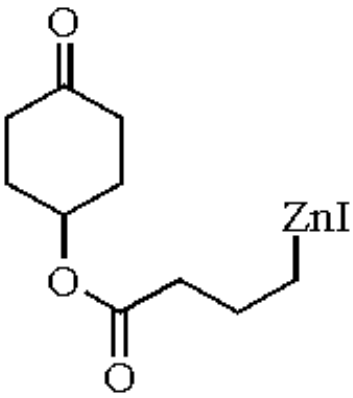

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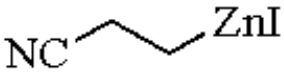

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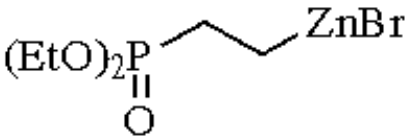

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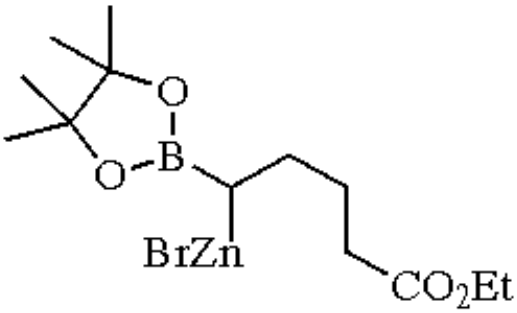

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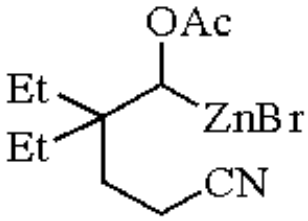

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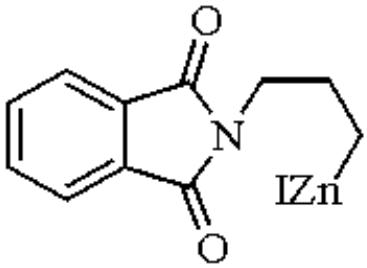

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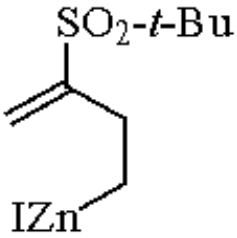

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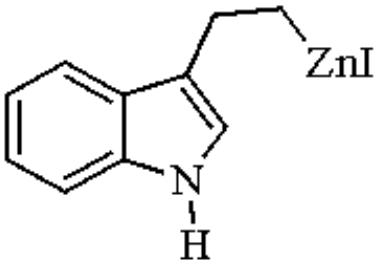

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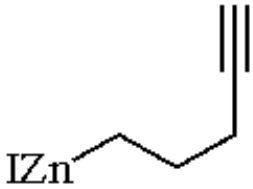

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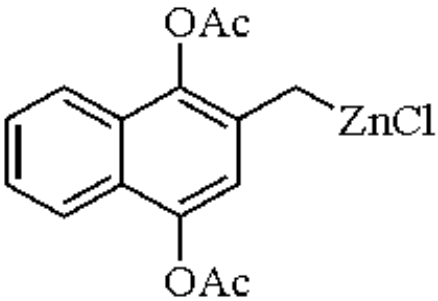

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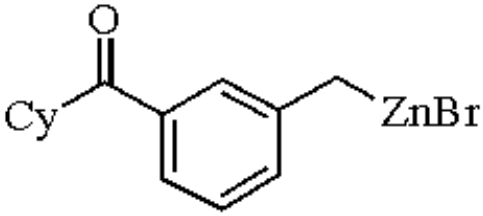

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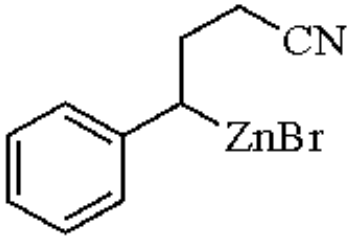

(14)

$$\text{FG-RX} + \text{Zn} \xrightarrow[\substack{5\text{-}45\ ^\circ\text{C} \\ >85\%}]{\text{THF}} \text{FG-RZnX} \qquad (37)$$

X = I, Br; R = alkyl, aryl, benzyl, allyl
FG = CO_2R, enoate, CN, enone, halide, $(RCO)_2N$, $(TMS)_2Si$, RNH, NH_2, RCONH, $(RO)_3Si$, $(RO)_2P(O)$, RS, RS(O), RSO_2, PhCOS

$$\text{FGR}^1\text{R}^2 \xleftarrow[\text{Pd}^0]{\text{R}^2\text{X}} \text{FGR}^1\text{ZnX} \xrightarrow[\text{2. E}^+]{\text{1. CuCN} \cdot \text{2LiCl}} \text{FGR}^1\text{E} \qquad (38)$$

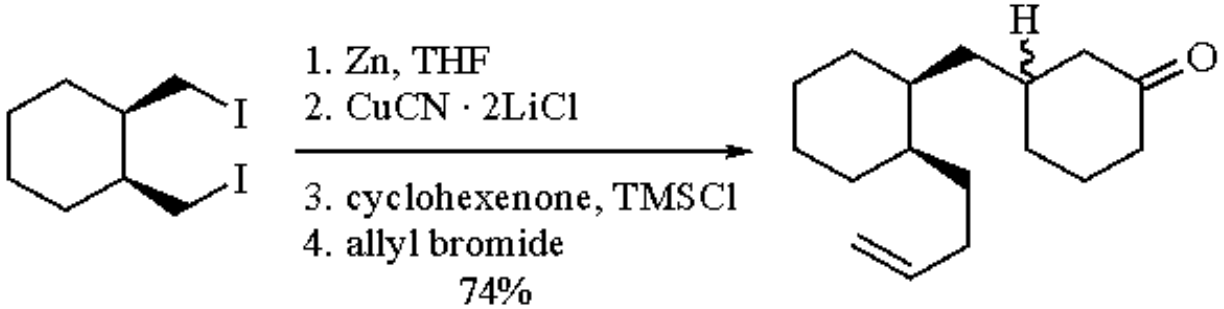
1. Zn, THF
2. CuCN · 2LiCl
3. cyclohexenone, TMSCl
4. allyl bromide
74%

(39)

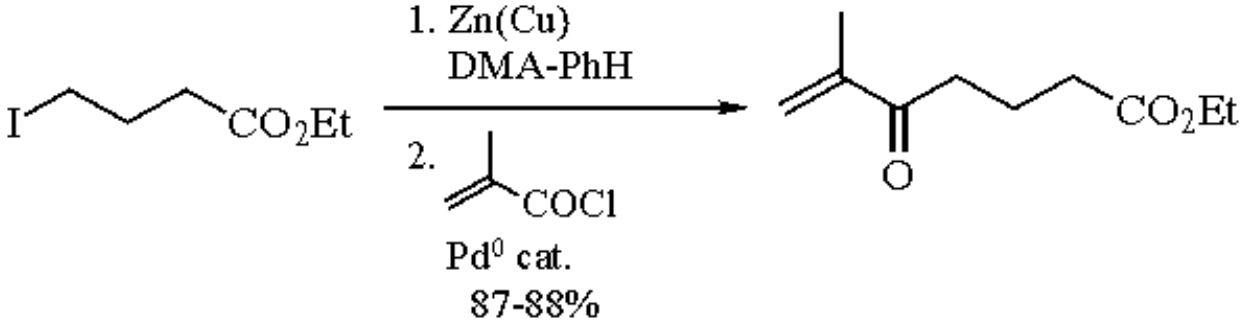
1. Zn(Cu)
DMA-PhH
2.
Pd0 cat.
87-88%

(40)

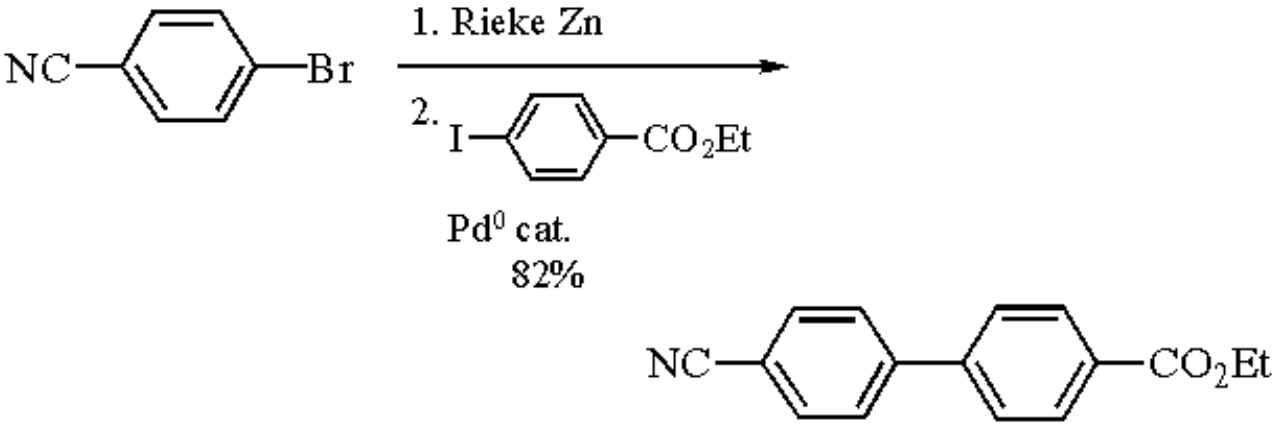
1. Rieke Zn
2.
Pd0 cat.
82%

(41)

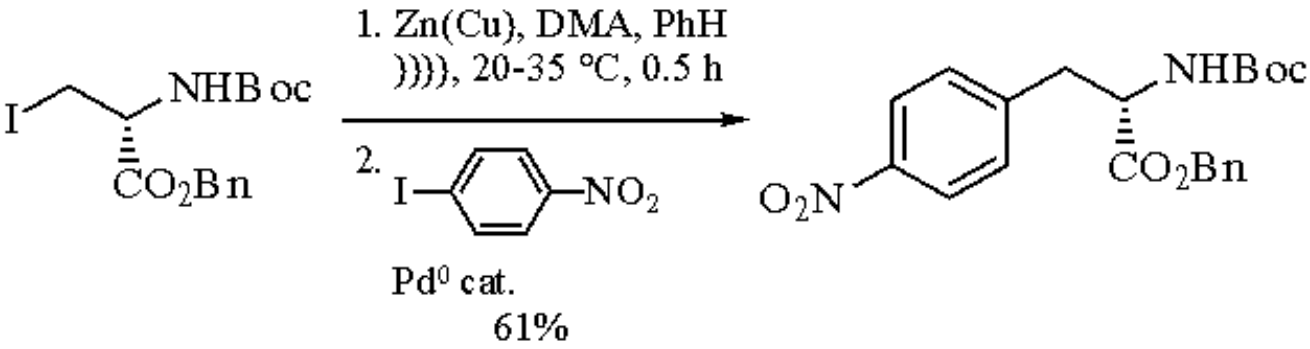
1. Zn(Cu), DMA, PhH
))))), 20-35 °C, 0.5 h
2.
Pd0 cat.
61%

(42)

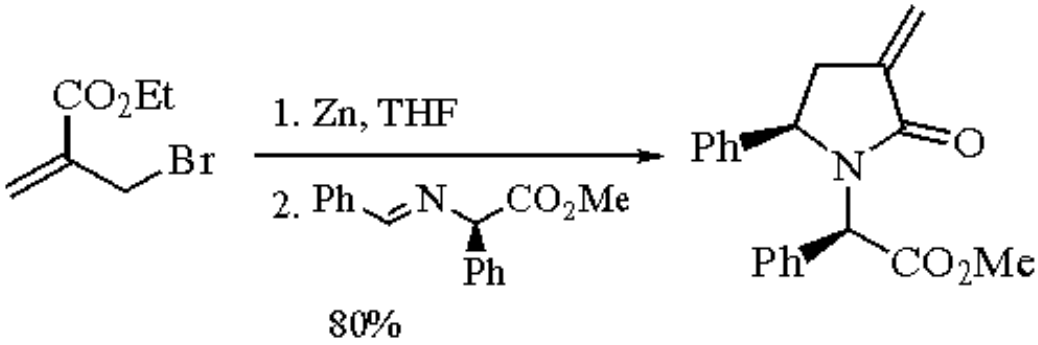
1. Zn, THF
2.
80%

(43)

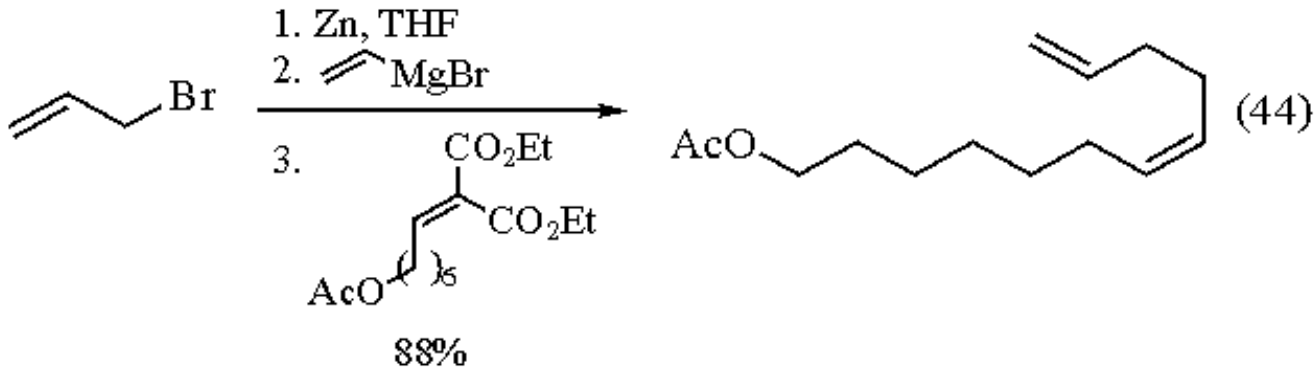

Related Reagents.

Dibromomethane-Zinc-Titanium(IV) Chloride; ***Dichlorobis(cyclopentadienyl)zirconium-Zinc-Dibromomethane***; ***Diiodomethane-Zinc-Titanium(IV) Chloride***; ***Molybdenum(V) Chloride-Zinc***; ***Niobium(V) Chloride-Zinc***; ***Phosphorus(III) Bromide-Copper(I) Bromide-Zinc***; ***Potassium Hexachloroosmate(IV)-Zinc***; ***Titanium(IV) Chloride-Zinc***; ***Zinc-Acetic Acid***; ***Zinc Amalgam***; ***Zinc-Copper(II) Acetate-Silver Nitrate***; ***Zinc-Copper(I) Chloride***; ***Zinc/Copper Couple***; ***Zinc-1,2-Dibromoethane***; ***Zinc-Dimethylformamide***; ***Zinc-Graphite***; ***Zinc/Nickel Couple***; ***Zinc/Silver Couple***; ***Zinc-Zinc Chloride***.

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Zinc-Acetic Acid[1]

Zn-AcOH

(Zn)

[7440-66-6] · Zn · Zinc-Acetic Acid · (MW 65.39) (AcOH)

[64-19-7] · $C_2H_4O_2$ · Zinc-Acetic Acid · (MW 60.06)

(reducing agent; causes reductive elimination of vicinal heteroatoms;[2-15] cleaves heteroatom-heteroatom bonds;[16-27] reduces allylic, benzylic, or α-carbonyl-substituted heteroatoms,[28-34] activated carbonyls,[35-37] and alkenes[38-40])

Physical Data: see entries for ***Zinc*** and ***Acetic Acid***.

Form Supplied in: although zinc is available in a variety of forms, the overwhelming majority of zinc-acetic acid reductions use zinc powder.

Purification: acid washing is not uncommon, but not always vital.

Introduction.

Zinc in acetic acid is capable of a wide range of reduction reactions. Although many of these can also be performed by a great number of other reagents, this reagent is of particular value in that good chemoselectivities can often be achieved. Some such instances are noted in the text and equations below; many of the references have also been chosen to demonstrate selective reduction in sensitive, polyfunctional molecules.

Reductive Elimination of Vicinal Heteroatoms.[2-15]

A great variety of combinations of heteroatom substituents has been successfully reductively eliminated by Zn/AcOH (eq 1 and Table 1). Cosolvents such as ether, THF, CH_2Cl_2, *i*-PrOH, or water have all been used. Reaction temperatures vary from case to case, but yields reported are typically good to excellent.

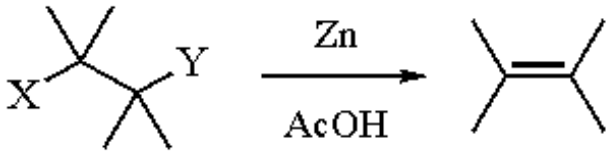

(1)

Table 1 Reductive Eliminations of Vicinal Heterosubstituents (eq 1)

X	Y	Yield (%)
Cl	OR	see next section
Cl	Cl	96[2]
Cl	SO_2R	87[3]
Cl	NO_2	79[4]
Br	OR	88[5]
Br	Br	94[6]
OR	OR	92[7]

A set of protecting groups, based upon Zn/AcOH elimination of the 2,2,2-trichloroethoxy group, has been developed, and is discussed below as a special case. Table 1 records several of the combinations of heteroatoms successfully eliminated under these conditions. Perhaps surprisingly, the relative stereochemistry of the two carbon centers does not have to permit *trans* coplanarity of the heteroatoms.[4,7]

Heterocyclic rings may be cleaved by these reactions. Thus, effective reversal of iodolactonization (eq 2)[8] or of epoxidation (after iodide ring opening) (eq 3)[9] may be achieved.

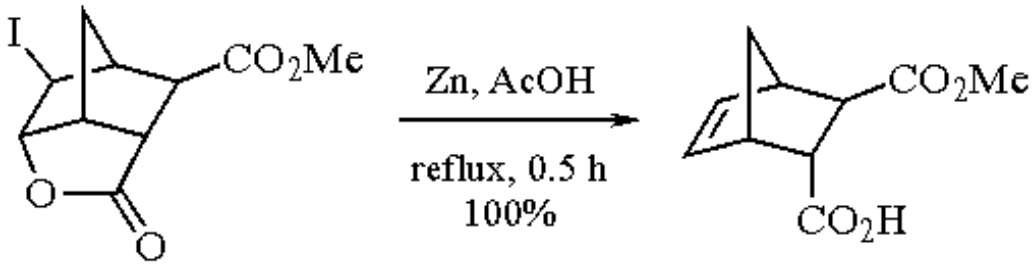

(2)

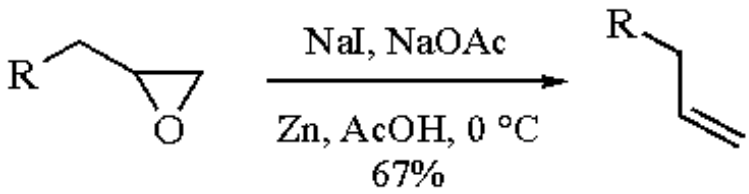

(3)

Halogenated oximes (**1**) eliminate to give the nitrile in variable, but often good to excellent, yields (eq 4).[10]

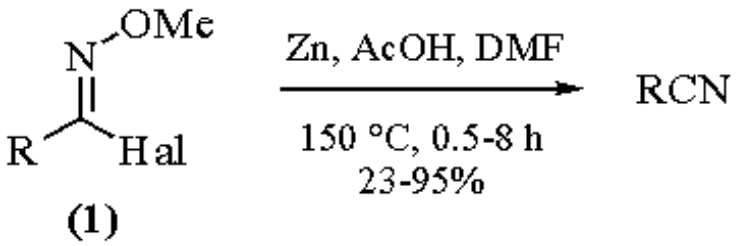

(1)

(4)

2,2,2-Trichloroethoxy-Based Protecting Groups.[11-15]

Valuable protecting groups for alcohols,[11] phenols,[11c] amines,[11c] and carboxylic acids,[12] and an introduction/protection reagent for thiols,[13] all dependent upon the lability of this group to Zn/AcOH reductive elimination, have been developed. They are summarized in Table 2.

Table 2 Protecting Groups Based on OCH_2CCl_3 Elimination

Functionality	Protected form
ROH[11a]	$ROCH_2CCl_3$
ROH[11b]	$ROCH_2OCH_2CCl_3$
ROH[11c,d]	$ROC(O)OCH_2CCl_3$
ROH[11e]	$ROC(O)OCMe_2CCl_3$
ArOH[11c]	$ArOC(O)OCH_2CCl_3$
R_2NH[11c]	$R_2NC(O)OCH_2CCl_3$
RCO_2H[12]	$RC(O)OCH_2CCl_3$
RSH[13]	$RSC(O)OCH_2CCl_3$

The trichloroacetylidene acetal has also been proposed as a potential protection for diols, similarly deprotectable.[14] Also, along similar lines, the 2-iodoethyl carbamate protection for amines, deprotectable by Zn dust alone in MeOH, has been proposed,[15] but has found relatively little use.

Heteroatom-Heteroatom Cleavage.[16-27]

N=N double bonds can be cleaved[16] by Zn/AcOH; less frequently, hydrazines[17] may be obtained from the reduction (eqs 5 and 6).[17] Hydrazones may also be reduced to amines,[18] as used[18b] in a variant of the classical Knorr pyrrole synthesis. Diazo ketone (**2**) has been successfully reduced, despite the apparent potential for adverse side reactions (eq 7).[19]

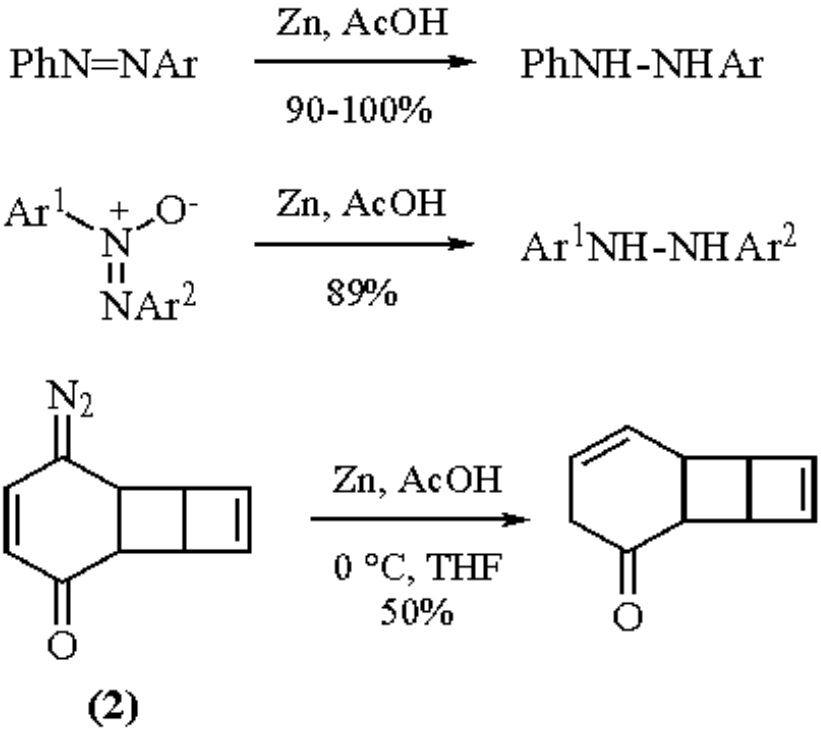

Aromatic nitro groups[20a] (aliphatic nitro groups can yield oximes,[20b] even though not all such would be stable under all reaction conditions), hydroxylamines,[21] oximes[22] (once again, finding use[22b] in a Knorr pyrrole synthesis), *N*-nitro-[23a] and *N*-nitrosoamines,[23b] aromatic *N*-oxides,[24] and aromatic N-S bonds[25] have all been reduced to amines with Zn/AcOH. These references include ample evidence of the ability of this reagent to perform the desired reaction, while leaving intact, for example, bromides,[22] carbon-bonded sulfur atoms,[20,23b] and isolated C=C double bonds.[21] It will, of course, be understood that the newly liberated amines often undergo spontaneous intramolecular reactions.

Sulfonamides[26] can also be reduced to the thiols.

Zn/AcOH can act as a useful alternative reagent for reductive workup of ozonolysis reactions,[27] which can be considered, at least formally, to involve O-O bond cleavage (see ***Ozone***).

Curiously, the vigor of the conditions reported to have been employed for these disparate reactions does not seem to follow any consistent pattern; reaction conditions, therefore, may need individual determination in many cases.

Carbon-Heteroatom Cleavage.[28-34]

Substitution of N,[28] O,[29] S,[30] or halogen,[31] for example, at an allylic, benzylic, or α-carbonyl-substituted carbon atom renders the heteroatom liable to cleavage with Zn/AcOH. In allylic systems, double bond migration usually occurs. If conjugated to a carbonyl group, migration still occurs, giving the β,γ-product (eq 8),[32a] but these can be easily reconjugated (eq 9).[32b] Homoallylic reduction[33] has also been reported in a constrained system (eq 10).

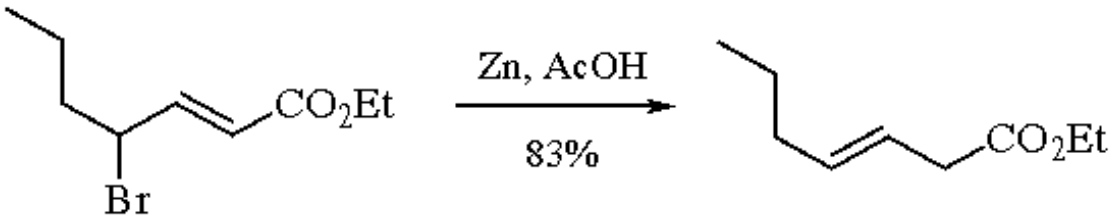

(8)

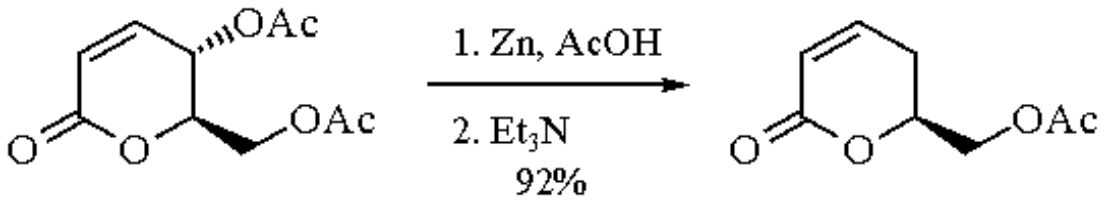

(9)

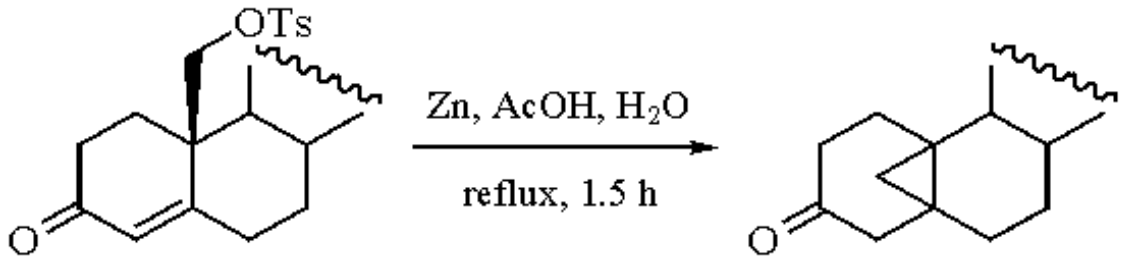

(10)

Cleavage α to a carbonyl group has been exploited in the use of phenacyl protecting groups.[34] The reduction of compounds such as (**3**) (for their formation, via ***Dichloroketene*** see ***Trichloroacetyl Chloride***) retains the strained four-membered ring, and often gives excellent yields (eq 11).[31c]

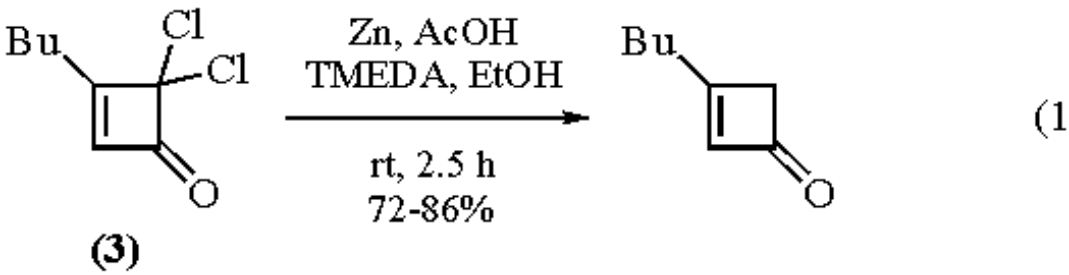

(11)

Carbonyl Reduction.[35-37]

Quinones are reduced to hydroquinones by Zn/AcOH at reflux.[35a] Incorporation of Ac_2O into the reaction mixture gives the respective diacetate.[35a] Under milder conditions (rt), the intermediate γ-hydroxycyclohexenone may be intercepted in surprisingly high yield (72-90%).[35b]

Diaryl ketones may be reduced to the alcohols,[36a] but a competing dimerization has also been reported[36b] in some unusual cases. Reduction of phthalimide (**4**) proceeds well and, notably, with regiospecificity (eq 12).[37]

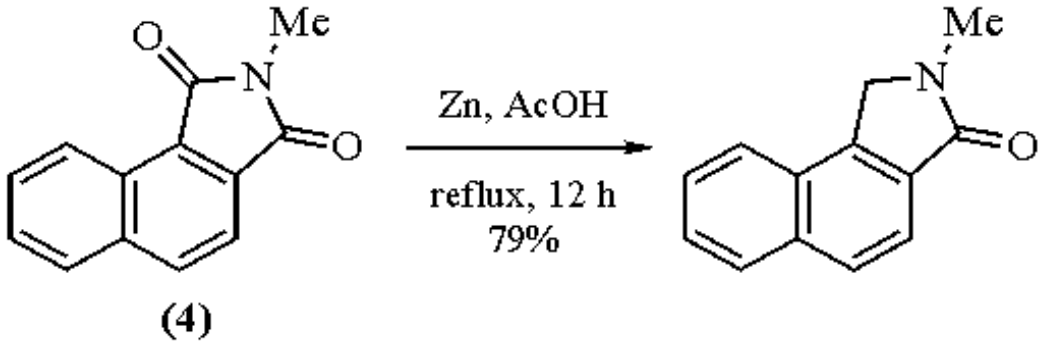

(12)

Reduction of Activated Alkenes.[38-40]

Carbonyl (mono-[38a] or di-[38b]) substitution renders a C=C double bond liable to reduction by Zn/AcOH. α,β,γ,δ-Dienones may yield either α,β-[38a] or β,γ-enones[38c] in equally high yields. A recent modification,[39] at lower temperature (rt), and with much shorter reaction times, uses ultrasonication; excellent yields were achieved.

α,β-Unsaturated nitro compounds can also be reduced.[40] Under mild conditions an oxime can be obtained (eq 13)[40a] (cf. ***Sodium Borohydride***, which reduces the C=C double bond); more vigorous reaction leads to the corresponding ketone.[40b]

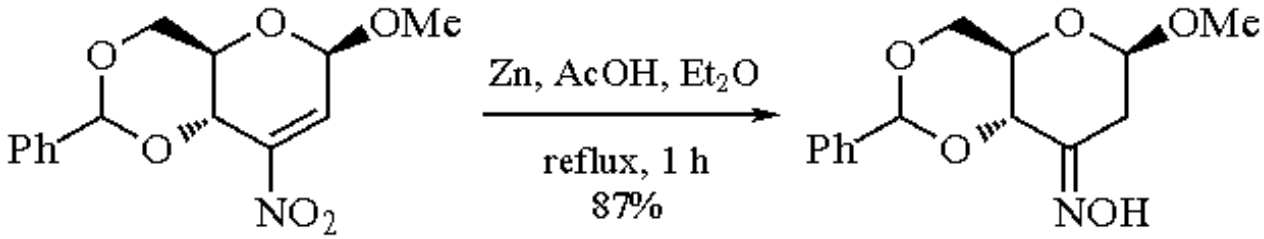

(13)

Aza-Heterocycle Ring Contraction.

A variety of polyaza six-ring heterocycles undergo contraction with formal excision of N, e.g. eq 14.[41a] Further heteroatoms in the ring are tolerated: 1,2,3-triazines yield pyrazoles[41b] and 1,2,4-triazines yield imidazoles,[41c] with the latter usually requiring reflux temperature. The utility of indole syntheses from cinnolines[41d] by this method should be noted. Adjacency of heteroatoms is not required: conversions of pyrimidine to pyrrole[42a,b] and 1,3,5-triazine to imidazole[42c] have been recorded. The mechanism of these conversions is unclear, but ring dihydro derivatives[41a,42b] are thought to be involved.

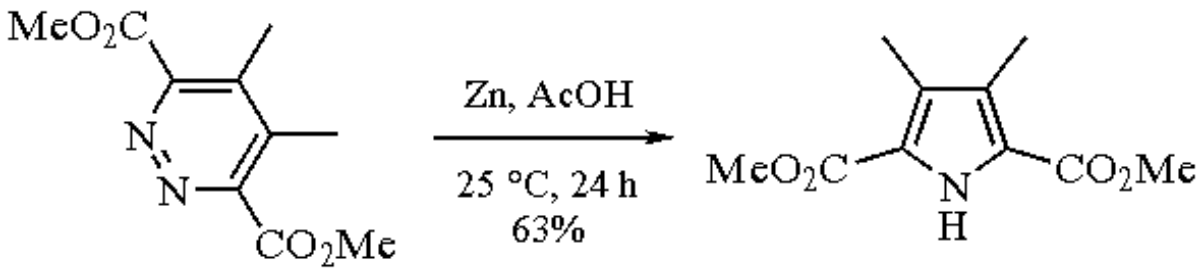

(14)

Reduction of Aryl Substituents.

Although, as mentioned above, many potentially labile functionalities are stable to Zn/AcOH, aryl iodides may be dehalogenated.[43] Substitution of Cl or Br at the 2-position of heteroaromatics also renders them liable to reduction, often with superb selectivity (eqs 15 and 16).[44]

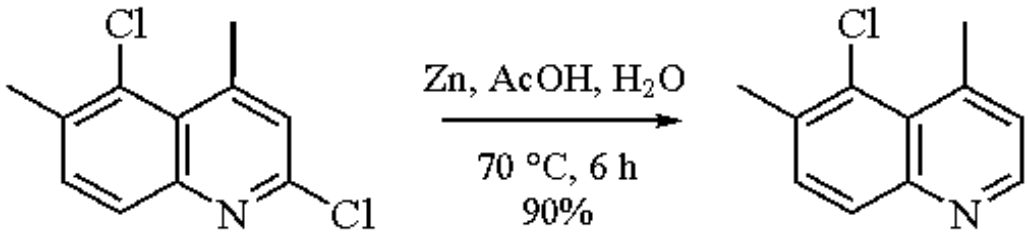

(15)

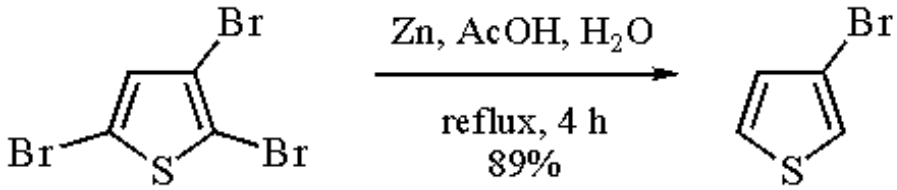

(16)

Related Reagents.

Iron; ***Tin***; ***Zinc Amalgam***; ***Zinc-Zinc Chloride***.

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Peter Ham

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Zinc Amalgam[1]

Zn/Hg

(Zn)

[7440-66-6] · Zn · Zinc Amalgam · (MW 65.39) (Hg)

[7439-97-6] · Hg · Zinc Amalgam · (MW 200.59)

(reducing agent in the Clemmensen reduction,[1] principally of aryl ketones to alkanes)

Solubility: insol organic solvents.

Preparative Methods: various forms of zinc (zinc turnings, wool, or powder, or mossy or granulated zinc) have been successfully employed, with preliminary activation of the metal by washing with hot HCl reportedly being of advantage. Amalgam formation is then accomplished by treatment of the zinc metal with an aqueous, possibly very slightly acidic, solution of $HgCl_2$. After an appropriate length of time, the aq solution is decanted, replaced by fresh HCl, and the amalgam is used immediately.[1a]

Handling, Storage, and Precautions: as well as the corrosive nature of the (usually conc) HCl often employed, requiring normal chemical precautions, the mercury-containing wastes must be disposed of with due attention.

Clemmensen Reduction.[1]

The reagent as prepared above has been successfully used to reduce a wide variety of substances. If the substrate is not adequately soluble in the aqueous acidic solution, a miscible organic cosolvent may, on occasion, be usefully added. An immiscible solvent such as toluene, however, is commonly employed, but efficient stirring, and extended reaction times at reflux, are often required.

A more modern variant uses Zn/Hg (or Zn alone[1]) with HCl in anhydrous solvents. Reaction can often proceed much more rapidly, even at the lower temperatures sometimes used - a clear advantage if the substrate is not fully stable to acidic conditions. Phenolic acetate esters, for example, are typically cleaved under the classical reaction conditions.[2]

A great number of ketones, and some aldehydes, have been reduced by this method to the corresponding alkanes (eq 1), often in excellent yields.[1] The reaction can tolerate a wide variety of aryl substituents.

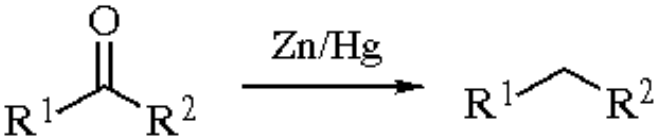

(1)

R^1 usually aryl

Polyfunctional substrates, however, may exhibit some differences of reactivity. Thus, for example, α-, but not β- or longer, keto acids[1a] are reduced to α-hydroxy acids. Acyloins (**1**) may be completely reduced,[3] or reduced only to the ketone[4] or alkene (stilbene).[5] $ArCOCCl_3$ is reduced near-quantitatively to $ArCH_2CH_3$[6] (aromatic Cl[7a] or Br[7b] substitutents are usually retained, but dehalogenation may occur rarely as a side reaction[7c]). The α-thioether linkage of (**2**) is retained,[8a] but the S atom of (**3**) is excised[8b] before reduction of the carbonyls.

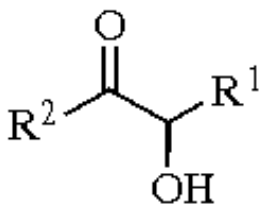

(1)

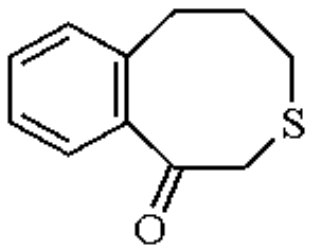

(2)

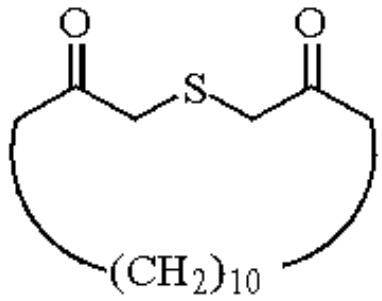

(3)

Some benzophenones may react as expected,[1a] but dimerization to pinacols has also been recorded in certain cases.[9] Rarely, the alcohol may be formed,[10] possibly intramolecularly trapped.[6b] α,β-Unsaturated ketones may reduce normally (but with competing dimerization)[11a] or cyclize[1,11b] (eq 2).[11b] On occasion, diketones may react by intramolecular pinacol coupling,[12] but further reactions are common.[1b]

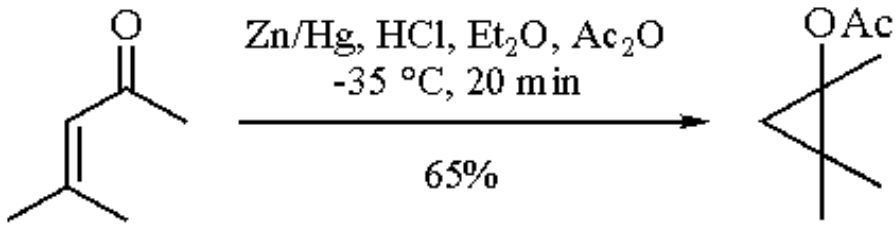

(2)

Compounds not suitable for reduction under these acidic Clemmensen conditions may still be reduced by the Wolff-Kishner[13a] reduction (or, better, its Huang-Minlon modification[13b]), which, being performed under basic conditions, serves as a complementary procedure.

Other Reductions.

The dithioesters RCS_2Me may be reduced to the thioethers RCH_2SMe,[14] but with unspectacular yields. Nitro groups may also be reduced to amines.[15] Certain benzylic alcohols[16a] or alcohol derivatives (e.g. a lactone[16b]) are cleaved to the alkane. Allylic alcohols[17a] or acetates[17b] are reduced with migration of the double bond. Sulfonyl chlorides may be reduced to the thiol.[18]

Ring Contractions.

3-Oxopiperidine (**4**) undergoes ring contraction[19a,b] under Clemmensen conditions (eq 3). The corresponding (3-oxo)azepine[19c] and their thia analogs[19d] react similarly, although the latter do so in lower yields.

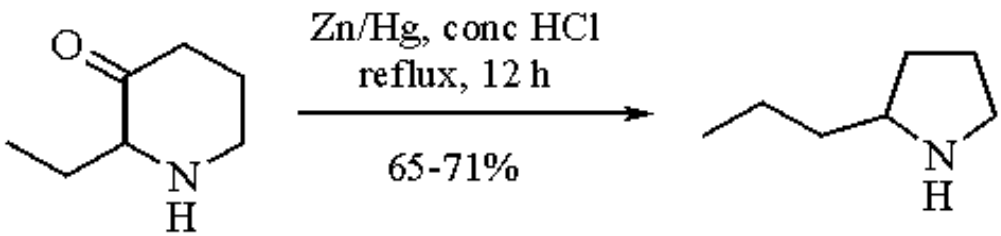

(4)

(3)

3-Arylindoles[20a] and azaindoles[20b] can be formed by reduction of, for example, (**5**) in AcOH (eq 4) (see also ***Zinc-Acetic Acid*** for similar reactions).

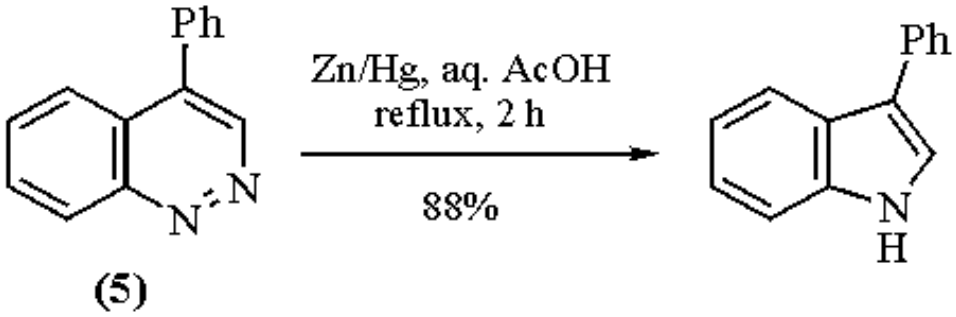

(4)

Reformatsky-Type Reactions.

Zn/Hg has been noted to effect this reaction in a few cases, such as the propargyl bromide hydroxymethylation with ***Formaldehyde*** (eq 5)[21] (note: no allene formed), and γ-addition of a crotyl group (from the bromide) to a ketone.[22]

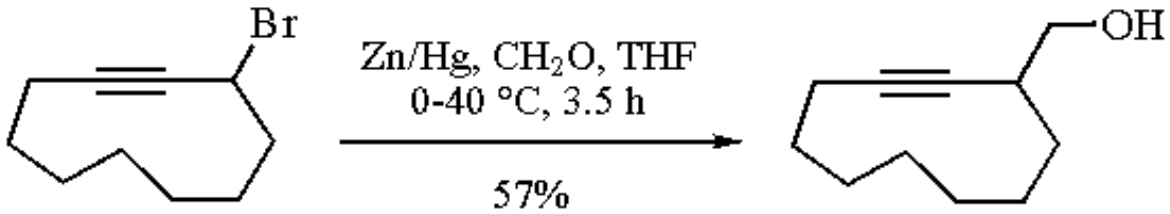

(5)

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Zinc Borohydride[1]

$Zn(BH_4)_2$

[17611-70-0] · B_2H_8Zn · Zinc Borohydride · (MW 95.09)

(mild reducing agent for carbonyl groups;[1] can be used in the presence of base-sensitive functional groups; stereoselective reducing agent[2])

Solubility: sol ether, DMF, CH_2Cl_2, toluene, THF.

Preparative Method: commercially available anhydrous ***Zinc Chloride*** (ca. 10 g) in a 200 mL flask was fused three or four times under reduced pressure and then anhydrous ether (ca. 100 mL) was added. The mixture was refluxed for 1-2 h under argon and allowed to stand at 23 °C. The supernatant sat. solution of $ZnCl_2$ (0.69 M) in ether (80 mL; 55 mmol) was added to a stirred suspension of ***Sodium Borohydride*** (4 g; 106 mmol) in anhydrous ether (300 mL). The mixture was stirred for 2 d and stored at rt under argon. The supernatant solution was used for reduction.[3]

Handling, Storage, and Precautions: the solutions are sensitive to moisture and must be flushed with N_2 or argon. However, it is preferable to use freshly prepared reagent.

Mild Reducing Agent.

$Zn(BH_4)_2$ is a mild reducing agent and only aldehydes, ketones, and azomethines[4] are reduced to the corresponding alcohols and amines under normal conditions. Moreover, the ether solutions are almost neutral and thus can be used for the chemoselective reduction of aldehydes and ketones in the presence of nitrile,[5] ester,[5,6] γ-lactone,[7] aliphatic nitro,[8] and base-sensitive functional groups (eqs 1 and 2).[5,9] Selective reduction of saturated ketones and conjugated aldehydes over conjugated enones can also be effected with $Zn(BH_4)_2$ in DME (eq 3).[10]

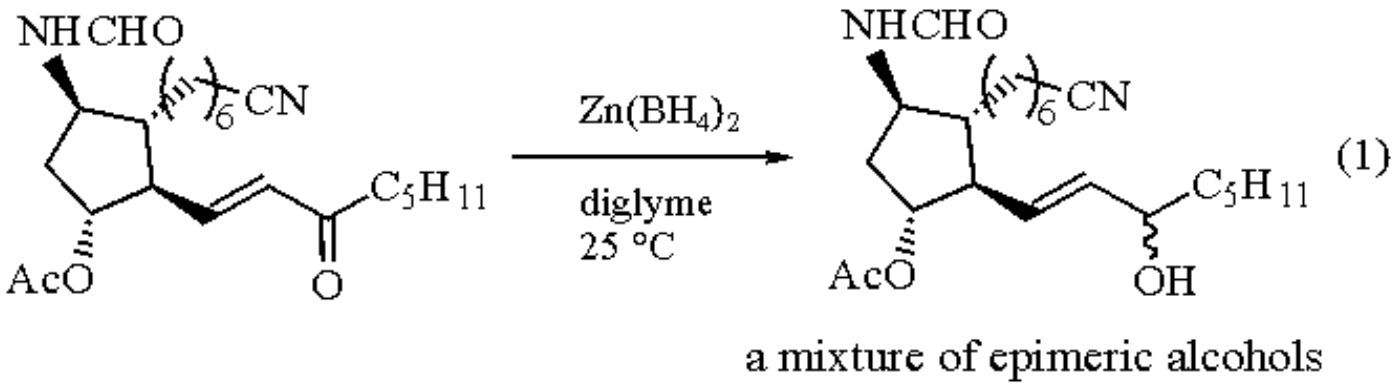

(1)

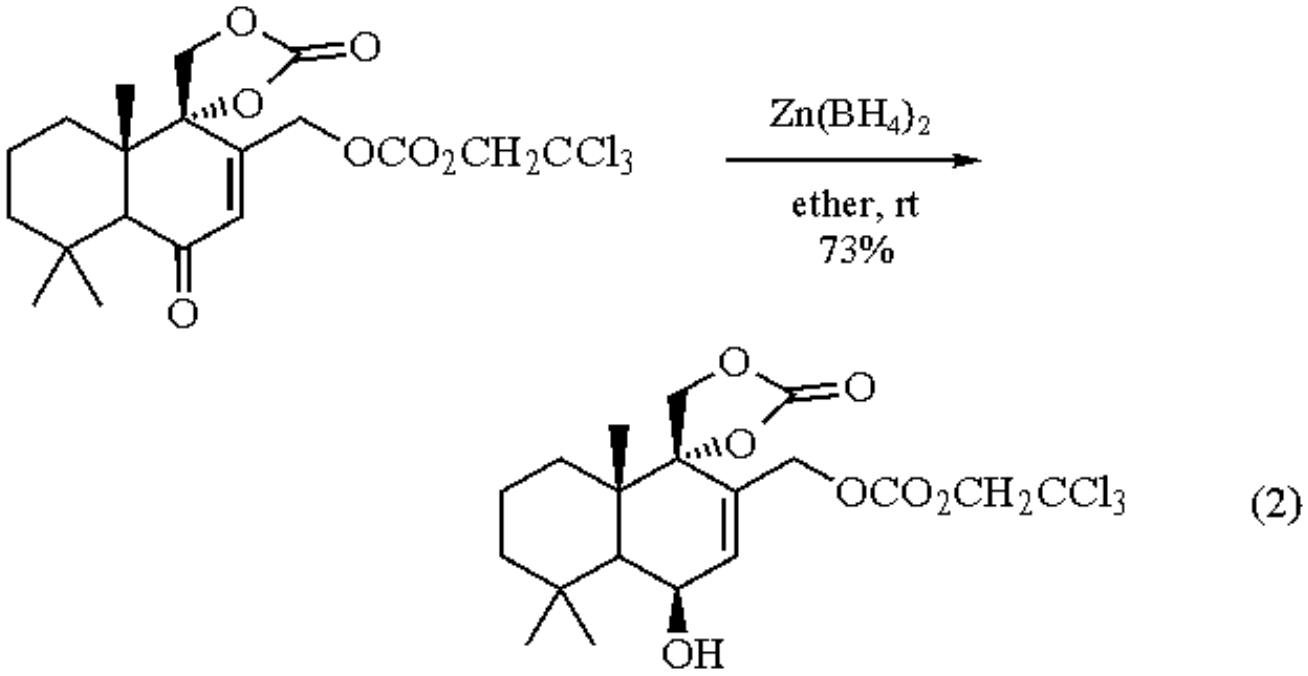

(2)

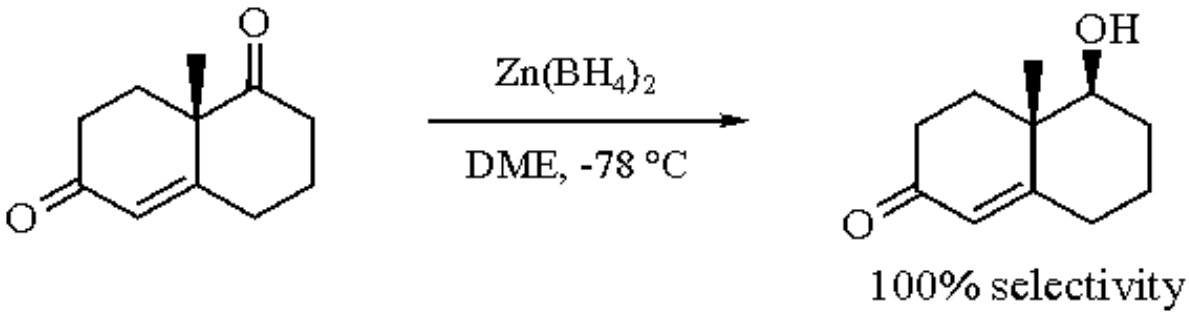

(3)

Although $Zn(BH_4)_2$ is usually unreactive towards carboxylic acids and esters, activated esters (eq 4)[11] and thiol esters (eq 5)[12] undergo reduction, giving alcohols. Even carboxylic acids can be reduced to alcohols with this reagent in the presence of ***Trifluoroacetic Anhydride*** (TFAA) (eq 6)[13] and acid chlorides undergo reduction by the addition of ***N,N,N´,N´-Tetramethylethylenediamine*** (eq 7).[14] Acetals are reductively cleaved to ethers when ***Chlorotrimethylsilane*** is added (eq 8).[15]

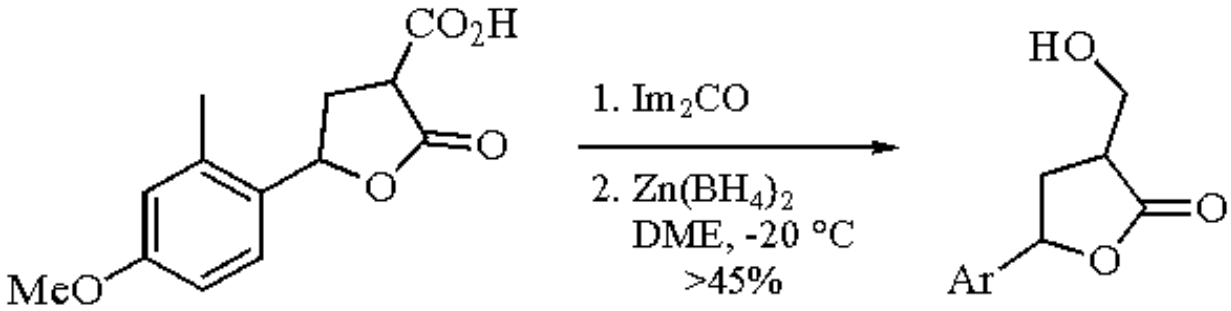

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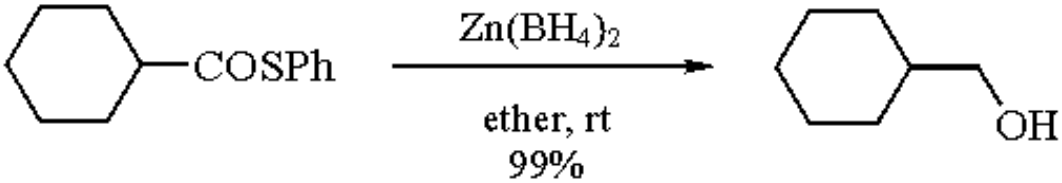

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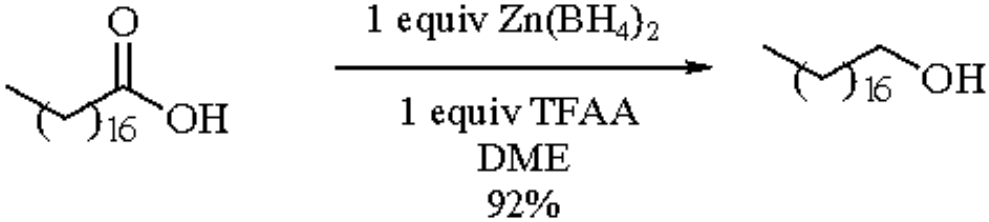

(6)

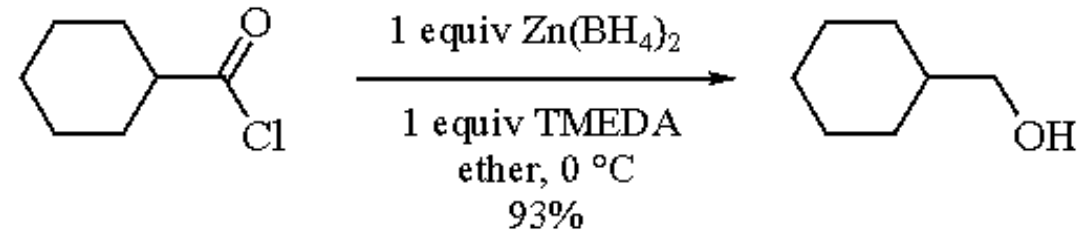

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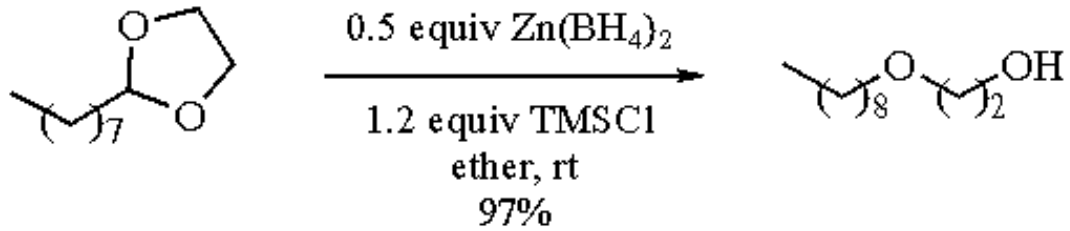

(8)

Reduction of aliphatic carboxylic esters takes place under ultrasonic activation to give alcohols.[16] The reducing ability of this system is enhanced by the addition of a catalytic amount of *N*,*N*-dimethylaniline and thus aromatic esters which are unaffected under the normal conditions undergo reduction (eqs 9 and 10).[16]

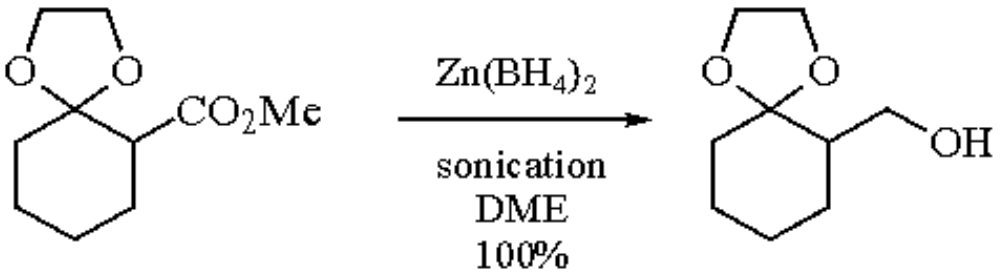

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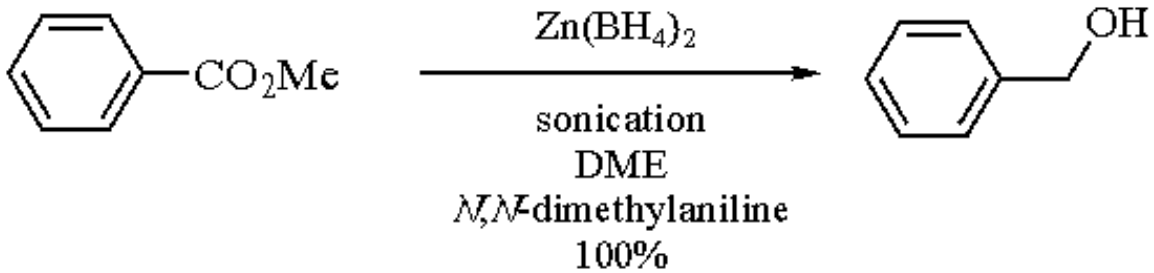

(10)

Unsymmetrical epoxides are reductively cleaved to the less substituted alcohols by the use of silica gel-supported $Zn(BH_4)_2$ (eq 11).[17,18] The same reagent is effective for regioselective 1,2-reduction of conjugated ketones and aldehydes to give allylic alcohols (eq 12).[19] $Zn(BH_4)_2$ supported on cross-linked ***Poly(4-vinylpyridine)*** (XP4) reduces aldehydes in the presence of ketones with high chemoselectivity (eqs 13 and 14).[20] This polymer-supported reagent can be stored at rt without appreciable change in its reactivity.

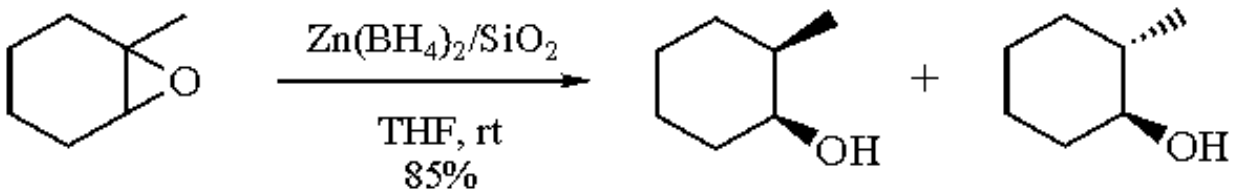

(11)

cis:*trans* = 90:10

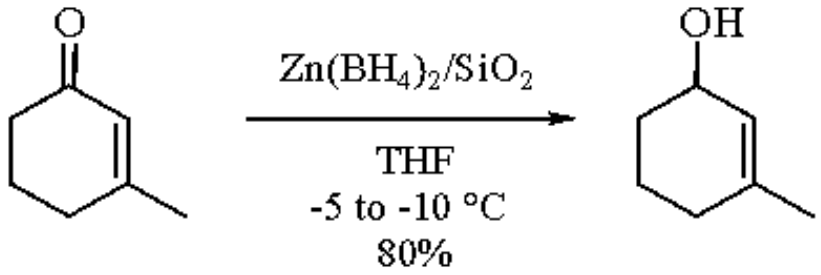

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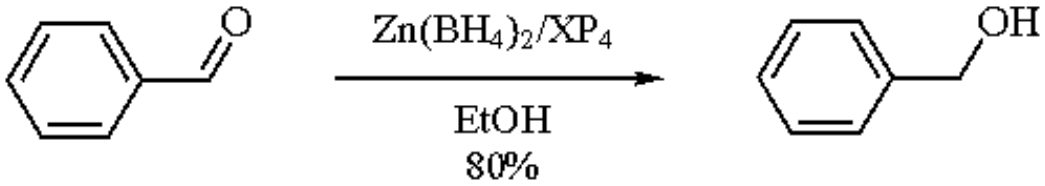

(13)

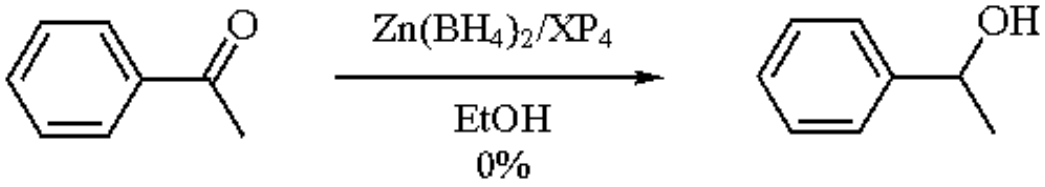

(14)

Tertiary and benzylic halides are reductively dehalogenated with $Zn(BH_4)_2$ (eq 15).[21] This process has been applied for the selective reduction of the distant double bond(s) in geranyl farnesyl and geranyl geranyl derivatives.[22]

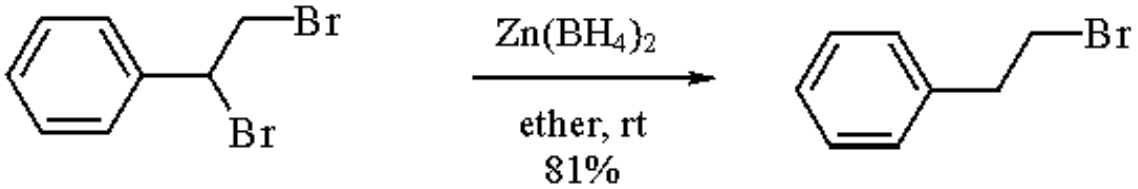

(15)

Stereoselective Reductions.

syn-α-Methyl-β-hydroxy esters or their equivalents which repeatedly appear in the framework of polyoxomacrolide antibiotics are synthesized stereoselectively by the reduction of the corresponding α-methyl-β-keto esters[23,24] or α-methyl-β-hydroxy ketones[25] with $Zn(BH_4)_2$ in ether. Excellent selectivities are obtained when the carbonyl group is conjugated with phenyl or vinyl groups (eq 16)[23-25] or the esters in α-methyl-β-keto esters are replaced by the amides (eq 17).[26] Ketones having a phosphine oxide group in place of esters or amides produce *syn* products by the $Zn(BH_4)_2$ reduction, while reduction with ***Lithium Triethylborohydride*** gives the *anti* isomer stereoselectively (eq 18).[27] The *syn*-directing reduction is presumed to proceed through a metal-mediated cyclic transition state and thus the use of a complex hydride like $Zn(BH_4)_2$, whose metal possesses a high coordinating ability, is advantageous for producing excellent selectivity.

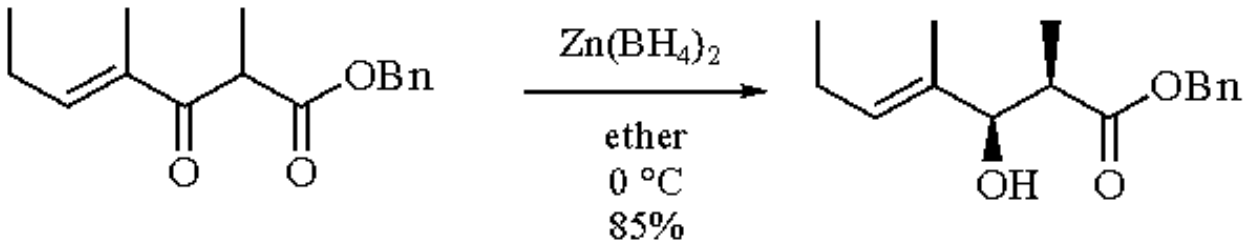

(16)

syn:*anti* = >99:1

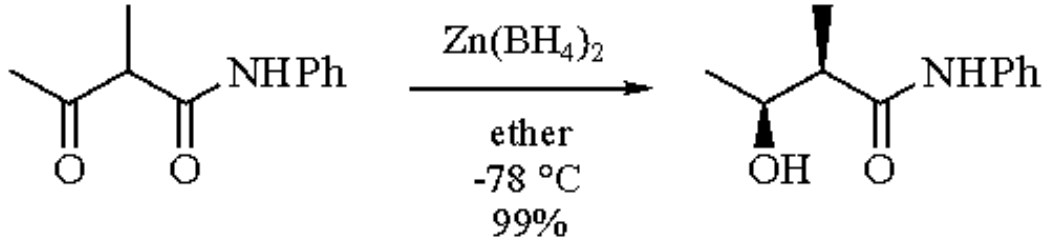

(17)

syn:*anti* = 98:2

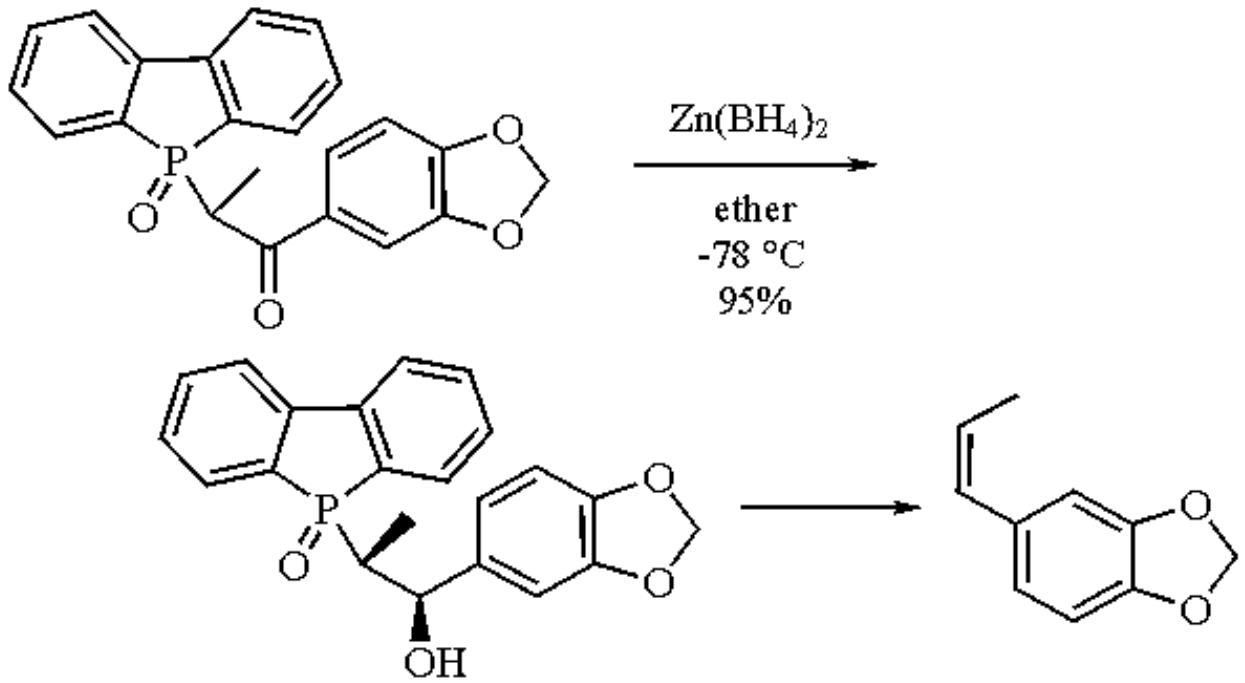

(18)

syn:*anti* = 98:<2

Acylation of chiral *N*-propionyloxazolidinones gives chiral α-methyl-β-keto imides, whose $Zn(BH_4)_2$ reduction affords optically active *syn*-α-methyl-β-hydroxy derivatives with virtually complete stereoselectivity (eq 19).[28,29] In the same way, chiral carboxamides (eq 20)[30] and (*R*)-*N*-acylsultams (eq 21)[31] also afford chiral *syn* products with high selectivities.

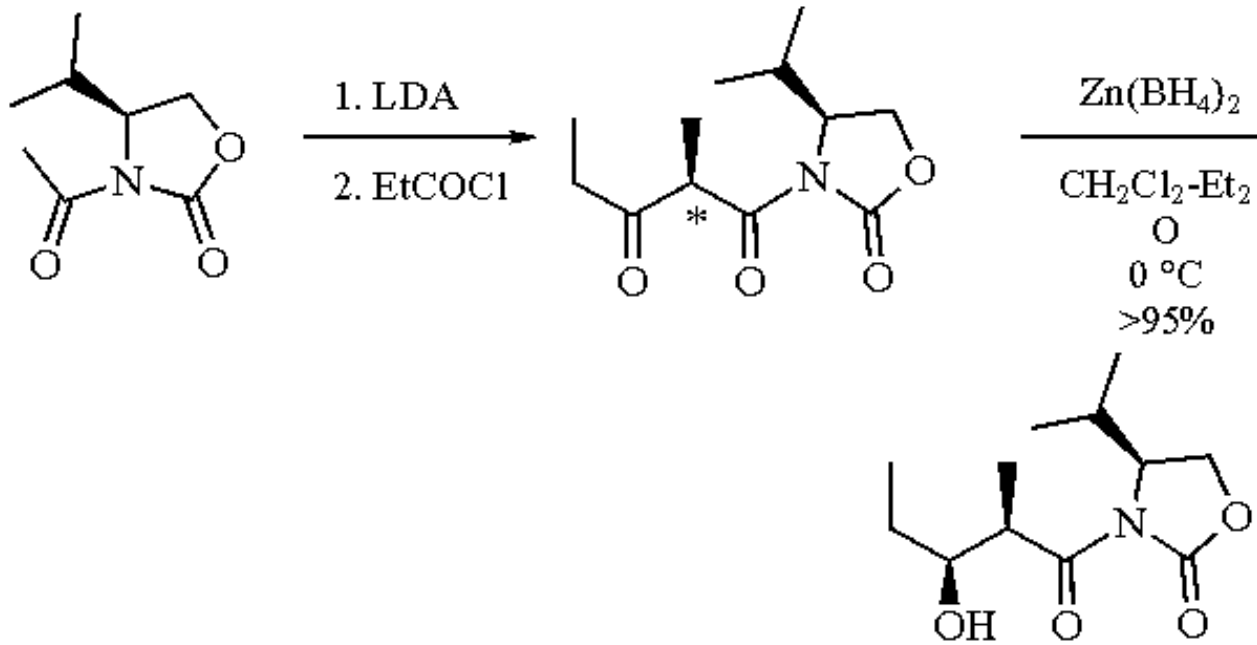

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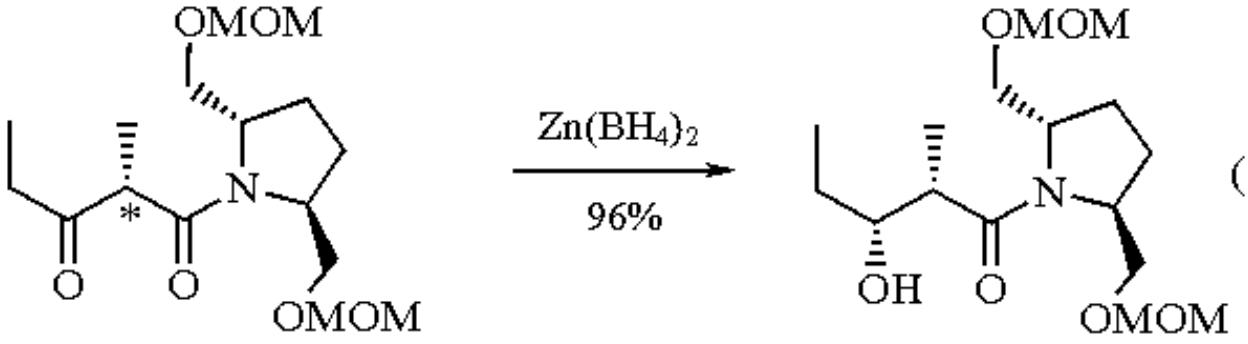

(20)

syn:*anti* = 99:1

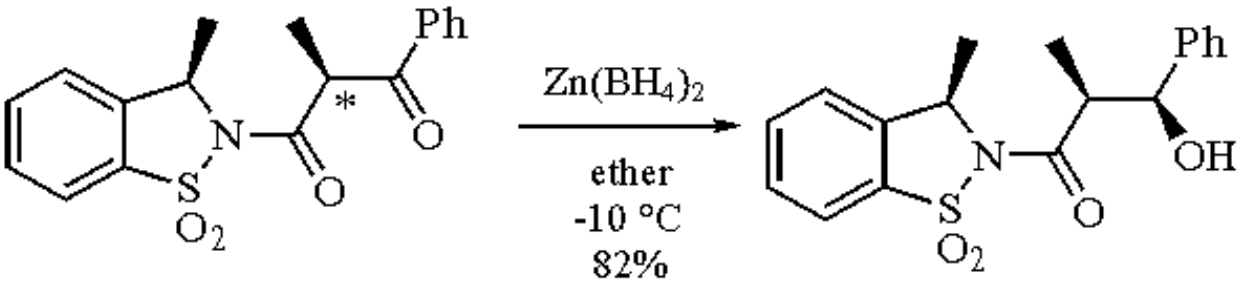

(21)

syn:*anti* = 99.1:0.9

Selectivity of $Zn(BH_4)_2$ reductions of β-hydroxy[32,33] or *N*-aryl-β-amino[34] ketones lacking α-substituents is generally unsatisfactory. A case where an excellent result is obtained is shown in eq 22.[32] For the stereoselective preparation of *syn*- and *anti*-1,3-diols the use of other reagents is recommended.[35] However, in the reduction of β-keto esters, with chiral ester units, the *syn* selectivity is improved significantly (eq 23).[36] Reduction of the same keto ester with DIBAL-BHT (***Diisobutylaluminum 2,6-Di-t-butyl-4-methylphenoxide***) affords the diastereomer with high selectivity (eq 24).[36]

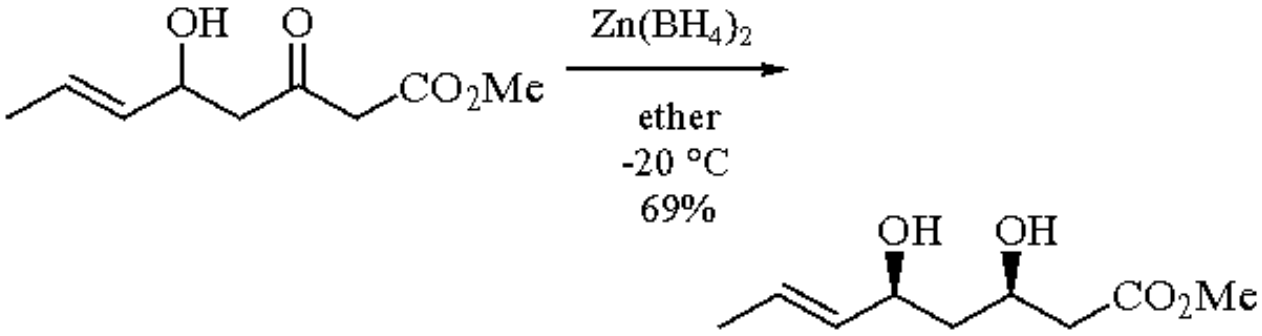

(22)

syn:*anti* = 91:9

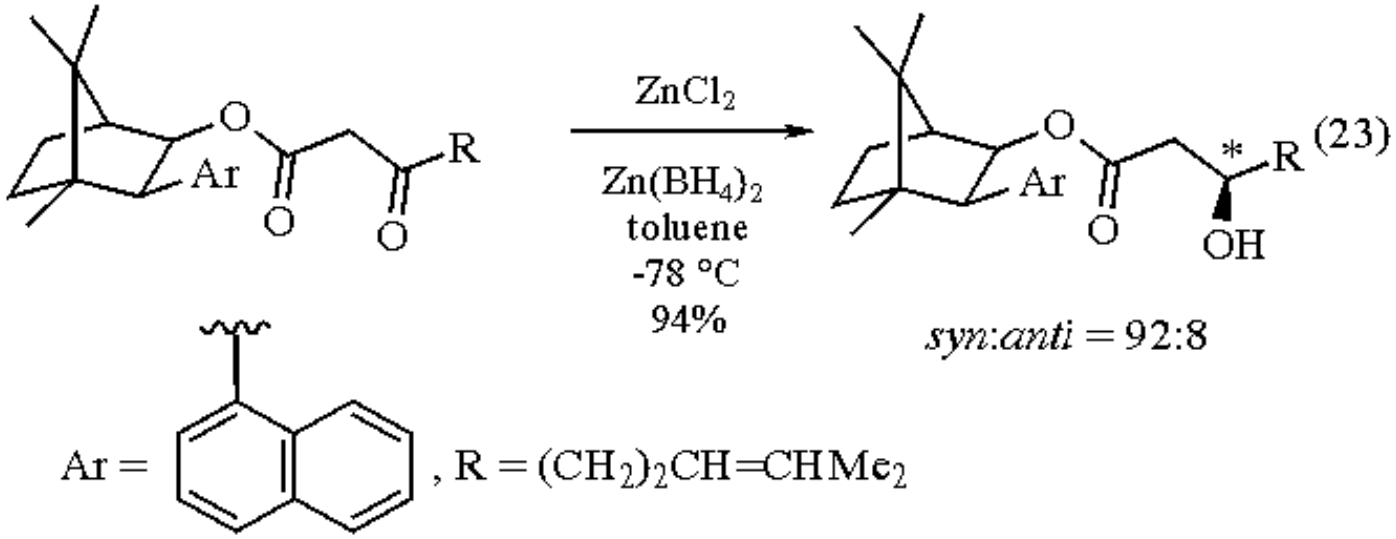

(23)

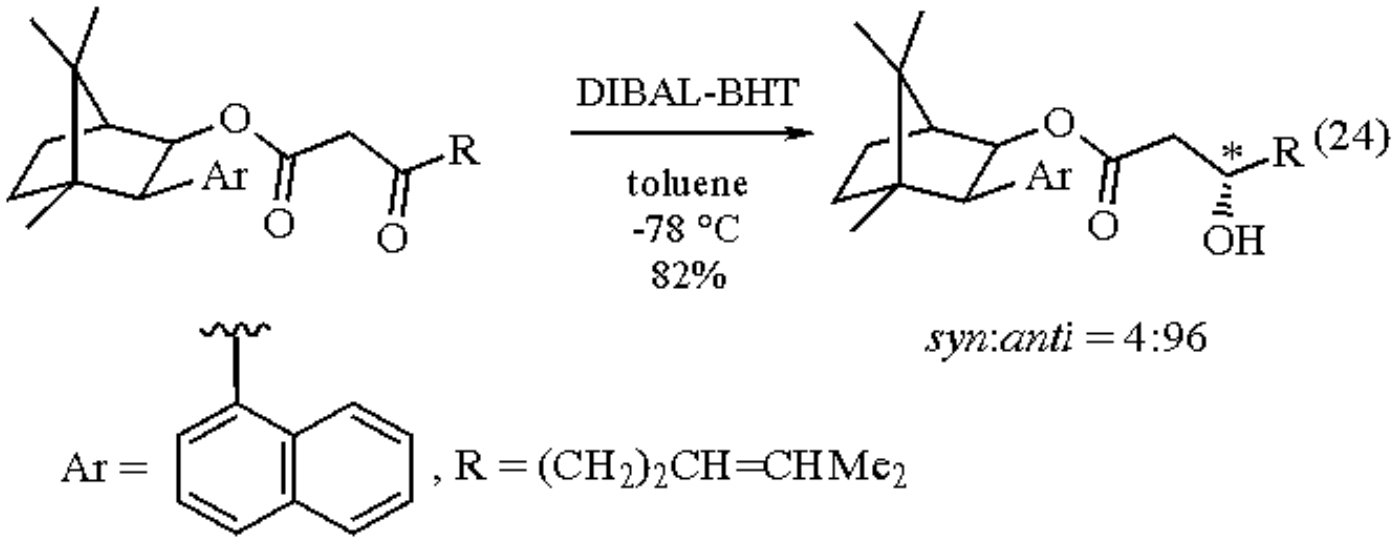

(24)

$Zn(BH_4)_2$ reduction of α-hydroxy ketones gives *anti* products predominantly over *syn* products. The selectivity is dependent on the substitution pattern of the α-hydroxy ketones. When R^1 is phenyl or R^2 is a sterically demanding group, *anti* selectivity is excellent (eq 25).[37] This is reasonably explained by considering a zinc-chelated five-membered transition state.[1,37] Other highly selective examples of $Zn(BH_4)_2$ reductions[38-42] of α-hydroxy ketones are shown in eqs 26 and 27.[38,41]

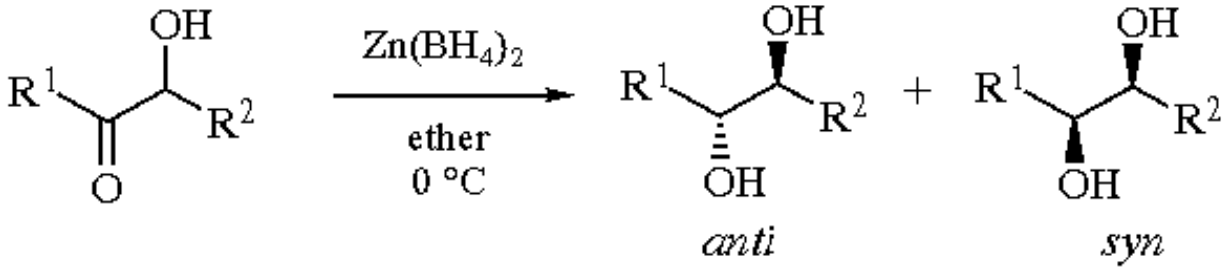

(25)

$R^1 = Ph, R^2 = Me$	98:2
$R^1 = Pr, R^2 = i\text{-}Pr$	96:4

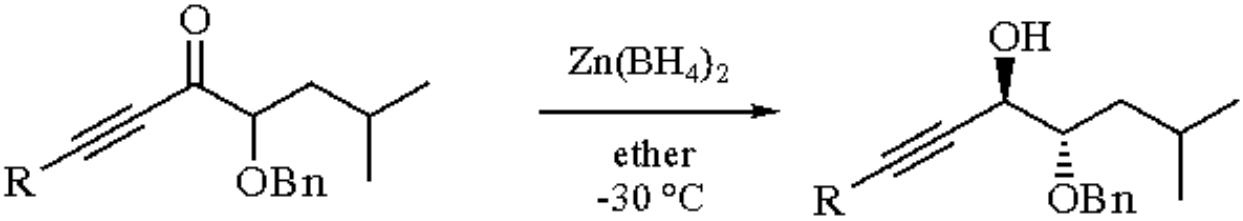

(26)

$R = (CH_2)_2OTHP$ *anti*:*syn* = 95:5

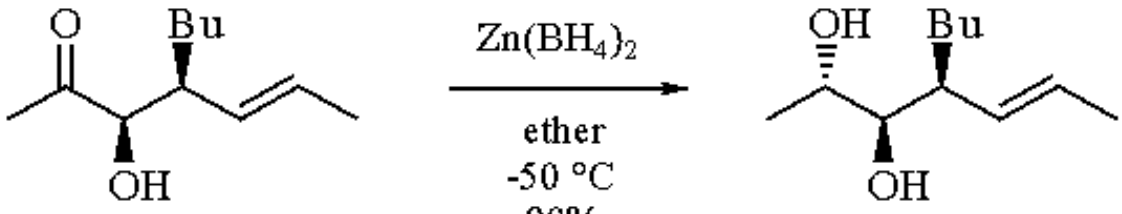

(27)

anti:*syn* = 98.5:1.5

In the cases where two functional groups are present on the α- or β-position of the keto group, reduction proceeds through the more stable transition state. When alkoxy and alkylthio functions are present on the α-position of the keto group, $Zn(BH_4)_2$ coordinates preferentially with the former (eq 28).[43] Reduction of a ketone having two alkoxy groups on the α- and β-positions produces the *anti*-2-alkoxy alcohol almost exclusively, showing that a five-membered transition state involving the α-alkoxy group is contributing far more than six-membered one (eq 29).[44] There is also a case where the three-dimensional structure of the ketone governs the selection of the transition state (eq 30).[45]

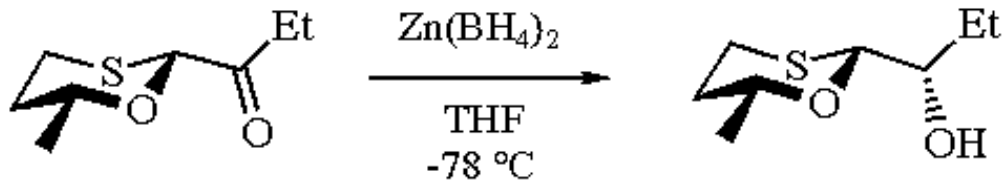

(28)

anti:*syn* = 99:1

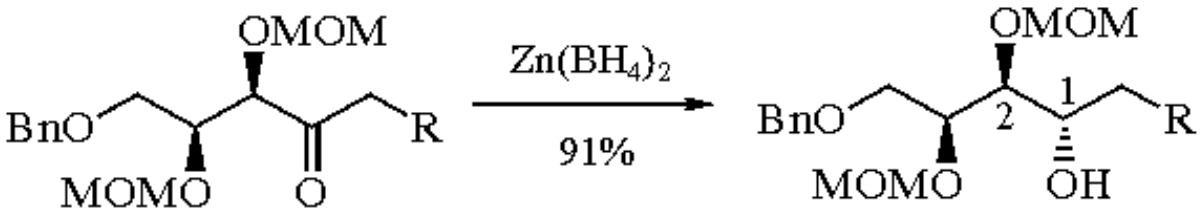

(29)

$R = p\text{-}MeOC_6H_4$ 1,2-*anti*:1,2-*syn* = >99:1

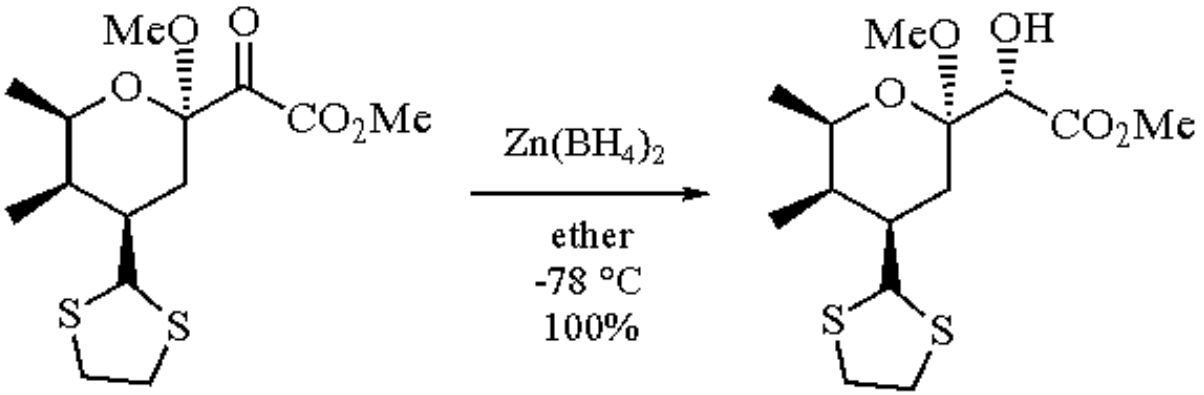

(30)

α-OH:β-OH = 17:1

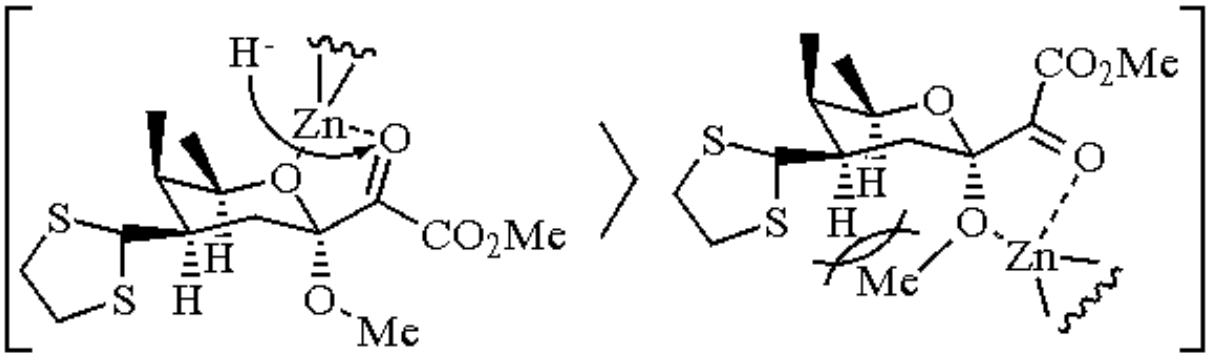

Optically active α-hydroxy imines are reduced with $Zn(BH_4)_2$ to give *anti*-hydroxy amines (eq 31).[46] α,β-Epoxy ketones produce *anti*-epoxy alcohols with high selectivity, irrespective of the substitution pattern of the epoxide (eq 32).[47,48] The corresponding aziridino ketones and imines are also reduced with $Zn(BH_4)_2$ to the *anti* isomer with high selectivity (eqs 33 and 34).[49]

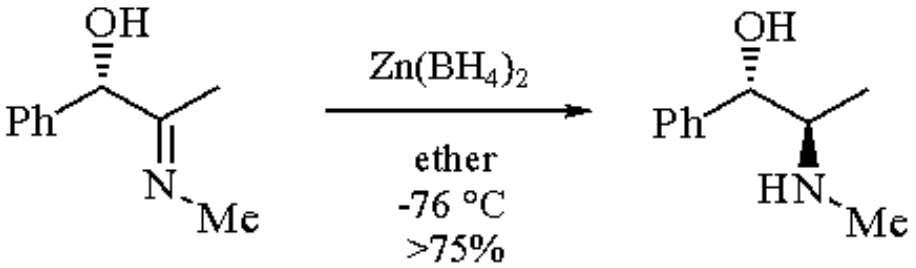

(31)

Ephedrine
anti:*syn* = 97:3

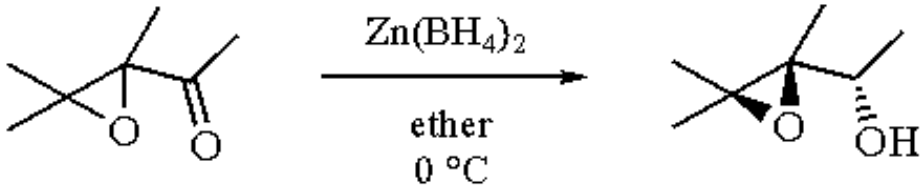

(32)

anti:*syn* = >99:1

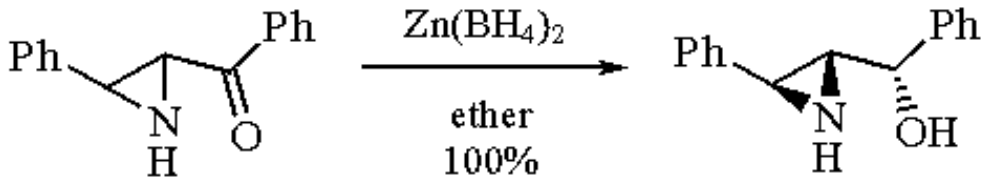

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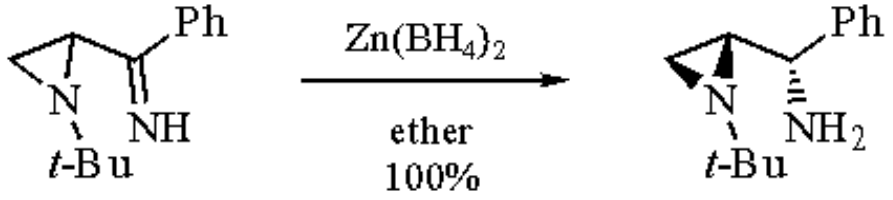

(34)

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Zinc Bromide[1]

$ZnBr_2$

[7699-45-8] · Br_2Zn · Zinc Bromide · (MW 225.19)

(used in the preparation of organozinc reagents via transmetalation;[1] a mild Lewis acid useful for promoting addition[2] and substitution reactions[3])

Physical Data: mp 394 °C; bp 697 °C (dec); *d* 4.201 g cm^{-3}.

Solubility: sol Et_2O, H_2O (1 g/25 mL), 90% EtOH (1 g/0.5 mL).

Form Supplied in: granular white powder; principal impurity is H_2O.

Analysis of Reagent Purity: melting point.

Purification: heat to 300 °C under vacuum (2×10^{-2} mmHg) for 1 h, then sublime.

Handling, Storage, and Precautions: very hygroscopic; store under anhydrous conditions. Irritant.

Organozinc Reagents.

The transmetalation of organomagnesium, organolithium, and organocopper reagents by anhydrous $ZnBr_2$ in ethereal solvents offers a convenient method of preparing organozinc bromides and diorganozinc reagents.[1a] Alternatively, anhydrous $ZnBr_2$ may be reduced by potassium metal to result in highly activated Zn^0, which is useful for the preparation of zinc reagents through oxidative addition to organic halides.[4] Alkyl, allylic, and propargylic zinc reagents derived by these methods have shown considerable value in their stereoselective and regioselective addition reactions with aldehydes, ketones, imines, and iminium salts.[1a,5] Zinc enolates used in the Reformatsky reaction may also be prepared through transmetalation using $ZnBr_2$.[1b] Organozinc species are especially useful in palladium- and nickel-catalyzed coupling reactions of sp^2 carbon centers. In this fashion, sp^2-sp^3 (eq 1)[6] and sp^2-sp^2 (eqs 2 and 3)[7,8] carbon-carbon bonds are formed selectively in high yields. The enantioselective cross coupling of secondary Grignard reagents with vinyl bromide is strongly affected by the presence of $ZnBr_2$, which accelerates the reaction and inverts its enantioselectivity (eq 4).[9]

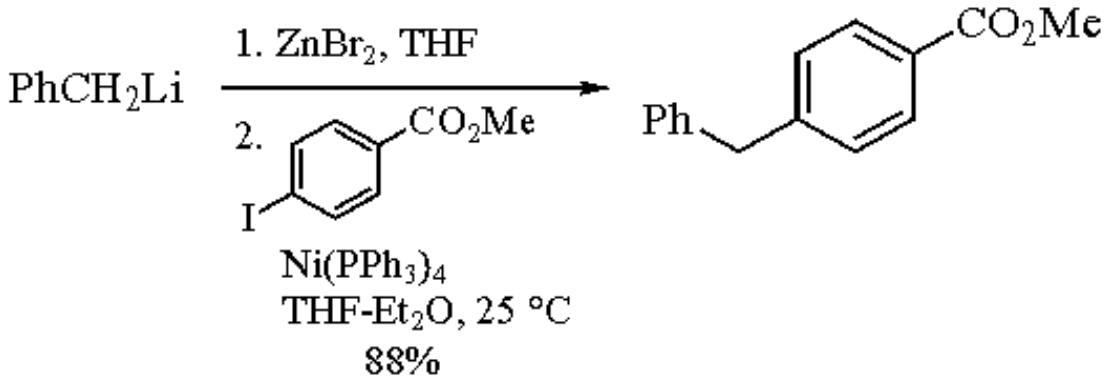

(1)

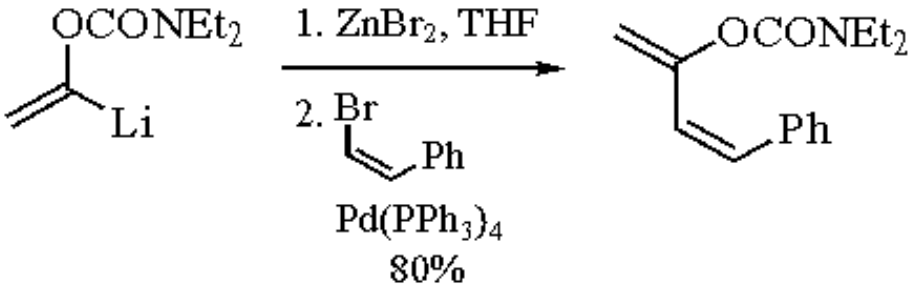

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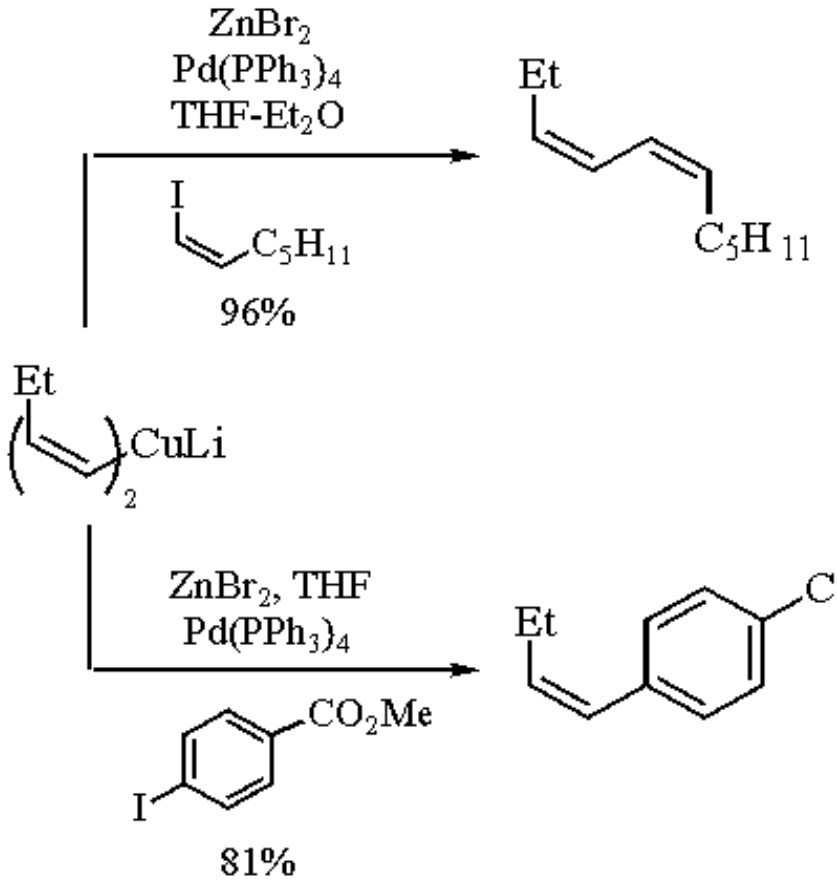

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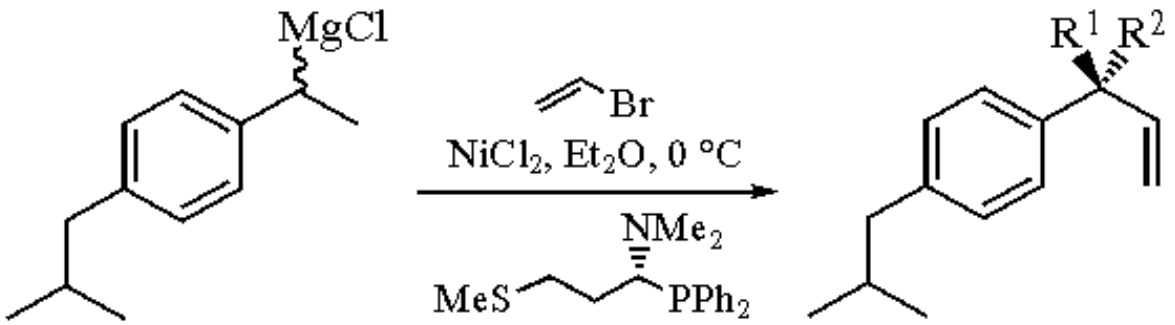

(4)

without $ZnBr_2$ $R^1 = Me, R^2 = H$; >95% (52% ee)
with $ZnBr_2$ $R^1 = H, R^2 = Me$; >95% (49% ee)

Organozinc intermediates formed via transmetalation using $ZnBr_2$ have been used to effect carbozincation of alkenes and alkynes through metallo-ene and metallo-Claisen reactions. Both intermolecular and intramolecular variants of these reactions have been described, often proceeding with high levels of stereoselectivity and affording organometallic products that may be used in subsequent transformations (eqs 5 and 6),[10] including alkenation (eq 6).[10b,c] Bimetallic zinc-zirconium reagents have also been developed that offer a method for the alkenation of carbonyl compounds (eq 7).[11]

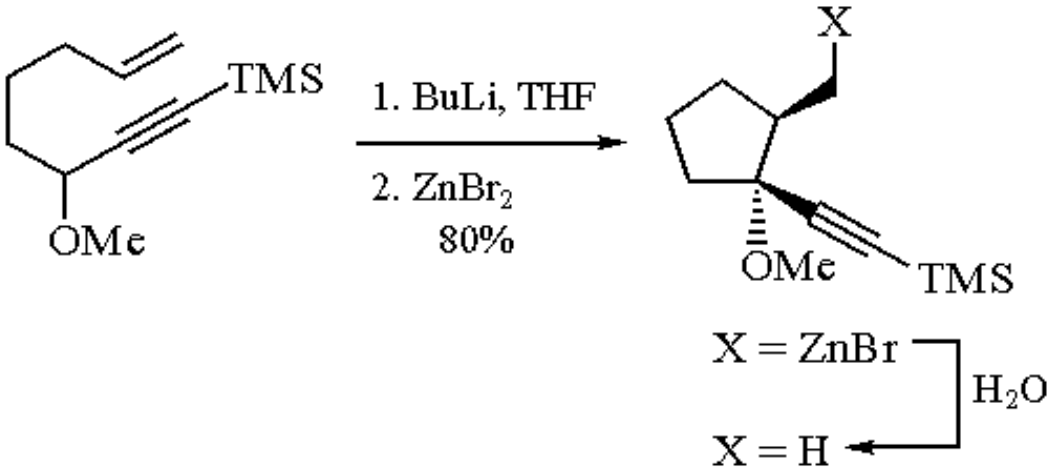
TMS
OMe
1. BuLi, THF
2. ZnBr2
80%
X
OMe
TMS
X = ZnBr
H2O
X = H

(5)

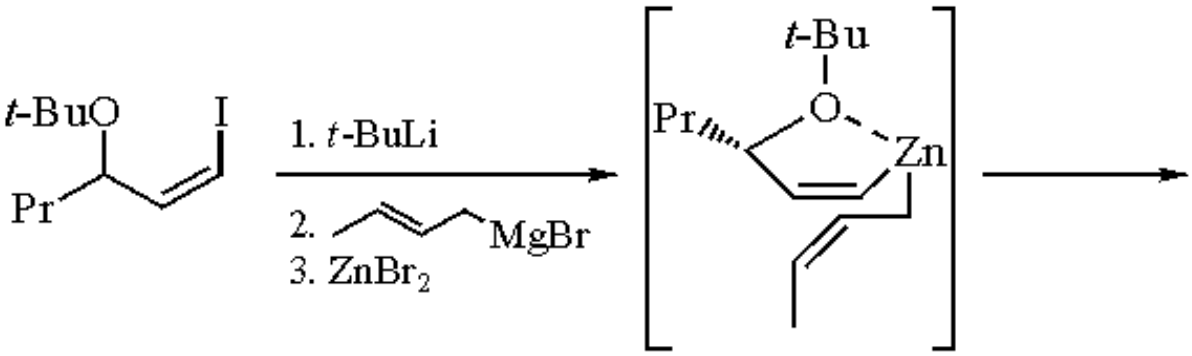
t-BuO
I
Pr
1. t-BuLi
2.
MgBr
3. ZnBr2
t-Bu
O
Pr
Zn

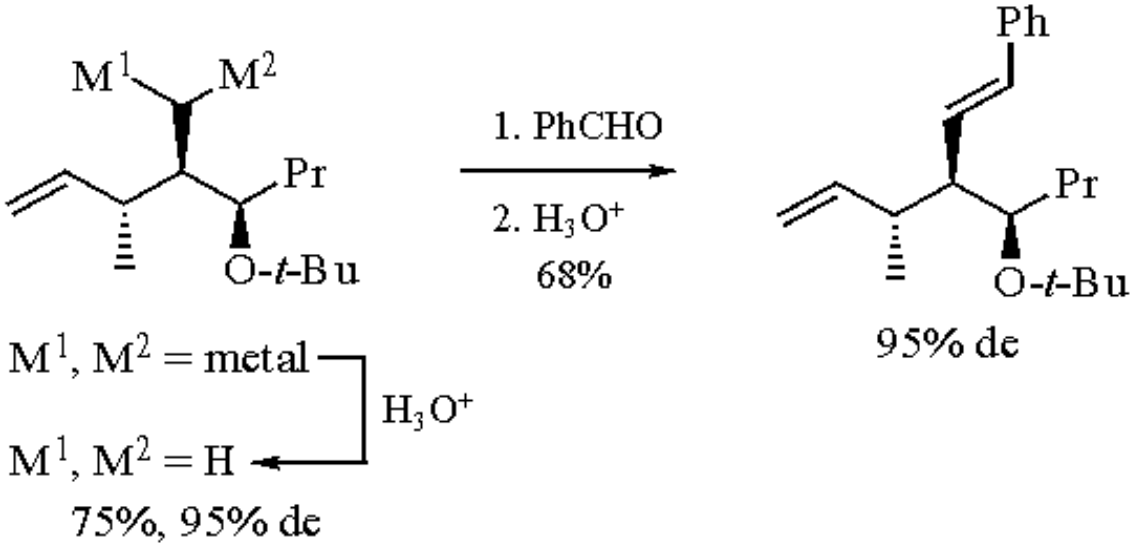
M1
M2
Pr
O-t-Bu
1. PhCHO
2. H3O+
68%
Ph
Pr
O-t-Bu
95% de
M1, M2 = metal
H3O+
M1, M2 = H
75%, 95% de

(6)

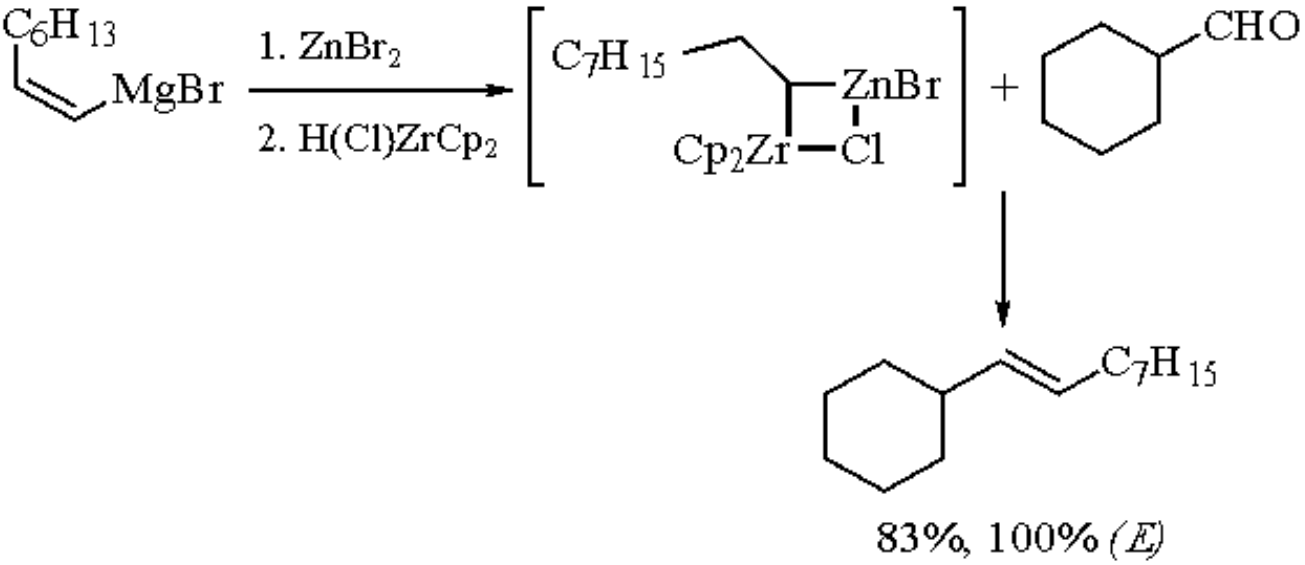
C6H13
MgBr
1. ZnBr2
2. H(Cl)ZrCp2
C7H15
ZnBr
Cp2Zr
Cl
CHO
C7H15
83%, 100% (E)

(7)

Concerted Ring-Forming Reactions.

The mild Lewis acid character of $ZnBr_2$ sometime imparts a catalytic effect on thermally allowed pericyclic reactions. The rate and stereoselectivity of cycloaddition reactions (eq 8),[12] including dipolar cycloadditions (eq 9),[13] are significantly improved by the presence of this zinc salt.

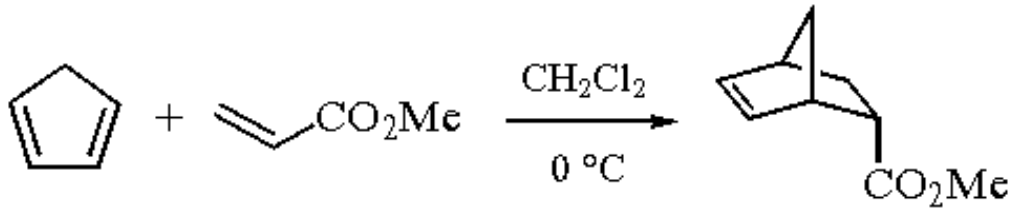

(8)

no catalyst, 5 h 70%, 78% *endo*
with $ZnBr_2$, 3 h 80%, 95% *endo*

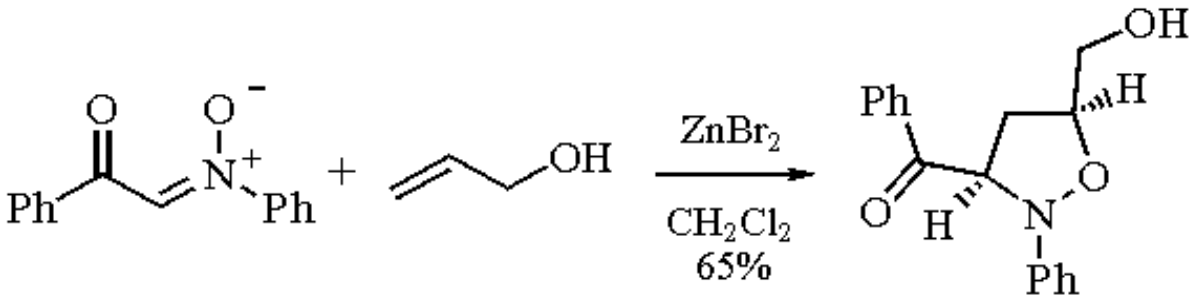

(9)

single isomer

Some intramolecular ene reactions benefit from $ZnBr_2$ catalysis to afford the cyclic products under milder conditions, in higher yields and selectivities (eqs 10 and 11).[14,15] Generally, the use of $ZnBr_2$ is preferred over ***Zinc Chloride*** or ***Zinc Iodide*** in this type of reaction.[15]

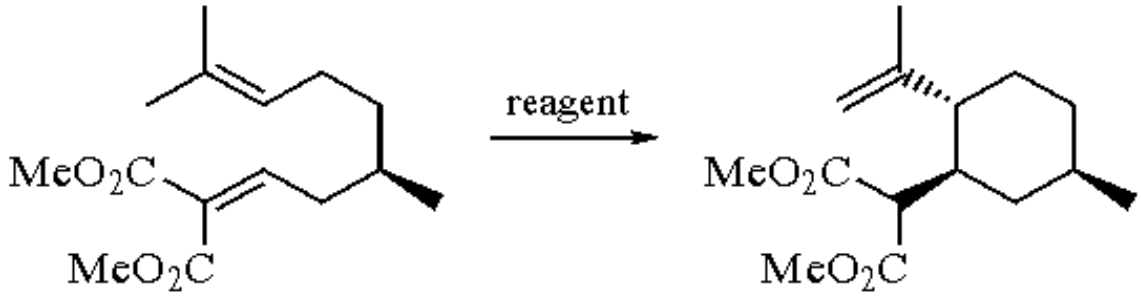

(10)

180 °C, *o*-dichlorobenzene 66% (83% de)
$ZnBr_2$, CH_2Cl_2, 25 °C 79% (95% de)

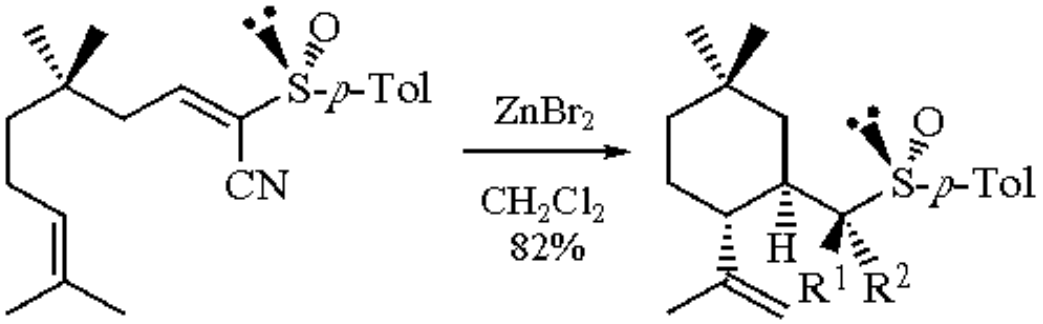

(11)

$(R^1 = CN, R^2 = H):(R^1 = H, R^2 = CN) = 88:12$

Activation of C=X Bonds.

Lewis acid activation of carbonyl compounds by $ZnBr_2$ promotes the addition of allylsilanes and silyl ketene acetals.[16] Addition to imines has also been reported.[17] In general, other Lewis acids have been found to be more useful, though in some instances $ZnBr_2$ has proven to be advantageous (eq 12).[2]

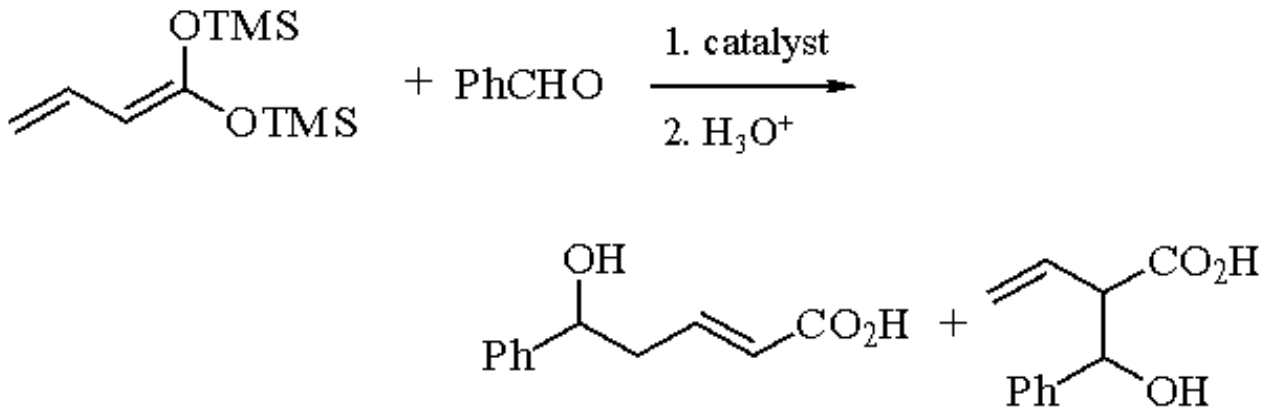

(12)

$ZnBr_2$, THF, 20 °C, 6 h	100:0
CsF, CH_2Cl_2. 20 °C, 14 h	5:95

Activation of C-X Bonds.

Even more important than carbonyl activation, $ZnBr_2$ promotes substitution reactions with suitably active organic halides with a variety of nucleophiles. Alkylation of silyl enol ethers and silyl ketene acetals using benzyl and allyl halides proceeds smoothly (eq 13).[3] Especially useful electrophiles are α-thio halides which afford products that may be desulfurized or oxidatively eliminated to result in α,β-unsaturated ketones, esters, and lactones (eq 14).[18] Other electrophiles that have been used with these alkenic nucleophiles include ***Chloromethyl Methyl Ether***, $HC(OMe)_3$, and ***Acetyl Chloride***.[3,19]

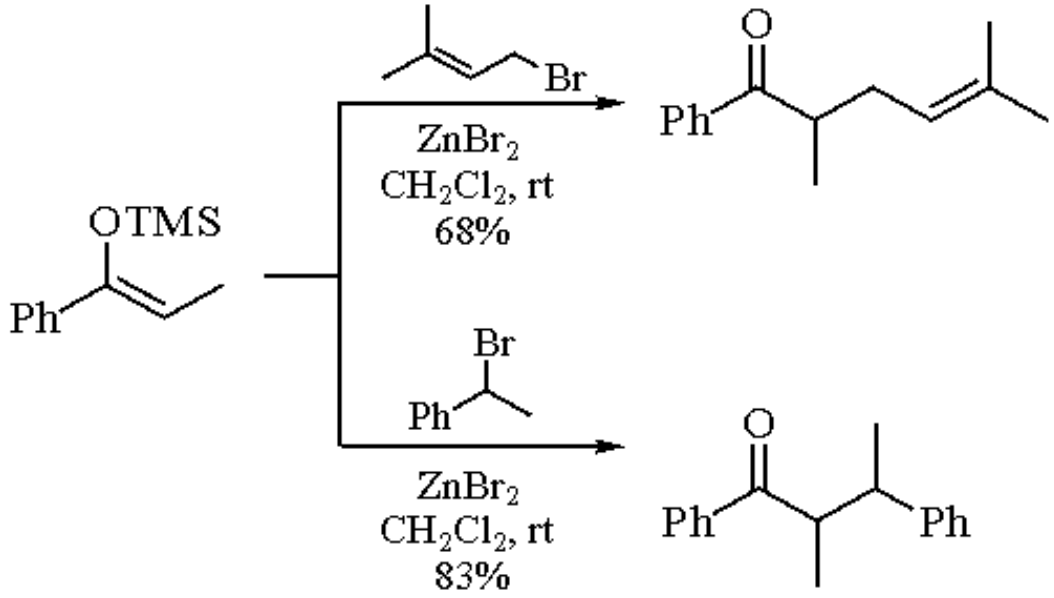

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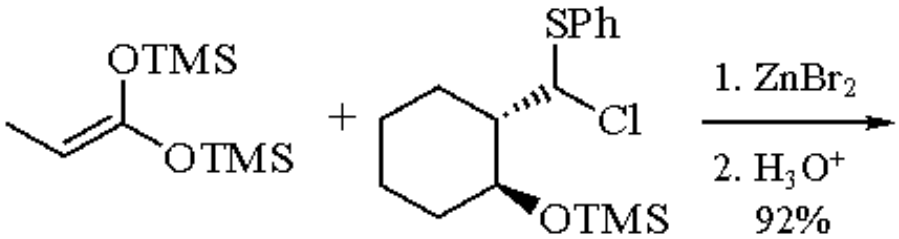

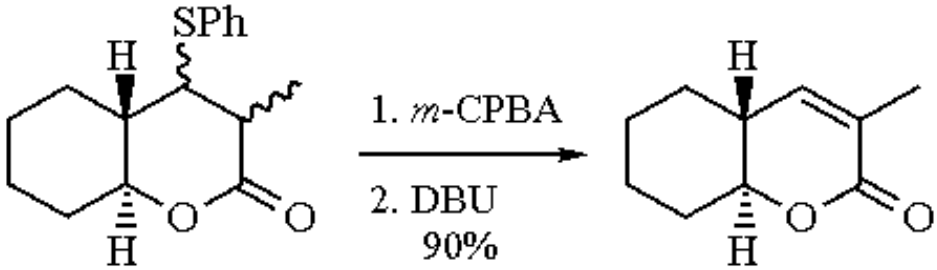

(14)

Enol ethers and allylic silanes and stannanes will engage cyclic α-seleno sulfoxides,[20] o-acetoxy lactams,[21] and acyl glycosides (eq 15)[22] in the presence of $ZnBr_2$ catalysis. Along these lines, it has been found that $ZnBr_2$ is superior to ***Boron Trifluoride Etherate*** in promoting glycoside bond formation using trichloroimidate-activated glycosides (eq 16).[23] Imidazole carbamates are also effective activating groups for $ZnBr_2$-mediated glycosylation (eq 17).[24]

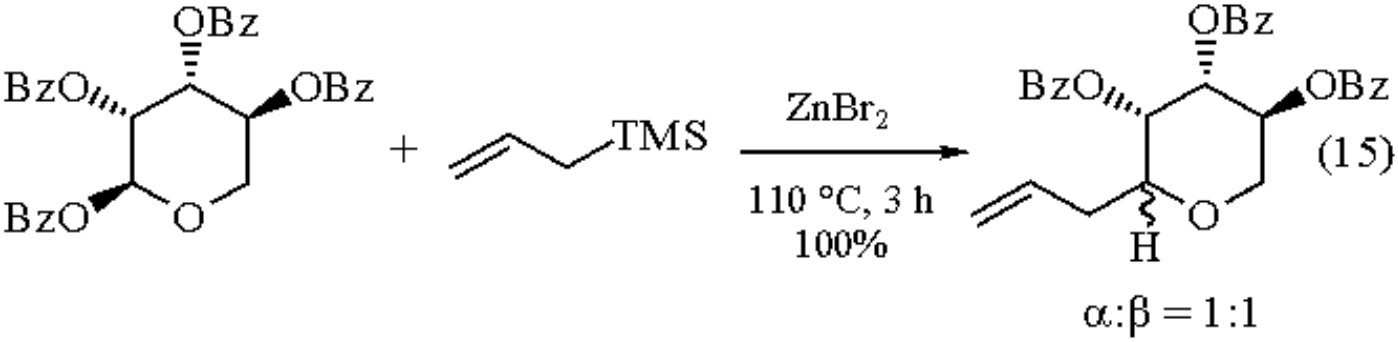

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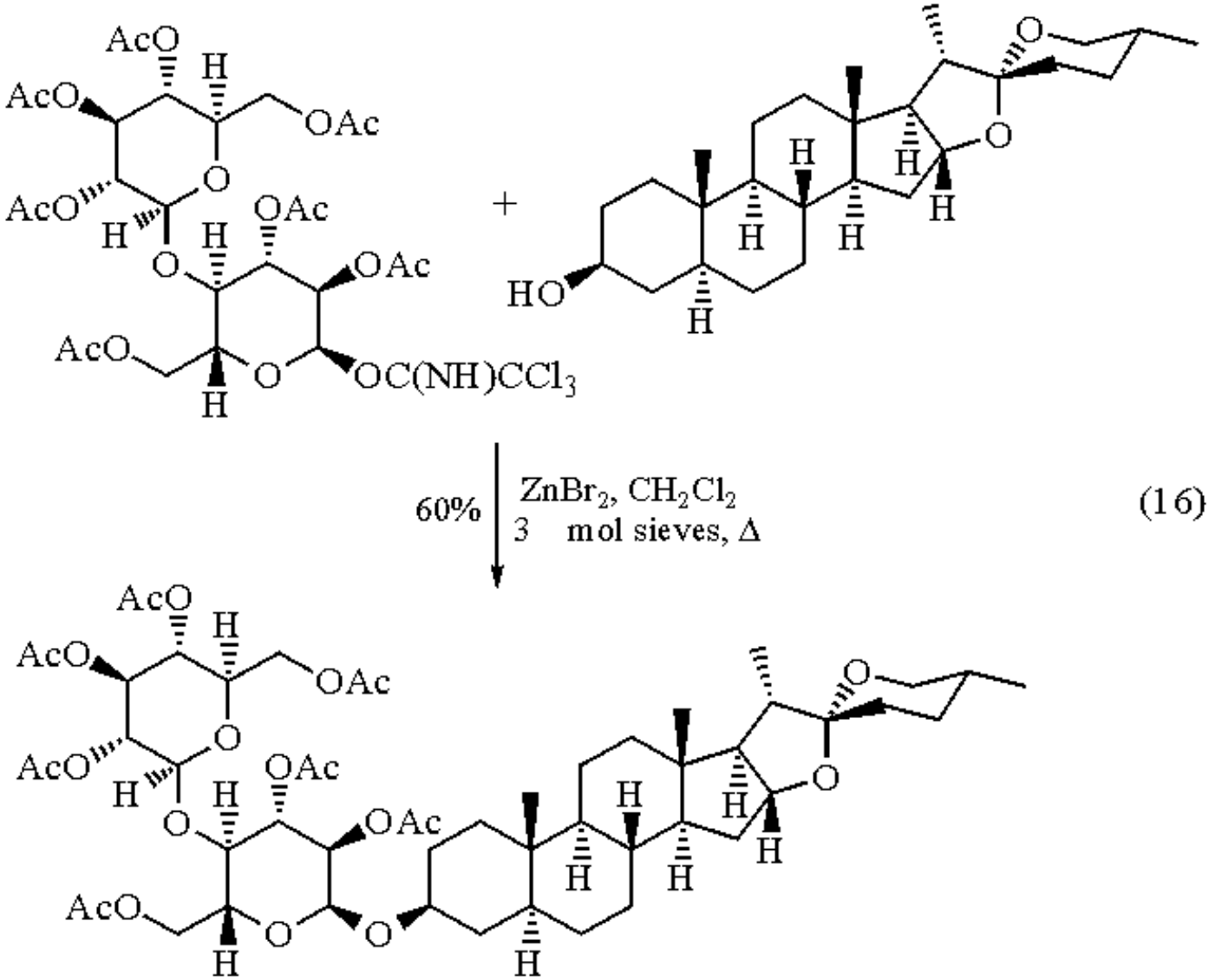

(16)

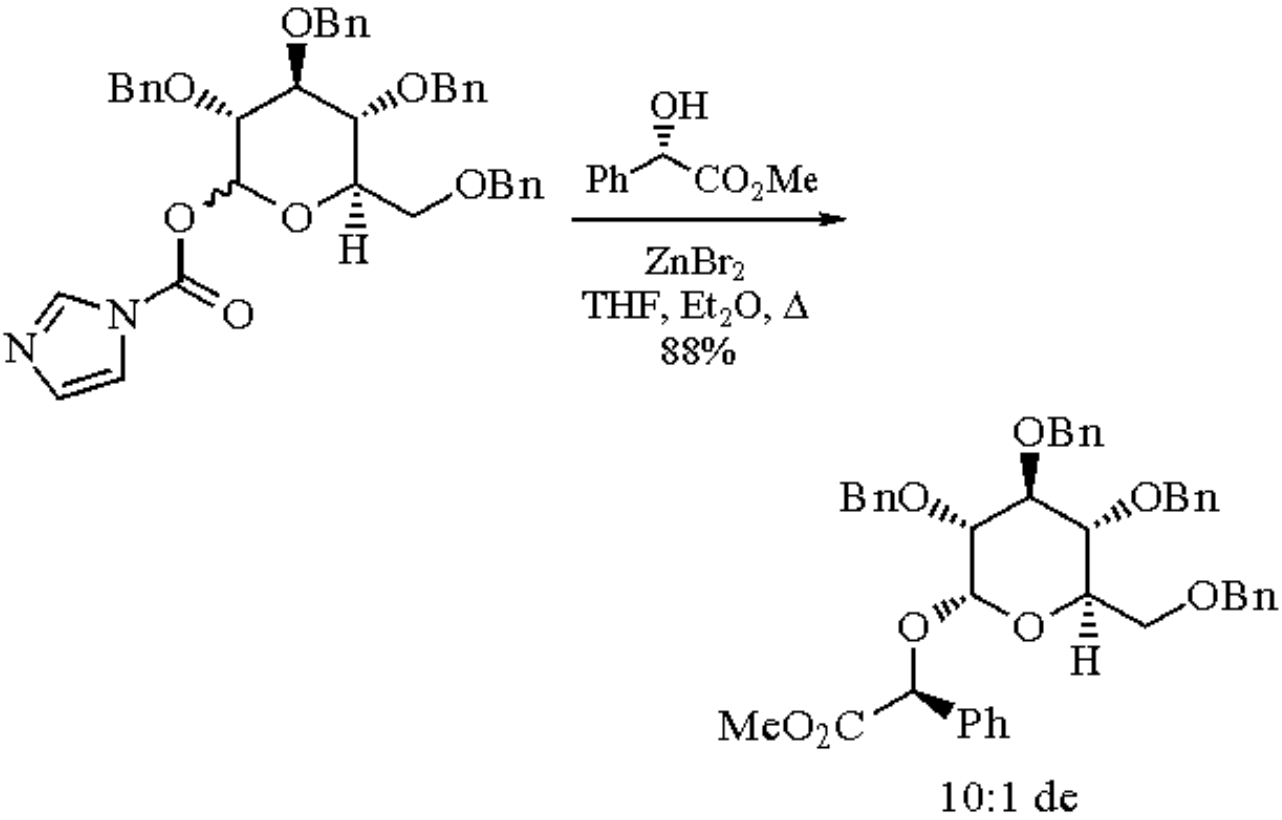

(17)

Cyclic acetals also undergo highly selective, Lewis acid-dependent ring opening substitution with ***Cyanotrimethylsilane*** (eq 18).[25]

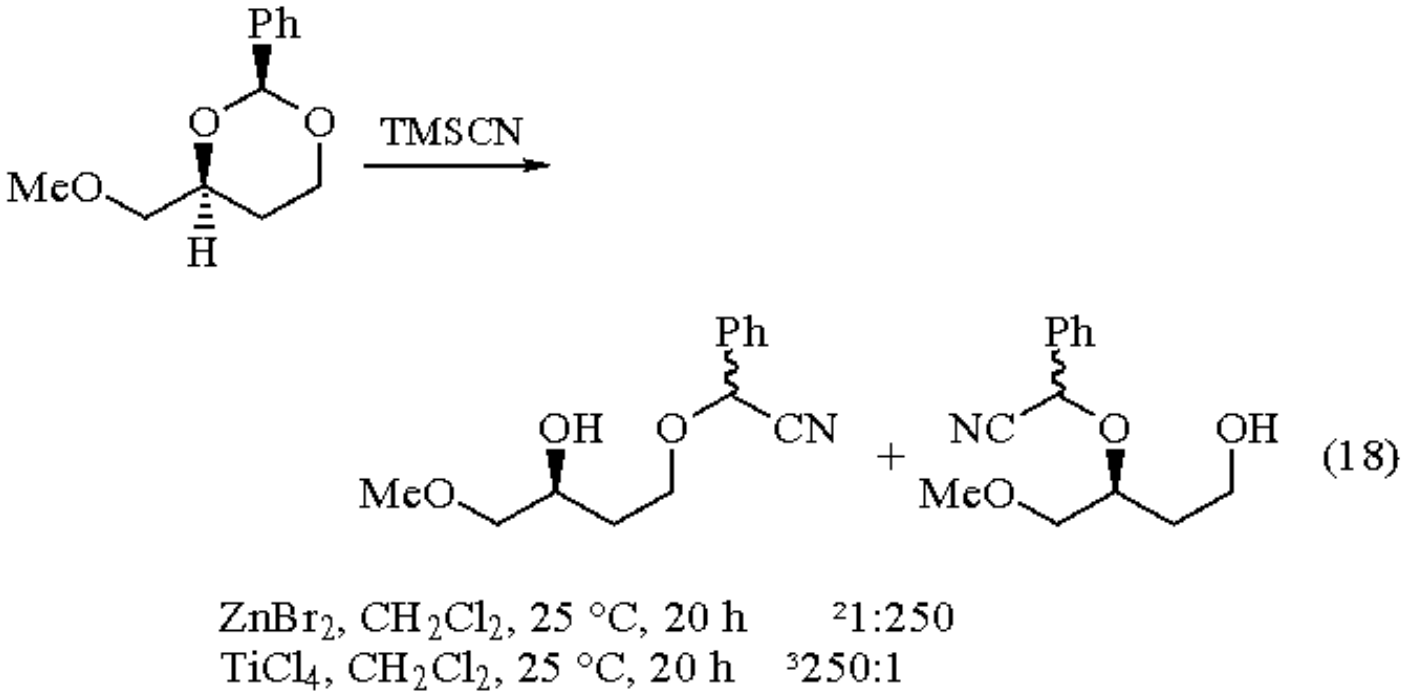

Reduction.

Complexation with $ZnBr_2$ has been shown to markedly improve stereoselectivity in the reduction of certain heteroatom-substituted ketones (eqs 19 and 20).[26,27] Furthermore, the *anti* selectivity observed in $BF_3.OEt_2$-mediated intramolecular hydrosilylation of ketones is reversed when $ZnBr_2$ is used instead (eq 21).[28]

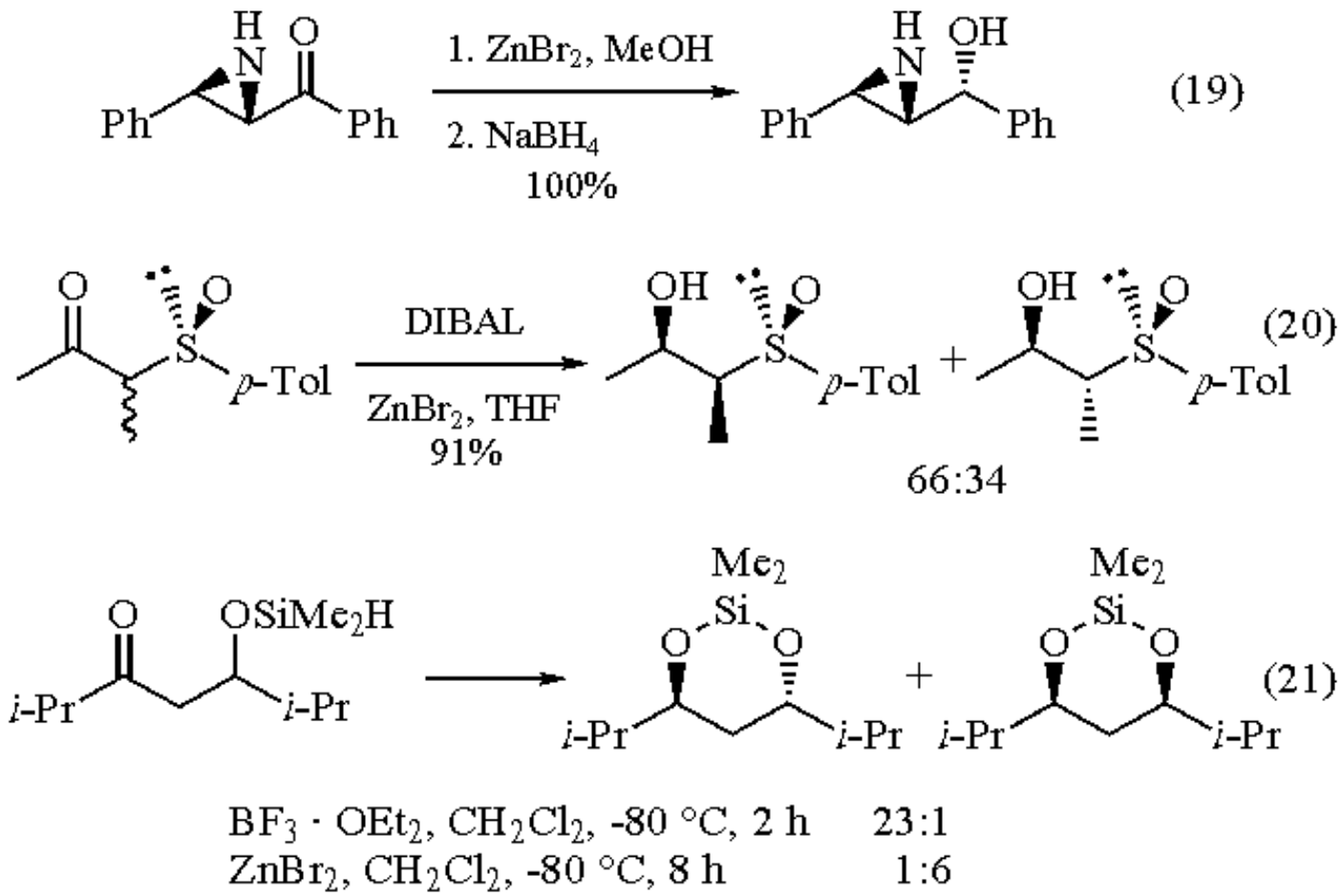

Deprotection.

$ZnBr_2$ is a very mild reagent for several deprotection protocols, including the detritylation of nucleotides[29] and deoxynucleotides,[30] *N*-deacylation of *N*,*O*-peracylated nucleotides,[31] and the selective removal of Boc groups from secondary amines in the presence of Boc-protected primary amines.[32] Perhaps the most widespread use of $ZnBr_2$ for deprotection is in the mild removal of MEM ethers to afford free alcohols (eq 22).[33]

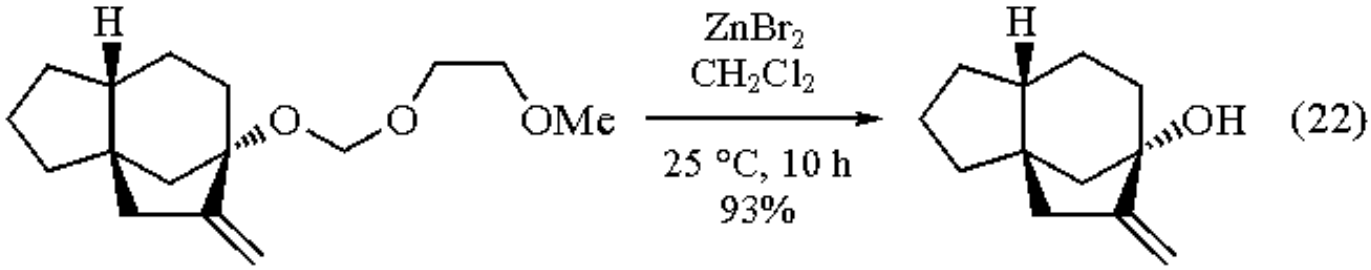

Miscellaneous.

An important method for the synthesis of stereodefined trisubstituted double bonds involves the treatment of cyclopropyl bromides with $ZnBr_2$. The (*E*) isomer is obtained almost exclusively by this method (eq 23).[34]

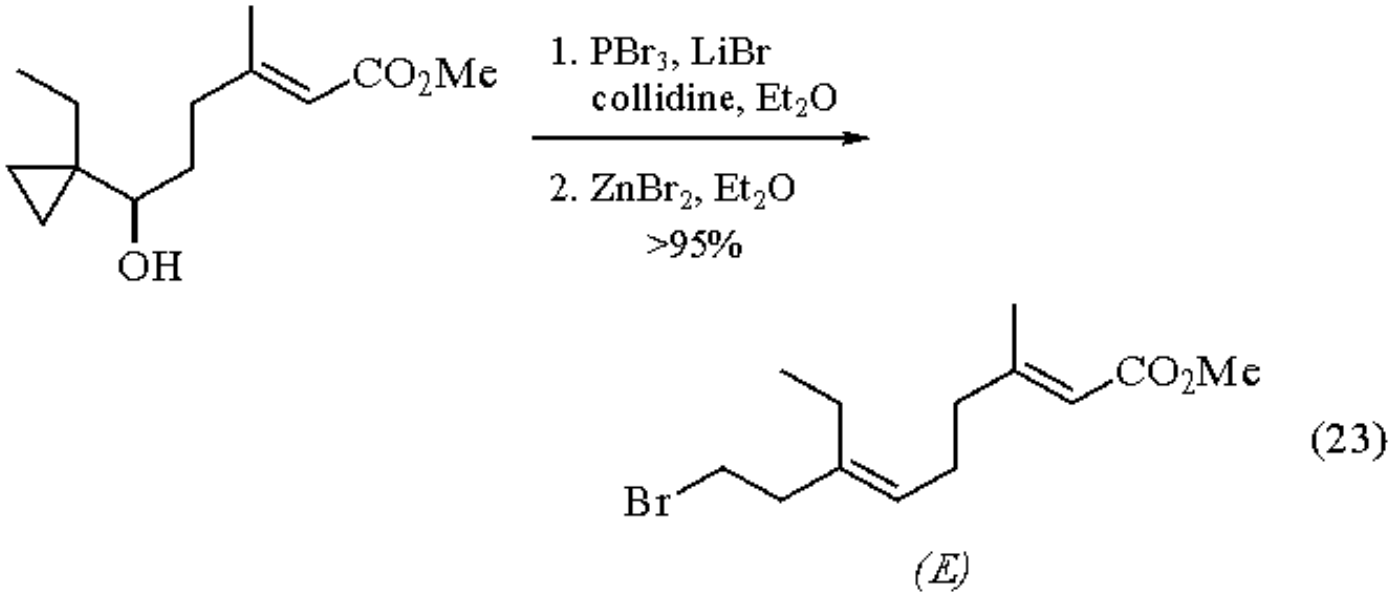

The rearrangement of a variety of terpene oxides has been examined (eq 24).[35] While $ZnBr_2$ is generally a satisfactory catalyst for this purpose, other Lewis acids, including $ZnCl_2$[36] and ***Magnesium Bromide***,[37] are advantageous in some instances.

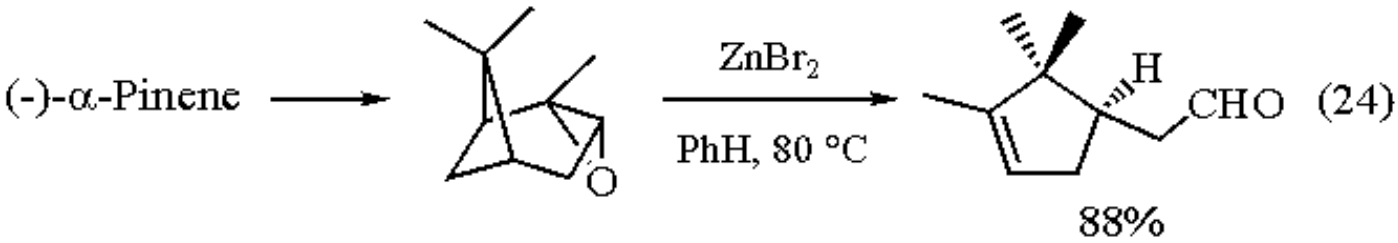

In the presence of $ZnBr_2$/48% ***Hydrobromic Acid***, suitably functionalized cyclopropanes undergo ring expansion to afford cyclobutane (eq 25)[38] and α-methylene butyrolactone products (eq 26).[39] One-carbon ring expansion has been reported when certain trimethylsilyl dimethyl acetals are exposed to $ZnBr_2$ with warming (eq 27).[40]

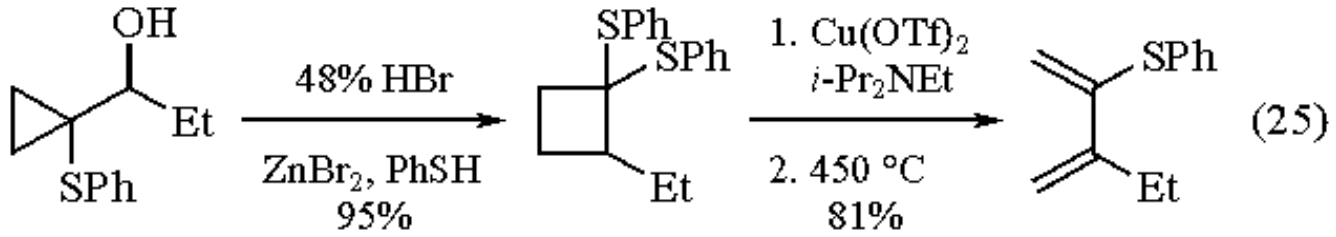

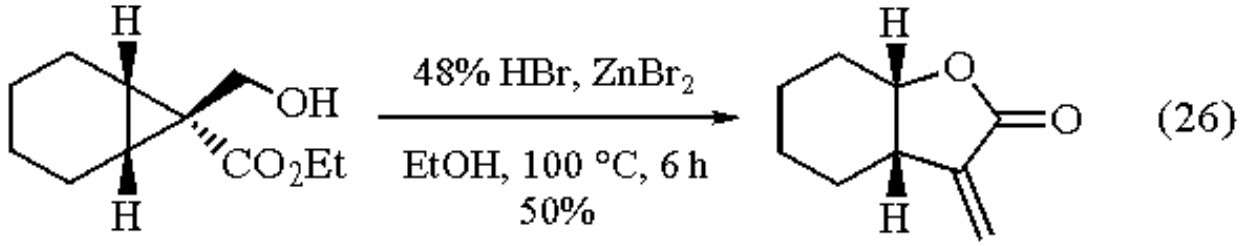

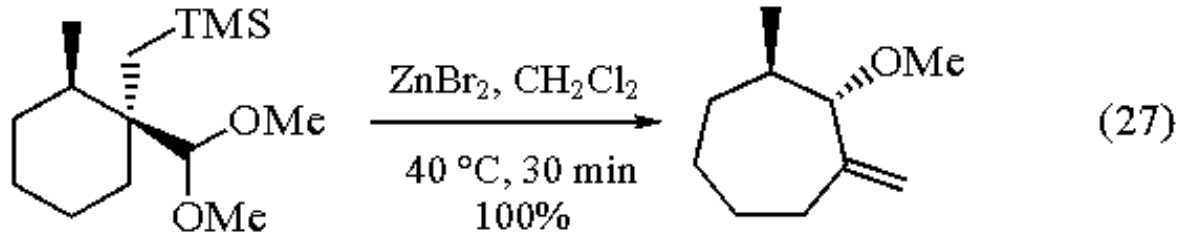

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Zinc Carbonate

$ZnCO_3$

[3486-35-9] · CO_3Zn · Zinc Carbonate · (MW 125.40)

(mild inorganic base, capable of chelation;[1] catalyst for heterocyclization[2,3] and Claisen rearrangement[4,5])

Physical Data: dec with evolution of CO_2 at 300 °C; *d* 4.42-4.45 g cm^{-3}.

Solubility: insol H_2O, organic solvents.

Form Supplied in: white crystalline powder; commercially available.

Preparative Method: addition of 0.1M Na_2CO_3 to 0.1M $ZnSO_4$ gives a precipitate of zinc carbonate, which is filtered off, and dried in vacuo.[1]

Handling, Storage, and Precautions: reputed to be nontoxic.

Coumarin Ring Synthesis.[1]

The specific chelating properties of zinc (or magnesium) carbonate were required in the formation of coumarin (**2**) from phenol (**1**) (eq 1). The nonchelating sodium or potassium carbonates do not effect this transformation. Although yields are only moderate, (**1**) is exceptionally sensitive to acidic reagents[1], rendering some other procedures for coumarin synthesis under acidic conditions[6] impractical in this case. Moreover, this cyclization step to the aflatoxin system had proved difficult in a previous synthesis.[7]

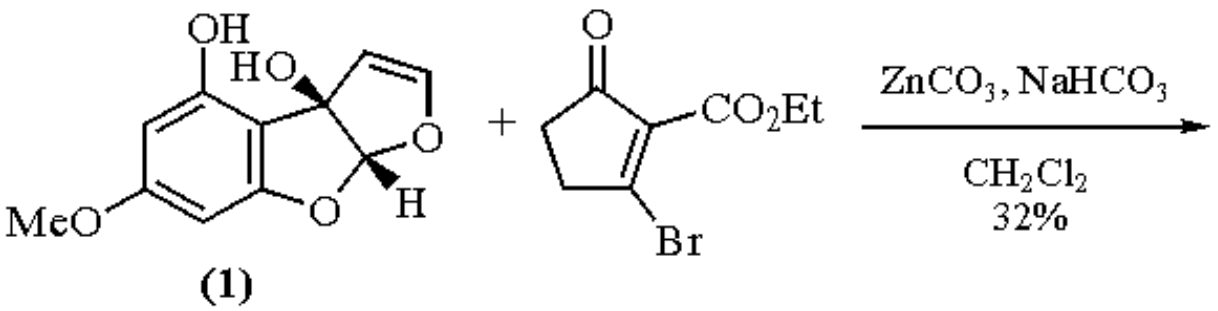

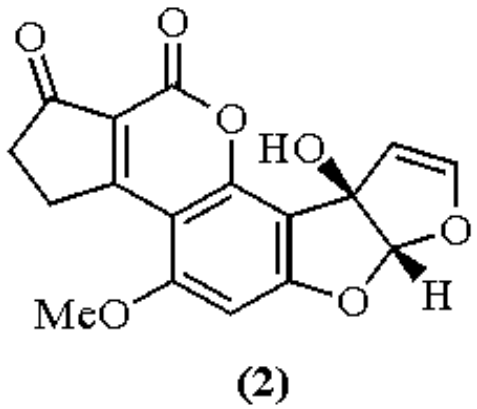

(1)

Heterocyclization.

Phenolic[2] and enolic[3] alkynes are cyclized to furans or pyrans (eqs 2-4) with, in some cases, very small catalytic quantities of $ZnCO_3$.

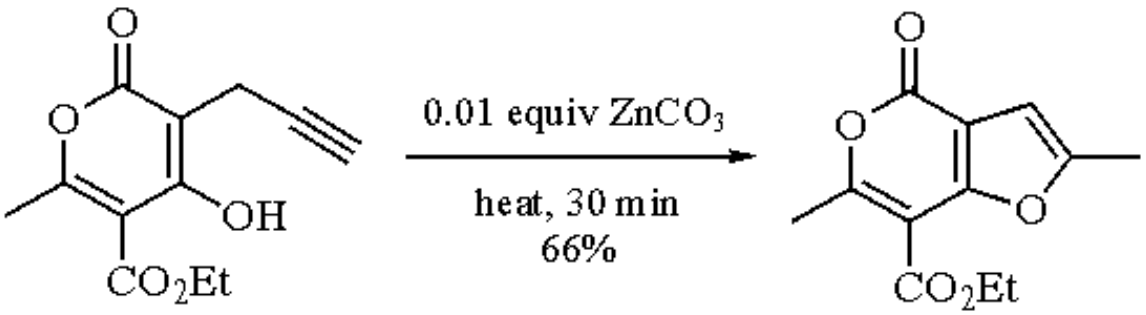

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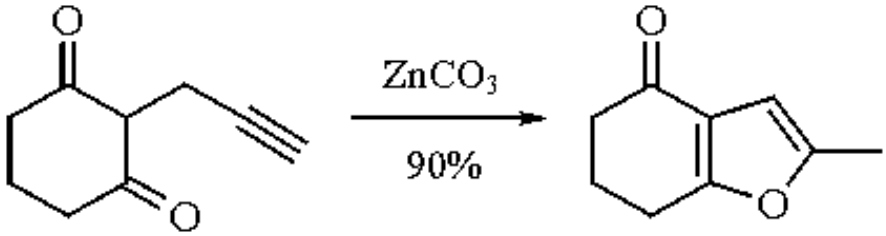

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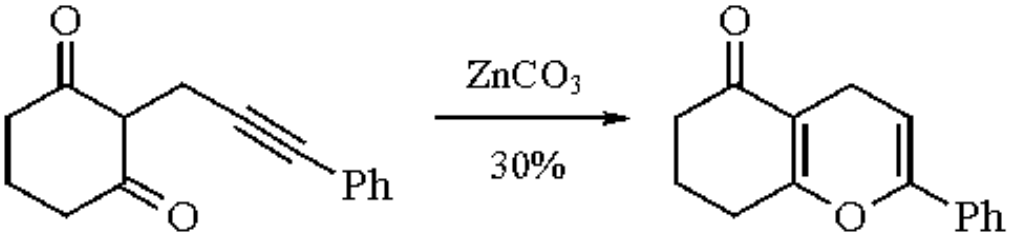

(4)

Claisen Rearrangements.

Various dienals[4] and dienones[5] can be prepared by Claisen rearrangement of enol sulfoxides (**3**), followed by PhSOH elimination (eq 5). The rearrangement occurs on distillation from small amounts of $ZnCO_3$. These fairly vigorous conditions, however, suggest that alternative catalysts[8] would often be preferred with less robust molecules.

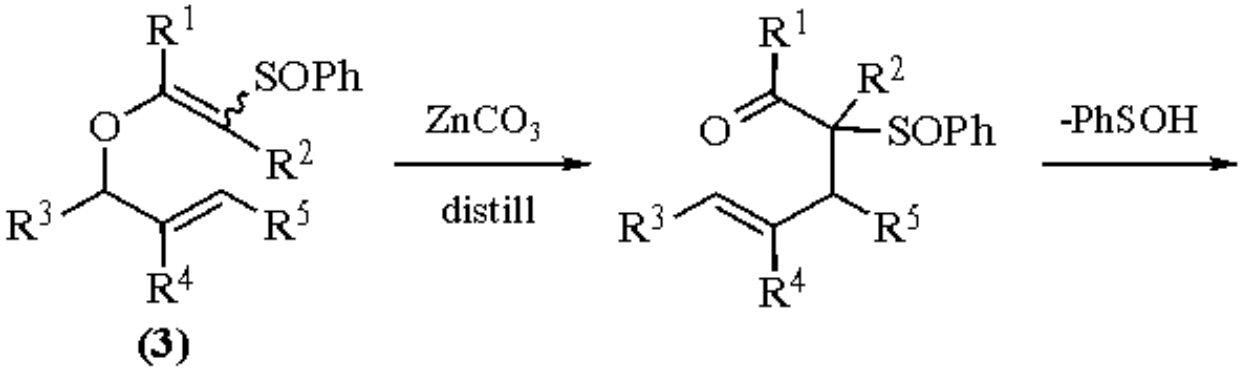

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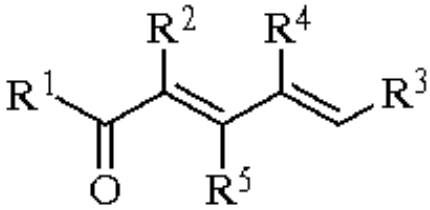

(5)

R^1-R^5 = alkyl, 58-85%

Zinc Carboxylate Salts.[9]

$ZnCO_3$ reacts with carboxylic acids to form the zinc salts, which can be used to effect solvolysis of tertiary halides (see ***Zinc Oxide***).

---

1. Büchi, G.; Weinreb, S. M. *JACS* **1971**, *93*, 746.
2. (a) Schulte, K. E.; Reisch, J.; Kauder, K. H. *AP* **1962**, *295*, 801 (*CA* **1963**, *58*, 11 337). (b) Schulte, K. E.; Reisch, J.; Mock, A.; Kauder, K. H. *AP* **1963**, *296*, 235 (*CA* **1963**, *59*, 6398).
3. Schulte, K. E.; Reisch, J.; Mock, A. *AP* **1962**, *295*, 645 (*CA* **1963**, *59*, 1575).
4. Cookson, R. C.; Gopalan, R. *CC* **1978**, 924.
5. Cookson, R. C.; Gopalan, R. *CC* **1978**, 608.
6. (a) Sethna, S.; Phadke, R. *OR* **1953**, *7*, 1. (b) Darbarwar, M.; Sundaramurthy, V. *S* **1982**, 337.
7. Büchi, G.; Foulkes, D. M.; Kurono, M.; Mitchell, G. F.; Schneider, R. S. *JACS* **1967**, *89*, 6745.
8. (a) Lutz, R. P. *CRV* **1984**, *84*, 205. (b) Overman, L. E. *AG(E)* **1984**, *23*, 579.
9. (a) Ravindranath, B.; Srinivas, P. *T* **1984**, *40*, 1623. (b) Anandaraman, S.; Gurudutt, K. N.; Natarajan, C. P.; Ravindranath, B. *TL* **1980**, *21*, 2189.

Peter Ham

SmithKline Beecham Pharmaceuticals, Harlow, UK

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Zinc Chloride[1]

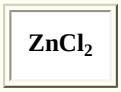

[7646-85-7] · Cl_2Zn · Zinc Chloride · (MW 136.29)

(used in the preparation of organozinc reagents via transmetalation;[1] a mild Lewis acid useful for promoting cycloaddition,[2] substitution,[3] and addition reactions,[4] including electrophilic aromatic additions;[5] has found use in selective reductions[6])

Physical Data: mp 293 °C; bp 732 °C; *d* 2.907 g cm^{-3}.

Solubility: sol H_2O (432 g/100 g at 25 °C), EtOH (1 g/1.3 mL), glycerol (1 g/2 mL).

Form Supplied in: white, odorless, very deliquescent granules; principal impurities are H_2O and zinc oxychloride.

Analysis of Reagent Purity: melting point.

Purification: reflux (50 g) in dioxane (400 mL) in the presence of Zn^0 dust, then filter hot and allow to cool to precipitate purified $ZnCl_2$. Also, anhydrous material may be sublimed under a stream of dry HCl, followed by heating to 400 °C in a stream of dry N_2.

Handling, Storage, and Precautions: very hygroscopic; store under anhydrous conditions; moderately irritating to skin and mucous membranes.

Organozinc Reagents.

The transmetalation of organomagnesium, organolithium, and organocopper reagents is an important and versatile method of preparing useful zinc reagents.[1a] Alternatively, $ZnCl_2$ may be employed for direct insertion of Zn^0 into carbon-halogen bonds using Mg^0/ultrasound[7] or prior reduction with K^0.[8] The addition of the resulting allylic and propargylic or allenic zinc reagents to carbonyl compounds, imines, and iminium salts represents an important method of selective carbon-carbon bond formation.[9,11] These reactions are generally guided by chelation and the Zimmerman-Traxler transition state[10] to control the relative stereochemistry about the new carbon-carbon bond (eq 1),[12] as well as with respect to preexisting stereocenters (eq 2).[13] Anions derived from propargylic deprotonation add to carbonyl compounds with a high degree of regiochemical integrity in the presence of $ZnCl_2$, i.e. allenic organozinc intermediates cleanly afford the propargylic product (eq 3).[11b]

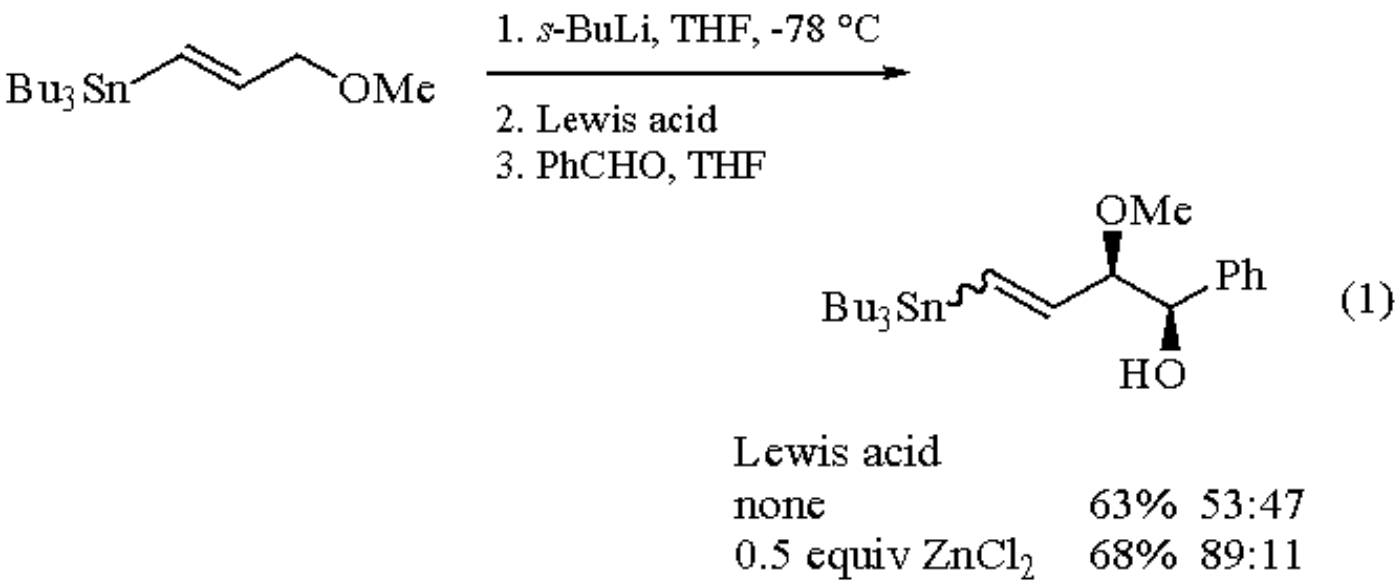

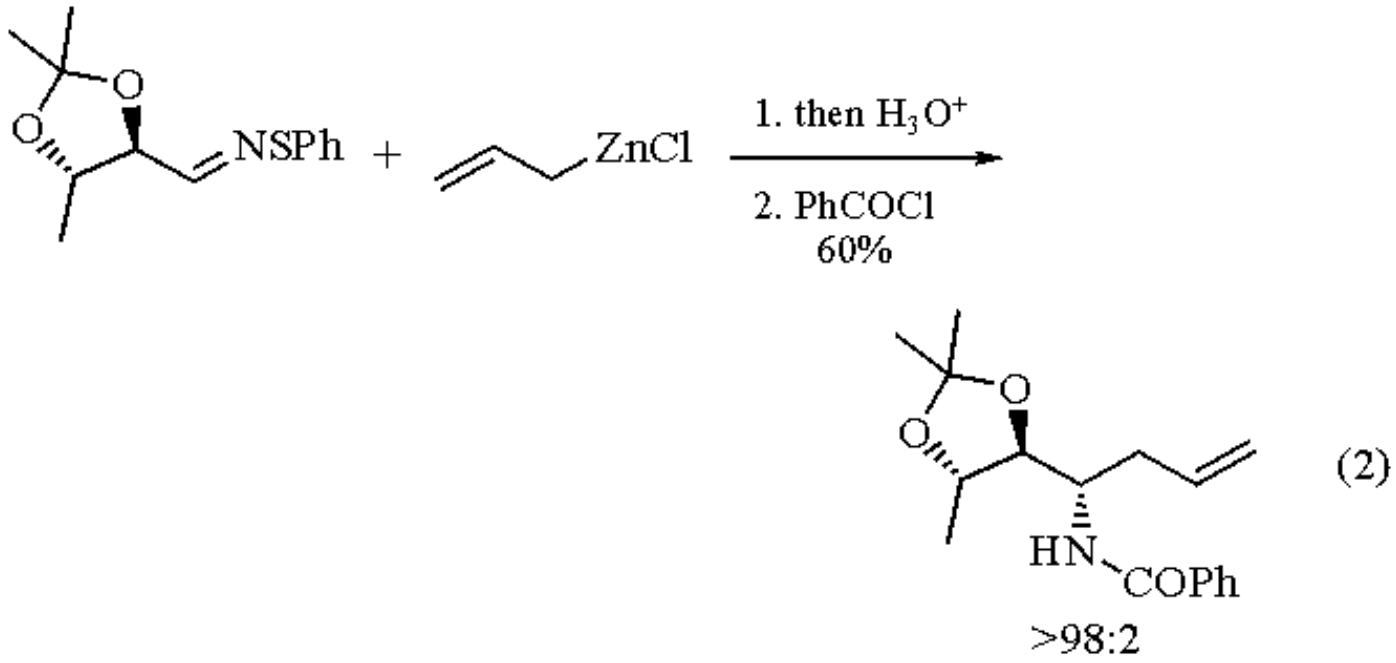

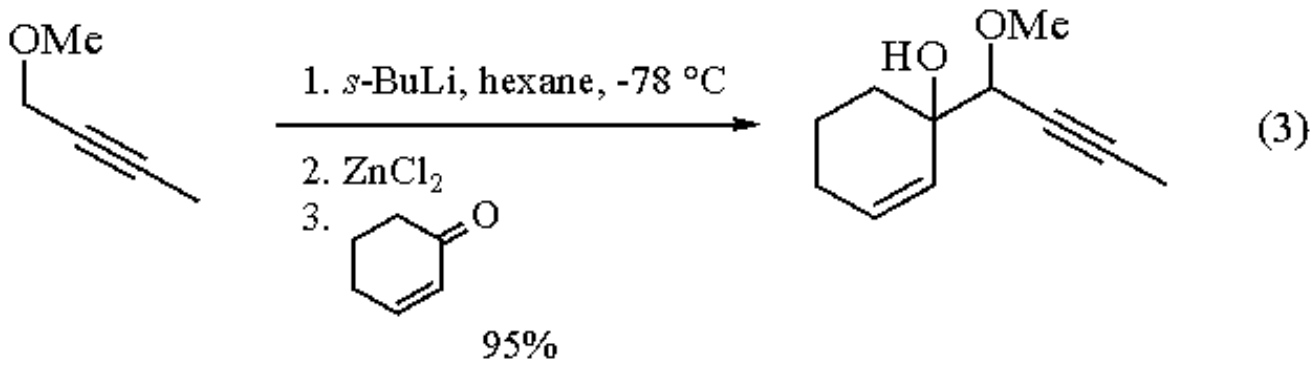

Alkylzinc reagents, often in the presence of copper salts, effectively participate in conjugate addition reactions[14] and clean S_N2' reactions (eq 4).[15]

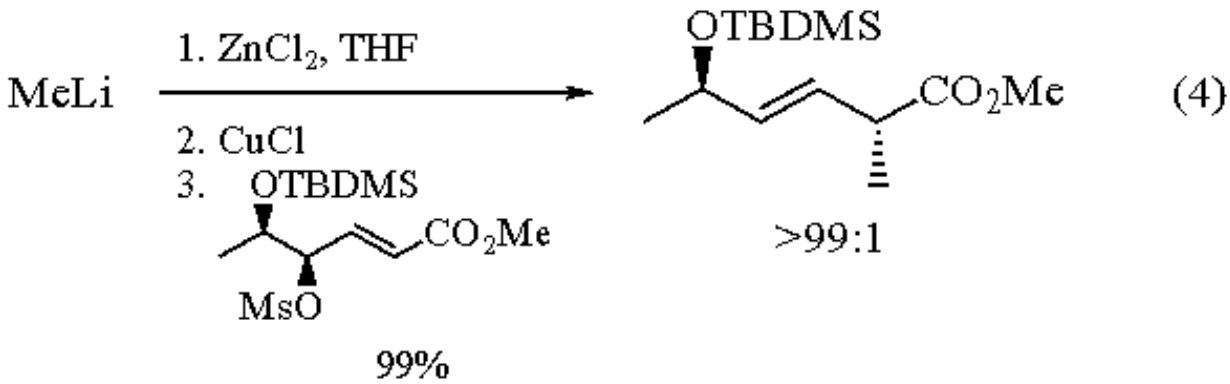

Organozinc reagents are superior species for palladium- and nickel-catalyzed coupling reactions.[16] This offers an exceptional method for the selective formation of sp^2-sp^3 (eq 5),[17] sp^2-sp^2 (eqs 6 and 7),[18,19] and sp^2-sp (eq 8)[20] carbon-carbon bonds. In addition, the palladium-catalyzed coupling reactions of sp and sp^2 halides with vinylalanes (eq 9),[21] vinylcuprates,[22] vinylzirconium (eq 10)[23] and acyliron species[24] often proceed more effectively in the presence of $ZnCl_2$. This effect has been noted in other metal-mediated carbon bond formations,[25] though the role of this $ZnCl_2$ catalysis is not understood at present.

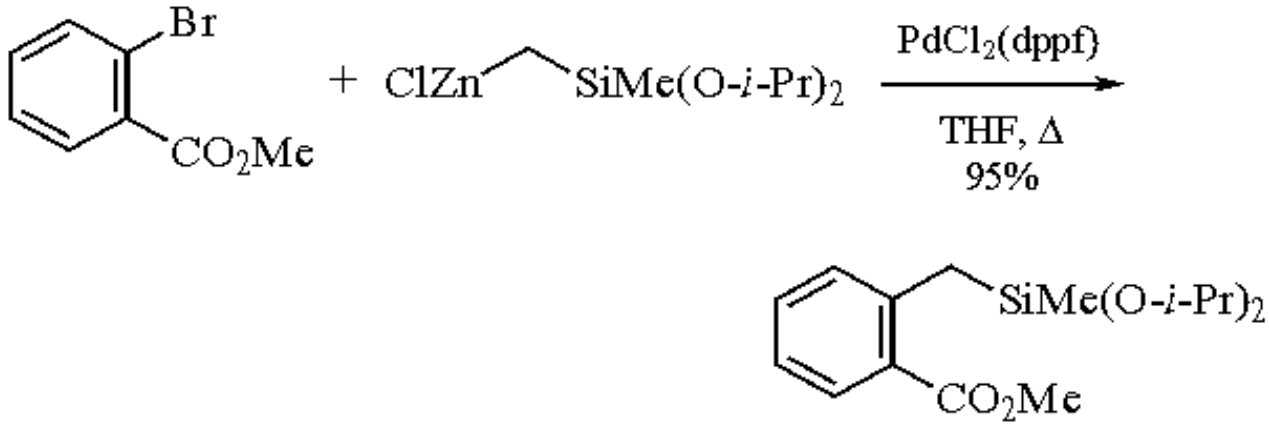
Br
CO2Me
ClZn
SiMe(O-i-Pr)2
PdCl2(dppf)
THF, Δ
95%
SiMe(O-i-Pr)2
CO2Me

(5)

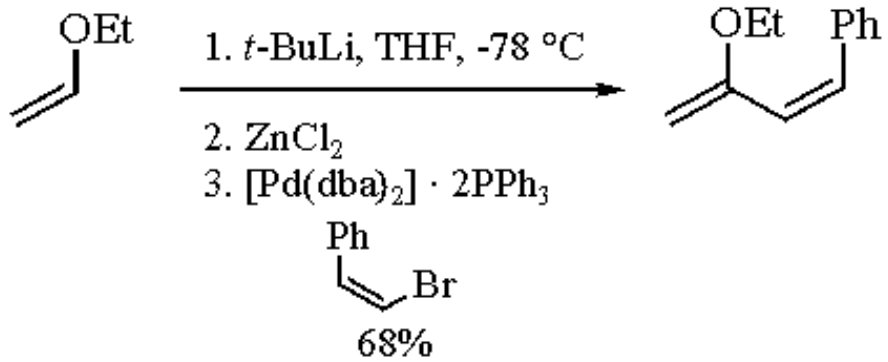
OEt
1. t-BuLi, THF, -78 °C
2. ZnCl2
3. [Pd(dba)2] · 2PPh3
Ph
Br
68%
OEt
Ph

(6)

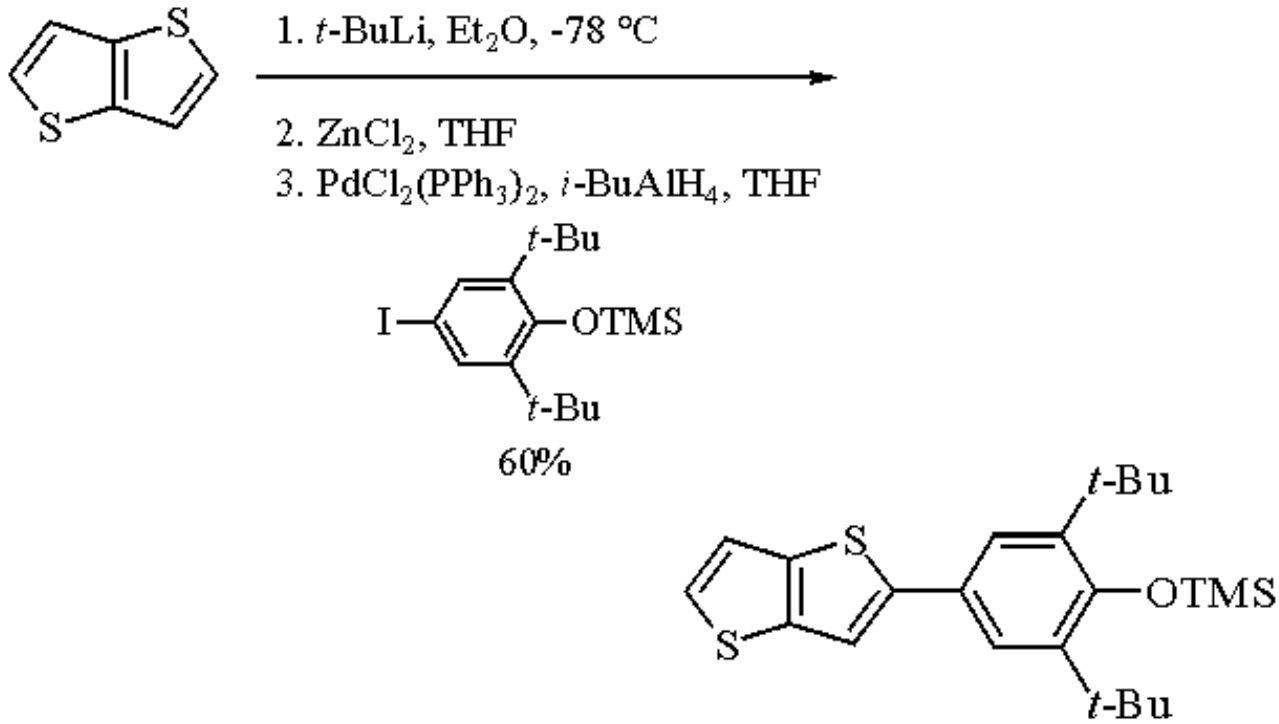
S
S
1. t-BuLi, Et2O, -78 °C
2. ZnCl2, THF
3. PdCl2(PPh3)2, i-BuAlH4, THF
t-Bu
I
OTMS
t-Bu
60%
t-Bu
S
S
OTMS
t-Bu

(7)

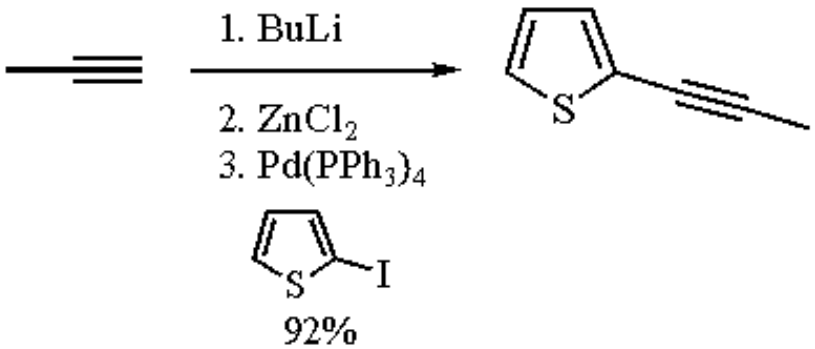
1. BuLi
2. ZnCl2
3. Pd(PPh3)4
S
I
92%
S

(8)

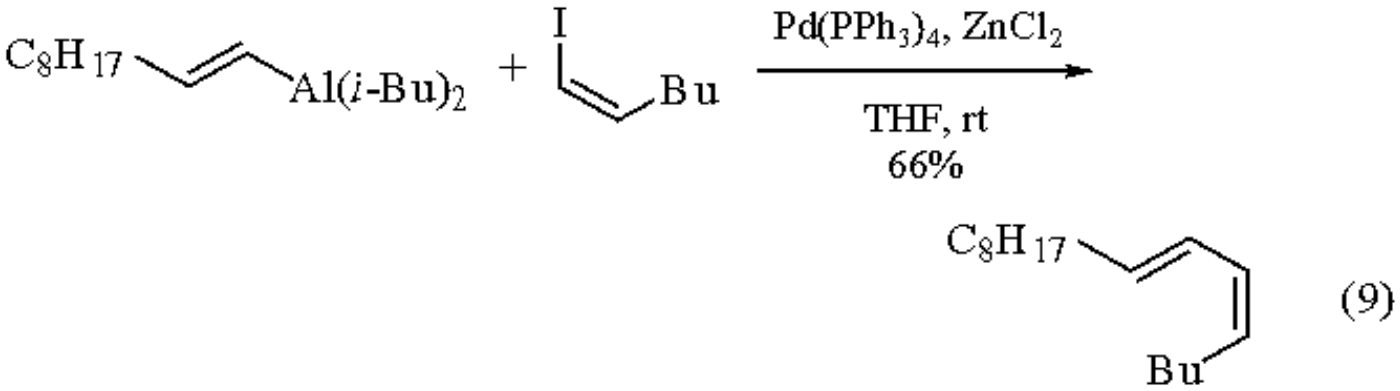

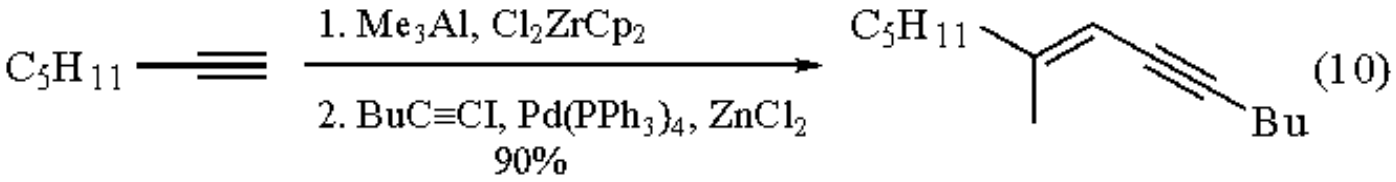

Organozinc reagents have been successfully exploited in asymmetric carbon bond formation.[26] Chiral glyoxylate esters engage organozinc species derived from Grignard reagents in selective addition reactions to afford enantiomerically enriched α-hydroxy acids (eq 11).[27] Enantioselective addition reactions of Grignard reagents have been achieved by sequential addition of $ZnCl_2$ and a chiral catalyst to afford secondary alcohols (eq 12).[28]

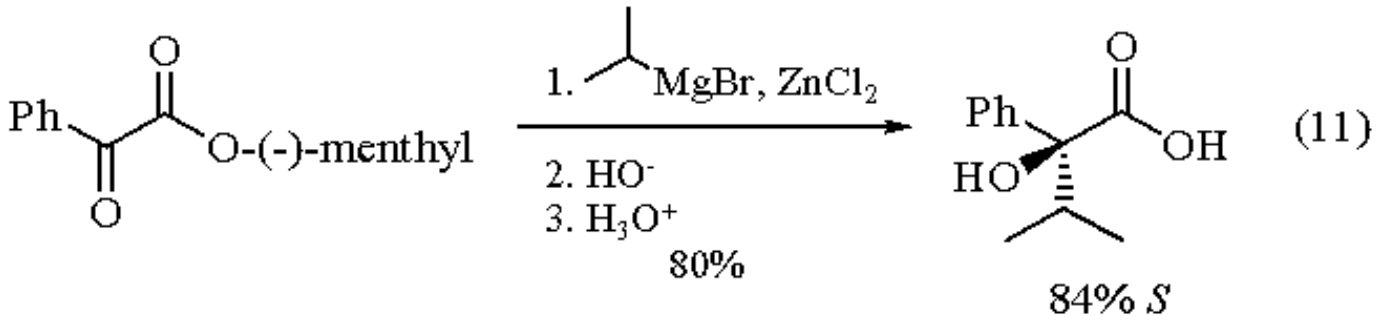

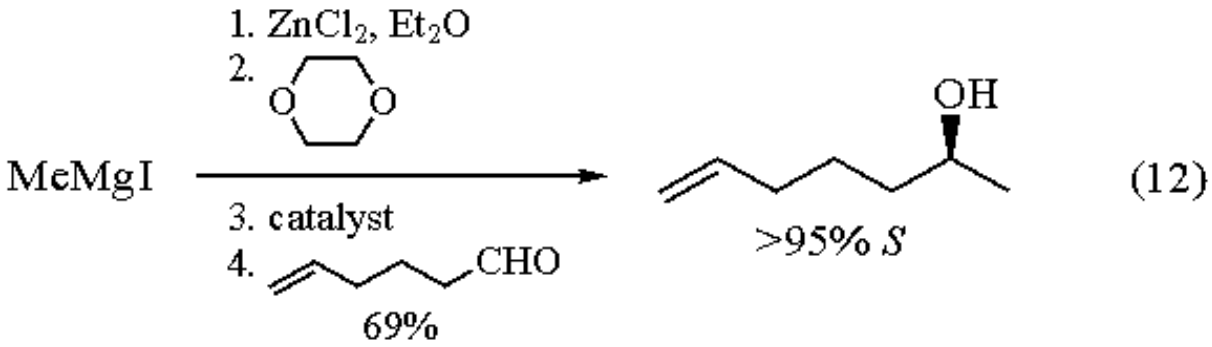

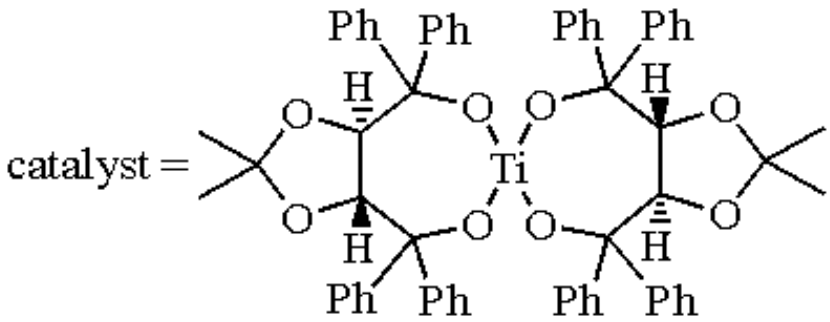

Zinc Enolates.

Zinc enolates can be prepared by deprotonation of carbonyl compounds using standard bases, followed by transmetalation with $ZnCl_2$.[1b]

These enolates offer important opportunities for stereoselective aldol condensations, including higher yields and stereochemical selection for *threo* crossed-aldol products (eq 13).[29] Both of these consequences are the result of the reversible formation of a six-membered zinc chelate intermediate (**1**) which favors the *anti* disposition of its substituents. Though their use has been mostly replaced by kinetically controlled aldol methodology, zinc enolates sometimes present advantages in specific cases.[30] For example, chelated zinc enolates derived from α-amino acids have been shown to be of value in the stereoselective synthesis of β-lactams (eq 14).[31] Controlled monoalkylation of unsymmetrical ketones has been accomplished via treatment of zinc enolates with α-chlorothio ethers (eq 15),[32] and mild allylation of β-dicarbonyl compounds may be realized through exposure of the corresponding zinc enolate to an allyl alcohol in the presence of a palladium catalyst (eq 16).[33]

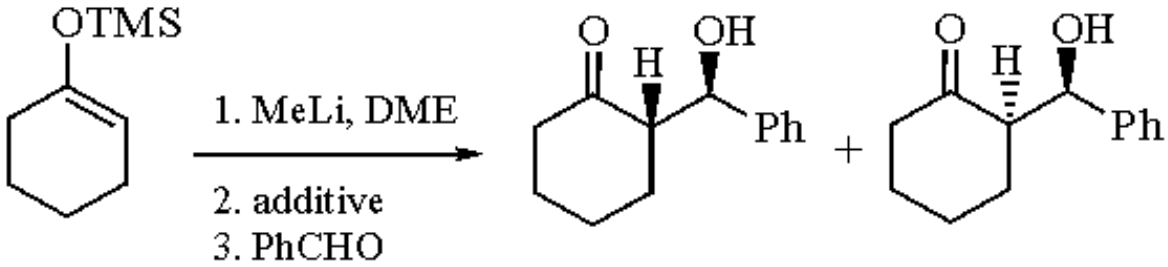

(13)

additive	
none, -72 °C	52:48
$ZnCl_2$, DME, 14 °C	83:17

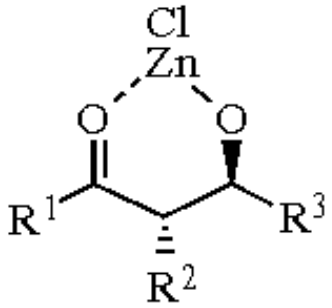

(1)

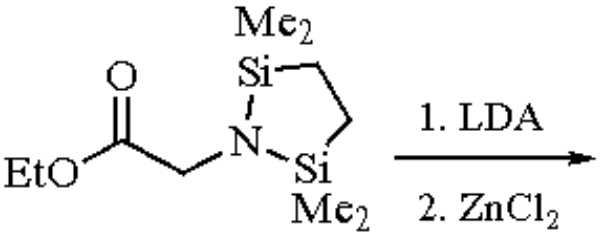

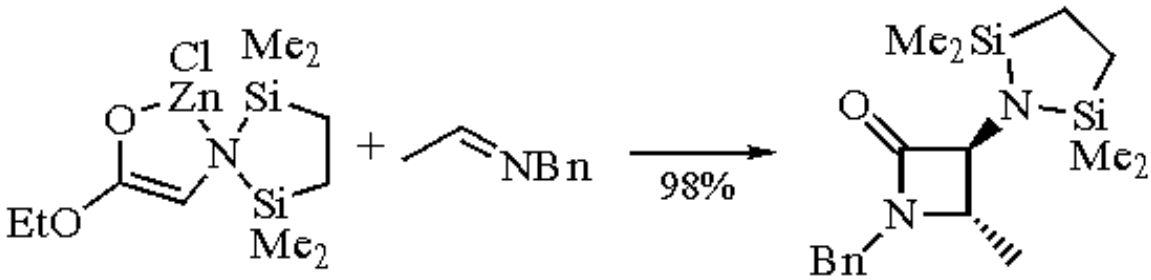

(14)

100% *trans*

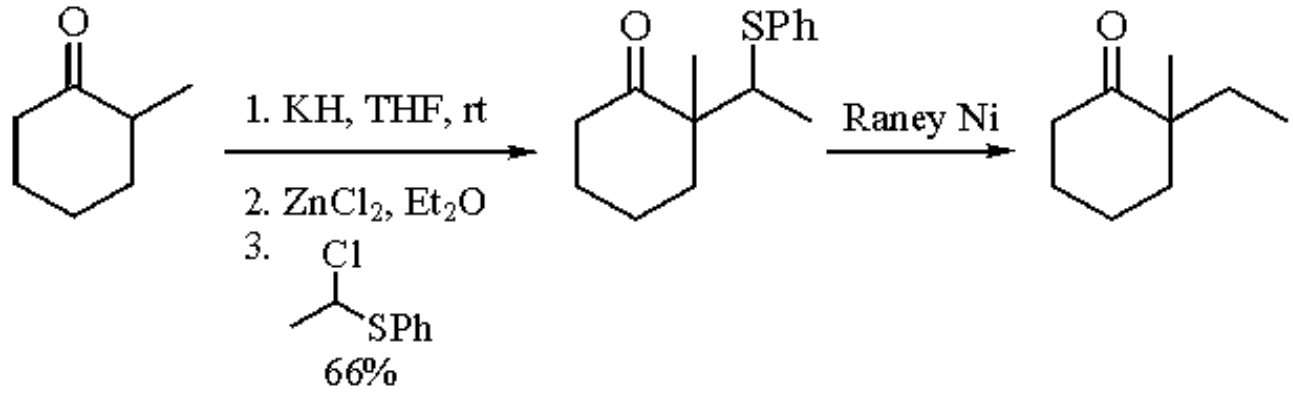

(15)

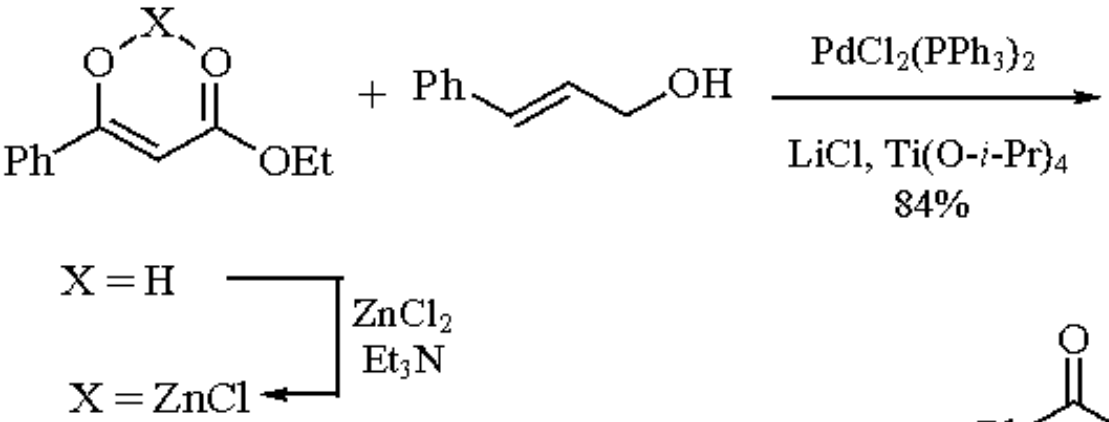

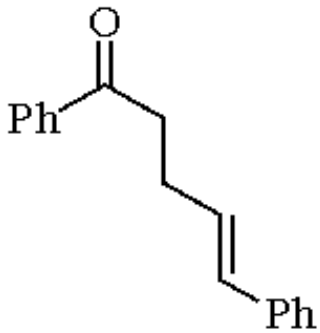

(16)

Homoenolates.

Readily available mixed Me_3Si/alkyl acetals are converted into zinc homoenolates in high yield through exposure to $ZnCl_2$ in Et_2O (eq 17).[34] These mildly reactive species, which tolerate asymmetry α to the carbonyl, are useful for a variety of bond-forming reactions. In the presence of Me_3Si activation they undergo addition to aldehydes and, when admixed with CuBr.DMS (see ***Copper(I) Bromide***), can be allylated or conjugatively introduced to α,β-unsaturated ketones (eq 18).[35] Copper salts are not required for conjugate addition to propargylic esters (eq 19).[36] These zinc species also participate in useful palladium-catalyzed bond-forming processes (eq 20).[37]

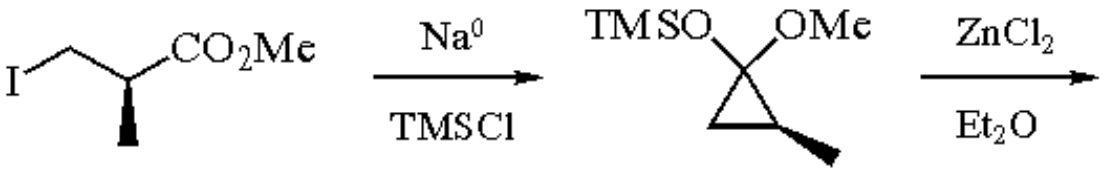

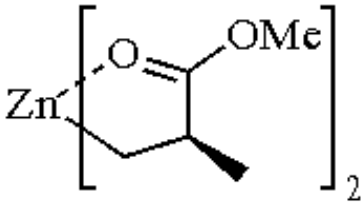

(17)

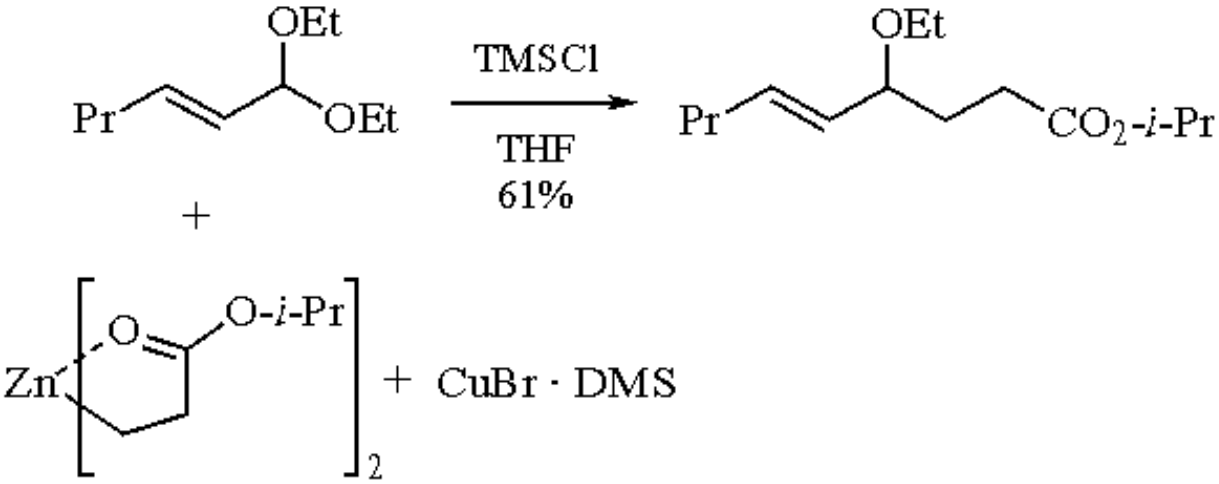
OEt
Pr
OEt
TMSCl
THF
61%
OEt
Pr
CO2-i-Pr
+
O
O-i-Pr
Zn
2
+ CuBr · DMS

(18)

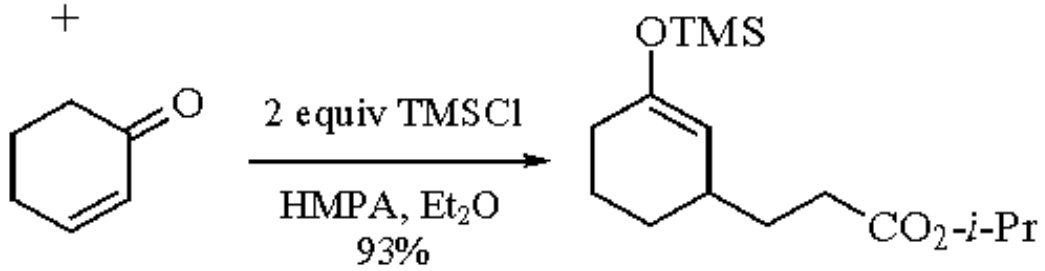
+
O
2 equiv TMSCl
HMPA, Et2O
93%
OTMS
CO2-i-Pr

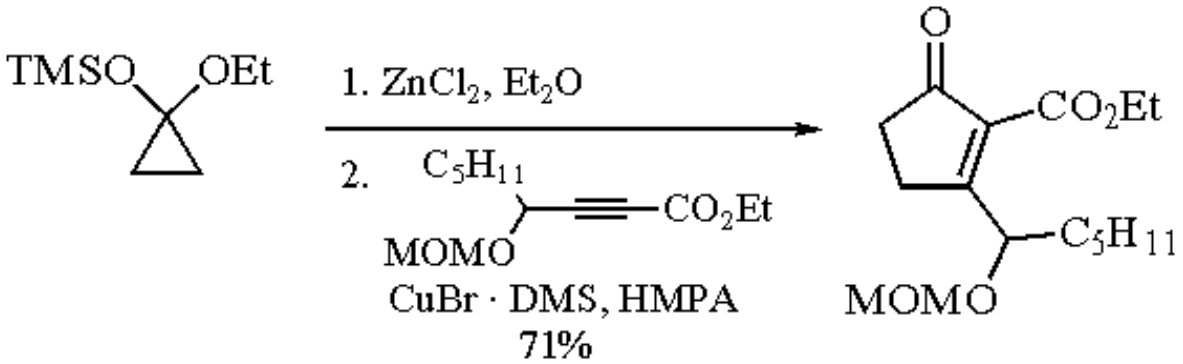
TMSO
OEt
1. ZnCl2, Et2O
2.
C5H11
CO2Et
MOMO
CuBr · DMS, HMPA
71%
O
CO2Et
C5H11
MOMO

(19)

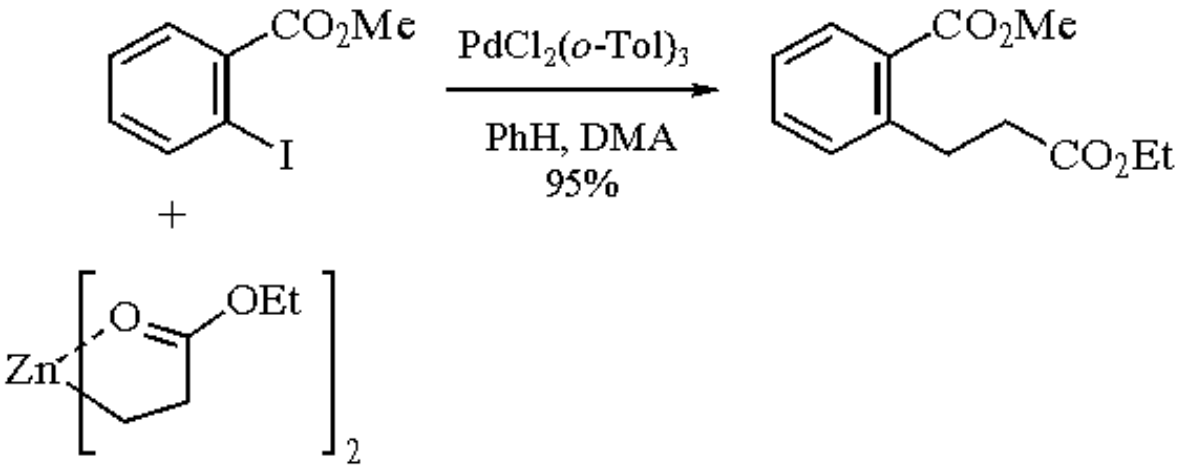
CO2Me
I
PdCl2(o-Tol)3
PhH, DMA
95%
CO2Me
CO2Et
+
O
OEt
Zn
2
+
Ph
COCl
Pd(PPh3)4
DMA
92%
O
Ph
CO2Et

(20)

Cycloaddition Reactions.

Catalysis by $ZnCl_2$ is often a powerful influence on cycloaddition reactions.[2] In addition to improving the rate of Diels-Alder reactions, enhanced control over regioselectivity (eq 21)[2c] and stereochemistry (eq 22)[2e] may be observed. An exceedingly important application of $ZnCl_2$ catalysis is found in the reaction of electron-rich dienes with carbonyl compounds.[2a,b] Intensive mechanistic studies on these reactions has uncovered two mechanistic pathways that afford stereochemically contrasting products, depending upon which Lewis acid is employed (eq 23).[38] It was concluded that cycloaddition reactions catalyzed by $ZnCl_2$ proceed via a classical [4 + 2] concerted process, whereas Lewis acids such as ***Boron Trifluoride Etherate*** and ***Titanium(IV) Chloride*** afford products through sequential aldol/cyclization processes. Examples abound wherein advantage has been taken of the predictable Cram-Felkin selectivity of this $ZnCl_2$ catalysis to exploit asymmetric variants of this reaction to synthesize a variety of natural products (eq 24).[39] The selective cycloaddition of electron-rich dienes with imines has also been catalyzed by $ZnCl_2$ (eq 25).[40]

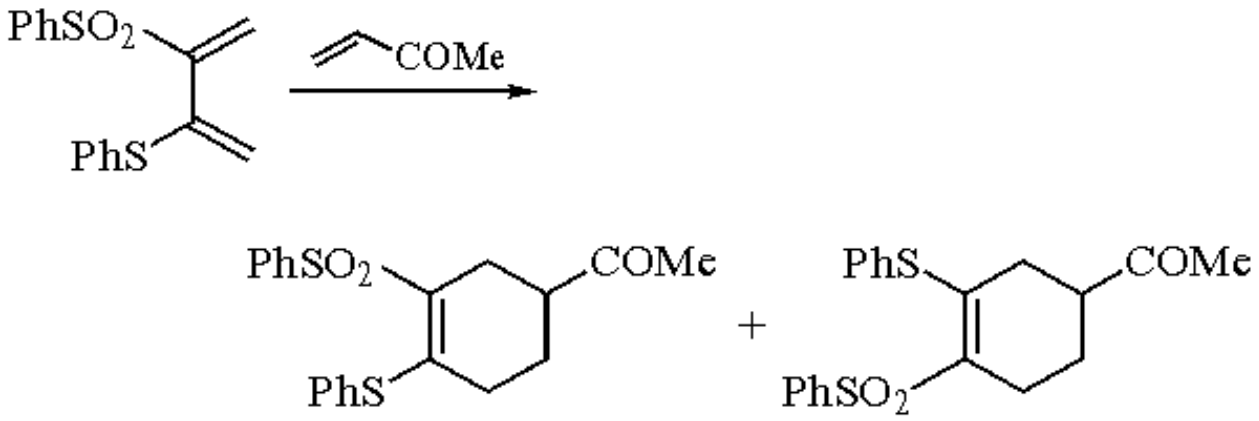

(21)

190 °C, 7 h	81%	3:1
$ZnCl_2$, rt, 24 h	90%	100:0

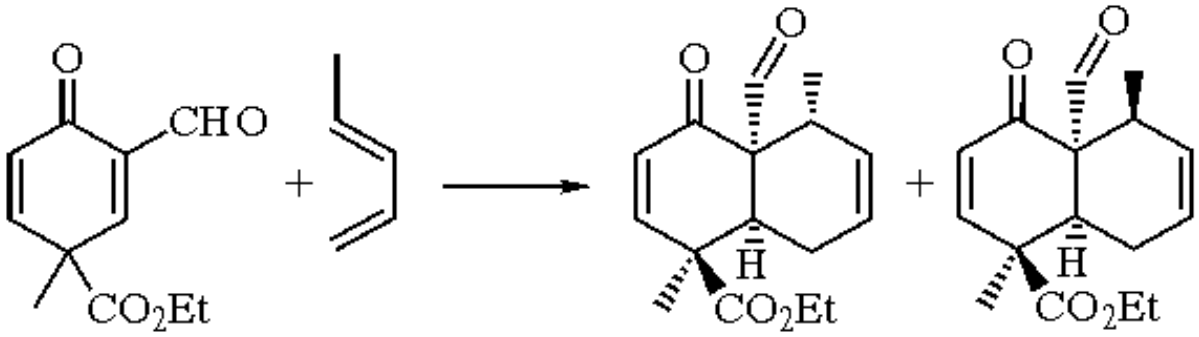

(22)

78 °C, 24 h	4.5:1
$ZnCl_2$, 0 °C, 5 h, 95%	100:0

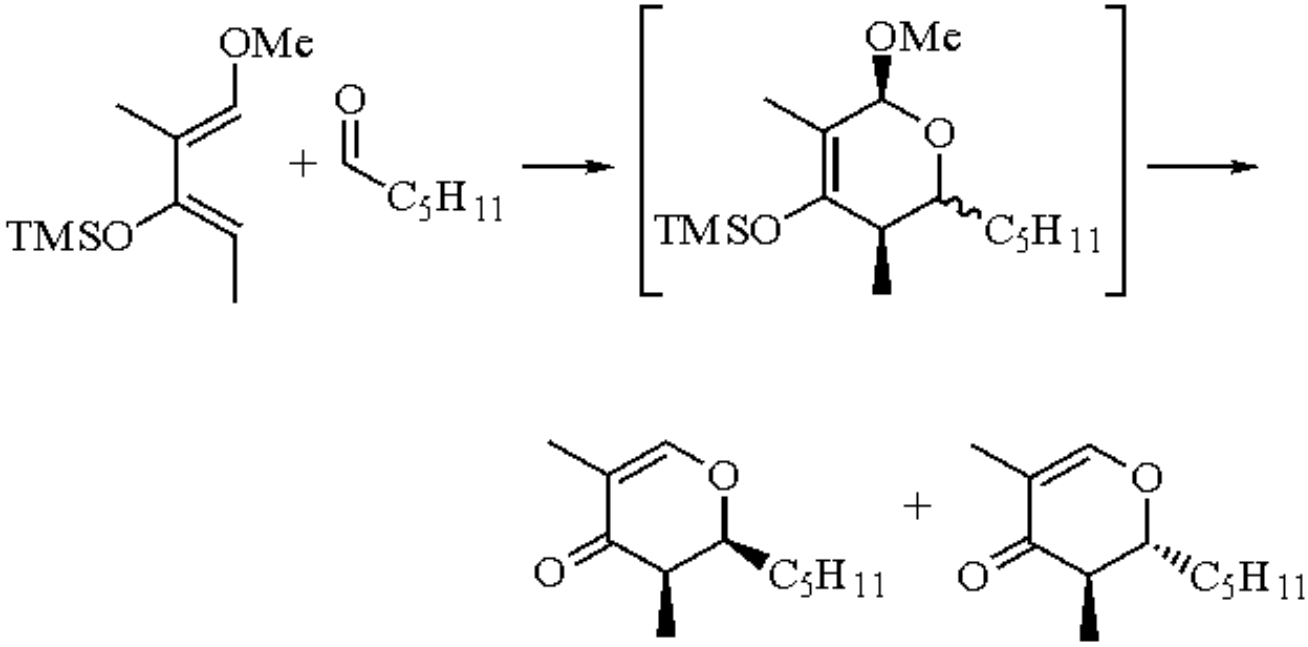

(23)

$BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C	21%	69%
$ZnCl_2$, THF, 25 °C	91%	2%

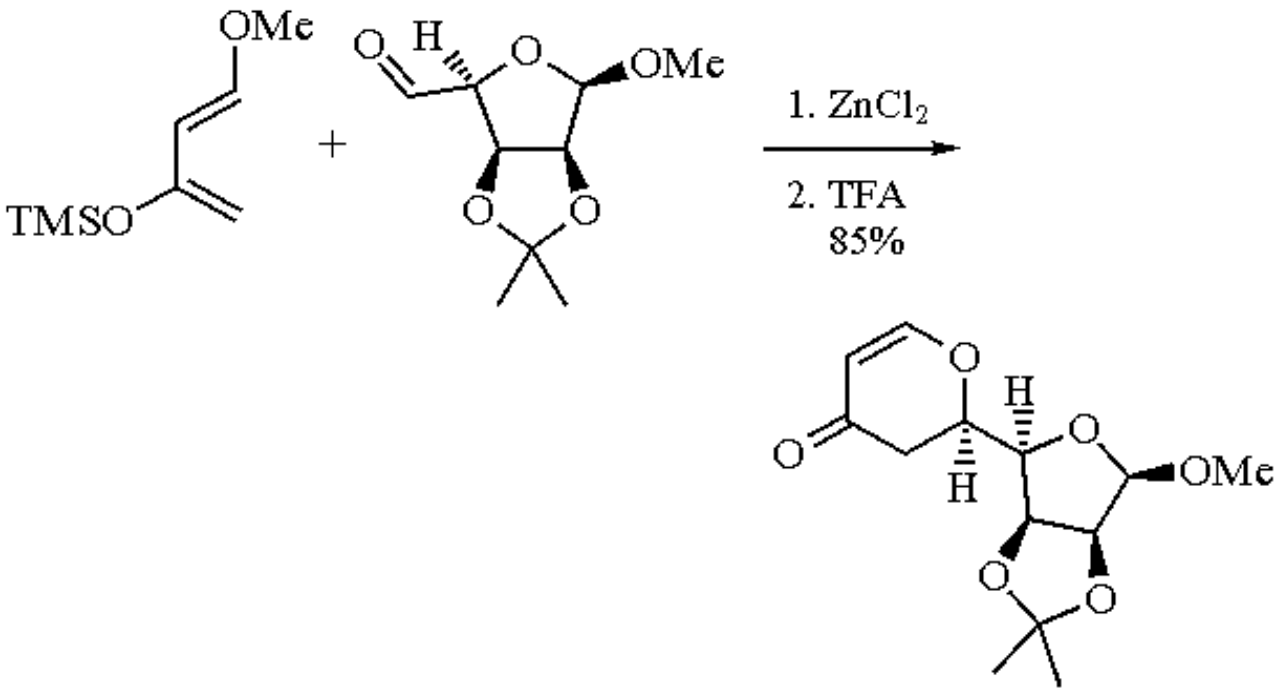

(24)

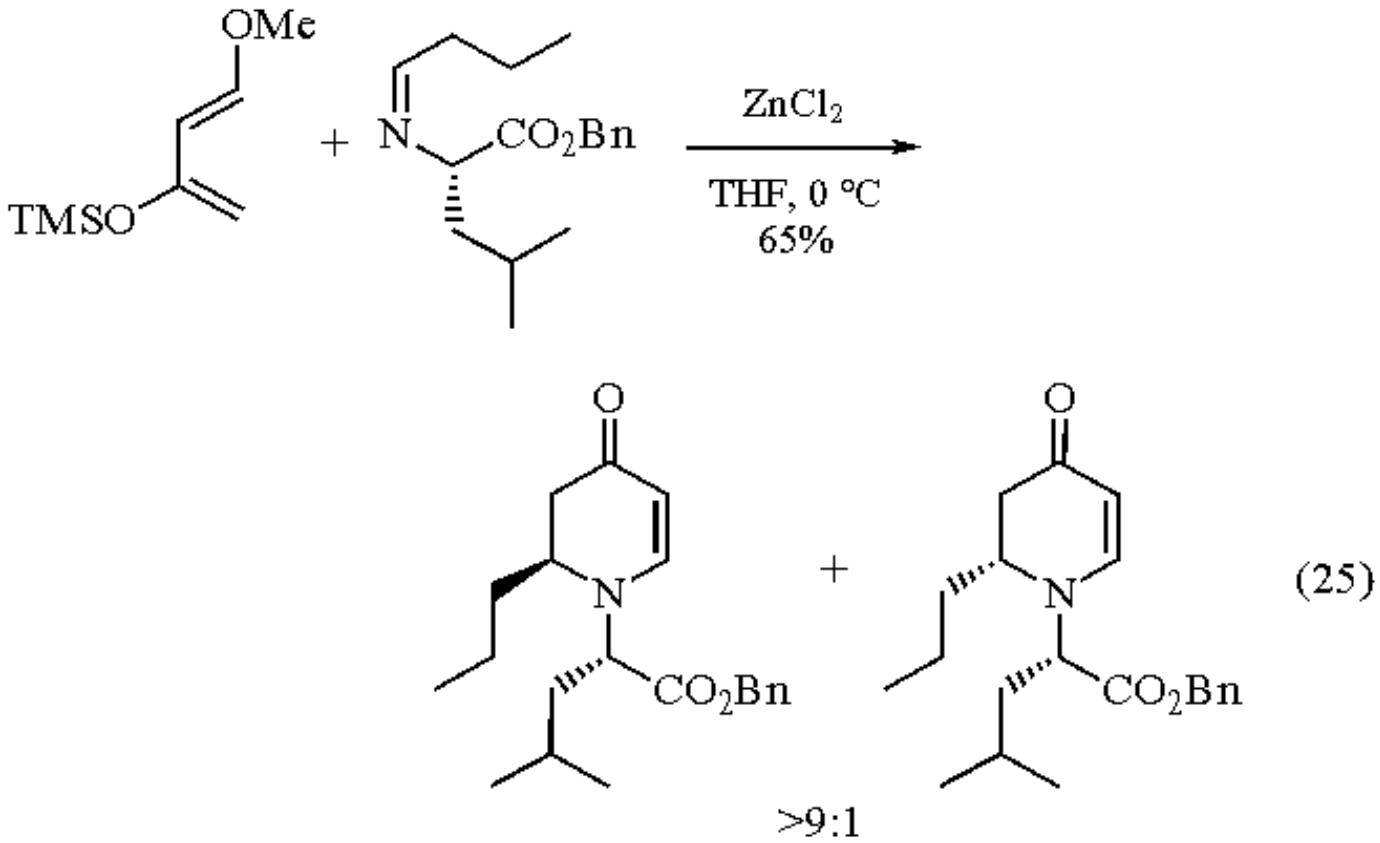

(25)

Activation of C=X Bonds.

The mild Lewis acid character of $ZnCl_2$ is frequently exploited to promote the addition of various nucleophiles to carbon-heteroatom double bonds.[4] The well-established Knoevenagel condensation and related reactions have been effectively catalyzed by $ZnCl_2$ (eq 26).[41] The addition of enol ethers and ketene acetals to aldehydes and ketones has been noted (eq 27),[42] though $ZnCl_2$ has been used less widely in these aldol-type condensations than other Lewis acids, including $TiCl_4$, ***Magnesium Bromide***, and ***Tin(IV) Chloride***, to name a few.[4] In some instances, excellent levels of stereocontrol have been observed (eq 28).[43] Analogous additions to imines have been noted as well.[4e-g,44] Some conjugate addition reactions may also benefit from $ZnCl_2$ catalysis (eq 29).[45]

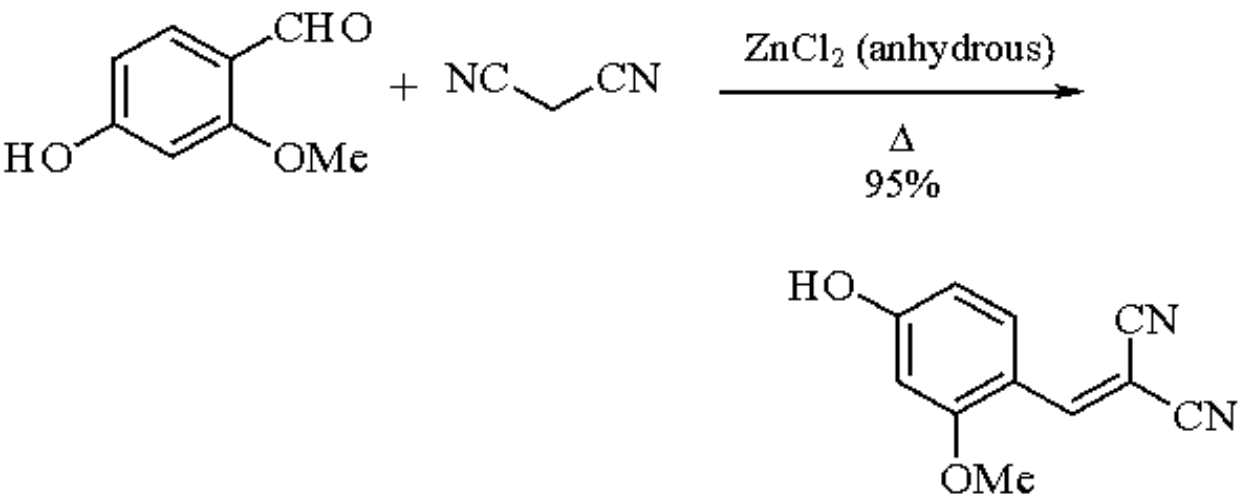

(26)

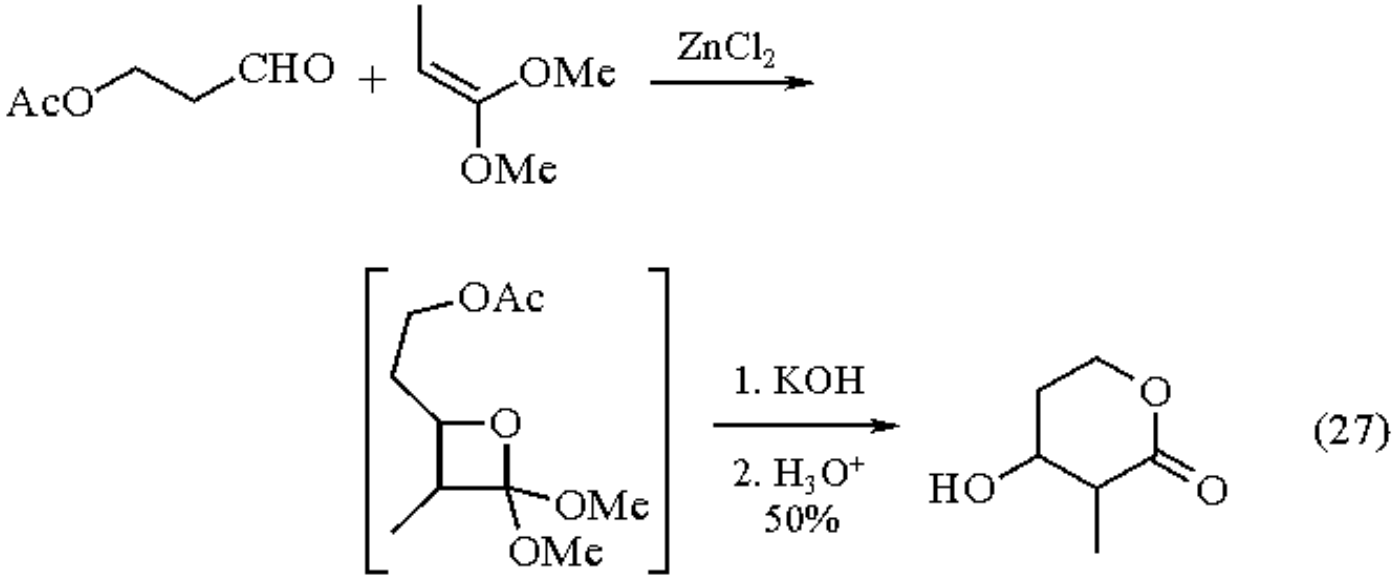

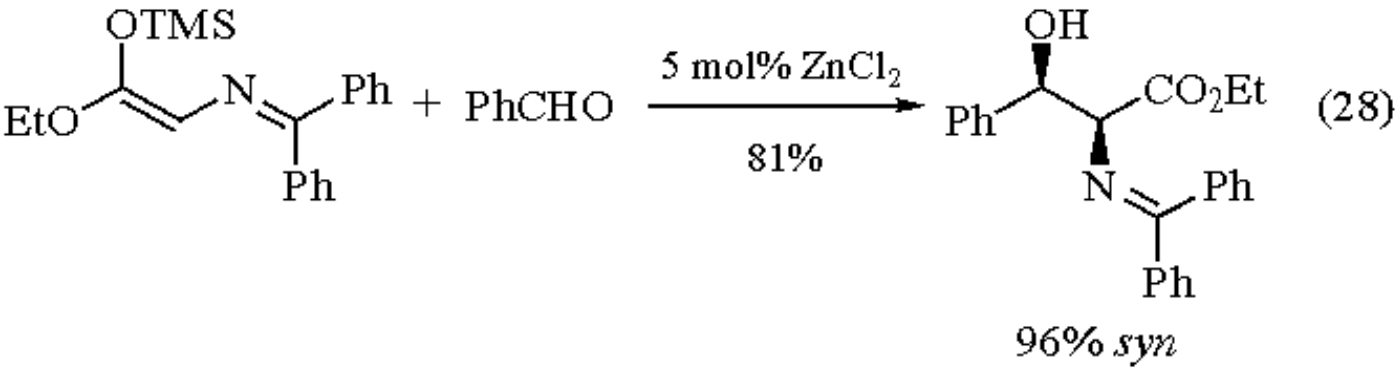

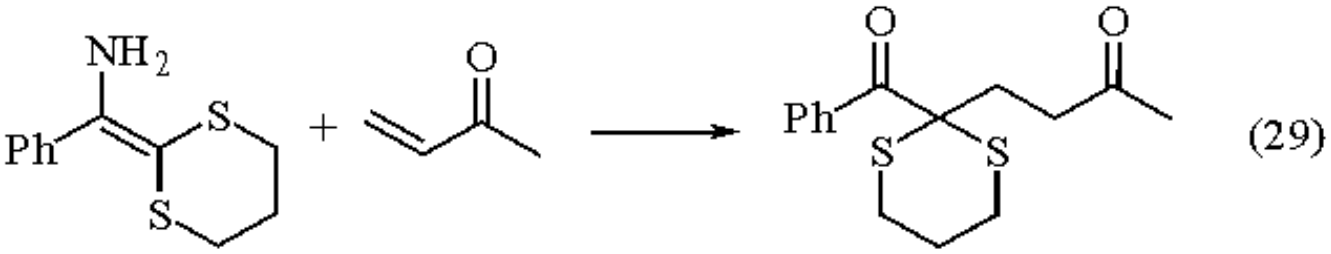

Δ, PhMe, 24 h	50%
1 equiv $ZnCl_2$, CH_2Cl_2, 0 °C, 2 d	98%

The formation of cyanohydrins using ***Cyanotrimethylsilane*** and ***Isoselenocyanatotrimethylsilane*** has been effectively catalyzed by $ZnCl_2$ (eq 30),[46] as has Strecker amino acid synthesis via the treatment of imines with $Me_3SiCN/ZnCl_2$.[47] The combination of carbonyl compounds with ***Acetyl Chloride*** or ***Acetyl Bromide*** may be promoted by $ZnCl_2$ to afford protected vicinal halohydrins (eq 31).[48]

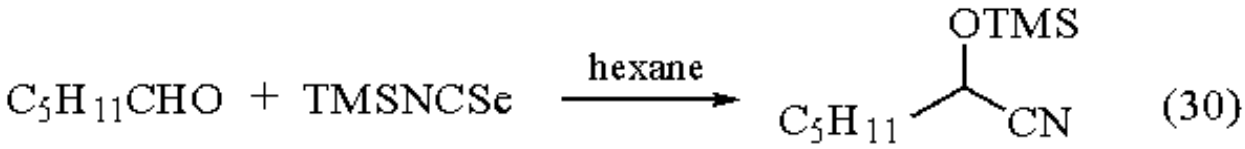

no $ZnCl_2$	78%
with $ZnCl_2$	>95%

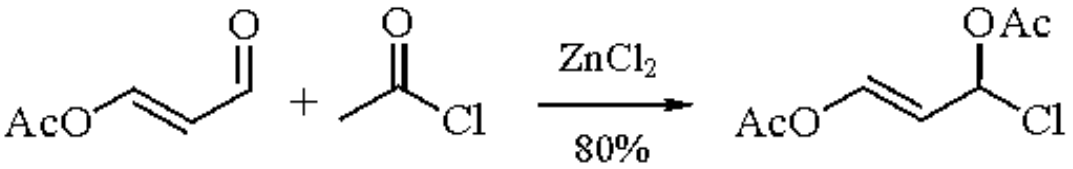

(31)

It is noteworthy that the treatment of carbonyl compounds with ***Chlorotrimethylsilane***/$ZnCl_2$ results in a useful synthesis of Me_3Si enol ethers which, in turn, may be useful for other carbon bond-forming processes (eq 32).[49]

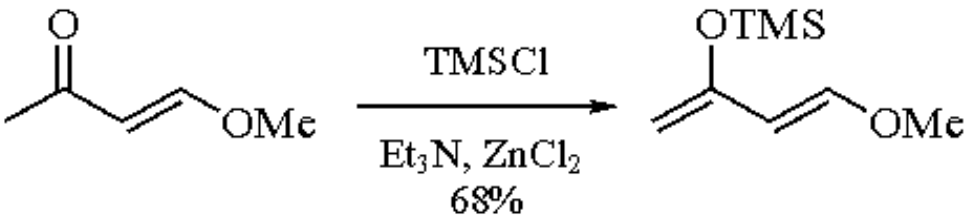

(32)

Activation of C-X Bonds.

The activation of C-X single bonds toward nucleophilic substitution is also mediated by the Lewis acidic character of $ZnCl_2$.[3] Benzylic (eq 33),[50] allylic (eq 34),[3d,51] propargylic,[52] and tertiary halides (eq 35)[53] undergo substitution with mild carbon and heteroatom[3e] nucleophiles.

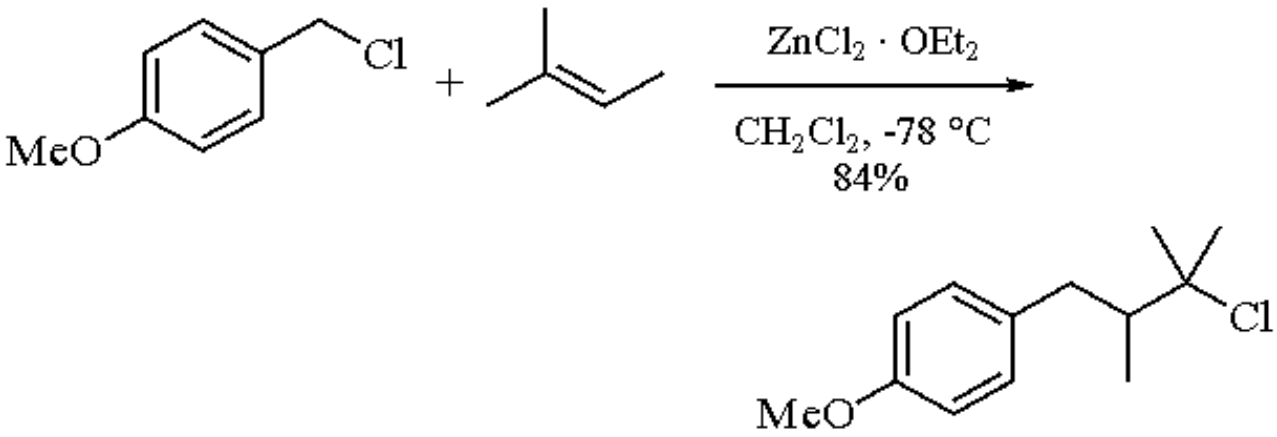

(33)

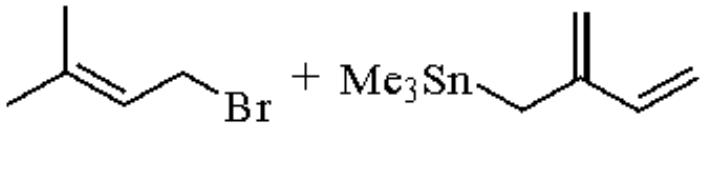

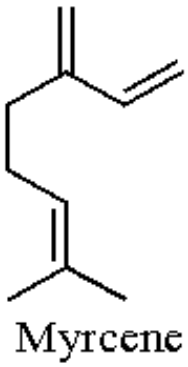

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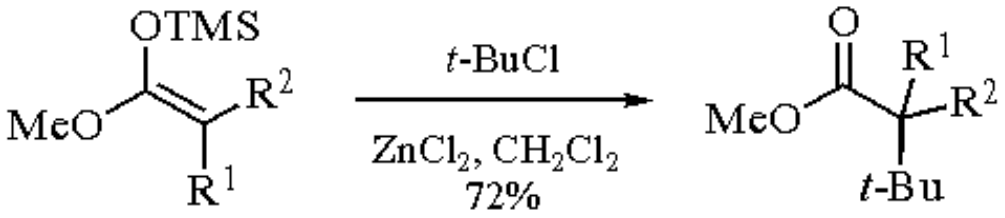

(35)

In a similar fashion, acetals (eq 36)[54] and orthoesters (eq 37)[55] may be used as electrophiles in substitution reactions with electron-rich alkenic nucleophiles. The combination of $ZnCl_2$ with co-catalysts has sometimes proven advantageous in these reactions (eq 38).[56]

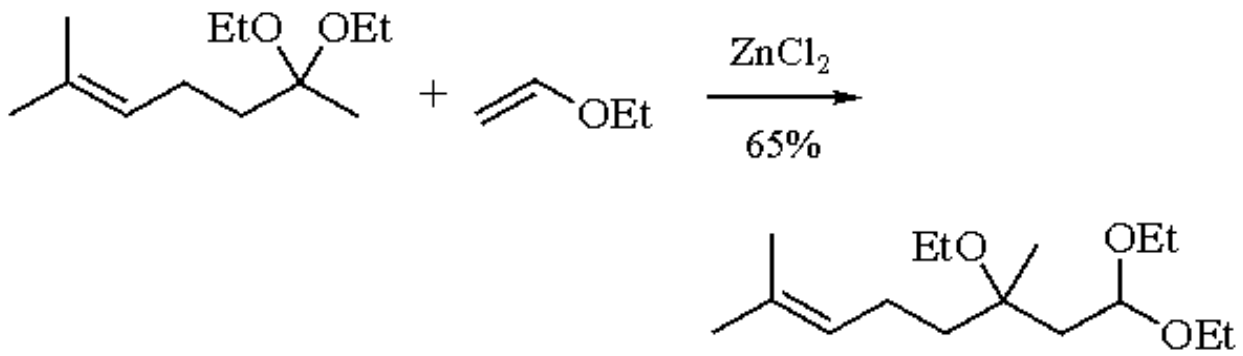

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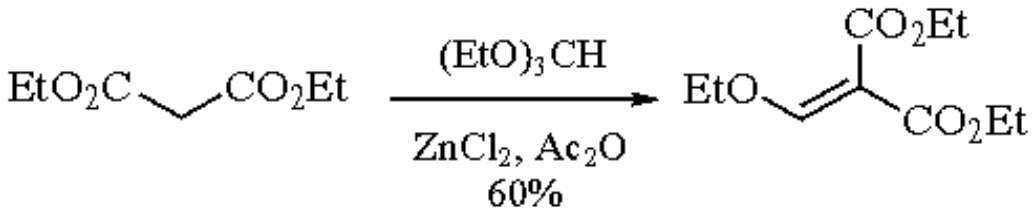

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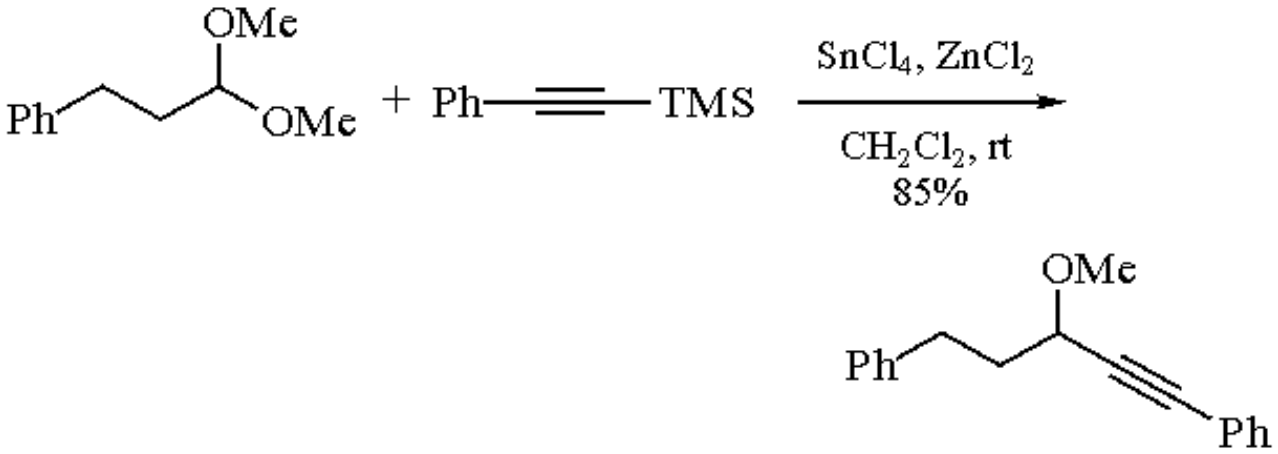

(38)

The regioselective ring opening reactions of epoxides (eq 39),[57,58] oxetanes,[58] and tetrahydrofurans (eq 40)[59] has been promoted by $ZnCl_2$ to afford adducts with suitable nucleophiles.

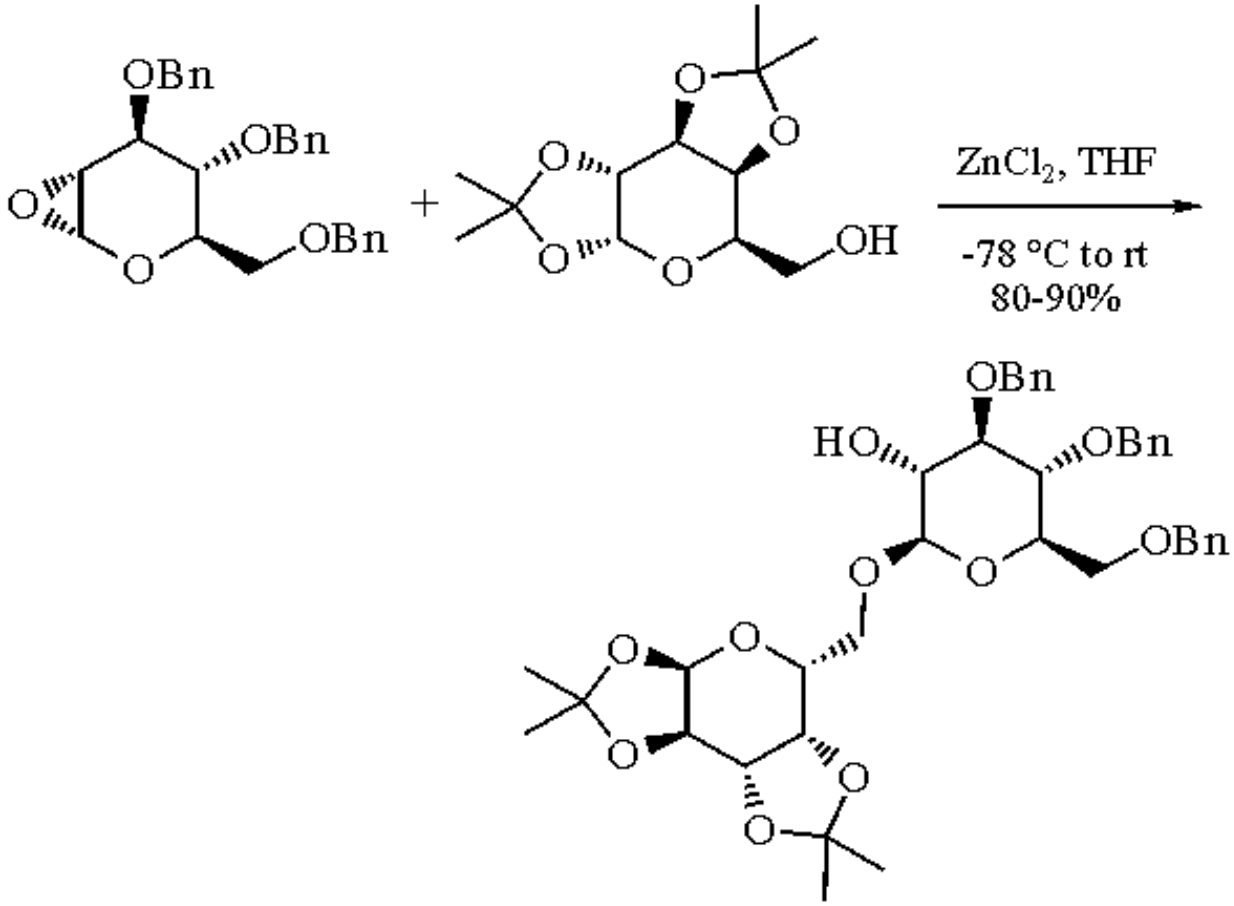

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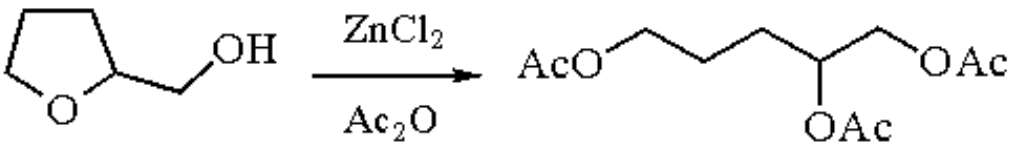

(40)

Activation by $ZnCl_2$ of allylic (eq 41)[60] and propargylic chlorides (eq 42),[61] as well as α-chloroenamines (eq 43),[62] in the presence of simple alkenes has been shown to yield four-membered and five-membered cycloadducts.

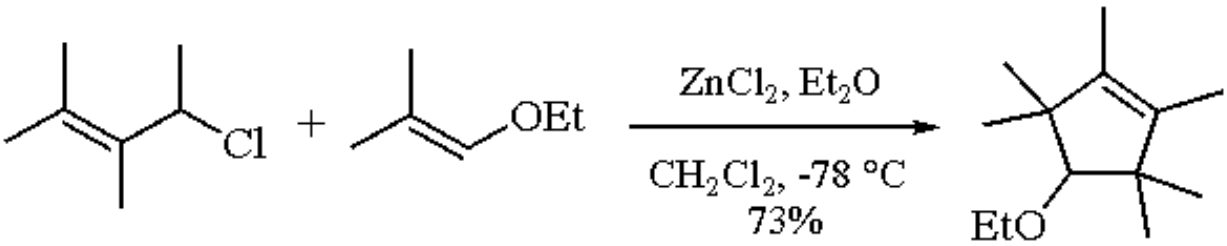

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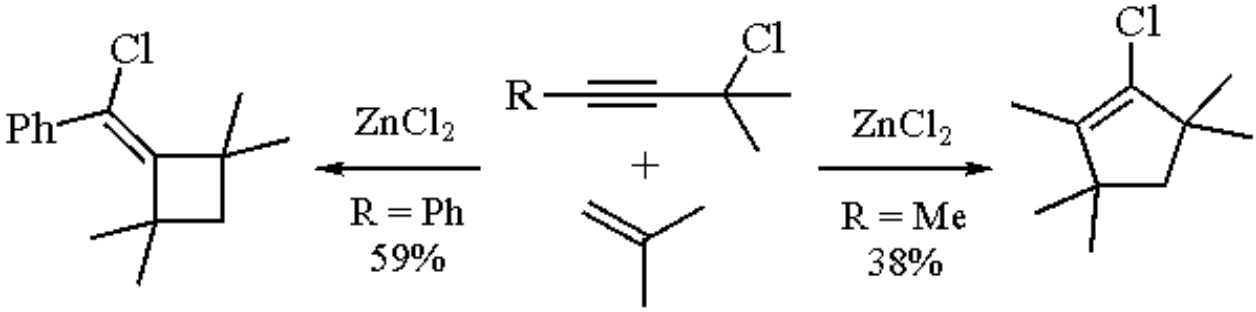

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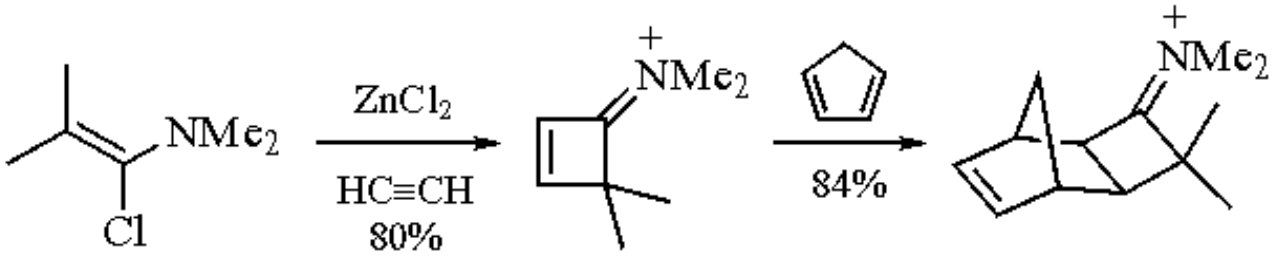

(43)

Chlorination of alcohols by ***Thionyl Chloride***,[63] the preparation of acyl chlorides from lactones and anhydrides,[64] and the bromination and iodination of aromatic rings by ***Benzyltrimethylammonium Tribromide*** and ***Benzyltrimethylammonium Dichloroiodate***, respectively,[65] are all effectively catalyzed by the presence of $ZnCl_2$. In addition, $ZnCl_2$ acts as a source of chloride for the halogenation of primary, secondary, and allylic alcohols using ***Triphenylphosphine-Diethyl Azodicarboxylate***.[66]

Reduction.

The very useful reducing agent ***Zinc Borohydride*** is prepared by exposure of $NaBH_4$ to $ZnCl_2$ in ether solvents.[67] Its use in selective reductions is described elsewhere.[6a] A complex reducing agent resulting from the mixture of NaH/*t*-pentyl-OH/$ZnCl_2$, given the acronym ZnCRA (***Zinc Complex Reducing Agents***), is found to open epoxides in a highly regioselective fashion, favoring hydride delivery at the least hindered position.[68] A related reagent, ZnCRASi, which includes Me_3SiCl in the mixture, selectively reduces ketones in high yield, though the levels of selectivity do not compete with other selective reagents.[69]

The reduction of ketones and aldehydes by silicon and tin hydrides in the presence of $ZnCl_2$ has been documented.[70] In the presence of Pd^0 catalysts and $ZnCl_2$, these hydrides selectively reduce α,β-unsaturated aldehydes and ketones to the corresponding saturated products (eq 44).[71] The presence of $ZnCl_2$ has been shown to modify the reactivity of several common reducing agents. For example, the mixture of ***Sodium Cyanoborohydride*** and $ZnCl_2$ selectively reduces tertiary, allylic, and benzylic halides (eq 45),[72] ***Sodium Borohydride***, in the presence of $ZnCl_2$ and $PhNMe_2$ will reduce aryl esters to primary alcohols,[73] and ***Lithium Aluminum Hydride*** with $ZnCl_2/CuCl_2$ desulfurizes dithianes (eq 46).[74]

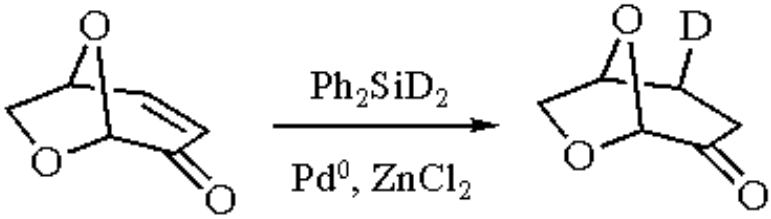

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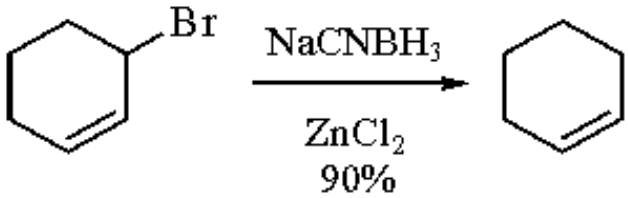

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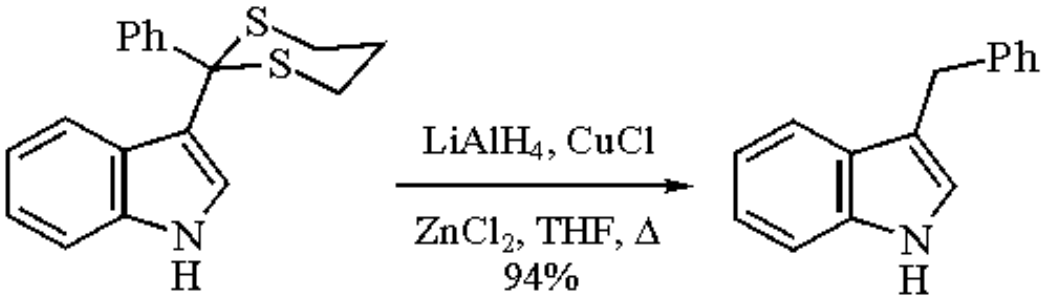

(46)

Stereoselectivity is also modified by the presence of $ZnCl_2$ (eq 47).[75] Enantioselective reduction of aryl ketones has been observed with ***Diisobutylaluminum Hydride*** (DIBAL) modified by $ZnCl_2$ and chiral diamine ligands (eq 48).[76]

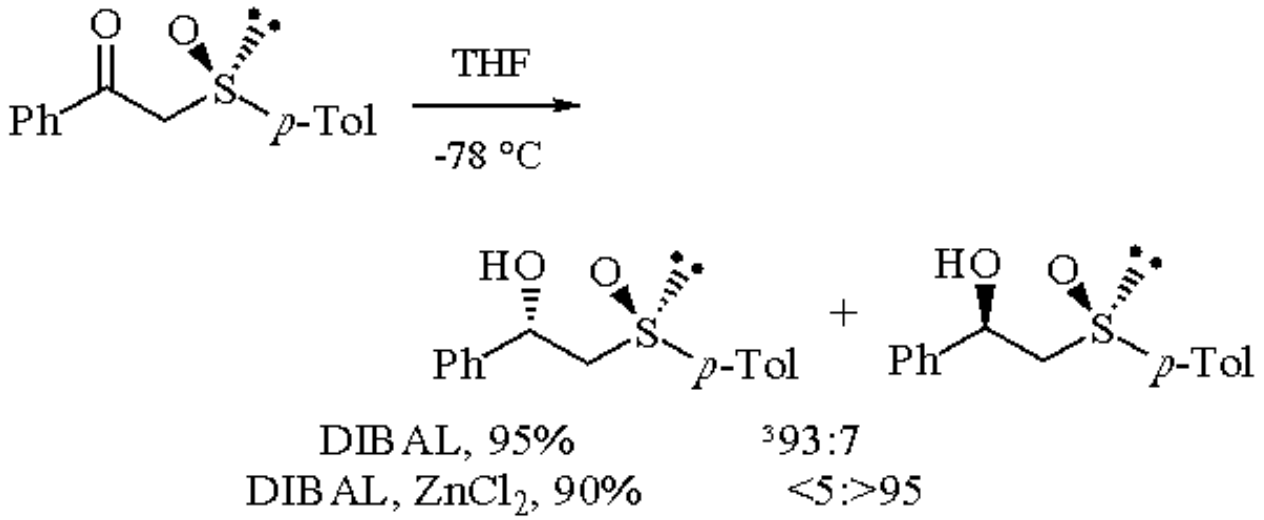

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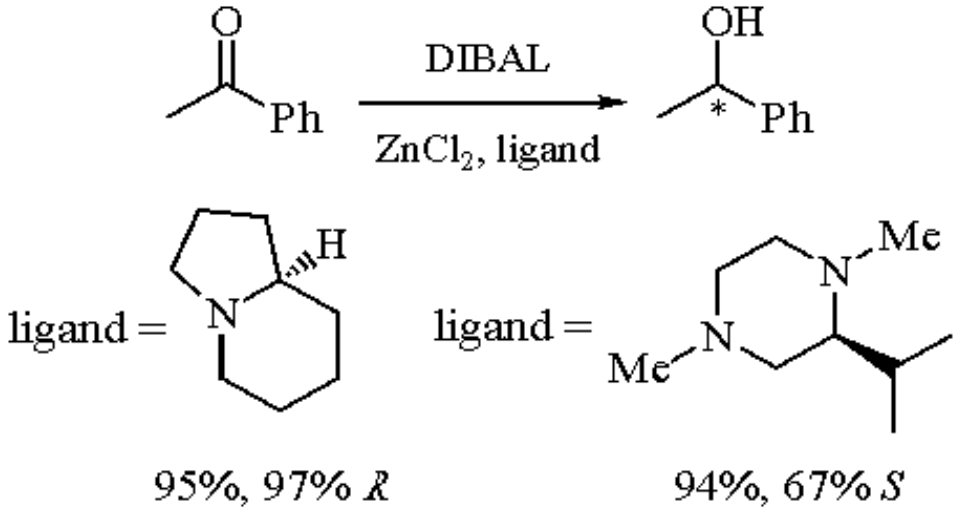

(48)

Protection/Deprotection.

The acetylation of carbohydrates and other alcohols has been realized using ***Acetic Anhydride***/$ZnCl_2$ (eq 49).[77] It is found that $ZnCl_2$ imparts selectivity to both acetylation[78] and acetonide formation[79] of polyols, which is useful in the synthetic manipulation of carbohydrates. Synthetically useful selective deprotection of acetates (eq 50)[80] and dimethyl acetals (eq 51)[81] has been reported to be mediated by $ZnCl_2$.

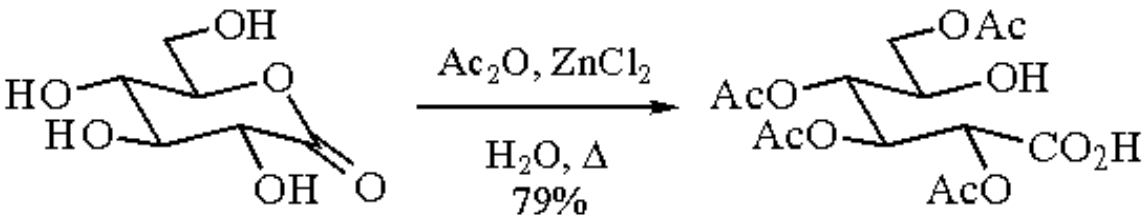

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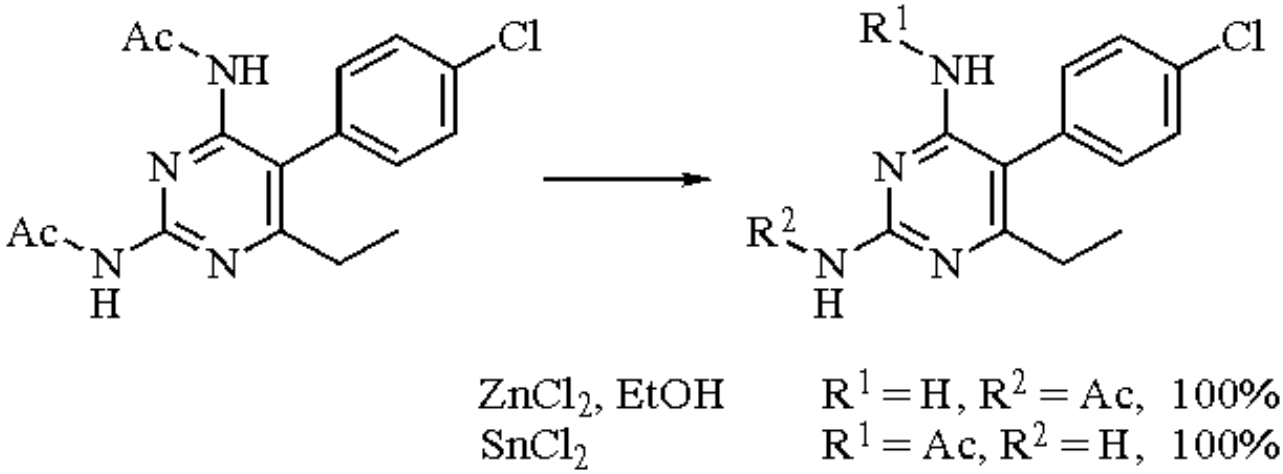

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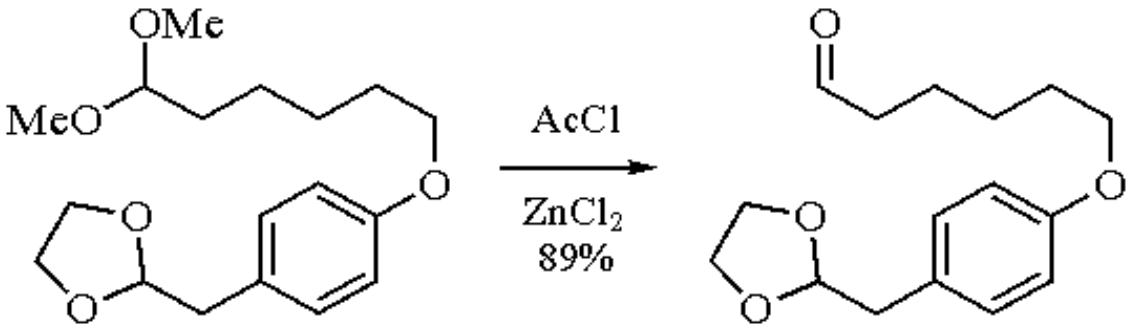

(51)

Acylation.

Unsaturated esters are obtained through acylation of alkenes by anhydrides using activation by $ZnCl_2$ (eq 52).[82] The mixture of $RCOCl/ZnCl_2$ is effective in the acylation of silyl enol ethers to afford β-dicarbonyl products (eq 53).[83] Friedel-Crafts acylation is catalyzed by $ZnCl_2$, using anhydrides or acyl halides as the electrophiles (eqs 54 and 55).[84,85]

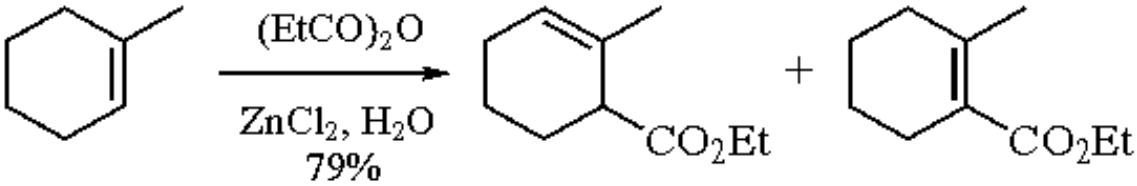

(52)

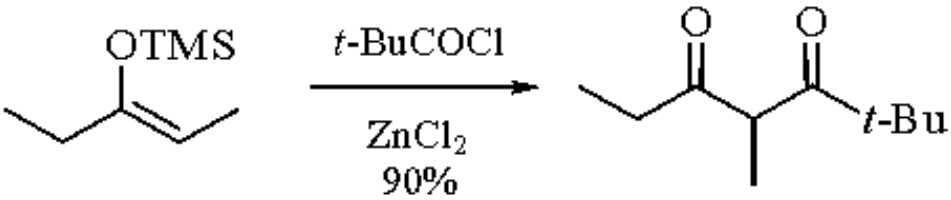

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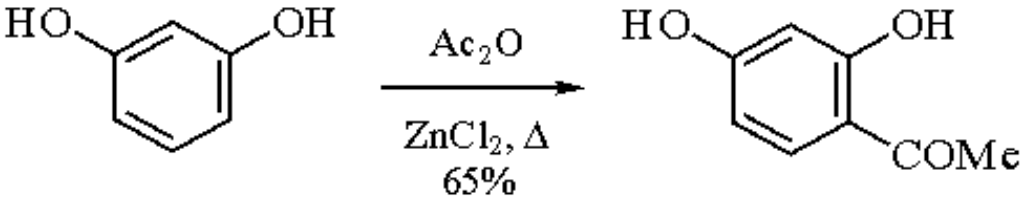

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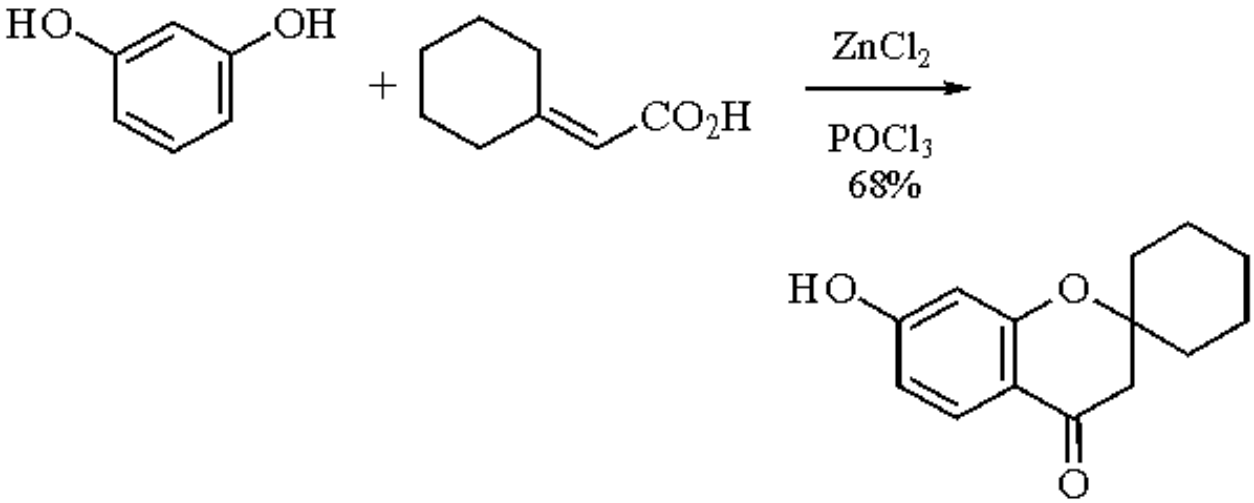

(55)

Aromatic Substitution.

Several important classes of aromatic substitutions are mediated by $ZnCl_2$, including the Hoesch reaction (eq 56)[86] and the Fischer indole synthesis (eq 57).[87] Haloalkylation of aromatic rings using ***Formaldehyde*** or ***Chloromethyl Methyl Ether*** is readily accomplished through the agency of $ZnCl_2$ and warming (eq 58).[88]

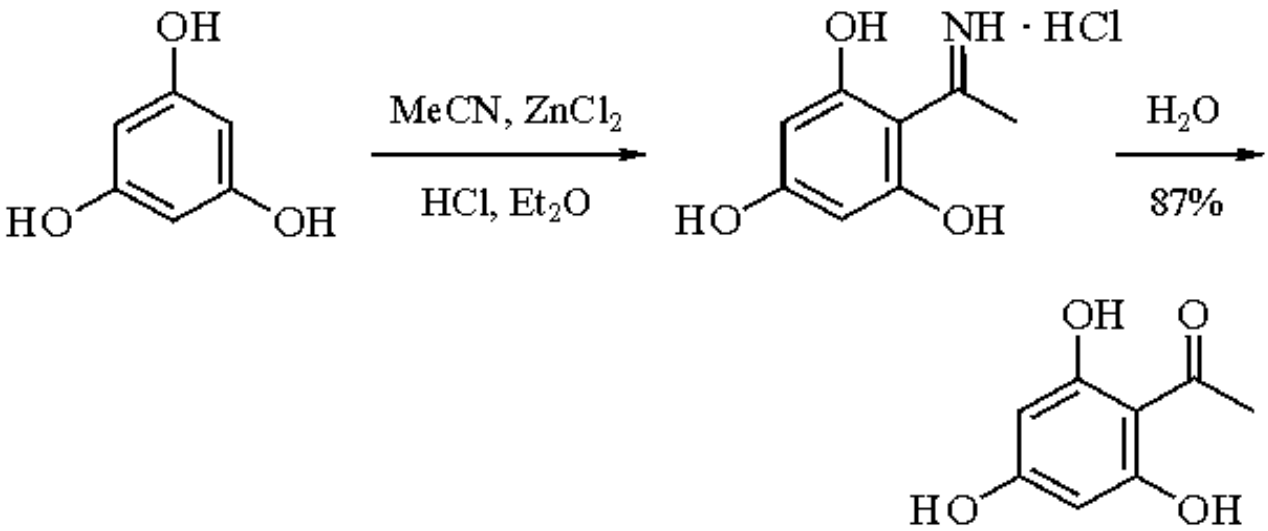

(56)

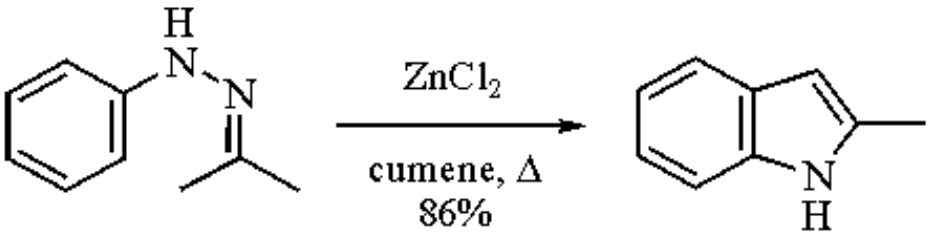

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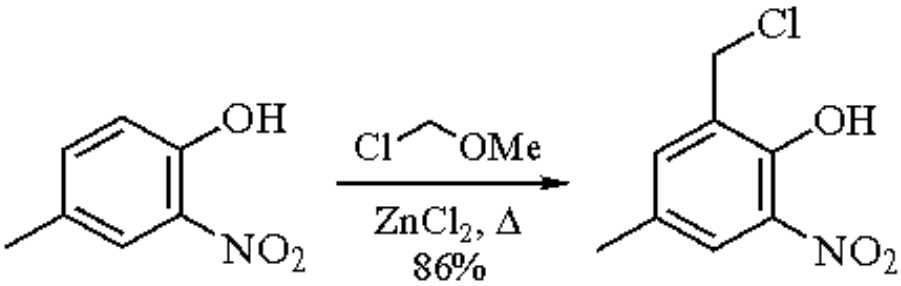

(58)

Related Reagents.

Aluminum Chloride; ***Diphenylsilane-Tetrakis(triphenylphosphine)palladium(0)-Zinc Chloride***; ***Phosphorus(III) Chloride-Zinc(II) Chloride***; ***Phosphorus Oxychloride-Zinc(II) Chloride***; ***Tin(IV) Chloride***; ***Tin(IV) Chloride-Zinc Chloride***; ***Titanium(IV) Chloride***.

---

1. (a) Knochel, P. *COS* **1991**, *1*, Chapter 1.7. (b) Rathke, M. W.; Weipert, P. *COS* **1991**, *2*, Chapter 1.8.
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4. For examples: (a) Eliel, E. L.; Hutchins, Sr., R. O.; Knoeber, M. *OS* **1970**, *50*, 38. (b) Angle, S. R.; Turnbull, K. D. *JACS* **1989**, *111*, 1136. (c) Takai, K.; Heathcock, C. H. *JOC* **1985**, *50*, 3247. (d) Chiba, T.; Nakai, T. *CL* **1987**, 2187. (e) Taguchi, T.; Kitagawa, O.; Suda, Y.; Ohkawa, W.; Hashimoto, A.; Iitaka, Y.; Kobayashi, Y. *TL* **1988**, *29*, 5291. (f) Kunz, H.; Pfrengle, W. *AG(E)* **1989**, *28*, 1067. (g) Kunz, H.; Pfrengle, W. *JOC* **1989**, *54*, 4261.
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6. For examples: (a) Oishi, T.; Nakata, T. *ACR* **1983**, *24*, 2653. (b) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubère, P. *JOC* **1990**, *55*, 5911. (c) Solladié, G.; Demailly, G.; Greck, C. *OS* **1977**, *56*, 8.
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8. Rieke, R. D.; Uhm, S. J. *S* **1975**, 452.
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Zinc Chloride Etherate in Dichloromethane[1]

$ZnCl_2.OEt_2$

[21512-92-5] · $C_4H_{10}Cl_2OZn$ · Zinc Chloride Etherate · (MW 210.43)

(Lewis acid catalyst solution that is considerably more active than $ZnCl_2$ in either diethyl ether or dichloromethane)

Physical Data: density depends on solvent composition; see Table 1.

Solubility: sol a variety of inert solvents.

Form Supplied in: 2.2 M solution in dichloromethane.

Preparative Methods: ***Zinc Chloride*** (20.0 g, 0.147 mol) is dissolved in dry diethyl ether with initial cooling (exothermic!) and shaking, which takes up to 12 h for the more concentrated solutions. These solutions (which are very viscous when less than 30 mL of ether are used) are diluted with CH_2Cl_2 to obtain the 1.47 M catalyst solutions shown in Table 1.

Table 1 Zinc Chloride Diethyl Ether Complex Solutions in Dichloromethane

Et_2O (ml)	CH_2Cl_2 (ml)	$[Et_2O]/[ZnCl_2]$	d (g cm^{-3})	Rel. activity[a]
17.0	76.3	1.12	1.33	1460
25.0	69.3	1.64	1.30	305
36.5	58.4	2.40	1.23	41
46.0	49.1	3.00	1.18	18
61.0	33.7	4.02	1.09	3
77.0	18.3	5.06	0.994	1

[a] Activity of solutions observed by dissolving 1 mL of these solutions in 15 mL of CH_2Cl_2. For details see Mayr and Striepe.[1]

Handling, Storage, and Precautions: the solutions described in Table 1 can be stored at ambient temperature for several months. Precipitation of $ZnCl_2$ takes place when solutions with a $[Et_2O]/[ZnCl_2]$ ratio <2 are diluted with CH_2Cl_2 at room temperature. Separation can be avoided by cooling the catalyst solution at -70 °C before addition of the extra solvent and the reactants. The reagent is relatively insensitive toward traces of moisture;[1] tentative addition of water causes a similar reduction in the catalytic activity as the same molar amount of ether.[1]

Catalytic Activity of Zinc Chloride Solutions.

Because of its low solubility in inert solvents (e.g. chlorinated hydrocarbons), zinc chloride acts as a weak Lewis acid catalyst for a variety of organic reactions.[2] It is highly soluble in ether and related solvents,[3] but the catalytic activity of such solutions is low because of coordinative saturation of the

catalytic sites. Highly active forms of $ZnCl_2$ can be obtained, however, when small amounts of ether are used to solubilize $ZnCl_2$ in inert solvents, and it has been shown that solutions of $ZnCl_2.Et_2O$ in dichloromethane possess a catalytic activity that is 10^3-10^4 times greater than that of the ether-free reagent. Dichloromethane solutions, in which the molar ratio $[Et_2O]/[ZnCl_2]$ exceeds 5-8, possess a lower catalytic activity than heterogeneous $ZnCl_2/CH_2Cl_2$ systems.

Alkylations and Related Reactions.

Zinc chloride etherate in dichloromethane has most frequently been used to catalyze additions of alkyl,[4] benzyl,[4,5] allyl[6] and propargyl chlorides[7] to alkenes and dienes (eqs 1-3). The major advantage of this catalyst system is that it works well for polymerization-sensitive compounds such as allylic chlorides or conjugated π-systems. The scope of these reactions has been discussed.[4]

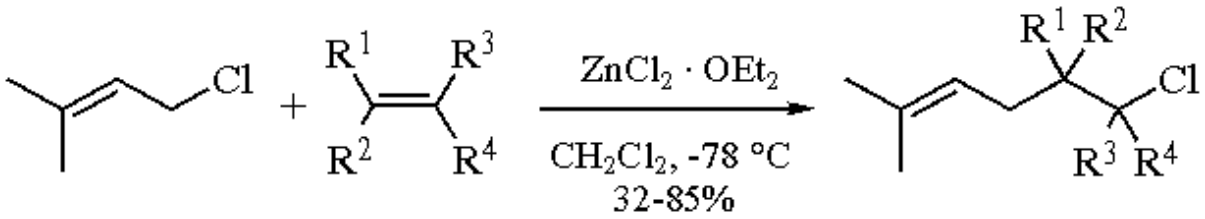

(1)

$R^1, R^2, R^3 = H$, alkyl; R^4 = alkyl

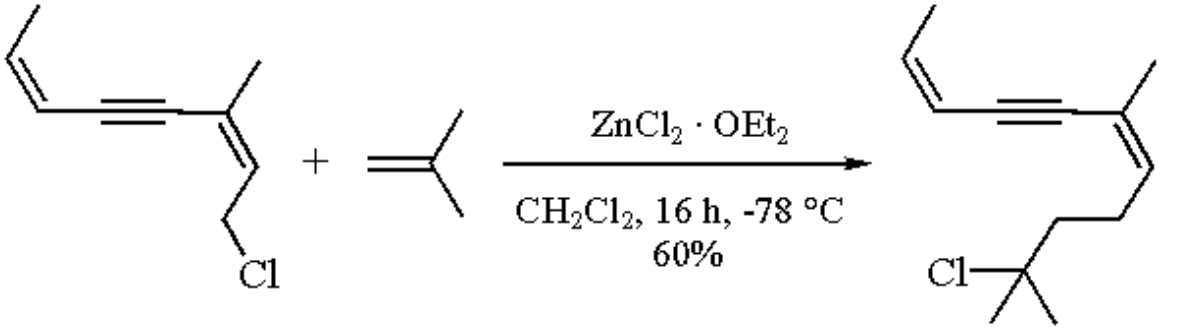

(2)

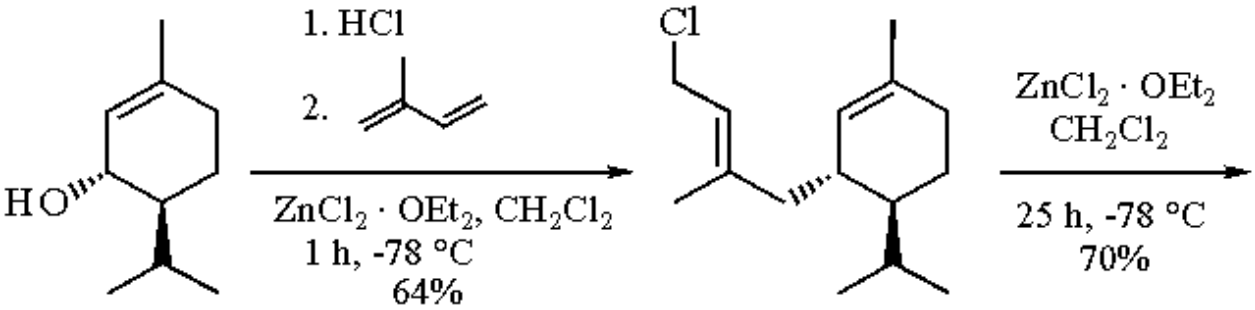

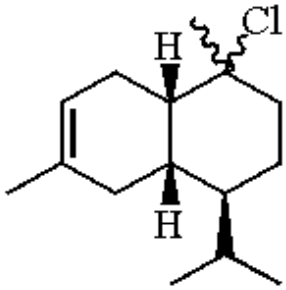

(3)

Carbocationic cycloadditions of allyl[6,8] and propargyl cations[9] with alkenes and dienes have been induced with this reagent (eqs 4 and 5).

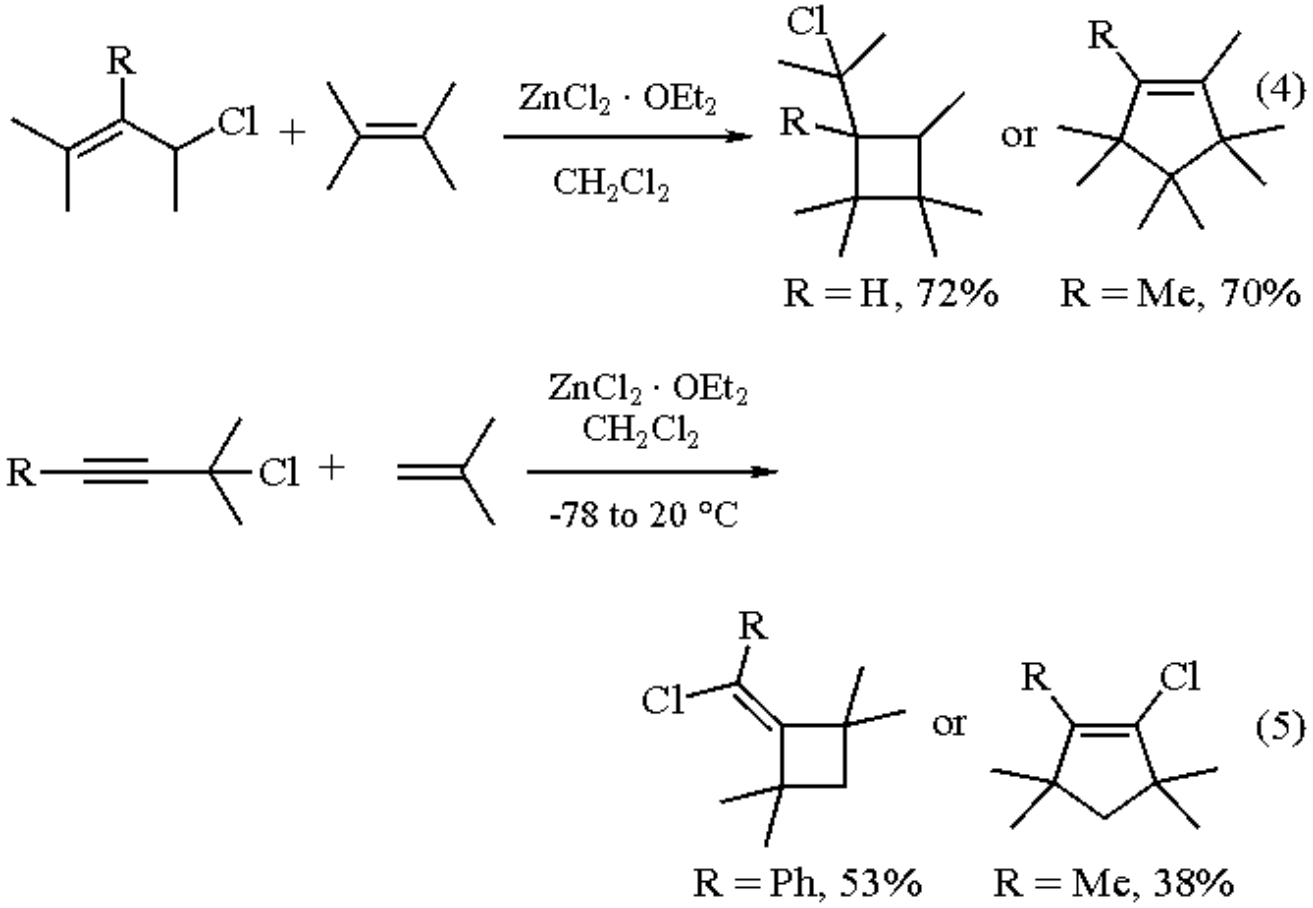

Acetylcyclopentadienes have been obtained by $ZnCl_2.OEt_2$-catalyzed reactions of allyl chlorides with 2,4-pentanedione (eq 6).[10]

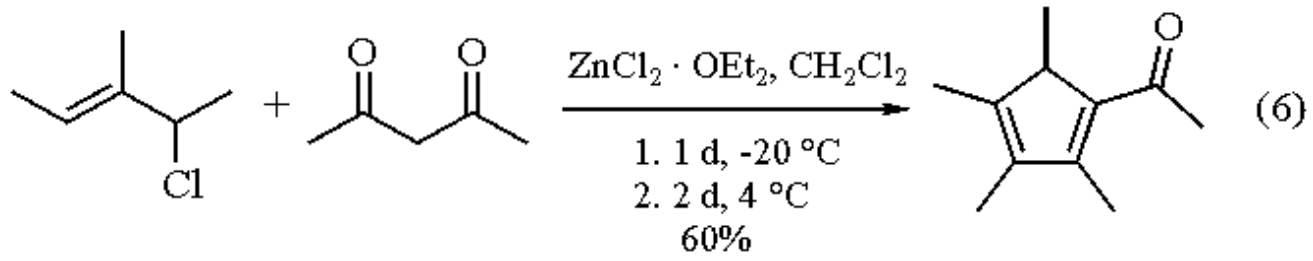

Alkoxyalkylations of allylsilanes with α-halogeno ethers and acetals have been reported.[11] In addition, $ZnCl_2.OEt_2/CH_2Cl_2$ is useful for *C*-glycosidations, as demonstrated by reaction of the *O*-benzyl protected glucopyranosyl trichloroacetimidate (**1**) with ***Furan*** to give the 2-glucosylfuran (**2**) (eq 7).[12] Similar results have been reported for related heteroarenes.[12]

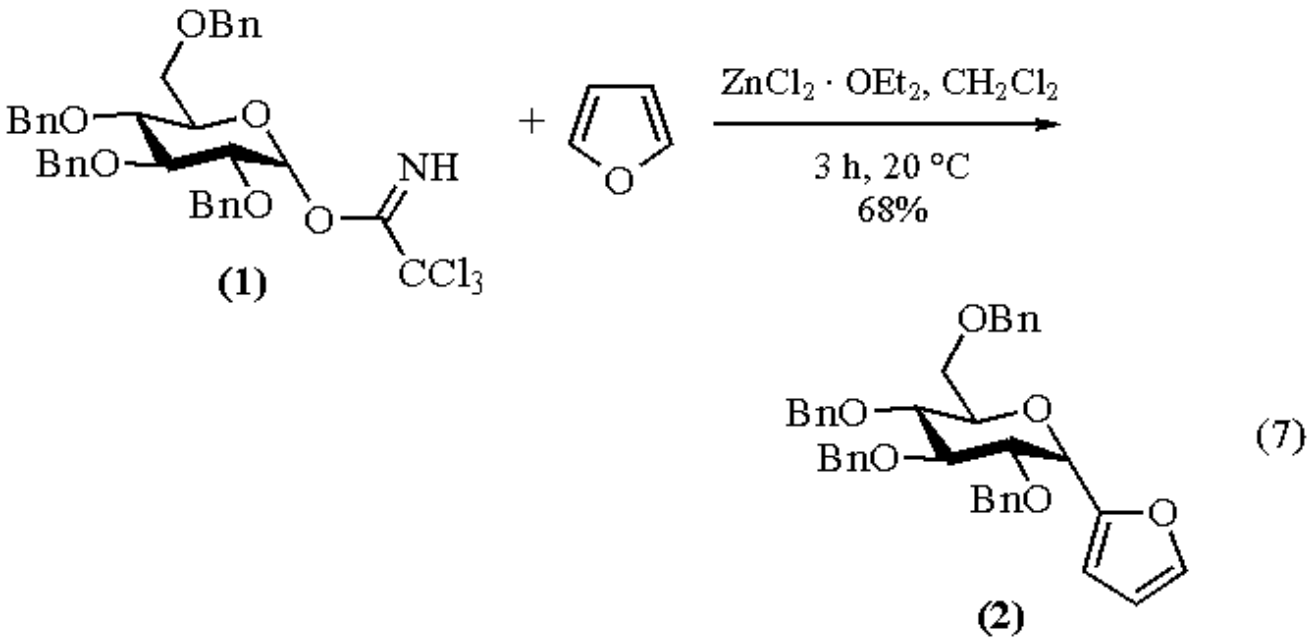

Zinc chloride etherate in 1,2-dichloroethane has been found to be superior to ***Tin(IV) Chloride*** in *O*-glycosidation reactions. While benzoate (**3**) and the sensitive enynol (**4**) gave the acetal (**5**) in 61% yield in presence of $ZnCl_2.OEt_2$ (eq 8), the corresponding reaction with $SnCl_4$ gave only 23% of the desired acetal.[13]

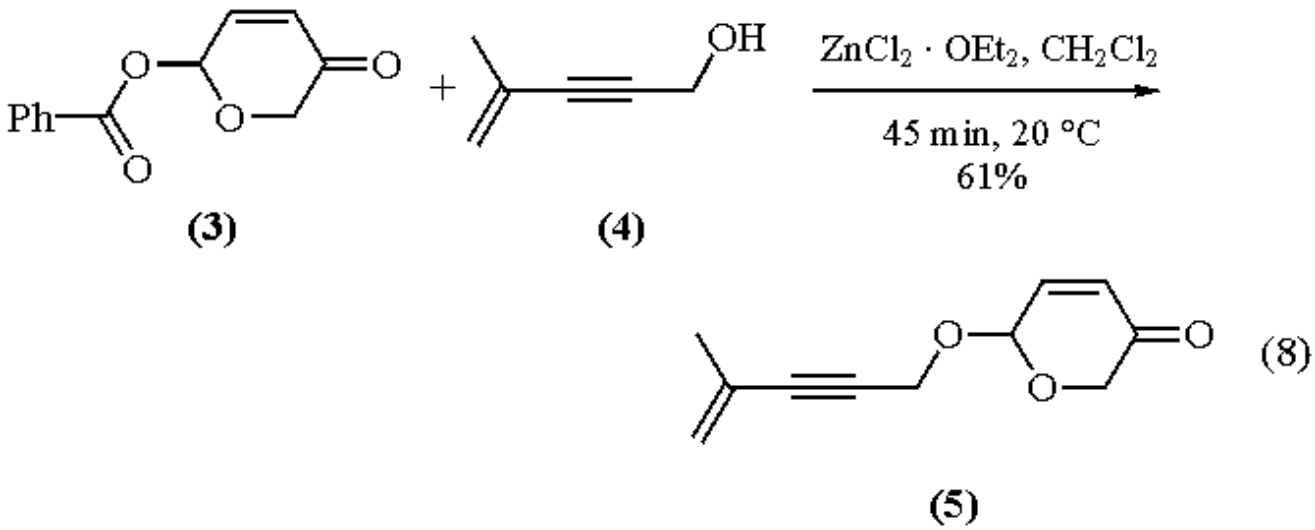

Dialkoxyalkylations of silyl enol ethers have been achieved with orthoesters in the presence of this catalyst (eqs 9 and 10).[14]

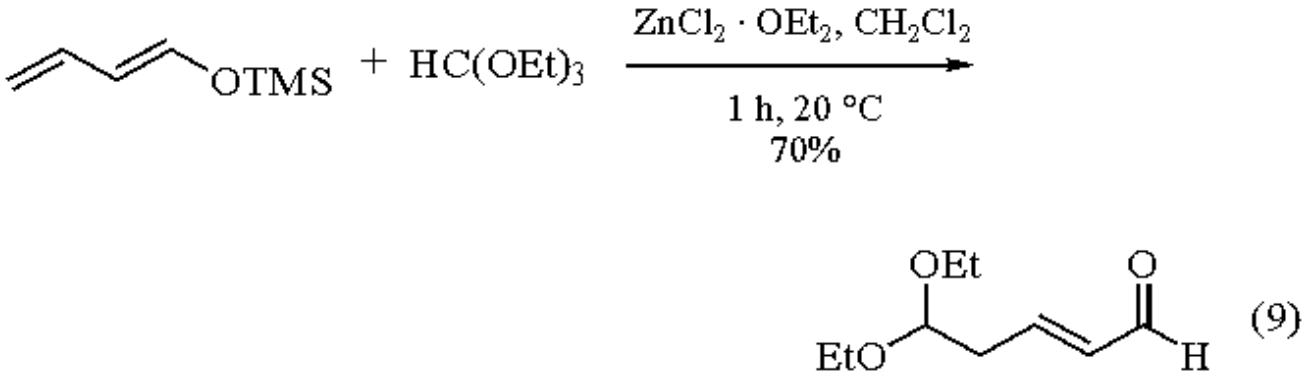

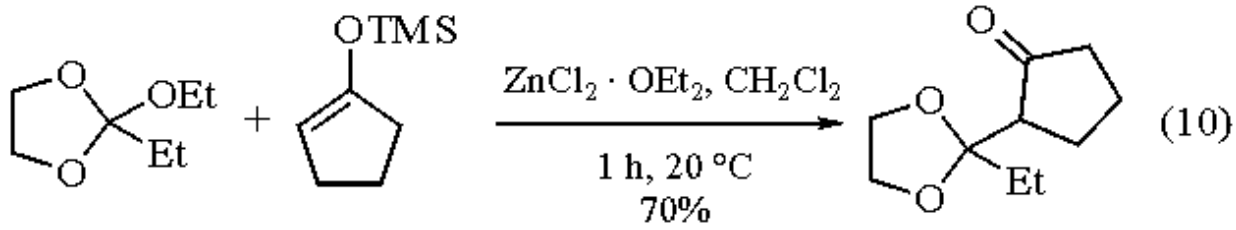

While the reactions of orthoformates with allylsilanes in presence of ***Titanium(IV) Chloride*** (>1 equiv) gave only bisallylic ethers, the corresponding reactions with catalytic amounts of $ZnCl_2.OEt_2/CH_2Cl_2$ gave homoallyl acetals selectively (eq 11).[15]

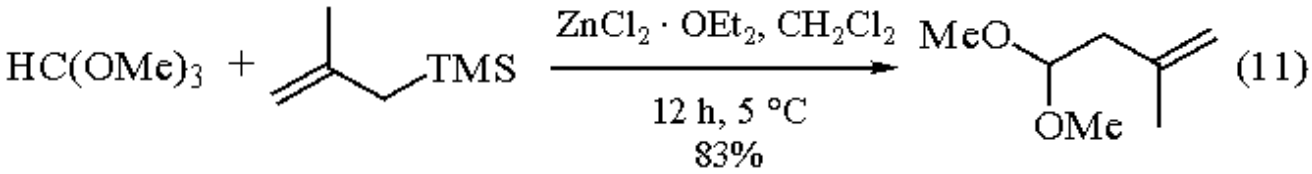

Acylations.

Acylations of silylated enol ethers and alkenes have also been reported (eq 12).[16]

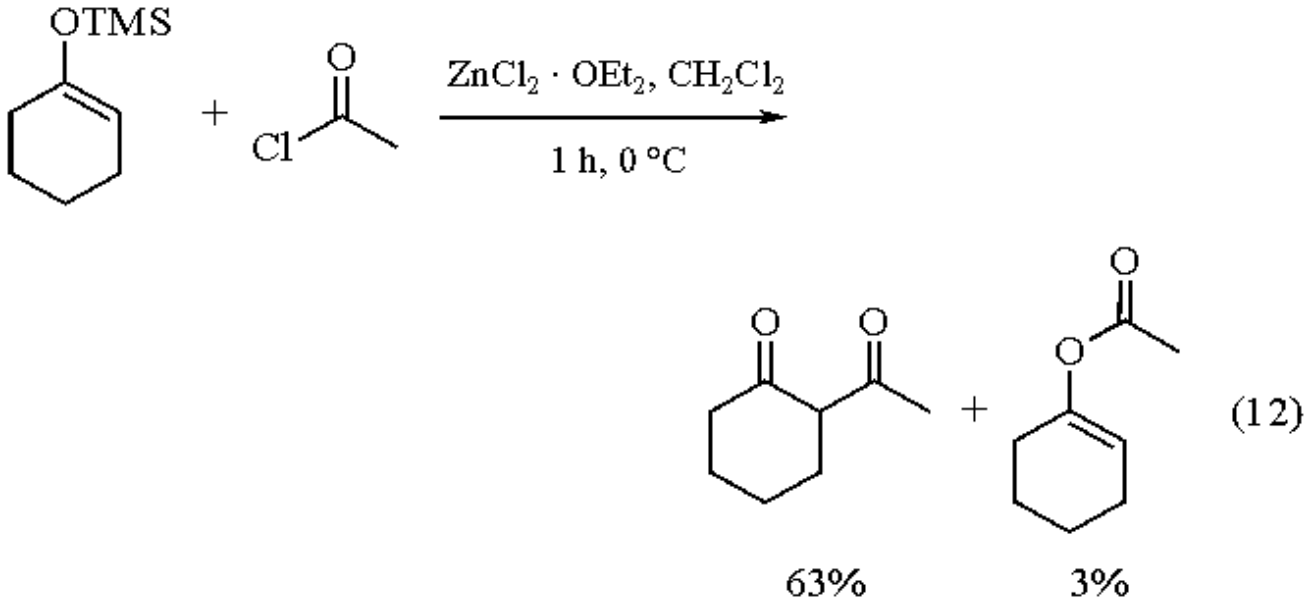

Diels-Alder Reaction.

The reaction of (**6**) with (**7**) with formation of the dihydropyran (**8**) took place exclusively with $ZnCl_2.OEt_2$ as the catalyst while the thermal reaction of (**6**) with (**7**) predominantly gave an ene product (eq 13).[17]

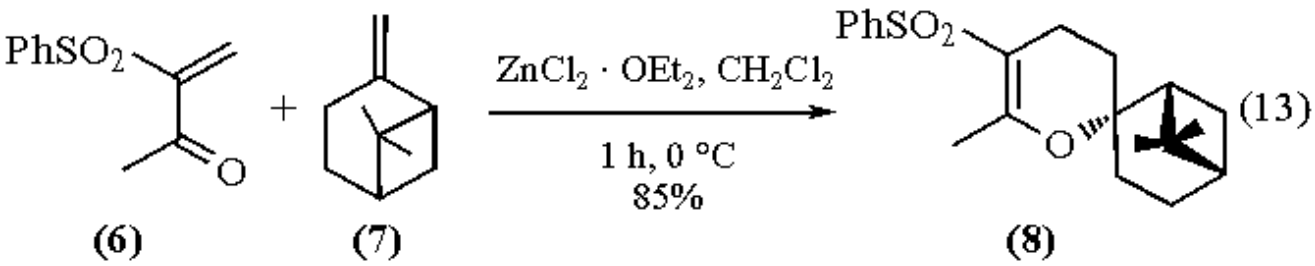

Ene Reaction.

Catalytic amounts of $ZnCl_2.OEt_2$ in CH_2Cl_2 provide a selective and simple preparative procedure to convert citronellal (**9**) in high yields into the isomers of isopulegol (**10**) (eq 14).[18]

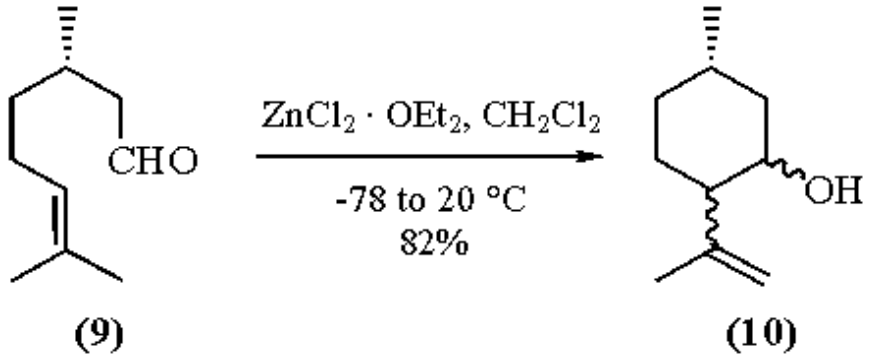

(14)

Ether Cleavage.

Attempted deprotection of 2-(trimethylsilyl)ethyl ether (**11**) with anhydrous ***Tetra-n-butylammonium Fluoride*** under various conditions resulted in complete decomposition. Treatment of (**11**) with zinc chloride etherate, however, afforded racemic terrein (*rac*-**12**) in almost quantitative yield (eq 15).[19]

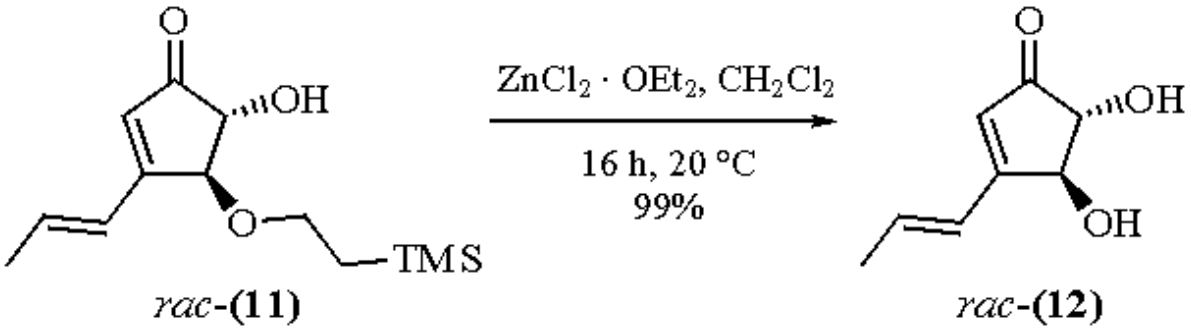

(15)

Related Reagents.

Titanium(IV) Chloride; ***Zinc Bromide***; ***Zinc Chloride***; ***Zinc Trifluoromethanesulfonate***.

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Zinc Complex Reducing Agents[1]

NaH-*t*-C_5H_{11}ONa-ZnX_2

(NaH)

[7646-69-7] · HNa · Zinc Complex Reducing Agents · (MW 24.00) (*t*-C_5H_{11}ONa)

[14593-46-8] · $C_5H_{11}NaO$ · Zinc Complex Reducing Agents · (MW 110.15) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Zinc Complex Reducing Agents · (MW 136.29) ($Zn(OAc)_2.2H_2O$)

[5970-45-6] · $C_4H_{10}O_6Zn$ · Zinc Complex Reducing Agents · (MW 219.53)

(zinc-containing complex reducing agents (ZnCRAs); reduces many functional groups[1])

Physical Data: light gray solid of uncertain structure containing Zn^0 species.[2]

Solubility: insol organic solvents.

Preparative Methods: *t*-C_5H_{11}ONa-ZnCRA (*x.y.z*) is conveniently prepared by the reaction of *t*-C_5H_{11}OH (*y* equiv) with a mixture of ***Sodium Hydride*** (*x* + *y* equiv) and ZnX_2 (X = Cl, OAc) (*z* equiv) in THF or DME. Commercial NaH (55-60% in oil) is used after three washings with anhydrous THF or DME under N_2. *t*-C_5H_{11}OH is distilled from sodium. ZnX_2 is dried in vacuo (15 mmHg) for 16 h at 100-110 °C.

Handling, Storage, and Precautions: ZnCRAs are nonpyrophoric but are handled and stored under inert atmosphere (N_2 or, better, Ar). Hydrolysis must be performed by slow addition of cold water or EtOH to destroy the reagent.

Designation.

t-C_5H_{11}ONa-ZnCRA (*x.y.z*) means a reagent obtained from *x*, *y*, and *z* equivalents of NaH, *t*-C_5H_{11}ONa, and ZnX_2 (X = Cl, OAc), respectively.

Reduction of Organic Halides.

t-C_5H_{11}ONa-ZnCRAs are very mild and thus selective reducing agents. They are appreciably less basic than NaH and *t*-C_5H_{11}ONa.

t-C_5H_{11}ONa-ZnCRA (4.2.1) reduces alkyl halides in THF or DME (primary >> secondary >>> tertiary and I > Br >> Cl). Moreover, benzyl halides are easily reduced while vinyl halides are unreactive. Thus selective reductions may be easily performed, as exemplified in eqs 1 and 2.[3]

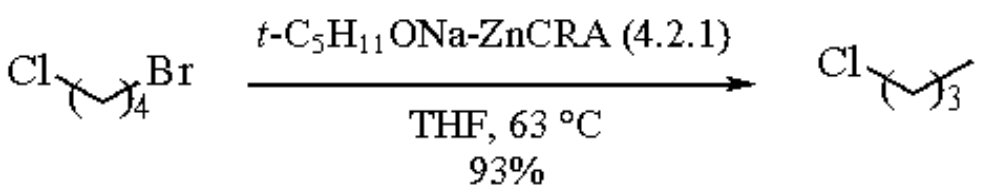

(1)

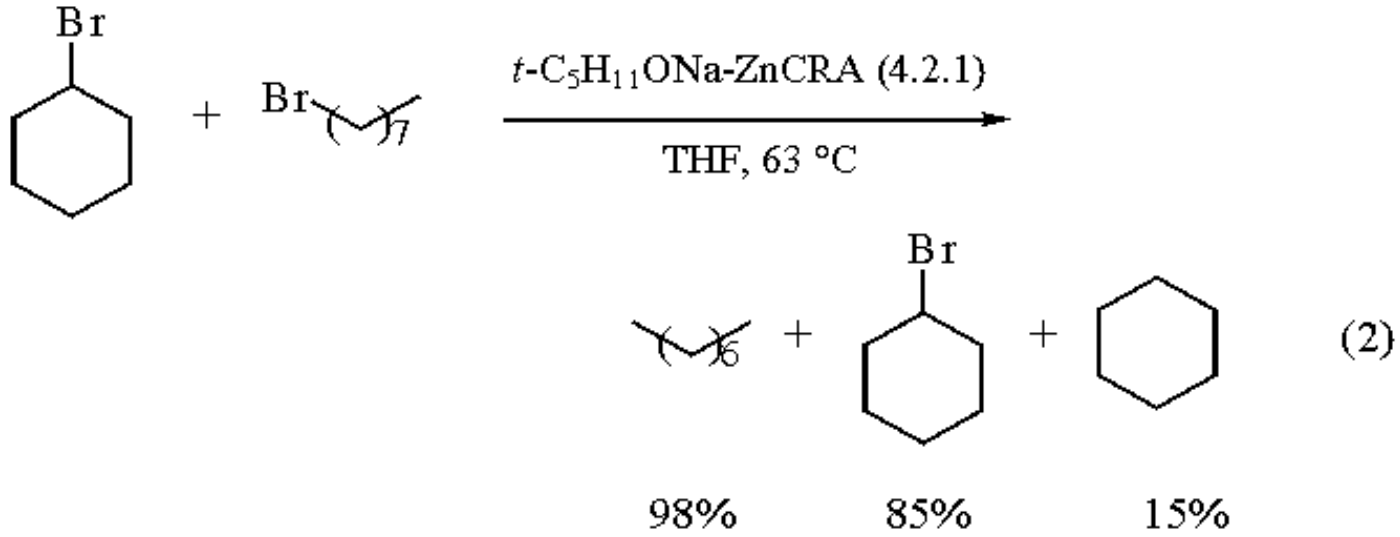

(2)

Ketones and nitriles are tolerated during the reduction of reactive halides (eqs 3 and 4).[3]

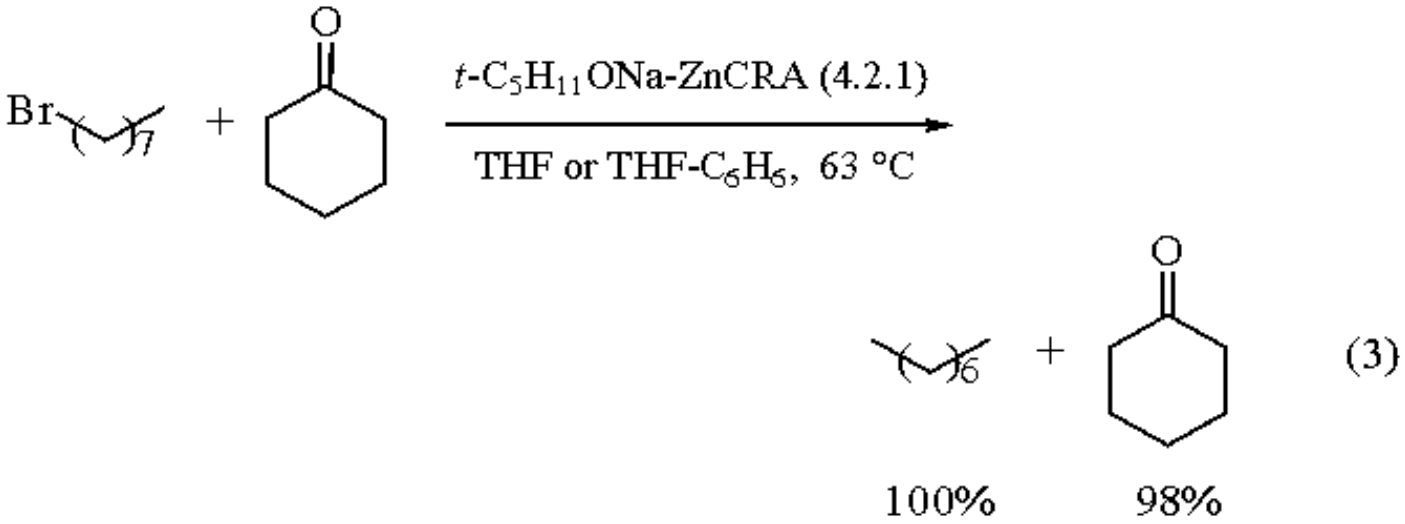

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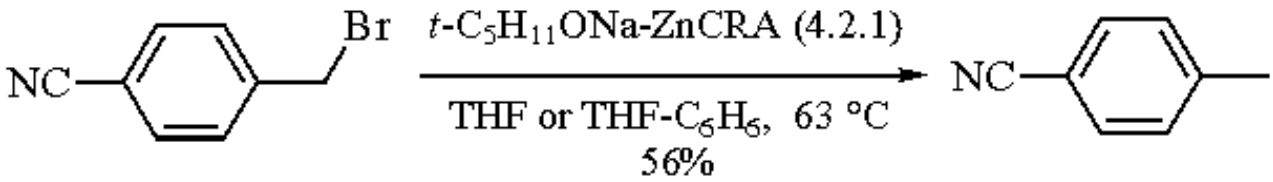

(4)

Reduction of Ketones.

t-C_5H_{11}ONa-ZnCRA (4.1.1) alone or, better, in the presence of ***Magnesium Bromide*** (electrophilic assistance), easily reduces saturated ketones under mild conditions and in very good yields.[4,5] Although able to reduce hindered ketones, the reagent is sensitive to steric hindrance, leading to stereoselective reductions (eqs 5 and 6).[5]

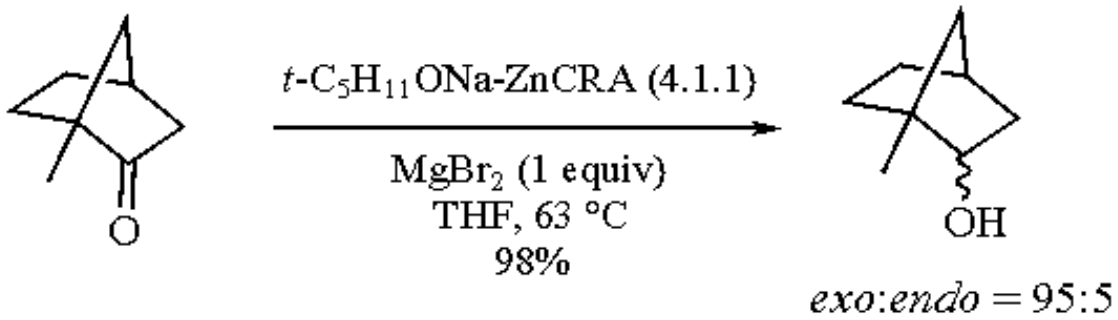

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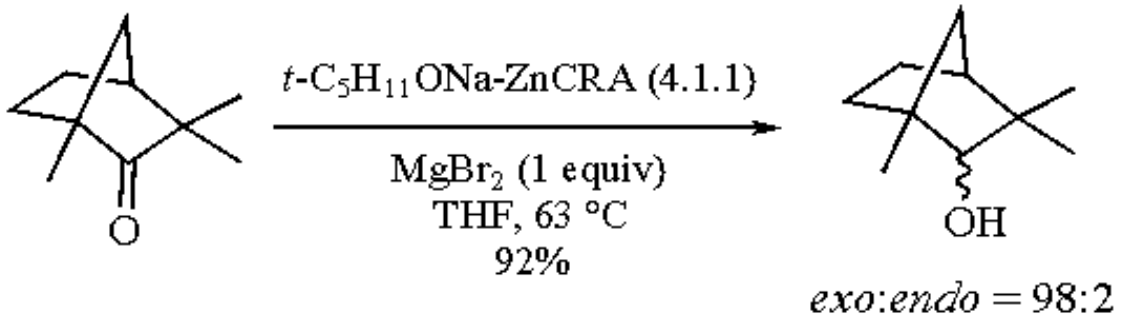

(6)

t-C_5H_{11}ONa-ZnCRA (4.1.1) does not reduce carbon-carbon double bonds and is well suited for the selective reduction of α,β-unsaturated ketones to the corresponding allylic alcohols.[6]

Efficiency and chemoselectivity of *t*-C_5H_{11}ONa-ZnCRA may be considerably improved by addition of ***Chlorotrimethylsilane*** (ZnCRASi).[7] Thus ketones as well as highly enolizable aldehydes are very rapidly reduced in excellent yields (eqs 7 and 8). The stereoselectivity of ZnCRASi broadly resembles one ZnCRA.[5] *t*-C_5H_{11}ONa-ZnCRASi is highly chemoselective in the reduction of the carbonyl groups of ketones and aldehydes in the presence of carbon-carbon double bonds (eqs 9 and 10).

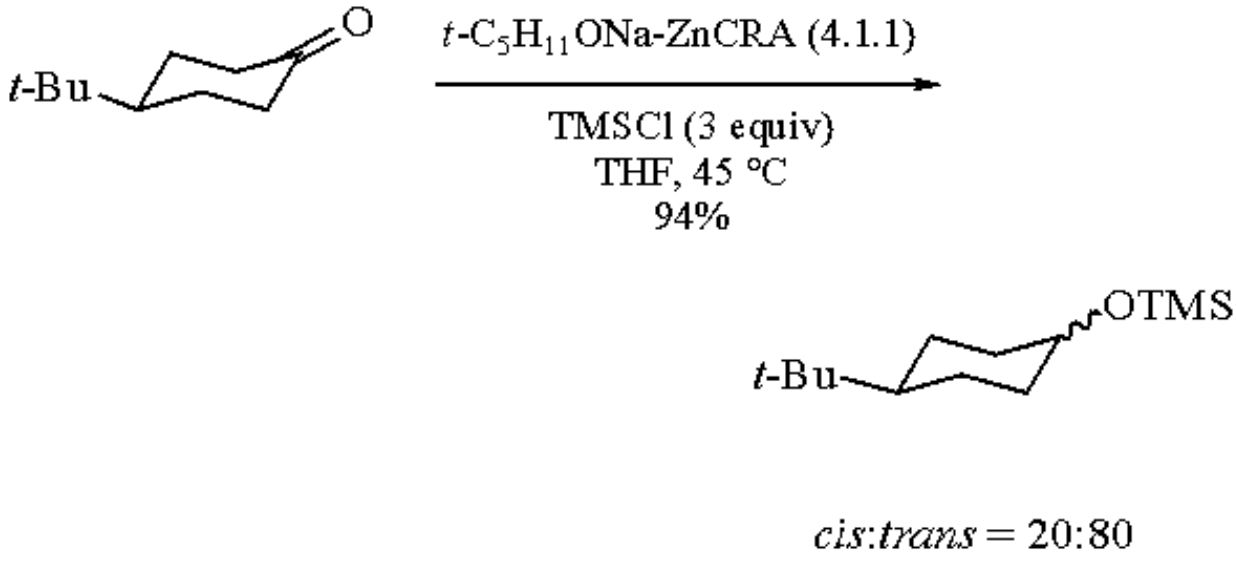

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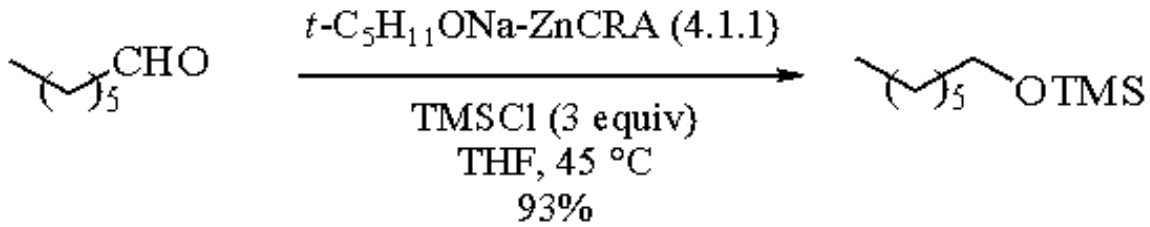

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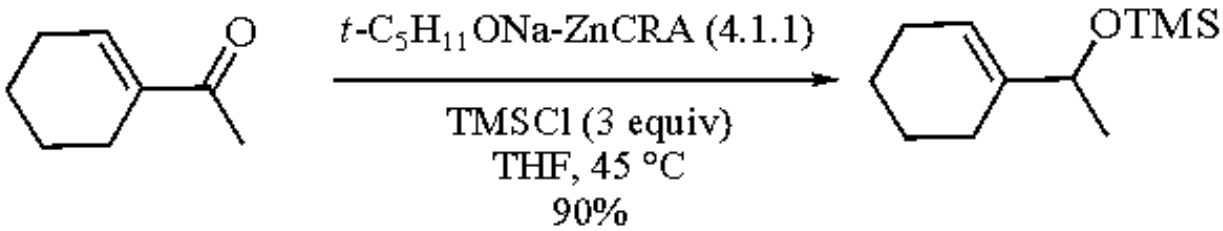

(9)

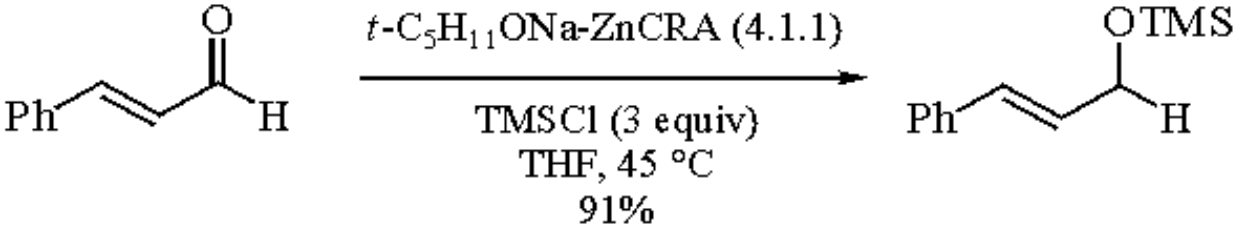

(10)

Finally, excellent chemoselectivity was also found during the reduction of aldehydes and ketones in the presence of halides, acetals, and nitro aromatic derivatives, as illustrated in eqs 11 and 12.[8]

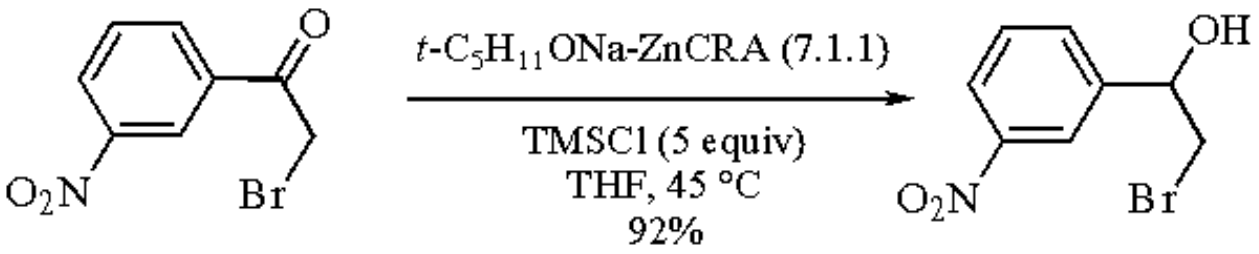

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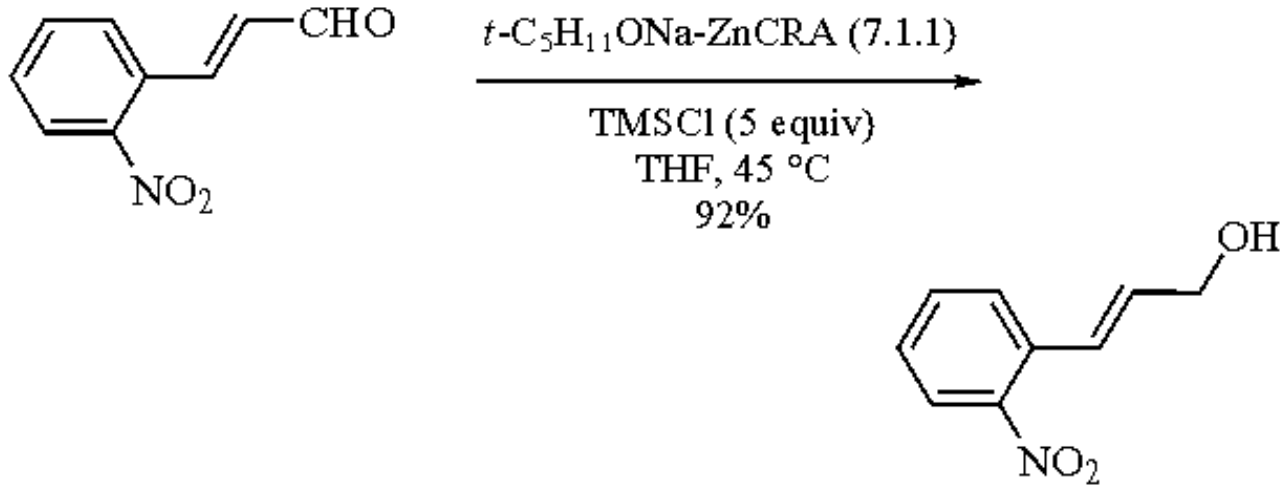

(12)

ZnCRAs and especially ZnCRASis are more efficient and chemoselective than NiCRAs (see ***Nickel Complex Reducing Agents***) in the reduction of ketones and aldehydes.

Reduction of Epoxides.

t-C_5H_{11}ONa-ZnCRA (4.2.1) reduces epoxides regioselectively at the less substituted carbon atom (eq 13).[9]

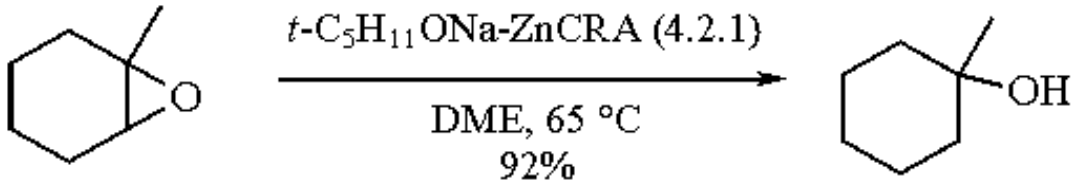

(13)

With less reactive epoxides, the constitution of the reagent must be changed and a (8.2.1) ratio of the constituents is necessary.[9] The regioselectivity is not changed under such conditions (eq 14). Interestingly, the regioselectivity of these reductions is opposite to that observed with NiCRAs.

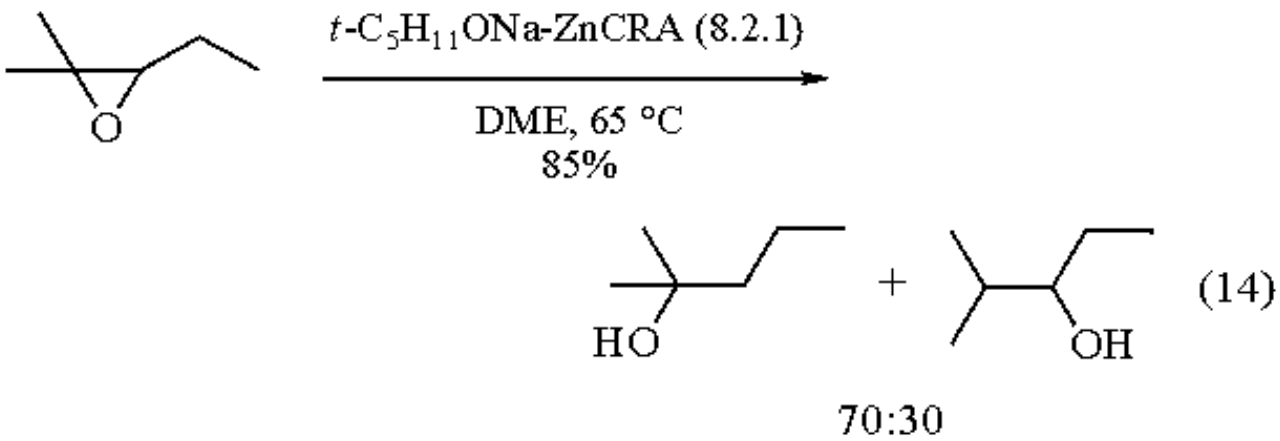

(14)

Reduction of Aromatic Nitro Compounds.

In the presence of $MgBr_2$, t-$C_5H_{11}ONa$-ZnCRA (7.1.1) selectively reduces a number of aromatic nitro compounds to their azoxy derivatives in good to excellent yields (eqs 15 and 16).[10] A few percent of azo derivatives are sometimes also produced. Note that under such conditions NiCRAs lead to the corresponding anilines.

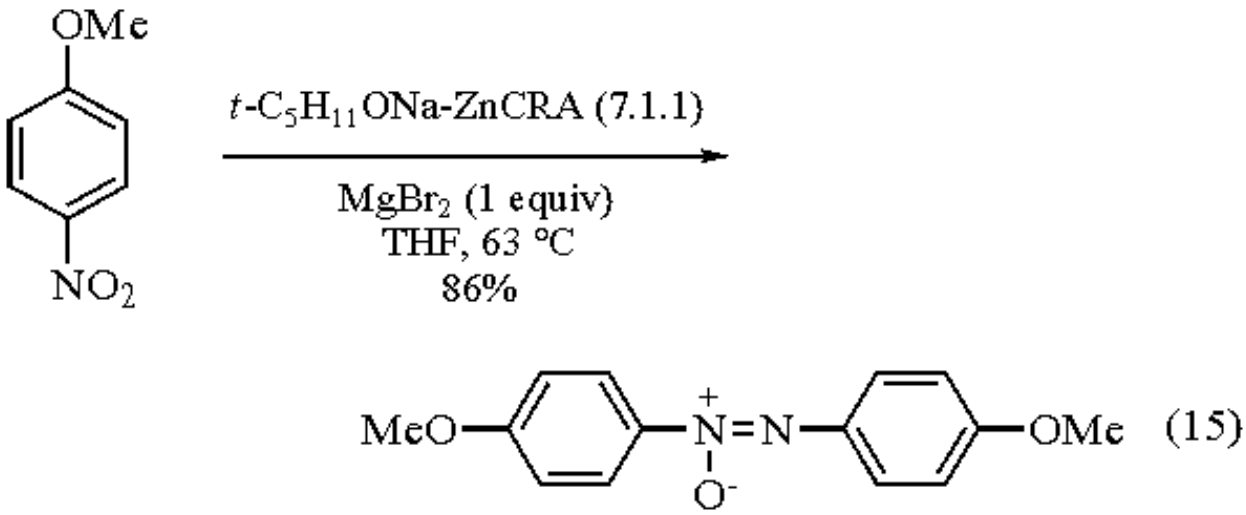

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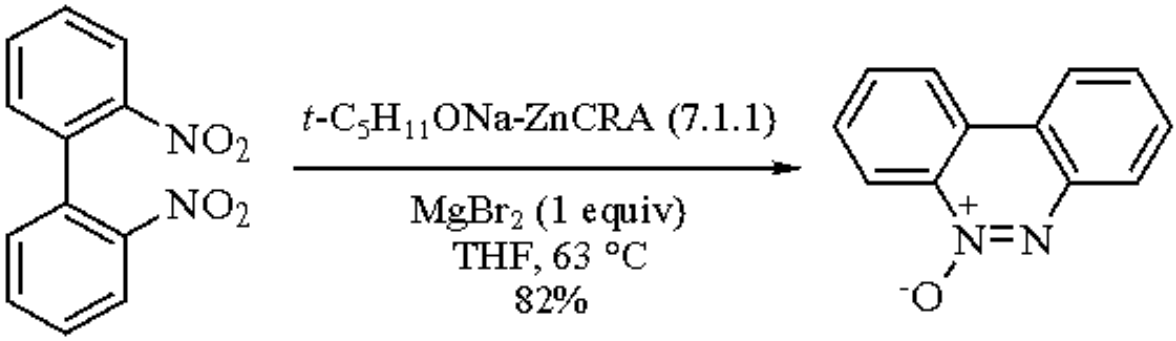

(16)

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Zinc-Copper(II) Acetate-Silver Nitrate

Zn(Cu/Ag)

(Zn)

[7440-66-6] · Zn · Zinc-Copper(II) Acetate-Silver Nitrate · (MW 65.39) ($AgNO_3$)

[7761-88-8] · $AgNO_3$ · Zinc-Copper(II) Acetate-Silver Nitrate · (MW 169.88) ($Cu(OAc)_2.H_2O$)

[6046-93-1] · $C_4H_8CuO_5$ · Zinc-Copper(II) Acetate-Silver Nitrate · (MW 199.67)

(reagent for selective reduction of activated or conjugated triple bonds to (*Z*)-alkenes;[1,2] compatible with many functional groups)

Physical Data: see ***Zinc***, ***Copper(II) Acetate***, and ***Silver(I) Nitrate***.

Solubility: insol organic solvents and water; reacts with dilute acids and bases.

Preparative Method: argon is passed for ca. 15 min through a well stirred suspension of commercial zinc dust (5.0 g, ca. <60 µm; >230 mesh ASTM) in water (30 mL). $Cu(OAc)_2.H_2O$ (0.5 g) is added and after 15 min $AgNO_3$ (0.5 g) is introduced (exothermic reaction). The mixture is stirred for 30 min, and the activated metal is collected by suction filtration under argon. The dark solid is washed with water (2 × 30 mL), MeOH (2 × 30 mL), acetone (2 × 30 mL), and Et_2O (2 × 30 mL). The Et_2O-moist Zn dust is transferred into 20 mL $MeOH/H_2O$ (1:1, v/v) and is ready for use.

Handling, Storage, and Precautions: the reagent has to be freshly prepared prior to use. The activated metal may be briefly stored covered with solvent (e.g. $MeOH/H_2O$; 1/1, v/v) in the absence of oxygen. The dry reagent is pyrophoric!

Reduction of Triple Bonds.

Zinc metal, previously activated by successive treatment with $Cu(OAc)_2$ (10%) and $AgNO_3$ (10%), reduces conjugated or activated triple bonds stereospecifically to (*Z*)-alkenes.[1,2] Best results are obtained in a polar protic solvent like $MeOH/H_2O$ (1:1, v/v) under neutral conditions. The conditions are exceptionally mild and most reductions can be conducted at 25 °C using an excess of activated metal (ca. 1:10 -> 100). As a consequence, even a thermolabile, acid- and base-sensitive tetraene like the naturally occurring 2*Z*,4*Z*,6*E*,8*Z*-undecatetraene (eq 1) can be prepared without competing isomerization and polymerization. Unlike Lindlar's catalyst (see ***Palladium on Calcium Carbonate (Lead Poisoned)***), Zn(Cu/Ag) does not reduce simple, nonactivated alkynes. However, nonconjugated propargylic alcohols are readily reduced at 25 °C.

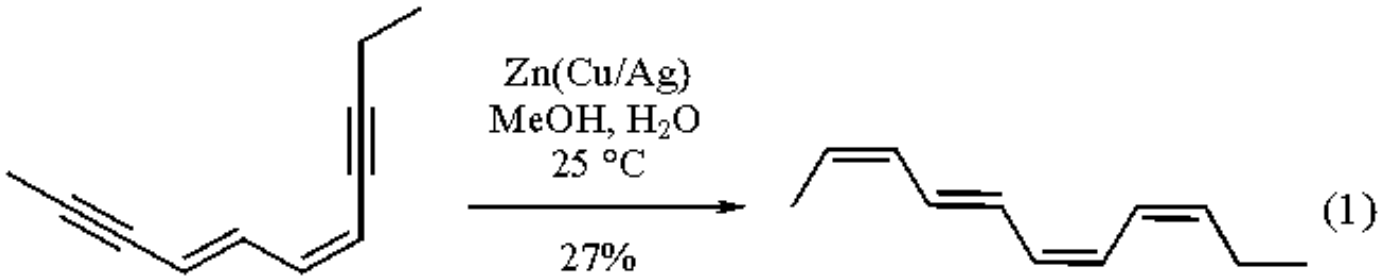

The reduction of (*Z*)-enynes is effected at 25 °C, but temperatures of 40-50 °C are necessary for simple (*E*)-enynes. The reduction of highly unsaturated dienediynes (eqs 1 and 2) proceeds at 25 °C independent of the enyne stereochemistry.[1] Overreduced products are usually not observed. Both α- and β-branched enynes react sluggishly at elevated temperatures (40-50 °C; eq 3).[3]

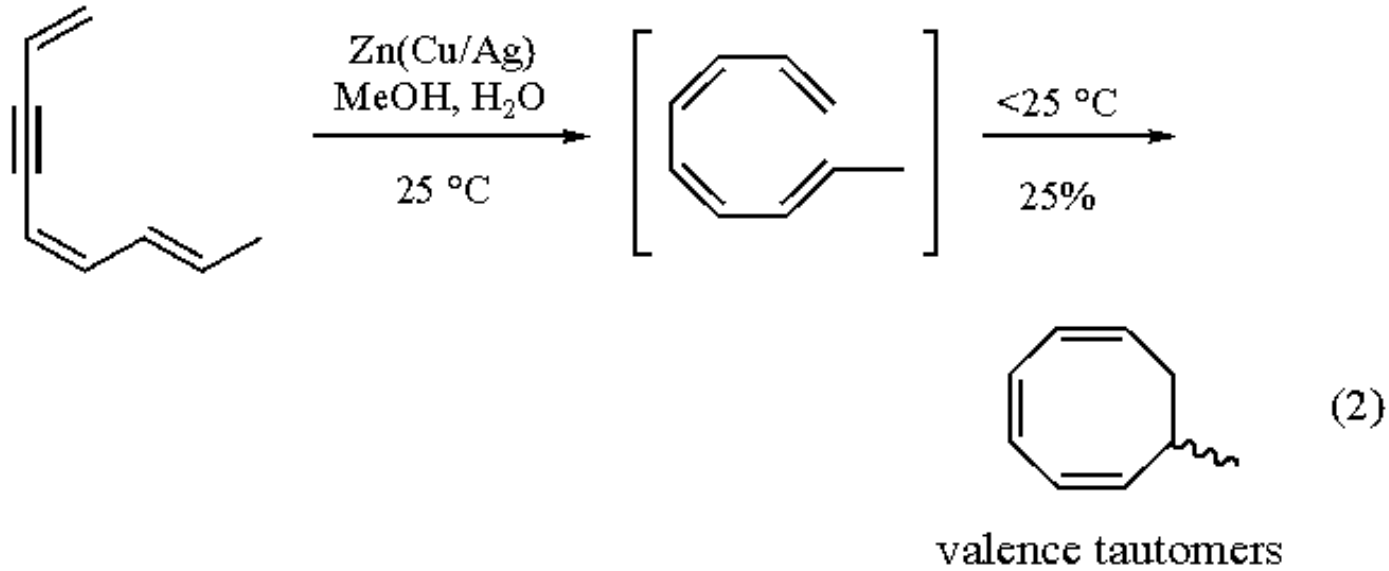

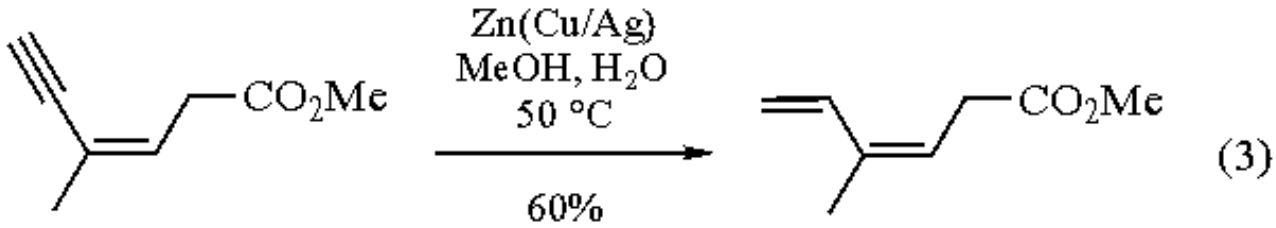

The stereospecific reduction of conjugated enynes to (*Z*)-alkenes is ideally suited for the synthesis of leukotriene B_4 (eq 4)[4,5] and other fatty acid-derived polyenoic metabolites like (5*S*,12*S*)-DiHETE,[6] (12*R*)- or (12*S*)-HETE,[7] and (13*S*)-HODE.[8] Hydrogenolytic fission of allylic alcohols, ethers, and esters does not occur.[9,10] Reactive halides may be incompatible with the reagent. Ketones and esters are tolerated; however, aldehydes are reduced to alcohols. In general, Zn(Cu/Ag) exhibits a somewhat higher reactivity, but similar selectivity, to Rieke zinc metal which can be used for analogous reductions of propargylic alcohols at 65 °C in polar protic solvents.[11] Introduction of deuterium atoms is possible using deuterated solvents ($MeOD/D_2O$) and Zn(Cu/Ag), but complete deuteration is difficult to achieve. A recently disclosed stereoselective synthesis of conjugated (*E*)-trienes from 1.6-dibenzoate-2,4-dienes utilizes Zn(Cu/Ag) for the generation of the dienediol intermediates from readily available diynoic precursors (eq 5).[12] The sequence has been extended to LTB_4.[10]

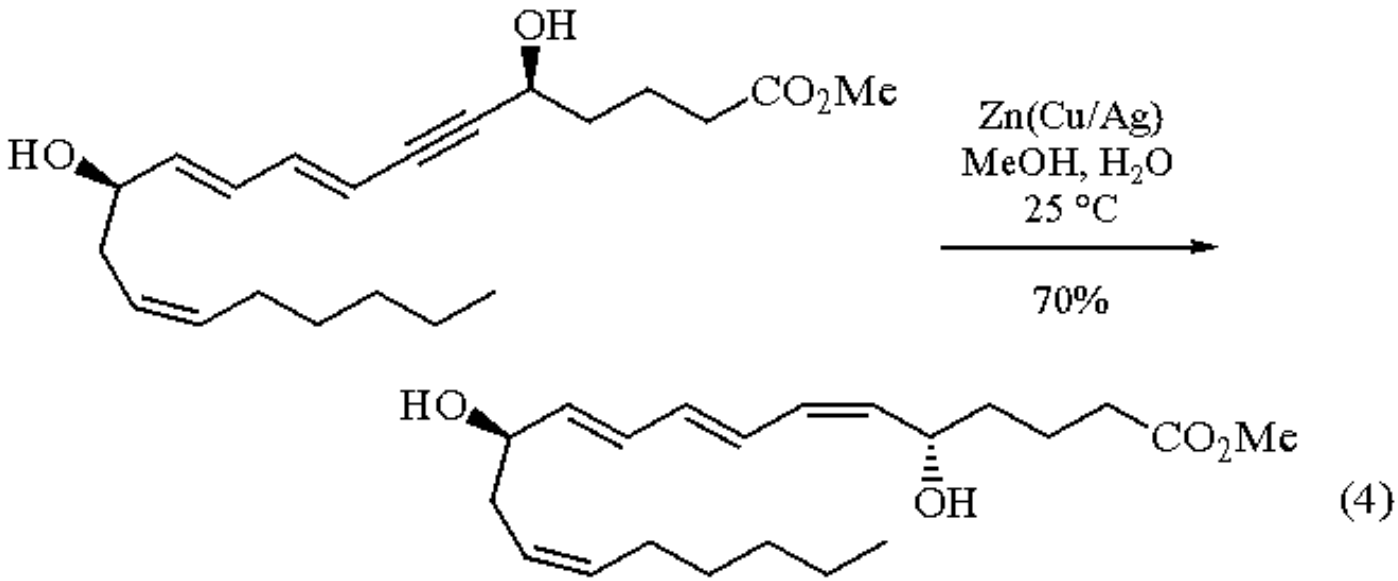

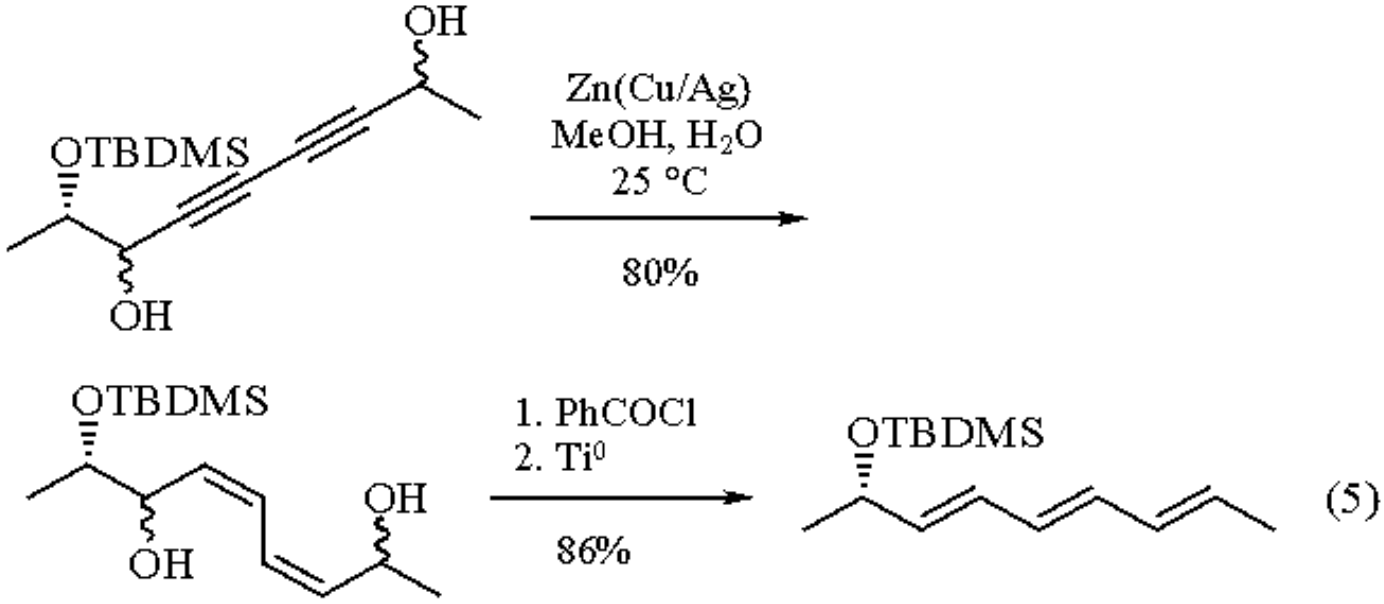

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Zinc-Copper(I) Chloride

Zn-CuCl

(Zn)

[7440-66-6] · Zn · Zinc-Copper(I) Chloride · (MW 65.39) (CuCl)

[7758-89-6] · ClCu · Zinc-Copper(I) Chloride · (MW 99.00)

(forms zinc-copper couple;[1] thence capable of initiating Reformatsky[2] and related reactions, and Simmons-Smith methylenation[3])

Physical Data: see ***Copper(I) Chloride*** and ***Zinc***

Zinc-Copper Couple.[1]

A typical procedure involves mixture of zinc, usually activated,[4] and a catalytic amount of CuCl, often 10 mol %, before introduction of the organic halide appropriate for subsequent reaction. Enhancement of the procedure can be effected by the use of ultrasound,[5] substitution of ***Silver(I) Acetate***[2c,6] for CuCl, or, in certain cases, incorporation of ***Chlorotrimethylsilane***.[7]

Reformatsky Reactions.[2]

The multiply halogenated ester (**1**) reacts with aldehydes in the presence of Zn/CuCl, 4Å molecular sieve (MS), and ***Acetic Anhydride*** to give unsaturated esters (**2**) (eq 1).[2a] The double bonds are predominantly or exclusively in the (*Z*) configuration. Omission of Ac_2O from the reaction leads to lower yields of (**2**) and substantial amounts of β-hydroxycarboxylate. Ketones react poorly in this procedure (20%). Similar reactivity has been demonstrated with the ester $CF_3CCl_2CO_2Me$,[2b] giving α-trifluoromethyl-α,β-unsaturated esters. The α-halo ketones (**3**) react similarly (eq 2),[2c,2d] but only with aldehydes; ketones react only if CuCl is replaced by AgOAc and ***Diethylaluminum Chloride*** is also required.

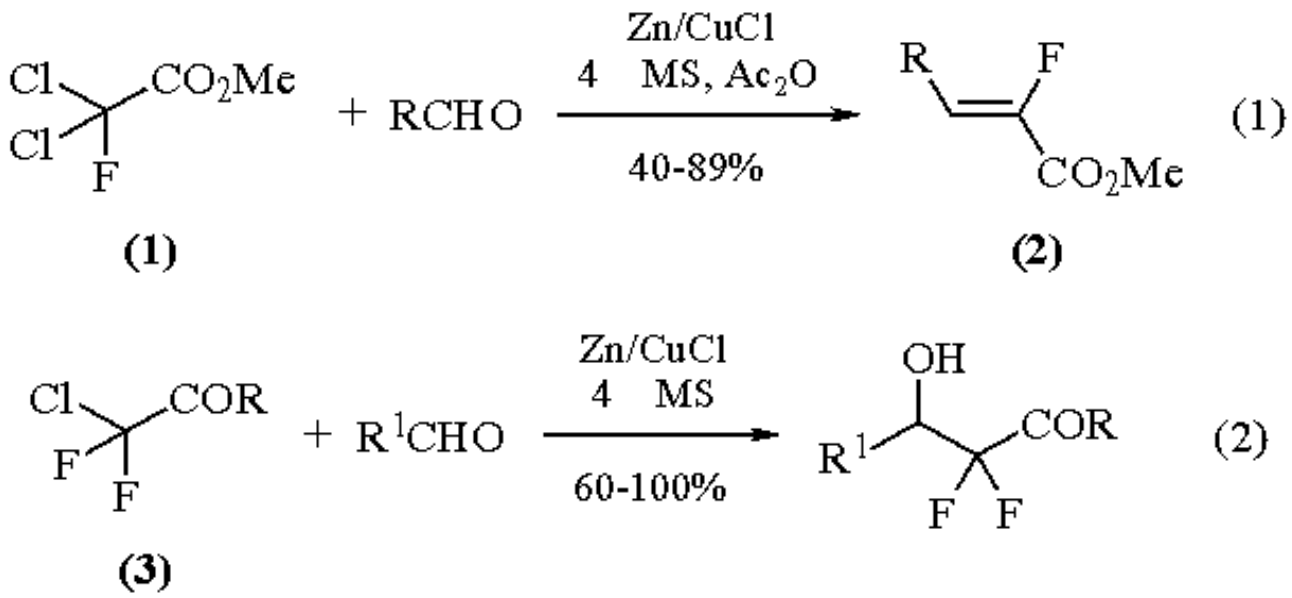

Reformatsky-Type Reaction of an Allylic Halide.[2e]

The allylic trihalide (**4**) undergoes exactly analogous reactions with both aldehydes and ketones, although the latter react more sluggishly,

and usually in lower yield (eq 3). In some cases, AgOAc is still preferred to CuCl, but the reagents seem more equivalent in this case than in those cited above. Reactivity at the α-position of the allylzinc reagent is noteworthy, since γ-alkylation of carbonyls is more usual.[8]

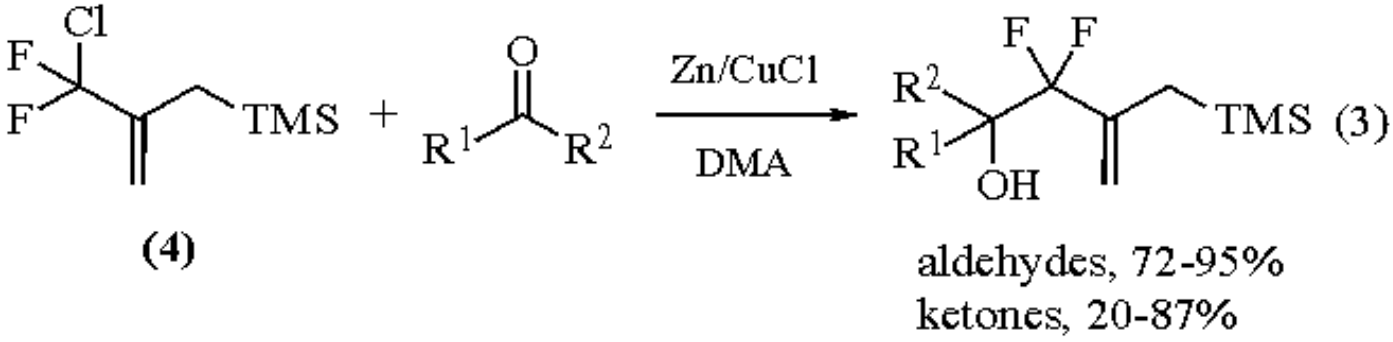

α,α´-Dibromo Ketone Cycloaddition.[5,7,9]

Zn/CuCl can cause a cycloaddition reaction between an α,α´-dibromo ketone and a suitable diene, as in eq 4, leading to seven-membered rings. A similar reaction, but superior in terms of yield, uses ***Nonacarbonyldiiron***,[10] but this reagent is appreciably more toxic and expensive. The Zn/CuCl reaction is substantially improved by addition of Me_3SiCl[7] or, even better, ultrasonication.[5]

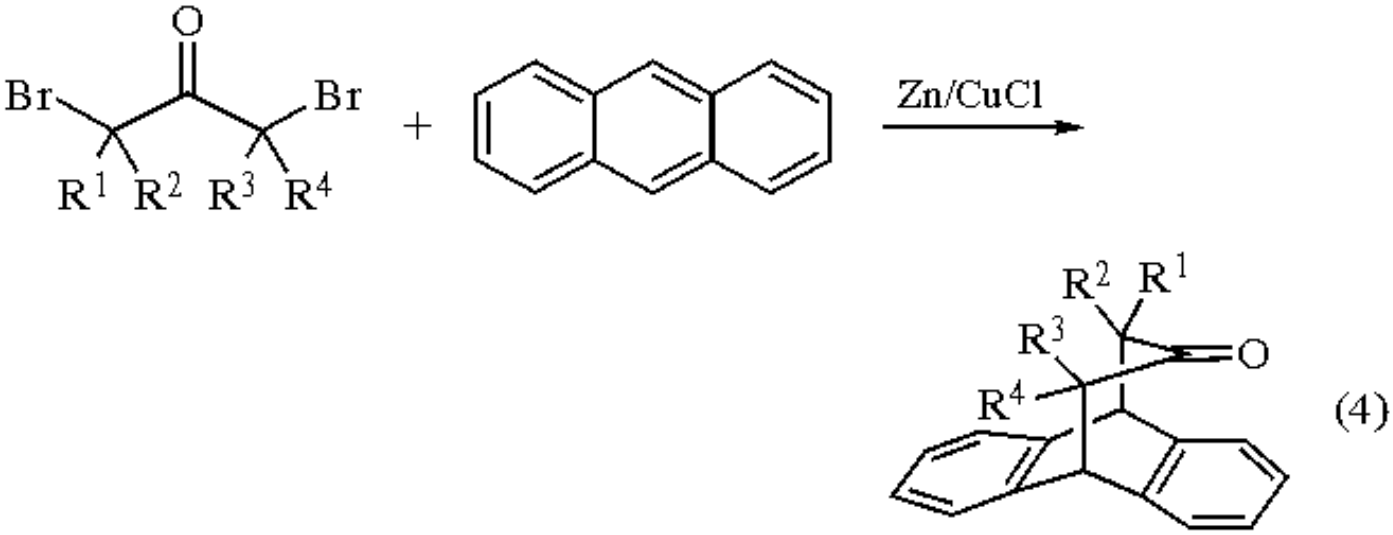

Alkene Acylation.[11]

Acylation of alkenes by acyl chlorides (eq 5) is promoted by zinc activated by any of a number of reagents, the best of which appears to be Zn/CuCl and ***Diiodomethane***. Although this normally gives rise to the so-called Simmons-Smith reagent (see below),[3] no trace of alkene methylenation is observed under these conditions. Other catalysts such as ***Aluminum Chloride***, ***Zinc Iodide***, or ***Zinc Chloride*** may also effect the reaction in certain cases, but with inferior yields.

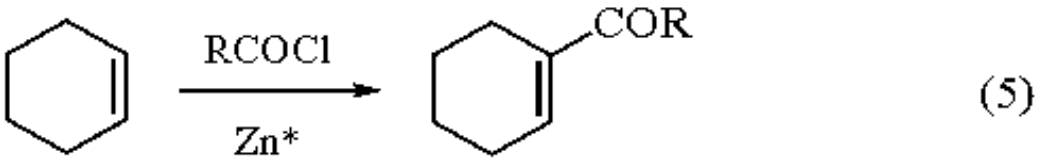

Simmons-Smith Reaction.[3]

This reaction, as demonstrated originally for cyclohexene (eq 6), is treated at length elsewhere (see ***Zinc/Copper Couple*** and ***Diiodomethane***).

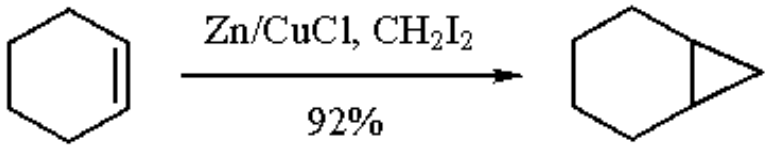

(6)

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Zinc/Copper Couple[1]

Zn(Cu)

[12019-27-1] · Zn · Zinc/Copper Couple · (MW 65.39)

(an activated form of zinc metal that can be used for cyclopropanation;[1] conjugate addition of alkyl iodides to enones;[2] preparation of dichloroketene;[3] preparation of 2-oxyallyl cations for cycloaddition reactions[4])

Physical Data: see ***Zinc***.

Solubility: insol organic solvents and H_2O.

Form Supplied in: reddish-brown or dark gray powder; often prepared directly before use.

Preparative Methods: although zinc-copper couple is commercially available, freshly prepared reagents are often more active. Of the many preparations described in the literature,[1] LeGoff's is both simple and results in a very active zinc-copper couple.[5] Zinc dust (35 g) was added to a rapidly stirred solution of 2.0 g $Cu(OAc)_2.H_2O$ (see ***Copper(II) Acetate***) in 50 mL of hot acetic acid. After 30 s the couple was allowed to settle, decanted, and washed once with acetic acid and three times with ether. A less reactive couple can be prepared from granular zinc using the same procedure. Modified procedures for preparing zinc-copper couples are given in many of the references.

Handling, Storage, and Precautions: zinc-copper couple deteriorates in moist air and should be stored under nitrogen. Very active zinc-copper couple is oxygen sensitive. It evolves hydrogen on contact with strong aqueous acids.

Introduction.

Zinc-copper couple is an active form of zinc metal, and for many reactions the presence of copper does not appear to exert any special influence beyond activating the surface of the zinc. Many of the reactions of zinc-copper couple could probably be effected using zinc metal activated in situ with ***Chlorotrimethylsilane*** or ***1,2-Dibromoethane***,[6] but the advantage of zinc-copper couple is that it is a storable form of activated zinc that is easily prepared and handled.

Simmons-Smith Cyclopropanation.[1,7]

Zinc-copper couple reduces ***Diiodomethane*** to generate ***Iodomethylzinc Iodide***, which is in equilibrium with bis(iodomethyl)zinc and zinc iodide.[8] This Simmons-Smith reagent is widely used to cyclopropanate alkenes. As shown in eqs 1 and 2, the cyclopropanation is stereospecific, with methylene adding cis to the starting alkene.[7]

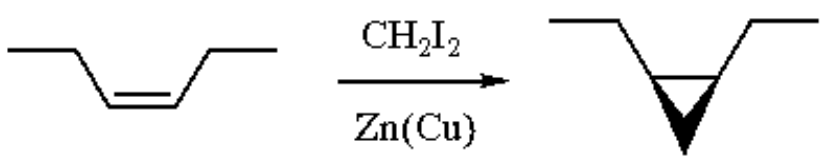

(1)

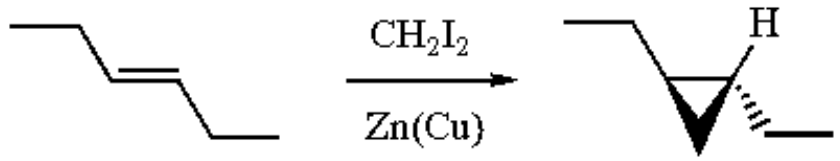

(2)

Hydroxyl groups or sterically accessible ethers will direct the Simmons-Smith reagent to the proximate face of an alkene,[9] and this stereoselectivity has been used extensively in synthesis (eq 3).[10]

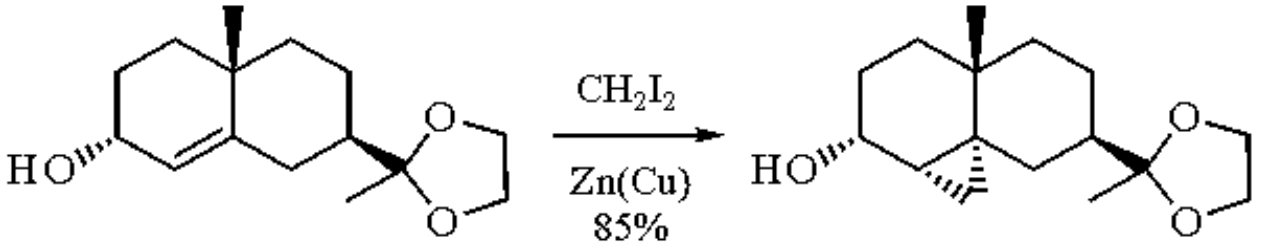

(3)

One important application of directed cyclopropanation is the stereoselective introduction of methyl groups in terpene synthesis. In eq 4 the allylic alcohol is again used to direct the cyclopropanation to the desired face of the ketone.[11] Oxidation to the ketone and lithium-ammonia reduction gave the β-methyl ketone. This stepwise approach to β-methyl substitution of an enone complements a ***Lithium Dimethylcuprate*** addition because it can be carried out on β-disubstituted enones and the stereochemistry is reliably predictable based on the alcohol stereochemistry.

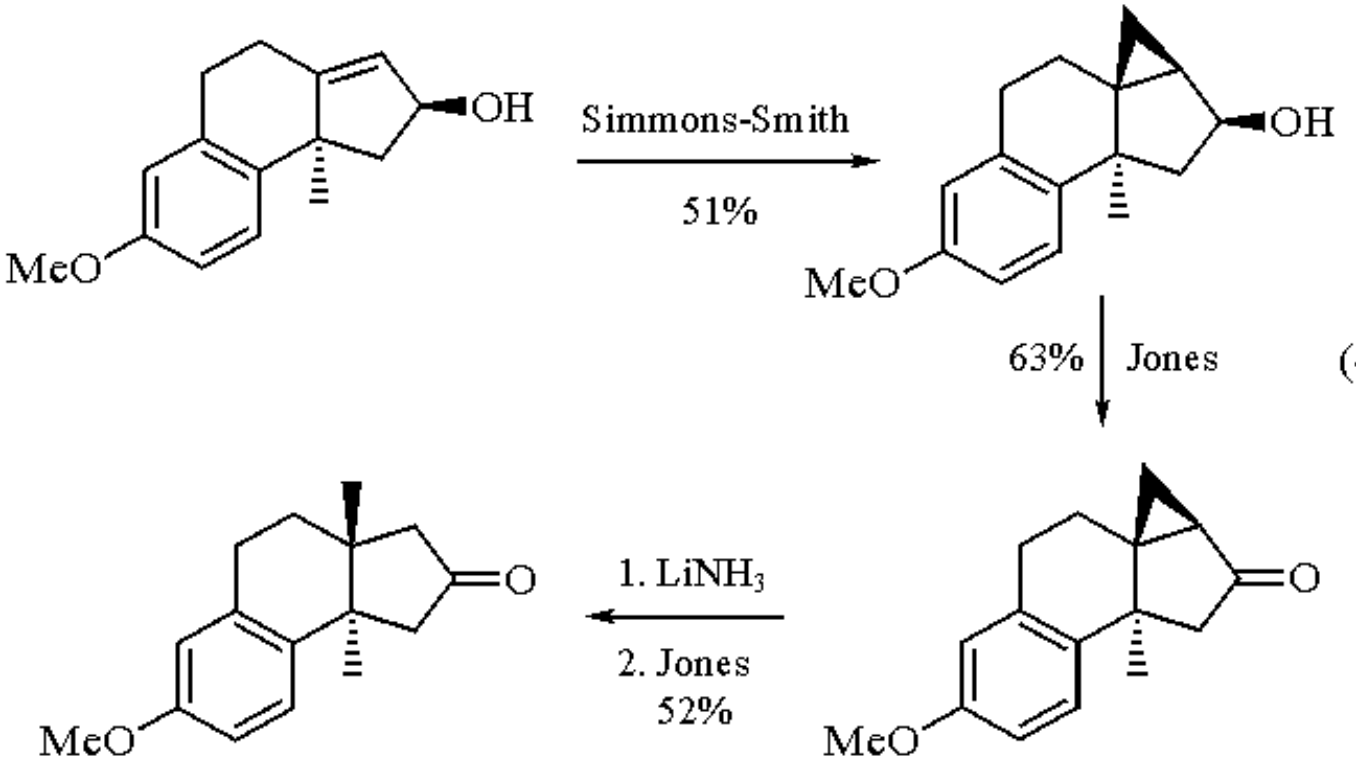

(4)

Wenkert developed an alternative to the classic alkylation of ketones by cyclopropanating the derived enol ether, followed by acid catalyzed hydrolysis of the cyclopropyl ether. This sequence was used to introduce the angular methyl group of (-)-valeranone with complete control of stereochemistry (eq 5).[12]

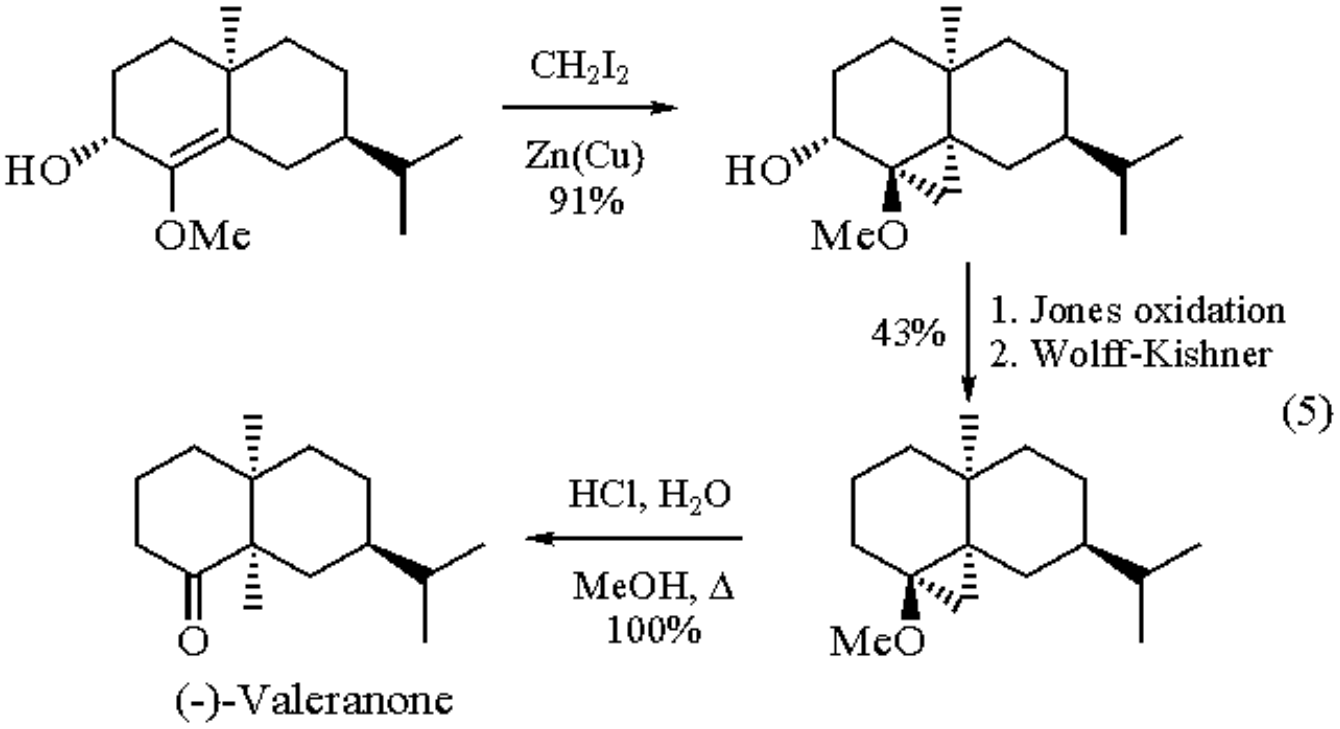

Mash has found that optically pure acetals prepared from chiral diols and cycloalkanones will cyclopropanate with good diastereoselectivity (eq 6), presumably through selective coordination of the Simmons-Smith reagent to the more accessible acetal oxygen. Hydrolysis of the acetals leads to bicyclo[*n*.1.0]alkanones in good to excellent optical purity.

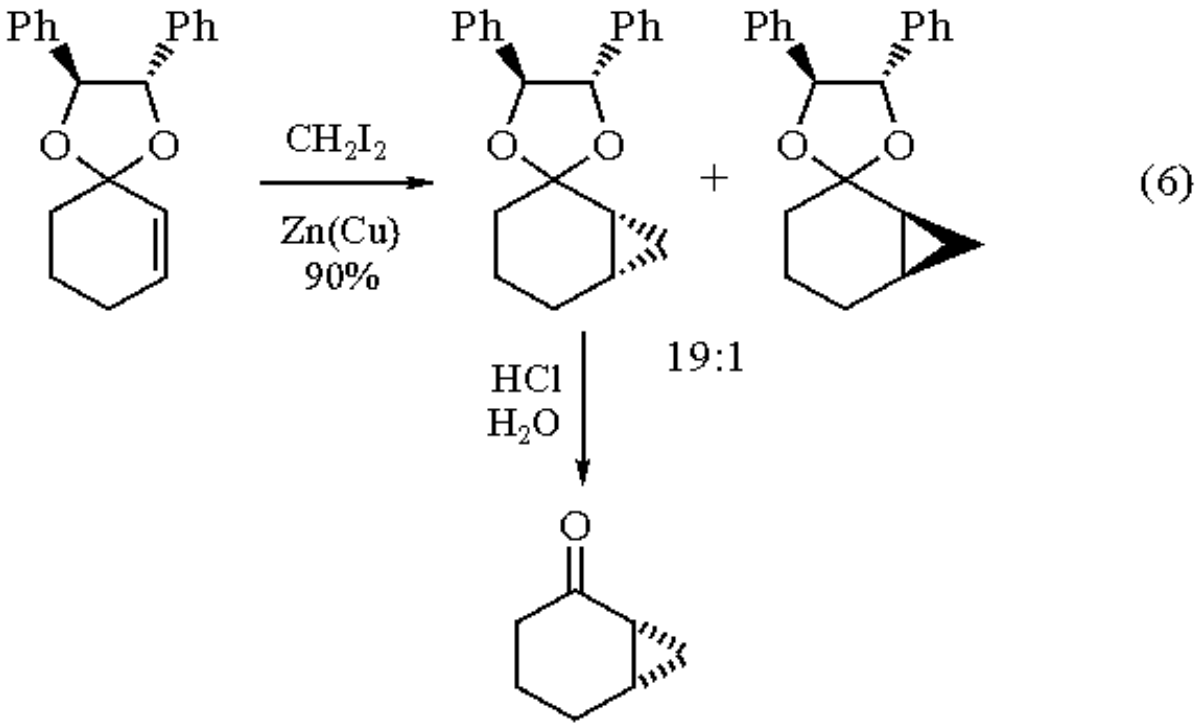

Alkyl Zinc Preparations and Reactions.

Dialkylzinc compounds have been prepared from the corresponding alkyl iodides and zinc-copper couple,[13] but are more commonly prepared using activated zinc or from the appropriate Grignard reagent and ***Zinc Chloride***. Zinc-copper couple is useful for preparing a variety of unusual alkyl zinc compounds such as (iodomethyl)zinc iodide. Apart from cyclopropanations, (iodomethyl)zinc iodide reacts with ***Tri-n-butylchlorostannane*** to give ***RI031M***, an important reagent in the preparation of α-alkoxylithium reagents (eq 7).[14]

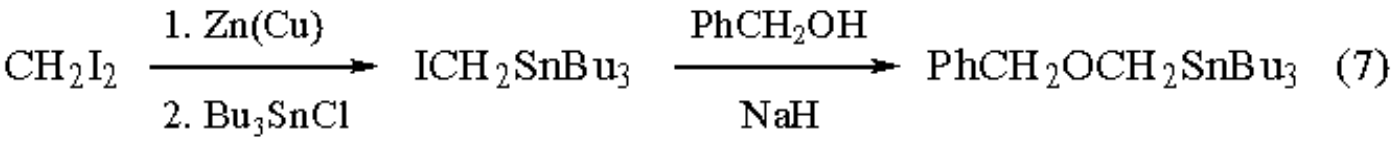

Propargyl bromide (see ***Propargyl Chloride***) reacts with zinc-copper couple in the presence of an aromatic aldehyde to produce the alkyne adduct in good yield (eq 8). Presumably the allenylzinc bromide is formed in situ and reacts with 1,3-rearrangement; none of the allene adduct is reported.[15]

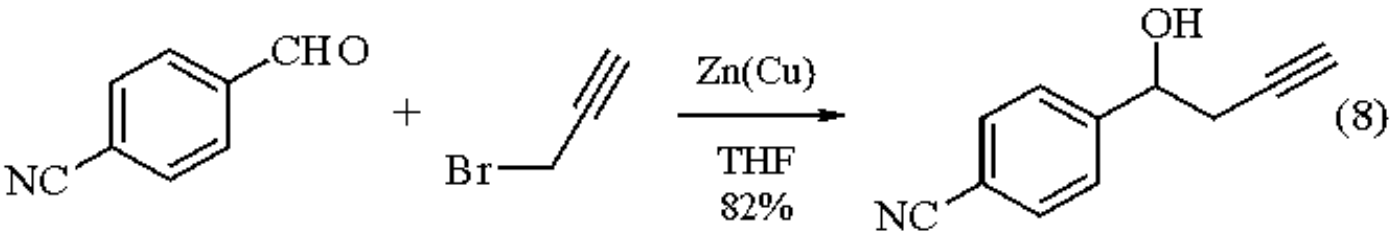

Yoshida's group found that zinc-copper couple was very effective in the preparation of zinc homoenolates and bishomoenolates. Reaction of ethyl 4-iodobutyrate with zinc-copper couple in benzene and DMA gave the homoenolate (**1**), which coupled with acyl chlorides, vinyl iodides, or vinyl triflates in the presence of ***Tetrakis(triphenylphosphine)palladium(0)*** (eq 9).[16]

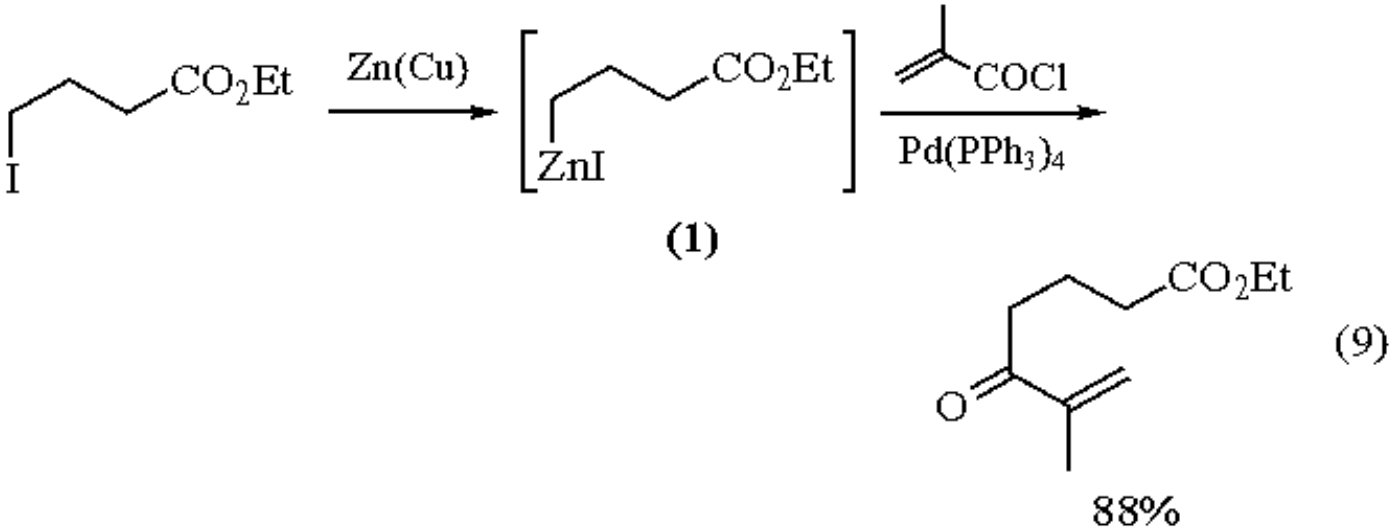

Zinc homoenolates prepared in this manner can be transmetalated to titanium homoenolates and coupled with aldehydes (eq 10),[17] or reacted with ***t-Butyldimethylchlorosilane*** to give the cyclopropyl ethers.[18]

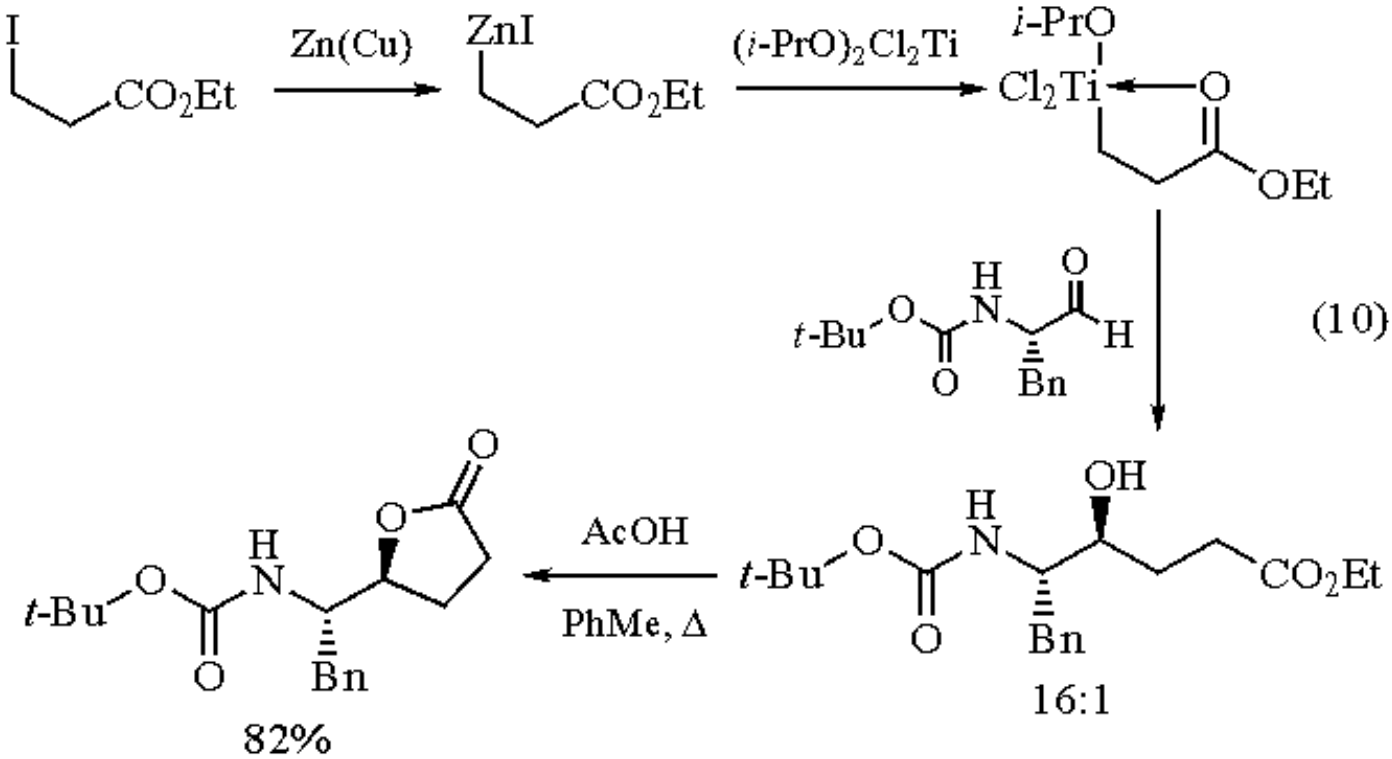

Zinc-copper couple leads to higher yield and faster reactions in the Reformatsky reaction than the more commonly used zinc metal (eq

11).[19]

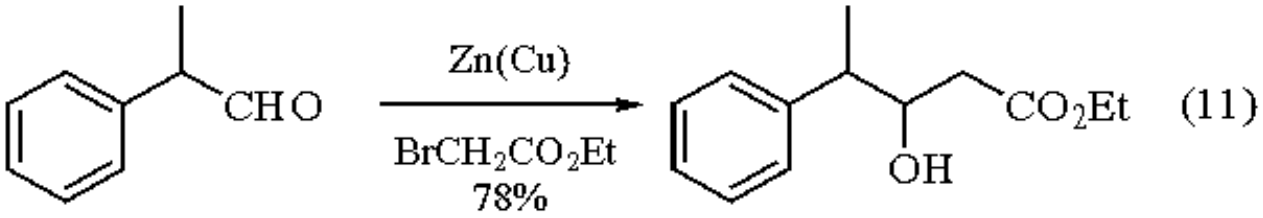

Semmelhack reported an unusual cyclization reaction that probably proceeds through an allylic zinc intermediate (eq 12).[20] Model cyclizations were carried out using allylic bromides, but the actual cyclization was performed on the allylic sulfonium salt. In contrast to the result with zinc-copper couple, cyclization of the sulfonium salt intermediate with ***Bis(1,5-cyclooctadiene)nickel(0)*** gave the other *cis*-fused lactone in 43% overall yield.

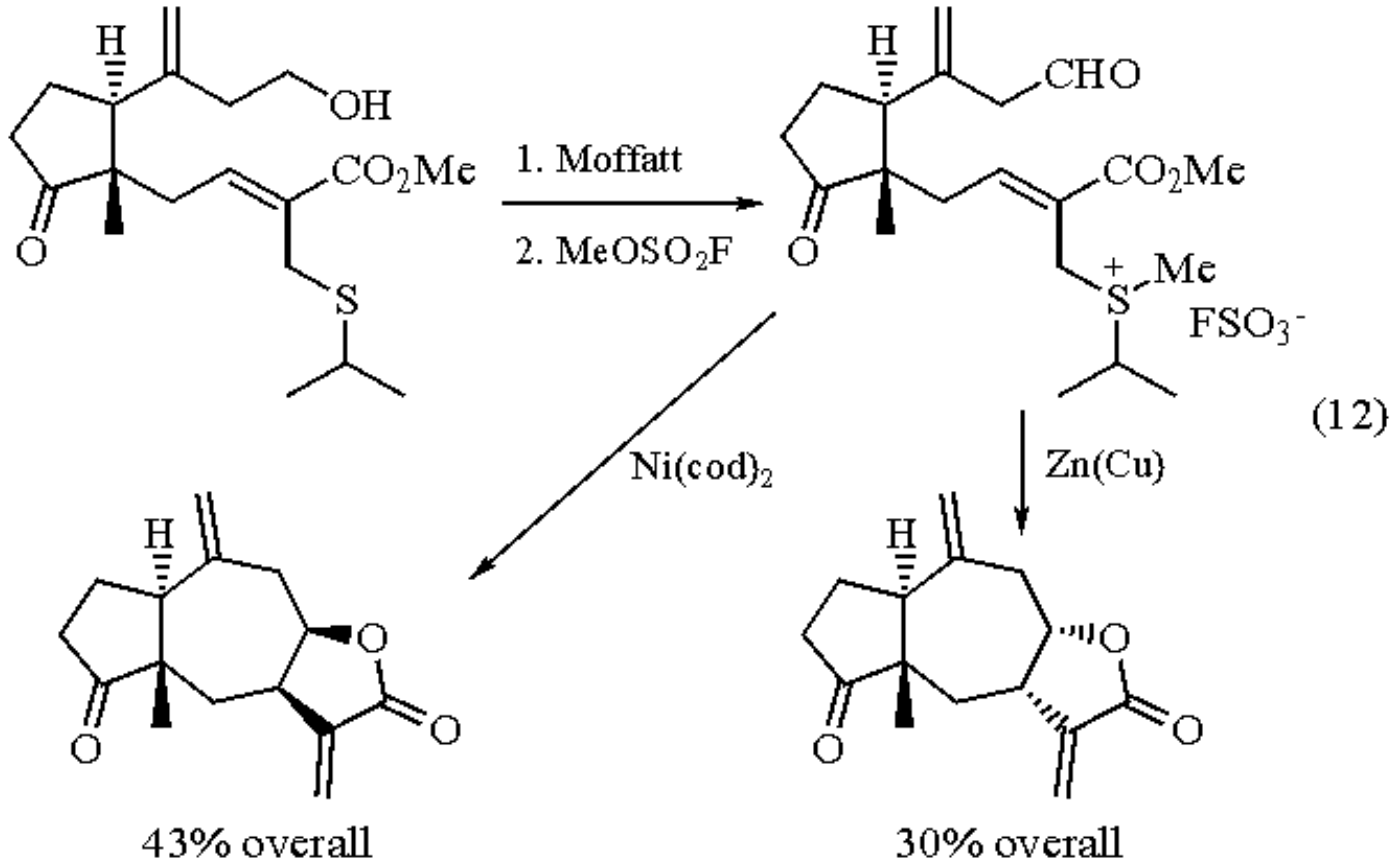

Conjugate Additions of Alkyl Iodides to Alkenes.

An intriguing new carbon-carbon bond forming reaction has been developed that promises to be very useful in synthesis. Luche's group found that alkyl iodides will add to alkenes bearing a strong electron-withdrawing group when sonicated with zinc-copper couple in an aqueous solvent.[21] This reaction is notable because the conditions are very mild, it is compatible with many reactive functional groups, and moderately hindered carbon-carbon bonds can be formed in good yield. Luche proposed that the reaction proceeds through a radical intermediate generated in the reduction of the alkyl iodide with zinc-copper couple, but the evidence is not completely clear. When the reaction is conducted in a solvent system with a good deuterium atom donor and a good proton source, the proton is incorporated into the product, whereas when the role of the hydrogen and deuterium are reversed, deuterium is incorporated into the product (eq 13).[2]

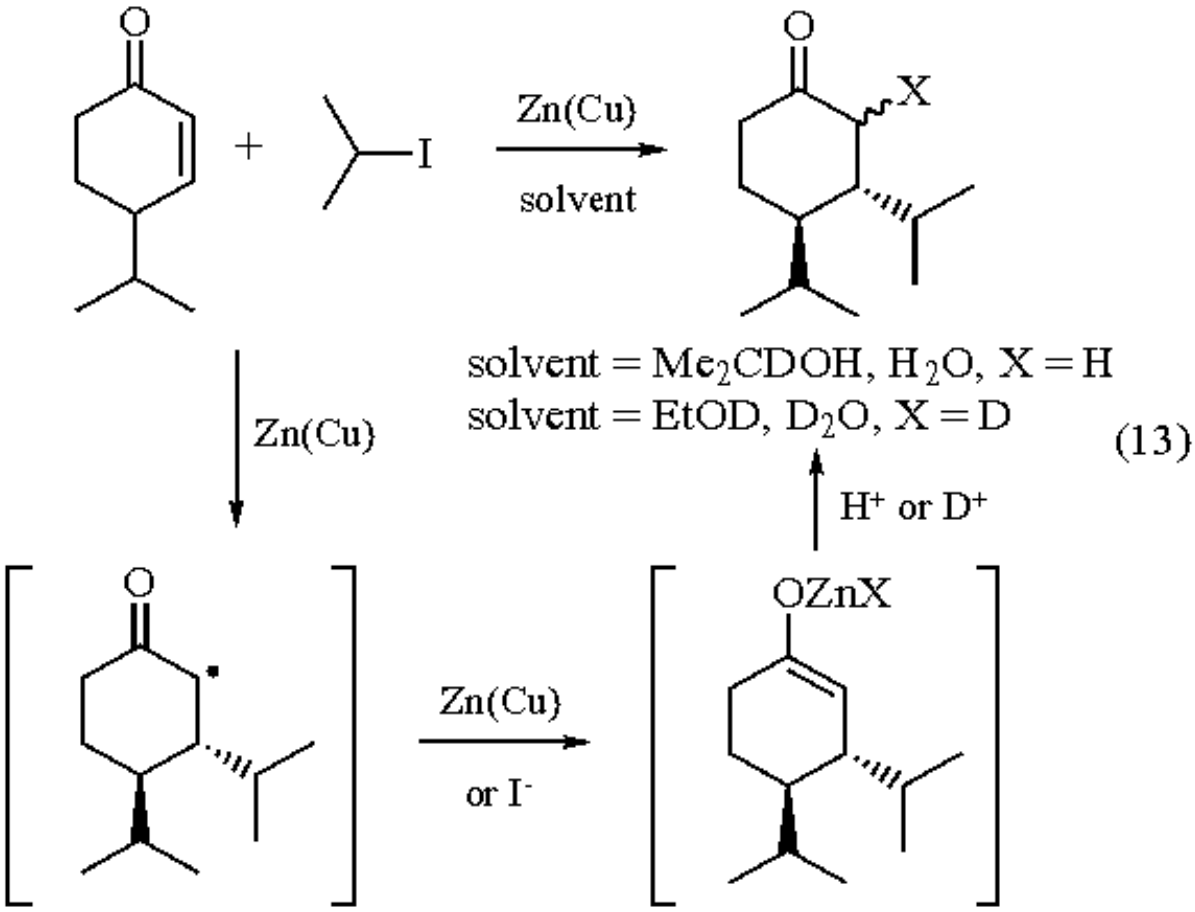

A radical intermediate should give the opposite incorporation pattern, but Luche invokes a rapid reduction of the α-keto radical to give the enolate, which would give the observed incorporation. Thus the addition can still proceed through a radical even though the quenching is ionic. The best direct evidence of radical involvement is cyclization of the radical intermediate in eq 14, but the yield is quite low.

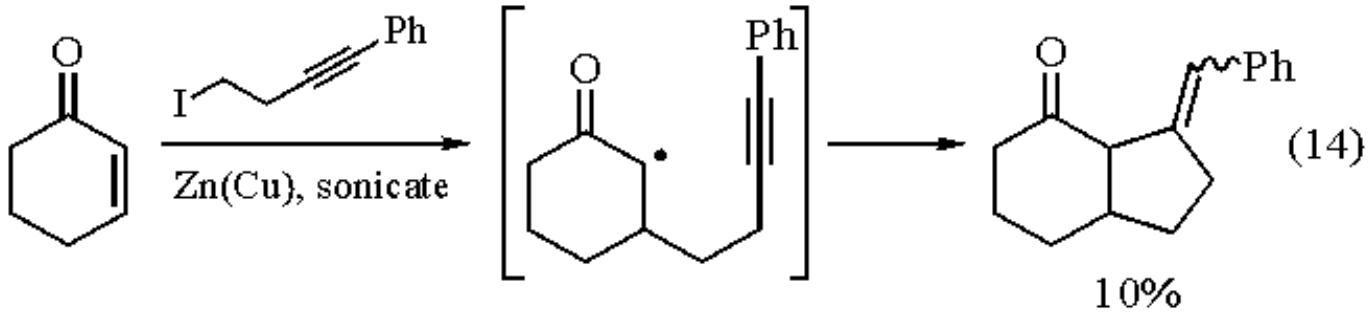

Several other features of this reaction are noteworthy: both water and copper are required, and (*S*)-octyl iodide couples well but leads to a racemic product.

The conjugate addition reactions of alkyl iodides work well in complex and highly functionalized molecules. The side chain of a vitamin D analog was prepared using the reaction shown in eq 15.[22] Unlike most transition metal-catalyzed reactions, this procedure did not affect the vinyl triflate.

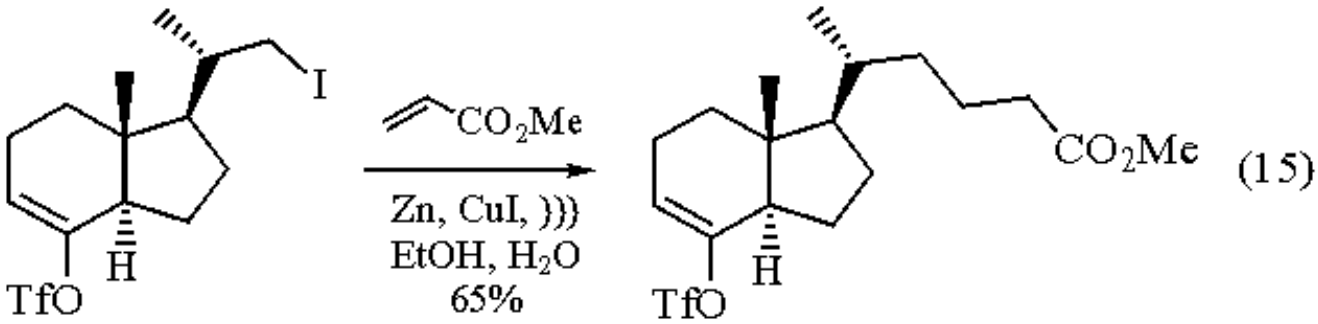

Surprisingly, the coupling reaction will also work in carbohydrate systems. The alkyl iodide derived from ribose was coupled in good yield

with 2-butenenitrile (eq 16), without undergoing reductive elimination to form an alkene.[23] This new coupling procedure promises to be very useful in synthesis.

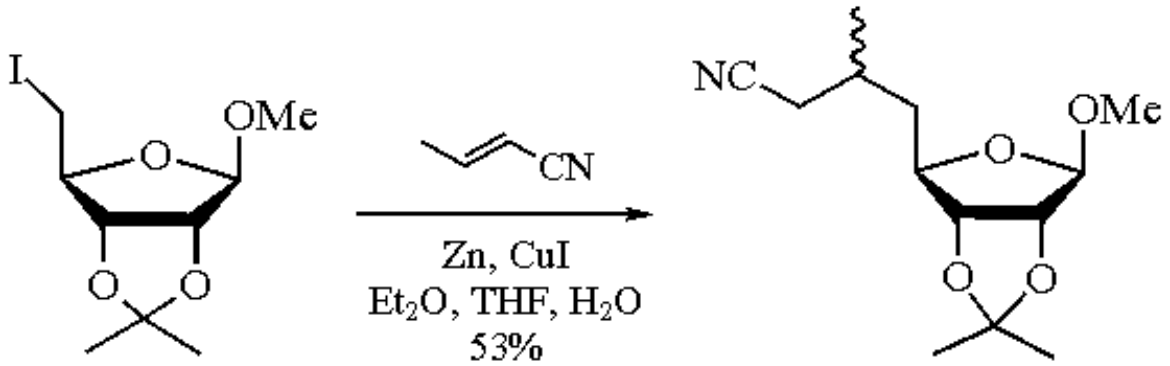

(16)

Reductive Coupling of Carbonyl Compounds.

Carbonyl compounds can be reductively dimerized to diols or alkenes. A pinacol cross-coupling reaction between α,β-unsaturated ketones and acetone has been reported. When carvone is sonicated with zinc dust and ***Copper(II) Chloride*** in acetone/water, the cross-coupling product is isolated in 92% yield (eq 17).[24] Acetone itself does not dimerize under the reaction conditions, and β,β-disubstituted enones fail to react, presumably due to a higher reduction potential.

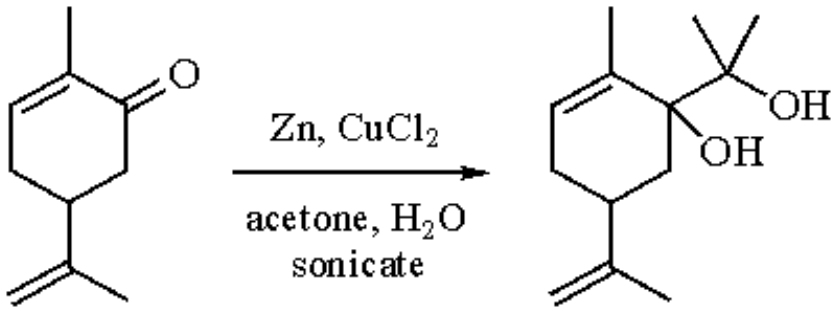

(17)

The McMurry coupling uses low valent titanium to reductively dimerize carbonyl compounds to alkenes.[25] The reagent is usually prepared from ***Titanium(III) Chloride*** and an added reducing agent like ***Potassium***, ***Lithium***, or ***Lithium Aluminum Hydride***. One of the best reagents is prepared from $TiCl_3(DME)_{1.5}$ and zinc-copper couple (eq 18).[26] The same dimerization gives only 12% yield with $TiCl_3/LiAlH_4$.

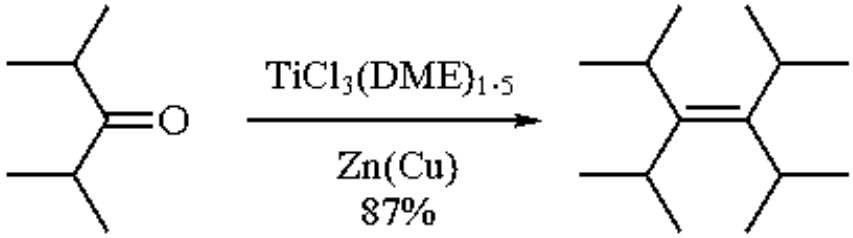

(18)

Preparation of Dichloroketene.

Dichloroketene can be prepared by reducing ***Trichloroacetyl Chloride*** with zinc-copper couple.[3] Dichloroketene undergoes facile [2 + 2] cycloadditions with alkenes[27] and alkynes[28] to give cyclobutanones and cyclobutenones.[29] Recently the use of a chiral auxiliary has been reported to control the facial selectivity of dichloroketene additions (eq 19).[30] Ring expansion with ***Diazomethane*** gave the dichlorocyclopentanone, and subsequent reduction removed the chiral auxiliary and gave the optically enriched cyclopentenone.

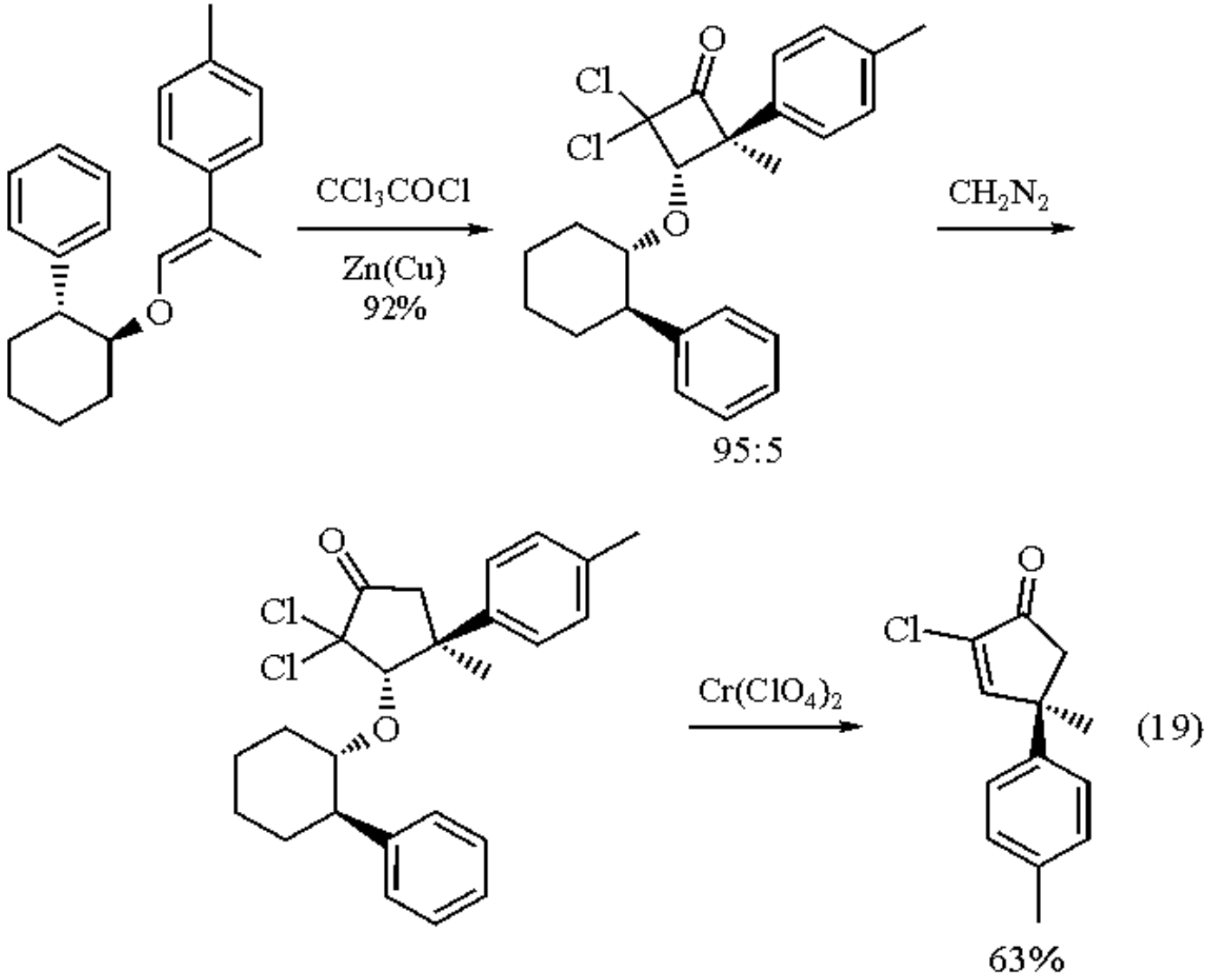

Dichloroketene will react with vinyl sulfoxides to give γ-lactones with efficient stereochemical transfer from the sulfoxide stereogenic center (eq 20).[31] Optically pure vinyl sulfoxides give lactones with high enantiomeric excesses. The chlorine atoms can be removed by reduction with zinc-copper couple or ***Aluminum Amalgam*** to give the lactone.

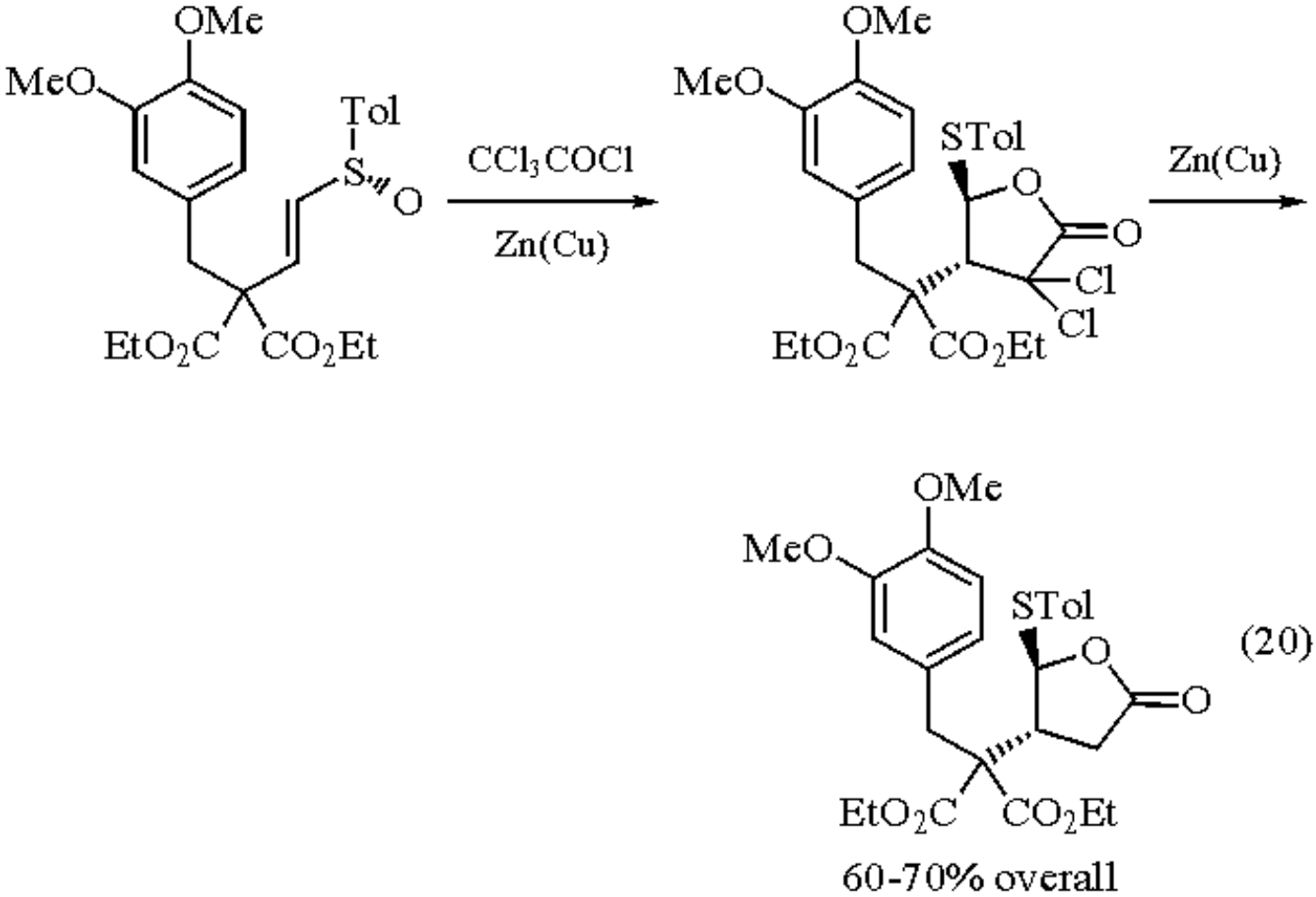

(20)

Reduction of α-halo acyl chlorides normally gives ketenes, but Hoffmann has reported an unusual reductive trimerization of 1-bromocyclopropanecarbonyl chloride that does not proceed through the corresponding ketene.[32] Reduction with zinc-copper couple in MeCN gave the unusual trimer in 20% yield (eq 21), whereas the corresponding ketene is known to dimerize. Hoffmann suggests that a Reformatsky-type intermediate may react with a second molecule of acyl chloride rather than eliminating to generate the ketene.

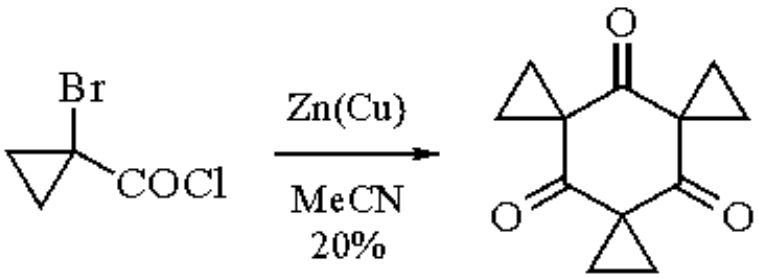

(21)

Preparation of 2-Oxyallyl Cations.

Zinc-copper couple reduces α,α´-dibromo ketones to zinc oxyallyl cations, and these allyl cations will undergo [3 + 4] cycloadditions with dienes (eq 22).[33]

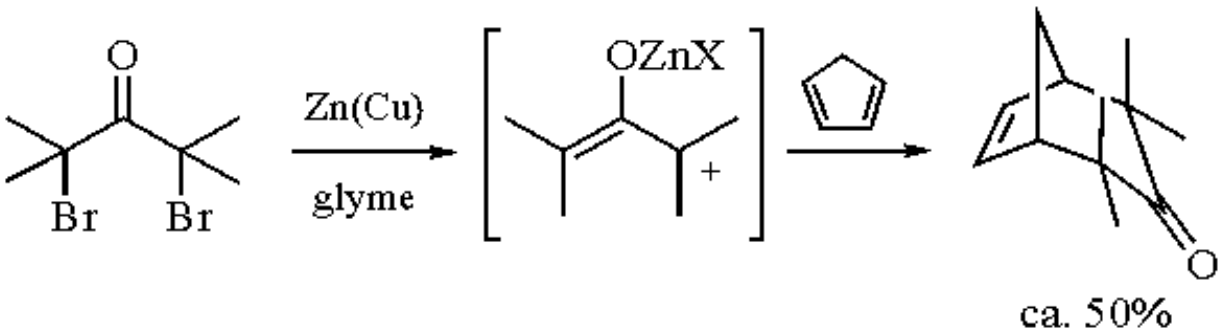

(22)

The original procedure used zinc-copper couple directly, but more recently sonicating the reactions has been reported to improve the yields significantly: the coupling in eq 23 gives 60% yield without sonication and 91% yield with sonication.[4]

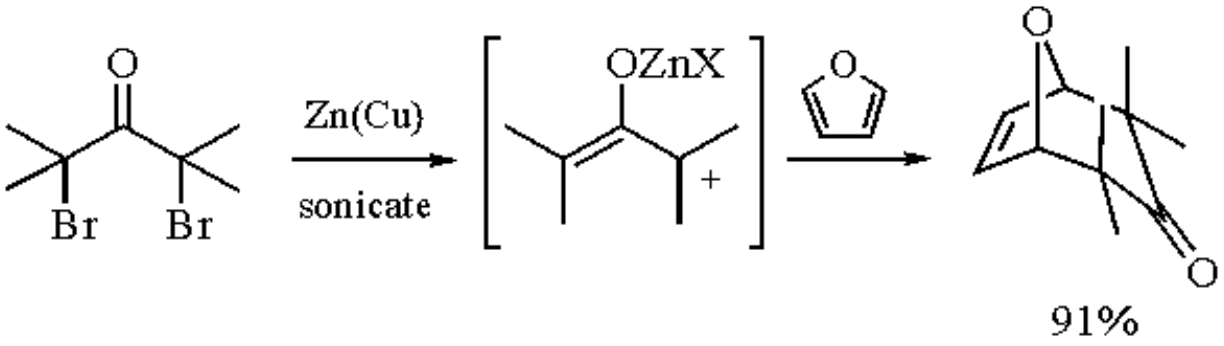

(23)

These reactions can be carried out using ***Nonacarbonyldiiron*** as the reducing agent in comparable yield, but the iron reagent is quite toxic and does not offer any advantage in simple cases.[34]

Reduction of α,α´-dibromo ketones under slightly different conditions, using *N*-methylformamide as the solvent without diene or sonication, leads to 1,4-diketones (eq 24).[35] Unsymmetrically substituted ketones give statistical mixtures of products.

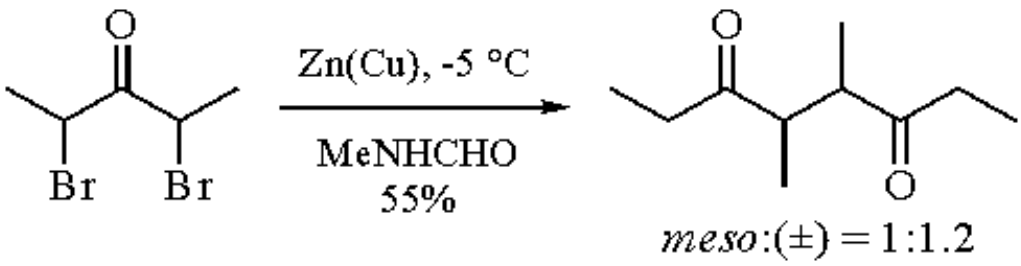

(24)

Reduction of 1,2- and 1,3-Dihalides and Halo Ethers.

Zinc-Acetic Acid is commonly used to reduce 1,2-dihalides to alkenes. Several modifications of this procedure use zinc-copper couple as the reducing agent.[36] Bromooxiranes prepared from allyl alcohols are reduced with zinc-copper couple and sonication to give the 1,3-transposed allylic alcohol (eq 25).[37] The oxirane ring strain facilitates the alkene formation; notice that the tetrahydrofuran in eq 16 does not form an alkene.

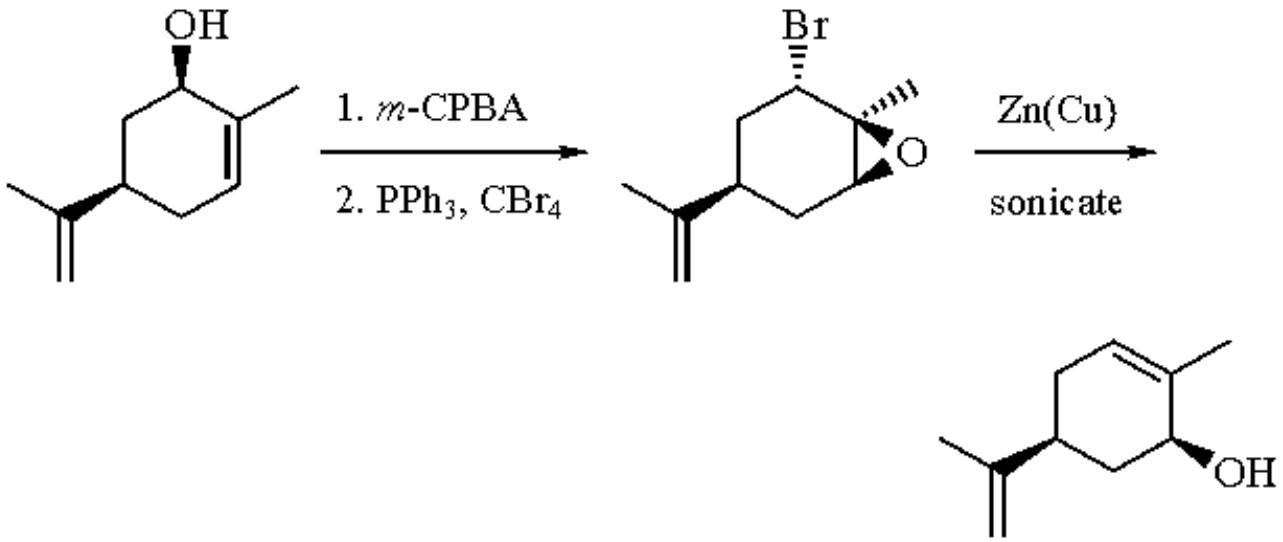

(25)

The 2,2,2-trichloroethyl group is used as a protecting group for many functional groups such as carboxylic acids and carbamic acids (amines), and is usually removed by reduction with zinc metal. In some cases it is advantageous to remove these protecting groups with zinc-copper couple.[38]

Under forcing conditions, oxiranes can be reduced to the corresponding alkene. Reaction of eupachloroxin with zinc-copper couple in refluxing ethanol for 3 d gave eupachlorin without reducing the many other functional groups in the molecule (eq 26).[39] The reduction is stereoselective: *cis*-oxiranes give *cis*-alkenes and *trans*-oxiranes give *trans*-alkenes.

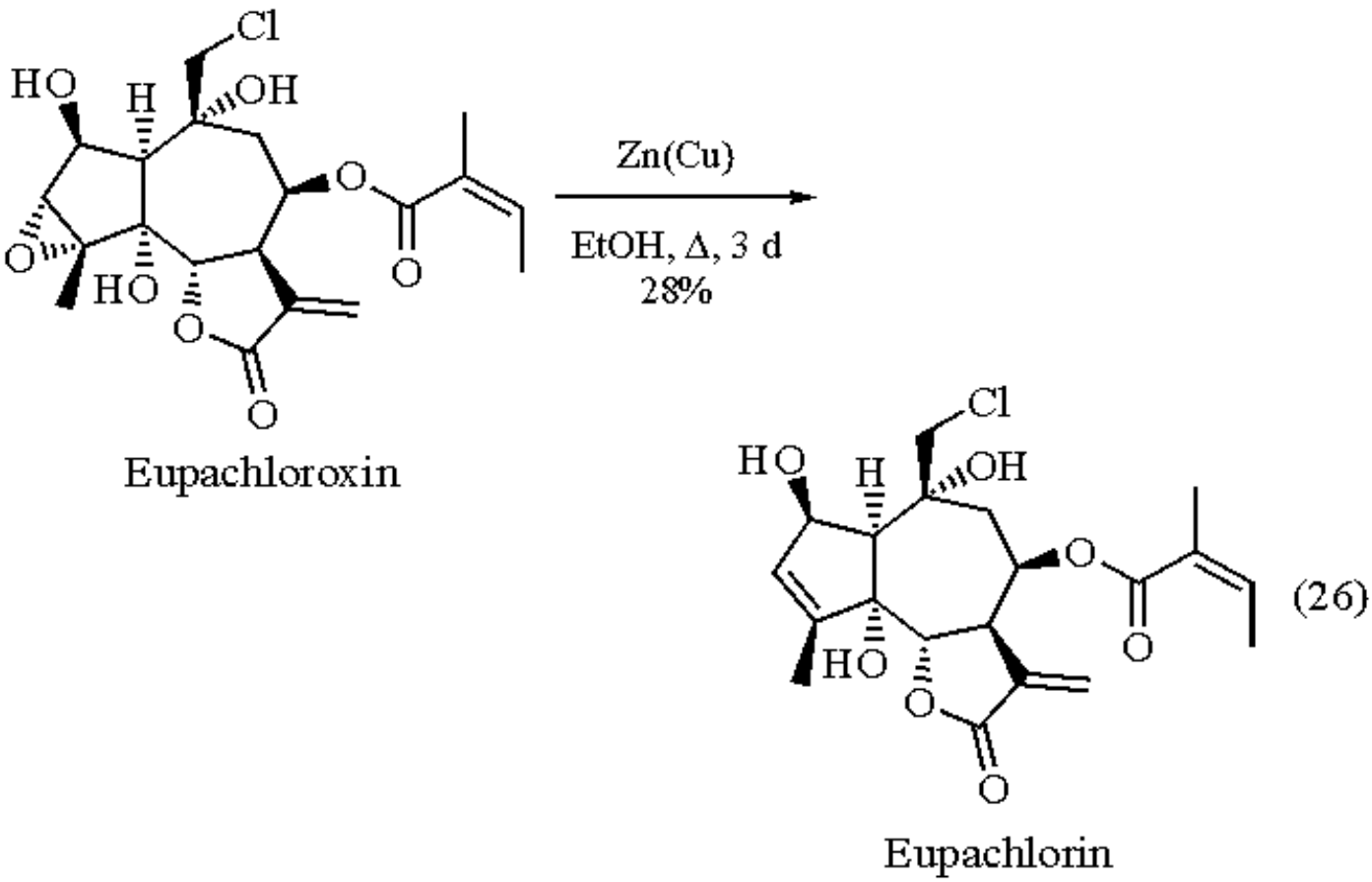

Reduction of 1,3-dibromides with zinc-copper couple gives cyclopropanes (eq 27).[40] Cyclopropanes are also formed when 2-bromoethyloxiranes are reduced using zinc-copper couple with sonication.[41]

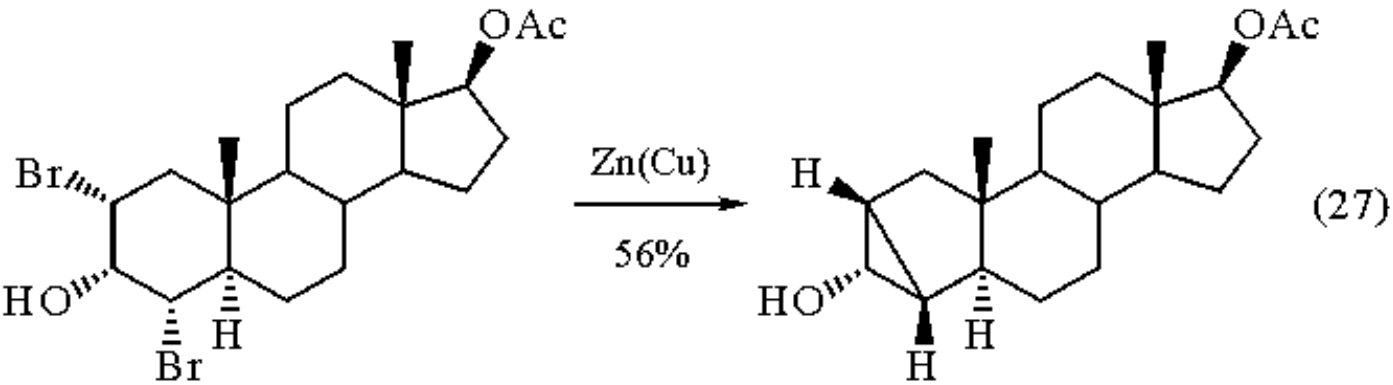

Reduction of C-C Multiple Bonds.

Alkenes with powerful electron-withdrawing groups like esters, ketones, or nitriles are reduced with zinc-copper couple in refluxing methanol (eq 28).[42] Isolated alkenes are not reduced.

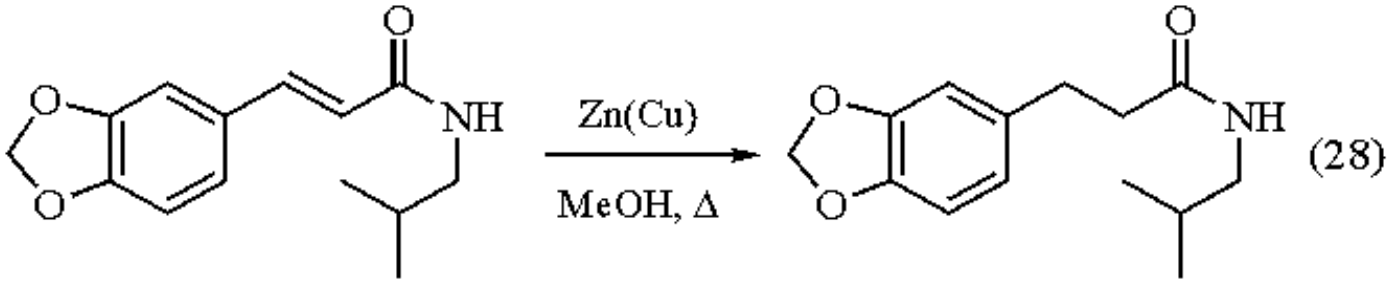

Unactivated alkynes are reduced to (*Z*)-alkenes under the same conditions.[43] Terminal alkynes are reduced to vinyl groups without the over-reduction that can sometimes accompany Birch-type reductions. This reduction was recently applied to the synthesis of leukotriene B_4 (eq

29).[44]

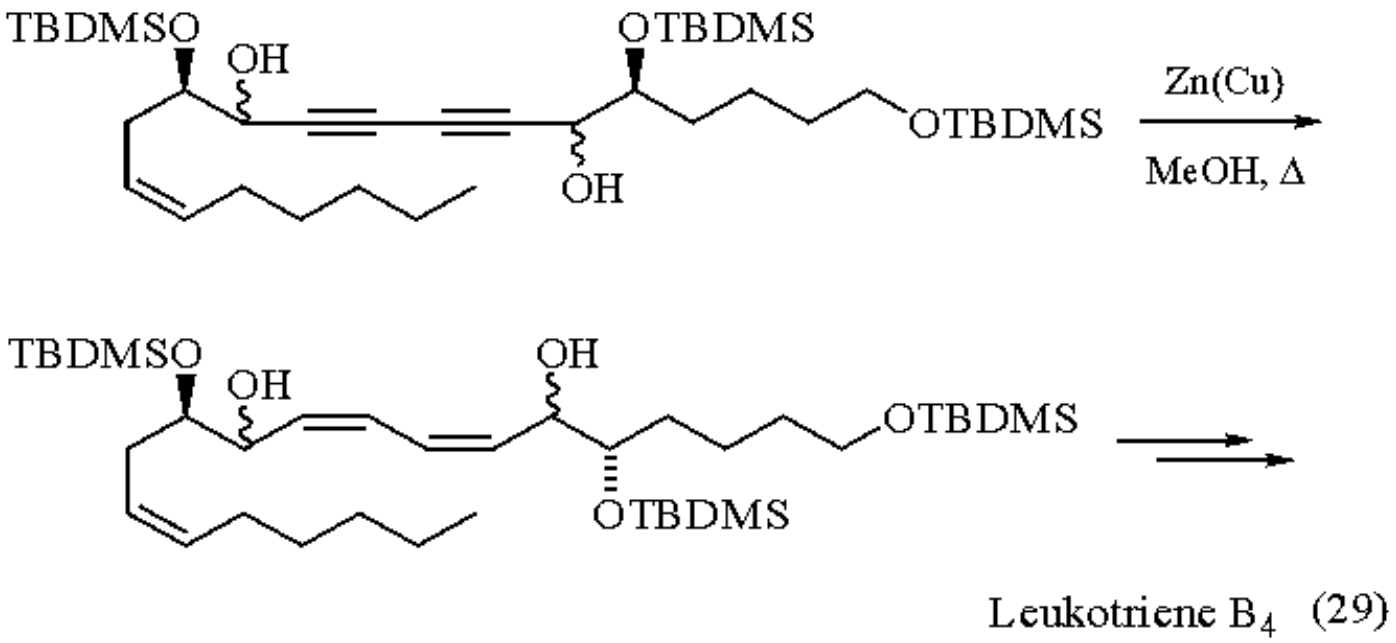

Reduction of Other Functional Groups.

Zinc metal has been used to reduce many functional groups and zinc-copper couple would be effective in most of these reactions. Zinc-copper couple reduces alkyl halide to the corresponding hydrocarbon, and in the presence of D_2O this leads to an expedient synthesis of specifically deuterated materials (eq 30).[45]

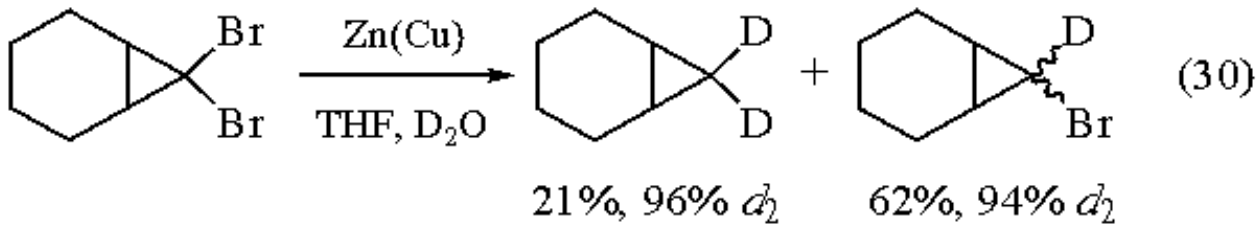

Aromatic nitro compounds are reduced to the protected hydroxylamines, *N*-acetoxy-*N*-acetylarylamines, with zinc-copper couple in the presence of acetic acid and acetic anhydride. In contrast, zinc metal reduces 4-nitrostilbene to azoxystilbene.[46] Oximes can be reduced to amines with zinc-copper couple, and this procedure is reported to be much more effective than an ***Aluminum Amalgam*** reduction (eq 31).[47]

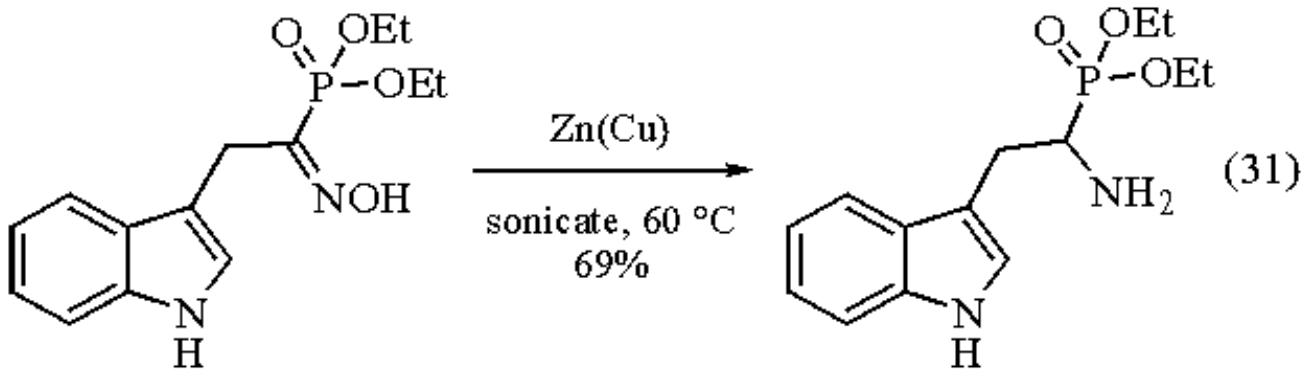

Related Reagents.

Chloroiodomethane-Zinc/Copper Couple; ***Dibromomethane-Zinc/Copper Couple***; ***Potassium Iodide-Zinc/Copper Couple***; ***Titanium(III) Chloride-Zinc/Copper Couple***.

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Zinc Cyanide[1]

$Zn(CN)_2$

[557-21-1] · C_2N_2Zn · Zinc Cyanide · (MW 117.43)

(mild Lewis acid used as an alternative to HCN in Gattermann formylation reactions, in the synthesis of α-cyanoenamines, and in the cyanosilylation of carbonyl compounds)

Physical Data: mp 800 °C (dec).

Solubility: practically insol water, alcohols; sol aq solutions of alkali cyanides.

Form Supplied in: white crystalline powder, with alkali metal chlorides as possible impurities. *Drying:* one of the cyanides most stable to heat, it volatilizes only to a small extent on strong heating.[2]

Preparative Methods: can be made by the action of cyanogen on the metal at 300 °C, by dissolving ***Zinc Oxide*** in ***Hydrogen Cyanide***, or by a metathetical reaction (see below).

Handling, Storage, and Precautions: as required by national poisons rules; extremely toxic by ingestion, inhalation, and skin contact. Irritating to the eyes. All work must be carried out in an efficient fume hood.

Gattermann Reactions.

In the classical Gattermann aldehyde synthesis, hydrogen cyanide and ***Hydrogen Chloride*** are used together with a Lewis acid such as ***Aluminum Chloride*** or ***Zinc Chloride***. In the Adams modification,[3] zinc cyanide is used together with hydrogen chloride as a more convenient reagent system, effectively generating hydrogen cyanide and zinc chloride. Any phenol that can be formylated using the classical Gattermann reaction conditions can be converted equally well into a hydroxy aldehyde by the Adams method. Pure zinc cyanide is said to be ineffective but may be activated by the addition of potassium chloride.[4]

Although the mechanism of the Gattermann reaction has not been investigated in detail, it is known that an initial nitrogen-containing product is hydrolyzed to the aldehyde (eq 1). It has been suggested that the electrophile may be a protonated dimer of HCN.[5] In some cases the hydrocyanic acidium ion may be involved; in others, a Lewis acid complex could be formed between hydrogen cyanide and, for example, zinc chloride or aluminum chloride. In this connection, a very high acidity is required for reaction to occur with benzene; evidence has been presented in favor of a diprotonated HCN in that case.[6] In reactions involving the system $Zn(CN)_2$-HCl-$AlCl_3$, a relative rate for the formylation of toluene versus benzene (K_T/K_B) of 128 was obtained.[7]

$$\mathrm{ArH} + \mathrm{Zn(CN)_2} \xrightarrow{\mathrm{HCl}} \mathrm{ArCH{=}\overset{+}{N}H_2\ Cl^-} \xrightarrow{\mathrm{H_2O}} \mathrm{ArCHO} \qquad (1)$$

Early examples showed that both α- and β-naphthol could be formylated in good yields, in the absence of a Lewis acid other than the zinc chloride, as indicated (eq 2).[3a] Anisole (eq 3) and resorcinol dimethyl ether are converted in good yields into the expected aldehydes in the presence of added aluminum chloride.[3b] Another improvement in the experimental procedures involves the use of tetrachloroethane as the solvent; this method has been used in the formylation of hindered systems such as 1,3,5-triisopropylbenzene.[8] A detailed and checked method for the preparation of mesitaldehyde is available.[9] The first stage in the synthesis of a number of fungal metabolites involves the formylation of orcinol at the 4-position.[10] Another recent example is shown in eq 4,[11] and others are known.[12] As with Friedel-Crafts alkylation and acylation reactions of alkylarenes, it is not unusual to observe rearrangement of the substrate in the presence of aluminum chloride. Thus, although 2,3-dimethylnaphthalene was formylated to give the expected product at 55 °C, at temperatures in excess of 65 °C 1-formyl-2,4-dimethylnaphthalene was formed in good yield (eq 5).[13]

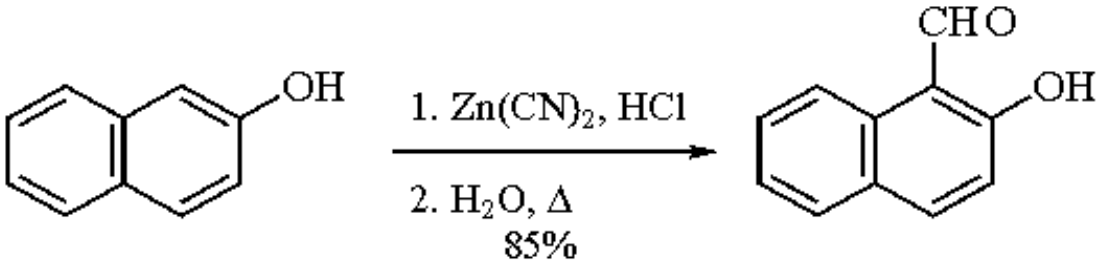

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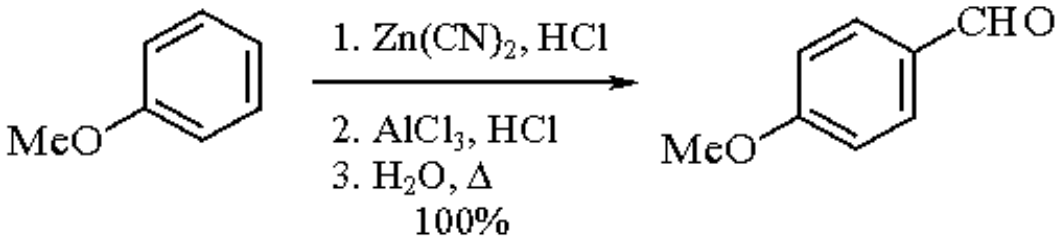

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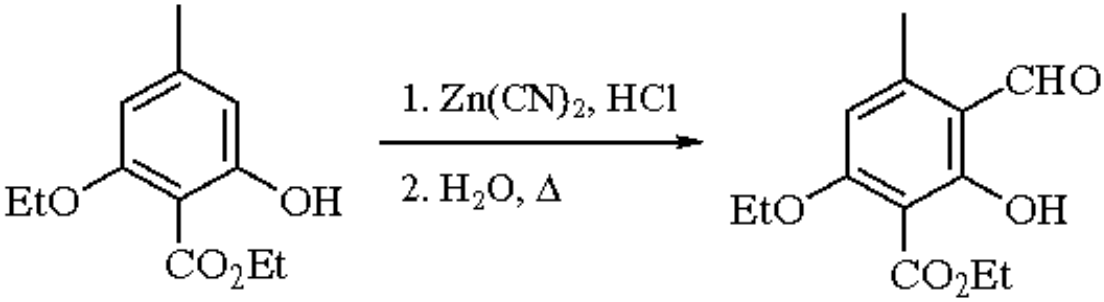

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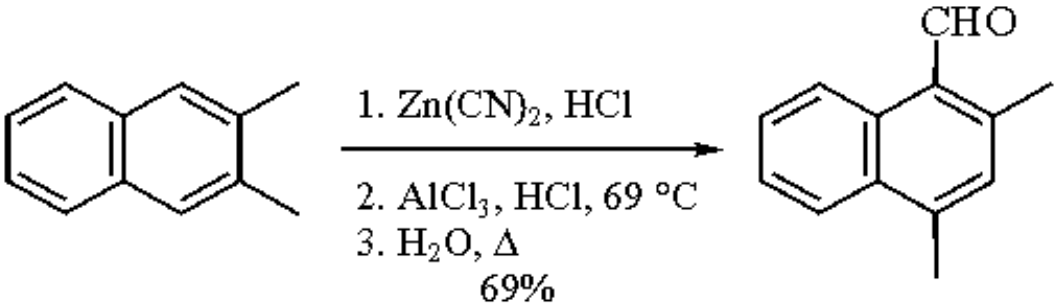

(5)

Electron-rich heterocycles are formylated particularly easily; the product shown in eq 6 was obtained in a quantitative yield.[14]

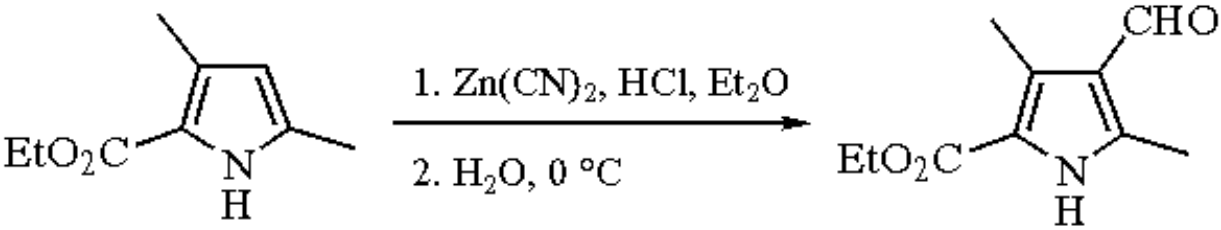

(6)

The reaction of a suitably activated phenylacetonitrile can lead to the formation of isoquinoline derivatives. The method can be regarded as a modification of the Gattermann reactions of 3,5-dihydroxybenzyl ketones, which lead to the corresponding 3-alkyl-6,8-dihydroxyisoquinolines. The cyclization of the intermediate imine was assumed to occur during the workup.[15] In the reaction of 3,5-dimethoxyphenylacetonitrile using zinc cyanide and either ***Hydrogen Bromide*** or hydrogen chloride (eq 7), ^{15}N-labeling showed that the nitrogen in the product came from the zinc cyanide.[16] It is noteworthy that two activating substituents are required; an attempted reaction was unsuccessful using 3,4-dimethoxyphenylacetonitrile. β-Oxoaldimines are formed when ketones such as deoxybenzoin are reacted under Gattermann conditions.[17] Hydrolysis of the products leads to β-keto aldehydes and so, with a suitable phenol, a one-step synthesis of an isoflavone can be accomplished.[18] This method is exemplified in the synthesis of pseudobaptigenin (eq 8).[19]

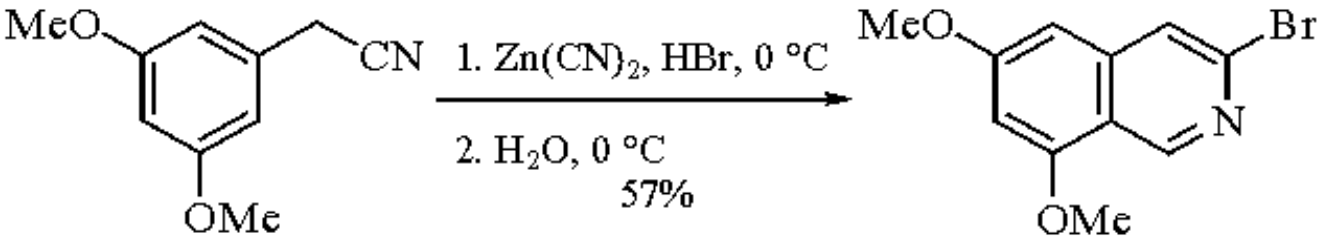

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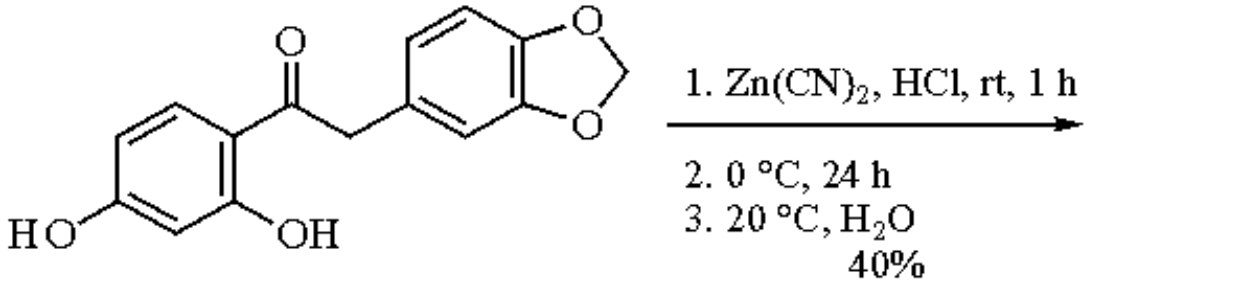

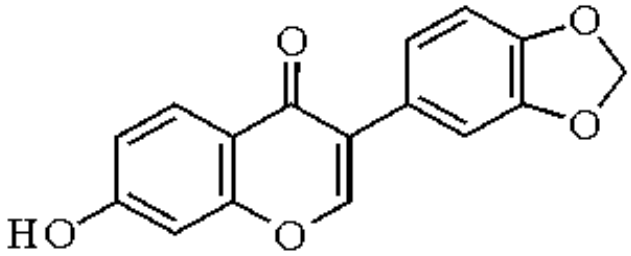

(8)

Cyanoenamine Formation.

A number of methods are available for the conversion of α-chloroenamines into α-cyanoenamines. The α-chloroenamines, which can function as keteniminium chlorides, are able to undergo nucleophilic substitution with cyanide ion. Substrates such as 1,2-dichloro-*N*,*N*-dimethylpropenylamine (eq 9) require a Lewis acid catalyst, and zinc cyanide in chloroform was found to be satisfactory.[20]

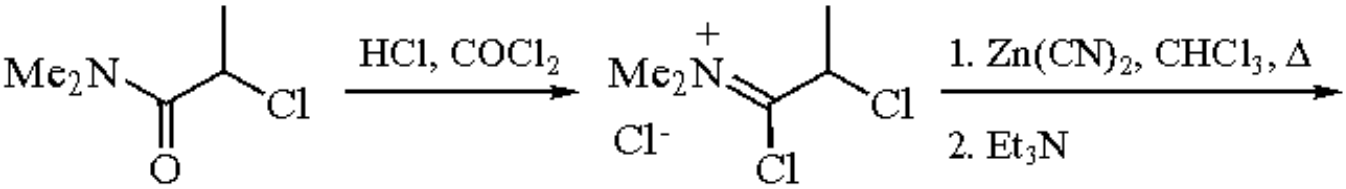

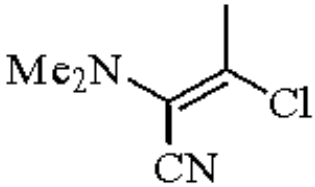

(9)

Cyanosilylation of Carbonyl Compounds.

A development from an in situ procedure, in which ***Chlorotrimethylsilane*** and a cyanide are used to replace ***Cyanotrimethylsilane***,[21] uses zinc cyanide to obtain cyanohydrin trimethylsilyl ethers (eq 10)[22] in good yields.[23] Other silylated cyanohydrins have been prepared by a development of the in situ method.[24] For example, 1-benzenesulfonyl-2-formylpyrrole was converted into its cyanohydrin *t*-butyldimethylsilyl ether, and piperonal into the *t*-butyldiphenylsilyl and triisopropylsilyl analogs in very high yields by using ***Potassium Cyanide***, ***Zinc Iodide***, and the appropriate chlorosilane.

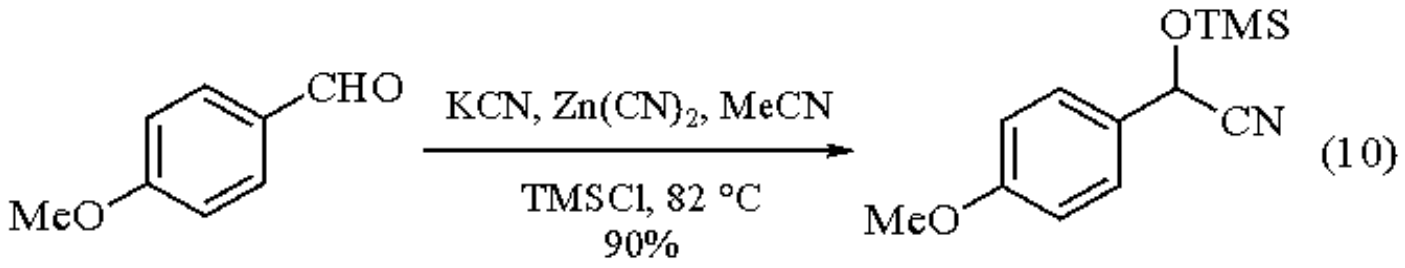

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Zinc-1,2-Dibromoethane[1]

Zn-$BrCH_2CH_2Br$

(Zn)

[7440-66-6] · Zn · Zinc-1,2-Dibromoethane · (MW 65.39) ($BrCH_2CH_2Br$)

[106-93-4] · $C_2H_4Br_2$ · Zinc-1,2-Dibromoethane · (MW 187.86)

(combination reagent used for the regio- and *cis*-stereospecific reduction of alkynes)

Physical Data: zinc: mp 419.5 °C; *d* 7.140 g cm^{-3}; 1,2-dibromoethane: mp 9-10 °C; bp 131-132 °C; *d* 2.18 g cm^{-3}.

Solubility: 1,2-dibromoethane: sol alcohol, ether, acetone, benzene.

Form Supplied in: zinc: dust, foil, granular, mossy, pieces, powder, shot, splatter, sticks, wire; 1,2-dibromoethane: clear oil.

Preparative Method: the reducing agent is prepared by refluxing Zn and 1,2-dibromoethane in ethanol until evolution of ethylene has subsided.

Purification: the reducing agent is not purified prior to use.

Handling, Storage, and Precautions: for specific information, consult ***Zinc*** and ***1,2-Dibromoethane***.

General Discussion.

1,2-Dibromoethane-activated zinc serves as a versatile, mild reducing agent for alkynes. The products are exclusively (*Z*)-alkenes with yields ranging from 70-90%.[1] In substrates containing two differentiated alkyne linkages the reagent exhibits selectivity. Conjugated triple bonds are reduced preferentially over nonconjugated bonds. Terminal alkynes are reduced over internal alkynes (eq 1). However, if the terminal alkyne has an appending silyl group, the internal bond is reduced (eq 2).

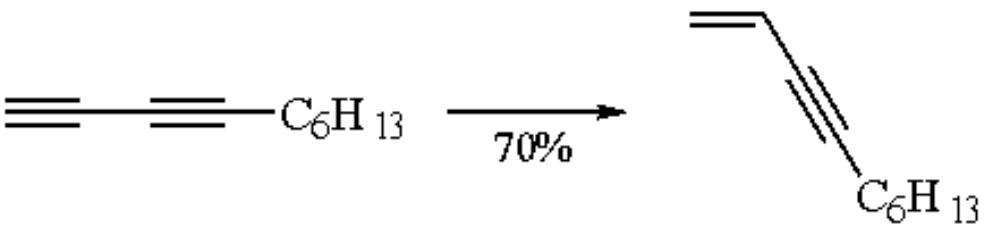

(1)

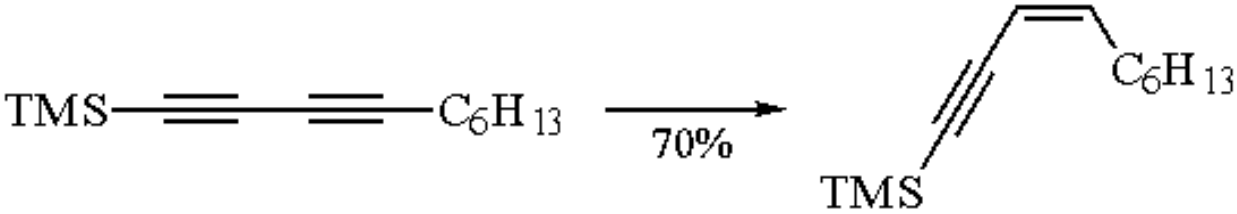

(2)

Hetero-substituted diynes yield products with the triple bond nearest the heteroatom being reduced. Sulfur does not poison the

reaction: 2-thienylacetylene was converted to 2-vinylthiophene (80%). Other heteroatoms (OR, NR_2) are also stable under these conditions.

The activity of this reagent can be improved, at the expense of selectivity, by adding ***Copper(I) Bromide*/*Lithium Bromide*** to the zinc/1,2-dibromoethane mixture prior to the addition of the substrate.[2] Under these conditions, monoalkynes containing a heteroatom (OR, NR_2) are reduced to (*Z*)-alkenes. Sulfides are not reduced under these conditions.

---

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Zinc-Dimethylformamide[1]

Zn-Me_2NCHO

(Zn)

[7440-66-6] · Zn · Zinc-Dimethylformamide · (MW 65.39) (DMF)

[68-12-2] · C_3H_7NO · Zinc-Dimethylformamide · (MW 73.11)

(reducing agent for halides,[3] azides,[10] and aldehydes[11])

Physical Data: zinc: mp 419.5 °C; *d* 7.140 g cm^{-3}; DMF: bp 153 °C; *d* 0.944 g cm^{-3}.

Solubility: sol DMF, THF, Et_2O, toluene, alcohol.

Preparative Methods: see text.

Handling, Storage, and Precautions: see ***Zinc*** and ***N,N-Dimethylformamide***.

Reduction of Halides.

The first use of a mixture of zinc and DMF as a dehalogenating reagent was employed by Alder and Fremery in 1961.[1] In a study of formation of *ortho* biradicals, they employed Zn/DMF to reduce α,α´-dibromoxylene (eq 1) which generated unstable 5,6-dimethylene-1,3-cyclohexadiene. This diene undergoes a Diels-Alder reaction with dienophiles like ***Acrylonitrile***, ***Acrolein***, and ***Ethyl Acrylate*** in high yield. A similar reaction has also been employed in the dimethylenecyclooctatriene system.[2]

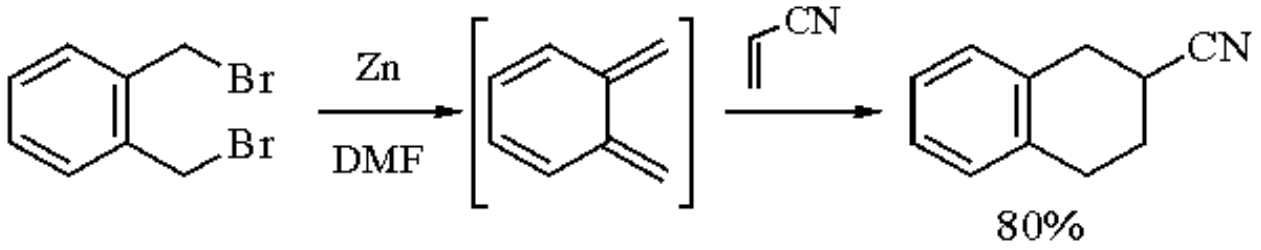

(1)

A systematic study of Zn/DMF as a dehalogenating reagent was investigated by Mehta and Kapoor.[3] It was found that ordinary zinc powder reacts with a variety of alkyl halides in DMF to furnish the corresponding organozinc compounds. Aqueous decomposition of these solutions gave the expected hydrocarbons in good yield. The procedure is a satisfactory alternative for dehalogenation when the commonly employed hydride complexes[4] or metal amines[5] cannot be used. For example, 8,15-dibromolongibornan-9-one was reduced to longibornan-9-one in 82% yield using Zn/DMF (eq 2).

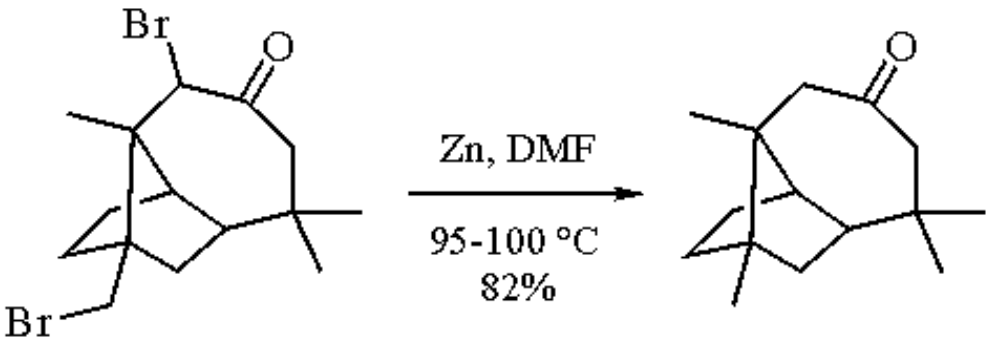

(2)

In a subsequent study, reaction of dibromocyclopropane with Zn/DMF gave monobromocyclopropane (eq 3), allene (eq 4), or a mixture of

products (eq 5), depending on the ring system of the substrate.[6] Thus no generalization could be made. The yields of some of the products formed from *gem*-dibromocyclopropanes were comparable to those obtained by other methods.

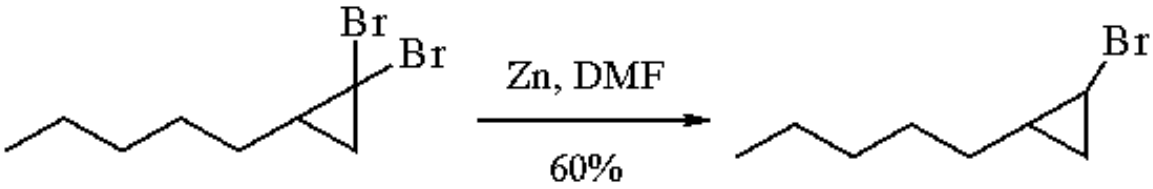

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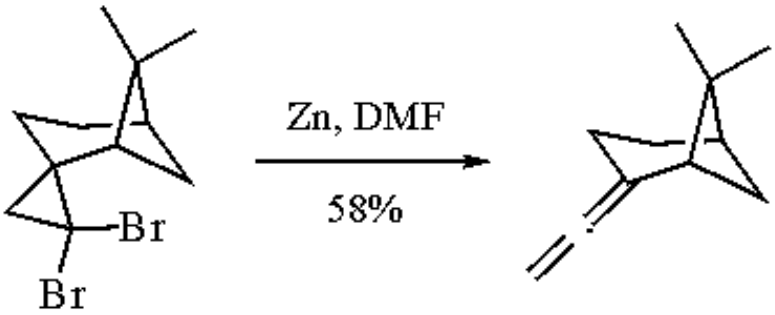

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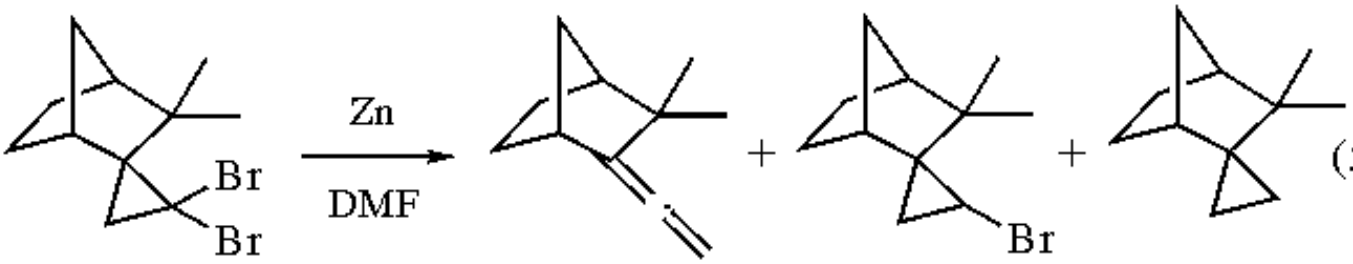

(5)

Reduction of Azides.

Carbohydrate azides are valuable intermediates for the synthesis of amino sugars. This transformation is commonly brought about by catalytic reduction[7] or by treatment with ***Lithium Aluminum Hydride***[8] or ***Sodium Borohydride***.[9] Ohrui and Emoto discovered that Zn/aq DMF is an excellent reagent to reduce an azide group to the corresponding amine group (eq 6).[10] This reaction was complete in 45 min whereas the corresponding sodium borohydride reduction required 20-30 h.

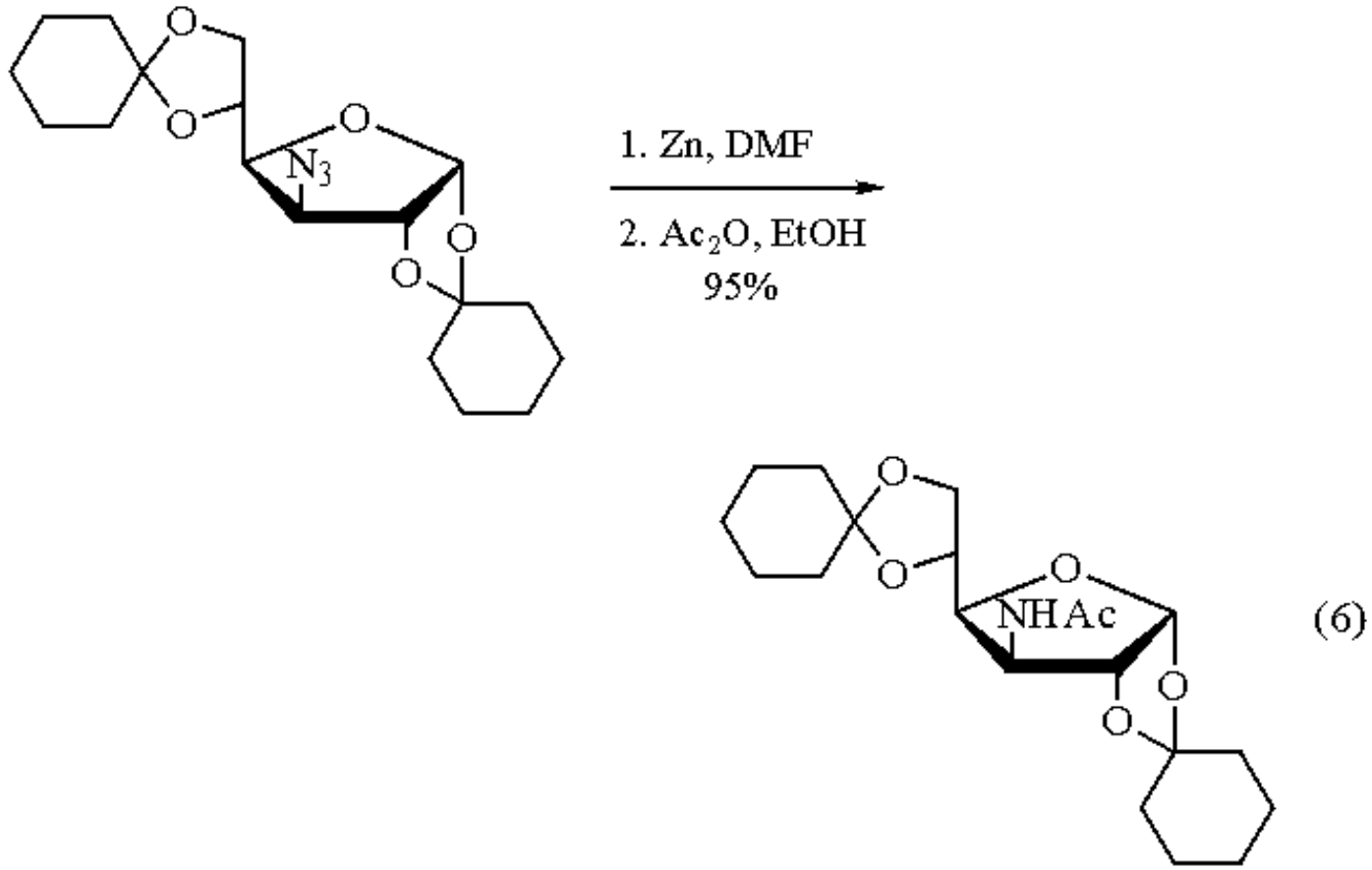

Reduction of Aldehydes to Alcohols.

A mixture of Zn and ***Antimony(III) Chloride*** in aqueous DMF reduces aldehydes to the corresponding alcohols in excellent yield.[11] A variety of aliphatic (eq 7), aromatic (eq 8), and α,β-unsaturated (eq 9) aldehydes were reduced to alcohols under relatively mild conditions.

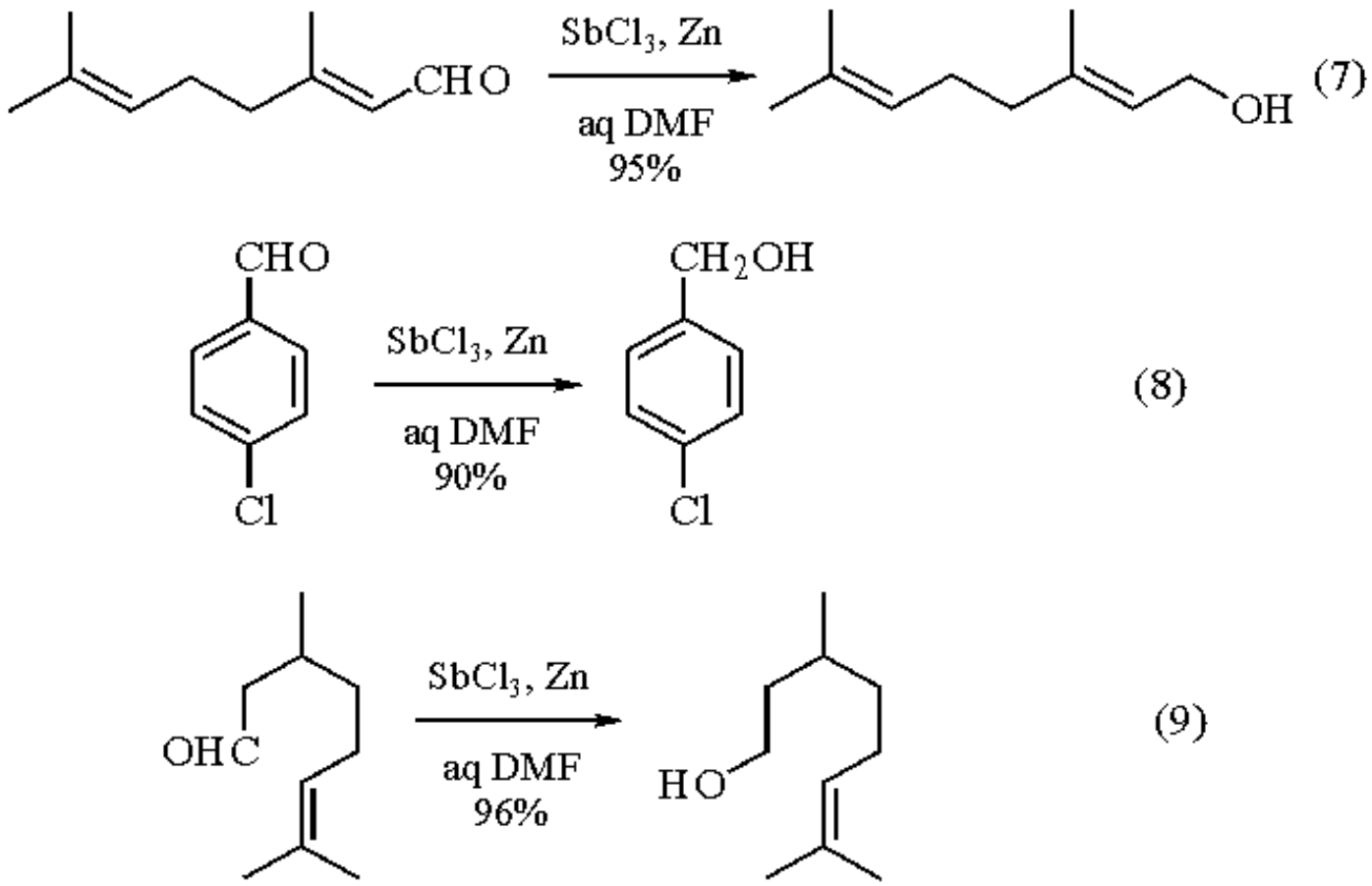

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Zinc-Graphite[1]

Zn-Gr

[7440-66-6] · Zn · Zinc-Graphite · (MW 65.39)

(very highly activated form of zinc, able to convert halides into organozinc species under mild conditions;[2,3] eliminates α-oxy halides to alkenes[4])

Solubility: insol in all common solvents; compatible with THF and other ethereal solvents.

Preparative Methods: ***Potassium-Graphite*** is prepared by reaction between ***Potassium*** metal and degassed graphite at 150 °C. When cool the potassium graphite is suspended in THF. ***Zinc Chloride*** is added and a very vigorous reaction ensues before the THF is heated to reflux to ensure complete reaction. Zinc/silver-graphite is prepared by the addition of 10 mol % ***Silver(I) Acetate*** to the zinc chloride mixture. These preparations have only been reported on a 15 mmol scale; because molten potassium is used and the reduction of zinc chloride is highly exothermic, great caution should be exercised in any scale-up.[3,5]

Handling, Storage, and Precautions: the reagent consists of highly active metal particles; it should be handled under argon and used immediately after preparation.

Introduction.

The reagent prepared by reduction of zinc chloride with potassium graphite does not consist of intercalated zinc; instead, very fine particles of zinc are deposited upon the graphite, which serves as an inert carrier.[1a] A comparison of the conditions required to condense ethyl bromoacetate with cyclohexanone was used to demonstrate that more active zinc is formed by this method than by other activation methods. The superiority of zinc/silver-graphite over simple zinc-graphite is also apparent (Table 1).[5]

Table 1 Comparison of Zinc Reagents

Zinc reagent	Temp. (°C)	Yield (%)
Zinc dust	80	56
Zn Cu couple	66	82
Rieke zinc	25	95
$ZnCl_2$/Li naphthalenide	25	95 98
Zinc graphite	0	75
Zinc/silver graphite	- 78	92

The advantages of using zinc-graphite are that the workup of the reaction is simple, substrates formerly considered as poor may be converted to zinc reagents in good yield and, because low temperatures are used, stereocontrol may be better. Graphite may be removed from the reaction mixtures after quenching by simple filtration, in contrast to the soluble reagents like naphthalene used in Rieke and similar methods, which are usually removed by chromatography.

Organozinc Reagents.

Zinc-graphite and zinc/silver-graphite have been used to generate organozinc reagents from α-chloro[2,3] and α-bromo[2,3] esters and lactones, γ-bromo crotonates,[3,5] allylic bromides,[3,6] and 2-bromomethyl-2-propenoates.[3,7]

One class of substrate where the high reactivity of zinc/silver-graphite has been used to effect a previously difficult transformation is α,α-dihaloacetates. Use of zinc/silver-graphite allows the synthesis of α-halo-β-hydroxy esters in excellent yield.[8] If ***Potassium Carbonate*** is added during workup, then glycidic esters may be isolated directly (eq 1).[8]

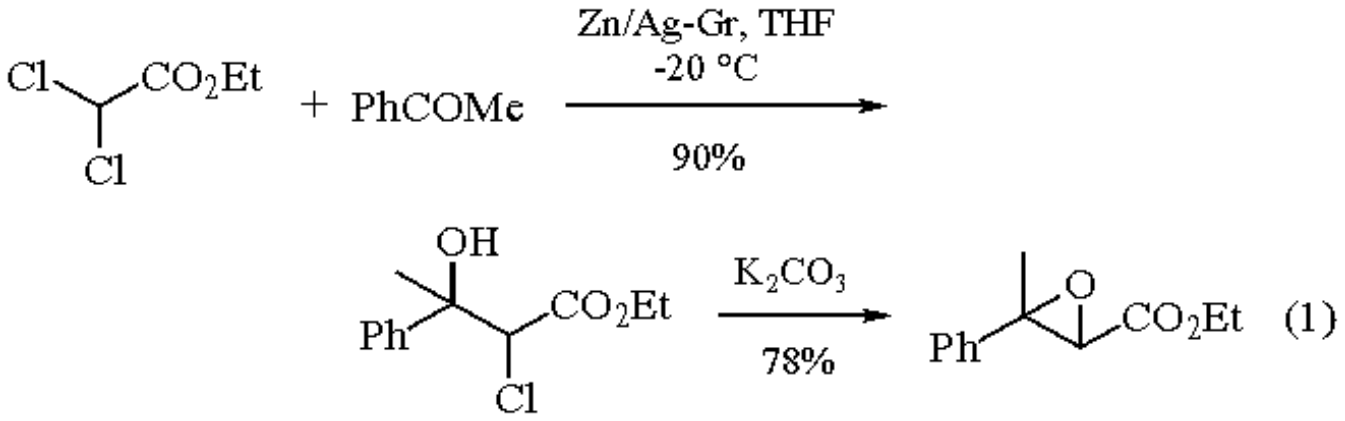

Examples of the improved stereoselectivity achievable by the use of zinc/silver-graphite have been found in the reactions of 2-bromomethyl-2-propenoates with chiral ketones (eq 2).[5,7]

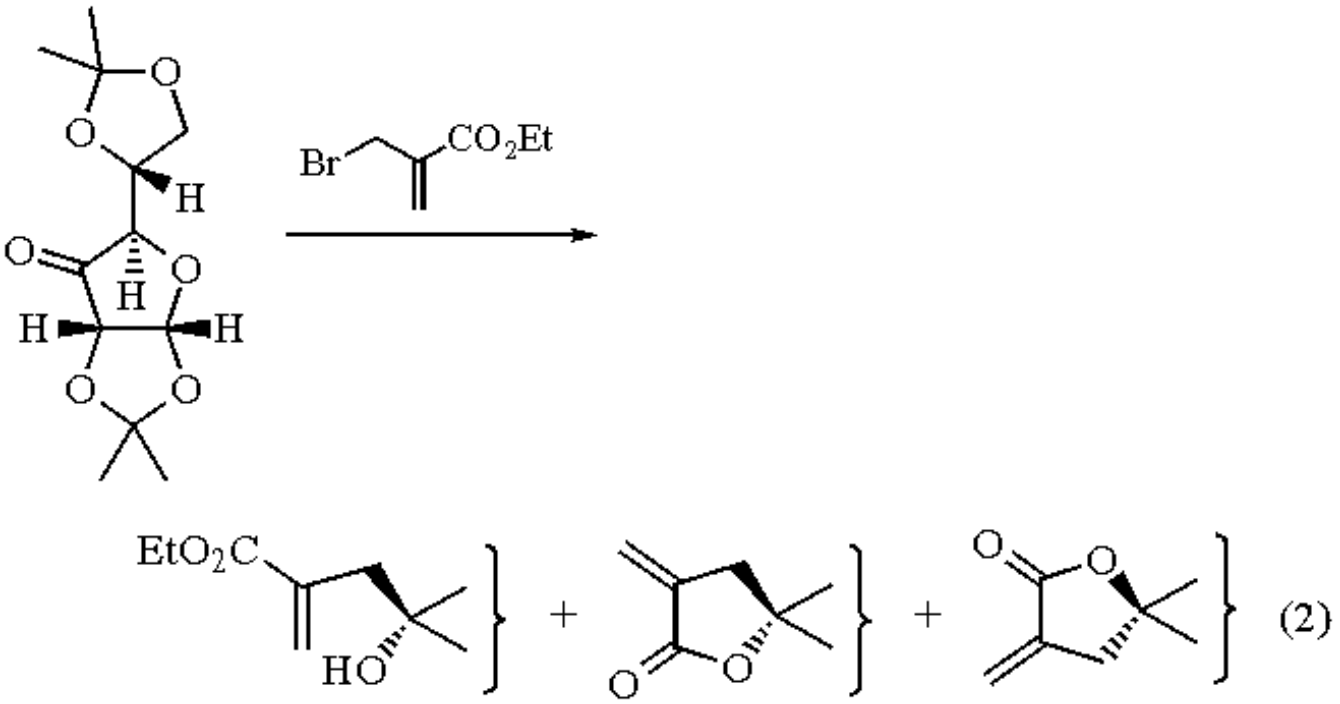

Zn dust 50 °C, 1 h	41	35	24
Zn/Ag-Gr -78 °C, 10 min	0	96	0

Eliminations.

The use of zinc/silver-graphite for the synthesis of glycals and eliminative ring opening of sugar derivatives has been reviewed.[1a] The advantages of using zinc/silver-graphite are that yields are high and, because low temperatures are used, most protecting groups are compatible.

The conversion of glycosyl bromides to glycals is typical of these reactions (eq 3). This reaction can not be carried out using Rieke zinc. In the presence of azido groups, either in the substrate or in another compound in the flask, the mechanism changes and reduction occurs (eq 3). This type of elimination has found application in a novel unmasking reaction used by Ireland in an approach to FK506 synthesis.[9]

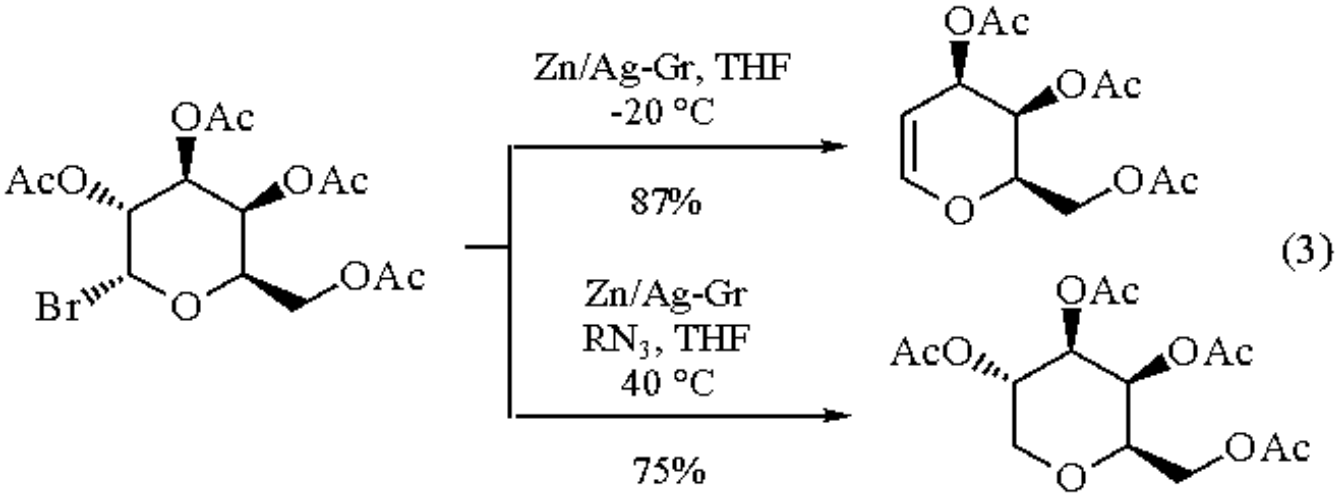

Related Reagents.

Nickel-Graphite; ***Palladium-Graphite***; ***Zinc***; ***Zinc/Copper Couple***; ***Zinc/Nickel Couple***; ***Zinc/Silver Couple***.

---

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Zinc Iodide[1]

ZnI_2

[10139-47-6] · I_2Zn · Zinc Iodide · (MW 319.19)

(used in the preparation of organozinc reagents via transmetalation;[1] a mild Lewis acid useful for promoting addition[2] and substitution reactions[3])

Physical Data: mp 446 °C; bp 625 °C (dec); *d* 4.740 g cm^{-3}.

Solubility: sol H_2O (1 g/0.3 mL), glycerol (1 g/2 mL); freely sol EtOH, Et_2O.

Form Supplied in: white, odorless, granular solid; principal impurities are H_2O and iodine.

Analysis of Reagent Purity: mp.

Purification: heat to 300 °C under vacuum for 1 h, then sublime.

Handling, Storage, and Precautions: very hygroscopic and light sensitive; store under anhydrous conditions in the absence of light.

Organozinc Reagents.

Organozinc reagents may be prepared through transmetalation of organolithium, organomagnesium, and organocopper species with ZnI_2, although ***Zinc Chloride*** and ***Zinc Bromide*** are used far more frequently.[1a] It is more usually the case that organozinc iodides are prepared by zinc insertion into alkyl iodides using ***Zinc/Copper Couple***.[1a] These zinc reagents possess reactivity analogous to the other organozinc halides, finding particular use in palladium-catalyzed coupling reactions (eq 1).[4] An alternative method for the preparation of the Simmons-Smith reagent (***Iodomethylzinc Iodide***) involving the treatment of ***Diazomethane*** with ZnI_2 has been reported (eq 2).[5]

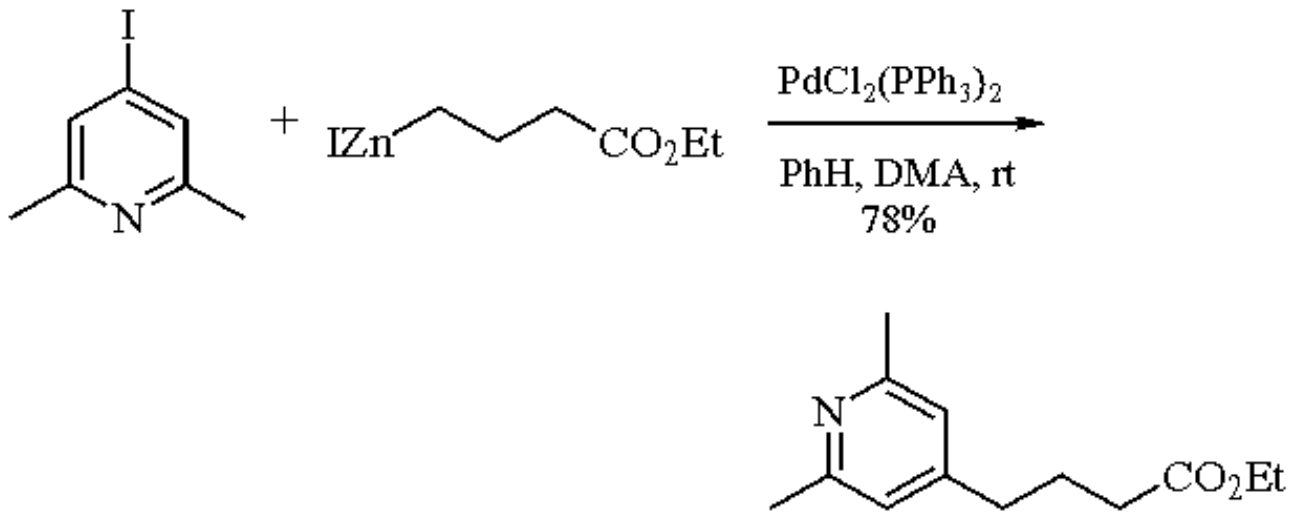

(1)

$$CH_2N_2 + ZnI_2 \longrightarrow ICH_2ZnI + N_2 \qquad (2)$$

Cycloaddition Reactions.

The catalytic effect of ZnI_2 on the Diels-Alder reaction has been noted (eq 3),[6] but its use in such cycloaddition reactions is rare compared with $ZnCl_2$ and $ZnBr_2$.

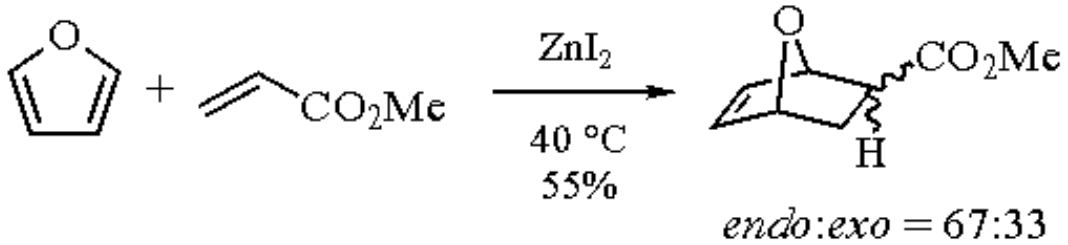

(3)

Activation of C=X Bonds.

Catalysis of aldol condensation reactions using silyl ketene acetals and ZnI_2 has been the subject of several studies.[7] It is observed that ZnI_2 favors the activation of functionalized carbonyl compounds via β-chelates to impart useful stereoselectivity (eq 4).[7a] In analogous fashion, diastereoselective additions to imines and nitrones have been reported which offer useful access to β-lactams (eq 5).[8] α,β-Unsaturated esters are subject to conjugate addition reactions by silyl ketene acetals, also through the agency of ZnI_2 activation (eq 6).[9]

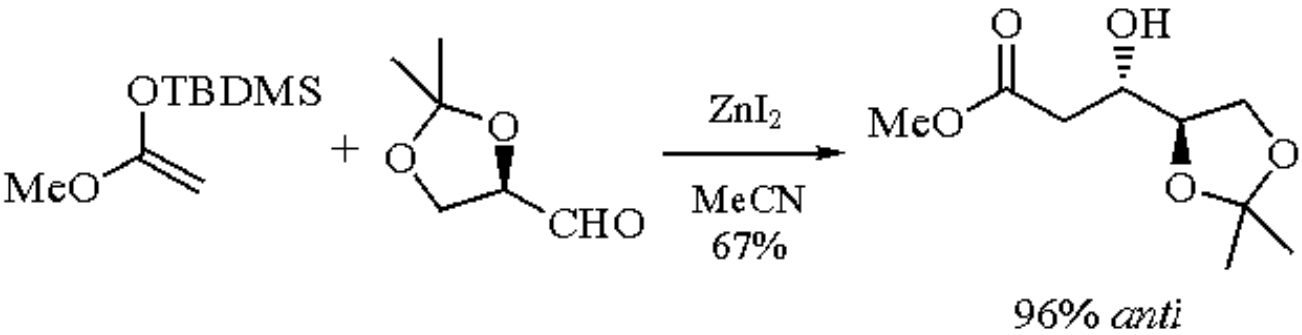

(4)

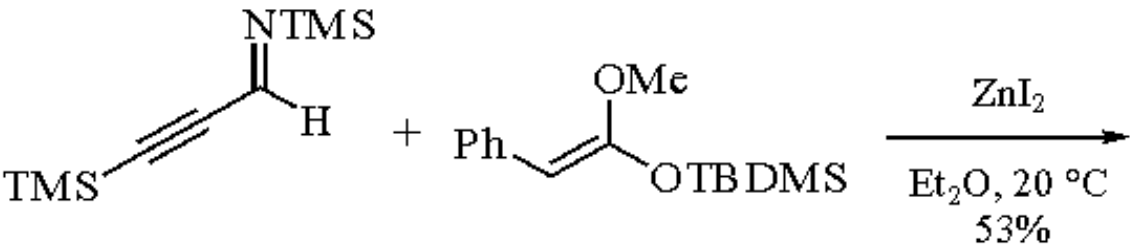

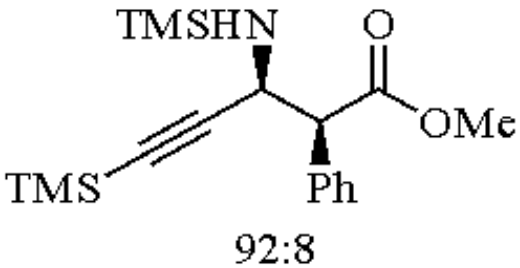

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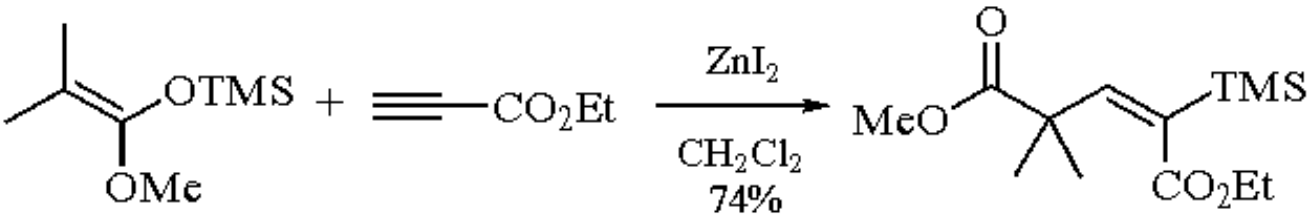

(6)

An important role for ZnI_2 has been found in the catalysis of R_3SiCN addition to ketones and aldehydes to afford silyl protected cyanohydrins.[10] This is a very general reaction that is effective even with very hindered carbonyl compounds (eq 7).[11] Diastereoselective

cyanohydrin formation has been reported when these reaction conditions are applied to asymmetric carbonyl substrates (eq 8).[2a]

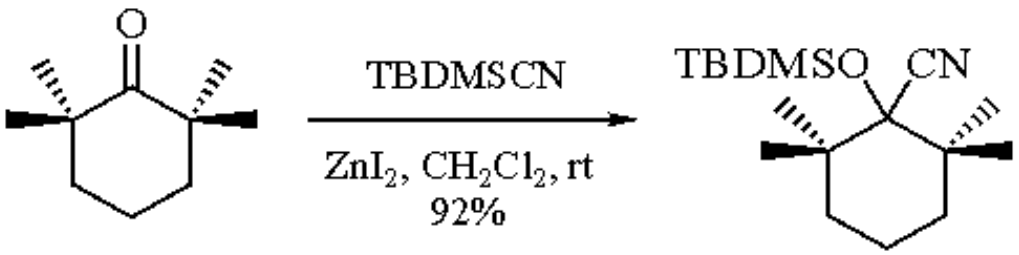

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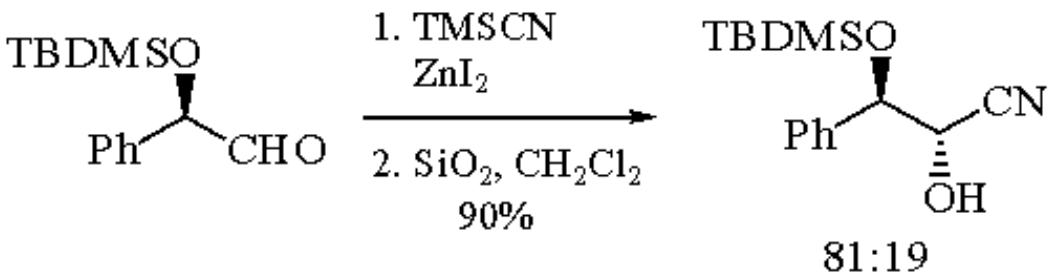

(8)

Activation of C-X Bonds.

The Lewis acidity of ZnI_2 may be exploited to activate various carbon-heteroatom bonds to nucleophilic substitution. Treatment of epoxides and oxetanes with ***Cyanotrimethylsilane***/ZnI_2 results in selective C-N bond formation with ring opening (eq 9).[12] Similarly, C-S and C-Se bonds may be formed by treating cyclic ethers with ZnI_2 and $RSSiMe_3$ and $RSeSiMe_3$, respectively (eq 10).[13]

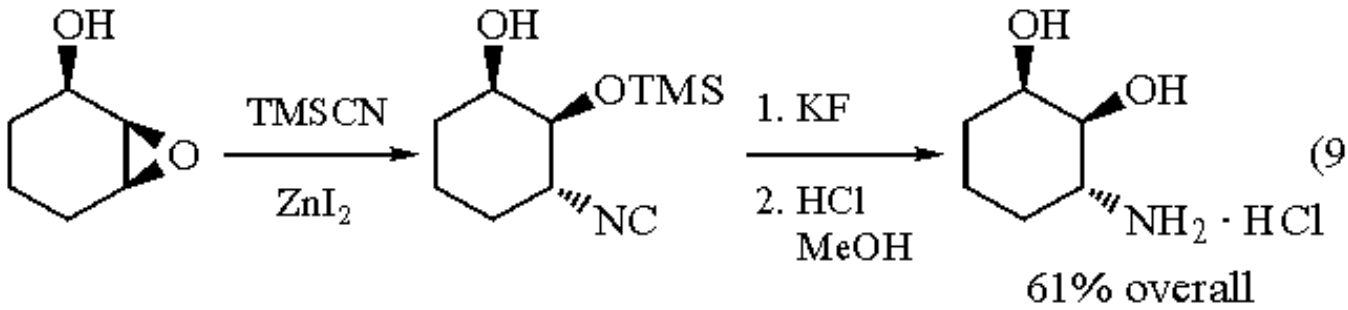

(9)

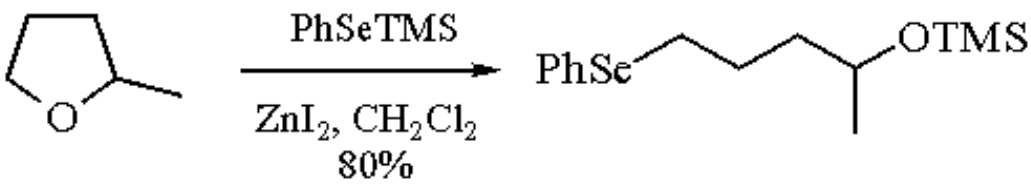

(10)

Treatment of 4-acetoxy- and 4-sulfoxyazetidin-2-ones with ZnI_2 results in the formation of the corresponding imine or iminium species which subsequently suffers silyl-mediated addition. These reactions result in the formation of *trans* substitution (eqs 11 and 12).[14,15]

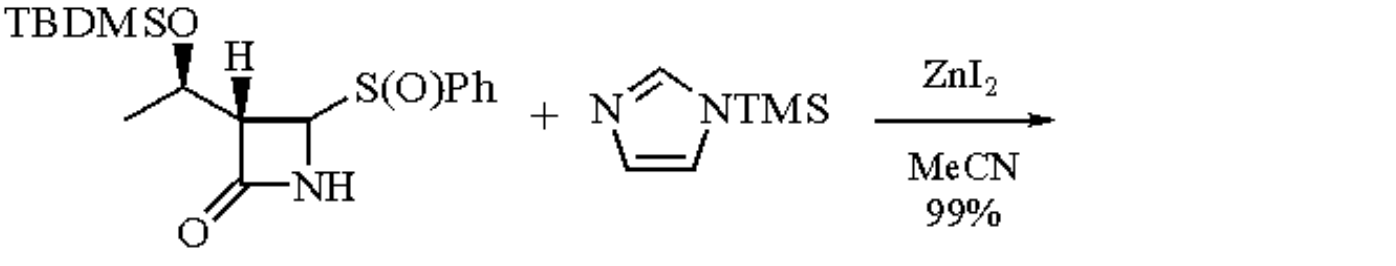

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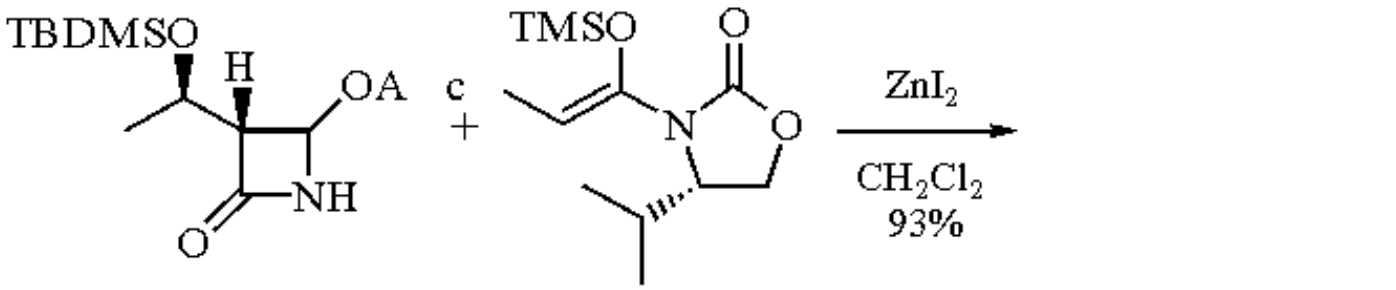

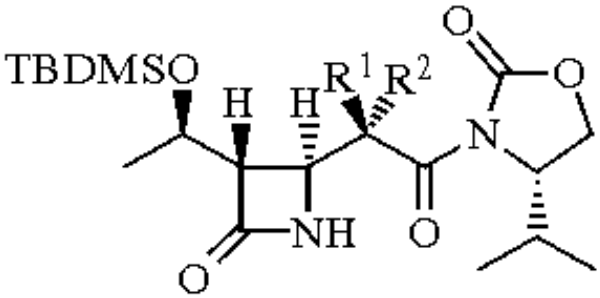

(12)

$(R^1 = Me, R^2 = H):(R^1 = H, R^2 = Me) = 3:1$

Substitution reactions of orthoesters[3b] and acetals,[3c] including anomeric bond formation in carbohydrates (eq 13),[16] have been catalyzed by ZnI_2.

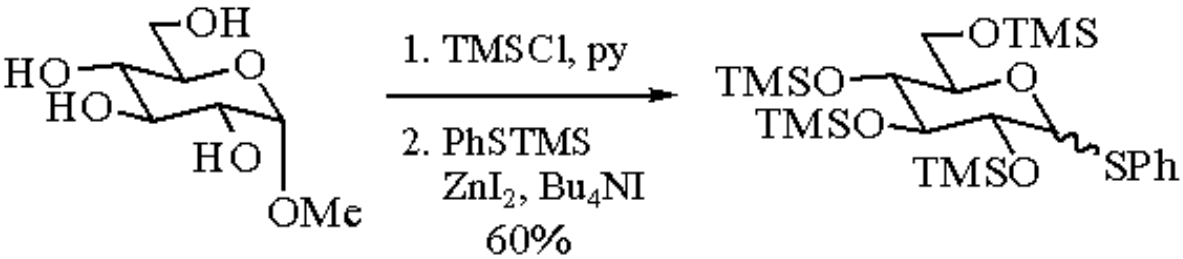

(13)

Reduction.

Allyl and aryl ketones, aldehydes, and alcohols are reduced to the corresponding hydrocarbon by ***Sodium Cyanoborohydride***/ZnI_2 (eq 14).[17] This is a reasonably reactive reducing mixture which will also attack nitro and ester groups.

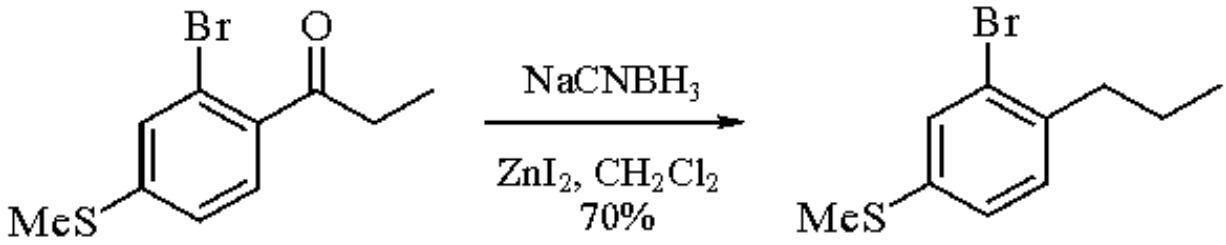

(14)

Deprotection.

Methyl and benzyl ethers may be cleaved by the combination of ***(Phenylthio)trimethylsilane***/ZnI_2 (eq 15).[18] Similar cleavage of alkyl and benzyl ethers takes place using ***Acetic Anhydride***/ZnI_2 to afford the corresponding acetate (eq 16).[19]

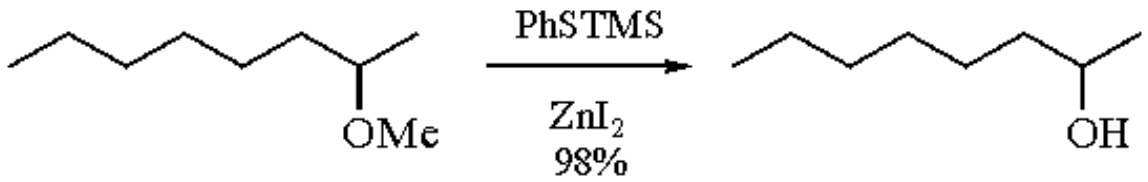

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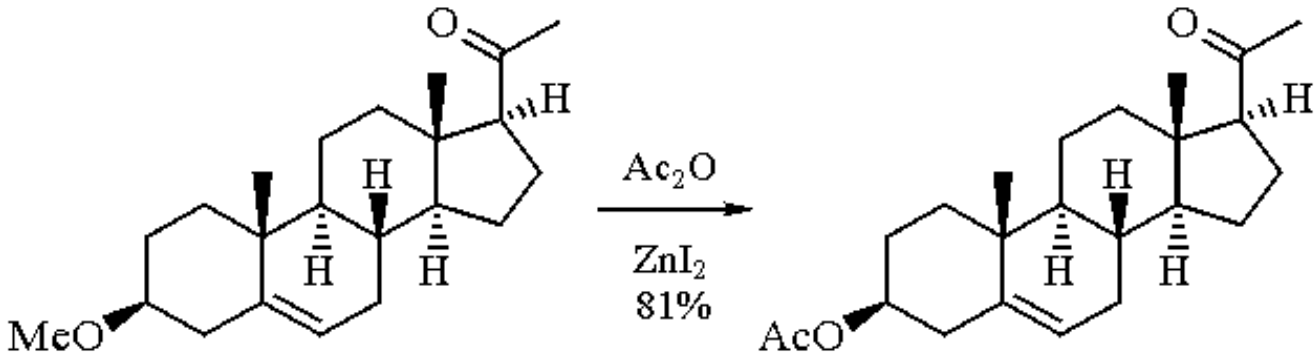

(16)

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12. (a) Gassman, P. G.; Gremban, R. S. *TL* **1984**, *25*, 3259. (b) See also: Gassman, P. G.; Haberman, L. M. *TL* **1985**, *26*, 4971.
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14. (a) Kita, Y.; Shibata, N.; Yoshida, N.; Tohjo, T. *TL* **1991**, *32*, 2375. (b) See also: Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *CC* **1990**, 727.
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Zinc/Nickel Couple[1]

Zn/Ni

[7440-66-6] · Zn · Zinc/Nickel Couple · (MW 65.39)

(reducing reagent for a variety of organic functional groups;[2] coupling agent for alkenyl and aryl halides;[3] induces addition of organic halides to alkenes;[4] reagent for Simmons-Smith cyclopropanation[5])

Physical Data: dark gray powder, of variable composition.

Preparative Methods: the zinc/nickel couple is usually prepared from zinc dust and ***Nickel(II) Chloride*** or ***Nickel(II) Bromide*** (dry or hydrate). Zinc dust (10 g) suspended in water (3 mL) and 4.04 g of $NiCl_2.6H_2O$ were added to 10 mL of water at 60 °C. After disappearance of Ni^{II} coloration, the solid is filtered, washed, and dried under reduced pressure. The couple is frequently prepared immediately before use. It can be prepared in the presence of the organic substrates in alcohols or DMF, etc., and in the presence of ***Triphenylphosphine***, ***Potassium Iodide***, or ***Pyridine***. Sonication at room temperature improves both the preparation and the reaction step.

Handling, Storage, and Precautions: the Zn/Ni couple seems to have good stability in air.

Hydrogenation Reagent.

Many organic functionalities can be reduced by the zinc/nickel couple in water or aqueous organic solvents.[1,6] It has been reported that nitriles are reduced to primary amines with almost no secondary amine (eq 1),[2] but this result has not been confirmed. Nitro groups are reduced to amines in high yields (eq 2).

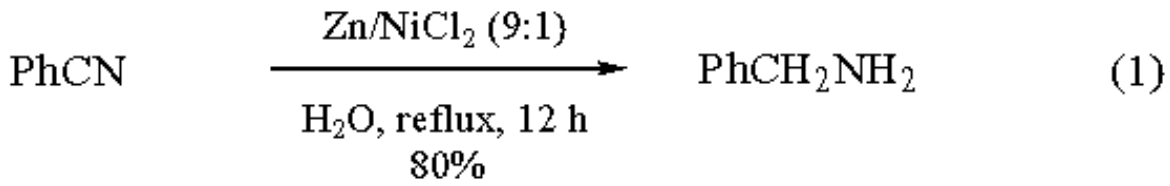

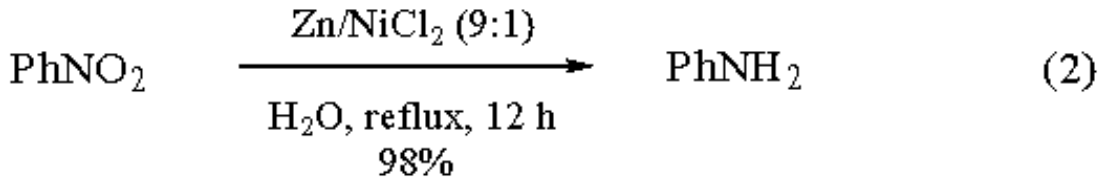

Halides, alkenes, saturated aldehydes, and ketones react readily with the Zn/Ni couple.[1,2] Water is essential as the source of hydrogen. Hydrogenation of alkenes proceeds rapidly, but that of carbonyl groups more slowly. Although original reaction conditions involved heating, improved yields were obtained by sonication (eq 3).[7,8] Adjusting the pH (eq 4) and the nickel to zinc ratio (eq 5) change the selectivity. Use of D_2O instead of water as the hydrogen source yields 1,2-dideuterated alkanes.[9]

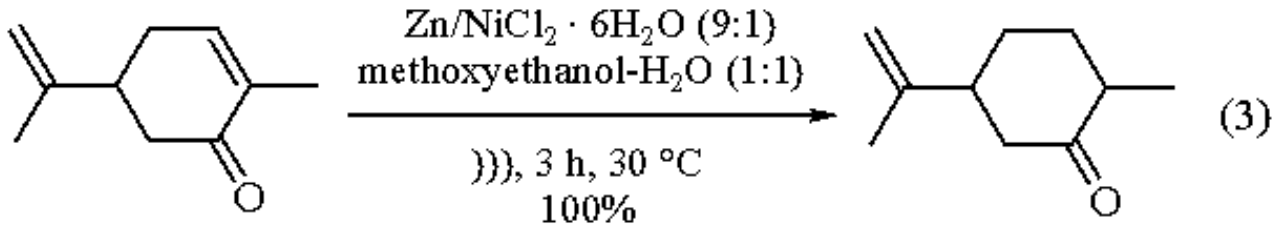

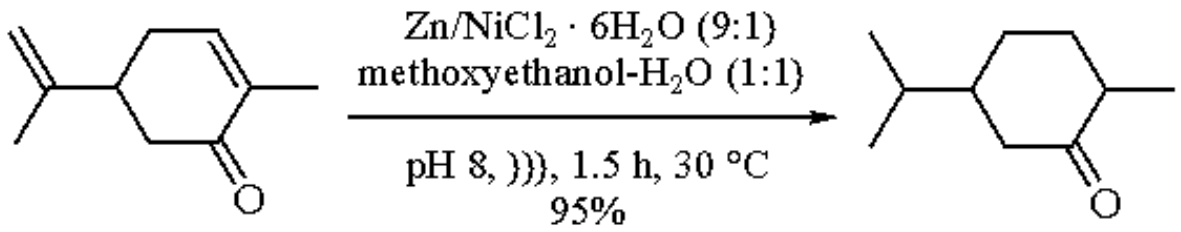

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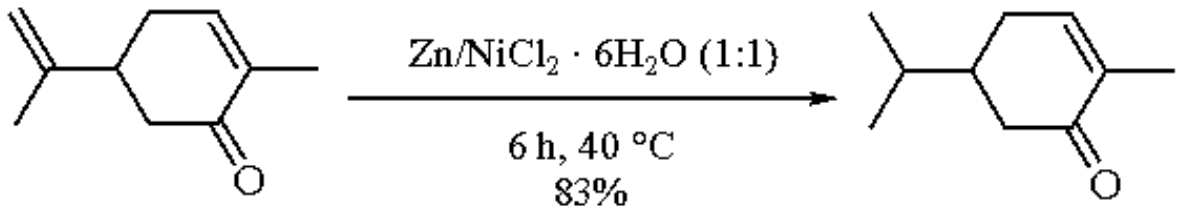

(5)

Coupling of Alkenyl and Aryl Halides.

Alkenyl halides couple to provide dienes in the presence of Zn, $NiCl_2$, and ***Potassium Iodide*** (eqs 6 and 7). The KI helps the formation of the Zn/Ni couple and exchanges the substrate halogen atom for iodine.[3] Reaction with Ni^0 occurs in the next step, followed by the coupling itself. Chlorides do not react. Generally, one alkenic unit retains its configuration, but the second one is frequently isomerized (eq 7).

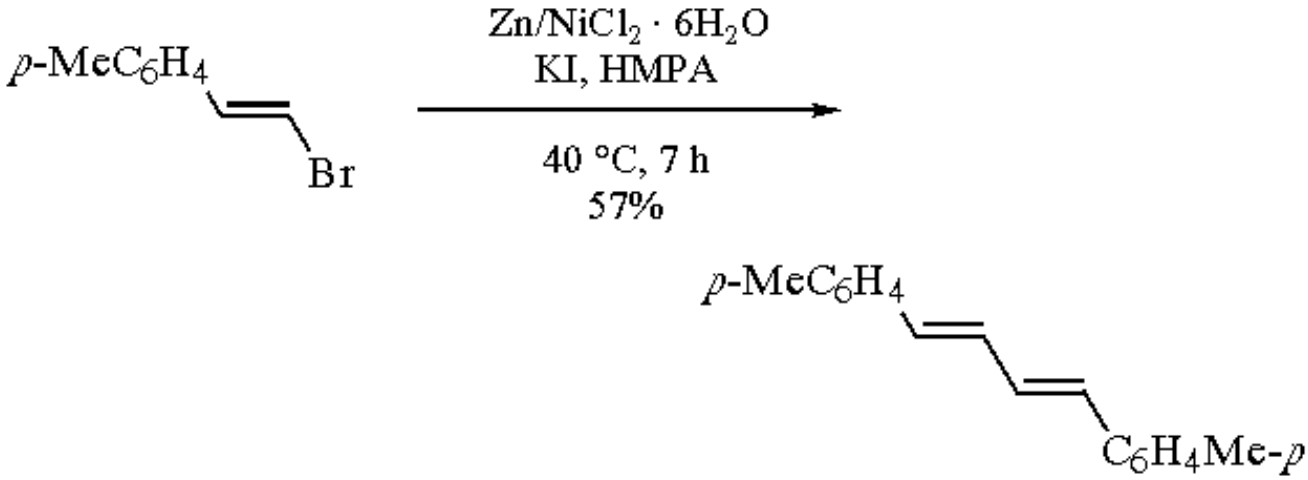

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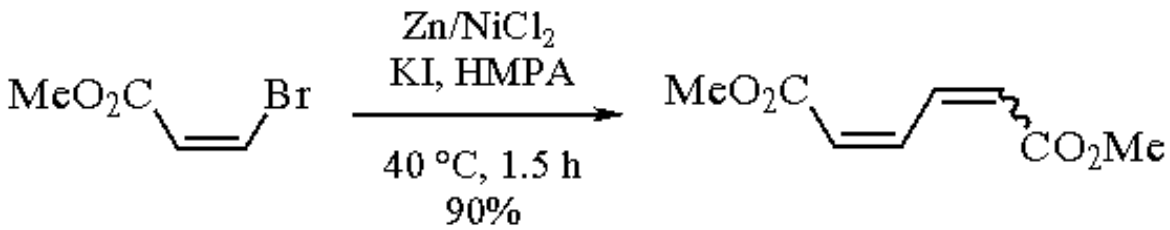

(7)

Aryl and heteroaryl halides undergo the Ullmann coupling in high yields under mild conditions.[10] The method was used in cyclophane synthesis (eq 8).[11] Aryl trifluoromethanesulfonates are equally successfully coupled under sonication (eq 9).[12]

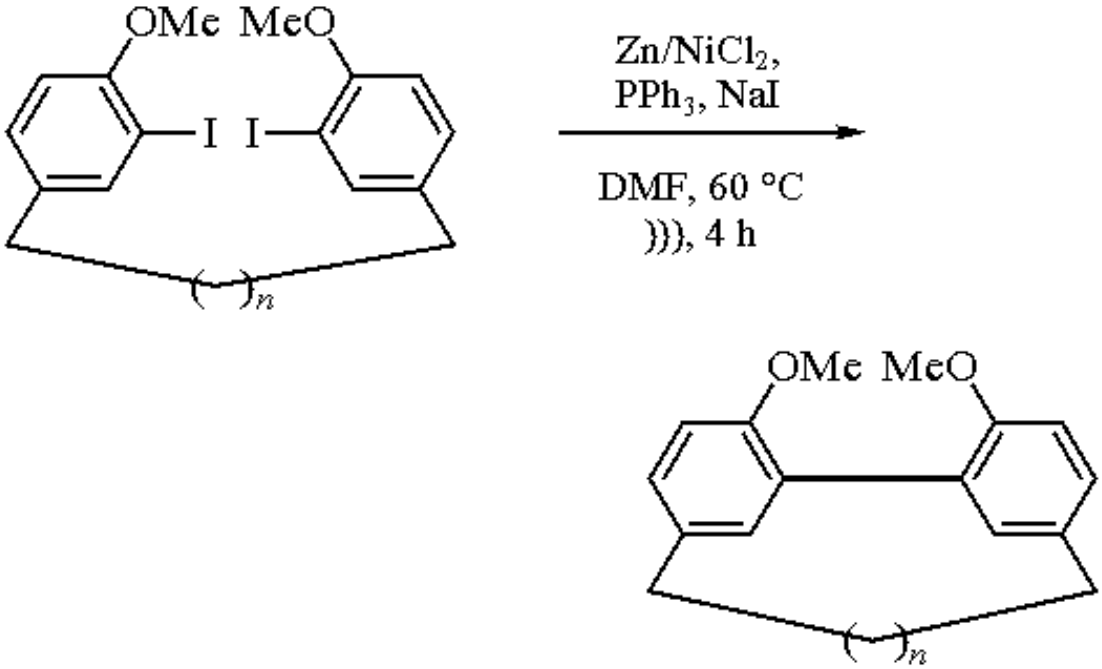

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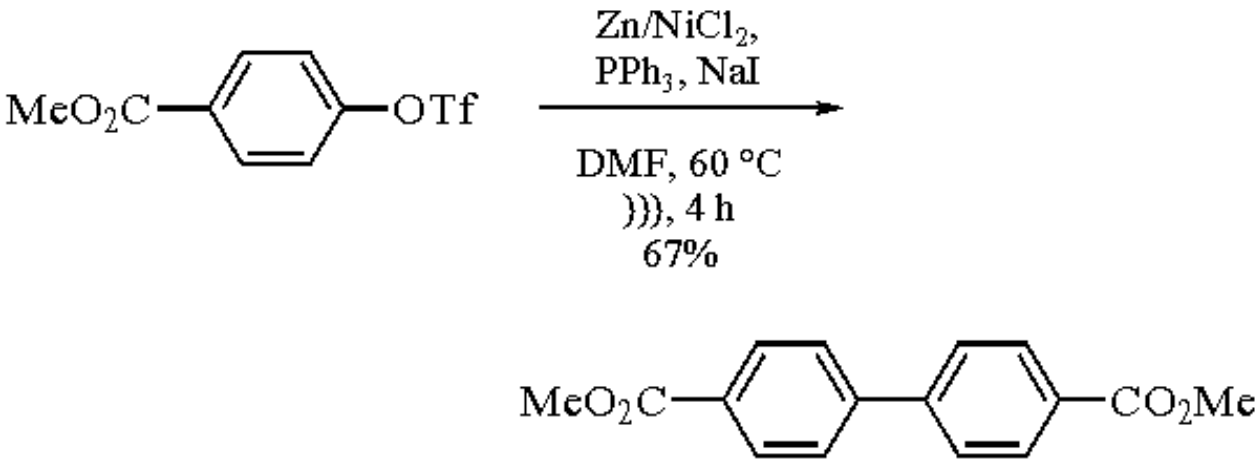

(9)

Additions of Alkyl, Alkenyl, or Aryl Groups to Alkenes.

The Zn/Ni couple is an example of the new class of reagents that permit organometallic-like reactions under nonanhydrous conditions (see also ***Zinc/Copper Couple***). With styrene, a Heck-type addition-elimination sequence is observed (eq 10).[4] A Reformatsky-like reaction occurs between ethyl difluoroiodoacetate and nonactivated alkenes (eq 11).[13] Conjugate additions take place with activated alkenes (eq 12), even when alkenyl or aryl halides are used which are inert with the Zn/Cu couple.[14]

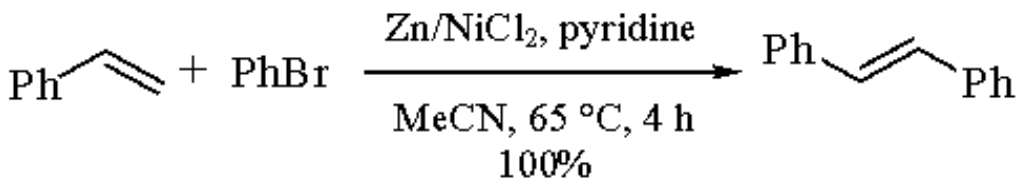

(10)

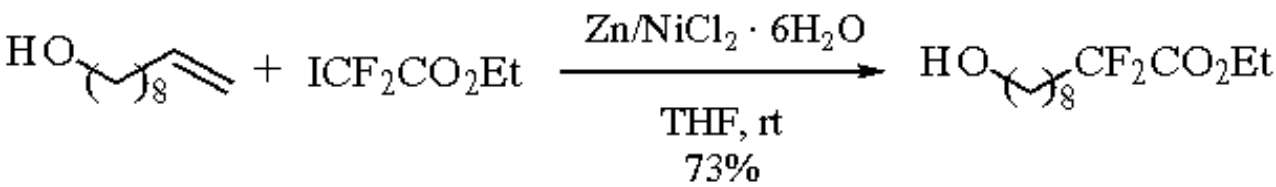

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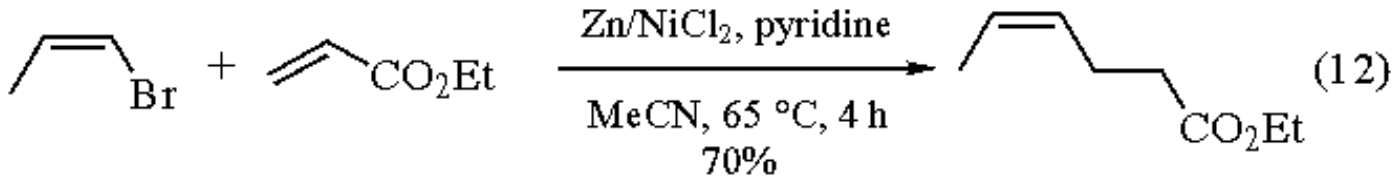

Cyclopropanation.

Electron-deficient alkenes undergo the Simmons-Smith cyclopropanation in the presence of NaI and ***Dibromomethane*** (eq 13). With fumarate and maleate esters, the reaction proves to be nonstereoselective, in contrast to the zinc/cobalt couple.[5]

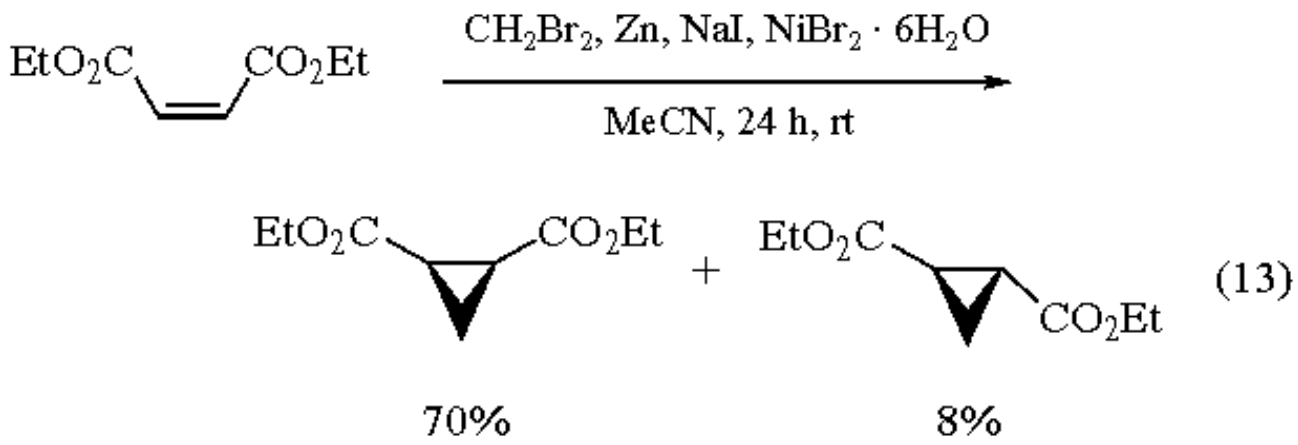

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Zinc Oxide

ZnO

[1314-13-2] · OZn · Zinc Oxide · (MW 81.39)

(mild base; forms salts which effect tertiary alkyl halide solvolysis;[1] acid scavenger;[2] catalyst of aldol,[3] Wittig,[4] Knoevenagel,[4] and other reactions)

Physical Data: mp 1975 °C; *d* 5.47 g cm^{-3}.

Solubility: insol H_2O, alcohol; sol acids, alkalis.

Form Supplied in: the commercial material is often obtained as a coarse white or grayish powder. This has a much lower water content and surface area[4] than that produced by drying $Zn(OH)_2$, and for some reactions is much less suitable.

Preparative Methods: by drying $Zn(OH)_2$,[4] precipitated from $Zn(NO_3)_2$ by addition of NaOH.

Handling, Storage, and Precautions: reputedly nontoxic as powder, but ZnO fume is harmful by inhalation. Should be stored sealed, as it will absorb CO_2 from air.

Tertiary Alkyl Halide Solvolysis.[1]

ZnO (or ***Zinc Carbonate***) reacts with carboxylic acids to form zinc salts. These salts, either preformed or formed in situ, react with tertiary (but not reliably with primary, secondary, or α-carbonyl-substituted) halides to give the corresponding esters (eq 1). Five equiv of the acid as solvent (in situ generation) or aprotic solvents are suitable. Similarly, in aqueous (e.g. 80% aq acetone), alcoholic, or phenolic solvents, ZnO causes formation of the alcohol or appropriate ether (eq 2). The former reaction is particularly useful for formation of *t*-butyl esters (yields 91-95%), as a protection for carboxylic acids.

$$Zn(OCOR)_2 + t\text{-}R^1\text{-}Hal \longrightarrow t\text{-}R^1OCOR \qquad (1)$$

$$t\text{-}R^1\text{-}Hal \xrightarrow[ROH]{ZnO} t\text{-}R^1OR \qquad (2)$$

Acid Scavenger.[2]

The presence of small quantities of ZnO (and/or ***Potassium Carbonate***) is reported to improve yields greatly in particularly acid-sensitive *o*-quinodimethane reactions. Such activity could find more general use.

Basic/Amphoteric Catalyst.

ZnO gave a good yield in an intramolecular aldol reaction (eq 3),[3] slightly superior to the use of other inorganic catalysts (TiO_2, ThO_2, ***Alumina***) (yields 73-75%).

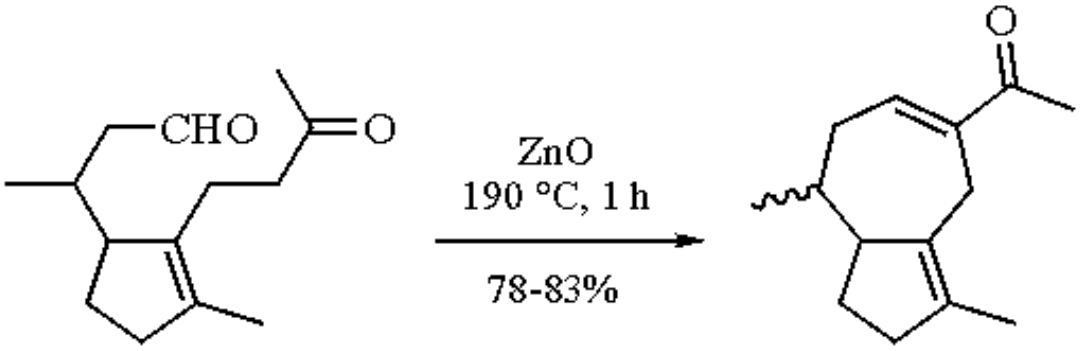

(3)

ZnO (or ***Magnesium Oxide***) is also able to catalyze Wittig, Wittig-Horner, and Knoevenagel reactions.[4] Commercial ZnO may be rendered more efficient by addition of a limited amount of water or polar organic solvent. In a reaction where the Wittig-Horner and Knoevenagel pathways may compete (eq 4), the proportions of products (**1**) and (**2**) are greatly influenced by these small amounts of added solvents, or by addition of small amounts of other metal salts. Thus ***Hexamethylphosphoric Triamide*** favours formation of (**2**), but ***Mercury(II) Chloride*** or ***Cadmium Chloride*** (among others) favor (**1**). These results were rationalized in terms of properties of both basic and acidic sites on the catalyst surface, as also noted[5] as an explanation of the catalytic utility of ZnO in several industrial scale processes.

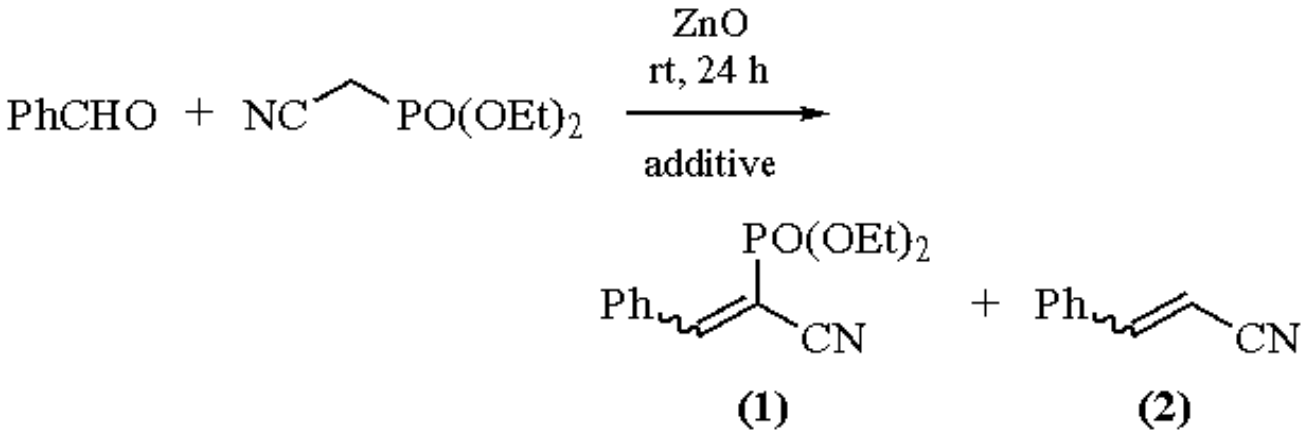

(4)

Two-carbon homologation of ketones is made possible via ZnO-catalyzed rearrangement of alkynic acetates (**3**) (eq 5).[6] The allenic acetate (**4**) is then easily hydrolyzed to the α,β-unsaturated aldehyde.[6b]

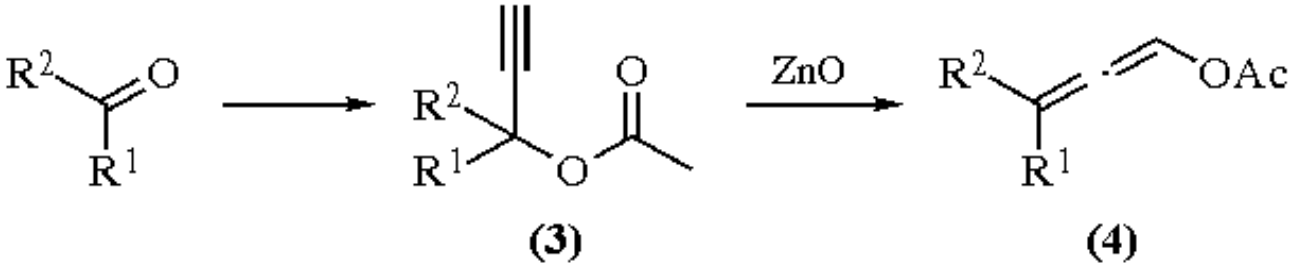

(5)

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Zinc/Silver Couple

Zn/Ag

[7440-66-6] · Zn · Zinc/Silver Couple · (MW 65.39)

(dehalogenation; preparation of organozinc compounds for carbon-carbon bond formation; cyclopropanations)

Physical Data: Zn: mp 419.5 °C; *d* 7.140 g cm^{-3}.

Solubility: insol most solvents. The reactions are typically run as suspensions with THF as solvent for preparation of organozinc reagents and MeOH utilized for most of the reductions. Et_2O, DMSO, and DMA have also been used as solvents.

Preparative Methods: ***Zinc*** powder (100 g) is added all at once to a refluxing solution of ***Silver(I) Acetate*** (100 mg) in 200 mL of acetic acid. The mixture is stirred for 30 s and quickly cooled. The zinc/silver couple is isolated by decantation and washed with anhydrous ether (6 × 100 mL), dried under vacuum, and stored at room temperature.[1] An alternative method uses zinc dust that has been prewashed with 10% HCl and uses a slightly higher Ag to Zn ratio.[2]

Handling, Storage, and Precautions: Zn is a moisture-sensitive, flammable solid. The Zn/Ag couple appears to be stable for months at room temperature if stored under an inert atmosphere.

Reductions.

The Zn/Ag couple is a very effective reducing agent for carbon-halogen bonds. It has been used to dehalogenate β-chloro-α,β-unsaturated ketones in good yield (eqs 1 and 2).[2,3]

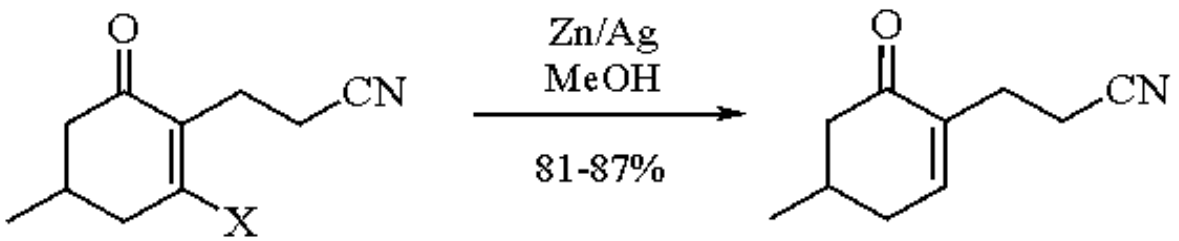

(1)

X = Cl, Br

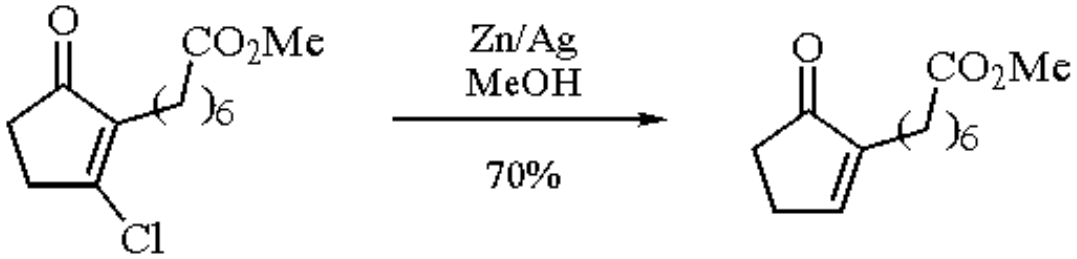

(2)

Aldehydes and ketones can be protected as their 5,5-dibromo-1,3-dioxane derivatives by reaction with 2,2-dibromo-1,3-propanediol. This carbonyl protecting group introduces no new chirality and is stable to a number of reagents that would normally react with the carbonyl. These derivatives can be deprotected under neutral conditions using Zn/Ag couple (eq 3).[4]

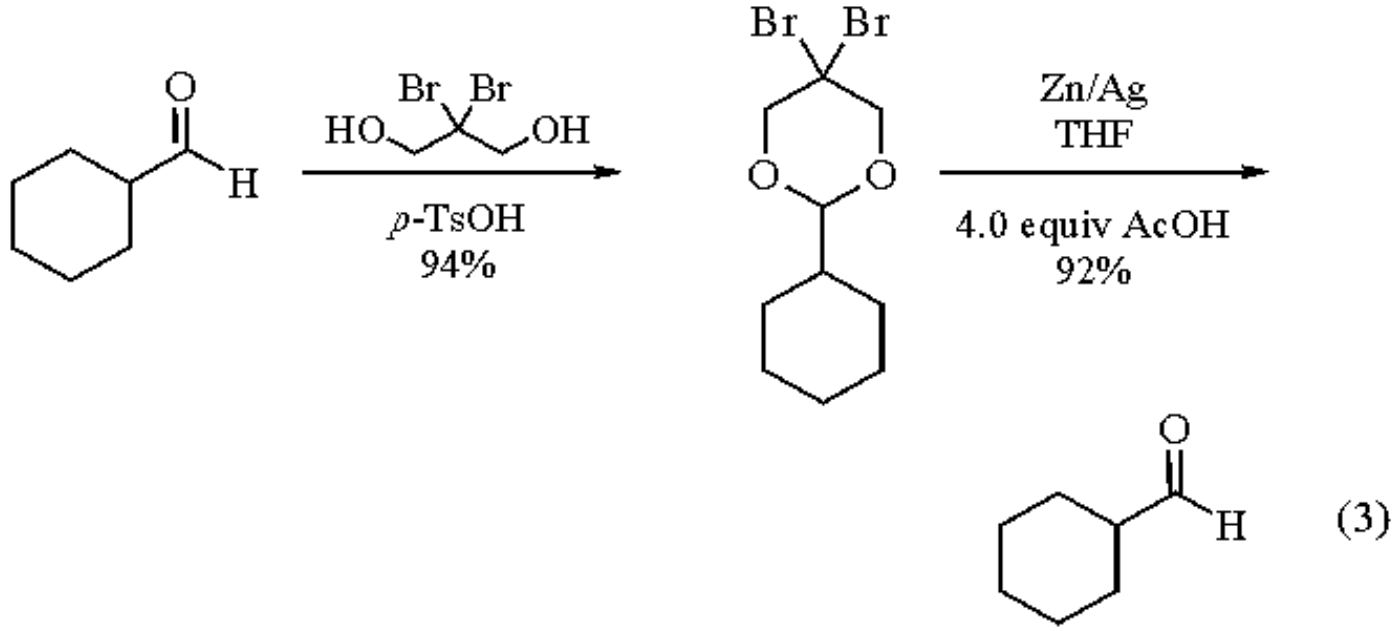

(3)

The debromination of 1,2-dibromides to form the corresponding alkene can be accomplished with Zn/Ag couple, as shown for the preparation of the Dewar benzene derivative (eq 4).[5]

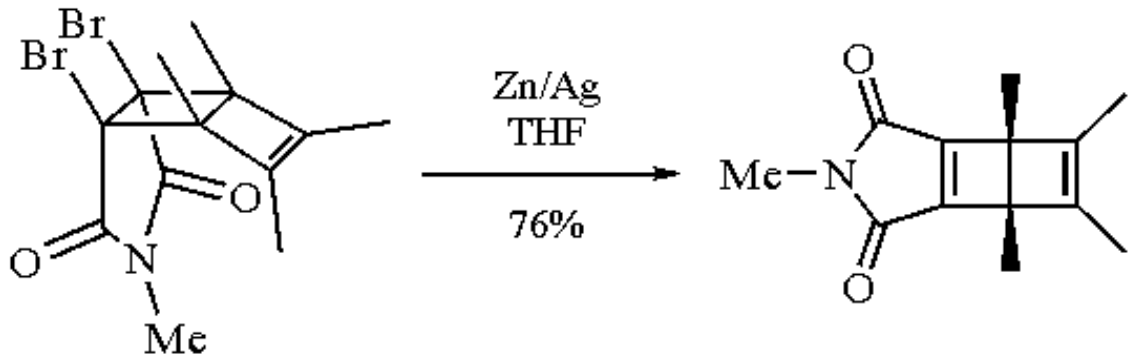

(4)

The final steps in the synthesis of one of the tricothecenes required the alkene and hydroxymethyl group to be simultaneously protected as the intramolecular bromo ether. The unraveling of the bromo ether was accomplished using Zn/Ag couple (eq 5).[6]

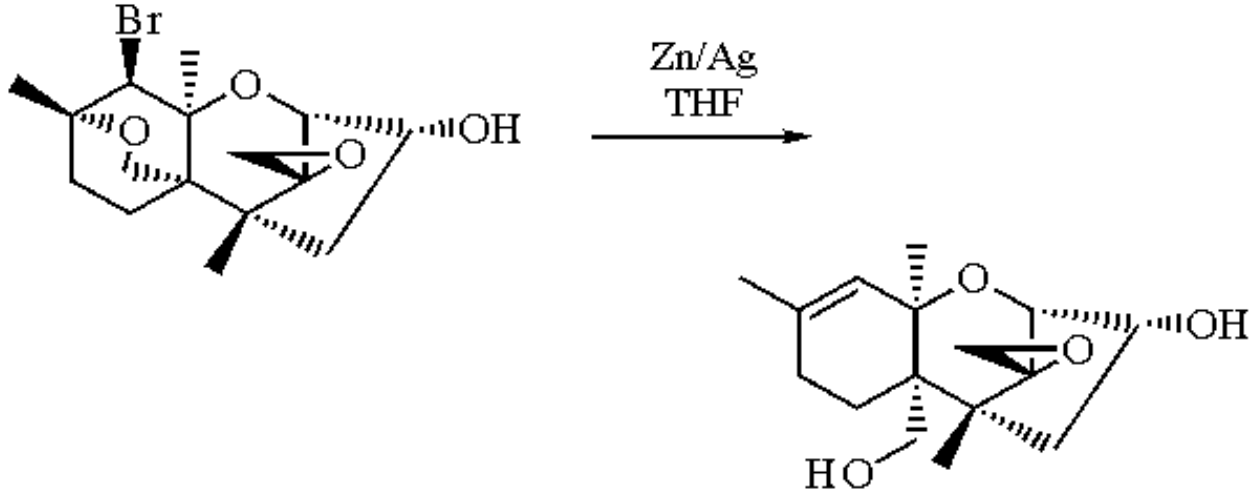

(5)

Zn/Ag couple has been utilized to debrominate selectively the bromohydrin penicillinate (eq 6). This produces a mixture of diastereomers in the ratio indicated.[7]

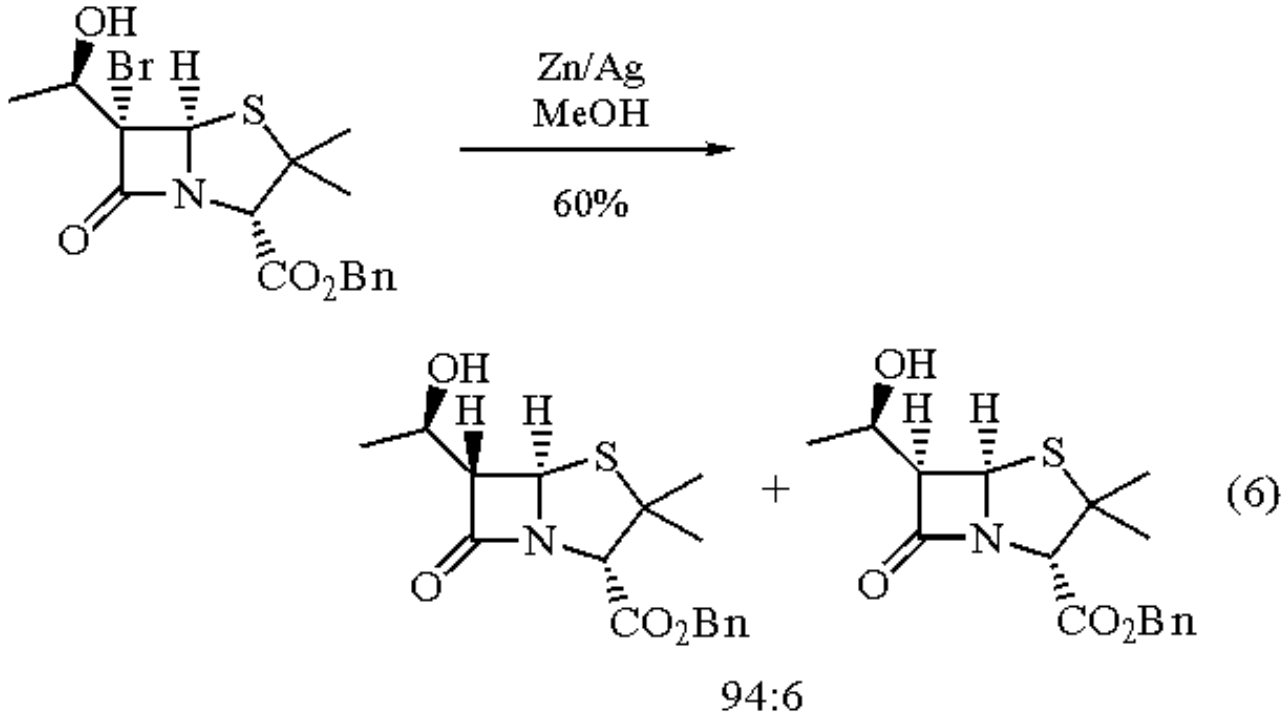

Reduction of the α-bromoacylphosphate produces the intermediate ketene which undergoes cycloaddition to produce the cyclobutanedione (eq 7). Attempts to prepare the acid chloride to use in place of the phosphate failed.[8]

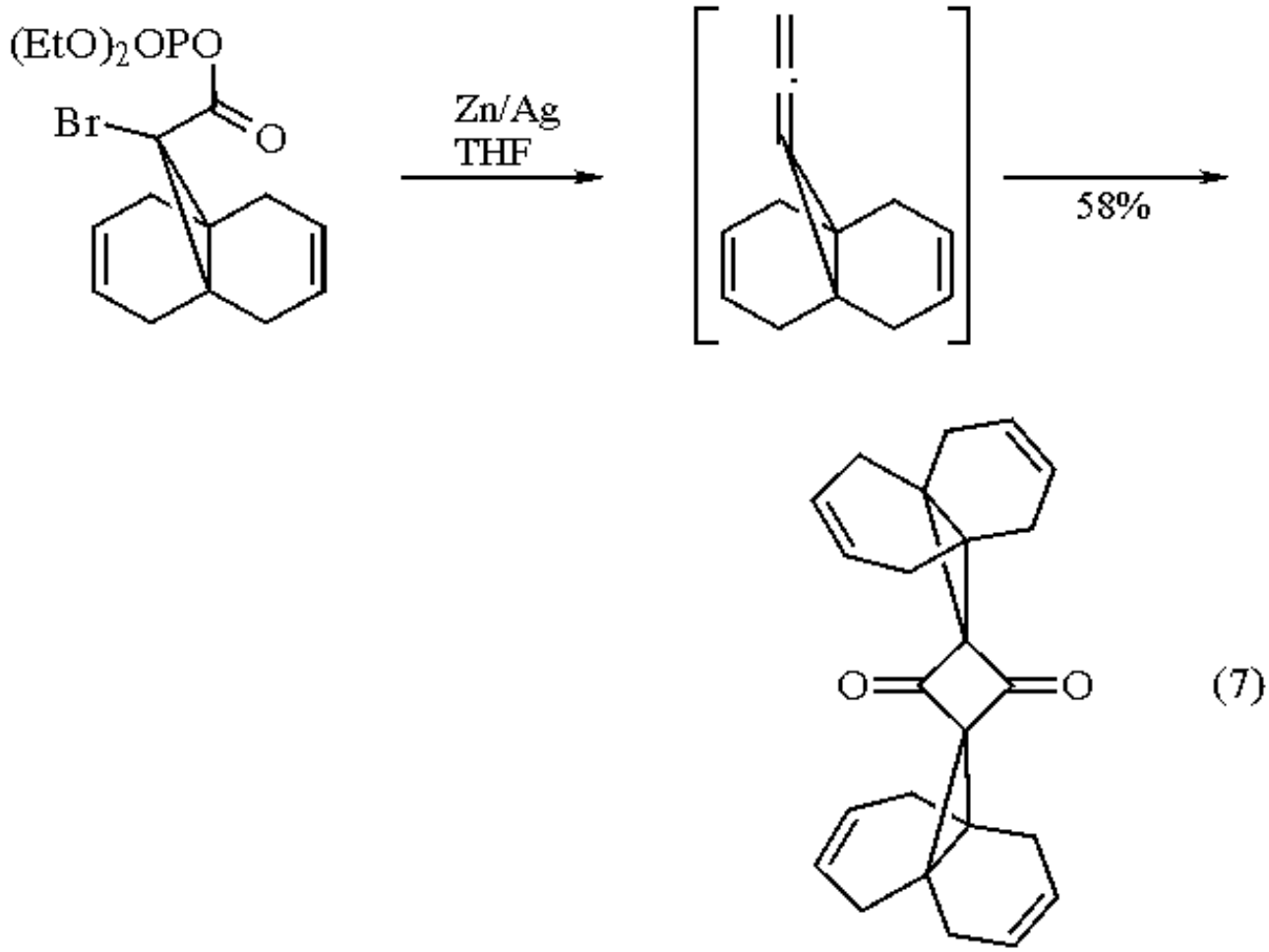

Carbon-Carbon Bond Formation.

Zn/Ag couple is an effective alternative to the commonly employed ***Zinc/Copper Couple*** couple in the Simmons-Smith reaction. It is reportedly superior for cyclopropanations of α,β-unsaturated carbonyl compounds, conjugated alkenes, and alkenes derived from ketones (enol derivatives) because of increased reactivity, better yields, and short reaction times (eqs 8 and 9).[9]

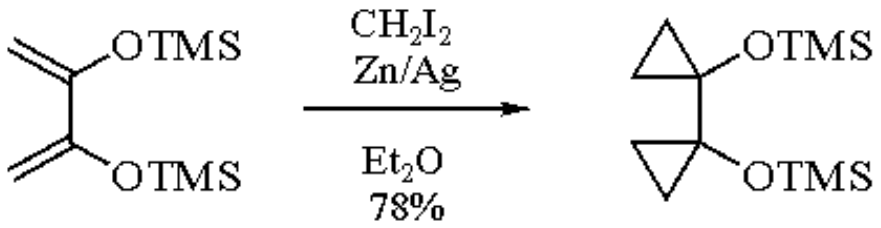

(8)

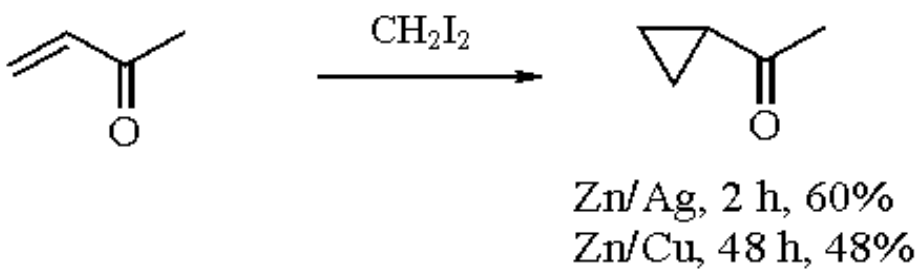

(9)

The use of the Zn/Ag couple has been suggested for the large scale [4 + 3] cycloaddition of α,α,α´,α´-tetrabromoacetone and furan. The yield is lower than the iron carbonyl promoted reaction but has advantages in terms of economics and operational simplicity (eq 10).[10]

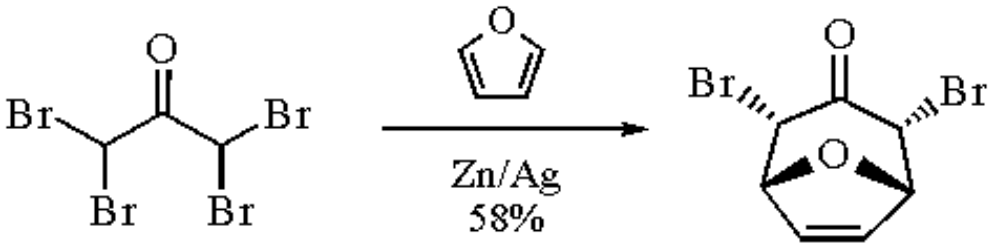

(10)

The synthesis of β,γ-unsaturated ketones from nitriles and allylic bromides has been improved by employing the Zn/Ag couple. The method is simple and provides the ketones in good to excellent yield. The use of crotyl or isopropenyl bromides results in the formation of the products from γ-attack (eq 11). The reactions can be run in ether, benzene, or THF. The use of THF tends to suppress Wurtz couplings.[1]

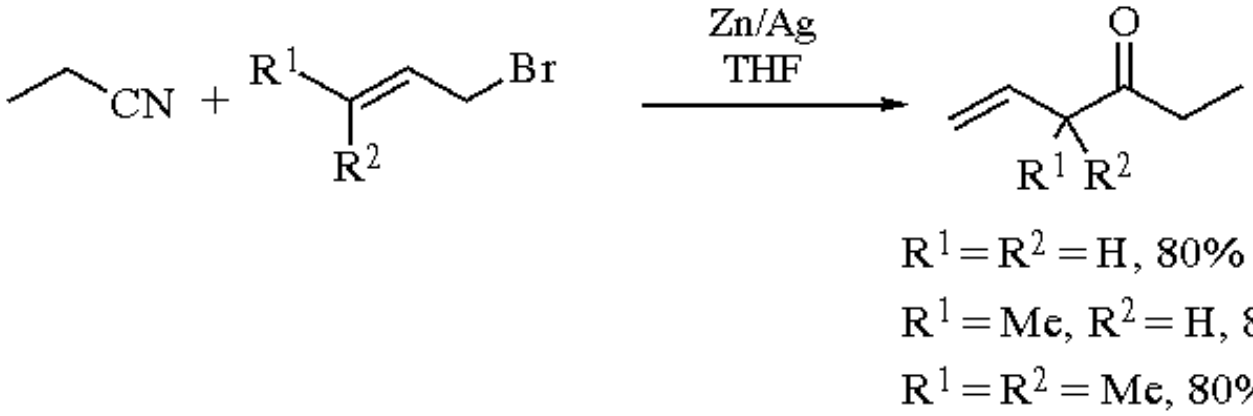

(11)

(Trimethylsilylmethyl)difluorochloropropene regioselectively couples with carbonyl compounds to afford 2,2-difluoro-3-[(trimethylsilyl)methyl]-3-butenols in good yield (eq 12).[11]

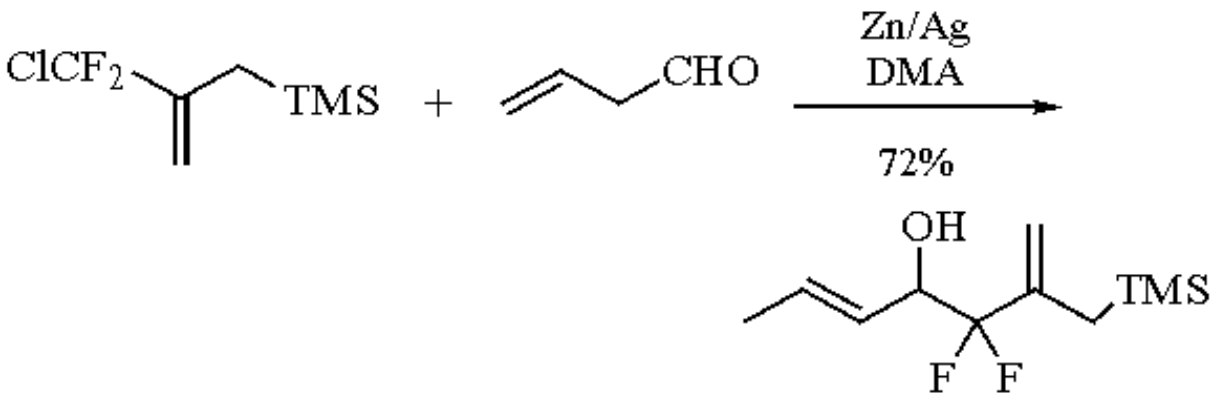

(12)

In a synthesis of steganone, the diketo dibromide was intramolecularly cyclized utilizing Zn/Ag couple (eq 13).[12]

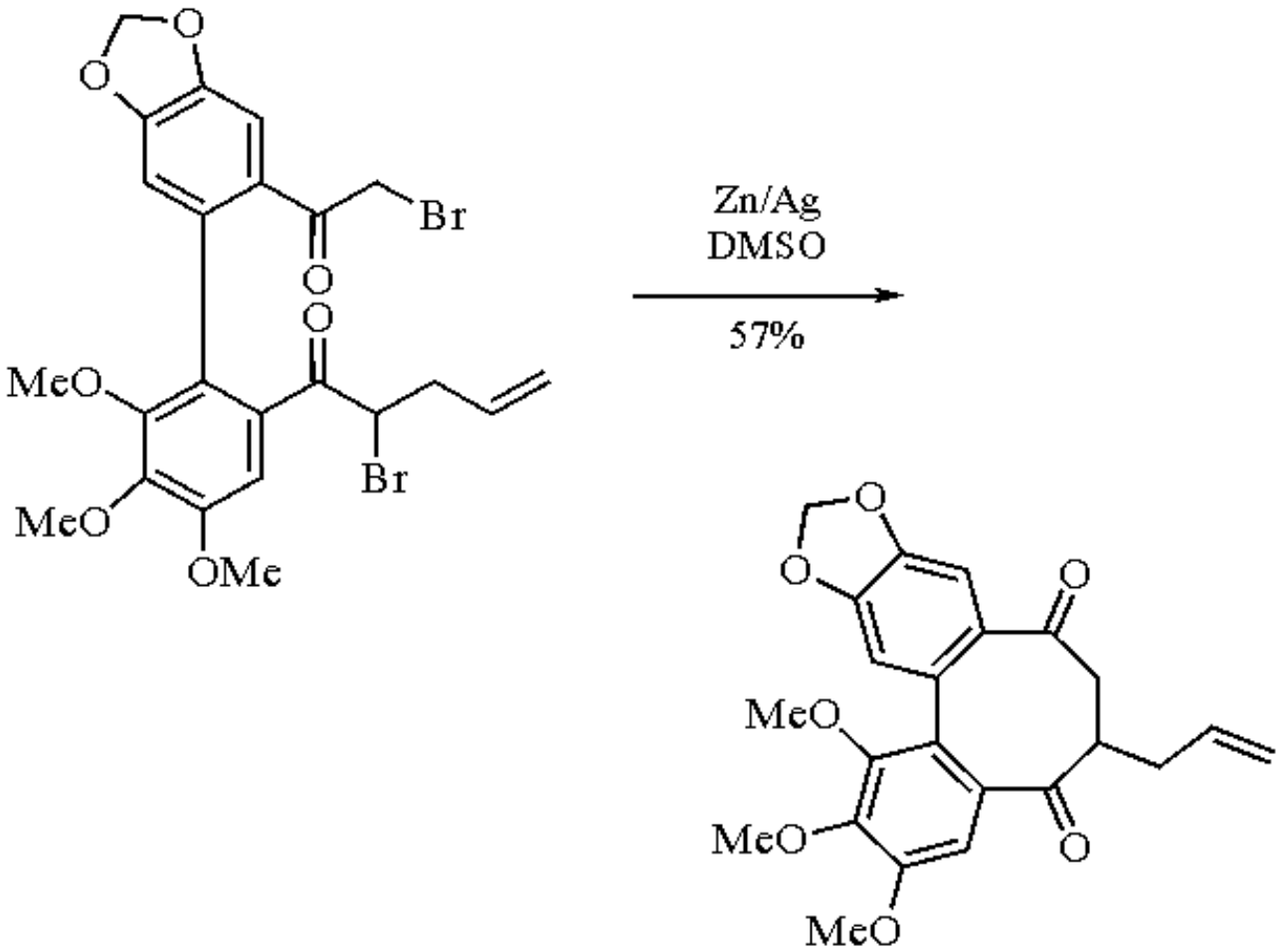

(13)

Zn/Ag couple is an effective reagent for use in the Reformatsky reaction. If bromocrotonates are employed, there is the possibility of either α- or γ-attack. In the case of the crotonates, unlike the allylic halides, the product is dependent on the choice of solvent. When ether is used, the products arise from α-attack, while products derived from γ-attack are formed if THF is used (eq 14).[13]

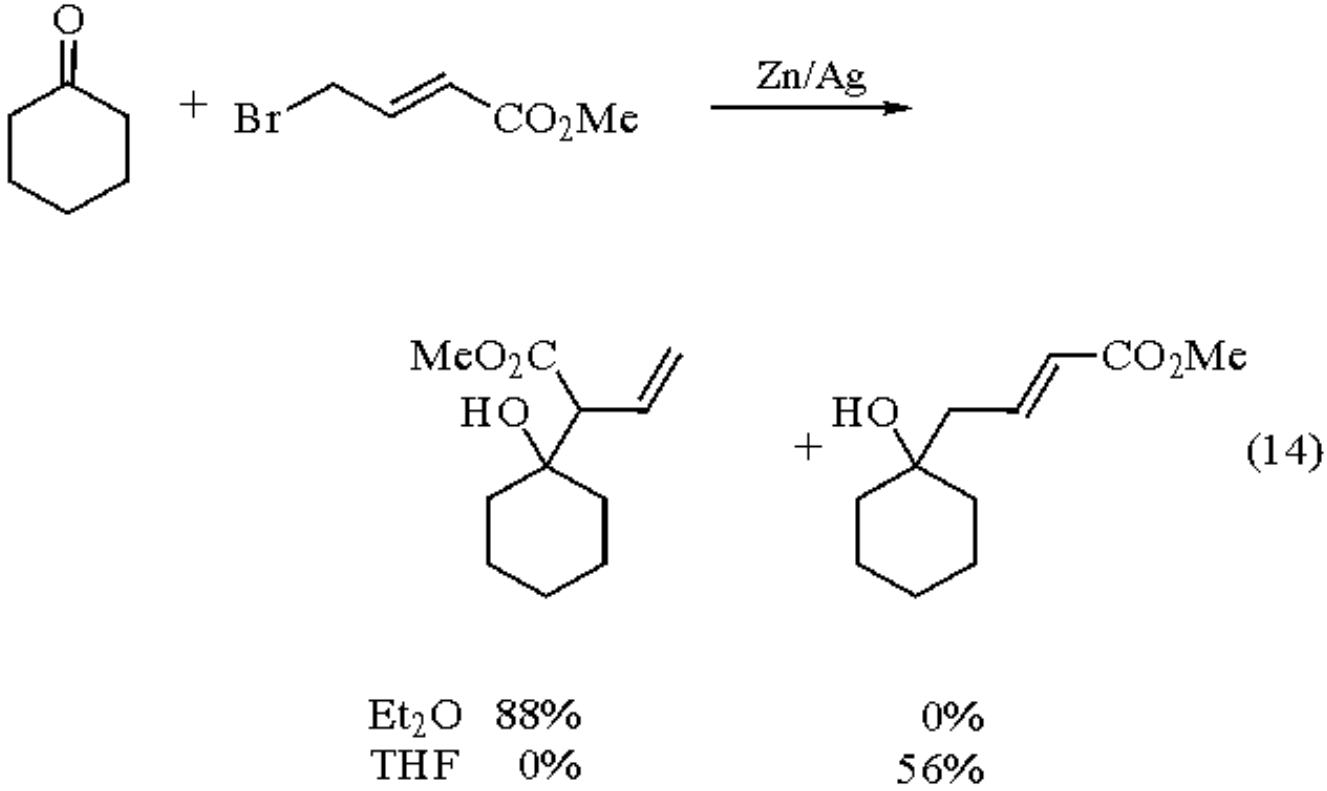

An intramolecular version of the Blaise reaction was employed in the synthesis of corynantheine alkaloids. This variant of the Blaise reaction utilized Zn/Ag couple and ultrasonic irradiation (eq 15). The use of other forms of activated Zn or the omission of ultrasound resulted in poor or nonexistent yields of products.[14]

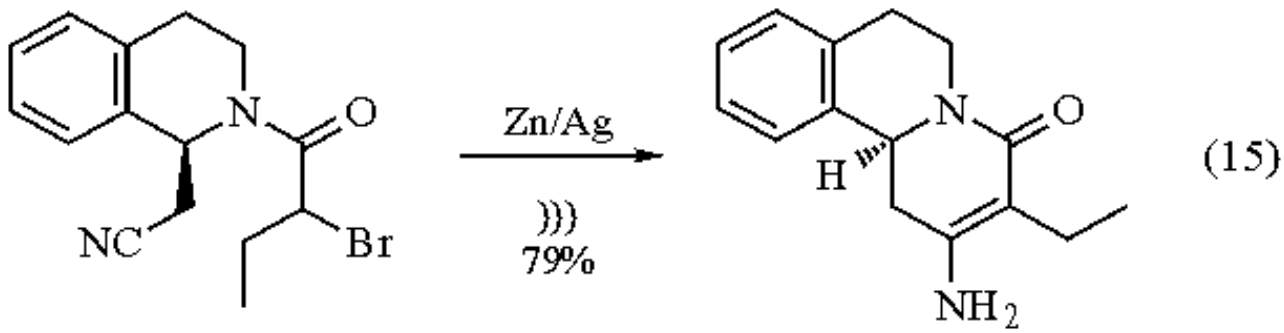

The use of ultrasound also resulted in an increase in yield for a Zn/Ag mediated coupling of the allylic bromide of the dihydrothiophene *S,S*-dioxide (eq 16).[15]

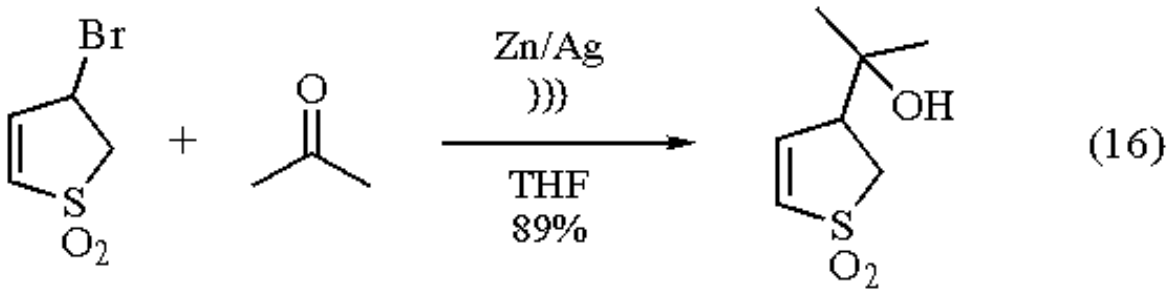

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Zinc *p*-Toluenesulfonate

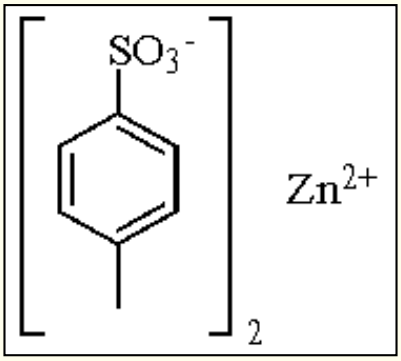

[13438-45-4] · $C_{14}H_{14}O_6S_2Zn$ · Zinc *p*-Toluenesulfonate · (MW 407.81) (.6H_2O)

[60553-56-2] (.*x*H_2O; hydrate)

[123334-05-4]

(agent for tosylation[1] under mild Mitsunobu conditions, usually with inversion)

Alternate Name: zinc tosylate.

Solubility: insol H_2O, benzene.

Form Supplied in: white solid; the hydrate is commercially available.

Preparative Method: anhydrous material[1] is prepared when the precipitate formed from mixture of ***p-Toluenesulfonic Acid*** and ***Zinc Chloride*** in water is filtered off and dried in vacuo at rt for 1 h. Purification is not usually required.

Handling, Storage, and Precautions: no unusual precautions are noted, but storage in a well stoppered container is advisable.

Tosylate Formation with Inversion of Configuration.

Alkyl tosylates can be formed directly from secondary alcohol functionality with retention of carbon stereochemistry by treatment with ***p-Toluenesulfonyl Chloride*** and ***Pyridine***. However, conversion of an alcohol to the corresponding tosylate of opposite stereochemistry typically requires a minimum of three steps. For example, inversion of the stereocenter with benzoic acid under Mitsunobu reaction conditions, hydrolysis of the resulting ester, and finally conventional tosylation of the alcohol, provides an attractive route for this transformation.[2] A similar route, the inversion of a secondary alcohol directly with *p*-TsOH, ***Diethyl Azodicarboxylate*** (DEAD), and ***Triphenylphosphine***, does not produce the desired tosylate product.[1]

Modification of this procedure, through the use of bis(*p*-toluenesulfonato)zinc ((*p*-TsO)$_2$Zn) with Mitsunobu conditions, allows this transformation to proceed in a single step.[1] Although somewhat slower than the analogous inversion with benzoic acid, treatment of secondary alcohols with (*p*-TsO)$_2$Zn, DEAD, and Ph_3P gives the desired tosylate product in high yield. This reaction is effective for tosylate formation from either acyclic or cyclic secondary alcohols with clean inversion of stereochemistry (eq 1). As expected, this reaction is very sensitive to the steric hindrance at the reacting sp^3 center; moderately hindered alcohols, e.g. (**1**), require longer reaction times and greater quantities of DEAD and Ph_3P to undergo the transformation in high yield (eq 2). Similarly, the use of *p*-TsOLi is effective for this transformation, but yields are slightly lower than those obtained with (*p*-TsO)$_2$Zn.

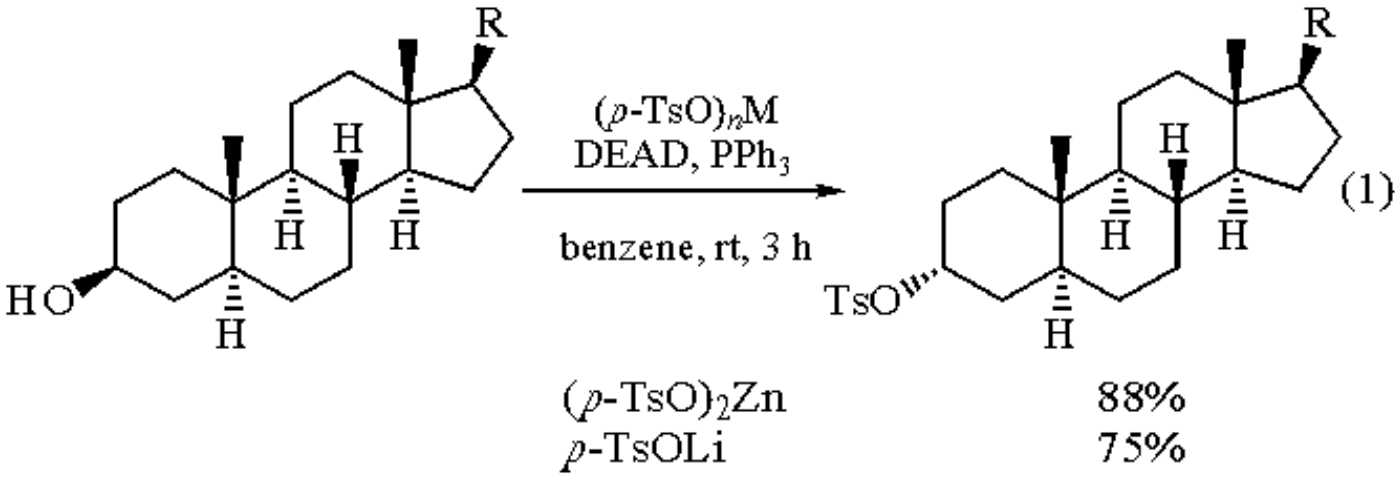

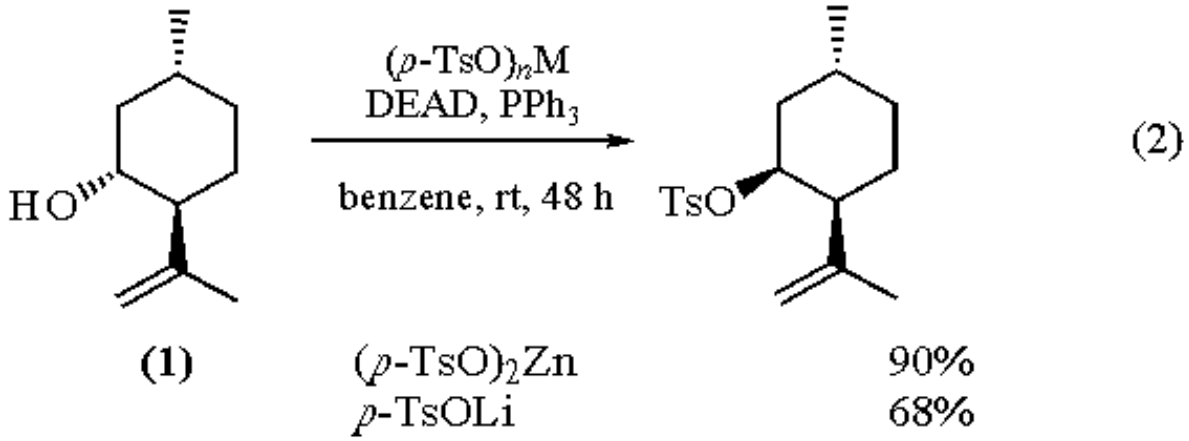

Tosylation with Retention of Stereochemistry.[1]

Although dihydrocholesterol (**2**) undergoes clean tosylation with inversion in 88% yield using the procedure described above, cholesterol (**3a**) itself gives an 85% yield of the 3β-tosylate (**3b**).

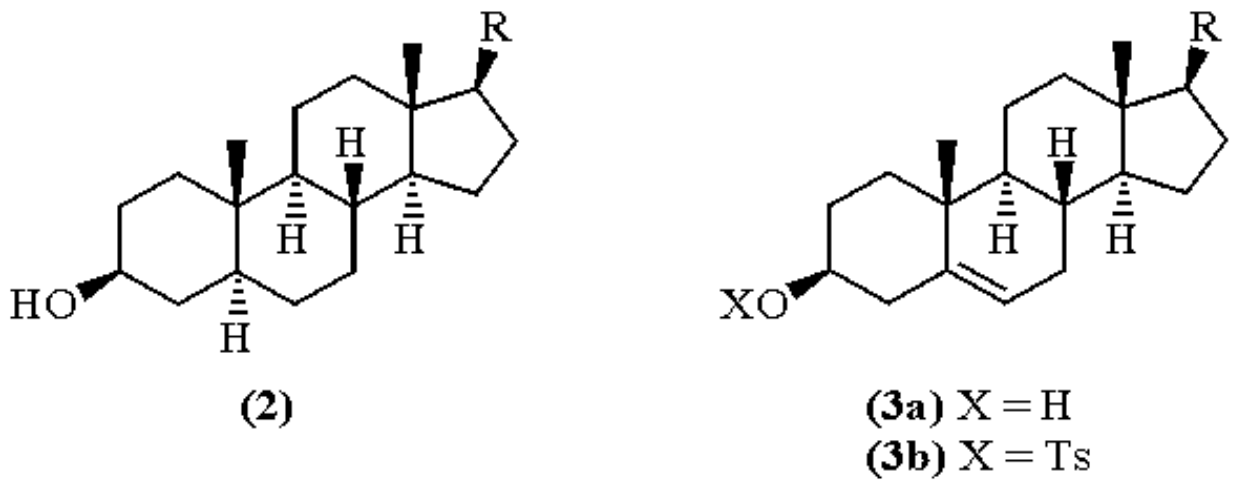

It was suggested that this anomaly could be explained by the intermediacy of a cyclopropylmethyl/homoallylic species, trapped by addition of tosylate ion. Indeed, the more vigorous Mitsunobu reaction[2] of (**3a**) with benzoic acid leads to a mixture of four products, confirming involvement of this type of homoallylic rearrangement.

Although anomalous, it is conceivable that this Mitsunobu procedure could be of use in effecting tosylation with retention in less common systems in which neighboring group effects, for example, override the normal stereochemical outcome.

---

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Zinc Trifluoromethanesulfonate

$(CF_3SO_3)_2Zn$

[54010-75-2] · $C_2F_6O_6S_2Zn$ · Zinc Trifluoromethanesulfonate · (MW 363.55)

(mild Lewis acid; catalyst for a variety of reactions)

Alternate Name: zinc triflate.

Physical Data: mp >300 °C.

Solubility: insol CH_2Cl_2; slightly sol MeOH; sol MeCN, H_2O.

Form Supplied in: white powder; commercially available.

Preparative Method: may be prepared from addition[1] of ***Trifluoromethanesulfonic Acid*** to ***Zinc Carbonate*** in MeOH, filtration, and drying in vacuo.

Handling, Storage, and Precautions: moderately hygroscopic; store well sealed.

Introduction.

The mild Lewis acidic properties of this metal trifluoromethanesulfonate, similar in many ways to magnesium triflate[1] but with some distinct differences from other metal triflates[2] (notably ***Copper(II) Trifluoromethanesulfonate***[2c]), have been exploited in several delicate synthetic operations. It will undoubtedly find more uses in the future. Some specific examples follow.

Thioacetalization.[1]

The thioacetalization of (**1**) with ethane-1,2-dithiol proved to be impossible by a variety of more traditional methods,[3] but could be effected by zinc triflate without β-elimination of the lactone oxygen (eq 1).

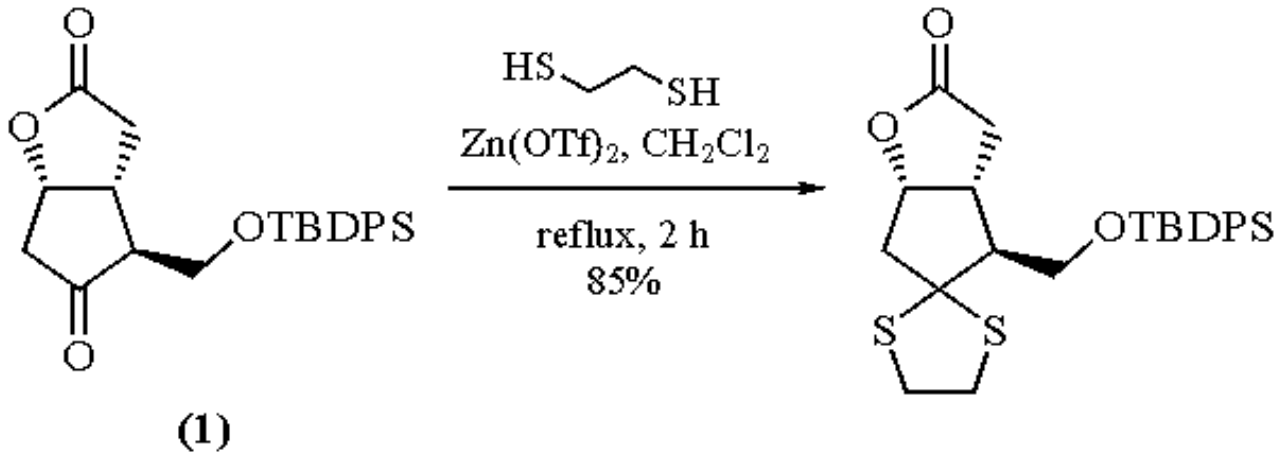

Magnesium triflate can similarly be used to effect the reaction, but on occasion may require a more extended reaction time. In the case of Δ^4-cholesten-3-one, however, magnesium triflate (but not the zinc reagent) causes some double bond isomerization. α,β-Unsaturated ketones may also react by conjugate addition of the thiol in addition to acetalization.

Glycosylation.[4]

Zinc triflate is one of a number of Lewis acids which can catalyze glycosylation reactions (eq 2). The choice of catalyst is highly dependent upon substrate and leaving group OX, and on occasion zinc triflate can be more suitable than, for example, ***Boron Trifluoride Etherate*** or ***Trimethylsilyl Trifluoromethanesulfonate***. Stereochemical control at the anomeric center, however, is also variable, and far from complete.

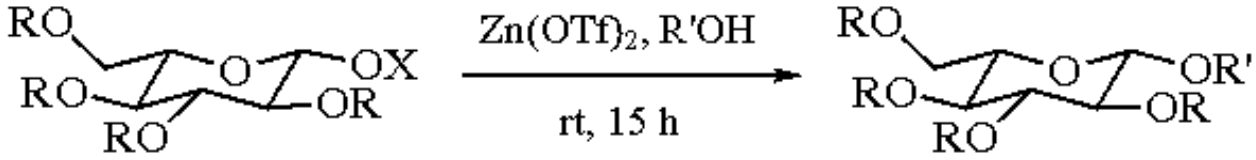

(2)

A catalytic amount (0.1 mol %) of $Zn(OTf)_2$ gives low stereoselectivity in reaction of cholesterol with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride.[4b] Other zinc salts, notably zinc *p*-(*t*-butyl)benzoate,[4b] give a much more selective β-glycosylation product.

Onium Ion Formation.[5]

$Zn(OTf)_2$ permits replacement of the MeO group of (**2**) with a carbon substituent (eq 3), presumably via onium ion intermediates.[5a] Reaction with ***Titanium(IV) Chloride*** in CH_2Cl_2, however, resulted in cleavage of the alternative (endocyclic) acetal bond, possibly owing to coordination[5a] to both O and N atoms. *O*-Addition to such onium ions may also be effected with zinc triflate.[5b]

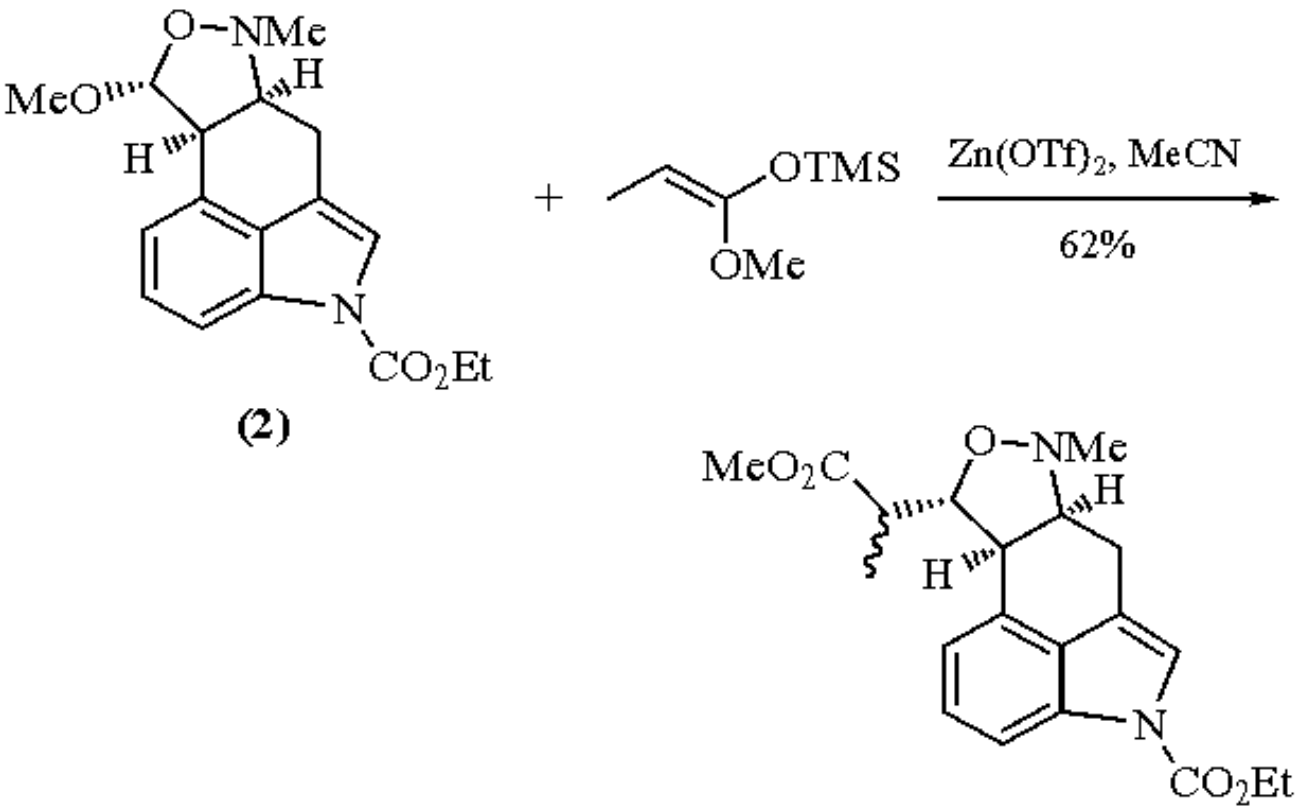

(3)

Alkylation of Electron-Rich Aromatics.

Aziridines (**3**) react with indoles (X = electron-releasing group) to give tryptophan derivatives only in the presence of $Zn(OTf)_2$ (eq 4).[6a] Although yields are fairly poor (19-60%), optical purity is excellent (>95%). Addition of other carbon nucleophiles (organocuprates[7]) to (**3**) can also lead to mixtures of products, in which α-amino acid derivatives may predominate.

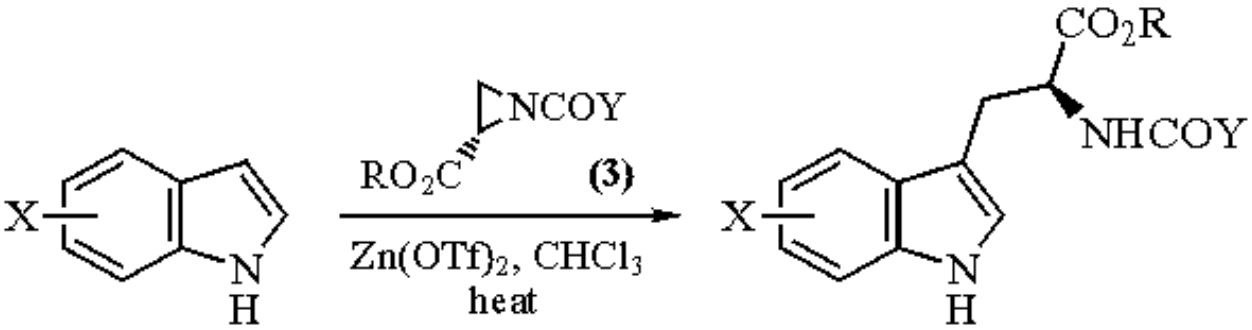

(4)

Intramolecular alkylation of electron-rich aromatics (eq 5)[6b] can be an effective procedure, giving rise to benzofurans, benzothiophenes, indoles, or naphthalene derivatives. TMS triflate is also effective.

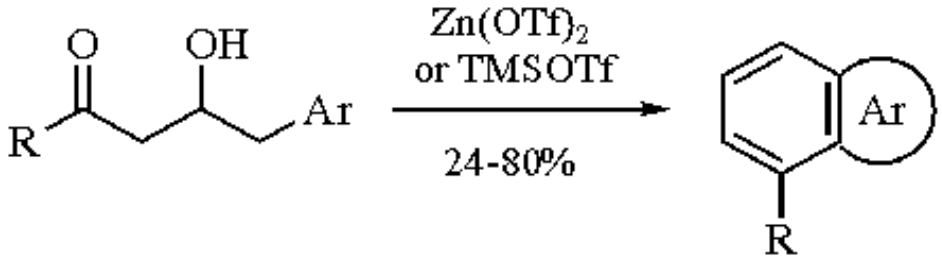

(5)

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Zinc-Zinc Chloride

Zn-$ZnCl_2$

(Zn)

[7440-66-6] · Zn · Zinc-Zinc Chloride · (MW 65.39) ($ZnCl_2$)

[7646-85-7] · Cl_2Zn · Zinc-Zinc Chloride · (MW 136.29)

(mild reducing agent; causes reductive elimination of vicinal heteroatoms;[1-3] reduces activated carbonyls[4] and alkenes;[5] reductively opens some strained rings[6])

Physical Data: see ***Zinc*** and ***Zinc Chloride***.

Form Supplied in: $ZnCl_2$ is available both as solid and in ether solution. The latter has not been used in most of the following examples, but is very likely to be suitable in many cases. Various grades of Zn or $ZnCl_2$ can find use. Utilization under moist conditions (as well as anhydrous) has been noted.

Reductive Vicinal Eliminations.[1-3]

Zinc powder in the presence of catalytic amounts of $ZnCl_2$ causes reductive elimination of vicinal halogens (except fluorine, which is inert to these conditions), thereby yielding alkenes[1] or alkynes.[2] These reactions, performed in alcoholic solvents, are essentially similar to those effected by ***Zinc-Acetic Acid***. Similar treatment of bromo ether (**1**) also results in alkene formation (eq 1).[3]

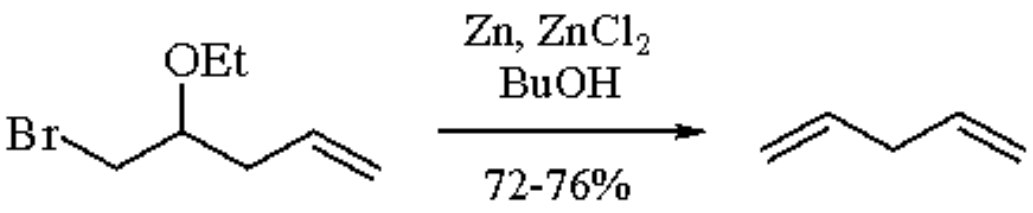

(1)

(1)

Reduction.[4,5]

The keto group of α-ketoamides,[4] and a single carbonyl of α-diketones,[4] are reduced efficiently to the alcohol by Zn/$ZnCl_2$ in EtOH. This reaction, of course, can be carried out by a host of other reagents. Quinones[4] are also reduced to hydroquinones, in a reaction claimed to be superior to the procedure using ***Chromium(II) Chloride***.[7] The presence of $ZnCl_2$, however, is not crucial to this reaction; it can be omitted, or replaced by a variety of other metal salts.[4] Activated alkenes may also be reduced, as shown in eqs 2[5a] and 3[5b].

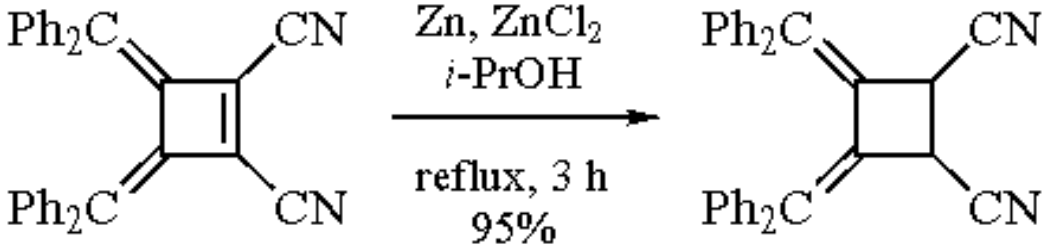

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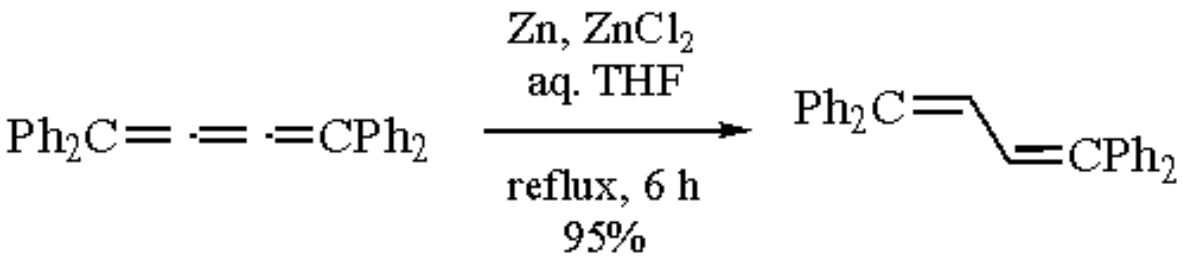

(3)

Reductive Ring Opening.[6]

Strained (three- or four-membered) carbocyclic ring systems (**2**) may be reductively opened by $Zn/ZnCl_2$ in protic solvents, if substituted by carbonyl groups (eq 4). For four-membered rings, two carbonyl substituents (i.e. $R^2 = COR^3$) are required;[6a] a similar reaction can also be effected by Zn/AcOH.[8] Three-membered rings react much more readily;[6a] the greater strain in this case permits cleavage of (**2**) (R^2 = aryl) by a very much extended reaction time,[6c] and even with Zn/AcOH.[6c]

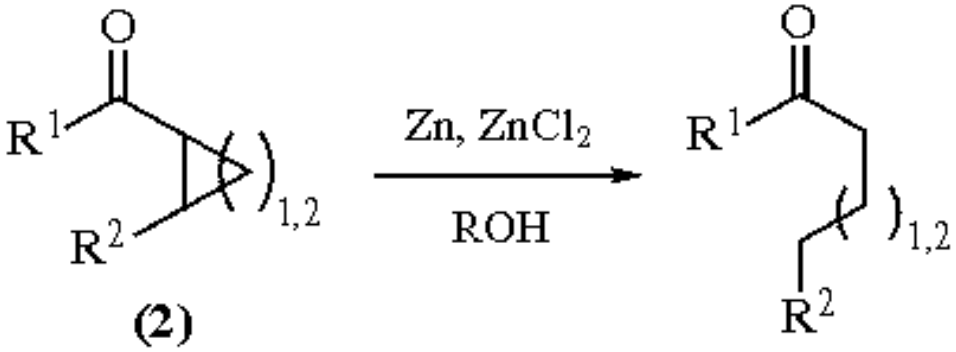

(4)

Reductive Coupling.[9]

Aryl aldehydes, on exposure to $Zn/ZnCl_2$, usually react to give a mixture of the respective benzyl alcohol and the dimerized α-glycol (**3**) (R = H), the latter being favored by absence of solvent during the reaction. In aq THF, solvent composition affects the isomeric composition of the glycols. Acetophenones and diaryl ketones yield the glycols in excellent yields. This reagent is insensitive to oxygen, and reacts efficiently at room temperature, giving appreciable advantage over other favored reagents such as ***Aluminum***, ***Titanium(IV) Chloride***, or ***RZ021-***.[9]

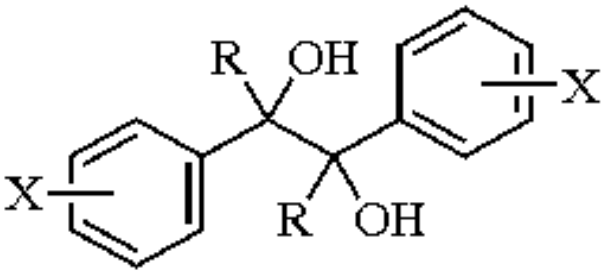

(3)
R = H, Me, Ar

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Zirconium(IV) Chloride

$ZrCl_4$

[10026-11-6] · Cl_4Zr · Zirconium(IV) Chloride · (MW 233.02)

(Lewis acid)

Physical Data: subl. 331 °C, mp 437 °C/25 atm; *d* 2.803 g cm^{-3}.

Solubility: sol alcohol, ether.

Form Supplied in: white solid; widely available.

Purification: crystallize repeatedly from conc hydrochloric acid.

Handling, Storage, and Precautions: extremely hygroscopic; decomposed by water to $ZrOCl_2$ and HCl. Reagent causes burns, and is harmful if inhaled or swallowed or if it comes in contact with skin. It is stable at high temperatures under N_2, H_2, or O_2. Use in a fume hood.

Precursor for Other Zirconium Reagents.

$ZrCl_4$ is used as starting material for other zirconium derivatives. Its Lewis acid character is involved in most of its reactions. As a Lewis acid its catalytic power is comparable with that of ***Titanium(IV) Chloride*** in Friedel-Crafts reactions.[1]

Diels-Alder Reactions.

$ZrCl_4$ has been employed as one of the Lewis acid catalysts in the addition of the acrylate of (*S*)-ethyl lactate with cyclopentadiene,[2] and further in asymmetric Diels-Alder cycloaddition reactions with chiral α,β-unsaturated *N*-acyloxazolidinones.[3]

[2 + 2] Adduct Formation.

$ZrCl_4$ is a good catalyst for the [2 + 2] adduct formation between ethyl propiolate and TMS enol ethers (eq 1).[4]

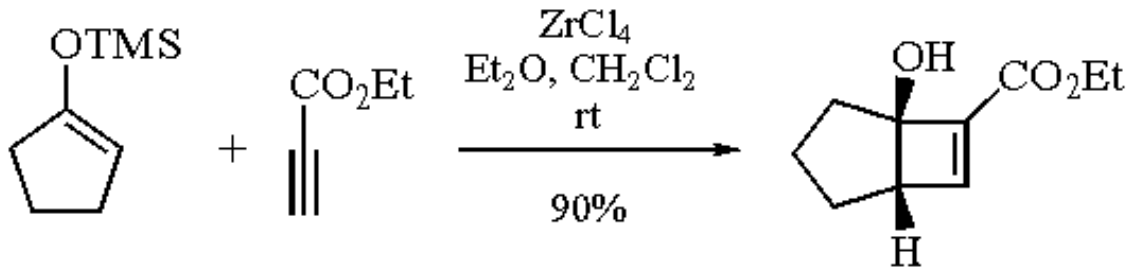

(1)

Carbonyl Addition Reactions.

Like $TiCl_4$ and other Lewis acids, $ZrCl_4$ is a good catalyst in aldol coupling reactions. $ZrCl_4$ is not superior, however, to other Lewis acids in a stereochemical study of the reactions of allylstannanes and a methyl homolog with aldehydes.[5] Corresponding intramolecular cyclization reactions are fast, selective, and insensitive to the nature of the Lewis acid (87-99% *syn*).[6] Stereoisomeric ratios and yields were relatively insensitive to the nature of the Lewis acid catalyst in adduct formation between ***Allyltrimethylsilane*** and methyl β-

formylcarboxylate (eq 2).[7]

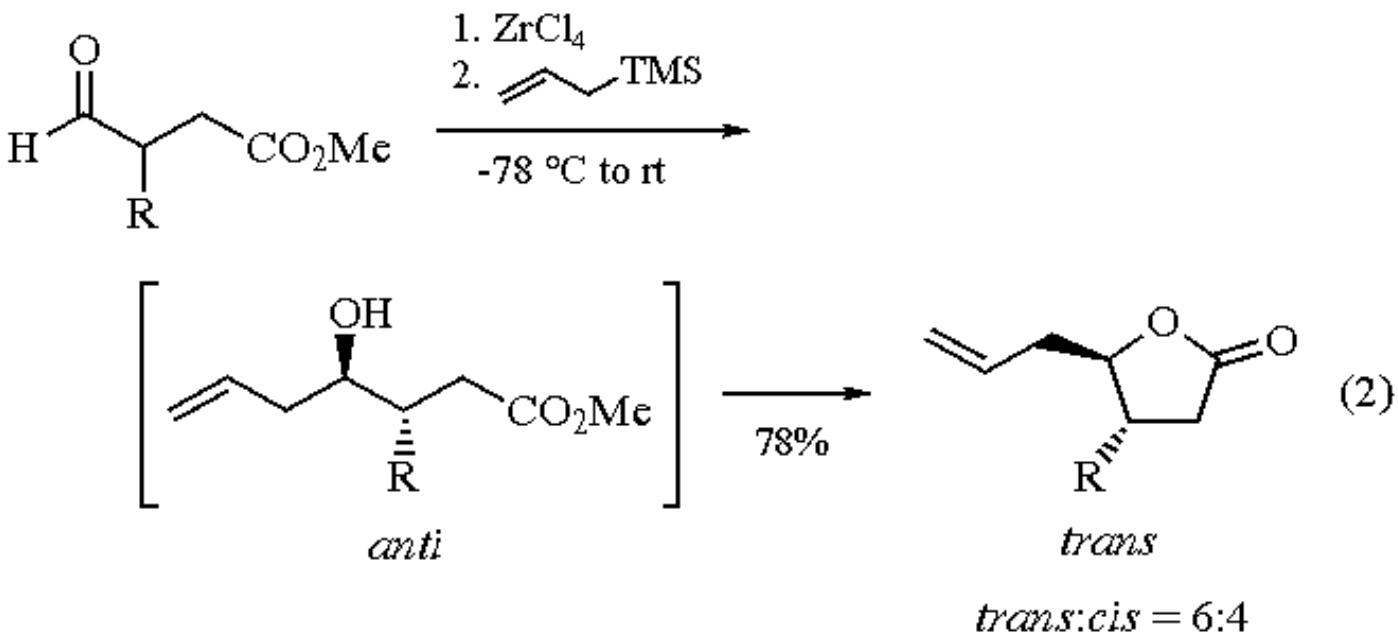

In the aldol reaction between menthyl pyruvate and 1-naphthol, the de of the menthyl 2-(1-hydroxy-2-naphthyl)propionate adduct was 74%, the yield 92%.[8] The adduct of 1-naphthol and ethyl pyruvate using the chiral dibornacyclopentadienyl ligated zirconium chloride (**1**) had an ee >84% (eq 3).[9]

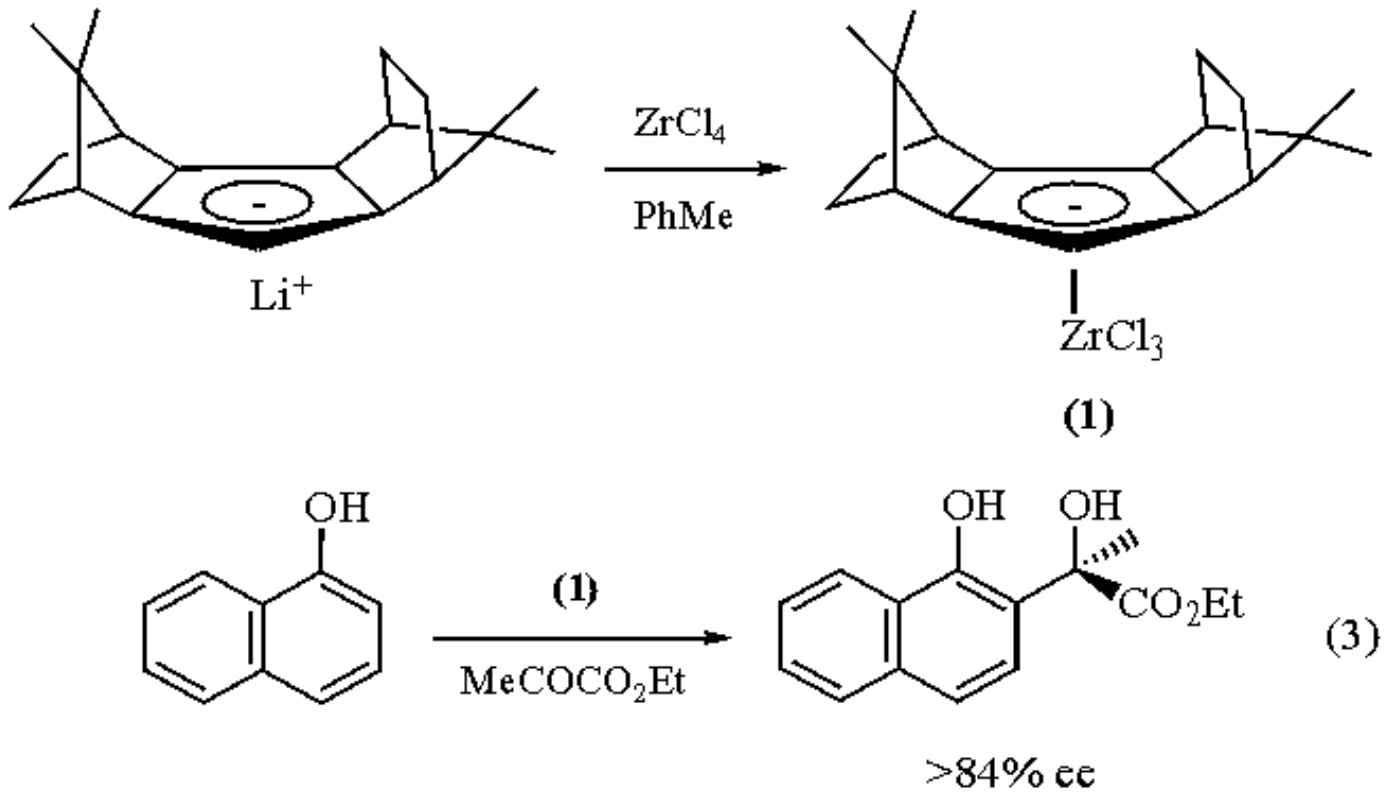

Hydroalumination Reactions.

$ZrCl_4$ will promote the addition of ***Lithium Aluminum Hydride*** to alkenes under mild conditions to yield hydroaluminated intermediates for further transformations (eq 4).[10] The reaction has been extended to allylic alcohols. Deoxygenation accompanied the use of titanium analogs.[11]

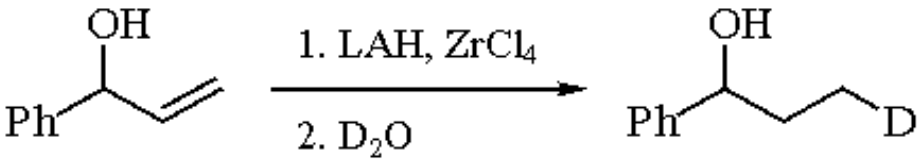

(4)

Esters and Amides.

Mild esterification conditions utilizing $ZrCl_4$ and ***Silver(I) Trifluoromethanesulfonate*** will effect reaction between silyl carboxylates and silyl ethers.[12] Chemoselective amination of the ester function in α-chlorocarboxylic methyl esters can also be effected (eq 5). $ZrCl_4$ and ***Aluminum Chloride*** are good Lewis acids for this transformation, which proceeds without significant epimerization of enantiomerically enriched chloropropionate.[13]

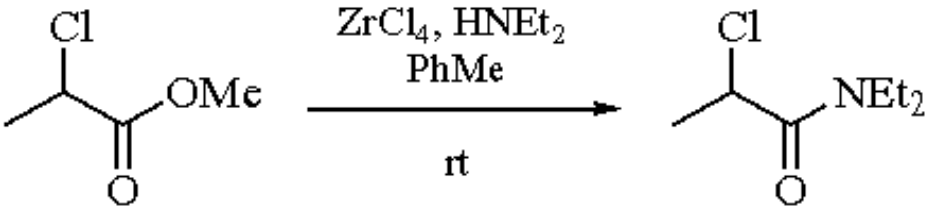

(5)

The affinity for oxygenated functions can be used to effect ring-opening reactions of cyclic ethers, leading to 6-hydroxy-2,4-cycloheptadien-1-ones.[14]

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Zirconium(III) Chloride

$ZrCl_3$

[10241-03-9] · Cl_3Zr · Zirconium(III) Chloride · (MW 197.57)

(complex formation, potential reducing agent)

Physical Data: mp above 400 °C (disproportionation to Zr and $ZrCl_4$); *d* 3.0 g cm^{-3}.

Solubility: reacts with protic solvents with formation of H_2 gas; sol benzene, toluene, CS_2.

Form Supplied in: blue-black solid; changes to brown upon air exposure; not widely available. Synthesized from Zr and $ZrCl_4$.[1]

Purification: none, except new synthesis.

Handling, Storage, and Precautions: extremely hygroscopic; decomposed by moist air. Dissolving in H_2O destroys the compound with $ZrOCl_2$, H_2, and HCl formation. Heating in air forms $ZrCl_4$ needles and ZrO_2. Disproportionates to Zr and $ZrCl_4$ above 400 °C. Reagent causes burns, and is harmful if inhaled or swallowed. Use in a fume hood.

General Discussion.

Zirconium trichloride can be prepared from finely divided zirconium metal and ***Zirconium(IV) Chloride*** at elevated temperature (500 °C or more).[1,2]

The chemistry of tervalent zirconium halides is relatively unexplored. So far, the main interest has been directed towards complex formation with mono- and bidentate nitrogen donor ligands, e.g. acetonitrile, pyridine, lutidines, bipyridine, and phenanthroline.[2-4]

There appear to be no reports in the literature on the use of zirconium trichloride nor its complexes in directed organic reactions. This stands in contrast to the wide use of ***Titanium(III) Chloride*** in reductive coupling reactions of oxo compounds to vicinal diols and alkenes and reduction of functional groups.

---

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Zirconium Tetraisopropoxide

$Zr(O\text{-}i\text{-}Pr)_4$

[2171-98-4] · $C_{12}H_{28}O_4Zr$ · Zirconium Tetraisopropoxide · (MW 327.62) (.*i*-PrOH)

[50939-84-9] · $C_{15}H_{36}O_5Zr$ · Zirconium Tetraisopropoxide-Isopropanol · (MW 387.73)

(hydrogenation catalyst; Meerwein-Ponndorf-Verley reduction; Oppenauer oxidation; ester synthesis; diketopiperazine synthesis)

Physical Data: $Zr(O\text{-}i\text{-}Pr)_4$: bp 160 °C/0.1 mmHg; $Zr(O\text{-}i\text{-}Pr)_4$.*i*-PrOH: mp 138-141 °C.[1]

Solubility: $Zr(O\text{-}i\text{-}Pr)_4$ readily sol organic solvents; $Zr(O\text{-}i\text{-}Pr)_4$.*i*-PrOH sparingly sol isopropanol.

Form Supplied in: $Zr(O\text{-}i\text{-}Pr)_4$.*i*-PrOH: white solid.

Purification: $Zr(O\text{-}i\text{-}Pr)_4$.*i*-PrOH: crystallization from isopropanol followed by drying at rt/0.5 mmHg. $Zr(O\text{-}i\text{-}Pr)_4$: heating of $Zr(O\text{-}i\text{-}Pr)_4$.*i*-PrOH at 90-120 °C/1 mmHg to remove isopropanol followed by distillation.[1]

Handling, Storage, and Precautions: moisture sensitive; irritating to eyes, respiratory system, and skin. Use in a fume hood.

Preparation of $ClZr(O\text{-}i\text{-}Pr)_3$.

$Zr(O\text{-}i\text{-}Pr)_4$ is a good substrate for the preparation of $ClZr(O\text{-}i\text{-}Pr)_3$ (eq 1),[2-4] which is a useful reagent for further conversion to other organozirconium reagents ($RZr(O\text{-}i\text{-}Pr)_3$) by organolithium or Grignard derivatives as described for the titanium analogs (see ***Titanium Tetraisopropoxide***).[5]

$$3\ Zr(O\text{-}i\text{-}Pr)_4 + ZrCl_4 \longrightarrow 4\ ClZr(O\text{-}i\text{-}Pr)_3 \qquad (1)$$

Meerwein-Ponndorf-Verley Reduction and Oppenauer Oxidation.

The zirconate reagent in the Meerwein-Ponndorf-Verley reduction is known to show high functional group selectivity due to both steric and electronic effects. Thus aldehydes are reduced in preference to ketones, and selective reduction of the carbonyl group occurs in α,β-unsaturated carbonyl compounds.[2,6] The sensitivity to electronic effects was demonstrated in a study of the reduction of benzaldehydes: the efficiency and rate of the aldehyde conversion to the benzyl alcohol was dependent on the electron-withdrawing properties of the *p*-substituent.[2,6] In the dihydro formation of 5-halo-2-pyrimidinones, regioselective formation of the 3,4-dihydro isomer predominates whereas the 3,6-dihydro isomer is formed with ***Lithium Tri-t-butoxyaluminum Hydride***.[7]

In the reverse reaction, the Oppenauer oxidation, studies on the oxidation of secondary alcohols with ***Chloral*** as the hydride acceptor again demonstrate the sensitive nature of $Zr(O\text{-}i\text{-}Pr)_4$ to electronic and steric effects (eqs 2 and 3).[2]

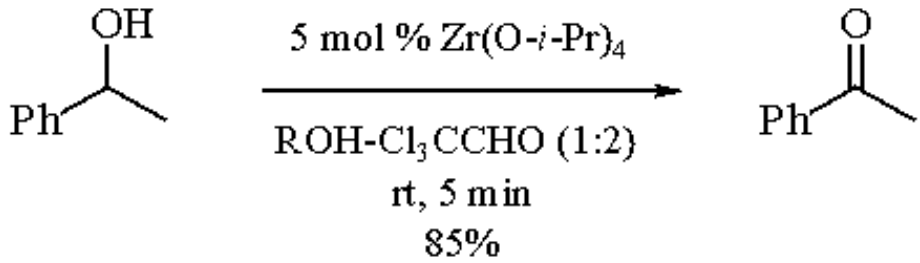

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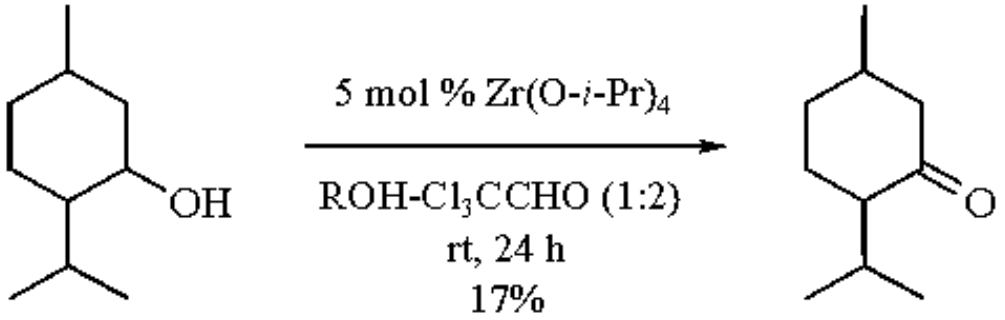

(3)

$Zr(O\text{-}i\text{-}Pr)_4$ is not a good catalyst for the oxidation of allylic alcohols to α,β-unsaturated aldehydes, in contrast to $Cp_2Zr(O\text{-}i\text{-}Pr)_2$ and ***Bis(η^5-cyclopentadienyl)dihydridozirconium***.[8]

Michael-Aldol Reaction.

In an intramolecular Michael-aldol reaction, the *n*-propoxide $Zr(O\text{-}n\text{-}Pr)_4$ was far superior to the isopropoxide $Zr(O\text{-}i\text{-}Pr)_4$.[9]

Ester Synthesis.

Isopropoxide groups in $Zr(O\text{-}i\text{-}Pr)_4$ are readily exchanged by other alkoxy groups,[1] and by aryloxy and iminoxy (oxime) groups.[10] In salicylaldehyde the initial ester exchange at room temperature is succeeded by a Meerwein-Ponndorf-Verley reduction of the formyl group on heating the zirconium phenoxide in benzene.[11]

Zirconates, like titanates,[2] should be useful reagents for esterification or reesterification, especially when either or both of the ester components are acid or base sensitive. In carbonylation reactions with aryl, vinyl, or alkyl bromides and rhodium or palladium catalysis, good yields of the corresponding esters are formed in the presence of zirconates or titanates.[12] In another esterification and catalysis process, ketenes react with aldehydes and ketones in the presence of titanium or zirconium alkoxides to form essentially β-hydroxy esters.[13] $Zr(O\text{-}i\text{-}Pr)_4$, although giving 83% yield in the above reaction, was not in any way superior but only complementary to $Zr(O\text{-}n\text{-}Bu)_4$, $Zr(O\text{-}n\text{-}Pr)_4$, $Zr(OEt)_4$, $Ti(O\text{-}t\text{-}Bu)_4$, $Ti(O\text{-}n\text{-}Bu)_4$, $Ti(O\text{-}n\text{-}Pr)_4$, and $Ti(OEt)_4$.

Diketopiperazine Synthesis.

Zirconates are water absorbents. Thus $Zr(O\text{-}i\text{-}Pr)_4$ effects dimerization of amino acids (glycine, alanine) to the corresponding diketopiperazines (eq 4).[14] The reaction proceeds in a similar fashion if the corresponding titanium reagent is employed.

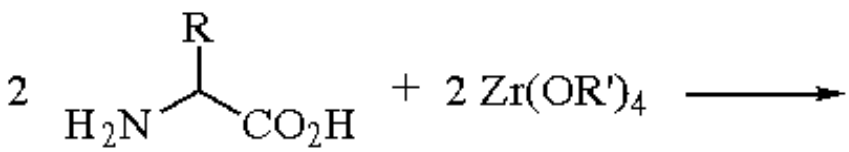

$$[RCHCONH]_2 + 2\,Zr(OR')_2O + 4\,R'OH \qquad (4)$$

$$R = H,\ Me;\ R' = i\text{-}Pr,\ Bu$$

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2-Chloro-1,3-dimethylimidazolidium Hexafluorophosphate

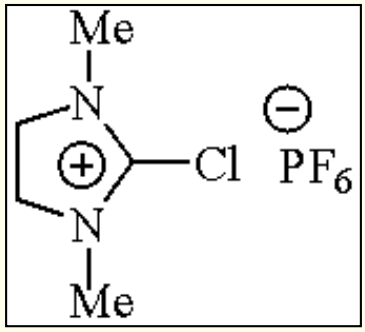

[101385-69-7] · $C_5H_{10}N_2Cl{\cdot}PF_6$ · (278.57)

(reagent used for the coupling and esterification of sterically hindered amino acids[1])

Physical Data: mp 227-229 °C.

Solubility: soluble in DMF; partially soluble in H_2O, MeOH, EtOAc, CH_2Cl_2, and $CHCl_3$.

Form Supplied in: colorless solid; available from Aldrich, Fluka, and Watanabe Chemical Industries.

Analysis of Reagent Purity: IR (KBr), 1650, 1555, 1420, 1345, 1310, 840 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6) δ 3.07 (s, 6H), 3.64 (s, 4H).

Handling, Storage, and Precautions: can be stored refrigerated for at least 5 years without loss of reactivity. 2-Chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP) is an irritant and should be used in a fumehood, when possible.

Scope

2-Chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP), in the presence of an additive, is best suited for the coupling of sterically hindered α,α-dialkylamino acids, *N*-methylamino acids, and peptide fragments. The coupling reaction proceeds under slightly basic conditions, with diisopropylethylamine generally being used as an organic base. A catalytic amount of the additive is sufficient for the coupling reaction to proceed, and a suitable additive can be selected for each reaction type. 1-Hydroxy-7-azabenzotriazole (HOAt, **1**)[2] or *N*-dimethylaminopyridine (DMAP, **2**)[3] is generally best suited for use as an additive. An optically active α-amino acid can be activated by CIP to yield the coupling product with negligible racemization.

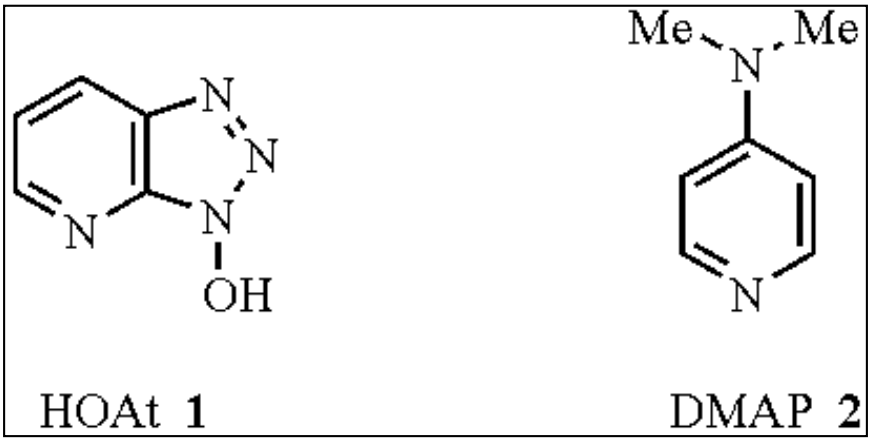

Coupling of α,α-Dialkylamino Acid

The efficient coupling of an α,α-dialkylamino acid is particularly difficult when the carboxyl and amino components are both α,α-dialkylamino acids.[4] In the presence of 0.25 equiv of HOAt as an additive, CIP mediates the solution-phase coupling of an α,α-dimethylamino acid (Aib, α-aminoisobutyric acid) to yield Z-Aib-Aib-OMe, in 82% yield (1).[5] The reaction proceeds at 25 °C in less than 60 min. The same dipeptide ester was prepared using PyBrop,[6] a typical coupling reagent in peptide synthesis, under the same conditions in 17% yield. The amount of D-Val in the Z-Val-Aib-OMe, which was prepared by the CIP/HOAt procedure, was less than 0.5%. In the CIP-mediated Aib coupling, a Z or Fmoc group as an amino protecting group gave much better results than a Boc protecting group, probably due to the facile formation of the *N*-carboxy anhydride during the activation of the Boc amino acid.[7]

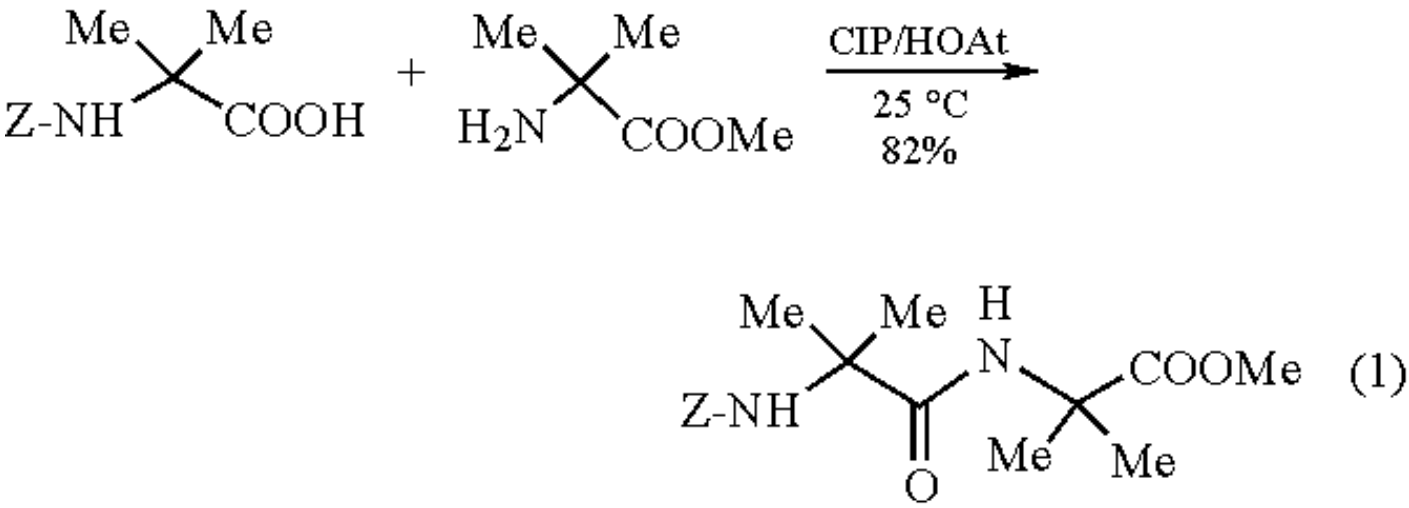

The CIP-mediated coupling of Aib proceeds through the oxazolone,[8] followed by its transformation to a highly active HOAt ester. The active intermediate ester reacts quickly with an amino component to give the condensation product and HOAt. The liberated HOAt functions as a catalyst for the coupling. The coupling procedure was successfully applied to an efficient synthesis of Alamethicin F30, a linear peptide consisting of 19 α-amino acids including eight Aib residues and a C-terminal α,α-aminoalcohol, phenylalaninol (Pheol). The stepwise coupling of Aib residues using CIP/HOAt proceeded nearly quantitatively in CH_2Cl_2 or DMF at 25 °C within 60 min to yield the necessary fragments without any difficulty.[9]

More complex and hindered α,α-dialkylamino acids can also be coupled with CIP/HOAt. CIP-mediated activation was applied for the difficult coupling of three adjacent α-methylcysteine residues. The coupling reaction proceeded at 25 °C in a 60% yield (2).[10]

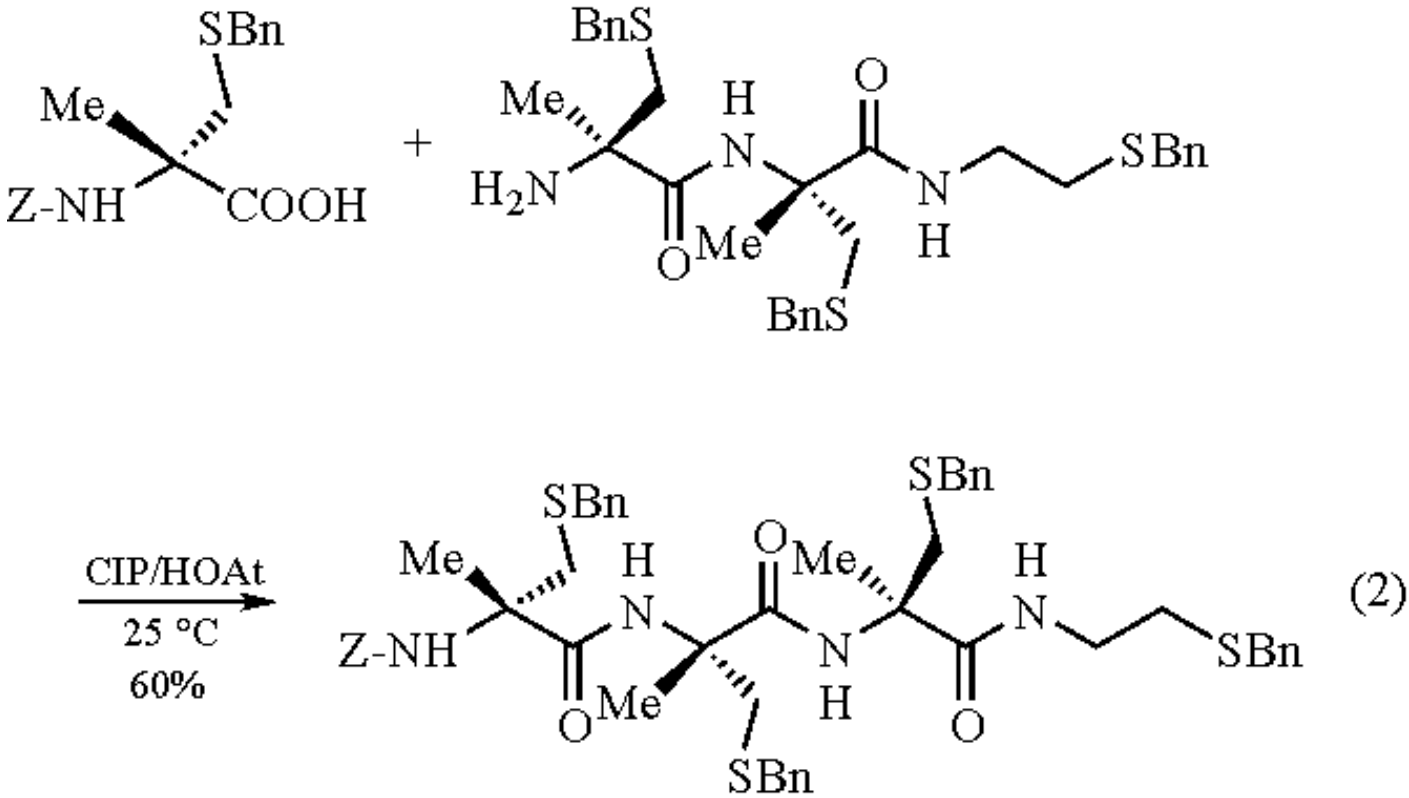

The procedure was the key step in the convergent syntheses of the polythiazoline alkaloids, mirabazole B (**3**),[11] mirabazole C (**4**),[10] and thiangazole(**5**).[12]

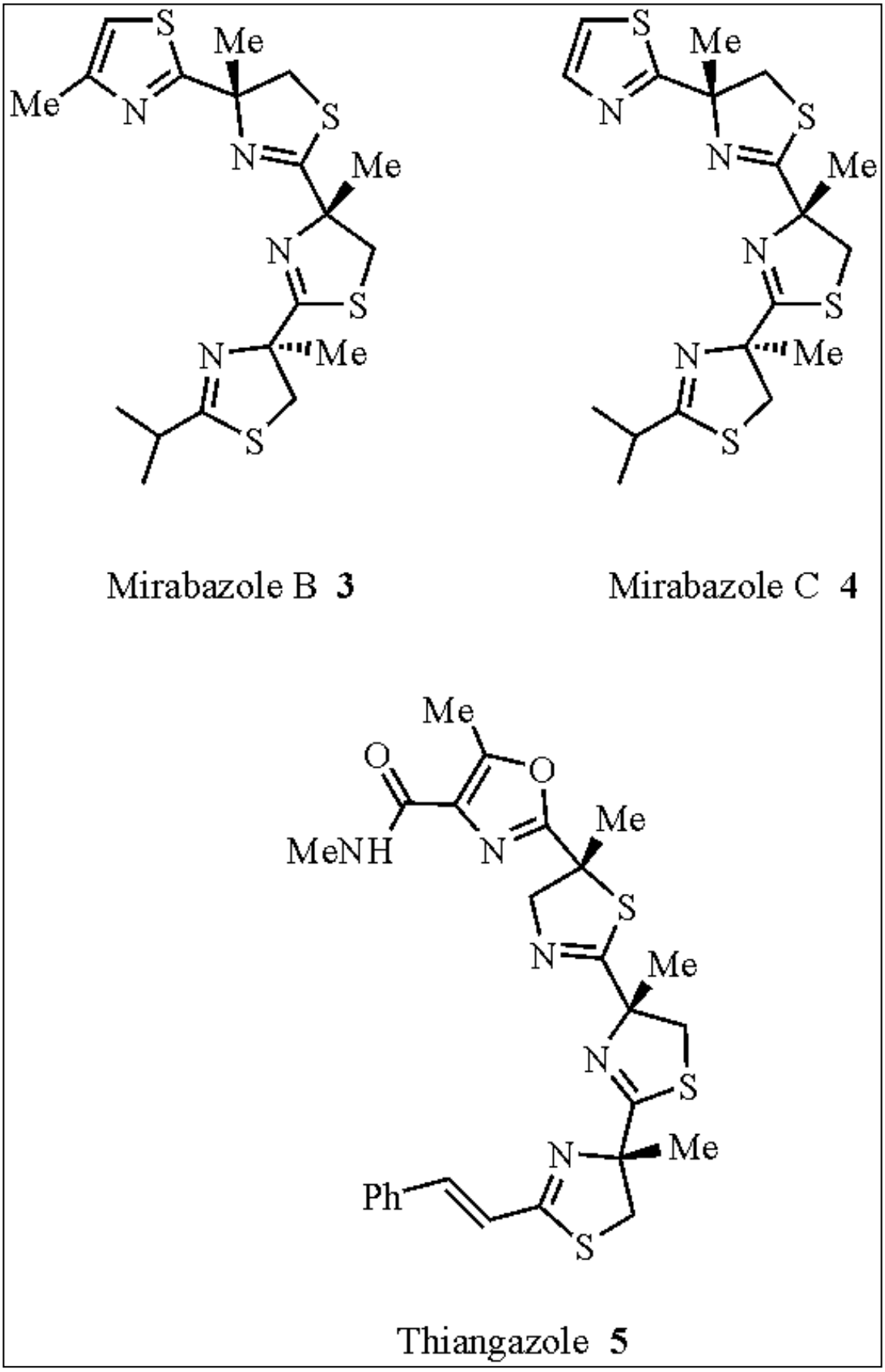

Coupling of *N*-methylamino Acid

An *N*-methylamino acid is incorporated with difficulty using conventional peptide coupling reagents because of its steric hindrance and marked tendency to racemize.[13] CIP/HOAt was found to mediate the solution-phase coupling of the *N*-methylamino acid at 25 °C in CH_2Cl_2 in quantitative yield. The most hindered coupling between two *N*-methylated residues proceeds within 3 h, to give a 97% yield of the product with no detectable racemization: the corresponding D-isomer was produced in less than 0.5% yield (3).[14]

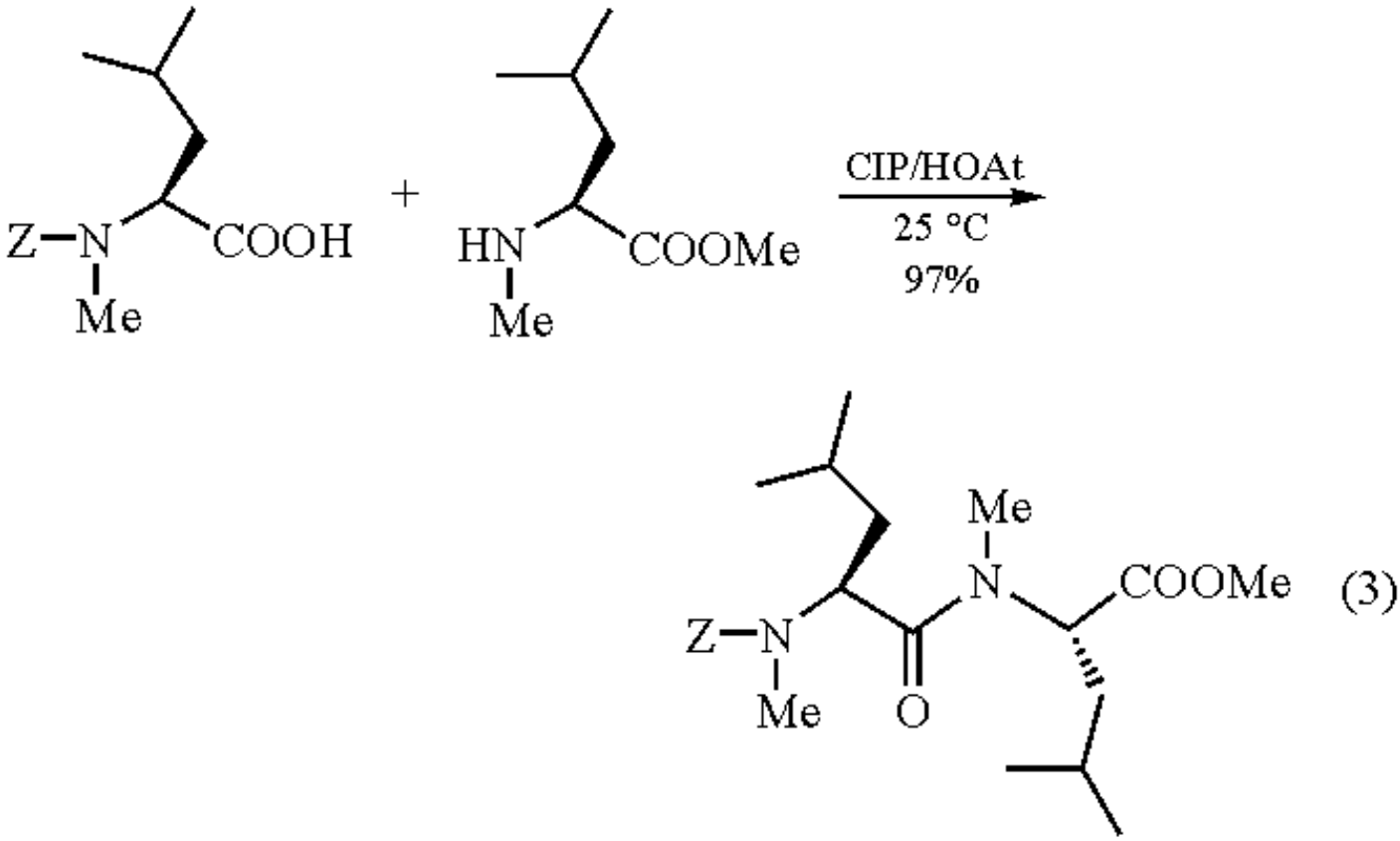

In the coupling of Z-MeVal-OH with MeAla-NHNH-Boc in solution phase, an efficient conventional reagent, BOP-Cl,[15] resulted in an 87% yield after an 18 h reaction time providing <0.5% isomerization, whereas the 1,3-dicyclohexylcarbodiimide (DCC)/DMAP procedure resulted in a 72% yield after a 24 h reaction, with 37% isomerization.[16]

The CIP-mediated activation procedure can be applied to the coupling of *N*-methylamino acids on solid support.[14,17] Quantitative-to-moderate coupling yields were obtained by a single coupling reaction (1-3 h) at 25 °C with practically no racemization. The coupling between two *N*-methylated amino acids proceeded on solid support in 53% yield after a 3 h single coupling reaction (4). The content of the D-isomer was less than 2%. As a reaction solvent, the use of DMF resulted in better yields than CH_2Cl_2.

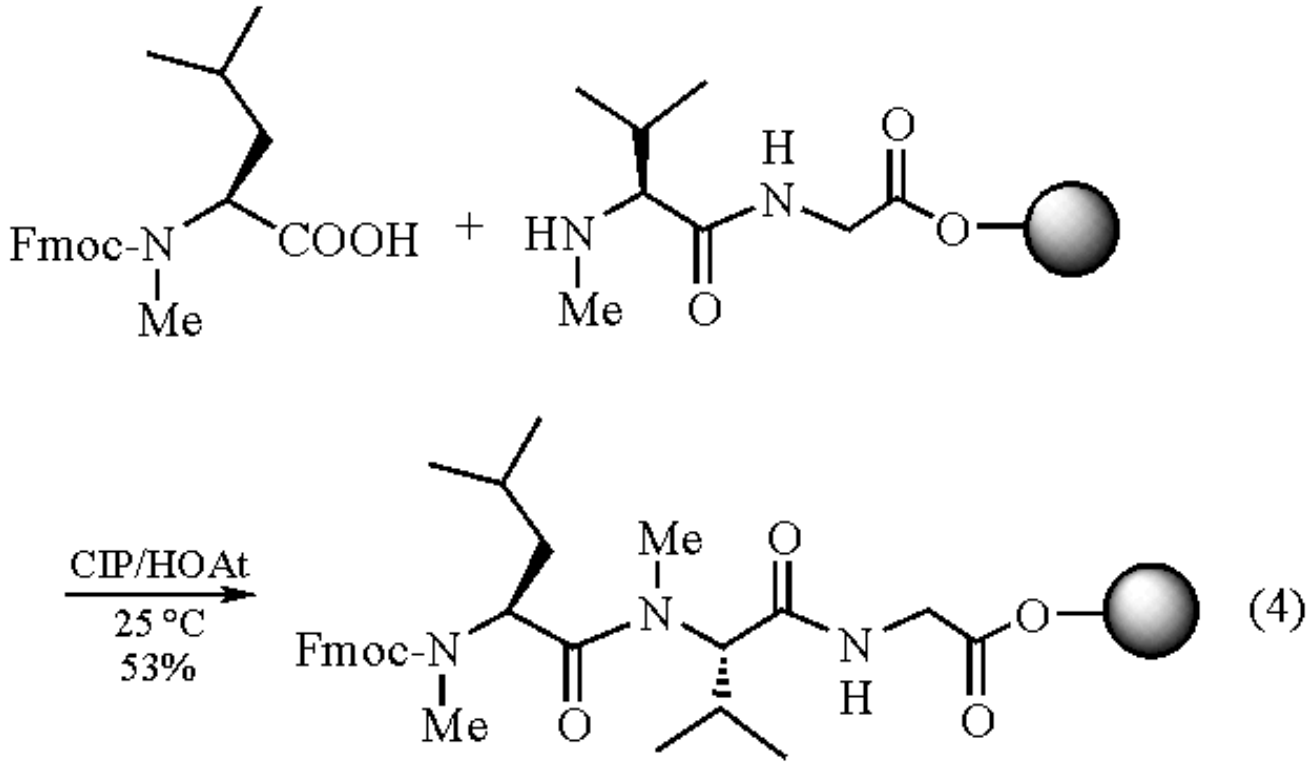

Solid phase coupling using CIP/HOAt was successfully applied to a convergent synthesis of Dolastatin 15, a cytostatic depsipeptide isolated from a marine mollusk. A tetrapeptide fragment was obtained by cleavage of **6**, which was prepared by the successive CIP-mediated coupling of *N*-methylamino acids on a 2-chlorotrityl polystyrene resin. The overall yield based on starting resin was 50%.[14]

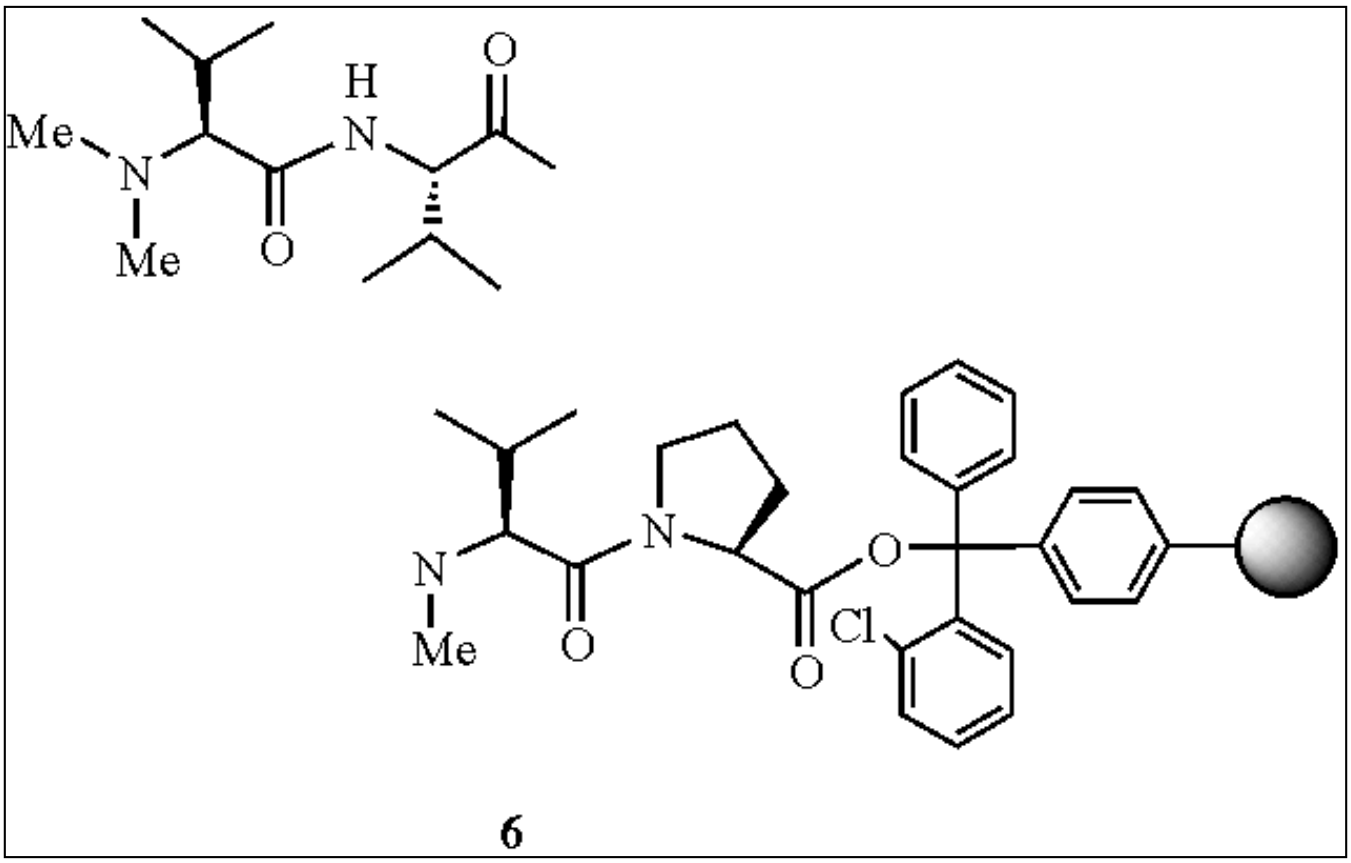

Fragment Coupling

The reaction efficiency of fragment coupling is generally low, compared with the coupling of a single amino acid. A greater fragment size results in a lower coupling efficiency. Fragment coupling is also prone to racemization via the oxazolone, which is formed during the activation of the C-terminus, i.e. during the activation of the *N*-acylamino acid.[18] These difficulties can be avoided by taking advantage of the high reactivity of a coupling reagent combined with a judicious choice of coupling position.

CIP/HOAt was employed for the coupling of an *N*-terminal 11-residue fragment with a Gly residue at its C-terminus, and a C-terminal nine-residue fragment to yield protected Alamethicin F-30. The coupling reaction proceeded at 25 °C within 60 min to yield 66% of the homogeneous product after purification.[19] The same coupling procedure was used in the final coupling reaction in the synthesis of Dolastatin 15 (**7**). The coupling reaction at the Pro residue proceeded at 25 °C within 2 h to yield Dolastatin 15 in 89% yield.[14]

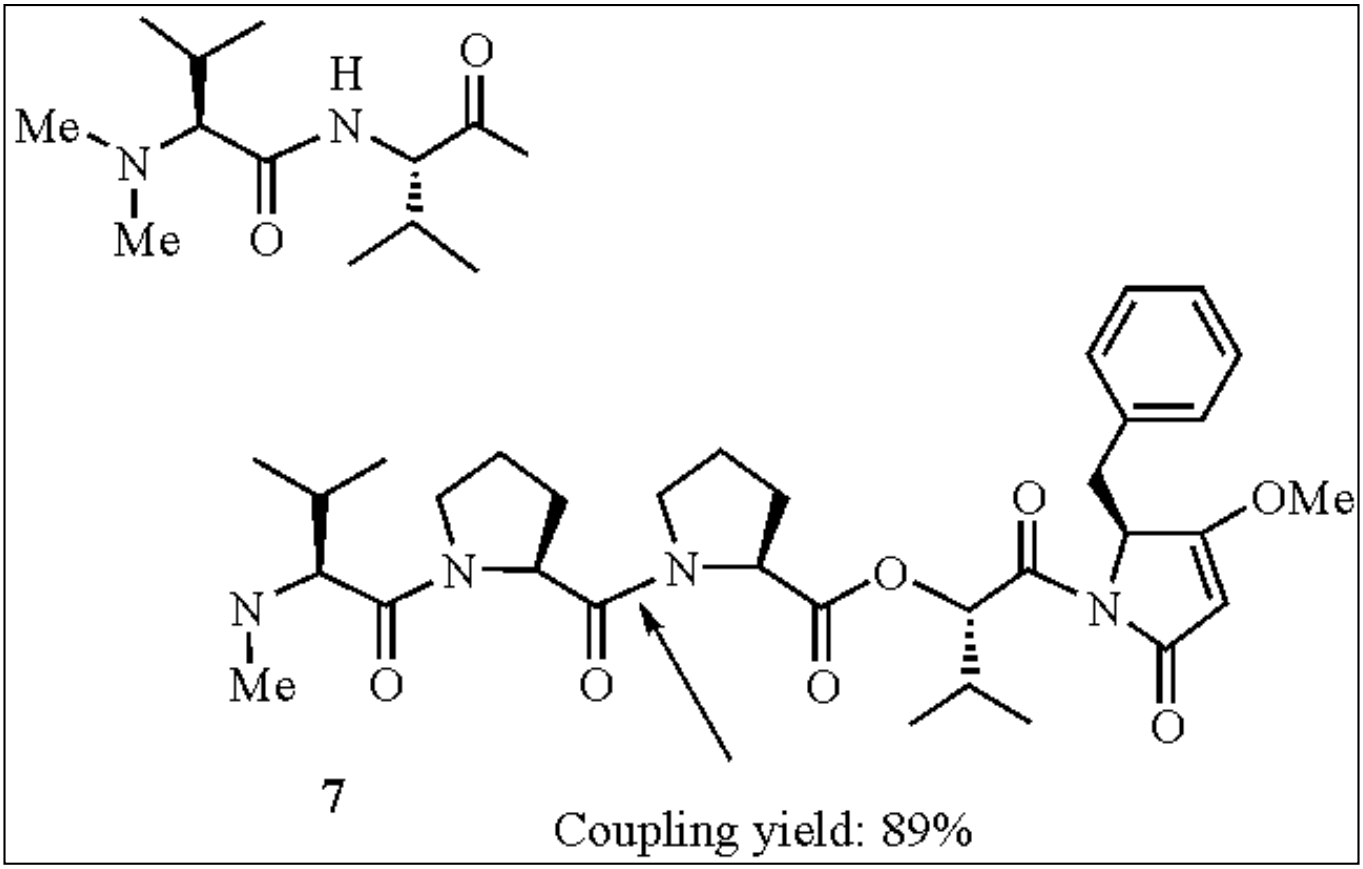

CIP/HOAt can also be applied to the coupling of fragments with an optically active α-amino acid at the C-terminus. In the synthesis of Trichovirin I4A (**8**) using CIP/HOAt, coupling efficiency and the rate of racemization were found to be greatly dependent on the coupling site. Fragment coupling between the Ala and Val residues proceeded within 60 min at 25 °C in 81% yield with no detectable racemization, whereas fragment coupling between the more hindered Val and Aib residues resulted in a lower yield (69%) of the epimerized product.[19]

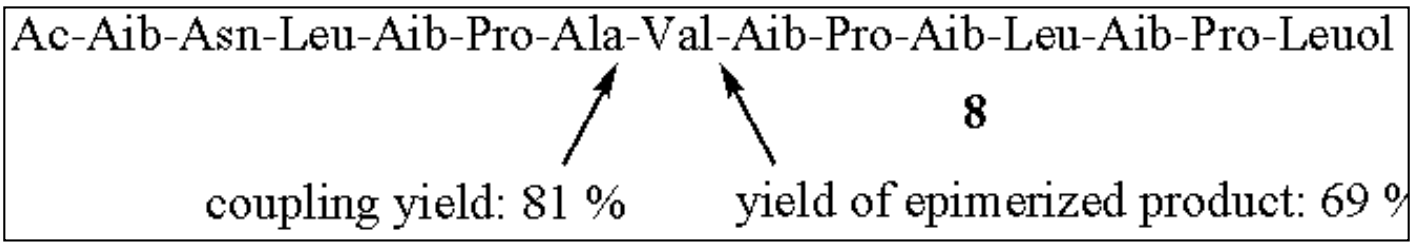

Macrocyclization

Head-to-tail cyclization represents a type of intramolecular fragment coupling and an efficient coupling reagent required for this transformation. A low reaction rate, as the result of an improper choice of the coupling reagent or the coupling site, facilitates extensive side reactions such as dimerization, oligomerization, and racemization.

CIP/HOAt was employed for the intramolecular cyclization to yield the key intermediate **9** in the synthesis of MEN11420, a glycosylated bicyclic peptide which has potent tachykinin antagonistic activity. CIP-mediated cyclization at the site between Dap(Boc) and Phe proceeded in DMF within 15 min to yield the cyclized monomeric product containing 6% of the D-Phe isomer. In contrast, cyclization at the more hindered site between the glycosylated-Asn and Leu proceeded in the presence of an excess amount of CIP (9 equiv) within 15 min to yield the monomeric product contaminated with 33% of the D-Leu isomer.[20]

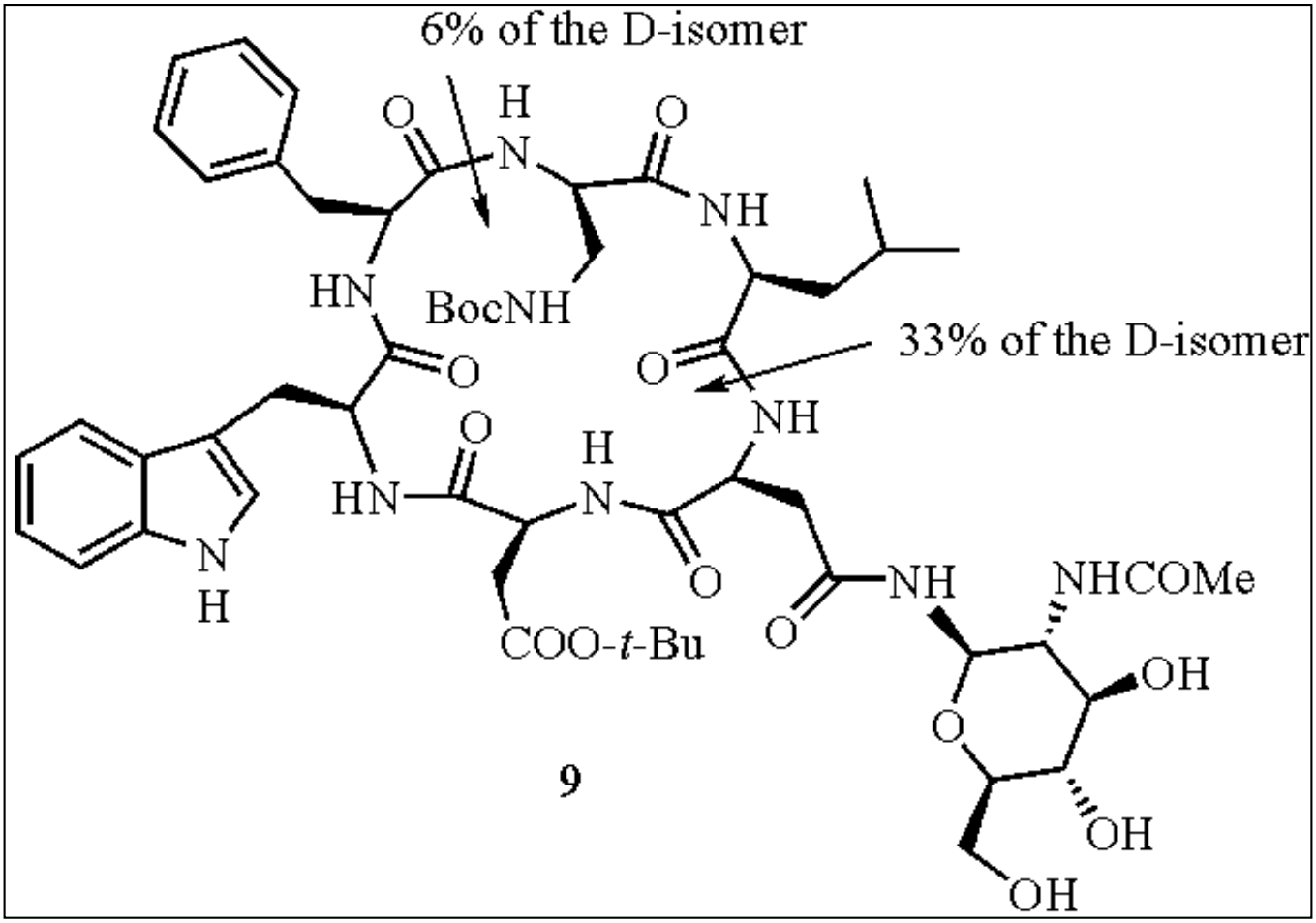

Esterification

CIP can be used for the esterification of a carboxylic acid to a hindered alcohol, such as a hindered secondary alcohol and a resin-bound alcohol. The CIP-mediated esterification of an Fmoc amino acid to a 4-alkoxybenzylalcohol resin was conducted at 25 °C within 60 min using 3 equiv of the Fmoc amino acid and 6 equiv of CIP in pyridine/CH_2Cl_2 (1:1). The reaction proceeded faster, with the same or lower level of racemization than the anchoring reaction using DIPCDI or PyBrop. For example, Fmoc-Lys(Boc)-OH was anchored to the alcohol resin in 74% yield accompanied by an 0.8% formation of the corresponding D-isomer, whereas a 57% yield using DIPCDI and a 33% yield using PyBrop was obtained.[21]

The esterification of Boc-Pro-OH with a secondary alcohol was achieved, after a 10 h reaction at 25 °C, using CIP in the presence of an additive (5).[14] The additive, DMAP, gave better results than HOAt, giving the desired product in 92% yield.

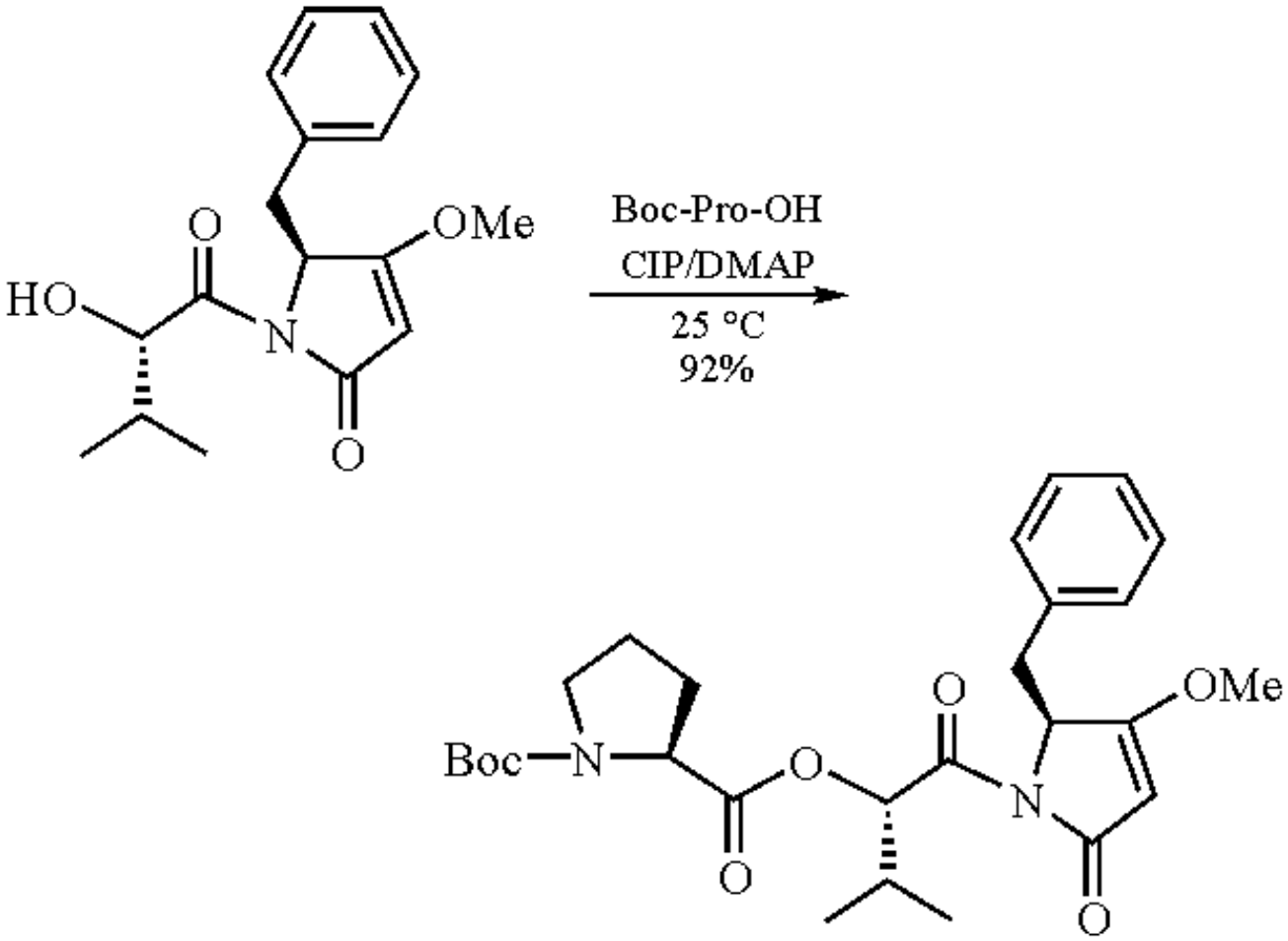

(5)

CIP can also be used for the introduction of a sterically hindered 2-azidomethylbenzoyl (AZMB) group into the 3´-hydroxy function of nucleosides (6). The esterification reaction proceeded within 2 h at 25 °C to yield the desired product in 66% isolated yield.[22] An excess amount of CIP (2.5 equiv) was necessary for a smooth reaction because of the steric hindrance involved.

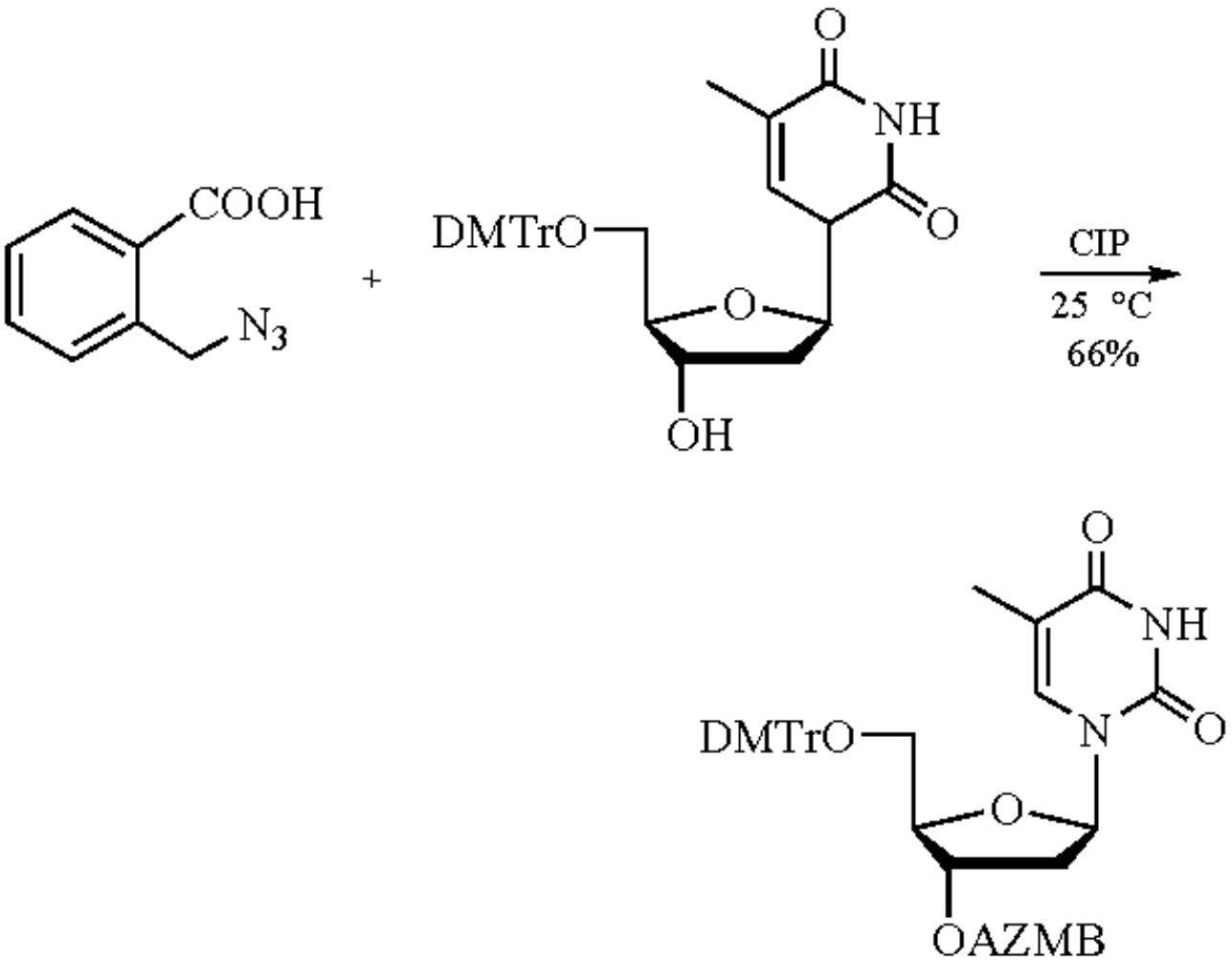

(6)

Related Reagents.

3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT);[23] ethyl 1-hydroxy-1H-1,2,3-triazole-4-carboxylate (HOCt);[24] 5-(1H-benzotriazol-1-yloxy)-3,4-dihydro-1-methyl 2H-pyrrolium hexachloroantimonate (BDMP);[25] 2-bromo-3-ethyl-4-methyl thiazolium tetrafluoroborate (BEMT).[26]

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Bis(tricyclohexylphosphine)(4-polystyrylmethylidene)ruthenium Dichloride

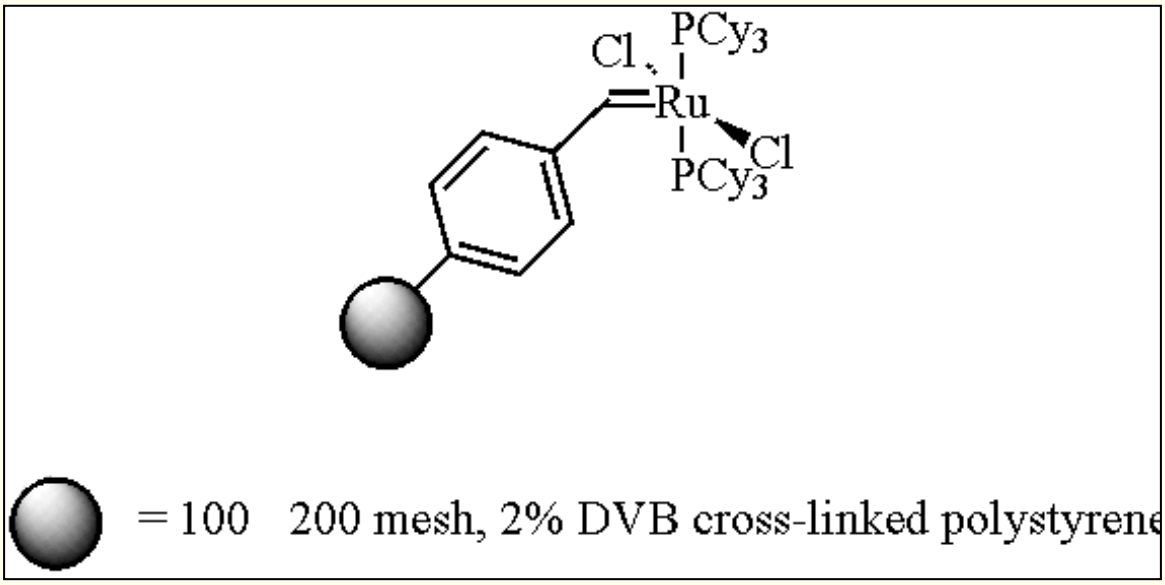

[223415-64-3]P · $[Cl_2(PCy_3)_2Ru{=}CHC_6H_4CHCH_2)]_m(C_6H_5CHCH_2)_n$loading ca. 0.1 mmol g^{-1}

(polymer ‘boomerang’ supported alkene metathesis complex that catalyses ring-closing metathesis of dienes, minimizes ruthenium contamination of the ring-closed adduct without chromatography, and can be recycled and re-used by simple filtration)

Alternate Name: vinyl polystyrene polymer-supported Grubbs' catalyst, ‘Boomerang’ catalyst.

Solubility: insoluble in all solvents; swells in CH_2Cl_2, toluene and THF; does not swell in MeOH.

Form Supplied in: commercially available from NovaBiochem as a lilac powder.

Preparative Methods: Bis(tricyclohexylphosphine)(4-polystyrylmethylidene)ruthenium dichloride (PS-Grubbs' catalyst) is commercially available from NovaBiochem.[1] It can also be conveniently prepared by shaking Grubbs' catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$[2] with vinylpolystyrene[3] (1-2% cross-linked with divinylbenzene) in dichloromethane solution for 1-2 h, followed by filtration (1).

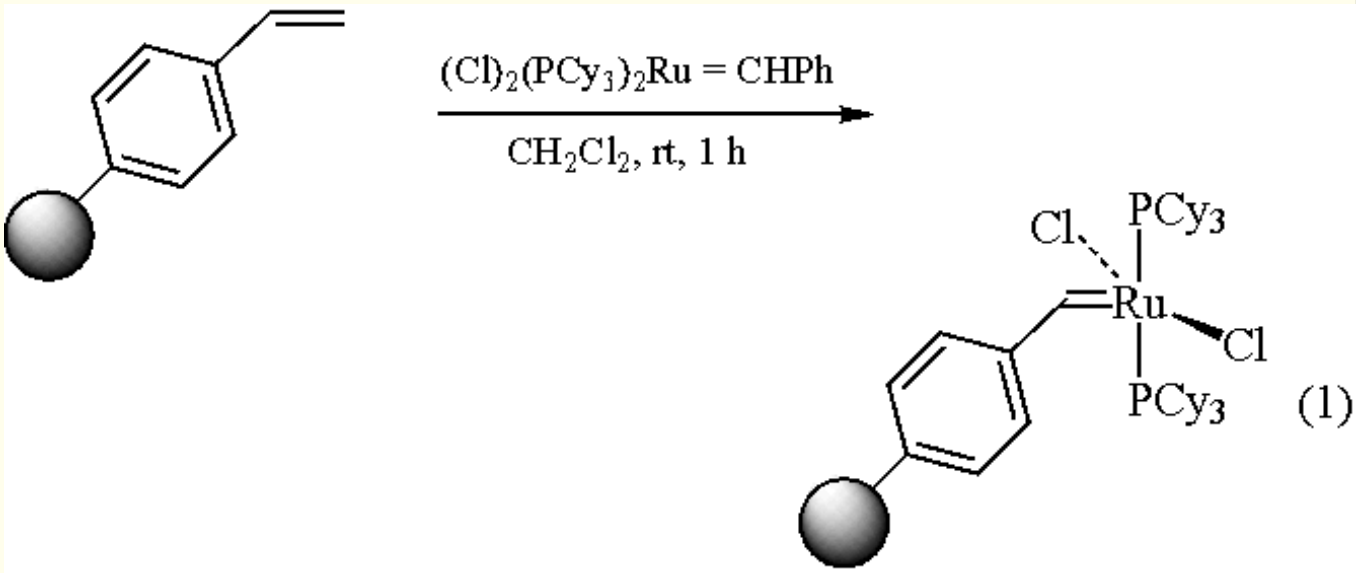

Handling, Storage, and Precautions: when dry may be stored in a sealed vessel for a period of months.

Ring-Closing Metathesis

PS-Grubbs' catalyst is used for ring-closing metathesis, minimizes the ruthenium contamination of the ring-closed adduct without extensive chromatography, and can be recycled and re-used by simple filtration.[4] Specifically, it has been applied for the preparation of five-membered carbocycles (2),[4] dihydropyrans (3),[4] bicyclic β-lactams (4)[4] and sulfonamides (5).[5]

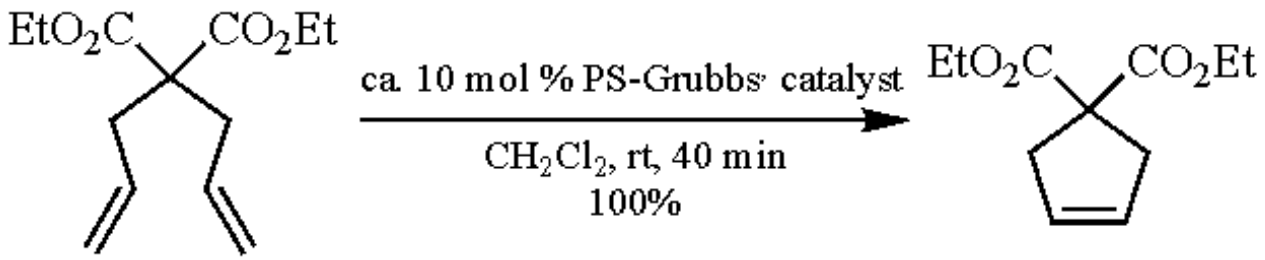

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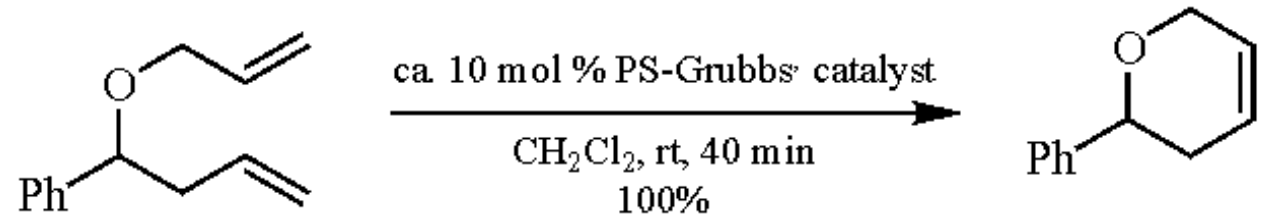

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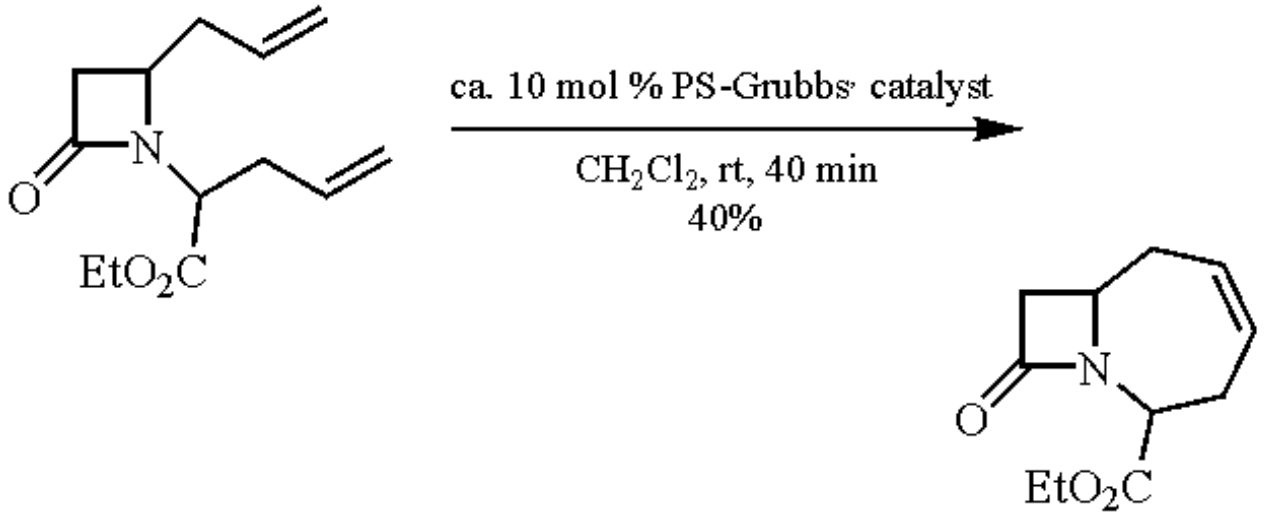

(4)

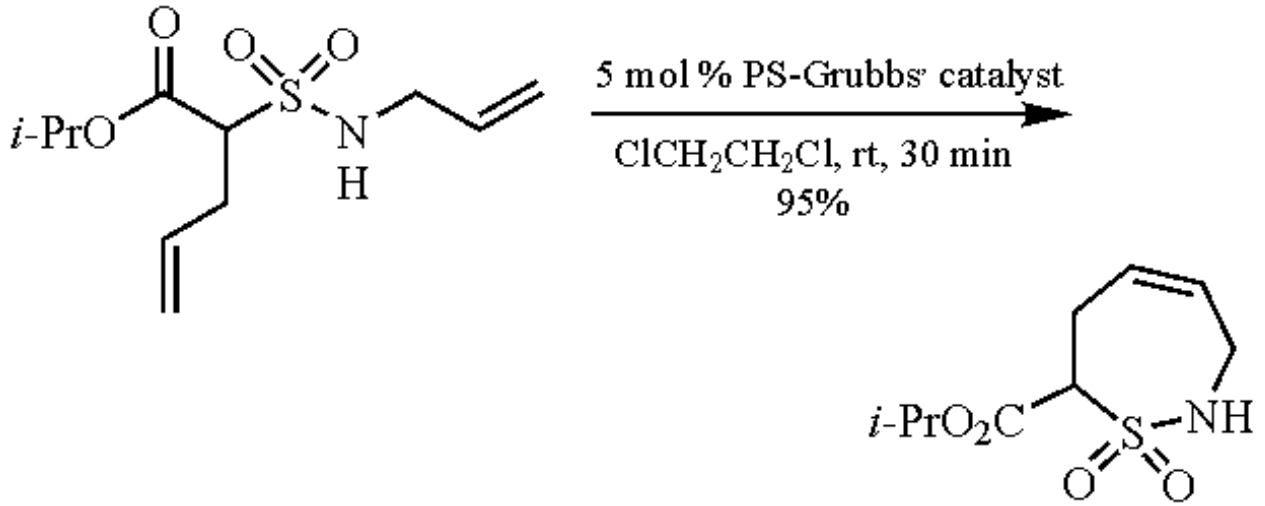

(5)

The advantage of the PS-Grubbs' catalyst over the traditional Grubbs' catalyst is that ruthenium contamination of the product is minimized and its use is simplified. Typically, the PS-Grubbs' catalyst is suspended in dichloromethane, the diene added and the mixture shaken for 40 min, followed by filtration. The product is obtained by simple evaporation of the washings, with minimal ruthenium contamination. The recovered catalyst can be re-used but is less active. The lifetime and activity of a given batch of PS-Grubbs' catalyst can be extended to allow three recycles by the simple addition of hex-1-ene or 3,3-dimethylbut-1-ene (9 mol%) to the mixture.[4] These volatile alkenes are removed with the dichloromethane solvent in the evaporation stage to obtain the product.

The mechanism by which the PS-Grubbs' catalyst operates has been dubbed a ‘boomerang’ process. Initial metathesis with a given diene releases the catalyst from the solid support into solution. Homogeneous alkylidene [$Cl_2(PCy_3)_2Ru{=}CHR$] catalysed metathesis ensues and the system therefore displays very similar activities to the homogeneous Grubbs' catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$]. It is therefore expected that for any ring-closing metathesis that Grubbs' catalyst [$Cl_2(PCy_3)_2Ru{=}CHPh$] can catalyse, PS-supported Grubbs' catalyst will be equally effective. After metathesis is complete, the resin recaptures the catalyst at a vacant vinyl site.

Recent improvements in the catalyst design to allow extended catalyst recycling and re-use (up to five times) have been achieved by the incorporation of an imidazol-2-ylidene ligand *in lieu* of one the PCy_3 ligands (6).[6] In this system oct-1-ene (10 mol %) and PPh_3 (5 mol %) were used as additives to extend catalyst lifetime in re-cycle mode. Other ‘boomerang’ catalysts for ring-closing metathesis have been reported by Jafarpour & Nolan,[7] Yao,[8] Garber et al.[9] and Dowden.[10]

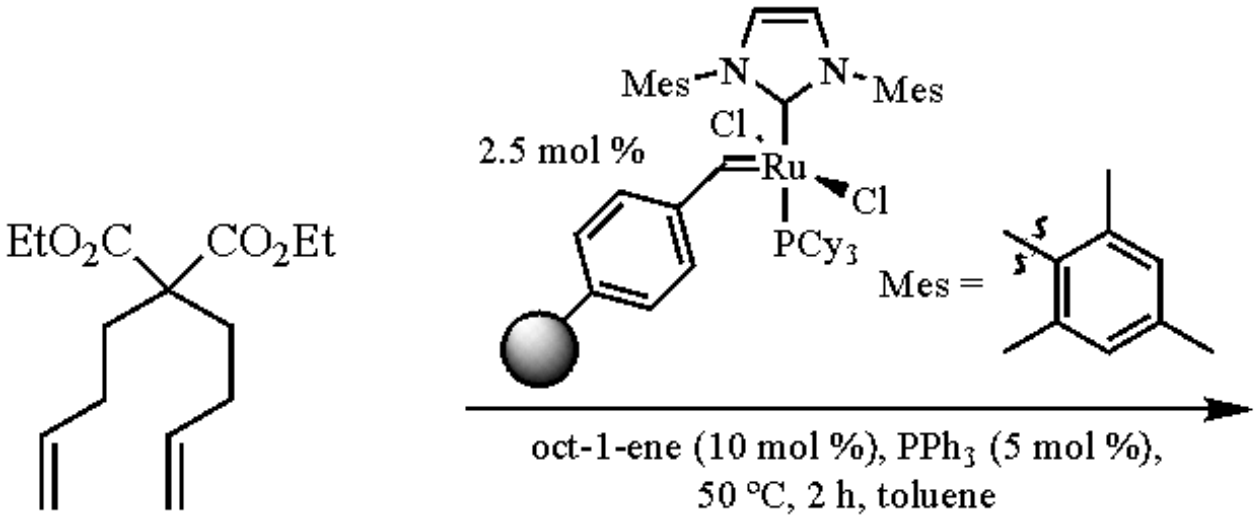

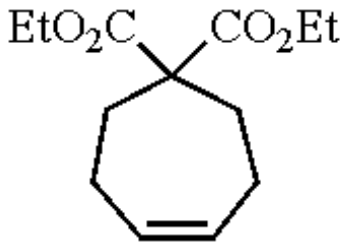

100%
5 consecutive recycles:
100%; 100%; 94%; 42%; 11%

(6)

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10. Dowden, J.; Savovic, J., *Chem. Commun.* **2001**, 37.

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Imperial College, London, UK

Poly(*exo-N*-hydroxy-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide)

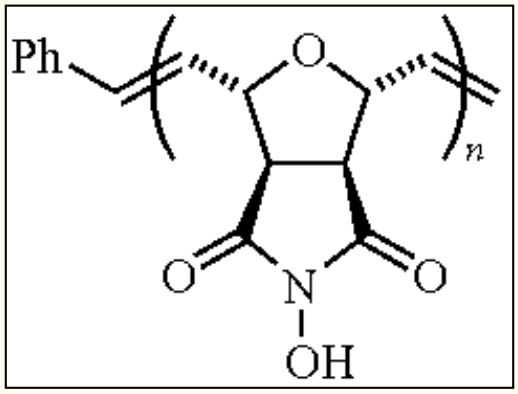

[259796-15-1]F · $(C_8H_7NO_4)_n$ · (181.15)

(polymeric acyl transfer reagent for activated carboxylic acids, chloroformates and isocyanates in amine acylation and related reactions)

Alternate Name: ROMPGEL-*N*-hydroxysuccinimide.

Solubility: soluble in DMF, DMSO; insoluble in H_2O, most organic solvents.

Form Supplied in: gray granular solid.

Analysis of Reagent Purity: the purity of the precursor polymer is verified by ^{1}H NMR. IR confirms complete desilylation of the product.

Preparative Methods: see text.[1]

Purification: stirring in methanolic ammonia in THF overnight followed by filtration, sequential washing with H_2O, THF, CH_2Cl_2 and diethyl ether and drying at 40 °C and 20 mmHg.

Handling, Storage, and Precautions: stable to air, light and heat.

Peptide Bond Formation

This polymeric reagent bears the same functionality and follows the same reactivity as N-**hydroxysuccinimide** (HOSu), namely as an acyl transfer reagent. The reagent can be prepared by ring-opening metathesis polymerization (ROMP) of the TBS-protected ether (**1**) using **benzylidenebis(tricyclohexylphosphine)dichlororuthenium**[2] (Grubbs' catalyst) (**2**), followed by removal of the silyl group, optimally with **triethylamine trihydrofluoride**,[3] precipitating the granular polymer (1).[1]

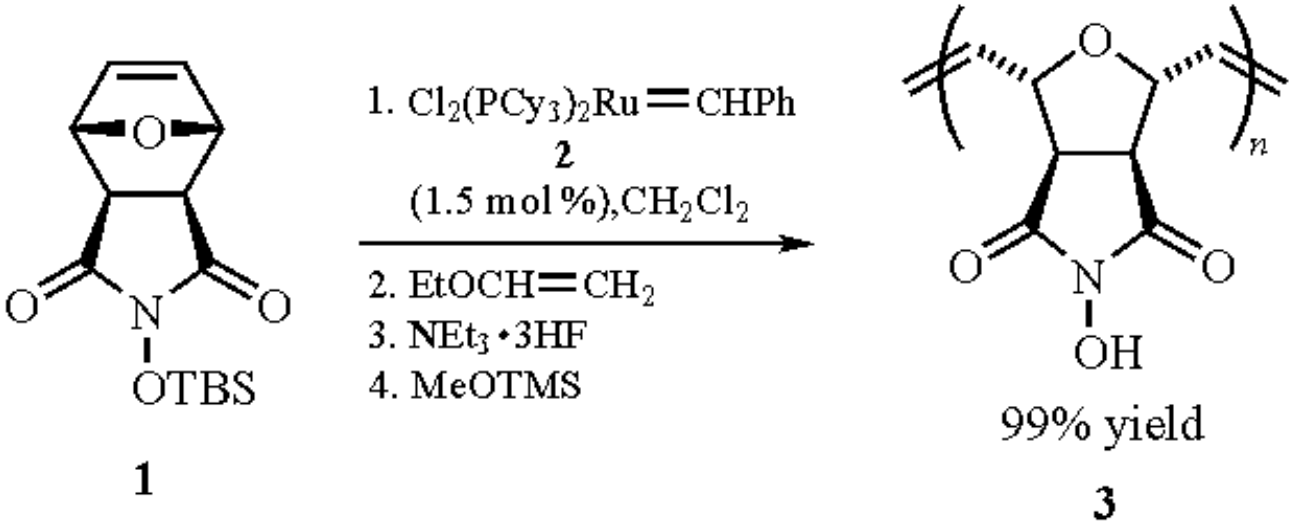

(1)

Once formed, the hydroxy functionality can be derivatized to give activated esters, either by using an acid chloride and **triethylamine** as base (2), or with a carboxylic acid and using **1,3-dicyclohexylcarbodiimide** (DCC) as the coupling reagent (3). The polymer is purified by washing away the solution-based reagents with excess solvent. The polymer can also be converted to an activated carbonate (chloroformate and **triethylamine** as base, 4), or to an activated carbamate by reaction with an isocyanate (5).

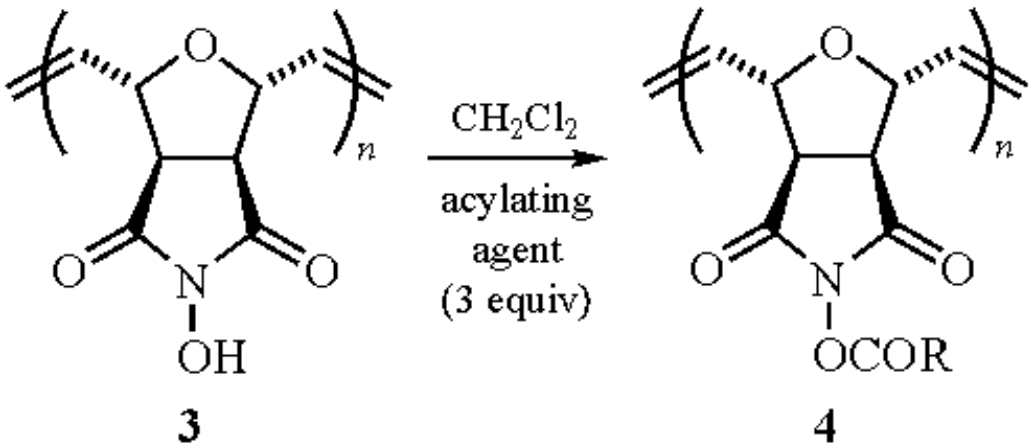

Acid chloride, NEt_3	R = Alkyl, Ar	(2)
Carboxylic acid, DCC	R = Alkyl, Ar	(3)
Chloroformate, NEt_3	R = OAlkyl	(4)
Isocyanate	R = NHAlkyl	(5)

The stable esters (**4**) can be reacted with a range of nucleophiles, with acyl transfer. Traditional usage of HOSu involves at least an aqueous wash to remove the polar succinimide and, more often, further chromatographic purification of the product. Reaction of an amine nucleophile with 1.3 equiv of a ROMPGEL-*N*-hydroxysuccinimide-supported ester is sufficient to give essentially quantitative conversion to the product. Here, since both the remaining unreacted activated ester and the *N*-hydroxysuccinimide by-product are bound in the polymer matrix, both can be removed by a single filtration. Evaporation of the solvent gives essentially pure product in excellent isolated yields. Amines can be effectively acylated in this way (6). Polystyrene-supported *ortho*-nitrophenol[4] and polystyrene-supported *N*-hydroxybenzotriazole[5] are other examples of polymer-supported acyl transfer reagents.

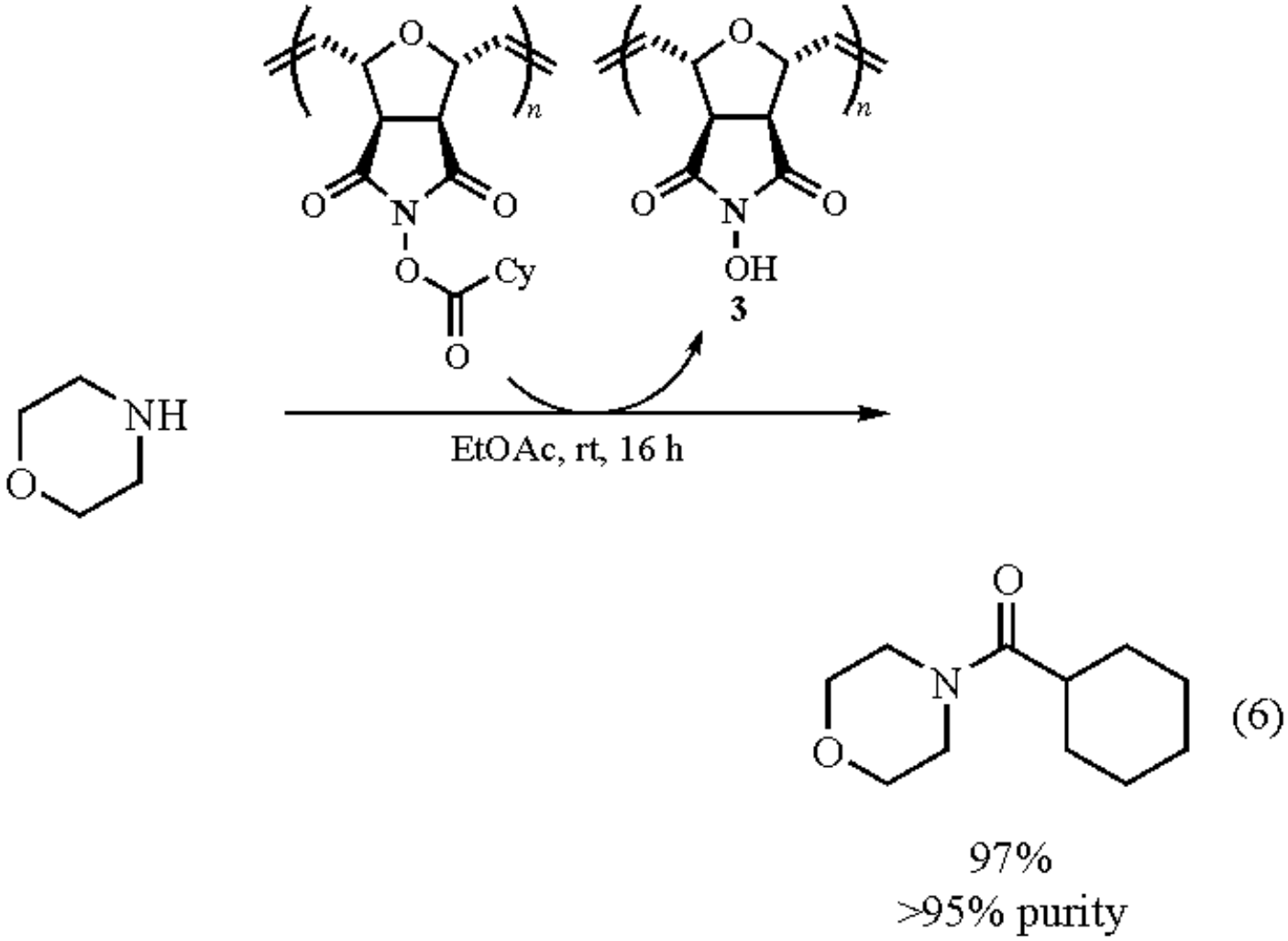

Amine hydrochloride salts can also be acylated directly, employing **triethylamine** as an HCl shuttle and the strong base polystyrene-supported triazabicyclo[3.3.0]decane[6] (P-TBD) as the HCl sink (7). Amino acid esters are acylated with minimal (<1%) racemization.

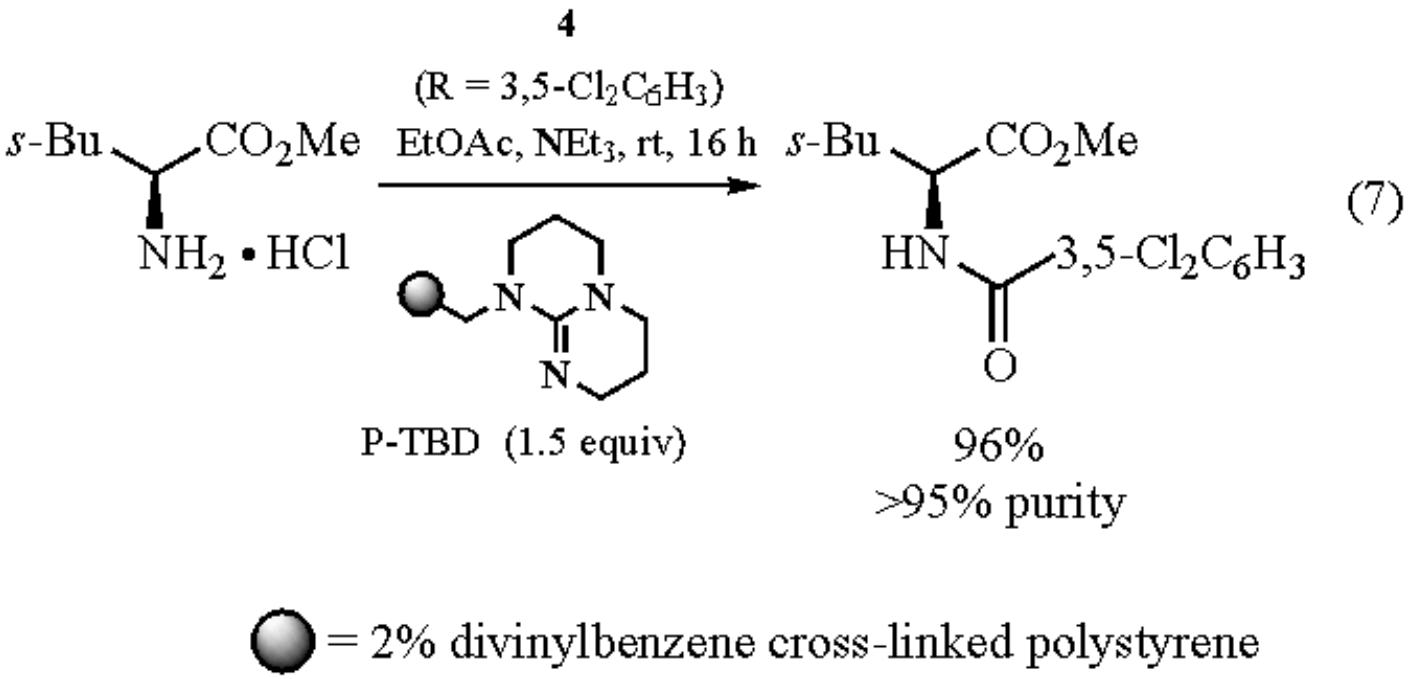

ROMPGEL-*N*-hydroxysuccinimide can also be used to form carbamates (8) and ureas (9).

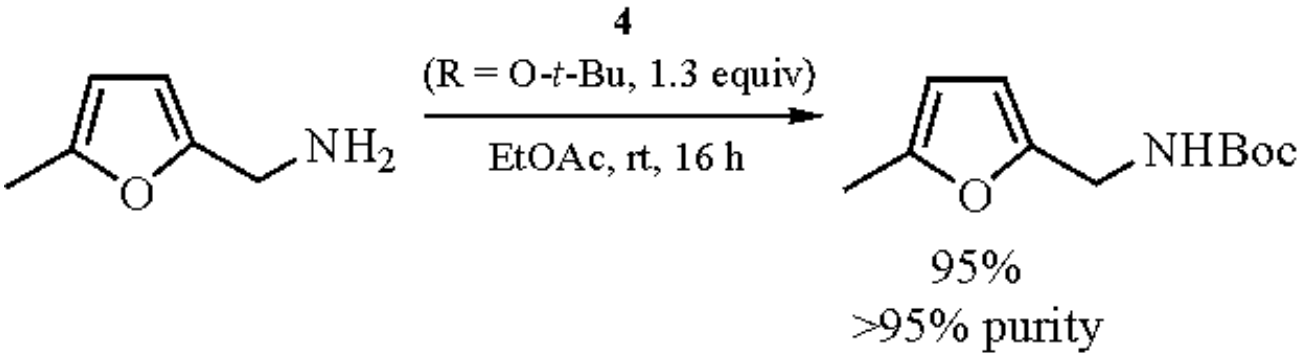

95%
>95% purity

(8)

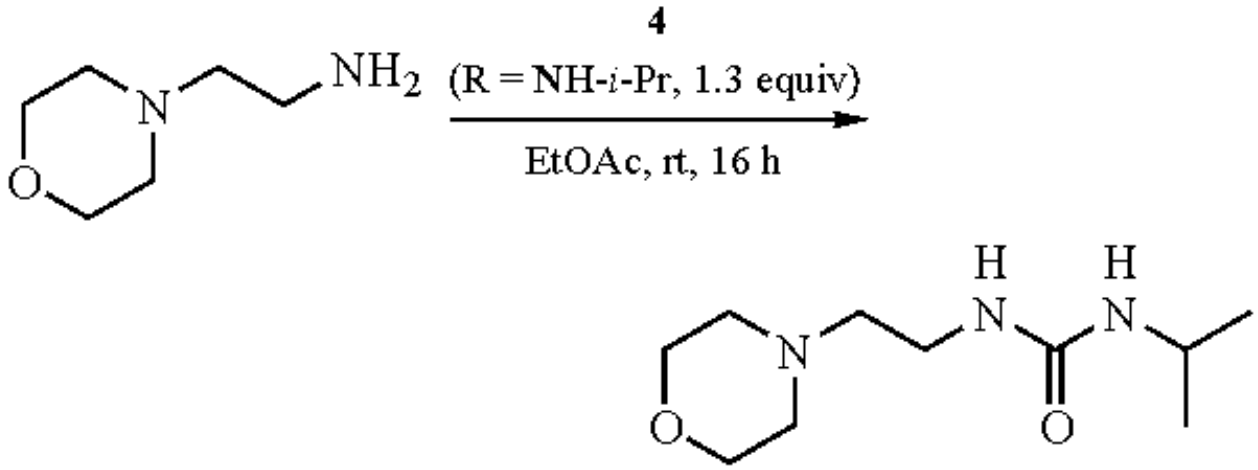

92%
>95% purity

(9)

For bulk acylation purposes (where the same acyl group is to be transferred to a range of nucleophiles), it is more convenient to acylate the monomer (**5**) and to polymerize this derivative directly. Low molecular weight monomers may lead to liquid ROM-polymers, so between 5-30 mol % **norbornadienene** (NBD) can be added, forming cross-links[7] between neighboring linear chains and giving the required insoluble polymer gel (**4**)[1,8] (10).

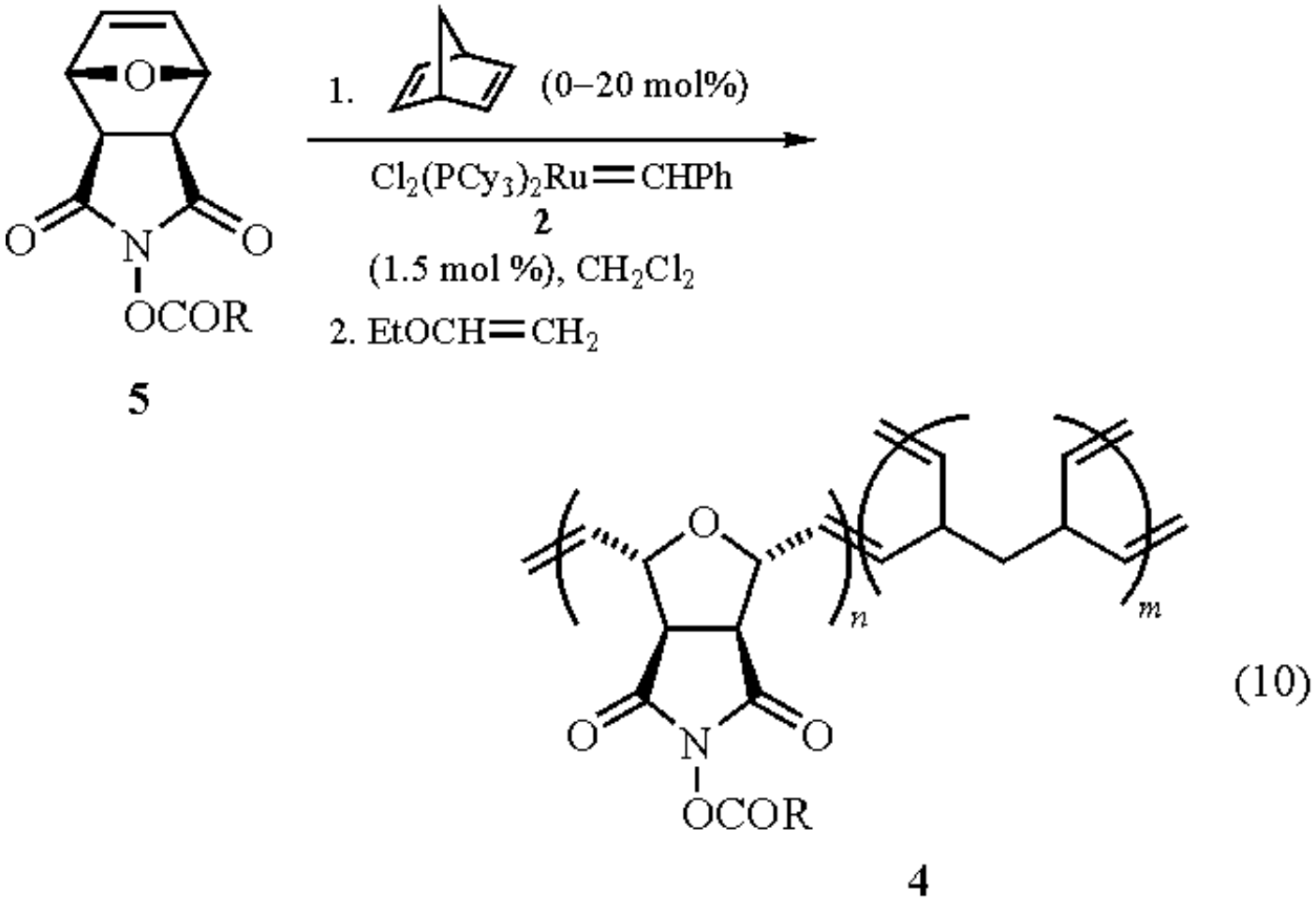

R = Alkyl, Ar, OAlkyl, NHAlkyl

Hydroxylamine (released from the hydrochloride salt in situ by adding solid potassium hydroxide) is cleanly acylated and with a single filtration and evaporation gives hydroxamic acids (11). Replacing hydroxylamine with N,O-**dimethylhydroxylamine** gives the corresponding Weinreb amides.[9]

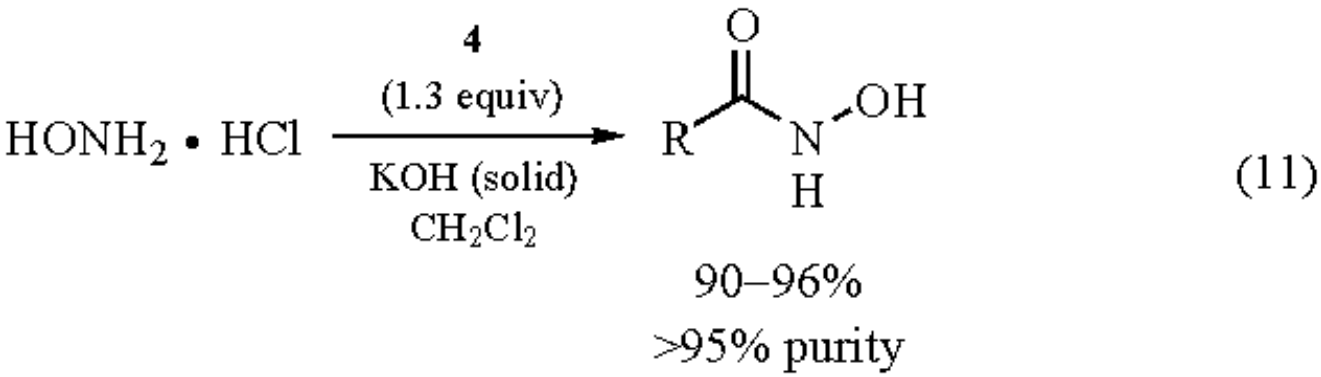

Amidoximes can also be acylated, initially on oxygen. If the reaction is carried out in the presence of P-TBD, dehydrative cyclization occurs to give the corresponding 1,2,4-oxadiazoles in good-to-excellent yield and essentially pure, after a single filtration and evaporation (12).[8]

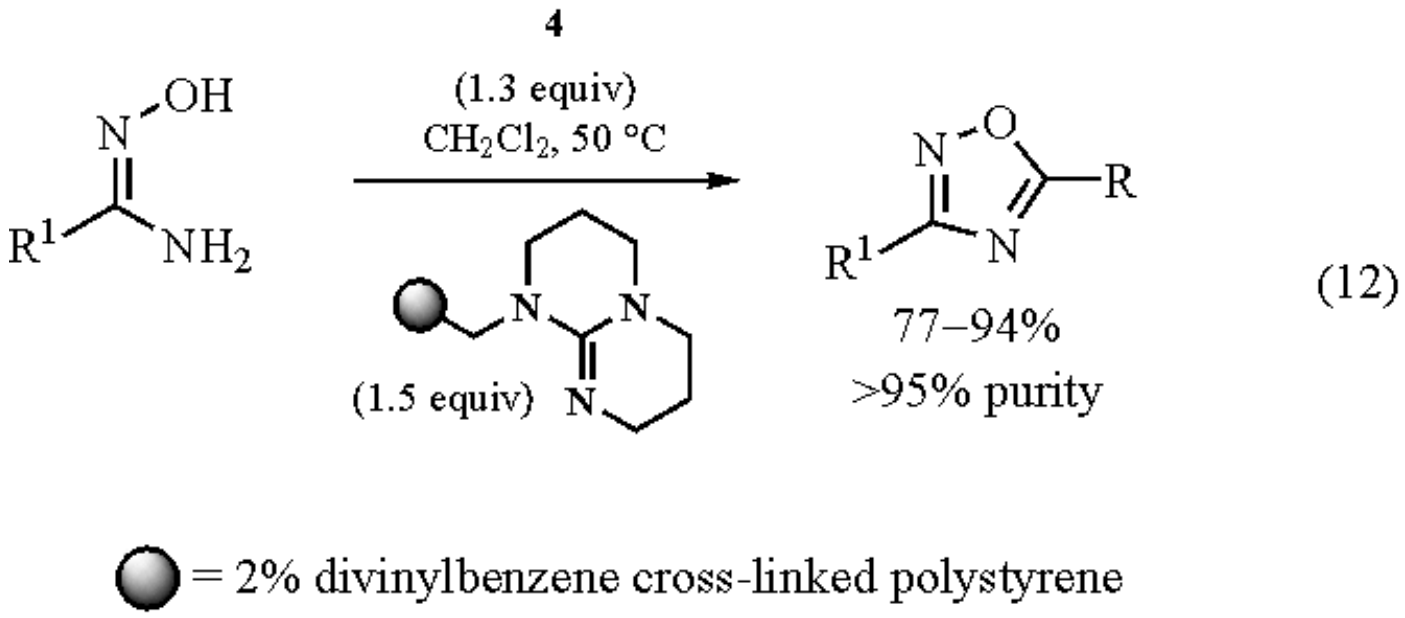

In general, ROMPGEL-supported esters react only with amine nucleophiles. For electron-poor acyl groups, however, some *O*-acylation can be observed (13).[1]

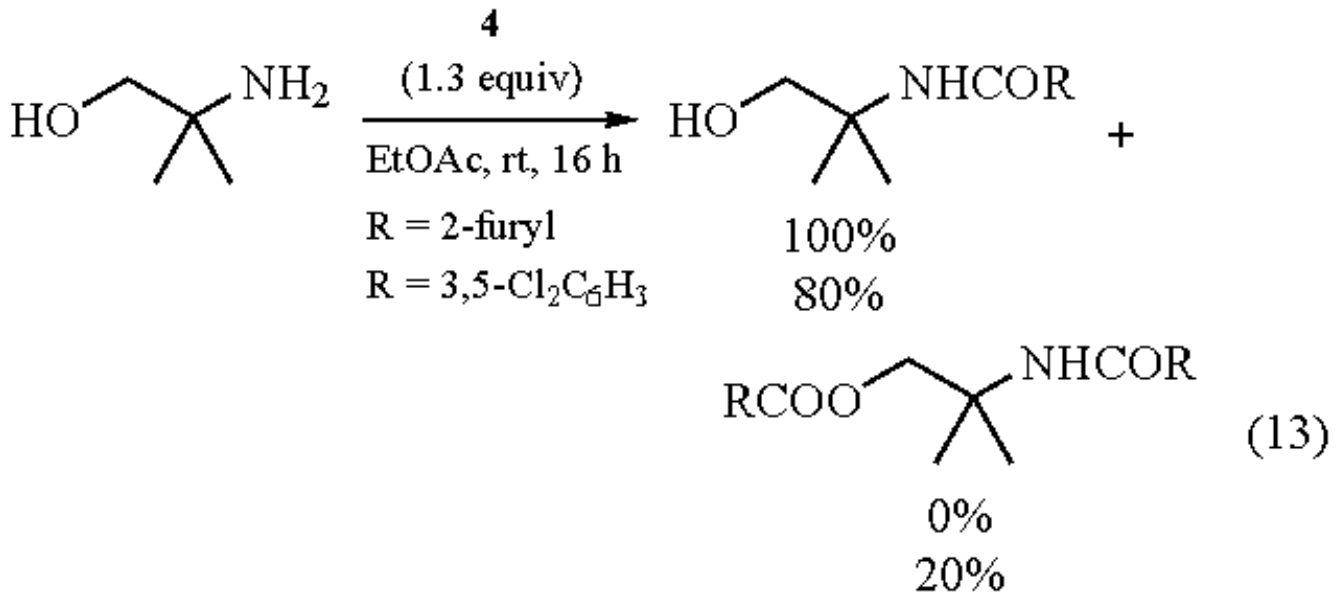

Finally, the polymer can be recycled after use by washing with methanolic **ammonia** to remove any remaining acyl group. Re-acylation and subsequent reaction give the new product in >95% purity with no sign of the remnant acyl group being incorporated (14).[1]

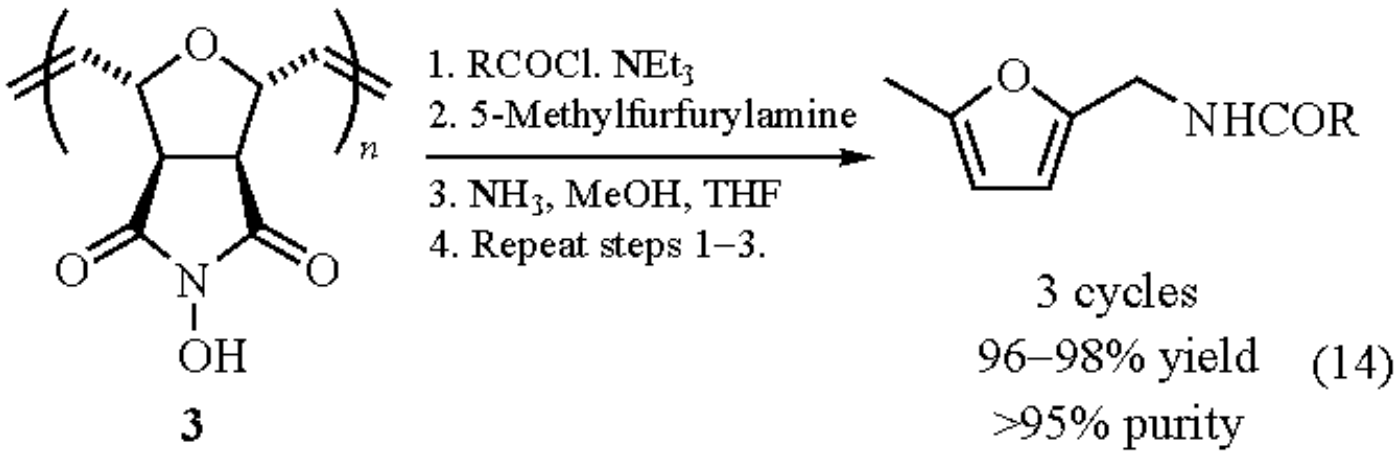

Related Reagents.

N-hydroxysuccinimide; N-hydroxybenzotriazole; polystyrene-supported N-hydroxybenzotriazole.

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(*S*,*S*)-1,2-Bis(2,5-diethylphospholano)benzene

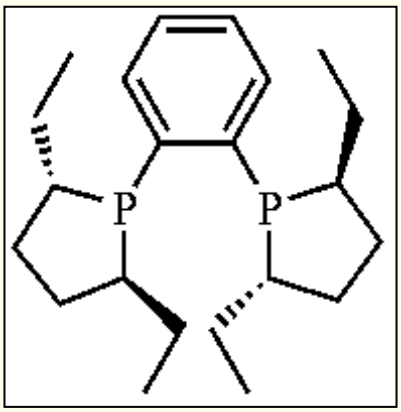

[136779-28-7] · $C_{22}H_{36}P_2$ · (362.47)

(ligand for asymmetric catalysis; rhodium(I) complexes are efficient catalysts in highly enantioselective hydrogenation of various unsaturated substrates [enol acylates,[1,2] (*N*-acylamino)acrylates,[1,3,4] and *N*-acylhydrazones[5]])

Alternate Name: (*S*,*S*)-ethyl-DuPHOS

Physical Data: bp 138-145 °C/0.04 mmHg; $[\alpha]_D$ +265 (*c* 1, hexane).

Solubility: soluble in most organic solvents.

Form Supplied in: colorless oil; commercially available.

Analysis of Reagent Purity: optical rotation; NMR spectroscopy.

Preparative Methods: the preparation of (*S*,*S*)-ethyl-DuPHOS is based on (3*R*,6*R*)-octane-3,6-diol as an enantiomerically pure starting compound.[1,3] The latter is synthesized by a three-step procedure[6,7] starting from methyl 3-oxopentanoate, which is transformed to methyl (*R*)-3-hydroxypentanoate (99% ee) by enantioselective hydrogenation with a Ru-(*R*)-BINAP catalyst,[8] followed by hydrolysis to the hydroxy acid. The subsequent electrochemical Kolbe coupling reaction leads to (3*R*,6*R*)-octane-3,6-diol in a protocol that can be scaled up to multigram quantities (1).[3,6]

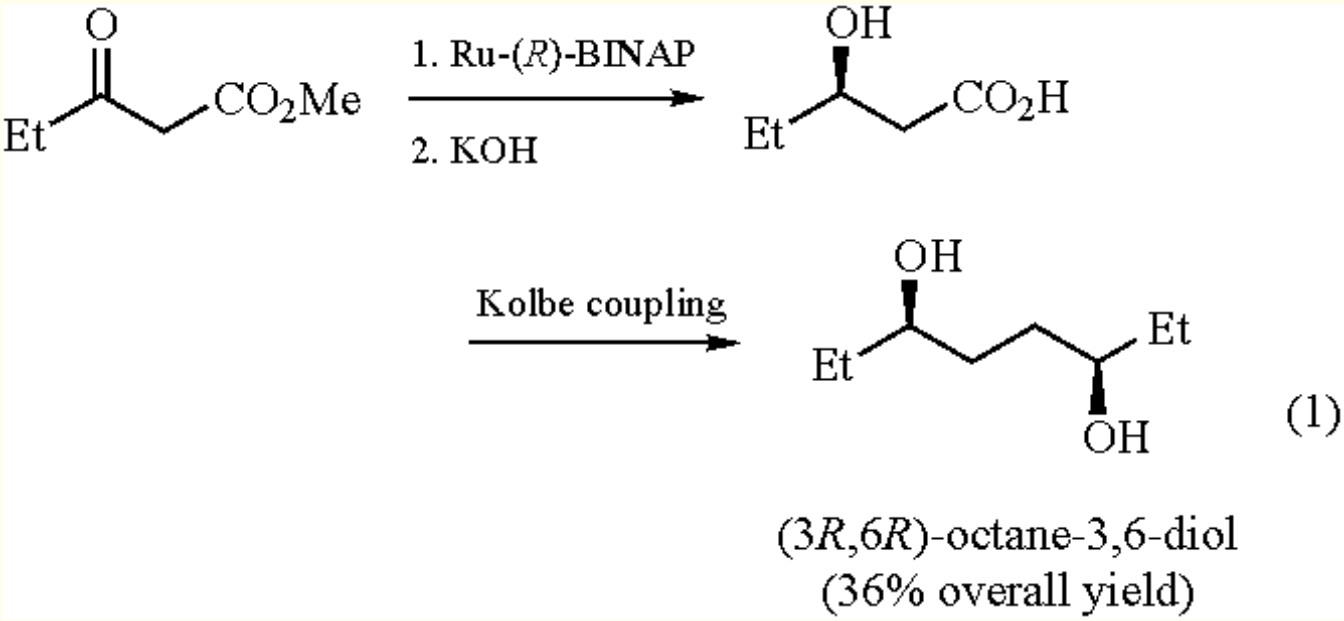

The chiral octanediol in turn is converted into the corresponding cyclic sulfate by reaction with **thionyl chloride** and subsequent oxidation with **sodium periodate** and a catalytic amount of **ruthenium(III) chloride** (0.1 mol%) (2).[3] In the final step, 1,2-diphosphinobenzene[9] is lithiated by treatment with n-**butyllithium** (*n*-BuLi; 2 equiv, 1.6 mol% in hexane) followed by the addition of the (3*R*,6*R*)-octane-3,6-diol cyclic sulfate (2 equiv) and a further addition of 2.2 equiv of *n*-BuLi. (*S*,*S*)-Ethyl-DuPHOS is obtained

in a yield of over 70% [78% yield was described for the (*R*,*R*)-enantiomer by an analogous method[3]].[1] In addition to (*S*,*S*)-ethyl-DuPHOS, a variety of related bisphospholanes either linked by an ethylene bridge, or bearing other 2,5-alkyl substituents, or with opposite configuration have been prepared by this methodology.[1,3]

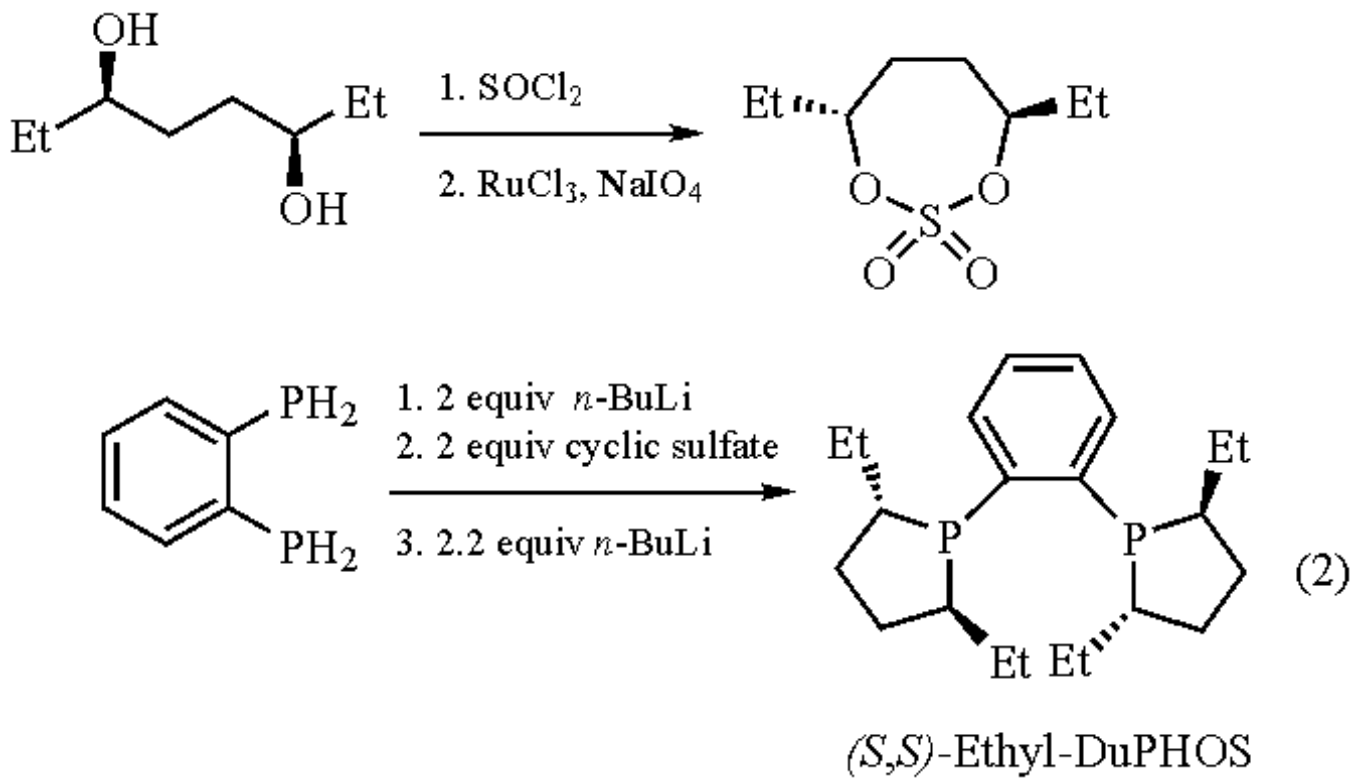

Handling, Storage, and Precautions: the reagent is sensitive to air and should be handled and stored under argon or nitrogen.

Catalyst Precursors

Rhodium Complexes

Cationic rhodium(I) complexes such as {Rh[(*S*,*S*)-ethyl-DuPHOS](cod)}$^+$X$^-$ (X=OTf, PF_6, BF_4, SbF_6) are usually employed as precatalysts for enantioselective hydrogenation[1-4] or hydrosilylation[10] reactions. The precatalysts can be prepared from the chiral ligand and [Rh(cod)$_2$]$^+$X$^-$-complexes by a standard method.[3,11] The corresponding {Rh[(*S*,*S*)-ethyl-DuPHOS](nbd)} complex can be accessed equally well by the method of Schrock and Osborne[11] or by exchange of cod in the relevant rhodium complex by norbornadiene (nbd).[12]

Enantioselective Hydrogenations

C=C Double Bond

The most commonly used reactions that employ {Rh[(*S*,*S*)-Et-DuPHOS](cod)}$^+$X$^-$ complexes involve the enantioselective hydrogenation of α-(*N*-acyl)enamide carboxylates. α-Amino acids are obtained in quantitative yield with high optical purity (95-99% ee) (3).[1,3,4]

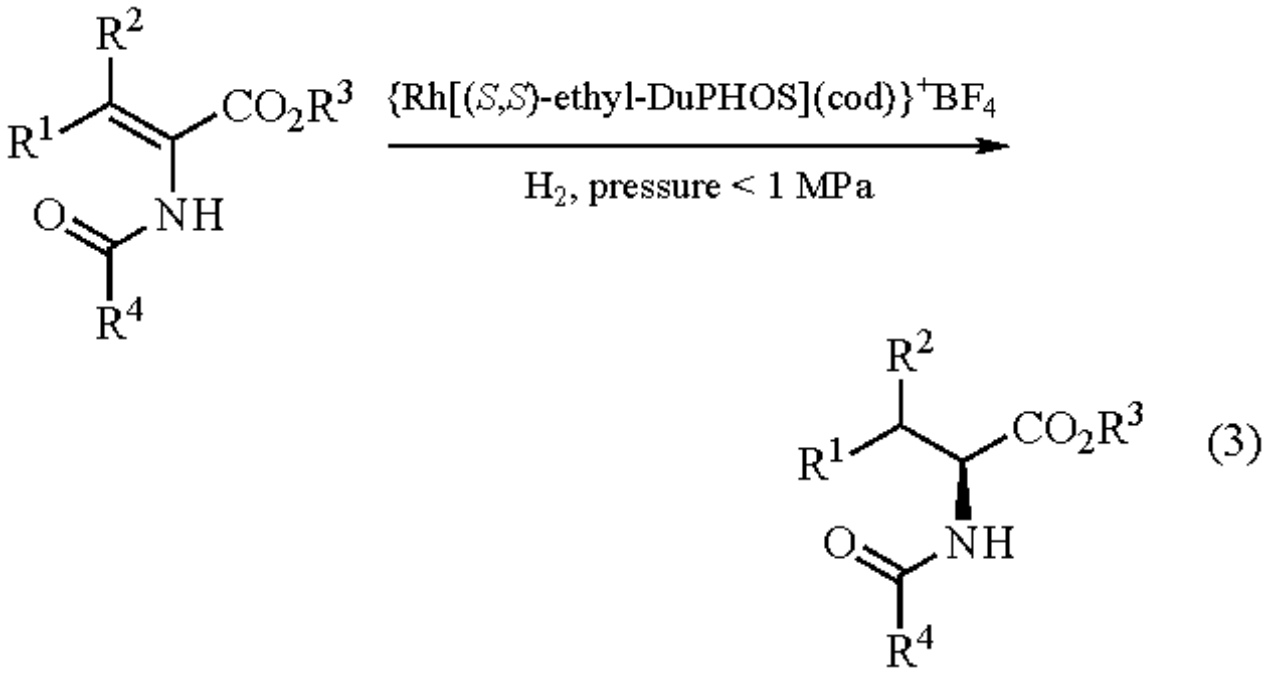

(3)

In this reaction, the (*S*,*S*)-ethyl-DuPHOS-catalyst produces the *S*-configurated α-amino acid derivatives when the substrate has one substituent in the β-position (R^2=H). The catalyst tolerates a range of substituents R^1 in the unsaturated substrate. The reaction conditions are mild (25 °C, MeOH, low hydrogen pressure) and the reaction proceeds rapidly (turnover frequencies 5000 h^{-1}). High substrate-to-catalyst ratios can be employed (up to 50 000). In general, high enatiomeric excesses are observed, independent of the geometry of the enamide (*E*- or *Z*-isomer) used. This feature is advantageous because frequently the unsaturated α-enamide carboxylic acids derivatives are synthesized as a mixture of both stereoisomers. Due to the high stereodiscriminating ability of the catalyst, separation prior to hydrogenation is not required. Access to a great number of natural, unnatural and nonproteogenic amino acids is possible in this manner (Table 1).

Table 2 Enantioselective hydrogenation of dehydroamino alcohols and dehydro-α-amino aldoximes with {Rh[(*S*,*S*)-ethyl-DuPHOS](cod)} OTf (MeOH or THF, 25 °C, 0.2 MPa H_2, 12 h, S/C = 1000:1)

R^1	R^2	% ee amino alcohol	% ee amino aldoxime
Me	H	95	94
Ph	H	93	90
Cy	H	96	99
2-MeOPh	H	93	88
Bn	H	>99	98
2-Naphthyl	Ac	98	81
2-Furanyl	Ac	98	–
2-Thienyl	Ac	96	–

The highly enantioselective hydrogenation of the corresponding dehydroamino acids (R^3=H) and the synthesis of *N*-Cbz-protected α-amino acids (R^4=OBn) are likewise possible.[3,16] Enantioselectivities of >99% can be achieved after 20-40 hours. Amino acid esters can be used directly for the synthesis of peptides. Deprotection of the amino groups can be carried out under mild conditions, thus avoiding racemization reactions.

Evidence has been given that the use of the Rh(P_2)(nbd) precatalyst is favored over the application of the corresponding cod-precatalyst. Börner and Heller[17] found that hydrogenation of the cod of the precatalyst takes place in parallel to the enantioselective hydrogenation of methyl (*Z*)-*N*-acetylaminocinnamate.[17,18] About 50% of the Rh-precatalyst remained unchanged after complete hydrogenation of the prochiral substrate. Therefore, precious ligand and Rh complex are wasted. This can be avoided by the application of {Rh[(*S*,*S*)-ethyl-DuPHOS](nbd)}$^+X^-$ as precatalyst. The hydrogenation of nbd proceeds much faster than that of cyclooctadiene. As an alternative, prehydrogenation of the cod-precatalyst in MeOH is possible for generating the catalytically active species.

Excellent enantio- and regioselectivities were also observed when *N*-acetylamino acrylates bearing additional functional groups, e.g. alkenes, were applied as substrates (4).[3,4]

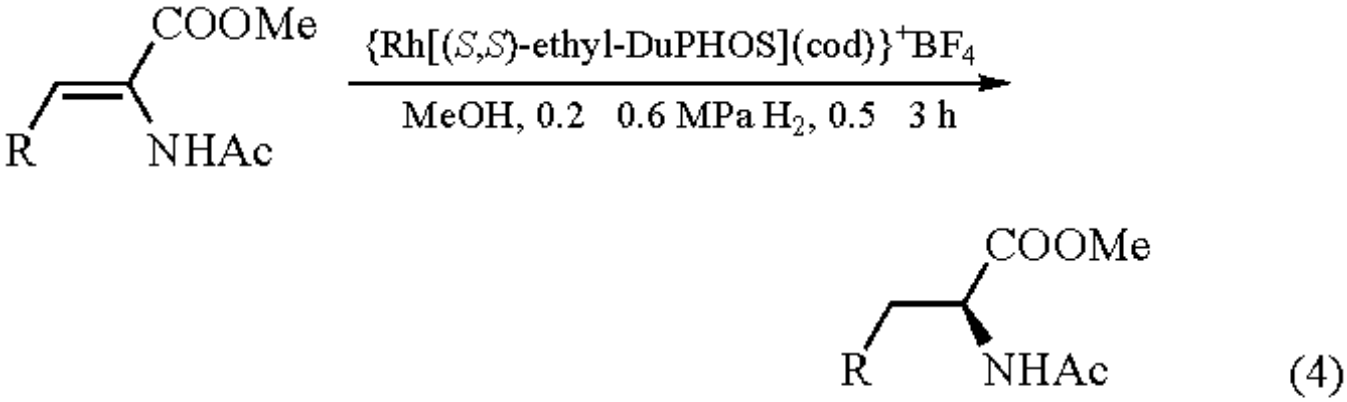

regioselectivity: > 98 %
enantioselectivity: > 99 %

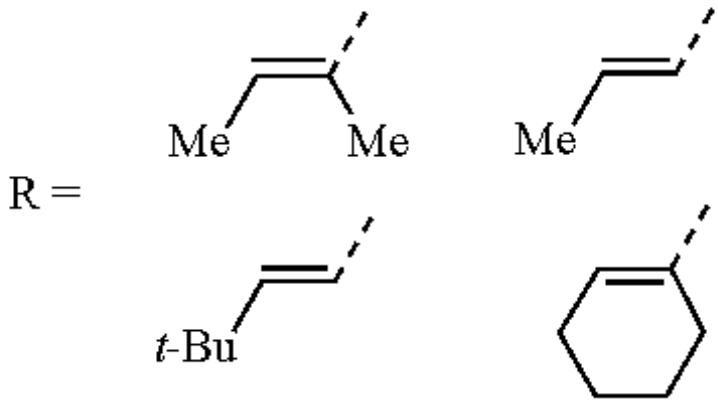

In these hydrogenations, less than 2% of the γ,δ-double bond was reduced. This feature indicates the ethyl-DuPHOS ligand to be superior in comparison to related DuPHOS/BPE-ligands or other chelating diphosphines. Other functional groups that are generally sensitive to reduction such as carbonyl groups, nitro groups, and halides also survive under the mild conditions applied to hydrogenation of the double bond adjacent to the acylamino group.

Diastereoselective hydrogenation of a bis(dehydroamino acid) derivative, recognized to be important for the syntheses of isotyrosine, in the presence of {Rh[(*S*,*S*)-ethyl-DuPHOS](cod)}$^{+}$OTf^{-} as catalyst yielded excellent results (5).[19]

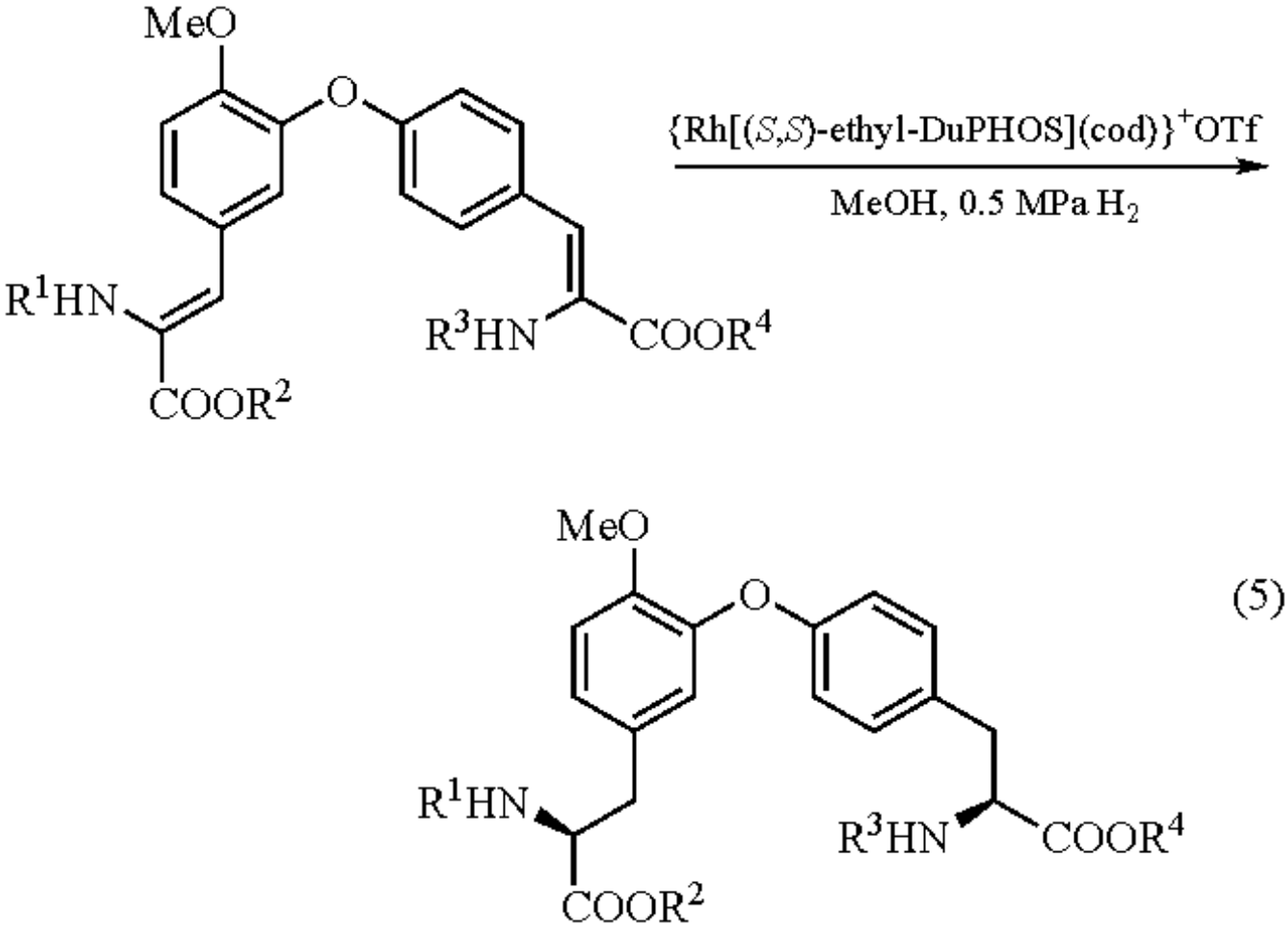

(5)

a **c:** $R^1 = R^3 =$ Cbz, Boc, Ac, $R^2 = R^4 =$ Me

d: $R^1 =$ Cbz, $R^2 =$ TMSE, $R^3 =$ Boc, $R^4 =$ Me

The possibility of preparing an isotyrosine derivative with four orthogonal protecting groups gives access to a highly versatile building block for several biologically active natural compounds. Enantioselectivities in excess of 98% ee for the *S,S*-enantiomer and diastereoselectivities above 84% have been observed. In general, the yields exceeded 90%.

The formation of stereogenic C-N bonds by hydrogenation of the enamine structure is not only limited to amino acids. Likewise, chiral 1,2-aminoalcohols or 1,2-diamines can be produced by the enantioselective hydrogenation of dehydro-β-amino alcohols (or their esters) and of dehydro-α-amino aldoximes, respectively (6 and 7, Table 2).[20] Esters and aldoximes thus obtained can be converted into the corresponding alcohols or diamines by standard methods. By this means, simple amines with one aryl group attached to the double bond can also be hydrogenated with high enantioselectivity.[21]

Table 2 Enantioselective hydrogenation of dehydroamino alcohols and dehydro-α-amino aldoximes with {Rh[(*S,S*)-ethyl-DuPHOS](cod)}$^+$OTf$^-$ (MeOH or THF, 25 °C, 0.2 MPa H_2, 12 h, S/C = 1000:1)

R^1	R^2	% ee amino alcohol	% ee amino aldoxime
Me	H	95	94
Ph	H	93	90
Cy	H	96	99
2-MeOPh	H	93	88
Bn	H	>99	98
2-Naphthyl	Ac	98	81
2-Furanyl	Ac	98	–
2-Thienyl	Ac	96	–

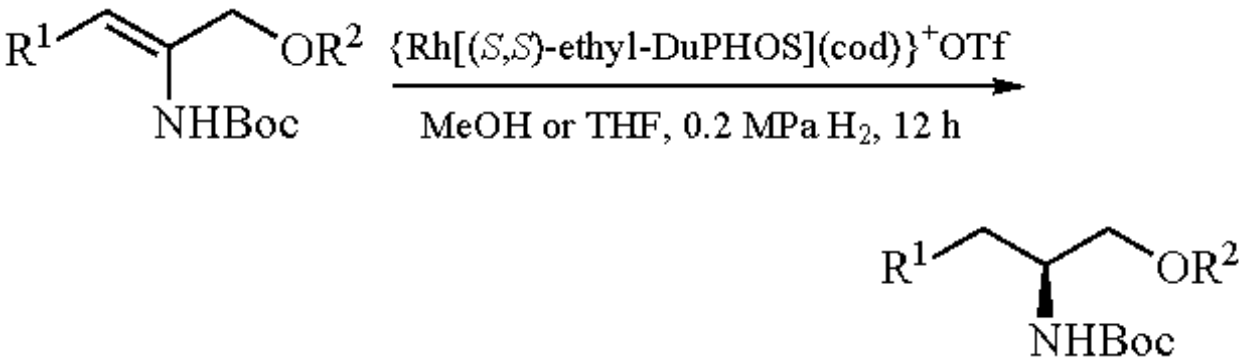

(6)

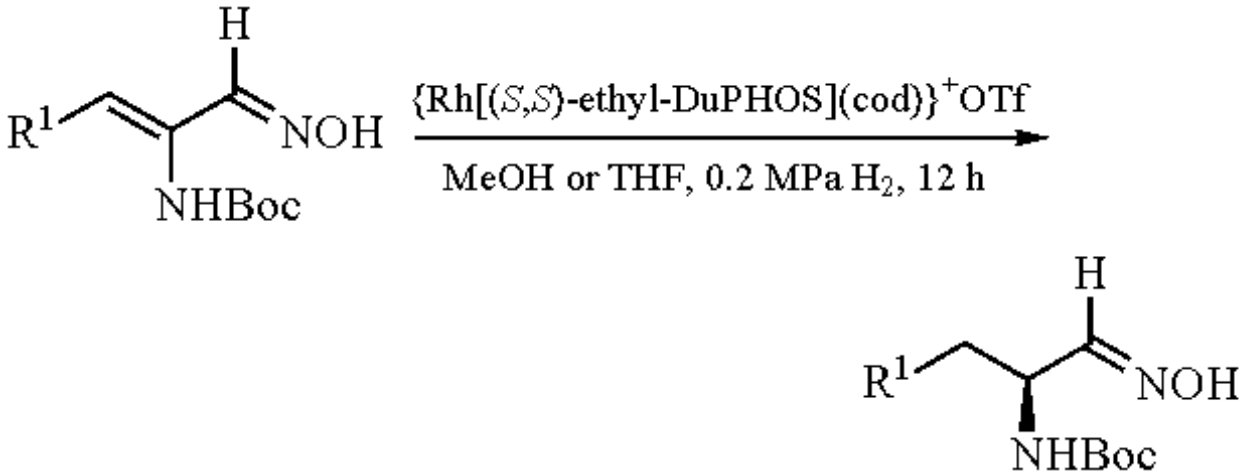

(7)

Enol acetates and corresponding derivatives constitute another class of unsaturated compounds that can advantageously be hydrogenated with high enantiomeric excess. This reaction is related to the enantioselective reduction of ketones. Acylated enol carboxylates (as an equivalent of α-keto carboxylic acid) can likewise be successfully reduced with rhodium(I) catalysts based on (*S*,*S*)-ethyl-DuPHOS (8).[2] Subsequent deprotection of the hydroxyl group or reduction of the carboxylic acid derivatives so obtained deliver chiral α-hydroxy carboxylates and 1,2-diols, respectively.

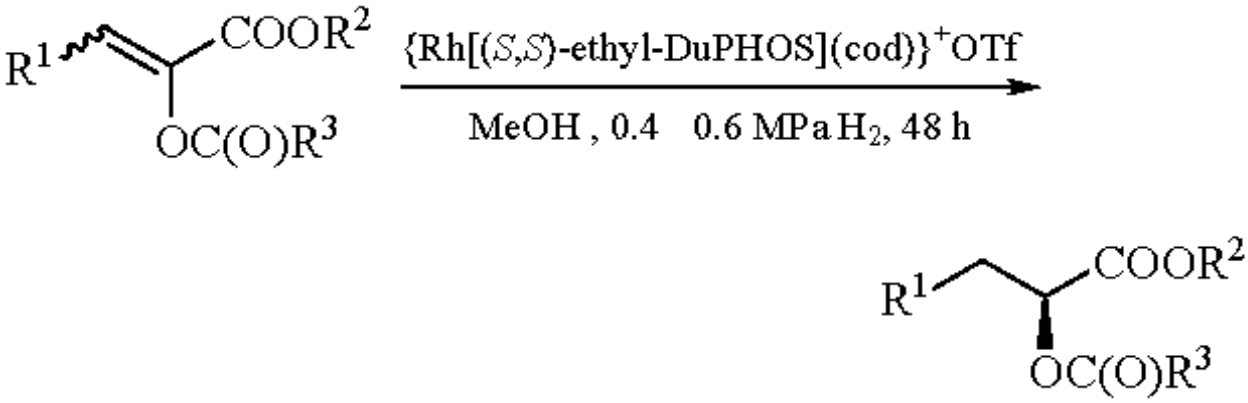

(8)

Burk et al.[2] showed that the Rh-(*S*,*S*)-ethyl-DuPHOS complex is able to reduce acylated α-hydroxy carboxylates with high enantiomeric excess independently of the *E*:*Z* ratio of the alkene substrate (Table 3). However, the reaction failed when substrates branched in β-position were tested.

Table 3 Enantioselective hydrogenation of various enol esters with {Rh[(*S*,*S*)-ethyl-DuPHOS](cod)} OTf complex (MeOH, 25 °C, 0.4–0.6 MPa H_2, 48 h, S/C = 500:1)

R^1	R^2	R^3	E/Z ratio	% ee[a]
H	Et	Ac	–	>99
Me	Et	Bz	3	96.0
n-Pr	Me	Bz	3	98.0
i-Pr	Et	Ac	6	96.1
i-Pr	Et	Bz	6	96.9
Ph	Et	Ac	9	95.6
Ph	Et	Bz	10	98.0
α-Naphthyl	Et	Bz	3	93.2

[a] *S*-configurated products were obtained.

Finally, several examples of the enantioselective hydrogenation of unsaturated substrates without any heteroatom attached to the olefinic double bond are noteworthy. Of particular relevance to the production of pharmaceutics, agrochemicals, flavors and aroma stuffs is the formation of the chiral 2-substituted succinates based on relevant itaconic acid derivatives. Burk et al.[22] demonstrated that a rhodium(I) catalyst derived from (*S*,*S*)-ethyl-DuPHOS is able to hydrogenate aryl- or alkyl-substituted itaconic acid derivatives with excellent enantioselectivity (9, Table 4).

Table 4 Enantioselective hydrogenation of itaconic acid derivatives with {Rh[(*S*,*S*)-ethyl-DuPHOS](cod)}$^+$ BF_4 (MeOH, 25 °C, 0.56 MPa H_2)

R	S/C	Time (h)	% ee[a]
Et	1000	1	99
i-Pr	3000	2	99
n-Bu	1500	2	97
CH_2CH_2Ph	2000	2	99
Cyclohexyl	1500	3	98
Ph	3000	12	97
1-Naphthyl	3000	12	98

[a] *R*-configuration was obtained.

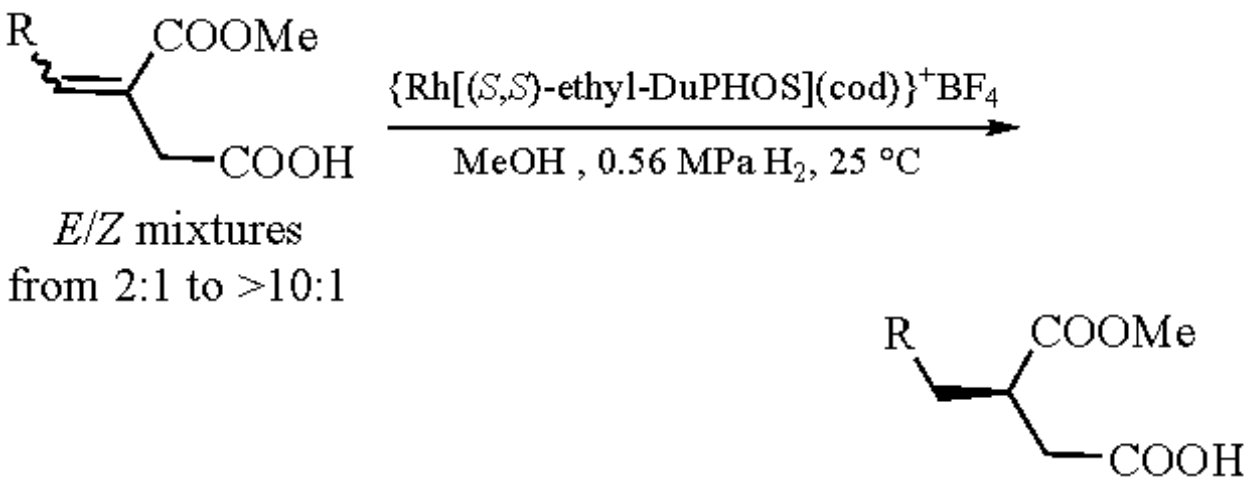

(9)

Prior separation of the *E*:*Z* mixtures of the itaconic acid substrates (usually representing mixtures of 2:1 to more than 10:1) and also by-products of the synthesis do not affect the results.

A catalyst based on ethyl-DuPHOS also showed its high potential in the enantioselective hydrogenation of a sodium glutarate as the pivotal intermediate in the multi-step synthesis of candoxatril (10).[23]

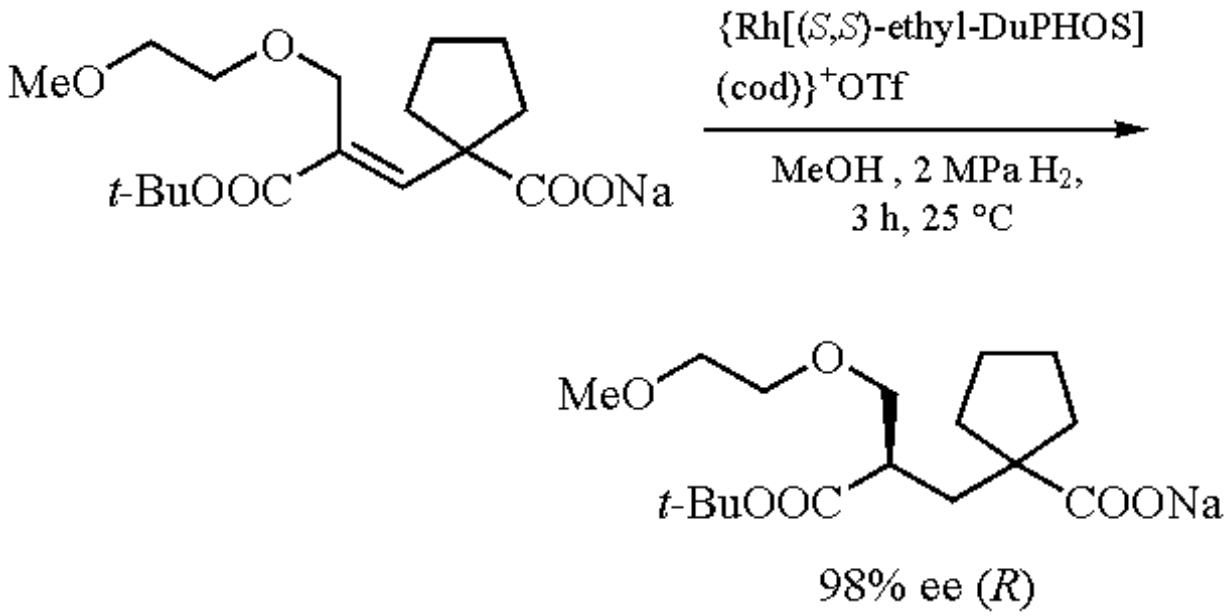

(10)

By application of the relevant Rh-(*S*,*S*)-ethyl-DuPHOS catalyst, no isomerization of the starting material to the enol ether occurred by migration of the double bond. This side reaction operates in the presence of the corresponding ruthenium catalysts. When (*S*,*S*)-ethyl-DuPHOS was applied as ligand the *R*-enantiomer was formed instead of the desired *S*-enantiomer, necessary for the synthesis of candoxatril.

Another example of the synthesis of a compound with pharmaceutical relevance is the chemical transformation of *rac*-warfarin into enantiomerically pure (*R*)- or (*S*)-warfarin.[24] In the first step, *rac*-warfarin is oxidized to the corresponding α,β-unsaturated ketone. The latter can be easily hydrogenated to the desired enantiomer by application of the appropriate DuPHOS-catalyst (11). Prior transformation of dehydrowarfarin into the sodium salt or its methyl ether improved the yield and suppressed side reactions. Simultaneously, the enantioselectivity of the hydrogenation product was enhanced. The (*S*,*S*)-ethyl-DuPHOS-complex leads to *R*-configured warfarin.

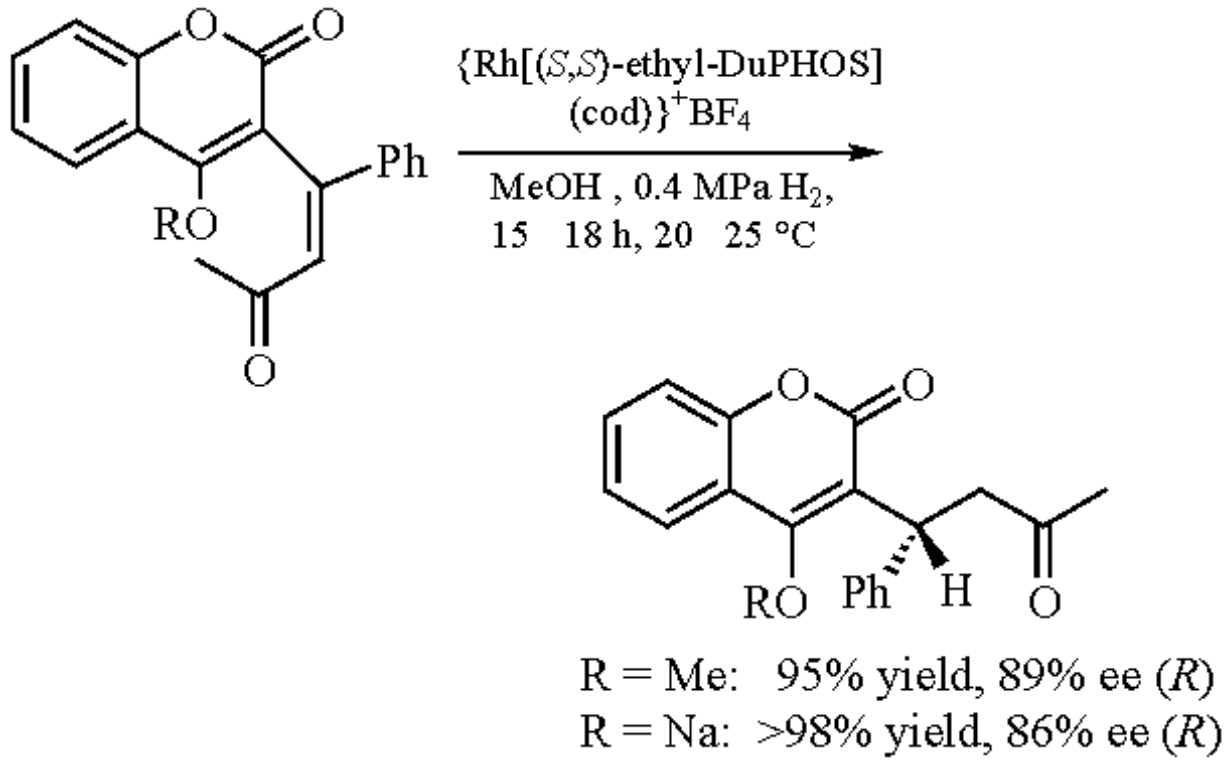

(11)

C=N Double Bond

The enantioselective reduction of a C=N double bond is an interesting alternative for the production of chiral amines by hydrogenation of enamides. Required imines or oximes can be prepared by reaction of ketones with amines or hydroxylamines. However, to date, trials to reduce these substrates with ethyl-DuPHOS catalysts gave no satisfying results. Therefore, transformation of ketones or α-keto acids into acylhydrazones and subsequent enantioselective hydrogenation has proven advantageous (12, Table 5).[25,26]

Table 5 Enantioselective hydrogenation of benzoylhydrazones with $\{Rh[(S,S)\text{-ethyl-DuPHOS}](cod)\}^{+}OTf^{-}$ catalyst (*i*-PrOH, 0.4 MPa H_2, S/C = 500:1)[a]

R^1	R^2	Temperature (°C)	Time (h)	% ee
Ph	Me	−10	24	95
p-MeO-Ph	Me	0	12	88
p-EtO_2C-Ph	Me	0	12	96
Ph	Bn	−10	24	84
CO_2Me	Et	0	36	91
CO_2Me	Pr	0	36	90
CO_2Me	Ph	0	36	91
i-Pr	Me	−10	36	73
Et	Me	−10	36	43

[a] The reactions were preferentially carried out by employment of (*R*,*R*)-ethyl-DuPHOS giving rise to the *S*-configurated product. However, as Burk et al.[26] pointed out, the antipodal (*S*,*S*)-configurated ligand gave same yields and enantiomeric excess, but products with *R*-configuration.

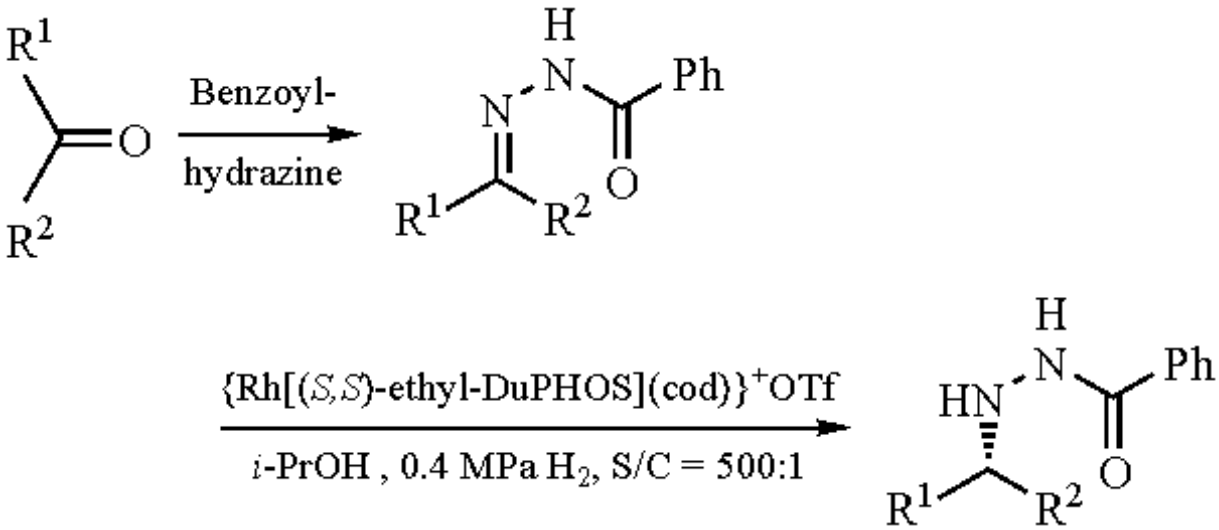

(12)

Chiral hydrazines can be transformed to α-amino acids and amines by cleavage of the N-N bond. Conversion to α-hydrazino acids by hydrolysis of the esters or into hydrazines by deacylation is likewise possible.[26]

(*S*,*S*)-Ethyl-DuPHOS has been employed mainly for enantioselective hydrogenation. Several types of reaction can be run very successfully. In other enantioselective reactions, this ligand has been used only rarely, one example being the enantioselective allylation of benzaldehyde by application of the corresponding silver(I) catalyst. However, in this example, the reaction failed.[27]

It is likely that several results obtained with the homologous ligands of R-DuPHOS (R=Me, Pr) or their opposite enantiomers can be related also to (*S*,*S*)-ethyl-DuPHOS. Recently, Burk has published a review about the application of phospholane ligands in asymmetric catalysis, which gives a good survey of the use of DuPHOS- and BPE-ligands.[28]

Related Reagents.

The homologous derivatives of DuPHOS- and BPE-ligands. RoPHOS;[29-33] PennPHOS;[34] BASPHOS;[35] CnrPHOS.[36-39]

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Di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl Diazenedicarboxylate

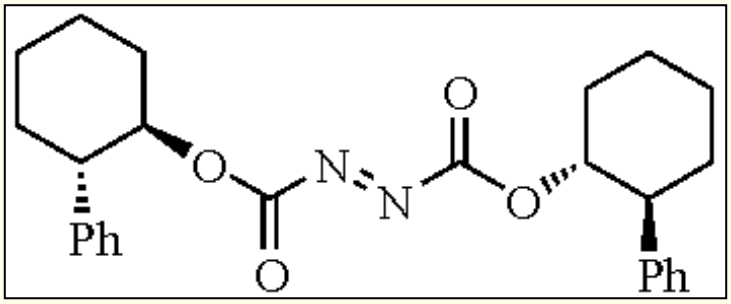

[206359-91-3] · $C_{26}H_{30}N_2O_4$ · (434.53)

(reagent used as a chiral azo-enophile in asymmetric azo-ene reactions)

Alternate Name: (1*R*-{1α[*E*(1*R**,2*S**)],2β})-Bis(2-phenylcyclohexyl) diazenedicarboxylate.

Physical Data: $[\alpha]_D$ -56.9 (*c* 0.65, $CHCl_3$).

Solubility: soluble in CH_2Cl_2, diethyl ether, and most organic solvents.

Form Supplied in: yellow oil.

Analysis of Reagent Purity: ^{1}H NMR, IR, TLC, elemental analysis.

Preparative Methods: The title reagent is prepared[1] by reaction of (1*R*, 2*S*)-2-phenyl-1-cyclohexanol with excess phosgene in the presence of quinoline to afford a chloroformate which is treated directly with hydrazine monohydrate (0.5 equiv) to afford di-(-)-(1*R*, 2*S*)-2-phenyl-1-cyclohexyl diazanedicarboxylate. Oxidation of the diazanedicarboxylate to the diazenedicarboxylate is then readily effected using *N*-bromosuccinimide and pyridine (1).

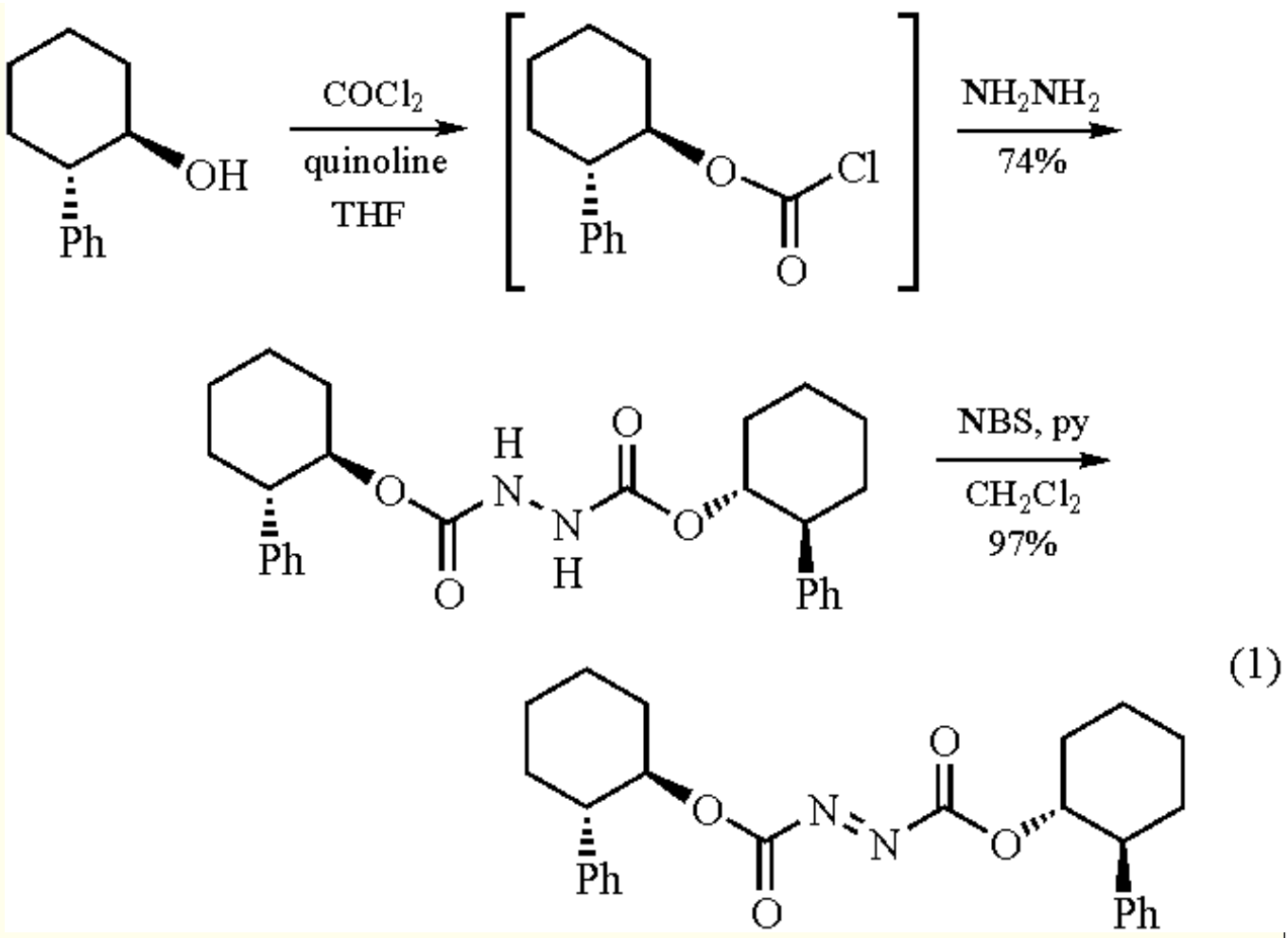

Purification: flash chromatography using hexane-ethyl acetate (9:1) as eluent.

Handling, Storage, and Precautions: store in closed vessels under an inert atmosphere in the refrigerator. Protect from light.

Azo-ene reactions

The ene reaction[1] provides a powerful method for C-C bond formation with concomitant activation of an allylic C-H bond. A variety of functionalized carbon skeletons can be constructed due to the range of enophiles which can be used. For example, carbonyl compounds give homoallylic alcohols[2] and imino derivatives of aldehydes afford homoallylic amines.[3] The azo-ene reaction offers a method for effecting allylic amination by treatment of an alkene with an azo-diester to afford a diacyl hydrazine which upon N-N cleavage furnishes a carbamate. Subsequent hydrolysis of the carbamate provides an allylic amine. Use of chiral diazenedicarboxylates provides a method for effecting stereoselective electrophilic amination.

Lewis acid-mediated ene reaction of di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate with cyclohexene using tin(IV) chloride in dichloromethane at -60 °C for 5 min afforded the azo-ene adduct in 80% yield after purification by flash chromatography (2).[4] The ^{1}H NMR spectrum of the azo-ene adduct recorded at 380 K in deuterated toluene established the presence of only one diastereomer. Further analysis of the ene adduct by HPLC on a Whatman Partisil 5 normal phase silica column using hexane-ethyl acetate (9:1) as eluent confirmed the presence of only one diastereomer.

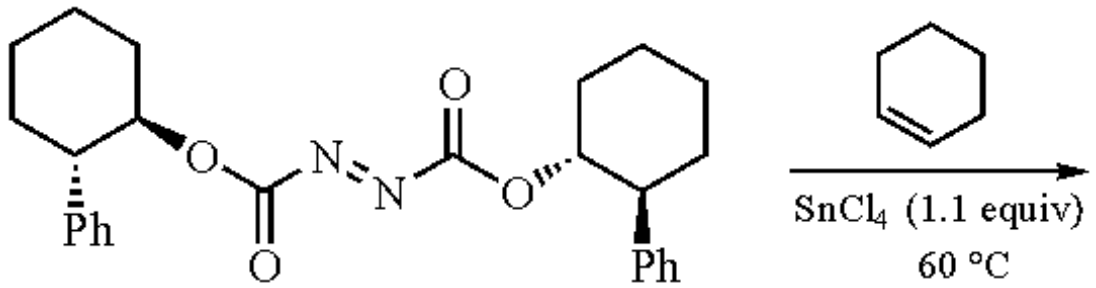

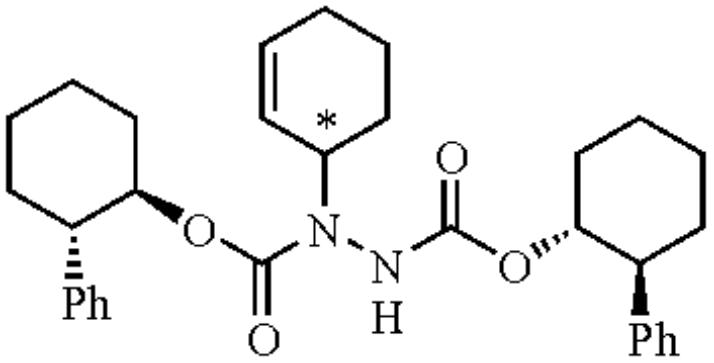

(2)

80% >97:3

Use of cyclopentene, *trans*-hex-3-ene and *trans*-oct-4-ene afforded the ene adducts in good yield with a diastereomeric excess of 86:14 in each case. The diastereoselectivity observed using di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate as a chiral azo-enophile offered a significant improvement over the use of di-(-)-menthyl azodicarboxylate where the level of asymmetric induction achieved in Lewis acid-mediated ene reactions with simple alkenes was not impressive.[5] Moreover, it proved difficult to cleave the N-N bond in the menthyl ester azo-ene adducts whereas sodium/liquid ammonia was used to smoothly cleave the N-N bond in the diacylhydrazine adducts formed using di-(-)-(1*R*,2*S*)-2-phenyl-1-cyclohexyl diazenedicarboxylate as azo-enophile.

The absolute stereochemistry at the newly formed stereogenic carbon of the major diastereomer of the ene adduct can be predicted by analysis of the transition model for the ene reaction (3). The (1*R*,2*S*)-2-phenyl-1-cyclohexyl chiral auxiliary adopts a chair conformation with equatorial placement of the bulky phenyl group. Complexation of the carbonyl group to the Lewis acid affords the more stable *s-trans* conformation about the C-N sigma bond. In this conformation, the phenyl group shields the N_β-*re*-face. Therefore the cyclic alkene preferentially attacks from the less hindered N_β-*si*-face. Ene reaction proceeds through a six-membered cyclic transition state affording the (1´*R*)-diastereomer of the ene adduct.

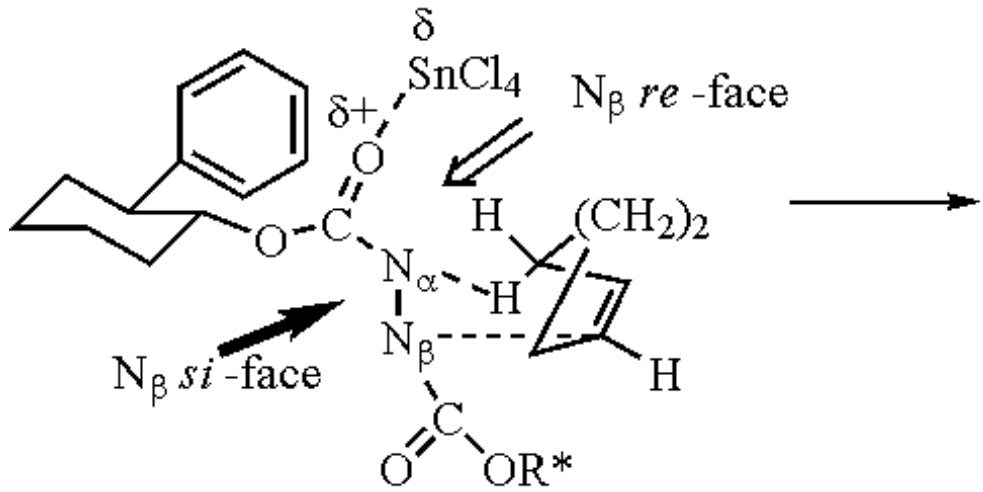

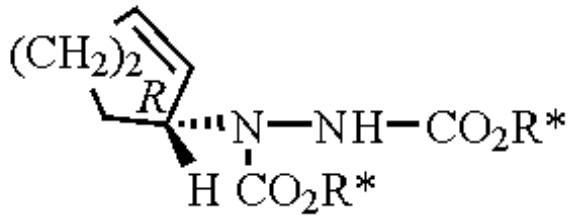

(3)

Related Reagents.

The synthesis of chiral diazenedicarboxylates as potential chiral electrophilic aminating agents has received little attention. A series of chiral bornyl, isobornyl and menthyl diazenedicarboxylates has been reported[6] and their reaction with achiral enolates of esters and *N*,*N*-dimethyl amides afforded α-hydrazino acid derivatives with little or no selectivity. Incorporation of a chiral azodicarboxamide unit into a chiral bridging binaphthyl moiety afforded α-hydrazino acid derivatives with high stereoselectivity in reactions with achiral oxazolidinone anions.[7]

---

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(+/-)-Boc-α-phosphonoglycine Trimethyl Ester

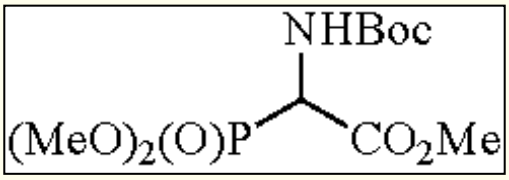

[89524-98-1] · $C_{10}H_{20}NO_7P$ · (294.24)

[synthon for α,β-dehydroamino acids (DAA) and amino acids]

Alternate Name: methyl 2-(*t*-butoxycarbonylamino)-2-(dimethoxyphosphinyl)acetate.

Physical Data: white solid, mp 47-48 °C.

Solubility: alcohol and most organic solvents.

Form Supplied in: Form Supplied in: available in six steps from crude glyoxylic acid.[1] The first four steps[2] can be carried out on a kilogram scale. Deprotection of the *N*-benzyloxycarbonyl-2-(dimethoxylphosphinyl)glycine methyl ester and reaction with Boc_2O affords the title compound (1).

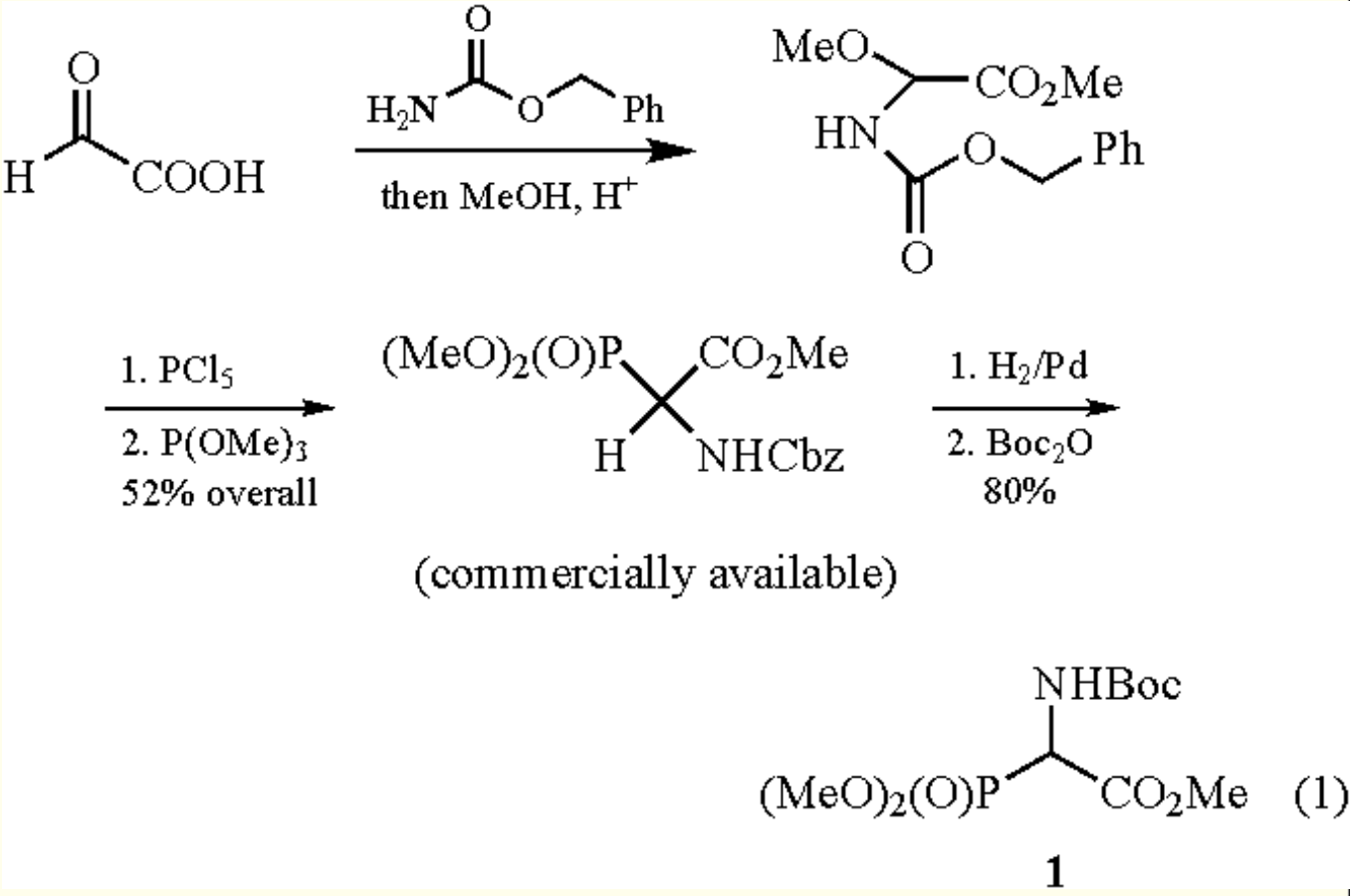

Purification: recrystallization from diethyl ether/pentane (1:1) at 0 °C.

Handling, Storage, and Precautions: reagent should be used in a fume hood.

Reaction with Aldehydes

The main use of phosphoglycinate is to synthesize α,β-dehydroamino acids (DAA) by condensation with an aldehyde in a Wittig-Horner-type olefination (2).[3]

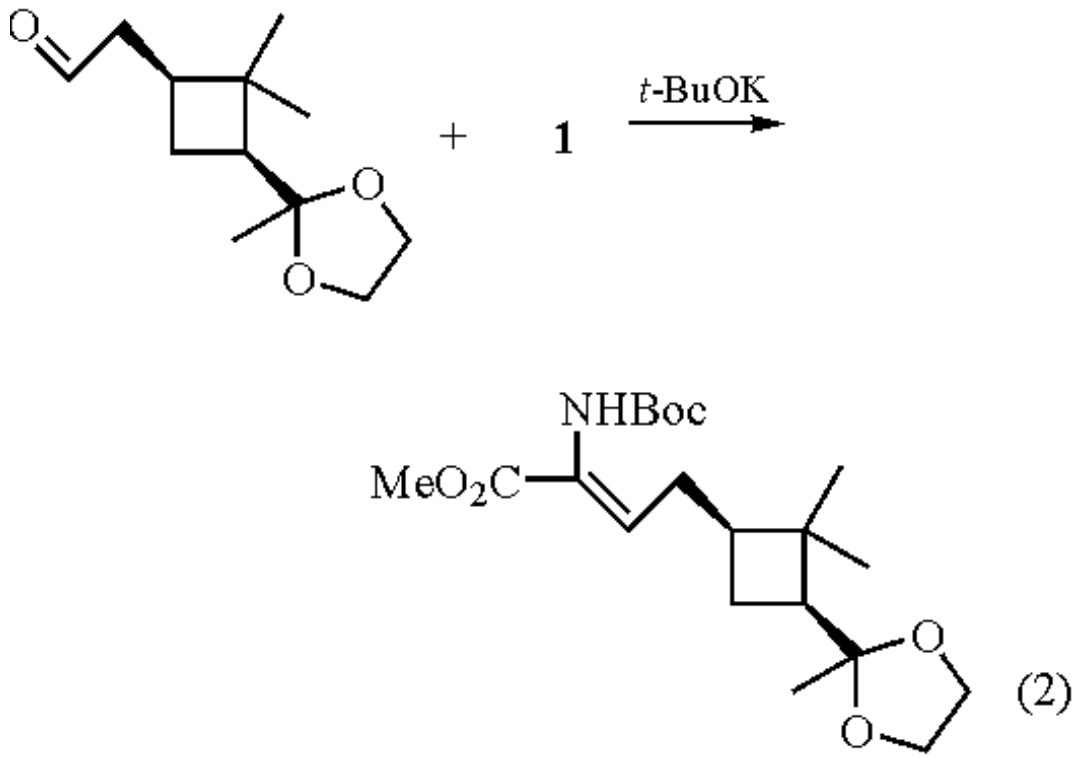

In order to obtain high yields and to limit the amounts of by-products, the choice of base is critical. The use of *t*-BuOK, NaH, lithium diisopropylamide, or potassium hexamethyldisilazide affords yields ranging from 70 to 95%,[4] along with small amounts of side-products, which are often difficult to separate from the DAA. This is of paramount importance if the next step is a metal-catalyzed hydrogenation, since the impurities can poison the catalyst. Also, in most cases, the diastereoselectivity of double bond formation is fairly low. Nevertheless, the use of DBU or NEt_3 in CH_2Cl_2 is often superior to alkali bases, resulting in nearly quantitative yields and high diastereoselectivities (3). Addition of LiCl is not necessary and may be detrimental in terms of yields.

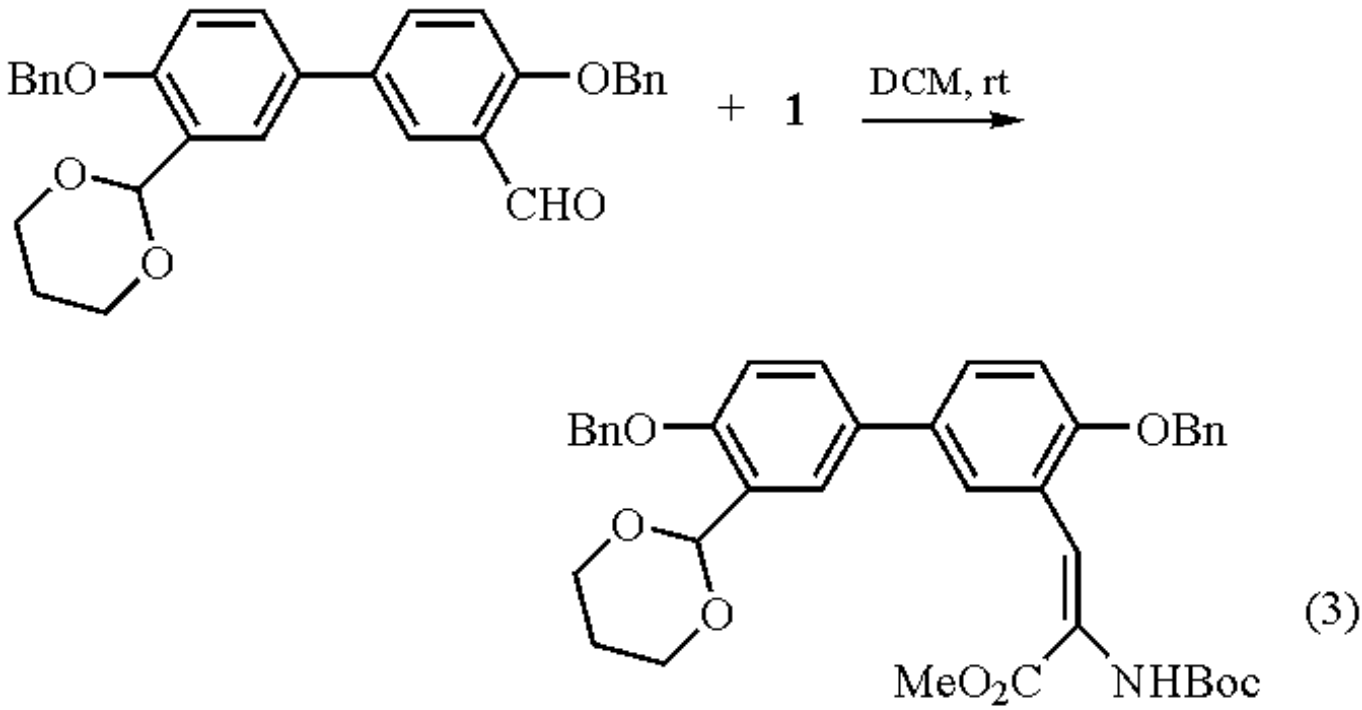

Base	*E*/*Z*	Yield (%)
t-BuOK	27:73	94
DBU	5:95	100

Also, the use of TMG [4-6] as base in THF at -70 °C to +20 °C is reported to give rise to even better *Z*-diastereoselectivity, yield, and product purity. All types of aldehyde can react, except 2-alkenals, which suffer decomposition in the basic reaction medium. Complex or sterically hindered aldehydes react well. The olefination is applicable to the synthesis of non-conjugated 2-amino-2,*n*-alkadienoic esters which can be selectively hydrogenated to give (,(- and (,(-dehydroamino acid derivatives. Also, the reaction conditions (neutral or alkaline) are compatible with aldehydes that contain acid-sensitive groups.[7] Aldehydes can also be coupled to di- or tripeptides containing a phosphoglycinate unit (4).

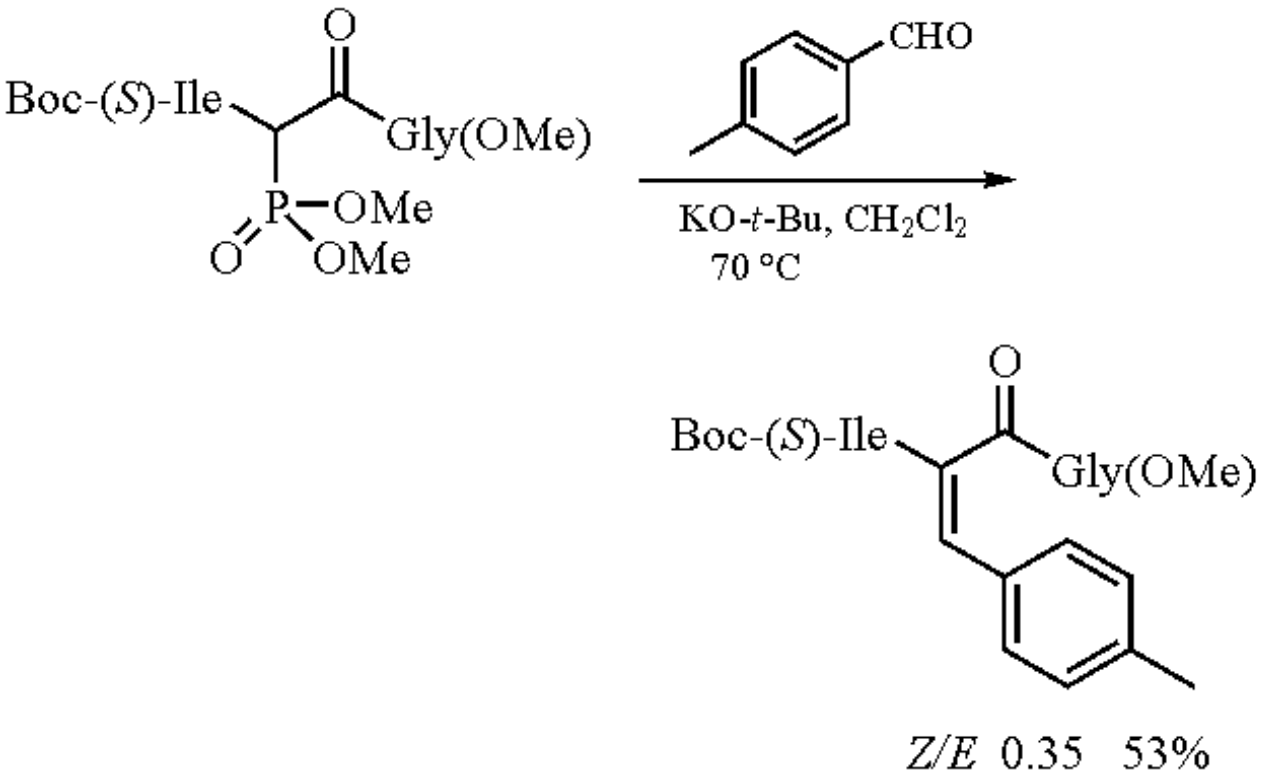

(4)

If the reaction is applied to the synthesis of histidine or tryptophane derivatives, the nitrogen atom in the heterocyclic moiety must be protected. No racemization was observed during the olefination of the above dipeptide.

The stereocontrol of double bond geometry depends heavily on the base used during the olefination. In most cases, *Z*-geometry prevails. The *E*-isomer can be converted to the *Z*-isomer by means of HCl/Et_2O,[8] NEt_3/charcoal in $MeOH/CHCl_3$, thiophenol/AIBN/benzene at 80 °C,[9] illumination[10] or DBU/charcoal in $MeOH/CHCl_3$ at 20 °C (5).[3]

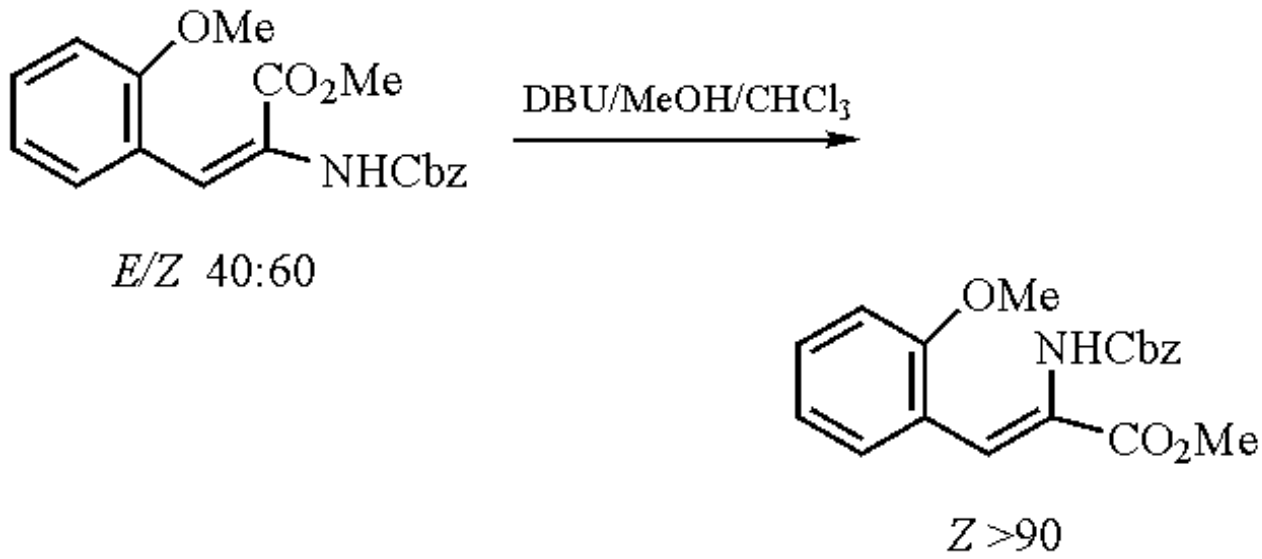

(5)

The protecting group associated with **1** can be easily changed. *N*-*t*-butoxycarbonyl- can be replaced by *N*-Benzyloxycarbonyl-, *N*-acetyl-, *N*-chloroacetyl-, and *N*-formyl, in the fifth step of 1 without any problem and the methyl ester can be replaced by $-CH_2CH_2TMS$ (TMSE). Any type of combination can be realized. Orthogonally protected phosphoglycinates have been prepared (6).[11]

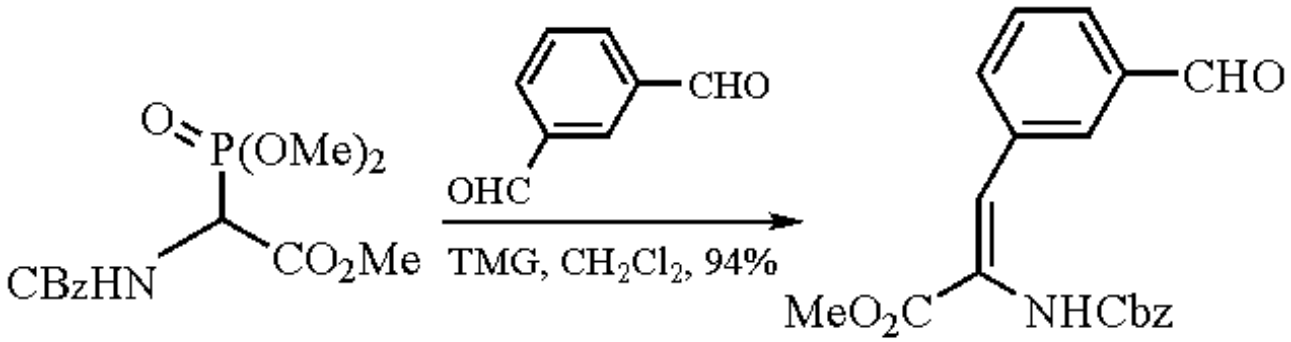

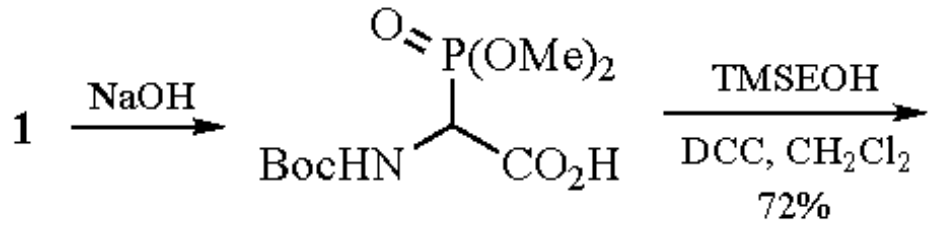

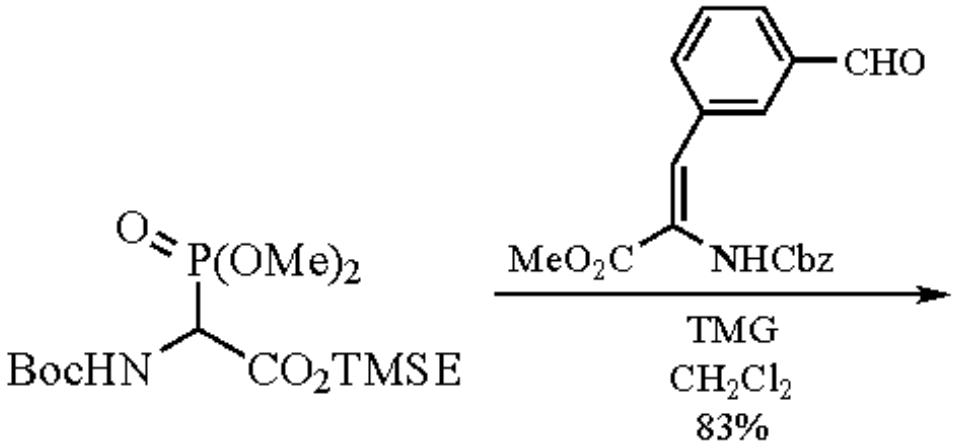

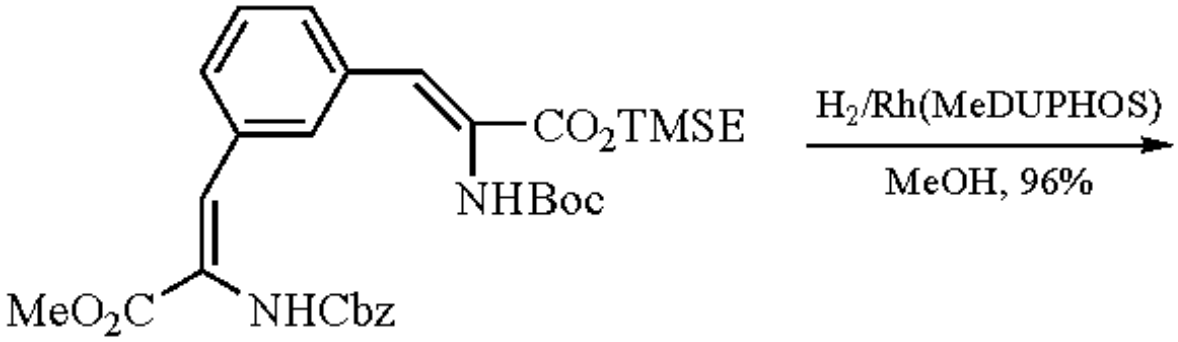

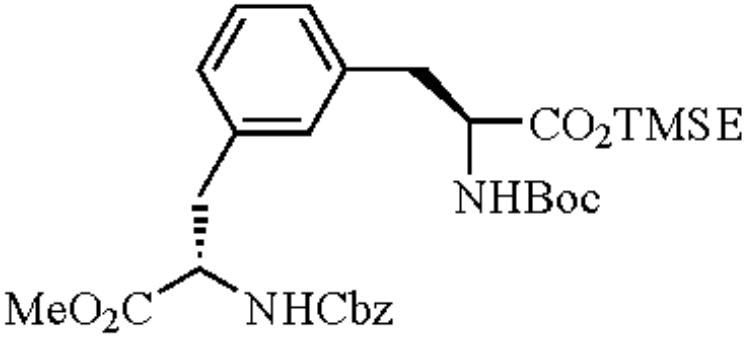

(6)

98:2 diasteriomeric ratio

Different protecting groups on **1** can affect the yield of the olefination (7),[6] as well as the *E*/*Z* ratio. Methyl esters are preferred over ethyl esters

due to their ease of hydrolysis.

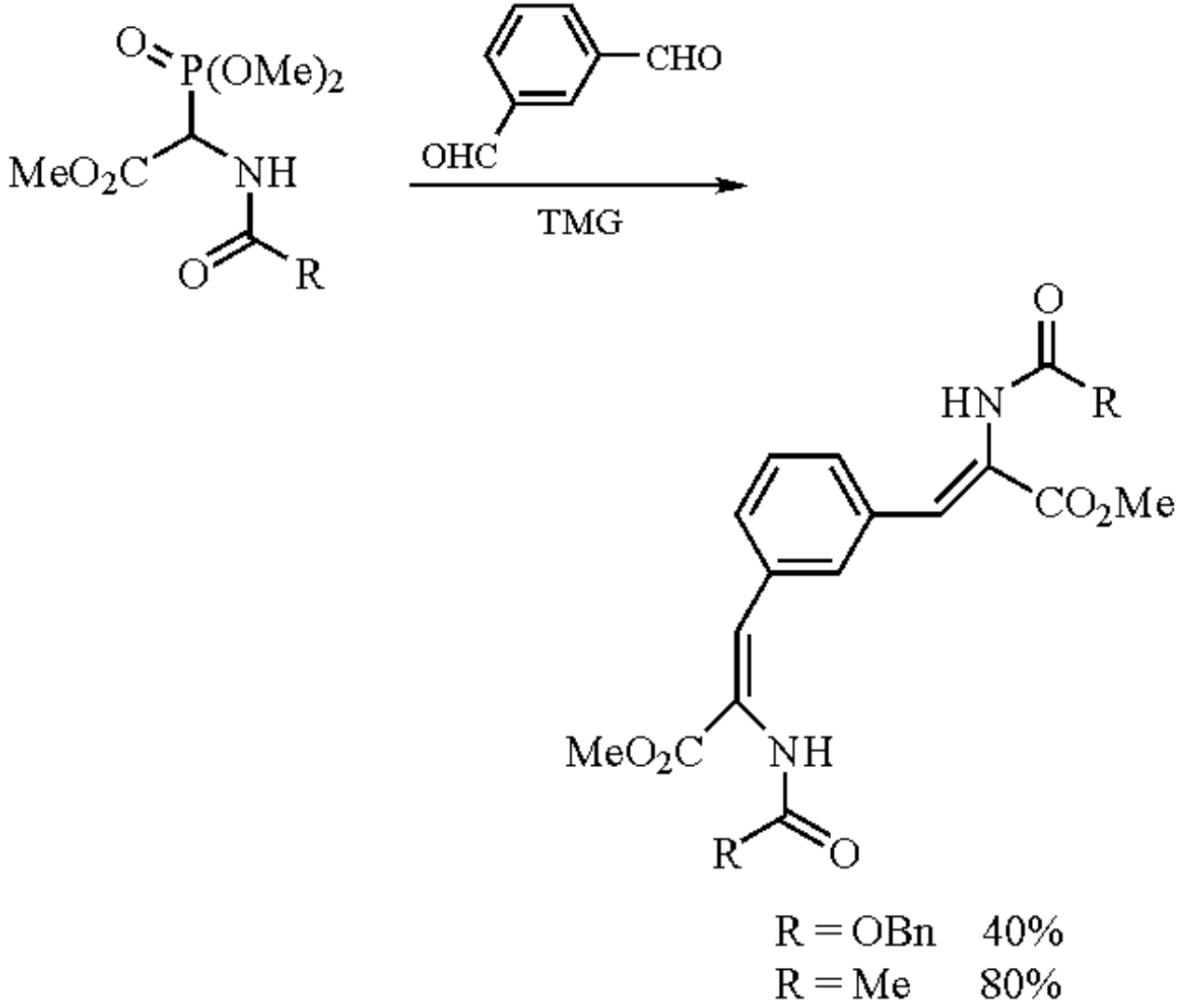

(7)

Reaction with Ketones

Ketones react with **1**, or its analogs, in the presence of TMG as base. Good *Z*-selectivity is observed. Recourse to DBU is synthetically useless since a large excess of ketone is required for the olefination to proceed.[3]

Related Reagents.

N-benzyloxycarbonyl-2-(diethoxyphosphinyl)glycine ethyl ester; N-benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycine methyl ester; N-chloroacetyl-2-(dimethoxyphosphinyl)glycine methyl ester; N-formyl-2-(dimethoxyphosphinyl)glycine methyl ester; N-acetyl-2-(dimethoxyphosphinyl)glycine methyl ester.

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(+)-*N*-Fluoro-2,10-(3,3-dichlorocamphorsultam)[1]

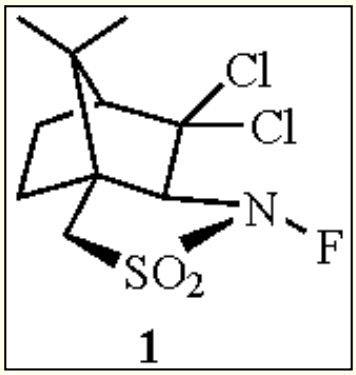

[151556-58-0] · $C_{10}H_{14}Cl_2FNO_2S$ · (302.19)

(neutral, aprotic, electrophilic fluorinating agent for the asymmetric α-fluorination of enolates[1])

Physical Data: mp 161-162 °C, $[\alpha]^{20}_D$ +16.4 (*c* 1.3, $CHCl_3$).

Solubility: soluble in THF, CH_2Cl_2, $CHCl_3$; insoluble in hexane, pentane, H_2O.

Form Supplied in: white solid.

Preparative Methods: the title reagent **1** can be prepared by fluorination of the corresponding (+)-2,10-(3,3-dichlorocamphorsultam)[2] using 10% F_2/N_2 in dry chloroform in the presence of sodium fluoride.[3,4]

Purification: purified by silica gel chromatography using a mixture of CH_2Cl_2/*n*-pentane (70:30) as eluent.

Handling, Storage, and Precautions: can be stored in a bottle in the refrigerator for months without noticeable decomposition.

Fluorination of Ketone Enolates

(+)-*N*-Fluoro-2,10-(3,3-dichlorocamphorsultam) (**1**) reacts with ketone enolates to give α-fluoro ketones. For example, reaction of the sodium enolate of propiophenone **2** gives α-fluoropropiophenone **3** in 41% isolated yield (1). No enantioselectivity, however, is observed due to racemization of the product under the reaction conditions.[4] When a tertiary substituted ketone such as α-methyltetralone (**4**) is employed, the desired α-fluorinated product (*S*)-(-)-**5** is obtained in 76% ee and 53% isolated yield (2).[4] In this reaction, (+)-**1** was found to be more reactive, affording higher yields and better enantioselectivities than its parent (-)-*N*-fluoro-2,10-camphorsultam; i.e., 35% ee, <5% yield.[5]

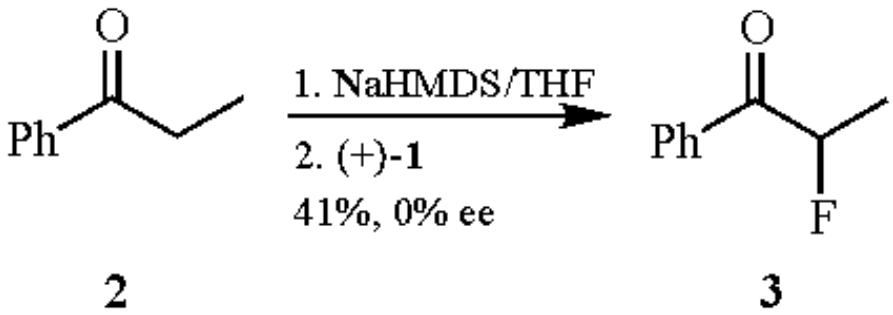

(1)

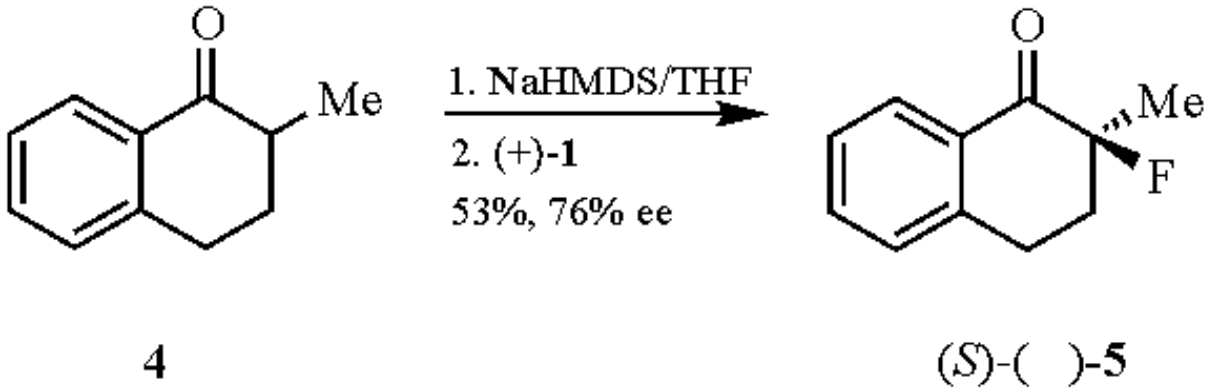

(2)

Fluorination of Ester Enolates

(+)-*N*-Fluoro-2,10-(3,3-dichlorocamphorsultam) (**1**) also reacts with the enolates generated from esters. For example, treatment of methyl 2-phenylpropionate **6** with NaHMDS in THF followed by addition of (+)-**1** affords the corresponding α-fluoro ester **7** in 54% yield and 33% ee (3). The absolute configuration was not determined. The enantioselectivity observed with (+)-**1** is better than (-)-*N*-fluoro-2,10-camphorsultam; i.e., < 10% ee (30% yield).[5]

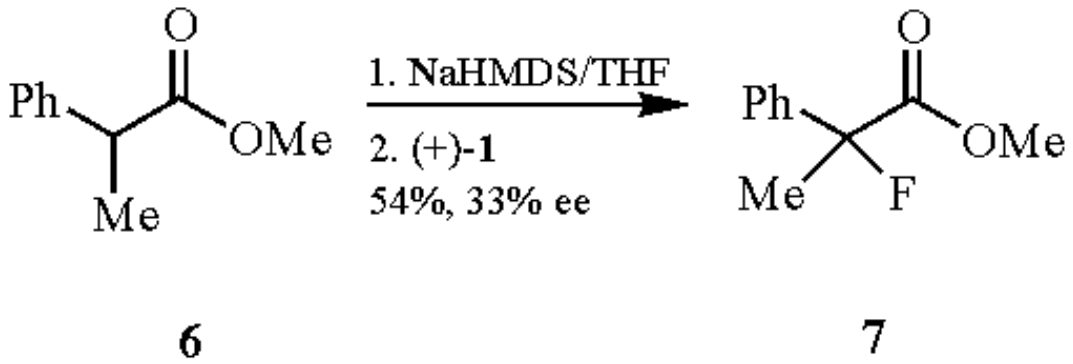

(3)

Fluorination of β-Ketoester Enolates

(+)-*N*-Fluoro-2,10-(3,3-dichlorocamphorsultam) (**1**) is reactive towards the enolates generated from β-ketoesters. Thus, treatment of the sodium enolate of **8** with (+)-**1** afforded the desired product **9** in 95% isolated yield and 46% ee with undetermined stereochemistry (4). Reduced yields and enantioselectivities were noted under similar conditions for (-)-*N*-fluoro-2,10-camphorsultam (28% yield, 25% ee).[4]

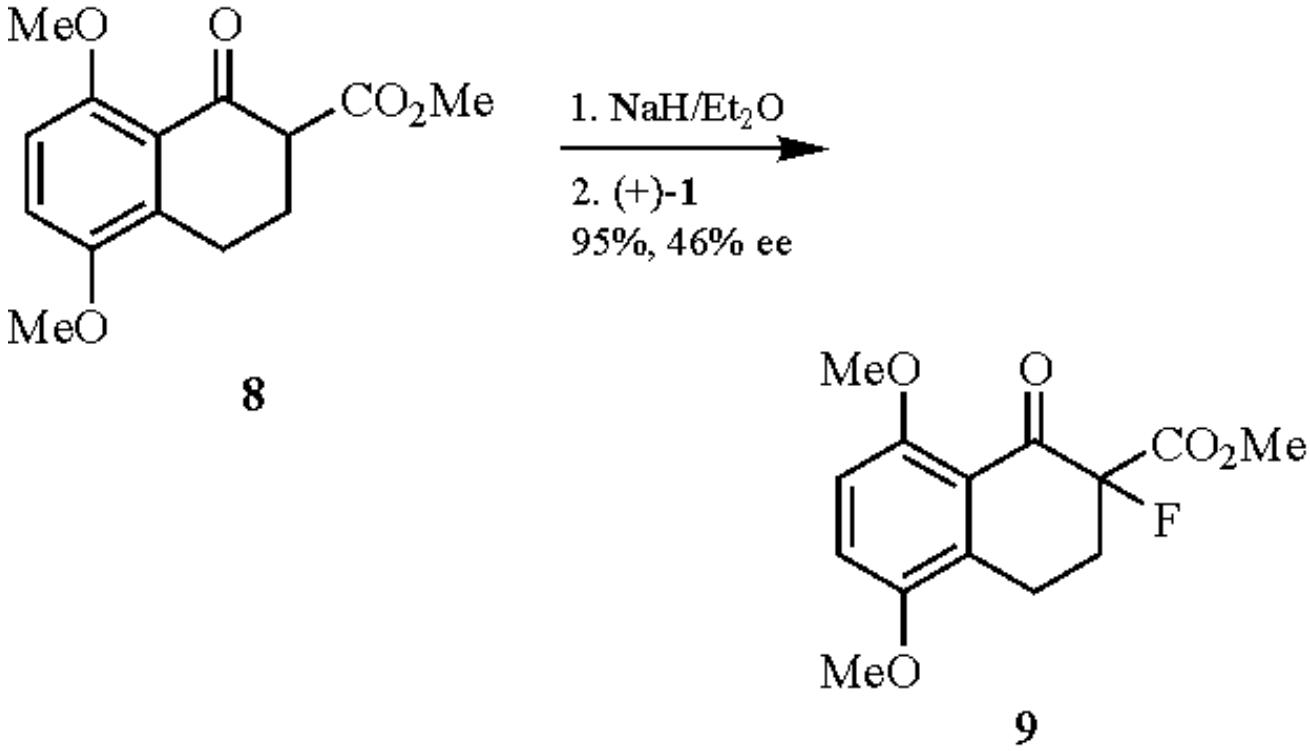

(4)

Related Reagents.

(+)-N-fluoro-2,10-camphorsultam;[4,5] (-)-N-fluoro-2,10-(3,3-dimethoxycamphorsultam);[4] (3S)-(−)-N-fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-d]isothiazole 1,1-dioxide;[6] N-fluoro-o-benzenesulfonimide;[7] N-fluorobenzenesulfonimide.[8]

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(*R*,*R*)-1,2-(Methanesulfonamido)-cyclohexane

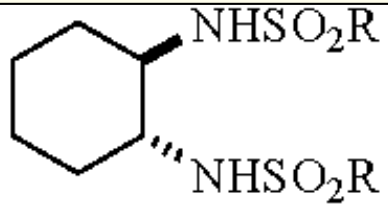

1a R = Me
1b R = CF_3 [CAS 122833-60-7]
1c R = *n*-Bu [CAS 290833-56-6]
1d R = 4-NO_2Ph [CAS 155237-72-2]
1e R = *i*-Pr [CAS 166109-85-9]
1f R = mesityl [CAS 263019-97-2]

[122833-58-3] · $C_8H_{18}N_2O_4S_2$ · (270.36)

(catalyst for organozinc-mediated additions to aldehydes,[1] catalyst for Simmons-Smith type cyclopropanation of allylic alcohols[2])

Physical Data: mp 157 °C; $[\alpha]_D^{20}$ -20.1 (*c* 3.07, pyridine).

Solubility: soluble in most organic solvents except hydrocarbons.

Form Supplied in: white solid.

Preparative Methods: The enantiopure sulfonamide **1a** is prepared via sulfonylation of (*R*,*R*)-1,2-diaminocyclohexane **2** in the presence of an excess of triethylamine (1).[3] Use of excess amine base is essential for obtaining a high yield of the bis-sulfonamide. Synthesis of related bis-sulfonamides is easily accomplished by substituting the desired sulfonyl chloride in the former procedure.

Recrystallization of the bis-sulfonamide **1a** from hexane/ethyl acetate and drying over P_2O_5 allows for isolation of the analytically pure reagent. Methanesulfonyl chloride and (*R*,*R*)-1,2-diaminocyclohexane **2** are commercially available from a number of sources. However it should be noted that racemic 1,2-diaminocyclohexane **2** can be resolved via formation of the tartrate salt.[4] Typically, the diamine can be obtained in >99:1 enantiomeric ratio (er) after two crystallizations from water. Determination of the enantiopurity of the diamine is accomplished via formation of the bis-3-toluyl amide and analysis via chiral stationary phase HPLC (Chiralcel AD; hexane/*i*-PrOH; 95:5, 1.0 mL min^{-1}).

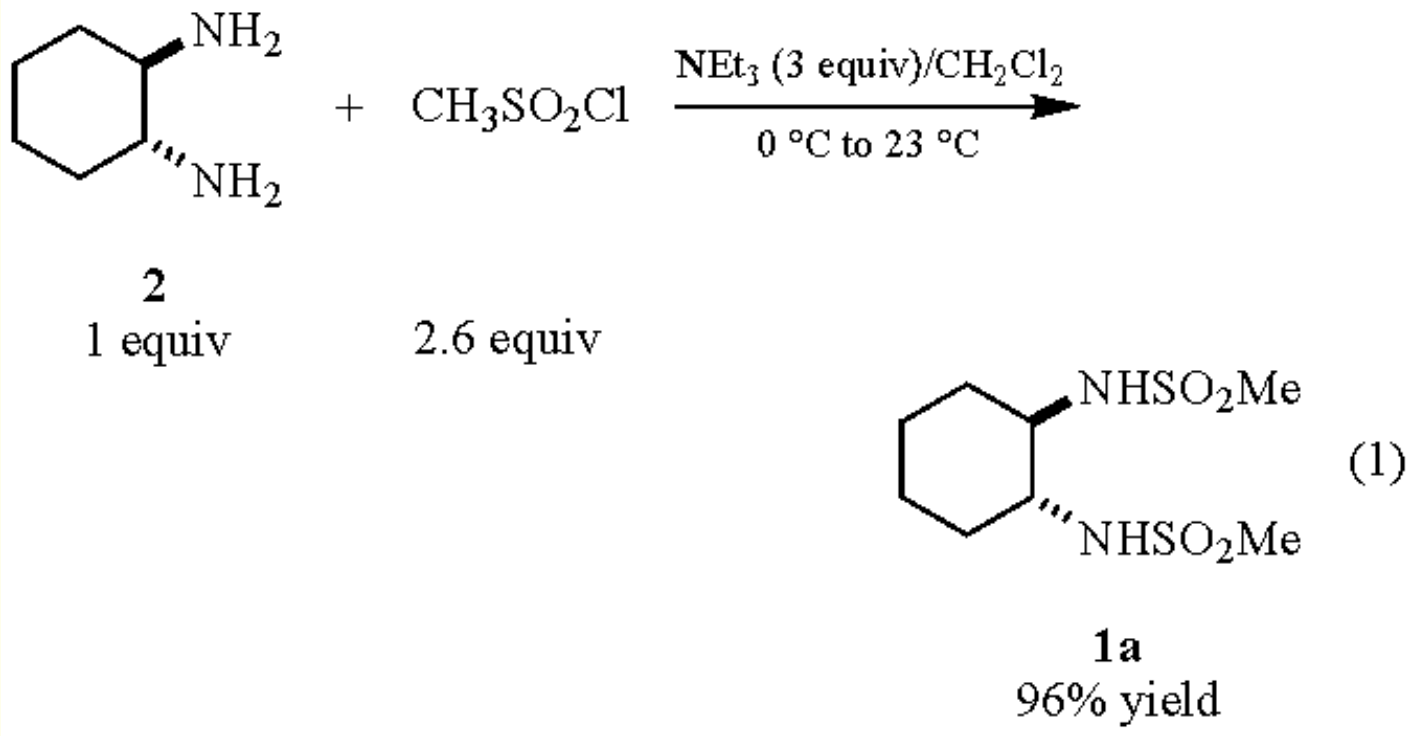

Handling, Storage, and Precautions: The sulfonamide is a shelf-stable, non-hygroscopic compound which does not require special precautions for storage or handling.

Introduction

The 1,2-bis-(methanesulfonamido)-cyclohexane **1a** is an important member of a larger class of C_2-symmetric bis-sulfonamide ligands which have had a powerful impact on the field of organozinc chemistry.[1,2] The success of these ligands is, in part, due to the straightforward installation of a variety of sulfonamide groups, providing access to a wide array of sterically and electronically diverse ligands.

Additions to Aldehydes

Alkylation of aromatic and aliphatic aldehydes with a combination of titanium tetraisopropoxide, $Ti(O\text{-}i\text{-}Pr)_4$, and diethylzinc, $ZnEt_2$, in the presence of a catalytic amount of the bis-sulfonamide **1a** leads to formation of (*S*)-1-phenyl-1-propanol **4** with high enantioselectivity (2, 1).[5] Use of the (*R*,*R*)-1,2-(trifluoromethanesulfonamido)-cyclohexane **1b** [CAS 122833-60-7] allows for an equally selective reaction, but at exceptionally low catalyst loadings. In the case of aromatic aldehydes, these reactions are fairly rapid, requiring at most 2 hours to reach full conversion.

Table 1 Alkylation of benzaldehyde in the presence of sulfonamide catalysts **1a–b**

R	Cat. loading (%)	Temp. (°C)	Yield (%)	**4** (er)
Me (**1a**)	4	23	90	95:5
Me (**1a**)	4	0	97	83:17
CF_3 (**1b**)	4	0	99	99:1
CF_3 (**1b**)	0.05	−20	97	99:1

er, enantiomeric ratio.

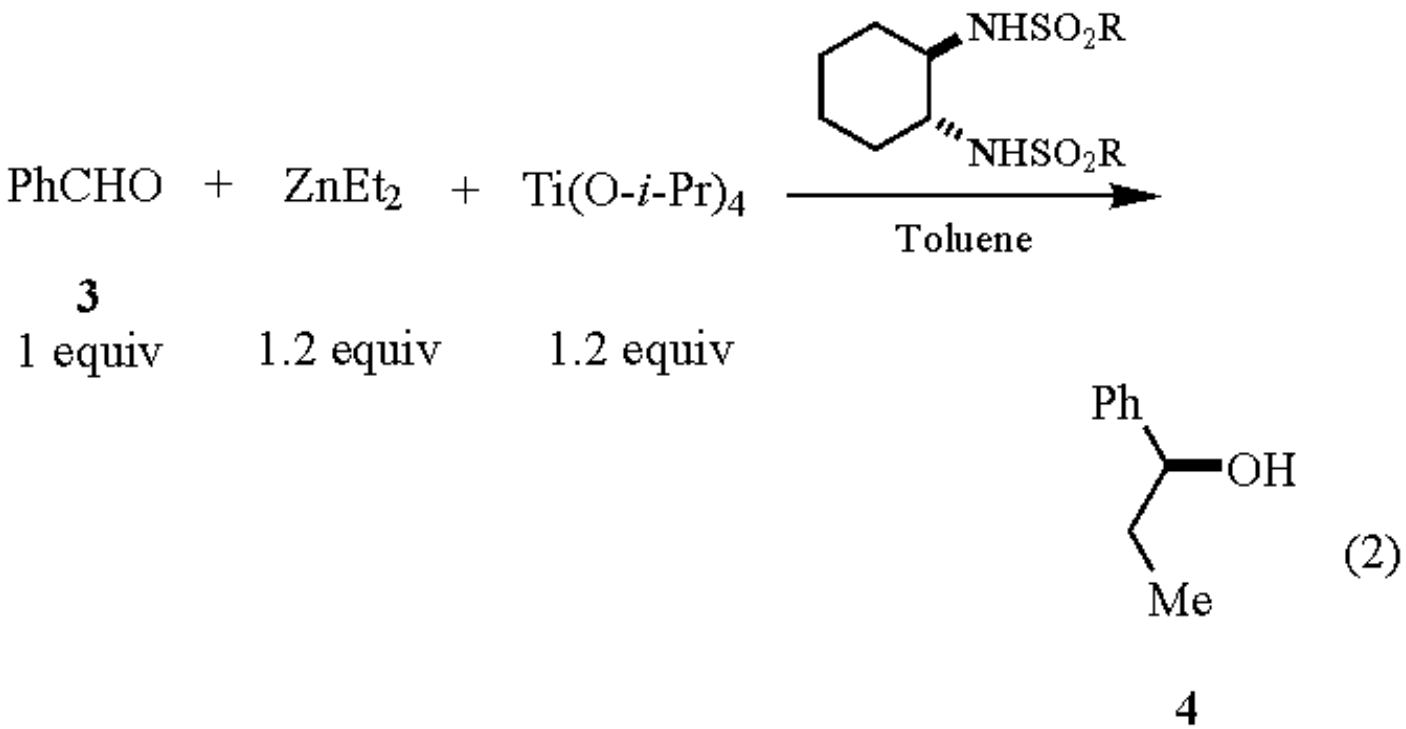

Through the use of the bis-sulfonamide **1b**, the scope of the reaction has been expanded to include a larger number of aldehydes and organozinc reagents (Table 2). High yields and selectivities are obtained in the alkylations of conjugated aldehydes (**5**) as well as simple aliphatic aldehydes (**7**,**9**). The broad scope of this reaction with respect to the electrophile contrasts the slightly limited scope of the reaction when

considering the structure of the nucleophile. The use of small alkylzinc reagents, such as dimethylzinc, leads to a depressed selectivity (entry 4). However, the use of larger alkylzinc reagents still provides the exceptional selectivity observed in the case of diethylzinc (entries 5 and 6).

Table 2 Substrate scope in the alkylation of aldehydes with sulfonamide **1b**

Entry	R^1	R^2	Loading (%)	Temp. (°C)	Yield (%)	Product	er
1	PhCH=CH (**5**)	CH_3CH_2	2	−50	85	**6**	>99:1
2	$PhCH_2CH_2$ (**7**)	CH_3CH_2	1	0	95	**8**	96:4
3	n-C_5H_{11} (**9**)	CH_3CH_2	4	−20	87	**10**	>99:1
4	Ph (**3**)	CH_3	4	0	99	**11**	86:14
5	Ph (**3**)	n-C_4H_9	2	−20	98	**12**	99:1
6	Ph (**3**)	n-C_5H_{11}	2	−50	99	**13**	>99:1

er, enantiomeric ratio.

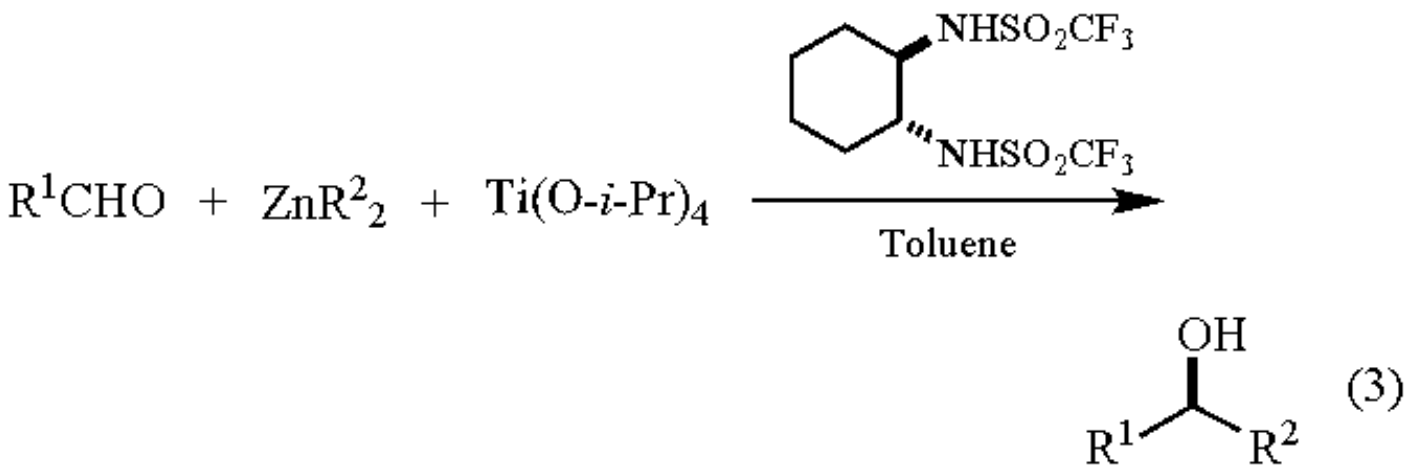

(3)

The scope of the reactive partners has been fully explored and expanded to include a diversity of functionalized organozinc reagents. Preparation of the functionalized organozinc reagent proceeds via hydroboration and boron-zinc exchange of a simple terminal alkene. The resulting organozinc reagent can then be used in an identical manner to that shown above. In the presence of <10 mol % of catalyst **1b**, high yields and selectivities can be obtained (4).[6] One drawback of this method is that 50% of the starting alkene must be sacrificed. However, recent reports have revealed that use of a mixed organozinc species, which is accessible by disproportionation of two symmetric organozinc reagents, obviates this wasteful complication (5).[7]

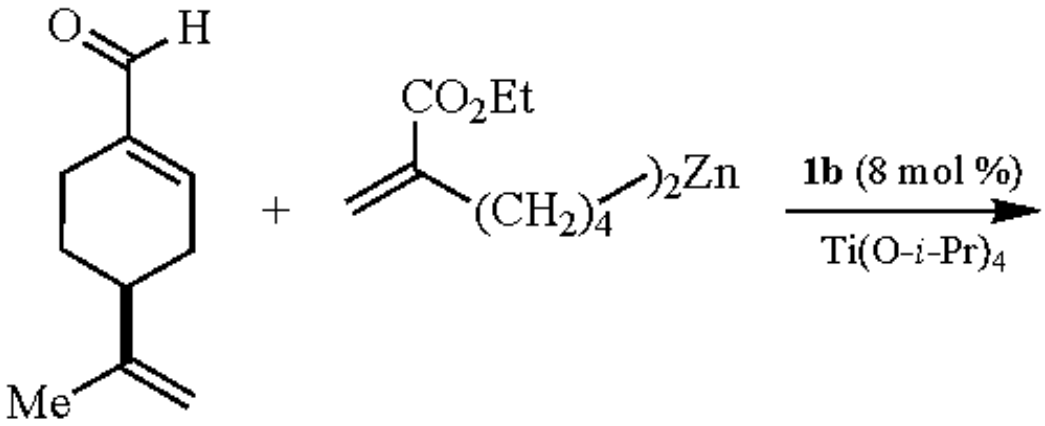

14 **15**

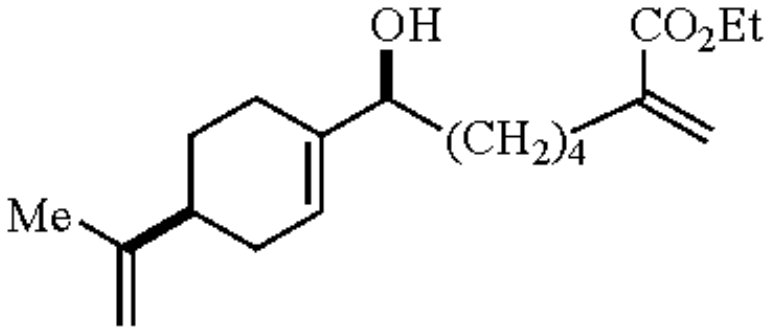

(4)

16
71% yield (93:7 er)

(R,R)-1,2-(Methanesulfonamido)-cyclohexane

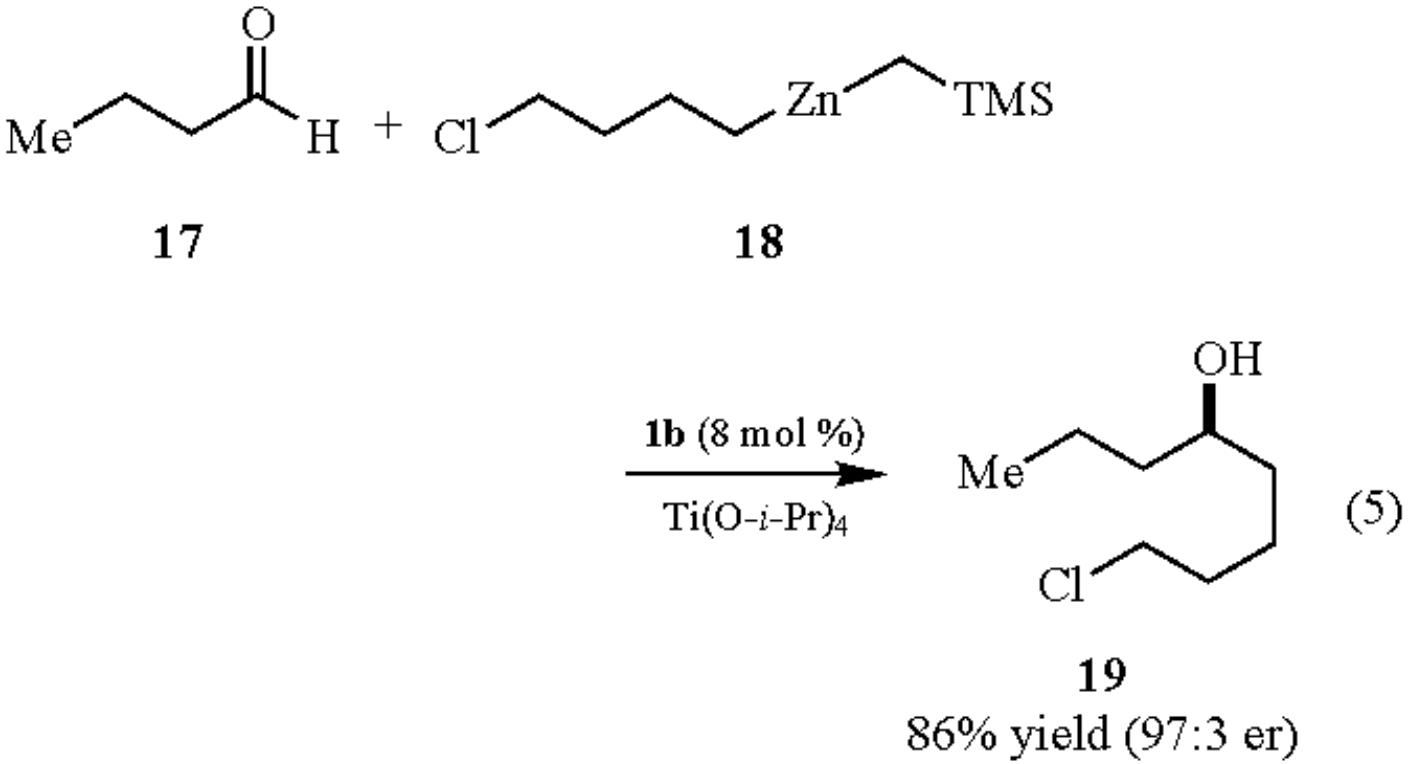

(5)

Comparable selectivity can be obtained in the alkylation of benzaldehyde **3** with diethylzinc using the titanium TADDOL complex **20** (>99:1 er) or 3-*exo*-(dimethylamino)isoborneol, **21** (>99:1 er), although both methods employ higher catalyst loadings.[8,9] While benzaldehyde is illustrative, the substrate scope is equally broad in the case of these two catalysts.

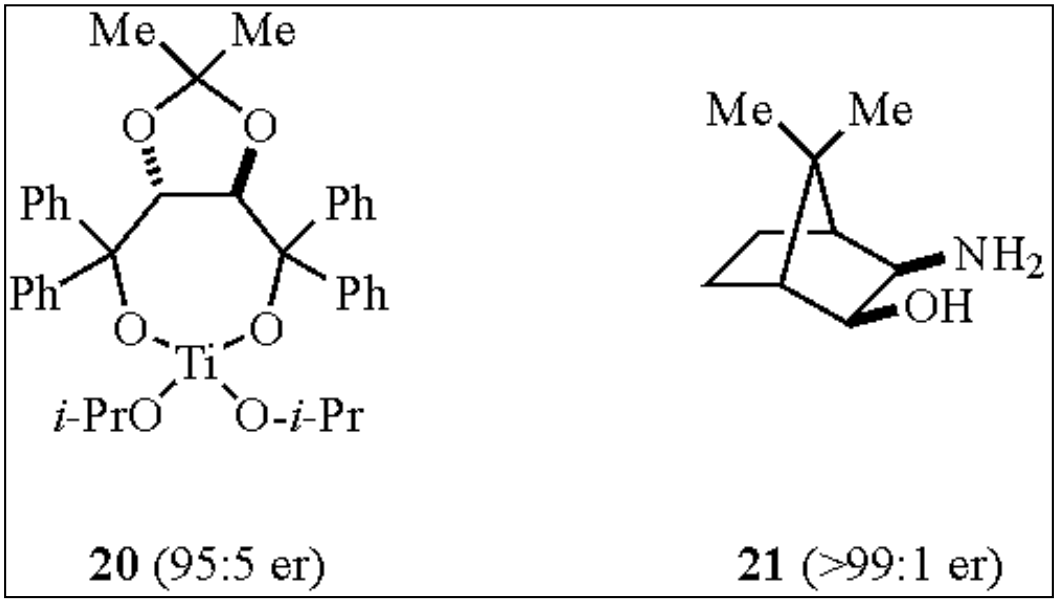

Cyclopropanation of Allylic Alcohols

Simmons-Smith type cyclopropanation of the allylic alcohol **22** in the presence of a catalytic amount of the bis-sulfonamide **1a** leads to formation of the corresponding cyclopropane **23** in high yield and selectivity (6, Table 3).[10] The reaction is rapid (<1 h) and can be performed at low temperature (either 0 °C or -20 °C). Substrate scope encompasses both di- and tri-substituted allylic alcohols (**24** and **26**). However, substitution at the 2 position, as in **28**, leads to a drastic decrease in selectivity. The presence of additional oxygenated functionality (**30**) in the proximity of the alkene also lessens selectivity.[11] The method is limited to the cyclopropanation of allylic alcohols. Other alkene-containing substrates, such as allylic ethers, homo-allylic alcohols and allylic carbamates, do not react with high selectivity.

Table 3 Substrate generality in the cyclopropanation using sulfonamide **1a**

Entry	Substrate	R^1	R^2	R^3	Yield (%)	Product	er
1	**22**	Ph	H	H	92	**23**	95:5
2	**24**	$PhCH_2CH_2$	H	H	88	**25**	95:5
3	**26**	Ph	Me	H	92	**27**	95:5
4	**28**	Ph	H	Me	91	**29**	51:49
5	**30**	$BnOCH_2$	H	H	70	**31**	68:32

er, enatiomeric ratio.

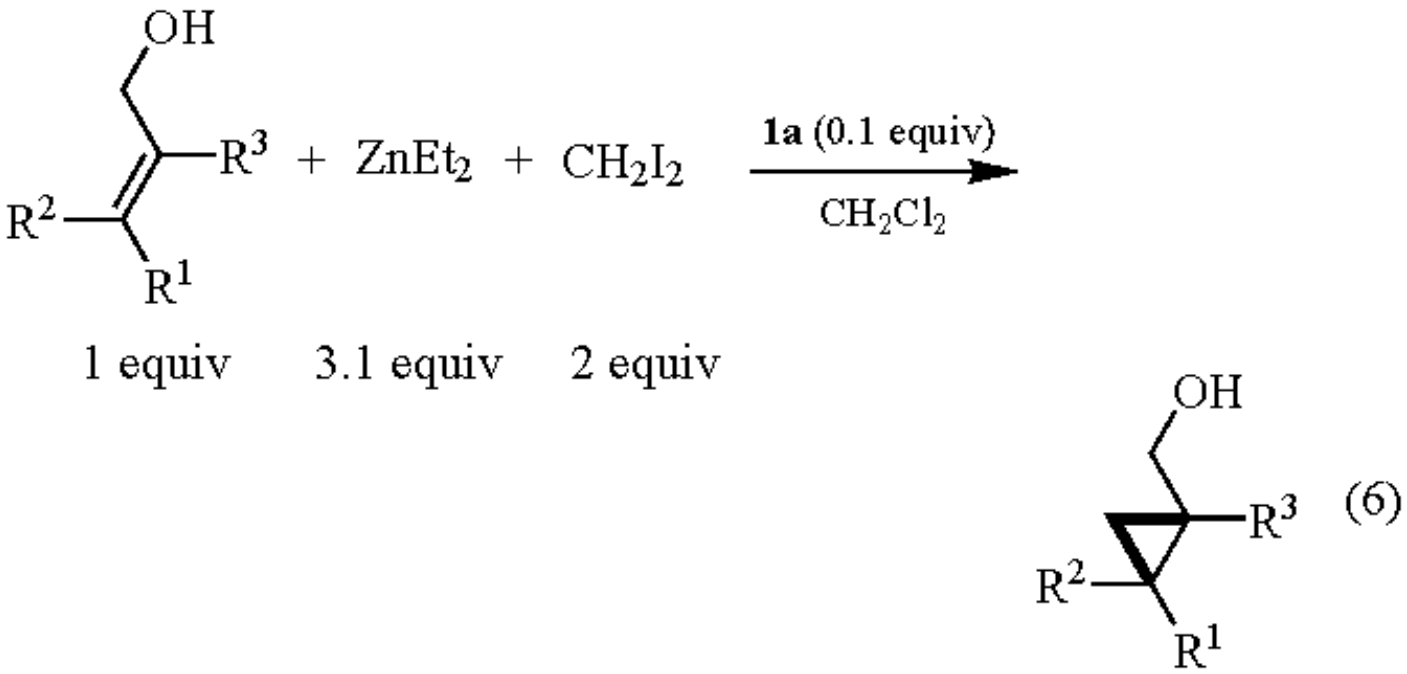

The optimal procedure calls for a three-flask protocol which segregates the individual reactive components. Pre-formation of the zinc alkoxide, zinc sulfonamide complex and the cyclopropanation reagent, $Zn(CH_2I)_2$, by combination of diethylzinc with the allylic alcohol, bis-sulfonamide and diiodomethane, respectively, is essential for high selectivity and reproducibility. While the individual reaction components are soluble in halogenated solvents such as dichloromethane, the zinc sulfonamide complex is a highly insoluble species which is prone to aggregation. Because of the nature of the zinc carbenoid, a heterogenous reaction is always observed. None of the related bis-sulfonamide catalysts shown in Table 4 are able to dissolve the precipitate. Still, a survey of catalyst structure reveals that large variations in sulfonamide structure can be tolerated without compromising selectivity (entries 1 and 2).[10,12] Bulky sulfonamide groups, however, clearly interfere with the selective cyclopropanation process (entries 3 and 4).

Table 4 Selectivity of various sulfonamides in the cyclopropanation of **22**

Entry	R	Compound	**23** (cr)
1	*n*-Bu	**1c**	92:8
2	4-$NO_2C_6H_4$	**1d**	89:11
3	*i*-Pr	**1e**	86:14
4	2,4,6-MeC_6H_2	**1f**	62:38

This method is comparable to similar, catalytic Simmons-Smith-type methods employing the titanium TADDOL catalyst **20** (95:5 er) or the C_1-symmetric bis-sulfonamide catalyst **32** (93:7 er) for the cyclopropanation of the allylic alcohol **22** (6).[13,14] However, due to the preliminary nature of these earlier investigations, substrate scope and generality have not been extensively documented. All of the aforementioned methods are limited by their dependence on the allylic alcohol functionality. Only one method for Simmons-Smith-type cyclopropanation of other substrate classes has been developed. Use of a stoichiometric, chiral dioxaborolane [CAS 161344-85-0] additive allows for selective cyclopropanation of allylic ethers, homo-allylic alcohols and allylic carbamates.[15]

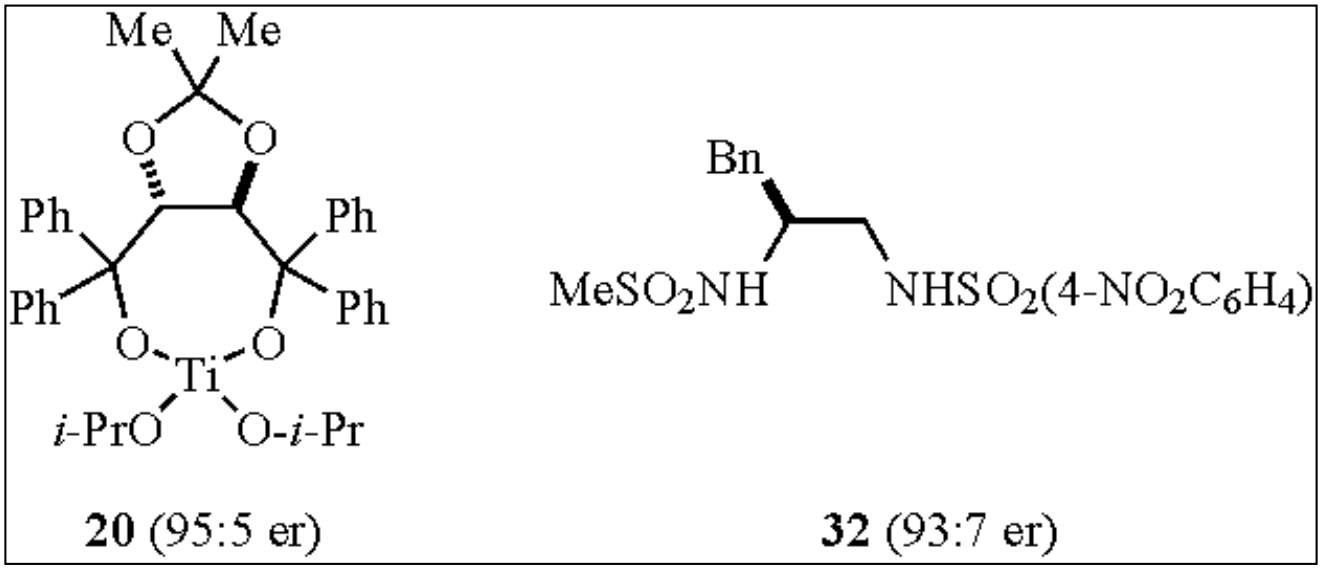

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[4*S*-(4α,5β)]-1-(1,3-Dimethyl-2-oxido-4,5-diphenyl-1,3,2-diazaphospholidine-2-yl)piperidine

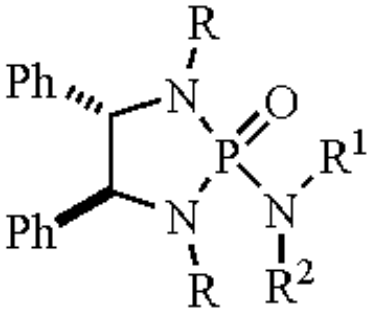

(*S*,*S*)-**1a**, R = Me, $R^1 = R^2 = -(CH_2)_5-$

(*S*,*S*)-**1b**, R = Ph, $R^1 = R^2 = -(CH_2)_5-$

(*S*,*S*)-**1c**, R = Me, $R^1 = R^2 = -(CH_2)_4-$

(*S*,*S*)-**1d**, R = $R^1 = R^2$ = Me

(*S*,*S*)-**1e**, R = Me, $R^1 = R^2$ = *i*-Pr

(*S*,*S*)-**1f**, R = Me, $R^1 = R^2$ = *n*-Pr

(*S*,*S*)-**1g**, R = Me, $R^1 = R^2$ = Ph

(*S*,*S*)-**1h**, R = Et, $R^1 = R^2 = -(CH_2)_5-$

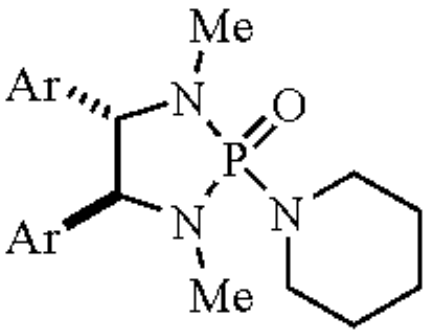

(*S*,*S*)-**2a**, Ar = 4-$CF_3C_6H_4$

(*S*,*S*)-**2b**, Ar = 4-$MeOC_6H_4$

(*S*,*S*)-**2c**, Ar = 3,5-$Me_2C_6H_4$

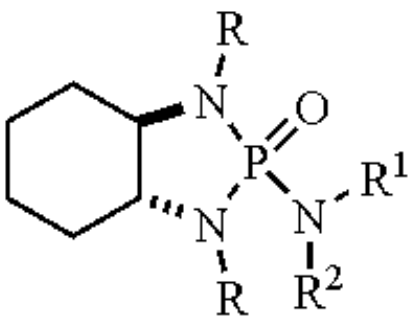

(*R*,*R*)-**3a**, R = Me, $R^1 = R^2 = -(CH_2)_5-$

(*R*,*R*)-**3b**, R = Me, $R^1 = -(CH_2)_4CH_3$, R^2 = Me

(*R*,*R*)-**3c**, R = Me, $R^1 = R^2 = i$-Pr

(*R*,*R*)-**3d**, R = Me, R^1 = Me, R^2 = (1'*S*)-PhCHMe

(*R*,*R*)-**3e**, R = CH_2Ph, $R^1 = R^2$ = Me

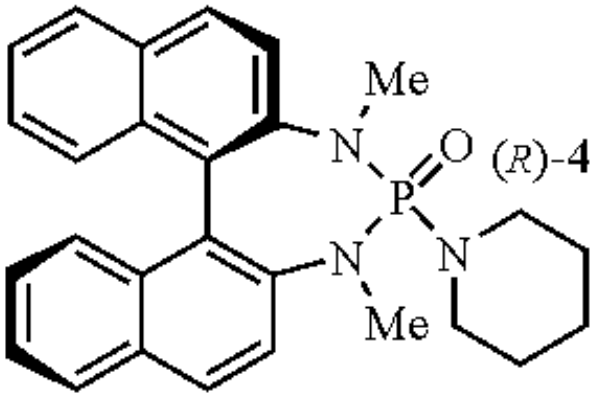

(*R*)-**4**

[180475-25-6] · $C_{21}H_{28}N_3OP$ · (369.45)

(catalyst for asymmetric aldol additions of trichlorosilyl enolates to aldehydes,[1] catalyst for asymmetric allylations and crotylations of allylic trichlorosilanes to aldehydes,[2] catalyst for asymmetric ring opening of epoxides using silicon tetrachloride[3])

Physical Data: mp 110 °C; $[\alpha]_D^{22}$ +18.2 (*c*=1.3, $CHCl_3$).

Solubility: soluble in most organic solvents except hydrocarbons.

Form Supplied in: white needles.

Preparative Methods: The enantiopure phosphoramide (*S*,*S*)-**1a** is prepared from treatment of (*S*,*S*)-*N*,*N*´-dimethyl-1,2-diphenyl-1,2-ethanediamine (**5**) with piperidinylphosphoric dichloride (**6**) and triethylamine (1).[4] Synthesis of related phosphoramides is easily accomplished by substituting the desired diamine backbone in the former procedure. Recrystallization of phosphoramide (*S*,*S*)-**1a** from hexane followed by drying over P_2O_5 allows for isolation of analytically pure material. Enantiopure 1,2-diphenyl-1,2-ethanediamine (**5**) can be prepared from benzil and cyclohexanone according to the method of Pikul & Corey.[5] Bis-formylation of the diamine with acetic formic anhydride followed by $LiAlH_4$ reduction affords *N*,*N*´-dimethyldiamine **5**. Alternatively, enantiopure **5** can be prepared directly from benzaldehyde and methylamine according to the method of Alexakis et al.[6] Piperidinylphosphoric dichloride (**6**) is prepared from piperidine, triethylamine and phosphorous oxychloride according to the modified procedure of Peyronel et al.[7]

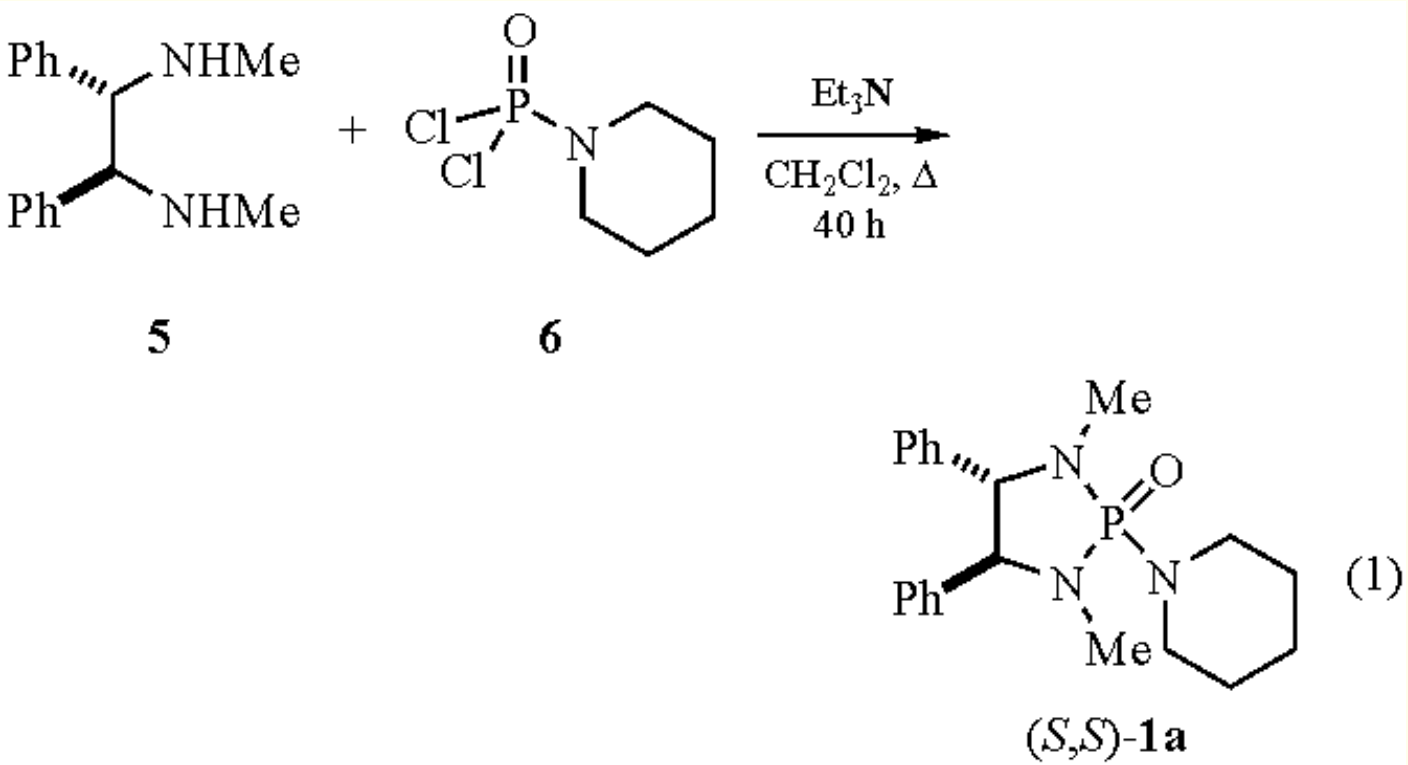

Handling, Storage, and Precautions: The phosphoramide is a stable, hygroscopic compound which is best stored in a dessicator or dry-box. Avoid prolonged exposure to air or moisture.

Introduction

[4*S*-(4α,5β)]-1-(1,3-Dimethyl-2-oxido-4,5-diph-enyl-1,3,2-diazaphospholidine-2-yl)piperidine (**1a**) and its derivatives are an important class of phosphoramides which have seen much success as Lewis-basic catalysts for aldol additions,[8] allylations,[9] crotylations, and epoxide openings.[10] The three nitrogen subunits of the phosphoramide provide the opportunity for a large number of structurally diverse analogs, allowing a wide spectrum of properties and shapes to be customized.[11]

Ester enolate aldol additions to aldehydes

Among the first examples of aldol additions employing chiral Lewis bases as catalysts were the additions of trichlorosilyl ketene acetals to aldehydes.[12] Silyl ketene acetal **7** could be generated by metathesis of methyl tributylstannylacetate with $SiCl_4$. Treatment of **7** with benzaldehyde and 10 mol % of a phosphoramide in CH_2Cl_2 at -78 °C afforded aldol products in good to high yields with moderate enantioselectivities for all phosphoramides employed. Reaction of **7** with pivalaldehyde provided aldol products in similar yields and with slightly improved enantioselectivities. The increase in stereoselection is presumably attributed to a less competent background reaction inherent with additions to more sterically encumbered aldehydes (2, Table 1).

Table 1 Phosphoramide-catalyzed addition of ketene acetal **6** to aldehydes

Entry	Catalyst	Aldehyde	er (configuration)
1	(*S*,*S*)-**1**	PhCHO	2.0:1 (*S*)
2	(*R*,*R*)-**3**	PhCHO	1.5:1 (*R*)
3	(*R*)-**4**	PhCHO	1.6:1 (*S*)
4	(*S*,*S*)-**1**	*t*-BuCHO	2.2:1 (*S*)
5	(*R*,*R*)-**3**	*t*-BuCHO	1.4:1 (*R*)
6	(*R*)-**4**	*t*-BuCHO	2.9:1 (*S*)

er, enantiomeric ratio.

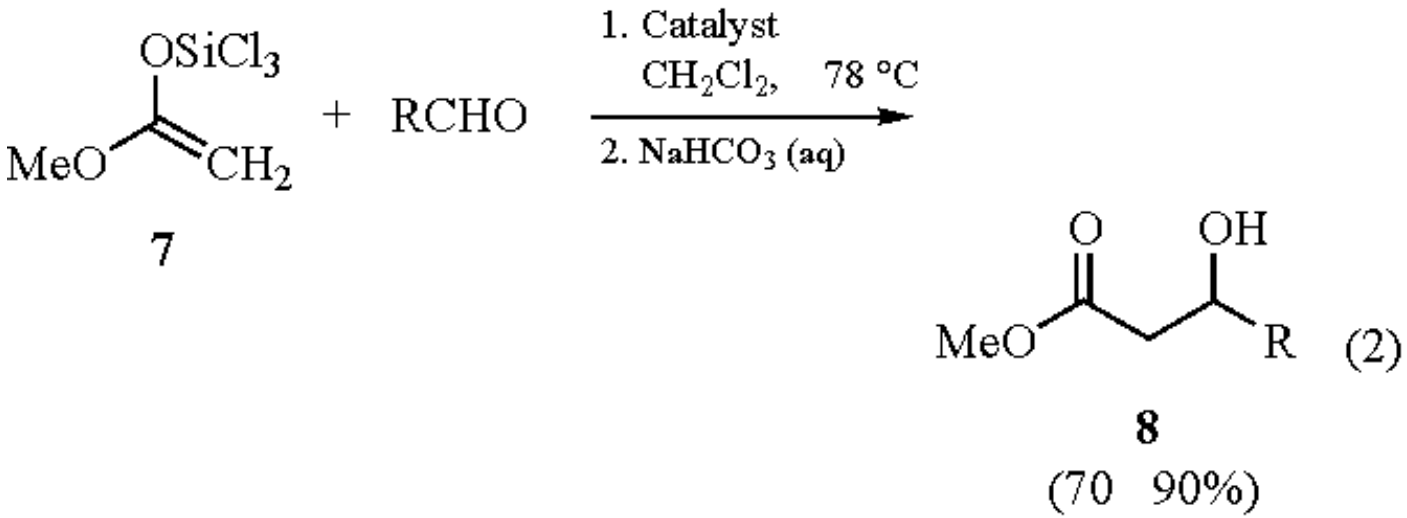

(2)

Ketone enolate aldol additions to aldehydes

Addition of methyl ketone trichlorosilyl enolate **9** to benzaldehyde in the presence of catalytic amounts of phosphoramide (*S*,*S*)-**1** affords aldol products in excellent yields.[13] The level of enantioselectivity was found to be dependent upon the amount of (*S*,*S*)-**1a** used, with higher loadings providing better selectivities. A typical procedure involves equilibration of a solution of trichlorosilyl enolate and (*S*,*S*)-**1a** in CH_2Cl_2 at -78 °C followed by addition of aldehyde. Reactions are quenched upon completion by quickly pouring the cold reaction mixture into a rapidly stirring aqueous $NaHCO_3$ solution placed in an ice bath. Alternatively, completed reactions may be quenched using a cold 1:1 mixture of a saturated aqueous KF solution and an aqueous 1 M KH_2PO_4 solution. In either case, rapid stirring of the cold quench mixture prevents acid-catalyzed β-elimination of the aldol products to give undesired α,β-unsaturated ketones (3, Table 2).

Table 2 Effect of catalyst loading on aldol additions with enolate **9**

Entry	Loading (mol %)	Conc. (M)	er	Yield (%)
1	10	0.1	11.3:1	90
2	20	0.1	12.3:1	89
3	10[a]	0.5	1:11.7	87
4	5	0.5	11.5:1	88
5	3	0.5	8.60:1	86
6	2	0.5	7.77:1	88
7	1	0.5	5.10:1	92

er, enantiomeric ratio. [a]Performed with 10 mol % (*R*,*R*)-**1a**.

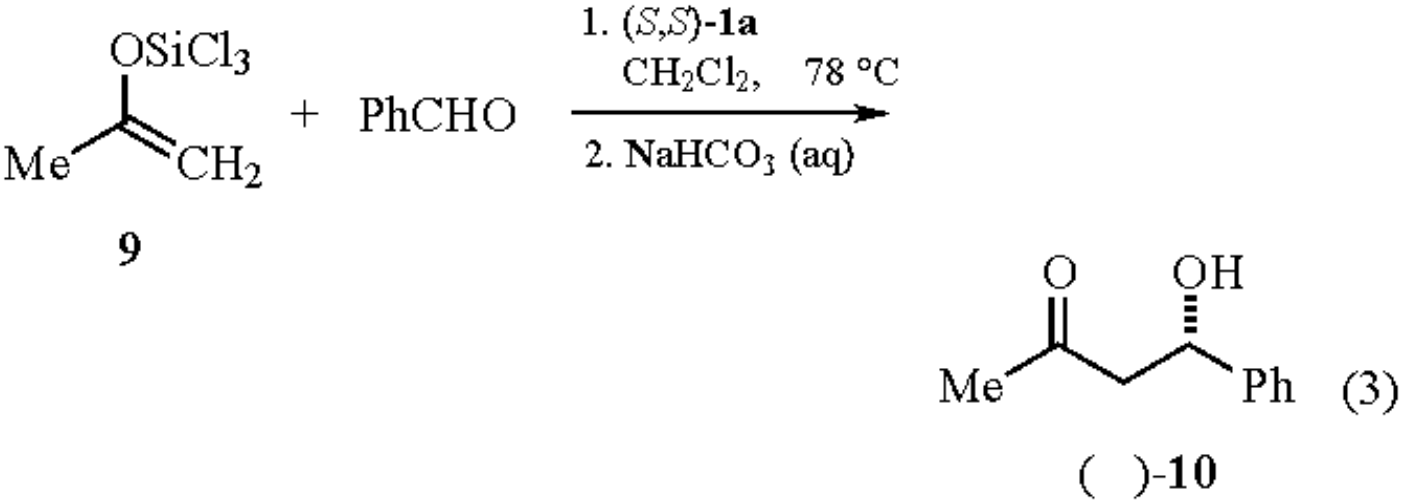

The generality of methyl ketone enolate additions to benzaldehyde was demonstrated by varying the spectator portion of the nucleophile.[13] In all cases, high yields were achieved using as little as 5 mol % (*S*,*S*)-**1a**. The enantioselectivity of the process, however, was sensitive to the enolate structure with larger groups, such as *t*-butyl and phenyl (4, Table 3, entries 5 and 6), providing lower enantioselectivities. The success of a functionalized enolate (4, Table 3, entry 7) demonstrated the tolerance for oxygenated substituents in the phosphoramide-catalyzed aldol addition, whereby no deleterious effect was observed on either the yield or enantioselectivity as compared with unfunctionalized enolates.

Table 3 Aldol additions of methyl ketone trichlorosilyl enolates to benzaldehyde catalyzed by (*S*,*S*)-**1a**

Entry	R	er	Yield (%)
1	Me	14.6:1	98
2	*n*-Bu	12.0:1	98
3	*i*-Bu	10.1:1	95
4	*i*-Pr	9.75:1	97
5	*t*-Bu	3.17:1	95
6	Ph	2.92:1	93
7	$TBSOCH_2$	13.5:1	94

er, enantiomeric ratio.

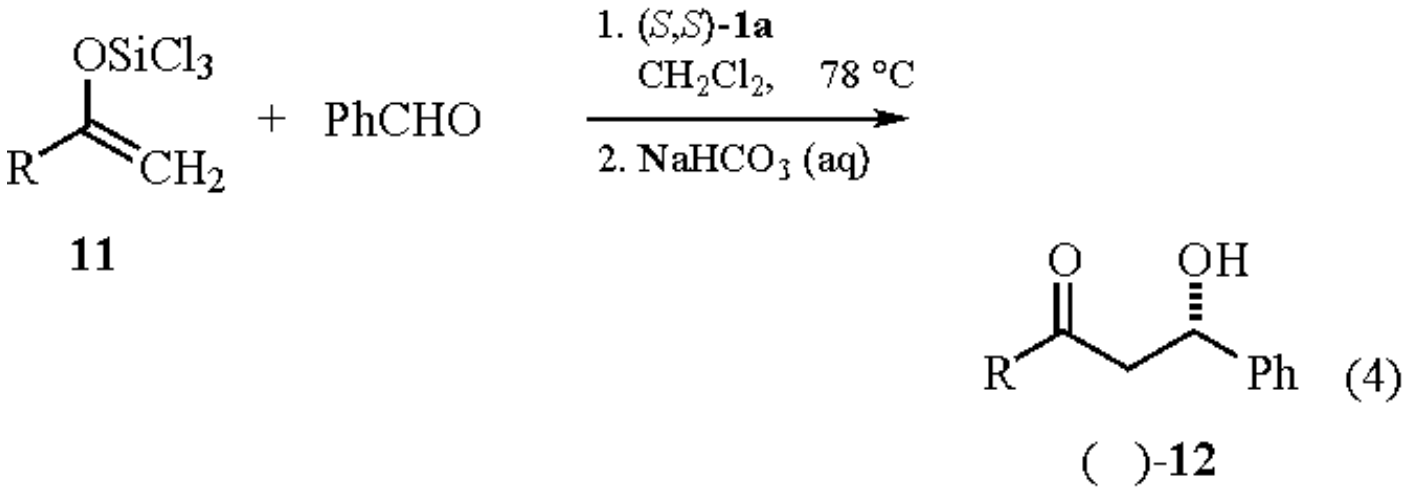

The phosphoramide-catalyzed aldol addition was less sensitive to variations on the electrophile. Using 2-hexanone trichlorosilyl enolate **13** as an example aldol additions to various aldehydes affords aldol products in good to high yields and with excellent enantioselectivities, using as little as 5 mol % catalyst.[13] Additions to branched aliphatic aldehydes, such as cyclohexanone and pivalaldehyde (5, Table 4, entries 5 and 6), were sluggish when using 5 mol % catalyst. However, increasing the catalyst loading to 10 mol % provides good yields of the aldol products after 6 h with excellent enantioselectivities.

Table 4 Aldol additions of enolate **13** to various aldehydes catalyzed by (*S*,*S*)-**1a**

Entry	Aldehyde	Loading (mol %)	Time (h)	er	Yield (%)
1	(*E*)-PhCH=CHCHO	5	2	14.6:1	94
2	(*E*)-PhCH=C(Me)CHO	5	2	21.7:1	95
3	1-NaphthylCHO	5	2	13.1:1	92
4	4-PhC_6H_4CHO	5	2	12.7:1	95
5	$C_6H_{11}CHO$	10	6	17.5:1	79
6	*t*-BuCHO	10	6	24.0:1	81

er, enantiomeric ratio.

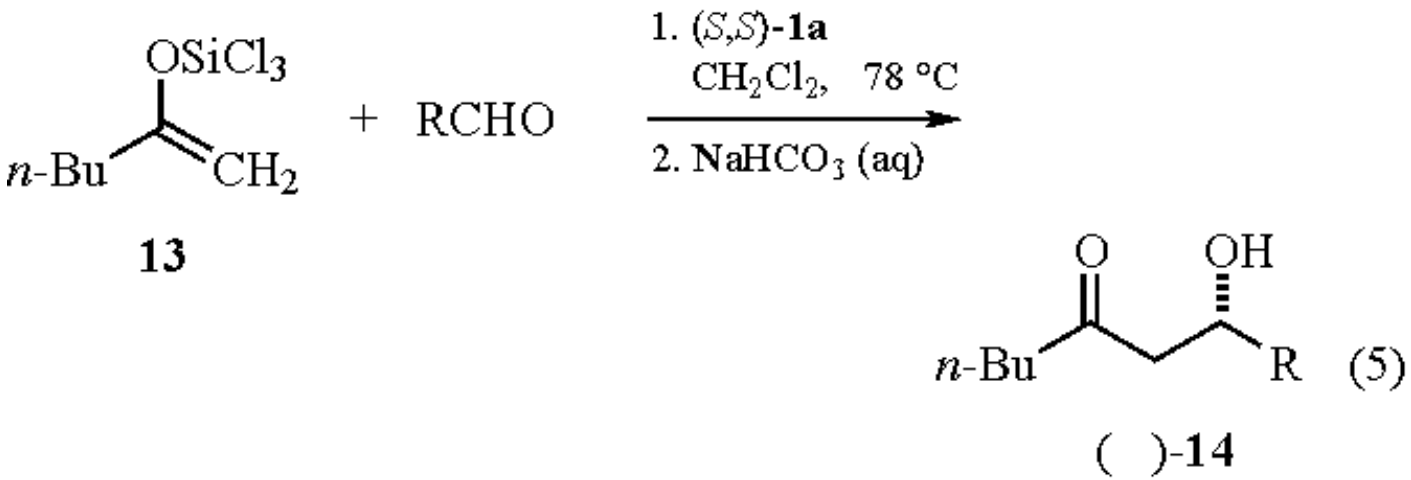

Recently, the synthetic utility of phosphoramide-catalyzed aldol additions of trichlorosilyl enolates to aldehydes has been enhanced by the ability to generate the delicate trichlorosilyl enolates in situ.[13] Treatment of the corresponding TMS enol ether with $Hg(OAc)_2$ followed by addition of a solution phosphoramide and aldehyde afford aldol products in high yields over two steps without affecting stereoselectivities. This is exemplified by the addition of chiral α-oxygenated trichlorosilyl enolates to benzaldehyde. Using the (*S*)-lactate-derived methyl ketone enol ether **15**, addition to benzaldehyde afforded aldol products in high diastereoselectivity for the matched-sense using (*R*,*R*)-**1a**.[13,14] Although the reaction was compatible with various oxygen functionalities, the stereoselectivity was highly dependent upon the nature of the protecting group, with the OTBS group superior to both the benzyloxy or pivaloyl protecting groups (6, Table 5).

Table 5 Addition of TMS enol ether **15** catalyzed by 5 mol % **1a**

Entry	R	Catalyst	*syn*/*anti*	Yield (%)
1	TBS	(*S*,*S*)-**1a**	1.5:1	85
2	Piv	(*S*,*S*)-**1a**	3.4:1	78
3	Bn	(*S*,*S*)-**1a**	1:1.1	78
4	TBS	(*R*,*R*)-**1a**	73:1	85
5	Piv	(*R*,*R*)-**1a**	20:1	78
6	Bn	(*R*,*R*)-**1a**	11:1	77

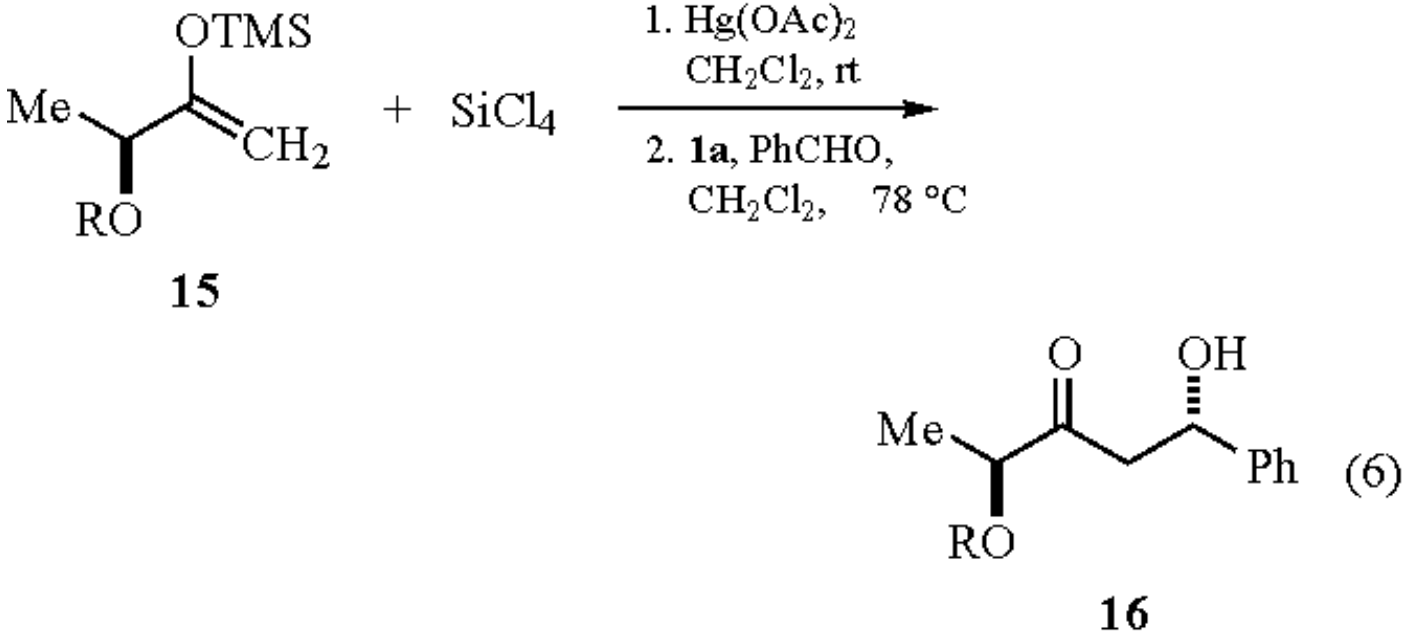

(6)

To further exemplify the dependence of the stereochemical course of chiral enolate additions catalyzed by phosphoramides, a detailed survey of additions to aldehydes using chiral β-hydroxyenolate **17** and 10 mol % of **1a** was performed.[15] Unlike additions of **15**, diastereoselectivities of the resultant aldol products using **17** could be switched depending upon the configuration of the phosphoramide employed (7, Table 6).

Table 6 Addition of TMS enol ether **17** to aldehydes catalyzed by **1a**

Entry	Catalyst	Aldehyde	*syn*/*anti*	Yield (%)
1	(*R*,*R*)-**1a**	PhCHO	19.0:1	80
2	(*S*,*S*)-**1a**	PhCHO	1:7.33	75
3	(*R*,*R*)-**1a**	1-NaphthylCHO	15.7:1	85
4	(*S*,*S*)-**1a**	1-NaphthylCHO	1:8.09	83
5	(*R*,*R*)-**1a**	(*E*)-PhCH=CHCHO	8.00:1	81
6	(*S*,*S*)-**1a**	(*E*)-PhCH=CHCHO	1:4.26	82
7	(*R*,*R*)-**1a**	*t*-BuCHO	27.9:1	73
8	(*S*,*S*)-**1a**	*t*-BuCHO	1:6.51	78

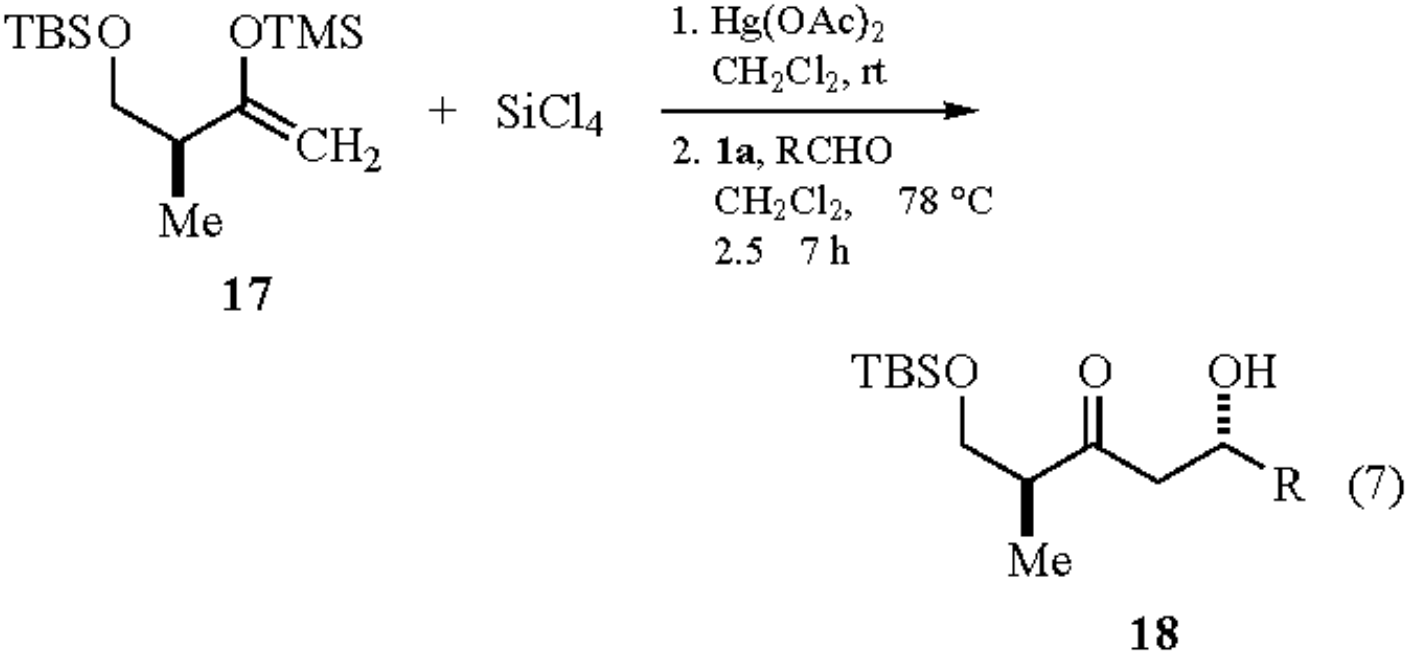

(7)

The phosphoramide-catalyzed aldol addition of substituted enolates to aldehydes provides the opportunity to generate disubstituted aldol products with high stereoselectivity. The (*S*,*S*)-**1a**-catalyzed addition of cyclohexanone trichlorosilyl enolate **19** to aldehydes has been well studied and demonstrates good substrate generality.[16] The aldol reactions of this *E*-enolate are rapid when 10 mol % of (*S*,*S*)-**1a** is used. Reactions are typically complete within 2 h affording *anti*-aldol products in high yields with excellent diastereo- and enantioselectivities. Although the typical procedure using methyl ketone enolates can be followed, higher diastereoselectivities may be achieved by slow addition of a solution of aldehyde to the mixture of enolate and catalyst in CH_2Cl_2 at -78 °C over several minutes.[17] Remarkably, a dramatic switch in diastereoselectivity is observed when phosphoramide **1b** (10 mol %) is employed as a catalyst (8, Table 7, entry 2). Although the level of enantioselectivity was modest, the change in diastereoselectivity demonstrates that small structural changes in the phosphoramide can have profound effects on the stereochemical course of the reaction. This is further exemplified through a systematic substitution of the internal

(phospholidino) nitrogens (8, Table 7, entries 1 and 8), the external nitrogen (8, Table 7, entries 1 and 3-7),[18,19] as well as changes to the electronic demand of the aryl substituent (8, Table 7, entries 1 and 9-11).[20]

Table 7 Aldol addition of enolate **19** catalyzed by 10 mol % (*S*,*S*)-**1** and (*S*,*S*)-**2**

Entry	Catalyst	Aldehyde	*anti*/*syn*	er (major)	Yield (%)
1	**1a**	C_6H_5CHO	61:1	27.6:1	95
2	**1b**	C_6H_5CHO	1:97	3.08:1	94
3	**1c**	C_6H_5CHO	8.1:1	7.33:1	89
4	**1d**	C_6H_5CHO	19:1	14.4:1	91
5	**1e**	C_6H_5CHO	1:32	1.00:1	90
6	**1f**	C_6H_5CHO	1:16	1.11:1	89
7	**1g**	C_6H_5CHO	1:1.9	2.39:1	86
8	**1h**	C_6H_5CHO	2.0:1	17.2:1	92
9	**2a**	C_6H_5CHO	2.5:1	12.0:1	80
10	**2b**	C_6H_5CHO	53:1	24.0:1	80
11	**2c**	C_6H_5CHO	10:1	9.50:1	98
12	**1a**	1-NaphthylCHO	>99:1	65.7:1	94
13	**1a**	(*E*)-PhCH=CHCHO	>99:1	15.7:1	94
14	**1a**	(*E*)-PhCH=C(Me)CHO	>99:1	24.0:1	98
15	**1a**	PhC≡CCHO	5.3:1	10.1:1	90

er, enantiomeric ratio.

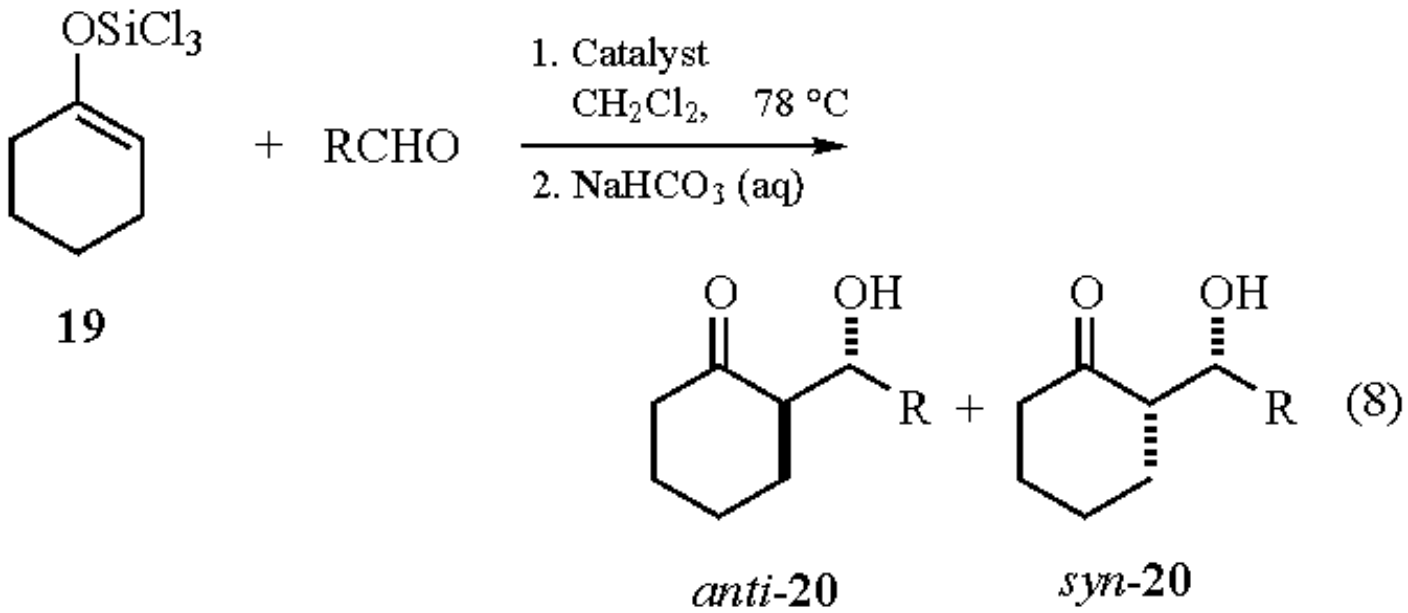

In contrast to the *E*-enolates derived from cyclic ketones, addition of propiophenone trichlorosilyl enolate (*Z*)-**21** to aldehydes requires longer reaction times and higher loadings of catalyst.[16] Although the yields of the aldol products remain high, both the diastereo- and enantioselectivities are attenuated as compared to their *E* counterparts (9, Table 8).

Table 8 Aldol addition of enolate **21** catalyzed by 15 mol % (*S,S*)-**1a**

Entry	Aldehyde	*syn*/*anti*	er (*syn*)	Yield (%)
1	C_6H_5CHO	18:1	39.0:1	95
2	1-NaphthylCHO	3.0:1	11.5:1	96
3	(*E*)-PhCH=CHCHO	9.4:1	24.0:1	97
4	PhC≡CCHO	1:3.5	3.76:1	92

er, enantiomeric ratio.

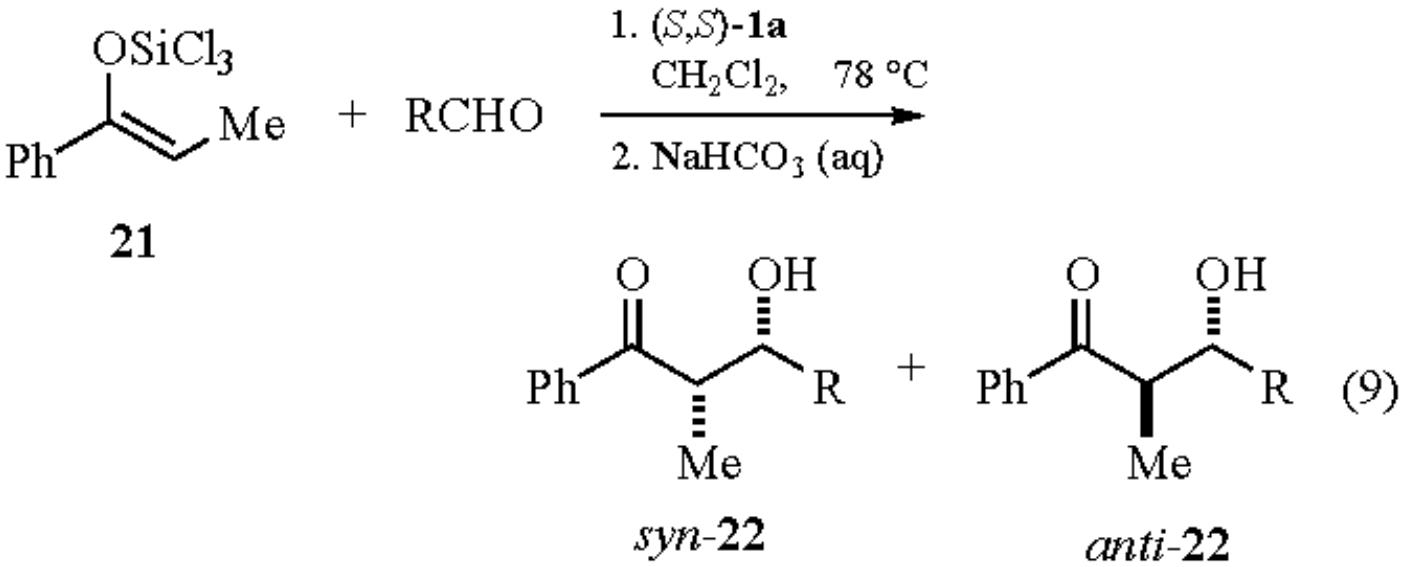

Allylic additions to aldehydes

Although phosphoramide **1** is capable of promoting the addition of allyltrichlorosilane to aldehydes, the enantioselectivities were modest at best compared with the cyclohexyldiamine analogs **3**.[21] Preliminary results showed the allylations to be high yielding but giving only moderate enantioselectivities when using one equivalent of phosphoramide as a promoter. As observed in the stereoselective aldol additions with phosphoramides, subtle changes to the nitrogen substituents also dramatically affect the stereochemical course of allylations using allylic trichlorosilanes (10, Table 9, entries 7-9).[22] Under optimized conditions, as few as 0.25 equivalents of phosphoramide may be used with little erosion in yield or stereoselectivity (10, Table 9, entries 3-5).

Table 9 Asymmetric allylation of aldehydes

Entry	Promoter	Equiv.	Conc. (M)	Aldehyde	er	Yield (%)
1	(*S*,*S*)-**1a**	1.0	1.0	C_6H_5CHO	2.0:1	NA
2	(*R*,*R*)-**3a**	1.0	1.0	C_6H_5CHO	4.0:1	81
3	(*R*,*R*)-**3a**	0.5	0.5	C_6H_5CHO	3.7:1	78
4	(*R*,*R*)-**3a**	0.25	0.5	C_6H_5CHO	3.9:1	74
5	(*R*,*R*)-**3a**	0.1	0.5	C_6H_5CHO	3.3:1	40
6	(*R*,*R*)-**3b**	1.0	1.0	C_6H_5CHO	3.1:1	73
7	(*R*,*R*)-**3c**	1.0	1.0	C_6H_5CHO	1.4:1	NA
8	(*R*,*R*)-**3d**	1.0	1.0	C_6H_5CHO	1.5:1	NA
9	(*R*,*R*)-**3e**	1.0	1.0	C_6H_5CHO	1.9:1	NA
10	(*R*,*R*)-**3a**	1.0	1.0	2-MeC_6H_4CHO	4.7:1	81
11	(*R*,*R*)-**3a**	1.0	1.0	4-$NO_2C_6H_4CHO$	1.5:1	76
12	(*R*,*R*)-**3a**	1.0	1.0	4-$MeOC_6H_4CHO$	3.0:1	80
13	(*R*,*R*)-**3a**	1.0	1.0	4-$NMe_2C_6H_4CHO$	2.0:1	69
14	(*R*,*R*)-**3a**	1.0	1.0	PhC≡CCHO	2.2:1	67

er, enantiomeric ratio; NA, not available.

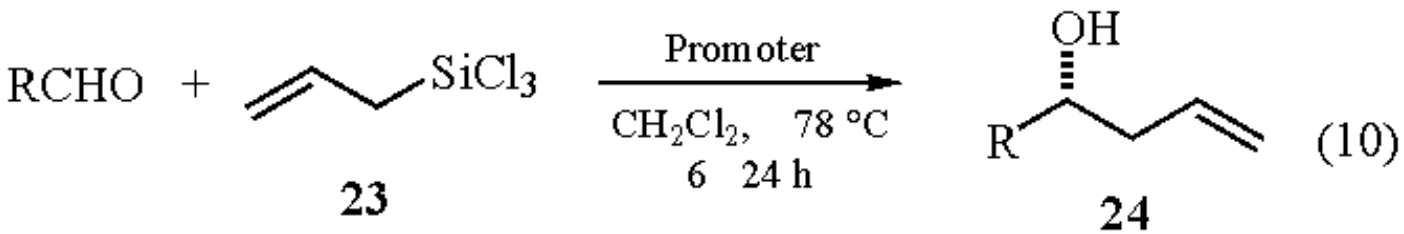

The phosphoramide-catalyzed allylic additions to aldehydes have also been extended to include stereoselective crotylations. When using geometrically defined 2-butenyltrichlorosilanes, additions to benzaldehyde afford homoallylic alcohols in good yields and excellent diastereoselectivity (11).[21a] Enantioselectivities, however, remain comparable to the results for allylic additions. Interestingly, the crotylation results suggest that addition proceeds through a cyclic transition structure.[23]

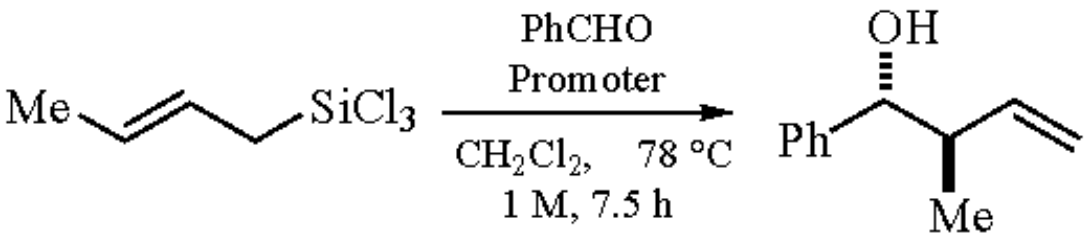

(*E*)-**25** >99:1 | 68% (98:2 *anti*/*syn*) 4.9:1 er (*anti*) | (1*R*,2*R*)-**26**

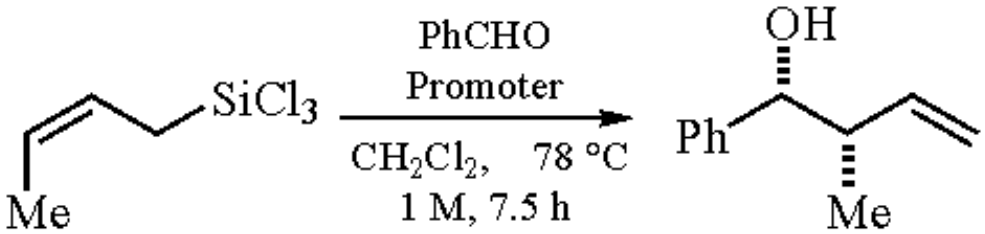

(11)

(*Z*)-**25** >99:1 | 72% (98:2 *syn*/*anti*) 4.0:1 er (*syn*) | (1*R*,2*S*)-**26**

Epoxide openings using $SiCl_4$

The binaphthyldiamine-derived phosphoramide (*R*)-**4** is an effective catalyst for the opening of various epoxides with $SiCl_4$ to afford chlorohydrins in high yields.[24] The rate and stereoselectivity for the ring opening of *meso*-epoxides are extremely dependent upon the structure of the epoxide. In the examples shown for epoxycycloalkanes, only cyclohexene oxide [10 mol % (*R*)-**4**] affords a chlorohydrin in high yield and good enantioselectivity (12, Table 10, entry 2). In contrast, cyclopentene oxide and cyclooctene oxide give essentially racemic chlorohydrin (12, Table 10, entries 1 and 3) with cyclooctene oxide requiring more than 5 days for complete reaction. In comparison to the cyclic epoxides, the acyclic substrates afford chlorohydrins with increased enantioselectivities (12, Table 10, entries 4 and 5). In a typical procedure, a solution of epoxide in CH_2Cl_2 is added to a mixture of $SiCl_4$ and phosphoramide at -78 °C in CH_2Cl_2. To avoid opening of epoxides by adventitious HCl,[25] it is essential to maintain $SiCl_4$ acid free.[26]

Table 10 Stereoselective ring opening of *meso*-epoxides catalyzed by (*R*)-**4**

Entry	Epoxide (R)	Time (h)	er	Yield (%)
1	$-(CH_2)_3-$	0.3	1.16:1	87
2	$-(CH_2)_4-$	0.3	3.13:1	90
3	$-(CH_2)_6-$	132	1.04:1	95
4	Ph	3	14.4:1	94
5	$BnOCH_2$	4	5.94:1	95

er, enantiomeric ratio.

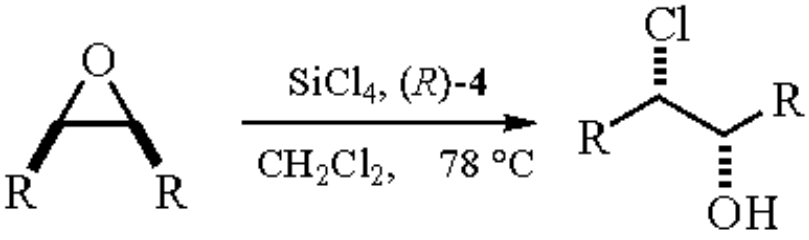

27 **28** (12)

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(-)-*endo*-Bornyltriazolinedione

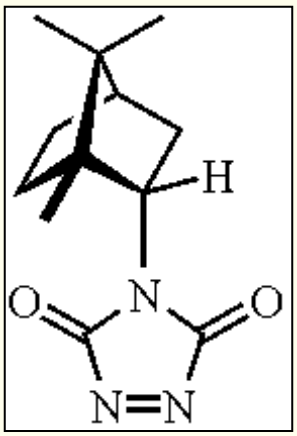

[73462-83-6] · $C_{12}H_{17}N_3O_2$ · (235.29)

(reagent used in cycloaddition reactions[1] as a dienophile of high reactivity for the trapping of unstable intermediates,[2,3] and 1,3-dienes,[4] the preparation of optically active axially symmetric molecules,[5] and the resolution of hydrocarbons and chiral dienes[6,7])

Alternate Name: 4-(1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)-[1,2,4]triazole-3,5-dione.

Physical Data: mp 152-154 °C; sublimation point 75-85 °C at 0.1 Torr; $[\alpha]^{20}_{D}$ -77 (*c* 5.7, CH_2Cl_2)

Form Supplied in: red solid prepared from optically pure *d*-camphor oxime[8] in a five-step sequence (1): reduction with sodium in *n*-amyl alcohol followed by fractional recrystallization of the resulting hydrochloride salts of bornylamines[9,10] gives the *endo*-isomer in enantiomerically pure form; treatment with phosgene and direct condensation of the isocyanate with (ethoxycarbonyl)hydrazine gives a compound which cyclizes upon treatment with base; subsequent nitrogen dioxide oxidation furnishes (-)-*endo*-bornyltriazolinedione as a red crystalline solid.[11-13]

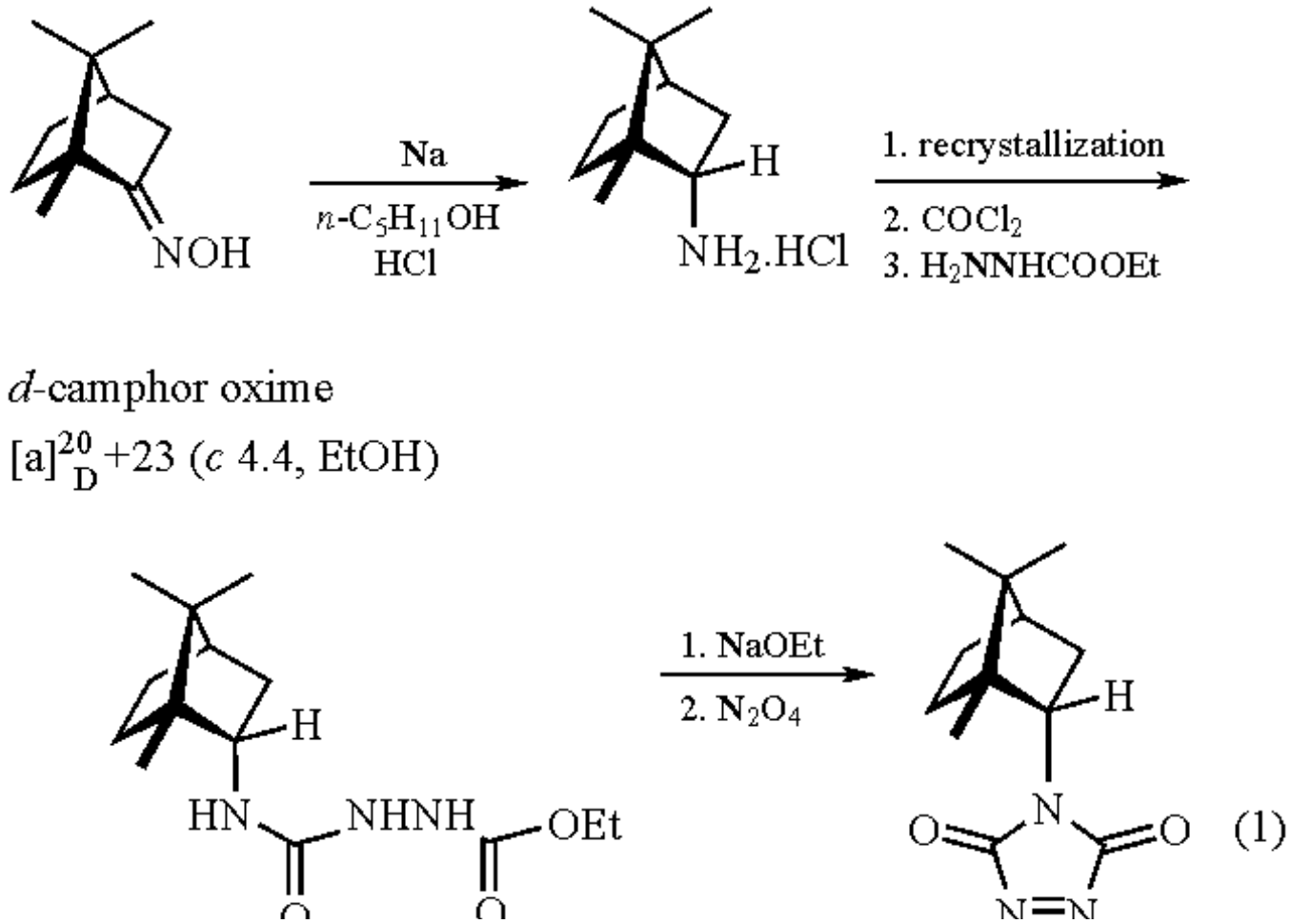

Form Supplied in:

Handling, Storage, and Precautions: stable for prolonged periods when stored cold in the absence of light; easy to handle; solid.

The main interest in (-)-*endo*-bornyltriazolinedione resides with its high dienophilic character in cycloaddition processes to yield separable mixtures of diastereoisomeric urazoles. The non-destructive resolution of cyclooctatetraenes, which allows direct access to optically pure derivatives, is a typical illustration and has been amply demonstrated.[14-19] Typically, (-)-*endo*-bornyltriazolinedione is heated with racemic 1,2,3-trimethylcyclooctatetraene in ethyl acetate to afford a mixture of diastereoisomeric adducts, which can be separated by fractional recrystallization from ethyl acetate and hexane. HPLC is an alternative separation technique leading to both enantiomerically pure antipodes. The chiral auxiliary is subsequently removed by basic hydrolysis-manganese dioxide oxidation to afford the optically pure cyclooctatetraenes (2).

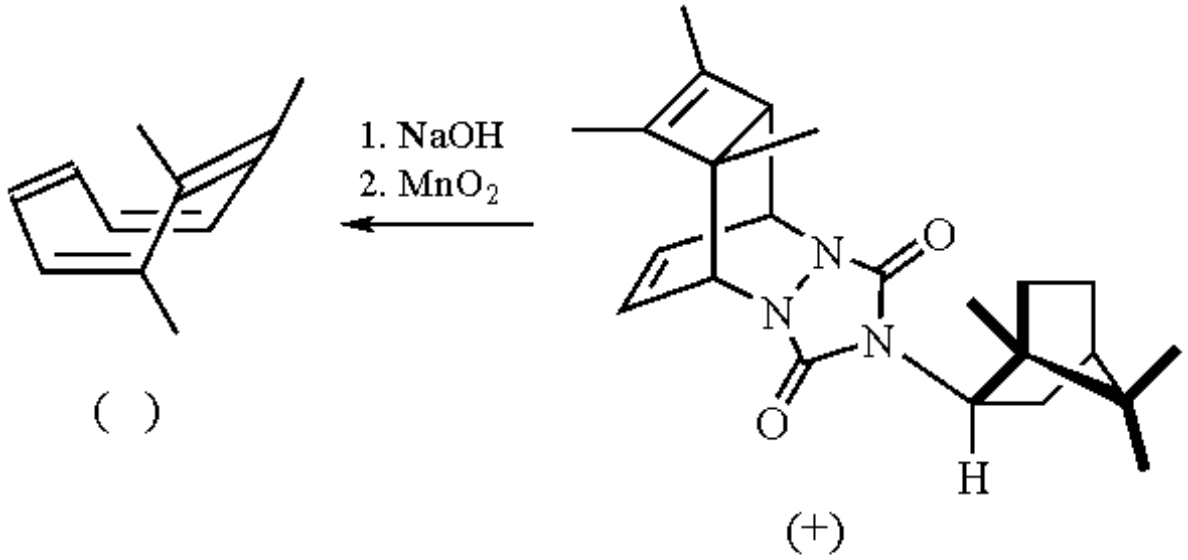

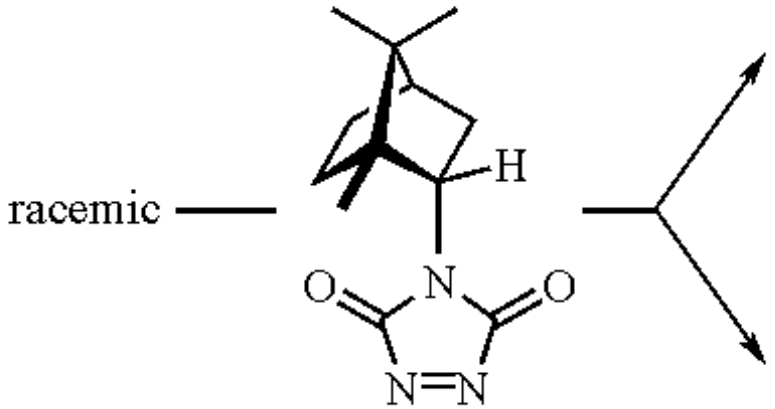

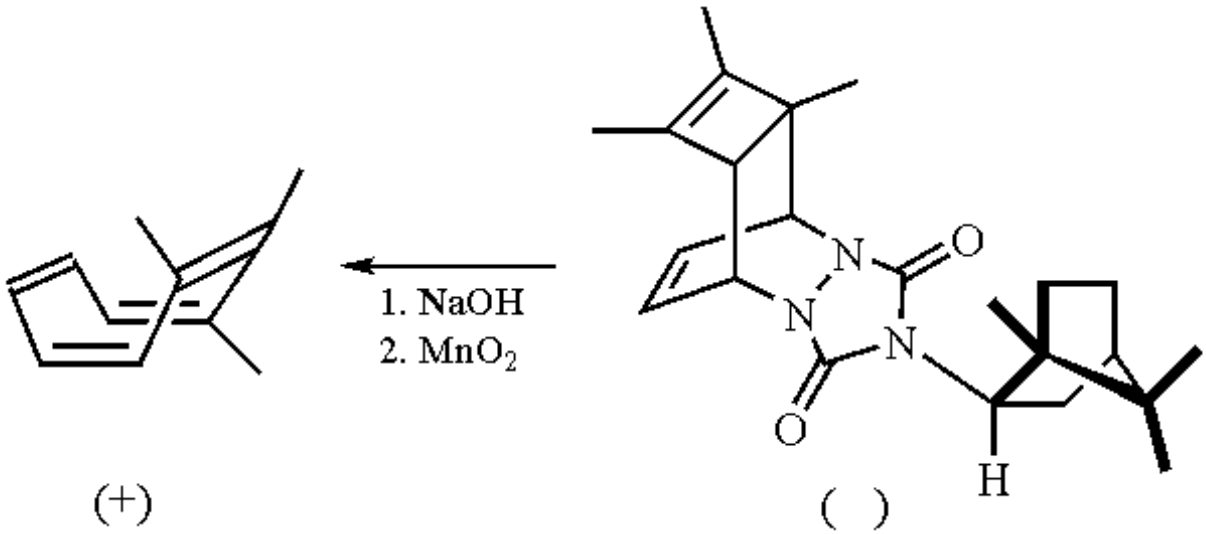

(2)

This method of resolution of polyolefins has been extensively studied for cyclooctatetraene systems where excellent enantiomeric excesses are normally observed. Lanthanide-induced shifting can be used to determine the diastereoisomeric composition of the urazoles.[14] Alternate means

for the resolution of polyenes based on kinetic resolution using (+)-tetra-2-pinanylborane have been described,[20,21] but this reagent consumes valuable substrate. Chiral platinum complexes[22] can also be used but at prohibitive cost on a large scale and with poor regioselectivity when several coordination sites are present.

The utilization of an optically active triazolinedione for asymmetric transfer has also led to the preparation of enantiomerically pure polycyclic hydrocarbons. The method provides a straightforward means for introducing optical activity into chiral propellanes that possess a conjugated diene unit. Racemic propellane[5] reacts with (-)-*endo*-bornyltriazolinedione in ethyl acetate at -78 °C to give, after HPLC separation, the two optically pure urazoles. Subsequent reduction with lithium aluminum hydride affords the two propellanes in enantiomerically pure form (3).

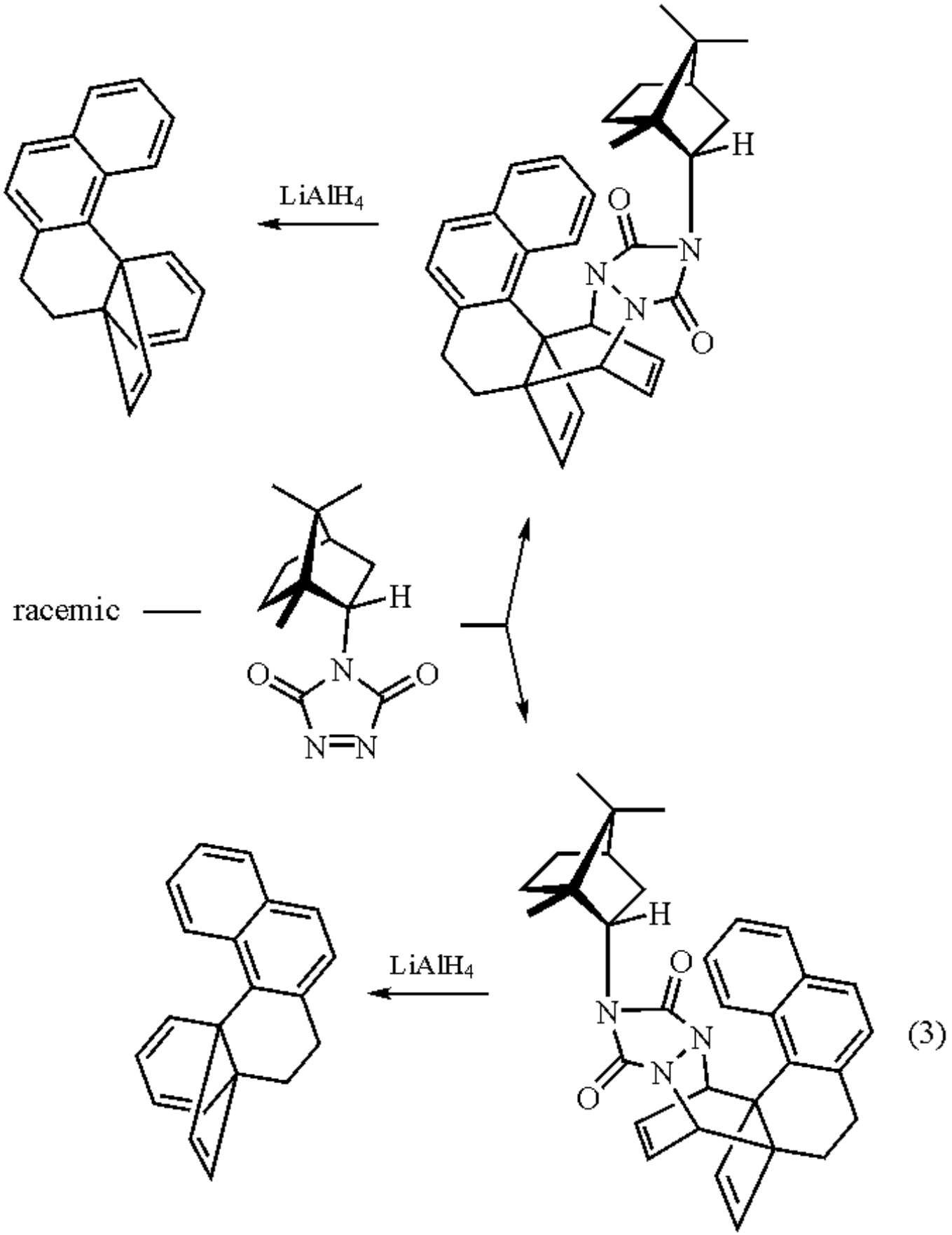

From a purely synthetic viewpoint, triazolinedione adducts have served as substrates for gaining access to numerous target molecules such as prismane,[23] semibullvalene,[24] bridged semibullvalenes,[25] elassovalene,[26] caged compounds,[27] and azoalkanes. Indeed, the title reagent can be used not only as a chiral source, but also as an azo donor. In the synthesis of 4,5-diazatwis-4-ene,[28] for example, (-)-*endo*-bornyltriazolinedione was a pivotal reactant that allowed incorporation of the azo unit in addition to providing a means for resolution. The first step involved cycloaddition to cyclooctatetraene dibromide with formation of a separable mixture of diastereoisomers. Eventual removal of the chiral moiety in a modified hydrolysis-oxidation sequence yielded the desired azo compound (4).

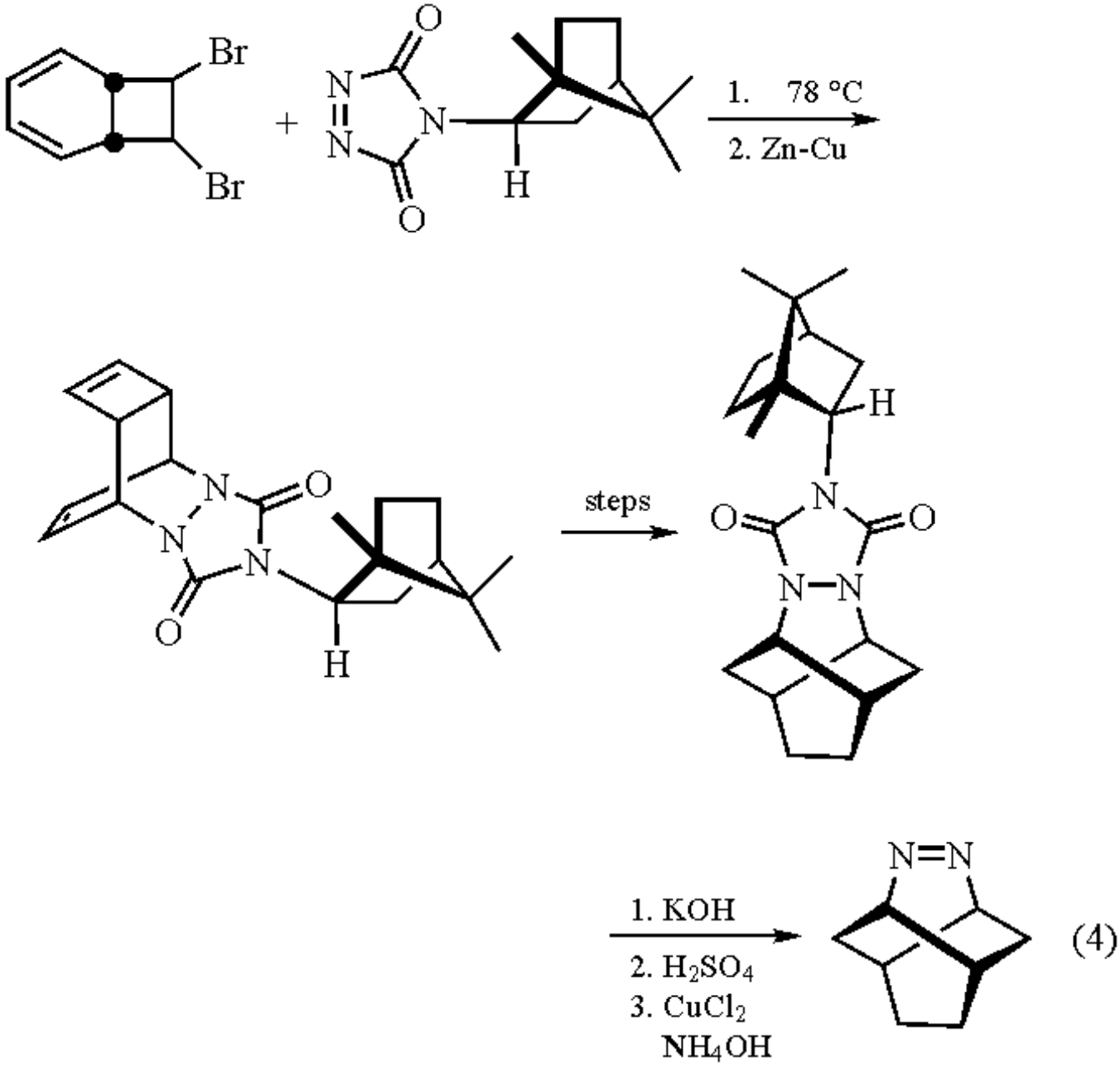

The high crystallinity of the urazole obtained by cycloaddition has also made (-)-*endo*-bornyltriazolinedione a useful reagent for obtaining crystalline derivatives. Diels-Alder cycloaddition of (-)-*endo*-bornyltriazolinedione to a diene of unknown configuration resulted in the formation of a single cycloadduct[4] whose structure was confirmed by X-ray diffraction analysis of the urazole (5).

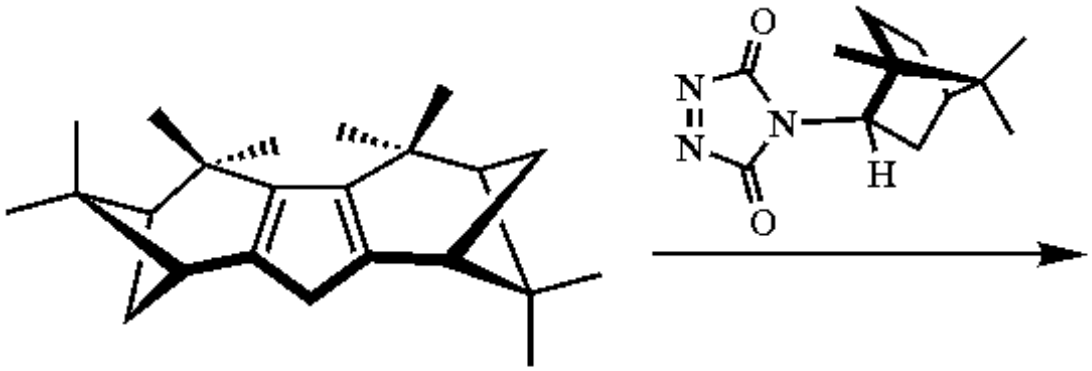

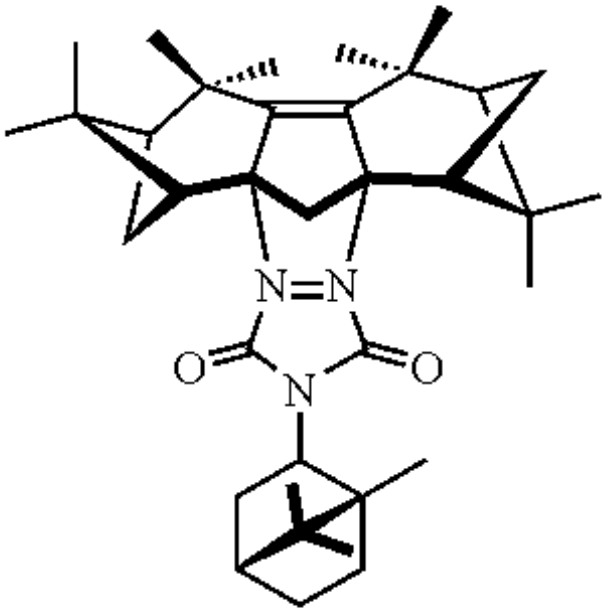

(5)

X-ray structure

Applications of (-)-*endo*-bornyltriazolinedione to asymmetric synthesis in cycloaddition reactions have shown low levels of induction. In the examples studied, (-)-*endo*-bornyltriazolinedione reacted almost instantaneously with various dienes even at low temperature (<96 °C) resulting in low asymmetric induction (<10%).[29] The high reactivity of triazolinedione in [4+2] π-cycloadditions due to its high dienophilicity minimized differentiation between the transition states and has to date impeded its use in asymmetric synthesis.

Related Reagents.

4-phenyl-1,2,4-triazoline-3,5-dione; (-)-(α)-(methylbenzyl) triazolinedione; (dehydroabiethyl)triazolinedione; (+)-tetra-2-pinanylborane; chiral platinum complexes.

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(*R*)-*B*-Methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine

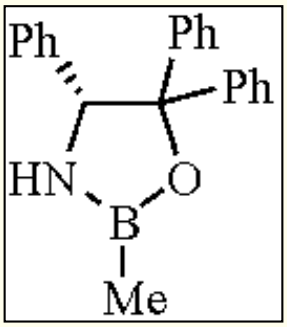

[155268-88-5] · $C_{21}H_{20}BNO$ · (313.21)

(catalyst used for the borane-mediated stereoselective reduction of ketones)

Solubility: soluble in most organic solvents, e.g. THF, diethyl ether, $CHCl_3$, toluene.

Analysis of Reagent Purity: ^1H NMR (C_6D_6).

Preparative Methods: (*R*)-1,1,2-Triphenyl-2-aminoethanol, the precursor of the oxazaborolidine, is prepared in 60-73% yield by portionwise addition of solid methyl (*R*)-phenylglycinate hydrochloride to an excess of **phenylmagnesium bromide** (3 M in diethyl ether) at 0 °C. The amino alcohol (>99% ee, after recrystallization from ethanol) is treated with trimethylboroxine in refluxing toluene in a flask provided with a Dean-Stark trap and under argon. Removal of all the volatiles under vacuum gives (*R*)-*B*-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine [(*R*)-**1**]as a colorless oil, which is then diluted with toluene up to a known concentration.[1]For reductions, a sample of that solution is transferred via cannula to another flask and the solvent is removed under vacuum and replaced by THF under argon. (*S*)-*B*-Methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine [(*S*)-**1**] can be obtained from methyl (*S*)-phenylglycinate hydrochloride in a similar way. Both enantiomers of methyl phenylglycinate hydrochloride are commercially available at moderate prices.

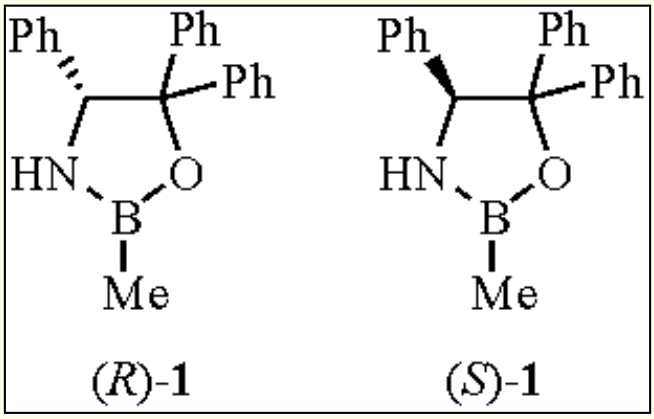

Purification: Occasionally in the ^1H NMR spectrum of the oxazaborolidine (C_6D_6), besides the expected signal at δ 5.38 ppm, a singlet at δ 4.93 ppm can be observed which is due to hydrolyzed, ring-cleaved material. The product may be purified by further treatment with a small amount of trimethylboroxine in refluxing toluene.

Handling, Storage, and Precautions: This oxazaborolidine is sensitive to water and to oxygen. However, its toluene solution can be stored at room temperature under argon for months with negligible loss of its catalytic activity. Care should be exercised to avoid contact of this compound with eyes and skin, and it should be manipulated in a well-ventilated fume hood.

Enantioselective Ketone Reduction

After the pioneering work of Itsuno et al.,[2] Corey's group isolated the 1,3,2-oxazaborolidine derived from chiral **α,α-diphenyl-2-pyrrolidinemethanol** (**2**) and applied it (and also other related *B*-alkyl compounds) to the stereoselective reduction of ketones with **borane-**

tetrahydrofuran, **borane-dimethyl sulfide** (BMS) or **catecholborane.**It was named the CBS method (after Corey, Bakshi, and Shibata).[3] Since then, the CBS method has become a standard and has been extensively used, specially for aromatic and α,β-unsaturated ketones, not only in academic laboratories but also in industrial processes.[4]

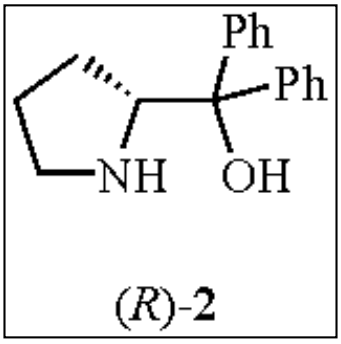

Among the diverse 1,2-amino alcohols described as precursors of oxazaborolidines,[5] the use of both enantiomers of highly enantioenriched 1,1,2-triphenyl-2-aminoethanol, which lead to oxazaborolidines (*R*)-**1** and (*S*)-**1**, is especially attractive as they arise from inexpensive (*R*)- or (*S*)-phenylglycine, respectively. Oxazaborolidines (*R*)-**1** and (*S*)-**1**are efficient catalysts in the borane-mediated stereoselective reduction of some types of prochiral ketones.

Typically, reductions are performed by slow addition (~15-30 min) of the ketone (1.0 mmol) to a solution of BMS (1.0 mmol) and 0.1-1.0 mmol of **1** (~1 M in THF) under argon at 0 °C (1). Yields are excellent in general after stirring for a further few minutes. The slow addition of ketone appears to enhance the stereoselectivity and in many cases causes the ee noted with 0.1 mmol of **1** to be similar or only slightly lower than that in the stoichiometric case.

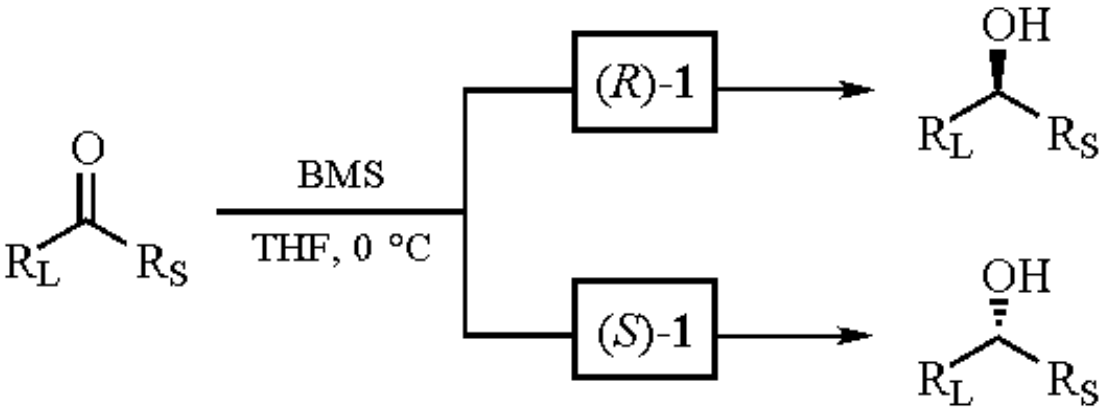

(1)

Alcohols **3**-**8**, obtained by the reduction of the corresponding ketones with equimolar amounts of BMS and (*R*)-**1**, are obtained with high ees (ee values given are obtained using 0.1 equiv of (*R*)-**1**). Enantioselectivity is excellent (often similar or only slightly lower than those reported in the CBS reduction) for aromatic and hindered methyl ketones,[1a,6] (e.g. **3**-**5**) and is also good for linear and α-monobranched enones[7] (e.g. **7** and **8**), but lower for linear methyl ketones like 2-octanone (**6**). In should be noted that in the reduction of unsaturated ketones, the time of addition is critical (the optimum being around 15-20 min) in order to avoid concomitant olefin hydroboration. In sharp contrast to the CBS process, the use of **catecholborane** (instead of BMS) or alternative solvents proved to be detrimental.

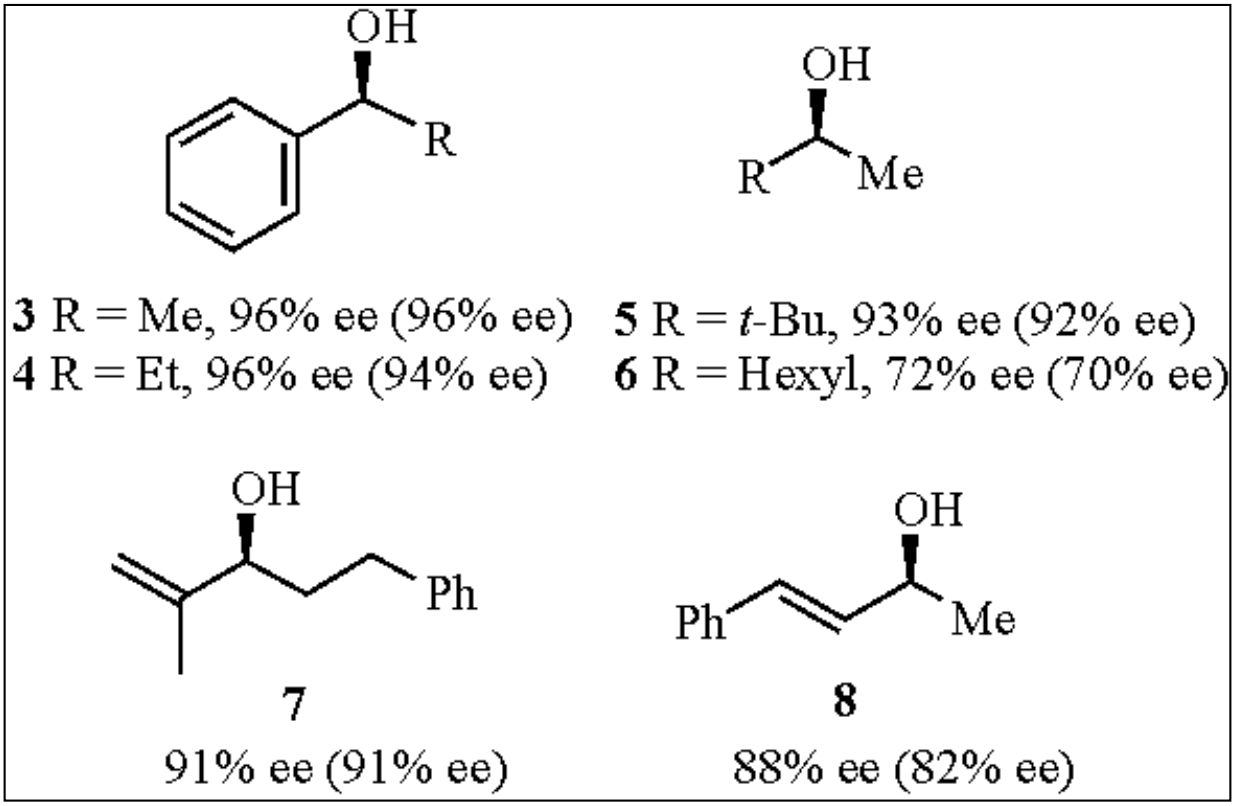

As far as the stereochemical course of the reaction is concerned, the configuration of the emergent stereocenter may be explained in terms of the mechanism proposed by Corey et al. for similar oxazaborolidine mediated reactions.[4] Thus, the transition state operates such that the bigger group (R_L) is located remotely from the methyl group on the boron atom (2).

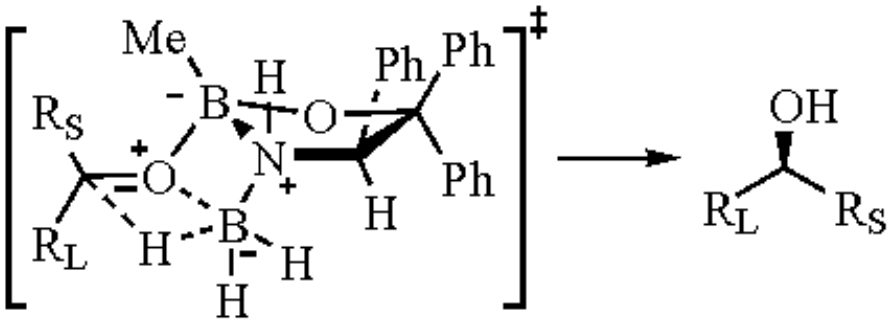

(2)

Accordingly, the experience gained with oxazaborolidine **1** suggests an order of 'empirical' size of R groups.[8] Obviously, better enantioselectivities in the reduction of the ketone carbonyl group are achieved when the substituents R_L and R_S are dissimilar.

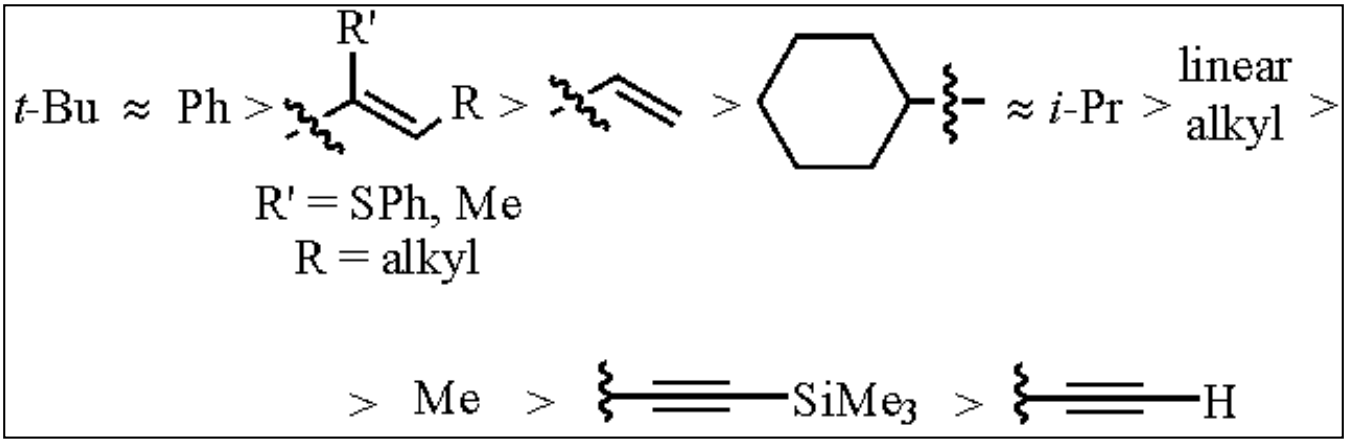

The reduction of α-phenylthio enones constitutes a recent application of these findings to the preparation of chiral α-hydroxy thioesters (3).[9]

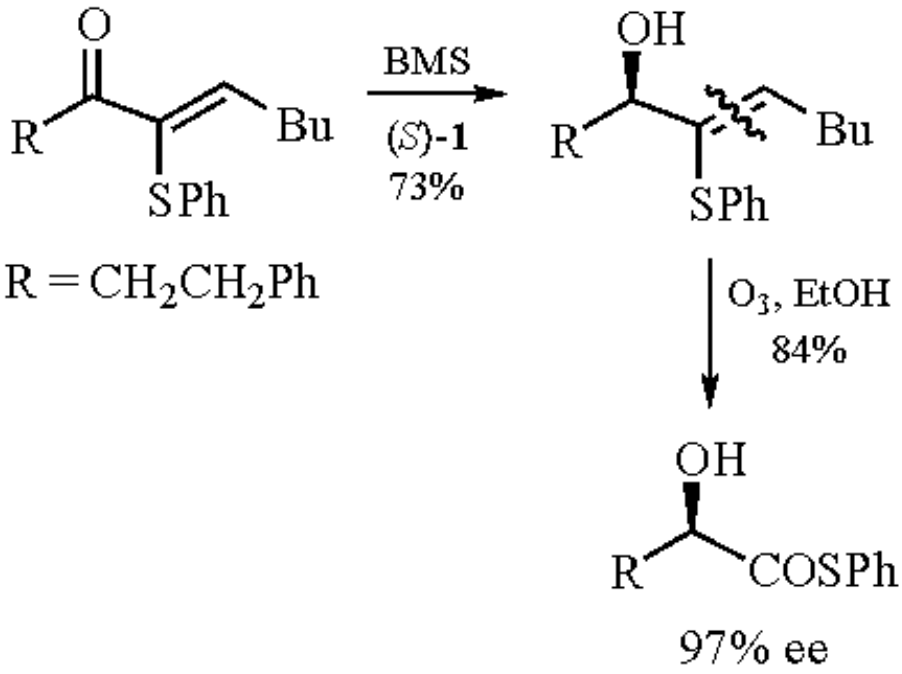

(3)

Reduction of Acetylenic Ketones

The enantioselective reduction of α,β-acetylenic ketones (R-CO-C&tbond;C-R´, R´ = H or TMS) with BMS and **1**affords the corresponding propargylic alcoholsin good to excellent yields and >90% ee (see eq 4 as and example).[1b] In some cases, the reductions of more sterically crowded hexacarbonyldicobalt complexes (e.g.**9**) derived from the acetylenic ketones also lead, after decomplexation with Cerium (IV) Ammonium Nitrate (CAN), to the same alcohols. However, the use of an oxazaborolidine with an α-face more available for complexation, such as those derived from commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol, is required (5).[10] Remarkably, the temporary transformation of the acetylenic moiety into its $Co_2(CO)_6$ complex, not only reverses the stereoselectivity in the reduction step, but also enhances it.

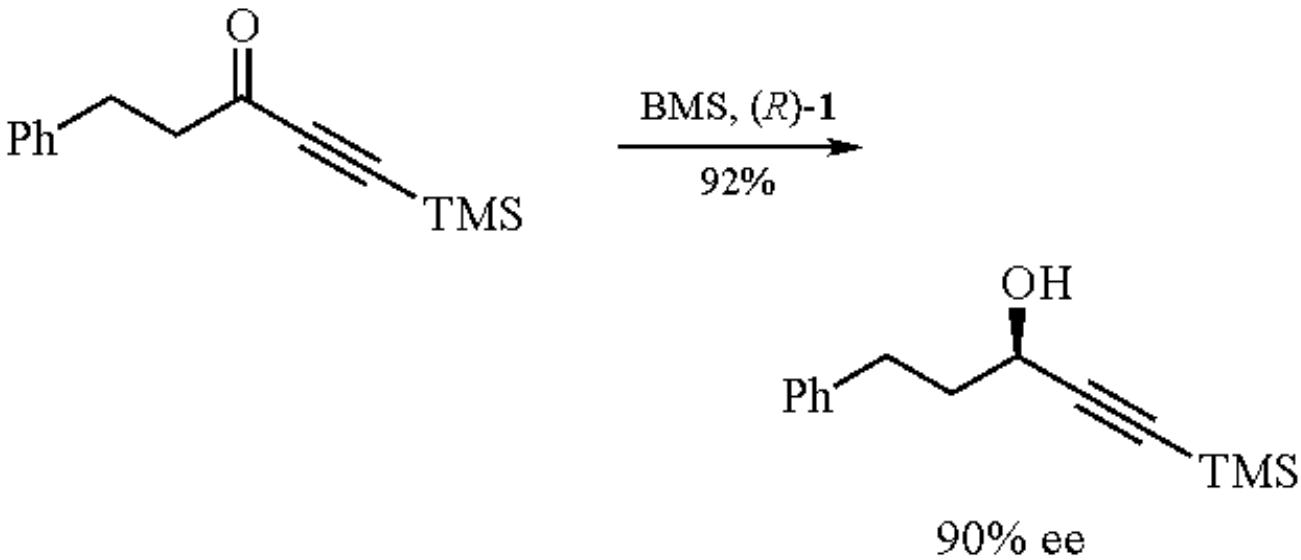

(4)

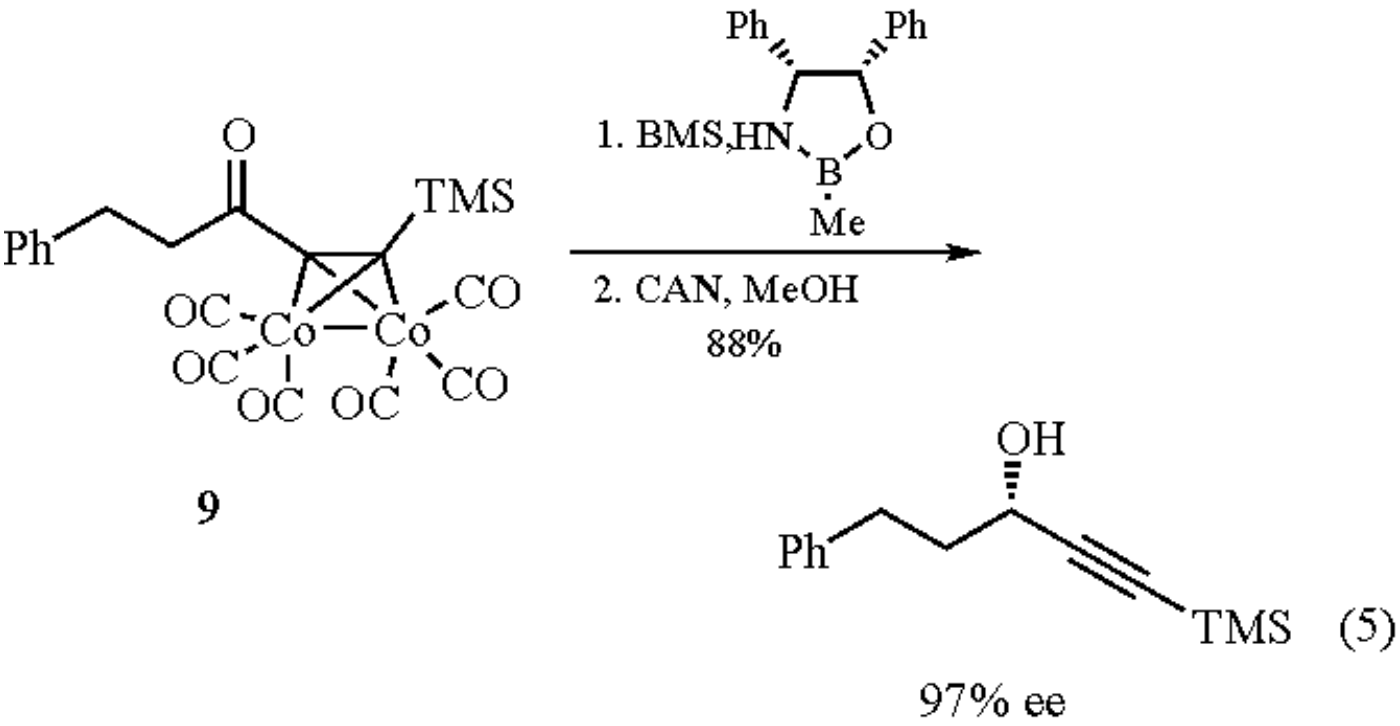

In addition, the highly enantioenriched propargylic alcohols obtained in such a way are versatile building blocks. Theyhave been applied to the syntheses of the alkyl side chains of zaragozic acids A and C,[11]several metabolites isolated from marine sponges,[12] and the octalactin A ring.[13]

On the other hand, the BMS/(*R*)- or (*S*)-**1** mixture is capable of displaying high asymmetric induction in the reduction of acetylenic ketones, thereby overriding the normally small diastereofacial selectivity of a chiral α-substituted 1-trialkylsilyl-1-alkyn-3-one (e.g. **10**) in a predictable and controlled manner (reagent control) (6). Remarkably, the stereoselectivity noted in such reductions has shown strong dependence upon the steric requirement of the C(1) substituent. Thus, an increasing stereoselectivity has been noted in the reduction of ketones **10**as R changes from Me to Et to *i*-Pr. An explanation for such an unexpected remote effect has been suggested based on abinitio calculations.[14]

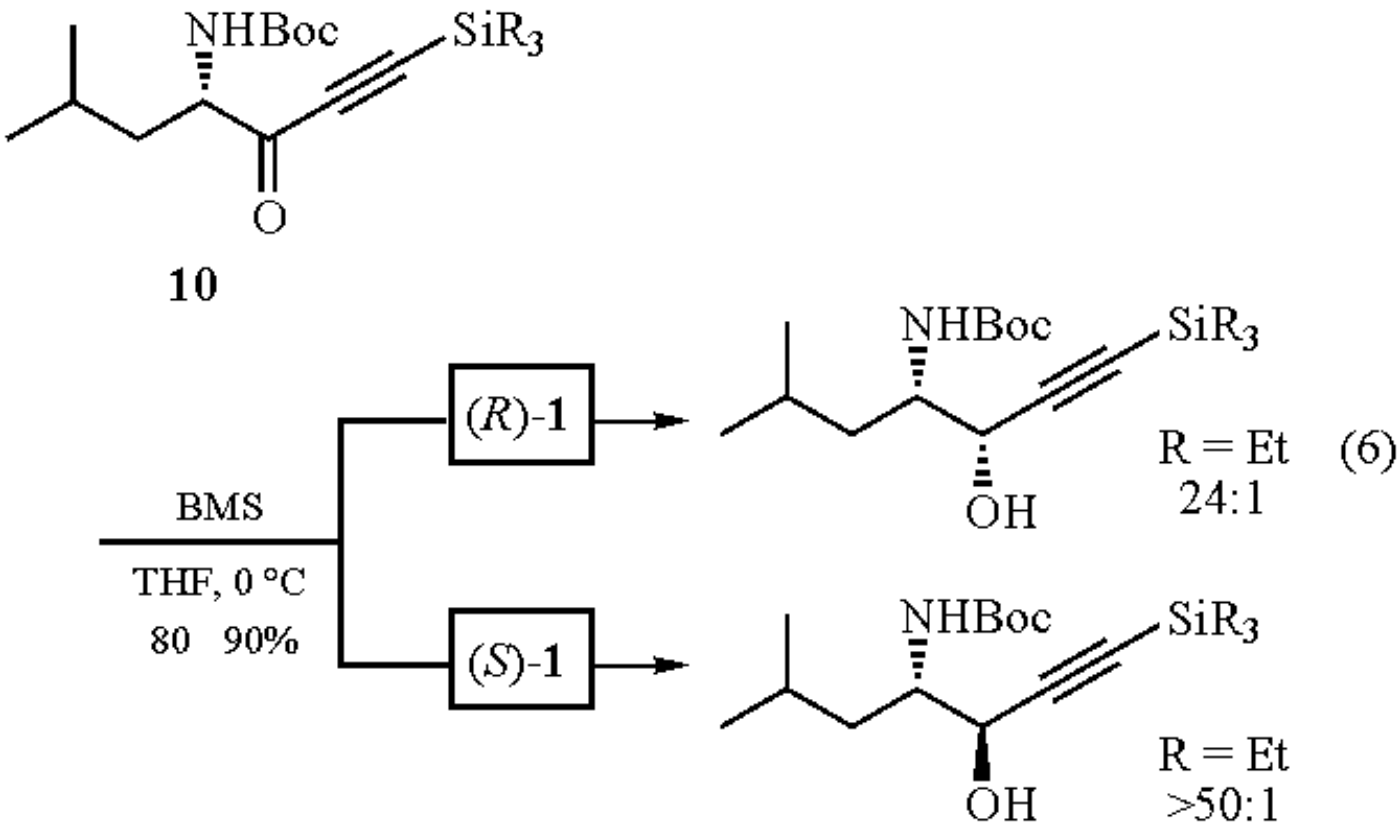

Further work according to this double asymmetric strategy has led to the establishment of a stereodivergent route to β-hydroxy γ-substituted carboxylic acids and α-hydroxy β-substituted carboxylic acids (including *N*-Boc-statine and *N*-Boc-norstatine).[15]

Reduction of 1,4-Diketones

Synthetic access to C_2-symmetric 1,4-diols, useful building blocks for the preparation of chiral 2,5-disubstituted pyrrolidines and phospholanes, involves reduction of the parent 2-alkane-1,4-diones, or, even better, reduction of the related (*E*)-alk-2-ene-1,4-diones (**11**) (7) or 2-alkyne-1,4-diones (**12**) (8), followed by catalytic hydrogenation.[16]

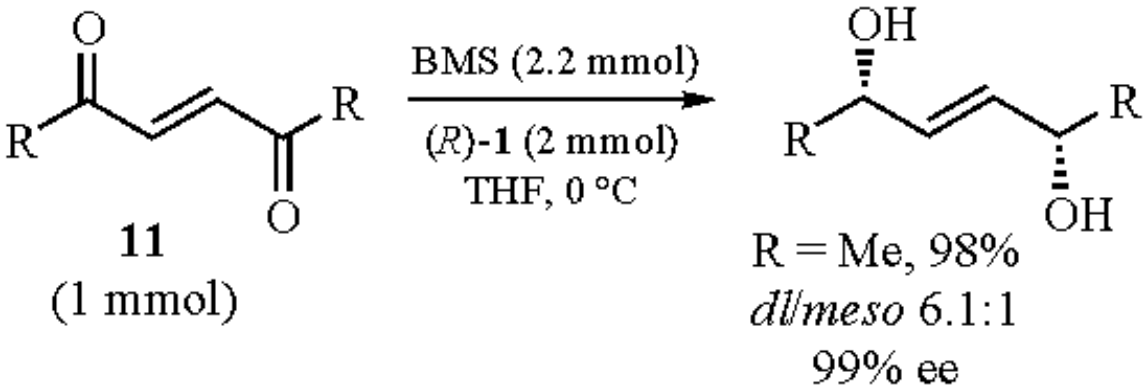

(7)

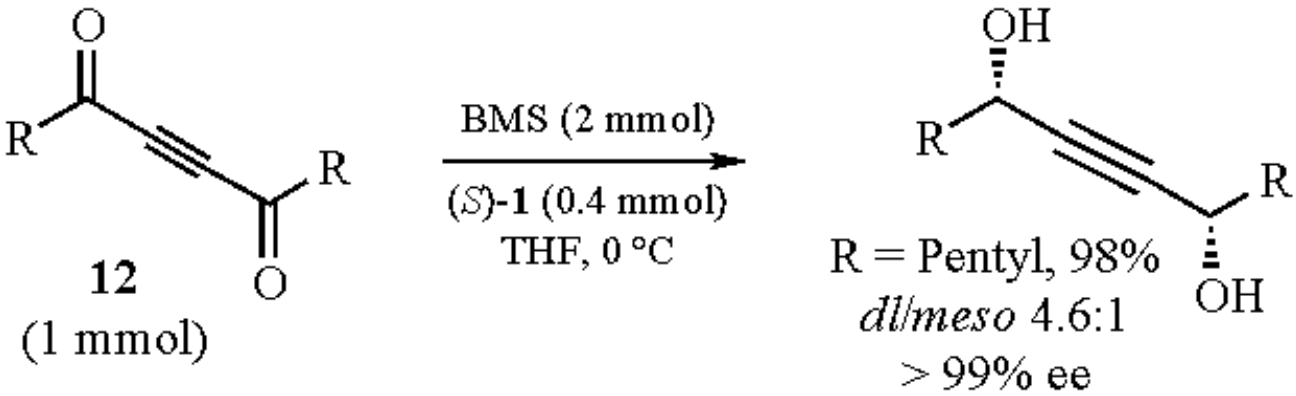

(8)

Generally, reduction of diketones **12** (or in some cases their hexacarbonyldicobalt complexes) yields better stereoselectivities than the related ethylenic diketones **11**, especially when R is a sterically demanding group. In addition, the propargylic diols obtained can be easily transformed not only into the saturated 1,4-diols, but also into (*Z*)- or (*E*)-alk-2-ene-1,4-diols. The C_2-symmetric allylic 1,4-diols have been very recently used as building blocks in a formal synthesis of (-)-methylenolactocin and (-)-phaseolinic acid.[17]Related to this, it should be noted that reduction of the unstable (*Z*)-alk-2-ene-1,4-diones (**13**) is an unsuitable route to (*Z*)-alk-2-ene-1,4-diols since a considerable amount of 1,4-reduction (9) is also observed.[17,18]

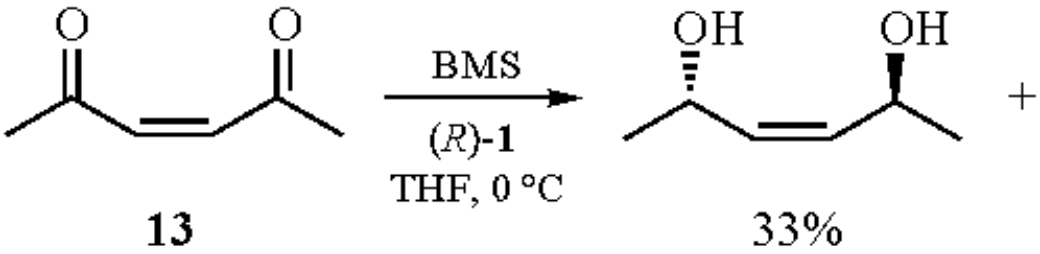

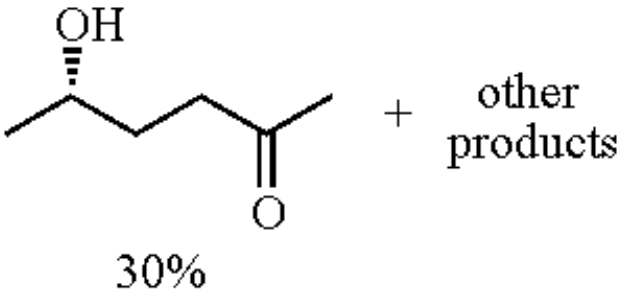

(9)

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S-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium Hexafluorophosphate (HOTT)

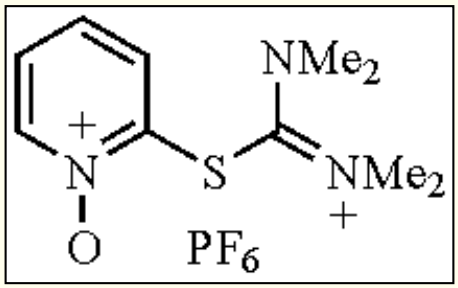

[212333-72-7] · $C_{10}H_{16}N_3OSPF_6$ · (371.28)

(reagent used to convert carboxylic acids into Barton esters and for peptide coupling/amidation)

Physical Data: mp 115-116°C.

Solubility: acetonitrile, CH_2Cl_2, THF (moderate solubility).

Form Supplied in: white solid.

Purification: recrystallized from CH_2Cl_2.

Handling, Storage, and Precautions: it is advised to protect the solid from prolonged exposure to light since 2-mercaptopyridine *N*-oxide and related compounds can be light-sensitive.

Preparative Methods: the title reagent can be prepared by slowly adding Et_3N to a dry CH_2Cl_2 solution of 2-mercaptopyridine-*N*-oxide and tetramethylchloroformamidinium hexafluorophosphate.[1] After removal of CH_2Cl_2 from the reaction mixture, the resulting solid mass is pulverized, washed with $CHCl_3$, and then filtered to give a white solid of sufficient purity to be used in subsequent reactions.[2]

Barton Esterification: Reductive Decarboxylation

O-Acyl thiohydroxamates or Barton esters are useful precursors of carbon-centered radicals via thermolysis or photolysis.[3] Several different methods are available for converting carboxylic acids into Barton esters (eq 1).[4] These reactions generally proceed via the attack of a 2-mercaptopyridine-*N*-oxide salt on an activated carboxylic acid that has either been preformed (acid chloride, mixed anhydride) or generated in situ (with 1,3-dicyclohexylcarbodiimide or tri-*n*-butylphosphine +2,2´-dithiodipyridine-1,1´-dioxide). However, HOTT has the distinct advantages of (1) being easy to prepare and handle without the need for any special precautions, (2) facilitates efficient Barton esterification of carboxylic acids, and (3) simplifies subsequent work-up and purifications by avoiding the need to remove by-products like 1,3-dicyclohexylurea.

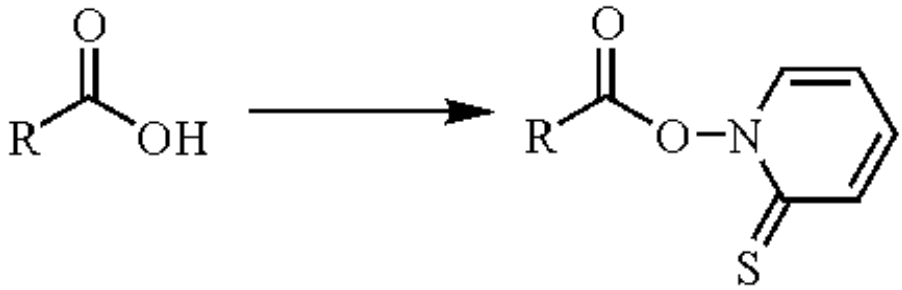

(1)

The HOTT reagent has been shown to significantly improve the yields of reductive decarboxylations of 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (eq 2) and peracetylated *N*-acetylneuraminic acid (eq 3).[2] In both cases, the yield of reduced product nearly doubled when HOTT was used to esterify these hindered carboxylic acids.

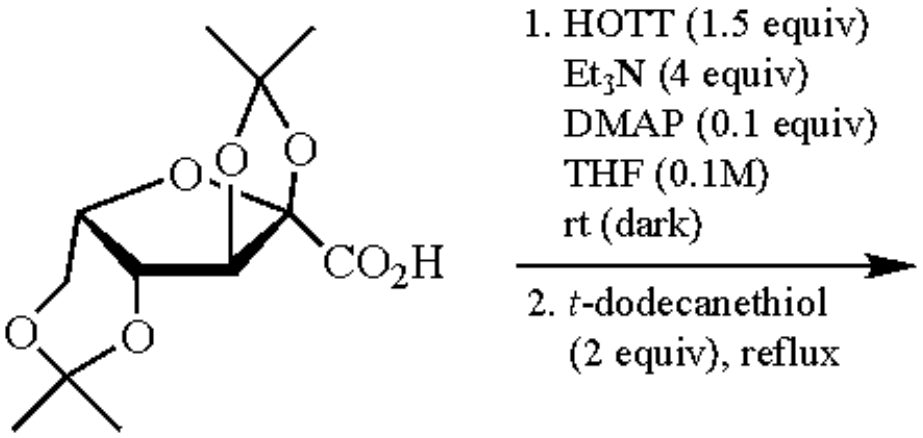

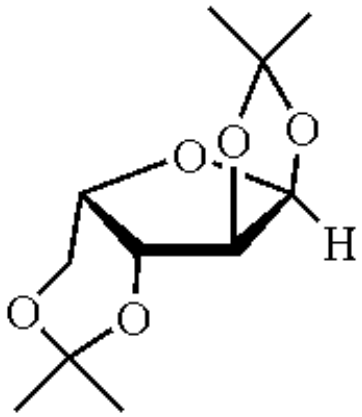

78% yield
(42% via acid chloride) (2)

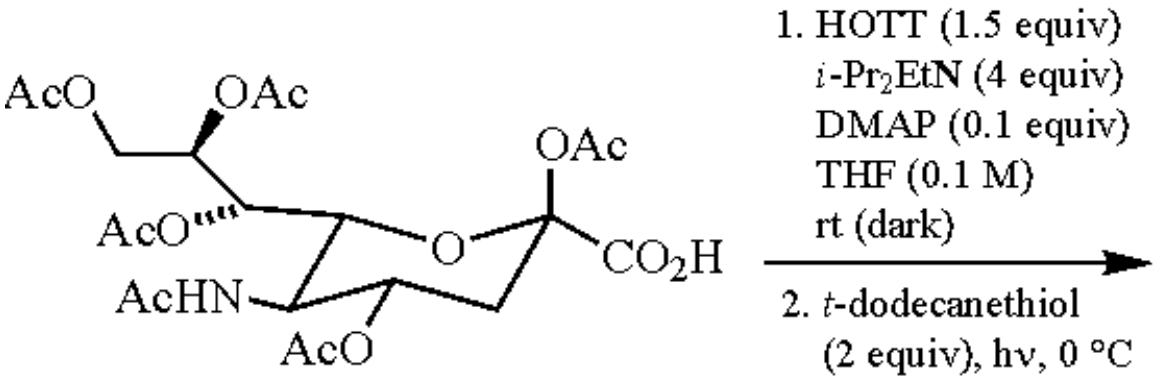

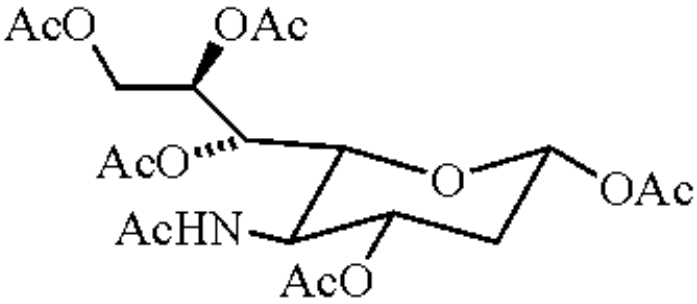

(3)

50% yield
(27% via carbodiimide)

Barton Esterification: Oxidative Decarboxylation

HOTT-mediated Barton esterification was coupled to oxidative decarboxylation in a synthesis of the sesquiterpene (+)-culmorin (eq 4).[5] Use of the HOTT reagent was clearly superior with this hindered substrate when compared with the acid chloride method.

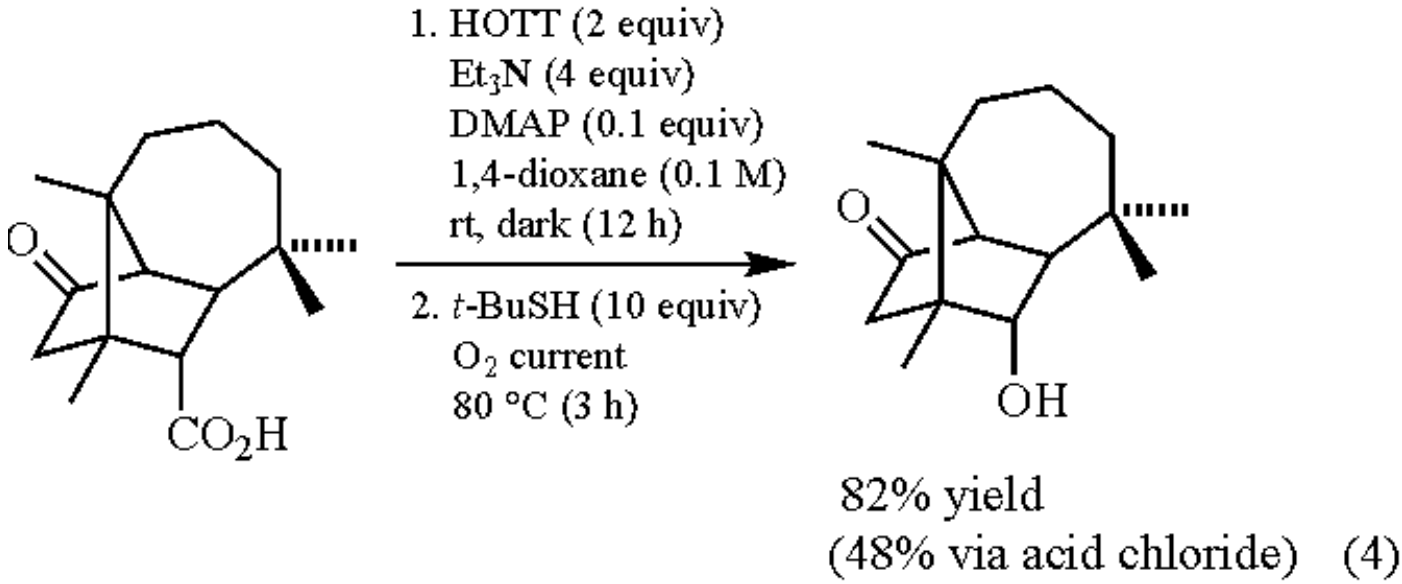

Barton Esterification: Radical Addition

One of the best examples illustrating the benefits of HOTT for this transformation is shown in eq 5. The Barton esterification of this very hindered acid was followed by IR spectroscopy by monitoring the disappearance of the carbonyl stretch of the acid (1740 cm^{-1}) and the appearance of the carbonyl stretch of the Barton ester (1810 cm^{-1}). Barton esterification using HOTT was complete within 20 min, whereas over 4 h was required when using the combination of DCC and 2-mercaptopyridine-*N*-oxide.

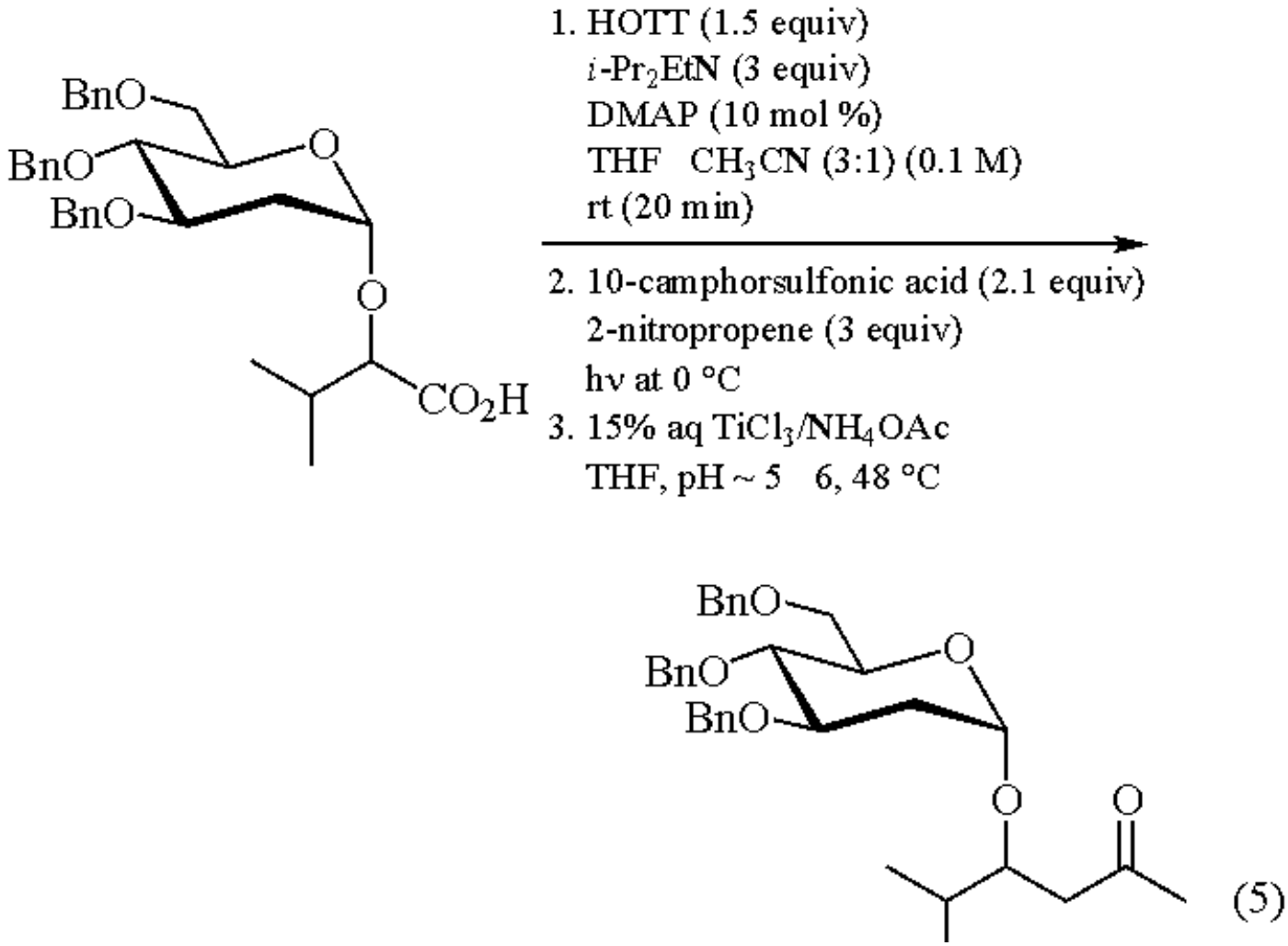

73% yield
(47% via carbodiimide)

HOTT was used to effect Barton esterification in a novel approach to 1, 3, 5,…(2*n*+1) polyols based on iterative stereocontrolled homologation of chiral hydroxyalkyl radicals (eq 6).[6]

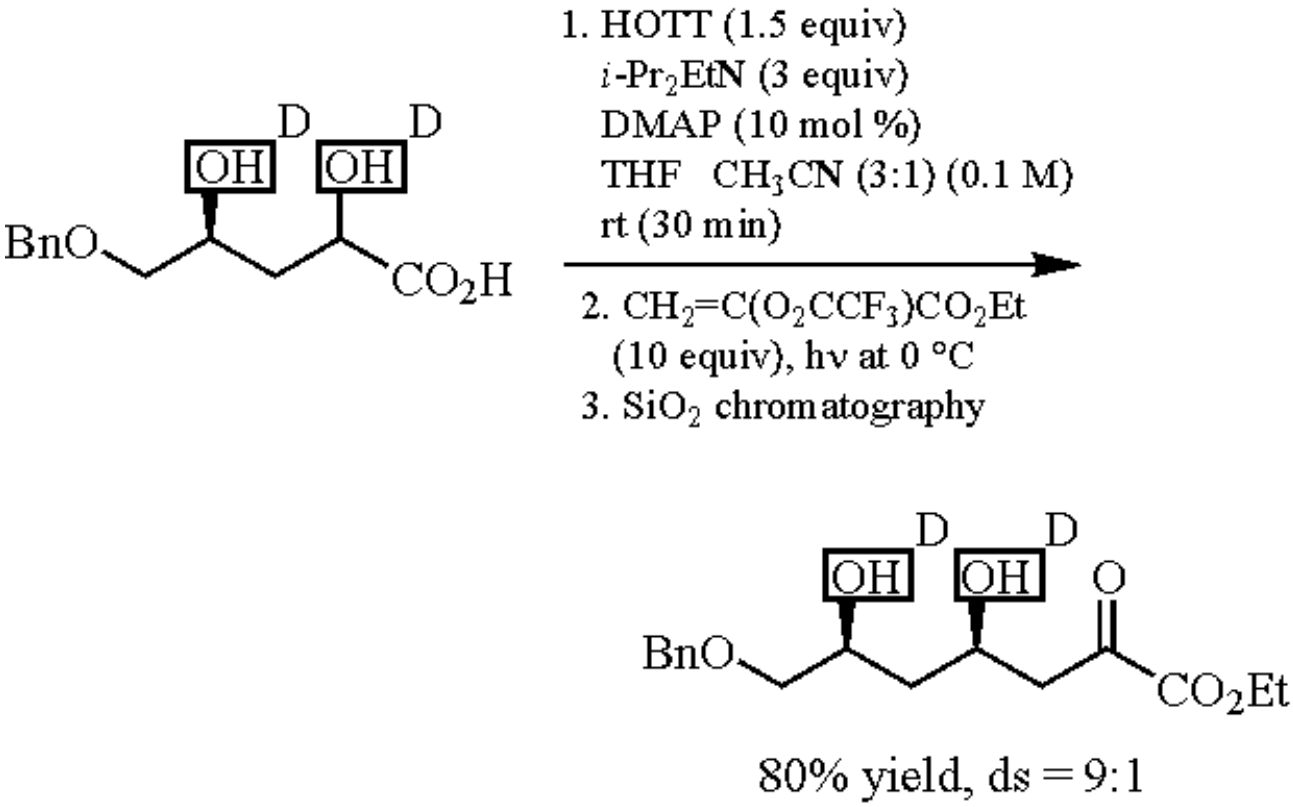

(6)

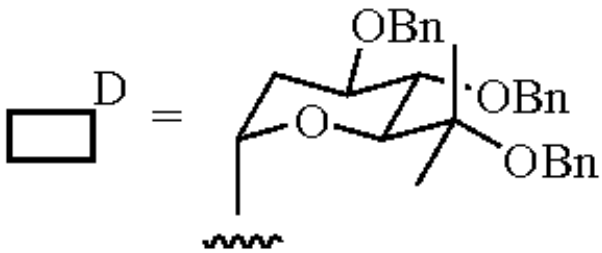

General notes: As with most Barton esterifications, the reaction should be performed in the dark and under anhydrous conditions.

Peptide Coupling

The HOTT reagent, as well as the corresponding tetrafluoroborate salt (TOTT), have also been reported to be inexpensive alternatives to uronium- and phosphonium-based peptide coupling reagents (eq 7).[7] Yields were generally on the same order as those observed with standard peptide coupling reagents. An advantage of these reagents -at least in some instances -may be a reduced propensity of the *N*-protected amino acid component to racemize during the coupling reaction.

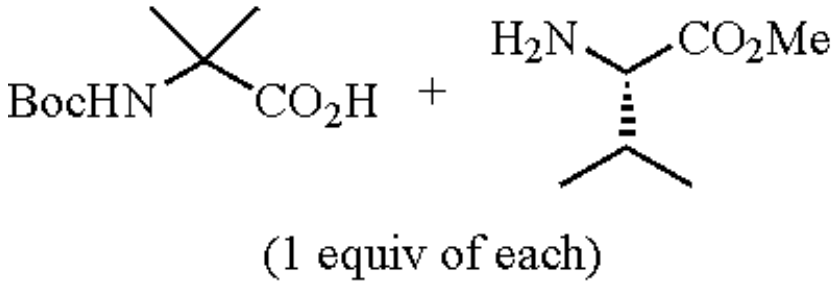

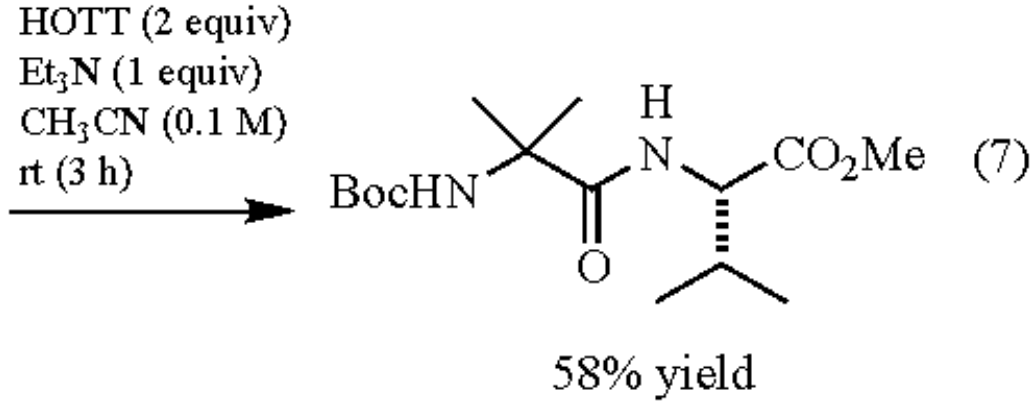

(7)

Synthesis of Primary Amides

Carboxylic acids can be converted to their primary amides using HOTT (or TOTT) as the coupling agent (eq 8 and 9).[8] The reaction conditions are very mild and do not adversely affect other functionality prone to nucleophilic attack by ammonia. A simple extractive work-up is sufficient to obtain the primary amides in pure form.

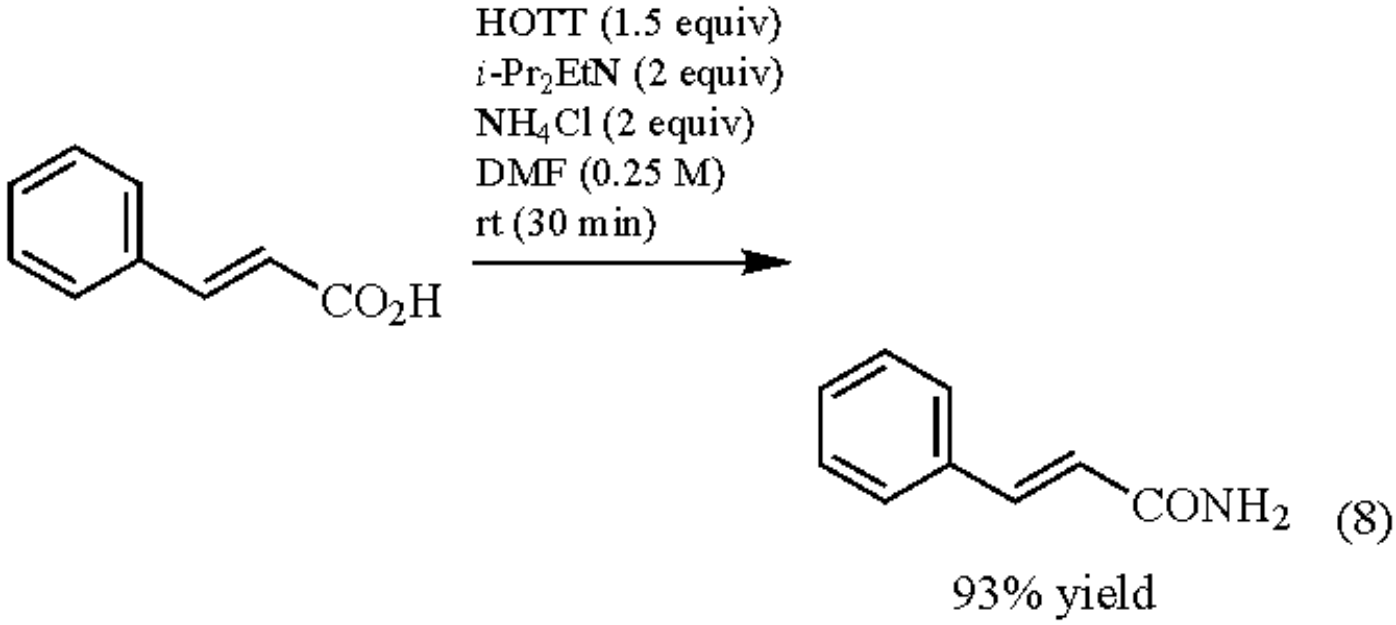

(8)

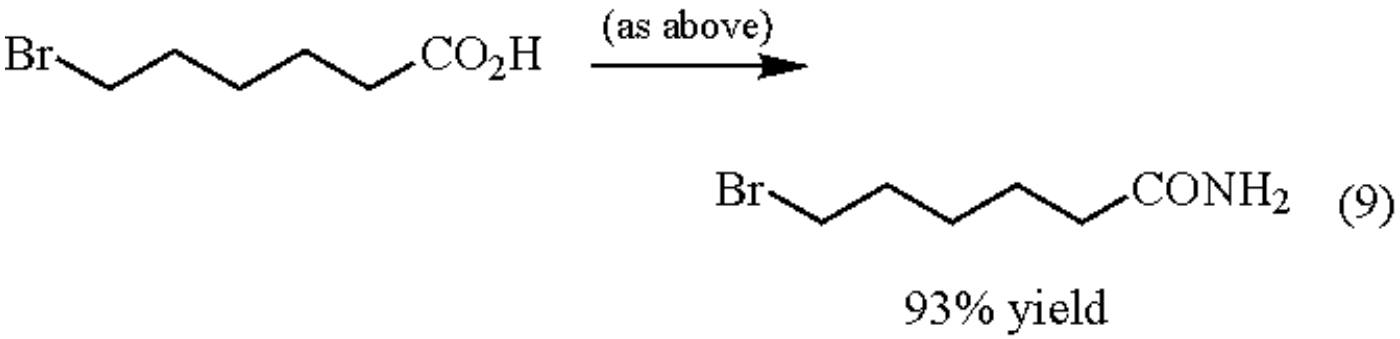

(9)

1. Dourtoglou, V.; Gross, B.; Lambropoulou, V.; Zioudrou, C., *Synthesis* **1984**, 572.
2. Garner, P.; Anderson, J. T.; Dey, S.; Youngs, W. J.; Galat, K., *J. Org. Chem.* **1998**, *63*, 5732.
3. Crich, D., *Aldrichimica Acta* **1987**, *20*, 35.
4. Barton, D. H. R.; Samadi, M., *Tetrahedron* **1992**, *48*, 7083.
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8. Bailén, M. A.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C., *Tetrahedron Lett.* **2000**, *41*, 9809.

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Chloro[(1,2,5,6*H*)-1,5-cyclooctadiene] (*H*5-2,4-Cyclopentadiene-1-yl) Ruthenium

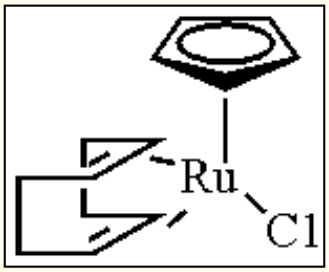

[97913-63-8] · $C_{13}H_{17}RuCl$ · (310)

(catalyzes the coupling reaction between alkenes and alkynes to yield Alder ene-type products)

Physical Data: air- and light-sensitive golden orange solid, mp 230-235°C.

Solubility: soluble in water and various organic solvents including alcohols, DMF and acetone.

Form Supplied in: readily synthesized in high yield.[1]

Cycloadditions

Chloro[(1,2,5,6*H*)-1,5-cyclooctadiene] (*H*5-2,4-cyclopentadiene-1-yl) ruthenium [CpRu(COD)Cl] catalyzes the cycloaddition of cyclooctadiene with a variety of alkynes to give the corresponding cycloadducts (eq 1).[2] Terminal alkynes also undergo this ruthenium-catalyzed cycloaddition process. The reaction is highly chemoselective. However, the presence of aromatic groups on the alkyne moiety greatly diminish the yield of the cycloadduct. Interestingly, hexa-1,5-diene and octa-2,6-diene do not undergo cycloaddition under similar conditions.

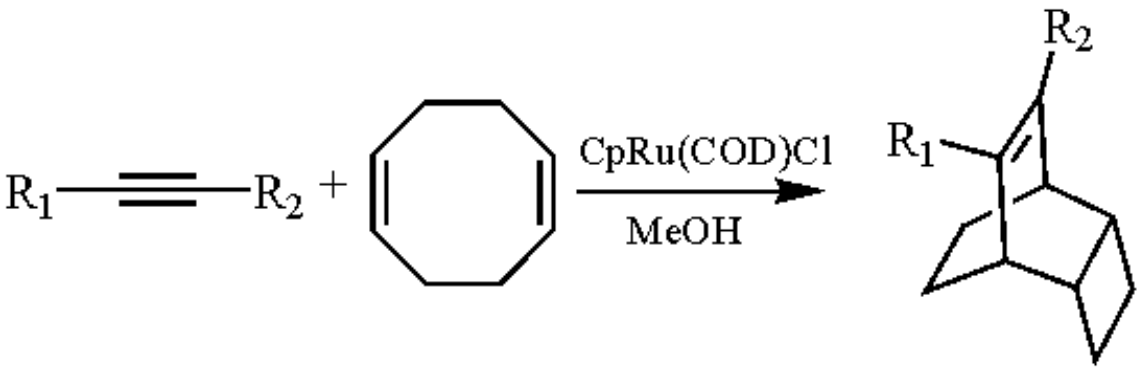

(1)

Sterically bulky alkynes undergo such cycloadditions, but at a much slower rate. This has been exploited in the cycloaddition of a diyne which cycloadds exclusively to the less sterically congested alkyne (eq 2).[2]

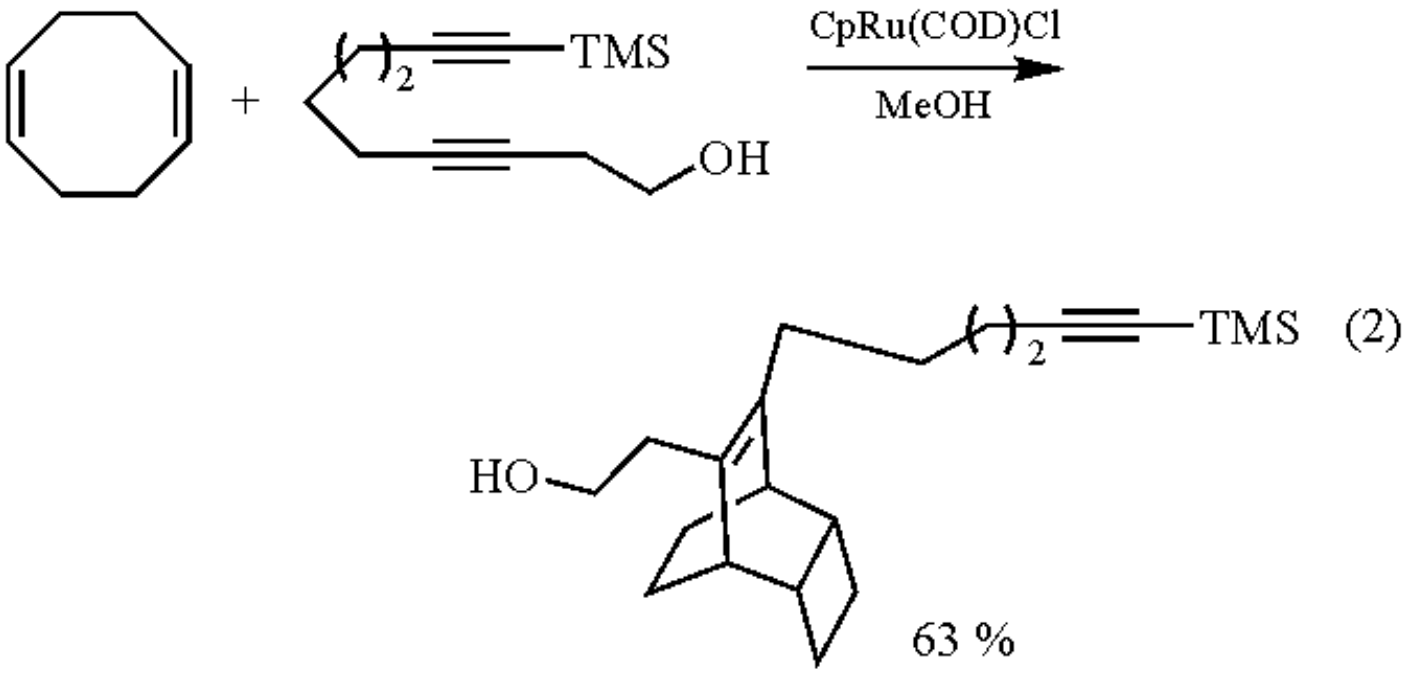

(2)

Alkene-Alkyne Coupling Reactions

The most important synthetic application of CpRu(COD)Cl is that it catalyzes the addition of terminal alkenes to terminal alkynes. Reacting oct-1-ene and oct-1-yne at elevated temperature in the presence of 5 mol% of CpRu(COD)Cl gave a 5:1 ratio of the branched and linear 1,4-diene (eq 3).[3] Other simple unfunctionalized alkenes/alkynes yielded the branched isomer as the major product. In a comparative study with other ruthenium complexes, CpRu(COD)Cl was found to be the most effective in such transformations.[4] Unlike arene ruthenium complexes, the use of CpRu(COD)Cl does not employ a promotor or phosphines to increase the effectiveness of the catalyst.

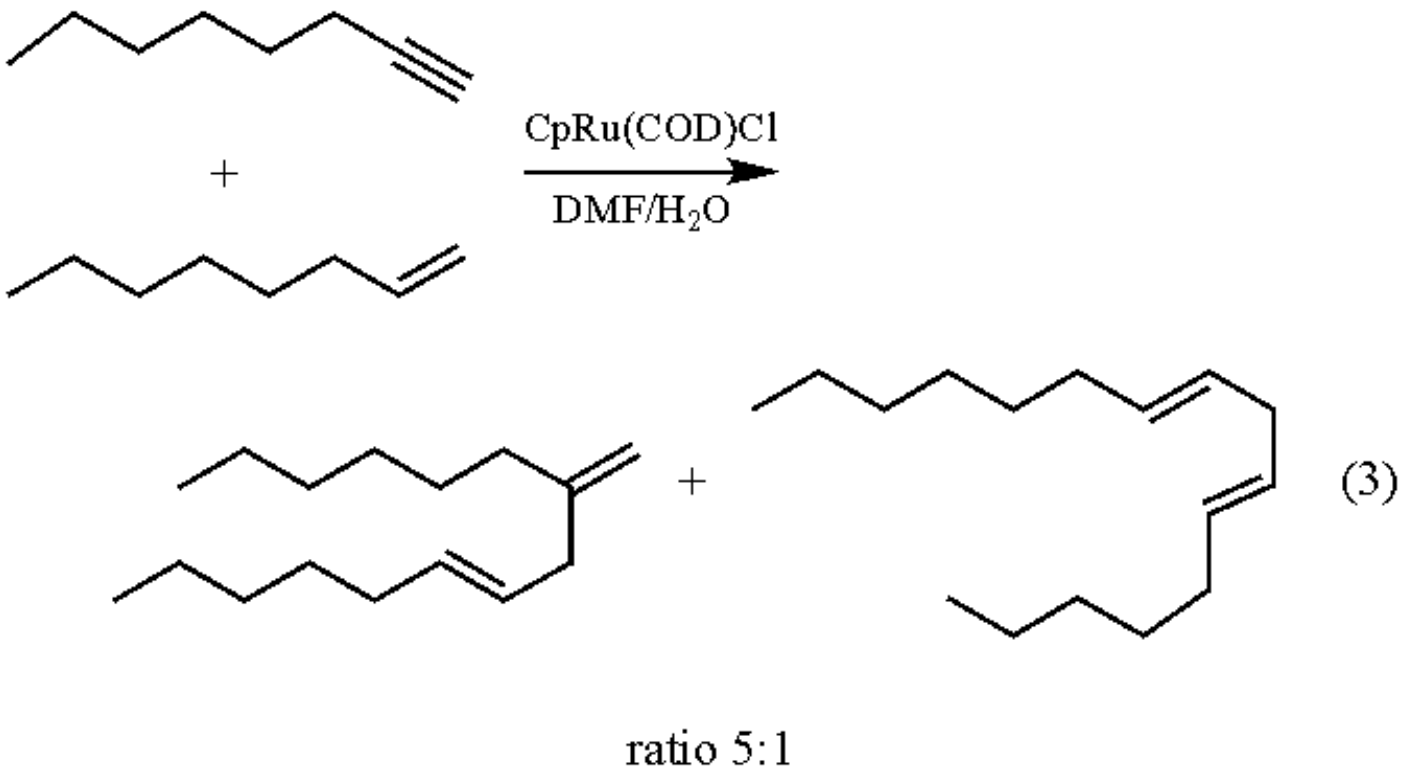

(3)

Remote functionality on the alkene tether (alcohols, esters, enoates and ketones) and on the alkyne tether (ester and silyl ethers) did not affect the process in terms of yield or selectivity.[3,4] Interestingly, a normally reactive enoate does not interfere with the coupling (eq 4).

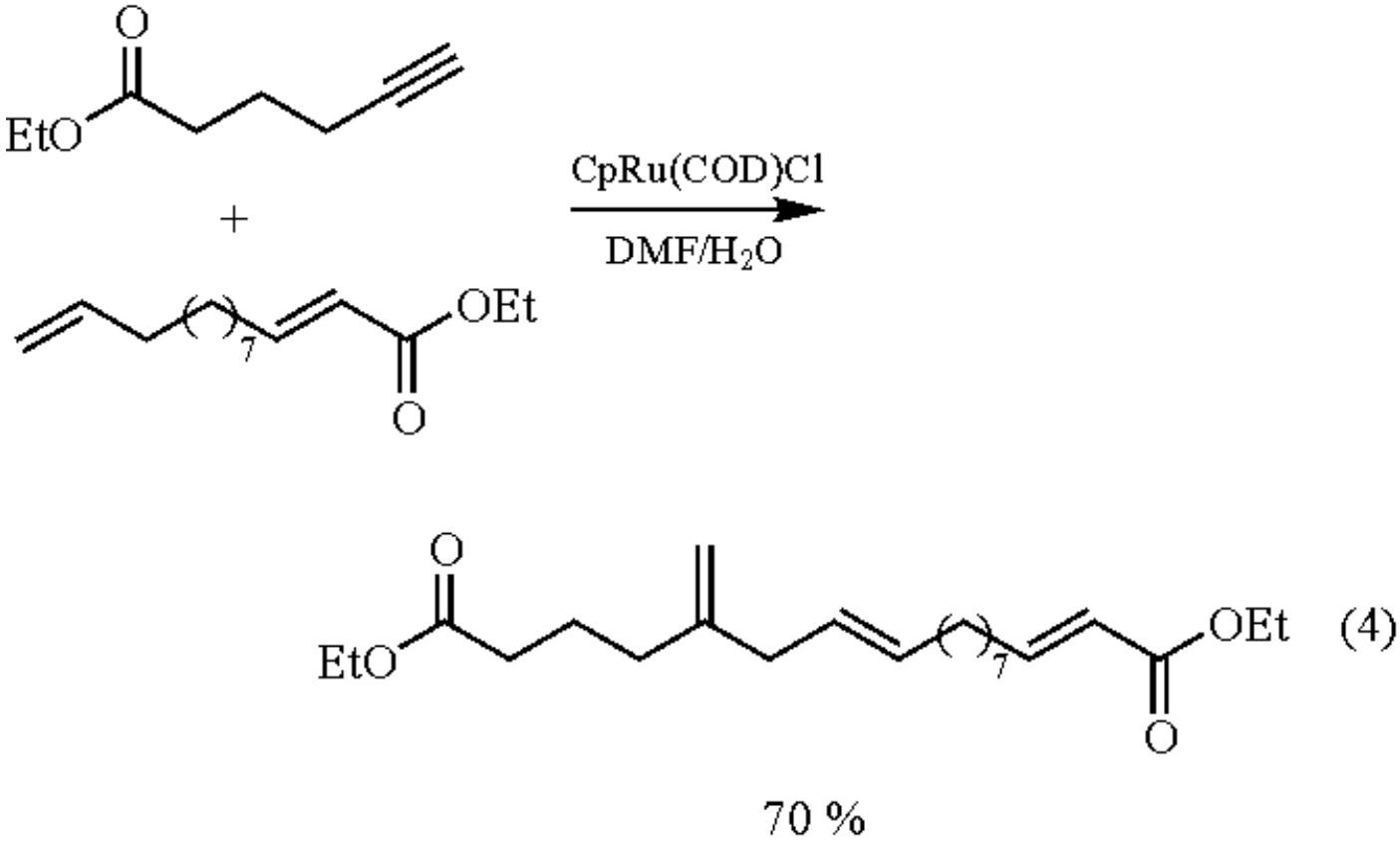

Internal alkynes also undergo coupling with terminal alkenes (eq 5). Only one regioisomer is possible.[3,4]

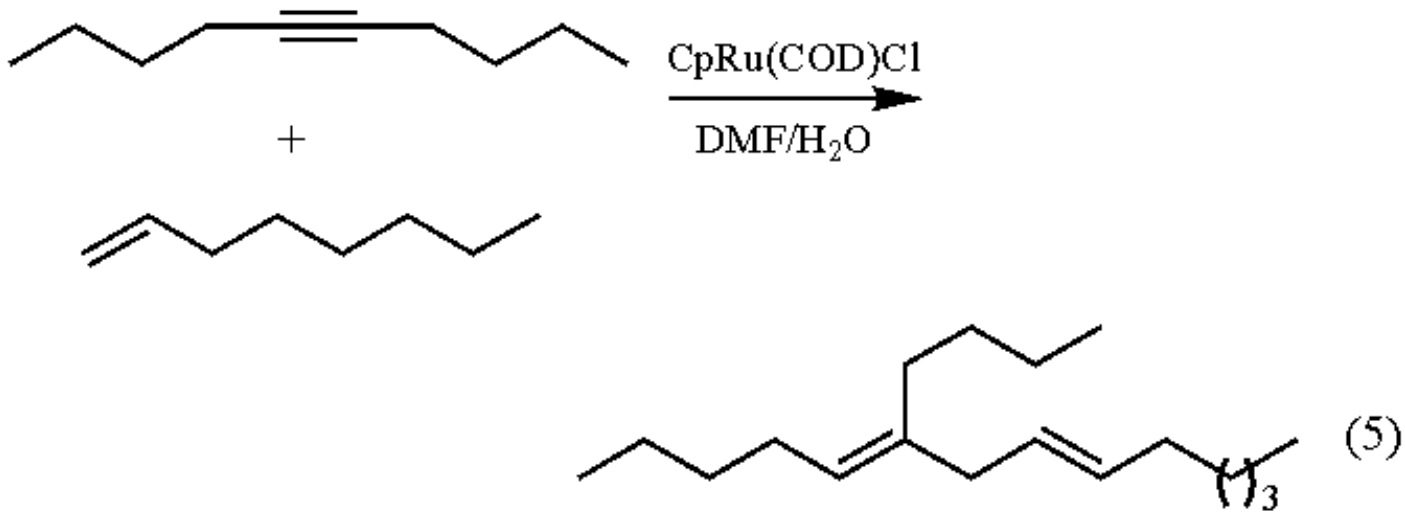

The ruthenium-catalyzed Alder ene-type reaction has been applied to the formal synthesis of alternaric acid.[5] In model studies it was found that relatively acidic substrates, such as carboxylic acids, inhibit the reaction. Esters, however, underwent clean conversion (eq 6).

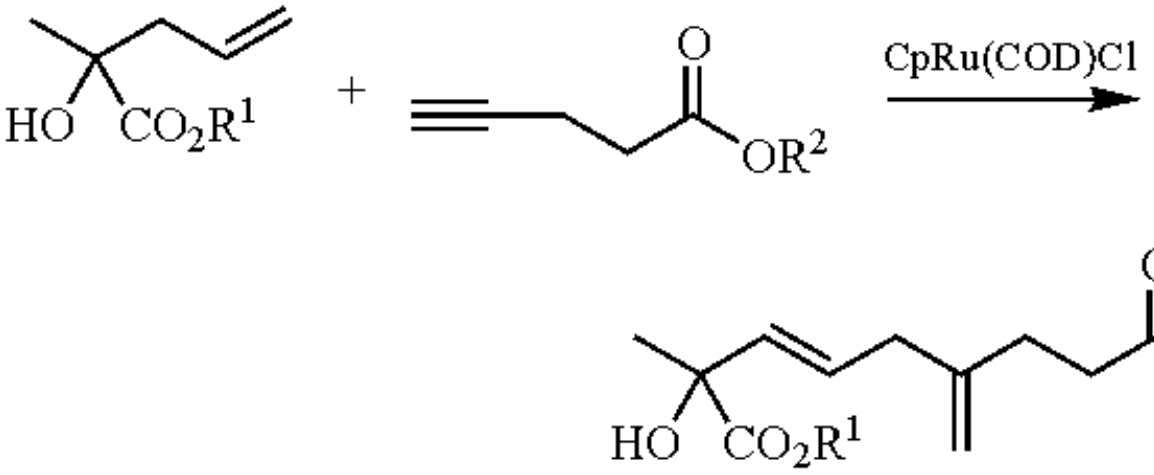

(6)

$R^1 = H$ trace

$R^1 = Me$ 49%

$R^2 = t\text{-}Bu$

In the key ruthenium-catalyzed coupling step, high regioselectivity was obtained with the free diol (protection reduced regioselectivity) and the Fmoc-protected ester (eq 7). The ratio of products was 8.9:1 in favor of the branched isomer.

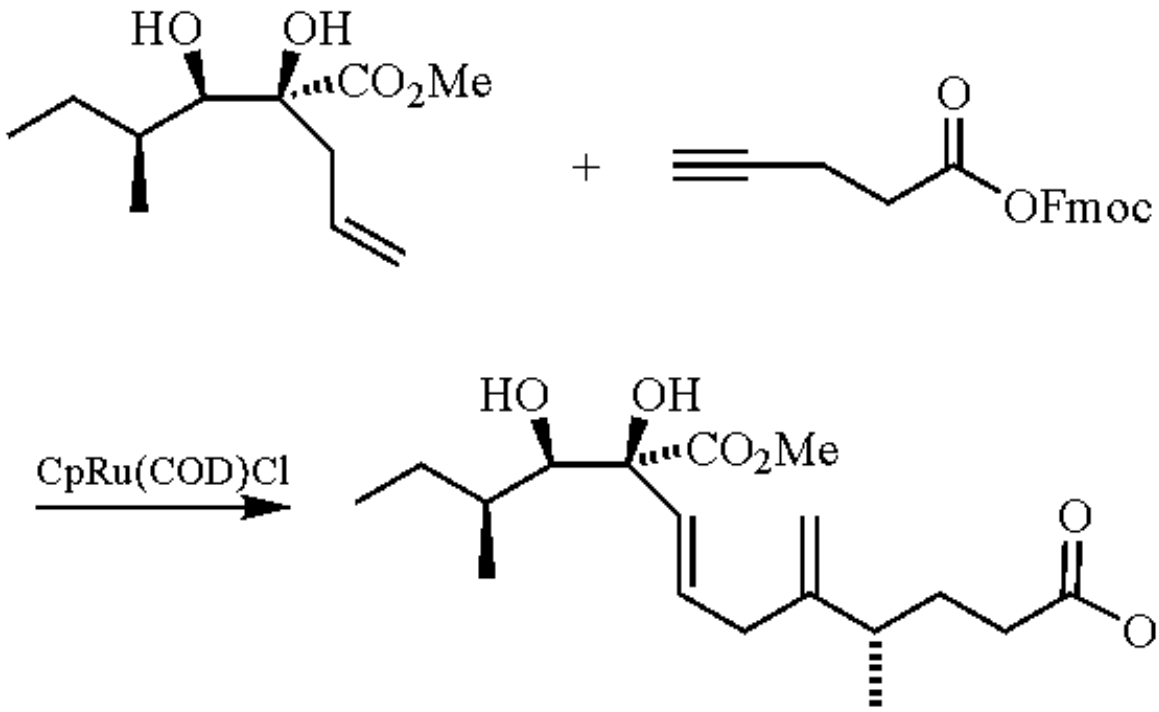

(7)

CpRu(COD)Cl catalyzes the coupling of γ-amido-α,β-alkynoate esters with monosubstituted alkenes (eq 8).[6] Carbon-carbon bond formation occurs at the α-carbon of the alkynoate (4.2:1 ratio of α/β-regioisomers). Interestingly the usually more reactive conjugated diene was a spectator in the reaction. No Diels-Alder-type products were observed. The reaction is tolerant of a range of functionality on the alkene moiety, including esters and propargyl alcohols. The integrity of stereogenic centers on the alkyne moiety was maintained throughout the reactions.

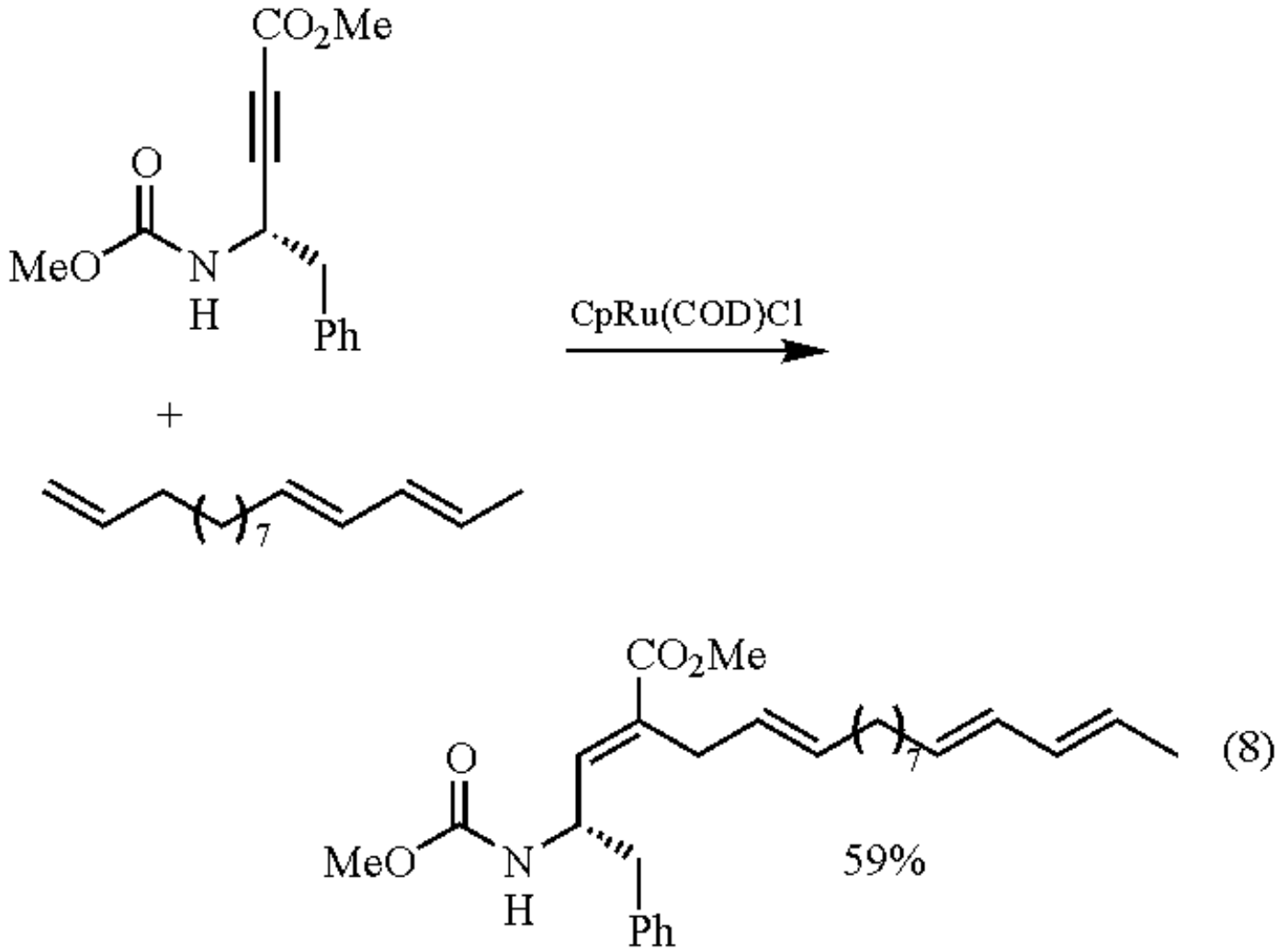

Propargyl Substituents

Substitution at the propargylic position of the alkyne moiety has a profound effect on the regioselectivity of the addition. A cyclohexane substituent at that center reduces selectivity.[3,4] Remarkably oxygen substituents reversed selectivity in favor of the linear product.[3,4] Placing an acetal at the propargylic position increased the linear to branched selectivity to 6:1 (eq 9). The acetal hydrolyzes under the reaction conditions.

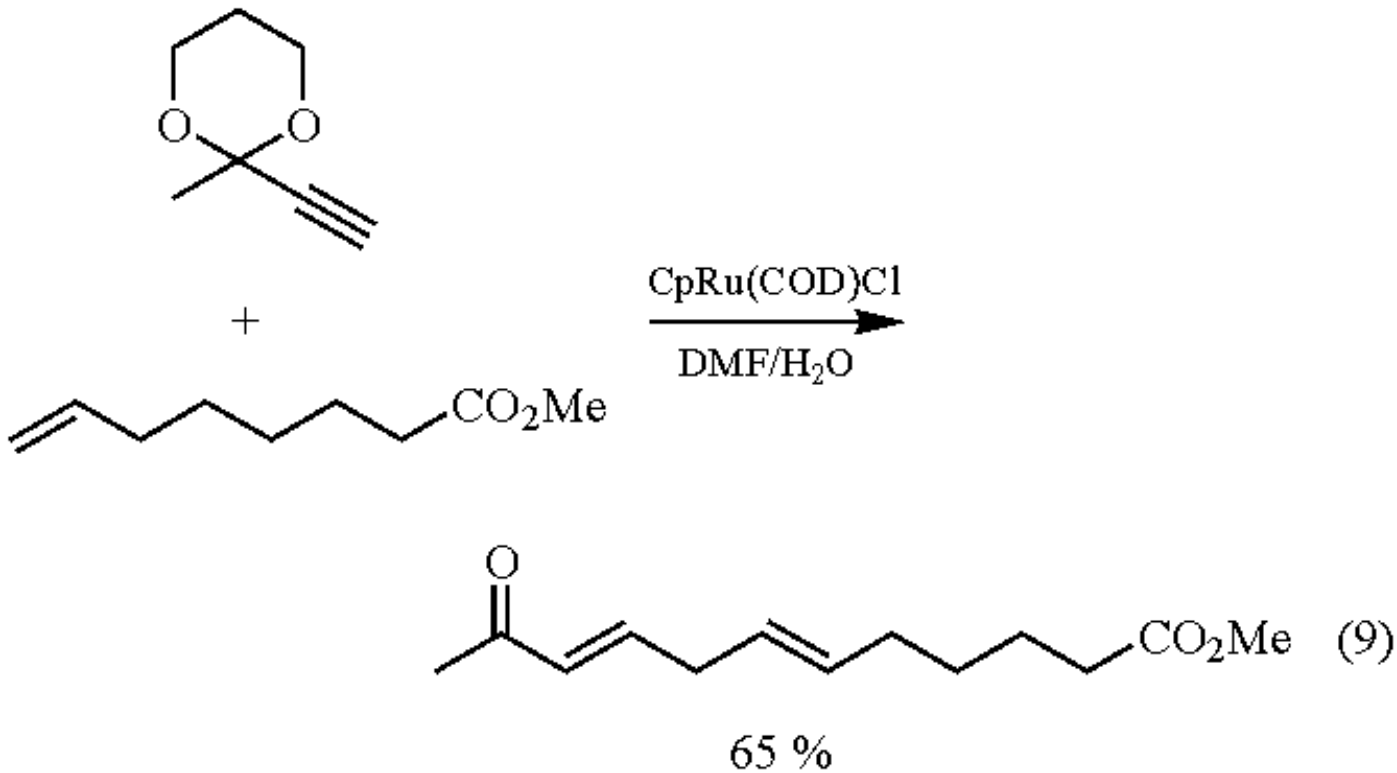

In optimization studies, using aqueous DMF as the solvent gave the highest yields and regioselectivity for the reaction of methyl 10-undecenoate and but-2-yn-1-ol (eq 10).[4] A methanol/Bu_4NCl system was found to give comparable yields to aqueous DMF but the regioselectivity of the reaction was diminished.

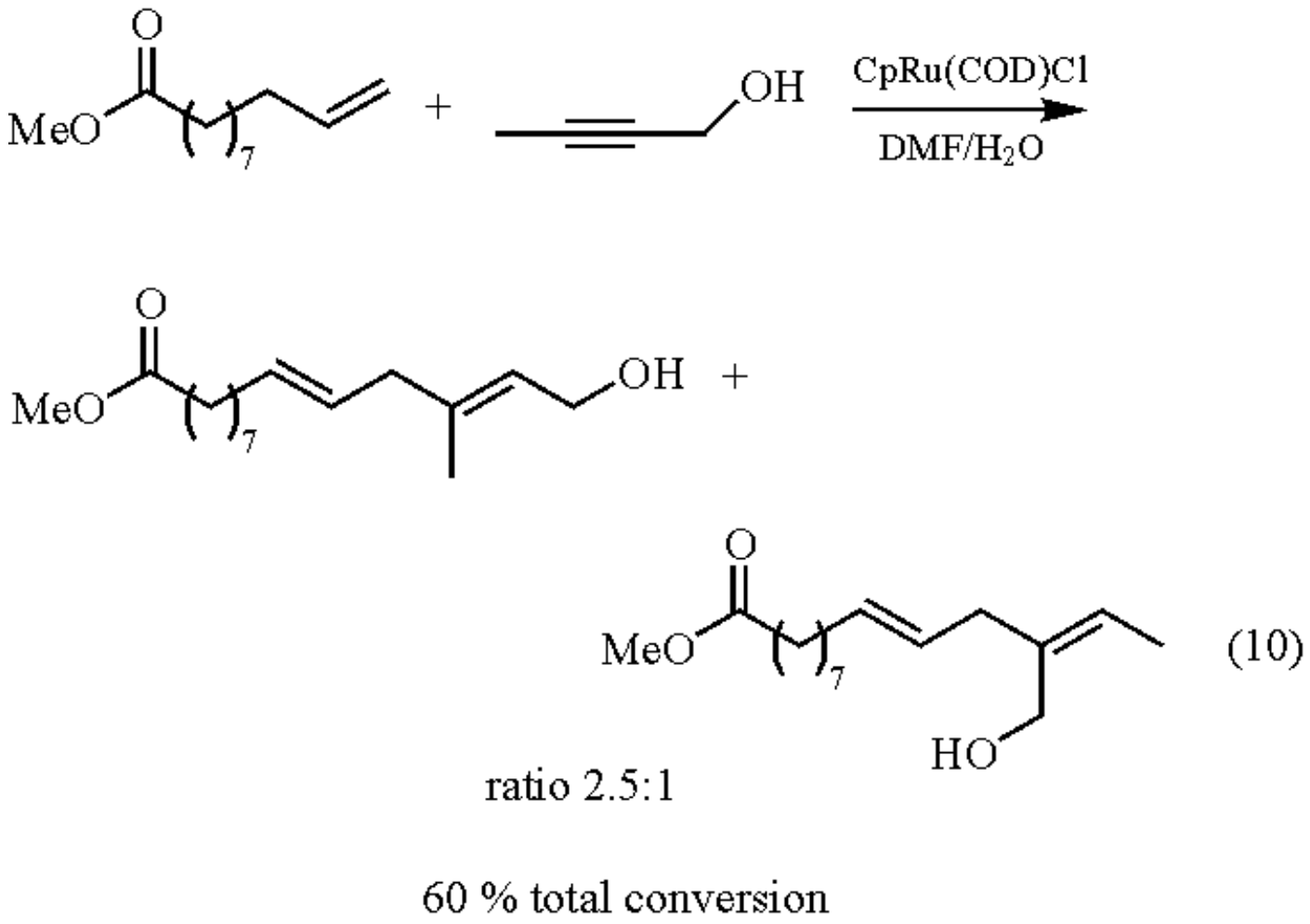

The combination of having oxygen substituents and branching at the propargylic center results in the highest regioselectivity (up to 9.9:1 in favor of the linear isomer).

Internal propargyl alcohols react with terminal alkenes to yield Baylis-Hillman-type products.[7] Baylis-Hillman reactions are usually quite limited to electrophilic partners that do not interfere with the nucleophile. Yields were good and the isomeric ratio high in favor of the branched isomer in many examples. Hydroxy- and cyano- groups on the propargyl alcohol moiety gave particularly high regioselectivities, yielding almost exclusively the branched product. The addition of indium triflate as a co-catalyst was found to improve regioselectivity towards the branched isomer. Alkyl substituents at the propargylic center had no significant effect on the outcome of the reaction. Remote functionality on the alkyne moiety (R^1) was found to have a large effect on regioselectivity (eq 11). Placement of a hydroxyl group two or three carbons away from the alkyne (R^1=-OH or -CH_2OH) led to only one regioisomer, the branched product. Placing cyano- or cyano/hydroxyl groups in a similar manner [R^1=-CN or -$CH(CN)CH_2OH$] yields only the branched isomer.

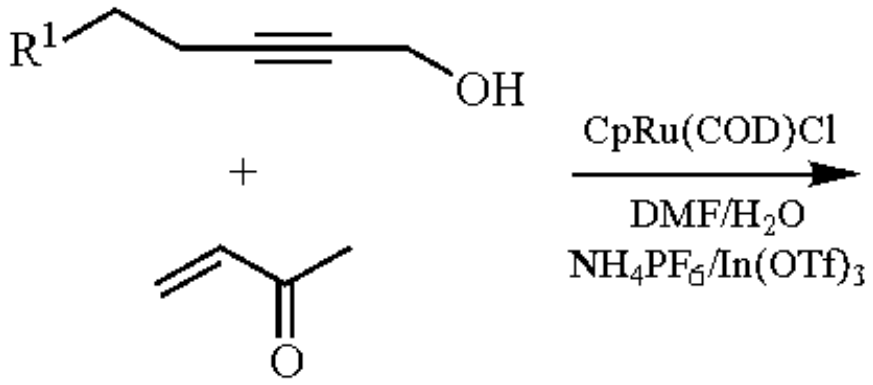

(11)

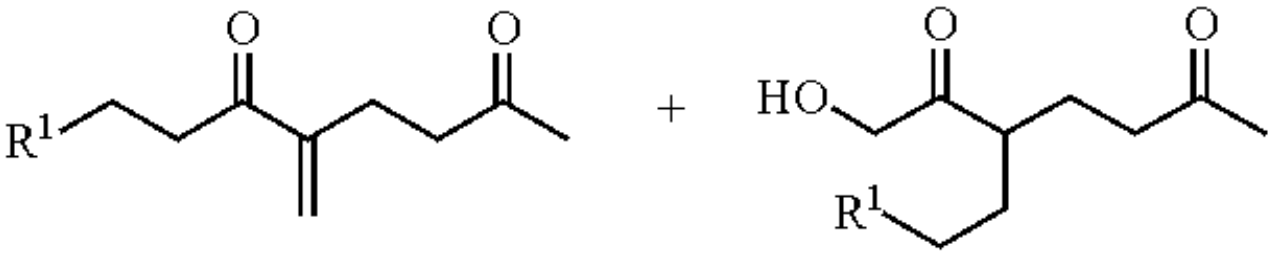

ratio 10:1

65 %

Silyl-alkynes are effective in controlling the regioselectivity of the coupling reaction with terminal alkenes.[8] Although terminal alkynes couplings proceed with high chemoselectivity, the reactions have previously produced mixtures of isomers. For example, propargyl alcohols react with oct-1-ene to yield a single product (eq 12). In comparison the same alkyne, without the silyl substituent, yields a 1:1.3 mixture of the branched and linear regioisomers. However, a more reactive ruthenium catalyst (with the absence of chloride ligands) has been shown to be more effective in such transformations.[8]

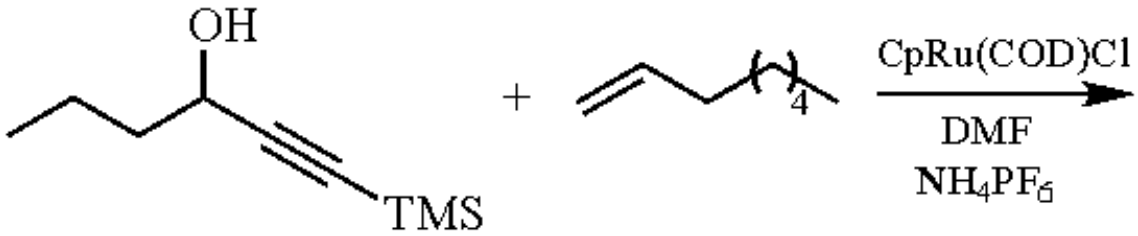

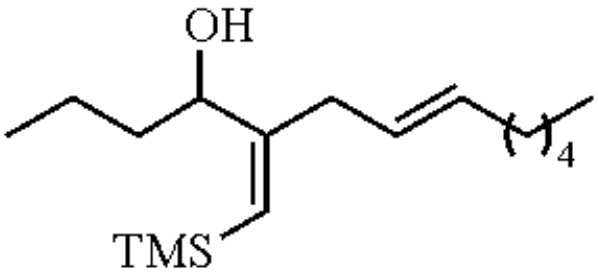

(12)

52%

Allylic Alcohols

CpRu(COD)Cl promotes the coupling of internal and terminal alkynes with allylic alcohols to yield linear and branched γ,δ-unsaturated ketones (eq 13 and 14).[9]

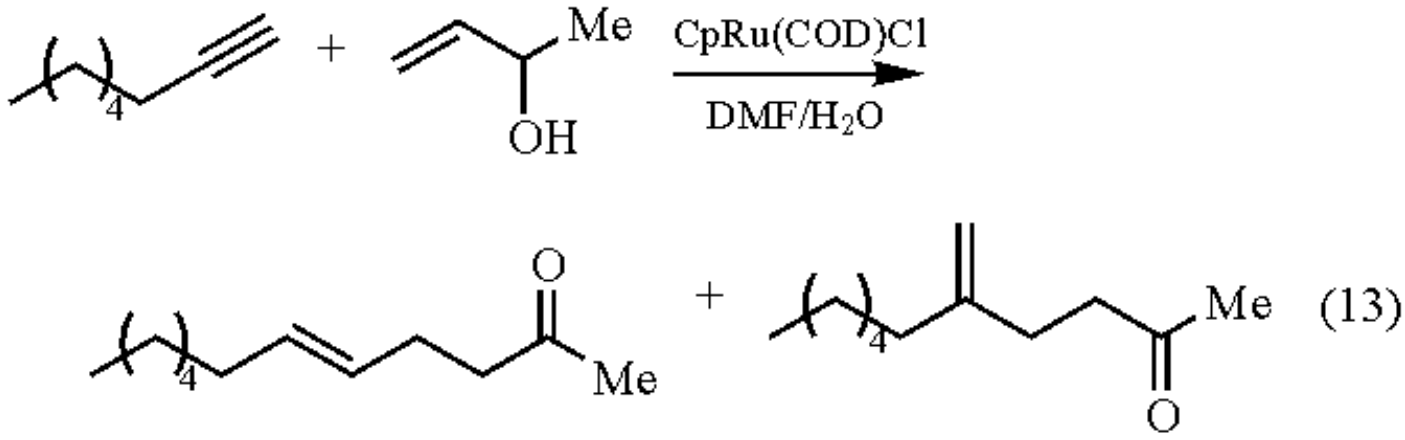

ratio 2.3:1

60%

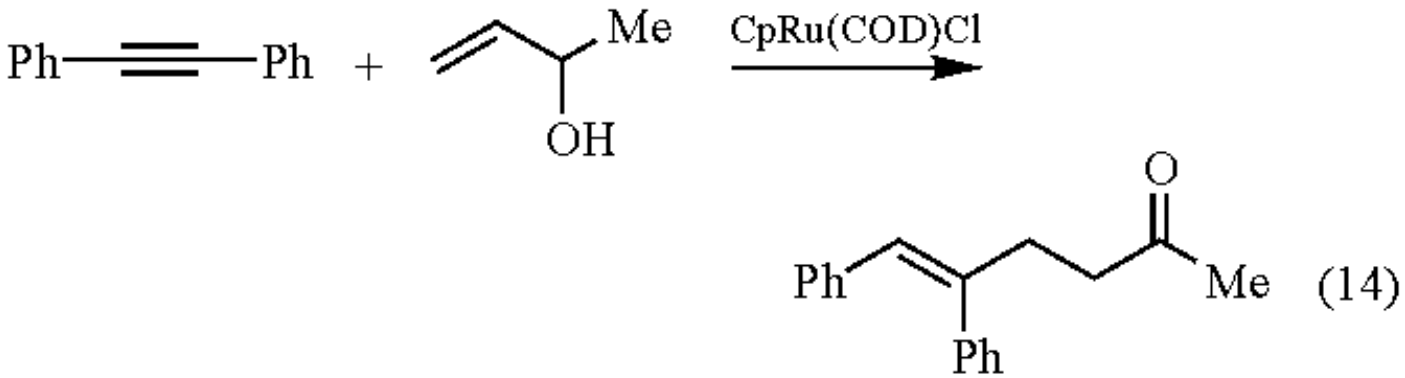

50%

In contrast to other ruthenium coupling reactions, both aliphatic and aromatic acetylenes are efficient partners. Aromatic alkynes frequently inhibit such reactions, a consequence of the ease in forming arene complexes. Aqueous DMF as the solvent gave the best rates of reaction and regioselectivity. Alkynes conjugated to esters gave similar yields and regioselectivity in comparison with terminal alkynes (eq 15).[9]

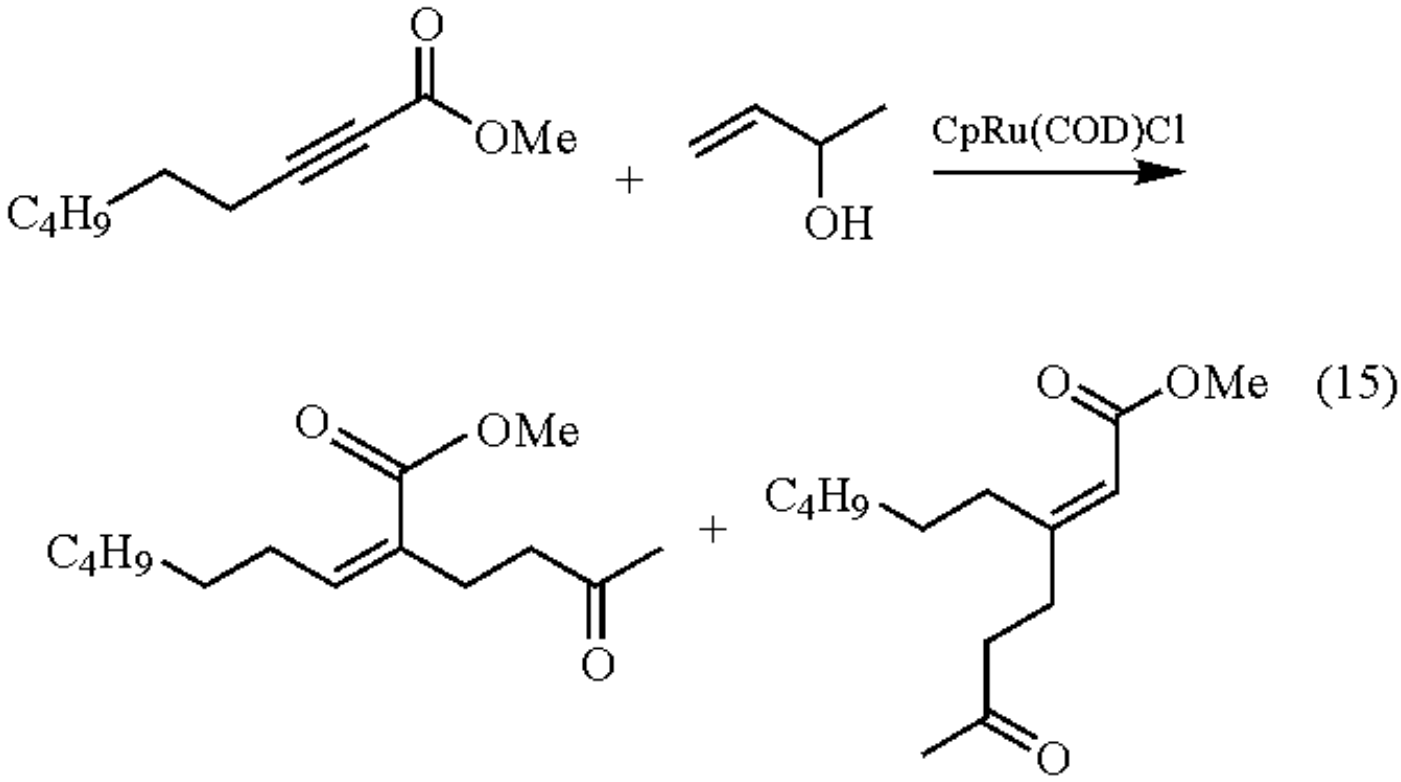

ratio 2.4:1

76 %

An application of this methodology has been achieved for the introduction of a steroid side chain (eq 16).[9] Reacting the alkyne with an allylic alcohol yielded the linear product in moderate yield.

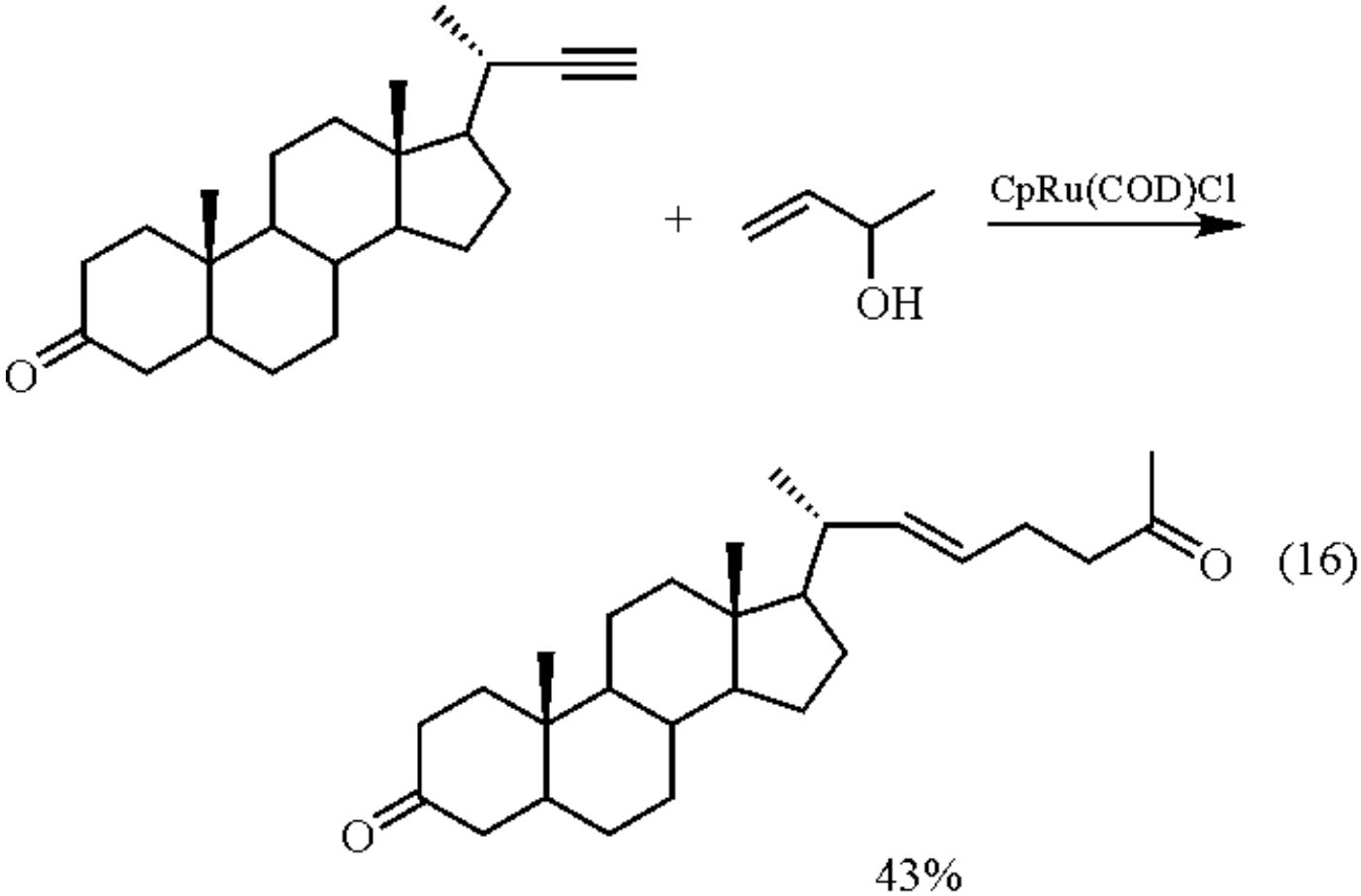

43%

The reaction of propargyl alcohol derivatives with allylic alcohols was found to give the highest regioselectivity in favor of the linear products in 50-60% isolated yields (eq 17).[9]

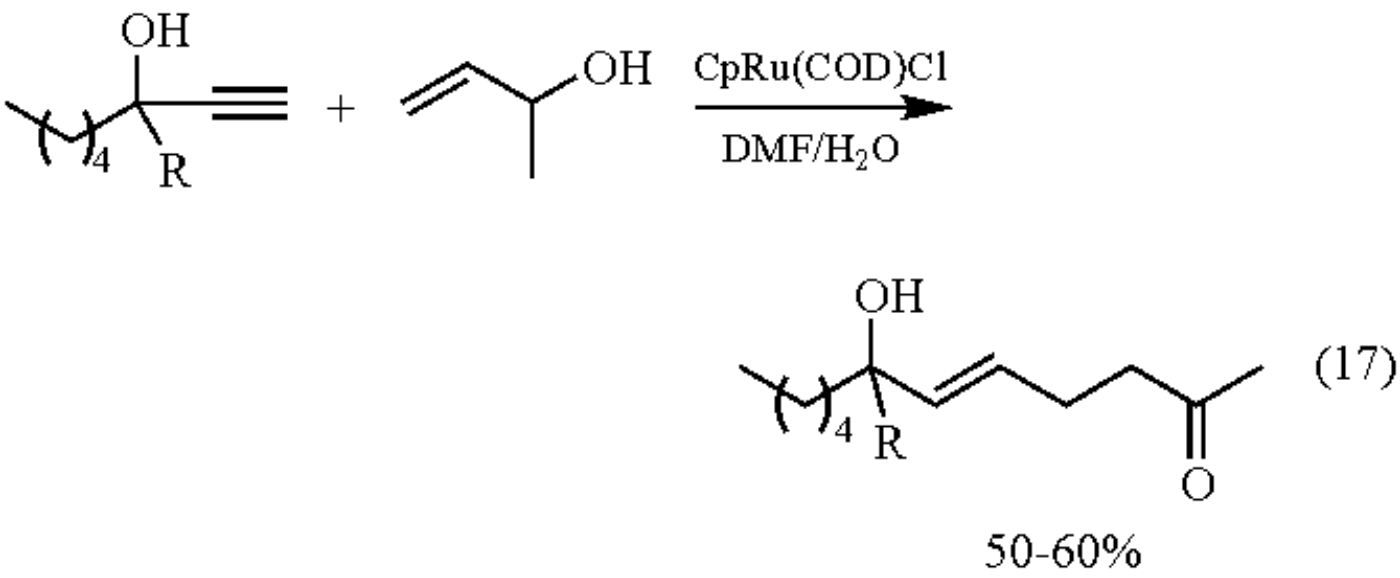

Butenolide Formation

CpRu(COD)Cl coupling reactions of an alkene to an alkyne have been utilized in the synthesis of butenolides. Methyl 10-undecenoate reacted with 4-hydroxybutynoate and 5 mol% of CpRu(COD)Cl to yield a 2.9:1 ratio of the butenolide and hydroxy ester (eq 18).[10,11] Butenolide formation proceeds via attack at the α-carbon of the acrylate followed by elimination of ethanol. Introducing alkyl substituents at the propargylic position increased regioselectivity towards the butenolide (eq 18; ratios given are for butenolide/ester).

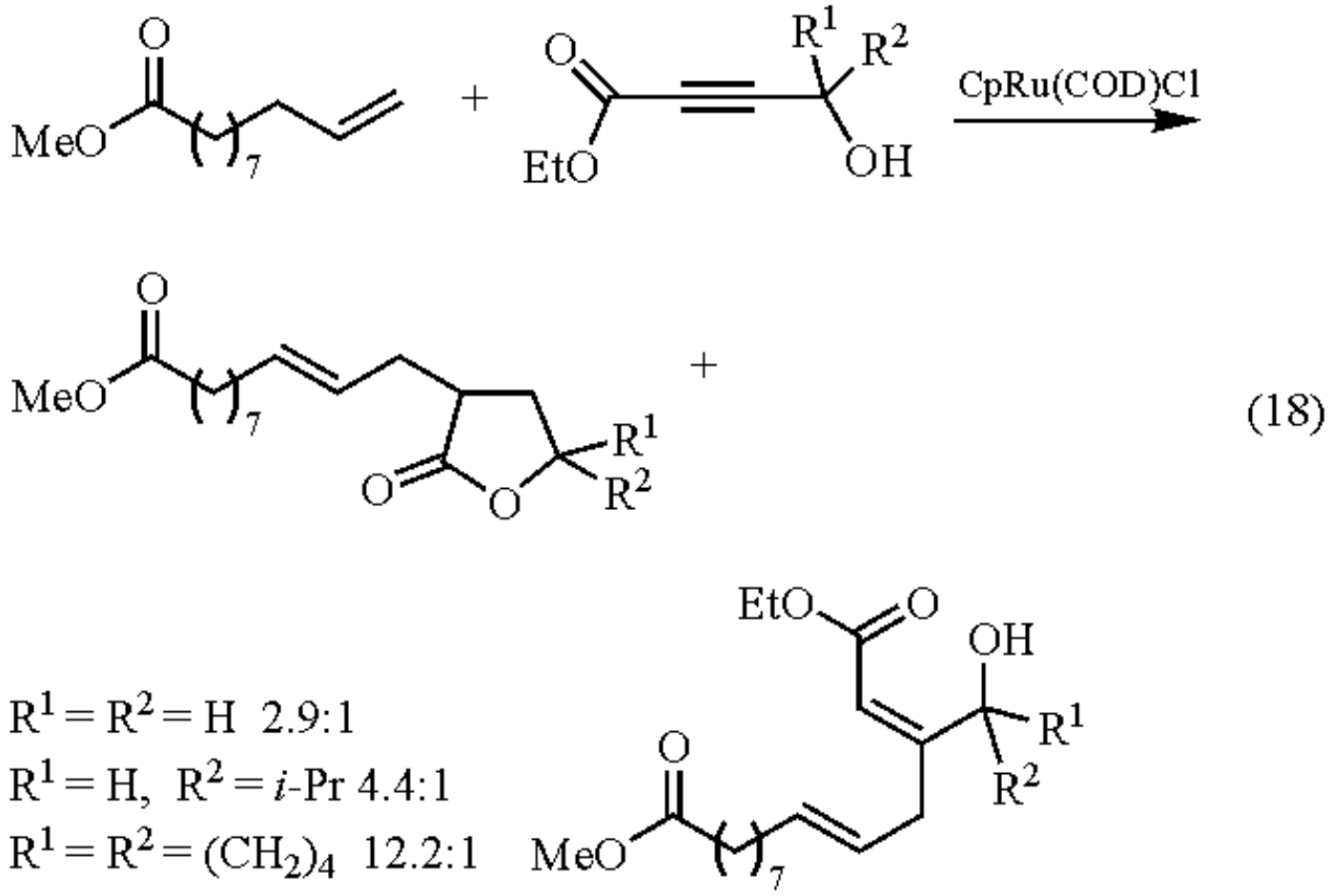

Studies have shown that the remote functionality in the terminal alkene has some effect on regioselectivity.[10] With an alcohol functionality on the alkene the corresponding butenolide was the only regioisomer obtained in 71% yield (eq 19).

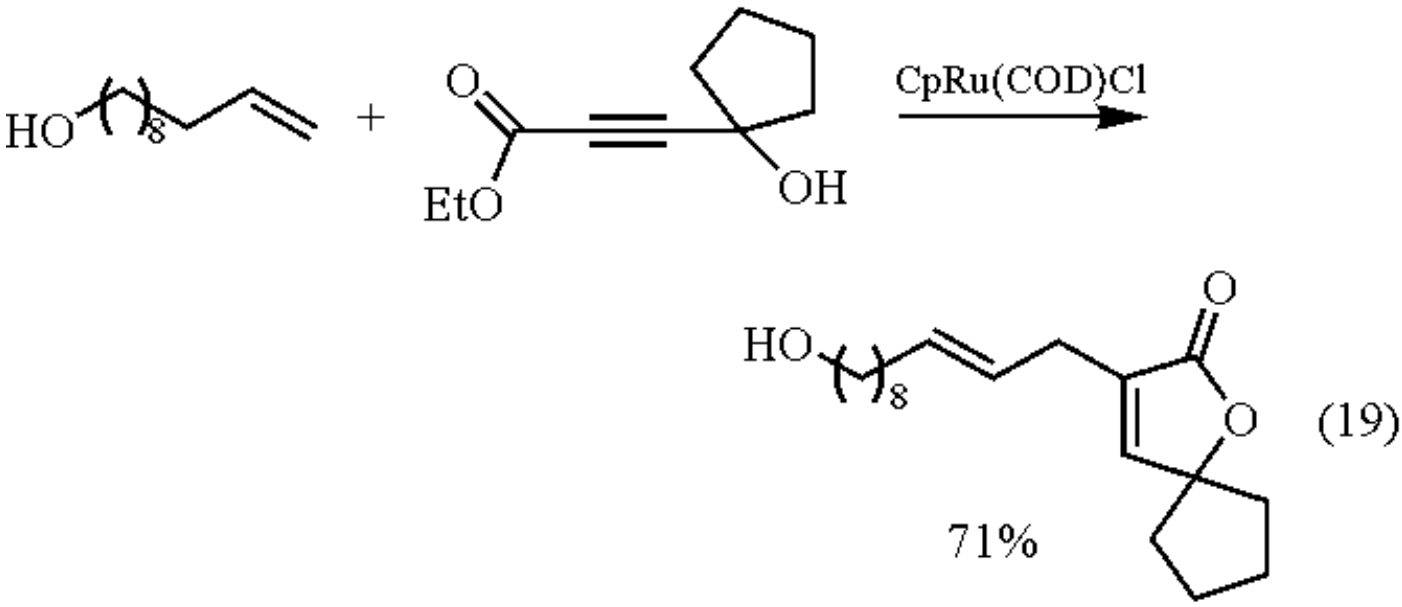

Of particular interest is that the ruthenium-catalyzed coupling of an alkene to an alkyne yields the corresponding butenolide with stereochemical information at the propargylic position intact (eq 20).[10]

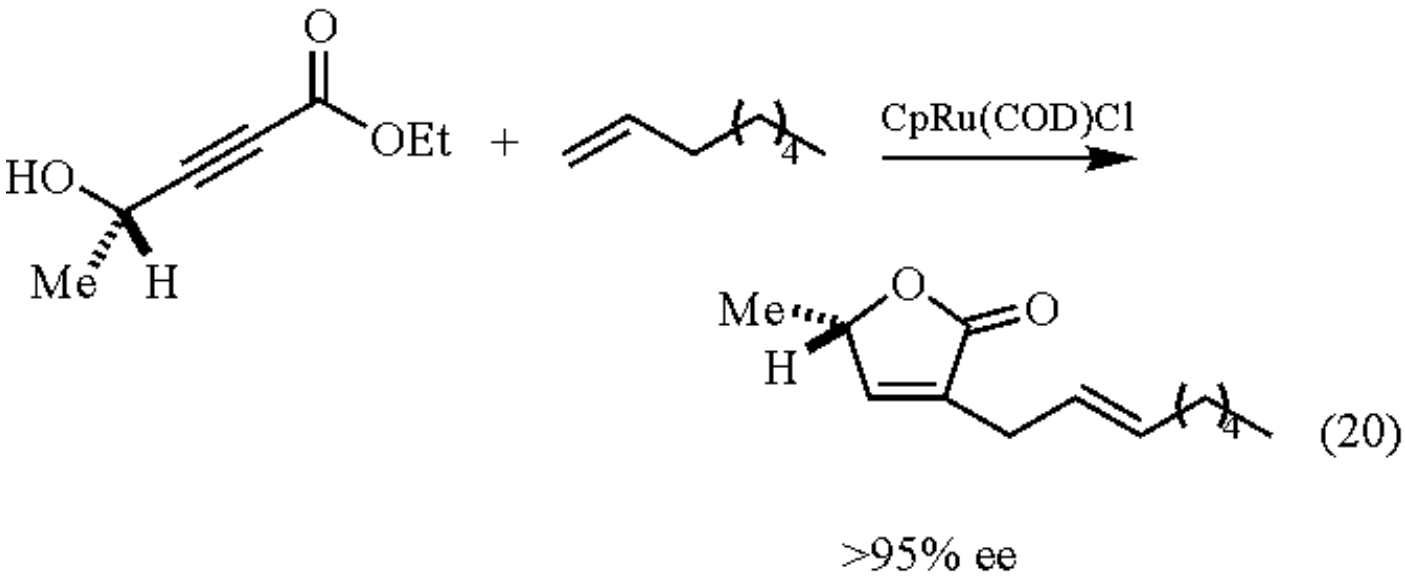

Pentenolides have been synthesized in much the same way (eq 21).[11]

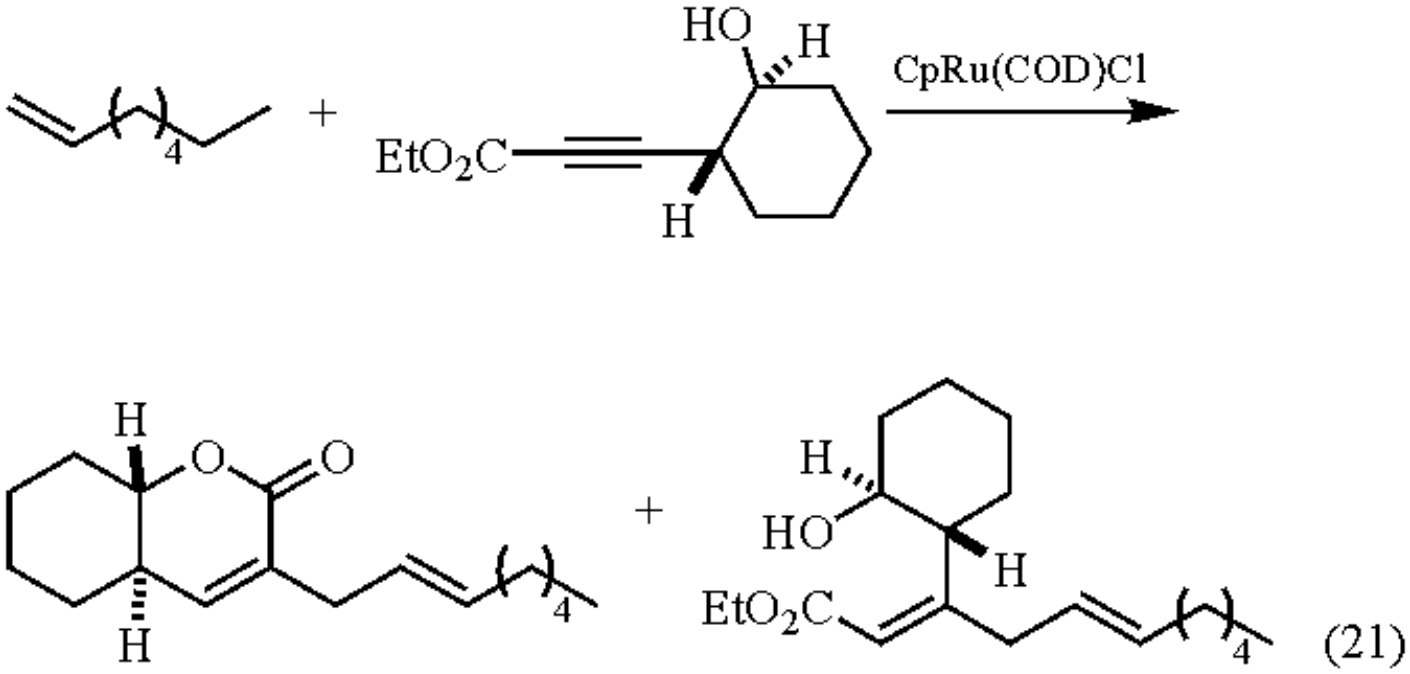

This methodology has been successfully applied to an efficient synthesis of ancepsenolide.[10,11] The key step involves the double addition of the alkyne to a diene with 10 mol% of CpRu(COD)Cl (eq 22).

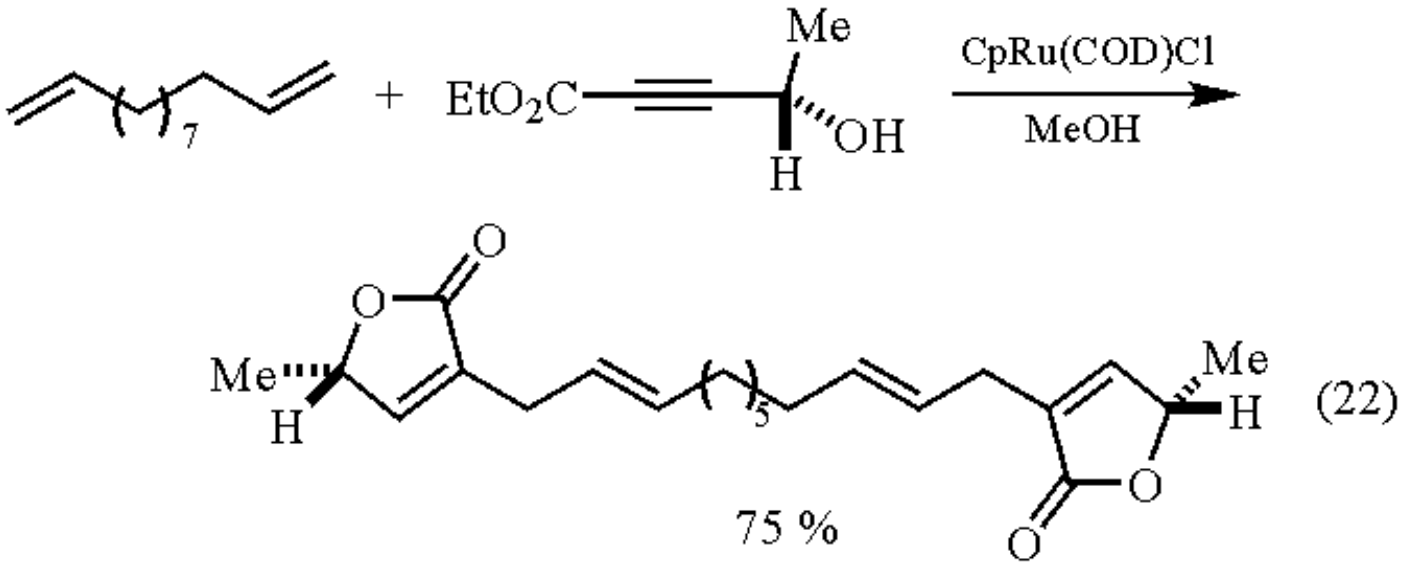

This type of coupling has been applied to the synthesis of the hydroxybutenolide terminus of the acetegenins.

Noteworthy is that, in general, electron-deficient alkynes produce predominantly the β-alkylated product in Lewis acid-assisted and thermal Alder ene-type reactions (path a; eq 23). In contrast the ruthenium-catalyzed Alder ene-type reaction yields predominantly α-alkylation (path b; eq 23). In addition, the reaction is more general than standard Alder ene-type reactions. Alder ene reactions are rarely used synthetic transformations due to the lack of generality and extreme conditions (temperatures in excess of 400°C have been used) associated with the reaction.

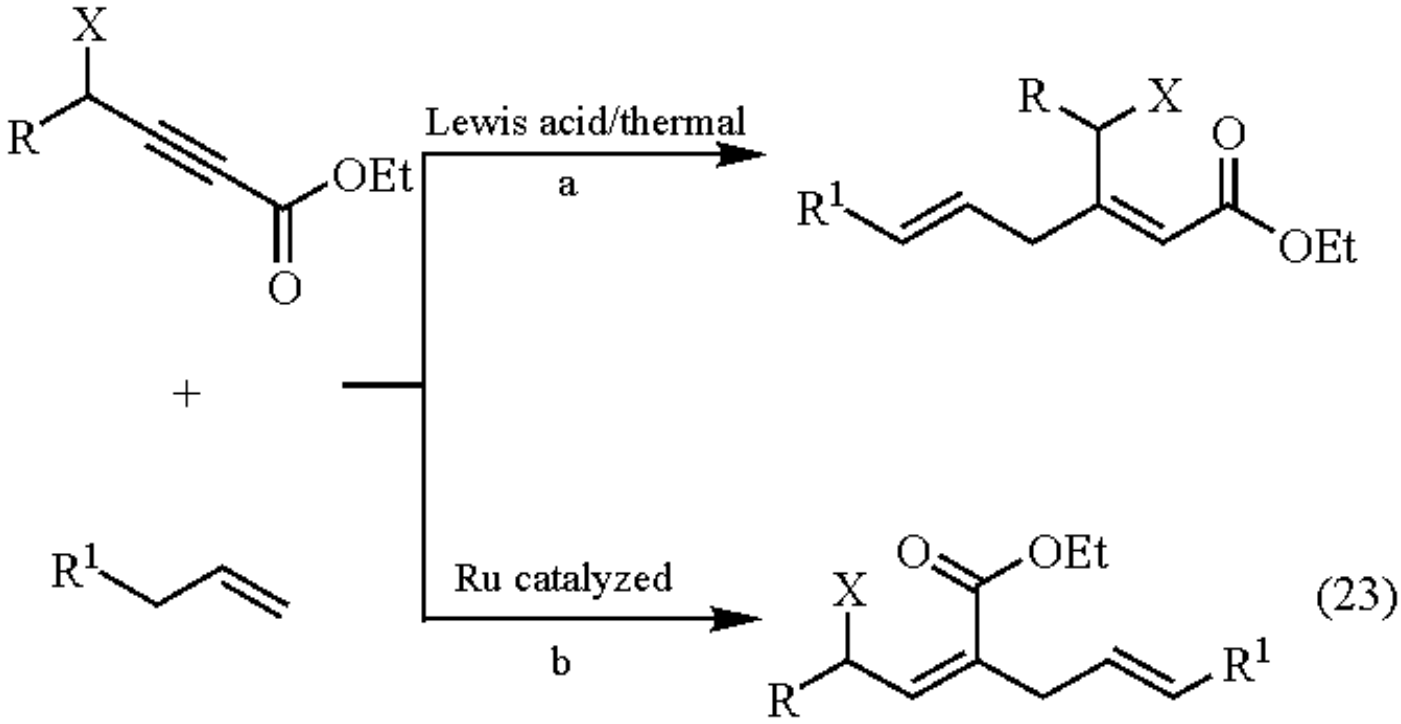

Allene-Alkene Coupling

Allenes have been utilized in replace of the alkyne component in the ruthenium-catalyzed coupling with terminal alkenes to yield 1,3-dienes (eq 24).[13] In such reactions, a dummy alkyne was added to activate the ruthenium catalyst. The reaction gave excellent chemoselectivity with a range of allene partners. Only the *E*-isomers of the dienes were obtained.

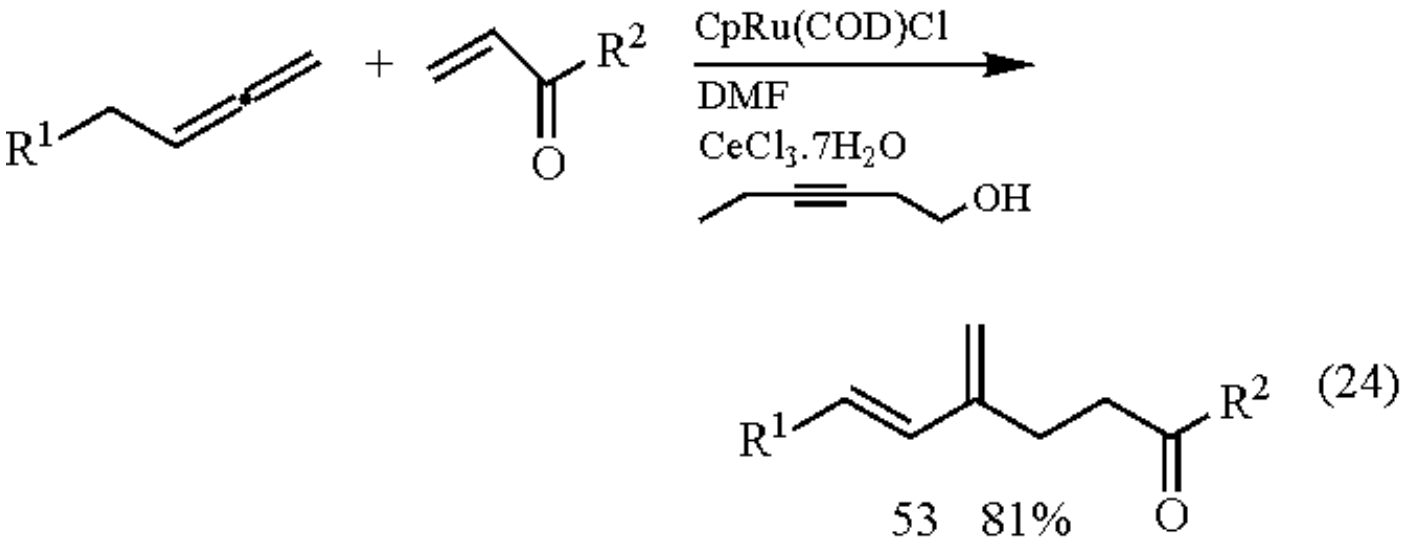

Three-Component Coupling Reactions

The ruthenium-catalyzed Alder ene-type reaction has been adapted to synthesize *E*-vinyl chlorides by the inclusion of chloride ions in the reaction mixture (eq 25).[14]

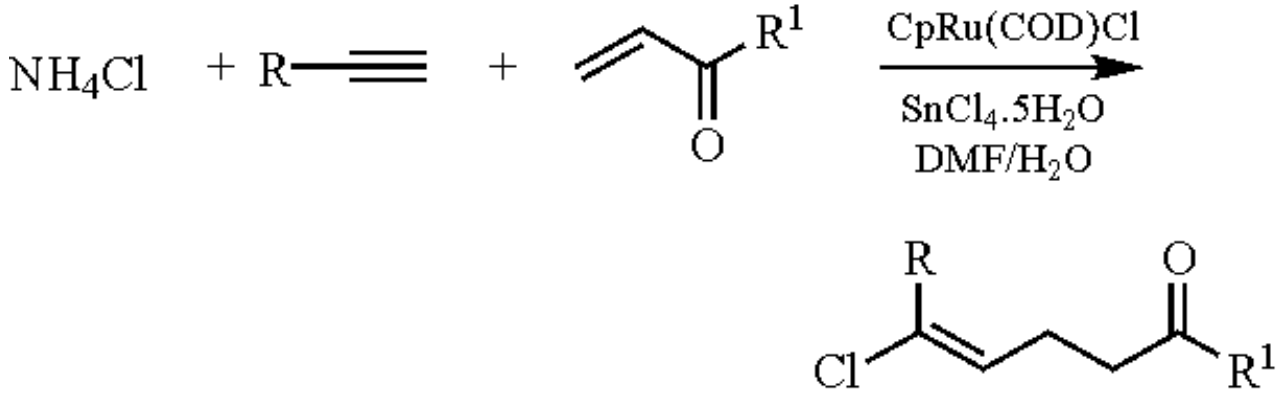

(25)

Once again excellent chemoselectivity is observed; phthalididimide, keto-, hydroxy- and ester groups are all tolerated. *E*/*Z* selectivities were generally high. Internal alkynes undergo a similar reaction to yield tetrasubstituted alkenes (eq 26). It should be noted that *cis*-vinyl chlorides are precursors to α-hydroxyesters upon dihydroxylation of the alkene.

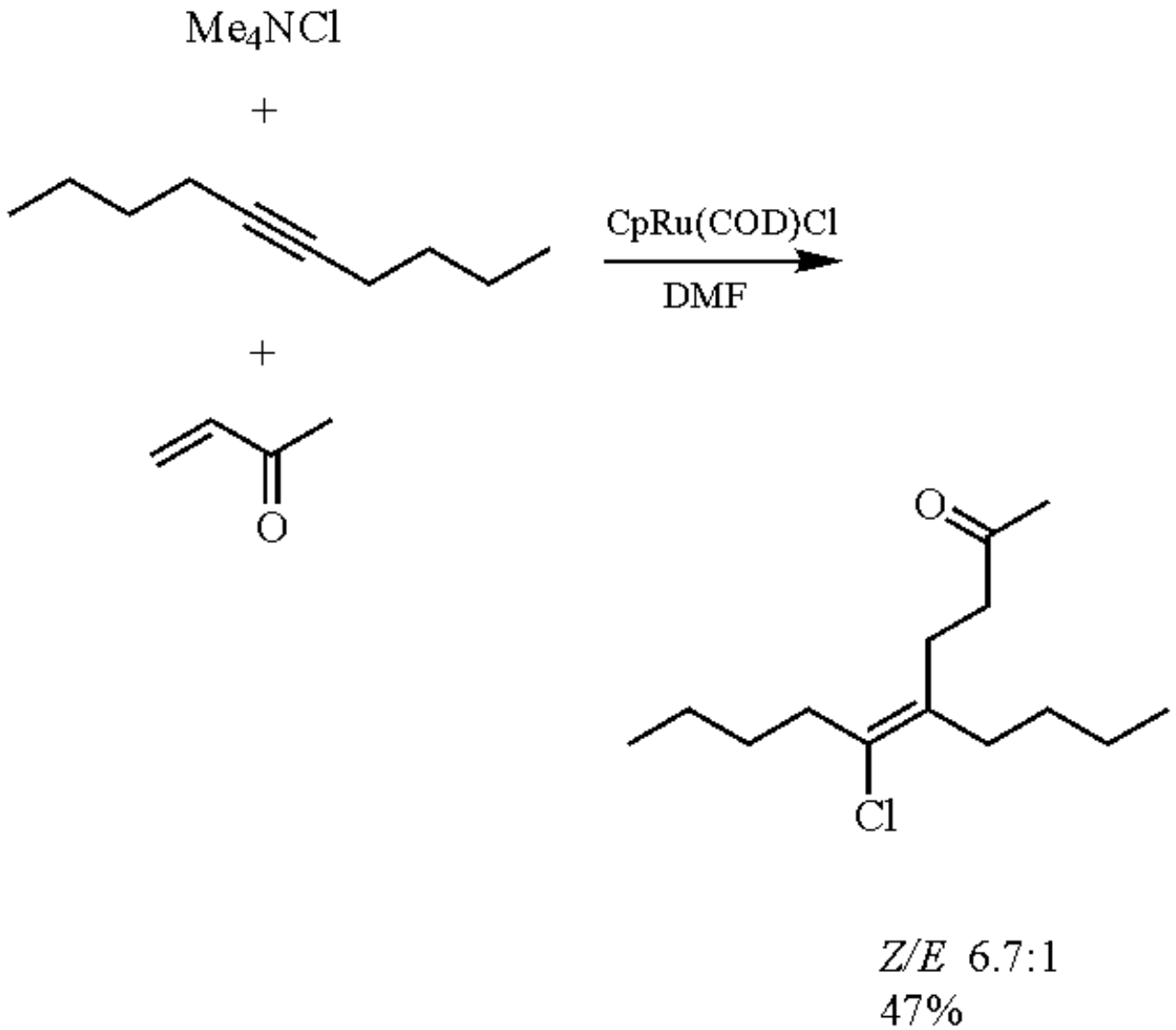

(26)

Such three component coupling reactions have been extended to the synthesis of 1,5-diketones using water as the additive (eq 27).[15] Indium salts were found to substantially increase the yield of the reaction. Chemoselectivity was high. Unfortunately the reaction conditions are quite harsh requiring the use of sealed tubes at 100°C.

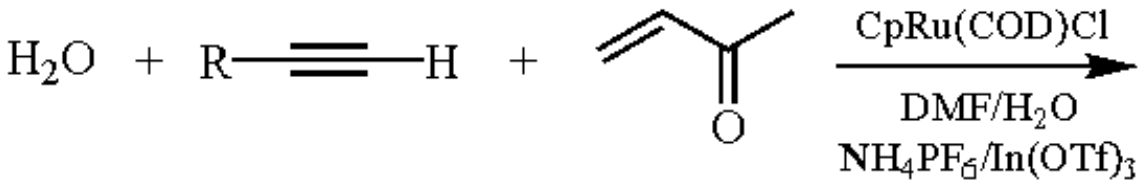

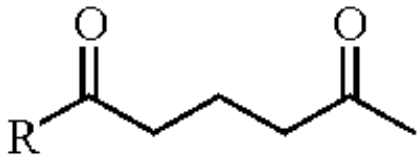

(27)

Cycloisomerization

CpRu(COD)Cl catalyzes the cycloisomerization-oxidation of homopropargyl alcohols to yield γ-butyrolactones (eq 28).[16] In this particular use of CpRu(COD)Cl, two phosphine ligands replaces the COD ligand in the first instance which is then the active catalyst in the system. The reaction is highly chemoselective and a number of examples have been performed. *N*-Hydroxysuccinimide was used as the oxidant - more conventional oxidants failed under the reaction conditions.

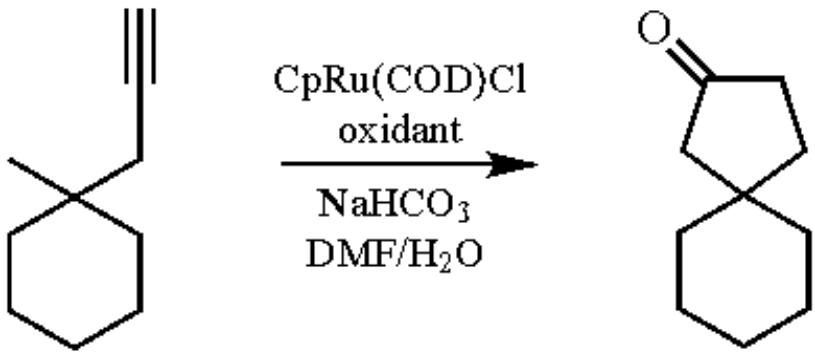

(28)

This methodology has been applied to the total synthesis of the acetogenin (-)-miricatacin (eq 29).[16] Stereochemical integrity was maintained throughout the reaction.

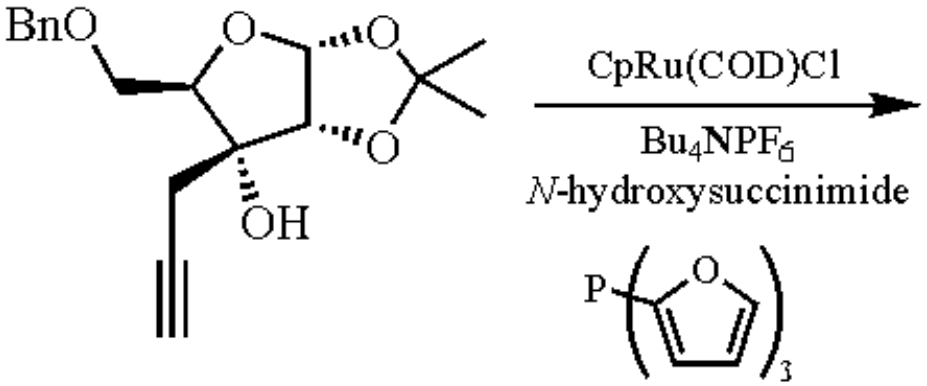

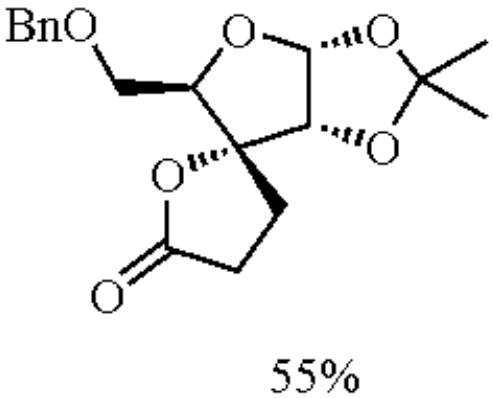

(29)

55%

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16. Trost, B. M.; Rhee, Y. H., *J. Am. Chem. Soc.* **1999**, *121*, 11680.

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1-Benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one

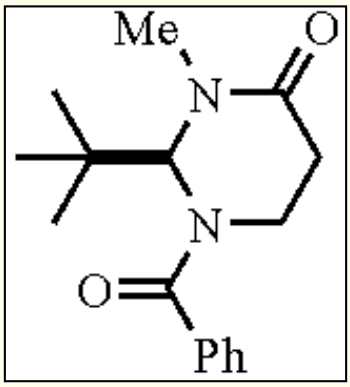

[139119-52-1] · $C_{16}H_{22}N_2O_2$ · (274.36)

(reagent used for the enantioselective synthesis of β-amino acids; in particular, α- and α,α-substituted β-amino acids.)

Physical Data: mp 99-100°C; $[\alpha]_D^{29}$ +51.2 (*c* 1, $CHCl_3$).

Solubility: soluble in THF and most organic solvents.

Preparative Methods: [1,2,3] Step 1:

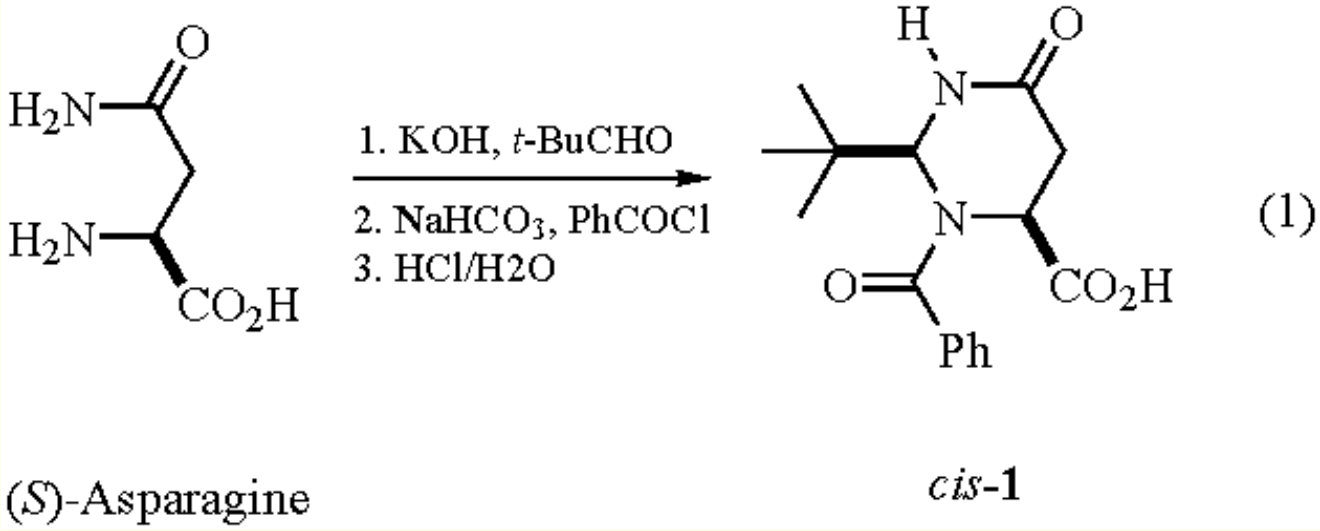

According to the procedure described by Lakner et al.,[1] with benzoyl chloride instead of methyl chloroformate, 13.2 g (0.2 mol) of KOH and 300 mL of water are placed in a 1 L round-bottomed flask before the addition of 30.0 g (0.2 mol) of L-(*S*)-asparagine with vigorous stirring. The resulting mixture is cooled to 0°C and treated with 25.0 mL (19.8 g, 0.23 mol) of pivalaldehyde. Stirring is continued for 1 h at 0°C and for 5 h at ambient temperature. The reaction mixture is cooled to 0°C before the addition of 16.8 g (0.2 mol) of $NaHCO_3$ and 23.2 mL (28.1 g, 0.2 mol) of benzoyl chloride, and stirring is continued for 2 h at ambient temperature prior to quenching with 73 mL of 10% aqueous HCl. The desired product, which precipitates from solution, is filtered, washed with cold water, and dried under vacuum to afford 54.0 g (88%) of 1-benzoyl-2(*S*)-*tert*-butyl-6(*S*)-carboxy-perhydropyrimidin-4-one [(2*S*,6*S*)-**1**], mp 202-203°C; $[\alpha]_D^{29}$ -107.0 (*c* 1, EtOH). Step 2:

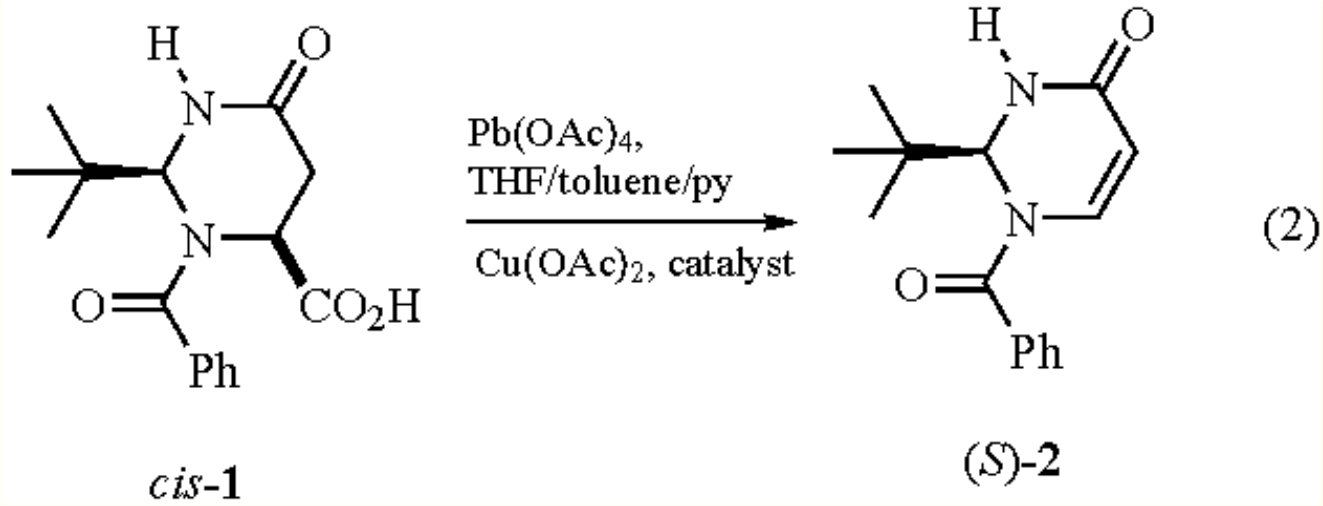

In a 3 L round-bottomed flask provided with a magnetic stirrer, 28.0 g (92 mmol) of (2*S*,6*S*)-**1** is dissolved in 900 mL of dry THF, 700 mL of toluene, and 11.2 mL (11.0 g, 138.4 mmol) of pyridine. The resulting solution is treated with 3.7 g (18.4 mmol) of copper diacetate monohydrate, and the resulting suspension is stirred at ambient temperature for 2 h. The reaction flask is then submerged in an ice-water bath before the addition of 61.6 g (138.8 mmol) of lead tetraacetate. The cooling bath is removed and the reaction mixture is heated to 80-90°C for 12 h. The precipitate is removed by filtration and washed several times with EtOAc until the extracts come out free of product (TLC). The organic extracts are combined with the original filtrate, dried over anhydrous Na_2SO_4, and concentrated. The crude product is purified by flash chromatography (eluent hexane-EtOAc, 80:20 r 50:50) to give 16.0 g (73%) of 1-benzoyl-2(*S*)-*tert*-butyl-2,3-dihydro-4(*H*)-pyrimidin-4-one [(*S*(-**2**], mp 209-210°C; $[\alpha]_D^{29}$ +556.4 (*c* 1, $CHCl_3$). Step 3:

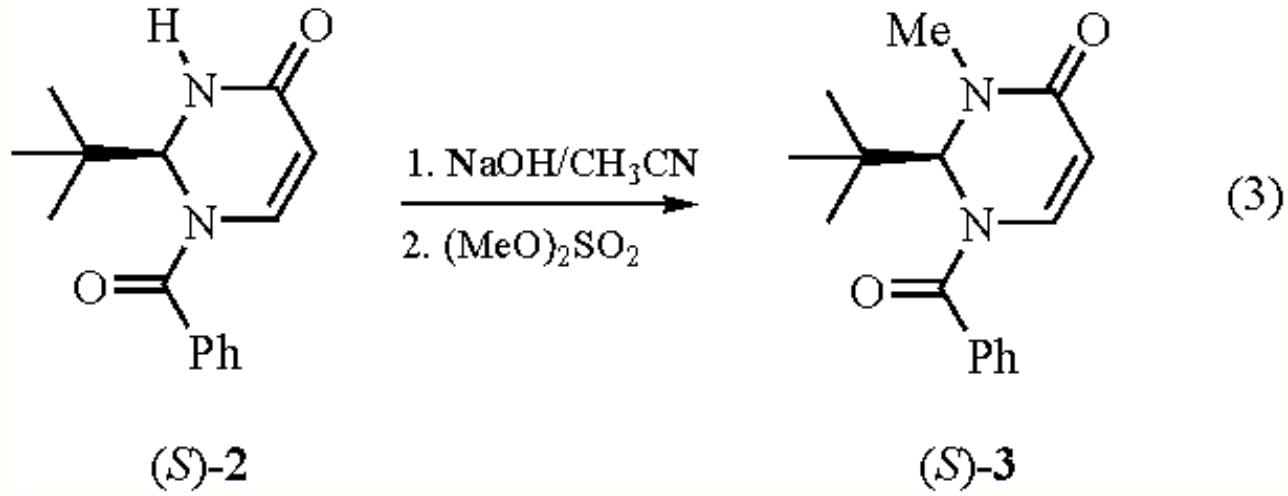

N-Methylation of (*S*)-**2** is best accomplished following the procedure of Juaristi et al.[3] In a 50 mL round-bottomed flask provided with magnetic stirrer is placed 3.0 g (11.6 mmol) of (*S*)-**2** and 15 mL of acetonitrile. The resulting solution is treated with 1.1 mL (11.6 mmol) of dimethyl sulfate (slow addition) and 0.5 g (11.6 mmol) of NaOH (slow addition). The reaction mixture is stirred for 3 h at 45-50°C (mineral oil bath) and the acetonitrile is removed at reduced pressure. The residue is suspended in 50 mL of water and extracted with three 50 mL portions of EtOAc. The combined organic extracts are dried over anhydrous Na_2SO_4 and concentrated to give the crude product that is purified by flash chromatography (hexane-EtOAc, 80:20 r 50:50) to afford 2.7 g (84%) of 1-benzoyl-2(*S*)-*tert*-butyl-3-methyl-2,3-dihydro-4(*H*)-pyrimidin-4-one, mp 141-142°C; $[\alpha]_D^{29}$ +560.2 (*c* 1, $CHCl_3$). Step 4:

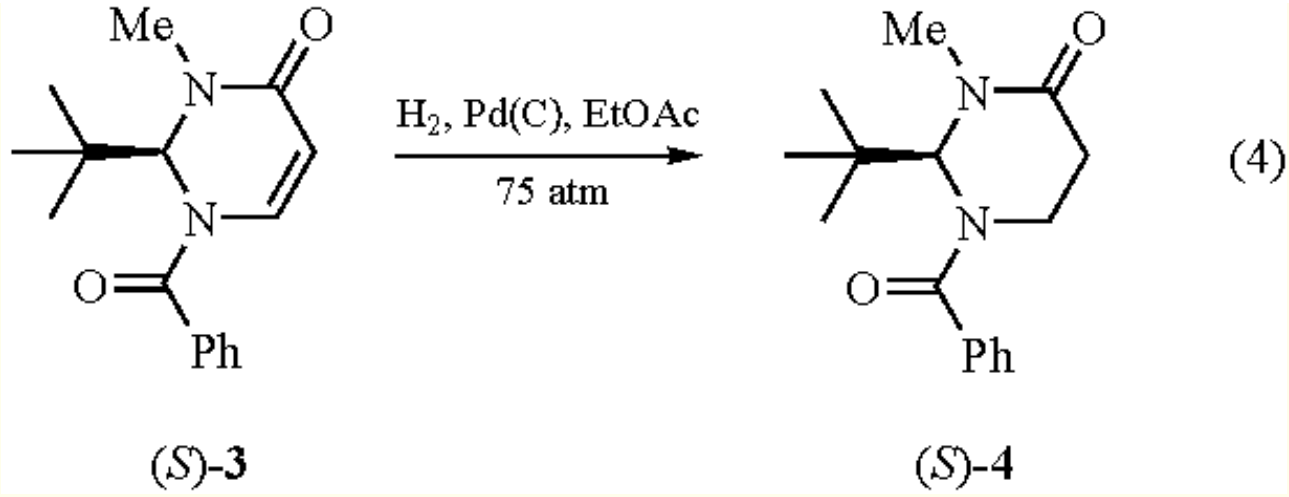

According to the procedure of Juaristi et al.,[2] heterocycle (*S*)-**3** (5.0 g, 18.4 mmol), 40 mL of EtOAc, 0.5 g of 10% Pd(C), and 0.4 mL of acetic acid is placed in a hydrogenation flask. The reaction mixture is pressurized to 75 atm of hydrogen, heated to 45°C, and stirred for 24 h. The catalyst is removed by filtration over Celite, the filtrate is washed with aqueous 10% $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and evaporated at reduced pressure to give 4.5 g (90%) of 1-benzoyl-2(*S*)-*tert*-butyl-3-methylperhydropyrimidin-4-one [(*S*(-**4**], mp 99-100°C; $[\alpha]_D^{29}$ +51.2 (*c* 1, $CHCl_3$). The overall yield in the preparation of (*S*)-**4** from (*S*)-asparagine (four steps) is 49%.

Preparation of enantiopure α-substituted β-amino acids[2,4]

In preliminary studies, racemic 2-*tert*-butyl-perhydropyrimidinone, *rac*-**4**, was alkylated with high diastereoselectivity via its corresponding enolate (eq 5).[5] The high stereoselectivity encountered in the reaction of *rac*-**4**-Li with various electrophiles was ascribed to steric hindrance generated by the axial disposition of the *tert*-butyl group at C(2),[5,6] which directs approach to the electrophile from the enolate face opposite to this group.

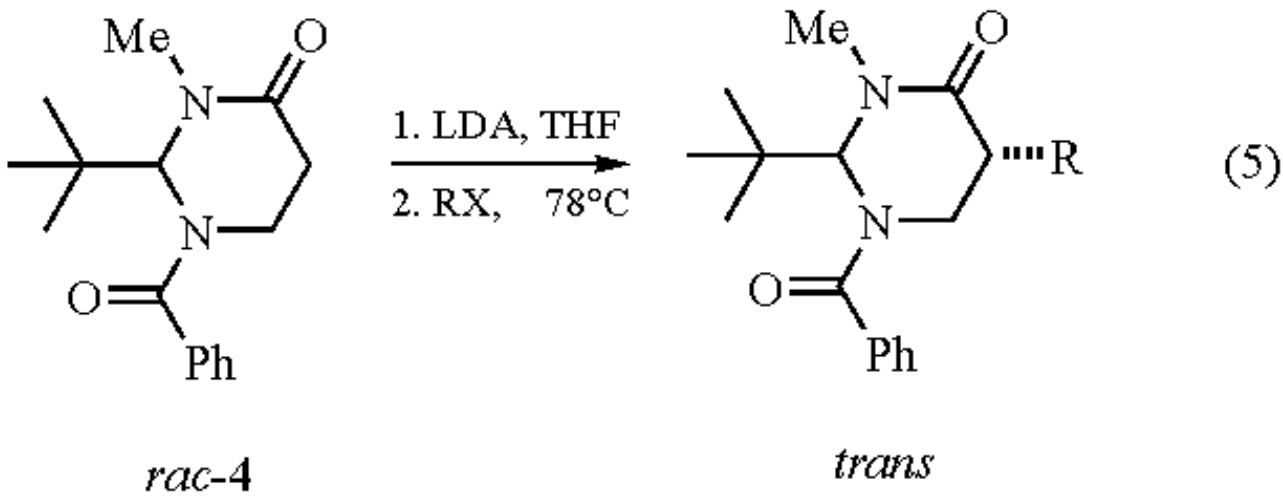

$$RX = CH_3I,\ PhCH_2Br,\ n\text{-}BuI,\ n\text{-}C_6H_{13}I,\ CH_2{=}CHCH_2Cl$$

These observations paved the road for the development of a new method for the asymmetric synthesis of α-substituted β-amino acids. Thus, an efficient protocol for the preparation of enantiopure pyrimidinone (*S*)-**4** was developed (vide supra, eq 1-4).

Enolate (*S*)-**4**-Li was generated upon treatment of the heterocycle with lithium diisopropylamide (LDA) in THF solution and under a nitrogen atmosphere. The electrophile was then added at -78°C to afford the *trans*-alkylated products with high diastereoselectivity and in good yields (eq 6, Table 1).

Table 1 Diastereoselectivity of enolate (*S*)-**4**-Li alkylation

Product	RX	ds (%)	mp (°C)	$[\alpha]_D^{20}$	Yield (%)
5	MeI	>96	121–2	+39.5	77
6	*n*-BuI	95	80–1	+26.7	75
7	*n*-$C_6H_{13}I$	96	70–1	+31.2	80
8	$PhCH_2Br$	>96	173–4	−64.0	80

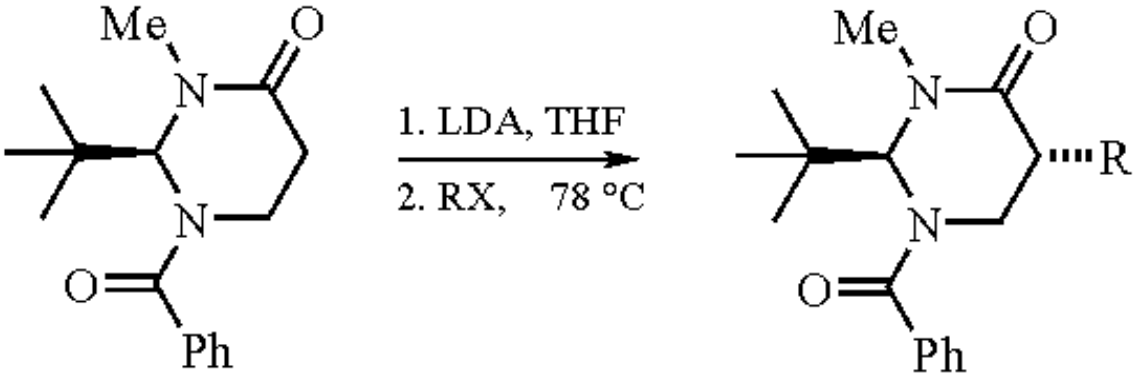

(6)

(*S*)-**4** (2*S*,5*R*)-**5-8**

The final step of the overall conversion of (*S*)-asparagine to 2-alkyl-3-aminopropanoic acid, the hydrolysis of heterocycles **5-8**, was achieved by heating with 6 N HCl in a sealed tube at 90-100°C. The free amino acids **9-12** were purified by chromatography on an ion-exchange column (eq 7, Table 2).

Table 2 Hydrolysis of products **5–8**

R	mp (°C)	$[\alpha]_D^{20}$	Yield (%)
Me	185–6	11.8	80
n-Bu	170–1	+5.3	80
n-C_6H_{13}	219–20	+6.6	80
$PhCH_2$	225–6	+11.3	85

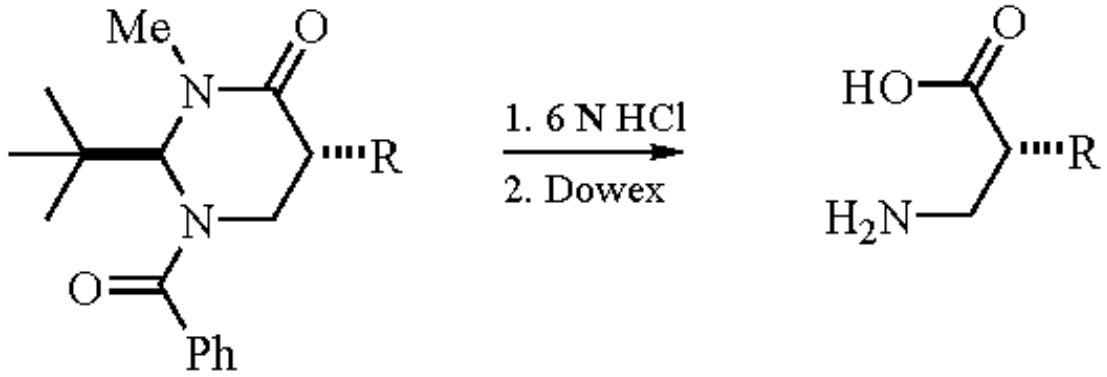

(7)

(2*S*,5*R*)-**5 8** (*R*)-**9 12**

Epimerization of adducts 5-8, and hydrolysis to give the enantiomeric α-alkylated β-aminopropionic acids

In principle, α-substituted β-amino acids of opposite configuration, (*S*)-**9-12**, can be obtained when enantiomeric pyrimidinone (*R*)-**4** [from (*R*)-asparagine] is used as the starting material, following the reaction sequence described above. Nevertheless, a practical alternative consisted in the epimerization of *trans*-adducts **5-8** to afford the *cis*-diastereoisomers **13-16** (eq 8). Hydrolysis of *cis*-**13-16** provided the desired (*S*)-α-substituted β-amino acids, (*S*)-**17-20** (eq 9).[2]

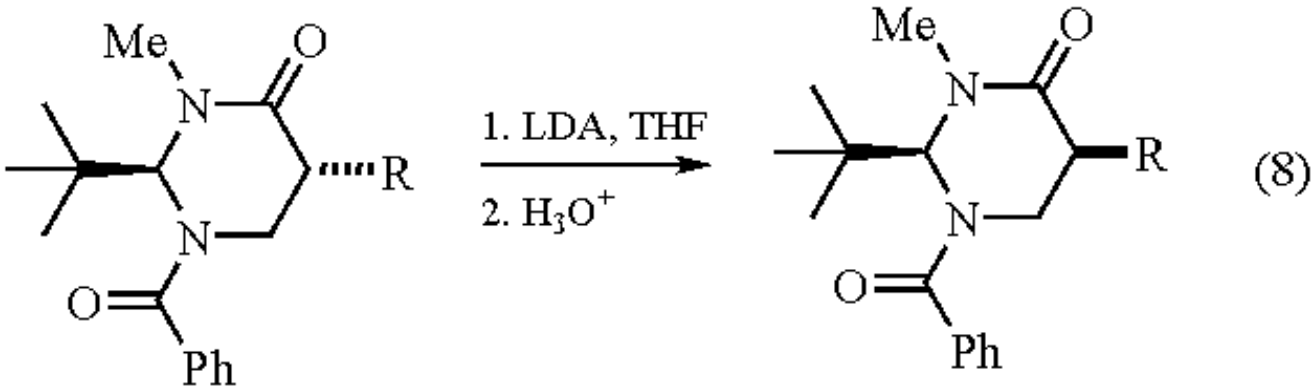

(2*S*,5*R*)-**5** **8** (2*S*,5*S*)-**13** **16**

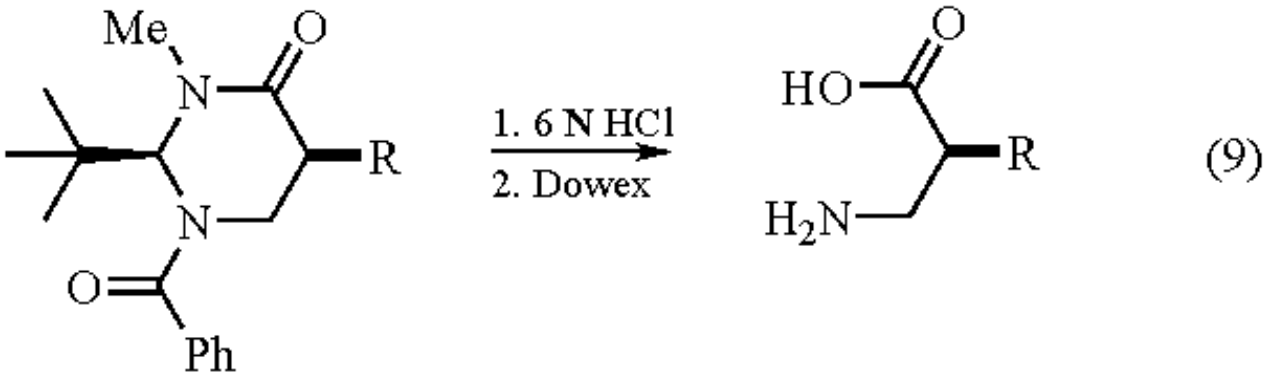

(2*S*,5*S*)-**13** **16** (*S*)-**17** **20**

Clearly, protonation (aqueous NH_4Cl) of the enolates generated from **5**-**8** takes place on the face opposite to the *tert*-butyl group, and this reaction is also highly stereoselective.

Preparation of enantiopure α,α-disubstituted β-amino acids[7,8]

(2*S*,5*R*)-**5**-**8** were alkylated via their corresponding enolates to provide suitable precursors of enantiopure α,α-dialkylated β-amino acids. Thus, enolates (2*S*)-**5**-**8**-Li were generated upon treatment of the appropriate heterocycle with LDA in THF solution and under nitrogen atmosphere. The electrophile (methyl iodide, ethyl iodide, *n*-butyl bromide, *n*-hexyl iodide, or benzyl bromide) in solvent *N,N´*-dimethylpropyleneurea (DMPU) was then added at -78°C to afford the dialkylated products with high diastereoselectivity and in excellent yields (Table 3). The use of DMPU as cosolvent was necessary to effect the dialkylation in high yield (eq 10).[9]

Table 3 Diastereoselectivity of enolate (2*S*)-**5**–**8**-Li alkylations

R^1	R^2	ds (%)	mp (°C)	$[\alpha]_D^{20}$	Yield (%)
Me	*n*-Bu	>97	184–5	+30.3	81
n-Bu	Me	>97	147–8	+12.6	88
Me	CH_2Ph	>97	209–10	−48.8	96
CH_2Ph	Me	>97	129–30	−38.7	92
CH_2Ph	Et	>97	106–7	−35.3	76
CH_2Ph	*n*-Bu	>97	[a]	−11.3	63

[a] Viscous oil.

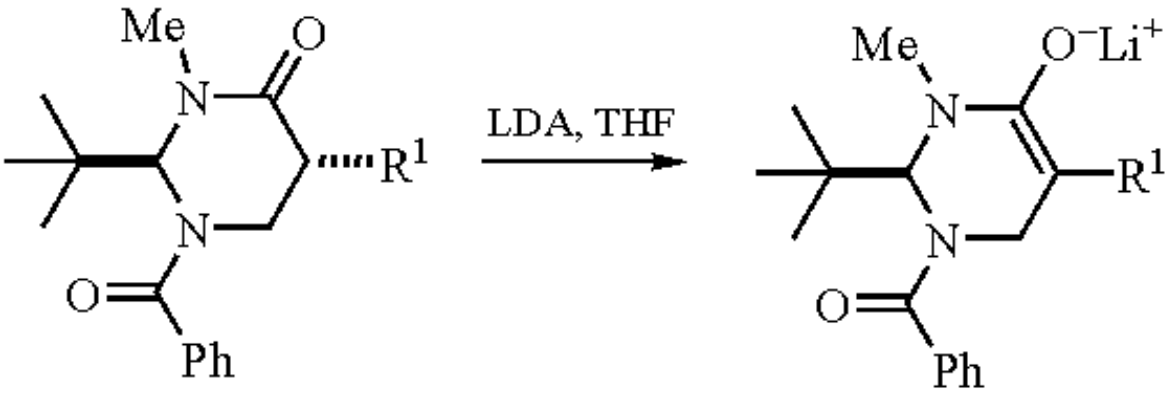

(2*S*,5*R*)-**5** **8** (2*S*)-**5** **8**-Li

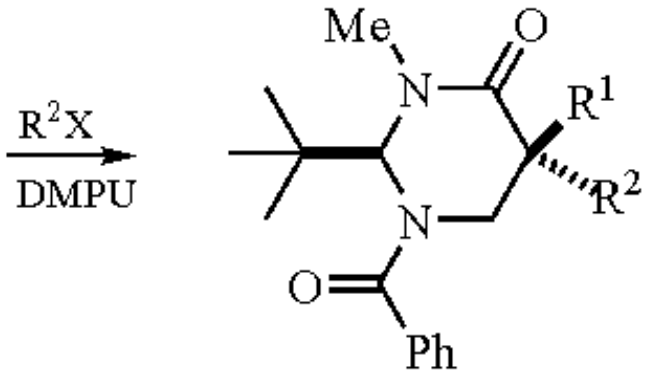

(10)

21 **26**

Hydrolysis of geminal disubstituted perhydropyrimidinones **21**-**26** necessitated drastic conditions: 8 N HCl at 100-140°C in a sealed tube. While these harsh conditions may not be tolerated by sensitive amino acids,[10] they proved harmless to the α,α-disubstituted β-amino acids **27**-**32**. Nevertheless, milder conditions could be employed when *p*-dioxane was used as cosolvent, since improved solubility of the substrate in the aqueous medium resulted in much faster hydrolysis (eq 11).

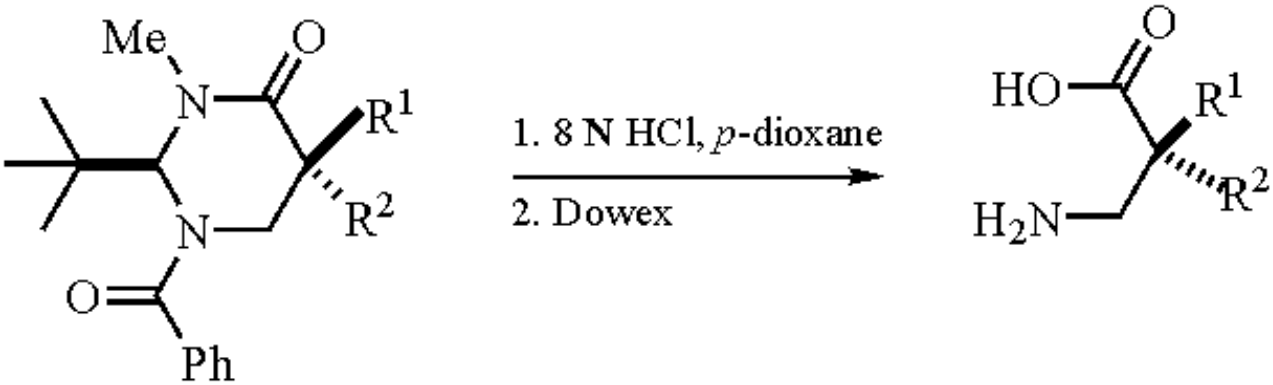

(11)

21 **26** **27** **32**

Related Reagents.

Owing to the high price of pivalaldehyde, we have substituted this aldehyde with isobutyraldehyde in the synthesis of imino ester (2*S*,6*S*)-**33**, which proved to be a convenient substrate for the enantioselective synthesis of α-substituted aspartic acids (eq 12).[11,12]

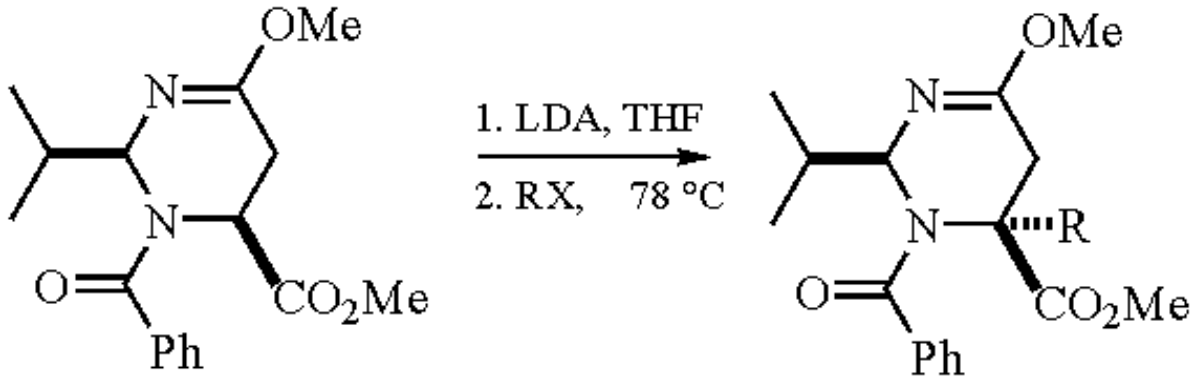

(12)

(2*S*,6*S*)-**33** (2*S*,6*S*)-**34-37**

Hydrolysis of the alkylated products (2*S*,6*S*)-**34-37** and isolation of the desired amino acids was facilitated by the presence of the labile imino group.[13] Indeed, hydrolysis was achieved by heating with 17% HCl in a sealed tube at 95°C. The free amino acids **38-41** were purified by chromatography on an ion-exchange column (eq 13).[8,11]

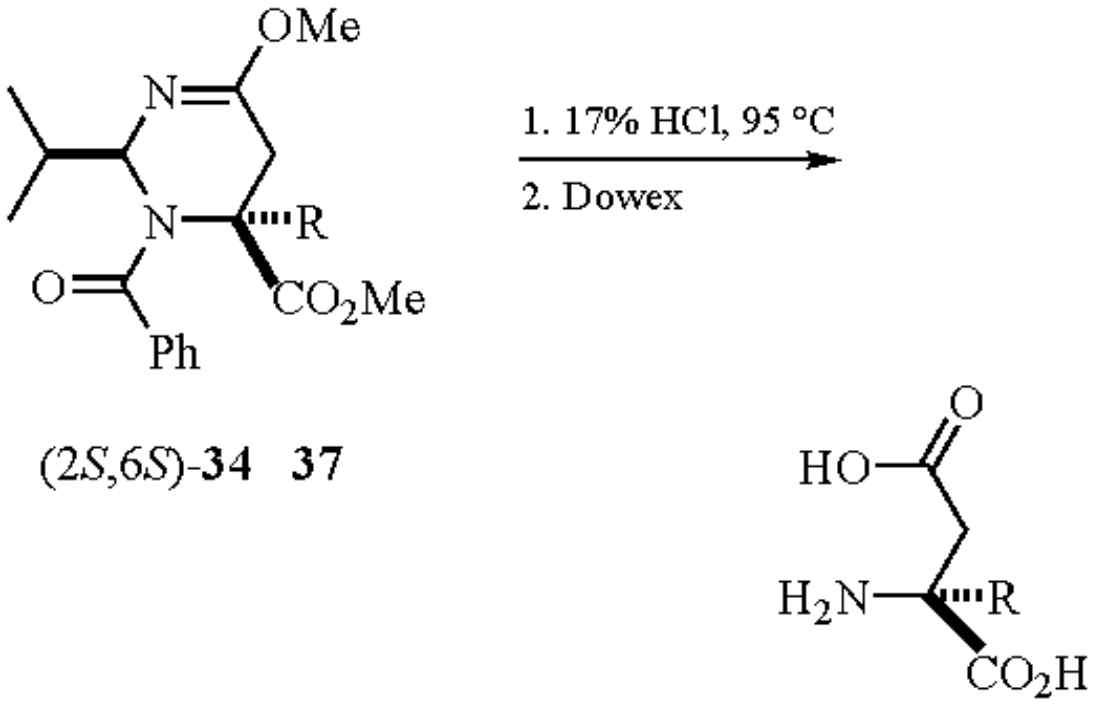

(2*S*,6*S*)-**34 37** (*S*)-**38 41**

R= Me, Et, *n*-Bu, CH_2Ph (13)

On the other hand, Beaulieu et al.[14] have reported the synthesis of unusually functionalized optically active β-substituted β-amino acids via the highly diastereoselective ((95:5) transformation of enantiopure *N*-(*o*-iodobenzoyl)-2-*tert*-butylperhydropyrimidinone [(*S*)-**42**] (eq 14).

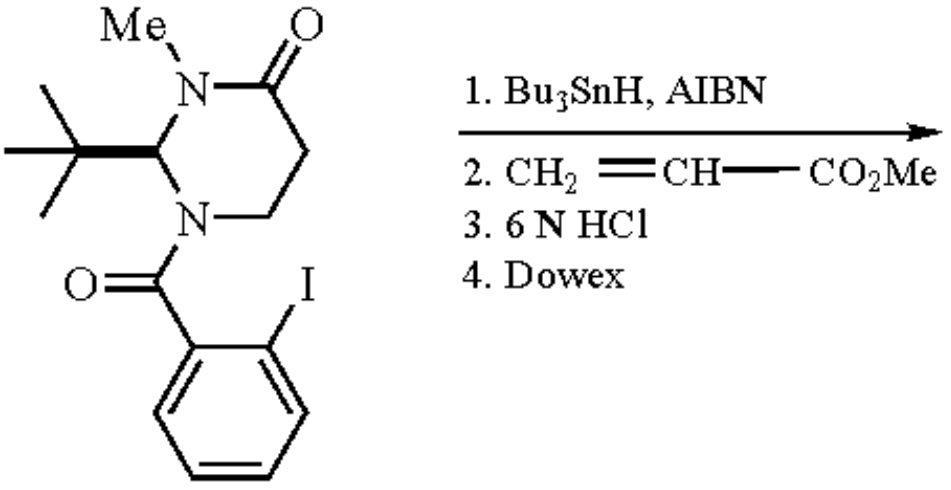

(*S*)-**42**

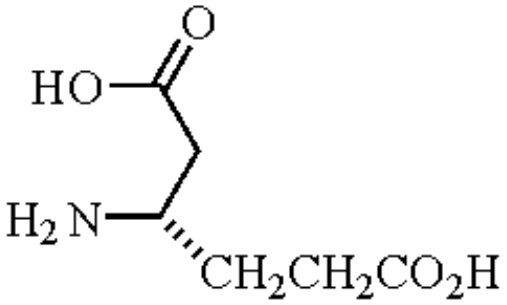

(14)

(*S*)-**43**

In this context, dihydropyrimidinone (*R*)-**44** has been exploited by Chu et al.[15] and Konopelski et al.[16] in the enantioselective synthesis of β-alkyl β-amino acids. Furthermore, *N*-phenethylperhydropyrimidinone (*S*)-**45**,[17,18] as well as the 6-substituted analogs **46**-**48** (configuration not indicated)[19-22] are useful substrates for the asymmetric synthesis of α,β-disubstituted β-amino acids.

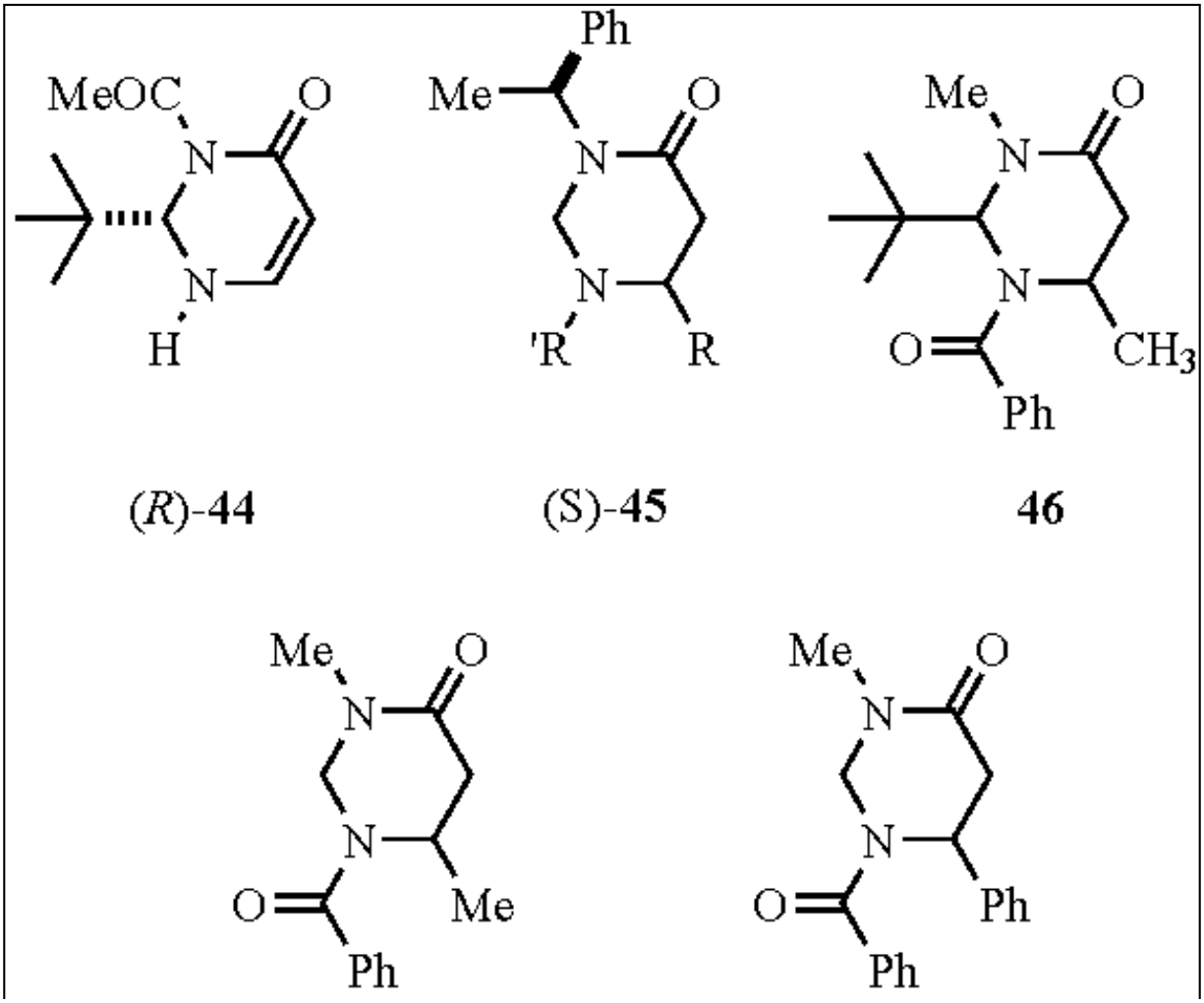

(*R*)-**44** (S)-**45** **46**

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Polymer-Supported Bis(acyloxy)iodate(I)

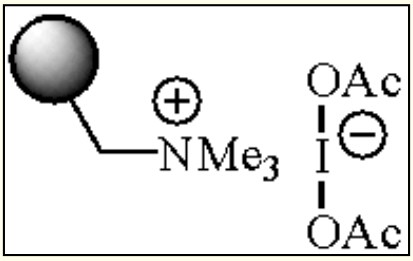

[68574-12-9]F

(a new electrophilic polymer-supported reagent which efficiently promotes iodo acetoxylations of alkenes as well as iodination of terminal alkynes[1])

Physical Data: Loading 2.1 mmol g^{-1} (based on the amount of iodide attached to the commercial resin, assuming that all iodide ions are transformed into the active species); polymer matrix: copoly(styrene-DVB), 20-50 mesh.

Solubility: insoluble in most organic and aqueous solvents.

Form Supplied in: macroscopic, light yellow resin beads; readily available by following the procedure provided below.

Preparative Methods: a suspension of polymer-bound iodide (available from Fluka; 1 equiv, 2.9 mmol g^{-1} resin) and $PhI(OAc)_2$ (1.8 equiv) in dry dichloromethane (3 mL $mmol^{-1}$ iodide) under nitrogen is shaken at 300 rpm for 6 h at room temperature. The brownish suspension was protected from light. Filtration and washing of the resin with dichloromethane (3×, 25 mL g^{-1} resin) and drying in vacuo affords the light yellow title polymer. The weight increase serves as an indicator for efficient ligand transfer onto polymer-bound iodide and gives most reproducible results (about 90% conversion with respect to theoretical iodide). Recycling: a suspension of the used polymer (18 g) in concentrated HI (25 mL, 67%) is stirred vigorously for 10 min. After addition of another 10 mL of distilled water, the suspension is stirred for an additional 30 min. Filtration and washing of the resin with $water_{(dest)}$ (500 mL), absolute methanol, (400 mL) and absolute dichloromethane (300 mL) affords the dark brown supported iodide resin which can be used again after treatment with $PhI(OAc)_2$ without substantial loss of activity.

Handling, Storage, and Precautions: The bis(acyloxy)iodate(I) resin can be prepared on a 100 g scale. It is the most labile resin (thermally and photochemically) among resin-bound haloates, including the bis(azido)iodate(I) resin and the bis(acyloxy)iodate(I) resin described so far. It can be stored below -15°C and protected from light for at least 1 week, but preferentially should be used shortly after its preparation. Because of its sensitivity to air and moisture, the resin should be stored under nitrogen. A strong smell of acetic acid indicates the decomposition of the active species. This resin is not yet fully tested and should be used only with the usual precautions.

Background

The development and use of polymer-supported reagents has seen a dramatic increase over the past 5 years, although the basic principles of this technique have been known for at least 30 years.[2] The advantage of this hybrid solid-solution-phase technique lies in the simple work-up and isolation of the reaction products, even if these reagents are used in excess in order to drive the reaction to completion. Haloate(I) complex **1** is a new electrophilic member of this class of reagents with diverse chemical properties[1,3-6] as is briefly depicted below.

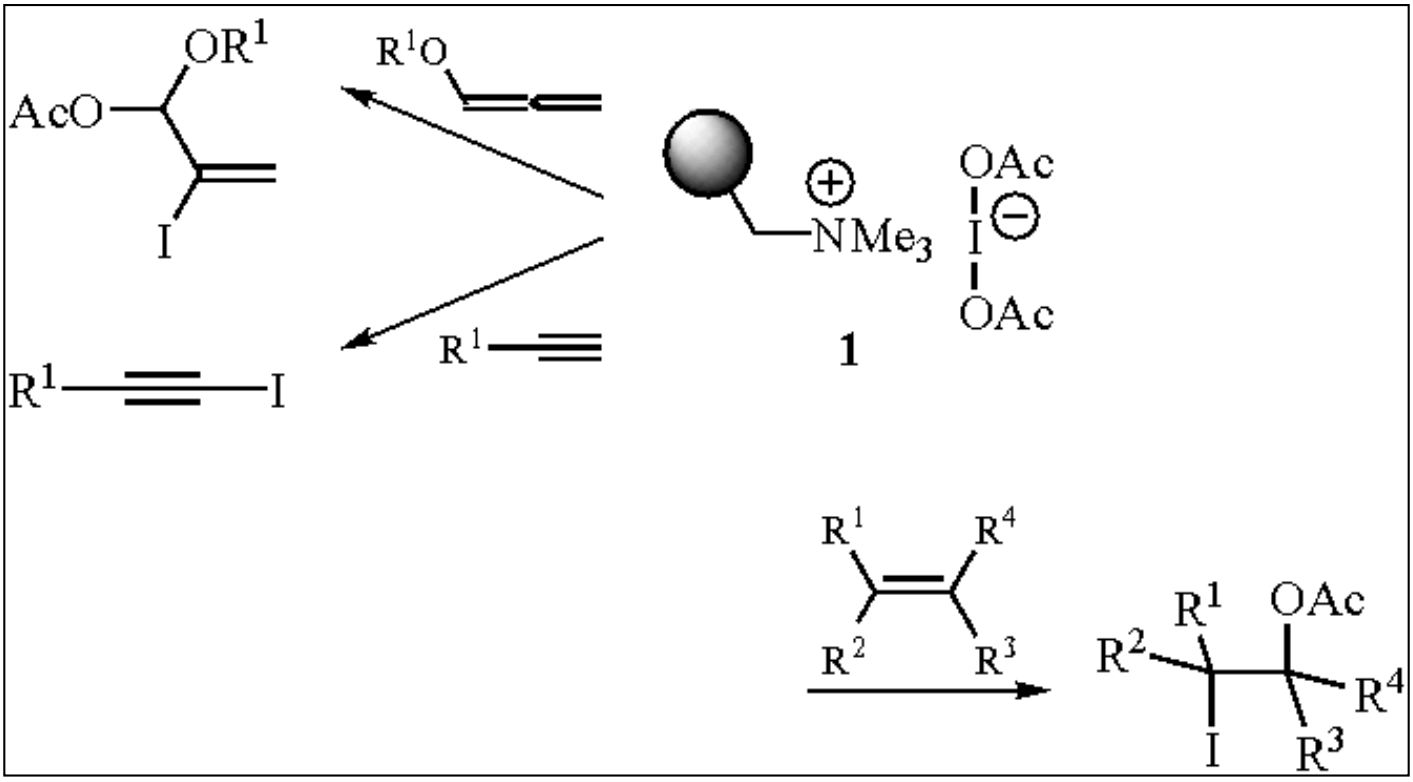

1,2-Iodoacetoxylations of alkenes[1,3-5]

General Procedure

A mixture of alkene or alkyne (1 equiv) and resin (3-4 equiv) is shaken at 300 rpm under protection from light in dry dichloromethane (1.5 mL $mmol^{-1}$) at room temperature. Completion of the reaction is monitored by TLC. Filtration terminates the reaction. The resin is washed with dichloromethane (3×40 mL g^{-1} resin), and the combined organic washings and filtrate are concentrated under reduced pressure. In some cases, further purification by column chromatography is necessary.

Following this general procedure (see also reference 1), in most cases, 1,2-functionalization of alkenes affords single iodoacetoxylation products **2-5**.

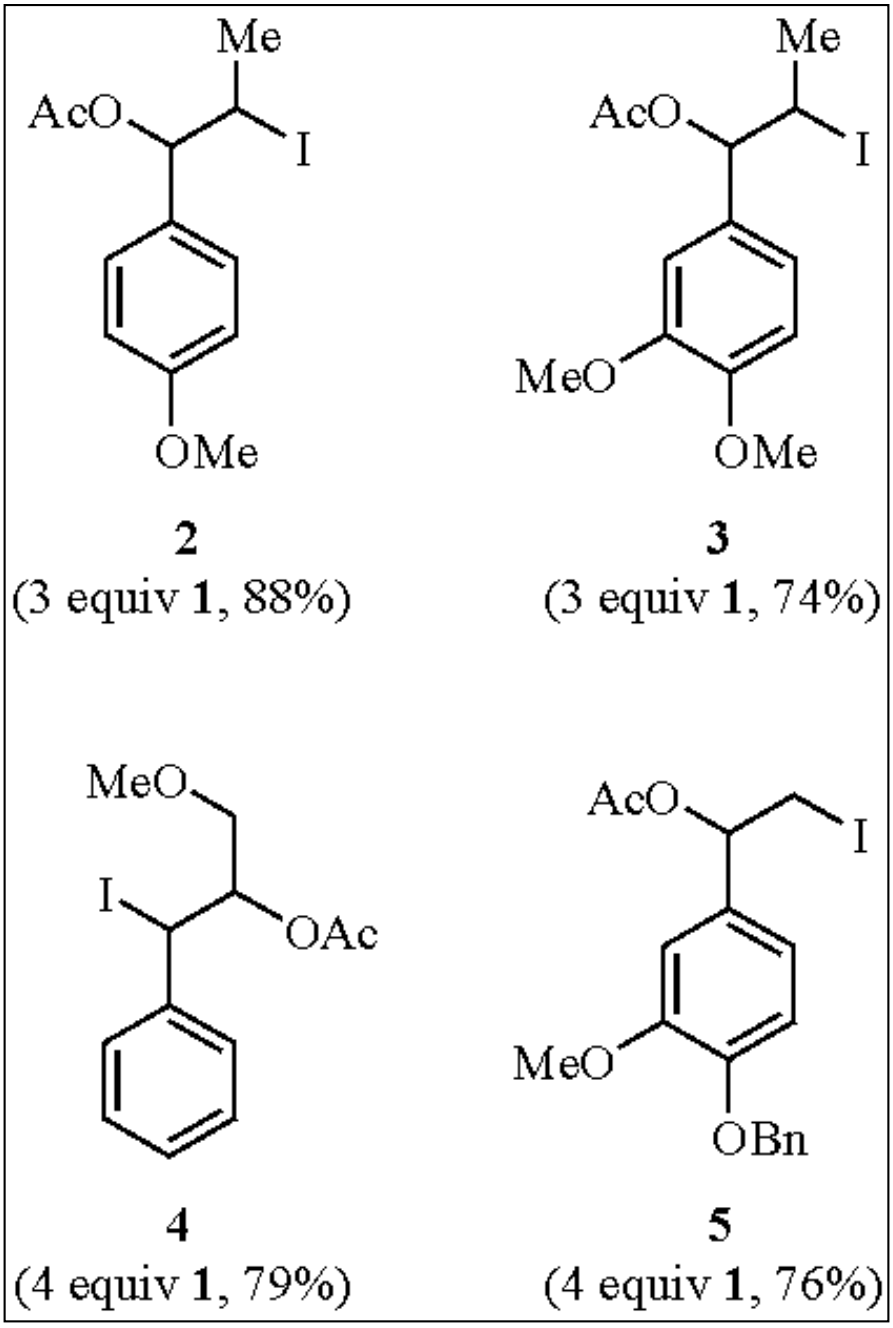

The addition proceeds with *trans* selectivity, as demonstrated for cyclohexene- and indene-transformation products **6** and **7**. The transformation of alkoxyallenes into the corresponding vinyliodides **8** and **9** demonstrates that inductive effects of the double bond substituents determine the chemoselectivity of the process.

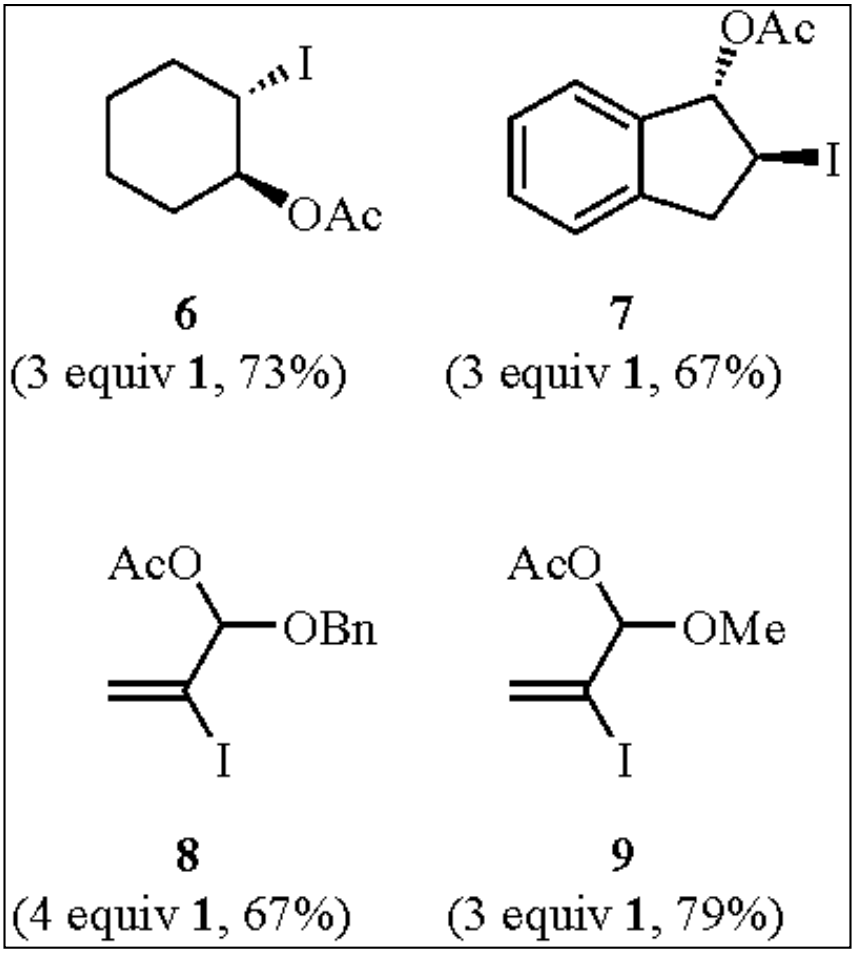

Halogenated substrates react very sluggishly at room temperature; at 80°C complete consumption of alkenes is achieved. Under these conditions 4-bromostyrene gives the desired 1,2-addition product **10** in moderate yield, while 3-chloro-1-phenylprop-1-ene yields iodoacetoxylation product **11** in low yield. In contrast, allyl chloride undergoes nucleophilic substitution to furnish allyl acetate **12** as the major product.

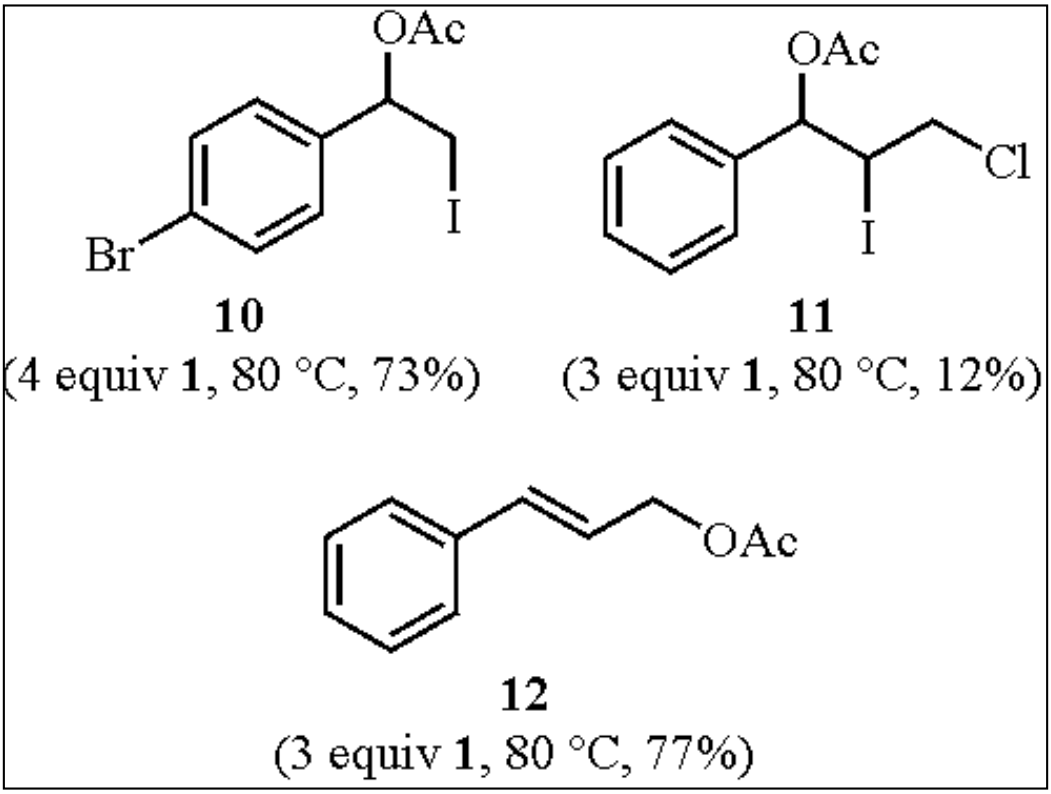

Importantly, hydroxy groups are tolerated under the reaction conditions but can be converted to derivatives. Allyl alcohol **13** affords acetate **15** in excellent yield, indicating that the expected addition to give **14** is followed by an acyl migration to the terminal alcohol group (eq 1). In contrast, the corresponding homoallyl alcohol gives an intermediate cation which is trapped in an intramolecular mode by the hydroxy group to furnish tetrahydofuran **16**.

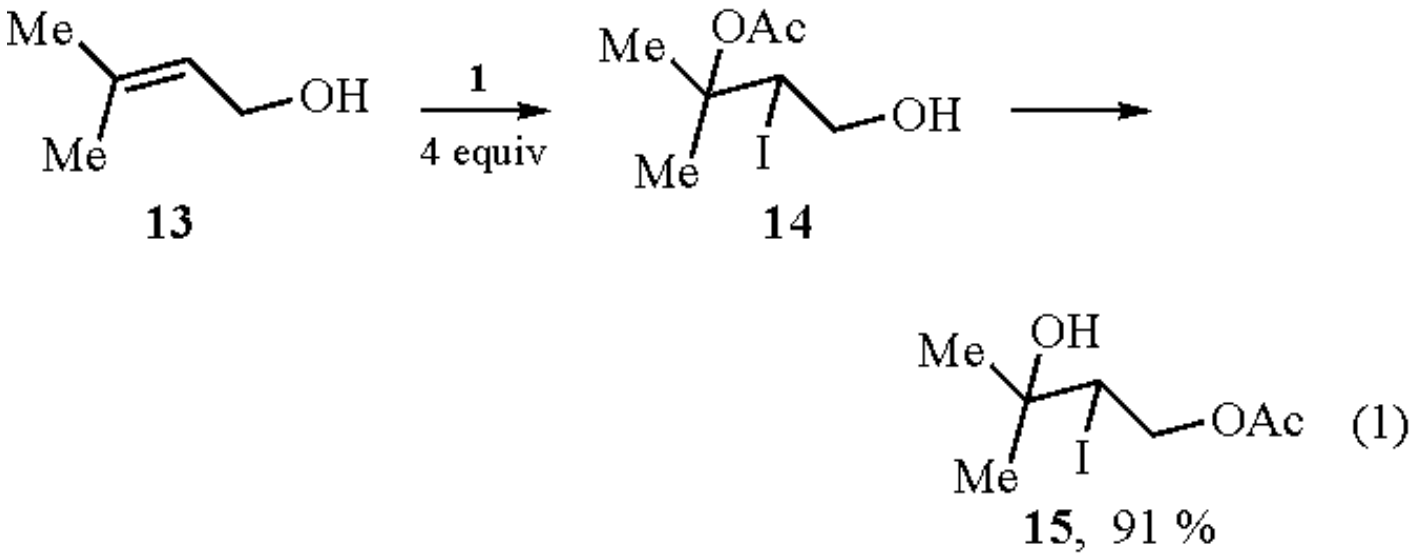

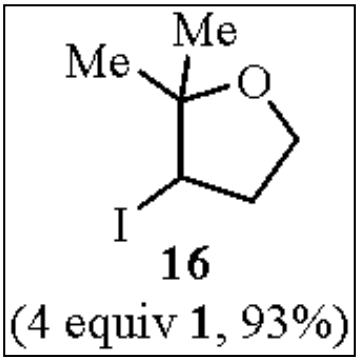

Likewise, partially, and even fully, unprotected glycals can, in the presence of reagent **1**, undergo a 1,2-functionalization as summarized for glycosyl acetates **22**, **24** and **17**. In addition, the iodoacetoxylation of protected carbohydrate-derived glycals is carried out in different solvents (see ref 3) with excellent yields of the corresponding 2-deoxy-2-iodo-glycosyl acetates (**18**-**21**, **23**). In most cases, filtration of the resin and removal of the solvent in vacuo affords the reaction products with high purity.

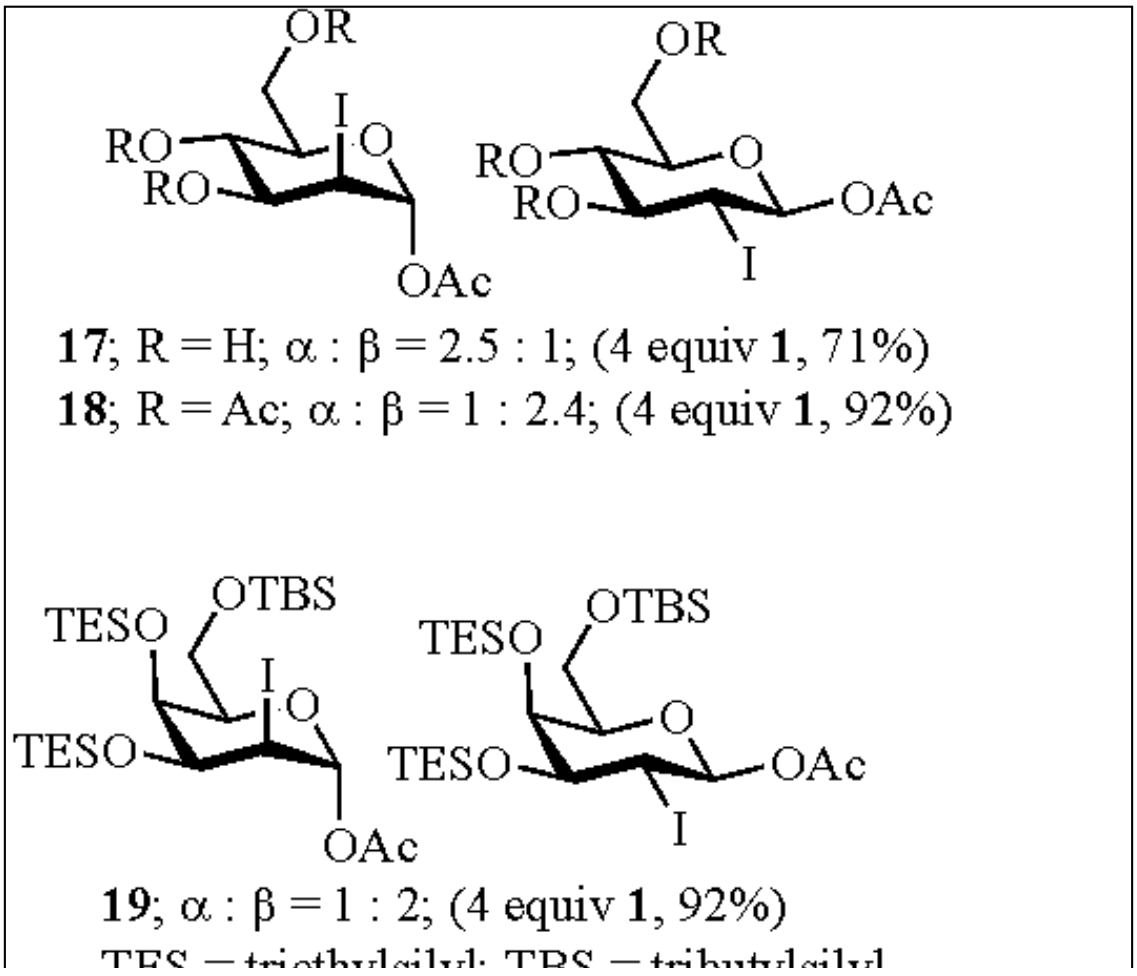

TES = triethylsilyl; TBS = tributylsilyl

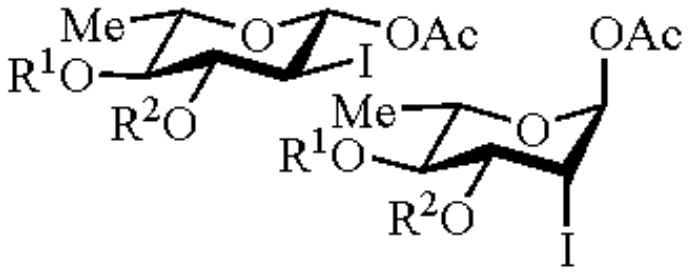

20; $R^1 = R^2 = Bn$; $\alpha : \beta = 1.5 : 1$; (3 equiv **1**, 92%)

21; $R^1 = R^2 = TBS$; $\alpha : \beta = 1.2 : 1$; (3 equiv **1**, 98%)

22; $R^1 = H$, $R^2 = TBS$; $\alpha : \beta = 2.5 : 1$; (4 equiv **1**, 83%)

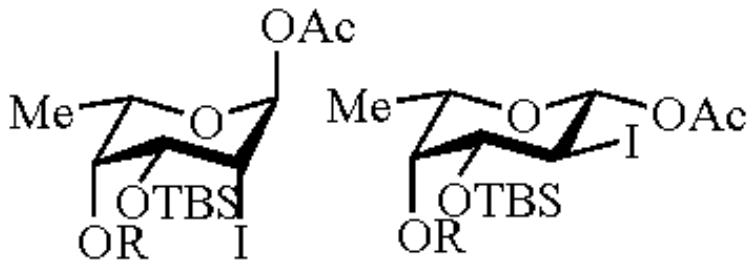

23; R = TBS; $\alpha : \beta = 1 : 1$; (4 equiv **1**, 97%)

24; R = H; $\alpha : \beta = 1 : 9$; (4 equiv **1**, 88%)

Furthermore, the title reagent **1** promotes transformation of vinyl and allyl silanes and, instead of the expected desilylation, the 1,2-addition products **25-29** are formed as major products (see ref 5).

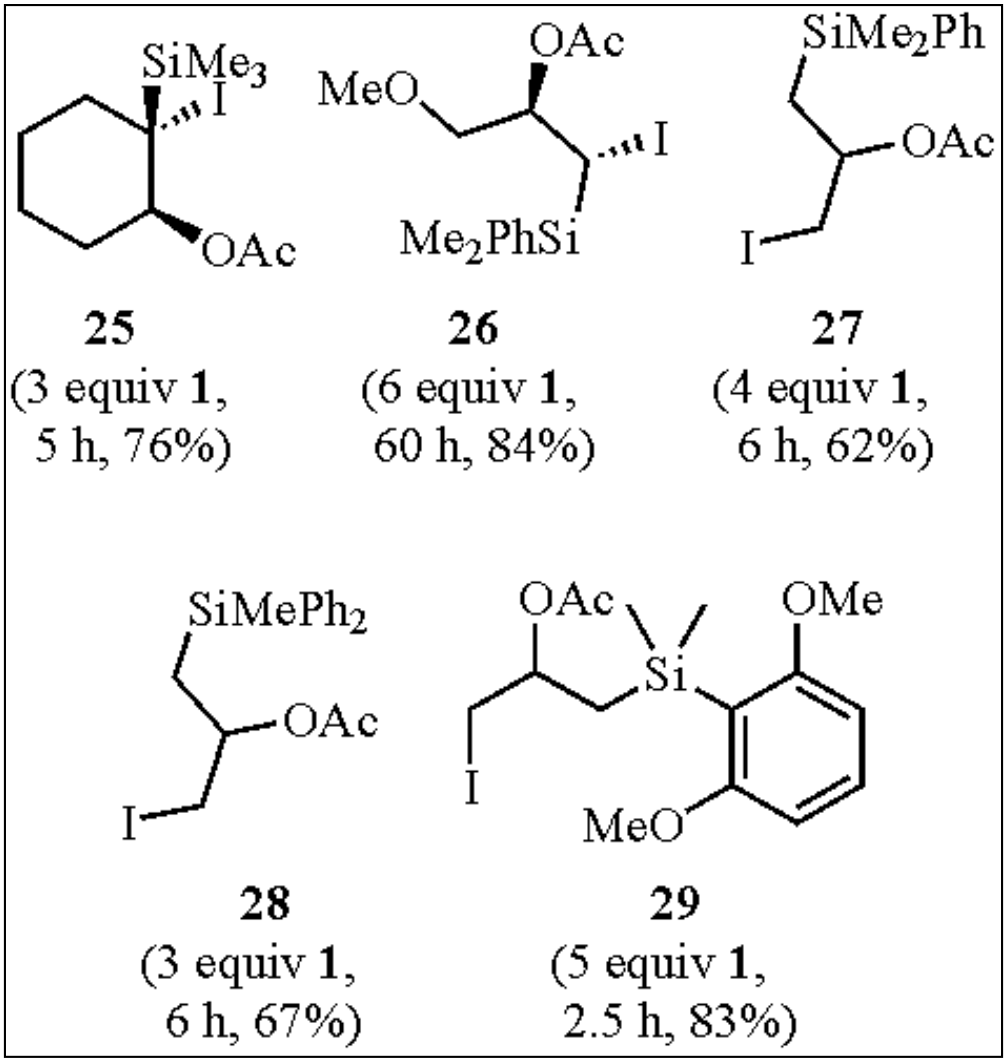

All transformations are achieved using an excess of the immobilized reagent **1**. This may be rationalized by assuming that only the most accessible haloate(I) anions are involved in the cohalogenation process. If acylated, hypohalites are the active species after release from the polymer, their degradation prior to the reaction with alkenes may also contribute to the need for a formal excess of reagent.

When comparing this polymer-supported technique with the solution variant[7-9] using tetraethylammonium iodide and (diacetoxyiodo)benzene for the in situ preparation of $Et_4NI(OAc)_2$ (see refs 7 and 8) and subsequent iodoacetoxylation, the isolated yields for the acetates that are derived from the solution variant are reduced due to their lability during the recommended reductive aqueous work-up.

Iodination of alkynes[1]

A second set of experiments using terminal alkynes for the transformation with the title reagent **1** affords alkynyl iodides **30**-**33**, presumably generated by electrophilic attack of the iodonium ion and formation of an intermediate vinyl cation followed by deprotonation. Remarkably, the nitrile functionality in **32** is tolerated.

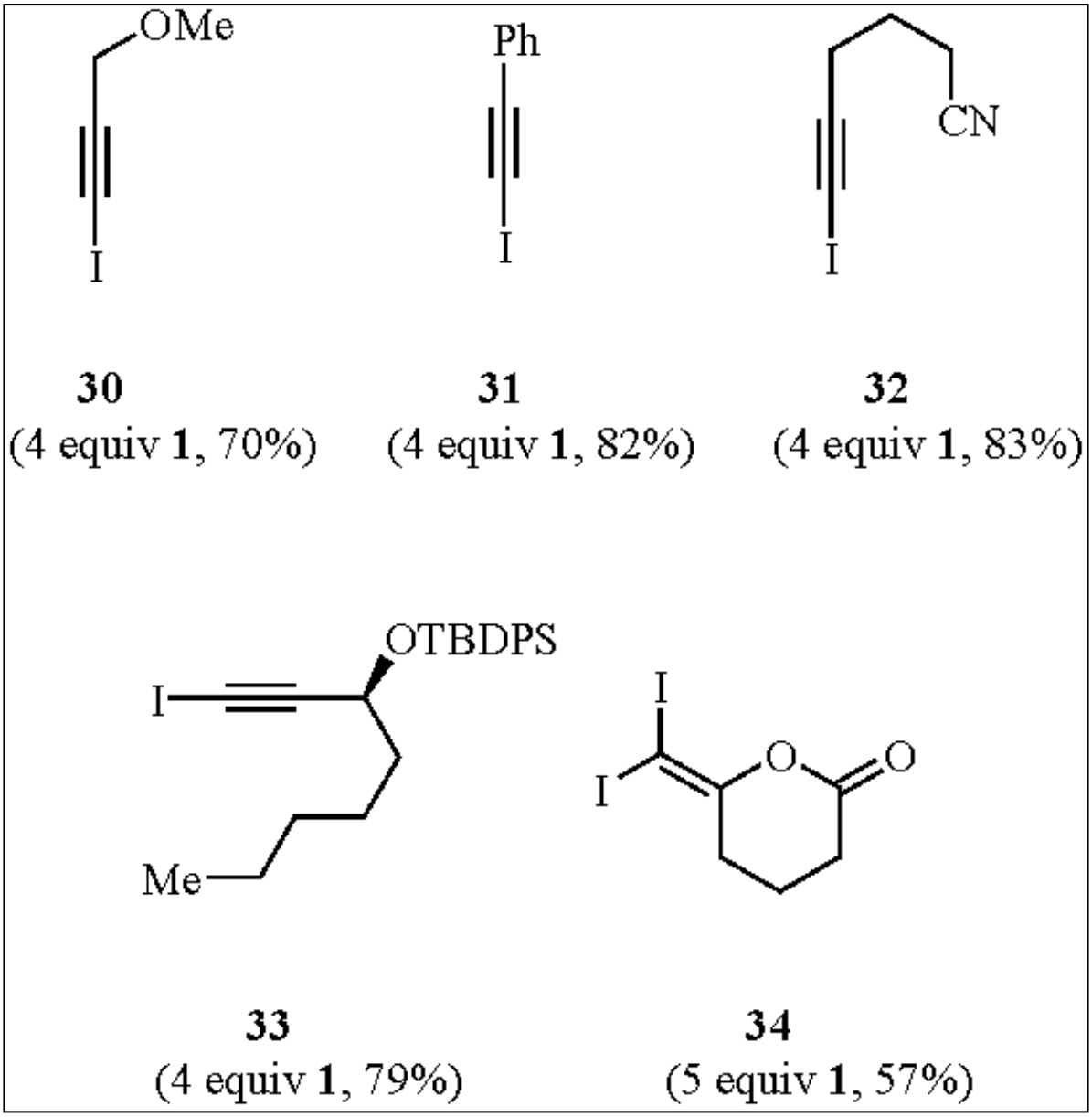

The formation of the unusual cyclization product **34**, generated from the corresponding acyclic terminal alkyne, may be rationalized by electrophilic attack of a second equivalent of the iodonium ion onto the triple bond in the corresponding intermediate iodoalkyne and subsequent cyclization.

It is noteworthy that, unlike classical reagents for the acetoxyiodination of alkenes, the use of the title reagent **1** does not require glacial acetic acid or heavy metals. More specific features and advantages of this reagent are: (1) the polymer is readily available, (2) the preparation is short and straightforward, (3) the work-up of the reaction products is simple filtration and concentration, (4) the reaction mixture is free of iodobenzene, which is the common by-product when hypervalent reagents like the starting diacetoxyiodobenzene are employed, (5) the reagent is storable to some extent, (6) the reagent is generated and can be applied in different organic solvents, and (7) the reagent is recyclable.

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Andreas Kirschning & Holger Monenschein

Polymer-Supported Bis(acyloxy)bromate(I)

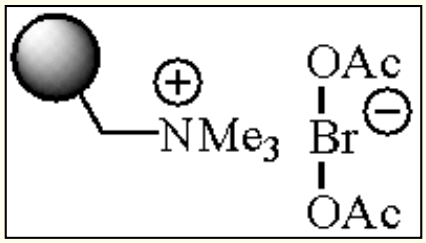

[256385-96-3]F

(a new polymer-supported oxidant described which performs the oxidation of primary and secondary alcohols into their corresponding carbonyl compounds[1])

Physical Data: 2.4 mmol g^{-1} (based on the amount of bromide attached to the commercial resin, assuming that all bromide ions are transformed into the active species; polymer matrix: copoly(styrene-DVB), 20-50 mesh.

Solubility: insoluble in organic solvents and aqueous solutions.

Form Supplied in: macroscopic, brown resin beads; available by following the procedure provided below.

Preparative Methods: a suspension of untreated polymer-bound bromide (e.g. available from Fluka; 1 equiv, 3.2 mmol g^{-1} resin) and $PhI(OAc)_2$ (1.8 equiv) in dry dichloromethane (3 mL $mmol^{-1}$ bromide) is shaken under nitrogen at 300 rpm for 8 h at room temperature. The brownish suspension is protected from light. Filtration and washing of the resin with dichloromethane (3×, 20 mL g^{-1} resin) and drying in vacuo affords the brown title polymer. The weight increase serves as an indicator for efficient ligand transfer onto polymer-bound bromide and gives the most reproducible results (about 85-90% conversion with respect to theoretical bromide). Recycling: a suspension of the used polymer (5 g) in NaOH (2×20 mL, 1 M) is stirred vigorously for 10 min. After washing with distilled water (2×25 mL), the wet resin is treated with HBr (2×25 mL, 2 N). Filtration and washing of the resin with $water_{(dest)}$, (40 ml) absolute methanol (30 mL) and absolute dichloromethane (30 mL) affords the light yellow supported bromide resin, which can be used again after treatment with $PhI(OAc)_2$ without substantial loss of activity.

Handling, Storage, and Precautions: The immobilized bis(acyloxy)bromate(I) complex can be prepared on a 100 g scale. Protected from light, it can be stored below -15°C for weeks without loss of activity. Because of its sensitivity to air and moisture, it should be stored under argon. A strong smell of acetic acid indicates the decomposition of the active species. This resin is not yet fully tested and should only be used with the usual precautions.

Background

Since the beginning of modern synthetic organic chemistry, the goal of chemists has been to produce single compounds in as pure form as possible. In this context, the development and applications of polymer-supported reagents has seen a dramatic increase in interest lately.[2] The advantage of this hybrid solid-solution-phase technique lies in the simple work-up and isolation of the reaction products, even if these reagents are used in excess in order to drive the reaction to completion.

Haloate(I) complex **1**[1] is a new member of this class of reagents with diverse chemical properties.[3-5]

Oxidation of Alcohols[1]

General Procedure

A mixture of alcohol (1 equiv), resin **1** (3-6 equiv) and catalytic amounts of 2,2,6,6-tetramethyl-l-piperinyloxyl (2 mol%) are shaken at 300 rpm in dry dichloromethane (1.5 mL $mmol^{-1}$) at room temperature. Completion of the reaction is monitored by TLC. Filtration terminates the reaction. The resin is washed with dichloromethane (3×40 mL g^{-1} resin), and the combined organic washings and filtrate are concentrated under reduced pressure. Generally, no further purification by column chromatography is necessary.

Under these conditions primary alcohols are oxidized into aldehydes **2-8** and, importantly, secondary alcohols are converted into ketones **9-15** in excellent yields (yields in parentheses refer to determination by GC).

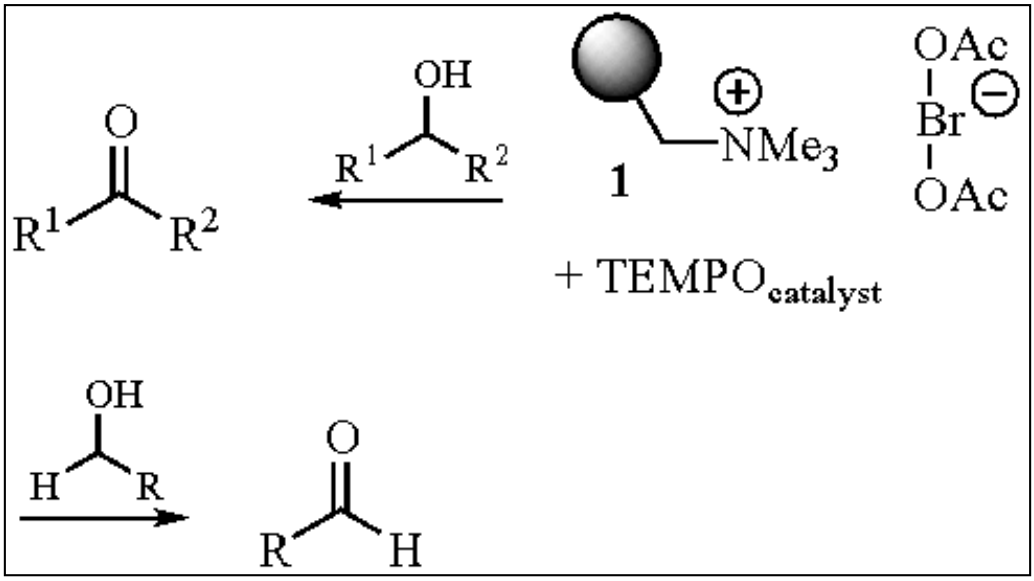

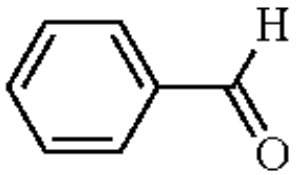

2
(3 equiv **1**, 94%)

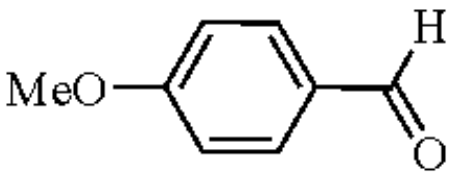

3
(3 equiv **1**, 78%)

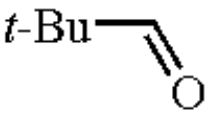

4
(3 equiv **1**, 95%)

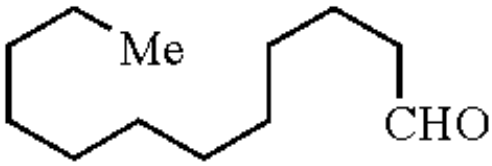

5
(3 equiv **1**, 93%)

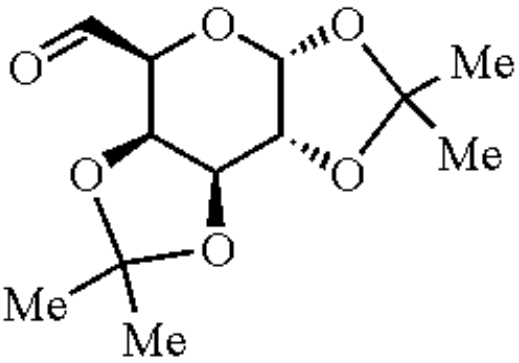

6
(3 equiv **1**, 97%)

(3 equiv **1**, 97%)

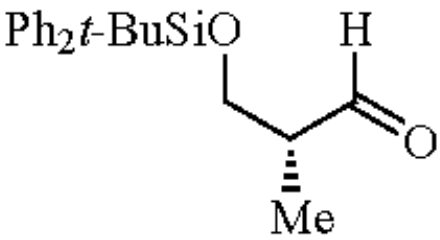

7
(4 equiv **1**, 99%)

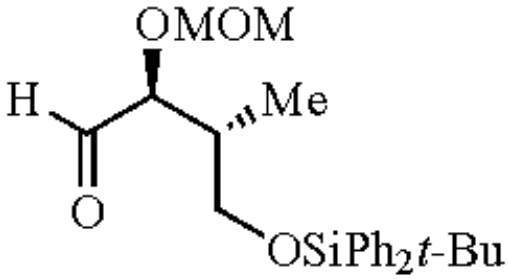

8
(4 equiv **1**, 99%)

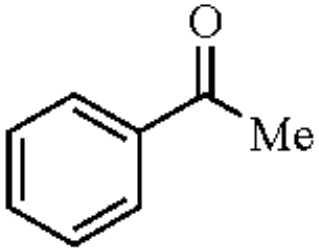

9
(3 equiv **1**, 92%)

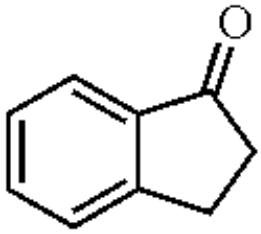

10
(3 equiv **1**, 81 (95)%)

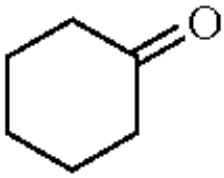

11
(3 equiv **1**, 78 %)

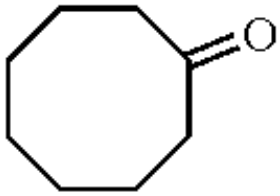

12
(3 equiv **1**, 80%)

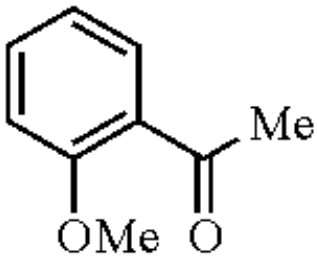

13
(3 equiv **1**, 96 (95)%)

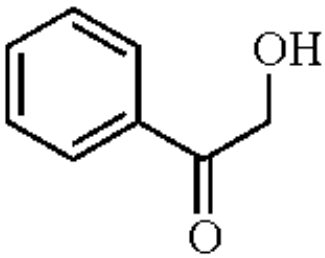

14
(3 equiv **1**, 44 (85)%)

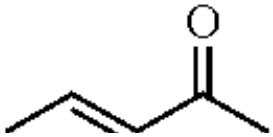

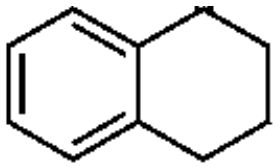

15
(3 equiv **1**, 94%)

Considering that a polymer-bound reagent is employed, the reactions proceed rather rapidly (see ref 1). In addition, no over-oxidation to the corresponding carboxylic acids is observed.

Following the general procedure, the products isolated after filtration and evaporation of the solvent are very pure and can be used directly in the next step. In this context, this new oxidation method is well suited for applications in natural product total synthesis because the integrity of a chiral center in the α-position is often a problem during the oxidation process and especially during work-up of the generated carbonyl compound. In fact, the transformation of a chiral alcohol into aldehyde **7** is achieved without any detectable racemization (>95% ee), while the Swern and, to a lesser extent, the Dess-Martin oxidation led to the partly racemized aldehyde **7**, either during the reaction or work-up by flash column chromatography.

In comparison with other polymer-supported oxidants, for example, Ley's immobilized perruthenate which is very efficient for oxidizing primary and secondary benzylic alcohols but cannot be employed for secondary alcohols, the title reagent **1** is a powerful tool for the oxidation of all kinds of alcohols. Olefinic double bonds, however, are not tolerated under these conditions.

1,2-Bromoacetoxylation of Alkenes[3]

General Procedure

A mixture of alkene (1 equiv) and resin **1** (3-7 equiv) is shaken at 300 rpm under light protection in dry dichloromethane (1.5 mL $mmol^{-1}$) at room temperature. Completion of the reaction is monitored by TLC. Filtration terminates the reaction. The resin is washed with dichloromethane (3×20 mL g^{-1} resin), and the combined organic washings and filtrate are concentrated under reduced pressure. In some cases, purification by column chromatography is necessary.

Similar to the analogous polymer-supported reagents for efficient iodoacetoxylation (see refs 6-8) and iodoazidation[9] of alkenes, the title reagent **1** is used to promote the corresponding 1,2-bromoacetoxylations. Following the general procedure, the addition often proceeds with *trans* selectivity, as demonstrated for cyclohexene and indene transformation products **16** and **17**. Reaction of alkoxyallene with resin **1** leads to vinylbromide **18**, clearly demonstrating that the relative electron density of the double bond determines the chemoselectivity of the process.

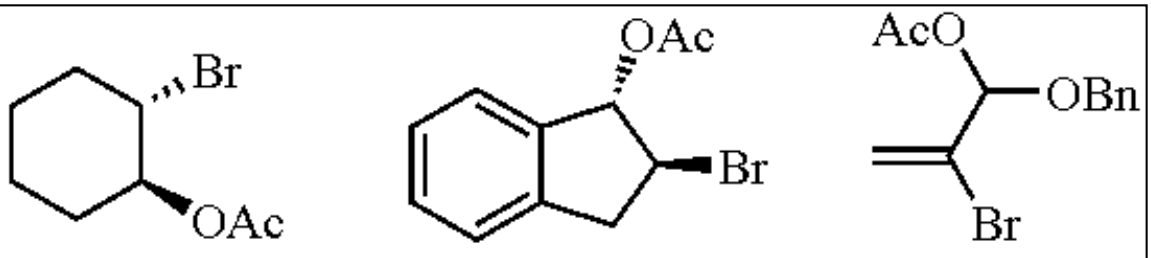

16 (5 equiv **1**, 63%) **17** (5 equiv **1**, 67%) **18** (4 equiv **1**, 60%)

In contrast to iodoacetoxylation[6-8] and iodoazidation,[9] however, this process often lacks good regio- and stereoselectivity. Two examples are depicted below (eq 1 and 2).

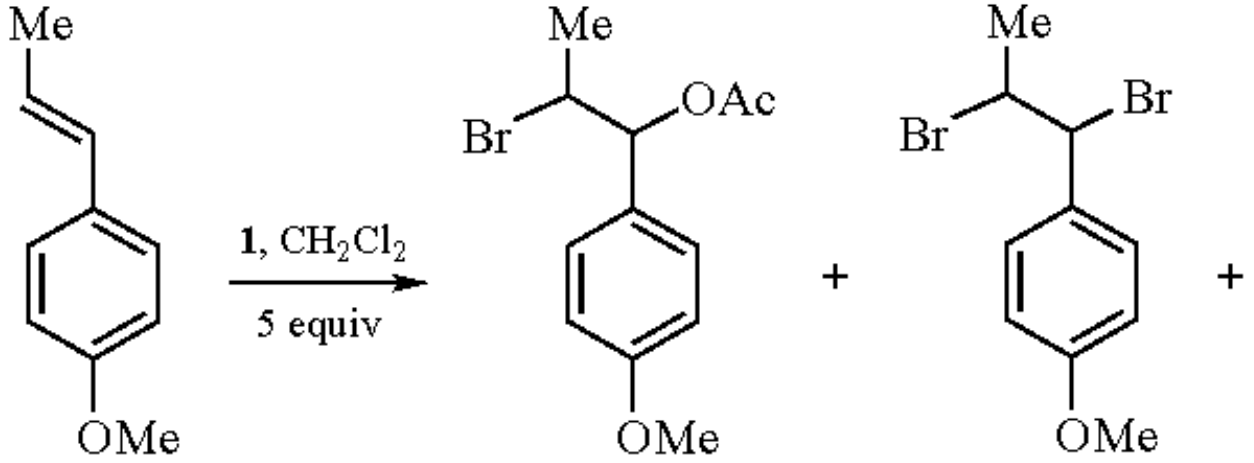

19 **20**, 43% **21**, 26% two diastereomers

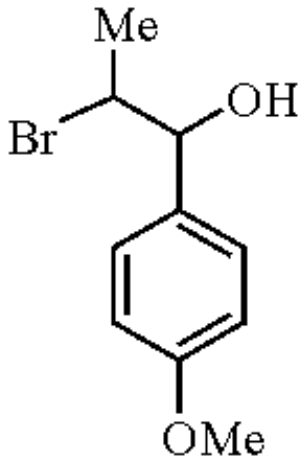

(1)

22, 8% two diastereomers

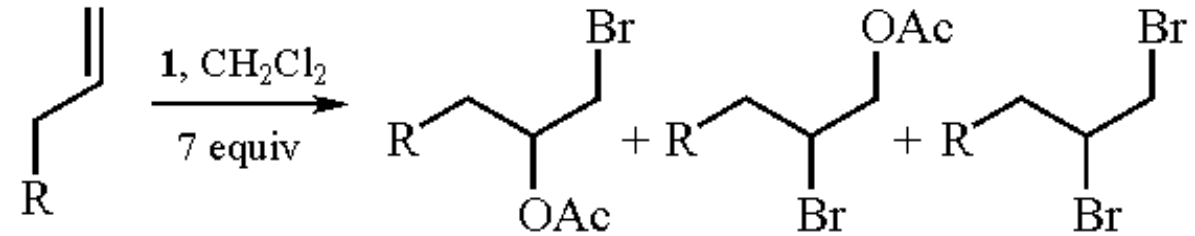

23 **24**, 12% **25**, 12% **26**, 30%

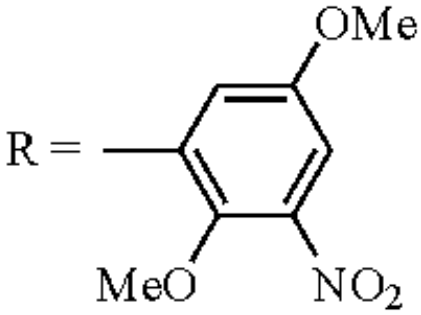

(2)

In contrast, the bromoacetoxylation of protected carbohydrate-derived glycals furnishes the corresponding 2-bromo-2-deoxy-glycosyl

acetates **27** and **28** in excellent yields.[7] In most cases, filtration of the resin and removal of the solvent in vacuo affords the reaction products in high purity.

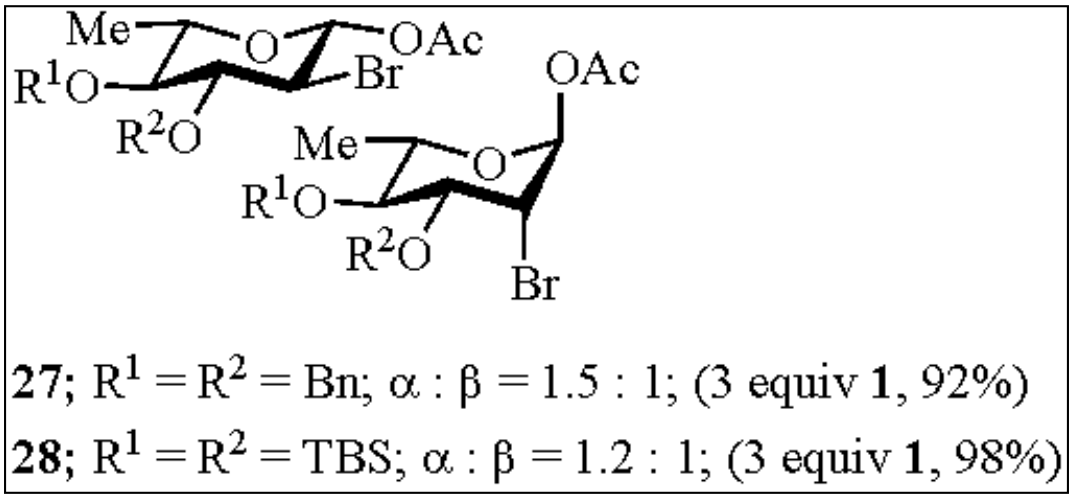

Furthermore, reaction of vinyl silane **29** with the title reagent **1** also affords the 1,2-addition product **30** in good yield (eq 3).[8] Remarkably, desilylation or formation of products derived from desilylation was not observed.

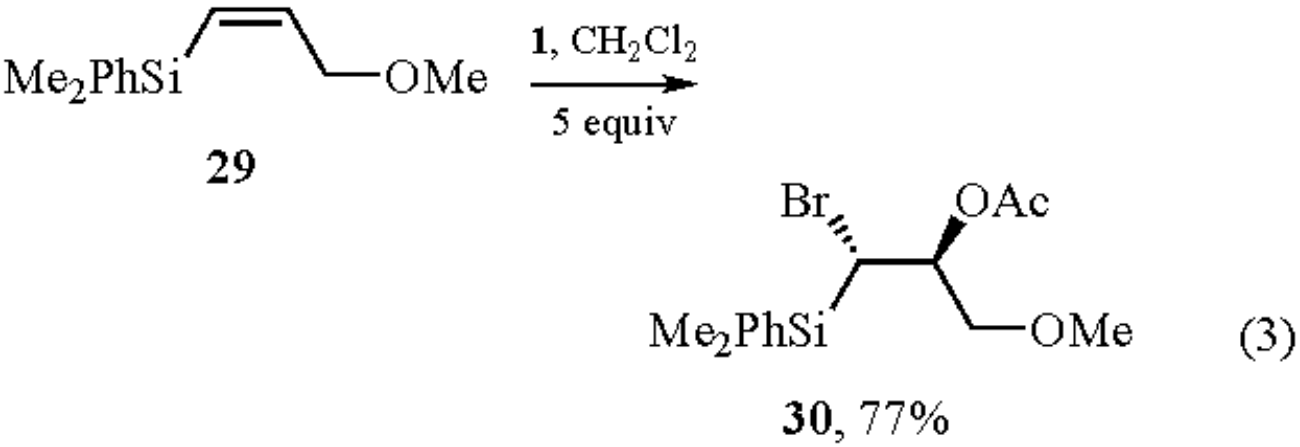

(3)

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4. Hashem, M. d. A.; Jung, A.; Ries, M.; Kirschning, A., *Synlett* **1998**, 195.
5. Kirschning, A.; Hashem, M. d. A.; Monenschein, H.; Rose, L.; Schöning, K.-U., *J. Org. Chem.* **1999**, *64*, 2720.
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9. Kirschning, A.; Monenschein, H.; Schmeck, C., *Angew. Chem., Int. Ed. Engl.* **1999**, *40*, 8999 and *Angew. Chem.* **1999**, *111*, 2720.

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Potassium Tris(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17-triacontafluoro-8,10-heptadecanedionato) Ruthenate

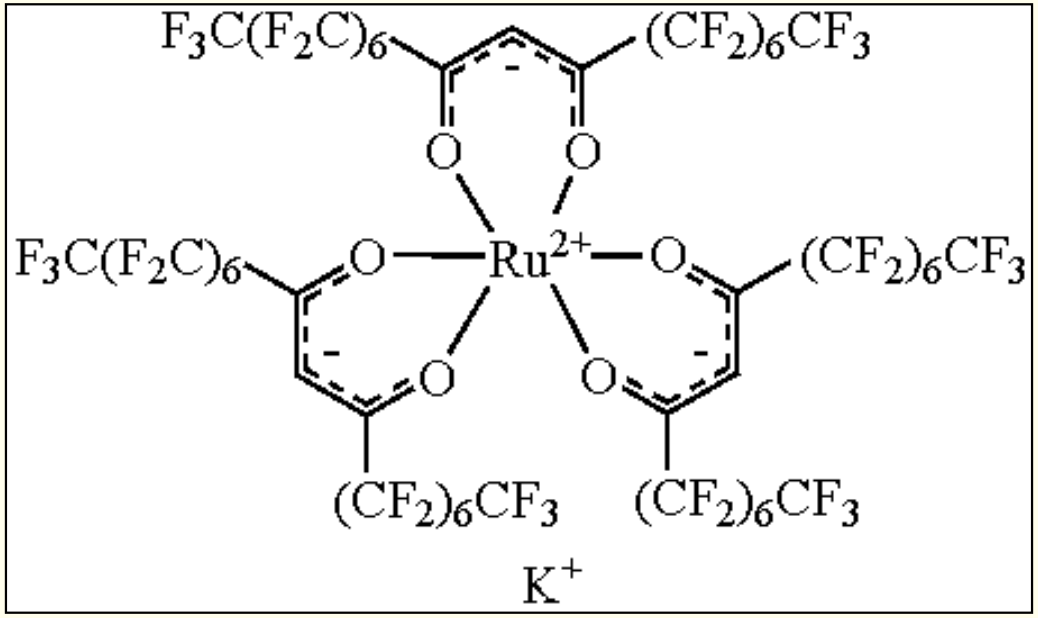

[195870-97-4] · $C_{51}H_3F_{90}O_6RuK$ · (2558.57)

(reagent used for epoxidation of alkenes)

Physical Data: mp 162-163°C.

Solubility: soluble in perfluorooctyl bromide and other perfluorinated solvents, MeOH and THF; slightly soluble in diethyl ether.

Form Supplied in: violet crystals, not commercially available; major impurity: perfluorohexane.

Preparative Methods: the complex is prepared from the corresponding diketone **1** and $RuCl_3$ in the presence of base (eq 1).[1]

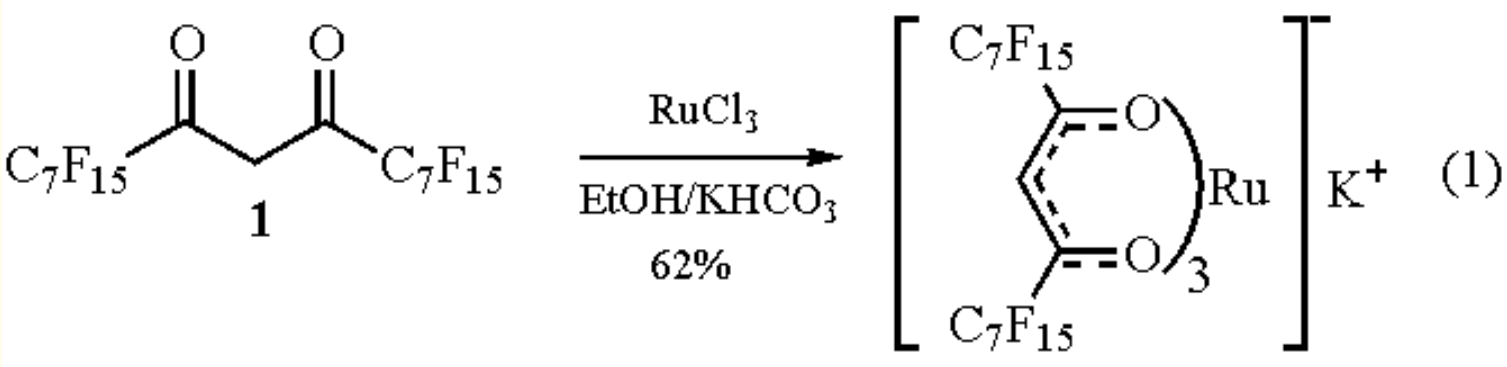

A ruthenium(III) chloride solution in water/EtOH is refluxed for 4 h, thereafter an ethereal solution of the perfluorinated diketone **1** is added, followed by potassium bicarbonate. The mixture is then left to reflux for 1 h. Extraction with perfluorohexane and further recrystallization from acetone/chloroform gives the product in a 62% yield. The above diketone **1** is obtained by condensation[2,3] of the corresponding perfluorinated methyl ester and perfluorinated methylketone in the presence of NaOMe in diethyl ether.

Handling, Storage, and Precautions: the compound can be stored at room temperature and in the presence of moisture for several months. It decomposes at temperatures >60°C. Data on toxicity are not known yet; it is suggested that use the same precautions as for the other salts of Ru(II) be used.

Epoxidation

The potassium tris(1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,11,11,12,12,13,13,14,14,15,15,16,16,17,17,17 triacontafluoro-8,10-heptadecanedionato) ruthenate complex has been used in fluorous biphasic system catalysis (FBS) for the epoxidation of disubstituted alkenes (eq 2).[1]

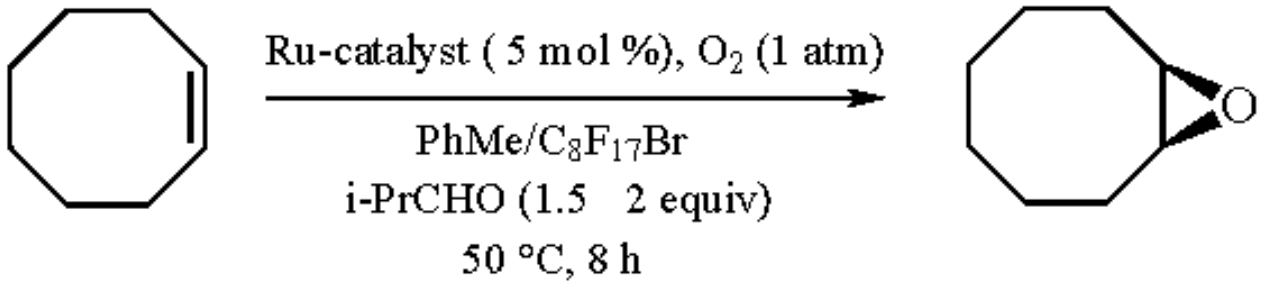

(2)

85% recovered yield (1st run);
catalyst recyclable for up to 10 runs
(85% conversion after the 10th run)

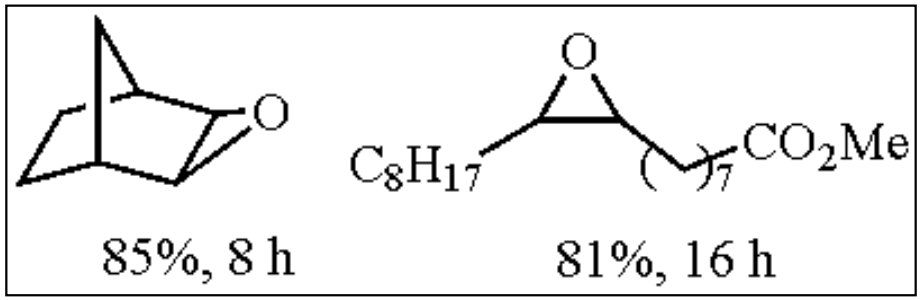

The FBS[4,5] is based on the property of perfluorinated solvents to be immiscible with most organic solvents at room temperature, and completely miscible with them at temperatures >50-60°C. In this way, a catalyst containing perfluorinated 'ponytails' is selectively soluble in a perfluorinated phase, but it reacts with the substrate in a homogeneous catalytic system when the temperature is increased. After cooling down, the reaction system separates into two phases again: the catalyst is recovered only in the perfluorinated one and can be easily recycled, while the products are in the organic solvent. Another advantage of the FBS is the high solubility of several gases[6] in the perfluorinated medium; consequently, it is suitable for 'green' oxidations[7-9] with molecular oxygen.

This ruthenium compound produces a violet solution in perfluorooctyl bromide, but in the presence of aldehydes and O_2 it quickly becomes brown; probably due to the formation of Ru(III) or oligomeric species with mixed valences. However, the brown solution shows the same activity as the violet one and can be recycled several times. It is important to carry out the reaction at the lowest temperature possible (not more than 60°C) in order to avoid the decomposition of the complex.

The compound is suitable for selective epoxidations of disubstituted alkenes in the presence of molecular oxygen and isopropylaldehyde,[1,10,11] with yields around 71-85% and reaction times between 8 and 16 h; functional groups such as esters or carboxylic acids are very well tolerated, and terminal double bonds are not reactive at all under these conditions. After the reaction, the

perfluorinated phase containing the ruthenium complex can be recycled up to ten times with negligible loss of activity[1] (from 100% conversion in the first run to 85% at the 10th run). Because of the recyclability of the catalyst, the work-up of the organic phase containing the product is quite simple and clean.

Related Reagents.

‘fluorous tin hydride’.

---

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11. Yamada, T.; Takai, T.; Rhode, O.; Mukaiyama, T., *Bull. Chem. Soc. Jpn* **1991**, *64* , 2109.

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Bis(η^5-2,4-cyclopentadienyl)bis(trimethylphosphine)titanium

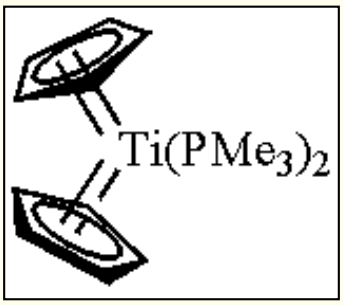

[95936-00-8] · $C_{16}H_{28}P_2Ti$ · (330.21)

(used as a source of 'Cp_2Ti')

Physical Data: mp (105°C decomposes); black needles.

Solubility: soluble in most organic solvents.

Preparative Methods: bis(η^5-2,4-cyclopentadienyl)bis(trimethylphosphine)titanium is prepared by the reduction of Cp_2TiCl_2 by magnesium in the presence of trimethylphosphine.[1] It may also be generated in situ from Cp_2TiCl_2, butyllithium and trimethylphosphine.

Handling, Storage, and Precautions: $Cp_2Ti(PMe_3)_2$ is pyrophoric and must be handled and stored in an argon filled glove-box.

Reductive Cyclization

One of the most important features of bis(η^5-2,4-cyclopentadienyl)bis(trimethylphosphine)titanium [$Cp_2Ti(PMe_3)_2$] is the ease of dissociation of both of the PMe_3 ligands to yield a complex with two open coordination sites. Treatment of enynes with a catalytic amount of $Cp_2Ti(PMe_3)_2$ in the presence of trialkylsilyl cyanides, followed by hydrolysis produces bicyclic cyclopentenones (eq 1).[2] Although a variety of metal complexes promote cyclopentenone formation, most require a stoichiometric amount of metal complex.

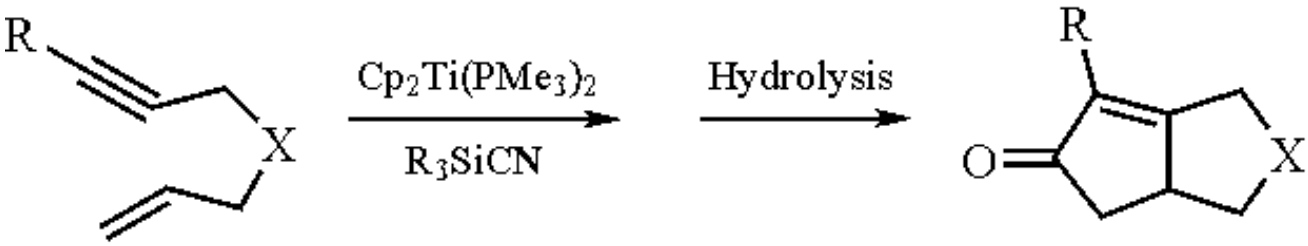

(1)

$Cp_2Ti(PMe_3)_2$ also catalyzes the reductive cyclization of 1,6-enones[3] and 1,6-enals[4] to cyclopentanols. These reactions proceed with good diastereoselectivity to produce predominately the *syn* diastereomer (eq 2).

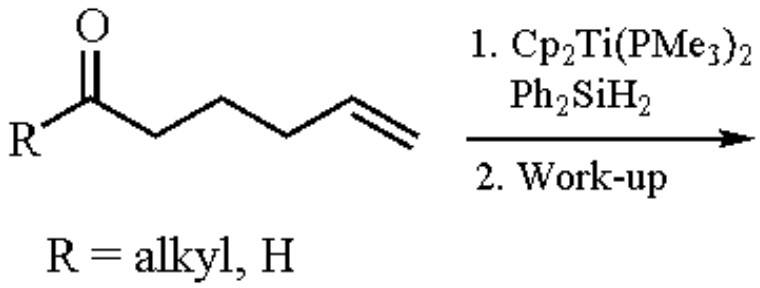

(2)

Imines also form the titanocycles, but do not cleave to form cyclopentylamines. When a stoichiometric amount of $Cp_2Ti(PMe_3)_2$ is used in the presence of enones, followed by CO, the CO inserts into the resulting metallacycle and, after thermal reductive elimination, produces γ-butyrolactones (eq 3).[5]

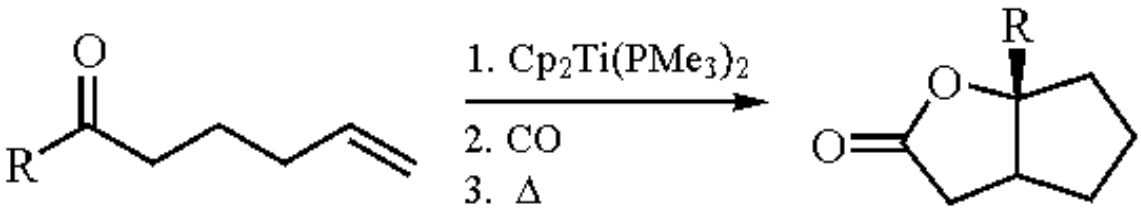

(3)

A catalytic version of this reaction which uses trialkylsilylcyanides as the CO equivalent, is also an effective method for generating lactones. However, generation of 'Cp_2Ti' is carried out in situ using 2 equiv of ethylmagnesium bromide or butyllithium.[6]

Related Reagents.

Cp_2TiCl_2 Cp_2ZrCl2.

---

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Dichloro[1,2-ethanediylbis(1,2,3,3*a*,7*a*-η)-4,5,6,7-tetrahydro-1*H*-indene-1-ylidene] titanium

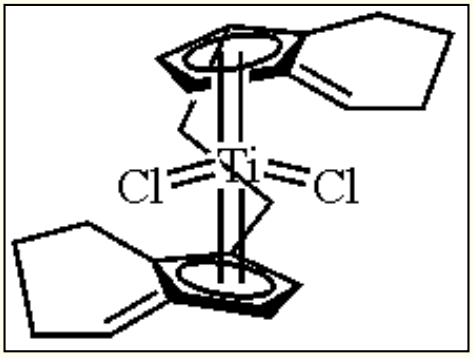

[] · $C_{20}H_{24}Cl_2Ti$ · (383.18)

(used as a source of 'Cp$_2$TiH')

Alternate Name: [(EBTHI)TiCl$_2$][1]

Physical Data: red solid; mp 256-261°C.

Solubility: THF, diethyl ether, dichloromethane.

Form Supplied in: (EBTHI)TiCl$_2$ is commercially available in the racemic form but can be resolved by using (*R*)-2,2´-binaphth-1,1´-diol and *p*-aminobenzoic acid.[2]

Handling, Storage, and Precautions: No special handling is required.

Synthesis of Homoallylic Alcohols

The complex (*S*,*S*)-dichloro[1,2-ethanediylbis(1,2,3,3*a*,7*a*-η)-4,5,6,7-tetrahydro-1*H*-indene-1-ylidene]titanium [(*S*,*S*)-EBTHITiCl$_2$] is a precatalyst for the formation of chiral allyl and crotyl titanium species. Activation of the catalyst with *n*-propylmagnesium bromide and allyl- or crotylmagnesium bromide followed by treatment with an aldehyde produces homoallylic alcohols in moderate enantioselectivity (eq 1).[3] Unfortunately, in the case of the crotyl species, high des are restricted to pivaldehyde and benzaldehyde.

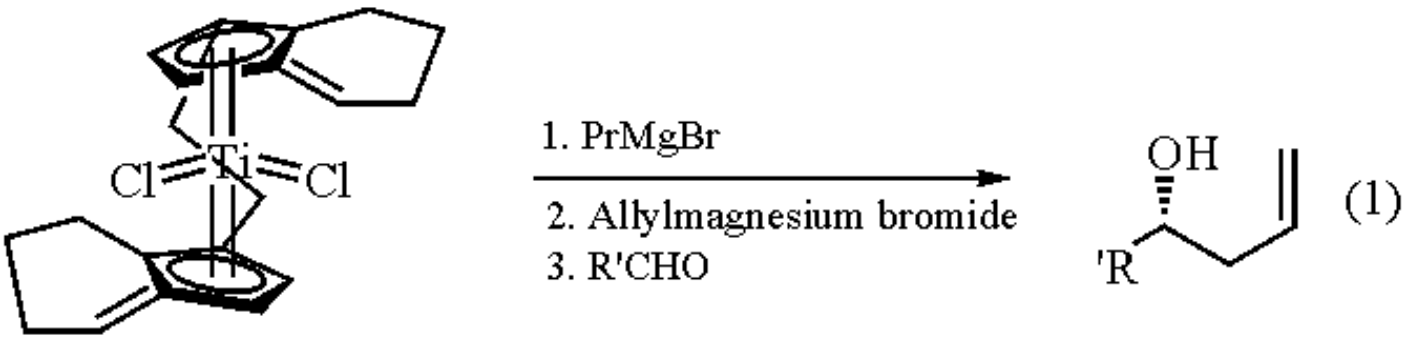

Reduction

In general, the reduction of dialkyl ketones proceeds with poor selectivity. Treatment of (*S*,*S*)-EBTHITiCl$_2$ with PhMeSiH$_2$ produces the active catalyst for the reduction of a variety of dialkyl ketones.[4] The yields of the reactions are good and the ee's are low to moderate, however the results are similar to other dialkyl ketone reductions in the literature (eq 2).[5]

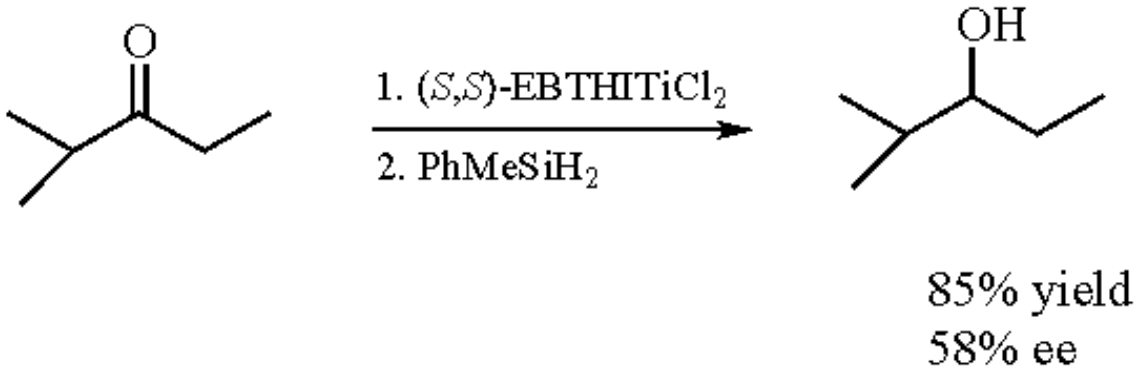

(2)

Reduction of esters using *rac*-EBTHITiCl$_2$ to the corresponding alcohols proceeds without opening of an epoxide.[6] Imines are reduced with (*R*,*R*)-EBTHITiCl$_2$, although the corresponding (*R*,*R*,*R*)-binaphth-1,1´-diol complex is more common. This reaction proceeds with good-to-excellent yields and high enantioselectivities.[7]

Cycloisomerization

Cycloisomerization of 1,6-dienes with *rac*-EBTHITiCl$_2$ is easily accomplished. Treatment of the diene with EBTHITiCl$_2$ and *n*-butylmagnesium bromide produces cyclohexenes, whereas the use of Cp$_2$TiCl$_2$ and *n*-butylmagnesium bromide yields cyclopentenes (eq 3).[8]

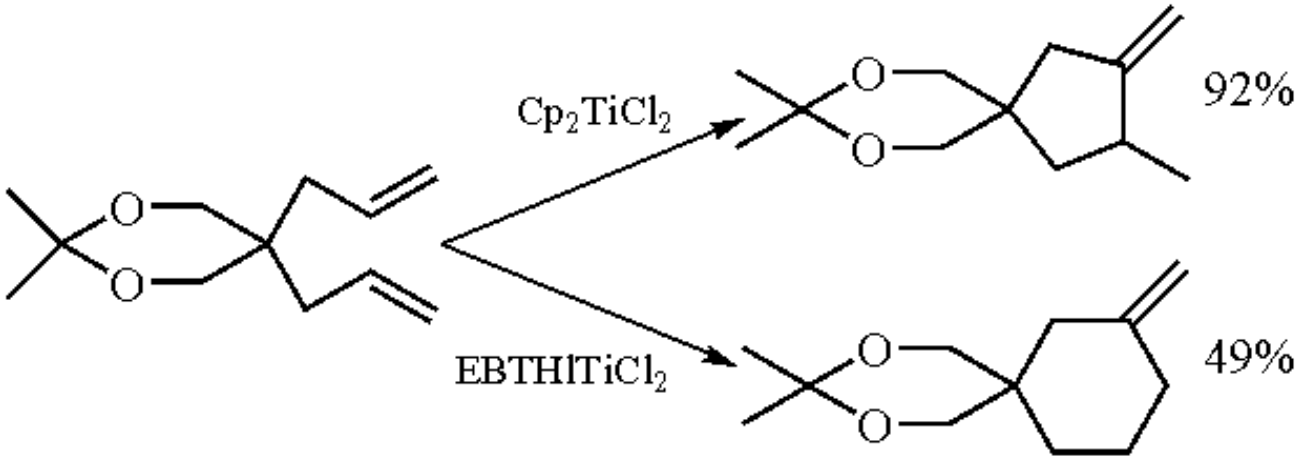

(3)

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Dicarbonyl(acetylacetonato) Rhodium(I)

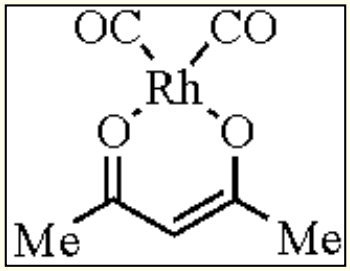

[14874-82-9] · $C_7H_7O_4Rh$ · (258.04)

(catalyst (precatalyst) for various carbonylation reactions, silylcarbocyclizations, conjugate additions to enones, carbamoylstannation, and reduction of aromatic nitro compounds)

Physical Data: mp 155°C[1]; IR (CCl_4) 2990, 2911, 1553, 1513, 1429, 1374, 1276, 1193, 1126, 1019, 933, 782 cm^{-1}; ^1H NMR (CCl_4) δ 5.52 (1H), 2.11 (6H).

Solubility: soluble in acetone, benzene, chlorinated solvents; sparingly soluble in MeOH, ether, aliphatic hydrocarbons.

Form Supplied in: dark green crystalline solid; commercially available.

Analysis of Reagent Purity: NMR, IR, mp.

Preparative Methods: prepared from tetracarbonyl-μ-dichlorodirhodium(I).[1]

Purification: vacuum sublimation at ca. 90°C.[1]

Handling, Storage, and Precautions: stable in air; best stored in a dry atmosphere.

Hydroformylation

Dicarbonyl(acetylacetonato) rhodium(I) [$Rh(acac)(CO)_2$] is a common precatalyst for the hydroformylation of alkenes.[2] In combination with ligands, alkenes are hydroformylated to aldehydes under mild conditions (eq 1). Chemo-, regio-, and stereoselectivity depend upon the nature of the substrate and upon the ligands employed.

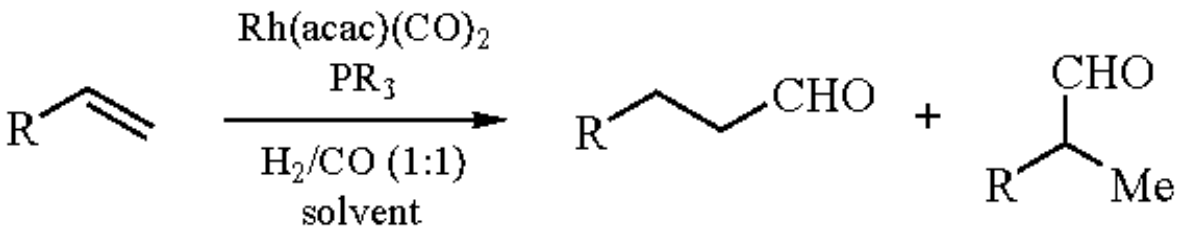

(1)

Silylformylation

The $Rh(acac)(CO)_2$-catalyzed intermolecular silylformylation of terminal alkynes with **dimethyl(phenyl)silane** and **carbon monoxide** affords (*Z*)-1-silyl-2-formylalk-1-enes with complete regio- and stereoselectivity (eq 2).[3]

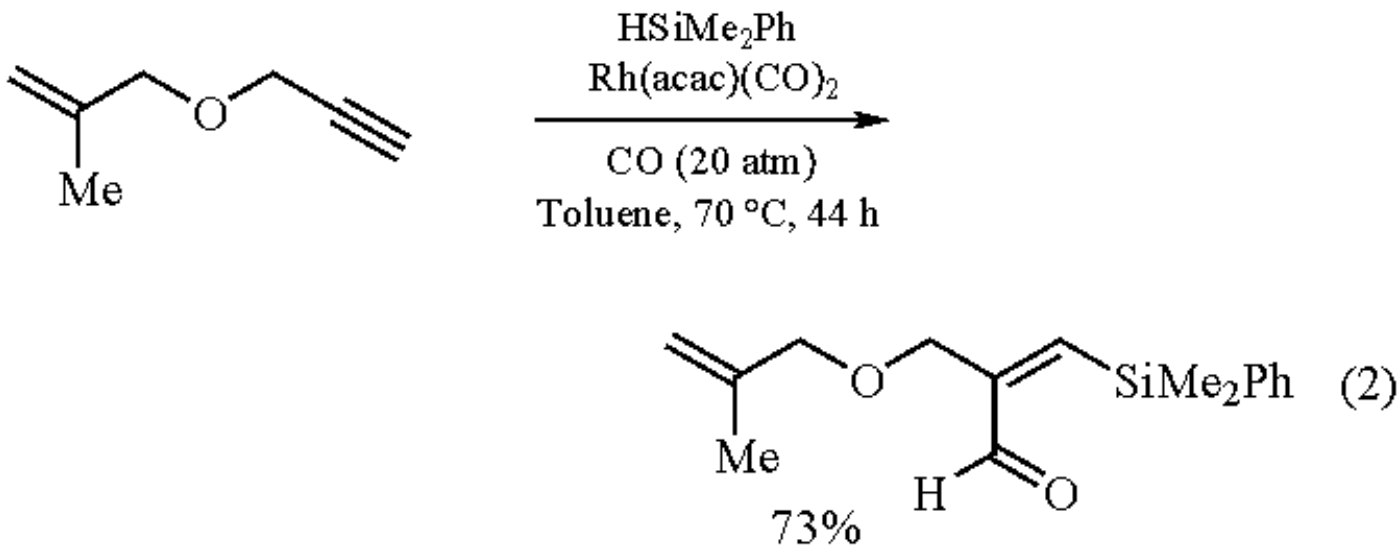

Triethylsilane and *tert*-butyldimethylsilane also participate in intermolecular silylformylation.[4] The regioselectivity is completely reversed in the intramolecular silylformylation of alkynes (eq 3).[5] Internal and terminal alkynes are silyformylated with complete regio- and stereoselectivity, with exclusive formation of products arising from *exo*-cyclization.

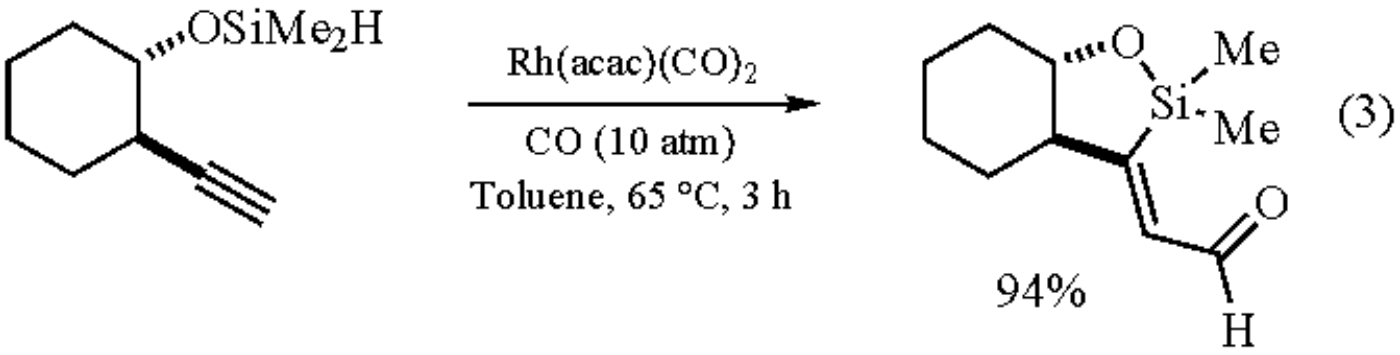

The intramolecular silylformylation of alkenes affords β-silyl aldehydes with exclusive formation of aldehydes arising from *exo*-cyclization (eq 4).[6] When the phenyl groups on silicon are replaced with allyl groups, tandem silyformylation-allylsilylation occurs to afford, after oxidation of the carbon-silicon bond, 1,3,5-*syn*-triols (eq 5).[7]

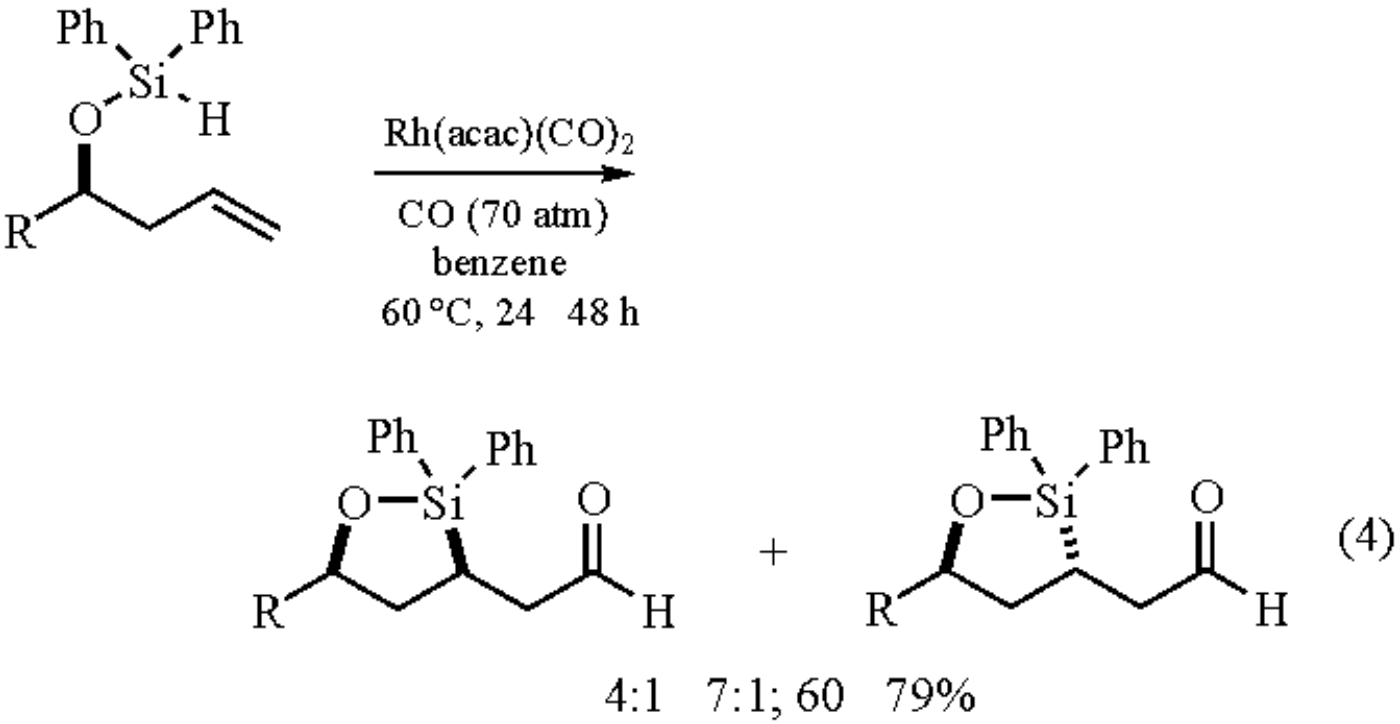

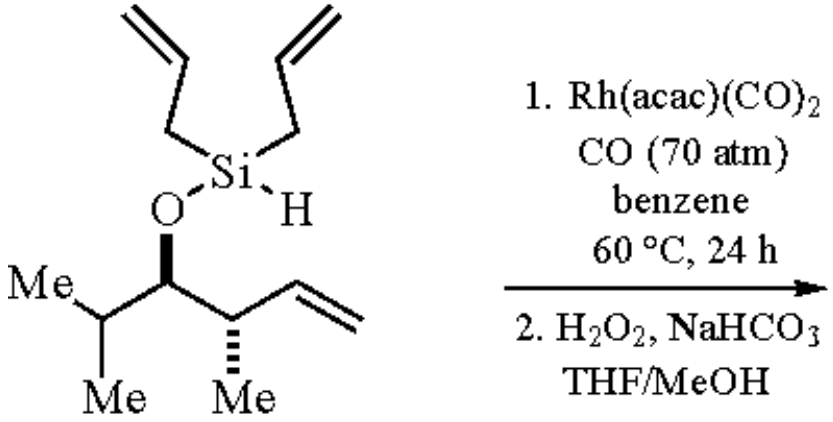

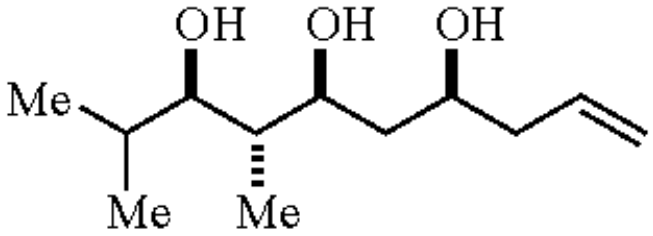

(5)

92:8; 59%

Carbocyclizations

Rh(acac)$(CO)_2$ catalyzes the intramolecular silylcarbocyclization of triynes,[8] enynes,[9] and ynals.[10] The silylcarbotricylization of enediynes affords bis-cyclopentyl products (eq 6).[11] This cascade carbometallation sequence proceeds stereospecifically, and complements traditional Heck chemistry.

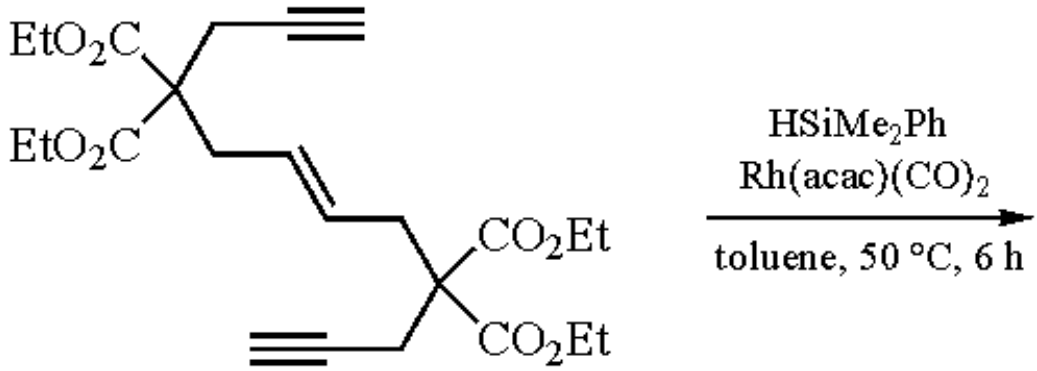

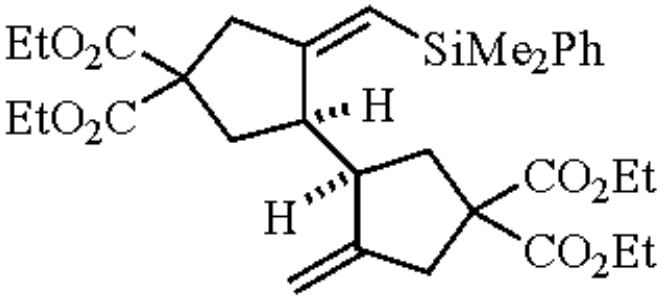

(6)

55%

The carbonylative carbotricyclization of enediynes is catalyzed by Rh(acac)$(CO)_2$ to afford fused 5-7-5 tricyclic products (eq 7).[12] In a reaction that complements the Pauson-Khand reaction, Rh(acac)$(CO)_2$ catalyzes the carbonylative bicyclization of 1,6-diynes to afford

bicyclo[3.3.0]octenones.[13]

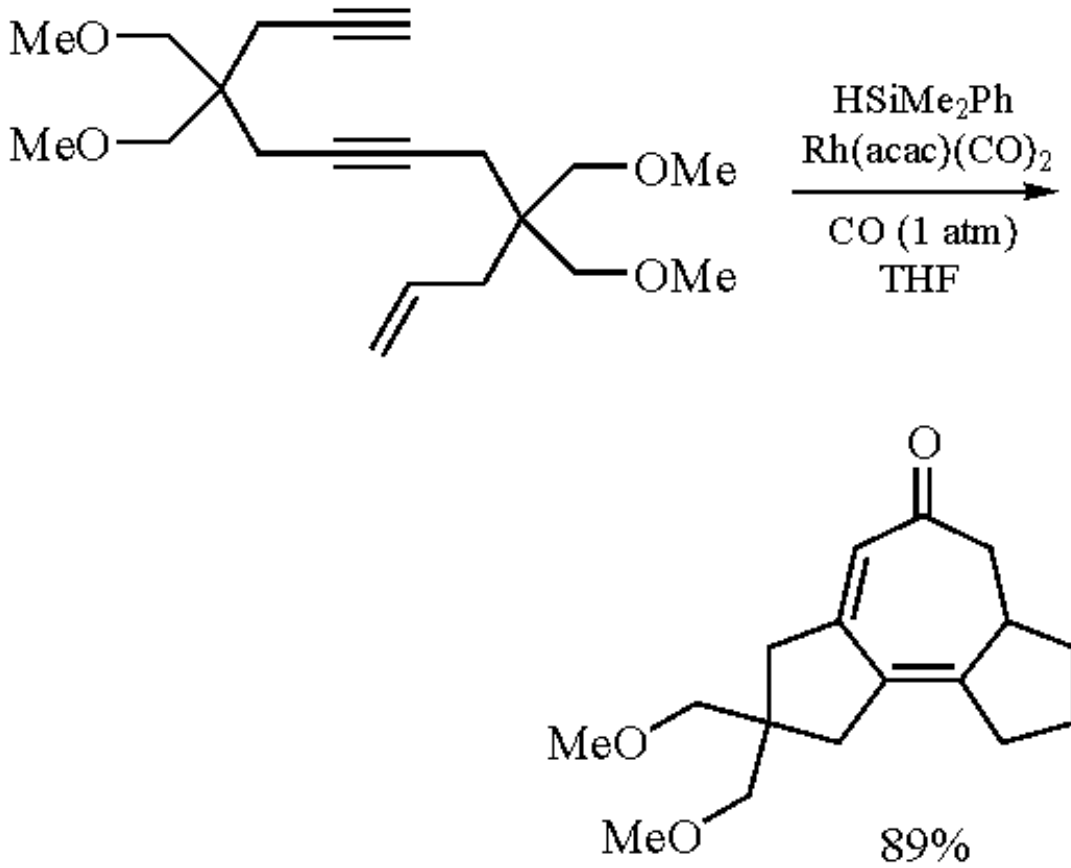

(7)

Conjugate Additions

The conjugate addition of aryl- and alkenylboronic acids to enones is catalyzed by $Rh(acac)(CO)_2$ (eq 8).[14]

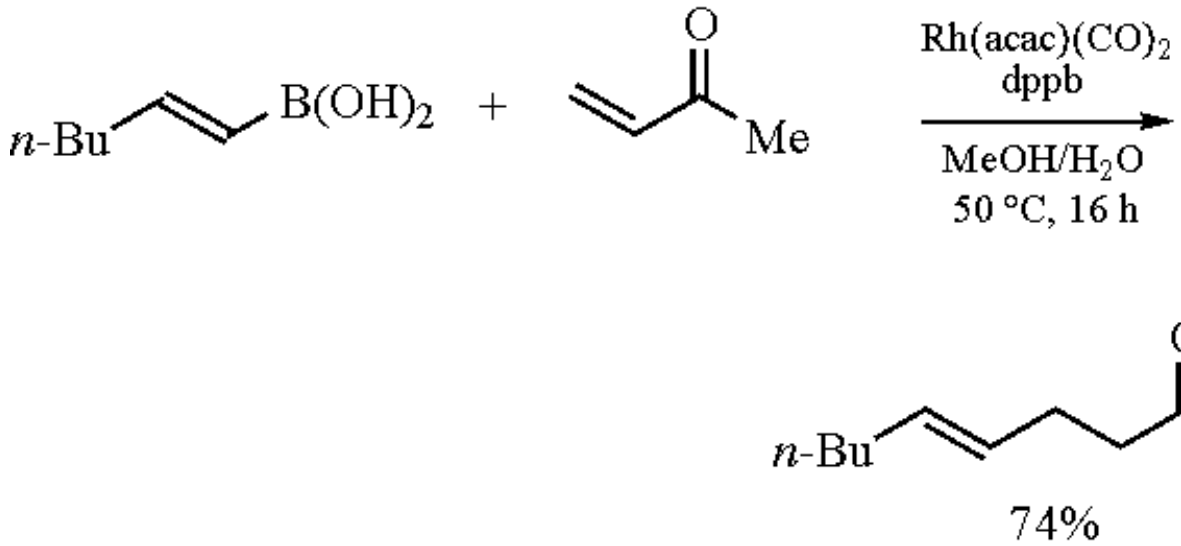

(8)

The asymmetric conjugate addition of α-cyano phosphonates[15] and α-cyano Weinreb amides[16] to enones and enals is catalyzed by $Rh(acac)(CO)_2$ in the presence of chiral ligands (eq 9).

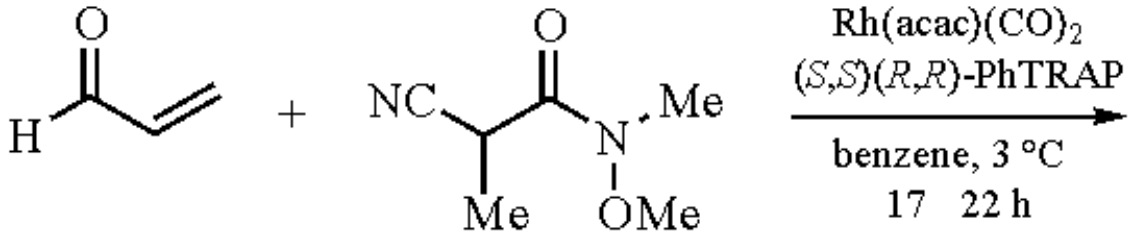

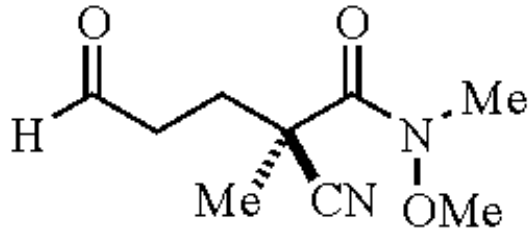

(9)

94%
ee = 89%

Other Transformations

Carbamoylstannation of terminal alkynes is catalyzed by Rh(acac)$(CO)_2$ to afford 3-trimethylstannyl-2-enamides (eq 10).[17]

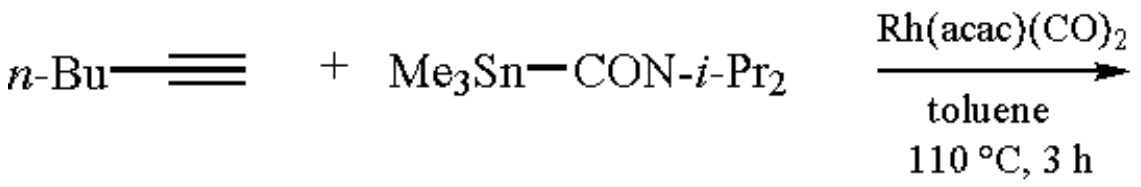

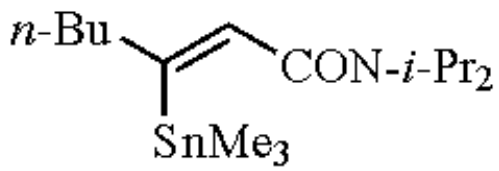

(10)

78%

In the presence of phosphine[18] and amine[19] ligands, Rh(acac)$(CO)_2$ catalyzes the reduction of aromatic nitro compounds to anilines with CO/H_2O. Rh(acac)$(CO)_2$ catalyzes the addition of aryl- and alkenylboronic acids to aldehydes,[20] and catalyzes the formylation of organomercurial chlorides (eq 11).[21]

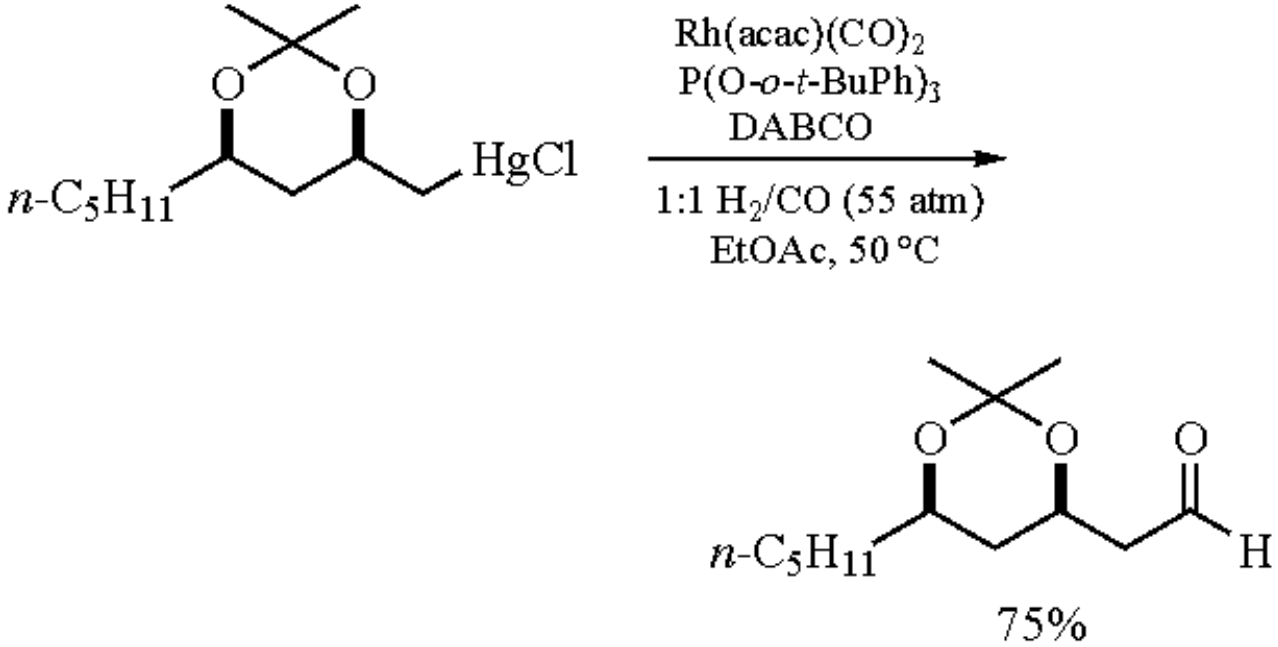

(11)

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(*R*,*R*)-1,2-Bis(aminocarbonylphenyl-2´-diphenylphosphino)cyclohexane

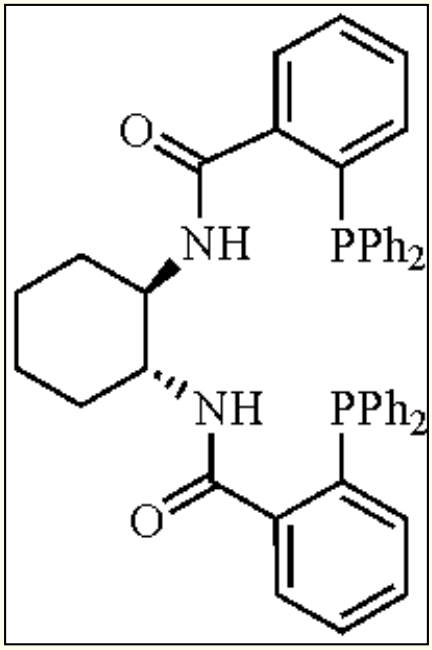

[138517-61-0] · $C_{44}H_{40}N_2O_2P_2$ · (690.76)

(chiral phosphine ligand used in asymmetric Pd^0-catalyzed allylic substitution reactions)[1]

Physical Data: mp 134-136°C.[2]

Solubility: soluble in chlorinated solvents, ethers, alcohols, toluene and most organic solvents. Partially soluble in acetonitrile.

Form Supplied in: white to off-white crystalline solid. Major impurity is the corresponding monophosphine oxide (<1%).

Analysis of Reagent Purity: NMR and IR details are available.[3,4] Optical rotation $[\alpha]_D^{25}$ +46.7 (*c* 2.4, CH_2Cl_2).[3] $[\alpha]_D^{25}$ +88 (*c* 7.0, CH_2Cl_2);[2] crystalline material. Chiral HPLC: Chiracel OD-R, UV 210 nm, 0.8 mL min^{-1}, 100% MeOH. Retention time (*R*,*R*)=6.3 min, retention time (*S*,*S*)=9.4 min. Achiral HPLC: Hypersil BDS C8, UV 254 nm, 1.0 mL min^{-1}, 85% MeOH, 15% H_2O. Retention time ligand=9.5 min, retention time monophosphine oxide=5.2 min, retention time bisphosphine oxide=3.6 min.

Preparative Methods: commercially available. The ligand can be prepared by the coupling of (1*R*,2*R*)-(-)-1,2-diaminocyclohexane [20439-47-8] with 2-(diphenylphosphino)benzoic acid [17261-28-8],[5] using reagents such as DCC.[3] An alternative procedure has been developed whereby (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt [39961-95-0][6] is coupled to a mixed anhydride of 2-(diphenylphosphino)benzoic acid and diphenylchlorophosphate.[2] The procedure is reproduced below 2-(Diphenylphosphino)benzoic acid (20 g, 65.3 mmol, 2 equiv) is suspended in dichloromethane (150 mL) and cooled in an ice-water bath to 0°C (internal temperature). Triethylamine (10.1 mL, 71.8 mmol, 2.2 equiv) is added dropwise and a clear solution is obtained. This process is exothermic and a rise in temperature to 5°C is observed. The solution is re-cooled to 0°C and diphenylchlorophosphate (13.4 mL, 64.7 mmol, 1.98 equiv) is added slowly, maintaining the internal temperature between 0-5°C. The yellow solution is stirred for 1 h at 0°C. (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-L-tartrate salt (8.63 g, 32.65 mmol, 1 equiv) is suspended in water (50 mL, 5.8 vol) and potassium carbonate (15 g, 107.8 mmol, 3.3 equiv) is added. This process is exothermic and a clear solution is obtained after approximately 10 min. After 30 min, the clear aqueous solution of diamine is added to the mixed anhydride solution at 0°C, and the resulting yellow two-phase mixture is stirred for 2 h at 0°C, then allowed to warm to room temperature. After 14 h, the mixture is poured into a separating funnel and 200 mL of dichloromethane and 100 mL of water are added. The organic phase is separated, washed with 2 N HCl (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL), then dried over magnesium sulfate. The dried organic phase is filtered through a silica pad and the pad is washed with dichloromethane (50 mL). The combined filtrates are evaporated to dryness under reduced pressure, producing a yellow foam (22.3 g, 99% crude). The foam is crystallized from boiling acetonitrile (390 mL, 17.5 vol) to afford a white crystalline solid. The solid is dried under vacuum to provide the phosphine ligand (15 g, 67%).

Purification: column chromatography on silica gel, eluting with 15-30% ethyl acetate/hexanes.[3,4] Recrystallization from hot

acetonitrile.[2,7]

Handling, Storage, and Precautions: store under nitrogen at room temperature. Oxidation to phosphine oxides may occur upon prolonged exposure to air. No known toxicology data.

Chiral Diphosphine Ligands

In 1992, Professor Barry Trost introduced a family of chiral diphosphine ligands for palladium(0)-catalyzed asymmetric allylic substitution reactions. The first ligands were based on 2-(diphenylphosphino)benzoic acid with a variety of chiral backbones.[3] The most useful of these backbones are *trans*-1,2-diaminocyclohexane, *trans*-1,2-diphenylethanediamine, and *trans*-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene. The ligand based on the diaminocyclohexane backbone has proved to be the most generically useful ligand, with the most reported applications. Throughout this text the term 'ligand' refers to (*R*,*R*)-1,2-bis(aminocarbonylphenyl-2´-diphenylphosphino)cyclohexane.

Catalyst Preparation

Two palladium sources are generally used to form the active precatalysts (**1**) and (**2**) in situ, the allylpalladium chloride dimer [12012095-2] and the tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct [52522-40-4]. For the palladium dibenzylideneacetone complex (**1**), NMR data to support the proposition that the bis-phosphine acts as a bidentate ligand has been reported.[8] A triflate salt of the π-allyl palladium complex has been isolated and is stable in the solid state. However, no crystals suitable for X-ray analysis were obtained.[7] An X-ray crystal structure of the ligand and a bis-palladium complex has been reported.[7] The palladium complexes are generated just before use under an inert atmosphere; exposure to air affords a catalytically inactive tetra-coordinated palladium(II) species.[8]

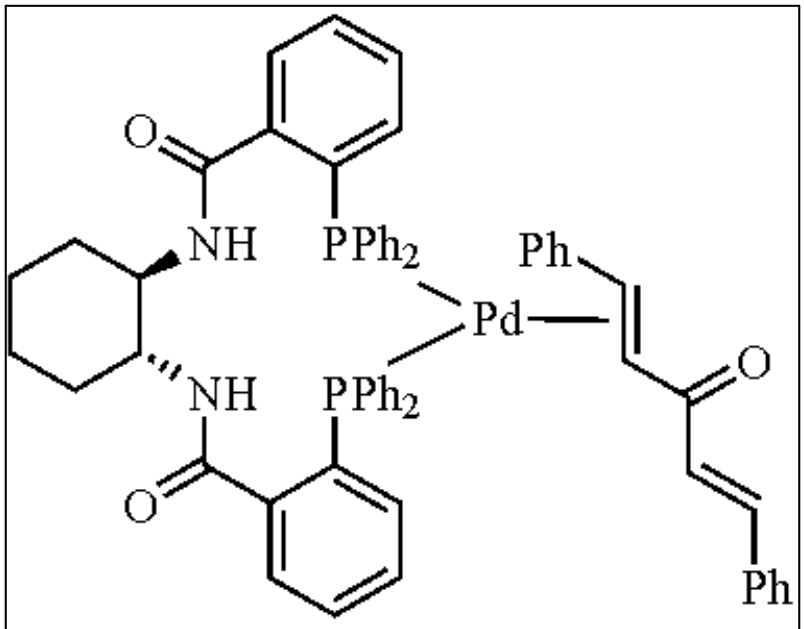

1

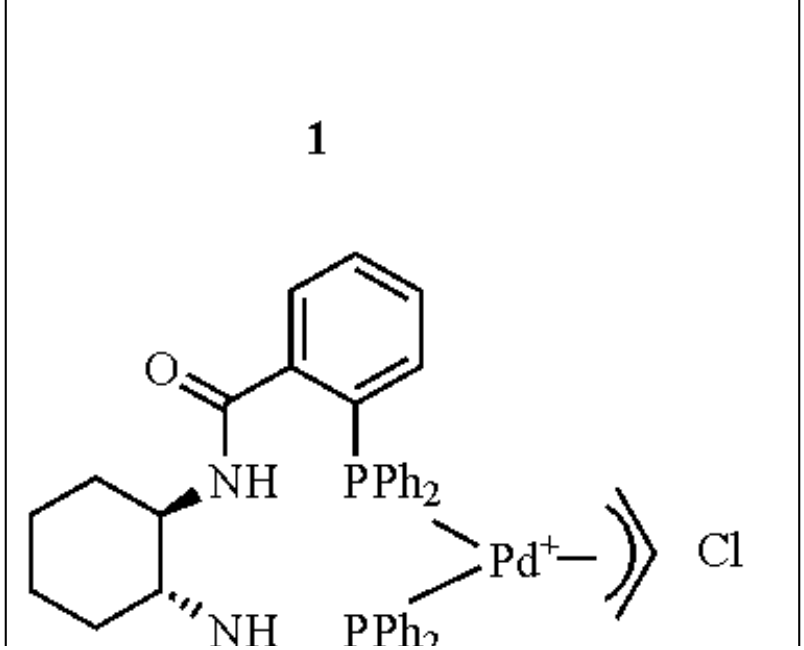

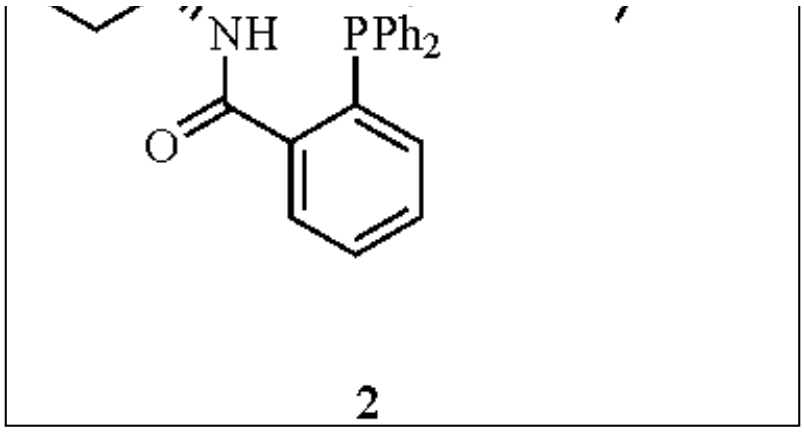

Reactions with Carbon Nucleophiles

A wide range of carbon nucleophiles have been used in asymmetric allylic alkylation reactions (AAA). The first reported reactions involved the use of the sodium salt of malonates as the nucleophile. Five-, six-, and seven-membered ring allylic acetates and carbonates (in general, the carbonates are more reactive substrates) are ionized by the catalyst, prepared from the ligand and a palladium source, to provide a single palladium(0) intermediate (eq 1). Reaction of the intermediate with the sodium malonate in the presence of tetra-*n*-hexylammonium bromide gives the malonate product in high yield (*n*=1, 81%) and enantiomeric excess (*n*=1, 98%).[9] The use of microwave radiation has been reported to accelerate the rate of this reaction with carbon, oxygen and nitrogen nucleophiles.[10]

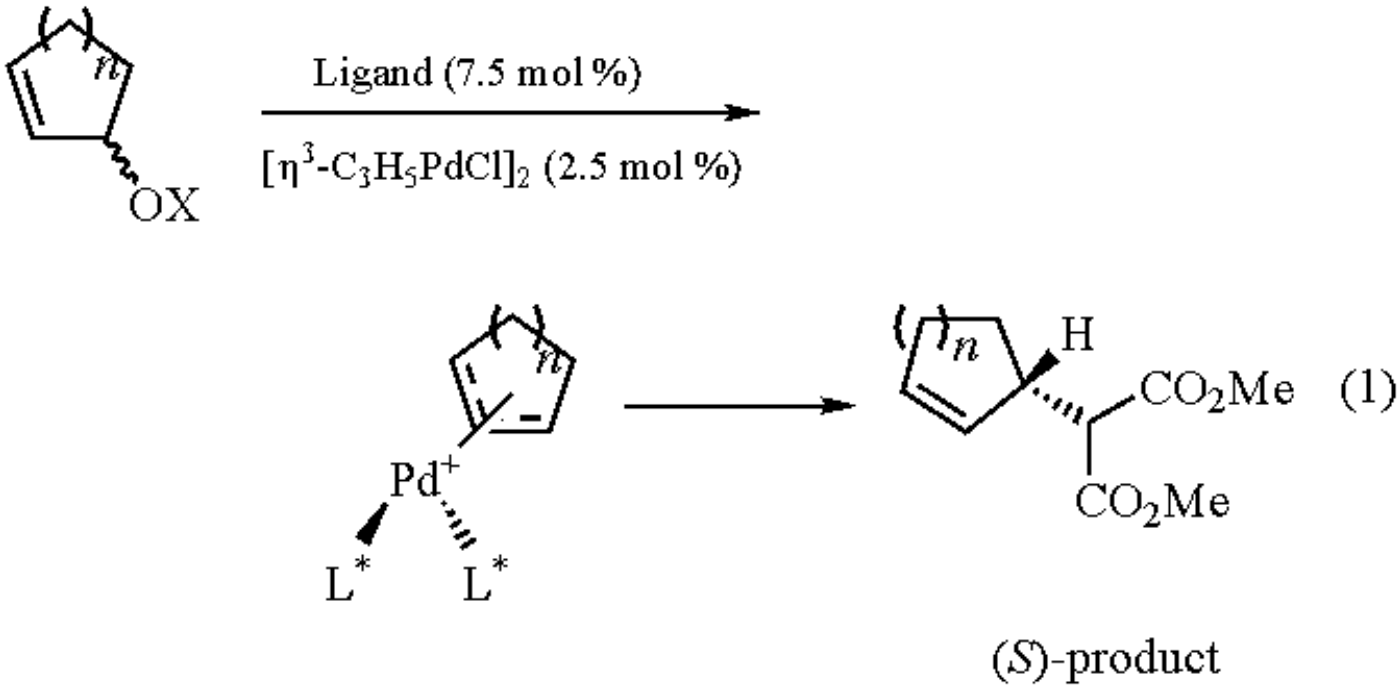

In addition to cyclic allylic substrates, malonate nucleophiles have been used in reactions with both symmetrical[11] and unsymmetrical[12] acyclic systems, and with geminal dicarboxylates.[13] Malonates and Meldrum's acid have also been used as nucleophiles in the desymmetrization of *meso* diesters.[14]

Azlactones have been used as nucleophiles to provide access to a variety of α-alkylated amino acid derivatives. This has been demonstrated with 3-acetoxycyclohexene and with geminal dicarboxylates (eq 2).[15] The enantiomeric and diastereoisomeric excess of the products increase with more bulky R groups.

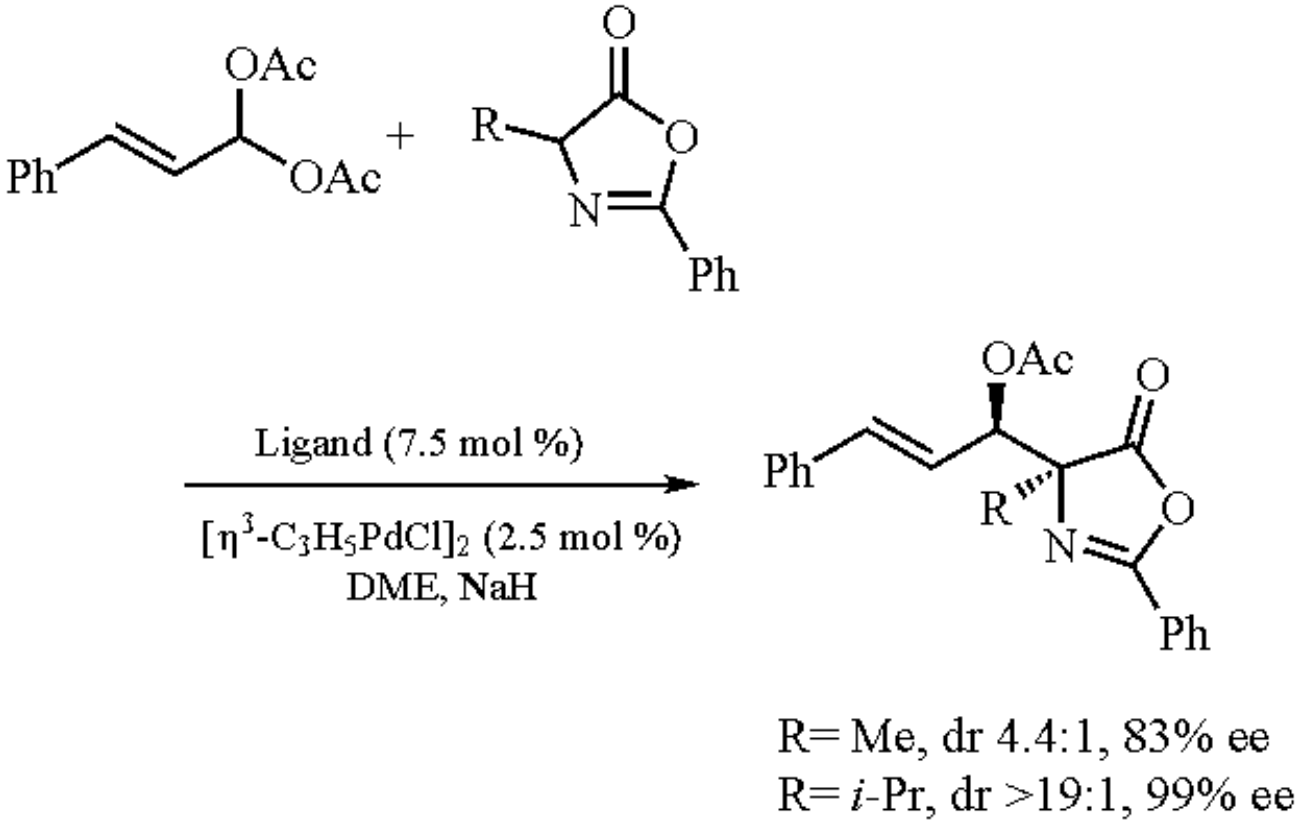

(2)

This method has also been applied to unsymmetrical acyclic allyl esters.[16] The reaction of an azlactone with a geminal diacetate substrate gave access to an advanced intermediate for the synthesis of sphingofungin F.[17]

This methodology has been used to provide efficient protocols for the asymmetric allylic alkylation of β-keto esters,[18] ketone enolates,[19] barbituric acid derivatives,[20] and nitroalkanes.[21]

Several natural products and analogs have been accessed using asymmetric desymmetrization of substrates with carbon nucleophiles. The palladium-catalyzed reaction of a dibenzoate with a sulfonylsuccinimide gave an advanced intermediate in the synthesis of L-showdomycin (eq 3).[22]

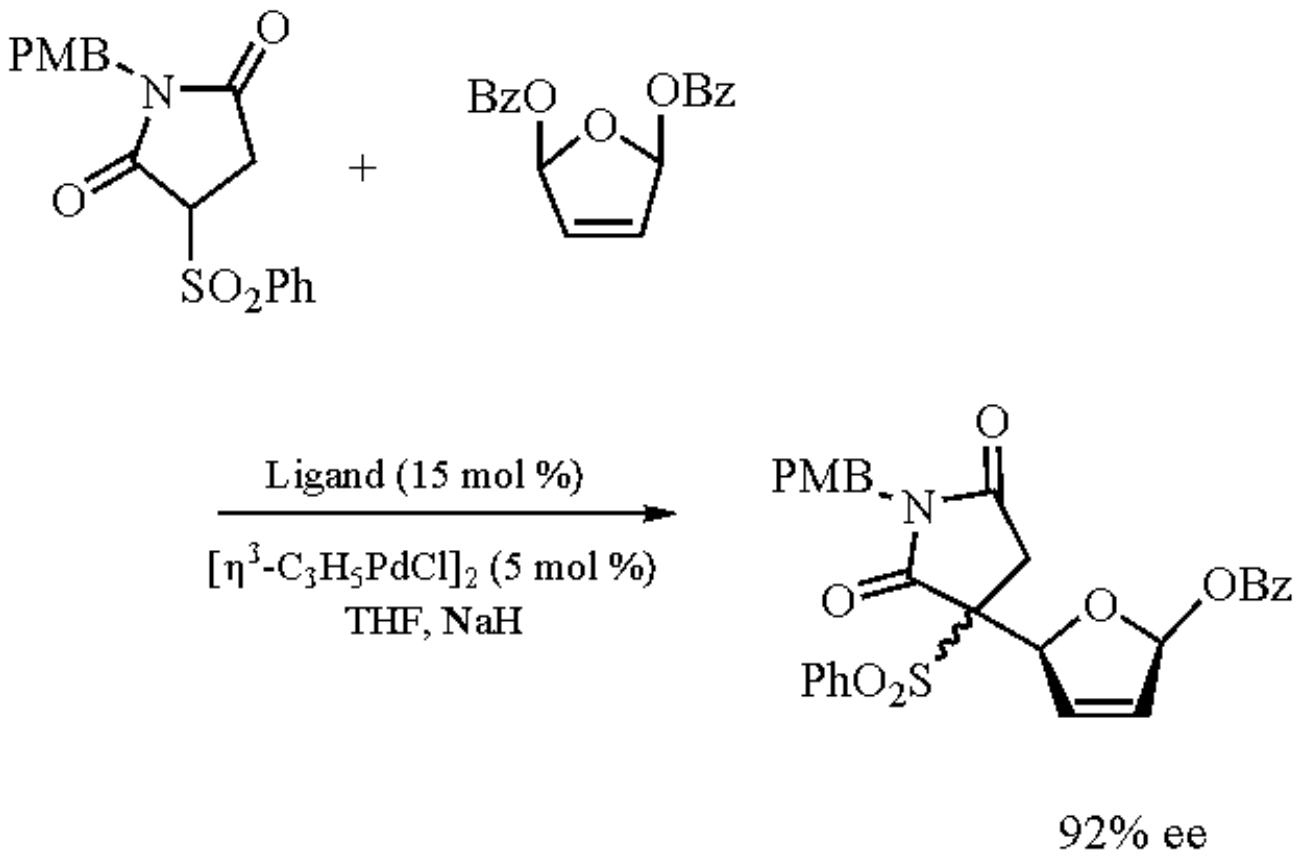

(3)

The alkylation of a dibenzoate with (phenylsulfonyl)nitromethane gave an intermediate for the synthesis of (+)-valienamine.[23]

The reaction of azlactones or a Meldrum's acid derivative with 2-phenylbut-3-ene-2-yl acetate, in the presence of the racemic ligand and a palladium source has provided a new method for controlling alkene geometry. By varying the reaction conditions excellent selectivities for either *E* or *Z* geometry could be obtained.[24]

Reactions with Nitrogen Nucleophiles

The palladium(0)-catalyzed asymmetric desymmetrization of *cis*-3,5-dibenzoyloxy-1-cyclopentene, with 6-chloropurine and 2-amino-6-chloropurine as nucleophiles, has been utilized in the synthesis of (-)-carbovir[25] and (-)-neplanocin.[26] In these examples, the diphenylethanediamine[3] and the anthracenyldiamine[3] based ligands were found to be superior to the standard ligand.

Phthalimide has been used as a nucleophile with cyclic (as depicted for carbon nucleophiles in eq 1)[9] and acyclic allylic carbonates.[27] In addition, phthalimide has been used for the amination of 3,4-epoxybut-1-ene and, in this case, the 1,2-bis(aminocarbonyl-1'-naphthyl-2´-diphenylphosphino)cyclohexane ligand was found to provide the catalyst of choice.[28]

Azide has been used as a nucleophile in the desymmetrization of a dicarbonate derivative (eq 4).[29] In this example, a key intermediate in the synthesis of (+)-pancratistatin was produced.

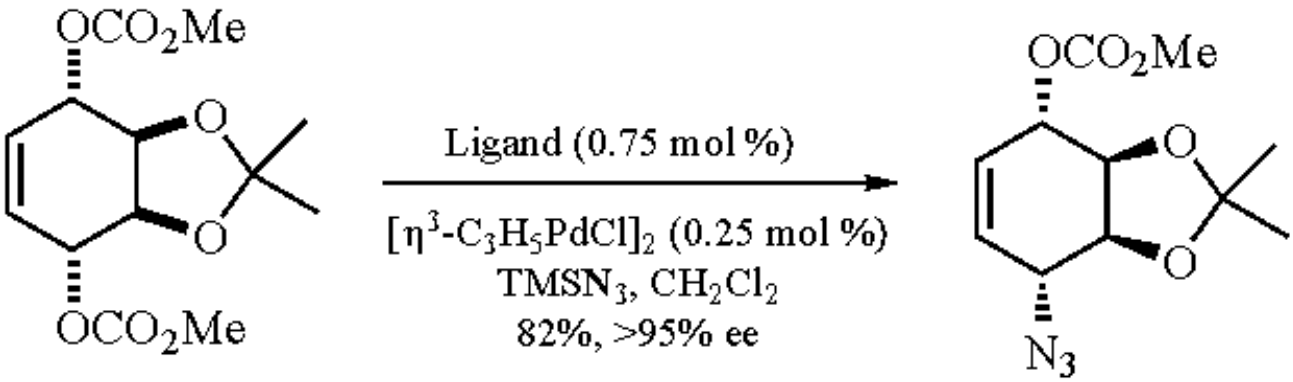

(4)

Basic hydrolysis of the allylic azide affords the rearranged 1,2-isomer, which was an intermediate in the synthesis of (+)-conduramine E.[30] Following a similar strategy, but starting with *cis*-3,6-dibenzoyloxycyclohex-1-ene, a total synthesis of the non-opioid analgesic (-)-epibatidine was developed.[31]

Trost has reported enhanced enantioselectivity in the desymmetrization of *meso*-biscarbamates in the presence of triethylamine.[32] Under these conditions, high yields (>80%) and enantiomeric excesses (93-99% ee) are obtained. This methodology has been applied to the synthesis of (-)-swainsonine.[33]

α-Amino esters have been used as nucleophiles in the reaction with acyclic allylic esters and isoprene monoepoxide, providing access to diastereoselective *N*-alkylated α-amino esters.[34] By employing the feature ligand, asymmetric palladium(0)-catalyzed cyclization of 2-(tosylamino)phenol with (*Z*)-1,4-bis[(methoxycarbonyl)oxy]but-2-ene provides 2-vinylbenzomorpholine in 79% ee.[35] A number of alternative diphosphine ligands were studied and found to be inferior.

The asymmetric synthesis of indolizidine alkaloids is described utilizing a palladium-catalyzed amination process. Ionization of an allylic carbonate provides a symmetrical π-allyl palladium complex, subsequent reaction with a protected homoallylamine gave the product in 93% yield and >99.5% ee (eq 5).[36]

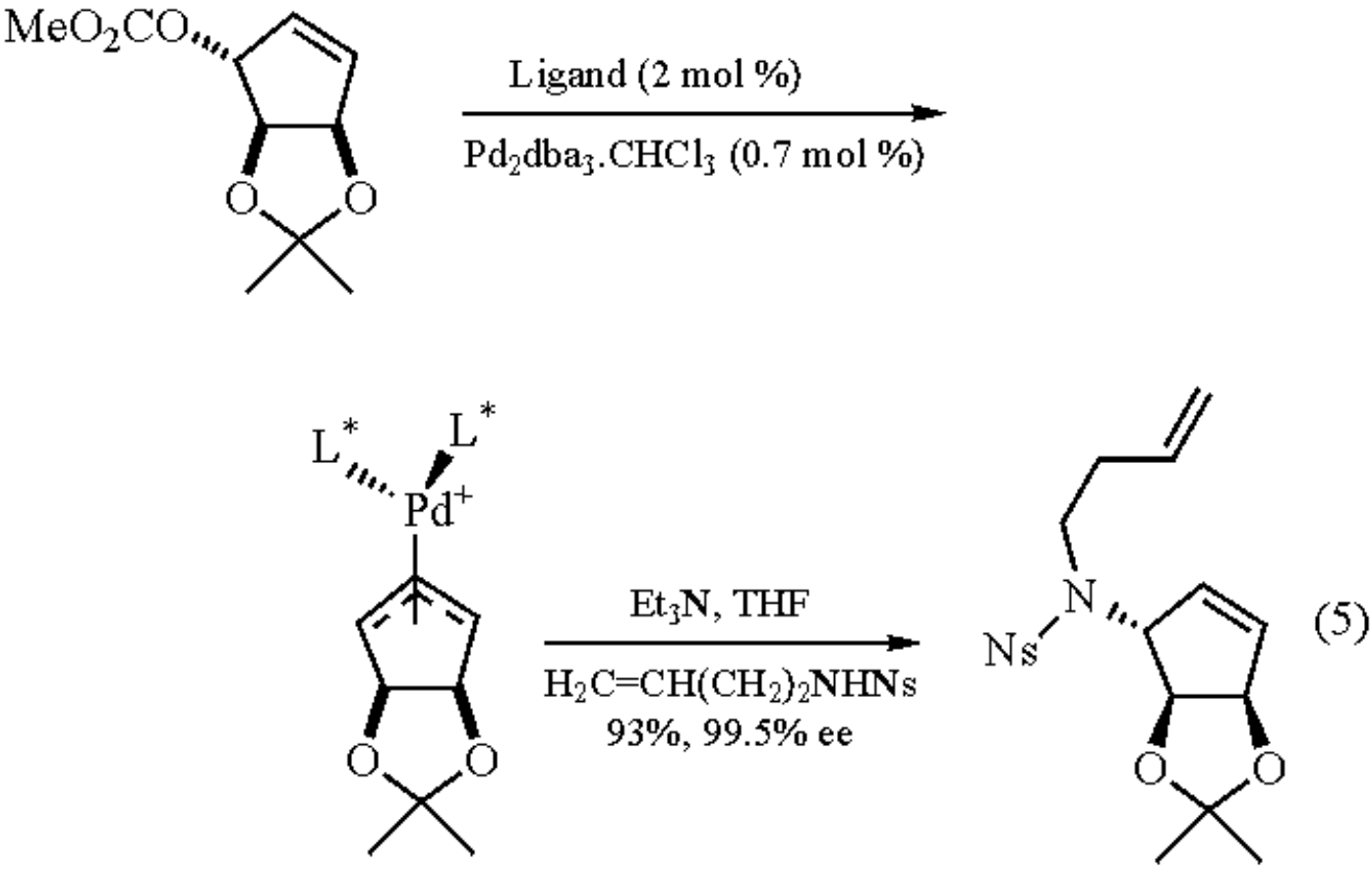

The product of the allylic amination process is set up for a ring-closing-ring-opening metathesis process, and subsequent elaboration to alkaloid derivatives.

Reactions with Oxygen Nucleophiles

The first report of the reaction of oxygen nucleophiles was for the deracemization of cyclic allylic ethers, for example, the palladium(0)-catalyzed reaction of 2-cyclohexenyl-1-methyl carbonate with sodium pivalate afforded the pivalate ester in 94% yield and 92% ee.[37] This reaction was extended to other cyclic allylic carbonates.

Racemic conduritol B acetates and carbonates provide very versatile substrates for asymmetric allylic substitution reactions. Reaction of conduritol B tetraacetate with sodium pivalate in the presence of a palladium catalyst, generated from the ligand and allylpalladium chloride dimer, resulted in a kinetic resolution to give the monosubstituted product in 44% yield (>99% ee) and the recovered tetraacetate in 50% yield (83% ee) (eq 6). This method provided a key intermediate for the synthesis of (+)-cyclophellitol.[38]

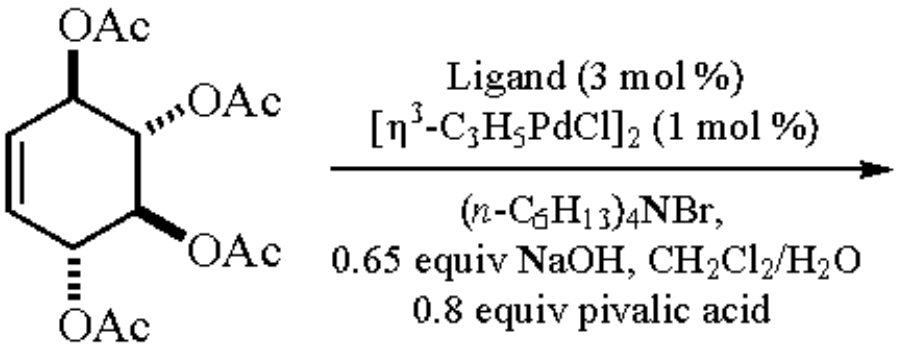

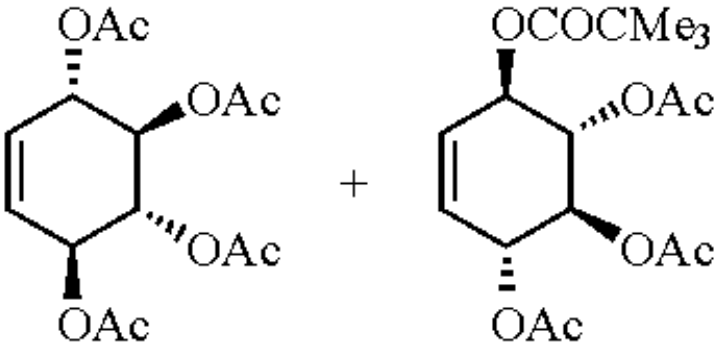

(6)

50%, 83% ee 44%, >99% ee

Later work has shown that a dynamic kinetic asymmetric transformation could be obtained if the acetates were converted into carbonate groups. With the tetra(2,2,2-trichloroethyl) carbonate derivative, reactions with carbon and nitrogen nucleophiles gave exclusively the monosubstituted products in high yield (61-95%) and excellent enantiomeric excesses (95-99%).[39] However, carboxylate nucleophiles afforded the disubstituted products in high yield and enantiomeric excess (eq 7).[39] This allowed an efficient synthesis of D-myo-inositol-1,4,5-trisphosphate to be devised.

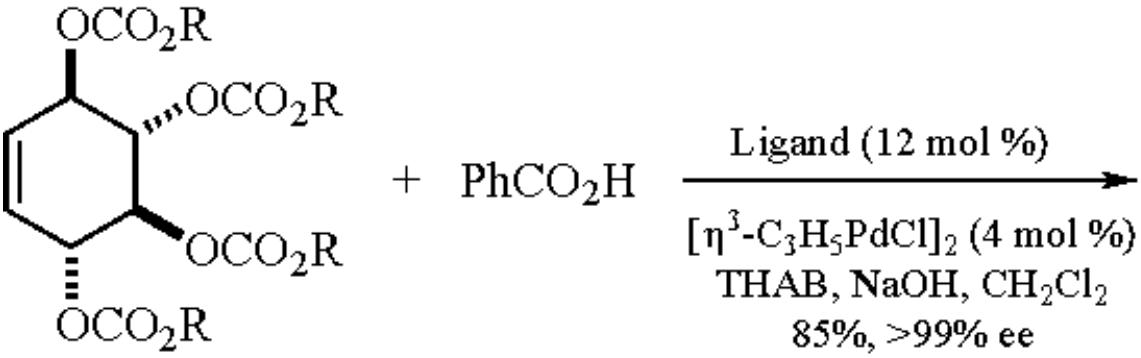

R = Me

R = CH_2CCl_3

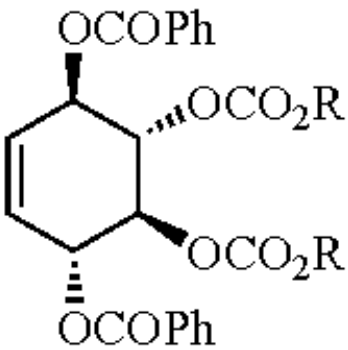

(7)

The reaction of isoprene monoxide with a range of alcohol pronucleophiles in the presence of the ligand (3 mol%), $Pd_2dba_3.CHCl_3$ (1 mol%) and triethylboron (1 mol%) gave the glycol monoethers in excellent yield and enantiomeric excess.[40] The use of *p*-methoxybenzyl alcohol and 3-nonyl-3,4-epoxybut-1-ene afforded an intermediate that was converted into (-)-malyngolide (eq 8).[41]

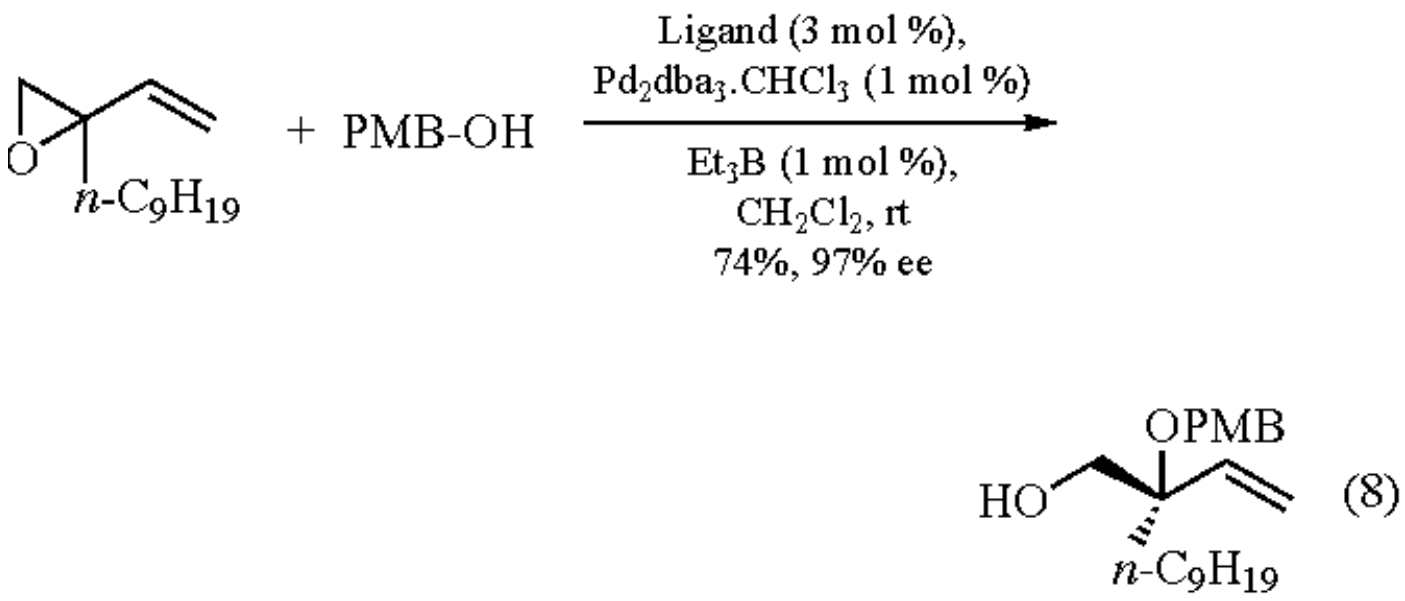

Extending this methodology to 3,4-epoxybut-1-ene was not successful with the featured ligand and the more sterically encumbered 1,2-bis(aminocarbonyl-1´-naphthyl-2´-diphenylphosphino)cyclohexane ligand was required.[40] The use of inorganic carbonates for the asymmetric synthesis of vinylglycidols has also been reported.[42] Reaction of isoprene monoxide with sodium bicarbonate, or sodium carbonate in the presence of the ligand, $Pd_2dba_3.CHCl_3$ and triethylboron afforded the diol in 91% yield and 97% ee. In the absence of triethylboron a cyclic carbonate was formed. Again, the 2-naphthyl ligand was required to provide optimum selectivity with 3,4-epoxybut-1-ene.[42]

The palladium(0)-catalyzed asymmetric *O*-allylation of phenols has been described using five-, six- and seven-membered ring allylic carbonates and acyclic allylic carbonates (eq 9).[43] The products from these reactions were subjected to a Claisen rearrangement to provide *C*-alkylated phenols. A study of various ligands for the reaction of phenol with 2-cyclohexenyl-1-methyl carbonate clearly showed that the Trost ligand is superior.[44]

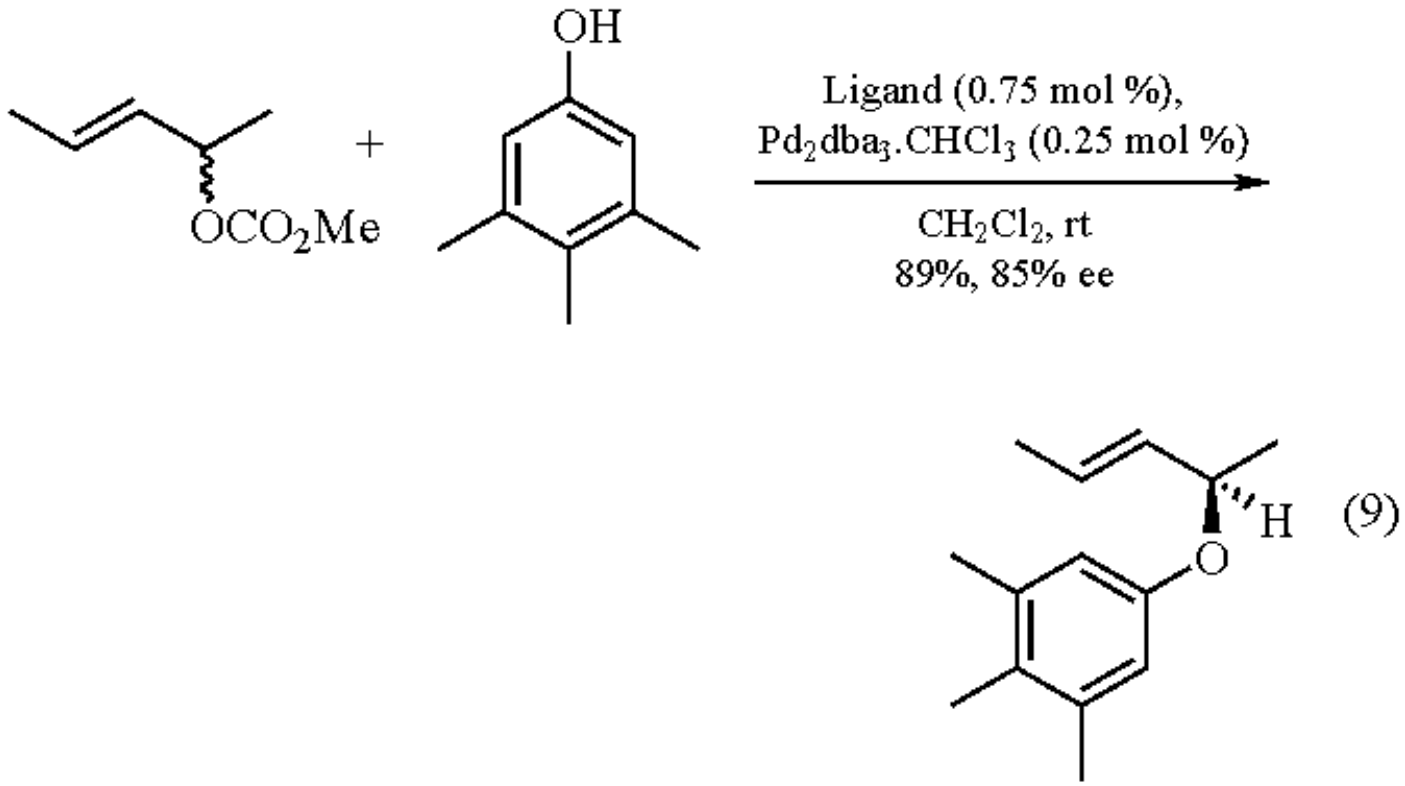

This methodology has been expanded to geranyl methyl carbonate for the synthesis of the vitamin E nucleus, and to tiglyl methyl carbonate for the synthesis of (-)-calanolide A and B.[45] In the latter example, the anthracenyldiamine[3]-based ligand was required for optimum selectivity. The synthesis of (-)-aflatoxin B lactone utilizes a dynamic kinetic asymmetric transformation, whereby a suitably functionalized

phenol reacts with a racemic 5-acyloxy-2-(5*H*)-furanone to provide a single product in 89% yield.[46] One final example of phenol as a nucleophile is for the deracemization of Baylis-Hillman adducts.[47]

Cyclic 1,2-diketones, such as 3-methylcyclopentane-1,2-dione, act as oxygen nucleophiles in palladium(0)-catalyzed reactions with a range of cyclic and acyclic allylic esters.[48] The products of these reactions were subjected to a lanthanide-catalyzed Claisen rearrangement to access the *C*-alkylated products.

Reactions with Sulfur Nucleophiles

The use of sulfur nucleophiles in palladium-catalyzed allylic substitution reactions is less well documented than that of carbon, nitrogen and oxygen nucleophiles. The asymmetric synthesis of allylic sulfones utilizing a catalytic phase transfer system has been used to produce (3*S*)-(phenylsulfonyl)cyclohex-1-ene on a 45 g scale (eq 10).[49] In many cases, it has been reported that allylic carbonates are more reactive than allylic acetates in asymmetric allylic substitution reactions.[49,50]

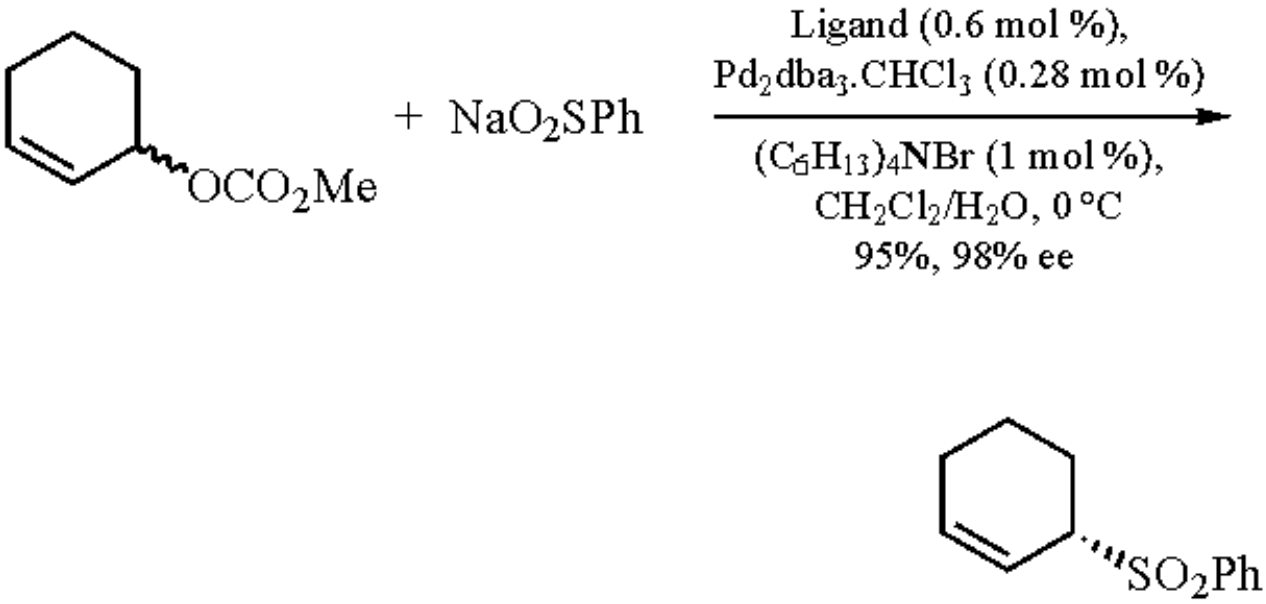

(10)

A range of cyclic allylic carbonates was found to be useful in this process and a myriad of useful functionalized building blocks were accessed via dihydroxylation and epoxidation reactions.[49] The reaction of lithium *tert*-butylsulfinate with acyclic allylic acetates in the presence of the ligand, $Pd_2(dba)_3.CHCl_3$ and tetrahexylammonium bromide under phase-transfer conditions (CH_2Cl_2/H_2O) led to a kinetic resolution whereby the starting material was isolated in 96% ee and the *tert*-butyl sulfone in 95% ee.[50] With cyclic allylic carbonates, a single *tert*-butyl sulfone is obtained in 76-92% yield and 89-93% ee.[50] However, stopping the reaction at 54% conversion gave the sulfone (49% yield, 98% ee) and the carbonate (34% yield, 99% ee), this kinetic resolution protocol was later extended to thiols with cyclic and acyclic allylic carbonates.[51] In general, the synthesis of allylic sulfides requires higher catalyst loading and was found to be unsuccessful for *tert*-butyl thiol and thiophenol.[52] However, cyclic and acyclic allylic *S*-*p*-chlorophenyl, *S*-2-pyridyl and *S*-2-pyrimidyl sulfides could be obtained in high yield and enantiomeric excess, in the presence of the ligand and $Pd_2(dba)_3.CHCl_3$ in organic solvent.[52]

A more efficient method to access single enantiomer thiols and sulfides has been developed using a palladium(0)-catalyzed rearrangement of *O*-allylic thiocarbamates (eq 11).[53]

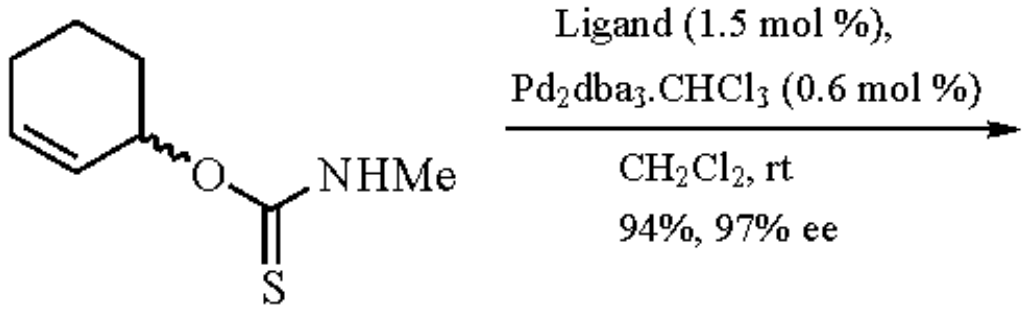

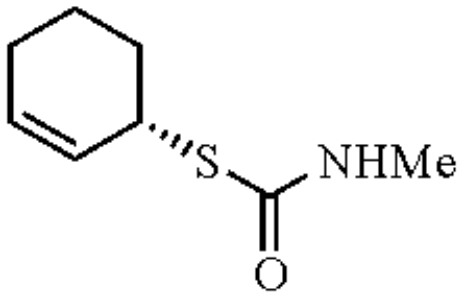

(11)

This reaction was carried out on cyclic and acyclic allylic carbonates. The *S*-allylic thiocarbamate products were hydrolyzed to the corresponding thiol or reacted with 2-chloropyrimidine in the presence of potassium hydroxide to provide the sulfide without any loss in stereochemical purity for either example.[53]

α-Acetoxysulfones can be regarded as acid-stable, but base-labile, chiral aldehyde equivalents. These can be accessed through the palladium(0)-catalyzed reaction of geminal esters with sodium benzenesulfinate under phase-transfer conditions (eq 12).[54]

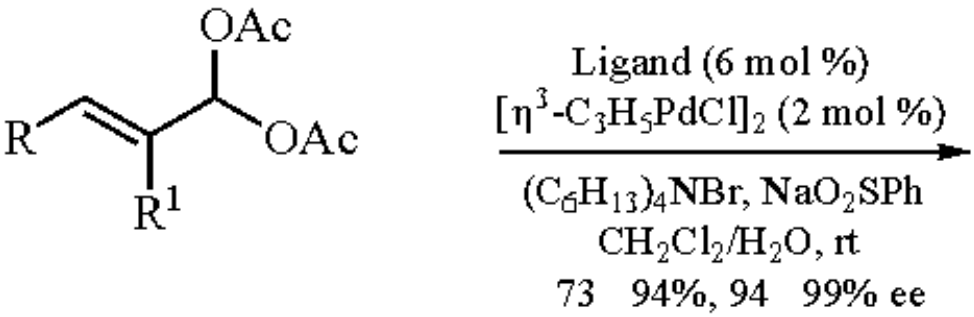

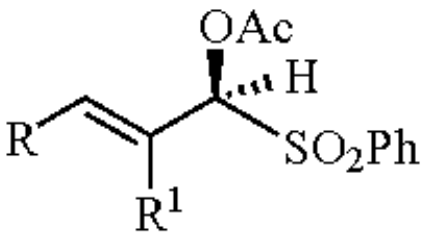

(12)

Osmium tetroxide-catalyzed dihydroxylation of the chiral α-acetoxysulfones and acetonide formation affords versatile chemical intermediates. Reduction with DIBAL-H provides primary alcohols, and addition of Grignard reagents provides secondary alcohols with excellent stereochemical control of the newly formed chiral center.[54]

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Ian C. Lennon

Chirotech Technology Limited, Cambridge, UK

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Polymer-Supported Schwesinger Base

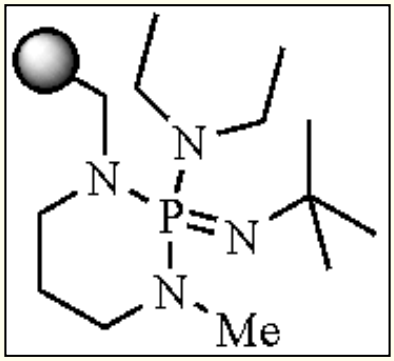

[98015-45-3]

(polymer-bound strong base for acylation and alkylation reactions)

Alternate Name: P-BEMP, PS-BEMP (BEMP=2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine).

Physical Data: loading 2.3 mmol g^{-1} on polymer (batch dependent).

Solubility: the reagent, immobilized on 1-2% cross-linked polystyrene divinylbenzene co-polymer, is insoluble in all common organic and aqueous solvents.

Form Supplied in: brown powder, commercially available.

Analysis of Reagent Purity: the loading of the reagent is best determined by elemental analysis. The functional activity can be determined by the degree of chemical transformation from use of stoichiometric quantities of reagents.

Handling, Storage, and Precautions: harmful if inhaled or ingested; irritant. Stable at room temperature.

Phosphazene bases have been shown to be useful alternatives to ionic bases for a number of chemical transformations.[1] Of these, 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) has a basicity (pK_B=27.5) comparable to 5 M aqueous potassium hydroxide/Bu_4N/acetonitrile and potassium carbonate/18-crown-6/acetonitrile.[2] The commercially available[3] polymer-supported equivalent, PS-BEMP,[2] retains the basicity of the solution phase reagent and has been exploited in the alkylation and acylation of weakly nucleophilic NH-containing compounds.

Alkylation of Heterocycles

In an early paper, Xu and co-workers[4] studied the *N*-alkylation of a number of weakly acidic NH-containing aromatic heterocycles. Indoles, pyrazoles, and phthalazinones were alkylated with α-bromo ketones or esters in the presence of PS-BEMP in acetonitrile at room temperature. Simple filtration and evaporation, after removal of excess alkylating agent with aminomethyl polystyrene, gave the required products in high chemical yield (93-98%) and high purity (93-99%). The use of more weakly basic resins resulted in no alkylation and this enabled the authors to develop a one-pot procedure for the selective dialkylation of a pyrazole (eq 1).

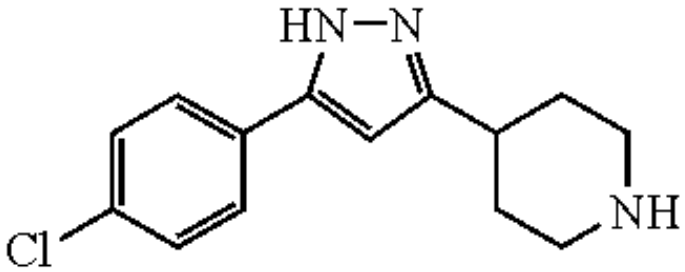

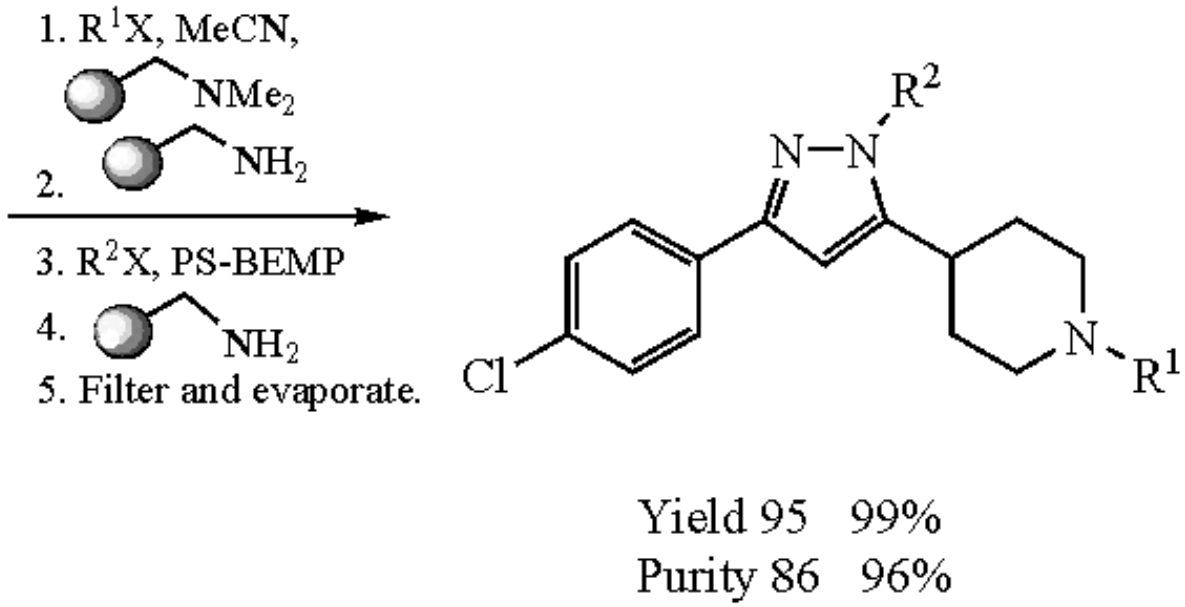

(1)

Similar procedures using PS-BEMP for the alkylation of purines[5] and pyrroles[6] and for S_NAr reactions towards fluoroquinolone antibacterial agents[7] have been reported.

Alkylation of Sulfonamides

The principle of orchestrated multi-step synthesis using polymer-supported reagents[8] has been applied to the preparation of a series of hydroxamic acids as potential matrix metalloproteinase inhibitors.[9] Alkylation of the weakly acidic sulfonamide NH with benzylic halides, a key step in the synthesis, was achieved utilizing PS-BEMP in dichloromethane. Scavenging of the excess alkylating agent with aminomethyl polystyrene followed by filtration and evaporation gave the required products in high yield and purity (eq 2).

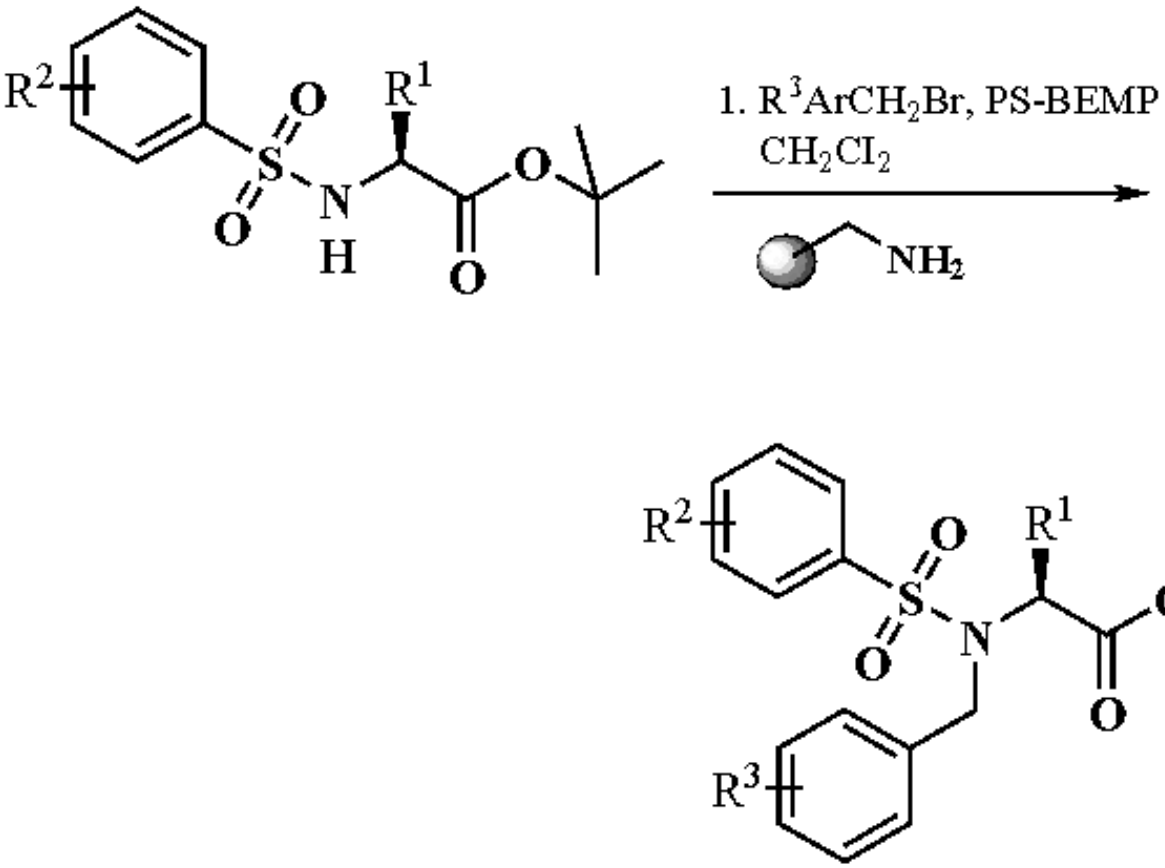

Alkylation and Acylation of Weakly Nucleophilic Species

In an analogous way to the alkylation of heterocycles, PS-BEMP has been utilized for the derivatization of weakly nucleophilic heterocyclic amines and hydrazones. Having investigated a range of polymer-bound acyl transfer reagents, Kim and Le found PS-BEMP in THF to be a superior reagent for the acylation of amino-pyridines, -pyrazoles, -thiazoles, -benzothiazoles, and -quinolines with acid chlorides.[10] Amides were produced in high purity but only in moderate yield using this chemistry. The alkylation of hydrazone **1**, a key intermediate towards the polymer-supported synthesis of sildenafil,[11] was achieved in excellent yield with the excess, unreacted α-bromoester being sequestered with aminomethyl polystyrene or polymer-supported trisamine (eq 3).

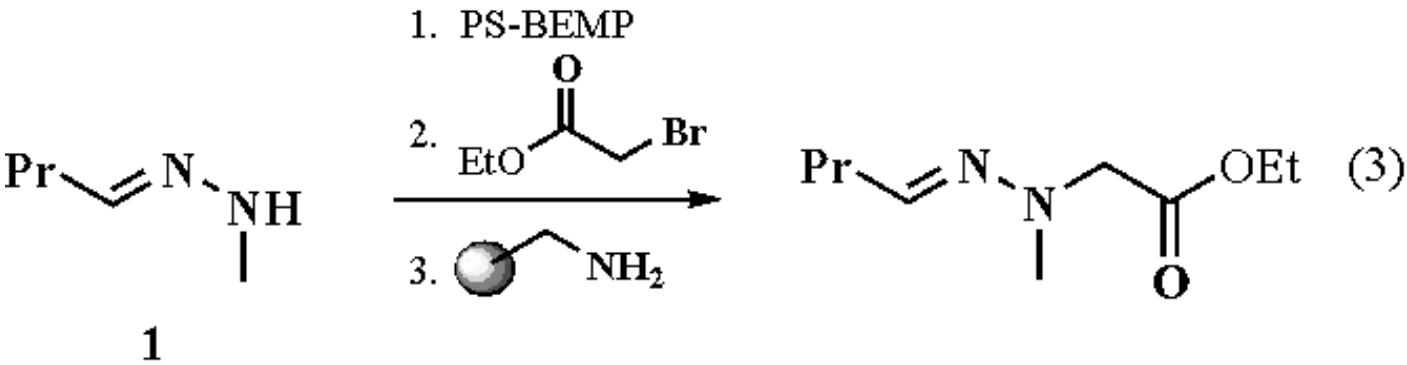

Application of PS-BEMP to Ring Forming Reactions

In a later stage of the same polymer-supported synthesis of sildenafil,[11] PS-BEMP was employed to effect the rapid deprotonation and concomitant cyclization of substituted hydrazone **2** to a tetrasubstituted pyrazole (eq 4).

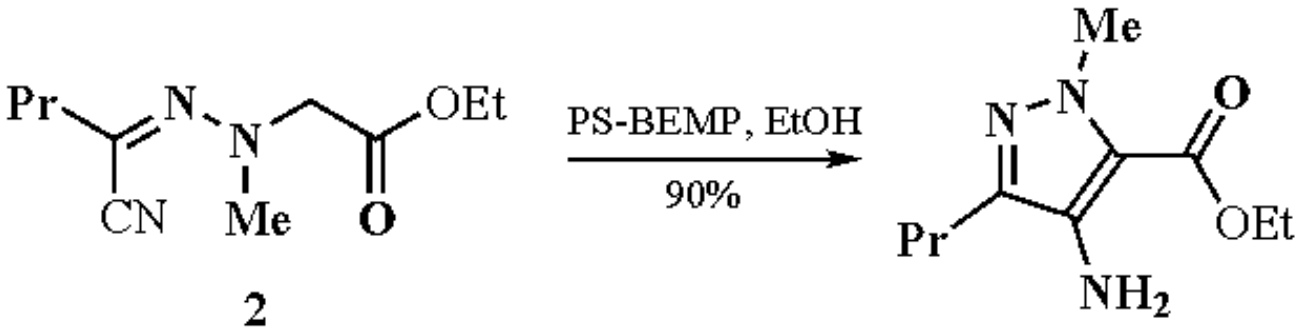

Using an orchestrated sequence of polymer-supported reagents, Ley and co-workers demonstrated the ten-step synthesis of (±)-epibatidine.[12] The key step in the formation of the epibatine framework, a transannular cyclization, was mediated by PS-BEMP (eq 5). The authors found that the supported phospazene base allowed the reaction to proceed in higher yield and more rapidly than under the thermal conditions reported in a previous synthesis. Additionally, no by-products arising from intermolecular alkylation were observed. The only impurity, approximately 10% of the unreacted starting material, could be sequestered using aminomethyl polystyrene.

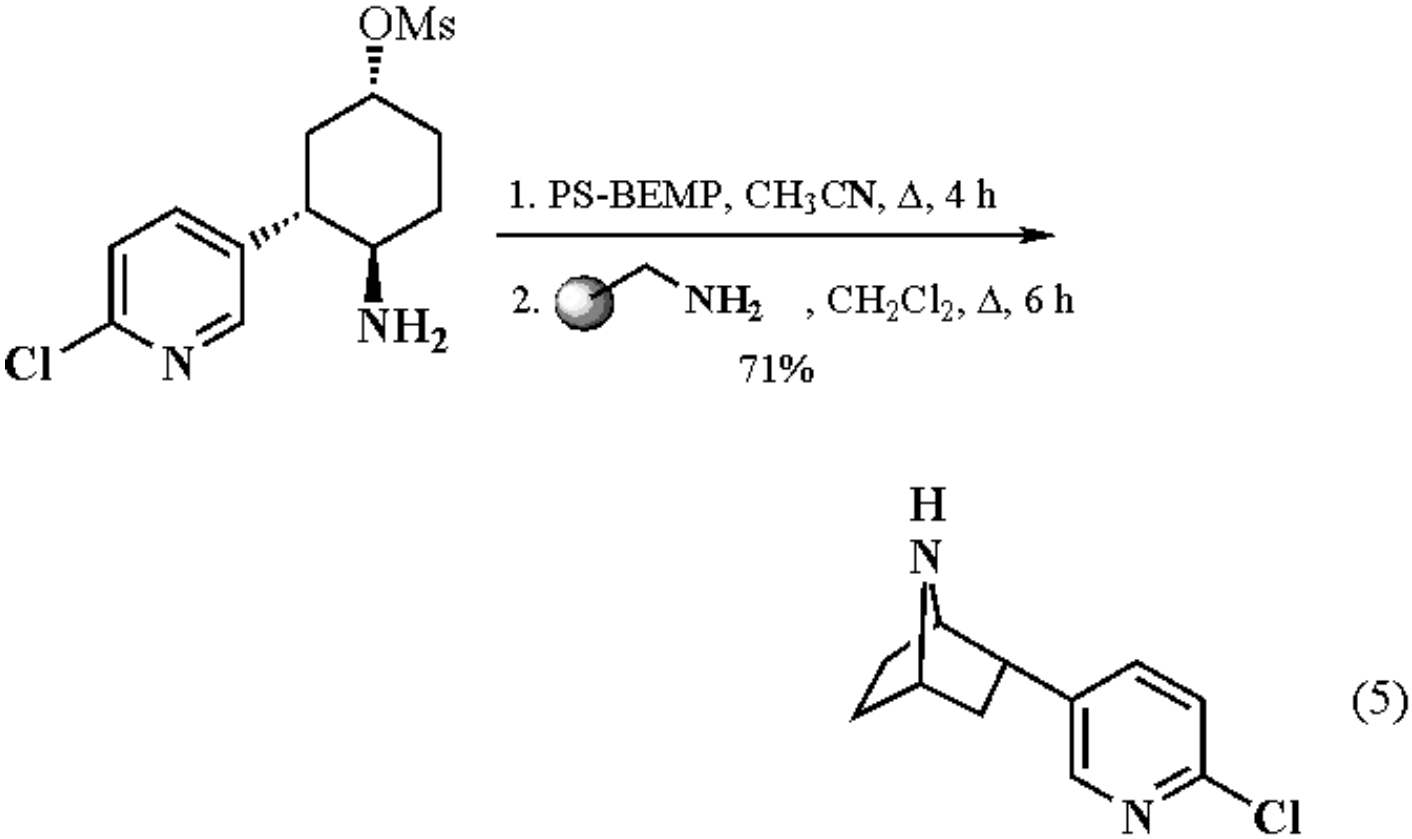

PS-BEMP has also been utilized in the synthesis of the bis(indole) marine alkaloid, rhopaladin D.[13] The key step, formation of the central imidazolinone ring, was effected by an aza-Wittig reaction of phosphorane **3** with indolyl-3-glyoxylyl chloride in the presence of PS-BEMP. Intramolecular cyclization of the resulting imidoyl chloride gave the required rhopaladin ring system (eq 6).

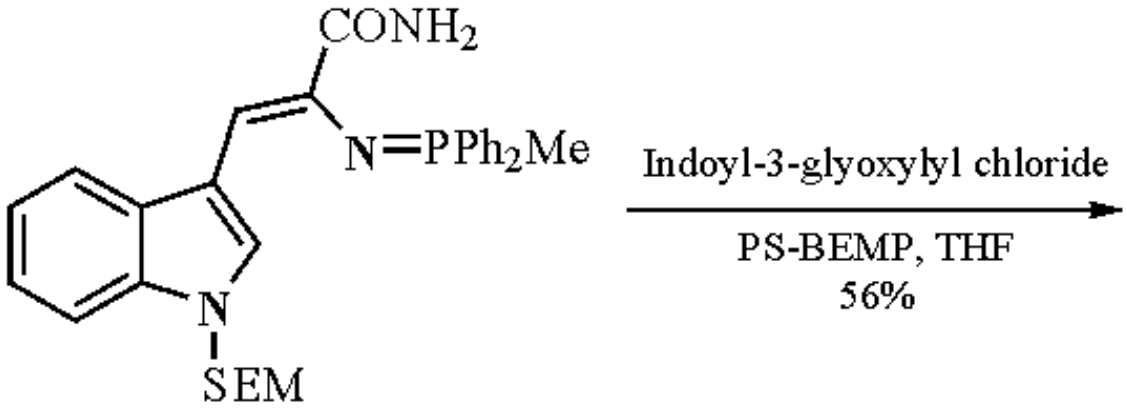

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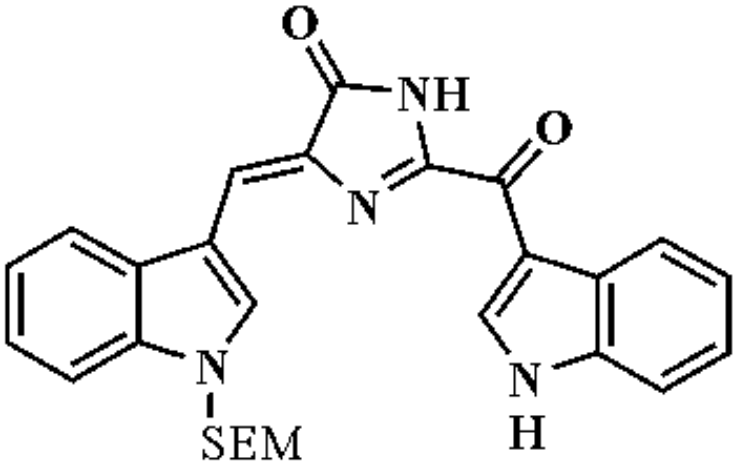

(6)

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University of Cambridge, Cambridge, UK

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Borohydride Exchange Resin

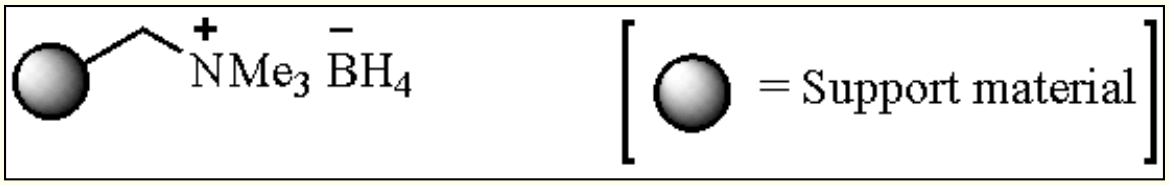

(chemoselective nucleophilic hydride reducing reagent for aldehydes and ketones, and many other functional groups in the presence of metal salt catalysts)

Physical Data: loading 2-3 mmol g^{-1} of boron on the polymer (batch dependent).

Solubility: cross-linked polystyrene divinylbenzene co-polymers are insoluble in all common solvents.

Form Supplied in: white microporous or macroreticular solid, available from several large international suppliers.

Analysis of Reagent Purity: the loading is usually obtained from elemental analysis.

Purification: polymer washed using water, then methanol. Drying may be completed in vacuo between 25°C and 60°C.

Handling, Storage, and Precautions: harmful if inhaled or ingested. Decomposition occurs under acidic conditions to form toxic diborane gas and flammable/explosive hydrogen gas. All reactions should be carried out under a well ventilated fumehood. Long-term storage should be in a refrigerator under nitrogen.

Borohydride Exchange Resin (BER)

For many years, insoluble cross-linked polystyrene resins with quaternary ammonium termini have been used as supports for anionic reagents in organic synthesis.[1-14] Polymer bound borohydride was first reported by two independent groups in 1961,[15,16] with the first published reports of borohydride supported on ion-exchange polymer **1** appearing over a decade later.[6,17]

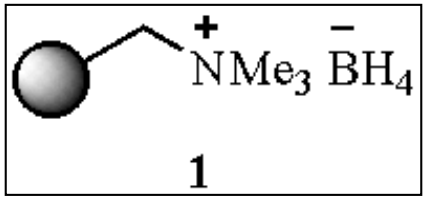

Borohydride exchange resin is available from several commercial suppliers.[18] It can also be prepared by the chemical modification of cross-linked polystyrene-based quaternary ammonium ion exchange polymers. The chloride forms of Amberlyst A-26, Amberlite IRA-400 or Amberlite IRA-900[19] are suspended in an aqueous solution of sodium borohydride for 1 h. The resin is then filtered and washed with distilled water and then methanol before drying under vacuum for several hours (eq 1).[17] After use, the polymeric reagent can easily be regenerated by washing with aqueous hydrochloric acid and water before refunctionalizing as above.

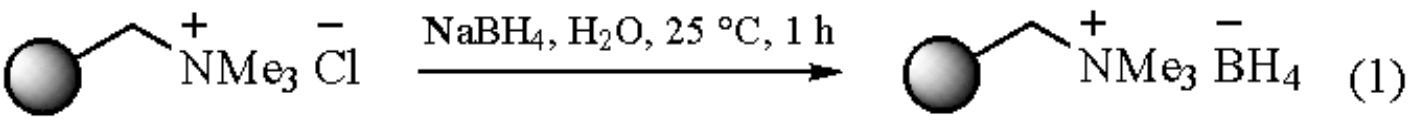

An important modification of reactions with borohydride exchange resin is its use in conjunction with catalytic metal salts which enhance its reducing power.[14]

Supported zinc[20,21] (**2**) and zirconium[22] (**3**) borohydrides have also been prepared on cross-linked poly(4-vinylpyridine). The unsupported forms of these reagents are unstable and require careful storage and use. However, the polymeric versions offer not only greater ease of handling, but can also be stored for several months at room temperature. Furthermore, these poly(4-vinylpyridine)-supported reagents have loadings which are approximately three times higher (~10 mmol g^{-1}) than the equivalent polystyrene-based polymers.

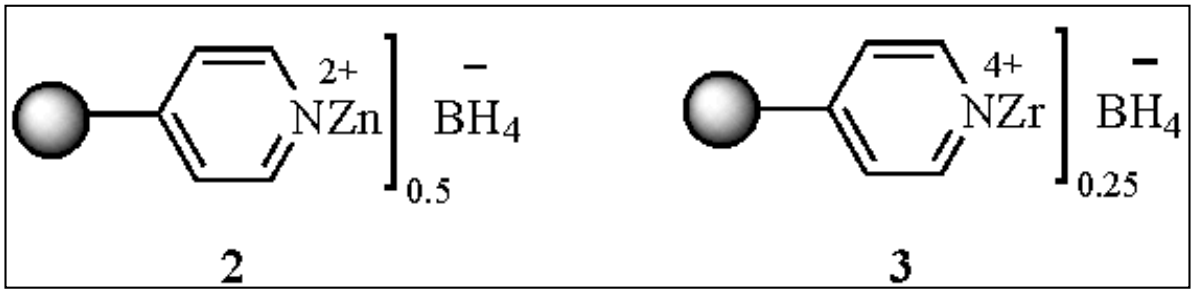

Reduction of Aldehydes and Ketones

Borohydride exchange resin readily reduces aldehydes and a variety of ketones to their respective alcohols without affecting esters (except aryl acetates)[23] or amides (eq 2). Reactions can be performed in either methanol or ethanol, but rates of reaction are much higher in methanol. Aldehydes are more reactive towards borohydride exchange resin than ketones and a high level of chemoselectivity has also been observed within these groups.[24]

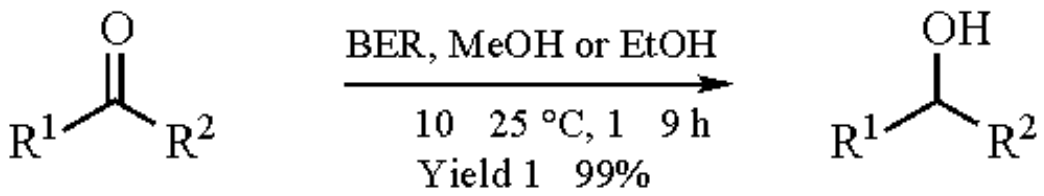

(2)

R^1= alkyl, aryl

R^2= H, alkyl

Enhanced rates of reaction and chemoselectivity have been seen using BER (borohydride exchange resin) with **lithium chloride** or **lithium nitrate** to reduce carbonyl groups in the presence of other reducible functionalities such as alkenes, amides, halides, nitriles, and nitro groups.[25] Improved rates of reduction also occur when BER is used in conjunction with **$Ni(OAc)_2$** or **$CuSO_4$**. Additionally, nickel catalysis has also been seen to further reduce aromatic aldehydes[26, 27] to methyl arenes (eq 3).

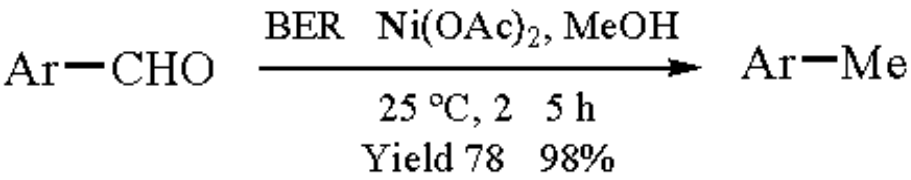

(3)

When BER reacts with α,β-unsaturated aldehydes and ketones, selective formation of the α,β-unsaturated alcohols occurs with no reduction of the double bond (eq 4).[19,28,29] This is in contrast to sodium borohydride, where conjugate reduction is found to be a substantial competing process.

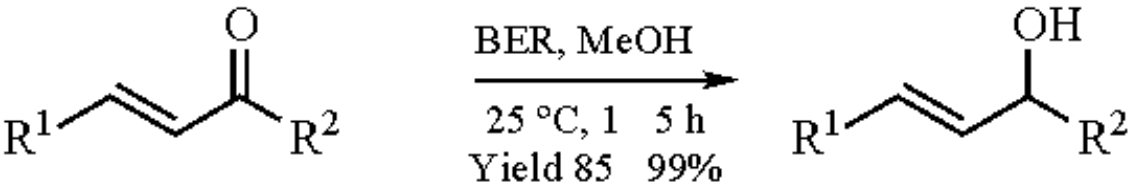

(4)

R^1= aryl

R^2= H, alkyl, aryl

For a comparison, **Amberlyst A-26**, **Amberlyst IRA-400**, and **sodium borohydride** on alumina were all tested. The A-26 was more reactive than IRA-400, but both showed similar selectivity. The alumina-supported material reacted fastest but showed reduced selectivity. The importance of the choice of supporting material is also highlighted in an alternative report, where the support used was Seralite-SRA-400. Here a complete reversal of selectivity was reported in which unsaturated ketones are reduced to saturated ketones and α,β-unsaturated aldehydes are reduced to saturated alcohols.[30] Also, if BER is used in conjunction with copper sulfate, most α,β-unsaturated ketones and aldehydes are reduced to the corresponding saturated alcohols.[31]

Poly(4-vinylpyridine)-supported zirconium borohydride is another reliable reagent for reduction of aldehydes or ketones and is reported to leave conjugated double bonds intact.[22] Zinc borohydride on poly-eta-(pyrazine)[32] can be used as an alternative. However, for absolute selectivity for aldehydes over ketones, zinc borohydride on poly(4-vinylpyridine)[20] can be applied.

Reduction of Nitro Compounds

Uncatalyzed BER reacts with nitroalkenes which are reduced to the respective nitroalkanes.[33] However, it is unable to reduce aliphatic or aromatic nitro groups unless it is employed in conjunction with a transition metal catalyst such as $Ni(OAc)_2$,[27] $NiCl_2.6H_2O$,[34] $PdCl_2$,[35,36] CuCl,[35] $Cu(OAc)_2.4H_2O$[35] $CuSO_4$,[37] or Ni_2B.[37] These systems give successful reduction of both aliphatic and aromatic nitro groups to the corresponding amines in excellent yields (eq 5).

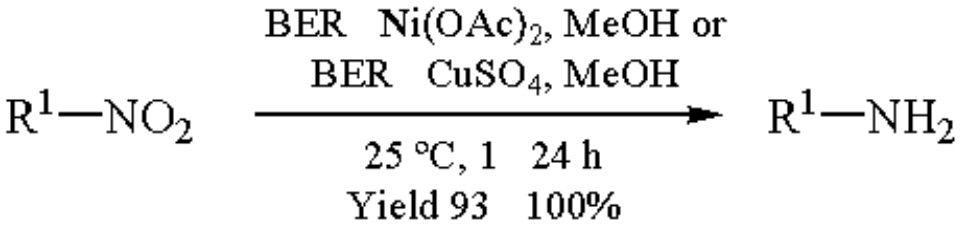

(5)

R^1= alkyl, aryl

Reduction of Azides

For the general reduction of aliphatic and aromatic azides, catalytic nickel acetate[38] or copper sulfate[37] are usually employed, although poly(4-vinylpyridine)-supported $Zr(BH_4)_2$ has also been reported to facilitate these reactions (eq 6).[22]

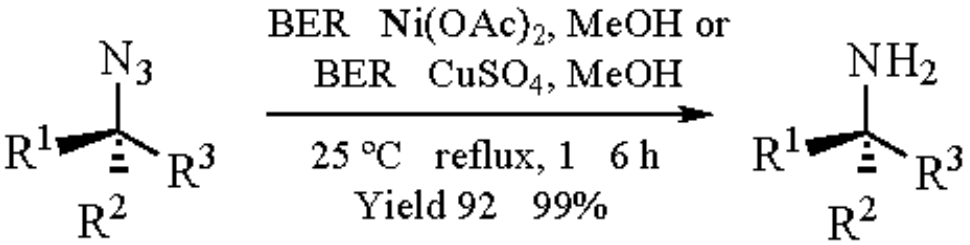

(6)

R^1= alkyl, aryl

R^2, R^3= H, alkyl, aryl

Borohydride exchange resin itself only reduces aryl azides and sulfonyl azides to the corresponding aryl amines and sulfonamides respectively.[39] Aryl azides with electron-withdrawing substituents are readily reduced at room temperature, whereas unactivated phenylic and benzylic azides require reflux for long periods. Aliphatic azides do not react under these conditions (eq 7).

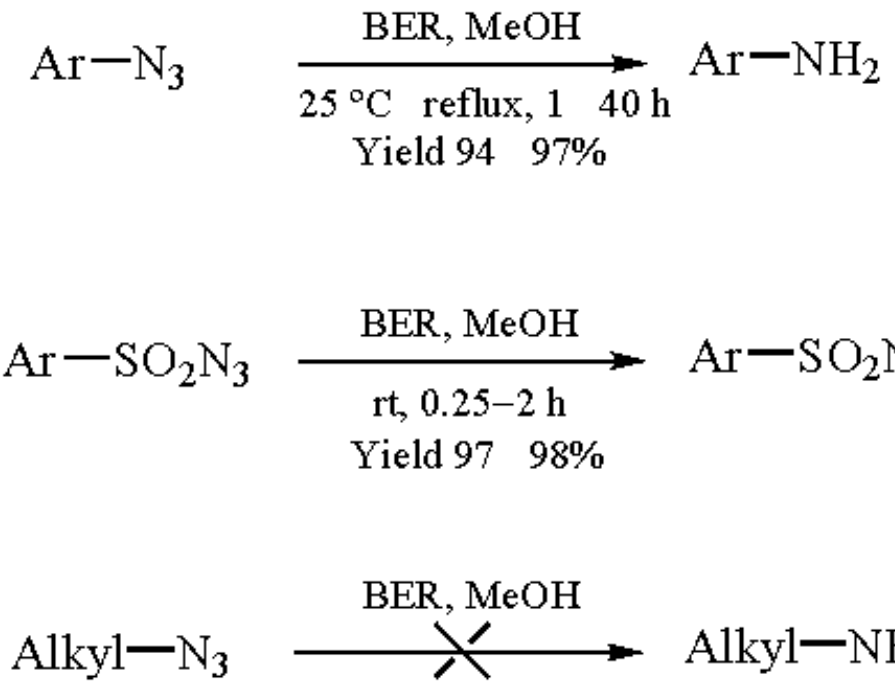

(7)

Reduction of Imines

BER is useful in the reductive amination of aldehydes and ketones in acidified methanol or ethanol.[40-43] Secondary or tertiary amines are produced in high yield from the reaction between aldehydes and primary or secondary amines (eq 8). Ketones react well when coupled with less hindered aliphatic amines, but low yields are obtained with aromatic amines.

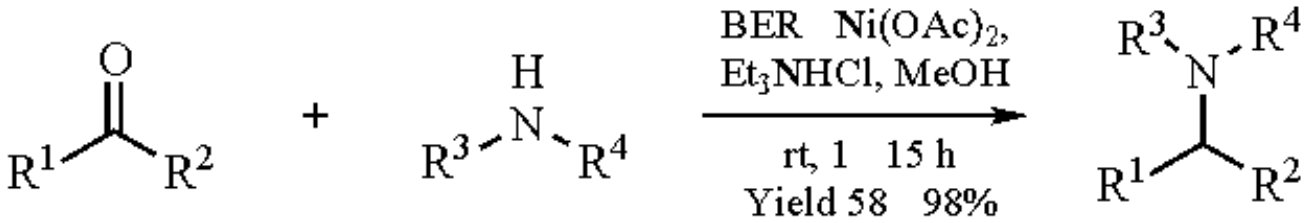

(8)

R^1= alkyl, aryl

R^2= H, alkyl, aryl

R^3, R^4= alkyl, benzyl

Although secondary and tertiary amines are prepared in good yield using these methods, yields of primary amines are moderate to poor. However, reductive amination of aldehydes and ketones with hydrazine has been found to be a good alternative (eq 9). The intermediate hydrazones undergo N-N cleavage with BER-$Ni(OAc)_2$ in refluxing methanol to afford the resultant primary amines in good yield.[44]

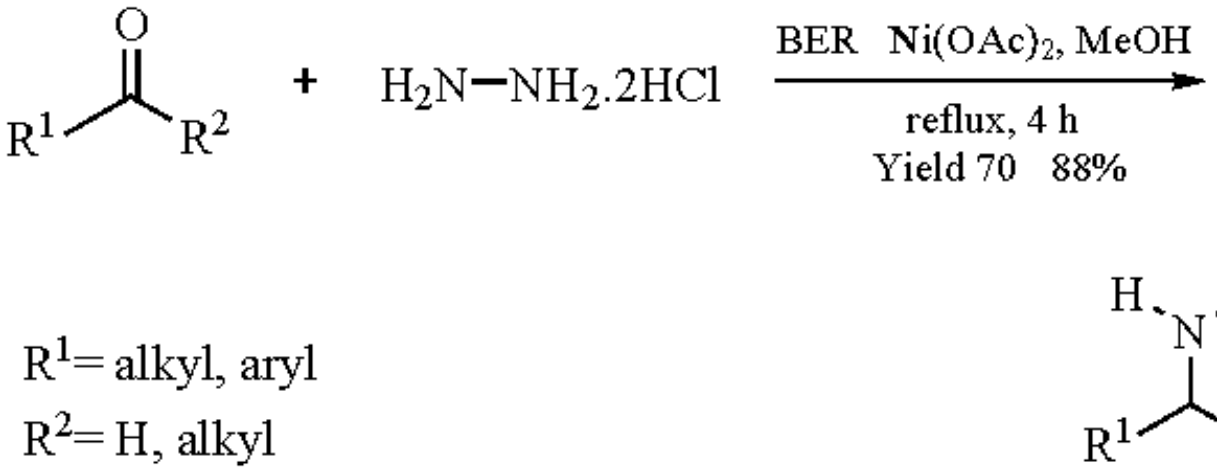

(9)

An alternative reducing reagent for reductive amination is supported cyanoborohydride **4**, which is commercially available or can be prepared in a similar manner to BER using sodium cyanoborohydride and the chloride form of the polymer.[45]

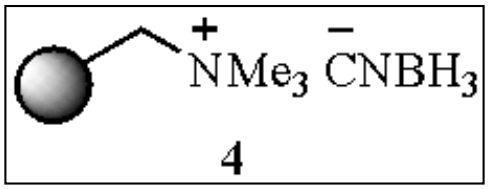

Reductions of Alkyl and Aryl Halides and Tosylates

Borohydride exchange resin alone is able to react with only certain halides.[46] However, in the presence of $Ni(OAc)_2$ most aliphatic or aromatic halides and tosylates are successfully reduced (eq 10).[47, 48]

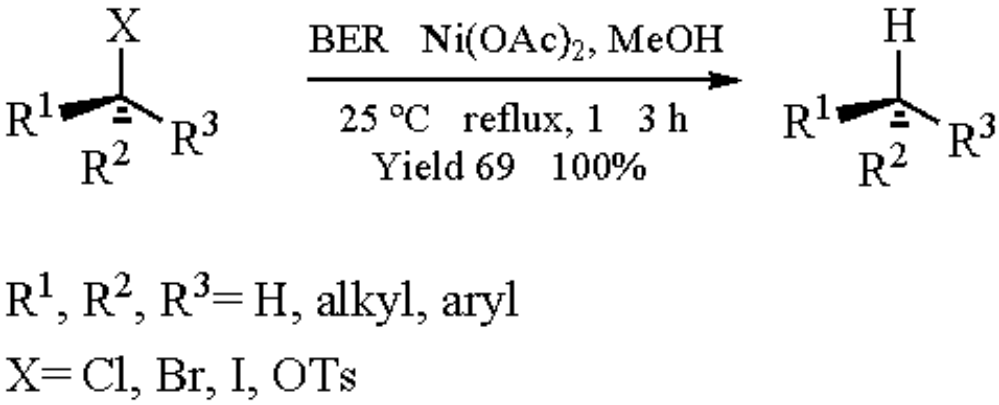

(10)

Borohydride exchange resin used in conjunction with $CuSO_4$ and BER-nickel boride (Ni_2B) has been successfully employed in the reduction of bromides and iodides or benzylic chlorides.[37]

A BER-Ni_2B system prepared in situ from BER-$Ni(OAc)_2$ in methanol has been used for a novel C-C bond formation via radical addition or radical cyclization of alkyl halides with electron deficient alkenes of α,β-unsaturated esters, ketones and nitriles.[49,50]

Reduction of Alkenes

Although most double bonds are unreactive to BER, an exception to this is conjugated nitroalkenes which can be efficiently reduced to saturated nitroalkanes (eq 11).[33]

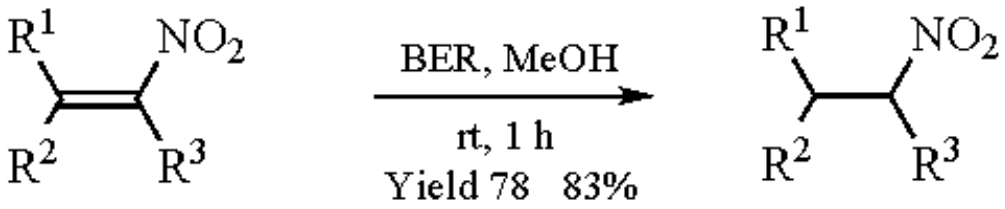

(11)

R^1, R^3= H, alkyl

R^2= H, alkyl, aryl

The reductions of α,β-unsaturated amides, esters, and nitriles using BER require a catalyst. When BER-$CuSO_4$ is used, the saturated species are formed with no concurrent reduction of the amide, ester, or nitrile functionalities (eq 12).[51]

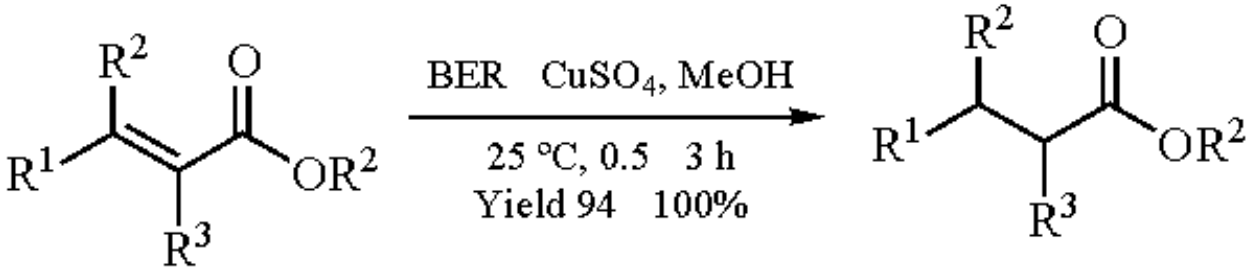

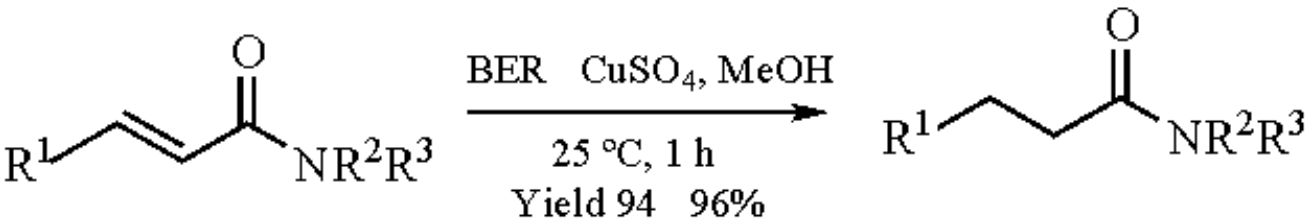

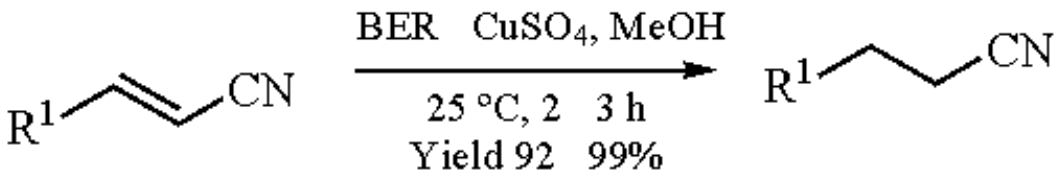

(12)

R^1, R^2, R^3= H, alkyl

When catalyzed by cobalt, nickel, or copper, BER has been shown to reduce a wide variety of isolated double bonds (eq 13).[52,53] Mono- and di-substituted alkenes are successfully reduced. Less hindered alkenes and those attached to electron-withdrawing substituents show enhanced rates, whereas hindered and trisubstituted olefins are not reduced.

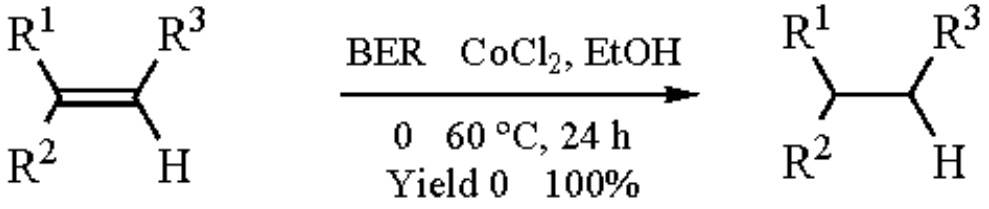

(13)

R^1= H, alkyl, aryl

R^2, R^3= H, alkyl

Nickel Boride (Ni_2B) also catalyses the selective borohydride exchange resin-mediated hydrogenation of mono- and di-substituted olefins. Monosubstituted alkenes are quantitatively hydrogenated in 1 h at 0°C in the presence of di-substituted alkenes and trisubstituted α,β-unsaturated acid derivatives. Disubstituted double bonds are hydrogenated at reflux in 1 h without affecting trisubstituted olefins, benzenes, or heteroaromatics.[54]

Reduction of Alkynes

It was reported that $Pd(OAc)_2$-doped BER in the presence of cesium iodide promotes hydrogenation of alkynes to give *cis*-alkenes (eq 14).[55] This method was excellent for the semihydrogenation of terminal and internal alkynes.

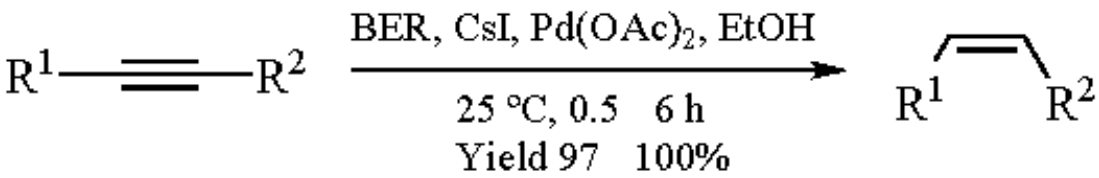

(14)

R^1= alkyl

R^2= H, alkyl

Reduction of Oximes

Oximes are resistant to reduction by BER, but aromatic oximes can be transformed to primary benzylamines using BER-$Ni(OAc)_2$ (eq 15).[56] Aryl aldoximines with electron-withdrawing substituents such as nitro and chloro are readily reduced, but simultaneous reduction of the nitro and chloro groups also occurs. Reduction of aryl aldoximes with electron-donating substituents is slow, but they can be successfully reduced using higher temperatures and longer reaction times.

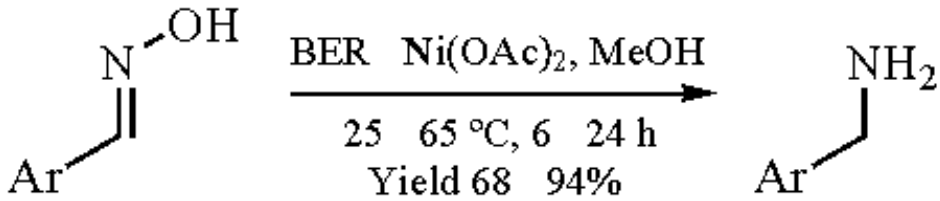

(15)

Reduction of Acid Chlorides and Epoxides

BER successfully reduces acid chlorides to alcohols.[34,57] Poly(4-vinylpyridine)-supported $Zr(BH_4)_4$ converts acid chlorides to aldehydes and epoxides to the more substituted alcohols (eq 16).[22] $AlCl_2(BH_4)$ supported on poly(4-vinylpyridine) has also been used to open epoxides in a similar manner.[58]

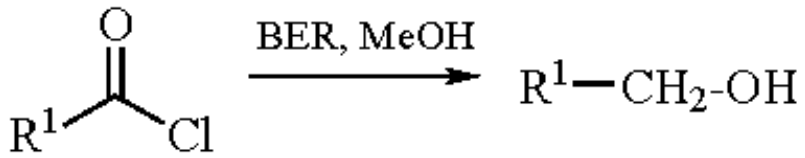

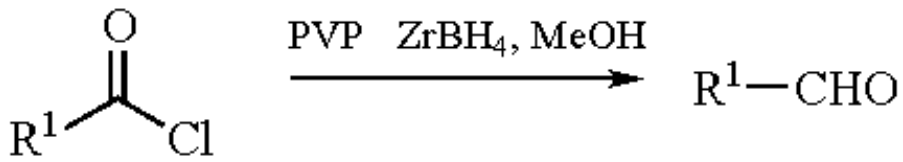

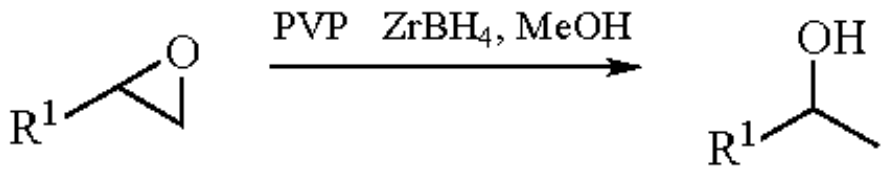

(16)

Reduction of Nitriles

Generally, nitriles are inert to BER and copper-catalyzed BER although benzonitriles can be converted to benzylamines using BER-$Ni(OAc)_2$ (eq 17).[27]

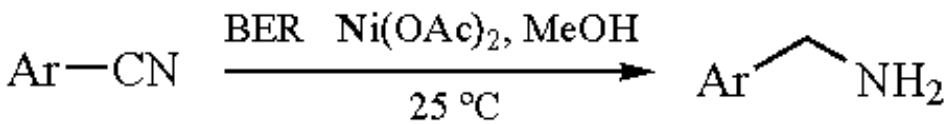

(17)

Deoxygenation of Amine *N*-Oxides

Under copper catalysis, BER quantitatively deoxygenates both tertiary amine *N*-oxides and heteroatomic *N*-oxides. For example, BER-$CuSO_4$ is able to cleanly reduce pyridine-*N*-oxide to pyridine in 99% yield in refluxing methanol (eq 18).[37,59]

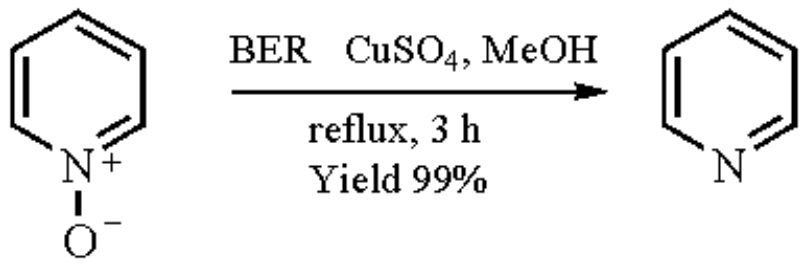

(18)

Reduction of Nitrosoamines

Nitrosoamines have been used for the introduction of alkyl groups at the α-position. BER-$CuSO_4$ has been successfully utilized in the reduction of nitroso compounds to give the corresponding secondary amines (eq 19).[60]

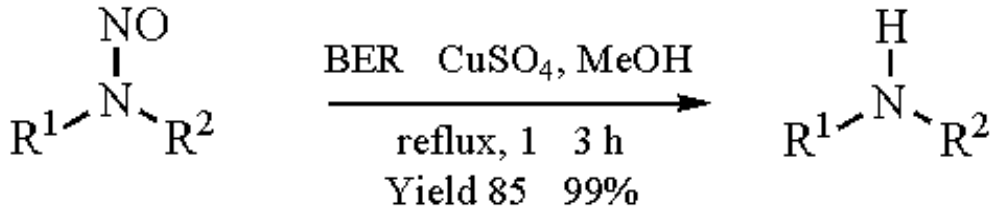

(19)

R^1, R^2= alkyl, aryl

Reduction of Mixed Anhydrides

BER-Ni$(OAc)_2$ converts mixed anhydrides of aromatic carboxylic acids to alcohols (eq 20).[61]

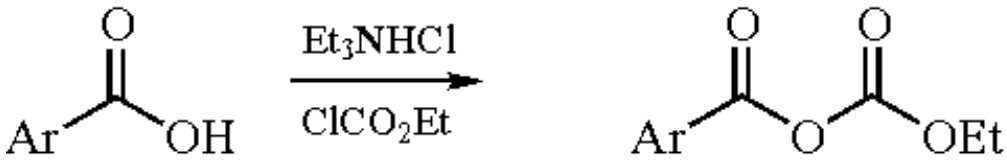

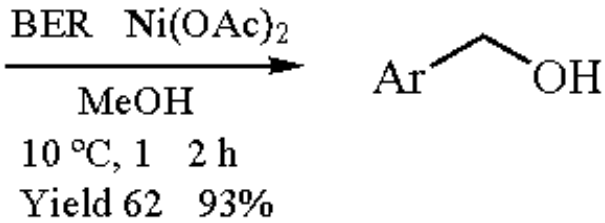

(20)

Reduction of Aryl Diazonium Fluoroborates

Borohydride exchange resin will reduce substituted aryl diazonium fluoroborates to the corresponding phenylhydrazines under mild conditions (eq 21).[62]

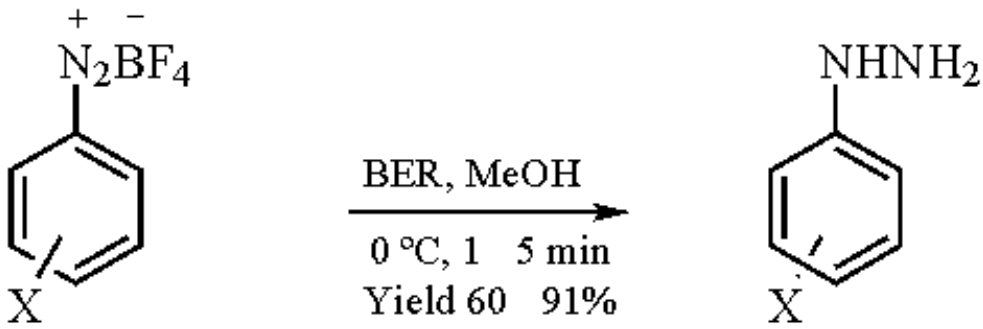

(21)

X = F, Cl, Br, NO_2

Formation of Phenyl Sulfides

Borohydride exchange resin readily reduces phenyl disulfides in methanol under neutral conditions. The resultant mixtures, on reaction with alkyl halides or epoxides, provide convenient and selective reagents for the preparation of phenyl sulfides (eq 22). Filtration of the resin leaves a solution of products which is essentially free from both sulfur- and boron-containing side products.[63]

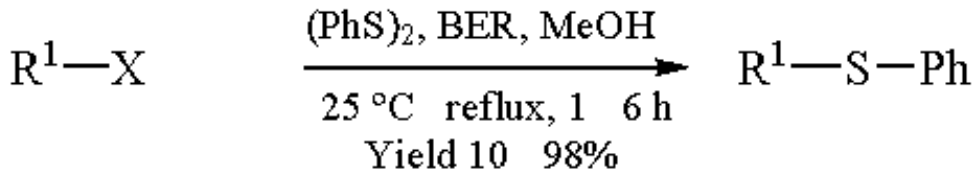

R^1= alkyl, allyl, aryl

X= Cl, Br, I, OTs

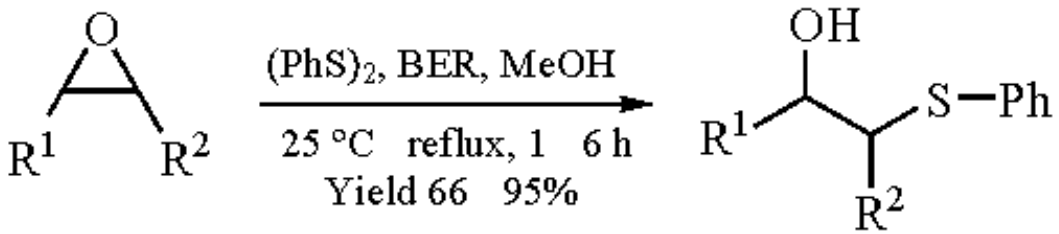

(22)

R^1= alkyl, aryl

R^2= H, alkyl

Formation of Thiols

After thioacetate formation by the reaction of a variety of halides with a polymer-supported thioacetate, a palladium-catalyzed methanolysis protocol yields thiols selectively in high yield in a one-pot reaction (eq 23).[64] This method, involving palladium deposited on BER, requires 3 equiv of BER to prevent the formation of disulfide by-products.

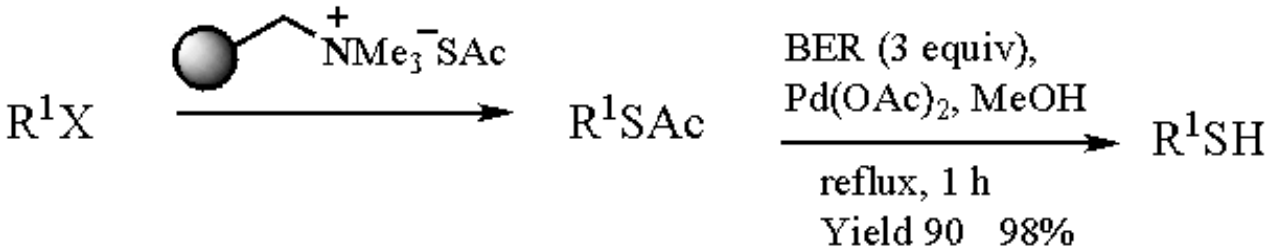

(23)

R^1= alkyl, aryl

X= Cl, Br, I, OTs

Reduction of Selenium

Selenium may be reduced by BER to give an immobilized selenide that reacts with alkyl halides or tosylates to form dialkyl selenides in high yields. No release of toxic or malodorous by-products occurs, as these are scavenged from the reaction by the polymer (eq 24).[65]

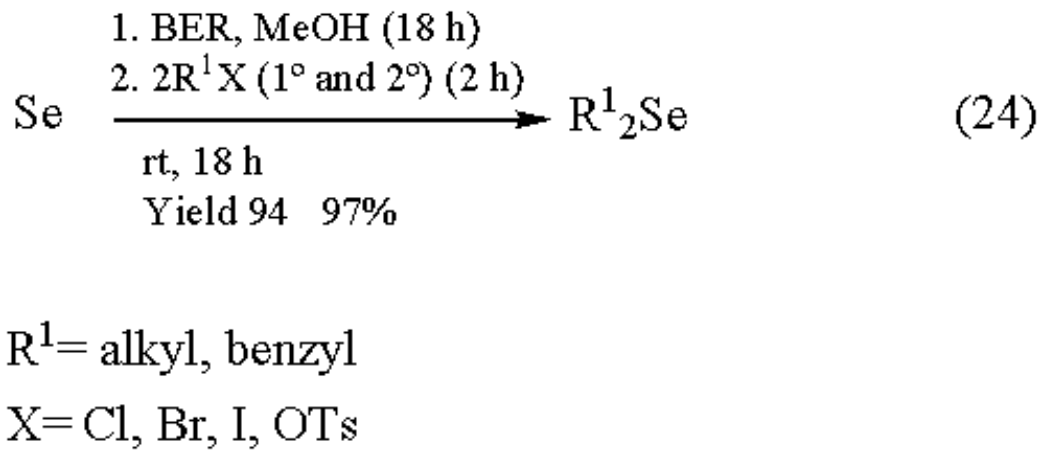

(24)

Related Reagents.

sodium borohydride, nickel boride, sodium cyanoborohydride.

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University Chemical Laboratories, Cambridge, UK

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Polymer-Supported Carbonate

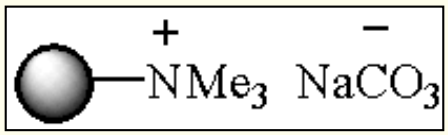

Physical Data: loading 3.5 mmol g^{-1}.

Solubility: the reagent is insoluble in all common aqueous and organic solvents.

Form Supplied in: white and brown beads, commercially available, containing 20% water. Commercial supplier: Fluka.

Purification: the polymer should be washed in dichloromethane and dried in vacuo prior to use.

Handling, Storage, and Precautions: powdered resin is harmful if inhaled or ingested. Stable at room temperature.

Polymer-supported carbonate (PS-carbonate), first described in 1981,[1] is a weakly basic reagent with several applications for organic synthesis, notably for the neutralization of acidic solutions, as a source of nucleophilic carbonate, and for mediating various functional group interconversions and deprotections.

The earliest application of carbonate resin was for the conversion of primary alkyl halides to alcohols under mild conditions in excellent yields (eq 1), although secondary halides gave some elimination products under the same conditions.[1] The order of reactivity was determined as $I^- Br^- Cl^-$.

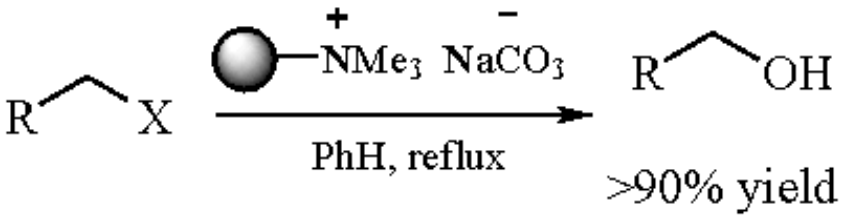

(1)

This reagent has also been applied to the formation of triols from α-iodo carbonates.[2] The reaction proceeds via an epoxide intermediate which is only hydrolysed in the presence of a proximal hydroxyl group (eq 2). This reaction elegantly overcomes the usual problematic aqueous work-up encountered due to the high solubility of the triol products in water.

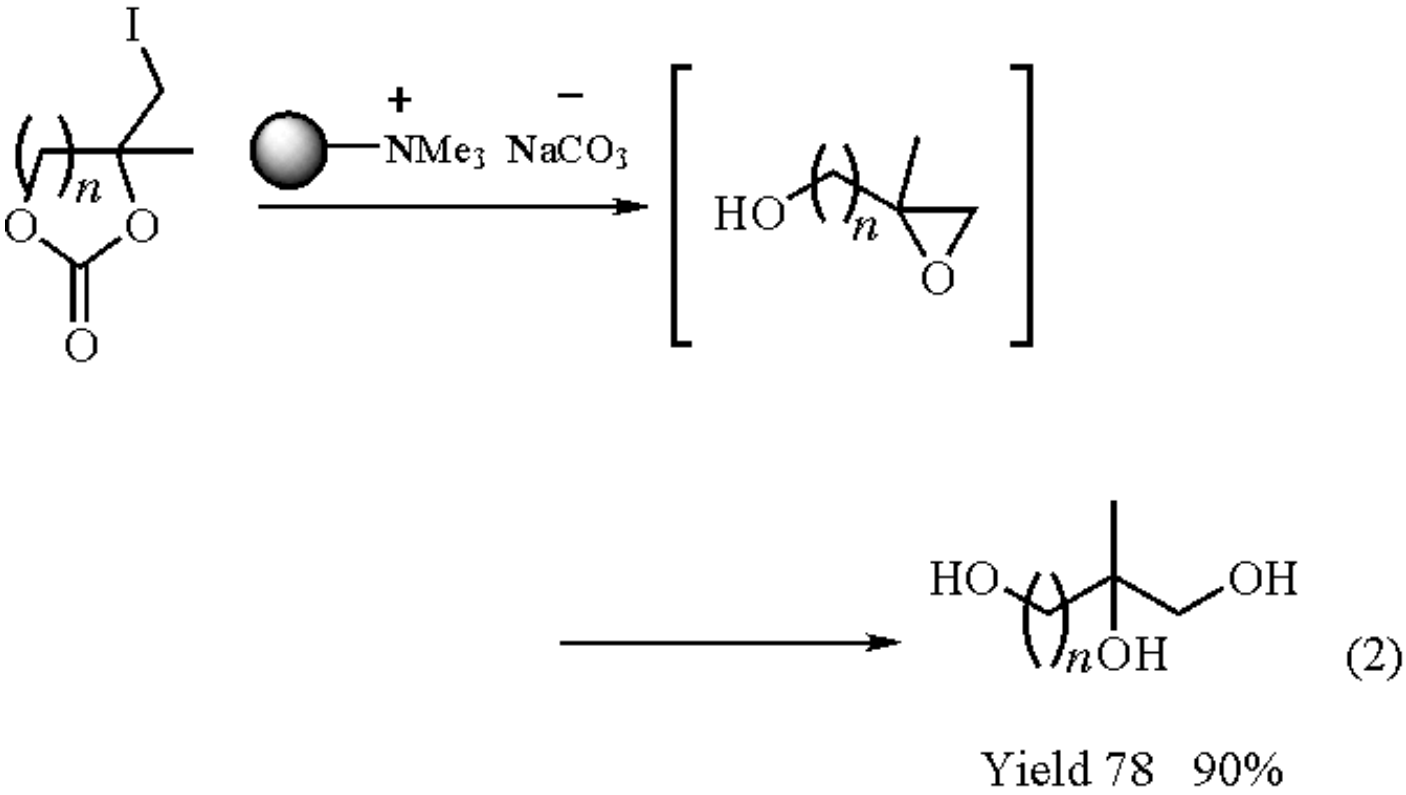

More recently, the synthesis of several heterocyclic systems has been achieved using PS-carbonate. Oxazoles were formed cleanly from α-iodotrichloroacetamides in high yield (eq 3),[3] and oxazolidin-2-ones were synthesized stereoselectively from β-iodo α-hydroxyammonium salts (eq 4).[4] The latter reaction involves insertion of carbon dioxide and proceeds via an α-epoxycarbamate intermediate.

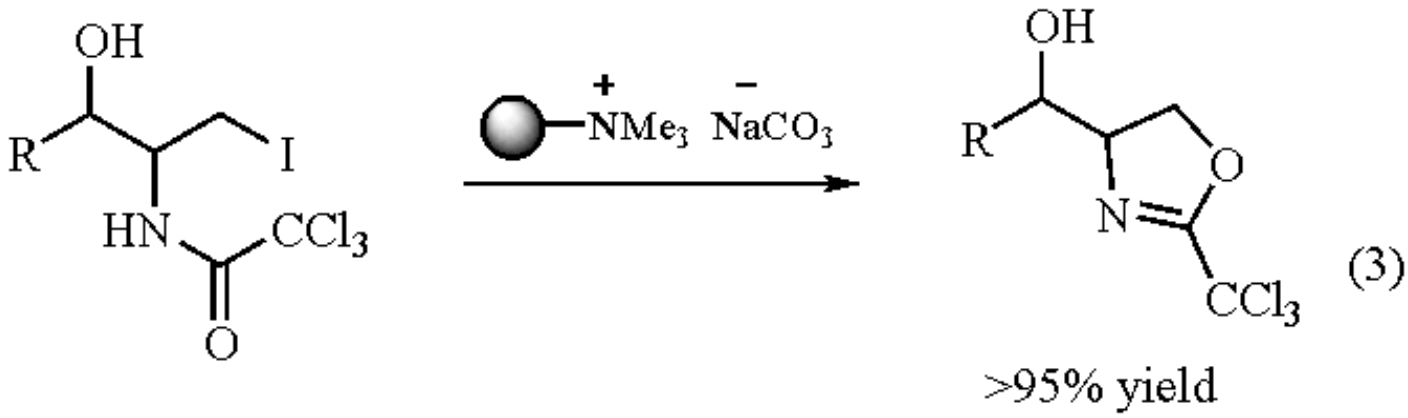

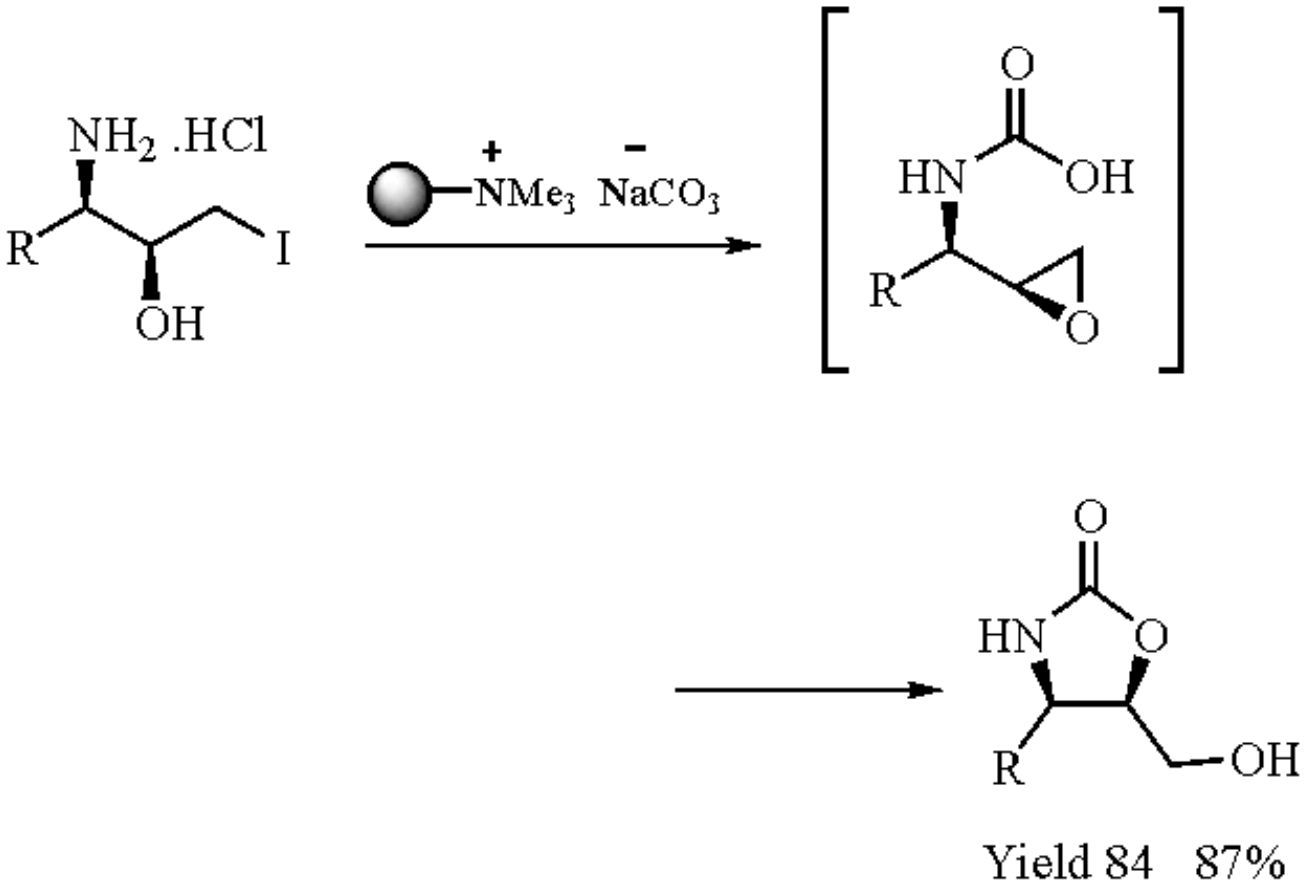

(4)

The formation of oxazolidin-2-ones has also been elegantly accomplished in one pot from enantiopure allylic amine salts using iodine adsorbed onto PS-carbonate as a supported source of both iodine for the iodolactonization and carbon dioxide for the carbamate formation (eq 5).[5] Selectivity for the *E* product increased upon benzyl protection of the ammonium salt.

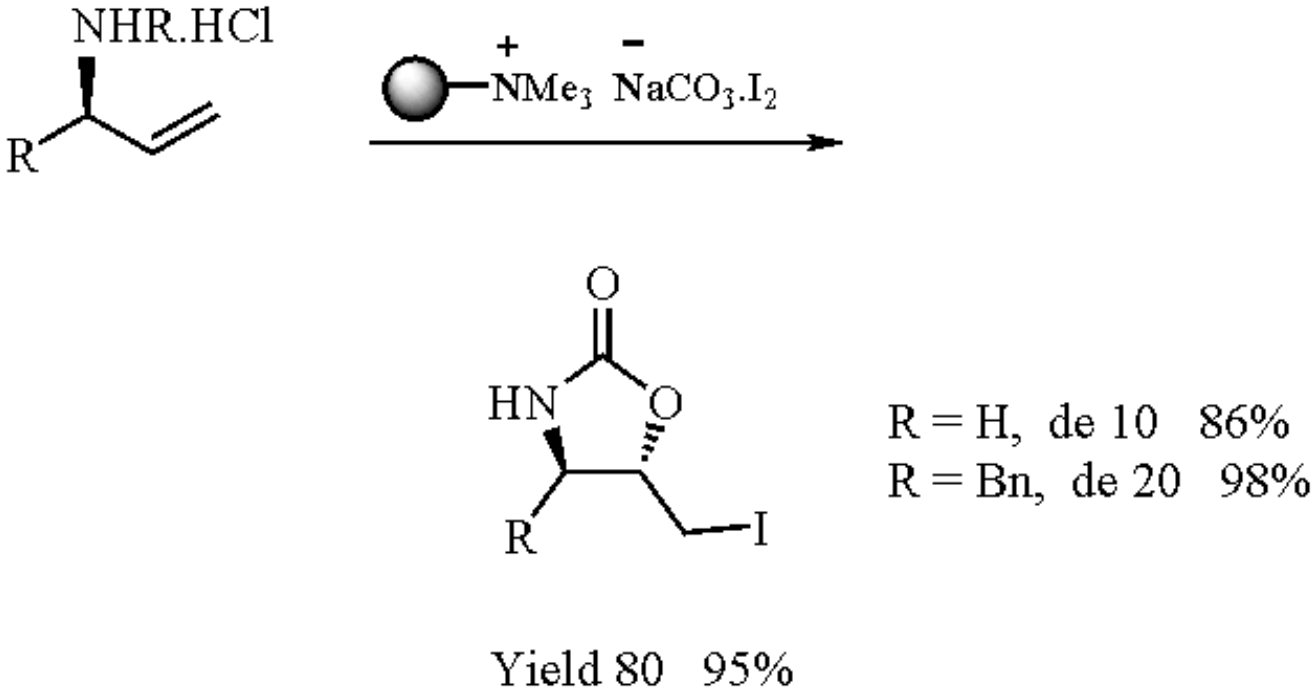

(5)

PS-carbonate has recently been used in several multi-step organic syntheses in conjunction with other polymeric reagents. Ley et al. reported the synthesis of (±)-oxomaritidine and some elaborated analogs,[6] in which carbonate resin was used in the final step to remove a trifluoroacetate protecting group and mediate an intramolecular 1,4-addition to cleanly furnish the target molecule (eq 6).

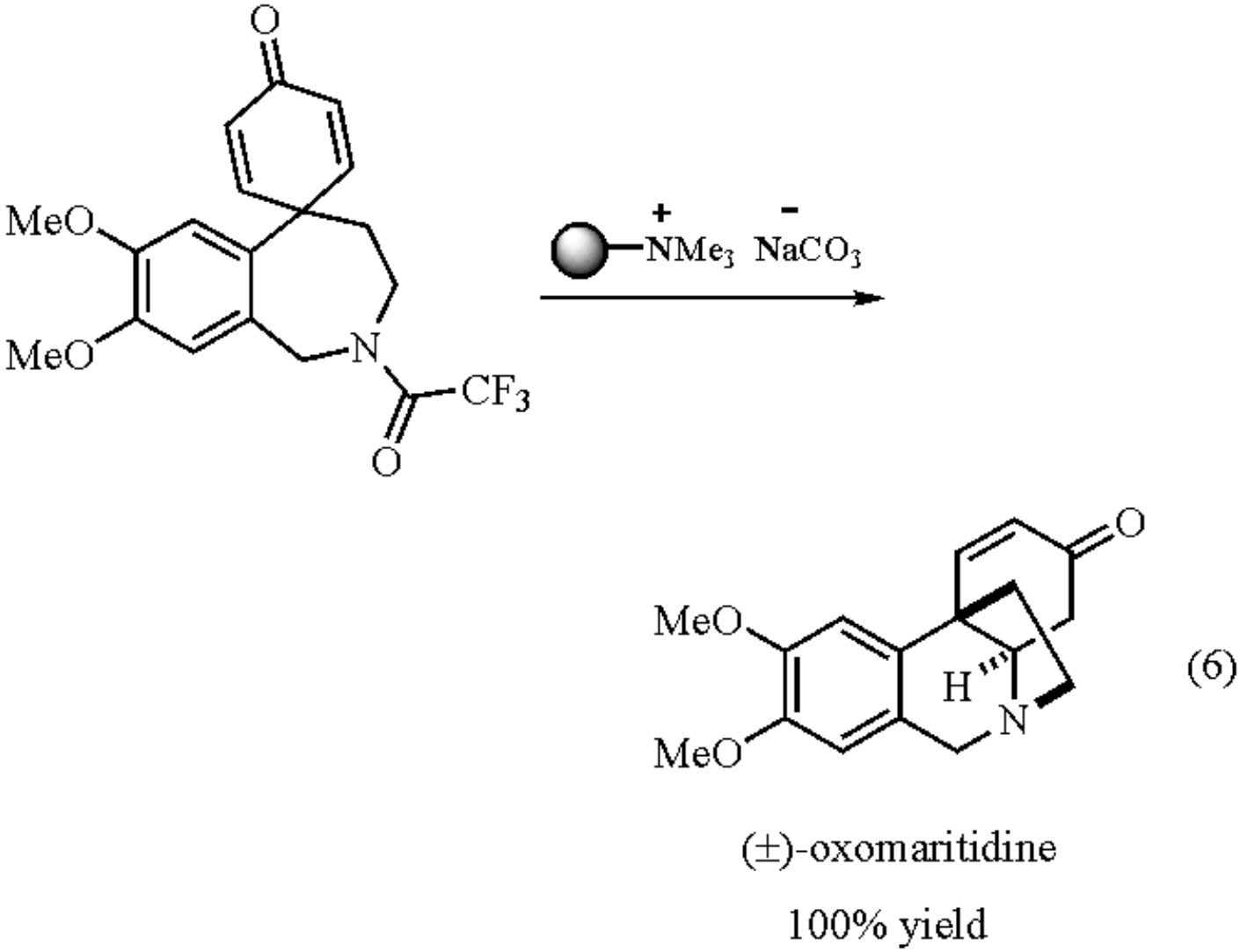

The same group has also reported the use of this reagent in the formation of a cyclic hemiacetal from α-bromoketones and catechol.[7] Aminomethylpolystyrene was added to remove any remaining α-bromoketone to give the desired product in high purity as a mixture of open and closed chain forms (eq 7).

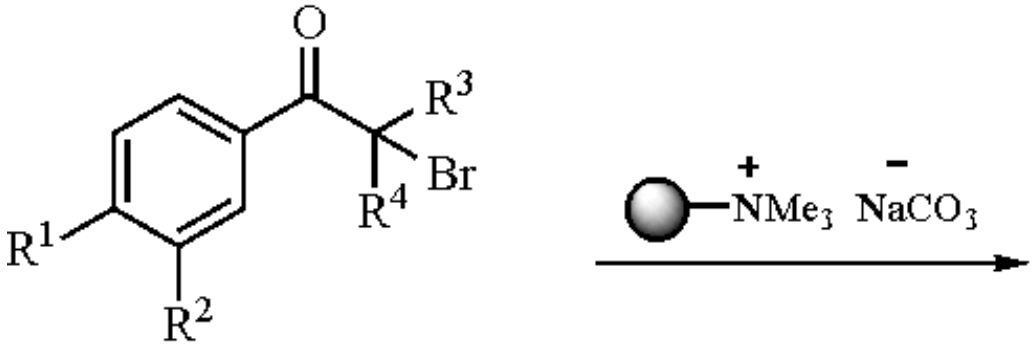

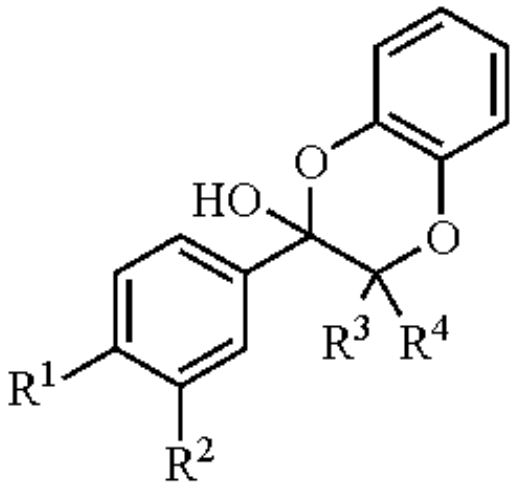

(7)

Yield 90 98%

A further application of this reagent is the neutralization of ammonium salts. Treatment of several salts with PS-carbonate in refluxing methanol yielded the free amines in clean fashion (eq 8).[3] This principle has been applied to the purification of a range of bicyclo[2.2.2]octane derivatives following an intermolecular cycloaddition step.[8] Polymer-supported thiol and diisopropylethylamine (DIPEA) were used to remove unreacted cyclohexenone and the resultant ammonium salts were neutralized with the carbonate resin to afford the desired product after simple filtration and evaporation (eq 9).

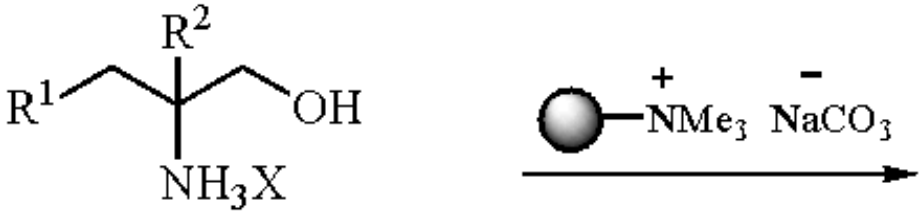

X = Cl or AcO

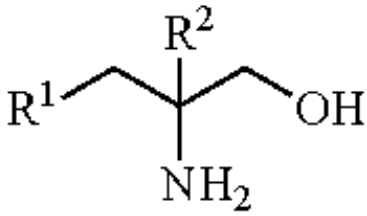

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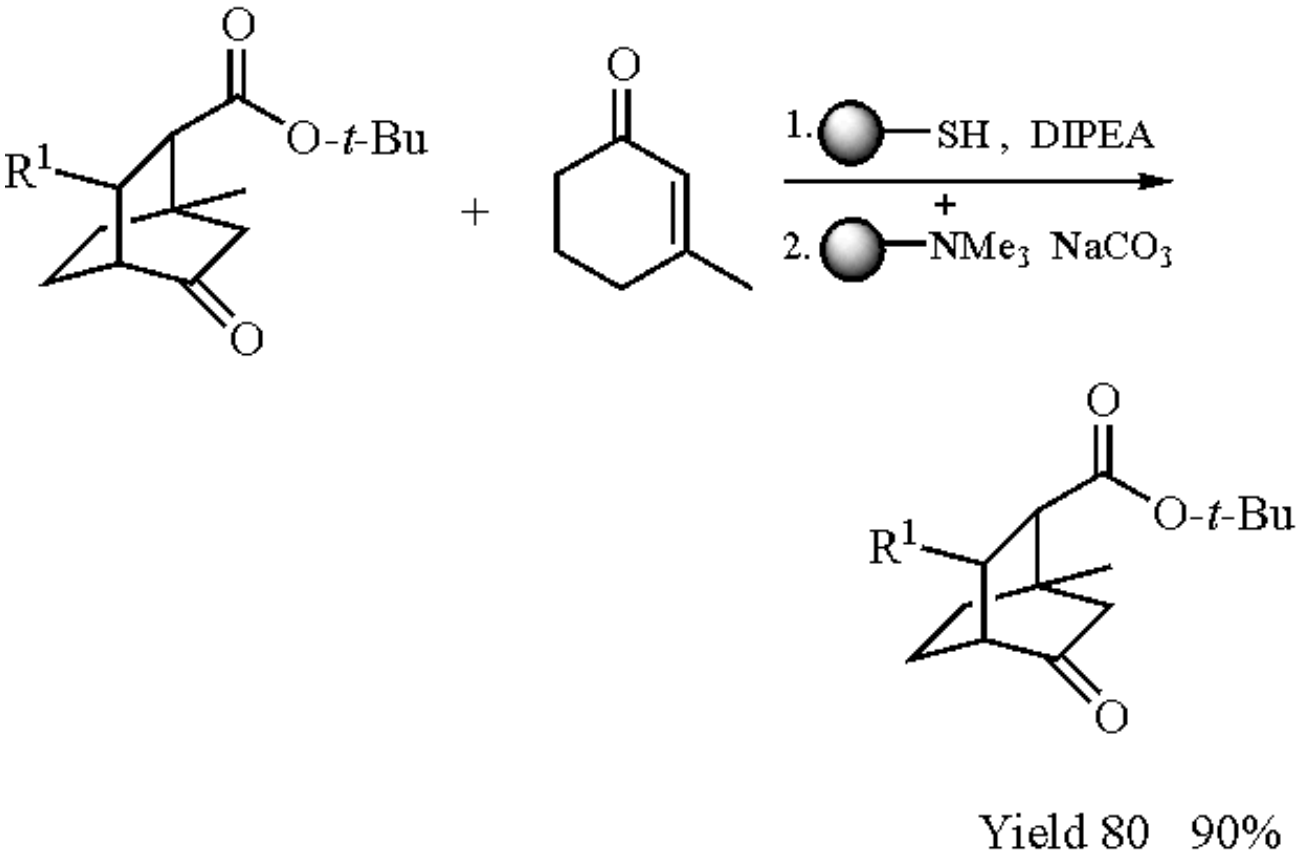

(9)

Yield 80 90%

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1. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S., *Synthesis* **1981**, 793.
2. Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S., *J. Org. Chem.* **1982**, *47*, 4626.
3. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S., *J. Chem. Soc. Chem. Commun.* **1982**, 1309.
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6. Ley, S. V.; Murray, P. J.; Schucht, O.; Thomas, A. W., *J. Chem. Soc., Perkin Trans. 1*. **1999**, 1251.
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Polymer-Supported Perruthenate

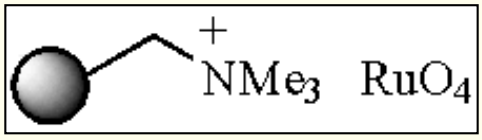

(reagent used for the oxidation of primary alcohols)

Physical Data: loading 1 mmol g^{-1} on polymer (batch dependent).

Solubility: cross-linked polystyrene divinylbenzene co-polymer is insoluble in all common aqueous and organic solvents.

Form Supplied in: black powder; commercially available.

Analysis of Reagent Purity: the loading is best determined by the degree of chemical transformation from use of a stoichiometric amount of the reagent. The loading can also be estimated by elemental analysis.

Purification: the polymer is washed successively using water, acetone and dichloromethane, and subsequently dried in vacuo.

Handling, Storage, and Precautions: harmful if inhaled or ingested. Stable at room temperature and may be stored for longer periods of time if kept refrigerated in the dark.

Polymer-supported perruthenate (PSP) is a mild and effective oxidant used mainly for the conversion of primary alcohols to aldehydes. This polymer-supported oxidant can be used either in stoichiometric amounts or as a catalyst in combination with a co-oxidant.[1] The reagent is prepared by adding Amberlyst A-26 anion exchange resin (which contains quaternary ammonium groups) to an aqueous solution of potassium perruthenate and sonicating the mixture until the solution turns clear. Alternatively, an aqueous solution of potassium perruthenate can be slowly eluted through a chromatographic column packed with Amberlyst A-26 (prewashed with water, dichloromethane, acetone, and toluene). The resulting black polymer beads are washed successively with water, acetone, and dichloromethane, and dried under vacuum at room temperature. Catalytic oxidations of primary alcohols containing a variety of functional groups can be carried out at room temperature in dichloromethane using *N*-methyl morpholine *N*-oxide as the co-oxidant in the presence of 4Å molecular sieves (eq 1).[2]

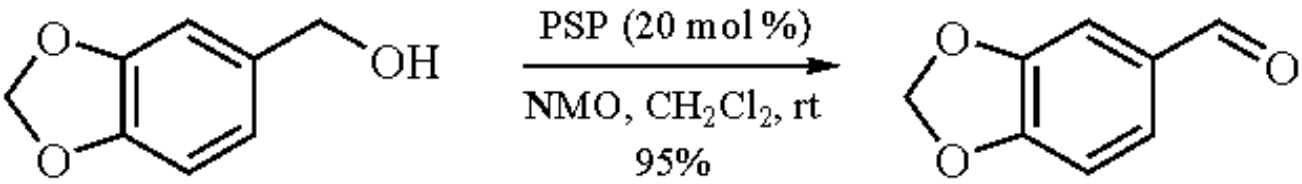

(1)

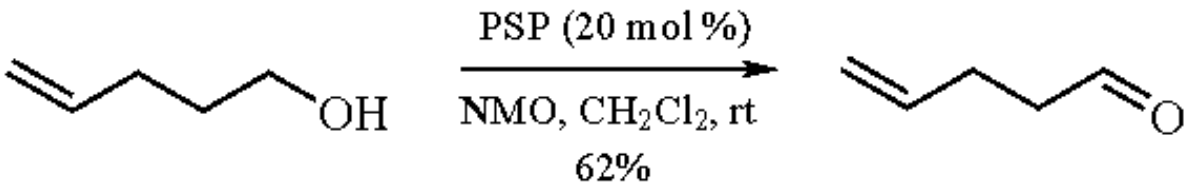

Clean oxidations can be carried out using stoichiometric amounts of PSP without the need for additives that result in product contamination. Alternatively, clean catalytic oxidations can be carried out by using molecular oxygen as the co-oxidant. These reactions are normally carried out in toluene (presaturated with oxygen) at 85°C under an atmosphere of oxygen (eq 2).[3] After the reaction is complete, PSP can be recovered by a simple filtration and the reduced reagent can be regenerated by external treatment with *N*-methyl morpholine *N*-oxide.

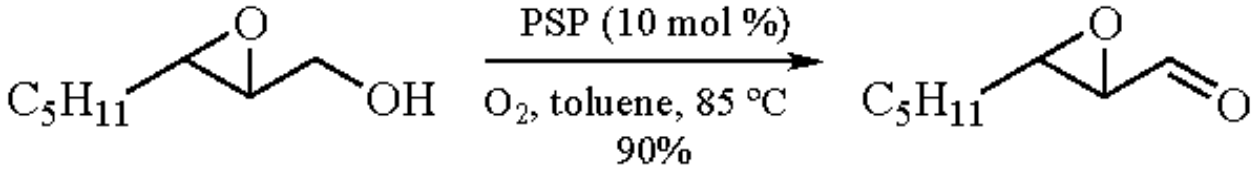

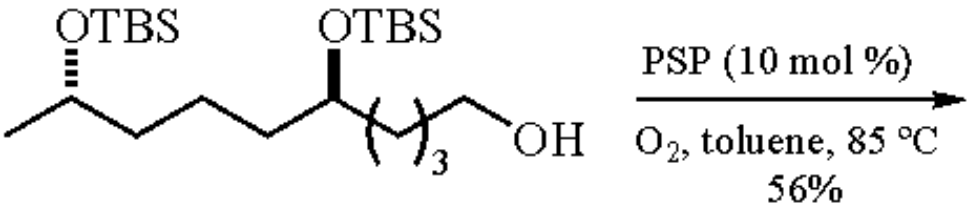

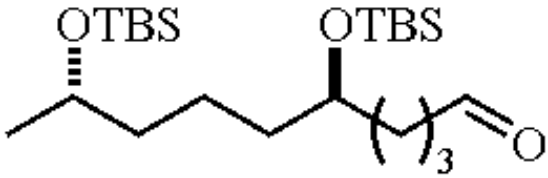

(2)

Secondary hydroxyl amines can be oxidized to the corresponding nitrones using PSP. Performing the operation in the presence of an electron-poor dipolarophile results in the formation of isoxazolidines through sequential oxidation and [2+3] cycloaddition (eq 3).[4]

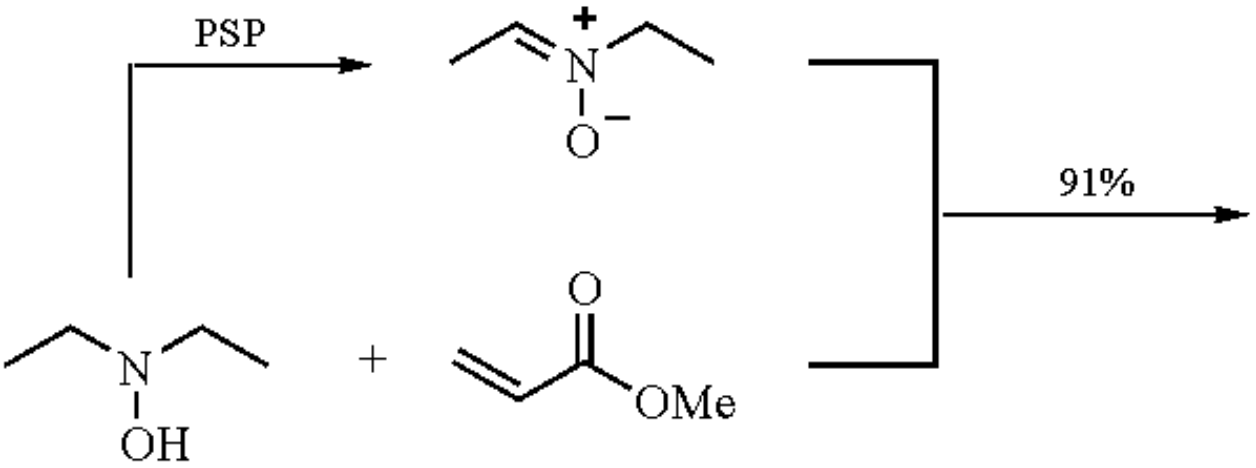

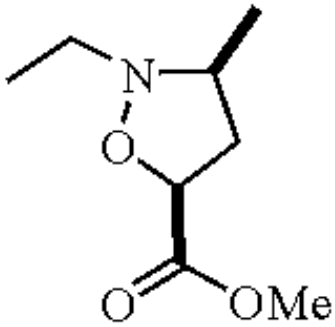

(3)

1. Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A. G.; Hall, B. J., *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239.
2. Hinzen, B.; Ley, S. V., *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907.
3. Hinzen, B.; Lenz, R.; Ley, S. V., *Synthesis* **1998**, 977.
4. Hinzen, B.; Ley, S. V., *J. Chem. Soc., Perkin Trans. 1* **1998**, 1.

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Polymer-Supported Ammonium Periodate

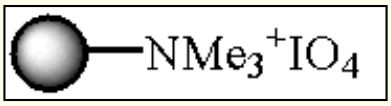

(an oxidizing reagent commonly used for the cleavage of 1,2-diols and the oxidation of sulfides to sulfoxides or sulfones)

Alternate Name: polymer-supported ammonium metaperiodate, polymer-supported quaternary ammonium periodate, polymer-supported quaternary ammonium metaperiodate.

Form Supplied in: commercially available as (polystyrylmethyl)trimethylammonium metaperiodate [polymer matrix is copoly(styrenedivinylbenzene) 20-50 mesh].

Purification: the polymer is washed with an appropriate solvent and dried in vacuo.

Handling, Storage, and Precautions: keep cool and dry, store under argon. Prolonged storage at <-18°C.

Introduction

Sodium and potassium periodates are frequently used to oxidize a variety of functional groups. However, due to the poor solubility of these salts, reactions are generally performed in protic media. In contrast, polymer-supported ammonium periodates can be used in a variety of solvents, including aprotic solvents, with the additional practical advantage that work-up is a simple filtration.

Oxidative Cleavage of 1,2-Diols

Harrison et al. demonstrated that polymer-supported ammonium periodate prepared from Amberlite IRA 904 or Amberlyst A26 cleaved 1,2-diols in high yield in a variety of solvents.[1] For the cleavage of cyclohexane-1,2-diol in dichloromethane (eq 1), it was observed that trace amounts of water accelerated the reaction, possibly by creating a favorable microenvironment in the resin.

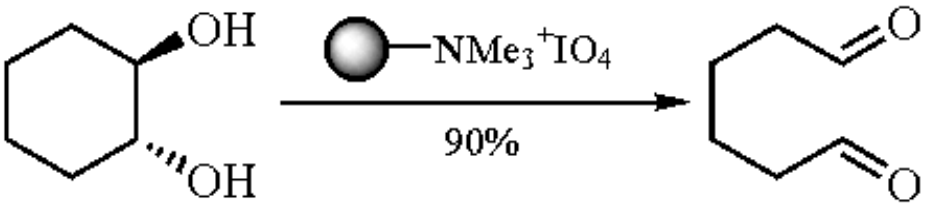

(1)

The synthesis of a series of trihydroxy nucleosides, using polymer-supported ammonium periodate prepared from Amberlyst A27 (chloride form), represents the first example of the concomitant use of two antagonistic reagents (eq 2).[3]

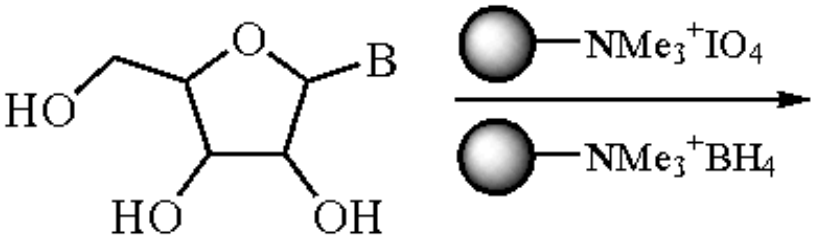

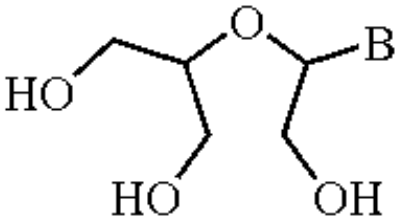

Base	Yield
Adenine	70%
Cytosine	79%
Guanine	40%
Uracil	73%

(2)

A solution of the diol was pumped through a column containing a mixture of the periodate and borohydride resins, which brought about the cleavage and in situ reduction of the unstable dialdehyde as soon as it formed.

A mixture of the polymer-supported ammonium periodate and borohydride reagents has also been used for the reduction of other diols to primary alcohols (eq 3).[3]

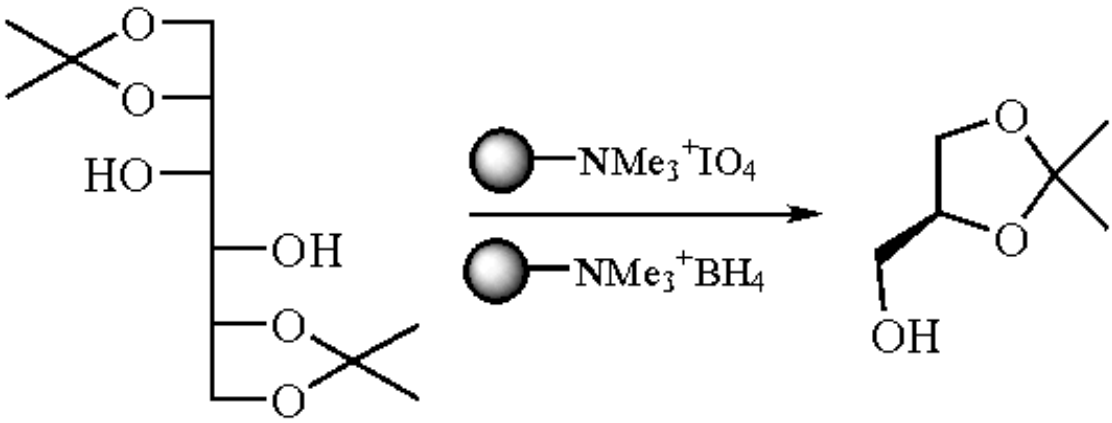

(3)

Oxidation of Alcohols to Carbonyls

The oxidation of benzylic alcohols to carbonyl compounds has been achieved with clay (K10-montmorillonite)-supported tetrabutylammonium periodate (TBAPI) (eq 4).[4] A series of primary and secondary alcohols were oxidized to the corresponding aldehydes or ketones with reasonable yields.

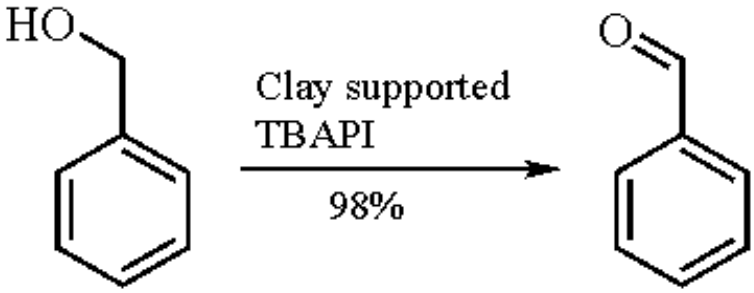

(4)

Interestingly, the addition of Lewis acid catalysts is not required, unlike solution-phase tetrabutylammonium periodate which alone is incapable of achieving these oxidations in aprotic solvents.

Oxidation of Quinols

A number of quinols (eq 5) and catechols (eq 6) have been oxidized using supported periodate, prepared from Amberlite IRA 904 (chloride

form), to give quinones in good yield.[1]

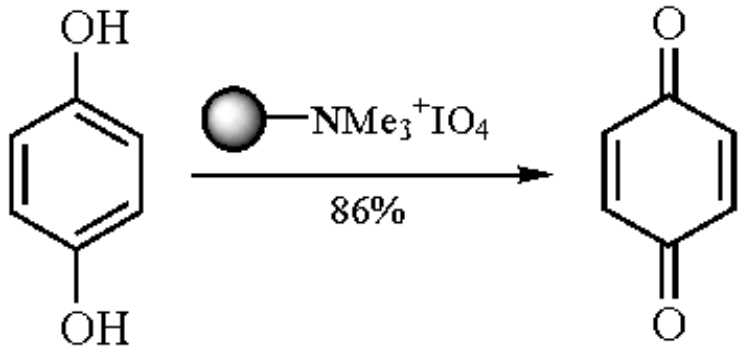

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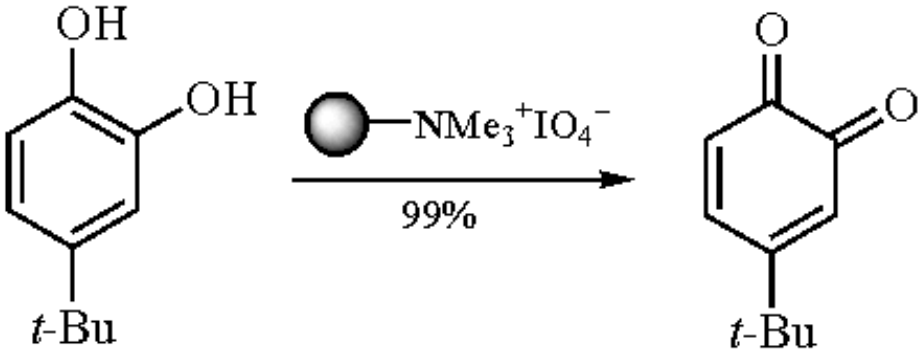

(6)

Oxidation of Sulfides to Sulfoxides

Polymer-supported ammonium periodate has been used for the oxidation of sulfides to sulfoxides, for example, the oxidation of methylpenicillin V was efficiently achieved in 89% using a periodate reagent prepared from Amberlyst A26 (eq 7).[1]

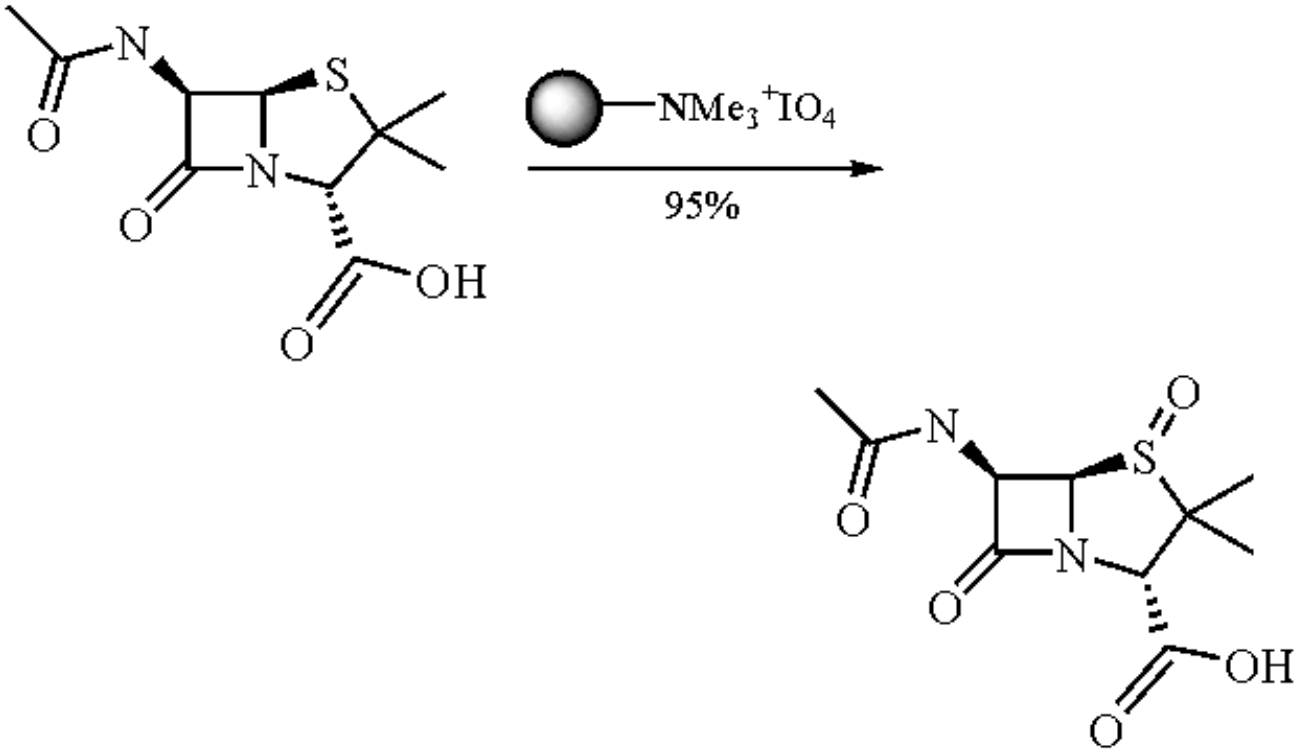

(7)

Similarly, a variety of aromatic and aliphatic sulfides were oxidized by periodate supported on strong anion exchange resin Amberlite IRA-400.[5]

Clay (K10-montmorillonite)-supported tetrabutylammonium periodate is a mild reagent for the facile oxidation of sulfides to sulfoxides in water.[4] The oxidation is faster and more efficient than its periodate or tetrabutyl ammonium periodate/aluminum trichloride solution-phase counterparts.

Miscellaneous Reactions

The versatility of the polymer-supported periodate has been demonstrated by the oxidation of α-haloketones to acids (eq 8) and the oxidative decarboxylation of arylacetic acids and α-hydroxy acids to carbonyl compounds (eq 9 and 10).[6] The reactions were performed in ethanol using the periodate form of IRA-400.

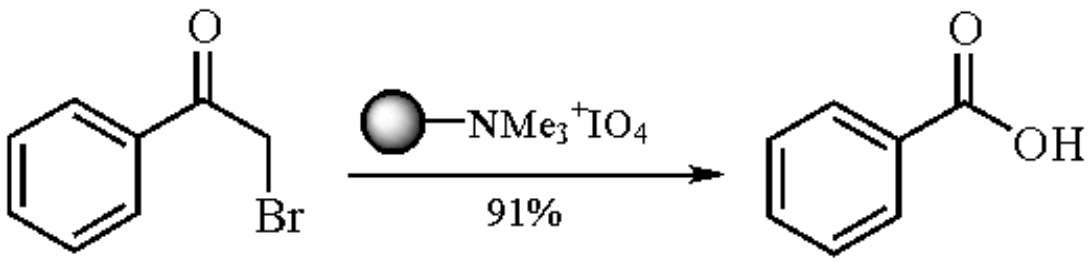

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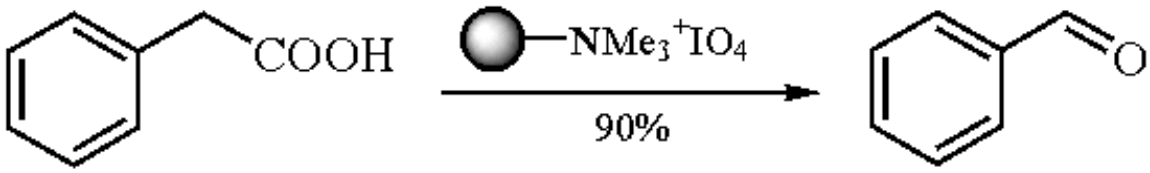

(9)

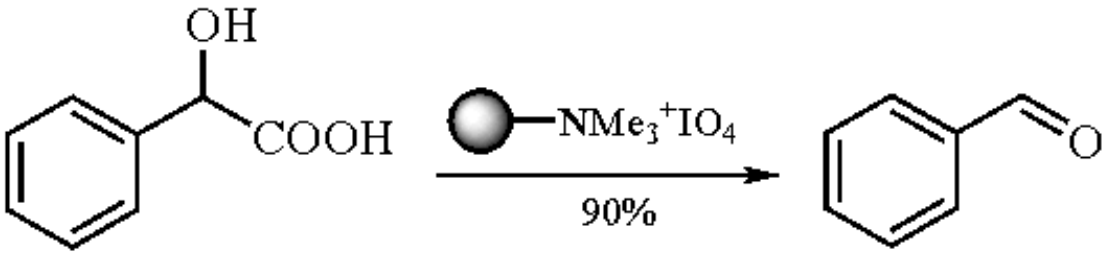

(10)

Salunkhe et al. have used a polymer-supported periodate generated from Amberlyst A26 to oxidize hydrazides to 1,2-diacyl hydrazines (eq 11).[7] It was found that the resin could be used repeatedly, as it was regenerated to its initial activity by treatment with dilute hydrochloric acid.

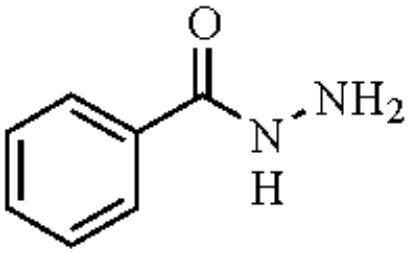

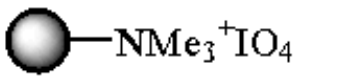

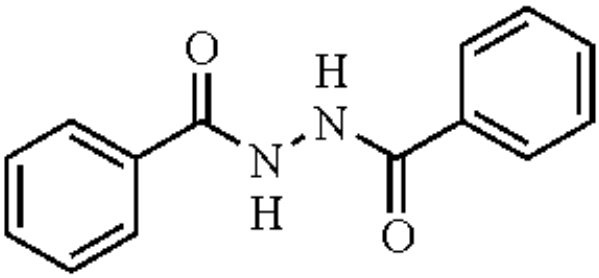

(11)

In addition, triphenylphosphine, hydrazobenzene, and benzohydroxamic acid are oxidized to triphenyl phosphine oxide, azobenzene, and nitrosocarbonylbenzene, respectively, using a supported ammonium periodate prepared from Amberlyst A26.[1]

Related Reagents.

tetrabutylammonium periodate has been immobilized on montmorillonite clay; sodium periodate has also been immobilized on a variety of mineral supports, such as alumina, clay, and silica.[8]

1. Harrison, C. R.; Hodge, P., *J. Chem. Soc., Perkin Trans 1* **1982**, 509.
2. Bessodes, M.; Antnakis, K., *Tetrahedron Lett.* **1985**, *26*, 1305.
3. Hebert, N.; Beck, A.; Lennox, R. B.; Just, G., *J. Org. Chem.* **1992**, *57*, 1777.
4. Venkatachalapathy, C.; Rajarajan, M.; Banu, H. S.; Pitchumani, K. *Tetrahedron* **1999**, *55*, 4071.
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8. (a) Lui, K. T.; Tong, Y. C., *J. Org. Chem.* **1978**, *43*, 2717. (b) Gupta, D. N.; Hodge, P.; Davies, J. E., *J. Chem. Soc., Perkin Trans. 1* **1981**, 2970. (c) Zhong, Y. L.; Shing, T. K. M., *J. Org. Chem.* **1997**, *62*, 2622. (d) Varma, R. S.; Saini, R. K.; Meshram, H. M., *Tetrahedron Lett*. **1997**, *38*, 6525. (e) Varma, R. S.; Dahiya, R.; Saini, R. K., *Tetrahedron Lett*. **1997**, *38*, 8819. (f) Painter, G. F.; Falshaw, A., *J. Chem. Soc., Perkin Trans. 1*. **2000**, 1157.

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Polymer-Supported Thiophenol

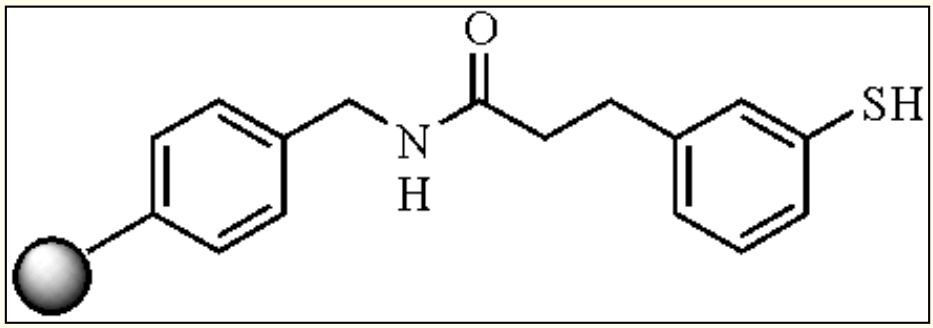

Physical Data: loading 1.0-1.5 mmol g^{-1} (based on benzyl bromide uptake).

Solubility: 1% cross-linked polystyrene backbone is insoluble in all common aqueous and organic solvents.

Form Supplied in: yellow powder; bead size 75-150 µm, 100-200 mesh (95% within). Commercially available; retailer: Argonaut Technologies.[1]

Purification: the polymer is washed in dichloromethane and dried in vacuo.

Handling, Storage, and Precautions: harmful if inhaled or ingested. Stable at room temperature.

Applications

Polymer-supported thiophenol (PS-thiophenol) has two principal applications in synthetic chemistry; it functions either as a scavenging agent or as a traceless solid-phase linker.[2] This functionalized polymer is commonly used as a phase transfer scavenger for a wide range of electrophiles including alkyl halides. It is easy to remove by filtration, thus enabling the preparation of products of high purity without the need for additional purification or isolation procedures. As with all scavenging procedures, 2 or 3 equiv of resin should be used to ensure complete removal of the surplus electrophile. The scavenging ability or nucleophilicity of PS-thiophenol has been found experimentally to be superior to the corresponding benzyl thiol attached to a polystyrene backbone.[1] Optimal scavenging results require either the formation of the potassium thiolate salt (formed using potassium trimethylsilylonate) (eq 1)[1] or the addition of diisopropylethylamine and mesoporous carbonate (eq 2).[1]

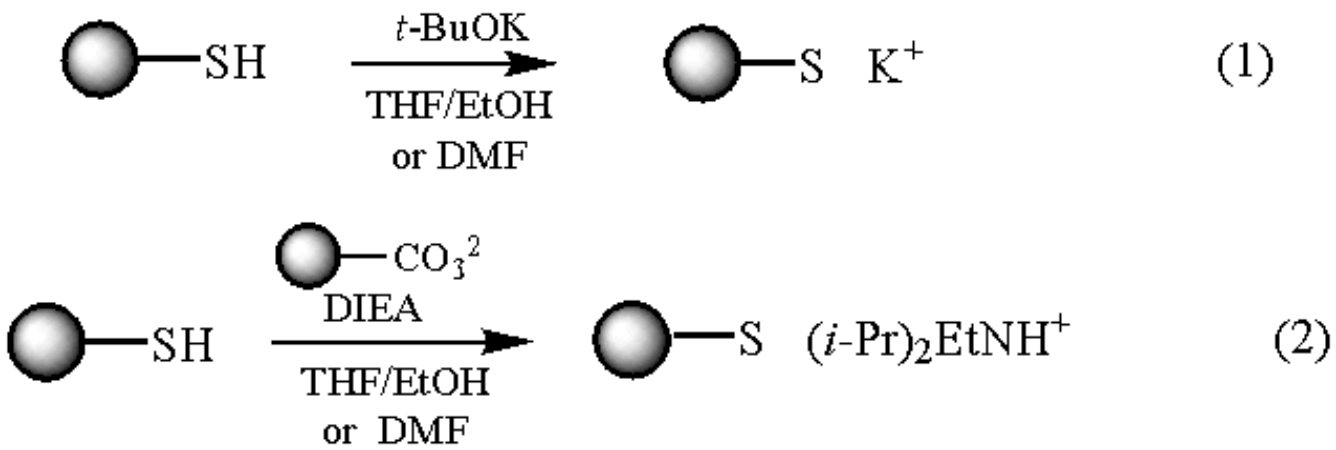

PS-thiophenol has been utilized in combinatorial library synthesis as an effective and clean method to remove excess electrophilic substrate[3] or alkylating reagent (eq 3).[4]

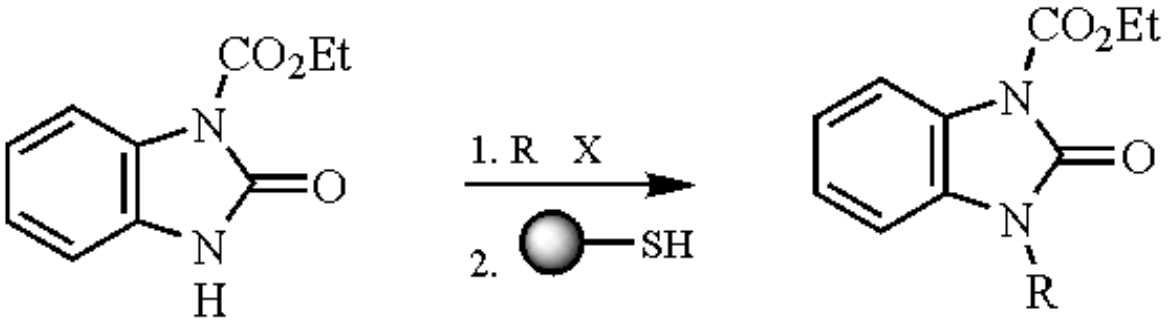

(3)

Another useful application of the resin involves amine deprotection reactions. PS-thiophenol/base can be used to remove the Fmoc protecting group and simultaneously capture the contaminating component (eq 4).[5]

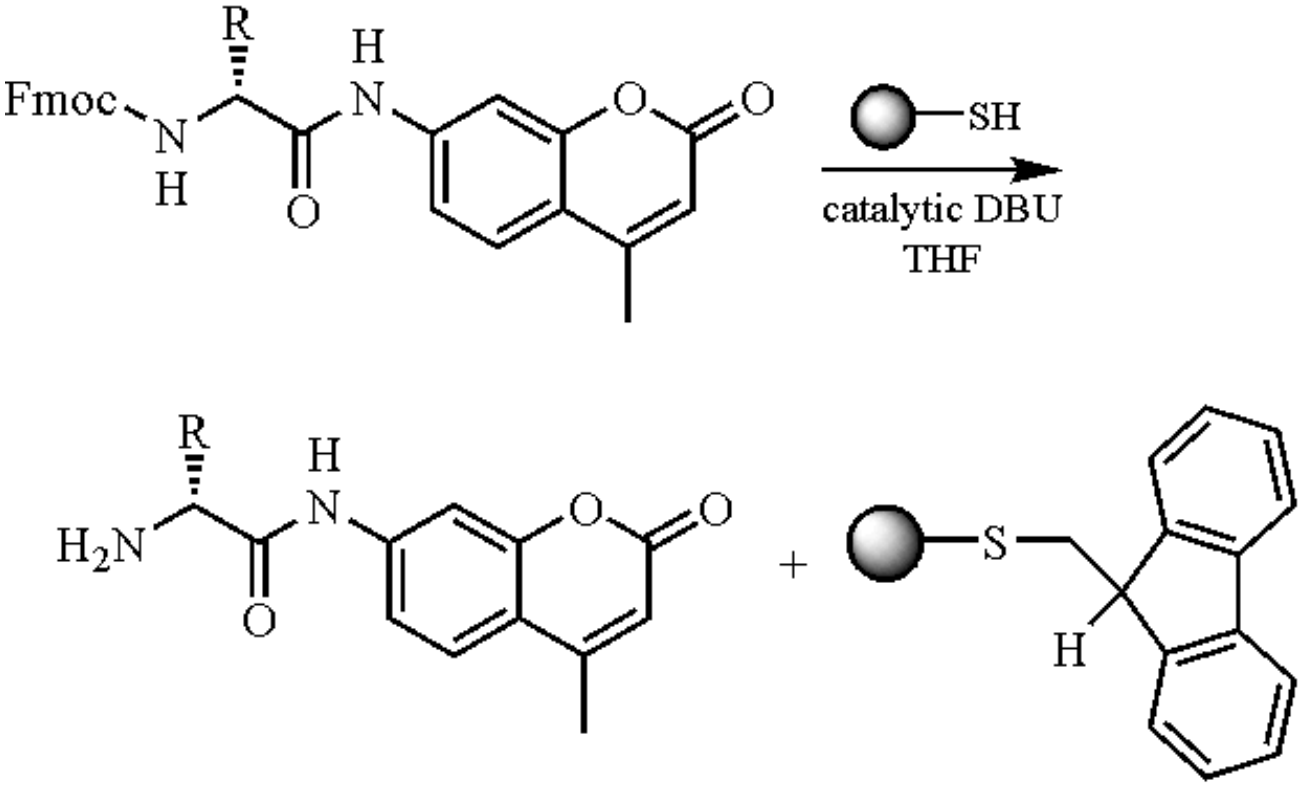

(4)

The reagent can also be used to attach suitable substrates, i.e. molecules susceptible to nucleophilic attack, onto the solid phase and thus facilitate a trivial purification procedure (eq 5).[6]

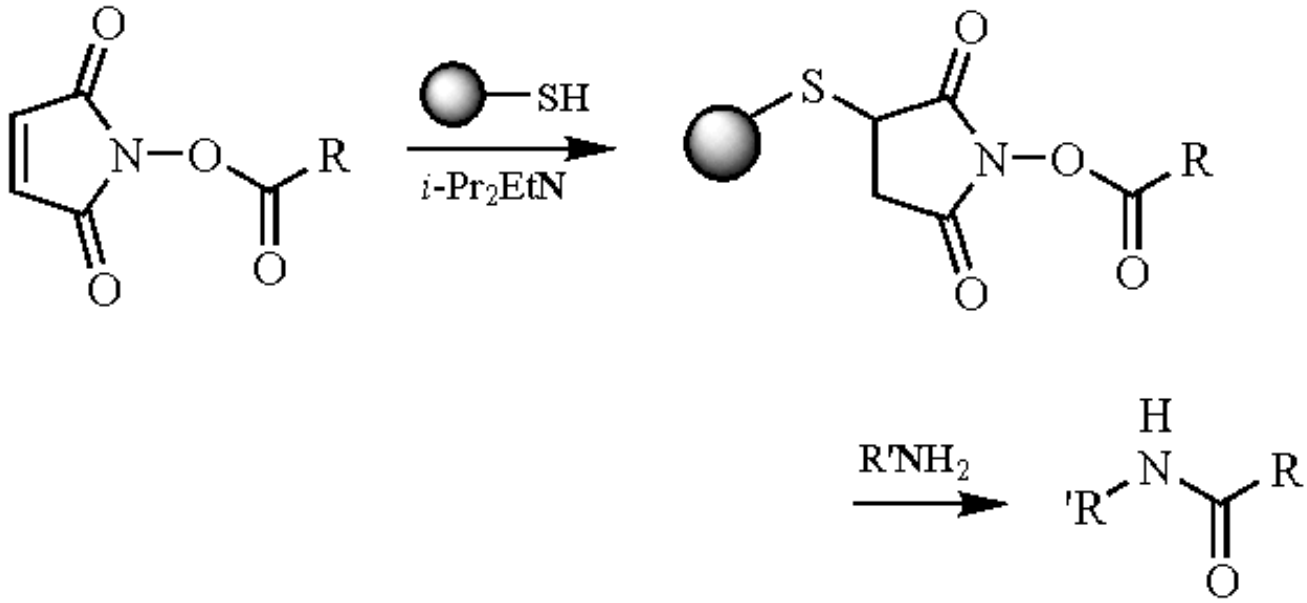

(5)

While attached to the resin, the isolated moiety can undergo further chemical manipulation with the PS-thiophenol acting as a linker moiety.[7] Cleavage is achieved by the addition of an amine (primary or secondary), causing nucleophilic displacement from the resin, which

also results in additional modification of the molecule (eq 6). The functionalized polymer acts as a traceless linker without the need for oxidation to the sulfone or sulfoxide.

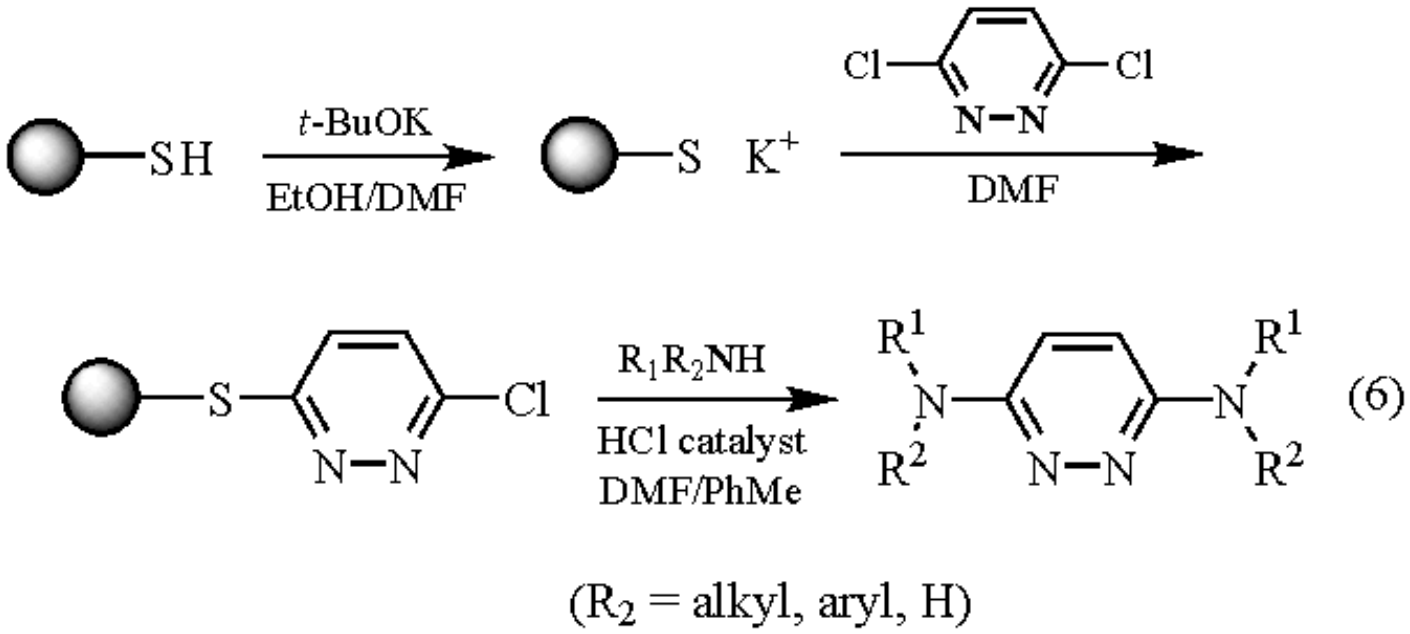

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(1*R*,5*R*)-2*H*-1,5-Benzodithiepin-3(4*H*)-one 1,5-Dioxide

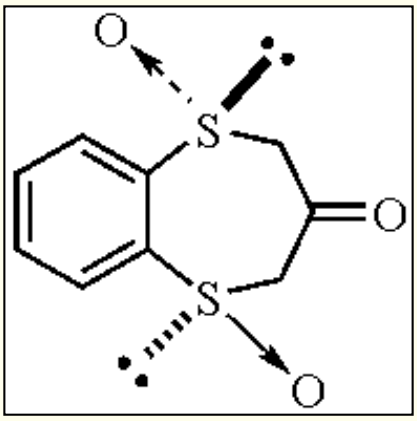

[183595-53-1] · $C_9H_8O_3S_2$ · (228.29)

(chiral auxiliary for asymmetric desymmetrization of cyclic *meso*-1,2-diols)

Alternate Name: 2*H*-1,5-benzodithiepin-3(4*H*)-one, 1,5-dioxide, (1*R*-*trans*)-; (1*R*,5*R*)-1,5-benzodithiepan-3-one 1,5-dioxide.

Physical Data: colorless prisms, mp 195.0-196.0°C (decomposes) (from hexane/EtOAc), $[\alpha]_D^{25}$-100.3 (*c* 0.29, $CHCl_3$).

Solubility: soluble in MeOH, acetone, EtOAc, THF, CH_2Cl_2, and $CHCl_3$.

Form Supplied in: colorless powder; not commercially available.

Analysis of Reagent Purity: ^1H and ^{13}C NMR; elemental analysis.

Preparative Methods: the title reagent can be prepared from commercially available (1,2-benzenedithiol[1] and 1,3-dichloroacetone. After condensation of these reagents in the presence of DMAP, the resulting 1,5-benzodithepan-3-one is enantioselectively oxidized to the (*R*)-monosulfoxide by modified Sharpless oxidation [cumene hydroperoxide, Ti(O-*i*-Pr)$_4$] in the presence of (+)-diethyl tartrate as a chiral ligand.[2,3] Subsequent dry ozonation[4] of the (*R*)-monosulfoxide affords (1*R*,5*R*)-bis-sulfoxide **1**, having >98% optical purity. Alternative use of (-)-diethyl tartrate in the modified Sharpless oxidation makes possible convenient access to enantiomeric (1*S*,5*S*)-**1**.[5,6]

Purification: purification is performed by column chromatography. Since unpurified (1*R*,5*R*)-bis-sulfoxide **1** is only slightly soluble in the eluent, the following procedure is convenient. The crude material is dissolved in EtOAc and mixed with silica gel (ca. 5 g silica gel per 1 g of crude reagent). After solvent evaporation, the silica gel residue containing **1** is added to the top of the column and eluted with hexane-EtOAc (2:1).

Handling, Storage, and Precautions: the reagent can be stored for at least 1 month at room temperature without loss of its chemical and optical purities.

Introduction

(1*R*,5*R*)-2*H*-1,5-Benzodithiepin-3(4*H*)-one 1,5-dioxide (C_2-symmetric bis-sulfoxide **1**) has been used as a chiral auxiliary for asymmetric desymmetrization of cyclic *meso*-1,2-diols via diastereoselective acetal cleavage reaction. The procedure consists of three steps (eq 1), that is, acetalization (step 1), acetal cleavage reaction followed by benzylation (step 2), and hydrolysis of the vinyl ether (step 3). Due to the C_2-symmetry of **1**, the chiral auxiliary gives only one product in step 1. In addition, no regio- or geometric isomers of the enol ether are formed in step 2. This reagent can be recovered by acid-promoted hydrolysis and reused.

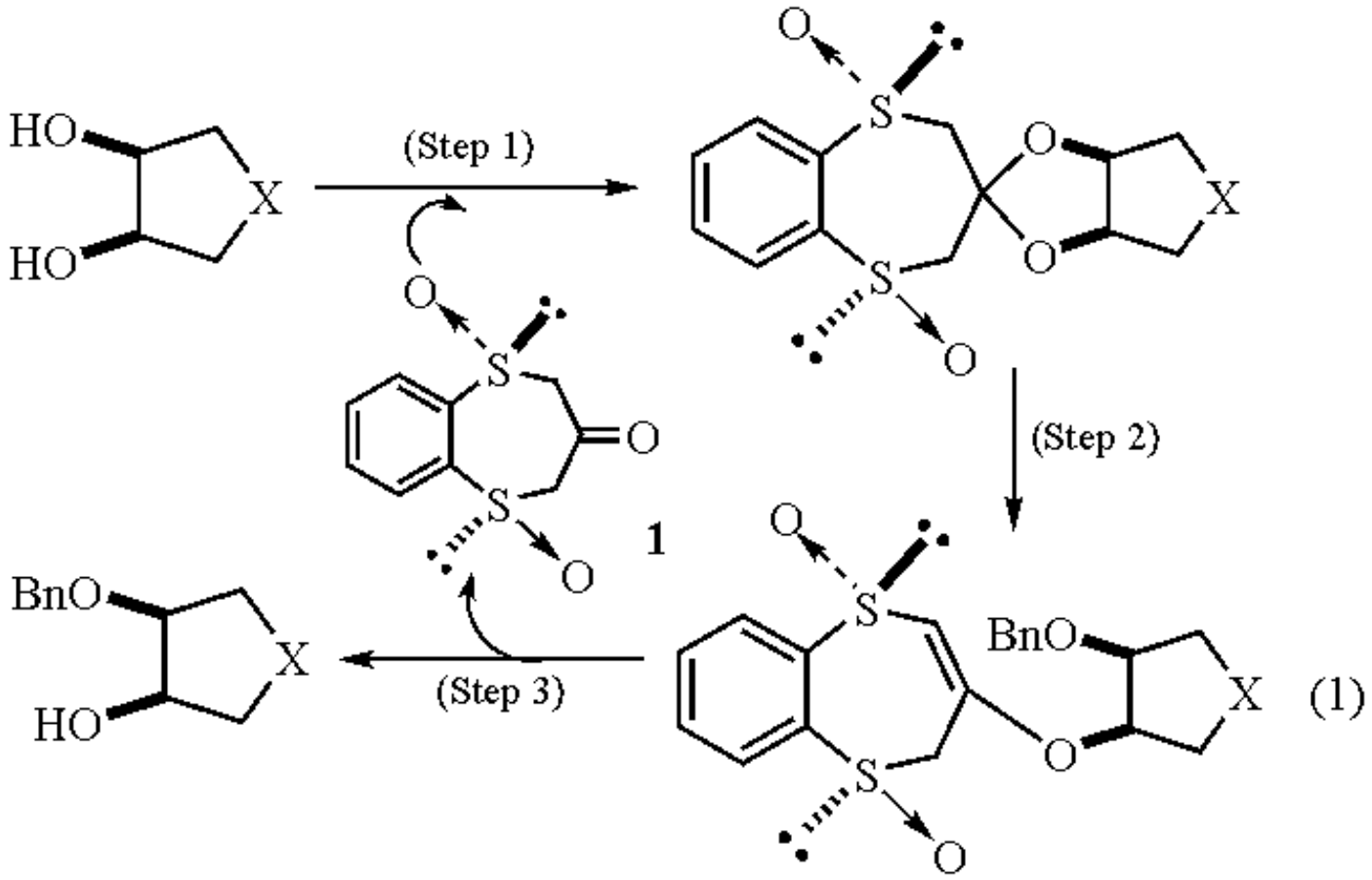

Acetal Formation Involving C_2-Symmetric bis-Sulfoxide and *meso*-1,2-Diols (Step 1)

Acetalization of *meso*-1,2-diols with this reagent should be conducted with TMSOTf and 2,6-lutidine in dichloromethane below 4°C.[7] Higher temperatures and prolonged reaction times cause undesirable racemization and decomposition of the reagent. When the reactivity of *meso*-1,2-diols with the chiral auxiliary is low, acetalization using the mono-TMS ether of *meso*-diols and TMSOTf is recommended.[8]

Diastereoselective Acetal Fission Followed by Benzylation (Step 2)

Upon treatment with KHMDS and 18-crown-6 in THF at -78°C, the acetal from the (*R*,*R*)-bis-sulfoxide is rapidly converted into the alkoxide having the (1*S*,2*R*) configuration. The counter cation of the base is very important for high selectivity. Diastereoselectivity was seen to increase in the order LiHMDS (8% de) <NaHMDS (90% de) <KHMDS (>96% de).

Hydrolysis of the Vinyl Ether and Reagent Recovery (Step 3)

The resulting vinyl ether can be hydrolyzed with 10% HCl in acetone at room temperature. The chiral auxiliary is recovered without loss of optical purity and is reusable.

Desymmetrization of Functionalized *meso*-1,2-diols

Using this methodology, various cyclic *meso*-1,2-diols can be desymmetrized with very high (>96% ee) and predictable selectivity. The enantiomers are obtained through use of an appropriate chiral auxiliary. Bis-sulfoxide **1** has been applied to the desymmetrization of a poly-oxygenated *meso*-diol containing five stereogenic centers (eq 2).

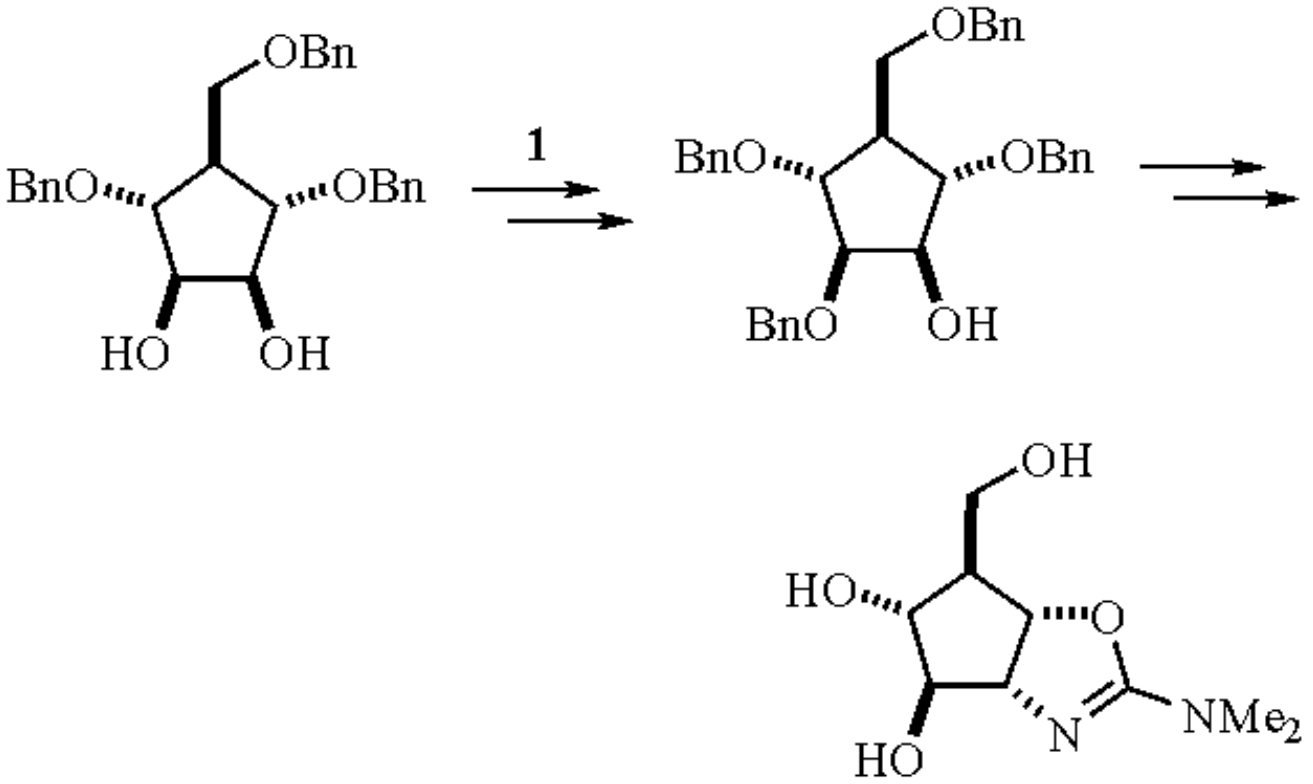

(2)

Allosamizoline

However, the same chiral auxiliary is not suited to the desymmetrization of acyclic *meso*-diols since the acetalization step is sluggish. Nonetheless, an acyclic *meso*-diol such as erythritol can be desymmetrized by prior protection of the terminal primary hydroxyl groups as an *o*-xylyl ether (eq 3).

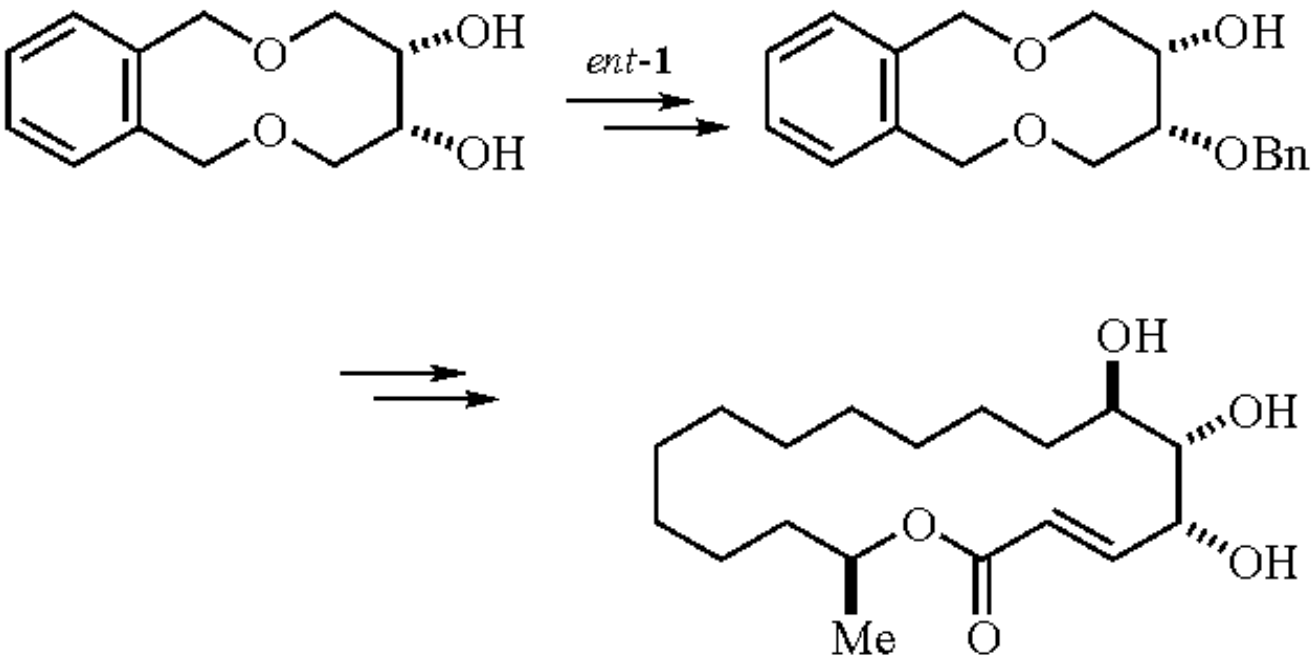

(3)

Aspicilin

Desymmetrization by means of this methodology was successfully applied to a synthesis of key intermediates for mosin B,[9] aspicilin,[10] *gala*-quercitol,[11] and allosamizoline.[8]

Related Reagents.

(1*S*,5*S*)-2*H*-1,5-benzodithiepin-3(4*H*)-one 1,5-dioxide.

---

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(*R*,*R*)-1,2-Diamino-1,2-di-*tert*-butylethane

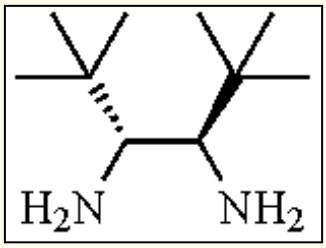

[171357-23-6] · $C_{10}H_{24}N_2$ · (172.31)

(vicinal diamine as a source of chirality; precursor for the synthesis of bidentate ligands)

Physical Data: bp 240°C; $[\alpha]_D^{25}$-15 (*c* 0.145, CH_2Cl_2).

Solubility: most organic solvents.

Form Supplied in: colorless liquid; not commercially available.

Purification: shake with powdered K_2CO_3 in diethyl ether, filter, concentrate, and distill under reduced pressure.

Analysis of Reagent Purity: ^{1}H and ^{13}C NMR.

Handling, Storage, and Precautions: store under argon or nitrogen atmosphere; may be corrosive, like other vicinal diamines.

Preparative Methods: although syntheses of enantiomerically pure diamines have been developed mainly through resolution of racemic diamines, few methods have been reported for the diastereoselective synthesis of vicinal diamines. In particular, the addition of Grignard or zinc reagents to the carbon-nitrogen double bonds of chiral 1,2-bisimines[1] derived from glyoxal and (*S*)- or (*R*)-phenethylamine, followed by removal of the phenethyl group, has been shown to be an attractive alternative method. Following a similar procedure, 1,2-diamino-1,2-di-*tert*-butylethane **3** can be synthesized in an optically pure form in three steps, as the *R*,*R*- or *S*,*S*-enantiomer, starting, respectively, from glyoxal and (*S*)- or (*R*)-phenethylamine.[2] Indeed, addition of the chiral (*S*,*S*)-1,2-bis-imine **1** to a suspension of *tert*-butylmagnesium chloride in hexane at 50°C leads cleanly and in good yield to a single diastereomer of the (*R*,*R*)-diamine (**2**) (eq 1).

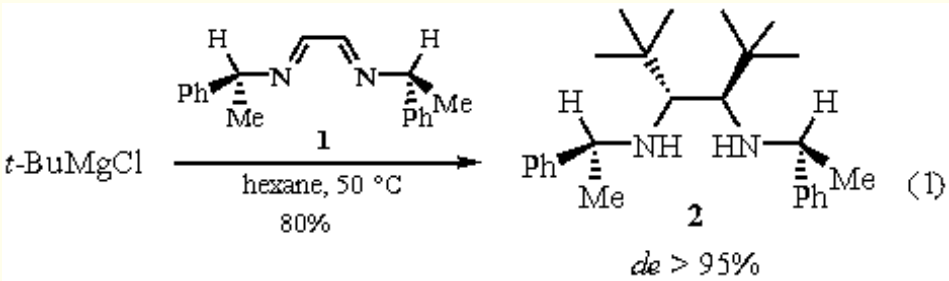

Deprotection of the chiral auxiliary groups is performed using ammonium formate, acetic acid, and palladium hydroxide in refluxing ethanol (eq 2). This sequence gives, after purification by distillation, the free optically pure (*R*,*R*)-diamine **3**.[3]

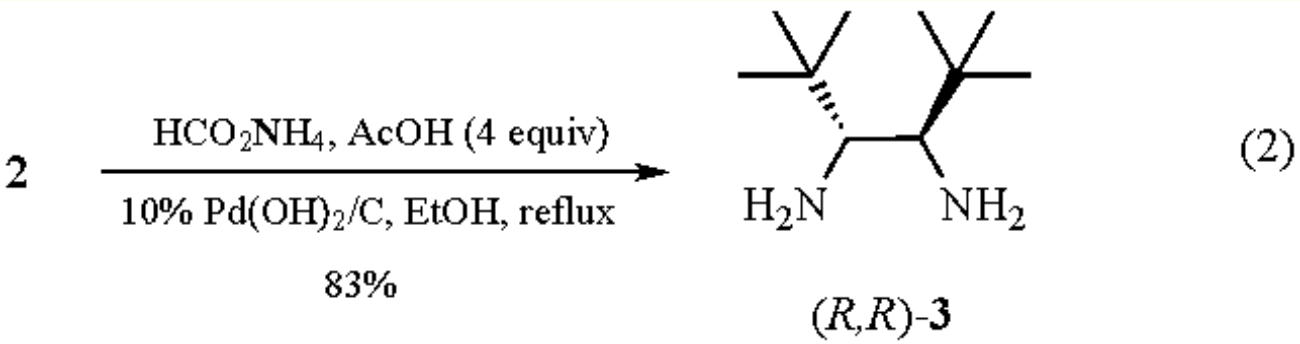

The *N*,*N*´-dimethyl derivative **4** is obtained in three steps by formation of the corresponding imidazolidine with acetone, alkylation with iodomethane, and hydrolysis (eq 3).

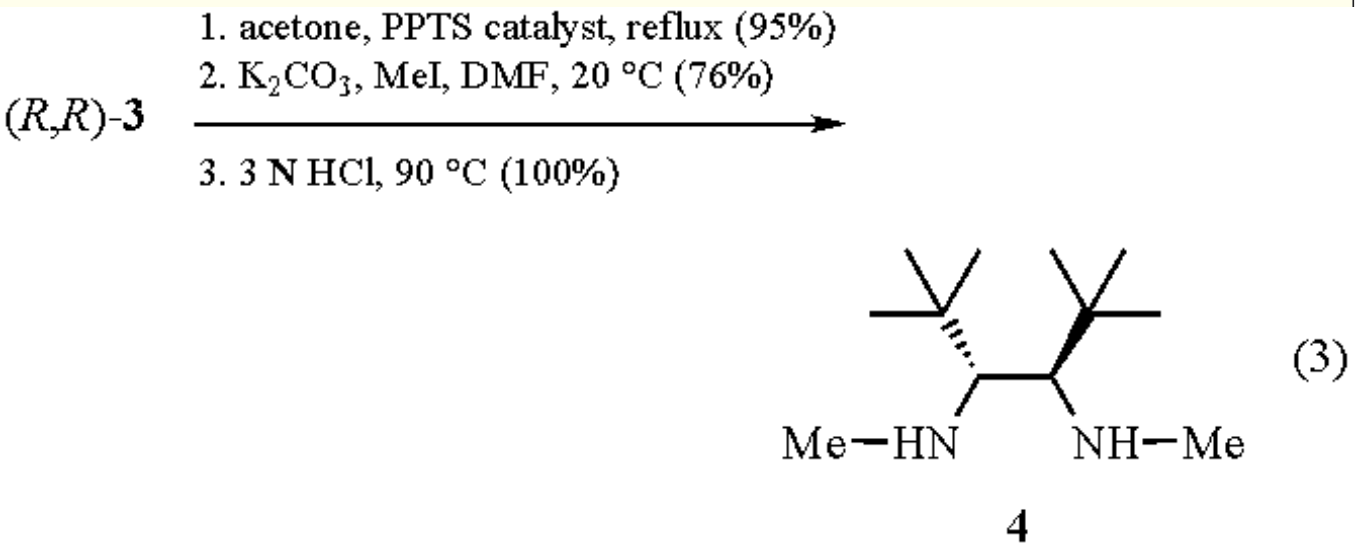

The *N*-tosyl derivative **5**, a possible precursor for the synthesis of ruthenium hydrogen transfer catalysts of type **6**,[4] is obtained in good yield by slow addition of TsCl in dichloromethane at 0°C (eq 4).

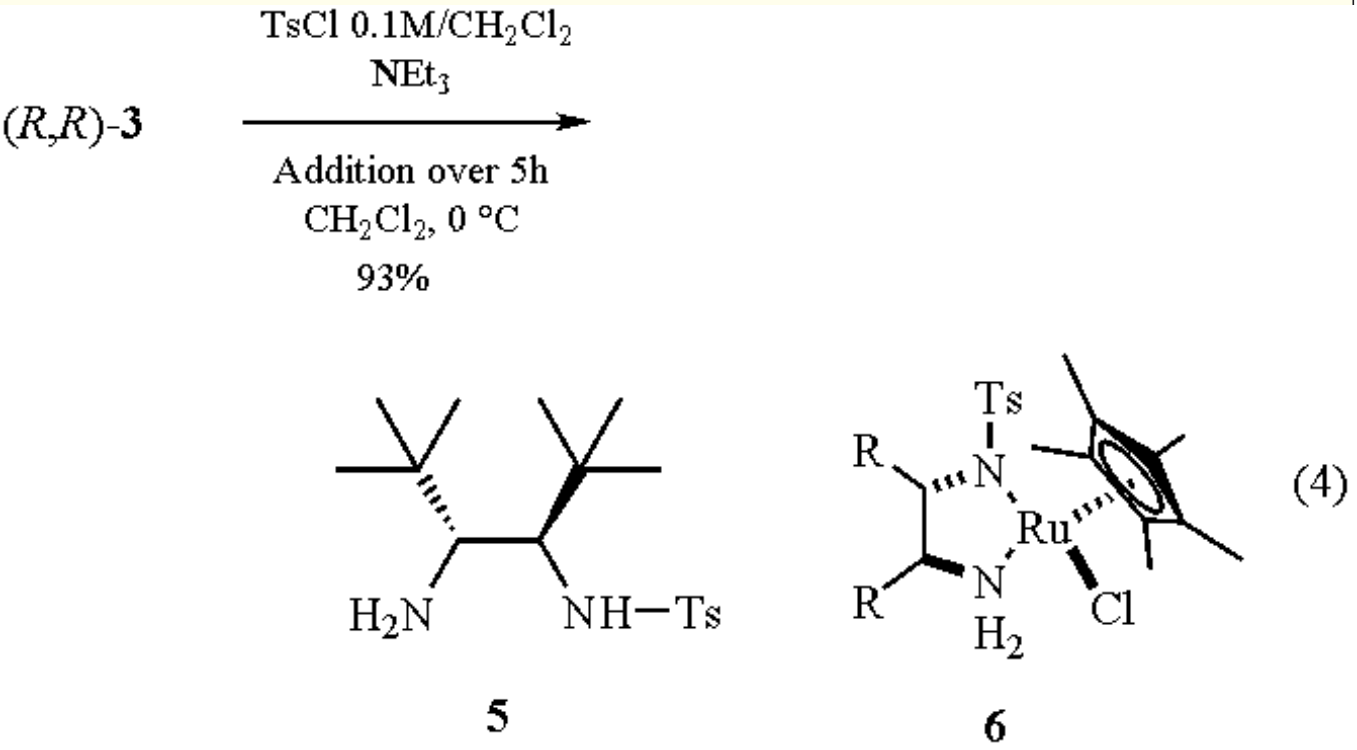

Utility

Many asymmetric syntheses have been developed using vicinal diamines as the source of chirality. The major interest lies in their use as precursors for the synthesis of a broad family of bidentate ligands.[5] Many reactions have also been described using the *N*-alkyl derivatives of these diamines as chiral auxiliaries and protecting groups of aldehydes.[6] Most of these applications generally use the framework of 1,2-diphenyl-1,2-diaminoethane (**7**) or 1,2-diaminocyclohexane (**8**), whose preparations have been fully described.[7]

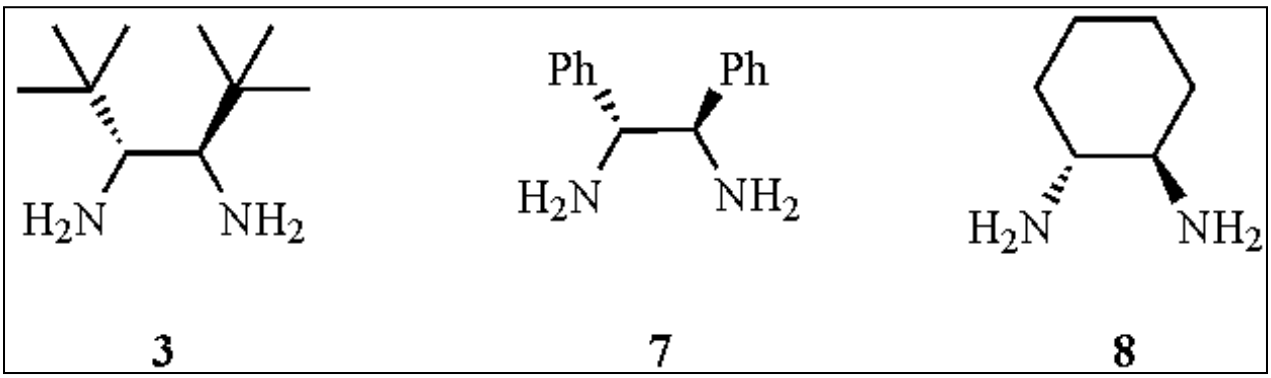

However, 1,2-diamino-1,2-di-*tert*-butylethane (**3**) holds particular interest because of its increased steric bulk and the absence of benzylic protons. Its recent ready availability should render it as attractive as the frequently used vicinal diamines **7** and **8**. To our knowledge, only one application of this diamine has been previously described in the literature (eq 5),[3b] where the regio- and enantioselective epoxidation of conjugated aliphatic dienes were studied using the chiral manganese salen complex (**9**).

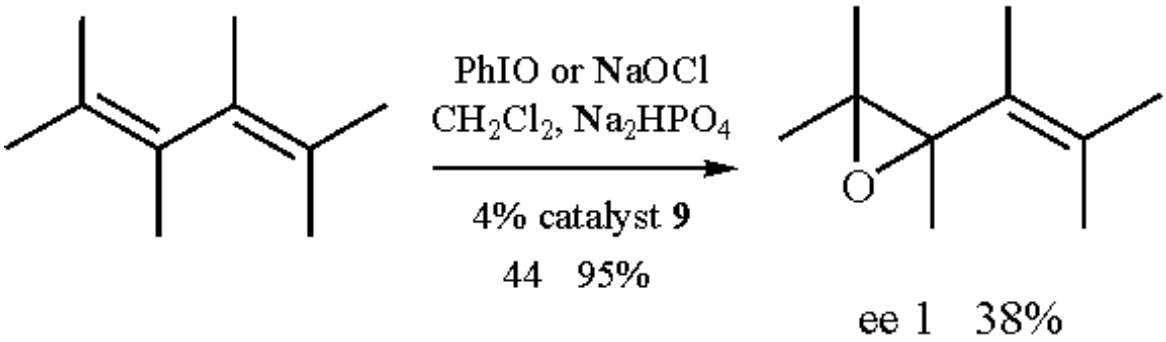

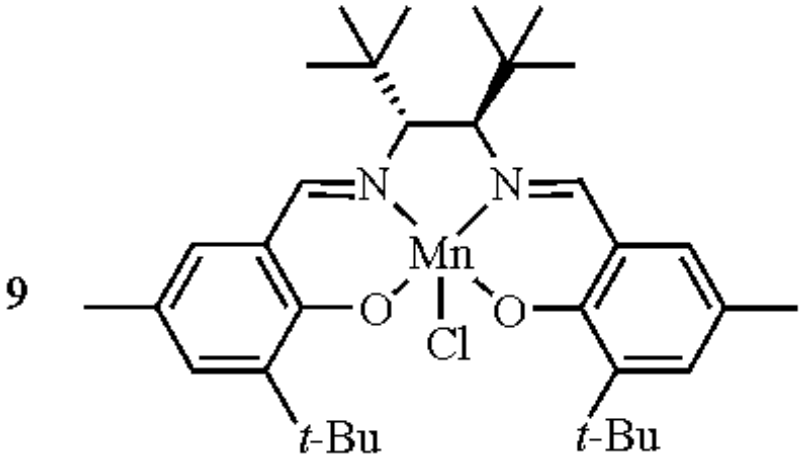

(5)

Related Reagents.

1,2-diphenyl-1,2-diaminoethane 1,2-diaminocyclohexane.

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3. To our knowledge, the only method previously described for the synthesis of **3** involved the coupling of a nitrile or an *N*-(trimethylsilyl)imine, promoted by $NbCl_4$(THF). In this procedure the (+)-diamine was obtained pure in 18% yield by resolution with (-)-mandelic acid: (a) Roskamp, E. J.; Pedersen, S. F., *J. Am. Chem. Soc.* **1987**, *109*, 3152. (b) Rasmussen, K. G.; Thomsen, D. S.; Jørgensen, K. A., *J. Chem. Soc., Perkin Trans 1* **1995**, 2009.
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Potassium (Diphenylphosphino)-1,3-pentadien-1-yl-5-ylidene Borate

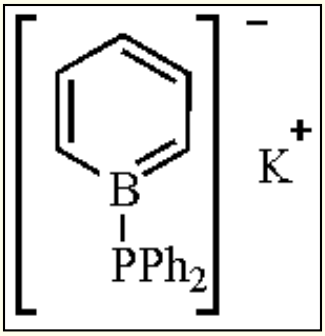

[178327-14-5] · $C_{17}H_{15}BPK$ · (300.18)

(triphenylphosphine analog[1])

Physical Data: white crystalline solid.

Solubility: not available.

Preparative Methods: 1-diphenylphosphinoboratabenzene is prepared by adding a 0.5 M solution of potassium diphenylphosphide in THF to borabenzene-trimethylphosphine at 20°C.[2,3]

Purification: recrystallized from THF at (-35°C).

Handling, Storage, and Precautions: air sensitive; all reactions are run in oven dried glassware under either an atmosphere of argon using Schlenk techniques or under an atmosphere of nitrogen inside a dry box.

Zirconium Complex

1-Diphenylphosphinoboratabenzene (DPB) σ bonds (η^1) to metal centers,[4,5] while the rest of the class of boratabenzenes,[6] such as 1-methylboratabenzene,[7] 1-phenylboratabenzene,[8] and 1-dimethylaminoboratabenzene,[9] act as surrogates of the cyclopentadiene anion by π-bonding (η^6) to the metal center.[10,11] One exception is a magnesium complex, magnesium (1-dimethylaminoboratabenzene)$_2$, where one ligand participates in η^6 bonding while the second η^1 bonds.[12] The electronic nature of the zirconecene catalyst can be tuned using DPB as a negatively charged analog of triphenylphosphine.[13] The X-ray crystal structures of K-DPB·(18-crown-6) and K-1-diphenylaminoboratabenzene·(18-crown-6) provide evidence that the 1-diphenylaminoboratabenzene N-B bond has significant π-bonding, while DPB shows little π-bonding with the boron atom.[5] Potassium 1-diphenylphosphinoboratabenzene is added to Cp_2ZrHCl (eq 1) to obtain the zirconecene complex in 49% yield.[4]

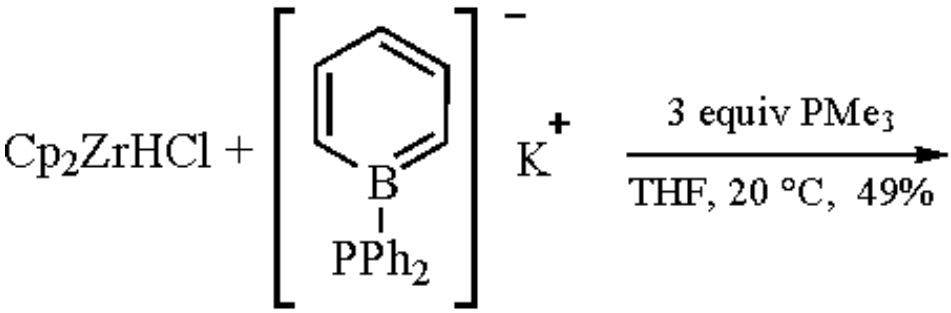

$Cp_2ZrH(DPB)(PMe_3)$ (1)

Iron Complex

Diphenylphosphide is a unique phosphorus(III) ligand because it has a set of electrons available which increases the electron density on a metal center.[4,13g] The isoelectronic iron complexes $[CpFe(CO)_2(PPh_3)]^{+}$[14] and $CpFe(CO)_2(PPh_2)$[15] allow for a variation of the electronic density on the metal center. DPB adds to $CpFe(CO)_2I$ which provides an iron complex where the electron density on the iron atom is greater than the PPh_3 complex and less than the PPh_2 (eq 2).[4]

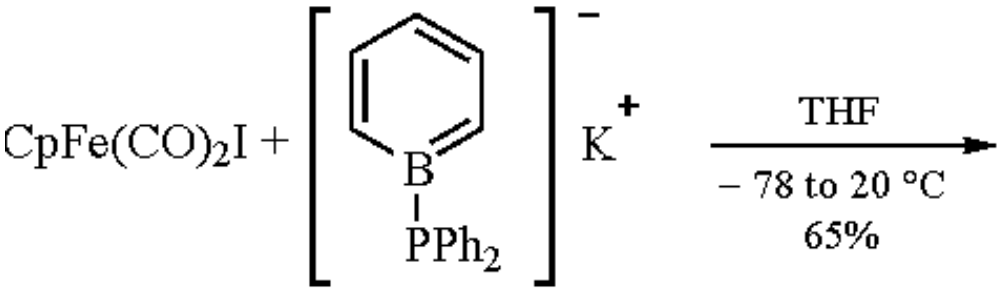

$CpFe(DPB)(CO)_2$ (2)

DPB is the only boratabenzene known to η^1 bond with iron metal. 1- Dimethylaminoboratabenzene bonds η^6 and it has recently found utility in iron complexes.[16]

Rhodium Complex

Recently, rhodium metal has been found to be extremely useful in organic synthesis. DPB was used to prepare the rhodium complex $Rh(PMe_3)_3(DPB)$ (eq 3).[4,17]

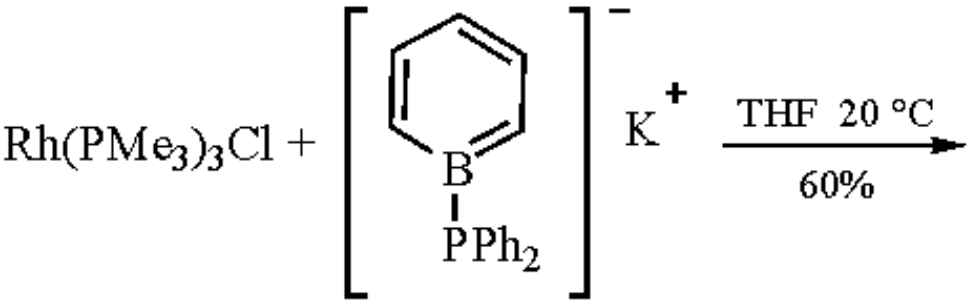

$Rh(PMe_3)_3(DPB)$ (3)

Related Reagents.

triphenylphosphine, trimethylphosphine, trimethylphosphite.

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(4*R*,5*R*)-4,5-Dicyclohexyl-2-ethyl-1,3,2-dioxaborolane[1]

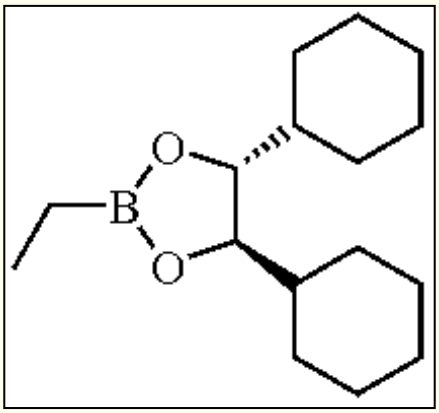

[152428-72-3] · $C_{16}H_{29}BO_2$ · (264.21)

(representative starting material for asymmetric synthesis via α-halo boronic esters[1,2])

Alternate Name: ethylboronic acid, (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol ester; (*R*,*R*)-DICHED ethylboronate.

Physical Data: bp 85-87°C (100-200 Pa); ^{1}H NMR δ 0.78 (q, BCH_2), 0.96 (t, CH_3), 0.90-1.28 Hz and 1.50-1.77 (m, cyclohexyl), 3.82 (m, OCH).[1]

Preparative Methods: transesterification of B(O-*i*-Pr)$_3$ with (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol[2] yields (4*R*,5*R*)-4,5-dicyclohexyl-2-isopropoxy-1,3,2-dioxaborolane, which reacts with ethylmagnesium chloride in THF at -78°C.[1]

Another simple route to (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol [(*R*,*R*)-DICHED] ethylboronate (**3**) involves transesterification of dibutyl ethylboronate (**1**) with (*R*,*R*)-DICHED (**2**) (eq 1).[1]

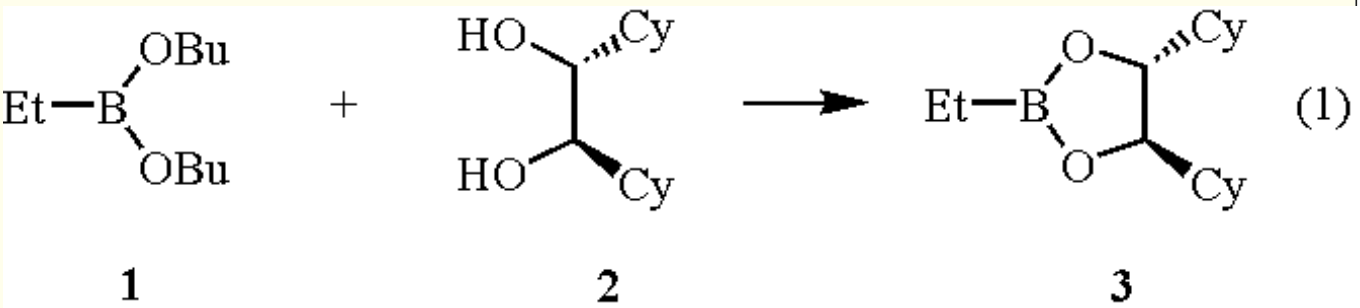

The original preparation of **2** by hydrogenation of 1,2-diphenyl-1,2-ethanediol (**4**) over a rhodium on alumina catalyst[2] has been substantially improved by in situ conversion of **4** to its methoxyborate ester (**5**) (eq 2), which allows the use of an active catalyst prepared in situ from rhodium chloride with ~2% reductive cleavage of the benzylic hydroxyl groups, a major side reaction if the free diol is hydrogenated.[3]

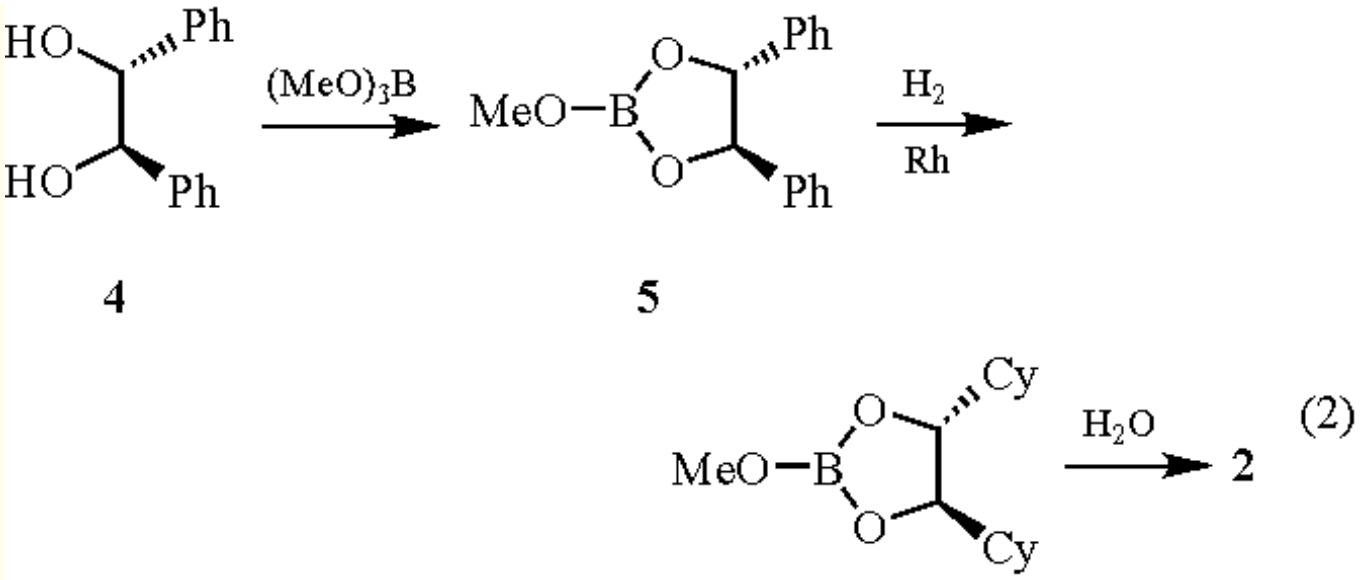

The hydrogenation is necessary because **4** is not a satisfactory chiral director.[2,3] The large-scale preparation of **4** or its (*S*,*S*)-enantiomer from *trans*-stilbene is easily accomplished via Sharpless dihydroxylation.[4] However, commercial samples of potassium osmate are sometimes less soluble than the batch used by Wang and Sharpless. The oxidation is fully reliable if the osmium compound is dissolved in water and added slowly to the reaction mixture.[3]

Ethylboronic esters such as **1** are readily accessible via the classical reaction of the ethyl Grignard reagent with a trialkoxyborane[5] or the recent hydroboration of ethylene with boron trichloride and triethylsilane.[6] However, an efficient and practical alternative is the direct ethylation of (*R*,*R*)-DICHED isopropoxyborate (**6**), prepared in situ from **2** and triisopropyl borate, with ethylmagnesium chloride (eq 3).[1] It is important to prepare **6** that is free from hydroxylic contaminants and to ethylate it with a full equivalent of Grignard reagent in order to avoid the formation of by-product difficult to separate by distillation, most likely the B-O-B linked dimeric anhydride of DICHED borate.

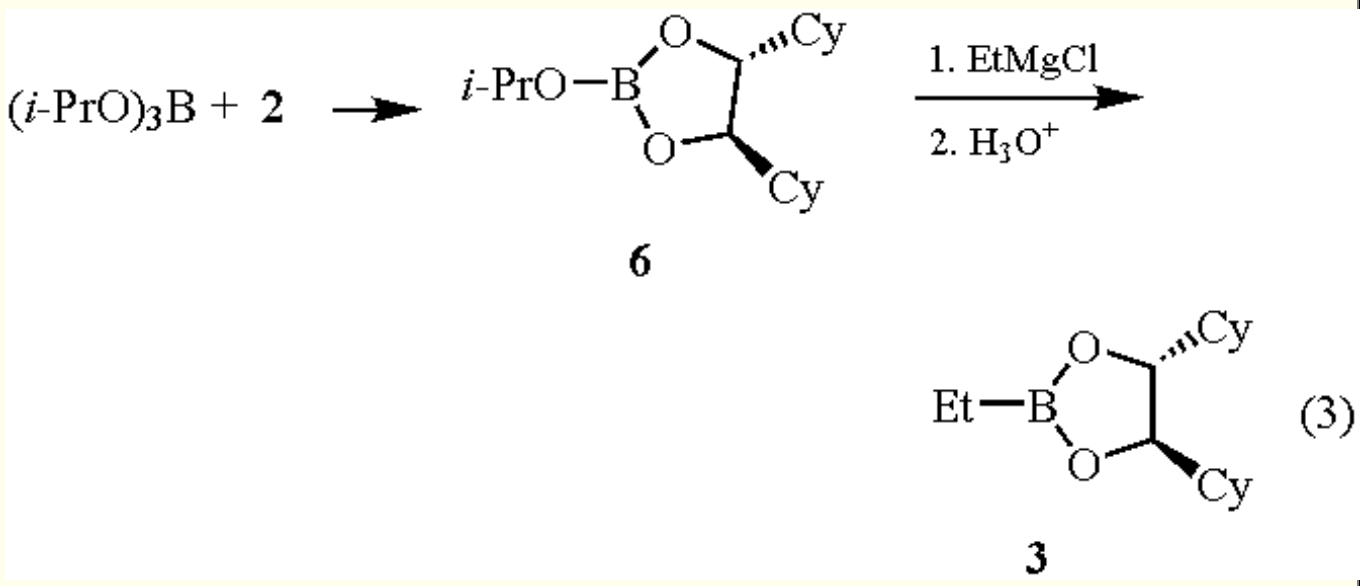

A close analog of **3**, (*R*,*R*)-DICHED methylboronate (**8**), has been made from commercially available trimethylboroxine and 1,2-diphenyl-1,2-ethanediol via the corresponding boronic ester (**7**) by hydrogenation over rhodium on alumina, prepared in situ from rhodium chloride (eq 4).[3] This hydrogenation resulted in no detectable benzylic cleavage. In any attempt to adapt this approach to compounds of higher molecular weight, it should be taken into account that diphenylethanediol esters such as **7** can decompose, probably via pinacol rearrangement, if overheated during distillation.

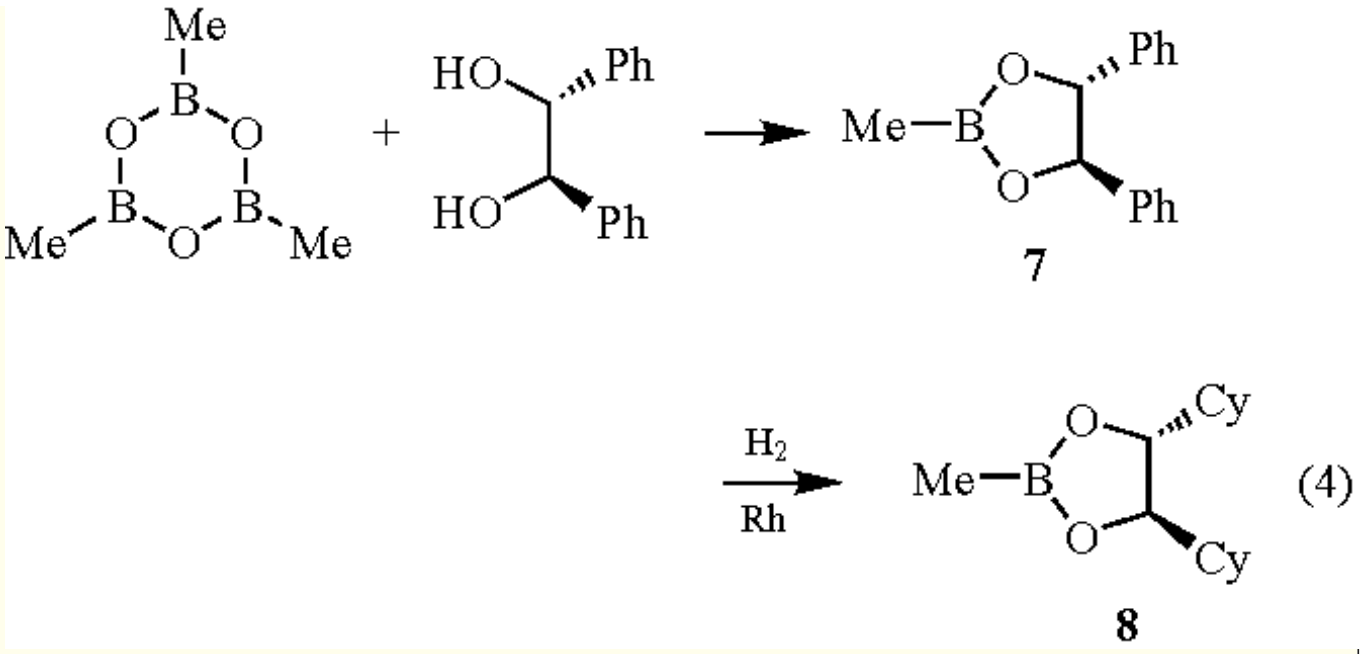

(4)

Handling, Storage, and Precautions: (*R*,*R*)-DICHED ethylboronate (**1**) and similar boronic esters are generally stable during transfer and weighing in air, and do not hydrolyze. Their susceptibility to autoxidation appears comparable to that of common aldehydes, and storage in rigorously sealed containers is advised. No special hazards are known.

Applications

The major use of DICHED ethylboronate (**3**) and similar compounds is as starting material for highly stereoselective asymmetric synthesis. Actual isomer ratios obtained with **3** have never been measured accurately, but the closely related 1,2-diisopropyl-1,2-ethanediol propylboronate has been shown to furnish stereoselection >1000:1 after homologation with $LiCHCl_2$ and substitution with methylmagnesium bromide.[7] This very high ratio is the result of a sequential double diastereoselection. The wide range of synthetic applications possible with this homologation and substitution chemistry has been reviewed.[8]

The homologation process is illustrated by the conversion of the DICHED ethylboronate (**3**) to the corresponding 1-chloropropylboronate (**10**) via a borate complex (**9**) (eq 5). The structure of the borate complex and geometry of the metal cation catalysis of the rearrangement are supported by theoretical calculations.[9] If zinc chloride is not added, the lithium ion from $LiCHCl_2$ presumably functions in the same way, but reactions are slower and stereoselection is not as high.

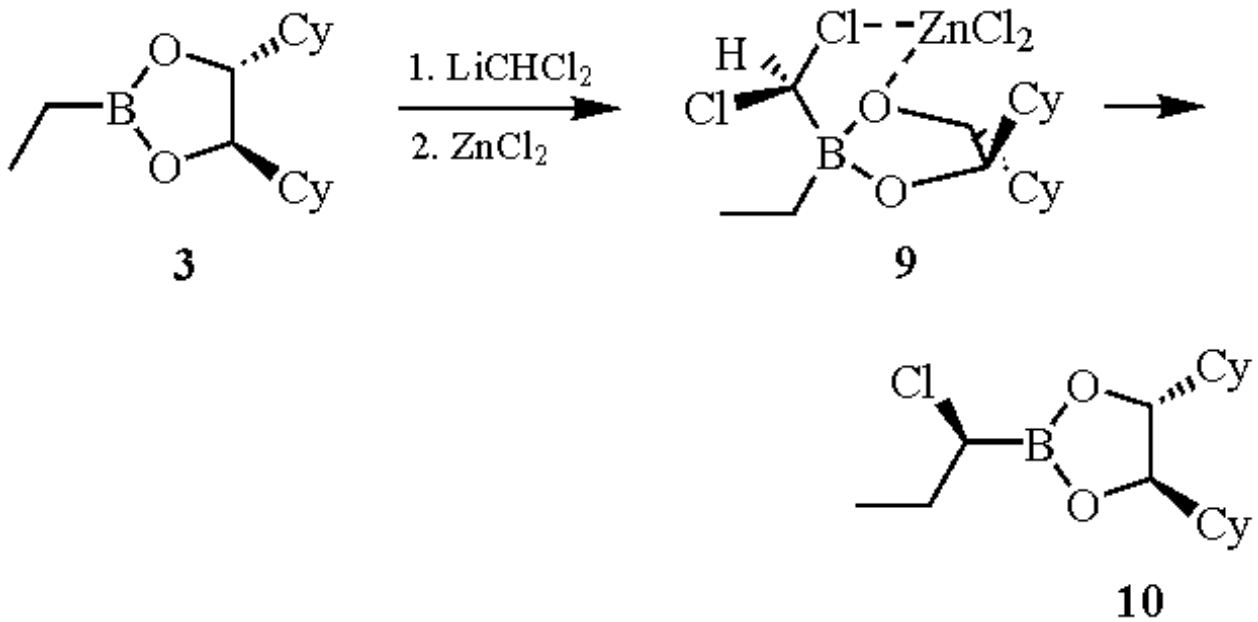

(5)

Displacement of chloride from **10** by nucleophiles follows an analogous pathway, illustrated here by the reaction of lithium benzyl oxide with **10** to produce cation-coordinated borate **11**, which rearranges to **12** (eq 6). Regardless of the mechanistic details, it is significant that the steric relationship of the alkyl substituent in intermediate **11** is similar to that of the chlorine atom that is not displaced in **9**.

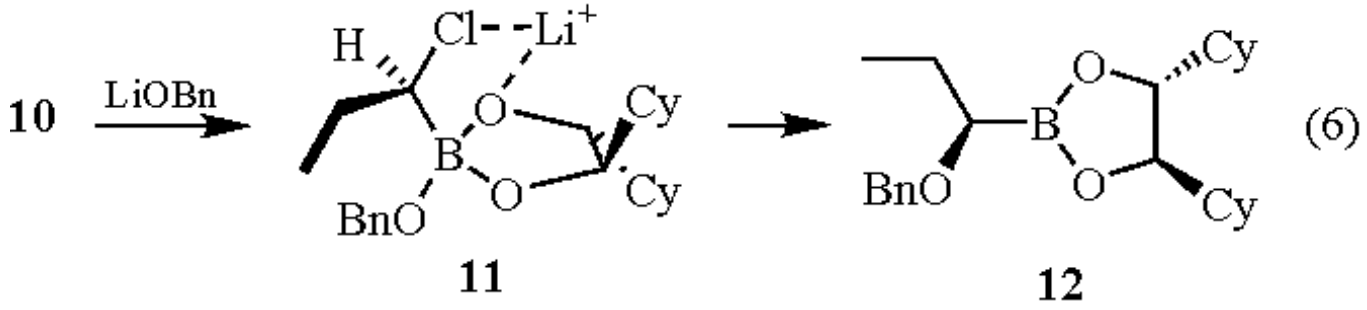

The 1-(benzyloxy)propyl boronic ester **12** was then used as an intermediate in the first synthesis of pure stegobinone, the pheromone of two anobiid beetle pests, the drugstore beetle and the furniture beetle. This pheromone is inactivated by small amounts of an epimer, and high stereopurity is therefore critical. Homologation of **12** with $LiCHCl_2$ and the usual zinc chloride catalyst followed by methylation yielded boronic ester **13**, which with $LiCHCl_2/ZnCl_2$ yielded chloro boronic ester **14** (eq 7).

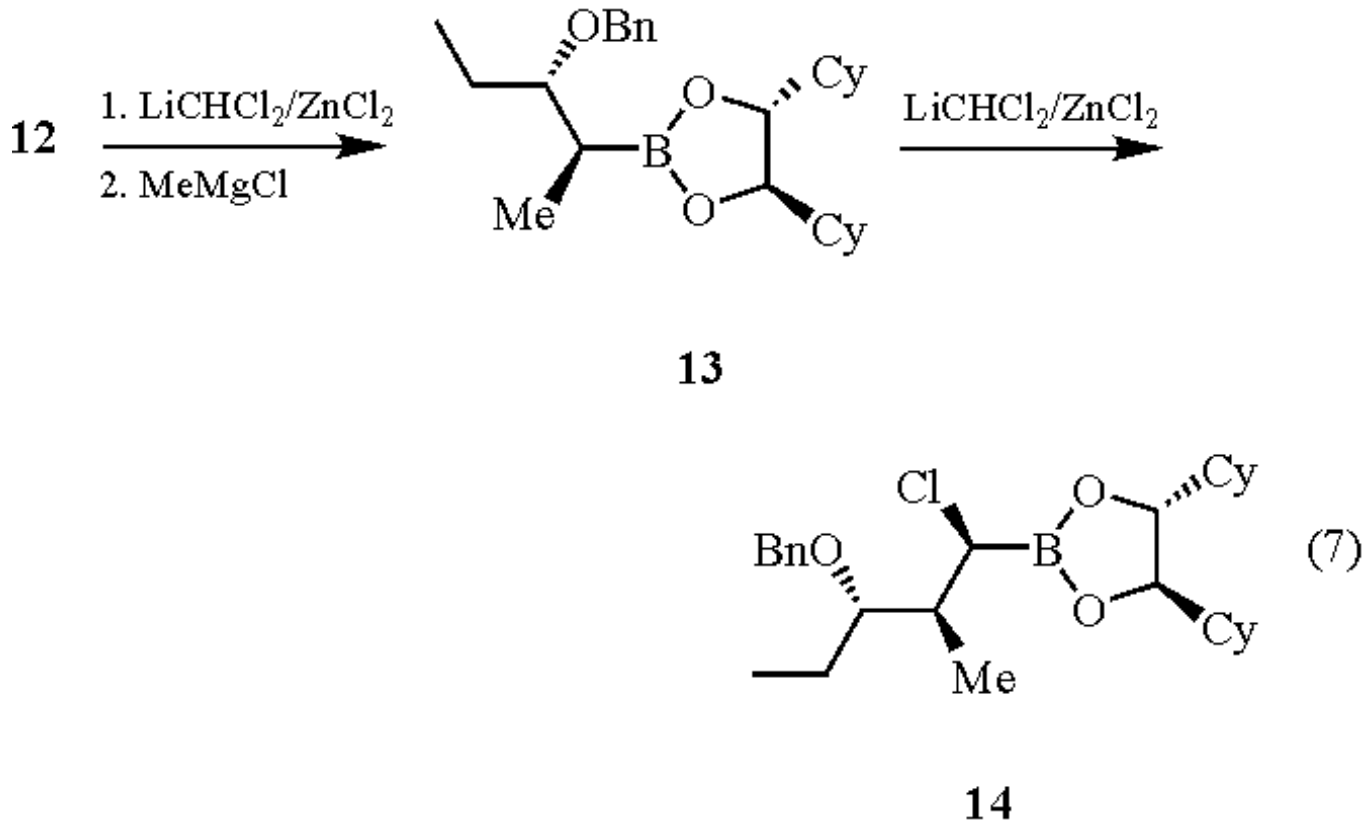

Intermediate **14** served as a source of both halves of stegobinone. Oxidation of **14** with hydrogen peroxide yielded aldehyde **15** (eq 8) in 50-55% based on **3**, diastereomeric purity >99%.[1]

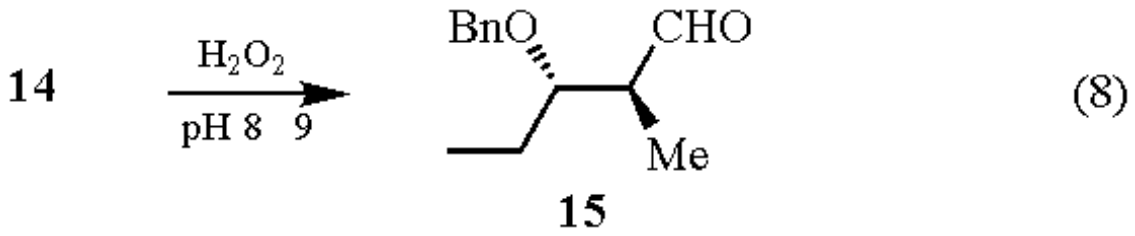

Methylation of **14** yielded boronic ester **16**, which was converted to ketone **17** in several steps (eq 9).[1]

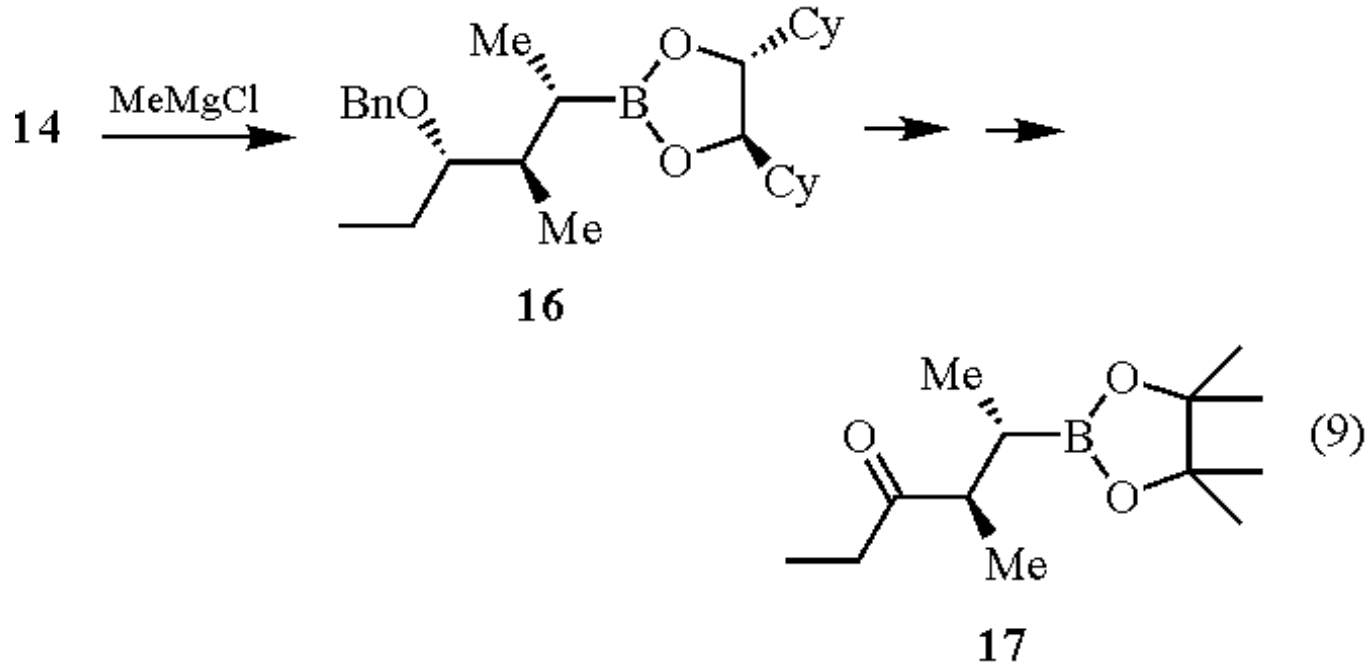

Ketonic boronic ester **17** was converted to a boron enolate **18** with 9-BBN triflate and used in an aldol condensation with aldehyde **15** to produce the complete carbon skeleton of stegobinone (**19**) (eq 10). The steps not illustrated are standard organic transformations.

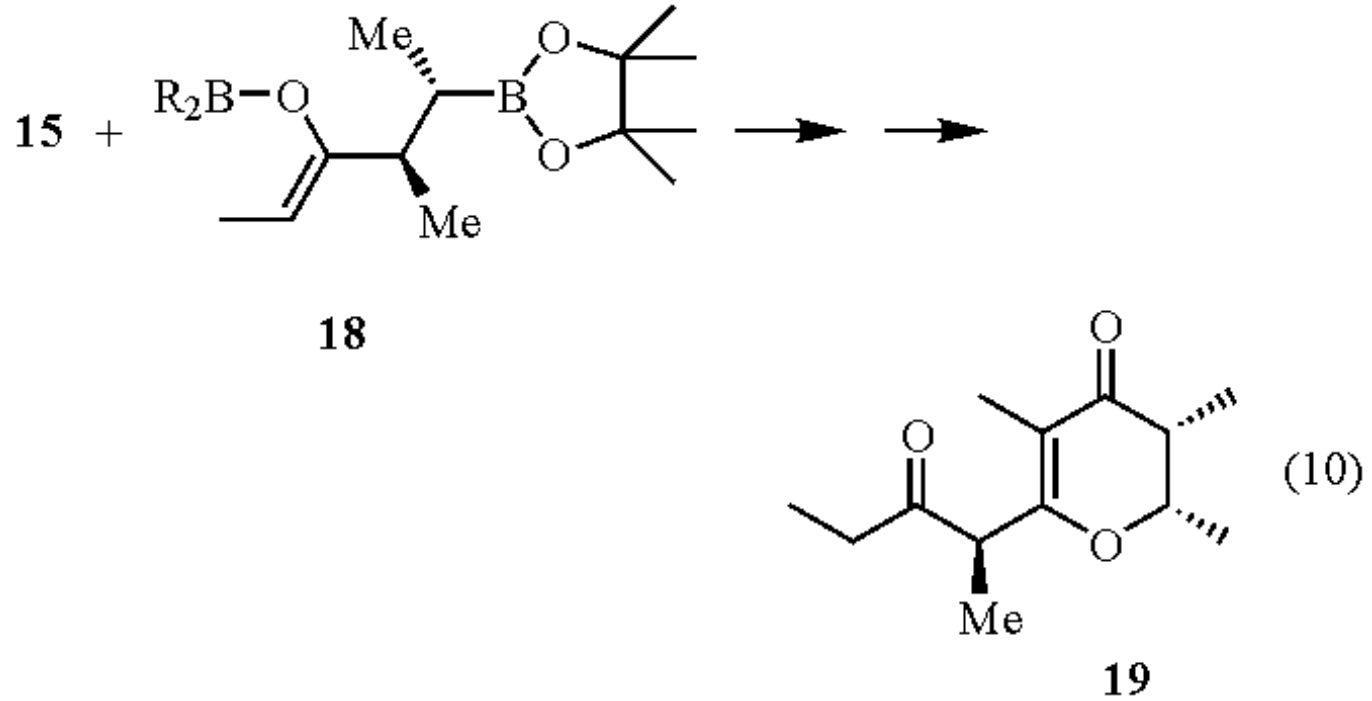

Stegobinone (**19**) epimerizes very easily at the enolizable asymmetric center, and the epimer is repellent to the insects. If the preparation does not supply very pure stegobinone initially, purification by standard methods is difficult. The boronic ester method is fairly lengthy but provides isomerically pure **19**. A synthetic equivalent of intermediate aldehyde **15** might alternatively be made via aldol chemistry, though not necessarily more efficiently. The boronic ester route described here is especially useful for the highly stereocontrolled synthesis of the paired methyl substituents in intermediate **17**.

---

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(Triethylamine)(pentacarbonyl)molybdenum

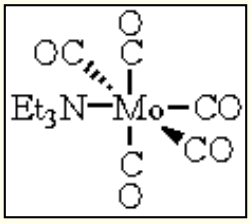

[33846-95-6] · $C_{11}H_{15}MoNO_5$ · (337.18)

(catalyst for cycloisomerizations of terminal alkynyl alcohols, and other mechanistically related transformations of terminal alkynes[1])

Physical Data: for $(Et_3N)Mo(CO)_5$: λ_{max} 393 nm; IR ν (trans CO stretch) 1915 cm^{-1}; for $(Me_3N)Mo(CO)_5$: mp 70°C[2], mp 80°C;[3] IR ν 2072, 1941, 1921 cm^{-1}.

Preparative Methods: $(Me_3N)Mo(CO)_5$ has been prepared by reaction of commercially available $Mo(CO)_6$ with trimethylamine *N*-oxide in dichloromethane, and purified by recrystallization from a pentane solution.[2] $(Et_3N)Mo(CO)_5$ is best prepared in situ by 350 nm irradiation of $Mo(CO)_6$ in an inert solvent such as cyclohexane or diethyl ether, in the presence of triethylamine.[4,5]

Handling, Storage, and Precautions: $(Et_3N)Mo(CO)_5$ is generated from $Mo(CO)_6$, which is a toxic solid compound. As the photochemical procedure for generating $(Et_3N)Mo(CO)_5$ also produces carbon monoxide, and decomposition of $(Et_3N)Mo(CO)_5$ may be reasonably expected to evolve carbon monoxide, all transformations of $(Et_3N)Mo(CO)_5$ and the $Mo(CO)_6$ precursor should be conducted in an efficient fume hood. $Mo(CO)_6$ is reported to be incompatible with strong oxidizing agents,[6] and diethyl ether solutions of $Mo(CO)_6$ may explode during storage.[7]

Cycloisomerizations of 4-Hydroxyalk-1-ynes to Dihydrofurans

$(Et_3N)Mo(CO)_5$ and $(Me_3N)Mo(CO)_5$ react with homopropargylic alcohols (4-hydroxyalk-1-ynes) to provide cycloisomeric dihydrofurans.[8] Yields are somewhat lower with $(Me_3N)Mo(CO)_5$ prepared from $Mo(CO)_6$ and trimethylamine *N*-oxide, so the photochemically generated $(Et_3N)Mo(CO)_5$ catalyst is currently preferred. This alkynol cycloisomerization transformation is compatible with aromatic rings, silyl ethers, and carboxylic esters and amides.[9] The stereochemical integrity of chiral secondary alcohol substrates is maintained under the reaction conditions. Dihydrofuran products from alkynol cycloisomerization have been converted into several biologically important nucleosides, including cordycepin (**5**), the anti-AIDS compound stavudine (**6**),[10] and puromycin aminonucleoside (**9**) (eq 1-3).[9]

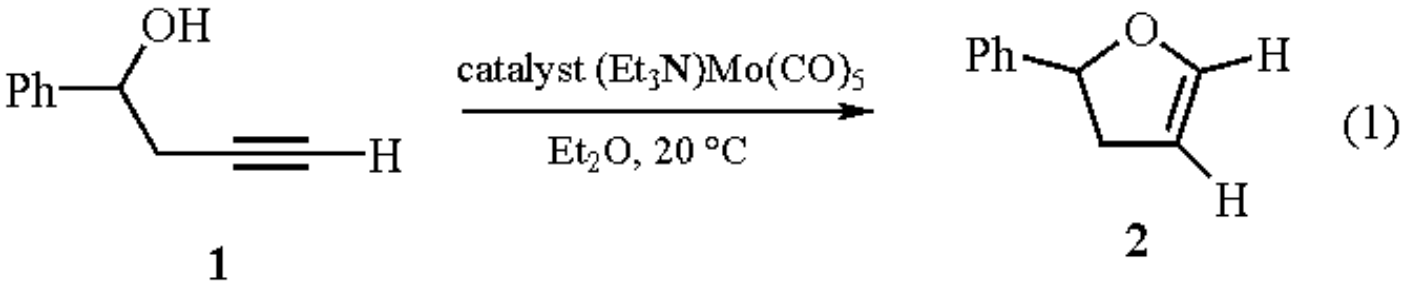

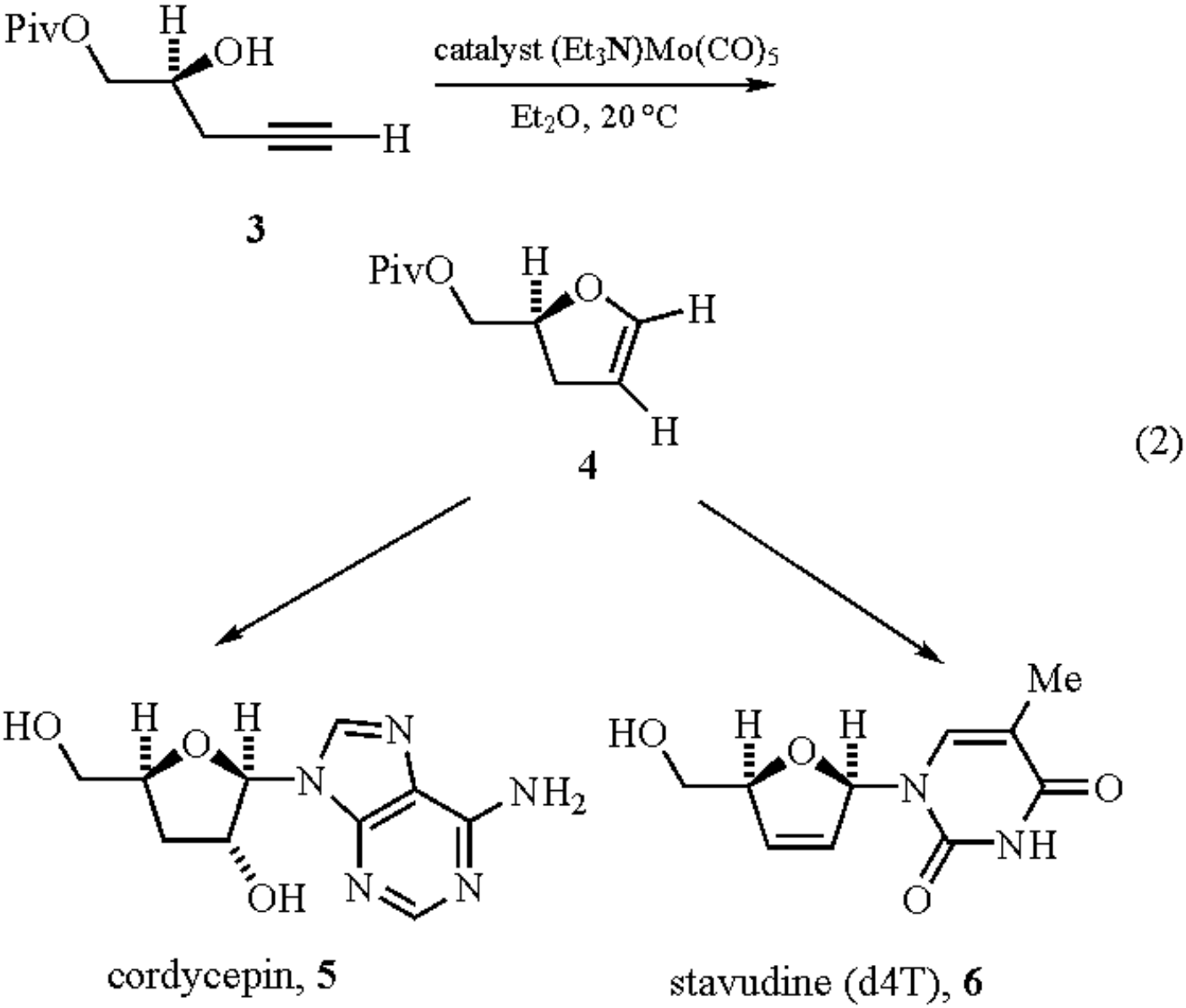
PivO
H
OH
H
catalyst $(Et_3N)Mo(CO)_5$
Et_2O, 20 °C
3
PivO
H
O
H
H
4
(2)
HO
H
O
H
N
N
N
N
NH_2
OH
cordycepin, 5
Me
HO
H
O
H
N
O
NH
O
stavudine (d4T), 6

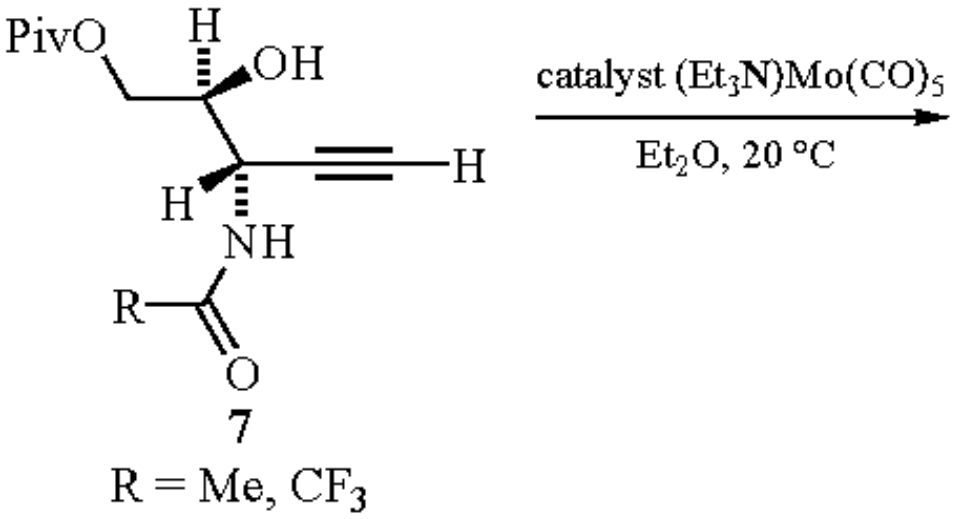

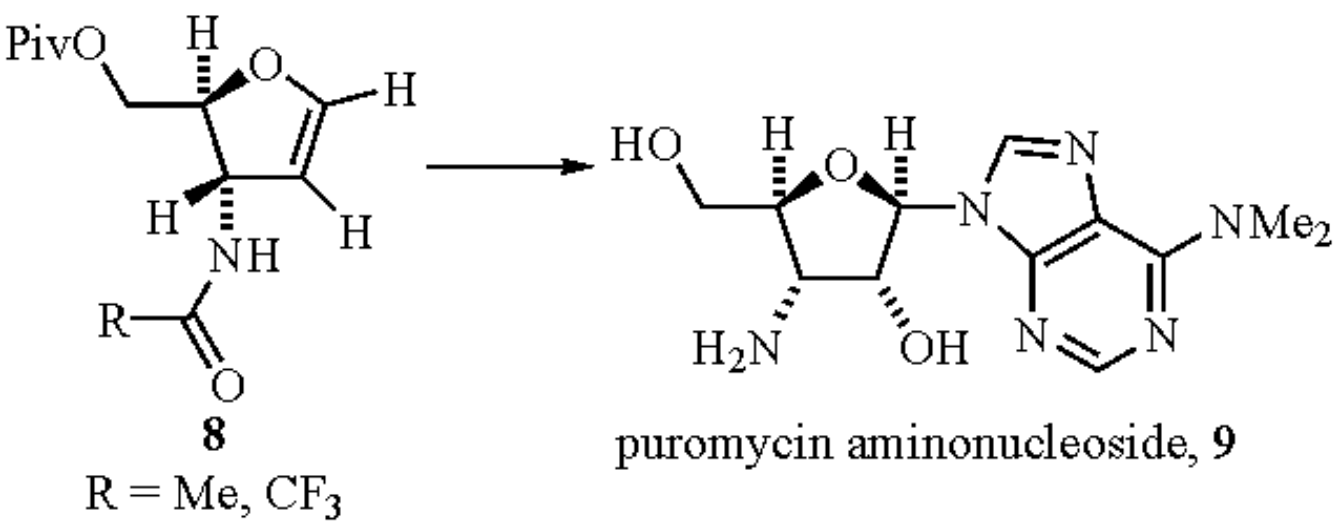

(3)

$(Et_3N)Mo(CO)_5$ is not a general catalyst for cycloisomerization of 5-hydroxyalk-1-ynes, although the cyclic carbamate-containing alkynyl alcohol **10** provided a modest yield of the highly substituted dihydropyran **11** (eq 4).[11] Tungsten carbonyl-catalyzed methods have subsequently been developed for high-yield cycloisomerizations of substituted 5-hydroxyalk-1-ynes to the corresponding dihydropyrans.[12] The enyne ester **12** undergoes cyclization with stoichiometric $(Et_3N)Mo(CO)_5$ to provide the molybdenum oxacarbene complex **13** (eq 5).[13]

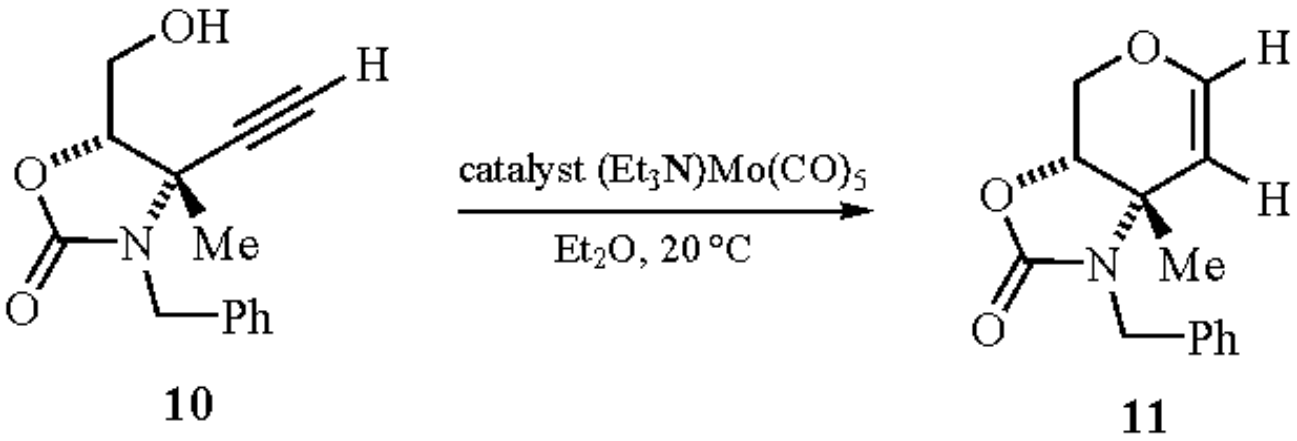

(4)

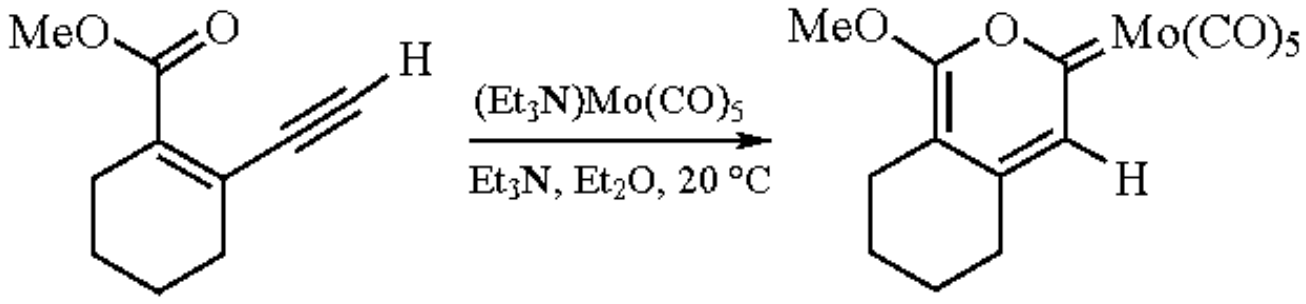

(5)

12 **13**

Cyclizations of 4-Hydroxyalk-1-ynes in the Presence of Electrophiles

$(Et_3N)Mo(CO)_5$-catalyzed cyclizations of 4-hydroxyalk-1-ynes in the presence of tributyltin triflate provide 1-(tributylstannyl)dihydrofurans in good yield, resulting from reaction of an organomolybdenum catalytic intermediate with tributyltin triflate (eq 6).[14] This transformation was utilized in a synthesis of the natural product manoalide (eq 7).[15]

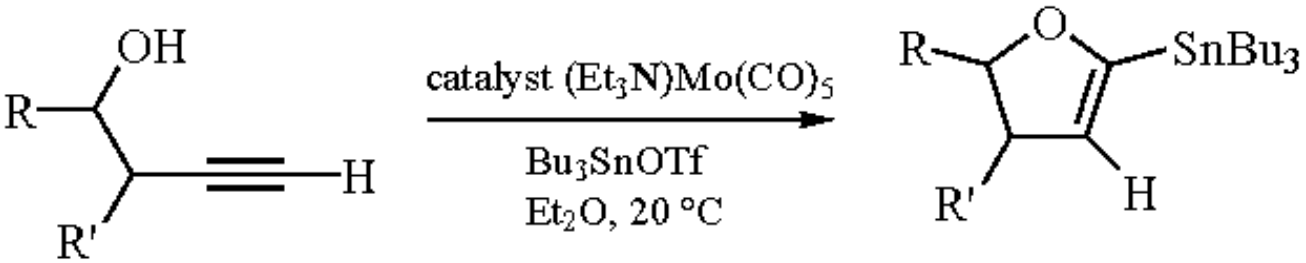

(6)

14 **15**

R = R' = H
R = Ph, R' = H
R = H, R' = Me

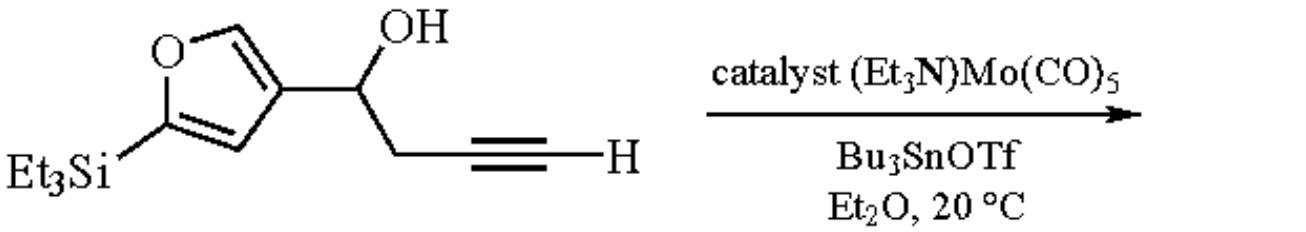

16

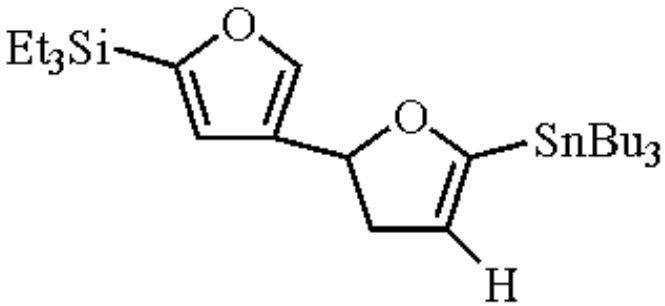

(7)

17

In contrast, alkynyl alcohol cyclizations in the presence of aldehydes are accompanied by carbon-carbon bond formation at C-2 of the

cyclization product, and enolizable aldehydes including acetaldehyde afford the conjugated diene **18** (eq 8).

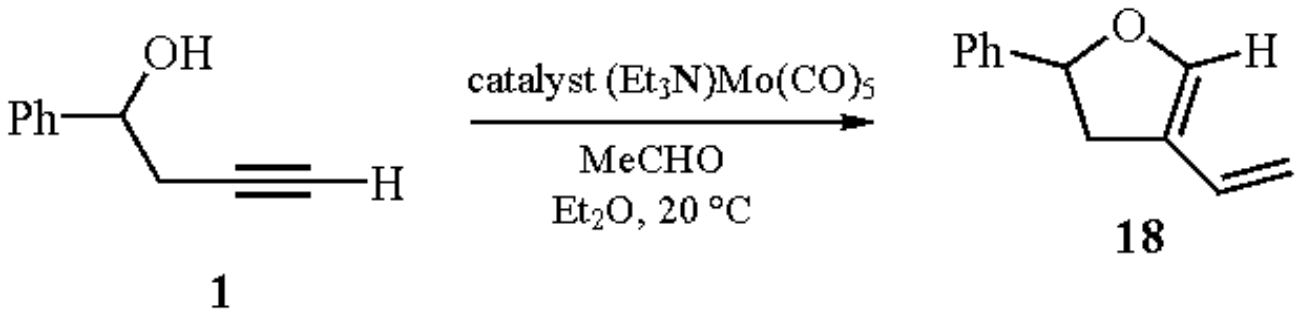

(8)

Cycloisomerization Syntheses of Furans.

Reactions of epoxyalkynes including **19** with $(Et_3N)Mo(CO)_5$ produce the corresponding furan **20** (eq 9). However, the substrate **21** affords furan **22** via a mechanism of alkynol cyclization coupled with opening of the epoxide leaving group (eq 10).[16] The cyclic hemiacetal substrate **23** also provides furan **24**, an intermediate in the total synthesis of salinomycin (eq 11).[17]

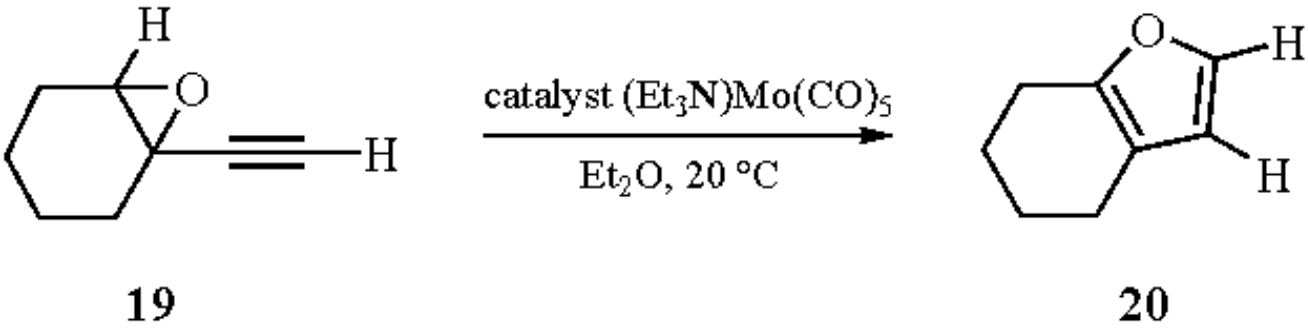

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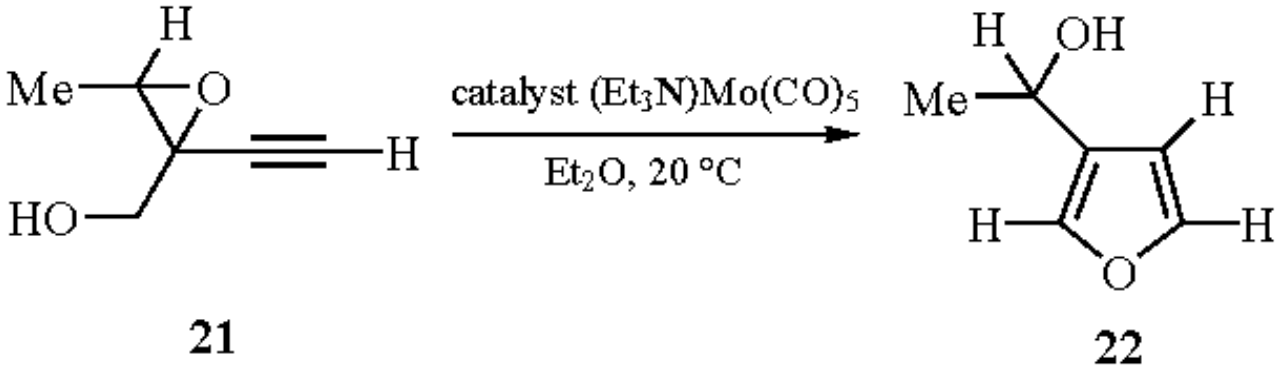

(10)

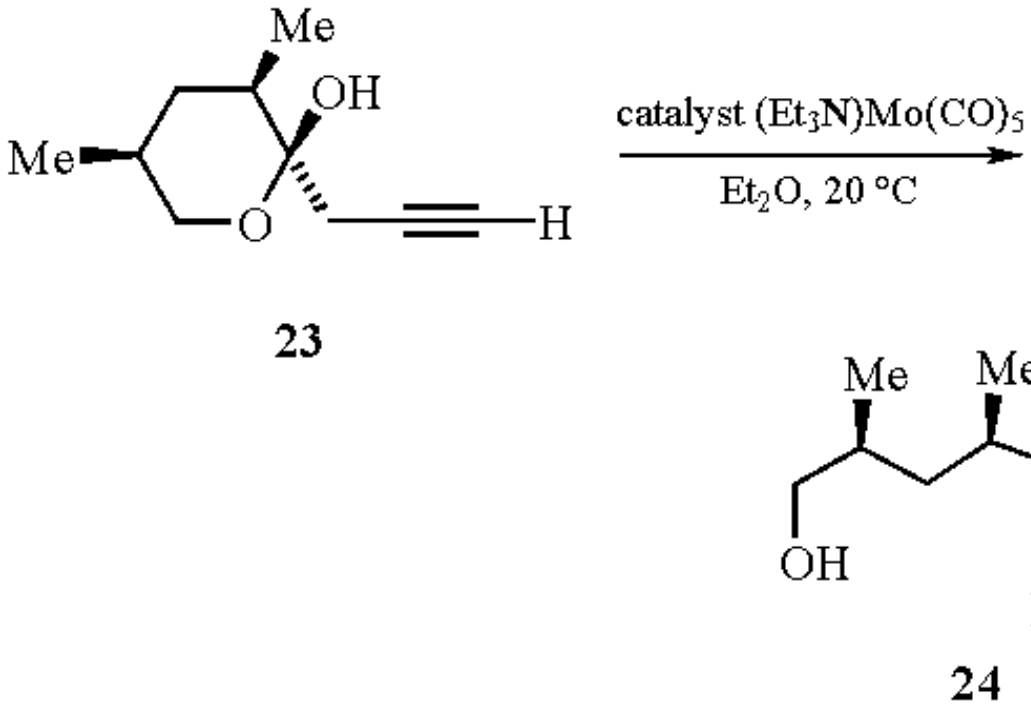

(11)

Cyclizations of Terminal Alkynes Tethered to Other Nucleophiles.

$(Et_3N)Mo(CO)_5$-promoted azacycloisomerizations of alkynes tethered to nitrogen nucleophiles have been explored. Although primary alkylamines are incompatible with the $(Et_3N)Mo(CO)_5$ catalyst and *N*-acetamide or *N*-sulfonamide substrates are unreactive, the *tert*-butylcarbamate derivative of 1-aminobut-3-yne **25** undergoes cycloisomerization to the corresponding cyclic enecarbamate **26** (eq 12). Similarly, *ortho*-aminophenylacetylene **27** undergoes cycloisomerization to indole **28** (eq 13).[18]

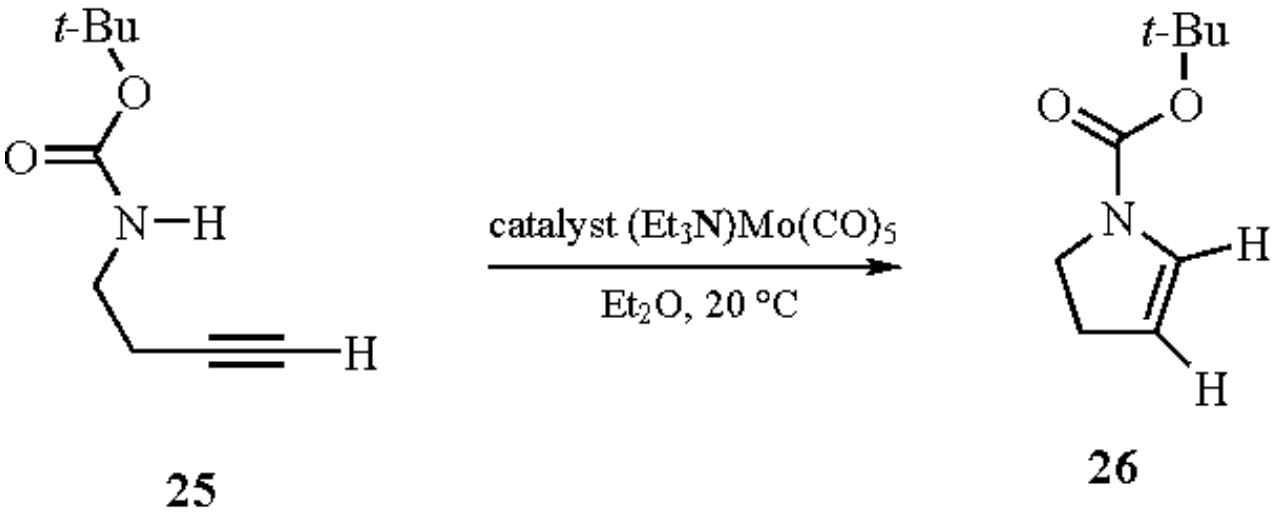

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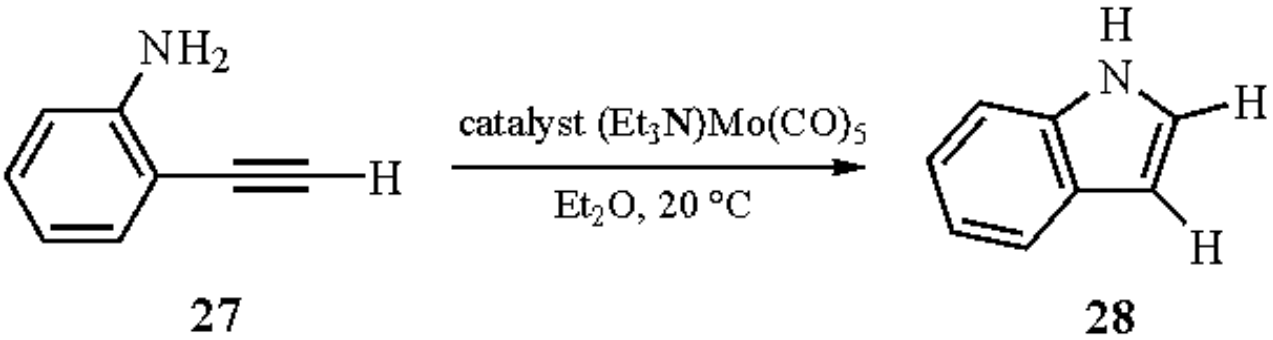

(13)

Stabilized enolates obtained from deprotonation of 1,3-diketones, β-ketoesters, or substituted malonate esters **29** undergo cyclization with stoichiometric $(Et_3N)Mo(CO)_5$ to provide substituted cyclopentenes **30** (eq 14).[19]

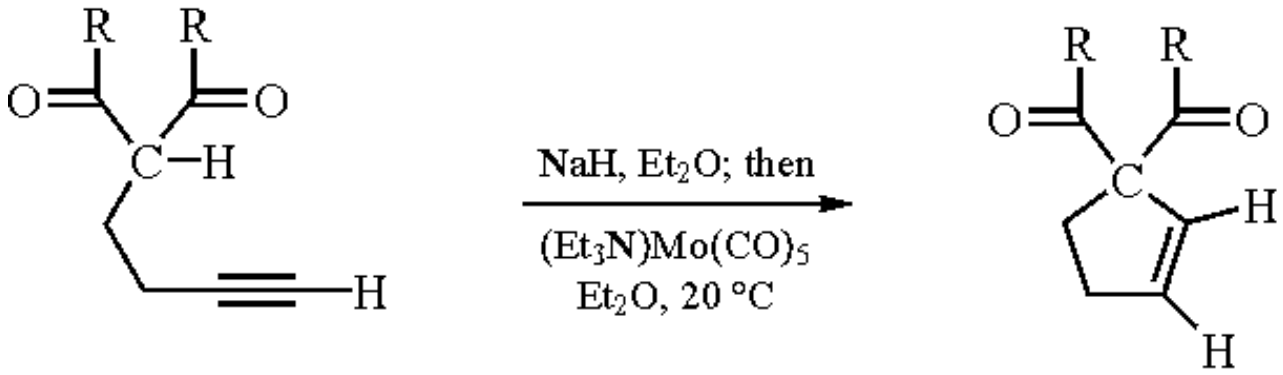

(14)

29 **30**

R = Me, OMe

Related Reagents.

(DABCO)tungsten pentacarbonyl, (Et_3N)tungsten pentacarbonyl.

---

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(1*R*,2*S*)-1-Lithio-1-phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}Oxirane

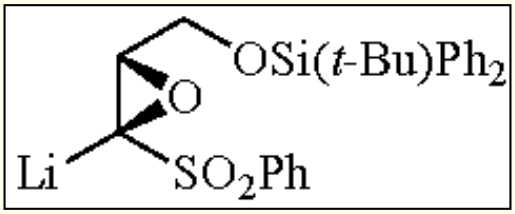

[181208-42-4] · $C_{25}H_{27}LiO_4SSi$ · (458.08)

(oxiranyllithium; oxiranyl anion; nucleophilic epoxide; acyl anion equivalent; epoxy sulfone)

Solubility: soluble in THF, diethyl ether.

Preparative Methods: prepared by lithiation of (1*R*,2*S*)-1-phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}oxirane (**1**, $[\alpha]_D$ +55.9 °, *c* 1.0, $CHCl_3$) (1.0 equiv) in THF (0.15 M solution) with *n*-BuLi (1 equiv, 1.6 M solution in hexane) in the presence of DMPU or hexamethylphosphoramide (HMPA) (3.0 equiv) at -100°C under argon. Deprotonation is completed within a few minutes (eq 1).[1]

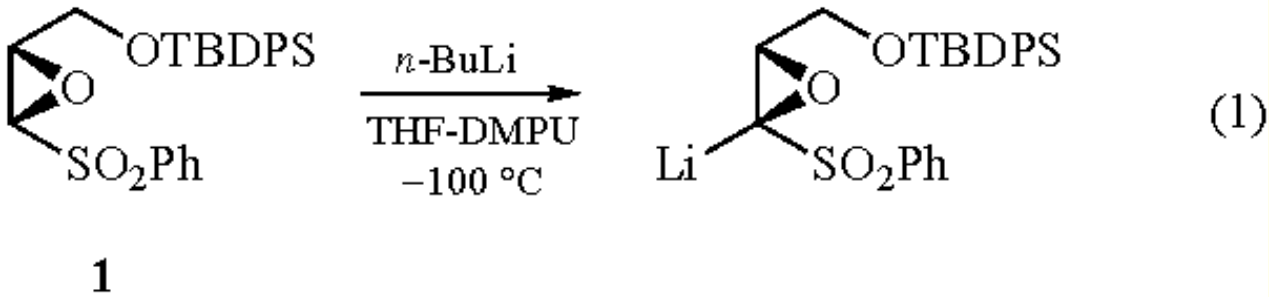

Handling, Storage, and Precautions: the oxiranyllithium is very unstable, even at -100°C under argon, and should be reacted with electrophiles immediately. The reagent is also conformationally unstable and slowly isomerizes to the *trans*-isomer when addition of an electrophile is delayed (about 5% isomerization after 20 min at -100°C). Elevated temperatures (>-78°C) cause rapid decomposition.[1,2]

Introduction

Although epoxides are widely recognized as extremely versatile synthetic intermediates in view of their electrophilic nature, the reaction of an epoxide as a nucleophile, i.e. an oxiranyl anion, is less common. Recently, cumulative studies on the chemistry of oxiranyl anions have appeared and some aspects of the anions have been discussed.[3,4]

Preparation of (1*R*,2*S*)-1-Phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}oxirane and Related Compounds

Epoxidation of (*Z*)-vinyl sulfone, which is available from the Peterson olefination of (*S*)-*O*-pentylideneglyceraldehyde[5] and phenyl trimethylsilylmethyl sulfone[6] in three steps (40% overall yield), with *t*-BuOOH/*t*-BuOK in THF gives epoxy sulfone (eq 2). Deprotection of the ketal group and recrystallization affords an optically pure epoxy diol, which is then treated with sodium periodate followed by sodium borohydride to give an alcohol. Protection of the resulting alcohol as its silyl ether yields (1*R*,2*S*)-1-phenylsulfonyl-2-{[(*tert*-butyldiphenyl)silyl]oxymethyl}oxirane (**1**).[7] Its enantiomer is available in the same manner starting from (*R*)-isopropylideneglyceraldehyde.[8]

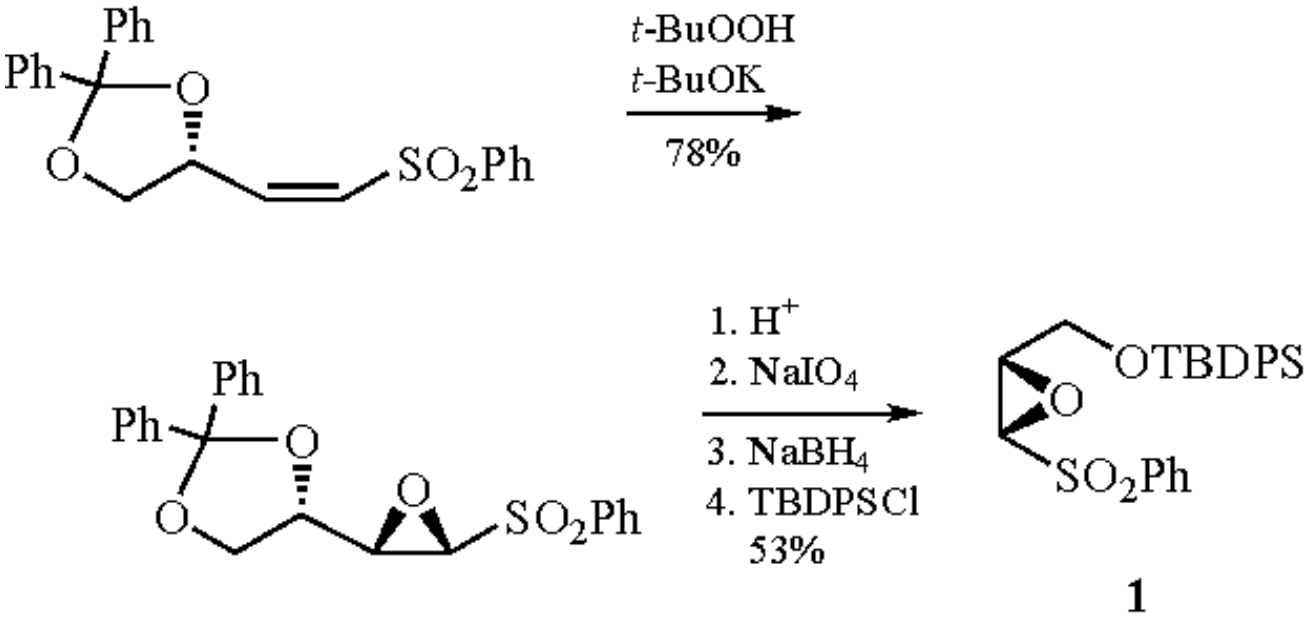

(2)

Racemic epoxy sulfone derivatives are easily prepared from allyl ethers by reaction with sodium *p*-toluenesulfinate in the presence of iodine followed by treatment with triethylamine, separation of *E*- and *Z*-isomers, and epoxidation with *t*-BuOOH and *n*-BuLi in THF (eq 3).[2]

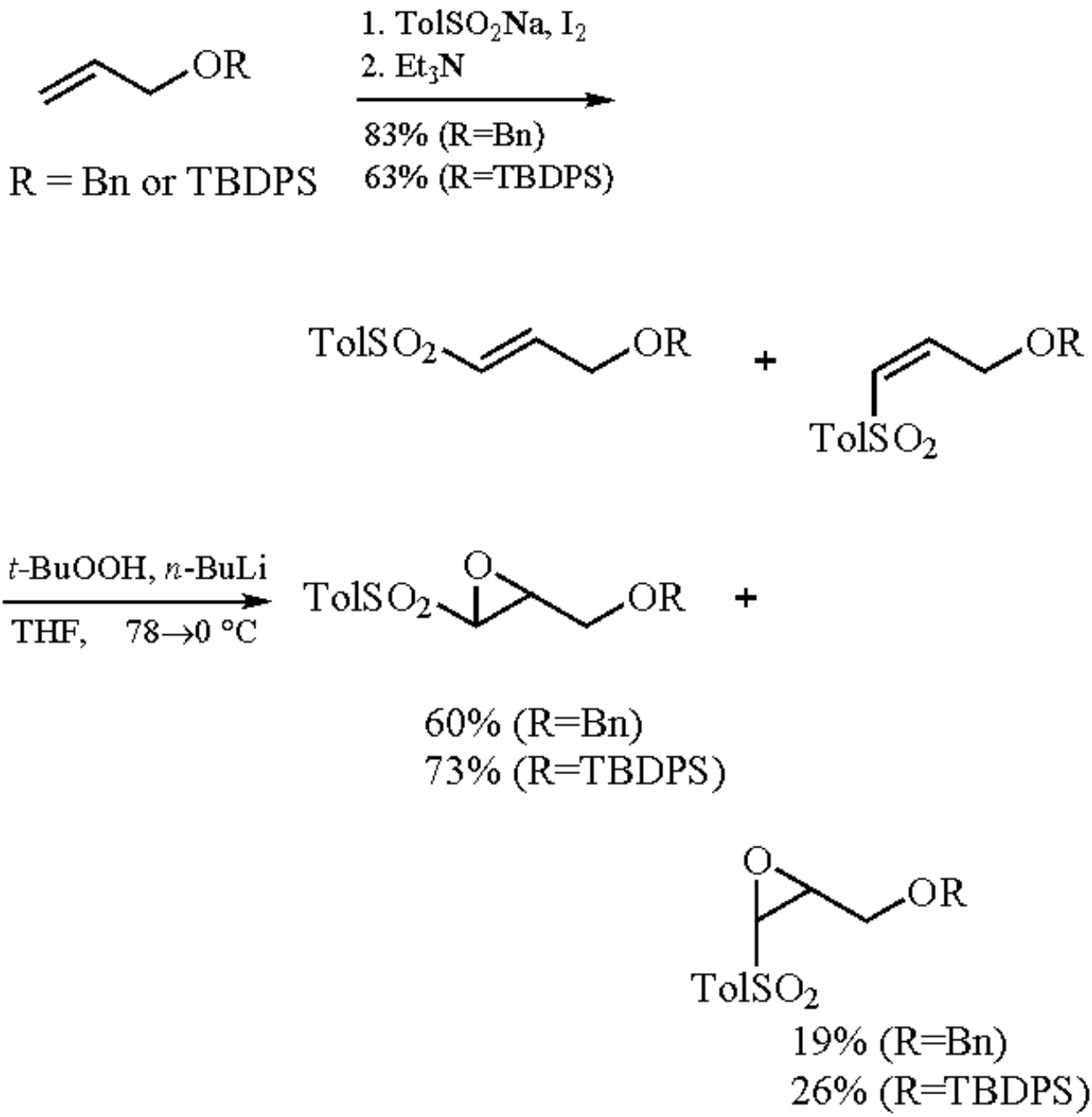

(3)

Reaction of Sulfonyl-Stabilized Oxiranyllithiums

Reaction of sulfonyl-stabilized oxiranyllithiums with primary alkyl halides gives acceptable yields of products.[1] More reactive alkyl triflates give generally better yields but, due to the instability of oxiranyllithiums, yields are often not reproducible when electrophiles are added to a solution of the preformed oxiranyllithiums. It is recommended that the alkylation reaction be carried out by an in situ trapping method.[2] Treatment of a solution of epoxy sulfone (1.0 equiv) and triflate (1.5 equiv) in THF-DMPU (or HMPA) at -100°C under argon with *n*-BuLi (1.0 equiv) followed by stirring for 30 min affords the coupled product in high yield (eq 4).[9] The product can be converted to a tetrahydropyranone derivative by exposure to *p*-toluenesulfonic acid. The strong electron-withdrawing ability of the sulfonyl group works against the adjacent C-O bond-breaking in an acid-catalyzed epoxide ring-opening process and, consequently, favors the 6-*endo* mode pathway which yields the tetrahydropyranone after elimination of phenylsulfinic acid. Reaction with a halogenated metal Lewis acid yields a halo ketone instead of a cyclization product (eq 4).[10] These reactions demonstrate that the oxiranyllithium reagent serves as a functionalized acyl anion equivalent and a three-carbon building block.

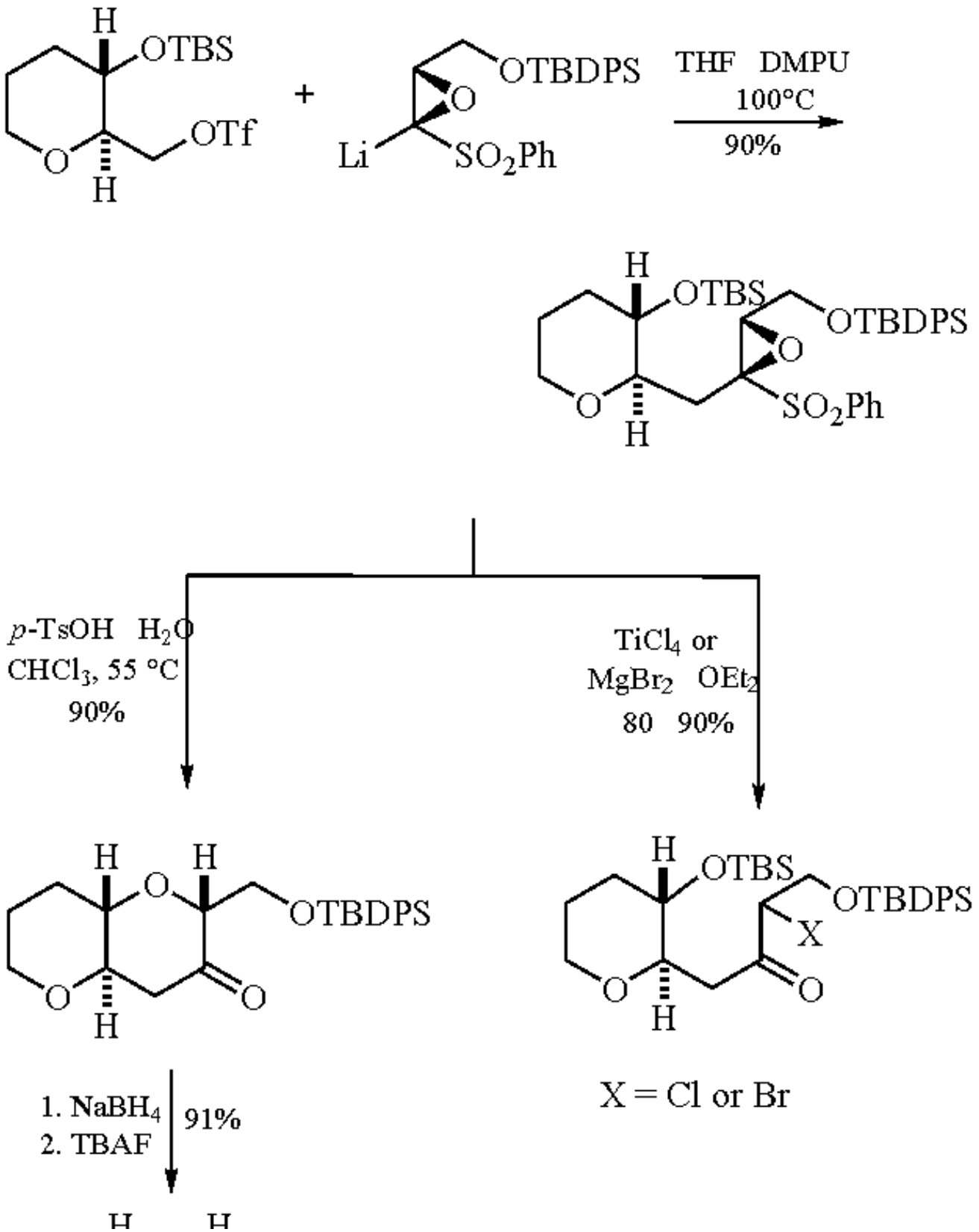

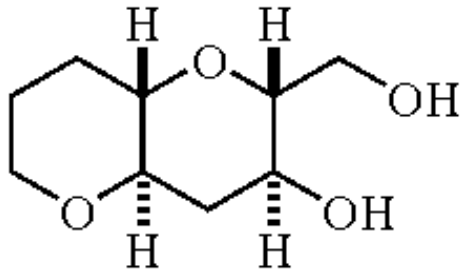

(4)

Reiterative application of this protocol has allowed the stereocontrolled construction of polytetrahydropyrans[9,10] and polycyclic ethers containing six- and seven-membered rings (eq 5).[7]

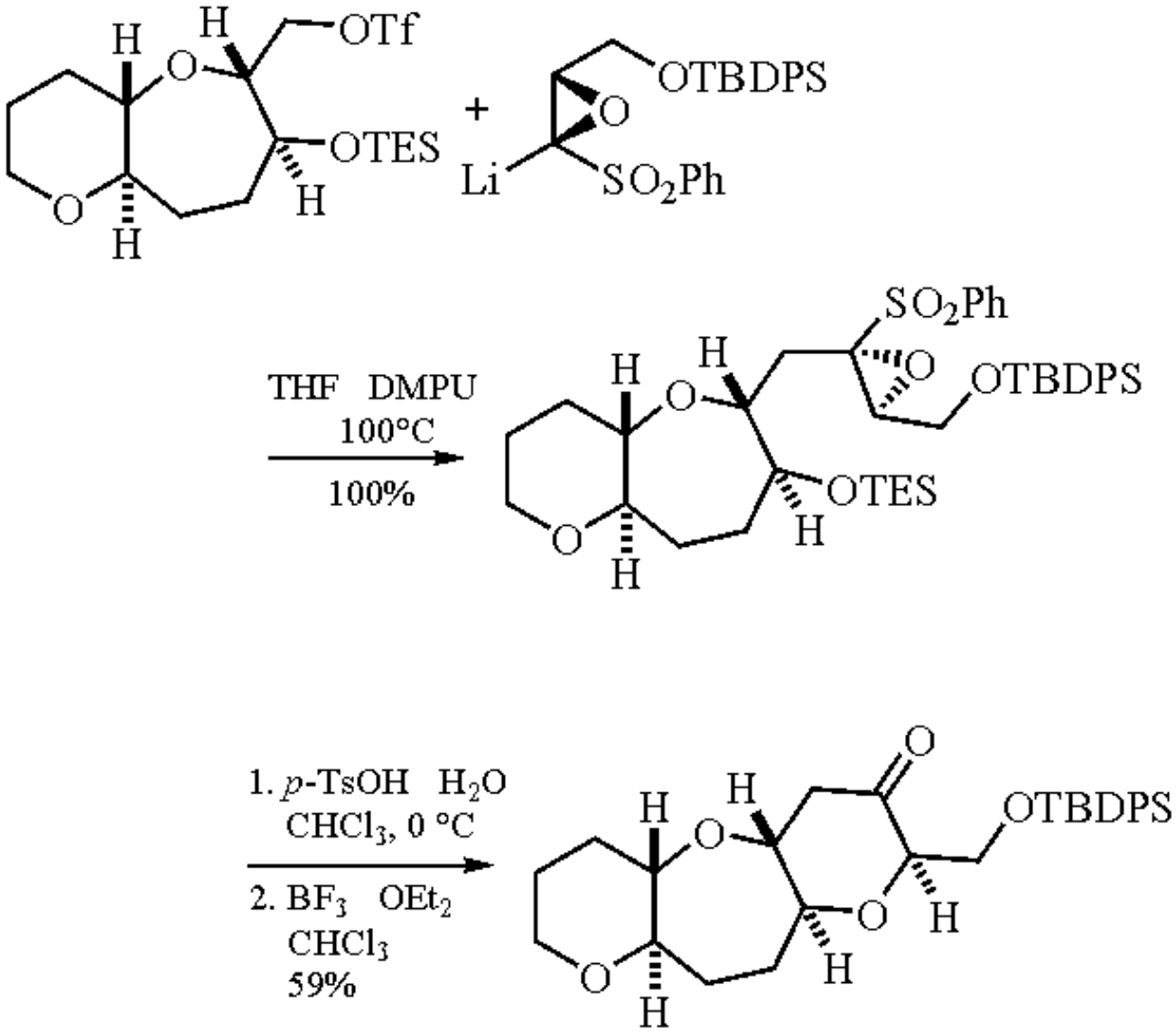

(5)

Reaction of the oxiranyllithium with aldehydes is also carried out by an in situ trapping method at very low temperatures in order to avoid decomposition of the reagent. Its applicability to a complex situation has been demonstrated in a synthesis of hemibrevetoxin B (eq 6).[11,12] It is noteworthy that deprotonation of **1** by *n*-BuLi is much faster than butyl addition to the aldehyde.

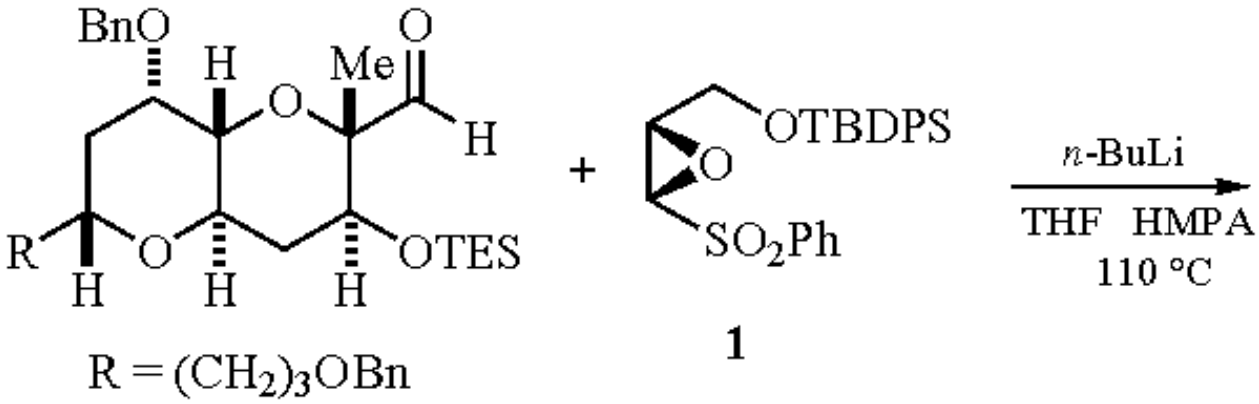

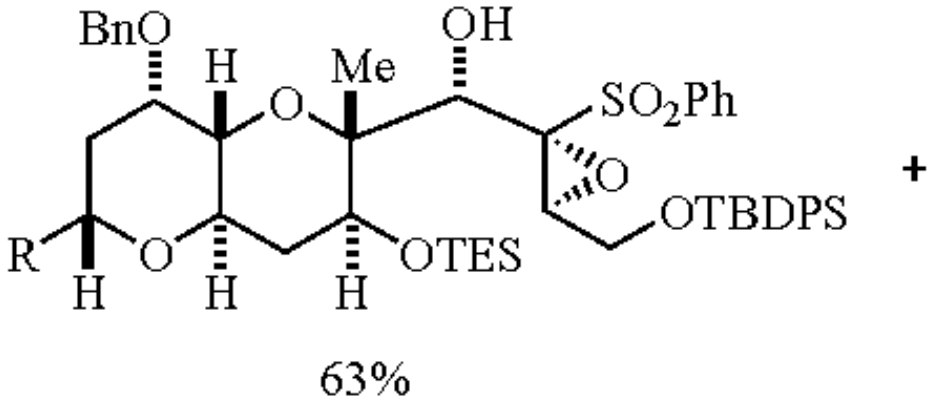

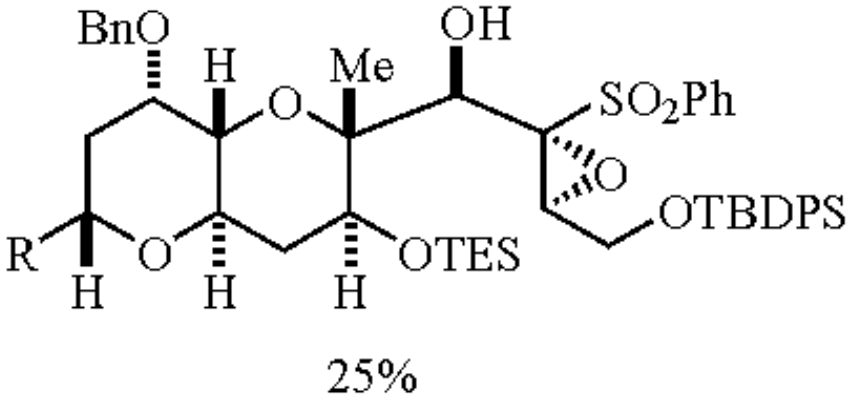

(6)

While alkylation of sulfonyl-stabilized oxiranyllithiums with primary alkyl triflates proceeds in high yield, the reaction towards epoxides is relatively slow (~2 h) and the decomposition of oxiranyllithium is marked, such that it decreases the yield, especially in the case of a *Z*-isomer (eq 7 and 8).[2] Addition of boron trifluoride diethyl etherate promotes this epoxide-epoxide coupling reaction. One of the diastereoisomers of eq 8 has been elaborated via 5-*endo* cyclization into a marine tetrahydrofuran isolated from a brown alga.[13]

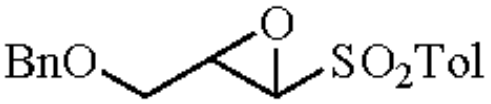
BnO
O
SO2Tol

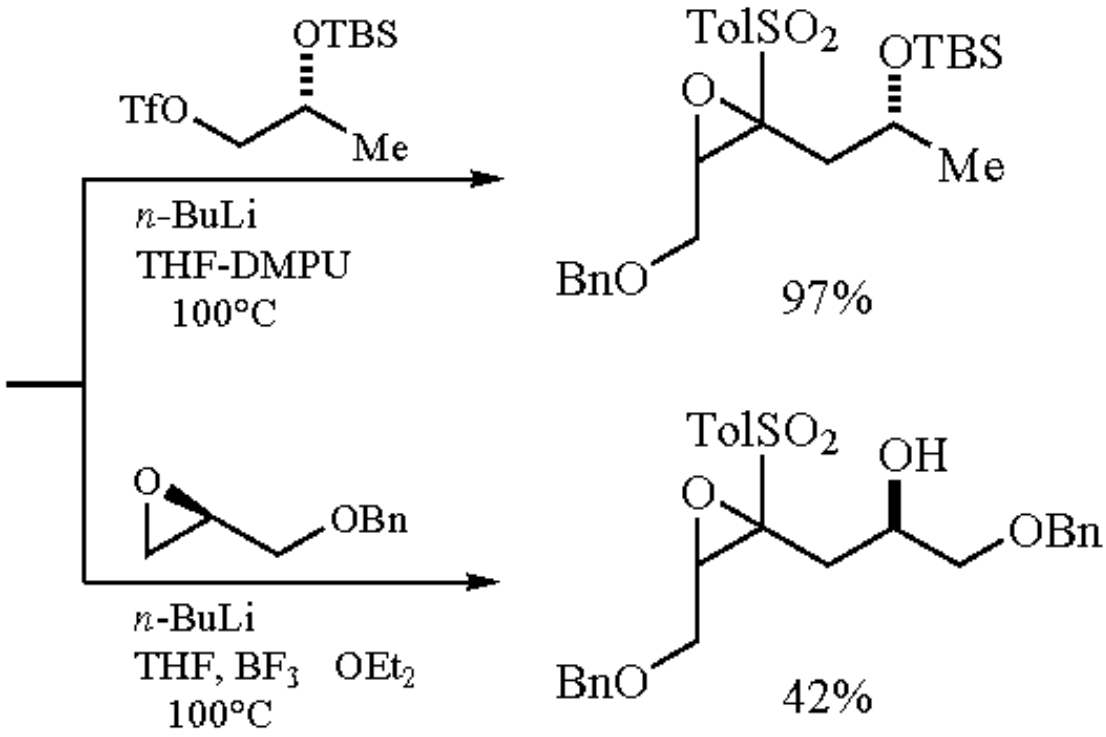
OTBS
TfO
Me
n-BuLi
THF-DMPU
100°C
TolSO2
OTBS
O
Me
BnO
97%
O
OBn
n-BuLi
THF, BF3 OEt2
100°C
TolSO2
OH
O
OBn
BnO
42%

(7)

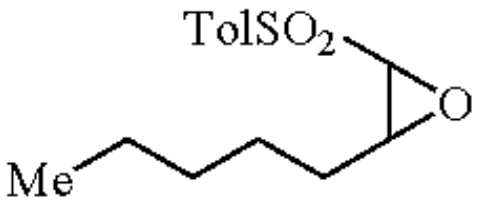
TolSO2
O
Me

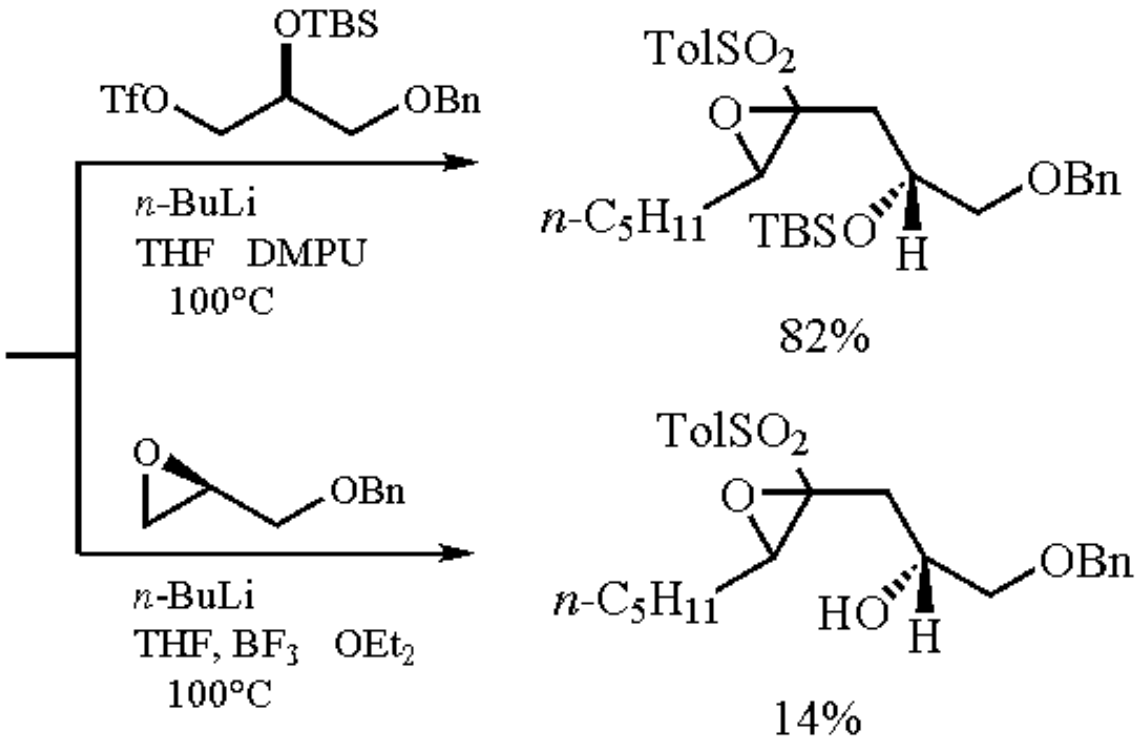
OTBS
TfO
OBn
n-BuLi
THF DMPU
100°C
TolSO2
O
OBn
n-C5H11
TBSO
H
82%
O
OBn
n-BuLi
THF, BF3 OEt2
100°C
TolSO2
O
OBn
n-C5H11
HO
H
14%

(8)

Related Reagents.

Optically active trisubstituted sulfonyl-stabilized oxiranyllithiums can be generated by deprotonation of the corresponding epoxy sulfones[14] (eq 9). Due to the diminished reactivity of the reagents by steric hindrance, the reaction with triflates requires HMPA to obtain a high yield of product (eq 10).[12]

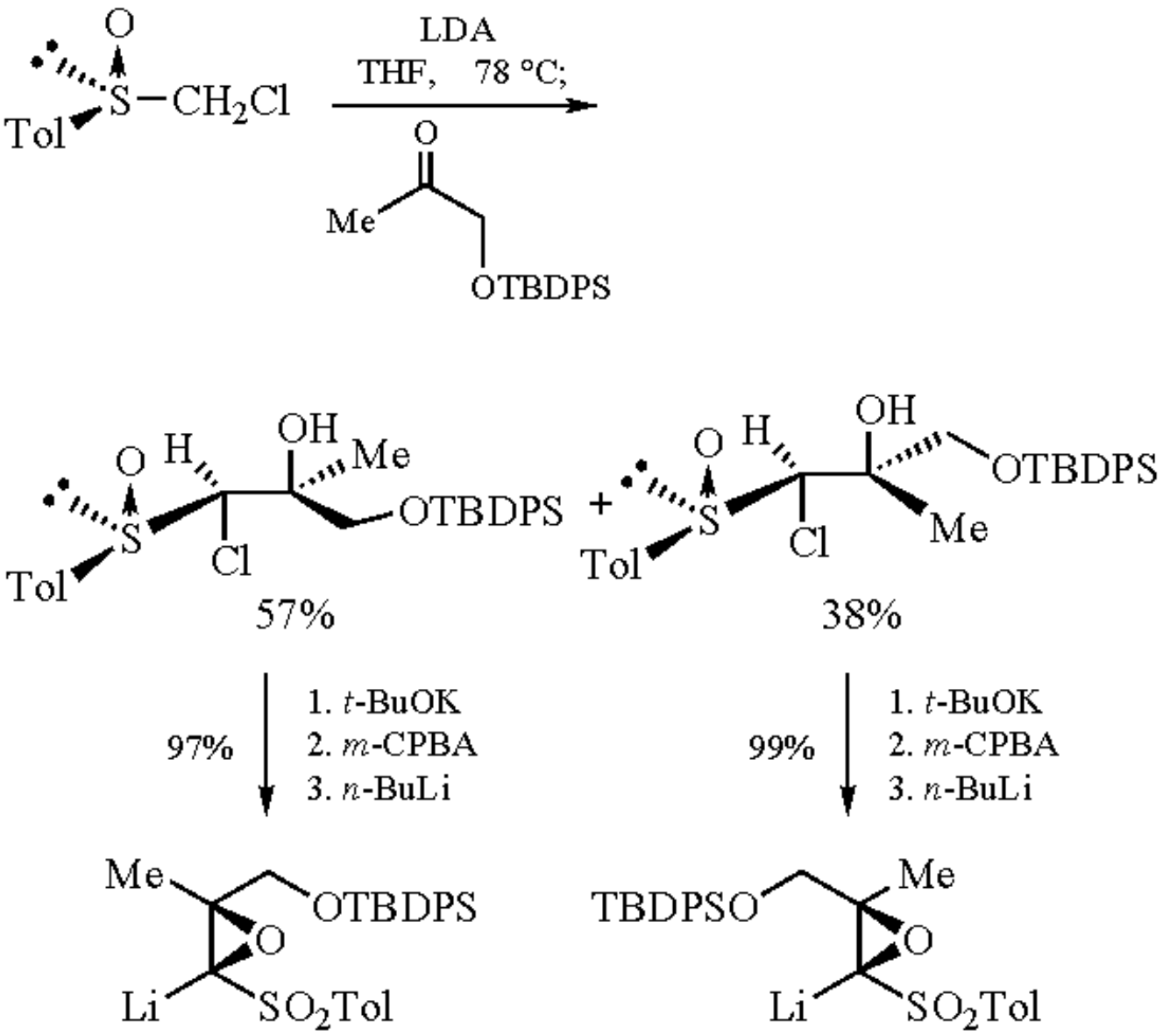

(9)

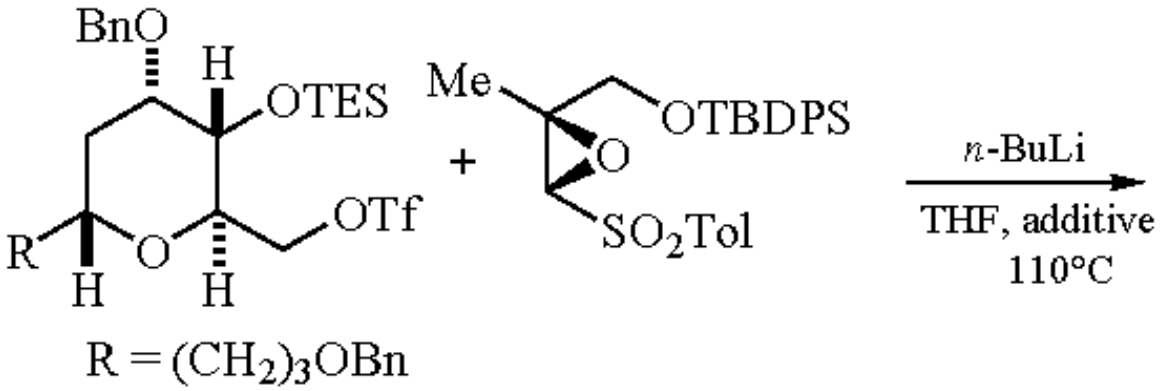

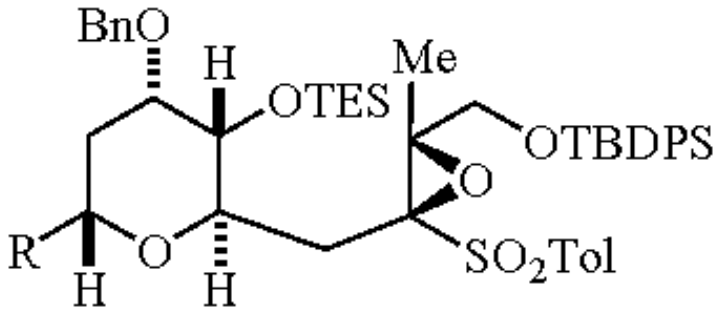

(10)

HMPA: 90%
DMPU: 57%

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1. (a) Ashwell, M.; Clegg, W.; Jackson, R. F. W., *J. Chem. Soc., Perkin Trans. 1* **1991**, 897. (b) Dunn, S. F. C.; Jackson, R. F. W., *J. Chem. Soc., Perkin Trans. 1* **1992**, 2863.
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Diisopropyl Squarate

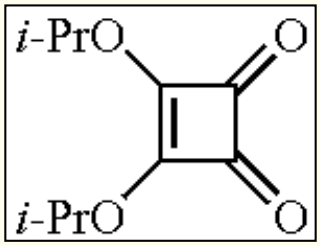

· $C_{10}H_{14}O_4$ · (198.22)

(reagent used as a highly oxygenated four-carbon building block in a wide variety of annulation reactions)

Physical Data: mp 43-44°C.

Solubility: soluble in alcohol, diethyl ether, and most organic solvents.

Form Supplied in: white crystalline solid readily prepared from squaric acid.

Purification: the compound is usually pure enough for subsequent use as obtained from the syntheses outlined below.

Preparative Methods: diisopropyl squarate (87%) is readily prepared by azeotropic removal of water from a solution of squaric acid in 1:1 benzene-2-propanol.[1,2] The same compound (81%), as well as examples of other dialkyl squarates that can not be prepared by the above route, are available from a general method involving refluxing a solution of squaric acid in the appropriate alcohol (solvent) in the presence of the corresponding orthoformate (eq 1).

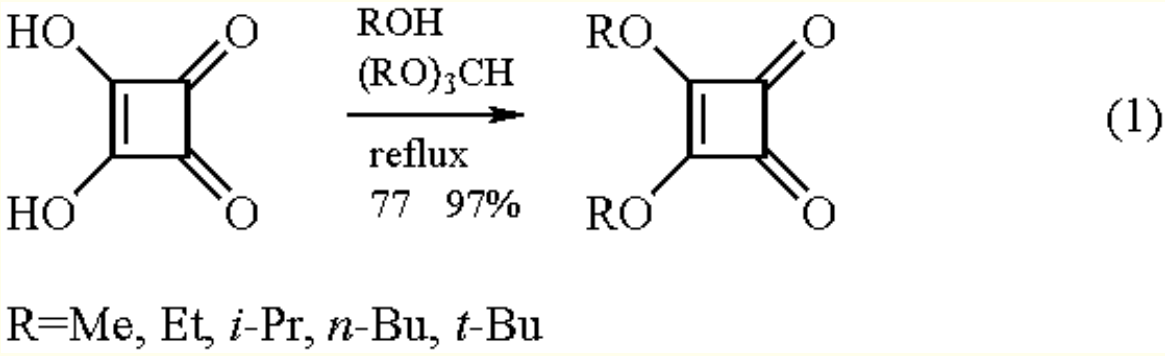

Handling, Storage, and Precautions: the solid can be stored under normal laboratory conditions for an extended period of time without apparent decomposition. However, as a precaution, storage in the refrigerator is recommended. One should be careful when preparing and handling dialkyl squarates since many members are powerful skin irritants and sensitizers.[3]

Synthesis of Substituted Cyclobutenones and Cyclobutenediones

Diisopropyl squarate and related esters are valuable synthetic intermediates for the construction of a variety of 4-substituted 3-alkoxycyclobutenediones. Monoalkylated cyclobutenones were prepared directly in one pot by treating a dialkyl squarate with the appropriate lithium reagent followed by quenching the reaction mixture with HCl or trifluoroacetic anhydride (TFAA) (eq 2).[2,4]

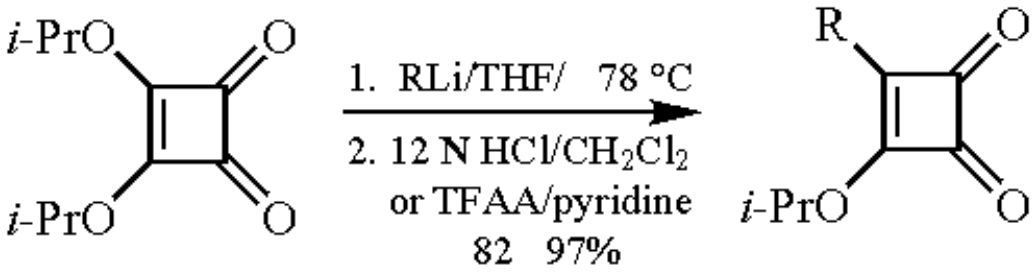

(2)

R = H, Me, C_6H_5, ≡—C_4H_9

A modification of the above procedure leads to a general synthesis of substituted cyclobutenedione monoketals.[5] An illustrative example is the synthesis of 2-phenyl-3,4,4-trimethoxycyclobutenone (85%) upon treatment of dimethyl squarate with phenyllithium followed by quenching with methanol and TFAA. Subsequent treatment of this product with methyllithium followed by TFAA gave 2-phenyl-3-methyl-4,4-dimethoxycyclobutenone in 94% yield (eq 3). By changing the order of substituent introduction, the regioisomer was obtained in good yield. These reaction sequences provide access to a variety of isomeric cyclobutenedione monoacetals in a regiodefined fashion. A related method leading to monoacetalization has also appeared.[6]

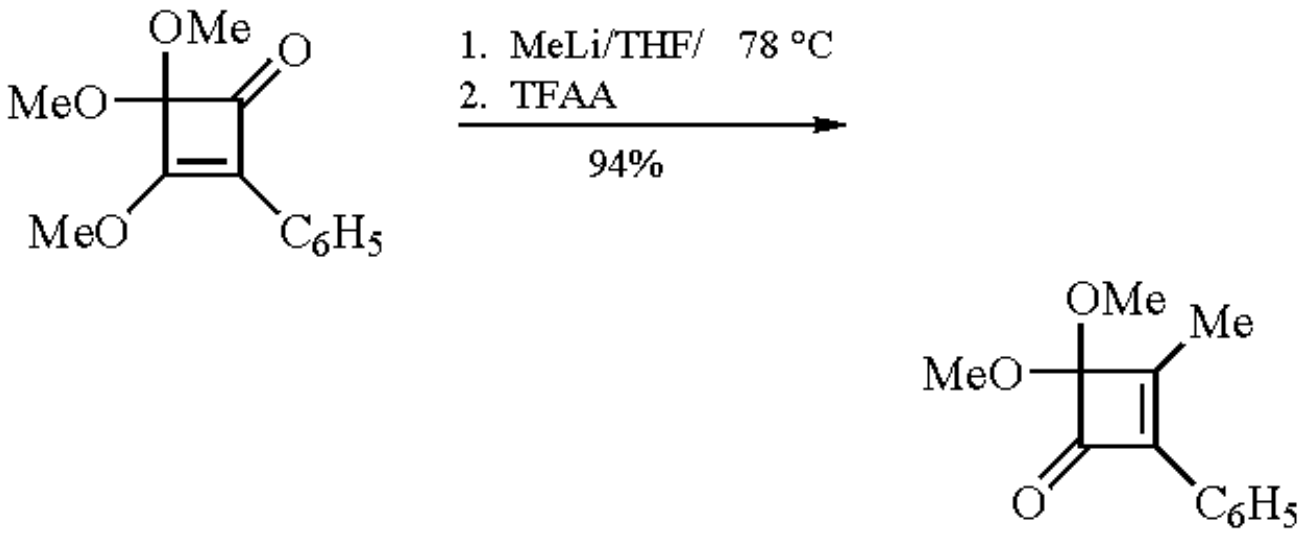

(3)

3-Tributylstannyl-4-isopropoxycyclobutenedione is readily prepared in 65% yield from diisopropyl squarate upon treatment with 1,1,1-trimethyl-2,2,2-tri-*n*-butyldistannane in the presence of a catalytic amount of cyanide ion.[7] Stille cross-coupling reactions with alkyl iodides then provide a complementary route to 3-alkyl-4-isopropoxycyclobutenediones. This work was extended to include the synthesis of 3-acylcyclobutenediones, a rare class of compounds in which the cyclobutenediones bear an electron-withdrawing group (eq 4).[8] The starting material is 3-(piperidinyl)-4-tri-*n*-butylstannylcyclobutenedione, prepared from 3-tri-*n*-butylstannyl-4-isopropoxycyclobutenedione upon treatment with piperidine.

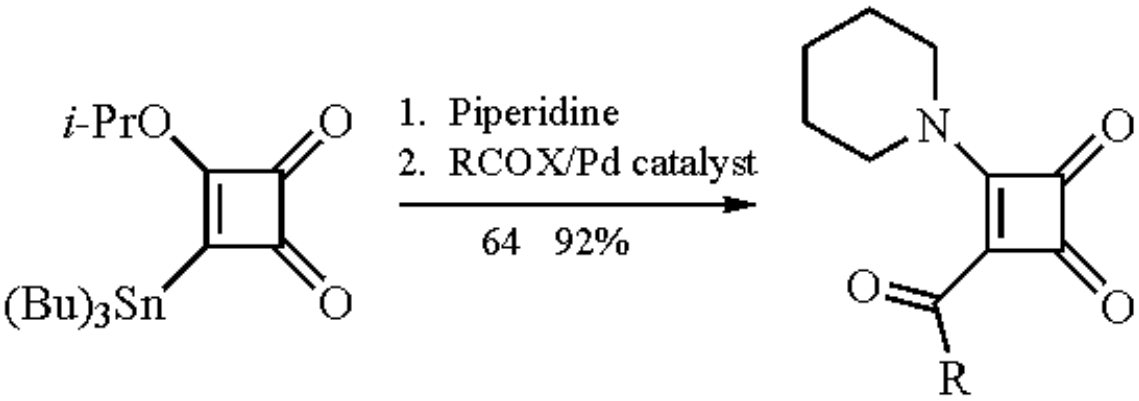

(4)

R=C_6H_5, *p*-(MeO)C_6H_4, Et, *o*-(MEM)C_6H_4

Numerous examples of 4-allylcyclobutenones are available from the corresponding 4-hydroxy or 4-alkoxy analogs upon treatment with allylsilanes in the presence of Lewis acids. The example outlined in eq 5 provides evidence for a carbocationic intermediate in such

transformations. Specifically, both regioisomeric starting cyclobutenones give nearly quantitative yields of a single adduct.[9] This and related examples lead to the general conclusion that allylation of unsymmetrically substituted 4-hydroxycyclobutenones takes place predominately at that site best able to stabilize cationic charge density. A number of heterocyclic, carbocyclic, and acyclic 4-allylcyclobutenones are available from readily available cyclobutenedione monoketals, a transformation that has recently been reviewed.[10] The example provided in eq 6 is illustrative.

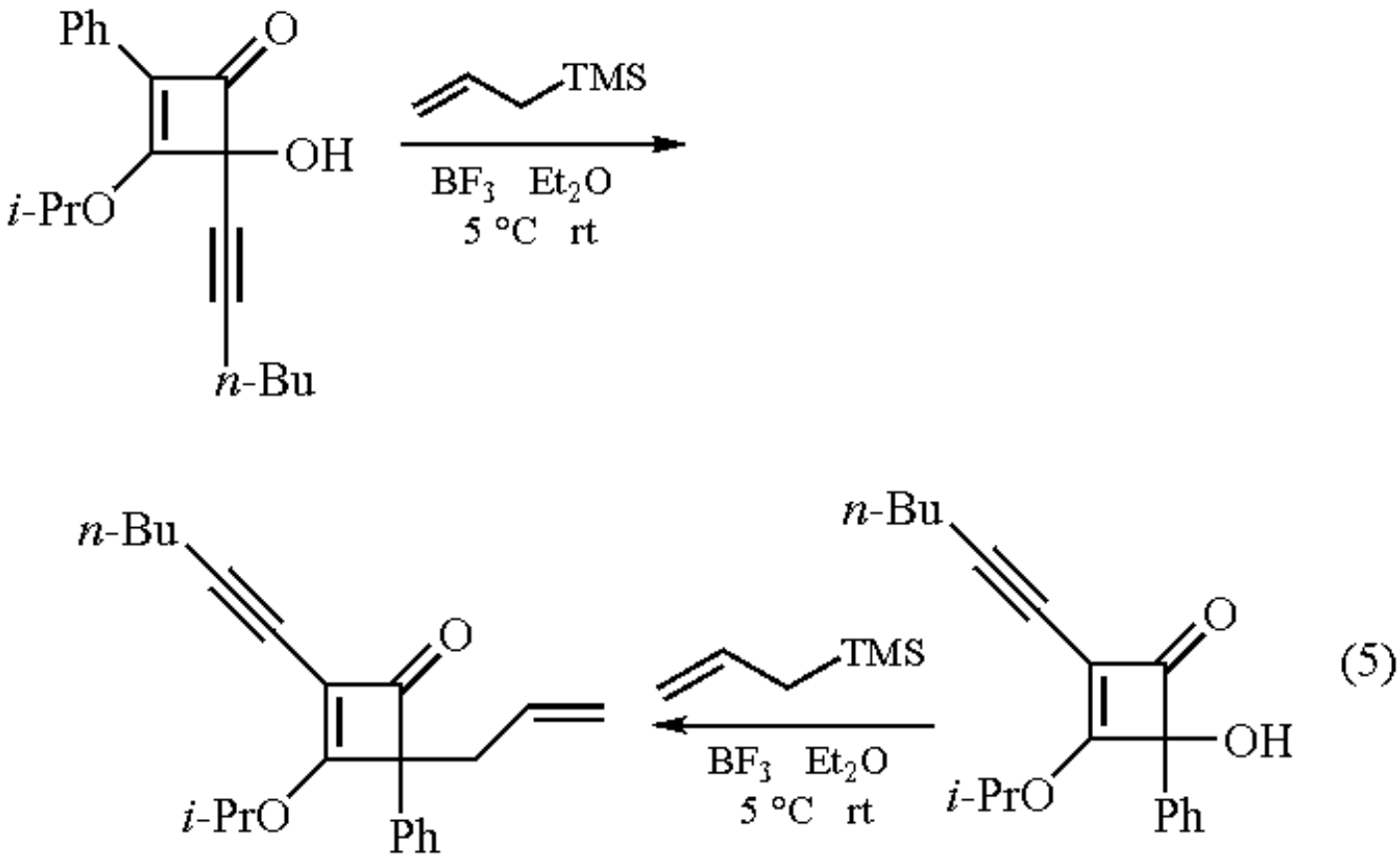

94 99%

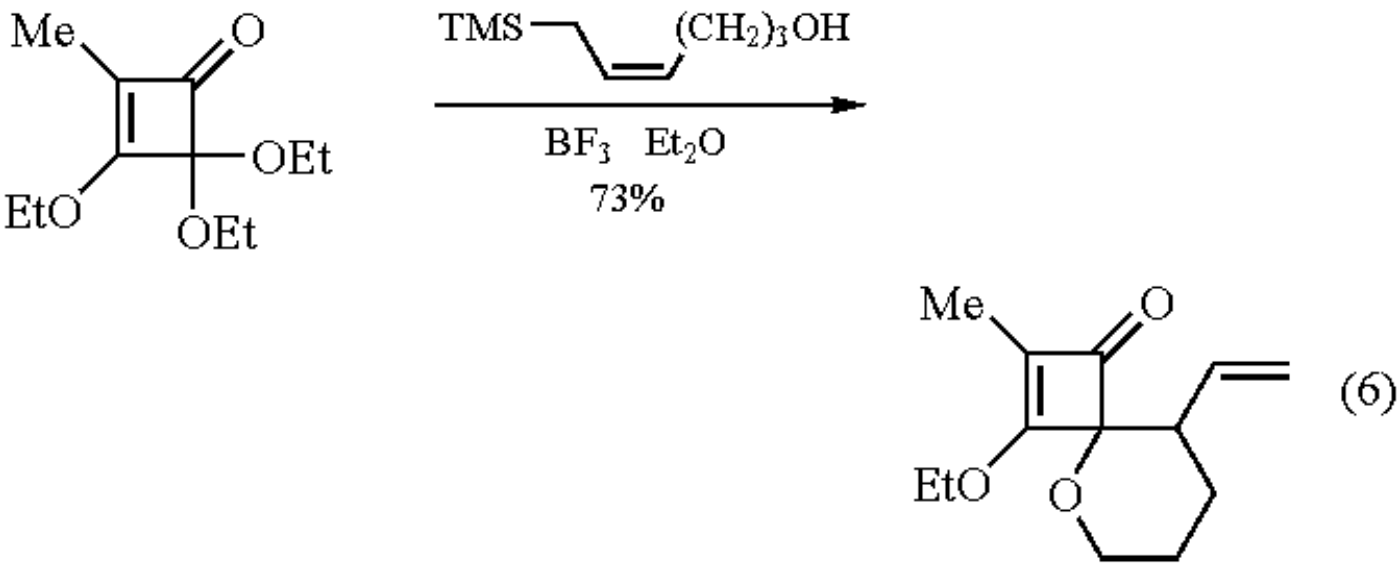

Synthesis of 4-Methylidenecyclobutenones

A variety of cyclobutenediones and cyclobutenones have been shown to react with dimethyl titanocene to provide the corresponding methylidene product.[11] For example, 3-phenyl-4-isopropoxycyclobutenedione reacts at the ketonic carbonyl group to give 4-methylidene-3-phenyl-2-isopropoxycyclobutenone in 75% yield (eq 7). The reaction also takes place with dialkoxy squarates. For example, diisopropyl squarate gives 4-methylidene-2,3-diisopropoxycyclobutenone in 80% yield.

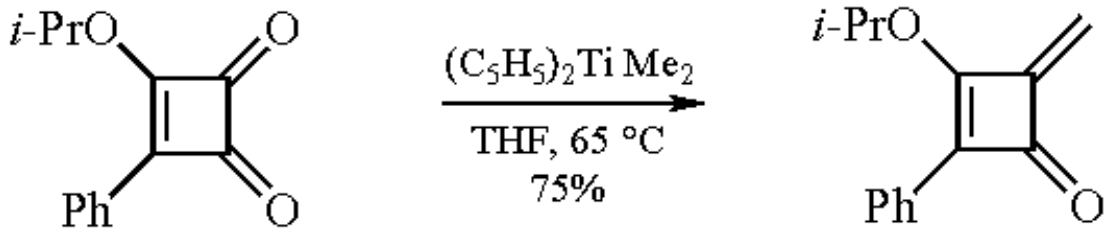

(7)

In a related study, dialkyl squarates were shown to undergo olefination under Wittig or Horner-Emmons reaction conditions.[12] For example, eq 8 outlines Wittig olefination of diisopropyl squarate to give the alkylidene product in 88% yield in an *E*/*Z* ratio of 1:1. Horner-Emmons conditions using a phosphonate gave the same product (91%) but in an *E*/*Z* ratio of 1:19. It is noteworthy that simple acid hydrolysis of the product gives squarylacetic acid esters, potentially valuable active methylene compounds.

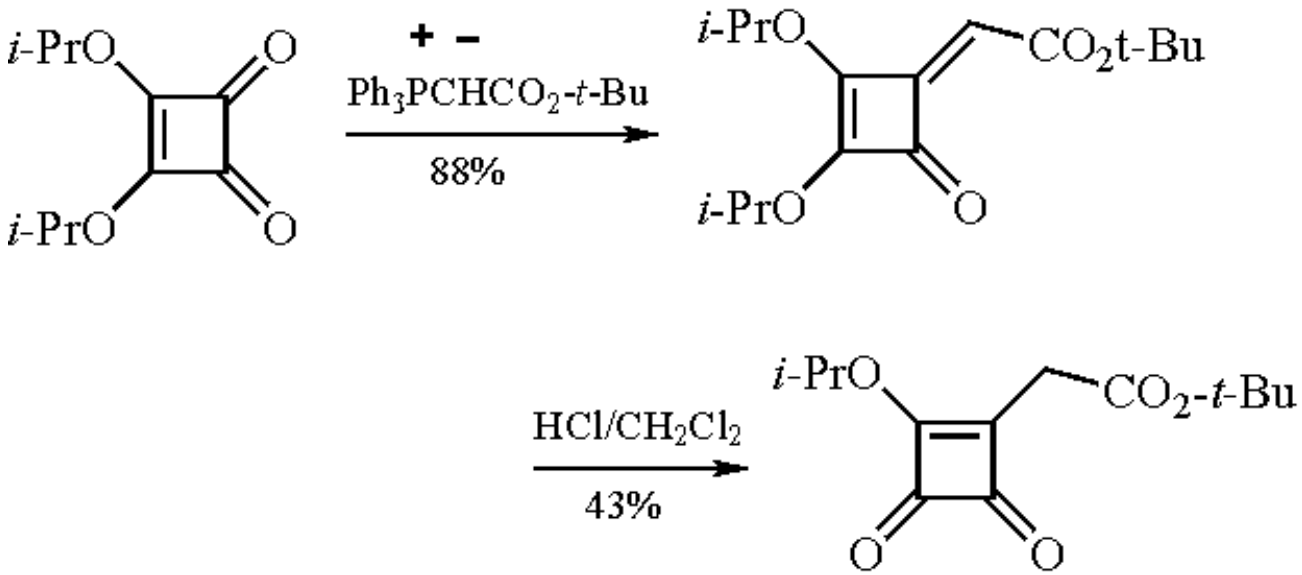

(8)

Synthesis of Bicyclo[3.2.0]heptenones

4-Allylcyclobutenones, available as described above or from direct allylation of cyclobutenediones upon treatment with allyllithium reagents, are valuable reagents for the synthesis of highly substituted bicyclo[3.2.0]heptenones. For example, thermolysis of dialkoxy squarate-derived 4-allyl-2-ethenyl-3-methyl-4-trimethylsiloxycyclobutenone (refluxing toluene) provides the corresponding bicycloheptenone in nearly quantitative yield (eq 9).[13] This general and efficient transformation is envisaged to proceed via electrocyclic ring opening of the starting cyclobutenone to give a vinylketene intermediate that is disposed to undergo intramolecular 2+2 cycloaddition to the proximal allyl double bond.

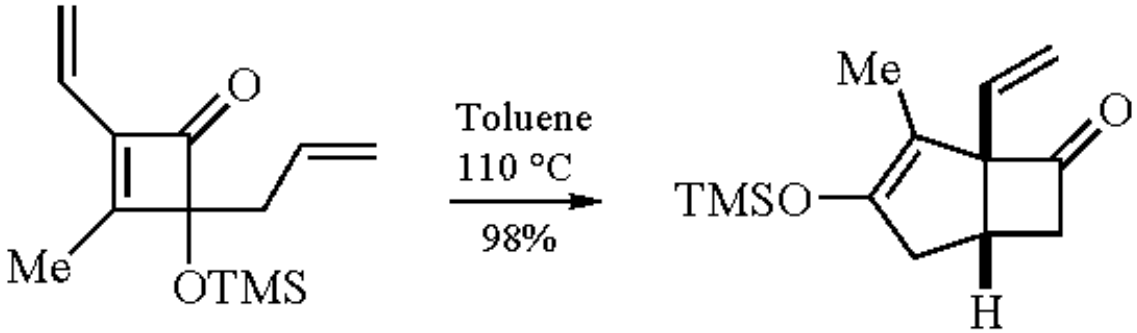

(9)

Synthesis of Quinones and Related Compounds

A particularly important transformation of dialkyl squarates is their conversion to cyclobutenones bearing a site of unsaturation at position 4. Such compounds undergo ring expansion to the corresponding aromatic compounds, thus constituting a valuable annulation method. Numerous examples of this method were reviewed in 1995.[14] Selected examples are provided in eq 10-13.[15-19] It is noted that the π-unsaturation at position 4 can be found in aryl, alkenyl, or acyl groups. The annulation method is general and accommodates multiple substitution patterns. An important example illustrating these points is its use as a key step in the synthesis of porphyrin-quinones as outlined in eq 13.

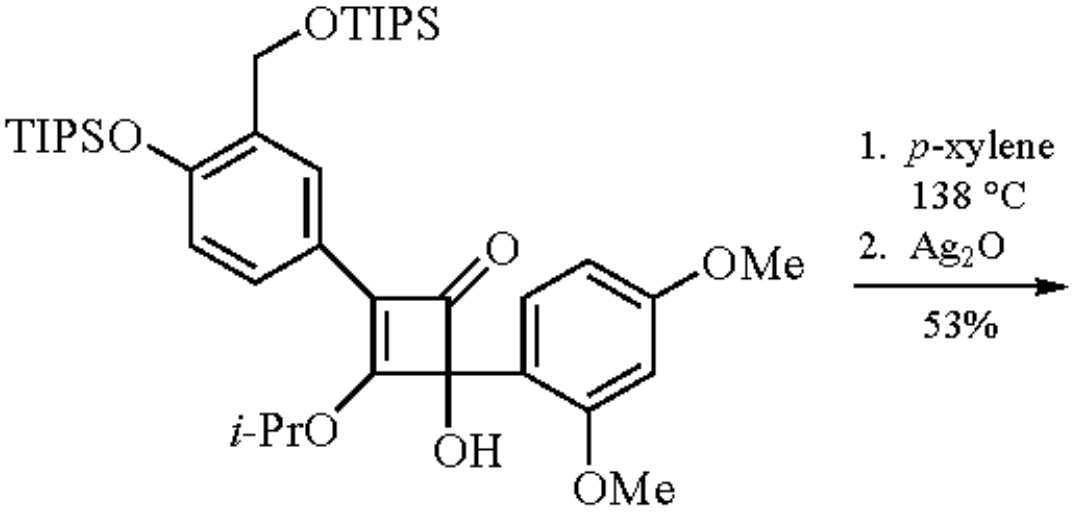
OTIPS
TIPSO
O
OMe
i-PrO
OH
OMe
1. p-xylene
138 °C
2. Ag2O
53%

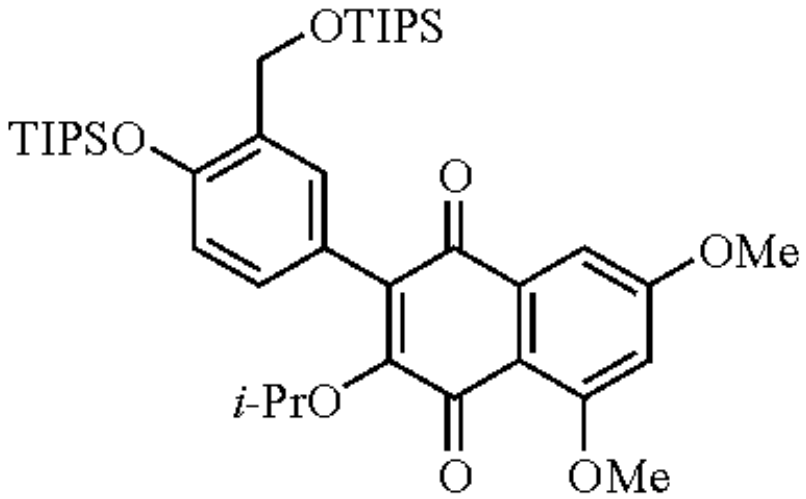
OTIPS
TIPSO
O
OMe
i-PrO
O
OMe

(10)

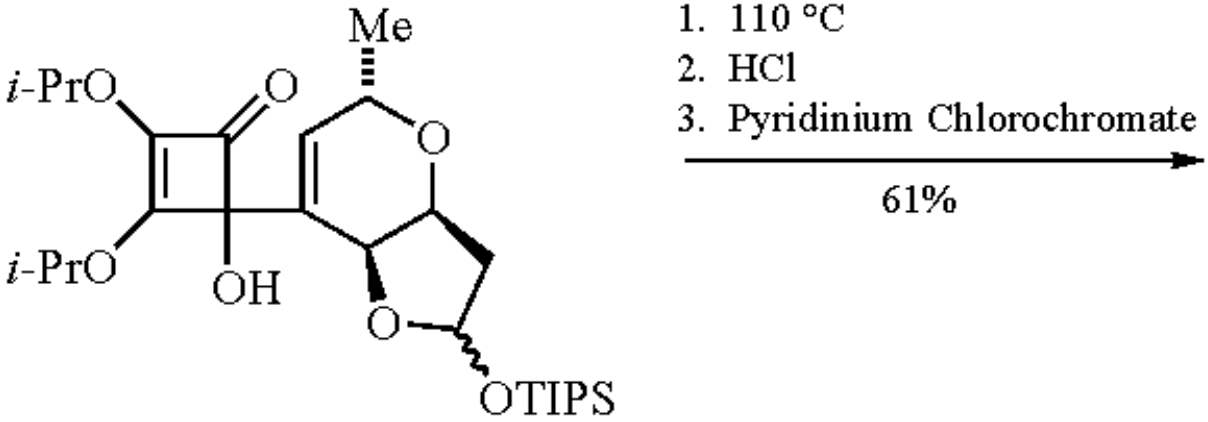
Me
i-PrO
O
O
i-PrO
OH
O
OTIPS
1. 110 °C
2. HCl
3. Pyridinium Chlorochromate
61%

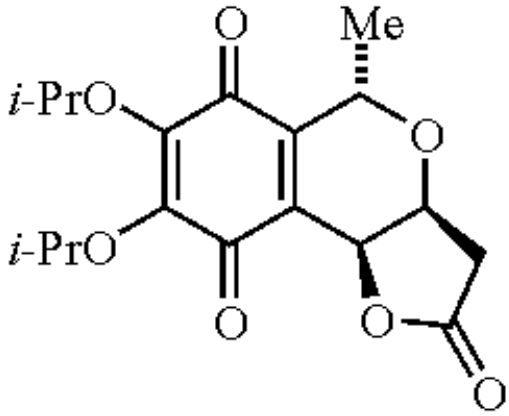
O
Me
i-PrO
O
i-PrO
O
O
O

(11)

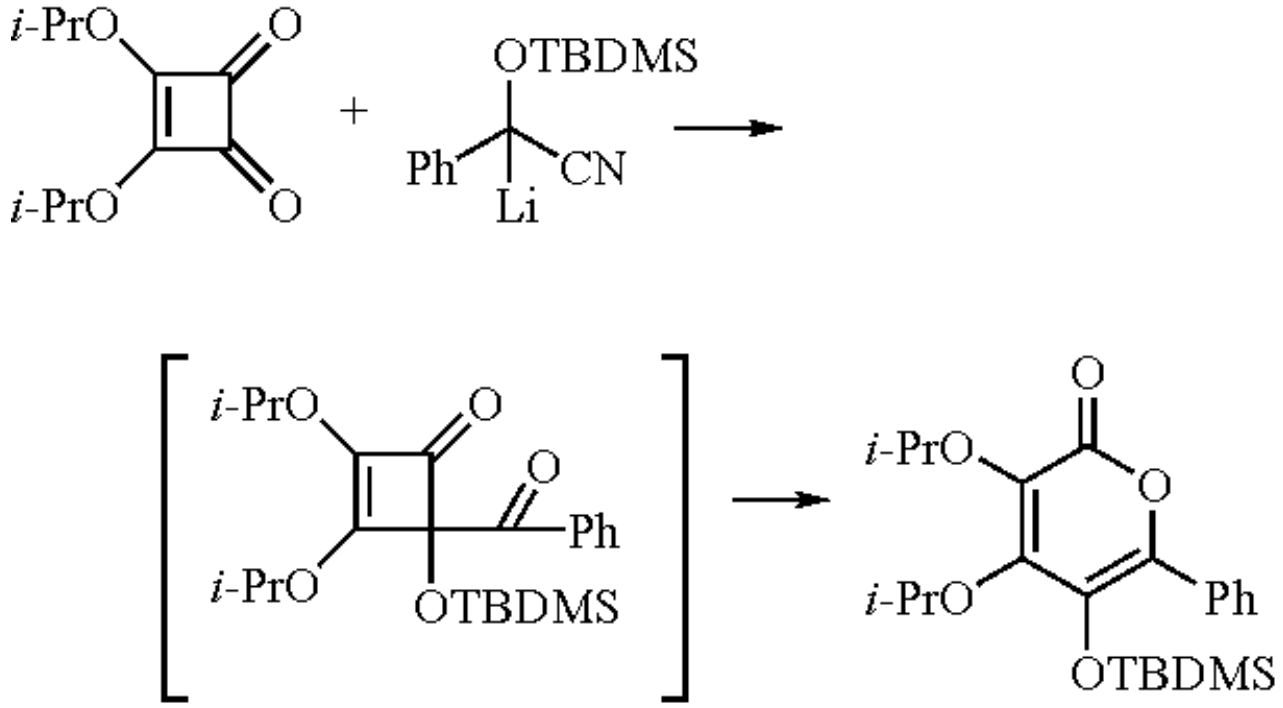

(12)

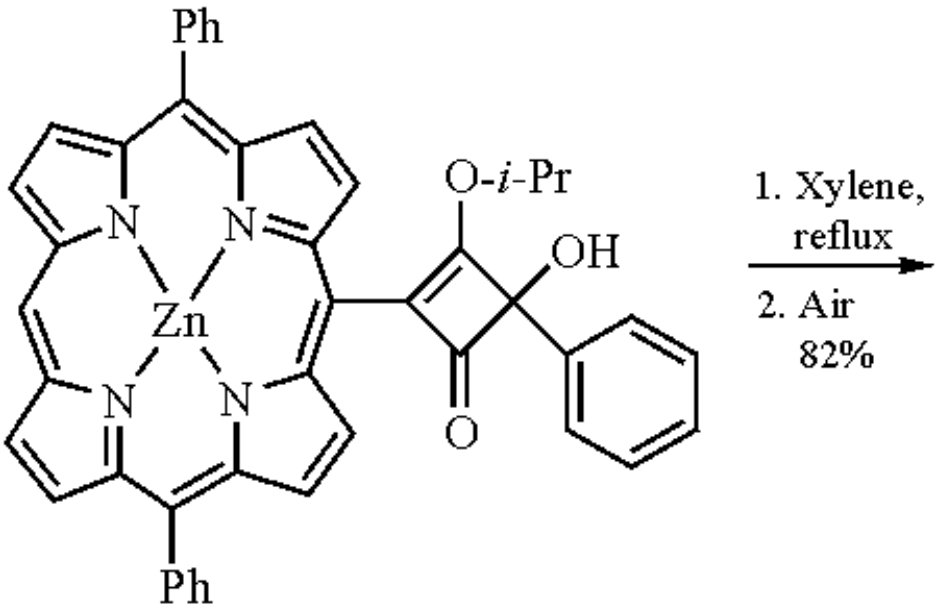

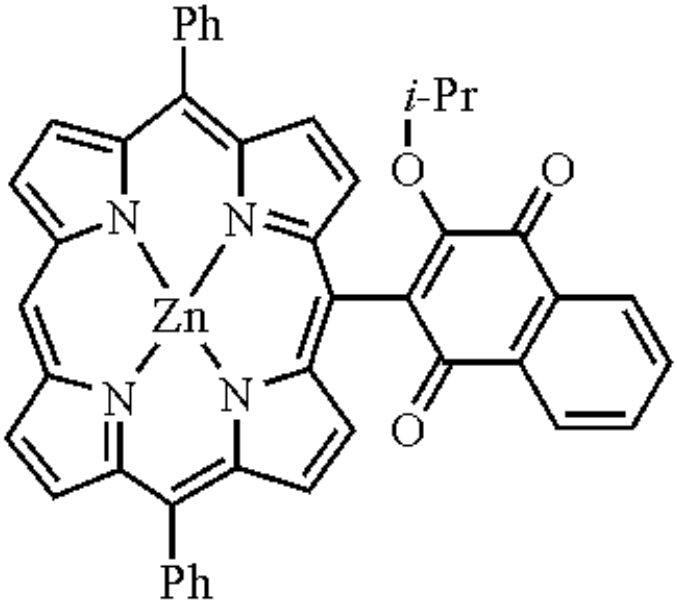

(13)

The above reactions are envisaged to involve 4π electrocyclic ring opening of the cyclobutenone followed by 6π electrocyclic ring closure of the resulting dienylketene.

Interesting variations of the above reactions are outlined in eq 14 and 15. The former depicts a general transformation of a 4-allenylcyclobutenone to a quinone methide intermediate that is trapped in an intramolecular Diels-Alder cycloaddition.[20] This appears to be a general reaction and represents one of the few known routes to these reactive intermediates under neutral (thermal) conditions. The latter provides an example of a general reaction of 4-alkynylcyclobutenones. These undergo electrocyclic ring opening to the corresponding dienynylketene followed by ring closure to a diradical intermediate which suffers H-atom transfer to give the quinone directly.[14,21,22]

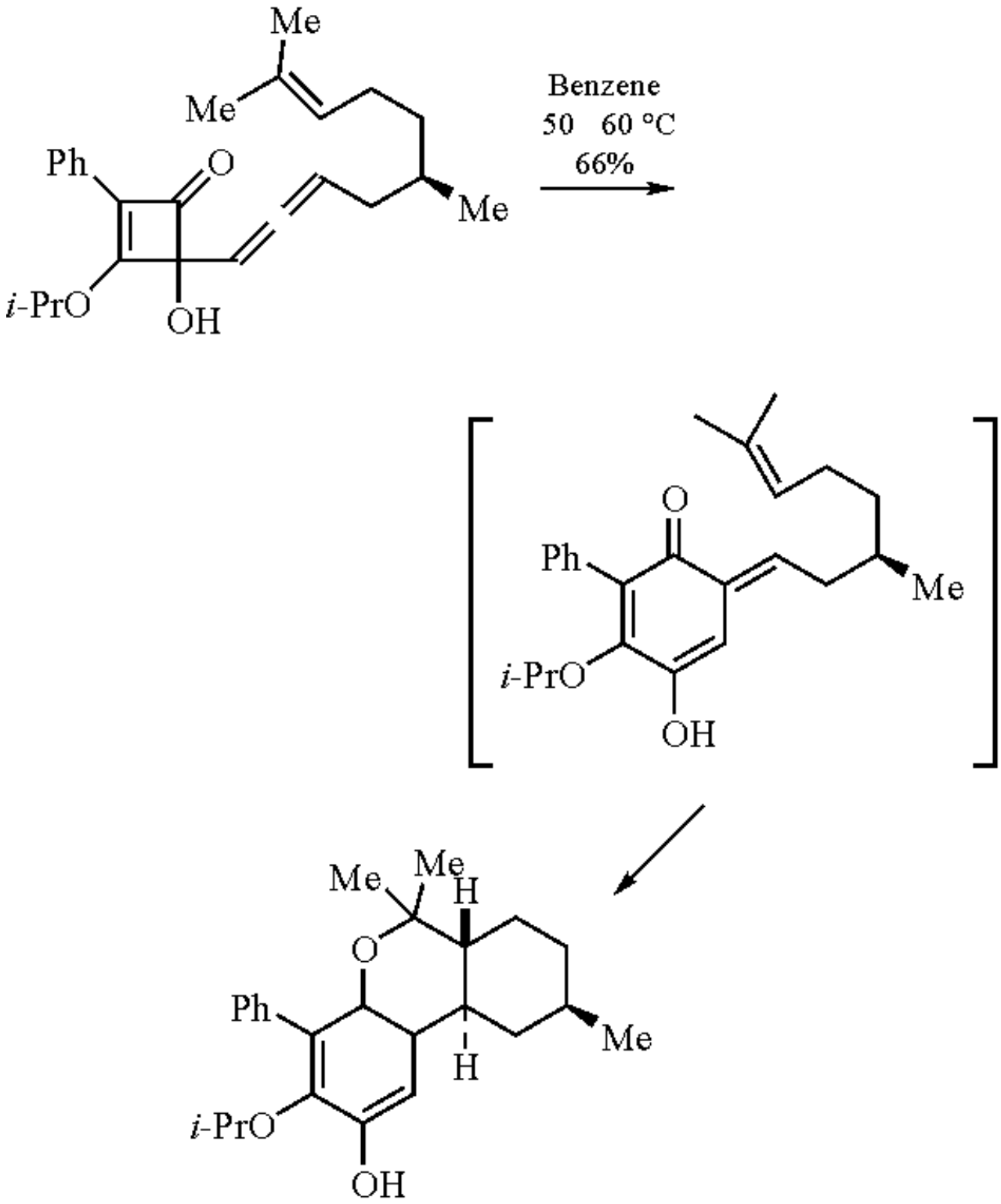

(14)

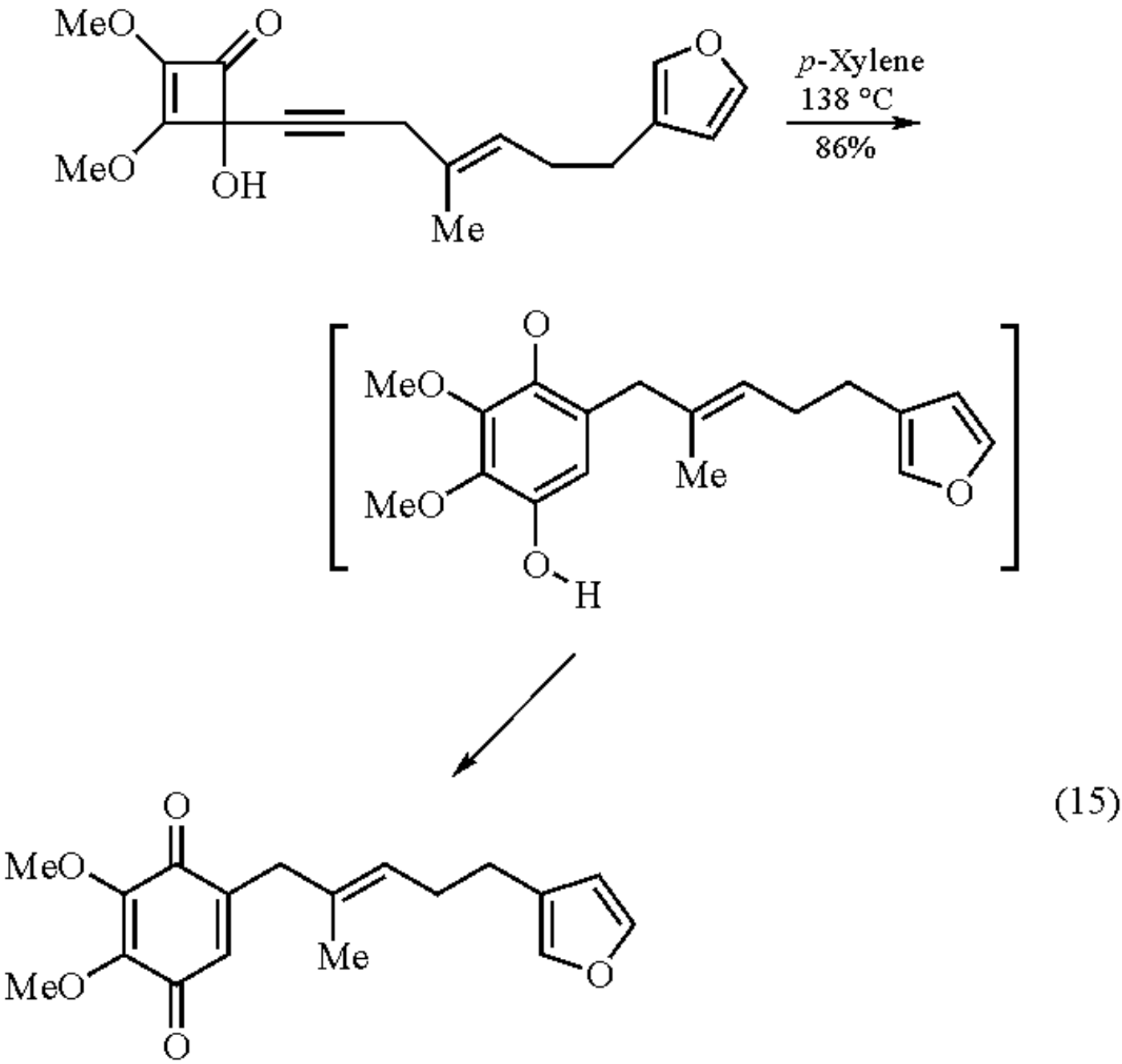

(15)

A diversity of compounds is available by this annulation methodology. Other ring systems stemming from this method include angucyclines,[23] benzophenanthridines,[24] piperidinoquinones,[25] benzofurans,[26] pyranoquinones,[27] naphthols,[28] naphthalenes,[29,30] indolizines,[31] naphthoquinones,[32] dihydroquinolines,[33] 2-pyridinones,[34] xanthones,[35,36] and highly oxygenated angularly fused polycyclic aromatic compounds.[37]

A particularly interesting example is outlined in eq 16.[29] Here the diisopropyl squarate-derived alkynylcyclobutenone provides the ring-opened allene upon treatment with butyllithium. Subsequently, the allene undergoes electrocyclic ring closure (toluene, 110°C) to give the substituted naphthalene.

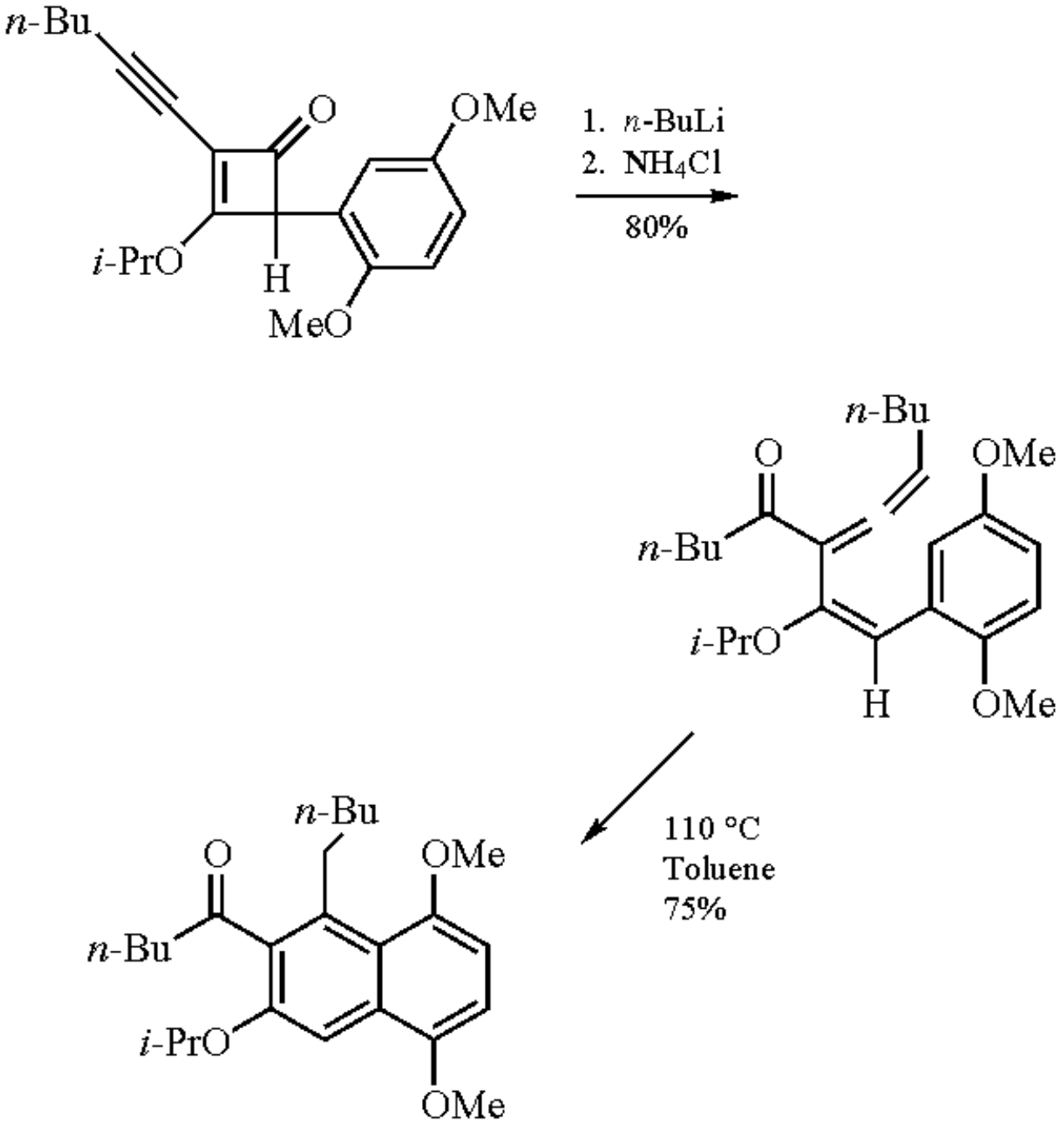

(16)

Cascade Rearrangements Leading to Polycyclic Compounds

A series of papers have appeared which outline a remarkable cascade rearrangement induced by the addition of 2 equiv of an alkenyl or alkynyl lithium reagent to squarate esters. These remarkable reactions result in the stereo- and regio-controlled conversion of achiral reagents to complex polycyclic products possessing several sterogenic centers.[38] A relatively simple example is outlined in eq 17, which shows the conversion of diisopropyl squarate to an α,β-bis(alkoxyl)-γ-hydroxycyclopentenone, a common structural array found in the products arising from most of the cascade rearrangements. The reader is referred to an excellent review of this topic for a detailed analysis of the mechanism as well as an overview of the synthetic scope of this remarkable reaction.[38] Selected examples revealing the exceptional complexity of structural features available in simple laboratory operations are provided in eq 18 and 19.

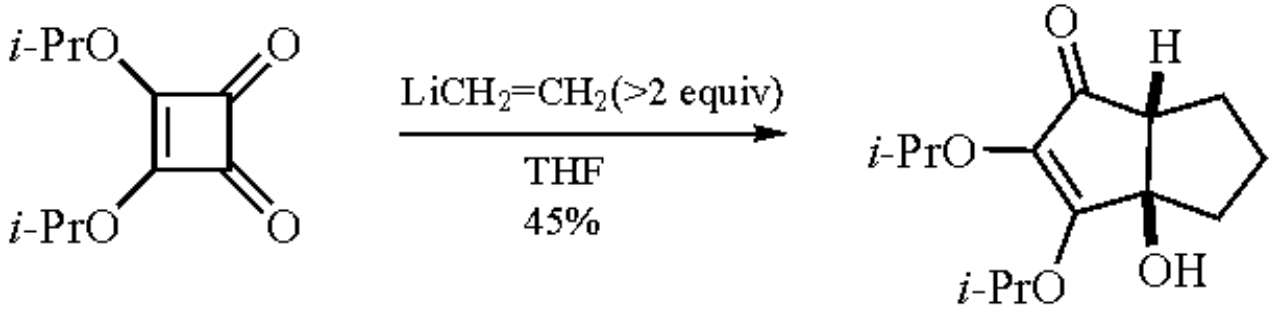

(17)

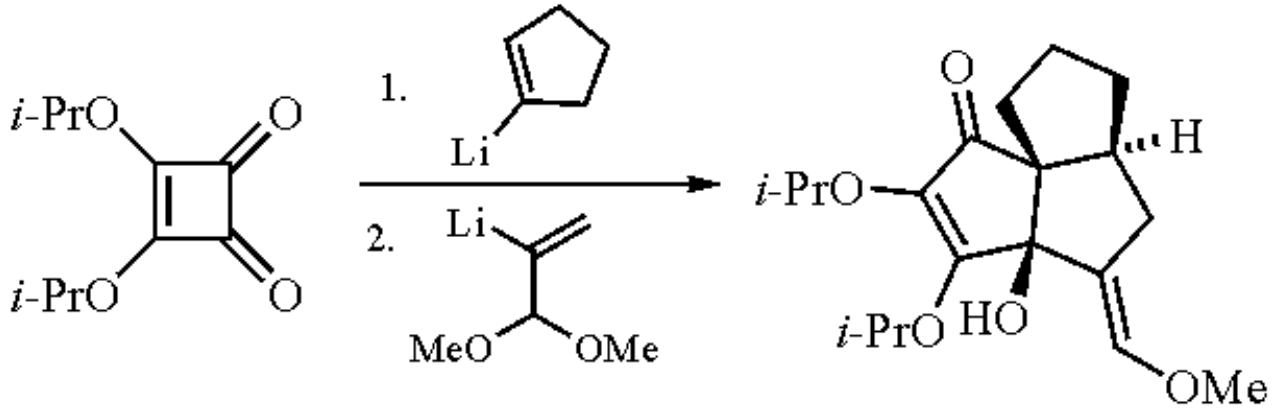

(18)

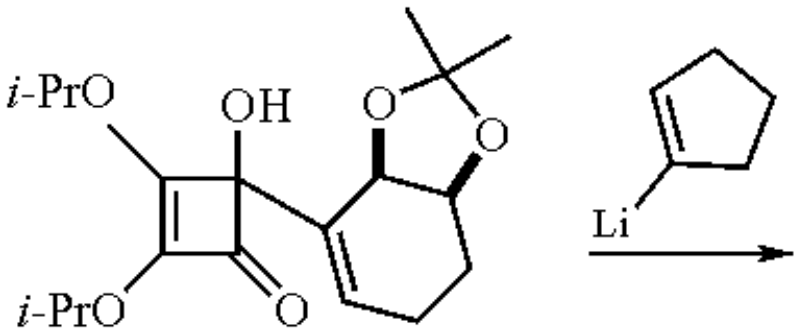

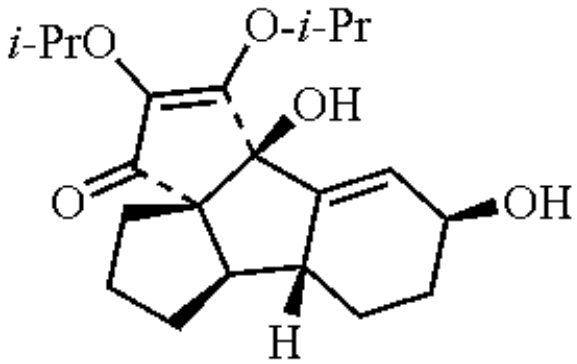

(19)

Synthesis of Polyquinanes from Dialkyl Squarate-derived Bicyclo[3.2.0]heptenones

A method complementary to the above squarate cascade starts with dialkyl squarate-derived bicyclo[3.2.0]heptenones.[39-42] Illustrative examples are outlined in eq 20-23. These reactions proceed via an initial oxy-Cope ring expansion upon treatment of the starting bicycloheptenone with an alkenyllithium reagent. The resulting bicyclo[6.2.0]undecenes are generally not isolated but subjected directly to work-up conditions that hydrolyze the trimethylsilyl enol ether and thus induce an intramolecular transannular ring closure to the corresponding polyquinanes.

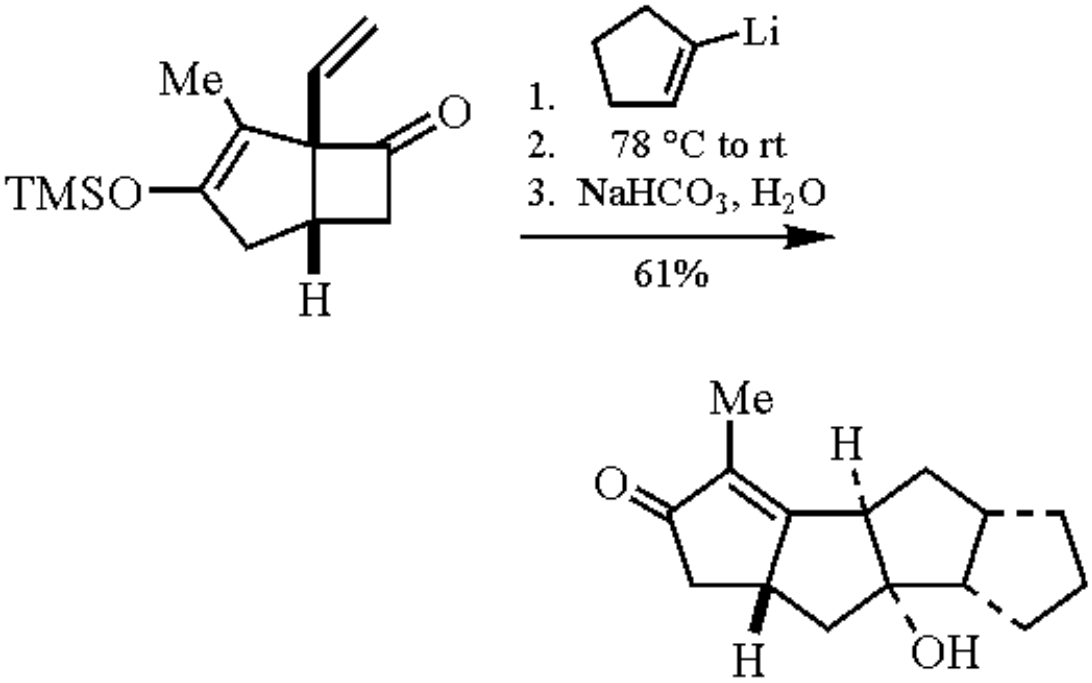
Me
O
TMSO
H
Li
1.
2. 78 °C to rt
3. NaHCO3, H2O
61%
Me
H
O
H
OH

(20)

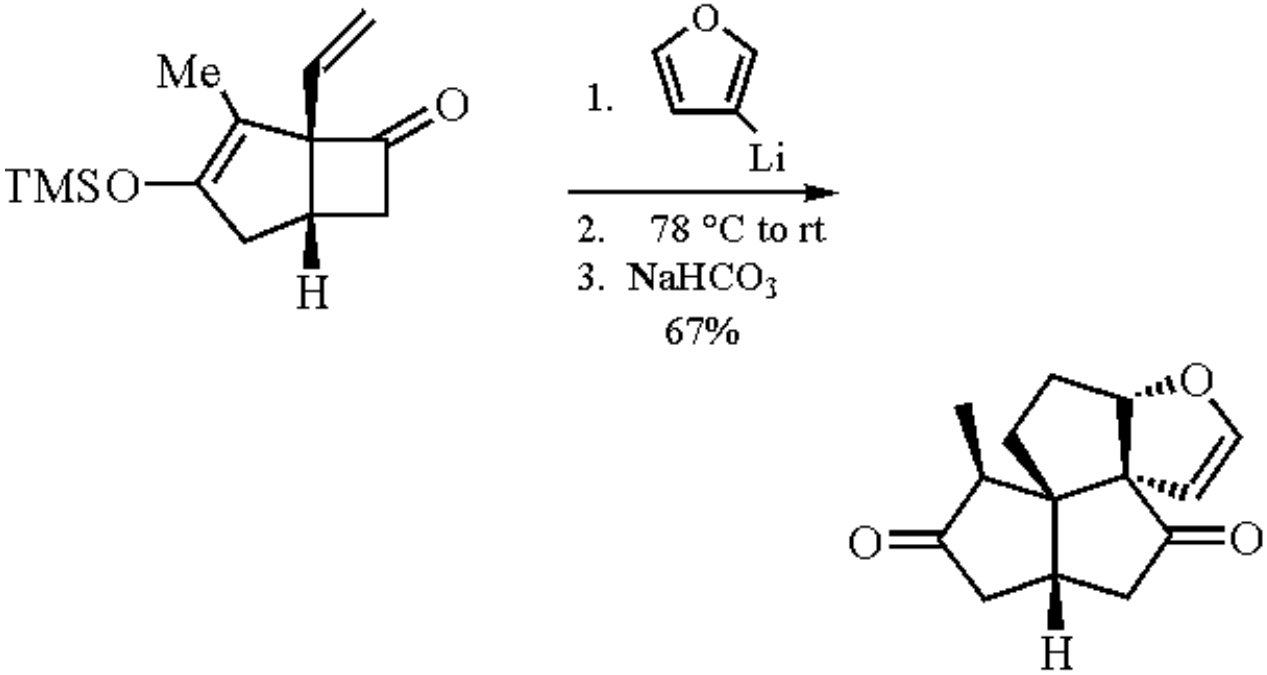
Me
O
TMSO
H
O
1.
Li
2. 78 °C to rt
3. NaHCO3
67%
O
O
O
H

(21)

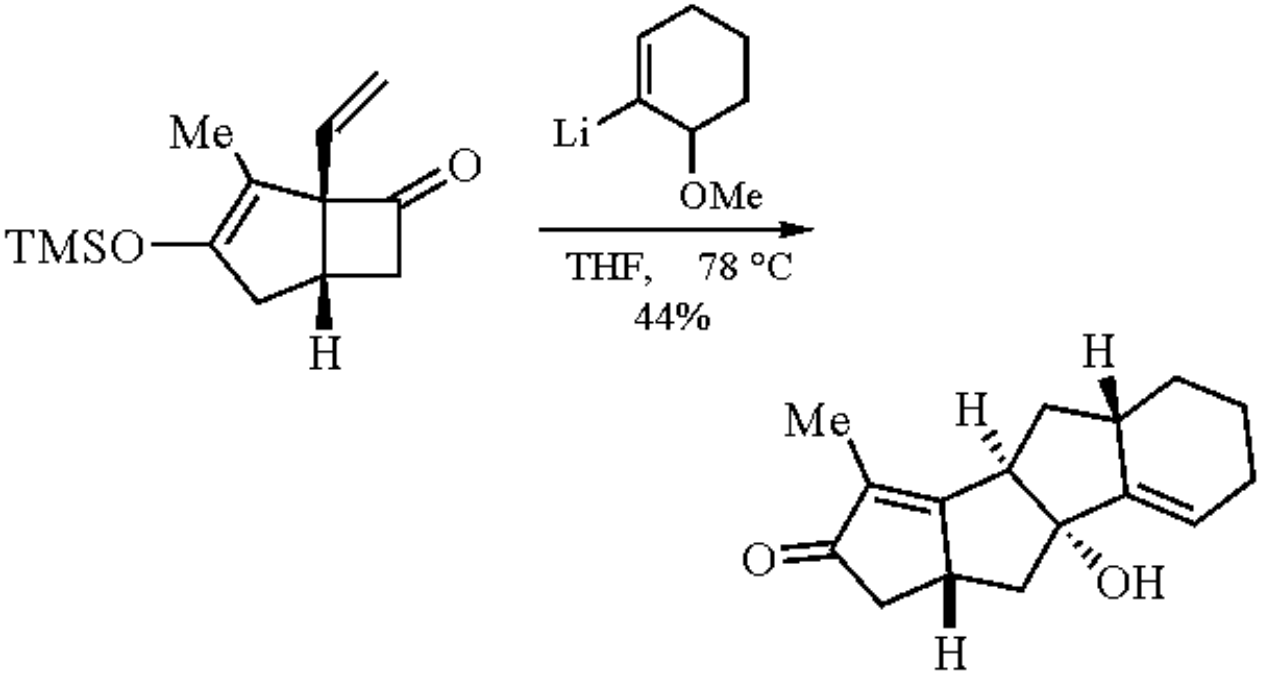

(22)

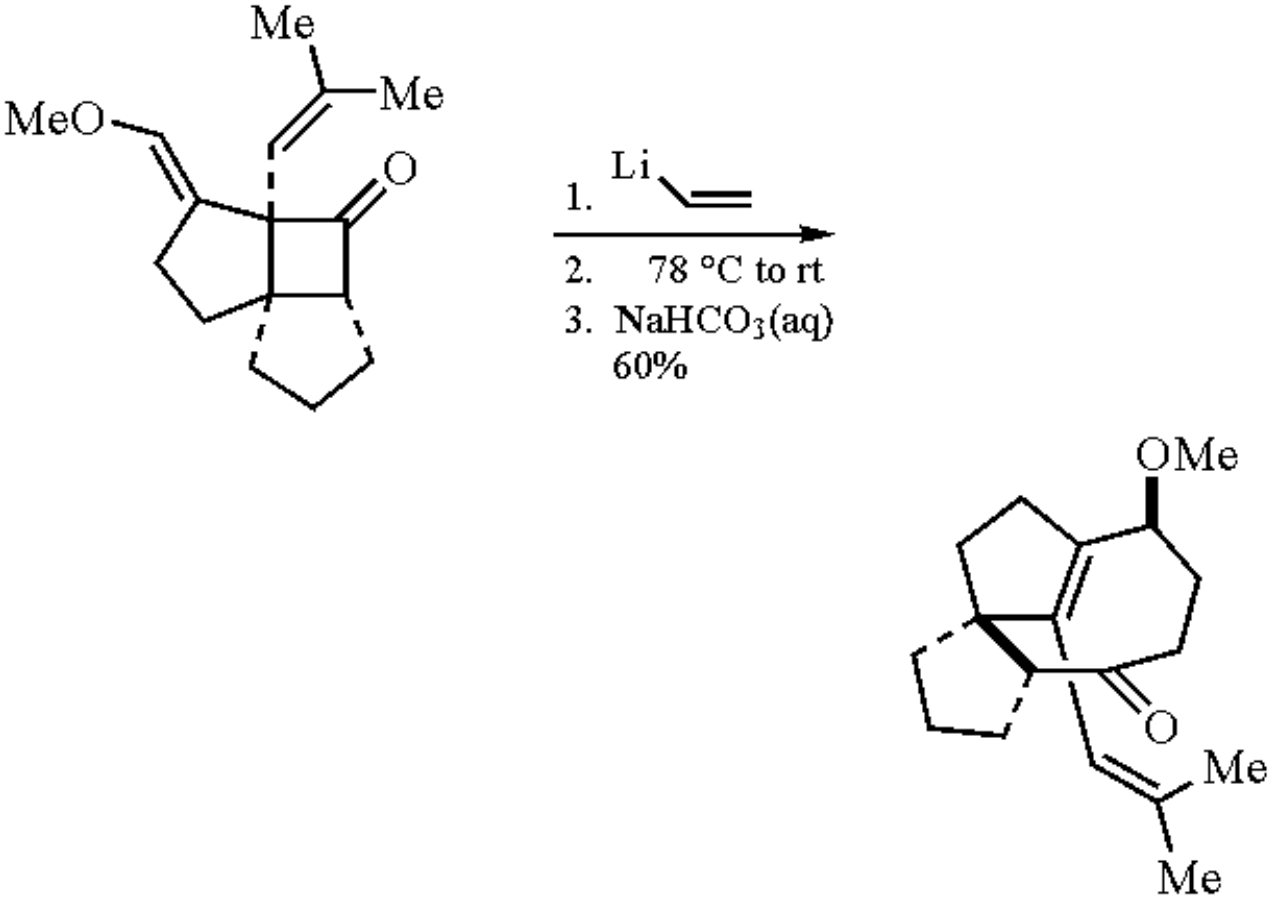

(23)

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Tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]chromium(0)[1]

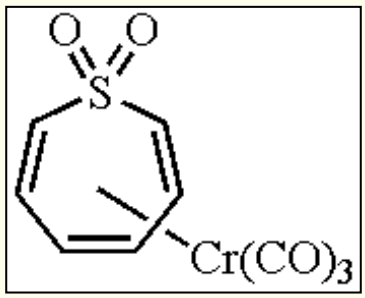

[1452247-44-5] · $C_9H_6CrO_5S$ · (278.201)

(reagent used for promotion of [6+2], [6+4], [6+2+2], and [6+2+2+2] higher-order cycloaddition reactions)

Physical Data: red solid; mp 173-174°C.

Solubility: THF, ethyl acetate, CH_2Cl_2, $CHCl_3$, and 1,2-dichloroethane.

Form Supplied in: prepared from thiepin-1,1-dioxide and trisacetonitriletricarbonylchromium.

Purification: flash column chromatography on silica gel using hexanes/ethyl acetate.

Handling, Storage, and Precautions: the compound can be handled in air and is generally stable for several months when stored in the freezer.

Preparative Methods: as shown below, thiepin chromium complex **1** is readily prepared via standard methods[1] from thiepin-1,1-dioxide[2] **2** and trisacetonitriletricarbonylchromium(0)[3] **3**. The reaction proceeds in 12 h at room temperature to give an 86% yield of the desired chromium complex 1 (eq 1).[4]

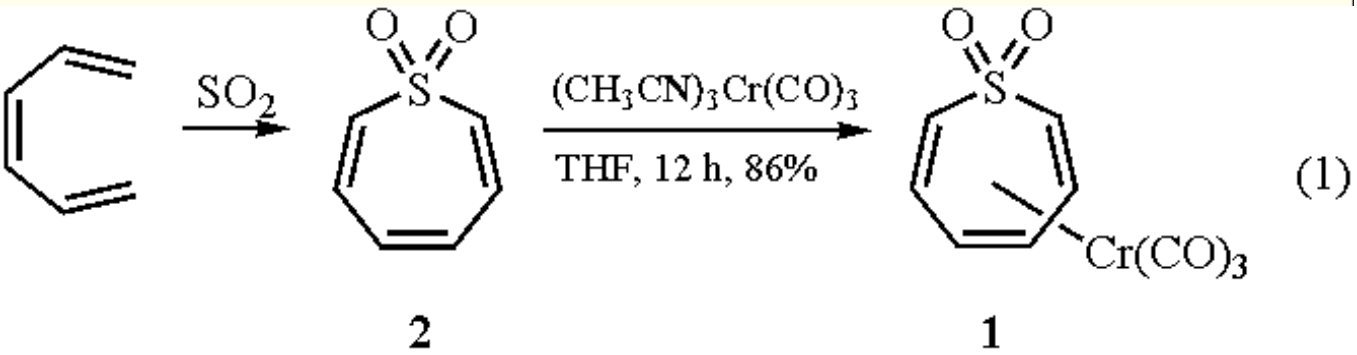

[6+2] Higher-Order Cycloaddition Reactions.

Chromium complex **1** undergoes a variety of higher-order cycloaddition reactions.[5] Thus, a reaction between complex **1** and disubstituted alkyne partners in the presence of UV light (uranium filter) produces [6π+2π] cycloadducts in good yields (eq 3, Table 1). Cyclooctyne (entry 5, Table 1) notably provides an 80% yield of the cycloadduct.[6]

Table 1

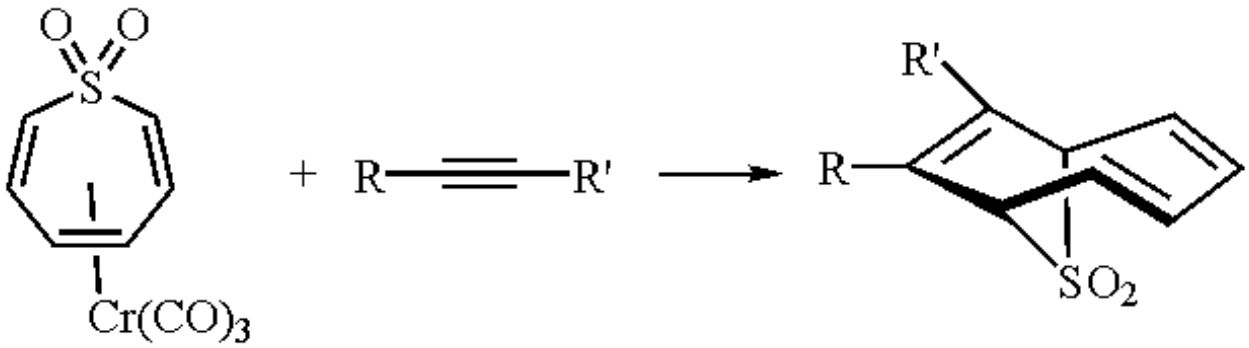

Entry	R	R'	Yield
1	Ph	TMS	78%
2	n-Pr	TMS	65%
3	n-Bu	TMS	65%
4	Ph	Et	42%
5	$(CH_2)_6$		80%

Surprisingly, unlike the tricarbonylcycloheptatriene chromium(0), complex **1** does not react with alkenes to give [6π+2π] cycloadducts.[7]

[6+2+2] Higher-Order Cycloaddition Reactions.

Rigby and coworkers have advanced the field of multicomponent cycloaddition reactions using thiepin chromium complex **1** and terminal alkynes.[8] The reaction proceeds via a process that can be viewed formally as two consecutive [6π+2π] cycloaddition events to give tetracycle **5** (eq 3). The cycloaddition events occur in the coordination sphere of the chromium, thus the reaction sets the six new stereogenic centers in tetracycle **5** stereospecifically, and only one diastereomer is observed.[9]

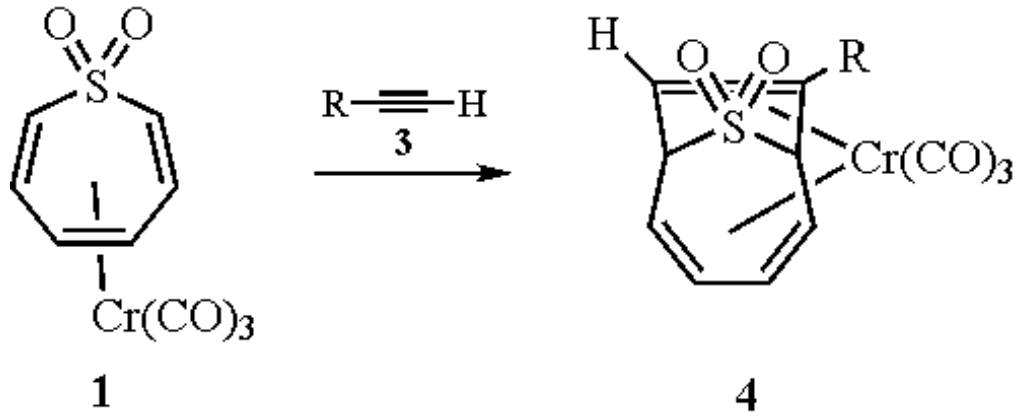

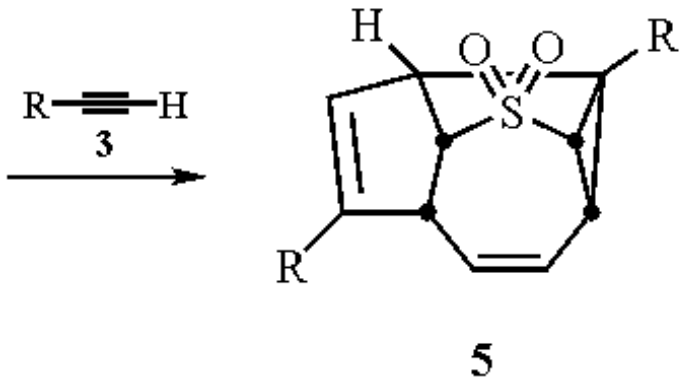

(3)

Examples of the [6+2+2] reaction are included in Table 2.[8a] The reaction requires either photochemical (entries 1-3) or thermal (entry 4) conditions to provide tetracycles**5**.

Table 2

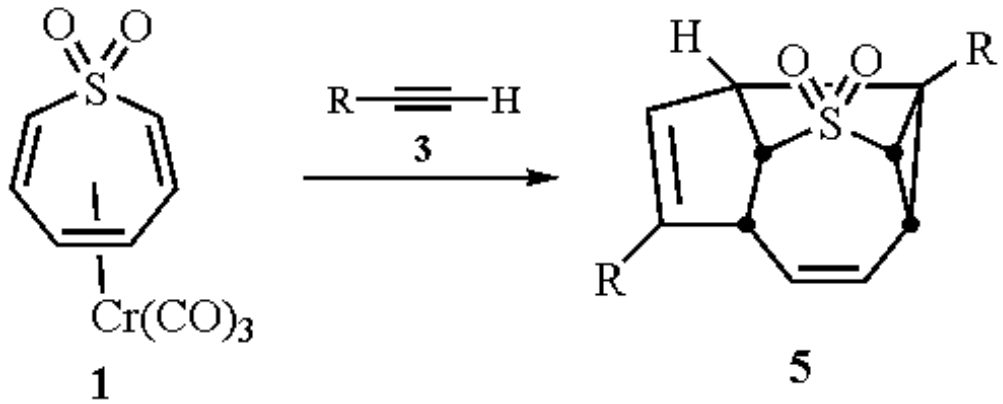

Entry	R	Conditions[a]	Yield
1	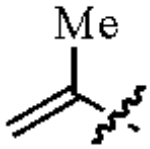	A	32
2	t-Bu	A	70

3	TMS	B	35
4	TMS	C	

[a] Reaction conditions: (A) hv, U-glass filter, 1,2-dichloroethane, 1 h. (B) hv, pyrex glass filter, 1,2-dichloroethane, 1 h. (C) 160 °C, sealed tube Bu_2O, 12 h.

Furthermore, the 2 components can be tethered together so the new product will have one additional ring. Thus, diyne **6** is slowly added over 2 h to a solution of complex **1** in a photochemical reactor to provide a 57% yield of pentacycle **8**. Likewise, slow addition of diyne **7** gives pentacycle **9** in a diminished yield, presumably due to competitive polymerization (eq 5).[10]

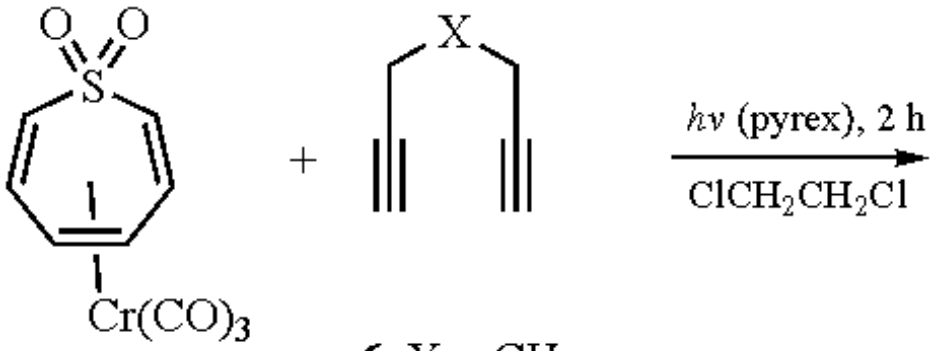

1

6 X = CH_2
7 X = $(CH_2)_2$

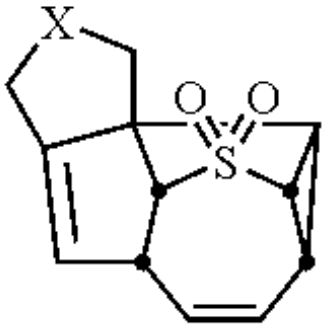

(5)

8 X = CH_2 57%
9 X = $(CH_2)_2$ 32%

[6+2+2+2] Higher-Order Cycloaddition Reactions.

Recently, Rigby and coworkers observed another product during their studies on the three component cycloaddition reactions using tethered alkynes. Thus, a photochemically promoted reaction between thiepin chromium complex **1** and excess octa-1,7-diyne **10** gave pentacycle **12** in 45% yield. Likewise, nonadiene **11** provided pentacycle **13** in 38% yield (eq 6).[11]

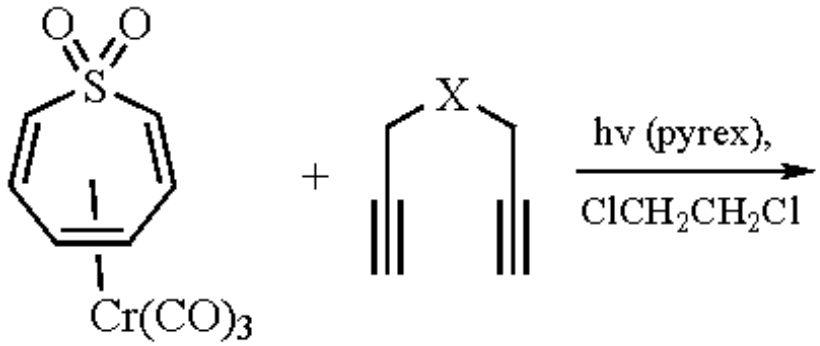

1 **10** X = $(CH_2)_2$

11 X = $(CH_2)_3$

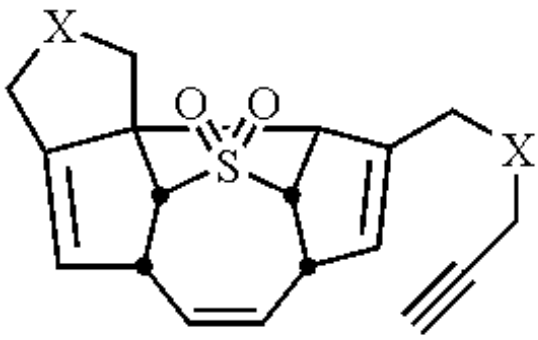

(6)

12 X = $(CH_2)_2$ 45%

13 X = $(CH_2)_3$ 38%

The mechanism leading to pentacycles **12** and **13** has not been established; however, the reaction may proceed via two sequential [6π+2π] cycloaddition reactions followed by a what appears to be a [3+2] cycloaddition. If the final step involves a [3+2] cycloaddition reaction, then these examples would represent the first examples of a chromium-mediated [3+2] cycloaddition reaction.[11]

[6+4] Higher-Order Cycloaddition Reactions.

By far, the most extensively investigated reaction of chromium complex **1** is the [6+4] cycloaddition reaction.[4,7a,12] The reaction between complex **1** and several dienes was examined, and it was determined that electron-rich 4 partners provided much higher yields than those of electron deficient partners. Thus, diene **14** reacts with chromium complex **1** under photochemical conditions to give an excellent yield of cycloadduct **15**, whereas, diene **16** gives a 38% yield of the corresponding cycloadduct **17** (eq 7).[12b]

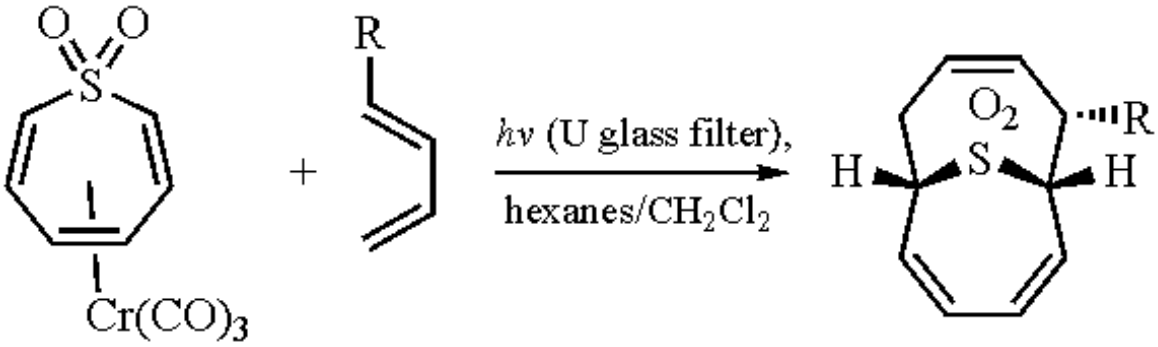

(7)

1 **14** R = OAc **15** R = OAc 78%

16 R = CO_2Me **17** R = CO_2Me 38%

Other more complex dienes have also been examined in this reaction and are listed below (eq 8-11).[7,13]

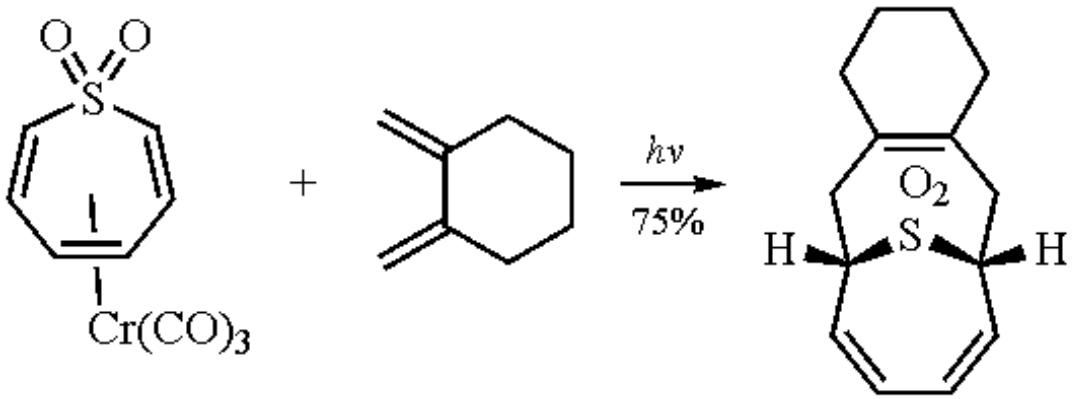

(8)

1 **18** **19**

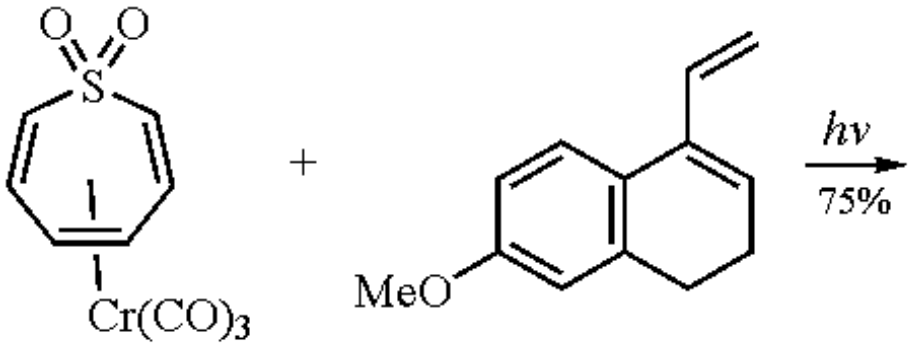

1 **20**

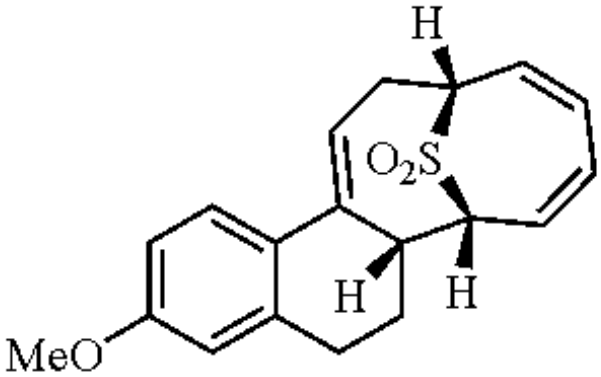

(9)

21

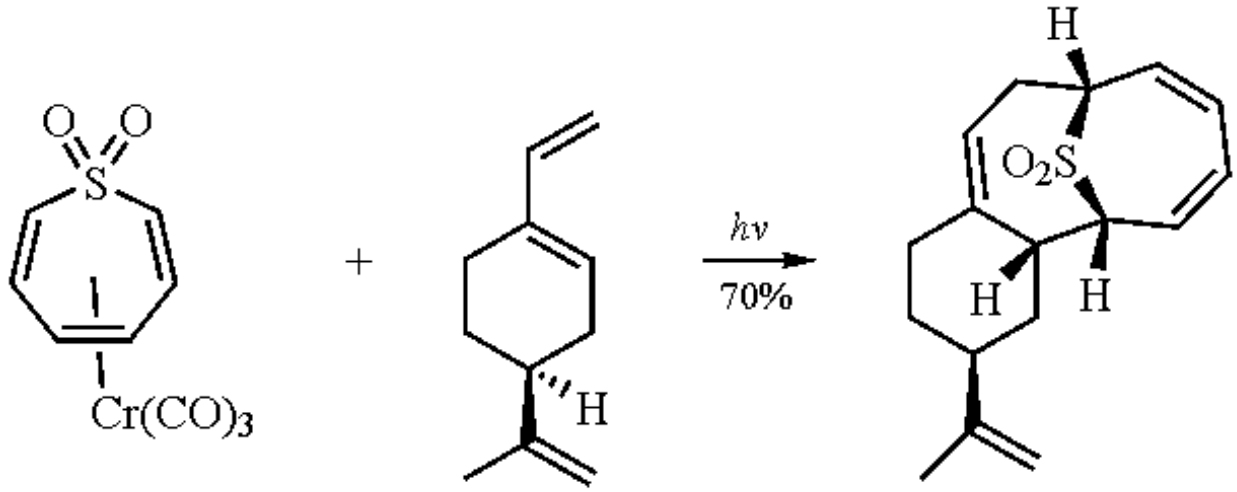

(10)

1 **22** **23**

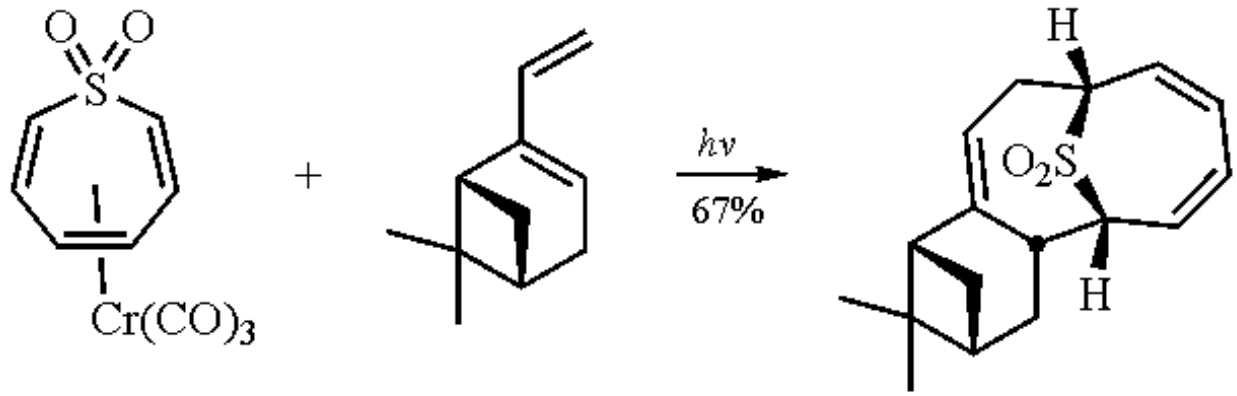

(11)

1 **24** **25**

The [6π+4π] cycloaddition reaction can also be promoted thermally. For example, a *tert*-butylmethylether solution of chromium complex **1** and diene **14** was heated to reflux (110°C) for 48 h. Upon isolation via column chromatography on silica gel, compound **15** was again obtained but with a diminished yield (47%) (eq 12).[12b]

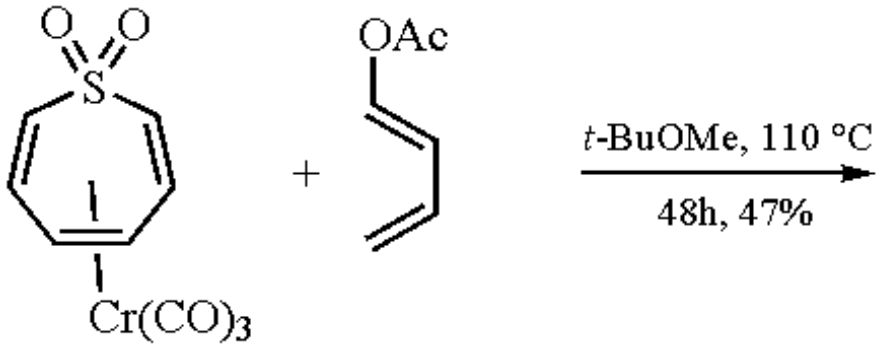

1 **14**

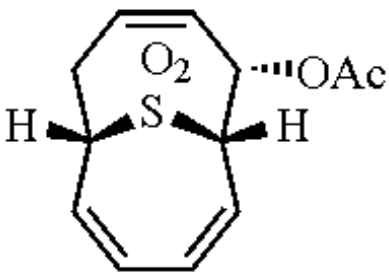

(12)

15

Sulfur Dioxide Extrusion and Applications Toward Total Synthesis.

The sulfur-containing products, which result from the higher-order cycloaddition reactions described above, have been submitted to various conditions to extrude the elements of sulfur dioxide. For example, photolysis (quartz filter) of cycloadduct **15** for 15 min promotes a cheletropic extrusion of sulfur dioxide to give a 54% yield of cyclodecatetraene **26** (eq 13).[4]

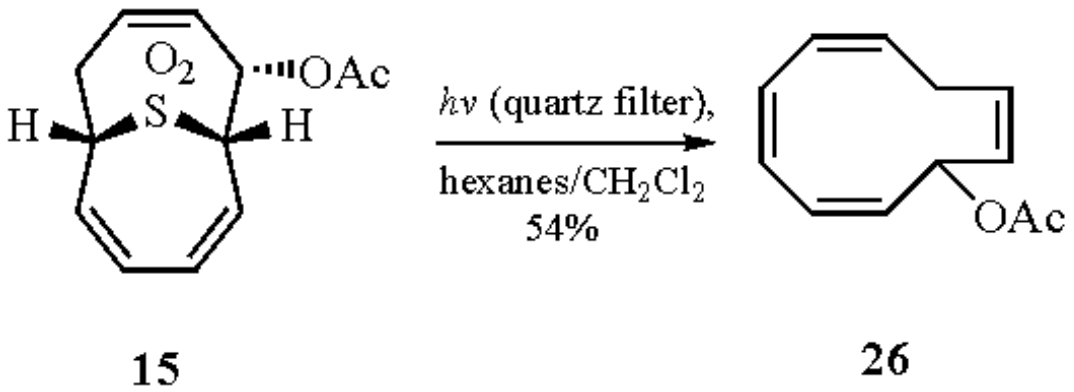

(13)

A very different sulfur dioxide extrusion protocol has been applied to the total synthesis of (+)-estradiol (**30**) by Rigby and coworkers.[13] In the event, the trimethylsilyl-substituted chromium thiepin complex **27** participated in a [6π+4π] cycloaddition reaction to provide a 70% yield of the structurally complex dihydrothepin **28**. Subsequent sulfur dioxide extrusion via a Ramberg-Bäcklund-type ring contraction gave tetracycle **29**. The total synthesis of (+)-estradiol (**30**) was completed using a four-step sequence of standard reactions (eq 14).[13]

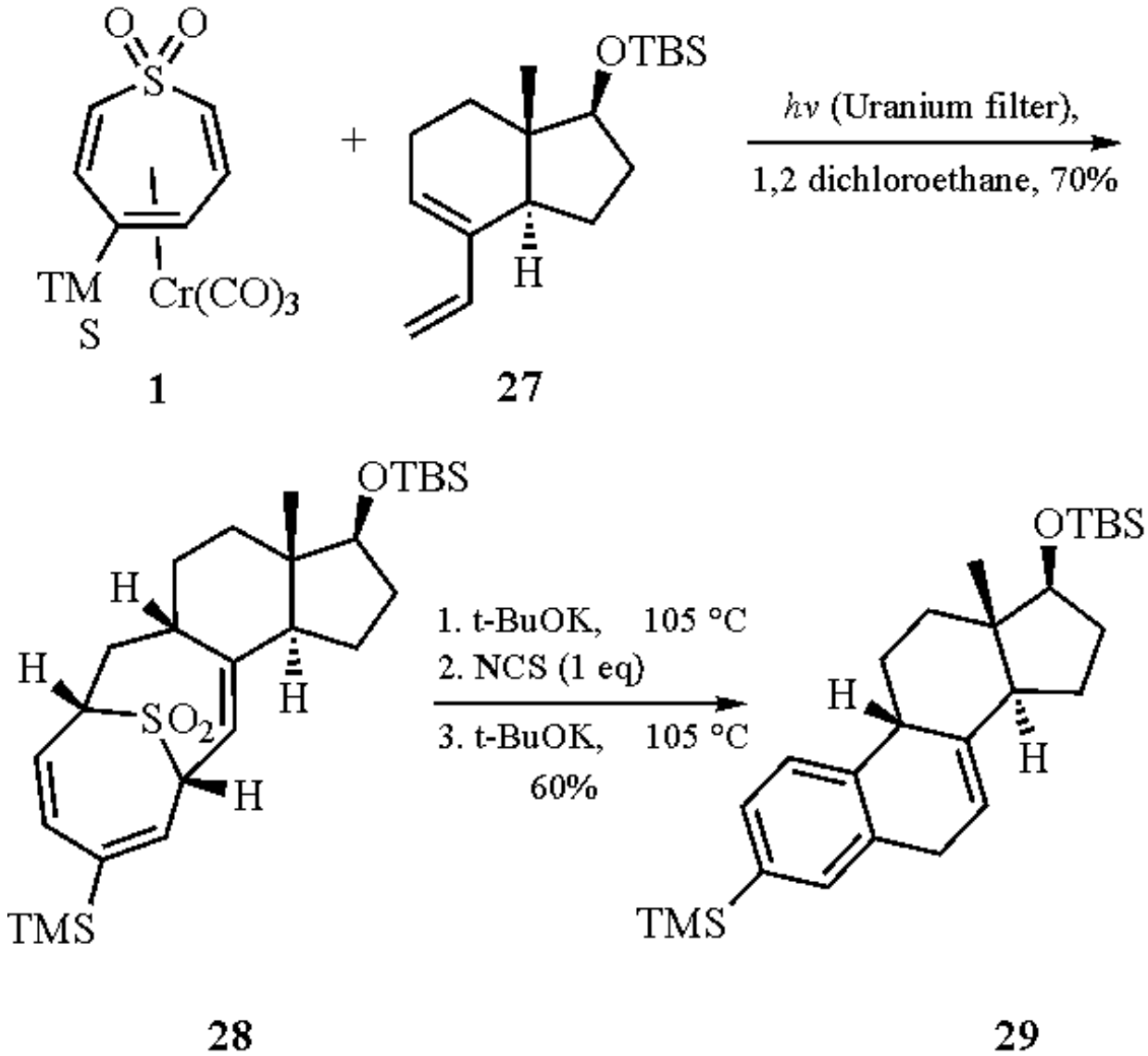

OH

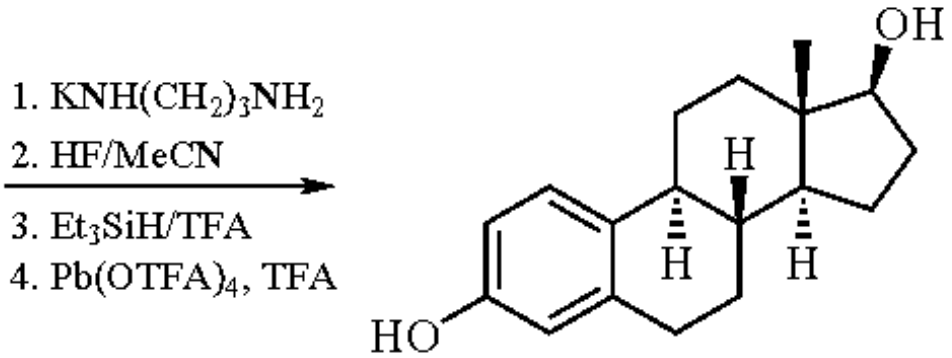

(14)

(+)-estradiol (**30**)

Related Reagents.

tricarbonyl[(2,3,4,5,6,7-η)-cyclo-heptatriene]chromium(0);[1] tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]molybdenum(0);[12b] tricarbonyl[(2,3,4,5,6,7-η)-thiepin-1,1-dioxide]tungsten(0);[12b] tricarbonyl[(2,3,4,5,6,7-η)-thiepin]iron(0);[14] tricarbonyl[(2,3,4,5,6,7-η)methyl-1H-azepine-1-carboxylate]chromium;[4] thiepin-1,1-dioxide;[2] trisaceto-nitriletricarbonyl-chromium(0).[3]

---

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2,5-Dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole

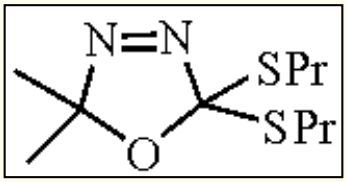

[222625-77-6] · $C_{10}H_{20}N_2OS_2$ · (248.41)

(reagent used as bis(propylthio)carbene precursor)

Physical Data: solid at -78°C, thermolysis occurs at 0°C and above.

Solubility: hexanes, cyclohexane, dichloromethane, benzene, toluene, xylene.

Form Supplied in: colorless oil as synthesized.

Purification: column chromatography at 0°C using hexanes-ethyl acetate (20:1); product elutes first; collect fractions in an ice bath; remove solvent in vacuo at 0°C; dry under high vacuum at 0°C for 1 h.

Handling, Storage, and Precautions: to prevent premature thermolysis, reagent should be stored in a sealed flask in a cooler with dry ice at -78°C. Since the reagent is thermally labile and thermolysis is exothermic, avoid exposure to heat to prevent rapid evolution of nitrogen gas leading to a possible explosion. Thermolysis will occur at 0°C and above. Use of an explosion shield and slow addition to refluxing solvents are recommended.

[1+4] Cycloaddition with Vinyl Isocyanates

Upon thermolysis in refluxing benzene, 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole yields the bis(propylthio)carbene precursor, which reacts as a 1,1-dipole equivalent in [1+4] cycloaddition reactions with various vinyl isocyanate substrates leading to highly functionalized adducts such as hydroindolones (eq 1).[1-3] Reductive desulfurization with Raney nickel yields the enamide or the fully reduced system (eq 2).[1] Cyclohexyl isocyanide also behaves as a 1,1-dipole equivalent in [1+4] cycloadditions with vinyl isocyanates, however the adducts are less functionalized.[4,5]

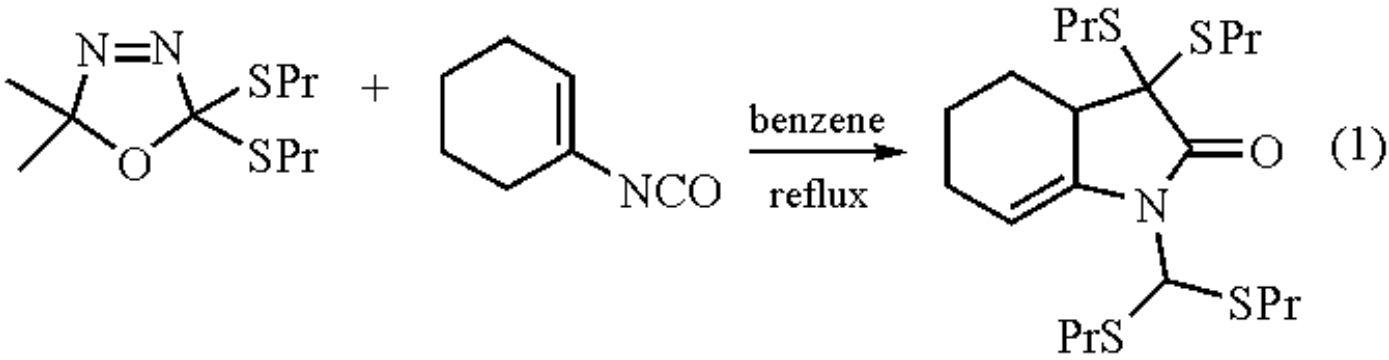

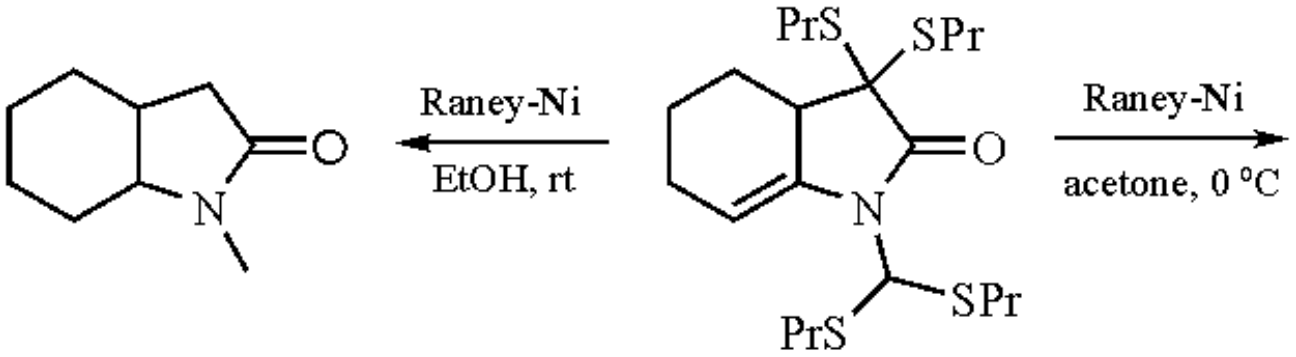

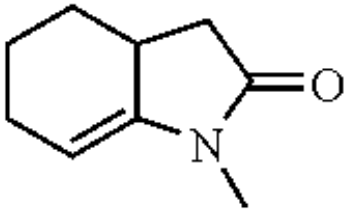

(2)

Dimethoxy carbene has been shown to behave as a carbonyl 1,1-dipole equivalent in [1+4] cycloadditions with vinyl isocyanates also yielding functionalized adducts.[6] However, the oxadiazole precursor requires higher thermolysis temperatures and hydrolysis of the acetals in the resultant adducts can be difficult for acid-sensitive systems.

[4+1+1] Cycloaddition with Vinyl Isocyanate

When a large excess of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole carbene precursor is added rapidly in refluxing benzene to a vinyl isocyanate, two equivalents of carbene add to the substrate prior to ring closure, leading to a six-membered adduct (eq 3).[1,2] However, no carbene insertion into the amide N-H bond occurs. This phenomenon is not observed with the dimethoxy carbene.[2]

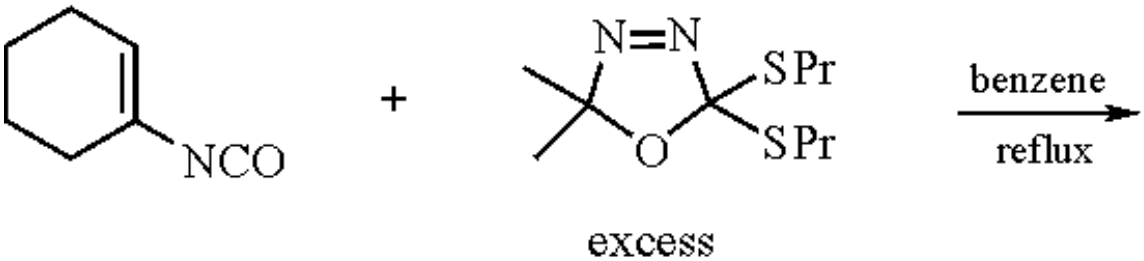

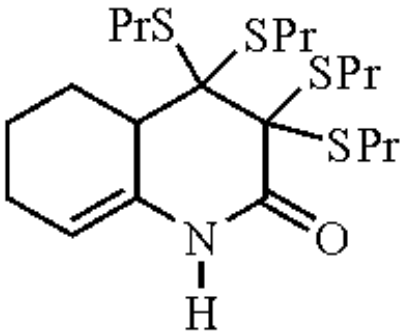

(3)

Addition of Bis(propylthio)carbenes to Aryl Isocyanates

Addition of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole in refluxing benzene and an aryl isocyanate releases the bis(propylthio)carbene in situ which then adds easily to the aryl isocyanate to yield a substituted isatin with the ketone functionality protected as a thioacetal (eq 4).[7] Ring closure also occurred when the 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole carbene precursor was added to 1-naphthyl isocyanate in refluxing acetonitrile (eq 5).[7] Formation of thioacetal protected isatin products are unique to the bis(propylthio)carbene as other nucleophilic carbenes added to aryl isocyanates afforded only modest yields of hydantoin products.[8]

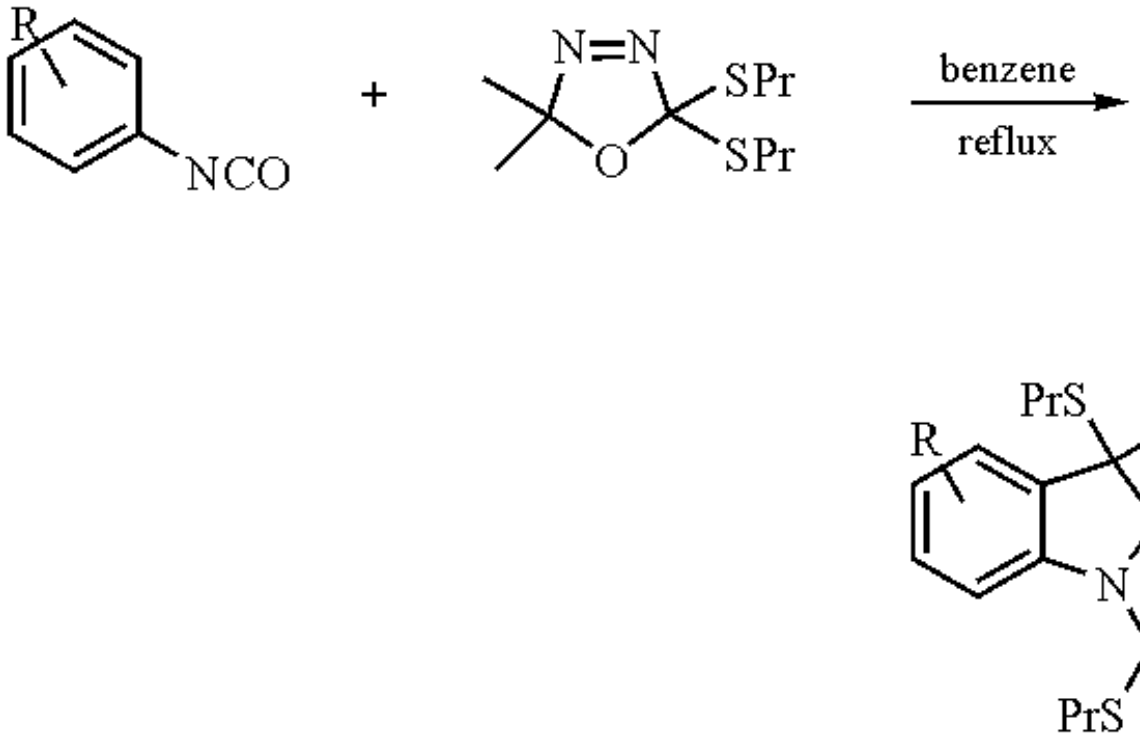

(4)

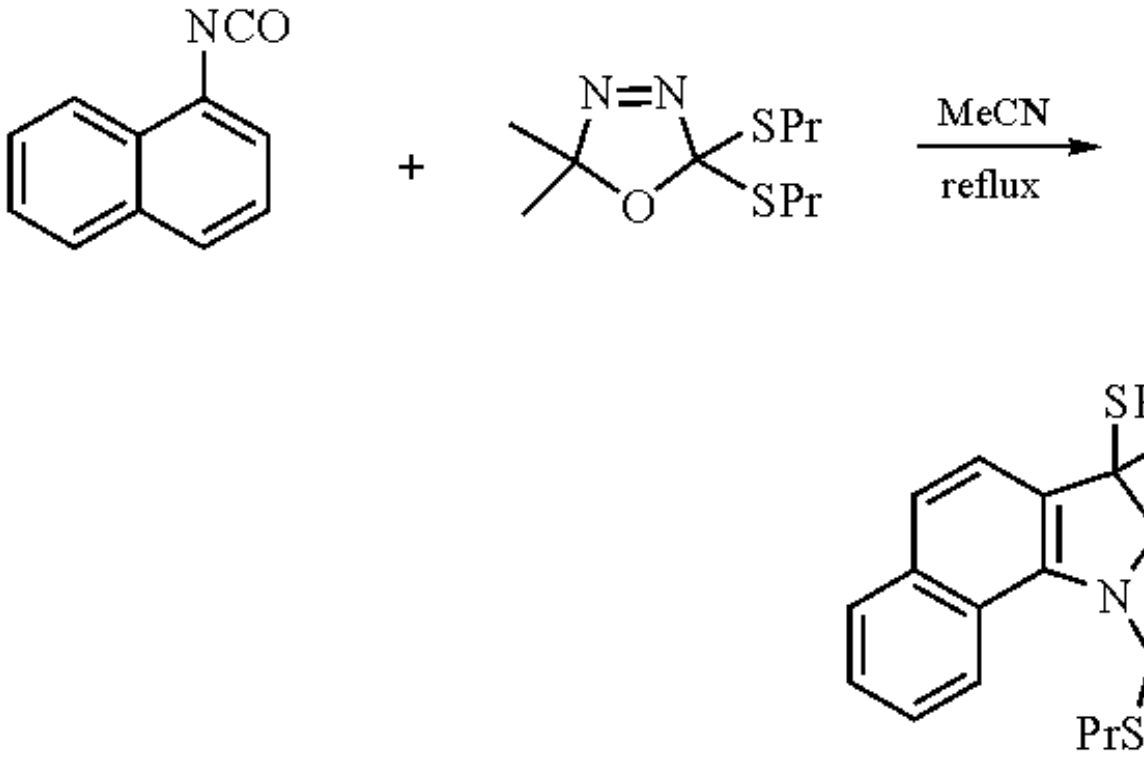

(5)

Dimerization

Upon thermolysis of 2,5-dihydro-2,2-dimethyl-5,5-bis(propylthio)-1,3,4-oxadiazole in refluxing benzene and in the absence of any electrophile, the resultant bis(propylthio)carbene will dimerize (eq 6).[1] Since the reaction is highly exothermic, care must be taken in the execution of this reaction. Use of an explosion shield and slow addition of the carbene precursor are recommended.

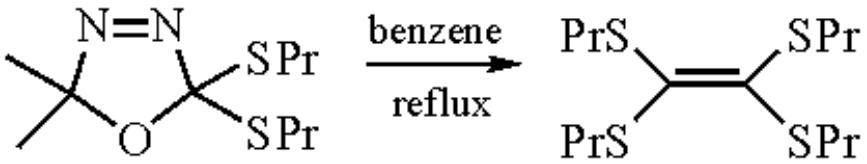

(6)

Related Reagents.

dimethoxy carbene, cyclohexyl isocyanide.

1. Rigby, J. H.; Laurent, S., *J. Org. Chem.* **1999**, *64*, 1766.
2. Rigby, J. H.; Laurent, S.; Dong, W.; Danca, M. D., *Tetrahedron* **2000**, *56*, 10101.
3. Rigby, J. H.; Dong, W., *Org. Lett.* **2000**, *2*, 1673.
4. Rigby, J. H.; Deur, C.; Heeg, M. J., *Tetrahedron Lett.* **1999**, *40*, 6887.
5. (a) Rigby, J. H.; Qabar, M., *J. Am. Chem. Soc.* **1991**, *113*, 8975. (b) Rigby, JH.; Qabar, M.; Ahmed, G.; Hughes, R. C., *Tetrahedron* **1993**, *49*, 10219.
6. Rigby, J. H.; Cavezza, A.; Heeg, M. J., *J. Am. Chem. Soc.* **1998**, *120*, 3664.
7. Rigby, J. H.; Danca, M. D., *Tetrahedron Lett.* **1999**, *40*, 6891.
8. (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B., *Chem. Ber.* **1973**, *106*, 2174. (b) Lemal, D. M.; Gosselink, E. P.; McGregor, S. D., *J. Am. Chem. Soc.* **1966**, *88*, 582. (c) El-Saidi, M.; Kassam, K.; Pole, DL.; Tadey, T.; Warkentin, J., *J. Am. Chem. Soc.* **1992**, *114*, 8751. (d) Hoffmann, RW.; Reiffen, M., *Chem. Ber.* **1976**, *109*, 2565.

Nancy A. Neale

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Cyanuric Fluoride

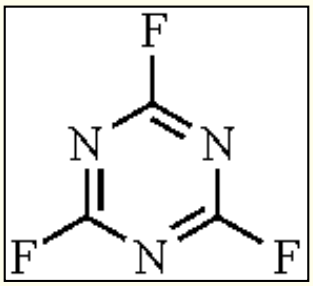

[675-14-9] · $C_3F_3N_3$ · (135.05)

(reagent used for conversion of carboxylic acids to acid fluorides; deoxygenation of alkyl sulfoxides; and activation of alkenyl boronic acids for 1,4-addition reactions)

Alternate Name: 2,4,6-trifluoro-1,3,5-triazine, cyanuryl fluoride.

Physical Data: mp -38°C; bp 72-74°C; d 1.574 g mL^{-1}.

Form Supplied in: colorless liquid.

Purification: the commercial reagent is generally used as received.

Handling, Storage, and Precautions: highly toxic; very toxic by inhalation, in contact with skin, and if swallowed. Causes burns. Readily absorbed through the skin. Lachrymator. In case of accident or if you feel ill, seek medical advice immediately (show the label when possible). In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Do not breath vapor. Wear suitable protective clothing, gloves, and face/eye protection. Refrigerate. Moisture sensitive; keep container tightly closed. Disposal: dissolve or mix with a combustible solvent and incinerate.

Acid Fluoride Synthesis

Cyanuric fluoride first appeared as a reagent for the mild and direct conversion of carboxylic acids into acid fluorides. This method represented a significant advancement for the preparation of acid fluorides.[1] Previously reported methods include treatment of acid chlorides with potassium fluoride,[2] potassium hydrogen fluoride,[3] or potassium fluorosulfinate.[4] Acid fluorides were also prepared from carboxylic acids using sulfur tetrafluoride,[5] diethyl(2-chloro-1,1,2-trifluoroethyl)amine,[6] thionyl fluoride,[7] benzoyl fluoride,[8] and selenium tetrafluoride.[9] These methods are less direct and are often incompatible with other functional groups in the substrate.

In a typical procedure,[1] a solution of 0.4 equiv of cyanuric fluoride in acetonitrile is added to a mixture of 1.0 equiv each of a carboxylic acid and pyridine in acetonitrile at room temperature. After being stirred for 1 h, the reaction is subjected to a standard aqueous work-up which then provides the desired acid fluoride in generally high yields for a variety of carboxylic acid starting materials (eq 1). Each mole equivalent of cyanuric fluoride reacts to give three moles of acyl fluoride.

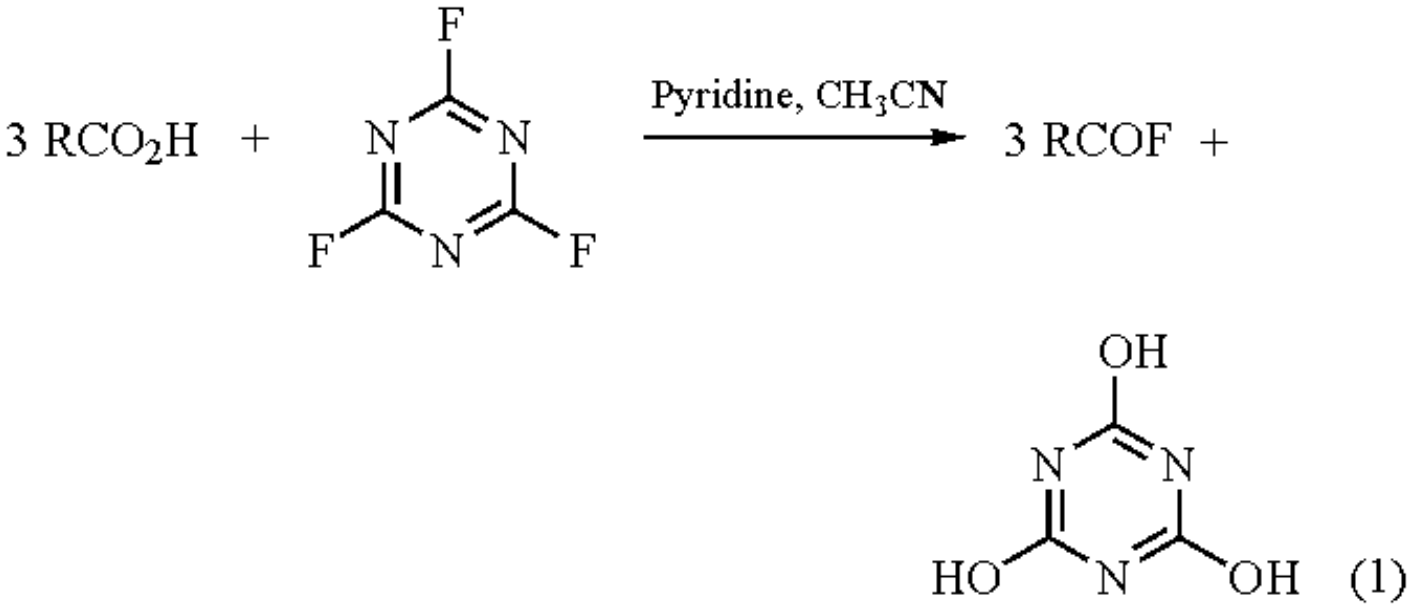

Acid	Yield (%)
Acetic acid	70
Propiolic acid	85
Cyclopentylcarboxylic acid	54
Cyclohexylcarboxylic acid	95
Cinnamic acid	95
Benzoic acid	97

The ability to prepare acid fluorides under these mild conditions opened up a number of synthetic applications. Perhaps the most significant application to date is the increased use of acid fluorides as activated intermediates in peptide bond formation.[10,11] The use of Fmoc amino acid chlorides as activated N-protected peptide building blocks has been limited by the propensity of *t*-butyl ester- or ether-protected side chains (e.g. serine, threonine, glutamate, aspartate) to cyclize onto the acid chloride with the loss of *t*-butyl chloride. Carpino et al. have shown that the corresponding amino acid fluorides are not subject to this same side reaction.[10] The general reactivity pattern for acid fluorides compared with acid chlorides is that they are less sensitive to uncharged oxygen nucleophiles such as water or methanol but display similar reactivity to charged or nitrogen nucleophiles. The Fmoc amino acid fluorides were prepared from the corresponding Fmoc amino acids under similar conditions to those described above and were isolated as white crystalline solids. A number of the exemplified amino acids contained protected acid and amide side chains (eq 2 and 3).

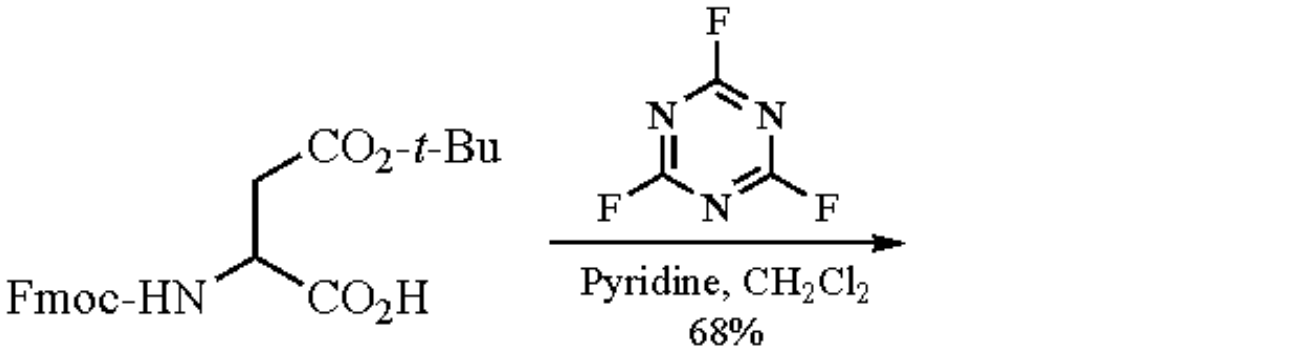

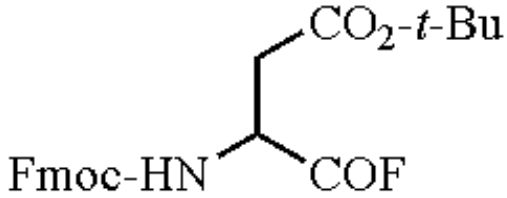

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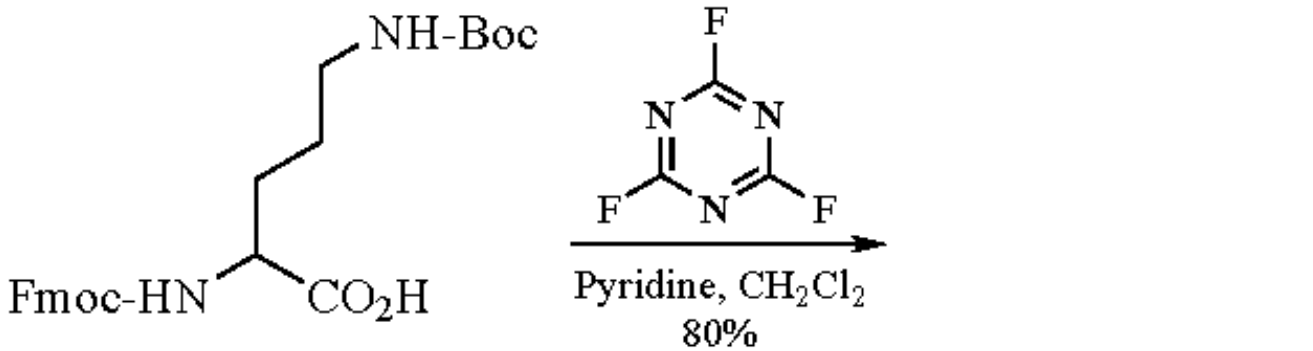

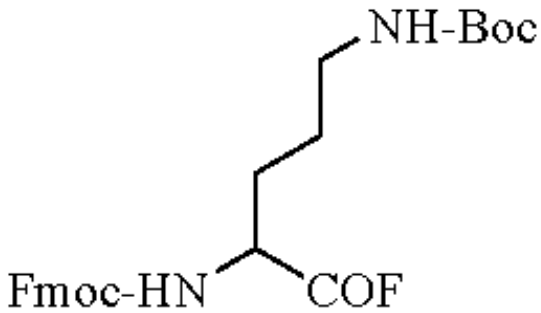

(3)

Acid fluorides have the additional advantage that they are more reactive in peptide coupling reactions of hindered amino acid derivatives. This is due at least in part to the small size of the fluoride leaving group.[12] Hindered acid fluorides like Fmoc-Aib-F can be prepared in the usual way with cyanuric fluoride.

Reduction of Acids to Alcohols

The mild conditions required for the conversion of carboxylic acids to acid fluorides has resulted in a method for the reduction of carboxylic acids to alcohols by way of the acid fluorides.[13] A variety of carboxylic acids were converted to acid fluorides under standard conditions. A quick aqueous work-up was followed by $NaBH_4$ reduction (eq 4). This mild reaction sequence has the distinct advantage over $NaBH_4$-I_2 in that it is compatible with N-protected amino acids. The resulting alcohols are obtained in generally high yields with no observable loss in enantiomeric purity.

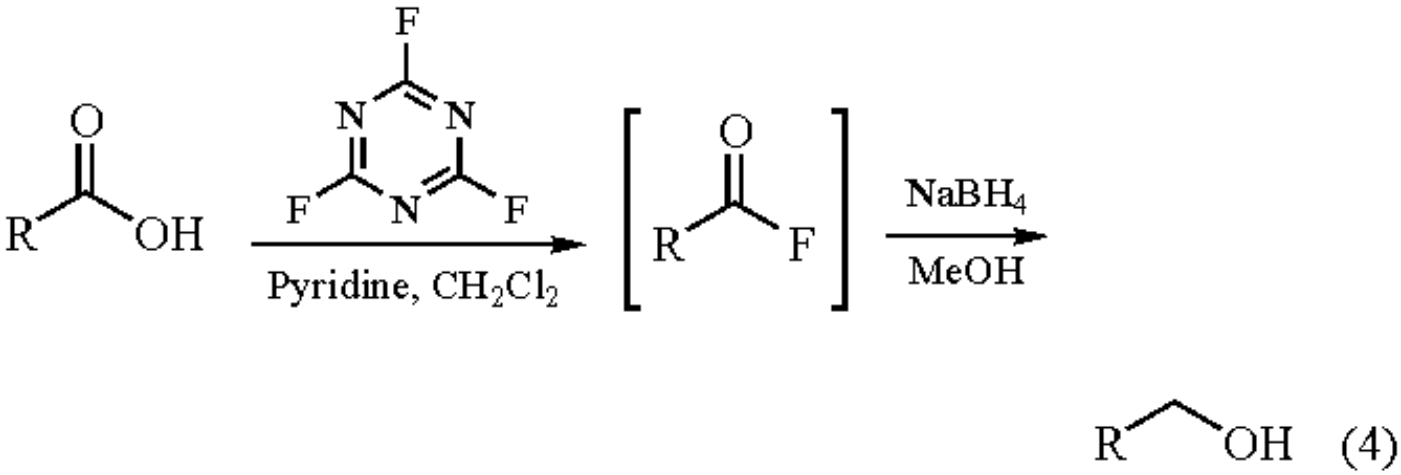

R	Yield (%)
Ph	95
Bn	94
$-(CH_2)_8Me$	92
Cbz-Phe	81
Fmoc-Leu	90

Other Uses

A recent use for cyanuric fluoride is the activation of alkenyl boronic acids for the 1,4 addition of α,β-unsaturated ketones.[14,15] Hara et al. have shown that alkenyl boronic acids when treated with cyanuric fluoride undergo 1,4 addition to unsaturated ketones.[14] Presumably, this reaction takes place via the alkenyl fluoro alkoxy borane intermediate followed by coordination of the carbonyl oxygen to the boron and intramolecular carbon-carbon bond formation (eq 5). Selective 1,4 additions to α,β,α´,β´-unsaturated ketones could be achieved by introducing substituents on one of the double bonds (eq 6).[15]

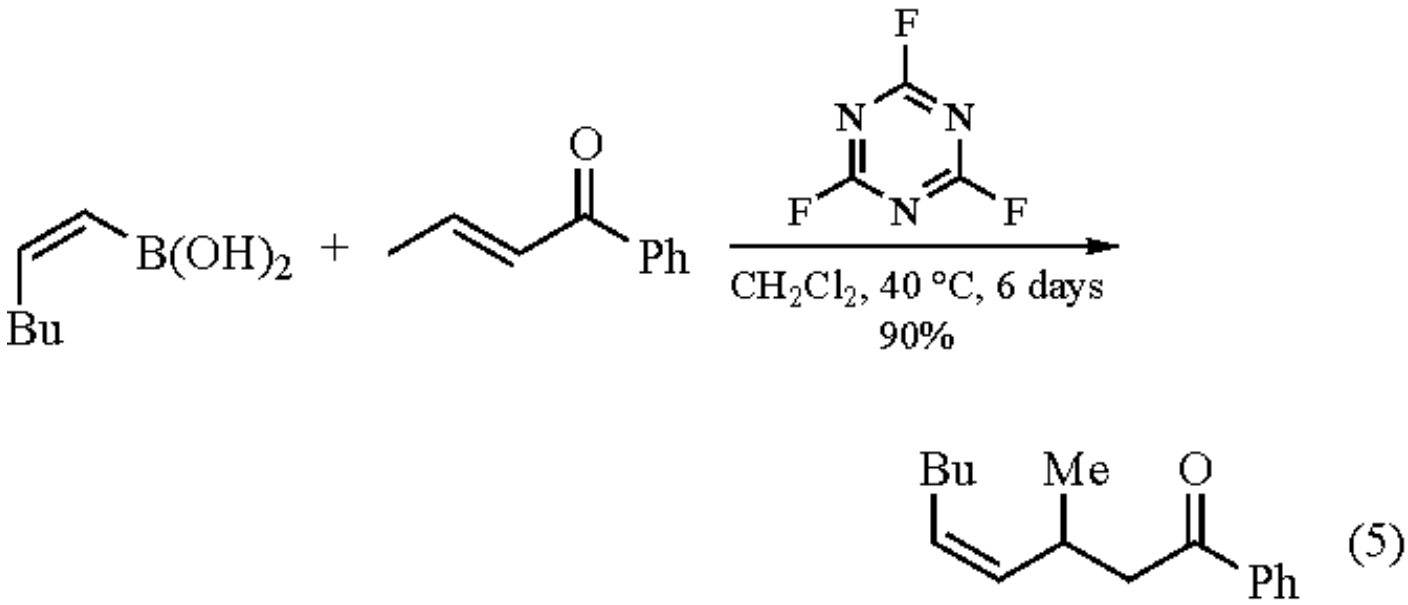

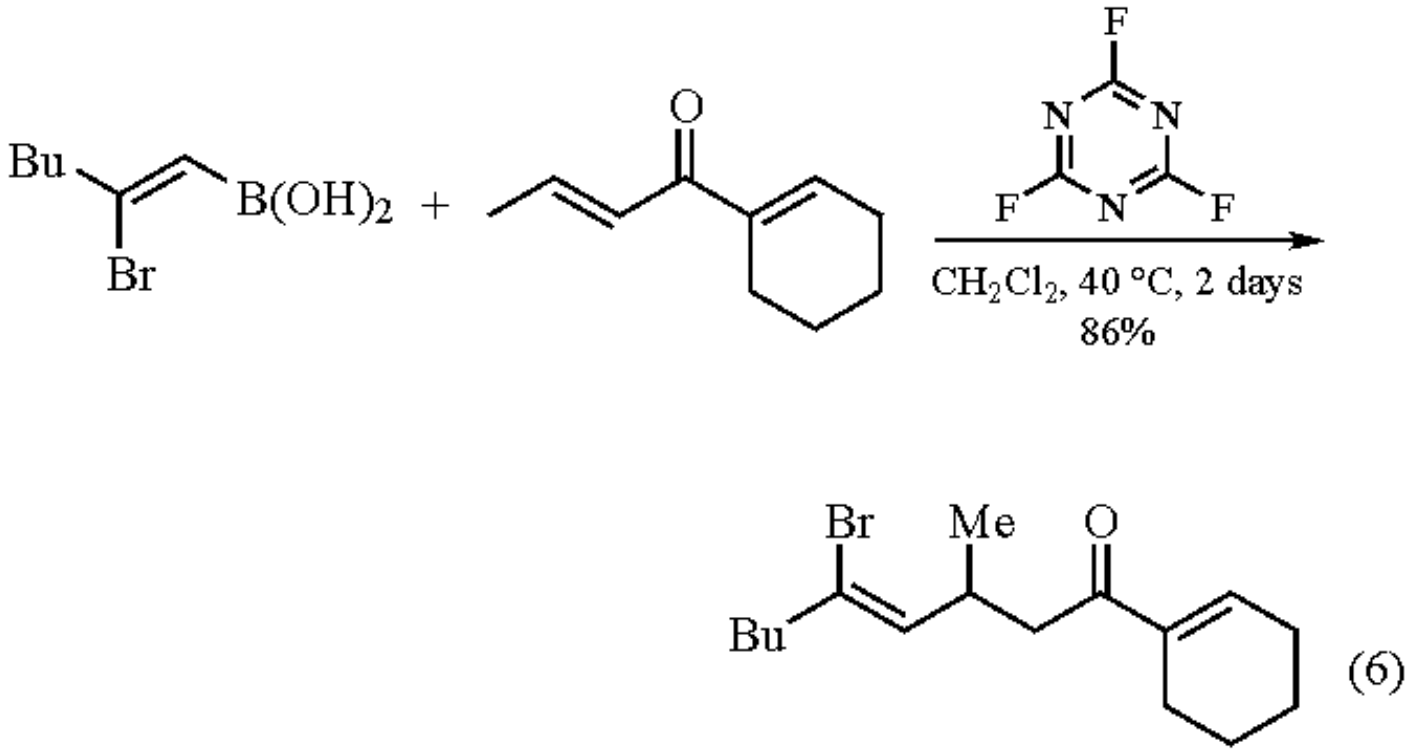

Cyanuric fluoride has also been used as a reagent for the selective deoxygenation of sulfoxides (eq 7 and 8).[16] Stirring the sulfoxide with cyanuric fluoride in dioxane followed by aqueous work-up gave good yields of the corresponding sulfides.

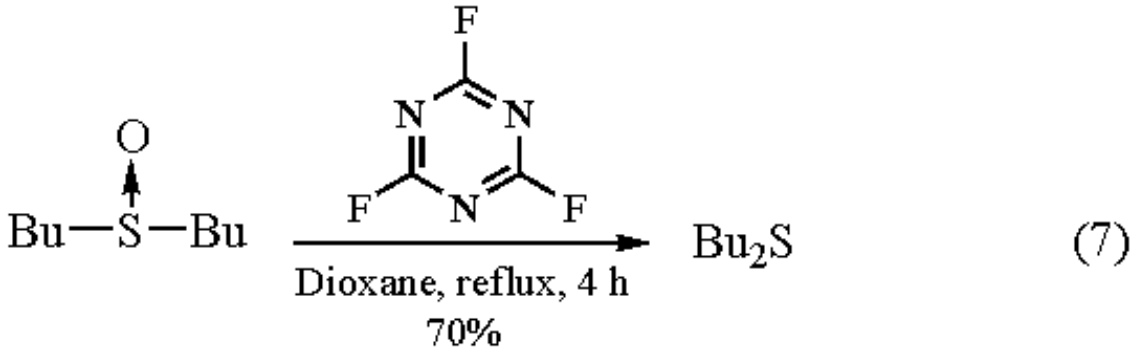

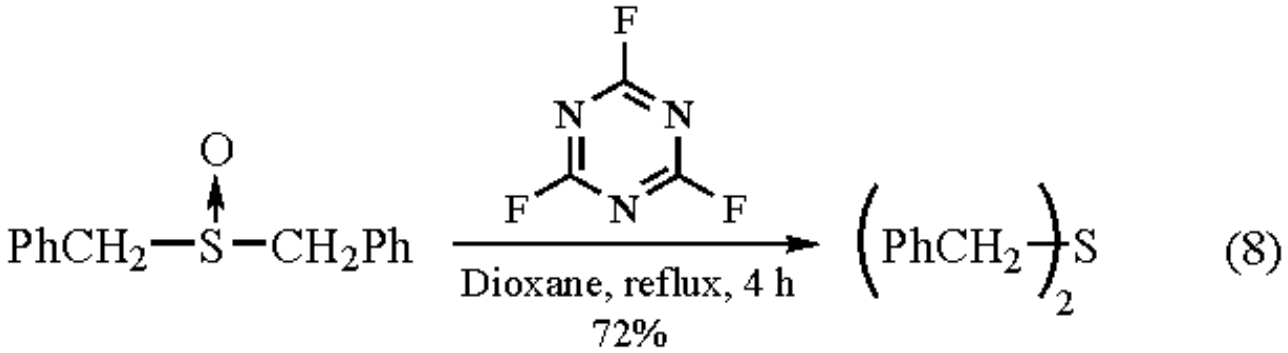

Finally, cyanuric fluoride has been used in solid-phase synthesis as a method for activating a carboxylic acid functionality on solid support for loading a nucleophile onto a resin.[17,18] For example, in 1998 Böhm et al. demonstrated carboxypolystyrene activation as the acyl fluoride followed by resin loading with a primary amine linker (eq 9).[17] In 1999, Sams et al. employed a similar method to activate substituted benzoic acids loaded onto Wang resin with *N*-methylmorpholine (NMM) in dichloromethane. The resulting acyl fluorides were coupled with derivatives of *N*-hydroxyamidine in the presence of *N*-methylmorpholine (eq 10).[18]

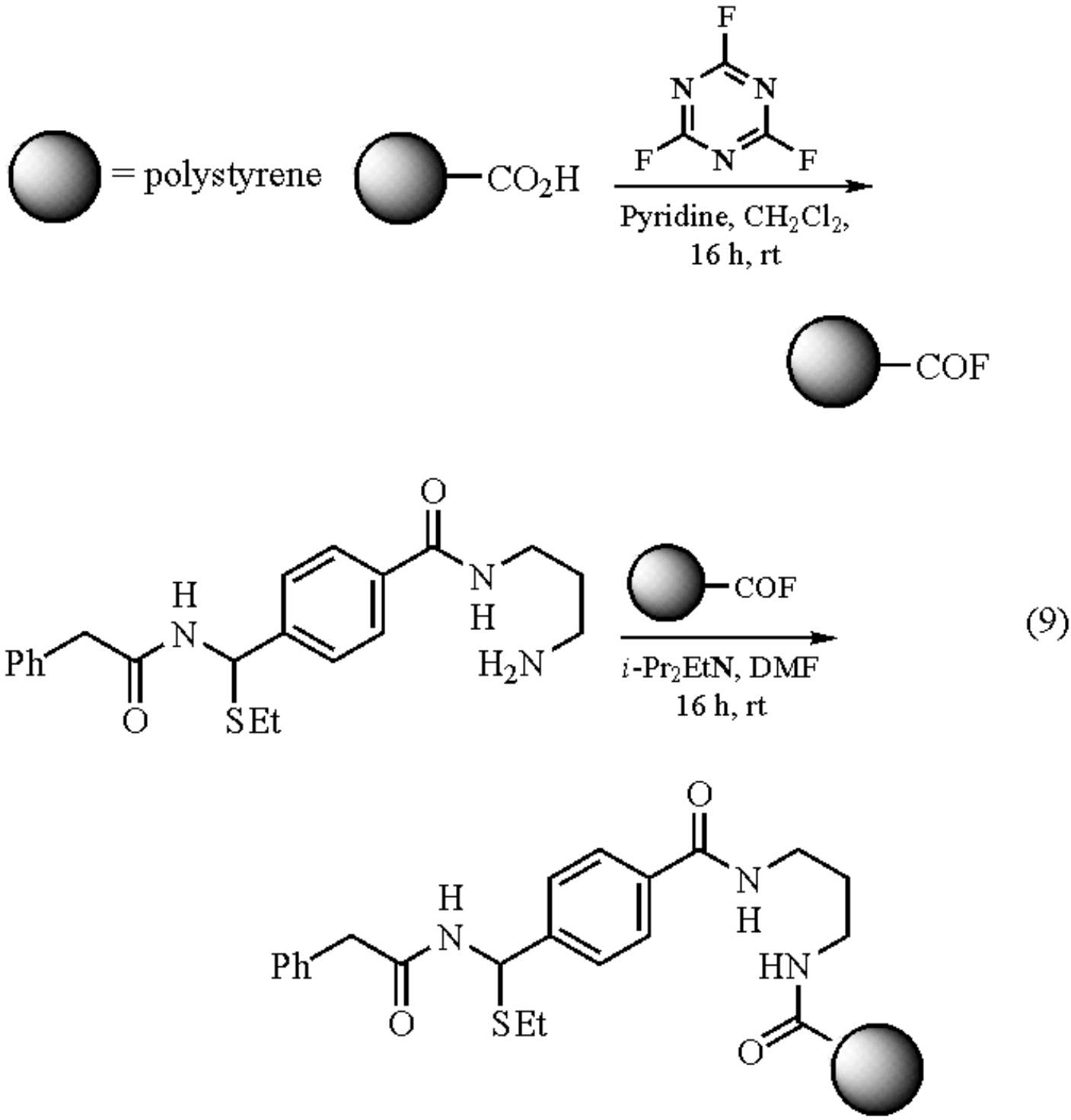
= polystyrene
CO2H
F
N
N
F
N
F
Pyridine, CH2Cl2,
16 h, rt
COF
O
H
N
Ph
O
SEt
N
H
H2N
COF
i-Pr2EtN, DMF
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HN
O

(9)

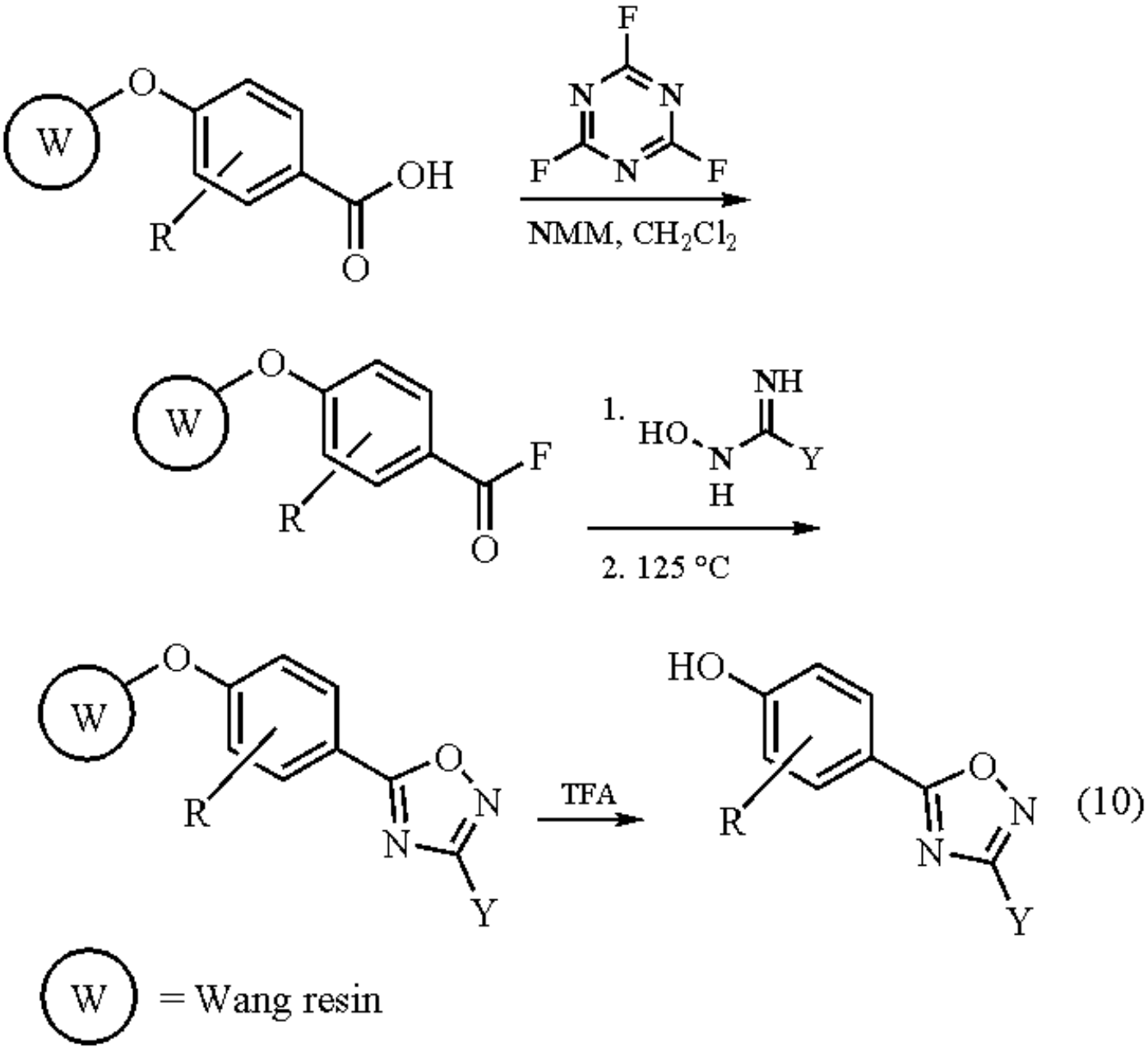

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17. Böhm, G.; Dowden, J.; Rice, D. C.; Burgess, I.; Pilard, J.-F.; Guilbert, B.; Haxton, A.; Hunter, R. C.; Turner, N. J.; Flitsch, S. L., *Tetrahedron Lett.* **1998**, *39*, 3819.
18. Sams, C. K.; Lau, J., *Tetrahedron Lett.* **1999**, *40*, 9359.

David A. IN, Barda

(*R*,*R*)-2-Butyl-4,5-bis(dimethylaminocarbonyl)-1,3-dioxaborolane[1]

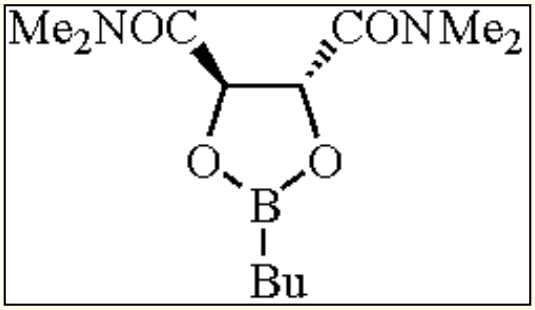

[161344-85-0] · $C_{12}H_{23}BN_2O_4$ · (270.13)

(enantioselective cyclopropanation[1])

Solubility: soluble in CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, benzene and most organic solvents.

Form Supplied in: colorless oil, not commercially available.

Analysis of Reagent Purity: NMR (^1H, ^{11}B).

Preparative Methods: the reagent is easily prepared from commercially available butylboronic acid (or its more stable diethanolamine complex) and (*R*,*R*)-(+)-*N*,*N*,*N*´,*N*´-tetramethyltartaric acid diamide.[2] The other enantiomer is also readily available from (*S*,*S*)-(+)-*N*,*N*,*N*´,*N*´-tetramethyltartaric acid diamide.

Purification: not easily purified since the reagent hydrolyzes slowly in the presence of moisture and oxidizes slowly in the presence of oxygen. The formation of crystals over time is an indication of decomposition.

Handling, Storage, and Precautions: the reagent is stable indefinitely when stored under an inert atmosphere.

Enantioselective Cyclopropanation of Allylic Alcohols

(*R*,*R*)-2-Butyl-4,5-bis(dimethylaminocarbonyl)-1,3-dioxaborolane (**1**) is one of the most effective chiral additives for the enantioselective cyclopropanation of allylic alcohols.[3] The synthesis of a wide range of substituted cyclopropylmethanols proceeds with excellent enantiocontrol (85-93% ee) when a solution of the alcohol and the dioxaborolane ligand is added to bis(iodomethyl)zinc. The use of the DME complex of bis(iodomethyl)zinc is preferable on large scale (eq 1).[4]

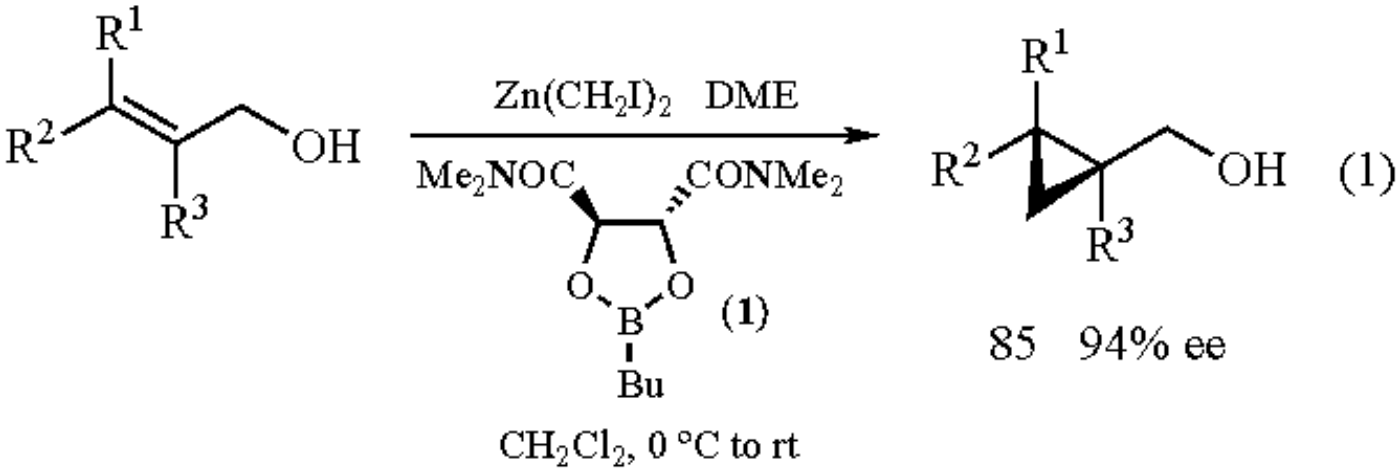

The reaction can also be used in bidirectional chain synthesis to generate bis(cyclopropyl) derivatives simultaneously (eq 2 and 3).[5] This reaction was used as the key step for elaboration of the polycyclopropane natural products FR-900848 and U-106305.

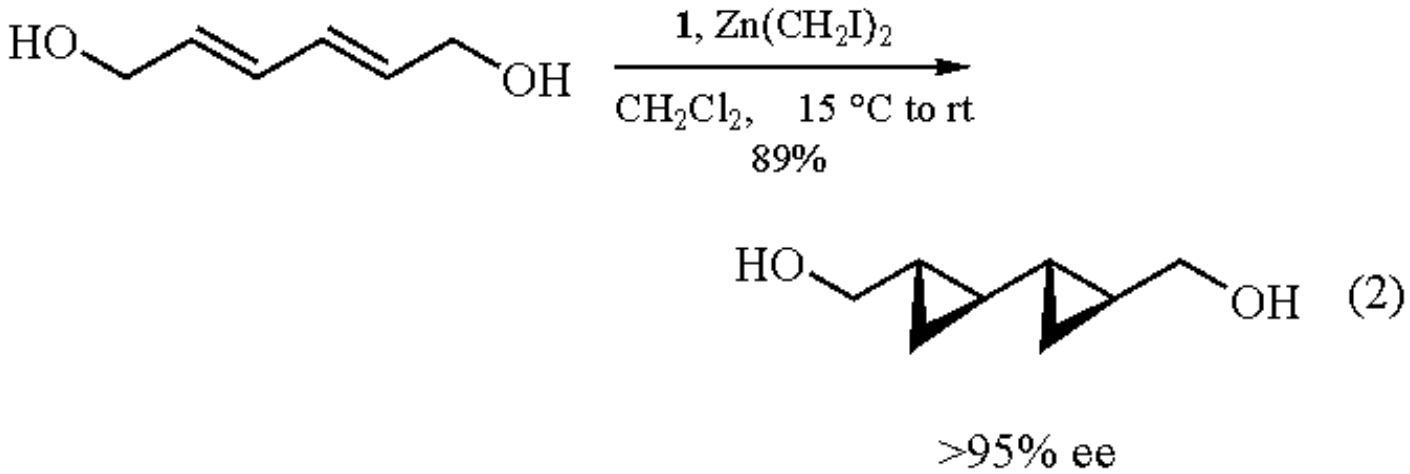

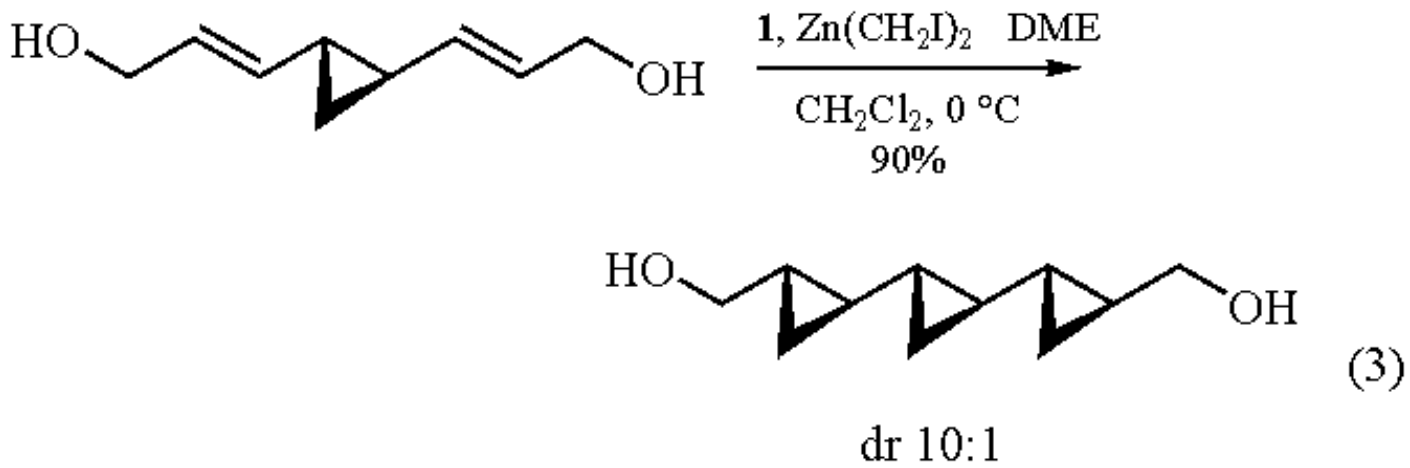

Extremely high diastereoselectivities are also observed when the antipode of the starting material is used, providing efficient access to the other diastereomer (eq 4).

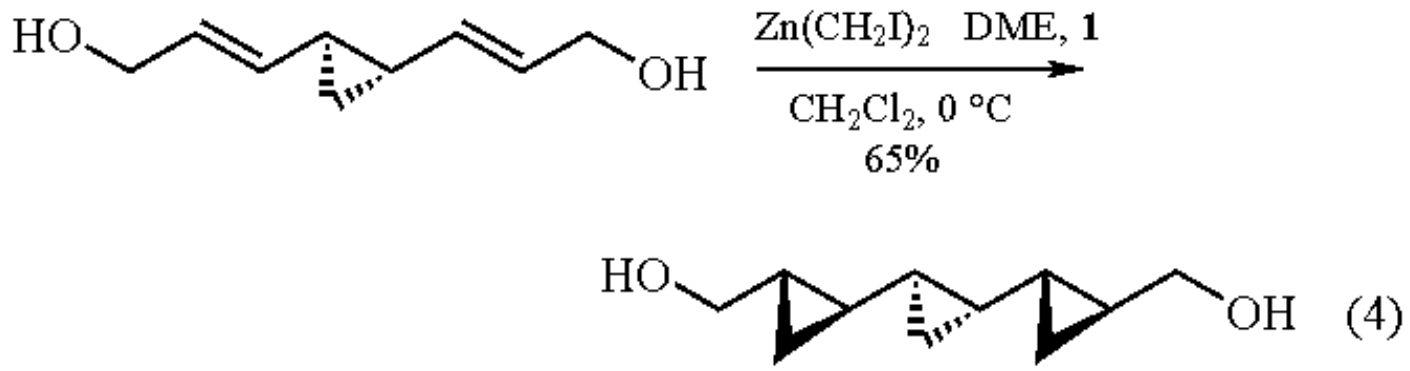

The reaction has also been extended to the enantioselective cyclopropanation of 3-tributylstannylprop-2-en-1-ol,[5a] to 3-iodo-[3a] and 3-chloroprop-2-en-1-ol.[6] The first two are useful precursors in palladium-catalyzed cross-coupling reactions[7] while the last was used in the total synthesis of callipeltoside A.

The enantioselective cyclopropanation reaction is quite general and practical. For example, the cyclopropanation reaction has been used to synthesize 3-methylcyclopropylmethanol, a precursor to curacin A.[8] Tri- and tetrasubstituted allylic alcohols are also converted into their corresponding cyclopropanes with high enantiocontrol (eq 5).

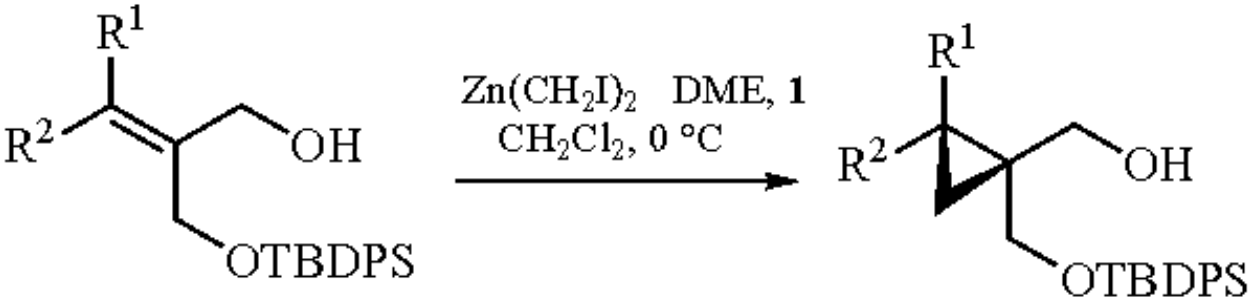

$R^1 = H, R^2 = Et$ >98% (89% ee)
$R^1 = Me, R^2 = Me$ 85% (88% ee) (5)

Polyenes can also be cyclopropanated at the allylic alcohol position with high chemo- and enantioselectivities due to the strong directing ability of the chiral ligand. This reaction has been used to generate key precursors of bicyclohumulenone (eq 6)[9] and noranthoplone (eq 7).[3a]

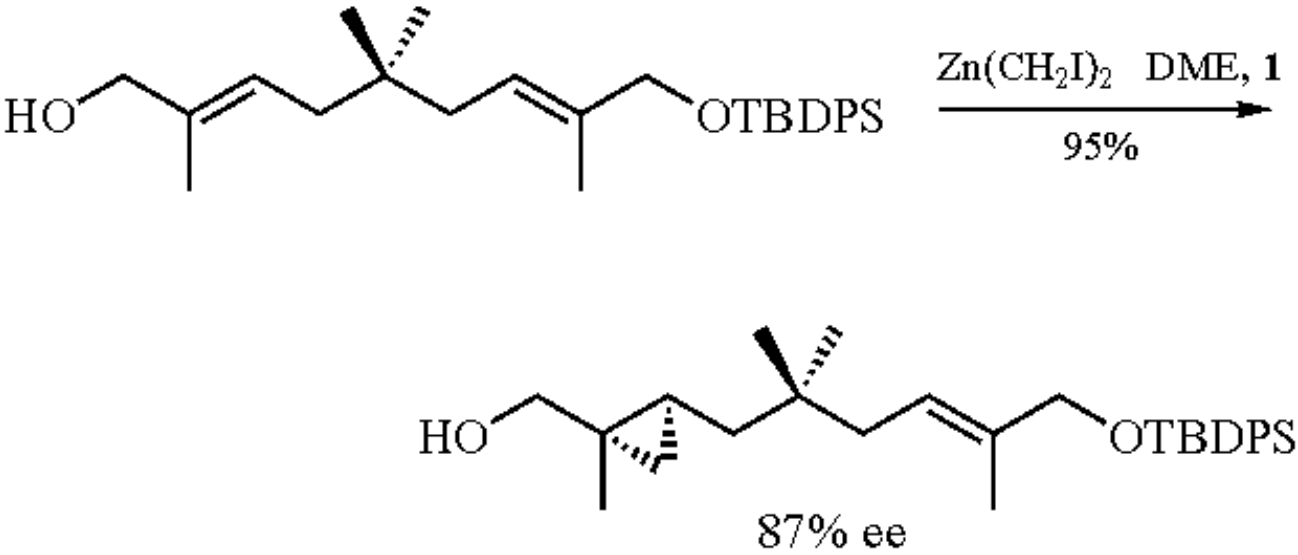

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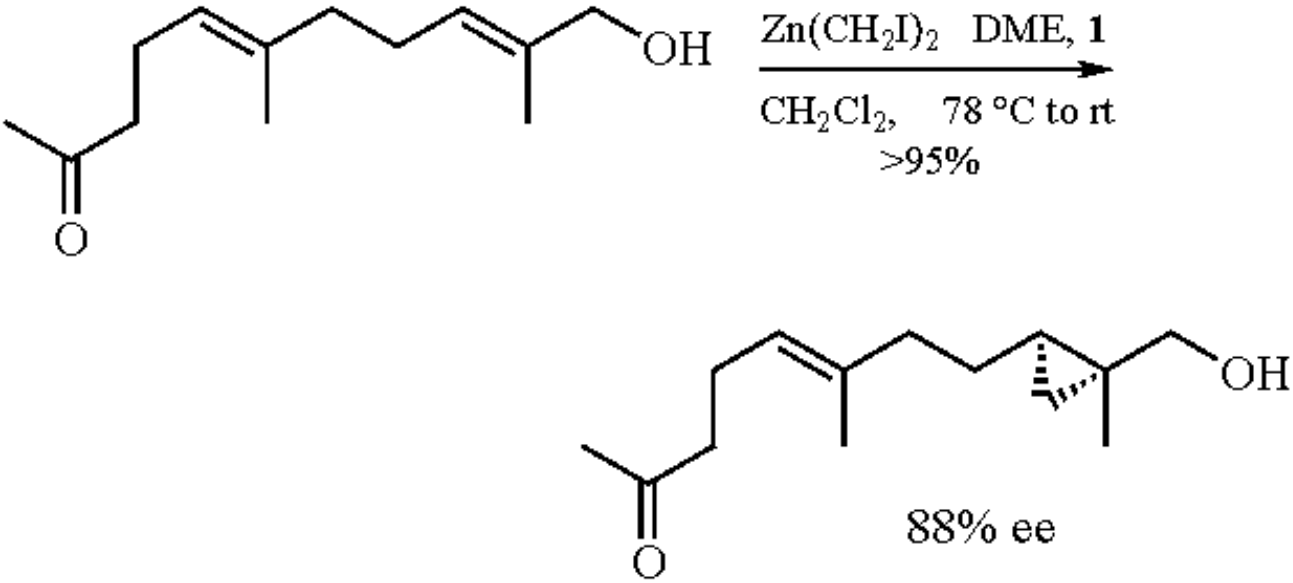

(7)

Unprecedented high *anti*-selectivities are obtained when *E*-substituted chiral allylic alcohols are treated with bis(iodomethyl)zinc and the dioxaborolane ligand (eq 8).[10] In contrast, the *syn*-isomer is obtained if the substrate is treated with the zinc reagent in the absence of the chiral ligand.[11] The method complements that involving the direct reduction of cyclopropylketones with $LiAlH_4$ or DIBAL-H.[12]

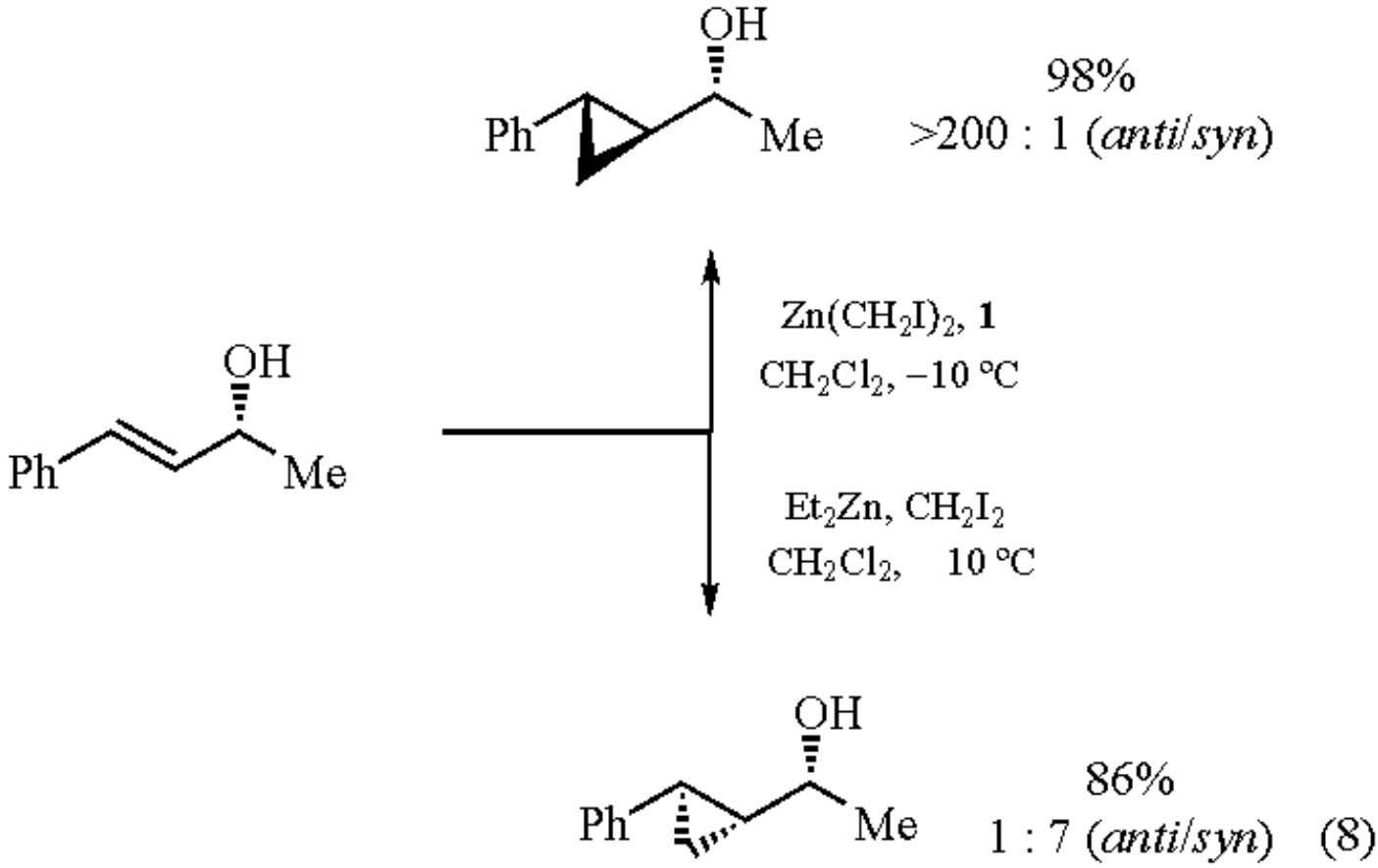

Enantioselective Synthesis of 1,2,3-trisubstituted Cyclopropanes

The chiral dioxaborolane ligand can also be used to generate 1,2,3-substituted cyclopropyl units when the appropriate 1,1-diiodoalkane is used in the preparation of the zinc reagent (eq 9).[13] The reaction affords 1,2,3-trisubstituted cyclopropanes with excellent enantio- and diastereocontrol, including those obtained from functionalized zinc reagents (eq 10).

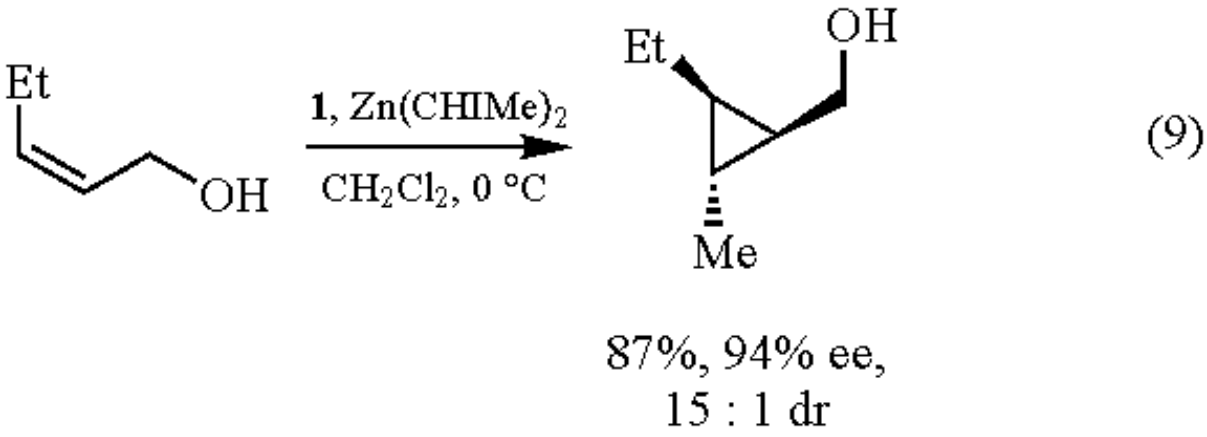

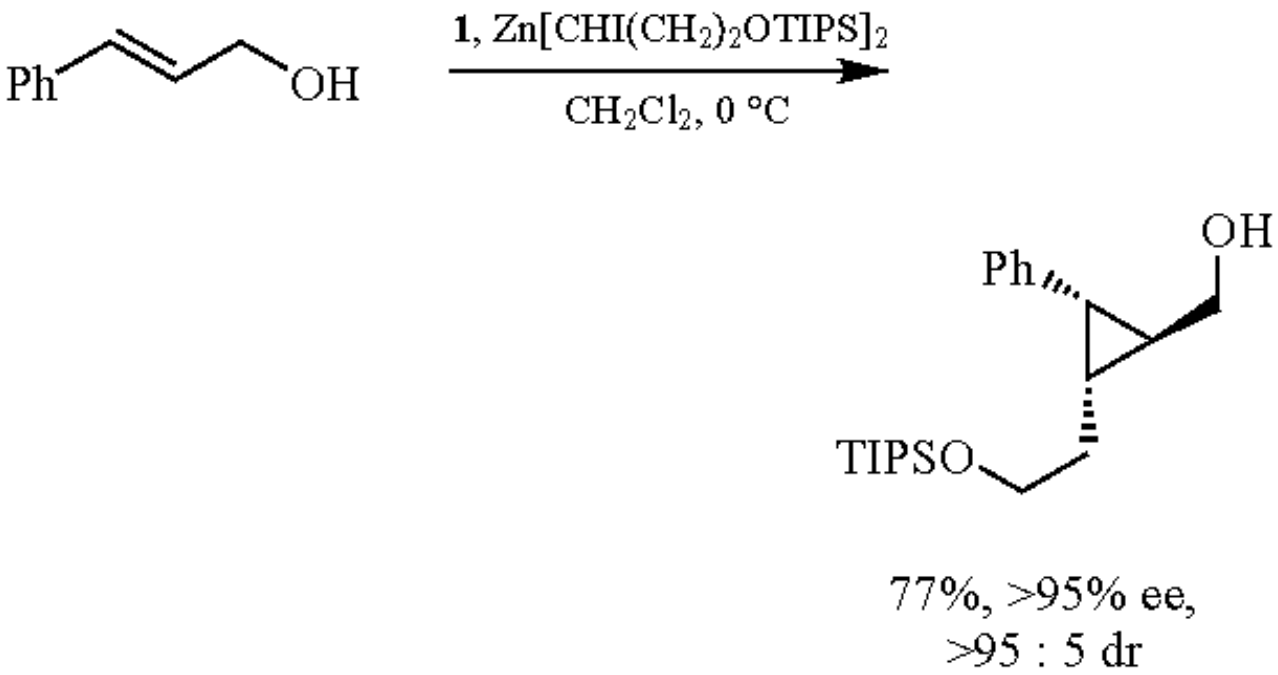

(10)

Use as a Chiral Auxiliary: Synthesis of Cyclopropylboronic Acids

The chiral dioxaborolane unit can also be used as an effective chiral auxiliary in the synthesis of enantiomerically enriched cyclopropylboronic acids. For example, 1-alkenylboronic esters bearing the tetramethyltartramide group undergo diastereoselective cyclopropanations to afford the cyclopropylboronic acid (eq 11).[14] These products can be used for *in situ* Suzuki coupling reactions[15] or can be oxidized to produce 2-substituted cyclopropanols.

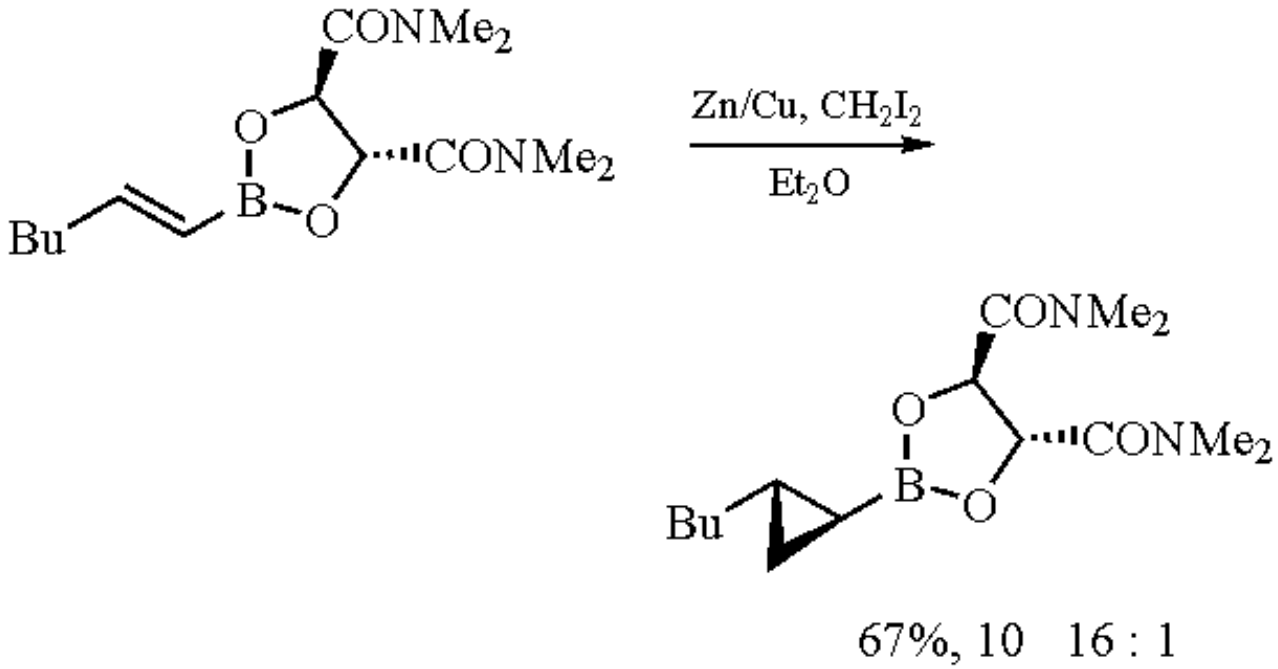

(11)

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6-Chloro-2,4-dimethoxy-s-triazine

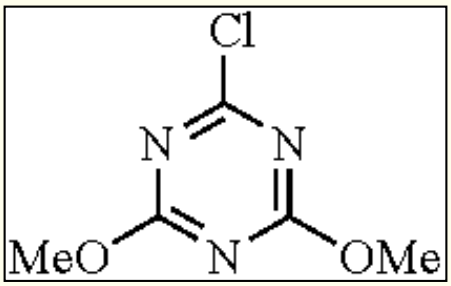

[3140-73-6] · $C_5H_6ClN_3O_2$ · (175.58)

(peptide coupling reagent; used to prepare active esters which can be used for the preparation of amides and esters;[1] used in the reduction of carboxylic acids to aldehydes or alcohols[2])

Alternate Name: CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine.

Physical Data: mp 71-74°C; bp 125-128°C/66.661 Pa.

Solubility: soluble in most organic solvents.

Form Supplied in: white solid; commercially available.

Preparative Methods: commercially available; prepared from cyanuric chloride and MeOH.[3] An improved procedure for a large-scale preparation has been reported.[4]

Purification: commercial reagent is generally used as received.

Handling, Storage, and Precautions: irritant; sternutator. Avoid inhalation. Should be handled with gloves in a fume hood. Relatively stable but should be stored under anhydrous conditions.

Amide Formation

6-Chloro-2,4-dimethoxy-s-triazine (CDMT) is utilized primarily as a coupling reagent in the condensation of amines and carboxylic acids for the preparation of peptides and other amides. Treatment of CDMT with a tertiary amine, preferably *N*-methylmorpholine (NMM), and a carboxylic acid yields an intermediate 6-acyloxy-2,4-dimethoxy-s-triazine (**1**) which serves as the acylating agent.[1,5] A typical example is shown in eq 1. The procedure involves adding *N*-methylmorpholine (1.02 equiv) to a solution of the corresponding carboxylic acid (1.02 equiv) and CDMT (1.0 equiv) at -5°C to 0°C in CH_2Cl_2, CH_3CN, THF, or DMF. The mixture is stirred for 1-4 h until formation of **1** is complete. The corresponding amine (1.0 equiv) and NMM (1.0 equiv) are then added, the mixture is allowed to warm to room temperature and stirred until the reaction is complete. Yields typically range from 75-98%. One major advantage offered by CDMT over other peptide coupling reagents, such as the carbodiimide reagents (see **1,3-dicyclohexylcarbodiimide**),[6] is the ease of purification. Since the triazine ring is weakly basic, a dilute acid wash will remove any by-products as well as any excess reagent from the reaction mixture. Furthermore, protected functional groups, as well as the unprotected hydroxyl group in serine, do not interfere with the coupling reactions, and racemization is not commonly observed. It is also worth noting that CDMT is inexpensive and has been used on kilogram scale.[7]

Studies directed toward a better understanding of the mechanism of activation of carboxylic acids by CDMT revealed that the reaction proceeds through quarternary triazinylammonium salts such as 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM) (**2**)[8,9] prior to formation of acyloxytriazines shown in eq 1. In fact, DMTMM, synthesized quantitatively by treatment of CDMT with NMM in THF (eq 2), is a white solid and is stable for a month at ambient temperature. It can be used directly in condensation reactions of amines and carboxylic acids,[10,11] thus providing a useful, “one-step” variant of CDMT. The example in eq 2 illustrates the complexity of amines and carboxylic acids that can be coupled using DMTMM or CDMT.[11,12] It should be noted that the stability of DMTMM varies in different solvents. For instance, DMTMM completely demethylates in CH_2Cl_2 in 3 h. Therefore, lower yields of amides are observed when CH_2Cl_2 is used as solvent for the condensation reactions. DMTMM is, however, very stable in THF and alcoholic solvents. Amides can be obtained from the condensation of carboxylic acids and amines with DMTMM in THF with yields similar to those observed in the CDMT-NMM system. A typical procedure involves adding DMTMM (1.1 equiv) to a mixture of the corresponding acid

(1.0 equiv) and amine (1.1 equiv) in THF and stirring at room temperature for 3-24 h. Furthermore, it is not necessary to dry the THF or perform the reaction under a N_2 atmosphere.

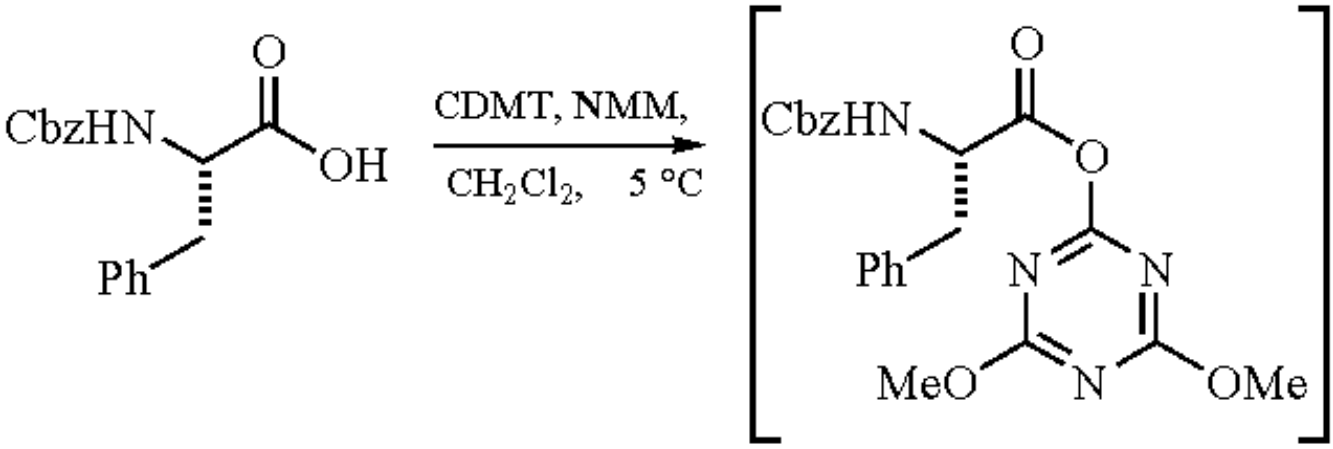

1

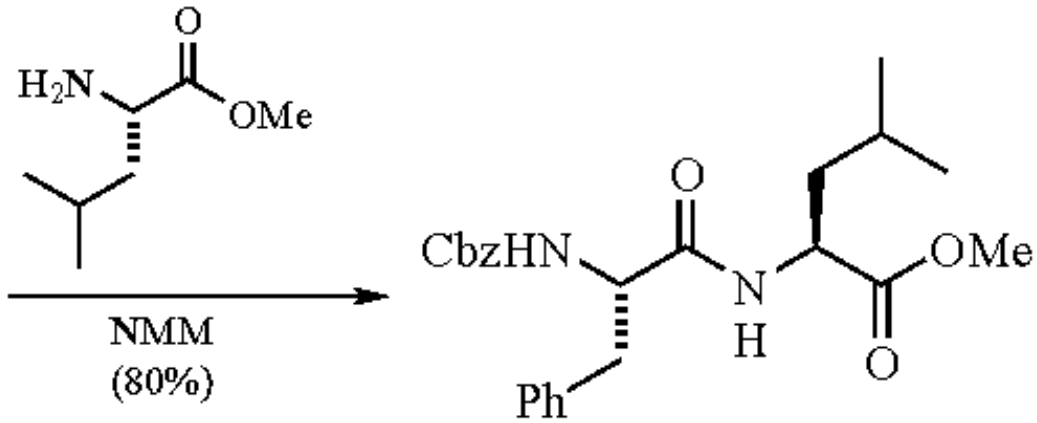

(1)

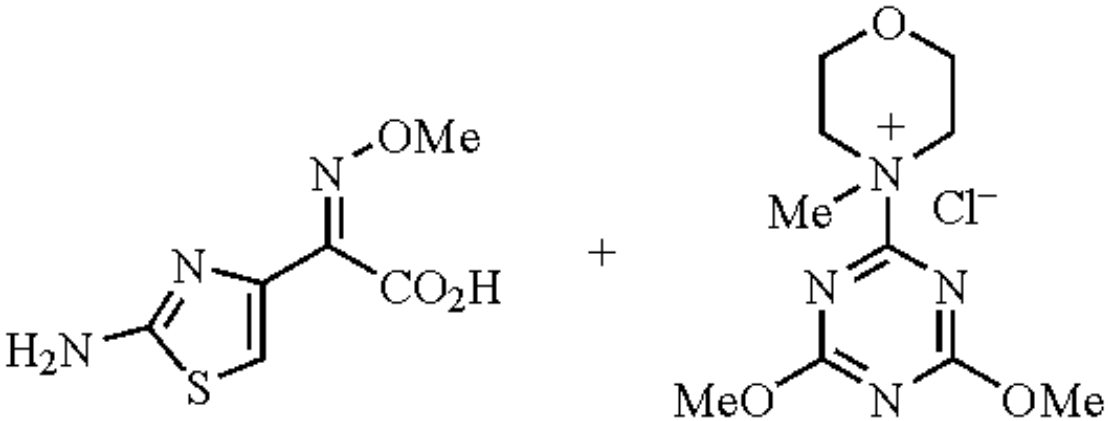

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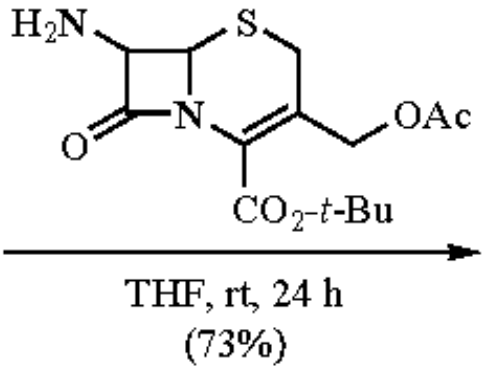

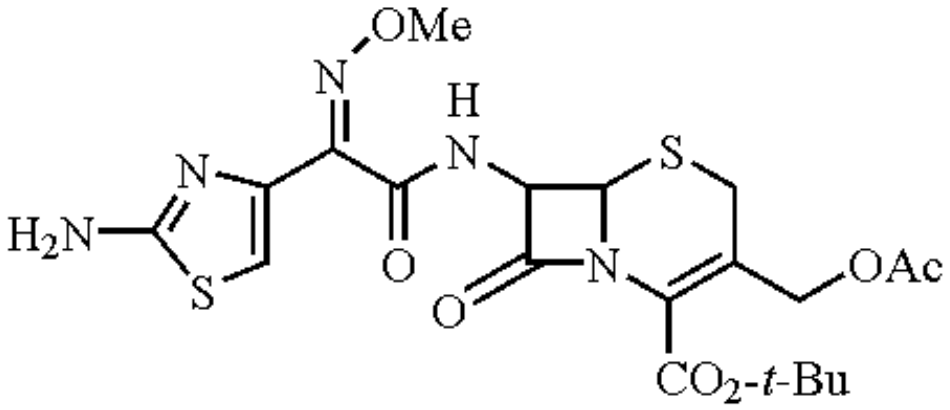

(2)

Ester Formation

Alcohols react much more slowly than amines with the 6-acyloxy-2,4-dimethoxy-s-triazine intermediates similar to **1**. Using typical CDMT-NMM conditions, ethyl benzoate was prepared by condensation of benzoic acid and ethanol in 65% yield, but the reaction time was 10 days.[1] It was later determined that ester formation proceeds much faster and in higher yields when the intermediate acyloxytriazine is isolated.[13] It was also determined that the rate of esterification can be increased by catalysis with 5 mol% $MgBr_2$ (eq 3). A typical procedure involves preparing the acyloxytriazine with CDMT, NMM and the corresponding carboxylic acid as described in the previous section. After work-up, the corresponding alcohol (10 equiv) and $MgBr_2$ (0.05 equiv) are then added to the crude, intermediate acyloxytriazine (1.0 equiv), and the mixture is stirred until the reaction is complete. Primary, secondary, and tertiary alcohols can be acylated under these conditions with yields between 44-92%. The reaction conditions are mild, but reaction times are somewhat long (typically 2-4 days), and the alcohol must be used in excess.

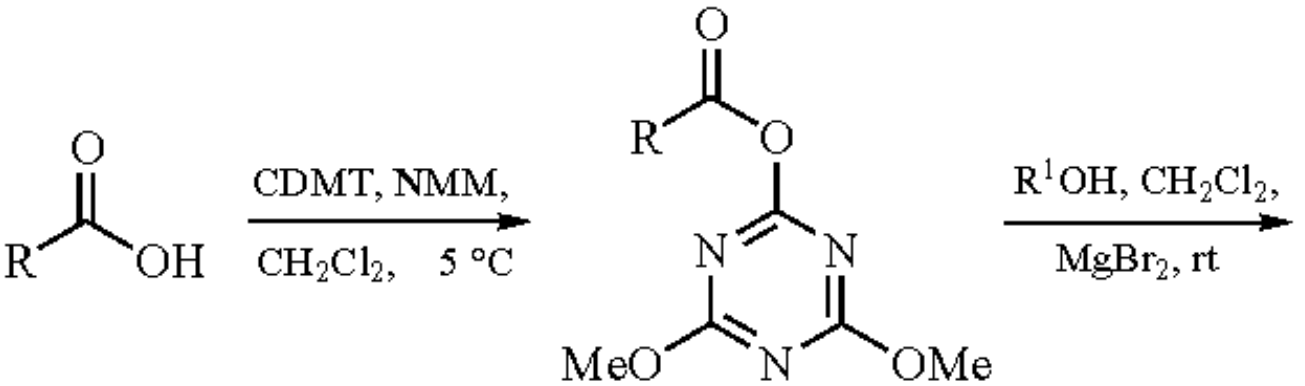

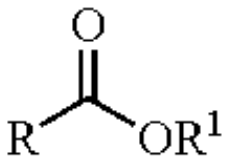

(3)

Carboxylic acids can also be esterified using DMTMM and the corresponding alcohols.[10,11] A typical procedure involves adding NMM (0.1-1.2 equiv) to a mixture of the carboxylic acid (1.0 equiv) and DMTMM (1.1-2.0 equiv) in the corresponding alcohol (solvent). Reaction times range from 4-21 h. The yields are quite good, but in most cases, the alcohol must be used in large excess.

Reduction of Carboxylic Acids

Active esters prepared from CDMT (e.g. 6-acyloxy-2,4-dimethoxy-s-triazines) can be reduced directly to aldehydes by treatment of hydrogen (1 atm) at room temperature in the presence of 10 mol% Pd/C (eq 4).[2] A typical procedure involves adding a carboxylic acid (1.0 equiv) to a mixture of DMTMM, prepared from CDMT (1.0 equiv) and NMM (1.02 equiv), in DME. The active ester is filtered, added to a mixture of Pd/C (10 mol%) in ethanol and stirred under a hydrogen atmosphere until the reaction is complete. Yields range from 75-84% when aliphatic carboxylic acids are used, but yields of aldehydes drop dramatically with aromatic carboxylic acids as substrates. The main product in these cases is the corresponding alcohol. Even with aliphatic carboxylic acids, the reactions have to be monitored carefully to avoid further reduction to the corresponding alcohols. In fact, if the hydrogen pressure is increased to 3-5 atm, alcohols can obtained in high yields.

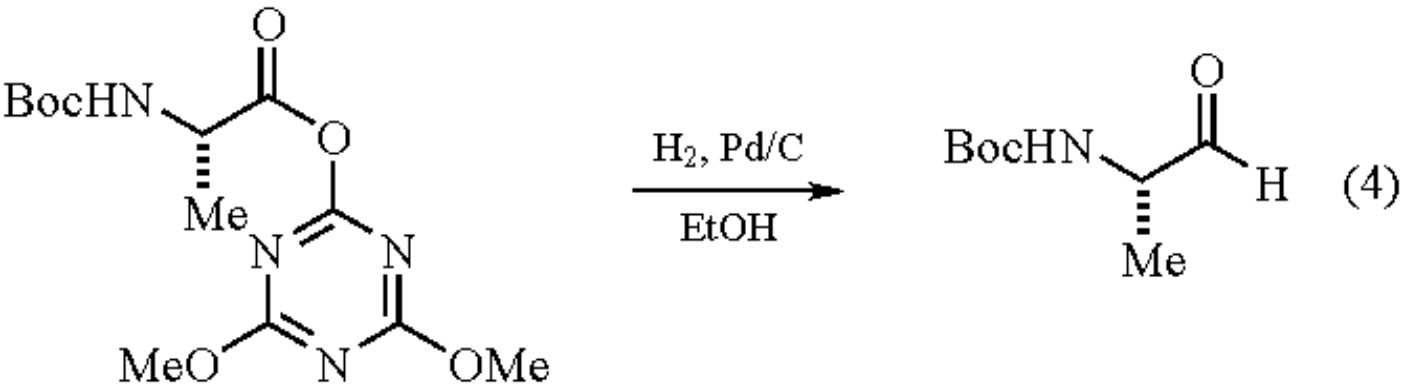

Other Uses

CDMT can be used as a source of 2,4-dimethoxy-s-triazine for the preparation of 6-substituted-2,4-dimethoxy-s-triazine derivatives. In these cases, substitution or coupling reactions occur at the carbon bearing the chlorine. Some examples include modified Sonogashira Pd-mediated couplings to form 6-alkynyl-2,4-dimethoxy-s-triazine derivatives,[14] glycosolations of thioglycosides,[15] nickel(0)-catalyzed cross-coupling reactions with arylboronic acids[16] and addition of amines to form 6-amino-2,4-dimethoxy-s-triazine derivatives.[17]

Related Reagents.

cyanuric chloride, benzotriazol-1-yloxytris(dimethylamino)phosphinium hexafluoro-phosphate (BOP), O-benzotriazol-1-yl-N,N,N´,N´-tetramethyluronium hexafluoro-phosphate (HBTU), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP), 1,3-dicyclohexylcarbodiimide (DCC), and 1-ethyl-3-(3´-dimethylaminopropyl)carbodiimide hydrochloride (EDCI).

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Tetrakis{1-[(4-dodecylphenyl)sulfonyl]-(2*S*)-prolinate} Dirhodium

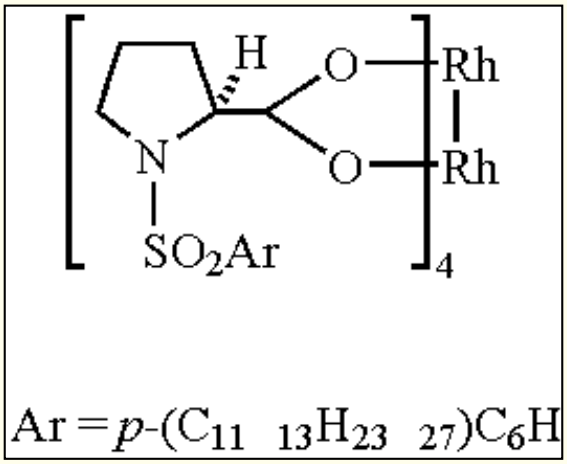

[179162-32-4] · $C_{90}H_{140}N_4O_{16}Rh_2S_4$ · (1866)

(chiral catalyst for asymmetric reactions of diazo compounds, especially aryldiazoacetates and vinyldiazoacetates[1])

Physical Data: mp 195-200°C $[\alpha]^{22}_D$ -165 ° (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.74 (d, 8 H, *J* = 9.2 Hz), 7.53 (d, 8 H, *J* = 9.2 Hz), 4.32 (m, 4 H), 3.25 (m, 4 H), 3.05 (m, 4 H), 2.07 (m, 4 H), 1.85 (m, 4 H), 1.57 (m, 8 H), 1.25 (bs, 36 H), 0.85 (m, 10 H).

Solubility: very soluble in most organic solvents including hydrocarbons.

Form Supplied in: green solid; available from Aldrich Chemical Co. The linear alkylbenzene side chains consist of a mixture of 1% C_{10}, 40% C_{11}, 28% C_{12} and 31% C_{13}.

Preparative Methods: from dirhodium tetraacetate by ligand exchange with *N*-[1-(dodecylphenyl)sulfonyl]-(2*S*)-prolinate.[2]

Purification: further purification is generally not necessary. May be dried by heating under vacuum at 100°C. May be purified by column chromatography on silica with ether/petroleum ether as solvent. If contaminated with the free ligand, can be purified by dissolving in diethyl ether and extracting the organic layer with aqueous sodium bicarbonate, followed by drying the organic layer over $MgSO_4$, then filtering and evaporation of the solvent.

Handling, Storage, and Precautions: the catalyst is moisture, air, and thermally stable. It may be stored at room temperature for extended periods of time without any apparent decomposition. The toxicity of the title reagent, Rh_2(*S*-DOSP)$_4$, is unknown. Strong nucleophiles such as nitriles, phosphines, amines, pyridines, and sulfides will tend to coordinate to the axial site of the catalyst. This may cause partial poisoning of the catalyst or catalyst decomposition, depending on the coordinating ligand. Reactions carried out under non-anhydrous conditions tend to result in lower enantioselectivity.[3]

Introduction

The title reagent Rh_2(*S*-DOSP)$_4$ and its *R*-enantiomer have been shown to be exceptional chiral catalysts for transformations of carbenes derived from aryldiazoacetates and vinyldiazoacetates. The related *p-tert*-butylphenyl prolinate derivative Rh_2(TBSP)$_4$ is also commercially available. All of these catalysts display higher levels of asymmetric induction in reactions that are carried out in hydrocarbon solvents and Rh_2(DOSP)$_4$ is generally favored over Rh_2(TBSP)$_4$ because it is soluble in hydrocarbon solvents even at -78°C. All of these catalysts are considered to be conformationally flexible but preferentially adopt a D_2-symmetric arrangement in solution.[1,2] This is a critical component for their effectiveness as chiral catalysts. Conformationally rigid analogs of Rh_2(*S*-DOSP)$_4$ have been reported[4] and these are also promising chiral catalysts.

Asymmetric Cyclopropanations

Rh_2(*S*-DOSP)$_4$ has been shown to be an exceptional chiral catalyst for asymmetric cyclopropanations of vinyldiazoacetates,[2,5] aryldiazoacetates,[6] and alkynyldiazoacetates.[7] Enantioselectivities of greater than 90% ee are very common with this catalyst. The decomposition of a vinyldiazoacetate by Rh_2(*S*-DOSP)$_4$ in the presence of styrene generates a vinylcyclopropane in 98% de and 98% ee (eq 1). This product has been applied to the asymmetric synthesis of (+)-sertraline[8] and the cyclopropane analogs of phenylalanine.[2]

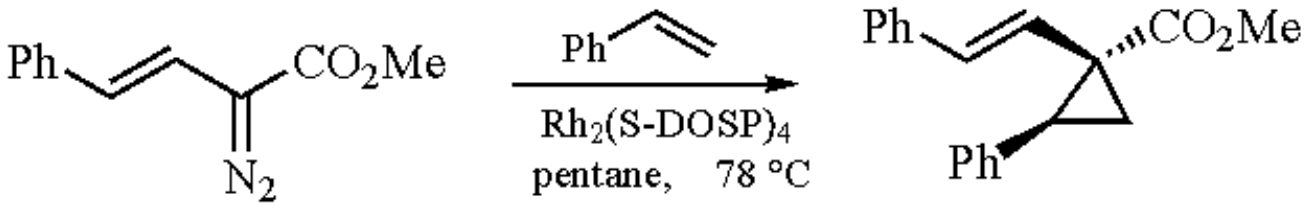

(1)

(69% yield, 98% ee, 98% de)

A special feature of Rh_2(*S*-DOSP)$_4$ is that it is designed for asymmetric transformations of donor/acceptor substituted carbenoids, unlike most of the chiral catalysts for diazo decomposition which are optimized for the cyclopropanation chemistry of unsubstituted diazoacetates.[9] Indeed, the rhodium prolinates rarely induce good asymmetric induction in the reactions of other classes of carbenoids.[2,10] The highest levels of enantioselectivity are obtained when the reactions are carried out in hydrocarbon solvents, and Rh_2(*S*-DOSP)$_4$ is ideally suited because it is soluble in hydrocarbon solvents even at -78°C.[2] Typically, 1 mol% of catalyst is used and the reactions are virtually instantaneous at room temperature, while at -78°C, the reaction times are 12-48 h. Several comparison studies with various other chiral rhodium and copper catalysts have been reported in recent years,[6b,c,11] but so far none have outperformed Rh_2(*S*-DOSP)$_4$ on a regular basis. Cyclopropanations with Rh_2(*S*-TBSP)$_4$ carried out under non-anhydrous reaction conditions result in considerable lowering of the enantioselectivity.[3] Using trioctylphosphine oxide as an additive can minimize this effect.[3] Asymmetric cyclopropanations have also been carried out with Rh_2(*S*-TBSP)$_4$ in supercritical fluids.[3]

Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of vinyldiazoacetates in the presence of vinyl ethers leads to donor/acceptor substituted vinylcyclopropanes.[12] On treatment with diethylaluminum chloride these vinylcyclopropanes undergo a stereoselective rearrangement to cyclopentanes. An illustrative example is shown in eq 2, whereby the tricyclic system is formed in 86% ee.[12] The extent of retention of the asymmetric induction during the vinylcyclopropane rearrangement is very dependent on the cyclopropane substitution pattern.

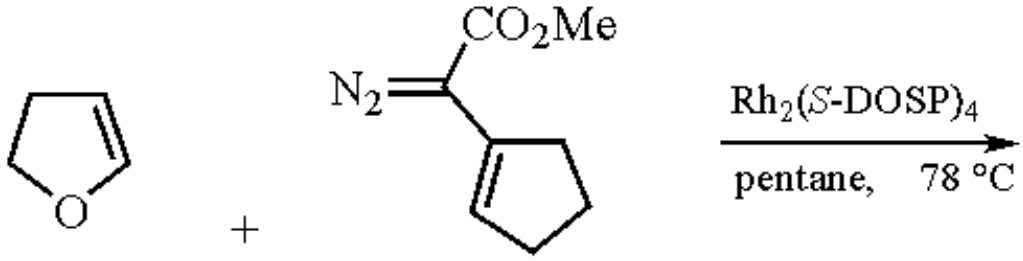

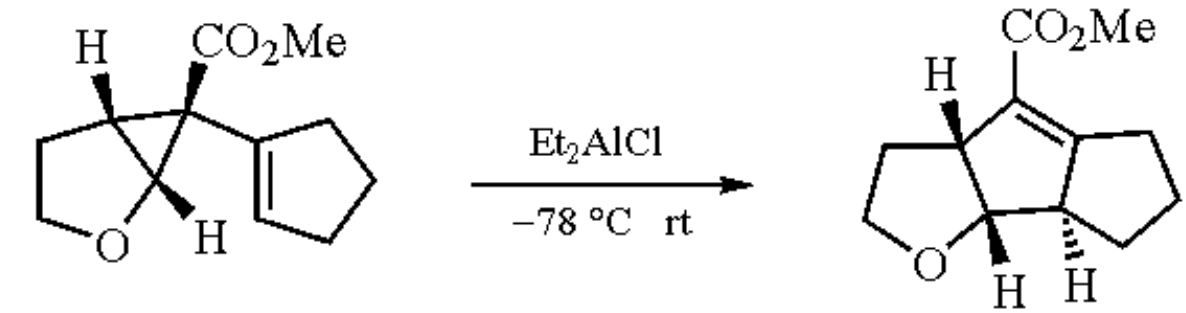

(2)

53% yield, 88% ee

79% yield, 86% ee

Rhodium(II) carboxylate-catalyzed decomposition of vinyldiazoacetates in the presence of dienes is a very effective stereoselective method for the construction of highly functionalized cycloheptadienes.[13] The [3+4] cycloaddition proceeds via a divinylcyclopropane, which undergoes a Cope rearrangement in a stereodefined manner, leading to cycloheptadienes with stereocontrol at up to three stereogenic centers. When these reactions are catalyzed by Rh_2(*S*-DOSP)$_4$ highly enantioselective reactions are obtained.[14] The reactions with phenylbutadiene and cyclopentadiene illustrate the synthetic potential of this chemistry (eq 3 and 4).[14] Asymmetric [3+4] cycloadditions are also possible between vinylcarbenoids and furans[15] or *N*-BOC-pyrroles[16] leading to the synthesis of 8-oxabicyclo[3.2.1]octadienes or tropanes.

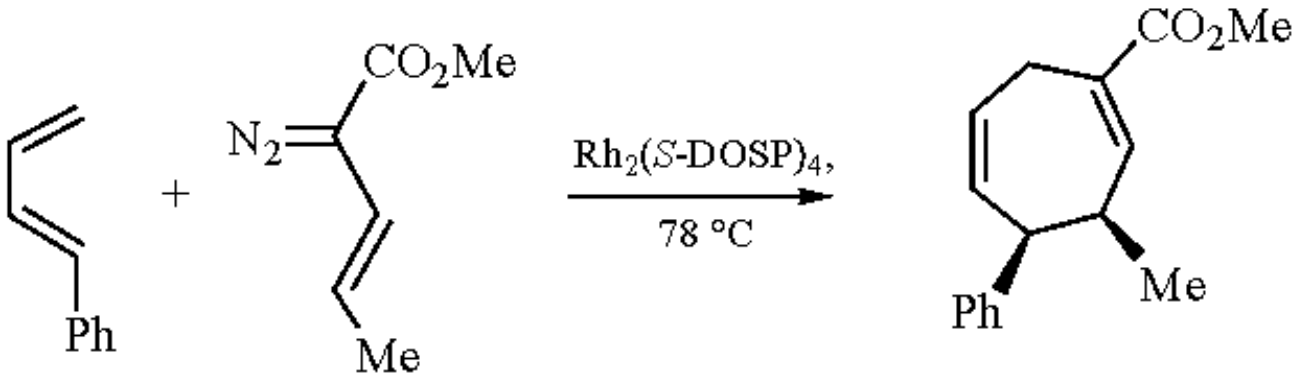

(3)

87% yield, 98% ee

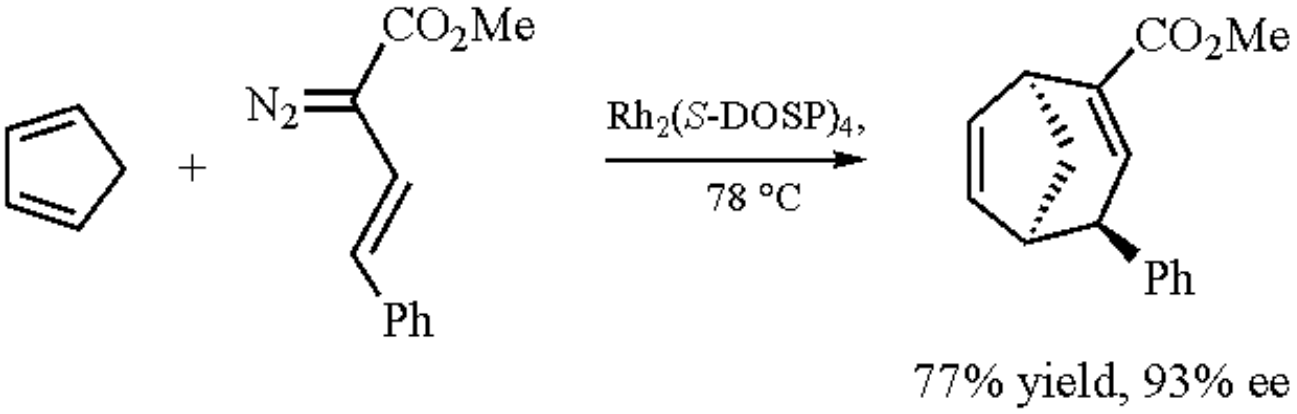

(4)

Reasonably high asymmetric induction can be obtained in intramolecular cyclopropanations.[17] Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of a *Z*,*E*-diene generated a tricyclic system in 93% ee with full control of relative stereochemistry (eq 5). As this reaction initially forms a *trans*-divinylcyclopropane, heating to 140°C is required to induce equilibration to the *cis*-divinylcyclopropane followed by the Cope rearrangement. In general, the intramolecular cyclopropanations are not as highly enantioselective as the intermolecular cyclopropanations, and with certain substrates, other chiral catalysts can result in higher enantioselectivity than Rh_2(*S*-DOSP)$_4$.[18]

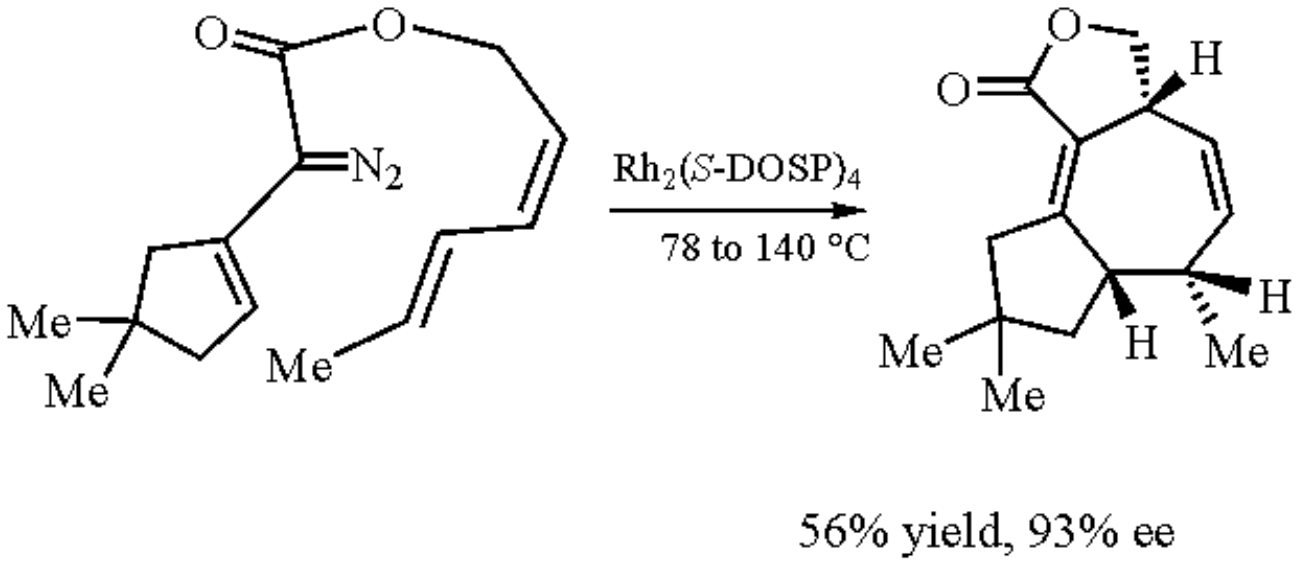

(5)

Aryldiazoacetates are capable of being used in solid-phase synthesis.[19] The traditional diazoacetates do not react effectively with substrates on solid support because the carbenoid intermediates are highly reactive and prone to dimerization.[20] The carbenoids derived from aryldiazoacetates are considerably more chemoselective,[21] and when Rh_2(*S*-DOSP)$_4$ is used as catalyst, effective asymmeric cyclopropanation of an alkene on a solid support is possible (eq 6).[19] This protocol can be used to achieve asymmetric cyclopropanation of elaborate alkenes because the alkene is used as the limiting reagent.

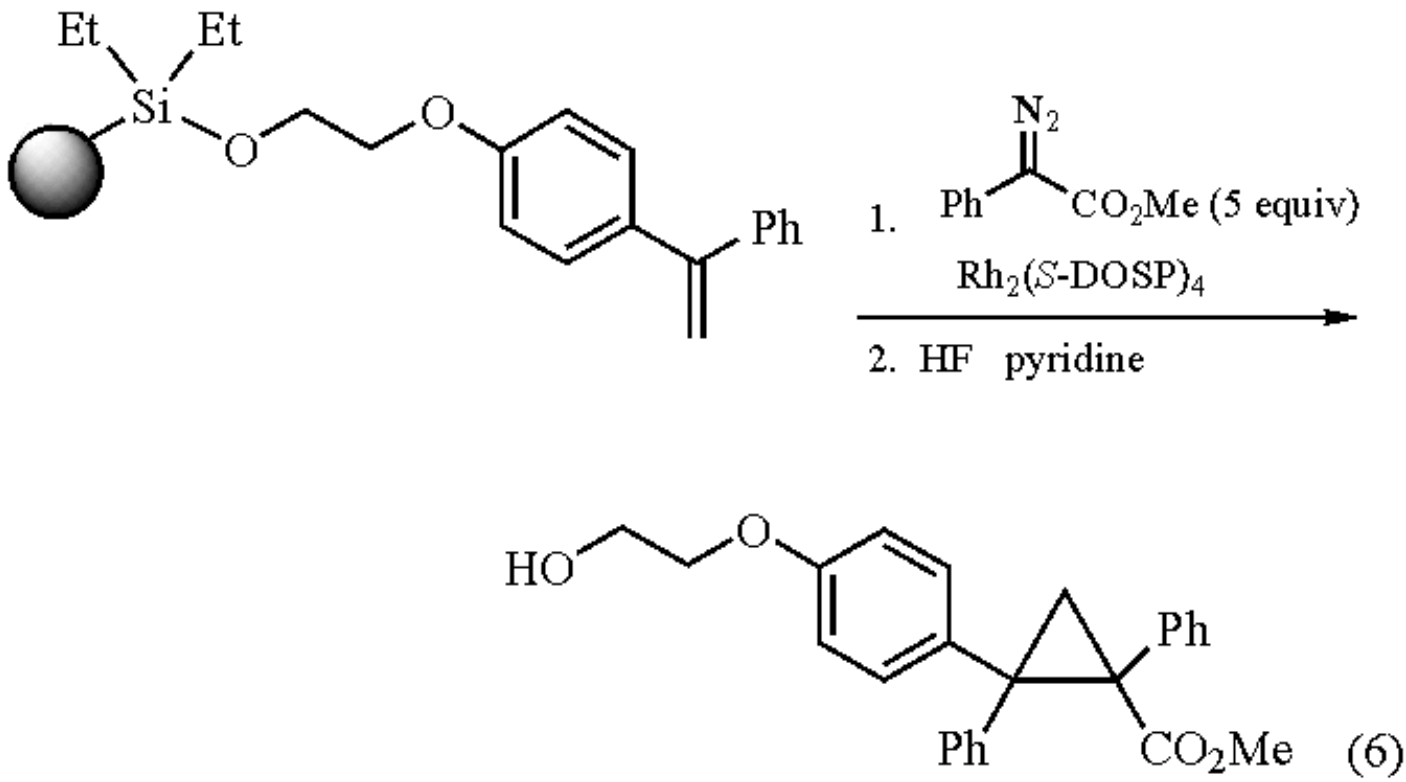

83% yield, 91% ee, 85:15 *E*/*Z*

[3+2] Cycloaddition

The Rh_2(*S*-DOSP)$_4$ catalyzed reaction of certain vinyldiazoacetates with styryl ethers results in a very unusual transformation.[22] As illustrated in eq 7, instead of the normal cyclopropanation, a [3+2] cycloaddition product is formed. Remarkably, this product is formed as the all *cis* diastereomer in 98% ee. Selective cuprate additions to these [3+2] cycloaddition products can generate, stereoselectively, cyclopentanes with five contiguous stereocenters.

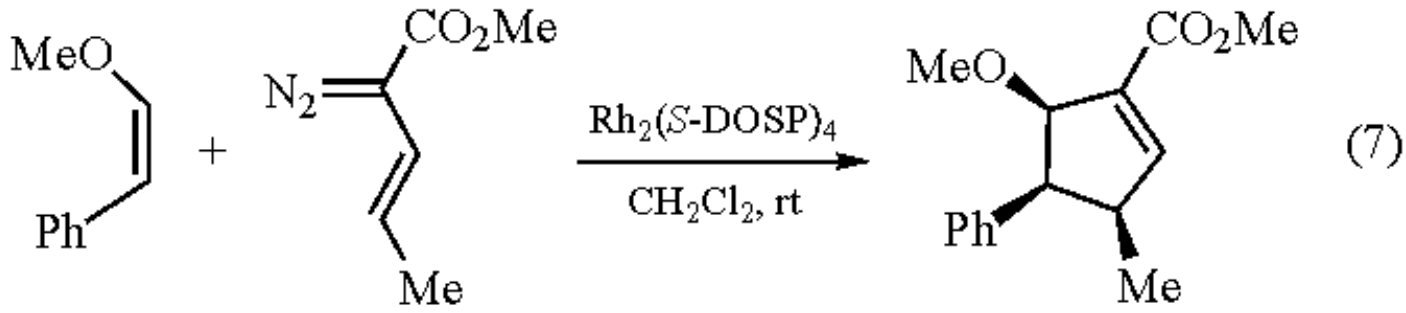

79% yield, 98% ee

Asymmetric C-H Insertion

A major advantage with the use of aryldiazoacetates is that effective intermolecular C-H insertions can be achieved.[23] Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl phenyldiazoacetate in the presence of cyclohexane results in the formation of the C-H insertion product in 95% ee (eq 8).[24] The reaction has been extended to a range of alkanes and the selectivity of competing insertions between secondary and tertiary C-H sites depends on a delicate balance between steric and electronic effects.[24]

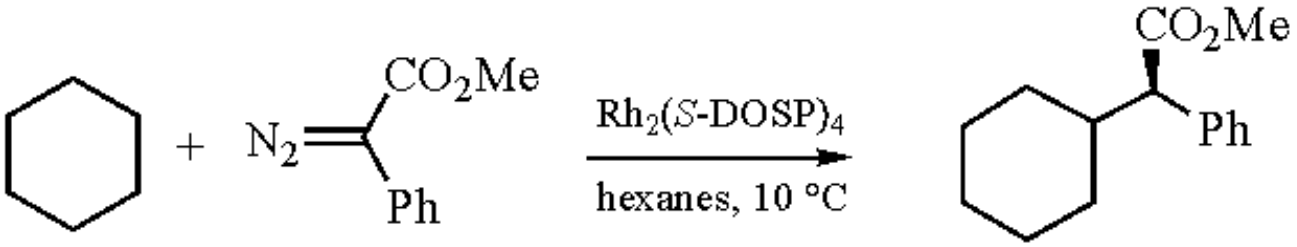

(8)

80% yield, 95% ee

Highly efficient C-H insertion into allylic C-H positions is possible as illustrated in the example with 1,4-cyclohexadiene shown in eq 9.[25] Similar highly enantioselective C-H insertions are possible with cycloheptatriene,[26] while the reaction with cyclohexene proceeded with moderate enantioselectivity but poor diastereoselectivity.[27]

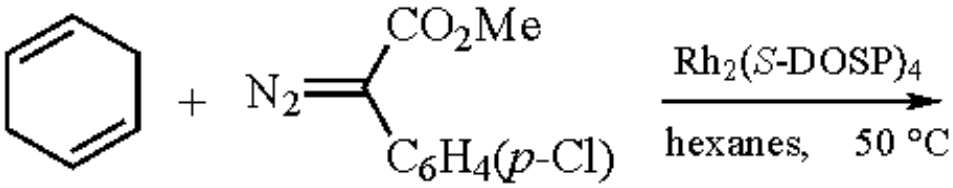

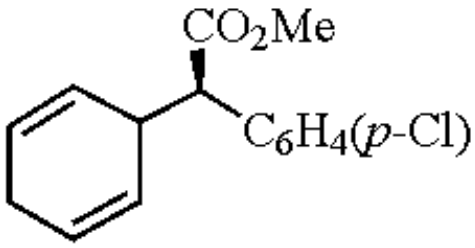

(9)

84% yield, 94% ee

The intermolecular C-H insertion is a very general method for C-H functionalization and represents a surrogate to many classic synthetic transformations. The allylic C-H insertion of trisubstituted vinyl silyl ethers shown in eq 10 represents the equivalent of an asymmetric Michael addition.[28] Remarkably, the C-H insertion product in this case is formed with very high diastereoselectivity. In general, high diastereoselectivity is observed for C-H insertions at methylene sites in which there is considerable size differential between the two substituents.[23]

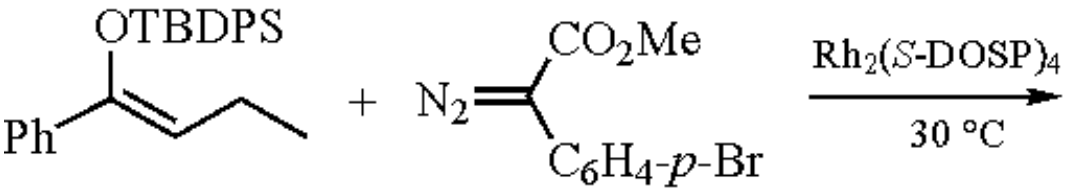

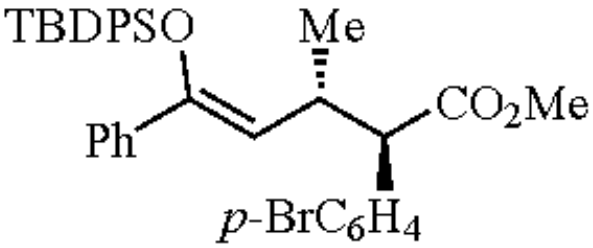

(10)

65% yield, 84% ee, >90% de

Another spectacular example of a highly diastereoselective intermolecular C-H insertions is the reaction between aryldiazoacetates and

tetralkoxysilanes, which generate silyl-protected β-hydroxy esters,[29] products that would be typically prepared by an aldol reaction. The utility of this reaction is illustrated in the example with tetraethoxysilane, in which the C-H insertion product is formed in 95% ee and >90% de (eq 11). Highly diastereoselective C-H insertions are also possible with allyl silyl ethers.[30]

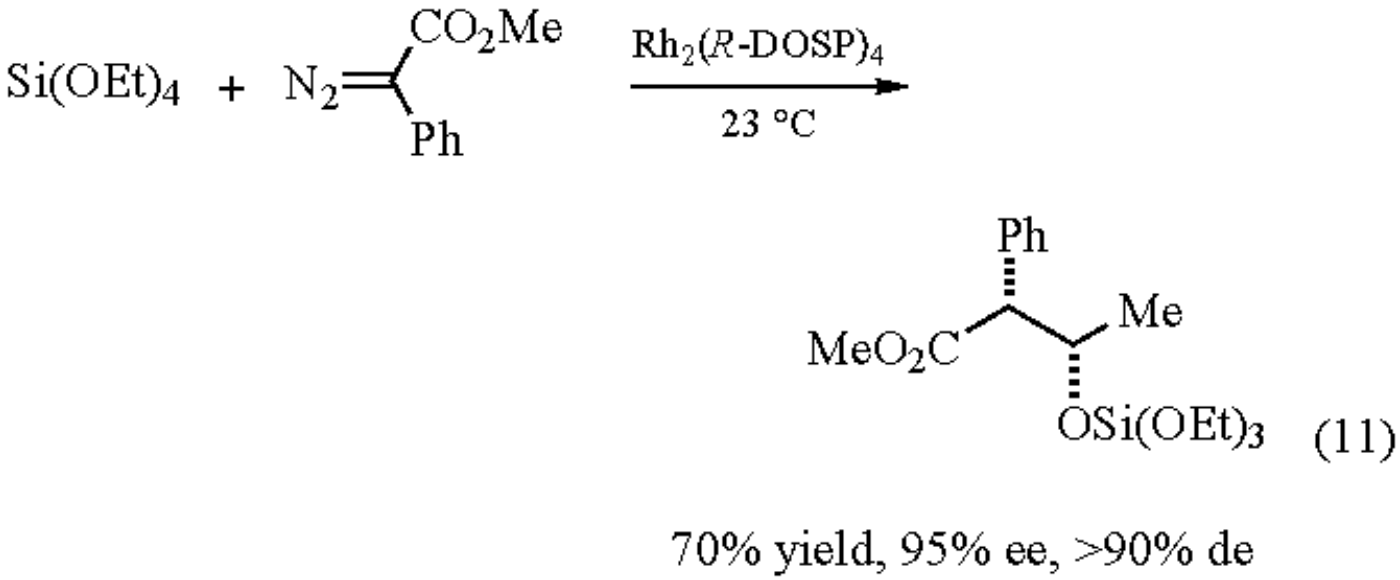

C-H insertions adjacent to nitrogen results in the formation of products that would be typically formed by a Mannich reaction. *N*-BOC-pyrrolidine is another substrate that undergoes highly diastereoselective C-H insertions, as illustrated in eq 12.[31] The related reaction with *N*-BOC-piperidine[31,32] is also a very important transformation because it represents a very direct synthesis of ritalin.

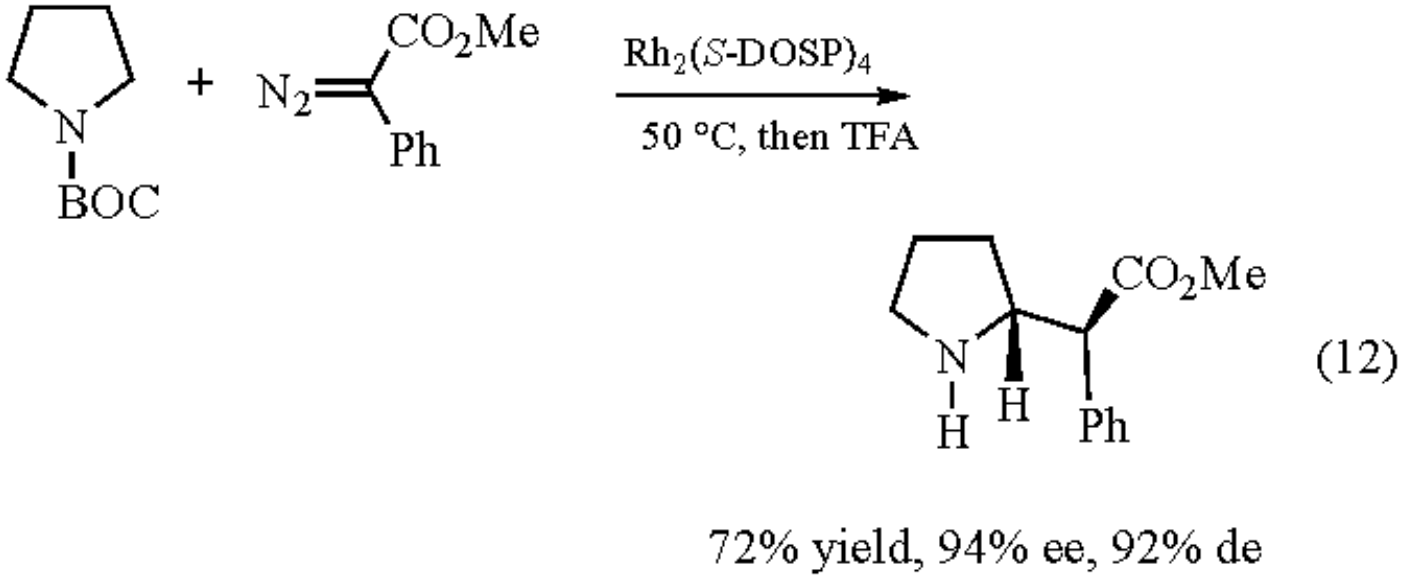

The chemoselectivity of the C-H insertion is sufficiently great that these reactions can display very impressive levels of kinetic resolution.[33] An illustrative example is the C-H insertion with the racemic 2-substituted pyrrolidine derivative shown in eq 13.[33] The C-H insertion product is formed in 98% ee with excellent control of stereochemistry at three stereogenic centers. By appropriate control of reaction conditions, a double C-H insertion on *N*-BOC-pyrrolidine is possible, generating a 2,5-disubstituted pyrrolidine with excellent control of stereochemistry at four stereogenic centers.[31]

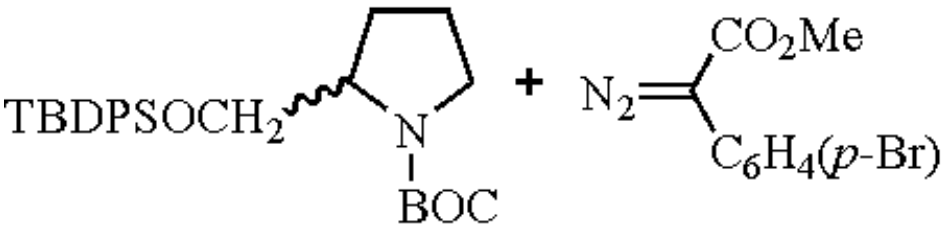

(2 equiv)

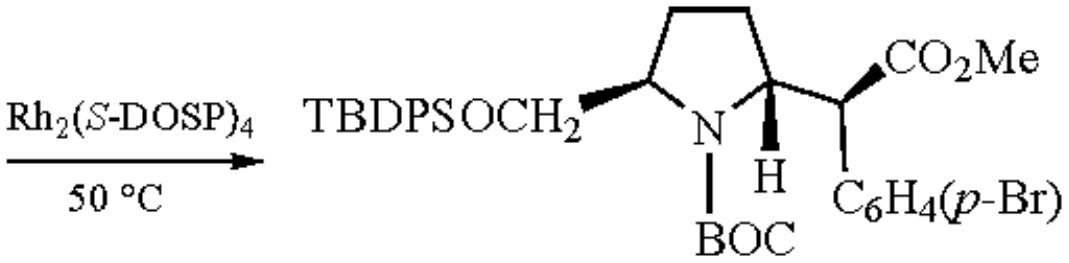

(13)

85% yield, 98% ee, >94% de

Highly asymmetric intramolecular C-H insertions are also possible in Rh_2(*S*-DOSP)$_4$-catalyzed reactions, as illustrated in eq 14.[34] The level of asymmetric induction is very dependent on the substitution pattern at the C-H insertion site, with the highest level of C-H insertion obtained for reactions at tertiary C-H sites.[34,35]

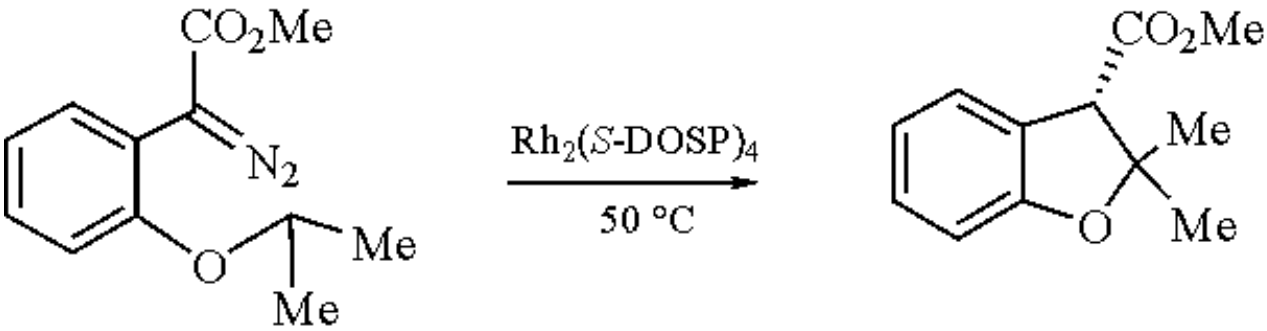

(14)

98% yield, 94% ee

Combined C-H Insertion Cope Rearrangement

The reaction of vinyldiazoacetates at allylic C-H sites does not result in the predominant formation of the products of a simple C-H insertion.[25] Instead, combined C-H insertion/Cope rearrangement products with very high enantioselectivity are formed, as illustrated in the example shown in eq 15.[25] This process has been applied to a very short asymmetric synthesis of (+)-sertraline.

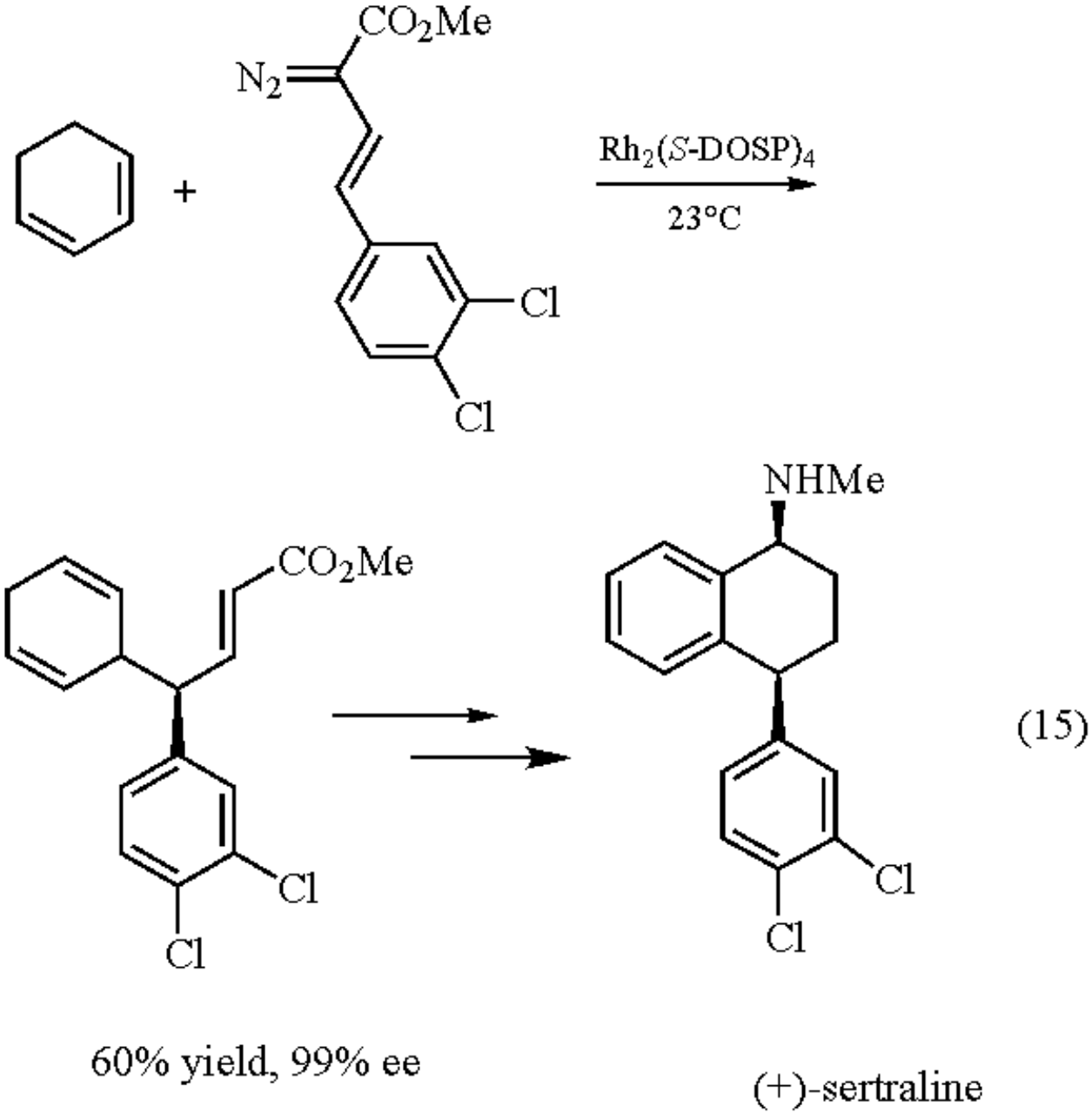

(15)

Si-H Insertions

Vinyldiazoacetates and aryldiazoacetates are capable of undergoing effective asymmetric Si-H insertions when the reaction is catalyzed by Rh_2(*S*-DOSP)$_4$. An illustrative example is shown in the reaction of a vinyldiazoacetate that results in the formation of an allylsilane in 95% ee (eq 16).[36]

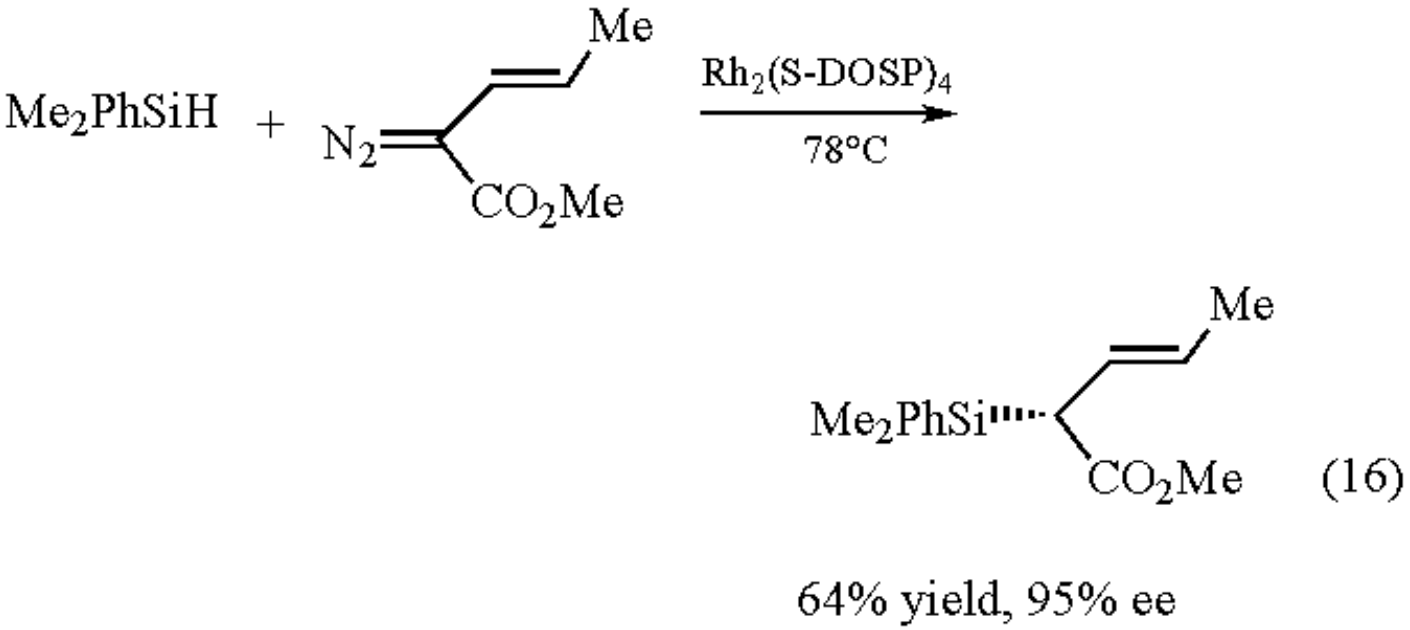

In summary, the Rh_2(*S*-DOSP)$_4$-catalyzed reactions of aryldiazoacetates and vinyldiazoacetates offer a wide range of applications in organic synthesis. The carbenoids derived from these diazo systems are highly chemoselective and the reactions catalyzed by Rh_2(*S*-DOSP)$_4$ are often highly enantioselective.

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(*S*,*S*)-1,2-Bis(*tert*-butylmethylphosphino)ethane[1]

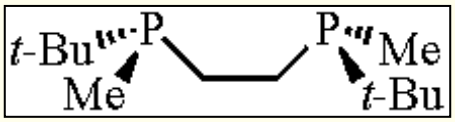

[20300-53-7] · $C_{12}H_{28}P_2$ · (234.30)

(a chiral ligand for transition metal-catalyzed asymmetric reactions)

Alternate Name: BisP*.

Physical Data: mp 23.5-25.5 °C.

Solubility: soluble in most organic solvents.

Form Supplied in: borane complex of **1** is commercially available as colorless crystals.

Preparative Methods: phosphorus trichloride is allowed to react sequentially with alkylmagnesium chloride, methylmagnesium bromide, and BH_3-THF complex in THF to give alkyldimethylphosphine-borane (eq 1).[1] The phosphine-borane so obtained is enantioselectively deprotonated by *s*-BuLi in the presence of (-)-sparteine in Et_2O at -78 °C to -50 °C, followed by oxidative coupling using $CuCl_2$ to give a BisP*-borane complex. Recrystallization from toluene affords enantiomerically pure product. The boranato group is removed by the reaction with trifluoromethanesulfonic acid in toluene, followed by treatment with aqueous KOH.

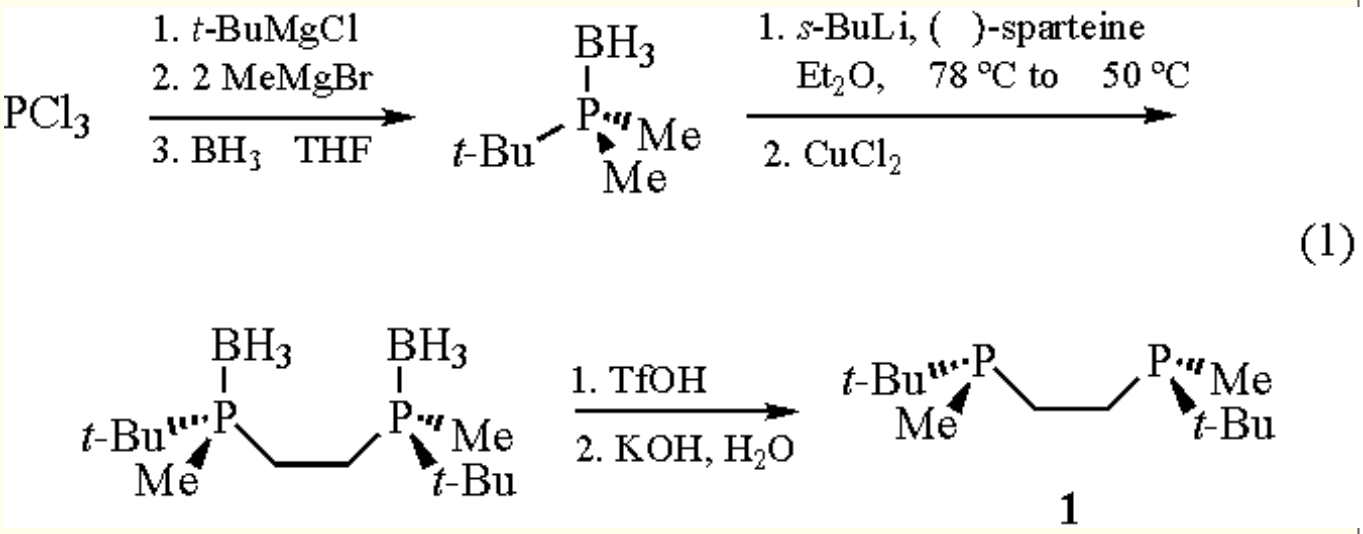

Purification: filtered through Al_2O_3 with Et_2O elution under N_2 or Ar atmosphere.

Handling, Storage, and Precautions: stench. Undergoes oxidation to the phosphine oxide on standing in air. Usually prepared before use by deboranation of the air stable phosphine-borane.

Rhodium-Catalyzed Asymmetric Hydrogenation of Olefins

A rhodium complex of BisP* (**1**) is a highly effective catalyst for asymmetric hydrogenation of some olefinic compounds.[1] BisP*-rhodium complex **2** is prepared from **1** and $[Rh(nbd)_2]BF_4$ in THF (eq 2). The hydrogenation of α-(acylamino)-acrylic derivatives are carried out at room temperature and an initial H_2 pressure of 2 or 6 atm in the presence of the catalyst (0.2 mol%). The reactions proceed rapidly and are complete within 0.2-2 h to afford α-amino acid derivatives with enantioselectivity of up to 99.9% (eq 3). This methodology can also be applicable to β-unsubstituted and β,β-disubstituted α-(acylamino)acrylates. The excellent enantioselectivities are again observed in hydrogenation of itaconic acids,[2] enamides,[3] and dehydro-β-amino acids[4] (eq 4-6).

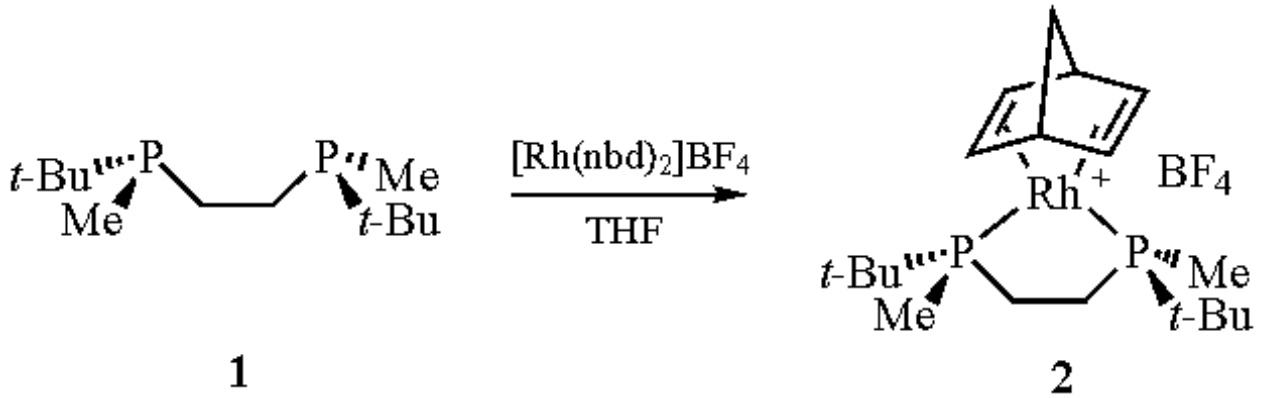

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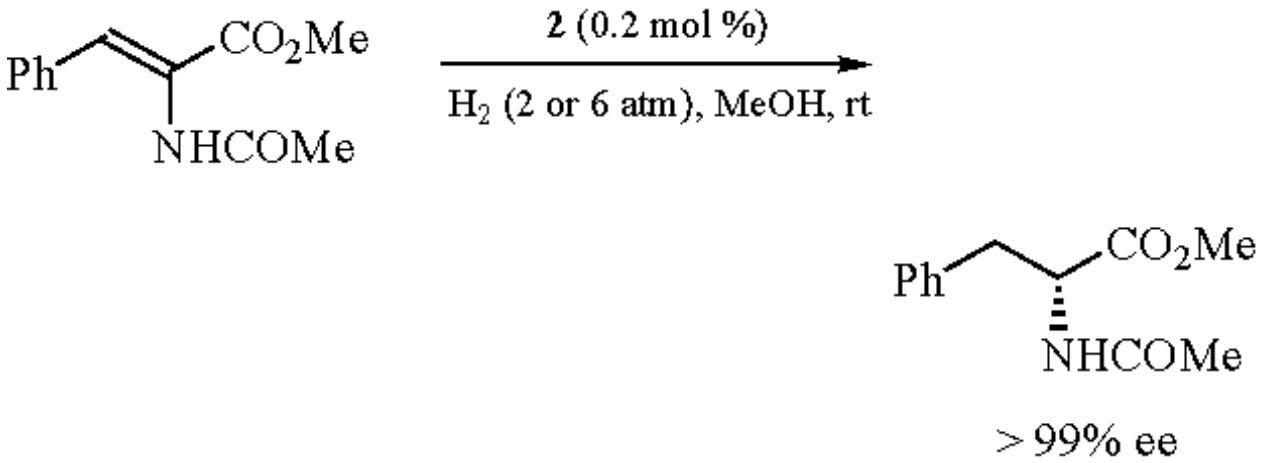

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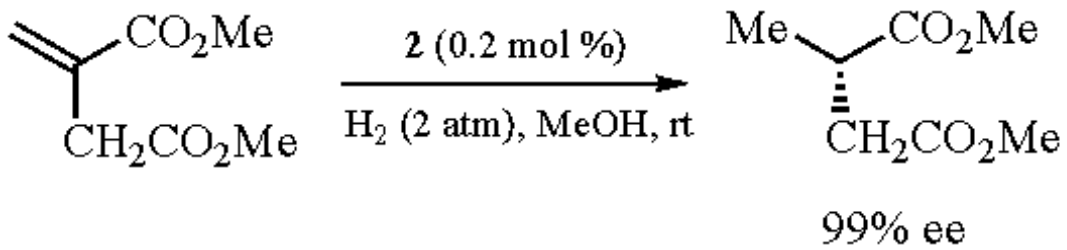

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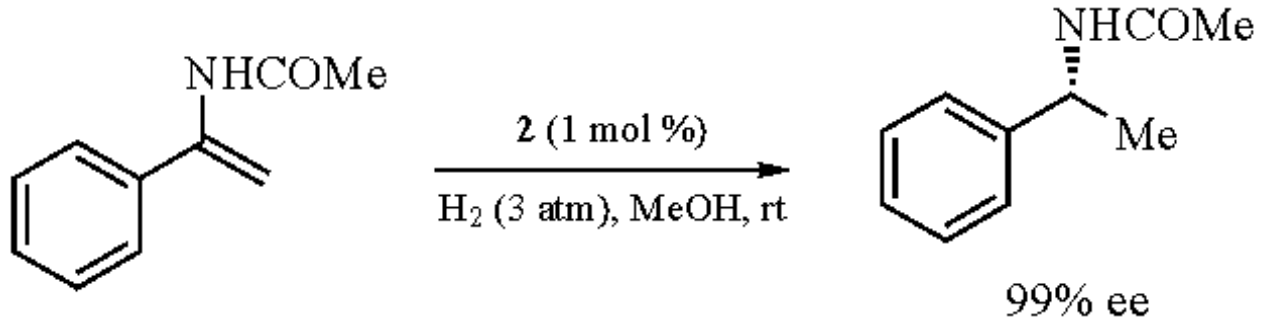

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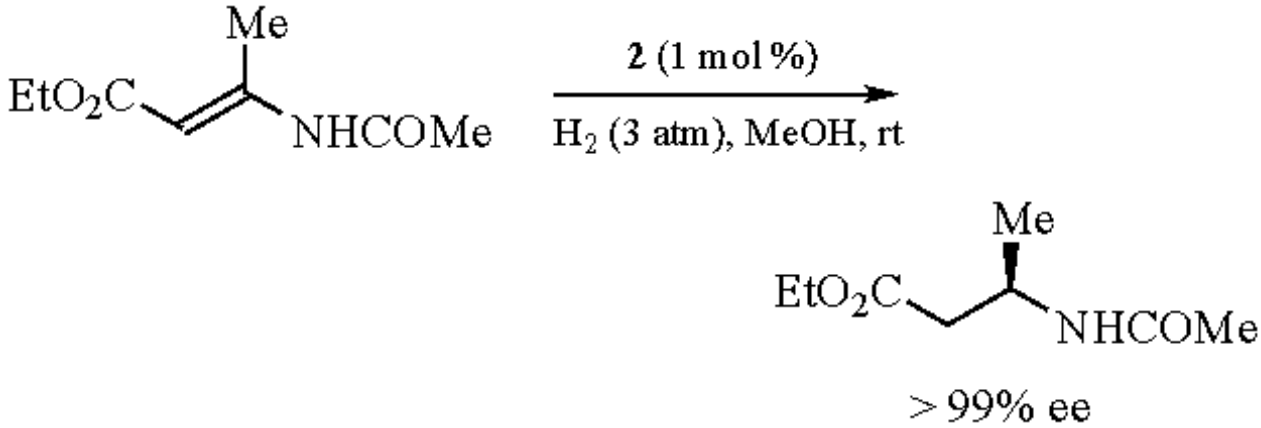

(6)

Ruthenium-Catalyzed Asymmetric Hydrogenation of β-Keto Esters

A ruthenium complex of **1** catalyzes enantioselective hydrogenation of β-keto esters.[5] The **1**-Ru complex is prepared by reacting **1** with (COD)Ru(2-methylallyl)$_2$, followed by treatment with methanolic HBr in acetone.[6] The hydrogenations are carried out at 50-70 °C and an initial H_2 pressure of 6 atm in the presence of the **1**-RuBr$_2$ complex (0.13-1.4 mol %). Various types of β-keto esters and related substrates are hydrogenated to afford β-hydroxy esters in high yield and with excellent enantioselectivity (eq 7). In the case of α-keto esters, slightly lower enantioselectivity is observed, and γ-keto esters are not subjected to hydrogenation under the conditions.

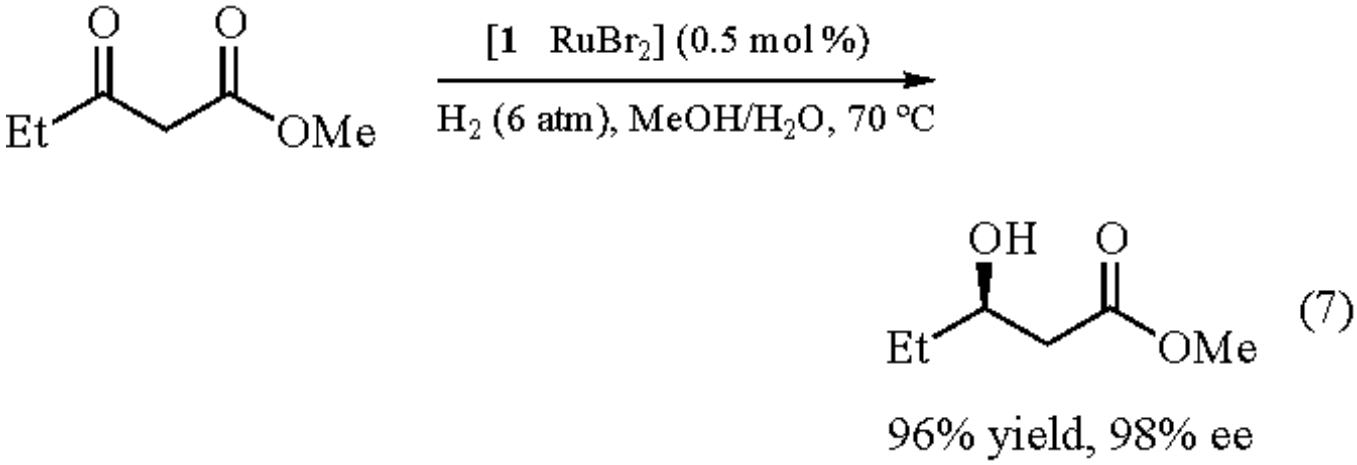

Related Reagents.

MiniPHOS;[7] DIOP;[8] BINAP;[9] CHIRAPHOS;[10] DIPAMP;[11] DuPHOS;[12] BPE;[12] TRAP;[13] PHANEPHOS.[14]

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1,1,3,3-Bis(tetramethylene)chlorouronium Hexafluorophosphate

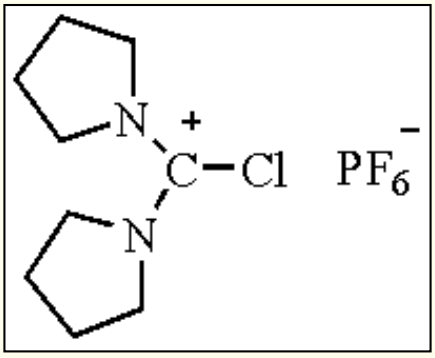

[207915-96-6; 135540-11-3] · $C_9H_{16}ClF_6N_2P$ · (332)

(peptide synthesis coupling reagent)

Alternate Name: PyClU,[1] BTCFH.[2]

Physical Data: mp 151-153 °C,[1] 146-148 °C.[3]

Solubility: soluble in CH_2Cl_2, $CHCl_3$, DMF, DMSO, NMP, acetone.

Form Supplied in: colorless crystals.

Analysis of Reagent Purity: ^{1}H-NMR; elemental analysis.

Preparative Methods: addition of $POCl_3$[1] or a 20% solution of phosgene in toluene[3,4] to the corresponding urea and then addition of KPF_6/H_2O.

Purification: recrystallization (acetone/Et_2O).

Handling, Storage, and Precautions: the toxicological properties of this reagent have not been investigated and no special instructions for storage and handling are mentioned in the literature.

Reagent for Peptide Synthesis

This reagent, which was designed for coupling *N*-methylated amino acids (eq 1), gives results comparable to those obtained with **PyBroP**.[1] Compared with the hydroxybenzotriazol-based activator **HBTU**, which produces the moderately activated benzotriazolyl esters from carboxylic acids, PyClU gives high yields and low racemization.[1,5] However, significant epimerization is observed during segment condensation.[6]

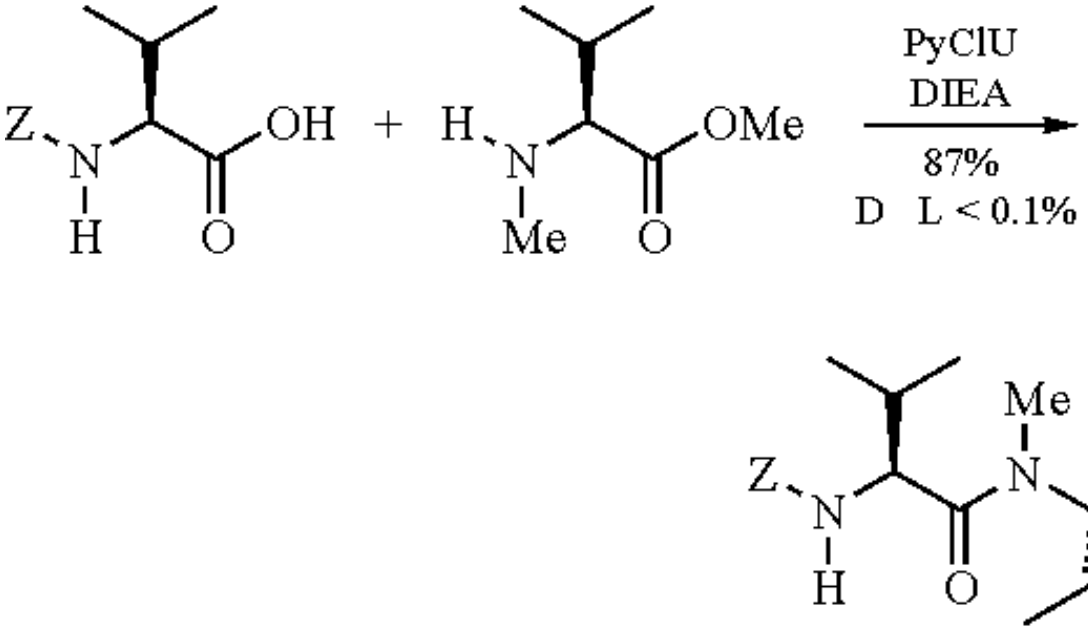

(1)

In addition, the homologous tetrafluoroborate salt TPyClU proved to be efficient for monoester formation from *N*-protected α-amino phosphonic acid (eq 2).[7]

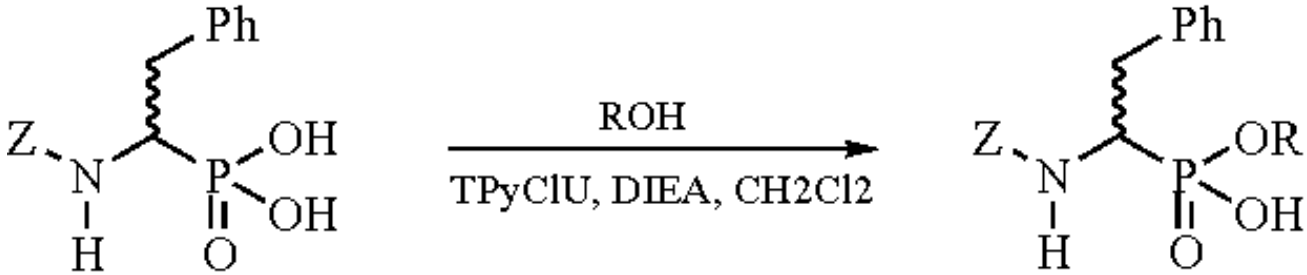

(2)

R = *i*-PrOH (83%), PhCH2OH (86%), *t*-BuOH (65%)

Preparation of Coupling Reagents for Peptide Synthesis

Several related uronium coupling reagents have been prepared from PyClU:

- Bis(tetramethylene)phenoxyformamidinium hexafluorophosphate derivatives PfPyU,[4] HPyOPFp, HpyOTcp, and HpyONp[8] (eq 3).

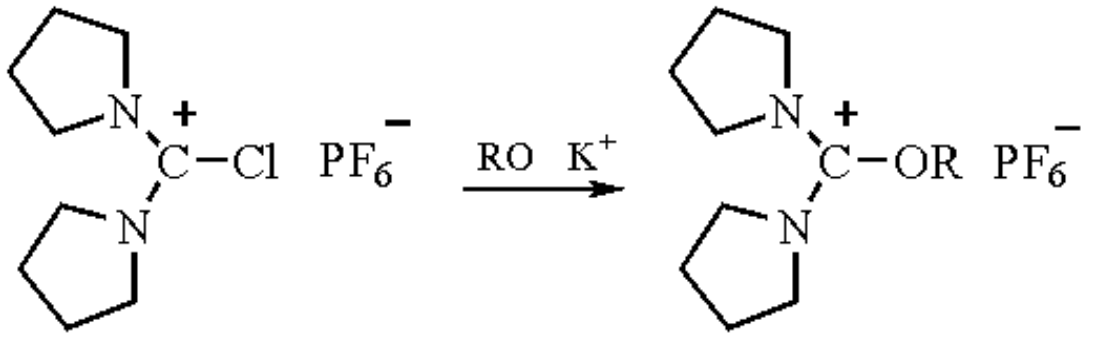

(3)

PyClU

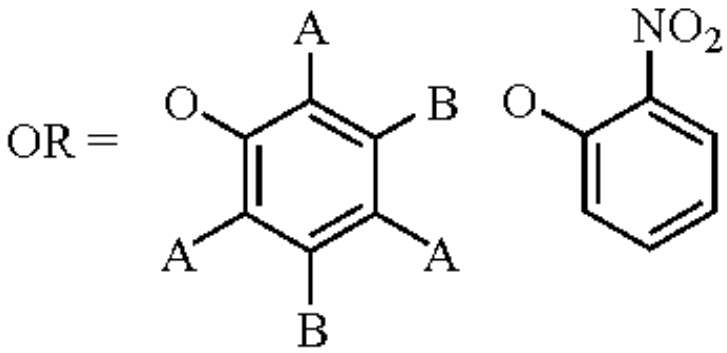

A = B = F HPyONp (88%)
PfPyU(90%)
(HPyOPFp)
A = Cl, B = H
HPyOTcp (86%)

- Benzotriazolyl-1,1,3,3-bis(tetramethylene)chlorouronium hexafluorophosphate (HBPyU[1] or BBC[3]) and its 7-azabenzotriazole[9] analog, reagents for peptide synthesis (eq 4).

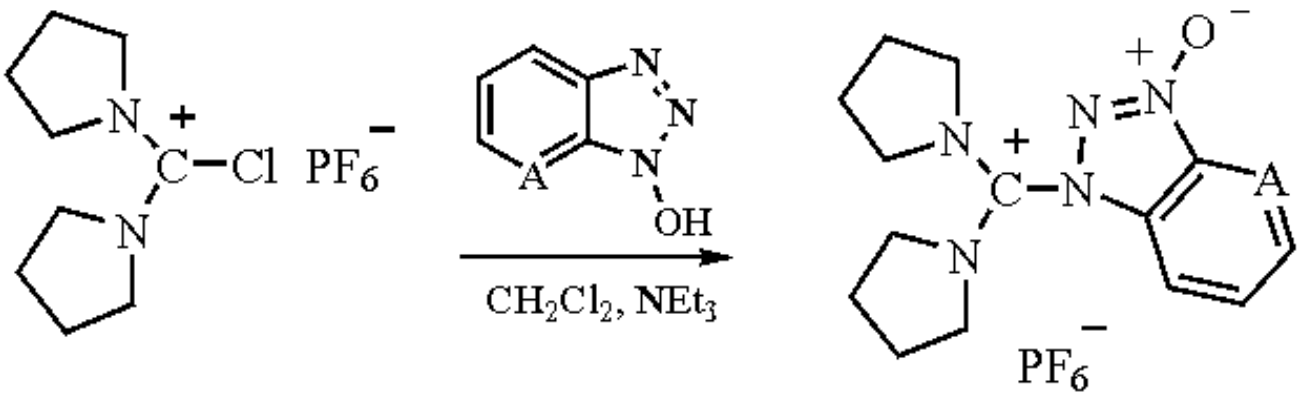

(4)

PyClU

A = C, HBPyU (BBC) (93%)
A = N, HAPyU (88%)

- Bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH), reagent for in situ conversion of amino acids into amino acid fluorides in peptide synthesis (eq 5).[2]

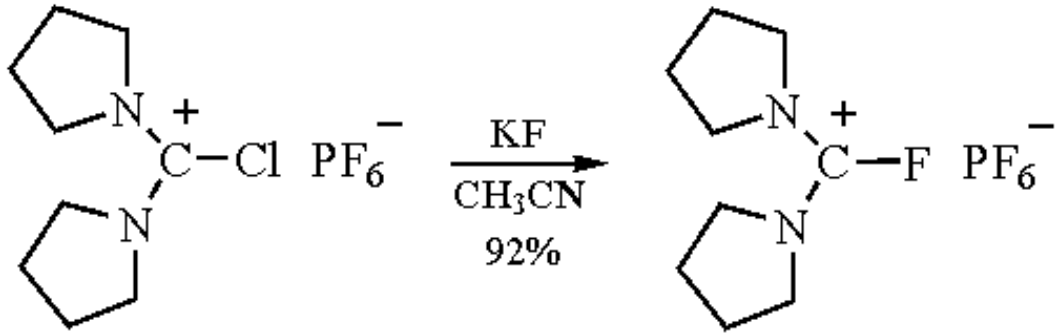

(5)

PyClU BTFFH

Related Reagents.

PyCloP (chlorotripyrrolidinophosphonium hexafluorophosphate); PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate); HBPyU [O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate]; HAPyU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate]; TpyClU [1,1,3,3-bis(tetramethylene)chlorouronium tetrafluoroborate]; CIP (2-chloro-1,3-dimethylimidazolidium hexafluorophosphate); HPyOPFp [(pentafluorophenyl)oxy-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate]; HpyOTcp [(2,4,5-trichlorophenyl)oxy-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate]; HPyONp [(2-nitrophenyl)oxy-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate]; BTFFH [bis(tetramethylene)fluoroformamidium hexafluorophosphate]; TFFH (tetramethylfluoroformamidium hexafluorophosphate).

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Bromotripyrrolidinophosphonium Hexafluorophosphate[1]

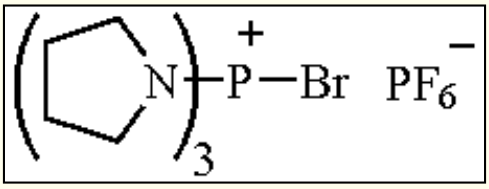

[132705-51-2] · $C_{12}H_{24}BrF_6N_3P_2$ · (466)

(reagent for carboxylic acid activation, particularly used for peptide synthesis; reagent for formamidine synthesis)

Alternate Name: PyBroP.

Physical Data: mp 138-139 °C.

Solubility: soluble in CH_2Cl_2, $CHCl_3$, DMF, DMSO, NMP, acetone.

Form Supplied in: colorless crystals.

Analysis of Reagent Purity: ^{31}P NMR, HPLC.

Preparative Methods: addition of Br_2 to tripyrrolidinophosphine[2] or addition of tripyrrolidinophosphine oxide to an acetonitrile solution of phosphoryl tribromide,[1,2] then addition to a KPF_6 solution in water.

Purification: recrystallization from CH_2Cl_2/Et_2O; CH_2Cl_2/hexane; acetone/Et_2O; EtOAc.

Handling, Storage, and Precautions: the toxicological properties of this reagent have not been investigated and no special instructions for storage and handling are mentioned in the literature.

Introduction

Treatment of a carboxylic acid with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) in the presence of base produces the unstable acylphosphonium intermediate. Such species directly react with a nucleophile or decompose into a different activated form (e.g. carboxylic anhydride).[1] The reagent was first designed for coupling in peptide synthesis but is also widely used for the synthesis of amides or esters, and for macrocyclization. This reagent gives results that are comparable to those obtained with BroP [bromotris(dimethylamino)phosphonium hexafluorophosphate][3] with the advantage of not producing the carcinogen **HMPA** as a side product of the coupling reaction.[4] By-products have been observed from slowly reacting activated carboxylates: (i) the formation of pyrrolidide derivatives due to the presence of small amounts of pyrrolidine in the commercial phosphonium salt (avoided by recrystallization of the reagent),[5] and (ii) a side reaction in DMF but favorable for the preparation of formamidines.[6]

Reagent for Peptide Synthesis

PyBroP was efficiently used in both liquid and solid phase peptide synthesis, but it can lead to epimerization when used for segment condensation.[7] Compared with hydroxybenzotriazol-based activators like BOP, PyBOP, HBTU or DCC/HOBT, which produce the moderately activated benzotriazolyl esters from carboxylic acids, PyBroP is highly recommended for coupling *N*-methylated amino acids,[1,8-14] as illustrated by the difficult coupling of NMeVal (eq 1),[1,8] and other *N*-alkylated amino acids[15-17] as well as α-disubstituted amino acids (e.g. α-MeSer,[18] Aib[19] or α-MeCys (eq 2).[20] Coupling of *N*-alkylated amino acids can be improved by addition of HOAt.[21] The addition of a catalytic amount of **DMAP** or **4-pyrrolidinopyridine** is recommended to improve both the rate and the yield of the coupling reaction for non-epimerizable substrates.[10,13,18-20] PyBroP activation of Boc-amino acids can, however, give moderate yields due to the formation of the *N*-carboxyanhydride (NCA).[1,22]

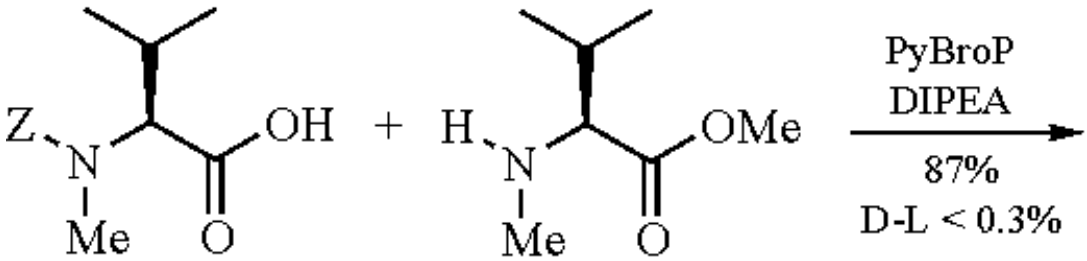

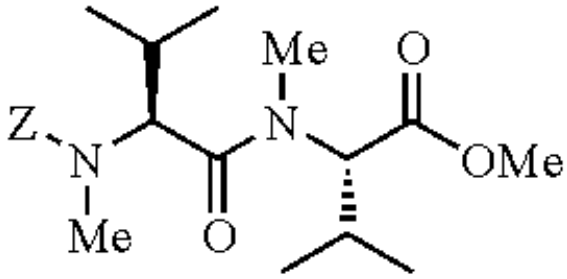

(1)

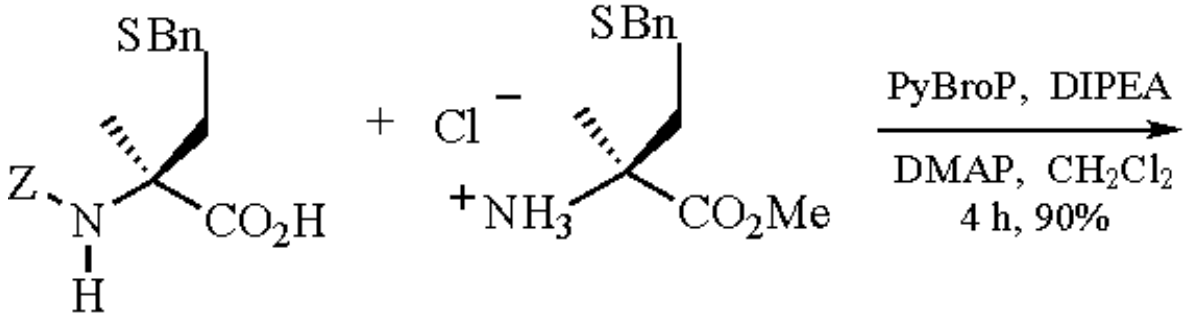

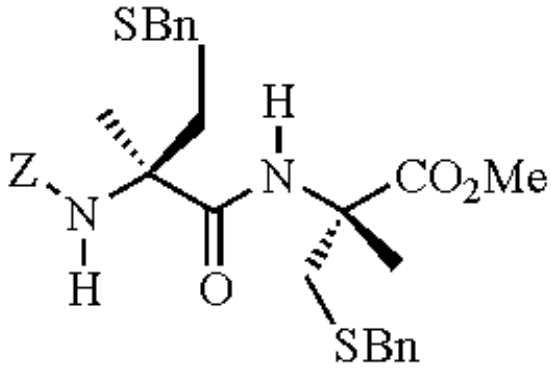

(2)

Synthesis of Amides

PyBroP has been employed in the synthesis of unsubstituted amides,[23] *N*-monosubstituted amides (eq 3),[24] and disubstituted amides, even from conformationally constrained derivatives (eq 4)[25] and anilines.[19,26,27] It has also been used for activation of conjugated carboxylic acids (eq 5).[28]

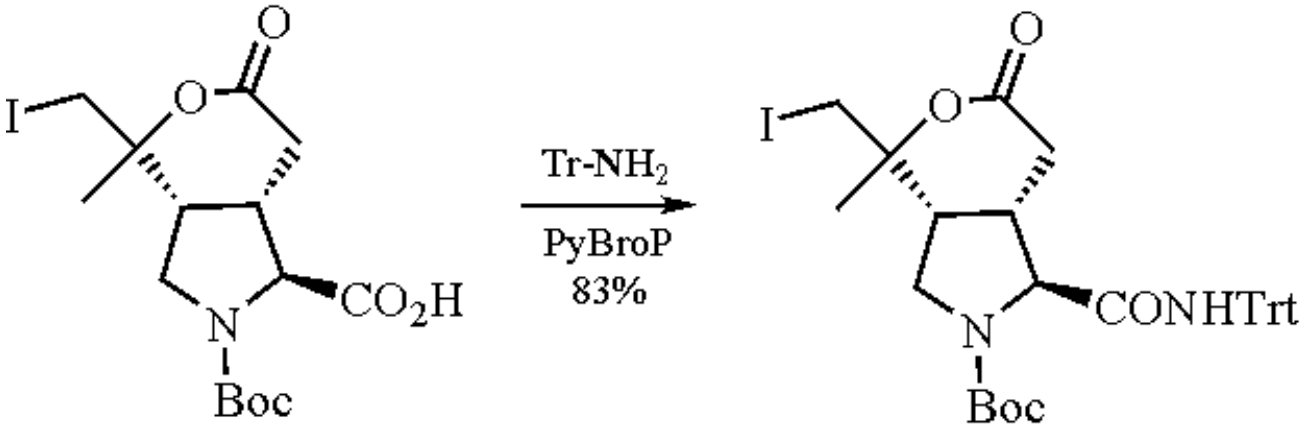
Tr-NH2
PyBroP
83%
CONHTrt
CO2H
Boc

(3)

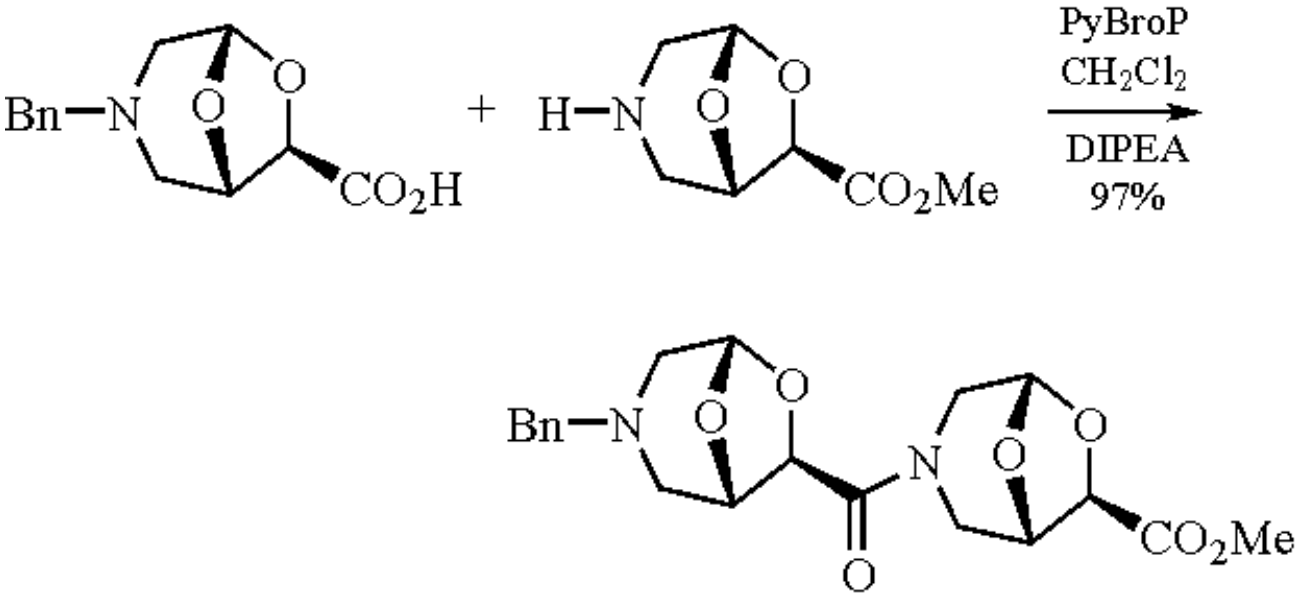
PyBroP
CH2Cl2
DIPEA
97%
Bn
CO2H
CO2Me

(4)

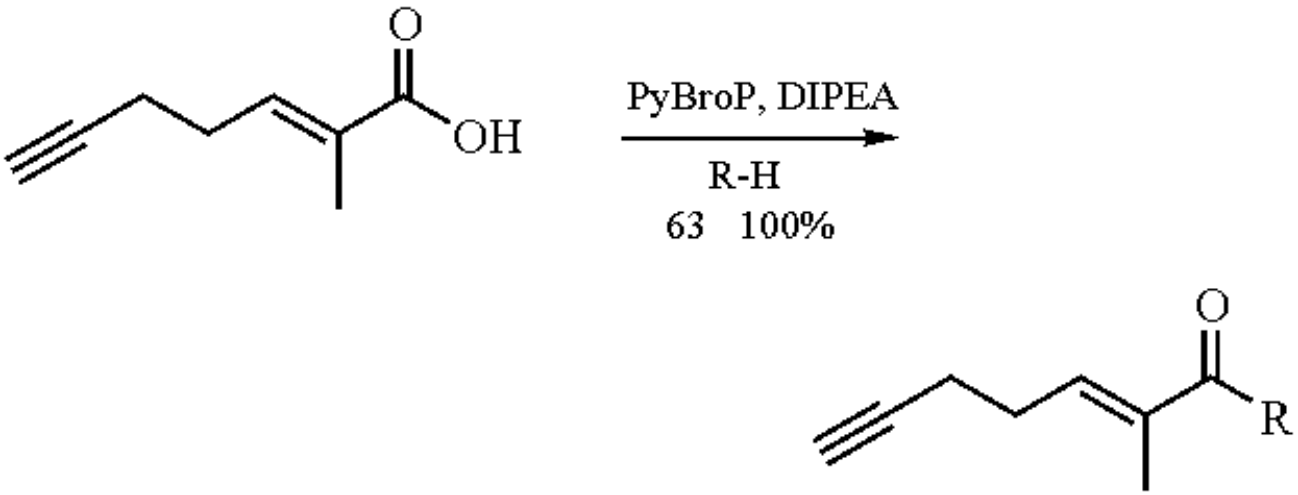
PyBroP, DIPEA
R-H
63 100%
OH
R
R =
NH
Bn
16
Ph
Me

(5)

PyBroP also gives good results for the synthesis of macrocyclic lactams (eq 6),[29] including cyclic peptides at high dilution[13] with addition of HOAt[30] or on solid phase.[31]

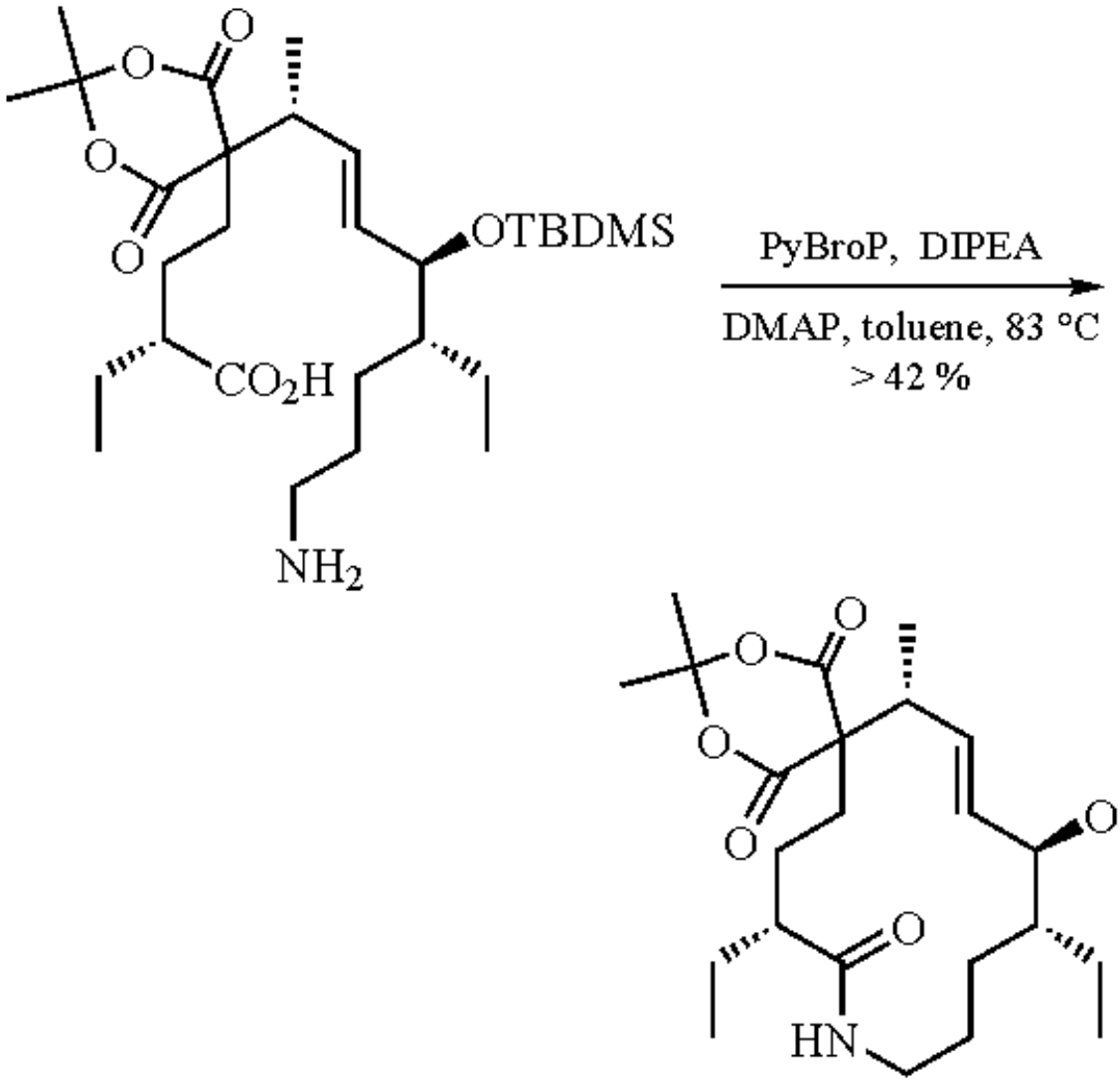

(6)

Synthesis of Carboxylic Esters

Ester linkage from carboxylic acid activation with PyBroP was reported for primary and secondary alcohols. This reagent gives impressive results for depsipeptide synthesis (eq 7).[32] PyBroP has been used to attach nucleosides to a hydroxylated solid support.[33]

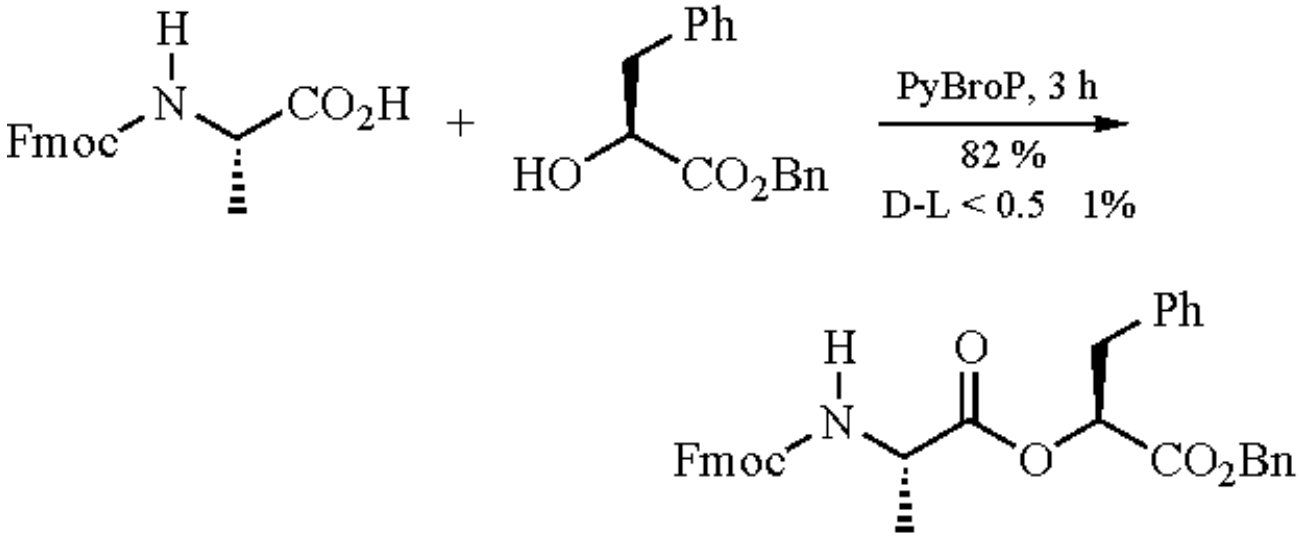

(7)

In addition, this activation was selected over carbodiimide-derived reagents for the preparation of polymer-bound activated esters derived from **1-hydroxybenzotriazole** (eq 8)[34,35] and for the preparation of the storable *p*-nitrophenyl esters in solution.[36]

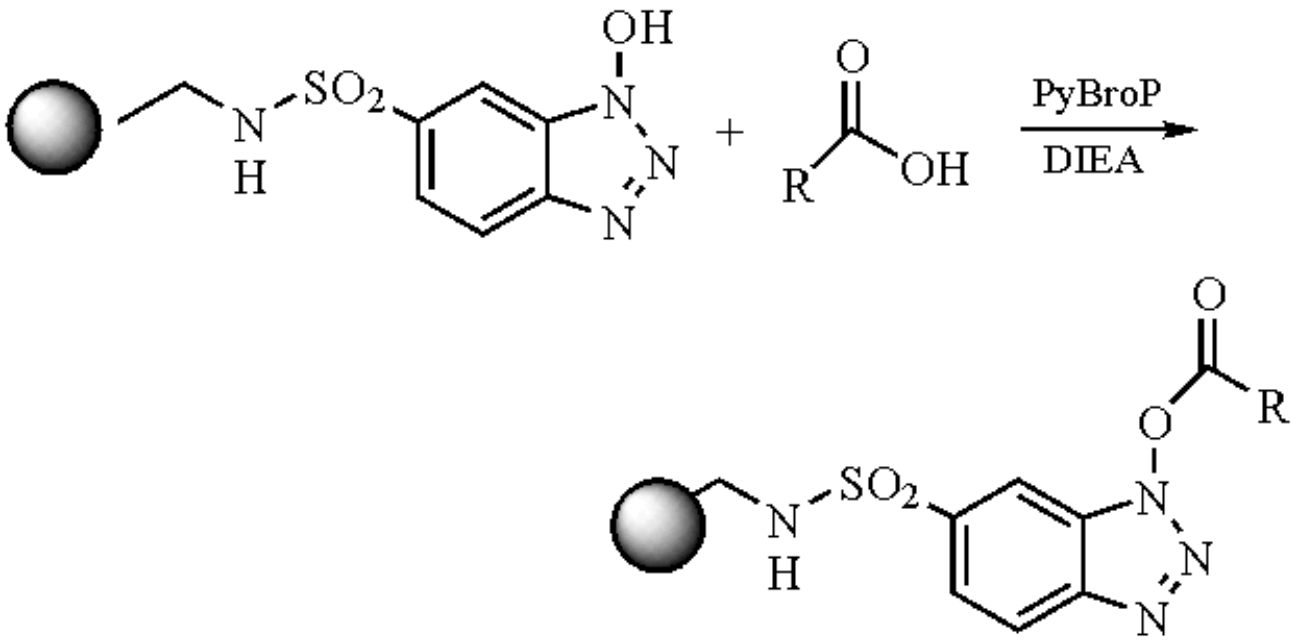

(8)

R=

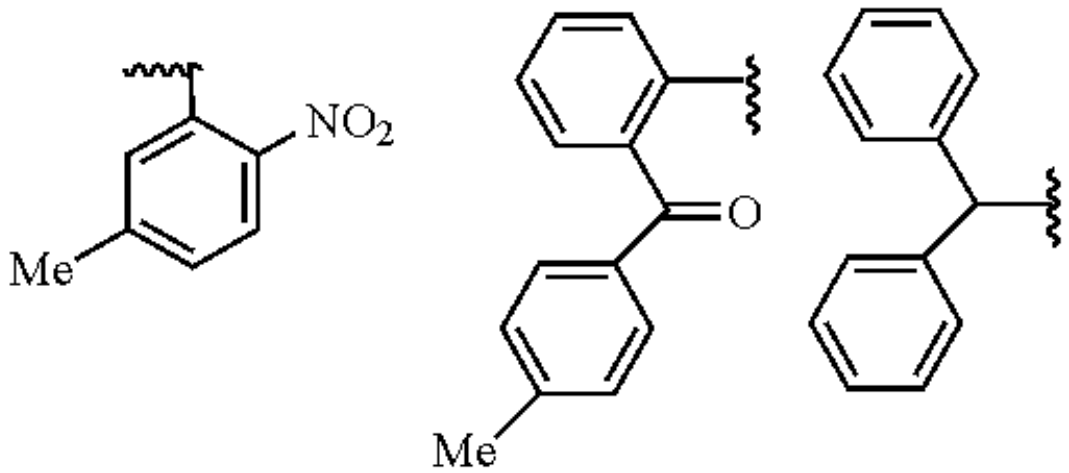

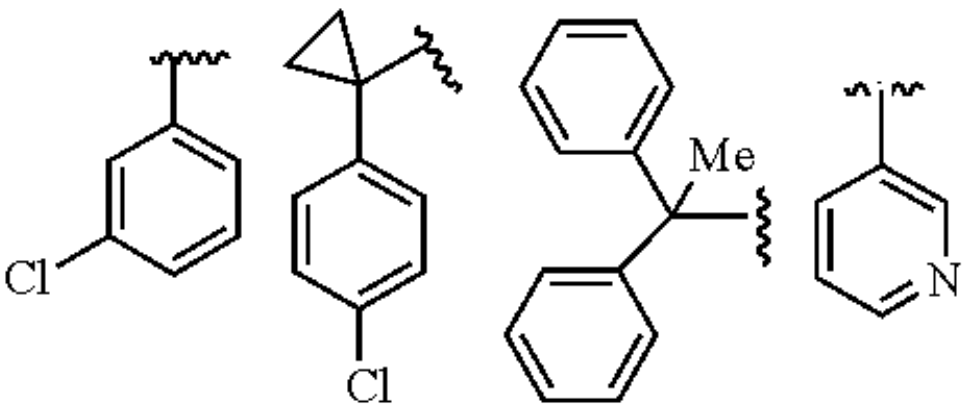

PyBroP gives improved yields for the cyclization step in the synthesis of the macrocyclic dynemicin A, when compared with the Yamaguchi macrolactonization protocol (eq 9).[37]

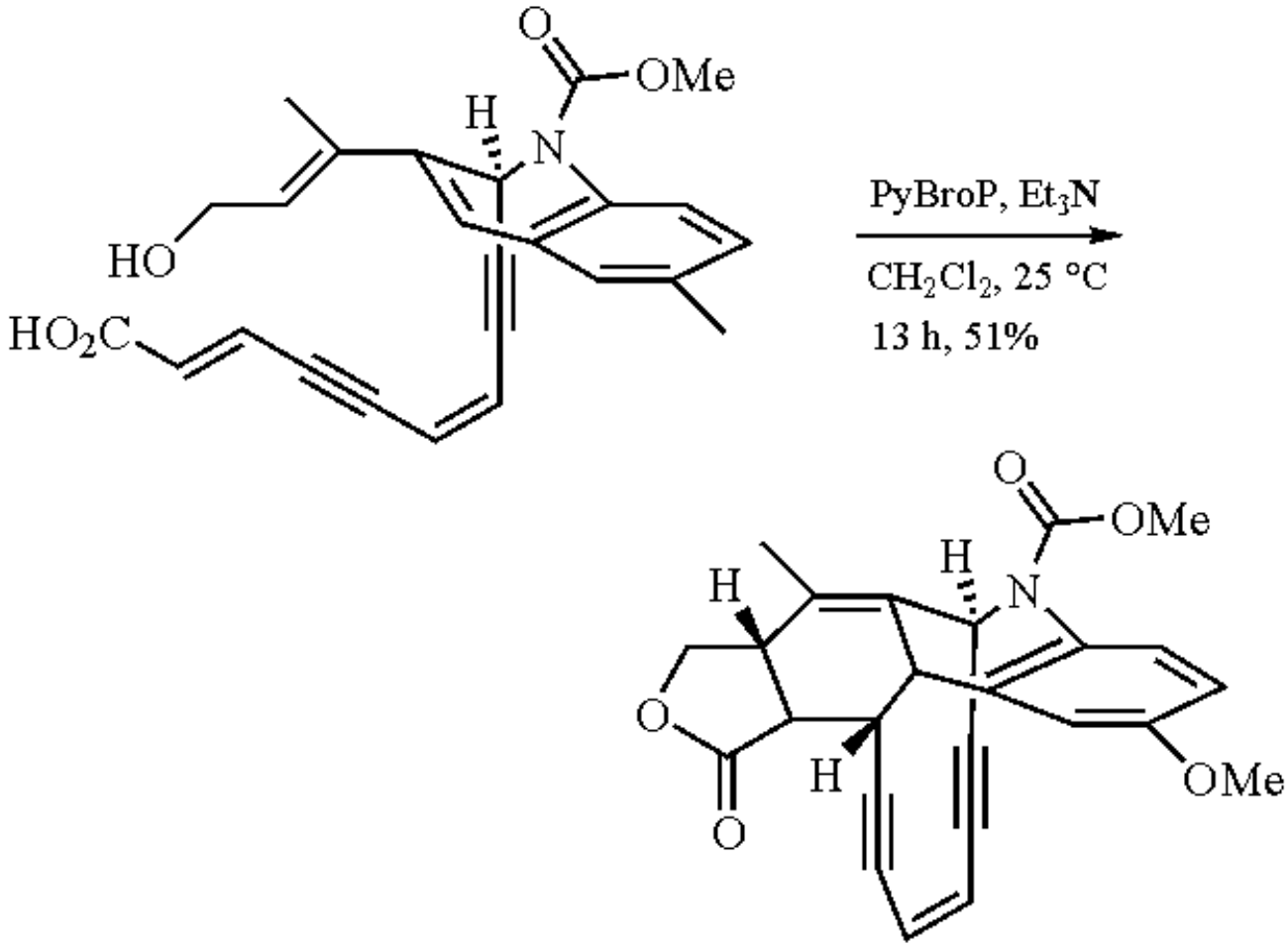

(9)

Synthesis of Amidines

Formamidinium formation has been reported as a side reaction of PyBroP with DMF in solid-phase peptide synthesis. This reaction proved to be suitable for the synthesis of formamidines from aliphatic or aromatic amines and DMF (eq 10).[6]

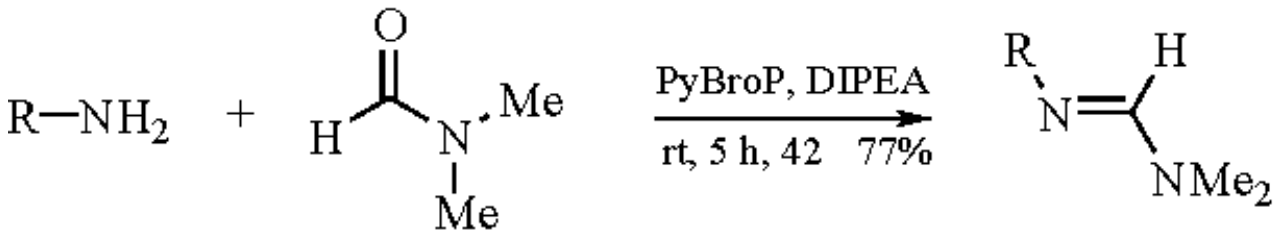

(10)

R-NH_2 = aniline (56%), benzyl amine (77%), benzene-1,3-diamine (53%), pyridine-2,6-diamine (48%)

Preparation of Coupling Reagents for Peptide Synthesis

Several phosphonium-related coupling reagents for peptide synthesis have been prepared from PyBroP (eq 11): PyBOP,[2] PyAOP,[38] and CF_3PyBOP.[39]

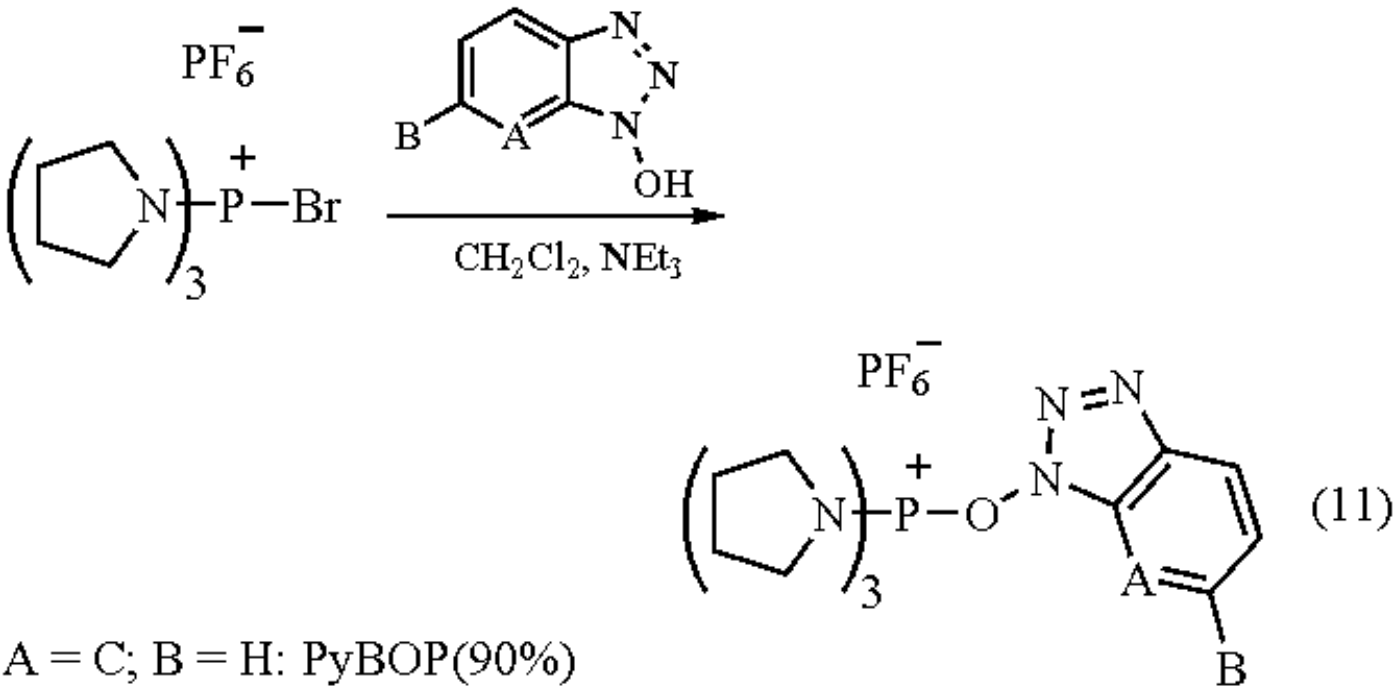

A = C; B = H: PyBOP(90%)
A = N; B = H: PyAOP (76%)
A = C; B = CF_3: CF_3PyBOP (69%)

Related Reagents.

BroP, bromotris(dimethylamino)phosphonium hexafluorophosphate; PyCloP, chlorotripyrrolidinophosphonium hexafluorophosphate; BOP, 1H-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate; PyBOP, 1H-benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; AOP, 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate; PyAOP, 7-azabenzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; HBTU, O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HATU, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBPyU, O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate; HAPyU, O-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate; BOP-Cl, bis(2-oxo-3-oxazolidinyl)phosphinic chloride; PyClU, 1,1,3,3-bis(tetramethylene)chlorouronium hexafluorophosphate; TpyClU, 1,1,3,3-bis(tetramethylene)chlorouronium tetrafluoroborate; CIP, 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate; TFFH, tetramethylfluoroformamidium hexafluorophosphate; BTFFH, bis(tetramethylene)fluoroformamidium hexafluorophosphate.

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Chlorotripyrrolidinophosphonium Hexafluorophosphate

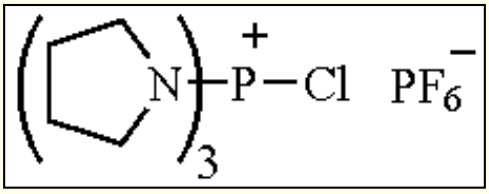

[133894-48-1] · $C_{12}H_{24}ClF_6N_3P_2$ · (421)

(reagent for carboxylic acid activation, coupling agent in peptide synthesis)

Alternate Name: PyCloP.

Physical Data: mp 150-151 °C.[1]

Solubility: soluble in CH_2Cl_2, $CHCl_3$, DMF, DMSO, NMP, acetone.

Form Supplied in: colorless crystals.

Analysis of Reagent Purity: ^{31}P NMR, HPLC.

Preparative Methods: addition of chlorine to a diethyl ether solution of tripyrrolidinophosphine, then addition of KPF_6 in water.[2] Addition of tripyrrolidinophosphine oxide to a DCM solution of phosphoryl trichloride, then addition of KPF_6 in water.[1-3]

Purification: recrystallization (CH_2Cl_2/Et_2O).

Handling, Storage, and Precautions: the toxicological properties of this reagent have not been investigated and no special instructions for storage and handling are mentioned in the literature.

Introduction

Treatment of a carboxylic acid with PyCloP in the presence of base produces the unstable acylphosphonium intermediate. This species directly reacts with a nucleophile or decomposes into a different activated form (e.g. carboxylic anhydride). This reagent gives results that are comparable to those obtained with **PyBroP** (bromotripyrrolidinophosphonium hexafluorophosphate).[1]

Reagent for Peptide Synthesis

Compared with hydroxybenzotriazol-based activators like BOP, PyBOP, HBTU, or DCC/HOBT, which produce moderately activated benzotriazolyl esters from carboxylic acids, PyCloP is highly recommended for coupling *N*-methylated amino acids, as illustrated by the difficult coupling of NMeVal (eq 1),[1,4] and used in the total synthesis of natural peptoids.[5-7] PyCloP activation of Boc-amino acids can, however, give moderate yields due to the formation of *N*-carboxyanhydride (NCA).[1,8]

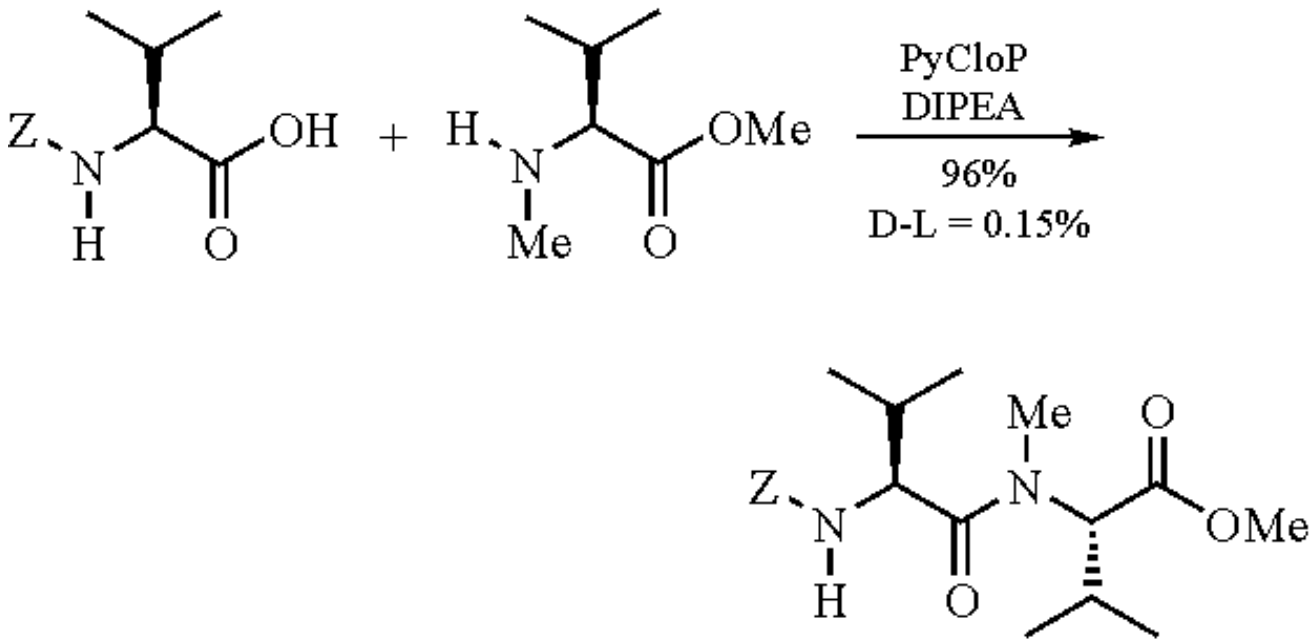

(1)

Activation of a Monothiocarboxylic Acid

Using different phosphorus reagents for activation of a monothiocarboxylic acid, the observed oxygen/sulfur selectivities correlate with the hardness/softness of the reaction center. Compared with the soft leaving bromine atom in PyBroP (S selective) or the hard oxygen atom in PyBOP (O selective), the PyCloP is borderline in O/S (25:47) selectivity (eq 2).[3]

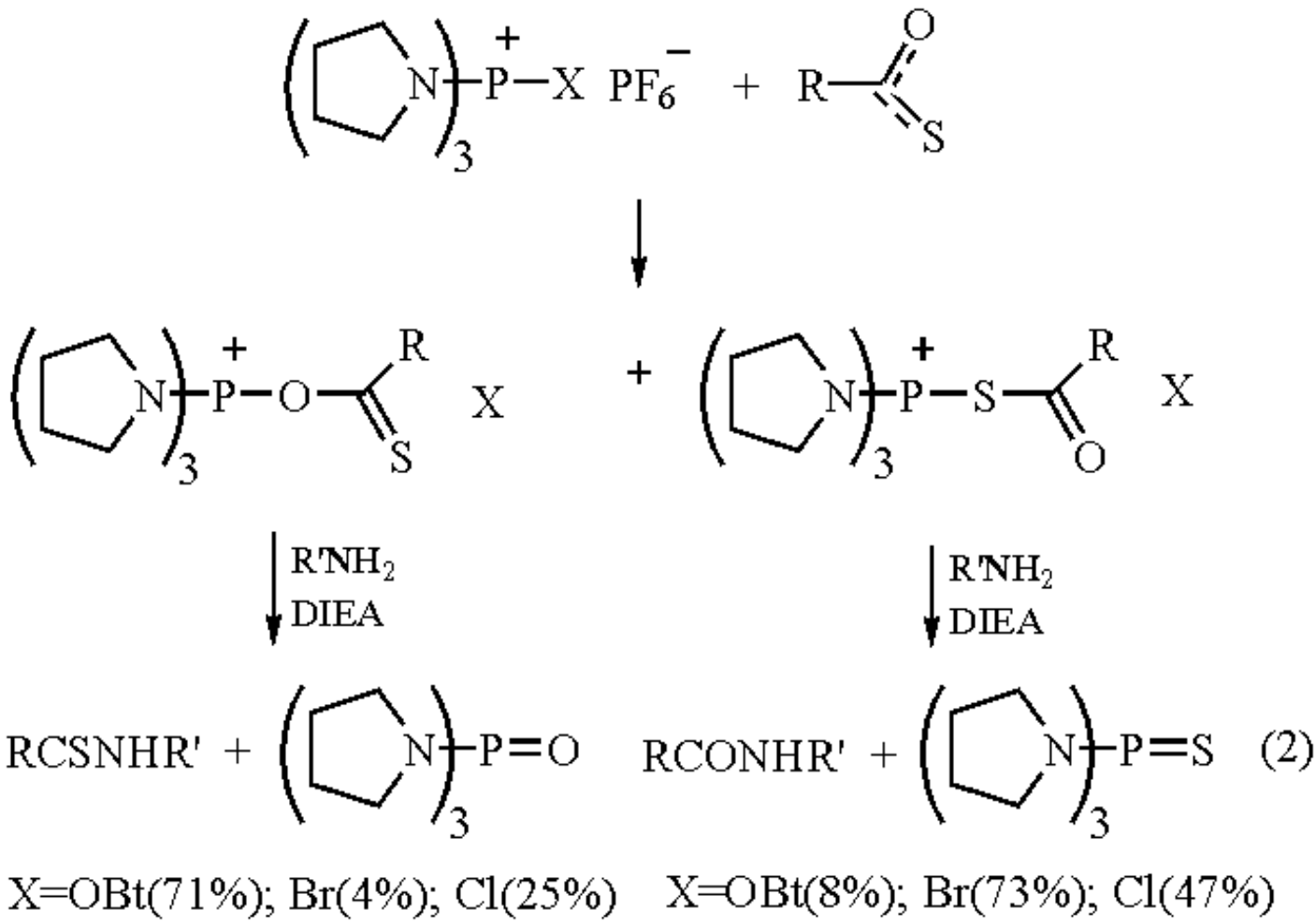

(2)

Preparation of Coupling Reagents for Peptide Synthesis

PyBOP, a related phosphonium coupling reagent for peptide synthesis, has been prepared from PyCloP,[2] and several analogs of PyBOP have also been prepared as reagents for thioacylation of monothiocarboxylic acid [3] (eq 3).

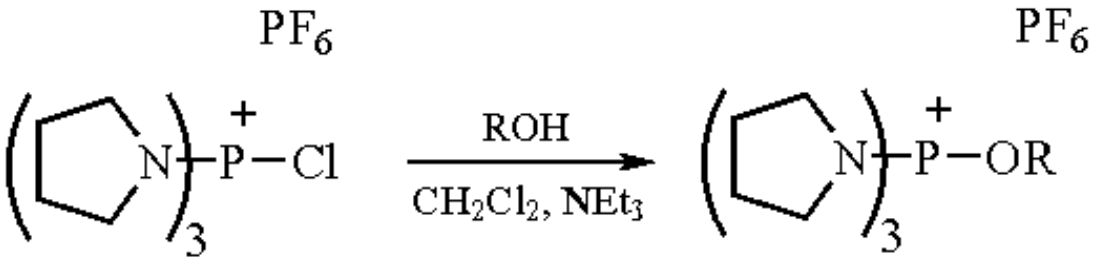

(3)

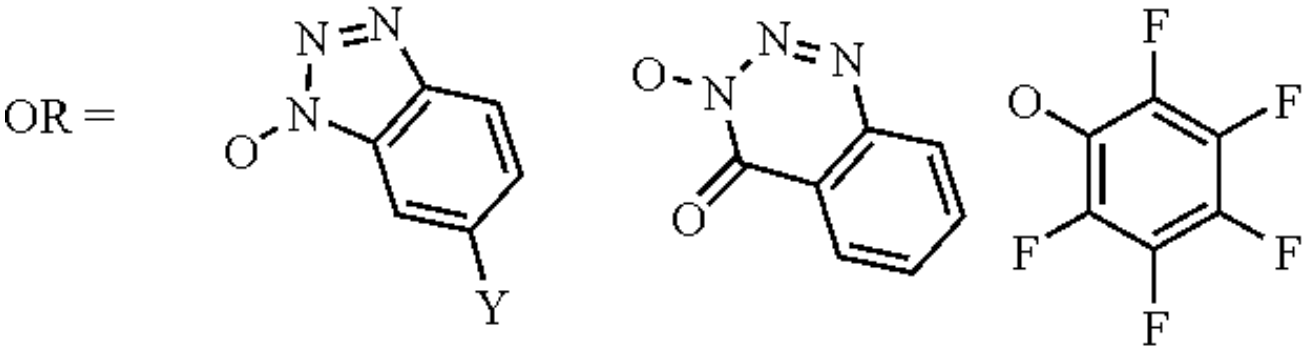

Y = H, PyBOP (75%)
NO_2, PyNOP (68%)
CF_3, PyFOP (92%)

PyDOP (94%)

PyPOP (92%)

Related Reagents.

PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate; PyBOP, (1H-benzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate; PyClU, 1,1,3,3-bis(tetramethylene)chlorouronium hexafluorophosphate; TpyClU, 1,1,3,3-bis(tetramethylene)chlorouronium tetrafluoroborate; CIP, 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate; PyAOP, (7-azabenzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate; PyPOP, (pentafluorophenyl)oxytripyrrolidinophosphonium hexafluorophosphate; PyNOP, (6-nitrobenzotriazol-1-yl)oxytripyrrolidinophosphonium hexafluorophosphate; PyFOP, [(6-trifluoromethyl)benzotriazol-1-yl]oxytripyrrolidinophosphonium hexafluorophosphate; PyDOP, (3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxytripyrrolidinophosphonium hexafluorophosphate.

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Pentafluorophenyl diphenylphosphinate (FDPP)

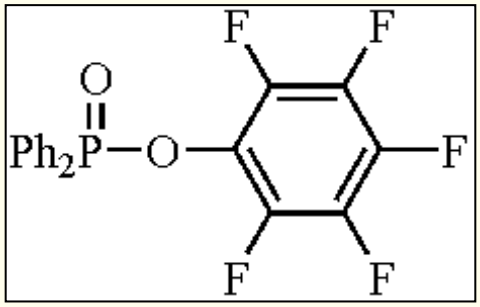

[138687-69-1] · $C_{18}H_{10}F_5PO_2$ · (384.25)

(reagent used as carboxyl activating group and coupling agent in a wide variety of amide bond formations)

Solubility: soluble in most organic solvents.

Form Supplied in: white powder and chunks.

Handling, Storage, and Precautions: decomposition occurs upon prolonged exposure to moisture in air. Storage in a cool dry place extends the life of the reagent. The toxicological properties have not been thoroughly investigated; however, hazardous combustion products may include, but are not limited to, carbon monoxide, carbon dioxide, hydrogen fluoride, and phosphorus oxides. FDPP is incompatible with strong oxidizing agents.

Physical Data: mp 47-50 °C

Purification: silica gel chromatography (short column to minimize decomposition) eluting with 20% ethyl acetate in petroleum ether followed by drying under reduced pressure for 2 days over phosphorus pentoxide.

Preparative Methods: FDPP can be conveniently prepared by mixing equimolar amounts of diphenylphosphinic chloride, pentafluorophenol, and imidazole in anhydrous CH_2Cl_2 at room temperature (eq 1).[1] There are slight procedural variations in the literature as to order of addition and reaction duration.[2,3] It has been found that using an excess of the diphenylphosphinic chloride (1.5-2 equiv) to drive the reaction to completion simplifies the purification, as the residual hydrolyzed reagent adheres tightly to the silica gel column and is, therefore, easier to separate than residual pentafluorophenol.[4]

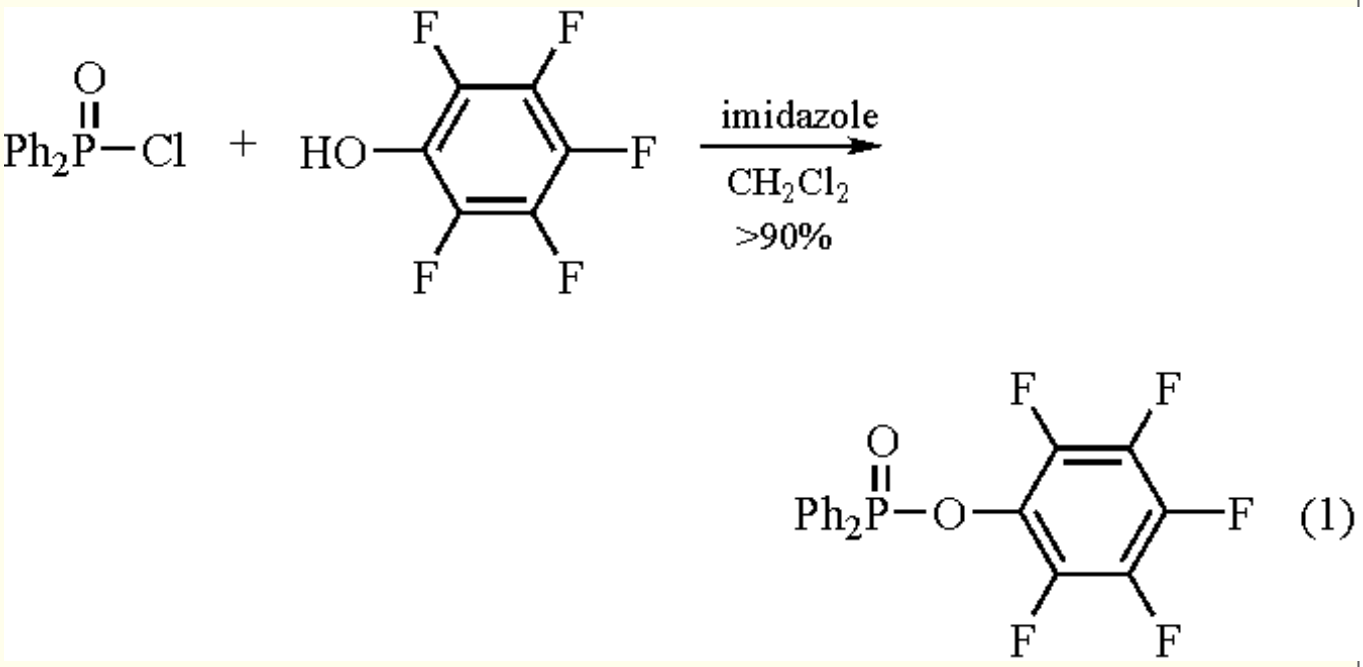

Coupling to Generate Linear Molecules

When Chen and Xu reported the new reagent, FDPP, in 1991,[1] the use of diphenylphosphinic mixed anhydrides in peptide chemistry was known,[5,6] as was the use of pentafluorophenyl esters.[7-11] However, the need to preactivate amino acids or to prepare active esters was unattractive. FDPP can be used directly as a coupling reagent without preactivation.[1] Chen and Xu demonstrated the utility of the reagent by preparing several small oligopeptides in solution and by preparing Leu-enkephalin via solid-phase synthesis.[1] Their solution-phase protocol called for equimolar amounts of the carboxyl and amine hydrochloride components, 3 equiv of Hünig's base, and 1.2 equiv of FDPP in DMF at room temperature for 1.5 h. The yields of isolated products were all greater than 80%. Using HPLC[12] (for the coupling product of Z-Gly-Phe-OH and Val-OMe·HCl) and the Young test[13] (for the coupling product of Bz-Leu-OH and Gly-OEt·HCl), they observed almost no racemization with FDPP; whereas, pentafluorophenyl diphenylphosphate (FDP)[14,15], 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate/1-hydroxybenzatriazole (BOP/HOBt), and dicyclohexylcarbodiimide (DCC) all showed significant levels of racemization. In the solid phase protocol, they employed the chloromethyl resin and carried out the reactions with 3 equiv of Boc-amino acid, FDPP, and 9 equiv of Hünig's base. This method provided extremely high yields and proved superior to the DCC method because no insoluble by-product was generated.

The use of FDPP in the formation of a variety of dipeptides has been studied in comparison to BOP, HBTU, and isobutyl chloroformate (IBCF).[3] Product yields, HPLC diastereomeric yields,[12] and optical rotations were measured for each example. In general, FDPP did give high yields and good optical purity. When Fmoc was used as the nitrogen protecting group, significantly lower yields and lower optical purity resulted. FDPP gave excellent yields for the formation of proline methyl ester dipeptides, outperforming HBTU, BOP, and IBCF; however, these reagents provided better optical purity than FDPP. Overall, BOP was the most successful coupling reagent for the dipeptides studied.

The search for an economical synthesis of the β-hydroxyproline fragment found in the cyclopeptide alkaloids nummularine F and mauritine was the impetus for another comparative study of carboxyl activating reagents (eq 2).[16] Relatively expensive isopropenyl chloroformate (IPCF) was used previously for this reaction. It was shown that the more affordable FDPP and BOP-Cl both possessed reactivity comparable to IPCF. In addition, the reactivity of FDPP in this reaction was shown to be greater than that of BOP, pentafluorophenol/DCC, phosgene, diphenylphosphinic chloride, DCC, *N*,*N*-carbodiimidazole, 2,4,6-trichlorobenzoyl chloride, pentafluorophenyl trifluoroacetate, and oxalyl chloride.

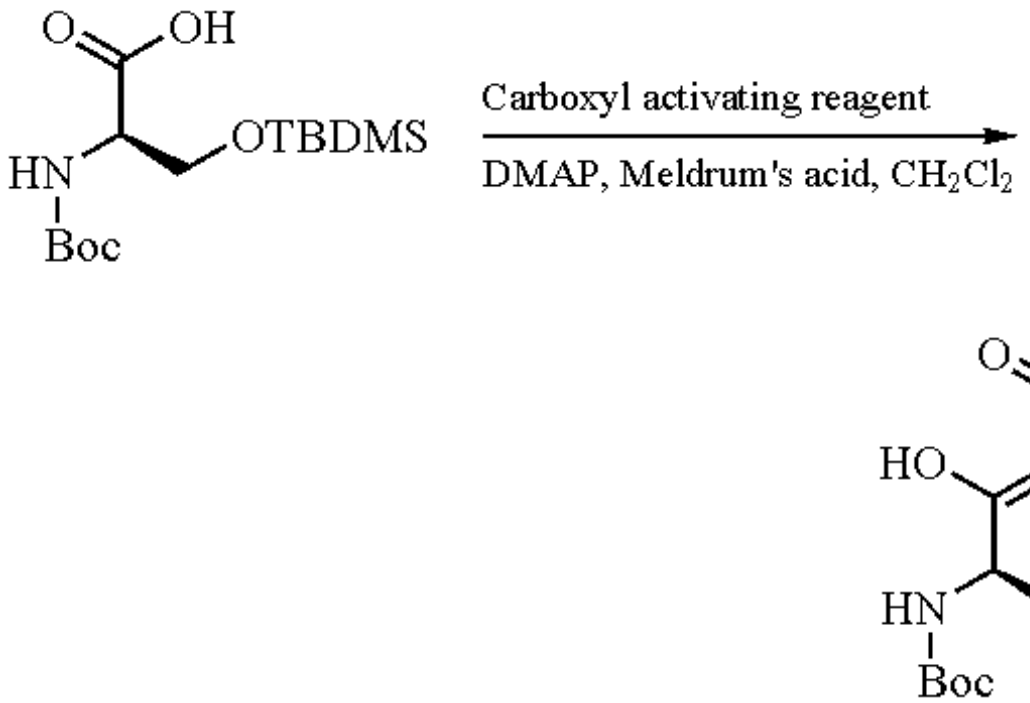

(2)

In the cryptophycin synthesis, FDPP was employed for the coupling shown in eq 3.[2] The amine component was used as its TFA salt, and when DCC/HOBt or BOP-Cl was used, the desired product was contaminated with the trifluoroacetamide to varying degrees. The problem could be circumvented by exchanging the counterion for tosylate, but this replacement incurred significantly longer reaction times. FDPP gave a comparable yield of product uncontaminated by the trifluoroacetamide.

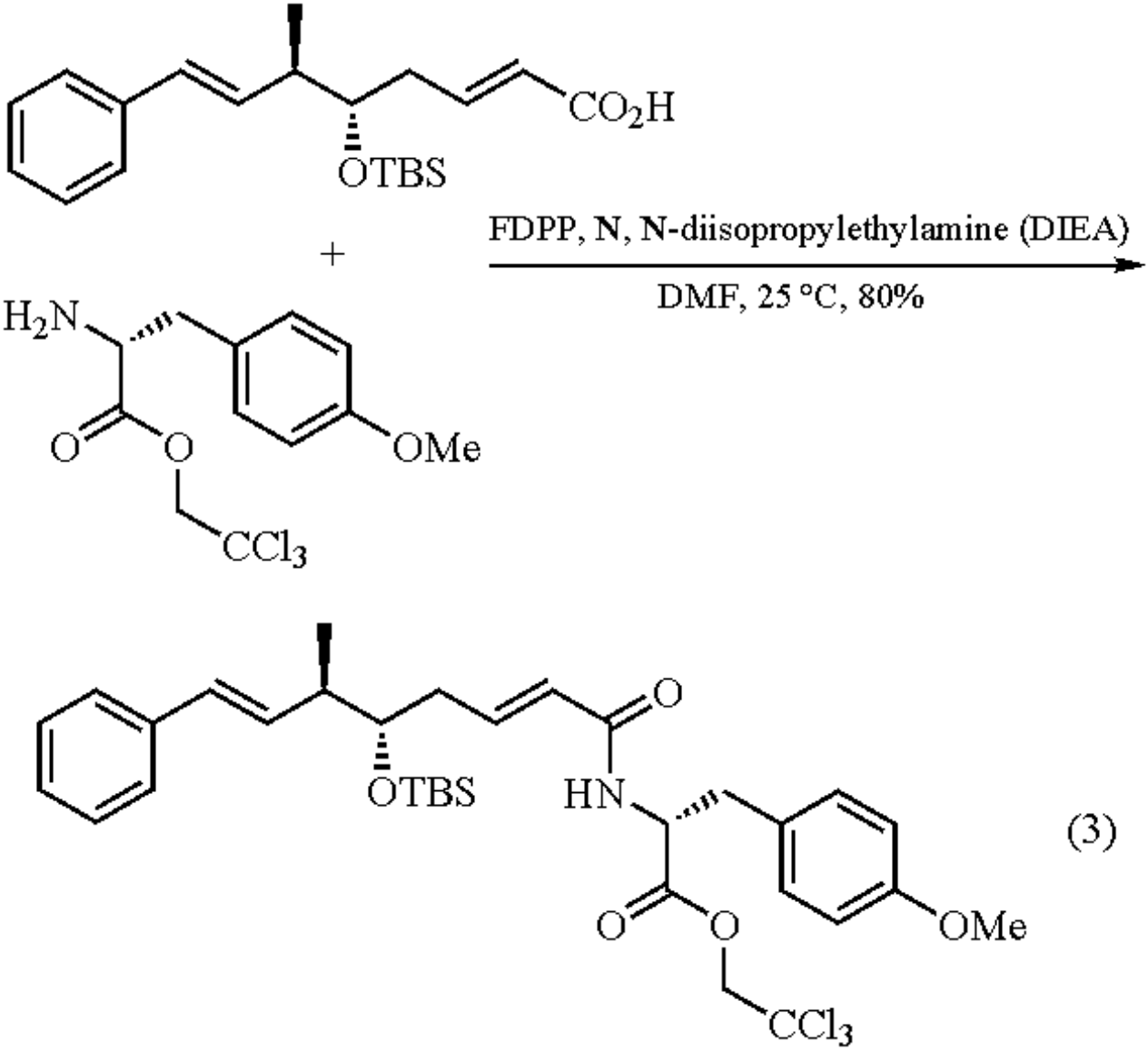

(3)

FDPP has also been employed in the coupling of *N*-protected amino acids to substituted γ-thiapyrone amines (eq 4).[17] When α-amino acids were used, the yields varied from 48-61% over a range of substitution patterns. The authors observed no signs of racemization in the ^{1}H and ^{13}C NMR spectra. Using Fmoc-protected β-amino acids, yields ranged from 39-46% for different substitution patterns, and longer reaction times (7-9 h) were required. Peptoid carboxyl components gave even lower yields at the same extended reaction time. It is unclear whether the low yields, with β-amino acids and peptoids, are due to the nature of these molecules or to the Fmoc protecting group, which is known to give lower coupling yields when used with FDPP.[3]

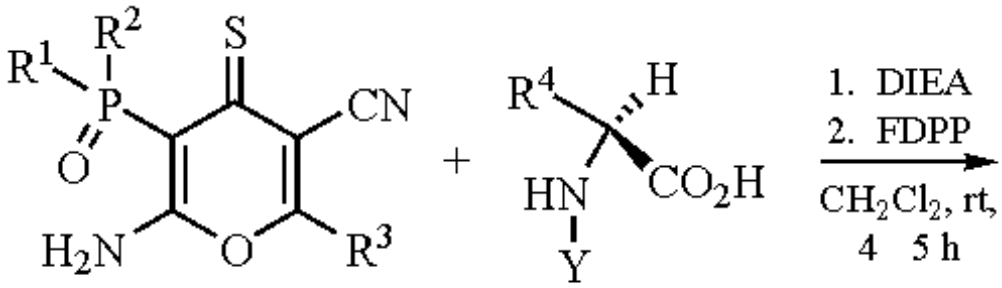

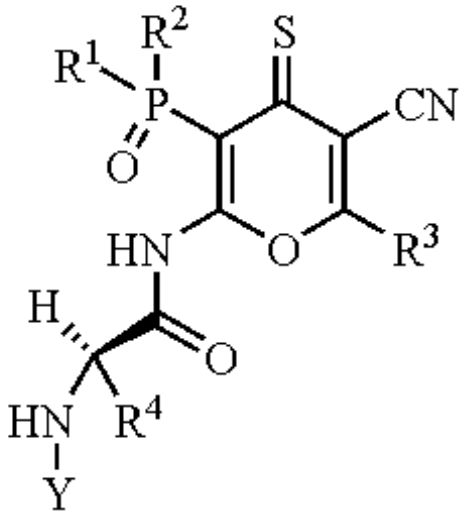

(4)

One way of immobilizing stationary phases onto silica gel involves amide bond formation; wherein the coupling partners are stationary phases derivatized with a free carboxylic acid and silica gel derivatized with an amino group. Low yields and racemization of chiral stationary phases often prove problematic, so Yang and co-workers investigated a variety of conditions and coupling reagents for this reaction.[18] While model reactions in solution phase gave generally high yields, the extent of racemization encountered with FDPP was greater than that found when using diisopropylcarbodiimide/1-hydroxy-7-azabenzotriazole (DIC/HOAt), DIC/HOBt, diphenylphosphoryl azide (DPPA), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*´,*N*´-tetramethyluronium hexafluorophosphate (HATU), and benzotriazolyloxy-tris[pyrrolidino]-phosphonium hexafluorophosphate (PyBop). However, for aminopropylsilica gel couplings (eq 5), yields were generally much lower, and the extent of racemization was much greater with all reagents except EEDQ. In this particular coupling, FDPP performed similarly to DIC/HOAt, DIC/HOBt, DPPA, HATU, and PyBop.

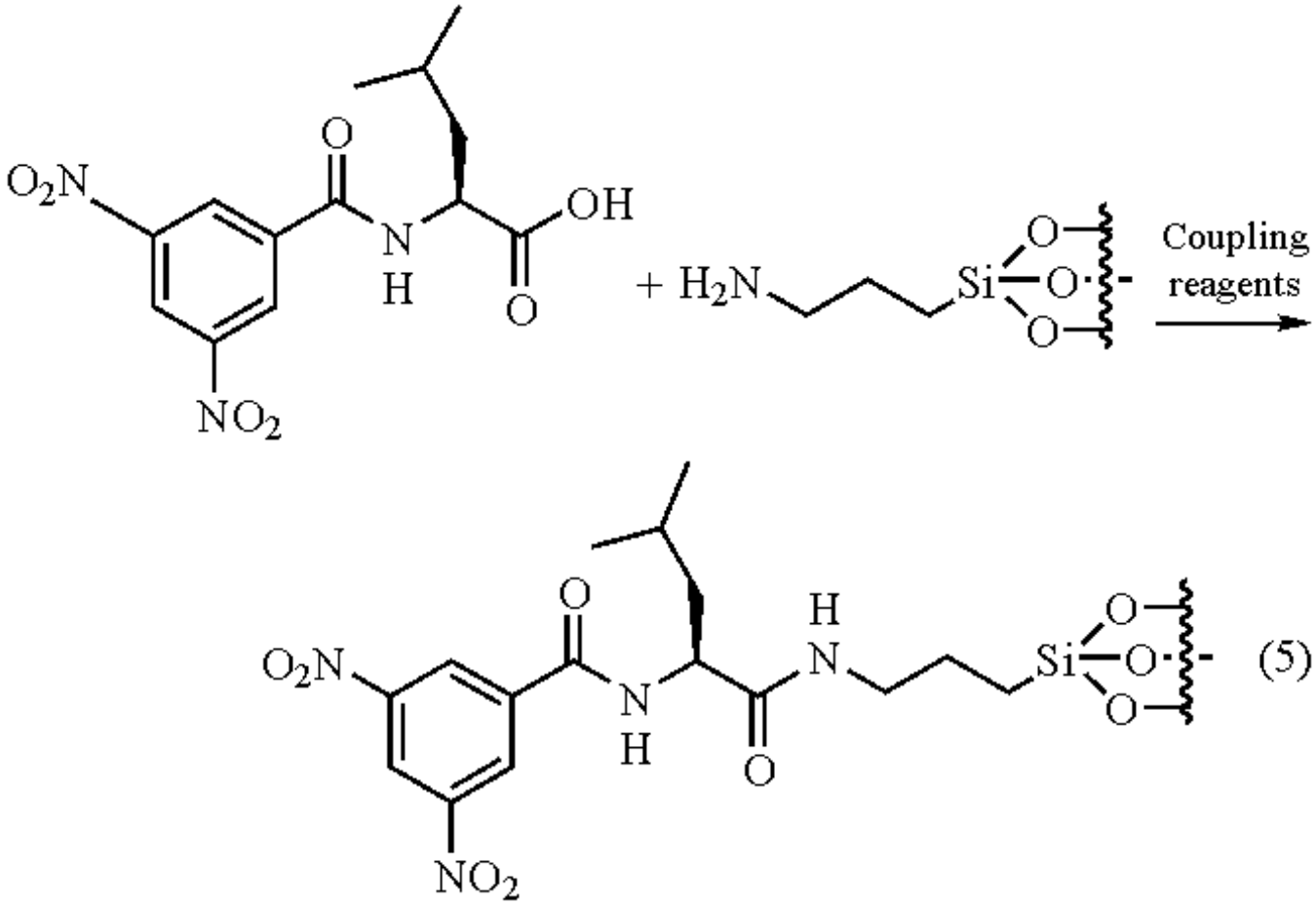

The use of FDPP has also been investigated for the thioacylation of iminoacid residues with monothioacids (eq 6).[19] FDPP gave a good yield of coupled product (81%) but a very low ratio of thio to oxo product. It was found that, for this reaction, coupling reagents with a leaving group bearing a delocalized charge, such as PfpO$^-$, had inherently lower selectivity for thioamide formation. Polar solvents also lowered the selectivity, and FDPP couplings are usually performed in DMF.

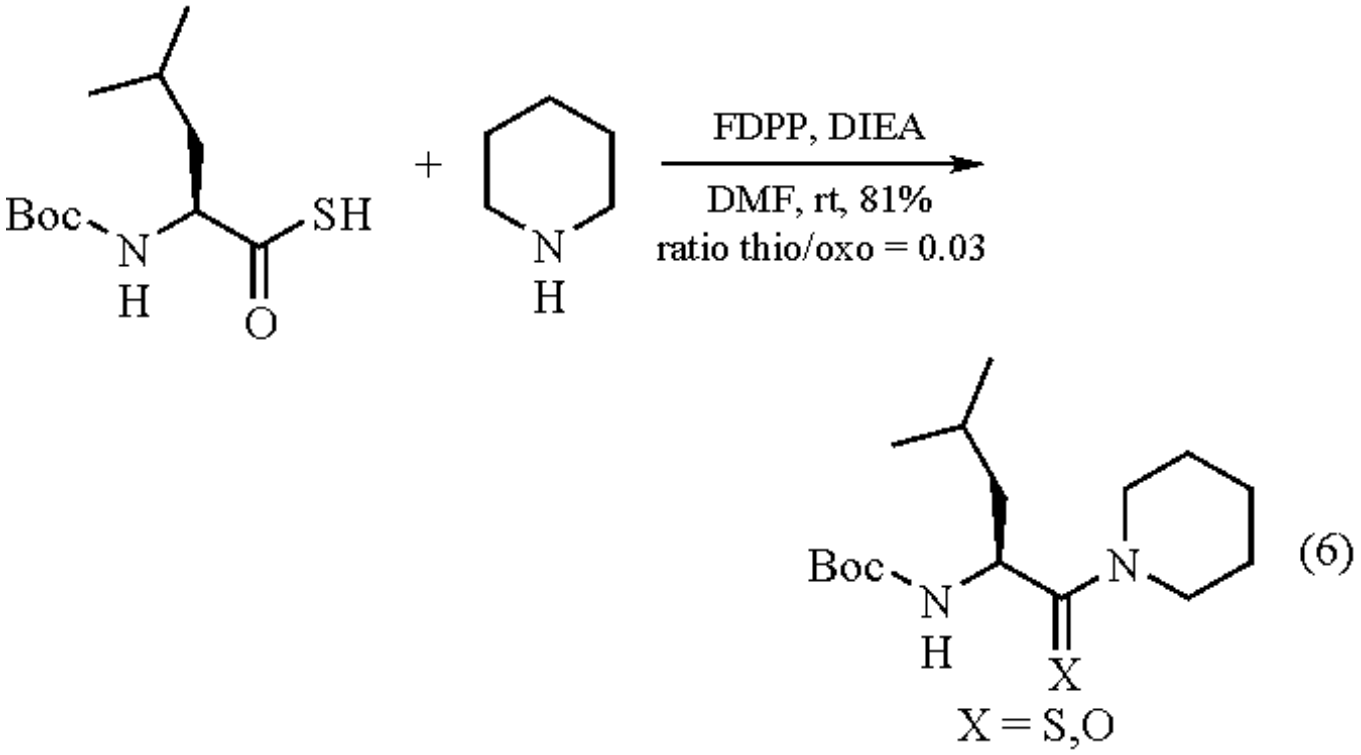

FDPP has also shown utility in the coupling of *N*-protected amino acid residues to linear diamino substrates bearing a free secondary hydroxyl group. The desired hydroxy amides were obtained in good yields for testing as HIV-1 protease inhibitors.[20]

Macrocyclization

While it is not always the reagent of choice, FDPP often provides excellent yields in macrocyclizations over a wide variety of substrates. In Deng and co-workers' 1994 synthesis of the macrocyclic pentapeptide cyclotheonamide B, FDPP was used to accomplish the macrolactamization in >80 % yield (eq 7).[21]

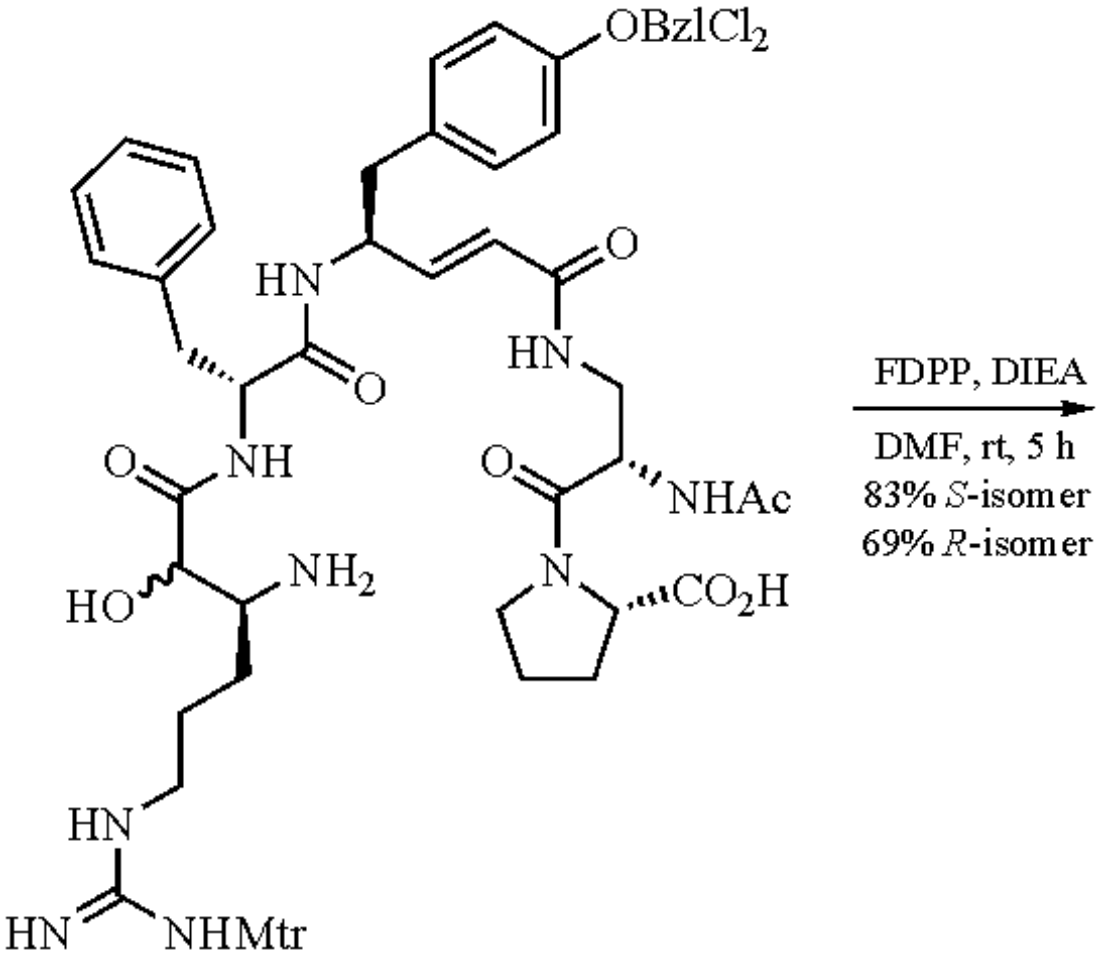

Mtr = 2,3,6-trimethyl-4-methoxy benzenesulfonyl

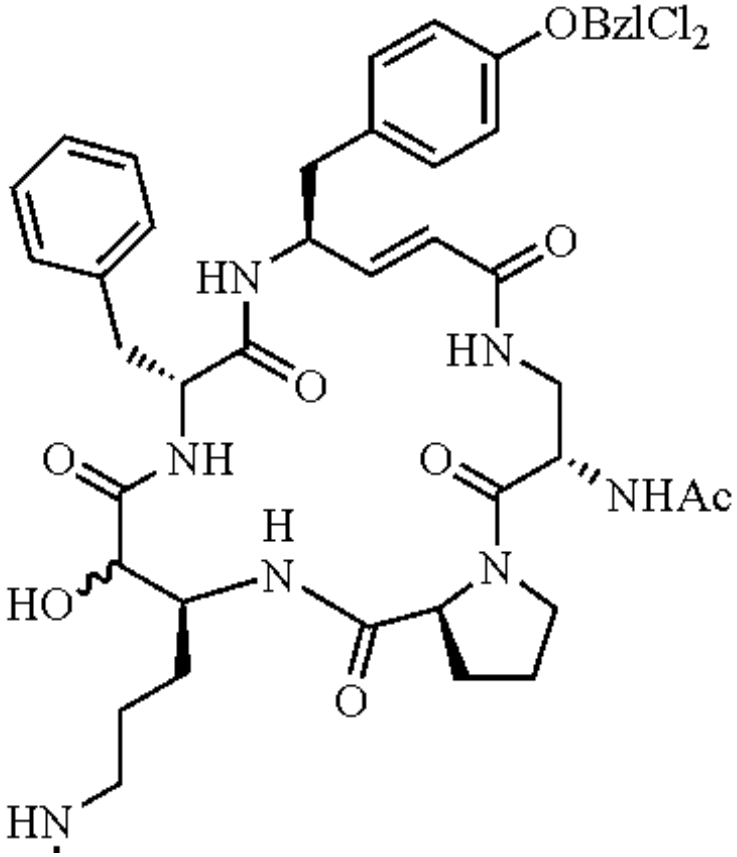

(7)

Pentafluorophenyl diphenylphosphinate (FDPP)

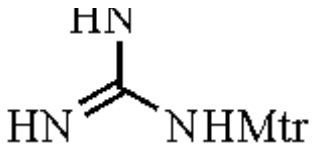

In their 1996 approach to the same molecule,[22] the WSCI/HOBt-mediated macrolactamization, which had been performed in 42% yield on an analog that had a vinylogous D-tyrosine in place of the vinylogous L-tyrosine, yielded only 16% for the desired substrate. DPPA and diethyl phosphorocyanidate (DEPC) gave only 8% and 12%, respectively, even after an extended reaction time of 3.5 days. The pentafluorophenyl ester also gave only 8% cyclized product. However, cyclization with FDPP gave 43% yield in only 4.5 h, and optimization increased the yield to 57% (eq 8).

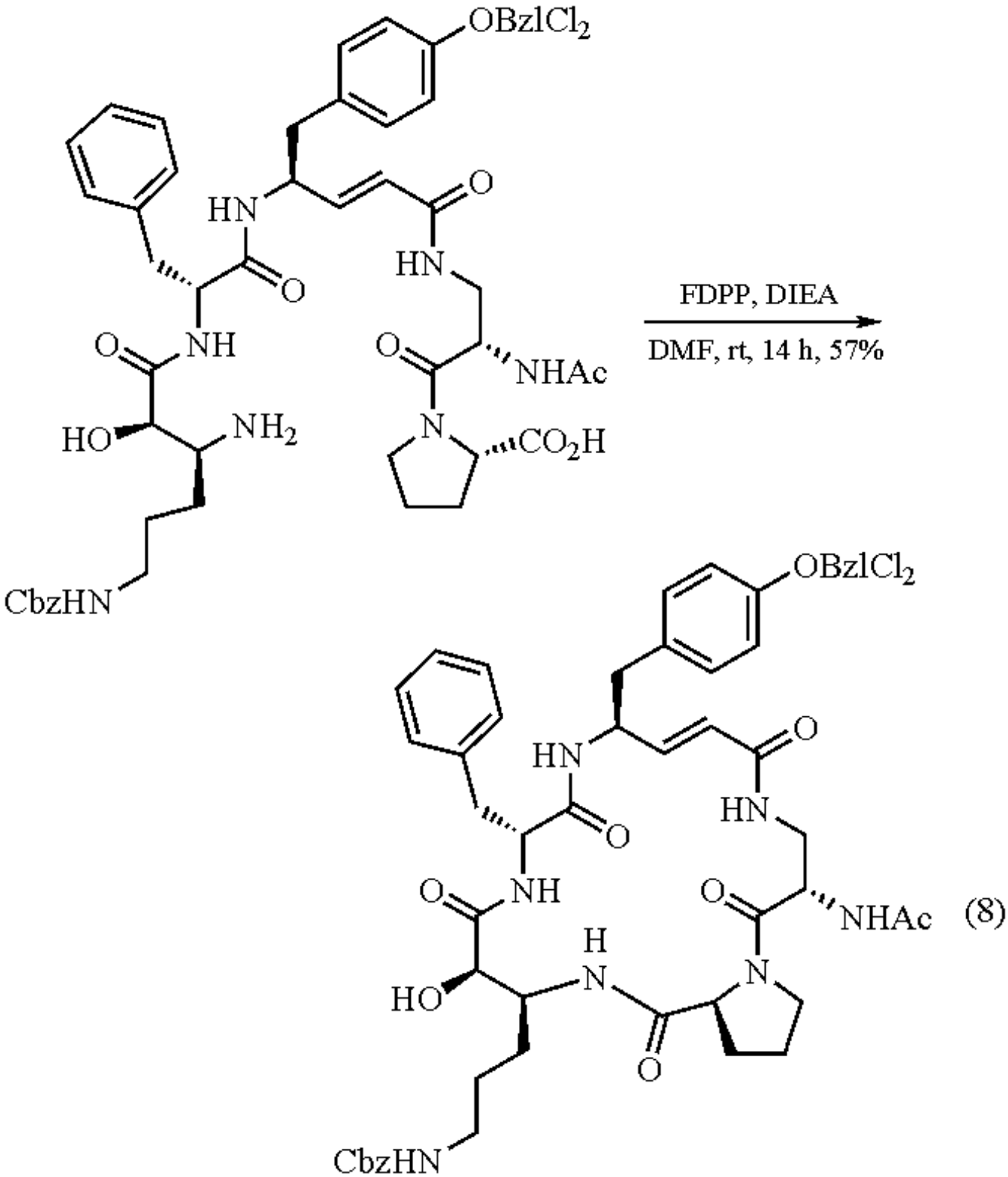

(8)

Deng and co-workers had similar success using FDPP for the macrolactamization en route to alterobactin A, a siderophore from an open ocean bacterium.[23,24] In this case, FDPP in the presence of NMM in DMF provided a 53% yield of cyclized product despite the relative steric congestion about the amino terminus (eq 9).

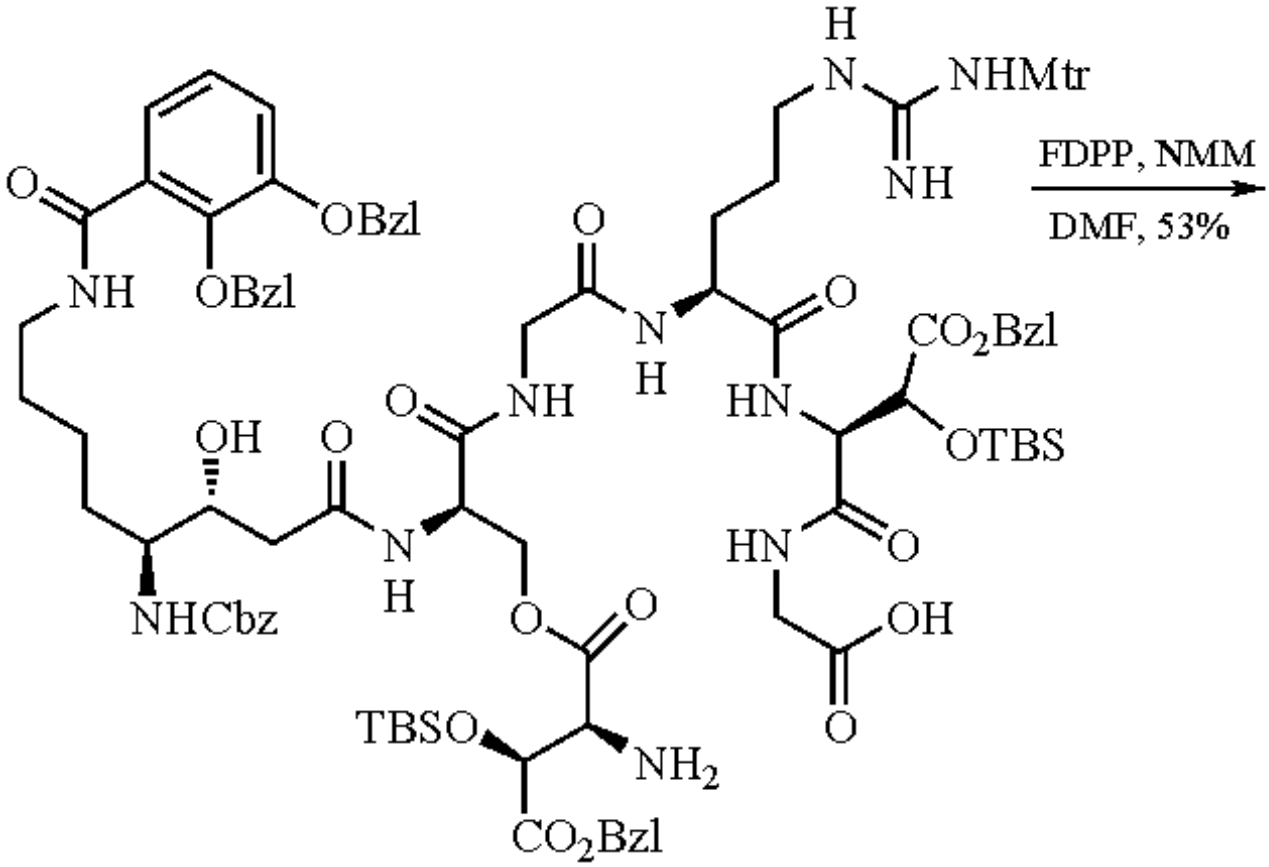

Mtr = 2,3,6-trimethyl-4-methoxy benzenesulfonyl

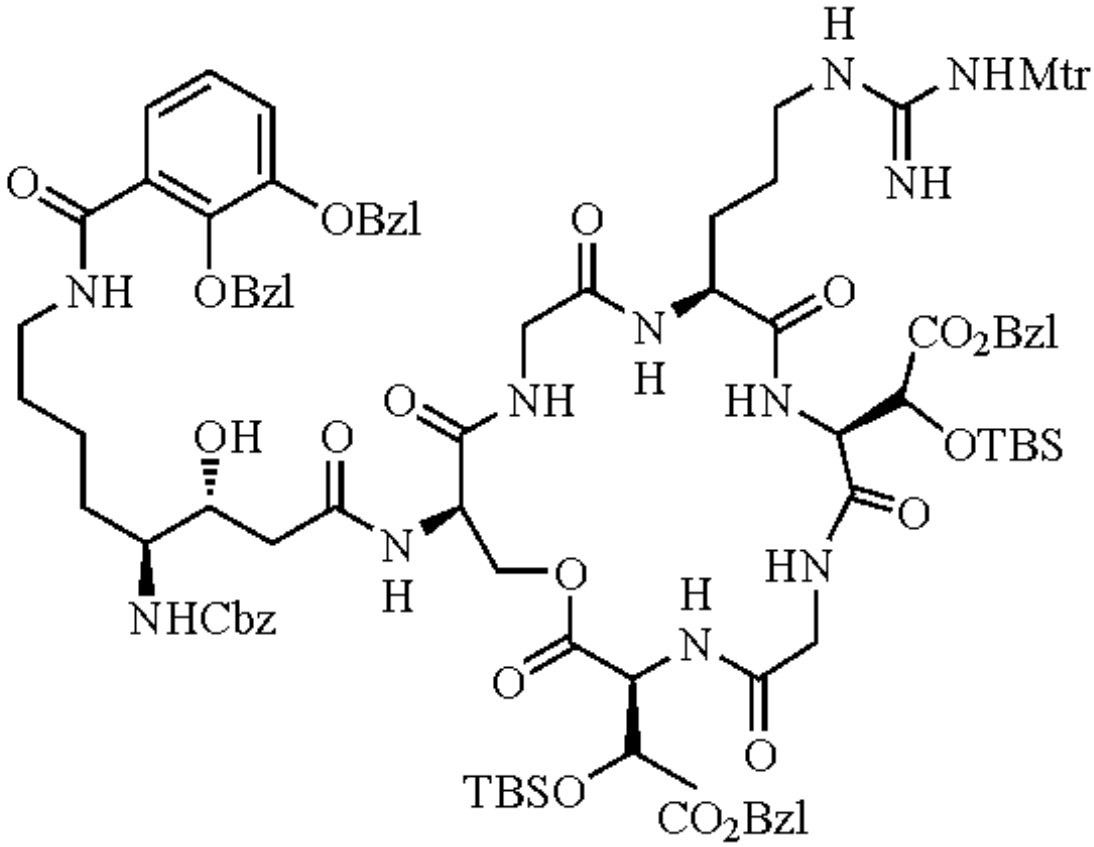

(9)

During the synthesis of new didemnin B analogs for investigation of the structure activity relationship of these cyclodepsipeptides,[25] improvements were made to the original[26] macrocycle synthesis. Among these modifications was the use of FDPP for the cyclization step. Previously, the best yields (42%) had been attained with DPPA after 72 h at 0 °C.[26] The product of dimerization was always a major contaminant

despite the use of very dilute conditions. The use of FDPP at room temperature for 3-4 h accomplished the cyclization in 68% yield (eq 10).[3,25]

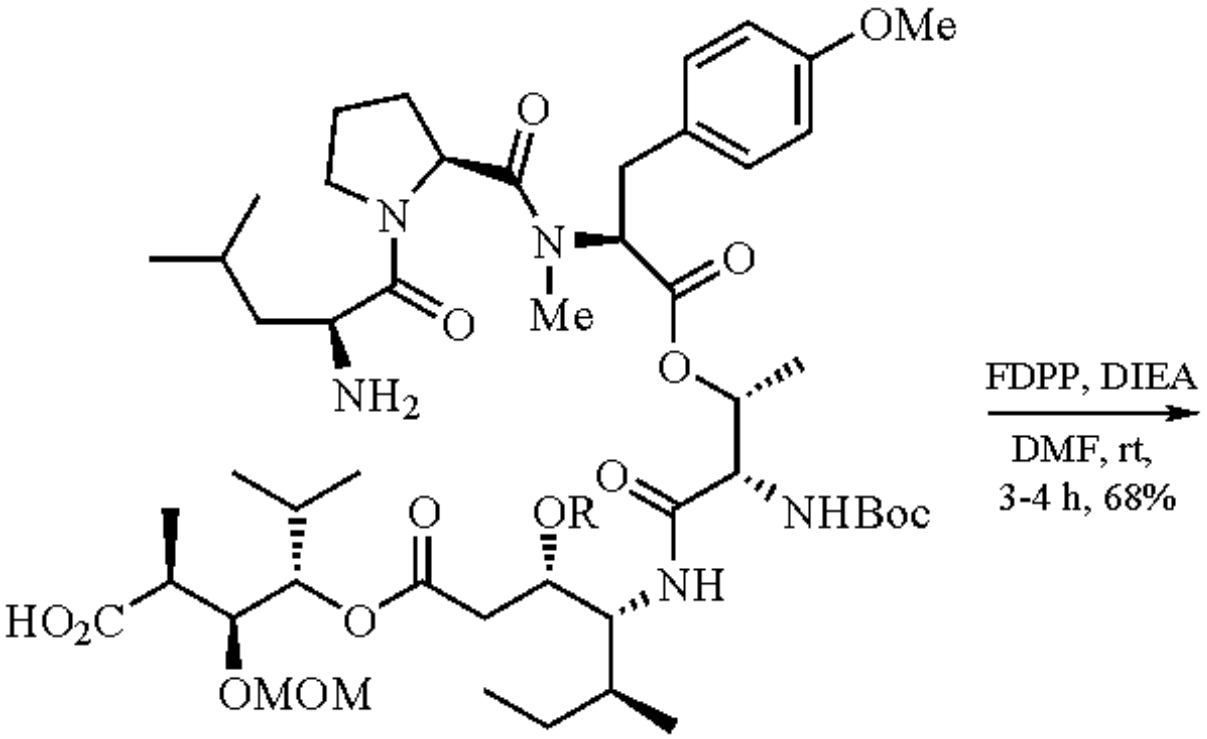

R = Si(*i*-Pr)$_3$

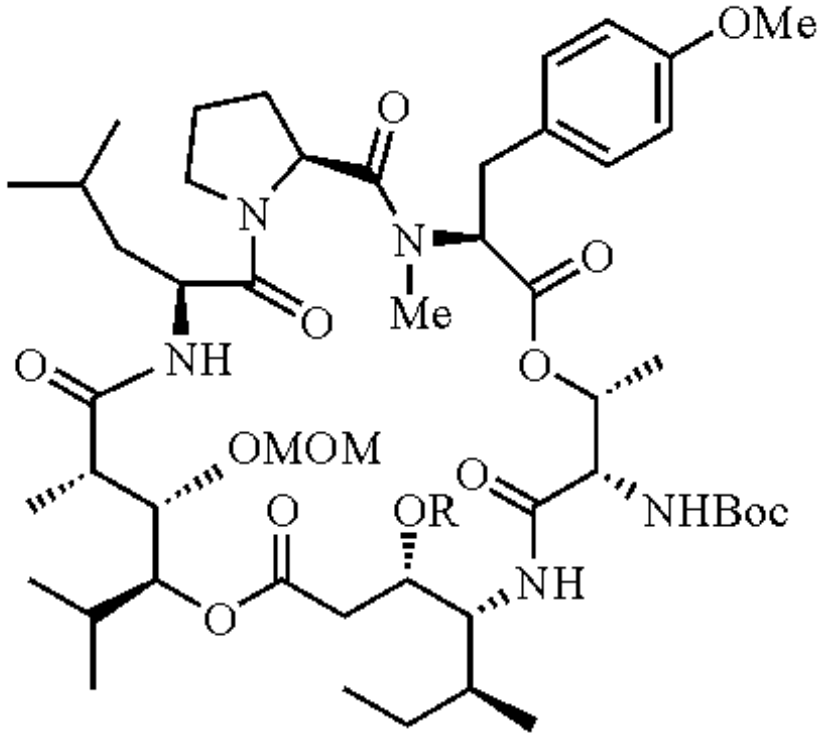

(10)

R = Si(*i*-Pr)$_3$

In a 1995 synthesis of the cryptophycins, FDPP was used for the macrolactamization reactions, giving a 62% yield of cryptophycin D (eq 11).[2,27,28]

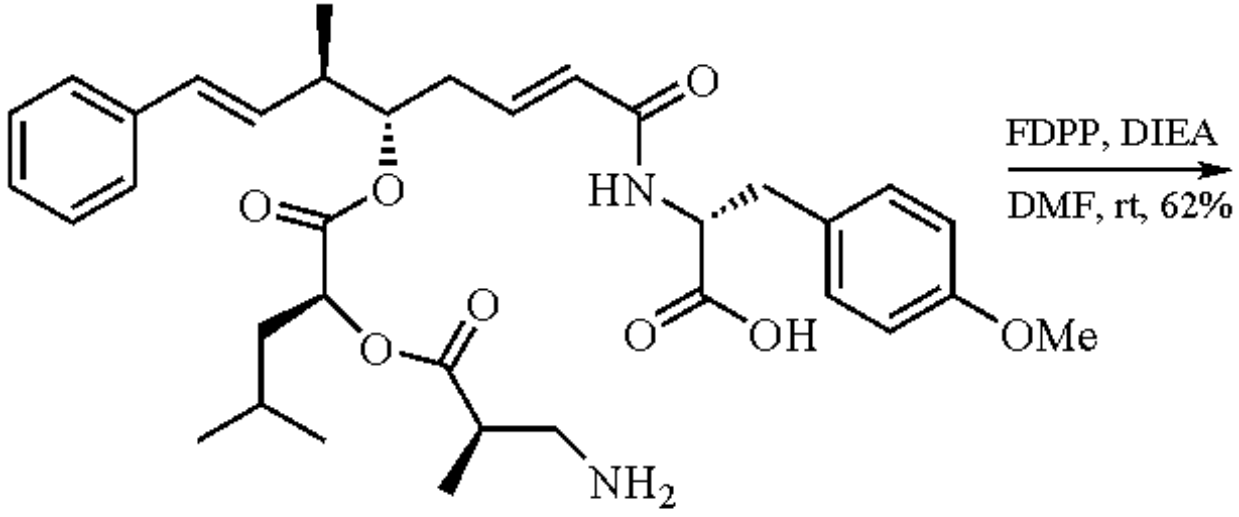

Cryptophycin D (11)

The same yield was achieved for a similar cyclization to give a product that proved not to be identical with cryptophycin C, leading to a revision of the structure of this natural product. The following year, a chemoenzymatic approach to the molecule was published by a different group in an effort to make the synthesis amenable to gram-scale preparation.[29] A more hindered site of cyclization was chosen, and FDPP cyclized in >70% yield in each case examined. A representative example is shown in eq 12.

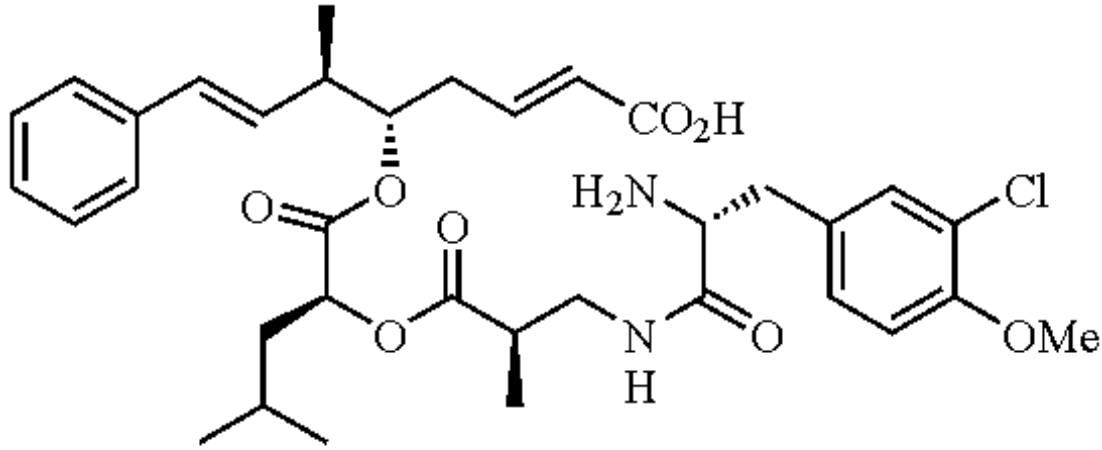

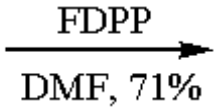

Cryptophycin C (12)

In the synthesis of astin G,[30] FDPP was useful for the coupling of the dipeptide and tripeptide fragments to form the linear precursor, giving the same yield (80%) as BOP. However, cyclization to form the 16-membered ring was unsuccessful with both FDPP and DPPA. HBTU proved to be the best reagent for this difficult cyclization, which proceeded in only 16% yield (eq 13).

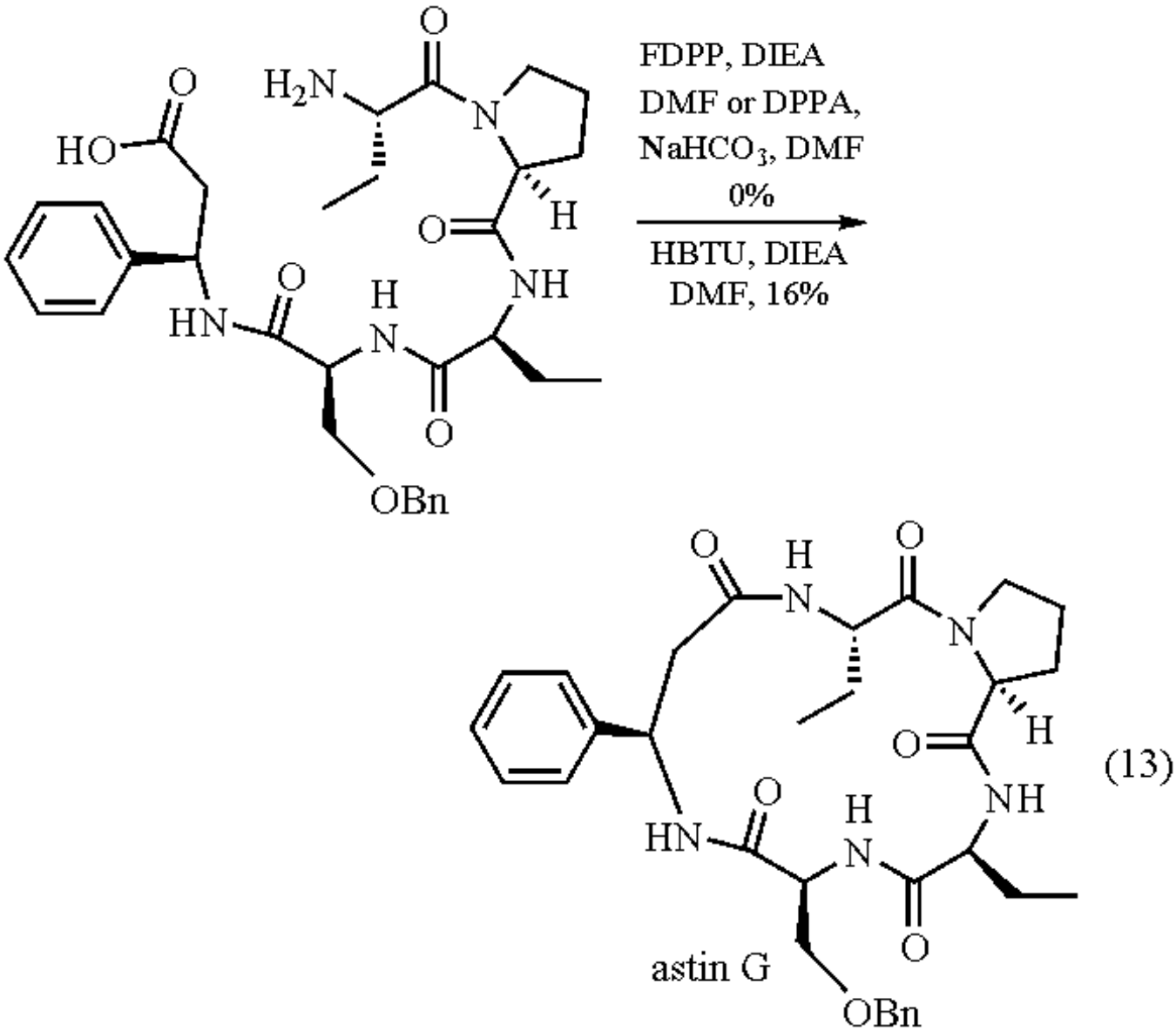

Cyclooligomerization

A less common use for FDPP is the cyclooligomerization reaction. Bertram et al. found that cyclic peptides containing thiazole moieties could be efficiently constructed in one step from the monomeric unit (eq 14).[31] They found that FDPP gave consistently high yields of cyclic products. The optimum procedure employed 3 equiv of Hünig's base and 1.5 equiv of FDPP added to a suspension of the monomer at a concentration of about 50 mM in acetonitrile. The reaction duration was approximately 18 h at room temperature. The yields were consistently >80% under these conditions, and the major products were the cyclic trimer and tetramer, in a ratio of 5:2.

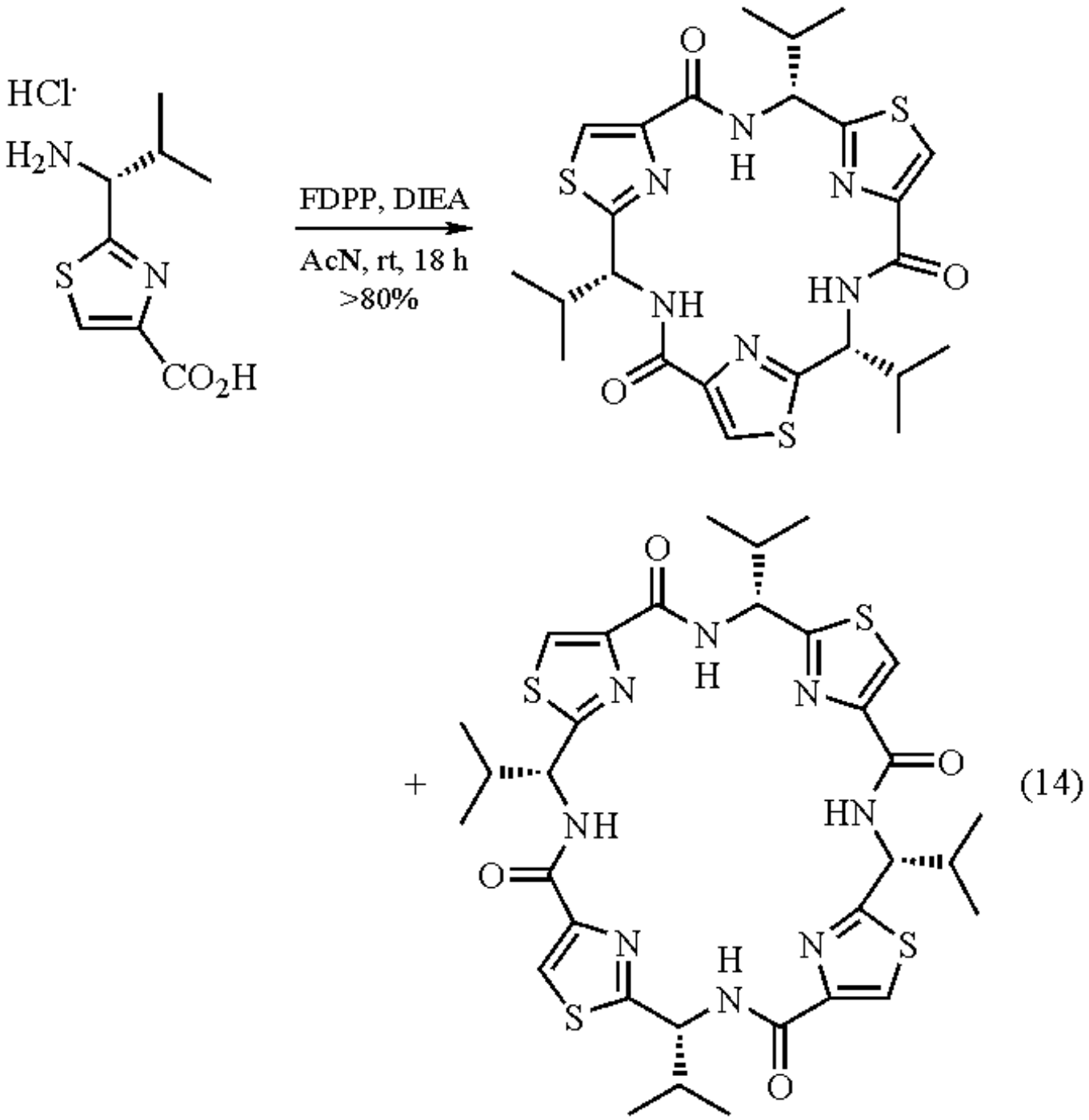

Couplings on Microarrays

In a recent adaptation of DNA microarray technology, Korbel et al. have used chiral fluorescent probes to measure the ee of tens of thousands of samples on reaction microarrays.[32] Their protocol employed an FDPP-mediated coupling of an equimolar mixture of two pseudoenantiomeric fluorescent reporters to the immobilized amino acid samples. During the coupling, the ee information of the sample becomes coded as a ratio of the fluorescent probes that is observable upon measurement of fluorescent emission at the appropriate excitation wavelength for each fluorophore.

Related Reagents.

DCC, EDAC, IPCF, DPPA, BOP, BOP-Cl, HBTU, HATU, DEPBT.

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Polymer-Supported Hydroxide[1]

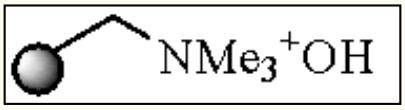

(the reagent is used as a base, a source of nucleophilic hydroxide, or a scavenger in a wide array of reactions[1])

Alternate Name: quaternary ammonium hydroxide anion exchange resin, Amberlite IRA-400 (OH^- form), Amberlite IRA 420 (OH^- form), Amberlite IRA 410 (OH^- form), Amberlite IRN-150, Amberlite IRA 900 (OH^- form), Amberlite IRA 904 (OH^- form), Amberlite IRA 910 (OH^- form), Amberlite A5836, Amberlyst A26 (OH^- form), Ambersep 900, Dowex-1 (OH^- form), Dowex-3 (OH^- form), Dowex 1-X4 (OH^- form), Dowex 1-I 9880, Dowex 1-I0131, Dowex 550 A (OH^- form), Amberjet 4400.

Form Supplied in: available on a variety of polystyrene-divinylbenzene cross-linked supports of both macroreticular and gel-type ion exchange resins. The reagent can be obtained with a range of basicities (pH) broadly characterized as weakly basic to strongly basic resins. The standard commercial form comes as large spherical beads (up to 4 mm in diameter) usually supplied with a water content of 30-60% by mass.

Purification: elute and wash with suitable solvents prior to use and dry under vacuum if required.

Handling, Storage, and Precautions: irritant; wear suitable protective clothing. Deactivates upon prolonged exposure to air by absorption of carbon dioxide. Decomposition of the tetraalkyl moiety can occur with strong acids/bases, oxidants and high temperatures.

General

Polymer-supported hydroxide has properties fully comparable to its solution phase counterparts. Some practical advantages of the polymer-supported hydroxide over the solution-phase bases is that no neutralization or separation steps are required other than simple filtration and evaporation of solvent leading to essentially pure products. The spent resin can also be easily regenerated and recycled by a simple base activation and washing sequence.[3] The resin also shows a good tolerance of most polar and nonpolar organic solvents although some protic and highly acid solvents can ion exchange with the hydroxide resin (e.g. alcohols, which can form the alkoxides on support).

Hydrolysis

Polymer-supported hydroxide serves as a nucleophile in various hydrolysis reactions. Hydrolysis of esters to the constituent acids and alcohols can be carried out under aqueous or methanolic conditions at ambient temperature.[4,5] Amides can also be formed from the corresponding nitriles[6] and cyclic iodo carbonates are smoothly converted into epoxy alcohols with retention of stereochemistry (eq 1).[7]

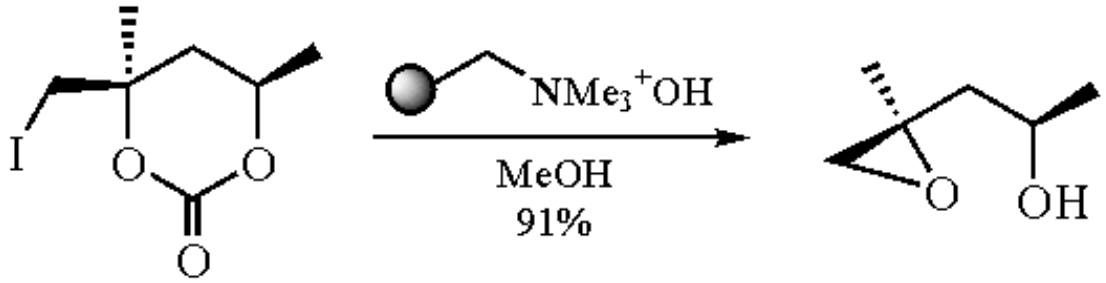

(1)

Elimination Reactions

Dehydrochlorination can be carried out efficiently using a strongly basic polymer supported hydroxide column and this method has been used to form indolium hydroxide (eq 2).[8] When an excess of base such as ammonia or triethylamine was used instead of the ion-exchange resin, a significant amount of undesired demethylation of the indolium salt was observed, forming 1-methylindole.

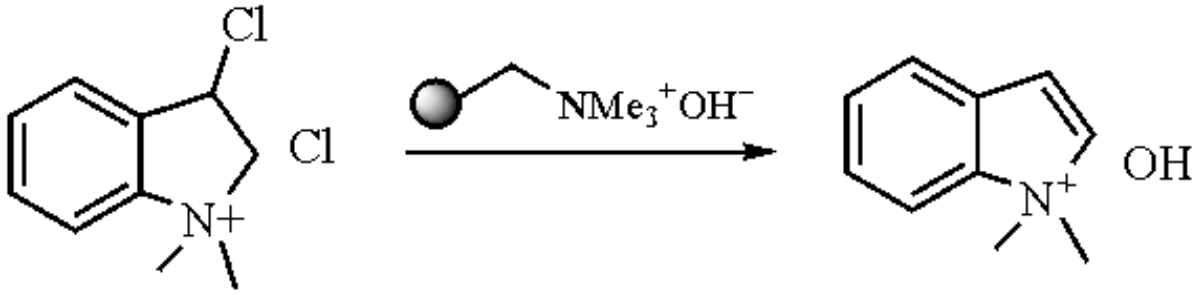

(2)

Condensation Reactions

The hydroxide anion-exchange resins have also been shown to be excellent catalysts in cyanohydrin formation,[9] aldol,[10] nitroaldol,[11-14] Knoevenagel, Claisen,[15] Dieckmann,[16] Cannizzaro,[11] and Michael condensations.[17-20] Amberlite IRA-420 (OH^-) has been employed as a strong polymer-supported base to effect the Henry reaction between various aldehydes and nitroalkanes (eq 3).[11-14] This reaction has also been utilized in a clean five-step synthesis of an array of 1,2,3,4-tetra-substituted pyrroles where all subsequent steps used polymer-supported reagents.[11] It should be noted that a large excess of the nitro compound (usually used neat) is needed for clean reactions and to prevent the Cannizzaro reaction on electron-poor aldehydes. The corresponding Henry reactions involving ketones proceed more slowly and with lower yields.[13]

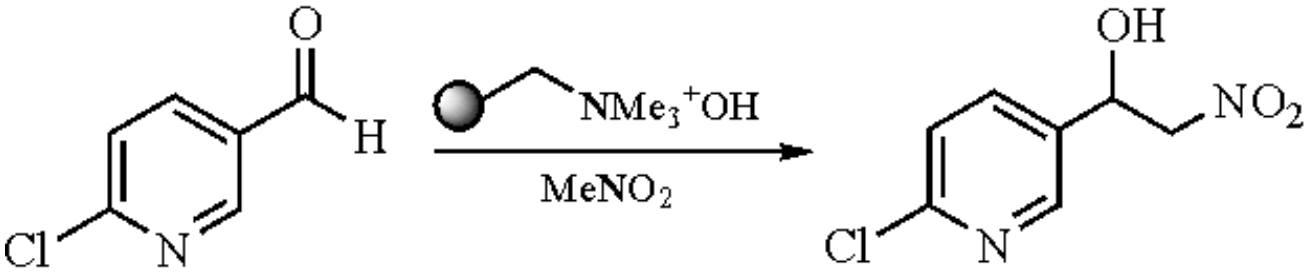

(3)

The same Amberlite IRA-420 resin under modified conditions has been used to effect a Cannizzaro reaction of electron-poor benzaldehydes.[11] In combination with a solid-supported oxidant to reoxidize the benzylic alcohols to the aldehydes, this method was used to generate quantities of benzoic acids.

Amberlite IRA-904 has been used in the dynamic resolution of cyanohydrins formed and racemized in situ by the basic anion exchange resin (eq 4).[9] The lipase used in the resolution was stable to the basic resin and enantiomeric excesses of up to 91% were achieved.

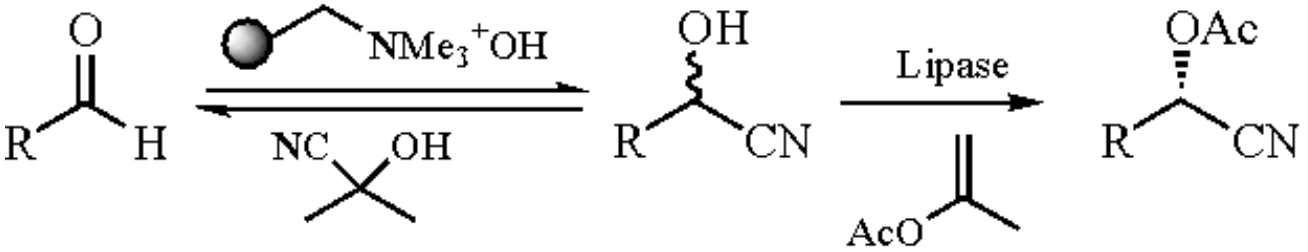

(4)

Aldol reactions have also been carried out using polymer-supported hydroxide for the synthesis of a variety of heterocyclic ketols and their dehydration products with improved yields over the conventional solution phase preparation.[10] The catalyzed reaction of a range of pyridinecarboxaldehydes and substituted acetophenones in ethanol furnished the corresponding aldol or α,β-unsaturated ketones, the propensity for dehydration was shown to be a direct function of the strength of the polymer base used.

In a similar way the polymer-supported hydroxide resin Ambersep 900 (OH^-) was used in the formation of a library of oxazoles via deprotonation of *p*-tolylsulfonylmethyl isocyanide (TosMIC) and subsequent addition to aromatic aldehydes.[21] A base-induced elimination of sulfinic acid which is sequestered by the basic resin leaves after filtering a clean solution of the oxazole product (eq 5).

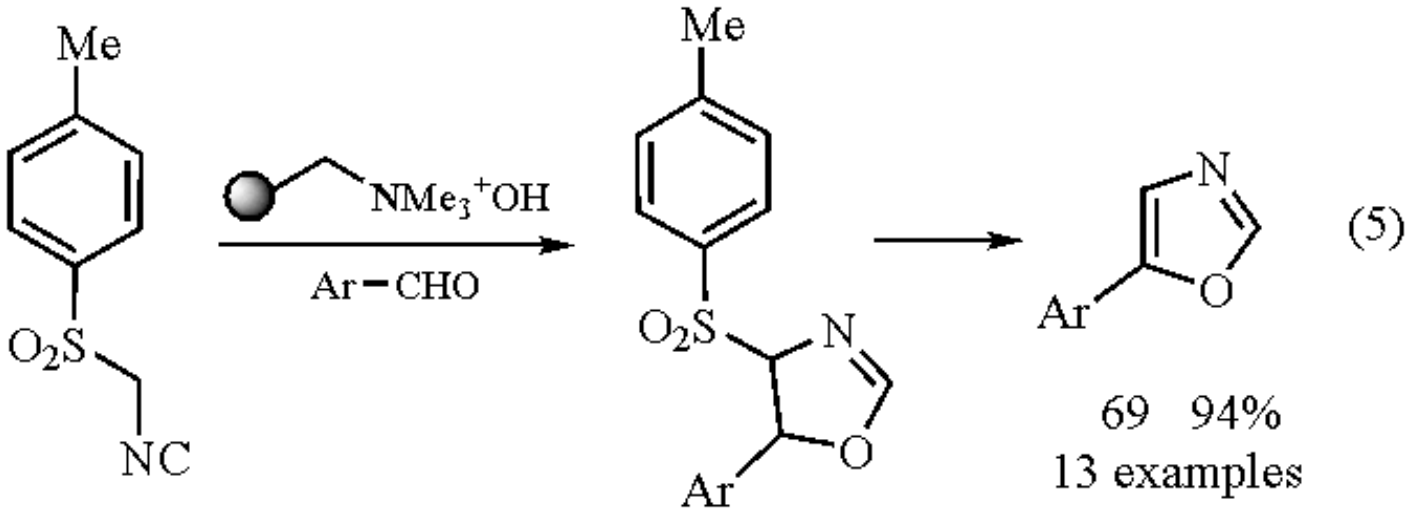

In library generation, purification by removal of impurities can be a tedious process, Beemashakar et al. have shown the advantage of using the hydroxide resin as both a reagent and purification aid in the combinatorial synthesis of 2,4-pyrrolidinediones.[22] In this synthesis, the hydroxide resin acts both as a base for the Dieckmann reaction and as product-sequestering agents in a 'catch-and-release' purification; the product remains tightly bound to the resin, enabling impurities to be removed by simple filtration and subsequent acidification releases the product into solution (eq 6).

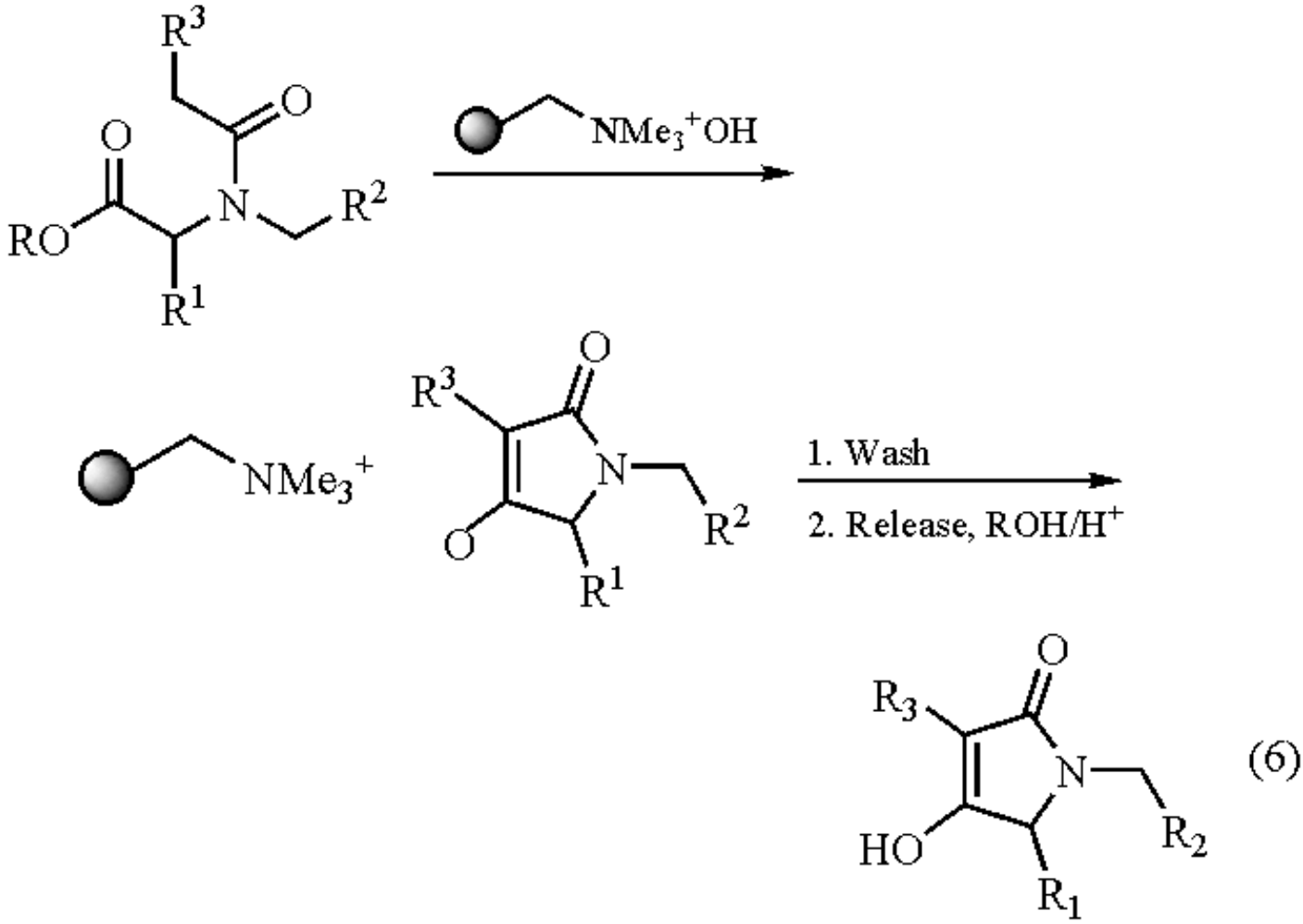

Alkylation Reactions

In the presence of a hydroxide resin, phenols can be converted to the corresponding ethers and acids to ester using alkyl halides or dialkyl sulfates; in this case any unreacted phenol or acid becomes bound to the basic resin aiding purification.[23-27] This protocol serves as a very facile method for carrying out *O*-alkylation of phenoxides with various alkyl halides. In these reactions, primary halides give higher yields than secondary, and bromides consistently give improved yields over chlorides.[25,26]

Shimo and Wakamatsu[3] and Gelbard[27] have reported the alkylation of various active methylene group-containing compounds like ethyl malonate, cyanoacetic esters and cyanoacetamides with various alkyl halides in the presence of Amberlite IRA-400 and IRA-900 (OH^-).[28]

Another interesting example is the intramolecular alkylation leading to ring closure and formation of β- and γ-lactams as demonstrated by Chatterjee et al. (eq 7).[29]

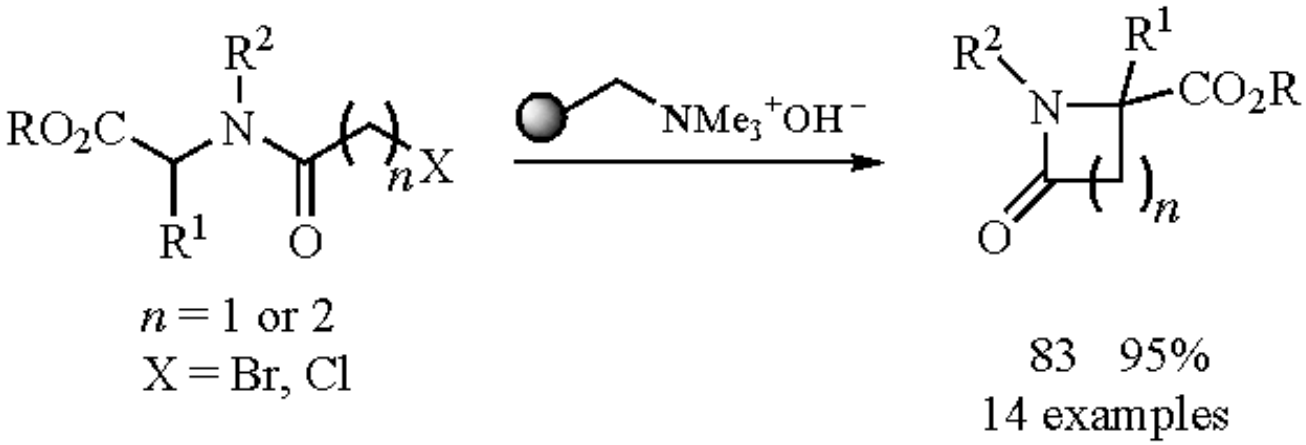

(7)

In a related process, Domann et al. have recently employed the polymeric resin Amberlyst A26 in the formation of epoxysilanes from vinyl silanes in a one-pot process (eq 8).[30] Starting from the vinylsilanes, the **polymer-bound haloate(I) reagent** generated the 1,2-cohalogenated product which under basic conditions was transformed to the corresponding epoxysilane in good yield and high purity.

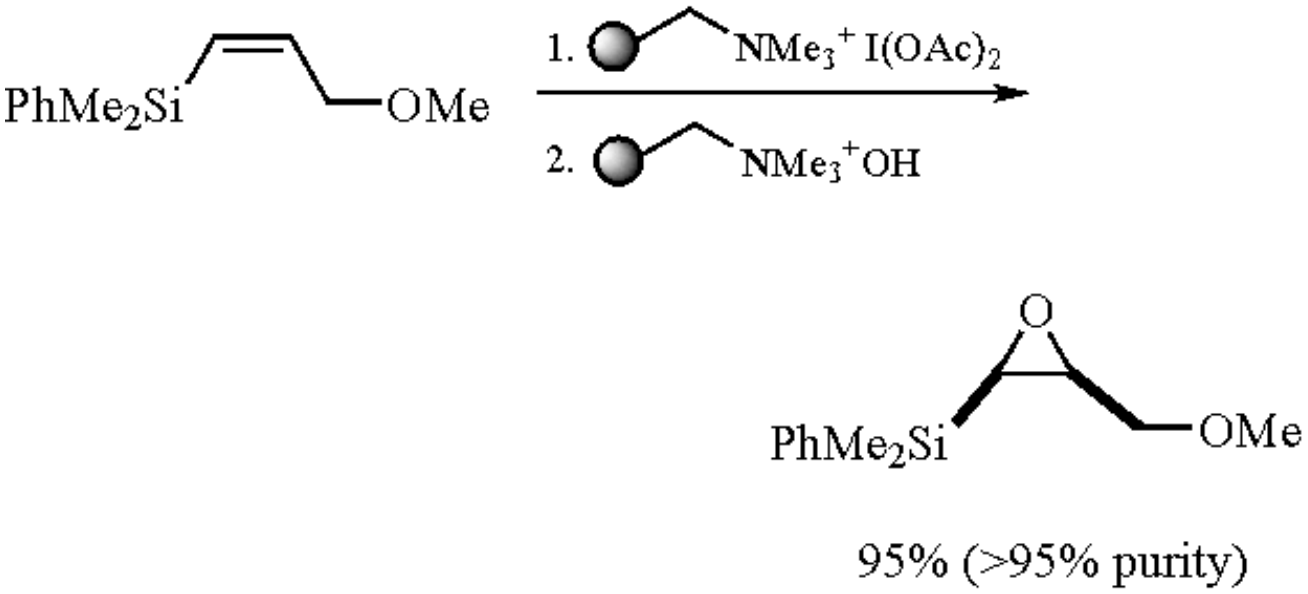

(8)

Horner-Wittig Reactions

Amberlyst A26 (OH^- form) has found use in the activation of stabilized phosphonates bearing α-nitrile or ester functionality for the olefination of carbonyl compounds (eq 9).[31] The reactions described gave good yields, although the *E*/*Z* ratio was not as high as would be expected under normal solution-phase conditions. It was however noted that the process was independent of the solvent used, with the resin providing a microenvironment making the reaction independent of the external medium (i.e. a greater range of solvents could be employed).

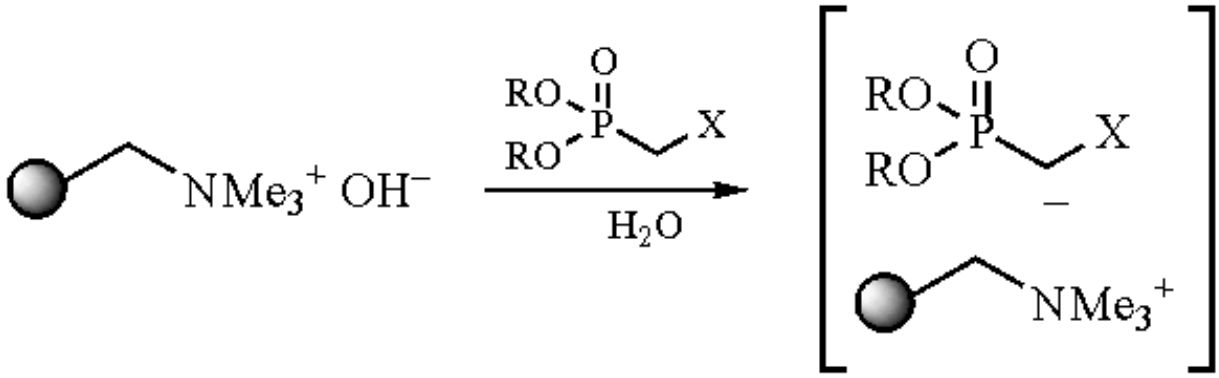

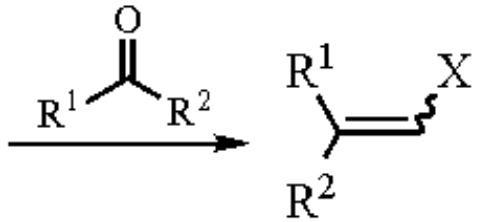

(9)

X= CN, CO_2R

Scavenging

The hydroxide resins have also been employed as purification aids, for example, in the preparation of a library of azo-dyes which were subjected to a 'catch-and-release' work-up which involved shaking the colored solution with Dowex(OH).[32] This procedure captured only the product leaving a colorless solution after filtration. The isolated resin was subsequently washed with acetic acid to release pure product. Amberlite IRA-420 has also been used as a scavenger to remove unreacted 2-aminothiophenol.[33] The polymer-supported hydroxide has also been employed extensively for the removal of acids and phenols and in a more conventional role for liberating the free base from protonated salts.

Related Reagents.

Quaternary tetraalkylammonium hydroxide has also been grafted onto other supports such as silica and MCM-41.[2]

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Cyclohexyl Chloroformate

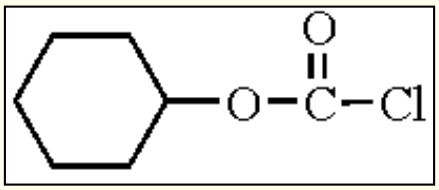

[13248-54-9] · $C_7H_{11}ClO_2$ · (162.62)

(cyclohexyloxycarbonyl (Hoc); amine and indole protecting group for peptide synthesis)

Alternate Name: carbonochloridic acid cyclohexyl ester; cyclohexyloxycarbonyl chloride; chloroformic acid cyclohexyl ester.

Analysis of Reagent Purity: ^{1}H NMR.

Form Supplied in: colorless liquid; not commercially available.

Solubility: soluble in most organic solvents.

Handling, Storage, and Precautions: decomposes to CO_2 and cyclohexyl chloride on prolonged storage. Store in a refrigerator. Bottles may develop pressure and should be cooled before opening. Use in a fume hood. Irritating to skin, eyes, mucous membranes.

Physical Data: bp 38-44 °C 2 mmHg;[1] n^{20}_D 1.4587.[1]

Preparative Methods: a 1 L round-bottomed flask equipped with a delivery tube extending to the bottom of the flask, a pressure-equalizing addition funnel and a cold-finger condenser cooled with dry ice-acetone were placed in an ice bath. The exit tube of the condenser was connected to a $CaCl_2$ drying tube and suitable trap for phosgene and HCl. Phosgene was introduced into the flask until 109 g (1.1 mol) has been condensed. The reaction flask is stirred while 100 g (1 mol) of cyclohexyl alcohol was added through the dropping funnel at a rate to keep the mixture in gentle reflux for 1 h. The flask was allowed to stand at room temperature with stirring for 2 h. The solution was then concentrated under reduced pressure at room temperature to remove HCl and the excess phosgene. The residue may be used without further purification.

Note: Phosgene is a highly toxic gas; use in a fume hood.

Introduction

The cyclohexyloxycarbonyl (Hoc) group was originally developed by McKay and Albertson as acid labile N^{α}-amino protection used for peptide synthesis.[2] The reagent used for the introduction of the Hoc group, cyclohexyl chlorofomate, is easily prepared from inexpensive starting materials, cyclohexyl alcohol, and phosgene (eq 1).

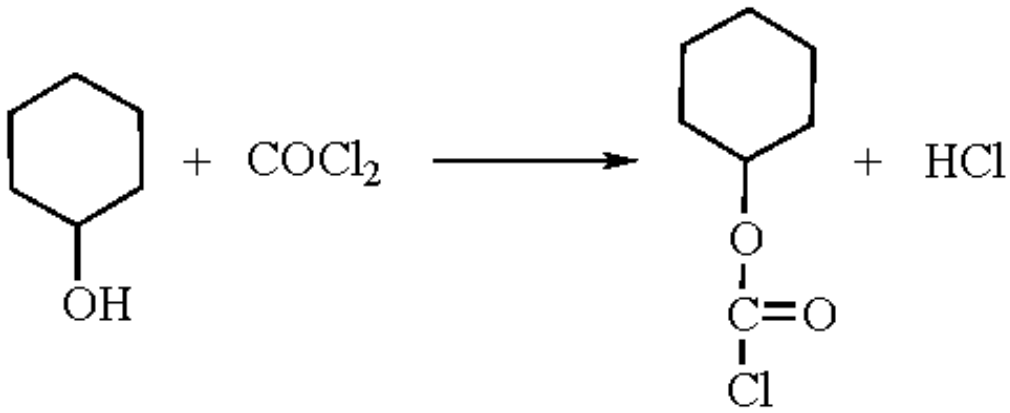

(1)

In elongating peptide chains properly, there must be a highly compatibility between the protecting groups for N^{α}-amino function and amino acid side-chain functional groups. The N^{α}-Hoc group is readily cleaved by strong acids such as hydrogen bromide (HBr) in acetic acid[2] or liquid hydrogen fluoride (HF),[3] although most side-chain protecting groups are also removed under these conditions. When compared with other N^{α}-amino protecting groups commonly used for *t*-butyloxycarbonyl or benzyloxycarbonyl (Z)-mediated peptide synthesis, however, the Boc and the Z groups can be selectively removed by much milder conditions such that the side-chain protecting groups remain intact. Therefore, the Hoc group has not gained the practical application for N^{α}-amino protection since it offers no advantage over the Boc and Z groups. However, recently the use of Hoc group has been used as the N^{in}-protecting group for the synthesis of tryptophan (Trp)-containing peptides[4] and also as another orthogonal amino-protecting group in Boc chemistry.[5]

Hoc Group as a Base-Resistant N^{in}-Protecting Group for Trp

The Hoc group, which is compatible with Boc-mediated peptide synthesis, was introduced to the indole moiety of Trp to avoid indole oxidation and alkylation during repetitive acid treatment such as with trifluoroacetic acid (TFA).[4,6] The Hoc group was introduced by acylation of Boc-Trp-OPac (Pac = phenacyl) or Boc-Trp-OBzl using cyclohexyl chloroformate in dichloromethane in the presence of pulverized NaOH and a catalytic amount of tetra-*n*-butyl ammonium hydrogensulfate (TBAHS) at room temperature for 1 h. Removal of the Pac or Bzl ester by using zinc dust in acetic acid or catalytic hydrogenation gave the Trp derivative (eq 2).

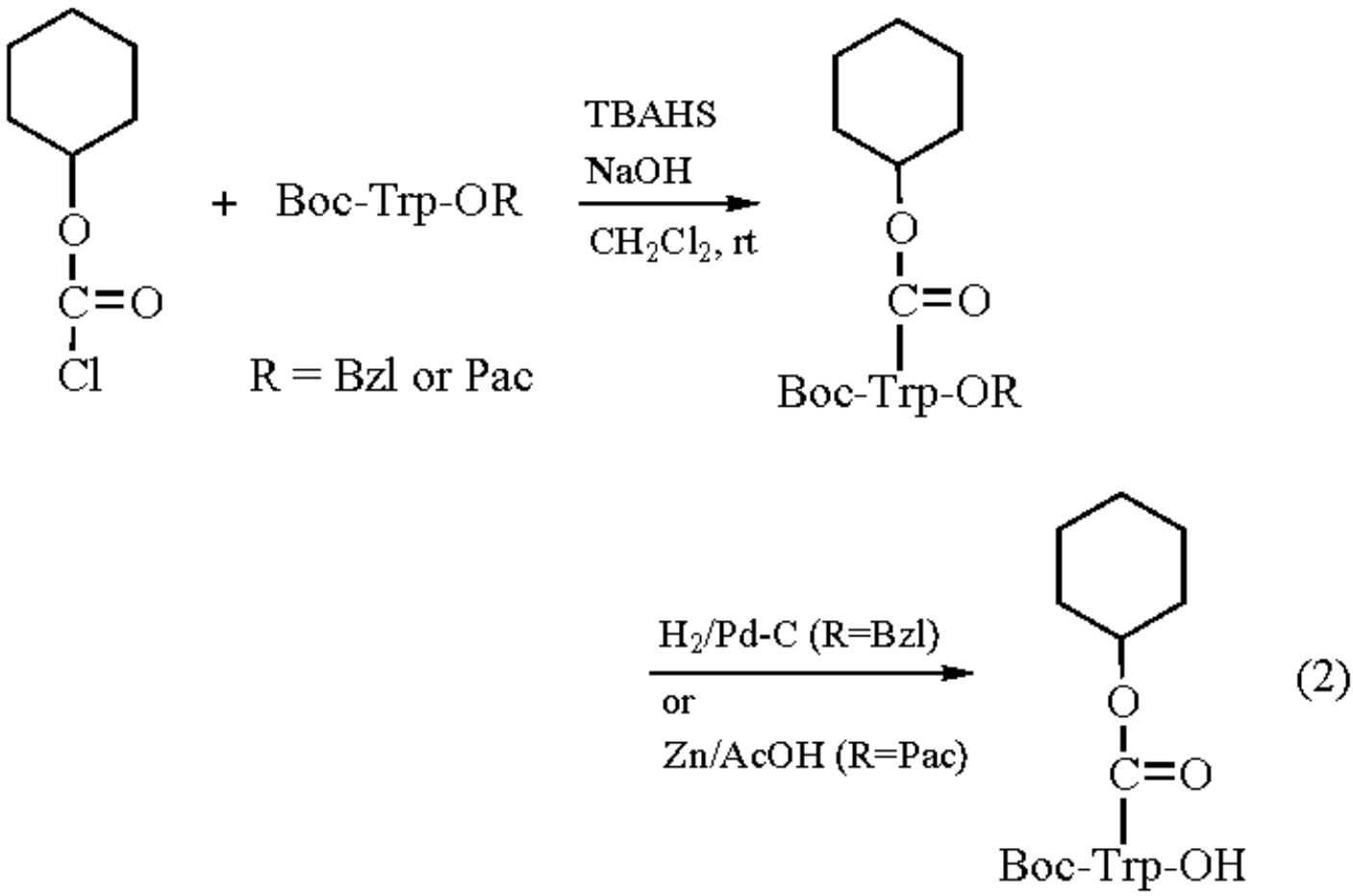

In contrast with the widely employed formyl protecting group for Trp,[7] the Hoc group is readily cleaved by HF without resorting to the use of thiols and is also far more stable under conditions using basic nucleophiles (e.g. morpholine and piperidine)[4] (Table 1).

Table 1 Stability of the side-chain protecting groups for Trp in acid and base. Determined by HPLC after treatment of Boc-Trp(X) under acidic (500 eq) or basic (100 eq) conditions (rt, 18 h)

	Loss of protecting group X (%)	
X–	Hoc	For
TFA	0	0
10% DIEA/DMF	0	28
10% piperidine/DMF	0	100
20% morpholine/DMF	0	100

When synthesizing Trp-containing peptides by the Boc-mediated peptide synthesis, therefore, the N^{in}-Hoc group is applicable not only to the standard solid-phase peptide synthesis but also to the preparation of protected peptide segments on base labile linkers such as an *N*-[9-(hydroxymethyl)-2-fluorenyl]succinamic acid (HMFS) linker.[8] The HMFS linker is designed to release fully protected segments with a free α-carboxyl group by treatment with 20% morpholine in DMF. The Hoc group on Trp is completely stable under basic conditions for detachment of the segments from the HMFS resin. The protected segments thus obtained are used for the subsequent segment condensation reaction performed using either solution or solid phase method. Employing this procedure based on performing segment assembly on the solid support and segment condensation in solution, the synthesis of muscarinic toxin 1 (a 66-residue peptide)[9] and green fluorescent protein (a 238-residue protein)[10] was reported. With accumulation of experiments employing the N^{in}-Hoc group, however, it became apparent that modification of Trp associated with use of this group produces two *trans*-isomers of 2-[2´-(*p*-cresol)]-2,3-dihydrotryptophan (**1**) during the HF reaction in the presence of *p*-cresol as a scavenger.[11]

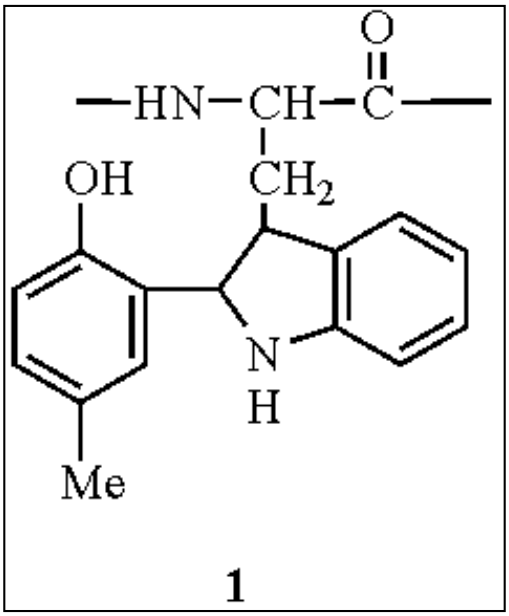

This side reaction for Trp proved to be inherent to the carbamate-type N^{in}-protecting groups (e.g. Hoc, Z and 2,4-dimethylpent-3-yloxycarbonyl[12]). The use of thiols such as butane-1,4-dithiol during the HF reaction was found to almost completely avoid this side reaction, although the Hoc group could be removed by HF without any thiol.

Hoc Group as Another Orthogonal Amino-Protecting Group in Boc Chemistry

In Boc-mediated peptide synthesis, the Boc group is used as N^{α} protection in combination with benzyl (Bzl)/cyclohexyl (Hex)-based side-chain protecting groups. Thus, the orthogonality of protecting scheme consists in the difference in reaction rate when acidolysis is used to remove different classes of protecting groups: generally TFA and HF are employed for removal of the Boc and the side-chain protecting groups, respectively. Regarding removal of the side-chain protecting groups, Bzl-based groups can be cleaved by 1M trimethylsilyl trifluoromethanesulphonate (TMSOTf)-thioanisole/TFA mixture[13] to which Hex-based groups are stable. Therefore, free amino and/or carboxyl groups protected by Bzl-based groups are available prior to cleaving Hex-based protecting groups. By taking advantage of the difference in their removability under acidic conditions, a possibility for the assembly of cyclic lactam peptides was demonstrated.[5]

Related Reagents.

2-(t-Butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), t-butylchloroformate (Boc-Cl), benzyl chloroformate.

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O-(*N*-Succinimidyl)-1,1,3,3-tetramethyluronium Tetrafluoroborate (TSTU)

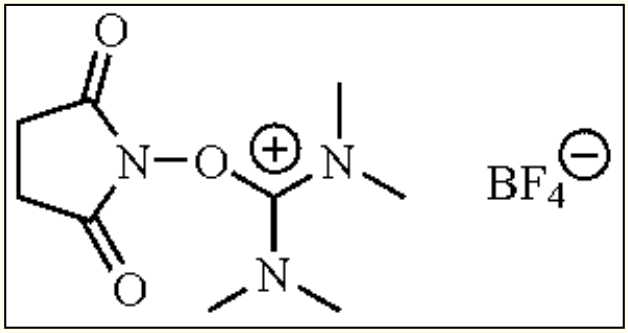

[105832-38-0] · $C_9H_{16}BF_4N_3O_3$ · (301.051)

(reagent for carboxamide formation from a carboxylic acid and a primary amine; peptide coupling reagent)

Physical Data: mp 198-201 °C.

Solubility: soluble in DMF, CH_2Cl_2, $CHCl_3$, CH_3CN (0.1 g mL^{-1}), DMF/1,4-dioxane/water (2:2:1).

Form Supplied in: colorless powder. Commercially available from Advanced ChemTech (Louisville, KY, USA), Aldrich (Milwaukee, WI, USA), and Fluka Chemical (Milwaukee, WI, USA).

Handling, Storage, and Precautions: irritant (eye, skin, respiratory tract). Avoid breathing dust, vapor, moisture, or gas. Avoid contact with skin, eyes and clothing. Moisture-sensitive. For long-term storage, keep under nitrogen atmosphere and refrigerate.

Carboxamide Formation

O-(*N*-Succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TSTU) reacts with carboxylic acids in the presence of ≥2 equiv base to give succinimidyl active esters,[1,2] which are capable of reacting with primary amines to afford carboxamides (eq 1). The coupling reactions between carboxylic acids and primary amines with TSTU can also be performed in situ. The reaction proceeds rapidly and efficiently with only a slight excess of TSTU. The coupling reaction can be carried out even in the presence of water, such as in DMF/1,4-dioxane/water mixtures.[3] This feature allows hydrophilic amines to be derivatized with hydrophobic carboxylic acids, as demonstrated in the coupling of bathophenanthroline-ruthenium(III) complexes and 5´-amino-5´-deoxy oligonucleotides.[1]

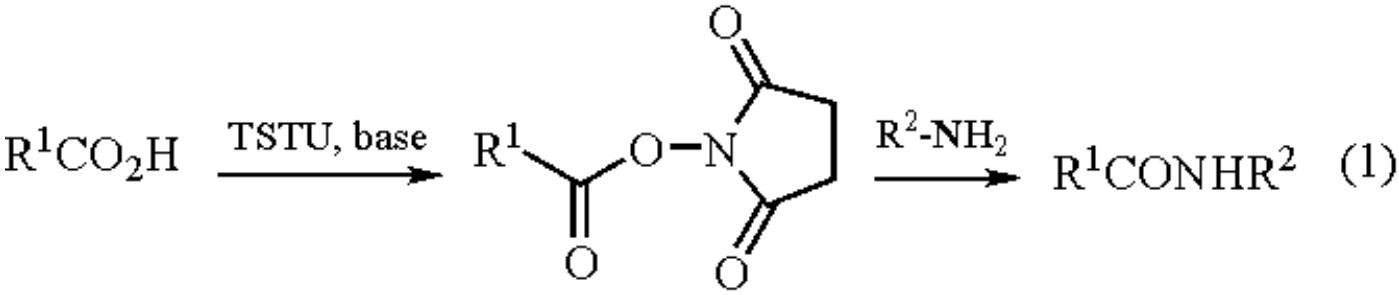

The amino group of an amino alcohol can be selectively acylated by using TSTU without *O*-protection (eq 2).

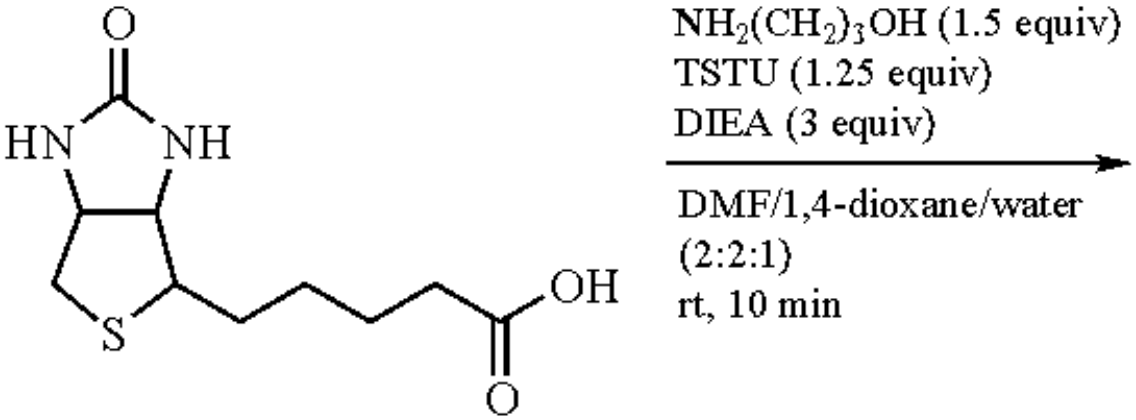

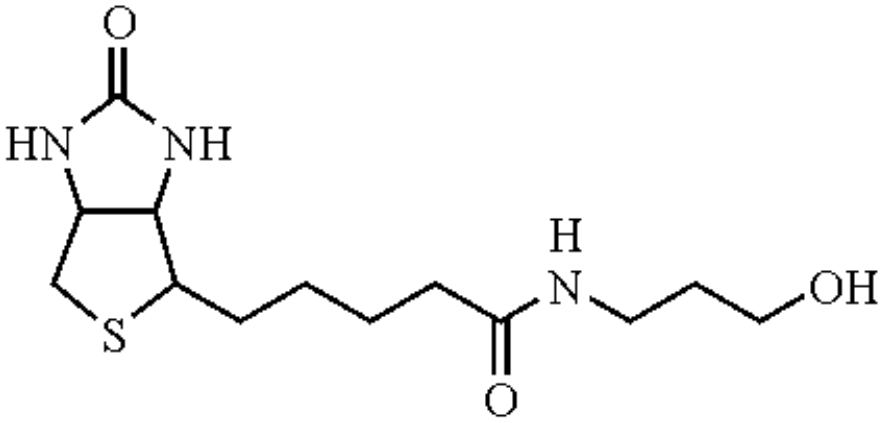

(2)

81%

TSTU can be employed as a coupling reagent in peptide synthesis, like analogous reagents (see Related Reagents). An amino acid, of which the α-amino group is protected with a urethane-type protecting group, e.g. Boc, Cbz, or Fmoc, can be coupled without a significant level of enantiomerization or epimerization. The segment condensation with these reagents, however, causes significant levels of epimerization of the carboxy-terminal amino acid residue of the acyl component except the cases where the carboxy-terminal residue is Gly or Pro.

Peptides having a *C*-terminal *N*-methylamino acid residue are highly prone to epimerization in the segment condensation. Simultaneous use of *N*-hydroxysuccinimide and $CuCl_2$ with TSTU eliminates the epimerization of the *N*-methylamino acid residue (eq 3), whereas analogous coupling reagents, (benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), give significant levels of epimerization, even in the presence of $CuCl_2$.[4]

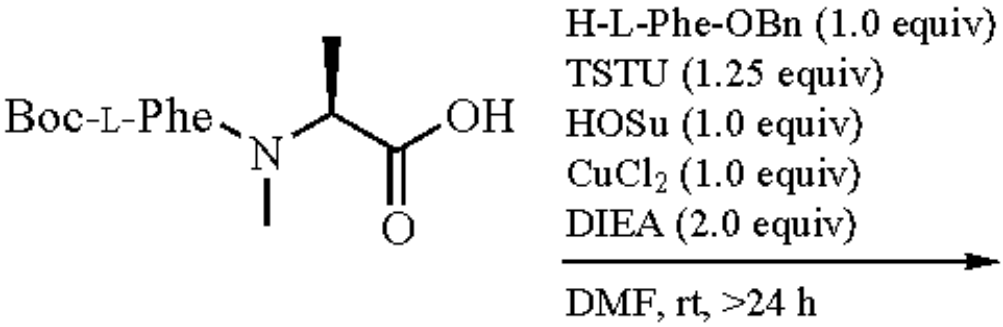

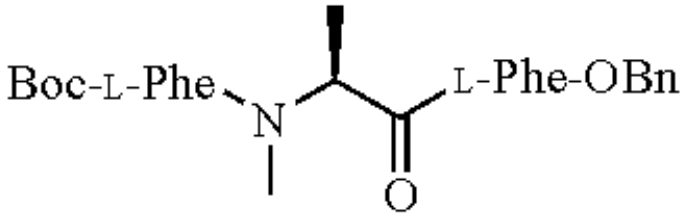

(3)

45 % (no detectable L-D-L)

Related Reagents.

(Benzotriazol-1-yl)oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) [56602-33-6];[5] (benzotriazol-1-yl)oxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) [128625-52-5];[6] O-(N-benzotriazolyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) [94790-37-1];[7] O-(N-benzotriazolyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) [125700-67-6];[2] 2-(5-norbornene-2,3-dicarboxamido)-1,1,3,3-tetramethyluronium tetrafluoroborate (TNTU) [125700-73-4];[2] (7-azabenzotriazol-1-yl)oxytris(pyrrolidino)phosphonium hexafluorophosphonate (PyAOP) [156311-83-0];[8] O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) [148893-10-1].[9]

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3,3´-PolyBINOL[1]

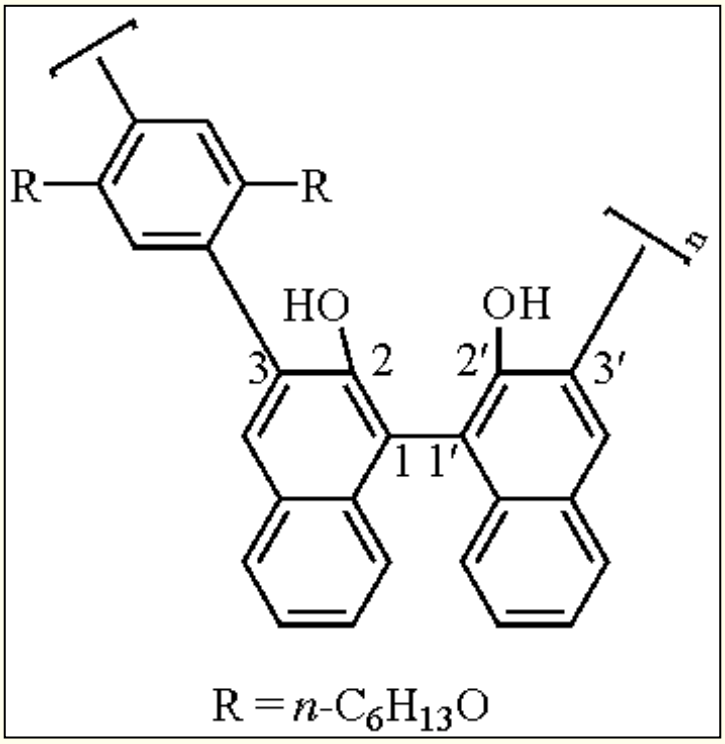

· $(C_{38}H_{40}O_4)_n$ · ([560.72]$_n$)

(used as an easily recyclable ligand for asymmetric Lewis acid catalysis)

Solubility: soluble in chloroform, methylene chloride, THF, and toluene. Insoluble in alcohols, H_2O, and hexane.

Form Supplied in: yellow solid.

Preparative Methods: [1,2] prepared from the Suzuki coupling of the phenylenediboronic acid[1] with the optically pure binaphthyl monomer (*R*)- or (*S*)-[2], made from optically pure 1,1´-bi-2-naphthol (BINOL), followed by acid hydrolysis. By using either $Pd(OAc)_2$ or $Pd(PPh_3)_4$ as the catalyst, 3,3´-polyBINOL was obtained with a molecular weight in the range of MW = 6700 to 24 300 (polydispersity index = 1.5-2.5) as determined by gel permeation chromatography relative to polystyrene standard. It was purified by repeated precipitation with methanol from a methylene chloride solution.

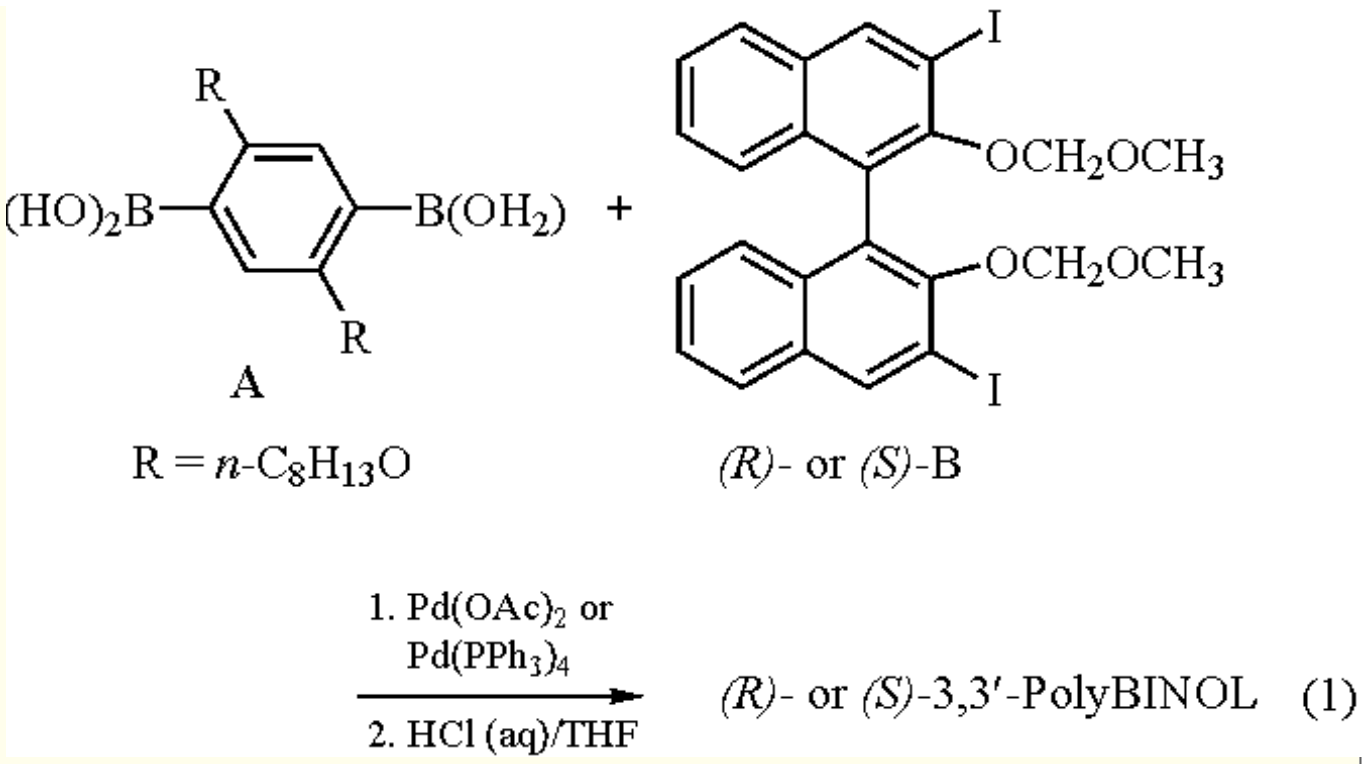

Handling, Storage, and Precautions: for long-term storage, keep in closed bottle in the absence of light.

Asymmetric Alkylzinc Addition to Aldehydes[1,2]

3,3´-PolyBINOL was used to catalyze the reaction of dialkylzincs with aldehydes to generate chiral secondary alcohols with good enantioselectivity. The reactions were normally carried out at 0 °C in toluene solution with 5 mol% (based on the repeating unit) of 3,3´-polyBINOL and 1-2 equiv of diethylzinc. The reactions of benzaldehyde and *para*-substituted benzaldehydes proceeded with up to 94% ee. The reactions of aliphatic aldehydes gave up to 83% ee. The polymer was recovered by precipitation with methanol and the recovered polymer showed the same catalytic properties as the original one. These reactions were also found to be independent of the molecular weight and molecular weight distribution of the polymer. The catalyst made of (*R*)-BINOL units gave (*R*)-alcohol products, and the (*S*)-BINOL derivative gave (*S*)-alcohols.

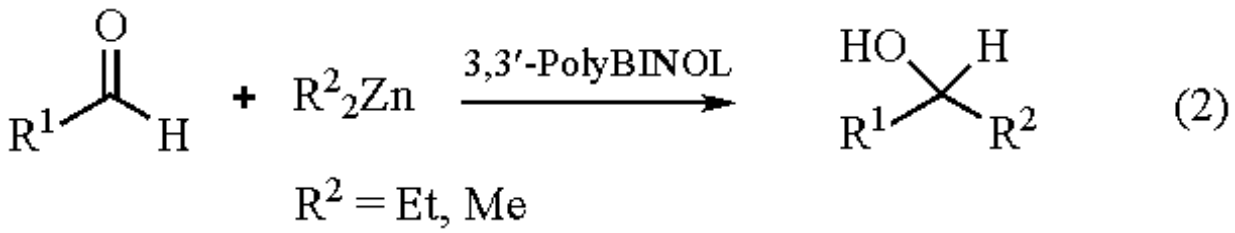

Asymmetric 1,3-Dipolar Cycloaddition of Nitrones to Vinyl Ethers[3]

(*R*)-3,3´-PolyBINOL in combination with $AlMe_3$ was used to catalyze the 1,3-dipolar cycloaddition of nitrones to vinyl ethers with excellent stereocontrol. The reactions were carried out at room temperature in methylene chloride in the presence of 20 mol% of (*R*)-3,3´-polyBINOL + $AlMe_3$. After precipitation and centrifugation to remove the polymer catalyst following completion of the reactions, the isoxazolidine products were essentially both chemically and enantiomerically pure. The *exo*/*endo* product ratio was generally >98:2 and the ee was 93-99%. The recovered polymer showed very similar catalytic properties as the original polymer.

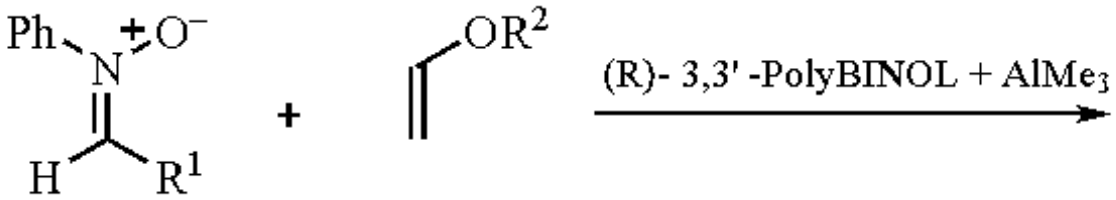

R^1 = Ph, p-tolyl R^2 = Et, Bn, ^{t}Bu

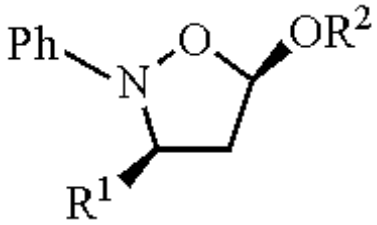

(3)

Asymmetric Epoxidation of α,β-Unsaturated Ketones[4]

The zinc complex of (*R*)-3,3´-polyBINOL catalyzed the asymmetric epoxidation of α,β-unsaturated ketones. The reaction was typically conducted by first mixing 0.2 equiv of (*R*)-3,3´-polyBINOL with 0.36 equiv of diethylzinc in diethyl ether at room temperature. Then an α,β-unsaturated ketone and *t*-BuOOH (1.2 equiv) were added. The reaction mixture was then stirred at room temperature for a few hours, after which time it was quenched with 1N HCl and extracted with ethyl acetate. The polymer was recovered by precipitation with methanol from the ethyl acetate solution. The α,β-epoxyketone products were obtained with up to 97% yield and 81% ee. The diastereoselectivity was generally >99%.

Asymmetric Reduction of Ketones[5]

(*S*)-3,3´-PolyBINOL in combination with diethylzinc catalyzed the asymmetric reduction of acetophenone with catecholborane. A 5.5 mol% of the polymer were mixed with 10 mol% of diethylzinc at room temperature, and the mixture was then combined with acetophenone. Subsequently, catecholborane (1.5 equiv) was added at -30 °C. The reaction mixture was stirred at this temperature for 48 h, and quenched with 1N HCl. The polymer was recovered by precipitation with methanol. The product (*R*)-1-phenylethanol was obtained with 62% ee and 90% yield.

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(*R*,*R*)-Bis(*tert*-butylmethylphosphino)methane[1]

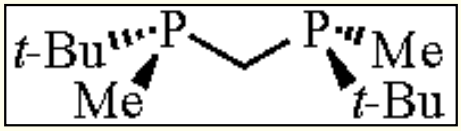

[224618-29-5] · $C_{11}H_{26}P_2$ · (220.27)

(a chiral ligand for transition metal-catalyzed asymmetric reactions)

Alternate Name: MiniPHOS.

Physical Data: colorless oil.

Solubility: soluble most organic solvents.

Preparative Methods: phosphorus trichloride is allowed to react sequentially with alkylmagnesium chloride, methylmagnesium bromide, and BH_3-THF complex in THF to give alkyldimethylphosphine-borane. The phosphine-borane so obtained is enantioselectively deprotonated by *s*-BuLi in the presence of (-)-sparteine in Et_2O at -78 to -50°C, followed by treatment with alkyldichlorophosphine, methylmagnesium bromide, and BH_3-THF complex to give a MiniPHOS-borane complex as a diastereomixture. After removal of the *meso*-isomer by silica gel chromatography, the enantiomerically pure product is obtained by recrystallization from methanol or ethanol. The boranato group is removed by reaction with trifluoromethanesulfonic acid in toluene, followed by treatment with aqueous KOH to give the desired diphosphine **1** (eq 1).

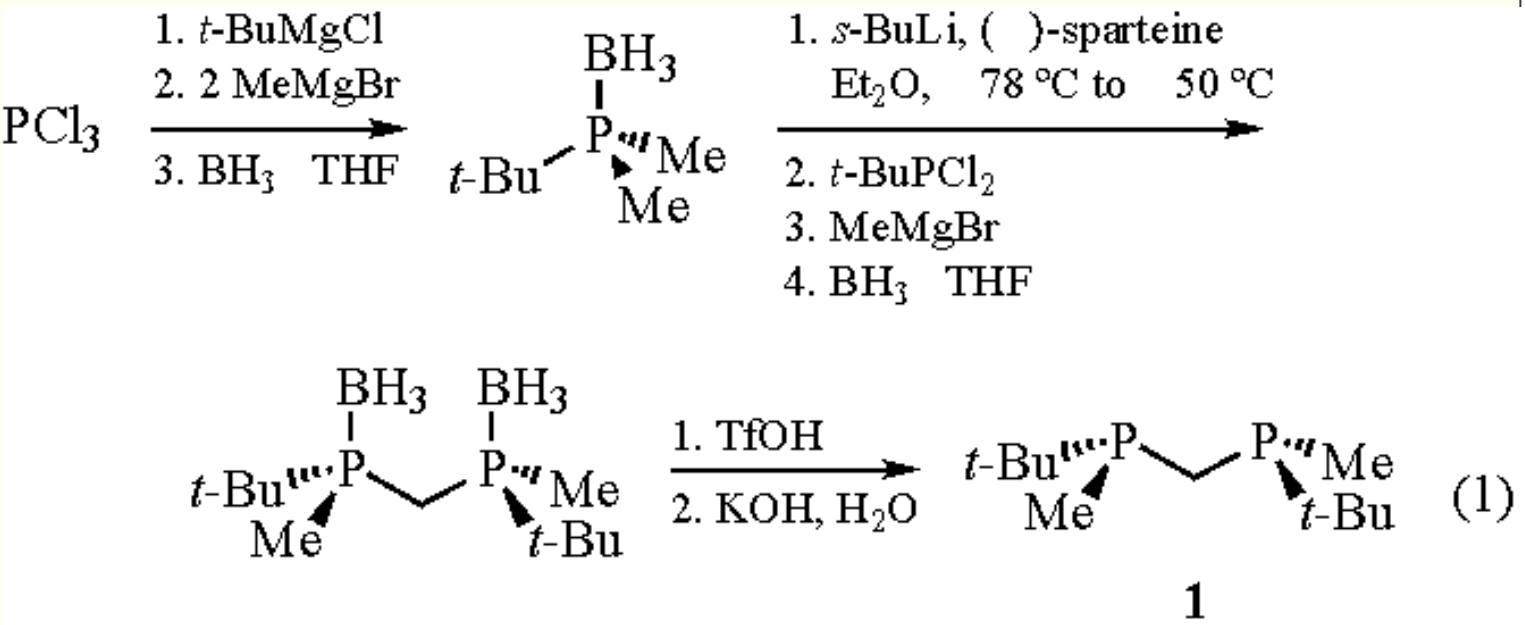

Purification: filtered through Al_2O_3 with Et_2O elution under N_2 or Ar atmosphere.

Handling, Storage, and Precautions: stench. Undergoes oxidation to the phosphine oxide on standing in air. Usually prepared before use by deboranation of the air stable phosphine-borane.

Rhodium-Catalyzed Asymmetric Hydrogenation of Olefins.

MiniPHOS (**1**) can be used in rhodium-catalyzed asymmetric hydrogenation of olefinic compounds.[1] The complexation with rhodium is carried out by treatment of **1** with $[Rh(nbd)_2]BF_4$in THF (eq 2). The hydrogenation of α-(acylamino)acrylic derivatives proceeds at room temperature and an initial H_2 pressure of 1 or 6 atm in the presence of the 0.2 mol% MiniPHOS-Rh complex **2**. The reactions are complete within 24-48 h to afford almost enantiomerically pure α-amino acids (eq 3). Itaconic acids,[2] enamides,[3] and dehydro-β-amino acids[4] can also be hydrogenated with excellent enantioselectivity (eq 4-6).

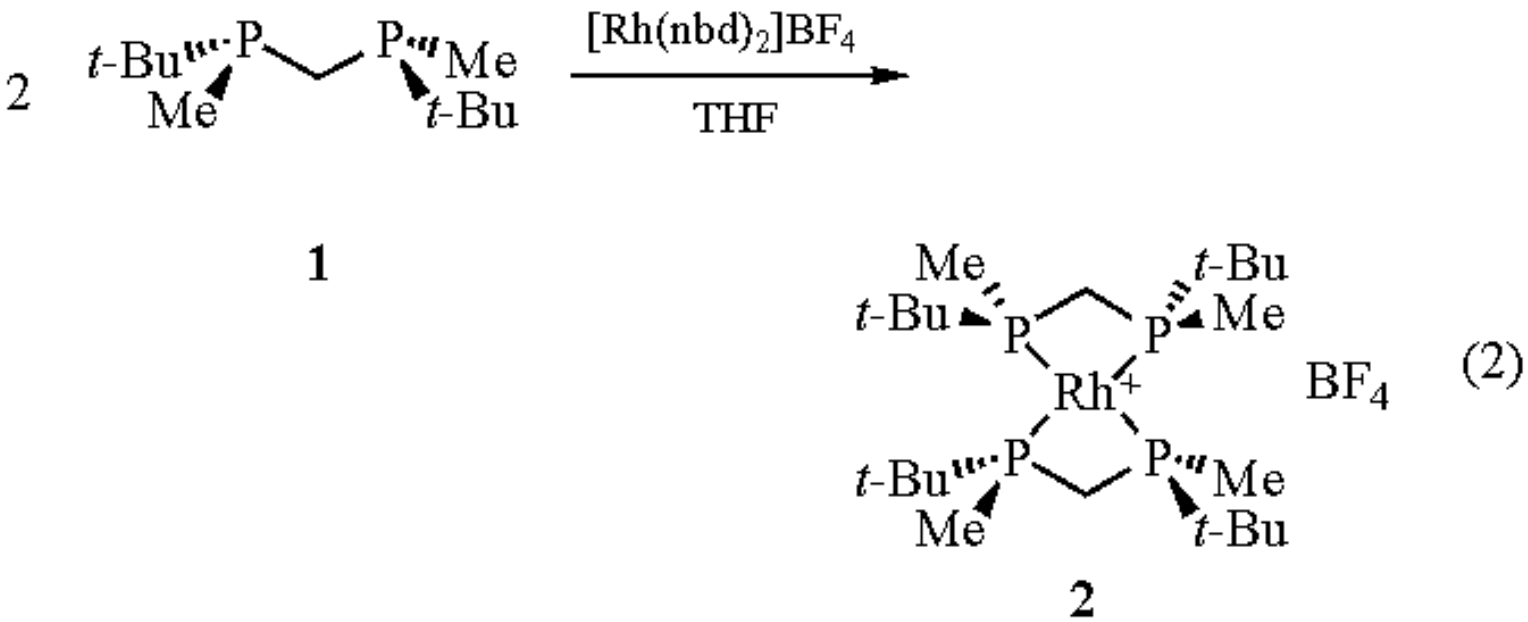

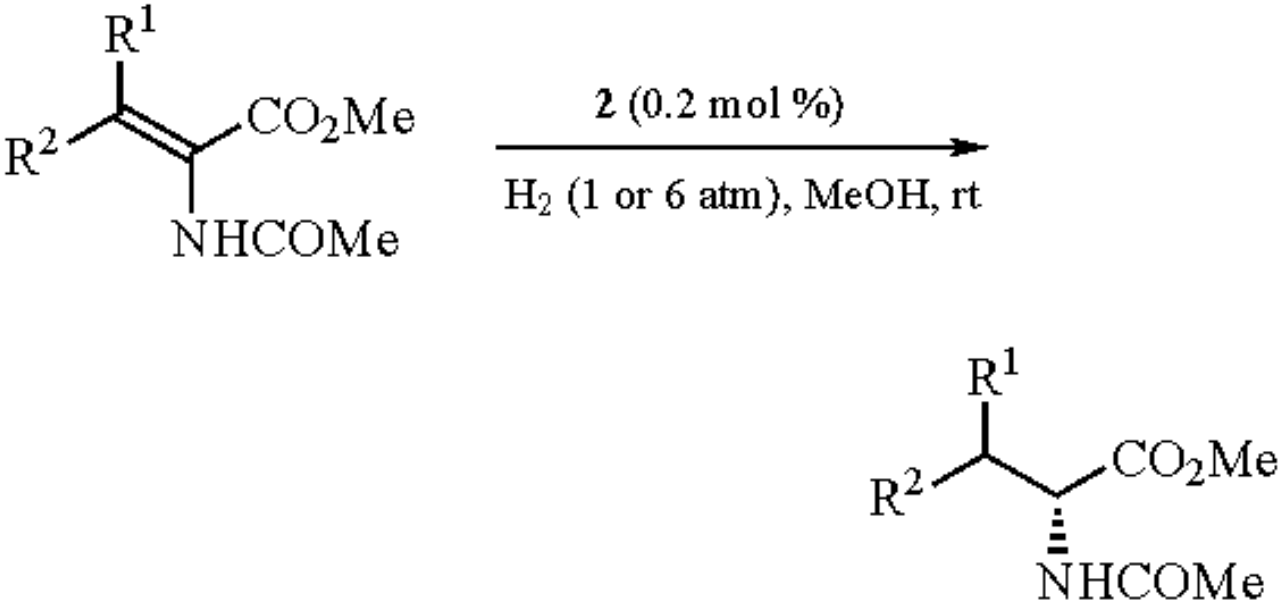

(3)

$R^1 = H$; $R^2 = Ph$, 98% ee

$R^1 = H$; $R^2 = H$, > 99% ee

$R^1, R^2 = (CH_2)_5$, 97% ee

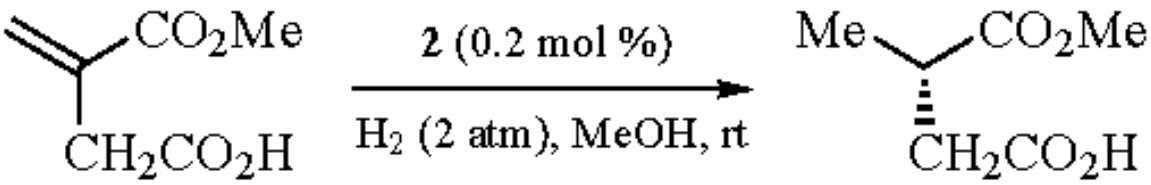

(4)

> 99% ee

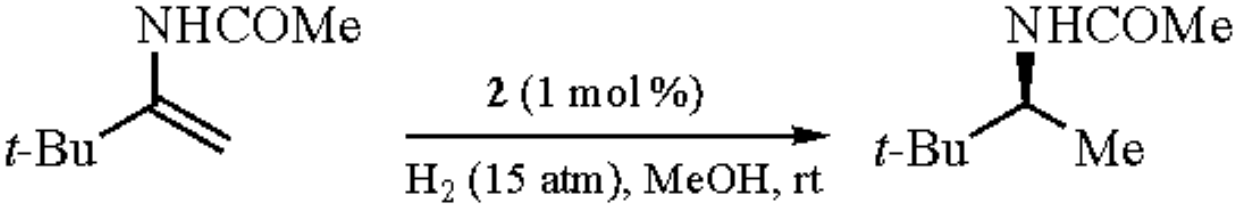

(5)

99% ee

(R,R)-Bis(tert-butylmethylphosphino)methane

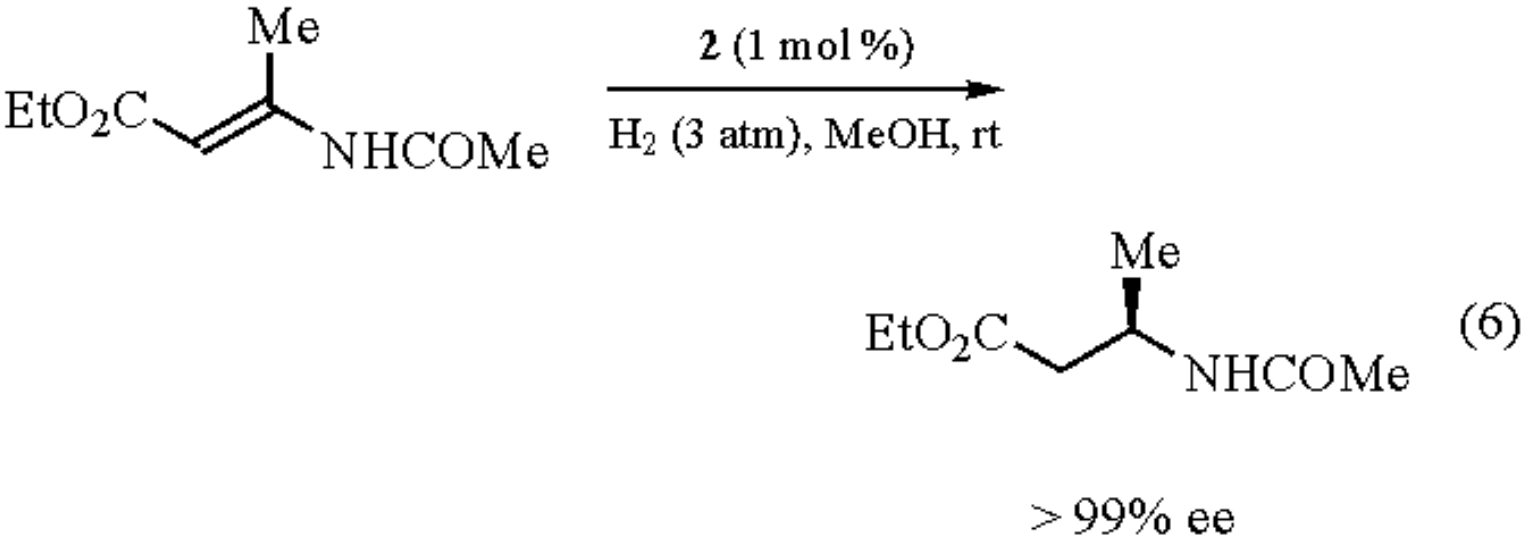

Rhodium-Catalyzed Asymmetric Hydrosilylation of Ketones

Complex **2** is a good catalyst for catalytic asymmetric hydrosilylation of ketones (eq 7).[1] The reactions are carried out by using 1-naphthylphenylsilane at -40°C in THF in the presence of **2** (1 mol%) for 3-4 days. Several types of ketones are hydrosilylated to afford optically active alcohols after acidic work-up.

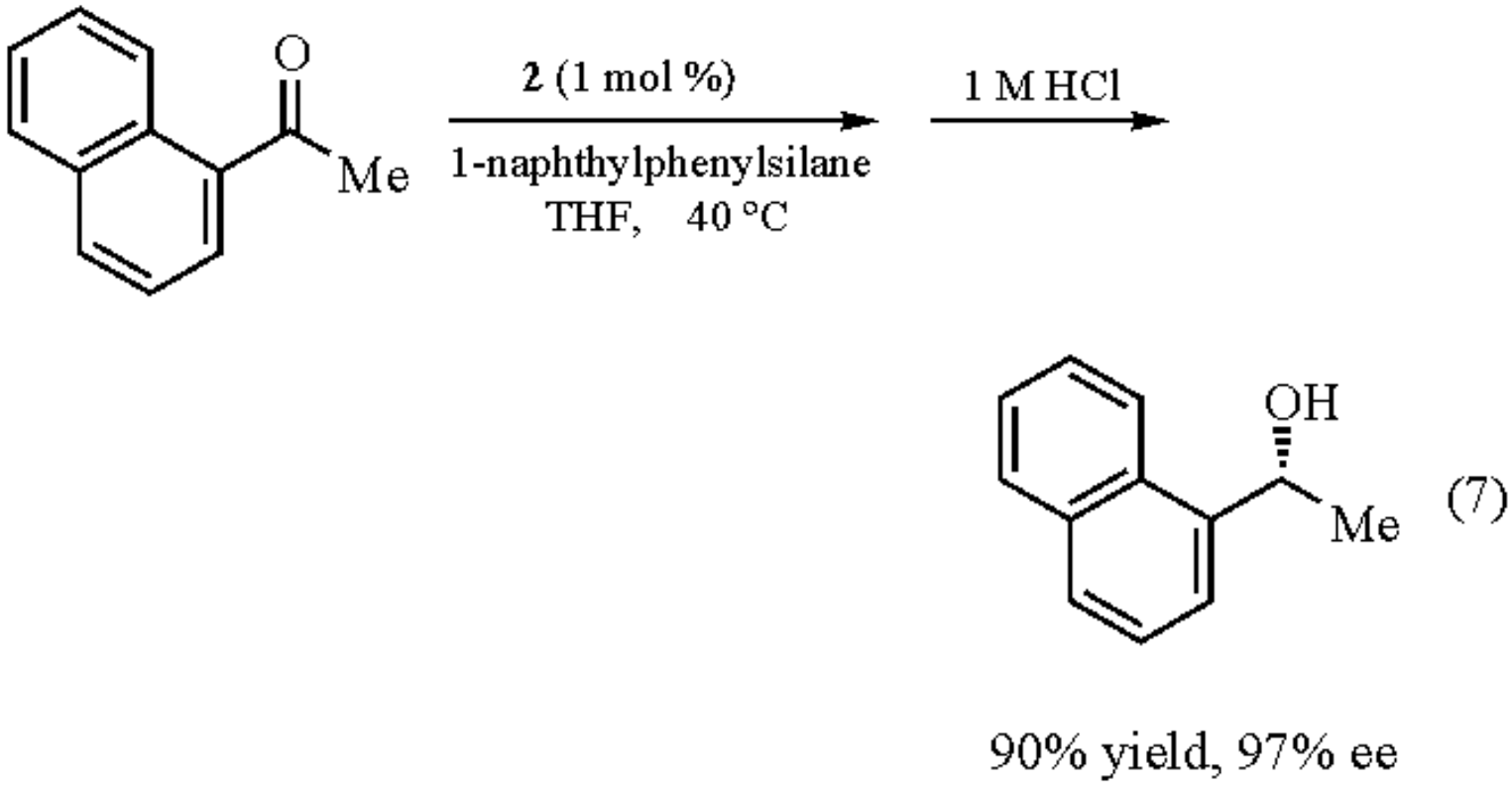

Related Reagents.

BisP*;[5] DIOP;[6] BINAP;[7] CHIRAPHOS;[8] DIPAMP;[9] DuPHOS;[10] BPE;[10] TRAP;[11] PHANEPHOS.[12]

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